Development of C–C Bond Forming Reactions Through C(sp^3)–H Bond Functionalization: Approach for the Construction of Novel (Spiro)heterocycles

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CERTIFICATE FROM THE SUPERVISOR

This is to certify that the thesis entitled **"Development of C–C Bond Forming Reactions Through C(sp^3)–H Bond Functionalization: Approach for the Construction of Novel (Spiro)heterocycles"** submitted by Sri **Arup Bhowmik** who got his name registered on **30.08.2018** for the award of **Ph.D. (Science)** degree (Index No.:**202/18/Chem./26**) of **Jadavpur University**, is absolutely based upon his own work under the supervision of **Dr. Indu Bhusan Deb** and that neither this thesis nor any part of it has been submitted for either any degree/diploma or any other academic award anywhere before.

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List of Abbreviations

AA	Anthranilic acid
Aβ	β-Amyloid
Ac	Acetyl
AcE	Angiotensin Converting Enzyme
Ach	Acetylcholine
AD	Alzheimer disease
Ac_2O	Acetic anhydride
AcOH	Acetic acid
Ad	Adamantyl
AIBN	Azobisisobutyronitrile
Am	Amyl
AQ	Aminoquinoline or 8-aminoquinoline
aq	aqueous
Ar	Aryl
BHT	Butylated hydroxytoluene
BIES	Base-assisted internal electrophilic substitution
BINAP	2,2′-bis(diphenylphosphino)-1,1′-binaphthyl
BIPHEMP	2,2′-bis(diphenylphosphino)-6,6′-dimethyl-1,1′-biphenyl
BM	Bond metathesis
Boc	*Tert*-butyloxycarbonyl
BQ	1,4-benzoquinone
BuChE	Butyryl cholinesterase
calcd	calculated
CAM	Complex assisted metathesis
CA4	Combretastatin A4
Cbz	Carboxybenzyl
CCDC	Cambridge crystallographic data centre
CDC	Cross-dehydrogenative coupling
CDI	1,1′-carbonyldiimidazole
CDK(s)	Cyclin-Dependent Protein Kinase(s)

CETP	Cholesteryl ester transfer protein
CFL	Compact fluorescent lamp
CGRP	Calcitonin gene-related peptide
CIF	Crystallographic information file
CMD	Concerted metalation-deprotonation
cod	1,5-cyclooctadiene
COSY	Correlation spectroscopy
COX	Cyclooxygenase
Cp	Cyclopentadienyl
Cy	Cyclohexyl
Cys	Cysteine
DABCO	1,4-diazabicyclo[2.2.2]octane
DBU	1,5-diazabicyclo[5.4.0]undec-5-ene
DCE	1,2-dichloroethane
DCM	Dichloromethane
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DEAD	Diethyl azodicarboxylate
DEPT	Distortionless enhancement by polarization transfer
DFT	Density functional theory
DG	Directing group
DIAD	Diisopropyl azodicarboxylate
DIPEA	*N*,*N*-diisopropylethylamine
DMAc	*N*,*N*-dimethylacetamide
DMAP	4-(dimethylamino)pyridine
DMF	*N*,*N*-dimethylformamide
DMPU	*N*,*N*-dimethylpropyleneurea
DMSO	Dimethyl sulfoxide
DPEPhos	(Oxydi-2,1-phenylene)bis(diphenylphosphine)
dr	diastereomeric ratio
DTBP	Di-*tert*-butyl peroxide
dtbpy	4,4′-di(*tert*-butyl)-2,2′-bipyridyl
EDWG	Electron donating and withdrawing group

ee	enantiomeric excess
EI	Electron ionization
er	enantiomeric ratio
ESI	Electrospray ionization
equiv	equivalent(s)
F	Faraday or Farad
FID	Flame ionization detector
FPT	Freeze Pump Thaw
GC	Gas chromatography
Gly	Glycine
HCV	Hepatitis C virus
HFIP	1,1,1,3,3,3-hexafluoroisopropanol
HIV	Human immunodeficiency virus
HMBC	Heteronuclear multiple bond coherence
HMDS	Hexamethyldisilane
HMQC	Heteronuclear multiple quantum coherence
HPLC	High performance liquid chromatography
HRMS	High resolution mass spectrometry
HT	Hydride transfer
[1,5]-HT	[1,5]- hydride transfer
Hz	Hertz
ICA	Indole-3-carboxylic acid
IMes	1,3-Dimesitylimidazolium
IPr	1,3-Bis(2,6-diisopropylphenyl)imidazolium
iPr or i-Pr or ^{i}Pr	isopropyl
IR	Infrared
J	Coupling constant
KIE	Kinetic isotope effect
LC	Liquid chromatography
LED	Light emitting diode
mA	milliampere
m-CPBA	*m*-Chloroperoxybenzoic acid

Mes	Mesityl
mp	melting point
MS	Mass spectrometry or molecular sieves
Ms	Mesyl
MW	Microwave
NBP	*N*-bromophthalimide
nBu or n-Bu or ^{n}Bu	n-butyl
nd	not detected
NHC	*N*-heterocyclic carbene
NIS	*N*-iodosuccinimide
NMO	*N*-methylmorpholine-*N*-oxide
NMP	*N*-methyl-2-pyrrolidone
NMR	Nuclear magnetic resonance
NNRTIs	Non-nucleoside reverse transcriptase inhibitors
NOESY	Nuclear overhauser effect spectroscopy
nr	no reaction
Ns	Nosyl
NSAID	Nonsteroidal anti-inflammatory drug
OA	Oxidative addition or oxalamide
O. S.	Oxidation state
OTf	Triflate
Oxa	2-aminophenyl oxazoline
PA	Picolinamide or 2-picolinamide
PEG	Polyethylene glycol
PFT	Protein farsenyl transferase
PIDA	Phenyliodonium diacetate
PIP	2-pyridylisopropylamine
Piv	Pivalic or pivaloyl
Ph	Phenyl
Phe	Phenylalanine
Py	Pyridyl
Pym	Pyrimidyl

PyO	Pyridine-*N*-oxide
PyPhos	2-(2-(Diphenylphosphino)ethyl)pyridine
rac	Racemic
Q	Quadrapole or quinoline
rds	rate determining step
rt	room temperature
RVA	Recombinant virus assay
RVC	Reticulated vitreous carbon
SC	Single crystal
$Sc(OTf)_3$	Scandium triflate
S_EAr	Electrophilic aromatic substitution
SET	Single electron transfer
SIMes	1,3-Bis(2,4,6-trimethylphenyl)imidazolinium
TBAB	Tetrabutylammonium bromide
TBAI	Tetrabutylammonium iodide
TBHP	*tert*-butyl hydroperoxide
tBu or t-Bu or ^{t}Bu	*tert*-butyl
TEMPO	(2,2,6,6-tetramethylpiperdin-1-yl)oxyl
TFA	Trifluoroacetic acid
TFE	2,2,2-trifluoroethanol
THF	Tetrahydrofuran
THIQ	Tetrahydroisoquinoline
THQ	Tetrahydroquinoline
TIPS	Triisopropylsilyl
TLC	Thin layer chromatography
TM	Transition metal
TMAO	Trimethylamine *N*-oxide
TMEDA	Tetramethylethylenediamine
TMS	Tetramethylsilane or trimethylsilyl
$TMSCF_3$	Trifluoromethyltrimethylsilane
TMSCN	Trimethylsilyl cyanide
TOAB	Tetraoctylammonium bromide

Tof	Time of flight
TosMIC	*p*-Tosylmethyl isocyanide
TPBP	*tert*-butyl peroxybenzoate
TS	Transition state
Ts	Tosyl
TsOH	*p*-Toluenesulfonic acid
WHO	World health organization
XRD	X-ray diffraction

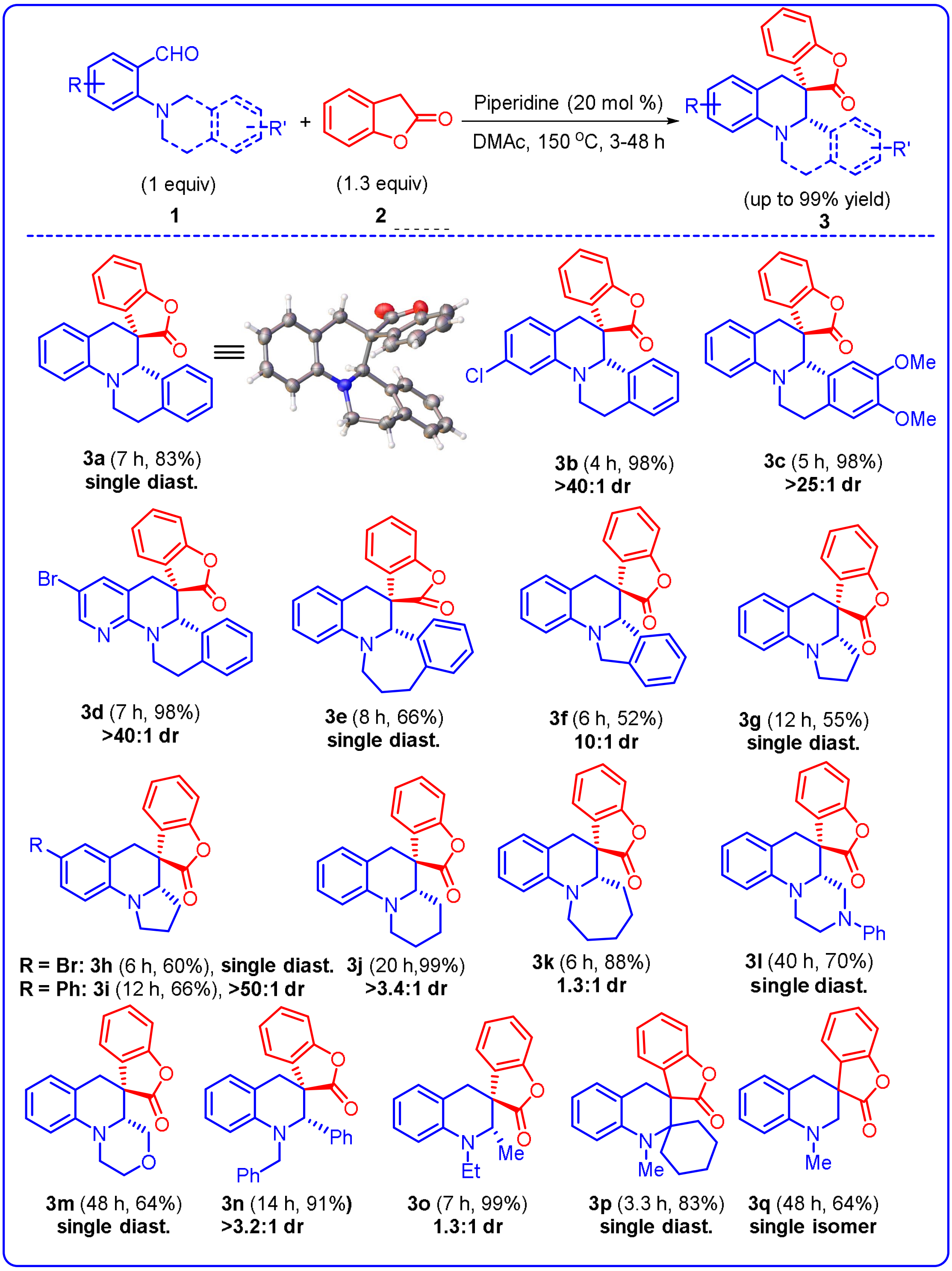
Synopsis

The thesis entitled "***Development of C–C Bond Forming Reactions Through C(sp^3)–H Bond Functionalization: Approach for the Construction of Novel (Spiro)heterocycles***" has been divided into five chapters based on the results obtained by the experiments conducted during the period of research. **Chapters 1** and **4** are introductory chapters on the brief history of 1,5-hydride transfer reaction and indole-3-carboxylic acid derivatives respectively. The rest of the three **Chapters** (**2**, **3**, **and 5**) emphasize the Lewis acid-free hydride transfer reaction, Lewis acid-catalyzed hydride transfer reaction, and expeditious synthesis of indole-3-carboxylic acid direct from isatin.

In **Chapter 1** and **Chapter 4**, a general overview of some biologically active pharmacophores, unreactive C(sp^3)–H bond functionalization 1,5-hydride transfer reaction, and indole-3-carboxylic acid derivatives have been discussed with a detailed scheme. **Chapter 1** gives an outline of some pharmacophore which has importance not only synthetically but also in chemical biology. This chapter consists of the origin of the hydride shift reaction field through unreactive C–H bond functionalization in a redox-free atom economical process and the brief history associated with it. The hydrogen atom transition from one carbon to another employing Lewis acid or none to develop C–C or C–hetero bond formation, the challenges associated with it, its classifications, and synthetic applications are also included. The importance of the cascade 1,5-hydride shift strategy and the generation of novel spiroheterocycles have been cultivated in this chapter. **Chapter 4** provides a brief history of indole-3-carboxylic acid derivatives. Preparation methods and the synthetic application of this key intermediate have been discussed briefly. The utilization of DMSO as a reagent not only a solvent, a good synthon, has been described. These two chapters are associated with the unreactive C(sp^3)–H bond functionalization, various modes of C–H activation, Lewis acid assisted or free hydride transfer/endo cyclization cascade methodology, the various types of bond forming reactions via C–H bond functionalization strategy, synthesis of a diverse novel (spiro)heterocycle, the importance of kinetic isotopic effect and other mechanistic studies to rationalize the mechanism of a reaction, are all discussed in detail. Enantioselective reactions employing several organocatalysts have transformed this field to a whole new level for the efficient synthesis of chiral architectures in an atom and a step-economic manner has also been exemplified.

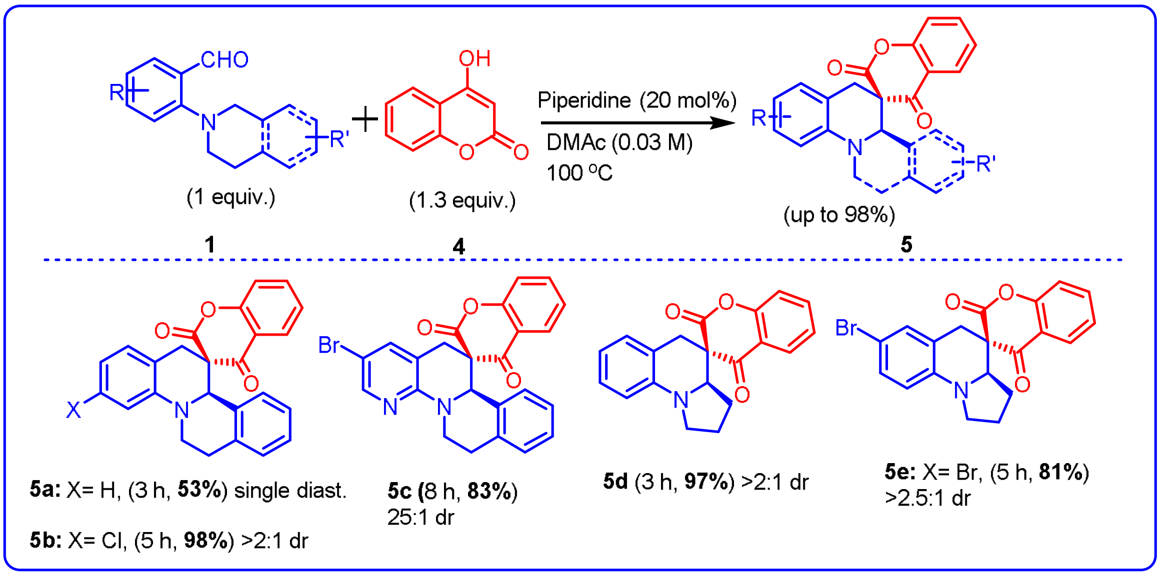
In **Chapter 2**, Lewis acid-free intramolecular C(sp^3)–H bond functionalization has been described, triggered by consecutive [1,5]-hydride shift /cyclization process, an approach for diastereoselective construction of novel spiroheterocycles in unprecedented cascade methods. Tetrahydro(iso)quinoline[1] and 2-coumaranone[2] are good pharmacophores present in several natural products and drugs. This method delivered access to the tetrahydroquinoline moiety through a novel hydride shift/ 6-endo-*trig* cyclization strategy. The development of a highly stereoselective and atom-economic cascade method for the construction of a spirocyclic scaffold containing 2-coumaranones fused with *N*-heterocycles has been explored.[3] Recently, hydride transfer followed by cyclization sequence has become an attractive complementary approach for C(sp^3)−H bond functionalization and novel spiroheterocycle preparation. Over the past few decades, substantial efforts have been made by various research groups to develop varieties of hydride transfer/cyclization cascade reactions for the construction of structurally diverse complex molecules.[4] In this chapter, we described a straightforward and practical approach towards the diastereoselective synthesis of spiro-*N*-heterocycles via cascade olefination, [1,5]-hydride transfer followed by cyclization strategy using corresponding aldehyde and coumaranone without using any transition metal or Lewis acid in one-pot operation.

We screened several reactions by taking tetrahydroisoquinoline substituted benzaldehyde (**1a**) with 2-coumaranone (**2**) using piperidine (20 mol %) as a catalyst to obtain spiroheterocycle **3a**. Among various solvents, DMAc showed the best result, and one pot cascade reaction was developed. To our delight, the desired spirocyclic product **3a** (as a major diastereomer) was obtained spontaneously in every case through olefin intermediate followed by [1,5]-hydride shift/cyclization sequence in one pot. A control experiment was conducted in the absence of piperidine and the formation of the product was observed and this result suggested that the piperidine is not essential for the reaction. However, a catalytic amount of piperidine accelerated the reaction to improve the yield of the product exquisitely, applicable in large-scale reactions. After figuring out the optimization condition, we explored the substrate scope of the 2-coumaranone with the diverse *ortho*-amino benzaldehydes as hydride donors (Scheme 1). In general, various substituted *ortho*-amino benzaldehydes are compatible with this reaction furnishing good yield with excellent diastereoselectivity. Tetrahydroisoquinoline moiety bearing several functional groups was suitable for this hydride transfer process and delivered good yield with excellent diastereoselectivity. Besides tetrahydroisoquinoline, several benzo-fused cyclic amines reacted well to provide molecular complexity (Scheme 1).



Scheme 1 Scope of 2-coumaranone containing spiroheterocycles

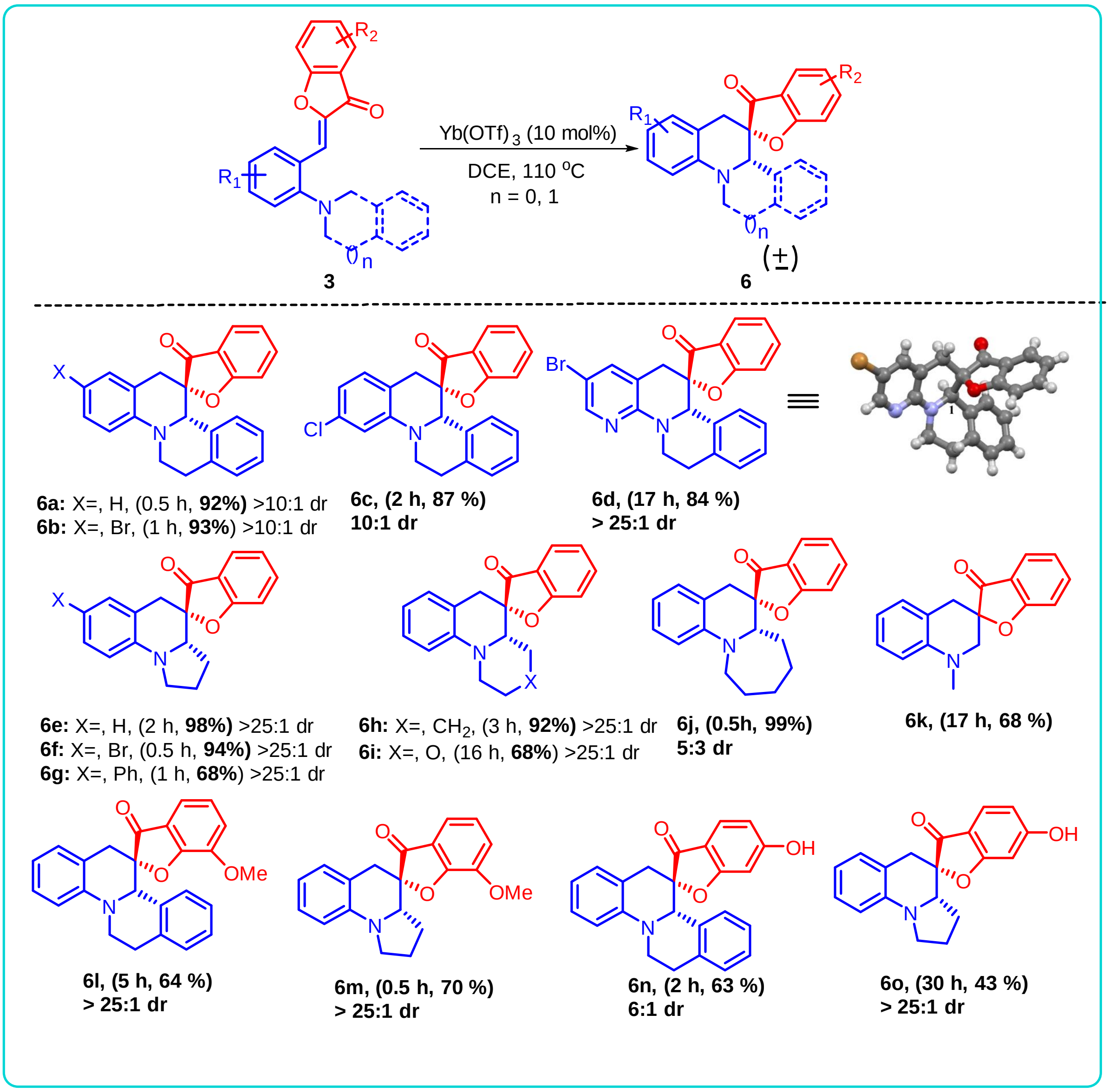
Apart from benzylamine, several cyclic and acyclic alkyl amines (α-CH_2 w.r.t. *N*) containing substrate underwent smooth hydride shift reaction. Pyrrolidine, Piperidine, azepane *N*-phenyl piperazine, morpholine *N*, *N*-dibenzyl, and *N*, *N*-diethyl substituted aldehydes showed their good hydride donor capability and reacted well to provide excellent desired products with excellent to good dr. *N*-methyl-*N*-cyclohexyl and *N*, *N*-dimethyl substituted aldehydes generated the cyclic products as a single isomer.



Scheme 2 Scope of 4-hydroxycoumarin containing spiroheterocycles

This substrate scope was further extended by taking another active partner 4-hydroxycoumarin, reacting with various *ortho*-amino benzaldehydes under standard conditions in one pot which made the method stronger (Scheme 2). THIQ-containing aldehydes were well tolerated and gave the corresponding products in good to excellent yield with good diastereoselectivity. Then, the reactions were carried out with pyrrolidine, and azepane substituted aldehydes and afforded the products in moderate to good yield with poor diastereoselectivity. The advantage of this method is no transition metal or Lewis acid or oxidant or highly expensive solvent is needed for this spirocyclization strategy, instead in a straightforward approach diastereoselective spiroheterocycles have been accessed. Based on several reports and our throughout research we proposed a route toward spirocyclization.

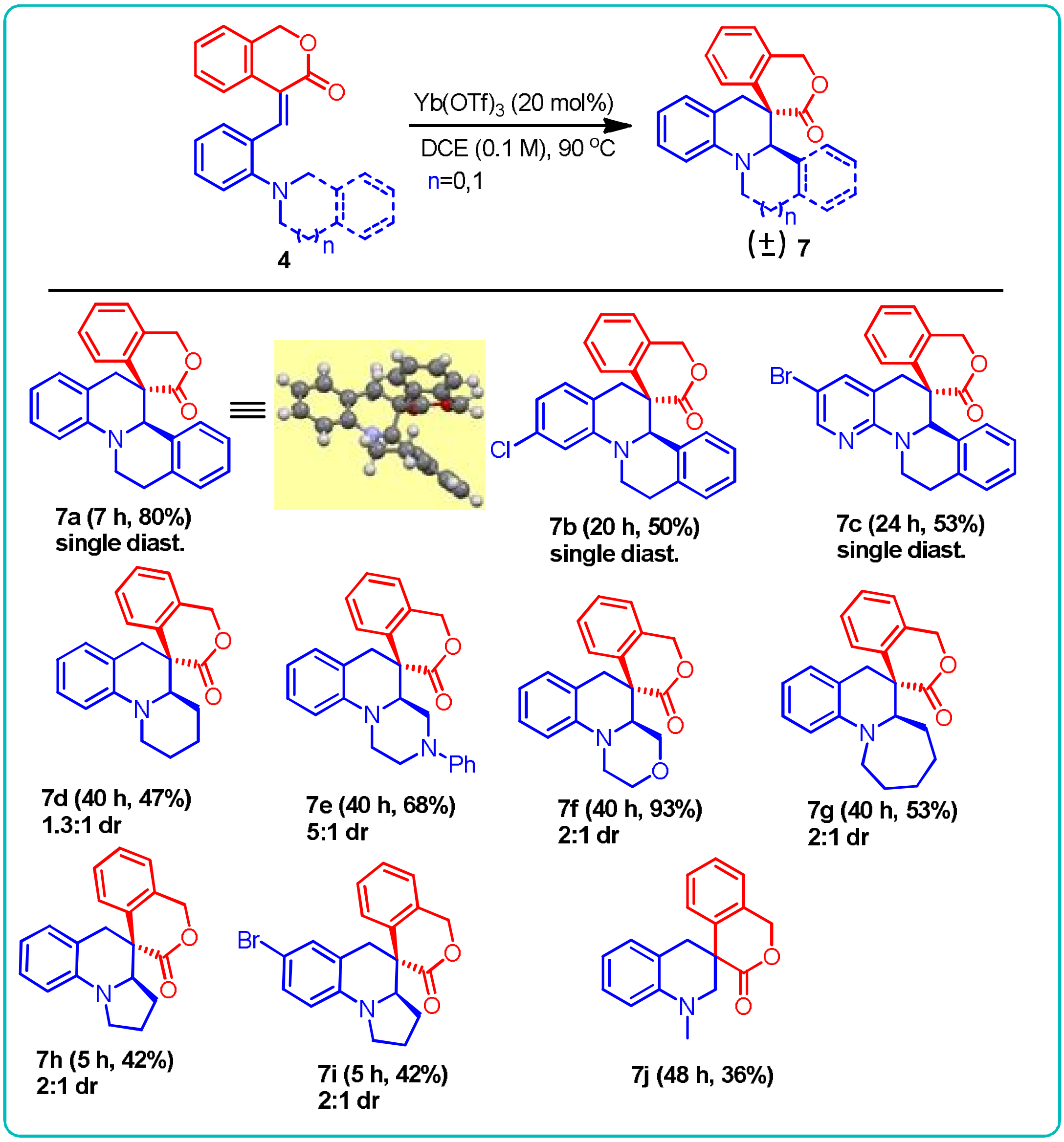
In **Chapter 3**, Lewis acid catalyzed intramolecular C(sp^3)–H bond functionalization demonstrated, triggered by consecutive [1,5]-hydride shift /cyclization process, an approach for diastereoselective construction of novel pharmaceutically relevant spiroheterocycles. Benzofuran-3-one,[5] 3-isochromanone,[6] succinimide,[7] and tetrahydro(iso)quinoline[1] are the privileged scaffolds in organic chemistry due to their presence in varieties of medicinally important molecules and drugs exhibit excellent activity against different biological targets. To achieve these pharmacophore-containing spiroheterocycles, we wanted to harness the power of Lewis acid-assisted transition metal-catalyzed direct C–H functionalization strategy. An extensive literature search showed that these pharmacophores had not been utilized for hydride shift reactions to date. Relying on substrate engineering, we aimed to develop a method to achieve diastereoselective [4.5] and [5.5] spiro-coumaranone/isochromanone containing tetrahydroquinolines utilizing Lewis acid-mediated catalytic C–H functionalizations which have great importance in complexity-enhancing potential synthetic application and in chemical biology. Succinimide does not perform Knoevenagel-type olefination reaction, hence, it is very difficult to synthesize corresponding spiroheterocycles through this methodology although its spiro-derivative is important in synthetic chemistry as well as in medicinal chemistry.[8] With our aim of developing a sustainable method for the synthesis of diverse spiroheterocycles, we set out to explore the power of cheap and abundant starting material, reagent, or solvent and thereby reported a stepwise olefination followed by hydride shift strategy outside of treating any oxidant and expensive transition metal catalyst.



Scheme 3 Scope of cyclization of benzofuran-3-one containing olefins

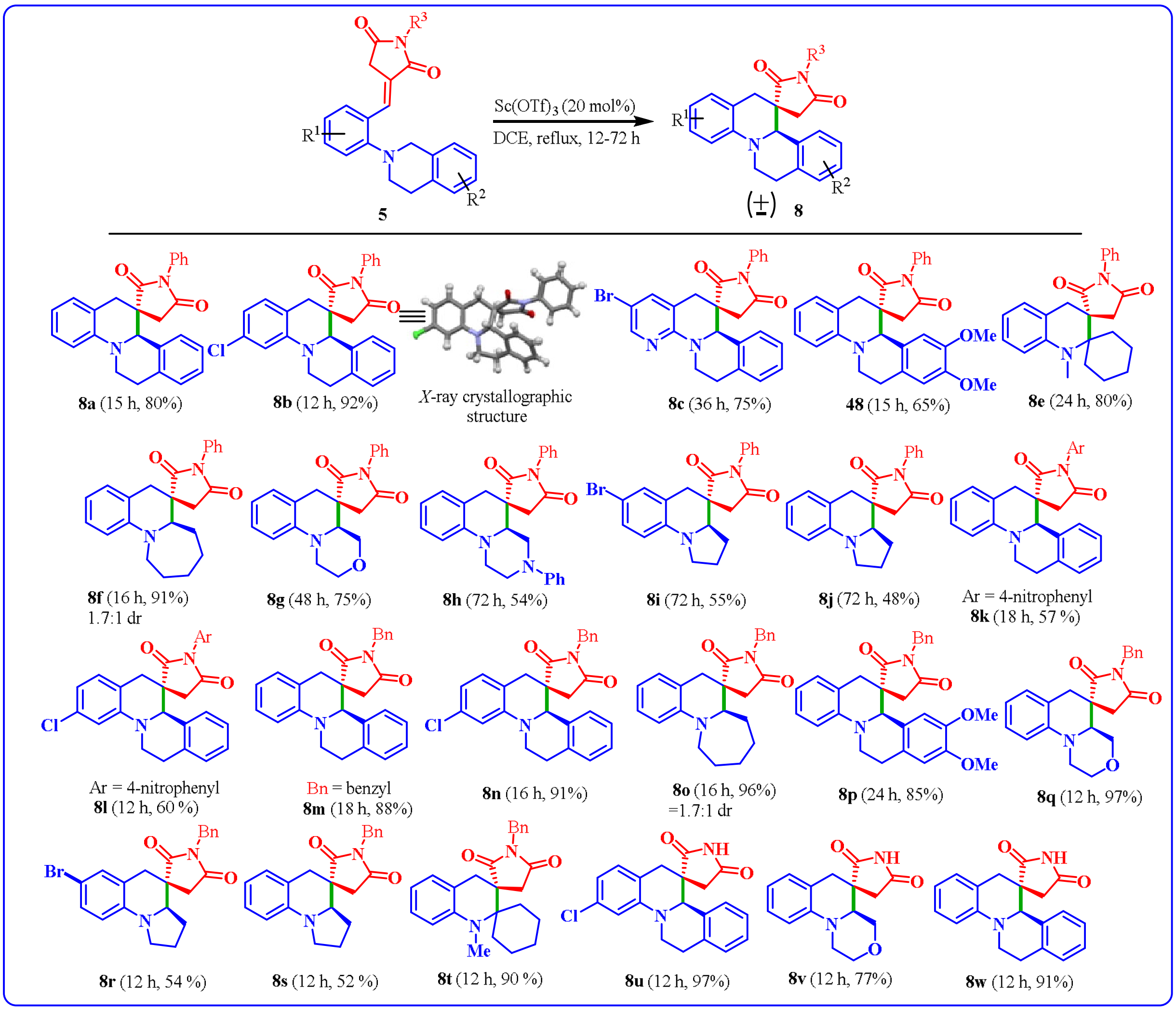
Various functional group tolerance benzofuran-3-one and 3-isochromanone containing olefins have been prepared through the Knoevenagel condensation method. A substitute Wittig reaction had been developed in the case of the preparation of succinimide containing olefin, utilizing triphenylphosphine with corresponding maleimide and aldehyde. Optimization studies towards spiroheterocycles from the corresponding olefin substrates led to the fact that $Yb(OTf)_3$ displayed the best result for benzofuran-3-one and 3-isochromanone mediated olefin substrates and $Sc(OTf)_3$ for succinimide containing substrate at the reflux condition in DCE solvent. Exploring substrates scope under the most efficient condition, we constructed a wide range of benzofuran-3-one containing spiroheterocycles, and the strategy was also fair throughout the functional group tolerance (Scheme 3). THIQ substituted various olefins underwent very smoothly in this reaction condition to provide the desired spirocyclic products in good to excellent yields with high diastereoselectivity (84-93%). Pyrrolidine, piperidine, azepane, and morpholine-substituted olefins showed their well-hydride donor capability in this condition. The advantage of this method is the synthesis of novel spiroheterocycle in an efficient straightforward way with an excellent diastereoselective manner.

To emphasize this methodology, we introduce another building block surrogate 3-isochromanone. This important pharmacophore was examined to construct a new class of spiro-heterocycles containing THIQ and 3-isochromanone moieties altogether. Despite their potential biological activities, no protocol is available to integrate these two pharmacophores to date. Delightfully, 3-isochromanone substituted olefin transformed very well to furnish the product **7a** as a single diastereomer in 80% yield in the presence of 20 mol % of $Yb(OTf)_3$ under reflux condition of the solvent DCE (Scheme 4). The substrates successfully furnished the corresponding 3-isochromanone containing spiroheterocycles **7b-j** in moderate to good yields (Scheme 4) implying that pyrrolidine, piperidine, azepane, and morpholine groups are well tolerable at this reaction condition.



Scheme 4 Scope of cyclization of 3-isochromanone containing spiroheterocycles

The spirocyclic motif is a key element in the natural products and discovery of new drugs due to their inherent three-dimensionality and structural novelty.[8,9] In contrast, succinimide is a constituent of natural products such as salfredinC-1, palasimide, and numerous spiro-succinimide identified as powerful orally potent aldose-reductase inhibitors.[10] Among various spirocyclic cores, we targeted [4.5] succinimide-based piperidine skeleton because it represents a unique class, such as useful in treating senile dementia, Alzheimer's disease, Huntington's chorea, and other diseases.[8] Prior literature reports say this scaffold could be synthesized from piperidine 3-carboxylate derivatives or their analogs in an ancient multistep uphill process. Therefore, the construction of these spiro scaffolds has drawn considerable interest.[11] Recent efforts by us have led to the creation of multifunctional 2,7-diazaspiro[4.5]decanes exploiting hydride shift methodology, which was highly challenging due to the inaccessibility of the corresponding synthetic precursor. Taking **5a** as a model substrate we screened several reactions and among various Lewis acid Sc(OTf)$_3$ delivered the desired spirocyclic product **8a** to a greater extent (Scheme 5) in DCE solvent. To evaluate the generality of this methodology, the scope of the spirocyclization of 2-aminobenzyledenesuccinimide derivatives was explored in the best reaction condition. Notably, it was a great achievement that the reaction exhibited producing a single diastereomeric product of **8a**, which may be generated via a thermodynamically controlled way. Remarkably, a variety of aminobenzyledene-succinimide derivatives were well compatible with the reaction system, producing the corresponding spiro-succinimide containing tetrahydroquinoline (THQ) **8** in moderate to high yields with excellent diatereoselectivity (Scheme 5). Not only were various amines displayed as good hydride donor capability but several succinimides also showed good acceptance capability leading to the construction of desired spiroheterocycles diastereoselectively.

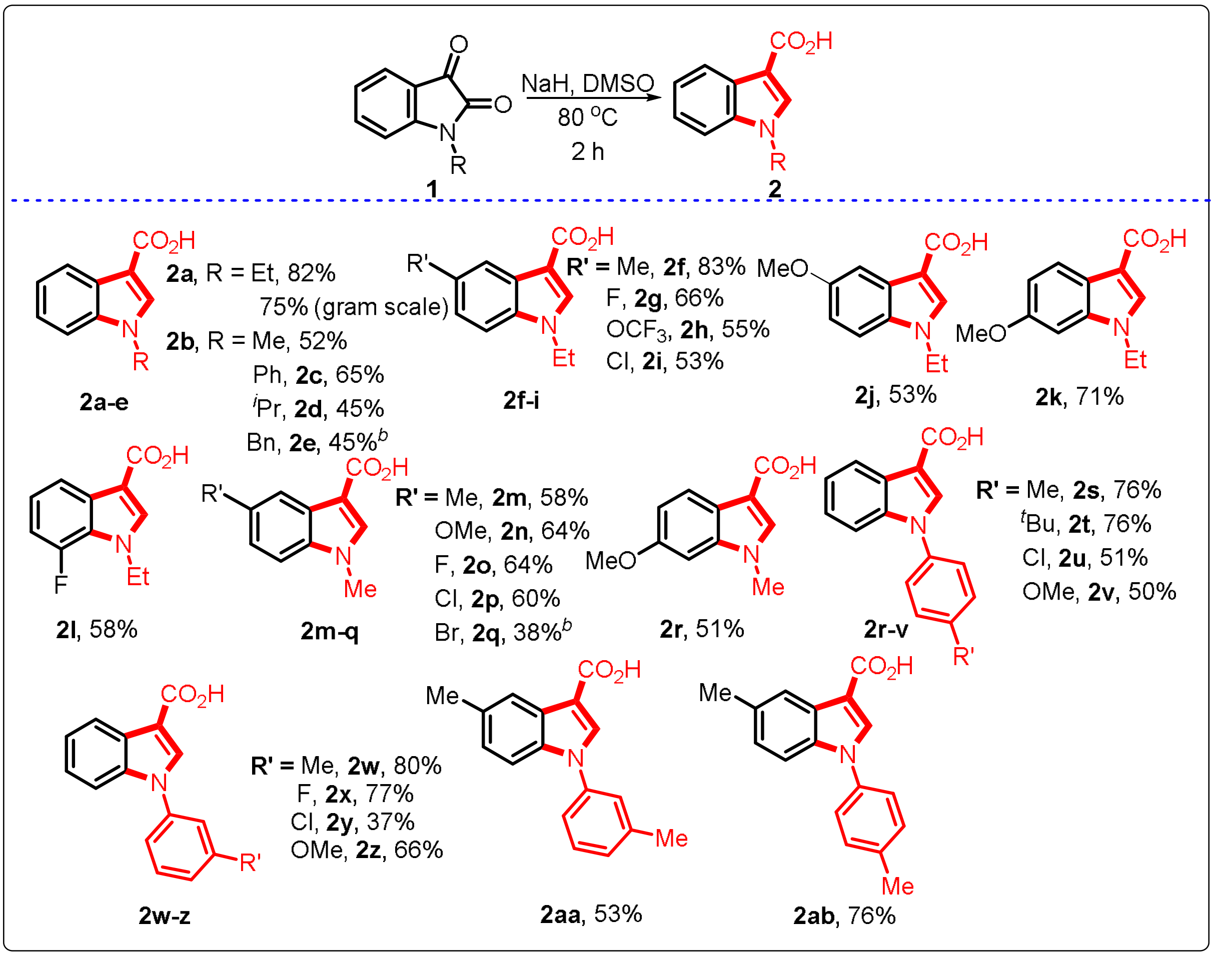


Scheme 5 Substrate scope of the cascade reaction towards succinimide containing spiro-heterocycles

Chapter 4 discusses a brief overview of the indole-3-carboxylic acid derivative.[12] The preparation method of this key intermediate from ancient days to nowadays and the application has been speculated in shortly. All the previous report such as C–H bond activation, C–Br bond activation strategy, the electrophilic substitution of indole, and electron catalyzed C–N bond formation method, and the importance of DMSO as a synthon has been described briefly.

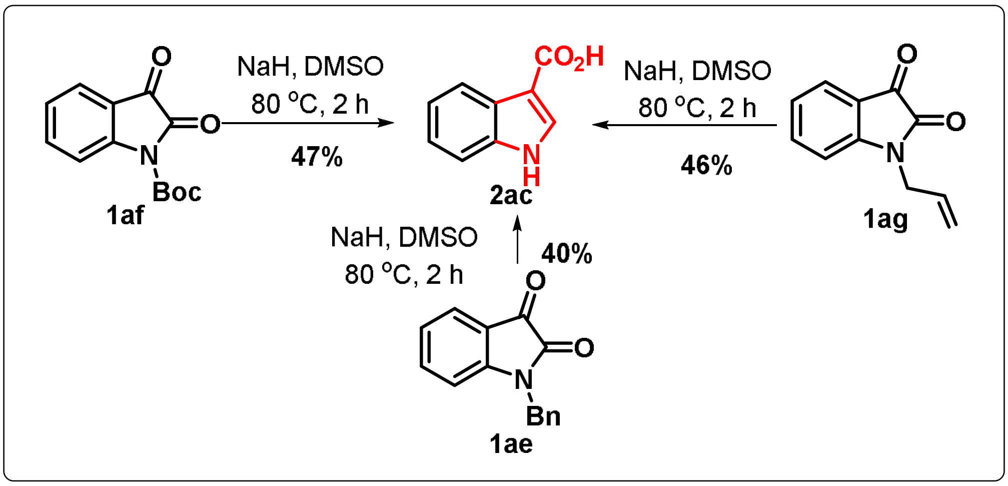
Chapter 5 reveals unorthodox cascade redox reactions of isatin using DMSO as a methine source for expeditious route to indole-3-carboxylic acids, and anthranilic acids. The event of reduction or oxidation of any organic molecule without helping of so-called reducing and oxidizing agents is very challenging.[13] We created a device to cause a transformation of indole-3-carboxylic acid (ICA) and anthranilic acid (AA) derivatives directly from isatin derivatives distinctly. Indole-3-carboxyl moiety is widely present in numerous natural products, and ICA has also been used to construct several artificial drugs such as arbidol, tropisetron, dolasetron, etc., or its derivatives broadly used as (a) anticancer agents (CPI-1205), (b) serotonin 5-HT4 and 5-HT6 antagonists, (c) EphB3 receptor tyrosine kinase inhibitors, (d) potential therapeutic agents for Alzheimer's disease.[14] Hence, ICA has great importance as a prodrug or a versatile key intermediate of several drug candidates. On the other hand, anthranilic acid (AA) plays a pivotal role as a building block and a key intermediate in the biosynthesis of acridone or quinoline alkaloids, metabolites for the production of the neurotransmitter serotonin.[15] The biggest advantages of methodology are the preparation of key intermediate ICA derivatives (an overall reduced product) utilizing none reducing agents, transition metal catalyst, Lewis acid, or employing an expensive directing group, and the same for AA (an overall oxidized product) employing none oxidizing agent externally in economically viable and operationally simple conditions. Indeed, there exists no direct route for the synthesis of the key intermediate ICA from isatin and previous literature report says it has been prepared in an expensive multistep process. A few methods are available to synthesize AA derivatives employing external oxidizing agents (eg. H_2O_2, CrO_3, etc).[16] To the best of our knowledge, without oxidizing agents it is not known in the literature to date. We wish to report herein, we demonstrated an overall oxidized or reduced structural motif (AA and ICA derivatives respectively) outside of treating any oxidizing or reducing agents as well as any transition metal at mild conditions employing cheap starting material isatin derivatives in one pot.

Thorough optimization led us to the optimal conditions for the transformation of isatin to ICA derivatives in one pot employing sodium hydride as a base and DMSO as a reacting partner as well as solvent. Utilizing freeze-pump-thaw method 6 equiv. NaH gave the best result at 80 □ and this condition provided access to several ICA derivatives in a very short time. The best thing about this method is the development of an overall reduced product without using any reducing agents.



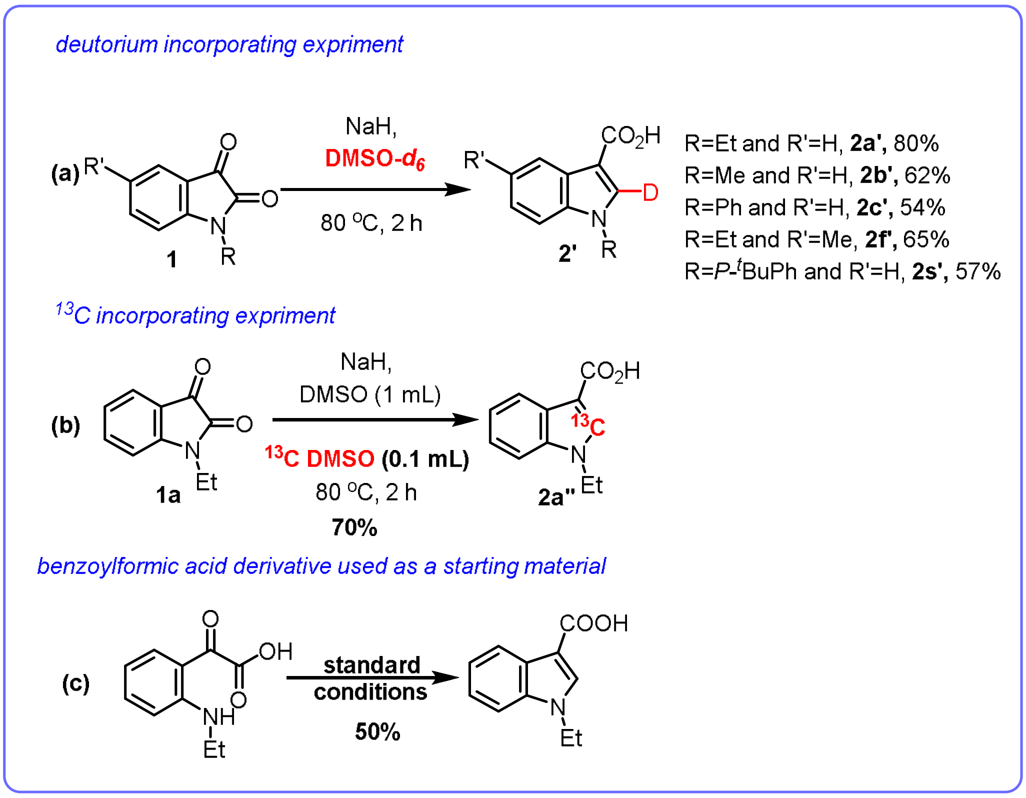
Scheme 6 Synthesis of indole-3-carboxylic acid derivatives from isatin derivatives

Several *N*–protected isatin derivatives such as Me, Et, Ph, ^{i}Pr, and Bn played well furnishing good to moderate yield (**2a-2e**) (Scheme 6). Various *N*-ethyl and *N*-methyl isatin derivatives with diverse functional groups (substituted at C_4, C_5, C_6, and C_7 position with EDG and EWG) performed well producing building-block ICA derivatives (**2f-2r**). Different functional groups such as Me, ^{t}Bu, OMe, F, Cl, etc present in the *N*-protected phenyl ring (in C_3', C_4' position) were well tolerable, providing good yield in this conversion (**2r-2ab**) (Scheme 6). Indole-3-carboxylic acid (ICA) is a precursor of several biologically active molecules, although single-step preparation from isatin derivative is highly challenging, succeeded by our methods.



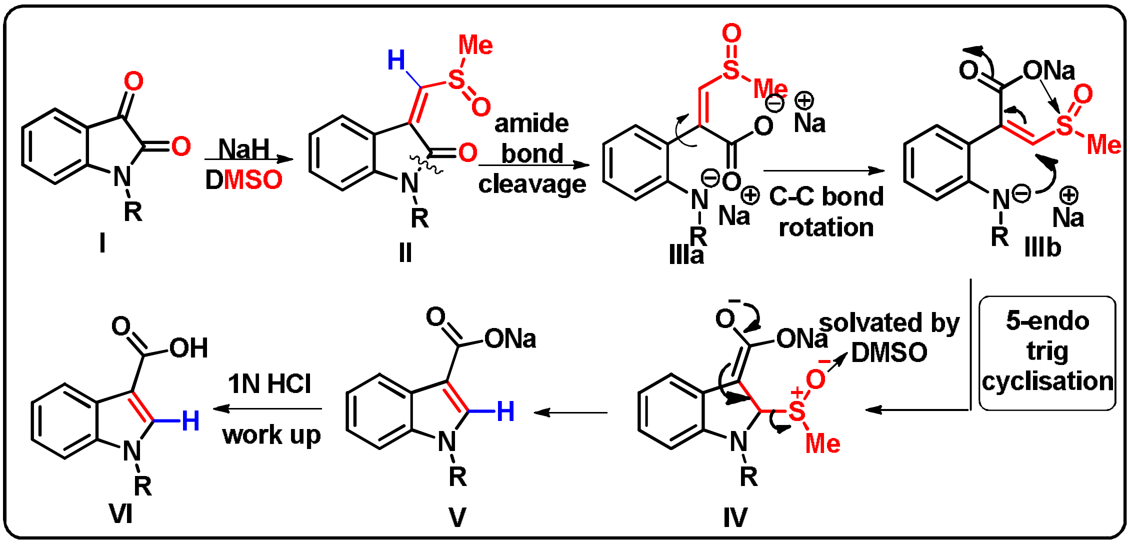
Scheme 7 Direct indole-3-carboxylic acid formation from different *n*-substituted isatin derivatives

We produced this important key intermediate from isatin derivatives such as *N*-Boc/*N*-allyl/*N*-benzyl isatin (**1af**, **1ag**, and **1ae**) in one pot with a moderate yield (Scheme 7). To understand the mechanistic path we conducted several experiments such as deuterium incorporating experiment, ^{13}C incorporating experiment, etc., and proved that extra carbon in ICA is coming from DMSO, behaving as a one-carbon synthon (Scheme 8). Hence, we proposed a mechanism for the synthesis of ICA derivatives direct from isatin described in this chapter elaborately.



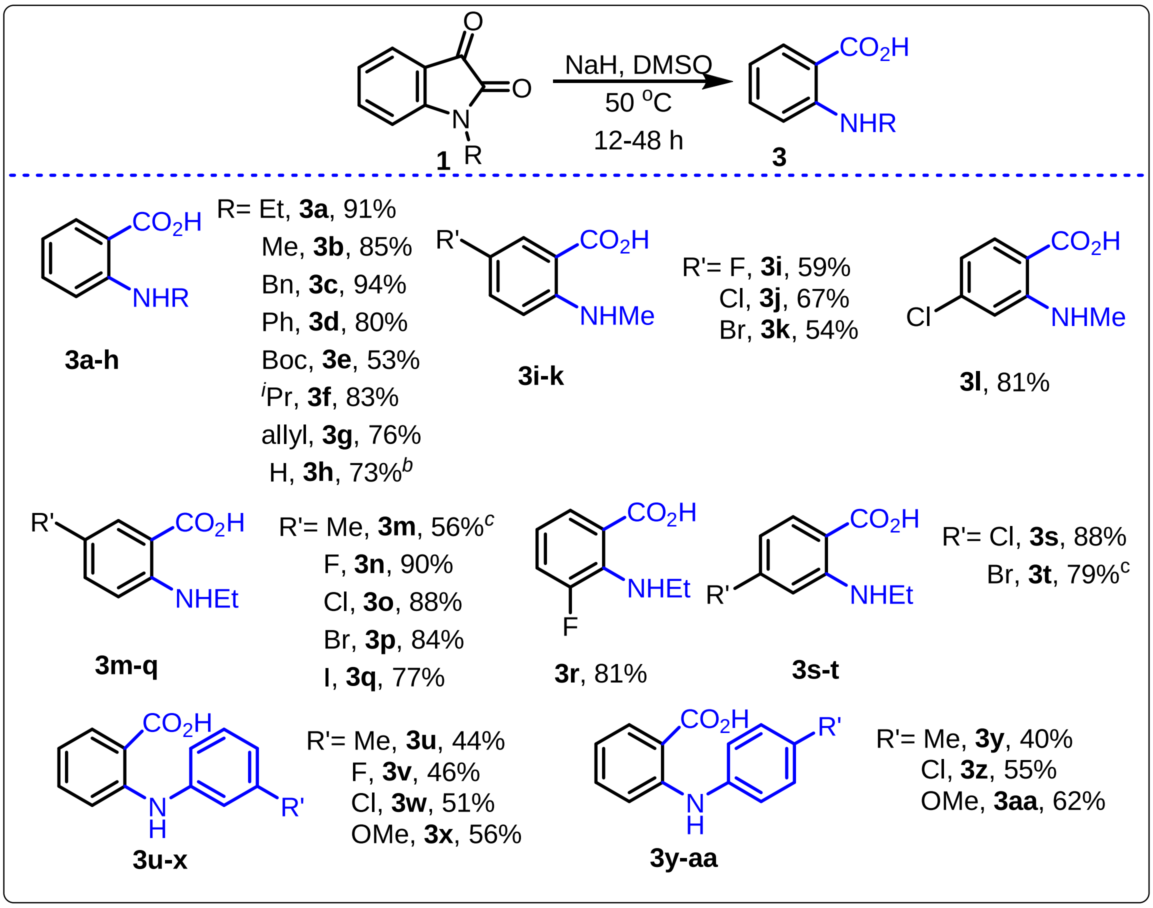
Scheme 8 Mechanistic studies for ICA

Our presumption was the intermediate olefin derivative **II** could be formed from **I**, as the concentration of dimsyl anion was greater in the reaction medium (Scheme 9). The basic condition (especially the formation of a sodium oxide) helps to facile the amide bond cleavage producing **IIIa** from **II** and followed by intramolecular Michael type addition (ring-closing) through 5-endo trig cyclization of **IIIb** generates **IV** (Scheme 9). Bulk DMSO might be responsible for the solvation of the sulfoxide group of **IV**and helps to transform it into a leaving group at this condition and elimination take place which produces **V**. After workup of the reaction mixture with 1N HCl we could reach the desired ICA derivative **VI**.



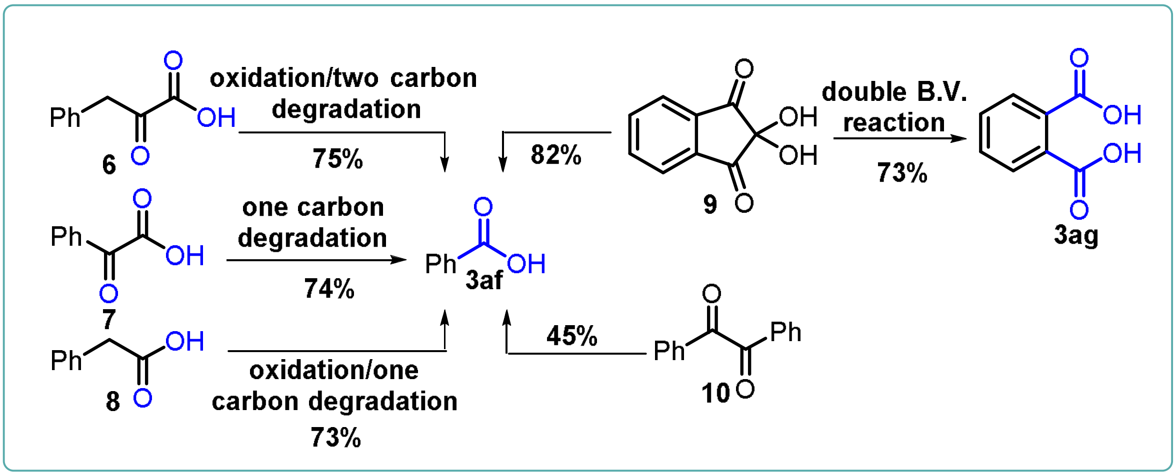
Scheme 9 Plausible mechanism for ICA

With the slight change in the reaction condition, we were able to produce a completely different product i.e. AA derivatives (an overall oxidized product) without the help of any oxidant. Hence, realized that dissolved oxygen (DO) present in the solvent reacting with sodium hydride may be generating hydroperoxide which is responsible for this conversion. After figuring out the optimal condition by taking *N*-ethyl isatin as a model substrate we explored the substrate scope (Scheme 10). Several *N*-substituted isatin derivatives containing various functional groups such as Et, Me, Bn, Ph, Boc, *i*Pr, allyl, and H, etc. were endurable in this condition and could be converted easily to the anthranilic acid derivative (**3a**-**3h**). Several *N*-Me, Et isatin derivatives containing electron-donating and withdrawing groups at the different positions of isatin performed well producing AA derivatives with good to excellent yield very smoothly (**3i**-**3t**) in this reaction condition (Scheme 10). Development of various fenamic acid derivatives (*N*-aryl anthranilic acid derivatives) (**3u**-**3aa**) was very significant, as these are building block molecules widely used as anti-inflammatory drugs (NSAIDs).[15]



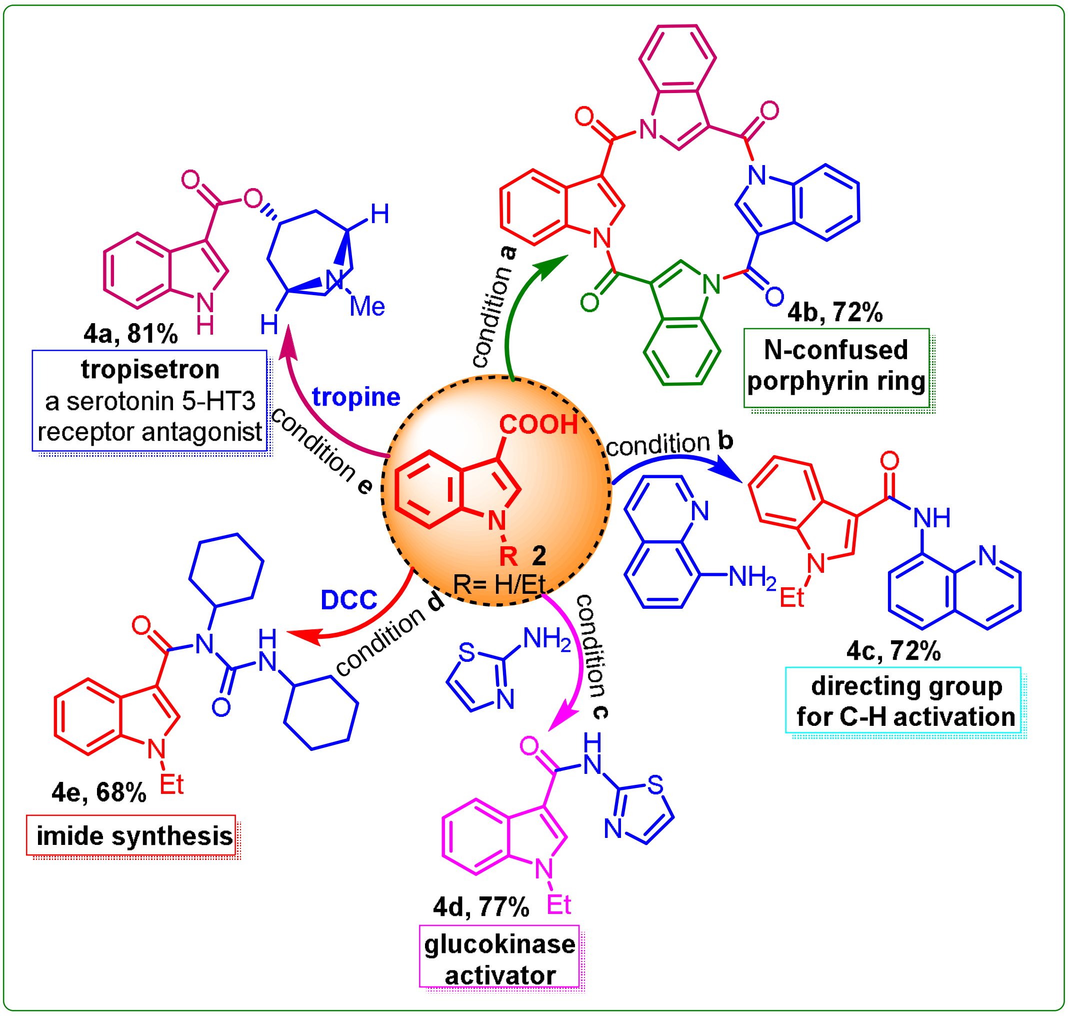
Scheme 10 Synthesis of anthranilic acid derivatives (oxidised product) from isatin derivatives

In this chapter, we described the oxidative dehomologation method employing NaH-DMF composite in the reaction medium. In this oxidative reaction condition phenyl pyruvic acid (**6**) and phenylacetic acid (**8**) get oxidized first then dehomologation happened via Bieyer Villiger (B.V.) type reaction (Scheme 11). Notably, benzoyl formic acid (**7**) and benzil (**10**) were transformed to **3af** very quickly (Scheme 11).



Scheme 11 Scope of benzoic acid and phthalic acid

Phthalic acid (**3ag**) was smoothly obtained from ninhydrin (**9**) via a selective double B.V. reaction. Extrusion of CO_2 at high-temperature compound **9** produces benzoic acid exclusively via the intermediate **3ag** (Scheme 11). We described oxidative dehomologation (up to two carbon degradation) of various acids in this chapter without using any oxidizing agents or transition metal catalysts. Indeed, it is highly demanding as very limited reports are available to date.[17]



Scheme 12 Applications of ICA derivatives

Indole-3-carboxylic acid (ICA) derivatives are good building blocks that have been used to synthesize several biologically active compounds. Synthesis of tropisetron (**4a**) described here with 81% yield, an excellent 5-HT3 receptor antagonist, used mainly as an antiemetic to treat nausea and vomiting following chemotherapy and as an analgesic in cases of fibromyalgia (Scheme 12).[18] Furthermore, we showed an amide formation reaction of **2a** in EDC.HCl condition with moderate (**4c**, 72% yield) to good yield (**4d**, 77% yield). We are familiar that **4c** has already been utilized as a good directing group for C–H bond activation reaction[19] whereas **4d** is a very good glucokinase activator, useful for increasing insulin secretion in the treatment of type II diabetes.[20] Imide (**4e**, 68%) was also produced from **2a** with another partner (DCU) which was in-situ formed from DCC and has biological importance.[21] *N*-confused porphyrin ring (**4b**, 72%) has a good synthetic utility and has been synthesized from ICA in one step in EDC.HCl condiition.[22]

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Chapter 1: **Introduction Part-I**

A Brief Overview of Some Biologically Active Pharmacophores and Hydride Shift Reaction

1.1 Introduction of Hydride Shift Reaction

The functionalization of relatively unreactive inert C–H bonds in a transition metal-free way is an attractive research topic in synthetic organic chemistry, particularly from the viewpoint of efficiency and sustainability in organic synthesis. Direct modifications of the omnipresent C–H bonds of simple or complex organic molecules without pre-activation to meet the reactions intrinsically environmentally sustainable and atom efficient. Goldberg and Goldman have entitled C–H bond "the unfunctional group," highlighting its privileged status both as a tool for synthesis and as a target for methodology.[1] Many notable examples of inert C–H bond functionalization are there in organic chemistry which include oxidation, photoredox catalysis, site-selective transition metal catalyzed/free C–H oxidation, C–H functionalization based on carbene insertion, and many name reactions which involve radical hydrogen atom abstraction.[1]

1.1.1 Hydride Shift Reaction

Hydride shift reactions are a common phenomenon in synthetic organic chemistry. In a classical hydride shift reaction, there should be occurred a transfer of hydrogen atoms with their pair of electrons from one carbon atom to another. To perform this classical reaction a hydride donor and acceptor are needed. In such reactions, the hydride donor and acceptor can be present on the same or different molecules. If the hydride acceptor and donor are present in the same molecule which is connected by a linker intra molecular hydride shift occurs and leads to cyclized product (Figure 1.1.1.1). Inert C–H bond functionalization by 'intramolecular hydride shift' is a recent concept in organic chemistry that enabled a significant way to produce diverse molecules especially complex novel bioactive molecules that's opened a new door of medicinal chemistry. During the hydride transfer reaction, simultaneous oxidation of the hydride donor and reduction of hydride acceptor will occur which results in the formation of zwitterionic intermediate **B** and finally leads to C–H bond functionalization to get cyclized product **C**.[1] From the mechanistic point of view, intra molecular hydride shift is a key step for 'redox-neutral' C–H functionalization reactions, as there is no change in the oxidation state of substrate or product (Figure 1.1.1.1).[1]

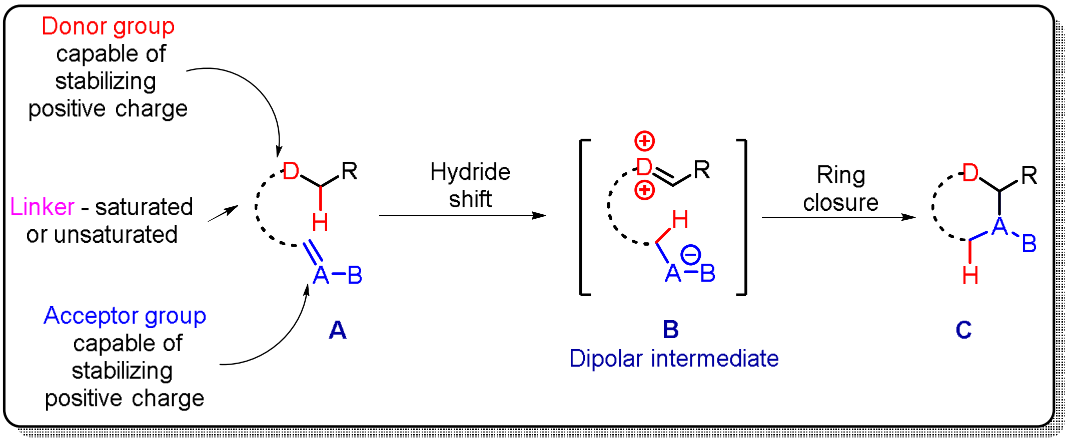


Figure 1.1.1.1 Concept of the intramolecular hydride shift reaction

The rich history of hydride shift reaction started in 1853 with Cannizzaro's report on the base-mediated disproportionation reaction of benzaldehyde into benzyl alcohol (reduced product) and benzoic acid (oxidized product). In 1924, Meerwein-Ponndorf-Verley reduction was reported and after several years in 1932, Duff reported the synthesis of various aromatic aldehydes through the intramolecular hydride shift/ hydrolysis of arene-hexamethylenetetramine adducts [2,3] (Figure 1.1.1.2). Intermolecular hydride transfer is more difficult than intra-process because, in the case of the former, the transition state should be stabilized otherwise it will not occur.

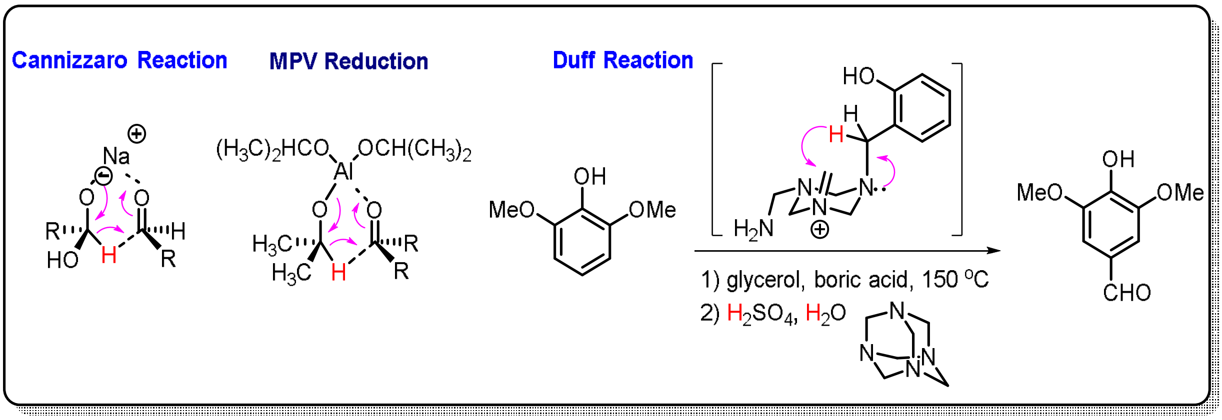


Figure 1.1.1.2 Classical example of the hydride shift reaction

1.1.2 Examples of Hydride Donor and Acceptor

Hydride is nothing but an anion of hydrogen, which is usually transferred from one donor to another acceptor partner. Hydride donor atoms can be simple benzylic CH_2, or N and O; hydride acceptors can be olefin, activated olefin, allenes, ketone, acyl halides, alkynes, or carbocations (Figure 1.1.2). [1]

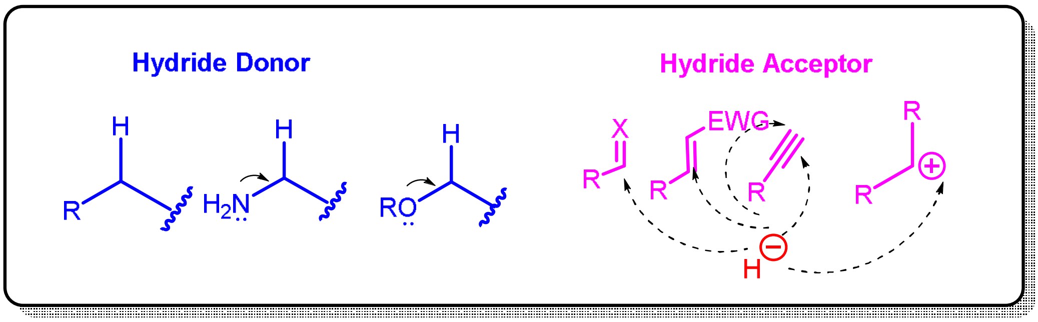


Figure 1.1.2 Examples of hydride donors and acceptors

1.1.3 Scope of the Study

Reactions involving intramolecular hydride transfer have been known for over a century, but they have recently resurfaced in interest. The resurgence of hydride shift reactions both in the intramolecular and intermolecular processes has shown their potency as an important synthetic tool in the creation of complex molecules, which comprise two or more individually biofunctional moieties. The stitching together may lead to multiple targeting in certain diseased states. The redox-neutral behavior of these complexity-enhancing synthetic transformations enabled them ideal for sustainable method development. Also, 1,5-hydride shift/cyclization reactions are a step forward toward green chemistry as they occur smoothly without the use of any transition metal. As the world is moving towards green chemistry and at the same time a focus resides on the economical synthesis of bioactive molecules, 'intramolecular redox neutral C–H bond functionalization' reactions paves the way for same and are very much valuable in medicinal chemistry for synthesizing potential hybrid bioactive molecules.

1.2 Importance of Hydride Transfer Reaction

The direct and selective inert $C(sp^3)$–H bond functionalization has become an attracted field in fundamental organic chemistry as an influence of its atom and step economy. Recently, the $C(sp^3)$−H bond functionalization through hydride shift followed by cyclization process, that is namely, the "internal redox process," has attracted significantly for its unique features. The key factor of this transformation is that [1,5]-hydride shift event of the $C(sp^3)$−H bond α to the "N" or another hetero atom of the heterocycle.[4] Because of valuable synthetic utility, several groups have developed hydride shift strategy and constructed useful skeletons such as benzopyrans, tetralins, indanes, spirooxindoles, tetrahydroquinolines, and tetrahydroisoquinolines.[5] Tetrahydro(iso)quinoline skeleton is an important structural moiety commonly encountered in naturally occurring alkaloids of vegetal origin, which have a vast range of biological properties, including antimicrobial, antiplasmodial, anticancer, multiple cardiovascular and CNS activities.[6] Synthesis of THIQ derivative is a point of attraction in the chemical, medicinal (**I** is an orphan drug and **II** uses as an antiprotozoal drug) and pharmaceutical field, as THIQ pharmacophore shows neuroprotective, acetylcholinesterase and amyloid–β (**IV** exhibits) inhibitory effects and evaluated as CXCR-4 antagonist for treatment in HIV also (Figure 1.2.1).[7] Nowadays benzofuran-3-one scaffold is a center of attraction for its broad spectrum biological activity and its huge space of applicability as a synthetic tool in the area of drug design and synthesis of various bioactive molecules.[8] If one could consolidate these two types of pharmacophore through C(sp^3)−H bond activation as the sequential [1,5]-hydride shift process/ *endo-trig* cyclization is a promising approach to construct complex poly heterocycles which were not submissive.

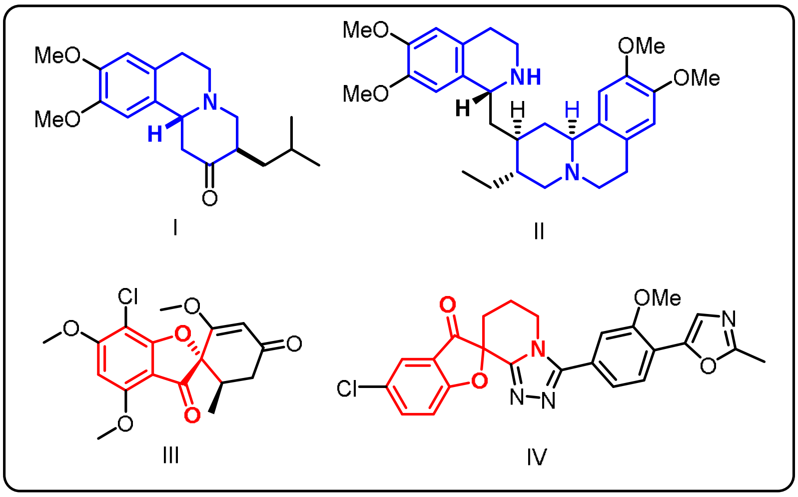


Figure 1.2.1 Representative examples of bioactive compound

Griseofulvin analogs **III** (spirocyclic benzofuran -3-one derivative) inhibit tumor growth in the breast cancer cell and suppressed hepatitis C virus replication. Various spirocyclic benzofuran-3-one derivatives show inhibition of human peptidyl-prolyl cis/trans isomerizes NIMA-interacting 1 encoded by Pin1 gene which is nourishing for certain immune disorders like atherosclerosis, rheumatoid arthritis, etc. Constructing an *N*-containing 6-member heterocycle (**I**, **II,** and **IV**) scaffold with spiro constituent HT methodology has significant importance.[8] In situ generation of amino-substituted benzylidenes through Knoevenagel condensation reaction from 2-amino benzaldehyde derivatives reacted with another partner such as 2-coumaranone, 4-hydroxycoumarin, benzofuran-3-one, and 3-isochromanone are the precursors of spiroheterocycles. These activated methylene scaffolds have diverse potent activity in the biological system and it was not introduced for hydride shift reaction to construct novel spiroheterocycles. Both benzofuran-3-one[8] and tetrahydroisoquinoline[7] are powerful building block that constructs a variety of pharmacological molecule distinctly. No protocols are available to consolidate these two alluring bioactive scaffolds to date. Due to the potent hydride shift ability of the *α*-H with respect to *N*-atom to activated olefin itself, our hypothesis was to demonstrate a one-pot Lewis acid catalyst-free reaction because most of the internal redox reactions are disclosed so far involve a [1, 5]-hydride shift in one step from 2-amino benzaldehyde is rare (Figure 1.2.2).

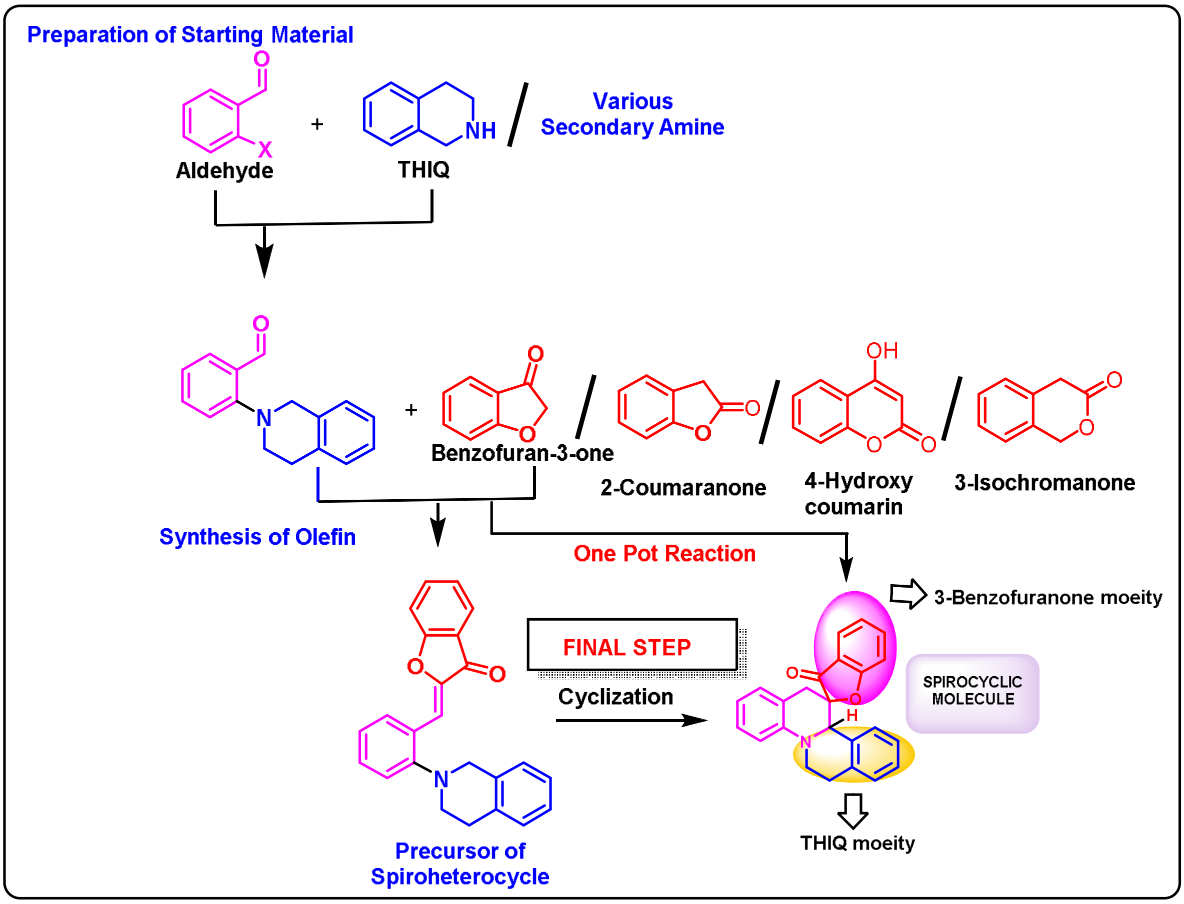


Figure 1.2.2 Objective of the project

1.3 A Brief Overview of Several Bioactive Scaffolds Introduced in Hydride Shift Reaction

The development of a new methodology for the direct functionalization of unreactive C–H bonds has grown into a major area of research interest nowadays; it represents one of the most ideal redox-neutral strategies for the synthesis of structurally diverse (spiro)heterocycles which includes potential bioactive organic molecules and natural product analogs. Functionalization of the C(sp^3)–H bond through the hydride shift/cyclization process, a type of internal redox process has drawn much attention on account of its novel strategic approaches for the synthesis in the absence of transition metal.[1]

1.3.1 Benzofuran-3-one

1.3.1.1 Benzofuran-3-one and Its Importance

The nucleus of benzofuran-3-one derivatives privileged with benzofuran core is one of the most smeared heterocyclic scaffolds by synthetic and medicinal chemists. Nowadays the benzofuran-3-one scaffold (Figure 1.3.1.1) is a center of attraction for its broad spectrum biological activity and its huge space of applicability as a synthetic tool in the area of drug design and synthesis of various bioactive molecules.

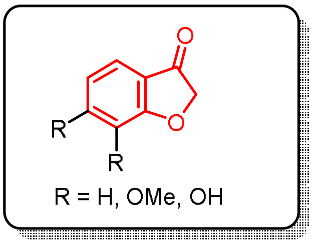


Figure 1.3.1.1 Benzofuran-3-one

The benzofuran-3-one scaffold is extensively found in various natural and synthetic compounds, such as griseofulvin, an antifungal agent. Important benzofuran-3-one containing natural and synthetic bioactive compounds are discussed below.[8]

1.3.1.1.1 Naturally Occurring Benzofuran-3-one Derivatives

Various Benzofuran-3-one derivatives are widely distributed in nature and exhibit a wide range of biological activity. The aurones and the 2-isopropylidene-benzofuran-3-one derivatives are widely studied natural products and exhibit interesting biological activities, including anti-protozoal[9a] and anti-cancer[9b]. Many naturally occurring compounds containing benzofuran-3-one motif are shown below (Figure 1.3.1.1.1.1).

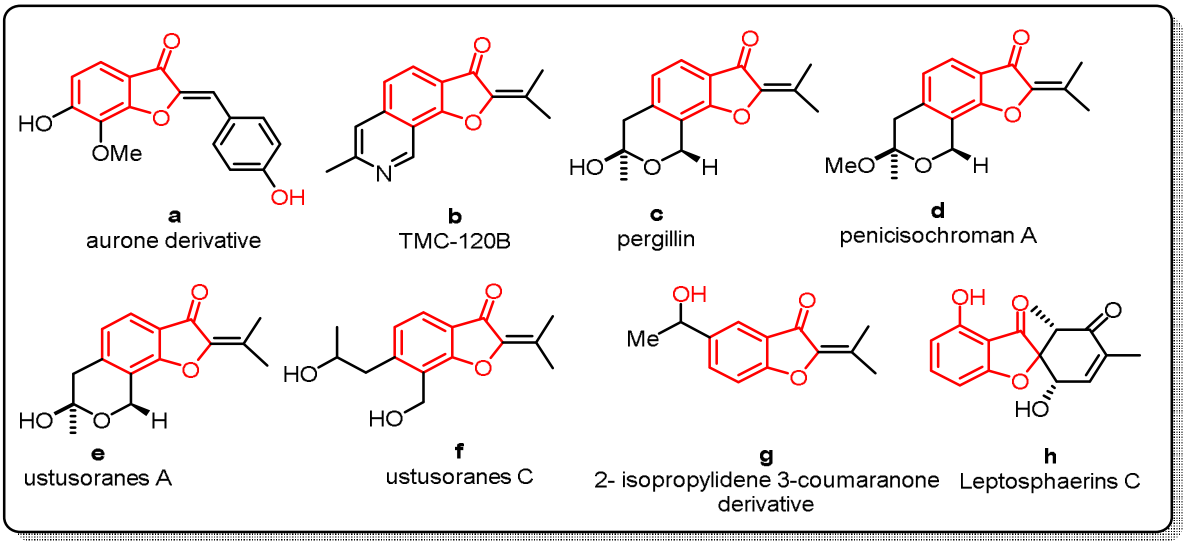


Figure 1.3.1.1.1.1 Benzofuran-3-one containing natural products

The 2-Isopropylidine-benzofuran-3-one derivative is the only known heterocycle produced by the species of *Verbesina*[9c].

Many naturally-derived benzofuran-3-one derivatives (Figure 1.3.1.1.1.1, **a-g**) include aurone derivatives, pergilin, penicisochroman A, ustusoranes A, ustusoranes C, TMC-120B, and 2-isopropylidene.[9d] Leptosphaerins C (Figure 1.3.1.1.1.1, entry **h**) is a polyketide derivative extracted from the solid cultures of the ascomycete fungus *Leptosphaeria sp.*[9e]. Among these, the biological activity of aurones is widely studied.

Phainanoids are those classes of compounds, which are isolated from a Chinese herb known as *Phyllanthus hainanensis* in which the species of this plant is used as folk medicine to treat various infections, diabetes, and hepatitis **B** (Figure 1.3.1.1.1.2).

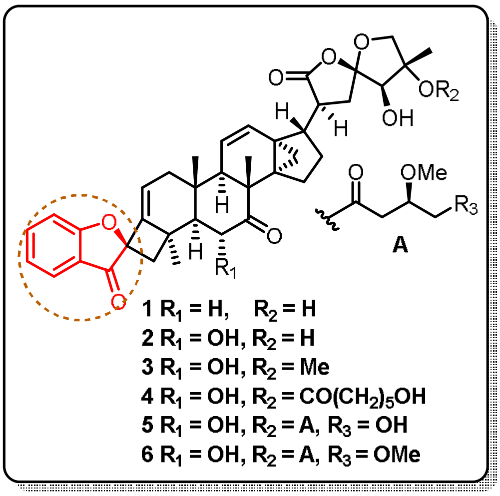


Figure 1.3.1.1.1.2 Structure of phainanoid derivatives

Phainanoids, which are isolated from *Phyllanthus hainanensis* by Yue's group have immunosuppressive activity at the nanomolar level which is about 221 times more potent than standard drug cyclosporine A in inhibiting B lymphocytes.[9f] Recently, in May 2017, Dong and group successfully attempted to synthesize diastereoselectively the western part of phainanoid, which gave an insight into the total synthesis of phainanoid series.[9g]

Aurones, which are structural isomers of flavones, are minor tricyclic flavanoids that build-up a benzofuranone ring connected with a carbon-carbon double bond to a phenyl moiety (Figure 1.3.1.1.1.3).

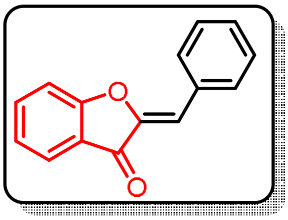


Figure 1.3.1.1.1.3 Structure of aurones

Among the large family of flavones, aurones hold less space in nature. However, the reactivity of aurones in vegetables remains critical for many species and their therapeutic potential for humans is also pregnant. Even though aurones are distributed in many families and genera, including various plants broadly used in folk medicine such as *Ceanothusamericanus*, *Glyzyrrhizaglabra*, or *Vacciniumoxycoccus*, a clear correlation cannot be established between these plants, especially their therapeutic use. The probable reason for its availability is remarkably low in plants compared to other flavanoids.[9h] However, the potential bioactivity of aurones is well explored in a semisynthetic way which is explained in the following section.

1.3.1.1.2 Bioactive Benzofuran-3-one Scaffolds

Benzofuran-3-one-containing compounds are an important class of bioactive molecules showing a wide range of biological activity (Figure 1.3.1.1.2.1). These molecules hold a special role due to the profound importance of such compounds by virtue of their role in the biological domain.

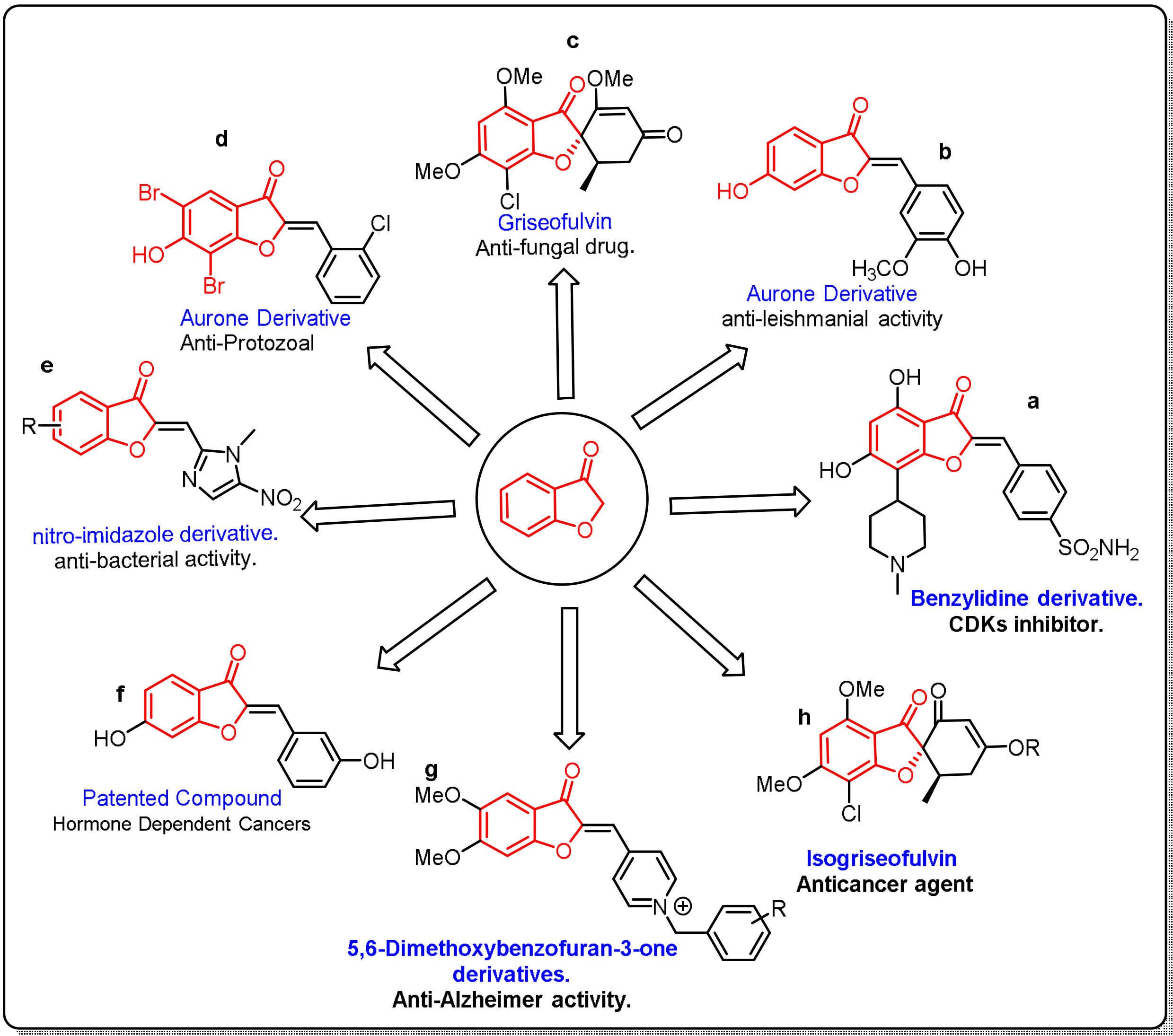


Figure 1.3.1.1.2.1 Benzofuran-3-one containing compounds showing diverse activities

As CDK Inhibitor: Cyclin-Dependent Protein Kinase (Cdks) is an enzyme that connects the negatively charged phosphate groups to the other molecules in a process called phosphorylation. Cdks signal the cell that is ready to pass into the next stage of the cell cycle through phosphorylation. Among various CDKs, CDK1, CDK2, and CDK4 are the most established oncology targets.

The inhibition of cyclin-dependent kinases (CDKs) has now emerged as a significant research topic as an anticancer agent. Compounds enhanced to inhibit the activity of these crucial enzymes are the cell division regulators cycle, expected to have anti-proliferative properties. Among the small molecule drugs, 2-Benzylidene-benzofuran-3-one derivatives (Figure 1.3.1.1.2.2) showed excellent inhibitory activity against CDKs, especially against CDK1 and CDK2.[9i]

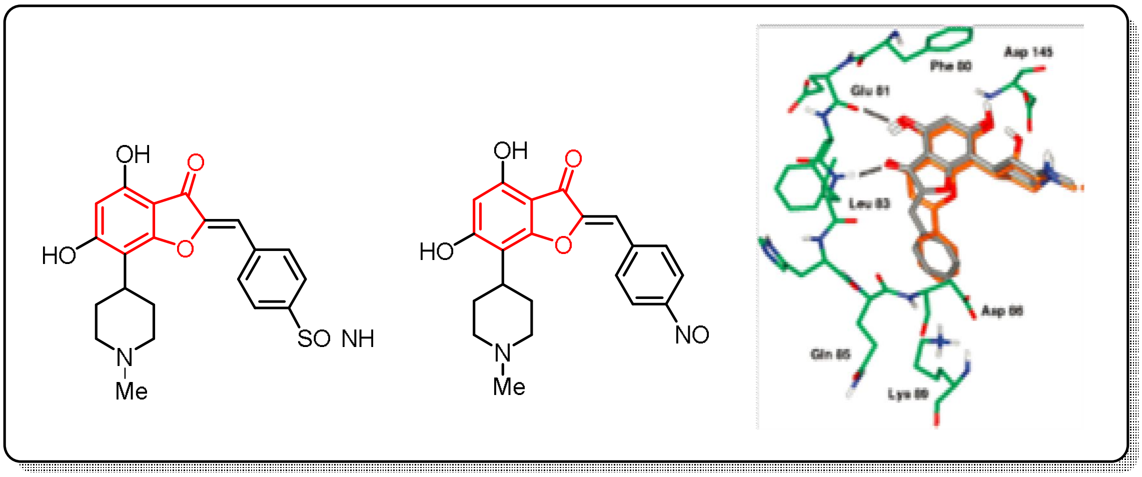


Figure 1.3.1.1.2.2 Benzylidene-benzofuran-3-one derivatives as CDKs inhibitor

For Alzheimer's disease: Alzheimer's disease (AD) is a progressive neurodegenerative brain disorder dependent on age. The etiology of the disease is unknown, although many diverse factors such as **β-amyloid (Aβ) aggregation, hippocampal acetylcholine (Ach) decrease**, and **τ-protein deposits** are important things for the initiation and progression of the disease. As we know, hydrolysis of acetylcholine **Acetylcholinesterase (AChE)** has an important role in the synaptic cleft. Therefore, employing **AChE inhibitors** could be a wonderful strategy to raise the level of acetylcholine in the affected cholinergic neurons.

Furthermore, it has been concluded that the inhibition of AChE may increment **Butyrylcholinesterase (BuChE)** reactivity in a new strategy in the hippocampus that occurred hydrolysis of ACh. The AChE/BuChE activity ratio should be proper in the hippocampus as seen in a normal healthy brain, which could improve the symptoms of AD. So, there is no doubt that dual AChE/BuChE inhibitors have the potential to be more potent agents to treat AD. Some of the reported benzofuran-3-one derivatives having dual AChE/BuChE inhibitory activity are shown below (Figure 1.3.1.1.2.3).[9j]

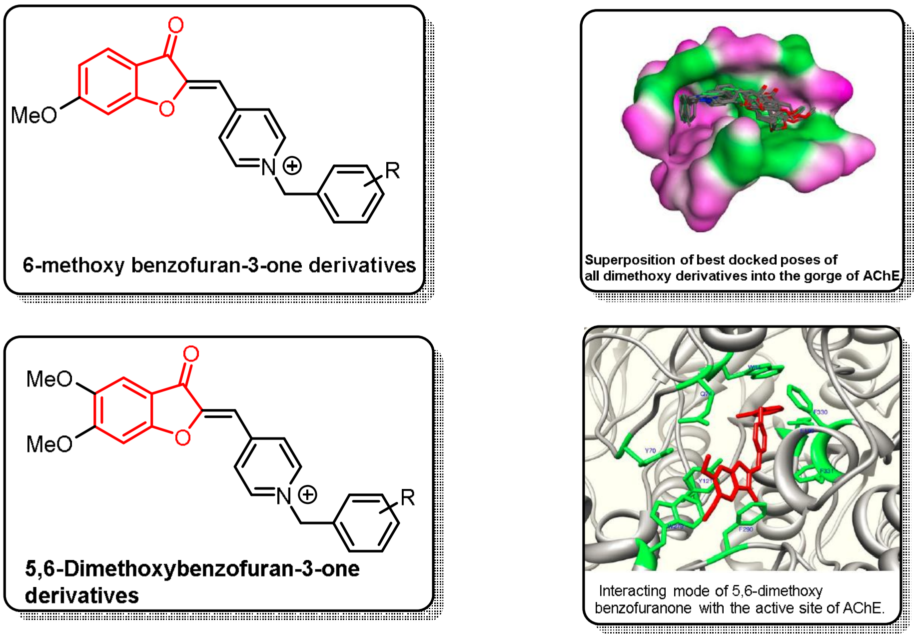


Figure 1.3.1.1.2.3 Benzofuran-3-one derivatives showing anti-Alzheimer activity and its interacting mode with the active site

Griseofulvin as an antifungal agent: Griseofulvin (Figure 1.3.1.1.2.4) is a conventional oral antifungal drug used to treat different types of dermatophytoses (ringworm infection). It can also be used for various skin and nail fungal infections when other antifungal creams are not working. It is one of the WHO's lists of essential medicine, the most effective and safer medicines needed in a health care system.[9k]

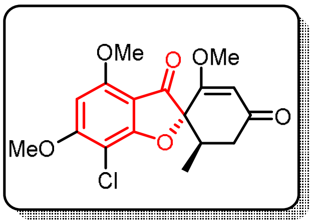


Figure 1.3.1.1.2.4 Structure of Griseofulvin

Griseofulvin for the treatment of breast cancer: Griseofulvin can potentially inhibit tumor growth in breast cancer cells. Mechanistically griseofulvin binds at the paclitaxel site along the side of the microtubules, and arrests the cell MCF-7 at mitosis and that agitates microtubule dynamic instability in the cell (Figure 1.3.1.1.2.5).

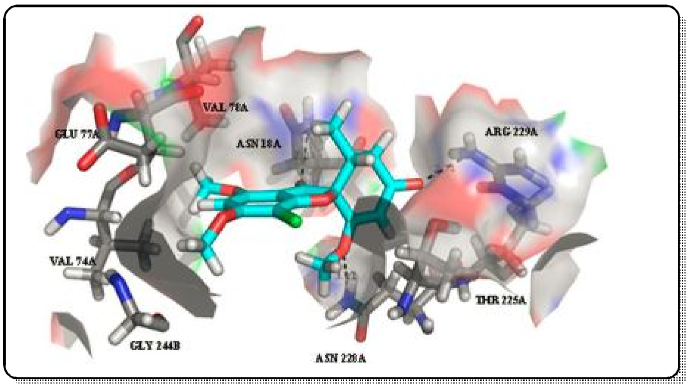


Figure 1.3.1.1.2.5 Mode of the Interaction of Griseofulvin with tubulin

Also, griseofulvin shows synergistic antiproliferative activity along with vinblastine in MCF-7 cell lines and these two drug combinations can be successfully used in the treatment of breast cancer.[9l]

Griseofulvin for HCV infection: Griseofulvin also showed the 'suppression of hepatitis C virus replication' in vitro. It was found that griseofulvin exerts its pharmacological action by blocking the cell cycle individually in the HCV subgenomic replicon cells at the G2/M phase.[9m] This invitro study suggests a new approach for the development of novel therapeutics for HCV infection.

Griseofulvin as an inhibitor of centrosomal clustering in cancer cells: Many Griseofulvin analogs (Figure 1.3.1.1.2.6) showed inhibitory activity against centrosomal clustering in cancer cells. Many analogs are more active than the parent compound, i.e. griseofulvin. As this kind of binding is a particular phenotype that is unique in cancer cells, there is more possibility for these molecules to bind specifically with cancer cells.[9n]

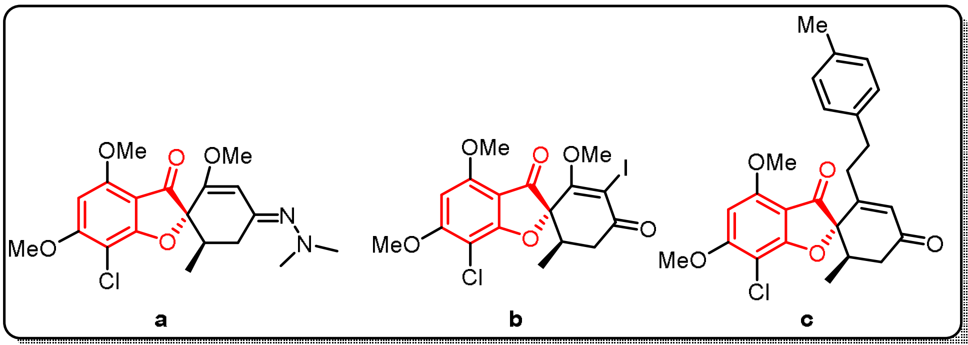


Figure 1.3.1.1.2.6 Griseofulvin analogs showing anticancer activity

The importance of benzofuran-3-one is elaborately discussed in Chapter 3.

1.3.2 Benzofuran-2-one/ 2-Coumaranone

The 2-Coumaranone nucleus consists of a benzofuran core and is one of the most significant heterocyclic structural units present in several natural products and synthetic drug molecules, now a topic of research by synthetic and medicinal chemists. Nowadays the 2-Coumaranone scaffold (Figure 1.3.2) is a center of attraction for its broad spectrum biological activity and its huge space of applicability as a synthetic tool in the area of drug design and synthesis of various bioactive molecules.

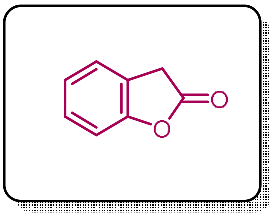


Figure 1.3.2 2-Coumaranone

2-Coumaranone scaffold is widely found in natural and synthetic compounds.[10] Important 2-Coumaranone containing natural and synthetic bioactive compounds are discussed below.

1.3.2.1 Importance of 2-Coumranone

1.3.2.1.1 Analgesic/Antidepressants

Several (3-aryl-2,3-dihydrobenzofuran-3-yl)alkanamines have been synthesized from 2-coumaranone, a significantly designed molecule used as a potential antidepressant agent with analgesic properties, were pharmacologically evaluated[10h] (Figure 1.3.2.1.1).

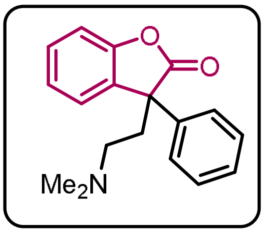


Figure 1.3.2.1.1 (3-aryl-2,3-dihydrobenzofuran-3-yl)Alkanamine

1.3.2.1.2 CA4 Analogues as Human Tumor Cell Inhibitor

Utilizing Domino Heck–Suzuki–Miyaura coupling method a series of combretastatin A4 (CA4) analogues with a fused lactam or lactone ring to the trimethoxyphenyl or the B-phenyl moiety has been synthesized in an efficient and stereoselective manner (Figure 1.3.2.1.2). The vascular-disrupting potential of these CA4 analogs that were conformationally restricted was assessed by various in vitro assays: tubulin polymerization inhibition process, a new developing method of endothelial cell morphology, and disruption of endothelial cell cords. These compounds have shown good growth inhibitory effects against murine and human tumor cells. An oxindole ring present in B-ring-constrained derivatives (in contrast to compounds specifically with a benzofuranone ring), in another way a six-membered lactone core fused analogs bearing to the trimethoxyphenyl ring, are conferred with a significant biological activity.[10i]

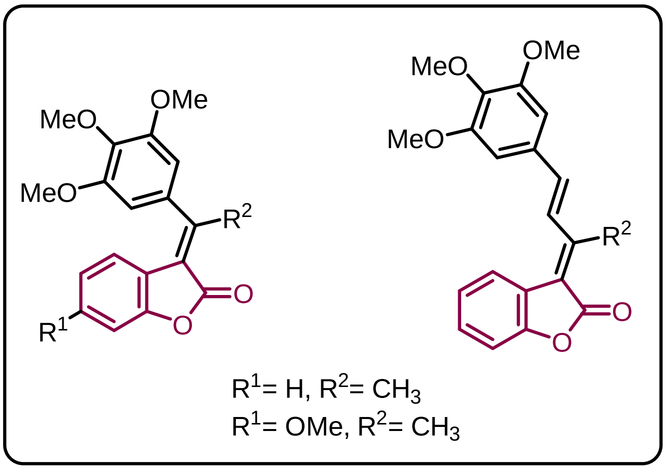


Figure 1.3.2.1.2 CA4 analogues

The importance of benzofuran-3-one is elaborately discussed in Chapter 2.

1.3.3 3-Isochromanone

The 3-Isochromanone scaffold is widely found in natural and synthetic compounds.[11] Nowadays the 3-Isochromanone scaffold (Figure 1.3.3) is a center of attraction for its broad spectrum biological activity and its huge space of applicability as a synthetic tool in the area of drug design and synthesis of various bioactive molecules. Important 3-Isochromanone containing natural and synthetic bioactive compounds are discussed below.

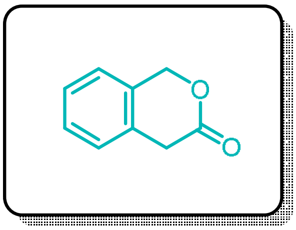


Figure 1.3.3 3-Isochromanone

1.3.3.1 Several 3-Isochromanone Derivatives and Their Activity

Isochroman-3-one is an important pharmacophore present in several biologically active molecules (Figure 1.3.3.1). This scaffold is very much possessive for lifespan as well as plant growth regulators. Hence synthesis of these isochroman-3-one derivatives is very much important in recent days. Without any substituent on the lactone ring of isochroman-3-one no activity was notable on hypocotyl and radicule elongations of lettuce seedlings at 10 ppm. Several substituted compounds such as 1-phenyl, benzyl, and stryl containing 3-isochromanone promoted the radicule elongation at the time of inhibition of hypocotyl elongation of lettuce seedlings at 10 ppm. Probably the inhibition is attributed to auxin transport inhibition and the elongation might be ascribed to antiauxin activeness.[11a]

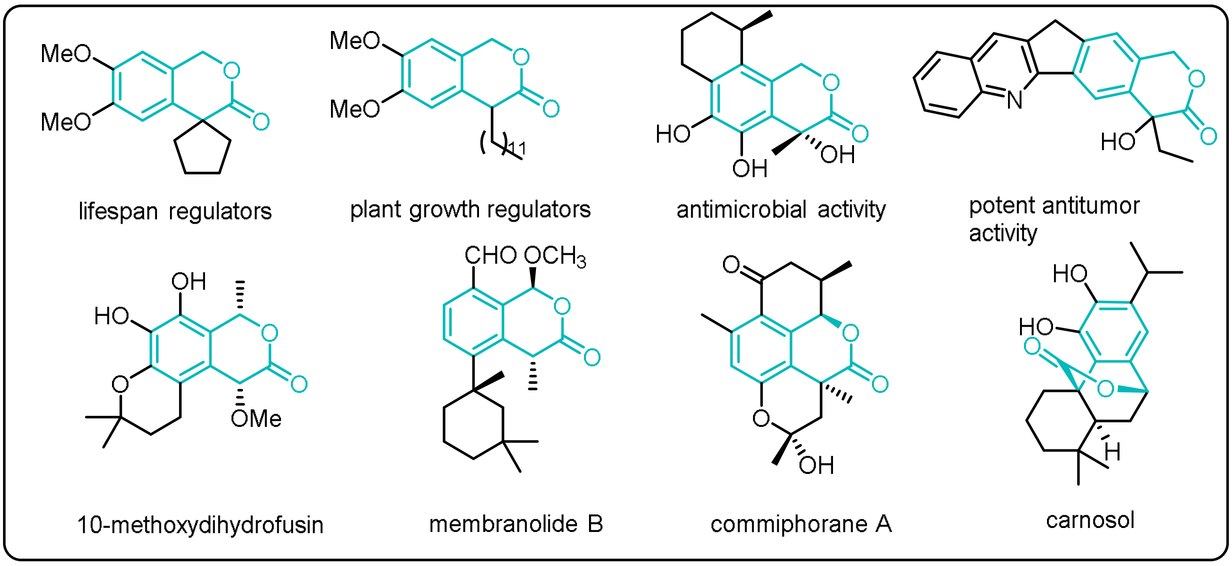


Figure 1.3.3.1 Several 3-Isochromanone derivatives

1.3.3.2 Benzo and Isobenzo-20-S-CPT as Novel Topoisomerase I (Top1) Inhibitors

CPT has the ability to bind in the DNA helix to the place of the +1 purine and could be bonded with the +1 purine externally through pi-stacking interaction from the duplex DNA structure (Figure 1.3.3.2). Furthermore, structural research studies are ongoing for the generation and investigation of novel topoisomerase I (top1) inhibitors.[11b]

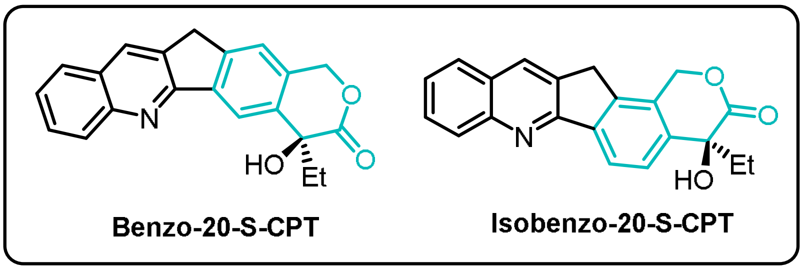


Figure 1.3.3.2 Benzo and Isobenzo-20-S-CPT

1.3.3.3 Antimicrobial Activities of Radulifolin A (I) and *Epi*-Radulifolin A (II)

Psacalium radulifolium, a member of the matarique complex of medicinal plants has been studied (especially its roots) for the investigation of the chemical constituents including several members of the Asteraceae, which resulted in the isolation of radulifolin A (**I**) and *epi*-radulifolin A (**II**) and other new modified eremophilanes (Figure 1.3.3.3). These two isolated compounds had been examined for several antimicrobial activities against *Pseudomonas aeruginosa*, *Proteus mirabilis, Staphylococcus aureus, Escherichia coli*, and *Candida albicans.* The adequate mixture of radulifolin A and *epi*-radulifolin A displayed selective but moderate activities against *S. Aureus* (Figure 1.3.3.3).[11b]

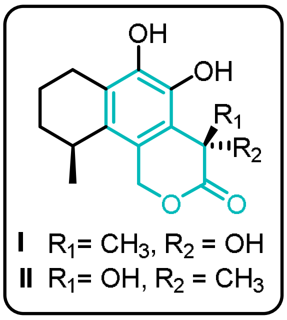


Figure 1.3.3.3 Radulifolin A (**I**) and *epi*-radulifolin A (**II**)

1.3.3.4 10-Methoxydihydrofuscin as Anti HIV-1 Target Activity

10-methoxydihydrofuscin (**1**) has been extracted from the fungus *Oidiodendron griseum* that grows up in humid soil. These types of compounds were characterized and tested for several biological studies. 10-methoxydihydrofuscin (**1** and **2**) has the ability to bind with human CCR5 found to compete effectively with macrophage inflammatory protein (MIP)-1R, which is an important anti-HIV-1 target that could interact with HIV entry into cells (Figure 1.3.3.4).[11c]

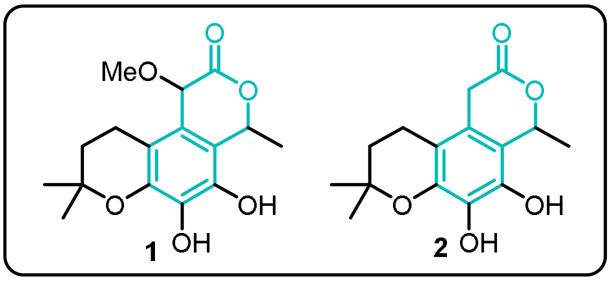


Figure 1.3.3.4 10-methoxydihydrofuscin (**1**) and it's derivative

The importance of benzofuran-3-one is elaborately discussed in Chapter 3.

1.3.4 Succinimide

1.3.4.1 Succinimide and Its Scope

Succinimide is a compound containing an imide group. In striking contrast, succinimide is a constituent of natural products such as salfredin C-1 and palasimide,[12a-e] as well as potent drugs such as phensuximide, lurasidone, and thalidomide (Figure 1.3.4.1). Several other succinimides, including ethosuximide, and methsuximide, are used as anticonvulsant drugs.[12]

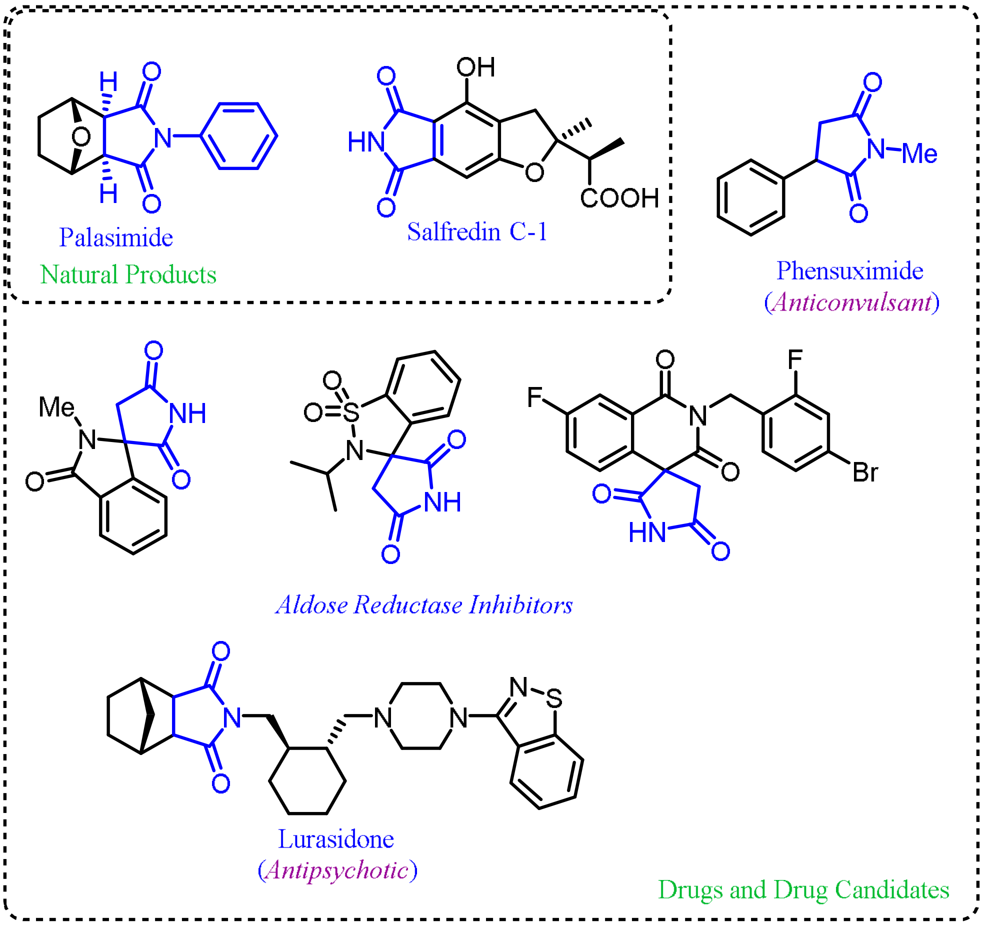


Figure 1.3.4.1 Succinimide skeletal natural products, drugs, and drug candidates.

Many spiro-succinimides have been shown to inhibit aldose reductase when taken orally.[12f] It is interesting to note that maleimides are optimum activated alkenes that are well-suited for introducing succinimide moiety by cycloaddition, conjugate addition, or cross-coupling reactions. Various [4.5] Succinimide based piperidine has represented a unique class in chemical biologies, such as being useful in treating senile dementia, Alzheimer's disease, Huntington's chorea, acetyl-coA carboxylase inhibitor, muscarinic agonists, tardive dyskinesia, hyperk-inesia and mania. [12g-h]

1.3.5 Tetrahydroisoquinolines

1.3.5.1 Tetrahydroisoquinolines and Their Scope

Rapid progress in synthetic organic chemistry has been associated with not only the discovery of a new methodology but the construction of new compounds with desired properties also which means chemical biology, which is the most significant topic in pharmaceutical industries. The isoquinoline scaffold is a heterocyclic ring that is frequently present among natural, synthetic as well as semi-synthetic bioactive molecules. Tetrahydroisoquinoline (Figure 1.3.5.1) has been derived from the hydrogenation reaction of isoquinolines. THIQ is a privileged scaffold as it is found as a constituent in versatile natural products and pharmaceutical compounds, that’s why synthesis of its derivative has now converted to a new research area for the last two decades.[13]

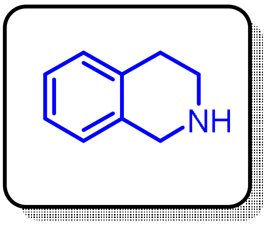


Figure 1.3.5.1 Tetrahydroisoquinoline

Tetrahydroisoquinoline derivatives have a wide range of bioactivities including anti-tussive properties, anti-HIV, anti-cancer, anti-parkinson, anti-tumour, anti-bacterial, anti-viral, anti-inflammatory, etc. In the era of structural activity relationship and structure-based drug design, THIQ has gained increasing attention due to its synthetic utility owing to the potential biological activities and their increasing biological, biochemical, pharmacological, and organic synthetic interest.[13]

1.3.5.1.1 Naturally Occurring Tetrahydroisoquinolines

Tetrahydroisoquinoline alkaloids and natural products are the beauty of biologically active compounds with a wide range of therapeutic activities. Tubocurarin is an isoquinoline alkaloid; historically it was used as an arrow poison as it was showing skeletal muscle relaxant properties. Naturally occurring THIQ includes cherylline and latifine; which are the 4-aryl THIQ alkaloids usually isolated from *Amarylllidaceae* plant. Emetine is an alkaloid, extracted from *Cephaelis ipecacuanha* and it is used as an emetic and antiprotozoal drug [48, 49]. Many THIQ-containing bioactive compounds have been isolated from different parts of *Erythrina variegate* including erysodine, erythraline, erysotrine, erythritol, and isococolinine (Figure 1.3.5.1.1.1).[13f] Various extracts from different parts of *Erythrina variegate* show a wide variety of activities. Methanolic extract from the leaf shows analgesic properties through the prostaglandin pathway.[13f]

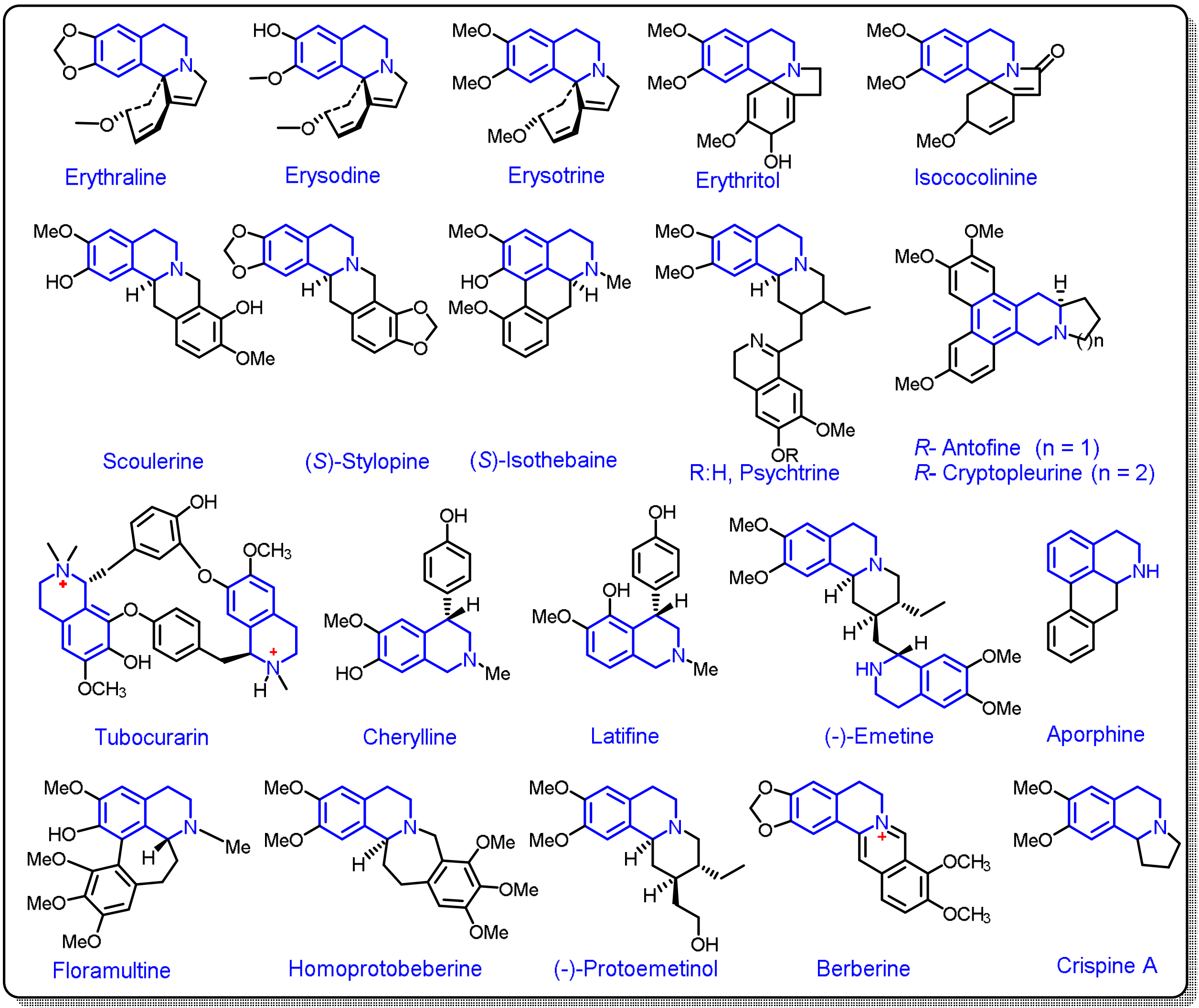


Figure 1.3.5.1.1.1 THIQ alkaloids and natural products

Also, the ethanolic extract of the leaf shows antibacterial and antifungal activity with unknown mechanisms.[13g] Leaf of this plant is widely used for the treatment of fever in folklore medicine but not scientifically documented. The antimicrobial and antipyretic activity of this plant, especially the leaf needs to be attended.

Tetrahydroisoquinoline scaffold is an important pharmacophore commonly present in naturally occurring alkaloids of vegetal origin like arizonine, gigantine and salsolinol (Figure 1.3.5.1.1.2) with interesting biological properties, including antimicrobial, antiplasmodial, anticancer, multiple cardiovascular activities, anti-inflammatory and acetylcholinesterase inhibitory effects.[13h]

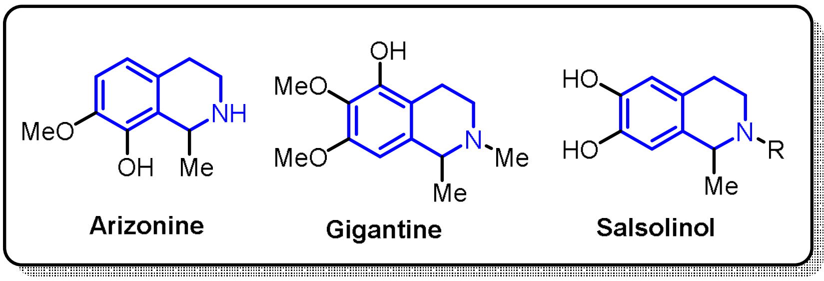


Figure 1.3.5.1.1.2 THIQ alkaloids of vegetal origin

1.3.5.1.2 Bioactive Tetrahydroisoquinolines

Known for over a century, THIQs are the most bioactive molecules with a vast range of pharmacological activity. For example, nomifensin and dichlofensin are the two most important drugs for depression; which exhibit CNS activity *via* inhibition of serotonin and dopamine reuptake mechanism. The hypotensive activity of esporoquin is a great achievement in the medical sciences which inhibit α- adrenergic receptor (Figure 1.3.5.1.2.1).[13i]

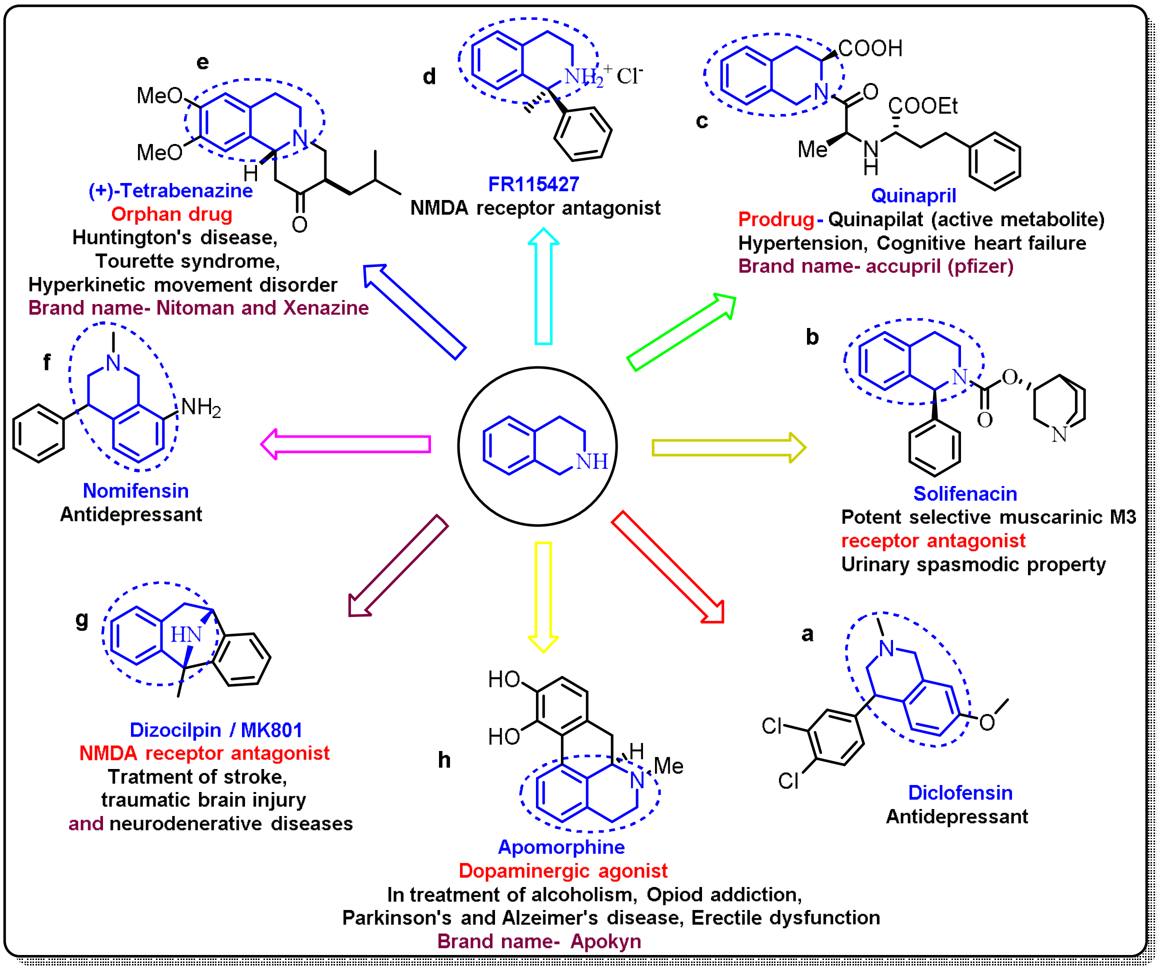


Figure 1.3.5.1.2.1 Bioactive tetrahydroisoquinolines

Solifenacin, branded as 'Vesicare', manufactured and marketed by Glaxosmithkline, Astellas, and Teva pharmaceuticals, has an antimuscarinic drug (Figure 1.3.5.1.2.1, entry **b**) and is a very useful drug in the treatment of frequent urination and urge incontinence.[13j]

THIQ as NMDA receptor antagonist: 1-Aryl-1,2,3,4-THIQ (Figure 1.3.5.1.2.2) exhibits affinity towards the ion channel binding site of the NMDA receptors; i.e. PCP binding site. Lodge *et al*. demonstrated phencyclidine (PCP) as a non-competitive NMDA antagonist that can bind to an unknown discrete site situated in the cationic ion channel and thereby imminent ion passage via an open channel.[13k]

Antagonism of a receptor-mediated process may be achieved pharmacologically by the attraction with the various NMDA receptor complex binding sites, like the glycine co-agonist site, glutamate binding site, redox modulatory site, and polyamine binding site.

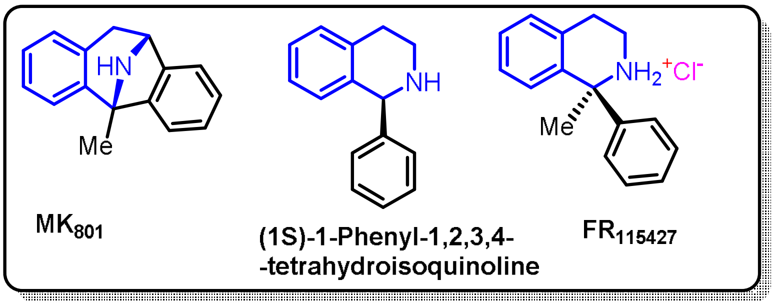


Figure 1.3.5.1.2.2 NMDA receptor antagonists acting at the PCP binding site

THIQ as neuroprotectant: 1,2,3,4-tetrahydroisoquinoline and its derivative 1-methyl-1,2,3,4-tetrahydroisoquinoline (Figure 1.3.5.1.2.3) are endogenous substance which shows huge therapeutic potential and a broad spectrum of action in the brain.[13l]

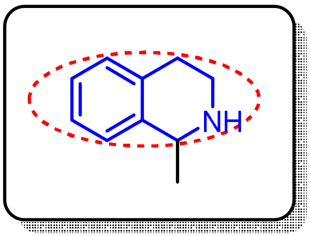


Figure 1.3.5.1.2.3 1-methyl-1,2,3,4-tetrahydroisoquinoline

THIQ as anti-HIV drug: THIQs are important building blocks in natural products; hence it is a point of attraction in organic synthesis, medicinal and pharmaceutical field. THIQ derivatives (Figure 1.3.5.1.2.4) have been developed and evaluated as CXCR-4 antagonists for treatment in HIV.[13m-n]

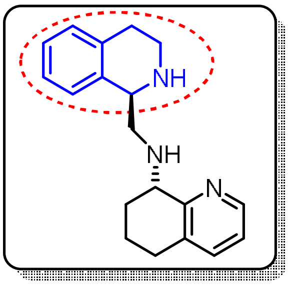


Figure 1.3.5.1.2.4 CXCR-4 antagonist - HIV-related drug

Tetrahydroisoquinoline containing natural as well as synthetic molecules was the preferred scaffold for anti-retroviral therapy for the treatment of HIV infection. Natural tetrahydroisoquinoline as an inhibitor of non-nucleoside reverse transcriptase enzyme was frequently reported in the works of literature such as michellamine B, chelidoneme, magnoflorine, *O*-methyl psychotrinesulphate and *R*-coclaurine.[13m-n]

Docked pose of THIQ at the non-nucleoside reverse transcriptase binding pocket is indicating a strong hydrophobic and hydrogen-bond interaction (Figure 1.3.5.1.2.5) designated by green and pink dotted lines respectively.

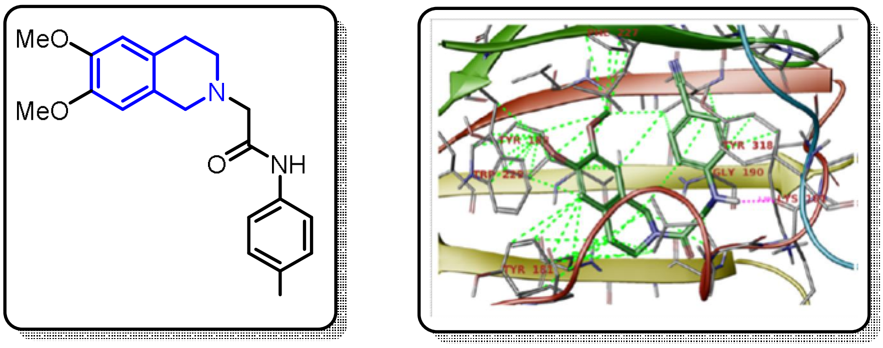


Figure 1.3.5.1.2.5 Hydrophobic interaction and hydrogen-bond formation between THIQ and NNRTs receptor

THIQ as an antitumor drug: Marine natural products containing THIQs also have potential therapeutic activities such as renieramycin being used as an antitumor drug. Renieramycin M was isolated from the Thai blue sponge *Xestosponsia sp*. It exhibits promising anticancer activity.[13o] They belong to Histone deacetylase inhibitors, which have been identified as a new class of anticancer agents (Figure 1.3.5.1.2.6)

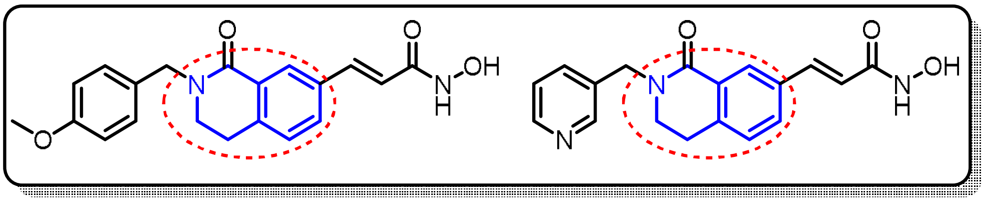


Figure 1.3.5.1.2.6 THIQ as anticancer

1.3.6 Tetrahydroquinolines

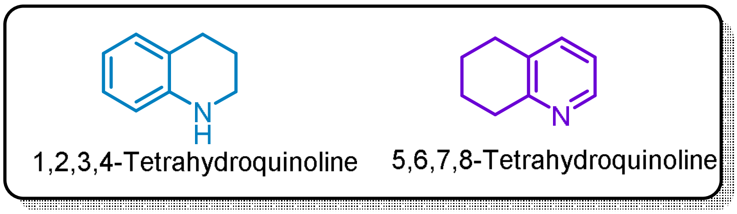


Figure 1.3.6 Molecular framework of 1,2,3,4-tetrahydro- and 5,6,7,8-tetrahydroquinoline.

In chemistry and biology, nitrogen heterocycles play a crucial role, as well as in pharmaceuticals and agrochemicals. Among the most important simple nitrogen heterocycles, tetrahydroquinoline (THQ) is widely distributed in nature and found as a constituent of a variety of compounds with pharmacological activity. We reviewed the most commonly occurring THQ, 1,2,3,4-tetrahydroquinoline, didn't discuss less common ones i.e., 5,6,7,8-tetrahydroquinoline (Figure 1.3.6).[14a-f]

1.3.6.1 Tetrahydroquinolines and Their Scope

Many natural and unnatural compounds with interesting biological properties incorporate tetrahydroquinoline (THQ), one of the most important heterocyclic systems. The development of a new synthetic methodology that can achieve the THQ skeleton has received much attention because of its importance.

1.3.6.1.1 Naturally Occurring Tetrahydroquinolines

There are a large number of natural products based on 1,2,3,4-tetrahydroquinoline, and many of them show interesting pharmacological properties. The current section will focus on compounds for which significant progress has been made in chemical knowledge between 2010 and 2018. The variety of natural products derived from tetrahydroquinoline includes alkyl derivatives and polycyclic compounds. In the first place, we will mention (−)-angustureine, (−)-cuspareine, (−)-galipeine, and (−)-galipinine, which were primarily isolated from the species angostura (*Angostura trifoliate, Galipea officinalis*), a Venezuelan shrub-like small tree with a broad medicinal activity (Figure 1.3.6.1.1).[14g-i] Virantmycin is a member of the benzastatin family.[14j] Biosynthetic benzastatins are synthesized from geranylated p-aminobenzoic acids.[14k] 5-Alkyl-1,2,3,4-tetrahydroquinoline alkaloids were obtained from a combined culture of *Tsukamurella pulmonis* TP-B0596 and *Streptomyces nigrescens* HEK616. [14l] From plants and marine fungi, a family of 3,4-dioxygenated 3,4-dihydro 4-aryl-1,2,3,4-tetrahydroquinolin-2-(1*H*)-ones have been isolated, and several of its members showed interesting biological activity.[14m] Recently, aflaquinolones have been isolated from this family. Using a modified culture of *Aspergillus* species (section Flavipedes; MYC-2048, NRRL 58570), Gloer and his coworkers obtained aflaquinolones A and B and they reported also the related aflaquinolones C−G from the marine *Aspergillus sp.* SF-5044.[14n] Additional members of this family including aniduquinolones A−B were isolated from *Aspergillus nidulans* MA-143.[14o-p]

Finally, we notified that (+)-tortuosamine, an alkaloid isolated from the South African genus *Sceletium* that contains a 5,6,7,8-tetrahydroquinoline framework (Figure 1.3.6.1.1).[14q-r]

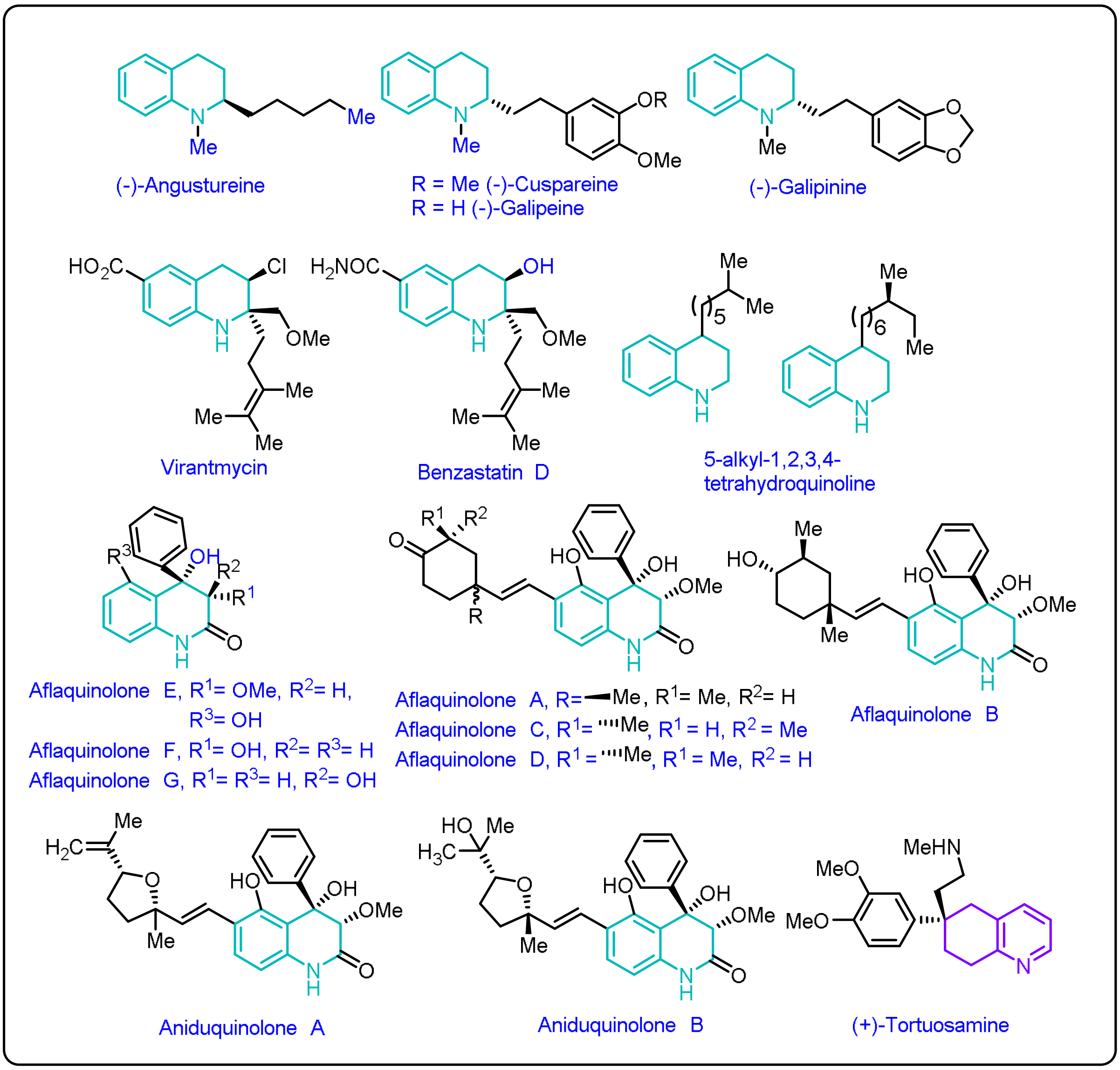


Figure 1.3.6.1.1 Representative members of 1,2,3,4-tetrahydro- and 5,6,7,8-tetrahydroquinoline based natural products

1.3.6.1.2 Tetrahydroquinoline-based Bioactive Compounds

1.3.6.1.2.1 Antiviral Tetrahydroquinolines

In a study by Bermejo and co-workers, 1,4-disubstituted 1,2,3,4-tetrahydroquinolines (**I**) were assessed against the human immunodeficiency virus (HIV), and quinolines resulting from their aromatizations (Figure 1.3.6.1.2.1). Despite the general superiority of aromatic compounds, some of the tetrahydroquinolines showed their activity in the recombinant virus assay (RVA). Various *N*-substituted tetrahydroquinolines (compounds **II**−**VI**) have demonstrated potent activity against HIV-1 reverse transcriptase, as well as anti-HIV-1 activity. The compounds are thus non-nucleoside reverse transcriptase inhibitors (NNRTIs), which are becoming progressively important as antiviral drugs.[15a-e]

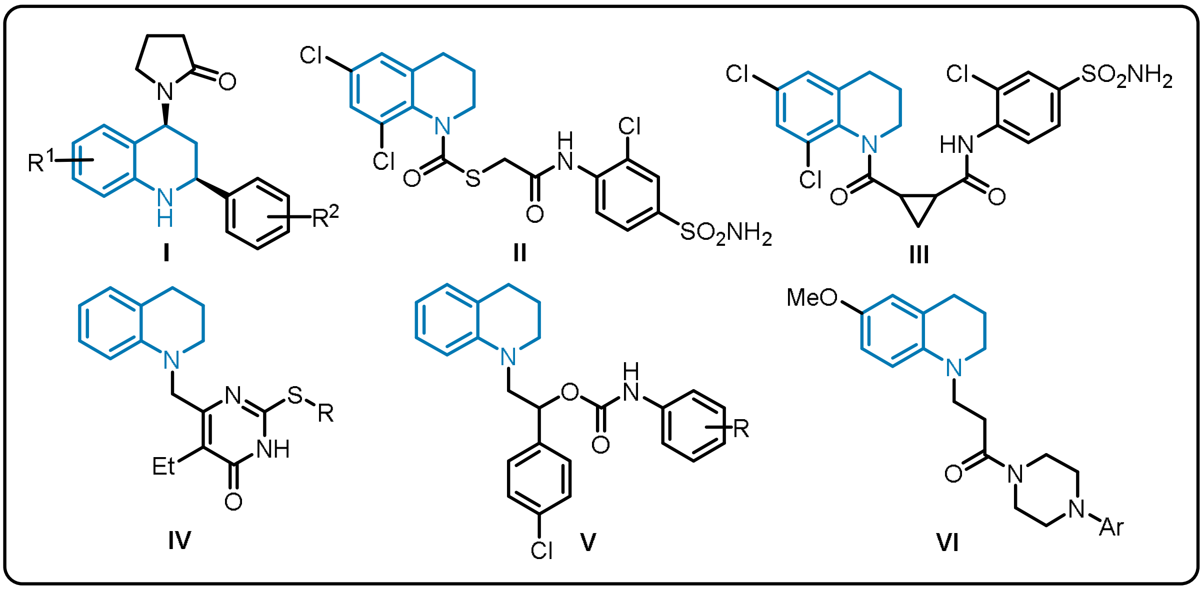


Figure 1.3.6.1.2.1 Representative antiviral tetrahydroquinolines

1.3.6.1.2.2 Antibacterial Tetrahydroquinolines

The antibacterial property of fused tetrahydroquinolines has been discovered. An antibacterial study was conducted on Compound **I**, arising from Povarov reactions, by separating it into its diastereomer and enantiomer components (Figure 1.3.6.1.2.2). Most compounds showed moderate potency, but the exo isomers were highly reactive compared to their endo counterparts. Several Povarov products strongly inhibited the growth of mycobacteria, especially compounds **II** which contain carbazolyl or dibenzofuranyl substituents. Although compound **III** is fluorescent due to the presence of the anthracene unit, they were found to be ineffective in the fluorescent imaging of bacteria. In contrast, aromatic quinoline derivatives have proven effective for detecting both Gram-positive and Gram-negative bacteria, effective at low concentrations also, though their mechanism of action has not yet been discovered.[15f-i]

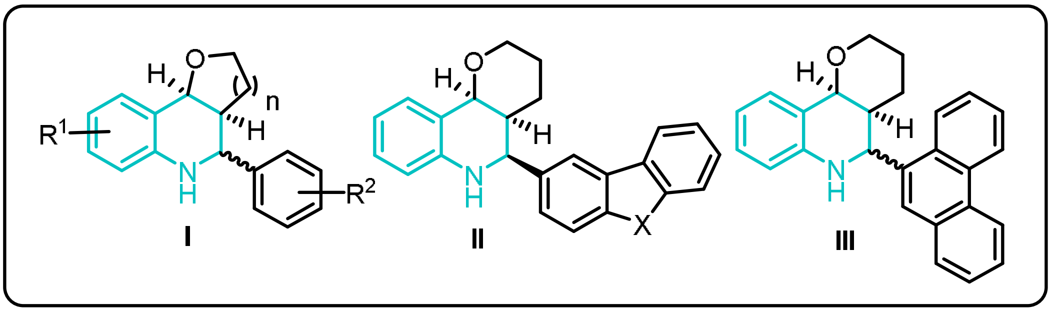


Figure 1.3.6.1.2.2 Representative antibacterial tetrahydroquinolines

1.3.6.1.2.3 Antifungal Tetrahydroquinolines

An isolate of 5-alkyl-1,2,3,4-tetrahydroquinolines was obtained through a combined culture of *Tsukamurella pulmonis* TP-B0596 and *Streptomyces nigrescens* HEK616 (Figure 1.3.6.1.2.3). Compound **I** resist yeast growth by targeting membrane lipids, likely through targeting the membrane lipids of yeast cells. In addition to 1-alkyl-1,2,3,4-tetrahydroquinolines **II**, a related compound was also investigated, though it did not seem to have any antifungal activity. On the other hand, trans-N-alkylperhydroquinolines **III** displayed comparable antimycotic activity to clotrimazole, one of the most widely used antifungals. Some tetrahydroquinolines have shown antifungal properties, including compound IV, whose MIC value was 13.75 g/mL against Cladosporium cladosporoides, and compound V, which had moderate antifungal activity against clinically active fungi such as yeasts, dermatophytes, and hypohyphomycetes.[15j-l]

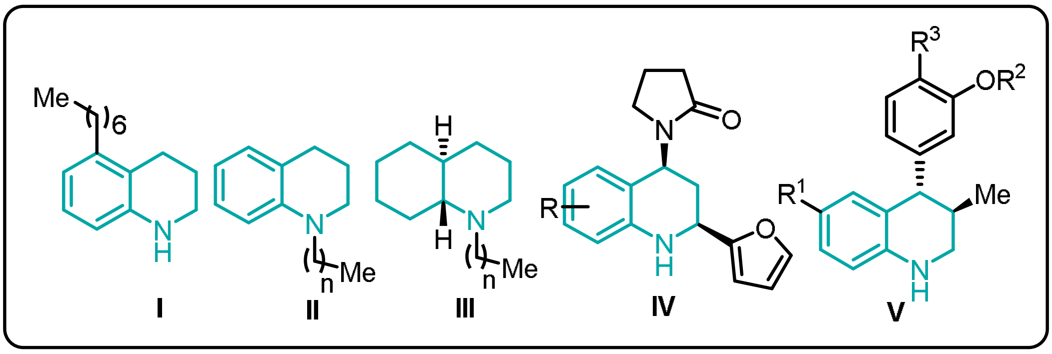


Figure 1.3.6.1.2.3 Several antifungal tetrahydroquinolines

1.3.6.1.2.4 Antiparasitic Tetrahydroquinolines

There were few 2,4-diaryl-1,2,3,4-tetrahydroquinoline derivatives with the common skeletal structure **I** that displayed selective toxicity for epimastigotes of *Trypanosoma cruzi*, as well as for promastigotes of *Leishmania chagasi*. It was found that these compounds showed better activity when the methyl substituent is present on C-3 (Figure 1.3.6.1.2.4). It has also been demonstrated that multiple relevant protozoal infections can be treated with compounds derived from the tetrahydroquinoline family with structure **II**. A good selectivity index and moderate growth inhibition were observed in two of these compounds against *Plasmodium falciparum*. Most compounds showed moderate activity against *Trypanosoma cruzi*, the responsible agent of the disease Chagas, but not against *Trypanosoma brucei rhodesiense*, the causative agent of African trypanosomiasis (sleeping sickness). Finally, two of the compounds inhibited *Leishmania donovani* growth moderately.[15m-o]

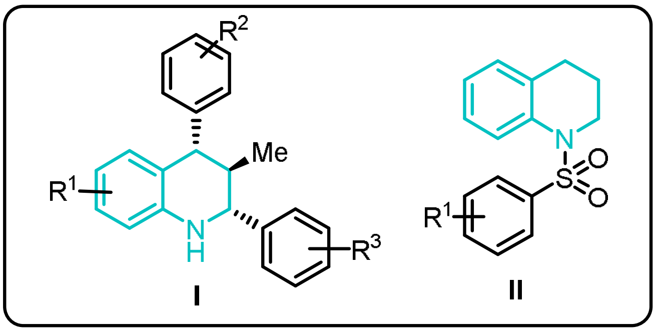


Figure 1.3.6.1.2.4 Representative antiparasitic tetrahydroquinolines

1.3.6.1.2.5 Anticancer Tetrahydroquinolines

The 1-acyl-2-benzamido-1,2,3,4-tetrahydroquinolines **I** inhibit the transcriptional activity of the NF- κB factor, which has multiple functions, including regulating cell growth and apoptosis (Figure 1.3.6.1.2.5).[15p] A few compounds were effective against a variety of cancer cells in sub-micromolar concentrations. Particularly, 1,2,3,4-tetrahydroquin-8-ol **II** displayed that it was capable of inducing apoptosis in Hep3B human carcinoma cells and cytotoxicity toward different human cancer cell lines. The antitumor activity of the xenograft was further confirmed in an experiment with a thymic nude mouse xenograft.[15q]

In a recent study, 1,2,3,4-tetrahydroquinolines **III** was discovered to be antitumor agents, specifically targeting tubulin's colchicine site. Further work was done on derivatives of 1-heteroaryl-6-methoxy-1,2,3,4-tetrahydroquinolines, such as **IV** and **V**, that prohibited tubulin interaction of colchicine, and exhibited good GI_{50} values in the nanomolar range in cell assays.[15r-s] A plenty number of cis-2,4-diaryl-*R*-3-methyl-1,2,3,4-tetrahydroquinolines (**VI** and **VII**) exhibited cytotoxic activity against human breast cancer cell lines. Among 1-arylsulfonyl-1,2,3,4-tetrahydroquinolines, compound **VIII** was highly cytotoxic to K562 cells.[15t-v] As a result, Zn^{2+} cation in the enzyme's active site coordinate with the hydroxamic acid unit, and compounds containing *N*-hydroxyacrylamide side chain (e.g., compound **IX**) have been shown to be histone deacetylase inhibitors. There is evidence that these compounds can suppress prostate cancer cell growth.[15w]

Regarding fused tetrahydroquinoline derivatives, furo[3,2-c]tetrahydroquinolines **X** inhibits cellular proliferation with IC_{50} values in the 2.5-16.7 µM range. It was found that fused-cis tetrahydrochromeno[4,3-b]quinolines **XI** showed very good antiproliferative activity against the breast cancer cell MCF-7.[15x-y]

The anticancer properties of some 5,6,7,8-tetrahydroquinolines and the fused derivatives of THQ (**XII** and **XIII**) have also been investigated.[15z]

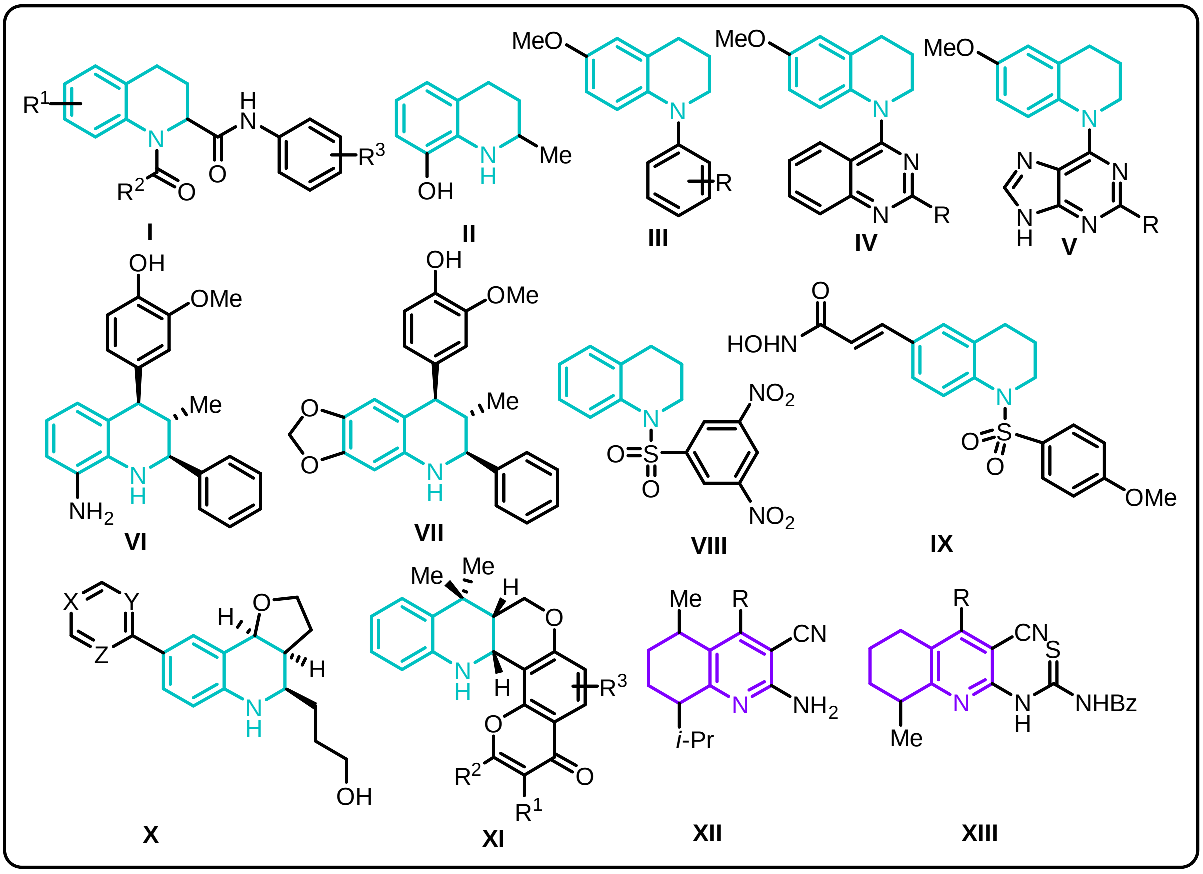


Figure 1.3.6.1.2.5 Representative anticancer tetrahydroquinolines

1.4 Spirocyclic Compounds in Medicinal Chemistry

Spiro compounds could be formed with two rings sharing one atom i.e., spiro atom. They are present in both natural and synthetic bioactive compounds. Spiro rings such as spiro-ketals are present in a variety of natural products like insect pheromones.[16a]

The most significant spiro ring system that has been developed in the last decades involves five and six-membered rings (Figure 1.4, **a–h**). The spiro-heterocyclic ring has been attached device into the ligands of GPCRs, enzyme inhibitors, aspartyl proteases, renin, epoxide hydrolase, etc.

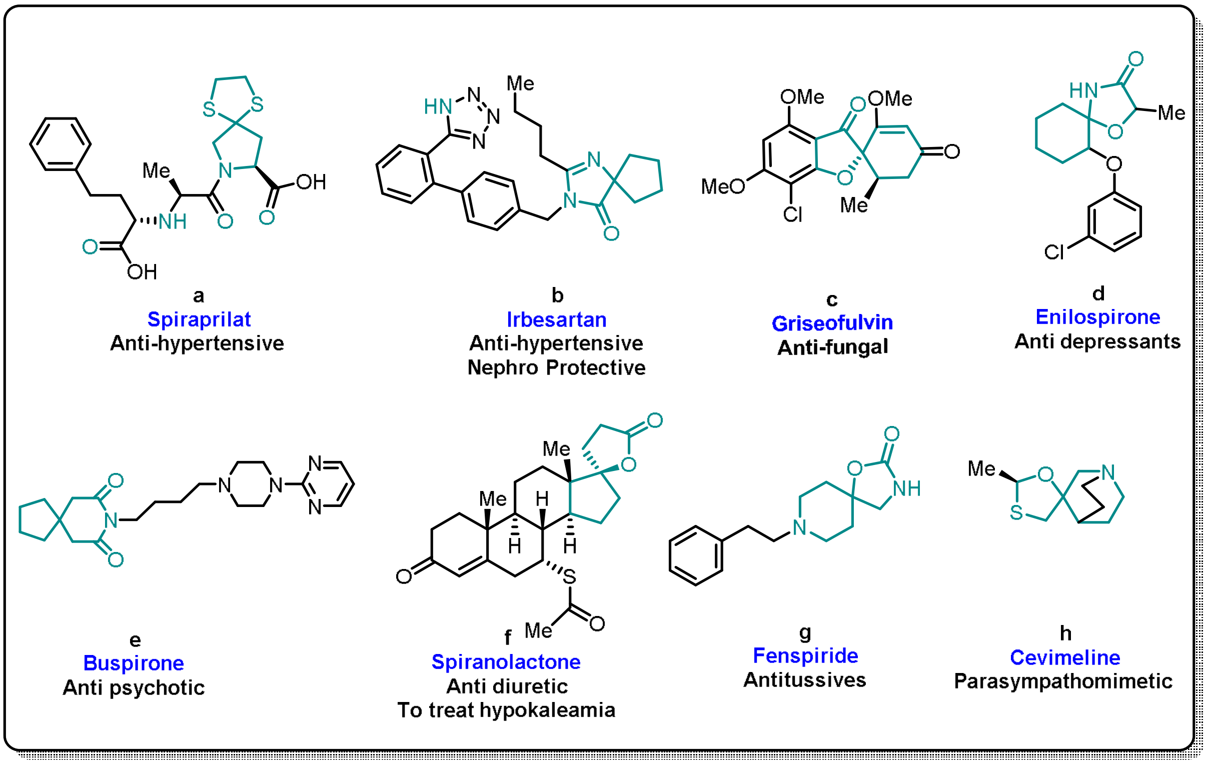


Figure 1.4.1 Some marketed drugs containing spirocyclic scaffolds

Spiro ring can be present within or at the periphery of a molecule. If it is present in the outer phase of a molecule, the impact of the conformation is limited and is mainly used to impart novelty for getting patentability for the molecule.[16b]

One of the common strategies in drug design is to rigidify the ligand molecule by introducing a (spiro) ring. At the time of binding to a protein with a ligand molecule, the conformation of the bound molecule may not be identical with low energy conformation. The difference in energy between both conformations is known as strain energy. If the stable conformation of the free ligand is almost similar to the bound conformation, entropic disadvantage can be reduced and ligand binding affinity can be enhanced due to reduced strain energy. The spiro ring or fused spiro ring system has the ability to conformational restrict on a molecule. In applicability, for ligand-protein binding interaction, spiro cyclization methods develop an excellent way to re-enforce the desired conformation.[16c]

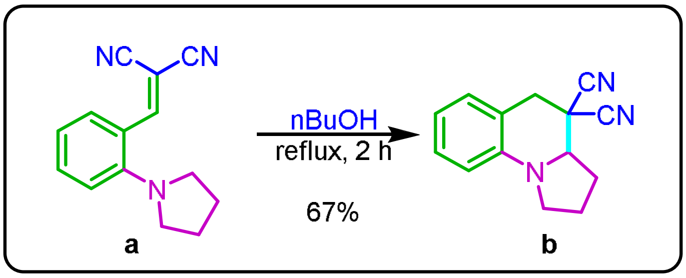
Spiro ring formation also improves bioavailability and the stability of the metabolic system. Moreover, conformational restriction can decrease off-target activities and undesired enzyme activity.[16d] Also we can correlate the spirocyclic compounds to their biological activity for already marketed drugs. Some spirocyclic fusion in compounds is essential to bind specifically with the receptor and to exhibit activity. Compounds like **spiraprilat** and **irbesartan** (Figure 1.3.6.1.2.5, **a, b**) are an antihypertensive class of compounds and have common 5/5 ring fusion which exert their activity by inhibiting Angiotensin Converting Enzyme (AcE). Ring fusion might be essential for activity.

With the recent advances in synthetic methodology to construct several spiroheterocyles and the interest in the activeness of their three dimensionalities, more biologically active spiro compounds will be exploited in drug discovery.

1.5 Previous Report of Hydride Transfer Reaction

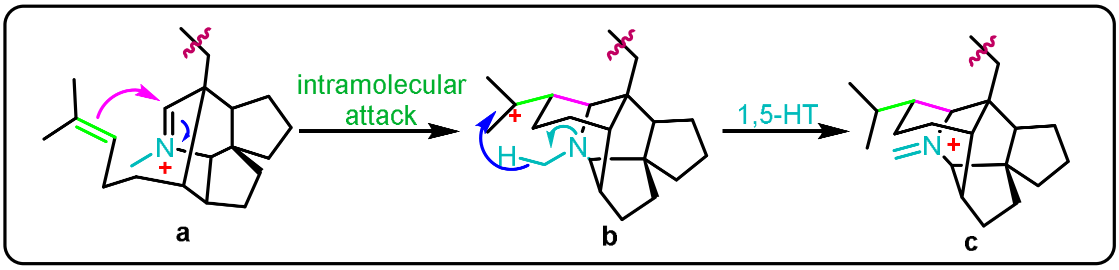
In 1885, despite being developed by Pinnow, the 1,5-hydride shift was relatively obscure for most of the subsequent century, with Meth-Cohn's two major reviews in 1972 and 1996 being the most important work in the area.[1] They coined the term *tert*-amino effect as a way of enabling these hydride shifts followed by cyclization processes that occur adjacent to amines, but other heteroatoms and even without a heteroatom have been reported as well. These reactions have steadily gained interest in the past 10-20 years, mainly in the last ten, driven by the same motives that moved C–H activation research toward atom-efficient “green’’ chemistry.[1] Recently, the hydride shift reactions have proved to be very important and remarkably versatile in the field of organic reaction as shown below in the pictorial representation (Figure 1.5.1).[1]

The 1,5-hydride shift was first demonstrated by Reinhoudt et al. in 1984[16] in their method of making substituted tetrahydroquinolines (Scheme 1.5.1). Upon heating the aniline derivative **a** in nBuOH for 2 hrs, tetrahydroquinoline **b** produced a 67% yield. Interestingly, Reinhoudt observed that the 1,5-hydride shift can be facilitated by a 6-membered heterocyclic ring in the backbone from the corresponding olefin substrate, as it furnished a closer skeleton to the required spatial orientation.[16]



Scheme 1.5.1 Tetrahydroquinoline formation through a 1,5-hydride shift

A new transformation of daphniphylline alkaloids (Scheme 1.5.1) was discovered in the 1990s by Heathcock *et al.*[17] Upon attack by the pendent alkene, iminium ion **a** was converted into the carbocation **b**, electrophilic carbocation part is hydride acceptor for a 1,5-hydride shift resulting the yield of second iminium ion **c** and followed by its hydrolysis happened.[17]



Scheme 1.5.2 Unexpected 1,5-hydride shift

Different hydride donor and acceptor atoms: As mentioned before, different donor atoms such as O, NR_2, and benzylic CH_2 have been used for hydride shift cyclization methodology for the synthesis of densely functionalized molecules. Different hydride acceptors like alkenes, activated alkenes or alkynes, or carbocations can also be involved in hydride shift reactions.

Oxygen as donor atom: In 2005, Sames *et al.* [18] reported the synthesis of a spirocyclic product (Figure 1.5.1, Scheme: **a)** from tetrahydropyran containing pendant alkylidene-malonate by applying scandium triflate (5 mol%) as a catalyst at room temperature. Different types of C–H bonds could also be functionalized through C–H bond activation, e.g. C–H bonds α to the carbamate nitrogen (Figure 1.5.1, Scheme: **b**) and benzylic C–H bonds (Figure 1.5.1, Scheme: **c**) by using $PtCl_4$ (30 mol%) as catalyst.[18] Akiyama and co-workers have demonstrated the functionalization of several benzylic and non-benzylic ethers via intramolecular redox isomerization (Figure 1.5.1, Scheme: **d)** by using tin tetrachloride (0.5 mol%). The presence of an ortho substituent and *tert*-butyl group on the substrate increases the reaction rate and lowers the catalyst loading.[19] Sames and McQuaid investigated the transformation of acetal into substituted tetrahydropyran (Figure 1.5.1, Scheme: **e**) *via* hydride transfer/cyclization process using $BF_3.OEt_2$ (50 mol%) as Lewis acid and ethylene glycol as organocatalyst (type of dual catalytic process), thereby improving alkylation reactions initiated by the hydride transfer incident at room temperature.[20]

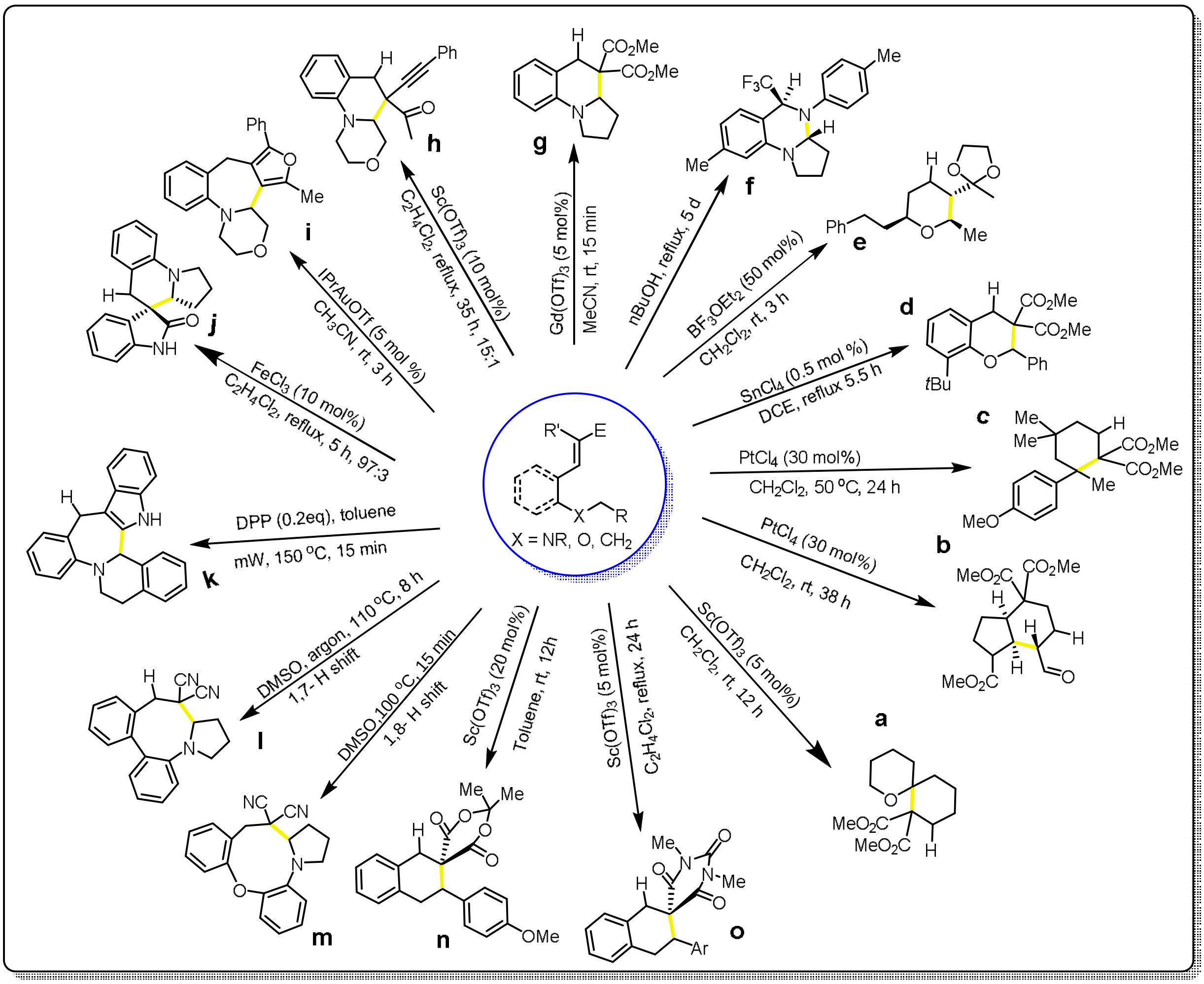


Figure 1.5.1 Scope of the hydride shift reaction

Nitrogen as donor atom: Reinhoudt and co-workers[21] developed imine to aminal rearrangement happened thermally (Figure 1.5.1, Scheme f). On the basis of the studies of Reinhoudt *et al.* many organic and medicinal chemists reported various routes for the synthesis of potentially bioactive molecules. Seidel group [23] reported one-pot bronsted acid catalyzed approach to the above transformation which can be applicable to tertiary amino benzaldehydes and primary amines, including aliphatic amines. Traditionally, reactions associated with the *tert*-amino effect responsible for the formation of new heterocycle, have been occurred in thermal conditions. Recently, Seidel group has introduced the hydride shift concept using 2-amino benzaldehyde for the synthesis of complex polycyclic tetrahydroisoquinoline containing bioactive molecules by using simple Lewis acids at room temperature.[22] Here the amino group is in the tertiary state and reaction following general pathway shown below (Figure 1.5.2) have been classified under the term “tert amino effect”.[23]

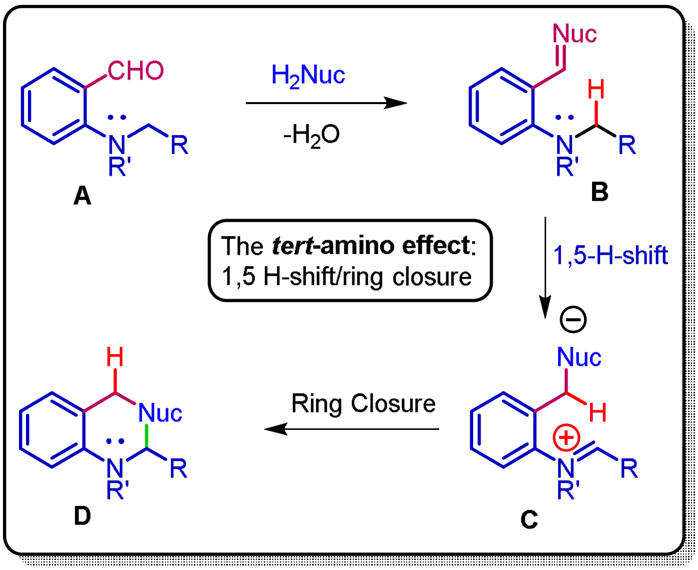
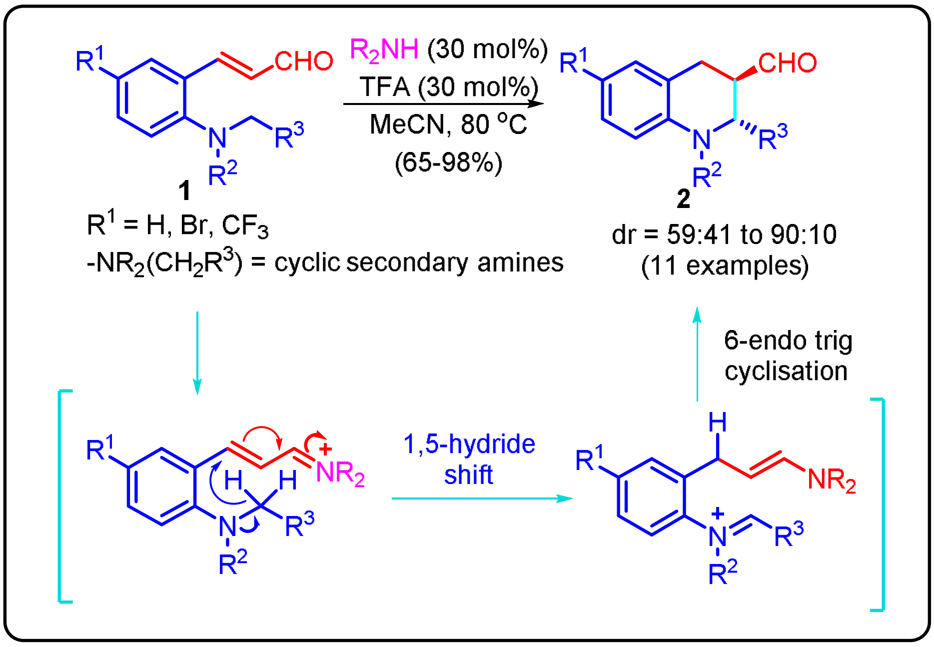


Figure 1.5.2 1,5-hydride shift reaction of aminoaldehyde

Employing this concept, they have investigated the rearrangement of pyrrolidinealkylidenemalonate to tricyclic tetrahydroquinolines (Figure 5, Scheme: **g**) using Lewis acid (5 mol%) as a catalyst.[22] Zhang *et al.* [24] reported Scandium triflate-catalyzed synthesis of spirocyclic compounds (Figure 1.5.1, Scheme **h**) *via a* 1,5-hydride shift reaction. When the catalyst was changed to a cationic gold complex, furan-fused benzazepine (Figure 1.5.1, Scheme **i**) species was generated through an intriguing cascade process. Yuan and co-workers reported the formation of spirooxindiles (Figure 1.5.1, Scheme **j**) by using Iron (III) chloride as a catalyst.[25] To develop complex molecules, Seidel and co-workers again in 2011 reported the synthesis of indole-fused benzazepine (Figure 1.5.1, Scheme **k**) from indole and aminoaldehyde under microwave irradiation by using diphenyl phosphate (20 mol%). The reaction could proceed by 1,5-hydride transfer through the formation of intermediate vinylogous iminium ion (azafulvenium), sequentially ring closure process.[26] Mátyus group showed remarkable extension of *t*-amino effect that is useful for the synthesis of larger heterocycle rings (Figure 1.5.1, Scheme: **l**, **m**).[27-28]

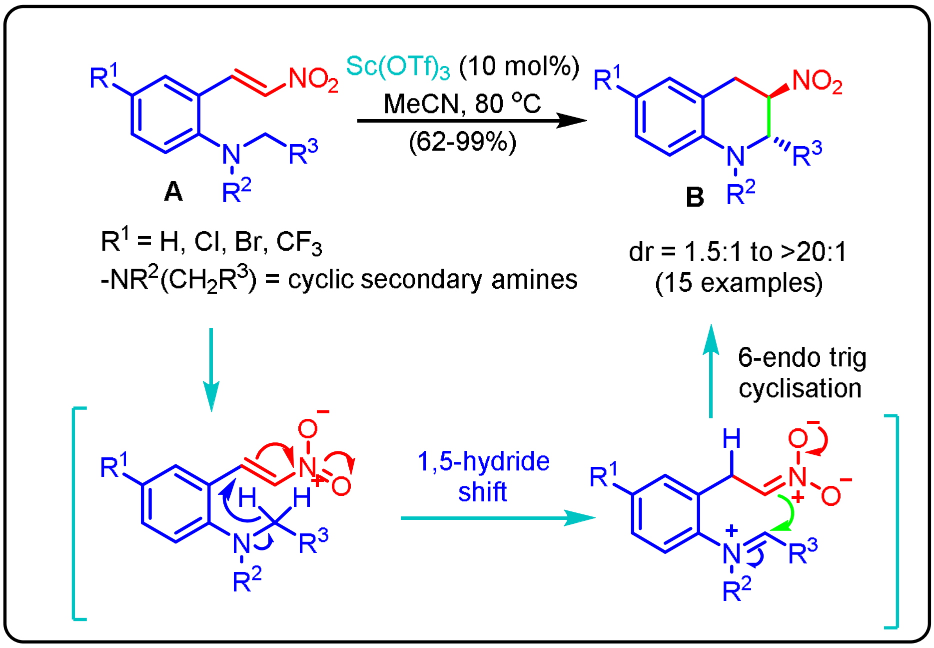
Benzylic CH$_2$ as donor atom: Functionalization of benzylic C–H bond by 1,5-hydride transfer followed by ring-closing reaction (Figure 1.5.1, Scheme: **n**) has been reported by the Fillion group using scandium (III) triflate as a catalyst.[29] In continuation of their work, the Akiama group extended the scope of the 1,5-hydride shift/ring closure reaction of benzylic C–H bonds of alkylidene barbiturates (Figure 1.5.1, Scheme: **o**) by using scandium triflate as catalyst.[30]

Kim reported[31] the synthesis of tetrahydroquinolines **2** from aldehydes **1** using an intramolecular *tert*-amino effect, i.e., sequential 1,5-hydride transfer/ enamine-iminium ring formation, in high yields (Scheme 1.5.3). Furthermore, this group detected the first enantioselective cascade 1,5-hydride transfer/ring closure process using an organocatalyst. To synthesize enantio-enriched THQs they employed a chiral secondary amine catalyst and (−)-Camphor Sulphonic Acid with excellent yield and enantioselectivities in the 85-99% range. This group also described the intramolecular sequential version of enamine catalysis and 1,5-hydride transfer followed by ring formation, with high diastereoselectivities and moderate to high yields for the synthesis of tetrahydroquinolines incorporating five- to nine-membered azacycles.[31]



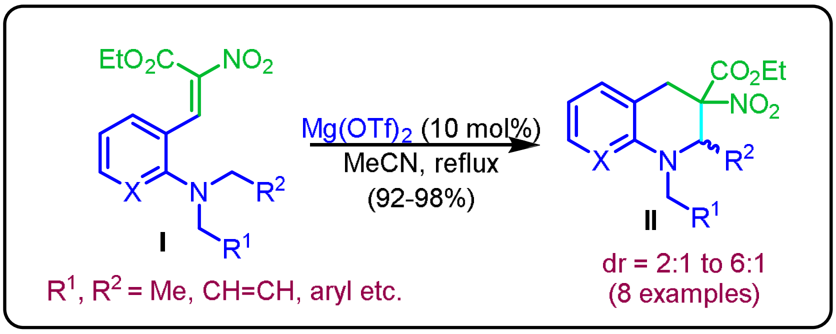
Scheme 1.5.3 Construction of 3-Formyltetrahydroquinolines via enamine formation

The same group described the synthesis of 3-nitrotetrahydroquinolines **B** from 2-(o-(dialkylamino)aryl)nitroalkenes **A** employing Lewis acid-catalyzed 1,5-hydride shift reaction (Scheme 1.5.4). Following Lewis acid optimization, $Sc(OTf)_3$ was used in acetonitrile at 80 °C to occur 1,5-hydride shift/6-endo cyclization which afforded 3-nitrotetrahydroquinolines with moderate yields and diastereoselectivities >20:1.[32]



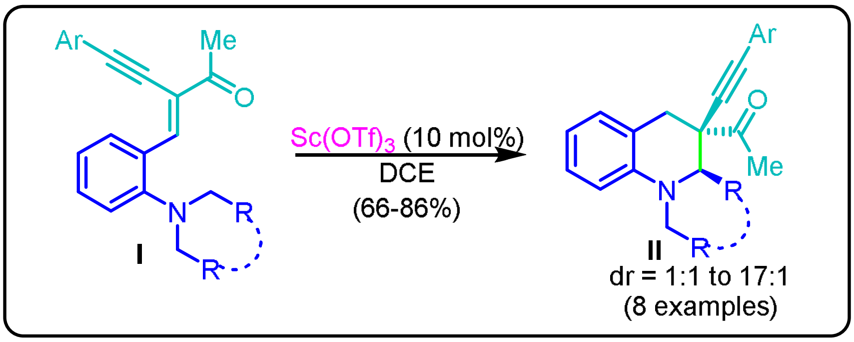
Scheme 1.5.4 3-Nitrotetrahydroquinolines synthesis via 1,5-hydride shift operation

Briones and Basarab's group demonstrated the synthesis of polysubstituted tetrahydroquinolines **II** employing Mg(OTf)$_2$ Lewis acid, via the *tert*-amino effect, i.e., by transferring 1,5-hydrides/closing rings starting from compounds **I** (Scheme 1.5.5).[33]



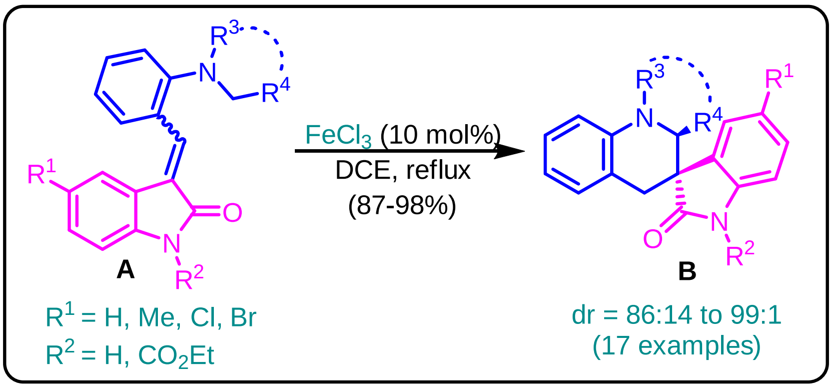
Scheme 1.5.5 C-3 α-Nitroester Functionalized Tetrahydroquinoline synthesis

Zhang and co-workers synthesized a variety of heterocycle-fused tetrahydroquinolines **II** from enynes/alkynes **I** utilizing Sc(OTf)$_3$-catalyzed cascade 1,5-hydride shift reaction (Scheme 1.5.6). It has been demonstrated that morpholine and piperidine-fused tetrahydroquinolines exhibit very good diastereoselectivity, whereas acyclic secondary amines or eight-membered amines display inferior diastereoselectivity.[34]



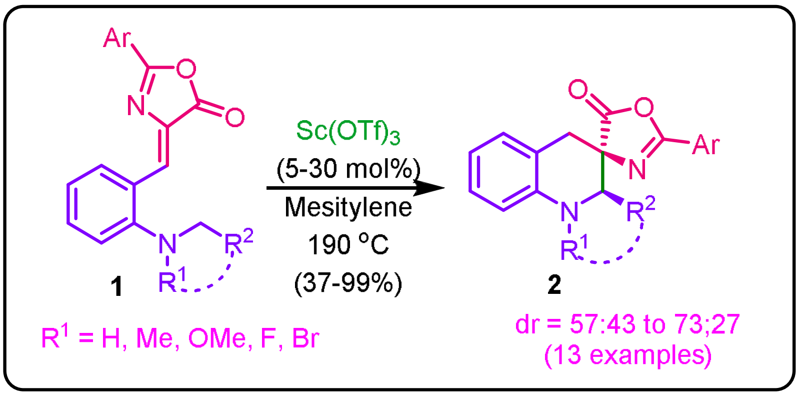
Scheme 1.5.6 Synthesis of tetrahydroquinolines from enyne employing $Sc(OTf)_3$ Lewis acid

For the synthesis of structurally diverse spirooxindole-tetrahydroquinolines **B** with good to excellent diastereoselectivity, Yuan's group demonstrated $FeCl_3$-catalyzed an efficient cascade 1,5-hydride transfer/ring closure reaction of compounds **A** (Scheme 1.5.7) [35] with high yields (up to 98%). Furthermore, they described a chiral BINOL-derived phosphoric acid-mediated asymmetric version of this process that provided enantiomerically excess (54% ee) spirooxindole-tetrahydroquinoline in excellent yield (95%) with 94:6 dr.[35]



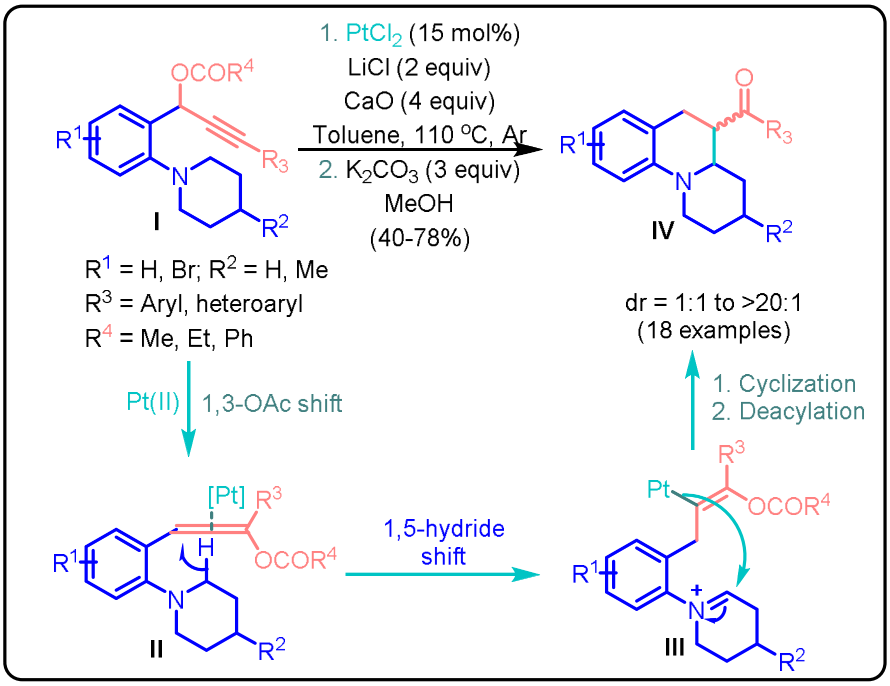
Scheme 1.5.7 Spirooxindole tetrahydroquinolines synthesis using the *tert*-Amino Effect

Using $Sc(OTf)_3$, Yuan and colleagues synthesized spiro-fused tetracyclic and pentacyclic tetrahydroquinoline derivatives **2** by intramolecular tandem 1,5-hydride transfers/cyclizations of alkylidene azalactones **1** (Scheme 1.5.8).[36] To synthesize THQs **2**, (*Z*)-alkylidene azalactones (olefin) **1** have been utilized along with various triflate catalysts, such as CuOTf, $Cu(OTf)_2$, $Zn(OTf)_2$, $Sc(OTf)_3$ and various Lewis acids like $Mg(ClO_4)_2$, $Ni(OAc)_2$, $NiCl_2$, $FeCl_3$, and $AgNO_3$. $Sc(OTf)_3$ was the most promising catalyst among others in mesitylene solvent at 190 °C for the preparation of tetrahydroquinoline derivatives in excellent yields (up to 99%) with moderate diastereoselectivity. The treatment of NaOMe in compound **2** in methanol solvent led to the formation of the respective acyclic 3-amino-3-carboxy-tetrahydroquinolines carrying carboxylic and amino functionalities.[36]



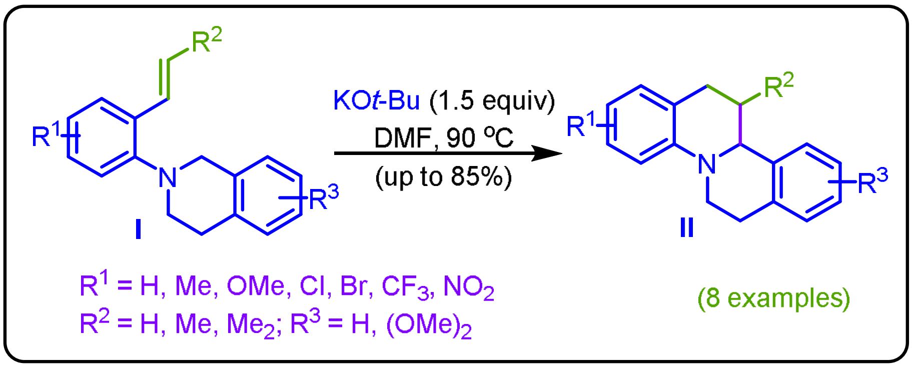
Scheme 1.5.8 Synthesis of azalactone containing spirotetrahydroquinolines

Liang and co-workers screened several reactions employing a variety of Lewis acids, after observing $PtCl_2$ was the best among all which promote an intramolecular cyclization reaction, that served the new synthetic route of benzo[a]quinolizidines **IV**, bearing a ring-fused tetrahydroquinoline scaffold from 3-aryl-1-(2-(piperidin-1-yl)aryl)prop-2-ynyl esters **I**, in good yields and with moderate to good diastereoselectivity (Scheme 1.5.9).[37] It is a domino transformation that proceeds via a series of transformations such as the 1,3-OAc transferring process, 1,5-hydride shifts, and intranuclear cyclization through the intermediates **II** and **III**, followed by a hydrolysis step in MeOH with the help of mild base K_2CO_3 (Scheme 1.5.9). The addition of LiCl to $PtCl_2$ increased its catalytic activity, as well as the use of dehydrating agents such as molecular sieves and CaO.[37]



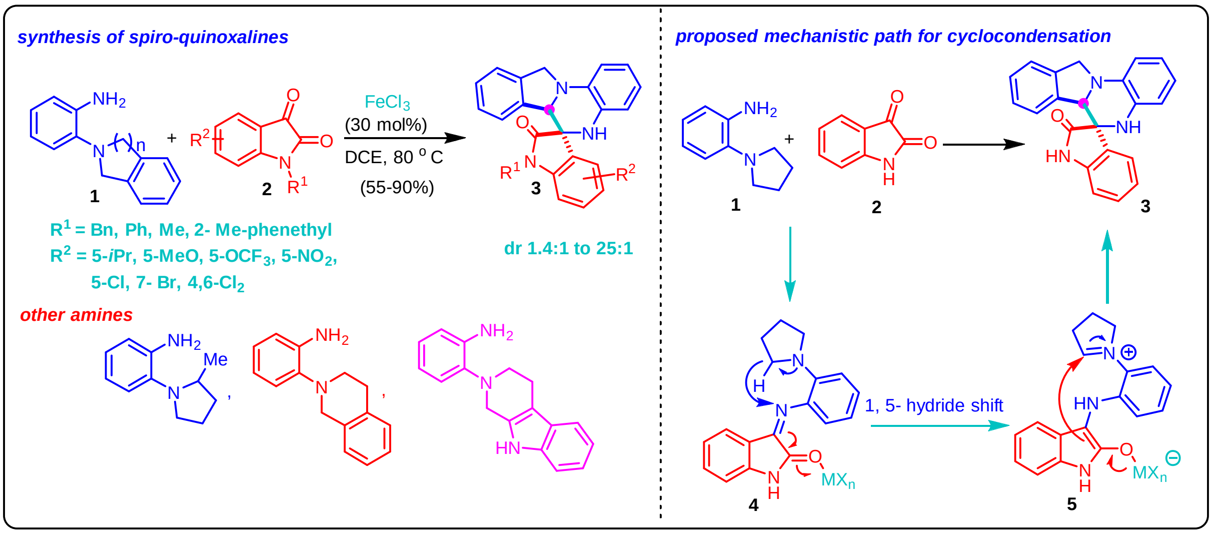
Scheme 1.5.9 Benzo[*a*]quinolizidines synthesis via a 1,3- OAc Migration/1,5-Hydride Shift/Cyclization Sequence

Yan’s research group reported a base-promoted cyclization (KO-*t*-Bu-mediated reaction) for the synthesis of fused tetrahydroquinoline derivatives from the corresponding olefin (Scheme 1.5.10). Synthesize of varieties of olefins is important as it is a precursor for this hydride shift reaction. The precursor *N*-2-(ethenylphenyl)tetrahydroisoquinoline I was cyclized in dimethylformamide under reflux conditions in the presence of KO*t*-Bu to produce compounds II (Scheme 1.5.10).[38] Based on the observation of radical coupled products employing radical scavengers, a single electron transfer mechanism had been proposed.[38]



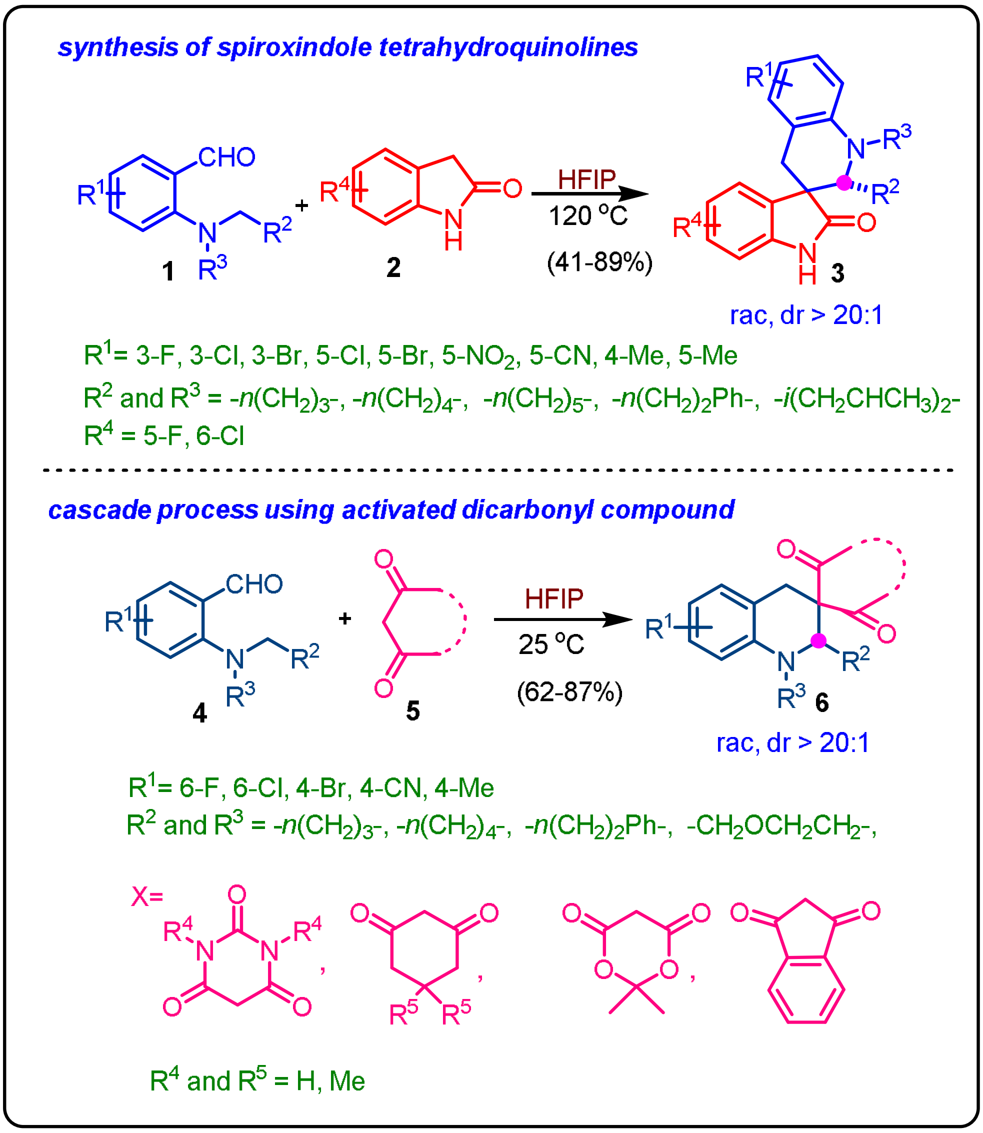
Scheme 1.5.10 Synthesis of dibenzo[*af*]quinolizidines stimulated by Potassium *tert*-Butoxide via the SET method

Tunge's group demonstrated in 2017 that diamines **1** and isatin **2** could be used to synthesize spiro tetrahydroquinoxalines through Lewis acid catalysis (Scheme 1.5.11).[39] The condensation reaction of diamine **1** containing α-dicarbonyl substrate produces an intermediate imine **4**, in which [1,5]-hydride shift happened and produced compound **3** (Scheme 1.5.11).[39] The $FeCl_3$ promoter enabled the induction of hydride shift and different functional groups at various positions of the precursor were compatible, giving rise to spiroheterocycles **3** with moderate to excellent yields (55–90%) and diastereoselectivity (1.4:1 to 25:1) also.[39]



Scheme 1.5.11 Construction of spiro tetrahydroquinoxalines via hydride shift/cyclization sequence

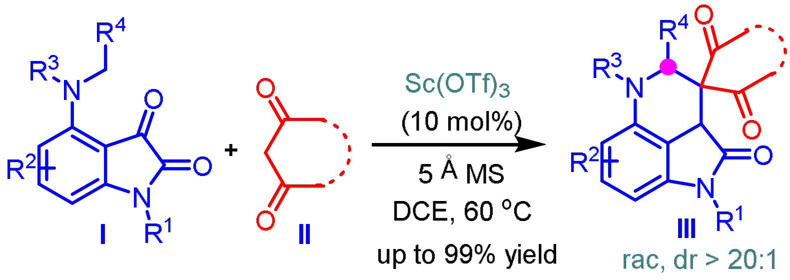
An oxindole moiety was incorporated into tetrahydroquinolines by Li's group by utilizing a fluorinated alcohol-mediated [1,5]-hydride shift/cyclization reaction (Scheme 1.5.12).[40] The efficacy of transformation was significantly influenced by hexafluoroisopropanol (HFIP) in a recent study. The knoevenagel condensation reaction of 2-(pyrrolidin-1-yl)benzaldehyde **1** and indolin-2-one **2** constitute olefin in situ, followed by a hydride shift process produced spirooxindole-fused tetrahydroquinolines **3** with structural diversity (Scheme 1.5.12). [40] Among various solvents HFIP was notable due to its smoothness to produce spiro heterocycles, the strategy accepted a good tolerance of a variety of substrates, enabled the products with moderate to excellent yields (32%-89%) and moderate to excellent diastereoselectivities (61:39 to >20:1 dr). Various activated 1,3-dicarbonyl system exhibit their HT capability in this reaction condition. According to their mechanistic study, HFIP exhibits dual hydrogen bonds with the enol moiety of intermediates which influenced 1,5-HT.[40]



Scheme 1.5.12 Construction of tetrahydroquinolines induced by HFIP

After a year, Xiao's and coworkers reported scandium triflate catalyzed another domino [1,5]-hydride shift/ring closure strategy of the substituted C_4-amine isatins **I** with 1,3-dicarbonyl species **II** (Scheme 1.5.13). [41] The 1,3-dicarbonyl intermediate (olefin) acted as a hydride ion acceptor for this reaction. After several screenings utilizing plenty of solvent dichloroethane (DCE) gave the best among others and the optimized condition had defined with this solvent, 5-Å molecular sieves and $Sc(OTf)_3$ have been used as an additive and Lewis acid catalyst, furnishing various spiroheterocycles **III** with good to excellent yields (48%–99%) and moderate to excellent diastereoselectivity (1:1 to >20:1 dr). It is interesting to note that asymmetric *N*-benzyl-*N*-methylamine substrates permitted in this reaction have never been achieved previously in most hydride shift reactions. The asymmetric reaction has been tested by introducing chiral phosphoric acid, unfortunately, poor enantioselectivity was notable. [41]

hydride-shift/cyclisation towards spiroxindole tetrahydroquinolines



R^1 = H, Bn, 2-Cl-Bn, 4-Cl-Bn, 4-Me-Bn, CH_2-1-napthyl, allyl, Ph, Me, Et, CO_2Et, cyclopropylmethyl, cyclopropyl

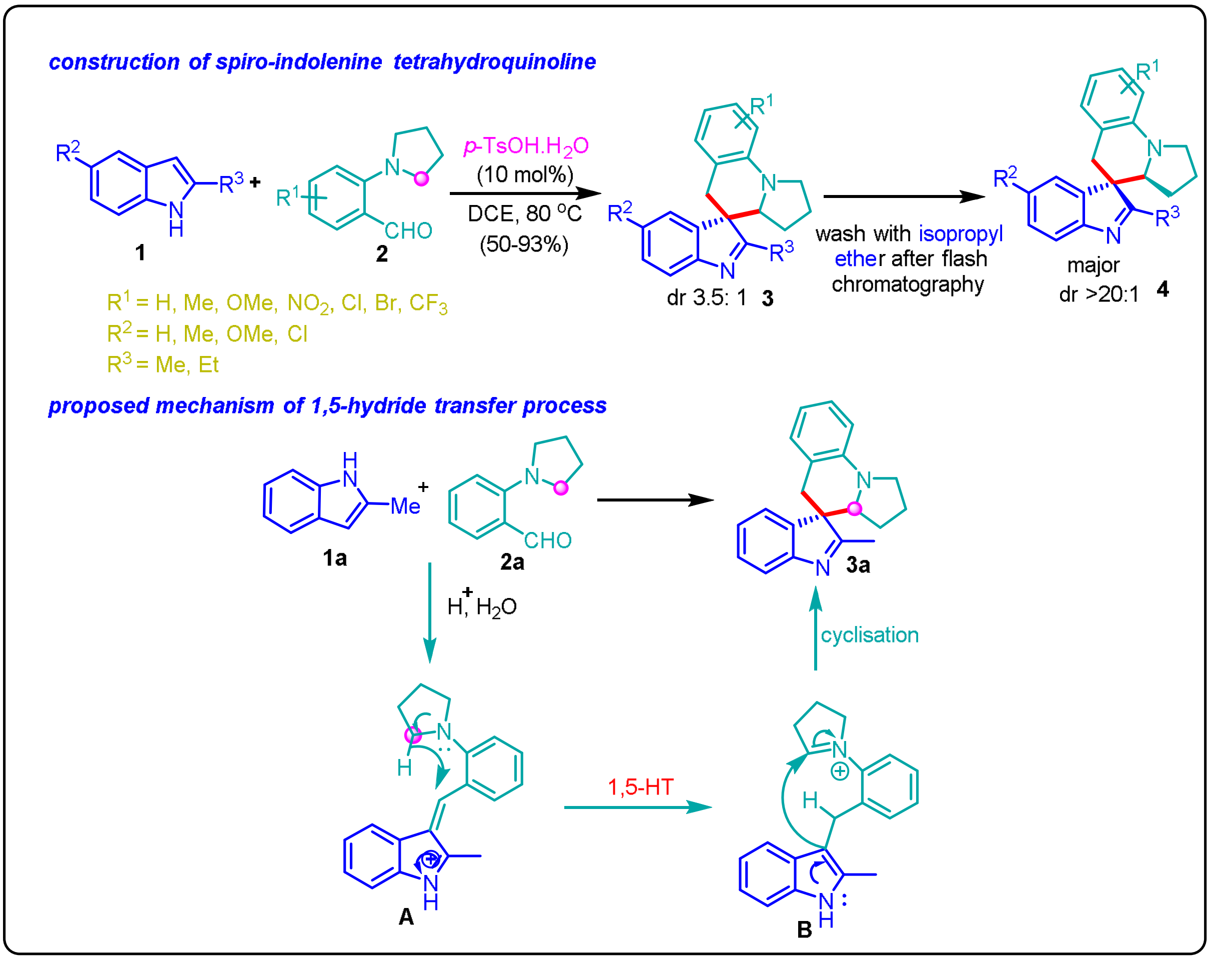
R^2 = 5-Me, 7-Cl

R^3 and R^4 = -*n*$(CH_2)_3$-, -*n*$(CH_2)_4$-, -*n*$(CH_2)_5$-, -*n*$(CH_2)_2CHCH_3CH_2$-, -*n*$(CH_2)_2OCH_2$-, Me, Ph

II = 1,3-indanedione, 1,3-dimethylbarbituric acid

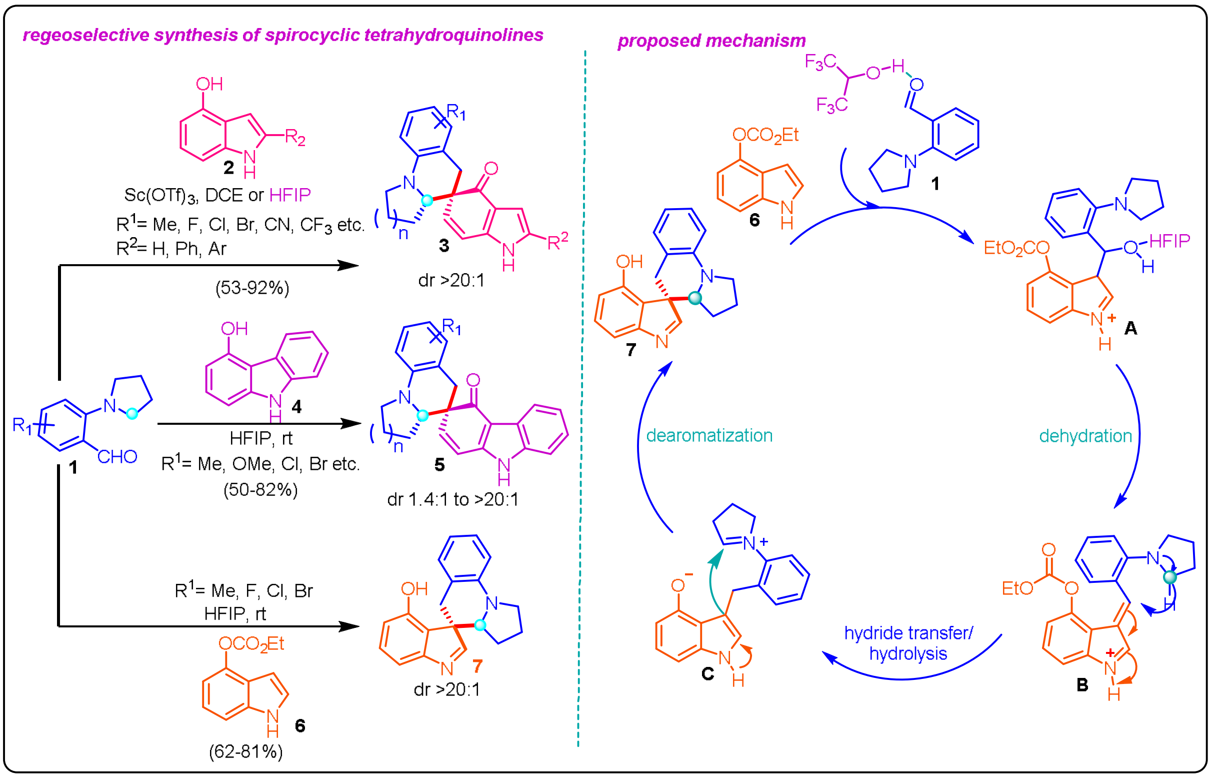
Scheme 1.5.13 Synthesis of oxindole-fused tetrahydroquinolines through cascade [1,5]-hydride shift/cyclization strategy

As an alternative to oxindole substrate, indole substrates have the ability to perform [1,5]-hydride shift process/cyclization reaction. By Sun and Xu's research group, in 2015, a modified method was revealed to build diverse spiro-tetrahydroquinolines that contain an indolenine moiety **3** through *the* hydride transfer/cyclization process (Scheme 1.5.14).[42] Dehydration of the substrate-induced the formation of iminium **A**, the hydride acceptor that triggers hydride shift/cyclization processes under acidic conditions. The reaction was carried out by indole derivative **1** with 2-(pyrrolidin-1-yl)benzaldehydes **2** in DCE solvent and *p*-TsOH·H_2O catalyst led to the successful synthesis of a wide range of desirable target products **3** with good to excellent yields and diastereoselectivity (Scheme 1.5.14). It was interesting to note that after rapid chromatography the diastereoisomers mixed in an indistinguishable manner, could be separated by the washing with isopropyl ether and observed the dr up to a 20:1 ratio. Additionally, an enantioselective reaction using chiral BINOL-phosphoric acid was carried out under standard reaction conditions, although they observed low enantioselectivity for the corresponding compound. A plausible reaction mechanism of the hydride transfer methods has been proposed in Scheme 1.5.14.[42]



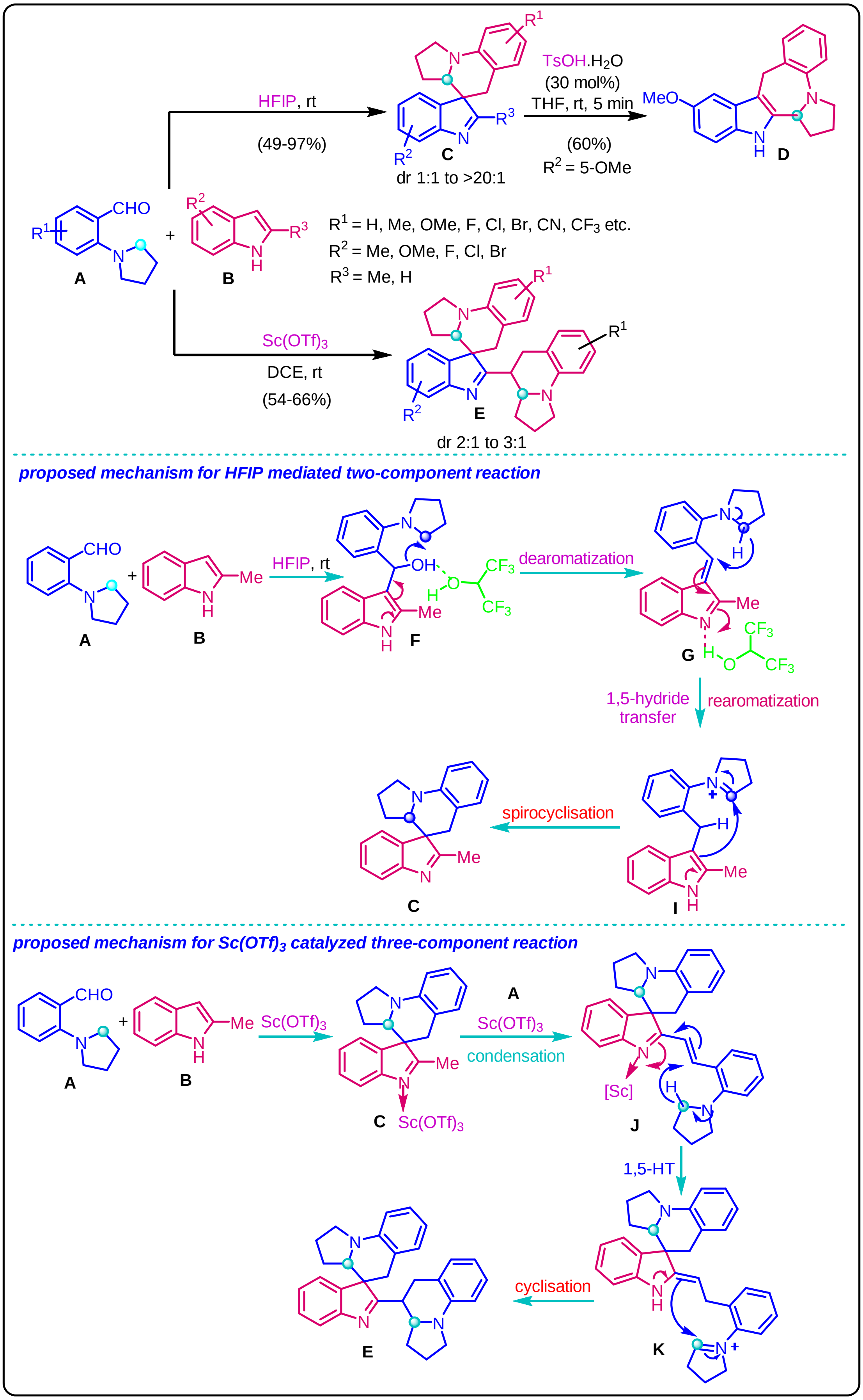
Scheme 1.5.14 Synthesis of spiro-indolenine tetrahydroquinolines

In a recent report, first regioselective dearomatization was developed by Xiao's group using 4-hydroxindole **2** or 4-hydroxycarbazole **4** and 2-aminobenzaldehydes **1** to make spiro-tetrahydroquinolines *via* hydride shift process where aromatization was the driving force (Scheme 1.5.15).[43] Several spirocyclic molecules including indoles and carbazole moieties were prepared under the catalysis of scandium complex and HFIP with moderate to high yield. During this period, this group investigated that the formic ester protecting OH group of 4-hydroxyindole displayed more effectiveness in HFIP solvent to generate spiroindolenine. Further exploration of switchable dearomatization events of the pyrrole ring and in the carbocyclic ring of indoles were conducted by reacting various 2-aminobenzaldehydes **1** with ethyl (1*H*-indol-4-yl)carbonate **6**, which resulted in spiroindolenines **7** yielding 62%–81% with excellent diastereoselectivity (>20:1 dr) (Scheme 1.5.15). Possibly, the hydroxyl group protection (**6**) moved the direction of the reaction to the electron-rich position of the indole C-3 to for the successful completion of this HT process. The switchable dearomatization of fused bicyclic aromatic compounds was enabled by this strategy.[43]



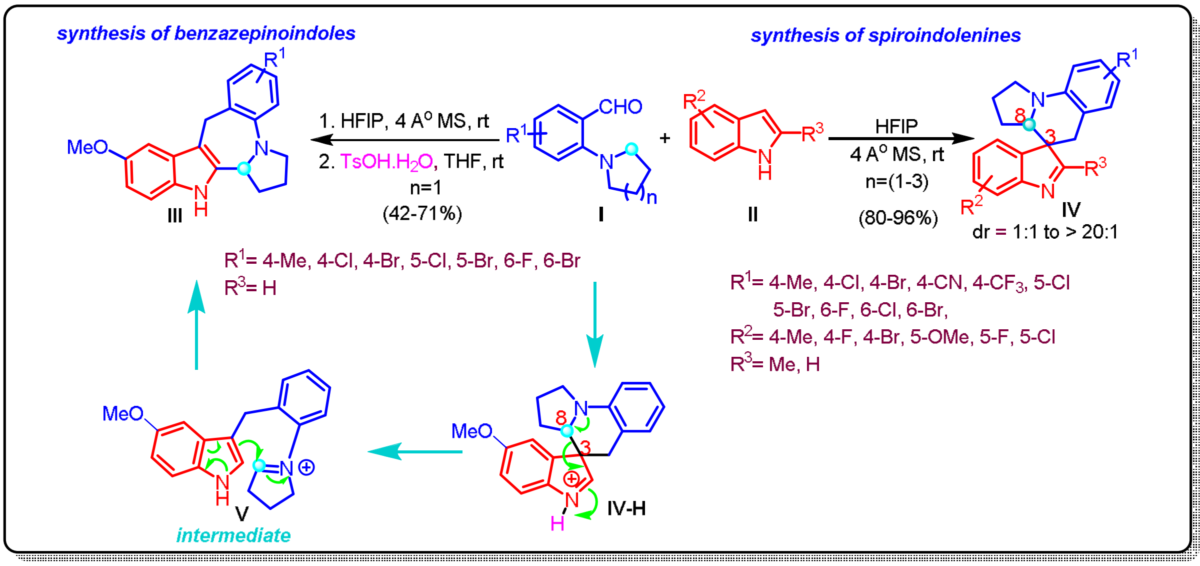
Scheme 1.5.15 Synthesis of spiro-tetrahydroquinolines through regioselective dearomatization

Similarly, spiroindolenines containing tetrahydroquinoline have been synthesized (by Shen et al., 2019) via dearomatizations of indoles using ortho-aminobenzaldehydes as a substrate driven by the rearomatization force in the hydride transfer process (Scheme 1.5.16).[44] The selection of substrate and catalyst was an important factor in this domino cascade synthetic process leading to the desired spirocyclic compounds. HFIP influenced as the reaction promoter, as well as solvent, a wide range of tetrahydroquinoline-fused spiroindolenines **C** bearing diverse functional moiety on the aromatic ring of both substrates **A** and **B** have been synthesized in a 47%–97% yield range with good to excellent (>20:1) diastereoselectivity. Furthermore, $TsOH{\cdot}H_2O$ makes the acid-catalyzed reaction, enabling the transformation of spiroindolenine to the ring-expanded derivatives **D** via 1,2-migration events. While $Sc(OTf)_3$ was employed as a catalyst in the reaction mixture in DCE solvent instead of HFIP at room temperature, tetrahydroquinoline-fused indolenines **E** were formed through the three-



Scheme 1.5.16 Divergent synthesis of tetrahydroquinoline-fused spiroindolenines.

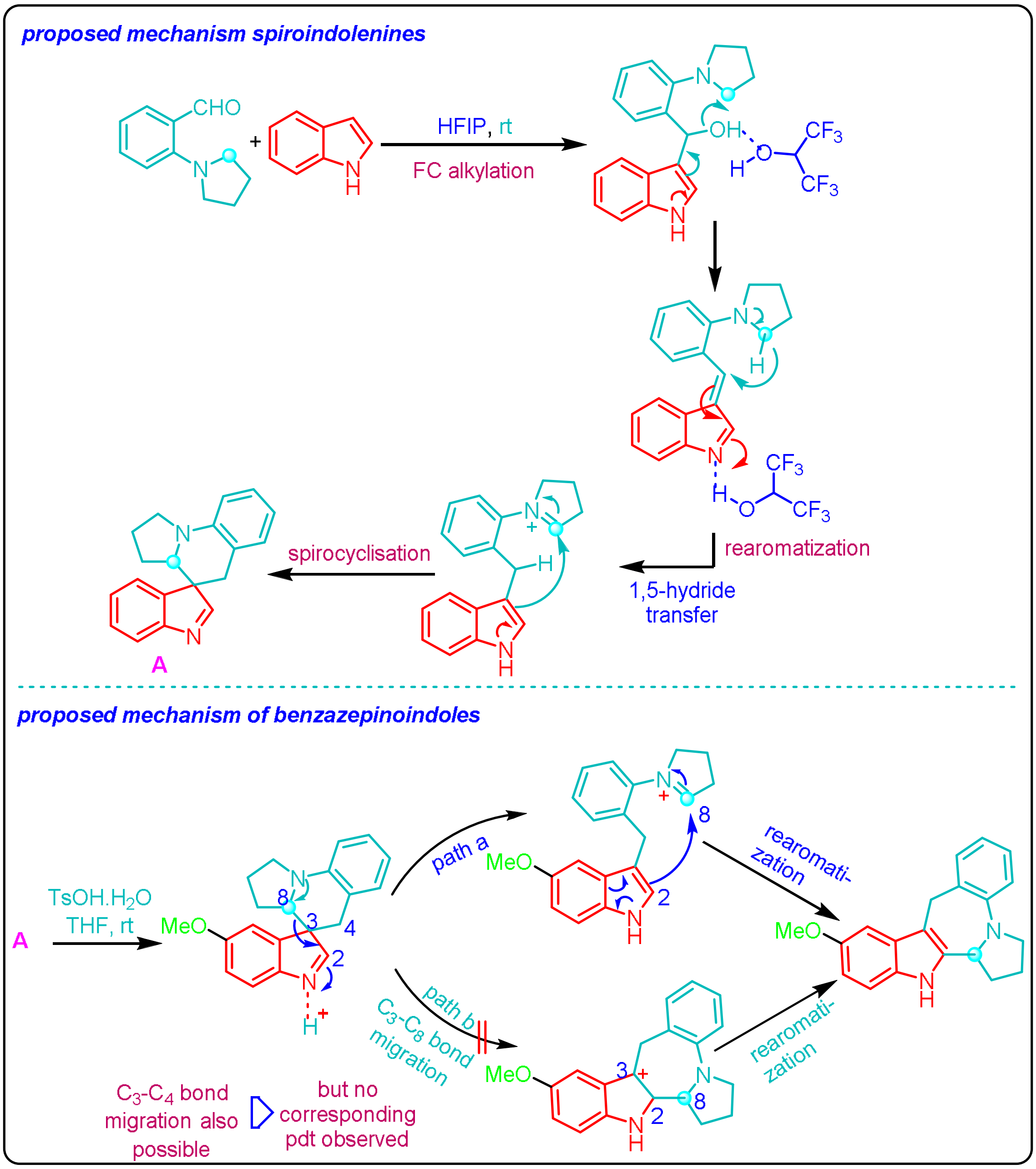
Component cascade reactions, yielding desired product in a 54%–66% range with 2:1 to 3:1 dr. The mechanism was proposed by this group described in Scheme 11.5.16 to explain the divergent synthesis of these spiroheterocycles. Product **C** was synthesized through sequential Friedel-Crafts alkylation/hydrolyzation/[1,5]- hydride shift/spirocyclization methods, which was very close to a previous Xiao's work with the help of HFIP. Substrate **E** could be synthesized, $Sc(OTf)_3$ has a significant role to generate the α,β-unsaturated indolenine intermediate **J** and hydride acceptance capability/cyclization processes delivered the desired target products **E.**[44]



Scheme 1.5.17 Synthesis of divergent product benzazepinoindoles and spiroindolenines

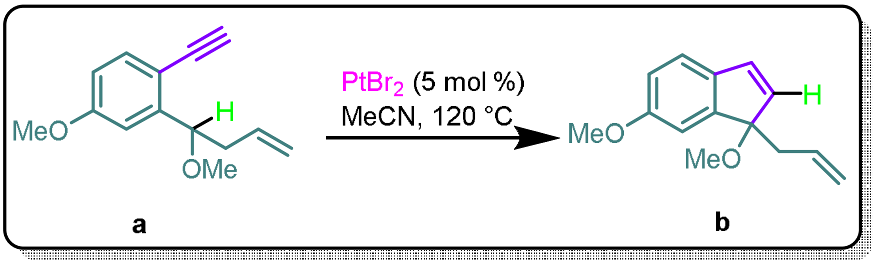
In addition to Xiao's work, a manageable and divergent synthesis of benzazepinoindoles and spiroindolenines was demonstrated by Li and Wang's research group with the help of HFIP-solvent through sequential [1,5]-hydride shift/cyclization methodology (Scheme 1.5.17)[45] (Bai et al., 2019). This controllable reaction process of the two important skeletons **III**/**IV** attributes high reaction efficiency, smooth reaction conditions, and well-functional group tolerable, yielding divergent products in high yield with excellent diastereoselectivity (in the case of **IV**). The plausible mechanism of the two divergent products **III**/**IV** was described, and the addition of $TsOH\cdot H_2O$ is significant as it is a controllable method (Scheme 1.5.17).[45] The mechanism of spiroindolenines was interesting, first Friedel Craft reaction happens followed by reactive intermediate olefin formation which is activated by HFIP-mediated H-bonding interaction and served as a hydride acceptor. Hence, dearomatization product **IV** was formed after the nucleophilic attack of the indole derivative through the C_3 position and sequential cyclization process. The mechanistic path for the synthesis of benzazepinoindoles was interesting, initially protonation of spiroindolenine insists to generate an iminium intermediate **IV-H** and afterward C_3–C_8 bond cleavage promoted by rearomatization furnishes intermediate **V**. Hence, the seven-membered fused thermodynamic benzazepinoindole (**III**) was formed through a nucleophilic attack of the C_2 position in the indole ring. There is another possible migration approach by which two different seven-membered products should be formed. However, they observed only one product (**III**) in the $TsOH{\cdot}H_2O$ mediated reaction medium, which disposes of migration approaches.

The plausible mechanism of the formation of benzazepinoindoles and spiroindolenines was elaborately discussed in Scheme 1.5.18.[45]



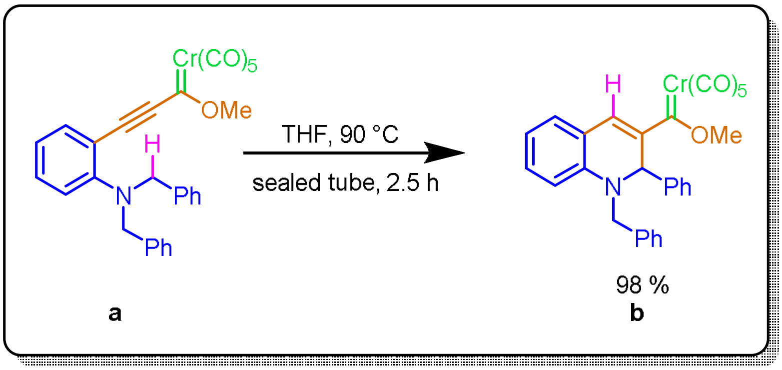
Scheme 1.5.18 Controllable syntheses of spiroindolenines and benzazepinoindoles

Alkynes hydride acceptors: In the year 2006, Yamamoto and his group [46] demonstrated first the alkynes-mediated hydride shift transformation to a carbocycle. They first reported as alkyne was a good hydride acceptance capability in this condition. They disclosed the formation of indene derivatives **b** from *O*-alkylphenyl acetylenes **a** by using $PtBr_2$ as a catalyst in MeCN (Scheme 1.5.19). [46]



Scheme 1.5.19 Alkyne as hydride acceptor

In 2008, Barluenga's research group gave importance to this type of reaction by alkyne acceptors with diverse amine hydride donors. Electrophilic alkynyl Fischer carbine **a** underwent a 1,5-hydride shift reaction in thermal conditions to generate 1,2-dihydroquinolinyl carbine **b** (Scheme 1.5.20) *via* zwitterionic intermediate. [47]

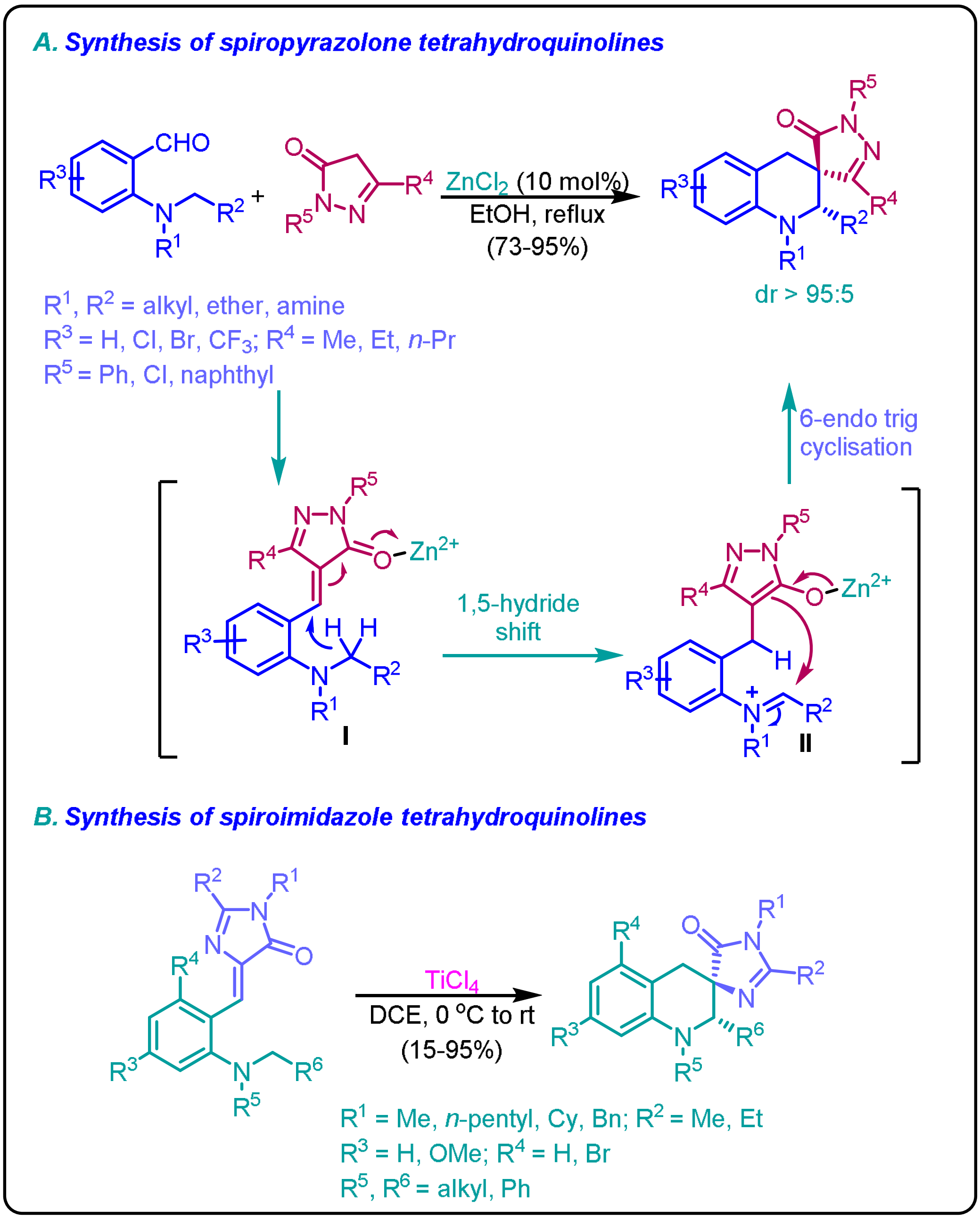


Scheme 1.5.20 Example for alkynyl Fischer carbene as a hydride acceptor

1.5.1 Development of Pyrazolone and Imidazole Unit Containing Spiro-Tetrahydroquinoline Skeleton

Pyrazolone molecules are broadly used in pharmaceutical drugs, hence this bioactive scaffold intriguing into a spiro-tetrahydroquinoline skeleton through a [1,5]-HT/ cyclization method could be a novel approach for the creation of new series of significant heterocycles or drugs. In 2015, Wang's group reported a $ZnCl_2$-catalyzed reaction methodology to synthesize a range of pyrazolone-fused spiroterahydroquinolines via cascade [1,5]-hydride shift/

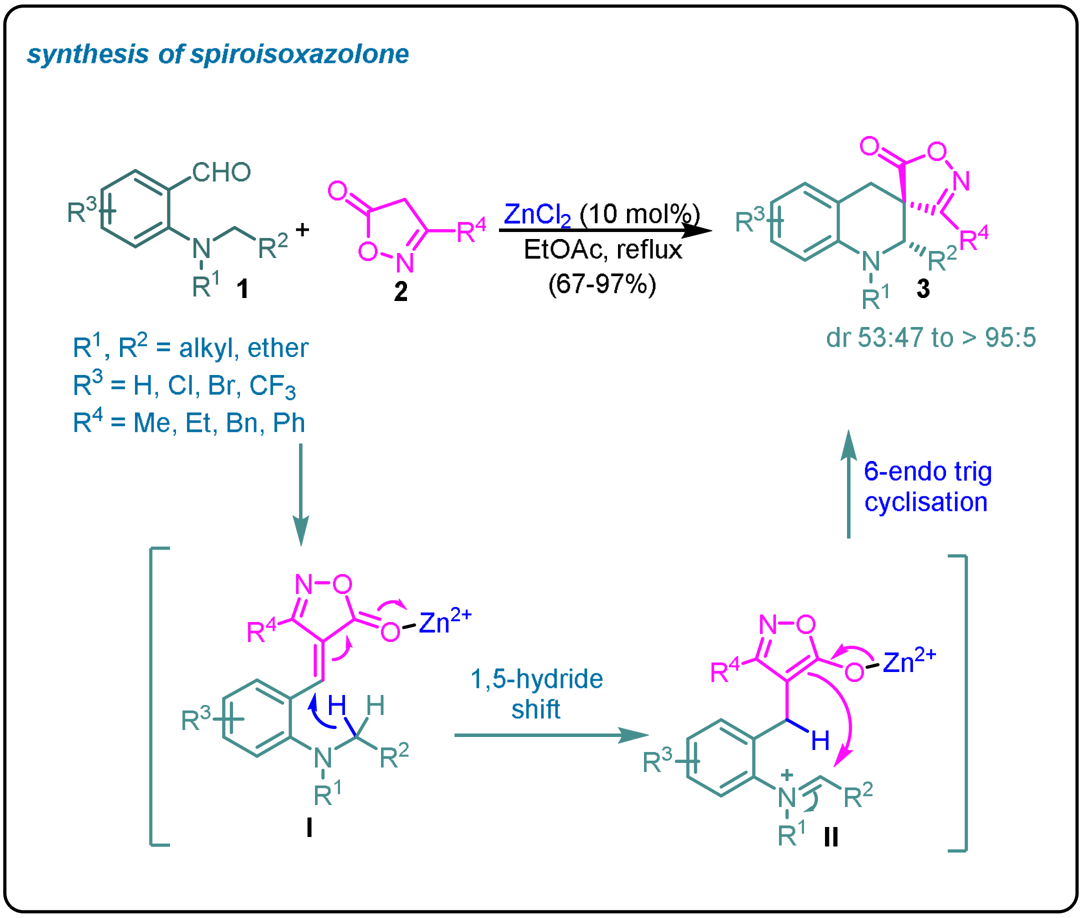
cyclization sequence (Scheme 1.5.21A).[48a] In situ formation the α,β-unsaturated pyrazolone intermediate **I** exhibited a good hydride acceptance capability for 1,5-hydride shift/cyclization sequence and this methodology revealed the wide scope of substrates, with high yields (up to 95% yield) and good to excellent diastereoselectivities (up to >95:5 dr). The mechanism they proposed for the development of pyrazolone containing spiro-tetrahydroquinoline is depicted in Scheme 1.5.21A. In the year 2021, Smirnov's group developed $TiCl_4$ catalyzed an intramolecular cascade [1,5]-hydride shift/cyclization reaction to construct diverse imidazole containing spirocyclic tetrahydroquinoline derivatives. *α,β*-Unsaturated imidazole intermediate was the precursor of spiroheterocycle that triggered the hydride shift process (Scheme 1.5.21B).[48b] This reaction was well functional group tolerable in mild reaction conditions, producing the desirable spiroheterocycle with 25%–95% yield. Furthermore, the gram-scale reaction yielded well (93%) proves that the methodology was good, and it creates a new way for potential research of antibacterial activity of those bioactive molecules.[48b]



Scheme 1.5.21 Concise synthesis of Spiro-pyrazolone (A) and imidazole tetrahydroquinoline

1.5.2 Synthesis of Isoxazolone Unit Containing Spiro-Tetrahydroquinolines through Cascade Hydride Shift Methodology:

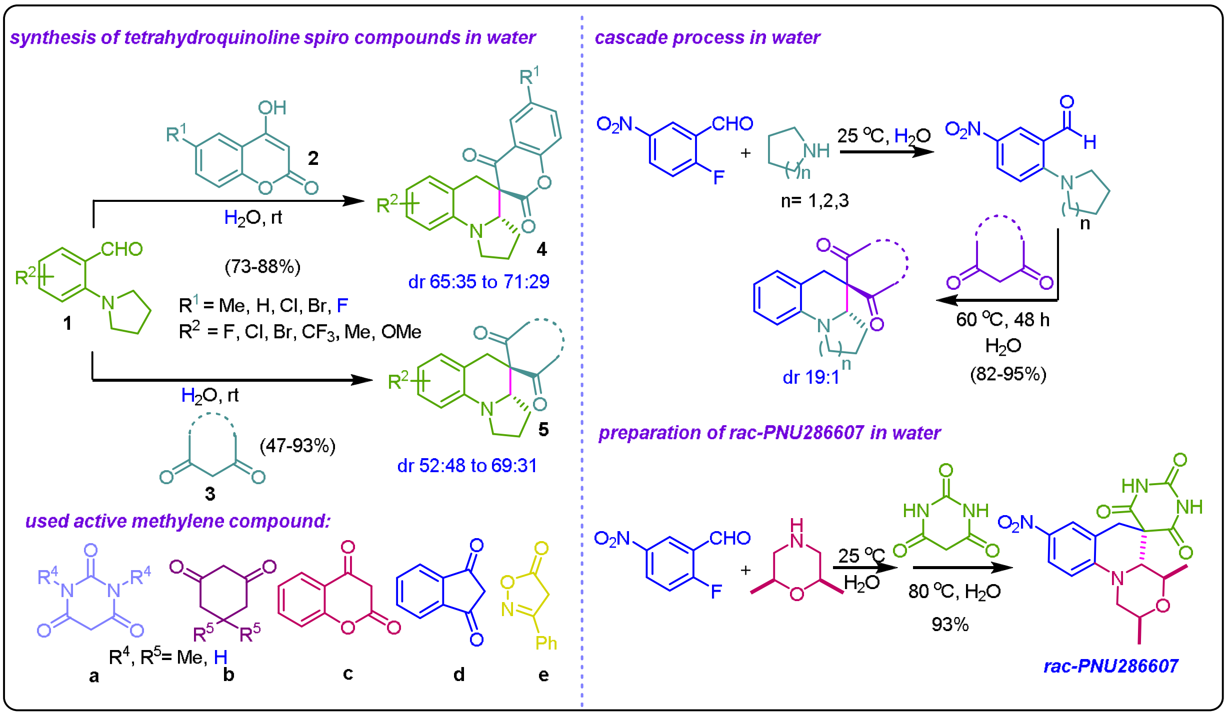
Isoxazol-5-one and tetrahydroquinoline are good heterocyclic pharmacophores available in a wide range of medicines and bioactive natural products. Hence, attaching these two scaffolds through synthetic methods to novel spirocyclic molecules could be an attractive avenue for the generation of several bioactive drugs. In the year 2013, the Yuan group discovered $Sc(OTf)_3$ catalyzed an intramolecular 1,5-hydride transfer/cyclization reaction to build up isoxazolone containing spirotetrahydroquinolines and 3-amino-3-carboxytetrahydroquinoline derivatives. After three years, in 2016, Wang's group modified this reaction and reported a $ZnCl_2$-catalyzed cascade Knoevenagel condensation/[1,5]-HT /cyclization reaction to construct a variety of novel spiroisoxazol-5-onetetrahydroquinolines (Scheme 1.5.22).[49] These methods demonstrate that initially the condensation of 2-(pyrrolidin-1-yl)benzaldehyde **1** and 3-methylisoxazol-5(4*H*)-one **2** produces the reactive intermediate **I**, which encounter of a subsequent [1,5]-HT /cyclization process smoothly to construct desired product **3**. Notably this reaction featured a broad substrate scope in mild reaction conditions, featuring the desired spirocyclic products **3** up to 97% yield and with >95:5 dr, which signifies the efficacy of this strategy.[49]



Scheme 1.5.22 Synthesis of novel spiroisoxazol-5-one containing tetrahydroquinolines

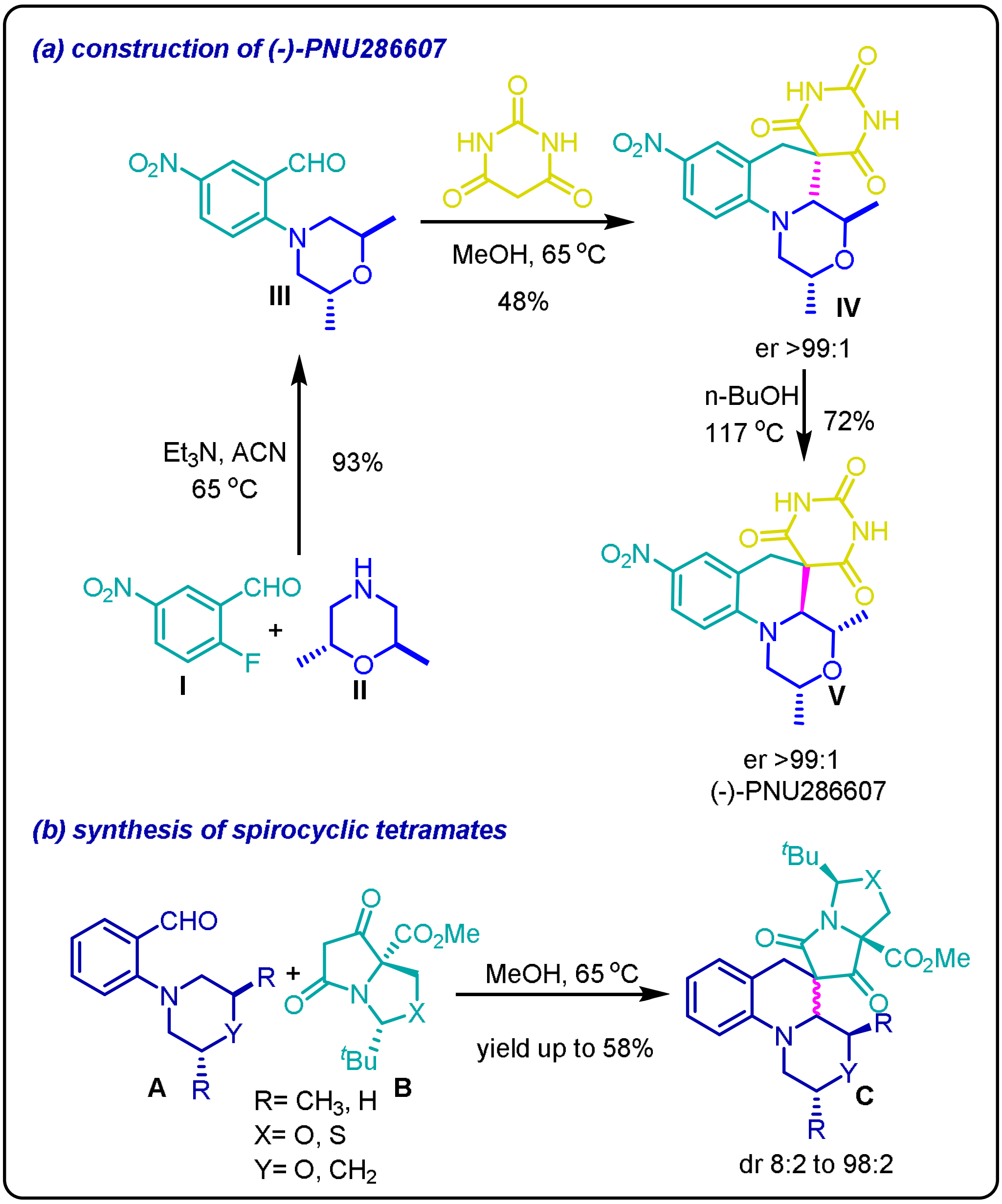
1.5.3 Development of Coumarin Unit Containing Spiro-Tetrahydroquinoline Skeleton:

In the year 2017, Xiao's and his coworker developed a green reaction method which is operationally very simple. They performed a water catalysis reaction to assemble novel spiro-tetrahydroquinoline compounds through a sequential domino SN_{Ar}/Knoevenagel condensation/[1,5]-HT/cyclization reaction (Scheme 1.5.23).[50] Compared with the previous work, this methodology signifies the advancement of the cascade C(sp^3)–H functionalization sequence mediated on the water under mild conditions. Activated olefin could be accessed through the Knoevenagel condensation reaction of 2-aminobenzaldehydes **1** with 1,3-dicarbonyl **2** compounds, which is the precursor of coumarin containing novel spiroheteroycle. Various substrates containing different functional groups were compatible and produced the desired product **4**/**5** in an atom and step economic way with good yield and dr. Notably the fruitful conversion of (−)-PNU-286607, a significant anti-bacterial agent, was conducted very smoothly obtaining 93% of yield which further revealed the importance of methodology.[50]



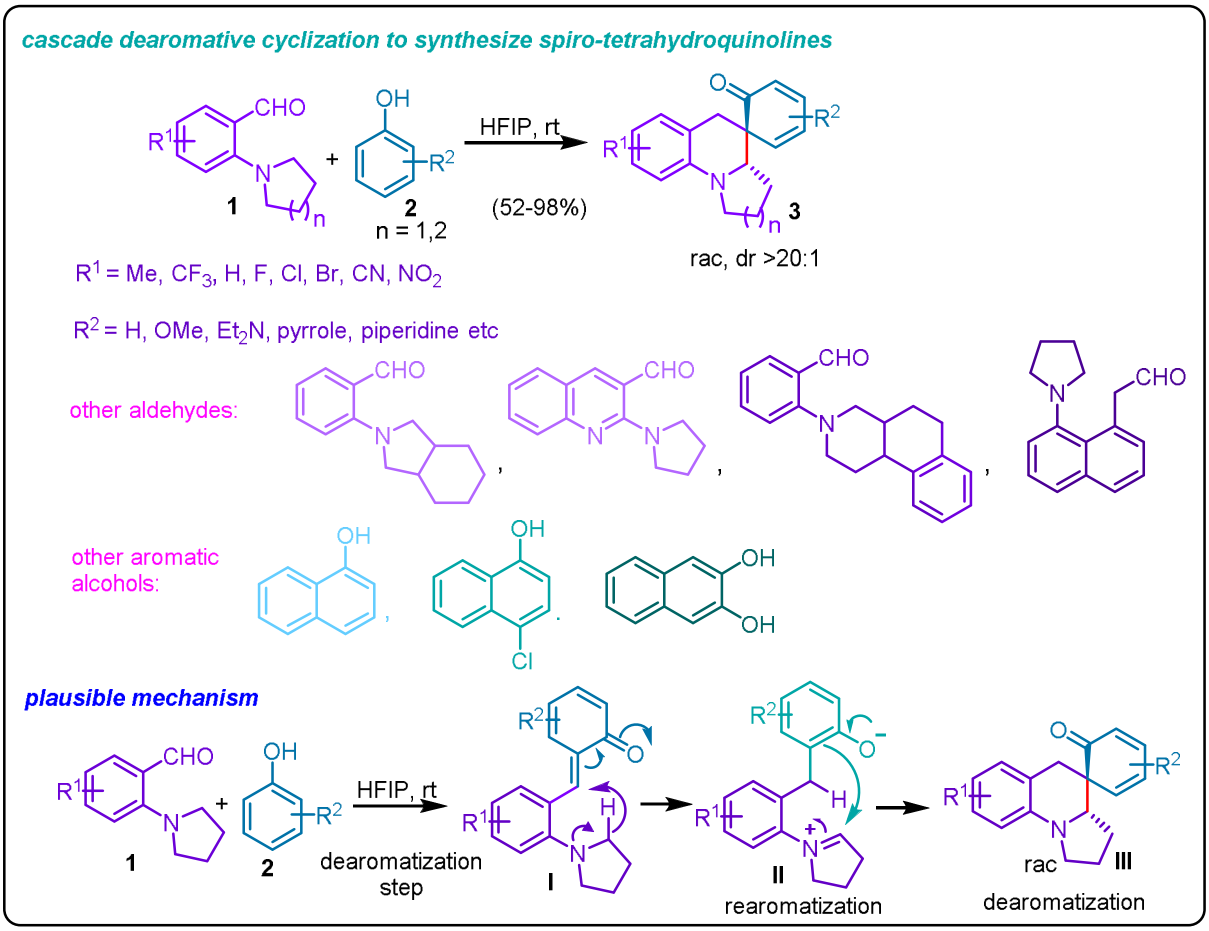
Scheme 1.5.23 The water-mediated reaction methods to synthesize various spiro-tetrahydroquinolines

In 2009 Kamilar group demonstrated an asymmetric synthesis of the (-)-PNU-286607, a practical two-step route promising spirocyclic tetrahydroquinoline compound bearing barbituric acid moiety (Scheme 1.5.24a).[51a] Utilizing chiral trans-dimethylmorpholine **II** in MeCN solvent at 65°C temperature desirable chiral amino substituted aldehyde **III** would be produced primarily. Then it was subjected to olefination/1,5-HT reactions and spiroheterocycle **IV** had been formed with excellent stereochemical control. Notably, spiroheterocycle **IV** isomerizes to the desired **V** in n-BuOH solvent at high temperature with an excellent enantiomeric excess (Scheme 1.5.24a). [51a] Inspired by Kamilar's work, Moloney's group devise a plan where tetramates **B** has been used with aminobenzaldehydes **A** to furnish the functionalized spirocyclic tetramates **C** (Scheme 1.5.24b).[51b] The α,β-unsaturated 1,3-dicarbonyl intermediate species have been formed in situ very easily and this activated olefin converted to a good hydride acceptor. Depending on the solvent the stability of the desired product varies with the reactivity azacycle, and obtained low to good yields with up to 98:2 dr.[51b]



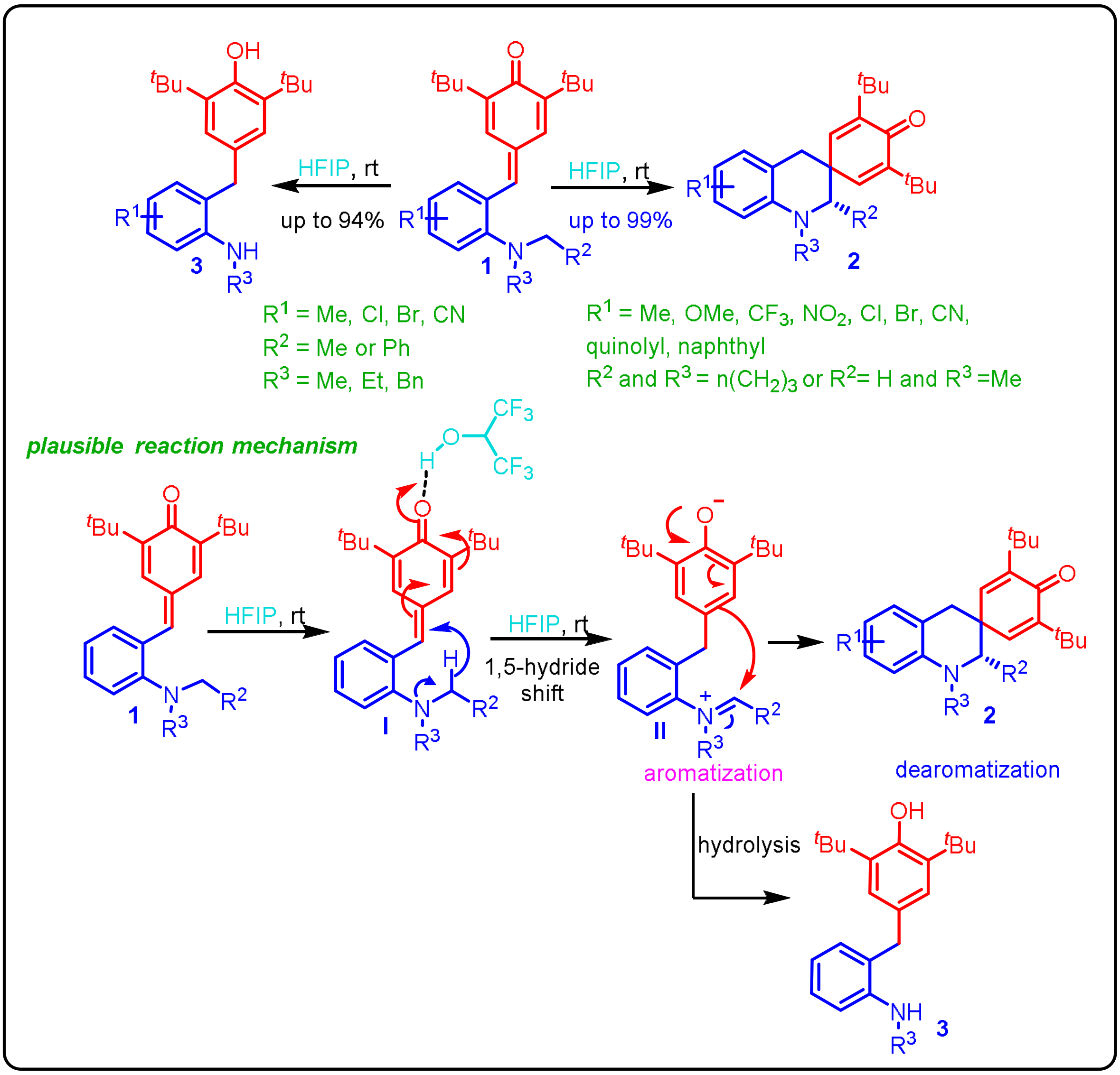
Scheme 1.5.24 synthesis of (-)-PNU-286607 and spirocyclic tetramates.

One year later, Xiao and his co-worker demonstrated an expeditious route to synthesize different polycyclic derivatives in one step from phenols **2** and orthoaminobenzaldehydes **1** through the domino [1,5]-HT/dearomative cyclizations (Scheme 1.5.25).[52] This is very challenging because dearomatization takes place. HFIP behaves as the reaction promoter as well as solvent, hence, one- step construction of spirotetrahydroquinolines happened smoothly furnishing a good yield (up to 98%) and high diastereoselectivities (up to >20:1). The reaction methods were good functional group tolerable and gram-scale capable. This was an unprecedented strategy where aromatization is the driving force to initiate the hydride shift process followed by dearomative cyclization. Undoubtedly, this novel method pretends a new way to assemble diverse biologically active units based on the conventional cascade hydride shift/cyclization method. The mechanism has been proposed by this group where rearomatization/dearomatization processes have occurred in this system (Scheme 1.5.25).[52]



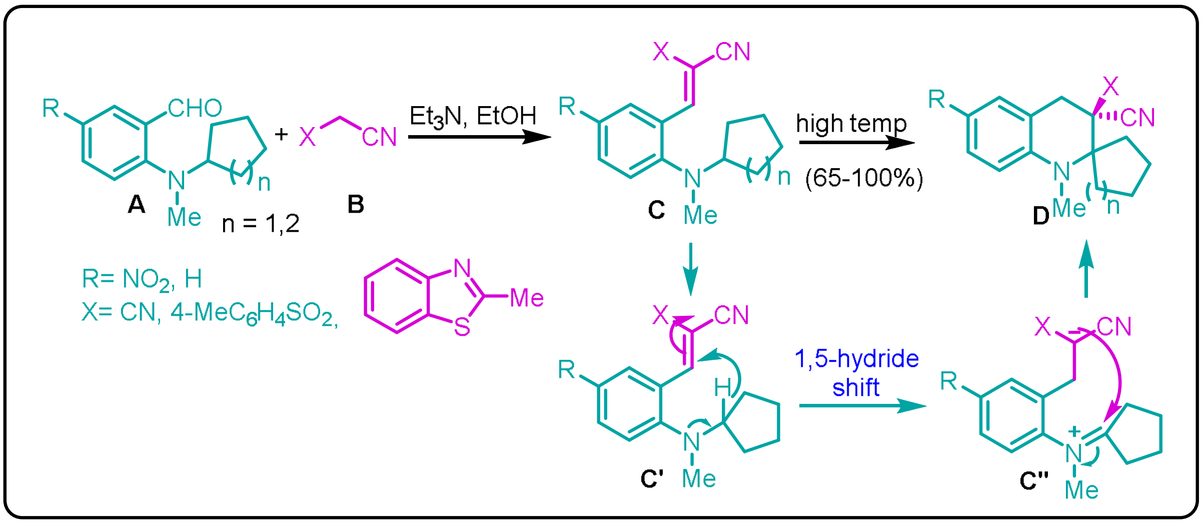
Scheme 1.5.25 Spiroheterocycle synthesis direct from aromatic alcohol through cascade dearomative cyclization

Based on the previous work, in 2019, the same group demonstrated HFIP mediated [1,5]-hydride shift/spirocyclization strategy of their designed substrate *p*-quinone methides(QMs) (Scheme 1.5.26).[53] In a straightforward way they synthesized spiroheterocycles **2** with moderate to excellent yields (52%–99%) at room temperature, additive-free mild reaction condition (Scheme 1.5.26).[53] Gratifyingly ortho-benzylated anilines **3** were obtained with good yields at the time of uses of several acyclic amines such as *N*-methyl-*N*′-benzyl, *N*,*N*′-dibenzyl, and *N*,*N*′-diethyl amines. The proposed path has been described here where HFIP activated olefin **I** which triggered the HT process leading to the rearomatic complex **II** which has two ways to neutralize. One is dearomatization and another is the hydrolysis path which produces compounds **2** and **3** respectively. Henceforth, Xiao's group revealed that aromatization could trigger the 1,5-hydride shift events followed by the dearomative cascade spirocyclization process to construct architecturally complex diverse spiroheterocycles. [53]



Scheme 1.2.26 Aromatization-driven hydride transfer process to synthesize spiroheterocycles

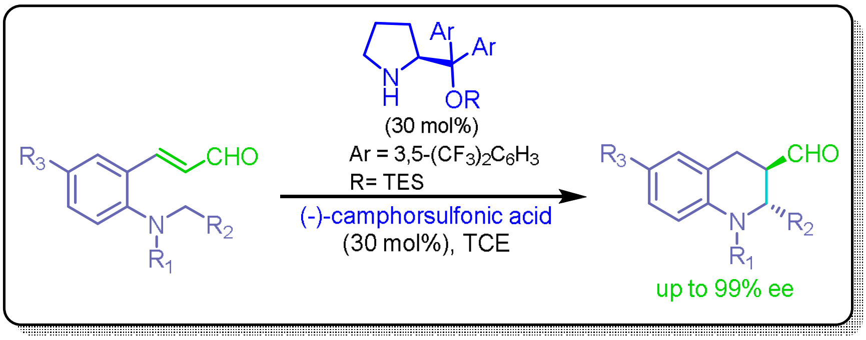
Additionally, in all works listed above, this domino cascade HT strategy demonstrated a cycloalkane unit containing spirocyclic tetrahydroquinolines through the in situ formation of activated olefin substrate. In the year 2006, Tverdokhlebov's research group reported a one-pot reaction of ortho-aminobenzaldehydes **A** with substituted acetonitriles **B** catalyzed by Et_3N in ethanol solvent at high temperature to produce tetrahydroquinoline-2-spirocycloalkanes **D** with high yields (Scheme 1.5.27). [54] The reaction path proceeded via sequential Knoevenagel condensation of the corresponding two substrates /[1,5]-hydrogen shift (due to *tert* amino effect)/6-endo ring closure process. These methods developed a good way to furnish several spiro alkane heterocycles. [54]



Scheme 1.5.27 The construction of tetrahydroquinoline-2-spirocycloalkanes

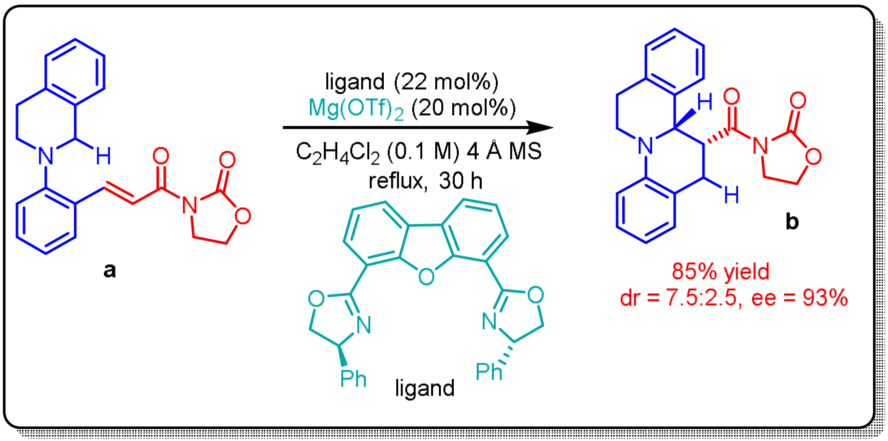
1.5.4 Asymmetric Hydride Shift Reactions

The development of methodology for the synthesis of chiral heterocycles is an attractive research area in organic chemistry. Enantioselective C–H bond functionalization *via* hydride shift reaction has taken much interest in the field of asymmetric synthesis. Few examples of an enantioselective version of hydride shift reactions are known in literature: Kim and his research group revealed the first organo-catalytic enantioselective 1,5-hydride transfer and subsequent ring closure to synthesize ring fused tetrahydroquinoline derivatives (Scheme 1.5.4.1). [55]



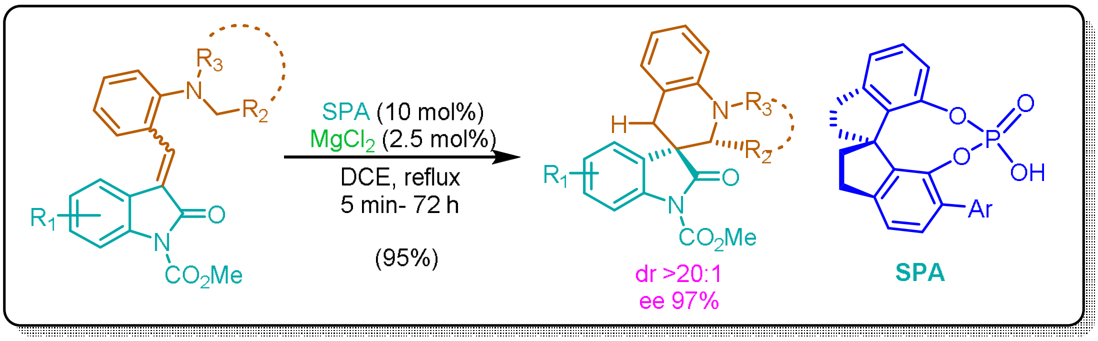
Scheme 1.5.4.1 Example of the enantioselective hydride shift reaction

In 2009, Seidel *et al.* [56] published their work in a high-impact journal where they were enabled to achieve catalytic enantioselective C–H functionalization successfully through the intramolecular hydride shift and cyclization sequence. Chiral magnesium (II) DBFox mediated enantioselective operation applied on oxazolidinone molecule **a** in DCE solvent under thermal conditions. Desired heterocycle **b** was obtained with good yield and excellent enantioselectivity (Scheme 1.5.4.2). [56]



Scheme 1.5.4.2 Enantioselective hydride shift reaction

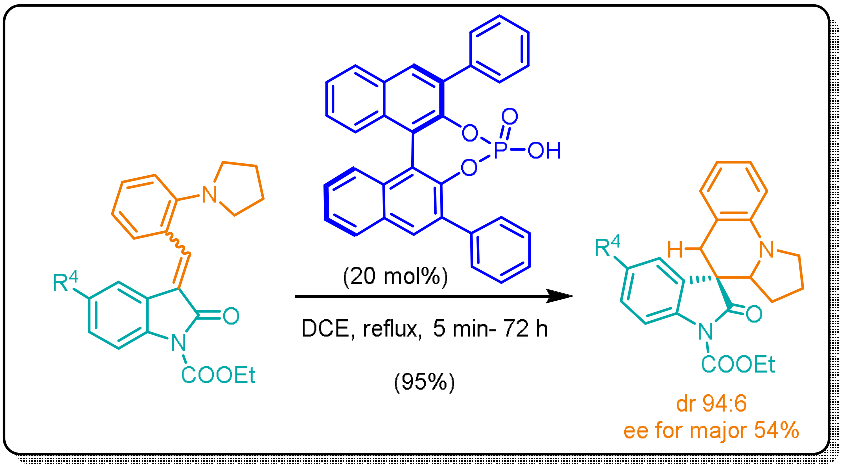
The importance of diversity in structure is remarkable in the pharmaceutical and medicinal field and it is constructed by organic synthetic chemists. Here a wide variety of spirooxindole tetrahydroquinolines were synthesized in excellent yield with high diastereo- and enantio-selectivity, where chiral spirocyclic phosphoric acid and magnesium chloride combination was used as catalyst, to undergo asymmetric intramolecular tandem 1,5-hydride transfer reaction (Scheme 1.5.4.3). [57]



Scheme 1.5.4.3 Enantioselective hydride shift reaction

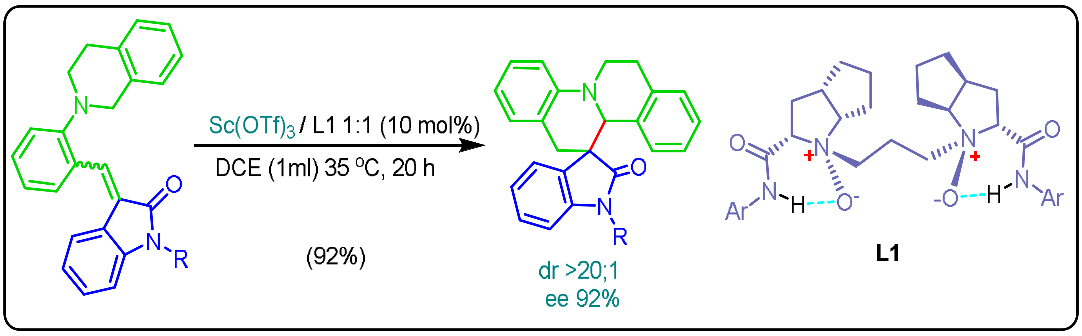
Han *et al.* reported a systematic $FeCl_3$ Lewis acid catalyzed stereo-selective intramolecular cascade 1,5-HT reaction to construct spiro-oxindole tetrahydroquinolines (Scheme 1.5.4.4). [58]

In DCE solvent at reflux condition they introduced Binolphosphoric acid to access enantiomeric excess product.



Scheme 1.5.4.4 Enantioselective hydride shift reaction

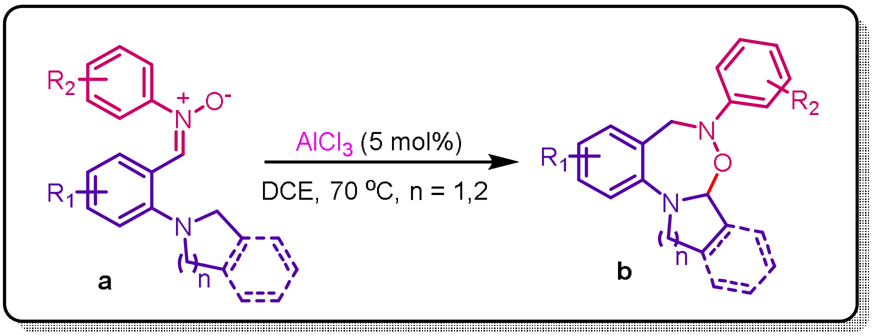
Quaternary or tertiary stereogenic carbon centers containing optically active spiro-oxindole tetrahydroquinolines were synthesized *via* immediate functionalization of C(sp^3) –H bond through 1,5-HT reaction. This method employing the scandium complex of *N*, *N′*- dioxides results in excellent diastereoselectivity and enantioselectivity (Scheme 1.5.4.5). [59]



Scheme 1.5.4.5 Enantioselective hydride shift reaction

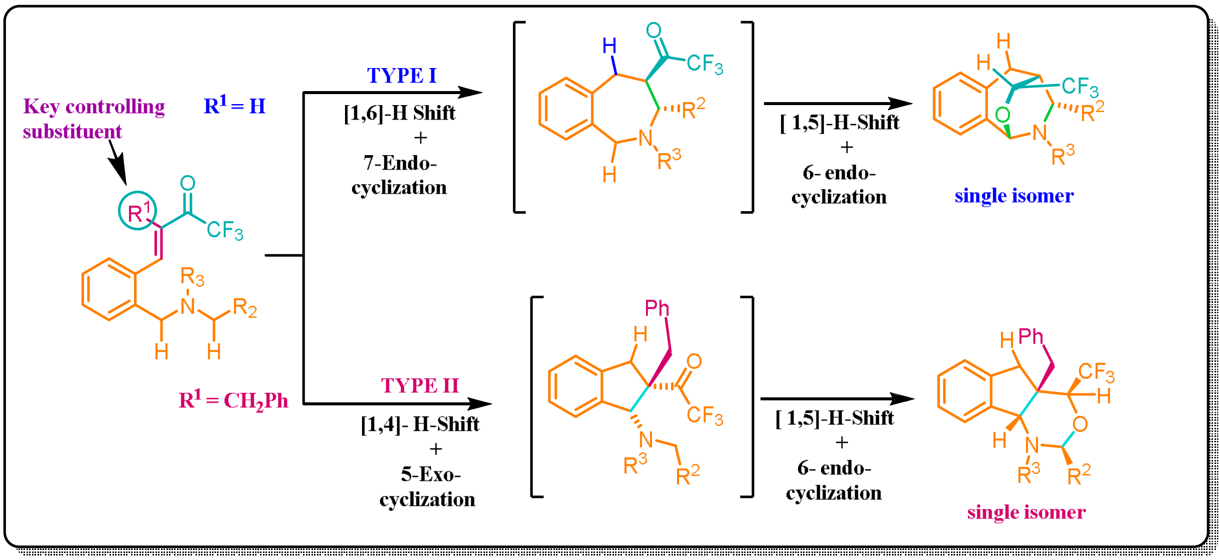
1.5.5 Miscellaneous Hydride Shift Reactions

Various pyrrolidine or tetrahydroisoquinoline-containing oxadiazepine derivatives can be synthesized by 1,5-hydride-shift/cyclization of nitrones, where 1,3-dipole of nitrone is serving as hydride acceptors. [60] When pyrrolidine or tetrahydroisoquinoline containing nitrones **a** were heated with $AlCl_3$ in DCE at 70 °C, it undergoes cyclization to form various substituted ozadiazepines **b** (Scheme 1.5.5.1) in excellent yield.



Scheme 1.5.5.1 Different acceptor for hydride shift reaction

Mori and co-workers [61] reported one-after-one C(sp^3)–H bond functionalization influenced by sequential hydride transfer reactions in one pot. The electrophilic moiety of the substrate regulates the reaction course which is 1,4 or 1,6- hydride shift reaction (Scheme 1.5.5.2).[61]



Scheme 1.5.5.2 Selectivity in hydride shift reaction

1.6 Conclusion

We have presented a series of spiroheterocycles constructed via Lewis acid-free or catalyzed [1,5]-hydride shift/6-endo cyclization sequences from various substituted aldehyde or olefin. The synthetically efficacious ring-fused spiro heterocycle derivatives were achieved in moderate to high yield with dr. This straightforward internal redox process has a unique feature with respect to their hydride donors and acceptors' skeletons. This research field still faces several challenges despite significant improvements in the last decades, such as diversity of substrate scope, complex reaction conditions, reactivity issues, and large-scale synthesis difficulties. Indeed, advancement of the methodology permitting the variation of the substrates for this diastereoselective/enantioselective reaction where unreactive benzylic/non-benzylic C(sp^3)–H bonds have hydride donor capability and activated alkenes/alkynes/1,3-dipole compounds behave as hydride acceptors, is highly challenging work. Our recent research investigation deals with the efficient development of molecular complexity towards novel spiro heterocycles and their biological applicability based on internal cascade redox reactions. In continuation of our research interest in C–H bond functionalization *via* Lewis acid or Lewis acid-free catalyzed reaction, we would like to pursue the same soon also. Our main goal will be to develop newer methodologies for the construction of potent biologically active heterocycles as well as their modification. Apart from those the scope of other medicinally relevant heterocyclic moieties will also be tested. We are focusing on that reaction to get good enantiomeric excess using various chiral organocatalysts. The goal is an asymmetric version of our hydride shift reaction through organocatalyst.

1.7 References

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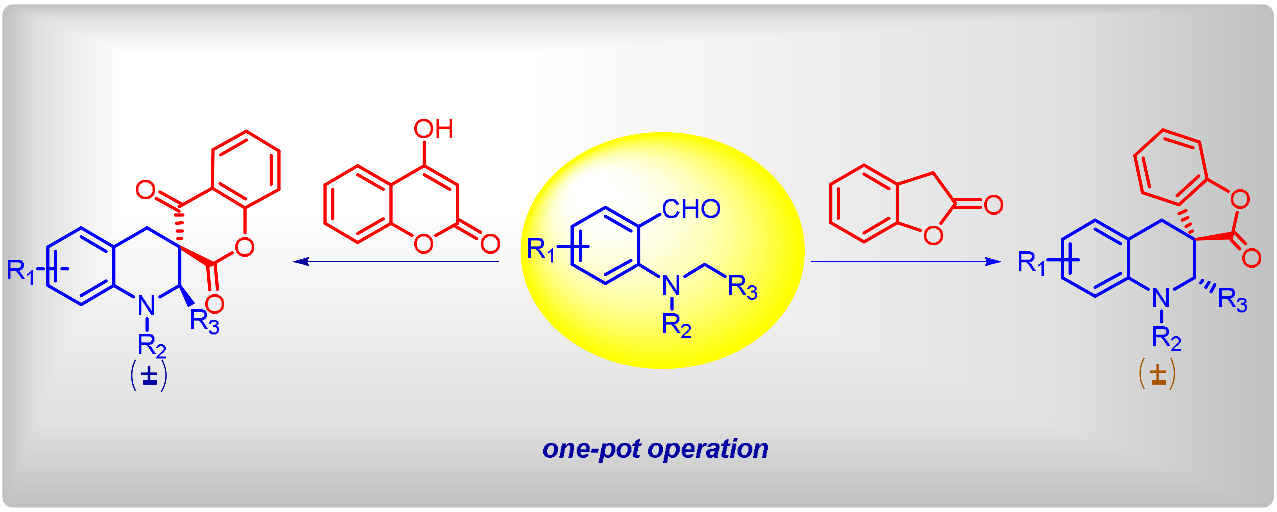
Chapter 2: **Lewis Acid Free Intramolecular C(sp^3)–H Bond Functionalization**

Lewis Acid Free Intramolecular C(sp^3)–H Bond Functionalization Triggered by Consecutive [1,5]-Hydride Shift /Cyclization Process: Approach for Diastereoselective Construction of Novel Spiroheterocycles



2.1 Introduction

2.1.1 Benzofuran-2-one/ 2-Coumaranone

In recent years heterocyclic compounds have acquired more attention because of their wide range of applications. The 2-Coumaranone nucleus which consists of a benzofuran core, is one of the most significant heterocyclic structural units present in several natural products and synthetic drug molecules, now a topic of research by synthetic and medicinal chemists. Nowadays the 2-Coumaranone scaffold (Figure 2.1.1.1) is a center of attraction for its broad spectrum biological activity and its huge space of applicability as a synthetic tool in the area of drug design and synthesis of various bioactive molecules.[1]

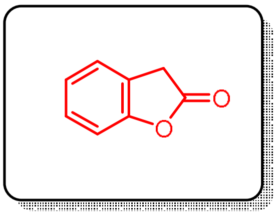


Figure 2.1.1.1 2-Coumaranone

2-Coumaranone scaffold is widely found in natural and synthetic compounds. Important 2-Coumaranone containing natural and synthetic bioactive compounds is discussed below.

2.1.1.1 Isolation of Eremophilanes

Based on the study of *Psacalium radulifolium* roots, a member of the matarique complex of medicinal plants involving several members of the Asteraceae family, four new modified eremophilanes, including radulifolin B, were isolated from the roots. In addition, several other members such as cacalol, *epi*-cacalone, cacalone, adenostin A, O-methyl-1,2-dehydrocacalol, neoadenostylone, and decomposition have been extracted from the same source.[2] Calaol was identified as the major active compound in the extracts and isolated compounds after antimicrobial tests.

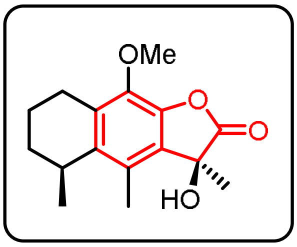


Figure 2.1.1.1.1 Radulifolin B

2.1.1.2 Analgesic/Antidepressants: (3-Aryl-2,3-dihydrobenzofuran-3-yl)alkanamines

Several (3-aryl-2,3-dihydrobenzofuran-3-yl)alkanamines have been synthesized from 2-coumaranone, a significantly designed molecule used as a potential antidepressant agent with analgesic properties, were pharmacologically evaluated (Figure 2.1.1.2.1).[3]

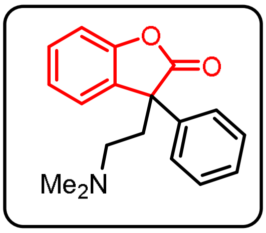
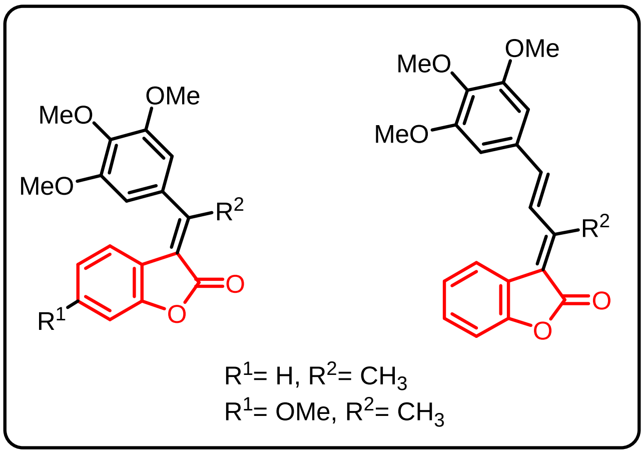


Figure 2.1.1.2.1 (3-Aryl-2,3-dihydrobenzofuran-3-yl)alkanamine

2.1.1.3 CA4 Analogs as Human Tumor Cell Inhibitor

Utilizing Domino Heck–Suzuki–Miyaura coupling method a series fused lactam or lactone ring assembled trimethoxyphenyl or the B-phenyl derivative has been synthesized in an efficient and stereoselective manner i.e., combretastatin A4 (CA4) analogs (Figure 2.1.1.3.1). The vascular-disrupting potential of these CA4 analogs that were conformationally restricted was assessed by various in vitro assays: tubulin polymerization inhibition process, a new developing method of disruption of endothelial cords, and morphology of endothelial cells. These analogs have displayed good growth inhibitory effects against human tumors and murine cells. An oxindole scaffold present in B-ring-constrained derivatives (in contrast to compounds specifically with a benzofuranone ring), in another way a trimethoxyphenyl analogs fused with six-membered lactone core were conferred with good biological properties.[4]



R^1= H, R^2= CH_3
R^1= OMe, R^2= CH_3

Figure 2.1.1.3.1 CA4 analogues

2.1.1.4 Commiphoranes C−D Terpenoids and Its Activity

Commiphoranes C−D are two novel aromatic terpenoids structurally consisting of three fused rings, extracted from Resina Commiphora.[5] In contrast, compounds C and D are sesquiterpenoids assembling with a 5/6/7 cyclic carbon skeleton. A biological analysis suggests that C significantly attenuates the overproduction of collagen I, fibronectin, and α-SMA in TGF-β1-induced rat renal proximal tubular cells. With this, antifibrotic activities of commiphoranes C and D were introduced in TGF-β1- induced renal proximal tubular cells of rat/mice. Overproduction of collagen I and that α-SMA was reduced effectively by C because of its good reactivity. The mechanism action of C was further determined after the consideration of the TGF-β1/Smads central mediators fibrosis pathway. It was notable that effects of C were embodied through a non-Smad pathway as it does not affect phosphorylation of Smad 2/3.[5]

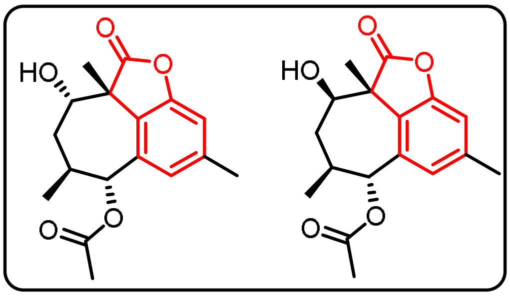


Figure 2.1.1.4.1 Commiphoranes C and D

2.1.1.5 Other Bioactive 2-Coumaranone Derivatives

2-Coumaranone containing scaffolds have drawn much attention since aeon due to their presence in many biologically relevant molecules such as naturally occurring isoaurones, isoaurostatin, marginalin, pterocarposide radulifolin-B, pteroisoauride, commiphoranes, rosmadial an orally active antimycotic drug (Figure 2.1.1.5.1). Various spirocyclic 2-coumaranones, isoaurones derivatives are well-known pharmaceutically important compounds and natural products to exhibit excellent activity against different biological targets.[6]

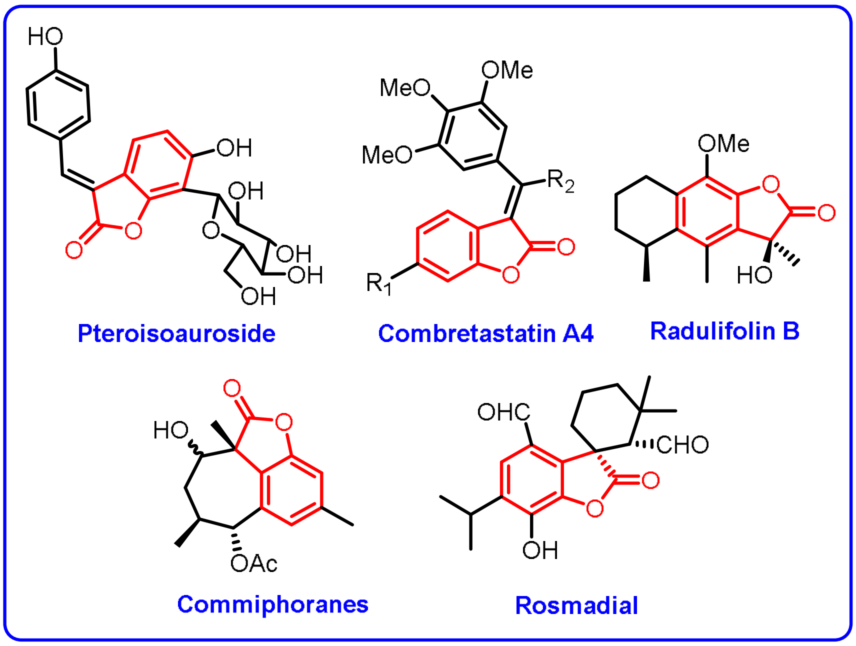


Figure 2.1.1.5.1 Representative examples of bioactive molecules

Radulifolin B (**a**) shows antimicrobial properties and various combretastatin A4 (CA4) analogues (**b** and **e**) are used as the treatment of tumor cell inhibitors (Figure 2.1.1.5.2). This analogue has been synthesized through the Knoevenagel reaction condition, where 2-coumaranone was treated with pyrogalolaldehyde/ester/keto derivatives. Commiphoranes C−D (**d** and **c**) are two novel aromatic terpenoids with 5/6/7 fused carbon skeletons, isolated from Resina Commiphora. Its usefulness we discussed previously. C_3-alkyl amine-derivatives of 2-coumaranone (**f**) have been used as an antidepressant agent.

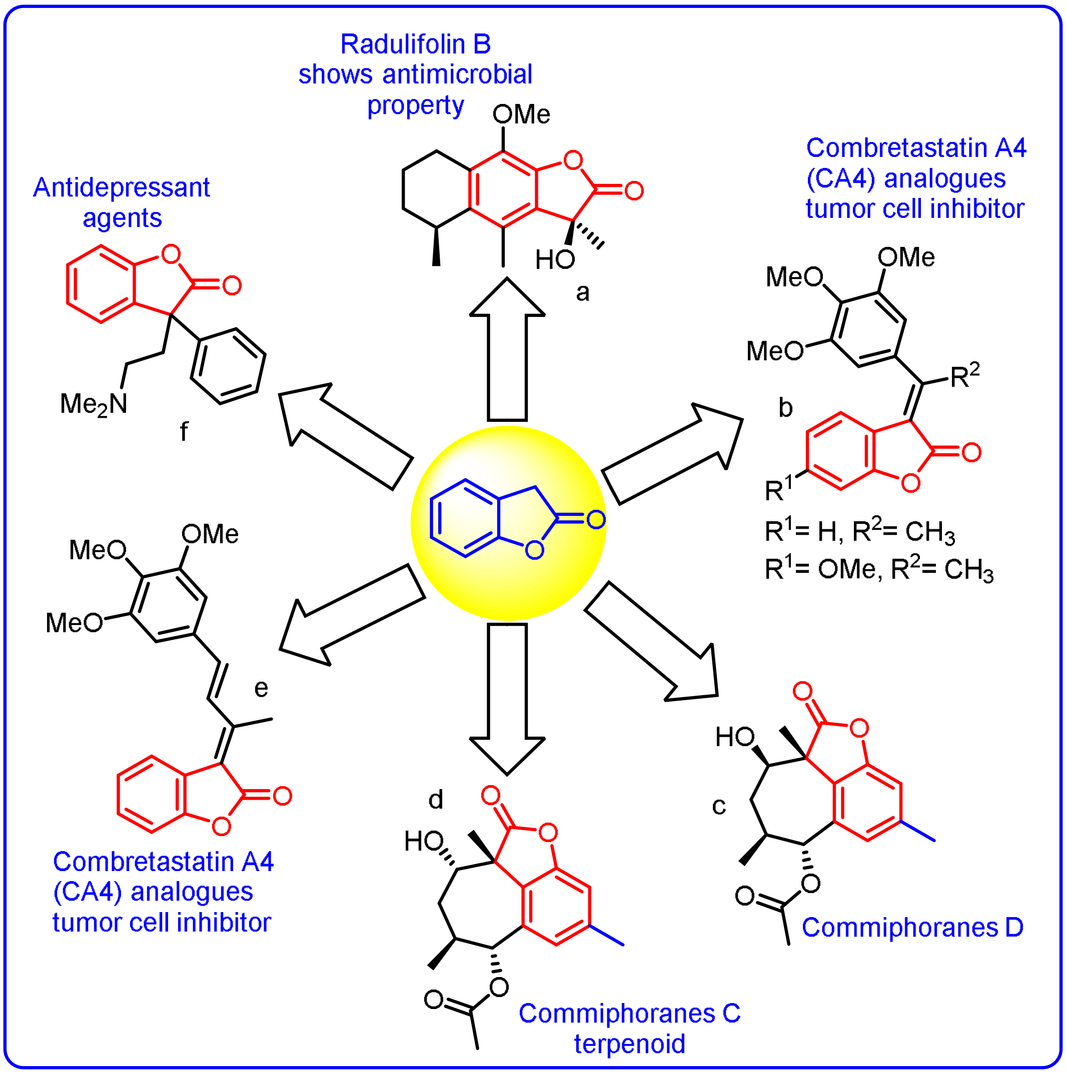
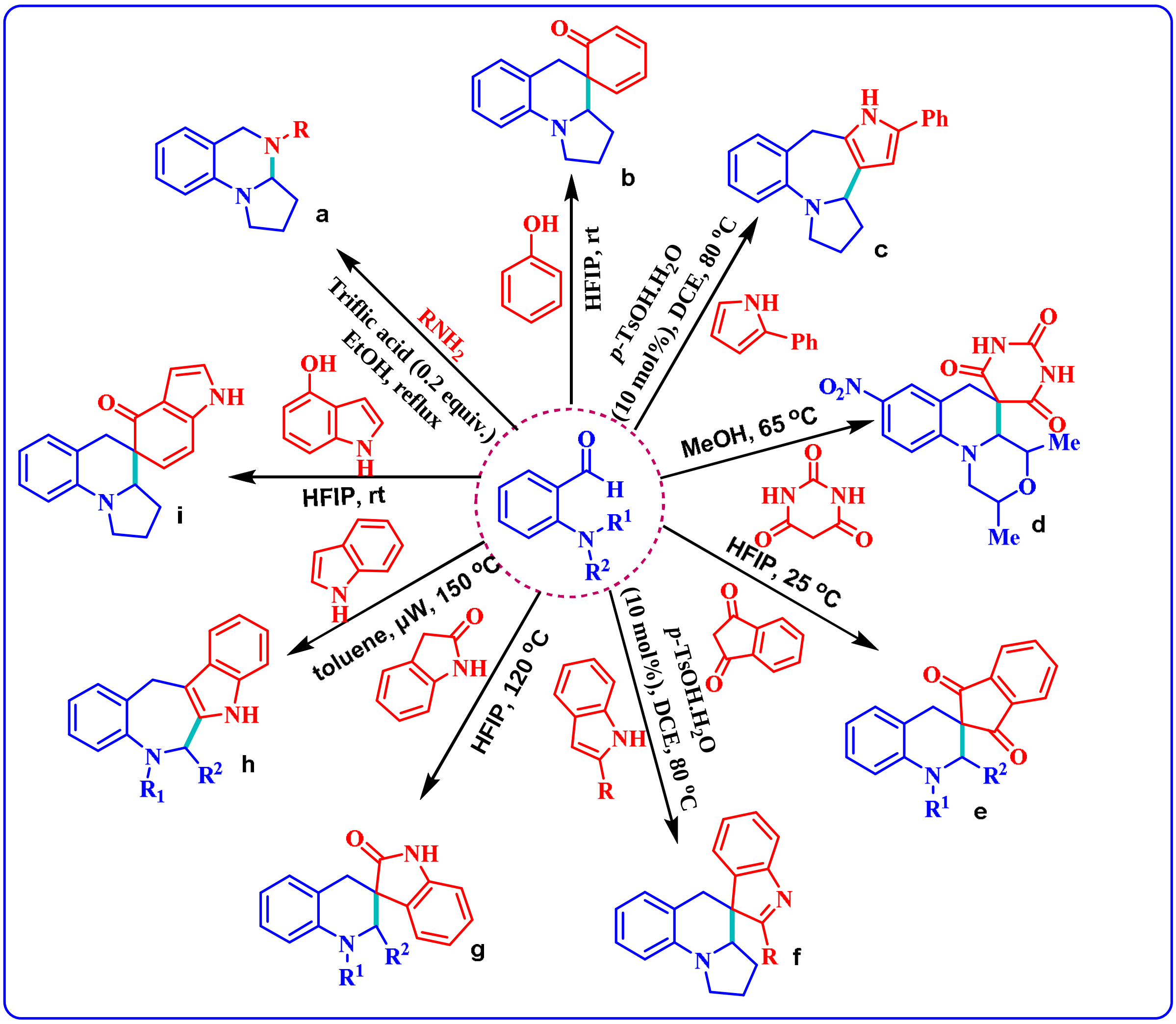


Figure 2.1.1.5.2 Representative examples of 2-coumaranone containing molecules

2.1.2 Literature Reports of Cascade [1,5]-Hydride Transfer/Cyclization Process

The direct functionalization of the unreactive C(sp^3)–H bond in an effortless way is an effective and powerful strategy in modern synthetic organic chemistry due to its wide constructive novelty. It is very challenging to design a structurally complex and biologically active scaffold containing pharmacophores via metal-free C–H functionalization processes. Indeed, the development of new synthetic strategies for the construction of novel spiroheterocycles through the functionalization of inert C(sp^3)–H bonds has become a significant research area nowadays. In 1895 intramolecular redox-neutral process was developed first through the “*tert*-amino effect” for the cyclization process initiated by hydride transfer methodology. This method enabled a significant way to activate the inert C(sp^3)–H bonds. This novel [1,5]-hydride transfer/cyclization cascade strategy attracted much attention for considerable interest in an application through the creation of different (spiro)cyclic compounds and the formation of heterocyclic bonds. The internal redox process happened through the involvement of a hydride shift process from C(sp^3)–H bonds to *tert*-amines, benzylic C(sp^3)–H bonds, ethereal oxygen, and non-benzylic C(sp^3)–H bonds to a hydride acceptor agent such as electrophilic aldehydes, ketones, alkenes, imines, alkynes, enals, enones, allene etc. An organocatalytic cascade redox process is attractive due to its effectiveness in a metal-free, cost-effective greenery approach. The following organo-catalyzed internal redox cascade reactions depicted in scheme 2.1 enabled the one-pot synthesis of a diverse pharmaceutically active scaffold containing (spiro)heterocycles dealing with the reactivity of hydride ion donor and acceptor partner.

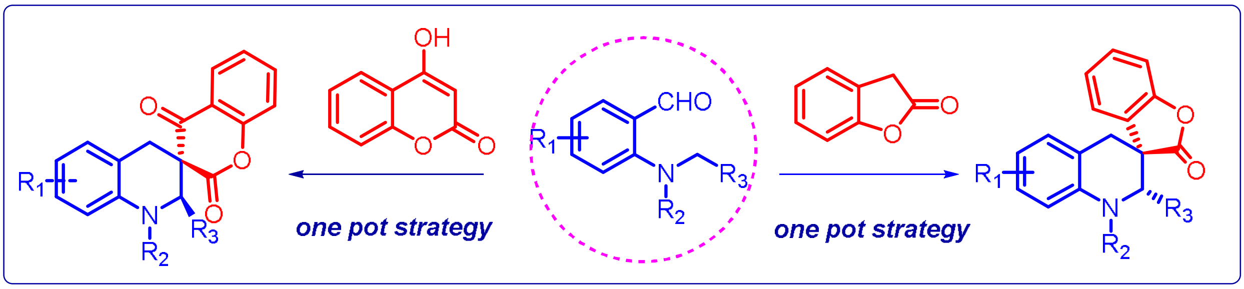


Scheme 2.1.2 Literature reports of cascade hydride shift/cyclization process

Two decades earlier Reinhoudt research group demonstrated the [1,5]-hydride-shift/cyclization strategy to achieve cyclic aminal through the in situ preparation of trifluoromethyl substituted imine. Utilizing electron-deficient imine has a well-hydride acceptor capability, they revealed the wide scope of aminal molecules direct from amine in one pot. Inspired by Reinhoudt's work, Seidel and Akiyama's group walked in the same way. Developing modified organocatalytic methods they achieved cyclic aminals utilizing o-dialkylaminobenzaldehdyde and primary amines (Scheme 2.1a). Xiao's group demonstrated a rapid synthesis of polycyclic skeleton directly from phenols and orthoaminobenzaldehydes via cascade [1,5]-HT/dearomative cyclizations (Scheme 2.1. b). Similar reactions were reported by the same group using 4-hydroxindole (Scheme 2.1i). This is very challenging because dearomatization takes place. Pyrrole and indole have been used as good coupling partners not only for fused ring formation (Scheme 2.1c,h) but also for spirocyclization (Scheme 2.1f). Several active methylene scaffolds enabled the synthesis of spiroheterocycles through HT/cyclization cascade methodology (Scheme 2.1 d, e, g).

2.2 Objective

There has been enormous progress in the area of spirocyclic chemistry,[7] however the development of a highly stereoselective and atom-economic method for the construction of spirocyclic scaffold containing 2-coumaranones fused with *N*-heterocycles has hardly been explored.[8] Then there is tetrahydroisoquinoline, a notable powerful building block that constructs a variety of bioactive molecules.[9] Yet, no protocol is available to integrate these two alluring bioactive scaffolds to date and 2-coumaranone and 3-isochromanone have not been used in the hydride shift reaction cascade. Recently, hydride transfer followed by cyclization sequence has become an attractive complementary approach for C(sp^3)–H bond functionalization. After a groundbreaking finding by Reinhoudt, the hydride shift reaction has been popularized mainly by Seidel, Sames, Akiyama, and Maulide research group.[10]



Scheme 2.2 Objective of this work: one pot cascade hydride shift/cyclization methods

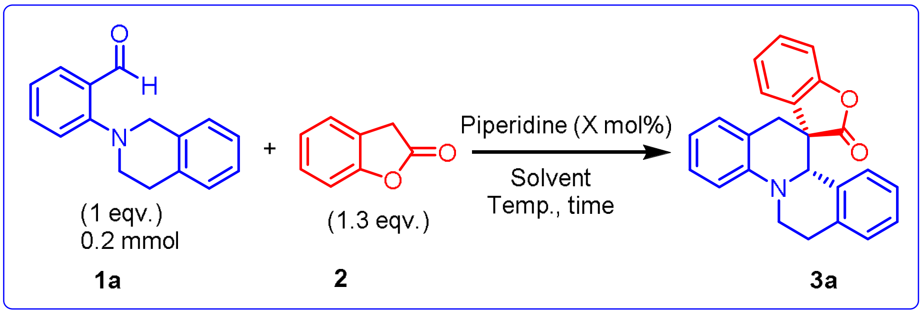
Over the past few decades, substantial efforts have been made by various research groups to develop varieties of hydride transfer/cyclization cascade reactions for the construction of structurally diverse complex molecules.[11] Taking account of the importance of building block coumaranone isochromanone, 4-hydroxycoumarin scaffold and in continuation to our ongoing interests toward the synthesis of densely functionalized (spiro) heterocycles via C-H bond activation,[12] we, herein report a straight forward and practical approach towards the synthesis of spiro-*N*-heterocycles via olefination, [1,5]-hydride transfer followed by cyclization strategy using corresponding aldehyde and coumaranone in one-pot operation.

2.3 Results and Discussion

2.3.1 Optimization Studies

We commenced the study by taking 1.3 equiv of 2-coumaranone (**2**) and 1 equiv of tetrahydroisoquinoline substituted benzaldehyde (**1a**) as the representative substrate using piperidine (20 mol %) as a catalyst in toluene at 120 ^{o}C for 24 h. To our delight, the desired spirocyclic product **3a** as a major diastereomer was obtained spontaneously in 75% isolated yield in one pot via olefin intermediate followed by [1,5]-hydride shift/cyclization sequence (Table 2.3.1.1, entry 1). A similar result was observed when the reaction time was reduced to 5 h (Table 2.3.1.1, entry 2). This result encouraged us to screen various high boiling solvents such as *m*-xylene, chlorobenzene, DMF, DMSO, DMAc, H_2O, and CH_3CN (Table 2.3.1.1, entries 3-9) to elevate the reaction efficacy and DMAc was found to be more effective compared to others. Decreasing the loading of the catalyst gave a diminished yield of 75% of **3a** (Table 2.3.1.1, entry 10) whereas increasing the loading of the catalyst showed an almost similar result (Table 2.3.1.1, entry 11). Increasing the amount of 2-coumaranone (1.4 equiv) gave a diminished yield of 75% of **3a** (Table 2.3.1.1, entry 12). A control experiment was conducted in the absence of piperidine and the formation of the product was observed this result suggested that the piperidine is not essential for the reaction (Table 2.3.1.1, entries 13). However, a catalytic amount of piperidine accelerated the reaction to improve the yield of the product exquisitely.

Table 2.3.1.1 Optimization of Reaction Condition[a]



entry	Piperidine (x mol %)	Solvent (0.034M)	Temp (°C)	time (h)	yield (%) of **3a** [a,b]
1	20	Toluene	120	24	75
2	20	Toluene	120	5	77
3	20	*m*-Xylene	150	5	71
4	20	Chlorobenzene	150	5	60
5	20	DMF	150	5	71
6	20	DMSO	150	5	65
7	20	DMAc	150	5	83
8	20	H_2O	100	12	40
9	20	CH_3CN	100	12	40
10	10	DMAc	150	5	75
11	30	DMAc	150	5	79
12[c]	20	DMAc	150	5	75
13[d]	-	DMAc	150	6/5	70

aThe reaction was carried out using 0.2 mmol of 1a (1equiv) with 2-Coumaranone 2 (1.3 equiv.) in presence of 20 mol % of piperidine. bIsolated yield. c Using 1.4 equiv of 2-coumaranone 2. dAbsence of piperidine.

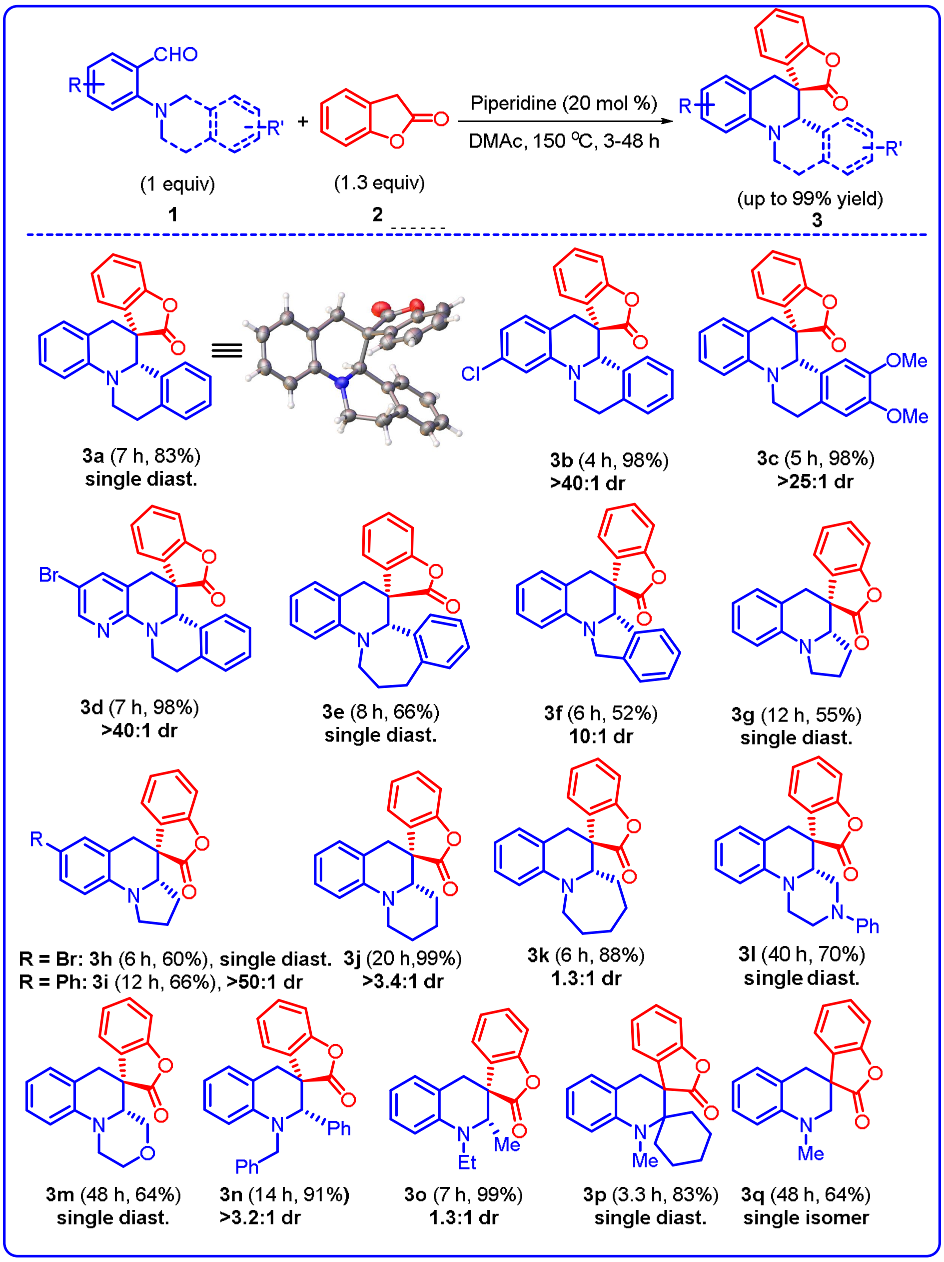
With the standard conditions in hand, we investigated the scope of the cyclization reaction using 2-coumaranone **2** and the diverse *ortho*-amino benzaldehydes **1** as hydride donors (Scheme 1). In general, various substituted *ortho*-amino benzaldehydes are compatible with this reaction. Chloro-substituted amino benzaldehyde produced the desired product **3b** in 98% yield with excellent diastereoselectivity (dr: 40:1). The dimethoxy containing tetrahydroisoquinoline substituted corresponding aldehyde **1c** underwent the reaction smoothly to afford **3c** in excellent yield with 25:1 diastereoselectivity. THIQ substituted 3-

bromo pyridine 3-carboxaldehyde reacted well and delivered the product **3d** in excellent yield (98%) with excellent selectivity (dr: >40:1). Besides tetrahydroisoquinoline, several benzo-fused cyclic amines reacted well to provide molecular complexity. Tetrahydro-1H-benzo[c]azepine substituted aldehyde provided the single diastereomer of **3e** in moderate yield. However, dihydroisoindoline substituted aldehyde **1f** provided the product **3f** with moderate yield and selectivity. Apart from benzylamine, several cyclic and acyclic alkyl amines (α-CH_2 w.r.t. *N*) containing substrate underwent smooth hydride shift reaction. Pyrrolidine substituted aldehydes performed very well and produced **3g**, **3h** and **3i** in moderate to good yields with excellent selectivity.

2.3.2 Scope of One-pot Strategy for Spiroheterocycles[a]

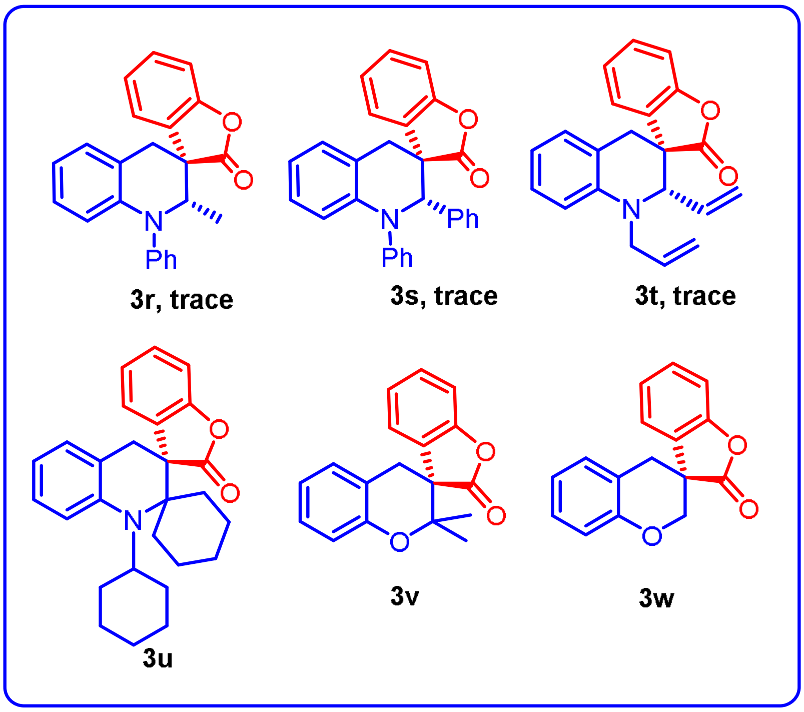
Piperidine, azepane containing aldehydes afforded the products **3j-k** in excellent yields with poor diastereoselectivity. The slow rate of reaction was observed in the case of *N*-phenyl piperazine and morpholine substituted aldehyde. However, these two substrates provided the products as single diastereomer (**3l** and **3m**) for both cases. *N*, *N*-dibenzyl and N, *N*-diethyl substituted aldehydes (**1n** and **1o**) reacted well to provide the desired products **3n** and **3o** in good with poor dr. ratio. *N*-methyl-*N*-cyclohexyl and *N*, *N*-dimethyl substituted aldehydes generated the cyclic products **3p** and **3q** as single diastereomer in 83% and 64% yields respectively.

Table 2.3.2.1 Scope of 2-Coumaranone Containing Spiroheterocycles[a]



[a]Reaction conditions: all reactions were performed with a mixture of **1** (0.2 mmol), 2-coumaranone **2** (1.3 equiv). dr given is calculated by ^{1}H NMR.

Table 2.3.2.1 Unsuccessful Substrates of 2-Coumaranone Containing Spiroheterocycles



3r, trace

3s, trace

3t, trace

3u

3v

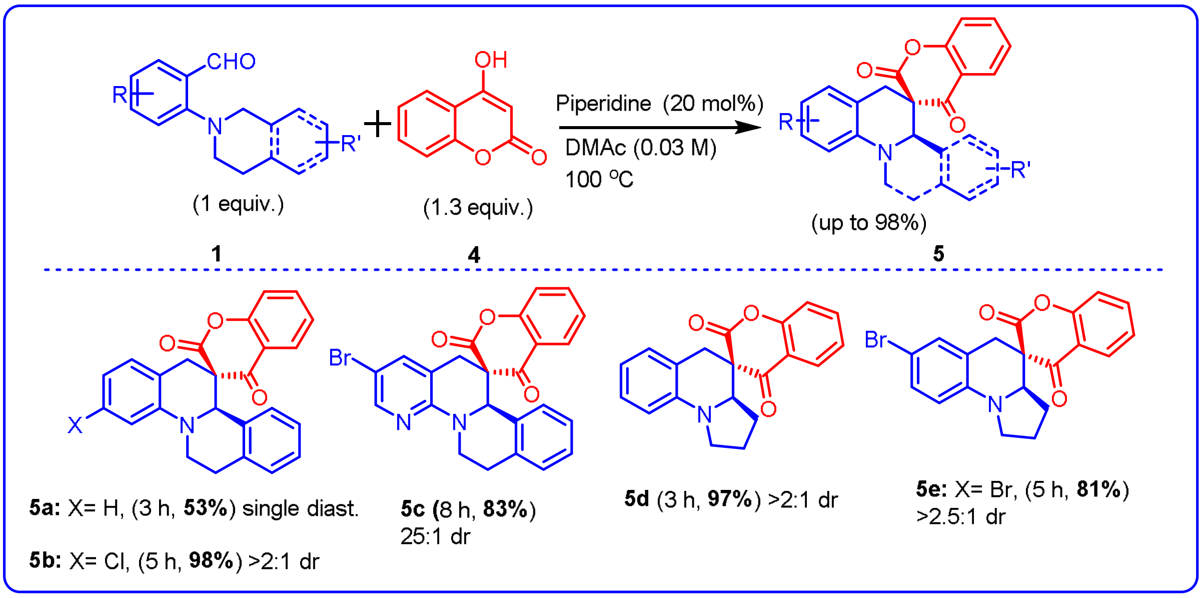
3w

In our one-pot spirocyclization method, hydride transfer capability and 6-endo cyclization methodology were not suitable for some cases such that **3r**, **3s,** and **3t** have been produced with a trace amount of yield. Unfortunately, **3u**, **3v,** and **3w** had not been produced due to some steric or electronic factor.

2.3.3 Scope of Cyclization of 4-Hydroxycoumarin[a]

The substrate scope was further extended by taking another active partner 4-hydroxycoumarin, as it is scarcely studied, reacting with various *ortho*-amino benzaldehydes **1** under the standard condition in one pot (Table 2.3.3.1). THIQ-containing aldehydes were well tolerated and gave the products **5a-c** in good to excellent yield with good diastereoselectivity. Then, the reactions were carried out with pyrrolidine, and azepane substituted aldehydes and afforded the products **5d-f** in moderate to good yield with poor diastereoselectivity.

Table 2.3.3.1 Scope of 4-Hydroxycoumarin Containing Spiroheterocycles [a]



5a: X= H, (3 h, **53%**) single diast.

5b: X= Cl, (5 h, **98%**) >2:1 dr

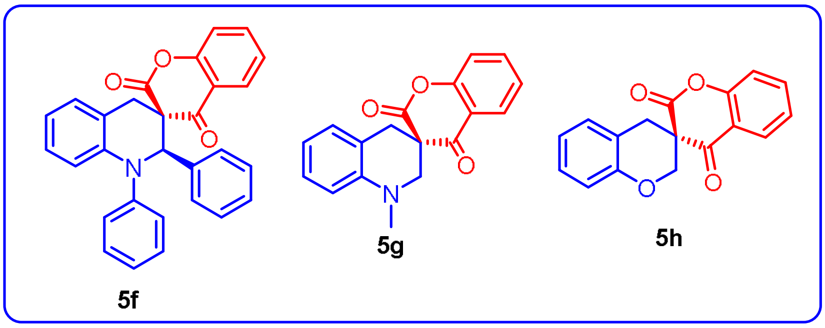
5c (8 h, **83%**) 25:1 dr

5d (3 h, **97%**) >2:1 dr

5e: X= Br, (5 h, **81%**) >2.5:1 dr

[a]Reaction conditions: all reactions were performed with a mixture of **1** (0.2 mmol), 4-hydroxycoumarine **4** (1.3 equiv). dr given is calculated by ^{1}H NMR.

Table 2.3.3.2 Unsuccessful Substrates of 4-Hydroxycoumarin containing Spiroheterocycles

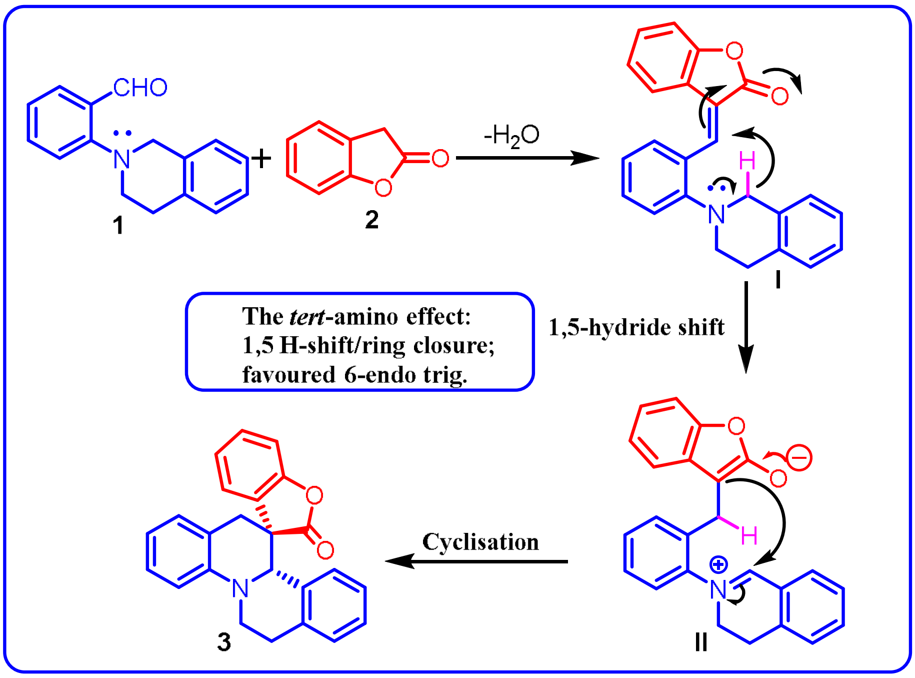


5f **5g** **5h**

In our one-pot spirocyclization method, hydride transfer capability and 6-endo cyclization methodology were not suitable for some cases such that **5f**, **5g,** and **5h** have been produced with a trace amount of yield.

2.3.4 Plausible Mechanism

Initially, the Knoevenagel Condensation reaction happened and produced olefin **I** from the corresponding aldehyde (**1**) and active methylene derivative (**2**) which was catalyzed by piperidine (Scheme 2.3.4). Then 1,5-hydride transfer occurred which is thermally allowed and followed by 6-endo trig. cyclization of **II** gave spirohetrocycle **3**. Hydride transfer enabled by the neighboring tertiary amine group termed as *tert* amino effect.



Scheme 2.3.4 Proposed mechanism

2.4 Conclusion

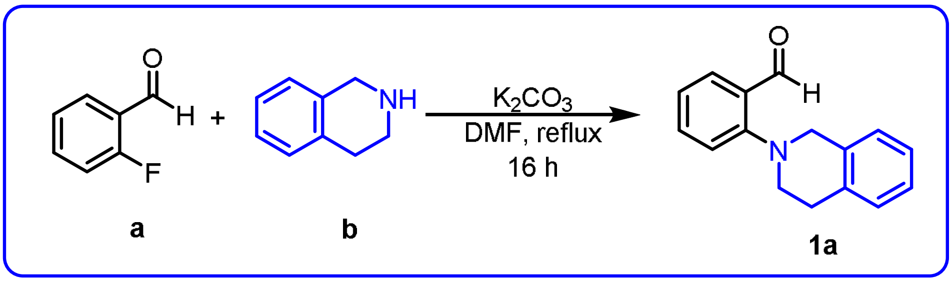
We have demonstrated a transition metal-free cascade olefin formation/hydride transfer/spirocyclization process in one pot under mild reaction conditions. A range of wide substrate bearing various functional groups was well tolerable in this reaction condition. This strategy features the construction of novel spiroheterocycles (especially benzofuranone and coumaranone-bearing spirotetrahydroquinolines) in a convenient pathway furnishing excellent yield and diastereoselectivity. We performed an enantioselective reaction employing organocatalysts but unfortunately, we got a poor enantiomeric excess product, hence our research group focussed on it. Our future plan is to discover the biological activity of the spiroheterocycles by molecular docking technique as both partner 2-coumaranone and tetrahyroisoquinoline are a highly potential bioactive motifs.

2.5 Experimental Section

2.5.1 General Information

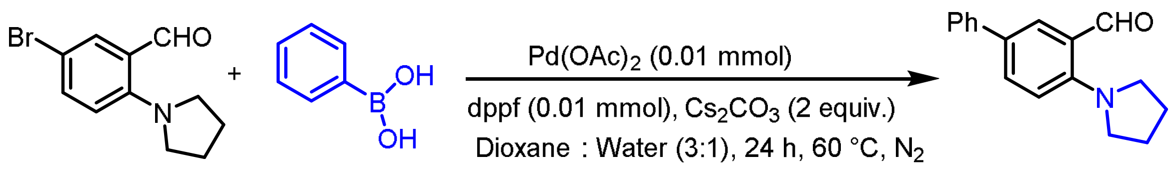
All reactions were carried out in an oven-dry reaction vessel under N_2 atmosphere unless otherwise stated. Commercial reagents were purchased from Sigma-Aldrich, Alfa Aesar, Acros, and other commercial suppliers and used as received without further purification. Anhydrous DCE was purchased from Sigma-Aldrich and used as received. TLC analysis was performed on Merck 60 F_{254} silica gel TLC plates. Column chromatography was done using 230-400 mesh silica gel by applying pressure through an air pump. ^1H and ^{13}C NMR spectra were recorded in Bruker 300, 600 MHz, and JEOL 400 MHz spectrometer, and are reported as chemical shifts (δ) in parts per million (ppm). Internal standards or residual solvents were used as a reference. HRMS (m/z) were recorded in the Q-Tof Micromass spectrometer (LC-MS, ESI mode) and JOEL-JMS 700 (EI mode). Melting points were determined in a capillary melting point apparatus and are uncorrected. Single crystal X-ray data was recorded in a Bruker Kappa APEX2 CCD diffractometer with MoKα radiation. The structures were solved by SHELXT and refined with SHElXL using the Olex2 program. CCDC (1996347-1996349).

2.5.2 General Procedure for the Preparation of 2-Aminobenzaldehyde Derivative 1a



The compound was prepared following literature procedure.[13] To an oven-dried 10 mL round-bottom flask attached to a condenser under N_2 atmosphere, 2-fluorobenzaldehyde (0.037 g, 0.3 mmol), 1,2,3,4-tetrahydroisoquinoline (0.05 g, 0.37 mmol) and potassium carbonate (0.055 g, 0.40 mmol) were taken and the mixture was dissolved in DMF (6 mL). The bath temperature was slowly increased to the reflux temperature of DMF and stirred for 16 h. After the completion of the reaction, monitored by TLC, the organic layer was extracted with ethyl acetate (3 × 20 mL) and dried over anhydrous Na_2SO_4. The combined organic layers were concentrated under vacuo and purified by column chromatography on silica gel (230-400 mesh) using petroleum ether/ethyl acetate (97:3) as eluent to afford product **1a** with 70% yield.

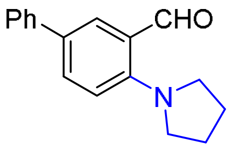
2.5.3 Preparation of 3-Aryl Substituted Aldehyde 1i



1h **1i, 95%**

The compound was prepared following literature procedure.[14] To an oven-dried 10 mL round-bottom flask attached to a condenser under N_2 atmosphere, 5-Bromo-2-(pyrrolidin-1-yl)benzaldehyde (0.10 g, 0.3 mmol), phenylboronic acid (0.06 g, 0.47 mmol), cesium carbonate (0.25 g, 0.6 mmol), dppf (0.007 g, 0.01 mmol) and palladium acetate (0.003 g, 0.01 mmol) were taken and the mixture was dissolved in dioxane (1.25 mL) and water (0.5 mL). The bath temperature was slowly increased to 60 °C and stirred for 24 h. After the completion of reaction, monitored by TLC, the organic layer was extracted with ethyl acetate (3 × 20 mL) and dried over anhydrous Na_2SO_4. The combined organic layers was concentrated under vacuo and purified by column chromatography on silica gel (230-400 mesh) using petroleum ether/ethyl acetate (95:5) as eluent to afford the product **1i** in 95% yield.

2.5.4 Characterization of 3-Aryl Substituted Aldehyde 1i

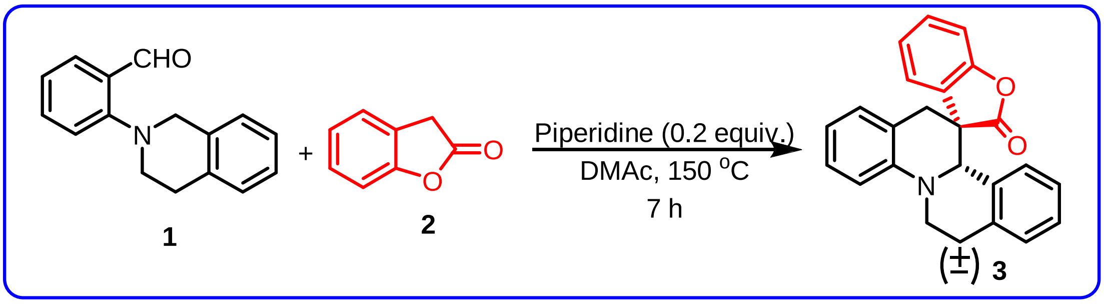


1i

4-(Pyrrolidin-1-yl)-[1,1'-biphenyl]-3-carbaldehyde (1i):

Yellow solid (94.7 mg, 95% yield); column chromatography eluent, petroleum ether/EtOAc = 50:1; mp84–85 ^{o}C; **^{1}H NMR (300 MHz, Chloroform-*d*)** δ 10.17 (s, 1H), 7.97 (d, *J* = 2.4 Hz, 1H), 7.66 (dd, *J* = 9.0, 2.4 Hz, 1H), 7.60 – 7.57 (comp, 2H), 7.45 – 7.40 (comp, 2H), 7.33 – 7.27 (m, 1H), 6.92 (d, *J* = 9.0 Hz, 1H), 3.44 – 3.40 (m, 4H), 2.04 – 1.99 (m, 4H);**^{13}C NMR (75 MHz, Chloroform-*d*)** δ 190.1, 149.2, 139.9, 132.7, 131.0, 129.2, 128.8, 126.5, 126.1, 122.9, 115.1, 52.8, 25.9.

2.5.5 General Procedure for the Synthesis of the Final Product 3a



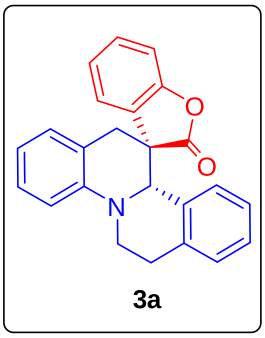
(Miligram scale reaction)

To an oven-dried 25 mL round-bottom flask attached with condenser under nitrogen, 2-(3,4-dihydroisoquinolin-2(1H)-yl)benzaldehyde (**1a**) (0.2 mmol) and 2-coumaranone (**2**) (0.26 mmol) were taken, dissolved in anhydrous DMAc (6 mL) and the bath temperature was slowly increased to 150 °C. The reaction mixture was kept under the same temperature until the intermediate olefin was consumed completely as monitored by TLC. The solvent was removed from the organic layer by workup with EtOAc (2 x10 mL) and cold water; brine wash needed. Then the organic layer passed through anhydrous Na_2SO_4 and concentrated under vacuo. Finally, it was purified by column chromatography on silica gel (230-400 mesh) using petroleum ether/ethyl acetate (99:1) as eluent to obtain the desired spiro-heterocyclic product (3S,11b'S)-6',7',11b',13'-tetrahydro-2H-spiro[benzofuran-3,12'-isoquinolino[2,1-a]quinolin] 2-one (**3a**) in 83% (58 mg) yield.

(Gram scale reaction)

To an oven-dried 100 mL round-bottom flask attached with condenser under nitrogen, 2-(3,4-dihydroisoquinolin-2(1H)-yl)benzaldehyde (**1a**) (1 g, 4.2 mmol) and 2-coumaranone (**2**) (0.742 g, 5.46 mmol) were taken, dissolved in anhydrous DMAc (42 mL) and the bath temperature was slowly increased to 150 °C. The reaction mixture was kept under the same temperature until the intermediate olefin was consumed completely as monitored by TLC. The solvent was removed from the organic layer by workup with EtOAc (2 x100 mL) and cold water; brine wash needed. Then the organic layer passed through anhydrous Na_2SO_4 and concentrated under vacuo. Finally, it was purified by column chromatography on silica gel (230-400 mesh) using petroleum ether/ethyl acetate (99:1) as eluent to obtain the desired spiro-heterocyclic product (3S,11b'S)-6',7',11b',13'-tetrahydro-2H-spiro[benzofuran-3,12'-isoquinolino[2,1-a]quinolin] 2-one (**3a**) in 69% (1.04 g) yield.

2.5.6 Characterization of the Products 3a-3q:

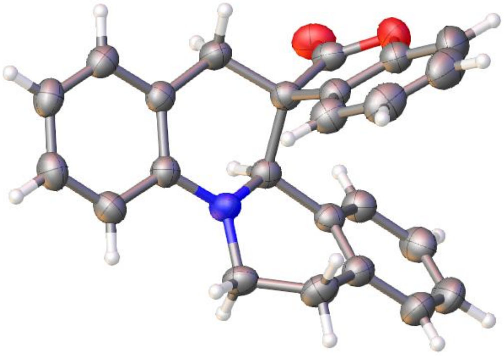


3a

(3S*,11b'S*)-6',7',11b',13'-tetrahydro-2H-spiro[benzofuran-3,12'-isoquinolino[2,1-a]quinolin] 2-one (3a):

Colourless solid (58 mg, 83% yield); column chromatography eluent, petroleum ether/EtOAc = 50:1; mp 168-170 °C; single diastereomer; **^{1}H NMR (600 MHz, Chloroform-*d*)** δ 7.33 (d, *J* = 7.8 Hz, 1H), 7.29 – 7.26 (m, 1H), 7.17 – 7.12 (comp, 3H), 7.09 (t, *J* = 7.2 Hz, 1H), 6.93 – 6.90 (comp, 3H), 6.87 (d, *J* = 7.2 Hz, 1H), 6.84 – 6.81 (comp, 2H), 4.92 (s, 1H), 4.00 (ddd, *J* = 11.5, 5.1, 2.3 Hz, 1H), 3.85 (d, *J* = 16.2 Hz, 1H), 3.26 (td, *J* = 11.4, 3.6 Hz, 1H), 2.94 (d, *J* = 16.2 Hz, 1H), 2.54 – 2.45 (m, 2H); **^{13}C NMR (150 MHz, Chloroform-*d*)** δ 178.7, 152.6, 145.7, 135.9, 131.8, 129.8, 128.8, 128.6, 128.0, 127.6, 127.5, 127.3, 126.4, 125.9, 123.6, 118.9, 117.8, 112.1, 109.8, 62.7, 52.1, 42.8, 37.6, 29.7; **HRMS**(EI, m/z) calcd for $C_{24}H_{19}NO_2$ $[M]^+$ 353.1416, found 353.1421.

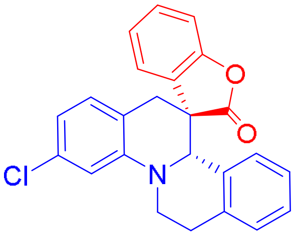
Table 2.5.3.1 Crystal Data and Structure Refinement for 3a



3a (CCDC -1996347)

Empirical formula	$C_{24}H_{19}NO_2$
Formula weight	353.40
Temperature/K	298.0
Crystal system	trigonal
Space group	R-3
a/Å	34.347(7)

b/Å	34.347(7)
c/Å	7.696(2)
α/°	90.00(3)
β/°	90.00(3)
γ/°	120.00(3)
Volume/Å^3	7863(4)
Z	18
ρ_{calc}g/cm^3	1.343
μ/mm^{-1}	0.676
F(000)	3348.0
Crystal size/mm^3	0.35 × 0.3 × 0.2
Radiation	CuKα (λ = 1.54184)
2Θ range for data collection/°	5.146 to 128.422
Index ranges	$-38 \le h \le 39$, $-39 \le k \le 39$, $-8 \le l \le 8$
Reflections collected	22050
Independent reflections	2783 [R_{int} = 0.0501, R_{sigma} = 0.0320]
Data/restraints/parameters	2783/0/244
Goodness-of-fit on F^2	1.081
Final R indexes [I>=2σ (I)]	R_1 = 0.0432, wR_2 = 0.1002
Final R indexes [all data]	R_1 = 0.0447, wR_2 = 0.1012
Largest diff. peak/hole / e Å^{-3}	0.17/-0.14

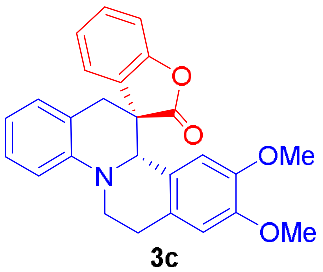


3b

(3S*,11b'S*)-3'-chloro-6',7',11b',13'-tetrahydro-2H-spiro[benzofuran-3,12'-isoquinolino[2,1 a]quinolin]-2-one (3b):

Colourless solid (76.3 mg, 98% yield); mp 152-154^{o}C; *dr*>40:1; Data for major diastereomer; column chromatography eluent, petroleum ether/EtOAc = 50:1; **^{1}H NMR (600 MHz, Chloroform-*d*)** δ 7.32 (d, *J* = 7.8 Hz, 1H), 7.17 – 7.14 (comp , 2H), 7.10 (t, *J* = 7.2 Hz, 1H), 7.03 (d, *J* = 7.8 Hz, 1H), 6.94 – 6.92 (m, 1H), 6.90 (d, *J* = 1.8 Hz, 1H), 6.87 (app d, *J* = 7.8 Hz, 2H), 6.82 (d, *J* = 7.8 Hz, 1H), 6.78 (dd, *J* = 7.8, 1.8 Hz, 1H), 4.91 (s, 1H), 3.95 (ddd, *J* = 11.3, 4.5, 2.4 Hz, 1H), 3.78 (d, *J* = 16.2 Hz, 1H), 3.25 (td, *J* = 11.2, 4.2 Hz, 1H), 2.89 (d, *J* =

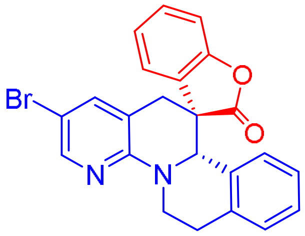
16.2 Hz, 1H), 2.46 – 2.53 (m, 2H); **^{13}C NMR (150 MHz, Chloroform-*d*)** δ 178.5, 152.6, 146.6, 135.6, 133.2, 131.3, 130.7, 129.0, 128.1, 128.1, 127.6, 127.5, 126.5, 125.7, 123.7, 117.7, 117.3, 112.2, 109.9, 62.5, 51.7, 43.1, 37.3, 29.5; **HRMS**(ESI, m/z) calcd for $C_{24}H_{18}ClNO_2$ $[M+H]^+$ 388.1104, found 388.1108.



3c

(3S*,11b'S*)-9',10'-dimethoxy-6',7',11b',13'-tetrahydro-2H-spiro[benzofuran-3,12'-isoquinolino[2,1-a]quinolin]-2-one (3c):

Yellow solid (81 mg, 98% yield); column chromatography eluent, petroleum ether/EtOAc = 50:1; mp 108-110°C; *dr*>25:1; Data for major diastereomer;**^{1}H NMR (600 MHz, Chloroform-*d*)** δ 7.28 – 7.25 (m, 1H), 7.16 – 7.12 (comp, 2H), 6.92 – 6.88 (comp, 2H), 6.85– 6.83 (comp, 2H), 6.81 (app t, *J* = 7.2 Hz, 1H), 6.34 (s, 1H), 4.85 (s, 1H), 4.00 – 3.97 (m, 1H), 3.86 (s, 3H), 3.82 (d, *J* = 16.8 Hz, 1H), 3.76 (s, 3H), 3.24 (td, *J* = 11.6, 3.3 Hz, 1H), 2.93 (d, *J* = 16.8 Hz, 1H), 2.45 (td, *J* = 13.5, 11.8, 5.0 Hz, 1H), 2.38 (d, *J* = 15.0 Hz, 1H);**^{13}C NMR (150 MHz, Chloroform-*d*)** δ 179.2, 152.7, 147.7, 147.1, 145.7, 129.8, 128.7, 128.7, 128.1, 127.5, 125.8, 123.5, 123.5, 118.9, 117.8, 112.0, 110.5, 110.3, 109.8, 62.4, 55.9, 55.6, 52.2, 42.8, 37.7, 29.0; **HRMS**(ESI, m/z) calcd for $C_{26}H_{23}NO_4$ $[M+H]^+$ 414.1705, found 414.1703.

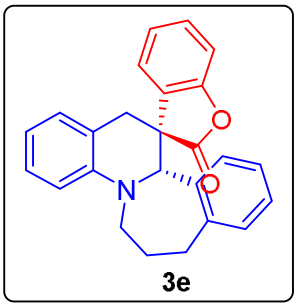


3d

(3S*,11b'S*)-2'-bromo-6',7',11b',13'-tetrahydro-2H-spiro[benzofuran-3,12'-isoquinolino[2,1-a][1,8]naphthyridin]-2-one (3d):

Yellow solid (85.2 mg, 98% yield); column chromatography eluent, petroleum ether/EtOAc = 50:1; mp 182-184 °C; *dr*>40:1; Data for major diastereomer; **^{1}H NMR (300 MHz, Chloroform-*d*)** δ 8.23 (d, *J* = 2.4 Hz, 1H), 7.41 – 7.40 (m, 1H), 7.33 (d, *J* = 7.5 Hz, 1H), 7.13

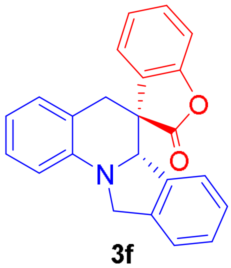
(td, *J* = 7.9, 1.4 Hz, 2H), 7.06 (td, *J* = 7.4, 1.4 Hz, 1H), 6.93 – 6.81 (m, 3H), 6.70 (dd, *J* = 7.5, 1.5 Hz, 1H), 5.20 – 5.13 (m, 1H), 5.12 (s, 1H), 3.73 (dd, *J* = 16.2, 1.5 Hz, 1H), 3.04 – 2.94 (m, 2H), 2.81 (d, *J* = 16.5 Hz, 1H), 2.53 – 2.48 (m, 1H); **^{13}C NMR (150 MHz, Chloroform-*d*)** δ 178.3, 153.3, 152.5, 147.1, 139.1, 137.0, 131.3, 129.3, 128.6, 127.4, 127.1, 126.8, 126.5, 125.1, 123.9, 114.9, 110.1, 107.3, 62.3, 50.5, 40.1, 36.6, 29.7; **HRMS** (ESI, m/z) calcd for $C_{23}H_{17}BrN_2O_2$ $[M+H]^+$ 433.0552, found 433.0550.



3e

(3'S*,12bS*)-7,8,12b,14-tetrahydro-2'H,6H-spiro[benzo[3,4]azepino[1,2-a]quinoline-13,3'-benzofuran]-2'-one (3e):

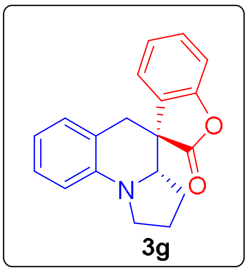
Colourless solid (48.2 mg, 66% yield); column chromatography eluent, petroleum ether/EtOAc = 50:1; mp 195-197 °C; single diastereomer; **^{1}H NMR (600 MHz, Chloroform-*d*)** δ 7.28 – 7.26 (comp, 2H), 7.11 (dt, *J* = 15.8, 7.6 Hz, 2H), 7.06 (app t, *J* = 7.2 Hz, 1H), 6.99 (d, *J* = 7.2 Hz, 1H), 6.83 (app t, *J* = 7.2 Hz, 2H), 6.80 (d, *J* = 7.8 Hz, 1H), 6.77 (d, *J* = 7.8 Hz, 1H), 6.73 (d, *J* = 7.2 Hz, 1H), 6.69 (app t, *J* = 7.2 Hz, 1H), 5.29 (s, 1H), 3.69 (d, *J* = 15.0 Hz, 2H), 3.44 – 3.39 (m, 1H), 2.96 (td, *J* = 13.1, 6.5 Hz, 1H), 2.78 (d, *J* = 15.6 Hz, 1H), 2.32 – 2.25 (m, 1H), 2.12 (dd, *J* = 13.2, 4.8 Hz, 1H), 1.56 – 1.50 (m, 1H); **^{13}C NMR (150 MHz, Chloroform-*d*)** δ 178.5 , 152.5 , 144.5 , 138.3 , 135.3 , 130.4 , 129.8 , 128.9 , 128.6 , 128.4 , 128.3 , 127.5 , 126.6 , 125.7 , 123.4 , 117.5 , 116.1 , 110.0 , 109.7 , 70.8 , 51.7 , 45.3 , 37.8 , 30.4 , 25.7; **HRMS**(ESI, m/z) calcd for $C_{25}H_{21}NO_2$ $[M+H]^+$ 368.1650, found 368.1660.



3f

(3S*, 6a'S*)-6a',11'-dihydro-2H,5'H-spiro[benzofuran-3,6'-isoindolo[2,1-a]quinolin]-2-one (3f):

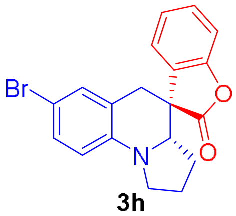
Colourless solid (35.4 mg, 52% yield); column chromatography eluent, petroleum ether/EtOAc = 50:1; mp 128–130 °C; *dr*10:1; Data for major diastereomer; **^{1}H NMR (300 MHz, Chloroform-*d*)** δ 7.33 (app t, *J* = 7.8 Hz, 1H), 7.22 – 7.10 (comp, 5H), 7.04 (td, *J* = 7.8, 1.2 Hz, 1H), 6.95 (d, *J* = 7.5 Hz, 1H), 6.80 (dt, *J* = 9.2, 5.1 Hz, 2H), 6.71 (td, *J* = 7.5, 1.2 Hz, 1H), 6.36 (dd, *J* = 7.8, 0.6 Hz, 1H), 5.25 (d, *J* = 1.5 Hz, 1H), 4.94 (d, *J* = 12.9 Hz, 1H), 4.59 (dd, *J* = 13.2, 3.6 Hz, 1H), 3.71 (d, *J* = 15.6 Hz, 1H), 2.96 (d, *J* = 15.9 Hz, 1H);**^{13}C NMR (150 MHz, Chloroform-*d*)** δ 178.9 , 152.8 , 143.2 , 137.2 , 136.6 , 129.9 , 128.5 , 128.3 , 128.2 , 127.5 , 127.2 , 124.1 , 124.0 , 122.4 , 121.8 , 117.4 , 117.4 , 111.9 , 110.1 , 68.0 , 55.3 , 47.0 , 37.9 ; **HRMS** (ESI, m/z) calcd for $C_{23}H_{17}NO_2$ $[M]^+$ 340.1338, found 340.1329.



3g

(3S*,3a'S*)-2',3',3a',5'-tetrahydro-1'H,2H-spiro[benzofuran-3,4'-pyrrolo[1,2-a]quinolin]-2-one (3g):

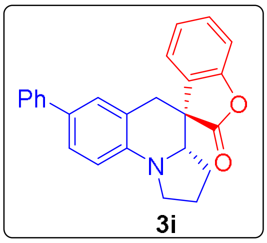
White solid (32.5 mg, 55% yield); column chromatography eluent, petroleum ether/EtOAc = 50:1; mp 158-160 °C; single diastereomer; **^{1}H NMR (600 MHz, Chloroform-*d*)** δ 7.30–7.26 (comp, 2H), 7.18 (d, *J* = 7.8 Hz, 1H), 7.06 (d, *J* = 7.2 Hz, 1H), 6.95 (td, *J* = 7.8, 1.2 Hz, 1H), 6.72 – 6.69 (m, 1H), 6.64 (d, *J* = 8.4 Hz, 1H), 6.44 (dd, *J* = 7.2, 1.2 Hz, 1H), 3.96 (dd, *J* = 9.6, 5.4 Hz, 1H), 3.57 (td, *J* = 8.4, 1.8 Hz, 1H), 3.52 (d, *J* = 15.6 Hz, 1H), 3.27 (q, *J* = 8.4 Hz, 1H), 2.89 (d, *J* = 15.0 Hz, 1H), 2.01 – 1.94 (m, 2H), 1.92 – 1.88 (m, 1H), 1.03 – 0.96 (m, 1H); **^{13}C NMR (150 MHz, Chloroform-*d*)** δ 178.8 , 153.2 , 143.4 , 129.7 , 128.6 , 128.2 , 127.5 , 125.0 , 124.4 , 117.0 , 116.1 , 110.3 , 110.3 , 62.8 , 47.3 , 45.8 , 37.9 , 27.5 , 23.3 ; **HRMS** (ESI, m/z) calcd for $C_{19}H_{17}NO_2$ $[M+H]^+$ 292.1338, found 292.1326.



3h

(3S*, 3a'S*)-7'-bromo-2',3',3a',5'-tetrahydro-1'H,2H-spiro[benzofuran-3,4'-pyrrolo[1,2-a]quinolin]-2-one (3h):

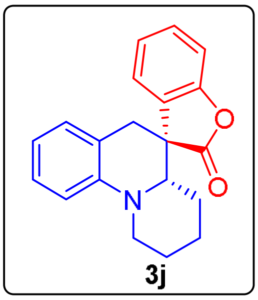
Yellow solid (44.4 mg, 60% yield); column chromatography eluent, petroleum ether/EtOAc = 50:1; mp 180-182 °C; single diastereomer; **^{1}H NMR (600 MHz, Chloroform-*d*)** δ 7.31 (d, *J* = 8.4 Hz, 1H), 7.28 – 7.26 (m, 1H), 7.16 – 7.13 (comp , 2H), 6.94 (app t, *J* = 7.2 Hz, 1H), 6.47 (d, *J* = 8.4 Hz, 1H), 6.39 (d, *J* = 7.8 Hz, 1H), 3.90 (dd, *J* = 9.6, 4.8 Hz, 1H), 3.51 (t, *J* = 8.4 Hz, 1H), 3.44 (d, *J* = 15.6 Hz, 1H), 3.19 (q, *J* = 8.4 Hz, 1H), 2.81 (d, *J* = 15.6 Hz, 1H), 1.95 – 1.86 (m, 3H), 0.98 – 0.92 (m, 1H); **^{13}C NMR (150 MHz, Chloroform-*d*)** δ 178.3 , 153.1 , 142.4 , 132.0 , 130.9 , 128.9 , 127.1 , 124.8 , 124.5 , 119.1 , 111.8 , 110.5 , 107.7 , 62.8 , 47.5 , 45.4 , 37.5 , 27.4 , 23.2 ; **HRMS** (ESI, m/z) calcd for $C_{19}H_{16}BrNO_2$ $[M+H]^+$ 370.0443, found 370.0438.



3i

(3S*,3a'S*)-7'-phenyl-2',3',3a',5'-tetrahydro-1'H,2H-spiro[benzofuran-3,4'-pyrrolo[1,2-a]quinolin]-2-one (3i):

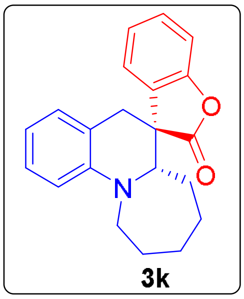
Colourless solid (48.9 mg, 66% yield); column chromatography eluent, petroleum ether/EtOAc = 50:1; mp 100-101 °C; *dr*>50:1; Data for major diastereomer; **^{1}H NMR (400 MHz, Chloroform-*d*)** δ 7.56 – 7.54 (comp, 2H), 7.52 (dd, *J* = 4.4, 2.0 Hz, 1H), 7.39 (app t, *J* = 7.6 Hz, 2H), 7.31 (s, 1H), 7.28 – 7.23 (comp, 2H), 7.16 (d, *J* = 8.0 Hz, 1H), 6.93 (t, *J* = 7.6 Hz, 1H), 6.68 (d, *J* = 8.4 Hz, 1H), 6.48 (d, *J* = 7.6 Hz, 1H), 3.97 (dd, *J* = 9.6, 5.2 Hz, 1H), 3.62 – 3.53 (m, 2H), 3.29 (q, *J* = 8.4 Hz, 1H), 2.93 (d, *J* = 15.6 Hz, 1H), 2.00 – 1.86 (m, 3H), 1.04 – 0.95 (m, 1H); **^{13}C NMR (100 MHz, Chloroform-*d*)** δ 178.6 , 153.2 , 142.9 , 140.9 , 128.9 , 128.7 , 128.7 , 128.3 , 127.5 , 126.8 , 126.1 , 126.0 , 125.0 , 124.5 , 117.5 , 110.7 , 110.4 , 63.0 , 47.4 , 45.9 , 38.0 , 27.5 , 23.3 ; **HRMS** (ESI, m/z) calcd for $C_{25}H_{21}NO_2$ $[M+H]^+$ 368.1651, found 368.1650.



3j

(3S*,4a'S*)-1',2',3',4',4a',6'-hexahydro-2H-spiro[benzofuran-3,5'-pyrido[1,2-a]quinolin]-2-one (3j):

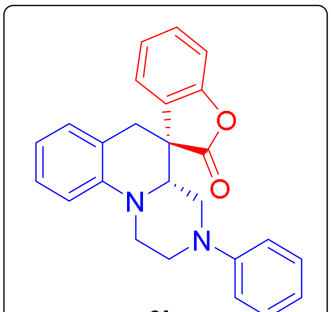
Colourless solid (60.4 mg, 99% yield);column chromatography eluent, petroleum ether/EtOAc = 50:1;mp 134-136°C; *dr*>3.4:1; Data for major diastereomer;^{1}**H NMR (600 MHz, Chloroform-*d*)** δ 7.30 (app t, *J* = 8.4 Hz, 1H), 7.25 (app t, *J* = 7.8 Hz, 1H), 7.17 (d, *J* = 7.8 Hz, 1H), 7.04 (d, *J* = 8.4 Hz, 1H), 7.00 (app t, *J* = 7.2 Hz, 1H), 6.96 (d, *J* = 7.2 Hz, 1H), 6.80 – 6.76 (comp, 2H), 4.13 (d, *J* = 12.0 Hz, 1H), 3.57 (d, *J* = 15.6 Hz, 1H), 3.41 (dd, *J* = 12.0, 2.4 Hz, 1H), 2.83 (td, *J* = 12.0, 2.4 Hz, 1H), 2.77 (d, *J* = 15.6 Hz, 1H), 1.82 – 1.80 (m, 1H), 1.71 (d, *J* = 12.6 Hz, 1H), 1.60 (d, *J* = 12.6 Hz, 1H), 1.50 – 1.36 (m, 2H), 0.78 (qd, *J* = 12.5, 3.8 Hz, 1H); ^{13}**C NMR (150 MHz, CDCl$_3$)** δ 178.4, 153.0, 146.2, 130.1, 128.6, 128.4, 128.0, 125.8, 124.3, 119.4, 118.4, 113.4, 110.1, 60.3, 49.7, 48.4, 37.9, 27.6, 25.5, 23.1; **HRMS** (ESI, m/z) calcd for $C_{20}H_{19}NO_2$ $[M+H]^+$ 306.1494, found 304.1496.



3k

(3'S*,6aS*)-6a,7,8,9,10,11-hexahydro-2'H,5H-spiro[azepino[1,2-a]quinoline-6,3'-benzofuran]-2'-one (3k):

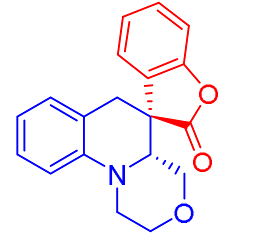
Colourless liquid (56.3 mg, 88% yield); column chromatography eluent, petroleum ether/EtOAc = 50:1; *dr* 1.3:1; Data for inseparable diastereomeric mixture; ^{1}**H NMR (600 MHz, Chloroform-*d*, mixture of diastereomer)** δ 7.29 – 7.24 (m, 1H), 7.21 (app t, *J* = 7.8 Hz, 2H), 7.14 (d, *J* = 7.8 Hz, 1H), 7.12 (d, *J* = 7.8 Hz, 1H), 7.02 (app t, *J* = 7.2 Hz, 2H), 6.98 – 6.94 (comp, 2H), 6.86 (d, *J* = 7.8 Hz, 1H), 6.77 – 6.72 (comp, 3H), 6.69 (app t, *J* = 7.2 Hz, 1H), 4.00 (ddd, *J* = 15.3, 6.4, 2.2 Hz, 1H), 3.70 (dd, *J* = 10.2, 4.2 Hz, 1H), 3.59-3.54 (m, 2H), 3.51 (d, *J* = 16.2 Hz, 1H), 3.39-3.35 (m, 1H), 3.23 (dd, *J* = 11.4, 4.2 Hz, 1H), 2.97-2.92 (m, 1H), 2.85 (d, *J* = 16.2 Hz, 1H), 2.72 (d, *J* = 16.2 Hz, 1H), 2.21 – 2.16 (m, 1H), 2.14 – 2.07 (m, 1H), 1.84 – 1.80 (m, 1H), 1.74 – 1.70 (m, 1H), 1.66 – 1.57 (m, 4H), 1.54 – 1.46 (m, 2H), 1.42 – 1.28 (m, 3H); ^{13}**C NMR (150 MHz, Chloroform-*d*, major diastereomer)** δ 177.8, 151.9, 143.0, 131.5, 130.0, 128.5, 128.1, 125.1, 124.2, 117.3, 116.3, 110.3, 110.1, 63.0, 50.6, 46.0, 32.0, 30.1, 27.4, 25.8, 25.7; ^{13}**C NMR (150 MHz, Chloroform-*d*, minor diastereomer)** δ 178.8, 153.1, 147.0, 129.8, 128.6, 128.2, 127.6, 125.4, 124.1, 118.8, 115.7, 113.5, 110.3, 63.8, 50.1, 48.6, 37.7, 30.2, 29.0, 28.8, 26.4; **HRMS**(ESI, m/z) calcd for $C_{21}H_{21}NO_2$ $[M+Na]^+$ 342.1470, found 342.1463.



3l

(3S*,4a'R*)-3'-phenyl-1',2',3',4',4a',6'-hexahydro-2H-spiro[benzofuran-3,5'-pyrazino[1,2-a]quinolin]-2-one (3l):

Yellow solid (53.3 mg, 70 % yield); column chromatography eluent, petroleum ether/EtOAc = 50:1; mp 206-208 °C; Single diastereomer; **^{1}H NMR (600 MHz, Chloroform-*d*)** δ 7.30 – 7.27 (comp, 2H), 7.25 (app t, *J* = 7.8 Hz, 2H), 7.17 (d, *J* = 7.8 Hz, 1H), 7.07 (d, *J* = 8.4 Hz, 1H), 7.01 – 6.99 (comp, 2H), 6.89 – 6.86 (comp, 4H), 6.84 (app t, *J* = 7.2 Hz, 1H), 4.09 (d, *J* = 11.4 Hz, 1H), 3.78 (dd, *J* = 10.8, 2.4 Hz, 1H), 3.67 – 3.62 (m, 2H), 3.49 (d, *J* = 11.4 Hz, 1H), 3.20 (td, *J* = 11.8, 3.0 Hz, 1H), 2.84 – 2.80 (m, 2H), 2.11 (t, *J* = 10.8 Hz, 1H); **^{13}C NMR (151 MHz, Chloroform-*d*)** δ 177.8 , 152.8 , 150.4 , 145.2 , 130.2 , 129.2, 128.9 , 128.1 , 127.9 , 125.9 , 124.5 , 120.5 , 119.3 , 119.2 , 116.7 , 113.0 , 110.4 , 58.4 , 51.4 , 48.9 , 47.6 , 46.7 , 38.1; **HRMS**(ESI, m/z) calcd for $C_{25}H_{22}N_2O_2$ $[M+H]^+$ 383.1760, found 383.1773.

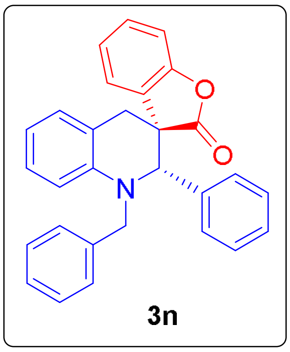


3m

(3'S*,4aR*)-2,4,4a,6-tetrahydro-1H,2'H-spiro[[1,4]oxazino[4,3-a]quinoline-5,3'-benzofuran]-2'-one (3m):

Colourless solid (39.7 mg, 64% yield); column chromatography eluent, petroleum ether/EtOAc = 50:1; mp 142-143 °C; Single diastereomer; **^{1}H NMR (600 MHz, Chloroform-*d*)** δ 7.30 (app t, *J* = 7.8 Hz, 1H), 7.27 – 7.24 (m, 1H), 7.15 (d, *J* = 8.4 Hz, 1H), 7.01 (app t, *J* = 7.2 Hz, 1H), 6.97 (app t, *J* = 8.4 Hz, 2H), 6.88 (d, *J* = 7.2 Hz, 1H), 6.82 (t, *J* = 7.2 Hz, 1H), 3.97 (dd, *J* = 11.4, 3.0 Hz, 1H), 3.78 (dd, *J* = 12.0, 1.2 Hz, 1H), 3.74 (dd, *J* = 10.8, 2.4 Hz, 1H), 3.62 (dd, *J* = 10.8, 3.6 Hz, 1H), 3.57 (d, *J* = 15.6 Hz, 1H), 3.48 (td, *J* = 12.0, 3.0 Hz, 1H), 3.08 (td, *J* = 12.0, 3.6 Hz, 1H), 2.77 (d, *J* = 15.6 Hz, 1H), 2.73 (t, *J* = 10.8 Hz, 1H); **^{13}C NMR (150 MHz, Chloroform-*d*)** δ 177.4 , 152.7 , 145.0 , 130.3 , 129.0 , 128.1

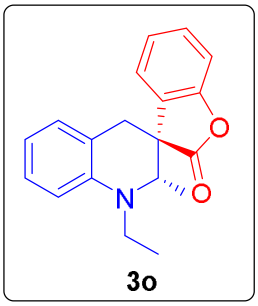
, 127.8 , 125.9 , 124.6 , 119.3 , 119.1 , 112.4 , 110.5 , 67.4 , 66.8 , 57.9 , 46.3 , 46.3 , 37.9 ; **HRMS** (ESI, m/z) calcd for $C_{19}H_{17}NO_3$ $[M+Na]^+$ 330.1106, found 330.1109.



3n

(2'S,3S)-1'-benzyl-2'-phenyl-2',4'-dihydro-1'H,2H-spiro[benzofuran-3,3'-quinolin]-2-one (3n):

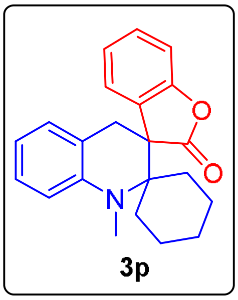
Yellow solid (76.5 mg, 91% yield); column chromatography eluent, petroleum ether/EtOAc = 50:1; mp 137-140 °C; *dr*>3.2:1; Data for major diastereomer; **^{1}H NMR (600 MHz, Chloroform-*d*)** δ 7.29 – 7.26 (comp, 3H), 7.25 – 7.22 (comp, 3H), 7.21 – 7.18 (comp, 2H), 7.14 (d, *J* = 7.2 Hz, 2H), 7.07 (d, *J* = 7.2 Hz, 2H), 7.03 – 6.99 (comp, 3H), 6.91 (d, *J* = 7.8 Hz, 1H), 6.82 (app t, *J* = 7.2 Hz, 1H), 6.71 (dd, *J* = 7.2, 1.2 Hz, 1H), 4.89 (s, 1H), 4.78 (d, *J* = 17.4 Hz, 1H), 4.18 (d, *J* = 16.8 Hz, 1H), 3.62 (d, *J* = 15.6 Hz, 1H), 3.00 (d, *J* = 15.6 Hz, 1H); **^{13}C NMR (150 MHz, Chloroform-*d*)** δ 177.0 , 152.8 , 145.9 , 138.1 , 136.0 , 129.9 , 129.0 , 128.5 , 128.4 , 128.4 , 128.3 , 127.7 , 126.9 , 126.9 , 126.8 , 126.0 , 123.8 , 119.2 , 118.1 , 114.0 , 110.2 , 67.1 , 52.6 , 50.4 , 36.8 ; **HRMS** (ESI, m/z) calcd for $C_{29}H_{23}NO_2$ $[M+H]^+$ 418.1807, found 353.1816.



3o

(2'S*,3S*)-1'-ethyl-2'-methyl-2',4'-dihydro-1'H,2H-spiro[benzofuran-3,3'-quinolin]-2-one (3o):

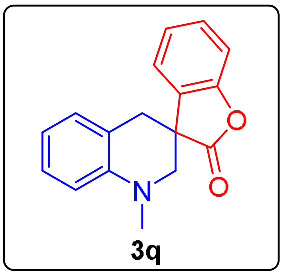
Colourless liquid (59.4 mg, 99% yield); column chromatography eluent, petroleum ether/EtOAc = 50:1; *dr* 1.3:1; Data for inseparable diastereomeric mixture; **^{1}H NMR (600 MHz, Chloroform-*d*, major diastereomer)** δ 7.24 – 7.20 (comp, 2H), 7.12 (d, *J* = 7.8 Hz, 1H), 7.04 (d, *J* = 7.2 Hz, 1H), 6.94 (app t, *J* = 7.2 Hz, 1H), 6.75 (dd, *J* = 4.5, 3.9 Hz, 1H), 6.72 – 6.68 (comp, 2H), 3.55 (d, *J* = 16.2 Hz, 1H), 3.45 – 3.39 (m, 1H), 3.32 – 3.29 (m, 1H), 3.28 – 3.22 (m, 1H), 2.71 (d, *J* = 16.2 Hz, 1H), 1.37 (d, *J* = 6.6 Hz, 3H), 1.12 (t, *J* = 7.2 Hz, 3H); **^{1}H NMR (600 MHz, Chloroform-*d*, minor diastereomer)** δ 7.29 – 7.27 (comp, 2H), 7.15 (d, *J* = 8.4 Hz, 1H), 6.98 (app t, *J* = 7.5 Hz, 2H), 6.87 (d, *J* = 8.4 Hz, 1H), 6.73 (dd, *J* = 6.0, 0.6 Hz, 2H), 3.82 (q, *J* = 6.6 Hz, 1H), 3.65 – 3.58 (m, 1H), 3.47 (d, *J* = 15.6 Hz, 1H), 3.38 – 3.33 (m, 1H), 2.78 (d, *J* = 15.6 Hz, 1H), 1.17 (t, *J* = 7.2 Hz, 3H), 1.00 (d, *J* = 6.0 Hz, 3H); **^{13}C NMR (150 MHz, Chloroform-*d*, major diastereomer)** δ 177.7, 152.0, 142.3, 130.2, 128.6, 128.0, 125.6, 125.6, 124.0, 117.0, 116.3, 110.8, 110.1, 58.2, 46.4, 45.2, 31.6, 14.6, 13.3; **^{13}C NMR (150 MHz, Chloroform-*d*, minor diastereomer)** δ 178.5, 153.0, 144.9, 131.1, 129.9, 128.7, 128.0, 127.8, 124.3, 118.4, 116.2, 112.1, 110.2, 55.6, 49.5, 41.0, 37.3, 16.0, 12.6; **HRMS**(ESI, m/z) calcd for $C_{19}H_{18}NO_2$ $[M]^+$ 294.1494, found 294.1497.



3p

1'H-spiro[cyclohexane-1,2'-quinoline]-1'-methyl-2',4'-dihydro-1'H,2H-spiro[benzofuran-3,3'-quinolin]-2-one (3p):

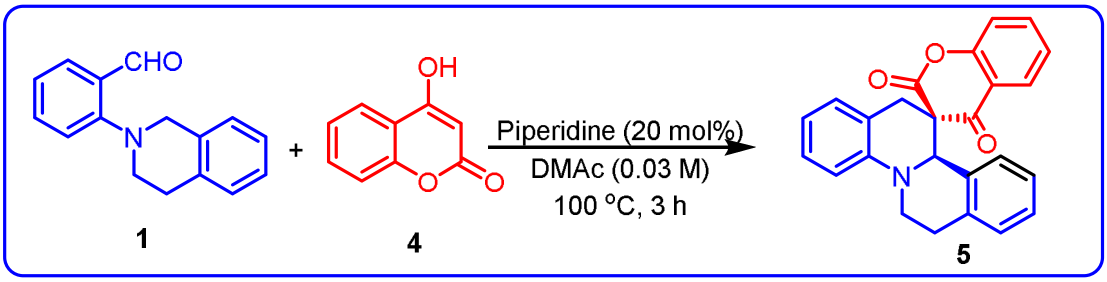
Colourless solid (55.6 mg, 83% yield); column chromatography eluent, petroleum ether/EtOAc = 50:1; mp 140-142 °C; Data for single isomer; **^{1}H NMR (600 MHz, Chloroform-*d*)** δ 7.30 – 7.26 (comp, 1H), 7.13 (d, *J* = 7.2 Hz, 1H), 7.07 (d, *J* = 7.2 Hz, 1H), 6.98 (dt, *J* = 7.6, 4.4 Hz, 1H), 6.91 (d, *J* = 7.8 Hz, 1H), 6.81 – 6.79 (m, 1H), 6.64 (dd, *J* = 6.6, 0.6 Hz, 1H), 3.57 (d, *J* = 16.8 Hz, 1H), 3.19 (s, 3H), 2.78 (d, *J* = 16.8 Hz, 1H), 2.08 – 2.03 (m, 1H), 1.82 – 1.79 (m, 1H), 1.73 – 1.71 (m, 1H), 1.65 – 1.60 (m, 2H), 1.53 (d, *J* = 16.8 Hz, 2H), 1.49 – 1.43 (m, 1H), 1.29 – 1.22 (m, 2H); **^{13}C NMR (150 MHz, Chloroform-*d*)** δ 178.8 , 152.8 , 145.9 , 129.9 , 129.2 , 128.4 , 127.4 , 125.1 , 124.1 , 119.1 , 117.3 , 114.7 , 109.9 , 61.1 , 52.3 , 38.2 , 33.9 , 30.1 , 29.6 , 25.1 , 23.3 , 22.1;**HRMS**(ESI, m/z) calcd for $C_{22}H_{23}NO_2$ $[M+H]^+$ 334.1807, found 334.1801.



3q

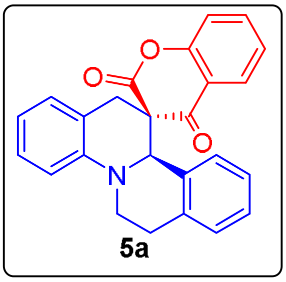
1'-methyl-2',4'-dihydro-1'H,2H-spiro[benzofuran-3,3'-quinolin]-2-one (3q): White solid (33.9 mg, 53% yield); column chromatography eluent, petroleum ether/EtOAc = 50:1; mp 118-120 °C; **^{1}H NMR (600 MHz, Chloroform-*d*)** δ 7.31 (app t, *J* = 7.2 Hz, 1H), 7.29 – 7.26 (m, 1H), 7.19 (d, *J* = 8.4 Hz, 1H), 7.03 – 6.99 (comp, 2H), 6.81 – 6.79 (comp, 2H), 6.76 (app t, *J* = 7.2 Hz, 1H), 3.76 (d, *J* = 11.4 Hz, 1H), 3.48 (d, *J* = 15.6 Hz, 1H), 3.18 (dd, *J* = 10.8, 2.4 Hz, 1H), 3.03 (s, 3H), 2.83 (dd, *J* = 15.6, 2.4 Hz, 1H); **^{13}CNMR (150 MHz, $CDCl_3$)**δ 178.0, 152.4, 144.8, 130.3, 129.8, 128.7, 128.1, 124.9, 124.3, 117.8, 117.2, 110.9, 110.4, 56.6, 43.8, 39.2, 36.5; **HRMS** (ESI, m/z) calcd for $C_{17}H_{15}NO_2$ $[M+H]^+$ 266.1181, found 266.1186.

2.5.7 General Procedure for the Synthesis of the Final Product 5a



To an oven-dried 25 mL round-bottom flask attached with condenser under nitrogen, 2-(3,4-dihydroisoquinolin-2(1H)-yl)benzaldehyde (**1a**) (0.2 mmol) and 4-hydroxy coumarin (**4**) (0.26 mmol) were taken in anhydrous DMAc (6 mL) and the bath temperature was slowly increased to 100 °C. The reaction mixture was kept under the same temperature until the intermediate olefin was consumed completely as monitored by TLC. The reaction mixture worked up with EtOAc (2 x10 mL) and cold water; brine wash needed. Then the organic layer passed through anhydrous Na_2SO_4 and concentrated under vacuo. Finally, it was purified by silica gel (230-400 mesh) column chromatography using petroleum ether/ethyl acetate (20:1) as eluent to obtain the desired spiro-heterocyclic product (3R,11b'R)-6',7',11b',13'-tetrahydrospiro[chroman-3,12'-isoquinolino[2,1-a]quinoline]-2,4-dione (**5a**) in 53% (40.8 mg) yield.

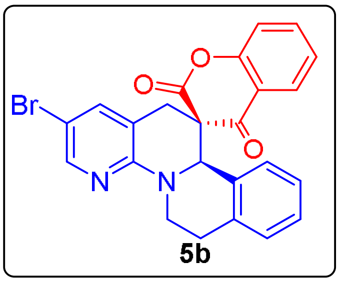
2.5.8 Characterization of Substrates 5a-5e



5a

(3R*,11b'R*)-6',7',11b',13'-tetrahydrospiro[chroman-3,12'-isoquinolino[2,1-a]quinoline]-2,4-dione (5a):

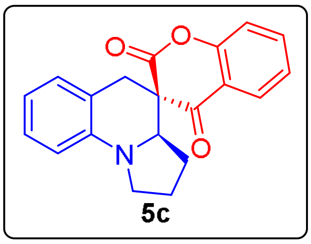
Yellow solid (40.8 mg, 53% yield); column chromatography eluent, petroleum ether/EtOAc = 20:1; mp 150-152 °C; Single diastereomer; **^{1}H NMR (300 MHz, Chloroform-*d*)** δ 7.72 (dd, *J* = 7.8, 1.5 Hz, 1H), 7.37 – 7.29 (m, 1H), 7.29 – 7.24 (m, 1H), 7.23 – 7.16 (m, 1H), 7.07 (t, *J* = 7.6 Hz, 1H), 6.98 – 6.89 (m, 3H), 6.88 – 6.79 (m, 3H), 6.67 (d, *J* = 8.2 Hz, 1H), 4.69 (s, 1H), 4.09 (d, *J* = 17.2 Hz, 1H), 3.91 – 3.79 (m, 1H), 3.44 – 3.29 (m, 1H), 3.18 (d, *J* = 16.9 Hz, 1H), 2.92 – 2.76 (m, 1H), 2.62 (t, *J* = 16.2 Hz, 1H) ; **^{13}C NMR (101 MHz, Chloroform-*d*)** δ 191.3 , 167.8 , 154.0 , 145.3 , 136.1 , 136 , 129.9 , 128.8 , 128.1 , 127.6 , 126.4 , 125.9 , 124.3(x2) , 121.7 , 119.9 , 118.5 , 116.5(x2) , 113.1 , 68.7 , 44.3 , 32.7 , 29.7 , 29.2; **HRMS** (ESI, m/z) calcd for $C_{25}H_{19}NO_3$ $[M+H]^+$ 382.1443, found 382.1440.



5b

(3R*,11b'R*)-2'-bromo-6',7',11b',13'-tetrahydrospiro[chroman-3,12'-isoquinolino[2,1-a][1,8]naphthyridine]-2,4-dione (5b):

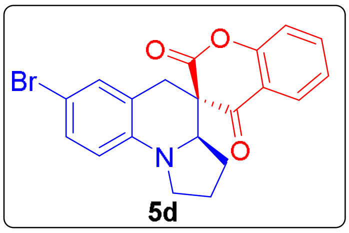
Yellow solid (76.4 mg, 83% yield); column chromatography eluent, petroleum ether/EtOAc = 20:1; mp 204-206 °C; *dr* 25:1; Data for major diastereomer; **^{1}H NMR (400 MHz, Chloroform-*d*)** δ 8.18 (s, 1H), 7.59 – 7.57 (comp, 2H), 7.36 (dt, *J* = 30.7, 7.4 Hz, 1H), 7.22 – 7.13 (comp, 2H), 7.05 (dd, *J* = 16.0, 8.0 Hz, 1H), 6.95 (dt, *J* = 15.8, 7.2 Hz, 1H), 6.72 – 6.64 (comp, 2H), 4.79 (s, 1H), 4.74 – 4.63 (m, 1H), 3.98 (dd, *J* = 25.2, 17.6 Hz, 1H), 3.26 – 2.96 (m, 3H), 2.49 – 2.39 (m, 1H); **^{13}C NMR (100 MHz, Chloroform-*d*)** δ 191.5 , 168.2 , 153.3 , 145.6 , 138.1 , 137.1 , 137.0 , 136.2 , 129.1 , 128.4 , 128.1 , 127.4 , 126.4 , 125.3 , 124.7 , 119.9 , 118.3 , 116.4 , 108.4 , 67.0 , 60.5 , 41.4 , 32.4 , 29.4; **HRMS**(ESI, m/z) calcd for $C_{24}H_{17}BrN_2O_3$ $[M+H]^+$ 461.0501, found 461.0492.



5c

(3R*,3a'R*)-2',3',3a',5'-tetrahydro-1'H-spiro[chroman-3,4'-pyrrolo[1,2-a]quinoline]-2,4-dione (5c):

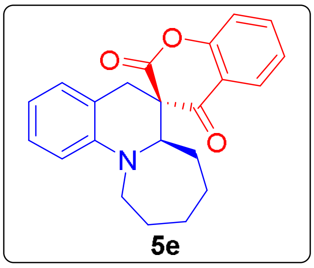
White solid (62.1 mg, 97% yield); column chromatography eluent, petroleum ether/EtOAc = 20:1; mp 150–152 °C; *dr*>2:1; Data for inseparable diastereomeric mixture; **^{1}H NMR (600 MHz, Chloroform-*d*, mixture of diastereomer)** δ 8.02 (d, *J* = 7.8 Hz, 1H), 7.78 (d, *J* = 7.2 Hz, 1H), 7.72 (app t, *J* = 7.2 Hz, 1H), 7.67 (app t, *J* = 7.8 Hz, 1H), 7.34 (app t, *J* = 7.5 Hz, 1H), 7.28 (d, *J* = 6.6 Hz, 1H), 7.24 (d, *J* = 7.8 Hz, 1H), 7.20 (app t, *J* = 6.6 Hz, 1H), 7.10 (d, *J* = 7.2 Hz, 1H), 7.00 (d, *J* = 7.2 Hz, 1H), 6.71 (app t, *J* = 7.2 Hz, 1H), 6.69 – 6.64 (comp, 2H), 4.17 – 4.10 (m, 1H), 3.92 – 3.89 (m, 1H), 3.65 – 3.57 (m, 3H), 3.41 – 3.39 (m, 1H), 3.11 (d, *J* = 16.2 Hz, 1H), 3.18 (d, *J* = 15.6 Hz, 1H), 2.24 – 2.19 (m, 1H), 2.08 – 2.04 (m, 1H), 2.02 – 1.94 (m, 3H), 1.70 – 1.64 (m, 1H); **^{13}C NMR (150 MHz, Chloroform-*d*, major diastereomer)** δ 192.7, 164.8, 155.2, 143.1, 137.3, 128.3, 127.5, 127.1, 124.9, 118.3, 117.6, 117.3, 116.2, 111.2, 63.8, 55.1, 47.4, 36.2, 28.0, 23.4; **^{13}C NMR (150 MHz, Chloroform-*d*, minor diastereomer)** δ 189.4, 170.2, 154.1, 143.6, 136.5, 130.2, 128.2, 127.8, 127.1, 125.2, 119.2, 117.0, 116.1, 111.1, 63.8, 54.2, 48.0, 37.8, 27.7, 23.5; **HRMS**(ESI, m/z) calcd for $C_{20}H_{17}NO_3$ $[M+H]^+$ 320.1287, found 320.1289.



5d

(3R*,3a'R*)-7'-bromo-2',3',3a',5'-tetrahydro-1'H-spiro[chroman-3,4'-pyrrolo[1,2-a]quinoline]-2,4-dione (5d):

Yellow solid (64.8 mg, 81% yield);column chromatography eluent, petroleum ether/EtOAc = 20:1;mp 152-154°C; *dr*>2.5:1; Data for major isomer in an inseparable diastereomeric mixture;**^{1}H NMR (600 MHz, Chloroform-*d*)** δ 8.02 (dd, *J* = 7.8, 1.8 Hz, 1H), 7.75 – 7.72 (m, 1H), 7.36 (app t, *J* = 7.2 Hz, 1H), 7.29 – 7.27 (m, 1H), 7.25 (d, *J* = 7.8 Hz, 1H), 7.21 (s, 1H), 6.51 (dd, *J* = 8.4, 2.4 Hz, 1H), 3.86 (dd, *J* = 9.6, 5.4 Hz, 1H), 3.60 (d, *J* = 6.4 Hz, 1H), 3.58 – 3.56 (m, 1H), 3.35 (dtd, *J* = 13.3, 8.8, 8.1, 4.6 Hz, 1H), 3.05 (d, *J* = 16.2 Hz, 1H), 2.07 (dddd, *J* = 11.6, 9.4, 6.0, 2.3 Hz, 1H), 2.00 – 1.95 (m, 2H), 1.68 – 1.61 (m, 1H);**^{13}C NMR (150 MHz, Chloroform-*d*)** δ 192.2 , 164.8 , 155.1 , 142.1 , 137.5 , 130.7 , 130.1 , 127.2 , 125.1 , 120.5 , 118.2 , 117.7 , 112.7 , 107.9 , 63.9 , 54.6 , 47.5 , 35.6 , 28.0 , 23.3 ;**HRMS** (ESI, m/z) calcd for $C_{20}H_{16}BrNO_3$ $[M+H]^+$ 398.0392, found 398.0389.



5e

(3'R*,6aR*)-6a,7,8,9,10,11-hexahydro-5H-spiro[azepino[1,2-a]quinoline-6,3'-chroman]-2',4'-dione (5e):

White solid (22.1 mg, 32% yield); column chromatography eluent, petroleum ether/EtOAc = 20:1;mp 86-88°C; *dr* >2.8:1; Data for major isomer in an inseparable diastereomeric mixture;**^{1}H NMR (400 MHz, Chloroform-*d*)** δ 7.88 (dd, *J* = 14.4, 8.0 Hz, 1H), 7.67 (q, *J* = 7.0 Hz, 1H), 7.29 (td, *J* = 7.6, 4.0 Hz, 1H), 7.24 (d, *J* = 8.0 Hz, 1H), 7.20 (d, *J* = 7.2 Hz, 1H), 7.11 (app t, *J* = 8.0 Hz, 1H), 6.77 (q, *J* = 7.7 Hz, 1H), 6.68 (dd, *J* = 11.2, 8.8 Hz, 1H), 3.81 – 3.64 (m, 3H), 3.51 – 3.40 (m, 1H), 3.13 – 3.06 (m, 1H), 2.02 – 1.98 (m, 1H), 1.73 – 1.65 (m, 1H), 1.59 – 1.54 (m, 2H), 1.44 – 1.40 (m, 4H);**^{13}C NMR (100 MHz, Chloroform-*d*)** δ 190.9 , 167.7 , 154.8 , 142.3 , 136.8 , 129.0 , 127.3 , 126.9 , 124.9 , 119.1 , 118.7 , 117.3 , 117.1 , 111.5 , 64.2 , 60.1 , 50.6 , 29.5 , 27.9 , 26.0 , 25.5 , 25.2 ;**HRMS**(ESI, m/z) calcd for $C_{22}H_{21}NO_3$ $[M+H]^+$ 348.1600, found 348.1598.

Table 2.5.9 Enantioselective Approach of One-pot [1,5]-Hydride Shift/6-Endocyclisation Process of 2-Coumaranone Using Organocatalyst

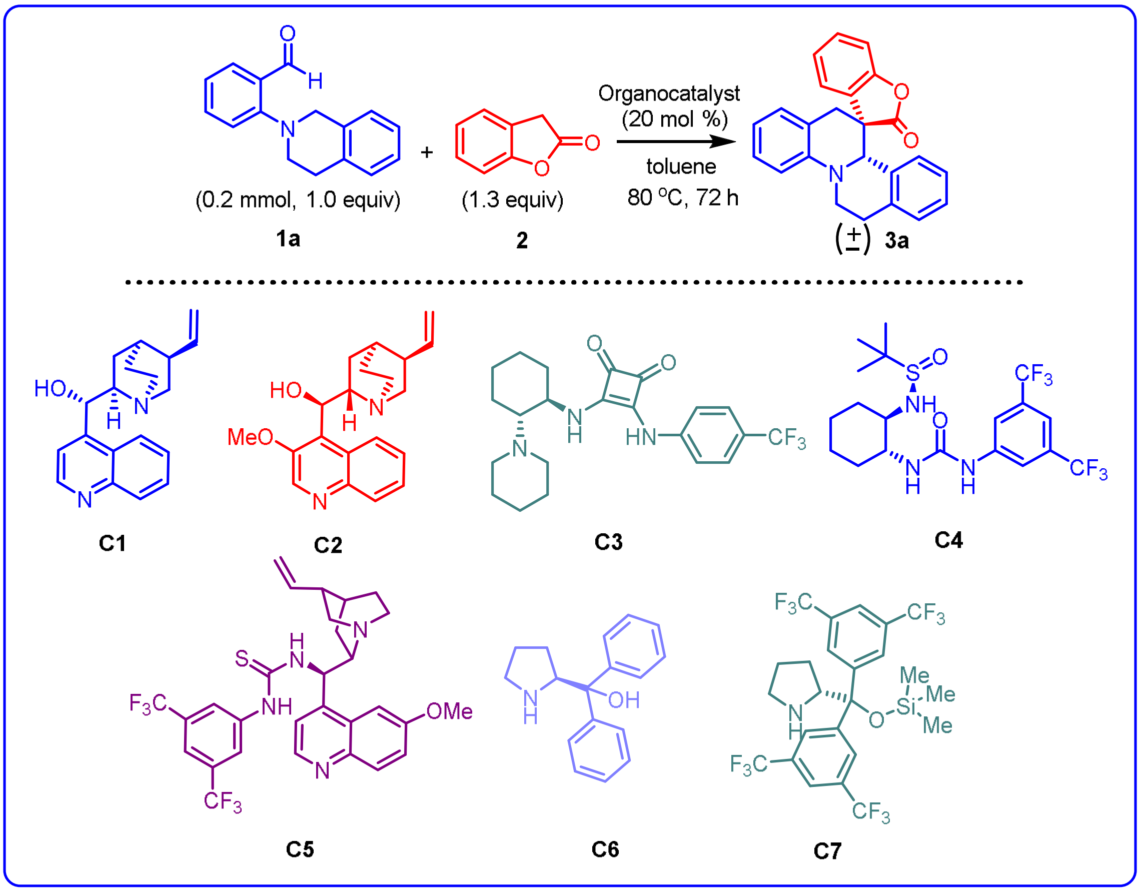


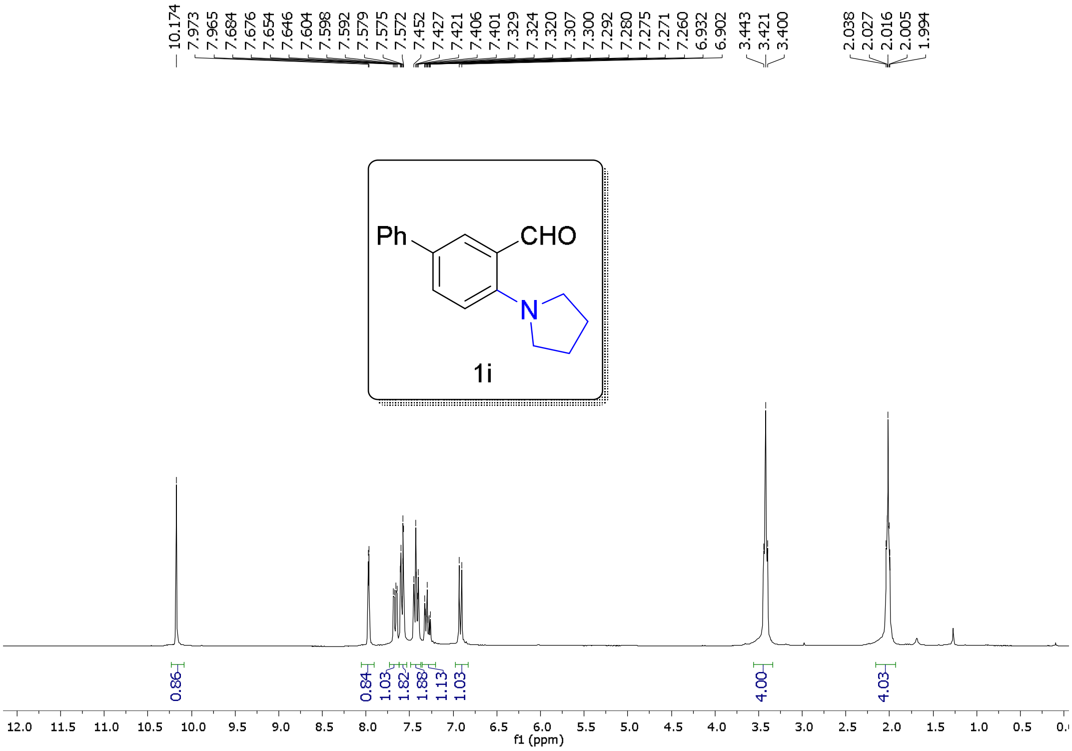
Figure 2.5.9 Representative examples of organocatalysts

entry	organocatalyst	yield[a] (%)	er
1	C1	50	49:51
2	C2	54	50:50
3	C3	60	51:49
4	C4	58	55:45
5	C5	65	52:48
6	C6	56	51:49
7	C7	56	51:49

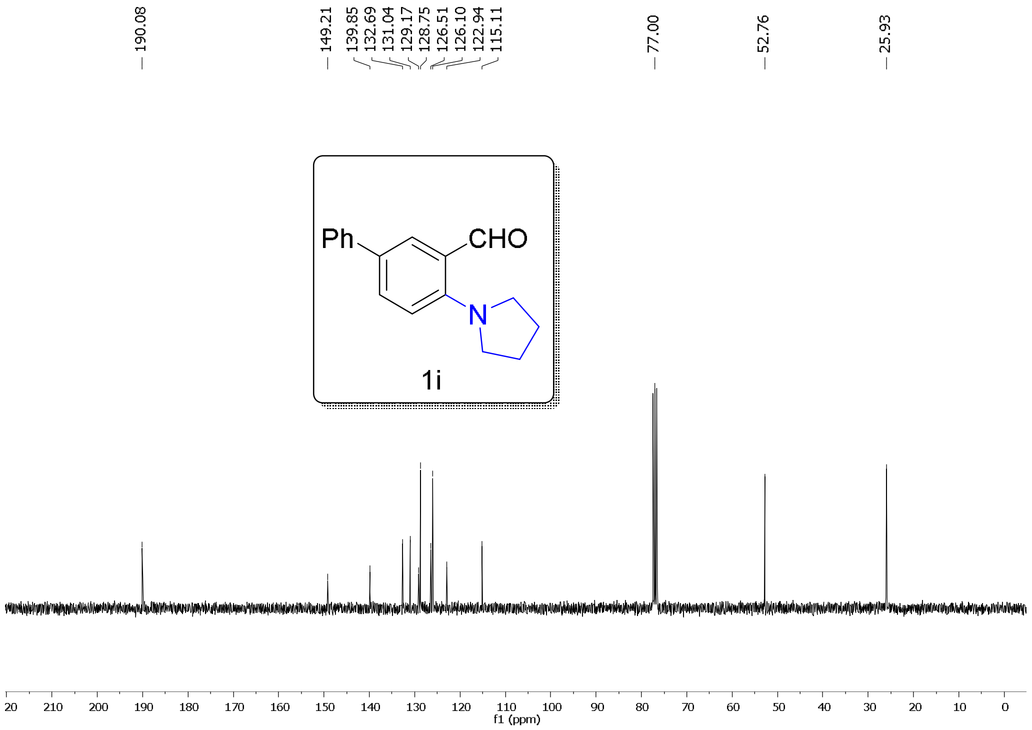
Unless otherwise mentioned, all reactions was done with 0.1 mmol of **1a** and 0.13 mmol of **2** with 20 mol% organocatalyst at 80 °Cin toluene (2 mL) under nitrogen. [a]Isolated yield.

2.5.10 ^{1}H and ^{13}C NMR of Compounds

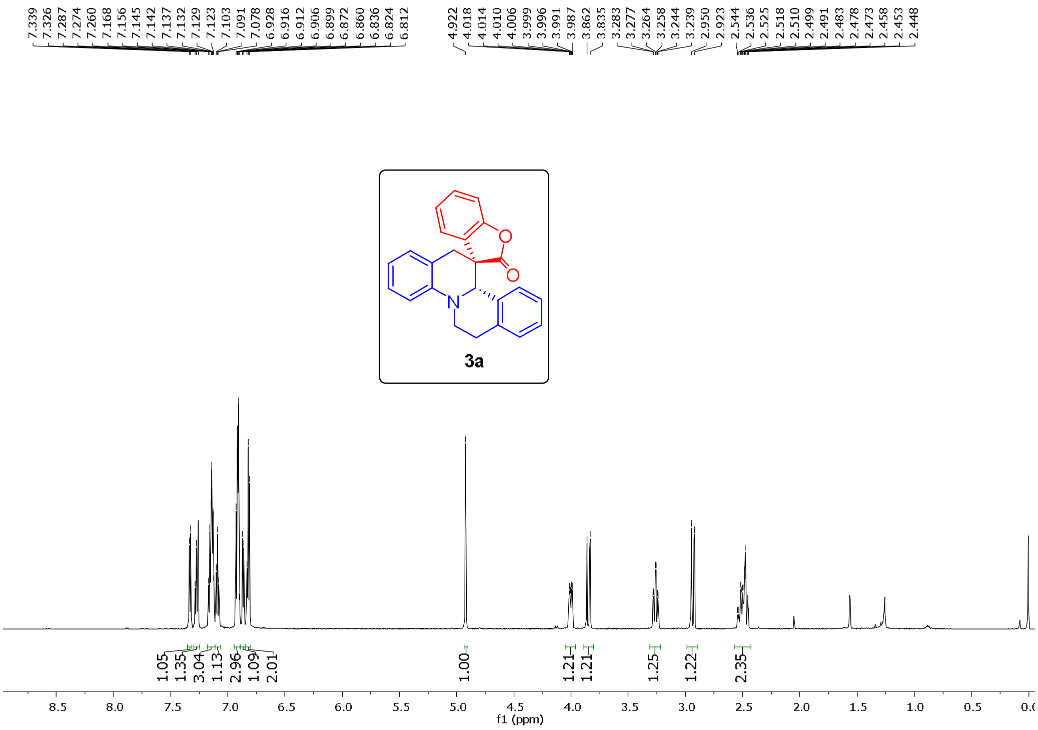
^{1}H NMR of **1i** (300 MHz, Chloroform-*d*)



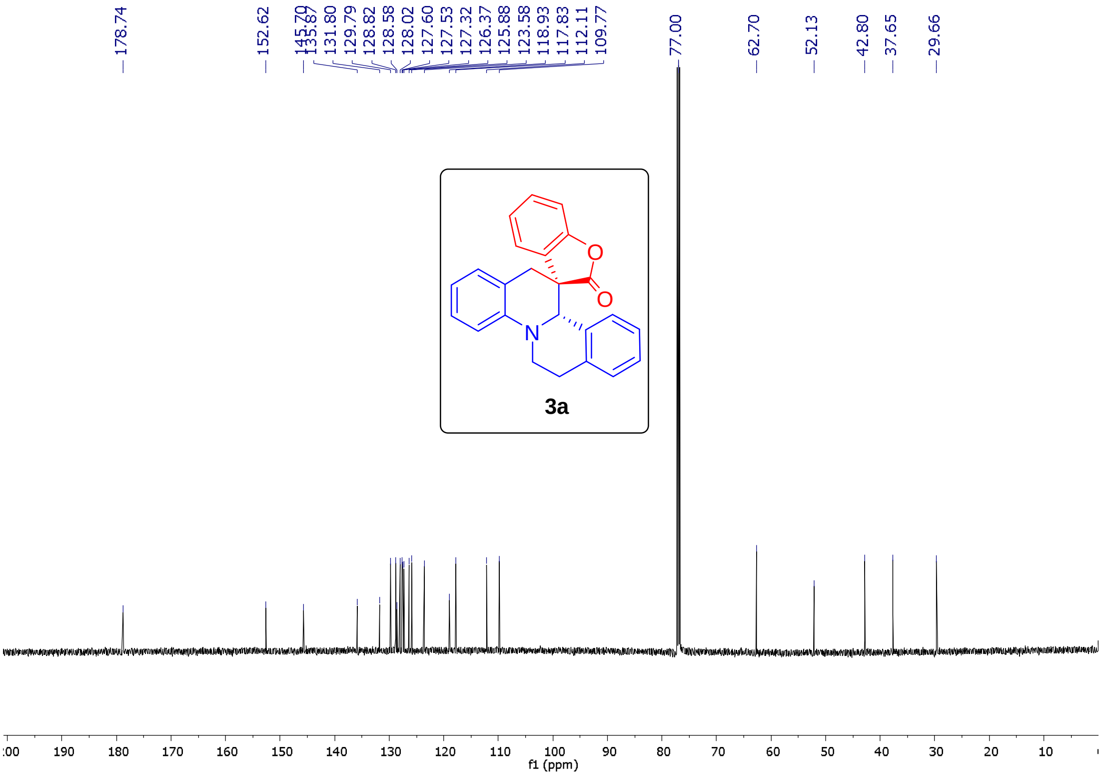
^{13}C NMR of **1i** (75 MHz, CDCl$_3$)



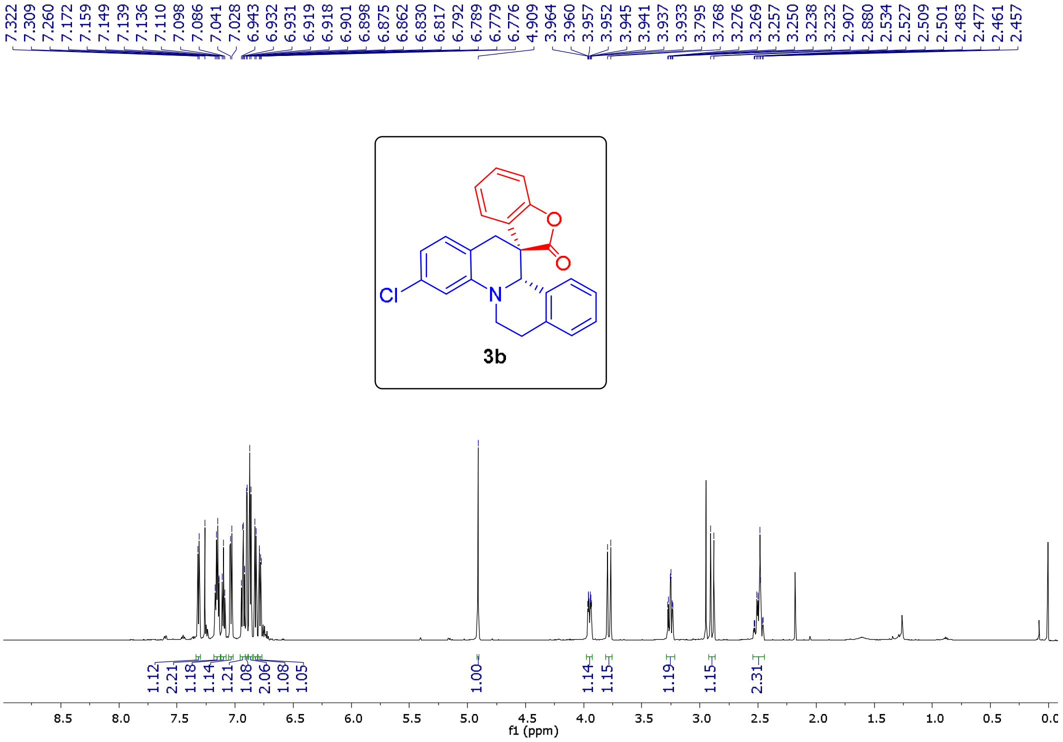
^{1}H NMR of **3a** (600 MHz, Chloroform-*d*)



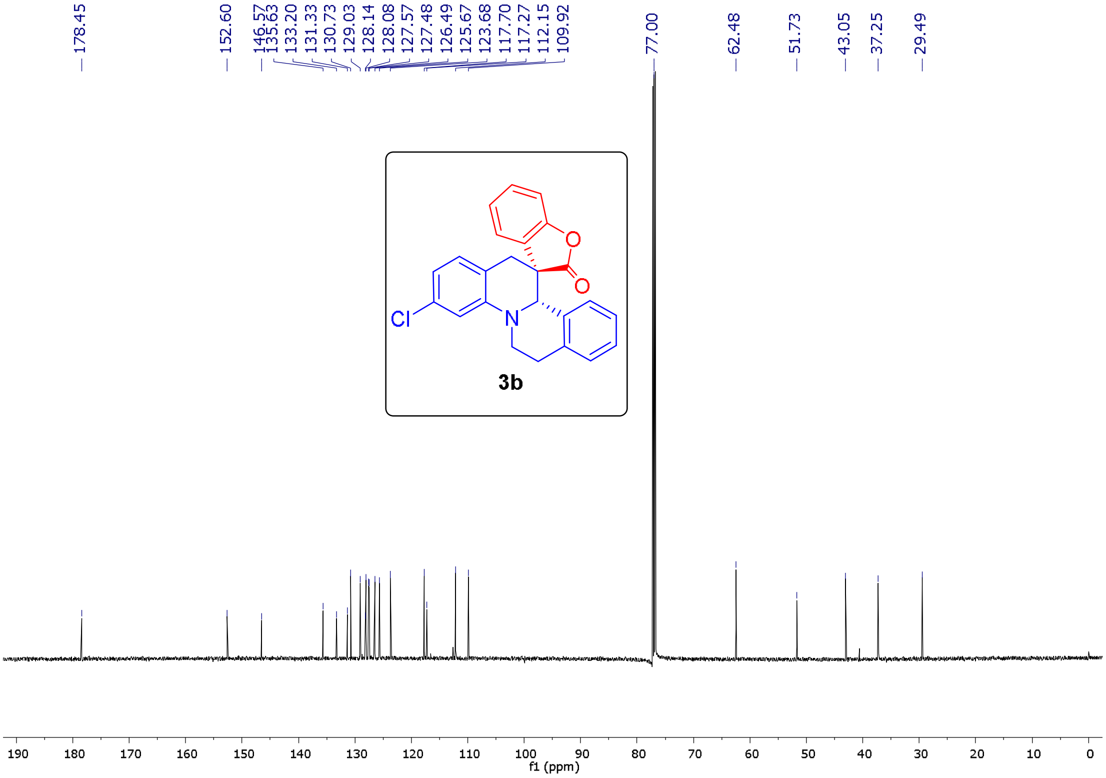
^{13}C NMR of **3a** (151 MHz, $CDCl_3$)



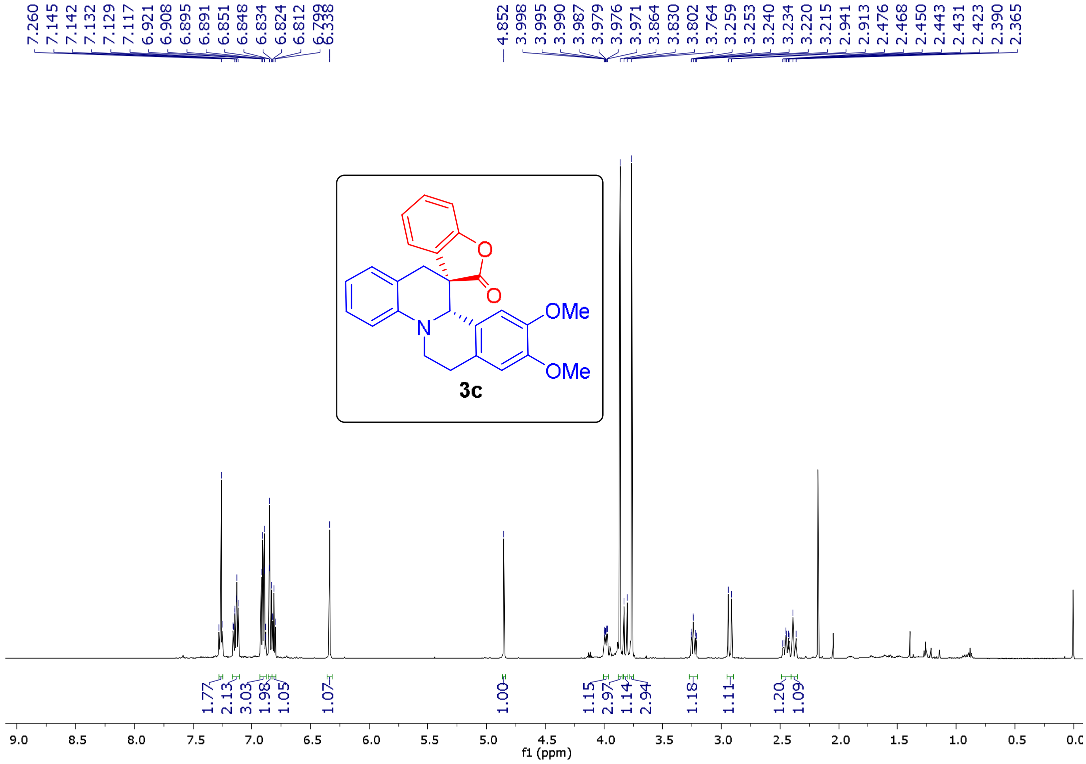
^{1}H NMR of **3b** (600 MHz, Chloroform-*d*)



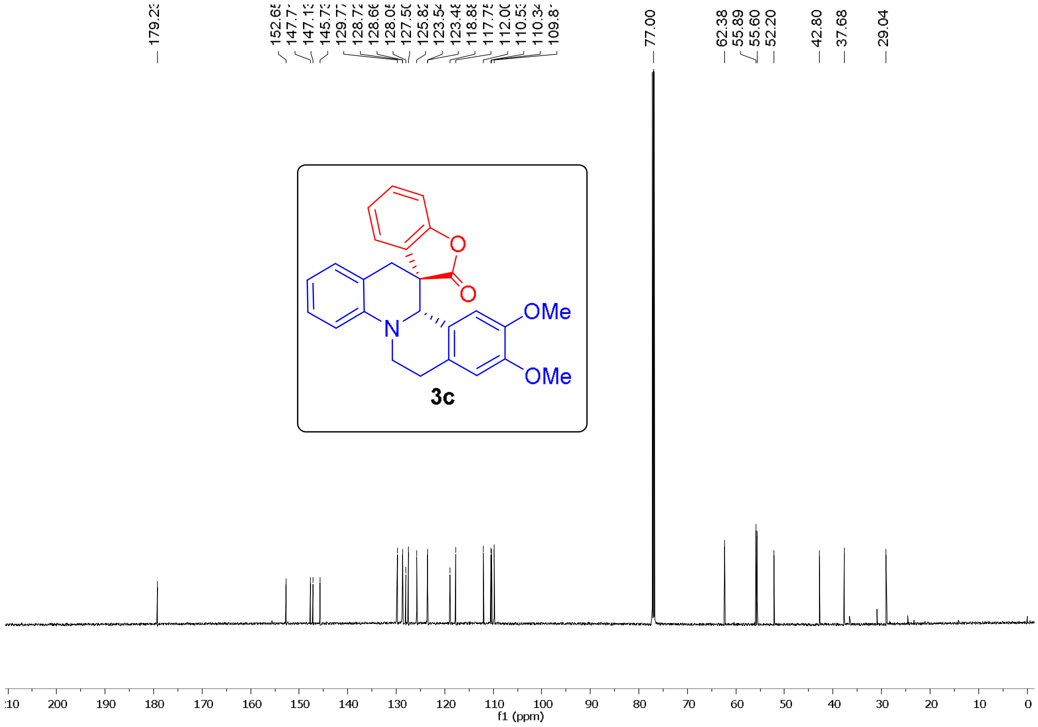
^{13}C NMR of **3b** (151 MHz, $CDCl_3$)



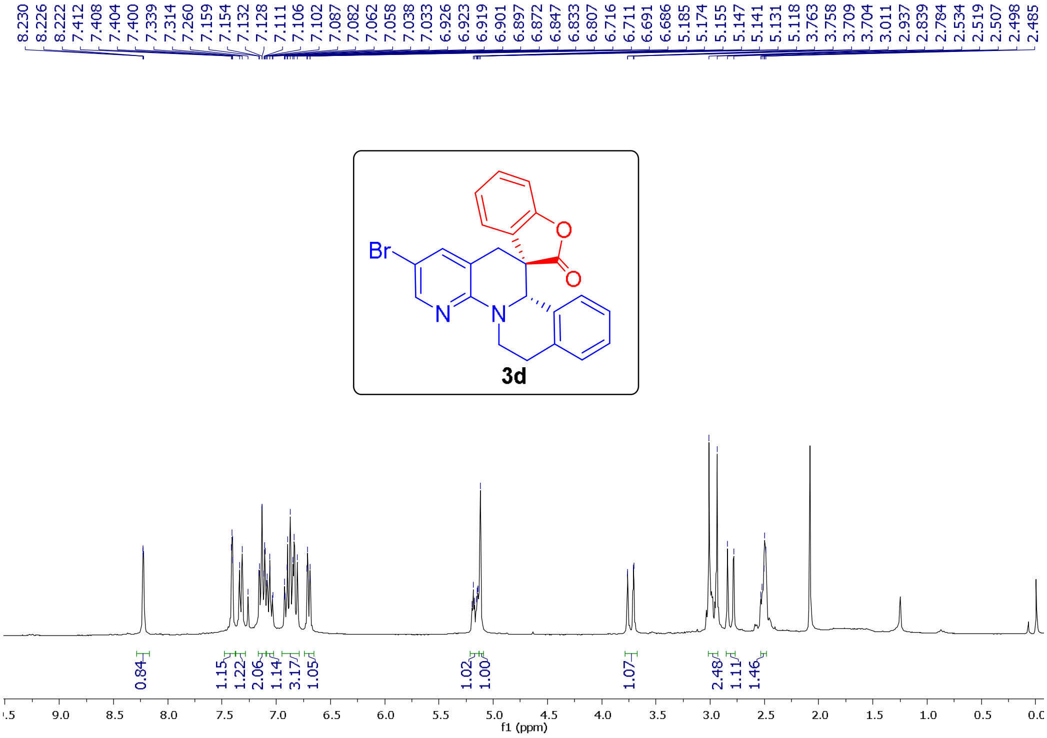
^{1}H NMR of **3c** (600 MHz, Chloroform-*d*)



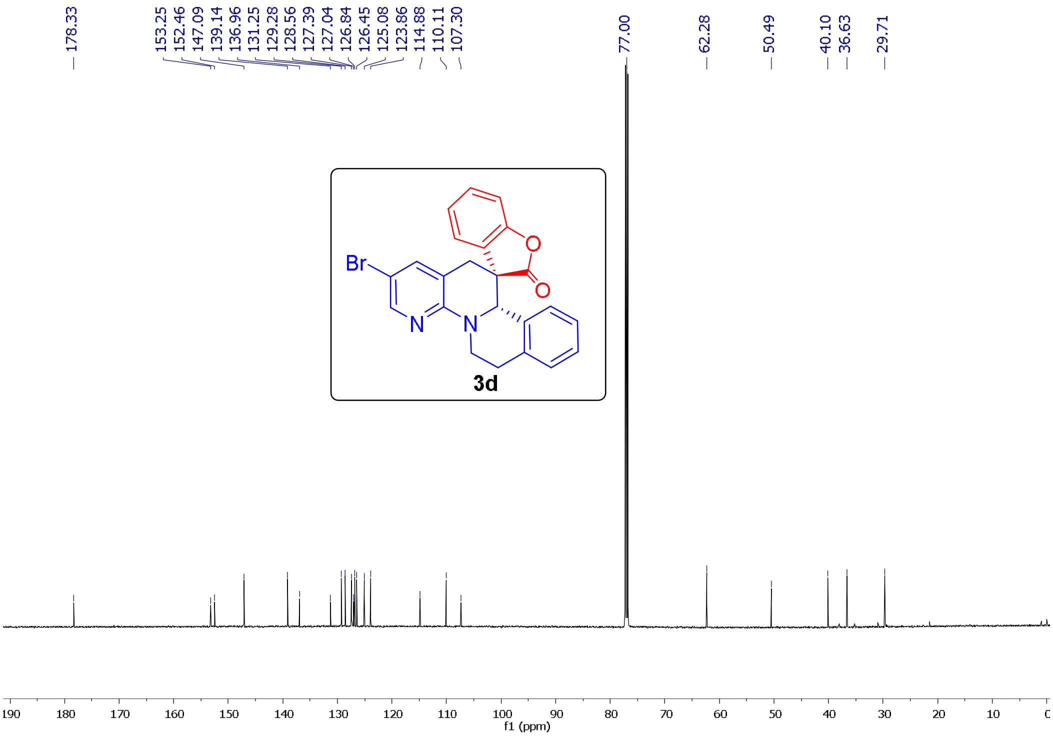
^{13}C NMR of **3c** (151 MHz, CDCl$_3$)



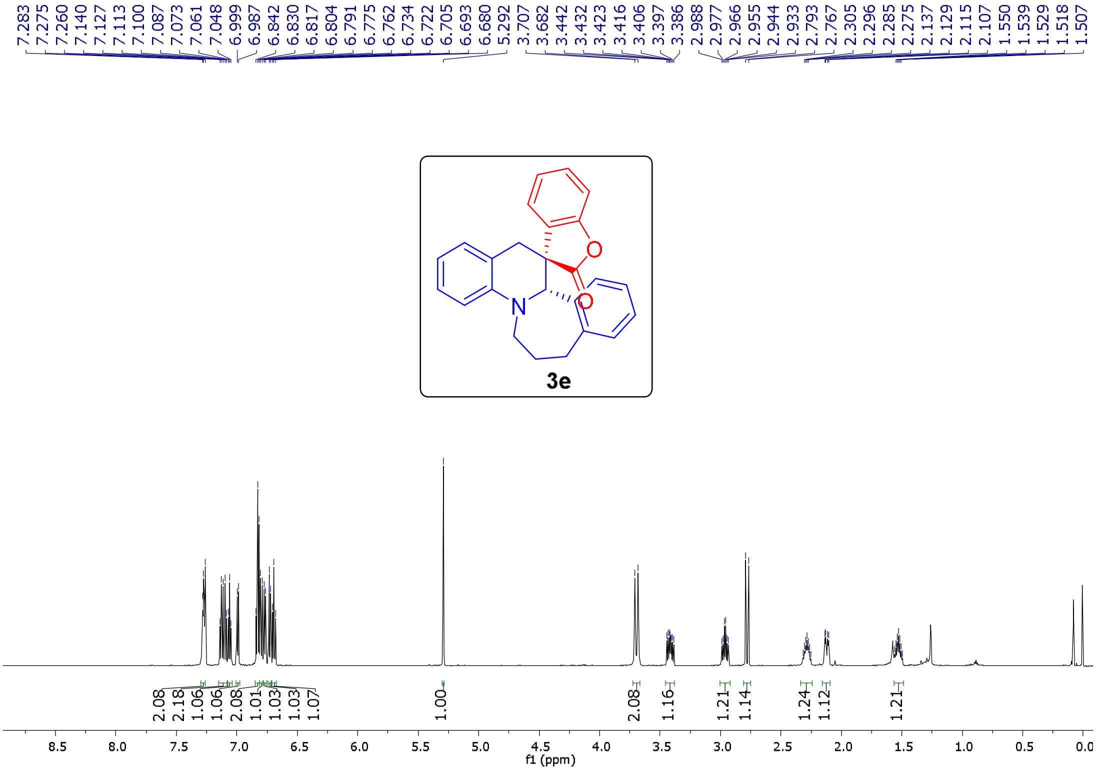
^{1}H NMR of **3d** (300 MHz, Chloroform-*d*)



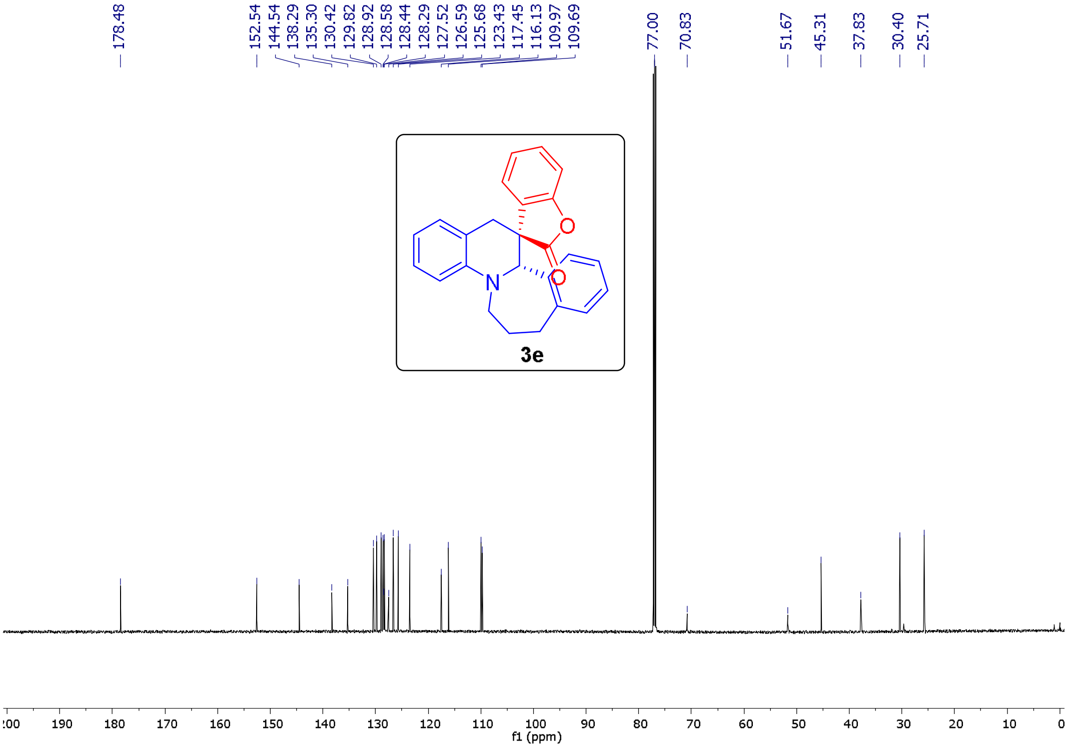
^{13}C NMR of **3d** (151 MHz, $CDCl_3$)



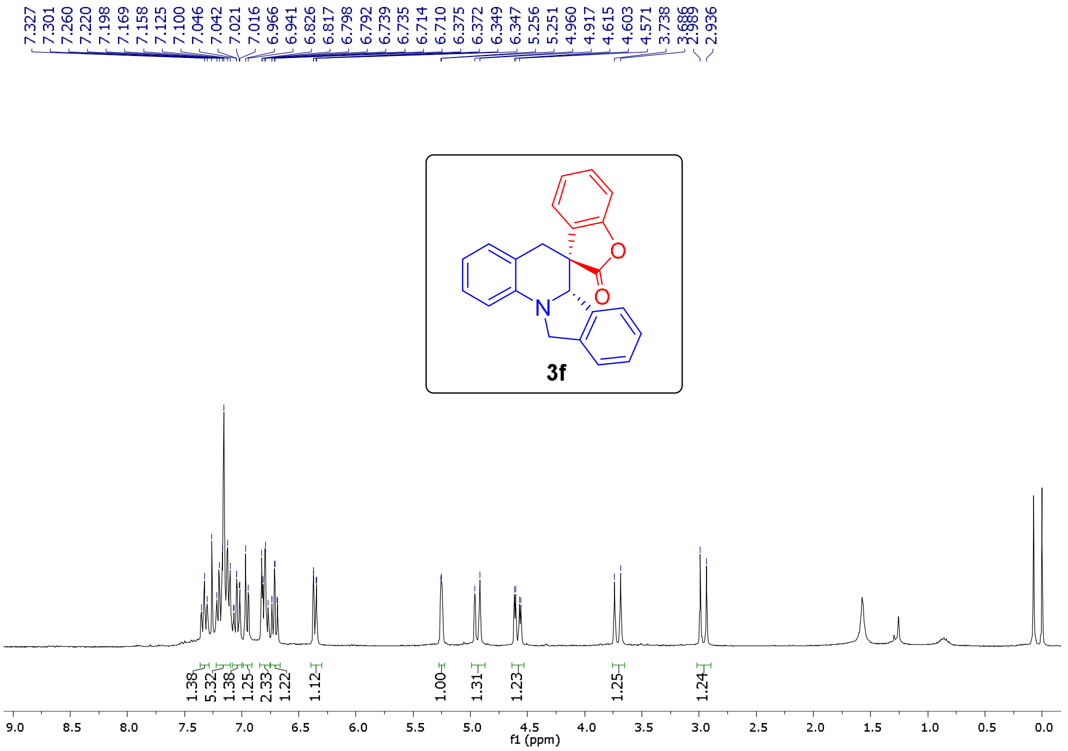
^{1}H NMR of **3e** (600 MHz, Chloroform-*d*)



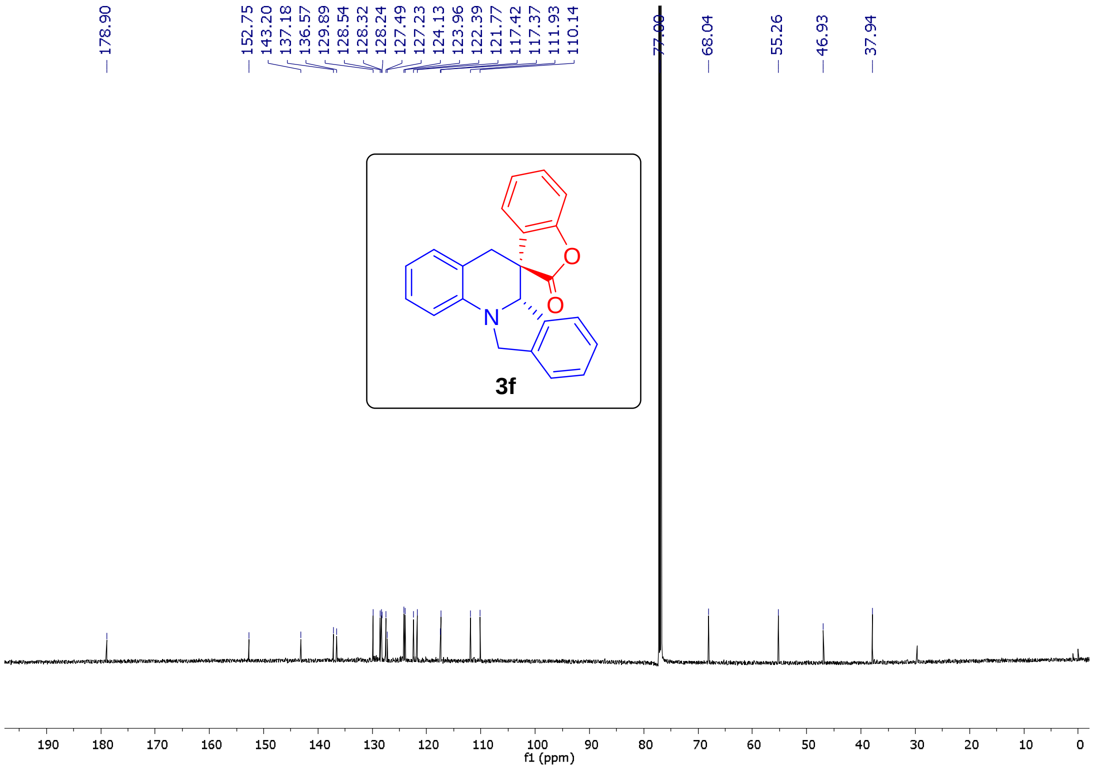
^{13}C NMR of **3e** (151 MHz, CDCl$_3$)



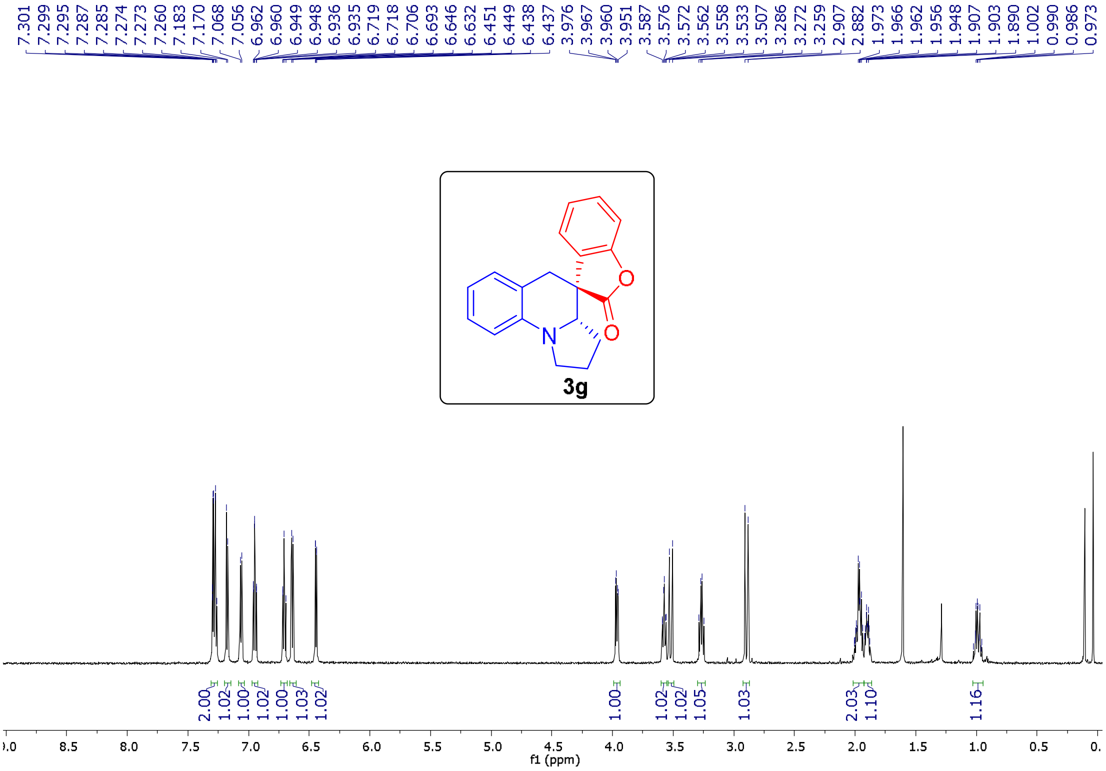
^{1}H NMR of **3f** (300 MHz, Chloroform-*d*)



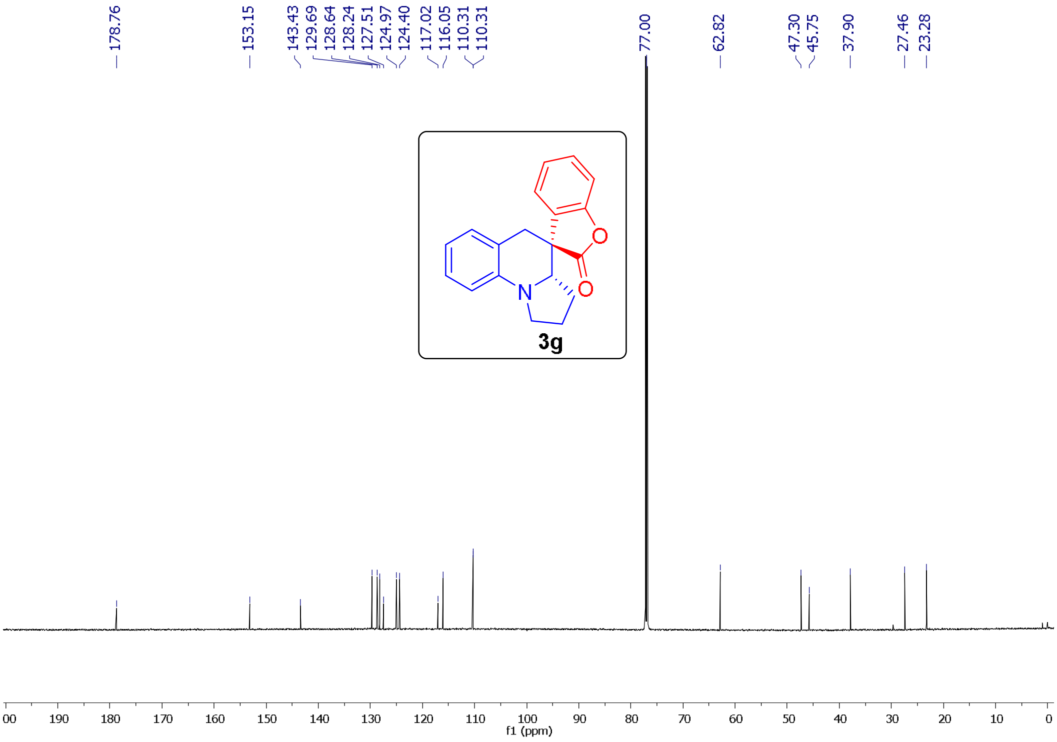
^{13}C NMR of **3f** (151 MHz, CDCl$_3$)



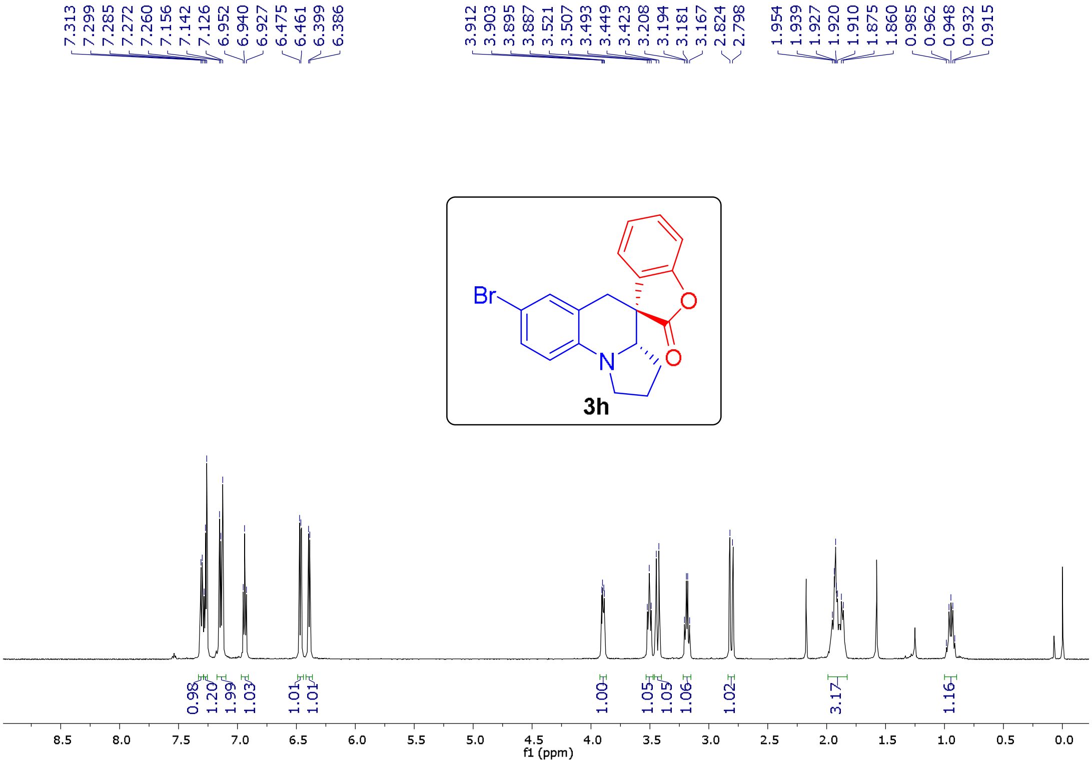
^{1}H NMR of **3g** (600 MHz, Chloroform-*d*)



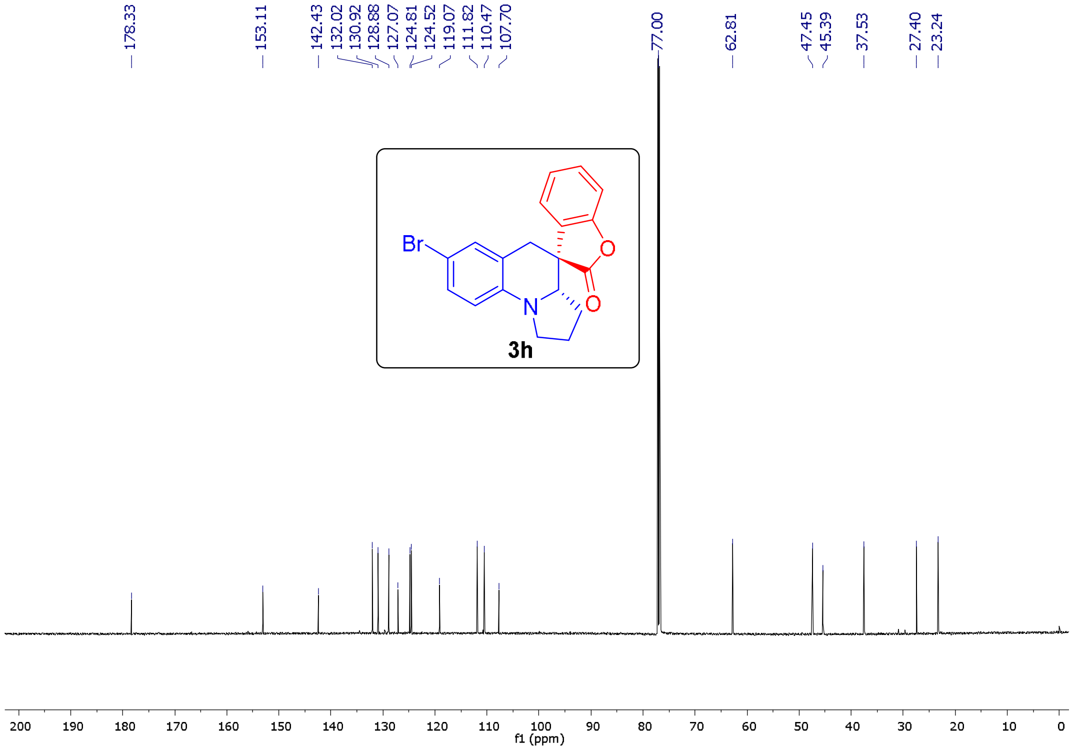
^{13}C NMR of **3g** (151 MHz, $CDCl_3$)



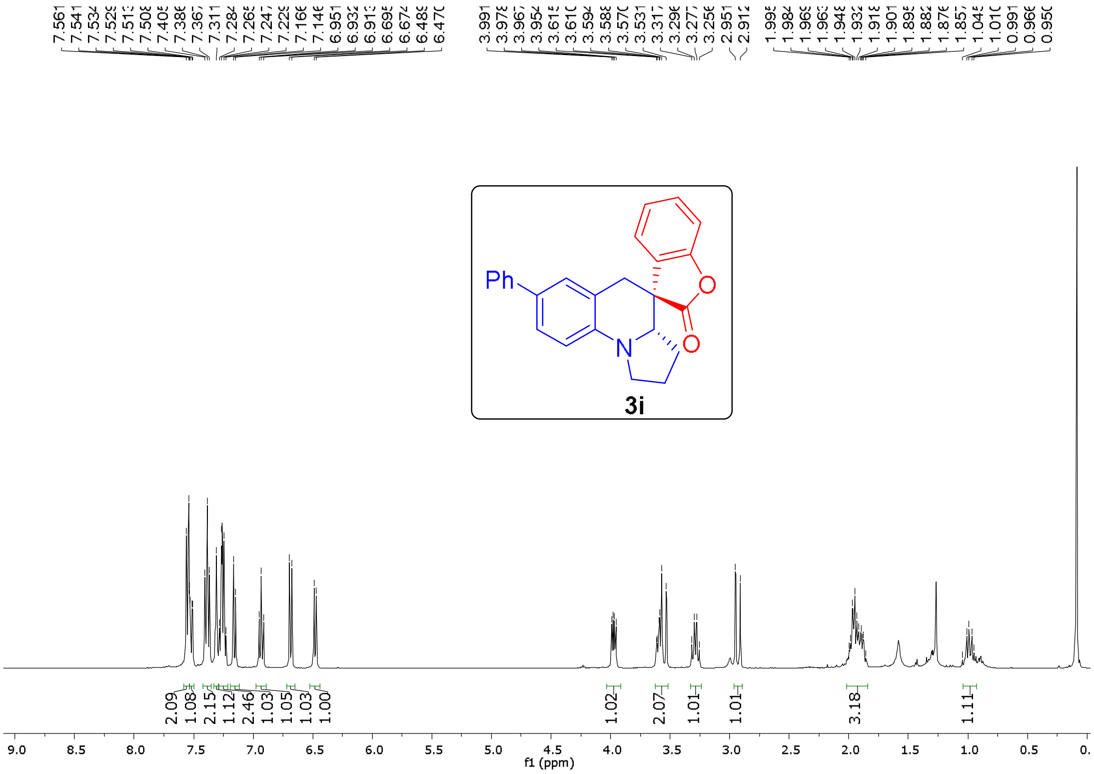
^{1}H NMR of **3h** (600 MHz, Chloroform-*d*)



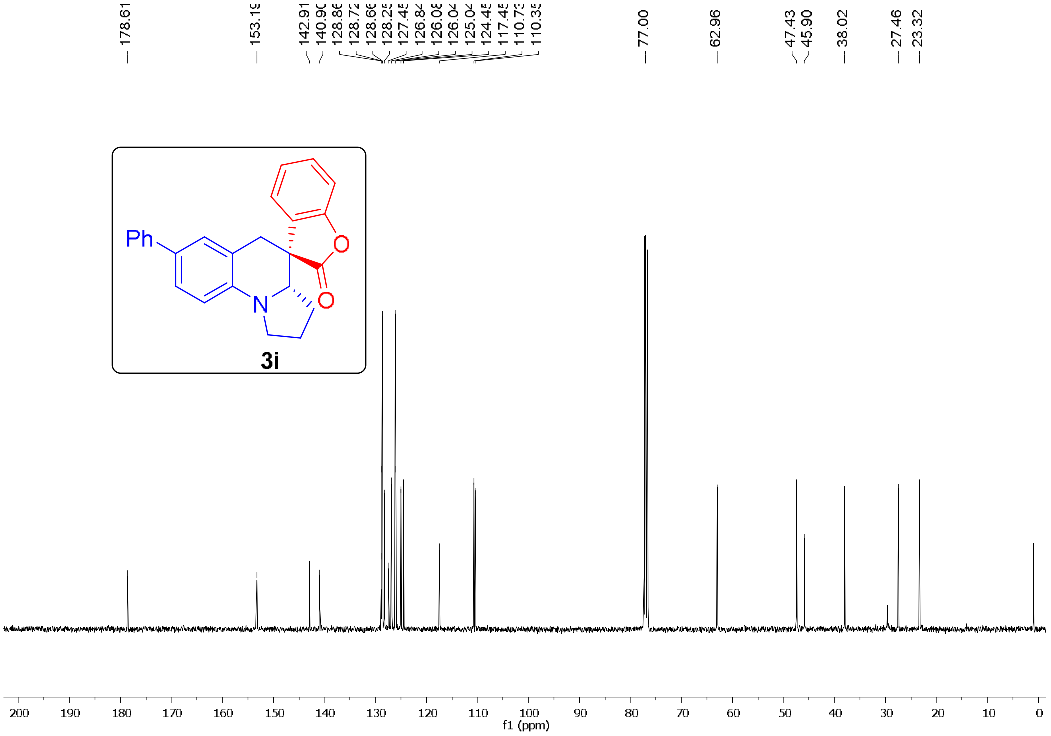
^{13}C NMR of **3h** (151 MHz, $CDCl_3$)



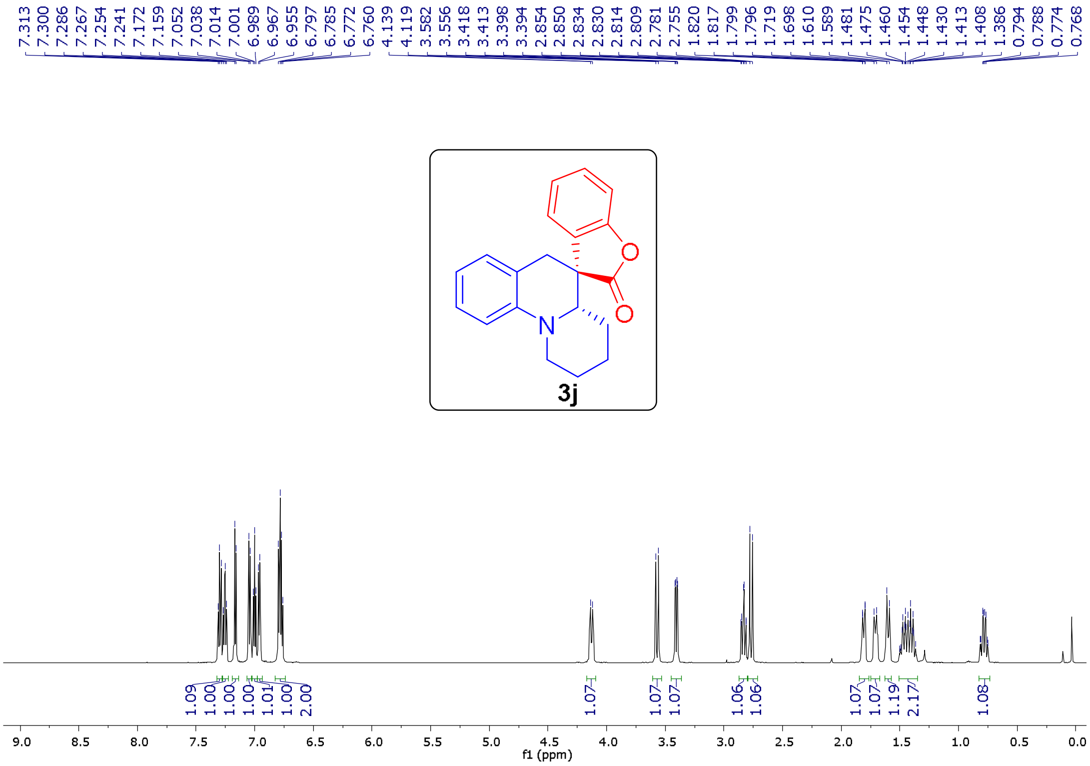
^{1}H NMR of **3i** (400 MHz, Chloroform-*d*)



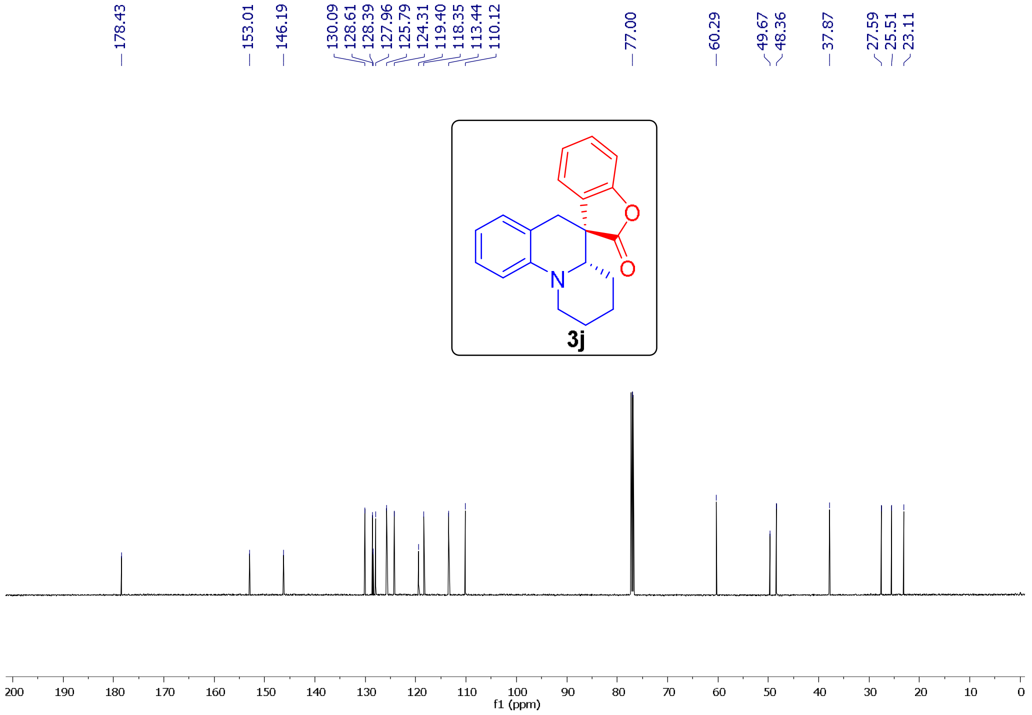
^{13}C NMR of **3i** (101 MHz, $CDCl_3$)



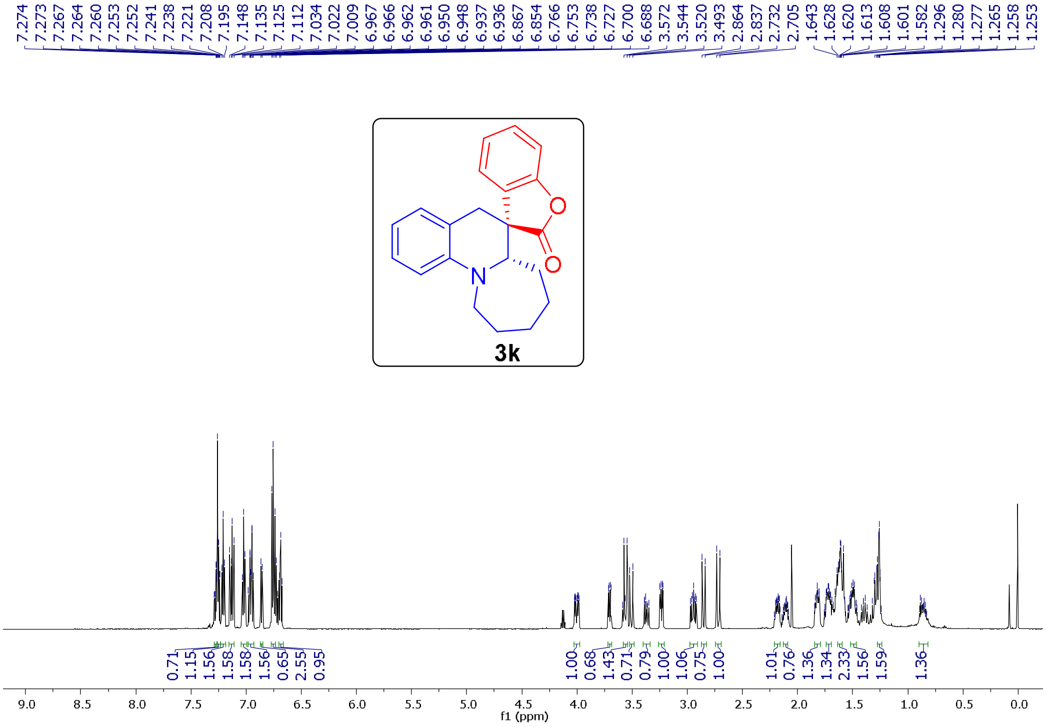
^{1}H NMR of **3j** (600 MHz, Chloroform-*d*)



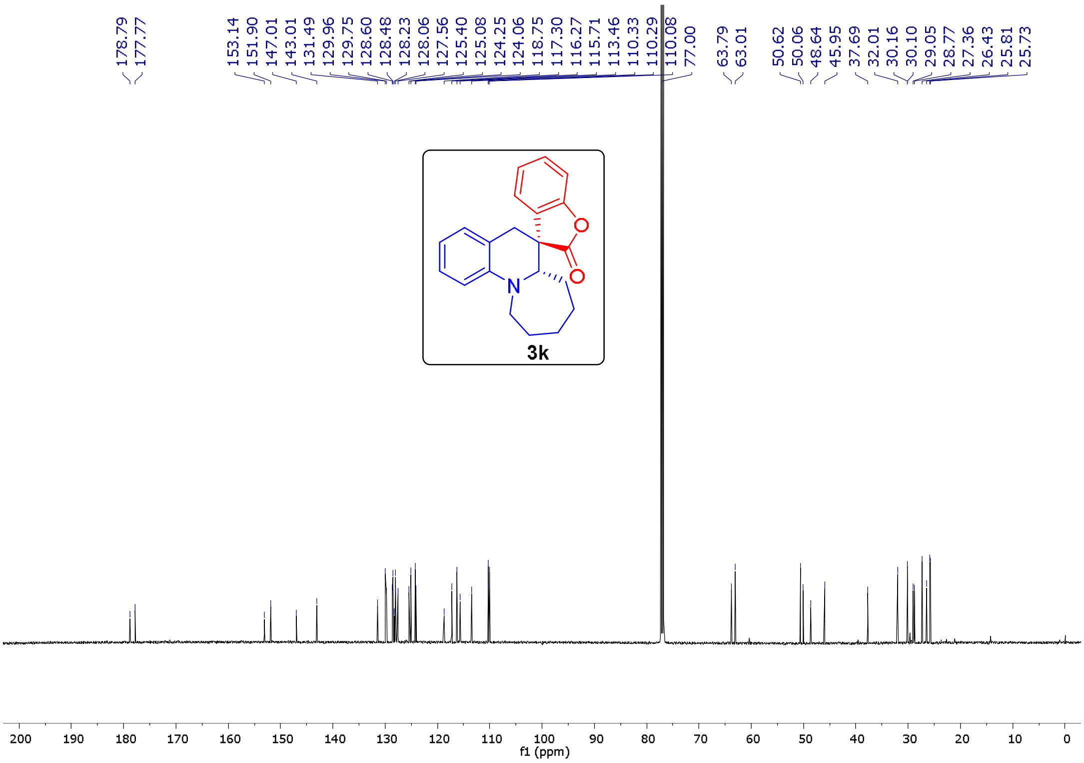
^{13}C NMR of **3j** (151 MHz, CDCl$_3$)



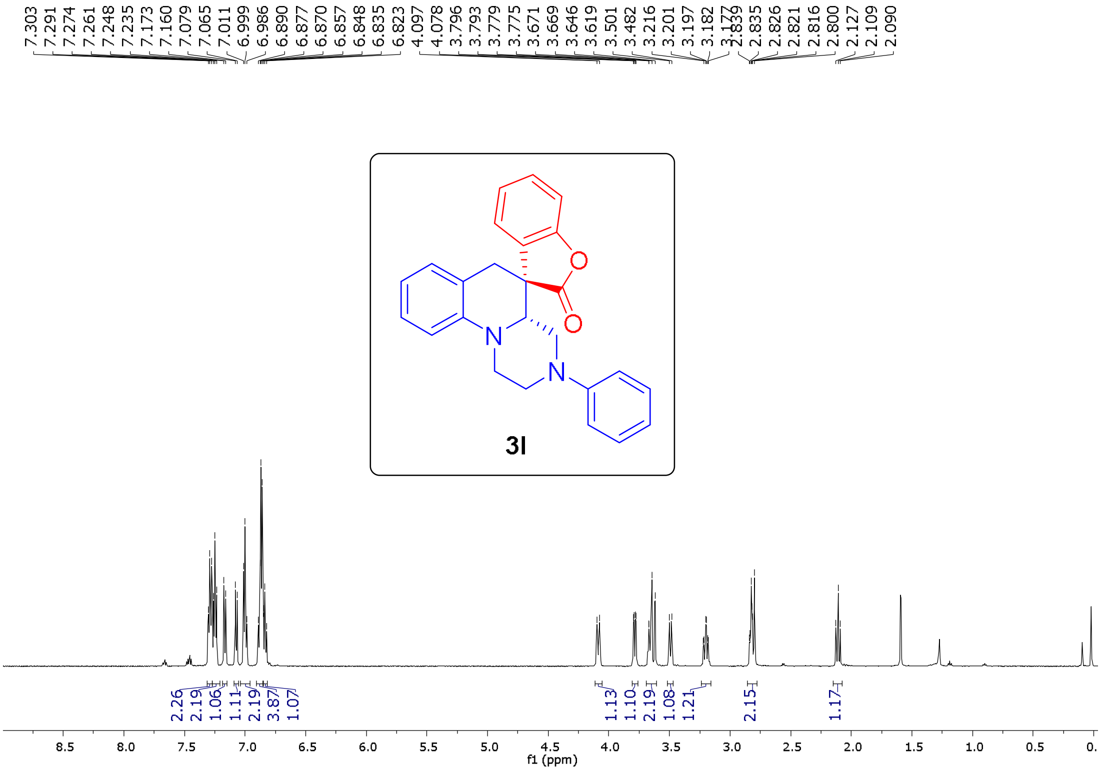
^{1}H NMR of **3k** (600 MHz, Chloroform-*d*)



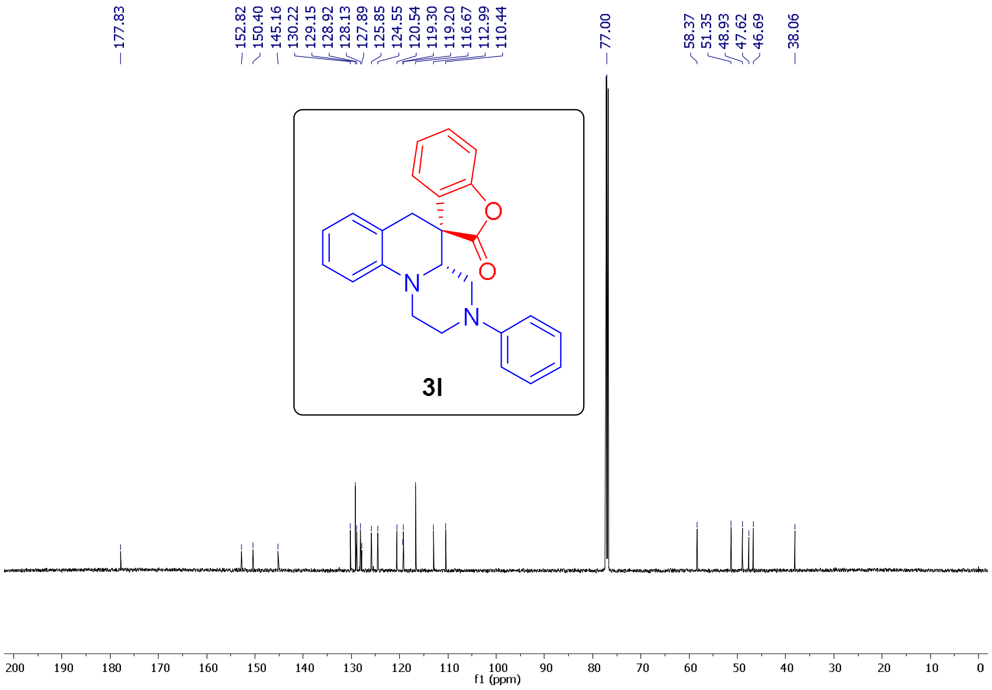
^{13}C NMR of **3k** (151 MHz, $CDCl_3$)



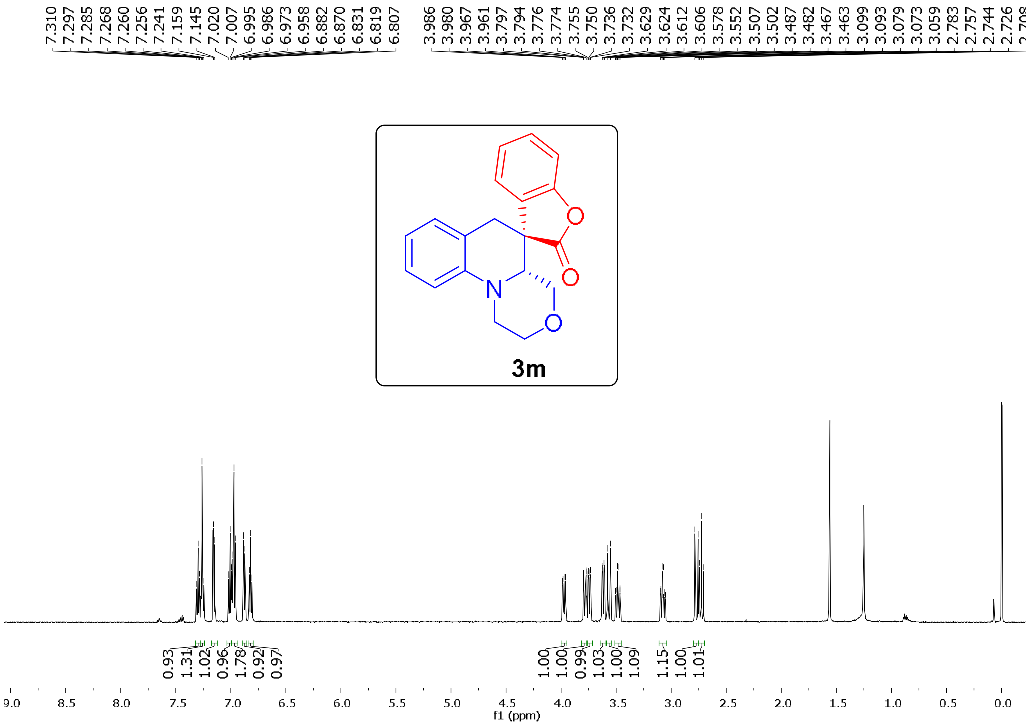
^{1}H NMR of **3l** (600 MHz, Chloroform-*d*)



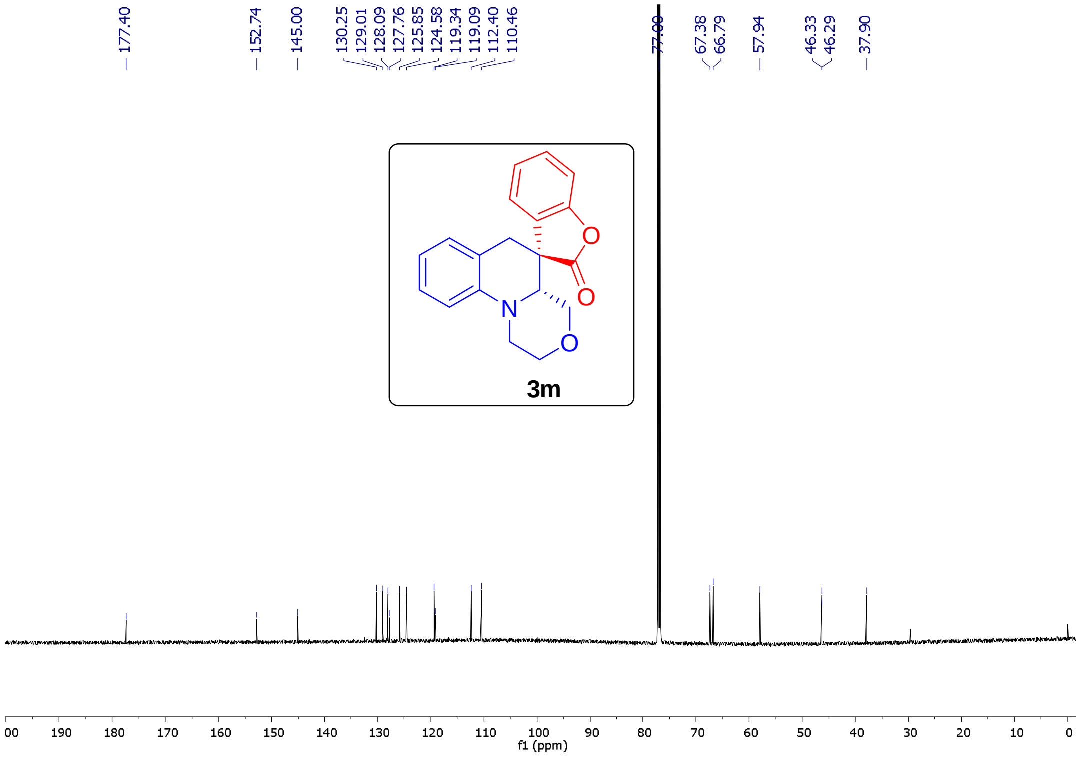
^{13}C NMR of **3l** (151 MHz, $CDCl_3$)



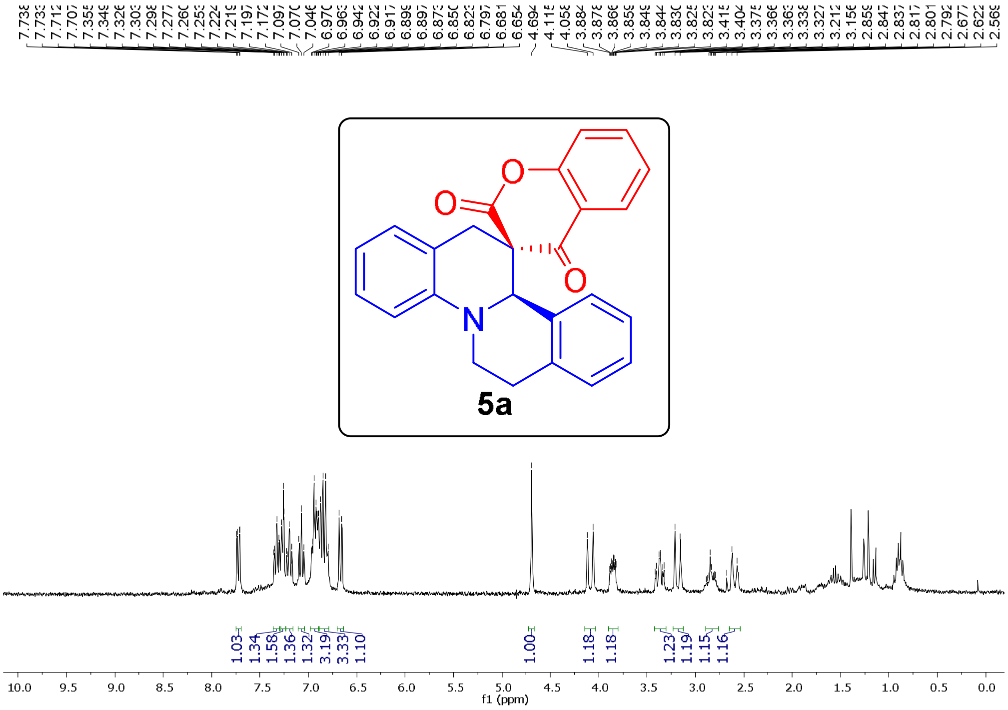
^{1}H NMR of **3m** (600 MHz, Chloroform-*d*)



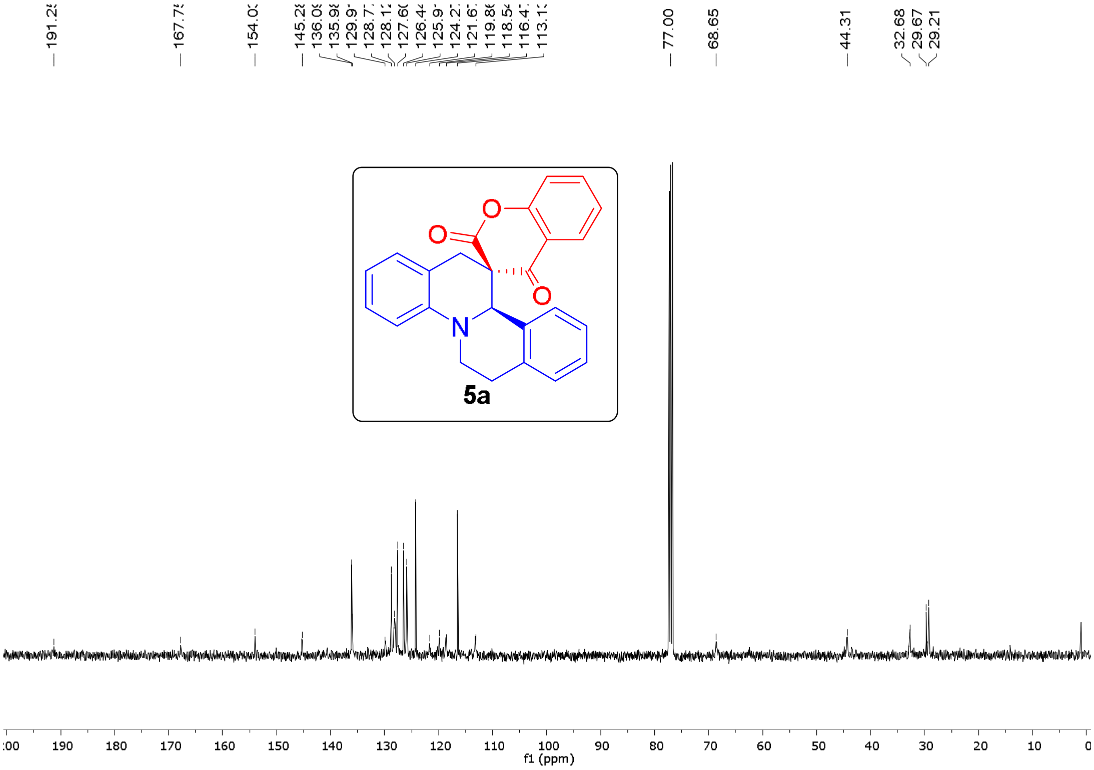
^{13}C NMR of **3m** (151 MHz, CDCl$_3$)



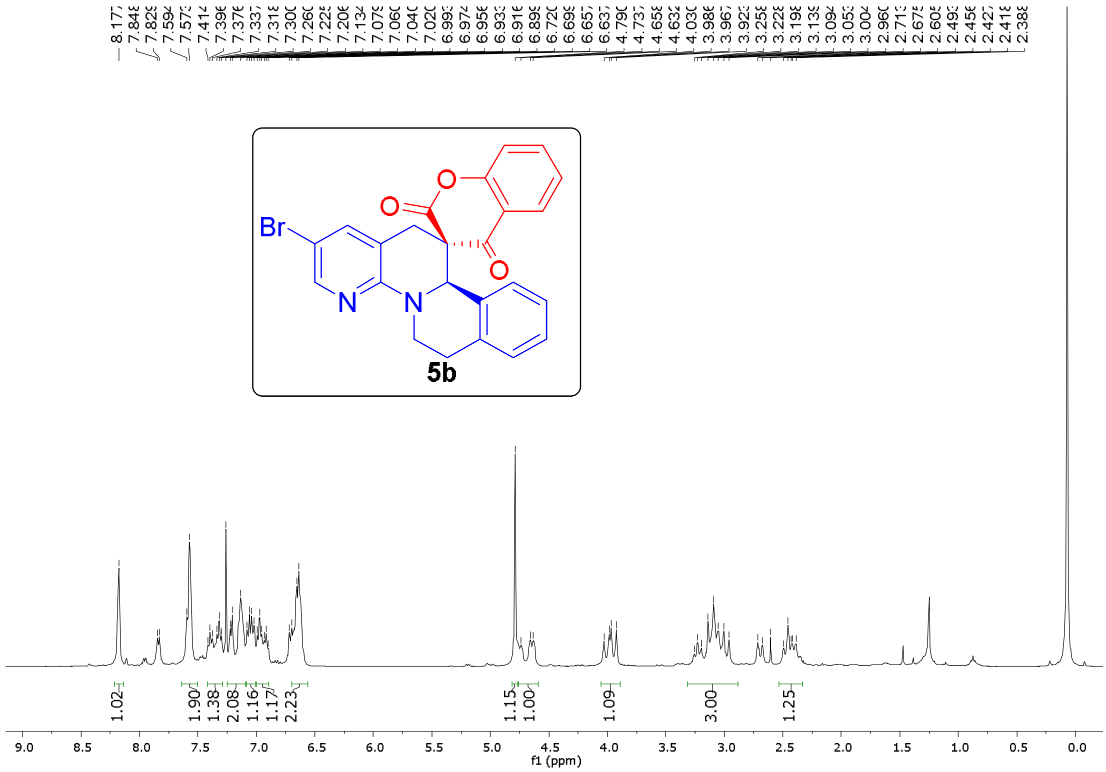
^{1}H NMR of **5a** (300 MHz, Chloroform-*d*)



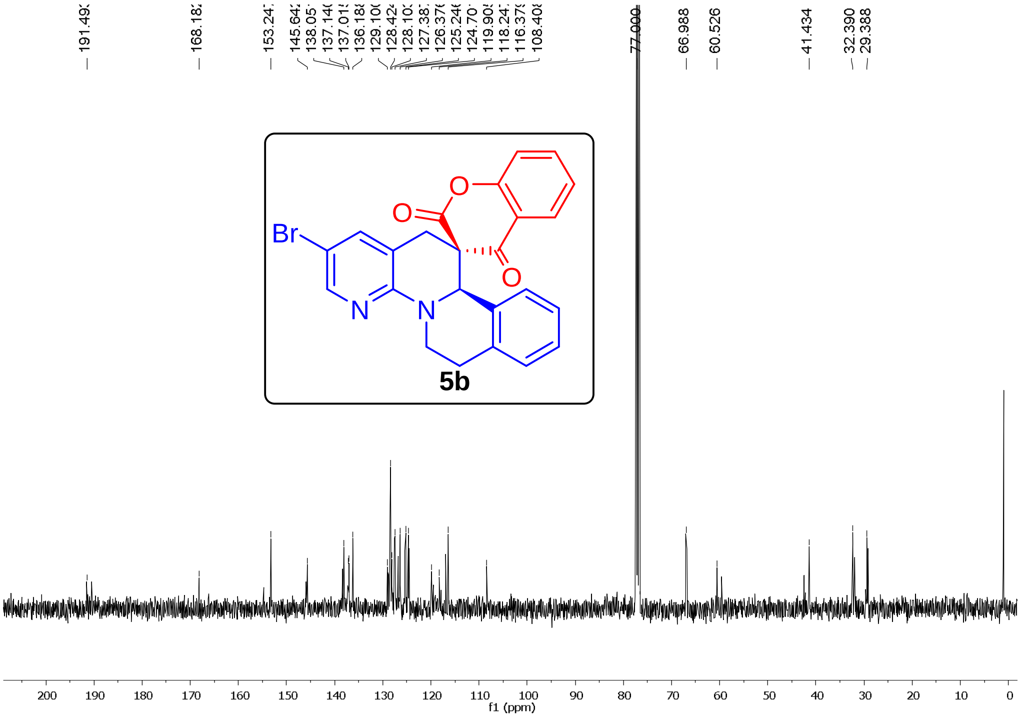
^{13}C NMR of **5a** (101 MHz, CDCl$_3$)



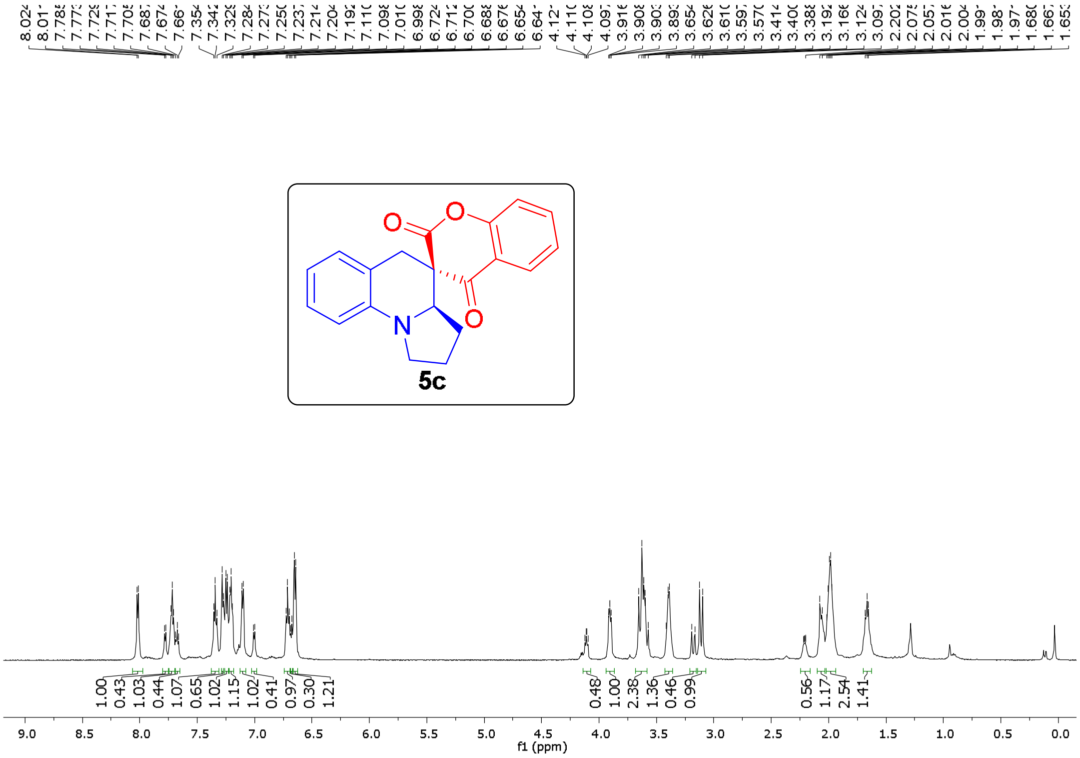
^{1}H NMR of **5b** (400 MHz, Chloroform-*d*)



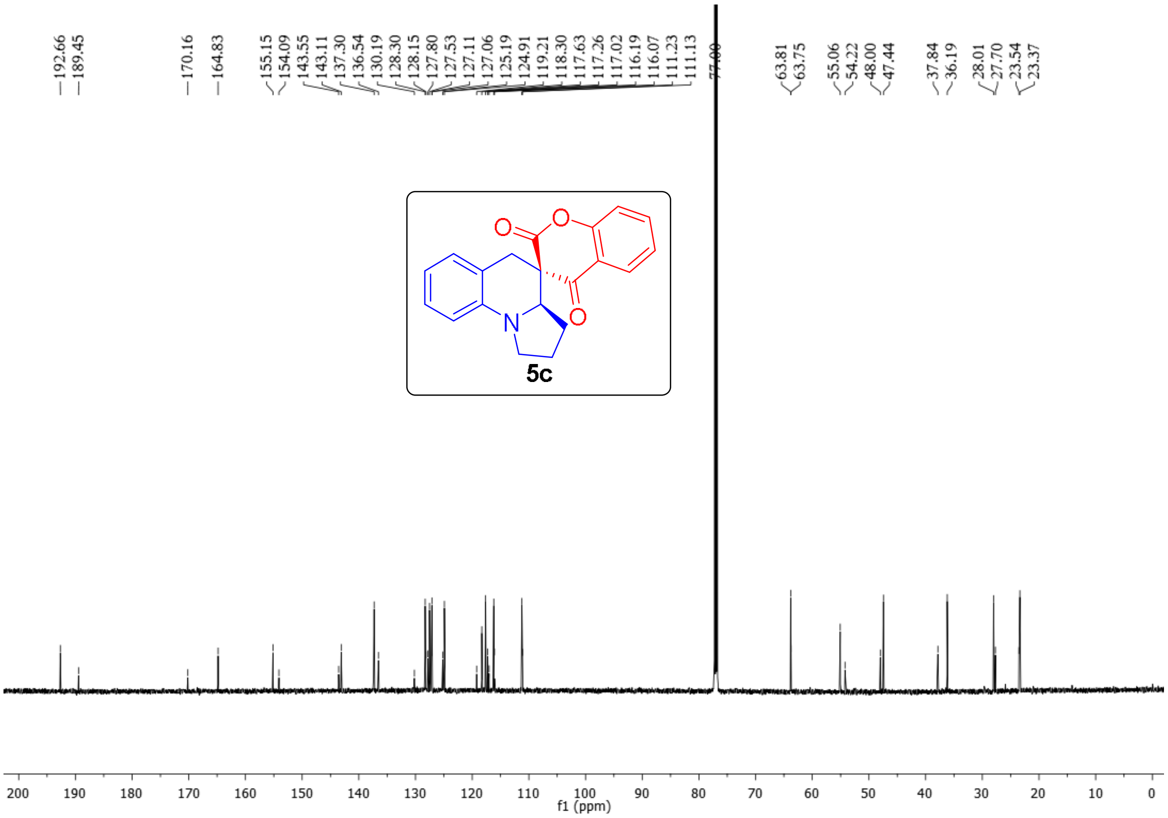
^{13}C NMR of **5b** (101 MHz, CDCl$_3$)



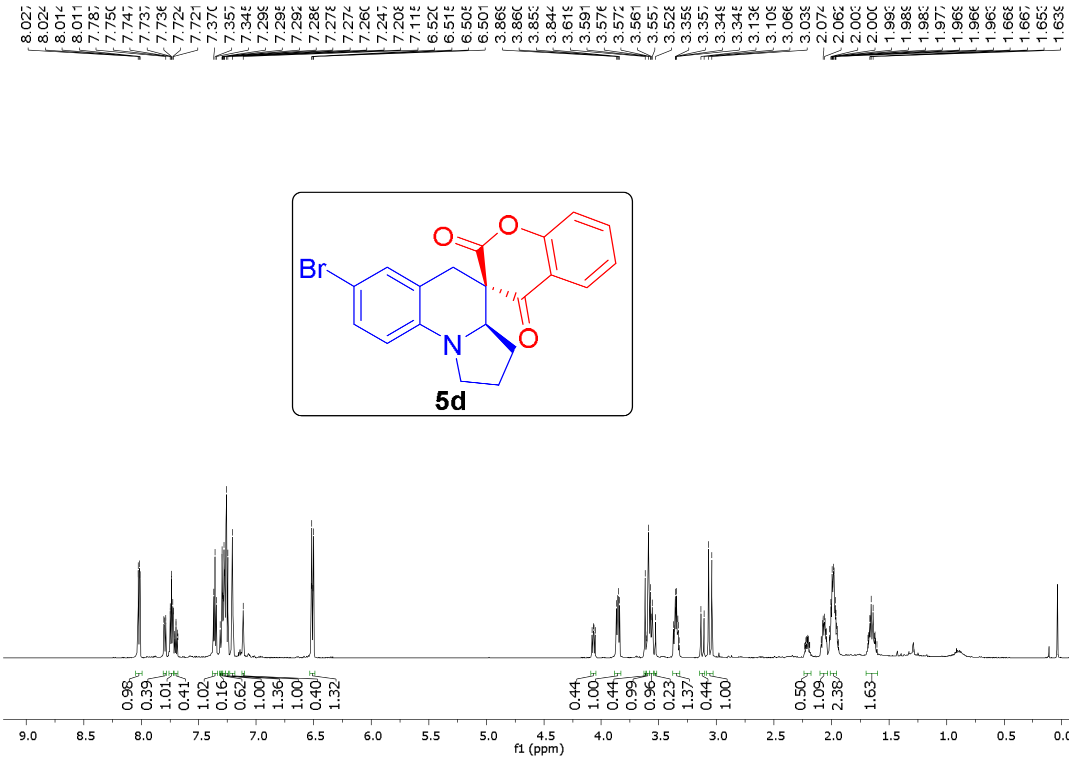
^{1}H NMR of **5c** (600 MHz, Chloroform-*d*)



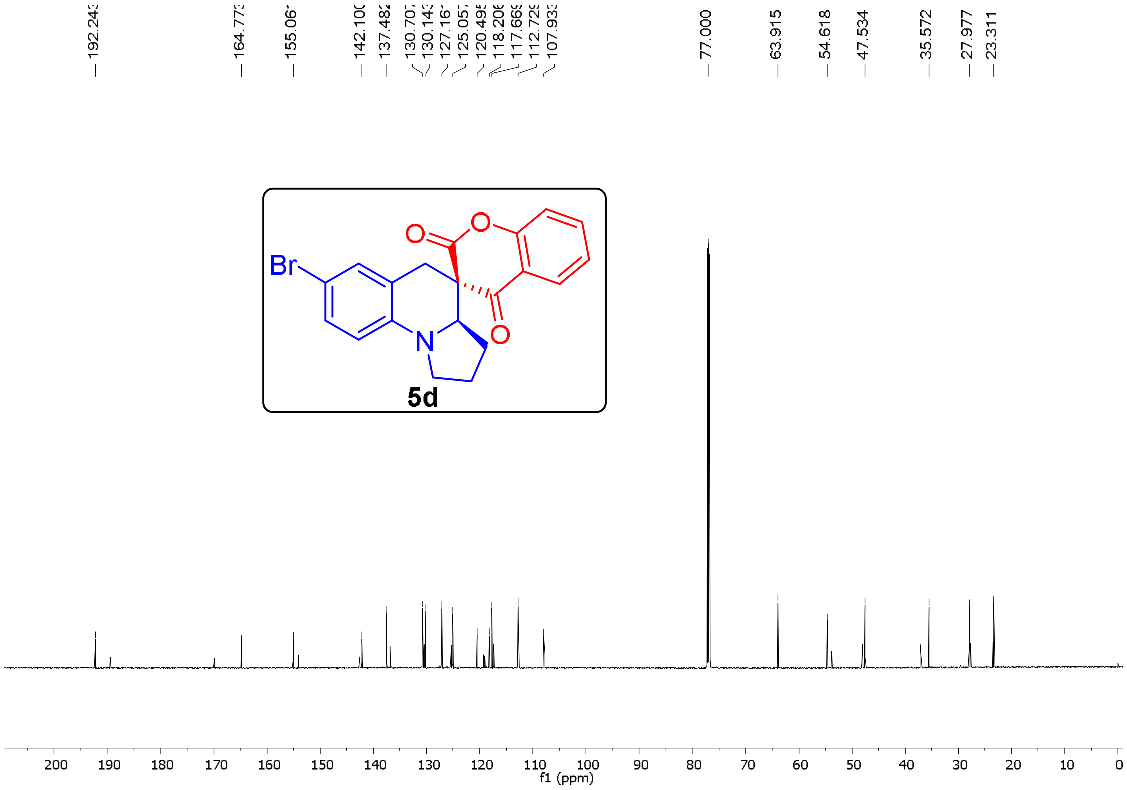
^{13}C NMR of **5c** (151 MHz, CDCl$_3$)



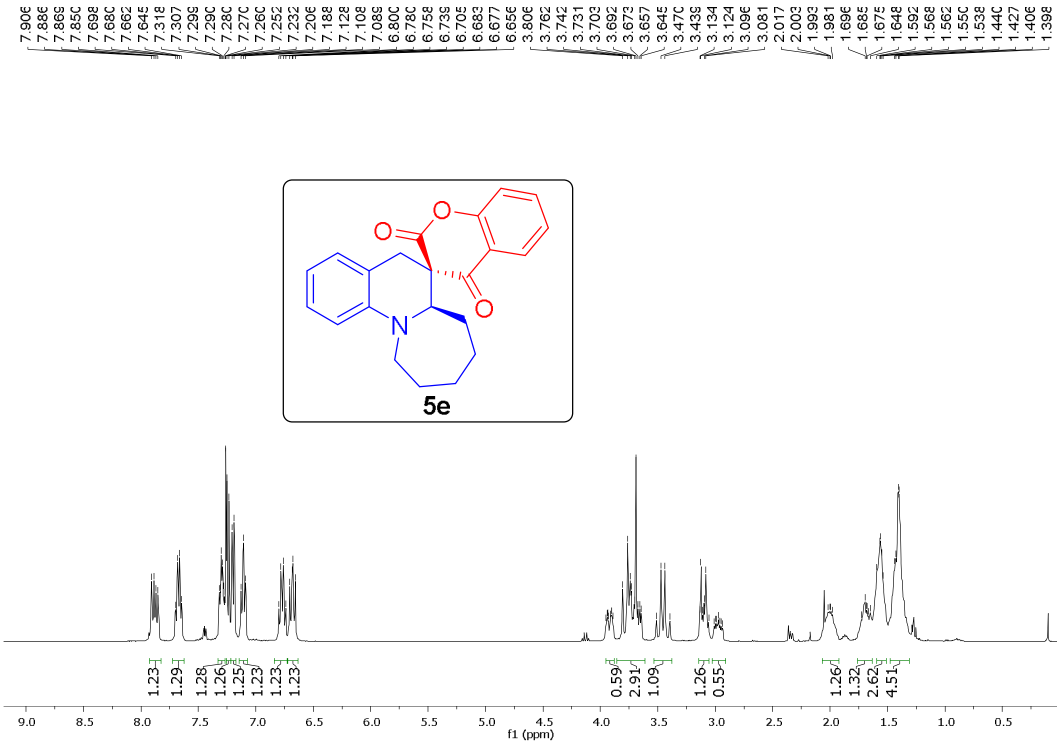
^{1}H NMR of **5d** (600 MHz, Chloroform-*d*)



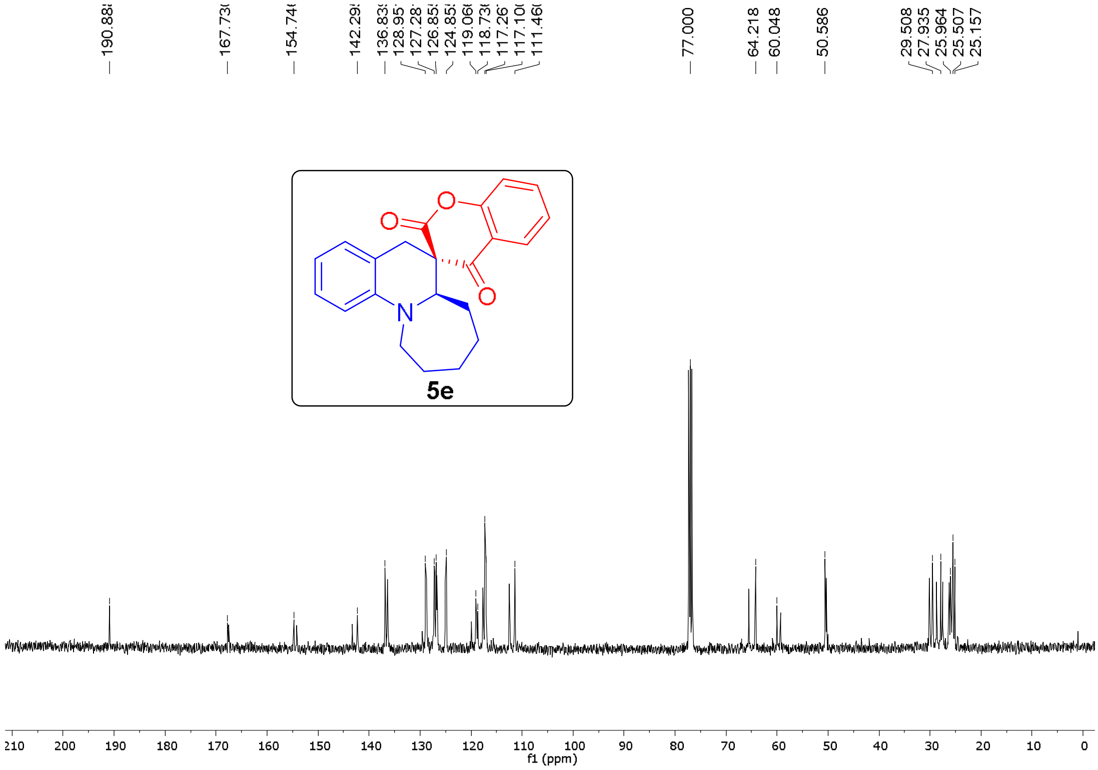
^{13}C NMR of **5d** (151 MHz, CDCl$_3$)



^{1}H NMR of **5e** (600 MHz, Chloroform-*d*)

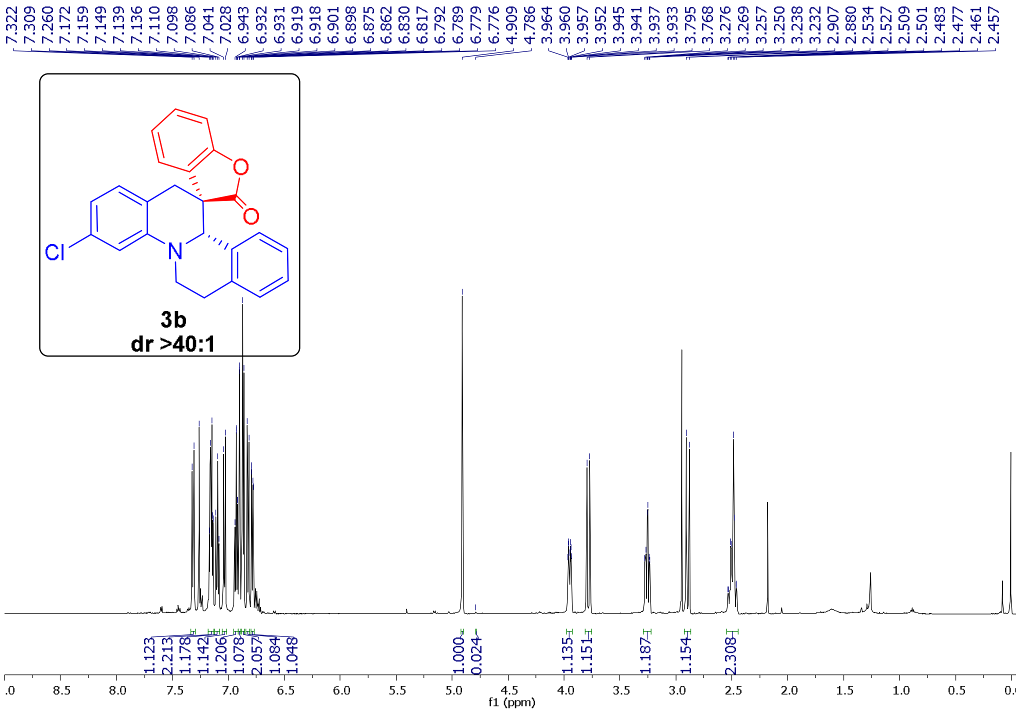


^{13}C NMR of **5e** (151 MHz, CDCl$_3$)

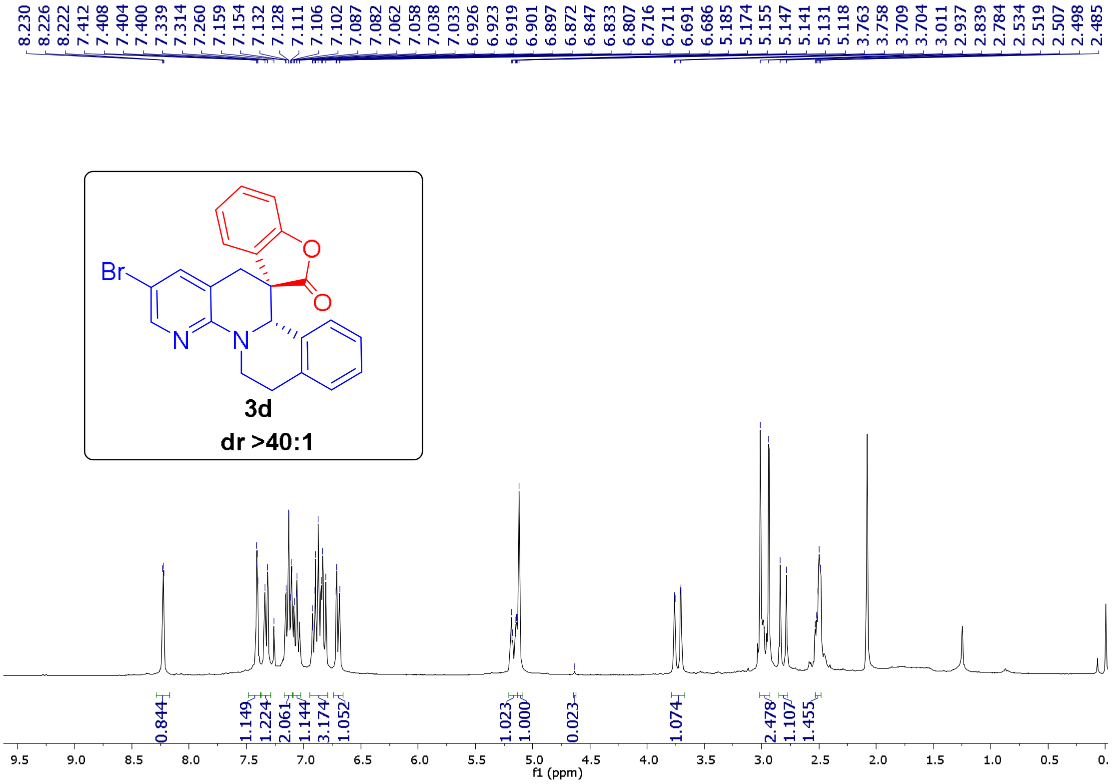


2.5.11 Crude ^{1}H NMR:

Crude ^{1}H NMR of 3b

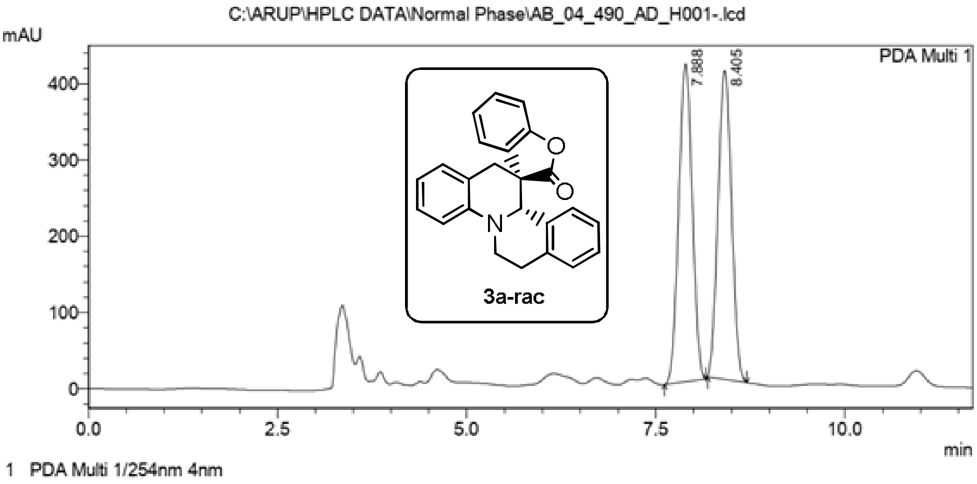


Crude ^{1}H NMR of 3d



2.5.12 HPLC Data:

Data for racemic mixture of 3a

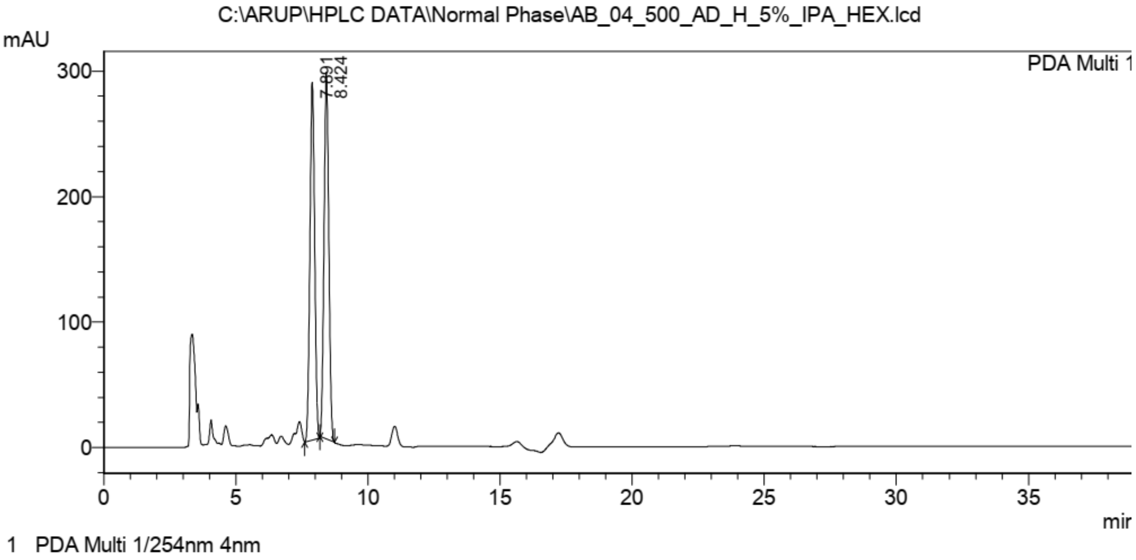


PeakTable

PDA Ch1 254nm 4nm

Peak#	Ret. Time	Area	Area %	Height
1	7.888	5192173	50.720	416716
2	8.405	5044781	49.280	404874
Total		10236954	100.000	821589

Data for C1 (entry 1, table 2.5.9)

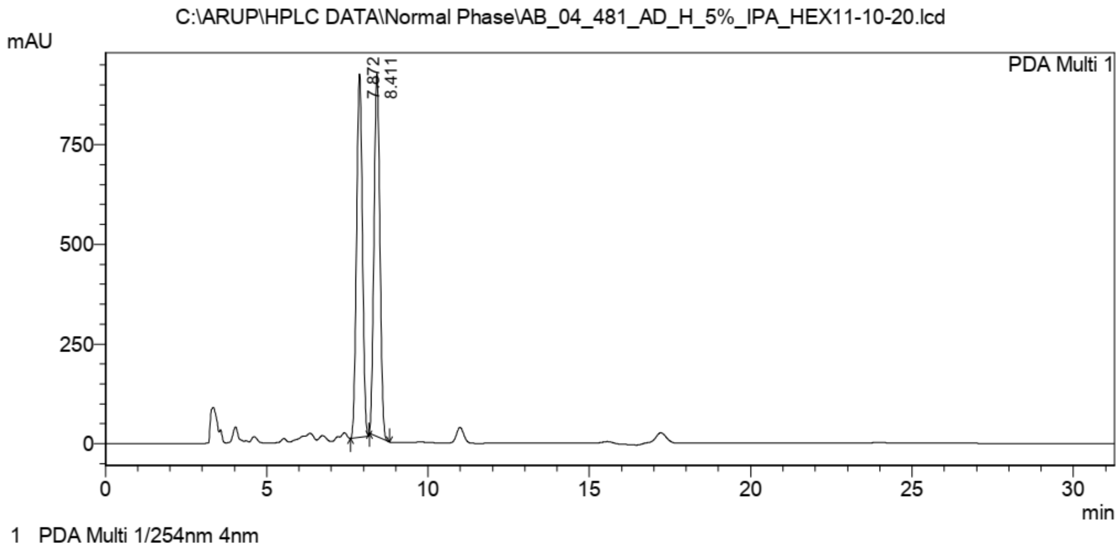


PeakTable

PDA Ch1 254nm 4nm

Peak#	Ret. Time	Area	Area %	Height
1	7.891	3569172	49.170	284709
2	8.424	3689723	50.830	291859
Total		7258896	100.000	576568

Data for C2 (entry 2, table 2.5.9)

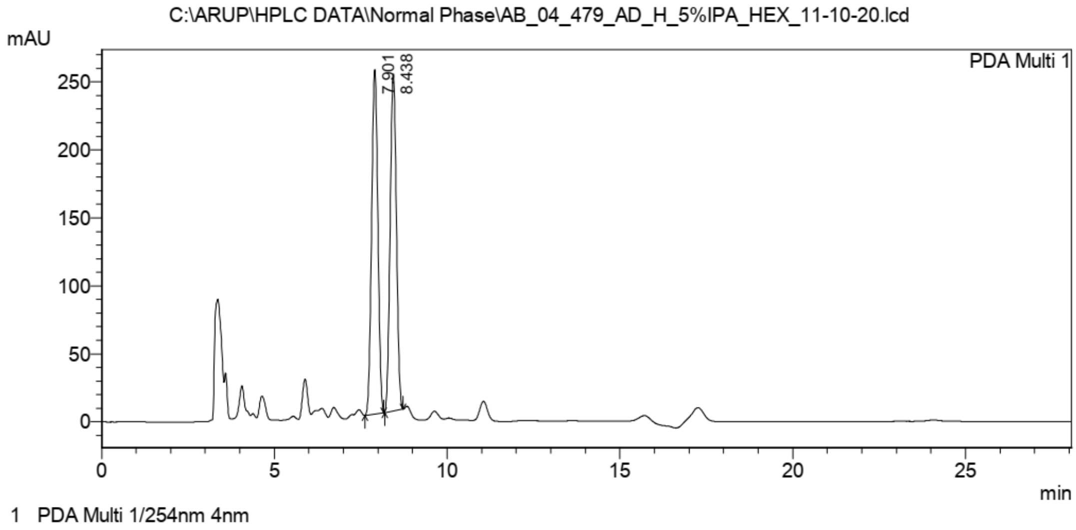


PeakTable

PDA Ch1 254nm 4nm

Peak#	Ret. Time	Area	Area %	Height
1	7.872	11484382	49.847	911407
2	8.411	11555044	50.153	910261
Total		23039426	100.000	1821668

Data for C3 (entry 3, table 2.5.9)

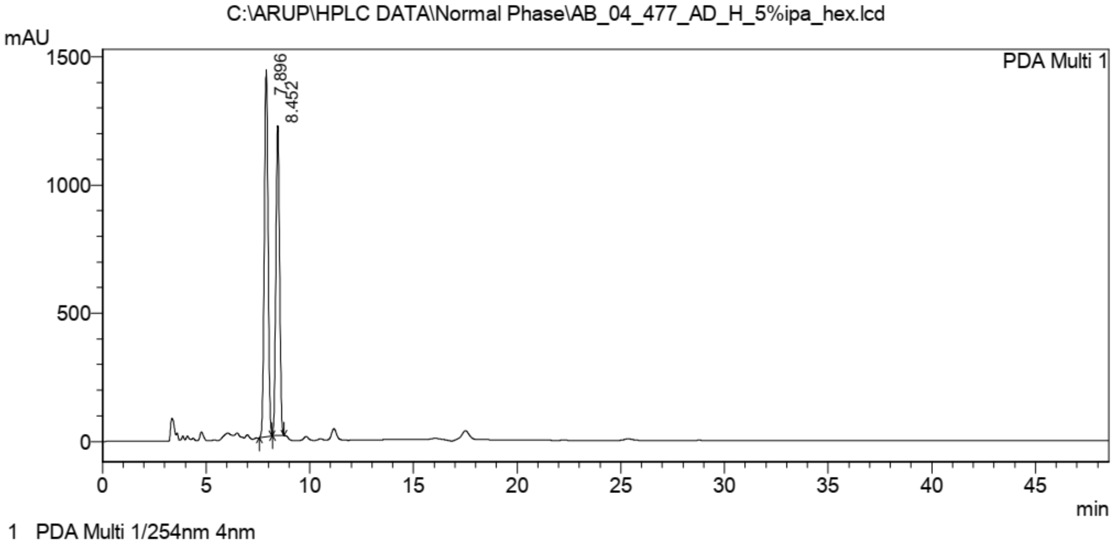


PeakTable

PDA Ch1 254nm 4nm

Peak#	Ret. Time	Area	Area %	Height
1	7.901	3183734	50.513	253110
2	8.438	3119088	49.487	248001
Total		6302821	100.000	501111

Data for C4 (entry 4, table 2.5.9)

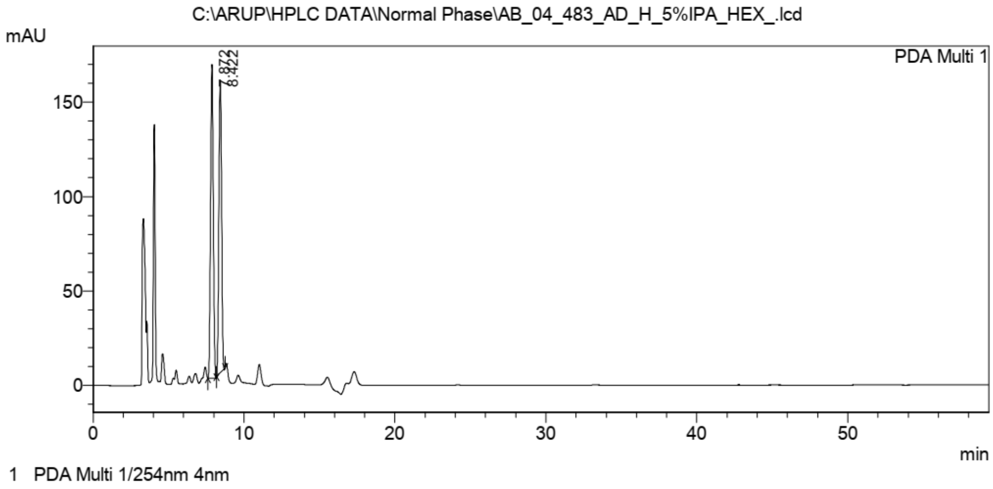


PeakTable

PDA Ch1 254nm 4nm

Peak#	Ret. Time	Area	Area %	Height
1	7.896	17917147	54.583	1429248
2	8.452	14908096	45.417	1207734
Total		32825242	100.000	2636982

Data for C5 (entry 5, table 2.5.9)

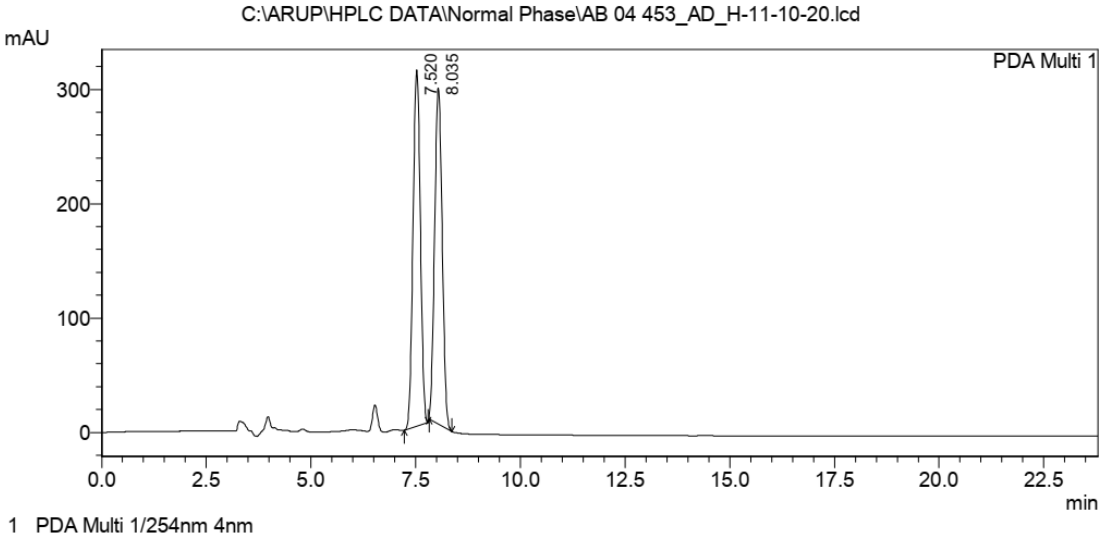


PeakTable

PDA Ch1 254nm 4nm

Peak#	Ret. Time	Area	Area %	Height
1	7.872	2081407	52.108	166055
2	8.422	1913028	47.892	154853
Total		3994435	100.000	320907

Data for C6 (entry 6, table 2.5.9)

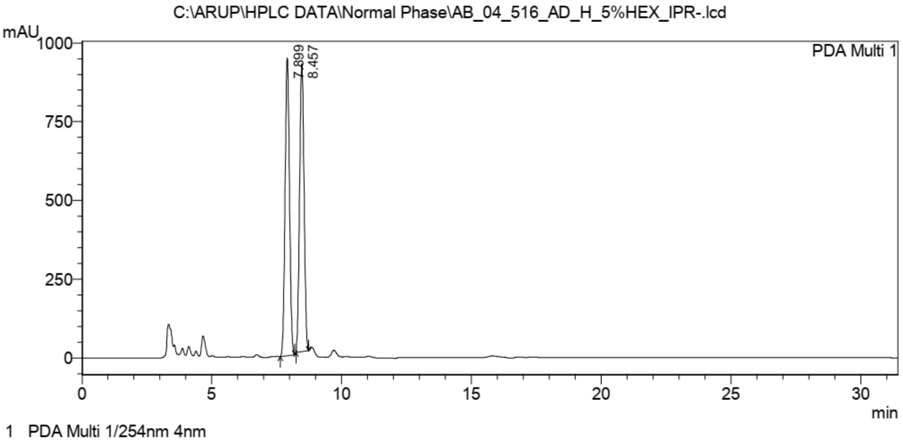


PeakTable

PDA Ch1 254nm 4nm

Peak#	Ret. Time	Area	Area %	Height
1	7.520	3787906	50.622	311744
2	8.035	3694748	49.378	294123
Total		7482654	100.000	605867

Data for C7 (entry 7, table 2.5.9)



PeakTable

PDA Ch1 254nm 4nm

Peak#	Ret. Time	Area	Area %	Height
1	7.899	11262002	50.892	944973
2	8.457	10867222	49.108	913558
Total		22129224	100.000	1858530

2.6 References

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4. Arthuis, M.; Pontikis, R.; Chabot, G. G.; Seguin, J.; Quentin, L.; Bourg, S.; Morin-Allory, L.; Florent, J.-C. *ChemMedChem*, **2011**, *6*, 1693-1705
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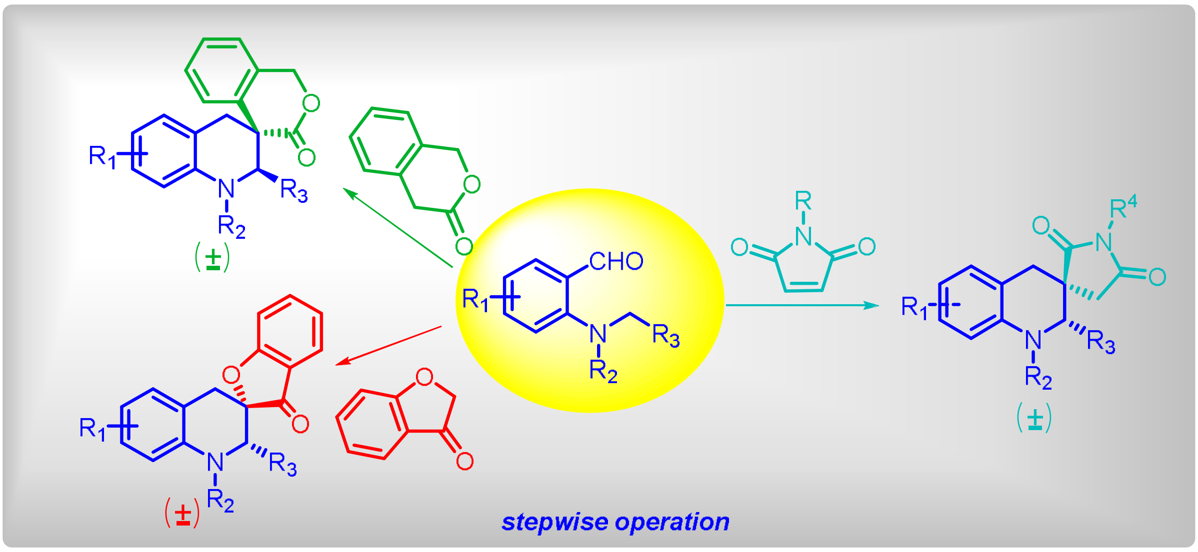
Chapter 3: **Lewis Acid Catalyzed Intramolecular C(sp^3)–H Bond Functionalization**

Lewis Acid Catalyzed Intramolecular C(sp^3)–H Bond Functionalization Triggered by Consecutive [1,5]-Hydride Shift /Cyclization Process: Approach for Diastereoselective Construction of Novel Spiroheterocycles



3.1 Introduction

3.1.1 Benzofuran-3-one/ 3-Coumaranone and Its Importance

In recent years heterocyclic compounds have acquired more attention because of their wide range of applications. The benzofuran-3-one nucleus, a derivative of the privileged benzofuran core, is one of the most studied heterocyclic structural units by synthetic and medicinal chemists. Nowadays the benzofuran-3-one scaffold (Figure 3.1.1) is a center of attraction for its broad spectrum biological activity and its huge space of applicability as a synthetic tool in the area of drug design and synthesis of various bioactive molecules.

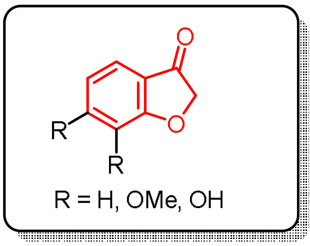


Figure 3.1.1 Benzofuran-3-one

The benzofuran-3-one scaffold is widely found in natural and synthetic compounds, such as the antifungal agent griseofulvin. Important benzofuran-3-one containing natural and synthetic bioactive compounds are discussed below.[1]

3.1.1.1 Naturally Occurring Benzofuran-3-one Derivatives

Many Benzofuran-3-one derivatives are widely distributed in nature and exhibit a wide range of biological activity. The aurones and the 2-isopropylidene-benzofuran-3-one derivatives are widely studied natural products and exhibit interesting biological activities, including anti-protozoal[2a] and anti-cancer[2b]. Many naturally occurring compounds containing benzofuran-3-one motif are shown below (Figure 3.1.1.1a).

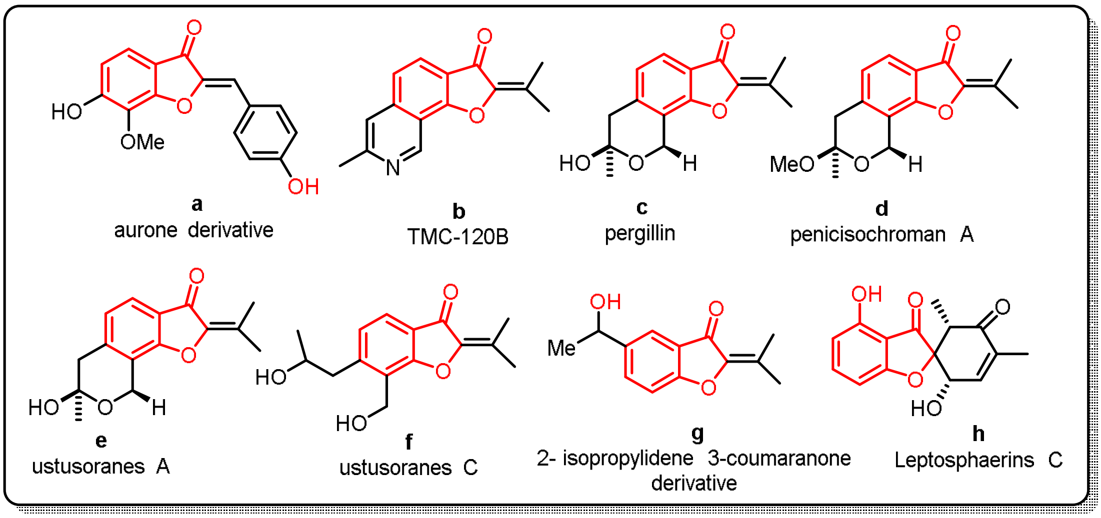
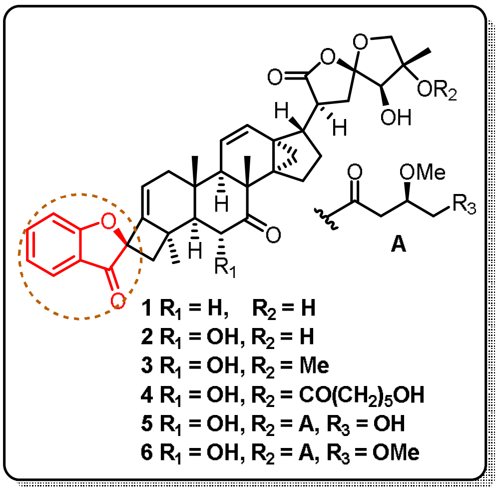


Figure 3.1.1.1a Benzofuran-3-one containing natural products

2-isopropylidine-benzofuran-3-one derivative (Figure 3.1.1.1a, **g**) is isolated from green bush *Verbesina luetzelburgii*, where this plant was used as a wound healing agent, a folk medicine that treats digestive and respiratory problems. The 2-Isopropylidine-benzofuran-3-one derivative is the only known heterocycle produced by the species of *Verbesina*[2c].

Many naturally-derived benzofuran-3-one derivatives (Figure 3.1.1.1a, **a-g**) include aurone derivatives, pergilin, penicisochroman A, ustusoranes A, ustusoranes C, TMC-120B, and 2-isopropylidene.[2d] Leptosphaerins C (Figure 3.1.1.1a, entry **h**) is a polyketide derivative extracted from the solid cultures of the ascomycete fungus *Leptosphaeria sp.*[2e]. Among these, the biological activity of aurones is widely studied.

Phainanoids are those classes of compounds, which are isolated from a Chinese herb known as *Phyllanthus hainanensis* in which the species of this plant is used as folk medicine to treat various infections, diabetes, and hepatitis **B** (Figure 3.1.1.1b).



1 R_1 = H, R_2 = H
2 R_1 = OH, R_2 = H
3 R_1 = OH, R_2 = Me
4 R_1 = OH, R_2 = $CO(CH_2)_5OH$
5 R_1 = OH, R_2 = A, R_3 = OH
6 R_1 = OH, R_2 = A, R_3 = OMe

Figure 3.1.1.1b Structure of phainanoid derivatives

Phainanoids, which are isolated from *Phyllanthus hainanensis* by Yue's group have immunosuppressive activity at the nanomolar level which is about 221 times more potent than standard drug cyclosporine A in inhibiting B lymphocytes.[2f] Recently, in May 2017, Dong and group successfully attempted to synthesize diastereoselectively the western part of phainanoid, which gave an insight into the total synthesis of the phainanoid series.[2g]

Aurones, which are structural isomers of flavones, are minor tricyclic flavanoids that build up a benzofuran-one ring connected with a carbon-carbon double bond to a phenyl moiety (Figure 3.1.1.1c).

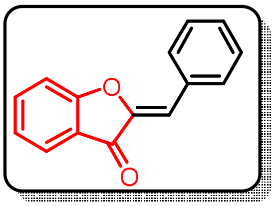


Figure 3.1.1.1c Structure of aurones

Aurones are found in fruits and flowers, where they play an important role in pigmentation. Among the large family of flavones, aurones hold less space in nature. However, the reactivity of aurones in vegetables remains critical for many species and their therapeutic potential for humans is also pregnant. Eventhough aurones are distributed in many families and genera, including various plants broadly used in folk medicine such as *Ceanothusamericanus*, *Glyzyrrhizaglabra*, or *Vacciniumoxycoccus*, a clear correlation cannot be established between these plants, especially their therapeutic use. The probable reason for its availability is remarkably low in plants compared to other flavanoids.[2h] However, the potential bioactivity of aurones is well explored in a semisynthetic way which is explained in the following section.

3.1.1.2 Bioactive Benzofuran-3-one Scaffolds

Benzofuran-3-one-containing compounds are an important class of bioactive molecules showing a wide range of biological activity (Figure 3.1.1.2). These molecules hold a special role due to the profound importance of such compounds under their role in the biological domain.

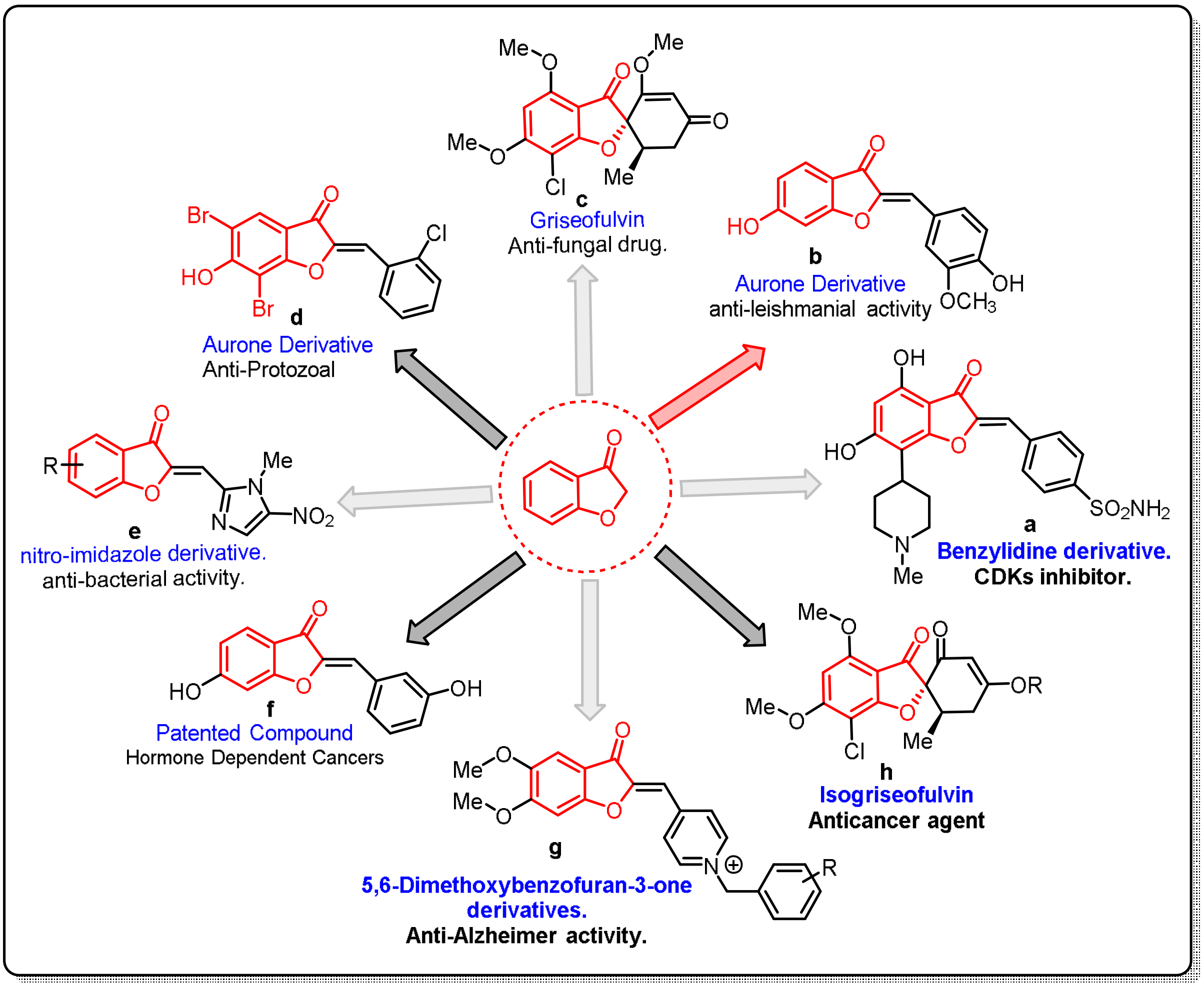


Figure 3.1.1.2 Benzofuran-3-one containing compounds showing diverse activities

As CDK Inhibitor: Cyclin-dependent kinases (CDKs) are a class of protein kinases has a significant contribution to regulating the cell cycle, discovered in recent times. They are present in all known eukaryotes. CDK can bind with a regulatory protein to control the progression of a cell called a cyclin. CDK displayed moderate kinase activity without cyclin; hence it is clear that the cyclin-CDK complex is an active kinase only. Cyclin-Dependent Protein Kinase (Cdks) enzyme connects with the negatively charged phosphate groups in an intermolecular manner called phosphorylation. Through this method, Cdks signal the cell to proceed into the next stage of the cell cycle. Among various CDKs, CDK1, CDK2, and CDK4 are the most established oncology targets.

The inhibition of cyclin-dependent kinases (CDKs) has now emerged as a significant research topic as an anticancer agent. Compounds enhanced to slow down the activity of these pivotal enzymes in the cell division regulators cycle have an anti-proliferative activity. In the small molecule drug class, 2-Benzylidene-benzofuran-3-one derivatives (Figure 3.1.13) showed excellent inhibitory activity against CDKs, especially against CDK1 and CDK2.[2i]

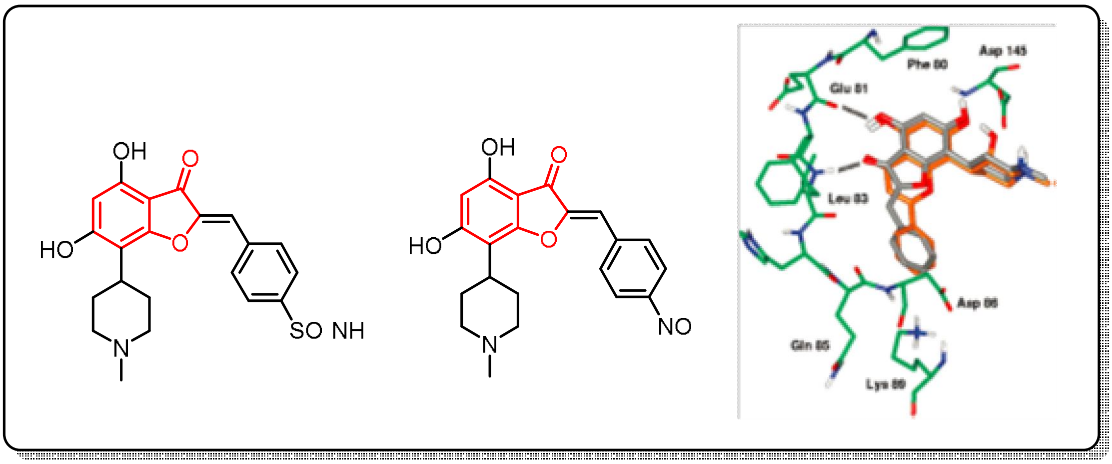


Figure 3.1.1.3 Benzylidene-benzofuran-3-one derivatives as CDKs inhibitor

For Alzheimer's disease: Alzheimer's disease (AD) is a progressive neurodegenerative brain disorder dependent on age. The etiology of the disease is unknown, although many diverse factors such as **β-amyloid (Aβ) aggregation, hippocampal acetylcholine (Ach) decrease**, and **τ-protein deposits** are important things for the initiation and progression of the disease. As we know, hydrolysis of acetylcholine **Acetylcholinesterase (AChE)** has an important role in the synaptic cleft. Therefore, employing **AChE inhibitors** could be a wonderful strategy to raise the level of acetylcholine in the affected cholinergic neurons.

Furthermore, it has been concluded that the inhibition of AChE may increment **Butyrylcholinesterase (BuChE)** reactivity in a new strategy in the hippocampus that occurred hydrolysis of ACh. The AChE/BuChE activity ratio should be proper in the hippocampus as seen in a normal healthy brain, which could improve the symptoms of AD. So, there is no doubt that dual AChE/BuChE inhibitors have the potential to be more potent agents to treat AD. Some of the reported benzofuran-3-one derivatives having dual AChE/BuChE inhibitory activity are shown below (Figure 3.1.1.4).[2j]

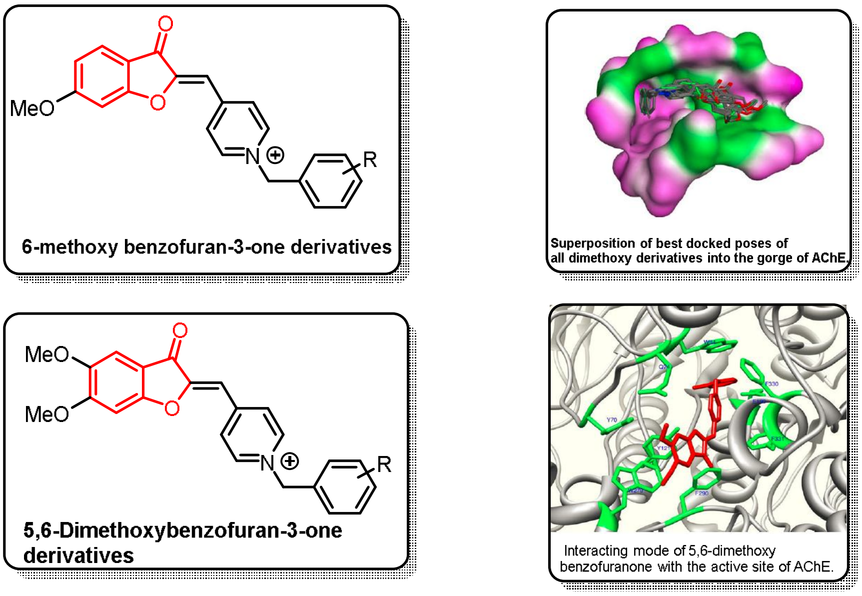


Figure 3.1.1.4 Benzofuran-3-one derivatives showing anti-Alzheimer activity and its interacting mode with the active site

As anti-bacterial agents: Various (*Z*)-2-(1-methyl-5-nitroimidazole-2-ylmethylene)-3(2*H*)-benzofuran-ones have been prepared utilizing the Knoevenagel condensation method (Figure 3.1.1.5). These molecules displayedexcellentinhibitory effectina wide spectrum of gram-positive bacteria like *Streptococcus epidermidis, Staphylococcus aureus*, Methicillin-resistant *Staphylococcus aureus*, and *Bacillus subtilis* and some gram-negative bacteria like *Klebsiella pneumonia*.[2k]

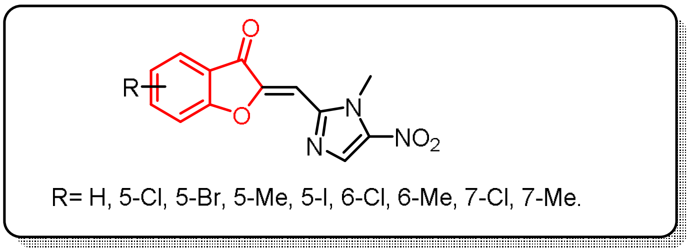


Figure 3.1.1.5 Nitro-imidazole benzofuranone derivatives showing antibacterial activity

As an Inhibitor of human peptidyl-prolyl cis/trans isomerize Pin1: Pin1 gene encoded peptidyl-prolyl cis/trans isomerase NIMA-interactingenzyme in humans. Pin1 has an enormous contribution to various diseases.

Up-regulation of this enzyme can assist certain cancers and various immune disorders like atherosclerosis, arthritis, etc. So by inhibiting this enzyme, we can achieve therapeutic implications in various diseases like cancer and other immune disorders like rheumatoid arthritis.[2l] Various spirocyclic benzofuran-3-one derivatives which show inhibition of human peptidyl-prolyl cis/trans isomerize Pin1 are shown below (Figure 3.1.1.6).

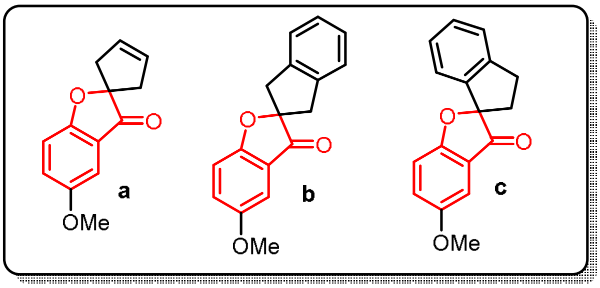


Figure 3.1.1.6 Inhibitors of human peptidyl-prolyl cis/trans isomerize Pin1

Griseofulvin as an antifungal agent: Griseofulvin (Figure 3.1.1.7) is a conventional oral antifungal drug used to treat different types of dermatophytoses (ringworm infection). It can also be used for various skin and nail fungal infections when other antifungal creams are not working. It is one of the WHO's lists of essential medicine, the most effective and safer medicines needed in a health care system.[2m]

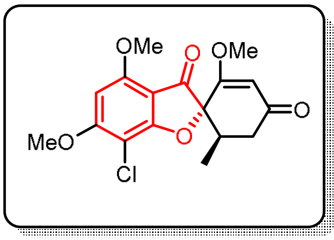


Figure 3.1.1.7 Structure of Griseofulvin

Griseofulvin for the treatment of breast cancer: Griseofulvin can potentially inhibit tumor growth in breast cancer cells. Mechanistically griseofulvin binds at the paclitaxel site along the side of the microtubules, and arrests the cell MCF-7 at mitosis and which agitates microtubule dynamic instability in the cell (Figure 3.1.1.8).

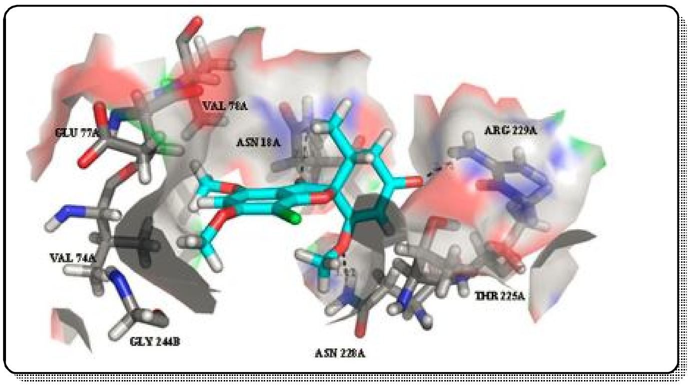


Figure 3.1.1.8 Mode of the interaction of Griseofulvin with tubulin

Also, griseofulvin shows synergistic antiproliferative activity along with vinblastine in MCF-7 cell lines and these two drug combinations can be successfully used in the treatment of breast cancer.[2n]

Griseofulvin for HCV infection: Griseofulvin also showed the 'suppression of hepatitis C virus replication' in vitro. It was found that griseofulvin exerts its pharmacological action by blocking the cell cycle individually in the HCV subgenomic replicon cells at the G2/M phase.[2o] This invitro study suggests a new approach to the development of novel therapeutics for HCV infection.

Griseofulvin as an inhibitor of centrosomal clustering in cancer cells: Many Griseofulvin analogs (Figure 3.1.1.9) showed inhibitory activity against centrosomal clustering in cancer cells. Many analogs are more active than the parent compound, i.e. griseofulvin. As this kind of binding is a particular phenotype that is unique in cancer cells, there is more possibility for these molecules to bind specifically with cancer cells.[2p]

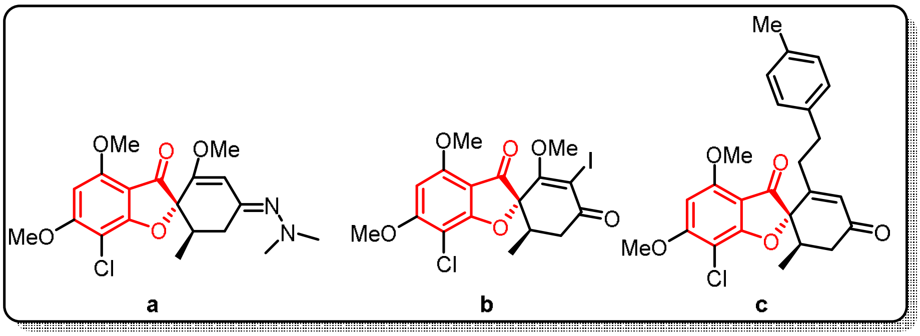
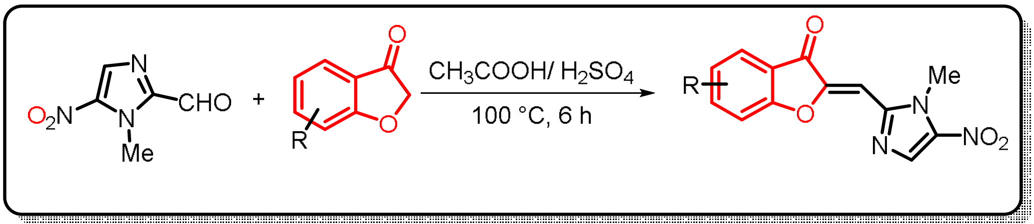


Figure 3.1.1.9 Griseofulvin analogs showing anticancer activity

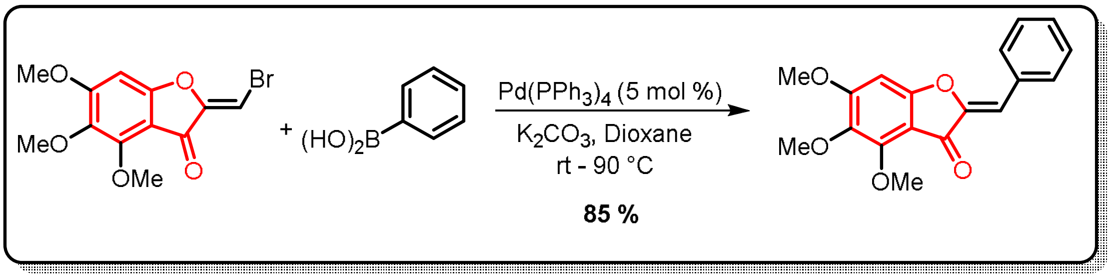
3.1.2 Synthesis of Various Benzofuran-3-one Derivatives

N.Hadj-Esfandiari *et al.*[2k] reported the synthesis of different derivatives of (Z)-2-(nitroimidazolylmethylene)-3(2*H*)-benzofuranone in the presence of sulphuric acid where acetone was used as a solvent (Scheme 3.1.2a).



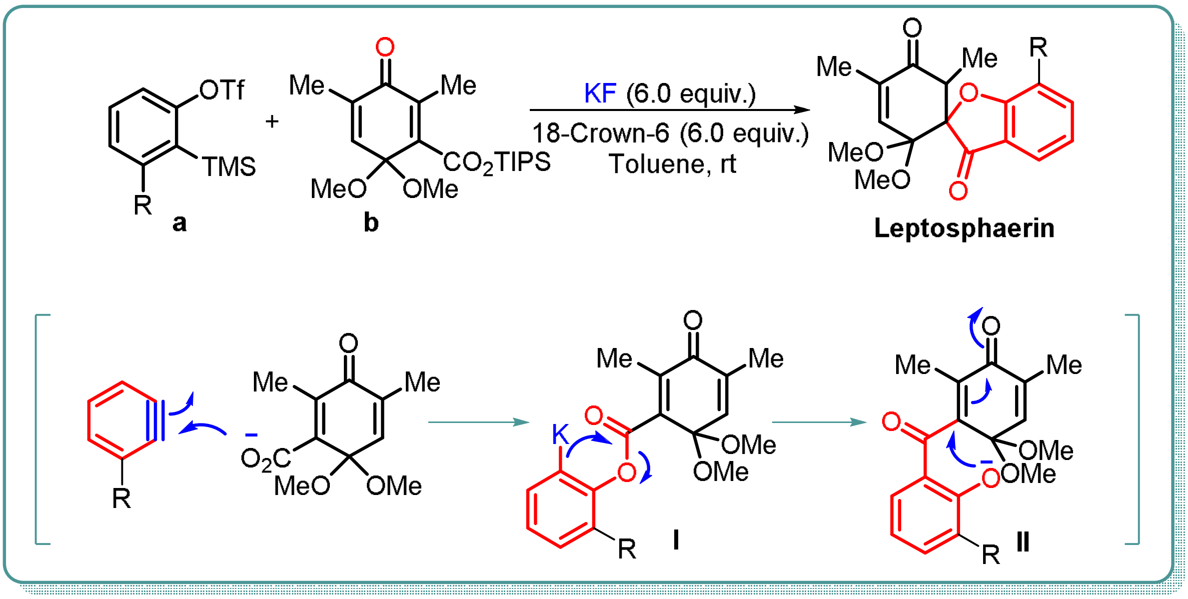
Scheme 3.1.2a Synthesis of nitroimidazolyl benzofuranone derivative

Suzuki coupling of the benzofuran-3-one derivative with phenylboronic acid provides aurones in good yield (Scheme 3.1.2b). This is a type of Suzuki coupling reaction where the phenyl group of boronic acid couples with the bromo derivative to get the desired aurone derivatives.[2q]



Scheme 3.1.2b Synthesis of aurone derivative

Mhaske *et al.*[2r] recently reported a concise method for the synthesis of benzofuran-3-one containing the natural product Leptosphaerin C derivative. Initially, nucleophile fluoride ions insist on the generation of aryne from the compound**a**and free carboxylate derivative from **b** which react with one anotherleadingtothe formation of**I**. As it is unstable it quickly transforms to **II** through the intramolecular carbonylation method. Then intramolecular Michael addition of oxide ion in toluene at room temperature furnished Leptosphaerin (Scheme 3.1.2c).



Scheme 3.1.2c Synthesis of leptosphaerin

3.1.3 3-Isochromanone

Nowadays the 3-Isochromanone scaffold (Figure 3.1.3) is a center of attraction for its broad spectrum biological activity and its huge space of applicability as a synthetic tool in the area of drug design and synthesis of various bioactive molecules. The 3-Isochromanone scaffold is widely found in natural and synthetic compounds. Important 3-Isochromanone containing natural and synthetic bioactive compounds are discussed below.[3]

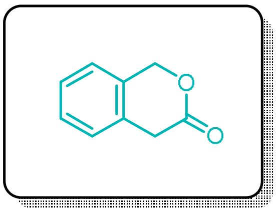


Figure 3.1.3 3-Isochromanone

3.1.3.1 Several 3-Isochromanone Derivatives and Their Activity

Isochroman-3-one is an important pharmacophore present in several biologically active molecules. This scaffold is very much possessive for lifespan as well as plant growth regulators. Hence synthesis of these isochroman-3-one derivatives is very much important in recent days. The isochroman-3-ones without substituent on the lactone ring had no activity on hypocotyl and radicule elongations of lettuce seedlings were observed at 10 ppm. The 1-phenyl, benzyl, and styryl substituted compounds promoted the radicule elongation while inhibiting the hypocotyl elongation of lettuce seedlings at 10 ppm. The inhibition might be attributed to auxin transport inhibition and the elongation might be attributed to antiauxin activity (Figure 3.1.3.1).[3a]

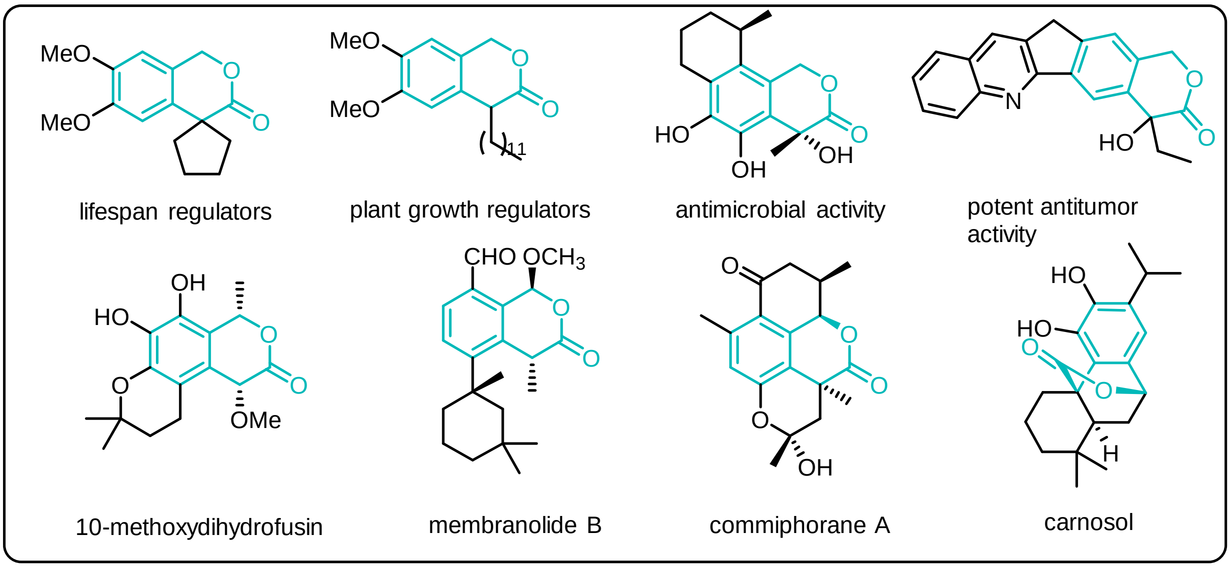


Figure 3.1.3.1 Several 3-Isochromanone derivatives

3.1.3.2 Benzo and Isobenzo-20-S-CPT as Novel Topoisomerase I (Top1) Inhibitors

CPT binds to the DNA helix in the place of the +1 purine and is also stacked with the +1 purine externally from the duplex DNA structure. Further structural studies are ongoing for the generation and testing of novel topoisomerase I (top1) inhibitors (Figure 3.1.3.2).[3b]

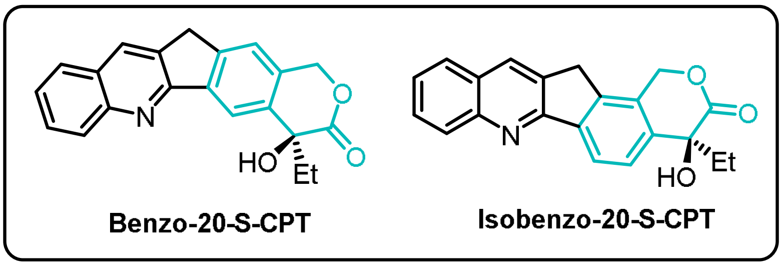


Figure 3.1.3.2 Benzo and Isobenzo-20-S-CPT

3.1.3.3 Antimicrobial Activities of Radulifolin A (I) and *Epi*-Radulifolin A (II)

The investigation of the chemical constituents from the roots of *Psacalium radulifolium*, a member ofthe matarique complex of medicinal plants, which includes several members of the Asteraceae, resulted in the isolation of four new modified eremophilanes including radulifolin A (**I**), and *epi*-radulifolin A (**II**). These two isolated compounds had been tested for antimicrobial activities against *Staphylococcus aureus, Escherichia coli, Pseudomonas aeruginosa*, *Proteus mirabilis,* and *Candida albicans.* The mixture of other radulifolin A and *epi*-radulifolin Adisplayed selective but moderate activities against *S. Aureus* (Figure 3.1.3.3).[3b]

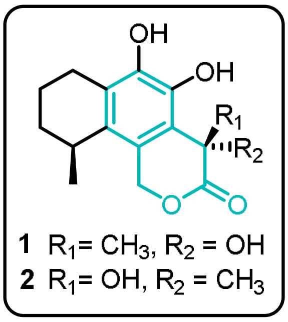


Figure 3.1.3.3 Radulifolin A (**1**) and *epi*-radulifolin A (**2**)

3.1.3.4 10-Methoxydihydrofuscin as Anti HIV-1 Target Activity

10-methoxydihydrofuscin (**1**) has been isolated from the soil fungus *Oidiodendron griseum.* These compounds were found to compete effectively with macrophage inflammatory protein (MIP)-1R for binding to human CCR5, an important anti-HIV-1 target that interferes with HIV entry into cells (Figure 3.1.3.4).[3c]

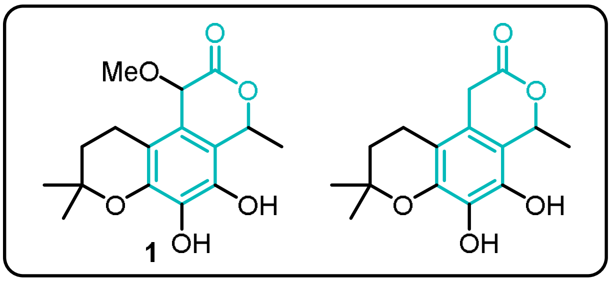


Figure 3.1.3.4 10-methoxydihydrofuscin (**1**) and it's derivative

3.1.3.5 Diterpenes Isolated from Sponge

Diterpenes, membranolides B was obtained from the Antarctic sponge *Dendrilla membranosa*(Figure 3.1.3.5).[3d]

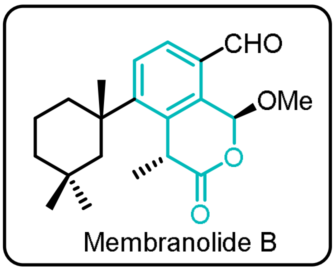


Figure 3.1.3.5 membranolides B

3.1.3.6 Cytosporones O(1) and Dothiorelone H(2)

During a chemotaxonomic study of fungal endophytes, Cytosporones O and Dothiorelone H were extracted from the ascomycete fungus Cytospora sp. belonging to the related genera Cytospora and Phomopsis from Brazil (Figure 3.1.3.6).[3e]

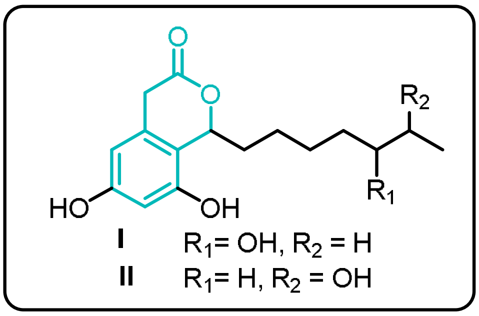


Figure 3.1.3.6 Cytosporones O (**I**) and Dothiorelone H (**II**)

3.1.3.7 3-Isochromanones Displayed Anti-tubulin Activity

Several 3-isochromanone derivatives such as 1, 2, and 3 are fused heterocycles bearing with trimethoxyphenyl displayed good biological properties which indicate that a lactone moiety is well tolerated in both series (Figure 3.1.3.7). These compounds showed significant anti-tubulin activity indicating that structural modification was accomplished on this A-part of the CA4 molecule, that access towards novel antivascular compounds (Figure 3.1.3.7).[3f]

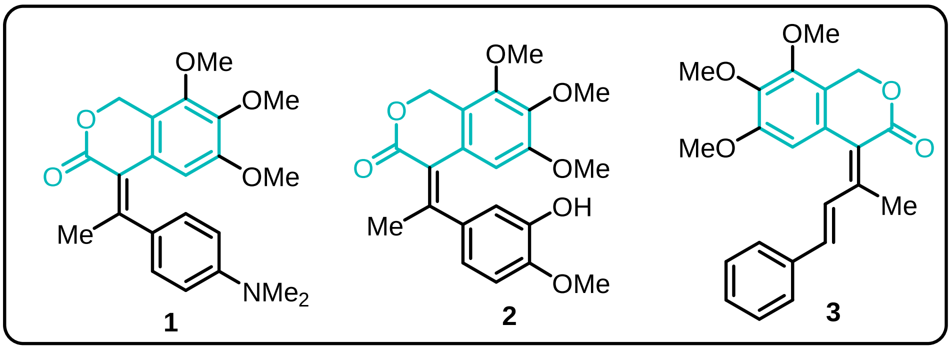


Figure 3.1.3.7 Derivatives of 3-isochromanones

3.1.3.8 Cytosporone S and D as an Antimicrobial Agent

Cytosporone S (1), a new class of microbial metabolite, was isolated from the fermentation of the fungus Trichoderma sp. FKI-6626. The chemical structure of Cytosporone S and Cytosporone D wascharacterized by mass and NMR spectroscopy and confirmed by *X-ray* crystallography. These compounds showed good antimicrobial activity against several fungi, and Gram-positive and Gram-negative bacteria (Figure 3.1.3.8).[3g]

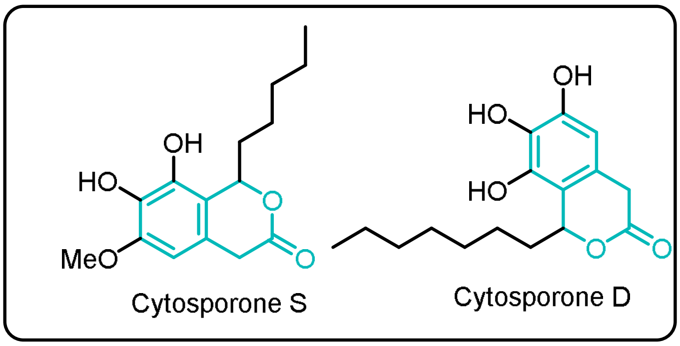


Figure 3.1.3.8 Cytosporone S and D

3.1.3.9 Carnosol as a Useful Building Block

Carnosol belongs to a group of 7–20 oxabridged dinorditerpenes. This is a useful building block for the total synthesis of (+)-elevenol and (+)-przewalskin. (+)-Elevenol is an anti-hepatitis C active compoundfound in Fluegga virosa (Figure 3.1.3.9).[3h]

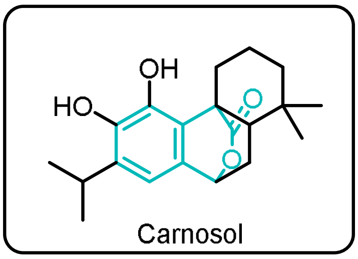


Figure 3.1.3.9 Carnosol

3.1.3.10 Commiphoranes A and B Terpenoids

Commiphoranes A–B, two novel aromatic terpenoids constituted as uncommon skeletons, were separated from *Resina Commiphora sp.* (Figure 3.1.3.10). Structures of these derivatives were identified by NMR spectroscopic and crystallographic methods. Compounds A and B are dinorditerpenoids, structurally bridgehead-fused heterocycles with a 6/6/6/6 ring system. They significantly reduced the overproduction of fibronectin, collagen I, and α-SMA in TGF-β1-induced rat renal proximal tubular cells.[3i]

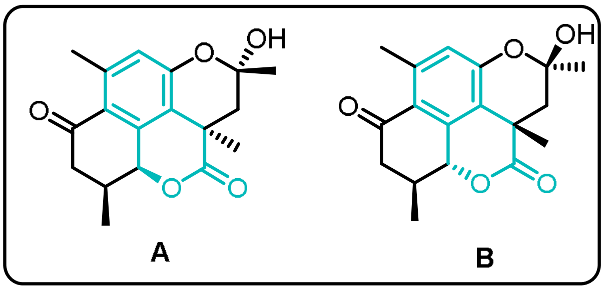
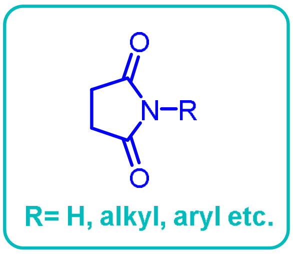


Figure 3.1.3.10 Commiphoranes A and B

3.1.4 Succinimide



3.1.4.1 Succinimide and Its Scope

Succinimide is a compound containing an imide group. In striking contrast, succinimide is a constituent of natural products such as salfredin C-1 and palasimide,[4a-c] as well as potent drugs such as phensuximide, lurasidone, and thalidomide.[4d-i] Several other succinimides, including ethosuximide, and methsuximide, are used as anticonvulsant drugs (Figure 3.1.4.1).[4e-f]

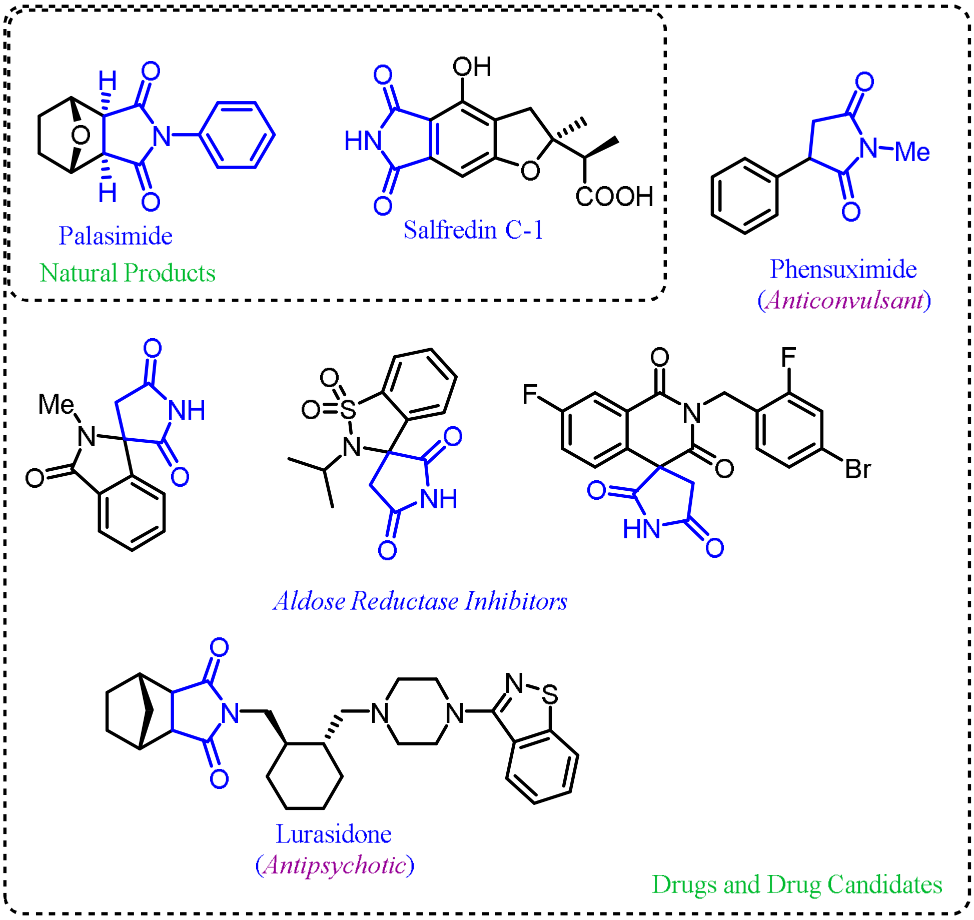


Figure 3.1.4.1 Succinimide skeletal natural products, drugs, and drug candidates.

There are many spiro-succinimides[4j-n] that have shown aldose-reductase inhibition when taken orally. It is interesting to note that maleimides are optimum activated alkenes that are well-suited for introducing succinimide moiety by cycloaddition,[5] conjugate addition,[6] or cross-coupling reactions.[7]

3.1.5 Importance of Spiroheterocycles

3.1.5.1 Benzofuran-3-one Containing Spiroheterocycles

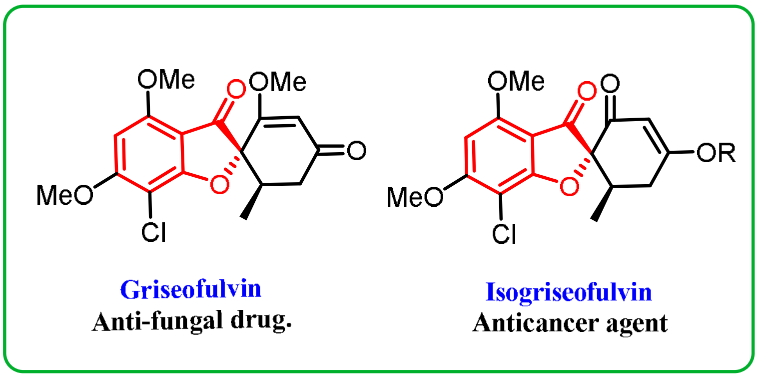


Figure 3.1.5.1 Benzofuran-3-one containing spirocyclic scaffold.

Among various spirocyclic molecules containing benzofuran-3-one scaffold Griseofulvin and Isogriseofulvin attracted much attention due to their anti-fungal and anticancer property respectively (Figure 3.1.5.1).[8]

3.1.5.2 Succinimide Containing Spiroheterocycles

Synthesis of various *N*-substituted succinimide skeletal spiro heterocycles, basically 2,7-diazaspiro[4.5]decane derivatives is important not only in synthetic chemistry but also in chemical biology as it's a new field of drug discovery. Now it is under research that these molecules especially compound **I** have wide activity in several diseases such as senile dementia, Alzheimer's disease, Huntington's chorea, tardive dyskinesia, hyperk-inesia, etc., and compound **II** exhibits Acetyl-coA carboxylase inhibition (Figure 3.1.5.2).[9]

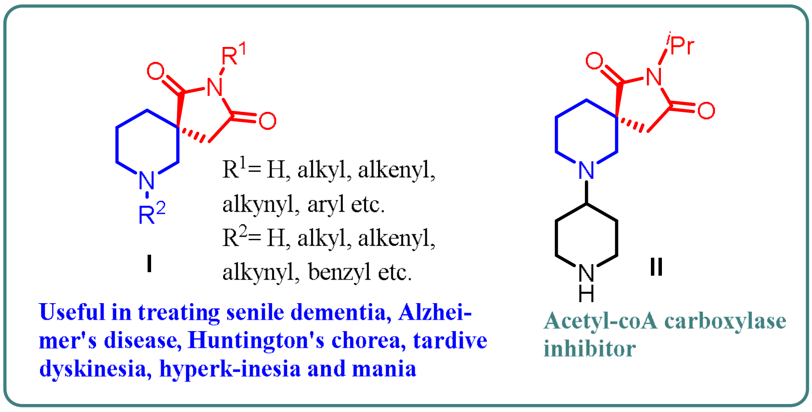


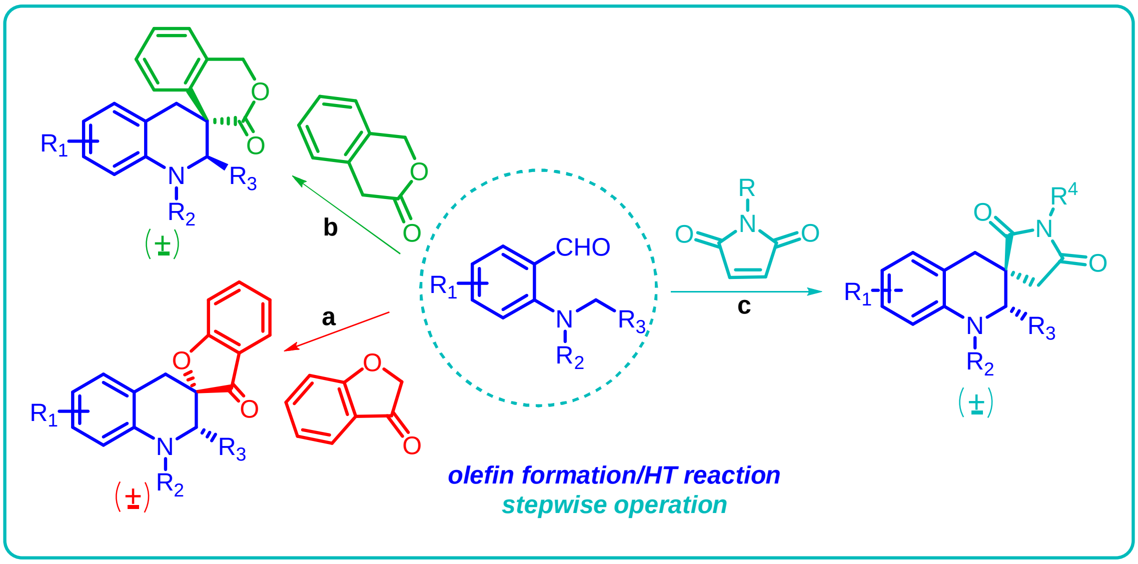
Figure 3.1.5.2 Representative bioactive molecules containing succinimide skeletal [4.5] spirocyclic scaffold.

3.2 Objectives

Researchers have been investigating direct and selective functionalizations of inert C–H bonds into C–C and/or C–X bonds (X = O, N, halogen, etc.) because they provide powerful tools for the synthesis of many complex molecules.[10] Recently, there has been much attention paid to the internal redox process involved in functionalizing the sp^3-C–H bond through [1,5]-hydride shift from one sp^3 carbon to another electrophilic sp^2 carbon/ heteroatom, followed by cyclization.[11] To achieve fused (spiro) heterocycles in an oxidant-free green process this atom-economic internal redox process has a good gravity.[12]

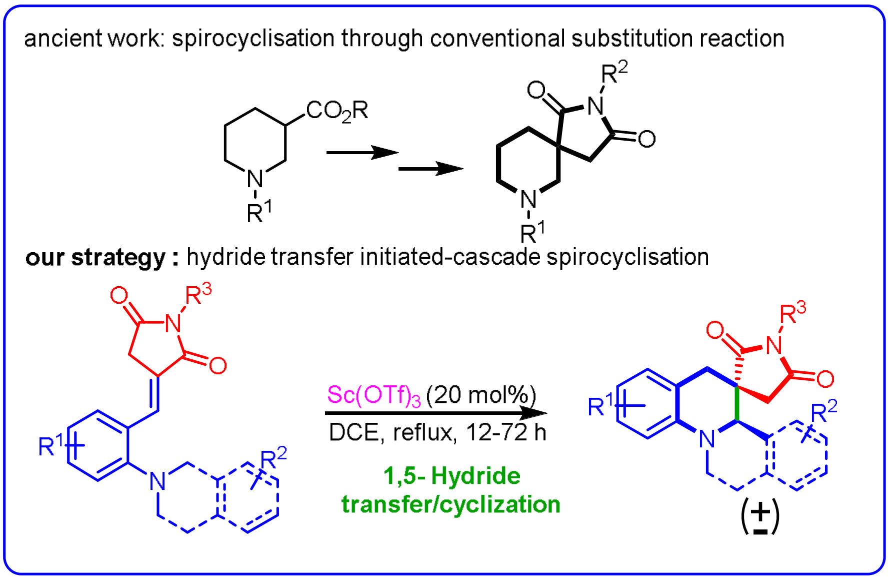
Coumaranone-containing scaffolds have drawn much attention since aeons due to their presence in many biologically relevant molecules such as naturally occurring isoaurones, isoaurostatin marginalin pterocarposide radulifolin-B, Commiphoranes, aurones, and spirocyclic Griseofulvin analogsan orally active antimycotic drug.[2] Various spirocyclic isoaurones, aurones[2d], and 3-isochromanone[3a] derivatives are well-known pharmaceutically important compounds and natural products to exhibit excellent activity against different biological targets. There has been enormous progress in the area of spirocyclic chemistry, however, the development of a highly stereoselective and atom-economic method for the construction of a spirocyclic scaffold containing 3-isochromanone fused with *N*-heterocycles has hardly been explored[13]. Then there is tetrahydroisoquinoline, a notable powerful building block that constructs a variety of bioactive molecules.[14] Yet, no protocol is available to integrate these alluring bioactive scaffolds to date, and benzofuran-3-one or 3-isochromanone has not been used in the hydride shift reaction cascade. Over the past few decades, substantial efforts have been made by various research groups to develop varieties of hydride transfer/cyclization cascade reactions for the construction of structurally diverse complex molecules. Taking account of the importance of building block 3-coumaranone, isochromanone scaffold our ongoing interests toward the synthesis of densely functionalized (spiro) heterocycles via C-H bond activation. Our main goal was straight forward and practical approach towards the synthesis of spiro-*N*-heterocycles via olefination, [1,5]-hydride transfer followed by cyclization strategy using corresponding aldehyde and coumaranone in one-pot (path **a** and **b** in Scheme 3.2.1).

Moreover, we focused on succinimide-containing spiroheterocycles as the construction of 2,7-diazaspiro[4.5]decanes has high demand which we discussed previously.[9] The hydride transfer may accomplish the success of the spiro-fused succinimide-containing tetrahydroquinolines induced by vinylogous iminium intermediates. A variety of 2,7-diazaspiro[4.5]decanes can be achieved from newly designed 2-amino substituted benzylidine derivatives with excellent yield and diastereoselectivity (path **c** in Scheme 3.2.1). The formidable challenge of [1,5]-hydride shift/cyclization process in this succinimide functionalized olefin was addressed.



Scheme 3.2.1 Our objectives towards spirocyclization through 1,5-HT/cyclization

The spirocyclic motif is a key element in the natural products and discovery of new drugs due to their inherent three-dimensionality and structural novelty. Relying on substrate engineering, we aimed to develop a method to achieve diastereoselective [4.5] and [5.5] spiro-coumaranone/isochromanone containing tetrahydroquinoline during our research program on catalytic C–H functionalizations which have great importance in complexity-enhancing potential synthetic application and in chemical biology.[15] The construction of useful skeletons, such as tetrahydroquinolines,[16] tetrahydroisoquinolines,[17] benzopyrans,[18] tetralins,[19] spirooxindoles,[20] and indanes,[21] are also important, could be achieved by several groups including ours utilizing a [1,n]-hydride shift (n = 4, 5, 6) strategy. In contrast, succinimide is a constituent of natural products[22a-b] such as salfredinC-1, palasimide, and numerous spiro-succinimide identified as powerful orally potent aldose-reductase inhibitors.[22c]Among various spirocyclic cores, we targeted [4.5] succinimide-based piperidine skeleton because it represents a unique class, such as useful in treating senile dementia, Alzheimer’s disease, Huntington’s chorea, and other diseases discussed above(Figure 3.1.5.2).[9] Prior literature reports inform this scaffold could be synthesized from piperidine 3-carboxylate derivatives or their analogs in an ancient multistep uphill process (Scheme 3.2.2). Therefore, the construction of these spiro scaffolds has drawn considerable interest.[23]



Scheme 3.2.2 Previous approaches and our strategy towards 2,7-diazaspiro[4.5]decanes

Recent efforts by us have led to the creation of multifunctional 2,7-diazaspiro[4.5]decanes exploiting hydride shift methodology, which was highly challenging due to the inaccessibility of the corresponding synthetic precursor. Because of the difficulties in the preparation of succinimide containing olefin, we devised a daedal plan to reach our goal. It is still quite a challenging task to develop the hydride shift from the non-benzylic position to the mild-activated olefin system, and its realization would improve the internal redox process in synthesizing organic compounds. To the best of our knowledge, moderately activated succinimide skeletal olefin has been introduced first for this HT reaction. It is noteworthy that this architectural complex structure was incomprehensible via a single-step methodology, despite their wideness as the biological-active compound.

We document herein a novel diastereoselective hydride shift/cyclization reaction assisted by a heteroatom. This may enable us to produce a key building block succinimide containing spiro-scaffold namely 2,7-diazaspiro[4.5]decanes.

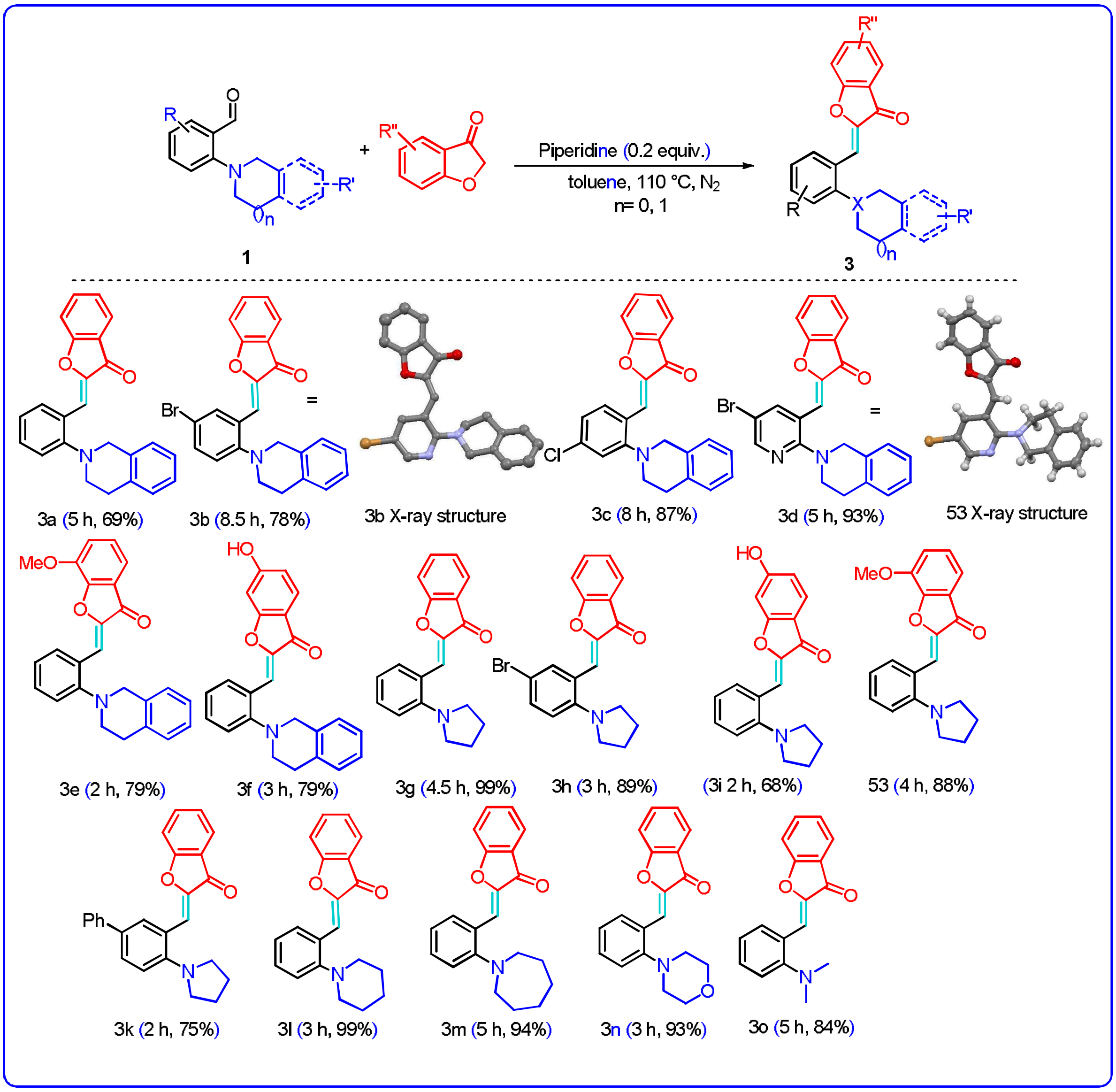
3.3 Results and Discussion

Based on the 1,5-hydride transfer methodology initially, we gave our attention to the use of good scaffold 3-coumaranone as a partner for the synthesis of spiroheterocycles. We attempted the one-pot olefination followed by [1,5]-hydride transfer process using THIQ aldehyde **1** and 3-coumaranone **2** under various conditions including different solvents, temperature, and Lewis acids but remained unsuccessful. Hence, various olefins **3a-3o**we prepared through the Knoevenagel condensation method,and thenthe hydride shift process followed by cyclization reaction was thoroughly optimized using **3a** as a model substrate under different conditions.

3.3.1 Scope of 3-Coumaranone Containing Olefins

Various 3-coumaranone-containing olefin has been prepared applying the Knoevenagel condensation method (Table 3.3.1). Several functional groups were well tolerable in this reaction condition where piperidine was used as acatalyst. Not only THIQ, but several other 2-amino substituted aldehydes such as pyrrolidine, piperidine, azepane, morpholine, and dialkyl amine also showed well conversion in this reaction. Hydroxy and methoxy substituted 3-coumaranones had been used for the production of corresponding olefin substrates and furnished a very good yield. Notably, we got *E* diastereomer as a major in this condition.

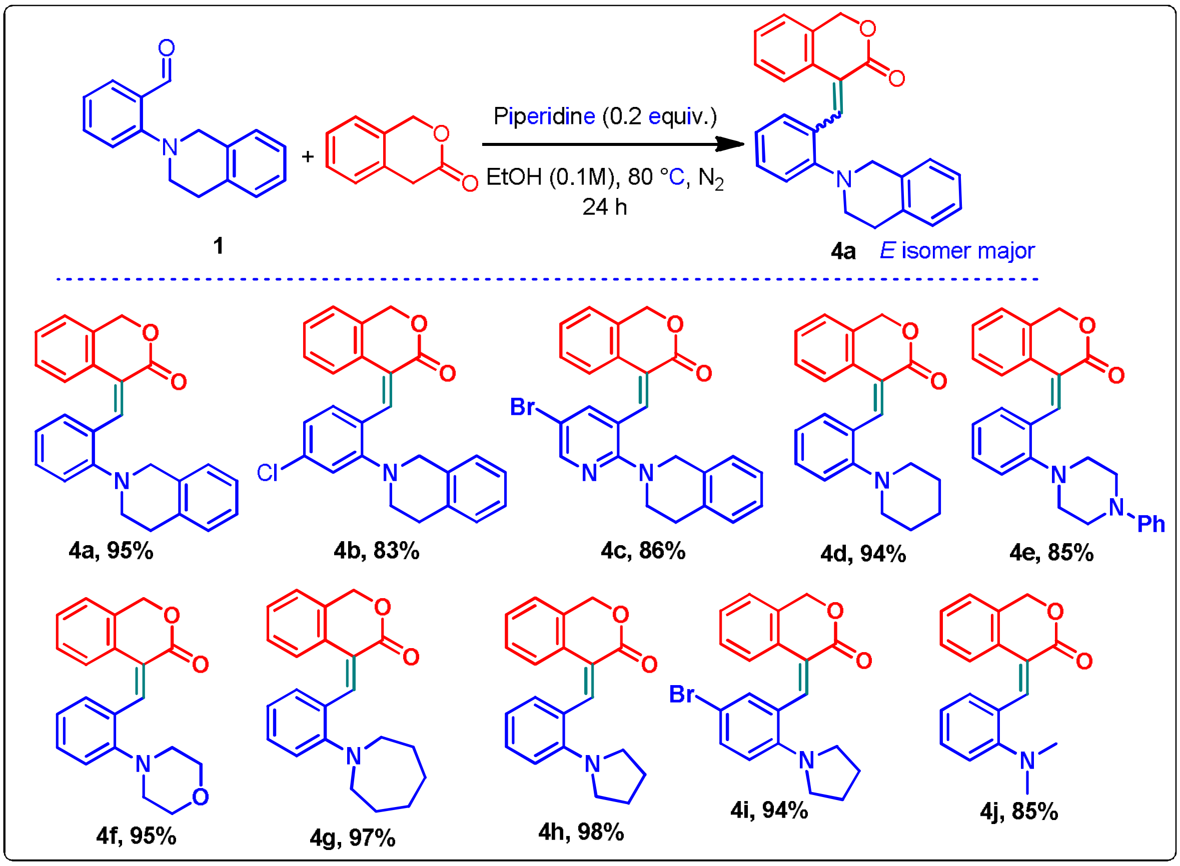
Table 3.3.1 Scope of 3-Coumaranone Containing Olefins



3.3.2 Scope of 3-Isochromanone Containing Olefins

Various 3-isochromanone containing olefin have been prepared applying the same Knoevenagel condensation method (Table 3.3.2). But here we applied ethanol instead of toluene as a solvent because ethanol gave the best result among others. Various functional groups were compatible in this reaction condition. Employing a piperidine catalyst we prepared a wide scope of olefin derivatives the precursor of spiro-heterocycles. Not only THIQ, but several other 2-amino substituted aldehydes such as pyrrolidine, piperidine, azepane, piperazine, morpholine, dialkyl amine, etc. also showed well conversion in this reaction. We observed that the *E* isomer formed exclusively over *Z* in most of the cases. But in some cases *Z* isomer was notable and we reported the ratio of these two diastereomer accordingly in spectral data (in experimental section).

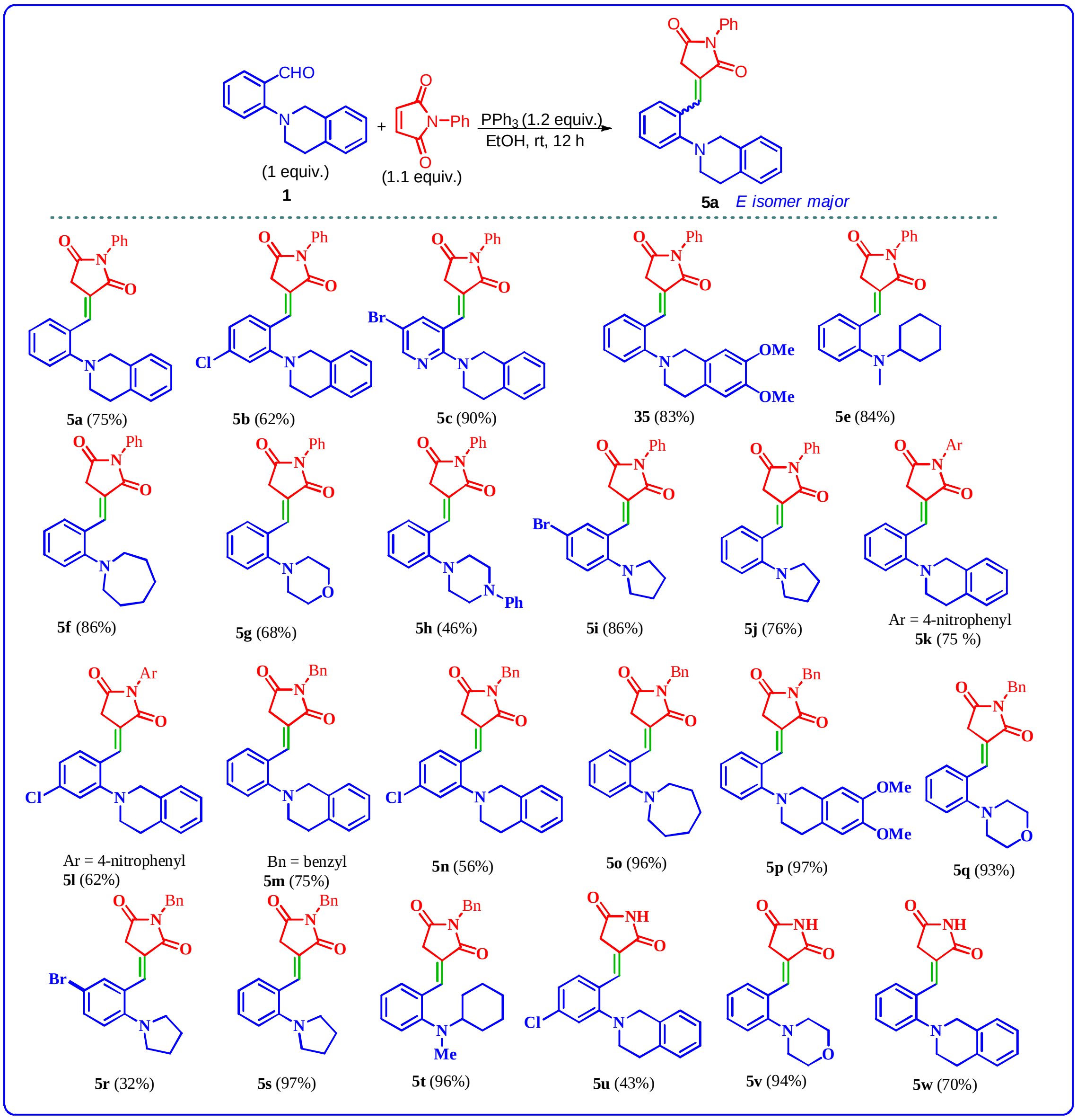
Table 3.3.2 Scope of 3-Isochromanone Containing Olefins



3.3.3 Scope of Succinimide Containing Olefins

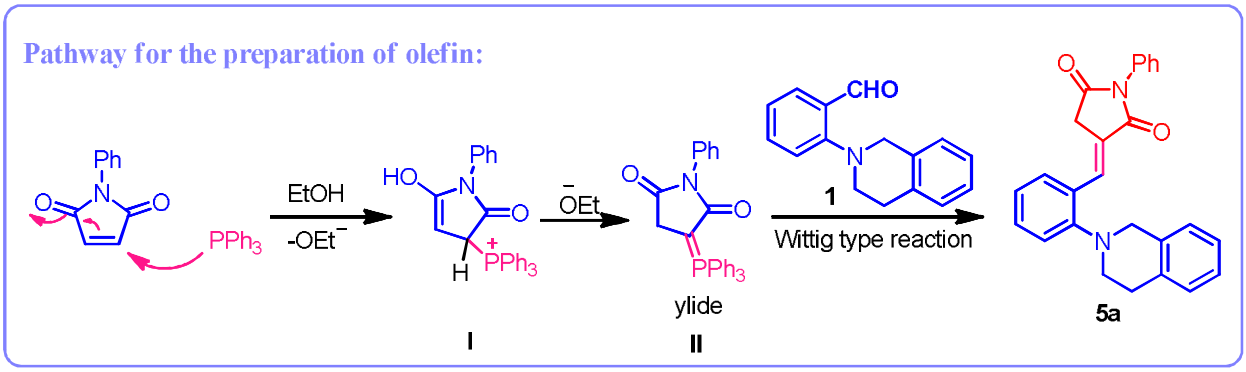
The preparation of succinimide containing olefin is highly challenging because of its inactive methylene group. It didn’t undergo a Knovenagel-type condensation reaction but in drastic conditions, it formed olefin with another coupling partner such as aldehyde or ketone derivatives. Hence, we thought of a substitute way to produce succinimide containing olefin, and applied a Wittig-type reaction as analternativetothe Knoevenagel condensation reaction. Triphenylphosphinereacts with Maleimide in ethanol solvent and produces ylide initially then substituted aldehyde was added to the reaction mixture. After a few hours, a yellow precipitate was observed and it was filtered through the funnel. The significance of this methodology is the good conversionat room temp and air, no moisture sensitivity,no base is required, and conversion happened very smoothly. Various functional groups were well tolerable in this reaction condition. Besides THIQ, several other 2-amino substituted aldehydes such as pyrrolidine, piperidine, azepane, piperazine, morpholine, dialkyl amine, etc. played well resulting in good conversion in this reaction (Table 3.3.3). Various maleimides such as *N*-H, *N*-Bn, and *N*-Ar were compatible in this condition. We observed that the *E* isomer formed exclusively over *Z* in most of the cases.

Table 3.3.3 Scope of Succinimide Containing Olefins



3.3.3.1 Proposed Pathway towards Olefin 5a

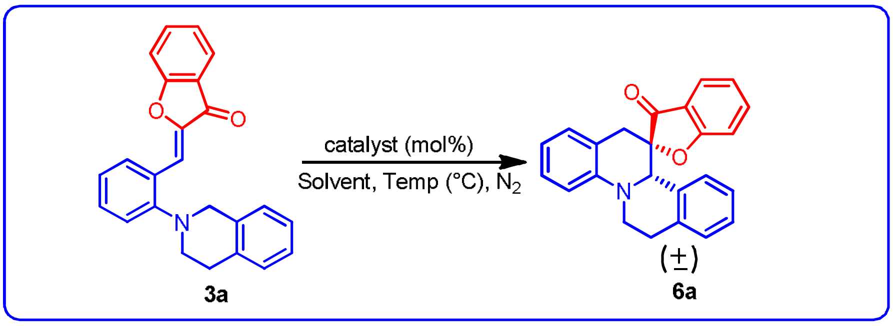
Triphenylphosphine initially reacts with maleimide and produces ylide **II** which is stabilized ylide (Scheme 3.3.3.1). Consequently,*E* olefin **5a**was formed through a Wittig type of reaction. This reaction happened smoothly in the air in EtOH solvent and no base was needed for this reaction. Hence it wasthebest alternative to Wittig reaction.



Scheme 3.3.3.1 Proposed pathway of 5a

3.3.4 Optimization Study

Table 3.3.4.1 Optimization of the Reaction Condition of 3a-6a



entry	catalyst (mol%)	solvent	temp (°C)	time (h)	yield ^{a}(%)
1	$Mg(OTf)_2$	DCE	90	26	6.7
2	$Cu(OTf)_2$	DCE	90	3	19
3	$Zn(OTf)_2$	DCE	90	17	67
4	$Ni(ClO_4)_2.6H_2O$	DCE	90	6	64
5	$Sc(OTf)_3$	DCE	90	3	69
6	$Gd(OTf)_3$	DCE	90	23	71

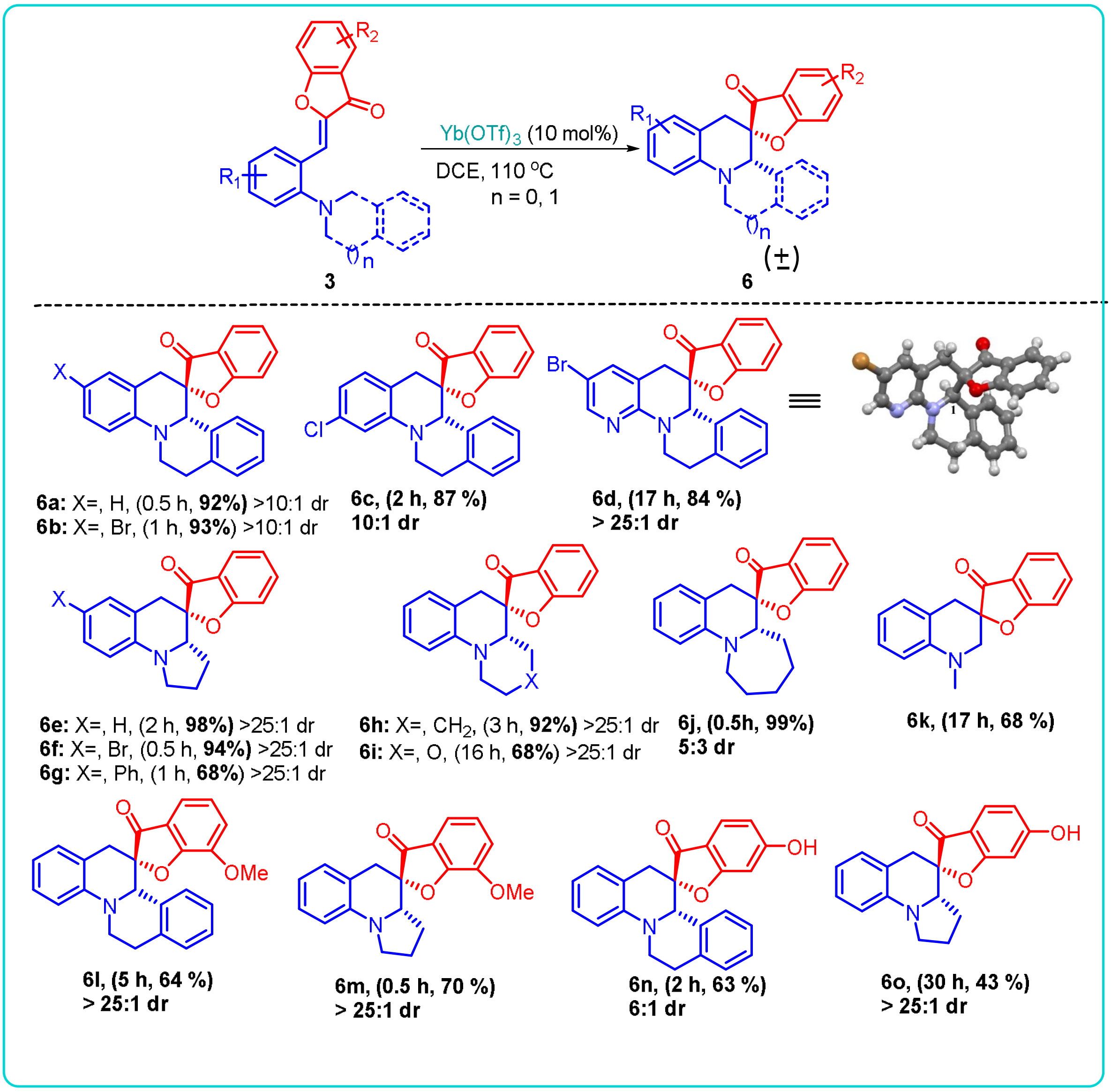
entry	**catalyst (mol%)**	**solvent**	**temp (^{o}C)**	**time (h)**	**yield ^{a}(%)**
7	In(OTf)$_3$	DCE	90	19	76
8	Yb(OTf)$_3$	DCE	90	3	81
9^{b}	Yb(OTf)$_3$	DCE	90	3	81
10^{b}	Yb(OTf)$_3$	THF	76	3	59
11^{b}	Yb(OTf)$_3$	n-Butanol	128	5	48
12^{b}	Yb(OTf)$_3$	Acetonitrile	92	3	85
13^{b}	Yb(OTf)$_3$	Toluene	110	3	35
14^{b}	**Yb(OTf)$_3$**	**DCE**	**110**	**3**	**81**

Unless otherwise mentioned, all reactions were done with 0.2 mmol of 3**a**, 20 mol% Yb(OTf)$_3$ as cat. at 90 in DCE under nitrogen. ^{a}Isolated yield. ^{b}10 mol% Yb(OTf)$_3$ was also used.

3.3.5 Scope of Cyclization of 3-Coumaranone Containing Olefins 3

After performing the reaction under several parameters, we decided to explore the scope of substrates under the most efficient condition using 10 mol % Yb(OTf)$_3$ as a catalyst in DCE at 110 °C (Table 3.3.5). 3-Coumaranone containing THIQ substituted various olefins **3a-d** underwent a smooth reaction to provide the desired cyclic products **6a-d** in good to excellent yields with high diastereoselectivity (84-93%).

Table 3.3.5 Scope of Cyclization of 3-Coumaranone Containing Olefins 3[a]



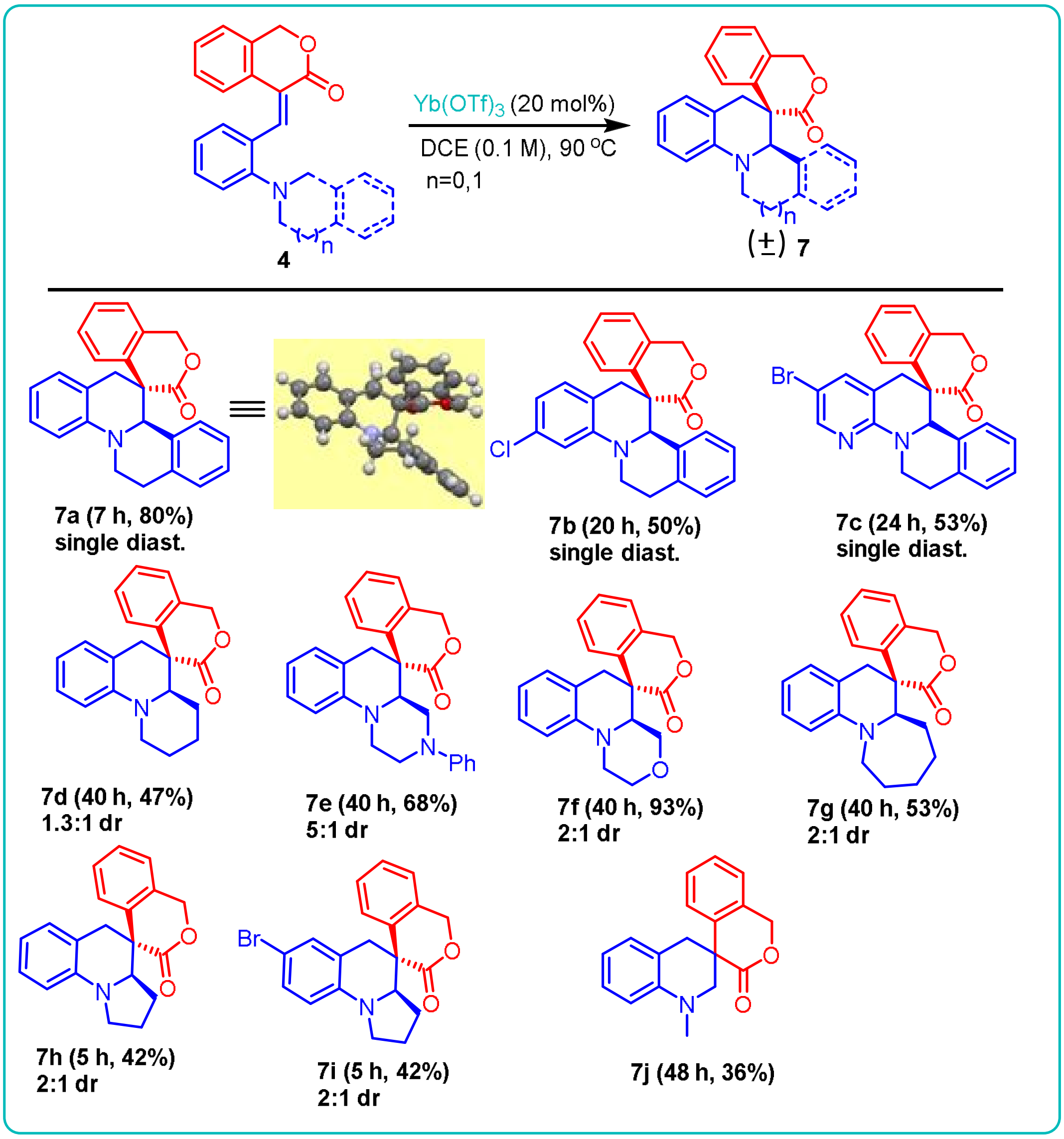
[a]Reaction conditions: all reactions were performed using olefin **3** (0.2 mmol). dr given is calculated by ^{1}H NMR.

The structure of major diastereomer **6d** was confirmed by single crystal *X-ray* analysis. To broaden the generality of the reaction, pyrrolidine, piperidine, and morpholine-substituted olefins **3e-g,3h,** and **3i** were used and successfully afforded the products **6e-g, 6h,** and **6i** in excellent yields with excellent selectivity. Formation of product **6j** with excellent yield (99%) was observed in the case of azepane-substituted substrate **3j**. Dimethyl substituted substrate **3k** afforded the product **6k** in good yield. Next, the reactions were carried out with methoxy and hydroxy-substituted 3-coumaranone containing olefins **3l-o** and we obtained the products **6l-o** in moderate to good yields and diastereoselectivity.

3.3.6 Scope of Cyclization of 3-Isochromanone Containing Spiroheterocycles [a, b]

To further expand the scope of the reaction, for emphasizing this methodology mainly, we introduce another building block surrogate 3-isochromanone.This important pharmacophore was examined to construct a new class of spiro-heterocycles containing THIQ and 3-isochromanone moieties altogether. Despite their potential biological activities, no protocol is available to integrate these two pharmacophores to date. Delightfully, 3-isochromanone substituted olefins **4a** reacted to furnish the product **7a** as a single diastereomer in 80% yield in the presence of 20 mol % of Yb(OTf)$_3$ under reflux temperature of the solvent DCE.

Table 3.3.6 Scope of Cyclization of 3-Isochromanone Containing Spiroheterocycles



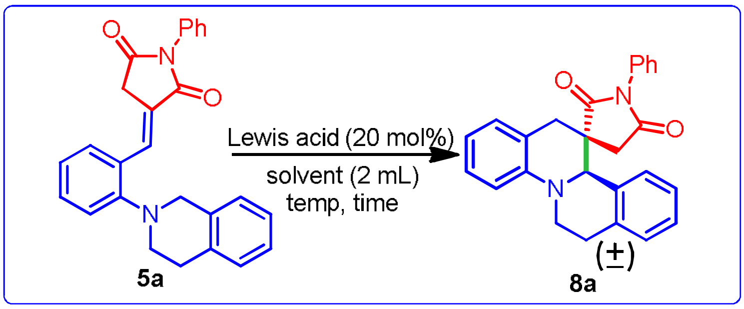
[a]Reaction conditions: all reactions were performed using olefin **4** (0.2 mmol). [b]dr given is calculated by ^{1}H NMR.

The substrates **4b-j** successfully furnished the corresponding 3-isochromanone containing spiroheterocycles **7b-j** in moderate to good yields (Table 3.3.6) implying that pyrrolidine, piperidine, azepane, and morpholine groups are well tolerable at this reaction condition.

3.3.7 Optimization Study towards 2,7-Diazaspiro[4.5]decanes

1,5-Hydride shift is well known methodology but the construction of the schematic scaffold is not accessible easily. The comprehension of the corresponding precursor is one of the challenging tasks because succinimide didn't undergo in Knoavenagel type of condensation reaction. Due to the presence of an unreactive methylene group, preparation of the corresponding olefin in other ways is also quite uphill. Hence, we applied a robust and easiest Wittig-type methodology cleverly taking maleimide as a starting material with 2-amino substituted benzaldehyde. From the literature background, a few reports are available to create benzylidine-succinimide, but this is the first report where our group synthesized plenty of 2-amino(*tert*) substituted benzylidine-succinimide employing triphenylphosphine reagent in ethanol solvent at room temperature which is the precursor of 2,7-diazaspiro[4.5]decanes.

Table 3.3.7.1 Optimization of Reaction Condition of 5a-8a[a]



entry	Lewis acid (20 mol%)	solvent (2 mL)	temp. (□)	time (h)	yield[b] (%)
1	$Sc(OTf)_3$	DCE	110	12	65
2	$Yb(OTf)_3$	DCE	110	12	25
3	$Ni(ClO_4)_2$	DCE	110	12	trace
4	$Ni(OAc)_2$	DCE	110	12	NR
5	$Gd(OTf)_3$	DCE	110	12	trace
6	$Mg(OTf)_2$	DCE	110	12	trace
7	$In(OTf)_3$	DCE	110	12	trace
8	$Cu(OTf)_2$	DCE	110	12	NR
9	$Zn(OTf)_2$	DCE	110	12	NR
10	$Sc(OTf)_3$	DCE	110	13	71
11	$AlCl_3$	DCE	110	12	38
12	**$Sc(OTf)_3$**	**DCE**	**110**	**15**	**80**
13	$Sc(OTf)_3$	toluene	130	15	74
14	$Sc(OTf)_3$	mesitylene	120	24	NR
15	$Sc(OTf)_3$	DMF	120	12	-
16	$Sc(OTf)_3$	DMSO	120	15	-

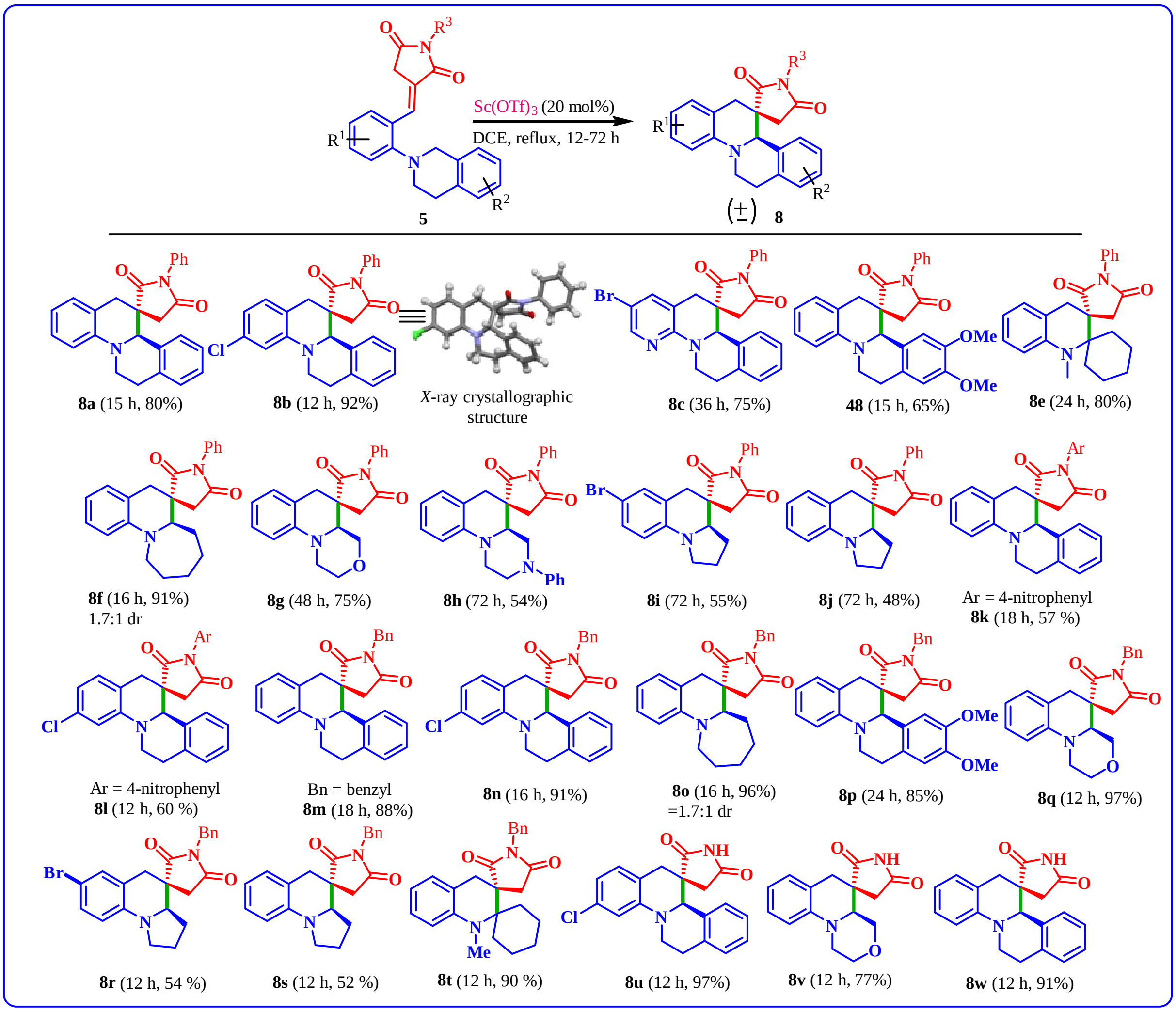
[a] Reaction conditions: **5a** (0.1 mmol), Lewis acidcatalyst (20 mol%), in 2.0 mL of solvent at indicated temperature under N_2, 12-24 h. [b] Isolated yield after column chromatography; single diastereomer, dr was determined by ^{1}H NMR spectroscopy.

Our efforts on the spirocyclization of the carbocyclic ring exploiting such a cascade reaction of (*E*)-3-(2-(3,4-dihydroisoquinolin-2(1*H*)-yl)benzylidene)-1-phenylpyrrolidine-2,5-dione **5a** which was prepared from the corresponding aldehyde and maleimide derivative (for details see experimental section). Taking **5a** as a model substrate initially we screened several reactions without involving any Lewis acid catalyst and also applied fluorinating solvent and other high boiling solvent but we failed to produce the desired spirocyclic product **8a**. Hence, we realized that Lewis acid has a great influence on this HT reaction. To examine the reaction, 20 mol% of Lewis acids were used as catalysts in DCE solvent at reflux temperature as shown in table 3.3.7.1. Among various Lewis acid $Sc(OTf)_3$, $Yb(OTf)_3$ and $AlCl_3$ (entries 1, 2 and 11 in table 3.3.7.1)gave the positive result whereas $Ni(ClO_4)_2$, $Ni(OAc)_2$, $Gd(OTf)_3$, $Mg(OTf)_2$, $In(OTf)_3$, $Cu(OTf)_2$ and $Zn(OTf)_2$ didn't provide any satisfactory results (entries 3-9 in table 3.3.7.1). To our delight, scandium triflate was the best choice as it provided good to better yield with the increase of the reaction time (entries 1, 10, and 12 in table 3.3.7.1). We accomplished the best result employing $Sc(OTf)_3$ catalyst in DCE solvent after 15 h (entry 12 in table 3.3.7.1) and to the best of our study it was the superior condition for the desired spiro-cyclization. However, various high boiling solvents such as mesitylene, DMF, and DMSO were helpless for the reaction (entries 14-16 in table 3.3.7.1). Although in toluene solvent the reaction happened and we isolated 74% of the desired product **8a** after 15 h (entry 13in table 3.3.7.1). It was a great achievement that the reaction exhibited a single diastereomeric product of **8a**, which may be undergoing via thermodynamically controlled product.

3.3.8 Substrate Scope of the Cascade Reaction towards Succinimide Containing Spiro-Heterocycles

To evaluate the generality of this methodology, the scope of 2-aminobenzyledenesuccinimide derivatives **5** was explored in the best reaction condition. Remarkably, a variety of aminobenzyledene-succinimide derivatives were well compatible with the reaction system, producing the corresponding spiro-succinimide containing tetrahydroquinoline (THQ) **8** in moderate to high yields with excellent stereocontrol. First, we examined the effectiveness of the hydride donor system by changing amino-aldehyde moieties, keeping unchanged the succinimide part (**5a-5j** in table 3.3.8). We all are familiar that the benzylic amine is the best for the 1,5-HT reaction. Apart from benzylic amine (**5a-5d**), other non-benzylic amines such as *N*-(methyl)cyclohexyl amine **5e**, azepane **5f**, morpholine **5g**, *N*-phenylpiperazine **5h**, pyrrolidine **5i-5j** showed their good hydride donor capability exemplifying a broad coverage of highly functionalized spiro-heterocycles with good to excellent yield in this reaction condition. Besides various functional groups (such as chloro, bromo, and methoxy) heterocycles are well tolerable (**8c**, 75%) (table 3.3.8). The structure of product **8b** had been confirmed absolutely by *X-ray* crystallographic analysis (see experimental section). Indeed, the stereochemistry of the desired molecule was controlled by the succinimide part of the substrate. The slower rate was noticed for the non-benzylic hydride donor substrate, which had taken more time for the conversion (**8e-8j**).

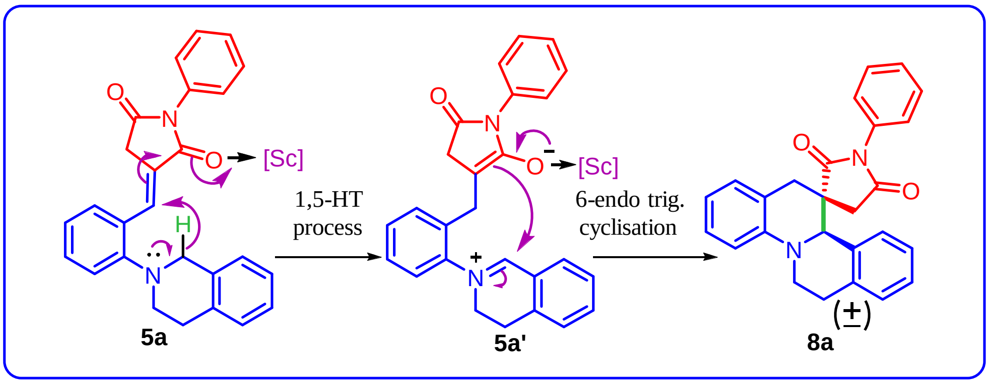
Table 3.3.8 Substrate Scope of the Cascade Reaction Towards Succinimide Containing Spiro-heterocycles[a]



Reactions were performed with **5** (0.1 mmol), and Sc(OTf)$_3$ (0.02 mmol) in 2 mL of DCE at reflux temperature for 12-72 h under an inert (using N$_2$ balloon) atmosphere. The products were isolated via column chromatography. Mainly single dr observed, except **8r** (dr 1.7:1) and **8s** dr (1.7:1), dr was determined by ^{1}H NMR spectroscopy.

Investigating the hydride donor substrate, we focussed on the hydride acceptance system i.e., succinimide scaffold. Electron withdrawing *N*-Aryl (*P*-NO_2Ph) **5k-5l** and electroneutral *N*-benzylic succinimide substrate **5m-5t** converted smoothly to the novel spiro-heterocycles with good to excellent yield. In addition, the *N*H-free succinimide substrate **5u-5w** proved to be a very good candidate for this application. The significance of this transformation is the wide scope of donor and acceptor moieties which furnishedavariety of succinimide-containing spiro-fused tetrahydroquinolines. It was noteworthy that, the maximum substrate converted to a single diastereomeric product. Particularly **8r** and **8s** gave 1.7:1 dr, which may be due to the flexibility of azepane.

3.3.9 Proposed Mechanism



Scheme 3.3.9 Plausible mechanism of the 1,5-HT reaction

In light of previous work and the results discussed above, the following mechanism is proposed for the construction of 2,7-diazaspiro[4.5]decanes (Scheme 3.3.9). Lewis acid $Sc(OTf)_3$ coordinate with the imide group of **5a** and activate the olefin which promotes to drive the initiation of [1,5]-hydride transfer. As a result of the HT, the iminium ion **5a'** is formed, which is trapped immediately by the succinimide C_3 position by 6-endo trig cyclization, resulting in a one-step construction of fused 2,7-diazaspiro[4.5]decanes **8a**.

3.4 Conclusion

In summary, we have developed a Lewis acid-catalyzed [1,5]-hydride shift followed by 6-endo cyclization sequences of 3-coumaranone, 3-isochromanone and succinimide containing olefins to afford several novel spiro-heterocycles. In other words, we have developed a new strategy to assemble fused 2,7-diazaspiro[4.5]decanes in one step which has great importance. This is the most effective method for creating this potential bio-active scaffold.

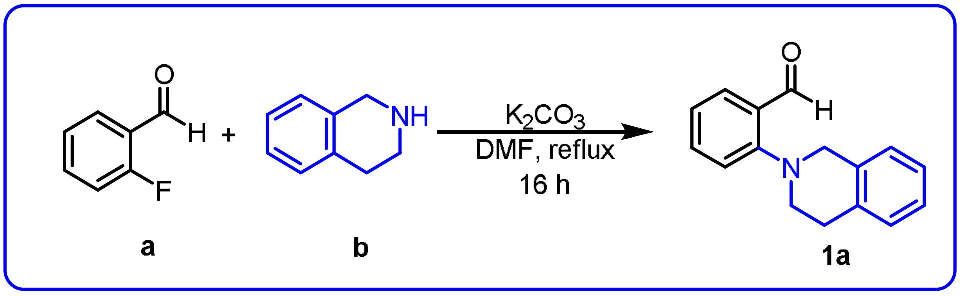
Redox-neutral, metal-free, and carried out under mild reaction conditions, the novel methodology boasts high stepeconomies and atom economies. Structurally diverse succinimide containing spiro fused THQ/THIQ could be furnished in good to excellent yield with a single diastereomeric product. Aside from solving the challenge of synthesizing six-membered THQ rings, this strategy opens up a new window for spiro succinimide synthesis by using hydride transfer chemistry. This reaction is currently being studied for its enantioselectivity through organocatalysis and we are also developing this strategy for achieving large and macrocyclic rings in our laboratory.Our current studies are focused on asymmetric internal cascade redox neutral reactions using chiral organocatalysts for the efficient construction of molecular complexity, which may have potential pharmaceutical applications in the future.

3.5 Experimental Section

3.5.1 General Information

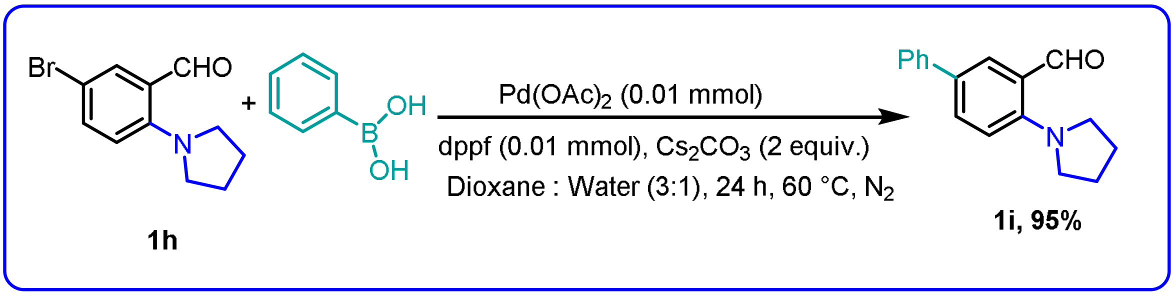
All reactions were carried out in an oven-dry reaction vessel under an N_2 atmosphere unless otherwise stated. Commercial reagents were purchased from Sigma-Aldrich, Alfa Aesar, Acros, and other commercial suppliers and used as received without further purification. Anhydrous DCE was purchased from Sigma-Aldrich and used as received. TLC analysis was performed on Merck 60 F_{254} silica gel TLC plates. Column chromatography was done using 230-400 mesh silica gel by applying pressure through an air pump. ^1H and ^{13}C NMR spectra were recorded in Bruker 300, 600 MHz, and JEOL 400 MHz spectrometer, and are reported as chemical shifts (δ) in parts per million (ppm). Internal standards or residual solvents were used as a reference. HRMS (m/z) were recorded in the Q-Tof Micromass spectrometer (LC-MS, ESI mode) and JOEL-JMS 700 (EI mode). Melting points were determined in a capillary melting point apparatus and are uncorrected. Single crystal X-ray data was recorded in a Bruker Kappa APEX2 CCD diffractometer with MoKα radiation. The structures were solved by SHELXT and refined with SHElXL using the Olex2 program. CCDC (1996347-1996349).

3.5.2 General Procedure for the Preparation of 2-Aminobenzaldehyde Derivative 1a



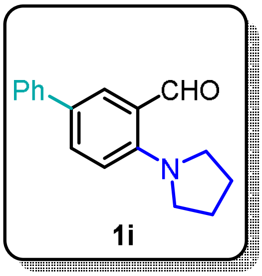
The compound was prepared following the literature procedure.[24] To an oven-dried 10 mL round-bottom flask attached to a condenser under N_2 atmosphere, 2-fluorobenzaldehyde (0.037 g, 0.3 mmol), 1,2,3,4-tetrahydroisoquinoline (0.05 g, 0.37 mmol) and potassium carbonate (0.055 g, 0.40 mmol) were taken and the mixture was dissolved in DMF (6 mL). The bath temperature was slowly increased to the reflux temperature of DMF and stirred for 16 h. After the completion of the reaction, monitored by TLC, the organic layer was extracted with ethyl acetate (3 × 20 mL) and dried over anhydrous Na_2SO_4. The combined organic layers was concentrated under vacuo and purified by column chromatography on silica gel (230-400 mesh) using petroleum ether/ethyl acetate (97:3) as eluent to afford product **1a** with 70% yield.

3.5.3 Preparation of 3-Aryl Substituted Aldehyde 1i



The compound was prepared following the literature procedure.[25] To an oven-dried 10 mL round-bottom flask attached to a condenser under N_2 atmosphere, 5-Bromo-2-(pyrrolidin-1-yl)benzaldehyde (0.10 g, 0.3 mmol), phenylboronic acid (0.06 g, 0.47 mmol), cesium carbonate (0.25 g, 0.6 mmol), dppf (0.007 g, 0.01 mmol) and palladium acetate (0.003 g, 0.01 mmol) were taken and the mixture was dissolved in dioxane (1.25 mL) and water (0.5 mL). The bath temperature was slowly increased to 60 °C and stirred for 24 h. After the completion of the reaction, monitored by TLC, the organic layer was extracted with ethyl acetate (3 × 20 mL) and dried over anhydrous Na_2SO_4. The combined organic layers were concentrated under vacuo and purified by column chromatography on silica gel (230-400 mesh) using petroleum ether/ethyl acetate (95:5) as eluent to afford the product **1i** in 95% yield.

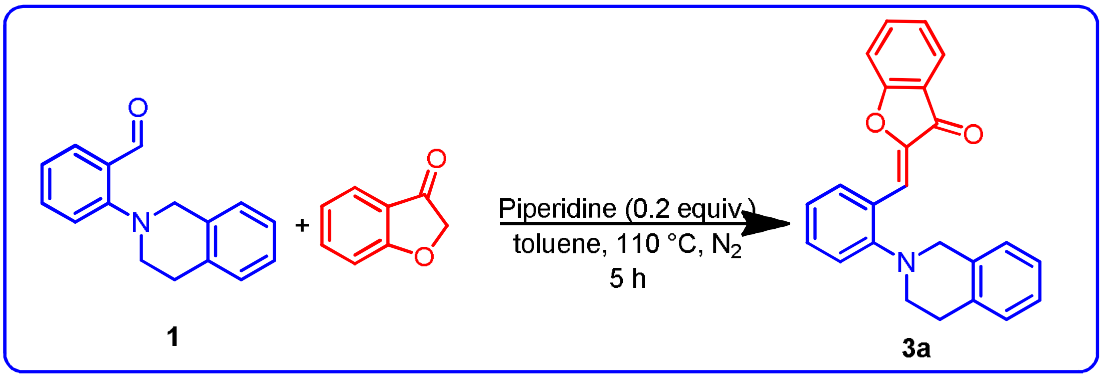
3.5.4 Characterization of 3-Aryl Substituted Aldehyde 1i



4-(Pyrrolidin-1-yl)-[1,1'-biphenyl]-3-carbaldehyde (1i):

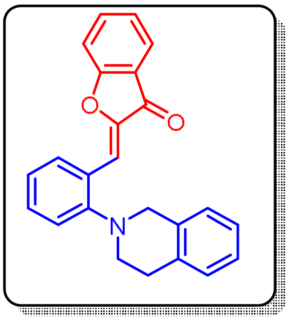
Yellow solid (94.7 mg, 95% yield); column chromatography eluent, petroleum ether/EtOAc = 50:1; mp84–85 °C; **^{1}H NMR (300 MHz, Chloroform-*d*)** δ 10.17 (s, 1H), 7.97 (d, *J* = 2.4 Hz, 1H), 7.66 (dd, *J* = 9.0, 2.4 Hz, 1H), 7.60 – 7.57 (comp, 2H), 7.45 – 7.40 (comp, 2H), 7.33 – 7.27 (m, 1H), 6.92 (d, *J* = 9.0 Hz, 1H), 3.44 – 3.40 (m, 4H), 2.04 – 1.99 (m, 4H);**^{13}C NMR (75 MHz, Chloroform-*d*)** δ 190.1, 149.2, 139.9, 132.7, 131.0, 129.2, 128.8, 126.5, 126.1, 122.9, 115.1, 52.8, 25.9.

3.5.5 Typical Procedure for the Preparation of 5a

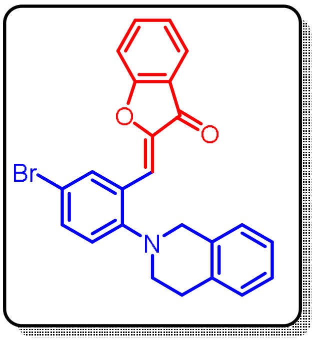


To an oven-dried round-bottom flask attached with a condenser under nitrogen, 2-(3,-dihydroisoquinolin-2(1*H*)-yl)benzaldehyde (**1a**) (93 g, 0.4 mmol) and benzofuran-3-one (70 mg, 0.52 mmol) was dissolved in anhydrous toluene (4 mL) Then piperidine (8 μL, 0.08 mmol) was added and the bath temperature was slowly increased to 110 °C. The reaction mixture was kept under stirring for 5 h. After the completion of the reaction, monitored by TLC, the solvent was removed under vacuo. The crude product was purified by column chromatography on silica gel (230-400 mesh) using petroleum ether/ethyl acetate (99:1) as eluent to afford (Z)-2-(2-(3, 4-Dihydroisoquinolin-2(1*H*)-yl)benzylidene)benzofuran-3(2*H*)-one(**3a**). We got 100 mg yellowish solid product with 69% yield.

3.5.6 Characterization of the Substrate 3a-3o

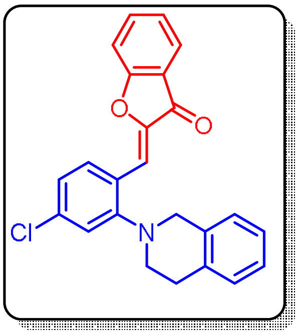


(Z)-2-(2-(3, 4-Dihydroisoquinolin-2(1*H*)-yl)benzylidene)benzofuran-3(2*H*)-one (3a):
Yellow solid (205 mg, 69% yield); column chromatography eluent, petroleum ether/EtOAc = 49:1; mp 148–149 °C; ^{1}**H NMR (300 MHz, Chloroform-*d*)** δ 8.27 (dd, *J* = 8.1, 1.5 Hz, 1H), 7.82 (dd, *J* = 7.8, 1.2 Hz, 1H), 7.68 – 7.63 (m, 1H), 7.41 (s, 1H), 7.38 – 7.32 (comp, 2H), 7.25 – 7.16 (comp, 6H), 7.11 – 7.08 (m, 1H), 4.29 (s, 2H), 3.33 (t, *J* = 6.0 Hz, 2H), 3.08 (t, *J* = 5.7Hz, 2H); ^{13}**C NMR (75 MHz, Chloroform-*d*)** δ 184.7 , 165.9 , 153.5 , 146.9 , 136.6 , 134.5 , 134.5 , 132.1 , 130.7 , 129.0 , 126.3 , 126.3 , 126.0 , 125.9 , 124.5 , 123.2 , 122.8 , 122.0 , 119.1 , 112.9 , 109.9 , 53.8 , 52.9 , 29.2 ;**HRMS**(EI, m/z) calcd for $C_{24}H_{19}NO_2$ $[M]^+$ 353.1416, found 353.1422.



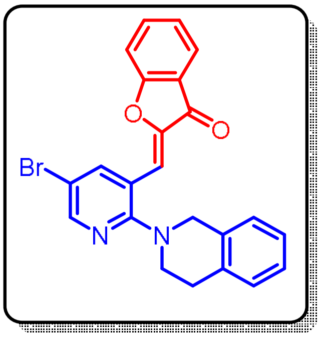
(Z)-2-(5-Bromo-2-(3,4-dihydroisoquinolin-2(1*H*)-yl)benzylidene)benzofuran-3(2*H*)-one (3b):

Yellow solid (161 mg, 78% yield);column chromatography eluent, petroleum ether/EtOAc = 49:1; mp175–176 °C; ^{1}**H NMR (300 MHz, Chloroform-*d*)** δ 8.50 (d, *J* = 2.4 Hz, 1H), 8.31 (d, *J* = 2.4 Hz, 1H), 7.83 (dd, *J* = 7.5, 1.5 Hz, 1H), 7.73 – 7.67 (m, 1H), 7.38 (d, *J* = 8.4 Hz, 1H), 7.24 – 7.29 (m, 1H), 7.19 – 7.17 (comp, 3H), 7.15 – 7.12 (comp, 2H), 6.94 (s, 1H), 4.57 (s, 2H), 3.56 (t, *J* = 6.0 Hz, 2H), 3.13 (t, *J* = 6.0 Hz, 2H); ^{13}**C NMR (75 MHz, Chloroform-*d*)** δ 184.0 , 165.9 , 160.5 , 148.9, 147.5 , 141.6 , 137.1 , 134.3 , 134.1 , 129.0 , 126.5 , 126.4 , 126.4 , 126.0 , 124.7 , 123.8 , 121.6 , 119.1 , 113.0 , 112.0 , 107.4 , 51.5 , 50.5 , 29.3 ; **HRMS** (ESI, m/z) calcd for $C_{24}H_{19}NO_2$ $[M + H^+]$ 435.0657 found 435.0666.



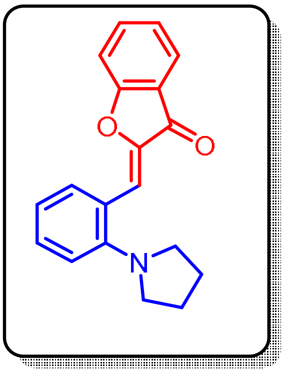
(Z)-2-(4-Chloro-2-(3, 4-dihydroisoquinolin-2(1*H*)-yl)benzylidene)benzofuran-3(2*H*)-one (3c):

Yellow solid (199 mg, 87% yield);column chromatography eluent, petroleum ether/EtOAc = 49:1; mp 64–65 °C; **^{1}H NMR (300 MHz, Methanol-d_4)** δ 8.12 (d, *J* = 9.0 Hz, 1H), 7.74 (dd, *J* = 7.8, 1.2 Hz, 1H), 7.62 – 7.56 (m, 1H), 7.26 (d, *J* = 8.1 Hz, 1H), 7.19 – 7.18 (m, 1H), 7.16 – 7.12 (comp, 4H), 7.07 (tt, *J* = 5.5, 2.7 Hz, 3H), 4.19 (s, 2H), 3.24 (t, *J* = 6.0 Hz, 2H), 3.02 (t, *J* = 6.0 Hz, 2H); **^{13}C NMR (75 MHz, Chloroform-*d*)** δ 184.6, 165.8, 154.4, 146.8, 136.7 , 136.3 , 134.2 , 133.9 , 133.0 , 129.1 , 126.5, 126.3 , 125.9 , 124.6 , 124.3 , 123.4 , 122.9 , 121.8 , 119.4 , 112.8 , 108.7 , 53.5 , 52.8 , 29.2; **HRMS** (EI, m/z) calcd for $C_{24}H_{18}ClNO_2$ $[M]^+$ 387.1026, found 387.1019.



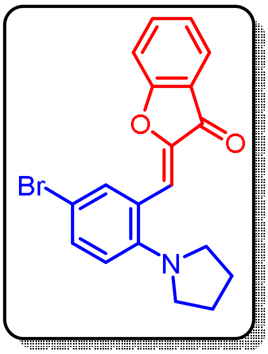
(Z)-2-((5-Bromo-2-(3,4-dihydroisoquinolin-2(1*H*)-yl)pyridin-3-yl)methylene)benzofuran-3(2*H*)-one (3d):

Red solid (255 mg, 93% yield);column chromatography eluent, petroleum ether/EtOAc = 49:1; mp 83–84 °C; **^{1}H NMR (600 MHz, Chloroform-*d*)** δ 8.51 (d, *J* = 2.4 Hz, 1H), 8.32 (d, *J* = 2.4 Hz, 1H), 7.84 (dd, *J* = 7.8, 1.2 Hz, 1H), 7.70 (td, *J* = 7.8, 7.2, 1.4 Hz, 1H), 7.39 (d, *J* = 8.4 Hz, 1H), 7.28 – 7.27 (m, 1H), 7.21 – 7.19 (comp, 3H), 7.16 – 7.14 (m, 1H), 6.94 (s, 1H), 4.58 (s, 2H), 3.57 (t, *J* = 6.0 Hz, 2H), 3.14 (t, *J* = 6.0 Hz, 2H); **^{13}C NMR (150 MHz, Chloroform-*d*)** δ 184.1 , 165.9 , 160.5 , 148.9 , 147.5 , 141.6 , 137.1 , 134.3 , 134.1 , 129.0 , 126.6 , 126.4 , 126.0 , 124.8 , 123.8 , 121.6 , 119.1 , 113.0 , 111.9 , 107.4 , 51.5 , 50.5 , 29.3; **HRMS** (EI, m/z) calcd for $C_{23}H_{17}BrN_2O_2$ $[M]^+$ 432.0473, found 432.0470.



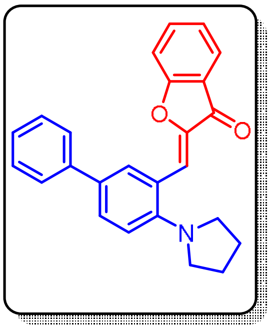
(Z)-2-(2-(Pyrrolidin-1-yl) benzylidene) benzofuran-3(2*H*)-one (3e):

Red solid (513 mg, 98% yield);column chromatography eluent, petroleum ether/EtOAc = 49:1; mp 51–52 °C; **^{1}H NMR (600 MHz, Chloroform-*d*)** δ 8.12 (dd, *J* = 7.8, 1.2 Hz, 1H), 7.84 (d, *J*= 7.8 Hz, 1H), 7.65 (app t, *J* = 7.8 Hz, 1H), 7.34 – 7.27 (comp, 3H), 7.22 (app t, *J* = 7.2 Hz, 1H), 6.98 – 6.93 (comp, 2H), 3.39 – 3.37 (m, 4H), 1.98 – 1.96 (m, 4H); **^{13}C NMR (150 MHz, Chloroform-*d*)** δ 184.4 , 165.8 , 151.5 , 145.4 , 136.3, 132.3, 130.5, 124.4 , 123.0 , 122.1, 121.2 , 119.3, 115.4, 113.0, 112.9, 52.7, 25.5 ; **HRMS**(EI, m/z) calcd for $C_{19}H_{17}NO_2$ $[M]^+$ 291.1259, found 291.1255.

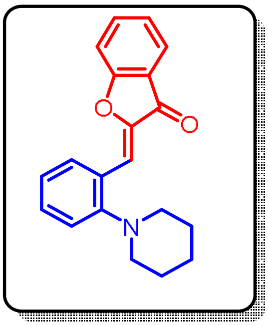


(Z)-2-(5-Bromo-2-(pyrrolidin-1-yl) benzylidene)benzofuran-3(2*H*)-one (3f):

Red solid (258 mg, 89% yield); column chromatography eluent, petroleum ether/EtOAc = 49:1; mp 127–128 °C; **^{1}H NMR (300 MHz, Chloroform-*d*)** δ 8.15 (d, *J* = 3.0 Hz, 1H), 7.80 (d, *J* = 7.8 Hz, 1H), 7.68 – 7.62 (m, 1H), 7.37 – 7.29 (comp, 2H), 7.22 (app t, *J* = 7.5 Hz, 1H), 7.13 (s, 1H), 6.76 (d, *J* = 8.7 Hz, 1H), 3.34 – 3.30 (m, 4H),1.97 – 1.90 (m, 4H);**^{13}C NMR (75 MHz, Chloroform-*d*)** δ 184.3 , 165.8 , 150.4 , 145.6 , 136.6 , 134.2 , 132.9 , 124.5 , 123.3 , 122.7 , 121.9 , 116.9 , 113.0 , 111.3 , 111.2 , 52.7 , 25.5; **HRMS**(EI, m/z) calcd for $C_{19}H_{16}BrNO_2$ $[M]^+$ 369.0364, found 369.0357.

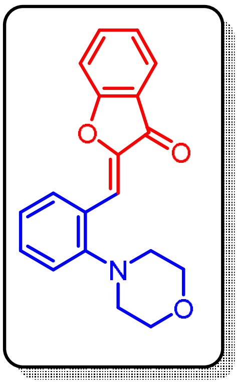


(Z)-2-((4-(Pyrrolidin-1-yl)-[1,1'-biphenyl]-3-yl)methylene)benzofuran-3(2*H*)-one (3g): Deep red solid (92.9 mg, 75% yield); column chromatography eluent, petroleum ether/EtOAc = 49:1; mp 130–131 °C; **^{1}H NMR (600 MHz, Chloroform-*d*)** δ 8.34 (d, *J* = 2.4 Hz, 1H), 7.84 (dd, *J* = 7.8, 1.2 Hz, 1H), 7.65 – 7.62 (comp, 3H), 7.52 (dd, *J* = 8.4, 2.4 Hz, 1H), 7.47 (app t, *J* = 7.8 Hz, 2H), 7.35 – 7.33 (comp, 3H), 7.22 (app t, *J* = 7.2 Hz, 1H), 6.97 (d, *J* = 9.0 Hz, 1H), 3.43 – 3.41 (m, 4H), 1.99 – 1.95 (m, 4H); **^{13}C NMR (150 MHz, Chloroform-*d*)** δ 184.4, 165.8 , 150.7, 145.4 , 140.6, 136.4 , 131.8, 130.6, 129.2, 128.7, 126.5 , 126.4 , 124.4, 123.1, 122.1, 120.9, 115.6, 113.03, 112.9, 52.7, 25.6 ; **HRMS**(EI, m/z) calcd for $C_{25}H_{21}NO_2$ $[M]^+$ 367.1572, found 367.1571.



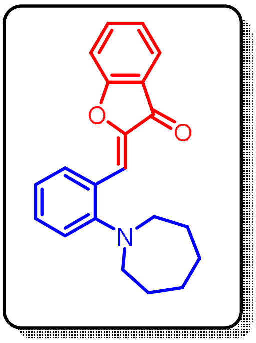
(Z)-2-(2-(Piperidin-1-yl)benzylidene)benzofuran-3(2*H*)-one (3h):

Yellow solid (246.5 mg, 99% yield); column chromatography eluent, petroleum ether/EtOAc = 49:1; mp 66–67 °C; **^{1}H NMR (300 MHz, Chloroform-*d*)** δ 8.23 (dd, *J* = 7.8, 1.8 Hz, 1H), 7.82 (dd, *J* = 7.5, 1.5 Hz, 1H), 7.67 – 7.61 (m, 1H), 7.40 – 7.30 (comp, 3H), 7.21 (app t, *J* = 7.2 Hz, 1H), 7.15 – 7.06 (comp, 2H), 2.96 – 2.93 (m, 4H), 1.75 – 1.84 (m, 4H), 1.64 – 1.59 (m, 2H); **^{13}C NMR (75 MHz, Methanol-*d*$_4$)** δ 184.7 , 165.8 , 155.2 , 146.7 , 136.5 , 131.9 , 130.7 , 126.0 , 124.5 , 123.1 , 122.4 , 122.0 , 118.9 , 112.8 , 110.2 , 54.7 , 26.3 , 24.2 ; **HRMS** (ESI, m/z) calcd for $C_{20}H_{20}NO_2$ $[M + H^+]$ 306.1494, found 306.1495.



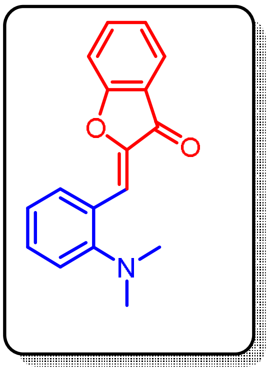
(Z)-2-(2-Morpholinobenzylidene)benzofuran-3(2*H*)-one (3i):

Light green solid (200 mg, 84% yield);column chromatography eluent, petroleum ether/EtOAc = 49:1; mp176–177 °C; **^{1}H NMR (300 MHz, Chloroform-*d*)**δ 8.25 (dd, *J* = 7.8, 1.5 Hz, 1H), 7.82 (dd, *J* = 7.8, 1.2 Hz, 1H), 7.65 (ddd, *J* = 8.5, 7.2, 1.5 Hz, 1H), 7.42 – 7.37 (comp, 2H), 7.32 (d, *J* = 8.1 Hz, 1H), 7.25 – 7.17 (comp, 2H), 7.11 (dd, *J* = 8.1, 1.2 Hz, 1H), 3.95 – 3.92 (m, 4H), 3.02 – 2.99 (m, 4H); **^{13}C NMR (75 MHz, Chloroform-*d*)** δ 184.7 , 165.9, 153.4, 146.9, 136.7, 132.1, 130.8 , 126.0 , 124.5, 123.3, 123.3, 121.8, 118.9, 112.9, 109.3, 67.1 , 53.4 ; **HRMS** (EI, m/z) calcd for $C_{19}H_{17}NO_3$ $[M]^+$ 307.1208, found 307.1213.



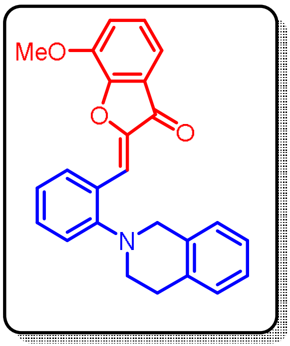
(Z)-2-(2-(Azepan-1-yl)benzylidene)benzofuran-3(2*H*)-one (3j):

Red solid (296.2 mg, 94% yield);column chromatography eluent, petroleum ether/EtOAc = 49:1; mp 92–93 °C; **^{1}H NMR (300 MHz, Chloroform-*d*)** δ 8.18 (dd, *J* = 7.8, 1.8 Hz, 1H), 7.82 (dd, *J* = 7.8, 1.2 Hz, 1H), 7.67 – 7.61 (m, 1H), 7.41 (s, 1H), 7.34 – 7.29 (comp, 2H), 7.21 (app t, *J* = 7.5 Hz, 1H), 7.14 (d, *J* = 8.1 Hz, 1H), 7.07 (app t, *J* = 7.5 Hz, 1H), 3.25 – 3.21 (m, 4H), 1.84 – 1.75 (m, 8H); **^{13}C NMR (75 MHz, Chloroform-*d*)** δ 184.6 , 165.9 , 156.6 , 146.4 , 136.4 , 131.9 , 130.4 , 125.5 , 124.5 , 123.1, 122.1, 121.6, 120.1, 112.9, 111.6, 56.7, 29.2, 27.2 ; **HRMS**(ESI, m/z) calcd for $C_{21}H_{22}NO_2$ $[M + H]^+$ 320.1651, found 320.1650.



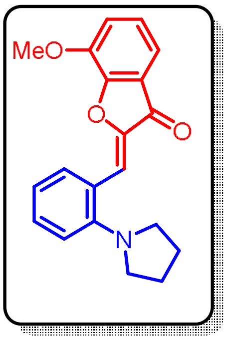
(Z)-2-(2-(Dimethylamino)benzylidene)benzofuran-3(2*H*)-one (5k):

Red solid (299.1 mg,84% yield);column chromatography eluent, petroleum ether/EtOAc = 49:1; mp 88–89 °C; **^{1}H NMR (300 MHz, Chloroform-*d*)** δ 8.22 (dd, *J* = 7.8, 1.8 Hz, 1H), 7.82 (dd, *J* = 7.8, 1.2 Hz, 1H), 7.67 – 7.62 (m, 1H), 7.39 – 7.30 (comp, 3H), 7.21 (app t, *J* = 7.5 Hz, 1H), 7.14 – 7.08 (comp, 2H), 2.80 (s, 6H); **^{13}C NMR (75 MHz, Chloroform-*d*)** δ 184.8, 165.9, 155.0, 146.6, 136.5, 132.1, 130.6 , 125.4, 124.5, 123.2, 122.2, 122.0, 118.4, 112.9, 110.7, 45.2; **HRMS**(EI, m/z) calcd for $C_{17}H_{15}NO_2$ $[M]^+$ 265.1103, found 265.1100.



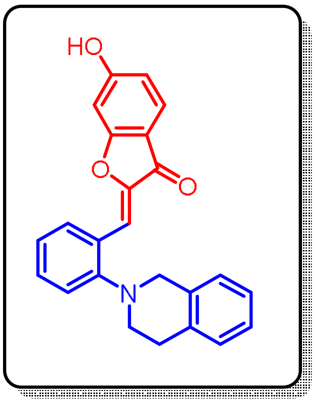
(Z)-2-(2-(3,4-Dihydroisoquinolin-2(1*H*)-yl)benzylidene)-7-methoxybenzofuran-3(2*H*)-one (3l):

Deep yellow solid (254 mg, 79% yield); column chromatography eluent, petroleum ether/EtOAc = 20:1; mp130–131 °C; **^{1}H NMR (600 MHz, Chloroform-*d*)** δ 8.31 (d, *J* = 7.8 Hz, 1H), 7.44 (s, 1H), 7.40 – 7.36 (comp, 2H), 7.21 – 7.18 (comp , 3H), 7.18 – 7.12 (comp, 4H), 7.10 (d, *J* = 7.2 Hz, 1H), 4.28 (s, 2H), 4.03 (s, 3H), 3.32 (t, *J* = 6.0 Hz, 2H), 3.07 (t, *J* = 6.0 Hz, 2H); **^{13}C NMR (150 MHz, Chloroform-*d*)** δ 184.8 , 155.6, 153.6, 146.9, 145.9, 134.5 , 134.5 , 132.3, 130.7, 129.0, 126.3 , 126.3, 126.0, 125.9, 123.7, 123.4, 123.0, 119.0, 118.4 , 115.8, 110.6, 56.4, 53.8, 52.9, 29.2 ; **HRMS** (EI, m/z) calcd for $C_{25}H_{21}NO_3$ $[M]^+$ 383.1521, found 383.1523.



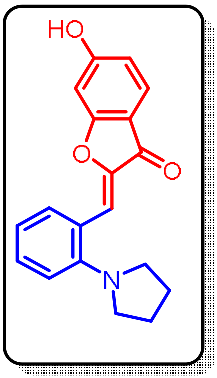
(Z)-7-Methoxy-2-(2-(pyrrolidin-1-ylbenzylidene)benzofuran-3(2*H*)-one (3m):

Deep red solid (346.4 mg, 88% yield);column chromatography eluent, petroleum ether/EtOAc = 20:1; mp 60–62 °C; **^{1}H NMR (300 MHz, Chloroform-*d*)** δ 8.27 (d, *J* = 7.8 Hz, 1H), 7.53 – 7.40 (comp, 3H), 7.27 – 7.26 (comp, 2H), 7.11 – 7.02 (comp, 2H), 4.14 (s, 3H), 3.49 – 3.48 (m, 4H), 2.09 – 2.08 (m, 4H); **^{13}C NMR (150 MHz, Chloroform-*d*)** δ 184.5, 155.4 , 151.6 , 145.9 , 145.3 , 132.4 , 130.6 , 123.5 , 123.5 , 121.2, 119.5, 118.2, 115.6, 115.3, 113.6, 56.3, 52.7, 25.4 ; **HRMS** (EI, m/z) calcd for $C_{20}H_{19}NO_3$ $[M]^+$ 321.1365, found 321.1371.



(Z)-2-(2-(3,4-Dihydroisoquinolin-2(1*H*)-yl)benzylidene)-6-hydroxybenzofuran-3(2*H*)-one (3n):

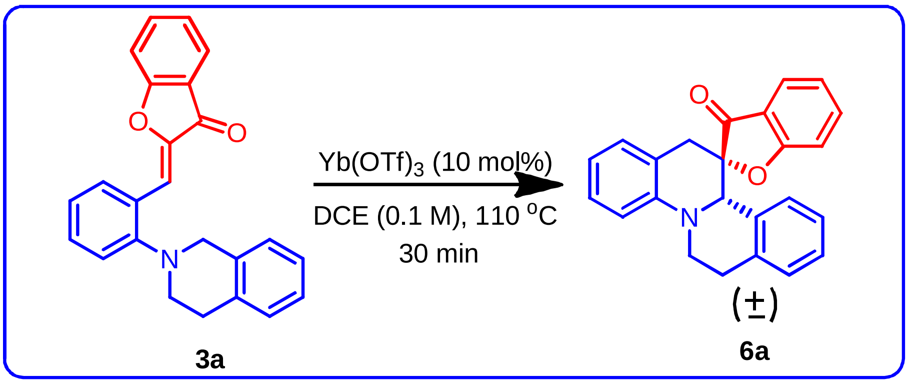
Yellow solid (114.6 mg, 79% yield); column chromatography eluent, petroleum ether/EtOAc = 15:1; mp 106–107 °C; **^{1}H NMR (600 MHz, DMSO-d_6)** δ 8.14 (d, *J* = 7.8 Hz, 1H), 7.62 (d, *J* = 8.4 Hz, 1H), 7.42 (app t, *J* = 7.8 Hz, 1H), 7.27 (d, *J* = 8.4 Hz, 1H), 7.22 – 7.13 (comp, 5H), 7.02 (s, 1H), 6.79 (s, 1H), 6.72 (d, *J* = 8.4 Hz, 1H), 4.18 (s, 2H), 3.22 (t, *J* = 6.0 Hz, 2H), 2.98 (t, *J* = 6.0 Hz, 2H); **^{13}C NMR (150 MHz, DMSO-d_6)** δ 181.7 , 167.9 , 166.6 , 153.0 , 147.4 , 134.6 , 133.9 , 131.4 , 130.7 , 128.8 , 126.5 , 126.4 , 126.0 , 125.9 , 125.5 , 123.2 , 119.6 , 113.1 , 113.0 , 106.5 , 98.7 , 53.9 , 52.0 , 28.9; **HRMS**(EI, m/z) calcd for $C_{24}H_{19}NO_3$ $[M]^+$ 369.1365, found 369.1364.



(Z)-6-Hydroxy-2-(2-(pyrrolidin-1-yl)benzylidene)benzofuran-3(2*H*)-one (3o):

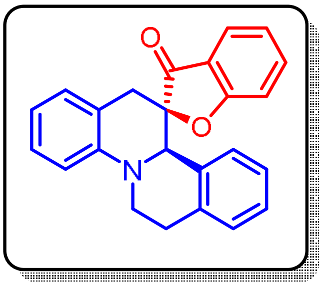
Red solid (177.9 mg, 68% yield);column chromatography eluent, petroleum ether/EtOAc = 15:1; mp 87–88 °C; **^{1}H NMR (400 MHz, DMSO-*d*$_6$)** δ 7.93 (dd, *J* = 7.8, 1.5 Hz, 1H), 7.61 (d, *J* = 8.4 Hz, 1H), 7.30 – 7.23 (m, 1H), 7.00 – 6.92 (m, 2H), 6.91 (s, 1H), 6.76 (d, *J* = 1.9 Hz, 1H), 6.71 (dd, *J* = 8.4, 2.0 Hz, 1H), 3.23 (t, *J* = 6.3 Hz, 4H), 1.89 (t, *J* = 6.3 Hz, 4H) ; **^{13}C NMR (101 MHz, DMSO-*d*$_6$)** δ 181.3 , 167.7 , 166.3 , 150.8 , 146.0 , 131.6 , 130.4 , 125.8 , 121.0 , 119.6 , 116.0 , 113.1 , 112.9 , 109.5 , 98.6 , 52.3 , 24.9; **HRMS** (EI, m/z) calcd for $C_{19}H_{17}NO_3$ $[M]^+$ 307.1208, found 307.1208.

3.5.7 General Procedure for the Synthesis of the Final Product 6a



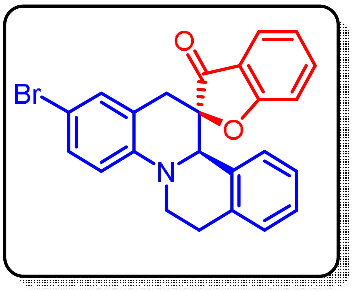
To an oven-dried 10 mL round-bottom flask attached with a condenser under nitrogen, (Z)-2-(2-(3,4-dihydroisoquinolin-2(1*H*)-yl)benzylidene benzofuran-3(2*H*)-one (**3a**)(0.07 g, 0.2 mmol) was taken and the mixture was dissolved in DCE (2 mL). To it, Yb(OTf)$_3$ (0.012 g, 0.02 mmol) was added and the bath temperature was slowly increased to 110 °C. The reaction mixture was kept stirring at the same temperature until the olefin was consumed completely as monitored by TLC. Then the solvent was removed under vacuo and it was purified by column chromatography on silica gel (230-400 mesh) using petroleum ether/ethyl acetate (99:1) as eluent to obtain the desired spirocyclic product 6',7',11b',13'-Tetrahydro-3*H*-spiro[benzofuran-2,12'-isoquinolino[2,1-a]quinolin]-3-one (**6a**) in 92% (65 mg) yield.

3.5.8 Characterization of the Final Product 6a-6o



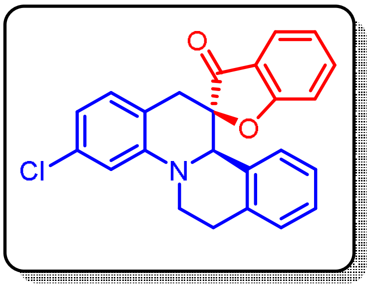
6',7',11b',13'-Tetrahydro-3*H*-spiro[benzofuran-2,12'-isoquinolino[2,1-a]quinolin]-3-one (6a):

Yellow solid (65 mg, 92% yield);column chromatography eluent, petroleum ether/EtOAc = 50:1; mp 129–130 ^{o}C; *dr*>10:1; Data for major diastereomer; **^{1}H NMR (600 MHz, Chloroform-*d*)** δ 7.46 (dd, *J* = 8.4, 1.2 Hz, 1H), 7.39 – 7.36 (m, 1H), 7.25 – 7.22 (m, 1H), 7.13 (d, *J* = 7.8 Hz, 1H), 7.10 (d, *J* = 7.2 Hz, 1H), 6.99 – 6.93 (comp, 3H), 6.90 – 6.86 (comp, 3H), 6.81 – 6.78 (m, 1H), 4.82 (s, 1H), 4.02 (ddd, *J* = 11.3, 5.1, 2.4 Hz, 1H), 3.69 (d, *J* = 17.4 Hz, 1H), 3.41 (td, *J* = 11.5, 2.9 Hz, 1H), 3.26 (ddd, *J* = 16.6, 12.1, 5.0 Hz, 1H), 2.91 (d, *J* = 17.4 Hz, 1H), 2.71 (dt, *J* = 14.4, 3.0 Hz, 1H); **^{13}C NMR (150 MHz, Chloroform-*d*)** δ 202.4 , 171.4, 145.7, 137.5, 137.1, 130.9, 129.2, 128.4, 127.8, 127.4, 127.1, 125.6, 123.8, 121.6, 121.3, 119.3 , 117.6 , 113.9 , 112.4 , 89.5, 60.8, 45.2 , 36.0, 30.4; **HRMS** (EI, m/z) calcd for $C_{24}H_{19}NO_2$ $[M]^+$ 353.1416, found 353.1409.



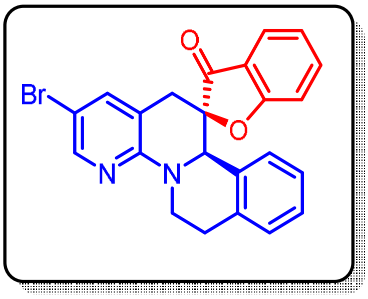
2'-Bromo-6',7',11b',13'-tetrahydro-3*H*-spiro[benzofuran-2,12'-isoquinolino[2,1-a]quinolin]-3-one (6b):

Light yellow solid (81.1 mg,93% yield);column chromatography eluent, petroleum ether/EtOAc = 50:1; mp180–181 ^{o}C; *dr*>10:1; Data for major diastereomer; **^{1}H NMR (600 MHz, Chloroform-*d*)** δ 8.18 (s, 1H), 7.47 (d, *J* = 8.4 Hz, 1H), 7.39 – 7.37 (comp, 2H), 7.09 (d, *J* = 7.8 Hz, 2H), 6.96 (app s, 2H), 6.90 (app t, *J* = 7.2 Hz, 2H), 6.81 (d, *J* = 8.4 Hz, 1H), 5.07 (d, *J* = 8.4 Hz, 1H), 5.01 (s, 1H), 3.57 (d, *J* = 16.8 Hz, 1H), 3.07 (d, *J* = 10.2 Hz, 2H), 2.76 (d, *J* = 17.4 Hz, 1H), 2.66 (d, *J* = 11.4 Hz, 1H);**^{13}CNMR (150 MHz, Chloroform-*d*)** δ 201.8 , 171.3 , 153.3 , 146.8 , 138.7 , 138.4 , 137.9 , 130.0 , 128.2 , 128.2 , 128.0 , 127.2 , 125.6 , 123.9 , 122.0 , 121.1 , 115.5 , 112.5 , 106.9 , 86.9 , 60.8 , 41.8 , 35.0 , 30.2 ;**HRMS**(ESI, m/z) calcd for $C_{24}H_{18}BrNO_2$ [M + H^+]431.0521, found 431.0520.



3'-Chloro-6',7',11b',13'-tetrahydro-3*H*-spiro[benzofuran-2,12'-isoquinolino[2,1-a]quinolin]-3-one (6c):

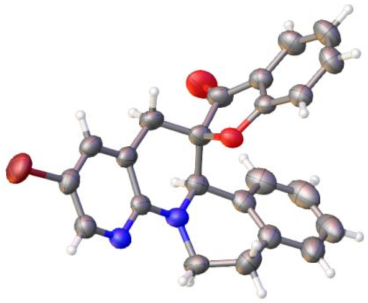
Light yellow solid (67.8 mg,92% yield);column chromatography eluent, petroleum ether/EtOAc = 50:1; mp 61–62 °C; *dr* 10:1; Data for major diastereomer; **^{1}H NMR (300 MHz, Chloroform-*d*)** δ 7.46 – 7.36 (comp, 2H), 7.05 (dd, *J* = 16.8, 7.5 Hz, 2H), 6.96 – 6.94 (comp, 3H), 6.87 (d, *J* = 6.9 Hz, 3H), 6.74 (d, *J* = 8.4 Hz, 1H), 4.79 (s, 1H), 3.97 – 3.93 (m, 1H), 3.62 (d, *J* = 17.4 Hz, 1H), 3.38 (t, *J* = 12.0 Hz, 1H), 3.23 (td, *J* = 13.6, 4.8 Hz, 1H), 2.85 (d, *J* = 17.7 Hz, 1H), 2.70 (d, *J* = 14.4 Hz, 1H);**^{13}C NMR (150 MHz, Chloroform-*d*)** δ 202.1 , 171.4 , 146.6 , 137.7 , 136.9 , 133.0 , 130.5 , 130.2 , 128.4 , 127.8 , 127.3 , 125.8 , 123.9 , 121.8 , 121.2 , 117.6 , 117.5 , 113.7 , 112.4 , 88.9 , 60.6 , 45.2 , 35.6 , 30.3 ;**HRMS**(EI, m/z) calcd for $C_{24}H_{18}ClNO_2$ [M]$^+$ 387.1026, found 387.1028.



2'-Bromo-6',7',11b',13'-tetrahydro-3*H*-spiro[benzofuran-2,12'-isoquinolino[2,1-a][1,8]naphthyridin]-3-one (6d):

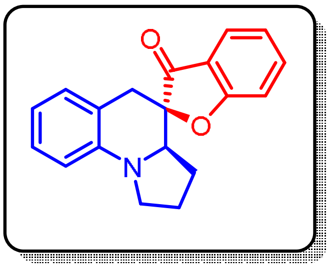
Yellow solid (72.7 mg,b92% yield);column chromatography eluent, petroleum ether/EtOAc = 50:1; mp195–196 °C; *dr* >25:1; Data for major diastereomer; **^{1}H NMR (600 MHz, Chloroform-*d*)** δ 8.18 (d, *J* = 1.8 Hz, 1H), 7.47 (dd, *J* = 7.8, 1.2 Hz, 1H), 7.39 – 7.36 (comp, 2H), 7.09 (d, *J* = 7.2 Hz, 1H), 6.96 – 6.95 (comp, 2H), 6.92 – 6.88 (comp, 2H), 6.81 (d, *J* = 8.4 Hz, 1H), 5.05 (dd, *J* = 8.4, 2.4 Hz, 1H), 5.01 (s, 1H), 3.56 (dd, *J* = 17.4, 1.2 Hz, 1H), 3.08 – 3.04 (m, 2H), 2.76 (d, *J* = 17.4 Hz, 1H), 2.67 – 2.64 (m, 1H); **^{13}C NMR (150 MHz, Chloroform-*d*)** δ 201.8 , 171.3 , 153.3 , 146.8 , 138.7 , 138.3 , 137.9 , 130.0 , 128.2 , 128.0 , 127.2 , 125.6 , 123.9 , 122.0 , 121.1 , 115.5 , 112.5 , 106.9 , 86.9 , 60.7 , 41.8 , 34.9 , 30.2 ; **HRMS** (EI, m/z) calcd for $C_{23}H_{17}BrN_2O_2$ $[M]^+$ 432.0473, found 432.0475.

Table 3.5.9 Crystal Data and Structure Refinement for 6d.



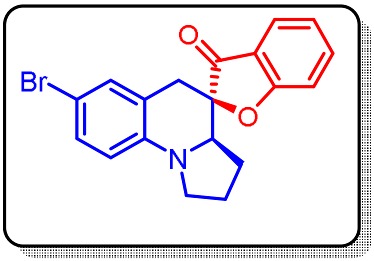
	6d(CCDC-1996348)
Empirical formula	$C_{23}H_{17}N_2O_2Br$
Formula weight	433.29
Temperature/K	296.15
Crystal system	Triclinic
Space group	P-1
a/Å	8.6868(5)
b/Å	8.7104(5)
c/Å	12.5743(7)
α/°	87.919(3)
β/°	81.208(3)
γ/°	89.922(3)
Volume/Å^3	939.63(9)
Z	2
ρ_{calc}g/cm^3	1.531
μ/mm^{-1}	2.209
F(000)	440.0
Crystal size/mm^3	0.64 × 0.63 × 0.31
Radiation	MoKα (λ = 0.71073)
2Θ range for data collection/°	4.68 to 54.81
Index ranges	$-11 \leq h \leq 11, -11 \leq k \leq 11, -16 \leq l \leq 16$
Reflections collected	28629
Independent reflections	4243 [R_{int} = 0.0373, R_{sigma} = 0.0218]
Data/restraints/parameters	4243/0/253
Goodness-of-fit on F^2	1.019
Final R indexes [I>=2σ (I)]	R_1 = 0.0386, wR_2 = 0.0926

Final R indexes [all data]	R_1 = 0.0535, wR_2 = 0.1002
Largest diff. peak/hole / e Å^{-3}	0.50/-0.47



2',3',3a',5'-Tetrahydro-1'H,3*H*-spiro[benzofuran-2,4'-pyrrolo[1,2-a]quinolin]-3-one (6e):

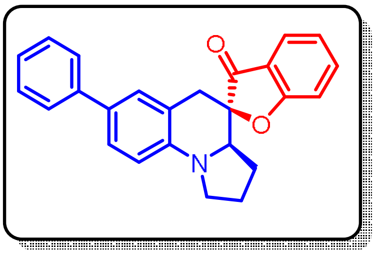
Yellow solid (59.1 mg, 99% yield);column chromatography eluent, petroleum ether/EtOAc = 50:1; mp180–181 °C; *dr*>25:1; Data for major diastereomer; **^{1}H NMR (600 MHz, Chloroform-*d*)** δ 7.72 (d, *J* = 7.8 Hz, 1H), 7.61 (app t, *J* = 7.8 Hz, 1H), 7.20 (app t, *J* = 7.8 Hz, 1H), 7.12 – 7.09 (comp, 2H), 7.06 (d, *J* = 7.2 Hz, 1H), 6.67 (app t, *J* = 7.2 Hz, 1H), 6.61 (d, *J* = 7.8 Hz, 1H), 3.86 (dd, *J* = 9.6, 6.0 Hz, 1H), 3.57 (t, *J* = 9.0 Hz, 1H), 3.36 (d, *J* = 16.8 Hz, 1H), 3.29 (q, *J* = 8.4 Hz, 1H), 2.83 (d, *J* = 16.8 Hz, 1H), 2.04 – 2.00 (m, 1H), 1.98 – 1.93 (m, 1H), 1.77 – 1.73 (m, 1H), 1.39 (p, *J* = 10.8 Hz, 1H);**^{13}C NMR (150 MHz, Chloroform-*d*)** δ 202.1 , 172.0 , 143.2 , 138.0 , 129.1 , 127.9 , 124.1 , 121.9 , 121.2 , 117.4 , 115.9 , 113.5 , 110.9 , 84.0 , 61.4 , 47.5 , 35.9 , 25.4 , 23.5 ;**HRMS**(EI, m/z) calcd for $C_{19}H_{17}NO_2$ $[M]^+$ 291.1259, found 291.1255.



7'-Bromo-2',3',3a',5'-tetrahydro-1'H,3*H*-spiro[benzofuran-2,4'-pyrrolo[1,2-a]quinolin]-3-one (6f):

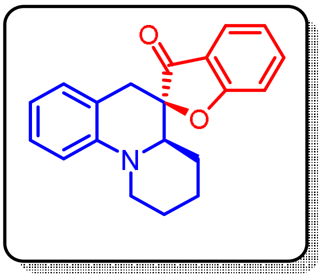
Yellow solid (70.1 mg, 94% yield);column chromatography eluent, petroleum ether/EtOAc = 50:1; mp194–195 °C; *dr*>25:1; Data for major diastereomer; **^{1}H NMR (300 MHz, Chloroform-*d*)** δ 7.71 (dd, *J* = 7.8, 1.5 Hz, 1H), 7.61 (ddd, *J* = 8.6, 7.2, 1.5 Hz, 1H), 7.27 – 7.23 (m, 1H), 7.14 – 7.07 (m, 3H), 6.45 (d, *J* = 8.7 Hz, 1H), 3.82 (dd, *J* = 10.2, 5.4 Hz, 1H), 3.52 (td, *J* = 8.6, 2.3 Hz, 1H), 3.33 – 3.18 (m, 2H), 2.76 (d, *J* = 16.5 Hz, 1H), 2.08 – 1.85 (m, 2H), 1.77 – 1.69 (m, 1H), 1.30 – 1.43 (m, 1H); **^{13}C NMR (150 MHz, Chloroform-*d*)** δ 201.6

, 171.8 , 142.3 , 138.2 , 131.4 , 130.5 , 124.2 , 122.1 , 121.0 , 119.5 , 113.5 , 112.4 , 107.4 , 83.3 , 61.4 , 47.6 , 35.6 , 25.4 , 23.5 ; **HRMS** (EI, m/z) calcd for $C_{19}H_{16}BrNO_2$ $[M]^+$ 369.0364, found 369.0362.



7'-Phenyl-2',3',3a',5'-tetrahydro-1'H,3*H*-spiro[benzofuran-2,4'-pyrrolo[1,2-a]quinolin]-3-one (6g):

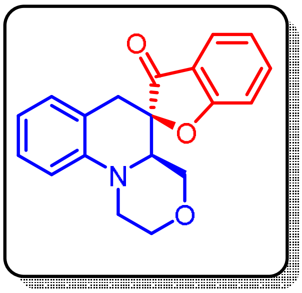
Yellow solid (50.4 mg, 68%);column chromatography eluent, petroleum ether/EtOAc = 50:1; mp180–181 °C; *dr*>25:1; Data for major diastereomer; **^{1}H NMR (600 MHz, Chloroform-*d*)** δ 7.76 (d, *J* = 7.8 Hz, 1H), 7.63 (app t, *J* = 7.8 Hz, 1H), 7.57 (d, *J* = 7.2 Hz, 2H), 7.49 (dd, *J* = 8.4, 2.4 Hz, 1H), 7.41 (app t, *J* = 7.2 Hz, 2H), 7.35 (d, *J* = 1.8 Hz, 1H), 7.28 – 7.26 (m, 1H), 7.14 (app t, *J* = 7.2 Hz, 2H), 6.71 (d, *J* = 8.4 Hz, 1H), 3.92 (dd, *J* = 9.6, 6.0 Hz, 1H), 3.65 – 3.62 (m, 1H), 3.44 (d, *J* = 16.8 Hz, 1H), 3.35 (td, *J* = 9.3, 6.9 Hz, 1H), 2.92 (d, *J* = 16.2 Hz, 1H), 2.09 – 2.05 (m, 1H), 2.03 – 1.95 (m, 1H), 1.79 (dt, *J* = 12.2, 6.2 Hz, 1H), 1.47 – 1.40 (m, 1H); **^{13}C NMR (150 MHz, Chloroform-*d*)** δ 202.0 , 172.0 , 142.7 , 141.2 , 138.1 , 128.7 , 128.6 , 127.8 , 126.6 , 126.2 , 125.9 , 124.2 , 122.0 , 121.1 , 117.8 , 113.6 , 111.2 , 84.0 , 61.5 , 47.6 , 36.0 , 25.5 , 23.6 ; **HRMS** (ESI, m/z) calcd for $C_{19}H_{17}NO_2$ $[M+H]^+$ 306.1494, found 306.1496.



1',2',3',4',4a',6'-Hexahydro-3*H*-spiro[benzofuran-2,5'-pyrido[1,2-a]quinolin]-3-one (6h):

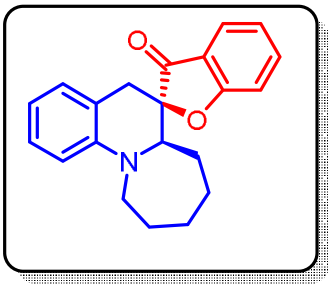
Light yellow solid (56.5 mg,92% yield);column chromatography eluent, petroleum ether/EtOAc = 50:1; mp142–143 °C; *dr*>25:1; Data for major diastereomer; **^{1}H NMR (600 MHz, Chloroform-*d*)** δ 7.70 (d, *J* = 7.8 Hz, 1H), 7.62 (app t, *J* = 7.8 Hz, 1H), 7.19 – 7.17 (comp, 2H), 7.10 (app t, *J* = 7.2 Hz, 1H), 7.00 (d, *J* = 8.4 Hz, 1H), 6.97 (d, *J* = 7.2 Hz, 1H), 6.74 (app t, *J* = 7.2 Hz, 1H), 4.13 (dt, *J* = 12.0, 3.6 Hz, 1H), 3.40 – 3.34 (m, 2H), 2.79 (td, *J* = 12.6, 3.0 Hz, 1H), 2.72 (d, *J* = 16.2 Hz, 1H), 1.80 – 1.78 (m, 1H), 1.75 – 1.73 (m, 1H), 1.68 –

1.61 (m, 1H), 1.44 – 1.40 (m, 1H), 1.39 – 1.31 (m, 2H); ^{13}**C NMR (150 MHz, Chloroform-*d*)** δ 201.9 , 172.3 , 145.1 , 138.3 , 129.6 , 127.7 , 124.2 , 121.9 , 120.9 , 119.8 , 118.2 , 113.8 , 113.5 , 88.1 , 59.8 , 48.7 , 35.9 , 25.6 , 25.3 , 23.3 ;**HRMS**(ESI, m/z) calcd for $C_{20}H_{19}NO_2$ [M + H^+]306.1494, found 306.1497.



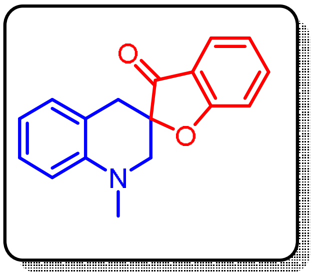
2,4,4a,6-Tetrahydro-1*H*,3'*H*-spiro[[1,4]oxazino[4,3-a]quinoline-5,2'-benzofuran]-3'-one (6i):

Light yellow solid (53.2 mg, 86% yield); column chromatography eluent, petroleum ether/EtOAc = 50:1; mp 153–154 °C; *dr*>25:1; Data for major diastereomer; ^{1}**H NMR (600 MHz, Chloroform-*d*)** δ 7.71 (d, *J* = 7.8 Hz, 1H), 7.65 (app t, *J* = 7.8 Hz, 1H), 7.22 – 7.18 (comp, 2H), 7.13 (app t, *J* = 7.2 Hz, 1H), 7.02 (d, *J* = 7.2 Hz, 1H), 6.94 (d, *J* = 8.4 Hz, 1H), 6.81 (app t, *J* = 7.2 Hz, 1H), 3.99 (dd, *J* = 11.4, 3.6 Hz, 1H), 3.81 (d, *J* = 12.0 Hz, 1H), 3.71 (td, *J* = 12.0, 3.0 Hz, 1H), 3.65 – 3.59 (m, 2H), 3.39 (d, *J* = 16.8 Hz, 1H), 3.28 (t, *J* = 10.8 Hz, 1H), 3.04 (td, *J* = 12.0, 4.2 Hz, 1H), 2.76 (d, *J* = 17.4 Hz, 1H); ^{13}**C NMR (150 MHz, Chloroform-*d*)** δ 200.5 , 171.8 , 144.1 , 138.6 , 129.8 , 127.8 , 124.4 , 122.4 , 120.5 , 119.6 , 119.1 , 113.9 , 112.6 , 85.8 , 66.6 , 65.8 , 57.7 , 46.5 , 36.0 ; **HRMS** (EI, m/z) calcd for $C_{19}H_{17}NO_3$ $[M]^+$ 307.1208, found 307.1204.



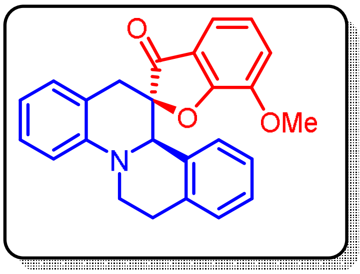
6a,7,8,9,10,11-hexahydro-3'*H*,5*H*-spiro[azepino[1,2-a]quinoline-6,2'-benzofuran]-3'-one (6j):

Light yellow solid (59 mg, 92% yield); column chromatography eluent, petroleum ether/EtOAc = 50:1; mp139–140 °C; *dr* 5:2; Data for major diastereomer in an inseparable diastereomeric mixture; ^{1}**H NMR (600 MHz, Chloroform-*d*)** δ 7.69 (app t, *J* = 7.2 Hz, 1H), 7.62 – 7.58 (m, 1H), 7.18 – 7.14 (m, 1H), 7.11 – 7.07 (m, 1H), 7.01 (dd, *J* = 19.2, 7.2 Hz, 1H), 6.69 (dd, *J* = 12.0, 7.2 Hz, 1H), 6.65 (app t, *J* = 7.2 Hz, 1H), 4.06 (dd, *J* = 15.6, 6.0 Hz, 1H), 3.73 – 3.68 (m, 1H), 3.43 (d, *J* = 16.8 Hz, 1H), 3.16 – 3.11 (m, 1H), 2.71 (d, *J* = 17.4 Hz, 1H), 2.16 – 2.12 (m, 1H), 1.70 (d, *J* = 7.8 Hz, 1H), 1.64 – 1.61 (m, 3H), 1.54 – 1.43 (m, 3H); **^{13}C NMR (101 MHz, Chloroform-*d*)**^{13}C NMR (101 MHz, Chloroform-*d*) δ 201.1 , 170.7 , 142.4 , 138.0 , 129.5 , 127.8 , 124.4 , 121.7 , 120.9 , 117.0 , 115.6 , 113.8 , 110.1 , 86.7 , 62.6 , 50.2 , 31.4 , 30.1 , 27.09 , 25.89 , 25.70; **HRMS** (ESI, m/z) calcd for $C_{20}H_{19}NO_2$ [M + H$^+$]306.1494, found 306.1497.



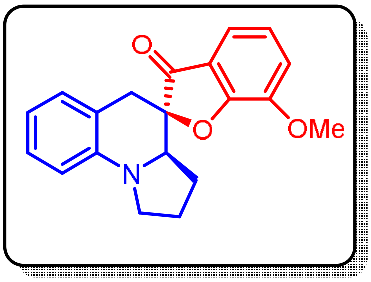
1'-Methyl-2',4'-dihydro-1'*H*,3*H*-spiro[benzofuran-2,3'-quinolin]-3-one (6k):

Yellow solid (36.4 mg, 68% yield);column chromatography eluent, petroleum ether/EtOAc = 50:1; mp 180–181 °C; **^{1}H NMR (600 MHz, Chloroform-*d*)** δ 7.72 (dd, *J* = 7.8, 1.2 Hz, 1H), 7.63 (ddd, *J* = 8.6, 7.1, 1.2 Hz, 1H), 7.20 (app t, *J* = 7.8 Hz, 1H), 7.14 – 7.11 (comp, 2H), 7.03 (d, *J* = 7.2 Hz, 1H), 6.77 (d, *J* = 8.4 Hz, 1H), 6.72 (td, *J* = 7.8, 1.2 Hz, 1H), 3.60 (d, *J* = 12.6 Hz, 1H), 3.32 (d, *J* = 16.8 Hz, 1H), 3.16 (dd, *J* = 12.6, 3.0 Hz, 1H), 3.01 (s, 3H), 2.79 (dd, *J* = 16.2, 3.0 Hz, 1H); **^{13}C NMR (150 MHz, Chloroform-*d*)** δ 201.0 , 171.4 , 144.5 , 138.3 , 129.3 , 127.9 , 124.5 , 122.1 , 120.0 , 118.5 , 117.1 , 114.0 , 111.3 , 85.6 , 55.3 , 39.0 , 34.6; **HRMS** (EI, m/z) calcd for $C_{17}H_{15}NO_2$ [M]$^+$ 265.1103, found 265.1100.



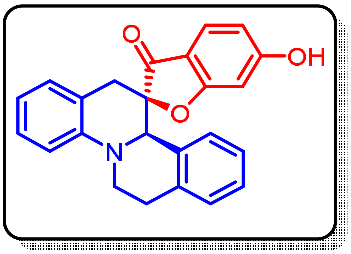
7-Methoxy-6',7',11b',13'-tetrahydro-3*H*-spiro[benzofuran-2,12'-isoquinolino[2,1-a]quinolin]-3-one (6l):

Yellow solid (49.6 mg, 64%yield);column chromatography eluent, petroleum ether/EtOAc = 20:1; mp195–196 °C; *dr*>25:1; Data for major diastereomer; **^{1}H NMR (400 MHz, Chloroform-*d*)** δ 7.20(app t, J = 7.5 Hz, 1H), 7.09 (dd, J = 10.8, 7.8 Hz, 2H), 7.01 (d, J = 7.6 Hz, 1H), 6.98 – 6.91 (m, 3H), 6.87 (dd, J = 7.8, 3.8 Hz, 2H), 6.78 (t, J = 7.8 Hz, 2H), 4.77 (s, 1H), 3.99 (q, J = 4.2, 2.9 Hz, 1H), 3.79 (s, 3H), 3.70 (d, J = 17.7 Hz, 1H), 3.47 – 3.34 (m, 2H), 2.94 (d, J = 17.8 Hz, 1H), 2.75 – 2.62 (m, 1H); **^{13}C NMR (100 MHz, Chloroform-*d*)** δ 202.5, 162.0, 146.2, 146.0, 137.4, 130.9, 129.2, 128.4, 127.7, 127.1(x2), 125.6, 122.6, 121.9, 119.7, 118.1, 117.8, 115.0, 114.4, 90.3, 60.9, 56.1, 45.5, 35.9, 30.3; **HRMS**(EI, m/z) calcd for $C_{25}H_{21}BrNO_3$ $[M]^+$ 383.1521, found 383.1525.



7-Methoxy-2',3',3a',5'-tetrahydro-1'*H*,3*H*-spiro[benzofuran-2,4'-pyrrolo[1,2-a]quinolin]-3-one (6m):

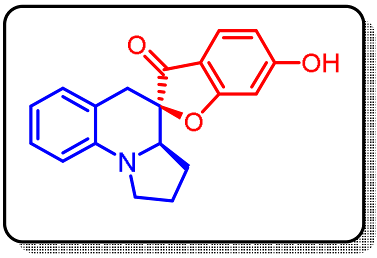
Orange solid (45.2 mg, 70%yield);column chromatography eluent, petroleum ether/EtOAc = 20:1; mp 148–149 °C; *dr*>25:1; Data for major diastereomer; **^{1}H NMR (300 MHz, Chloroform-*d*)** δ 7.28 (dd, *J* = 7.5, 1.2 Hz, 1H), 7.15 (app t, *J* = 7.8 Hz, 1H), 7.09 (dd, *J* = 7.8, 1.5 Hz, 1H), 7.03 (dt, *J* = 7.7, 3.9 Hz, 2H), 6.63 (app t, *J* = 7.2 Hz, 1H), 6.58 (d, *J* = 8.4 Hz, 1H), 3.84 (s, 3H), 3.82 – 3.79 (m, 1H), 3.53 (td, *J* = 8.7, 2.7 Hz, 1H), 3.38 – 3.27 (m, 2H), 2.83 (d, *J* = 16.8 Hz, 1H), 2.06 – 1.87 (m, 2H), 1.76 – 1.68 (m, 1H), 1.46 – 1.33 (m, 1H);**^{13}C NMR (150 MHz, Chloroform-*d*)** δ 202.2 , 162.3 , 146.5 , 143.3 , 129.0 , 127.6 , 122.4 , 122.3 , 118.6 , 117.4 , 115.7 , 115.1 , 111.0 , 84.7 , 61.2 , 55.9 , 47.2 , 35.8 , 25.3 , 23.4 ;**HRMS**(EI, m/z) calcd for $C_{20}H_{19}NO_3$ $[M]^+$ 321.1365, found 321.1365.



6-Hydroxy-6',7',11b',13'-tetrahydro-3*H*-spiro[benzofuran-2,12'-isoquinolino[2,1-a]quinolin]-3-one (6n):

Yellow solid (18.9 mg, 63% yield);column chromatography eluent, petroleum ether/EtOAc = 20:1; mp 180–181°C; *dr* 6:1; Data for major diastereomer; **^{1}H NMR (600 MHz, Methanol-*d*$_4$)** δ 7.26 (dd, *J* = 8.4, 1.8 Hz, 1H), 7.16 (app t, *J* = 7.8 Hz, 1H), 7.06 (dd, *J* = 14.4, 7.2 Hz, 2H), 7.01 (d, *J* = 4.8 Hz, 2H), 6.92 (dt, *J* = 8.5, 4.5 Hz, 1H), 6.87 (d, *J* = 8.4 Hz, 1H), 6.73 (app t, *J* = 7.2 Hz, 1H), 6.37 (dd, *J* = 9.0, 2.4 Hz, 1H), 6.18 (app t, *J* = 1.8 Hz, 1H), 4.68 (s, 1H), 4.00 – 3.97 (m, 1H), 3.54 (d, *J* = 17.4 Hz, 1H), 3.34 (dd, *J* = 14.4, 2.4 Hz, 1H), 3.22

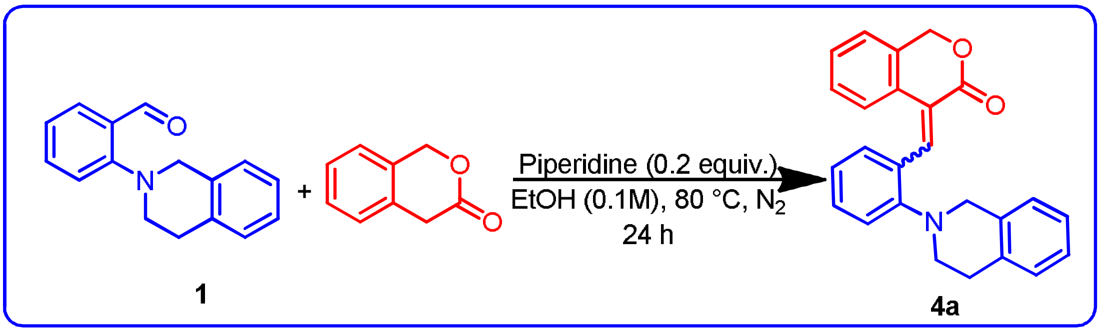
(ddd, *J* = 16.5, 12.4, 6.4 Hz, 1H), 2.81 (d, *J* = 17.4 Hz, 1H), 2.71 (dt, *J* = 15.0, 2.4 Hz, 1H);**^{13}C NMR (150 MHz, Methanol-*d*$_4$)** δ 201.8 , 175.5 , 168.9 , 147.3 , 138.7 , 132.5 , 130.1 , 129.4 , 129.0 , 128.3 , 128.27 , 126.5 , 126.3 , 120.9 , 118.7 , 115.1 , 114.5 , 113.1 , 98.3 , 91.6 , 62.2 , 46.6 , 37.1 , 31.4 ;**HRMS**(ESI, m/z) calcd for $C_{24}H_{19}NO_3$ [M + H$^+$]369.1365, found 369.1364.



6-Hydroxy-2',3',3a',5'-tetrahydro-1'*H*,3*H*-spiro[benzofuran-2,4'-pyrrolo[1,2 a]quinolin]-3-one (6o):

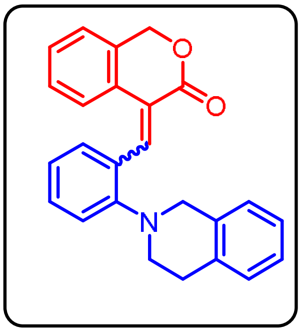
Orange solid (19.6 mg**,** 43% yield);column chromatography eluent, petroleum ether/EtOAc = 20:1; mp 258–259 °C; *dr*>25:1; Data for major diastereomer; **^{1}H NMR (600 MHz, DMSO-*d*$_6$)** δ 7.52 (d, *J* = 8.4 Hz, 1H), 7.07 (app t, *J* = 7.8 Hz, 1H), 6.99 (d, *J* = 7.8 Hz, 1H), 6.59 (d, *J* = 8.4 Hz, 1H), 6.56 – 6.51 (comp, 2H), 6.45 (s, 1H), 3.69 (dd, *J* = 10.2, 5.4 Hz, 1H), 3.15 (d, *J* = 21.0 Hz, 1H), 3.10 – 3.08 (m, 1H), 2.76 (d, *J* = 16.2 Hz, 1H), 1.97 – 1.93 (m, 1H), 1.90 – 1.85 (m, 1H), 1.63 – 1.59 (m, 1H), 1.25 – 1.20 (m, 1H);**^{13}C NMR (150 MHz, DMSO-*d*$_6$)** δ 198.0 , 173.6 , 167.7 , 143.2 , 129.0 , 127.6 , 125.6 , 117.6 , 115.3 , 112.5 , 112.2 , 110.7 , 98.1 , 83.7 , 61.0 , 47.3 , 35.2 , 25.1 , 23.1 ;**HRMS**(EI, m/z) calcd for $C_{19}H_{17}NO_2$ [M]$^+$ 307.1208, found 307.1213.

3.5.10General Procedure for the Preparation of 4a

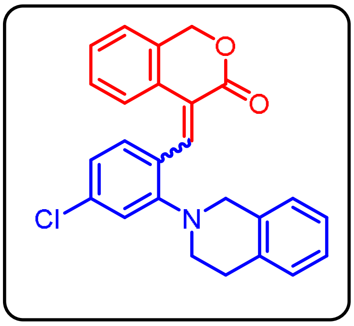


To an oven-dried round-bottom flask attached with a condenser under N_2, 2-(3,-dihydroisoquinolin-2(1*H*)-yl)benzaldehyde (**1a**) (93 mg, 0.4 mmol) and 3-isochromanone (77 mg, 0.52 mmol) was dissolved in ethanol (4 mL) (Scheme). Then piperidine (8 μL, 0.08 mmol) was added and the bath temperature was slowly increased to 80 °C. The reaction mixture was kept on stirring for 24 h at this temperature. After the completion of the reaction, which is monitored by TLC, the solvent was removed under vacuo The crude product was purified by column chromatography on silica gel (230-400 mesh) using petroleum ether/ethyl acetate (20:5) as eluent to afford (E)-4-(2-(3,4-dihydroisoquinolin-2(1H)-yl)benzylidene)isochroman-3-one (**4a**). Finally, we got 140 mg (95%) yellowish solid product (inseparable E/Z mixture) after keeping a few hours in a high vacuum condition.

3.5.11 Characterization of Final product 4a-4j

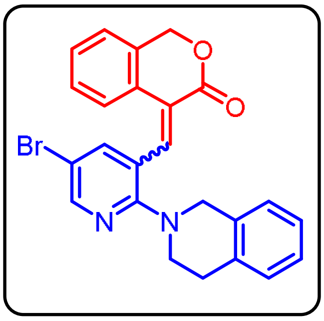


(*E*)-4-(2-(3,4-dihydroisoquinolin-2(1*H*)-yl)benzylidene)isochroman-3-one (4a):
Yellow solid (140 mg, 95% yield);E:Z=4.4:1; column chromatography eluent, petroleum ether/EtOAc = 20:1;mp 147-148 °C; **^{1}H NMR (400 MHz, Chloroform-*d*)** ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.02 (s, 1H), 7.42 (d, *J* = 7.9 Hz, 1H), 7.37 (d, *J* = 7.8 Hz, 1H), 7.33 – 7.30 (m, 2H), 7.26 (m, 1H), 7.23 – 7.21 (m, 1H), 7.20 (d, *J* = 2.3 Hz, 1H), 7.16 (d, *J* = 1.7 Hz, 2H), 7.13 (m, 1H), 7.09 (d, *J* = 4.0 Hz, 1H), 6.85 (t, *J* = 7.6 Hz, 1H), 5.19 (s, 2H), 4.31 (s, 2H), 3.37 (t, *J* = 5.8 Hz, 2H), 3.01 (t, *J* = 5.8 Hz, 2H); **^{13}C NMR (101 MHz, Chloroform-*d*)** δ 168.5 , 152.4 , 137.8 , 134.3 , 132.0 , 131.3 , 131.0 , 130.3 , 129.6 , 129.1 , 128.0 , 127.8 , 126.6 , 126.4 , 125.8 , 125.1 , 124.4 , 122.9 , 121.4 , 118.1 , 116.2 , 69.0 , 53.2 , 52.4 , 29.3 ; **HRMS**(ESI, m/z) calcd for $C_{25}H_{21}NO_2$ $[M+H]^+$ 368.1651, found 368.1656. (As the compound was relatively unstable, it was quickly subjected to final hydride shift reaction without thorough purification)



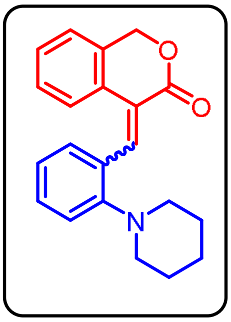
(*E*)-4-(4-chloro-2-(3,4-dihydroisoquinolin-2(1*H*)-yl)benzylidene)isochroman-3-one (4b):

Yellow solid (133.5 mg, 83% yield);E:Z=1.2:1; column chromatography eluent, petroleum ether/EtOAc = 20:1; mp 140-144°C; **^{1}H NMR (400 MHz, Chloroform-*d*)** δ 7.91 (s, 1H), 7.49 (s, 1H), 7.42 (d, *J* = 8.0 Hz, 1H), 7.35 (dd, *J* = 6.4, 1.6 Hz, 1H), 7.32 – 7.30 (m, 1H), 7.20 – 7.18 (comp, 2H), 7.21 – 7.20 (comp, 2H), 7.12 (d, *J* = 2.0 Hz, 1H), 7.09 (d, *J* = 2.0 Hz, 1H), 6.83 (dd, *J* = 8.4, 2.0 Hz, 1H), 5.21 (s, 2H), 4.31 (s, 2H), 3.40 – 3.36 (m, 3H), 3.06 – 3.03 (m, 3H);**^{13}C NMR (100 MHz, Chloroform-*d*)** δ 168.2 , 153.4 , 136.5 , 136.0 , 134.5 , 134.2 , 133.7 , 131.9 , 131.1 , 130.5 , 129.1 , 128.3 , 128.0 , 126.6 , 126.3 , 126.0 , 125.2 , 124.5 , 123.4 , 121.5 , 118.4 , 69.1, 53.0 , 52.2 , 29.3 ;**HRMS**(ESI, m/z) calcd for $C_{25}H_{20}ClNO_2$ $[M+H]^+$ 402.1261, found 402.1260.



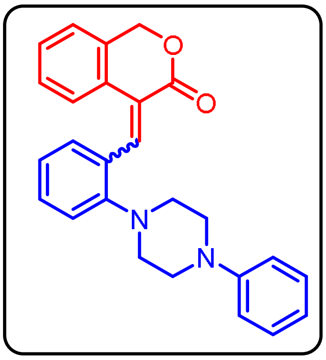
(*E*)-4-((5-bromo-2-(3,4-dihydroisoquinolin-2(1*H*)-yl)pyridin-3-yl)methylene)isochroman-3-one (4c):

Yellow solid (153.8 mg, 86% yield); E:Z=3.5:1; column chromatography eluent, petroleum ether/EtOAc = 20:1; mp 141-142 °C; **^{1}H NMR (400 MHz, Chloroform-*d*)** δ 8.27 (d, *J* = 2.4 Hz, 1H), 7.70 (s, 1H), 7.68 (dd, *J* = 2.4, 0.8 Hz, 1H), 7.43 (d, *J* = 8.0 Hz, 1H), 7.33 (td, *J* = 7.5, 1.1 Hz, 1H), 7.27 (d, *J* = 2.8 Hz, 1H), 7.24 (dd, *J* = 8.0, 1.2 Hz, 1H), 7.21 – 7.20 (m, 1H), 7.18 – 7.16 (comp, 2H), 7.15 – 7.11 (m, 1H), 5.26 (s, 2H), 4.59 (s, 2H), 3.64 (t, *J* = 5.6 Hz, 2H), 3.07 (t, *J* = 6.0 Hz, 2H); **^{13}C NMR (100 MHz, Chloroform-*d*)** δ 167.7 , 159.2 , 149.1 , 141.1, 139.4 , 134.6 , 134.4 , 133.9 , 132.2 , 129.0 , 128.9 , 128.3 , 126.5 , 126.4 , 126.1 , 125.5 , 124.6 , 124.1 , 120.5 , 110.1 , 69.2 , 51.1 , 49.2 , 29.4 ; **HRMS** (ESI, m/z) calcd for $C_{24}H_{19}BrN_2O_2$ $[M+H]^+$ 447.0708, found 447.0709.



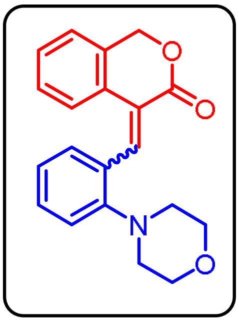
(*E*)-4-(2-(piperidin-1-yl)benzylidene)isochroman-3-one (4d):

Yellow solid (120 mg, 94% yield); E:Z=2.7:1;column chromatography eluent, petroleum ether/EtOAc = 20:1; mp 118-120 °C; **^{1}H NMR (400 MHz, Chloroform-*d*)** δ 8.05 (s, 1H), 7.42 (d, *J* = 8.0 Hz, 1H), 7.36 – 7.30 (comp, 2H), 7.26 – 7.24 (comp, 2H), 7.15 – 7.10 (m, 1H), 7.03 (app t, *J* = 7.6 Hz, 1H), 6.80 (app t, *J* = 7.2 Hz, 1H), 5.32 (s, 2H), 3.04 – 3.02 (m, 4H), 1.77 (p, *J* = 5.9 Hz, 4H), 1.63 – 1.60 (m, 2H); **^{13}C NMR (100 MHz, Chloroform-*d*)** δ 168.5 , 154.3 , 138.3 , 131.9 , 131.0 , 130.6 , 130.3 , 129.2 , 128.0 , 126.7 , 125.1 , 123.3 , 122.3 , 121.0 , 118.2 ,69.1 , 54.2 , 26.3 , 24.2; **HRMS** (ESI, m/z) calcd for $C_{21}H_{21}NO_2$ [M+Na]$^+$ 342.1470, found 342.1473.



(*E*)-4-(2-(4-phenylpiperazin-1-yl)benzylidene)isochroman-3-one (4e):

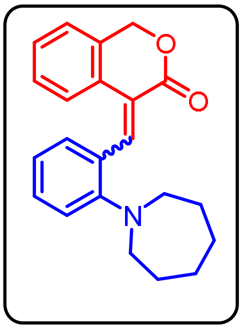
Yellow solid (135 mg, 85% yield);E:Z=4.9:1; column chromatography eluent, petroleum ether/EtOAc = 20:1; mp 128–130 °C; **^{1}H NMR (400 MHz, Chloroform-*d*)**δ 8.09 (s, 1H), 7.41 (d, *J* = 8.0 Hz, 1H), 7.36 (app t, *J* = 7.2 Hz, 2H),7.32 – 7.27 (comp, 4H), 7.17 – 7.12 (m, 1H), 7.10 (d, *J* = 8.0 Hz, 1H), 6.99 (d, *J* = 8.0 Hz, 2H), 6.88 (app t, *J* = 7.6 Hz, 2H), 5.33 (s, 2H), 3.41 – 3.38 (m, 4H), 3.27 – 3.24 (m, 4H); **^{13}C NMR (100 MHz, Chloroform-*d*)** δ 168.4 , 152.7 , 151.2 , 137.6 , 132.0 , 130.7 , 130.5 , 130.2 , 129.4 , 129.1 , 128.1 , 128.0 , 126.7 , 125.2 , 123.0 , 122.0 , 120.0 , 118.2 , 116.4 , 69.1 , 52.6 , 49.6; **HRMS**(ESI, m/z) calcd for $C_{26}H_{24}N2O_2$ [M+H]$^+$ 397.1916, found 397.1918.



(*E*)-4-(2-morpholinobenzylidene)isochroman-3-one (4f):

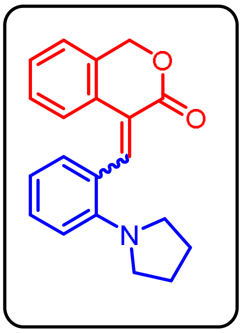
Yellow solid (122 mg, 95% yield); E:Z=2.6:1; column chromatography eluent, petroleum ether/EtOAc = 20:1; mp 82-84 °C; **^{1}H NMR (400 MHz, Chloroform-*d*)** δ 8.05 (s, 1H), 7.38

– 7.33 (comp, 3H), 7.26 – 7.25 (comp, 2H), 7.16 – 7.10 (m, 1H), 7.05 (t, *J* = 8.0 Hz, 1H), 6.87 (app t, *J* = 7.6 Hz, 1H), 5.33 (s, 2H), 3.90 – 3.88 (m, 4H), 3.09 – 3.05 (m, 4H); **^{13}C NMR (100 MHz, Chloroform-*d*)** δ 168.4 , 152.7 , 137.5 , 132.0 , 130.8 , 130.6 , 130.5 , 129.5 , 128.2 , 127.9 , 126.7 , 125.2 , 123.0 , 122.1 , 118.0 , 69.1 , 67.1 , 52.8; **HRMS** (ESI, m/z) calcd for $C_{20}H_{19}NO_3$ $[M+H]^+$ 322.1443, found 322.1455.



(*E*)-4-(2-(azepan-1-yl)benzylidene)isochroman-3-one (4g):

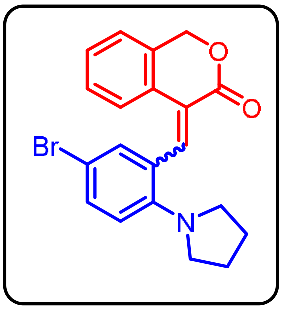
Yellow solid (130 mg, 97% yield); E:Z=2:1; column chromatography eluent, petroleum ether/EtOAc = 20:1; mp 121–123 °C; **^{1}H NMR (400 MHz, Chloroform-*d*)** δ 8.02 (s, 1H), 7.44 (d, *J* = 8.0 Hz, 1H), 7.36 – 7.32 (m, 1H), 7.29 – 7.27 (comp, 1H), 7.25 – 7.23 (comp, 3H), 7.14 (dd, *J* = 8.0, 4.0 Hz, 1H), 7.06 (d, *J* = 8.8 Hz, 1H), 6.71 (app t, *J* = 7.2 Hz, 1H), 5.32 (s, 2H), 3.35 – 3.32 (m, 4H), 1.84 – 1.79 (m, 4H), 1.75 – 1.71 (m, 4H); **^{13}C NMR (100 MHz, Chloroform-*d*)** δ 168.6 , 154.9 , 140.0 , 131.8 , 131.0 , 130.0 , 129.7 , 129.0 , 127.8 , 126.9 , 125.0 , 123.2 , 121.0 , 119.8 , 118.4 , 69.1 , 55.6 , 29.2 , 27.4 ; **HRMS** (ESI, m/z) calcd for $C_{22}H_{23}NO_2$ $[M+H]^+$ 334.1807, found 334.1808.



(*E*)-4-(2-(pyrrolidin-1-yl)benzylidene)isochroman-3-one (4h):

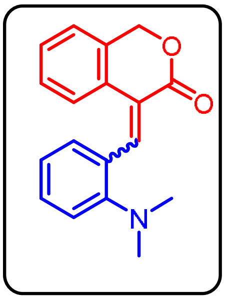
Yellow solid (120 mg, 98% yield); E:Z=2.3:1; column chromatography eluent, petroleum ether/EtOAc = 20:1; mp 100-101 °C; **^{1}H NMR (400 MHz, Chloroform-*d*)** δ 8.02 (s, 1H), 7.50 (d, *J* = 8.0 Hz, 1H), 7.42 (app t, *J* = 7.6 Hz, 1H), 7.24 – 7.23 (m, 1H), 7.23 – 7.22 (m, 1H), 7.21 – 7.20 (m, 1H), 7.15 – 7.11 (m, 1H), 6.83 (d, *J* = 8.0 Hz, 1H), 6.63 (app t, *J* = 7.2 Hz, 1H), 5.32 (s, 2H), 3.38 – 3.35 (m, 4H), 1.93 – 1.90 (m, 4H); **^{13}C NMR (100 MHz,**

Chloroform-*d*) δ 168.8 , 150.2 , 140.7 , 131.7 , 131.0 , 130.0 , 130.0 , 127.7 , 127.6 , 127.3 , 124.8 , 122.7 , 120.4 , 117.8 , 114.4 , 69.1 , 51.8 , 25.7 ; **HRMS**(ESI, m/z) calcd for $C_{20}H_{19}NO_2$ $[M+H]^+$ 306.1494, found 306.1491.



(*E*)-4-(5-bromo-2-(pyrrolidin-1-yl)benzylidene)isochroman-3-one (4i):

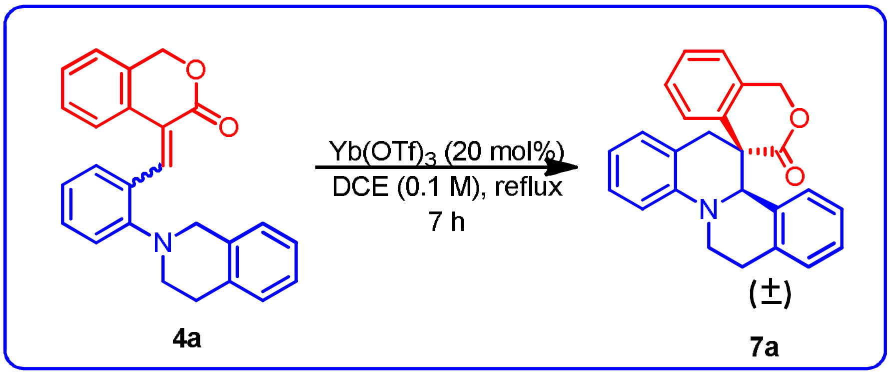
Yellow solid (145 mg, 94% yield); E:Z=2.7:1; column chromatography eluent, petroleum ether/EtOAc = 20:1; mp 140-144 °C; **^{1}H NMR (400 MHz, Chloroform-*d*)** δ 7.88 (s, 1H), 7.45 (d, *J* = 7.6 Hz, 1H), 7.26 (d, *J* = 2.4 Hz, 2H), 7.25 – 7.23 (comp, 2H), 7.19 – 7.14 (m, 1H), 6.68 (d, *J* = 9.2 Hz, 1H), 5.32 (s, 2H), 3.34 – 3.31 (m, 4H), 1.92 – 1.89 (m, 4H); **^{13}C NMR (100 MHz, Chloroform-*d*)** δ 168.5 , 149.0 , 138.7 , 133.1 , 132.4 , 131.8 , 130.2 , 128.1 , 127.8 , 127.2 , 125.0 , 124.2 , 121.4 , 116.0 , 109.6 , 69.1 , 51.8 , 25.7; **HRMS**(ESI, m/z) calcd for $C_{20}H_{18}BrNO_2$ $[M+H]^+$ 384.0599, found 384.0600.



(*E*)-4-(2-(dimethylamino)benzylidene)isochroman-3-one (4j):

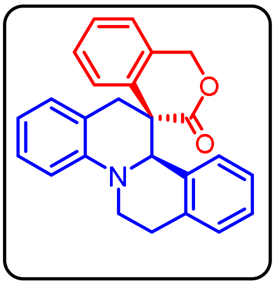
Yellow solid (95 mg, 85% yield); E:Z=1.4:1; column chromatography eluent, petroleum ether/EtOAc = 20:1; mp 112-114 °C; **^{1}H NMR (400 MHz, Chloroform-*d*)** δ 8.00 (s, 1H), 7.45 (d, *J* = 7.6 Hz, 1H), 7.30 (d, *J* = 7.6 Hz, 1H), 7.26 – 7.25 (comp, 3H), 7.16 – 7.11 (m, 1H), 7.04 (d, *J* = 9.2 Hz, 1H), 6.76 (app t, *J* = 7.6 Hz, 1H), 5.33 (s, 2H), 2.88 (s, 3H), 2.84 (s, 3H); **^{13}C NMR (100 MHz, Chloroform-*d*)** δ 168.7 , 154.0 , 138.8 , 131.9 , 130.9 , 130.3 , 129.5 , 127.9 , 127.8 , 126.9 , 125.1 , 123.4 , 121.4 , 120.6 , 117.4 , 69.1 , 44.5; **HRMS** (ESI, m/z) calcd for $C_{18}H_{17}NO_2$ $[M+H]^+$ 280.1338, found 280.1336.

3.5.12 General Procedure for the Synthesis of the Final Product 7a



To an oven-dried 10 mL round-bottom flask attached with condenser under nitrogen, (E)-4-(2-(3,4-dihydroisoquinolin-2(1*H*)-yl)benzylidene)isochroman-3-one (**4a**) (79 mg, 0.2 mmol) was taken and the mixture was dissolved in DCE (2 mL). To it, Yb(OTf)$_3$ (14.9 mg, 0.04 mmol) was added and the bath temperature was slowly increased to the reflux temperature. The reaction mixture was kept at the same temperature until the olefin was consumed completely as monitored by TLC. The solvent was removed under vacuo and it was purified by column chromatography on silica gel (230-400 mesh) using petroleum ether/ethyl acetate (20:1) as eluent to obtain the desired spirocyclic product (4R,11b'S)-6',7',11b',13'-tetrahydrospiro[isochroman-4,12'-isoquinolino[2,1-a]quinolin]-3-one (**7a**) in 80% (58.5 mg) yield.

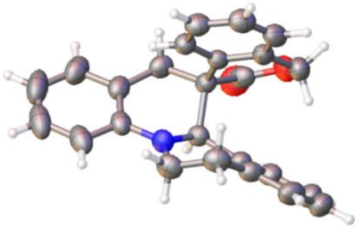
3.5.13 Characterization of the Final Product 7a-7j



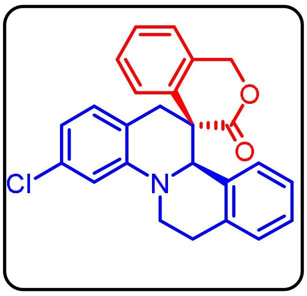
(4R*,11b'R*)-6',7',11b',13'-tetrahydrospiro[isochroman-4,12'-isoquinolino[2,1-a]quinolin]-3-one (7a):

Colourless solid (58.5 mg, 80% yield); column chromatography eluent, petroleum ether/EtOAc = 20:1; mp 128–130 °C; single diastereomer; **^{1}H NMR (400 MHz, Chloroform-*d*)** δ 7.36 – 7.34 (m, 1H), 7.29 – 7.27 (m, 1H), 7.26 – 7.22 (comp, 3H), 7.21 – 7.19 (m, 1H), 7.09 (app t, *J* = 7.6 Hz, 1H), 6.94 – 6.92 (m, 1H), 6.90 – 6.85 (comp, 2H), 6.80 (d, *J* = 7.6 Hz, 1H), 6.76 (d, *J* = 8.0 Hz, 1H), 4.72 (s, 1H), 4.64 (d, *J* = 14.8 Hz, 1H), 4.54 (d, *J* = 18.0 Hz, 1H), 3.49 (ddd, *J* = 10.5, 5.3, 1.6 Hz, 1H), 3.20 (ddd, *J* = 12.4, 10.7, 3.1 Hz, 1H), 3.10 (d, *J* = 10.0 Hz, 1H), 3.06 (d, *J* = 12.8 Hz, 1H), 2.23 (dt, *J* = 15.2, 2.4 Hz, 1H), 1.07 (ddd, *J* = 15.3, 12.5, 5.4 Hz, 1H); **^{13}C NMR (100 MHz, Chloroform-*d*)** δ 173.6 , 146.7 , 137.4 , 134.3 , 132.4 , 131.3 , 129.0 , 128.8 , 128.5 , 128.1 , 127.7, 127.6, 127.3, 126.7, 126.5 , 122.8 , 122.7, 117.9, 112.5, 68.9, 65.2, 51.7, 43.3, 38.5, 29.7; **HRMS**(ESI, m/z) calcd for $C_{25}H_{11}NO_2$ $[M+Na]^+$ 390.1470, found 390.1475.

Table 3.5.14 Crystal Data and Structure Refinement for 7a (CCDC-1996349)

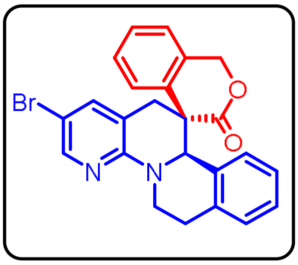


Empirical formula	$C_{25}H_{21}NO_2$
Formula weight	367.43
Temperature/K	298
Crystal system	trigonal
Space group	R3c
a/Å	33.691(4)
b/Å	33.691(4)
c/Å	7.4139(10)
α/°	90
β/°	90
γ/°	120
Volume/Å^3	7288(2)
Z	18
ρ_{calc}g/cm^3	1.507
μ/mm^{-1}	0.095
F(000)	3492.0
Crystal size/mm^3	0.3 × 0.3 × 0.25
Radiation	MoKα (λ = 0.71073)
2Θ range for data collection/°	4.836 to 56.226
Index ranges	$-44 \le h \le 44$, $-44 \le k \le 44$, $-6 \le l \le 9$
Reflections collected	34716
Independent reflections	3329 [R_{int} = 0.0502, R_{sigma} = 0.0254]
Data/restraints/parameters	3329/26/269
Goodness-of-fit on F^2	1.108
Final R indexes [I>=2σ (I)]	R_1 = 0.0385, wR_2 = 0.0837
Final R indexes [all data]	R_1 = 0.0504, wR_2 = 0.0895
Largest diff. peak/hole / e Å^{-3}	0.12/-0.19
Flack parameter	0.1(6)



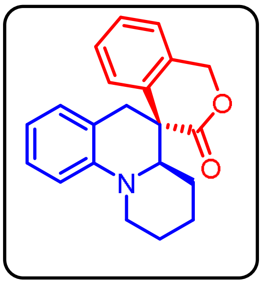
(4R*,11b'R*)-3'-chloro-6',7',11b',13'-tetrahydrospiro[isochroman-4,12'-isoquinolino[2,1-a]quinolin]-3-one (7b):

Colourless solid (40 mg, 50% yield); column chromatography eluent, petroleum ether/EtOAc = 20:1; mp 145-147 °C; *dr* 10:1; Data for major isomer in an inseparable diastereomeric mixture; **^{1}H NMR (400 MHz, Chloroform-*d*)** δ 7.35 – 7.33 (m, 1H), 7.28 (dd, *J* = 7.6, 1.6 Hz, 1H), 7.22 (app t, *J* = 8.0 Hz, 2H), 7.18 (d, *J* = 8.4 Hz, 1H), 7.11 (app t, *J* = 7.6 Hz, 1H), 6.93 (d, *J* = 6.4 Hz, 1H), 6.85 – 6.80 (comp, 3H), 6.74 (d, *J* = 1.6 Hz, 1H), 4.69 (s, 1H), 4.64 (d, *J* = 14.8 Hz, 1H), 4.48 (d, *J* = 17.6 Hz, 1H), 3.46 – 3.42 (m, 1H), 3.17 (td, *J* = 11.2, 3.2 Hz, 1H), 3.09 (d, *J* = 14.4 Hz, 1H), 3.02 (d, *J* = 18.0 Hz, 1H), 2.23 (d, *J* = 15.2 Hz, 1H), 1.05 (td, *J* = 14.0, 5.2 Hz, 1H); **^{13}C NMR (100 MHz, Chloroform-*d*)** δ 173.3 , 142.6 , 136.1 , 133.1 , 131.0 , 130.6 , 130.4 , 130.2 , 129.2 , 128.6 , 127.6 , 127.5 , 127.3 , 124.7 , 124.4 , 124.0 , 121.4 , 111.8 , 107.7 , 69.6 , 63.5 , 46.3 , 37.9 , 27.4 , 23.0 ; **HRMS** (ESI, m/z) calcd for $C_{25}H_{20}ClNO_2$ $[M+H]^+$ 402.1261, found 402.1263.



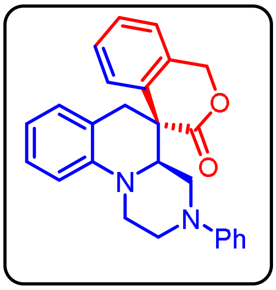
(4R*,11b'R*)-2'-bromo-6',7',11b',13'-tetrahydrospiro[isochroman-4,12'-isoquinolino[2,1-a][1,8]naphthyridin]-3-one (7c):

Colourless solid (47 mg, 53% yield);column chromatography eluent, petroleum ether/EtOAc = 20:1; mp 148-149 °C; single diastereomer; **^{1}H NMR (400 MHz, Chloroform-*d*)**δ 8.14 (d, *J* = 2.0 Hz, 1H), 7.59 – 7.58 (m, 1H), 7.29 (dd, *J* = 7.2, 1.6 Hz, 1H), 7.25 – 7.20 (comp, 2H), 7.19 (dd, *J* = 7.6, 0.8 Hz, 1H), 7.07 (app t, *J* = 7.6 Hz, 1H), 6.90 (d, *J* = 7.2 Hz, 1H), 6.79 (d, *J* = 7.6 Hz, 1H), 6.62 (d, *J* = 8.0 Hz, 1H), 4.71 (s, 1H), 4.60 (d, *J* = 14.8 Hz, 1H), 4.41 (d, *J* = 18.0 Hz, 1H), 4.16 (ddd, *J* = 12.0, 4.8, 2.0 Hz, 1H), 3.03 (d, *J* = 14.8 Hz, 1H), 2.99 – 2.92 (m, 2H), 2.20 (dt, *J* = 15.2, 2.4 Hz, 1H);**^{13}C NMR (100 MHz, Chloroform-*d*)** δ 173.0 , 154.5 , 145.9 , 138.2 , 132.7 , 131.4 , 131.0 , 128.4 , 128.3 , 128.0 , 128.0 , 127.9 , 127.9 , 127.7 , 126.8 , 123.2 , 119.3 , 107.9 , 69.0 , 64.6 , 50.6 , 41.3 , 37.1 , 28.5 ; **HRMS**(ESI, m/z) calcd for $C_{24}H_{19}BrN_2O_2$ $[M+H]^+$ 447.0708, found 447.0711.



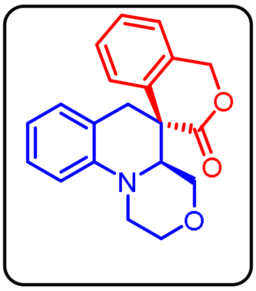
(4R*,4a'R*)-1',2',3',4',4a',6'-hexahydrospiro[isochroman-4,5'-pyrido[1,2-a]quinolin]-3-one (7d):

Colourless solid (30 mg, 47% yield); column chromatography eluent, petroleum ether/EtOAc = 20:1; mp 124-125 °C; *dr* 1.3:1; Data for inseparable diastereomeric mixture; **^{1}H NMR (300 MHz, Chloroform-*d*)** δ 7.48 – 7.42 (m, 1H), 7.17 (m, 3H), 7.06 (dt, J = 15.0, 6.7 Hz, 4H), 6.97 (d, J = 7.9 Hz, 1H), 6.92 (d, J = 7.3 Hz, 1H), 6.83 (d, J = 8.3 Hz, 1H), 6.73 – 6.67 (m, 2H), 6.62 (t, J = 7.3 Hz, 1H), 5.73 (d, J = 14.4 Hz, 1H), 5.53 (d, J = 12 Hz , 1H), 5.32 (d, J = 14.8 Hz, 1H), 5.20 (d, J = 14.8 Hz, 1H), 4.06 (d, J = 13.2 Hz, 1H), 3.95 (app t, J = 17.9 Hz, 2H), 3.69 – 3.59 (m, 1H), 3.44 (d, J = 8.0 Hz, 1H), 3.25 (app t, J = 8.0 Hz, 1H), 2.93 (d, J = 17.6 Hz, 1H), 2.85 (m, 1H), 2.72 – 2.58 (m, 1H), 1.84 – 1.75 (m, 1H), 1.72 – 1.63 (m, 1H), 1.58 – 1.46 (m, 5H), 1.29 (m, 2H); **^{13}C NMR (100 MHz, Chloroform-*d*, major diastereomer)** δ 172.0, 142.9, 138.0, 130.1, 129.0, 128.6, 127.4, 127.3, 126.4, 124.6, 121.5, 117.7, 112.9, 69.7, 59.0, 49.9, 48.0, 30.5, 26.3, 25.7, 21.1; **^{13}C NMR (100 MHz, Chloroform-*d*, minor diastereomer)** δ 172.7, 144.16, 134.4, 131.0, 129.2, 128.4, 127.3, 127.2, 126.4, 124.6, 121.5, 118.0, 113.5, 69.6, 60.1, 49.7, 47.9, 33.4, 25.2, 24.9, 23.4; **HRMS**(ESI, m/z) calcd for $C_{21}H_{21}NO_2$ $[M+Na]^+$ 342.1470, found 342.1481.



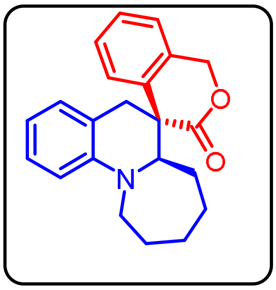
(4R*,4a'S*)-3'-phenyl-1',2',3',4',4a',6'-hexahydrospiro[isochroman-4,5'-pyrazino[1,2-a]quinolin]-3-one (7e):

Colourless solid (54 mg, 68% yield); column chromatography eluent, petroleum ether/EtOAc = 20:1; mp 135-136 °C; *dr* 5:1; Data for inseparable diastereomeric mixture; **^{1}H NMR (400 MHz, Chloroform-*d*)** δ 7.76 (d, *J* = 7.6 Hz, 1H), 7.36 – 7.32 (m, 1H), 7.32 – 7.27 (comp, 2H), 7.25 – 7.24 (comp, 2H), 7.23 – 7.21 (comp, 3H), 7.17 (app t, *J* = 8.4 Hz, 2H), 7.11 (d, *J* = 8.0 Hz, 1H), 7.01 (d, *J* = 8.0 Hz, 1H), 6.96 (d, *J* = 7.2 Hz, 1H), 6.91 – 6.83 (comp, 6H), 6.75 (app t, *J* = 7.2 Hz, 1H), 5.53 (s, 2H), 5.53 (s, 1H), 4.18 – 4.08 (m, 2H), 4.06 (d, *J* = 18.0 Hz, 1H), 3.63 (d, *J* = 11.6 Hz, 1H), 3.56 – 3.51 (m, 2H), 3.46 (d, *J* = 11.6 Hz, 1H), 3.39 (d, *J* = 15.6 Hz, 1H), 3.34 – 3.32 (m, 1H), 3.27 (dd, *J* = 12.0, 3.2 Hz, 1H), 3.19 (d, *J* = 15.6 Hz, 1H), 3.13 (d, *J* = 18.0 Hz, 1H), 3.02 – 2.92 (m, 2H), 2.76 (t, *J* = 11.2 Hz, 1H); **^{13}C NMR (100 MHz, Chloroform-*d*)** δ 172.7, 171.6, 150.7, 144.1, 137.2, 133.6, 130.5, 130.3, 129.5, 129.2, 129.2, 129.1, 129.1 (x 2), 128.8, 128.5, 127.9, 127.7, 127.6, 127.6, 127.5, 126.4, 124.8, 124.5, 121.9, 120.7, 120.3, 120.1, 118.8, 118.6, 116.3 (x 2), 113.7, 113.5, 69.8, 69.6, 59.0, 57.1, 53.4, 49.8, 49.1, 48.8, 48.1, 47.9, 46.6, 45.9, 36.0, 31.3; **HRMS**(ESI, m/z) calcd for $C_{26}H_{24}N2O_2$ [M+H]$^+$ 397.1916, found 397.1915.



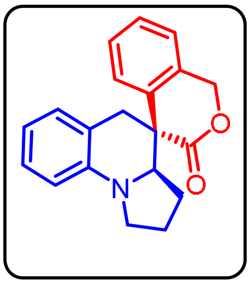
(4aS*,4'R*)-2,4,4a,6-tetrahydro-1H-spiro[[1,4]oxazino[4,3-a]quinoline-5,4'-isochroman]-3'-one (7f):

Colourless solid (65 mg, 93% yield); column chromatography eluent, petroleum ether/EtOAc = 20:1; mp 125-126 °C; *dr* 2:1; Data for inseparable diastereomeric mixture; **^{1}H NMR (400 MHz, Chloroform-*d*)** δ 7.69 (d, *J* = 7.9 Hz, 1H), 7.27 (td, *J* = 12.7, 11.2, 6.1 Hz, 3H), 7.22 – 7.12 (m, 6H), 7.08 (d, *J* = 8.1 Hz, 1H), 6.93 (d, *J* = 8.0 Hz, 2H), 6.88 – 6.80 (m, 1H), 6.76 (t, *J* = 7.4 Hz, 1H), 5.78 (d, *J* = 14.8 Hz, 1H), 5.55 – 5.43 (m, 2H), 5.36 (d, *J* = 14.8 Hz, 1H), 3.97 (dd, *J* = 10.8, 3.6 Hz, 2H), 3.92 – 3.80 (m, 3H), 3.77 – 3.69 (m, 2H), 3.68 – 3.56 (m, 4H), 3.34 (t, *J* = 10.7 Hz, 1H), 3.20 – 3.10 (m, 2H), 3.06 (d, *J* = 15.8 Hz, 1H) ; **^{13}C NMR (101 MHz, Chloroform-*d*)** δ 172.6 , 144.4 , 133.5 , 130.2 , 129.5 , 128.5 , 128.1 , 127.6 , 126.3 , 124.2 , 120.7 , 119.0 , 113.0 , 69.5 , 66.8 , 66.4 , 59.6 , 47.8 , 44.6 , 37.0; **HRMS** (ESI, m/z) calcd for $C_{20}H_{19}NO_3$ [M+H]$^+$ 322.1443, found 322.1455.



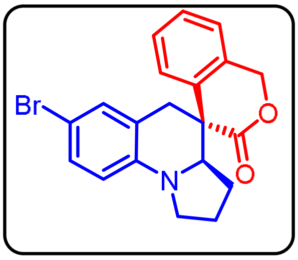
(4'R*,6aR*)-6a,7,8,9,10,11-hexahydro-5H-spiro[azepino[1,2-a]quinoline-6,4'-isochroman]-3'-one (7g):

Colourless solid (35.5 mg, 53% yield); column chromatography eluent, petroleum ether/EtOAc = 20:1; mp 128–130 °C; *dr* 2:1; Data for major diastereomer; **^{1}H NMR (400 MHz, Chloroform-*d*)** δ 7.25 – 7.21 (comp, 2H), 7.16 – 7.09 (comp, 3H), 6.93 (d, *J* = 7.6 Hz, 1H), 6.72 (app t, *J* = 7.2 Hz, 1H), 6.54 (d, *J* = 8.4 Hz, 1H), 5.79 (d, *J* = 14.8 Hz, 1H), 5.30 (d, *J* = 14.8 Hz, 1H), 4.11 (d, *J* = 18.0 Hz, 1H), 3.73 – 3.68 (m, 1H), 3.53 (dd, *J* = 10.4, 5.6 Hz, 1H), 3.01 (d, *J* = 18.0 Hz, 1H), 2.59 (ddd, *J* = 15.6, 11.0, 5.5 Hz, 1H), 2.05 – 1.98 (m, 1H), 1.74 (dd, *J* = 11.2, 5.6 Hz, 1H), 1.53 – 1.49 (m, 6H); **^{13}C NMR (101 MHz, Chloroform-*d*)** δ 172.5 , 142.8 , 138.3 , 129.9 , 128.7 , 128.6 , 127.2 , 127.1 , 126.6 , 124.3 , 119.3 , 116.3 , 110.3 , 69.5 , 60.6 , 50.8 , 47.3 , 31.7 , 30.0 , 27.6 , 26.1 , 25.3 ; **HRMS** (ESI, m/z) calcd for $C_{22}H_{23}NO_2$ $[M+H]^+$ 334.1807, found 334.1808.



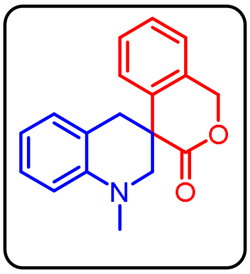
(3a'R*,4R*)-2',3',3a',5'-tetrahydro-1'H-spiro[isochroman-4,4'-pyrrolo[1,2-a]quinolin]-3-one (7h):

Yellow solid (25.6 mg, 42% yield);column chromatography eluent, petroleum ether/EtOAc = 20:1; mp 120 °C; *dr* 2:1; Data for major diastereomer; **^{1}H NMR (400 MHz, Chloroform-*d*)** δ 7.21 (app t, *J* = 7.6 Hz, 1H), 7.15 (app t, *J* = 8.0 Hz, 1H), 7.12 – 7.07 (comp, 2H), 6.99 (d, *J* = 7.6 Hz, 1H), 6.92 (d, *J* = 8.0 Hz, 1H), 6.62 (app t, *J* = 7.2 Hz, 1H), 6.52 (d, *J* = 8.0 Hz, 1H), 5.52 – 5.43 (m, 2H), 4.05 (dd, *J* = 10.4, 5.2 Hz, 1H), 3.79 (d, *J* = 16.0 Hz, 1H), 3.42 (td, *J* = 8.8, 4.1 Hz, 1H), 3.27 (q, *J* = 8.8 Hz, 1H), 3.03 (d, *J* = 16.4 Hz, 1H), 2.14 – 2.07 (m, 1H), 1.98 – 1.92 (m, 2H), 1.52 – 1.40 (m, 1H);**^{13}C NMR (101 MHz, Chloroform-*d*)** δ 173.7 , 143.7 , 133.6 , 130.6 , 128.6 , 128.5 , 127.9 , 127.5 , 127.1 , 123.8 , 119.4 , 116.1 , 110.4 , 69.6 , 63.5 , 46.2 , 44.2 , 38.2 , 27.5 , 23.0 ;**HRMS**(ESI, m/z) calcd for $C_{20}H_{19}NO_2$ $[M+H]^+$ 306.1494, found 306.1497.



(3a'R*,4R*)-7'-bromo-2',3',3a',5'-tetrahydro-1'H-spiro[isochroman-4,4'-pyrrolo[1,2-a]quinolin]-3-one (7i):

Yellow solid (30 mg, 40% yield); column chromatography eluent, petroleum ether/EtOAc = 20:1; mp 128–130 °C; *dr* 2:1; Data for inseparable diastereomeric mixture; **^{1}H NMR (400 MHz, Chloroform-*d*)** δ 7.43 (app t, *J* = 7.2 Hz, 1H), 7.12 (dt, *J* = 7.4, 0.9 Hz, 1H), 7.30 (d, *J* = 7.6 Hz, 1H), 7.23 – 7.19 (comp, 2H), 7.12 (d, *J* = 8.8 Hz, 1H), 7.09 (d, *J* = 0.8 Hz, 1H), 6.85 (d, *J* = 8.0 Hz, 1H), 6.41 (d, *J* = 8.8 Hz, 1H), 6.38 (d, *J* = 8.4 Hz, 1H), 5.56 – 5.51 (m, 1H), 5.47 – 5.42 (m, 2H), 5.38 – 5.33 (m, 1H), 4.08 (dd, *J* = 10.4, 5.6 Hz, 1H), 3.74 (d, *J* = 16.4 Hz, 1H), 4.03 (dd, *J* = 10.4, 5.6 Hz, 1H), 3.74 (d, *J* = 16.4 Hz, 1H), 3.58 – 3.53 (m, 1H), 3.41 – 3.36 (m, 1H), 3.23 (q, *J* = 8.4 Hz, 1H), 2.98 (d, *J* = 16.4 Hz, 1H), 2.14 – 2.06 (m, 1H), 2.02 – 1.92 (m, 2H), 1.52 – 1.42 (m, 1H); **^{13}C NMR (101 MHz, Chloroform-*d*)** δ 173.3, 168.4, 143.2, 142.6, 136.1, 133.1, 132.1, 131.0, 131.0, 130.6, 130.4, 130.2, 129.2, 128.6, 127.6, 127.5, 127.3, 124.6, 124.4, 124.0, 121.4, 120.8, 112.3, 111.8, 107.7, 106.9, 69.6, 69.2, 63.8, 63.5, 48.0, 46.3, 43.9, 38.7, 37.9, 29.7, 28.2, 27.4, 23.7, 23.0; **HRMS** (ESI, m/z) calcd for $C_{20}H_{18}BrNO_2$ $[M+H]^+$384.0599, found 384.0600.

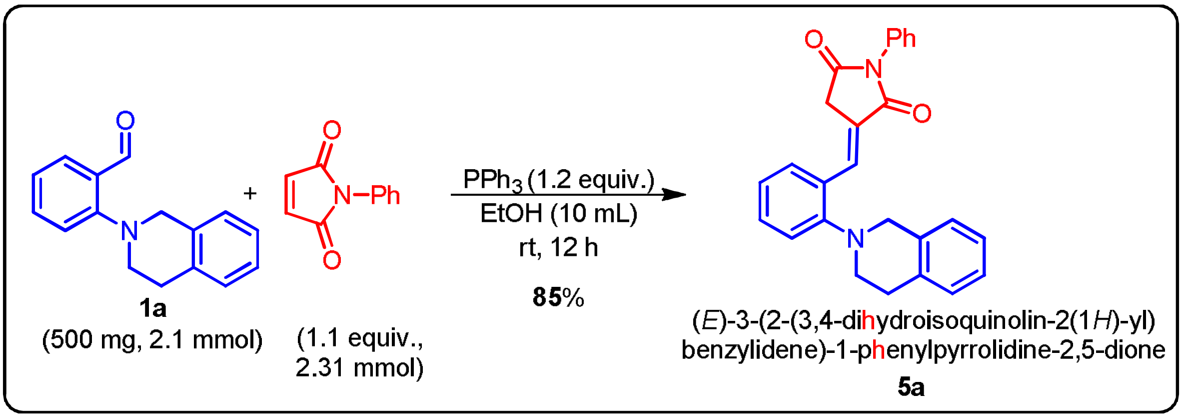


1'-methyl-2',4'-dihydro-1'H-spiro[isochroman-4,3'-quinolin]-3-one (7j):

White solid (20 mg, 36% yield);column chromatography eluent, petroleum ether/EtOAc = 20:1;mp 125-128°C; single isomer; **^{1}H NMR (400 MHz, Chloroform-*d*)** δ 7.33 (app t, *J* = 8.0 Hz, 1H), 7.25 – 7.24 (m, 1H), 7.19 – 7.13 (comp, 3H), 7.07 (d, *J* = 7.6 Hz, 1H), 6.72 (app t, *J* = 7.2 Hz, 1H), 6.66 (d, *J* = 8.4 Hz, 1H), 5.57 (d, *J* = 14.4 Hz, 1H), 5.46 (d, *J* = 14.4 Hz, 1H), 3.72 (d, *J* = 3.6 Hz, 1H), 3.67 (d, *J* = 12.0 Hz, 1H), 3.38 (dd, *J* = 11.6, 2.4 Hz, 1H), 3.14

(dd, *J*= 16.0, 1.6 Hz, 1H), 2.89 (s, 3H);**^{13}C NMR (101 MHz, Chloroform-*d*)** δ 172.6 , 145.3 , 136.4 , 130.4 , 128.8 , 128.8 , 127.4 , 127.4 , 127.1 , 126.4 , 124.6 , 120.5 , 117.5 , 111.3 , 69.5 , 55.0 , 44.3 , 39.2 , 34.2 ; **HRMS**(ESI, m/z) calcd for $C_{18}H_{17}NO_2$ $[M+H]^+$ 280.1338, found 280.1337.

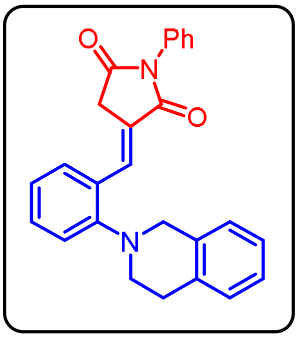
3.5.15 General Procedure for the Preparation of 2-Amino Substituted Olefin 5a



In an oven-dried round-bottom flask 1-phenyl-1*H*-pyrrole-2,5-dione (400 mg, 2.31 mmol) and Triphenylphosphine (PPh_3) (661 mg, 2.52 mmol) were dissolved in ethanol (10 mL) and stirred at room temperature for 5 min. Then 2-(3,4-dihydroisoquinolin-2(1*H*)-yl) benzaldehyde **1a** (500 mg, 2.1 mmol) was added to the reaction mixture. The reaction mixture was kept on stirring for 12 h at room temperature. A yellow precipitate was observed after a few hours. After the completion of the reaction, monitoring by TLC checked process, the resultant residue mass was filtered by Buchner's funnel and washed with EtOH. The solid product dried under a vacuum. If a solid not comes the whole reaction mixture were concentrated under vacuo. And the crude product was purified by column chromatography on silica gel (230-400 mesh) using petroleum ether/ethyl acetate (10:1) as eluent to afford (*E*)-3-(2-(3,4-dihydroisoquinolin-2(1*H*)-yl)benzylidene)-1- phenylpyrrolidine-2,5-dione (**5a**). Finally, we obtained 706 mg (85%) yellowish solid desired product after keeping a few hours in a high vacuum condition. The previous report helps to prepare this succinimide containing olefin.[26]

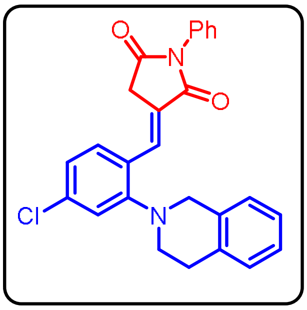
We observed that *E* isomer formed exclusively (from ^{1}H NMR), but in some cases,*Z* isomer also formed (minor) which is reported here. The same protocol we have followed to prepare several olefin substrates (**5b-5w)**.

3.5.16 Characterization of Olefin Substrates 5a-5w



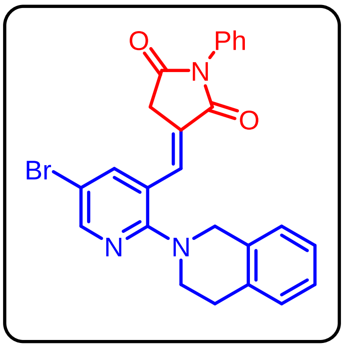
(*E*)-3-(2-(3,4-dihydroisoquinolin-2(1*H*)-yl)benzylidene)-1-phenylpyrrolidine-2,5-dione (**5a**)

Yellow solid (59.1 mg, 75% yield); **Rf** 0.30 (pet ether/ethyl acetate = 10:1); column chromatography eluent, petroleum ether/EtOAc = 10:1; **mp** 144-146 °C; single diastereomer; **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 8.12 (t, *J* = 2.3 Hz, 1H), 7.53 – 7.48 (comp, 3H), 7.43 – 7.39 (comp, 4H), 7.22 – 7.10 (comp, 6H), 4.30 (s, 2H), 3.76 (d, *J* = 2.4 Hz, 2H), 3.28 (t, *J* = 5.8 Hz, 2H), 3.06 (t, *J* = 5.7 Hz, 2H); **^{13}C NMR** (101 MHz, Chloroform-*d*) δ 173.3, 170.1, 153.3, 134.4, 134.3, 133.0, 132.1, 131.0, 129.0, 129.0, 128.4, 127.5, 126.4, 126.4, 126.4, 126.3, 125.9, 122.4, 122.0, 119.2, 53.4, 53.0, 34.0, 29.3; **HRMS** (ESI, m/z) calcd for $C_{26}H_{23}N_2O_2$ $[M+H]^+$ 395.1760, found 395.1761.



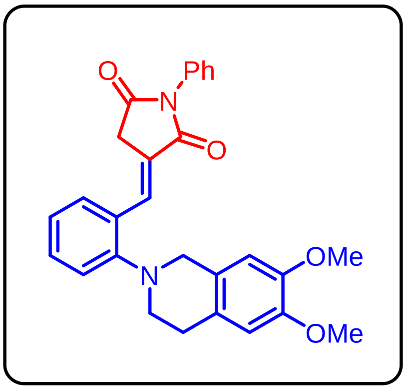
(*E*)-3-(4-chloro-2-(3,4-dihydroisoquinolin-2(1*H*)-yl)benzylidene)-1-phenylpyrrolidine-2,5-dione (**5b**)

Yellow solid (49.7 mg, 62% yield); **Rf** 0.30 (pet ether/ethyl acetate = 10:1); column chromatography eluent, petroleum ether/EtOAc = 10:1; **mp** 186-188 °C; single diastereomer; **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 8.00 (t, *J* = 2.2 Hz, 1H), 7.54 – 7.47 (comp, 2H), 7.43 – 7.38 (comp, 4H), 7.22 – 7.15 (comp, 4H), 7.13 – 7.08 (comp, 2H), 4.27 (s, 2H), 3.72 (d, *J* = 2.4 Hz, 2H), 3.28 (t, *J* = 5.8 Hz, 2H), 3.07 (t, *J* = 5.7 Hz, 2H); **^{13}C NMR** (101 MHz, Chloroform-*d*) δ 173.0, 169.9, 154.2, 136.9, 134.1, 133.7, 132.0, 131.9, 129.9, 129.1, 129.1, 128.5, 126.6, 126.4, 126.4, 126.1, 125.7, 122.5, 122.4, 119.6, 53.2, 53.0, 34.0, 29.3; **HRMS** (EI, m/z) calcd for $C_{26}H_{21}ClN_2O_2$ $[M]^+$ 428.1292, found 428.1278.



(*E*)-3-((5-bromo-2-(3,4-dihydroisoquinolin-2(1*H*)-yl)pyridin-3-yl)methylene)-1-phenylpyrrolidine-2,5-dione (5c)

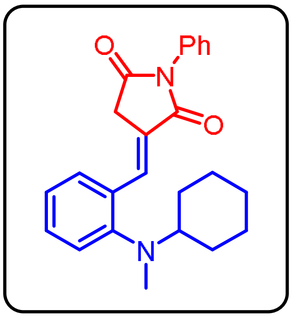
Yellow solid (85.2 mg, 90% yield); **Rf** 0.30 (pet ether/ethyl acetate = 10:1); column chromatography eluent, petroleum ether/EtOAc = 10:1; **mp** 180-182 °C; single diastereomer; **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 8.32 (d, *J* = 2.3 Hz, 1H), 7.73 (d, *J* = 2.3 Hz, 1H), 7.71 – 7.70 (m, 1H), 7.53 – 7.47 (comp, 2H), 7.43 – 7.38 (comp, 3H), 7.19 – 7.11 (comp, 4H), 4.54 (s, 2H), 3.65 (d, *J* = 2.4 Hz, 2H), 3.52 (t, *J* = 5.8 Hz, 2H), 3.06 (t, *J* = 5.7 Hz, 2H); **^{13}C NMR** (101 MHz, Chloroform-*d*) δ 172.4, 169.3, 159.7, 149.3, 139.1, 134.2, 133.9, 131.8, 130.6, 129.1, 128.9, 128.6, 126.5, 126.3, 126.1, 124.1, 120.2, 110.9, 51.2, 50.1, 33.5, 29.3; **HRMS** (EI, m/z) calcd for $C_{25}H_{20}BrN_3O_2$ $[M]^+$ 473.0739, found 473.0741.



(*E*)-3-(2-(6,7-dimethoxy-3,4-dihydroisoquinolin-2(1*H*)-yl)benzylidene)-1-phenylpyrrolidine-2,5-dione (5d)

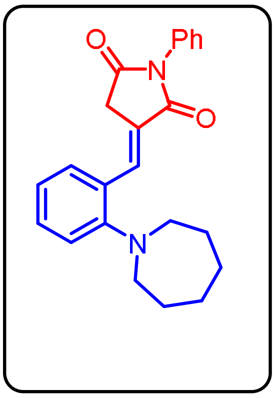
Yellow solid (52.7 mg, 83% yield); **Rf** 0.30 (pet ether/ethyl acetate = 5:1); column chromatography eluent, petroleum ether/EtOAc = 5:1; **mp** 142-145 °C; single diastereomer; **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 8.10 (t, *J* = 2.1 Hz, 1H), 7.52 – 7.48 (comp, 3H), 7.43

– 7.34 (comp, 4H), 7.17 (app d, *J* = 8.0 Hz, 1H), 7.15 – 7.11 (m, 1H), 6.63 (s, 1H), 6.59 (s, 1H), 4.21 (s, 2H), 3.87 (d, *J* = 5.6 Hz, 1H), 3.85 (d, *J* = 2.3 Hz, 6H), 3.75 (d, *J* = 1.9 Hz, 2H), 3.25 (t, *J* = 5.8 Hz, 2H), 2.94 (t, *J* = 5.6 Hz, 2H); **^{13}C NMR** (101 MHz, Chloroform-*d*) δ 173.3, 170.1, 153.3, 147.7, 147.5, 133.1, 132.1, 131.0, 129.1, 129.1, 128.4, 127.5, 126.6, 126.4, 126.1, 122.3, 122.0, 119.2, 111.7, 109.2, 56.0, 55.9, 53.1, 52.9, 34.0, 28.8; **HRMS** (ESI, m/z) calcd for $C_{28}H_{26}N_2O_4$ $[M]^+$ 454.1893, found 454.1846.



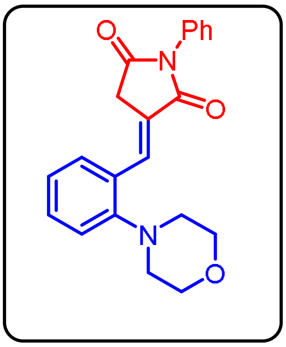
(*E*)-3-(2-(cyclohexyl(methyl)amino)benzylidene)-1-phenylpyrrolidine-2,5-dione (**5e**)

Off white solid (63 mg, 84% yield); **Rf** 0.30 (pet ether/ethyl acetate = 10:1); column chromatography eluent, petroleum ether/EtOAc = 10:1; **mp** 177-179 °C; single diastereomer; **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 8.07 (t, *J* = 2.2 Hz, 1H), 7.53 – 7.48 (comp, 2H), 7.47 – 7.44 (m, 1H), 7.44 – 7.33 (comp, 4H), 7.14 (app d, *J* = 8.1 Hz, 1H), 7.08 – 7.04 (m, 1H), 3.74 (d, *J* = 2.3 Hz, 2H), 2.79 (dt, J = 11.6, 3.4 Hz, 1H), 2.75 (s, 3H), 1.80 (dd, J = 25.0, 11.5 Hz, 4H), 1.64 – 1.43 (m, 3H), 1.11 (p, J = 12.6 Hz, 3H); **^{13}C NMR** (101 MHz, Chloroform-*d*) δ 173.5, 170.2, 154.5, 133.8, 132.2, 130.4, 129.0, 128.9, 128.3, 128.2, 126.4, 121.6, 121.2, 121.0, 65.3, 34.1, 34.0, 29.4, 26.0, 25.9; **HRMS** (ESI, m/z) calcd for $C_{24}H_{26}N_2O_2$ $[M]^+$ 374.1994, found 374.1993.



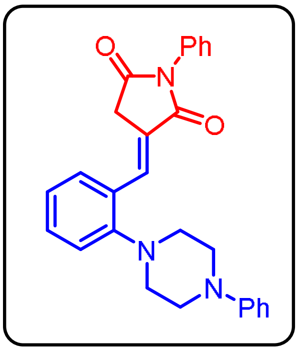
(*E*)-3-(2-(azepan-1-yl)benzylidene)-1-phenylpyrrolidine-2,5-dione (**5f**)

Off white solid (62 mg, 86% yield); **Rf** 0.30 (pet ether/ethyl acetate = 10:1); column chromatography eluent, petroleum ether/EtOAc = 10:1; **mp** 100-102 °C; diastereomeric ratio 1.7:1; inseparable diastereomeric mixture, ^{1}**H NMR** (400 MHz, Chloroform-*d*) δ 8.12 (t, *J* = 2.1 Hz, 1H), 7.53 – 7.47 (comp, 2H), 7.42 (comp, 4H), 7.37 – 7.31 (m, 1H), 7.17 (app d, *J* = 8.2 Hz, 1H), 7.04 – 7.00 (m, 1H), 3.70 (d, *J* = 2.3 Hz, 1H), 3.22 – 3.20 (m, 4H), 1.82 – 1.79 (m, 4H), 1.76 – 1.71 (m, 4H); ^{13}**C NMR** (101 MHz, Chloroform-*d*) δ 173.5, 170.2, 156.0, 134.6, 132.1, 130.7, 129.0, 128.9, 128.4, 127.0, 126.4, 121.2, 120.9, 120.2, 56.4, 33.9, 29.2, 27.2; **HRMS** (EI, m/z) calcd for $C_{23}H_{24}N_2O_2$ $[M]^+$ 360.1838, found 360.1827.



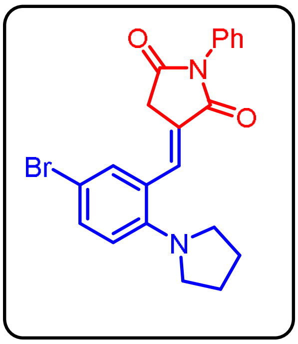
(*E*)-3-(2-morpholinobenzylidene)-1-phenylpyrrolidine-2,5-dione (**5g**)

Off white solid (47.3 mg, 68% yield); **Rf** 0.30 (pet ether/ethyl acetate = 10:1); column chromatography eluent, petroleum ether/EtOAc = 10:1; **mp** 184-186 °C; single diastereomer; ^{1}**H NMR** (400 MHz, Chloroform-*d*) δ 8.13 (t, *J* = 2.3 Hz, 1H), 7.53 – 7.47 (comp, 3H), 7.45 – 7.38 (comp, 4H), 7.19 – 7.11 (comp, 2H), 3.93 – 3.85 (m, 4H), 3.74 (d, *J* = 2.4 Hz, 2H), 2.99 – 2.98 (m, 4H); ^{13}**C NMR** (101 MHz, Chloroform-*d*) δ 173.1, 170.1, 153.3, 132.4, 132.0, 131.2, 129.1, 129.0, 128.5, 127.7, 126.3, 123.1, 122.3, 119.2, 67.0, 53.3, 33.9; **HRMS** (EI, m/z) calcd for $C_{21}H_{20}N_2O_3$ $[M]^+$ 348.1474, found 348.1472.



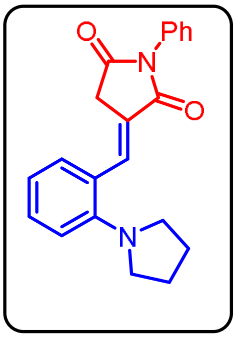
(*E*)-1-phenyl-3-(2-(4-phenylpiperazin-1-yl)benzylidene)pyrrolidine-2,5-dione (**5h**)

Yellow solid (58 mg, 45.7% yield); **Rf** 0.30 (pet ether/ethyl acetate = 10:1); column chromatography eluent, petroleum ether/EtOAc = 10:1; **mp** 162-165 °C; single diastereomer; **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 8.16 (t, *J* = 2.3 Hz, 1H), 7.53 – 7.46 (m, 3H), 7.46 – 7.37 (comp, 4H), 7.31 – 7.24 (comp, 2H), 7.18 – 7.14 (comp, 2H), 7.02 – 6.95 (comp, 2H), 6.90 – 6.87 (m, 1H), 3.75 (d, *J* = 2.4 Hz, 2H), 3.42 – 3.35 (m, 4H), 3.21 – 3.12 (m, 4H); **^{13}C NMR**(101 MHz, Chloroform-*d*) δ 173.2, 170.1, 153.4, 151.2, 132.6, 132.0, 131.2, 129.1, 129.1, 128.9, 128.5, 127.8, 126.6, 126.4, 123.0, 122.3, 119.3, 116.5, 53.0, 49.7, 34.0; **HRMS** (EI, m/z) calcd for $C_{27}H_{25}N_3O_2$ $[M]^+$ 423.1947, found 423.1945.



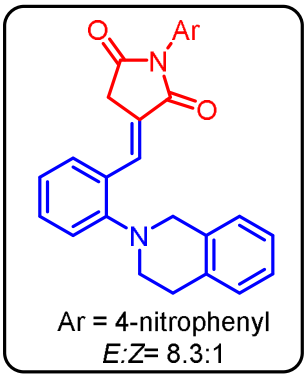
(*E*)-3-(5-bromo-2-(pyrrolidin-1-yl)benzylidene)-1-phenylpyrrolidine-2,5-dione (5i)

Yellow solid (70.5 mg, 86% yield); **Rf** 0.30 (pet ether/ethyl acetate = 10:1); column chromatography eluent, petroleum ether/EtOAc = 10:1; **mp** 144-148 °C; single diastereomer; **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 7.91 (t, *J* = 2.3 Hz, 1H), 7.51 –7.47 (comp, 2H), 7.43 – 7.37 (comp, 4H), 7.36 – 7.34 (m, 1H), 6.80 (d, *J* = 8.9 Hz, 1H), 3.47 (d, *J* = 2.4 Hz, 2H), 3.22 (t, J = 6.6 Hz, 4H), 2.00 – 1.92 (m, 4H); **^{13}C NMR** (101 MHz, Chloroform-*d*) δ 173.2, 169.8, 148.9, 134.7, 132.9, 132.0, 131.9, 129.1, 128.5, 126.4, 124.0, 122.1, 116.7, 110.3, 52.3, 33.7, 25.7; **HRMS** (EI, m/z) calcd for $C_{21}H_{19}BrN_2O_2$ $[M]^+$ 410.0630, found 410.0623.



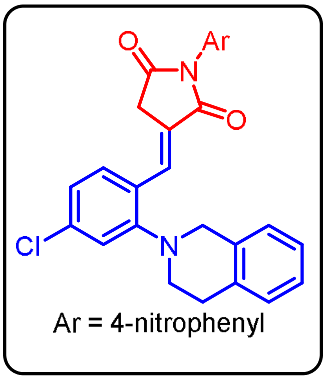
(*E*)-1-phenyl-3-(2-(pyrrolidin-1-yl)benzylidene)pyrrolidine-2,5-dione (5j)

Off white solid (50.5 mg, 76% yield); **Rf** 0.30 (pet ether/ethyl acetate = 10:1); column chromatography eluent, petroleum ether/EtOAc = 10:1; **mp** 140-142 °C; single diastereomer; **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 8.00 (t, *J* = 2.3 Hz, 1H), 7.51 – 7.46 (comp, 2H), 7.42 – 7.36 (comp, 3H), 7.34 – 7.25 (comp, 2H), 6.93 (d, *J* = 8.2 Hz, 1H), 6.90 – 6.84 (m, 1H), 3.46 (d, *J* = 2.4 Hz, 2H), 3.22 (t, *J* = 6.6 Hz, 4H), 1.99 – 1.89 (m, 4H); **^{13}C NMR** (101 MHz, Chloroform-*d*) δ 173.6, 170.2, 150.0, 136.1, 132.2, 130.5, 129.7, 129.0, 128.4, 126.4, 122.6, 120.8, 118.5, 115.2, 52.3, 33.9, 25.6; **HRMS** (EI, m/z) calcd for $C_{21}H_{20}N_2O_2$ $[M]^+$ 332.1525, found 332.1519.



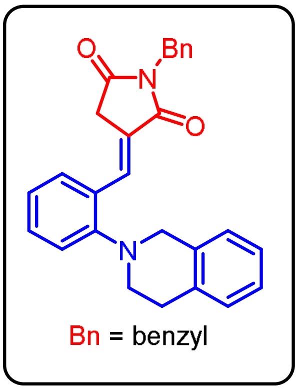
(*E*)-3-(2-(3,4-dihydroisoquinolin-2(1*H*)-yl)benzylidene)-1-(4-nitrophenyl)pyrrolidine-2,5-dione (**5k**)

Yellow solid (65.9 mg, 75% yield); **Rf** 0.30 (pet ether/ethyl acetate = 5:1); column chromatography eluent, petroleum ether/EtOAc = 5:1; **mp** 192-195 °C; single diastereomer; **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 8.36 – 8.32 (comp, 2H), 8.16 (t, *J* = 2.4 Hz, 1H), 7.75 – 7.70 (comp, 2H), 7.50 – 7.47 (m, 1H), 7.45 – 7.39 (m, 1H), 7.23 – 7.13 (comp, 5H), 7.12 – 7.08 (m, 1H), 4.28 (s, 2H), 3.79 (d, *J* = 2.4 Hz, 2H), 3.27 (t, *J* = 5.8 Hz, 2H), 3.04 (t, *J* = 5.7 Hz, 2H); **^{13}C NMR** (101 MHz, Chloroform-*d*) δ 172.5, 169.3, 153.5, 146.7, 137.7, 134.3, 134.2, 134.2, 131.5, 129.1, 129.1, 127.2, 126.7, 126.5, 126.3, 126.0, 124.2, 122.5, 121.0, 119.4, 53.5, 53.1, 34.1, 29.3; **HRMS** (EI, m/z) calcd for $C_{26}H_{21}N_3O_4$ $[M]^+$ 439.1532, found 439.1536.



(*E*)-3-(4-chloro-2-(3,4-dihydroisoquinolin-2(1*H*)-yl)benzylidene)-1-(4-nitrophenyl)pyrrolidine-2,5-dione (**5l**)

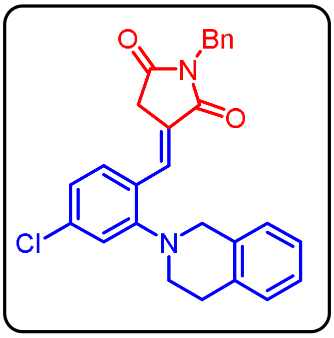
Yellow solid (58.7 mg, 62% yield); **Rf** 0.30 (pet ether/ethyl acetate = 5:1); column chromatography eluent, petroleum ether/EtOAc = 5:1; **mp** 200-201 °C; single diastereomer; **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 8.33 (d, *J* = 9.0 Hz, 2H), 8.03 (app s, 1H), 7.70 (d, *J* = 9.0 Hz, 2H), 7.39 (d, *J* = 8.3 Hz, 1H), 7.20 – 7.14 (comp, 4H), 7.12 – 7.08 (comp, 2H), 4.26 (s, 2H), 3.75 (d, *J* = 2.2 Hz, 2H), 3.26 (t, *J* = 5.7 Hz, 2H), 3.05 (t, *J* = 5.5 Hz, 2H); **^{13}C NMR** (101 MHz, Chloroform-*d*) δ 172.2, 169.1, 154.4, 146.7, 137.6, 137.3, 133.9, 133.6, 133.1, 129.9, 129.1, 126.7, 126.3, 126.1, 125.4, 124.4, 124.2, 122.5, 121.3, 119.7, 53.2, 53.0, 33.9, 29.3; **HRMS** (EI, m/z) calcd for $C_{26}H_{20}ClN_3O_4$ $[M]^+$ 473.1142, found 473.1146.



(*E*)-1-benzyl-3-(2-(3,4-dihydroisoquinolin-2(1*H*)-yl)benzylidene)pyrrolidine-2,5-dione (**5m**)

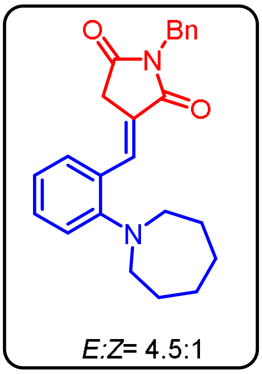
Yellow solid (61.2 mg, 75% yield); **Rf** 0.30 (pet ether/ethyl acetate = 10:1); column chromatography eluent, petroleum ether/EtOAc = 10:1; **mp** 186-188 °C; single diastereomer; **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 8.01 (app s, 1H), 7.47 (app d, *J* = 6.9 Hz, 2H), 7.44 – 7.29 (comp, 5H), 7.22 – 7.15 (comp, 4H), 7.12 – 7.08 (comp, 2H), 4.80 (s, 2H), 4.26 (s, 2H), 3.57 (d, *J* = 2.1 Hz, 2H), 3.24 (t, *J* = 5.7 Hz, 2H), 3.03 (t, *J* = 5.5 Hz, 2H); **^{13}C NMR** (101

MHz, Chloroform-*d*) δ 173.9, 170.7, 153.1, 136.0, 134.4, 134.3, 132.1, 130.8, 129.0, 129.0, 129.0, 128.6, 127.9, 127.7, 126.4, 126.3, 125.9, 122.6, 122.4, 119.3, 53.5, 52.8, 42.4, 33.9, 29.1 ; **HRMS** (EI, m/z) calcd for $C_{27}H_{24}N_2O_2$ $[M]^+$ 408.1838, found 408.1842.



(*E*)-1-benzyl-3-(4-chloro-2-(3,4-dihydroisoquinolin-2(1*H*)-yl)benzylidene)pyrrolidine-2,5-dione (**5n**)

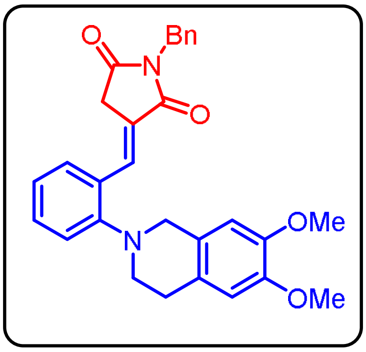
Yellow solid (50 mg, 56% yield); **Rf** 0.30 (pet ether/ethyl acetate = 10:1); column chromatography eluent, petroleum ether/EtOAc = 10:1; **mp** 167-169 °C; single diastereomer; ^{1}**H NMR** (400 MHz, Chloroform-*d*) δ 7.87 (t, J = 2.0 Hz, 1H), 7.48 – 7.41 (comp, 2H), 7.35 – 7.27 (comp, 4H), 7.21 – 7.15 (comp, 3H), 7.12 (d, *J* = 1.9 Hz, 1H), 7.10 – 7.02 (comp, 2H), 4.78 (s, 2H), 4.22 (s, 2H), 3.52 (d, *J* = 2.3 Hz, 2H), 3.22 (t, *J* = 5.8 Hz, 2H), 3.03 (t, *J* = 5.6 Hz, 2H); ^{13}**C NMR** (101 MHz, Chloroform-*d*) δ 173.6, 170.5, 154.1, 136.7, 135.9, 134.1, 133.7, 131.0, 129.9, 129.1, 129.0, 128.7, 128.0, 126.6, 126.3, 126.1, 125.9, 122.9, 122.5, 119.6, 53.3, 52.7, 42.5, 33.8, 29.2; **HRMS** (EI, m/z) calcd for $C_{27}H_{23}ClN_2O_2$ $[M]^+$ 442.1448, found 442.1446.



(*E*)-3-(2-(azepan-1-yl)benzylidene)-1-benzylpyrrolidine-2,5-dione (**5o**)

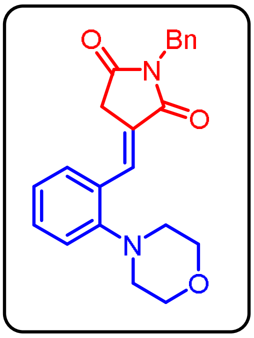
Off white solid (71.8 mg, 96% yield); **Rf** 0.30 (pet ether/ethyl acetate = 10:1); column chromatography eluent, petroleum ether/EtOAc = 10:1; **mp** 140-142 °C; single diastereomer; ^{1}**H NMR** (400 MHz, Chloroform-*d*) δ 7.98 (s, 1H), 7.46 – 7.42 (comp, 3H), 7.38 – 7.22

(comp, 7H), 7.12 (d, *J* = 8.0 Hz, 1H), 6.96 (t, *J* = 7.3 Hz, 1H), 4.78 (s, 2H), 3.49 (s, 3H), 3.26 – 3.07 (m, 5H), 1.86 – 1.64 (m, 10H); **^{13}C NMR** (101 MHz, Chloroform-*d*) δ 174.1, 170.9, 155.8, 136.1, 133.7, 130.5, 128.9, 128.8, 128.6, 127.8, 127.1, 121.4, 121.1, 120.1, 56.3, 42.4, 33.8, 29.1, 27.2; **HRMS** (EI, m/z) calcd for $C_{24}H_{26}N_2O_2$ $[M]^+$ 374.1994, found 374.1993.



(*E*)-1-benzyl-3-(2-(6,7-dimethoxy-3,4-dihydroisoquinolin-2(1*H*)-yl)benzylidene)pyrrolidine-2,5-dione (**5p**)

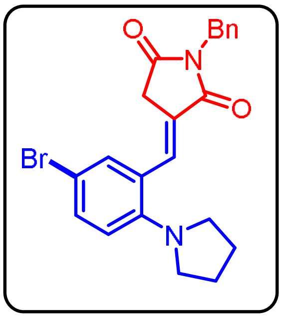
Yellow solid (91 mg, 97% yield); **Rf** 0.30 (pet ether/ethyl acetate = 5:1); column chromatography eluent, petroleum ether/EtOAc = 5:1; **mp** 175-177 °C; single diastereomer; **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 7.99 (t, *J* = 2.2 Hz, 1H), 7.71 – 7.64 (m, 1H), 7.49 – 7.44 (comp, 2H), 7.43 – 7.38 (m, 1H), 7.37 – 7.28 (comp, 3H), 7.18 – 7.13 (m, 1H), 7.10 – 7.06 (m, 1H), 6.66 (s, 1H), 6.58 (s, 1H), 4.79 (s, 2H), 4.18 (s, 2H), 3.87 (s, 3H), 3.85 (s, 3H), 3.57 (d, *J* = 2.3 Hz, 2H), 3.22 (t, *J* = 5.8 Hz, 2H), 2.92 (t, *J* = 5.6 Hz, 2H); **^{13}C NMR** (101 MHz, Chloroform-*d*) δ 174.0, 170.8, 153.2, 147.7, 147.4, 136.0, 132.2, 132.0, 130.8, 129.0, 128.6, 127.9, 127.6, 126.4, 126.2, 122.5, 122.3, 119.3, 111.7, 109.1, 56.0, 55.9, 53.1, 52.8, 33.9, 28.7; **HRMS** (EI, m/z) calcd for $C_{29}H_{28}N_2O_4$ $[M]^+$ 468.2049, found 468.2045.



(*E*)-1-benzyl-3-(2-morpholinobenzylidene)pyrrolidine-2,5-dione (**5q**)

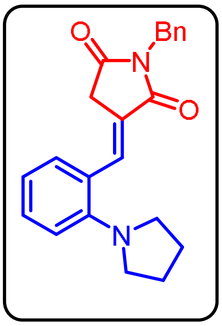
Off white solid (67.4 mg, 93% yield); **Rf** 0.30 (pet ether/ethyl acetate = 10:1); column chromatography eluent, petroleum ether/EtOAc = 10:1; **mp** 140-142 °C; single diastereomer;

^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.00 (t, *J* = 2.3 Hz, 1H), 7.48 – 7.43 (comp, 2H), 7.41 – 7.25 (comp, 5H), 7.12 – 7.08 (m, 2H), 4.78 (s, 2H), 3.92 – 3.83 (m, 4H), 3.54 (d, *J* = 2.4 Hz, 2H), 3.00 – 2.90 (m, 4H); **^{13}C NMR** (101 MHz, Chloroform-*d*) δ 173.8, 170.7, 153.2, 135.9, 131.5, 131.0, 129.0, 128.9, 128.6, 127.9, 127.8, 123.1, 122.8, 119.2, 67.1, 53.3, 42.5, 33.8; **HRMS** (EI, m/z) calcd for $C_{22}H_{22}N_2O_3$ $[M]^+$ 362.1630, found 362.1633.



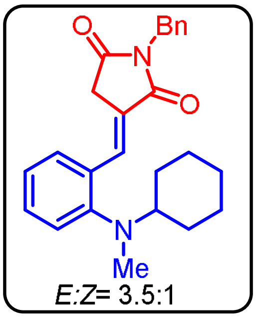
(*E*)-1-benzyl-3-(5-bromo-2-(pyrrolidin-1-yl)benzylidene)pyrrolidine-2,5-dione (5r)

Yellow solid (27.14 mg, 32% yield); **Rf** 0.30 (pet ether/ethyl acetate = 10:1); column chromatography eluent, petroleum ether/EtOAc = 10:1; **mp** 122-124 °C; single diastereomer; **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 7.76 (t, *J* = 2.3 Hz, 1H), 7.43 (dd, *J* = 7.0, 2.5 Hz, 2H), 7.30 (comp, 7H), 6.78 – 6.73 (m, 1H), 4.76 (s, 2H), 4.66 (s, 1H), 3.26 (d, *J* = 2.4 Hz, 2H), 3.19 – 3.11 (m, 4H), 1.96 – 1.86 (m, 4H); **^{13}C NMR** (101 MHz, Chloroform-*d*) δ 173.9, 170.5, 148.8, 136.0, 134.3, 133.8, 132.9, 131.9, 129.0, 128.8, 128.5, 128.0, 122.7, 116.9, 52.4, 42.6, 33.7, 25.7; **HRMS** (EI, m/z) calcd for $C_{22}H_{21}BrN_2O_2$ $[M]^+$ 424.0786, found 424.0788.



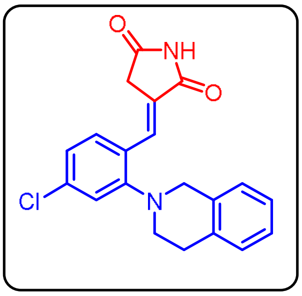
(*E*)-1-benzyl-3-(2-(pyrrolidin-1-yl)benzylidene)pyrrolidine-2,5-dione (5s)

Yellow solid (67.2 mg, 97% yield); **Rf** 0.30 (pet ether/ethyl acetate = 10:1); column chromatography eluent, petroleum ether/EtOAc = 10:1; **mp** 114-116 °C; single diastereomer; **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 7.87 (t, *J*= 2.3 Hz, 1H), 7.47 – 7.42 (comp, 2H), 7.34 – 7.26 (comp, 3H), 7.24 (d, *J* = 7.5 Hz, 2H), 6.89 (d, *J* = 8.6 Hz, 1H), 6.83 (t, *J* = 7.4 Hz, 1H), 4.76 (s, 2H), 3.28 (d, *J* = 2.3 Hz, 2H), 3.17 (t, *J* = 6.5 Hz, 4H), 1.96 – 1.86 (m, 4H); **^{13}C NMR** (101 MHz, Chloroform-*d*) δ 174.2, 170.9, 150.0, 136.1, 135.3, 130.3, 129.7, 129.0, 128.6, 127.9, 122.7, 121.3, 118.5, 115.2, 52.2, 42.4, 33.8, 25.6; **HRMS** (EI, m/z) calcd for $C_{22}H_{22}N_2O_2$ $[M]^+$ 346.1681, found 346.1680.



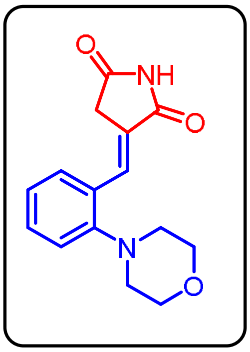
(*E*)-1-benzyl-3-(2-(cyclohexyl(methyl)amino)benzylidene)pyrrolidine-2,5-dione (**5t**)

Off white solid (74.5 mg, 96% yield); **Rf** 0.30 (pet ether/ethyl acetate = 10:1); column chromatography eluent, petroleum ether/EtOAc = 10:1; **mp** 178-180 °C; single diastereomer; **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 7.94 (t, *J* = 2.2 Hz, 1H), 7.43 (d, *J* = 6.9 Hz, 2H), 7.37 – 7.25 (comp, 5H), 7.09 (d, *J* = 8.1 Hz, 1H), 7.02 – 6.98 (m, 1H), 4.79 (s, 2H), 3.53 (d, *J* = 2.3 Hz, 2H), 2.70 (s, 3H), 2.68 (dd, *J* = 8.0, 2.8 Hz, 1H), 1.82 – 1.58 (m, 6H), 1.56 – 1.38 (m, 4H); **^{13}C NMR** (101 MHz, Chloroform-*d*) δ 174.1, 170.9, 154.3, 136.1, 133.1, 130.2, 128.9, 128.8, 128.6, 128.6, 128.2, 127.8, 121.6, 121.1, 65.1, 42.3, 34.1, 33.8, 29.5, 25.9, 25.9; **HRMS** (EI, m/z) calcd for $C_{25}H_{28}N_2O_2$ $[M]^+$ 388.2151, found 388.2155.



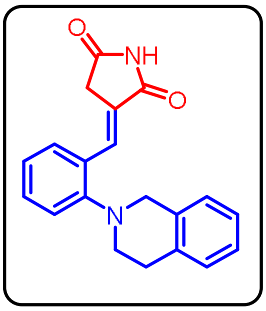
(*E*)-3-(4-chloro-2-(3,4-dihydroisoquinolin-2(1H)-yl)benzylidene)pyrrolidine-2,5-dione (5u)

Off white solid (30.2 mg, 43% yield); **Rf** 0.30 (pet ether/ethyl acetate = 5:1); column chromatography eluent, petroleum ether/EtOAc = 5:1; **mp** 156-159 °C; single diastereomer; **^{1}H NMR** (400 MHz, DMSO-*d*$_6$) δ 11.39 (s, 1H), 7.55 (d, *J* = 8.4 Hz, 1H), 7.45 (s, 1H), 7.24 – 7.19 (m, 1H), 7.18 – 7.09 (comp, 5H), 4.18 (s, 2H), 3.67 – 3.52 (m, 2H), 3.14 (t, *J* = 5.5 Hz, 2H), 3.00 – 2.82 (m, 2H); **^{13}C NMR** (101 MHz, DMSO-*d*$_6$) δ 175.8, 172.0, 153.7, 134.8, 134.2, 133.8, 130.5, 128.7, 127.3, 126.9, 126.5, 126.3, 126.2, 125.8, 122.1, 119.1, 52.7, 51.9, 34.3, 28.8; **HRMS** (EI, m/z) calcd for $C_{20}H_{17}ClN_2O_2$ $[M]^+$ 352.0979, found 352.0977.



(*E*)-3-(2-morpholinobenzylidene)pyrrolidine-2,5-dione (5v)

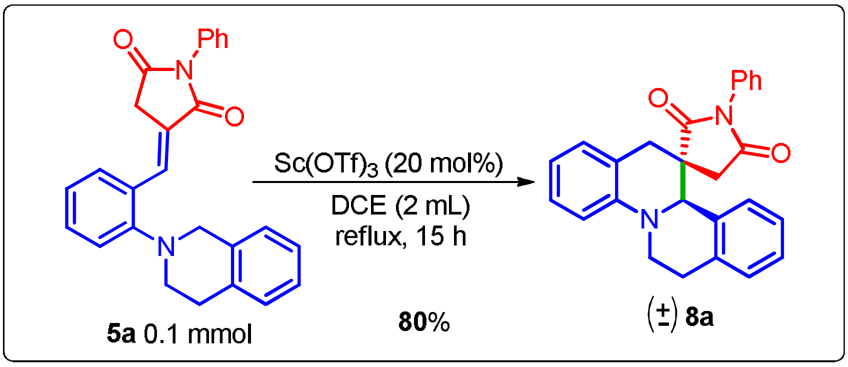
Off white solid (51.2 mg, 94% yield); **Rf** 0.30 (pet ether/ethyl acetate = 5:1); column chromatography eluent, petroleum ether/EtOAc = 5:1; **mp** 117-120 °C; single diastereomer; **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 7.88 – 7.80 (m, 1H), 7.38 – 7.24 (m, 2H), 7.03 (dd, J = 12.8, 7.8 Hz, 2H), 3.86 – 3.74 (m, 4H), 3.54 – 3.41 (m, 2H), 2.95 – 2.80 (m, 4H); **^{13}C NMR** (101 MHz, Chloroform-*d*) δ 175.7, 172.1, 152.9, 131.5, 131.0, 128.7, 127.5, 124.0, 122.9, 118.9, 66.9, 53.0, 34.5; **HRMS** (EI, m/z) calcd for $C_{15}H_{16}N_2O_3$ $[M]^+$ 272.1161, found 272.1166.



(*E*)-3-(2-(3,4-dihydroisoquinolin-2(1*H*)-yl)benzylidene)pyrrolidine-2,5-dione (5w)

Off white solid (44.5 mg, 70% yield); **Rf** 0.30 (pet ether/ethyl acetate = 5:1); column chromatography eluent, petroleum ether/EtOAc = 5:1; **mp** 152-155 °C; single diastereomer; **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 8.88 (s, 1H), 7.97 (t, *J* = 2.2 Hz, 1H), 7.66 – 7.60 (comp, 2H), 7.56 – 7.50 (comp, 2H), 7.41 (t, *J* = 8.0 Hz, 1H), 7.20 – 7.16 (comp, 2H), 7.13 – 7.07 (m, 1H), 4.26 (s, 2H), 3.59 (d, *J* = 2.4 Hz, 2H), 3.24 (t, *J* = 5.8 Hz, 2H), 3.06 – 2.98 (m, 2H); **^{13}C NMR** (101 MHz, Chloroform-*d*) δ 174.5, 171.2, 153.2, 134.3, 133.4, 133.3, 132.8, 132.7, 131.0, 129.3, 129.0, 126.4, 125.9, 123.5, 122.4, 119.3, 53.5, 52.8, 34.9, 29.1; **HRMS** (EI, m/z) calcd for $C_{20}H_{18}N_2O_2$ $[M]^+$ 318.1368, found 318.1366.

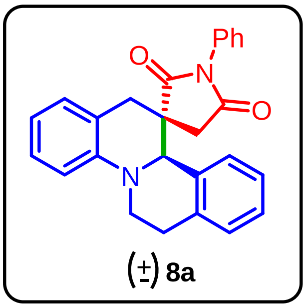
3.5.17General Procedure for the Synthesis of Product 8a (2,7-Diazaspiro[4.5]decanes)



(Miligram scale reaction) To an oven-dried 10 mL round-bottom flask attached with a condenser under nitrogen, (*E*)-3-(2-(3,4-dihydroisoquinolin-2(1*H*)-yl)benzylidene)-1-phenylpyrrolidine-2,5-dione (**5a**) (0.1 mmol) and Lewis acid Sc(OTf)$_3$ (20 mol%) were taken, dissolved in anhydrous DCE (2 mL) and the bath temperature was slowly increased to the refluxed condition. The reaction mixture was kept under the same temperature until the all olefin was consumed completely as monitored by TLC. The solvent was removed from the organic layer by workup with EtOAc (2 x10 mL) and cold water; brine wash was needed. Then the organic layer passed through anhydrous Na$_2$SO$_4$ and concentrated under vacuo. Finally, it was purified by column chromatography on silica gel (230-400 mesh) using petroleum ether/ethyl acetate (20:1) as eluent to obtain the desired spiro-heterocyclic product (3'R*,11bR*)-1'-phenyl-6,7,11b,13-tetrahydrospiro[isoquinolino[2,1-a]quinoline-12,3'-pyrrolidine]-2',5'-dione (**8a**) in 80% (31.5 mg) yield.

(Gram scale reaction) To an oven-dried 100 mL round-bottom flask attached with a condenser under nitrogen, (*E*)-3-(2-(3,4-dihydroisoquinolin-2(1*H*)-yl)benzylidene)-1-phenylpyrrolidine-2,5-dione (**5a**) (1 g, 2.5 mmol) and Lewis acid Sc(OTf)$_3$ (20 mol%) were taken, dissolved in anhydrous DCE (2 mL) and the bath temperature was slowly increased to the refluxed condition. The reaction mixture was kept under the same temperature until the all olefin was consumed completely as monitored by TLC. The solvent was removed from the organic layer by workup with EtOAc (2 x100 mL) and cold water; brine wash was needed. Then the organic layer passed through anhydrous Na$_2$SO$_4$ and concentrated under vacuo. Finally, it was purified by column chromatography on silica gel (230-400 mesh) using petroleum ether/ethyl acetate (20:1) as eluent to obtain the desired spiro-heterocyclic product (3'R*,11bR*)-1'-phenyl-6,7,11b,13-tetrahydrospiro[isoquinolino[2,1-a]quinoline-12,3'-pyrrolidine]-2',5'-dione (**8a**) in 71% (700 mg) yield.

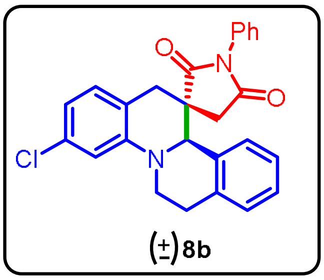
3.5.18Characterization of Substrates (2,7-Diazaspiro[4.5]decanes) 8a-8w



(±) **8a**

(3'R*,11bR*)-1'-phenyl-6,7,11b,13-tetrahydrospiro[isoquinolino[2,1-a]quinoline-12,3'-pyrrolidine]-2',5'-dione (**8a**)

Colourless solid (31.5 mg, 80% yield); **Rf** 0.30 (pet ether/ethyl acetate = 20:1); column chromatography eluent, petroleum ether/EtOAc = 20:1; **mp** 156-158 °C; single diastereomer; **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 7.46 – 7.41 (comp, 2H), 7.40 – 7.35 (m, 1H), 7.31 (d, *J* = 7.8 Hz, 1H), 7.26 – 7.10 (comp, 5H), 7.08 – 7.03 (comp, 2H), 6.85 (d, *J* = 8.3 Hz, 1H), 6.79 (t, *J* = 7.3 Hz, 1H), 4.93 (s, 1H), 4.15 – 4.00 (m, 1H), 3.88 (d, *J* = 16.5 Hz, 1H), 3.22 – 3.08 (m, 2H), 2.92 (d, *J* = 16.6 Hz, 1H), 2.88 – 2.82 (m, 1H), 2.70 (d, *J* = 18.9 Hz, 1H), 2.44 (d, *J* = 18.9 Hz, 1H); **^{13}C NMR** (101 MHz, Chloroform-*d*) δ 180.3, 174.7, 145.0, 136.5, 132.5, 131.7, 129.7, 129.4, 129.1, 128.7, 127.9, 127.6, 127.6, 126.6, 126.6, 119.2, 117.7, 111.6, 61.0, 49.2, 41.8, 38.7, 37.3, 30.5; **HRMS** (ESI, m/z) calcd for $C_{26}H_{23}N_2O_2$ $[M+H]^+$ 395.1760, found 395.1761.



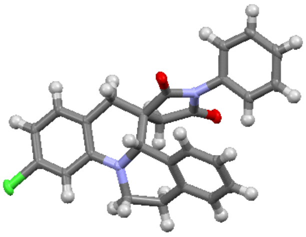
(±)**8b**

(3'R*,11bR*)-3-chloro-1'-phenyl-6,7,11b,13-tetrahydrospiro[isoquinolino[2,1-a]quinoline-12,3'-pyrrolidine]-2',5'-dione (**8b**)

Colourless solid (39.4 mg, 92% yield); **Rf** 0.30 (pet ether/ethyl acetate = 20:1); column chromatography eluent, petroleum ether/EtOAc = 20:1; **mp** 232-237 °C; single diastereomer; **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 7.47 – 7.41 (comp, 2H), 7.40 – 7.35 (m, 1H), 7.30 (d, *J* = 7.8 Hz, 1H), 7.28 – 7.20 (comp, 2H), 7.19 – 7.13 (m, 1H), 7.07 – 7.00 (comp, 3H), 6.82 (d, *J* = 1.8 Hz, 1H), 6.74 (dd, *J* = 8.0, 1.9 Hz, 1H), 4.93 (s, 1H), 4.05 – 3.96 (m, 1H), 3.80 (d, *J* =

16.5 Hz, 1H), 3.21 – 3.06 (m, 2H), 2.91 – 2.81 (m, 2H), 2.63 (d, *J* = 18.8 Hz, 1H), 2.39 (d, *J* = 18.8 Hz, 1H); **^{13}C NMR** (101 MHz, Chloroform-*d*) δ 180.0, 174.4, 145.8, 136.2, 133.3, 132.0, 131.6, 130.6, 129.5, 129.1, 129.1, 128.7, 127.8, 127.8, 126.7, 126.5, 117.5, 111.7, 60.9, 48.7, 42.0, 38.2, 37.0, 30.3; **HRMS** (ESI, m/z) calcd for $C_{26}H_{22}ClN_2O_2$ $[M+H]^+$ 429.1370, found 429.1371.

Table 3.5.19: Crystal Data and Structure of 8b

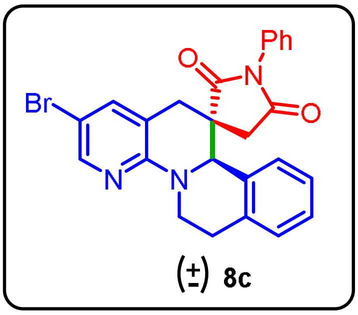


Empirical formula	$C_{26}H_{21}ClN_2O_2$
Formula weight	428.90
Temperature/K	121.00
Crystal system	orthorhombic
Space group	Pbca
a/Å	12.2220(10)
b/Å	7.9743(6)
c/Å	41.078(3)
α/°	90
β/°	90
γ/°	90
Volume/Å^3	4003.5(5)
Z	8
ρ_{calc}g/cm^3	1.423
μ/mm^{-1}	1.907
F(000)	1792.0
Crystal size/mm^3	0.25 × 0.18 × 0.15
Radiation	Cu Kα (λ = 1.54178)
2Θ range for data collection/°	11.254 to 132.682
Index ranges	$-14 \leq h \leq 14$, $-9 \leq k \leq 8$, $-48 \leq l \leq 48$
Reflections collected	47096
Independent reflections	3478 [R_{int} = 0.0667, R_{sigma} = 0.0305]
Data/restraints/parameters	3478/0/281
Goodness-of-fit on F^2	1.064

Final R indexes [I>=2σ (I)] $R_1 = 0.0508$, $wR_2 = 0.1298$

Final R indexes [all data] $R_1 = 0.0532$, $wR_2 = 0.1318$

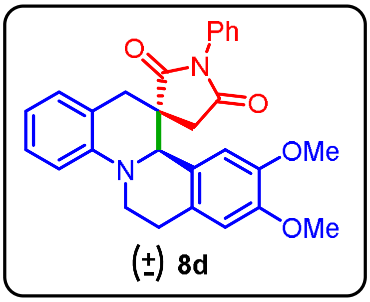
Largest diff. peak/hole / e $Å^{-3}$ 0.23/-0.41



(±) **8c**

(3'R*,11bR*)-2-bromo-1'-phenyl-6,7,11b,13-tetrahydrospiro[isoquinolino[2,1-a][1,8]naphthyridine-12,3'-pyrrolidine]-2',5'-dione (**8c**)

Off white solid (35.4 mg, 75% yield); **Rf** 0.30 (pet ether/ethyl acetate = 20:1); column chromatography eluent, petroleum ether/EtOAc = 20:1 to 15:1; **mp** 232-234 °C; single diastereomer; **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 8.17 – 8.14 (m, 1H), 7.49 – 7.43 (comp, 2H), 7.43 – 7.37 (comp, 2H), 7.32 (d, *J* = 7.8 Hz, 1H), 7.26 (td, *J* = 4.0, 2.0 Hz, 2H), 7.20 – 7.15 (m, 1H), 7.09 (dd, *J* = 7.0, 1.5 Hz, 2H), 5.30 – 5.24 (m, 1H), 5.16 (s, 1H), 3.79 – 3.70 (d, J = 16.4 Hz, 1H), 3.01 – 2.88 (m, 2H), 2.86 – 2.78 (m, 2H), 2.51 (d, *J* = 18.7 Hz, 1H), 2.30 (d, *J* = 18.7 Hz, 1H); **^{13}C NMR** (101 MHz, Chloroform-*d*) δ 179.8, 173.8, 152.7, 147.0, 138.9, 137.8, 131.8, 131.5, 129.9, 129.2, 128.9, 127.9, 127.5, 126.7, 126.4, 115.0, 107.1, 60.8, 47.2, 39.5, 37.2, 35.9, 30.5; **HRMS** (ESI, m/z) calcd for $C_{25}H_{21}BrN_3O_2$ $[M+H]^+$ 476.0797, found 476.0800.

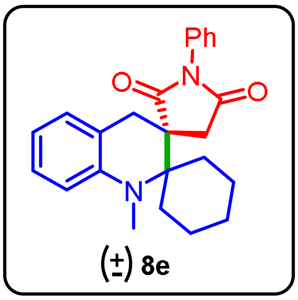


(±) **8d**

(3'R*,11bR*)-9,10-dimethoxy-1'-phenyl-6,7,11b,13-tetrahydrospiro[isoquinolino[2,1-a]quinoline-12,3'-pyrrolidine]-2',5'-dione (**8d**)

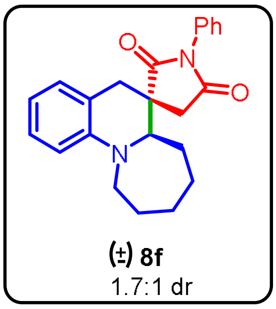
Yellow solid (29.5 mg, 65% yield); **Rf** 0.30 (pet ether/ethyl acetate = 10:1); column chromatography eluent, petroleum ether/EtOAc = 10:1; **mp** 159-161 °C; single diastereomer; **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 7.47 – 7.41 (comp, 2H), 7.41 – 7.35 (m, 1H), 7.21 (t, *J*

= 7.7 Hz, 1H), 7.14 (d, *J* = 7.3 Hz, 1H), 7.02 – 6.96 (comp, 2H), 6.85 (d, *J* = 8.3 Hz, 1H), 6.79 (t, *J* = 7.3 Hz, 1H), 6.73 (s, 1H), 6.68 (s, 1H), 4.80 (s, 1H), 4.09 – 4.00 (m, 1H), 3.91 (m, 4H), 3.42 (s, 3H), 3.18 – 3.03 (m, 2H), 2.94 (d, *J* = 16.6 Hz, 1H), 2.78 (d, *J* = 4.2 Hz, 1H), 2.74 (d, *J* = 9.7 Hz, 1H), 2.44 (d, *J* = 18.9 Hz, 1H); **^{13}C NMR** (101 MHz, Chloroform-*d*) δ 180.7, 174.9, 148.2, 147.5, 145.1, 131.6, 129.8, 129.2, 128.7, 128.5, 127.5, 126.6, 123.8, 119.2, 117.7, 111.7, 111.6, 110.4, 60.7, 55.8, 55.4, 49.4, 41.7, 38.5, 37.3, 30.0; **HRMS** (EI, m/z) calcd for $C_{28}H_{26}N_2O_4$ $[M+H]^+$ 454.1893, found 454.1876.



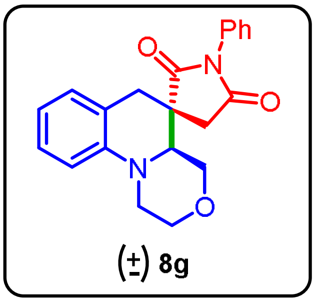
(R*)-1'-methyl-1''-phenyl-1',4'-dihydrodispiro[cyclohexane-1,2'-quinoline-3',3''-pyrrolidine]-2'',5''-dione (**8e**)

Off white solid (30 mg, 80% yield); **Rf** 0.30 (pet ether/ethyl acetate = 20:1); column chromatography eluent, petroleum ether/EtOAc = 20:1; **mp** 182-184 °C; single diastereomer; **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 7.50 (t, *J* = 7.6 Hz, 2H), 7.41 (t, *J* = 7.4 Hz, 1H), 7.34 – 7.29 (comp, 2H), 7.20 (t, *J* = 7.4 Hz, 1H), 7.06 (d, *J* = 7.3 Hz, 1H), 6.83 (d, *J* = 8.2 Hz, 1H), 6.76 (t, *J* = 7.3 Hz, 1H), 3.59 (d, *J* = 16.7 Hz, 1H), 3.28 (s, 3H), 2.77 (d, *J* = 19.1 Hz, 1H), 2.69 (d, *J* = 16.7 Hz, 1H), 2.33 (d, *J* = 19.1 Hz, 1H), 2.12 (d, *J* = 13.9 Hz, 1H), 1.96 (td, *J* = 13.0, 3.5 Hz, 1H), 1.86 – 1.70 (m, 4H), 1.51 (dd, *J* = 13.9, 5.3 Hz, 2H), 1.30 – 1.14 (m, 2H); **^{13}C NMR** (101 MHz, Chloroform-*d*) δ 180.0, 175.1, 145.7, 132.0, 129.4, 129.2, 128.6, 127.5, 126.4, 119.1, 117.3, 115.1, 60.5, 49.5, 38.7, 37.6, 35.5, 30.3, 29.7, 25.0, 23.5, 22.2; **HRMS** (ESI, m/z) calcd for $C_{24}H_{27}N_2O_2$ $[M+H]^+$ 375.2073, found 375.1740.



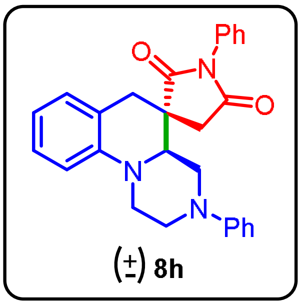
(3'R*,6aR*)-1'-phenyl-6a,7,8,9,10,11-hexahydro-5H-spiro[azepino[1,2-a]quinoline-6,3'-pyrrolidine]-2',5'-dione (**8f**)

Off white solid (32.8 mg, 91% yield); **Rf** 0.30 (pet ether/ethyl acetate = 20:1); column chromatography eluent, petroleum ether/EtOAc = 20:1; **mp** 135-137 °C; diastereomeric ratio 1.7:1; inseparable diastereomeric mixture, **^{1}H NMR** of mixture (400 MHz, Chloroform-*d*) δ 7.48 (t, *J* = 7.5 Hz, 4H), 7.43 – 7.36 (m, 2H), 7.32 (d, *J* = 7.4 Hz, 3H), 7.14 (t, *J* = 7.5 Hz, 1H), 7.03 (s, 1H), 6.78 – 6.62 (m, 3H), 4.06 (dd, *J* = 14.8, 5.2 Hz, 1H), 3.71 – 3.44 (comp, 4H), 3.28 – 3.20 (m, 1H), 3.15 (ddd, *J* = 15.5, 10.8, 5.5 Hz, 1H), 2.88 – 2.74 (m, 2H), 2.60 (dd, *J* = 29.4, 17.6 Hz, 2H), 2.45 (d, *J* = 18.9 Hz, 1H), 2.20 – 2.06 (m, 2H), 1.99 – 1.85 (m, 2H), 1.83 – 1.75 (m, 1H), 1.73 – 1.55 (m, 7H), 1.54 – 1.38 (m, 3H); **^{13}C NMR** of major diastereomer (101 MHz, Chloroform-*d*) δ 179.0, 174.7, 142.5, 131.9, 130.0, 129.1, 128.5, 128.0, 126.4, 117.0, 116.1, 110.5, 64.7, 50.4, 44.7, 41.8, 31.5, 28.7, 27.2, 26.7, 25.9; **HRMS** (ESI, m/z) calcd for $C_{23}H_{25}N_2O_2$ $[M+H]^+$ 361.1916, found 361.1993.



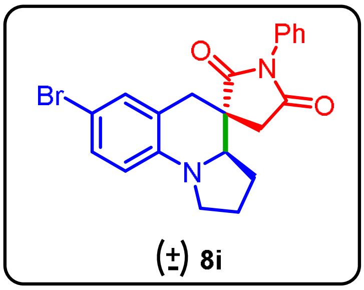
(3'R*,4aS*)-1'-phenyl-2,4,4a,6-tetrahydro-1H-spiro[[1,4]oxazino[4,3-a]quinoline-5,3'-pyrrolidine]-2',5'-dione (**8g**)

Off white solid (26.1 mg, 75% yield); **Rf** 0.30 (pet ether/ethyl acetate = 20:1); column chromatography eluent, petroleum ether/EtOAc = 20:1; **mp** 159-160 °C; single diastereomer; **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 7.50 (t, *J* = 7.5 Hz, 2H), 7.45 – 7.39 (m, 1H), 7.33 – 7.28 (comp, 2H), 7.20 (t, *J* = 7.7 Hz, 1H), 7.05 (d, *J* = 7.4 Hz, 1H), 6.89 (d, *J* = 8.3 Hz, 1H), 6.83 (t, *J* = 7.3 Hz, 1H), 4.11 – 4.04 (m, 1H), 3.94 (dd, *J* = 10.4, 3.0 Hz, 1H), 3.71 (td, *J* = 11.2, 5.8 Hz, 2H), 3.59 (d, *J* = 15.7 Hz, 1H), 3.54 (dd, *J* = 10.8, 3.3 Hz, 1H), 3.33 (t, *J* = 10.7 Hz, 1H), 3.13 (d, *J* = 19.2 Hz, 1H), 3.00 (td, *J* = 12.4, 11.9, 3.7 Hz, 1H), 2.76 (d, *J* = 15.8 Hz, 1H), 2.54 (d, *J* = 19.2 Hz, 1H); **^{13}C NMR** (101 MHz, Chloroform-*d*) δ 178.4, 174.5, 145.0, 131.5, 130.3, 129.3, 128.8, 128.0, 126.3, 119.9, 119.5, 113.2, 67.0, 66.5, 57.6, 46.6, 43.8, 38.7, 36.6; **HRMS** (ESI, m/z) calcd for $C_{21}H_{21}N_2O_3$ $[M+H]^+$ 349.1552, found 349.1554.



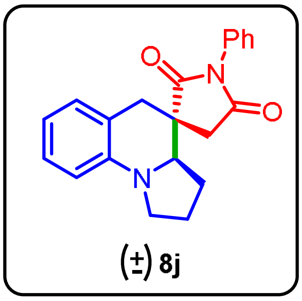
(3'R*,4aS*)-1',3-diphenyl-1,2,3,4,4a,6-hexahydrospiro[pyrazino[1,2-a]quinoline-5,3'-pyrrolidine]-2',5'-dione (**8h**)

Off white solid (22.9 mg, 54% yield); **Rf** 0.30 (pet ether/ethyl acetate = 15:1); column chromatography eluent, petroleum ether/EtOAc = 20:1; **mp** 172-174 °C; single diastereomer; **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 7.50 (td, *J* = 6.9, 1.6 Hz, 2H), 7.46 – 7.40 (m, 1H), 7.35 – 7.24 (comp, 4H), 7.20 (app t, *J* = 7.7 Hz, 1H), 7.05 (d, *J* = 7.4 Hz, 1H), 7.00 – 6.87 (comp, 4H), 6.85 – 6.79 (m, 1H), 4.04 – 3.96 (m, 1H), 3.77 – 3.57 (m, 4H), 3.15 (d, *J* = 19.2 Hz, 1H), 3.08 (dd, *J* = 11.4, 2.9 Hz, 1H), 3.00 (td, *J* = 11.7, 2.9 Hz, 1H), 2.78 (d, *J* = 15.7 Hz, 1H), 2.65 (t, *J* = 11.7 Hz, 1H), 2.55 (d, *J* = 19.2 Hz, 1H); **^{13}C NMR** (101 MHz, Chloroform-*d*) δ 178.9, 174.7, 150.5, 145.2, 131.6, 130.3, 129.4, 129.3, 128.8, 128.0, 126.3, 120.9, 120.1, 119.4, 116.9, 113.8, 57.8, 50.6, 49.4, 47.0, 44.9, 38.9, 36.6; **HRMS** (ESI, m/z) calcd for $C_{27}H_{25}N_3O_2$ $[M]^+$ 423.1947, found 423.1944.



(3R*,3a'R*)-7'-bromo-1-phenyl-2',3',3a',5'-tetrahydro-1'H-spiro[pyrrolidine-3,4'-pyrrolo[1,2-a]quinoline]-2,5-dione (**8i**)

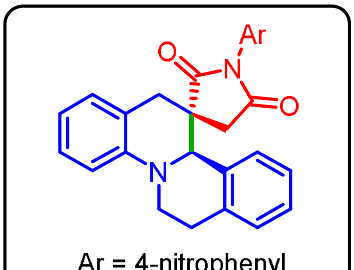
Yellow solid (22.6 mg, 55% yield); **Rf** 0.30 (pet ether/ethyl acetate = 20:1); column chromatography eluent, petroleum ether/EtOAc = 20:1; **mp** 156-158 °C; single diastereomer; **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 7.51 – 7.45 (m, 2H), 7.43 – 7.38 (m, 1H), 7.29 (d, *J* = 7.4 Hz, 2H), 7.24 – 7.20 (m, 1H), 7.17 (s, 1H), 6.37 (d, *J* = 8.6 Hz, 1H), 3.80 (dd, *J* = 10.2, 4.9 Hz, 1H), 3.50 – 3.39 (m, 2H), 3.30 (q, *J* = 8.3 Hz, 1H), 2.76 (d, *J* = 15.7 Hz, 1H), 2.52 (d, *J* = 18.9 Hz, 1H), 2.34 (d, *J* = 18.9 Hz, 1H), 2.19 – 2.11 (m, 1H), 2.06 (dt, *J* = 14.4, 7.1 Hz, 2H), 1.53 – 1.45 (m, 1H); **^{13}C NMR** (101 MHz, Chloroform-*d*) δ 179.4, 174.5, 142.1, 131.9, 130.7, 129.2, 129.1, 128.8, 126.3, 119.9, 112.2, 107.8, 62.0, 46.9, 42.8, 37.9, 35.2, 26.9, 23.2; **HRMS** (ESI, m/z) calcd for $C_{21}H_{20}BrN_2O_2$ [M+H]$^+$ 411.0708, found 411.0690.



(±) 8j

(3R*,3a'R*)-1-phenyl-2',3',3a',5'-tetrahydro-1'H-spiro[pyrrolidine-3,4'-pyrrolo[1,2-a]quinoline]-2,5-dione (**8j**)

Yellow solid (15.9 mg, 48% yield); **Rf** 0.30 (pet ether/ethyl acetate = 20:1); column chromatography eluent, petroleum ether/EtOAc = 20:1; **mp** 146-148 °C; single diastereomer; **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 7.49 (td, *J* = 6.9, 1.5 Hz, 2H), 7.45 – 7.38 (m, 1H), 7.34 – 7.28 (m, 2H), 7.16 (t, *J* = 7.7 Hz, 1H), 7.08 (d, *J* = 7.4 Hz, 1H), 6.66 (t, *J* = 7.4 Hz, 1H), 6.52 (d, *J* = 8.0 Hz, 1H), 3.83 (dd, *J* = 10.3, 5.0 Hz, 1H), 3.55 – 3.43 (m, 2H), 3.36 (q, *J* = 8.6 Hz, 1H), 2.82 (d, *J* = 15.6 Hz, 1H), 2.57 (d, *J* = 19.0 Hz, 1H), 2.38 (d, *J* = 19.0 Hz, 1H), 2.17 (dtd, *J* = 11.1, 7.9, 3.9 Hz, 1H), 2.11 – 1.99 (m, 2H), 1.54 – 1.45 (m, 1H).; **^{13}C NMR** (101 MHz, Chloroform-*d*) δ 179.8, 174.9, 143.1, 131.8, 129.5, 129.2, 128.7, 128.0, 126.4, 117.8, 116.1, 110.7, 61.9, 46.8, 43.1, 38.2, 35.4, 26.9, 232; **HRMS** (EI, m/z) calcd for $C_{21}H_{20}N_2O_2$ [M]$^+$ 332.1525, found 332.1538.

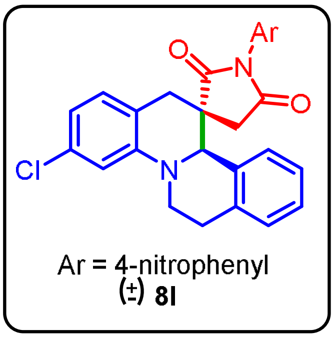


Ar = 4-nitrophenyl
(±) 8k

(3'R*,11bR*)-1'-(4-nitrophenyl)-6,7,11b,13-tetrahydrospiro[isoquinolino[2,1-a]quinoline-12,3'-pyrrolidine]-2',5'-dione (**8k**)

Off white solid (25 mg, 57% yield); **Rf** 0.30 (pet ether/ethyl acetate = 10:1); column chromatography eluent, petroleum ether/EtOAc = 10:1; **mp** 227-229 °C; single diastereomer;

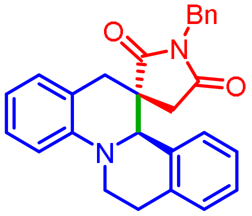
^{1}**H NMR** (400 MHz, Chloroform-*d*) δ 8.34 – 8.26 (comp, 2H), 7.36 – 7.29 (comp, 2H), 7.27 – 7.20 (comp, 4H), 7.15 (d, *J* = 7.3 Hz, 1H), 7.09 (ddd, *J* = 8.3, 5.5, 3.2 Hz, 1H), 6.87 (d, *J* = 8.3 Hz, 1H), 6.85 – 6.78 (m, 1H), 4.91 (s, 1H), 4.11 (dd, *J* = 14.6, 7.1 Hz, 1H), 3.92 (d, *J* = 16.5 Hz, 1H), 3.23 – 3.11 (m, 2H), 2.94 (d, *J* = 16.6 Hz, 1H), 2.91 – 2.84 (m, 1H), 2.79 (d, *J* = 19.0 Hz, 1H), 2.49 (d, *J* = 19.0 Hz, 1H); ^{13}**C NMR** (101 MHz, Chloroform-*d*) δ 179.4, 173.7, 147.0, 144.8, 137.1, 136.5, 132.1, 129.8, 129.7, 127.8, 127.7, 127.6, 127.0, 126.5, 124.2, 118.9, 117.9, 111.8, 61.2, 49.4, 41.7, 38.4, 37.5, 30.5; **HRMS** (EI, m/z) calcd for $C_{26}H_{21}N_3O_4$ $[M]^+$ 439.1532, found 439.1539.



(±) **8l**

(3'R*,11bR*)-1'-argio-3-chloro-6,7,11b,13-tetrahydrospiro[isoquinolino[2,1-a]quinoline-12,3'-pyrrolidine]-2',5'-dione (**8l**)

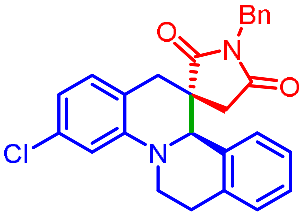
Colourless solid (28.4 mg, 60% yield); **Rf** 0.30 (pet ether/ethyl acetate = 10:1); column chromatography eluent, petroleum ether/EtOAc = 10:1; **mp** 213-215 °C; single diastereomer; ^{1}**H NMR** (400 MHz, Chloroform-*d*) δ 8.30 – 8.26 (dt, *J* = 9.7, 2.6 Hz, 2H), 7.30 (dt, *J* = 9.9, 2.7 Hz, 2H), 7.26 – 7.41 (comp, 2H), 7.19 (d, *J* = 7.8 Hz, 1H), 7.09 (td, *J* = 7.0, 5.9, 2.4 Hz, 1H), 7.03 (d, *J* = 8.0 Hz, 1H), 6.83 (d, *J* = 1.6 Hz, 1H), 6.75 (dd, *J* = 8.0, 1.8 Hz, 1H), 4.90 (s, 1H), 4.06 – 3.97 (m, 1H), 3.83 (d, *J* = 16.5 Hz, 1H), 3.24 – 3.07 (m, 2H), 2.88 (dd, *J* = 15.5, 5.8 Hz, 2H), 2.72 (d, *J* = 18.9 Hz, 1H), 2.44 (d, *J* = 19.0 Hz, 1H); ^{13}**C NMR** (101 MHz, Chloroform-*d*) δ 179.2, 173.5, 147.0, 145.7, 136.9, 136.3, 133.4, 131.6, 130.6, 129.7, 128.0, 127.5, 126.9, 126.7, 124.3, 117.8, 117.2, 111.9, 61.1, 49.0, 42.0, 38.0, 37.2, 30.4; **HRMS** (EI, m/z) calcd for $C_{26}H_{20}ClN_3O_4$ $[M]^+$ 473.1142, found 473.1128.



Bn = benzyl
(±) **8m**

(3'R*,11bR*)-1'-benzyl-6,7,11b,13-tetrahydrospiro[isoquinolino[2,1-a]quinoline-12,3'-pyrrolidine]-2',5'-dione (8m)

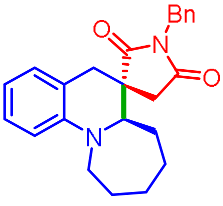
Off white solid (35.9 mg, 88% yield); **Rf** 0.30 (pet ether/ethyl acetate = 20:1); column chromatography eluent, petroleum ether/EtOAc = 20:1; **mp** 220-222 °C; single diastereomer; **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 7.31 – 7.27 (comp, 3H), 7.26 – 7.22 (comp, 2H), 7.17 (app t, *J*= 7.4 Hz, 1H), 7.12 – 7.00 (comp, 4H), 6.80 (d, *J* = 8.3 Hz, 1H), 6.74 (td, *J* = 7.4, 0.9 Hz, 1H), 6.68 (td, *J* = 8.7, 7.9, 1.4 Hz, 1H), 4.90 (s, 1H), 4.59 (d, *J* = 14.1 Hz, 1H), 4.48 (d, *J* = 14.1 Hz, 1H), 4.02 (dd, *J* = 10.4, 3.6 Hz, 1H), 3.71 (d, *J* = 16.4 Hz, 1H), 3.14 – 2.97 (m, 2H), 2.83 – 2.69 (m, 2H), 2.46 (d, *J* = 18.7 Hz, 1H), 2.26 (d, *J* = 18.7 Hz, 1H); **^{13}C NMR** (101 MHz, Chloroform-*d*) δ 181.1, 175.4, 144.9, 136.2, 135.4, 132.4, 129.6, 129.1, 128.8, 128.6, 127.8, 127.6, 127.5, 127.2, 126.4, 119.3, 117.5, 111.4, 60.7, 49.0, 42.4, 41.9, 38.7, 36.9, 30.3; **HRMS** (EI, m/z) calcd for $C_{27}H_{24}N_2O_2$ $[M]^+$ 408.1838, found 408.1833.



(±) **8n**

(3'R*,11bR*)-1'-benzyl-3-chloro-6,7,11b,13-tetrahydrospiro[isoquinolino[2,1-a]quinoline-12,3'-pyrrolidine]-2',5'-dione (8n)

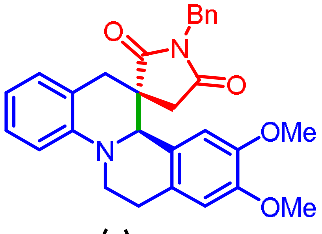
Colourless solid (40.2 mg, 91% yield); **Rf** 0.30 (pet ether/ethyl acetate = 20:1); column chromatography eluent, petroleum ether/EtOAc = 20:1; **mp** 158-160 °C; single diastereomer; **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 7.30 – 7.26 (comp, 2H), 7.25 – 7.21 (comp, 2H), 7.10 (d, *J* = 6.9 Hz, 1H), 7.08 – 7.04 (m, 1H), 7.00 (d, *J* = 7.9 Hz, 1H), 6.94 (d, *J* = 7.9 Hz, 1H), 6.77 (d, *J* = 1.8 Hz, 1H), 6.72 – 6.62 (m, 2H), 4.90 (s, 1H), 4.59 (d, *J* = 14.0 Hz, 1H), 4.48 (d, *J* = 14.0 Hz, 1H), 3.99 – 3.91 (m, 1H), 3.62 (d, *J* = 16.3 Hz, 1H), 3.13 – 3.06 (m, 1H), 3.01 (td, *J* = 13.5, 12.0, 3.8 Hz, 1H), 2.77 (d, *J* = 15.2 Hz, 1H), 2.68 (d, *J* = 16.4 Hz, 1H), 2.38 (d, *J* = 18.7 Hz, 1H), 2.20 (d, *J* = 18.7 Hz, 1H); **^{13}C NMR** (101 MHz, Chloroform-*d*) δ 180.8, 175.1, 145.8, 136.0, 135.3, 133.3, 132.0, 130.4, 129.2, 128.8, 128.6, 127.9, 127.4, 127.3, 126.6, 117.6, 117.3, 111.5, 60.6, 48.6, 42.5, 42.2, 38.2, 36.6, 30.1; **HRMS** (EI, m/z) calcd for $C_{27}H_{23}ClN_2O_2$ $[M]^+$ 442.1448, found 442.1457.



(±) **8o**
1.7:1 dr

(3'R*,6aR*)-1'-benzyl-6a,7,8,9,10,11-hexahydro-5H-spiro[azepino[1,2-a]quinoline-6,3'-pyrrolidine]-2',5'-dione (**8o**)

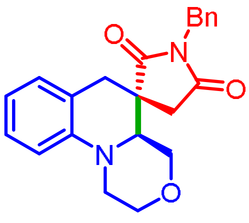
Off white solid (35.9 mg, 96% yield); **Rf** 0.30 (pet ether/ethyl acetate = 20:1); column chromatography eluent, petroleum ether/EtOAc = 20:1; **mp** 144-146 °C; single diastereomer; **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 7.44 – 7.36 (comp, 2H), 7.36 – 7.33 (comp, 3H), 7.11 (app t, *J* = 7.7 Hz, 1H), 7.01 – 6.93 (m, 1H), 6.71 (d, *J* = 8.2 Hz, 1H), 6.68 – 6.60 (m, 1H), 4.69 (d, *J* = 6.8 Hz, 3H), 4.00 (ddd, *J* = 15.1, 6.3, 2.1 Hz, 1H), 3.61 – 3.51 (m, 2H), 3.48 (d, *J* = 16.5 Hz, 1H), 3.35 (d, *J* = 16.0 Hz, 1H), 3.13 – 3.01 (m, 1H), 2.64 (dd, *J* = 20.6, 18.6 Hz, 2H), 2.47 (d, *J* = 16.3 Hz, 1H), 2.39 (d, *J* = 18.7 Hz, 1H), 2.28 (d, *J* = 18.8 Hz, 1H), 2.16 – 2.00 (m, 1H), 1.92 – 1.83 (m, 1H), 1.74 (ddd, *J* = 18.8, 10.4, 3.6 Hz, 2H), 1.65 – 1.52 (m, 5H), 1.48 – 1.35 (m, 3H); **^{13}C NMR** (101 MHz, Chloroform-*d*) δ 180.6, 175.7, 146.3, 135.8, 129.9, 128.7, 128.6, 127.9, 127.5, 116.9, 116.0, 113.0, 64.6, 50.3, 44.6, 42.5, 36.4, 31.5, 29.4, 28.7, 27.1, 25.9; **HRMS** (EI, m/z) calcd for $C_{24}H_{26}N_2O_2$ $[M]^+$ 374.1994, found 374.1999.



(±) **8p**

(3'R*,11bR*)-1'-benzyl-9,10-dimethoxy-6,7,11b,13-tetrahydrospiro[isoquinolino[2,1-a]quinoline-12,3'-pyrrolidine]-2',5'-dione (**8p**)

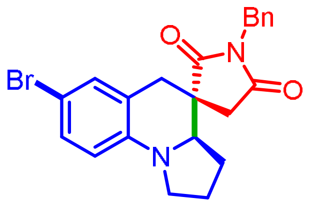
Off white solid (39.8 mg, 85% yield); **Rf** 0.30 (pet ether/ethyl acetate = 10:1); column chromatography eluent, petroleum ether/EtOAc = 5:1 to 10:1; **mp** 165-170 °C; single diastereomer; **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 7.26 (dd, *J* = 5.0, 1.9 Hz, 3H), 7.18 (app t, *J* = 7.3 Hz, 1H), 7.09 – 7.03 (comp, 3H), 6.81 (d, *J* = 8.3 Hz, 1H), 6.76 (d, *J* = 7.4 Hz, 1H), 6.73 (s, 1H), 6.64 (s, 1H), 4.82 (s, 1H), 4.62 (d, *J* = 14.5 Hz, 1H), 4.51 (d, *J* = 14.5 Hz, 1H), 4.04 – 3.95 (m, 1H), 3.89 (s, 3H), 3.72 (d, *J* = 16.4 Hz, 1H), 3.50 (s, 3H), 3.14 – 2.97 (m, 2H), 2.74 (dd, *J* = 15.5, 11.3 Hz, 2H), 2.60 (d, *J* = 18.7 Hz, 1H), 2.31 (d, *J* = 18.7 Hz, 1H); **^{13}C NMR** (101 MHz, Chloroform-*d*) δ 181.33 , 175.66 , 148.05 , 147.44 , 145.16 , 135.12 , 129.69 , 128.60 , 128.38 , 127.77 , 127.50 , 127.42 , 124.06 , 118.96 , 117.49 , 111.57 , 111.39 , 110.69 , 60.10 , 55.75 , 55.41 , 49.56 , 42.22 , 41.76 , 39.00 , 36.68 , 29.97; **HRMS** (EI, m/z) calcd for $C_{29}H_{28}N_2O_4$ [M]$^+$ 468.2049, found 468.2055.



(±) 8q

(3'R*,4aS*)-1'-benzyl-2,4,4a,6-tetrahydro-1H-spiro[[1,4]oxazino[4,3-a]quinoline-5,3'-pyrrolidine]-2',5'-dione (**8q**)

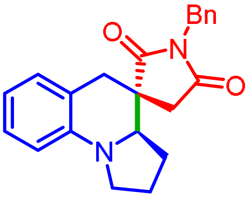
Colourless solid (35.1 mg, 97% yield); **Rf** 0.30 (pet ether/ethyl acetate = 20:1); column chromatography eluent, petroleum ether/EtOAc = 20:1; **mp** 170-174 °C; single diastereomer; **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 7.40 – 7.37 (comp, 2H), 7.36 – 7.29 (comp, 3H), 7.16 (app t, *J* = 7.6 Hz, 1H), 6.98 (d, *J* = 7.5 Hz, 1H), 6.84 (d, *J* = 8.3 Hz, 1H), 6.79 (app t, *J* = 7.4 Hz, 1H), 4.75 – 4.62 (m, 2H), 3.99 (dd, *J* = 11.5, 3.6 Hz, 1H), 3.69 – 3.64 (m, 1H), 3.60 (td, *J* = 11.7, 2.9 Hz, 1H), 3.55 – 3.51 (m, 1H), 3.48 (d, *J* = 15.8 Hz, 1H), 3.42 (dd, *J* = 10.7, 3.4 Hz, 1H), 3.02 (t, *J* = 10.8 Hz, 1H), 2.97 – 2.88 (m, 2H), 2.56 (d, *J* = 15.8 Hz, 1H), 2.36 (d, *J* = 19.1 Hz, 1H); **^{13}C NMR** (101 MHz, Chloroform-*d*) δ 179.0, 175.1, 145.0, 135.5, 130.2, 128.8, 128.7, 128.1, 127.9, 119.9, 119.4, 113.1, 66.8, 66.3, 57.4, 46.5, 43.7, 42.6, 38.4, 36.4; **HRMS** (EI, m/z) calcd for $C_{22}H_{22}N_2O_3$ [M]$^+$ 362.1630, found 362.1639.



(±) 8r

(3R*,3a'R*)-1-benzyl-7'-bromo-2',3',3a',5'-tetrahydro-1'H-spiro[pyrrolidine-3,4'-pyrrolo[1,2-a]quinoline]-2,5-dione (8r)

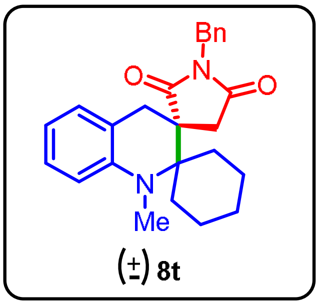
Yellow solid (22.9 mg, 54% yield); **Rf** 0.30 (pet ether/ethyl acetate = 20:1); column chromatography eluent, petroleum ether/EtOAc = 20:1; **mp** 144-146 °C; single diastereomer; **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 7.51 – 7.46 (m, 2H), 7.43 – 7.38 (m, 1H), 7.29 (d, *J* = 7.4 Hz, 2H), 7.24 – 7.20 (m, 1H), 7.17 (s, 1H), 6.37 (d, *J* = 8.6 Hz, 1H), 3.80 (dd, *J* = 10.2, 4.9 Hz, 1H), 3.50 – 3.38 (m, 2H), 3.30 (q, *J* = 8.3 Hz, 1H), 2.76 (d, *J* = 15.7 Hz, 1H), 2.52 (d, *J* = 18.9 Hz, 1H), 2.34 (d, *J* = 18.9 Hz, 1H), 2.20 – 2.10 (m, 1H), 2.06 (dt, *J* = 14.4, 7.1 Hz, 2H), 1.53 – 1.44 (m, 1H); **^{13}C NMR** (101 MHz, Chloroform-*d*) δ 179.5, 174.6, 142.1, 132.0, 130.8, 129.3, 129.2, 128.8, 126.4, 120.0, 112.3, 107.9, 62.1, 47.0, 42.9, 38.0, 35.3, 27.0, 23.3; **HRMS** (ESI, m/z) calcd for $C_{22}H_{21}BrN_2O_2$ $[M]^+$ 424.0786, found 424.0788.



(±) 8s

(3R*,3a'R*)-1-benzyl-2',3',3a',5'-tetrahydro-1'H-spiro[pyrrolidine-3,4'-pyrrolo[1,2-a]quinoline]-2,5-dione (8s)

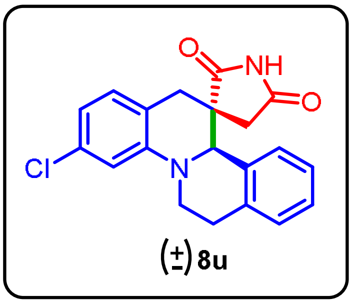
Yellow solid (18 mg, 52% yield); **Rf** 0.30 (pet ether/ethyl acetate = 20:1); column chromatography eluent, petroleum ether/EtOAc = 20:1; **mp** 148-150 °C; single diastereomer; **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 7.38 (dd, *J* = 7.9, 1.5 Hz, 2H), 7.31 (tdd, *J* = 8.7, 5.5, 3.7 Hz, 3H), 7.12 (t, *J* = 7.5 Hz, 1H), 7.01 (d, *J* = 7.4 Hz, 1H), 6.65 – 6.57 (m, 1H), 6.46 (d, *J* = 8.0 Hz, 1H), 4.74 – 4.63 (m, 2H), 3.70 (dd, *J* = 10.3, 5.5 Hz, 1H), 3.45 – 3.34 (m, 2H), 3.31 – 3.21 (m, 1H), 2.64 (d, *J* = 15.6 Hz, 1H), 2.39 (d, *J* = 18.9 Hz, 1H), 2.18 (d, *J* = 18.9 Hz, 1H), 2.07 – 1.97 (m, 1H), 1.91 (tdd, *J* = 12.6, 11.5, 5.7, 2.6 Hz, 1H), 1.70 – 1.63 (m, 1H), 1.27 – 1.12 (m, 1H); **^{13}C NMR** (101 MHz, Chloroform-d) δ 180.5, 175.6, 143.1, 135.9, 129.5, 128.7, 128.7, 128.7, 128.0, 117.8, 116.0, 110.6, 61.7, 46.7, 43.0, 42.5, 38.0, 35.2, 26.7, 23.1; **HRMS** (EI, m/z) calcd for $C_{22}H_{22}N_2O_2$ $[M]^+$ 346.1681, found 346.1688.



(±) **8t**

(R*)-1'-methyl-1''-benzyl-1',4'-dihydrodispiro[cyclohexane-1,2'-quinoline-3',3''-pyrrolidine]-2'',5''-dione (**8t**)

Colourless solid (35 mg, 90% yield); **Rf** 0.30 (pet ether/ethyl acetate = 20:1); column chromatography eluent, petroleum ether/EtOAc = 20:1; **mp** 137-139 °C; single diastereomer; ^{1}**H NMR** (400 MHz, Chloroform-*d*) δ 7.43 – 7.38 (comp, 2H), 7.35 – 7.29 (comp, 3H), 7.20 – 7.14 (m, 1H), 7.00 (d, *J* = 7.3 Hz, 1H), 6.77 (d, *J* = 8.0 Hz, 1H), 6.72 (td, *J* = 7.4, 1.0 Hz, 1H), 4.77 – 4.61 (m, 2H), 3.47 (d, *J* = 16.7 Hz, 1H), 3.19 (s, 3H), 2.59 (d, *J* = 18.9 Hz, 1H), 2.50 (d, *J* = 16.8 Hz, 1H), 2.14 (d, *J* = 19.0 Hz, 1H), 1.88 (td, *J* = 13.2, 3.5 Hz, 1H), 1.80 (d, *J* = 13.8 Hz, 1H), 1.72 – 1.62 (m, 3H), 1.62 – 1.53 (m, 1H), 1.49 – 1.42 (m, 1H), 1.11 (qd, *J* = 14.0, 11.8, 3.7 Hz, 3H); ^{13}**C NMR** (101 MHz, Chloroform-*d*) δ 180.6, 175.7, 145.7, 135.8, 129.3, 128.8, 128.6, 127.9, 127.3, 119.1, 117.1, 114.9, 60.1, 49.4, 42.5, 38.5, 37.4, 35.1, 30.2, 29.4, 25.0, 23.4, 22.2; **HRMS** (EI, m/z) calcd for $C_{25}H_{28}N_2O_2$ $[M]^+$ 388.2151, found 388.2144.

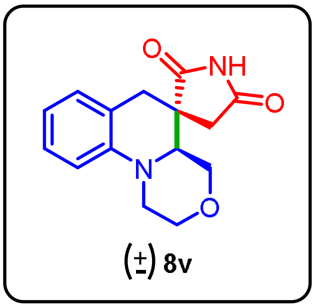


(±) **8u**

(3'R*,11bR*)-3-chloro-6,7,11b,13-tetrahydrospiro[isoquinolino[2,1-a]quinoline-12,3'-pyrrolidine]-2',5'-dione (**8u**)

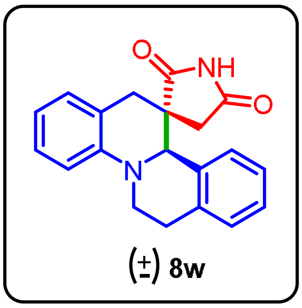
Off white solid (35.2 mg, 97% yield); **Rf** 0.30 (pet ether/ethyl acetate = 10:1); column chromatography eluent, petroleum ether/EtOAc = 10:1; **mp** 160-162 °C; single diastereomer; ^{1}**H NMR** (400 MHz, Chloroform-*d*) δ 8.15 (s, 1H), 7.30 (d, *J* = 7.7 Hz, 1H), 7.25 – 7.14

(comp, 3H), 6.98 (d, *J* = 8.0 Hz, 1H), 6.80 (d, *J* = 1.5 Hz, 1H), 6.72 (dd, *J* = 8.0, 1.6 Hz, 1H), 4.87 (s, 1H), 4.04 – 3.93 (m, 1H), 3.64 (d, *J* = 16.4 Hz, 1H), 3.20 – 2.99 (m, 2H), 2.81 (t, J = 16.2 Hz, 2H), 2.46 (d, *J* = 18.8 Hz, 1H), 2.25 (d, *J* = 18.8 Hz, 1H); **^{13}C NMR** (101 MHz, Chloroform-*d*) δ 181.2, 175.2, 145.7, 136.2, 133.4, 132.0, 130.5, 129.3, 127.7, 127.7, 126.8, 117.4, 117.3, 111.7, 60.4, 50.3, 42.1, 38.1, 37.5, 30.2; **HRMS** (EI, m/z) calcd for $C_{20}H_{17}ClN_2O_2$ $[M]^+$ 352.0979, found 352.0972.



(3'R*,4aS*)-2,4,4a,6-tetrahydro-1H-spiro[[1,4]oxazino[4,3-a]quinoline-5,3'-pyrrolidine]-2',5'-dione (**8v**)

Off white solid (21 mg, 77% yield); **Rf** 0.30 (pet ether/ethyl acetate = 10:1); column chromatography eluent, petroleum ether/EtOAc = 10:1; **mp** 190-192 °C; single diastereomer; **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 8.52 (s, 1H), 7.18 (app t, *J* = 7.6 Hz, 1H), 7.01 (d, *J* = 7.4 Hz, 1H), 6.86 (d, *J* = 8.3 Hz, 1H), 6.80 (app t, *J* = 7.4 Hz, 1H), 4.09 – 4.01 (m, 1H), 3.94 – 3.86 (m, 1H), 3.68 (td, *J* = 12.0, 2.8 Hz, 2H), 3.51 – 3.39 (m, 2H), 3.25 (t, *J* = 10.8 Hz, 1H), 3.04 – 2.91 (m, 2H), 2.68 (d, *J* = 15.8 Hz, 1H), 2.40 (d, *J* = 19.3 Hz, 1H); **^{13}C NMR** (101 MHz, Chloroform-*d*) δ 179.5, 175.6, 145.0, 130.3, 128.0, 119.7, 119.5, 113.2, 66.9, 66.6, 57.0, 46.6, 45.2, 38.6, 37.3; **HRMS** (EI, m/z) calcd for $C_{15}H_{16}N_2O_2$ $[M]^+$ 272.1161, found 272.1155.

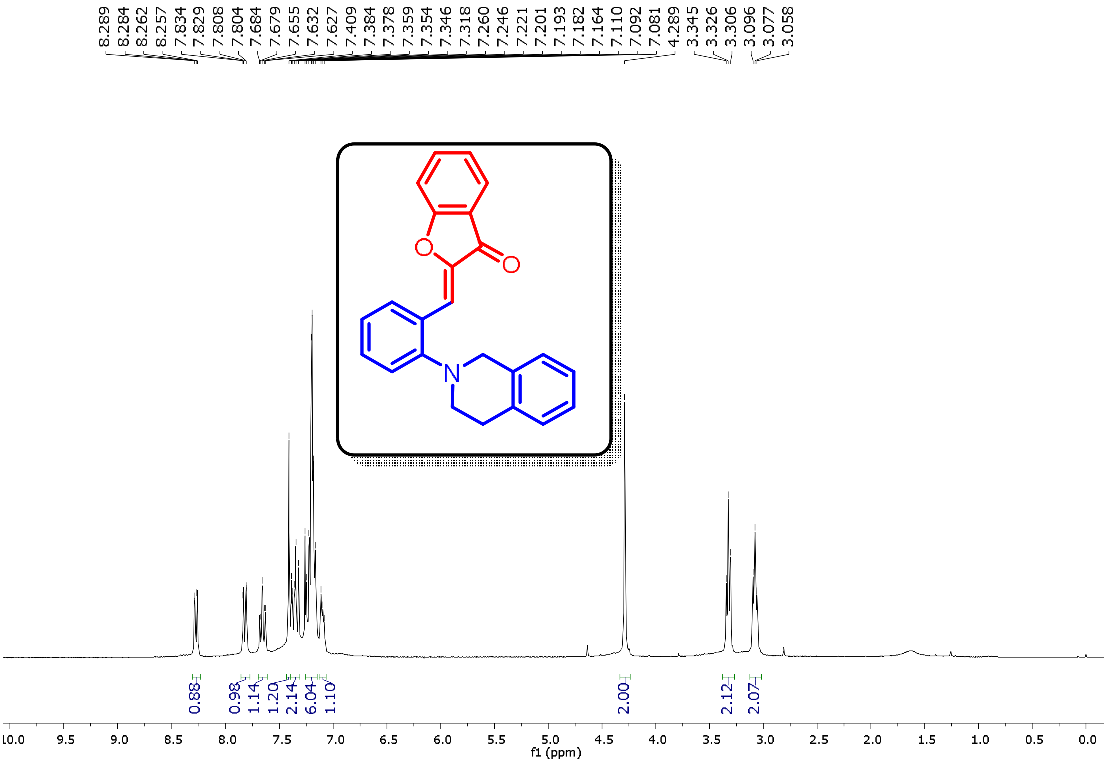


(3'R*,11bR*)-6,7,11b,13-tetrahydrospiro[isoquinolino[2,1-a]quinoline-12,3'-pyrrolidine]-2',5'-dione (**8w**)

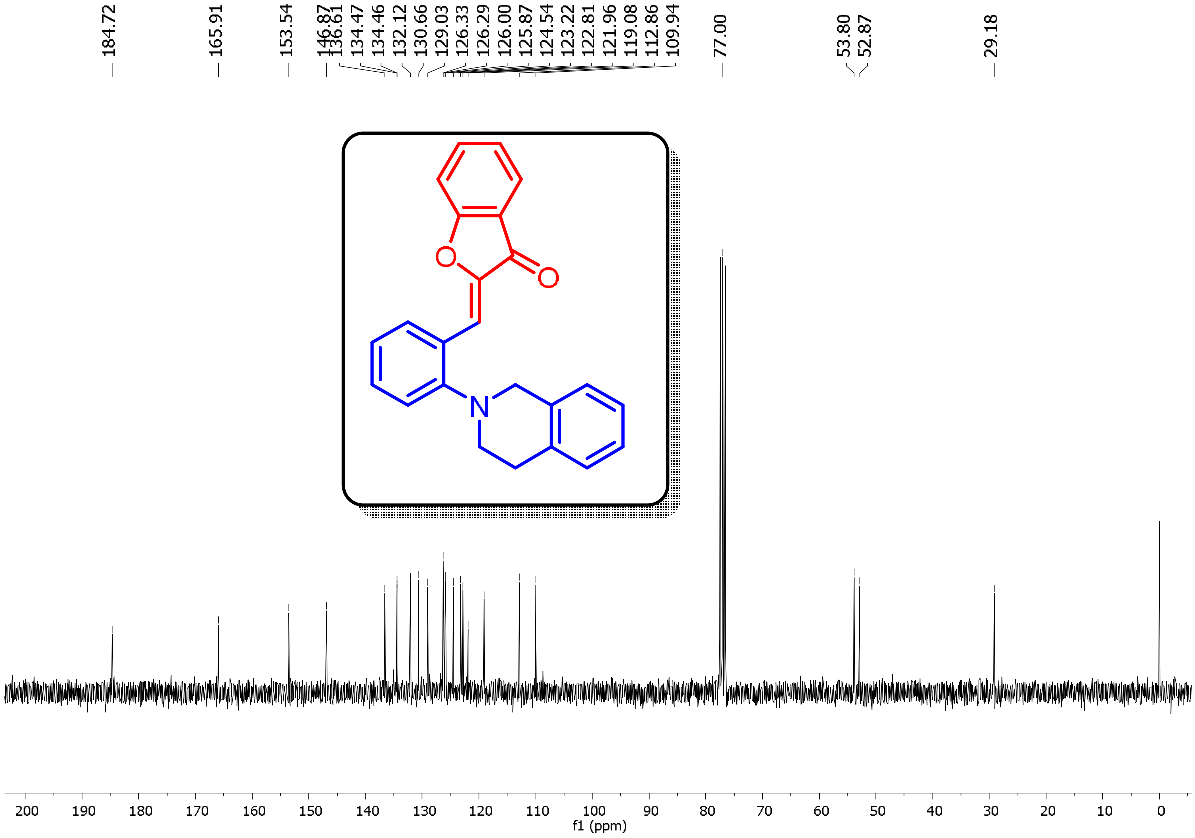
Colourless solid (29 mg, 91% yield); **Rf** 0.30 (pet ether/ethyl acetate = 10:1); column chromatography eluent, petroleum ether/EtOAc = 10:1; **mp** 160-162 °C; single diastereomer; **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 8.20 (s, 1H), 7.35 – 7.30 (m, 1H), 7.25 – 7.13 (comp, 4H), 7.09 (d, *J* = 7.3 Hz, 1H), 6.83 (d, *J* = 8.3 Hz, 1H), 6.77 (app t, *J* = 7.3 Hz, 1H), 4.87 (s, 1H), 4.08 – 4.01 (m, 1H), 3.73 (d, *J* = 16.4 Hz, 1H), 3.17 – 3.02 (m, 2H), 2.88 – 2.80 (m, 2H), 2.52 (d, *J* = 18.8 Hz, 1H), 2.30 (d, *J* = 18.8 Hz, 1H); **^{13}C NMR** (101 MHz, Chloroform-*d*) δ 181.6, 175.7, 144.9, 136.4, 132.4, 129.6, 129.3, 127.7, 127.6, 127.5, 126.6, 119.0, 117.6, 111.5, 60.5, 50.6, 41.8, 38.5, 37.8, 30.4; **HRMS** (EI, m/z) calcd for $C_{20}H_{18}N_2O_2$ $[M]^+$ 318.1368, found 318.1356.

3.5.20 ^{1}H and ^{13}C NMR of Compounds

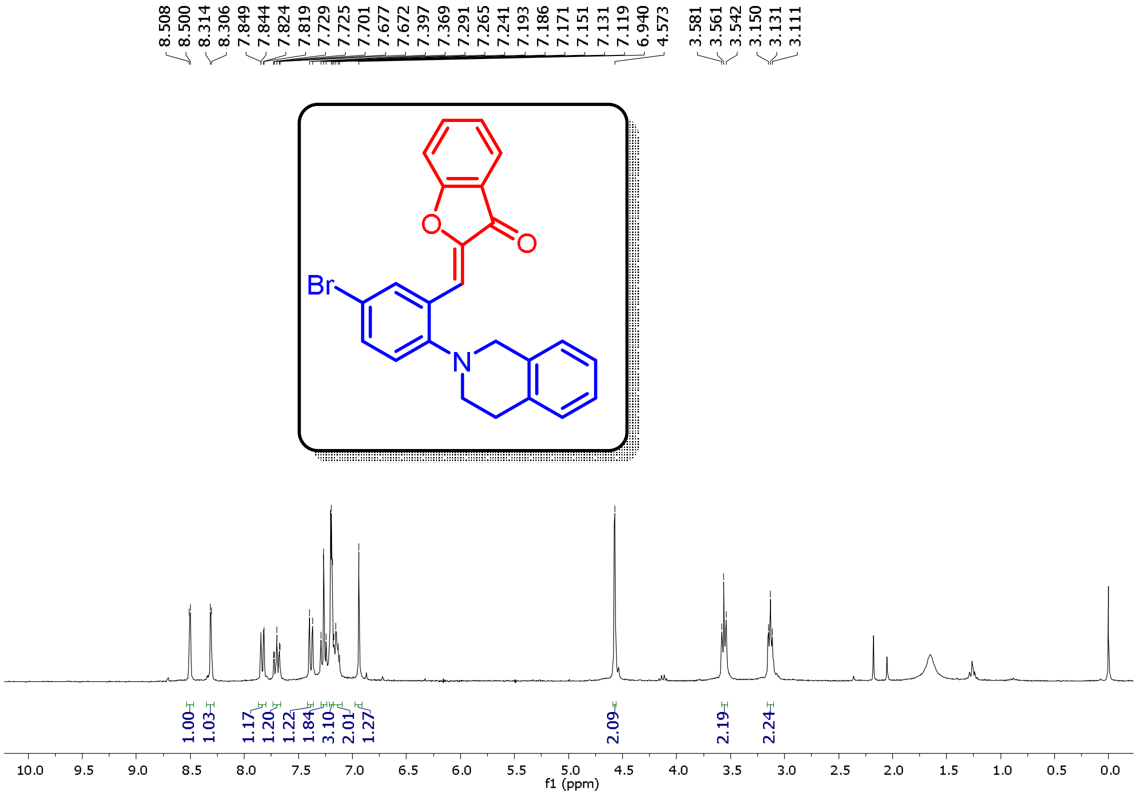
^{1}H NMR of **3a** (300 MHz, Chloroform-*d*)



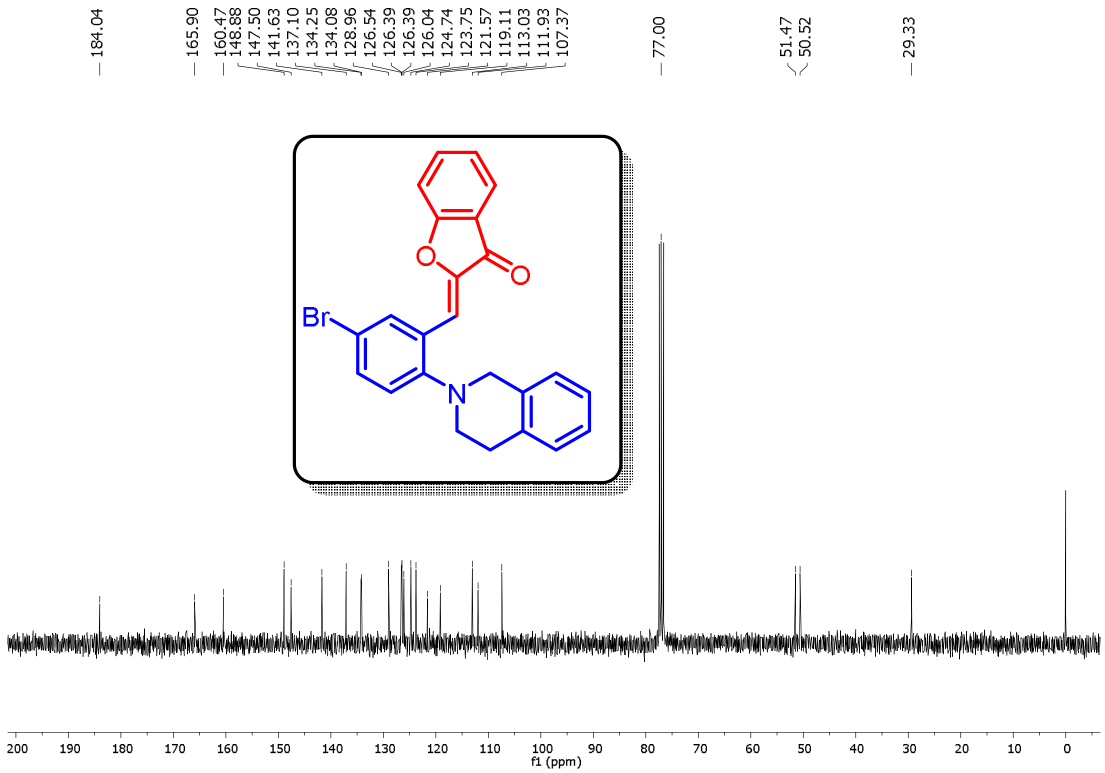
^{13}C NMR of **3a** (75 MHz, $CDCl_3$)



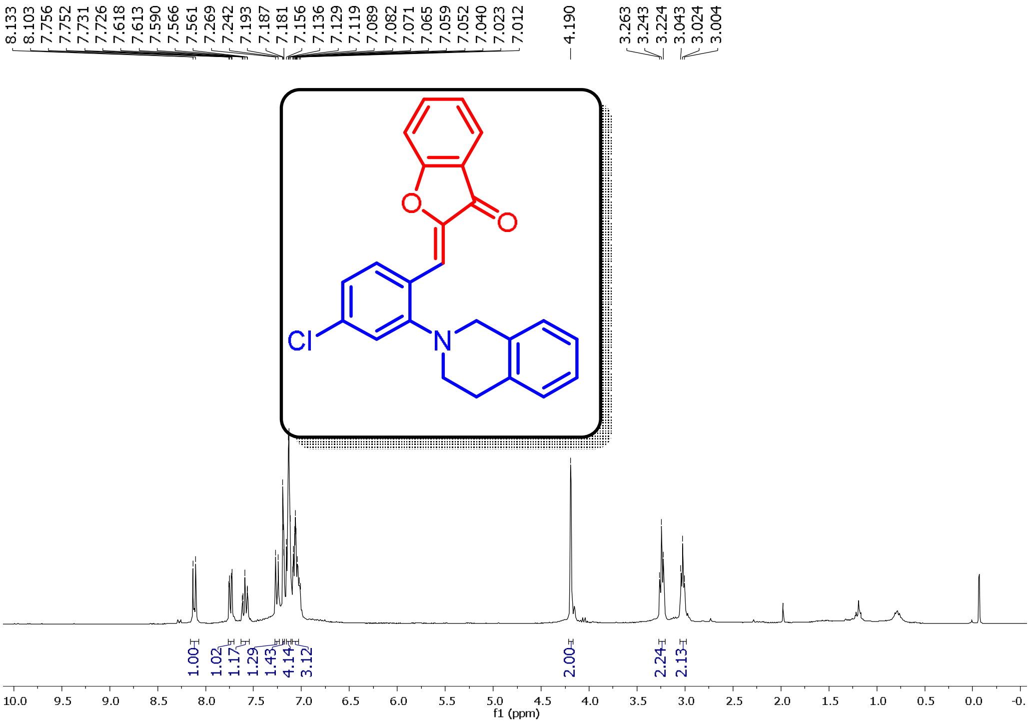
^{1}H NMR of **3b** (300 MHz, Chloroform-*d*)



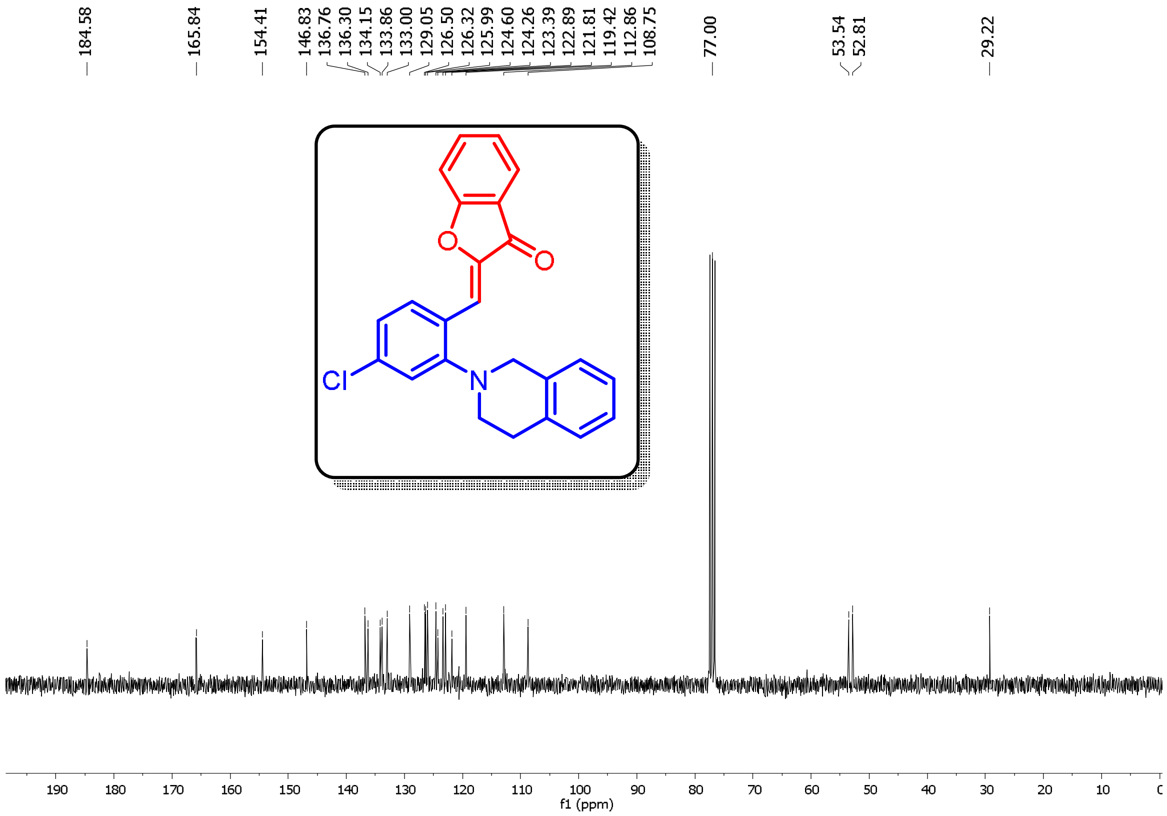
^{13}C NMR of **3b** (75 MHz, $CDCl_3$)



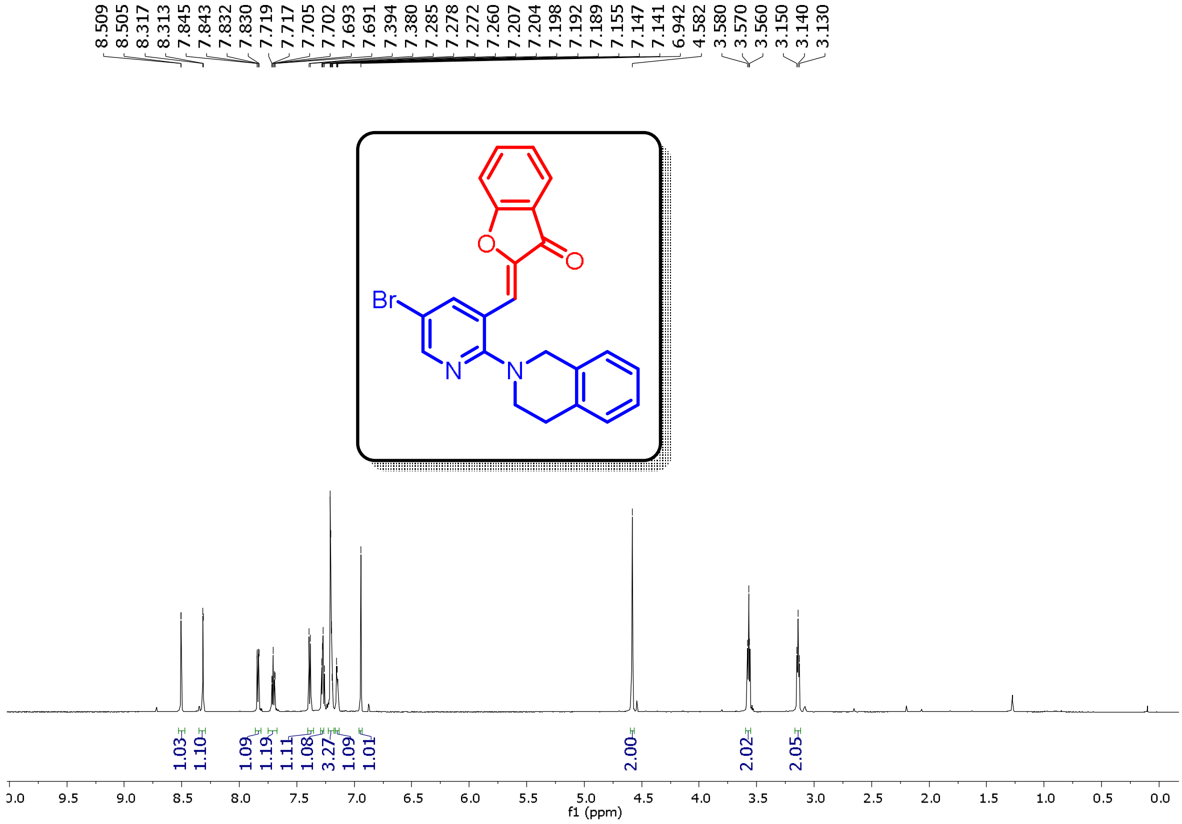
^{1}H NMR of **3c** (300 MHz, Methanol-d_4)



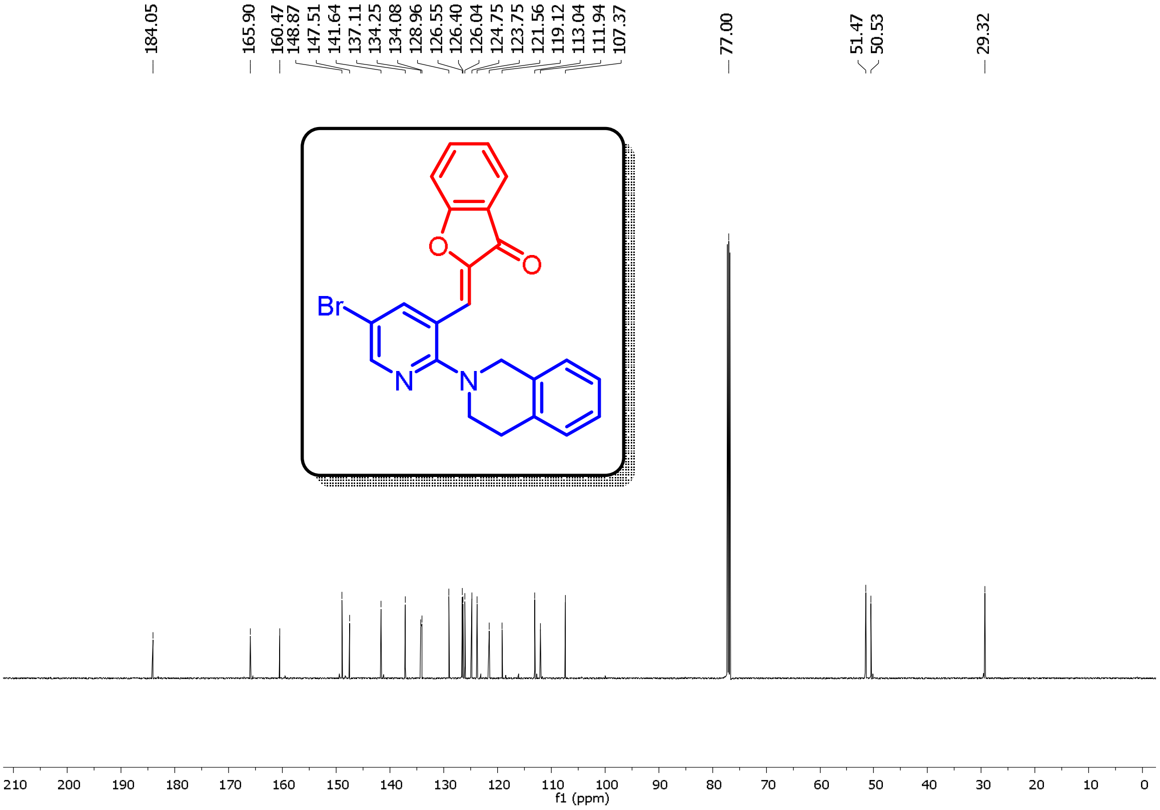
^{13}C NMR of **3c** (75 MHz, CDCl$_3$)



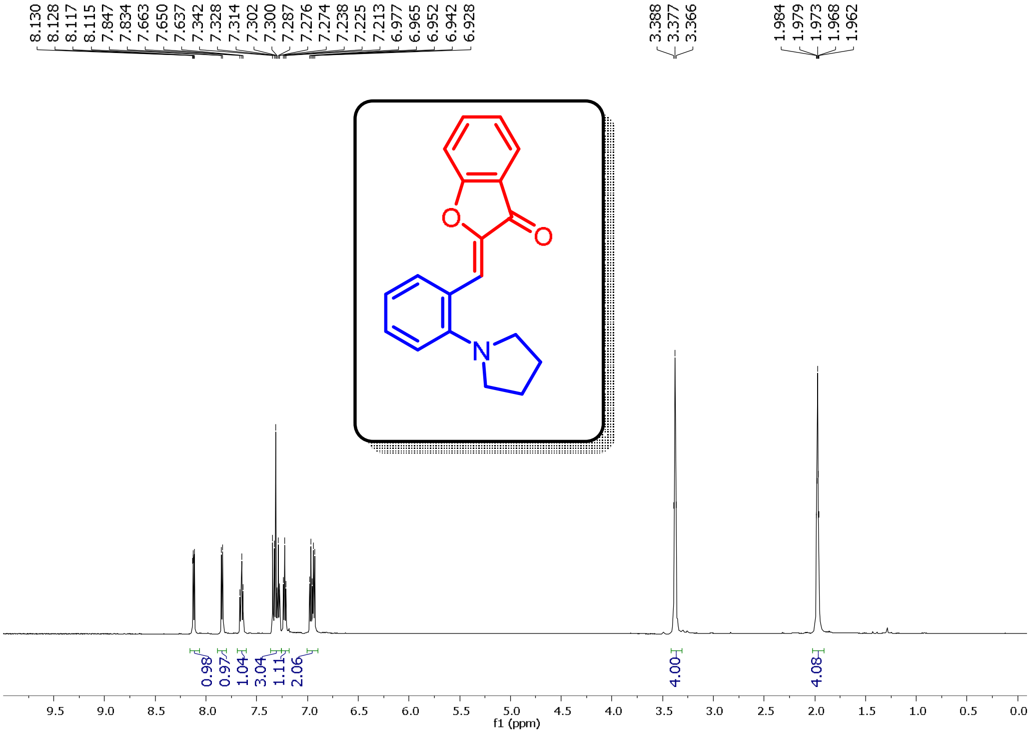
^{1}H NMR of **3d** (600 MHz, Chloroform-*d*)



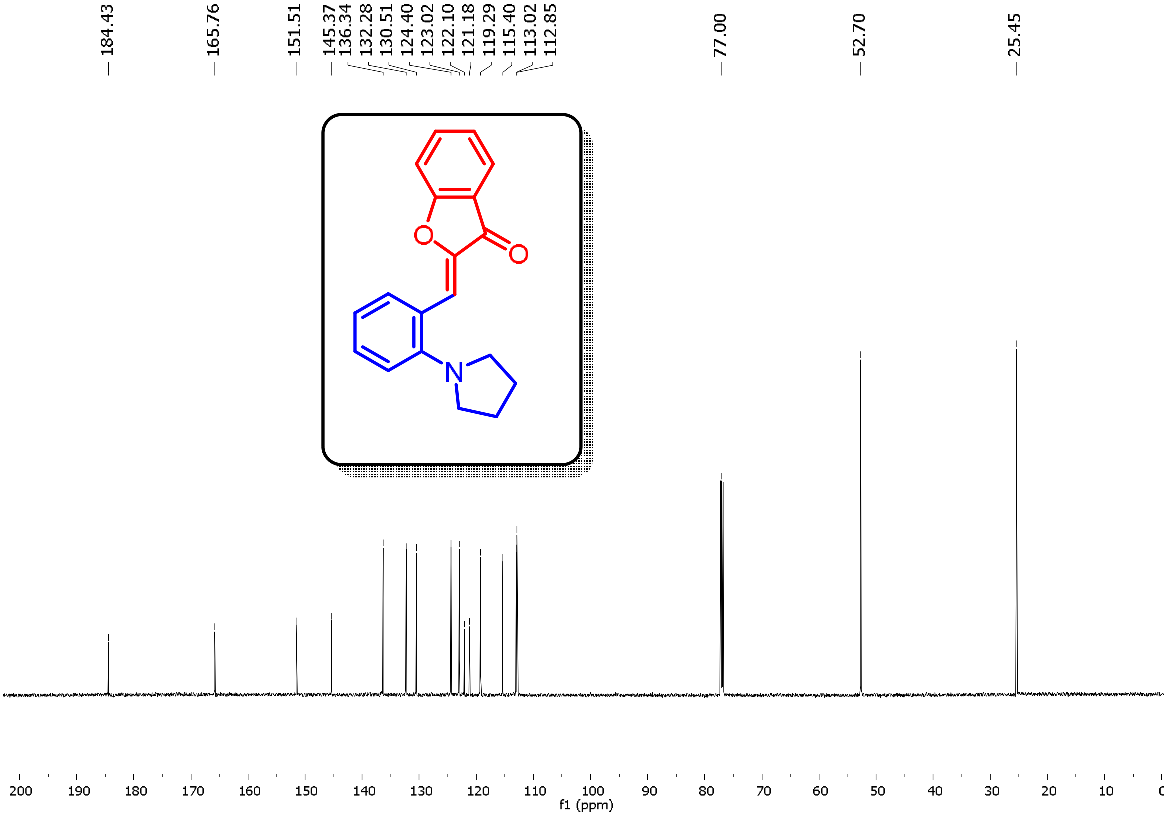
^{13}C NMR of **3d** (151 MHz, CDCl$_3$)



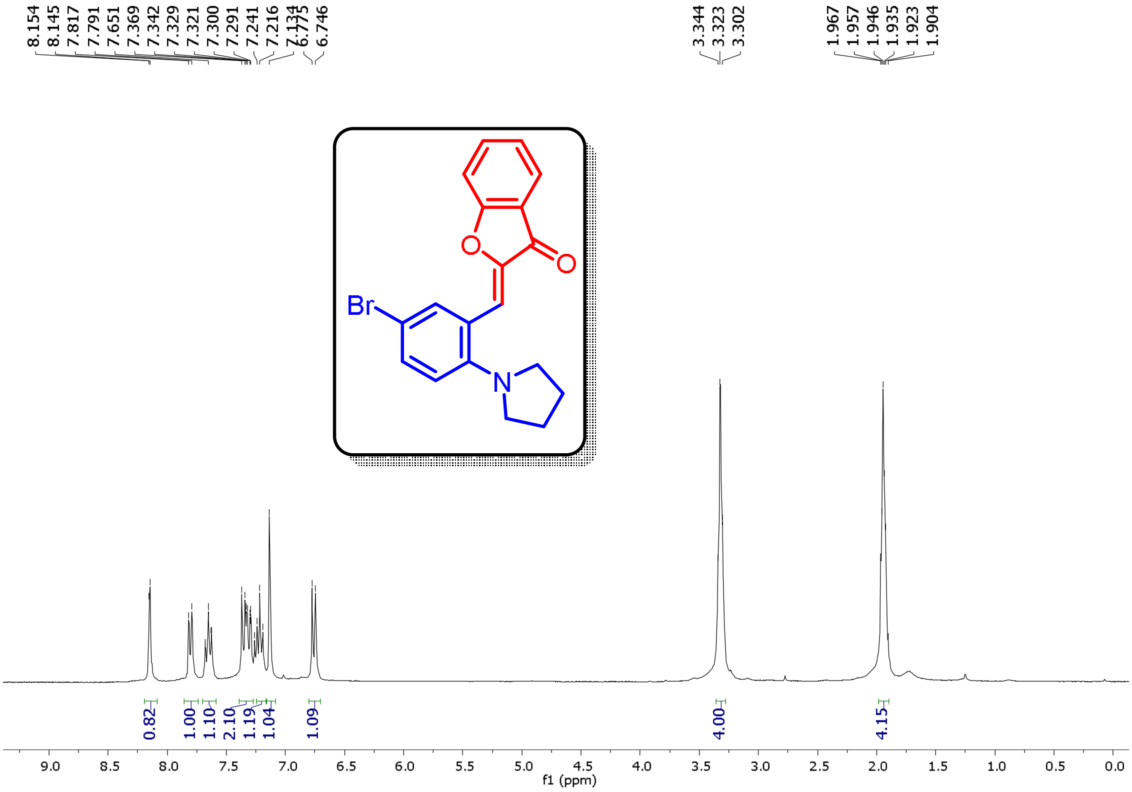
^{1}H NMR of **3e** (600 MHz, Chloroform-*d*)



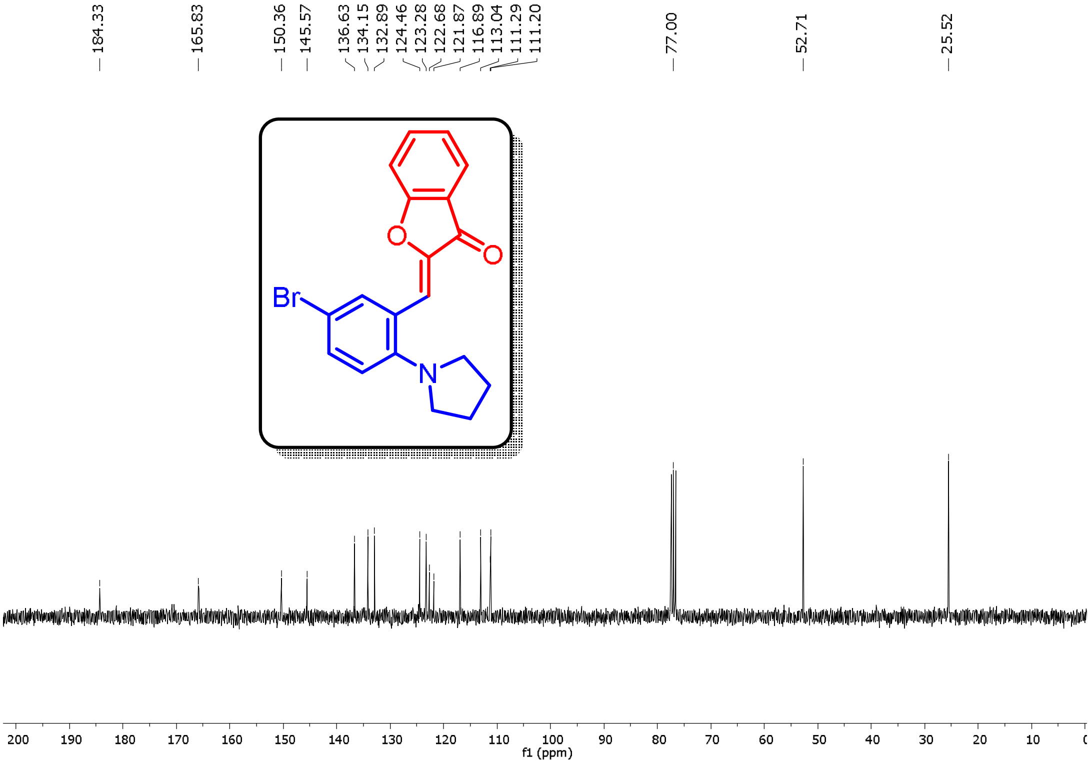
^{13}C NMR of **3e** (151 MHz, CDCl$_3$)



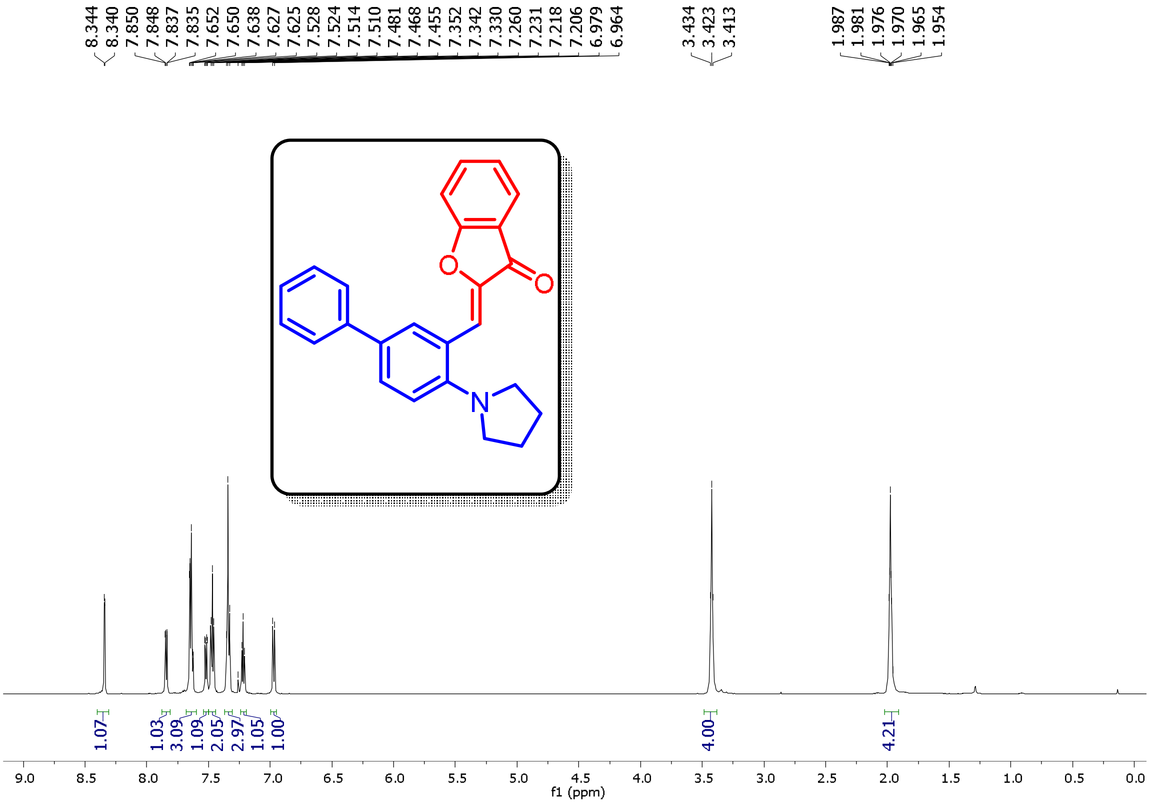
^{1}H NMR of **3f** (300 MHz, Chloroform-*d*)



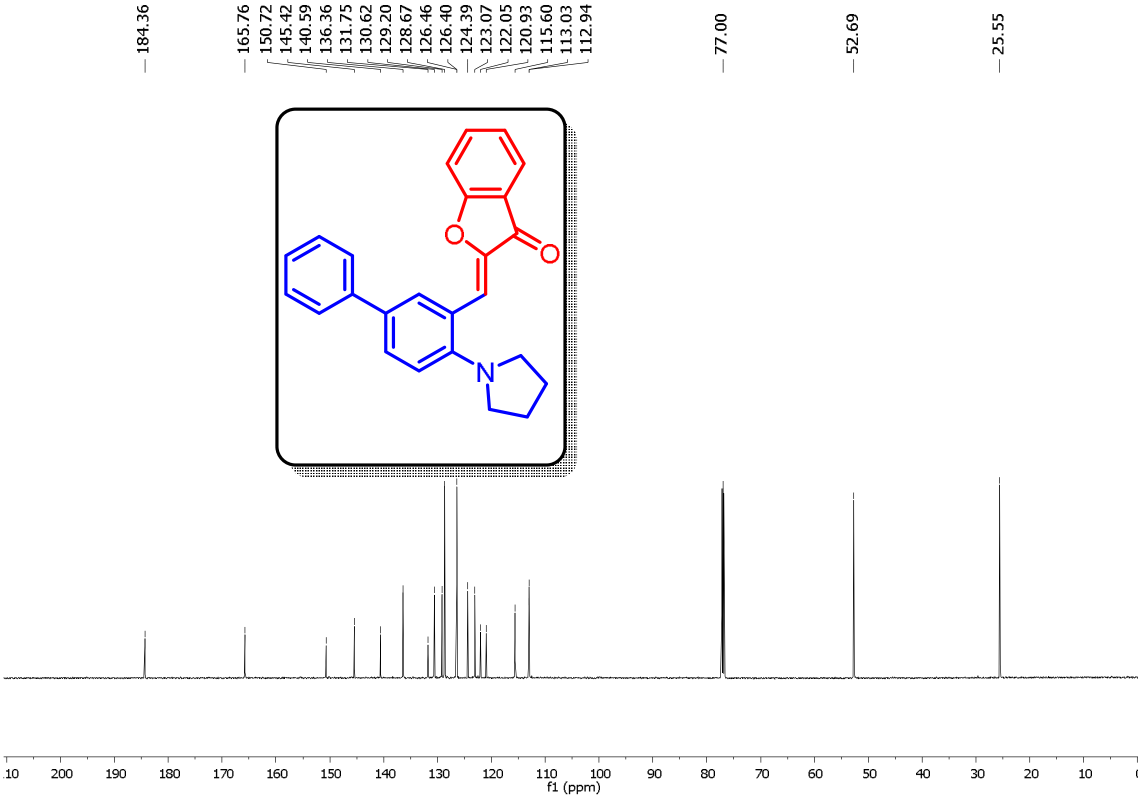
^{13}C NMR of **3f** (75 MHz, $CDCl_3$)



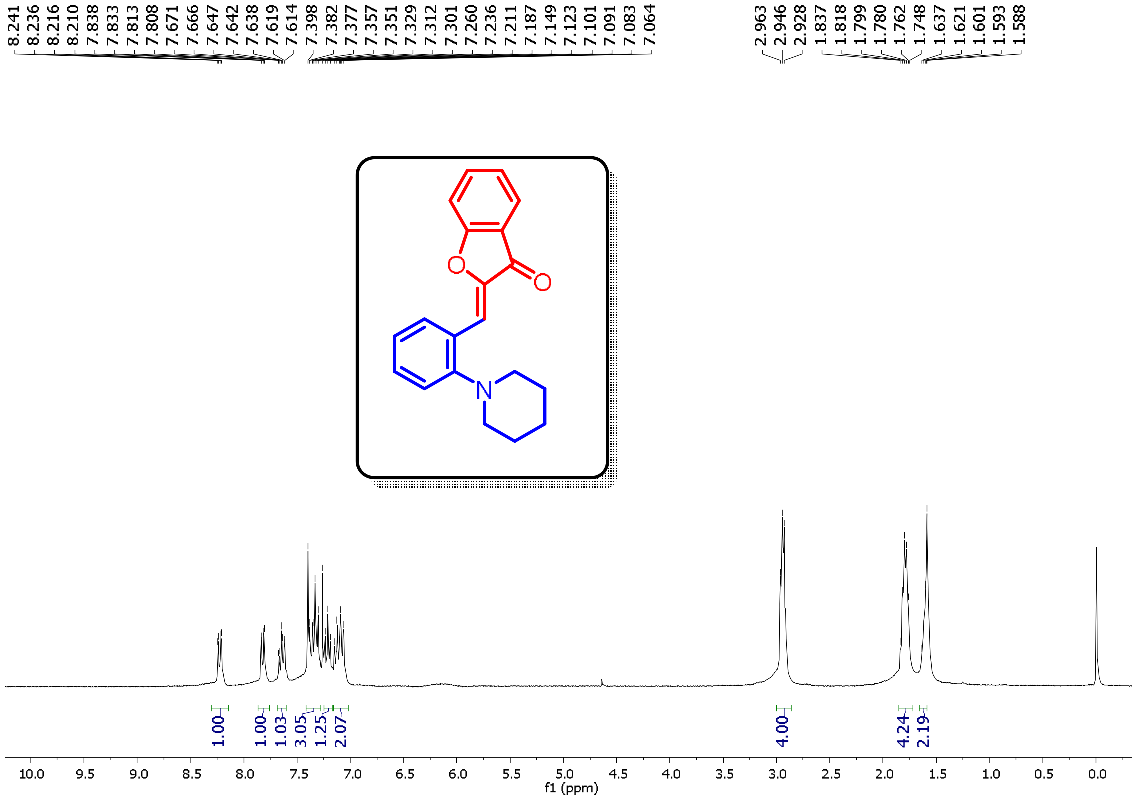
^{1}H NMR of **3g** (600 MHz, Chloroform-*d*)



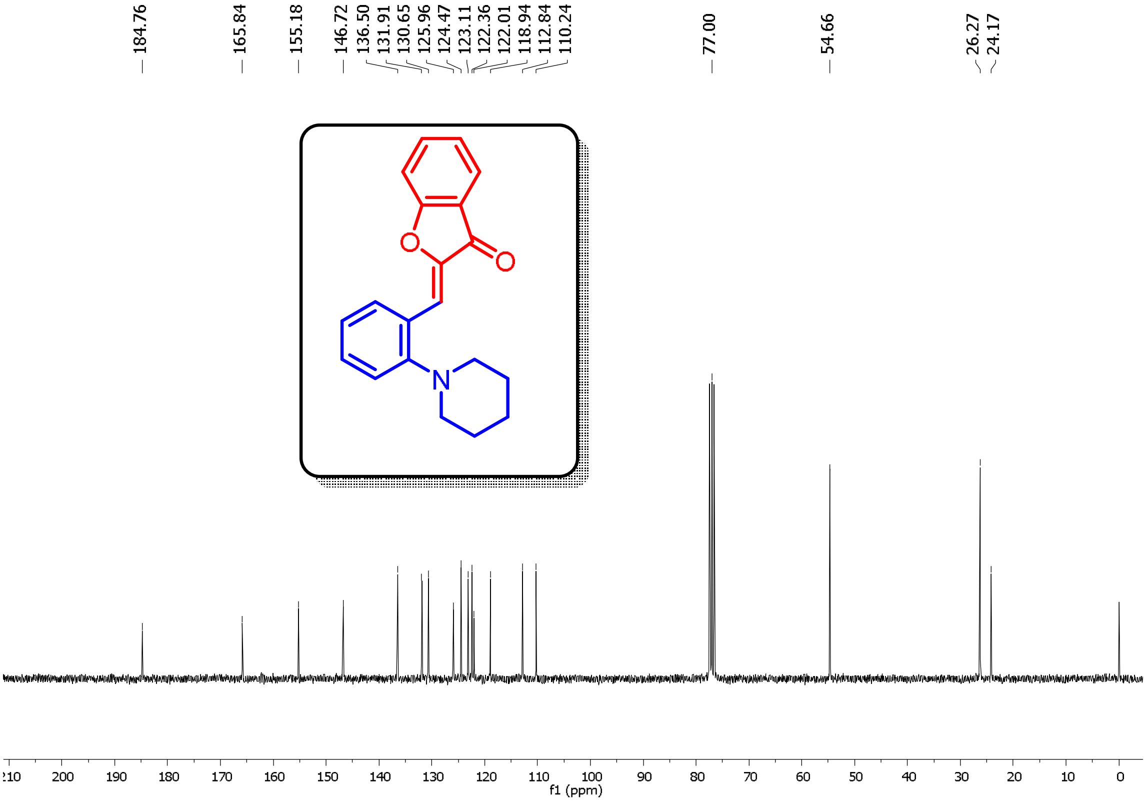
^{13}C NMR of **3g** (151 MHz, $CDCl_3$)



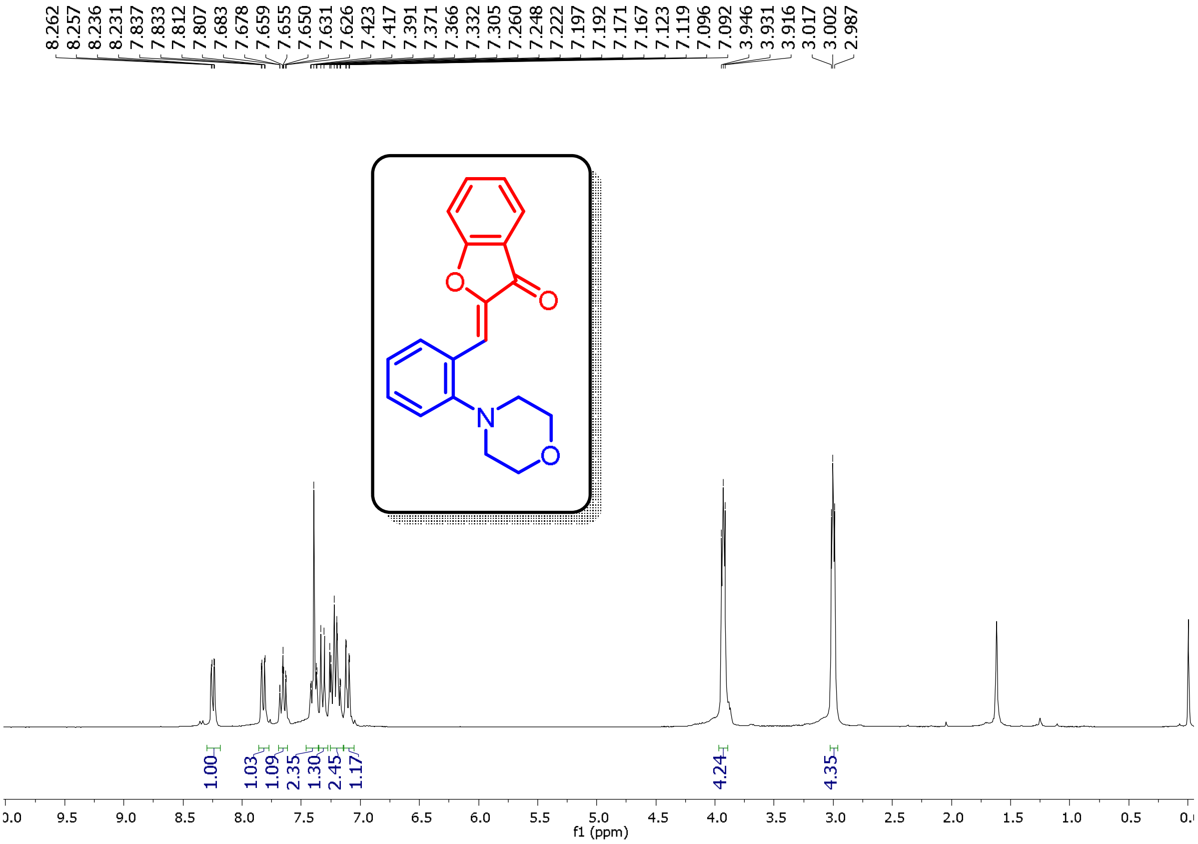
^{1}H NMR of **3h** (600 MHz, Chloroform-*d*)



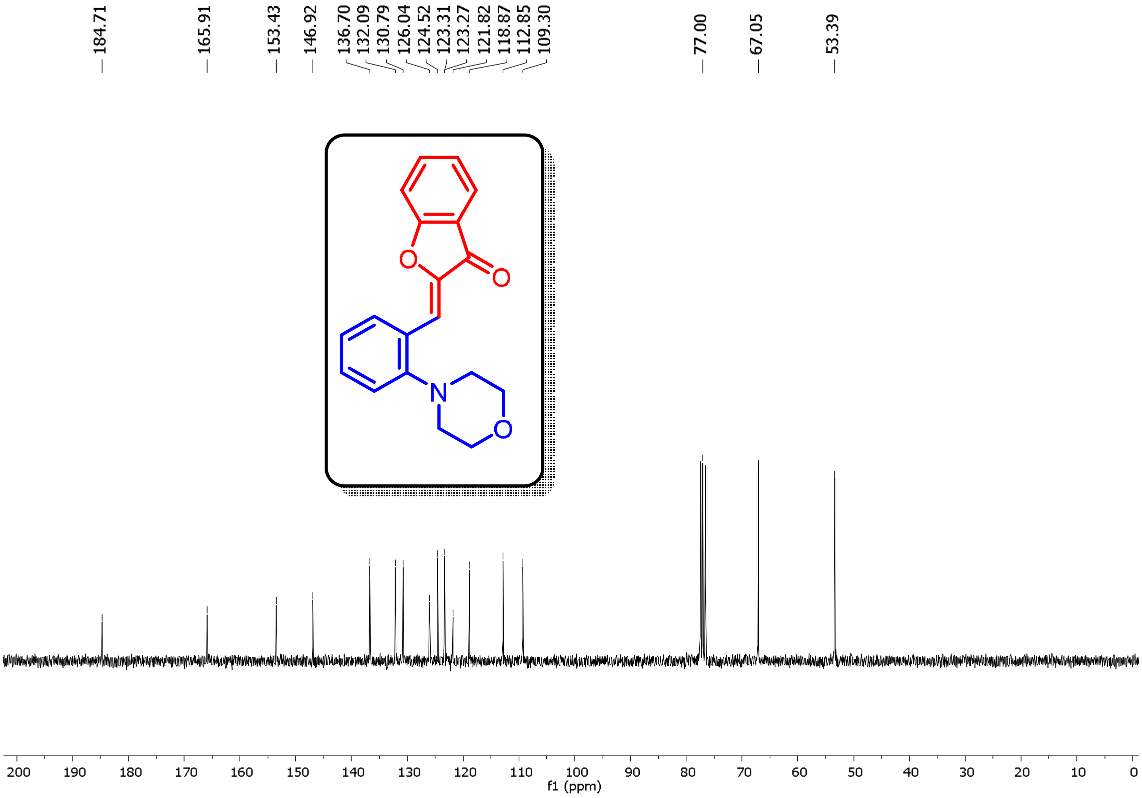
^{13}C NMR of **3h** (151 MHz, CDCl$_3$)



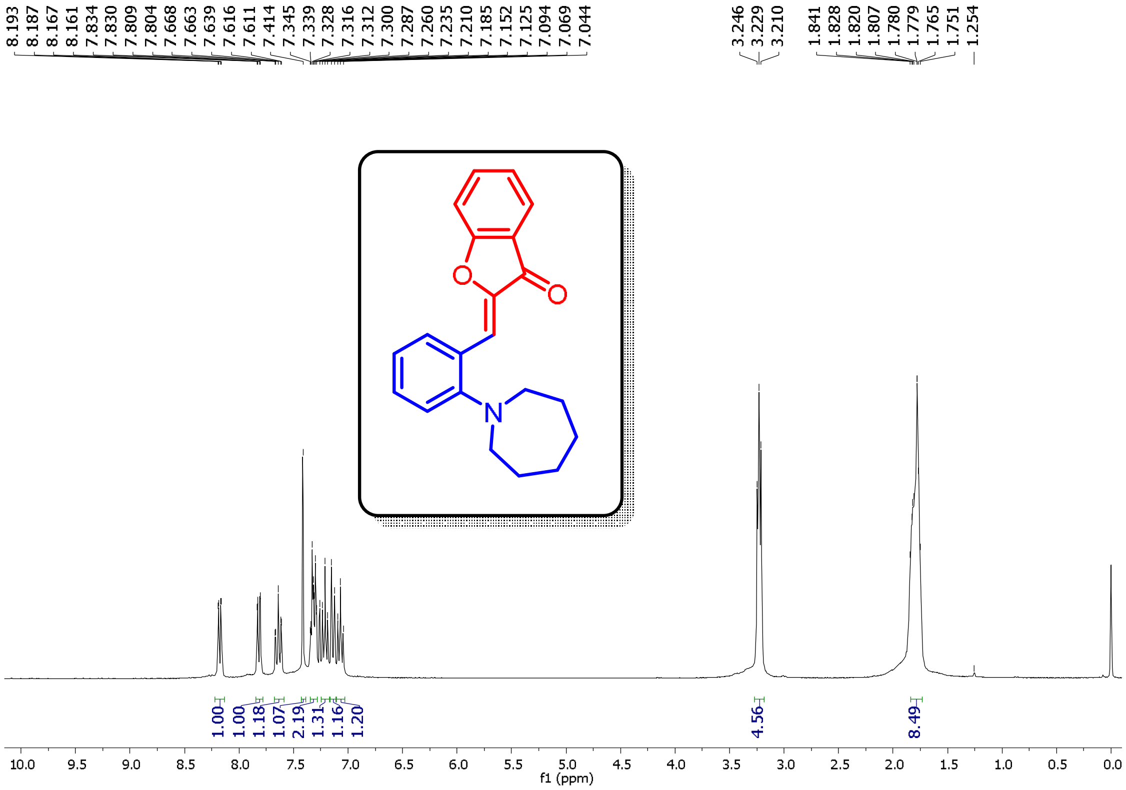
^{1}H NMR of **3i** (300 MHz, Chloroform-*d*)



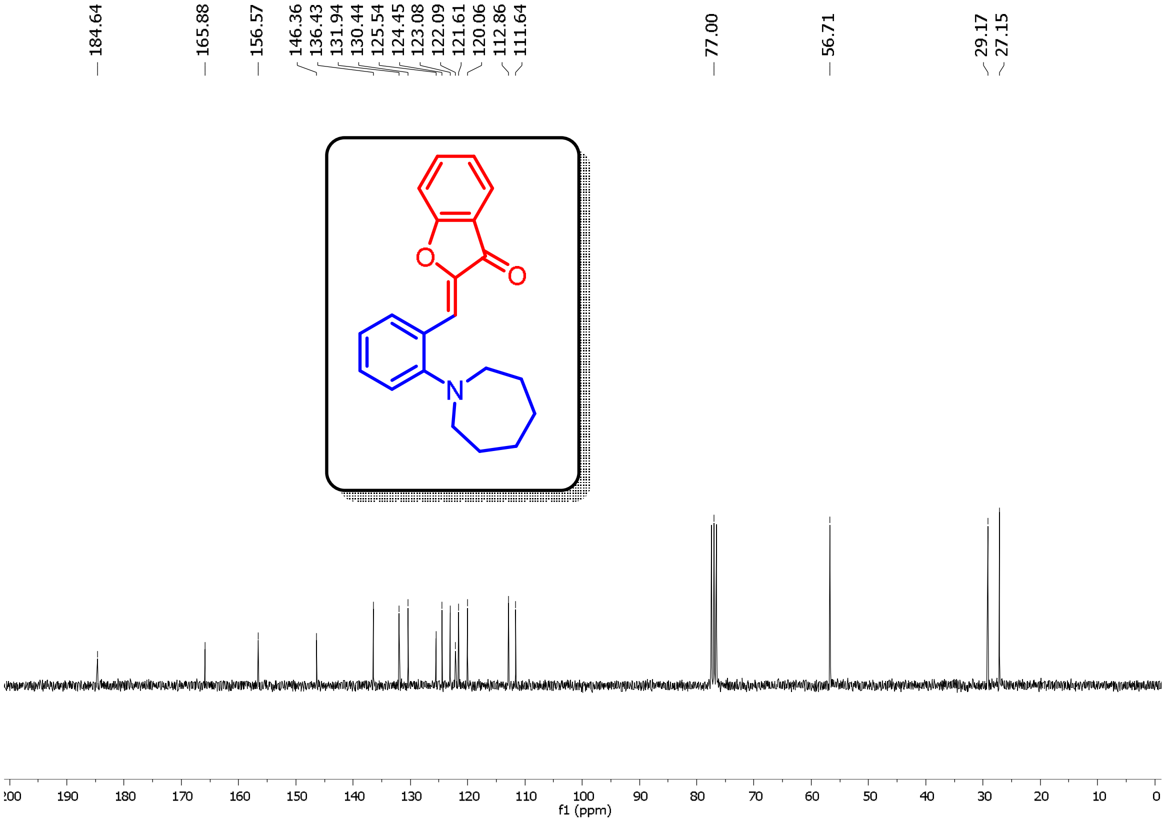
^{13}C NMR of **3i** (75 MHz, CDCl$_3$)



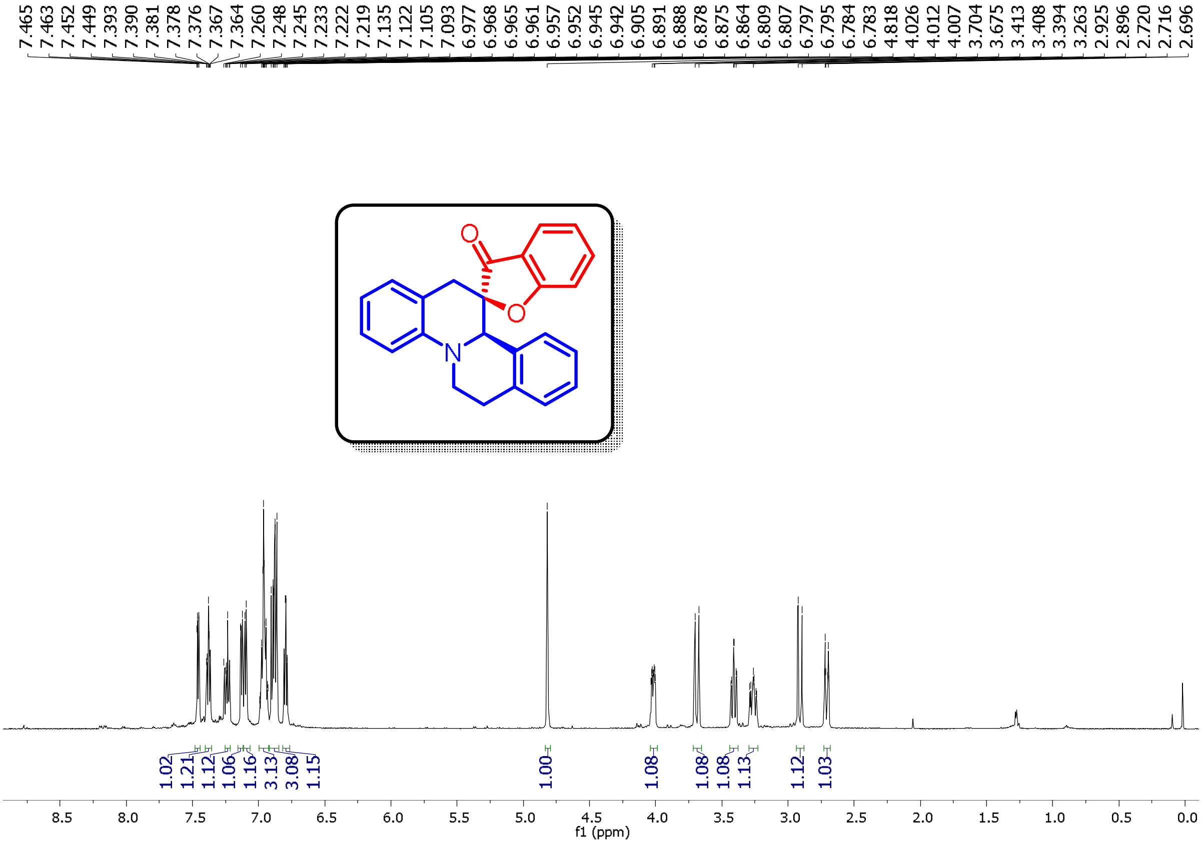
^{1}H NMR of **3j** (300 MHz, Chloroform-*d*)



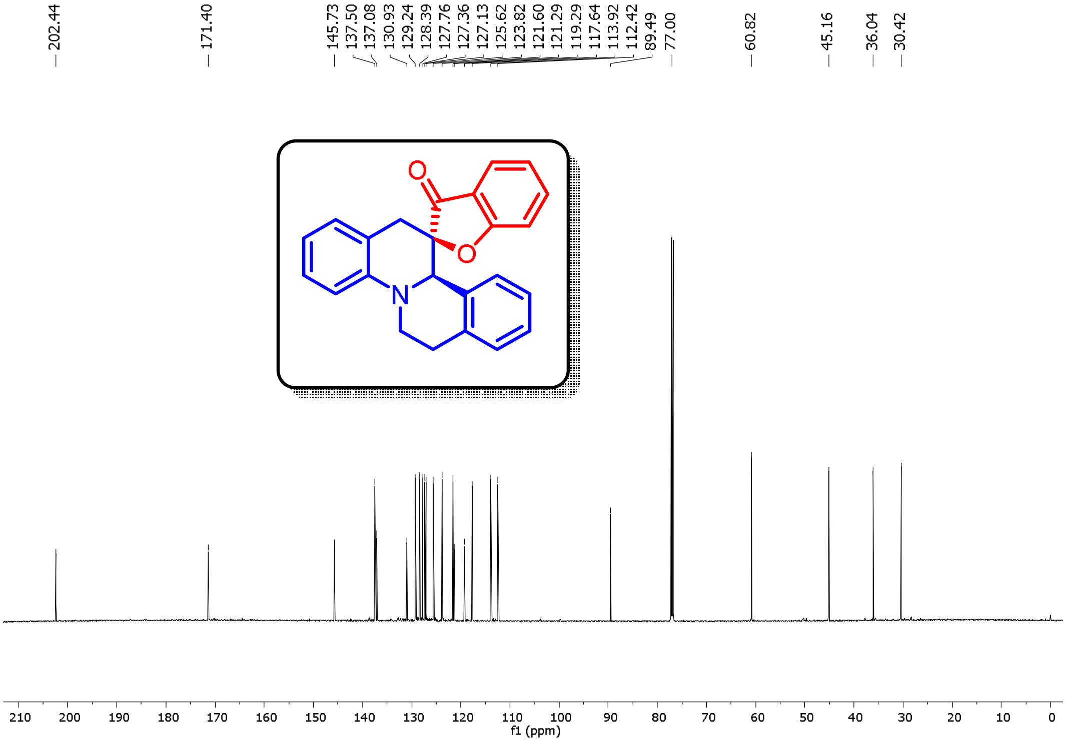
^{13}C NMR of **3j** (75 MHz, CDCl$_3$)



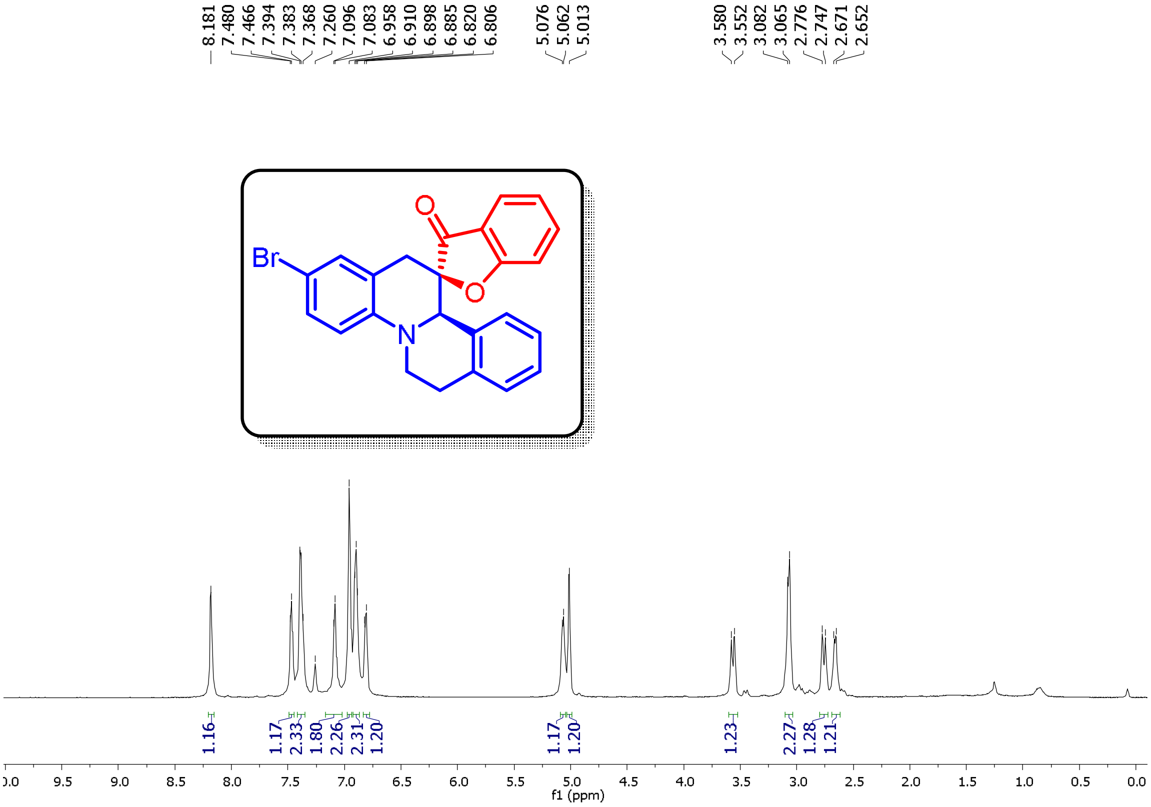
^{1}H NMR of **6a** (600 MHz, Chloroform-*d*)



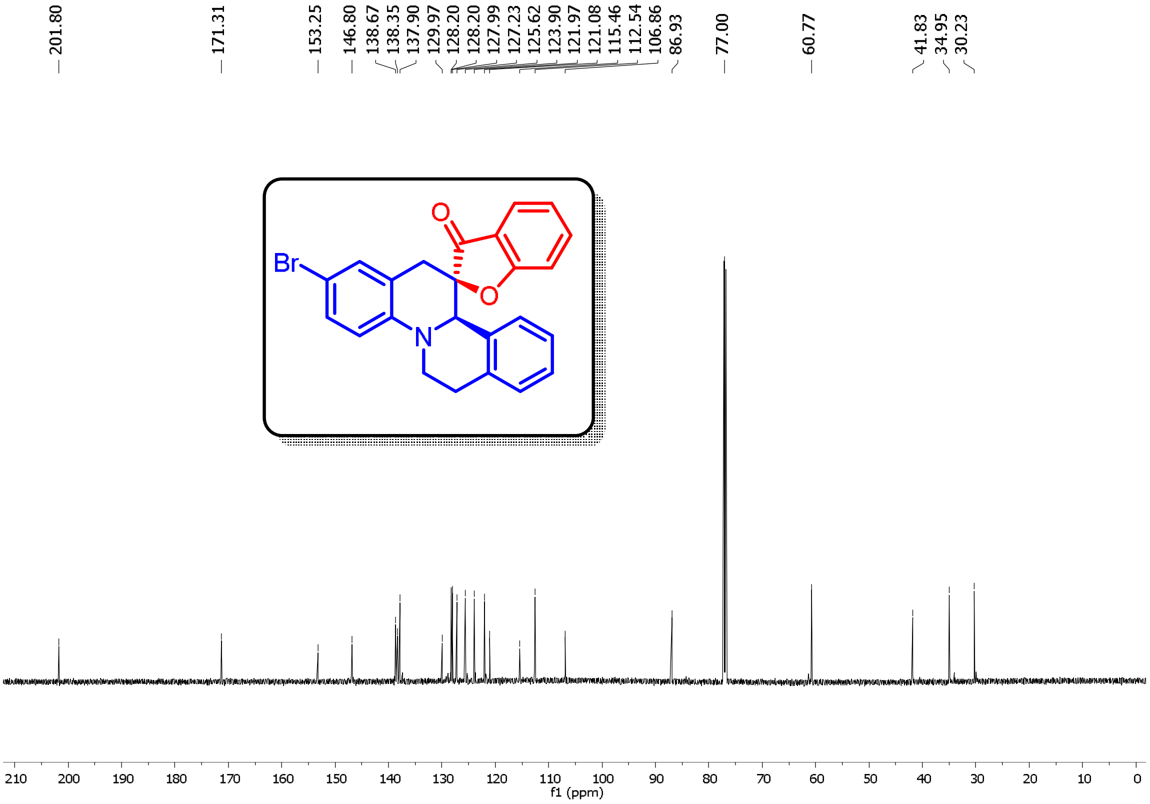
^{13}C NMR of **6a** (151 MHz, $CDCl_3$)



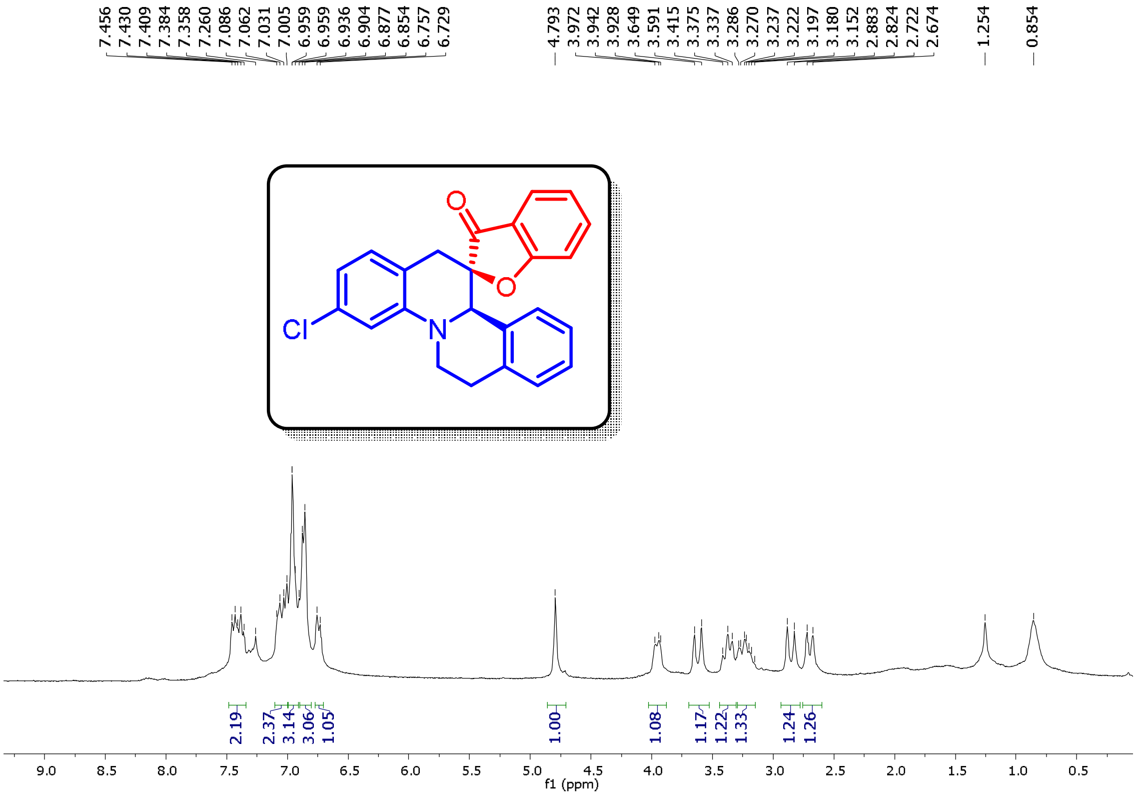
^{1}H NMR of **6b** (600 MHz, Chloroform-*d*)



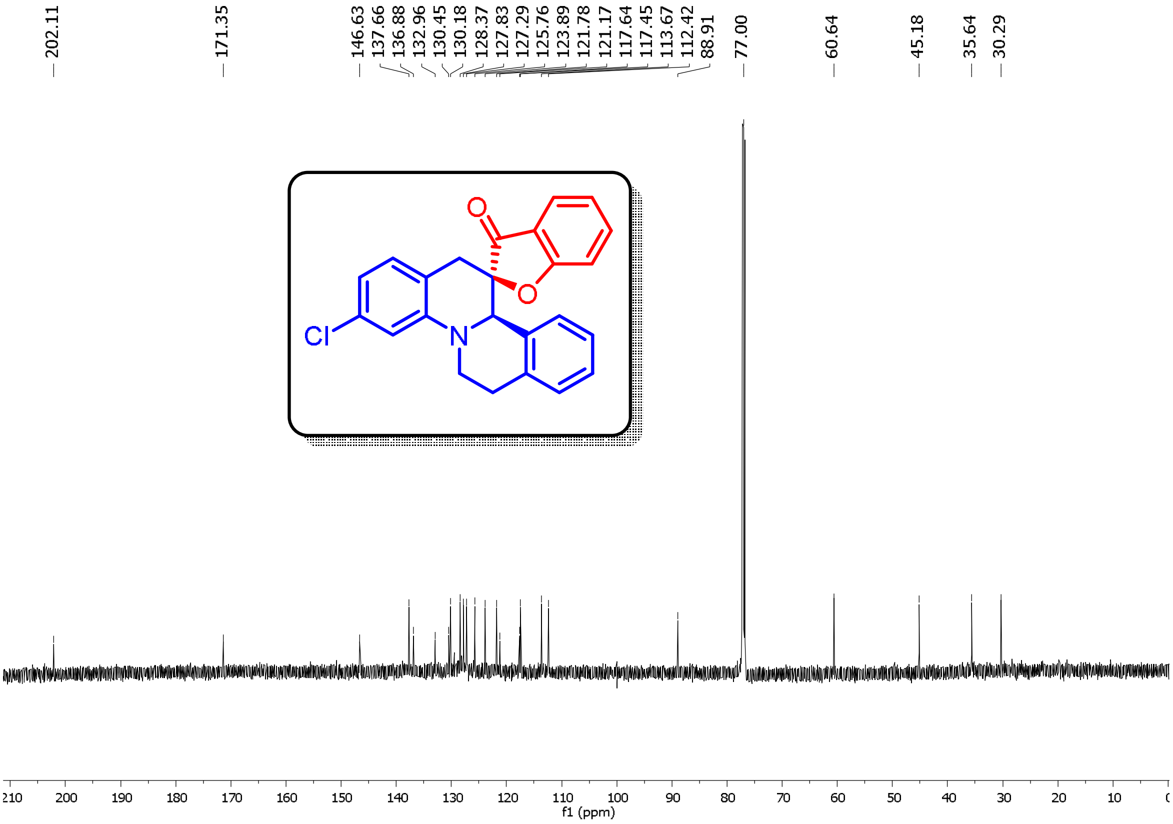
^{13}C NMR of **6b** (151 MHz, CDCl$_3$)



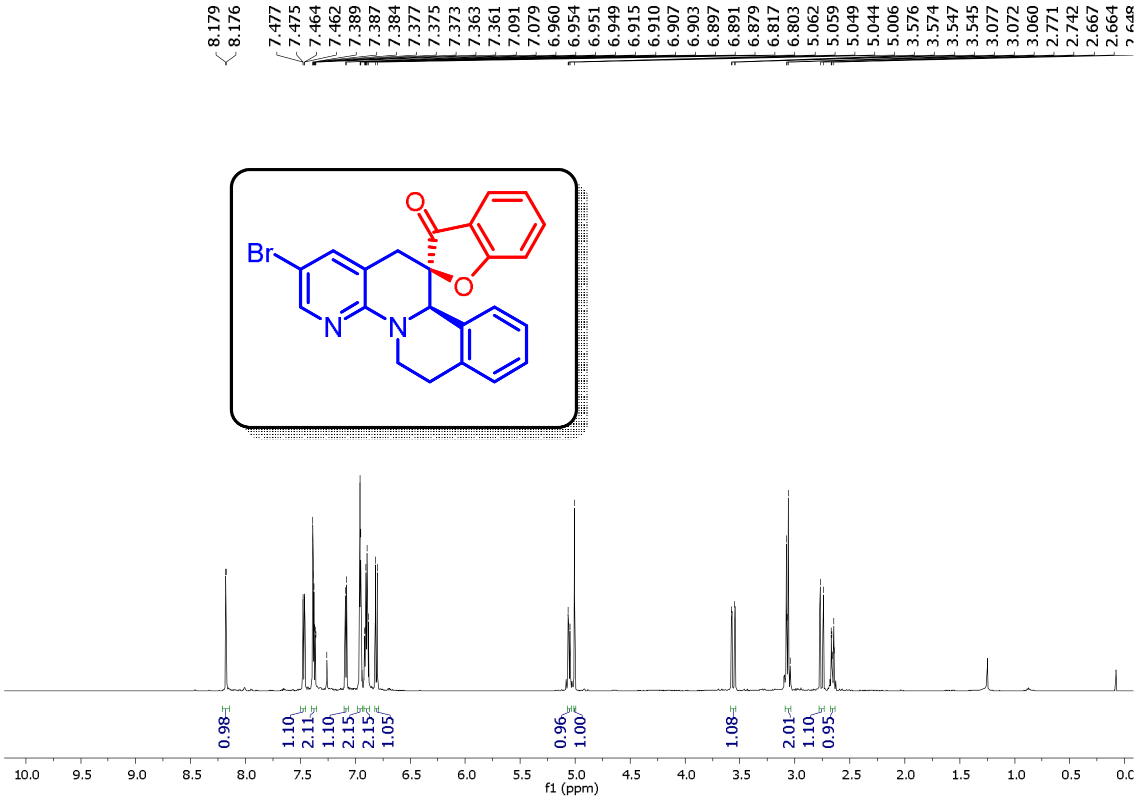
^{1}H NMR of **6c** (300 MHz, Chloroform-*d*)



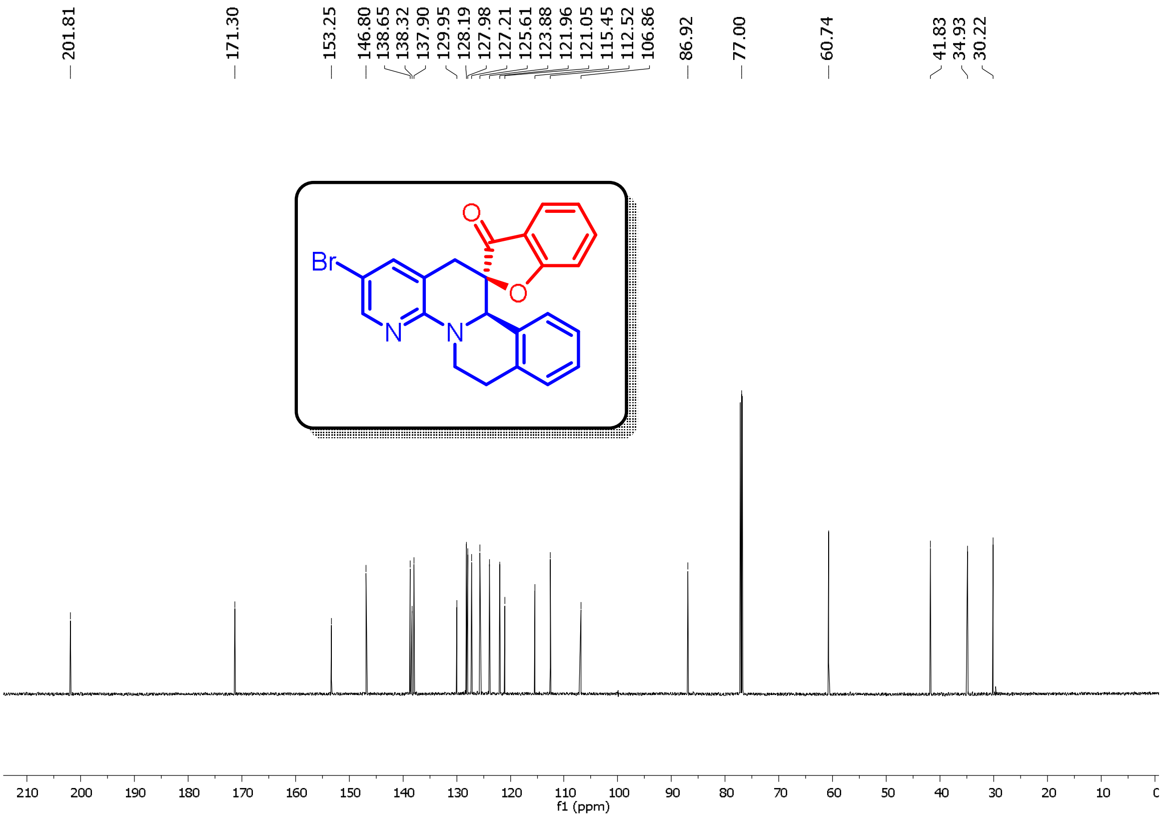
^{13}C NMR of **6c** (151 MHz, CDCl$_3$)



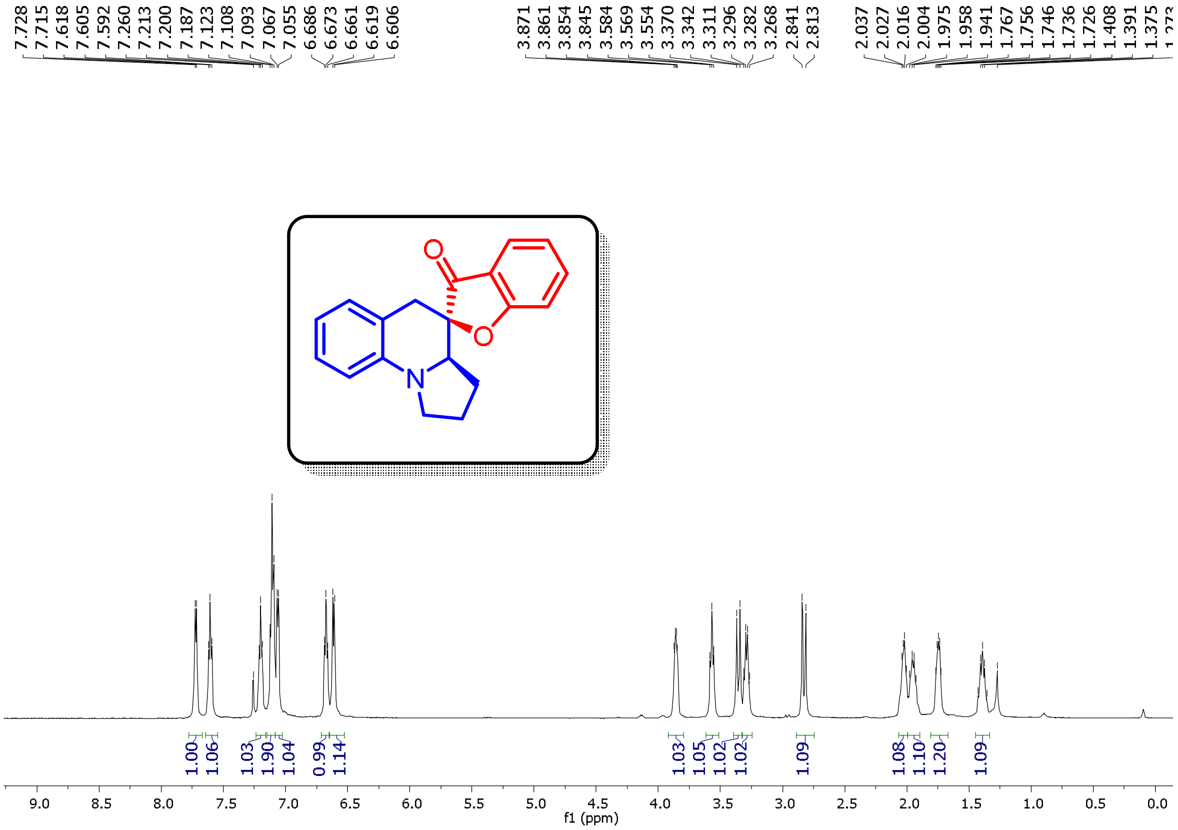
^{1}H NMR of **6d** (600 MHz, Chloroform-*d*)



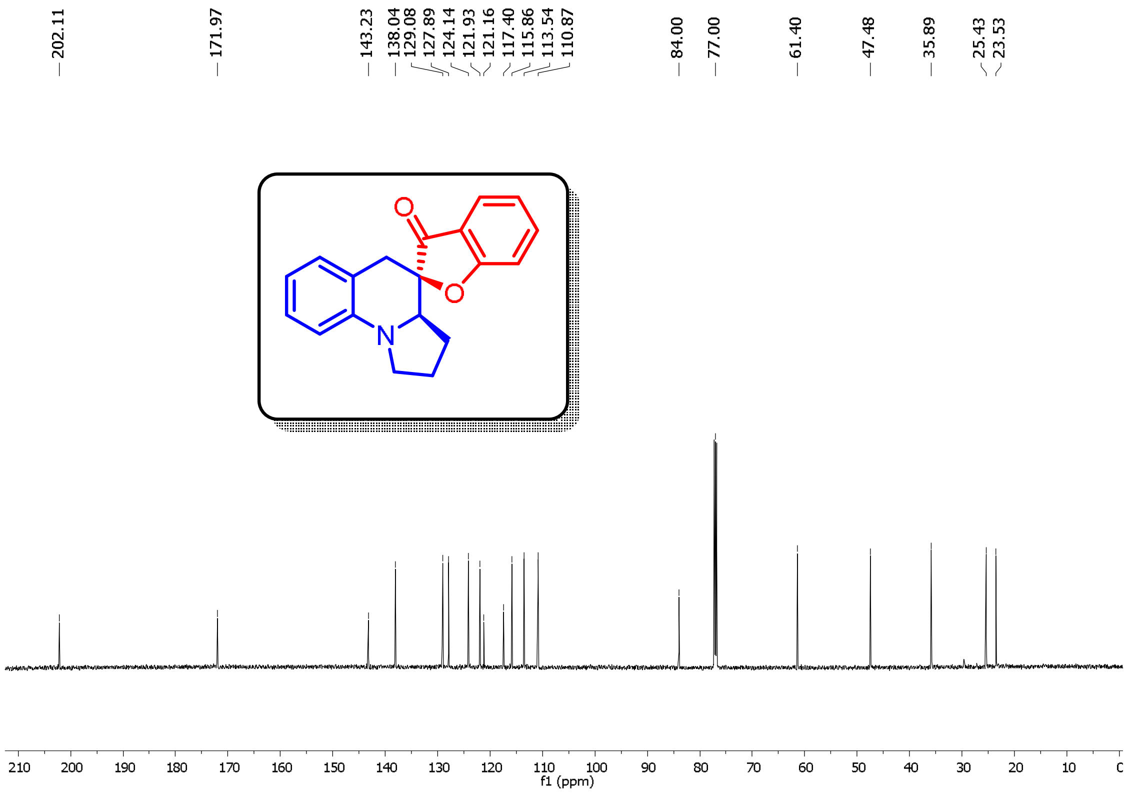
^{13}C NMR of **6d** (151 MHz, CDCl$_3$)



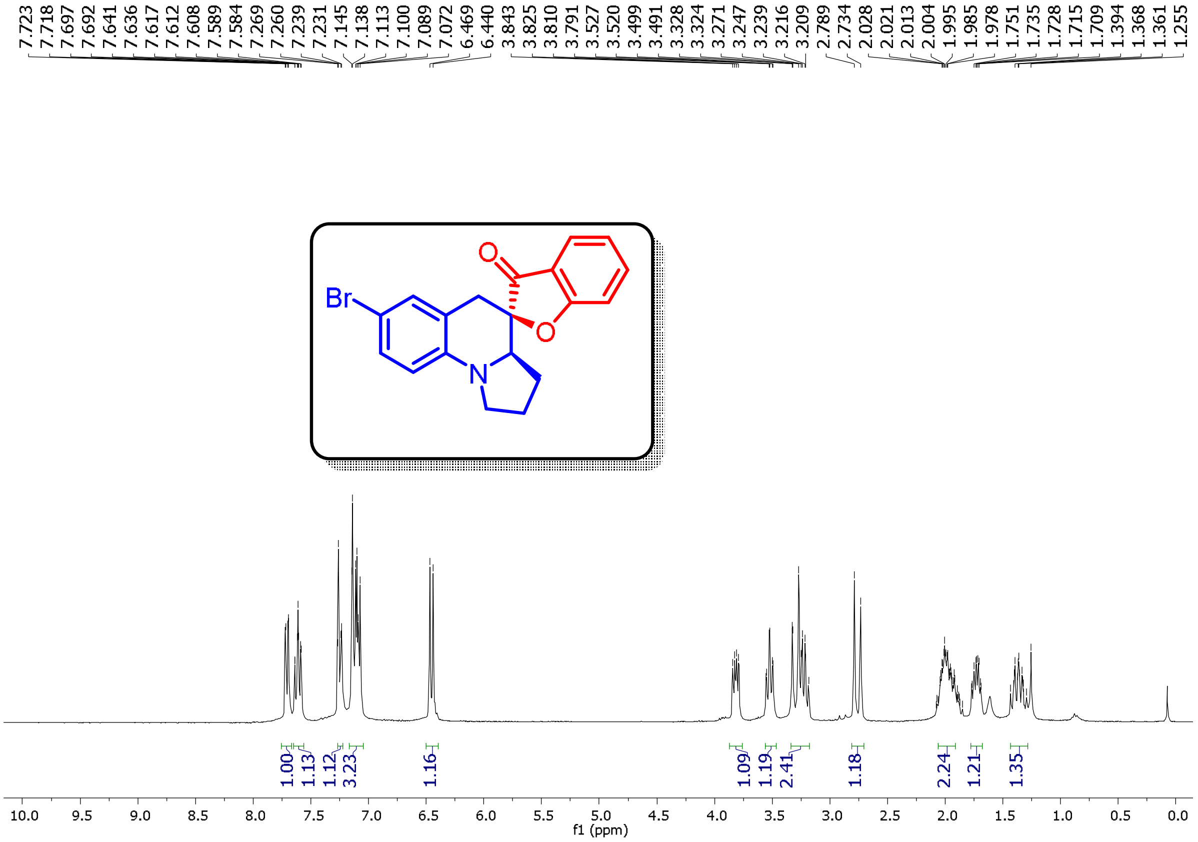
^{1}H NMR of **6e** (600 MHz, Chloroform-*d*)



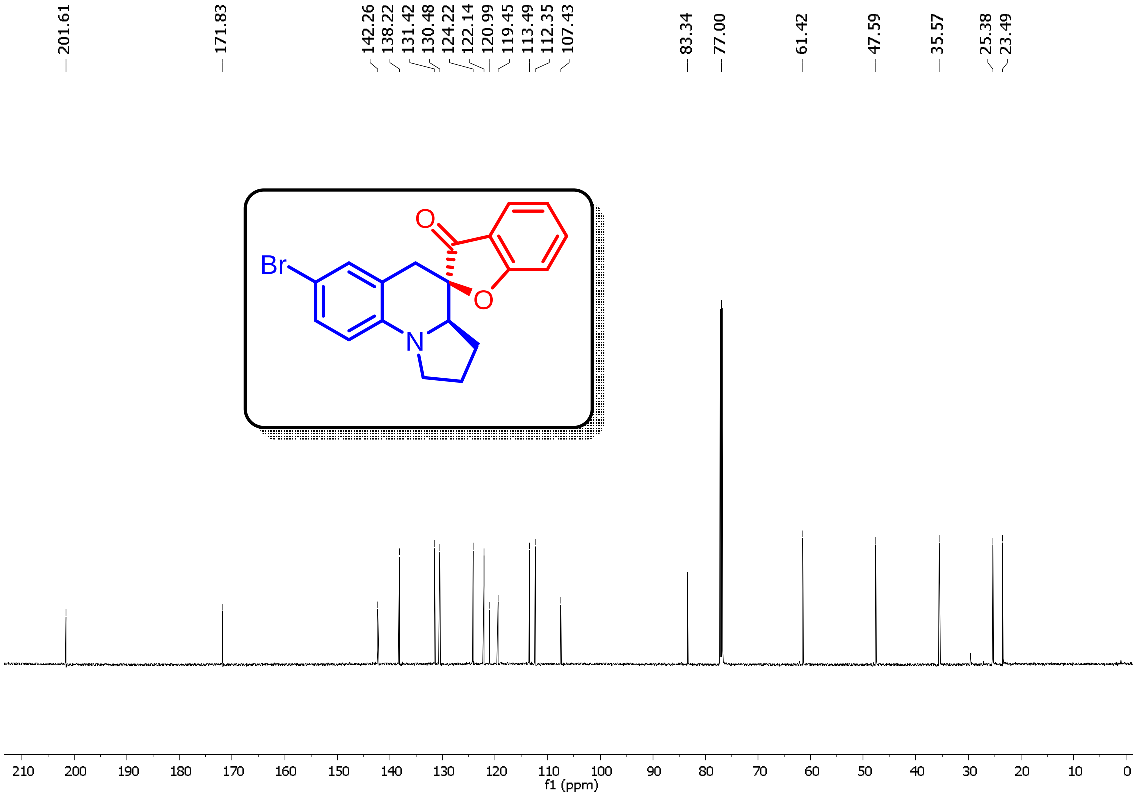
^{13}C NMR of **6e** (151 MHz, $CDCl_3$)



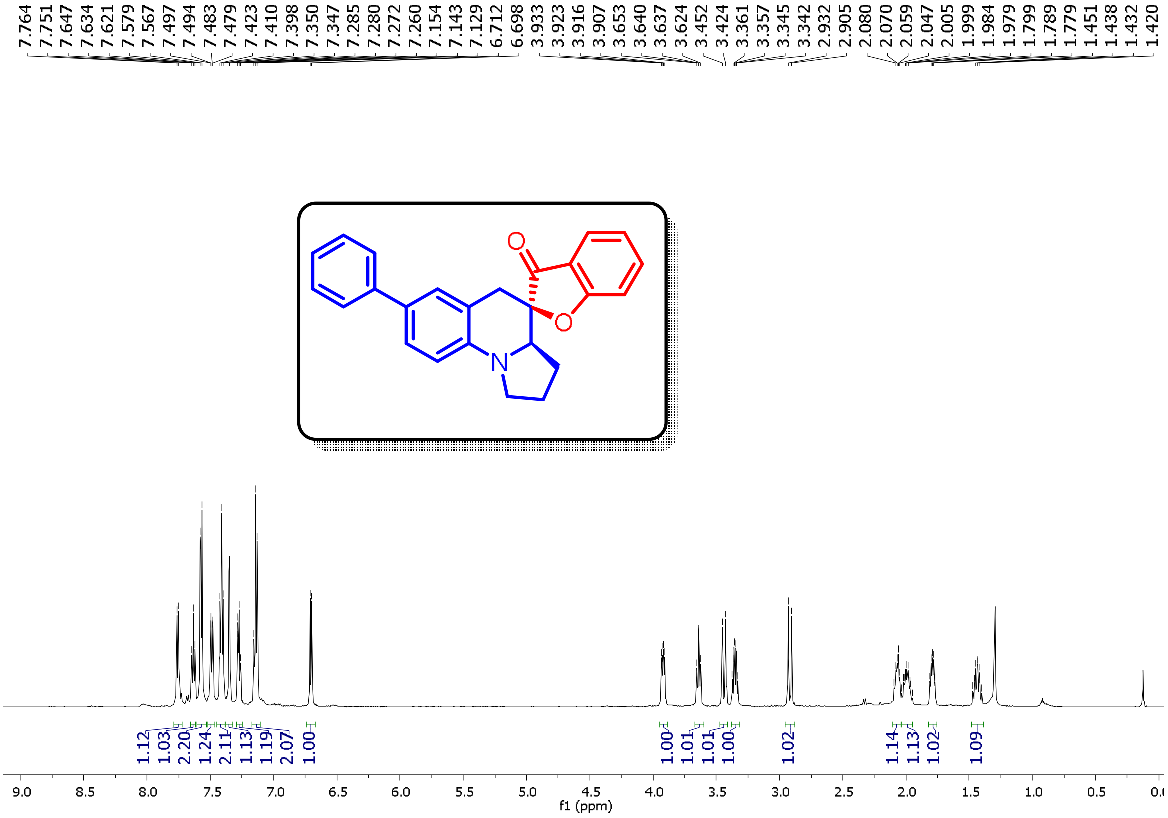
^{1}H NMR of **6f** (300 MHz, Chloroform-*d*)



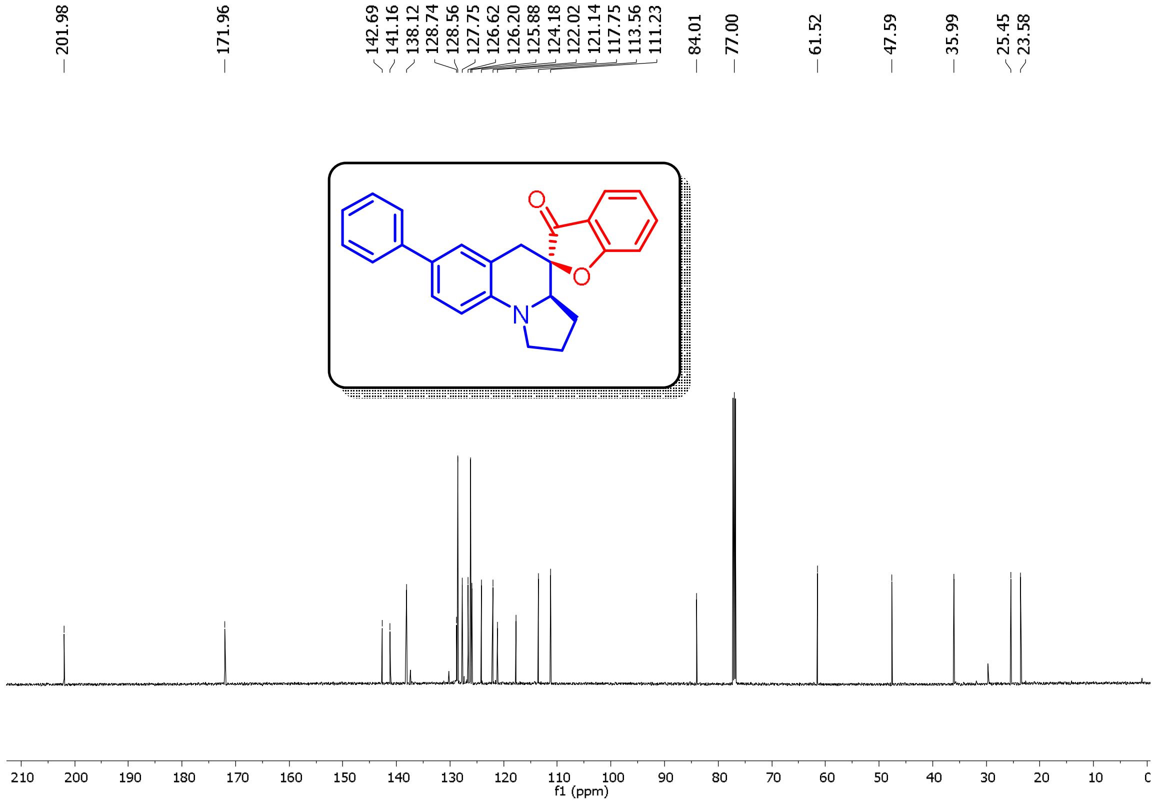
^{13}C NMR of **6f** (151 MHz, CDCl$_3$)



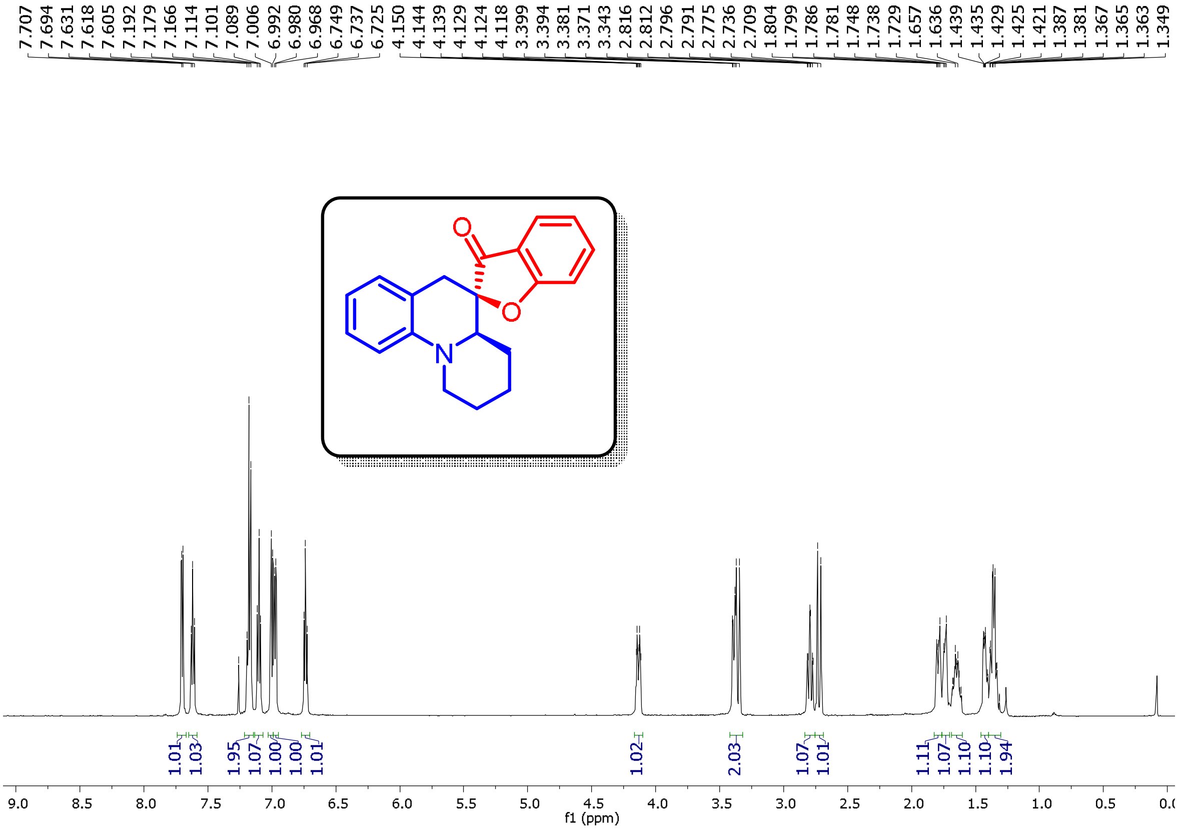
^{1}H NMR of **6g** (600 MHz, Chloroform-*d*)



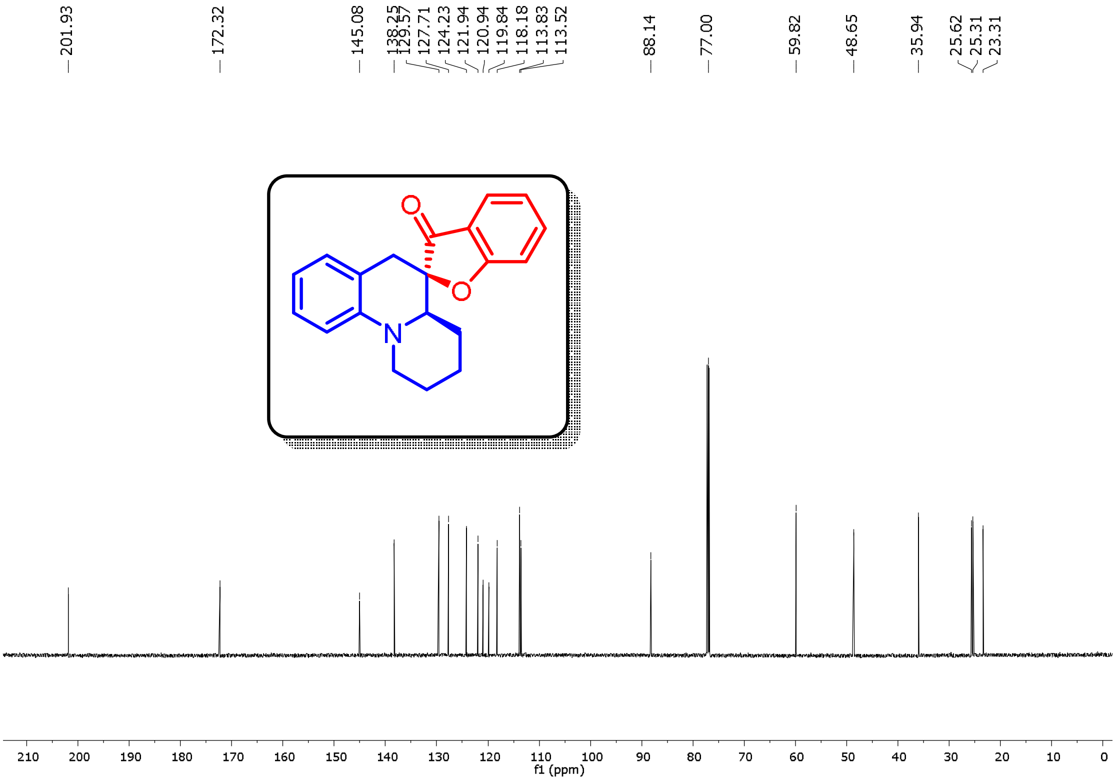
^{13}C NMR of **6g** (151 MHz, CDCl$_3$)



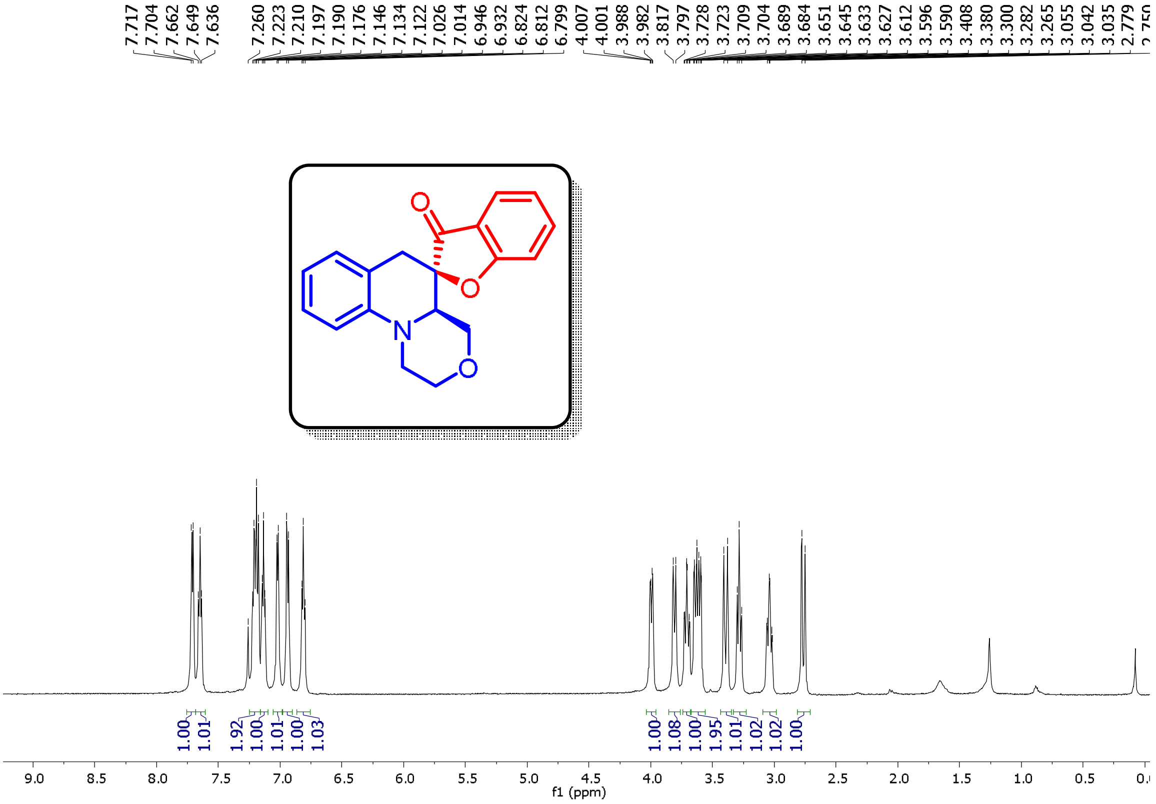
^{1}H NMR of **6h** (600 MHz, Chloroform-*d*)



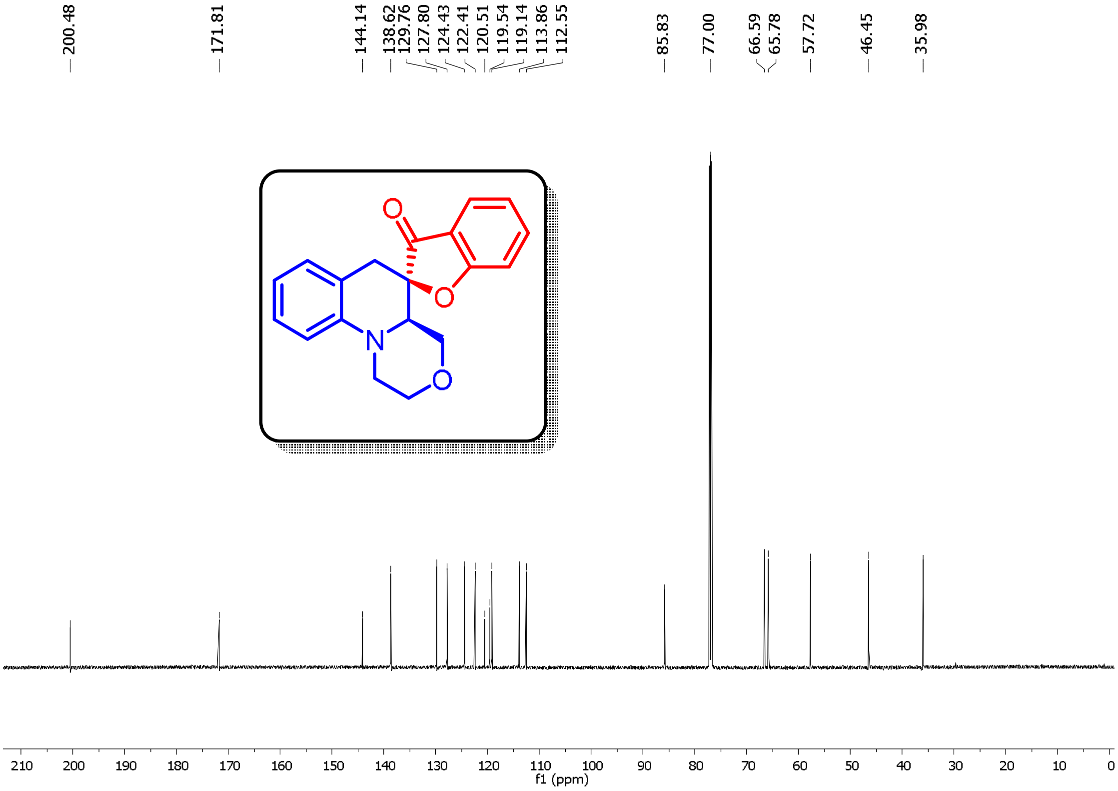
^{13}C NMR of **6h** (151 MHz, CDCl$_3$)



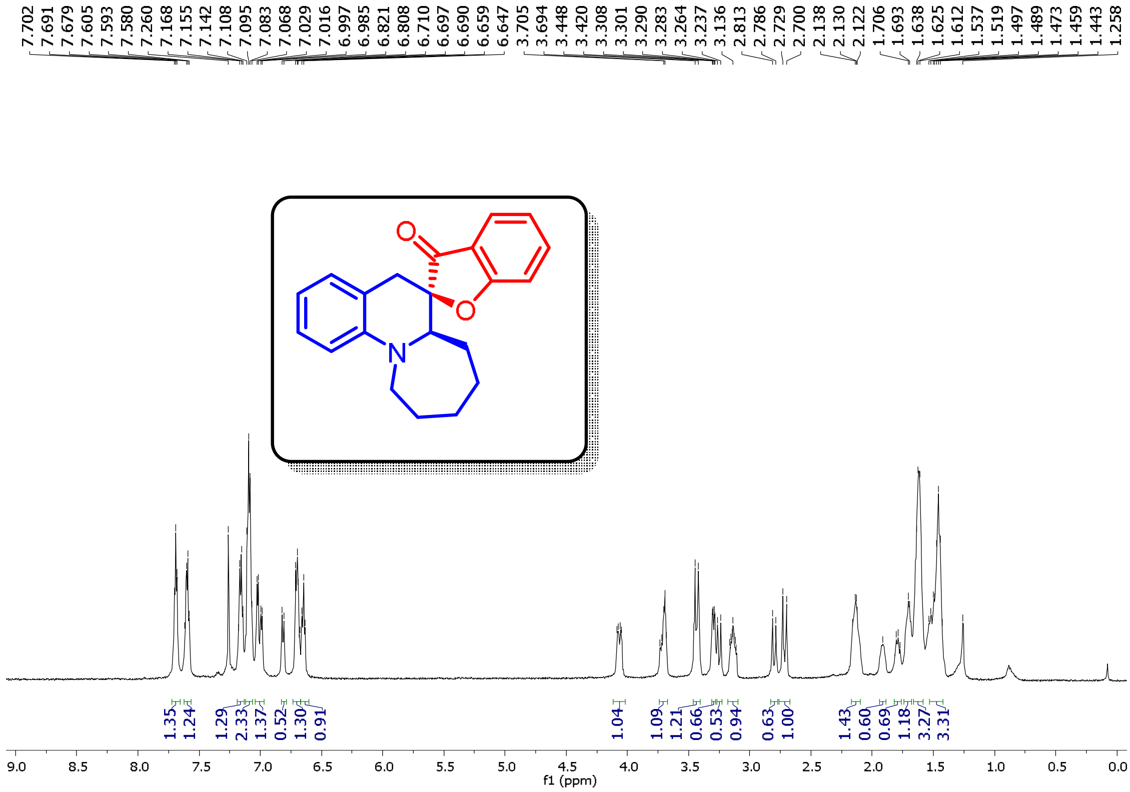
^{1}H NMR of **6i** (600 MHz, Chloroform-*d*)



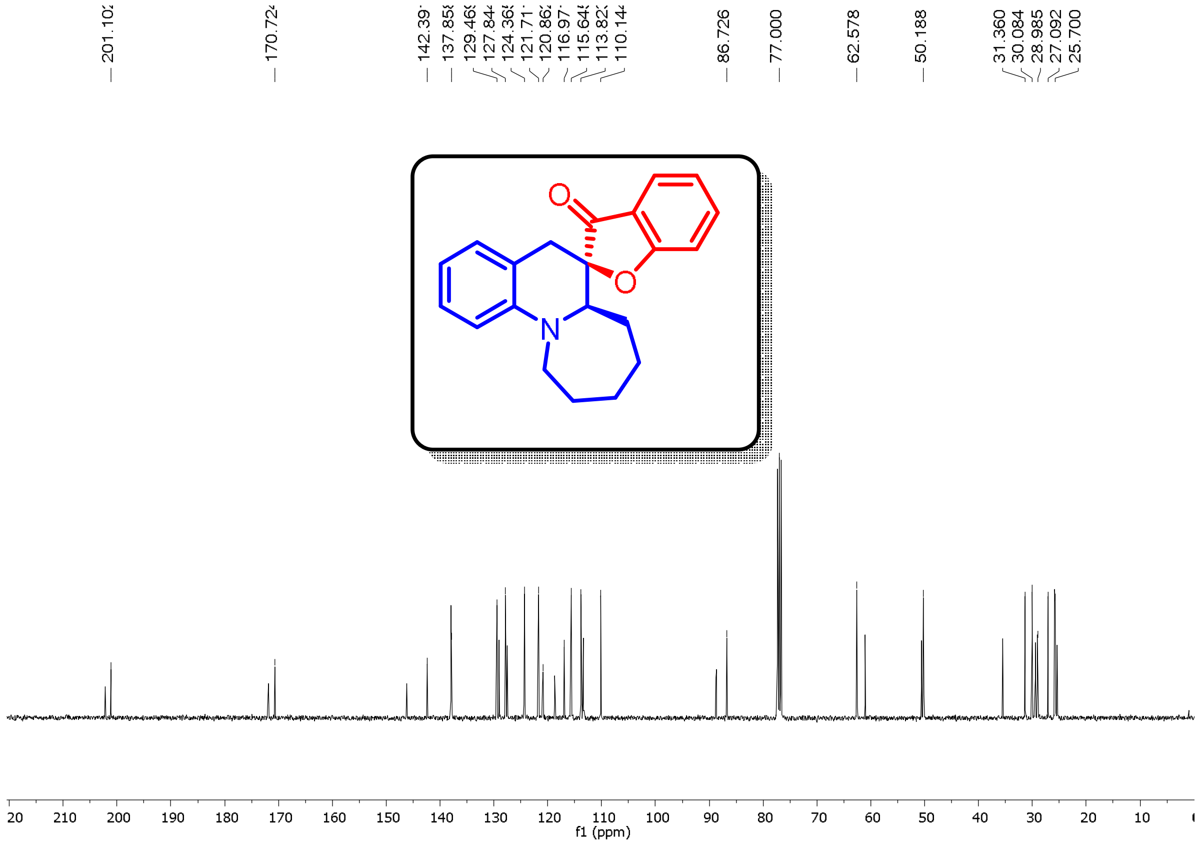
^{13}C NMR of **6i** (151 MHz, $CDCl_3$)



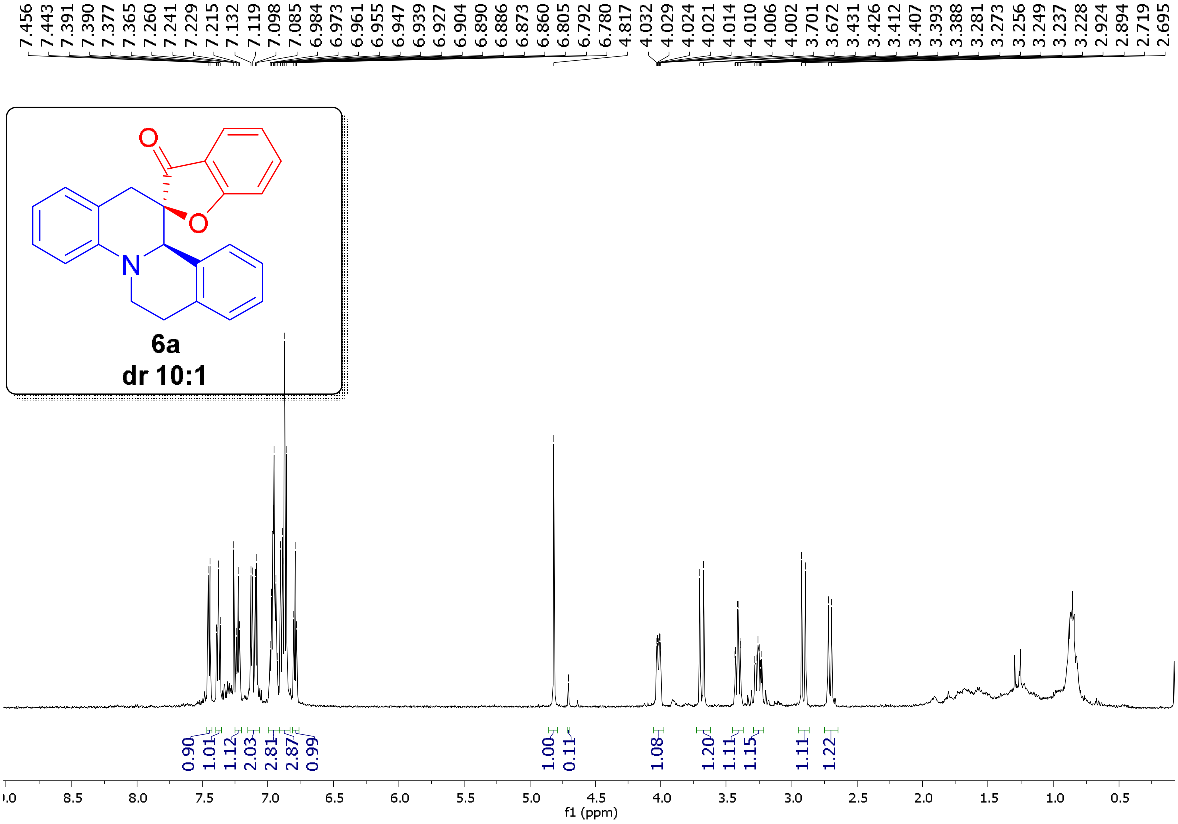
^{1}H NMR of **6j** (600 MHz, Chloroform-*d*)



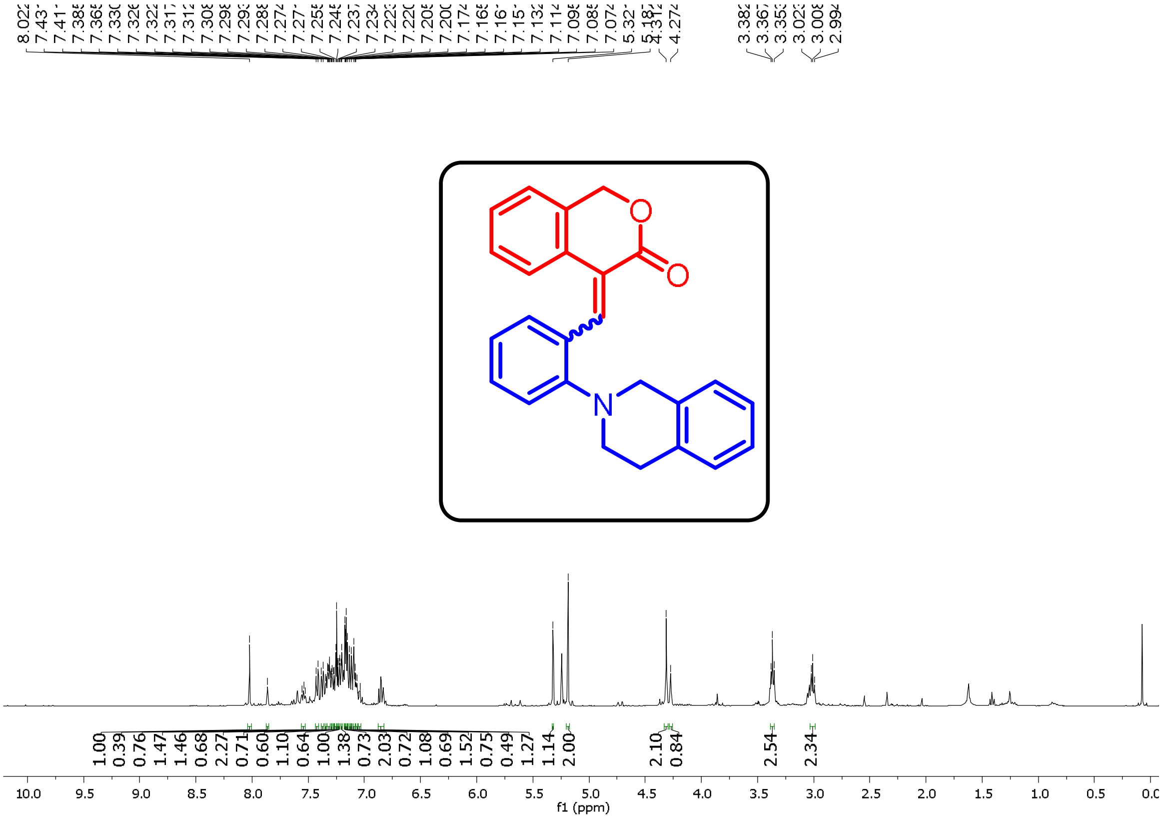
^{13}C NMR of **6j** (101 MHz, CDCl$_3$)



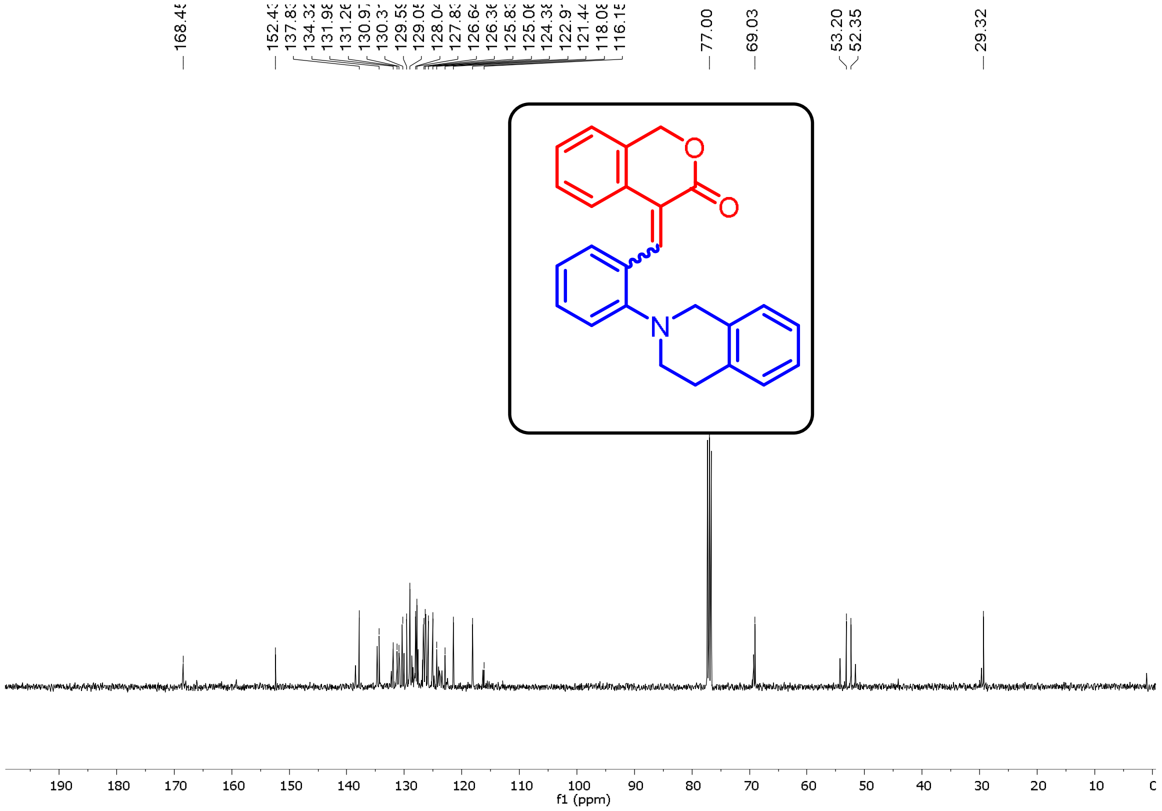
Crude ^{1}H NMR of 6a



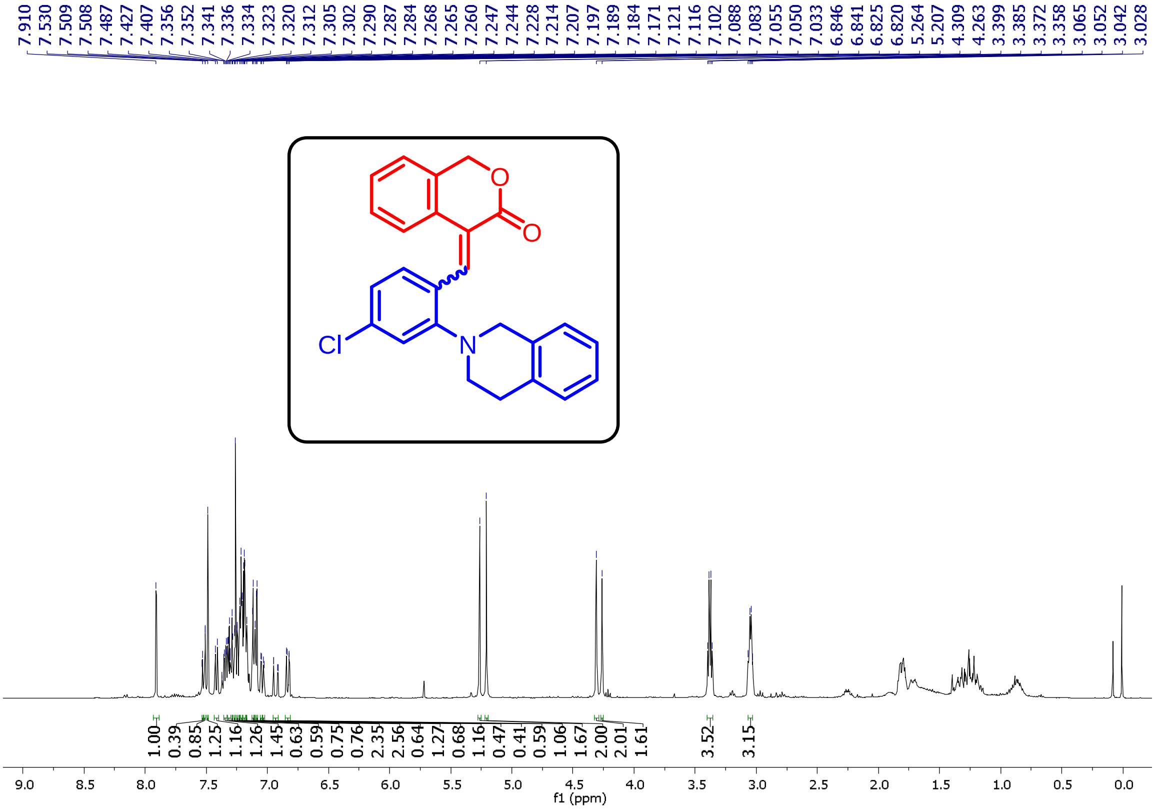
^{1}H NMR of **4a** (400 MHz, Chloroform-*d*)



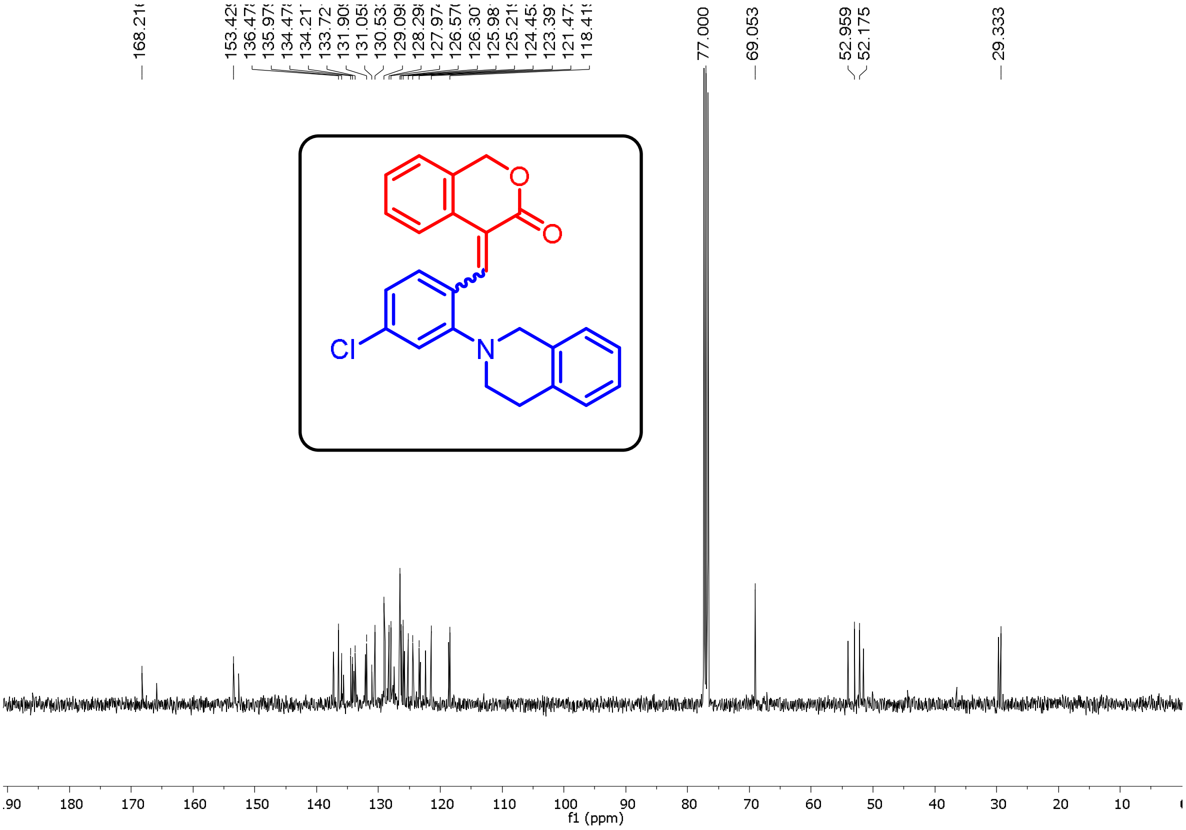
^{13}C NMR of **4a** (101 MHz, CDCl$_3$)



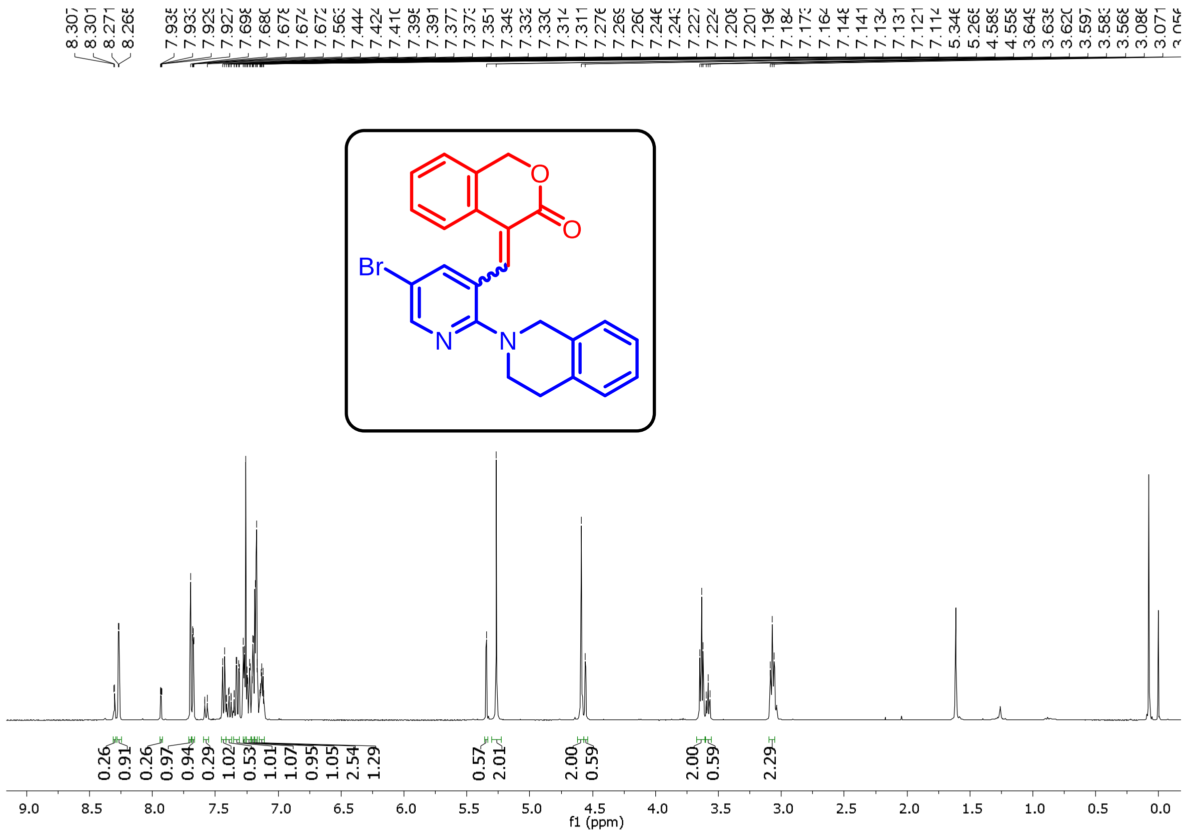
^{1}H NMR of **4b** (400 MHz, Chloroform-*d*)



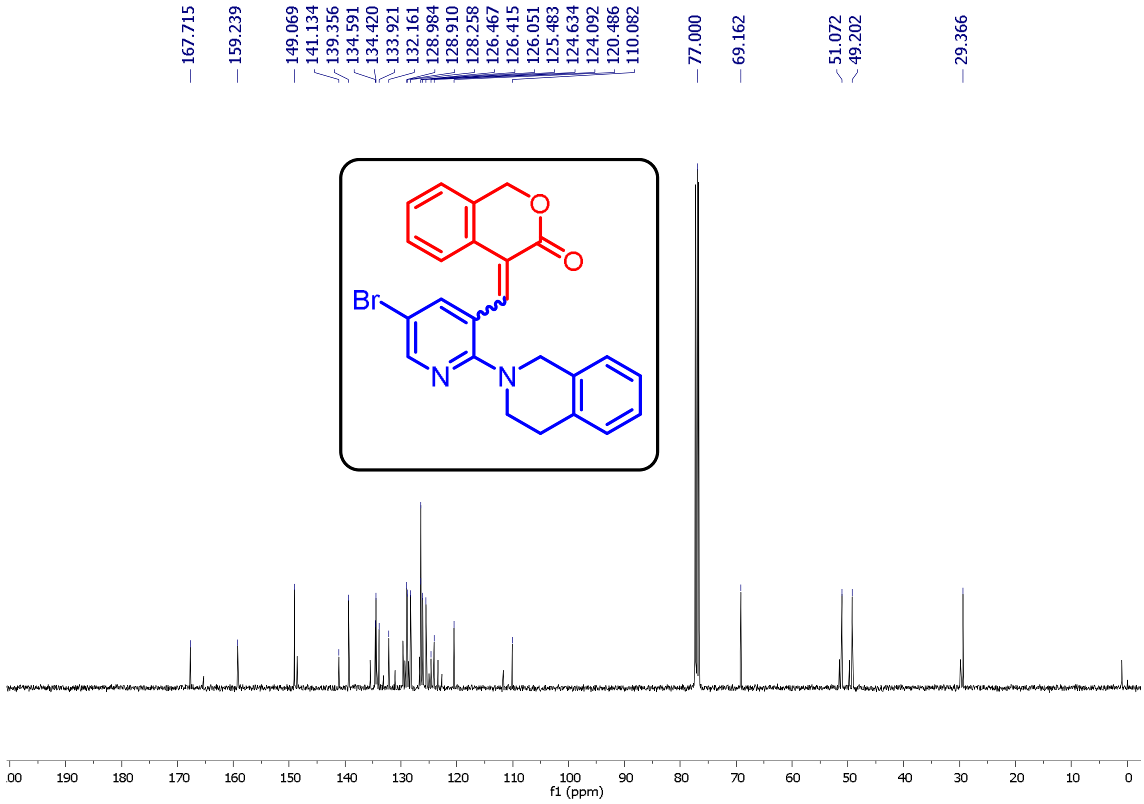
^{13}C NMR of **4b** (101 MHz, CDCl$_3$)



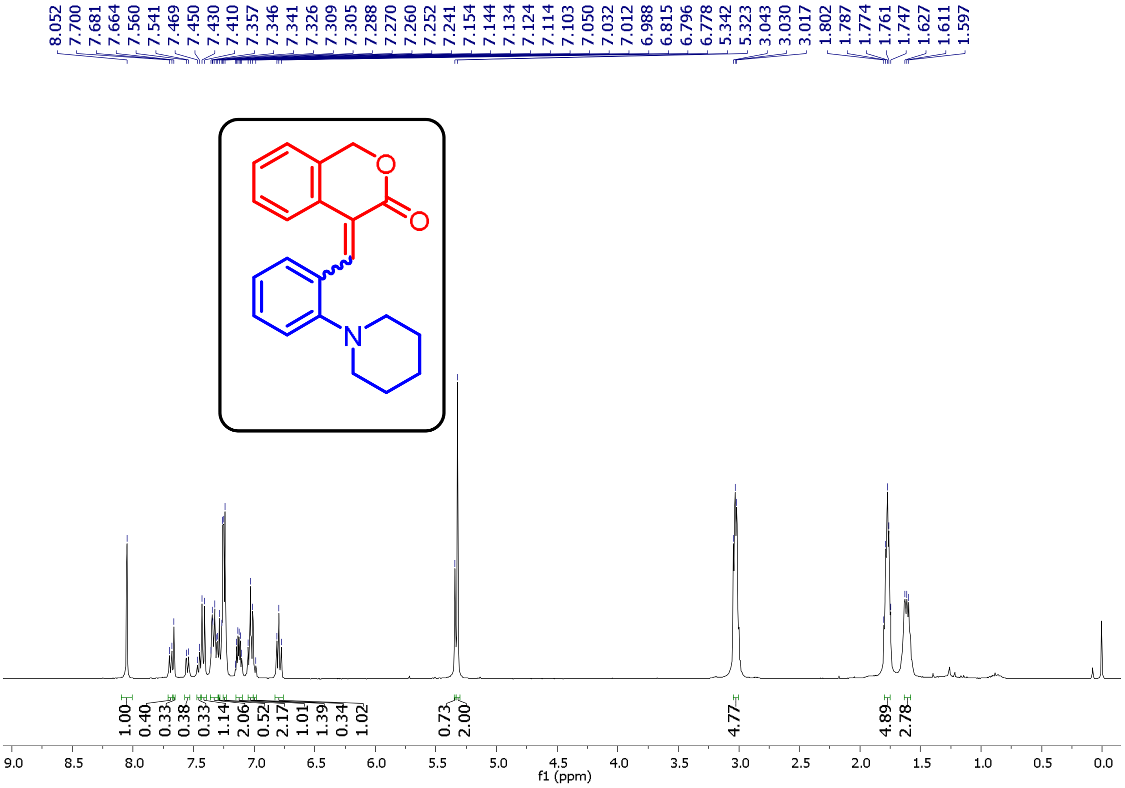
^{1}H NMR of **4c** (400 MHz, Chloroform-*d*)



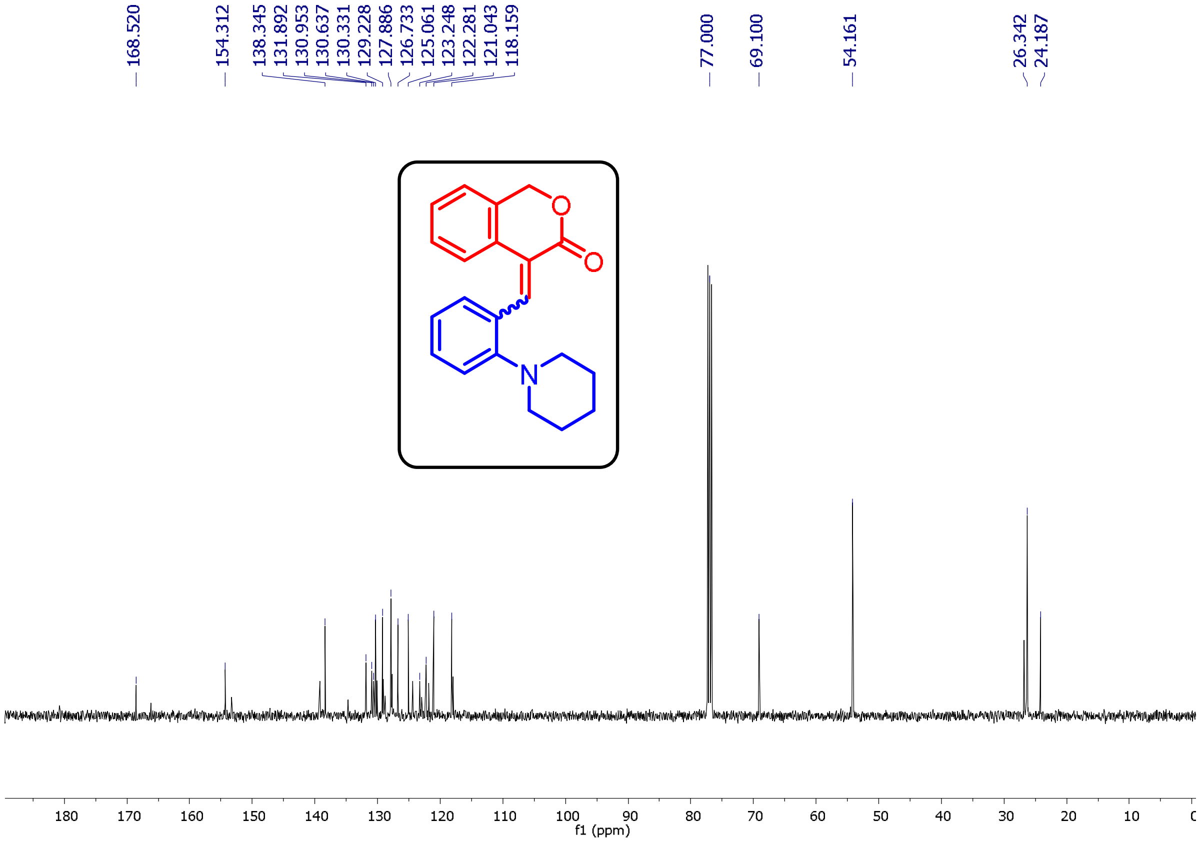
^{13}C NMR of **4c** (101 MHz, CDCl$_3$)



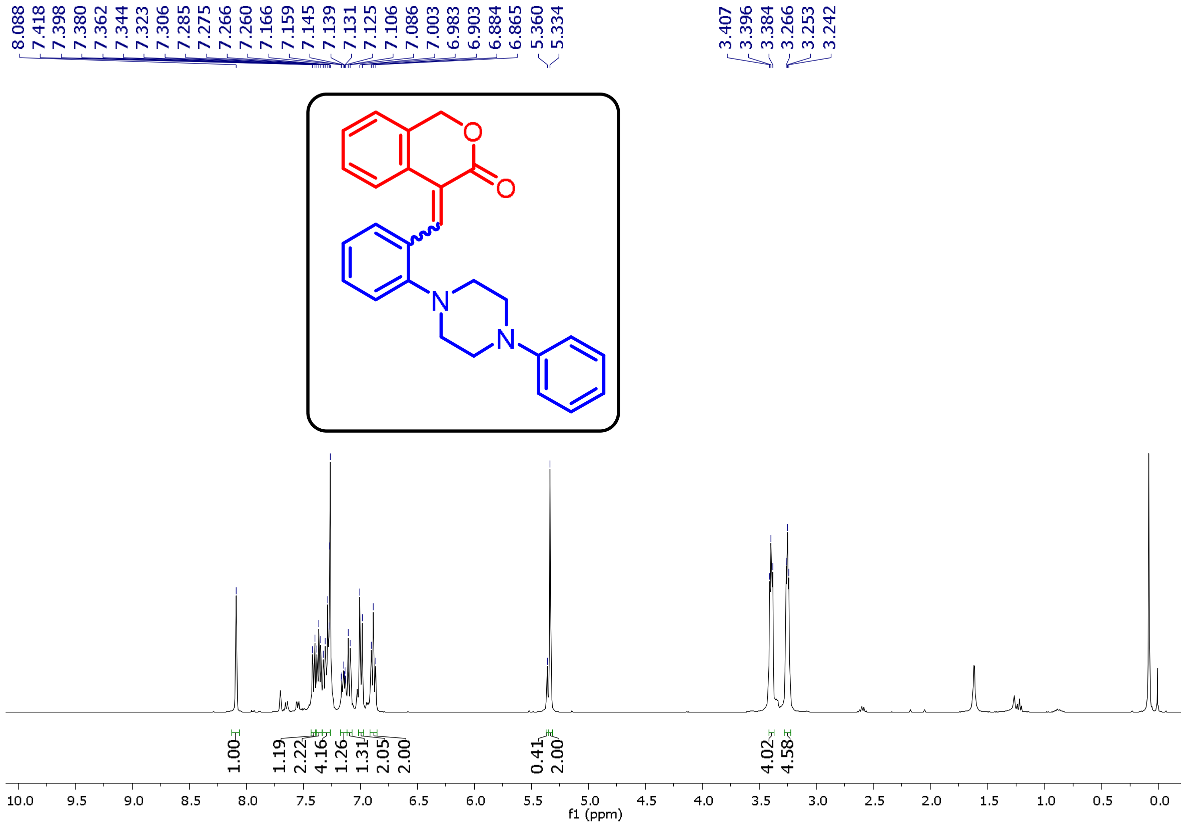
^{1}H NMR of **4d** (400 MHz, Chloroform-*d*)



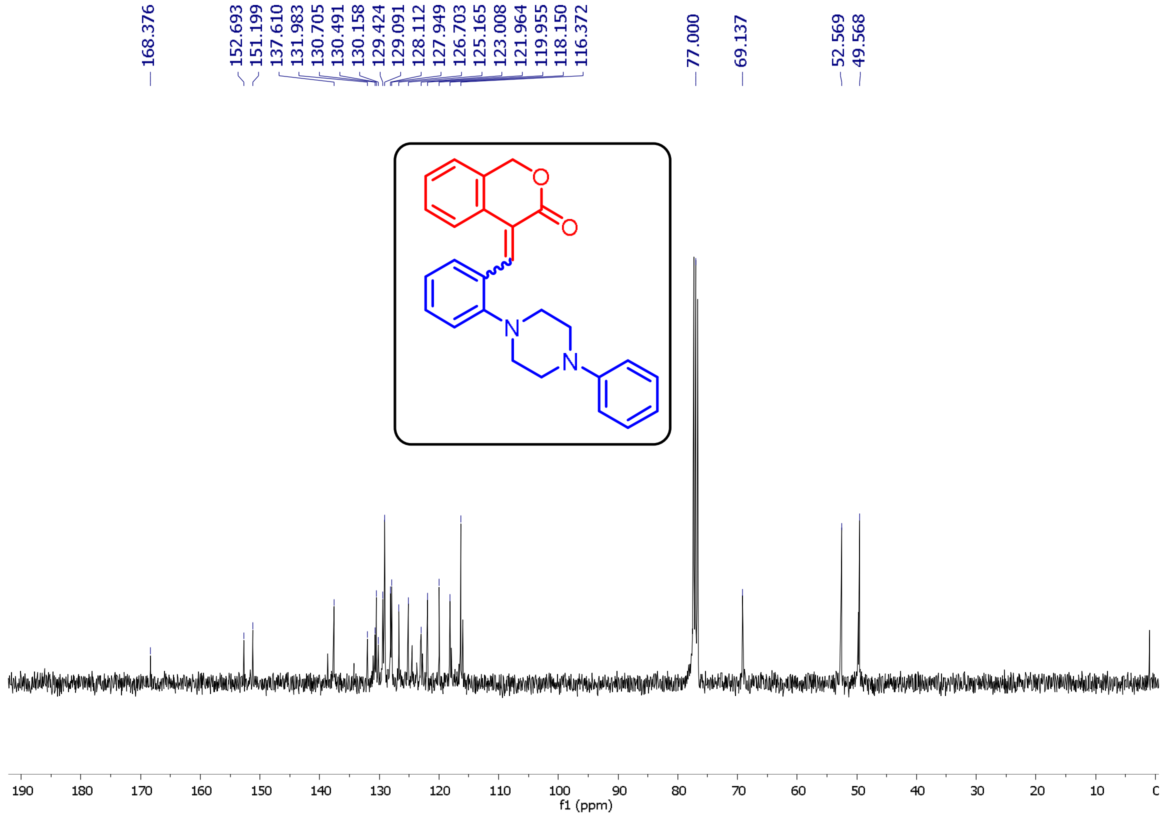
^{13}C NMR of **4d** (101 MHz, CDCl$_3$)



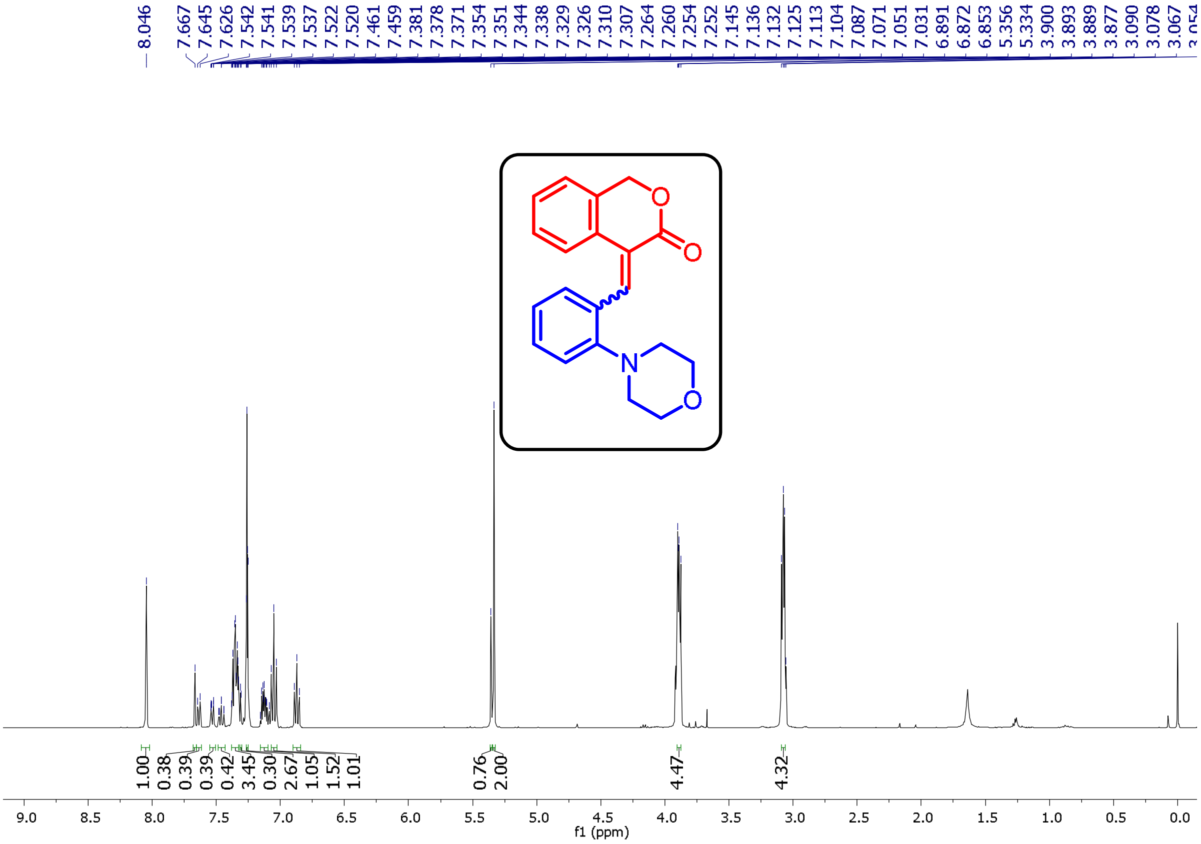
^{1}H NMR of **4e** (400 MHz, Chloroform-*d*)



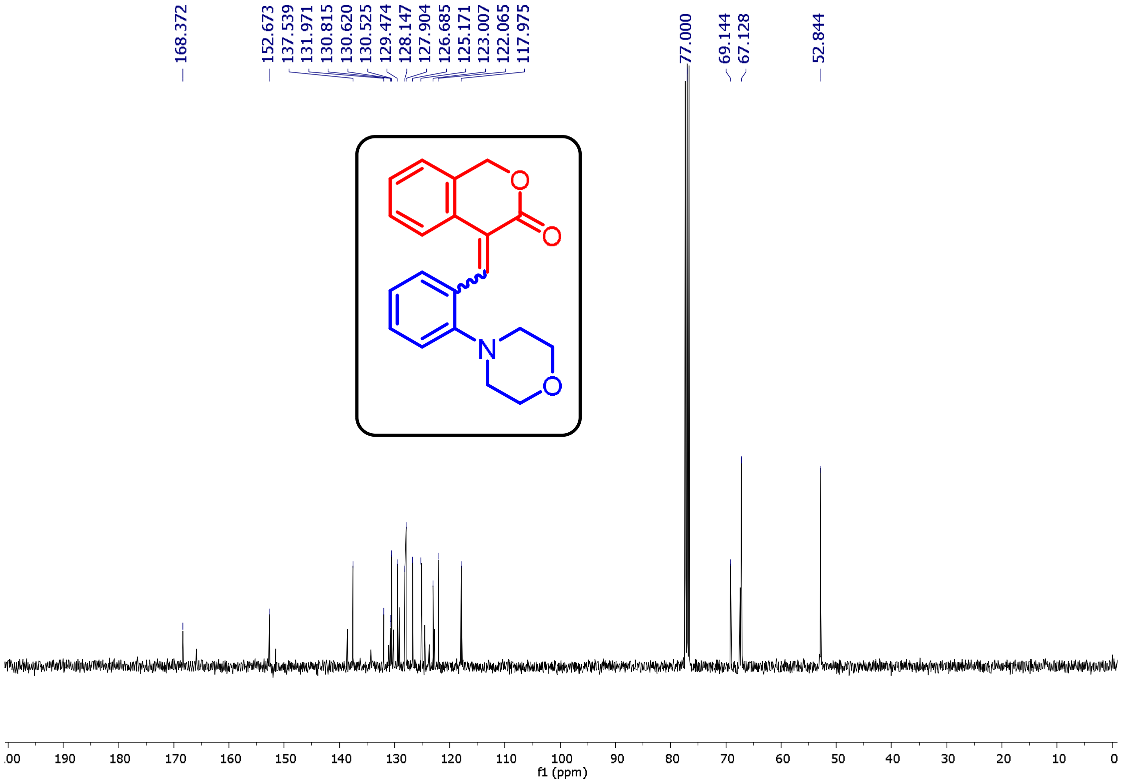
^{13}C NMR of **4e** (101 MHz, CDCl$_3$)



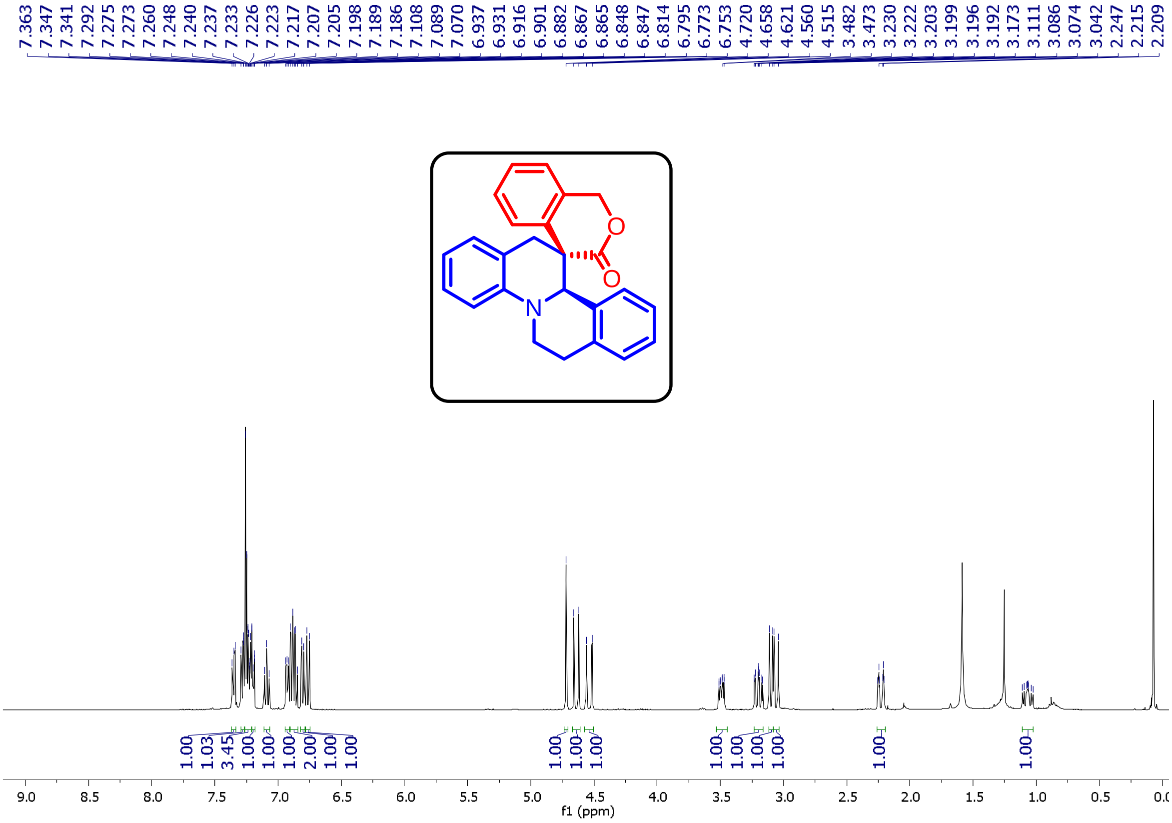
^{1}H NMR of **4f** (400 MHz, Chloroform-*d*)



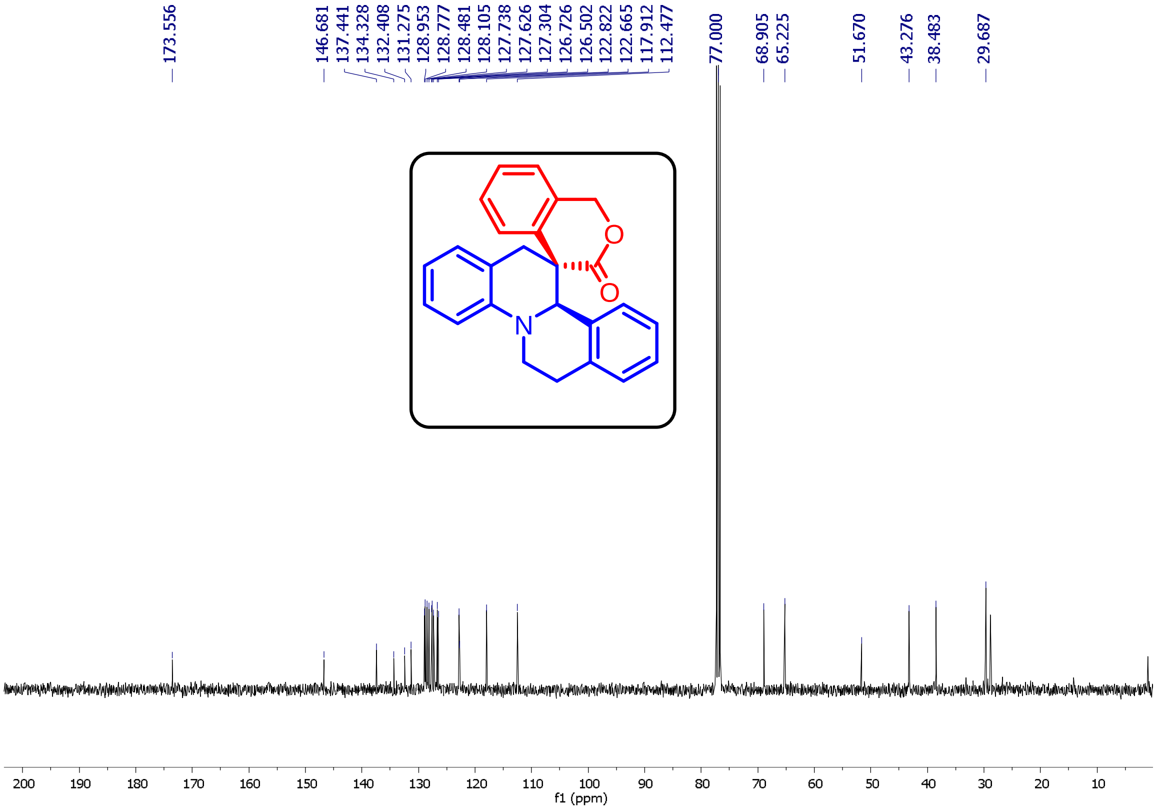
^{13}C NMR of **4f** (101 MHz, CDCl$_3$)



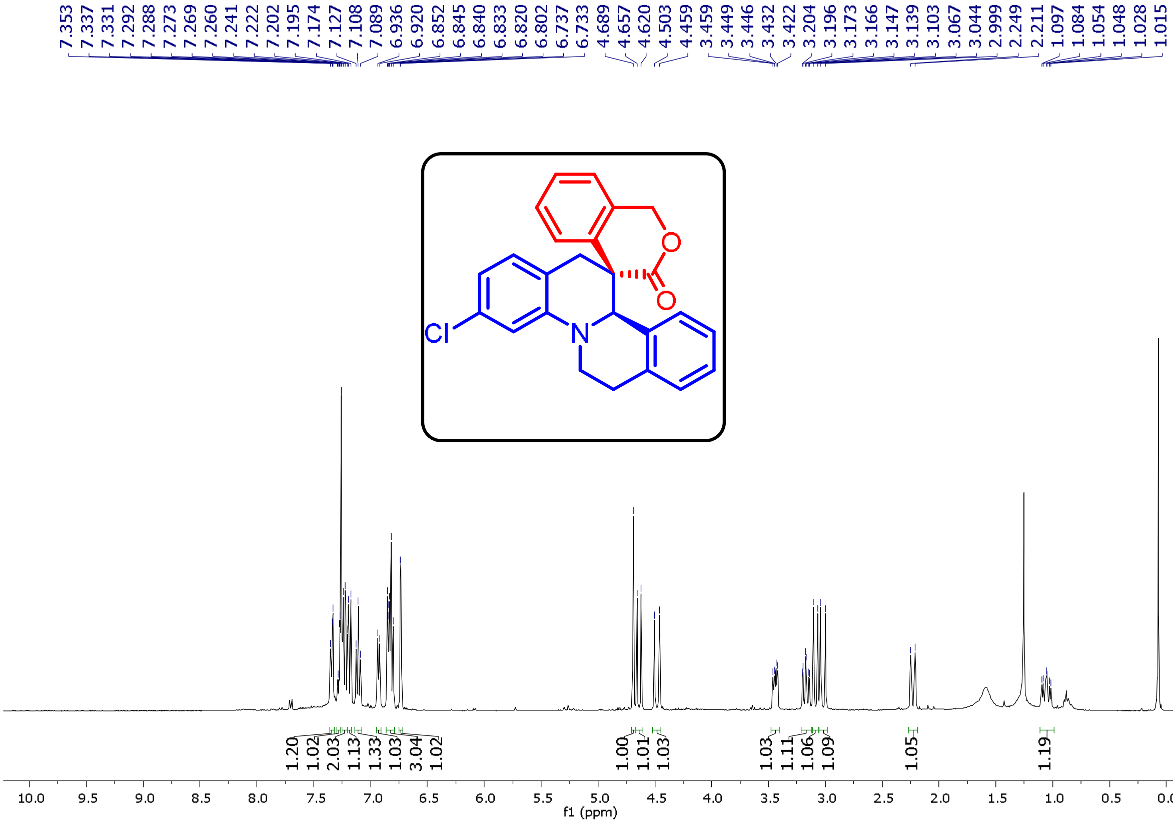
^{1}H NMR of **7a** (400 MHz, Chloroform-*d*)



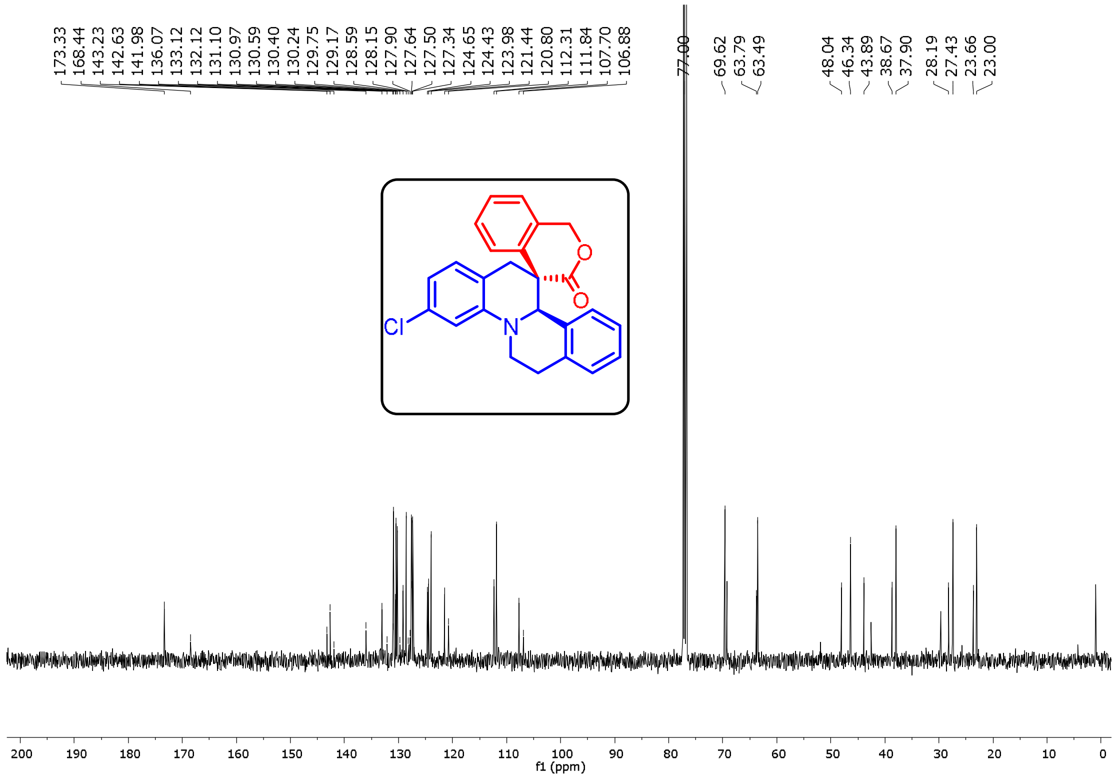
^{13}C NMR of **7a** (101 MHz, $CDCl_3$)



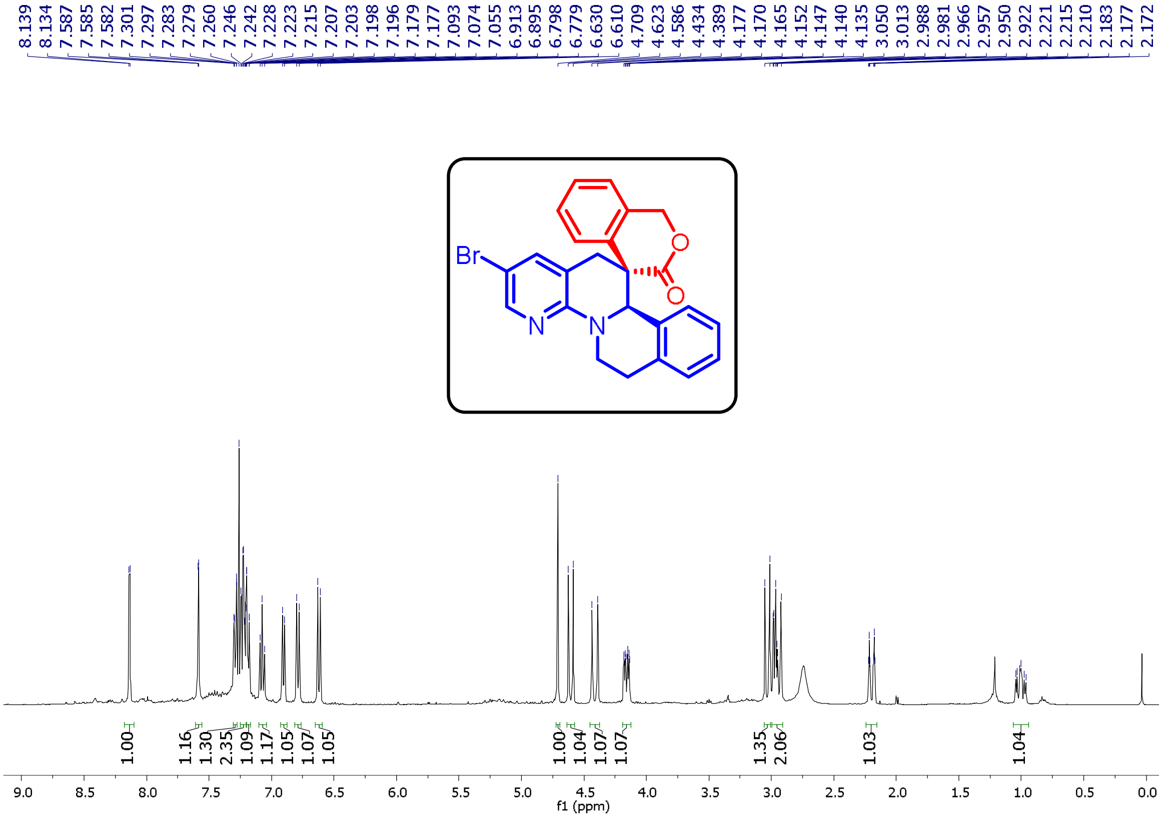
^{1}H NMR of **7b** (400 MHz, Chloroform-*d*)



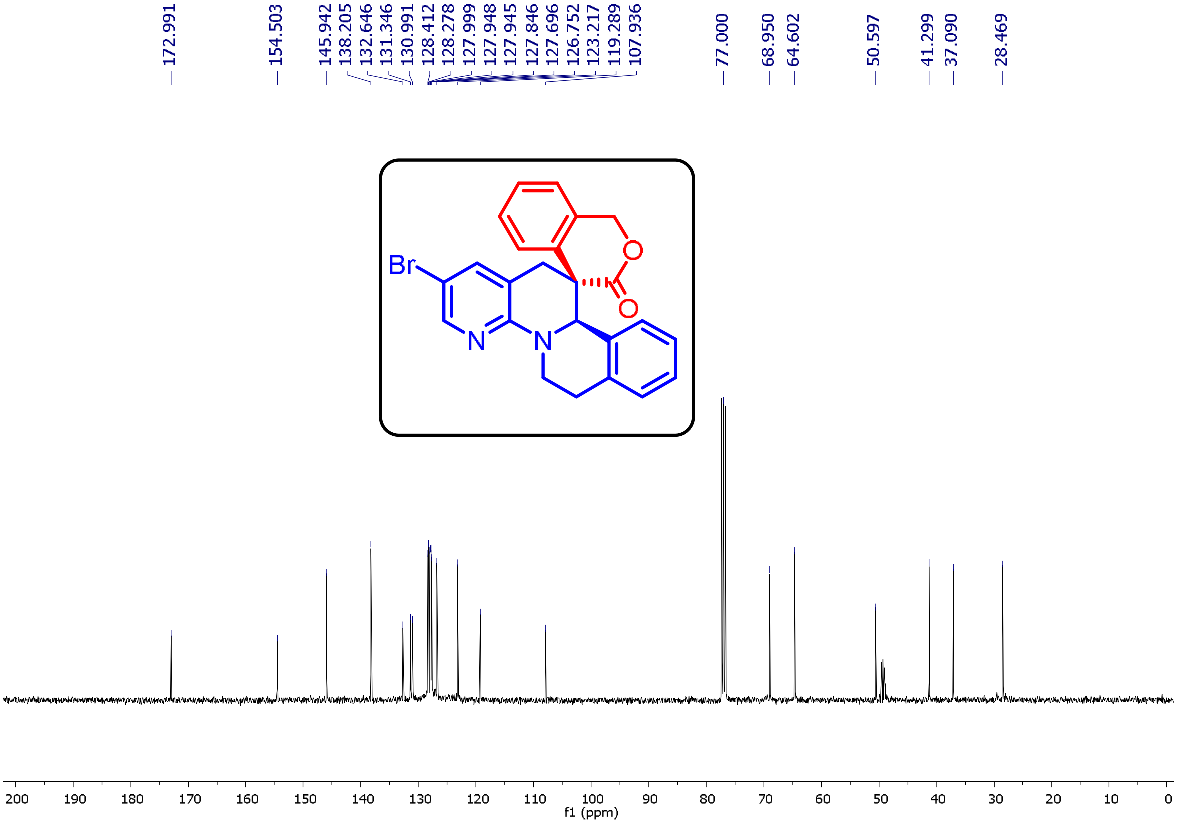
^{13}C NMR of **7b** (101 MHz, CDCl$_3$)



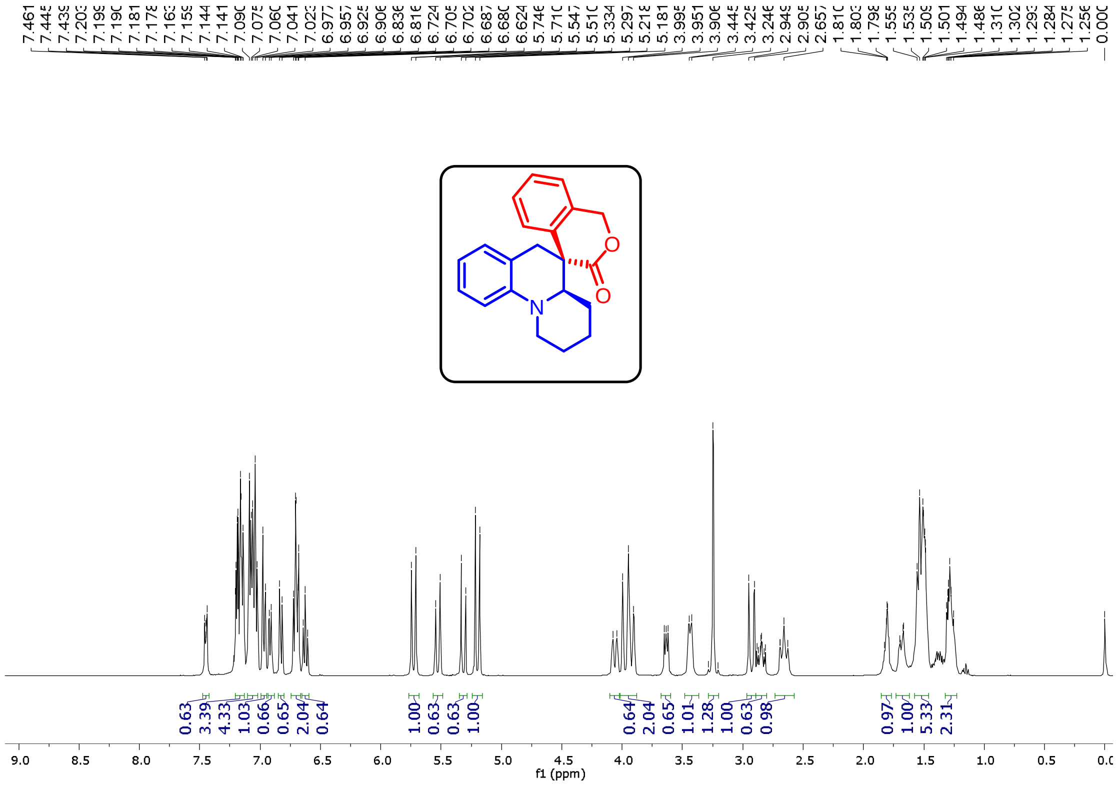
^{1}H NMR of **7c** (400 MHz, Chloroform-*d*)



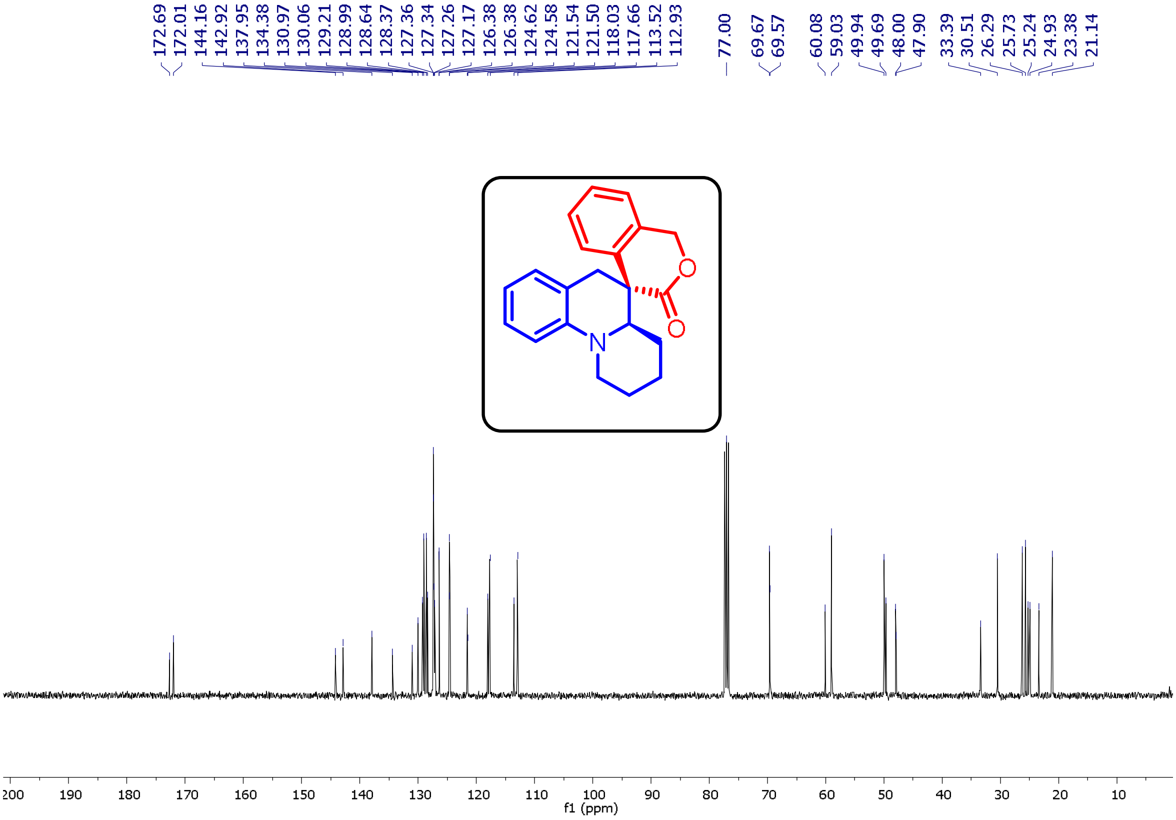
^{13}C NMR of **7c** (101 MHz, CDCl$_3$)



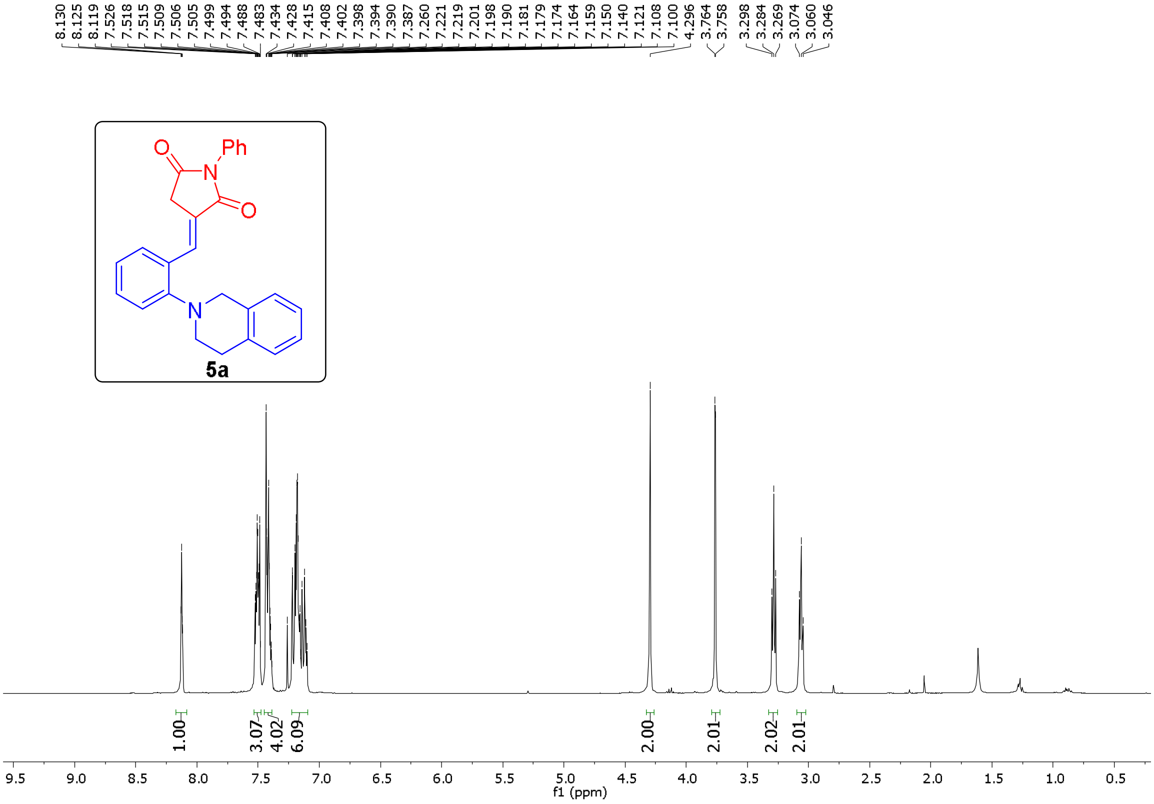
^{1}H NMR of **7d** (400 MHz, Chloroform-*d*)



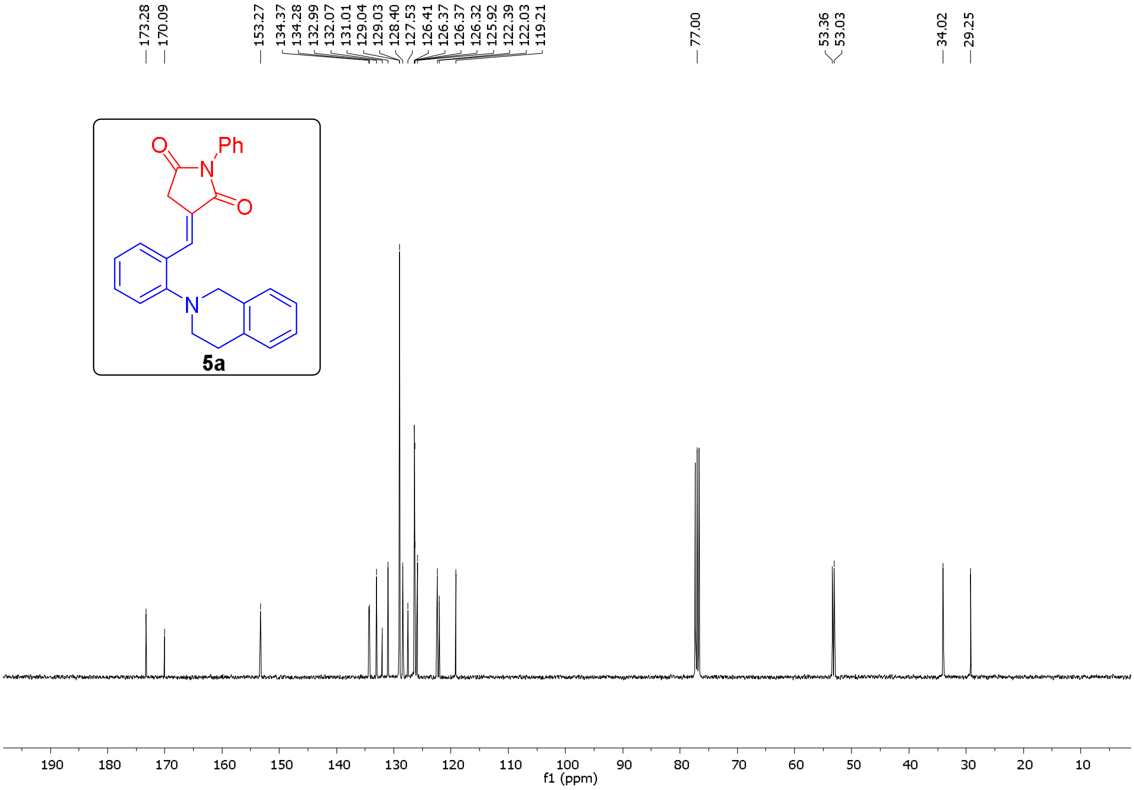
^{13}C NMR of **7d** (101 MHz, CDCl$_3$)



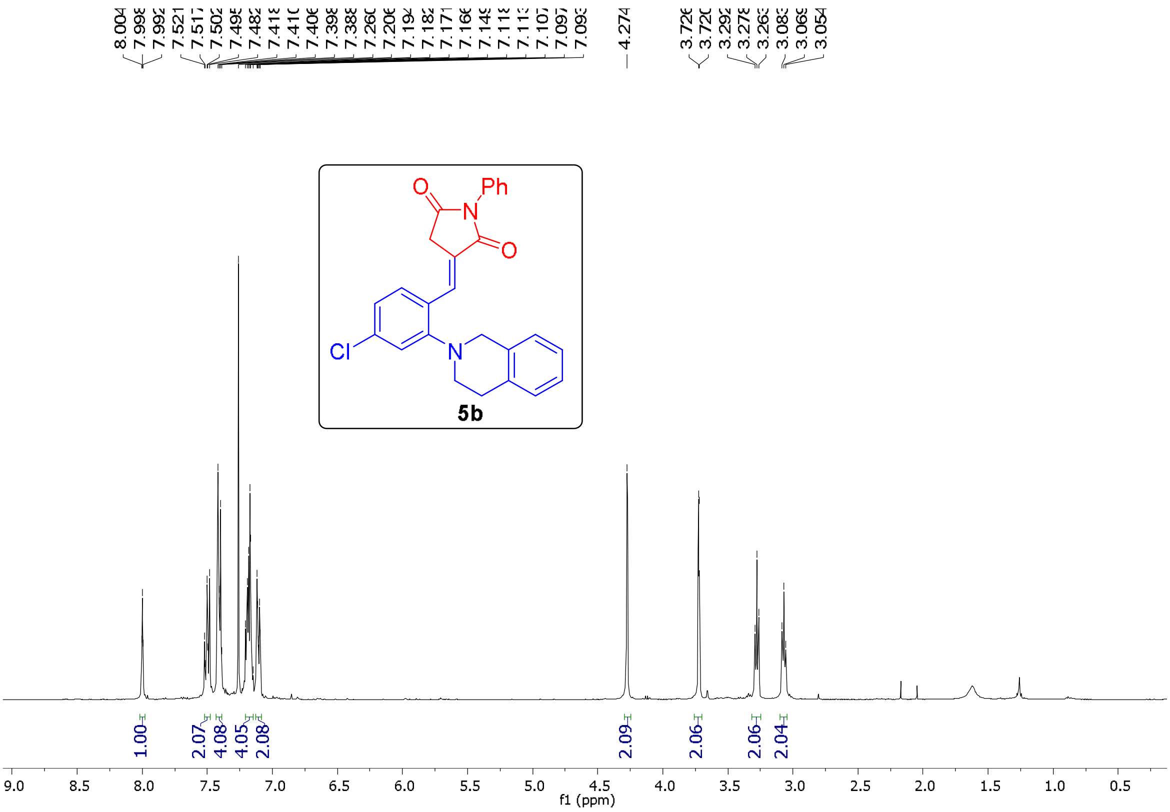
^{1}H NMR spectra of **5a** (400 MHz, Chloroform-*d*)



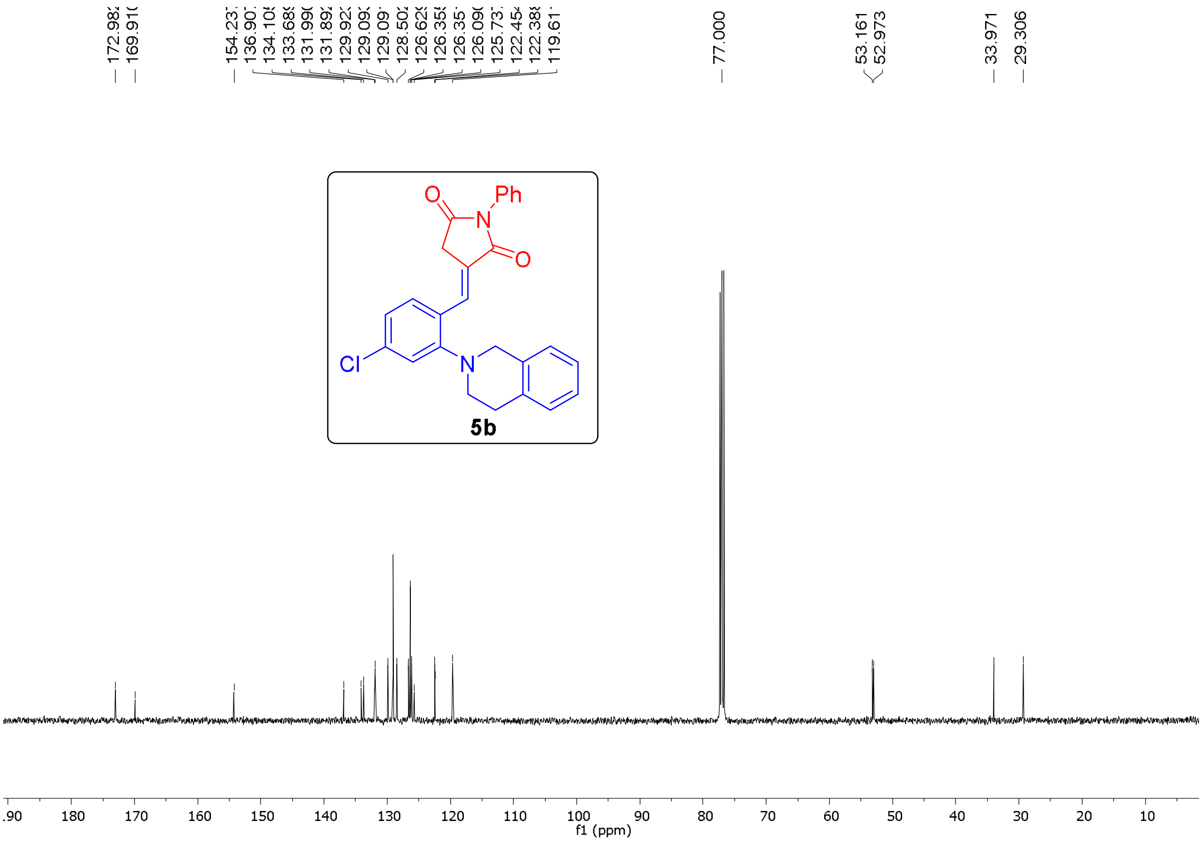
^{13}C NMR spectra of **5a** (101 MHz, Chloroform-*d*)



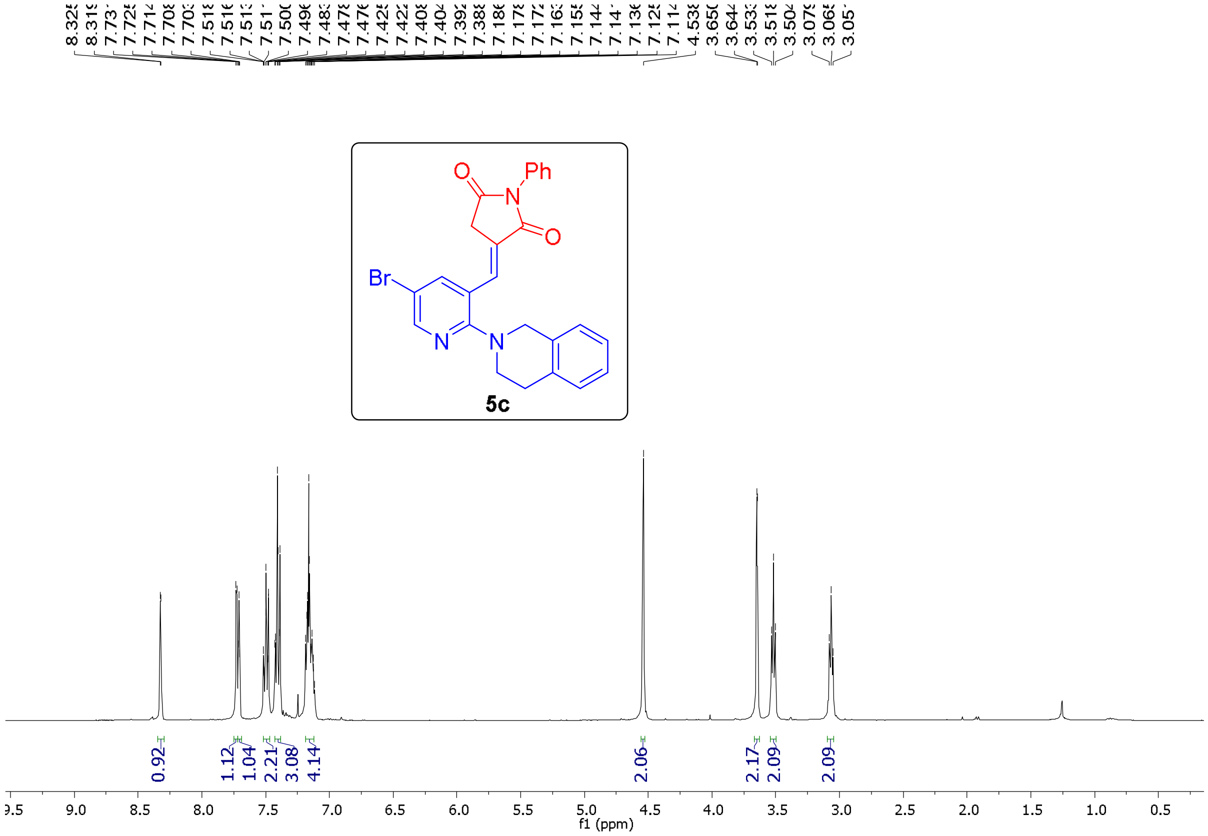
^{1}H NMR spectra of **5b** (400 MHz, Chloroform-*d*)



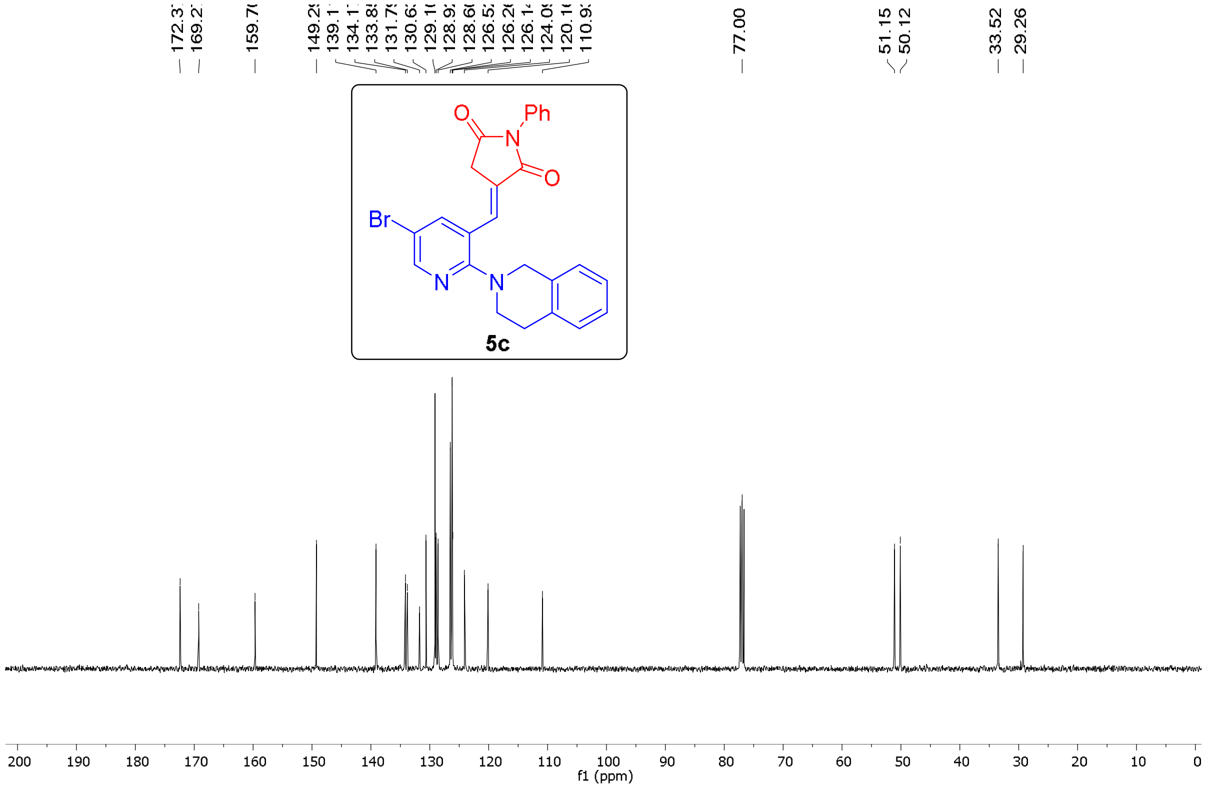
^{13}C NMR spectra of **5b** (101 MHz, Chloroform-*d*)



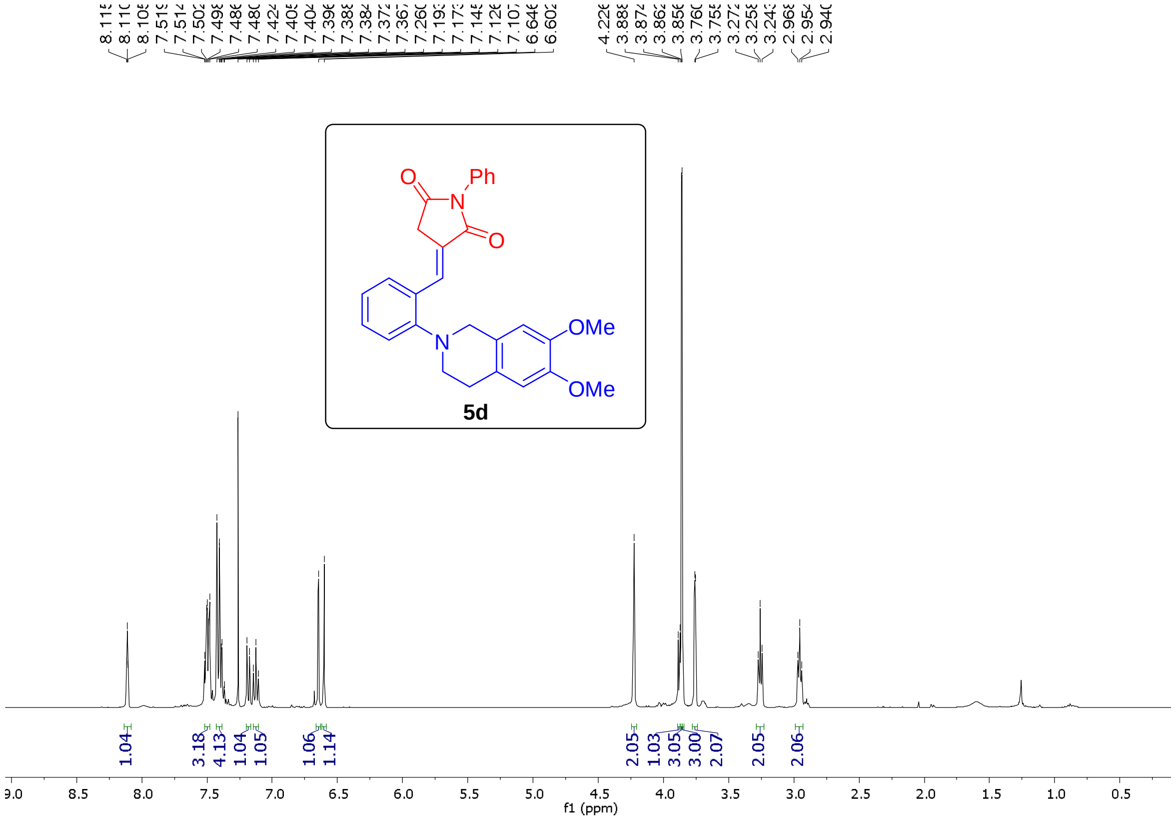
^{1}H NMR spectra of **5c** (400 MHz, Chloroform-*d*)



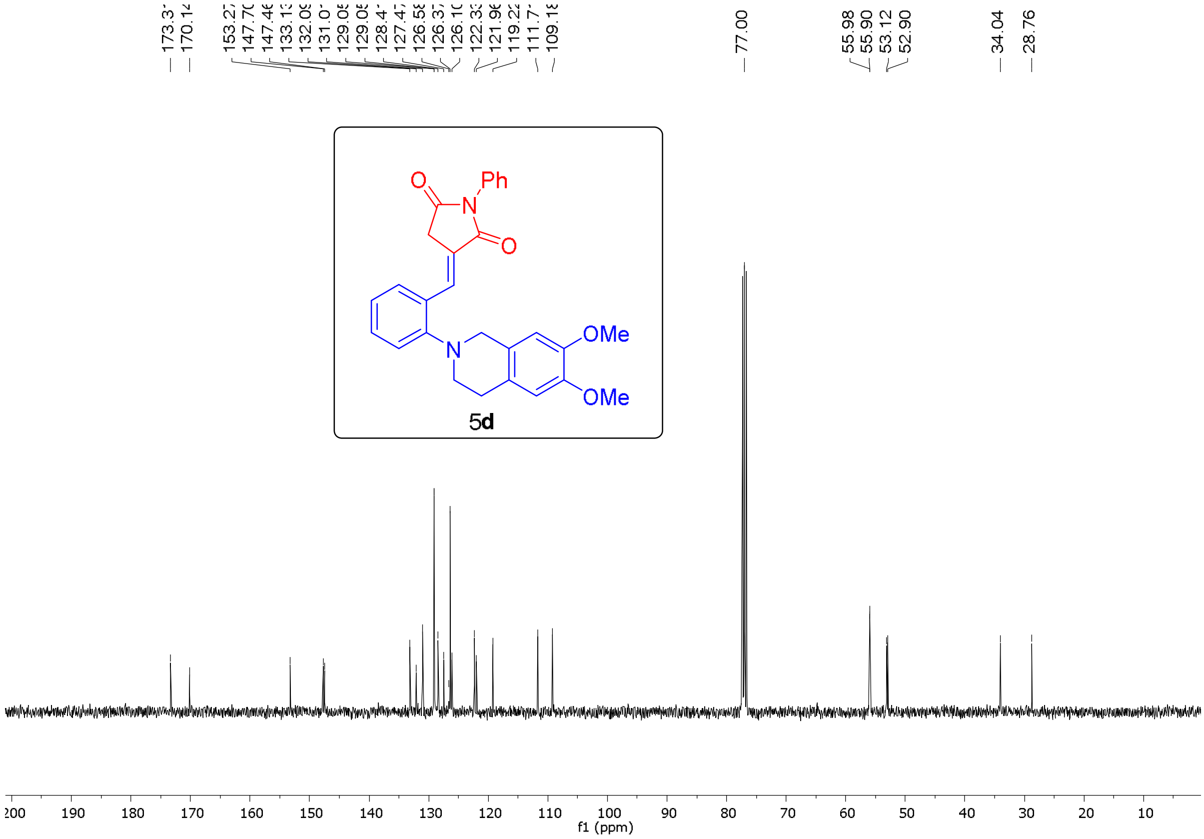
^{13}C NMR spectra of **5c** (101 MHz, Chloroform-*d*)



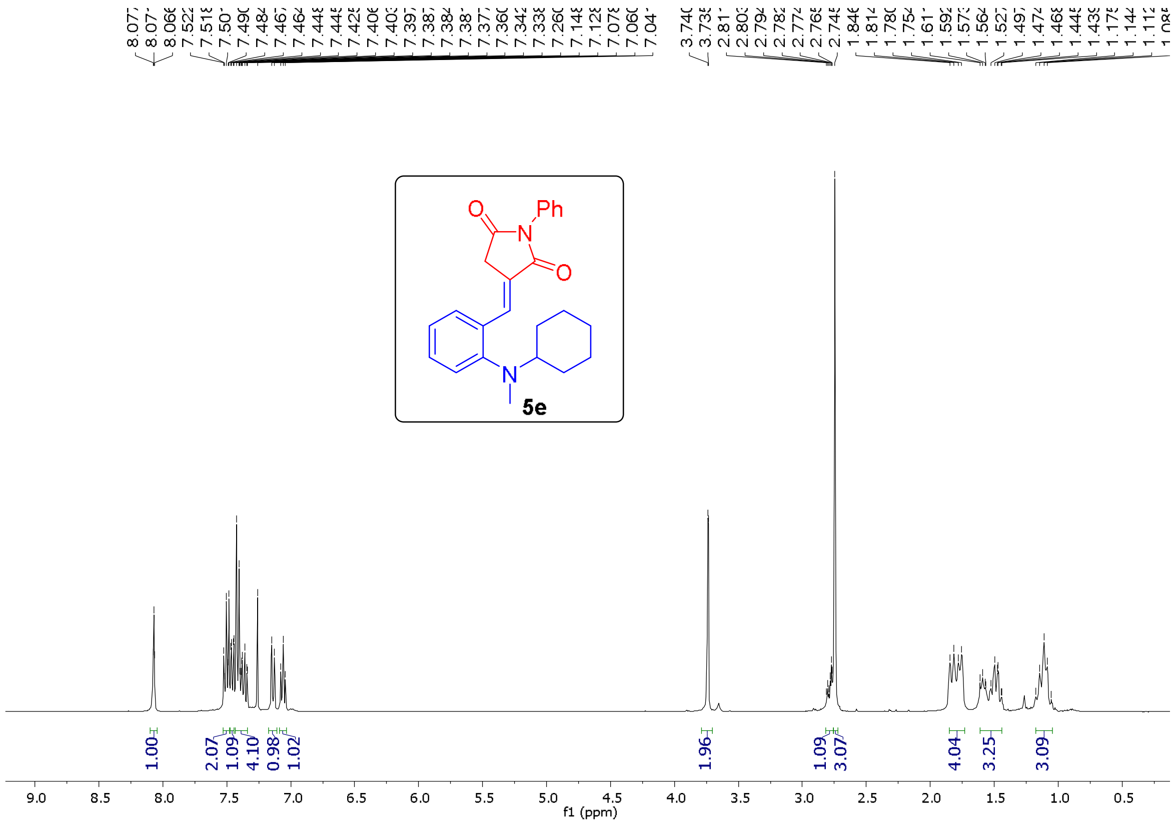
^{1}H NMR spectra of **5d** (400 MHz, Chloroform-*d*)



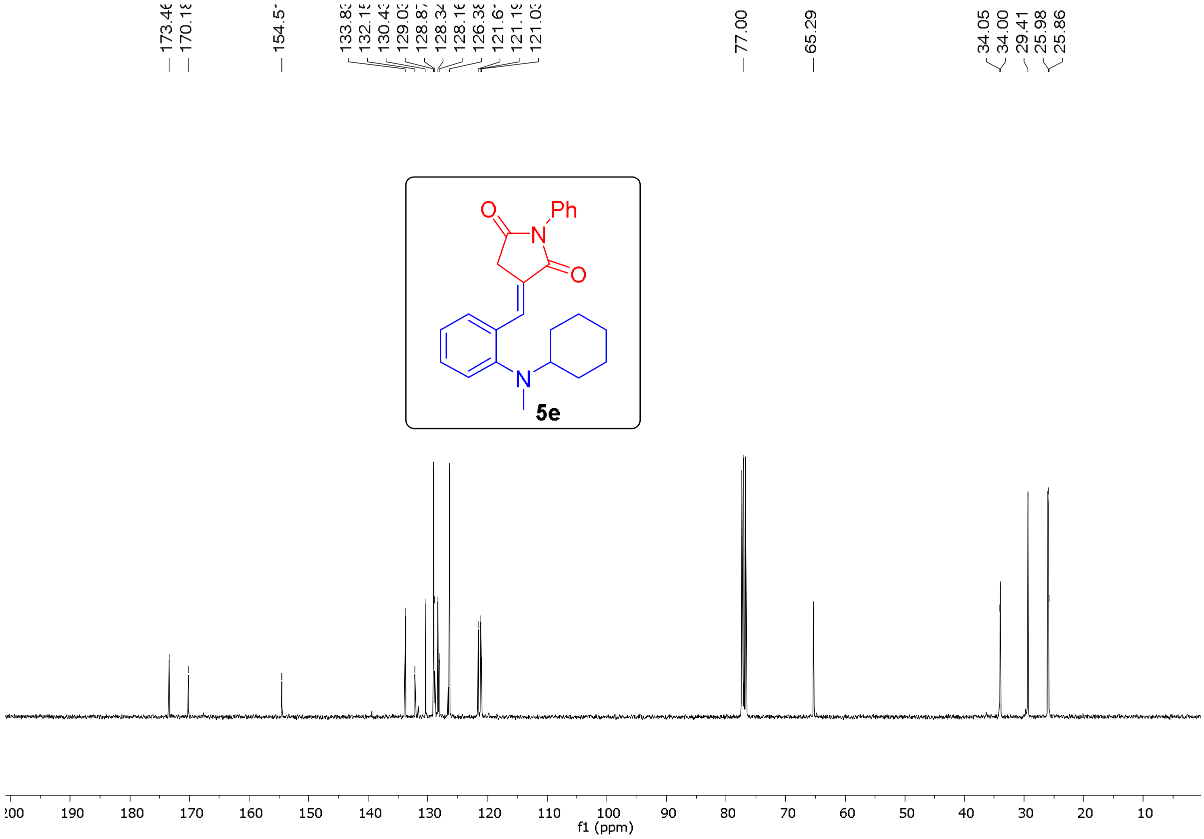
^{13}C NMR spectra of **5d** (101 MHz, Chloroform-*d*)



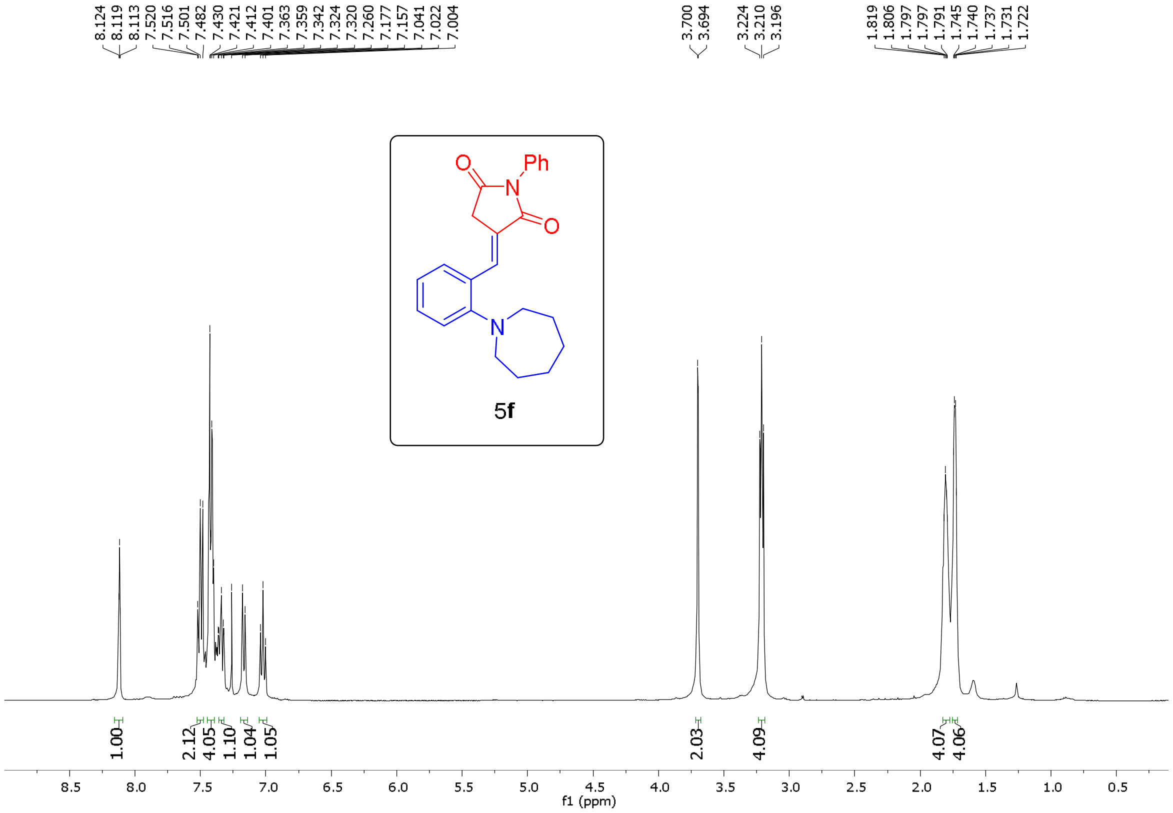
^{1}H NMR spectra of **5e** (400 MHz, Chloroform-*d*)



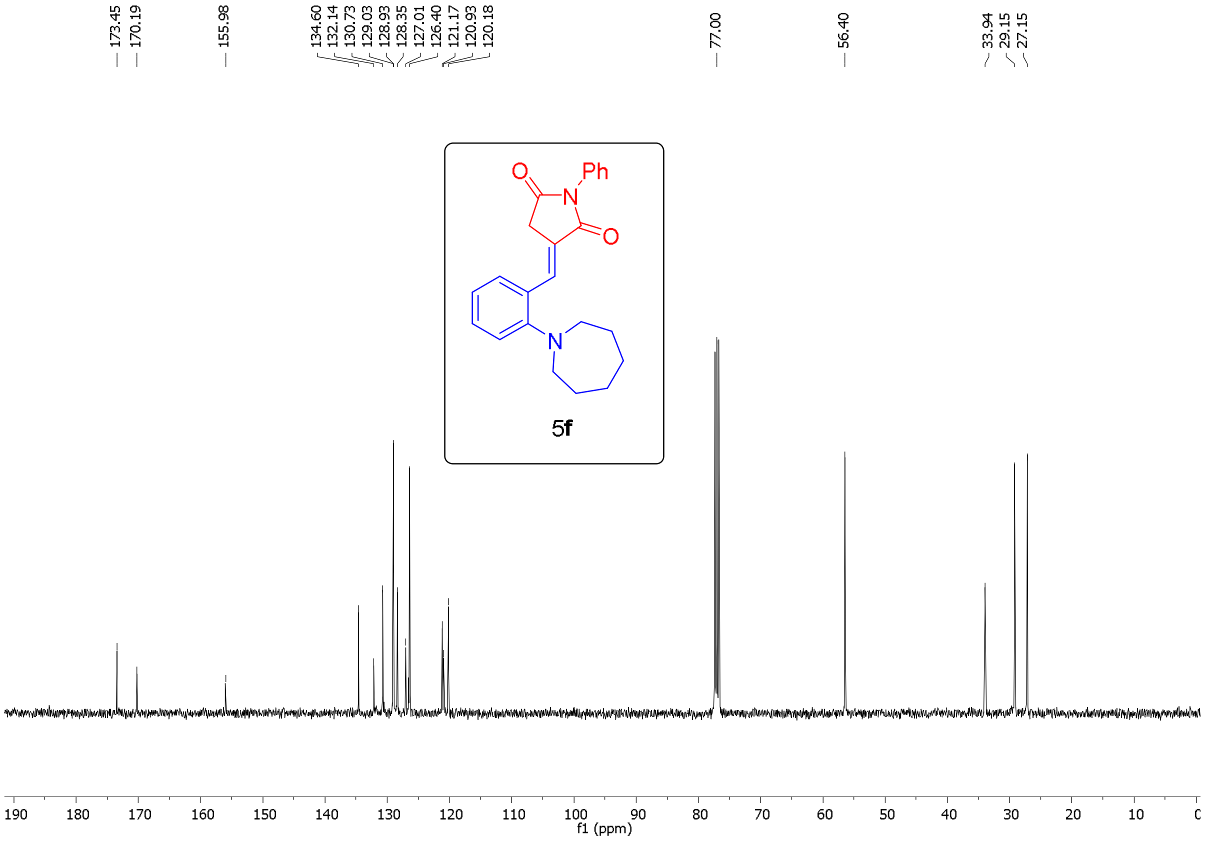
^{13}C NMR spectra of **5e** (101 MHz, Chloroform-*d*)



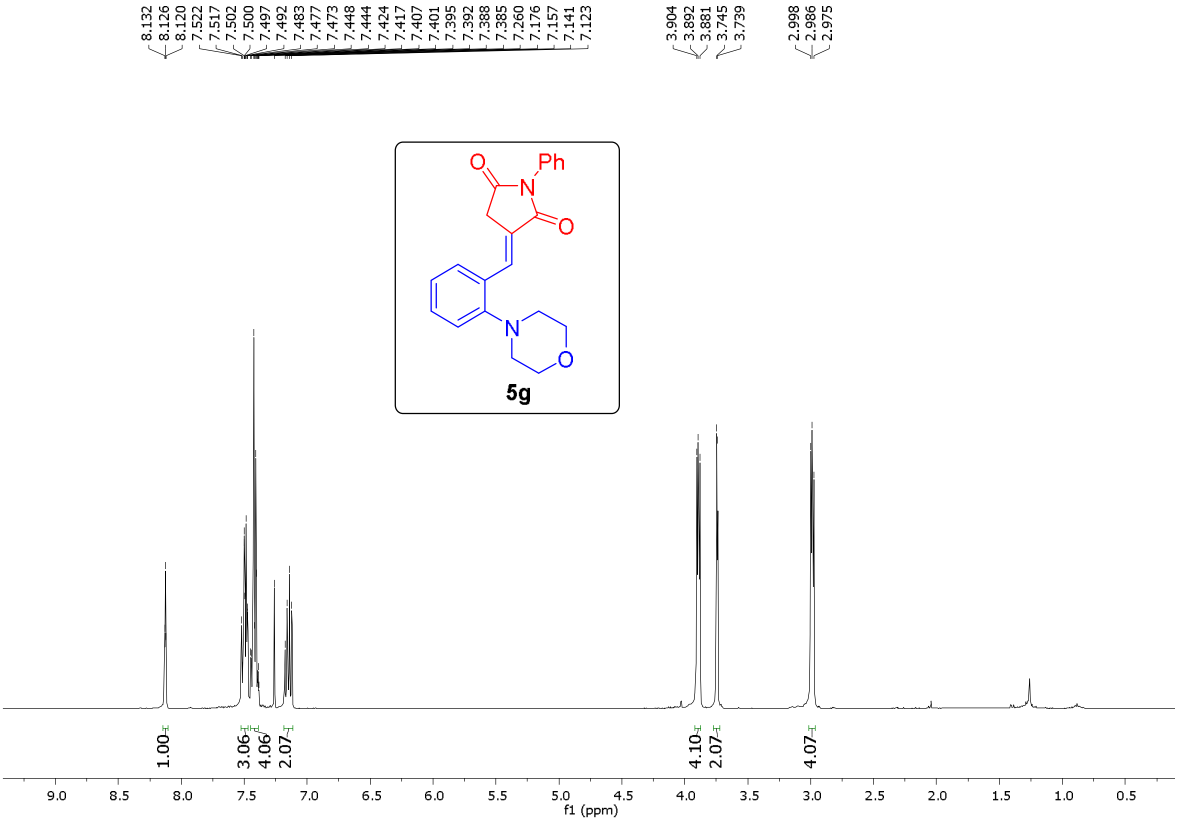
^{1}H NMR spectra of **5f** (400 MHz, Chloroform-*d*)



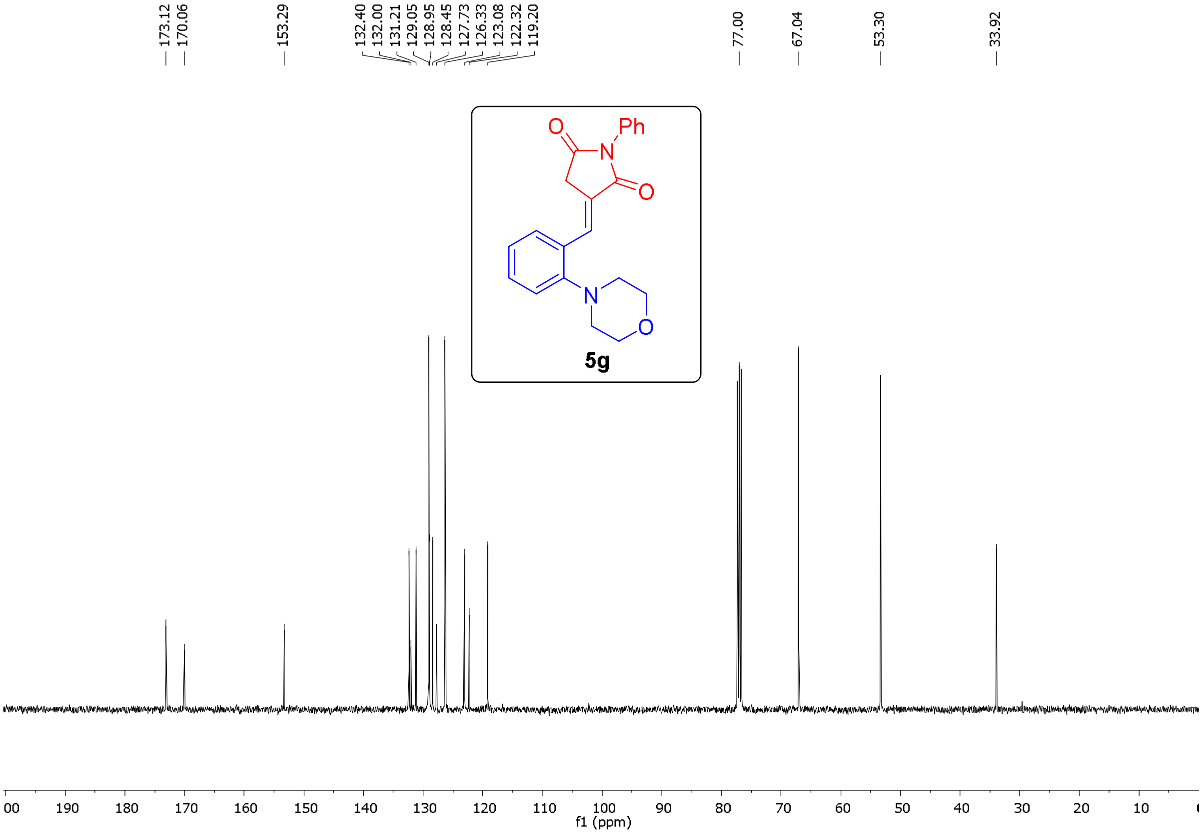
^{13}C NMR spectra of **5f** (101 MHz, Chloroform-*d*)



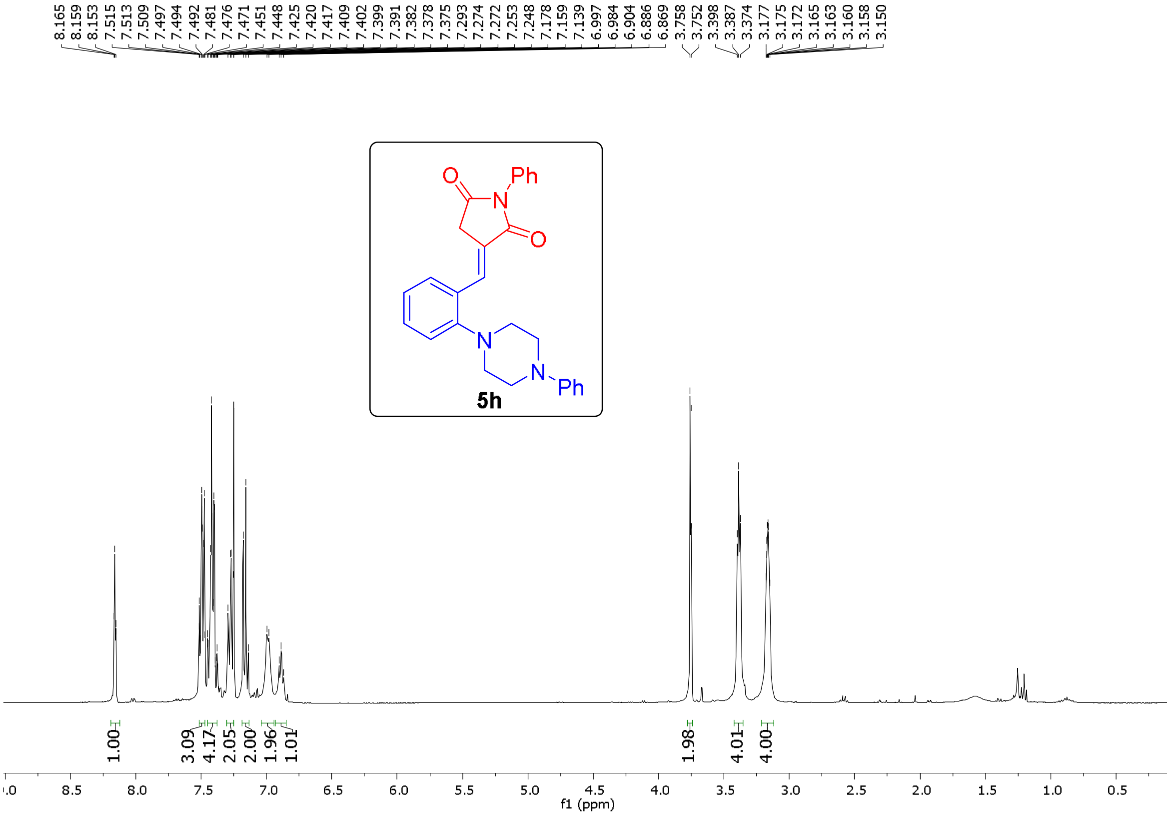
^{1}H NMR spectra of **5g** (400 MHz, Chloroform-*d*)



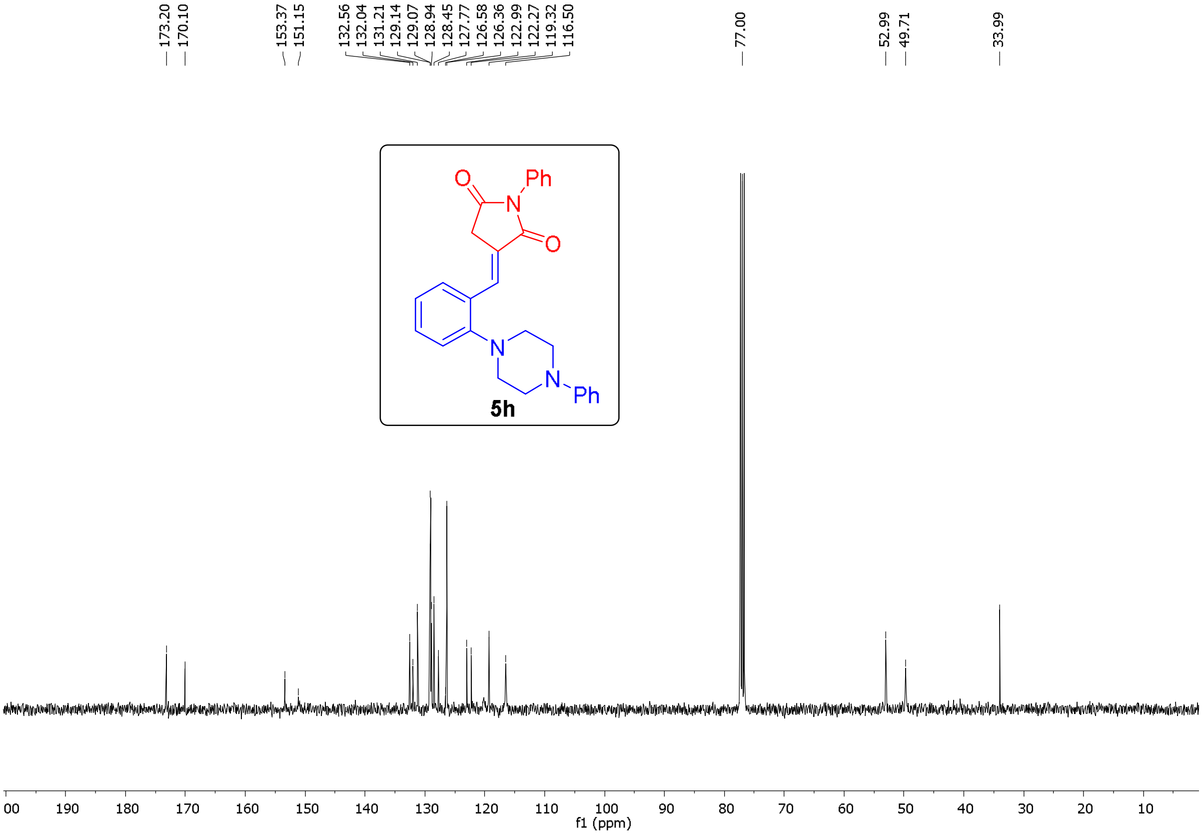
^{13}C NMR spectra of **5g** (101 MHz, Chloroform-*d*)



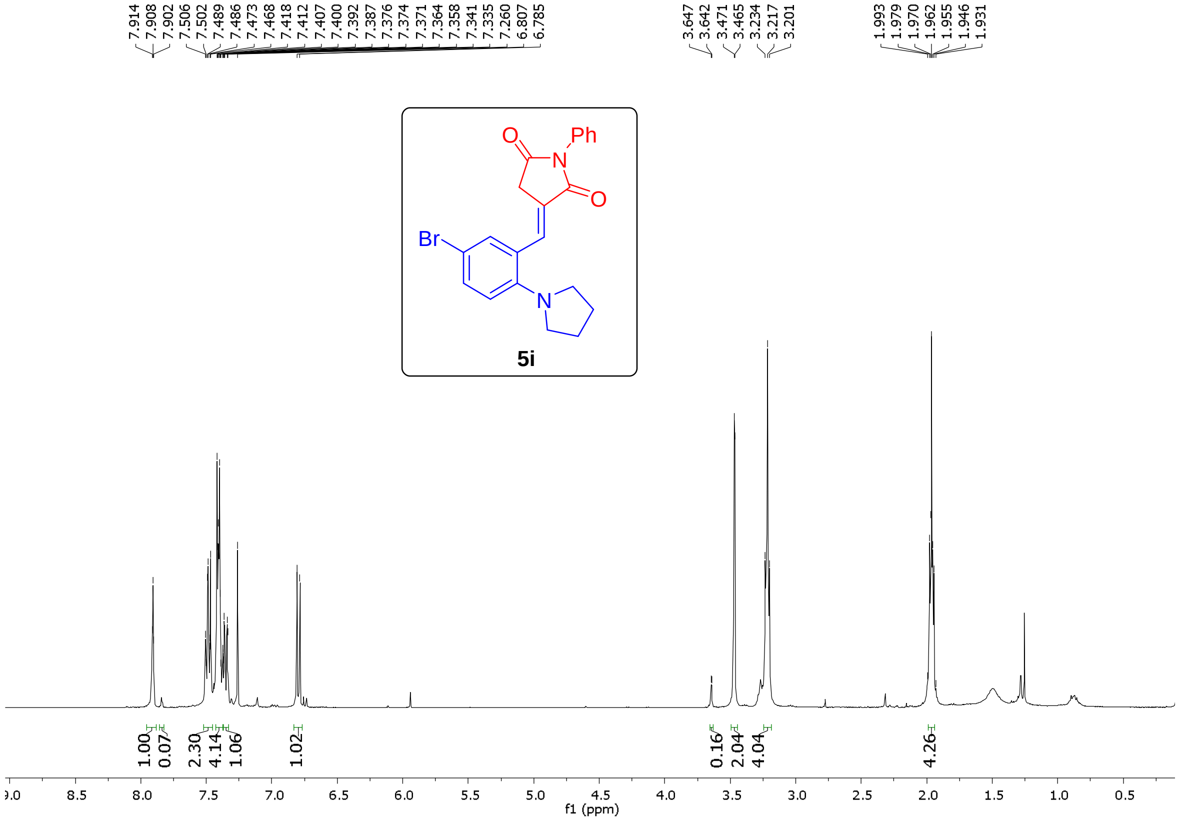
^{1}H NMR spectra of **5h** (400 MHz, Chloroform-*d*)



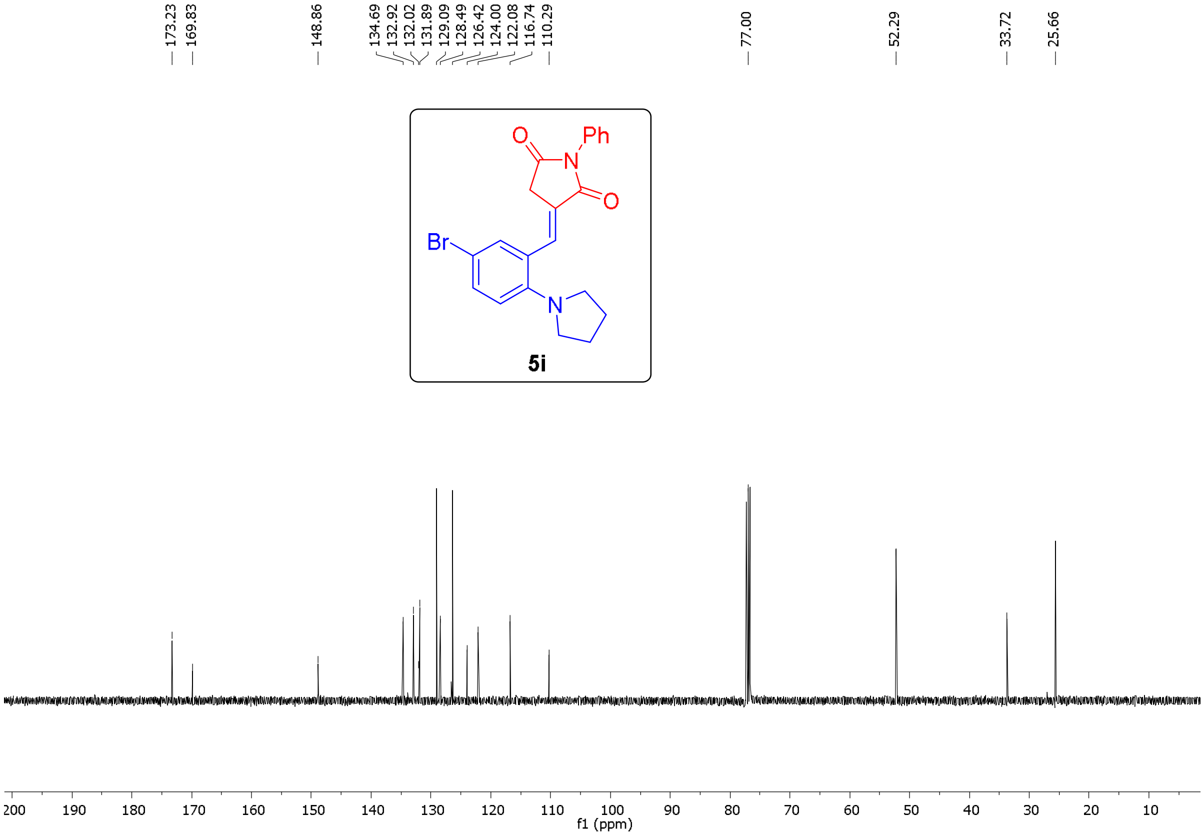
^{13}C NMR spectra of **5h** (101 MHz, Chloroform-*d*)



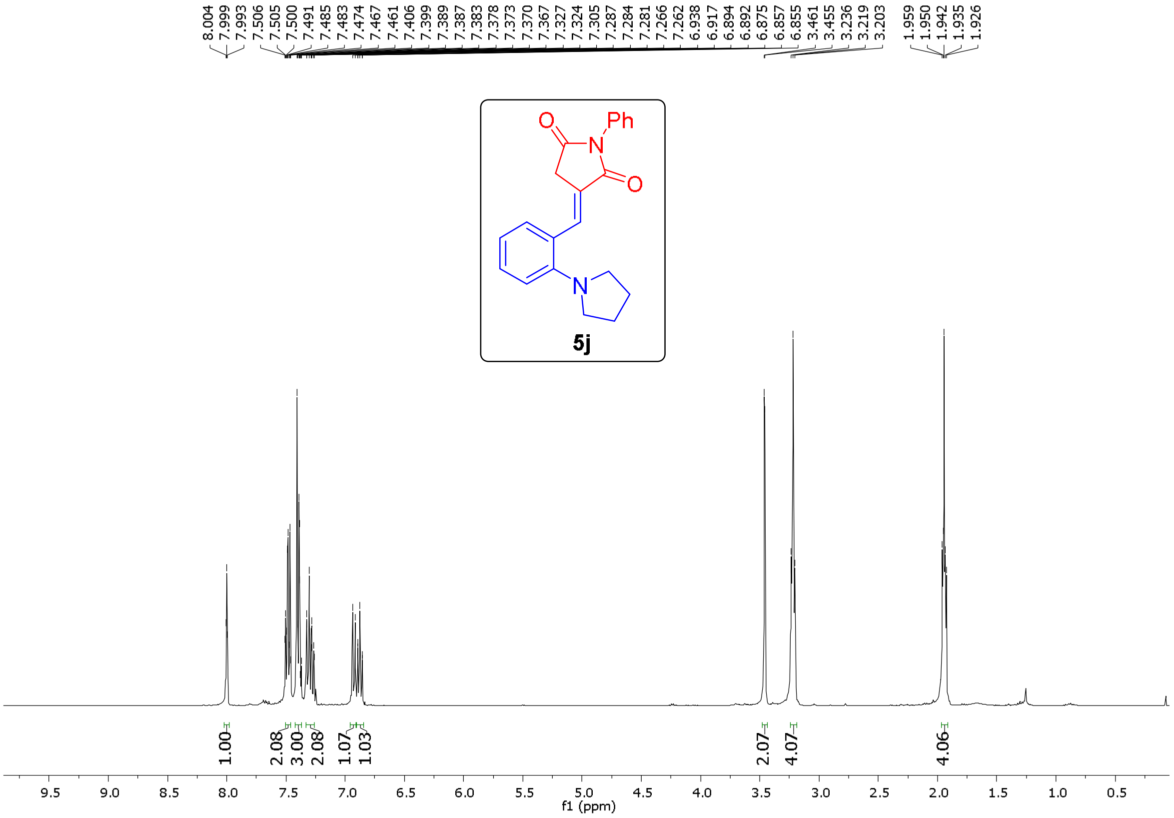
^{1}H NMR spectra of **5i** (400 MHz, Chloroform-*d*)



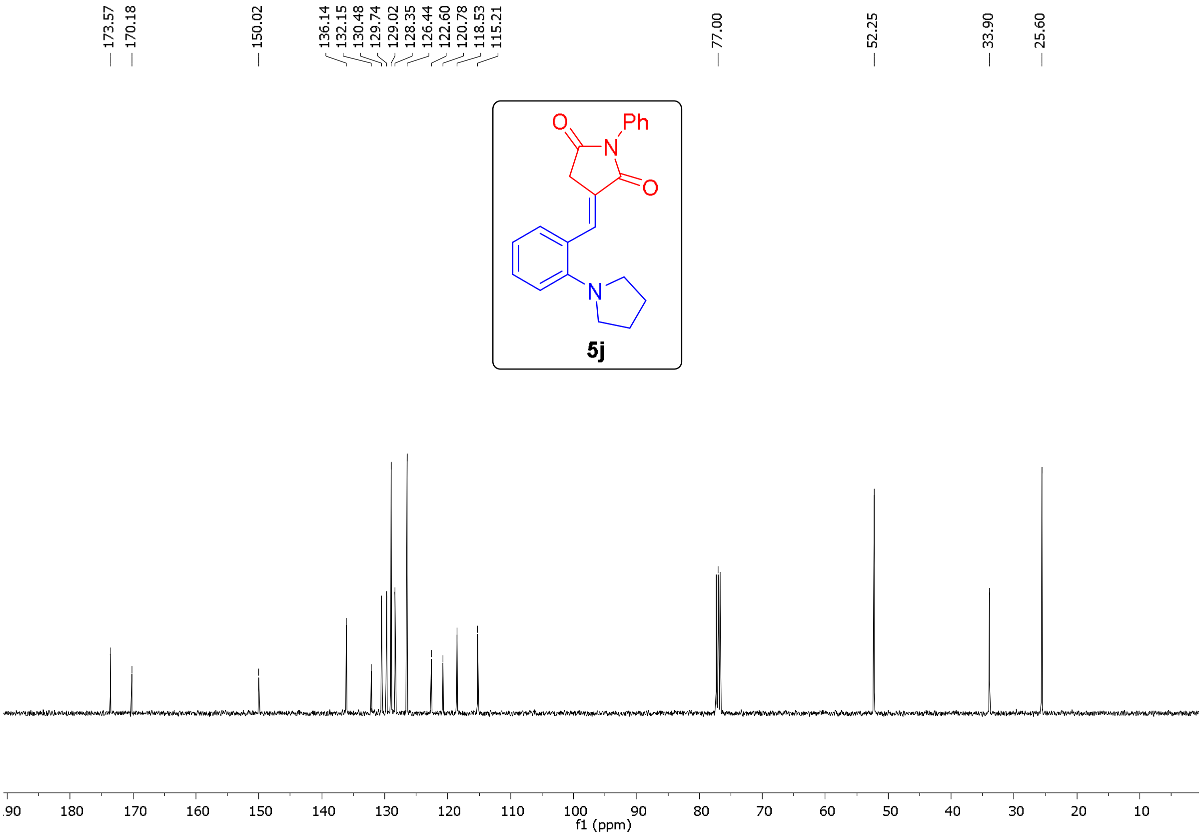
^{13}C NMR spectra of **5i** (101 MHz, Chloroform-*d*)



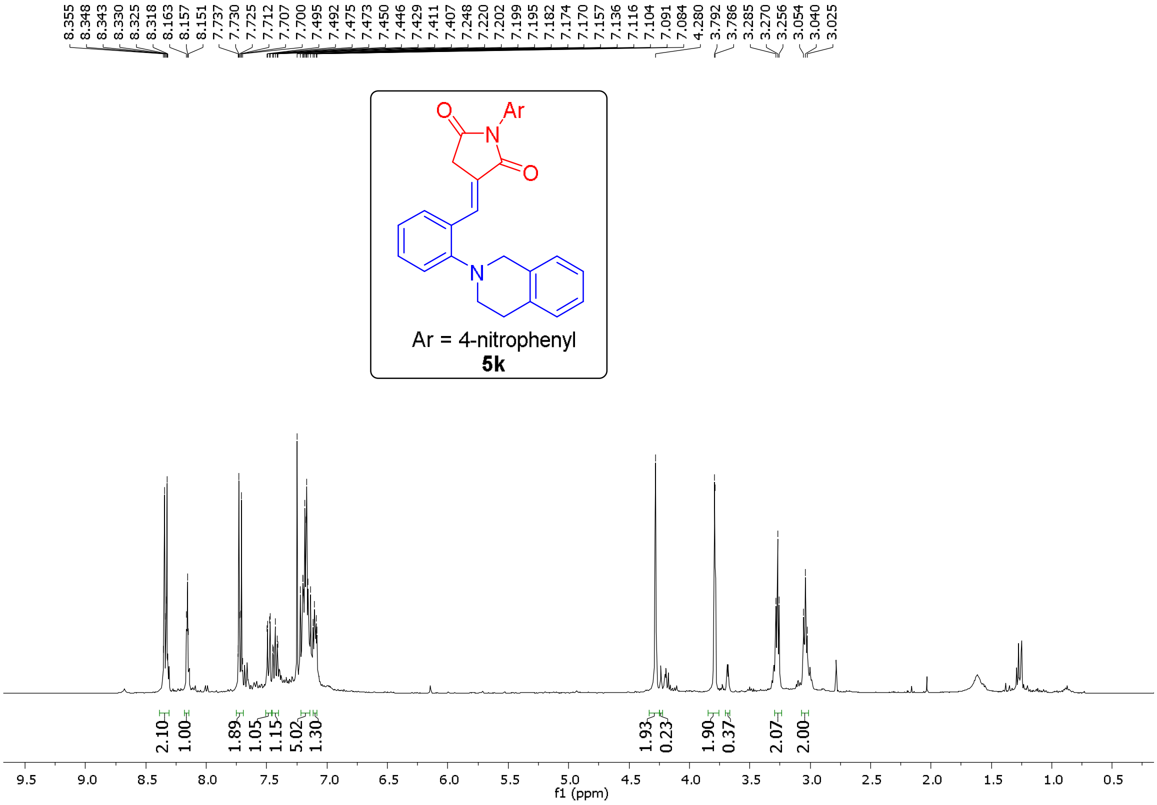
^{1}H NMR spectra of **5j** (400 MHz, Chloroform-*d*)



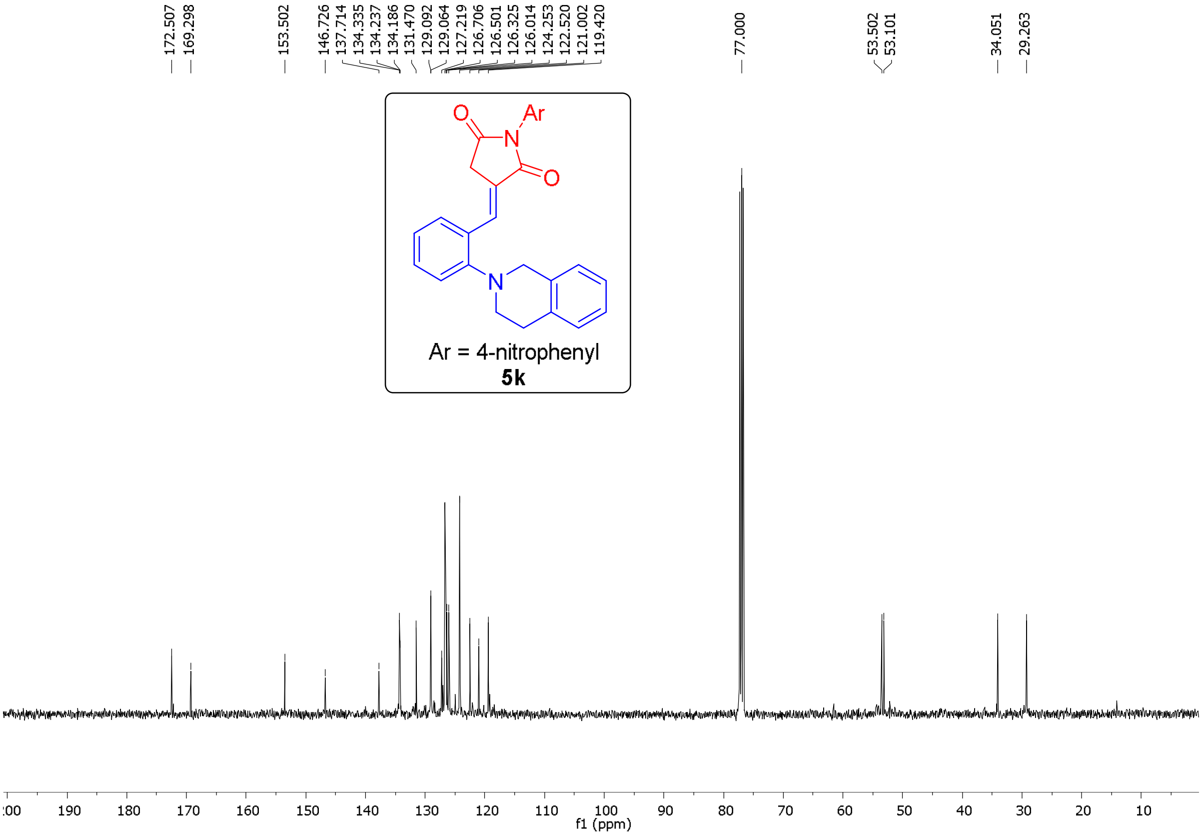
^{13}C NMR spectra of **5j** (101 MHz, Chloroform-*d*)



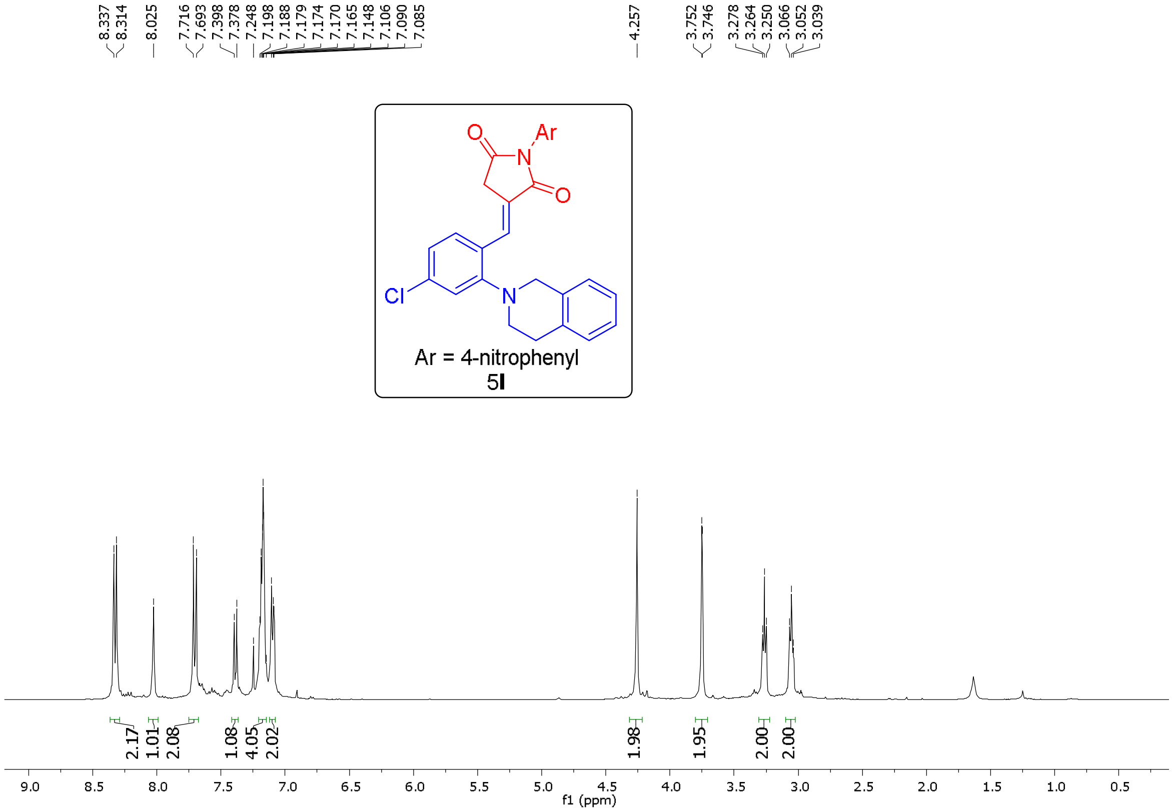
^{1}H NMR spectra of **5k** (400 MHz, Chloroform-*d*)



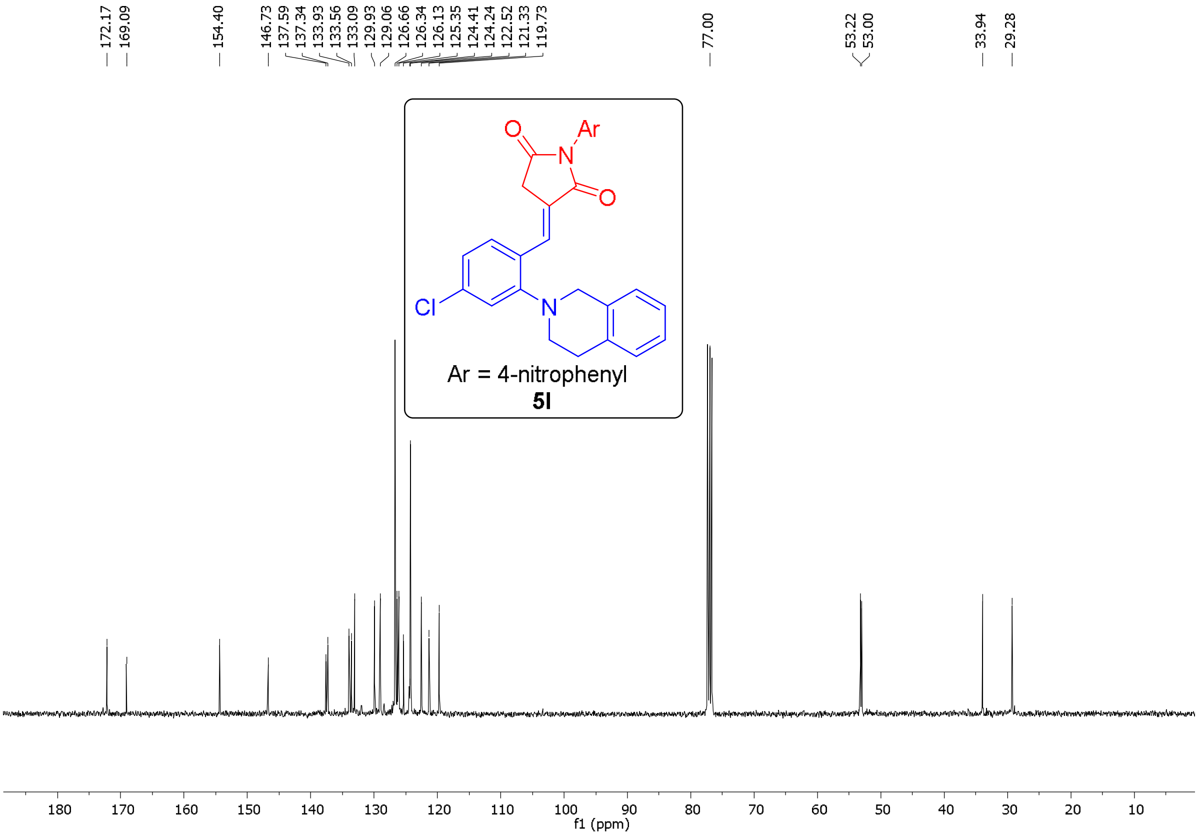
^{13}C NMR spectra of **5k** (101 MHz, Chloroform-*d*)



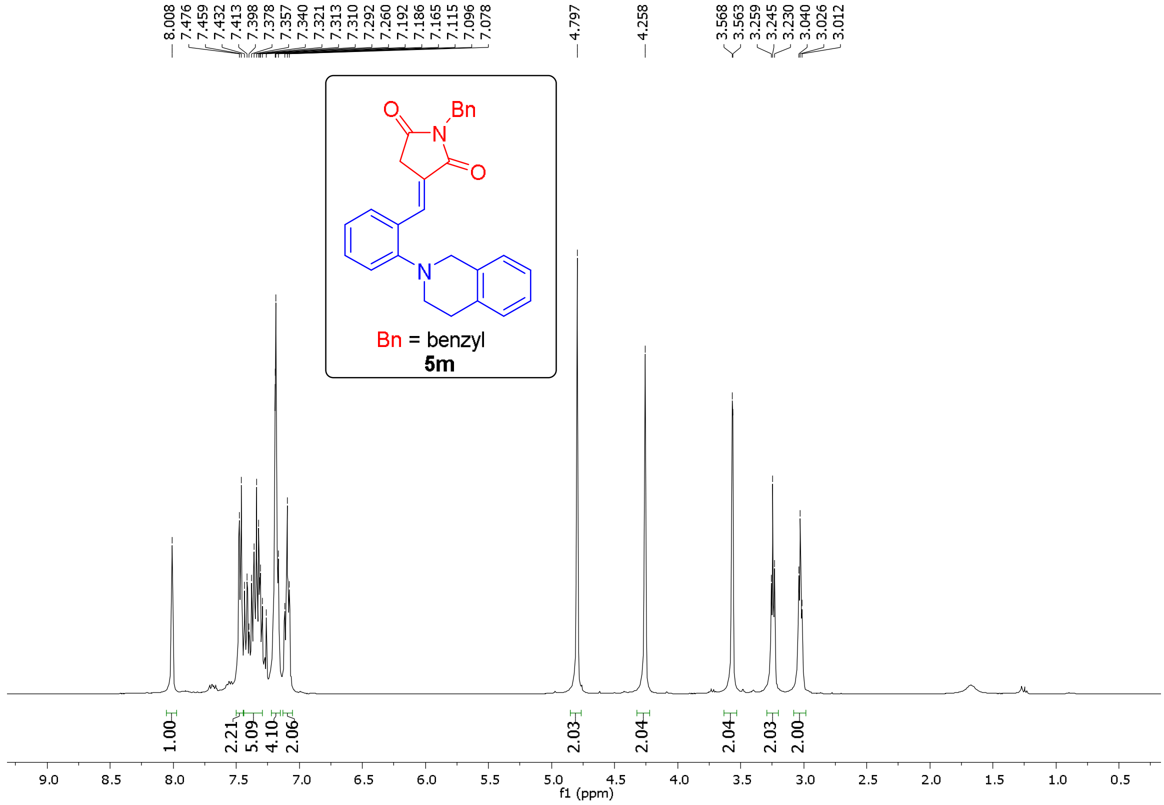
^{1}H NMR spectra of **5l** (400 MHz, Chloroform-*d*)



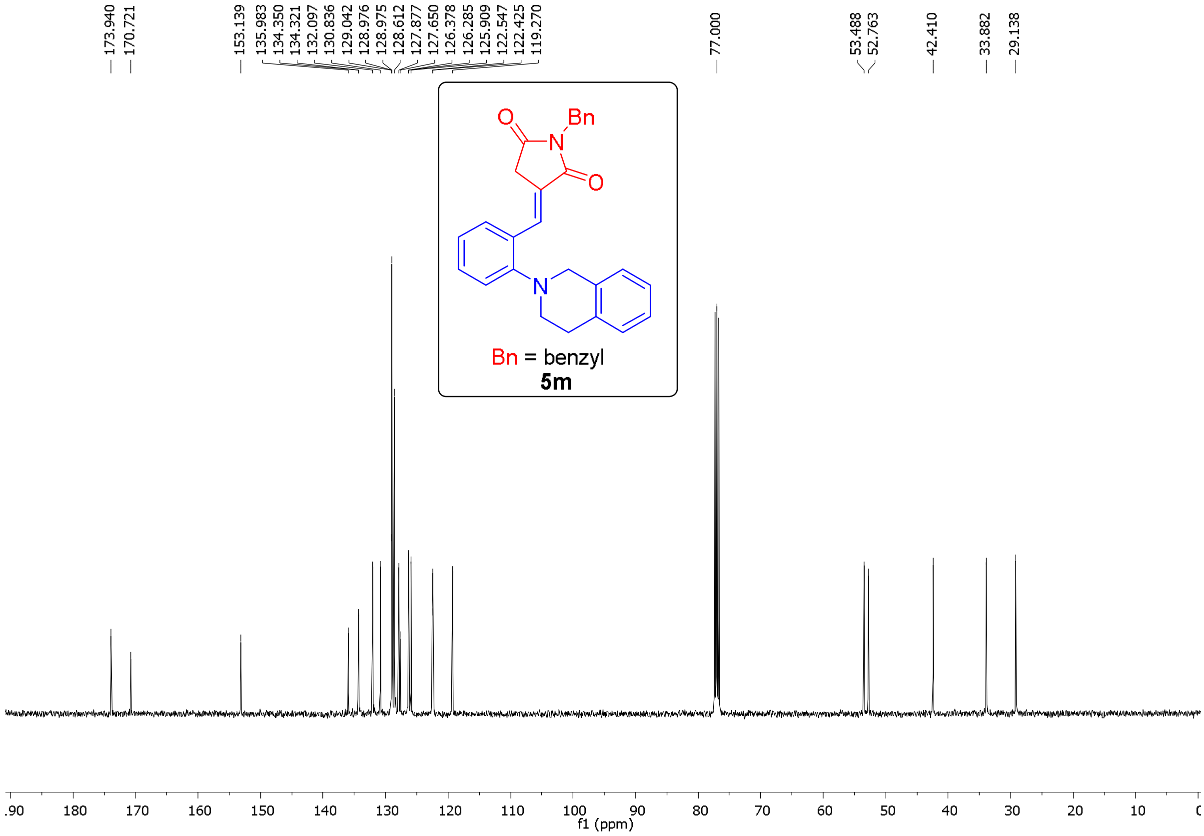
^{13}C NMR spectra of **5l** (101 MHz, Chloroform-*d*)



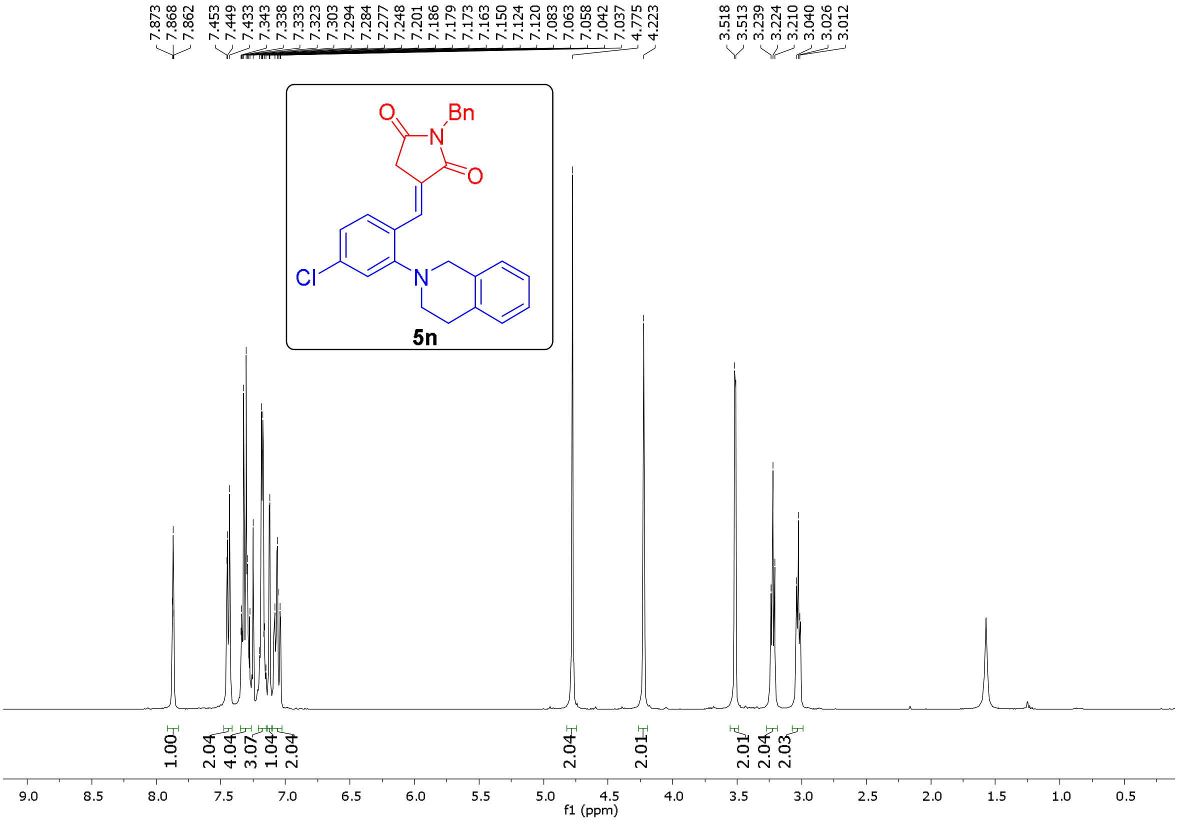
^{1}H NMR spectra of **5m** (400 MHz, Chloroform-*d*)



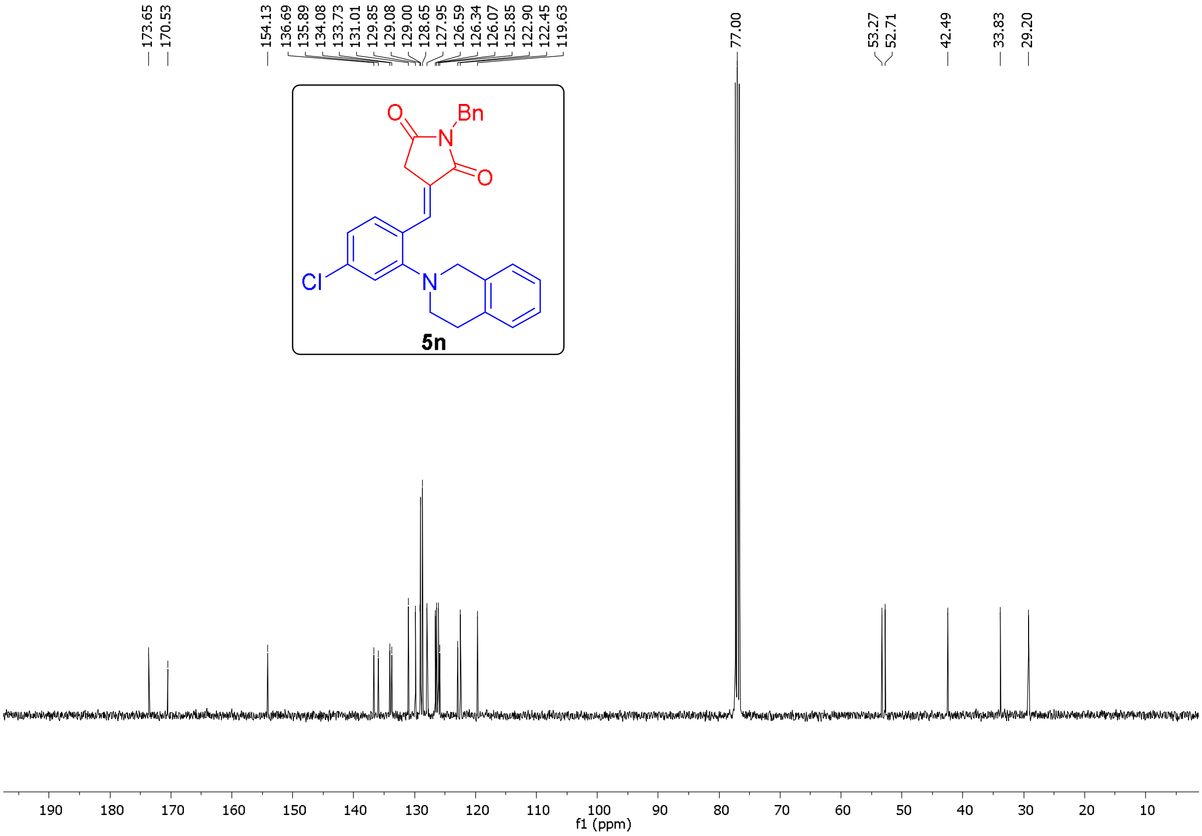
^{13}C NMR spectra of **5m** (101 MHz, Chloroform-*d*)



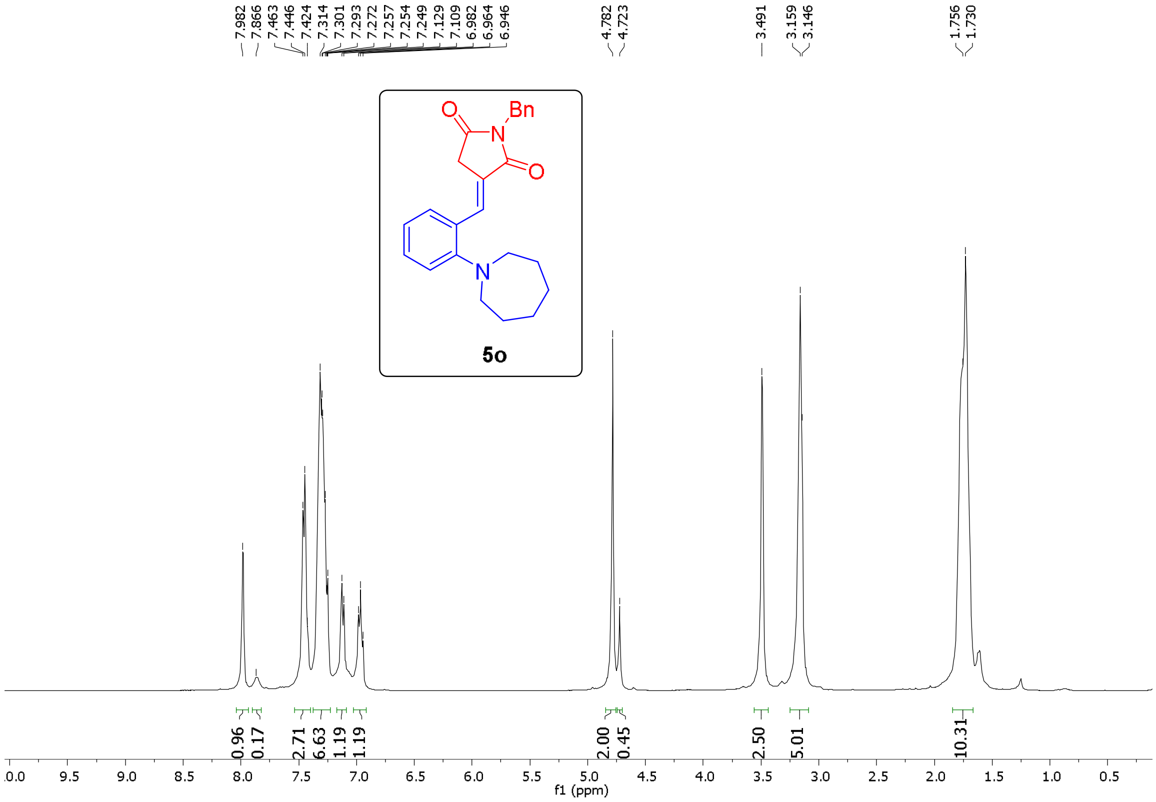
^{1}H NMR spectra of **5n** (400 MHz, Chloroform-*d*)



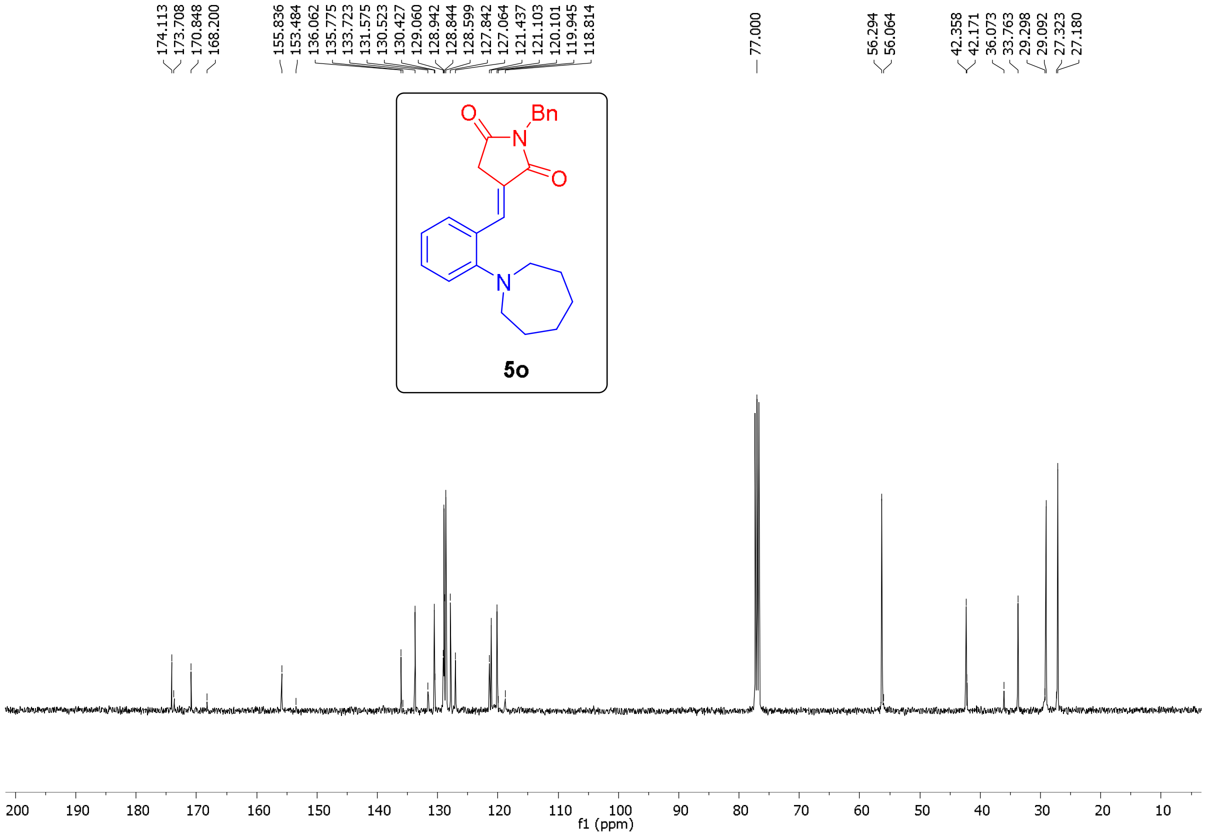
^{13}C NMR spectra of **5n** (101 MHz, Chloroform-*d*)



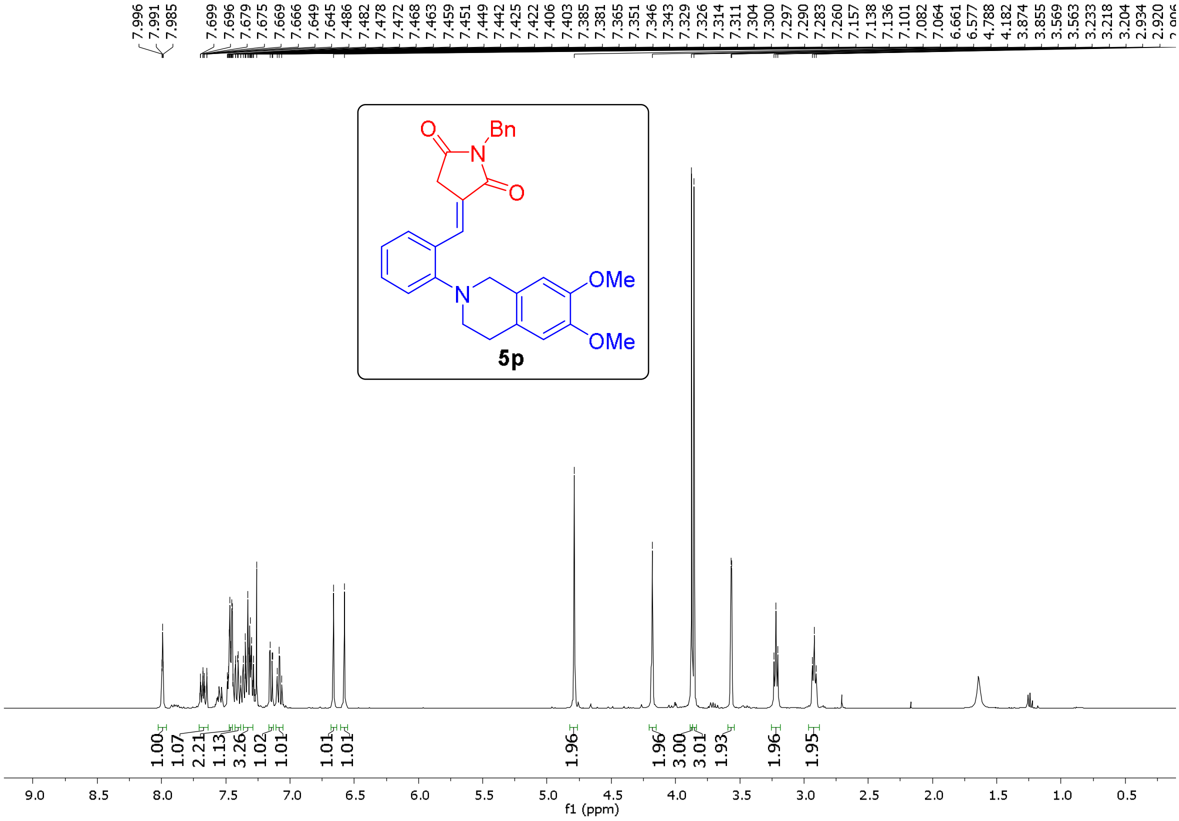
^{1}H NMR spectra of **5o** (400 MHz, Chloroform-*d*)



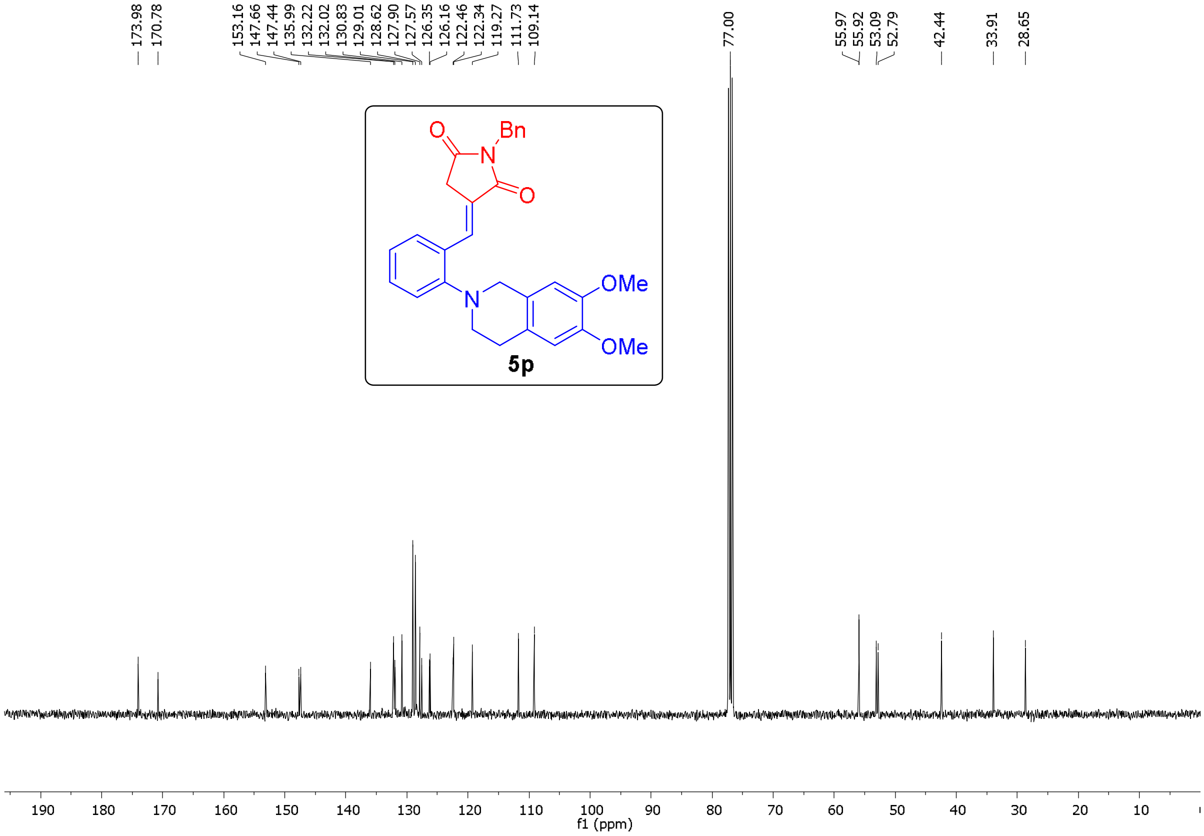
^{13}C NMR spectra of **5o** (101 MHz, Chloroform-*d*)



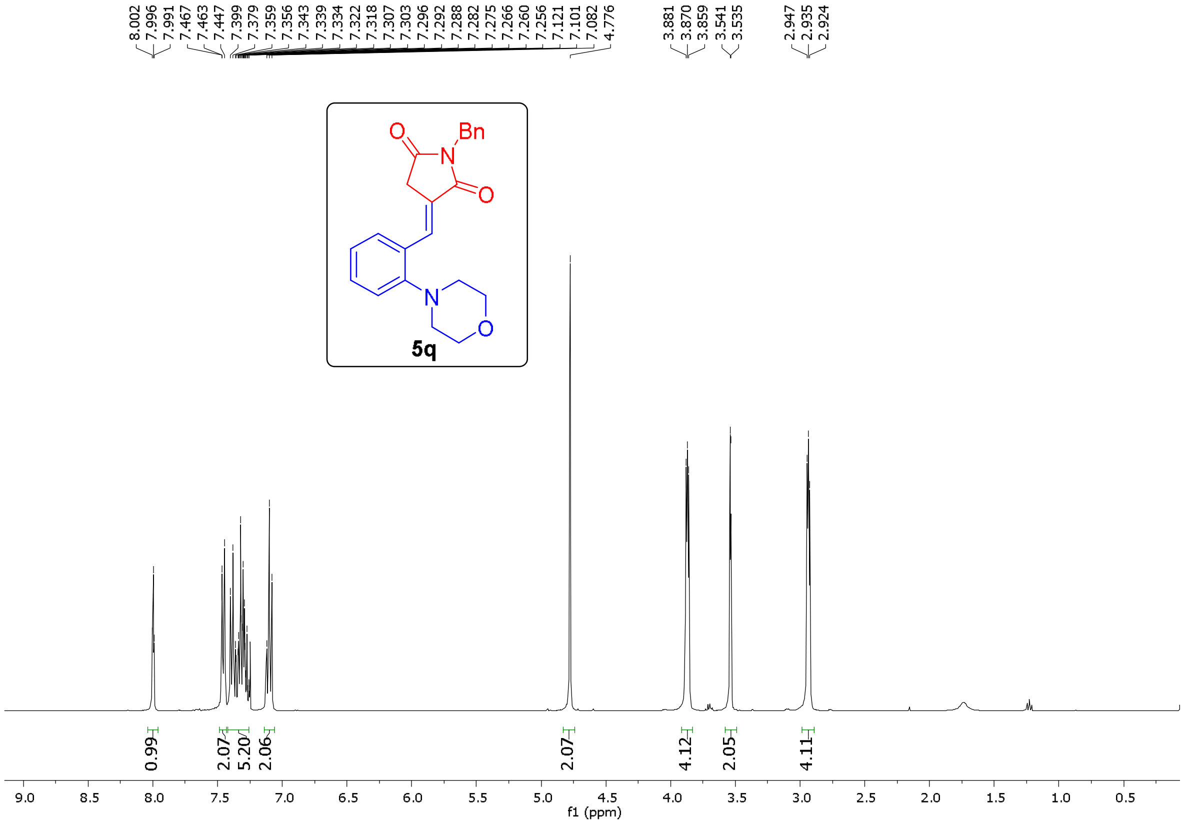
^{1}H NMR spectra of **5p** (400 MHz, Chloroform-*d*)



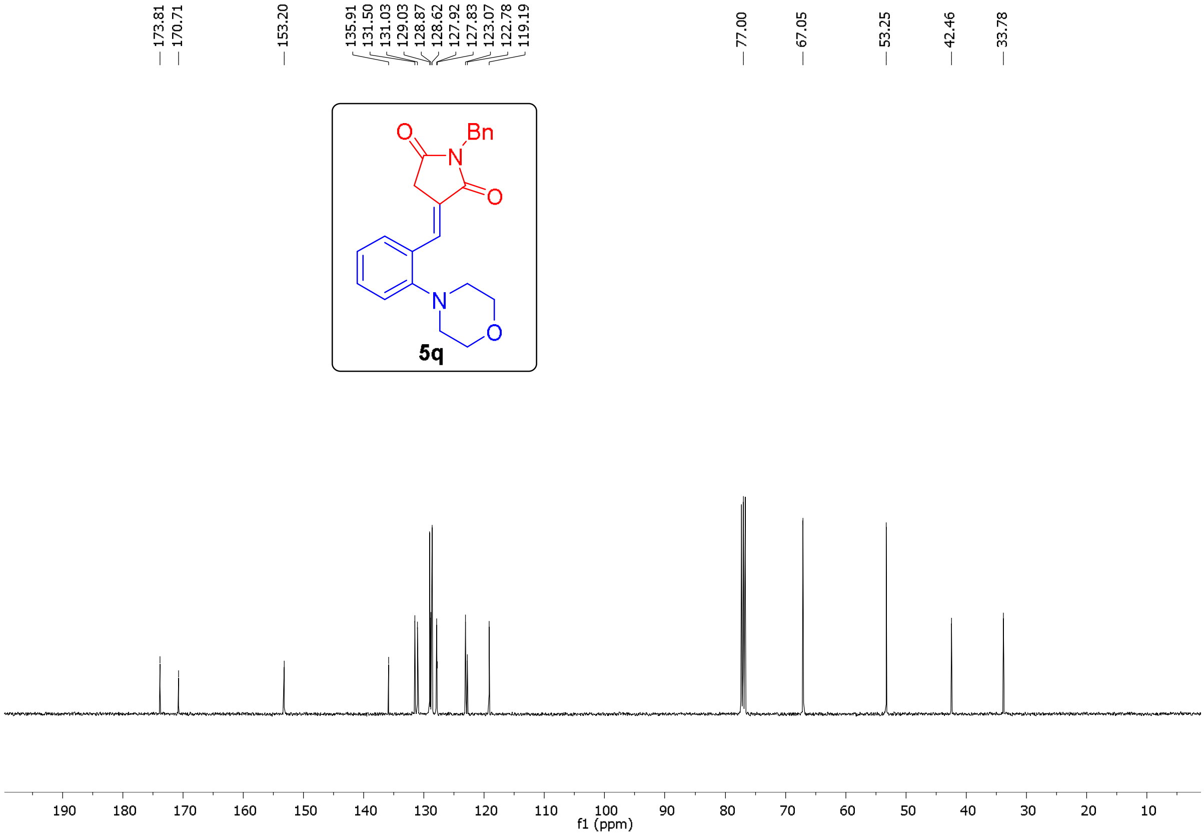
^{13}C NMR spectra of **5p** (101 MHz, Chloroform-*d*)



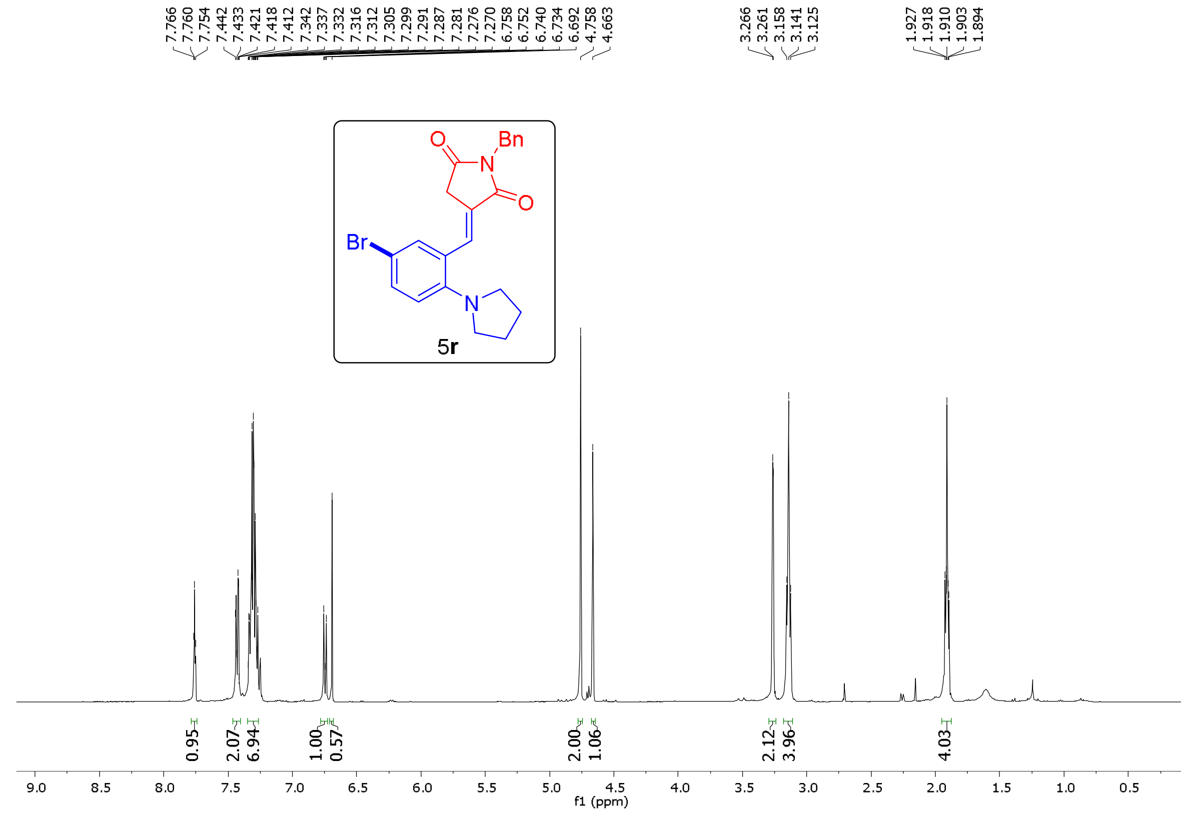
^{1}H NMR spectra of **5q** (400 MHz, Chloroform-*d*)



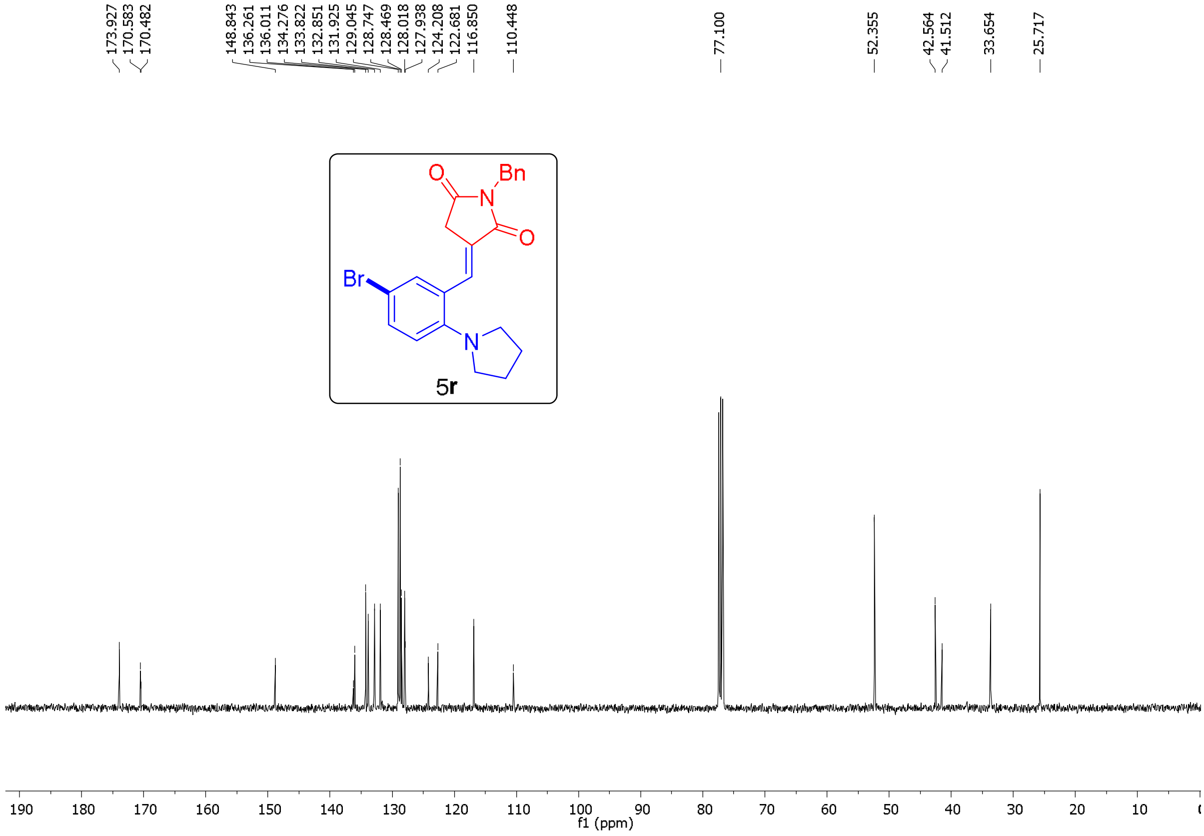
^{13}C NMR spectra of **5q** (101 MHz, Chloroform-*d*)



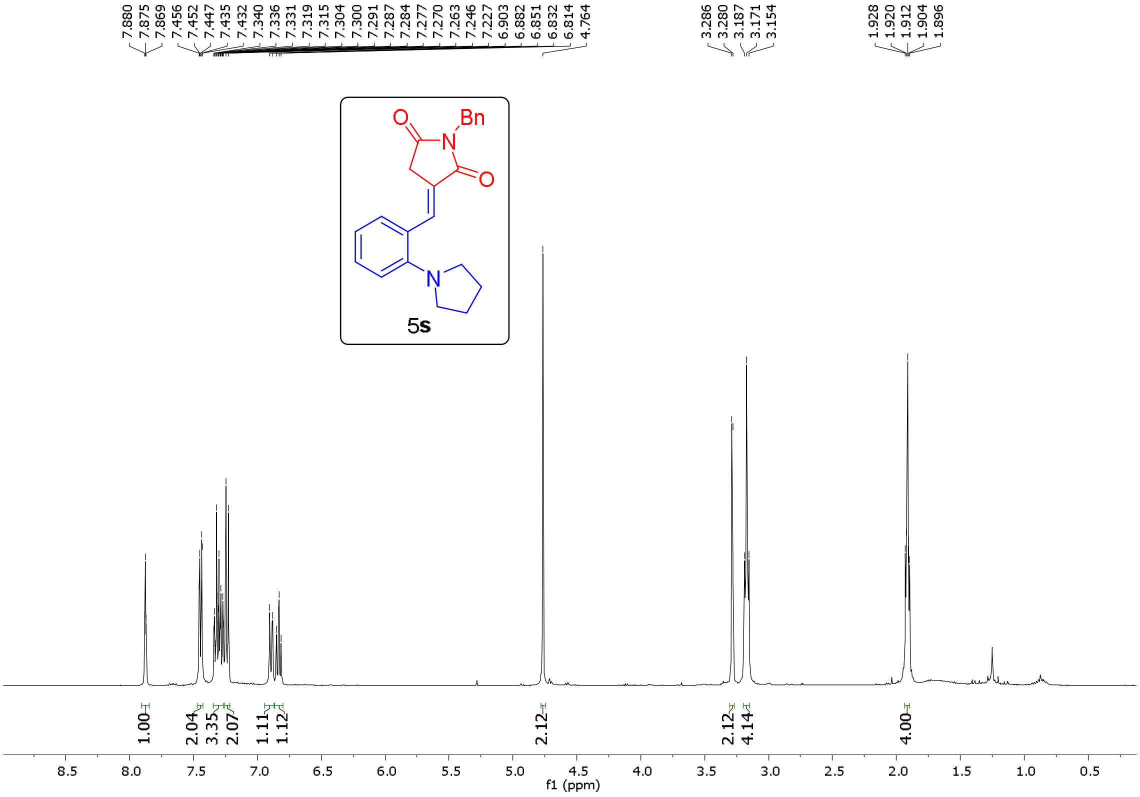
^{1}H NMR spectra of **5r** (400 MHz, Chloroform-*d*)



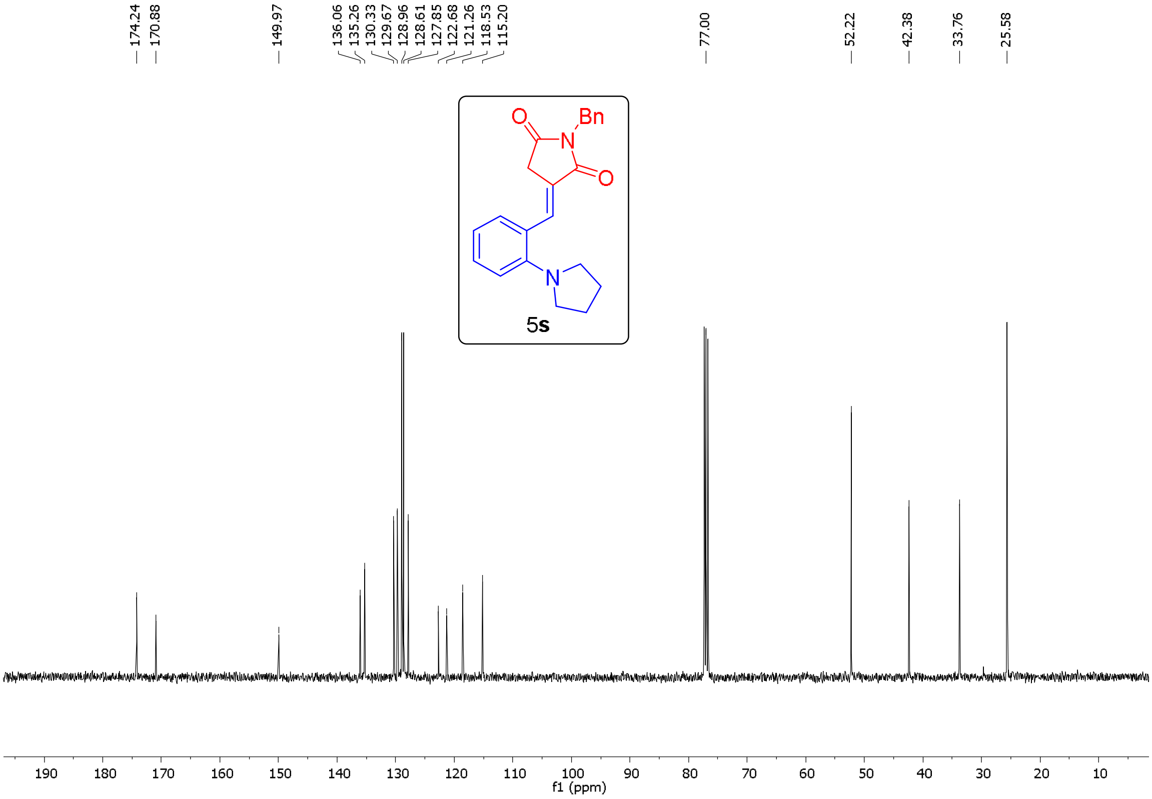
^{13}C NMR spectra of **5r** (101 MHz, Chloroform-*d*)



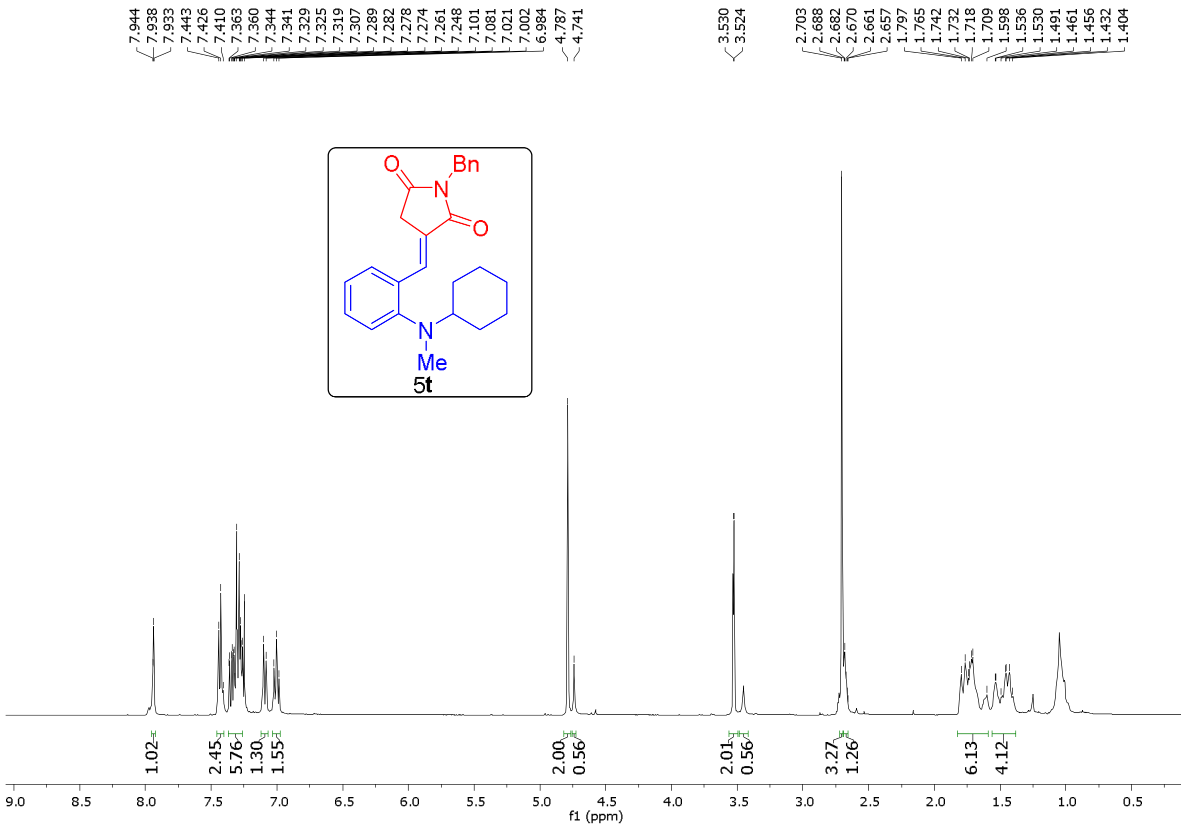
^{1}H NMR spectra of **5s** (400 MHz, Chloroform-*d*)



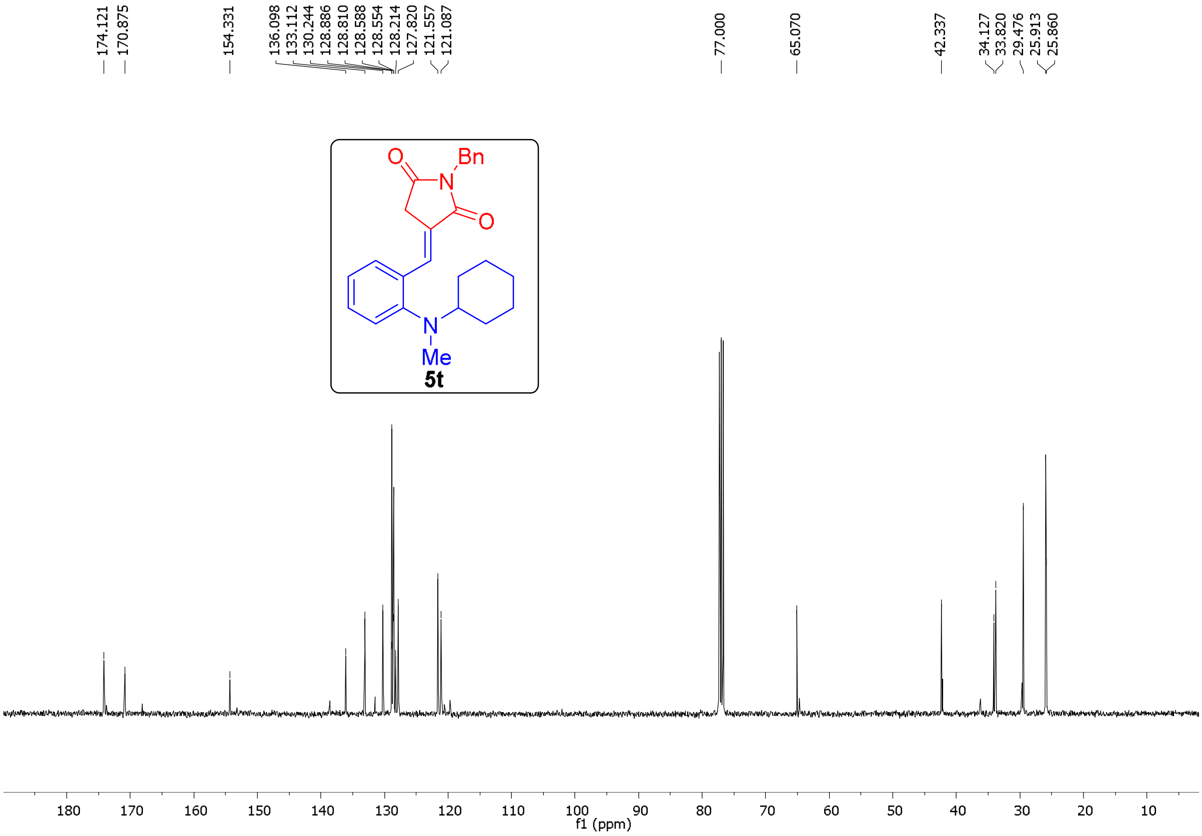
^{13}C NMR spectra of **5s** (101 MHz, Chloroform-*d*)



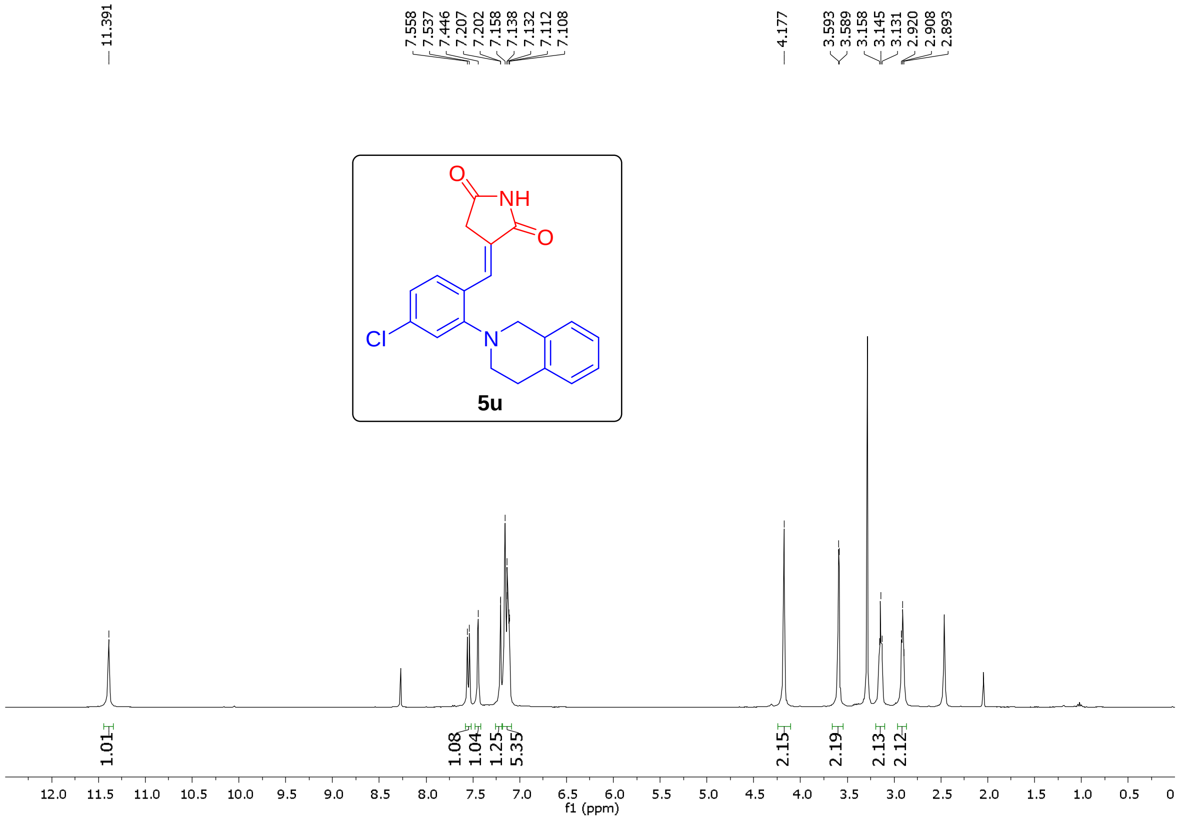
^{1}H NMR spectra of **5t** (400 MHz, Chloroform-*d*)



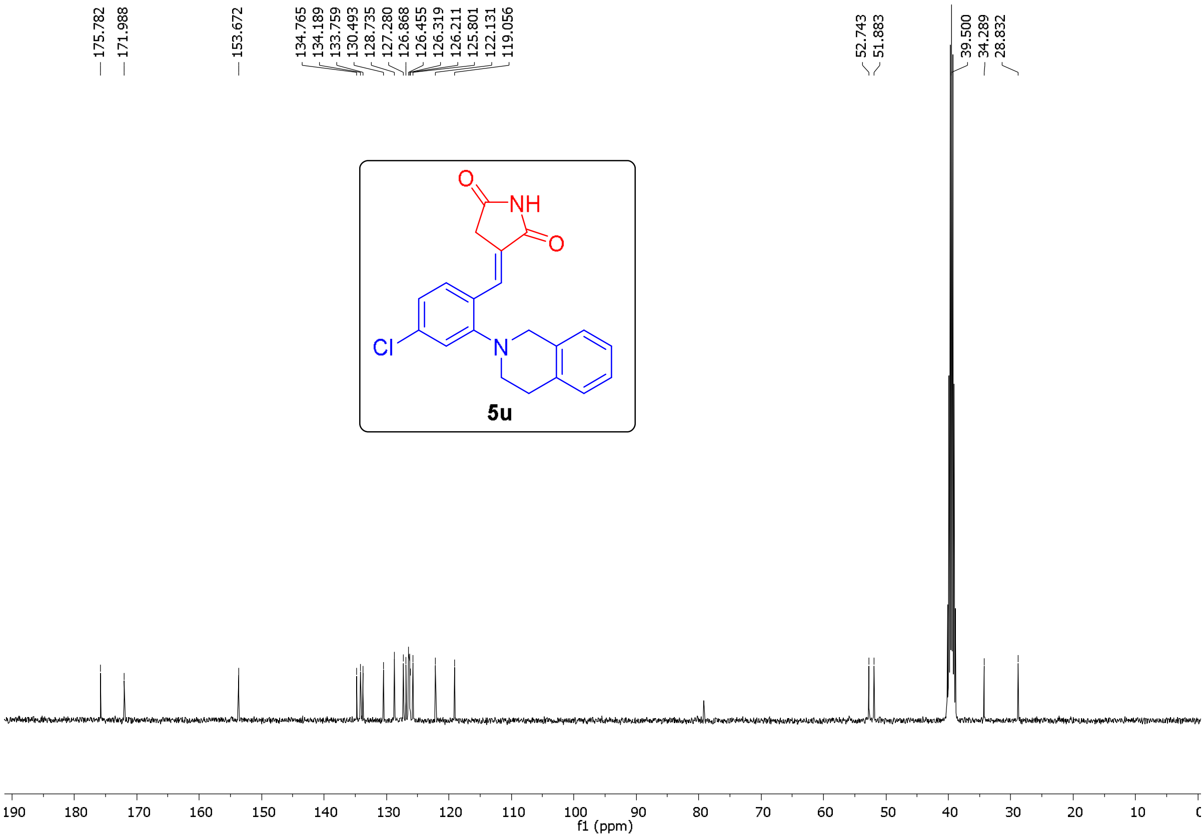
^{13}C NMR spectra of **5t** (101 MHz, Chloroform-*d*)



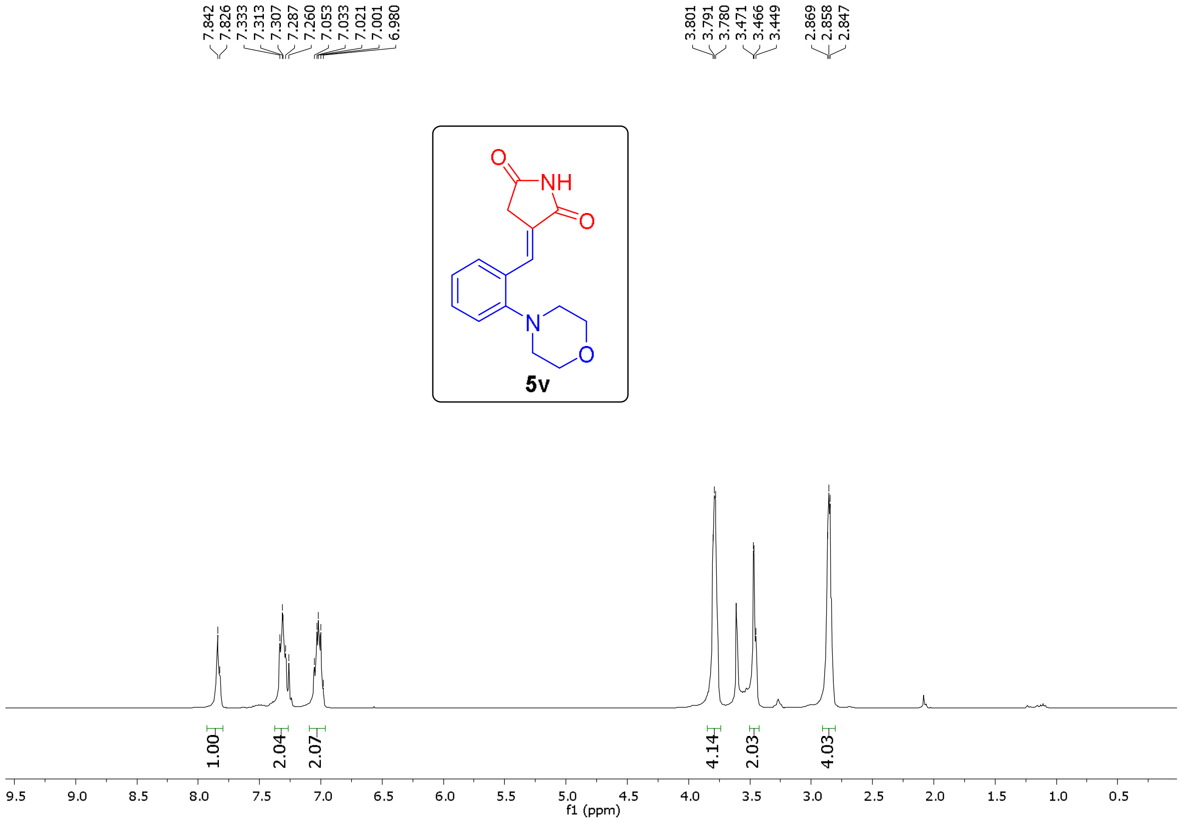
^{1}H NMR spectra of **5u** (400 MHz, DMSO-d_6)



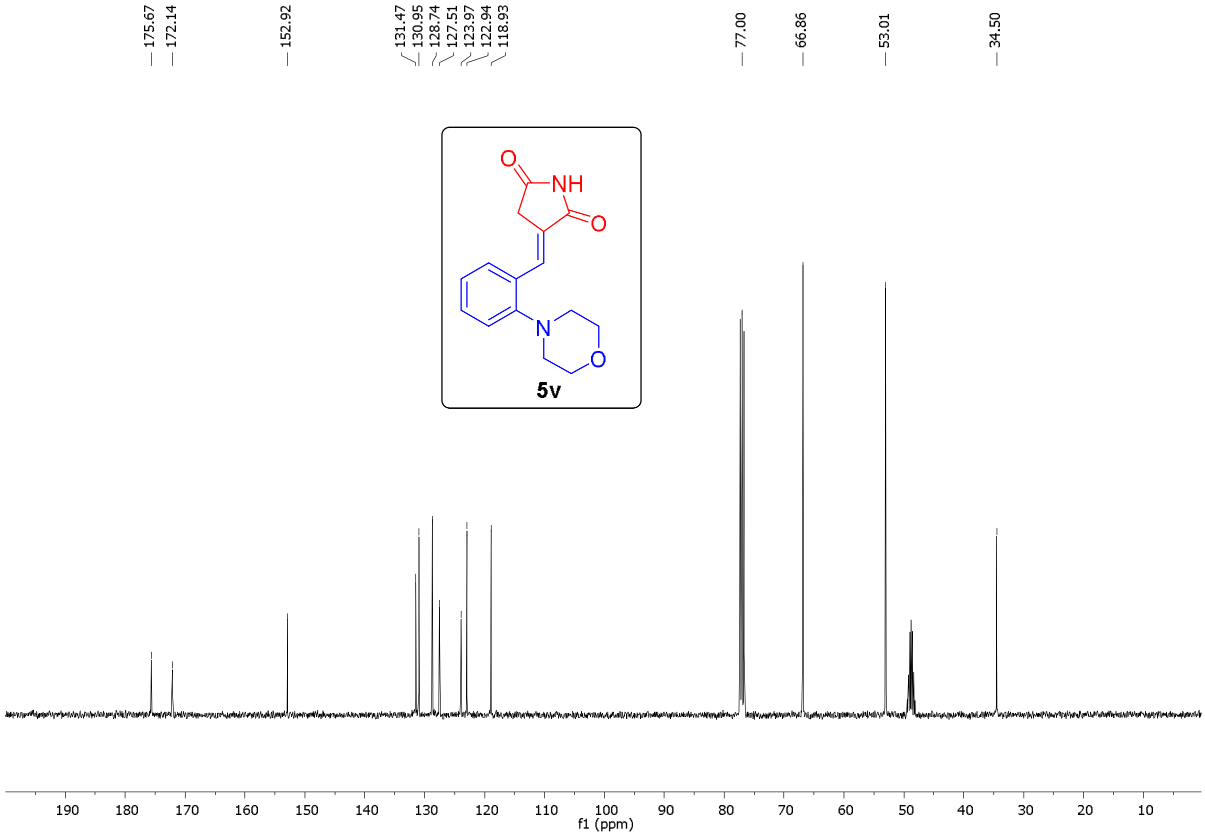
^{13}C NMR spectra of **5u** (101 MHz, DMSO-d_6)



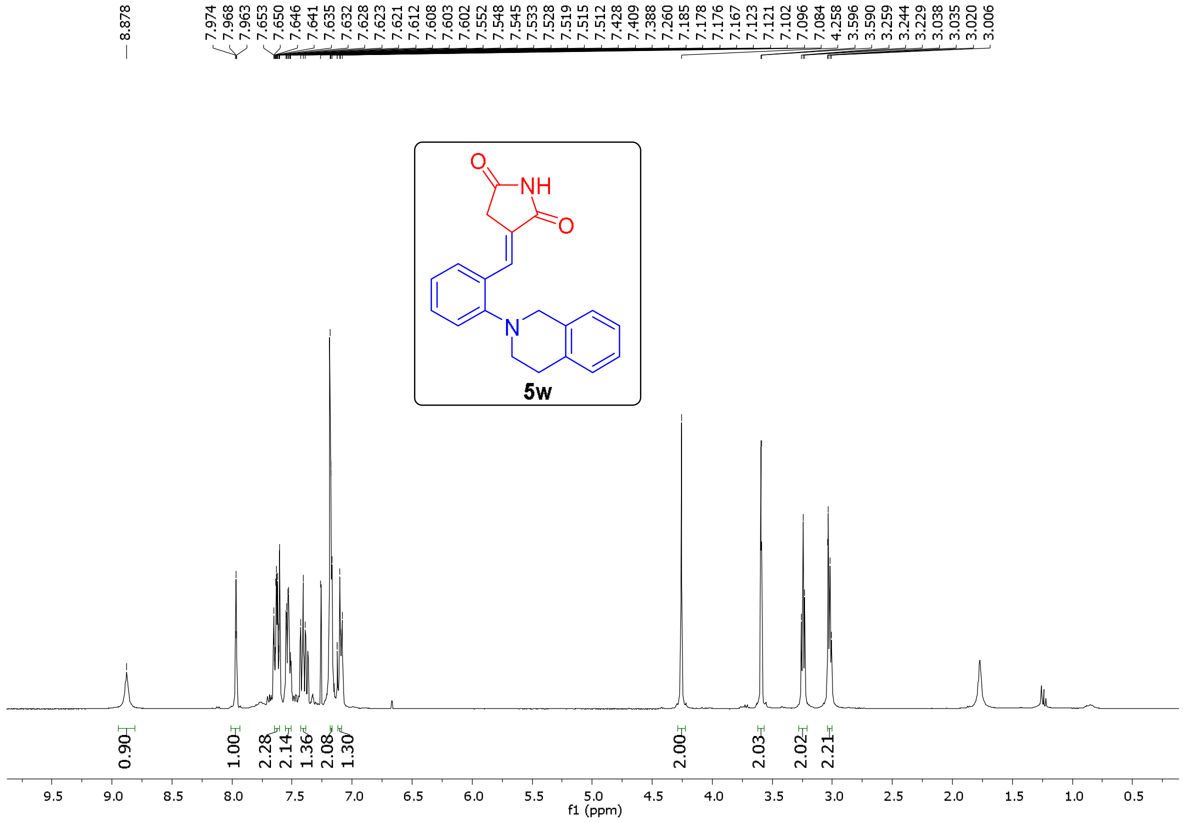
^{1}H NMR spectra of **5v** (400 MHz, Chloroform-*d*+ few drops CD_3OD)



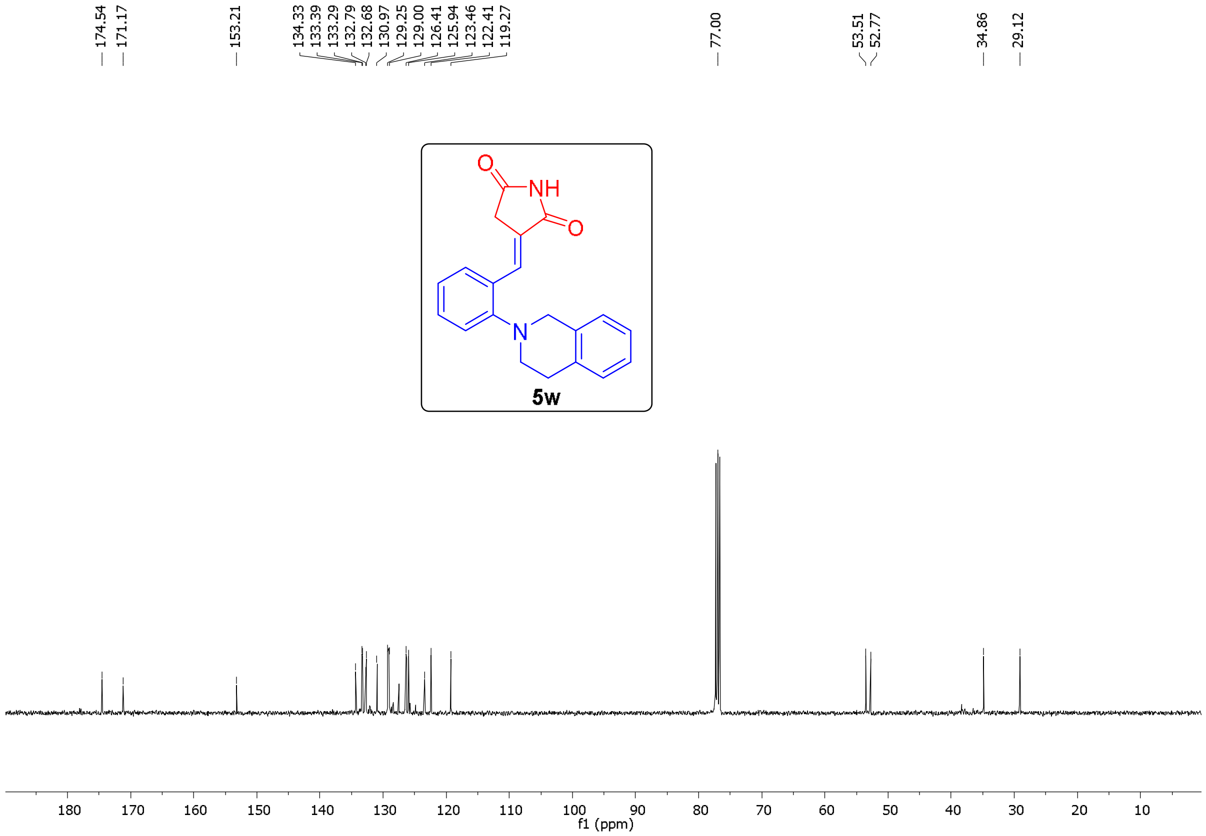
^{13}C NMR spectra of **5v** (101 MHz, Chloroform-*d* + few drops CD_3OD)



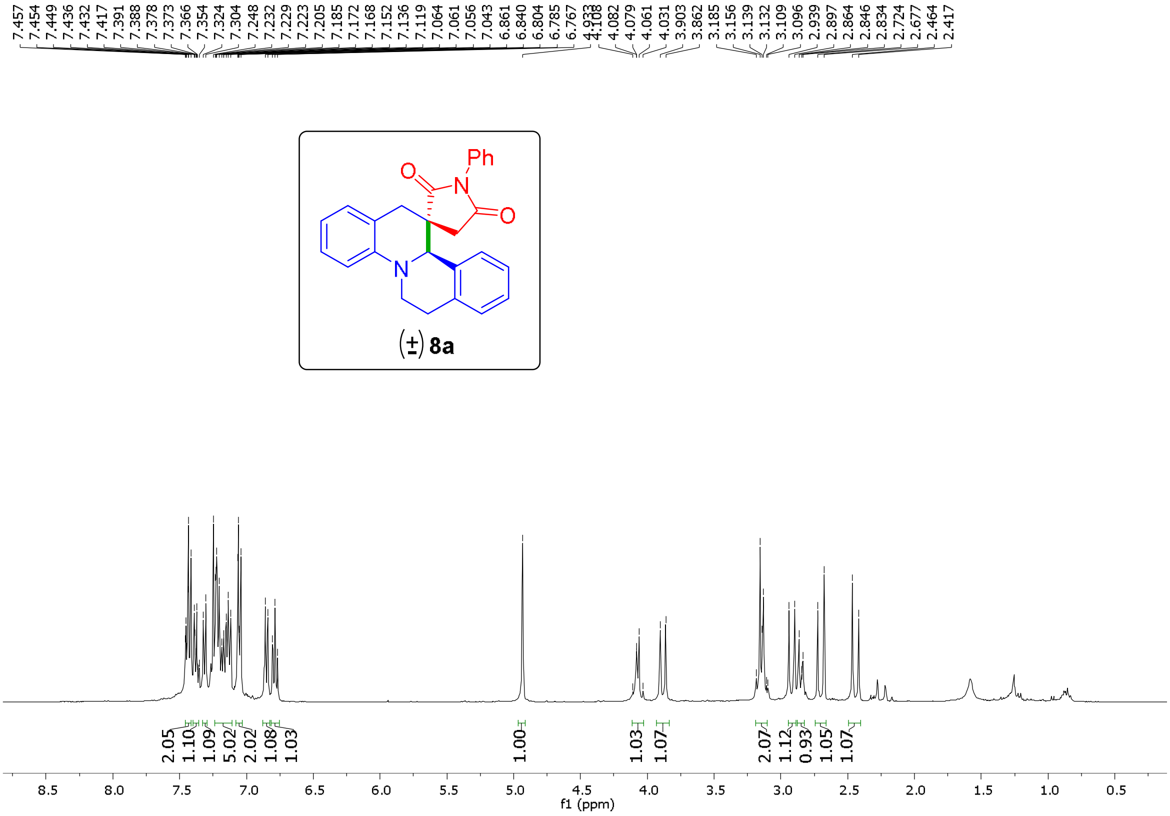
^{1}H NMR spectra of **5w** (400 MHz, Chloroform-*d*)



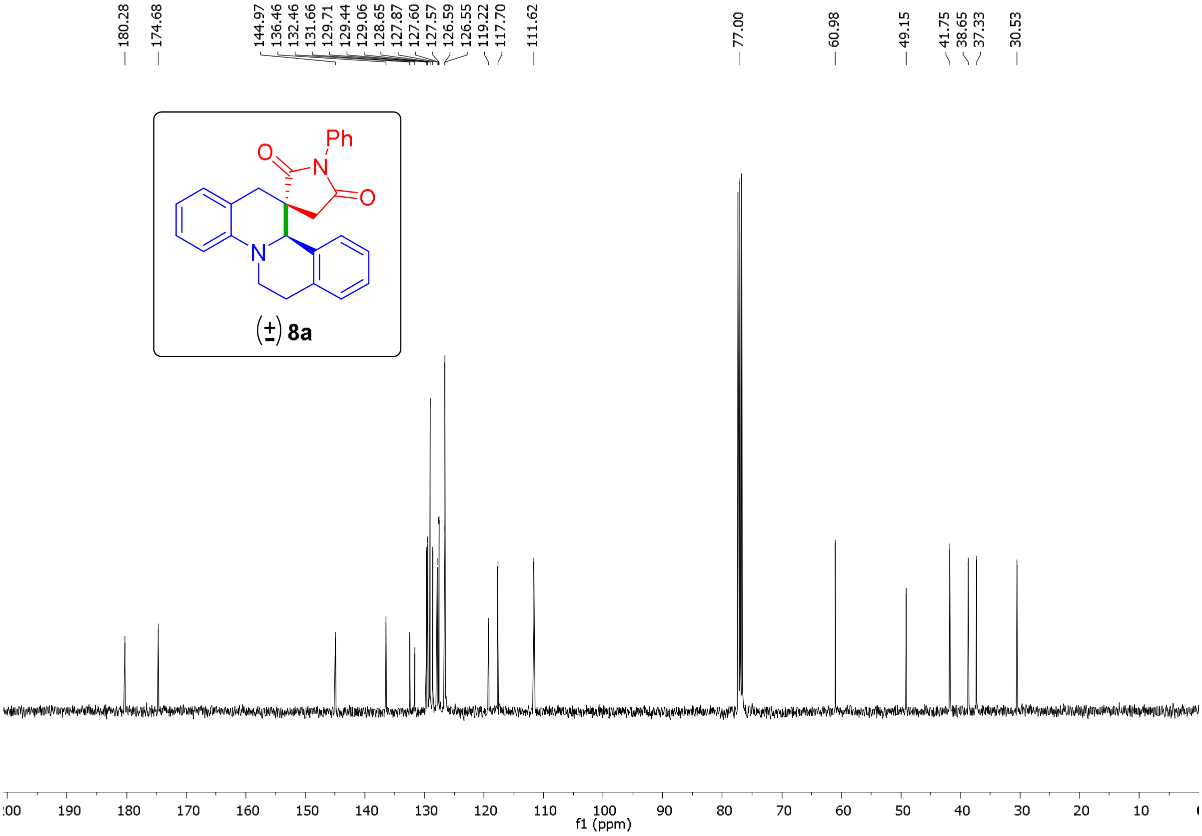
^{13}C NMR spectra of **5w** (101 MHz, Chloroform-*d*)



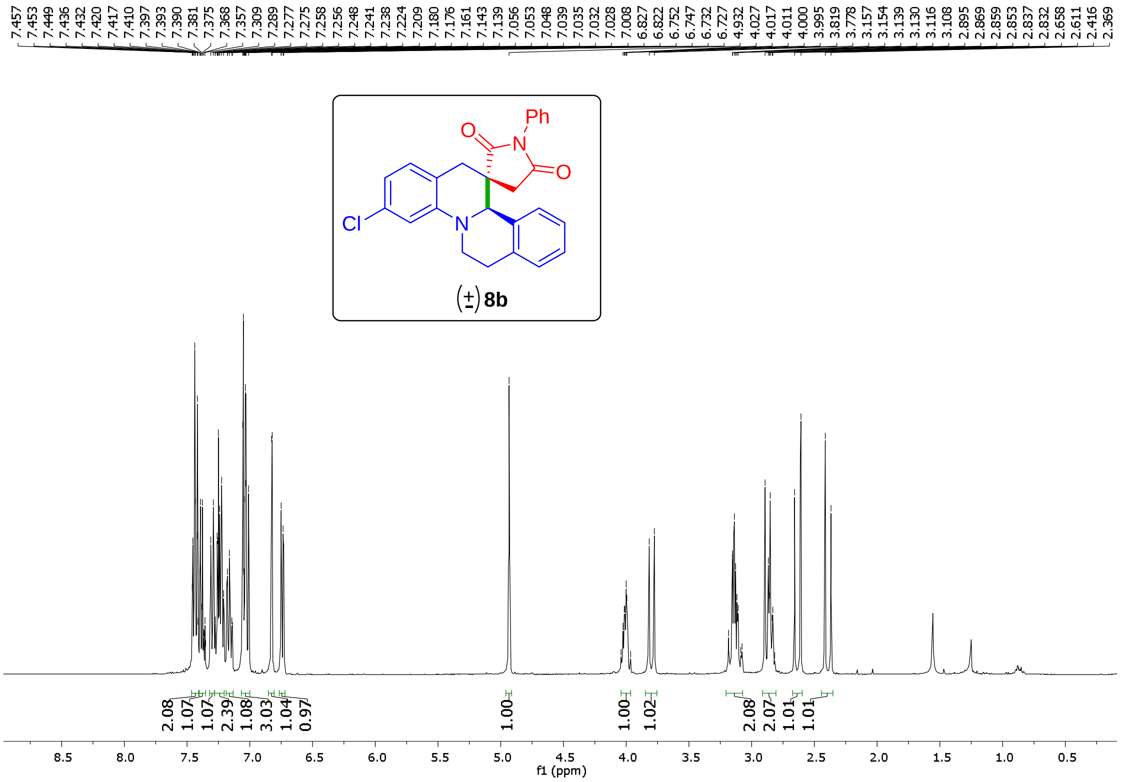
^{1}H NMR spectra of **8a** (400 MHz, Chloroform-*d*)



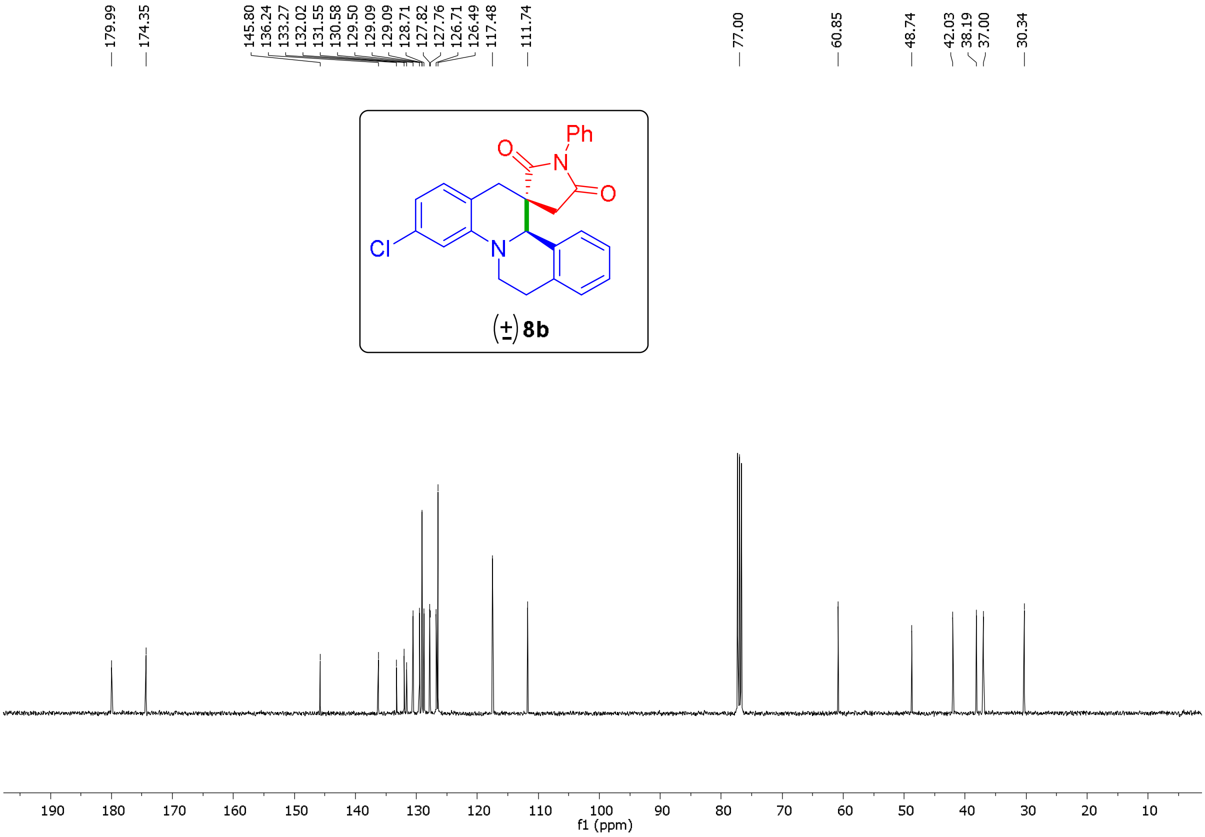
^{13}C NMR spectra of **8a** (101 MHz, Chloroform-*d*)



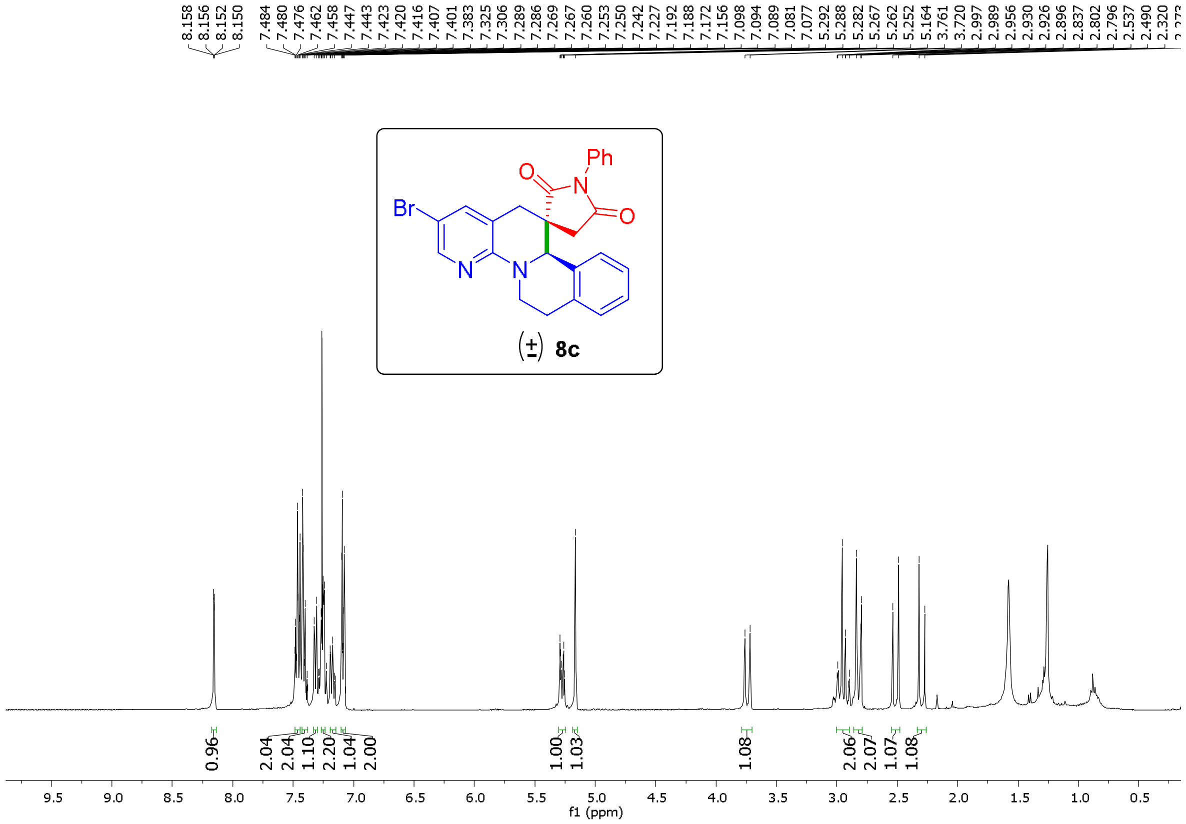
^{1}H NMR spectra of **8b** (400 MHz, Chloroform-*d*)



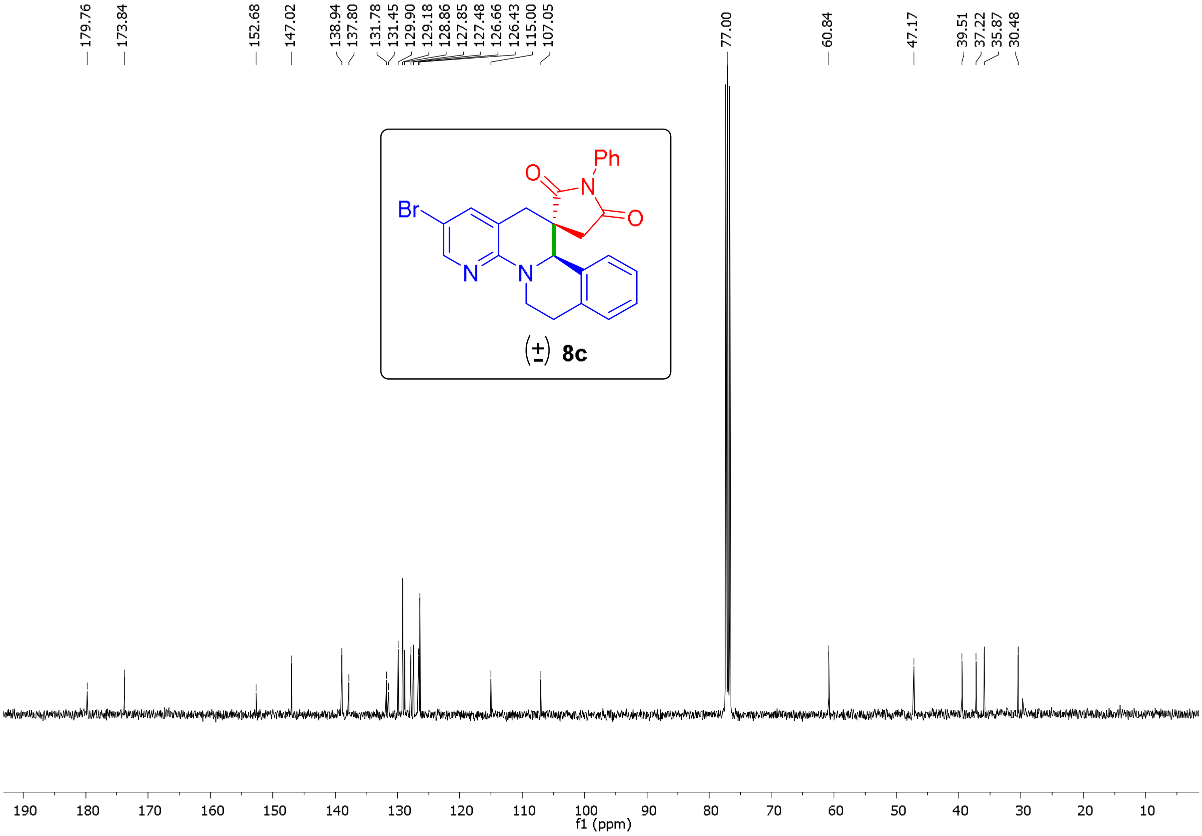
^{13}C NMR spectra of **8b** (101 MHz, Chloroform-*d*)



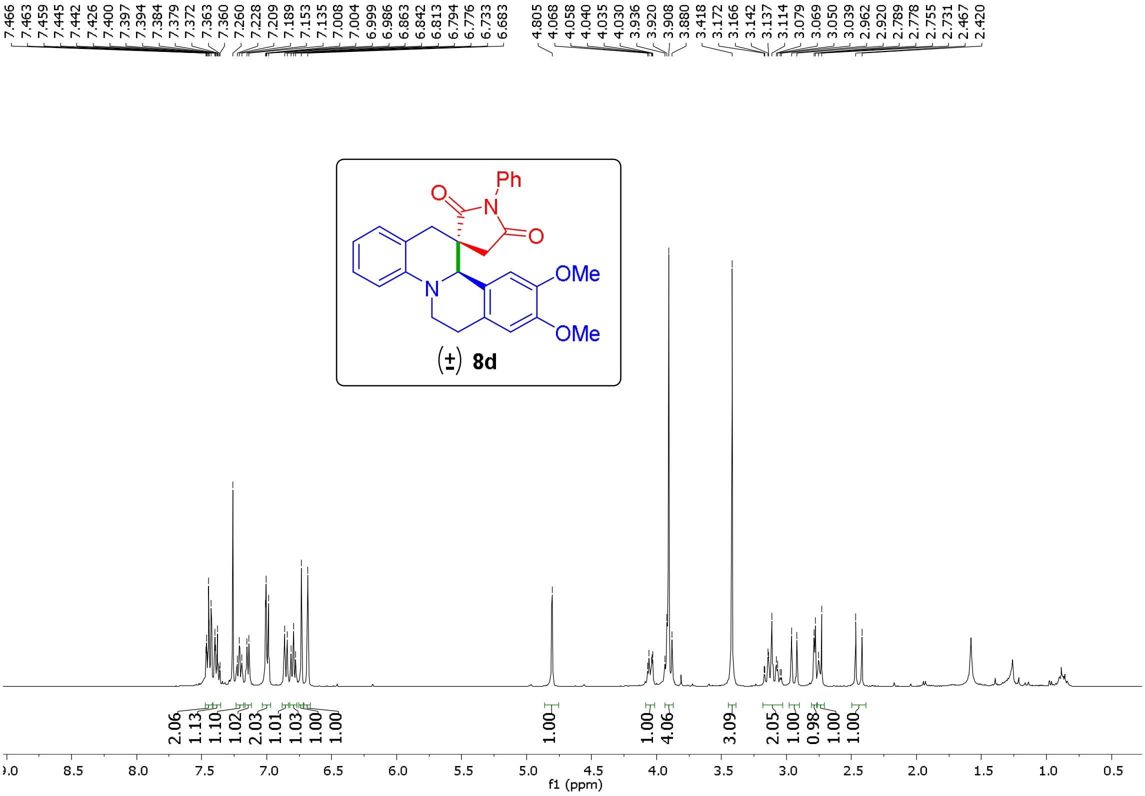
^{1}H NMR spectra of **8c** (400 MHz, Chloroform-*d*)



^{13}C NMR spectra of **8c** (101 MHz, Chloroform-*d*)



^{1}H NMR spectra of **8d** (400 MHz, Chloroform-*d*)



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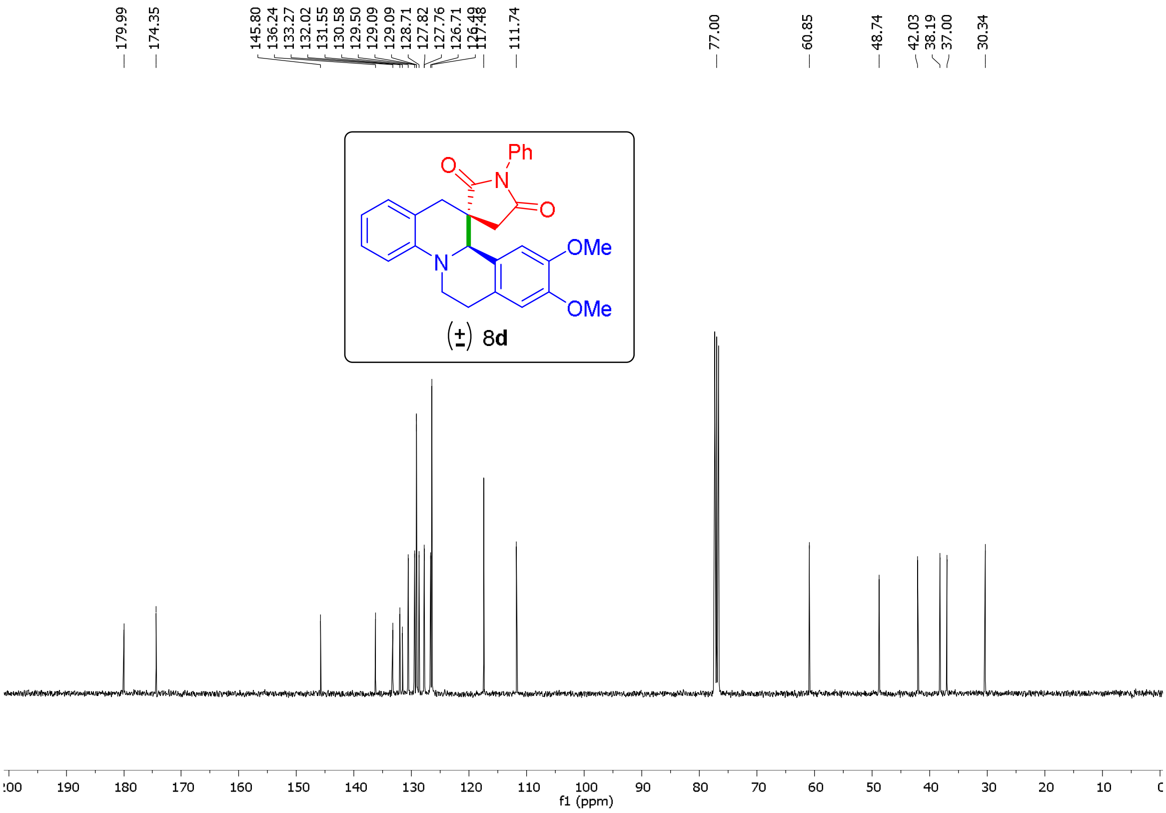
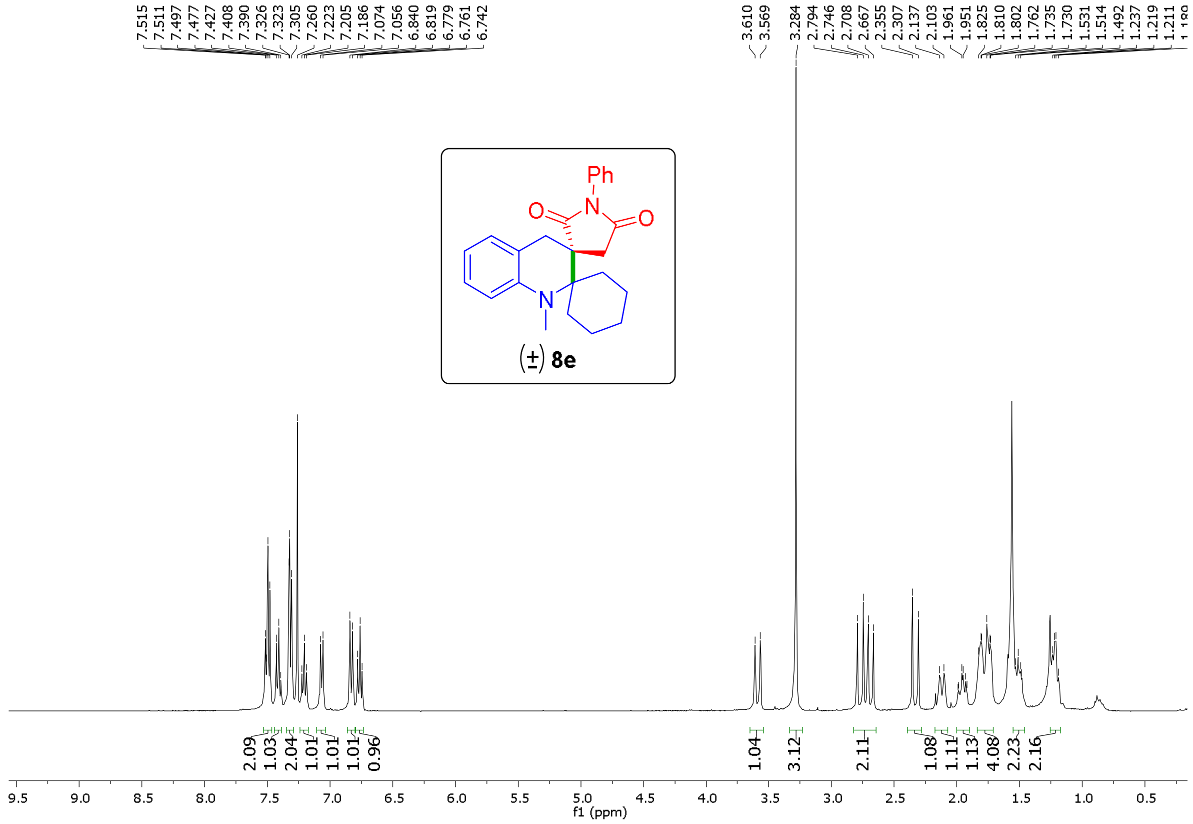


^{1}H NMR spectra of **8e** (400 MHz, Chloroform-*d*)



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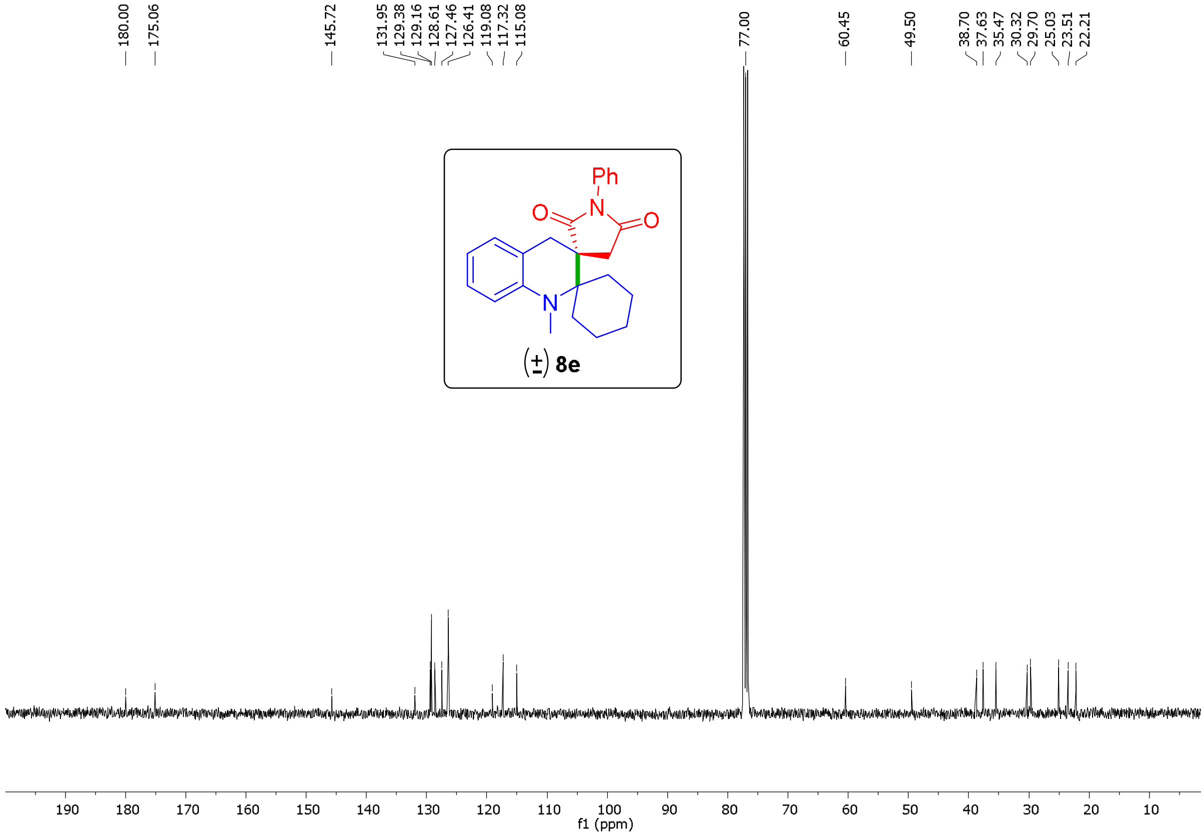
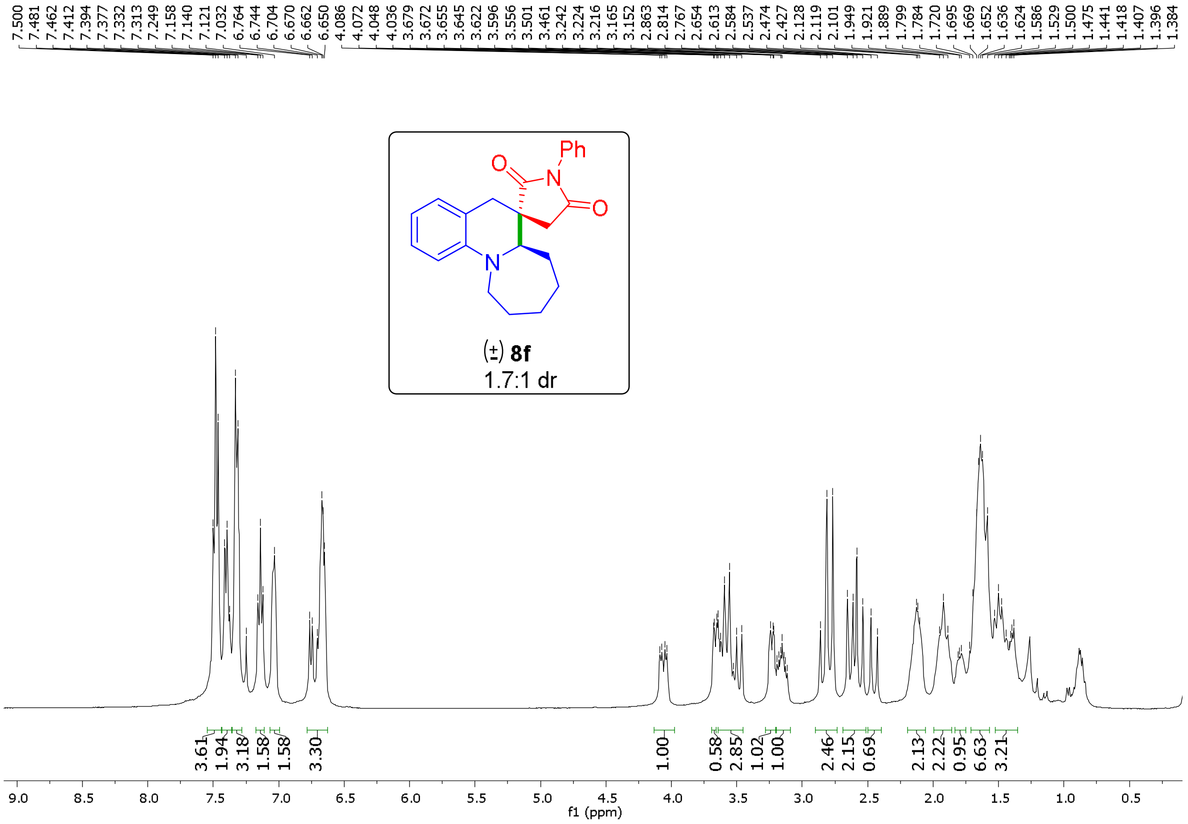
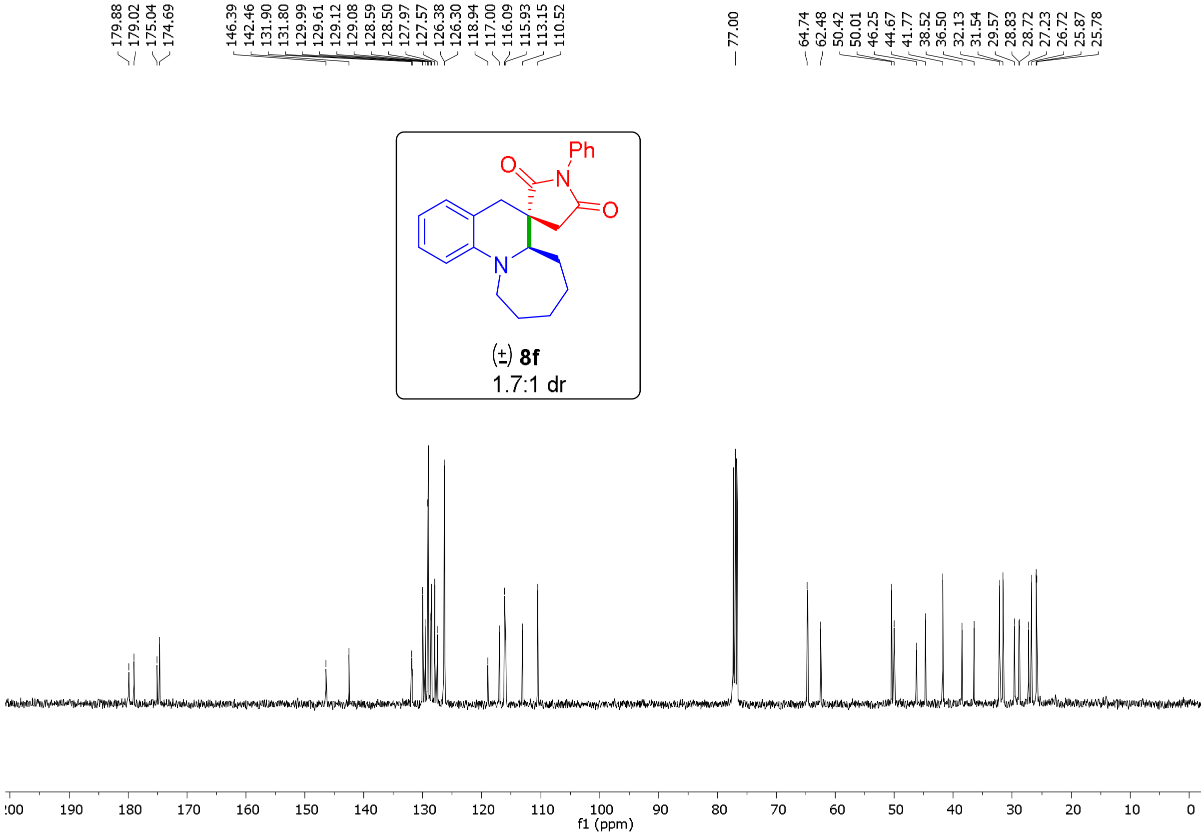


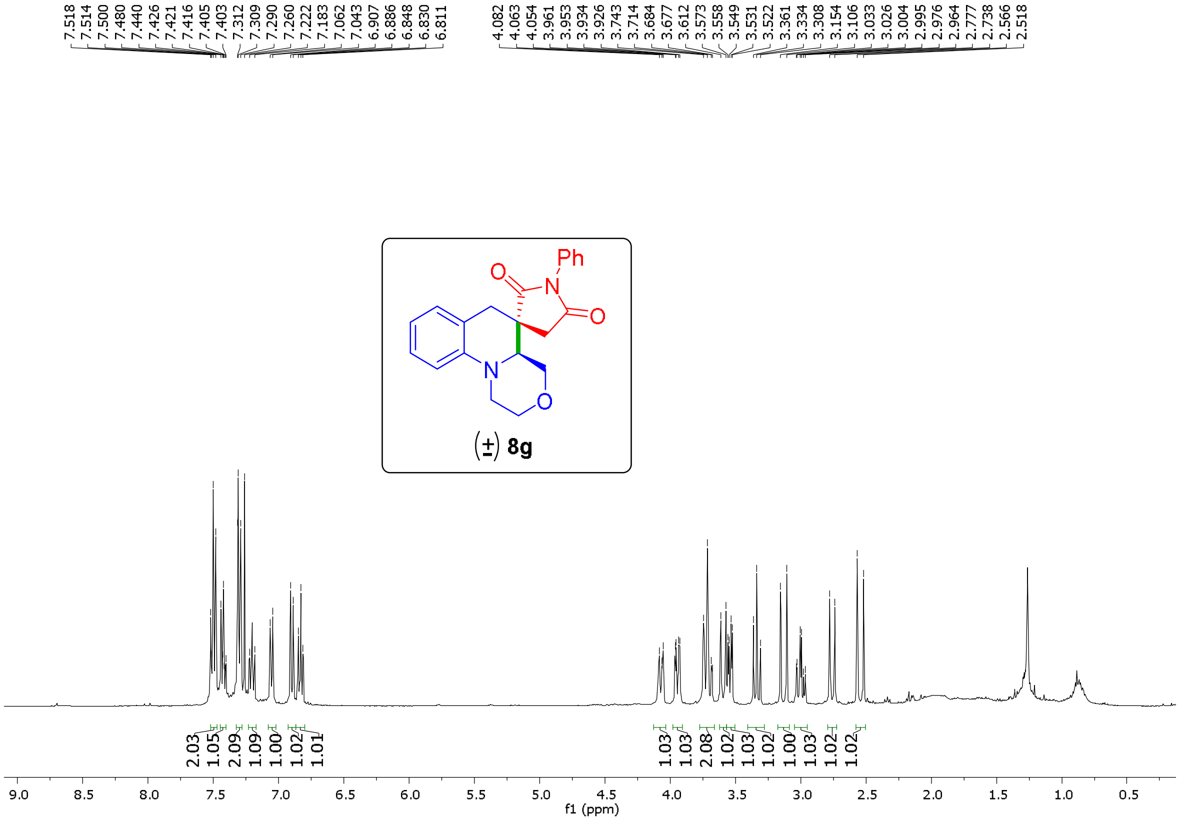
^{1}H NMR spectra of **8f** (400 MHz, Chloroform-*d*)



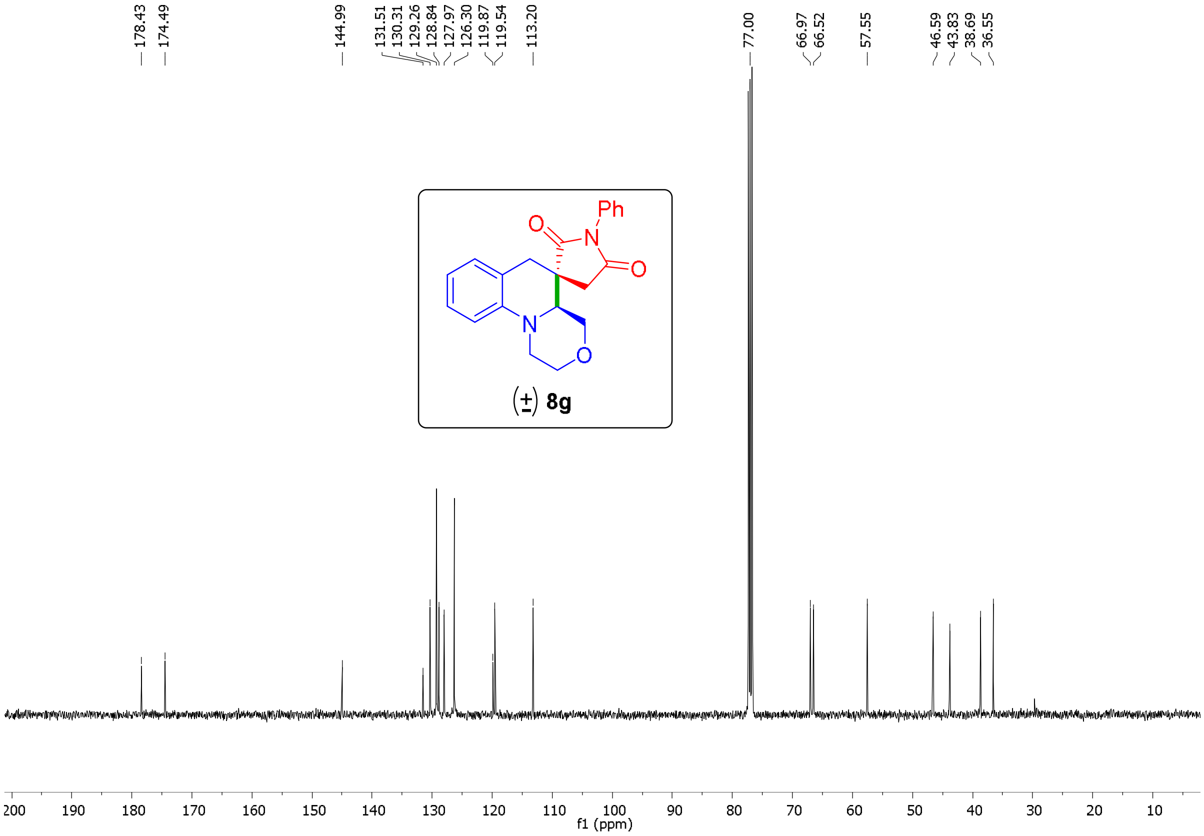
^{13}C NMR spectra of **8f** (101 MHz, Chloroform-*d*)



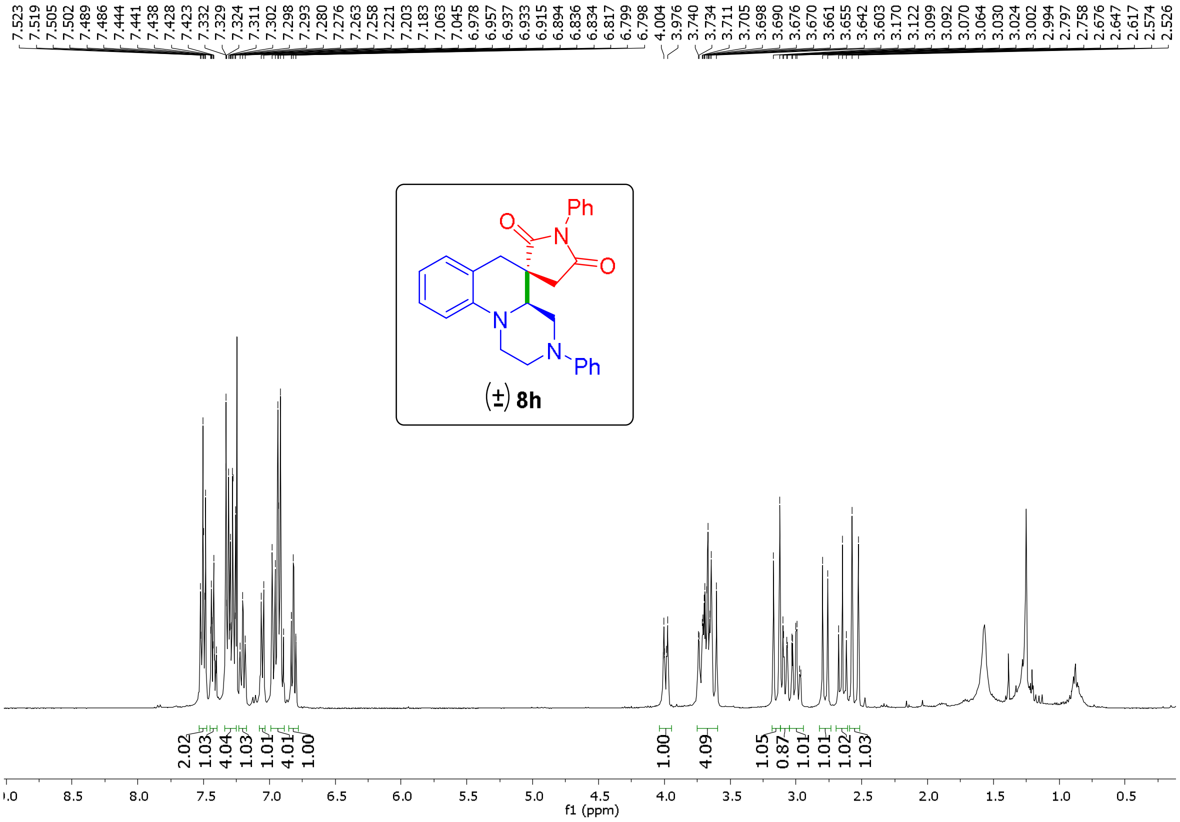
^{1}H NMR spectra of **8g** (400 MHz, Chloroform-*d*)



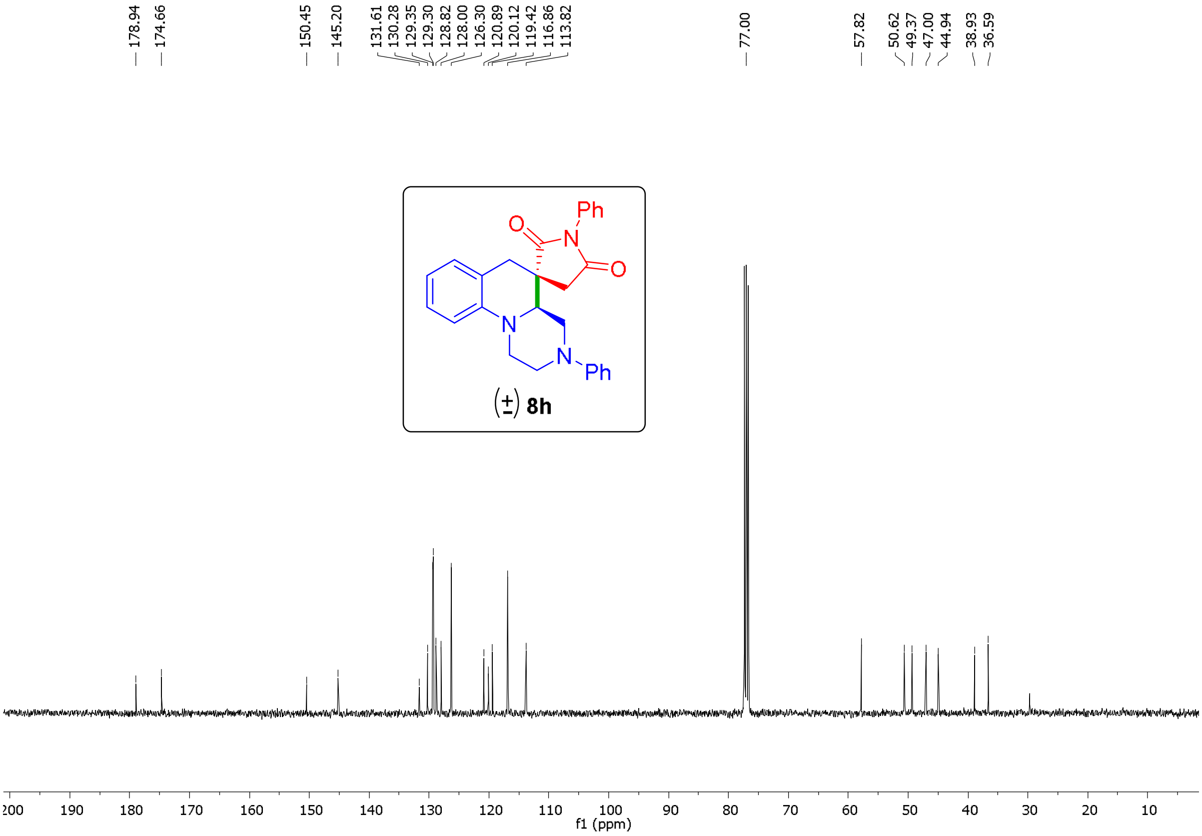
^{13}C NMR spectra of **8g** (101 MHz, Chloroform-*d*)



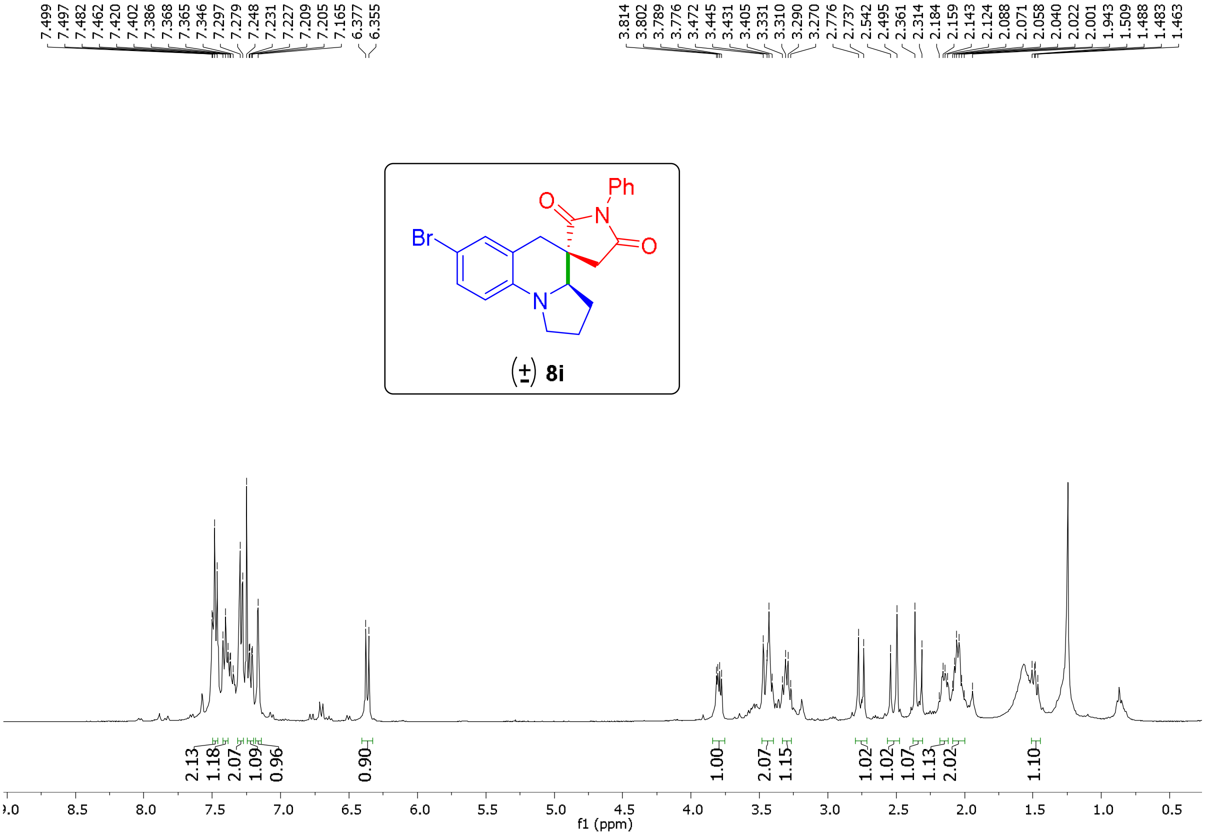
^{1}H NMR spectra of **8h** (400 MHz, Chloroform-*d*)



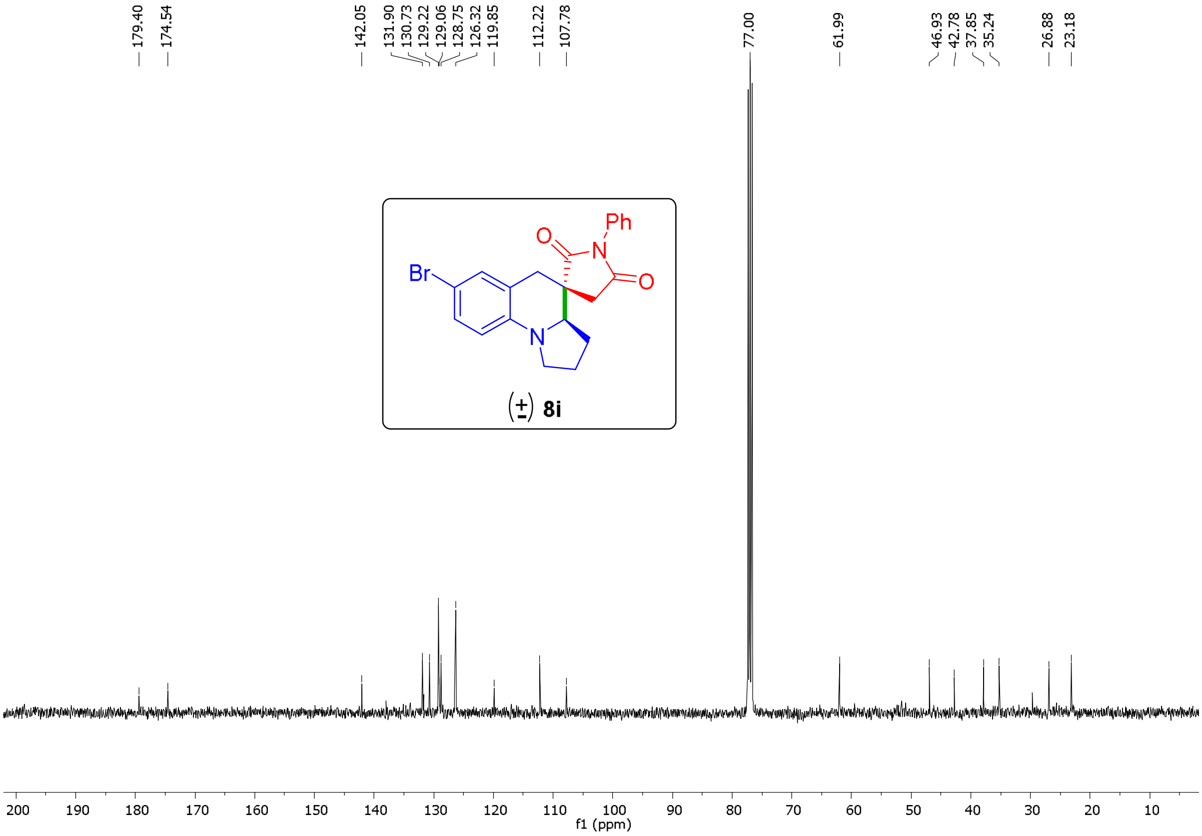
^{13}C NMR spectra of **8h** (101 MHz, Chloroform-*d*)



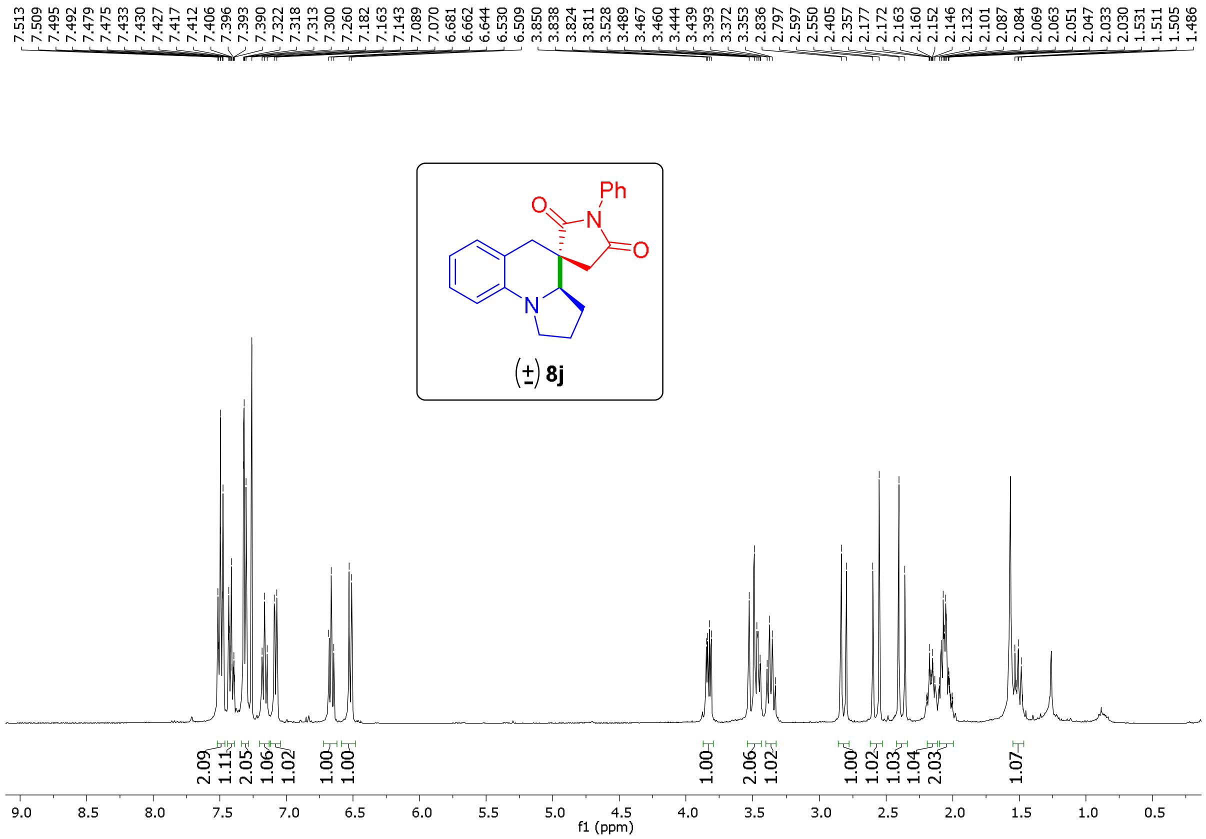
^{1}H NMR spectra of **8i** (400 MHz, Chloroform-*d*)



^{13}C NMR spectra of **8i** (101 MHz, Chloroform-*d*)



^{1}H NMR spectra of **8j** (400 MHz, Chloroform-*d*)



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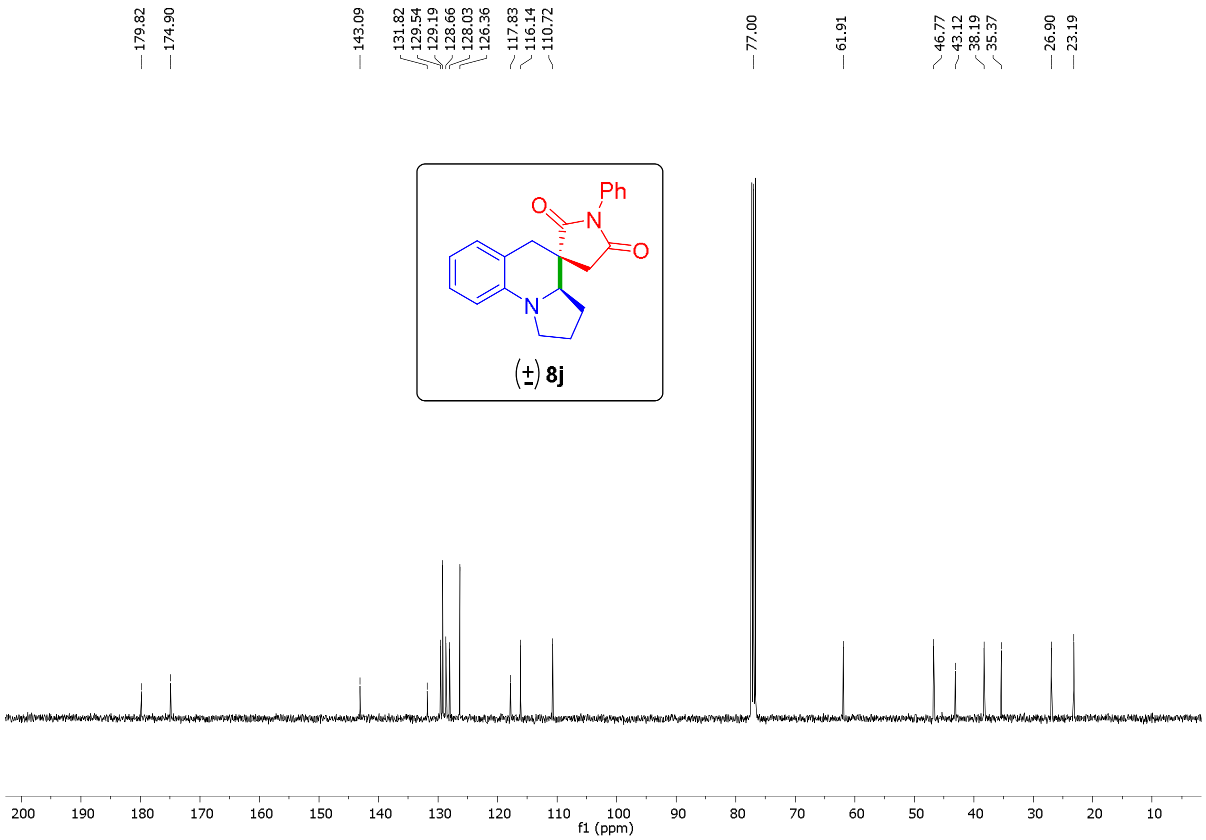
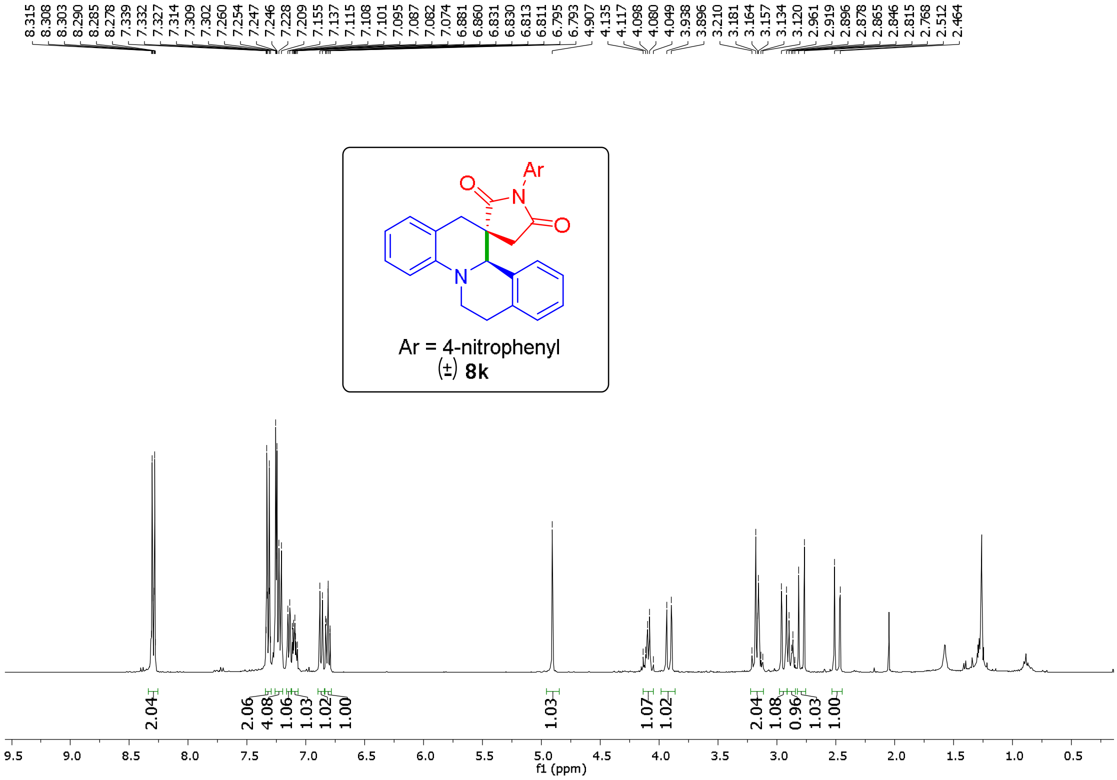
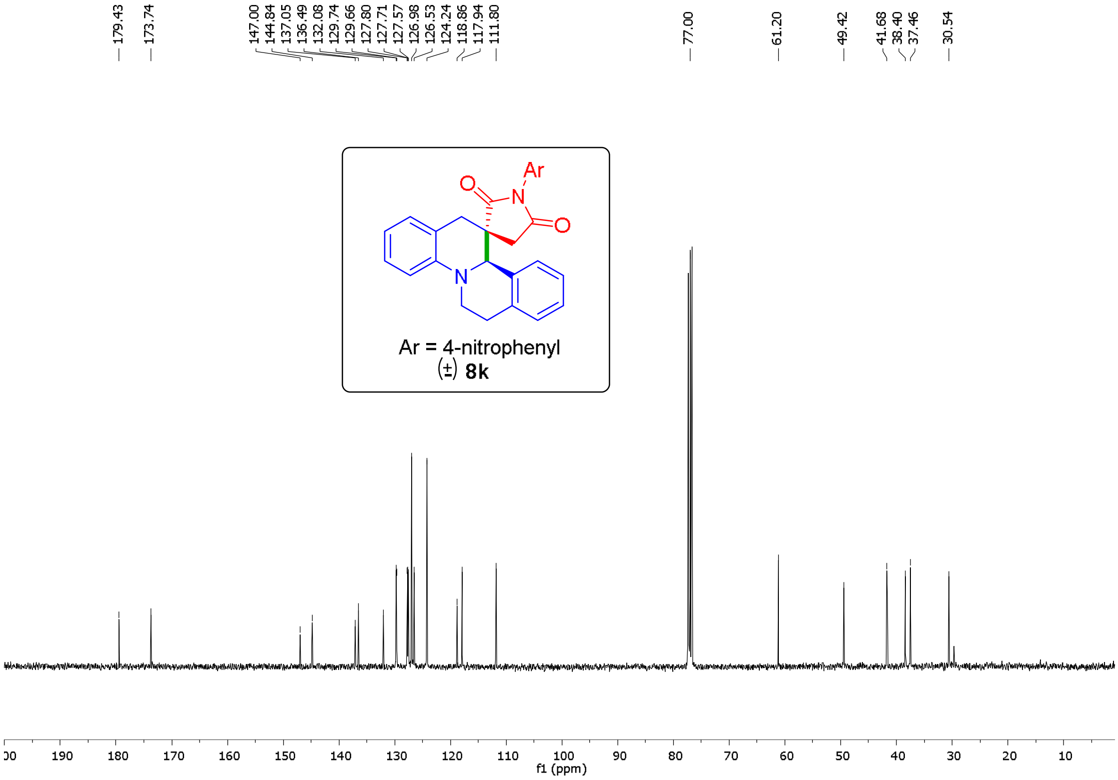


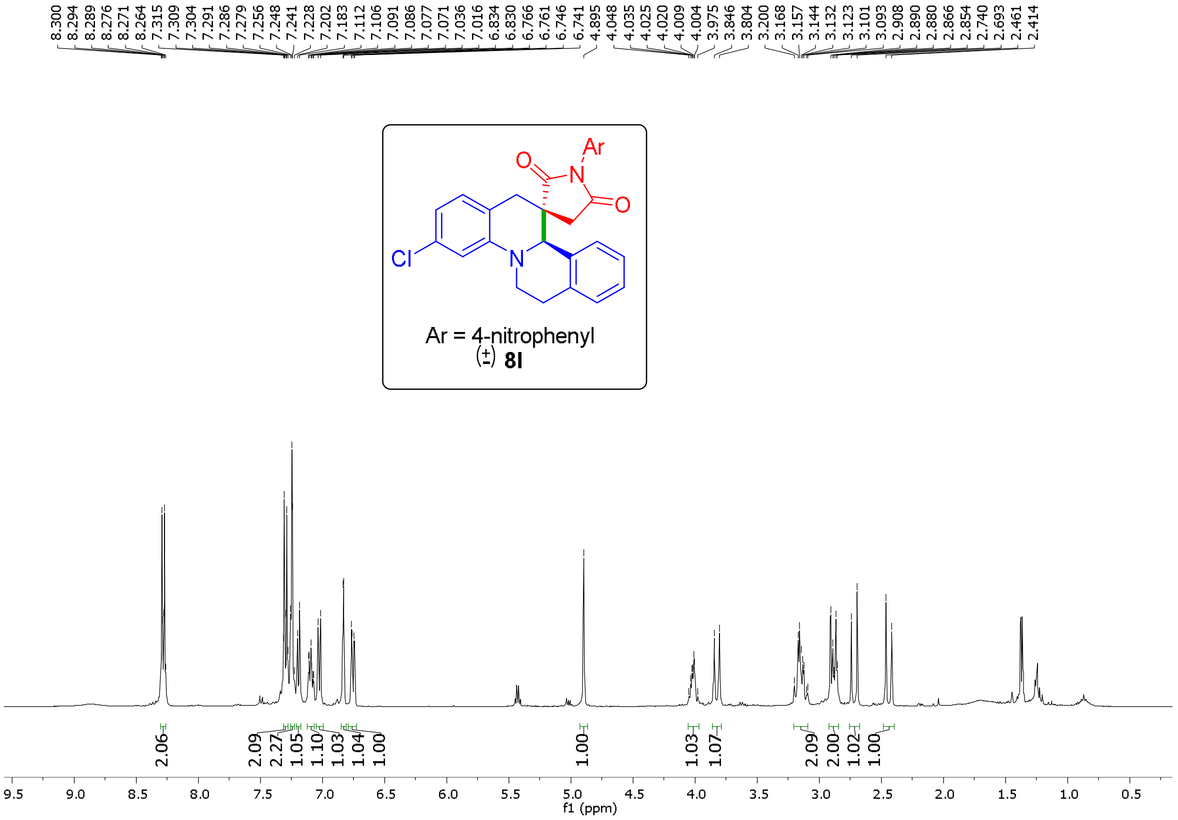
^{1}H NMR spectra of **8k** (400 MHz, Chloroform-*d*)



^{13}C NMR spectra of **8k** (101 MHz, Chloroform-*d*)



^{1}H NMR spectra of **8l** (400 MHz, Chloroform-*d*)



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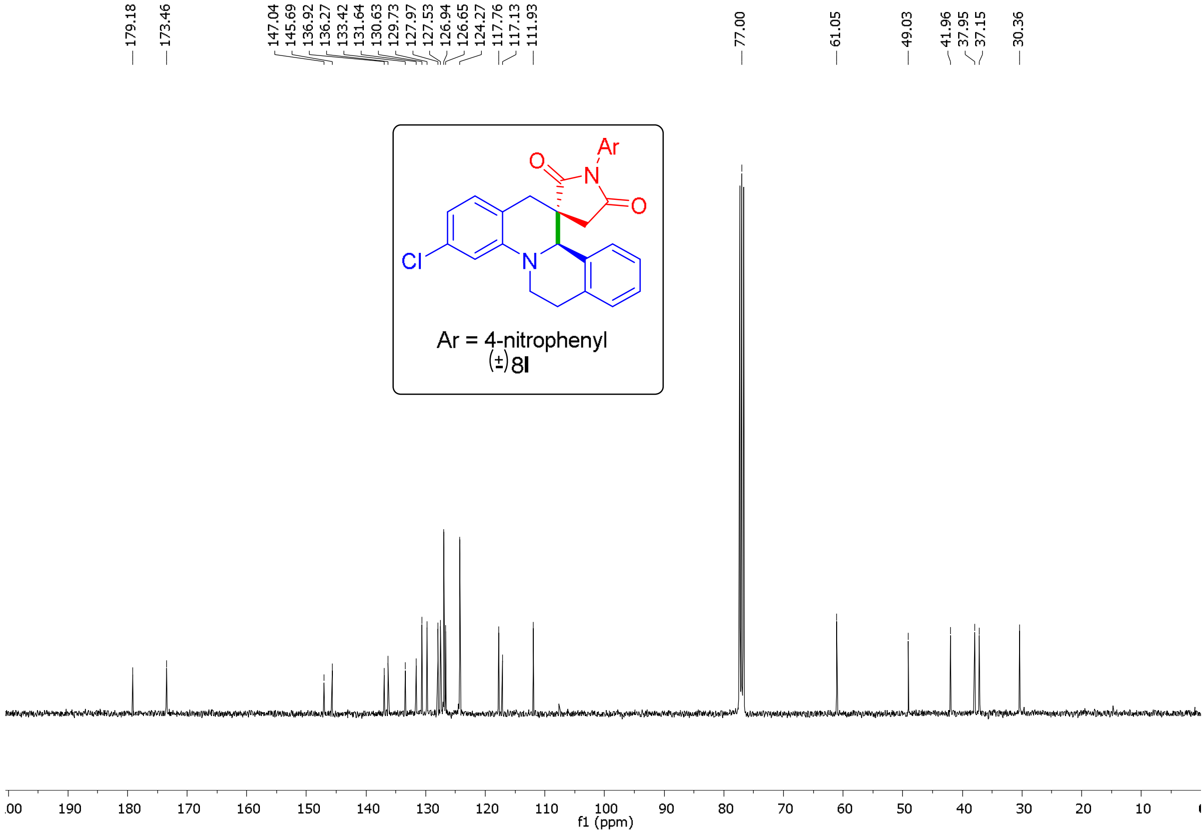
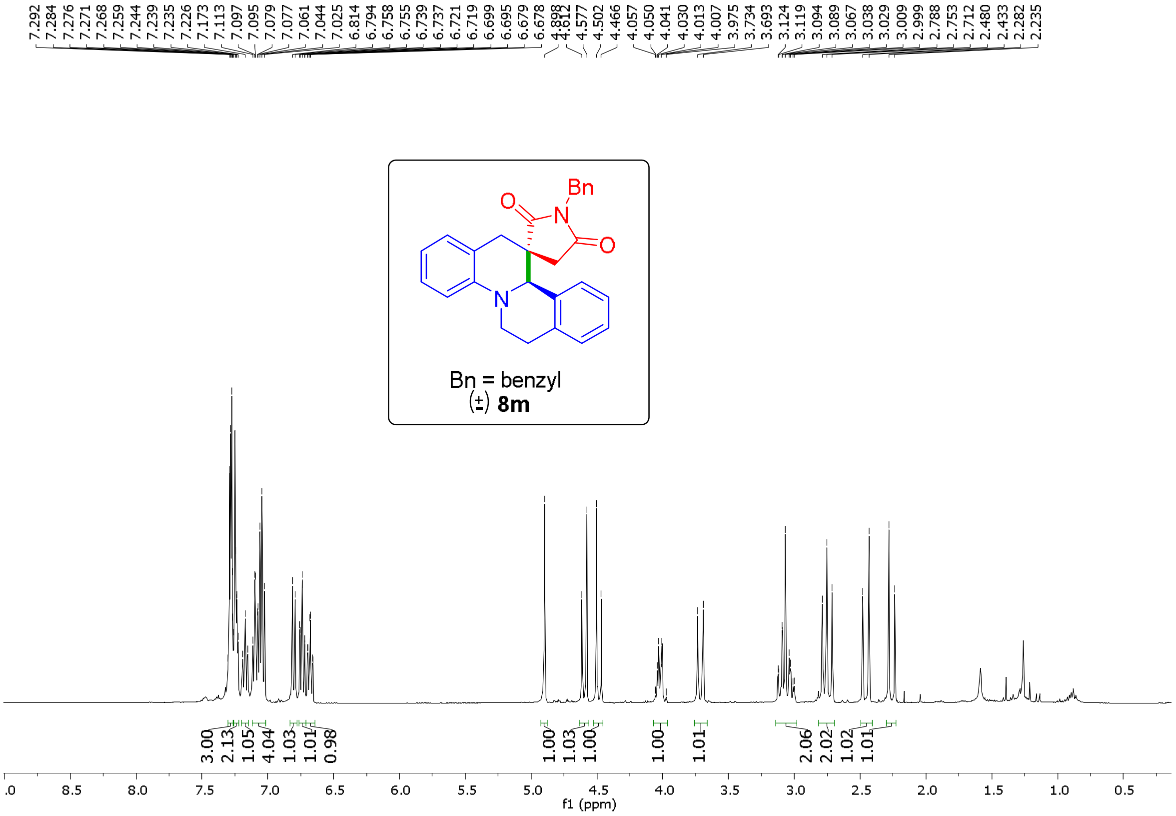


^{1}H NMR spectra of **8m** (400 MHz, Chloroform-*d*)



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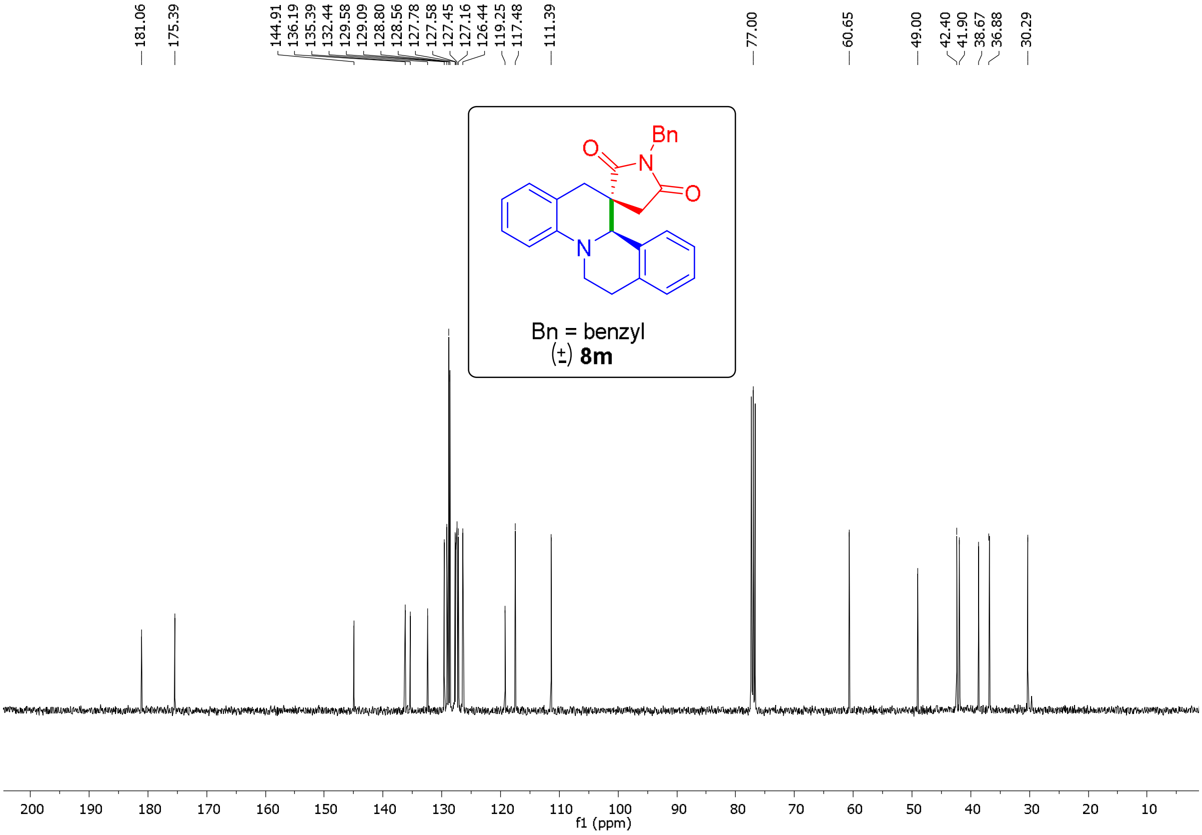
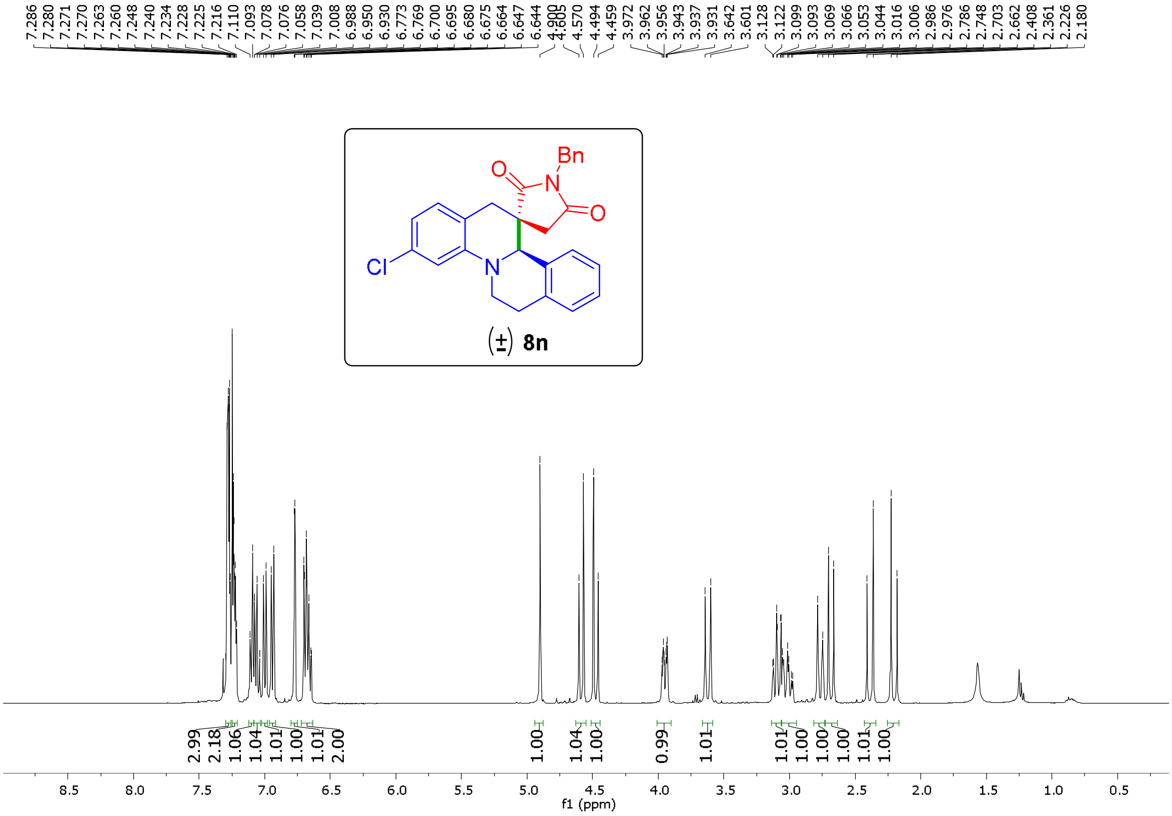


^{1}H NMR spectra of **8n** (400 MHz, Chloroform-*d*)



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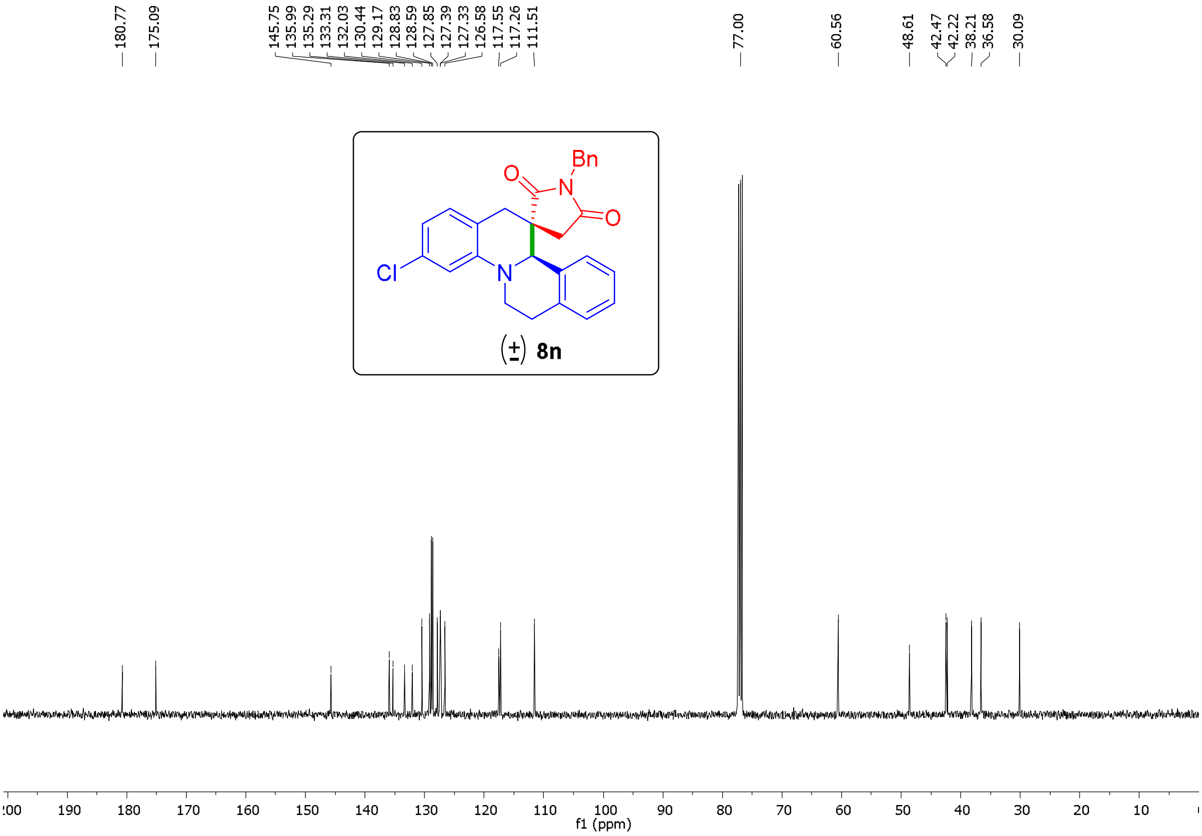
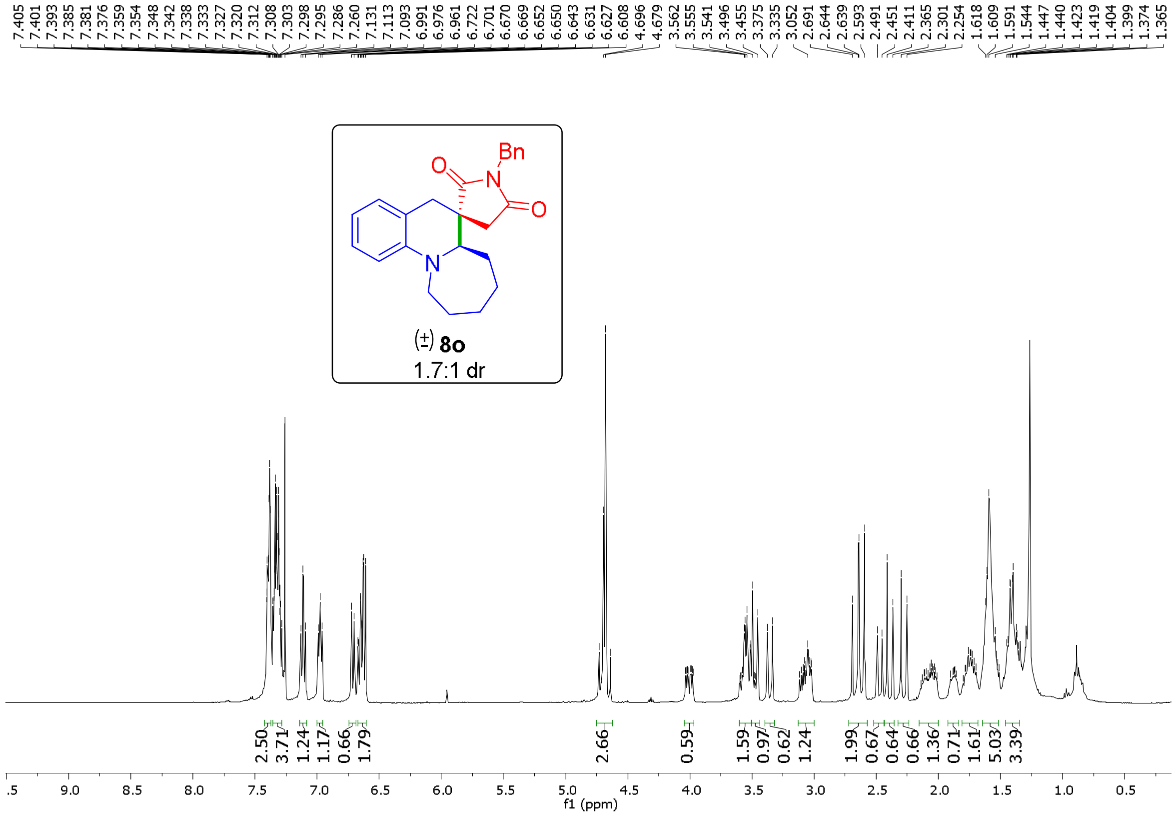
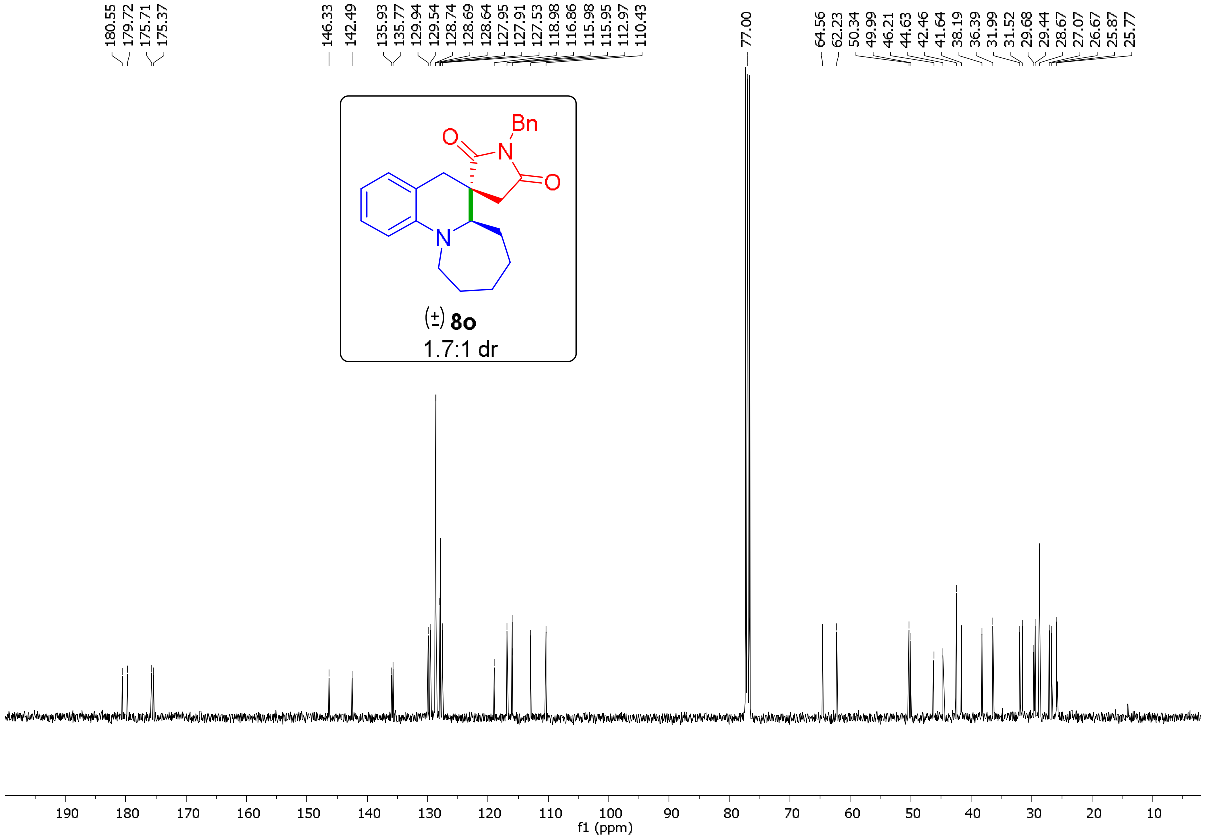


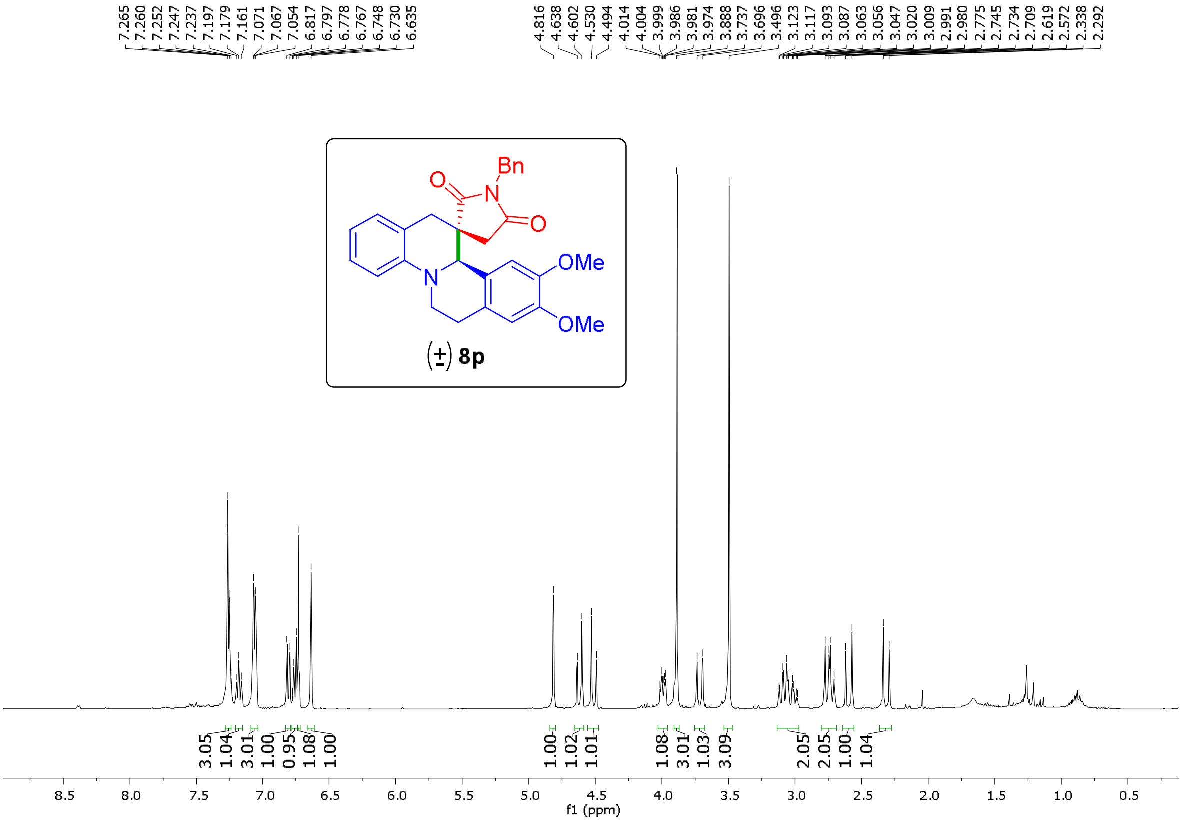
^{1}H NMR spectra of **8o** (400 MHz, Chloroform-*d*)



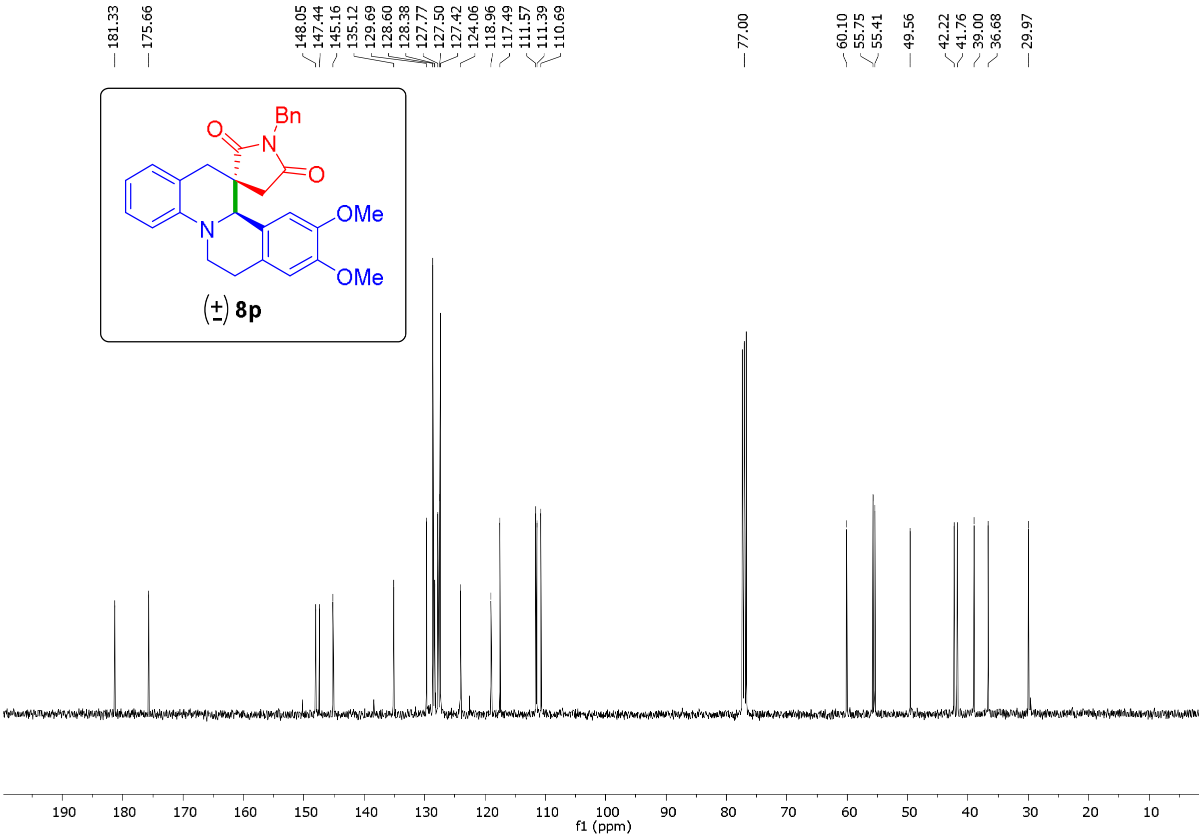
^{13}C NMR spectra of **8o** (101 MHz, Chloroform-*d*)



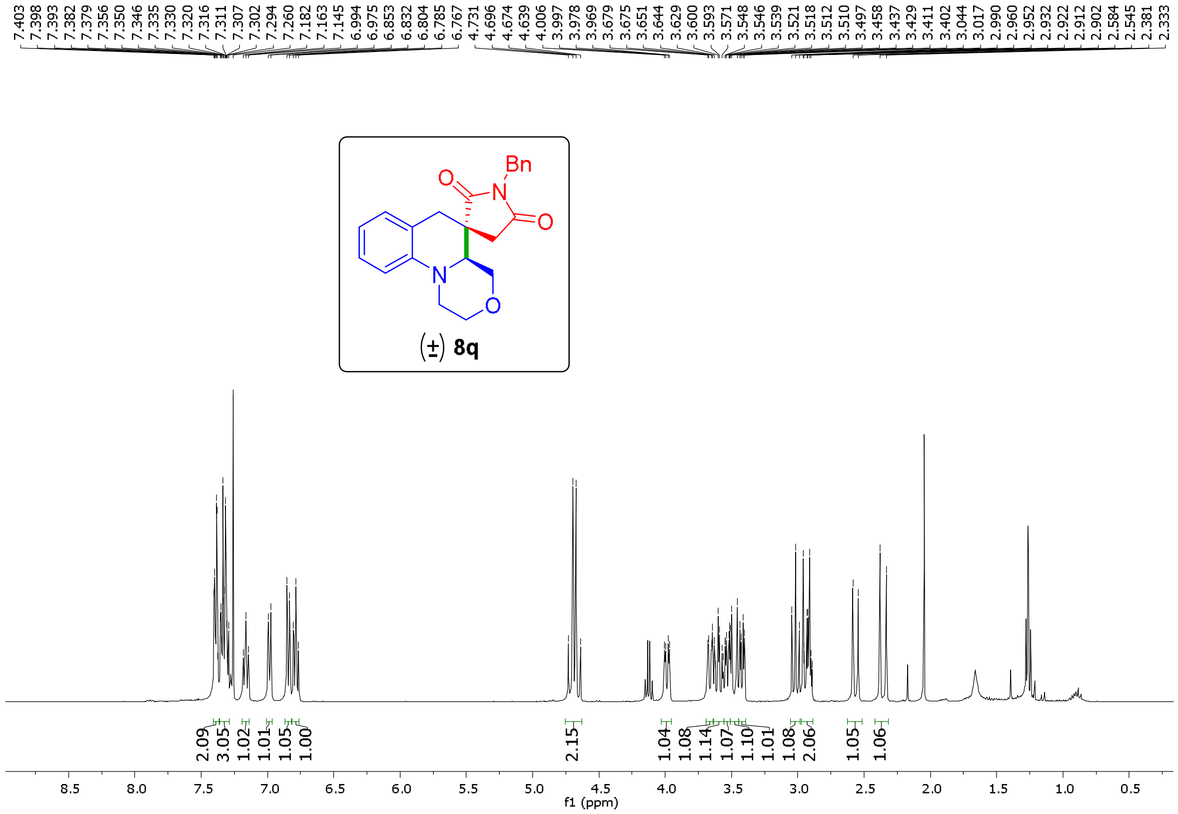
^{1}H NMR spectra of **8p** (400 MHz, Chloroform-*d*)



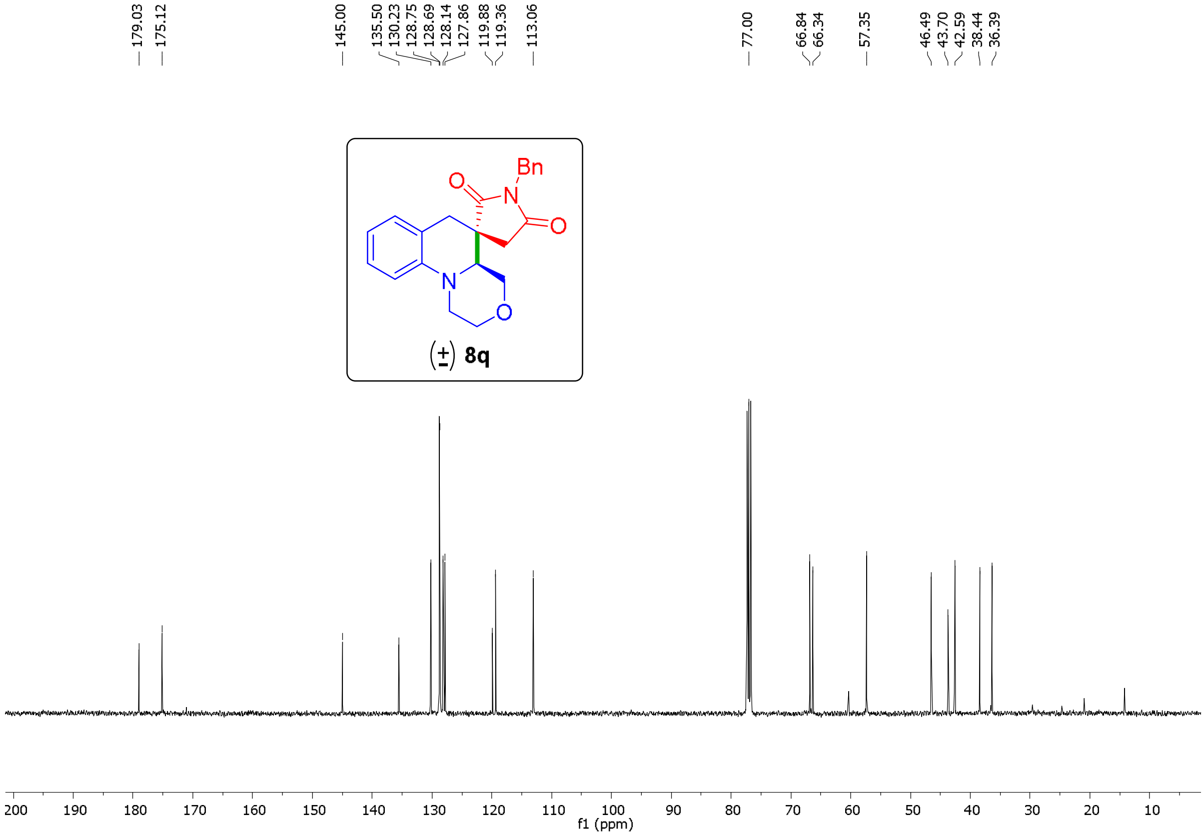
^{13}C NMR spectra of **8p** (101 MHz, Chloroform-*d*)



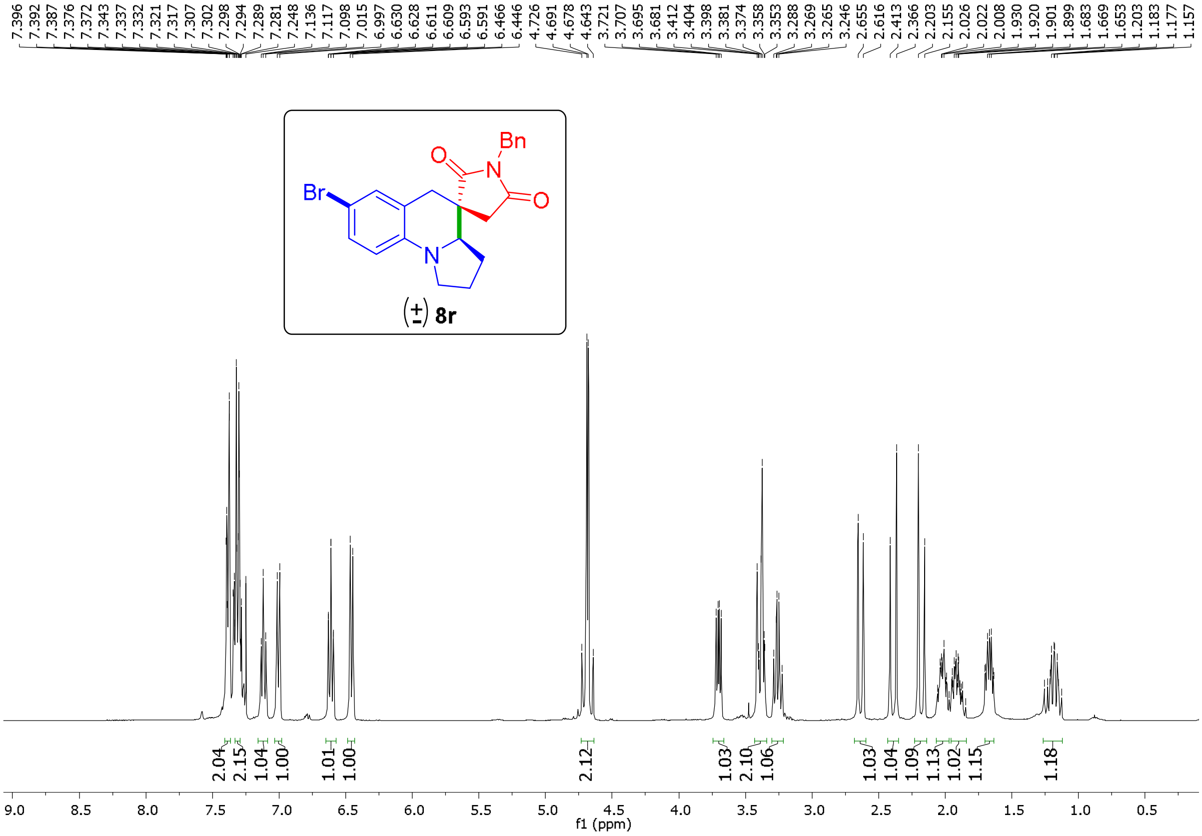
^{1}H NMR spectra of **8q** (400 MHz, Chloroform-*d*)



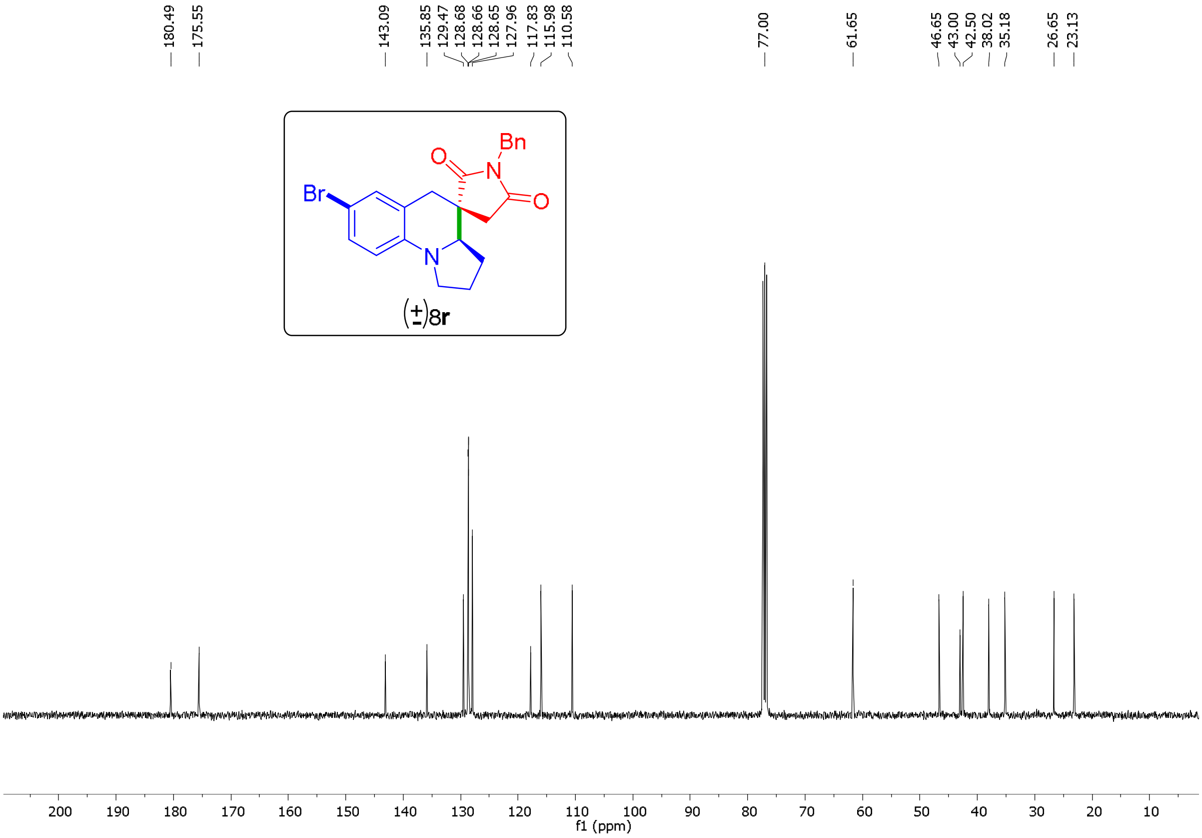
^{13}C NMR spectra of **8q** (101 MHz, Chloroform-*d*)



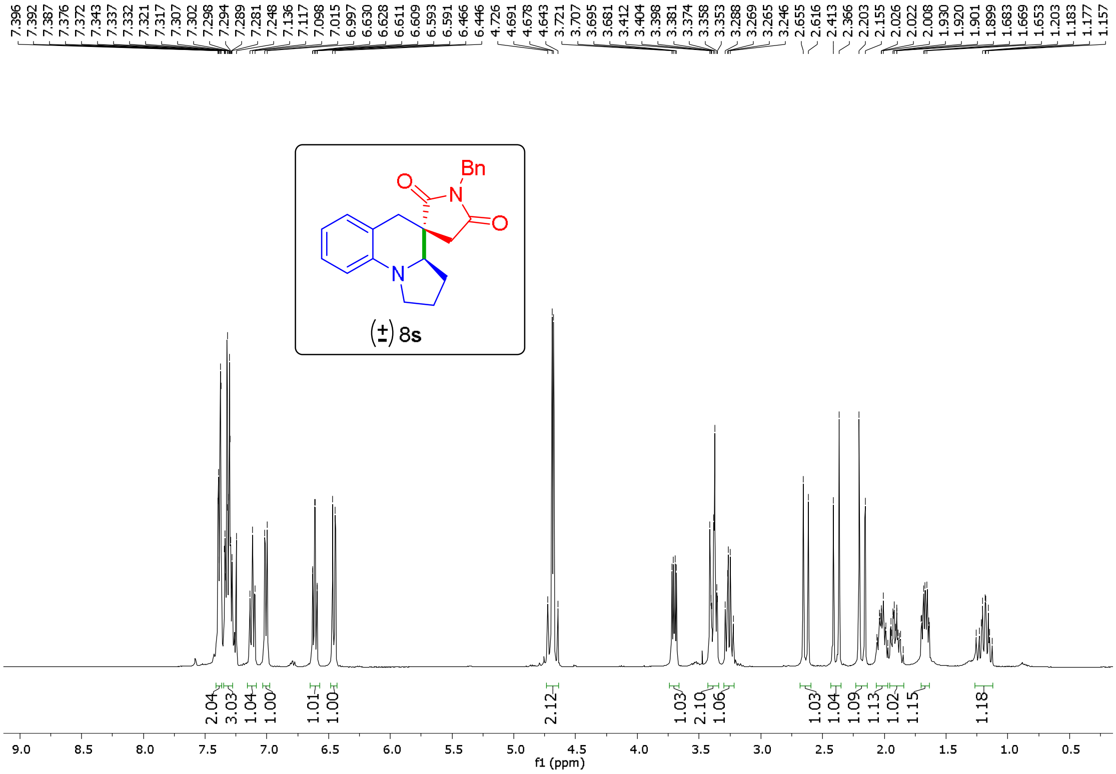
^{1}H NMR spectra of **8r** (400 MHz, Chloroform-*d*)



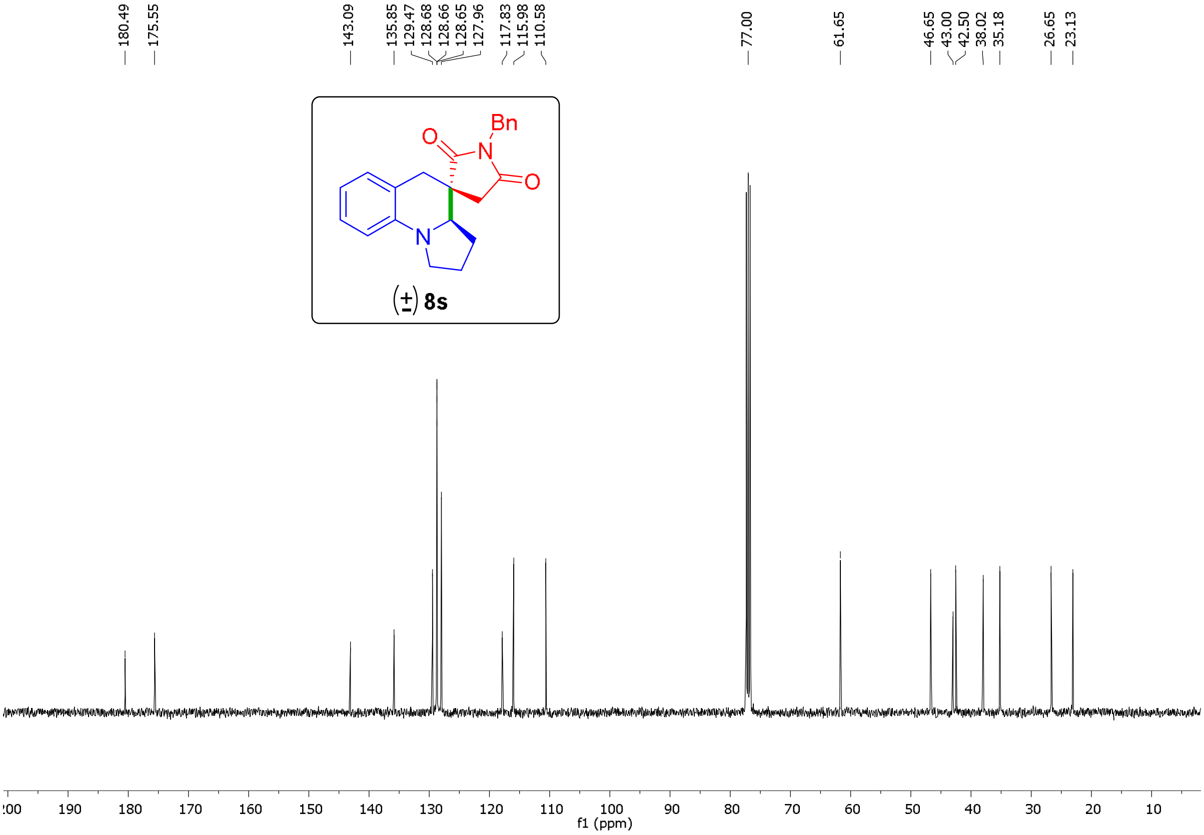
^{13}C NMR spectra of **8r** (101 MHz, Chloroform-*d*)



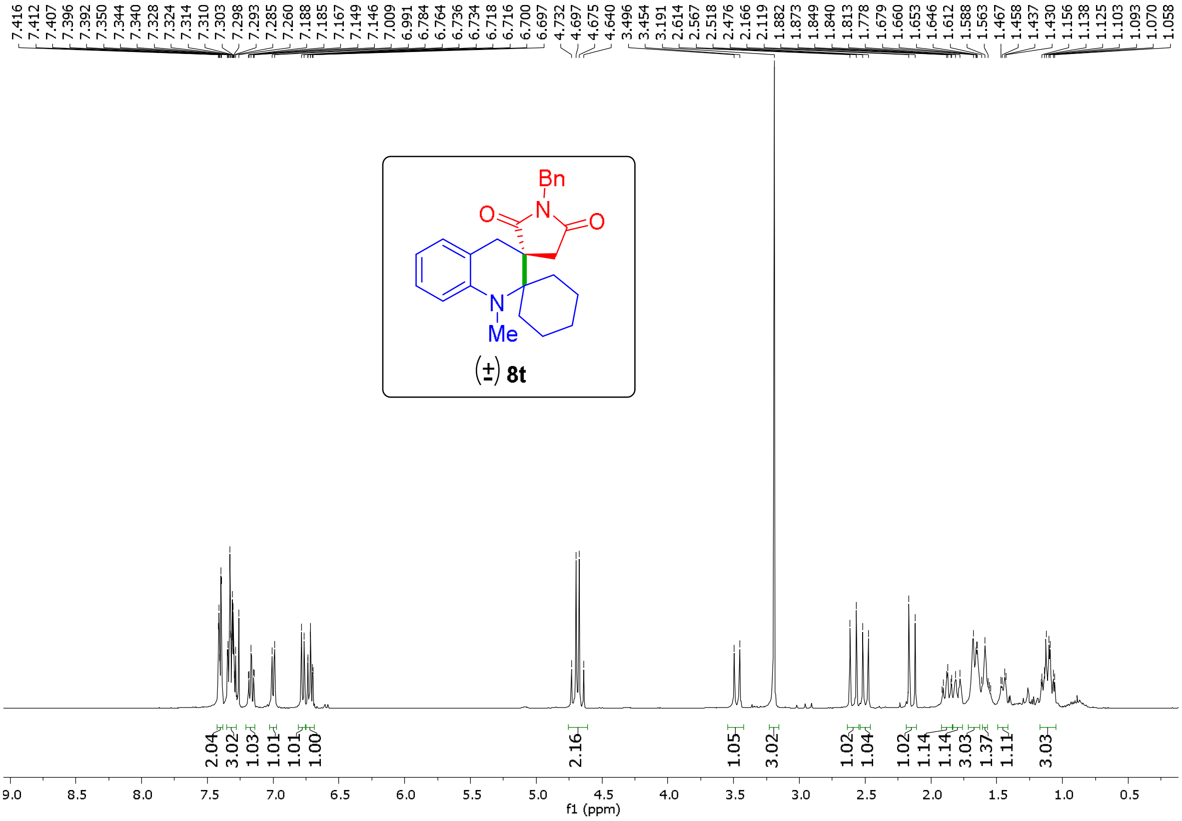
^{1}H NMR spectra of **8s** (400 MHz, Chloroform-*d*)



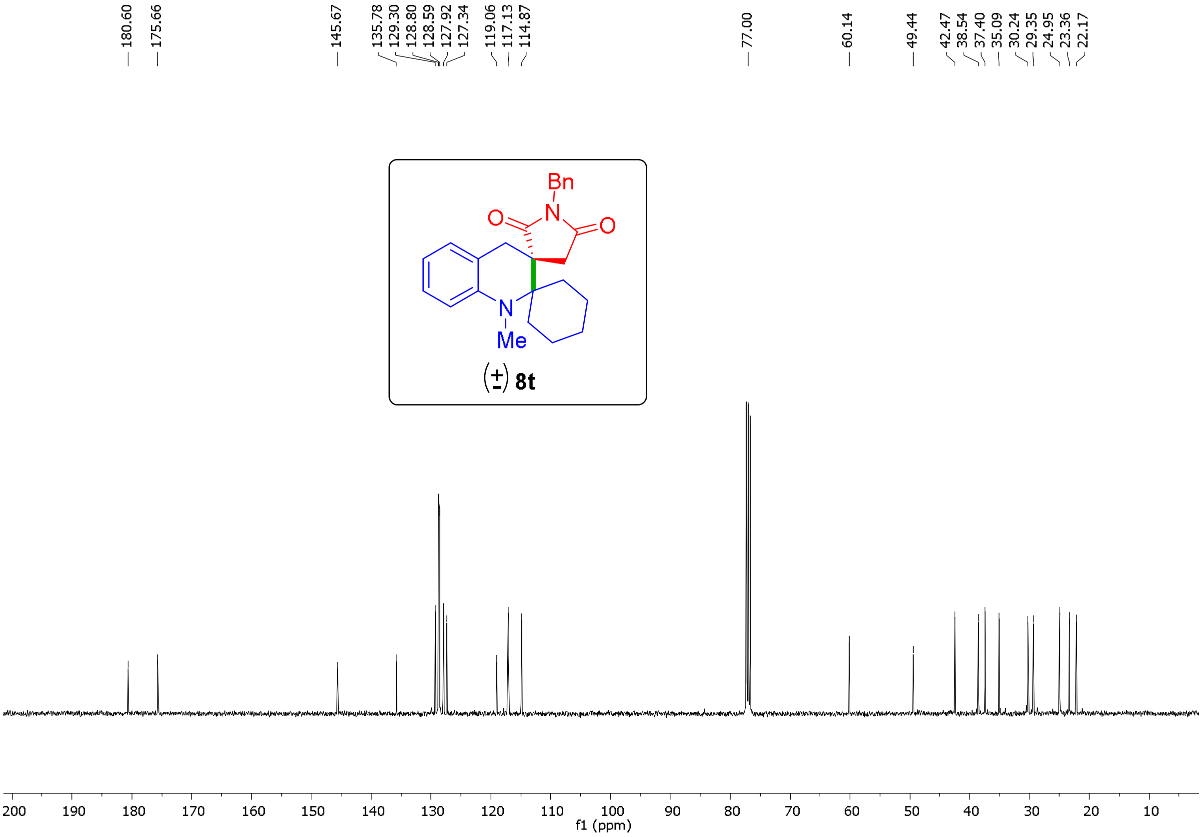
^{13}C NMR spectra of **8s** (101 MHz, Chloroform-*d*)



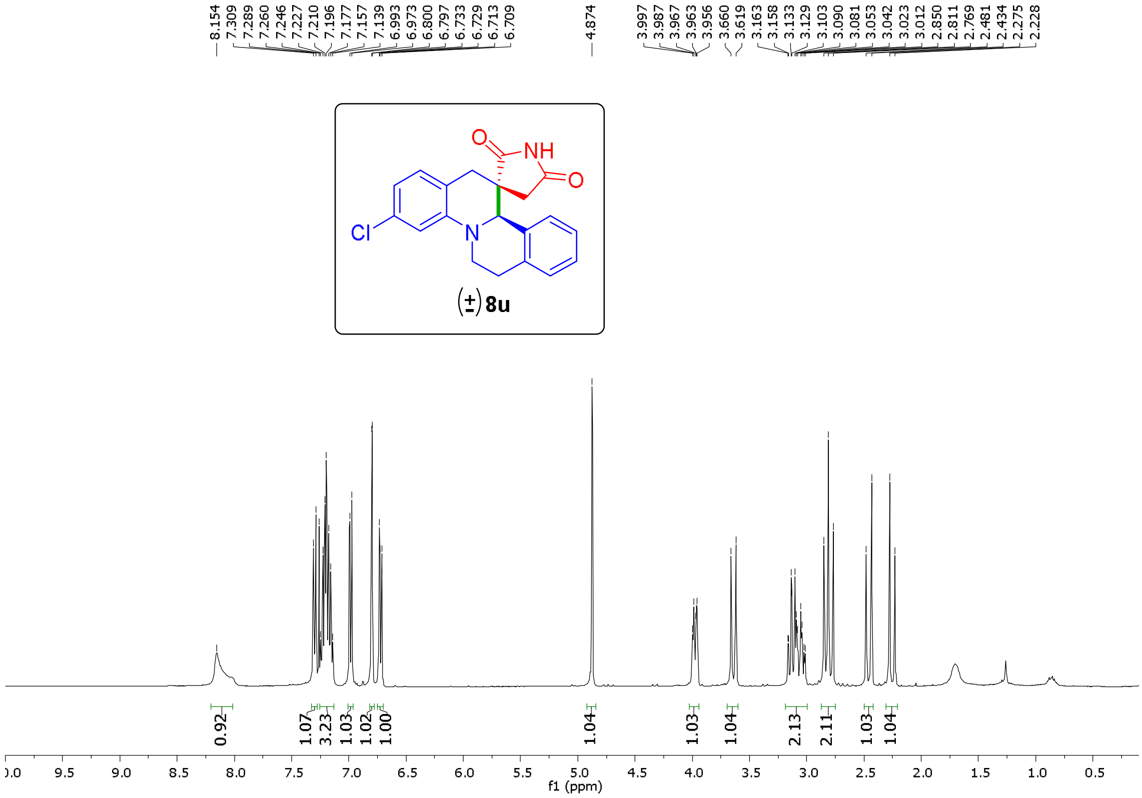
^{1}H NMR spectra of **8t** (400 MHz, Chloroform-*d*)



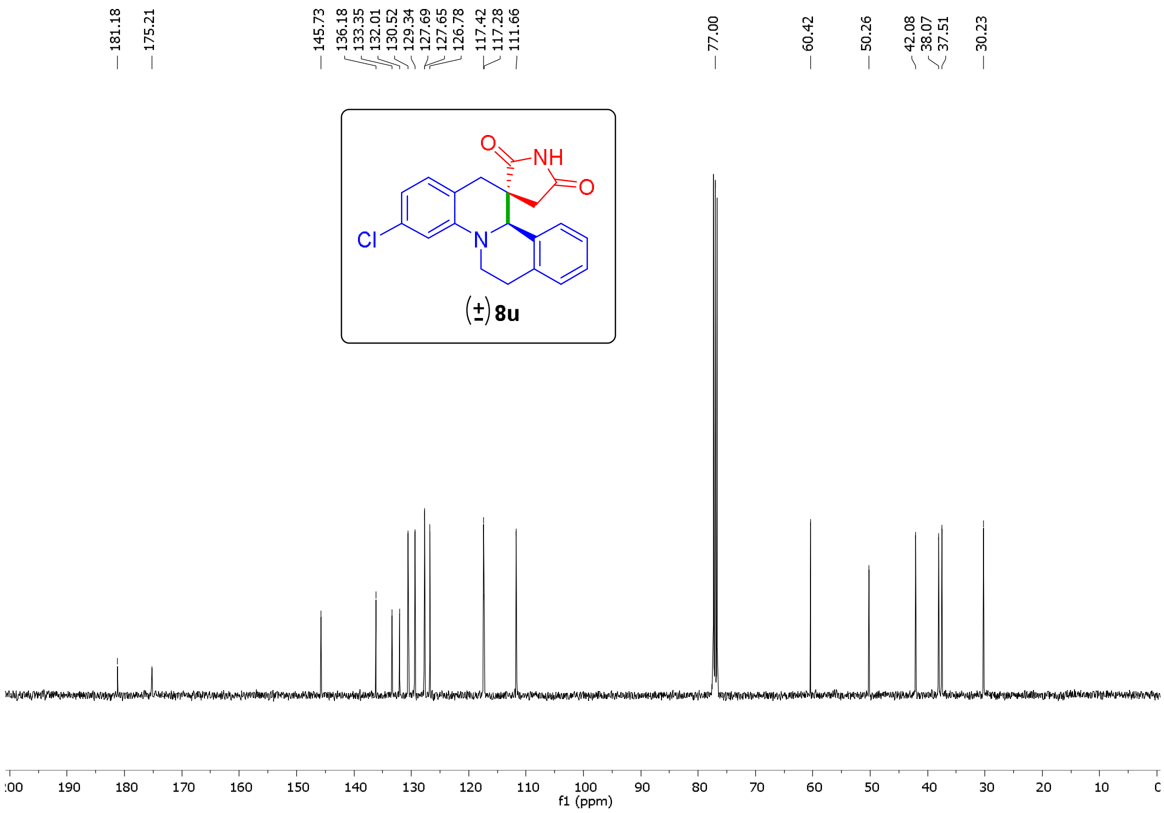
^{13}C NMR spectra of **8t** (101 MHz, Chloroform-*d*)



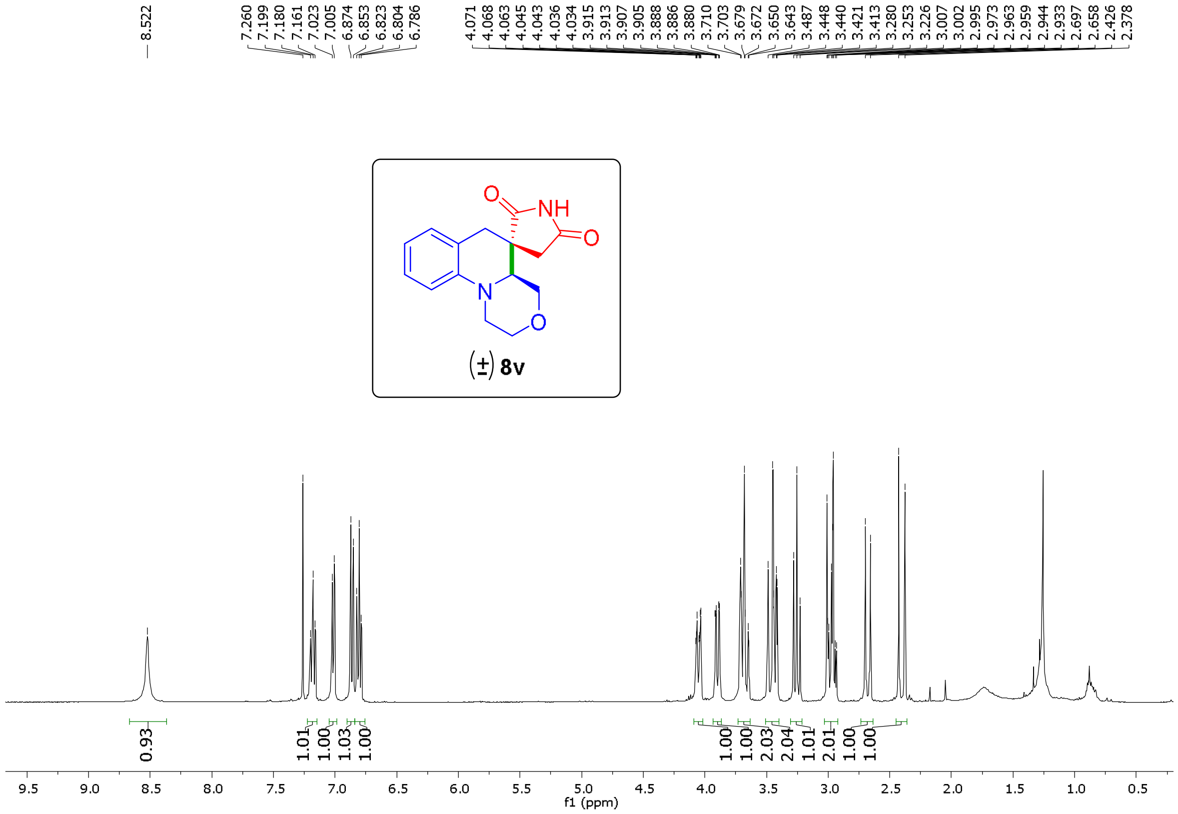
^{1}H NMR spectra of **8u** (400 MHz, Chloroform-*d*)



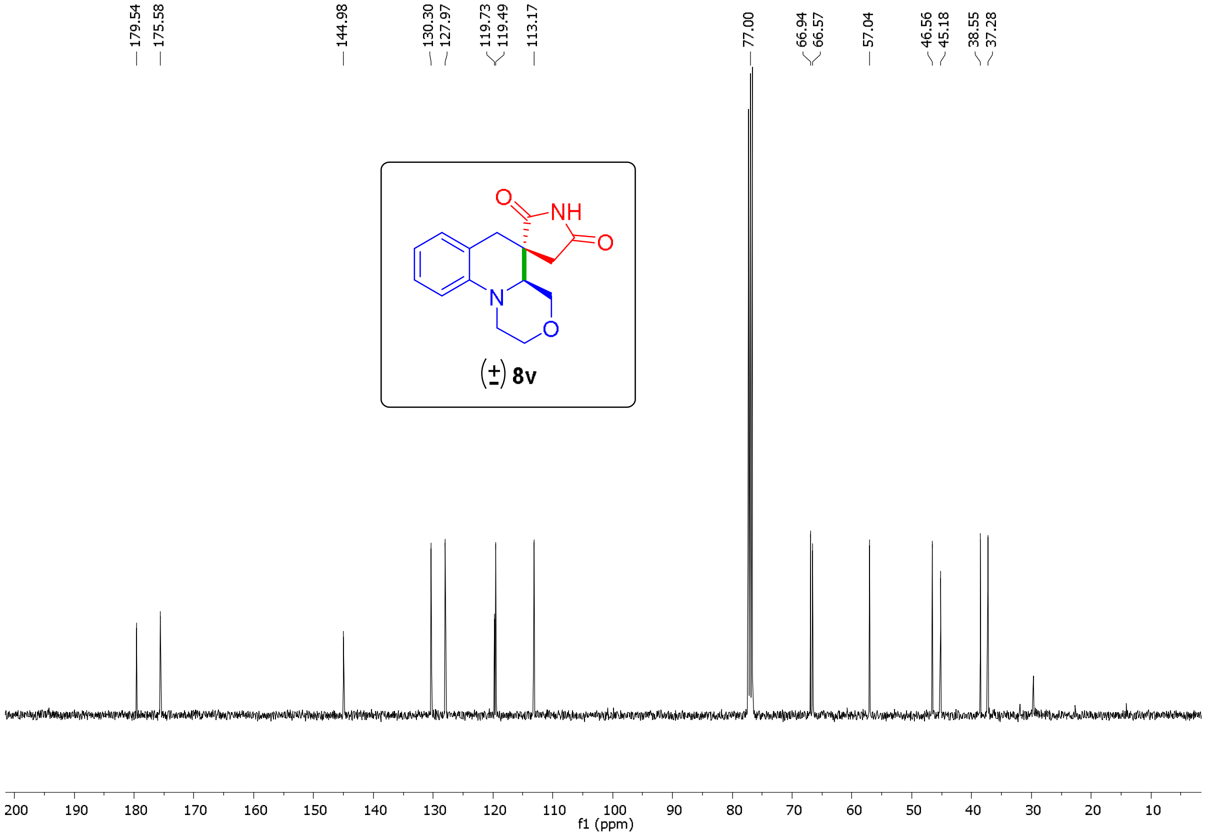
^{13}C NMR spectra of **8u** (101 MHz, Chloroform-*d*)



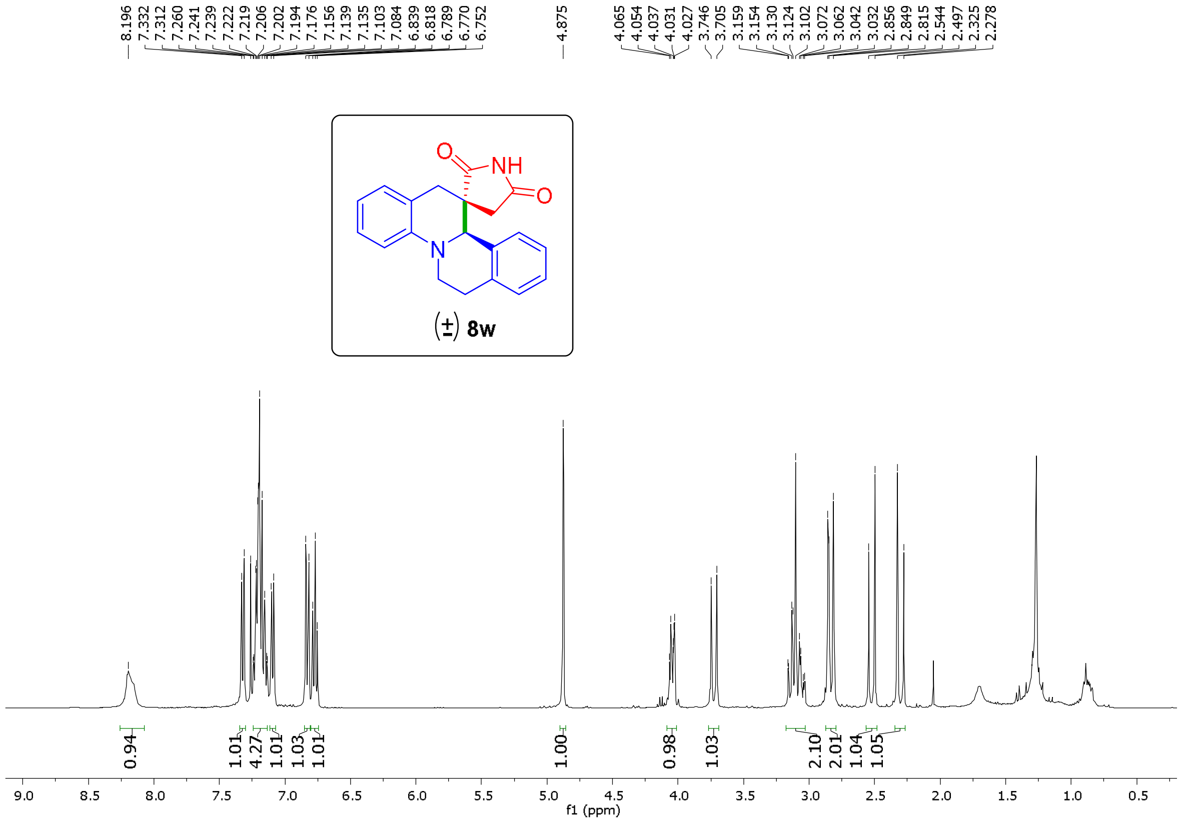
^{1}H NMR spectra of **8v** (400 MHz, Chloroform-*d*)



^{13}C NMR spectra of **8v** (101 MHz, Chloroform-*d*)



^{1}H NMR spectra of **8w** (400 MHz, Chloroform-*d*)



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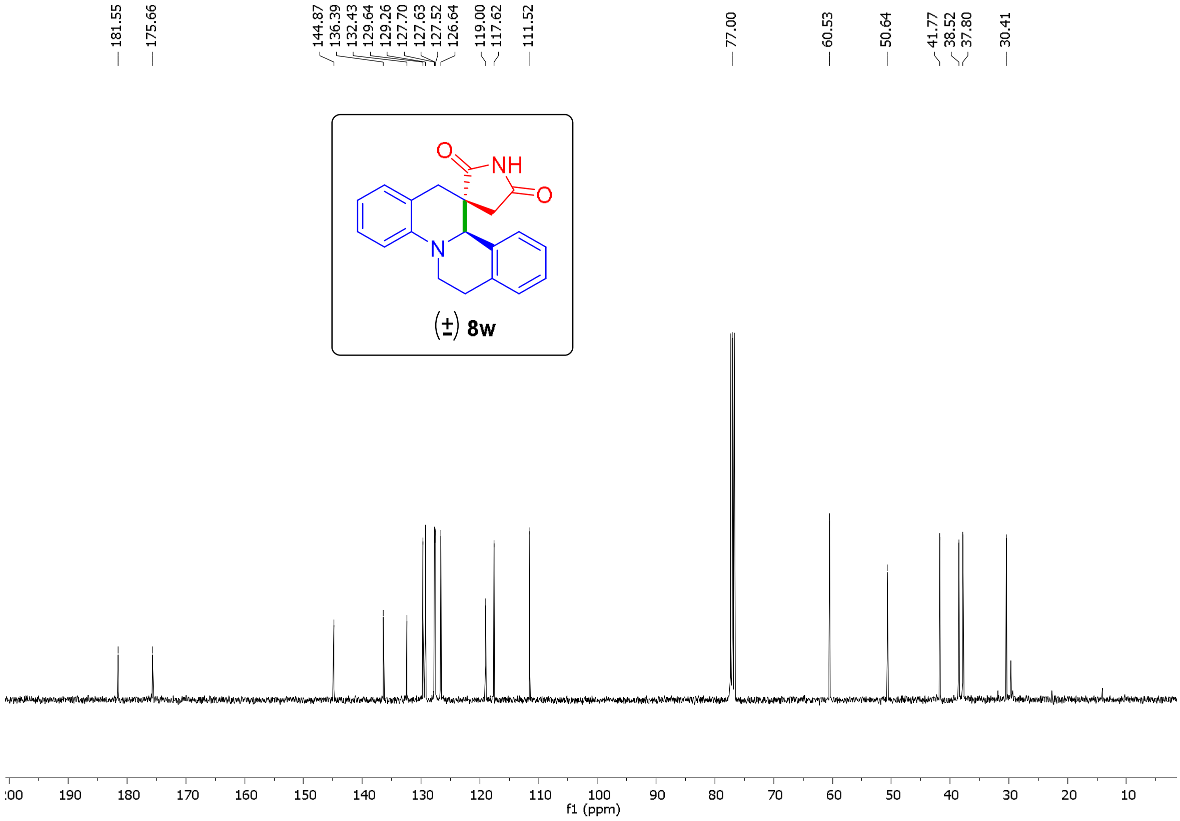

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Chapter 4: **Introduction Part-II**

A Brief Overview of Indole-3-carboxylic Acid and its Derivatives, and DMSO as Synthon

4.1 Introduction

4.1.1 Indole-3-Carboxylic Acid

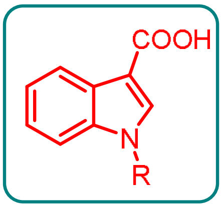


Figure 4.1.1 Indole-3-carboxylic acid derivatives

Indole-3-carboxylic acid is an indole-derivative carrying a carboxyl group at the C_3 position. It is a precursor of several biologically active drug molecules which has good medicinal importance (Figure 4.1.2). It has a good role as a human metabolite and a bacterial metabolite.[1]

4.1.2 Indole-3-Carboxyl Group: Bioactive Scaffold[2]

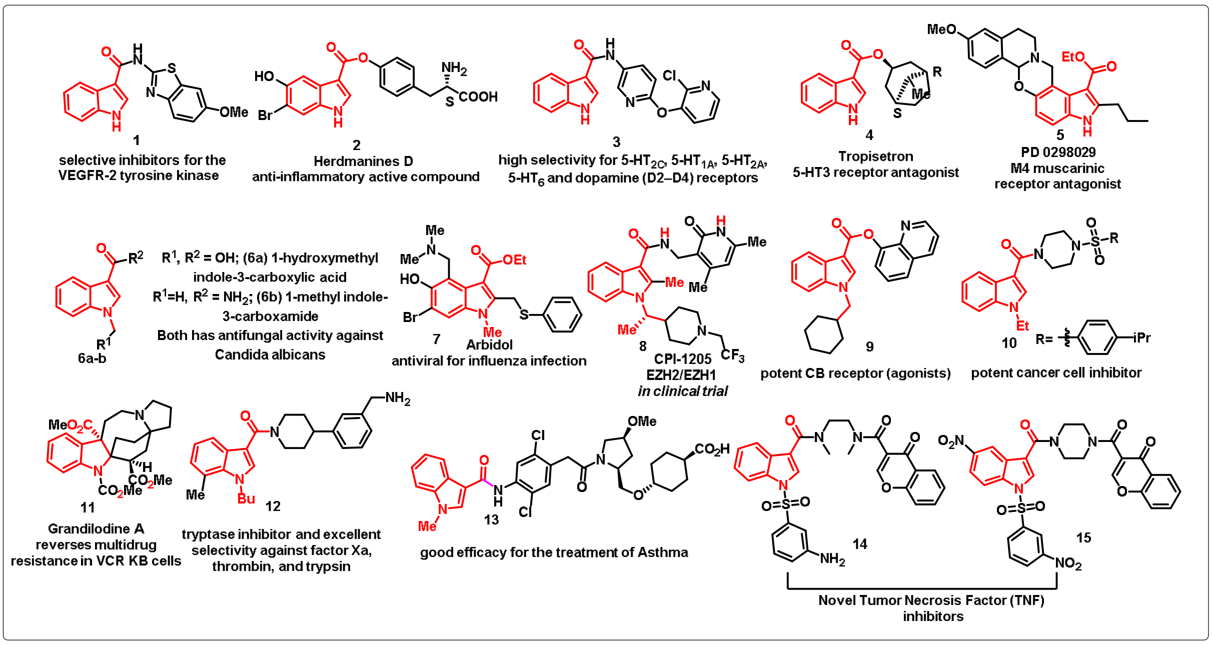
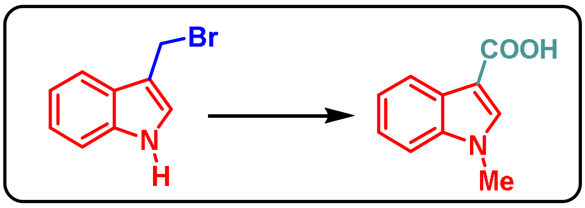


Figure 4.1.2 Representative examples of bioactive molecules

There are a series of biologically active compounds bearing indole-3-carboxyl scaffolds. Indole-3-carboxyl amide and ester have great significance among other derivatives. Various amides such as **1**, **3**, **8**, **10**, **12**, **13**, **14**, and **15** and esters such as **2**, **4**, **5**, **6**, **7**, **9**, and **11** displayed excellent activity (in Figure 4.1.2). Arbidol (**7**) is an antiviral drug treated mainly for influenza infection.

4.1.3 Previous Literature Report of Indole-3-carboxylic Acid and Its Analogues

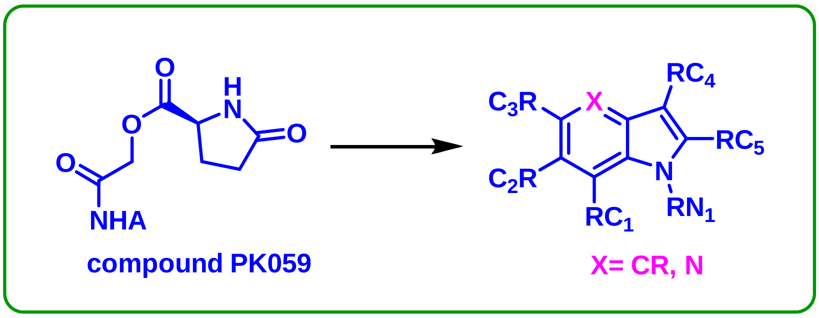
4.1.3.1 Conversion of Indole-3-carboxylic Acid from Indole-3-Alkylhalide



Scheme 4.1.3.1 Conversion of indole-3-carboxylic acid from indole-3-alkyl halide

In the year 1983 Vereshchagin et al., reported a straightforward method to prepare 3-indolylglyoxals,[3] they proposed two new methods to synthesize indolylglyoxal scaffold. One method consists of 3-hydroxy-acetyl indole oxidation with the dimethyl sulfoxide-oxalyl chloride complex, but for some reason, it is not properly applicable to the preparation of diverse indolylglyoxals. Another method, the reduction was the key step, employing trialkyltin hydrides the freshly prepared 3-indolylglyoxyl chlorides are reduced to the corresponding aldehydes with good yields.

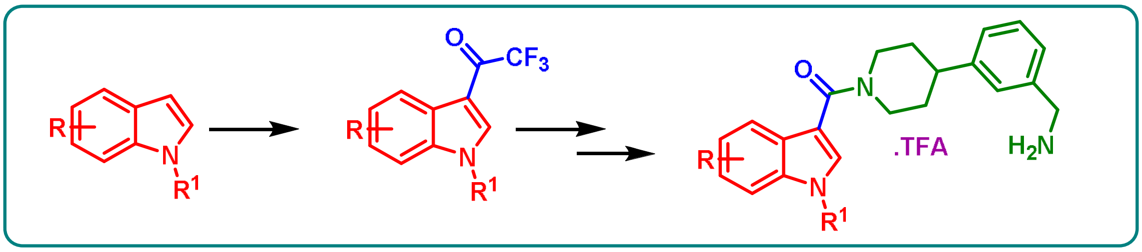
4.1.3.2 p53 Protein Binding ICA Derivatives



Scheme 4.1.3.2 ICA derivatives that bind with p53 protein

Application of indole backbone: Boeckler et al., synthesized (Patent: **US 20110059953 A1**) several biologically active compounds employing *N*-(9-ethyl-9H-carbazol-3-yl)-2,2,2-trifluoro-acetamide or indole derivative 1*H*-indole-3-carboxamide for treating a subject who has a lesion or a tumor in which p53 carries a Y220C mutation.[4] Their invention relates to compounds that can bind to p53 protein molecules.

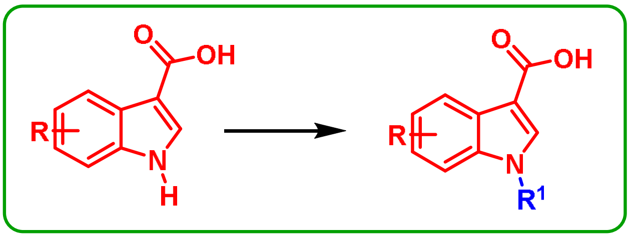
4.1.3.3 ICA Derivatives: Novel Mast Cell Tryptase Inhibitors



Scheme 4.1.3.3 ICA derivatives: novel mast cell tryptase inhibitors

Recently Hopkins group reported a series of novel mast cell tryptase inhibitors. They synthesized a novel amide functional molecule in multistep from indole which features the use of an indole structure as the hydrophobic substituent on an *m*-benzylaminepiperidine template.[5] These molecules display well activity in vitro and are highly selective against other serine proteases. They have synthesized largely and tested it. Excellent SAR evaluation proves that these are the novel class of small-molecule mast cell tryptase inhibitors. The compounds are very potent and could use an extension of their tryptase program, orally bioavailable inhibitors.

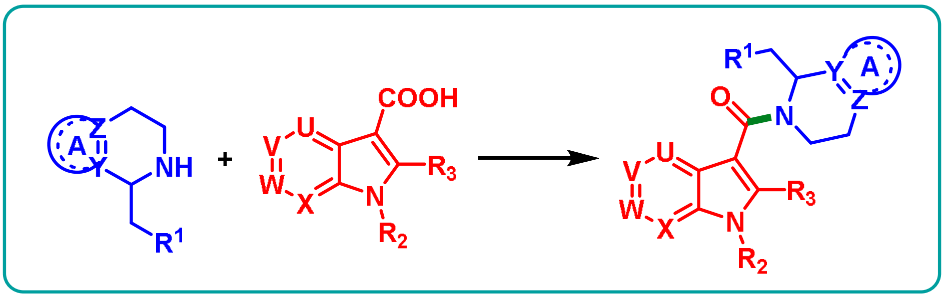
4.1.3.4 ICA Derivatives: Raw Material for Medicines and Agricultural Chemicals



Scheme 4.1.3.4 ICA derivatives: raw material for medicines and agricultural chemicals

Fujibayashi et al. showed the use of (Patent: **JP 2001261642 A**) several indole-3-carboxylic acid derivatives as raw material for medicines and agricultural chemicals purposes in their recent report.

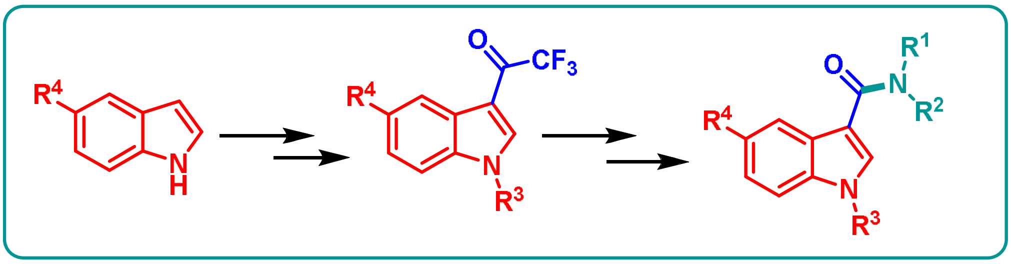
4.1.3.5 ICA Derivatives: an Orexin Receptor Antagonist



Scheme 4.1.3.5 ICA derivatives: orexin receptor antagonists

In 2012, Bolli's group invented (**WO 2012/114252 Al**) many novel indole and pyrrolopyridine amide derivatives and their importance in pharmacy.[6] Firstly they synthesized these novel amide derivatives in a good method and the invention concerns related to the pharmaceutical compositions, and especially their use in several biological tests. Indeed, it displays as an orexin receptor antagonist. Their compounds have been utilized for the prevention or treatment of diseases like sleep disorders, stress-related syndromes, addictions, cognitive and psychiatric, and neurologic disorders, and eating or drinking disorders.

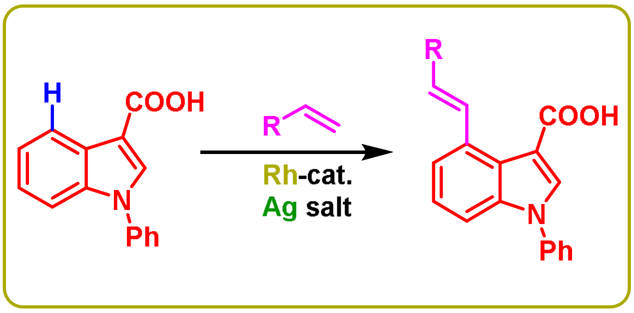
4.1.3.6 ICA Derivatives: Alpha 7 Nicotinic Acetylcholine Receptor



Scheme 4.1.3.6 ICA derivatives: alpha 7 nicotinic acetylcholine receptor

In the year 2014, the Harvey group invented (**WO 2014/172759 Al**) a remarkable work producing different important amide derivatives employing substituted indole-3-carboxylic acid as an intermediate starting from the indole derivative.[7] The usefulness of these amide compounds is the positive modulation of the alpha 7 nicotinic acetylcholine receptor(α_7 nAChR). These compounds showed a wide range of activities such as neurodegenerative neuropsychiatric diseases, inflammatory diseases, etc. The positive modulation of α_7 nAChR is very advantageous and applicable in a broad range of diseases.

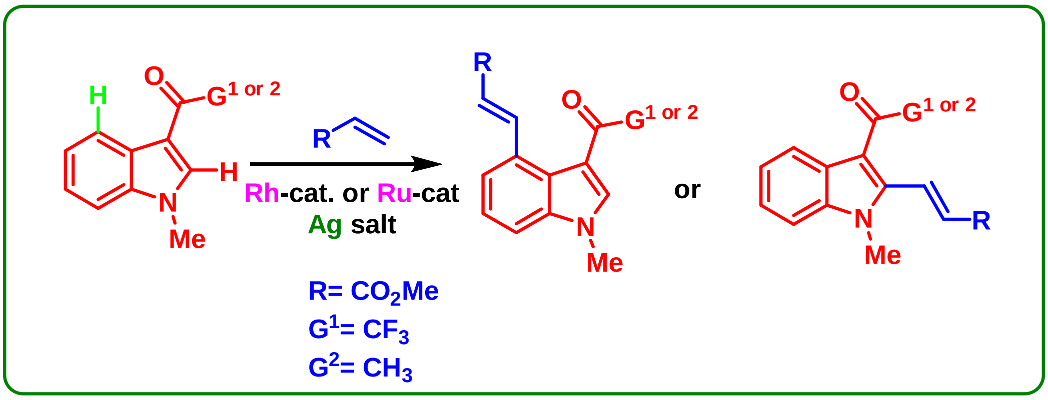
4.1.3.7 ICA Derivatives as a DG: Rhodium(III) Catalyzed C–H Bond Activation



Scheme 4.1.3.7 ICA derivatives as a DG: rhodium(III) catalyzed C–H bond activation

In 2018, Okada *et al*. demonstrated a rhodium (III) catalyzed silver salt oxidant-mediated regioselective C–H bond activation reaction. They selected *N*-phenylindole-3-carboxylic acids as a directing group that undergoes alkenylation at the C-4 position on treatment with alkenes such as acrylamide, acrylate ester, and acrylonitrile in the presence of silver salt.[8] This method would help to design a new catalytic substitution reaction to construct novel (fused)heteroarenes that have great importance in medicinal and materials chemistry.

4.1.3.8 ICA Derivatives as a DG: Rhodium or Ruthenium catalyzed C–H activation

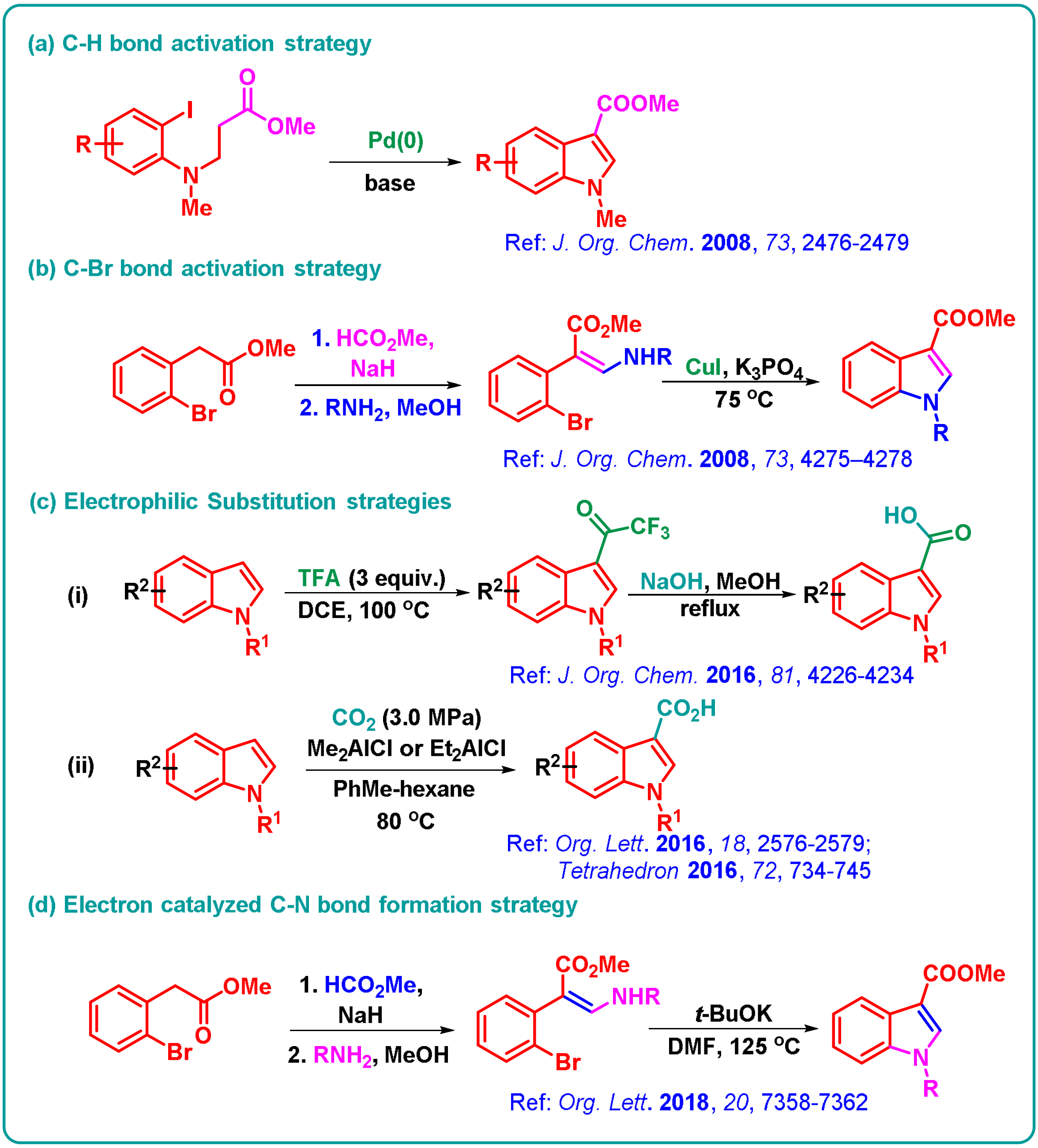


Scheme 4.1.3.8 ICA derivatives as DG: Rhodium or Ruthenium catalyzed C–H activation

Prabhu's group disclosed a new method where they utilized ketone as directing group. This was a site-selective C–H activation reaction between C-2 and C-4 positions in the indole framework. By altering the substrate they showed the selectiveness of this methodology. Utilizing methyl ketone as the directing group, they furnish exclusively C-2 alkenylated products, whereas trifluoromethyl ketone alters the selectivity to C-4. The electronic nature of the directing group controls the selection between a 5-membered and a 6-membered metallacycle which was the main reason behind it.[9] After screening the other carbonyl-derived directing groups they observed that the opposite selectivity happens when they use strong and weak directing groups accordingly.

4.1.3.9 Synthesis of Indole-3-Carboxylic Acid Derivatives in Other Methods

Several other methods are reported in the academic literature regarding the synthesis of indole-3-carboxylic acid derivatives.


(a) C-H bond activation strategy

Ref: *J. Org. Chem*. **2008**, *73*, 2476-2479

(b) C-Br bond activation strategy

Ref: *J. Org. Chem*. **2008**, *73*, 4275–4278

(c) Electrophilic Substitution strategies

Ref: *J. Org. Chem*. **2016**, *81*, 4226-4234

Ref: *Org. Lett*. **2016**, *18*, 2576-2579; *Tetrahedron* **2016**, *72*, 734-745

(d) Electron catalyzed C-N bond formation strategy

Ref: *Org. Lett*. **2018**, *20*, 7358-7362

Scheme 4.1.3.9 others synthetic strategies to access indole-3-carboxylic acid derivatives

The synthetic routes are described into four different categories mainly (Scheme 1): a) C-H bond activation strategy,[10] b) C-Br bond activation strategy,[11] c) electrophilic substitution strategies,[12] and d) electron-catalyzed C-N bond formation strategy.[13] Representative examples for each approach will be discussed to highlight the advantages and disadvantages.

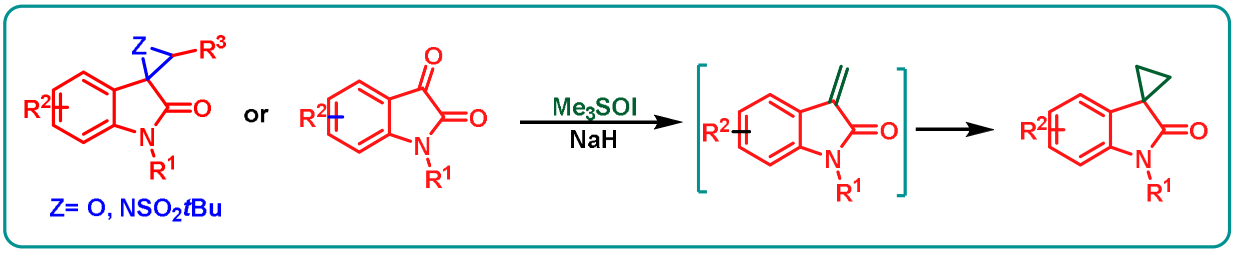
In recent times C–H bond activation strategy is an important tool for various synthetic transformations but it has some limitations such as the essentiality of transition metal and in most cases, it is not applicable for large-scale preparation. According to Sole's method β-(2-iodoanilino) esters derivatives could be converted to indole-3-carboxylic acid ester derivatives via intramolecular α-arylation in the presence of a catalytic amount of $Pd(PPh_3)_4$ and potassium phenoxide.[10] Preparation of the directing group from 2-iodoaniline derivative and methyl acrylate is another demerit, and the use of Pd on an industrial scale is not economical also. Moreover, the yield was poor in this intramolecular α-arylation of β-(2-iodoanilino)esters reaction. Applying the Ullmann reaction, C-N bond formation methodology through C-X(X=Br) bond activation employing Cu catalyst is a good achievement for ICA preparation. A series of *N*-alkylated and *N*-arylated substrates of methyl 1*H*-indole-3-carboxylate has been synthesized taking methyl 2-(2-bromophenyl)-2-formyl acetate with different primary amines employing Cu catalysts.[11] Indeed, starting material methyl 2-(2-bromophenyl)acetate preparation is a multistep process and it is highly expensive, these are the major problem for industrial preparation. Many reagents and solvents such as methyl formate, primary amine, K_3PO_4, NaH, MeOH, and DMF were essential for this reaction. They didn't explore simple N-H free indole-3-carboxylate.

Another promising route to prepare indole-3-carboxylic acid derivative for large-scale purposes is the Friedel-Craft reaction of indole derivative. In 2016, Guan[12] reported a Friedel-Craft reaction specifically a trifluoroacetylation reaction of indole derivatives using trifluoroacetic acid at 100 °C to prepare indolyl trifluoromethyl ketone derivatives which is the precursor of indole-3-carboxylic acid. After hydrolysis of these ketone derivatives (reflux in MeOH in the presence of NaOH), they got an indole-3-carboxylic acid derivative. Hattori's group found another way where they performed a Friedel-Craft reaction in the presence of Lewis acid (Me_2AlCl or $EtAlCl_2$) under 3.0 MPa pressure of CO_2.[13] They obtained a very poor yield of indole -3-carboxylic acid in cases of N-H free indole. The major drawbacks of these reactions for large-scale industrial preparation are the requirements of various indole derivatives, expensive Lewis acid, and high-pressure reaction equipment.

Electron-catalyzed C–N bond formation methodology is a good development in synthetic chemistry nowadays. Recently, Karchava's group disclosed a new synthetic strategy depending on electron-catalyzed intramolecular C−N bond formation reaction for the synthesis of *N*-functionalized indole-3-carboxylates, using the *t*-BuOK/DMF system at 125 ˚C employing 3-amino- 2-(2-bromphenyl)acrylate.[14] Due to the shortcomings of complexity and the high cost of starting material and high-temperature reactions it is very difficult for industrial preparation.

4.1.3.10 Synthesis of Spiro Cyclopropyl Oxindole Derivatives Employing Sulfur Ylide as One Carbon Synthon

Hajra et al. developed a sequential Corey−Chaykovsky reactions[15] of isatins, spiro-epoxy, or spiro-aziridine oxindoles through the reaction of sulfur ylide that has led to one-pot straightforward access to a range of spiro cyclopropyl oxindoles.



Scheme 4.1.3.10 ICA derivatives: novel mast cell tryptase inhibitors

4.1.4 Dimethyl Sulfoxide as a Synthon in Organic Chemistry:[16]

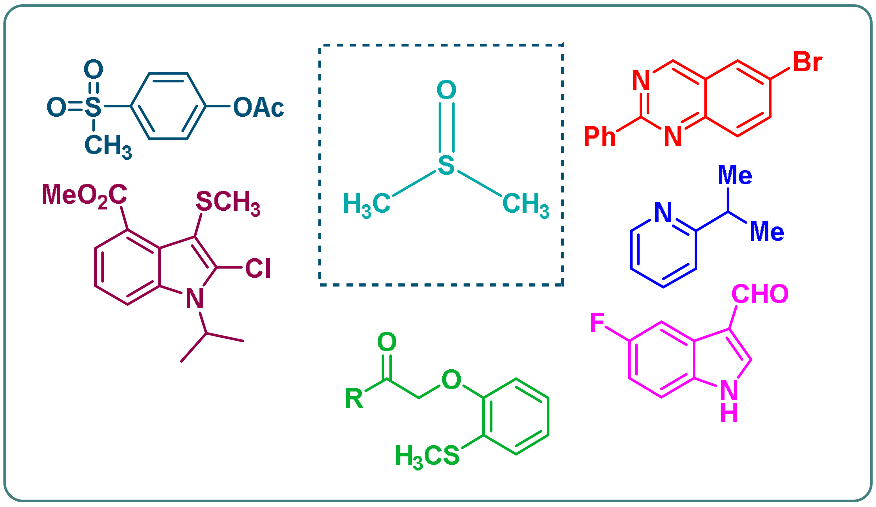


Figure 4.1.4 DMSO as a synthon

Classically dimethyl sulfoxide has been used as a solvent rather than an oxidant or, as a substrate, building block, or synthon in organic chemistry. However, recent reports have demonstrated dimethyl sulfoxide acting in diverse roles. It is now a topic of attraction from last decades due to its good coupling behavior. Synthetic transformations have been utilized to construct a new hetero/carbocycle through ‘C–S–C’, ‘C’, and ‘C–S’ fragment addition of dimethyl sulfoxide that behaves as building blocks. These fragments have come from DMSO itself at different thermal conditions. A recent report says that it has been employed for oxidation reaction, methylthiomethylation (–CH_2SMe). DMSO reacts with various organic/inorganic substrates as a one-carbon synthon. Moreover, DMSO-based methylenation (–CH_2–), DMSO-based methylation (–Me), DMSO-based annulation/aromatization (=CH–), DMSO-based cyanation (–CN), DMSO-based formylation (–CHO), DMSO-based thiomethylation (–SMe), DMSO-based methylsulfinylation (–SOMe), and DMSO-based methylsulfonylation (–SO_2Me) are significant research area nowadays. Indeed, DMSO is a synthon for ‘S–C’/‘C–S’ functionalities.

4.1.4.1 DMSO Yesterday’s Solvent, Today’s Reagent:[17]

In the past decades, Dimethyl sulfoxide (DMSO) has been used as a polar solvent and active pharmaceutical ingredient. In a basic medium dimsyl anion could be formed and employed as a reagent. In many cases, it has been utilized as one carbon synthon. However, DMSO has attracted the attention of scientists because it is a source of oxygen, carbon, or sulfur in a wide range of organic syntheses. At high-temperature C–S bond could cleave, hence new heterocycles were formed. In this review, DMSO has been utilized as a single or dual□synthon classifying excellent findings in this area.

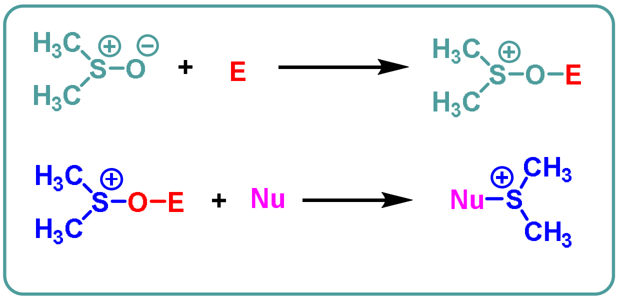


Figure 4.1.4.1 DMSO as a reagent

4.1.4.2 Activated Dimethyl Sulfoxide, Useful Reagents for Synthesis:[18]

Selected examples of the use of activated dimethyl sulfoxide reagents in organic synthesis are discussed with the emphasis being placed on low-temperature studies conducted in the author’s laboratory. Reactions of acetic anhydride, oxalyl chloride, t-butyl hypochlorite, or halogens (among others) with dimethyl sulfoxide at appropriate temperatures yield intermediate dimethyl sulfonium salts. These salts are mainly useful to derive a variety of sulfinimines and sulfoximines and the selective oxidation of structurally diverse alcohols to the corresponding carbonyl compounds.

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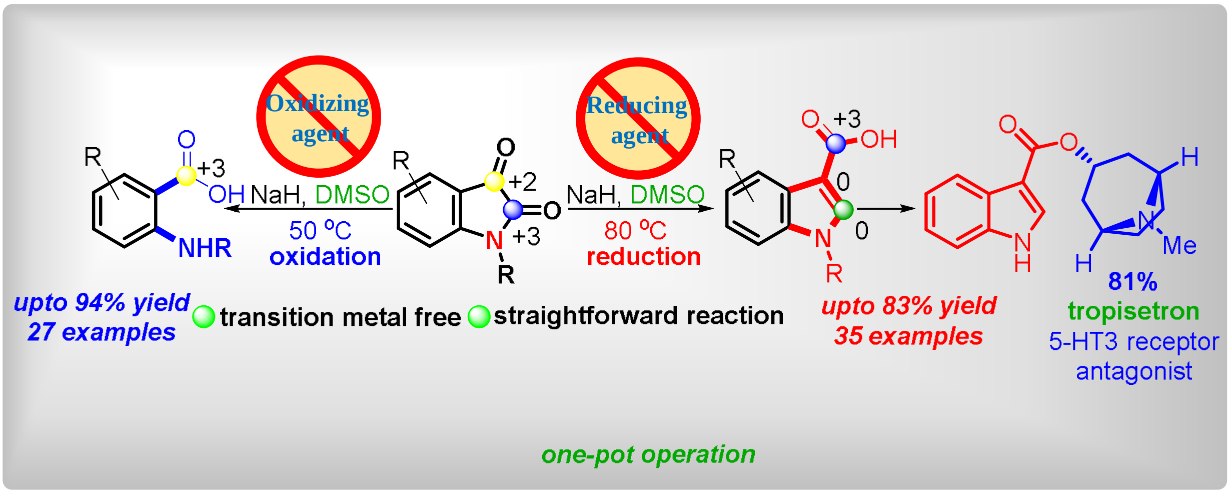
Chapter 5: **Unorthodox Cascade Redox Reactions of Isatin**

Unorthodox Cascade Redox Reactions of Isatin Using DMSO as a Methine Source for Expeditious Route to Indole-3-Carboxylic Acids, and Anthranilic Acids



5.1 Introduction

The event of reduction or oxidation of any organic molecule without so-called reducing and oxidizing agents or expensive reagents effortlessly is a significant researchable topic in synthetic organic chemistry.[1] Bring about oxidation and reduction of the same molecule without substantial change in reaction conditions is a challenging prospect for its implementation.

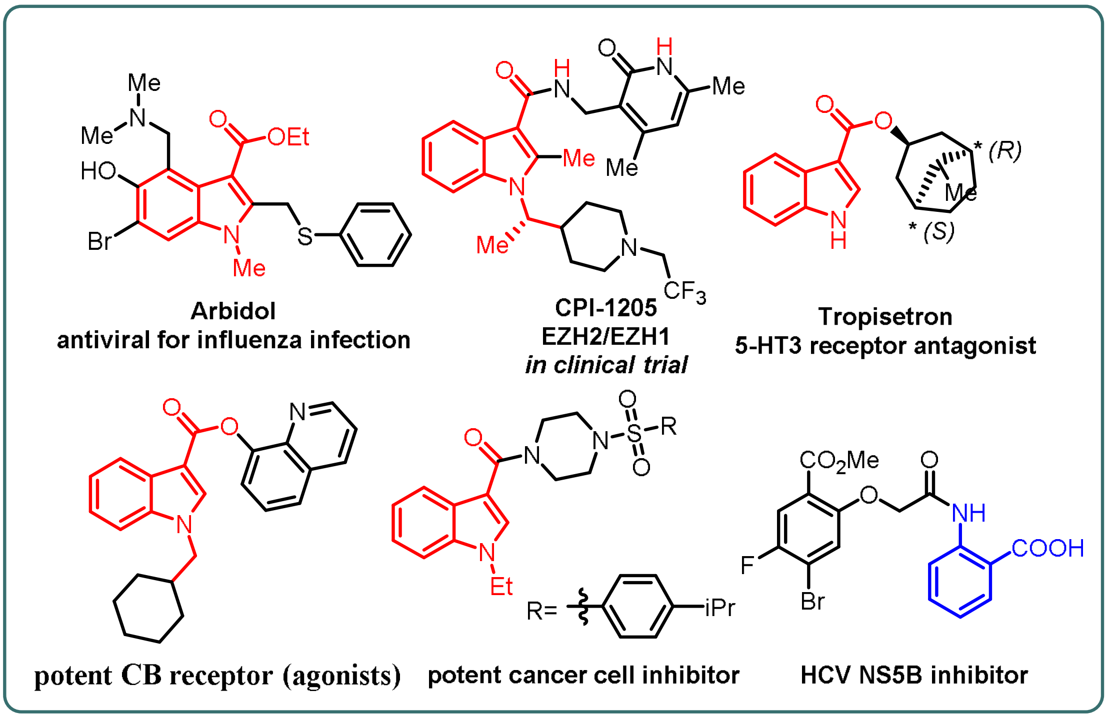


Figure 5.1.1 Biologically relevant drugs

ICA derivatives are known to be widely present in numerous natural products,[2a] has also been used to construct several artificial drugs such as arbidol,[2b] tropisetron,[2c] dolasetron,[2d] etc. or its derivatives broadly used as (a) anticancer agents (CPI-1205),[2e] (b) serotonin 5-HT4 and 5-HT6 antagonists,[2f] (c) EphB3 receptor tyrosine kinase inhibitors,[2g] (d) potential therapeutic agents for Alzheimer's disease (Figure 5.1.1).[2h] Hence, ICA has great importance as a prodrug or a versatile key intermediate of several drug candidates.

We focussed on the creation of a device for the generation of indole derivatives[3] direct from isatin derivatives. As it is a very challenging aspect without reducing agents, our initial target was the preparation of a straightforward olefin derivative (**B**) (Figure 5.1.2). Henceforth, the amide bond-breaking process employing a nucleophilic base (NB) and, intramolecular Michael addition followed by elimination reaction could reach our final destination **D**. We hypothesized based on the previous report[3] and selected DMSO as a coupling partner as its methyl sulfoxide group (CH_3-S=O) may be converted to a leaving group in the reaction medium which is vital for the transformation and it could open up a new avenue for the creation of unprecedented indole derivatives.[4] We thought that if our strategy works desired indole-3-carboxylic acid (ICA) derivative[2] (**D**) may form (Figure 5.1.2).

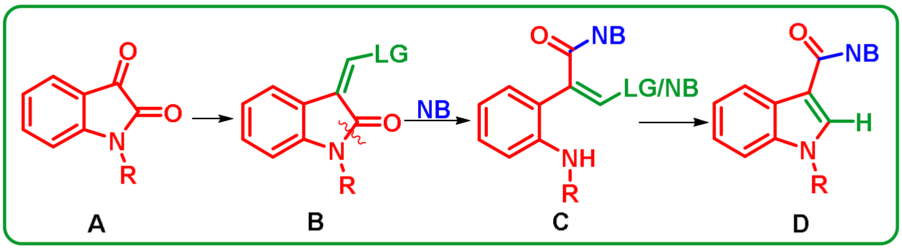


Figure 5.1.2 Our hypothesis

The biggest advantages of this hypothetical methodology are the preparation of key intermediate ICA derivatives (an overall reduced product) utilizing none reducing agents, transition metal catalyst, Lewis acid, or employing an expensive directing group.

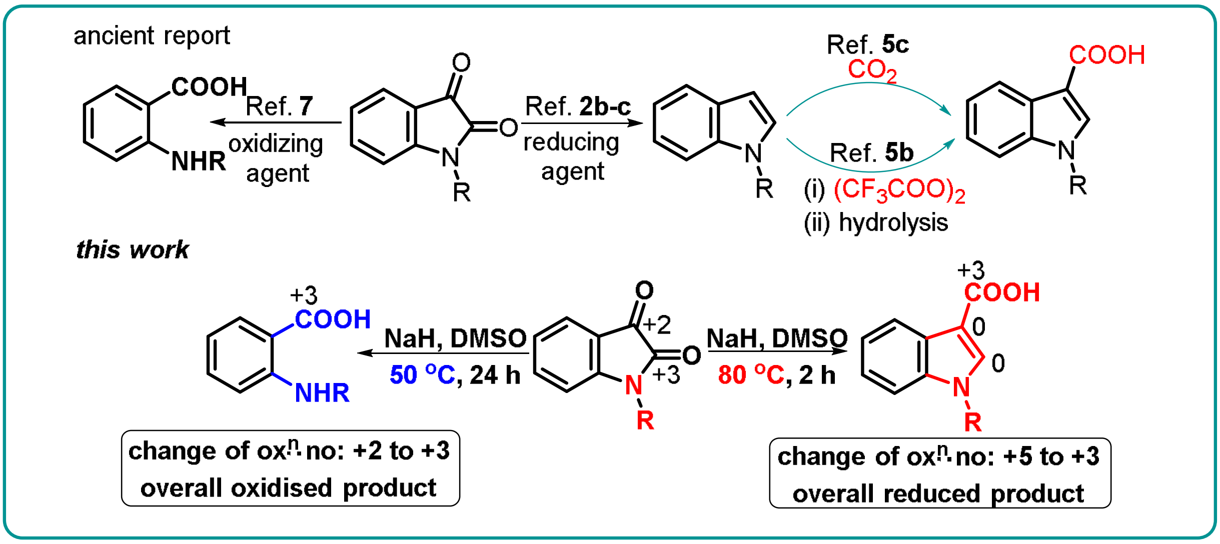
A few synthetic approaches reported in the literature to develop the indole-3-carboxylic acids through indole formation: include Friedel-Craft acylation followed by hydrolysis,[5a-b] Lewis acid (EtAlCl$_2$/Me$_2$AlCl) catalyzed carboxylations using CO$_2$ at high pressure,[5c-d] carbonation of aryl metal species,[5e] transition metal-catalyzed cyclization of aniline derivative and so on.[5f-i] However, there are several disadvantages in the existing synthetic method such as the requirement of an expensive transition metal catalyst, preparation of designed directing group, and multistep operation. Indeed, there exists no direct route for the synthesis of the key intermediate by which it can be produced from an easily available starting material and therefore is highly solicited. Hence we aimed for one-pot production of ICA derivatives from isatins without using any reducing agents or transition metals in the economically viable and operationally simple condition.

On the other hand, anthranilic acid (an overall oxidized product) has also been strategized from the same starting material isatins under similar reaction conditions without using an external oxidant. Anthranilic acid (AA) plays a pivotal role as a building block and a key intermediate in the biosynthesis of acridone or quinoline alkaloids, metabolites for the production of the neurotransmitter serotonin.[6] In addition, many of its derivatives are used in the production of saccharin, azo-dyes, perfumes, insect-repeller, and non-steroidal anti-inflammatory drugs (NSAIDs).[6] According to the previous report, a few methods are available to synthesize AA derivatives employing external oxidizing agents (eg. H$_2$O$_2$, CrO$_3$, etc).[7] But without oxidizing agents, it is not known in the literature to the best of our knowledge. Basically, molecular oxygen existent in the bulk solvent may be responsible for oxidation. We wish to report herein, we were able to raise an overall oxidized or reduced structural motif (AA and ICA derivatives respectively) outside of treating any oxidizing or reducing agents as well as any transition metal at mild conditions employing cheap starting material isatin derivatives in one pot.

5.2 Objective

All the previous literature reports show the key intermediate indole-3-carboxylic acid derivatives have been prepared in an expensive multistep process, but our one-pot production of indole-3-carboxylic acid derivative from isatin derivative is straightforward. Sodium hydride has been utilized in mild conditions for this conversion. To access ICA, several indole/other functional directing groups have been employed previously with the multistep process, but we did this transformation by taking a cheap starting material isatin derivatives in a single step (Scheme 5.2.1). This is the first report where an indole-3-carboxylic acid derivative has been made instead of treating any reducing agents or transition metals in the economically viable and operationally simple condition. Hence, it is suitable for large-scale industrial production. Herein, we report a new methodology for the preparation of indole-3-carboxylic acid derivatives.

The present reaction provides a new synthetic method for the preparation of indole-3-carboxylic acid (ICA) and anthranilic acid (AA) derivatives which are building blocks for several artificial drugs. An efficient, operationally simple, cost-effective method has been introduced utilizing easily available starting material, reagent, and solvent. The unique feature of this simple and straightforward methodology is the production of various novel ICA (overall reduced product) and AA derivatives (overall oxidized product) without using any reducing and oxidizing agents or metal catalysis. This is the first report of ICA derivatives that have been produced from isatin derivatives in one pot. The research of this methodology is attractive with much attention to a wide range of applications from the drug development and material synthesis point of view.



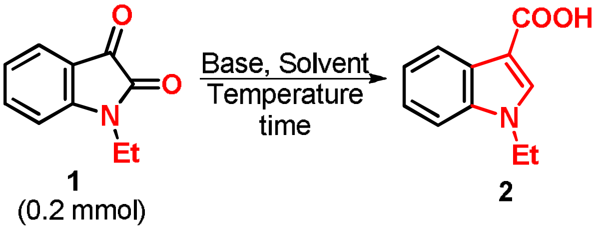
Scheme 5.2.1 Strategies for the synthesis of indole-3-carboxylic acid and anthranilic acid derivatives from isatin derivatives

5.3 Results and Discussion

5.3.1 Optimization Studies

Taking *N*-ethyl isatin as a model substrate, we set out to discover the best condition for the production of the ICA derivative. Initially, we selected sodium hydride (NaH) as a base as it rapidly produces dimsyl anion from the DMSO and it is the best solvent for the preparation of olefin in a basic medium.[3] Observing no reaction at room temperature (33 °C) loading of NaH was increased (entries 1 and 2 in table 5.3.1.1) in the reaction medium. We realized that the reaction temperature and loading of the base are most significant in this reaction as DMSO is being used here not only as a solvent but also as a coupling partner. Gratifyingly, ICA derivatives formed when 4 equiv. NaH had been used at 60 °C (entry 3 in table 5.3.1.1). We were overwhelmed by the thought that our presumption didn't go to the abyss at all, the nature of this reaction pathway we realized a little bit while ago. Improvement in the yield was noticed (increased up to 66%) when the temperature was increased to 80 °C from 60 °C (entry 4 in table 5.3.1.1). Thereafter, enhancement of base loading (4 equiv. to 6 equiv.) reached the highest yield (82% yield, entry 5 in table 5.3.1.1). The change of the yield could not be noticed majorly by the increasing or decreasing reaction time (more or less than 2 h) in this condition (entries 6 and 7 in table 5.3.1.1). In a concentrated medium, almost the same yield was observed. The vital matter of this reaction is the solvent that should be oxygen-free otherwise another oxidized product (anthranilic acid derivatives) will form predominantly.

Table 5.3.1.1 Studying the Role of Base and Solvent at Different Temperatures in the Redox Reaction



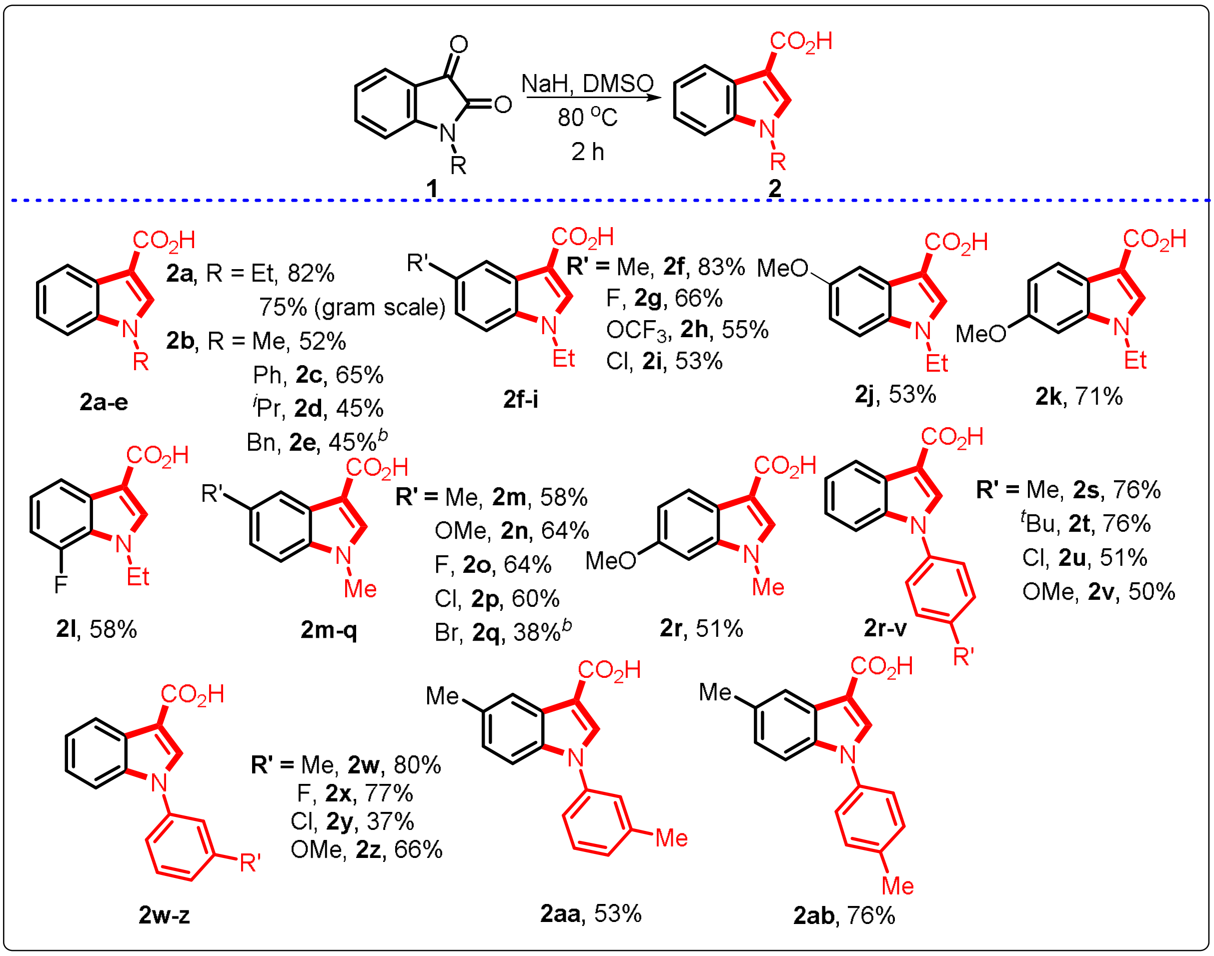
entry	base (x equiv.)	solvent (x mL)	temperature (°C)	time (h)	yield[b] (%)
1	NaH (2)	DMSO (2)	rt (33)	24	nr
2	NaH (6)	DMSO (2)	rt (33)	12	nr
3	NaH (4)	DMSO (2)	60	6	38
4	NaH (4)	DMSO (2)	80	2	66
5	**NaH (6)**	**DMSO (2)**	**80**	**2**	**82**[c](80)[d]
6	NaH (6)	DMSO (2)	80	3	78
7	NaH (6)	DMSO (2)	80	1.5	80
8	NaH (6)	DMSO (1)	80	2	78
9	NaH (6)	DMSO (1)	80	1	75
10	NaH (6)	DMSO (2)	90	2	66
11	NaH (6)	DMSO (2)	70	2	72
12	NaH (6)	DMSO (0.5) + DMF (1)	80	1	trace
13	KO^{t}Bu (6)	DMSO (1)	80	8	trace
14	KO^{t}Bu (6)	DMSO (1)	120	12	14
15	CaH_2 (3)	DMSO (1)	80-120	5	nr
16	LiH (6)	DMSO (2)	80	12	nr
17	NaOH (6)	DMSO (2)	80	12	trace
18	NaOMe (6)	DMSO (2)	80	12	trace
19	NaH (6)	DMSO (0.2) + THF (0.8)	80	1	47
20	NaH (6)	DMSO (0.2) + toluene (0.8)	80	1	48

[a]All reactions were set up on a 0.2 mmol scale in the presence of a base in DMSO solvent applying the Freeze-Pump-Thaw method. [b]Isolated yield. [c]Conditions: **1** (1 equiv.), NaH (6 equiv.) in an anhydrous DMSO solvent (2 mL) at 80 °C. [d]Conditions: **1** (1 equiv.), NaH (6 equiv.) in a bottle grade DMSO solvent (2 mL) at 80 °C. nr: No reaction

Due to this problem, we applied the Freeze-Pump-Thaw method for the screening of ICA preparation and one of the good things is that oxygen-free bottle-grade DMSO gave almost the same result (80% yield, entry 5 in table 4.3.1.1). Increment or decrement of the temperature from 80 °C was not good enough to reveal the best result (entries 10 and 11 in table 5.3.1.1) and the addition of another solvent like DMF, H_2O, etc. was not suitable for this conversion (entry 12 in table 5.3.1.1) rather the addition of water (equiv. amount) in this condition gave exclusively 2-amino benzoyl formic acid derivative (another bi-product). Other metal hydrides such as LiH, $CaH_{2,}$ or Bronsted bases like KO^{t}Bu, NaOH, NaOMe, etc. didn't carry out the satisfactory result for this conversion (entries 13-18, table 5.3.1.1). Curiously, DMSO has been treated like a reagent, especially a mixture of solvents introduced (entries 19 and 20, table 5.3.1.1) to carry out the conversion that resulted in moderate yield i.e. very significant for large-scale industrial production. As we didn't get a better yield even after using excess NaH at the best condition, based on our optimization study it is fair to say that entry 5 (table 5.3.1.1) is the best condition for this transformation. Notably bottle-grade DMSO was also efficient for this conversion (entry 5 in table 5.3.1.1).

5.3.2 Scope of ICA

Table 5.3.2.1 Synthesis of Indole-3-Carboxylic Acid Derivatives (Reduced Product) from Isatin Derivatives[a]

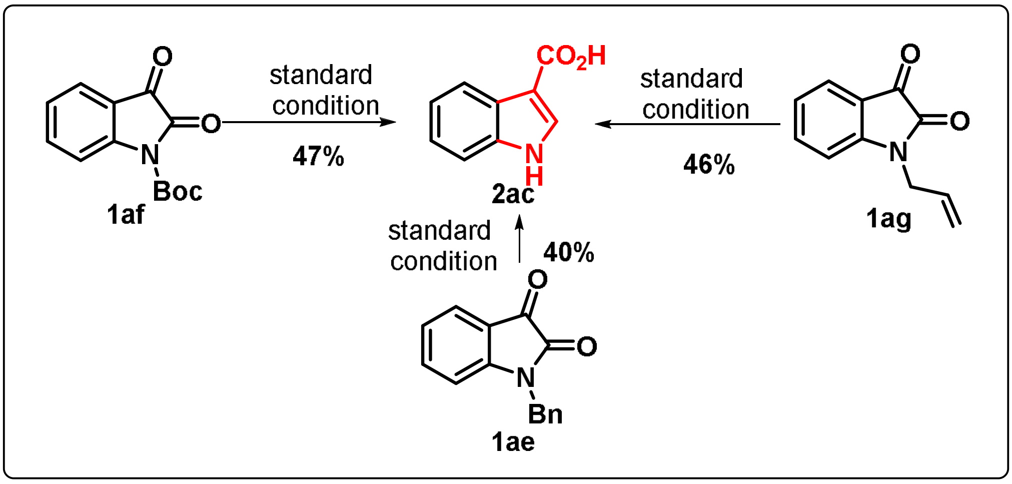


[a] All reactions were carried out in a 0.2 mmol scale of isatin derivative **1** in the presence of NaH (6 equiv.) in DMSO solvent (2 mL) applying the Freeze-Pump-Thaw method. After the pinch-wise addition of NaH at the inert condition the reaction mixture was stirred for 5 minutes then slowly increased the temperature to 80 °C and kept for 2 h. The isolated yield is given. [b] Debenzylation of **2e** and debromination of **2p** happened in these reaction conditions that's why the yield is less. Trace anthranilic acid (oxidized product) derivative was noteworthy in all cases.

After figuring out the optimized condition we explored the substrate scope taking several *N*–protected isatins. Free *N*-H of the isatin molecule was protected by several electron-donating groups (EDG) which were subjected to this reaction. Various *N*–protected isatin derivatives such as Et, Me, Ph, ^{i}Pr, and Bn played well furnishing good to moderate yield (**2a**-**2e**) (table 5.3.2.1). Various *N*-ethyl isatin derivatives with diverse functional groups (substituted at C_4, C_5, C_6, and C_7 position with EDG and EWG) performed well producing building-block ICA derivatives (**2f-2l**). Several *N*-methyl isatin derivatives with electron-donating and withdrawing functional groups (EDWFG) such as Me, F, Cl, Br, etc. were competently yielding well in this reaction condition (**2m-2r**). Various *N*-aryl isatin derivatives were well tolerable as **1s-1ab** reacted very smoothly. A variety of EDWFG such as Me, ^{t}Bu, OMe, F, Cl, etc present in the *N*-protected phenyl ring (in C_3', C_4' position) performed very well, providing good yield in this conversion (**2s-2ab**). An important aspect of this transformation is making an overall reduced product without introducing any reducing agents. For a good conversion, the reaction mixture needs to be deoxygenated otherwise anthranilic acid (AA) derivative will form primarily as it is an oxygen-sensitive reaction. Unfortunately, bromo, iodo, and nitro functional groups were not compatible in this condition, several spots were formed and sometimes dehalogenation happened. Furthermore, EWG-protected isatin (such as Boc, Cbz, etc.) couldn't tolerate the highly basic condition. Although in a few cases, we observed *N*–H free indole-3-carboxylic acid which was also a good achievement as it is an important key intermediate.

In one embodiment of the invention employing no reducing agent, Lewis acid, or transition metal catalysts various ICA derivatives could be produced in mild reaction conditions (NaH in DMSO at 80 °C). The reaction was operationally simple, fast (approximately 2 h reaction), economically viable, and straightforward one-pot process. It is feasible to produce in any laboratory as the transformation smoothly happens under atmospheric pressure and performed well in large-scale operation (75% yield in gram-scale reaction), various functional group tolerance in the anhydrous DMSO solvent (should be DO free).

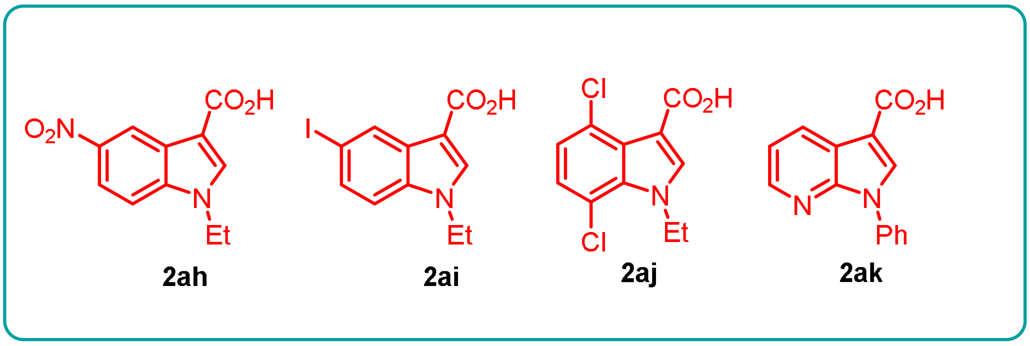
Table 5.3.2.2 Direct Indole-3-Carboxylic Acid Formation from Different *N*-Substituted Isatin Derivatives[a]



[a] All reactions were set up on a 0.2 mmol scale in the standard condition applying Freeze-Pump-Thaw (FPT) method. The isolated yield is given. If the FPT method is not applied then starting material is completely converted to the anthranilic acid derivative.

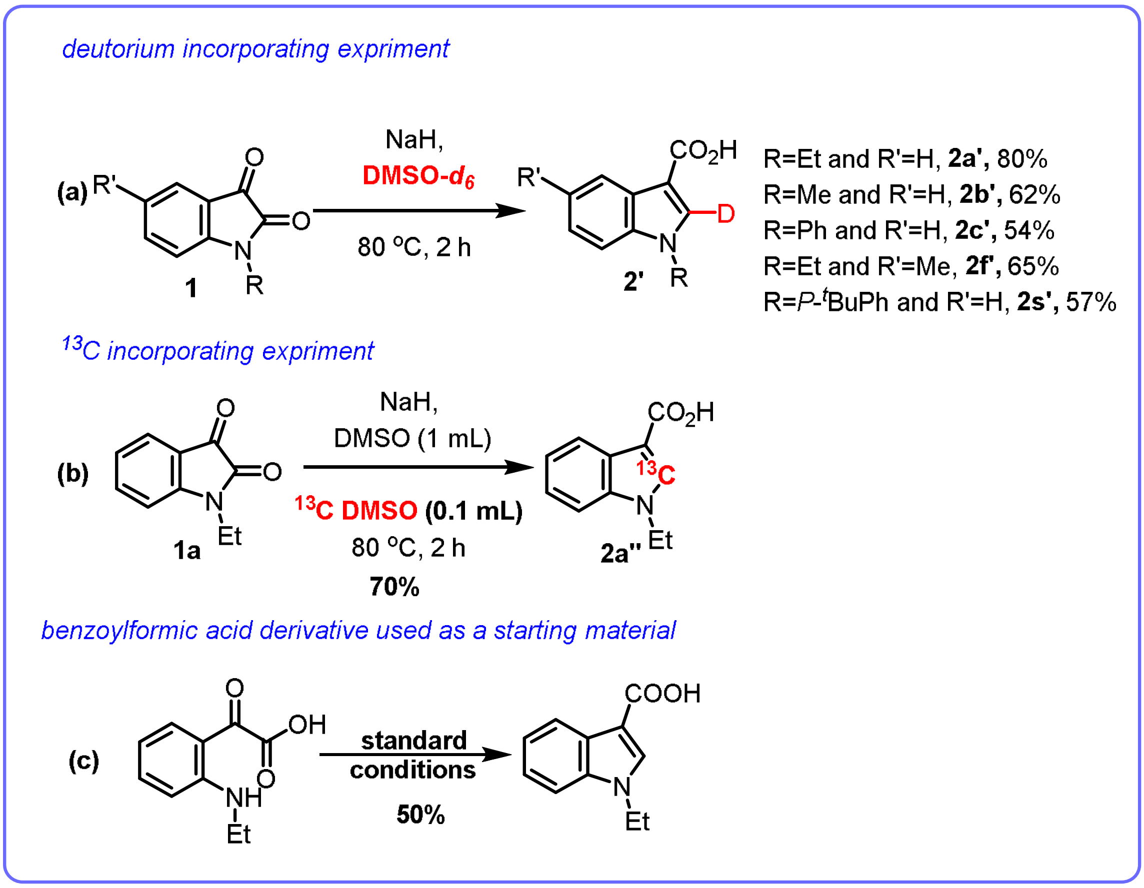
Indole-3-carboxylic acid (ICA) is a precursor of several biologically active molecules,[4] its preparation from isatin derivative is highly challenging in a single step. We produced this important key intermediate from some isatin derivatives such as *N*-Boc/*N*-allyl/*N*-benzyl isatin (**1af**, **1ag,** and **1ae**) in one pot in a very short time with a moderate yield (table 5.3.2.2). The reason behind the formation of the ICA product is that various nucleophiles (such as MeS$^-$, MeSO$^-$, MeSO$_2^-$, OH$^-$ etc.) could be generated in the reaction medium (as DMSO heated in basic medium) and hence deprotection happens easily, resulting in generates ICA.

Table 5.3.2.3 Unsuccessful substrate scope



In the standard reaction condition, dimsyl ion reacts with a nitro group, hence **2ah** reacts very fast and readily decomposes. Other halide substituents such as **2ai**, **2aj**, and heterocycle derivative **2ak** decompose in the reaction medium. Sometimes dehalogenation happened in this standard basic condition. Dimsyl anion may react as a nucleophile in the halide cavity and consequently, dehalogenation happens.

5.3.3 Mechanistic Studies for ICA

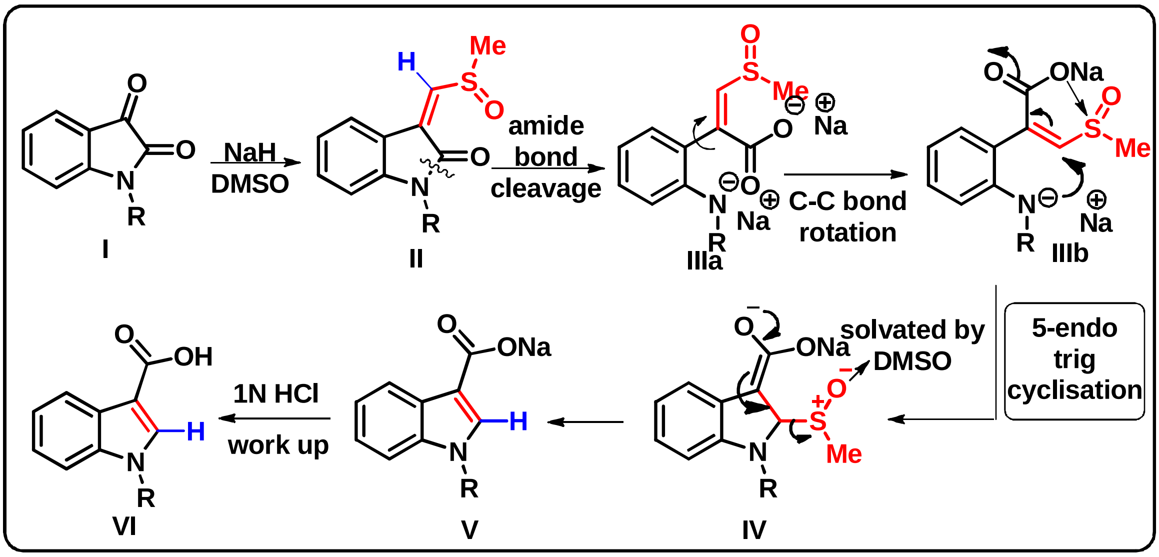


Scheme 5.3.3.1 Mechanistic investigation for the formation of ICA derivatives

To understand the ICA-making process from isatin derivatives, we conducted several experiments. To identify the source of extra carbon in the ICA derivative we were highly curious. The question now arises: Does DMSO behaves like a one-carbon synthon? We started an investigation by the set up of a reaction using DMSO-d_6 solvent instead of normal DMSO whether the deuterated product is formed (Scheme 5.3.3.1a) or not. After characterization of the desired product, it was noteworthy that the C_2 position of the ICA derivative gets deuterated. Utilizing this method we were able to synthesize several C_2-deuterated ICA derivatives (**2a′-2s′**) in a pot. This experiment suggests that the extra carbon present in the ICA derivative may be coming from the DMSO solvent. With curiosity, we did another experiment (Scheme 5.3.3.1c) to make out if the reaction mechanism was following our hypothesis or not. In short, it is the formation of the desired ICA derivative from the substituted 2-amino benzoyl formic acid derivative, and its results supported our hypothesis.

It is stated that only these two experiments do not prove that DMSO is the one carbon synthon in the ICA derivative. To know the carbon source as well as the reaction path we investigate a reaction (Scheme 5.3.3.1b) employing ^{13}C DMSO. ^{13}C NMR confirmed that DMSO delivered the extra carbon and it was responsible for the C_2 carbon in ICA derivatives specifically. By this time we were overwhelmed to think that our hypothesis was largely consistent and the mechanistic path of this reaction was clear in our eyes. Several HRMS data (see experimental section) of the reaction mixture in a time interval were matched with the reaction's intermediates which supports our reaction mechanism.

5.3.4 Plausible Mechanism for ICA

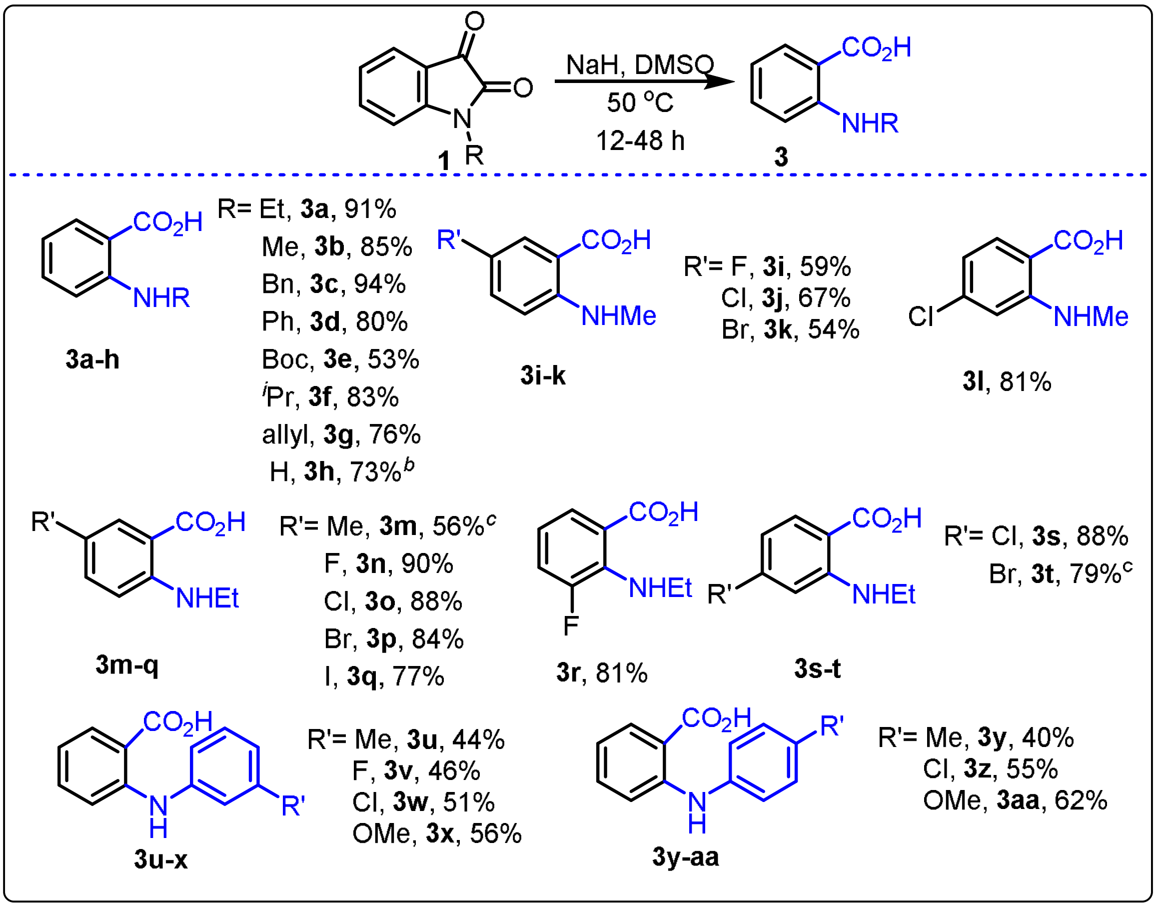


Scheme 4.3.4.1 Plausible mechanism for the synthesis of ICA derivatives

Hence, the proposed mechanism for the conversion of ICA derivatives is described below. Our presumption was the intermediate olefin derivative **II** could be formed from **I**, as the concentration of dimsyl anion was greater in the reaction medium. The basic condition (especially the formation of sodium oxide) helps to facile the amide bond cleavage producing **IIIa** from **II** and followed by intramolecular Michael type addition (ring-closing) through 5-endo trig cyclization of **IIIb** generates **IV**. Bulk DMSO might be responsible for the solvation of the sulfoxide group of **IV** and helps to transform it into a leaving group at this condition and elimination take place which produces **V**. After workup of the reaction mixture with 1N HCl we could reach the desired ICA derivative **VI**.

5.3.5 Scope of AA

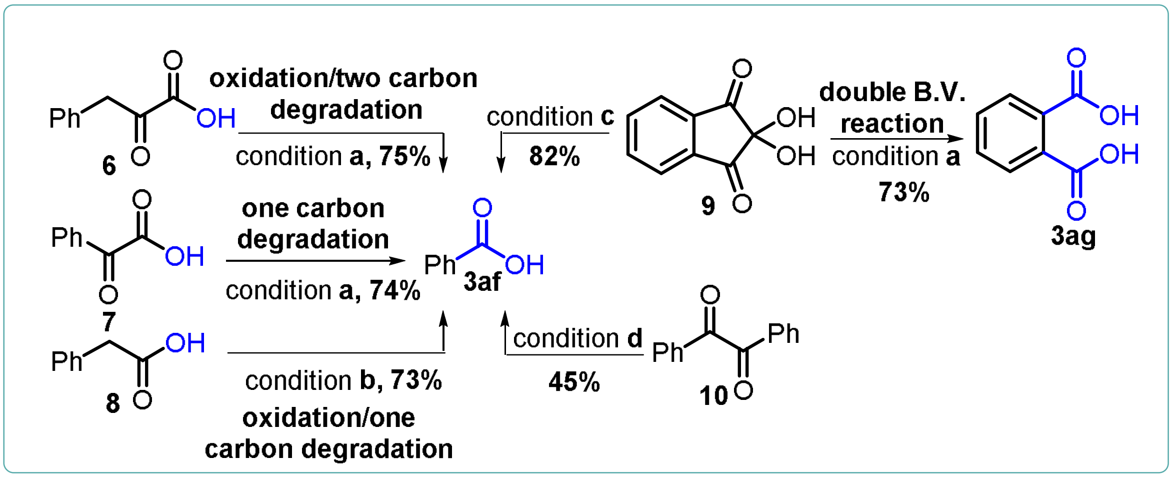
Table 5.3.5.1 Synthesis of Anthranilic Acid Derivatives (Oxidised Product) from Isatin Derivatives[a]



[a]All reactions were carried out on a 0.2 mmol scale (**1**) in the presence of NaH (6 equiv.) in a reagent grade DMSO solvent (2 mL) at 50 °C for 24 h. An isolated yield is given. [b]Conditions: **1** (1 equiv.), NaH (6 equiv.) in DMSO (2 mL) at 50 °C for 12 h. [c]Conditions: **1** (1 equiv.), NaH (6 equiv.) in DMSO (2 mL) at 50 °C for 48 h.

First, we discover this anthranilic acid derivative (overall oxidized product) as a by-product at the time of optimization study of ICA derivative from isatin. We studied the nature of the reaction after applying the Freeze-Pump-Thaw method and noticed that oxidized products get diminished. We realized that dissolved oxygen (DO) present in the solvent may be responsible for this conversion. Taking *N*-ethyl isatin as a model substrate several conditions are screened and reached the best (**3c**, 85% yield) (table 5.3.5.1). *N*-substituted isatin derivatives containing various functional groups such as Et, Me, Bn, Ph, Boc, *i*Pr, allyl, and H, etc. are endurable in this condition and could be converted easily to the anthranilic acid derivative (**3a-3h**) (table 5.3.5.1). It was also notable that bottle-grade DMSO solvent gave better results and it had been used to explore the substrate scope. Several *N*-Me, Et isatin derivatives containing electron-donating and withdrawing groups (EDWG) at the different positions of isatin performed well producing AA derivatives with good to excellent yield very smoothly (**3i-3t**) in this reaction condition. We were able to produce various fenamic acid derivatives (*N*-aryl anthranilic acid derivatives) (**3u-3aa**) which are significant building block molecules widely used as anti-inflammatory drugs (NSAIDs).[6]

5.3.6 Scope of Benzoic Acid and Phthalic Acid



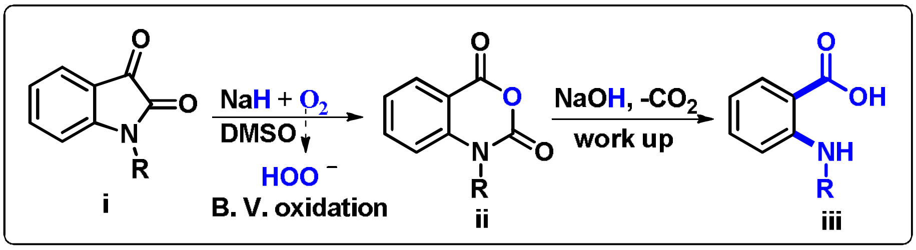
Reaction condition **a**: All reactions were set up on a 0.2mmol scale in the presence of NaH (6 equiv.) in DMF (2 mL) solvent initially at 0 °C (stirred for 10 minutes), then it was stirred for 10 h at rt (33 °C). Condition **b**: Reaction carried out in a 0.2 mmol scale in the presence of NaH (6 equiv.) in DMF (2 mL) solvent initially at rt (33 °C), then it was stirred for 24 h at 80 °C.Condition **c**: Reaction carried out in a 0.2 mmol scale in the presence of NaH (6 equiv.) in DMSO (2 mL) solvent initially at rt (33 °C), then temperature increased to 80 °C and stirred for 2 h. Condition **d**: Reaction run in a 0.2 mmol scale in the presence of NaH (4 equiv.) in DMF (2 mL) solvent initially at 0 °C (stirred for 10 minutes), then it was stirred for 6 h at rt (33 °C). The Isolated yield is given.

Scheme 5.3.6.1 Oxidation and Degradation Using Sodium Hydride and DMF Composite

We took notice of a similar conversion when we were working with benzoyl formic acid and phenyl pyruvic acid. Benzoic acid (**3af**) formed exclusively in each case in this NaH-DMSO condition but the NaH-DMF composite plays better producing a good yield (Scheme 5.3.6.1). In this oxidative reaction condition phenyl pyruvic acid (**6**) and phenylacetic acid (**8**) get oxidized first then dehomologation happened via Bieyer Villiger (B.V.) type reaction.[8a]

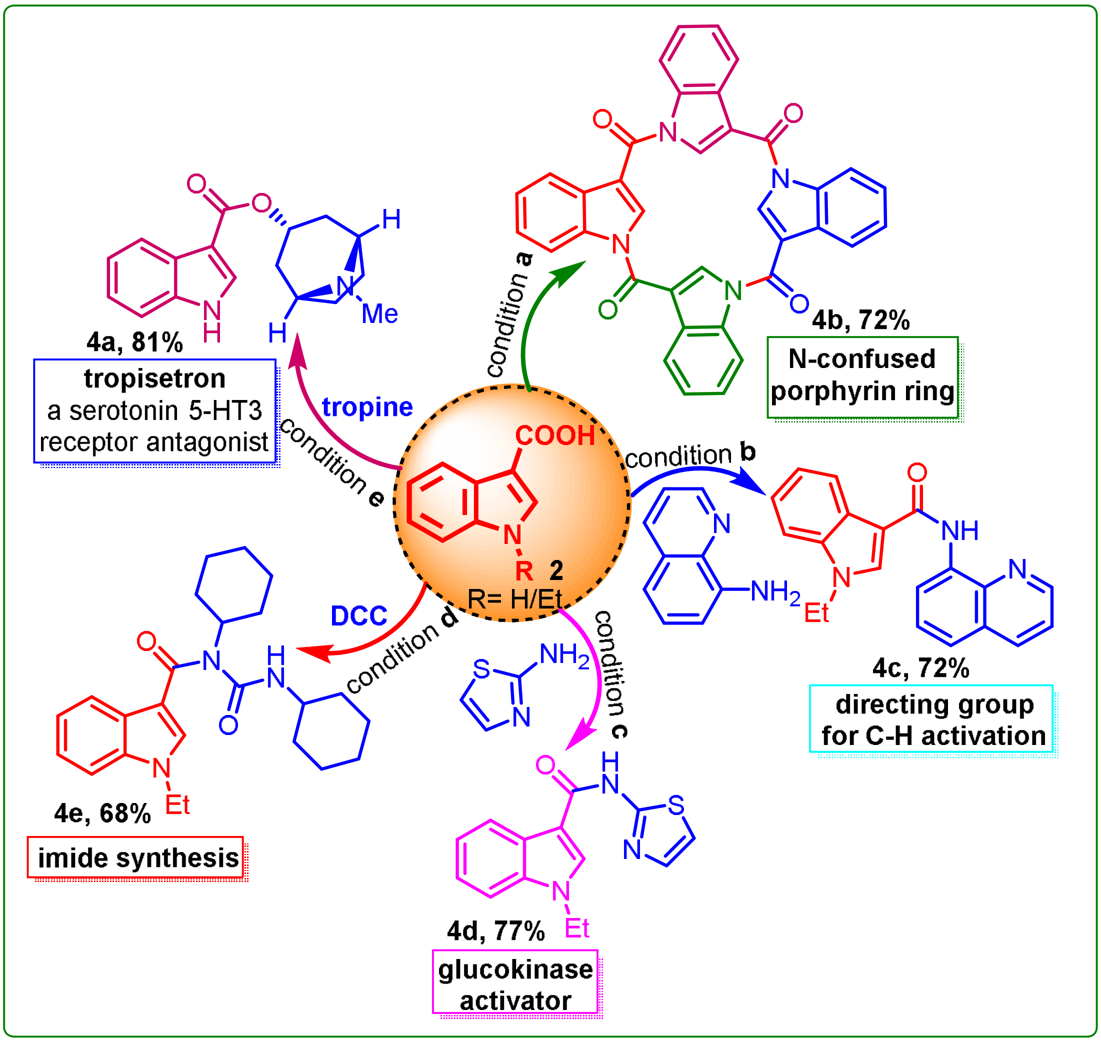
Notably, benzoyl formic acid (**7)** and benzil (**10**) were converted to **3af** very quickly. Phthalic acid (**3ag**) was smoothly obtained from ninhydrin (**9**) via a selective double B.V. reaction process. Extrusion of CO_2 at high-temperature compound **9** produces benzoic acid exclusively through the intermediate **3ag**. So oxidative dehomologation (up to two carbon degradation) of various acids without using any oxidizing agents or transition metal catalysts is highly demanding as limited reports are available to date.[8b] Hence, these experiments support the reaction path of AA where oxidation happens by DO. After reacting with NaH, hydroperoxide may be generated which was responsible for the B.V. type of oxidation. The proposed mechanism for the formation of AA derivatives from isatin derivatives is described below (Scheme 5.3.7.1). Intermediate **ii** could be formed from **i** via B.V. type of oxidation in this reaction condition. Then hydrolysis of **ii** followed by decarboxylation and finally workup with acid gave rise to the AA derivative **iii**.

5.3.7 Proposed Mechanism for AA



Scheme 5.3.7.1 Proposed Mechanism for the Synthesis of Anthranilic Acid Derivatives

5.3.8 Applications of ICA Derivatives



Reaction condition **a**: this reaction was carried out on a 0.4 mmol scale in the presence of EDC.HCl (2.5 equiv.) and DMAP (0.1 equiv.) in DCM (4 mL) initially at 0 °C (stirred for 10 minutes), then it was stirred for 12 h at rt (33 °C). Condition **b** and **c**: Reaction carried out in a 0.4mmol scale in the presence of EDC.HCl (2.5 equiv.) and DMAP (2 equiv.) in DCM (4 mL) solvent initially at 0 °C (stirred for 10 minutes), then it was stirred for 12 h at rt (33 °C). Condition **d**: The reaction was carried out in a 0.3mmol scale in the presence of DCC (3 equiv.) and H_2O (1.5 equiv.) in DMF (4 mL) solvent initially at 0 °C (stirred for 10 minutes), then it was stirred for 36 h at rt (33 °C). Condition **e**: Reaction carried out in a 3.1 mmol scale concerning indole-3-carboxylic acid in the presence of $(CF_3CO)_2O$ (2.3 equiv.) and CF_3COOH (0.4 equiv.) in DCM (8 mL) solvent initially at 0 °C (stirred for 10 minutes), then it was stirred for 2 h at rt (33 °C). Tropine (1 equiv.) solution (in DCM) was transferred to it at -5 °C and stirred for 4 h.

Scheme 5.3.8.1 Applications of indole-3-carboxylic acid derivatives

Indole-3-carboxylic acid (ICA) derivatives already have been used to synthesize several biologically active compounds as it is a good building block. The importance of this methodology is the creation of key intermediate ICA, with the help of which we can reach the diverse synthetic molecules and artificial drugs straightforwardly. We synthesized tropisetron (**4a**) with 81% yield, an excellent 5-HT3 receptor antagonist, used mainly as an antiemetic to treat nausea and vomiting following chemotherapy and as an analgesic in cases of fibromyalgia.[9] Furthermore, we performed an amide formation reaction of **2a** in EDC.HCl condition with moderate (**4c**, 72% yield) to good yield (**4d**, 77% yield). We are familiar that **4c** has already been utilized as a good directing group for C–H bond activation reaction[10] whereas **4d** is a very good glucokinase activator, useful for increasing insulin secretion in the treatment of type II diabetes.[11] Imide (**4e**, 68%) was also produced from **2a** with another partner DCU which was in-situ formed from DCC and has biological importance.[12] *N*-confused porphyrin ring (**4b**, 72%) has a good synthetic utility and has been synthesized from ICA in one step in EDC.HCl condition.[13]

5.4 Conclusion

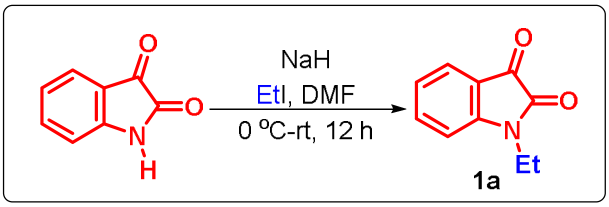
Above all, it is right to say that we have been able to execute a divergent synthesis from isatin by slightly switching the reaction conditions, determining the nature of the reaction path. We explored the scope of ICA and AA derivatives (overall reduced and oxidized products respectively) and their synthetic utility through this novel methodology without the treatment of any reducing and oxidizing agent from the outside. The making of desired ICA and AA derivatives is most important as these have been used as a key intermediate to synthesize several biologically active molecules, which we have shown a few examples of. Our next target is to invent another new methodology keeping in mind this mechanistic pathway and show their application in organic synthetic chemistry as well as medicinal chemistry.

5.5 Experimental Section

5.5.1 General Information

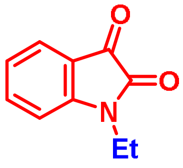
All reactions were carried out in an oven-dried reaction vessel under an N_2 atmosphere unless otherwise stated. Commercial reagents were purchased from Sigma-Aldrich, Alfa Aesar, Acros, and other commercial suppliers and used as received without further purification. Anhydrous DCE was purchased from Sigma-Aldrich and used as received. TLC analysis was performed on Merck 60 F_{254} silica gel TLC plates. Column chromatography was done using 230-400 mesh silica gel by applying pressure through an air pump. ^{1}H and ^{13}C NMR spectra were recorded in Bruker 300, 600 MHz, and JEOL 400 MHz spectrometer, and are reported as chemical shifts (δ) in parts per million (ppm). Internal standards or residual solvents were used as a reference. HRMS (m/z) were recorded in the Q-TofMicromass spectrometer (LC-MS, ESI mode) and JOEL-JMS 700 (EI mode). Melting points were determined in a capillary melting point apparatus and are uncorrected. Single crystal X-ray data was recorded in a Bruker Kappa APEX2 CCD diffractometer with CuKα/MoKα radiation. The structures were solved by SHELXT and refined with SHELXL using the Olex2 program. The CIF files were submitted to CCDC (2213915-2213920) and can be obtained at https://summary.ccdc.cam.ac.uk/structure-summaryform.

5.5.2 General procedure for the preparation of 1-ethylindoline-2,3-dione (1a):



To a suspension of isatin (3.5 mmol) in anhydrous DMF (30 mL), NaH (1.1 equiv.) was added in ice-cold conditions under an argon atmosphere. The reaction was stirred at 0 °C for 30 minutes. Then ethyl iodide (1.1 equiv.) was transferred to the reaction mixture and stirred at room temperature (33 °C) and kept overnight (12 h). After the full conversion was monitored by TLC, it was quenched with cold 1N HCl solution (200 mL). The organic part was extracted by EtOAc (3x100 mL) with brine, dried over Na_2SO_4, and concentrated under reduced pressure. Finally, it was purified by column chromatography on silica gel (230-400 mesh) using petroleum ether/ethyl acetate (6:1) as eluent to obtain the desired 1-ethylindoline-2,3-dione (**1a**) in 85% yield (520 mg). The compounds were eluted in 15% of ethyl acetate–petroleum ether. Several *N*-alkyl isatins were prepared following this protocol.[1]

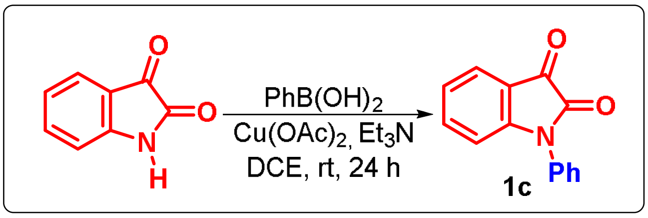
5.5.3 Characterization of 1-ethylindoline-2,3-dione (1a):



1a

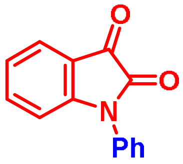
Red solid (520 mg, 85% yield); **column chromatography eluent** petroleum ether/EtOAc = 5:1; mp 88-90 ^{o}C; **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 7.57 (app t, *J* = 7.4 Hz, 2H), 7.09 (app t, *J* = 7.5 Hz, 1H), 6.90 (app d, *J* = 8.5 Hz, 1H), 3.76 (q, *J* = 7.2 Hz, 2H), 1.29 (t, *J* = 7.2 Hz, 3H); **^{13}C NMR** (101 MHz, Chloroform-*d*) δ 183.6, 157.8, 150.6, 138.3, 125.4, 123.6, 117.5, 110.0, 34.9, 12.4; **HRMS** (ESI, m/z) calcd for $C_{10}H_{10}NO_2$ $[M+H]^+$175.0633, found 175.0630.

5.5.4 General procedure for the preparation of 1-phenylindoline-2,3-dione (1c):



To a suspension of isatin (3 mmol) in anhydrous DCE (30 mL), anhydrous $Cu(OAc)_2$ (4.5 mmol), triethylamine (6 mmol) and the arylboronic acid (4.5 mmol) were added under an argon atmosphere. The reaction was stirred at room temperature for 16 h. After completion of the reaction, the mixture was filtered through a pad of celite and washed with dichloromethane. The filtrate was concentrated in vacuo to yield the crude compound, which was subjected to flash chromatography on silica. The compounds were eluted in 15% of ethyl acetate–petroleum ether. Several *N*-aryl isatins were prepared following this procedure.[2]

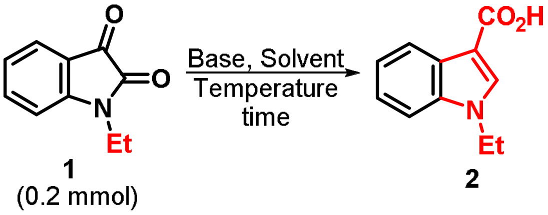
5.5.5 Characterization of 1-phenylindoline-2,3-dione (1c):



1c

Red solid (555 mg, 83% yield); **column chromatography eluent** petroleum ether/EtOAc = 4:1; mp 138-140 ^{o}C; **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 7.71 – 7.66 (m, 1H), 7.59 – 7.50 (m, 3H), 7.48 – 7.39 (m, 3H), 7.17 (td, *J* = 7.5, 0.6 Hz, 1H), 6.89 (d, *J* = 8.0 Hz, 1H); **^{13}C NMR** (101 MHz, Chloroform-*d*) δ 182.9, 157.3, 151.6, 138.3, 132.9, 129.9, 128.8, 126.0, 125.6, 124.3, 117.5, 111.3; **HRMS** (ESI, m/z) calcd for $C_{14}H_{10}NO_2$ $[M+H]^+$ 224.0712, found 224.0709.

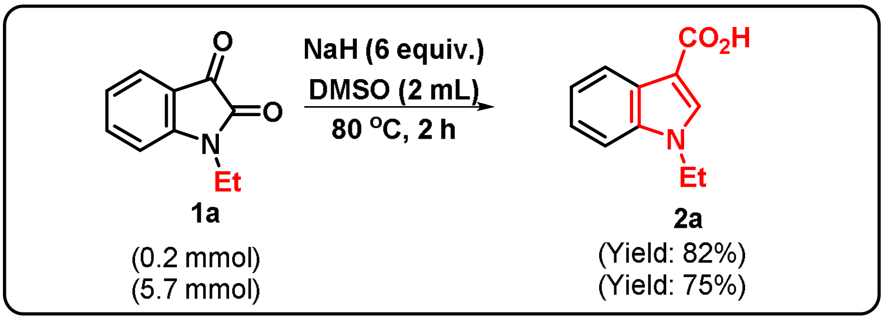
Table 5.5.6: Screening of the reaction conditions[a]



entry	base (x equiv.)	solvent (x mL)	temperature (°C)	time (h)	yield[b] (%)
21	NaH (2)	DMSO (2)	rt (33)	24	nr
22	NaH (6)	DMSO (2)	rt (33)	12	nr
23	NaH (4)	DMSO (2)	60	6	38
24	NaH (4)	DMSO (2)	80	2	66
25	**NaH (6)**	**DMSO (2)**	**80**	**2**	**82**[c](80)[d]
26	NaH (6)	DMSO (2)	80	3	78
27	NaH (6)	DMSO (2)	80	1.5	80
28	NaH (6)	DMSO (1)	80	2	78
29	NaH (6)	DMSO (1)	80	1	75
30	NaH (6)	DMSO (2)	90	2	66
31	NaH (6)	DMSO (2)	70	2	72
32	NaH (6)	DMSO (0.5) + DMF (1)	80	1	trace
33	KO^{t}Bu (6)	DMSO (1)	80	8	trace
34	KO^{t}Bu (6)	DMSO (1)	120	12	14
35	CaH_2 (3)	DMSO (1)	80-120	5	nr
36	LiH (6)	DMSO (2)	80	12	nr
37	NaOH (6)	DMSO (2)	80	12	trace
38	NaOMe (6)	DMSO (2)	80	12	trace
39	NaH (6)	DMSO (0.2) + THF (0.8)	80	1	47
40	NaH (6)	DMSO (0.2) + toluene (0.8)	80	1	48
41	NaH (6)	DMSO (0.2) + dioxane (0.8)	80	1	42
42	NaH (6)	DMSO (0.2) + DCE (0.8)	80	1	nr

[a]All reactions were set up on a 0.2 mmol scale in presence of a base in DMSO solvent applying the Freeze-Pump-Thaw method. [b]Isolated yield. [c]Conditions: **1** (1 equiv.), NaH (6 equiv.) in an anhydrous DMSO solvent (2 mL) at 80 °C. [d]Conditions: **1** (1 equiv.), NaH (6 equiv.) in a bottle grade DMSO solvent (2 mL) at 80 °C. nr: No reaction

5.5.7 General procedure for the preparation of 1-ethyl-1*H*-indole-3-carboxylic acid (2a):



(**Milligram scale**)

Into a 10 mL two-neck round bottom flask equipped with an electromagnetic stirrer *N*-ethyl isatin (**1a**) (1 equiv., 0.2 mmol, 35 mg) and DMSO solvent (2 mL, 0.1 M) were transferred under an inert atmosphere. Then, the whole reaction mixture was subjected to degas by the Freeze-Pump-Thaw method. After degassing, NaH (6 equiv., 1.2 mmol) was added portion-wise using a solid-additional funnel and stirred at room temperature (30°C) for 10 minutes. After that, the reaction mixture was warmed slowly to 80 °C and kept for 2 hours. After the full conversion was monitored by TLC, it was cooled to room temperature and quenched with cold aqueous 1N HCl solution (20 mL). The organic part was extracted by EtOAc (3x20 mL), washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. Finally, it was purified by column chromatography on silica gel (230-400 mesh) using petroleum ether/ethyl acetate (4:1) as eluent to obtain the desired 1-ethyl-1*H*-indole-3-carboxylic acid (**2a**) in 82% yield (31 mg). To avoid column purification, we also carried out a re-crystallization technique dissolving crude reaction mixture in hot ethanol and obtained the same yield.

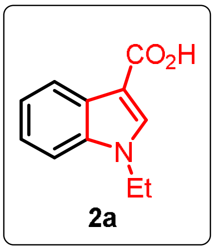
(**Gram scale**)

Into a 100 mL two-neck round bottom flask equipped with an electromagnetic stirrer *N*-ethyl isatin (1 equiv., 5.7 mmol, 1g) and DMSO solvent (57 mL, 0.1 M) were transferred under an inert atmosphere. Then, the whole reaction mixture was subjected to degas by the Freeze-Pump-Thaw method. After degassing, NaH (6 equiv., 34.2 mmol) was added portion-wise using a solid-additional funnel and stirred at room temperature (30 °C) for 10 minutes. After that, the reaction mixture was warmed slowly to 80 °C and kept for 2 hours. After the full conversion was monitored by TLC, it was cooled to room temperature and quenched with cold aqueous 1N HCl solution (200 mL). The organic part was extracted by EtOAc (3x100 mL), washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. Finally, it was purified by column chromatography on silica gel (230-400 mesh) using petroleum ether/ethyl acetate (4:1) as eluent to obtain the desired 1-ethyl-1*H*-indole-3-carboxylic acid (**2a**) in 75% yield (808 mg). To avoid column purification, we also carried out the re-crystallization method dissolving crude reaction mixture in hot ethanol and obtained the same yield.

We have followed the above procedure for the synthesis of **2b-2ab**. In cases of **1e**, **1e′**, and **1e′′** in-situ deprotection of the *N*-substitution took place and we obtained indole-3-carboxylic acid (**2ac**).

5.5.8 Characterization of the compounds 2a-2ab:

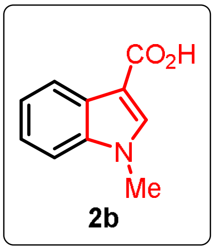
1-ethyl-1*H*-indole-3-carboxylic acid (2a):



2a

White solid (31 mg, 82% yield); column chromatography eluent, petroleum ether/EtOAc = 4:1; mp 138-139 °C; ^{1}**H NMR** (400 MHz, Chloroform-*d*) δ 8.29 – 8.24 (m, 1H), 7.97 (s, 1H), 7.41 – 7.38 (m, 1H), 7.34 – 7.30 (comp, 2H), 4.23 (q, *J* = 7.3 Hz, 2H), 1.54 (t, *J* = 7.3 Hz, 3H); ^{13}**C NMR** (101 MHz, Chloroform-*d*) δ 170.7, 136.5, 134.7, 127.0, 122.8, 122.1, 121.9, 109.9, 106.3, 41.7, 15.1; **HRMS** (ESI, m/z) calcd for $C_{11}H_{12}NO_2$ $[M+H]^+$ 190.0868, found 190.0866.

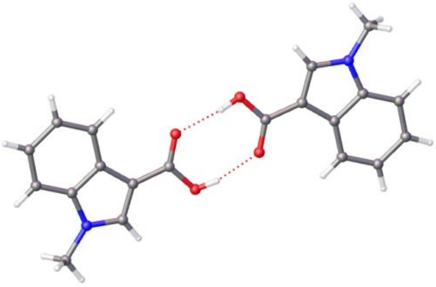
1-methyl-1*H*-indole-3-carboxylic acid (2b):



2b

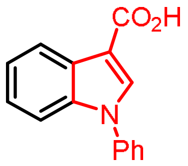
White solid (18.2mg, 52% yield); column chromatography eluent, petroleum ether/EtOAc = 4:1; mp 182-184 °C; (Due to solubility problem, a few drops of CD_3OD was added with $CDCl_3$) ^{1}**H NMR** (400 MHz, Chloroform-*d*) δ 8.14 – 8.12 (m, 1H), 7.78 (s, 1H), 7.32–7.29 (m, 1H), 7.27 – 7.21 (comp, 2H), 3.78 (s, 3H); ^{13}**C NMR** (101 MHz, Chloroform-*d*) δ 167.6, 137.2, 135.8, 126.7, 122.6, 121.8, 121.4, 109.7, 106.5, 33.2; **HRMS** (ESI, m/z) calcd for $C_{10}H_{10}NO_2$ $[M+H]^+$ 176.0712, found 176.0719.

Table 5.5.9 Crystal Data and Structure of 2b (CCDC No. **2213915**)



Identification code	AB_03_435_0m_a
Empirical formula	$C_{20}H_{18}N_2O_4$
Formula weight	350.377
Temperature/K	100.00
Crystal system	monoclinic
Space group	$P2_1$
a/Å	5.0202(4)
b/Å	29.187(2)
c/Å	5.9119(5)
α/°	90
β/°	100.468(3)
γ/°	90
Volume/Å^3	851.83(12)
Z	2
ρ_{calc}g/cm^3	1.366
μ/mm^{-1}	0.792
F(000)	369.3
Crystal size/mm^3	0.25 × 0.2 × 0.1
Radiation	Cu Kα (λ = 1.54178)
2Θ range for data collection/°	15.24 to 133.2
Index ranges	$-5 \leq h \leq 5$, $-34 \leq k \leq 34$, $-7 \leq l \leq 7$
Reflections collected	25396
Independent reflections	2910 [R_{int} = 0.0503, R_{sigma} = 0.0289]
Data/restraints/parameters	2910/1/240
Goodness-of-fit on F^2	1.043
Final R indexes [I>=2σ (I)]	R_1 = 0.0587, wR_2 = 0.1568
Final R indexes [all data]	R_1 = 0.0587, wR_2 = 0.1568
Largest diff. peak/hole / e Å^{-3}	0.35/-0.24
Flack parameter	0.3(3)

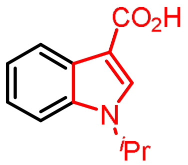
1-phenyl-1*H*-indole-3-carboxylic acid (2c):



2c

White solid (30.8 mg, 65% yield); column chromatography eluent, petroleum ether/EtOAc = 4:1; mp 160-162 °C; ^{1}**H NMR** (400 MHz, Chloroform-*d*) δ 10.00 (br s, 1H), 8.33 (d, *J* = 7.6 Hz, 1H), 8.14 (s, 1H), 7.59–7.50 (comp, 5H), 7.48 – 7.44 (m, 1H), 7.38 – 7.34 (m, 1H), 7.33 – 7.29 (m, 1H); ^{13}**C NMR** (101 MHz, Chloroform-*d*) δ 170.7, 138.3, 136.9, 135.4, 129.9, 128.0, 127.1, 124.9, 123.6, 122.8, 122.0, 111.1, 108.5; **HRMS** (ESI, m/z) calcd for $C_{15}H_{12}NO_2$ $[M+H]^+$238.0868, found 238.0870.

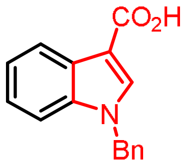
1-isopropyl-1*H*-indole-3-carboxylic acid (2d):



2d

Off-white solid (18.3 mg, 45% yield); column chromatography eluent, petroleum ether/EtOAc = 4:1; mp 183-184 °C; ^{1}**H NMR** (400 MHz, Chloroform-*d*) δ 8.26-8.22 (m,1H), 8.05 (s, 1H), 7.43-7.40 (m, 1H), 7.32-7.27 (comp, 2H), 4.72 (hept, *J* = 6.7 Hz, 1H), 1.59 (d, *J* = 6.7 Hz, 6H).^{13}**C NMR** (101 MHz, Chloroform-*d*) δ 170.7, 136.3, 131.9, 127.0, 122.7, 122.2, 121.9, 110.1, 106.4, 47.9, 22.6; **HRMS** (ESI, m/z) calcd for $C_{12}H_{14}NO_2$ $[M+H]^+$204.1025, found 204.1022.

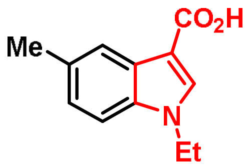
1-benzyl-1*H*-indole-3-carboxylic acid (2e):



2e

Off-white solid (22.6 mg, 45% yield); column chromatography eluent, petroleum ether/EtOAc = 4:1; mp 168-169 °C; ^{1}**H NMR** (400 MHz, Chloroform-*d*) δ 8.27 – 8.25 (m, 1H), 7.95 (s, 1H), 7.37 – 7.27 (m, 6H), 7.20 – 7.17 (m, 2H), 5.36 (s, 2H); ^{13}**C NMR** (101 MHz, Chloroform-*d*) δ 170.1, 136.9, 135.8, 135.7, 129.0, 128.2, 127.1, 127.0, 123.1, 122.3, 121.9, 110.4, 106.8, 50.9; **HRMS** (ESI, m/z) calcd for $C_{16}H_{14}NO_2$ $[M+H]^+$252.1025, found 252.1017.

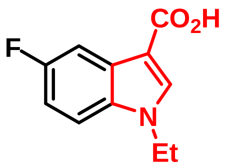
1-ethyl-5-methyl-1*H*-indole-3-carboxylic acid (2f):



2f

Off-white solid (33.7 mg, 83% yield); column chromatography eluent, petroleum ether/EtOAc = 4:1; mp 212-214 °C; (Due to solubility problem, a few drops of CD_3OD was added with $CDCl_3$) ^{1}**H NMR** (400 MHz, Chloroform-*d*)δ 7.95 – 7.94 (m, 1H), 7.82 (s, 1H), 7.22 (d, *J* = 8.4 Hz, 1H), 7.08 – 7.04 (m, 1H), 4.13 (q, *J* = 7.3 Hz, 2H), 2.44 (s, 3H), 1.46 (t, *J* = 7.3 Hz, 3H); ^{13}**C NMR** (101 MHz, Chloroform-*d*) δ 168.2, 134.7, 134.2, 131.4, 127.2, 124.1, 121.3, 109.5, 105.9, 41.5, 21.3, 15.0; **HRMS** (ESI, m/z) calcd for $C_{12}H_{14}NO_2$ $[M+H]^+$ 204.1025, found 204.1023.

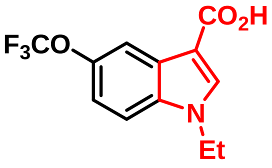
1-ethyl-5-fluoro-1*H*-indole-3-carboxylic acid (2g):



2g

Off-white solid (27.3 mg, 66% yield); column chromatography eluent, petroleum ether/EtOAc = 4:1; mp 182-184 °C; (Due to solubility problem, a few drops of CD$_3$OD was added with CDCl$_3$) **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 7.89 (s, 1H), 7.82 (dd, J = 9.7, 2.5 Hz, 1H), 7.28-7.25 (m, 1H), 6.99 (td, J = 9.0, 2.6 Hz, 1H), 4.16 (q, J = 7.3 Hz, 2H), 1.49 (t, J = 7.3 Hz, 3H); **^{13}C NMR** (101 MHz, Chloroform-*d*) δ 167.7, 159.2 (d, $^{1}J_{\text{F-C}}$ = 237.4 Hz), 135.3, 132.9, 127.7 (d, $^{3}J_{\text{F-C}}$ = 11.4 Hz), 111.1 (d, $^{2}J_{\text{F-C}}$ = 26.5 Hz), 110.6 (d, $^{3}J_{\text{F-C}}$ = 9.9 Hz), 107.0 (d, $^{2}J_{\text{F-C}}$= 24.2 Hz), 106.6 (d, $^{4}J_{\text{F-C}}$ = 5.0 Hz), 41.8, 15.0; **HRMS** (ESI, m/z) calcd for $C_{11}H_{11}FNO_2$ $[M+H]^+$208.0774, found 208.0772.

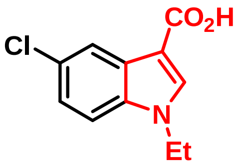
1-ethyl-5-(trifluoromethoxy)-1*H*-indole-3-carboxylic acid (2h):



2h

Off-white solid (30 mg, 55% yield); column chromatography eluent, petroleum ether/EtOAc = 4:1; mp 186-189 °C; (Due to solubility problem, a few drops of CD$_3$OD was added with CDCl$_3$) **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 7.97 (apps, 1H), 7.87 (s, 1H), 7.28 (d, J = 8.9 Hz, 1H), 7.07 (d, J = 8.8 Hz, 1H), 4.13 (q, J = 7.3 Hz, 2H), 1.44 (t, J = 7.3 Hz, 3H); **^{13}C NMR** (101 MHz, Chloroform-*d*) δ 167.3, 144.5, 135.5, 134.5, 127.3, 120.6 (q, J = 256.7 Hz), 116.5, 114.2, 110.6, 107.1, 41.8, 14.9; **HRMS** (ESI, m/z) calcd for $C_{12}H_{11}F_3NO_3$ $[M+H]^+$ 274.0691, found 274.0688.

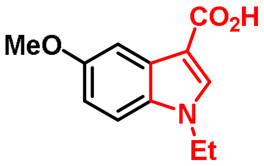
5-chloro-1-ethyl-1*H*-indole-3-carboxylic acid (2i):



2i

Off-white solid (23.7 mg, 53% yield); column chromatography eluent, petroleum ether/EtOAc = 4:1; mp 168-170 °C; (Due to solubility problem, a few drops of CD$_3$OD was added with CDCl$_3$) **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 8.14 (d, J = 2.0 Hz, 1H), 7.86 (s, 1H), 7.24 (d, J = 2.3 Hz, 1H), 7.19 (dd, J = 8.7, 2.0 Hz, 1H), 4.15 (q, J = 7.3 Hz, 2H), 1.47 (t, J = 7.3 Hz, 3H); **^{13}C NMR** (101 MHz, Chloroform-*d*) δ 167.6, 135.1, 134.7, 128.0, 127.9, 123.0, 121.3, 110.9, 106.4, 41.8, 15.0; **HRMS** (ESI, m/z) calcd for $C_{11}H_{11}ClNO_2$ $[M+H]^+$ 224.0478, found 224.0477.

1-ethyl-5-methoxy-1*H*-indole-3-carboxylic acid (2j):

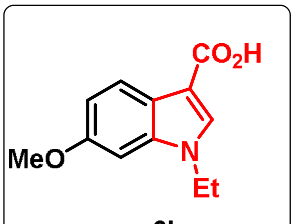


2j

Off-white solid (23 mg, 53% yield); column chromatography eluent, petroleum ether/EtOAc = 4:1; mp 168-170 °C; **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 7.89 (s, 1H), 7.70 (d, J = 2.4 Hz, 1H), 7.26 (d, J =

9.3 Hz, 1H), 6.93 (dd, J = 8.9, 2.5 Hz, 1H), 4.17 (q, J = 7.3 Hz, 2H), 3.91 (s, 3H), 1.52 (t, J = 7.3 Hz, 3H); **^{13}C NMR** (101 MHz, Chloroform-*d*) δ 170.7, 156.0, 134.6, 131.5, 127.9, 113.4, 110.8, 105.8, 103.1, 55.8, 41.9, 15.1; **HRMS** (ESI, m/z) calcd for $C_{12}H_{14}NO_3[M+H]^+$ 220.0974 found 220.0978.

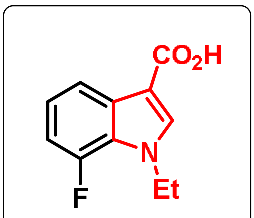
1-ethyl-6-methoxy-1*H*-indole-3-carboxylic acid (2k):



2k

Off-white solid (31 mg, 71% yield); column chromatography eluent, petroleum ether/EtOAc = 4:1; mp 168-170 °C; **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 8.11 (d, J = 8.7 Hz, 1H), 7.86 (s, 1H), 6.96 (dd, J = 8.8, 2.2 Hz, 1H), 6.83 (d, J = 2.1 Hz, 1H), 4.16 (q, J = 7.3 Hz, 2H), 3.89 (s, 3H), 1.53 (t, J = 7.3 Hz, 3H); **^{13}C NMR** (101 MHz, Chloroform-*d*) δ 170.6, 156.9, 137.2, 133.8, 122.6, 121.1, 111.5, 106.4, 93.7, 55.7, 41.6, 14.9; **HRMS** (ESI, m/z) calcd for $C_{12}H_{14}NO_3$ $[M+H]^+$ 220.0974, found 220.0976.

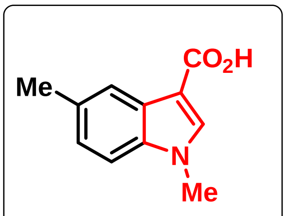
1-ethyl-7-fluoro-1*H*-indole-3-carboxylic acid (2l):



2l

Colorless solid (24 mg, 58% yield); column chromatography eluent, petroleum ether/EtOAc = 4:1; mp 172-174 °C; (Due to solubility problem, a few drops of CD_3OD was added with $CDCl_3$) **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 7.91 (d, J = 8.0 Hz, 1H), 7.80 (s, 1H), 7.11 (td, J = 8.0, 4.6 Hz, 1H), 6.93 – 6.88 (m, 1H), 4.32 (q, J = 7.2 Hz, 2H), 1.47 (t, J = 7.2 Hz, 3H); **^{13}C NMR** (101 MHz, Chloroform-*d*)δ 167.7, 149.9 (d, $^1J_{F\text{-}C}$ = 245.8 Hz), 135.7, 130.7 (d, $^3J_{F\text{-}C}$ = 4.7 Hz), 124.2 (d, $^2J_{F\text{-}C}$ = 9.9 Hz), 122.2 (d, $^3J_{F\text{-}C}$ = 6.6 Hz), 117.4 (d, $^4J_{F\text{-}C}$ = 3.4 Hz), 108.3 (d, $^2J_{F\text{-}C}$ = 17.9 Hz), 107.3, 44.6 (d, J = 5.3 Hz), 16.3; **HRMS** (ESI, m/z) calcd for $C_{11}H_{11}FNO_2$ $[M+H]^+$ 208.0774, found 208.0772.

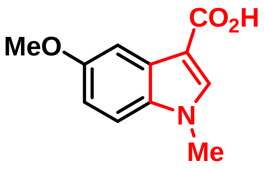
1,5-dimethyl-1*H*-indole-3-carboxylic acid (2m):



2m

Brown solid (22 mg, 58% yield); column chromatography eluent, petroleum ether/EtOAc = 4:1; mp 214-216 °C; (Due to solubility problem, a few drops of CD_3OD was added with $CDCl_3$) **^{1}H NMR** (400 MHz, Chloroform-*d*)δ 7.80 – 7.75 (m, 1H), 7.62 (s, 1H), 7.09 (d, J = 8.4 Hz, 1H), 6.97 – 6.94 (m, 1H), 3.66 (s, 3H), 2.31 (s, 3H); **^{13}C NMR** (101 MHz, Chloroform-*d*) δ 167.4, 135.6, 135.5, 131.1, 126.8, 124.0, 120.8, 109.2, 105.8, 33.0, 21.0; **HRMS** (ESI, m/z) calcd for $C_{11}H_{12}NO_2$ $[M+H]^+$ 190.0868, found 190.0867.

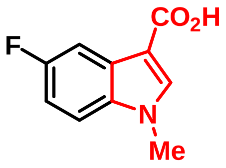
5-methoxy-1-methyl-1*H*-indole-3-carboxylic acid (2n)



2n

Brown solid (21 mg, 52% yield); column chromatography eluent, petroleum ether/EtOAc = 4:1; mp 212-214 °C; **^{1}H NMR** (400 MHz, DMSO-d_6) δ 7.95 (s, 1H), 7.48 (d, *J* = 2.4 Hz, 1H), 7.42 (d, *J* = 8.9 Hz, 1H), 6.87 (dd, *J* = 8.9, 2.5 Hz, 1H), 3.81 (s, 3H), 3.78 (s, 3H); **^{13}C NMR** (101 MHz, DMSO-d_6) δ 165.6, 155.1, 136.1, 132.1, 127.2, 112.2, 111.5, 105.7, 102.3, 55.3, 33.1; **HRMS** (ESI, m/z) calcd for $C_{11}H_{12}NO_3$ $[M+H]^+$ 206.0817, found 206.0809.

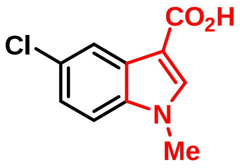
5-fluoro-1-methyl-1*H*-indole-3-carboxylic acid (2o)



2o

Brown solid (25 mg, 64% yield); column chromatography eluent, petroleum ether/EtOAc = 4:1; mp 214-216 °C; **^{1}H NMR** (400 MHz, Methanol-d_4) δ 7.95 (s, 1H), 7.72 (dd, *J* = 9.8, 2.5 Hz, 1H), 7.44 (dd, *J* = 8.9, 4.3 Hz, 1H), 7.04 (td, *J* = 9.1, 2.6 Hz, 1H), 3.87 (s, 3H); **^{13}C NMR** (101 MHz, Methanol-d_4) δ 168.4, 159.2 (d, $^1J_{F\text{-}C}$ = 237.4 Hz), 138.6, 135.5, 128.9 (d, $^3J_{F\text{-}C}$ = 11.0 Hz), 112.3 (d, $^3J_{F\text{-}C}$ = 10.1 Hz), 111.8 (d, $^2J_{F\text{-}C}$ = 27.3 Hz), 107.8 (d, $^4J_{F\text{-}C}$ = 4.0 Hz), 107.2 (d, $^2J_{F\text{-}C}$ = 25.1 Hz), 33.8; **HRMS**(ESI, m/z) calcd for $C_{10}H_9FNO_2$ $[M+H]^+$194.0617, found 194.0616.

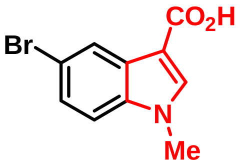
5-chloro-1-methyl-1*H*-indole-3-carboxylic acid (2p)



2p

Yellow solid (25.2 mg, 60% yield); column chromatography eluent, petroleum ether/EtOAc = 4:1; mp 217-218 °C; **^{1}H NMR** (400 MHz, Methanol-d_4) δ 8.06 (d, *J* = 1.9 Hz, 1H), 7.95 (s, 1H), 7.45 (d, *J* = 8.7 Hz, 1H), 7.24 (dd, *J* = 8.7, 2.0 Hz, 1H), 3.87 (s, 3H); **^{13}C NMR** (101 MHz, Methanol-d_4)δ 168.4, 138.3, 137.3, 129.3, 128.7, 127.8, 123.8, 121.7, 112.5, 33.7; **HRMS** (ESI, m/z) calcd for $C_{10}H_9ClNO_2$ $[M+H]^+$210.0322, found 210.0325.

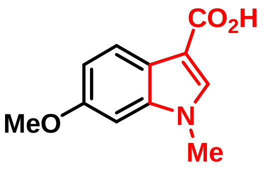
5-bromo-1-methyl-1*H*-indole-3-carboxylic acid (2q)



2q

Off-white solid (19.3 mg, 38% yield); column chromatography eluent, petroleum ether/EtOAc = 4:1; mp 193-196°C; **^{1}H NMR** (400 MHz, DMSO-d_6) δ 8.12 (d, *J* = 1.9 Hz, 1H), 8.08 (s, 1H), 7.53 (d, *J* = 8.7 Hz, 1H), 7.38 (dd, *J* = 8.7, 2.0 Hz, 1H), 3.85 (s, 3H); **^{13}C NMR** (101 MHz, DMSO-d_6) δ 165.2, 137.3, 135.8, 128.1, 124.7, 122.8, 114.3, 112.9, 105.8, 33.2; **HRMS** (ESI, m/z) calcd for $C_{10}H_9BrNO_2$ $[M+H]^+$ 253.9817, found 253.9806.

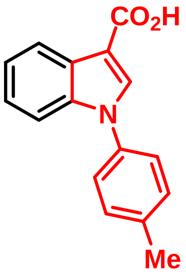
6-chloro-1-methyl-1*H*-indole-3-carboxylic acid (2r)



2r

Off-white solid (21 mg, 51% yield); column chromatography eluent, petroleum ether/EtOAc = 4:1; mp 155-157 °C; (Due to solubility problem, a few drops of CD_3OD was added with $CDCl_3$) **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 8.08 (d, *J* = 8.7 Hz, 1H), 7.78 (s, 1H), 6.96 (dd, *J* = 8.7, 2.0 Hz, 1H), 6.81 (d, *J* = 1.8 Hz, 1H), 3.90 (s, 3H), 3.81 (s, 3H); **^{13}C NMR** (101 MHz, Chloroform-*d*) δ 172.7, 156.9, 138.0, 135.1, 122.3, 120.9, 111.46, 106.5, 93.4, 55.7, 33.4; **HRMS** (ESI, m/z) calcd for $C_{11}H_{12}NO_3$ $[M+H]^+$ 206.0817, found 206.0816.

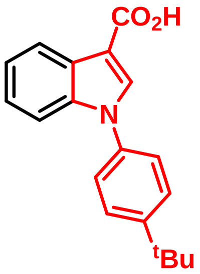
1-(p-tolyl)-1*H*-indole-3-carboxylic acid (2s)



2s

Off-white solid (38.2 mg, 76% yield); column chromatography eluent, petroleum ether/EtOAc = 4:1; mp 162-163 °C; **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 8.32 (d, *J* = 7.8 Hz, 1H), 8.11 (s, 1H), 7.49 (d, *J* = 8.1 Hz, 1H), 7.41 (d, *J* = 8.4 Hz, 2H), 7.38 – 7.28 (complex, 4H), 2.47 (s, 3H); **^{13}C NMR** (101 MHz, Chloroform-*d*) δ 170.5, 138.0, 137.0, 135.8, 135.5, 130.4, 127.0, 124.7, 123.5, 122.7, 121.9, 111.1, 108.1, 21.1; **HRMS** (ESI, m/z) calcd for $C_{16}H_{14}NO_2$ $[M+H]^+$252.1025, found 252.1032.

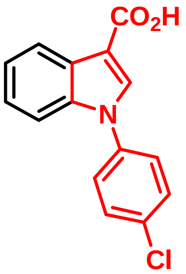
1-(4-(tert-butyl)phenyl)-1*H*-indole-3-carboxylic acid (2t)



2t

Off-white solid (45.6 mg, 76% yield); column chromatography eluent, petroleum ether/EtOAc = 4:1; mp 194-196 °C; (Due to solubility problem, a few drops of CD_3OD was added with $CDCl_3$) **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 8.25 – 8.20 (m, 1H), 8.02 (s, 1H), 7.55 – 7.49 (m, 2H), 7.47 (d, *J* = 7.8 Hz, 1H), 7.41 – 7.37 (complex, 2H), 7.31 – 7.20 (complex, 2H), 1.35 (s, 9H); **^{13}C NMR** (101 MHz, Chloroform-*d*) δ 167.9, 151.0, 136.8, 135.7 , 134.9, 127.0, 126.6, 124.3, 123.2, 122.3, 121.6, 111.1, 108.5, 31.2; **HRMS** (ESI, m/z) calcd for $C_{19}H_{20}NO_2$ $[M+H]^+$ 294.1494, found 294.1485.

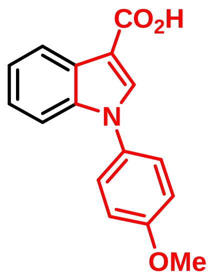
1-(4-chlorophenyl)-1*H*-indole-3-carboxylic acid (2u)



2u

Off-white solid(58 mg, 51% yield); column chromatography eluent, petroleum ether/EtOAc = 4:1; mp 193-194 °C; inseparable ICA and AA; **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 8.32 (d, *J* = 7.5 Hz, 1H), 8.09 (s, 1H), 7.58 – 7.53 (m, 2H), 7.51 – 7.45 (m, 2H), 7.40 – 7.30 (m, 2H), 7.23 – 7.15 (m, 1H); **^{13}C NMR** (101 MHz, Chloroform-*d*) δ 170.2, 136.8, 136.8, 135.1, 133.8, 130.1, 129.5, 126.1, 124.1, 123.9, 123.0, 122.1, 110.9; **HRMS** (ESI, m/z) calcd for $C_{15}H_{11}ClNO_2$ $[M+H]^+$272.0478, found 272.0466.

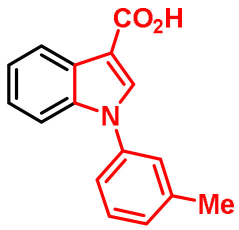
1-(4-methoxyphenyl)-1*H*-indole-3-carboxylic acid (2v)



2v

Off-white solid (26.7 mg, 50% yield); column chromatography eluent, petroleum ether/EtOAc = 4:1; mp 164-165 °C; **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 8.35 – 8.28 (m, 1H), 8.08 (s, 1H), 7.47 – 7.40 (m, 3H), 7.32 (comp, 2H), 7.11 – 7.03 (m, 2H), 3.90 (s, 3H); **^{13}C NMR** (101 MHz, Chloroform-*d*) δ 170.4, 159.3, 137.4, 135.7, 131.2, 126.9, 126.4, 123.4, 122.6, 121.9, 114.9, 111.0, 107.9, 55.6; **HRMS** (ESI, m/z) calcd for $C_{16}H_{14}NO_3$ $[M+H]^+$268.0974, found 268.0974.

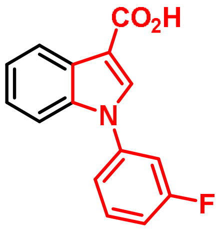
1-(m-tolyl)-1*H*-indole-3-carboxylic acid (2w)



2w

Off-white solid (40.2 mg, 80% yield); column chromatography eluent, petroleum ether/EtOAc = 4:1; mp 162-163 °C; **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 8.25 (d, *J* = 7.7 Hz, 1H), 8.05 (s, 1H), 7.44 (d, *J* = 8.0 Hz, 1H), 7.37 (t, *J* = 7.9 Hz, 1H), 7.23 (comp, 5H), 2.39 (s, 3H); **^{13}C NMR** (101 MHz, Chloroform-*d*)δ 170.7, 140.0, 138.3, 136.9, 135.5, 129.6, 128.7, 127.1, 125.4, 123.5, 122.7, 121.9, 121.9, 111.2, 108.2, 21.4; **HRMS** (ESI, m/z) calcd for $C_{16}H_{14}NO_2$ $[M+H]^+$252.1025, found 252.1032.

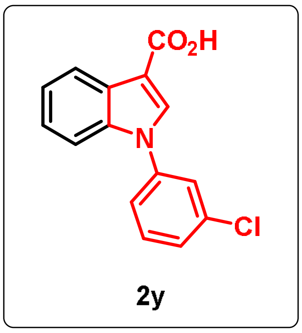
1-(3-fluorophenyl)-1*H*-indole-3-carboxylic acid (2x)



2x

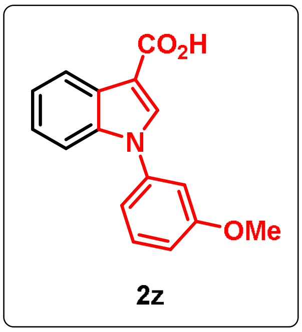
White solid (39.3 mg, 77% yield); column chromatography eluent, petroleum ether/EtOAc = 4:1; mp 162-164 °C; **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 8.35 – 8.30 (m, 1H), 8.12 (s, 1H), 7.59 – 7.51 (m, 2H), 7.41 – 7.32 (m, 3H), 7.29 (app dt, *J* = 9.3, 2.2 Hz, 1H), 7.22 – 7.16 (m, 1H); **^{13}C NMR** (101 MHz, Chloroform-*d*)δ 170.2, 163.3 (d, $^1J_{F\text{-}C}$ = 250.5 Hz), 139.7 (d, $^3J_{F\text{-}C}$ = 9.8 Hz), 136.6, 135.0, 131.2 (d, $^3J_{F\text{-}C}$ = 9.3 Hz), 127.1, 123.9, 123.1, 122.1, 120.4 (d, $^4J_{F\text{-}C}$ = 3.0 Hz), 115.0 (d, $^2J_{F\text{-}C}$ = 21.0 Hz), 112.3 (d, $^2J_{F\text{-}C}$ = 24.0 Hz), 110.9, 109.0; **HRMS** (ESI, m/z) calcd for $C_{15}H_{11}NO_2$ $[M+H]^+$ 256.0774, found 256.0771.

1-(3-chlorophenyl)-1*H*-indole-3-carboxylic acid (2y)


2y

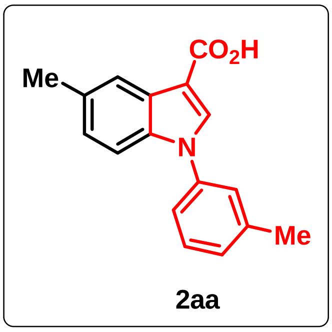
White solid (20.1 mg, 37% yield); column chromatography eluent, petroleum ether/EtOAc = 4:1; mp 207-209 °C; **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 8.22 – 8.13 (m, 1H), 7.96 (s, 1H), 7.51 – 7.38 (m, 3H), 7.37 – 7.31 (m, 2H), 7.24 (comp, 2H); **^{13}C NMR** (101 MHz, Chloroform-*d*) δ 167.1, 139.4, 136.4, 135.3, 134.2, 130.8, 127.8, 127.0, 124.8, 123.6, 122.7, 122.6, 121.8, 110.6, 109.6; **HRMS** (ESI, m/z) calcd for $C_{15}H_{11}ClNO_2$ $[M+H]^+$ 272.0478, found 272.0468.

1-(3-methoxyphenyl)-1*H*-indole-3-carboxylic acid (2z)


2z

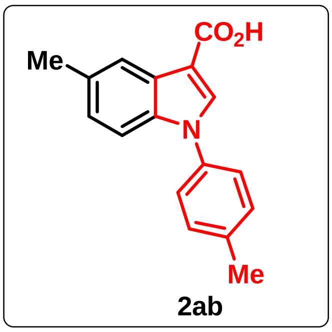
White solid (35.3 mg, 66% yield); column chromatography eluent, petroleum ether/EtOAc = 4:1; mp 190 °C; (Due to solubility problem, a few drops of CD_3OD was added with $CDCl_3$) **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 8.14 (app dd, *J* = 6.7, 1.8 Hz, 1H), 7.96 (s, 1H), 7.44 (app dd, *J* = 6.9, 1.5 Hz, 1H), 7.35 (t, *J* = 8.1 Hz, 1H), 7.20 (comp, 2H), 7.03 – 6.98 (m, 1H), 6.95 (app t, *J* = 2.2 Hz, 1H), 6.89 (app dd, *J* = 8.1, 2.2 Hz, 1H), 3.77 (s, 3H); **^{13}C NMR** (101 MHz, Chloroform-*d*) δ 167.3, 160.4, 139.3, 136.5, 134.5, 130.4, 126.9, 123.2, 122.3, 121.5, 116.7, 113.2, 110.9, 110.4, 108.8, 55.3; **HRMS** (ESI, m/z) calcd for $C_{10}H_{10}NO_2$ $[M+H]^+$ 268.0974, found 268.0966.

5-methyl-1-(m-tolyl)-1*H*-indole-3-carboxylic acid (2aa)


2aa

Colorless solid (28.1 mg, 53% yield); column chromatography eluent, petroleum ether/EtOAc = 4:1; mp 202-203 °C; (Due to solubility problem, a few drops of $CDCl_3$ was added with CD_3OD) **^{1}H NMR** (400 MHz, Methanol-d_4) δ 8.01 – 7.99 (m, 1H), 7.97 (s, 1H), 7.80 (d, *J* = 1.0 Hz, 1H), 7.43 (t, *J* = 7.7 Hz, 1H), 7.36 – 7.30 (comp, 2H), 7.29 – 7.24 (m, 1H), 7.07 (d, *J* = 8.5 Hz, 1H), 2.46 (s, 3H), 2.43 (s, 3H); **^{13}C NMR** (101 MHz, Methanol-d_4) δ 168.6, 141.2, 139.7, 136.4, 135.6, 132.8, 130.6, 129.4, 128.6, 126.1, 125.8, 122.6, 122.2, 111.7, 109.5, 21.7, 21.4; **HRMS** (ESI, m/z) calcd for $C_{17}H_{16}NO_2$ $[M+H]^+$ 266.1181, found 266.1183.

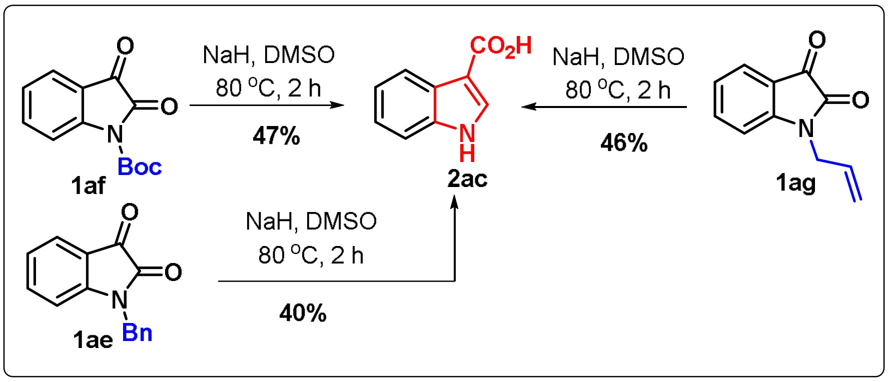
5-methyl-1-(*p*-tolyl)-1*H*-indole-3-carboxylic acid (2ab)


2ab

Off-white solid (40.3 mg, 76% yield); column chromatography eluent, petroleum ether/EtOAc = 4:1; mp 210-212 °C; (Due to solubility problem, a few drops of $CDCl_3$ was added with CD_3OD) **^{1}H NMR** (400 MHz, Methanol-*d*$_4$) δ 7.97 (d, *J* = 3.7 Hz, 2H), 7.67 (s, 1H), 7.38-7.35 (comp, 3H), 7.32 (d, *J* = 8.4 Hz, 1H), 7.06 (d, *J* = 8.3 Hz, 1H), 2.46 (s, 3H), 2.42 (s, 3H); **^{13}C NMR** (101 MHz, Methanol-*d*$_4$) δ 168.4, 138.6, 136.9, 136.2, 135.4, 132.6, 131.1, 128.2, 125.6, 125.3, 122.0, 111.5, 109.1, 21.7, 21.2; **HRMS** (ESI, m/z) calcd for $C_{17}H_{16}NO_2$ $[M+H]^+$ 266.1181, found 266.1183.

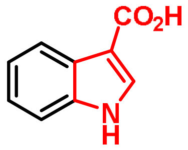
5.5.10 General procedure for the preparation of 1*H*-indole-3-carboxylic acid (2ac)

Into a 10 mL two-neck round bottom flask equipped with an electromagnetic stirrer N-alkyl isatins (1 equiv., 0.2 mmol) and DMSO solvent (2 mL, 0.1 M) were taken in an inert atmosphere. Then the whole reaction mixture was degassed by the Freeze-Pump-Thaw method. After degassing, NaH (6 equiv., 1.2 mmol) was added portion-wise using a solid additional funnel and stirred at room temperature (30 °C) for 10 minutes. After that, the reaction mixture was warmed slowly to 80 °C and kept for 2 hours. After the full conversion was monitored by TLC, it was cooled to room temperature and quenched with cold 1N HCl solution (20 mL). The organic part was extracted by EtOAc (3x20 mL) with brine, dried over Na_2SO_4, and concentrated under reduced pressure. Finally, it was purified by column chromatography on silica gel (230-400 mesh) using petroleum ether/ethyl acetate (4:1) as eluent to obtain the desired 1*H*-indole-3-carboxylic acid (**2ac**) in 40-47% yield.



5.5.11 Characterization of the substrate 2ac

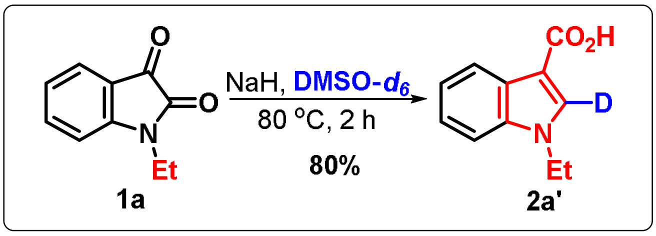
1*H*-indole-3-carboxylic acid (2ac)



2ac

White solid (40-47% yield); column chromatography eluent, petroleum ether/EtOAc = 4:1; mp 232-234 °C; ^{1}**H NMR** (400 MHz, Methanol-*d*^{4}) δ 8.11 – 8.03 (m, 1H), 7.94 (s, 1H), 7.46 – 7.39 (m, 1H), 7.24 – 7.12 (m, 2H); ^{13}**C NMR** (101 MHz, Methanol-*d*^{4}) δ 169.2, 138.2, 133.4, 127.6, 123.6, 122.4, 122.0, 112.9, 108.7; **HRMS** (ESI, m/z) calcd for $C_9H_8NO_2$ $[M+H]^+$ 162.0555, found 162.0556.

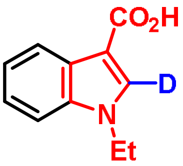
5.5.12 General procedure for the preparation of (2a′)



Into a 10 mL two neck round bottom flask equipped with an electromagnetic stirrer, N-ethyl isatin (1 equiv., 0.2 mmol, 35 mg) and DMSO-*d*$_6$ solvent (1 mL, 0.2 M) were taken under in an inert atmosphere. Then the whole reaction mixture was subjected to degas by the Freeze-Pump-Thaw method. After degassing, NaH (6 equiv., 1.2 mmol) was added portion-wise through an additional funnel and stirred at room temperature (30 °C) for 5 minutes. After that, the reaction mixture was warmed slowly to 80 °C and kept for 2 hours. After the full conversion was monitored by TLC, it was cooled to room temperature and quenched with cold 1N HCl solution (20 mL). The organic part was extracted by EtOAc (3x20 mL) with brine, dried over Na_2SO_4, and concentrated under reduced pressure. Finally, it was purified by column chromatography on silica gel (230-400 mesh) using petroleum ether/ethyl acetate (4:1) as eluent to obtain the desired 2-deuterio-1-ethyl indole-3-carboxylic acid **(2a′)** in 80% yield (30.4 mg). The rest all 2-deuterio indole-3-carboxylic acid derivatives were prepared following this procedure.

5.5.13 Characterization data of 2a′

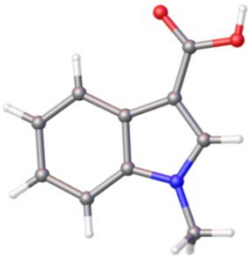
1-ethyl-1*H*-indole-3-carboxylic-2-d acid (2a′)



2a'

Colorless solid (30.4 mg, 80% yield); column chromatography eluent: petroleum ether/EtOAc = 4:1; mp 168-170 °C; ^{1}**H NMR (400 MHz, CDCl$_3$**) δ 8.28-8.24 (m, 1H), 7.41-7.38 (m, 1H), 7.34-7.29 (comp, 2H), 4.23 (q, $J = 7.2$ Hz, 2H), 1.55 (t, $J = 7.2$ Hz, 3H); ^{13}**C NMR (101MHz, CDCl$_3$**) δ 170.6, 136.4, 134.5 (t, $J = 2.8$ Hz), 127.0, 122.8, 122.1, 121.9, 109.9, 106.2, 41.7, 15.1; **HRMS** (ESI, m/z) calcd for $C_{11}H_{11}DNO_2$ $[M+H]^+$ 191.0931, found 191.0932.

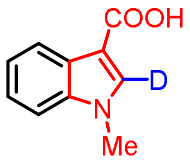
Table 5.5.14: Crystal Data and Structure of 2a′ (CCDC No. **2213917**)



Empirical formula	$C_{10}H_8DNO_2$
Formula weight	176.19
Temperature/K	150.0
Crystal system	monoclinic
Space group	$P2_1/n$
a/Å	5.0244(4)
b/Å	29.261(2)
c/Å	5.9187(5)
α/°	90
β/°	100.326(5)
γ/°	90
Volume/Å^3	856.08(12)
Z	4
ρ_{calc}g/cm^3	1.367
μ/mm^{-1}	0.788
F(000)	368.0
Crystal size/mm^3	0.15 × 0.12 × 0.06
Radiation	Cu Kα (λ = 1.54178)
2Θ range for data collection/°	6.04 to 133.4
Index ranges	$-5 \leq h \leq 5$, $-34 \leq k \leq 34$, $-7 \leq l \leq 7$
Reflections collected	12421
Independent reflections	1498 [R_{int} = 0.0777, R_{sigma} = 0.0446]
Data/restraints/parameters	1498/0/121
Goodness-of-fit on F^2	1.244
Final R indexes [I>=2σ (I)]	R_1 = 0.0913, wR_2 = 0.1625
Final R indexes [all data]	R_1 = 0.0962, wR_2 = 0.1647

5.5.15 Characterization of the compounds 2b′-2s′

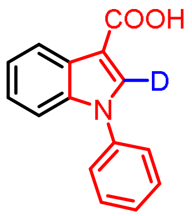
1-methyl-1*H*-indole-3-carboxylic-2-*d* acid (2b′):



2b'

Off-white solid (21.7 mg, 62% yield); column chromatography eluent: petroleum ether/EtOAc = 4:1; **^{1}H NMR (400 MHz, $CDCl_3$+0.1 mL CD_3OD)** δ 8.15-8.11 (m, 1H), 7.33-7.30 (m, 1H), 7.28-7.21 (comp, 2H), 3.80 (s, 3H); **^{13}C NMR (101 MHz, $CDCl_3$+0.1 mL CD_3OD)** δ 167.6, 137.2, 126.7, 122.6, 121.8, 121.5, 109.7, 106.3, 33.2; **HRMS** (ESI, m/z) calcd for $C_{10}H_9DNO_2$ $[M+H]^+$ 177.0774, found 177.0777.

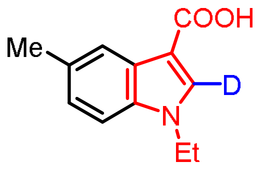
1-phenyl-1*H*-indole-3-carboxylic-2-*d* acid (2c′):



2c'

Colorless solid (25.6mg, 54% yield); column chromatography eluent: petroleum ether/EtOAc = 4:1; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.34 (dd, *J* = 7.2 Hz, 0.8 Hz, 1H), 7.60 – 7.52 (comp, 5H), 7.48 (tt, *J* = 7.2 Hz, 2.0 Hz, 1H), 7.40 – 7.36 (m, 1H), 7.34 – 7.30 (m, 1H); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 170.6, 138.3, 136.9, 129.9, 128.0, 127.1, 124.8, 123.6, 122.8, 122.0, 111.1, 108.3; **HRMS** (ESI, m/z) calcd for $C_{15}H_{11}DNO_2$ $[M+H]^+$ 239.0931, found 239.0932.

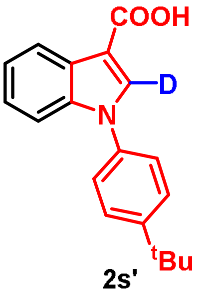
1-ethyl-5-methyl-1*H*-indole-3-carboxylic-2-*d* acid (2f′):



2f'

Colorless solid (26.5 mg, 65% yield); column chromatography eluent: petroleum ether/EtOAc = 4:1; **^{1}H NMR (400 MHz, $CDCl_3$+0.1 mL CD_3OD)** δ 7.99 (app s, 1H), 7.25 (app d, *J* = 7.6 Hz,1H), 7.10 (d, *J* = 8.0 Hz,1H),4.16 (q, *J* = 7.2 Hz, 2H), 2.48 (s, 1H), 1.49 (t, *J* = 7.2 Hz, 3H); **^{13}C NMR (101 MHz, $CDCl_3$+0.1 mL CD_3OD)** δ 168.5, 134.7, 131.5, 127.2, 124.2, 121.4, 109.5, 105.7, 41.6, 21.4, 15.0; **HRMS**(EI, m/z) calcd for $C_{12}H_{12}DNO_2$ $[M]^+$ 204.1009, found 204.1007.

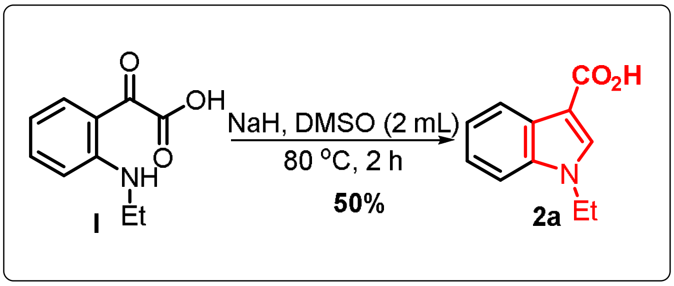
1-(4-(tert-butyl)phenyl)-1*H*-indole-3-carboxylic-2-*d* acid (2s′):



2s'

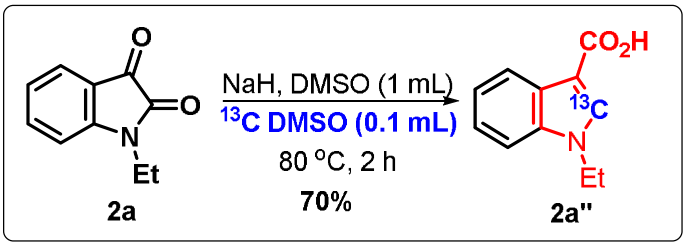
Off-white solid (33.8 mg, 57% yield); column chromatography eluent: petroleum ether/EtOAc = 4:1; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.33 (dd, *J* = 7.2 Hz, 0.8 Hz, 1H), 7.60 – 7.56 (comp, 2H), 7.53 (app d, *J* = 8.0 Hz, 1H), 7.48 – 7.44 (comp, 2H), 7.38 – 7.34 (m, 1H), 7.33 – 7.29 (m, 1H), 1.41 (s, 9H); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 170.6, 151.2, 137.0, 135.7, 135.6, 127.0, 126.7, 124.4, 123.4, 122.7, 121.9, 111.2, 108.0, 34.8, 31.3; **HRMS** (ESI, m/z) calcd for $C_{19}H_{19}DNO_2$ $[M+H]^+$ 295.1557, found 295.1556.

5.5.16 General procedure for the preparation of (2a) from compound I



Into a 10 mL two neck round bottom flask equipped with an electromagnetic stirrer, 2-(2-(ethylamino)phenyl)-2-oxoacetic acid (**4**) (1 equiv., 0.2 mmol, 39 mg) and DMSO solvent (2 mL, 0.1 M) was taken in an inert atmosphere. Then the whole reaction mixture was subjected to degas by the Freeze-Pump-Thaw method. After degassing, NaH (6 equiv., 1.2 mmol) was added portion-wise through an additional funnel and stirred at room temperature (30 °C) for 5 minutes. After that, the reaction mixture was warmed slowly to 80 °C and kept for 2 hours. After the full conversion was monitored by TLC, it was cooled to room temperature and quenched with cold 1N HCl solution (20 mL). The organic part was extracted by EtOAc (3x20 mL) with brine, dried over Na_2SO_4, and concentrated under reduced pressure. Finally, it was purified by column chromatography on silica gel (230-400 mesh) using petroleum ether/ethyl acetate (4:1) as eluent to obtain the desired 1-ethyl-1*H*-indole-3-carboxylic acid (**2a**) in 50% yield (19 mg).

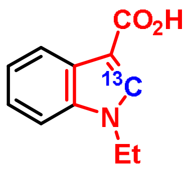
5.5.17 General procedure for the preparation of (2a″)



Into a 10 mL two neck round bottom flask equipped with an electromagnetic stirrer, N-ethyl isatin (1 equiv., 0.2 mmol, 35 mg), DMSO (1 mL, 0.2 M), and ^{13}C DMSO (0.1 mL) solvent were taken under in an inert atmosphere. Then the whole reaction mixture was subjected to degas by the Freeze-Pump-Thaw method. After degassing, NaH (6 equiv., 1.2 mmol) was added pinch-wise through an additional funnel and stirred at room temperature (30 °C) for 5 minutes. After that, the reaction mixture was warmed slowly to 80 °C and kept for 2 hours. After the full conversion was monitored by TLC, it was cooled to room temperature and quenched with cold 1N HCl solution (20 mL). The organic part was extracted by EtOAc (3x20 mL) with brine, dried over Na_2SO_4, and concentrated under reduced pressure. Finally, it was purified by column chromatography on silica gel (230-400 mesh) using petroleum ether/ethyl acetate (4:1) as eluent to obtain the desired 2-deuterio-1-ethyl-1H-indole-3-carboxylic acid (**2a′′**) in 70% yield (26.6 mg).

5.5.18 Characterization data of 2a′′

1-ethyl-1*H*-indole-3-carboxylic acid (C_2-^{13}C) (2a′′)

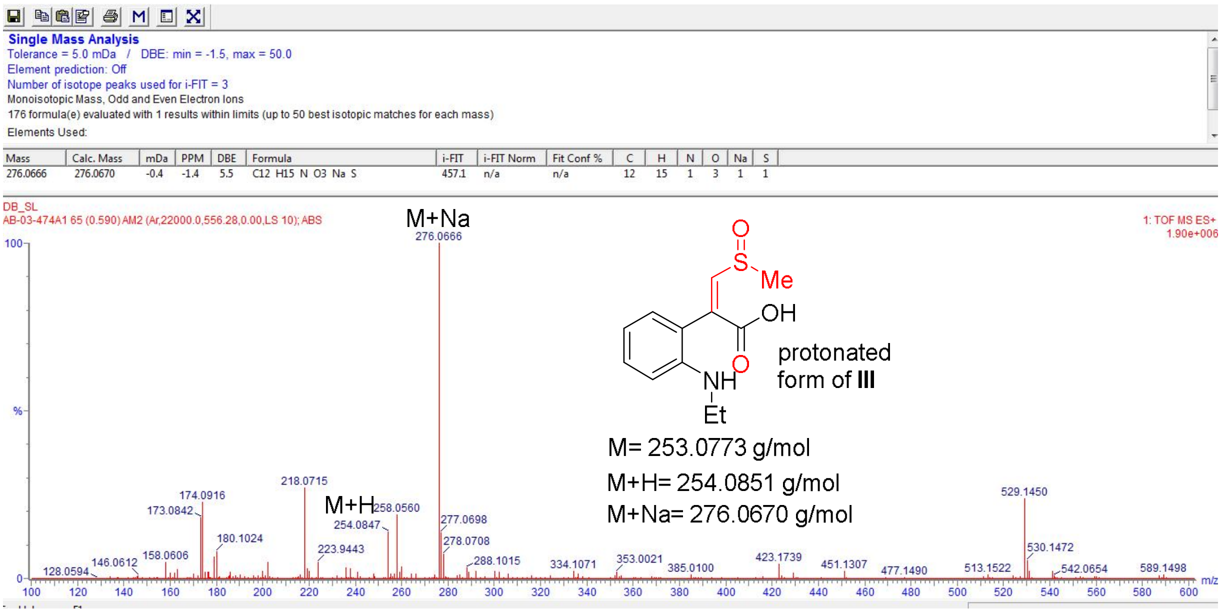


2a"

White solid (26.6 mg, 70% yield); column chromatography eluent, petroleum ether/EtOAc = 4:1; mp 168-170 °C; **^{1}H NMR (400 MHz, Chloroform-*d*)** δ 8.27 – 8.22 (m, 1H), 7.96 (s, 1H), 7.40 (app dt, *J* = 7.3, 3.2 Hz, 1H), 7.34 – 7.28 (m, 2H), 4.23 (q, *J* = 7.3 Hz, 2H), 1.55 (t, *J* = 7.3 Hz, 3H); **^{13}C NMR (101MHz, Chloroform-*d*)** δ 170.2, 136.5, 134.7(sharp), 127.0, 122.8, 122.1, 121.9, 109.9, 106.3, 41.7, 15.1; **HRMS**(ESI, m/z) calcd for $C_{11}H_{12}NO_2$ $[M+H]^+$191.0902, found 191.0898.

5.5.19 Detection of the intermediate III by ESIMS

The reaction was quenched after 30 minute and crude sample was submitted for ESIMS.

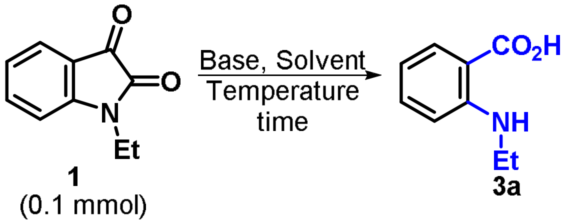


Single Mass Analysis
Tolerance = 5.0 mDa / DBE: min = -1.5, max = 50.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3
Monoisotopic Mass, Odd and Even Electron Ions
176 formula(e) evaluated with 1 results within limits (up to 50 best isotopic matches for each mass)
Elements Used:

Mass	Calc. Mass	mDa	PPM	DBE	Formula	i-FIT	i-FIT Norm	Fit Conf %	C	H	N	O	Na	S
276.0666	276.0670	-0.4	-1.4	5.5	C12 H15 N O3 Na S	457.1	n/a	n/a	12	15	1	3	1	1

DB_SL
AB-03-474A1 65 (0.590) AM2 (Ar,22000.0,556.28,0.00,LS 10); ABS

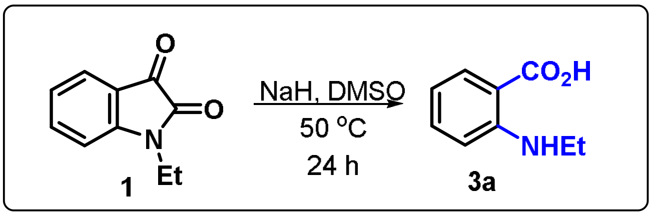
Table 5.5.20: Screening of the reaction conditions[a]



entry	base (x equiv.)	solvent (x mL)	temperature (°C)	reaction atmosphere	time (h)	yield[b] (%)
1[c]	NaH (4)	DMSO (1)	rt (33)	air	48	12
2[c]	NaH (4)	DMSO (1)	rt (33)	O_2 balloon	48	18
3[c]	NaH (6)	DMSO (1)	rt (33)	air	48	12
4[c]	NaH (6)	DMSO (1)	40-50	O_2 balloon	24	30
5[d]	NaH (6)	DMSO (1)	50	O_2 balloon	24	73
6[d]	**NaH (6)**	**DMSO (1)**	**50**	**air**	**24**	**85**
7[d]	NaH (6)	DMSO (1)	60	O_2 balloon	24	61
8[d]	NaH (6)	DMSO (1)	60	air	24	61
9[d]	NaH (4)	DMSO (1)	50	air	24	61
10[d,e]	NaH (6)	DMSO (1)	50	N_2 balloon	24	12
11[f]	NaH (6)	DMF (1)	50	air	24	67

[a]All reactions were set up on a 0.1 mmol scale in presence of NaH in DMSO solvent [b]Isolated yield. [c]Conditions: **1** (1 equiv.), NaH (4-6 equiv.) in an a bottle grade DMSO solvent (1 mL) at rt to 50 °C. [d]Conditions: **1** (1 equiv.), NaH (4-6 equiv.) in an anhydrous DMSO solvent (1 mL) at 50-60 °C. [e]Applying the Freeze-Pump-Thaw method. [f]Reaction happened in anhydrous DMF solvent.

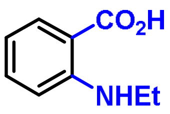
5.5.21 General procedure for the preparation of 2-(ethylamino)benzoic acid (3a)



Into a 10 mL two neck round bottom flask equipped with an electromagnetic stirrer, N-ethyl isatin (1 equiv., 0.2 mmol, 35 mg) and DMSO solvent (2 mL, 0.1 M) were taken in an inert atmosphere. Sodium hydride (6 equiv., 1.2 mmol) was added pinch-wise through an additional funnel and stirred at room temperature (30 °C) for 10 minutes. After that, the reaction mixture was warmed slowly to 50 °C and kept for 24 hours. After the full conversion was monitored by TLC, it was cooled to room temperature and quenched with cold 1N HCl solution (20 mL). The organic part was extracted by EtOAc (3x20 mL) with brine, dried over Na_2SO_4, and concentrated under reduced pressure. Finally, it was purified by column chromatography on silica gel (230-400 mesh) using petroleum ether/ethyl acetate (4:1) as eluent to obtain the desired 2-(ethylamino)benzoic acid (**3a**) in 85% yield (30 mg). The rest of the anthranilic acid derivatives were prepared following this procedure.

5.5.22 Characterization of the substrate 3a-3aa:

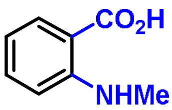
2-(ethylamino)benzoic acid (3a)



3a

Colorless solid (28 mg, 85% yield); column chromatography eluent, petroleum ether/EtOAc = 4:1; mp 148-152 °C; **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 7.98 (app dd, *J* = 8.1, 1.6 Hz, 1H), 7.40 (comp, 1H), 6.71 (app d, *J* = 8.5 Hz, 1H), 6.64 – 6.60 (m, 1H), 3.27 (q, *J* = 7.2 Hz, 2H), 1.33 (t, *J* = 7.2 Hz, 3H); **^{13}C NMR** (101MHz, Chloroform-*d*) δ 173.8, 151.6, 135.6, 132.7, 114.6, 111.5, 108.6, 37.5, 14.5; **HRMS** (ESI, m/z) calcd for $C_9H_{12}NO_2$ $[M+H]^+$166.0868, found 166.0869.

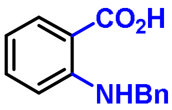
2-(methylamino)benzoic acid (3b)



3b

Yellowish solid (27.5 mg, 91% yield); column chromatography eluent, petroleum ether/EtOAc = 4:1; mp 176-178 °C; **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 7.99 (app dd, *J* = 8.0, 1.6 Hz, 1H), 7.44 (comp, 1H), 6.71 (d, *J*= 8.4 Hz, 1H),6.66-6.62 (m, 1H), 2.94 (s, 3H); **^{13}C NMR** (101MHz, Chloroform-*d*) δ 173.9, 152.4, 135.7, 132.6, 114.8, 111.1, 108.8, 29.7; **HRMS** (ESI, m/z) calcd for $C_8H_{10}NO_2$ $[M+H]^+$ 152.0712, found 152.0718.

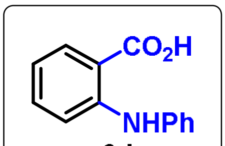
2-(benzylamino)benzoic acid (3c)



3c

Off-white solid (42.6 mg, 94% yield); column chromatography eluent, petroleum ether/EtOAc = 4:1; mp 166-168 °C; (Due to solubility problem, a few drops of CD_3OD was added with $CDCl_3$) **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 7.88 (app d, *J* = 8.0 Hz, 1H), 7.34 – 7.07 (comp, 6H), 6.54 (comp, 2H), 4.35 (d, *J* = 10.1 Hz, 2H); **^{13}C NMR** (101 MHz, Chloroform-*d*) δ 170.9, 150.8, 138.6, 134.5, 132.1, 128.4, 126.9, 126.9, 114.9, 111.6, 110.2, 46.8; **HRMS** (ESI, m/z) calcd for $C_{14}H_{14}NO_2$ $[M+H]^+$ 228.1025, found 228.1031.

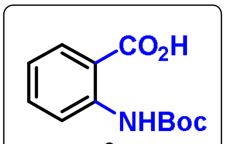
2-(phenylamino)benzoic acid (3d)



3d

Colorless solid (34.1 mg, 80% yield); column chromatography eluent, petroleum ether/EtOAc = 4:1; mp 184-186 °C; ^{1}**H NMR** (400 MHz, Chloroform-*d*) δ 9.32 (br s, 1H), 8.05 (app dd, *J* = 8.1, 1.5 Hz, 1H), 7.40 – 7.33 (comp, 3H), 7.30 – 7.25 (comp, 2H), 7.25 – 7.21 (m, 1H), 7.16 – 7.11 (m, 1H), 6.76 (app td, *J* = 7.6, 7.1, 1.0 Hz, 1H); ^{13}**C NMR** (101MHz, Chloroform-*d*) δ 173.3, 148.9, 140.3, 135.2, 132.6, 129.4, 124.1, 123.2, 117.2, 114.0, 110.4; **HRMS**(ESI, m/z) calcd for $C_{13}H_{12}NO_2$ $[M+H]^+$ 214.0868, found 214.0871.

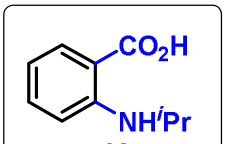
2-((tert-butoxycarbonyl)amino)benzoic acid (3e)



3e

Colorless solid (25.1 mg, 53% yield); column chromatography eluent, petroleum ether/EtOAc = 4:1; mp 165-166 °C; ^{1}**H NMR** (400 MHz, Chloroform-*d*) δ 10.02 (s, 1H), 8.47 (d, *J* = 8.5 Hz, 1H), 8.11 (app dd, *J* = 8.0, 1.6 Hz, 1H), 7.59 – 7.55 (m, 1H), 7.06 – 7.02 (m, 1H), 1.55 (s, 9H); ^{13}**C NMR** (101MHz, Chloroform-*d*) δ 172.4, 152.8, 142.9, 135.6, 131.9, 121.3, 119.0, 113.2, 80.9, 28.3; **HRMS** (ESI, m/z) calcd for $C_{12}H_{16}NO_4$ $[M+H]^+$ 238.1079, found 238.1078.

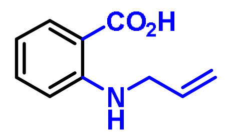
2-(isopropylamino)benzoic acid (3f)



3f

Colorless solid (29.7 mg, 83% yield); column chromatography eluent, petroleum ether/EtOAc = 4:1; mp 148-150 °C; ^{1}**H NMR** (400 MHz, Chloroform-*d*) δ 7.97 (app dd, *J* = 8.1, 1.7 Hz, 1H), 7.38 (comp, 1H), 6.71 (d, *J* = 8.6 Hz, 1H), 6.57 (comp, 1H), 3.74 (hept, *J* = 6.2 Hz, 1H), 1.29 (d, *J* = 6.3 Hz, 6H); ^{13}**C NMR** (101MHz, Chloroform-*d*) δ 173.4, 151.0, 135.5, 132.8, 114.2, 111.8, 108.3, 43.4, 22.8; **HRMS** (ESI, m/z) calcd for $C_{10}H_{14}NO_2$ $[M+H]^+$ 180.1025, found 180.1028.

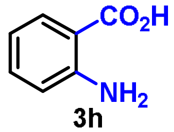
2-(allylamino)benzoic acid (3g)



3g

Colourless solid (26.9 mg, 76% yield); column chromatography eluent, petroleum ether/EtOAc = 4:1; mp 150-151 °C; ^{1}**H NMR** (400 MHz, Chloroform-*d*) δ 8.00 (app dd, *J* = 8.1, 1.7 Hz, 1H), 7.40 (comp, 1H), 6.69 (d, *J* = 8.5 Hz, 1H), 6.64 (comp, 1H), 5.97 (ddt, *J* = 17.2, 10.2, 5.0 Hz, 1H), 5.31 (dq, *J* = 17.2, 1.7 Hz, 1H), 5.21 (dq, *J* = 10.3, 1.5 Hz, 1H), 3.91 (dt, *J* = 4.9, 1.7 Hz, 2H); ^{13}**C NMR** (101MHz, Chloroform-*d*) δ 174.0, 151.5, 135.6, 134.3, 132.6, 116.2, 115.0, 111.8, 108.9, 45.3; **HRMS** (ESI, m/z) calcd for $C_{10}H_{12}NO_2$ $[M+H]^+$ 178.0868, found 178.08721.

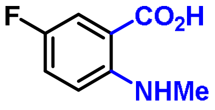
2-aminobenzoic acid (3h)



3h

Off-white solid (20 mg, 73% yield); column chromatography eluent, petroleum ether/EtOAc= 4:1; mp 146-148 °C; (Due to solubility problem, a few drops of CD_3OD was added with $CDCl_3$) **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 7.86 (d, *J* = 8.0 Hz, 1H), 7.32 – 7.14 (m, 1H), 6.75 – 6.51 (m, 2H), 4.84 (s, 2H); **^{13}C NMR** (101 MHz, Chloroform-*d*) δ 171.3, 150.5, 134.3, 131.8, 116.7, 116.4, 110.5; **HRMS** (ESI, m/z) calcd for $C_7H_8NO_2$ $[M+H]^+$ 138.0555, found 138.0570.

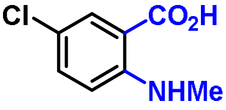
5-fluoro-2-(methylamino)benzoic acid (3i)



3i

Off-white solid (20 mg, 59% yield); column chromatography eluent, petroleum ether/EtOAc = 4:1; mp 193-195 °C; (Due to solubility problem, a few drops of CD_3OD was added with $CDCl_3$) **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 7.57-7.52 (m, 1H),7.10-7.03 (m, 1H), 6.55 (dd, *J* = 9.2, 4.4 Hz, 1H), 2.82 (s, 3H); **^{13}C NMR** (101MHz, Chloroform-*d*) δ 169.9, 153.0(d, $^1J_{F\text{-}C}$ = 233.3 Hz), 148.7, 121.6 (d, $^2J_{F\text{-}C}$ = 23.2 Hz), 117.2 (d, $^2J_{F\text{-}C}$ = 23.2 Hz), 111.8 (d, $^3J_{F\text{-}C}$ = 7.1 Hz), 109.9 (d, $^3J_{F\text{-}C}$ = 3.8 Hz), 29.7; **HRMS** (ESI, m/z) calcd for $C_8H_9FNO_2$ $[M+H]^+$ 170.0617, found 170.0621.

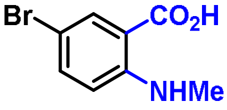
5-chloro-2-(methylamino)benzoic acid (3j)



3j

Colorless solid (24.8 mg, 67% yield); column chromatography eluent, petroleum ether/EtOAc = 4:1; mp 178-180 °C; (Due to solubility problem, a few drops of CD_3OD was added with $CDCl_3$) **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 7.81 (app dd, *J* = 2.6, 1.3 Hz, 1H), 7.23 (comp, 1H), 6.53 (d, *J* = 9.0 Hz, 1H), 2.81 (s, 3H); **^{13}C NMR** (101MHz, Chloroform-*d*) δ 170.0, 150.6, 134.4, 131.3, 118.8, 112.0, 110.6, 29.4; **HRMS** (ESI, m/z) calcd for $C_8H_9ClNO_2$ $[M+H]^+$ 186.0322, found 186.0330.

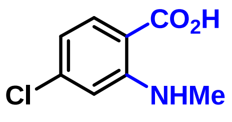
5-bromo-2-(methylamino)benzoic acid (3k)



3k

Off-white solid (24.8 mg, 54% yield); column chromatography eluent, petroleum ether/EtOAc = 4:1; mp 172-174 °C; **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 8.06 (d, *J* = 2.4 Hz, 1H), 7.47 (app dd, *J* = 9.0, 2.4 Hz, 1H), 6.59 (d, *J* = 9.1 Hz, 1H), 2.92 (s, 3H); **^{13}C NMR** (101MHz, Chloroform-*d*) δ 172.5, 151.3, 138.3, 134.5, 113.0, 110.0, 106.0, 29.8; **HRMS** (ESI, m/z) calcd for $C_8H_9BrNO_2$ $[M+2+H]^+$ 231.9817, found 231.9796.

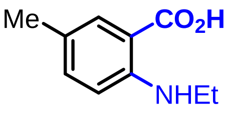
4-chloro-2-(methylamino)benzoic acid (3l)



3l

Off-white solid (30 mg, 81% yield); column chromatography eluent, petroleum ether/EtOAc = 4:1; mp 186-188 °C; **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 7.88 (d, *J* = 8.6 Hz, 1H), 6.67 (d, *J* = 1.9 Hz, 1H), 6.59 (app dd, *J* = 8.6, 1.9 Hz, 1H), 2.92 (s, 3H); **^{13}C NMR** (101MHz, Chloroform-*d*) δ 173.0, 153.1, 142.1, 133.9, 115.1, 110.8, 107.2, 29.6; **HRMS** (ESI, m/z) calcd for $C_8H_9ClNO_2$ $[M+H]^+$ 186.0322, found 186.0320.

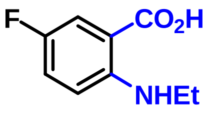
2-(ethylamino)-5-methylbenzoic acid (3m)



3m

Off-white solid (20 mg, 56% yield); column chromatography eluent, petroleum ether/EtOAc = 4:1; mp 155-156 °C; **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 7.82 – 7.75 (m, 1H), 7.24 (app dd, *J* = 8.6, 2.0 Hz, 1H), 6.66 (d, *J* = 8.6 Hz, 1H), 3.25 (q, *J* = 7.2 Hz, 2H), 2.25 (s, 3H), 1.32 (t, *J* = 7.2 Hz, 3H); **^{13}C NMR** (101MHz, Chloroform-*d*) δ 173.7, 149.5, 136.7, 132.2, 123.9, 111.9, 108.6, 37.8, 20.1, 14.5; **HRMS** (ESI, m/z) calcd for $C_{10}H_{14}NO_2$ $[M+H]^+$180.1025, found 180.1025.

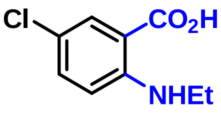
2-(ethylamino)-5-fluorobenzoic acid (3n)



3n

Yellow solid (33 mg, 90% yield); column chromatography eluent, petroleum ether/EtOAc = 4:1; mp 143-145 °C; **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 7.66 (app dd, *J* = 9.6, 3.1 Hz, 1H), 7.20-7.15 (m, 1H), 6.66 (app dd, *J* = 9.3, 4.4 Hz, 1H), 3.24 (q, *J* = 7.2 Hz, 2H), 1.33 (t, J = 7.2 Hz, 3H); **^{13}C NMR** (101MHz, Chloroform-*d*) δ 172.6, 152.9 (d, $^1J_{F-C}$= 232.3 Hz), 148.4, 123.5 (d, $^2J_{F-C}$ = 23.2 Hz), 117.4 (d, $^2J_{F-C}$ = 23.1 Hz), 112.8 (d, $^3J_{F-C}$ = 6.8 Hz), 108.3 (d, $^3J_{F-C}$ = 6.0 Hz), 38.0, 14.5; **HRMS** (ESI, m/z) calcd for $C_9H_{11}FNO_2$ $[M+H]^+$ 184.0774, found 184.0780.

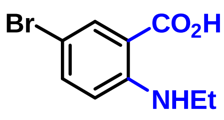
5-chloro-2-(ethylamino)benzoic acid (3o)



3o

Yellow solid (35 mg, 88% yield); column chromatography eluent, petroleum ether/EtOAc = 4:1; mp 168-170 °C; (Due to solubility problem, a few drops of CD_3OD was added with $CDCl_3$) **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 7.82 (d, *J* = 2.8 Hz, 1H), 7.21 (app dd, *J* = 9.0, 2.5 Hz, 1H), 6.55 (d, *J* = 9.0 Hz, 1H), 3.14 (q, *J* = 7.2 Hz, 2H), 1.23 (t, J = 7.2 Hz, 3H); **^{13}C NMR** (101MHz, Chloroform-*d*) δ 170.0, 149.6, 134.4, 131.3, 118.7, 112.5, 110.5, 37.3, 14.1; **HRMS** (ESI, m/z) calcd for $C_9H_{11}ClNO_2$ $[M+H]^+$ 200.0478, found 200.0481.

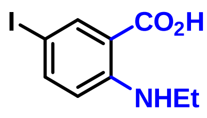
5-bromo-2-(ethylamino)benzoic acid (3p)



3p

Off-white solid (41 mg, 84% yield); column chromatography eluent, petroleum ether/EtOAc = 4:1; mp 178-180 °C; **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 8.07 (d, *J* = 2.5 Hz, 1H), 7.44 (app dd, *J* = 9.1, 2.5 Hz, 1H), 6.60 (d, *J* = 9.1 Hz, 1H), 3.24 (q, *J* = 7.2 Hz, 2H), 1.32 (t, *J* = 7.2 Hz, 3H); **^{13}C NMR** (101MHz, Chloroform-*d*) δ 172.3, 150.5, 138.2, 134.6, 113.3, 109.7, 105.8, 37.6, 14.4; **HRMS** (ESI, m/z) calcd for $C_9H_{11}BrNO_2$ $[M+H]^+$ 245.9953, found 245.9964.

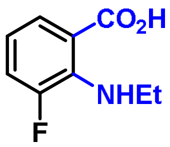
2-(ethylamino)-5-iodobenzoic acid (3q)



3q

Off-white solid (44.8 mg, 77% yield); column chromatography eluent, petroleum ether/EtOAc = 4:1; mp 174-176 °C; (Due to solubility problem, a few drops of CD_3OD was added with $CDCl_3$) **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 8.09 (d, *J* = 2.2 Hz, 1H), 7.44 (app dd, *J* = 8.9, 2.2 Hz, 1H), 6.37 (d, *J* = 8.9 Hz, 1H), 3.09 (q, *J* = 7.2 Hz, 2H), 1.18 (t, *J* = 7.2 Hz, 3H); **^{13}C NMR** (101MHz, Chloroform-*d*) δ 169.7, 150.4, 142.7, 140.3, 113.7, 112.0, 73.9, 37.2, 14.0; **HRMS** (ESI, m/z) calcd for $C_9H_{11}INO_2$ $[M+H]^+$ 291.9834, found 291.9842.

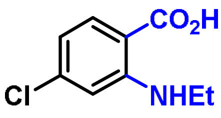
2-(ethylamino)-3-fluorobenzoic acid (3r)



3r

Colorless solid (29.6 mg, 81% yield); column chromatography eluent, petroleum ether/EtOAc = 4:1; mp 188-190 °C; **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 8.46 (s, 1H), 7.81 (app dt, *J* = 8.1, 1.1 Hz, 1H), 7.16 (comp, 1H), 6.66 (app td, *J* = 8.0, 4.5 Hz, 1H), 3.50 (qd, *J* = 7.2, 3.7 Hz, 2H), 1.30 – 1.25 (dt, 3H) ; **^{13}C NMR** (101MHz, Chloroform-*d*) δ 172.3(d, $^{4}J_{F\text{-}COOH}$ = 3.5 Hz), 152.9(d, $^{1}J_{F\text{-}C}$ = 243.7 Hz), 140.5 (d, $^{2}J_{F\text{-}C}$ = 10.5 Hz), 128.1(d, $^{4}J_{F\text{-}C}$ = 2.7 Hz), 121.5(d, $^{2}J_{F\text{-}C}$ = 20.6 Hz), 116.5(d, $^{3}J_{F\text{-}C}$ = 7.4 Hz), 114.4(d, $^{3}J_{F\text{-}C}$ = 4.5 Hz), 41.45 (d, $^{4}J_{F\text{-}CH2}$ = 10.9 Hz), 15.9(d, $^{5}J_{F\text{-}CH3}$ = 2.4 Hz); **HRMS**(ESI, m/z) calcd for $C_9H_{11}FNO_2$ $[M+H]^+$ 184.0774, found 184.0779.

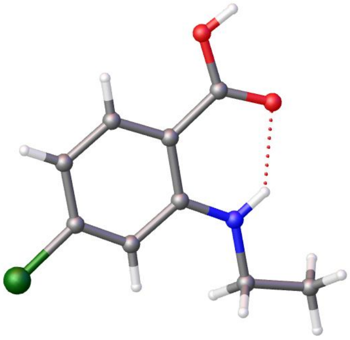
4-chloro-2-(ethylamino)benzoic acid (3s)



3s

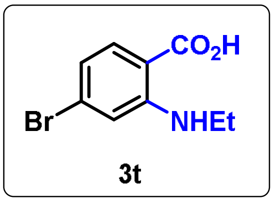
Off-white solid (35 mg, 88% yield); column chromatography eluent, petroleum ether/EtOAc = 4:1; mp 200-204 °C; (Due to solubility problem, a few drops of CD_3OD was added with $CDCl_3$) **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 7.77 (app d, *J* = 8.5 Hz, 1H), 6.57 (app s, 1H), 6.46 (app dd, *J* = 8.5, 2.0 Hz, 1H), 3.12 (q, *J* = 7.2 Hz, 2H), 1.23 (t, *J* = 7.2 Hz, 3H); **^{13}C NMR** (101MHz, Chloroform-*d*) δ 170.3, 151.7, 140.7, 133.5, 114.5, 110.7, 108.3, 37.3, 14.0; **HRMS** (ESI, m/z) calcd for $C_9H_{11}ClNO_2$ $[M+H]^+$ 200.0478, found 200.0483.

Table 5.5.23: Crystal Data and Structure of 3s (CCDC No. **2213916**)



Empirical formula	$C_9H_{10}ClNO_2$
Formula weight	199.63
Temperature/K	113.00
Crystal system	monoclinic
Space group	$P2_1/n$
a/Å	7.8685(6)
b/Å	7.0616(5)
c/Å	16.2493(12)
α/°	90
β/°	91.433(2)
γ/°	90
Volume/Å^3	902.60(12)
Z	4
ρ_{calc}g/cm^3	1.469
μ/mm^{-1}	3.473
F(000)	416.0
Crystal size/mm^3	0.5 × 0.45 × 0.4
Radiation	Cu Kα (λ = 1.54178)
2Θ range for data collection/°	16.634 to 130.178
Index ranges	$-9 \leq h \leq 9$, $-8 \leq k \leq 8$, $-18 \leq l \leq 19$
Reflections collected	9965
Independent reflections	1481 [R_{int} = 0.0541, R_{sigma} = 0.0394]
Data/restraints/parameters	1481/0/120
Goodness-of-fit on F^2	1.520
Final R indexes [I>=2σ (I)]	R_1 = 0.0522, wR_2 = 0.1272
Final R indexes [all data]	R_1 = 0.0523, wR_2 = 0.1273
Largest diff. peak/hole / e Å^{-3}	0.44/-0.99

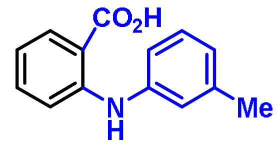
4-bromo-2-(ethylamino)benzoic acid (3t)



3t

Off-white solid (38.5 mg, 79% yield); column chromatography eluent, petroleum ether/EtOAc = 4:1; mp 190-192 °C; (Due to solubility problem, a few drops of CD_3OD was added with $CDCl_3$) **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 7.67 (d, *J* = 8.5 Hz, 1H), 6.72 (d, *J* = 1.7 Hz, 1H), 6.59 (dd, *J* = 8.5, 1.8 Hz, 1H), 3.10 (q, *J* = 7.2 Hz, 2H), 1.21 (t, *J* = 7.2 Hz, 3H); **^{13}C NMR** (101MHz, Chloroform-*d*) δ 170.4, 151.7, 133.5, 129.6, 117.3, 113.6, 108.5, 37.2, 14.0; **HRMS** (ESI, m/z) calcd for $C_9H_{11}BrNO_2[M+H+2]^+$ 245.9953, found 245.9961.

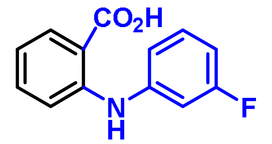
2-(m-tolylamino)benzoic acid (3u)



3u

Off-white solid (20 mg, 44% yield); column chromatography eluent, petroleum ether/EtOAc = 4:1; mp 142-144 °C; **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 9.27 (br s, 1H), 8.04 (app dd, *J* = 8.1, 1.5 Hz, 1H), 7.37-7.33 (m, 1H), 7.27 – 7.22 (comp, 2H), 7.09 (app d, *J* = 5.6 Hz, 2H), 6.95 (app d, *J* = 7.5 Hz, 1H), 6.77 – 6.73 (m, 1H), 2.36 (s, 3H); **^{13}C NMR** (101MHz, Chloroform-*d*) δ 173.0, 149.0, 140.2, 139.4, 135.1, 132.5, 129.2, 124.9, 123.8, 120.1, 117.0, 114.1, 110.2, 21.4; **HRMS**(ESI, m/z) calcd for $C_{14}H_{14}NO_2$ $[M+H]^+$ 228.1025, found 228.1023.

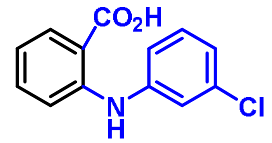
2-((3-fluorophenyl)amino)benzoic acid (3v)



3v

Off-white solid (21.3 mg, 46% yield); column chromatography eluent, petroleum ether/EtOAc = 4:1; mp 154-156 °C; **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 9.34 (br s, 1H), 8.07 (app dd, *J* = 8.1, 1.5 Hz, 1H), 7.41 (comp, 1H), 7.34 – 7.23 (comp, 2H), 7.08 – 6.94 (comp, 2H), 6.91 – 6.72 (comp, 2H); **^{13}C NMR** (101MHz, Chloroform-*d*) δ 173.3, 163.5 (d, $^1J_{F\text{-}C}$ = 245.7 Hz), 147.8, 142.3 (d, $^3J_{F\text{-}C}$ = 10.2 Hz), 135.3, 132.7, 130.5 (d, $^3J_{F\text{-}C}$ = 9.6 Hz), 118.1, 117.8 (d, $^4J_{F\text{-}C}$ = 2.5 Hz), 114.5, 111.2, 110.4 (d, $^2J_{F\text{-}C}$ = 21.2 Hz), 109.1 (d, $^2J_{F\text{-}C}$ = 23.6 Hz); **HRMS** (ESI, m/z) calcd for $C_{13}H_{11}FNO_2$ $[M+H]^+$ 232.0774, found 232.0771.

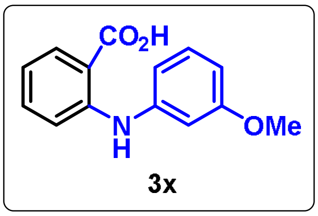
2-((3-chlorophenyl)amino)benzoic acid (3w)



3w

Colourless solid (25.3 mg, 51% yield); column chromatography eluent, petroleum ether/EtOAc = 4:1; mp 170-171 °C; **^{1}H NMR (**400 MHz, Chloroform-*d***)** δ 9.30 (s, 1H), 8.06 (app dd, *J* = 8.1, 1.5 Hz, 1H), 7.40 (comp, 1H), 7.27 (app t, *J* = 7.8 Hz, 3H), 7.19 – 7.11 (m, 1H), 7.11 – 7.04 (m, 1H), 6.86 – 6.75 (m, 1H); **^{13}C NMR** (101 MHz, Chloroform-*d*) δ 173.3, 147.9, 141.9, 135.3, 135.0, 132.7, 130.4, 123.7, 122.3, 120.4, 118.1, 114.4, 111.2; **HRMS**(ESI, m/z) calcd for $C_{13}H_{11}ClNO_2$ $[M+H]^+$ 248.0478, found 248.0482

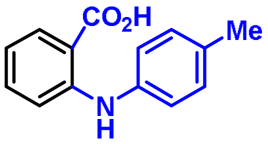
2-((3-methoxyphenyl)amino)benzoic acid (3x)



3x

White solid (27.2 mg, 56% yield); column chromatography eluent, petroleum ether/EtOAc = 4:1; mp 148-149 °C; **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 9.29 (br s, 1H), 8.05 (app dd, *J* = 8.1, 1.5 Hz, 1H), 7.38-7.34 (m, 1H), 7.29-7.24 (comp, 2H), 6.88 – 6.85 (m, 1H), 6.82 (app t, *J* = 2.2 Hz, 1H), 6.79 – 6.74 (m, 1H), 6.68 (app dd, *J* = 8.2, 2.4 Hz, 1H), 3.81 (s, 3H); **^{13}C NMR** (101MHz, Chloroform-*d*) δ 173.5, 160.6, 148.7, 141.6, 135.2, 132.6, 130.1, 117.3, 115.2, 114.5, 110.6, 109.6, 108.6, 55.3; **HRMS**(ESI, m/z) calcd for $C_{14}H_{14}NO_3$ $[M+H]^+$ 244.0974, found 244.0977.

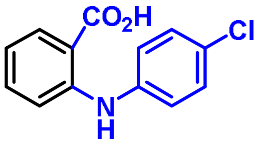
2-(p-tolylamino)benzoic acid (3y)



3y

White solid (18.2 mg, 40% yield); column chromatography eluent, petroleum ether/EtOAc = 4:1; mp 186-188 °C; **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 9.23 (br s, 1H), 8.03 (app dd, *J* = 8.1, 1.5 Hz, 1H), 7.34-7.30 (m, 1H), 7.20 – 7.11 (comp, 5H), 6.74 – 6.70 (m, 1H), 2.36 (s, 3H); **^{13}C NMR** (101MHz, Chloroform-*d*) δ 173.0, 149.6, 137.6, 135.1, 134.1, 132.5, 130.0, 123.8, 116.7, 113.8, 109.8, 20.9; **HRMS**(ESI, m/z) calcd for $C_{14}H_{14}NO_2$ $[M+H]^+$ 228.1025, found 228.1024.

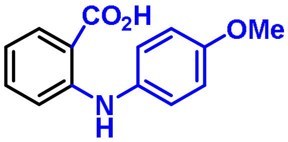
2-((4-chlorophenyl)amino)benzoic acid (3z)



3z

White solid (27.2 mg, 55% yield); column chromatography eluent, petroleum ether/EtOAc = 4:1; mp 150-152 °C; **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 9.26 (br s, 1H), 8.04 (app dd, *J* = 8.1, 1.6 Hz, 1H), 7.36 (comp, 1H), 7.33 – 7.29 (comp, 2H), 7.21 – 7.14 (comp, 3H), 6.81 – 6.74 (m, 1H); **^{13}C NMR** (101MHz, Chloroform-*d*) δ 173.2, 148.5, 139.0, 135.3, 132.7, 129.5, 129.0, 124.2, 117.6, 114.0, 110.7; **HRMS** (ESI, m/z) calcd for $C_{13}H_{11}ClNO_2$ $[M+H]^+$ 248.0478, found 248.0482.

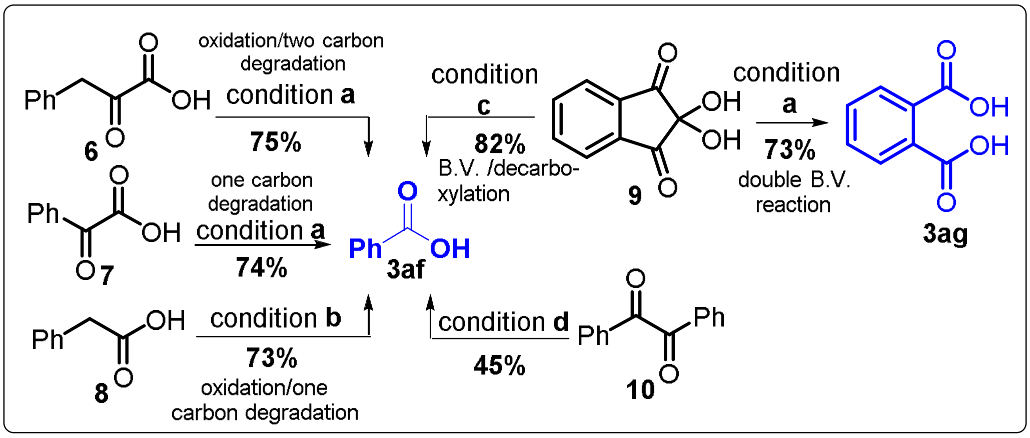
2-((4-methoxyphenyl)amino)benzoic acid (3aa)



3aa

Off-white solid (30.1 mg, 62% yield); column chromatography eluent, petroleum ether/EtOAc = 4:1; mp 170-172 °C; **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 9.13 (s, 1H), 8.02 (app dd, *J* = 8.0, 1.3 Hz, 1H), 7.32 – 7.28 (m, 1H), 7.19 (app d, *J* = 8.8 Hz, 2H), 6.96-6.92 (comp, 3H), 6.69 (app t, *J* = 7.5 Hz, 1H), 3.84 (s, 3H); **^{13}C NMR** (101MHz, Chloroform-*d*) δ 173.4, 157.0, 150.5, 135.2, 133.0, 132.5, 126.4, 116.3, 114.7, 113.5, 109.4, 55.5; **HRMS** (ESI, m/z) calcd for $C_{14}H_{14}NO_3$ $[M+H]^+$244.0974, found 244.0977.

5.5.24 General procedure (dehomologation process) for the preparation of benzoic acid (3af) and phthalic acid (3ag)



Reaction condition a:

Into a 10 mL two-neck round bottom flask equipped with an electromagnetic stirrer, compounds **6** or **7** or **9** (1 equiv., 0.2 mmol) and DMF solvent (2 mL, 0.1 M) were taken under an inert atmosphere at ice-cold conditions. NaH (6 equiv., 1.2 mmol) was added portion-wise through an additional funnel and stirred at room temperature (33 °C) for 10 h. After the full conversion was monitored by TLC, it was quenched with cold 1N HCl solution (20 mL). The organic part was extracted by EtOAc (3x20 mL) with brine, dried over Na_2SO_4, and concentrated under reduced pressure. Finally, it was purified by column chromatography on silica gel (230-400 mesh) using petroleum ether/ethyl acetate (4:1) as eluent to obtain the desired benzoic acid (**3af**) or phthalic acid (**3ag**) in 73-75% yield.

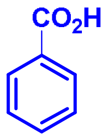
Condition b: Into a 10 mL two-neck round bottom flask equipped with an electromagnetic stirrer, compound **8** (1 equiv., 0.2 mmol) and DMF solvent (2 mL, 0.1 M) were taken in an inert atmosphere at ice cold condition. NaH (6 equiv., 1.2 mmol) was added portion-wise through an additional funnel and initially stirred at room temperature (33 °C). Then the whole reaction mixture was warmed to 80 °C and stirred for 24 h. After the full conversion was monitored by TLC, it was quenched with cold 1N HCl solution (20 mL). The organic part was extracted by EtOAc (3x20 mL) with brine, dried over Na_2SO_4, and concentrated under reduced pressure. Finally, it was purified by column chromatography on silica gel (230-400 mesh) using petroleum ether/ethyl acetate (4:1) as eluent to obtain the desired benzoic acid (**3af**) in a 73% yield.

Condition c: Into a 10 mL two-neck round bottom flask equipped with an electromagnetic stirrer, compound **8** (1 equiv., 0.2 mmol) and DMF solvent (2 mL, 0.1 M) were taken under an inert atmosphere at ice cold conditions. NaH (6 equiv., 1.2 mmol) was added portion-wise through an additional funnel and initially stirred at room temperature (33 °C). Then the whole reaction mixture was warmed to 80 °C and stirred for 2 h. After the full conversion was monitored by TLC, it was quenched with cold 1N HCl solution (20 mL). The organic part was extracted by EtOAc (3x20 mL) with brine, dried over Na_2SO_4, and concentrated under reduced pressure. Finally, it was purified by column chromatography on silica gel (230-400 mesh) using petroleum ether/ethyl acetate (4:1) as eluent to obtain the desired benzoic acid (**3af**) in 82% yield.

Condition d: Into a 10 mL two neck round bottom flask equipped with an electromagnetic stirrer, compounds **6** or **7**, or **9** (1 equiv., 0.2 mmol) and DMF solvent (2 mL, 0.1 M) were taken under in an inert atmosphere at ice cold condition. NaH (4 equiv., 0.8 mmol) was added portion-wise through an additional funnel and stirred at room temperature (33 °C) for 6 hours. After the full conversion was monitored by TLC, it was quenched with cold 1N HCl solution (20 mL). The organic part was extracted by EtOAc (3x20 mL) with brine, dried over Na_2SO_4, and concentrated under reduced pressure. Finally, it was purified by column chromatography on silica gel (230-400 mesh) using petroleum ether/ethyl acetate (4:1) as eluent to obtain the desired benzoic acid (**3af**) in 45% yield.

5.5.25 Characterization data of 3af

benzoic acid (3af)

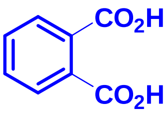


3af

White solid (45-82% yield); column chromatography eluent, petroleum ether/EtOAc = 4:1; mp 168-170 ^{o}C; ^{1}**H NMR** (400 MHz, Chloroform-*d*) δ 11.84 (s, 1H), 8.15 – 8.13 (comp, 2H), 7.63 (app t, *J* = 7.6, 1H), 7.51 – 7.47 (comp, 2H); ^{13}**C NMR** (101 MHz, Chloroform-*d*) δ 172.5, 133.8, 130.2, 129.3, 128.5; **HRMS** (ESI, m/z) calcd for $C_7H_7O_2$ $[M+H]^+$ 123.0446, found 123.0444.

5.5.26 Characterization data of 3ag

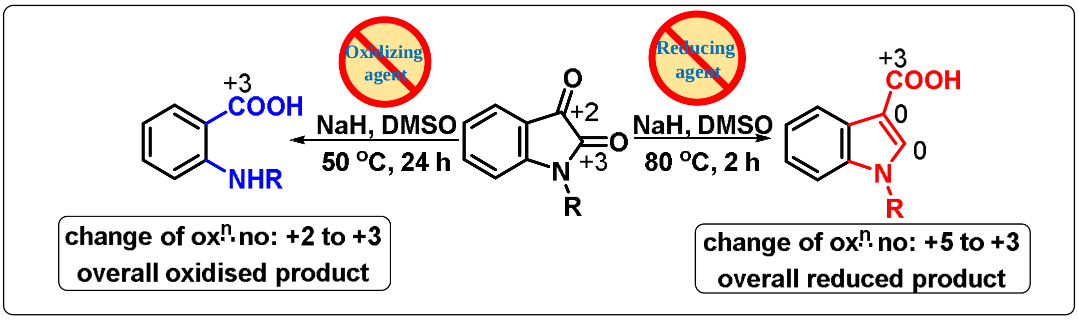
phthalic acid (3ag)



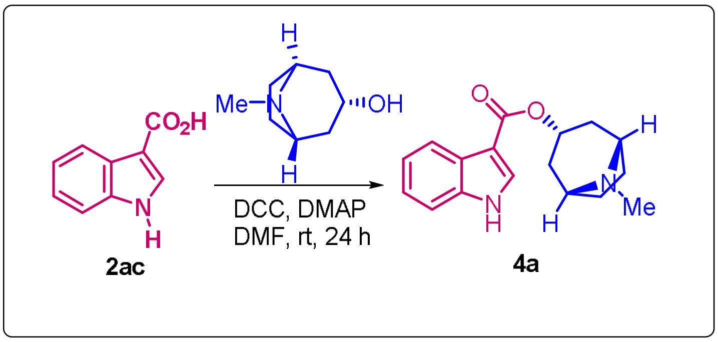
3ag

White solid (24.2 mg, 73% yield); column chromatography eluent, petroleum ether/EtOAc = 4:1; mp 168-170 ^{o}C; ^{1}**H NMR** (400 MHz, Chloroform-*d*) δ 7.86-7.82 (comp, 2H), 7.64-7.60 (comp, 2H); ^{13}**C NMR** (101MHz, Chloroform-*d*) δ 171.8, 134.6, 132.3, 130.6; **HRMS** (ESI, m/z) calcd for $C_8H_7O_4$ $[M+H]^+$ 167.0344, found 167.0346.

5.5.27 Schematic Representation for the Synthesis of ICA (Reduced Product) And AA Derivatives (Oxidized Product) from Isatins



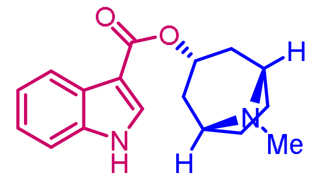
5.5.28 General Procedure for the Preparation of 4a:



500 mg (3.1 mmol, 1 equiv.) indole-3-carboxylic acid **2ac** was charged in an oven-dried clean 25 mL two neck round bottom flask containing magnetic stir bar in N_2 atmosphere. 4 mL DCM and 0.2 mL (0.4 equiv.) trifluoroacetic acid (TFA) was added respectively at rt (33 ^{o}C). After stirring for 5 minutes 1 mL $(CF_3CO)_2O$ (7.2 mmol, 2.3 equiv.) was added dropwise to the reaction mixture at 0 ^{o}C. Then it was warmed at rt and stirred for 2h for activating the acid group. After that, it was transferred to -5 ^{o}C and 4 mL tropine solution (450 mg, 1 equiv.) (made previously by 4 mL DCM at the inert condition) added dropwise for 30 minutes, and kept for 4h. After full conversion checking by TLC, the whole reaction mixture was quenched by 100 mL ice-cooled 1N NaOH solution followed by worked up with EtOAc and brine. Then the organic layer was passed through Na_2SO_4, kept for some time, and concentrated in the rotary evaporator. Then it was dissolved in EtOAc for crystallization, and 710 mg (81%) of desired tropisetron **4a** was obtained.

5.5.29 Characterization Data of 4a

8-methyl-8-azabicyclo[3.2.1]octan-3-yl *1H*-indole-3-carboxylate (4a)

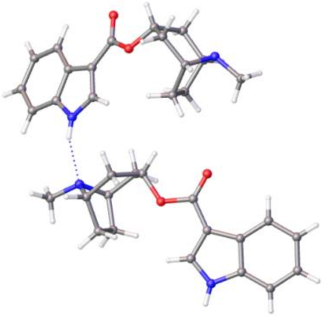


4a

White solid (710 mg, 81% yield); column chromatography eluent: petroleum ether/EtOAc = 5:1; mp 202-204 ^{o}C; ^{1}**H NMR** (400 MHz, $CDCl_3$) δ 9.88 (s, 1H), 8.26-8.22 (m, 1H), 7.84 (s, 1H), 7.43 – 7.38 (m, 1H), 7.29 – 7.23 (comp, 2H), 5.28 (app t, *J*

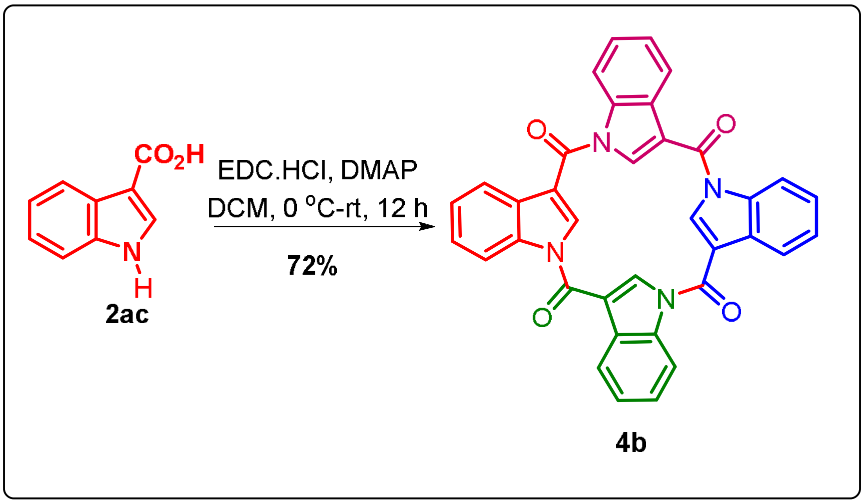
= 5.2 Hz, 1H), 3.22 – 3.20 (m, 2H), 2.35 (s, 3H), 2.31-2.25 (m, 2H), 2.15-2.07 (comp, 4H), 1.93 (app d, *J* = 14.8 Hz, 2H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 164.6, 136.3, 131.0, 126.0, 123.1, 121.9, 121.1, 111.6, 108.9, 66.4, 59.8, 40.1, 36.4, 25.9; **HRMS** (ESI, m/z) calcd for $C_{17}H_{21}N_2O_2$ $[M+H]^+$ 285.1603, found 285.1595.

Table 5.5.30: **Crystal Data and Structure of 4a** (CCDC No. **2213920**)



Empirical formula	$C_{34}H_{40}N_4O_4$
Formula weight	568.70
Temperature/K	100.0
Crystal system	triclinic
Space group	P-1
a/Å	10.1881(4)
b/Å	11.1979(4)
c/Å	13.8192(5)
α/°	81.9570(10)
β/°	78.9680(10)
γ/°	70.0130(10)
Volume/Å^3	1449.48(9)
Z	2
ρ_{calc}g/cm^3	1.303
μ/mm^{-1}	0.689
F(000)	608.0
Crystal size/mm^3	0.65 × 0.405 × 0.25
Radiation	Cu Kα (λ = 1.54178)
2Θ range for data collection/°	12.218 to 130.018
Index ranges	$-11 \le h \le 11$, $-13 \le k \le 13$, $-16 \le l \le 16$
Reflections collected	49799
Independent reflections	4716 [R_{int} = 0.0616, R_{sigma} = 0.0351]
Data/restraints/parameters	4716/0/382
Goodness-of-fit on F^2	1.101
Final R indexes [I>=2σ (I)]	R_1 = 0.0490, wR_2 = 0.1308
Final R indexes [all data]	R_1 = 0.0493, wR_2 = 0.1312
Largest diff. peak/hole / e Å^{-3}	0.27/-0.25

5.5.31 General Procedure for the Preparation of (4b)



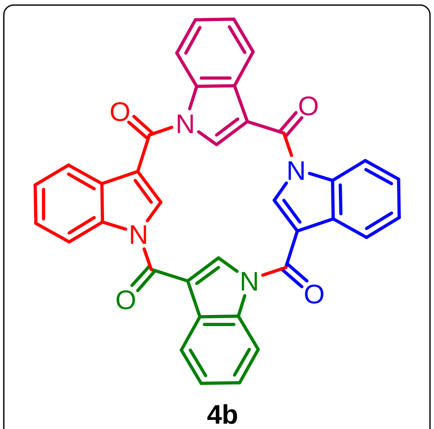
2ac

4b

Into a 10 mL two-neck round bottom flask equipped with an electromagnetic stirrer, transferred indole-3-carboxylic acid (**2**) (1 equiv., 0.4 mmol, 64.5 mg) and DCM solvent (4 mL, 0.1 M) in an inert atmosphere. The whole reaction mixture was subjected to cooling down at 0 °C using crushed ice. After that EDC.HCl (2.5 equiv.) and DMAP (0.1 equiv.) were added slowly to the reaction mixture. Then it was warmed at room temperature (33 °C) and stirred for 12 h. After the full conversion was monitored by TLC, it was quenched with aqueous $NaHCO_3$. The organic part was extracted by EtOAc (3x20 mL) with brine, dried over Na_2SO_4, and concentrated under reduced pressure. Finally, it was purified by column chromatography on silica gel (230-400 mesh) using petroleum ether/ethyl acetate (4:1) as eluent to obtain the desired N-confused porphyrin ring **4b** in 72% yield (40 mg).

5.5.32 Characterization Data of 4b

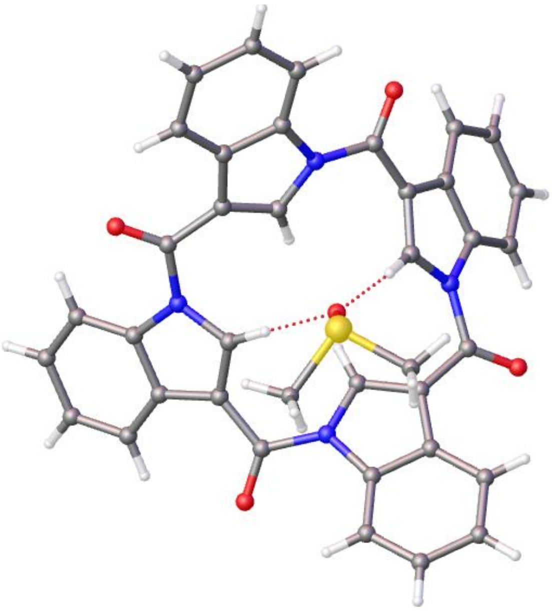
***N*-confused porphyrin ring: (1^2E,3^2E,5^2E,7^2E)-1^1H,3^1H,5^1H,7^1H-1(1,3),3,5,7(3,1)-tetraindolacyclooctaphane-2,4,6,8-tetraone (4b)**



4b

White solid (40 mg, 72% yield); column chromatography eluent: petroleum ether/EtOAc = 5:1; mp above 260 °C; **^{1}H NMR** (400 MHz, DMSO-*d*$_6$) δ 9.46 (s, 4H), 8.42-8.30 (comp, 4H), 8.19-8.17 (comp, 4H), 7.58-7.50 (comp, 8H); **^{13}C NMR** (101 MHz, DMSO-*d*$_6$) δ 163.1, 137.7, 135.8, 128.2, 125.9, 125.0, 120.9, 115.5, 112.6; **HRMS** (ESI, m/z) calcd for $C_{36}H_{21}N_4O_4$ $[M+H]^+$ 573.1563, found 573.1553.

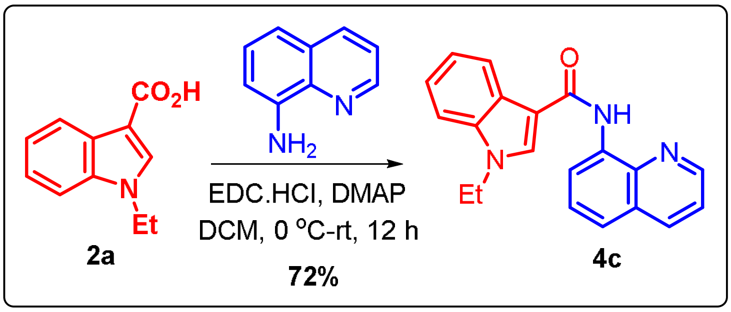
Table 5.5.33: **Crystal Data and Structure of 4b** (CCDC No. **2213919**)



Empirical formula	$C_{38}H_{26}N_4O_5S$
Formula weight	650.69
Temperature/K	100.0
Crystal system	monoclinic
Space group	$P2_1/c$
a/Å	15.3315(10)
b/Å	7.6770(5)
c/Å	25.9418(17)
α/°	90
β/°	96.515(3)
γ/°	90
Volume/Å^3	3033.6(3)
Z	4
ρ_{calc}g/cm^3	1.425
μ/mm^{-1}	1.400
F(000)	1352.0
Crystal size/mm^3	0.35 × 0.2 × 0.18
Radiation	Cu Kα (λ = 1.54178)
2Θ range for data collection/°	11.618 to 130.352

Index ranges	$-18 \le h \le 17$, $-8 \le k \le 9$, $-27 \le l \le 30$
Reflections collected	44102
Independent reflections	5057 [R_{int} = 0.0520, R_{sigma} = 0.0301]
Data/restraints/parameters	5057/0/435
Goodness-of-fit on F^2	1.077
Final R indexes [I>=2σ (I)]	R_1 = 0.0491, wR_2 = 0.1390
Final R indexes [all data]	R_1 = 0.0498, wR_2 = 0.1397
Largest diff. peak/hole / e Å^{-3}	0.44/-0.38

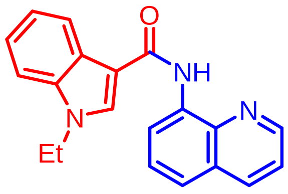
5.5.34 General Procedure for the Preparation of (4c)



Into a 10 mL two-neck round bottom flask equipped with an electromagnetic stirrer, transferred N-ethyl indole-3-carboxylic acid (**2a**) (1 equiv., 0.4 mmol, 76 mg) and DCM solvent (4 mL, 0.1 M) followed by 8-aminoquinoline (1.1 equiv., 64 mg) in an inert atmosphere. The whole reaction mixture was subjected to cooling down at 0 °C using crushed ice. After that EDC.HCl (2.5 equiv.) and DMAP (2 equiv.) were added slowly to the reaction mixture. Then it was warmed at room temperature (33 °C) and stirred for 12 h. After the full conversion was monitored by TLC, it was quenched with aqueous $NaHCO_3$. The organic part was extracted by EtOAc (3x20 mL) with brine, dried over Na_2SO_4, and concentrated under reduced pressure. Finally, it was purified by column chromatography on silica gel (230-400 mesh) using petroleum ether/ethyl acetate (2.3:1) as eluent to obtain the desired amide compound **4c** in 72% yield (91 mg).

5.5.35 Characterization Data of 4c

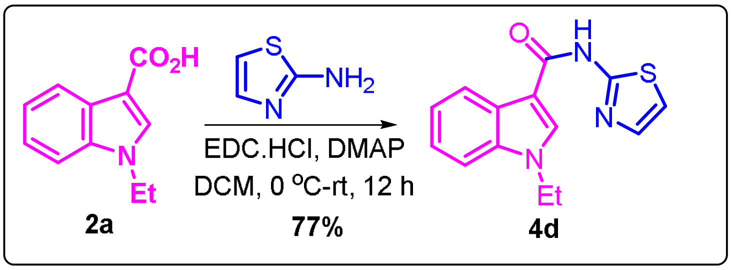
1-ethyl-N-(quinolin-8-yl)-1H-indole-3-carboxamide (4c)



4c

White solid (91 mg, 72% yield); column chromatography eluent: petroleum ether/EtOAc = 5:1; mp 120-122 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 10.57 (s, 1H), 8.98 (d, *J* = 8.0 Hz, 1H), 8.91-8.89 (m, 1H), 8.50 – 8.48 (m, 1H), 8.21-8.17 (m, 1H), 8.01-8.00 (m, 1H), 7.60 (td, *J* = 8.0 Hz, 2.0 Hz, 1H), 7.52-7.43 (comp, 3H), 7.41-7.33 (comp, 2H), 4.26 (q, *J* = 7.2 Hz, 2H), 1.56 (t, *J* = 7.2 Hz, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 163.4, 148.1, 138.6, 136.5, 136.4, 135.3, 131.6, 128.1, 127.6, 125.6, 122.5, 121.8, 121.5, 120.8, 120.8, 116.3, 111.9, 110.2, 41.6, 15.2; **HRMS** (ESI, m/z) calcd for $C_{20}H_{18}N_3O$ $[M+H]^+$ 316.1450, found 316.1440.

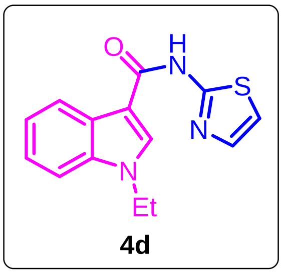
5.5.36 General Procedure for the Preparation of (4d)



Into a 10 mL two-neck round bottom flask equipped with an electromagnetic stirrer, transferred N-ethyl indole-3-carboxylic acid (**2a**) (1 equiv., 0.4 mmol, 76 mg) and DCM solvent (4 mL, 0.1 M) followed by thiazol-2-amine (1.1 equiv., 44 mg) in an inert atmosphere. The whole reaction mixture was subjected to cooling down at 0 °C using crushed ice. After that EDC.HCl (2.5 equiv.) and DMAP (2 equiv.) were added slowly to the reaction mixture. Then it was warmed at room temperature (33 °C) and stirred for 12 h. After the full conversion was monitored by TLC, it was quenched with aqueous $NaHCO_3$. The organic part was extracted by EtOAc (3x20 mL) with brine, dried over Na_2SO_4, and concentrated under reduced pressure. Finally, it was purified by column chromatography on silica gel (230-400 mesh) using petroleum ether/ethyl acetate (2.3:1) as eluent to obtain the desired amide compound **4d** in 77% yield (83 mg).

5.5.37 Characterization Data of 4d

1-ethyl-N-(thiazol-2-yl)-1H-indole-3-carboxamide (4d)



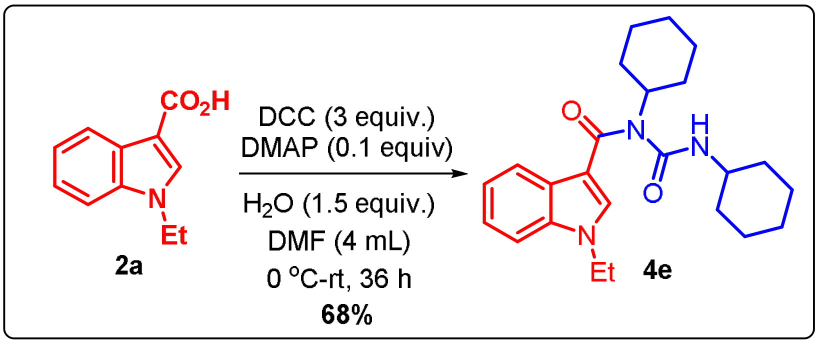
4d

White solid (83 mg, 77% yield); column chromatography eluent: petroleum ether/EtOAc = 5:1; mp 210-212 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.38 – 8.34 (m, 1H), 7.89 (s, 1H), 7.42 (dd, *J* = 6.4 Hz, 2.4 Hz, 1H), 7.36 – 7.30 (comp, 2H), 7.26 (d, *J* = 3.6 Hz, 1H), 6.95 (d, *J* = 3.6 Hz, 1H), 4.20 (q, *J* = 7.2 Hz, 2H), 1.50 (t, *J* = 7.2 Hz, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 162.4, 160.6, 136.4, 136.3, 131.0, 126.7, 123.2, 122.2, 121.7, 113.0, 110.0, 108.7, 41.7, 15.1; **HRMS** (ESI, m/z) calcd for $C_{14}H_{14}N_3OS$ $[M+H]^+$ 272.0858, found 272.0860.

Table 5.5.38: Crystal Data and Structure of 4d (CCDC No. **2213918**)

Empirical formula	$C_{14}H_{13}N_3OS$
Formula weight	271.33
Temperature/K	100.00
Crystal system	monoclinic
Space group	$P2_1/n$
a/Å	11.6575(11)
b/Å	7.8732(7)
c/Å	13.6308(13)
α/°	90
β/°	92.216(3)
γ/°	90
Volume/Å^3	1250.1(2)
Z	4
ρ_{calc}g/cm^3	1.442
μ/mm^{-1}	2.259
F(000)	568.0
Crystal size/mm^3	0.28 × 0.25 × 0.2
Radiation	CuKα (λ = 1.54178)
2Θ range for data collection/°	10.18 to 136.308
Index ranges	$-13 \leq h \leq 13$, $-9 \leq k \leq 9$, $-16 \leq l \leq 16$
Reflections collected	25825
Independent reflections	2258 [R_{int} = 0.0607, R_{sigma} = 0.0280]
Data/restraints/parameters	2258/0/173
Goodness-of-fit on F^2	1.085
Final R indexes [I>=2σ (I)]	R_1 = 0.0435, wR_2 = 0.1136
Final R indexes [all data]	R_1 = 0.0442, wR_2 = 0.1143
Largest diff. peak/hole / e Å^{-3}	0.36/-0.47

5.5.39 General procedure for the preparation of 4e:

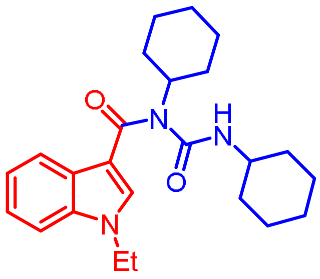


Into a 10 mL two neck round bottom flask equipped with an electromagnetic stirrer, transferred N-ethyl indole-3-carboxylic acid (**2a**) (1 equiv., 0.3 mmol, 57 mg) and DMF solvent (4 mL, 0.075 M) in an inert atmosphere. The whole reaction mixture was subjected to cool down at 0 °C using crushed ice. After that DCC (3.0 equiv.), DMAP (0.1 equiv.), and H_2O (1.5 equiv.) was added slowly to the reaction mixture. Then it was warmed at room temperature (33 °C) and stirred for 36 h. After the full conversion was monitored by TLC, it was quenched with H_2O. The organic part was extracted by EtOAc (3x20 mL) with brine, dried over Na_2SO_4, and concentrated under reduced pressure. Finally, it was purified by column chromatography on silica gel (230-400 mesh) using petroleum ether/ethyl acetate (4:1) as eluent to obtain the desired imide compound **4e** in 68% yield (81 mg).

5.5.40 Characterization data of 4e

N-cyclohexyl-N-(cyclohexylcarbamoyl)-1-ethyl-*1H*-indole-3-carboxamide (4e)

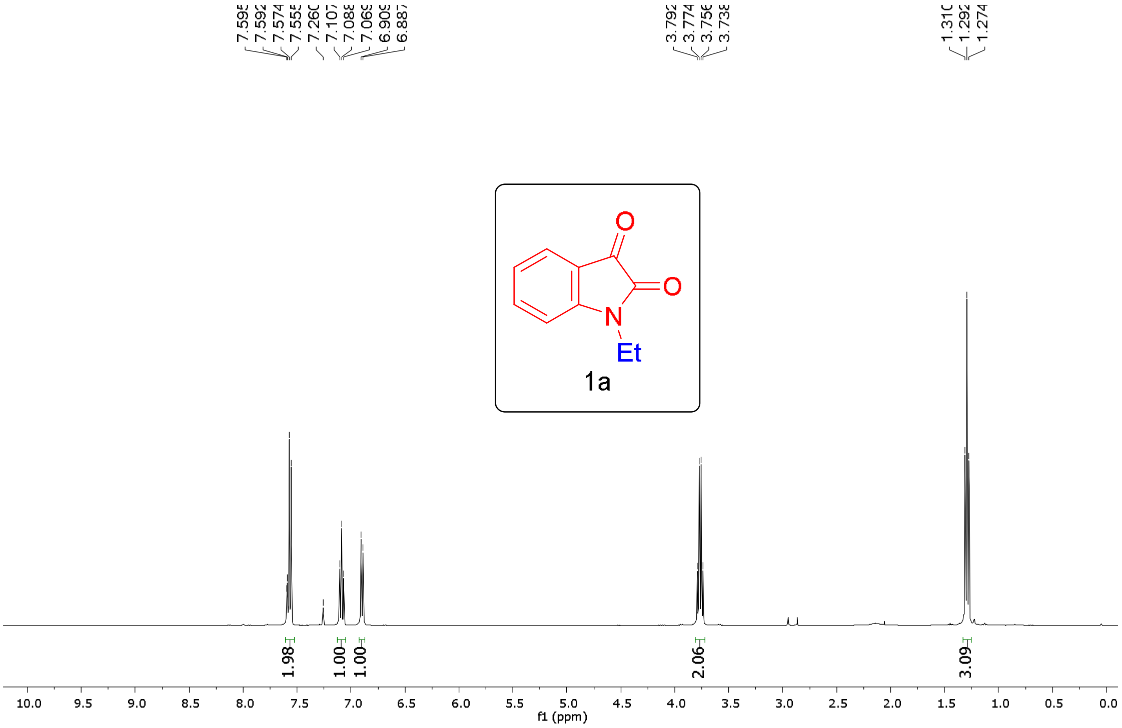
White solid (81 mg, 68% yield); column chromatography eluent: petroleum ether/EtOAc = 5:1; mp 148-150 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.06 – 8.04 (m, 1H), 7.59 (s, 1H), 7.35 (dd, *J* = 7.0, 1.4 Hz, 1H), 7.30 – 7.22 (comp, 2H), 5.90 (d, *J* = 8.0 Hz, 1H), 4.40-4.33 (m, 1H), 4.18 (q, *J* = 7.2 Hz, 2H), 3.58 – 3.49 (m, 1H), 2.10-2.00 (m, 2H), 1.93-1.86 (comp, 3H), 1.83-1.79 (m, 2H), 1.63 – 1.59 (comp, 3H), 1.47 (t, *J* = 7.2 Hz, 3H), 1.36 – 1.17 (comp, 6H), 1.12 – 1.00 (m, 2H), 0.89 – 0.89 (m, 2H); **^{13}C NMR** (101MHz,$CDCl_3$) δ 166.7, 155.5, 135.9, 130.4, 127.3, 122.9, 121.7, 121.6, 111.2, 109.7, 56.8, 49.7, 49.2, 41.5, 33.8, 32.4, 31.2, 26.3, 25.6, 25.4, 25.3, 24.9, 24.5, 15.3; **HRMS** (ESI, m/z) calcd for $C_{24}H_{34}N_3O_2$ $[M+H]^+$ 396.2651, found 396.2659.



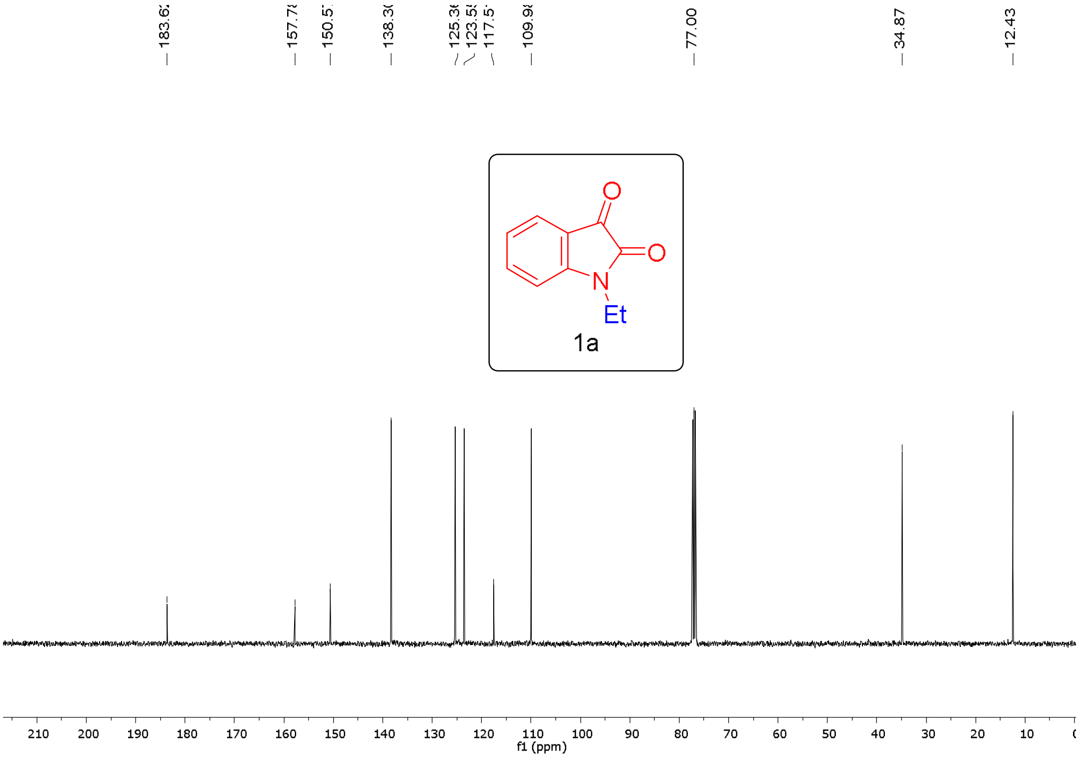
4e

5.6 ^{1}H and ^{13}C NMR Spectra of Compounds

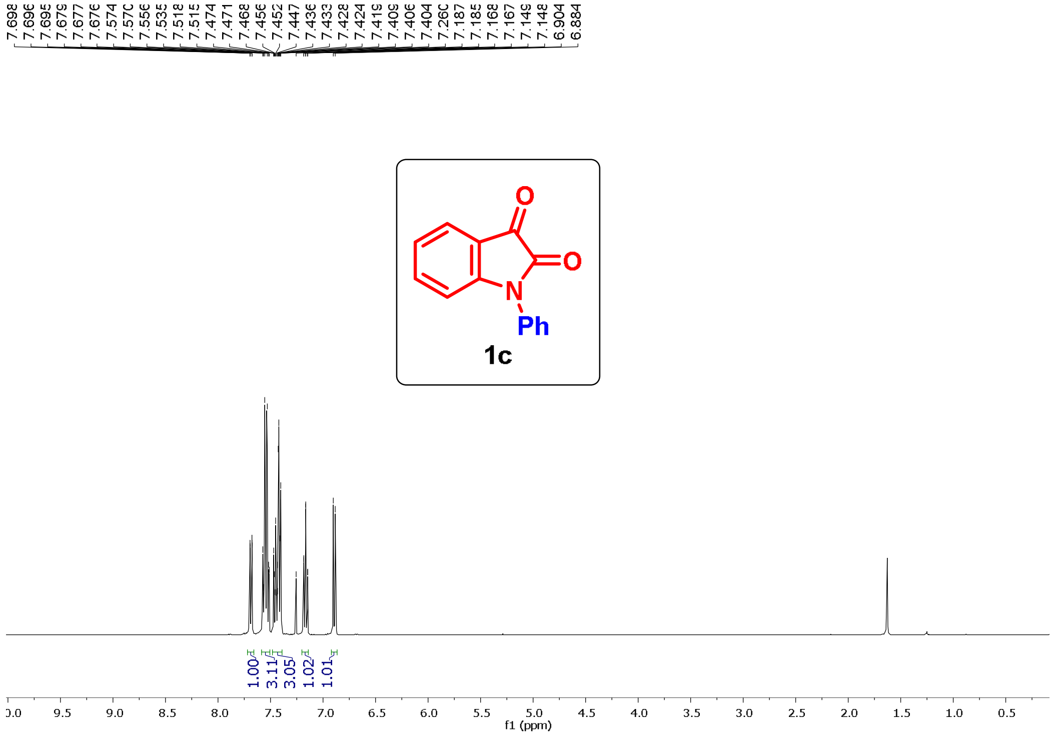
^{1}H NMR of **1a** (400 MHz, Chloroform-*d*)



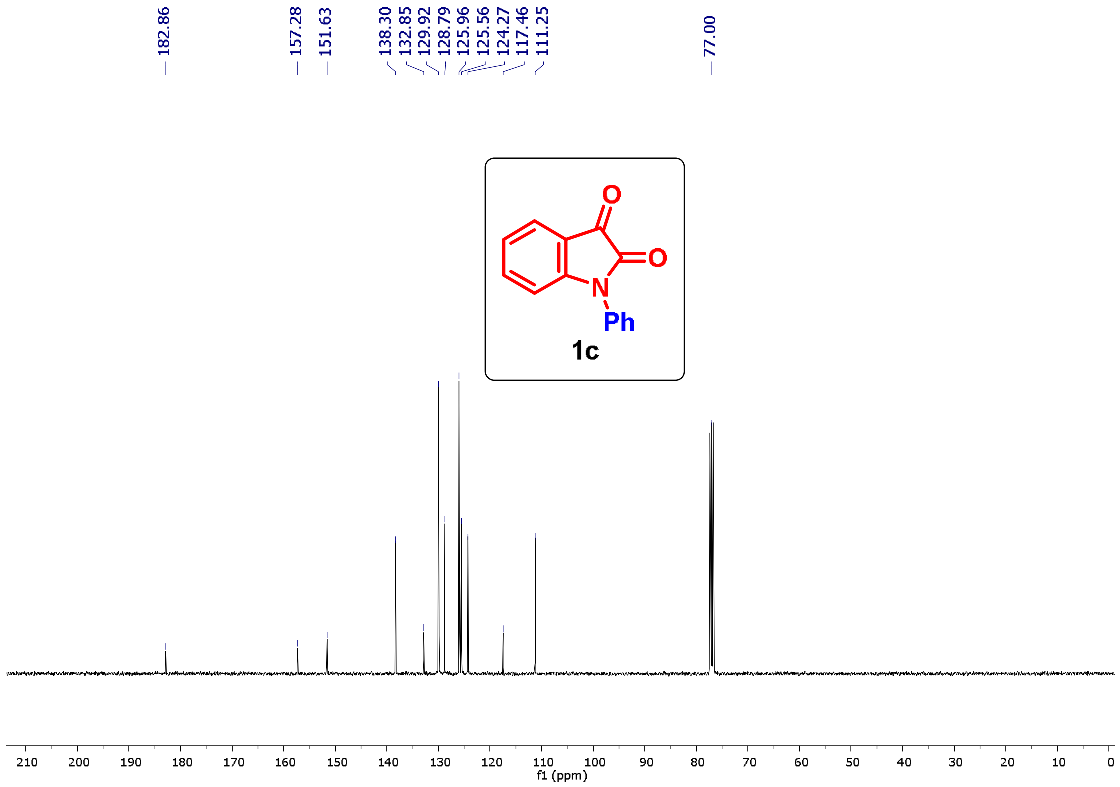
^{13}C NMR of **1a** (101 MHz, $CDCl_3$)



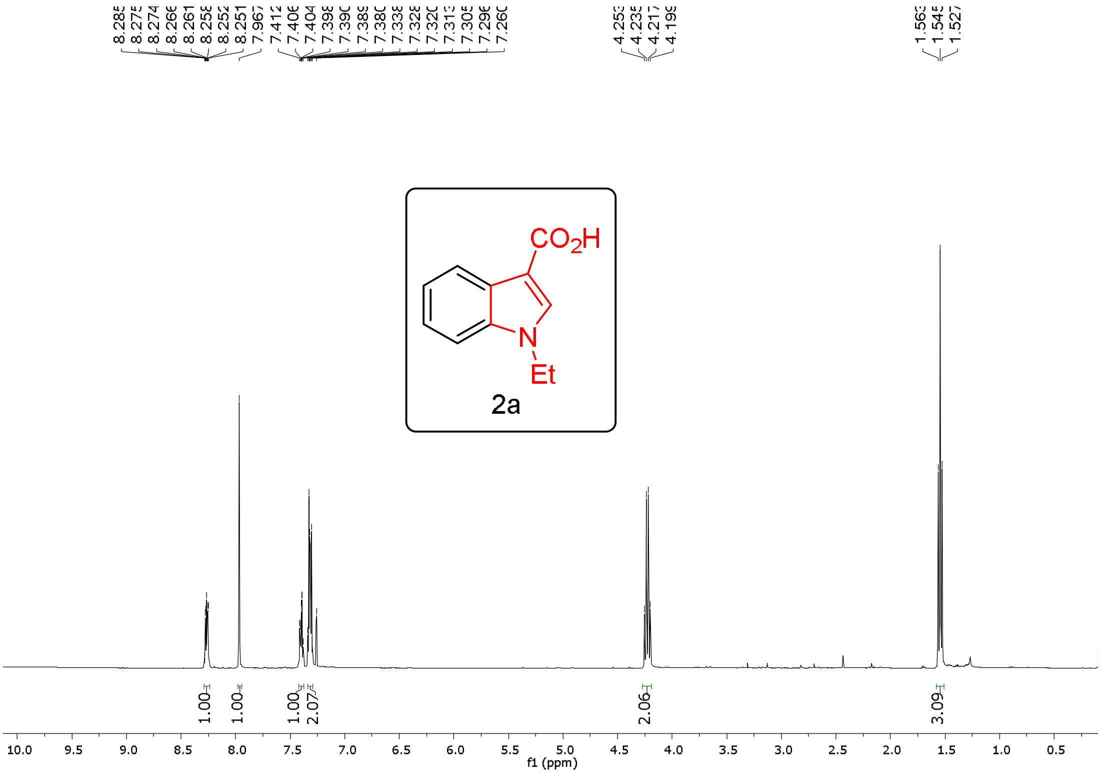
^{1}H NMR of **1c** (400 MHz, Chloroform-*d*)



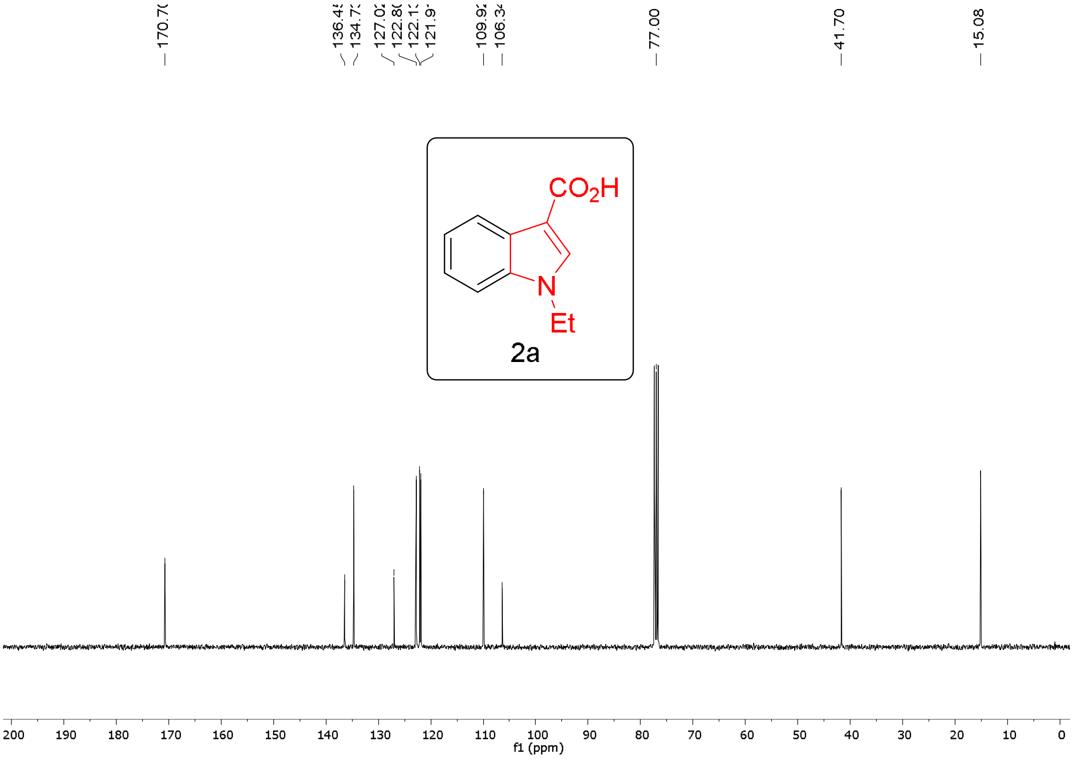
^{13}C NMR of **1c** (100 MHz, CDCl$_3$)



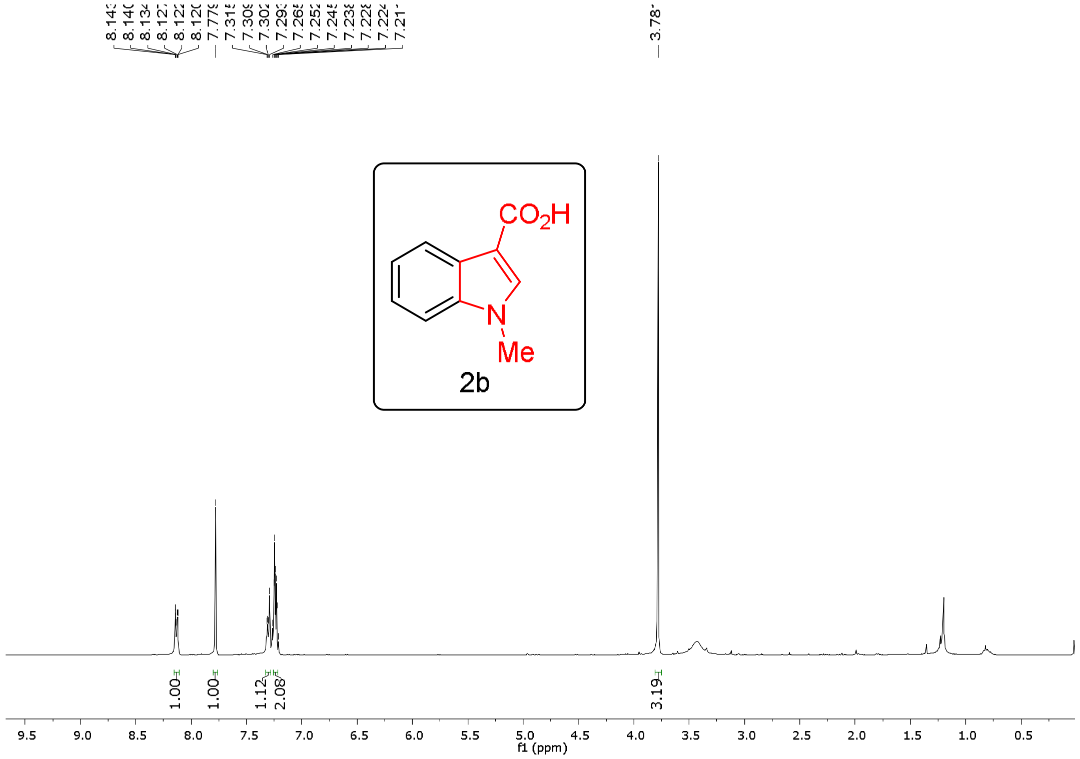
^{1}H NMR of **2a** (400 MHz, Chloroform-*d*)



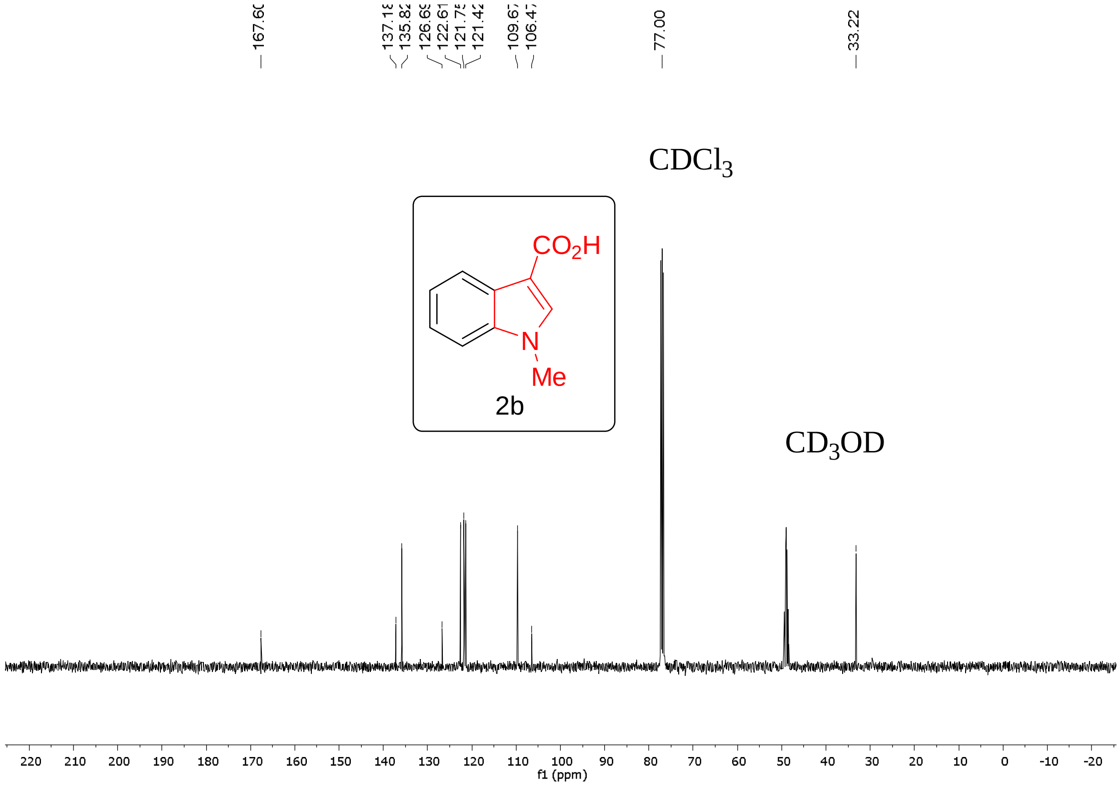
^{13}C NMR of **2a** (101 MHz, CDCl$_3$)



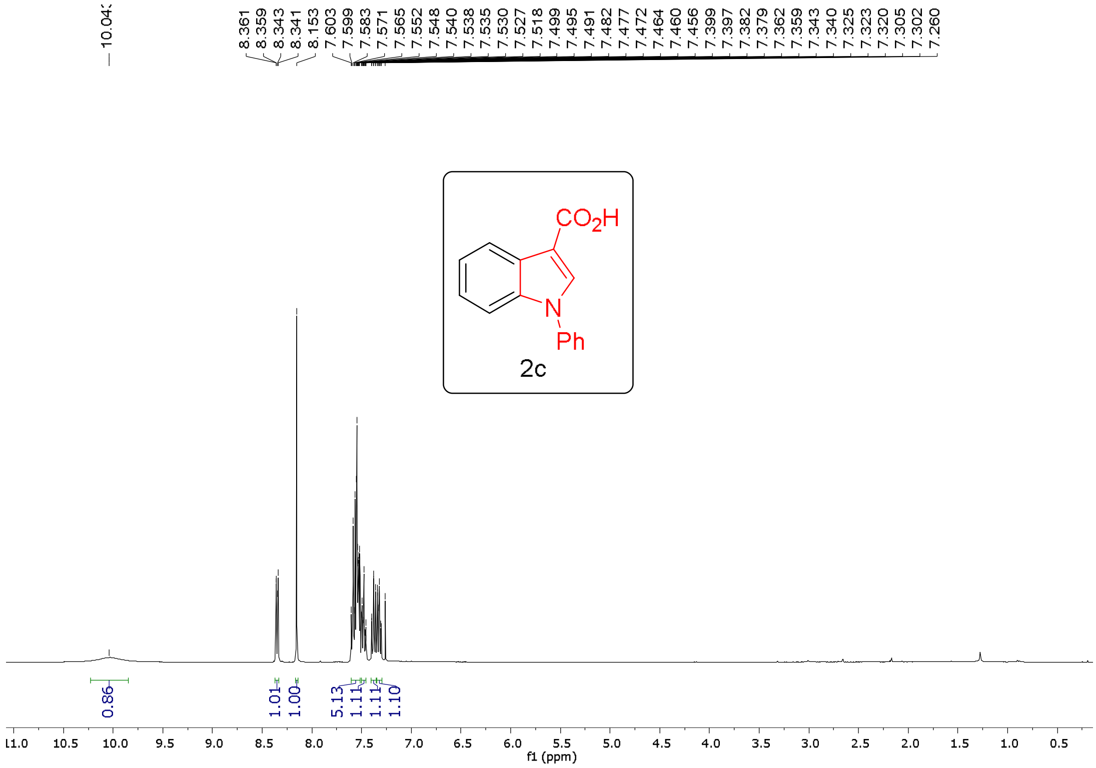
^{1}H NMR of **2b** (400 MHz, Chloroform-*d*)



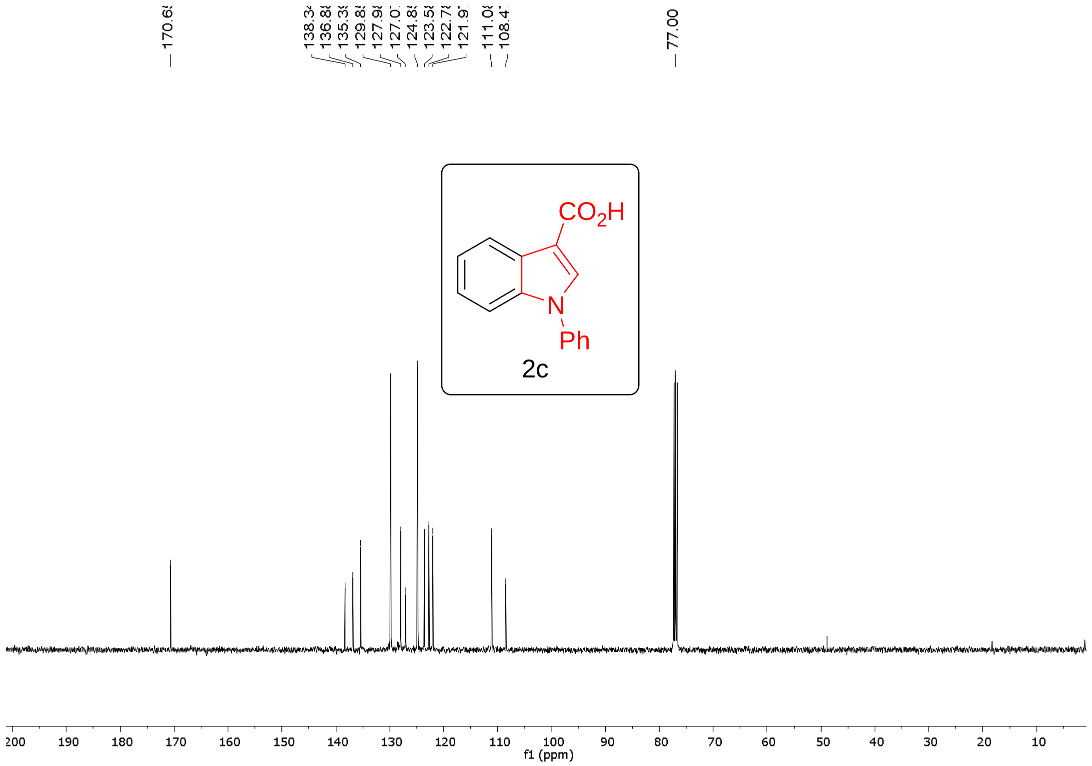
^{13}C NMR of **2b** (100 MHz, $CDCl_3$)



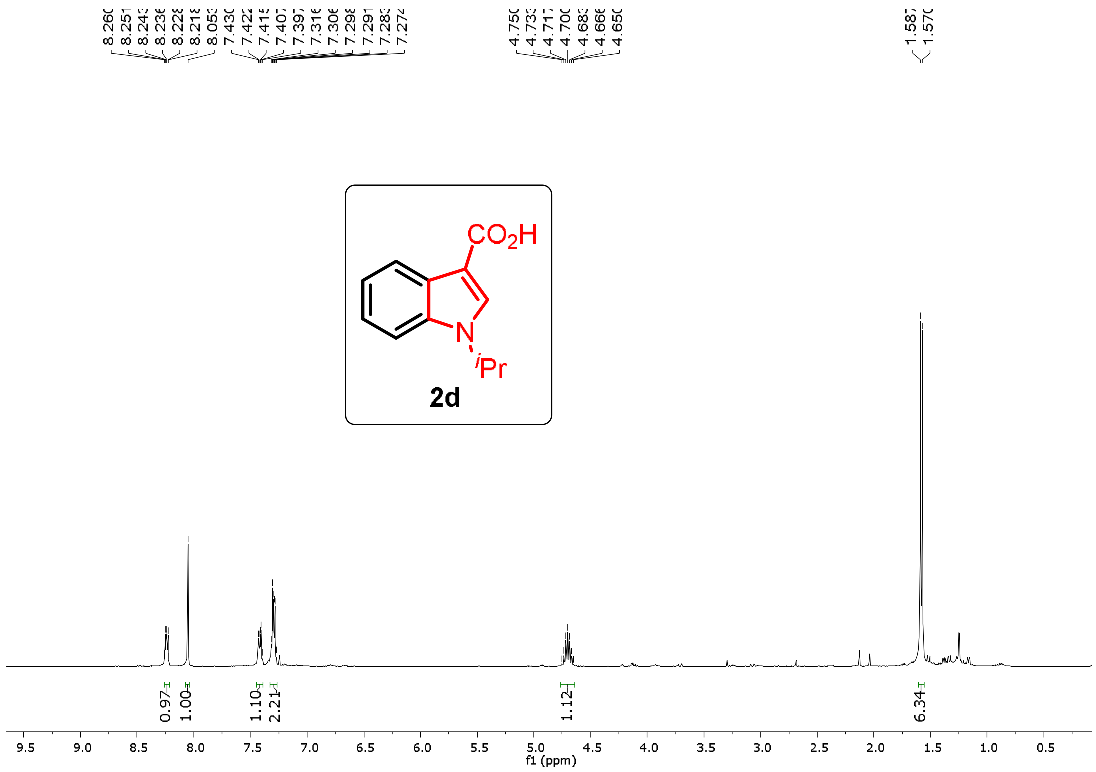
^{1}H NMR of **2c** (400 MHz, Chloroform-*d*)



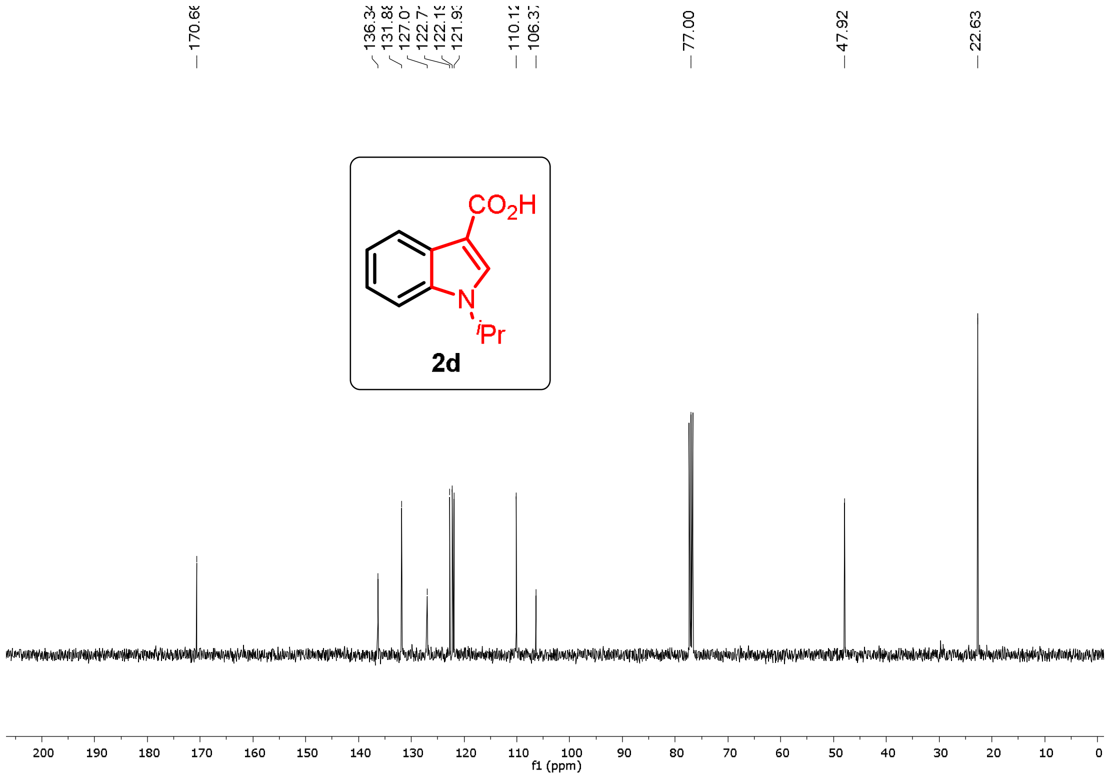
^{13}C NMR of **2c** (100 MHz, $CDCl_3$)



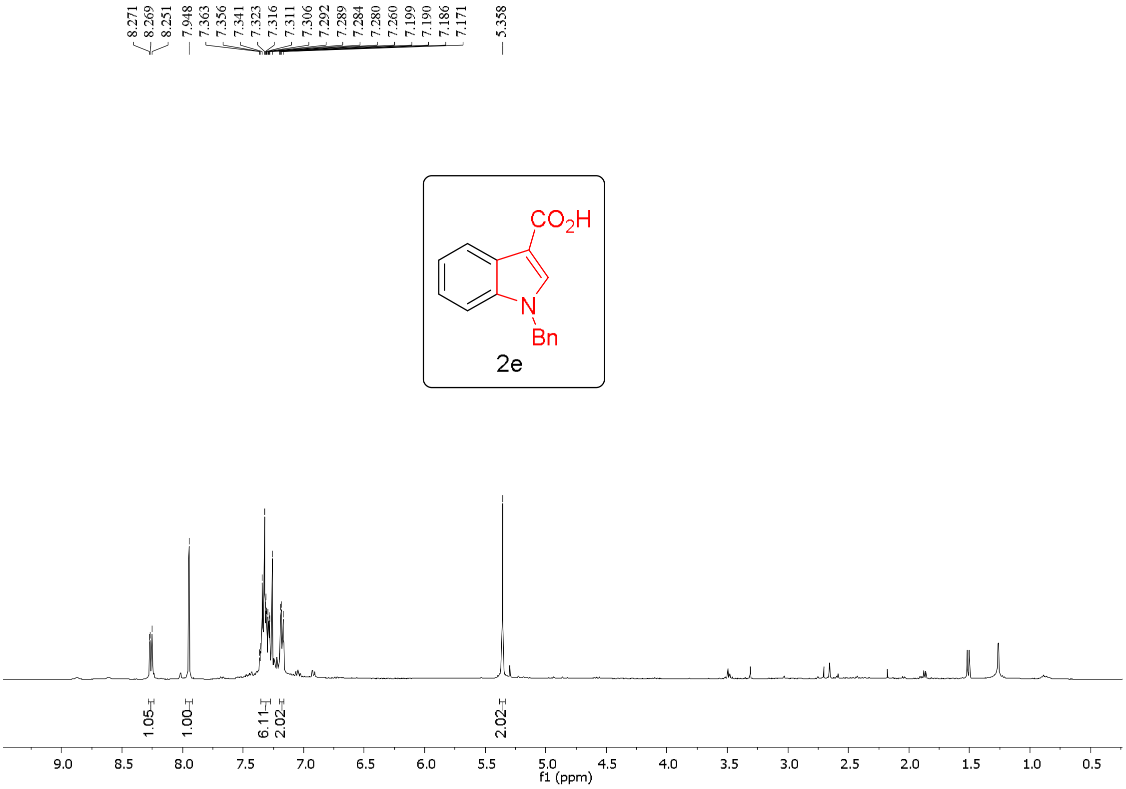
^{1}H NMR of **2d** (400 MHz, Chloroform-*d*)



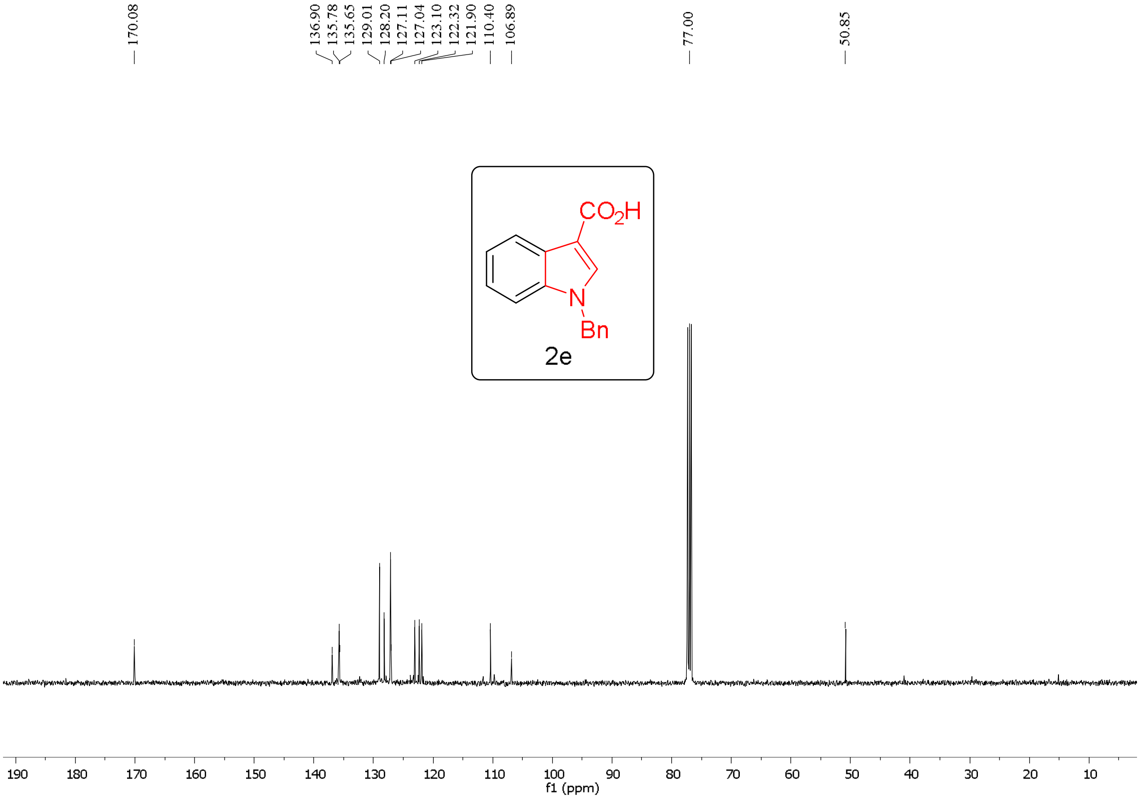
^{13}C NMR of **2d** (100 MHz, CDCl$_3$)



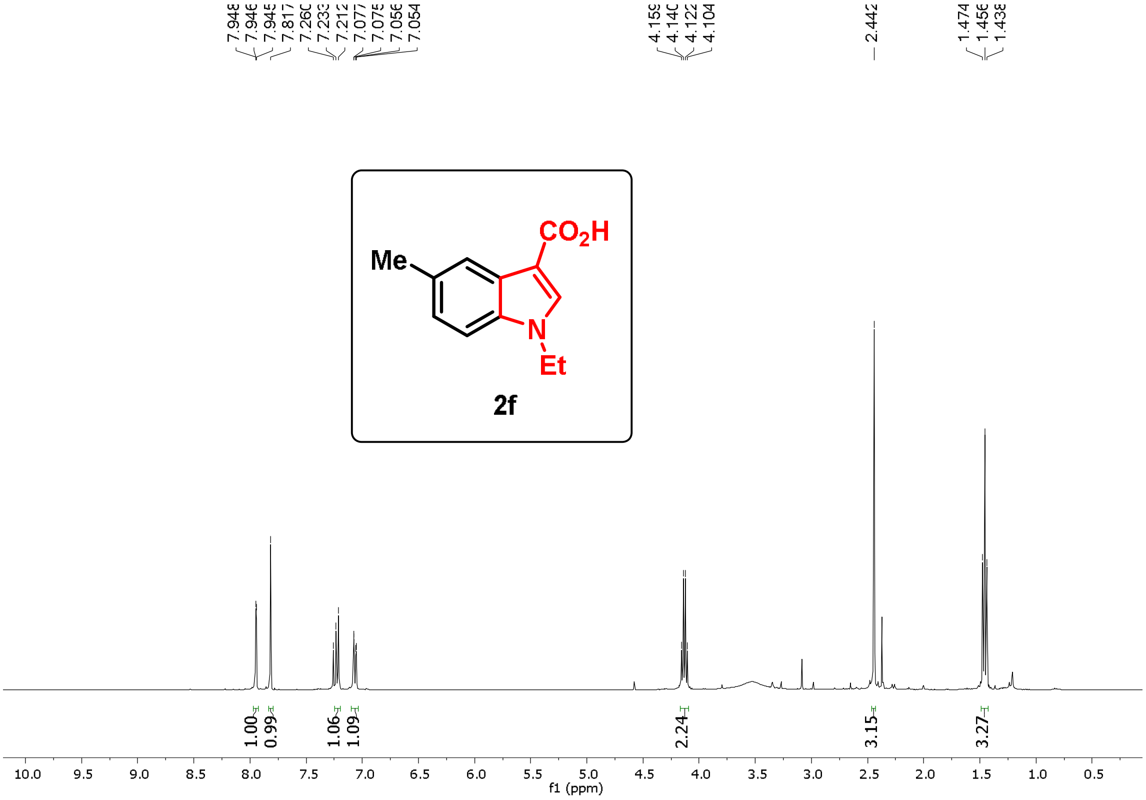
^{1}H NMR of **2e** (400 MHz, Chloroform-*d*)



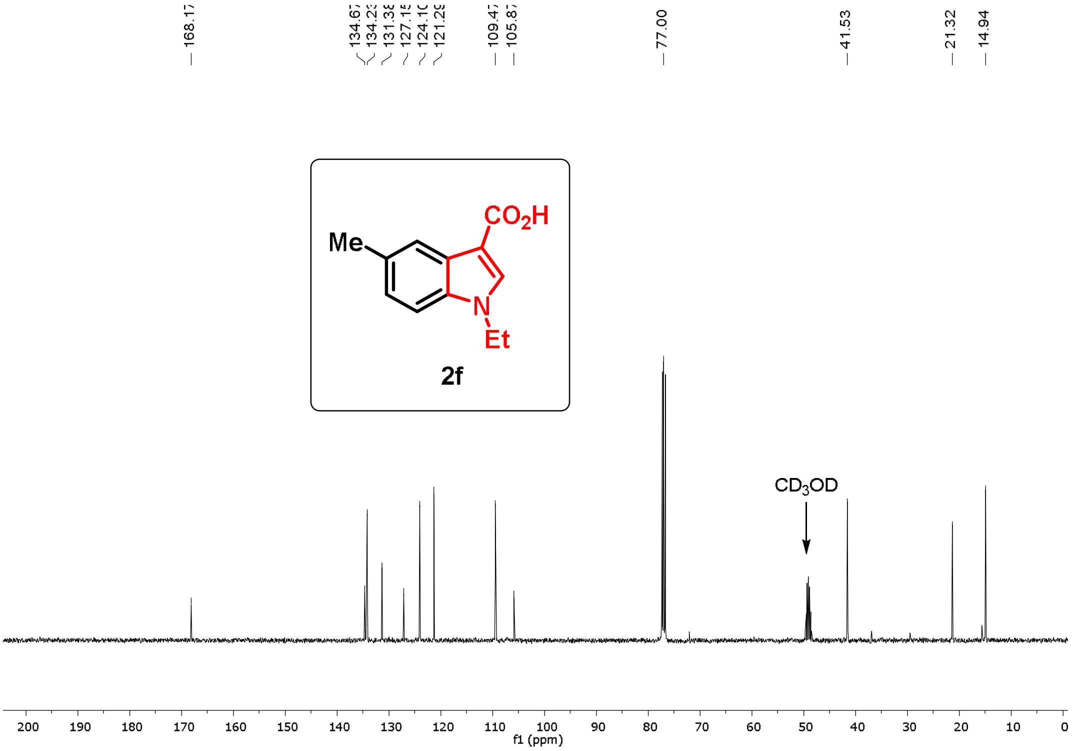
^{13}C NMR of **2e** (100 MHz, $CDCl_3$)



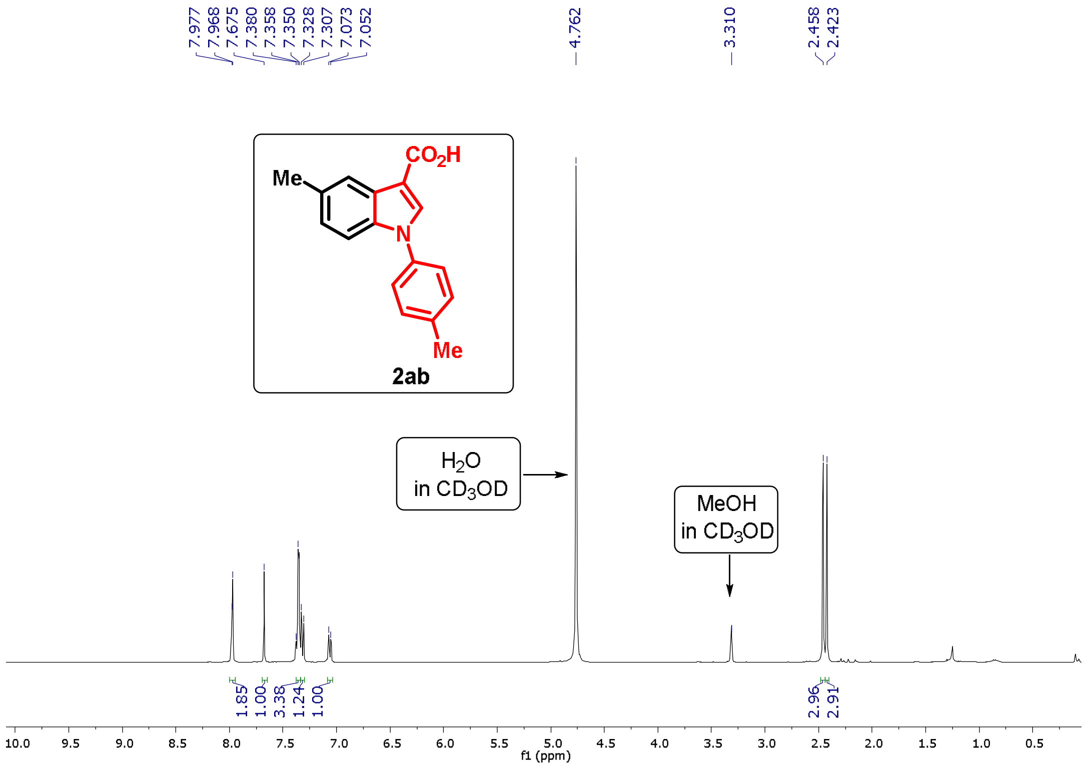
^{1}H NMR of **2f** (400 MHz, Chloroform-*d*)



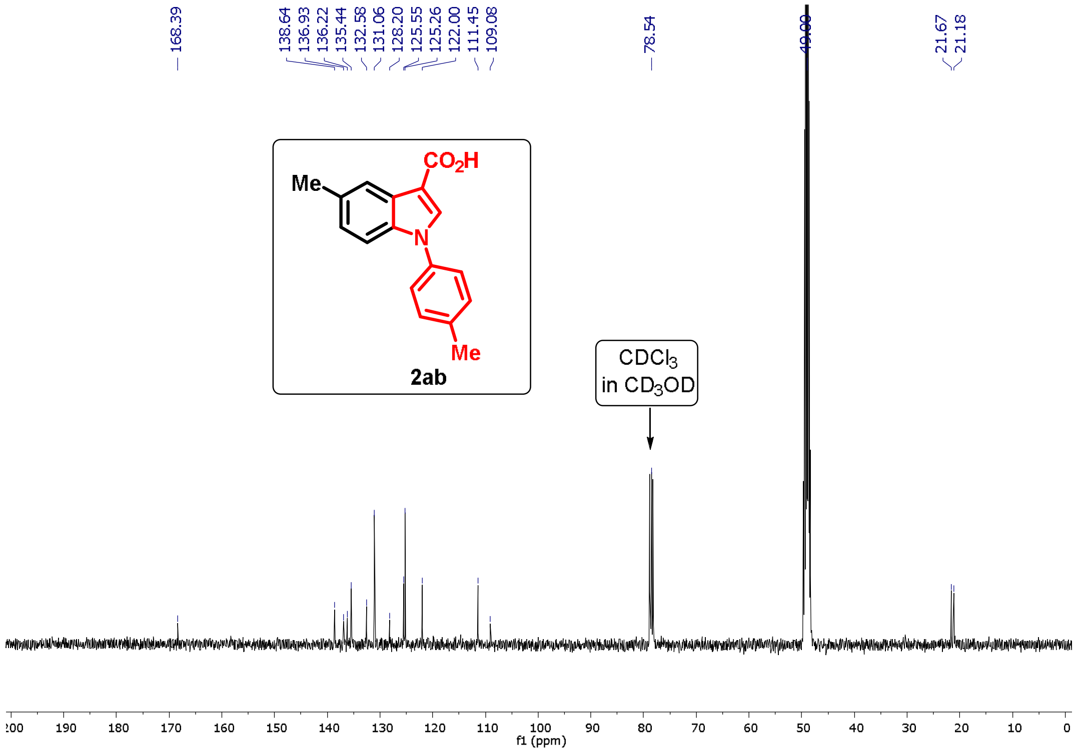
^{13}C NMR of **2f** (100 MHz, CDCl$_3$)



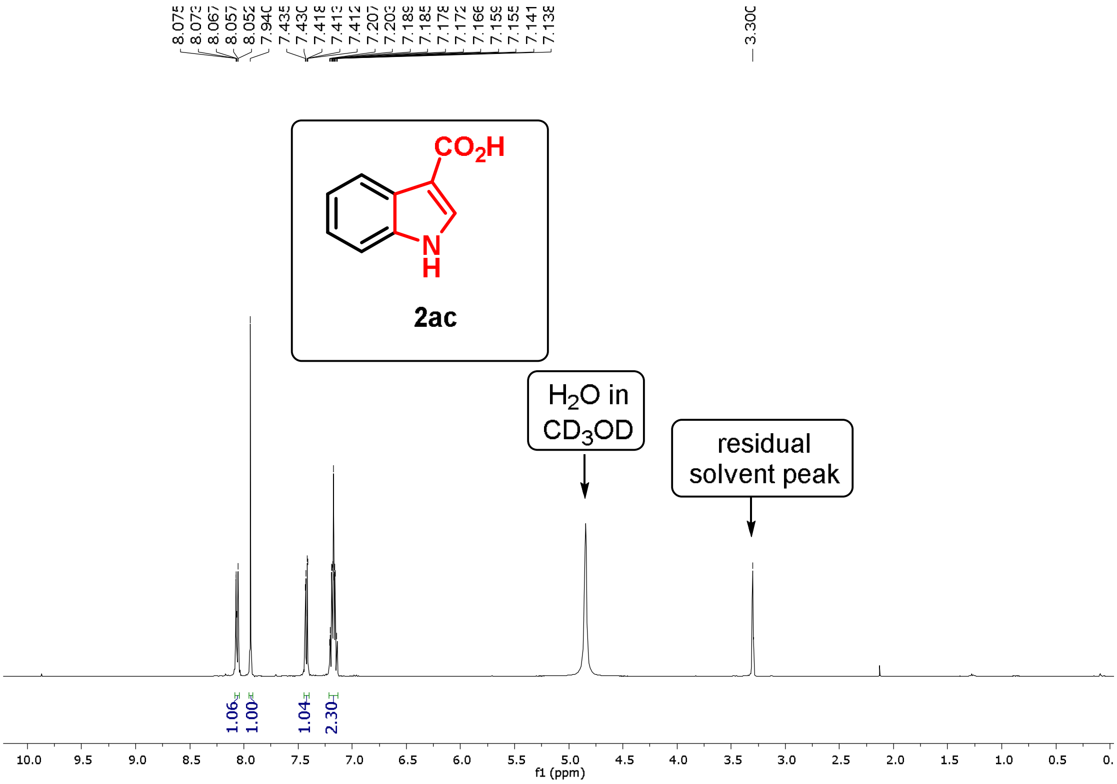
^{1}H NMR of **2ab** (400 MHz, Methanol-d^4)



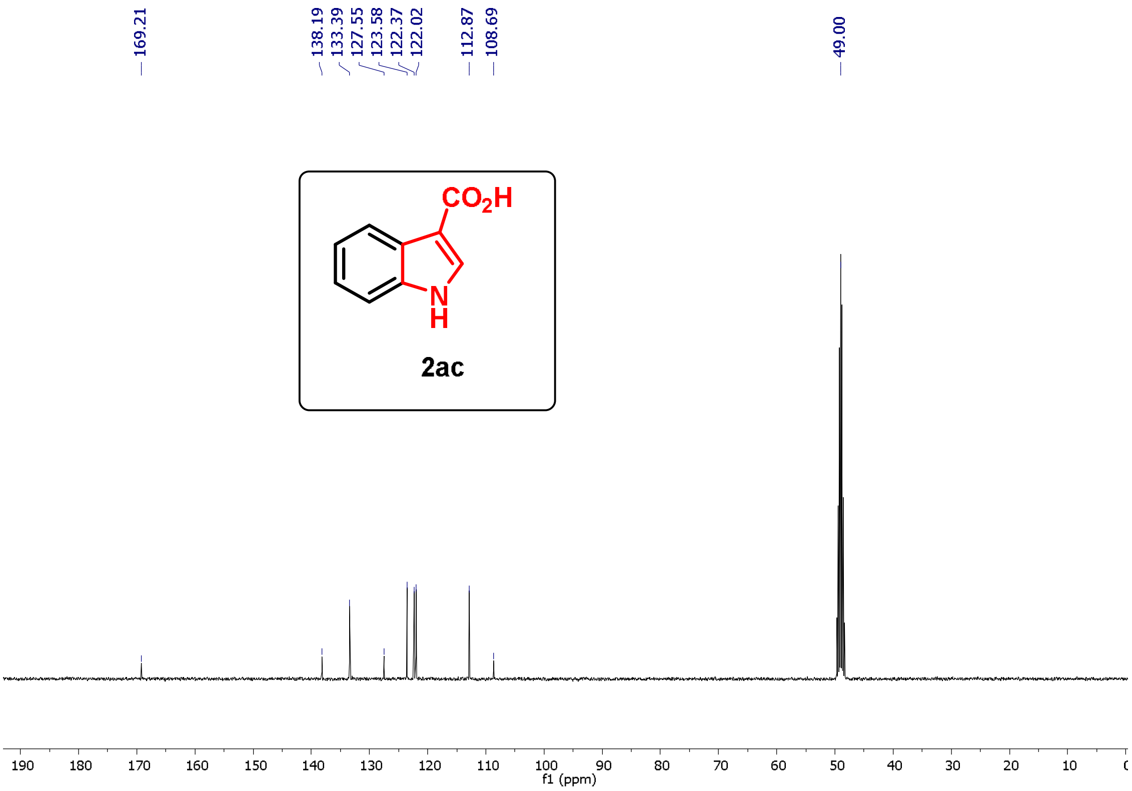
^{13}C NMR of **2ab** (100 MHz, Methanol-d^4)



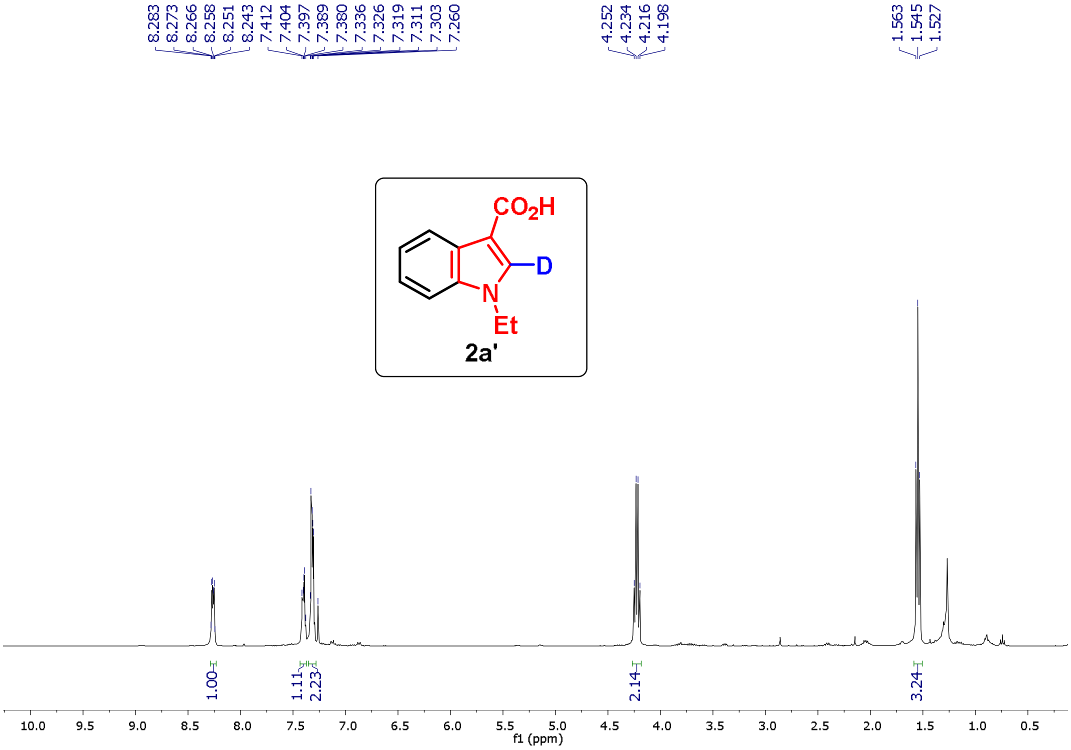
^{1}H NMR of **2ac** (400 MHz, Methanol-d^{4})



^{13}C NMR of **2ac** (100 MHz, CD$_3$OD)



^{1}H NMR of **2a′** (400 MHz, Chloroform-*d*)



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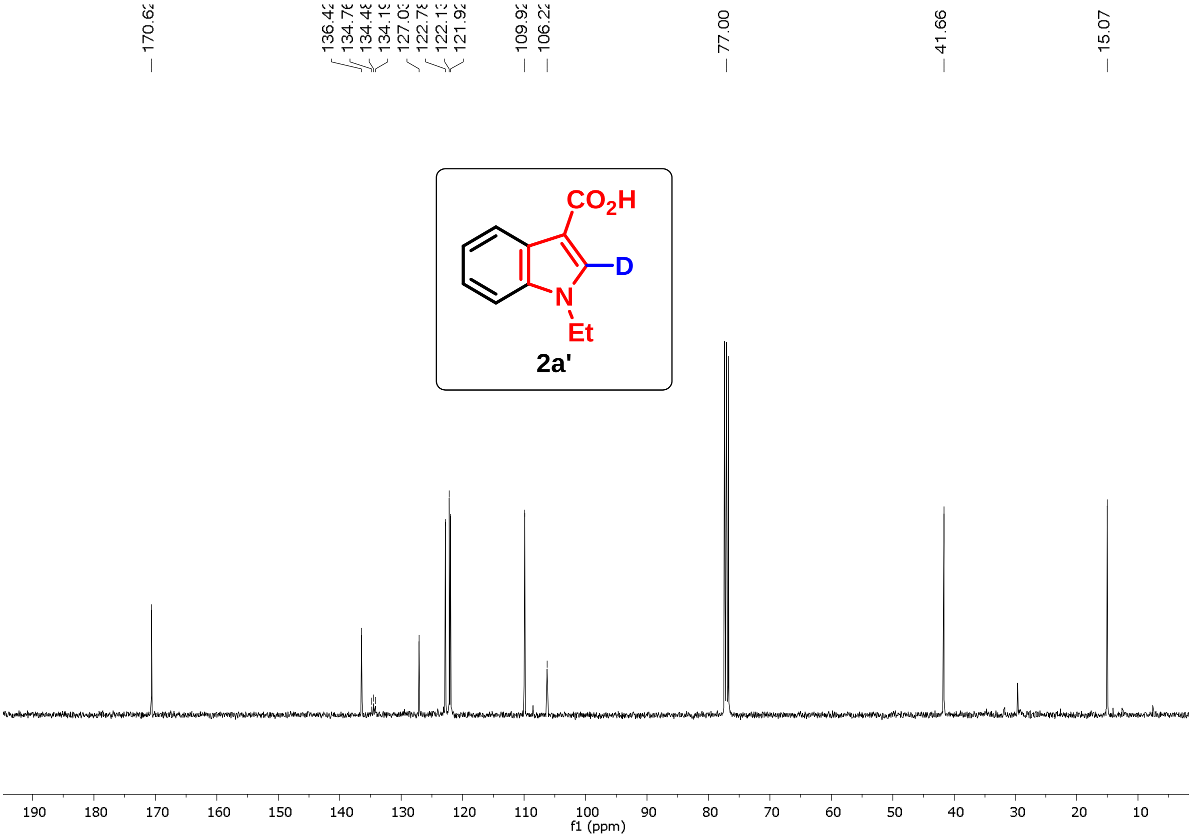

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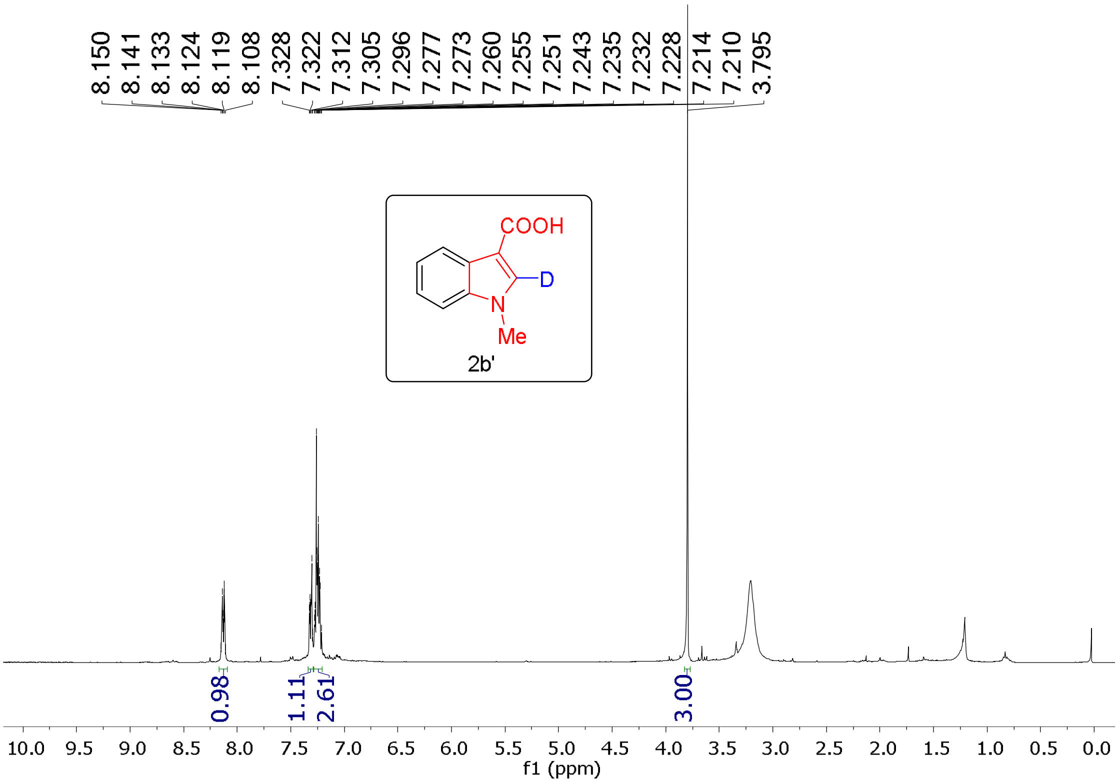

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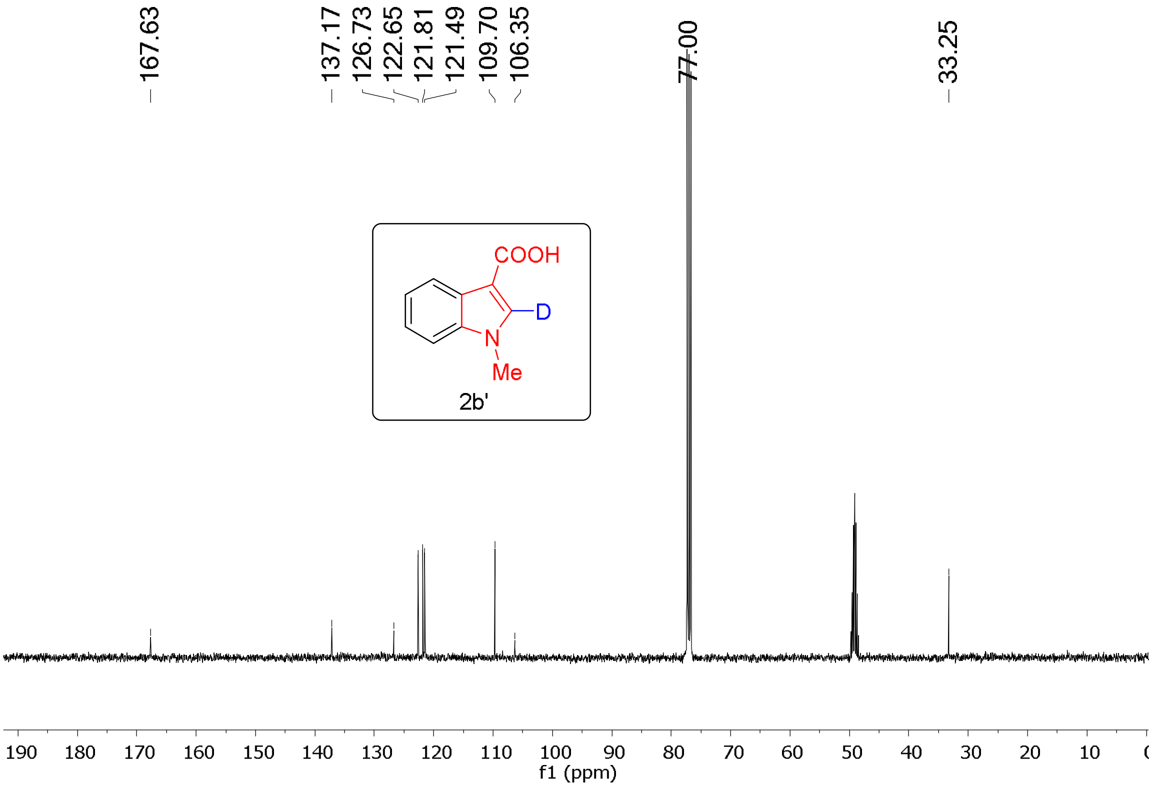

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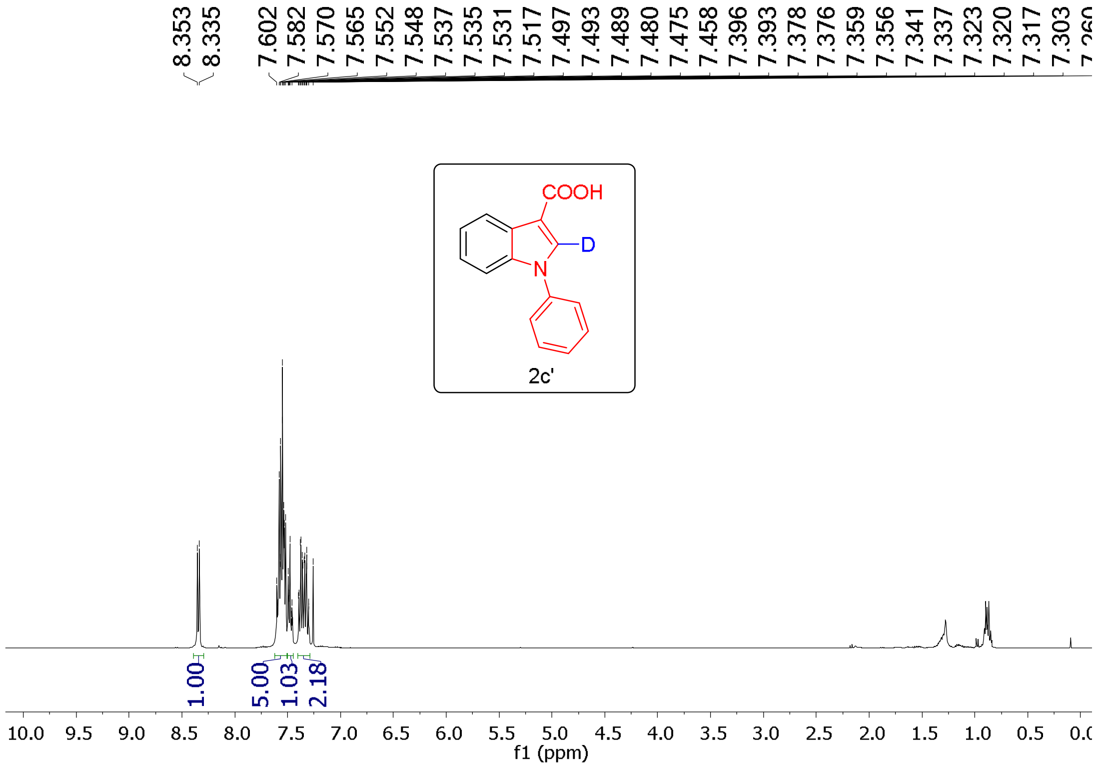

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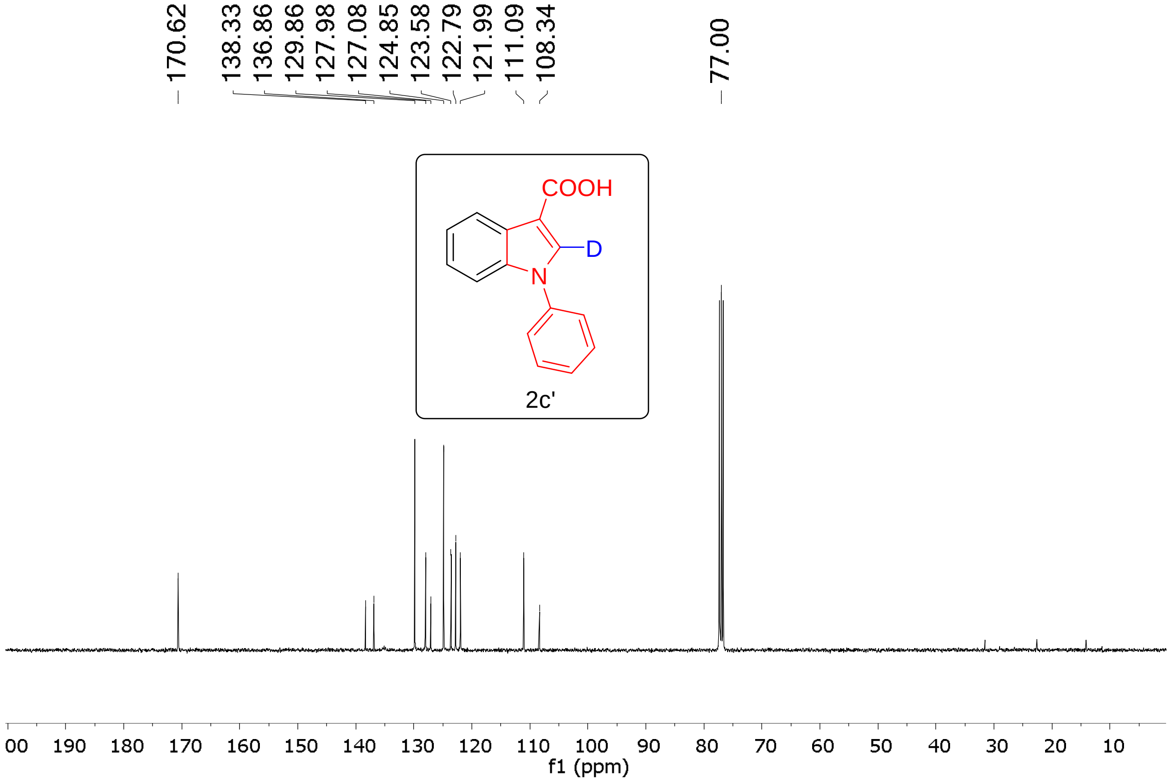

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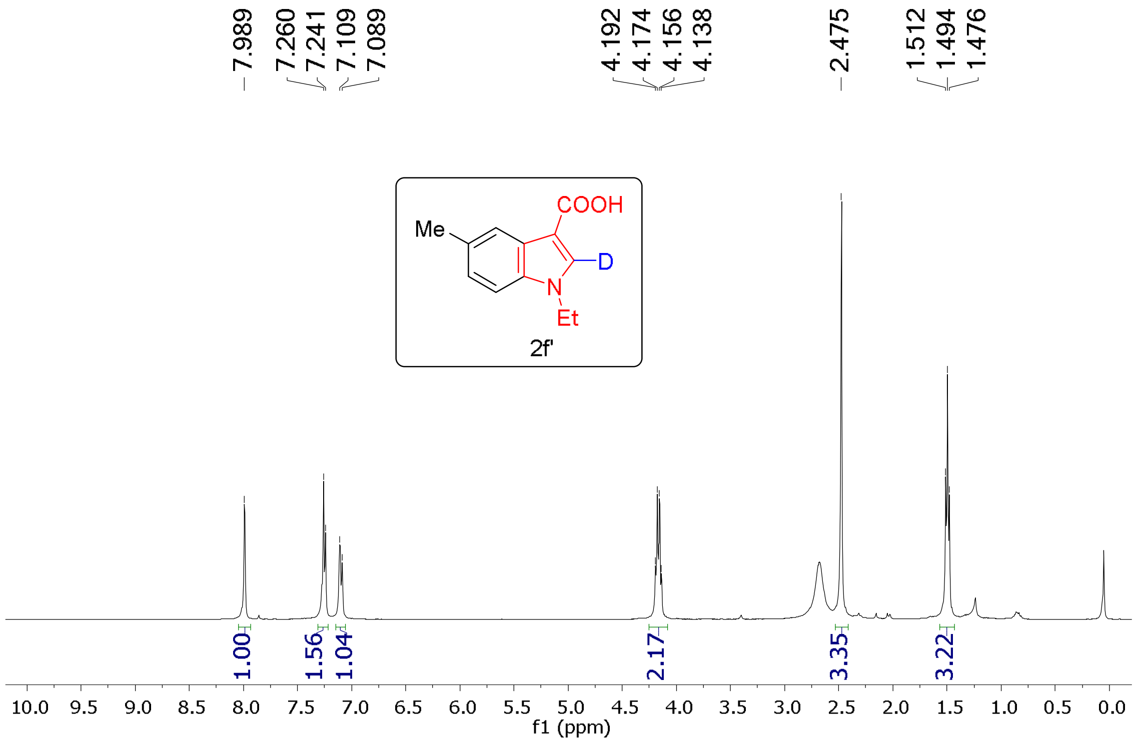

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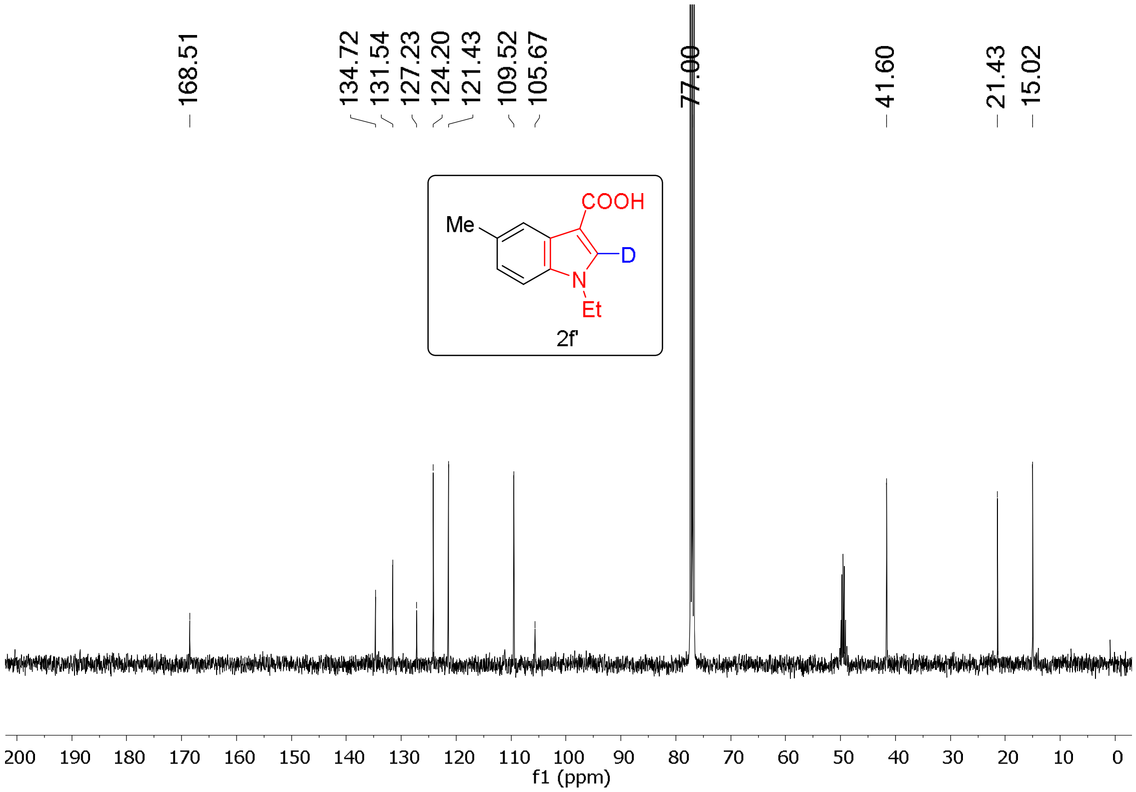

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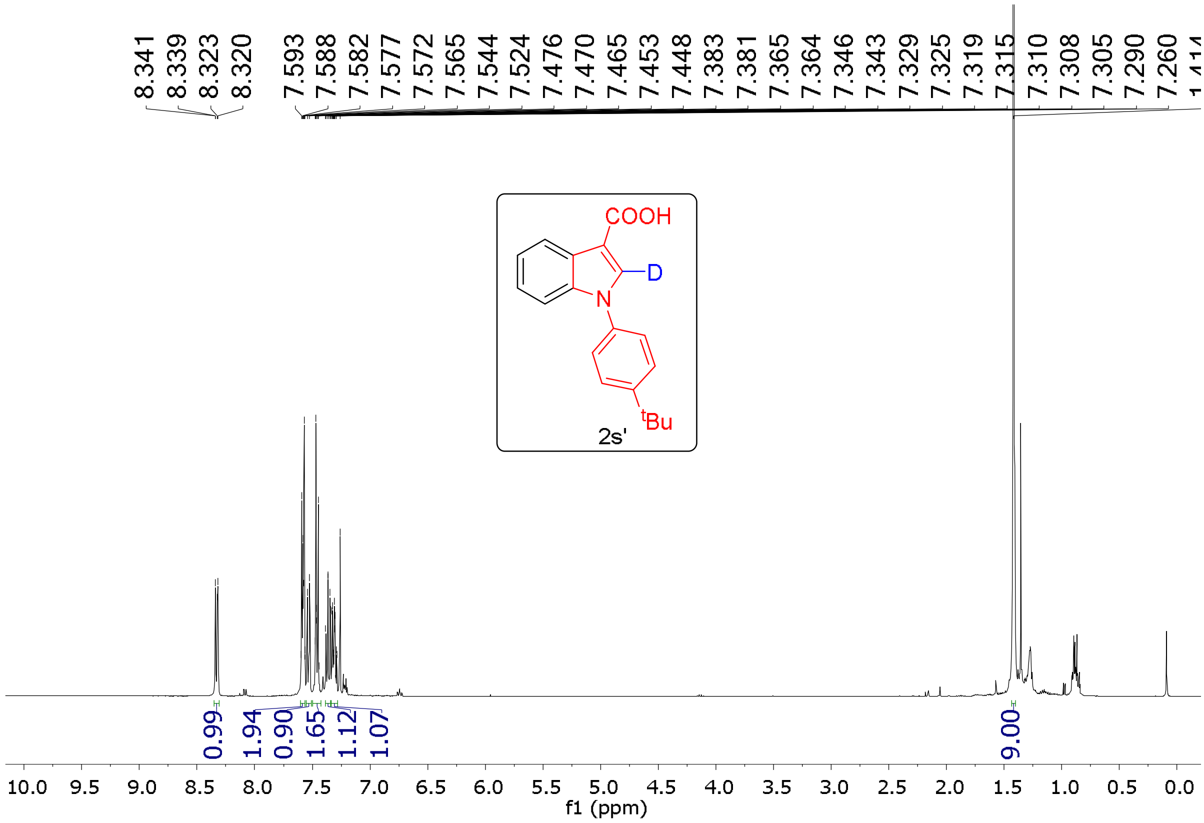

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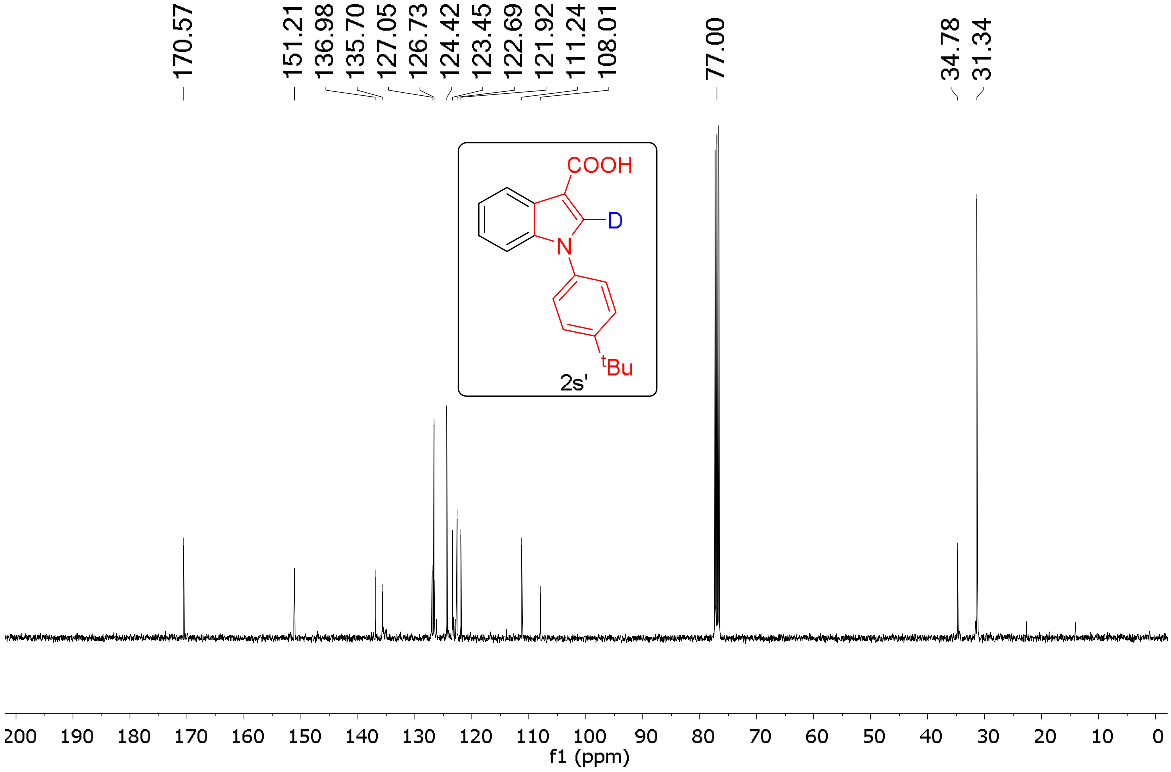

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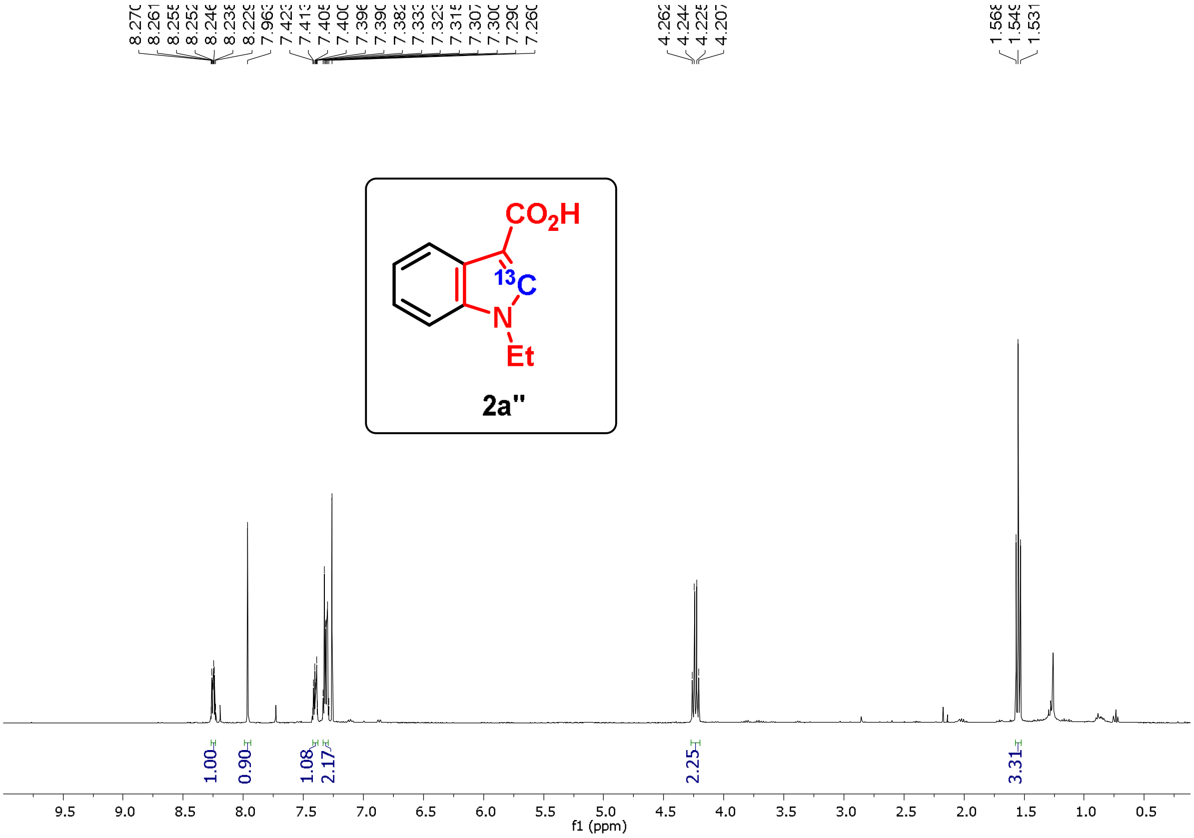

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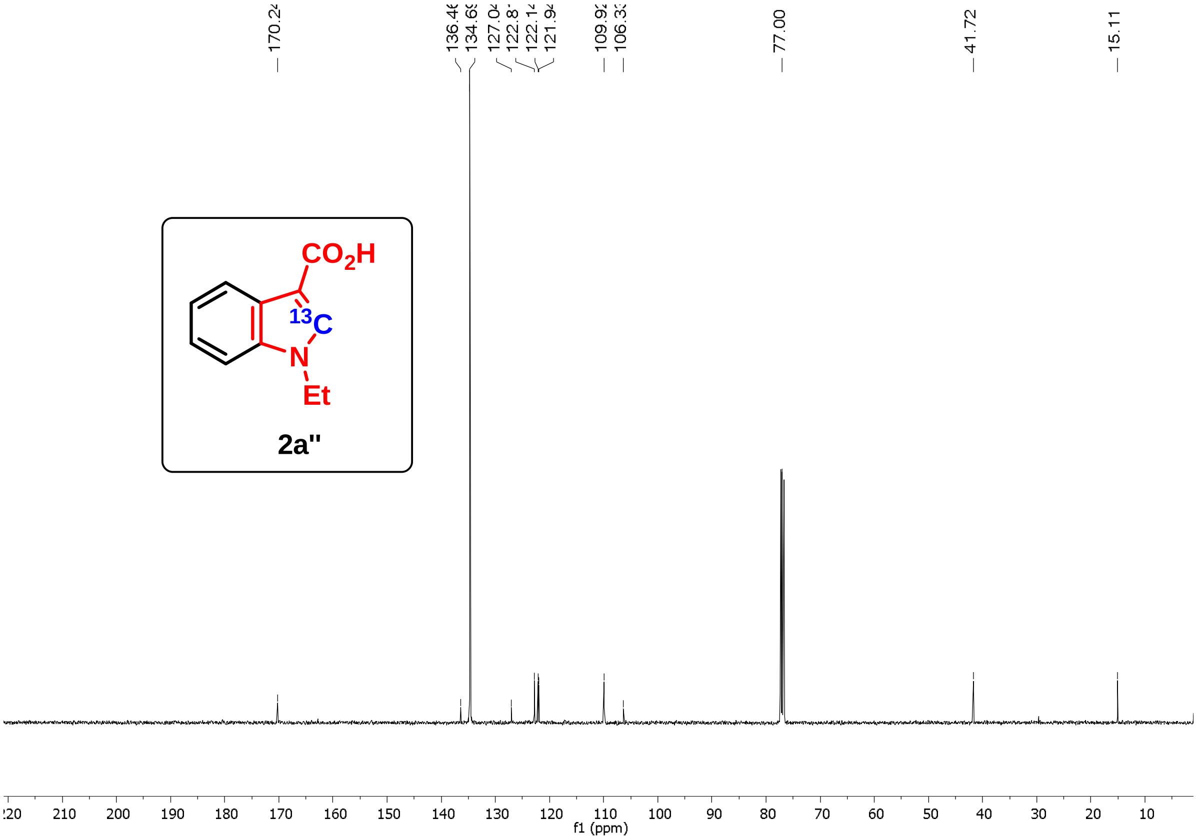

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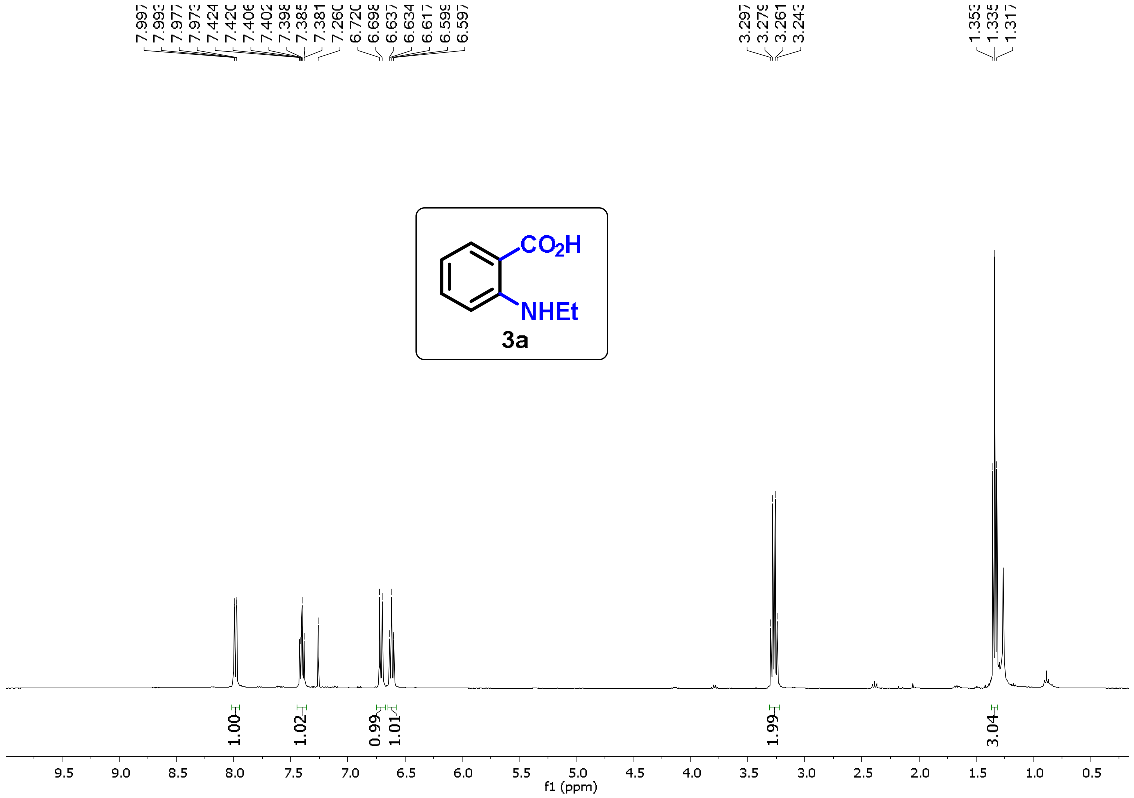
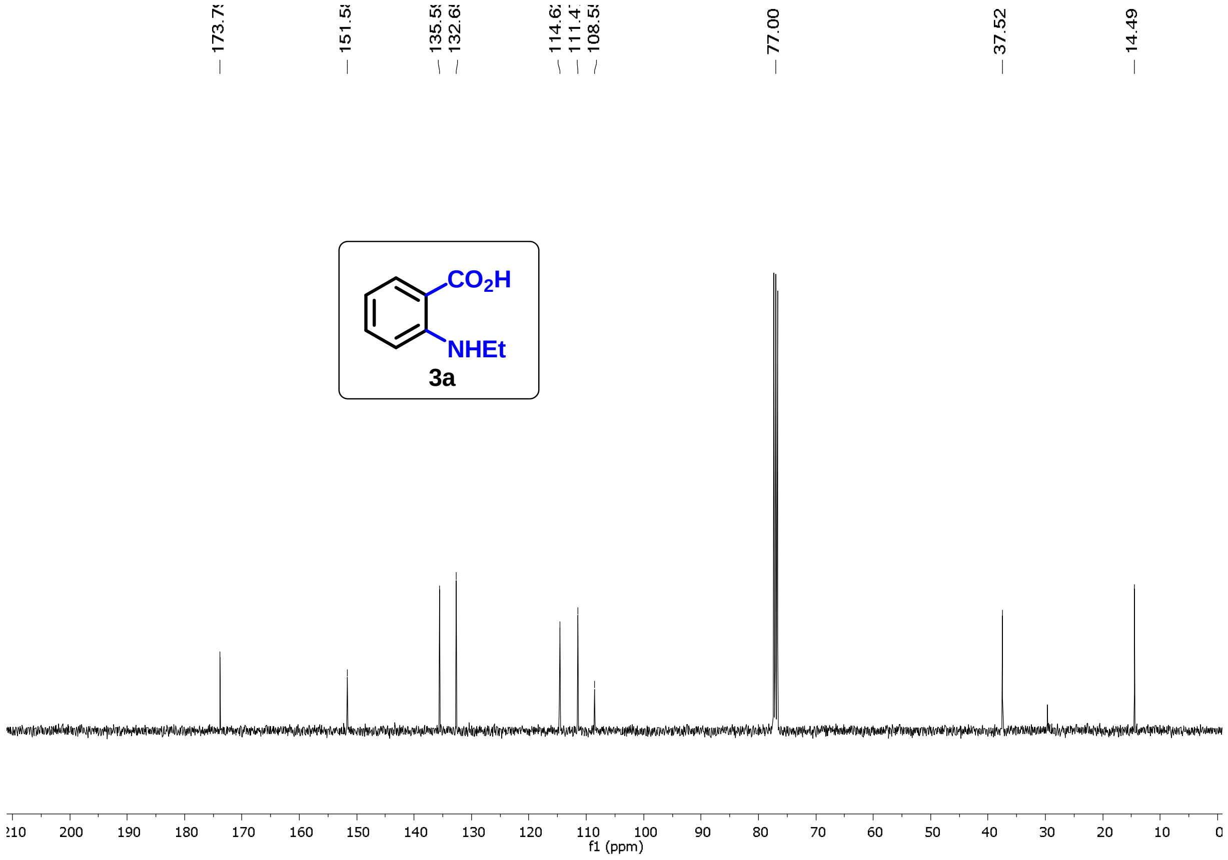
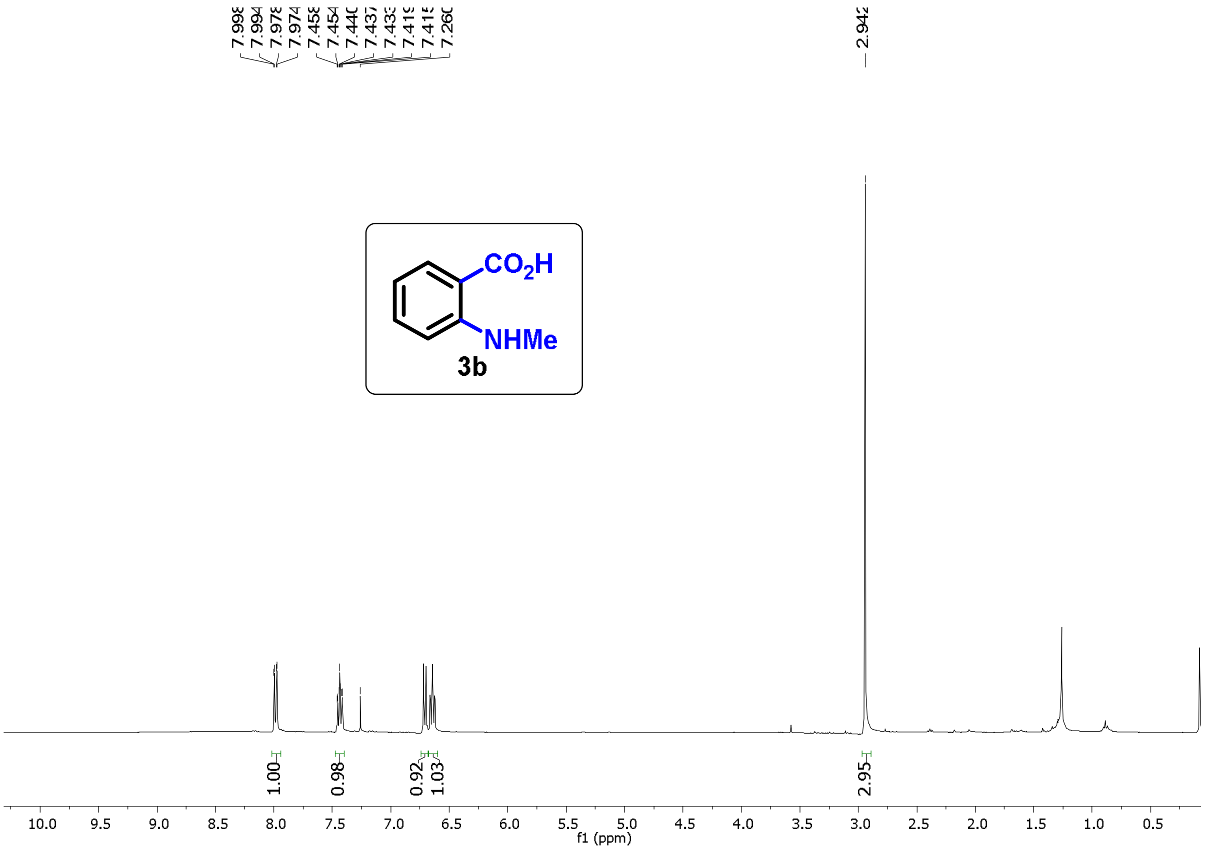


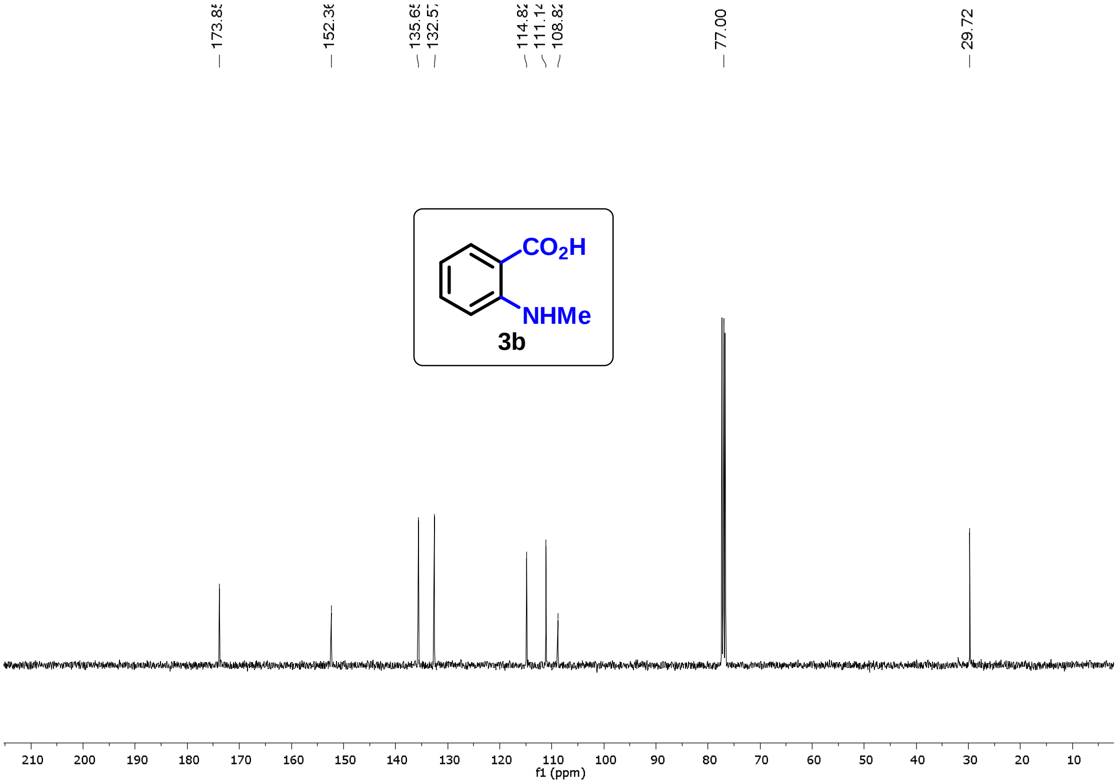
^{13}C NMR of **3a** (100 MHz, CDCl$_3$)



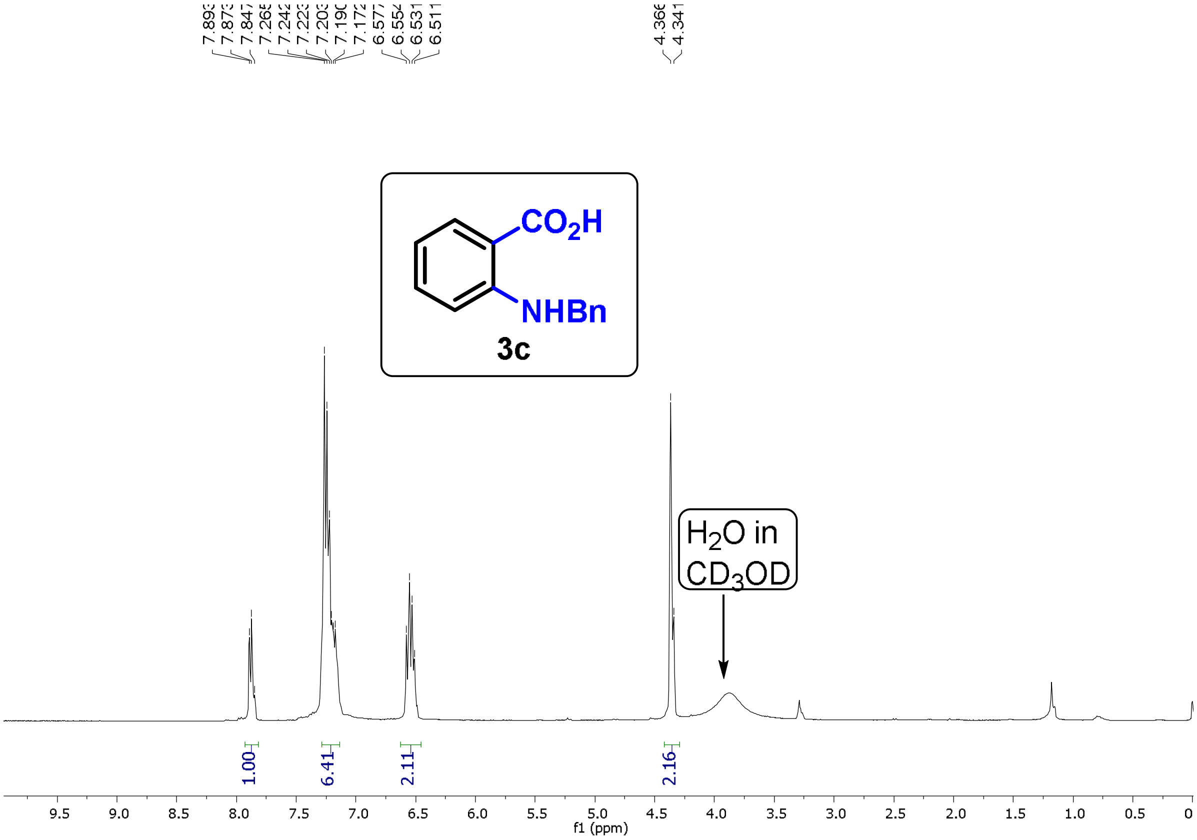
^{1}H NMR of **3b** (400 MHz, Chloroform-*d*)



^{13}C NMR of **3b** (100 MHz, CDCl$_3$)



^{1}H NMR of **3c** (400 MHz, Chloroform-*d*)



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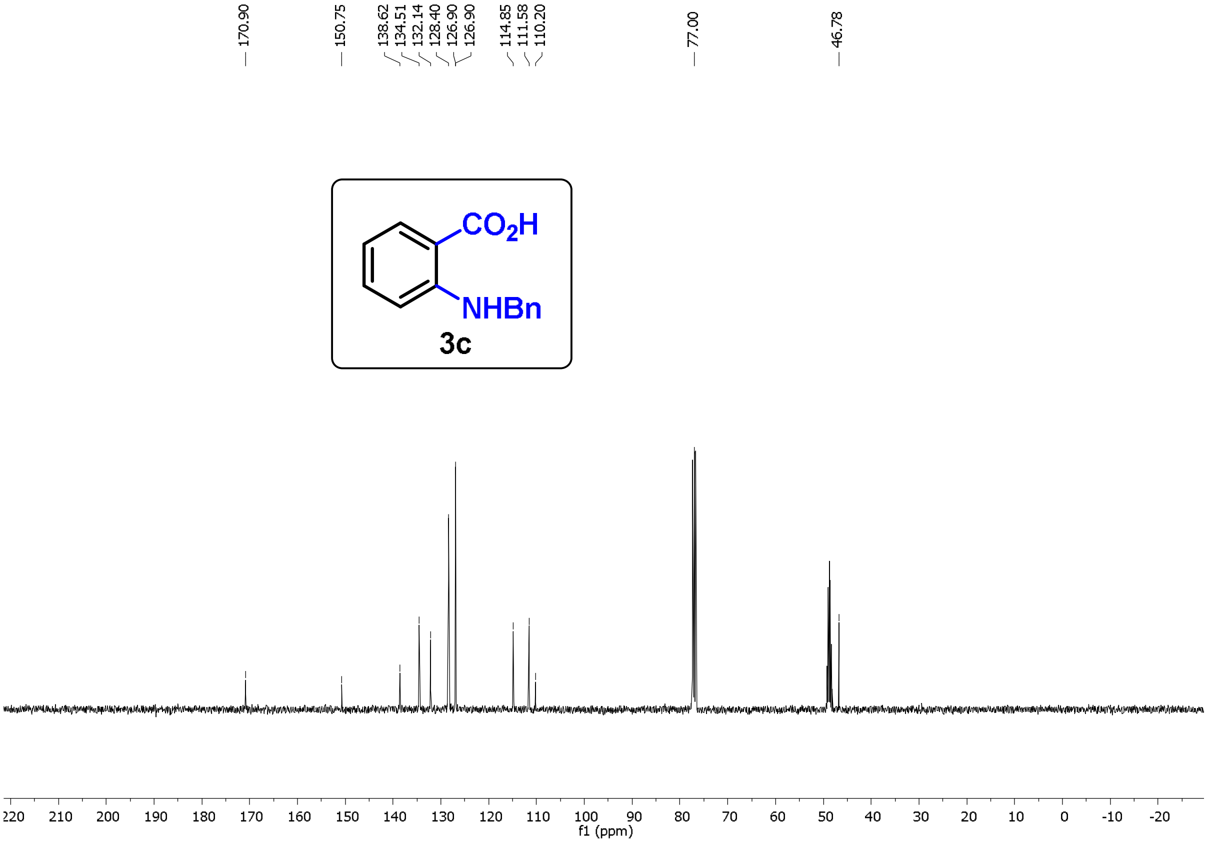
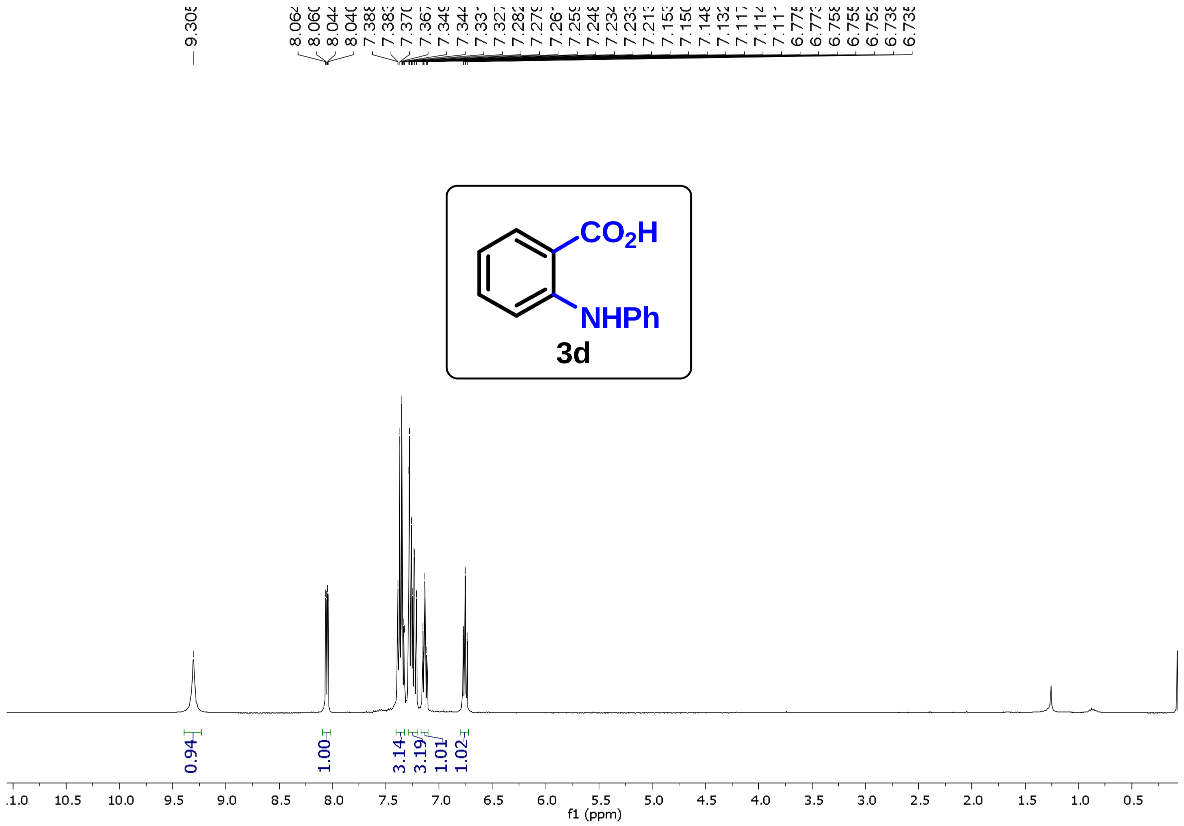


^{1}H NMR of **3d** (400 MHz, Chloroform-*d*)



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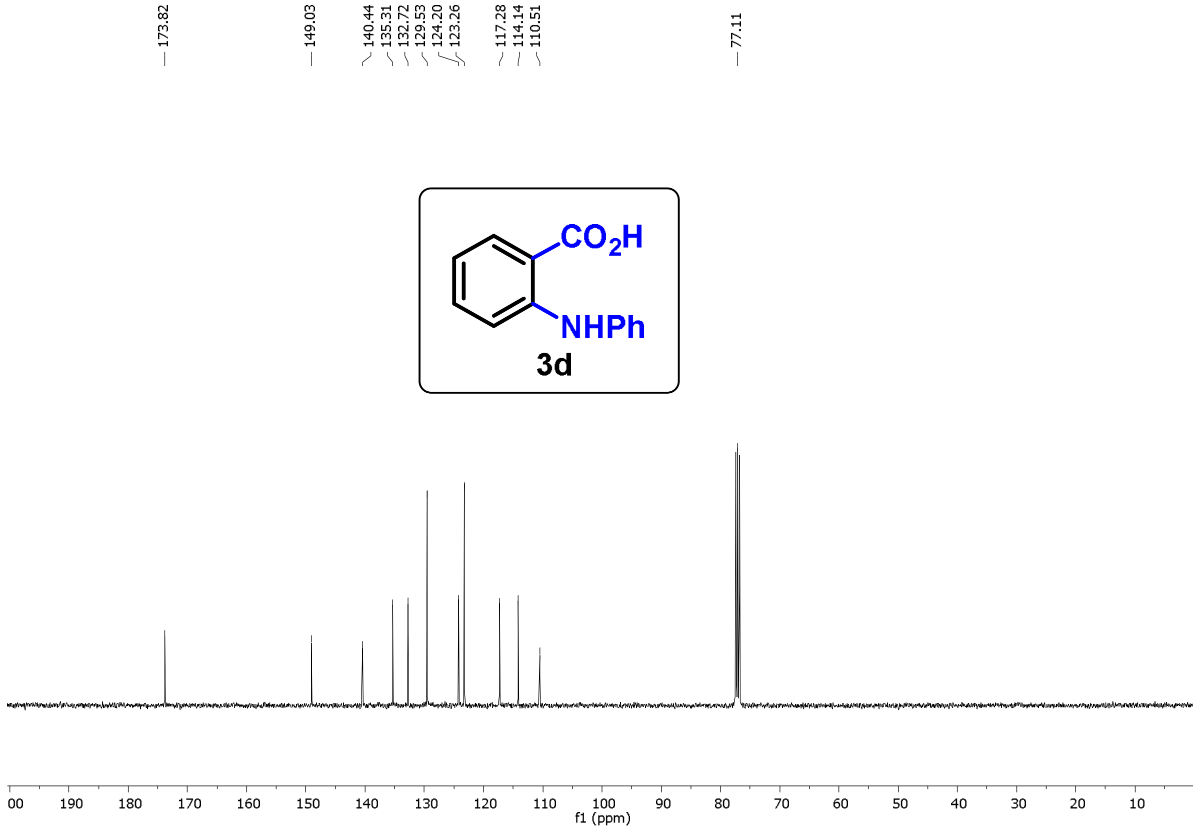

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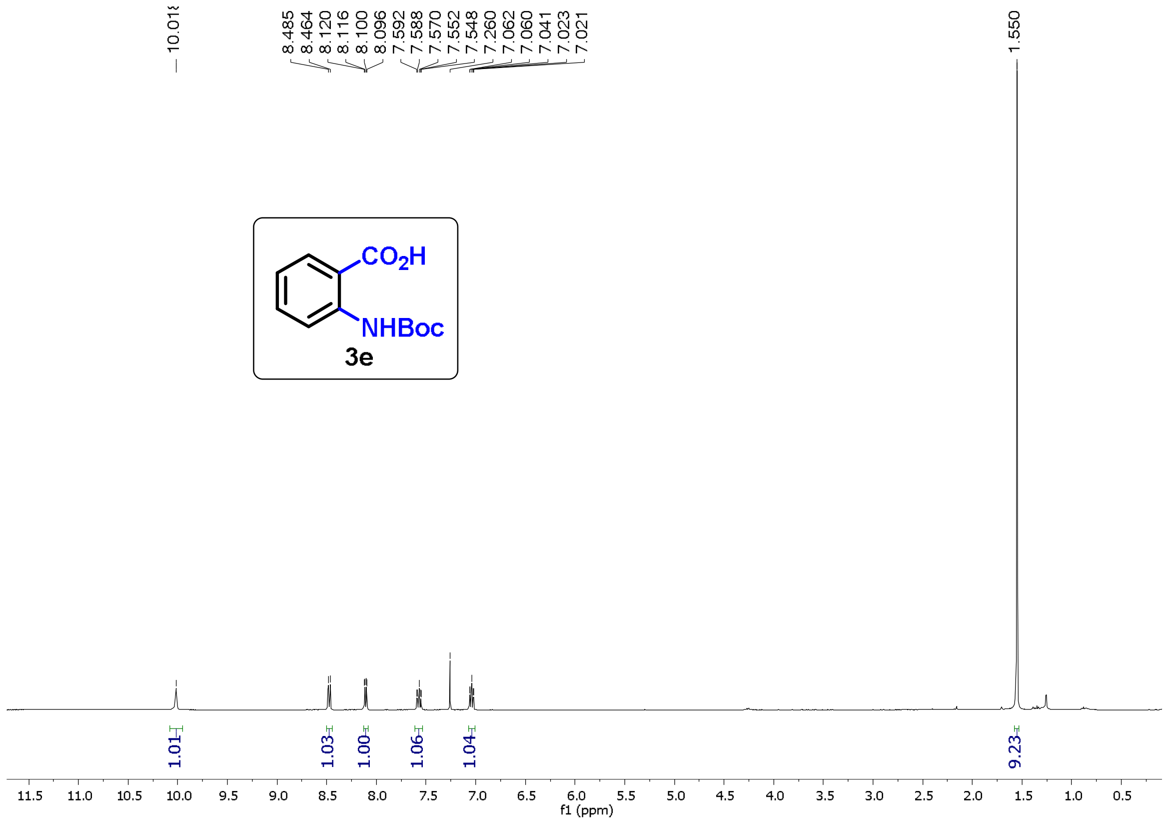

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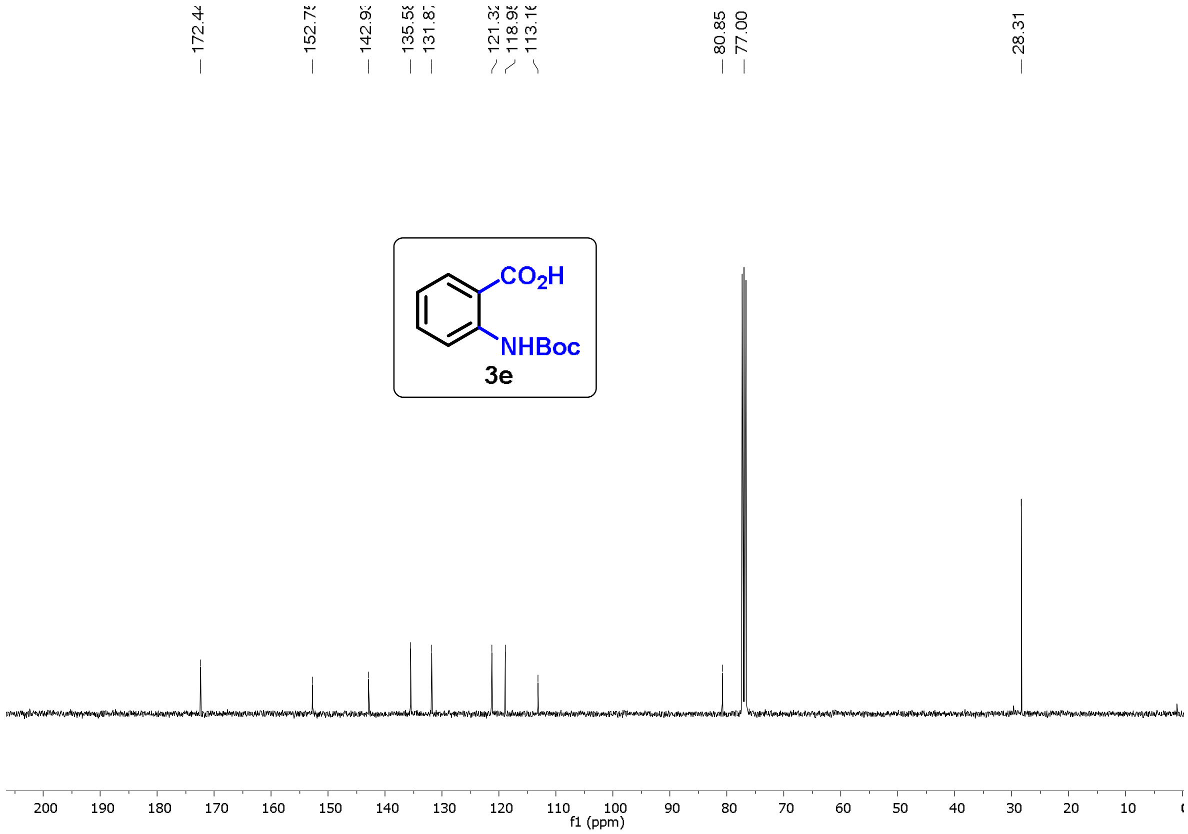
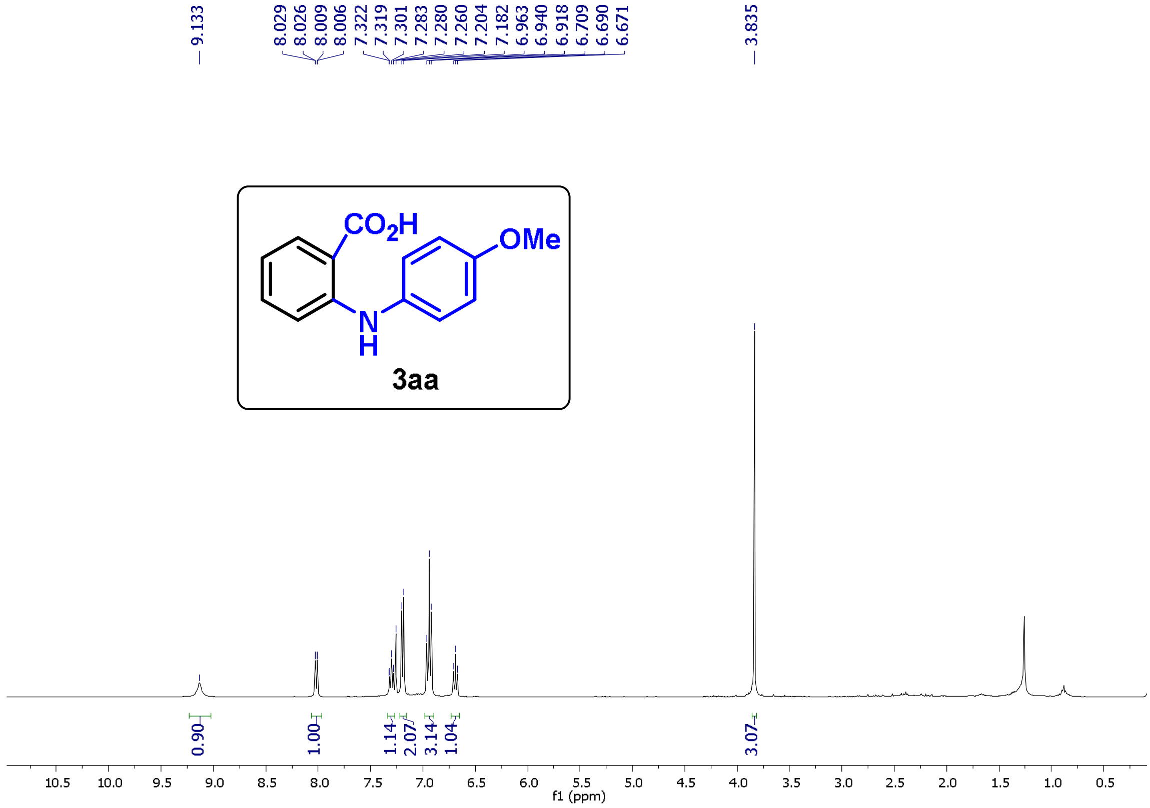


^{1}H NMR of **3aa** (400 MHz, Chloroform-*d*)



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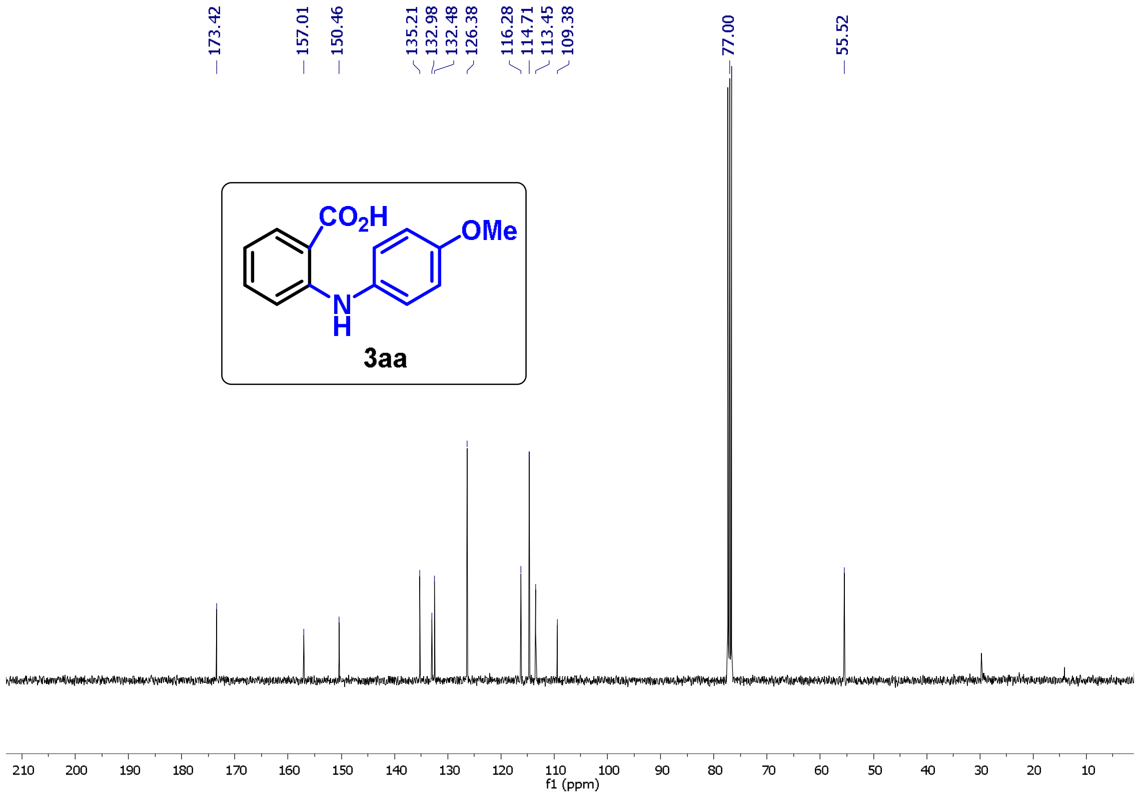
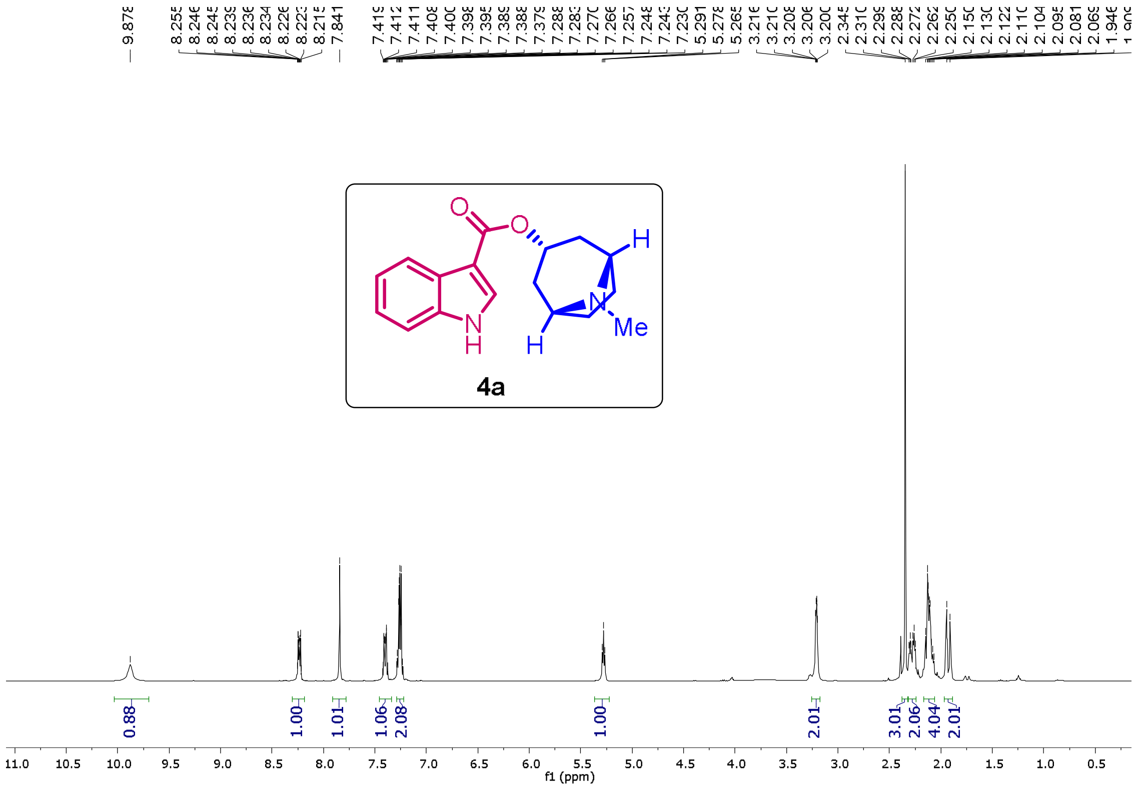


^{1}H NMR of **4a** (400 MHz, Chloroform-*d*)



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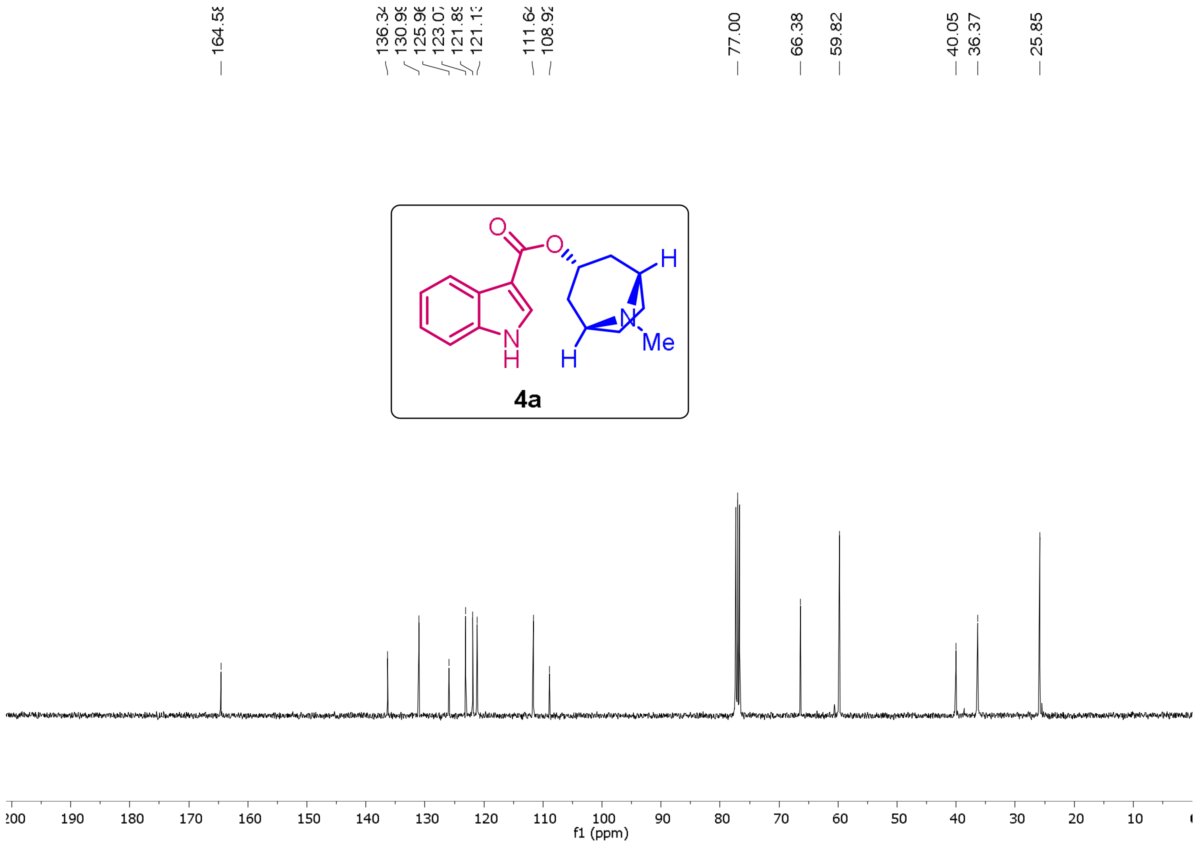
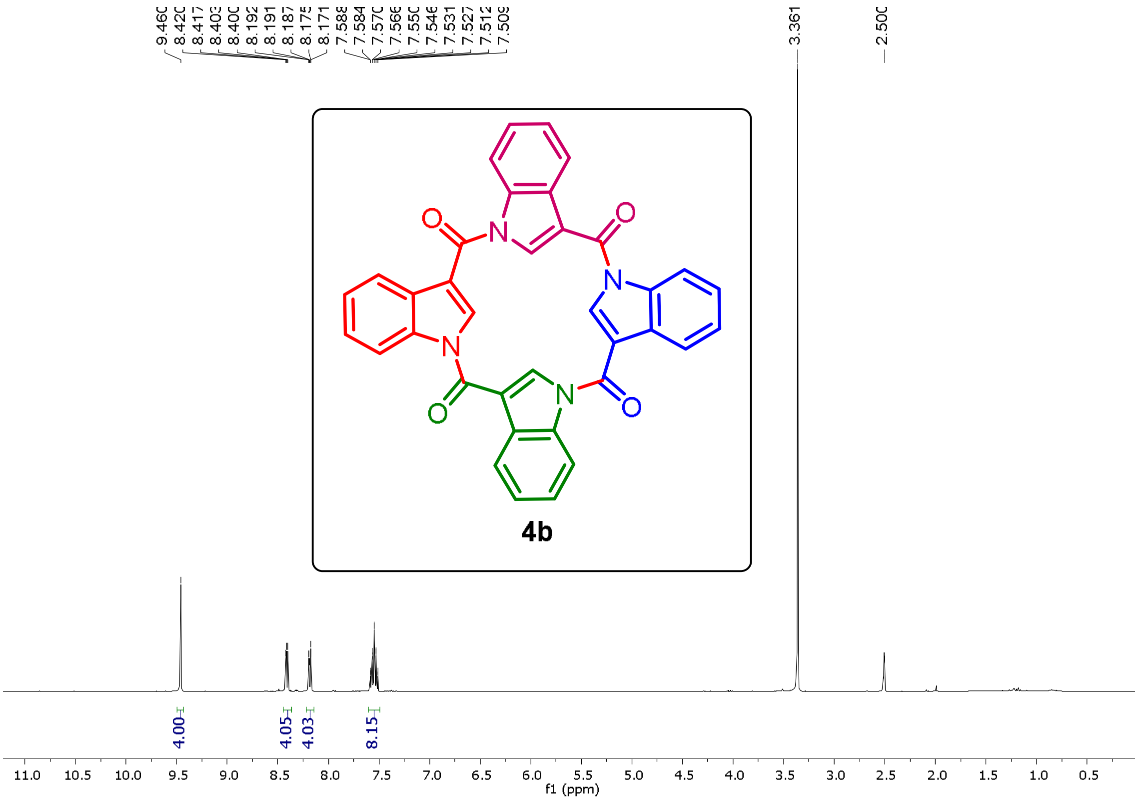
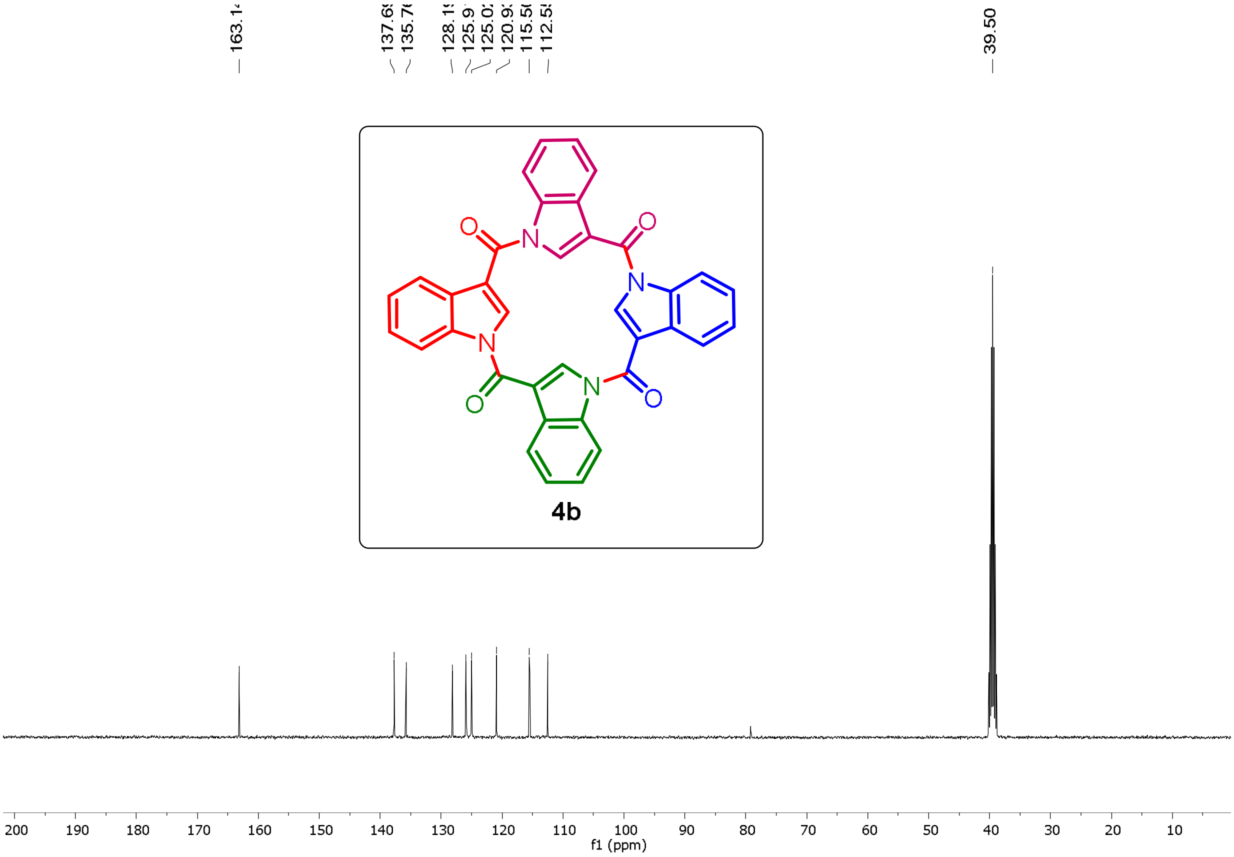


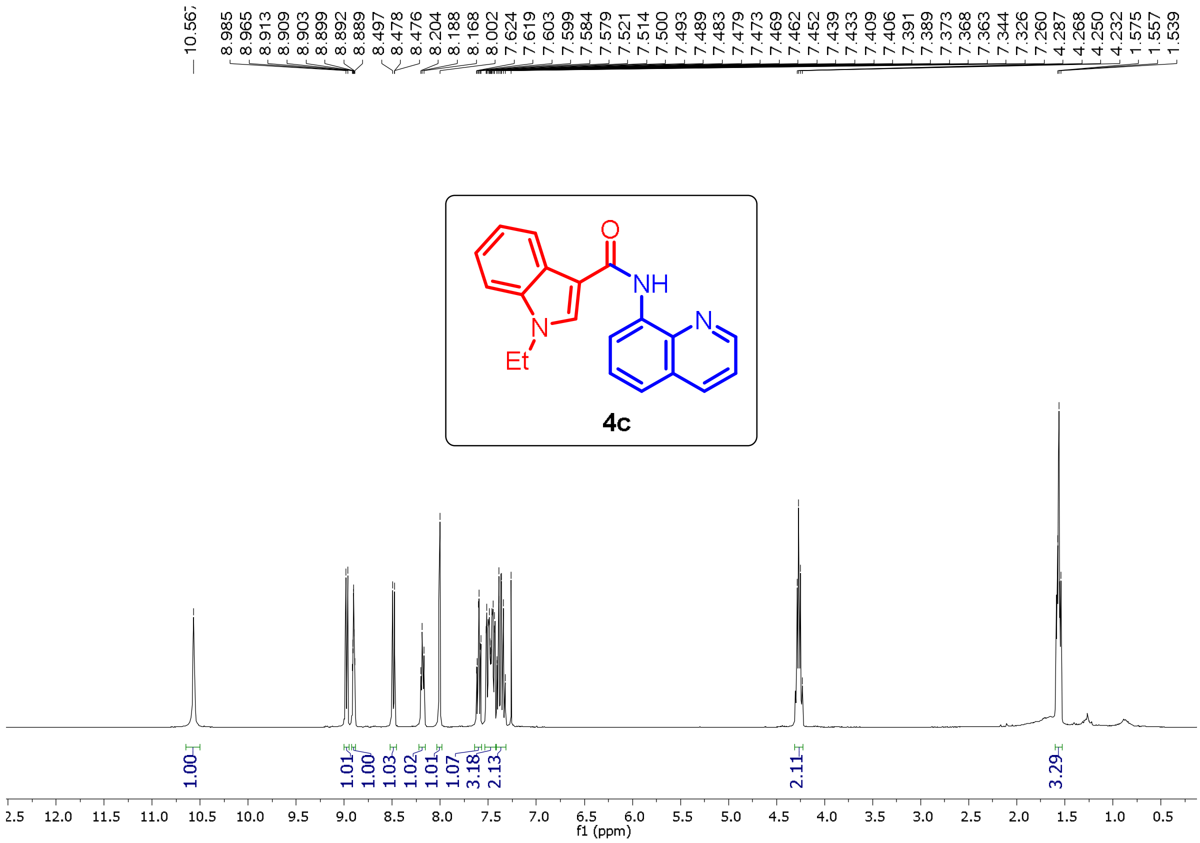
^{1}H NMR of **4b** (400 MHz, DMSO-d_6)



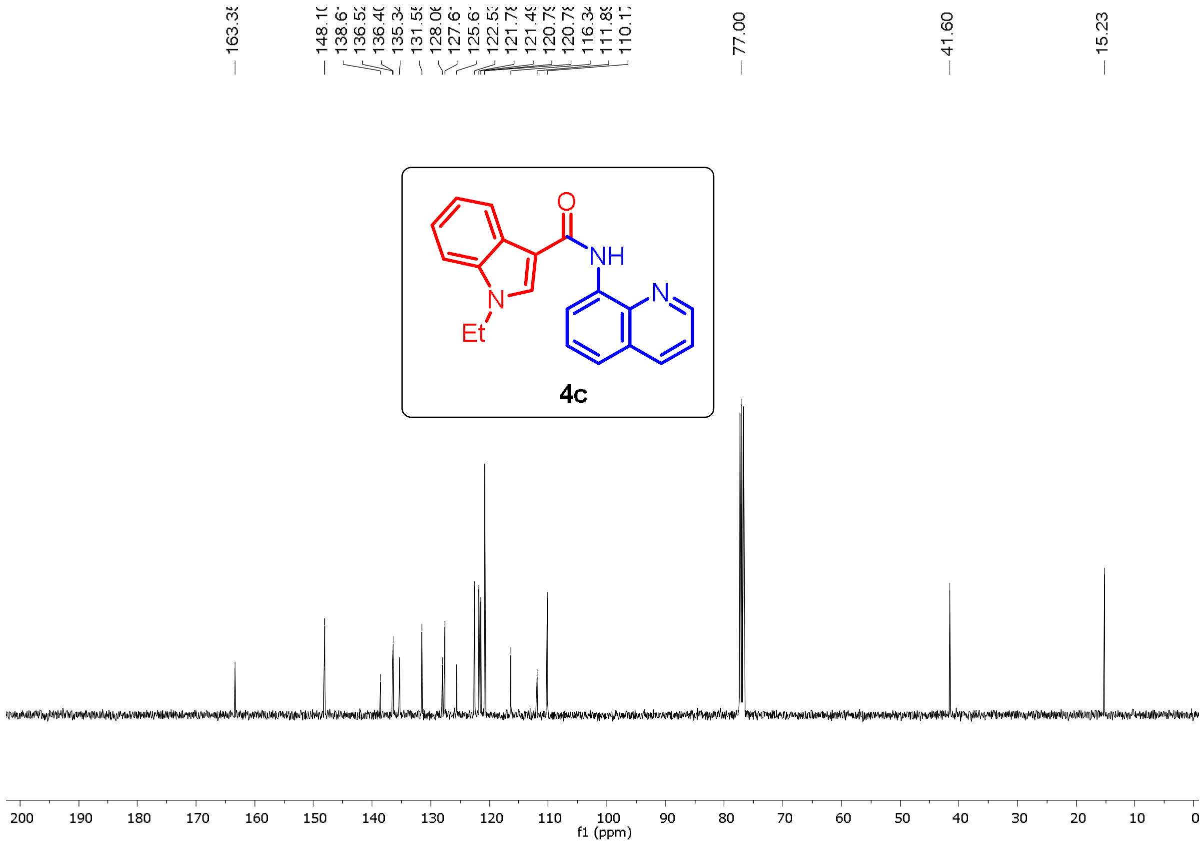
^{13}C NMR of **4b** (100 MHz, DMSO-d_6)



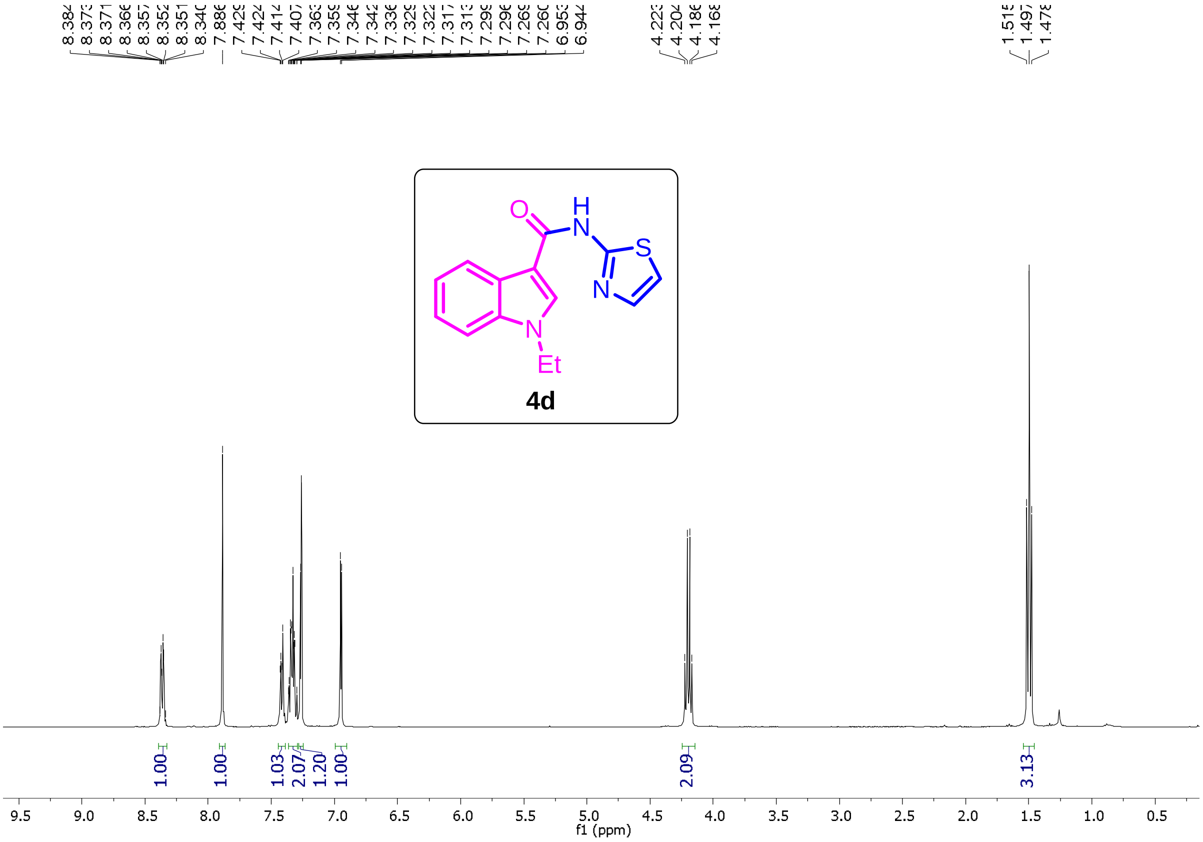
^{1}H NMR of **4c** (400 MHz, Chloroform-*d*)



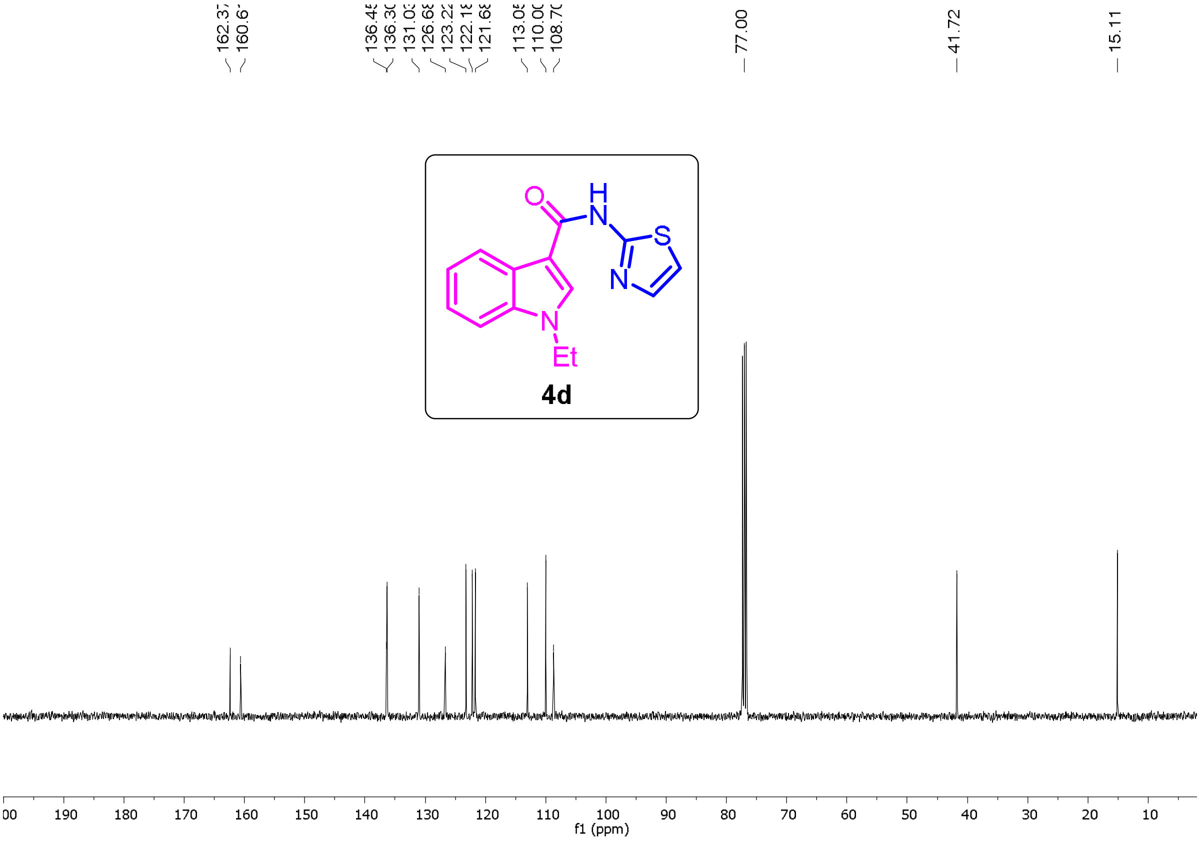
^{13}C NMR of **4c** (100 MHz, CDCl$_3$)



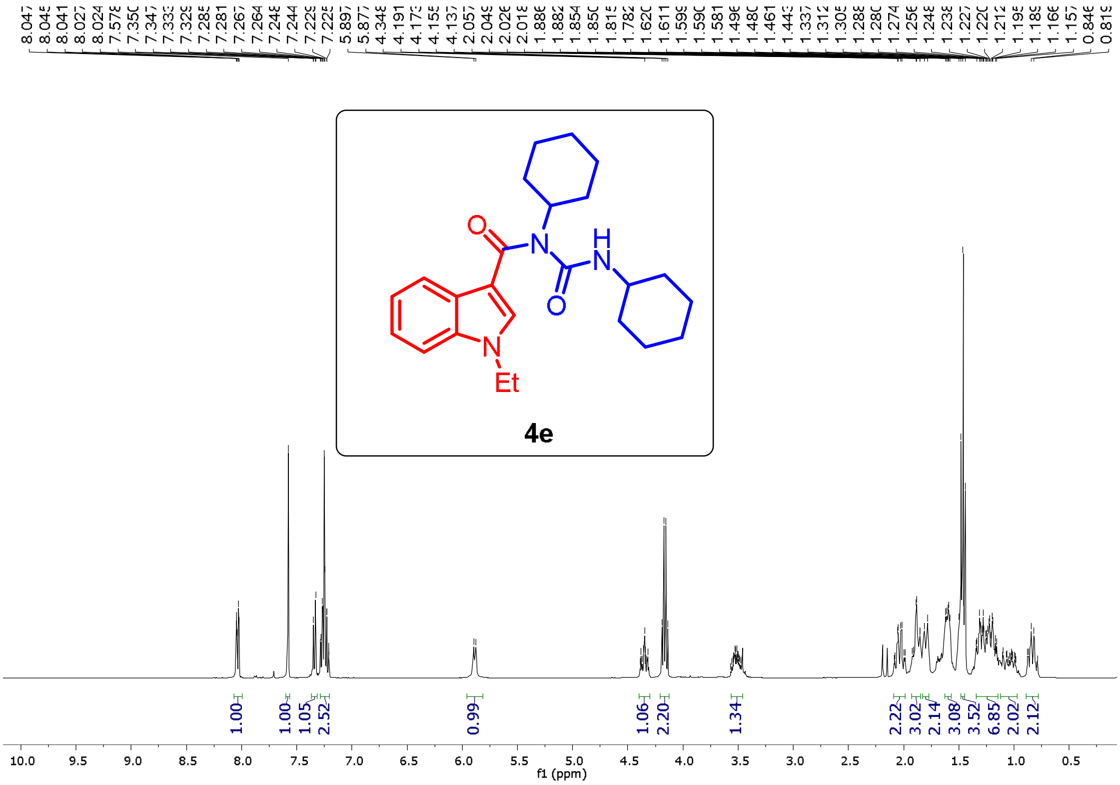
^{1}H NMR of **4d** (400 MHz, Chloroform-*d*)



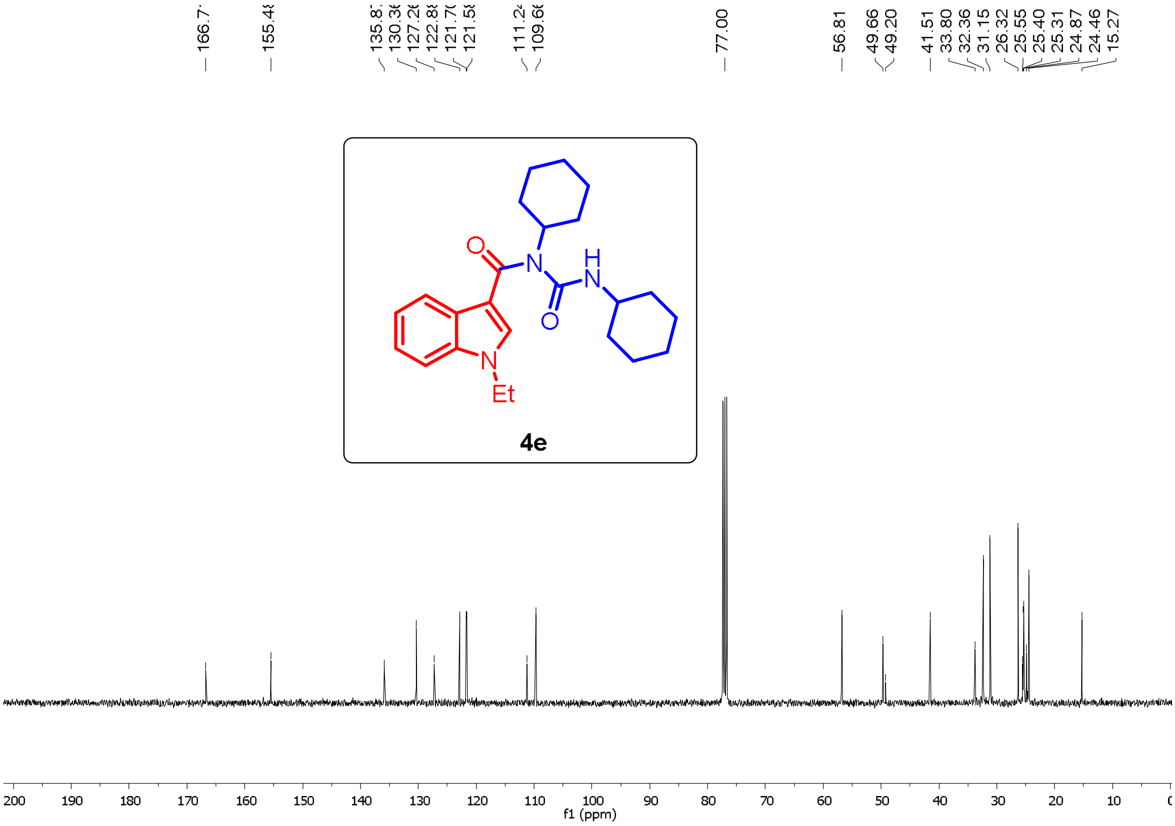
^{13}C NMR of **4d** (100 MHz, $CDCl_3$)



^{1}H NMR of **4e** (400 MHz, Chloroform-d)



^{13}C NMR of **4e** (100 MHz, CDCl$_3$)



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List of Publications

Publications Included in this Thesis

1) *"Diastereoselective Spirocyclization via Intramolecular C(sp^3)–H Bond Functionalization Triggered by Sequential [1,5]- Hydride Shift/Cyclization Process: Approach to Spiro- tetrahydroquinolines"* **Bhowmik, A.**; Das, S.; Sarkar, W.; Saidalvi, K. M.; Mishra, A.; Roy, A.; Deb, I.**Adv. Synth. Catal.* **2021**, *363*, 826-832.
2) *"Diastereoselective Spirocyclization via Intramolecular C(sp^3)−H Bond Functionalization Triggered by Sequential [1,5]-Hydride Shift/Cyclization Process: Approach to 2,7 diazaspiro[4.5]decanes"* **Bhowmik, A.**; Sahoo, A. and Deb, I.* (*Manuscript submitted*)
3) *"Unorthodox Cascade Redox Reactions of Isatin Using DMSO as a Methine Source for Expeditious Route to Indole-3-Carboxylic Acids"* **Bhowmik, A.** and Deb, I.* (*Manuscript submitted*)

Other Co-authored Publications

4) *"Iridium-Catalyzed Direct C–H Arylation of Cyclic N-Sulfonyl Ketimines with Arylsiloxanes at Ambient Temperature"* Sarkar, W.†; **Bhowmik, A.**†; Das, S.; Balaram Sulekha, A.; Mishra, A.; Deb, I.* *Org. Biomol. Chem*. **2020**, *18*, 7074-7078 (†Contributed equally)
5) *"Diastereoselective Spirocyclization of Benzoxazines with Nitroalkenes via Rhodium-Catalyzed C–H Functionalization/Annulation Cascade under Mild Conditions"* Mishra, A.; **Bhowmik, A.**; Samanta, S.; Sarkar, W.; Das, S.; Deb, I.* *Org. Lett.* **2020**, *22*, 1340-1344.
6) *"Copper-Catalyzed Direct sp^{2}C–H Silylation of Arylamides Using Disilanes"* Sarkar, W.*; Mishra, A.; **Bhowmik, A.**; Deb, I.* *Org. Lett.* **2021**, *21*, 4521-4526
7) *"Copper-Mediated Direct and Selective C–H Thiolation of Quinazolinones"* **Sarkar, W.**†; Mishra, A.†; **Bhowmik, A.**; Deb, I.**Asian J. Org. Chem*. **2019**, *8*, 819-822.
8) *"Cobalt-Catalyzed Directed sp^2 C–H Acetoxylation of Arenes Employing $Mn(OAc)_3 \cdot 2H_2O$ as Acetoxy Source"* Sarkar, W.; **Bhowmik, A.**; Mishra, A.; Vats, T. K.; Deb, I.**Adv. Synth. Catal.* **2018**, *360*, 3228-3232.
9) *"A Radical-Radical Cross-Coupling Reaction of Xanthene with Sulfonyl Hydrazides: Facile Access to Xanthen-9-sulfone Derivatives"* Das, S.; Roy, S.; **Bhowmik, A.**; Sarkar, W.;

Mondal, I.; Mishra, A.; Saha, S. J.; Karmakar, S.; Mishra, A.; Deb, I.**Chem Commun.* **2022**, *58*, 2902-2905.

10) *"Straightforward Access to Anthrone Functionalized Benzylic Amines via Organocatalytic 1,2-Addition of Anthrones to Imines at Ambient Temperature"* Das, S.; **Bhowmik, A.**; Sarkar, W.; Mishra, A.; Deb, I.**J. Org. Chem.* **2021**, *86*, 4131-4142.

11) *"Diastereoselective Spirocyclization of Cyclic N-Sulfonyl Ketimines with Nitroalkenes via Iridium-Catalyzed Redox-Neutral Cascade Reaction"* Mishra, A.; Mukherjee, U.; Sarkar, W.; Meduri, S. L.; **Bhowmik, A.**; Deb, I.* *Org. Lett.* **2019**, *21*, 2056-2059

Patents

1) *"An improved synthetic method for the preparation of indole-3-carboxylic acid derivatives: useful key intermediate for the synthesis of several biologically active molecules including tropisetron"* Deb, I. and **Bhowmik, A.** (Patent Filed) 202111047806 Ref No: 0163NF2021/IN, Dated: 28-Sep-2021

2) *"An improved synthetic method for indole-3-carboxylic acid and its derivatives"* Deb, I. and **Bhowmik, A**. *PCT:* PCT/IN2022/050940, 20/10/2022

3) *"An efficient method for the total synthesis of dolutegravir"* Deb, I. and **Bhowmik, A.** (*submitted for patent filed*)

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Cobalt-Catalyzed Directed sp^2 C–H Acetoxylation of Arenes Employing $Mn(OAc)_3.2H_2O$ as Acetoxy Source

Writhabrata Sarkar, Arup Bhowmik,[†] Aniket Mishra,[†] Tripta Kumari Vats and Indubhusan Deb*

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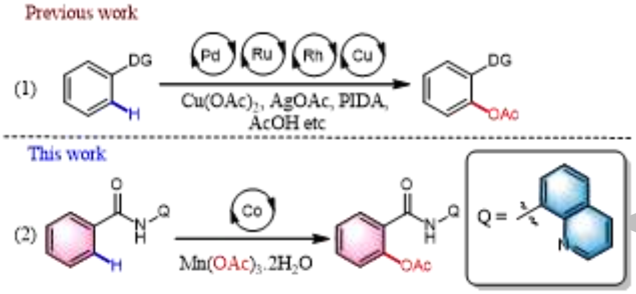
Abstract: A cobalt-catalyzed sp^2 C–H acetoxylation of amides having 8-aminoquinoline as a directing group has been achieved using manganese(III) acetate both as an oxidant and an acetoxy source. Operational simplicity, broad range of functional group tolerance, use of an earth abundant first row transition metal, and, most importantly, exploitation of an unprecedented acetoxy source are the key features. The method is scalable and does not require any additive. The mechanism of the reaction has been established by conducting a series of experiments.

Keywords: Cobalt; C–H bond activation; 8-aminoquinoline; manganese(III) acetate; acetoxylation

The acetoxy group acts as a functional group modifier while imparting polar nature to a molecule. It is ubiquitous in a plethora of pro-drugs, natural products, antimicrobial agents, and herbicidal materials.[1] Newer methods of regiospecifically introducing this group in organic molecules continues therefore to be of relevance. In this regard, metal based protocols depending on a suitable directing group have emerged as useful propositions for direct and regioselective acetoxylation of relatively inert C–H bonds in atom and step economic manner. Most of these methods rely on palladium,[2] ruthenium[3] and rhodium[4] catalysis. Apart from their expensive nature, the catalysts also suffer from their low earth abundance as well as bio-incompatibility. Though a handful of stoichiometric or sub-stoichiometric copper-mediated acetoxylation methods have also been reported[5] in the literature (Scheme 1, eq 1), an efficient catalytic method relying on the cheaper and earth-abundant first row transition metal catalysts in place of the expensive second row ones continues to be highly solicited in organic synthesis.

Very recently, several transformations have been reported in synthetic organic chemistry which rely on C–H activation using cobalt catalysts in different oxidation states.[6] Inspired by the pioneering research reported by Yoshikai using low valent cobalt and by Kanai using high valent Co(III), various methodologies have been designed by different research groups.[7,8] The major problems associated with these methods are the use of highly reactive Grignard reagents or expensive Cp* ligands. As an advancement, Daugulis *et al.* demonstrated 8-aminoquinoline[10] directed oxidative alkyne annulations[9a] using easily affordable cobalt salts in the presence of stoichiometric amounts of an oxidant. Most of the seminal works in this field concentrate on direct alkylation, alkenylation, arylation, alkynylation, cyanation, amination, and sulfenylation.[6-9] Although C–O bond formation by cobalt catalysis has been recently developed,[11] direct C–H acetoxylation still remains a challenge.



Scheme 1. Transition metal catalyzed C–H acetoxylation

We have recently reported a rhodium-catalyzed mild C–H acetoxylation reaction[4c] as a part of a continuing research endeavour in transition metal catalyzed C–H functionalizations.[12] Significant progress has been made exploiting various acetoxy sources such as $Cu(OAc)_2$, AgOAc, $PhI(OAc)_2$,

Copper-Mediated Direct and Selective C–H Thiolation of Quinazolinones

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Supporting information for this article is given via a link at the end of the document

Abstract: Direct thiolation of quinazolinones via selective cleavage of a relatively inert C–H bond, mediated by earth-abundant copper and guided by a pyridine or pyrimidine moiety, has been achieved under operationally simple conditions. The devised protocol does not require any toxic or reactive reagents and provides direct access to a broad spectrum of pharmaceutically relevant thioquinazolinones.

Quinazolinone is one of the most privileged scaffolds with a vast range of bio-activities and prevalent in a number of pharmaceutical molecules and drug candidates. 4-Quinazolinone derivatives such as the sedatives methaqualone, afloqualone, piriqualone, diproqualone and cloroqualone, the antimalarial febrifugine, and the diuretic metolazone are among commercially available marketed drugs (Figure 1).[1] On the other hand, thio-ethers constitute a unique class of structural element present in a number of drugs such as nelfinavir, albendazole, cimetidine, and tiodazosin. Additionally, organothio-ethers are common building blocks in organic synthesis and also highly useful as fluorescent probes.[2] Recently, quinazolinone tethered thioethers having anti-cancer, antiplatelet and anti-inflammatory activities have been reported (Figure 1),[3] underlining the immense importance of developing syntheses of thioquinazolinones.

Most of the practiced methods to synthesize thioquinazolinones (Scheme 1a) suffer from drawbacks such as the use of toxic starting materials, electronically biased substrates, or highly reactive reagents; additionally, these have low atom and step economy, offer low yields or demand harsh reaction conditions, calling for newer and more efficient approaches.[4]

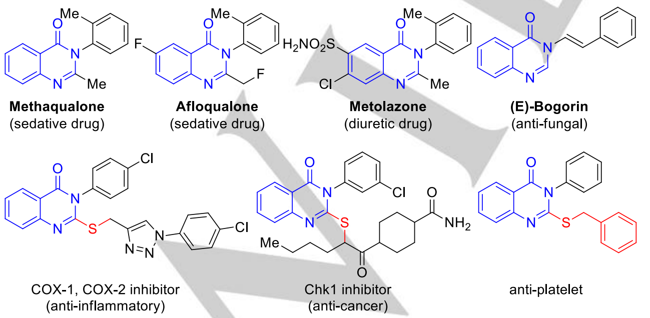
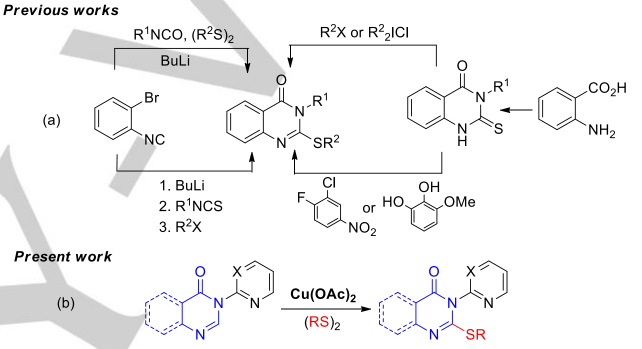


Figure 1. Representative related bio-active molecules.

In this context, we became interested in harnessing the power of transition metal promoted direct C–H activation strategy, which has witnessed enormous growth during the last two decades accomplishing various challenging synthetic tasks through shorter routes and exploiting readily available starting materials. Both expensive Pd, Rh, Ru as well as earth abundant Cu, Co, Ni etc have emerged as highly utilized transition metals for direct sulfenylation reactions.[5]



Scheme 1. Synthetic routes towards thioquinazolinones.

Such elegant synthetic approaches are mainly based on pyridine,[6] amide,[7] oxime,[8] acid,[9] pyrimidine,[10] 7-azaindole[11] and diverse bidentate auxiliaries.[12] But to our knowledge, quinazolinone substrates have hardly been explored through C–H activation strategy except for a few reports available in literature where they themselves have been used as a directing group[13] and directly functionalized.[14]

We set out to explore the possibility of developing an alternate and more practical method for the synthesis of thioquinazolinones employing C–H activation strategy, continuing our persistent efforts towards the development of sustainable metal catalyzed C–H activation[15] and in particular C–H sulfenylation.[11] Herein, we report a copper promoted direct sulfenylation of 4-quinazolinones using easily affordable disulfides (Scheme 1b).

We commenced the study with the model substrate 3-(pyridin-2-yl)quinazolin-4(3H)-one (**1a**) and 1.0 equiv. of diphenyl disulfide (**2a**) as the thiolating reagent in presence of 2.0 equiv. of $CuCl_2$ in DMSO at 140 °C for 24 h under N_2 atmosphere. The desired product 2-(phenylthio)-3-(pyridin-2-yl)quinazolin-4(3H)-one (**3aa**) was indeed obtained, though only in 12% yield (Table 1, entry 1). Following this result, a series of other copper sources were surveyed (Table 1, entry 2-5) to find that $Cu(OAc)_2$ gave the highest yield of 14% (Table 1, entry 4). Use of lower temperature (110 °C) resulted in a better yield of the product (Table 1, entry 6). Experiments with various solvents like DCE, 1,4-dioxane, DMF, MeCN, and toluene (Table 1, entry 7-11) identified DCE as the best, improving the yield to 32% (Table 1, entry 7).

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Diastereoselective Spirocyclization of Cyclic *N*-Sulfonyl Ketimines with Nitroalkenes via Iridium-Catalyzed Redox-Neutral Cascade Reaction

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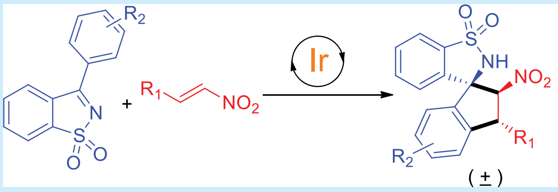
Supporting Information



- Cascade reaction with challenging nitroalkenes
- Construction of 3 stereogenic centers at a go
- Good to excellent diastereoselectivity
- No stoichiometric additive, base or ligand required

ABSTRACT: An Ir(III)-catalyzed [3 + 2] annulation of weakly coordinating *N*-sulfonyl ketimines with challenging α, β-unsaturated nitro olefins has been achieved via redox-neutral C−H functionalization in the presence of a catalytic amount of silver hexafluoroantimonate. The generation of three consecutive stereogenic centers in a single step via direct C−H functionalization is the prime feature of this methodology. A wide array of pharmaceutically relevant nitro-substituted spirocyclic benzosultams was synthesized with good to excellent diastereoselectivity as well as in high yield starting from easily accessible substrates.

Nitro olefins are versatile synthons employed in synthetic organic chemistry as Michael acceptors as well as dienophiles in Diels−Alder reactions, and the nitro group can be easily transformed into various useful functional groups;[1] however, nitro olefins have hardly been explored in the field of transition-metal-catalyzed C−H functionalizations presumably due to the strong affinity of them toward transition metals leading to catalyst deactivation. A major breakthrough was achieved by Ellman's group very recently when they reported the first rhodium-catalyzed addition of inert C−H bond to α,β-unsaturated nitroalkenes via amide assistance.[2a] Since then, few reports have emerged limited to rhodium catalysis only.[2b,c] Therefore, there is ample scope for further exploration of nitroalkenes in transition-metal-catalyzed C−H functionalization processes.

On the other hand, the directing-group-assisted C−H functionalization followed by annulation has recently emerged as a robust tool for the generation of molecular complexity.[3] In this context, [3 + 2] annulations have attracted the interest of organic chemists; however, only alkynes, allenes, acrylates, and maleimides are among the extensively used partners.[4] Various imine derivatives have served as ideal substrates for this type of transformation. Cyclic benzosultams are among medicinally privileged heterocycles[5] and spirocyclic benzosultams have been identified as potent antidiabatic[5a] and anticancer[5b] agents (Figure 1). Cyclic *N*-sulfonyl ketimines[6] could be a good choice as substrates for synthesizing them via C−H functionalization followed by annulation. However, the presence of the sulfonyl group makes the nitrogen weakly coordinating. As a result, these substrates have been less studied in such annulation reactions, and generation of more than one stereogenic center employing cyclic *N*-sulfonyl ketimines is particularly rare. In 2013, Nishimura reported Ir(I)-catalyzed [3 + 2] annulations between cyclic *N*-sulfonyl ketimines and 1,3-dienes via direct C−H functionalization for the first time.[7a] Since then, a few groups have reported annulation reactions employing alkynes, heterocycles, aryl halides, isocyanates, and CF_3-substituted enones under Rh(III), Co(III), and Pd(II) catalysis.[7] Recently, we have developed a mild and efficient Ir(III)-catalyzed C−H amidation of *N*-sulfonyl ketimines.[6g] In continuation of our interest in transition-metal-catalyzed C−H functionalization reactions,[8] herein we wish to report an Ir(III)-catalyzed diastereoselective spiroannulation of *N*-sulfonyl ketimines and α,β-unsaturated nitro olefins under a redox-neutral process.

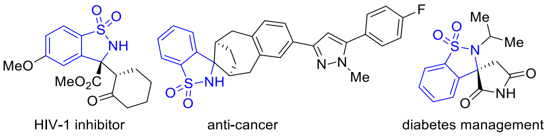


Figure 1. Representative bioactive benzosultams.

We initiated the study by taking the representative substrate 3-phenylbenzo[*d*]isothiazole 1,1-dioxide (**1a**, 0.1 mmol) with (*E*)-(2-nitrovinyl)benzene as the α,β-unsaturated nitroalkene

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Diastereoselective Spirocyclization via Intramolecular C(sp^3)–H Bond Functionalization Triggered by Sequential [1,5]-Hydride Shift/Cyclization Process: Approach to Spiro-tetrahydroquinolines

Arup Bhowmik,[a] Sumit Das[a,b] Writhabrata Sarkar,[a] K. M. Saidalavi,[a] Aniket Mishra,[a] Anupama Roy,[a] and Indubhusan Deb[a]*

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Abstract: A direct synthesis of spiro[5.5]and [5.4]-tetrahydroquinolines has been developed through C(sp^3)–H bond functionalization triggered by sequential [1,5]- hydride shift /cyclization sequence using *ortho* amino benzaldehydes and active methylene compounds such as 2-coumaranone, 4-hydroxycoumarin, 3-coumaranone, and 3-isochromanone. This protocol provides a Lewis acid catalyst-free straight forward one-pot reaction in cases of 2-coumaranone and 4-hydroxycoumarin, Lewis acid-catalyzed stepwise reaction for 3-coumaranone and 3-isochromanone to access a wide range of spiro-heterocycles in excellent to good yields and diastereoselectivity.

Keywords:[1,5]-hydride shift reaction; Lewis acid catalyst; Spirocycles; tetrahydroisoquinoline; 2-coumaranone; 3-isochromanone.

Introduction

Coumaranone containing scaffolds have drawn much attention since aeons due to their presence in many biologically relevant molecules such as naturally occurring isoaurones(**I**),[1] isoaurostatin[2] marginalin[3] pterocarposide[4] radulifolin-B,[5] Commiphoranes (**III**),[6] aurones[7] and spirocyclic Griseofulvin analogues (**IV**)[8] an orally active antimycotic drug (Figure 1).

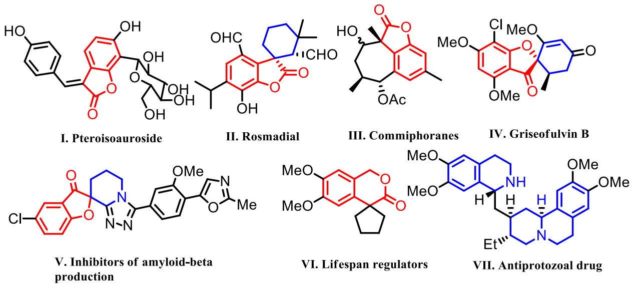
I. Pteroisoauroside
II. Rosmadial
III. Commiphoranes
IV. Griseofulvin B
V. Inhibitors of amyloid-beta production
VI. Lifespan regulators
VII. Antiprotozoal drug

Figure 1. Representative example of relevant bioactive molecules

Various spirocyclic 2-coumaranones (**II**), benzofuran-3-one (**V**), 3-isochromanone (**VI**)[8b,d-j] derivatives, and isoaurones, aurones are well known pharmaceutically important compounds and natural products to exhibit excellent activity against different biological targets.[9-10] There has been enormous progress in the area of spirocyclic chemistry,[11] however the development of a highly stereoselective and atom-economic method for the construction of spirocyclic scaffold containing 2-coumaranones fused with *N*-heterocycles has hardly been explored.[12] Moreover, the presence of tetrahydroisoquinoline (THIQ) moiety, a powerful building block has given another dimension to construct a variety of bioactive molecules.[13] Recently, hydride transfer followed by cyclization sequence has become an attractive complementary approach for C(sp^3)−H bond functionalization. After groundbreaking findings by Reinhoudt,[14] the hydride shift reaction has been popularized mainly by Seidel,[15] Sames,[16] Akiyama,[17] Maulide,[18] and Li.[19]Over the past few decades, substantial efforts have been made by various research groups to develop varieties of hydride transfer/cyclization cascade reactions for the construction of structurally diverse complex molecules.[20] Yet, no protocol is available to

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COMMUNICATION

Iridium-Catalyzed Direct C–H Arylation of Cyclic *N*-Sulfonyl Ketimines with Arylsiloxanes at Ambient Temperature

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An iridium-catalyzed *ortho*-selective C–H arylation of cyclic *N*-sulfonyl ketimines has been achieved with environmentally benign aryl siloxanes. The reaction is highly efficient and works at ambient temperature which is the key feature of the methodology considering the weak coordination nature of the substrate as well as sluggish reactivity of siloxanes. A wide array of pharmaceutically relevant novel class of biaryls has been synthesized under operationally simple conditions.

Among the C–C bond formation protocols, arylation has been a major preoccupation of organic chemists as most of the biaryl compounds are found as substructures of many bioactive scaffolds.[1] The Hiyama cross-coupling is considered as one of the most robust techniques for incorporating the aryl unit in an organic molecule. The use of organosilicon reagent is particularly advantageous over more frequently used organoboranes in terms of broad substrate scope, low toxicity and easier accessibility.[2] Unlike traditional cross-coupling reactions, the direct C–H arylation strategies preclude the prefunctionalization of substrates and hence are preferred over the former.[3]

A diverse array of reagents like halides/pseudohalides and metalloarenes (Ar–M, M = B, Mg) have been widely explored for such reactions or arylations.[3o] Despite significant advantages of organosilicon reagents over its counterparts, the direct C–H arylation employing them has been less studied owing to its low nucleophilicity.[2a-2c, 3o] Therefore, a handful number of reports have appeared in recent years limited to Pd,[4] Rh,[5] Ru[6] and Ni[7] catalysis only. Although directing group assisted C–H arylation strategies have witnessed tremendous progress in the last few decades, the established protocols still suffer major drawbacks in terms of longer reaction time, high temperature and strongly coordinating directing groups. Very recently, Chang *et al.* described an iridium-catalyzed C–H arylation of directing arenes under mild condition using aryl siloxanes and to the best of our knowledge, it is the only report for iridium-catalyzed C–H arylation by exploiting aryl siloxanes.[8a]

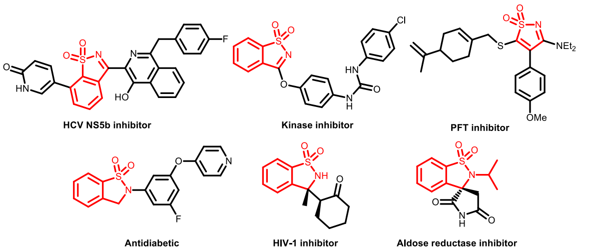

Figure 1 Representative bioactive molecules containing sulfonyl ketimine/amide scaffolds

On the other hand, the functionalized cyclic *N*-sulfonyl ketimine motif is widely present in various biologically active compounds including potential inhibitors against Hepatitis-C virus NS5b,[9a, 9b] and the protein farnesyltransferase,[9c] etc. They also appear to be the essential precursors for the synthesis of benzosultams, a medicinally important scaffold with a wide range of biological activities including anti-HIV, anti-diabetic and aldose reductase inhibitory properties (Figure 1).[10] However, a limited number of reports can be obtained in literature for the direct C–H functionalization of cyclic *N*-sulfonyl ketimines.[11] Very recently, our group has achieved an iridium-catalyzed mild C–H amidation[12a] as well as an iridium-catalyzed diastereoselective spirocyclization with nitroolefins of cyclic *N*-sulfonyl ketimines.[12b] Herein, we disclose an unprecedented Ir(III) catalyzed *ortho*-selective arylation strategy involving the relatively less explored aryl siloxanes and weakly directing cyclic *N*-sulfonyl ketimines.

We started the study by taking 3-phenylbenzo[d]isothiazole-1,1-dioxide **1a** (0.1 mmol) as the representative substrate and trimethoxyphenylsilane **2a** as the arylating partner (1.1 equiv), in presence of $[Cp^*IrCl_2]_2$ (5 mol %) as catalyst, $AgSbF_6$ (20 mol %) as chloride scavenger, $Cu(OAc)_2$ (50 mol %) as co-oxidant

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† WS and AB contributed equally.

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Diastereoselective Spirocyclization of Benzoxazines with Nitroalkenes via Rhodium-Catalyzed C−H Functionalization/Annulation Cascade under Mild Conditions

Aniket Mishra, Arup Bhowmik, Siddhartha Samanta, Writhabrata Sarkar, Sumit Das, and Indubhusan Deb*

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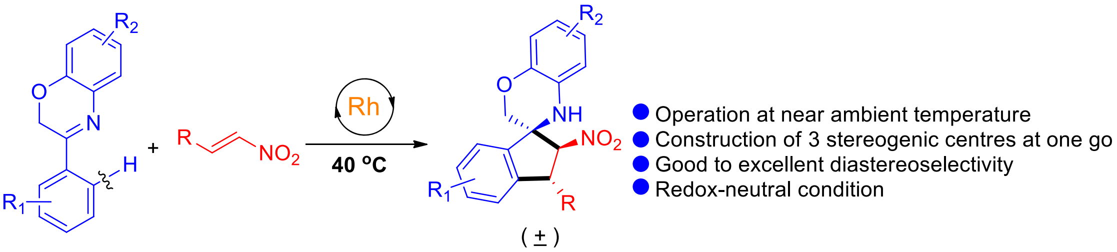

ABSTRACT: A Rh(III)-catalyzed [3 + 2] annulation of benzoxazines with nitroolefins that proceeds via redox-neutral C−H functionalization has been demonstrated, leading to the novel class of spirocycles in a single step. The construction of three continuous stereogenic centers has been achieved starting from easily accessible achiral substrates in an atom-efficient manner under mild reaction conditions. A broad range of pharmaceutically relevant nitro substituted spirocyclic 2,3-dihydro-1,4-benzoxazine derivatives has been synthesized in good to excellent yields with high diastereoselectivity.

A wide array of biologically active small molecules comprising of 2,3-dihydro-1,4-benzoxazine core has been identified with diverse biological activities such as antithrombotic, antihyperlipidemic, calcium antagonism, anti-arrythmic, etc. (Figure 1). Levofloxacin and ofloxacin are among the commercially available antibiotics, and obscurinervidine is a naturally occurring alkaloid containing this structural unit.[1] The most straightforward and practical approach for the synthesis of this type of molecules involves the reduction of 2*H*-1,4-benzoxazines,[2] but a conceivably more interesting approach capable of delivering new structural types would be to exploit the iminyl nitrogen capable of acting as a robust DG for transition-metal-catalyzed C−H functionalization chemistry. However, despite the remarkable development in the field in recent years, the benzoxazines have hardly been utilized in this area.[3n]

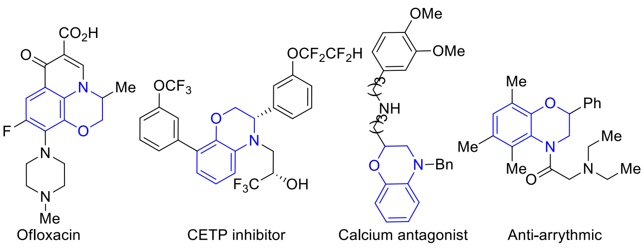

Figure 1. Representative bioactive 2,3-dihydro-1,4-benzoxazines.

Recently, C−H functionalization and subsequent [3 + 2] annulation guided by the imine functionality have been shown to have tremendous potential for the synthesis of interesting structural backbones.[3] But many established protocols still suffer from major issues like the requirement of using activated ketimines containing electron-withdrawing acyl, sulfonyl or phosphoryl groups, extensive dependence on some common partners such as alkynes, allenes, isocyanates, maleimides, or acrylates, high reaction temperature, etc. We noted that nitroalkenes, which have served as a versatile partner in various synthetic protocols,[4] have rarely been explored in transition-metal-catalyzed C−H functionalization reactions presumably due to their high affinity toward metal centers, which leads to catalyst poisoning. Though Ellman et al. demonstrated in 2017 that nitroolefins can be subjected to amide-directed C−H alkylation using rhodium catalysts, only a sporadic number of applications have appeared since.[5] Very recently, our group has reported a unique iridium-catalyzed diastereoselective spiroan-

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Straightforward Access to Anthrone Functionalized Benzylic Amines via Organocatalytic 1,2-Addition of Anthrones to Imines at Ambient Temperature

Sumit Das, Arup Bhowmik, Writhabrata Sarkar, Aniket Mishra, and Indubhusan Deb*

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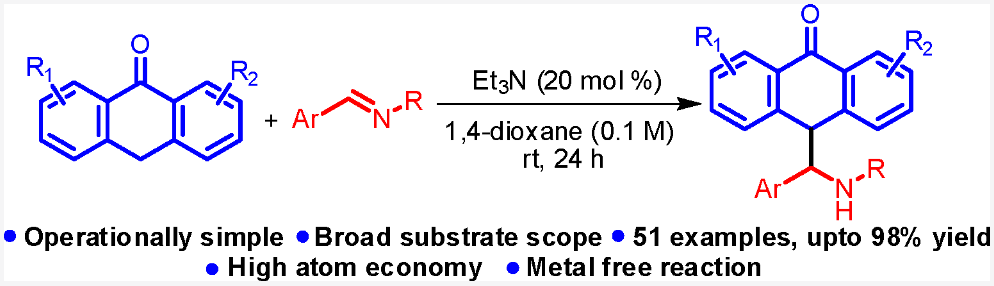

ABSTRACT: Activation of anthrone via benzylic deprotonation in the presence of triethylamine paves the way for the 1,2-addition reaction with imines to provide the desired functionalized anthrones in good to excellent yields under mild and operationally simple reaction conditions with a broad range of substrate scopes without using any external additives or toxic stoichiometric reagents.

■ INTRODUCTION

Anthrone and its reduced or oxidized forms are present in many pharmaceuticals, dyes, and optoelectronic materials.[1−4] It is also an imperative framework of many natural products and restorative drugs such as variecolortide (I, II), cassialoin (III), and knipholone (IV) (Figure 1).[5,6] A number of its derivatives have shown substantial clinical potency like antimicrobial, diuretic, antipsoriatic, telomerase inhibitory activities and selective antitumor activity[7] (Figure 1).

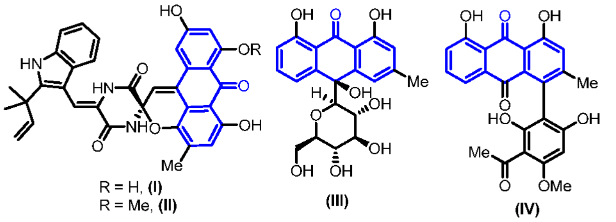

Figure 1. Representative bioactive molecules containing anthrone scaffolds.

Anthrone can be converted into its nucleophilic enolate under basic conditions or as a diene for Diels−Alder reactions under suitable conditions.[8] Various methodologies have been developed by different groups for the synthesis of functionalized anthrone derivatives employing nonasymmetric or asymmetric 1,4-addition and Diels−Alder reactions with different dienophiles under various catalytic conditions.[9,10] Sporadic examples of 1,2-addition of anthrone to iminium are known in the literature. In this context, Kitamura et al. reported the coupling reactions of 2-hydroxyindoline with anthrone in the presence of $BF_3{\cdot}Et_2O$ (Scheme 1a).[11] Later on, White's group developed a two-step methodology for the controlled oxidation of proline, catalyzed by Fe(PDP) followed by 1,2-addition of anthrone (Scheme 1b).[12] However, 1,2-addition of anthrone to imine as a coupling partner remains unknown to date (Scheme 1c).

N-Sulfonyl imine has been used as a reaction partner in various nucleophilic addition reactions,[13] radical reactions,[13a] and hetero Diels−Alder reactions.[14] *N*-Sulfonyl amide derivatives serve as an important class of structural motifs prevalent in numerous drugs such as thromboxane receptor antagonists,[15a] inhibitors of *Mycobacterium tuberculosis*,[15b] and antitrypanosomal agents.[15c] Taking account of the importance of anthrone and *N*-sulfonylamides and in continuation of our ongoing interests toward the synthesis of densely functionalized molecules,[16] herein for the first time we wish to report a triethylamine-catalyzed direct 1,2-addition of anthrone to *N*-sulfonylaldimines under mild reaction conditions toward the synthesis of benzyl amine functionalized anthrone (Scheme 1c).

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Copper-Catalyzed Direct sp^2 C−H Silylation of Arylamides Using Disilanes

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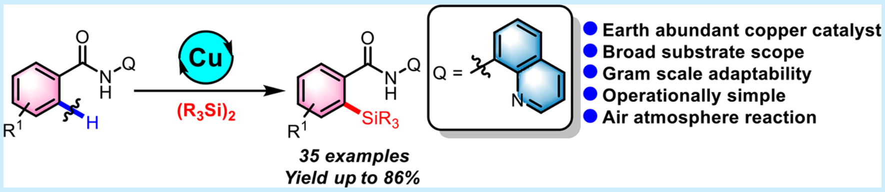
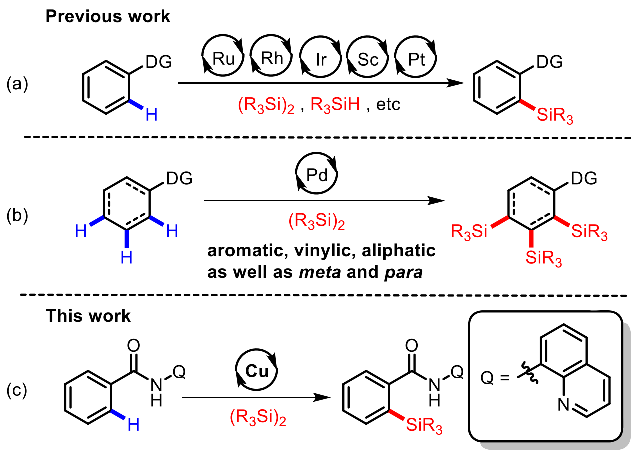


ABSTRACT: A copper-catalyzed method for direct intermolecular *ortho*-silylation of benzamides has been developed that affords organosilane products in moderate to high yields. The key features include: (i) use of commercially available disilanes as a silicon source with 8-aminoquinoline as a bidentate directing group, (ii) use of earth-abundant first-row transition metal, (iii) operationally simple conditions without the need of an inert atmosphere, and (iv) tolerance of a wide range of functional groups. The practicality and effectiveness of this method have been demonstrated by a gram-scale experiment. This strategy, therefore, constitutes a convenient way of constructing C−Si bonds useful for synthetic organic chemistry.

The C−Si bond possesses unique physical, chemical, and bioactive properties, and the development of methods for its formation is therefore indispensable in synthetic organic chemistry. The organosilicon compounds are valuable building blocks and have numerous applications in organic chemistry.[1] Besides, these have found potential uses in the fields of material science, polymer chemistry,[2] and pharmaceutical industries[3]—a growing number of reports in medicinal chemistry deal with the incorporation of silicon groups in diverse drug candidates.[4] In consequence, significant efforts have been made in recent years for the strategic installation of silyl groups into organic frameworks. Among these, the synthesis of organosilanes through transition-metal-catalyzed direct C−H bond functionalizations, as compared to traditional approaches of silylation reactions[5] and transition-metal-free techniques,[6] has emerged as the most sought-after protocol from the viewpoints of atom economy and high efficiency.[7−12] The high abundance, low cost, and environmentally benign nature of silicon have in addition allowed the development of catalytic silylation methods via C−H bond activation. In the past decades, several advances have been made in this field for the silylation of C(sp^2)−H as well as C(sp^3)−H variants using Ru,[7] Rh,[8] Ir,[9] Sc,[10] and Pt[11] as transition metal catalysts (Scheme 1a).

Kuninobu and Kanai reported the first Pd-catalyzed silylation of carboxamides with disilanes as silicon sources, applying a directing group strategy (Scheme 1b).[12a] Following this pioneering work, Zhang and Shi's groups developed elegant procedures for the silylation of aliphatic β-C(sp^3)−H bonds,[12c,d] which were then impressively extended to distal γ-C(sp^3)−H silylation by Maiti and co-workers.[12e] Maiti and Liu have made splendid breakthroughs in both regioselective *meta* and *para* C−H silylation techniques with the help of intricately designed directing templates suitable for C−H bond activation.[12g,h] In 2019, Yang et al. developed another approach for *meta* C−H silylation to access silicon-containing 1,1′-biaryl-2-acetamides employing palladium catalysis.[12i]

Scheme 1. Transition-Metal-Catalyzed C−H Silylation



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A radical–radical cross-coupling reaction of xanthene with sulfonyl hydrazides: facile access to xanthen-9-sulfone derivatives†

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A straightforward strategy for direct incorporation of sulfonyl units into a xanthene moiety for accessing xanthen-9-sulfone derivatives in good to excellent yields has been established *via* metal-free radical–radical cross-coupling reaction of xanthenes and sulfonyl hydrazides. Using easily accessible starting materials, this methodology proceeds efficiently with a high degree of functional group compatibility and with a wide scope of both xanthenes and sulfonyl hydrazides under operationally simple reaction conditions. Mechanistic investigations revealed that sulfonyl radicals could be generated from sulfonyl hydrazides in the presence of TBHP under an oxygen atmosphere.

Cross-coupling processes which involve a C–H functionalization step are well-known as straightforward and quick methods for carbon–carbon (C–C) and carbon–heteroatom (C–X) bond formation in an environmentally friendly, sustainable, and highly atom-efficient manner avoiding the use of halides, pseudohalides, and organometallic reagents.[1] In this context, carbon–heteroatom bond formation,[2] specifically C–H sulfonylation reaction has recently gained much attention for the synthesis of functionalized sulfones.[3] In particular, the sulfonyl radical has been used as an important reactive intermediate for the synthesis of various sulfone derivatives. There are extensive reports where the *in situ* generated sulfonyl radicals from various precursors undergo sulfonylation reaction with unsaturated hydrocarbons such as alkenes, alkynes and (hetero) arenes.[4–10] For example, in the presence of radical initiators and/or under photocatalytic conditions, sulfonyl halides,[5] cyanides,[6] azides,[7a] selenides,[7a,b] sodium sulfinates[8] and sulfonyl hydrazides[9,10] produce the corresponding sulfonyl radicals and react with different substrates. Despite the substantial development in sulfonylation reactions *via* a reactive sulfonyl radical intermediate generated *in situ* from sulfonyl hydrazides, their use in metal-free C(sp^3)–H sulfonylation remains underexplored. Sulfones, particularly aryl–alkyl sulfones, are well-known for their wide range of applications in pharmaceuticals, agrochemicals and materials science.[11,12] On the other hand, xanthene and its derivatives are widely reported as biologically active scaffolds present in various pharmaceuticals and imaging agents such as acrotrione, fluorescein, *etc.* (ESI,† Fig. S1).[13] For the synthesis of 9-substituted xanthenes, C(sp^3)–H functionalization with various nucleophiles has gained considerable attention. In this context, Klussmann and co-workers delineated an aerobic oxidative C–C bond formation approach to modify the 9-position of xanthene using sulfonic acid as the catalyst in the presence of molecular oxygen (Scheme 1a).[14] Subsequently, direct activation of the benzylic C(sp^3)–H bond of xanthenes to construct C–C, C–P and C–N bonds was independently reported by Jiao, Perica15 Loh, Zhang, Osuka,[16] Chen,[17] Zeng, and Li[18] (Scheme 1a–d). However, to the best of our knowledge, C(sp^3)–H sulfonylation at the 9-position of xanthenes *via* a radical–radical cross-coupling reaction using sulfonyl hydrazides remains unexplored. Continuing with our research interest in benzylic C(sp^3)–H functionalization, herein, for the first time we unveiled a straightforward radical–radical cross-coupling reaction between xanthenes and sulfonyl hydrazides for the synthesis of xanthen-9-sulfone derivatives using TBHP under an oxygen atmosphere (Scheme 1e).

In our initial study, xanthene **1a** and *p*-toluenesulfonyl hydrazide **2a** were selected to optimize the reaction conditions using different solvent combinations and oxidants (Table 1 and ESI,† Table S1). When the reaction was performed in THF using TBHP (1.5 equiv.) in the open air, the reaction yielded the corresponding sulfonylated product **3a** in 85% yield (Table 1,

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† Electronic supplementary information (ESI) available: Experimental procedures, characterization data, ^{1}H and ^{13}C NMR spectra of all new compounds (PDF) and single crystal X-ray diffraction data for compound **3a** (CIF). CCDC 2118371. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/d1cc07143b

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