DESIGN AND SYNTHESIS OF INDOLE CONTAINING HYBRID MOLECULES VIA TANDEM REACTIONS

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Doctor of Philosophy (Science)

By

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CERTIFICATE FROM THE SUPERVISOR

This is to certify that the thesis entitled **"DESIGN AND SYNTHESIS OF INDOLE CONTAINING HYBRID MOLECULES VIA TANDEM REACTIONS"** submitted by Sri **ABHISHEK KAR** who got his name registered on 12.03.2018 [Index. No.: 117/18/Chem./26] for the award of Ph.D. (Science) degree of Jadavpur University is absolutely based upon his own work under the supervision of Prof. Umasish Jana 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.

Date: 13/12/2024

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The thesis entitled as "**DESIGN AND SYNTHESIS OF INDOLE CONTAINING HYBRID MOLECULES *VIA* TANDEM REACTIONS**" represents a part of more than five years of research work that has been performed since I was introduced to Dr. Jana's lab, middle of the year 2017. Throughout this journey, I have had the privilege of interacting with numerous individuals who have contributed to the research and the completion of this thesis in various ways. I would like to take this opportunity to express my sincere gratitude to all those people who supported and guided me along the way, and whose contributions have been invaluable.

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PREFACE

The main proposal of the research work is to develop the synthetic method aimed at being straightforward, adaptable, cost-effective, and environmentally sustainable. These efforts resulted in the development of new methods for the synthesizing derivatives of indole-fluorene, indole-xanthydrol, indole-indazole hybrid molecule. The thesis has been divided into four chapters.

Chapter 1 introduces the readers to the recent developments in the synthesis of indole containing hybrid molecule. After giving the detailed review, the objectives of the works presented briefly in this thesis.

Chapter 2 describes a common method for the syntheses of indole tethered fluorene hybrid molecules. Initially, propargylated 2-haloanilnes were subjected to Pd-catalyzed reductive Heck reaction. Then this reductive Heck product underwent DDQ/$FeCl_3$-mediated tandem intramolecular carbon–carbon bond formation through allylic Csp^3–H oxidation to form the derivatives of indole-fluorene hybrid molecule in good to excellent yield. A plausible mechanism is proposed for this tandem process.

Chapter 3 presents a common strategy for the synthesis of indole-xanthydrol hybrid molecules via two-step process. At first substituted 2-bromo-*N*-(3-(2-phenoxyphenyl)prop-2-ynyl)-*N*-tosylbenzenamine underwent Pd-catalysed domino reductive Heck reaction. The reductive heck products then underwent iron-catalysed oxidative cycloisomerization/hydroxylation reaction to furnish indole-xanthydrol hybrids in high yields. The synthetic utility of this protocol was further explored by the one-pot synthesis of the highly substituted xanthene containing bis-indolylmethane derivative. This strategy proceeds through a series of reactions such as allylic oxidation, isomerization, cyclisation and hydroxylation in a tandem manner. The preliminary mechanistic studies implies that the generation of radicals in presence of catalytic iron(III)-salts initiates the reaction.

Chapter 4 presents a *tert*-butyl nitrite (TBN) mediated straightforward metal free approach for the synthesis of a diverse range of C-3-substituted indazole-indole hybrids using readily accessible 2-(indolin-3-ylidenemethyl)aniline derivatives in good to excellent yields. By employing this strategy, 7-azaindole-indazole and 3*H*-indazole-indole hybrids were also

synthesized. Since naturally occurring indoles lack protecting groups, we also performed the deprotection reaction of one of the synthesised indole-indazole hybrids. To further test the practical applicability of this methodology, a semi-large scale cyclisation reaction of our model substrate was caried out in a usual laboratory setup. To shed light on the mechanism, a few control experiments were conducted. Preliminary mechanistic studies revealed that the reaction progressed through a diazonium salt intermediate that is capable of cascade isomerization and intramolecular C−N bond formation through a 5-*endo*-*dig* cyclization.

Chapter 2, Chapter 3 and Chapter 4 each consist of a short introduction followed by a detailed description of reaction performed, experimental section involving details of methods with required spectroscopic and analytic data. Related references, some representative images of ^{1}H and ^{13}C NMR spectra, and finally single-XRD structure of our model hybrid product are also incorporated.

Abhishek Kar
Jadavpur, December 2024

LIST OF ABBREVIATIONS & GLOSSARY

Ac	Acetyl
atm	Atmospheric pressure
Ar	Argon
Bn	Benzyl
Boc	*tert*-Butyloxycarbonyl
BHT	butylated hydroxytoluene
calcd	Calculated
CCDC	The Cambridge Crystallographic Data Centre
Compd	Compound
CNS	Central nervous system
CAN	Ceric ammonium nitrate
COVID-19	Coronavirus Disease 2019
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DCE	1,2-Dichloroethane
DCM	Dichloromethane
DMF	*N*,*N*-Dimethylformamide
DMSO	Dimethyl sulfoxide
dppf	1,1'-Bis(diphenylphosphino)ferrocene
dr	Diastereomeric ratio
EDG	Electron-donating group
ESI-MS	Electrospray ionization mass spectrometry
EWG	Electron-withdrawing group
FDA	Food and Drug Administration
GSK	glycogen synthase kinase
HIV	Human Immunodeficiency Virus
HCV	Hepatitis C virus
HRMS	High resolution mass spectrometry

mp	Melting point
MS	Molecular sieves
Ms	Methanesulfonyl
MW	Microwave
NMR	Nuclear magnetic resonance
OLED	Organic light-emitting diode
OFET	Organic field-effect transistor
ORTEP	Oak Ridge Thermal Ellipsoid Plot
ppm	parts per million
PIDA	phenyliodine(III) diacetate
PTSA	*p*-Toluenesulfonic acid
rt	Room temperature
TBDPS	*tert*-Butyldiphenylsilyl
Tf	Trifluoromethanesulfonyl
THF	Tetrahydrofuran
TIPS	Triisopropylsilyl
TLC	Thin layer chromatography
TBN	Tetramethylguanidine
TMS	Trimethylsilyl
TOF	Time of flight
TEMPO	2,2,6,6-tetramethylpiperidinyl-1-oxyl
Ts	*p*-Toluenesulfonyl

CONTENTS

Chapter 1

INTRODUCTION

The term 'Hybrid' has a long history, first used in the early 1600s to understand the offspring of two different animals or plants of different species or varieties. It is taken from the Latin word '*Hybrida*'. In 21st century the term 'Hybrid' has been used in various fields such as science, technology, agriculture and more, to describe combinations of different elements. Over the past decade, such general term as 'Hybrid molecule' has grown increasingly frequent in the literature and has been successfully applied in the field of chemistry.[1] Hybrid molecules are defined as chemical entities that contain two or more structural domains, each of which has a separate biological purpose. To be more specific, hybrid molecules are the products of molecular hybridization, a process in which two or more separate molecules, each with unique properties, are integrated through the formation of covalent bonds.[2] Examples for hybrid molecules arises from naturally occurring proteins and small molecule such as microorganisms secreted botulinum toxin and bleomycin respectively.[3] Hybrid compounds are classified based on the type of linker used to connect the two molecular fragments, the method of interaction between each molecules and the biological targets, and the form in which they are presented.[4] Hybrid molecules play a vital role across diverse fields of chemistry.

In medicinal chemistry, Hybrid molecules act as separate pharmacophores within a single entity. Ehrlich defines a pharmacophore as a molecular farmwork that determines a drug's biological function. The hybrid molecule possesses a dual mode of action that permits it to act on multiple biological targets at the same time with better effectiveness and less susceptible to resistance. Additionally, hybrid molecules significantly enhance the efficacy of their individual components and exhibits synergism, when they function simultaneously or sequentially.[5] Therefore, in drug discovery, the synthesis of hybrid molecule has appeared as a promising strategy with remarkable advantages such as a lowered chance of drug-drug interaction, a minimized side effects, an intensified activity and a lower costs and better patient compliance.[6] In this regard, several hybrid compounds have been explored as potential anti-tubercular, antifungal, antibacterial, antimalarial, anti-inflammatory, anti-HIV, and anti-Alzheimer's agents.[7] Moreover, hybrid molecules have shown promising anticancer activity[8] and few of them have been the subject of clinical trials.[8d] Very recently, hybrid molecules respond effectively to emerging health threats like the coronavirus disease 2019 (COVID-19) pandemic, showcasing their versatility and rapid adaptability.[9]

In materials chemistry, hybrid molecules have been used in the designing of optoelectrical devises such as organic light-emitting diode (OLED), solar cell etc. Hybrid molecules are also utilized as fluorescent probes for detecting biomolecules and signals in living system.[10] Thus, the development of novel hybrid molecules has emerged as a significant field of research in modern times.

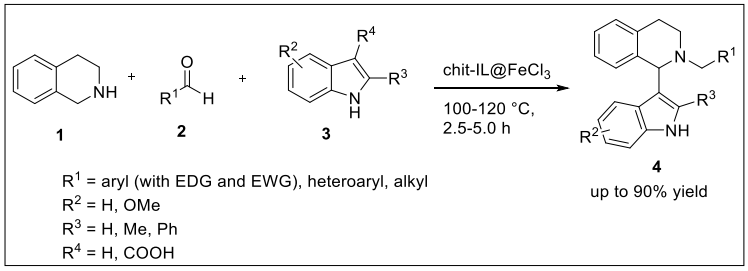
When discussing the living systems in nature, it is impossible to overlook the vast array of heterocyclic compounds. Among them, indoles and its derivatives are the most significant ones. Their occurrence in a wide range of natural products and biologically active compound are well documented.[11] Due to the biological importance of indoles and advancement of hybrid molecules, today indole containing hybrid molecules have gained considerable attention in medicinal chemistry and pharmaceutical industries.[12] Particularly, indole based hybrid heterocycles have generated more interest among the researchers owing to their existence in natural products and biologically active molecules, as well as their importance in pharmacology and medication development.[13] They are also used as molecular platforms for luminescent, hole transporting and nonlinear optical (NLO) materials in organic light-emitting didoes (OLEDs).[14] Because of all these factors, several methodologies have been developed for the synthesis of indole containing hybrid molecules.[15]

In both academia and industries one of most pressing challenges is the single step production of complex organic scaffolds from easily accessible staring material. Typically, the target products are synthesized through a multistep procedure that involves the addition of extra reagents and isolation of intermediates. Therefore, to avoid this process, the reactions capable of forming multiple bonds in the products are crucial for the synthesis of organic molecule. In this regard, tandem reactions have the ability to install the complexity in small molecule via sequential transformation.[16] Tandem reactions, sometimes also called domino or cascade reactions, are the processes in which several bonds are formed in one sequence without isolation of intermediates, the changing of reaction conditions, or the addition of reagents. The clear benefits of tandem reactions such as high atom and step economy, saving time and labor, better resource management, and reducing waste and production costs, escalate its utilization in organic synthesis.[17] Thus, tandem reactions have proved as ecologically and economically

favorable approach for the construction of indole based natural products and hybrid scaffolds.[18] This thesis will present three new approaches for the syntheses of three types of indole containing hybrid molecules, via tandem isomerization/cyclization strategies. Before discussing the details of those research, this chapter will provide an overview of recent developments in the syntheses of indole containing hybrid molecules.

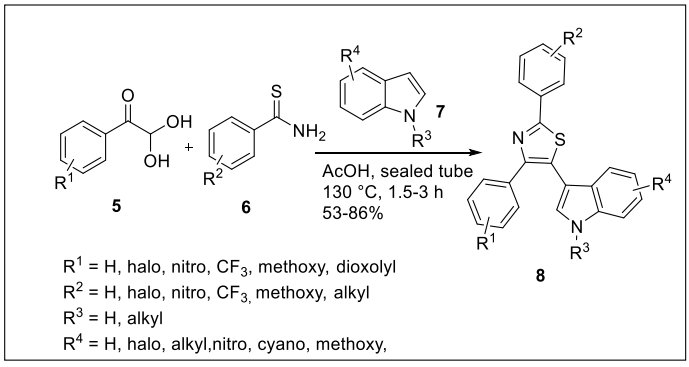
1.1 RECENT DEVELOPMENTS IN THE SYNTHESIS OF INDOLE CONTAINNING HYBRID MOLECULE

Multicomponent reactions (MCR) are one of the effective tools for organic synthesis due to their shortness and diversity. The report by Kumar *et al.* in 2023 describing a three-component coupling of tetrahydroisoquinoline (THIQ) **1**, aldehydes **2** and indoles or indole-3-carboxylic acid **3** led a route for accessing tetrahydroisoquinoline–indole hybrids **4** using chitosan-ionic liquid supported $FeCl_3$ (chit-IL@$FeCl_3$) as a recyclable heterogeneous catalyst. The group has also found the potent antiplasmodial activity of some synthesized hybrid compounds (**Scheme 1.1)**.[19]



Scheme 1.1. Chitosan-supported $FeCl_3$ catalyzed multicomponent synthesis of THIQ–indole Hybrids.

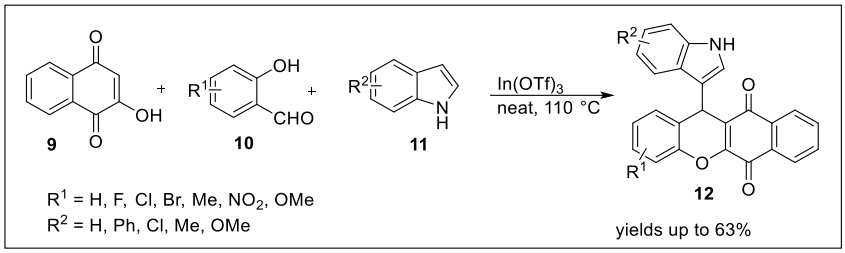
The Choudury's group in 2022 have demonstrated a method to afford indole–thiazole hybrids **8** in good to excellent yields via an acetic acid-mediated multicomponent reaction of



Scheme 1.2. Multicomponent synthesis of fluorescent thiazole−indole hybrids.

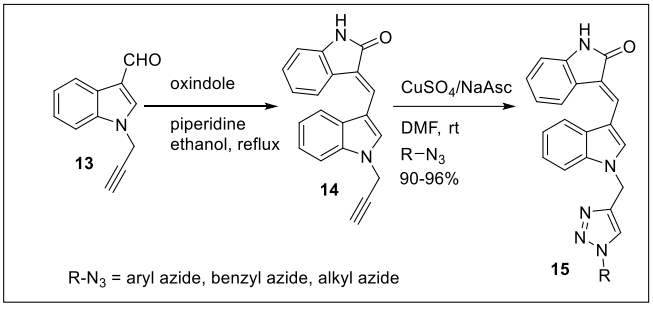
5, thiobenzamide **6** with indole **7** (**Scheme 1.2).**[20] Due the presence of extended π-conjugation the indole-thiazole compounds exhibit strong fluorescent intensity.

A green and efficient procedure for the synthesis of 1,4-naphthoquinones possessing indole scaffolds **12** by using $In(OTf)_3$ catalyzed MCR has been developed by Wu *et a*l. Reaction of 2-hydroxy-1,4-naphthoquinone **9**, substituted salicylic aldehydes **10** and indoles **11** in presence of $In(OTf)_3$ catalyst under solvent free condition afforded the desired hybrids **12** in low to moderate yields (**Scheme 1.3)**.[21]



Scheme 1.3. Synthesis of 1,4-naphthoquinones–indole hybrids via multicomponent reaction.

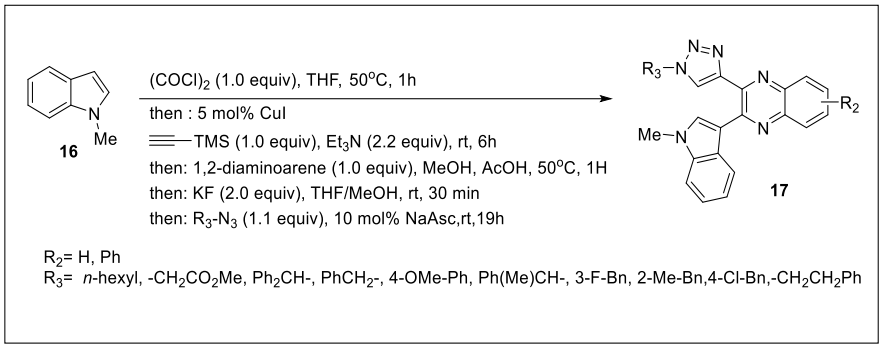
The copper catalyzed azide-alkyne cycloaddition (CuAAC) reaction has significantly used to join 1,2,3-triazoles with another heterocyclic compound. Patel *et al.* reported an efficient method to construct indole–oxindole clubbed 1,2,3- triazole hybrids **15** via Cu-catalyzed azide-alkyne cycloaddition (CuAAC) or click reaction of *N*-propargyl-3-substituted indole **14**. The precursor **14** was synthesized following the Claisen-Schmidt condensation reaction of *N*-propargyl-indole-3-carbaldehyde **13** and oxindole. The antimicrobial activity of each synthesized compound **15** was examined against various bacterial and fungal strains (**Scheme 1.4)**.[22]



Scheme 1.4. Synthesis of indole-oxindole clubbed 1,2,3-triazole hybrids.

Muller and his group have developed a straightforward approach to synthesize indole linked 3-triazolylquinoxaline hybrids **17** based upon a sequential Cu-catalyzed process, that involves

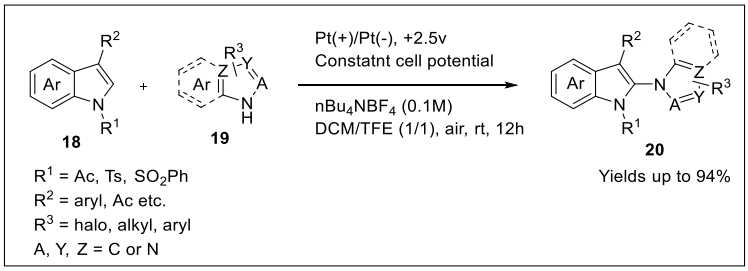
GACC-CuAAC (glyoxylation-alkynylation-cyclocondensation-Cu(I)-catalyzed azide-alkyne cycloaddition) sequence in a one-pot fashion. Desilylation of alkyne group is readily achieved upon addition of potassium fluoride in presence of azides, leading to the formation of indole-



Scheme 1.5. Sequential four-component AACC-CuAAC synthesis of indole containing triazolylquinoxalines hybrids.

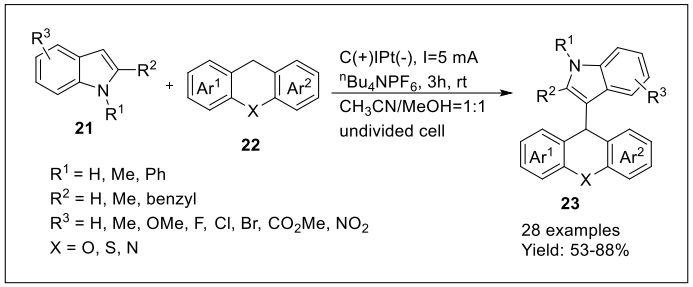
3-triazolylquinoxaline derivatives **17** in moderate to excellent yields (**Scheme 1.5).**[23]. This one-pot strategy is preferable to step wise reaction methods due to its diversity and 90% average yield per bond forming step. Photophysical studies reveled that all the synthesized compound **17** were shown to be luminescent in DCM solution. The reaction also proceeds smoothly when starts with other heteroarenes instead of indoles **16.**

In recent years, electrochemistry is a cost-effective, renewable and safe alternative to hazards and wasteful oxidants/reductants in organic transformation. It is becoming a powerful green strategy for organic synthesis.[24] In 2021, Feng *et al.* have developed a practical protocol to synthesize 3-substituent 2-azolylindole derivatives **20** via an electro-chemical oxidative cross coupling of indoles **18** with a wide range of azoles **19 (Scheme 1.6**).[25] This strategy tolerates a range of functional groups and conducts large scale reaction smoothly. However, very low yield (17%) was obtained from substrate having ester group on C-3 position of indole (R^2 = ester). 2-phenyl indole and simple indole derivatives did not give the desired product under this condition.



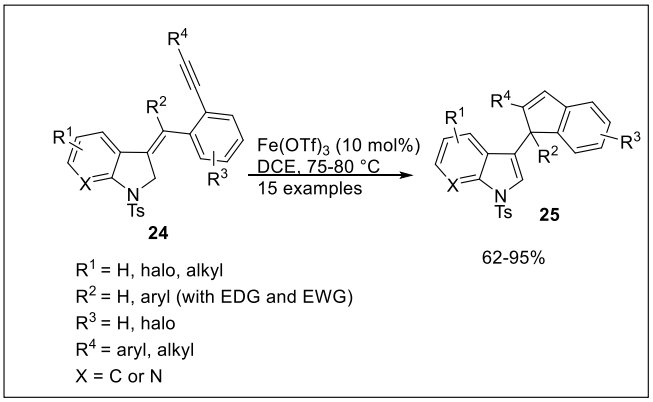
Scheme 1.6. Synthesis of 3-substituted 2-aazolyl indole derivatives through electrochemical oxidative cross coupling.

Li *et al*. reported an efficient electrochemical strategy for the cross-dehydrogenative coupling reaction of indoles **21** with xanthenes **22** at room temperature. The reaction proceeded without any metal catalyst or external oxidant, affording a variety of indole–xanthene hybrids **23** in moderate to good yields. Mechanistic studies reveled that this reaction system followed a radical pathway (**Scheme 1.7)**.[26]



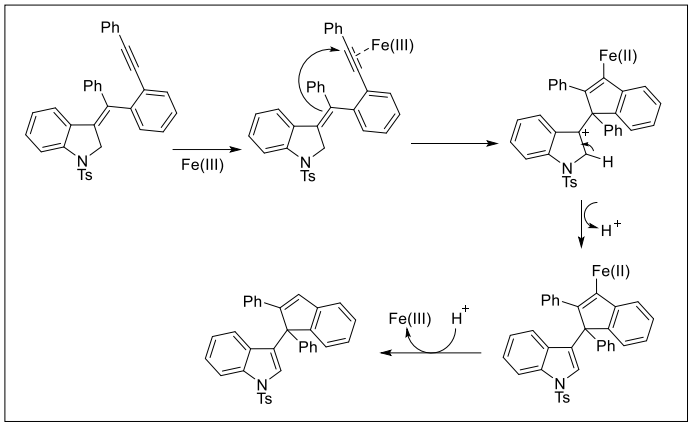
Scheme 1.7. electrochemical cross-dehydrogenative coupling of indoles with xanthenes.

The cycloisomerization, mediated by transition metal catalyst, is one of most important strategies for the construction of complex carbocycles and heterocycles.[27] Jana and coworkers reported an iron catalyzed enyne cycloisomerization for the synthesis of indole-indene hybrids **25**. Scheme 1.8 shows that $Fe(OTf)_3$ catalyzed the conversion of 1,5-enyne **24** to 3-(1-indenyl)indole derivatives **25**. Interestingly, the temperature is a crucial in determining the product. At 65 °C only the isomerization of indoline to indole occurs. At temperature 75-80 °C 1,5-enyne cycloisomerization proceeds smoothly to afford various indole-indene hybrids **25** in good yields. This strategy could also be applied to synthesize 7-azaindole tethered indene derivatives **(Scheme 1.8**).[28]



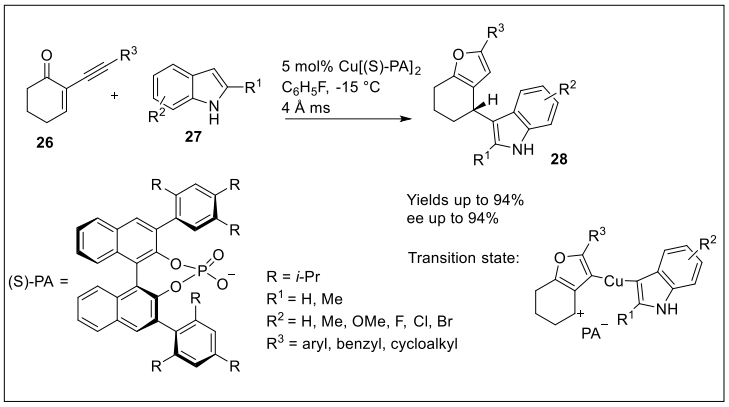
Scheme 1.8. Synthesis of 3-indenylindole derivatives by iron catalyzed 1,5-enyne cycloisomerization.

The proposed mechanism involves π-activation of alkyne by $Fe(OTf)_3$. This activation allows for nucleophilic attack by exocyclic double bond, resulting to cyclisation in 5-endo dig manner. Finally, isomerization followed by protonolysis generates the desired hybrid product **(Scheme 1.9**).



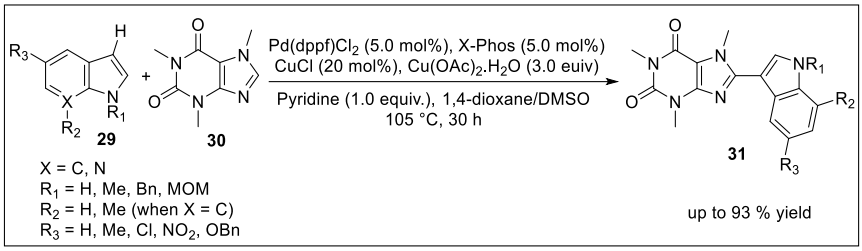
Scheme 1.9. Proposed mechanism for the synthesis of indole–indene hybrid.

In 2011, F. D. Toste demonstrated a copper (II) catalyzed asymmetric cycloisomerization-indole addition reaction for the synthesis of tetrehydrobenzofuran–indole hybrids **28**. Treating alkyne **26** with chiral ligand containing copper(II) catalyst, $Cu[(S)\text{-}PA]_2$ triggered an intramolecular heterocyclisation reaction and the resulting carbocation was then trapped by various indole derivatives **27** to produce the tetrehydrobenzofuran-indole hybrid products **28** with high yields and selectivity. The exact mechanism of the reaction is unclear, however the authors proposed that a copper (II)-indole complex is formed, whereas ion pairing between copper and phosphate anion governs the facial selectivity of indole attack **(Scheme 1.10**).[29]



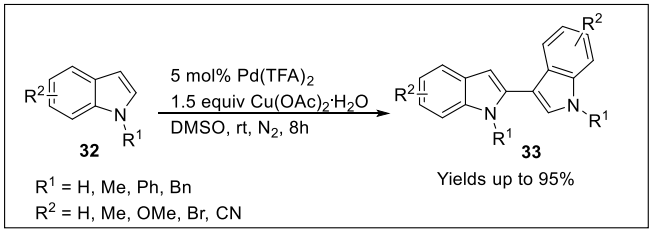
Scheme 1.10. Copper(II)-catalyzed reaction for the synthesis of indole linked tetrahydrobenzofuran derivatives.

The best strategy for connecting two heteroarene is metal catalyzed direct oxidative coupling via double C–H activation due to its atom economy and sustainability. This strategy avoids the need for prefunctionalization of both substrate before coupling. Wang and coworkers presented a methodology for the synthesis of indole–caffeine hybrids **31** with high yields. The method allows the highly regioselective C-3 heteroarylation of indoles **29** with an array of caffeine **30** via palladium catalyzed double C–H activation **(Scheme 1.11**).[30] The optimized reaction condition successfully suppressed the homocoupling and decomposition of the starting material and products.



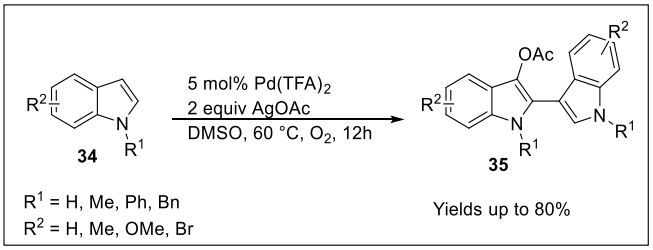
Scheme 1.11. Palladium-catalyzed synthesis of indole–caffeine hybrids.

A regioselective oxidative homocoupling of indoles **32** to synthesize 2,3′-biindolyls **33** at room temperature has been developed by Zhang *et al*. $Pd(TFA)_2$ and $Cu(OAc)_2 \cdot H_2O$ served as the catalyst and oxidant respectively, with DMSO as the optimal solvent **(Scheme 1.12**).[31] Electron rich and moderately electron poor indoles combine effectively to produce good to excellent yields. The reaction tolerates the bromide containing indoles.



Scheme 1.12. Palladium-catalyzed regioselective oxidative homocoupling of substituted indoles.

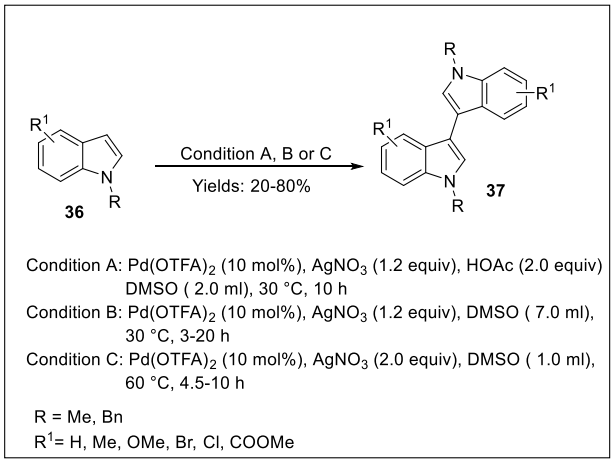
Notably, a one-pot approach for the preparation of C3-acetoxylated biindoles **35** was achieved, when AgOAc was employed as the oxidant. Oxygen was essential for the acetoxylation step.



Scheme 1.13. one-pot formation of acetoxylated biindolyl derivatives.

Only electron rich indoles **34** gave the C3-acetoxylated biindoles **35** following the one-pot sequence **(Scheme 1.13**).

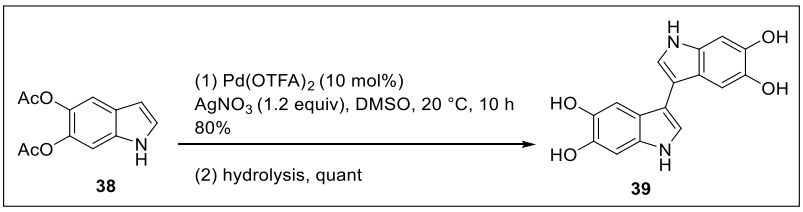
Biindole moieties are privileged structural scaffolds in many natural products.[32] Shi *et al*. demonstrated the oxidative homo dimerization of N-protected and free indole derivatives **36** toward 3,3′-linked biindolyl scaffolds **37** via Pd catalyzed direct C–H transformation.



Scheme 1.14. Homocoupling of several indole derivatives to synthesize 3,3′ -biindole derivatives.

The group reported that the presence of $AgNO_3$ is crucial in tuning the coupling pathway and 3,3′-dimer was obtained with high yield. To achieve high efficiency for different substrate, slight adjustment in reaction condition was necessary **(Scheme 1.14**).[33]

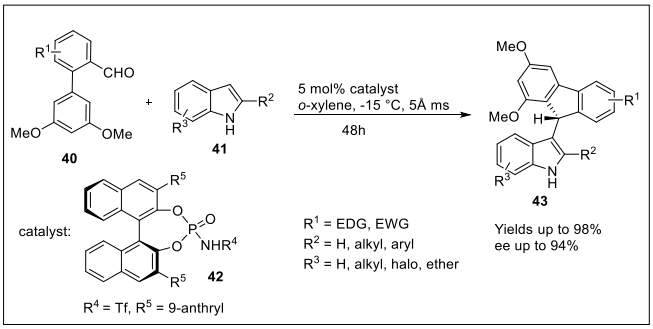
Furthermore, the 3,3′-homo dimerization strategy was also used to construct the structure of a phenolic antioxidant **39** present in beet root (Beta vulgaris) from commercially available indole derivatives **38** (**Scheme 1.15**).



Scheme 1.15. Synthesis of biologically active indole hybrid.

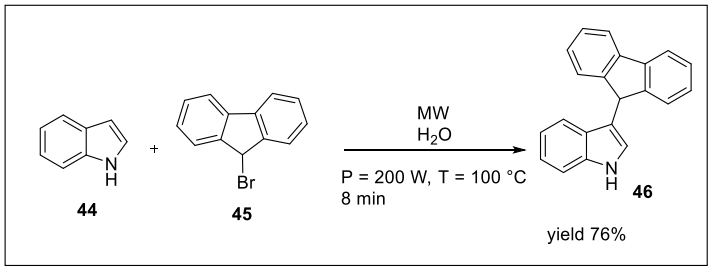
The Friedel–Crafts alkylation reaction is a traditional organic synthesis method that is still extensively employed today. The reaction is crucial for forming unique carbon-carbon bonds that would be difficult to achieve otherwise. S.-L. You and coworkers have developed a tandem double Friedel–Crafts reaction between 2-formylbiphenyl **40** and indoles **41** using chiral N-triflyl phosphoramide **42** as organocatalyst. Several 9-(3-indolyl) fluorene derivatives **43** were

synthesized with good yields and up to 94% enantioselectivity under mild condition (**Scheme 1.16**).[34] Unlike chiral phosphoric acids, these chiral *N*-triflyl phosphoramides **42** catalyzed reactions produced products with opposing absolute configuration. Various 2-methylindoles with both electron donating and withdrawing groups reacted well, yielding the cyclisation products with good enantioselectivity. However, using simple indoles significantly reduces both yield and enantioselectivity. The reaction with 2-phenyl indole achieved simply in a yield of 8% and enantioselectivity of 28%.



Scheme 1.16. Chiral *N*-triflyl phosphoramide-catalyzed synthesis of indole-fluorene hybrids.

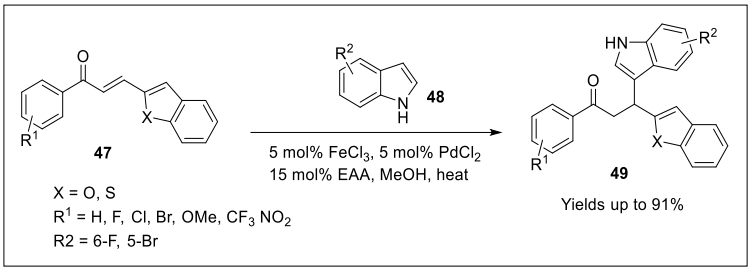
In 2010, Soriente *et al*. described an efficient and green alternative protocol for uncatalyzed Friedel–Crafts alkylation of indoles using microwave irradiation in water. The group synthesized a series of functionalized indole derivatives with moderate to good yields in a short time. For example, indole–fluorene hybrid **46** was synthesized in 76% yield by the reaction of indole **44** with fluorenyl bromide **45** (**Scheme 1.17**).[35] The combination of microwave and superheated water provides advantages over traditional methods including higher selectivity, faster reaction duration, simplicity, and no requirement for a catalyst.



Scheme 1.17. Microwave assisted synthesis of indole–fluorene hybrids.

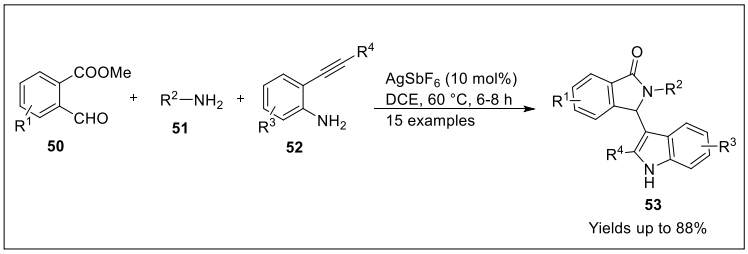
Islam and co-workers reported the Friedel–Crafts reaction of chalcones-based benzofuran or benzothiophene scaffolds **47** with substituted indoles **48** as nucleophiles by employing a bimetallic iron–palladium catalyst. This catalytic reaction offered the desired indole containing hybrid heterocycles **49** with low catalyst loading, a simple procedure, and with high yields

(**Scheme 1.18**).[36] All the synthesized compounds were evaluated for their anticancer activities against cervical cancer HeLa, prostate cancer PC3, and breast cancer MCF-7 cell lines. This examination showed excellent results, making them candidates for future research.



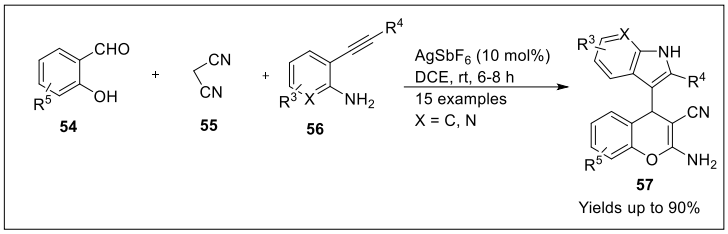
Scheme 1.18. Bimetallic iron–palladium Catalyzed Friedel–Crafts reaction to synthesize indole hybrids.

Very recently, Maiti *et al*. demonstrated a high yield cascade cyclization strategy for accessing valuable hybrid heterocycles. The rection involves the formation of four C–C/C–N/C–O bonds via Ag(I)-catalyzed cyclization with Friedel−Crafts alkylation reaction sequences. This domino approach successfully afforded indolylphthalimidines **53** in good to excellent yields by reacting substituted 2-formyl methylbenzoates **50**, electronically distinct amines **51**, and substituted *ortho*-alkynylanilines **52** (**Scheme 1.19**).[37]



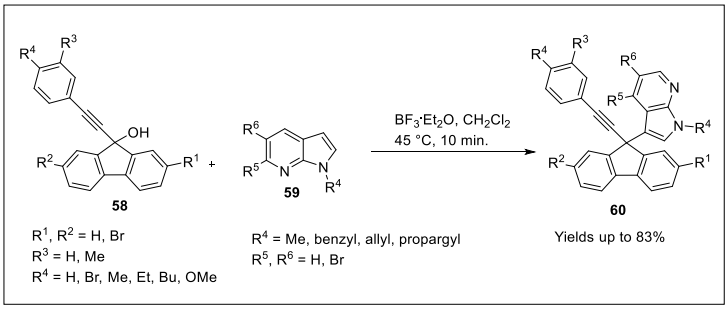
Scheme 1.19. Synthesis of indole-indolone hybrids through Ag(I)-catalyzed C–C/C–N/C–O bond formation.

With improved reaction condition, this group further expanded the scope of indolyzation with Friedel−Crafts alkylation to synthesize a series of indolylchromene derivatives **57**. The reaction among salicylaldehyde **54**, malononitrile **55**, and the unprotected *ortho*-alkynylanilines **56**, worked well in this cascade strategy, yielding indole–chromene hybrids **57** in high yields at room temperature with 10 mol % $AgSbF_6$ (**Scheme 1.20**).



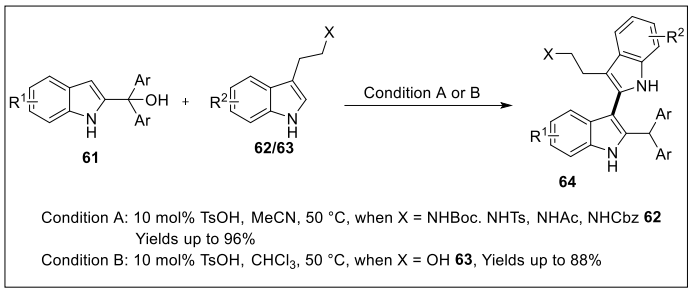
Scheme 1.20. Synthesis of highly functionalized indole–chromene hybrids.

The dehydrative functionalization of the C–OH bond is highly favorable reaction, as it generates only water as by-product. However, due to poor leaving nature of -OH group, the generation of carbocation from π-activated alcohols (benzylic, allylic, propargylic alcohols) requires Brønsted and Lewis acid. 7-Azaindoles an important bioisoster of indole have been found in various biological active compounds and are used for the treatment of various diseases.[38] Very recently, Harichandran *et al.* synthesized a number of highly functionalized 7-aza-*N*-methyl indole appended 9-(phenylethynyl)-fluorene derivatives **60** from various fluorene propargylic alcohols **58** and substituted-7-azaindoles **59** using $BF_3{\cdot}OEt_2$ as a catalyst (**Scheme 1.21**).[39] The reaction proceeds via propargylic carbocation to afford the desired hybrid product in low to good yields. The further synthetic transformations of desired product have been described by the Suzuki coupling and Click reaction. The photophysical studies of Suzuki compounds reveled that luminescence was exhibit in blue region.



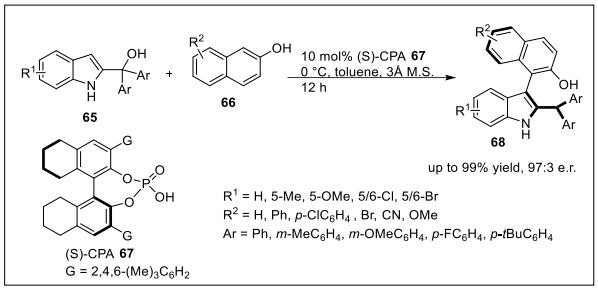
Scheme 1.21. Synthesis of blue emissive 7-azaindole tethered phenylethynylfluorene derivatives.

F. Shi *et al*. established a Brønsted acid-catalyzed dehydration reaction of 2-indolylmethanols **61** with tryptamines **62** and tryptophols **63**, leading to a series of potentially bioactive 2,3′-biindole derivatives **64** with a broad substrate scope and generally good yield (**Scheme 1.22**).[40] A possible reaction pathway for these direct C3-arylations of 2-indolylmethanols via an umpolung strategy is postulated.



Scheme 1.22. Construction of 2,3′-biindole scaffolds via an umpolung reaction.

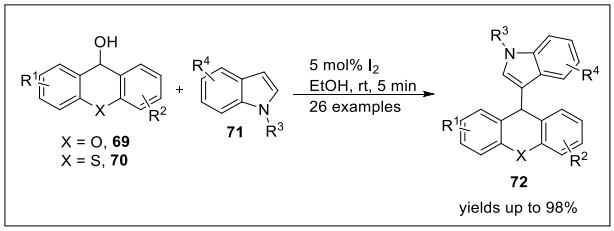
Based on the umpolung reactivity of 2-indolylmethanols **65**, in 2017, same group reported the (S)-CPA **67**-catalyzed asymmetric coupling reaction of 2-indolylmethanols



Scheme 1.23. Enantioselective synthesis of axially chiral naphthyl–indole hybrids.

65 and 2-naphthols **66**, which constructed axially chiral naphthyl–indole scaffolds **68** with yield as high as 99%. Also, the products were obtained with high enantioselectivities (**Scheme 1.23**).[41] This new catalytic enantioselective strategy takes the advantage of the C3-electrophilicity of 2- indolylmethanols for constructing axially chiral biaryl scaffolds

Wang and coworkers have developed an efficient iodine-catalyzed nucleophilic substitution reaction of xanthen-9-ol **69** and thioxanthen-9-ol **70** with indole **71** to

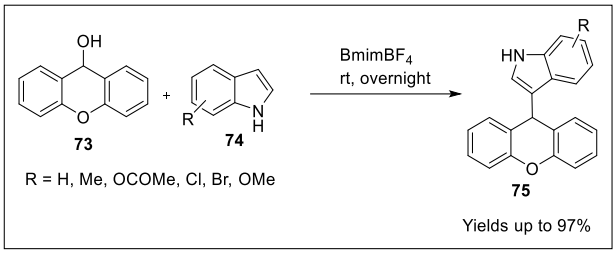


Scheme 1.24. I_2-catalyzed synthesis of xanthene/thioxanthene-indole hybrids.

synthesize xanthene/ thioxanthene-indole hybrids **72** in ethanol within just 5 min (**Scheme 1.24**).[42] This method demonstrated good substrate scope and was utilized to substitute with indoles and other nucleophile such as pyrrole, furan and 1,3-dicarbonyl compounds. Others

secondary alcohols like benzhydrols and ferrocenyl alcohols were also taken as substrates.

Ionic liquids (ILs) are recognized as green media in organic synthesis for their low flammability, volatility, toxicity, and recyclability. Thus, ILs have been extensively applied as environmentally benign solvents to substitute the common organic reaction medium.[43] In 2011, Liu *et al*. reported a simple, atom economical, protocol for the S_N1- type substitutions of 9*H*-

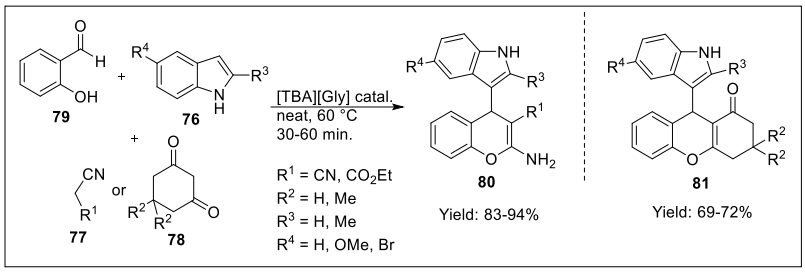


Scheme 1.25. direct substitutions of xanthenol with indoles in ionic liquid media.

-xanthen-9-ol **73** with indoles **74**. The said reactions progressed smoothly in the presence of $BmimBF_4$ at room temperature without the use of any external catalyst. By this method various indole–xanthene hybrids **75** were synthesized with high yields (**Scheme 1.25**).[44] After reaction, the products could be easily extracted with the ethyl ether, leaving behind the ILs that could be reused for further reactions. This strategy is also applicable for the S_N1-type substitutions of 9*H*-xanthen-9-ol with other nucleophiles such as diketone and pyrrole.

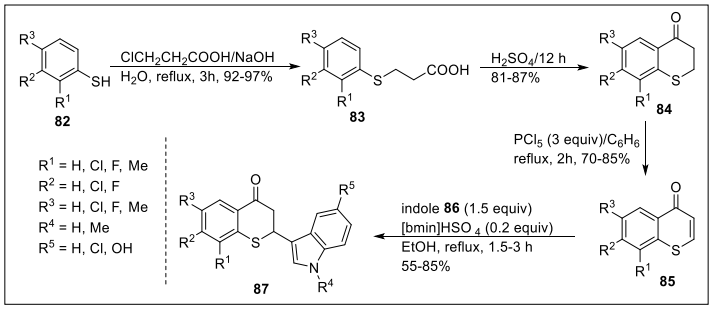
Rajesh[45] *et al*. has found Tetrabutylammonium glycinate [TBA][Gly] ionic liquid as an efficient recyclable and biodegradable organocatalyst for selective synthesis of 3-substituted indoles. They synthesized various 3-substituted indoles with higher yields under solvent free condition in presence of ionic liquid (IL), starting from indoles, malononitrile, and aromatic or aliphatic aldehydes.

Interestingly, the catalyst's effectiveness was proven by constructing indolylchromene derivatives **80** and **81** with high yields using [TBA][Gly] as IL catalyst. This was achieved by taking indole derivatives **76**, acyclic or cyclic active methylene compounds **77** and **78**, and salicylaldehyde **79** as starting materials (**Scheme 1.26**).



Scheme 1.26. ionic liquid promoted one-pot synthesis of indole–chromene hybrids.

Song and group described the synthesis of indolyl thiochroman derivatives **87** using ionic lquid 1-butyl-3-methylimidazolium hydrogen sulfate [bmim]HSO_4 and also examined for *in-vitro* antifungal activity. High yields of the desired product **87** was afforded from

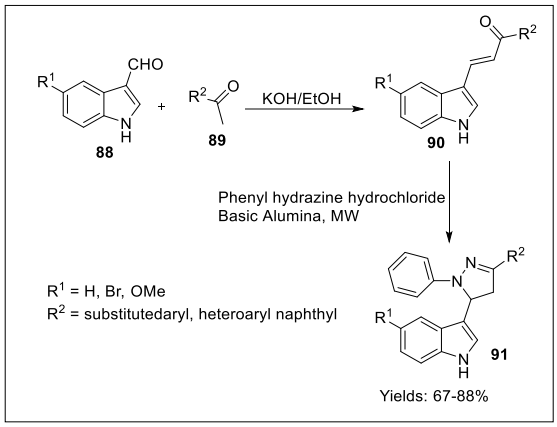


Scheme 1.27. Synthesis of antifungal active indole–thiochromanone hybrids via ionic liquid catalysis.

thiophenol **82**, chloropropionic acid and indole derivatives **86**. The reaction preceded through the formation of different intermediates like 3-(phenylthio)propanoic acid **83**, thiochroman-4-one **84** and thio–chromone **85** (**Scheme 1.27**).[46] Preliminary bioassay results indicated that most compounds have higher antifungal potency than fluconazole.

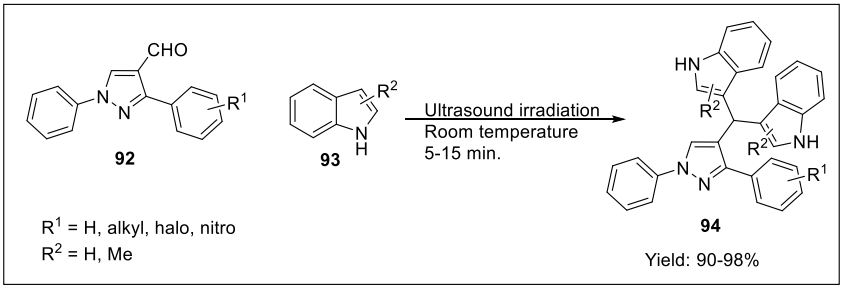
Greener synthetic routes to develop bioactive compounds have received a lot of interest in recent decades. Among them, microwave and ultrasonic assisted reactions have gained much popularity as they provide green method to activate reaction.[47] In 2013, Patil and his group utilized a green approach to synthesize indolyl pyrazoline derivatives **91** and evaluate their antidepressant and anticonvulsant activities. They demonstrated that the reaction of phenyl hydrazine hydrochloride with substituted indolyl chalcones **90** in the presence of basic alumina as the catalyst under solvent-free and microwave condition can produce substituted indolyl pyrazoline derivatives **91** with a higher yield in a short period of time. In this reaction, the precursor **90** was synthesized from the reaction of indole-3-carbaldehyde derivative **88** with

ketone derivative **89** in the presence of ethanolic KOH (**Scheme 1.28**).[48]



Scheme 1.28. Synthesis of biologically active indole–dihydropyrazole hybrids under microwave.

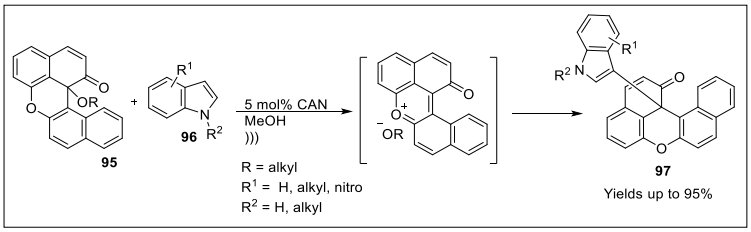
Nikpassand et al. developed a green approach for the synthesis of diindolylmethanes linked pyrazole moiety **94** in aqua media under ultrasound irradiation. The group examined the effect of various solvents, ultrasonic powers, catalysts and temperatures to optimized the reaction condition. Without any catalyst, the desired product **94** was achieved in 95% yield under ultrasonic irradiation (45 kHz) in water at room temperature. Using optimized condition, they synthesized various diindolylmethanes tethered pyrazole derivatives **94** yielding 90-98%, from reaction between indoles **93** and pyrazole derivatives **92**. The authors also found that steric hindrance decreased the reaction rate and yields of some derivatives (**Scheme 1.29**).[49]



Scheme 1.29. Synthesis of diindolylmethanes appended pyrazole derivatives under ultrasound irradiation.

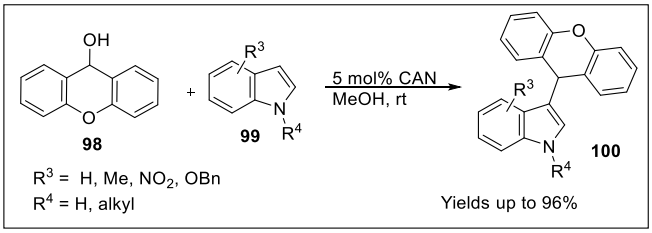
Wang[50] and co-workers proposed a convenient method for the alkylation of indoles and pyrrole through S_N1 reaction. The reaction has been accomplished by treatment with catalytic amounts of ceric ammonium nitrate (CAN) under ultrasound irradiation. The reaction of xanthene derivative **95** with indoles **96** afforded the substituted product **97** with high yield (**Scheme 1.30**). However, the 2 and 3-substituted indoles did not give the desired product due to steric repulsion. The less reactive nitroindole derivative also failed to react under this condition. Pyrrole yielded

the adduct substituted in 2-position with similar reactivity. The group reported that the reaction proceeded through a pyrillium intermediate.



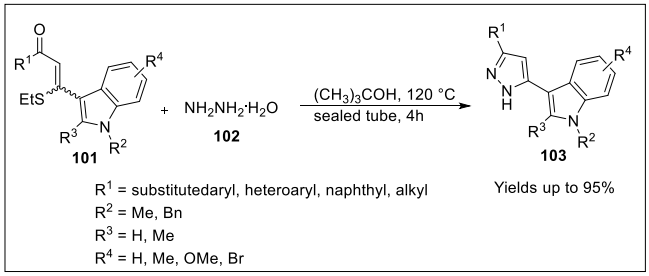
Scheme 1.30. CAN catalyzed reaction of indoles with pryllium for the synthesis of indole–xanthene hybrids.

Similarly, xanthene-9-ol reacted **98** with various indoles **99** in presence of CAN, providing the desired indole–xanthene hybrid **100** in good yields (**Scheme 1.31**). As expected, 3-unsubstituted indoles reacted at their C-3 position, while the only 3-substituted indole that was examined yielded the products substituted at C-2 without any yield loss.



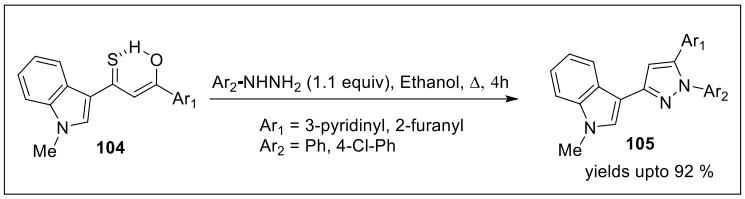
Scheme 1.31. CAN-catalyzed construction of indole–xanthene hybrids.

Cyclocondensation reactions between hydrazines and ketones are robust, efficient, and green methods widely adapted for synthesizing Nitrogen rich planner π-conjugated molecules. Very recently a catalyst free cyclocondensation reaction of β-ethylthio- β -indolyl-α, β -unsaturated ketones **101** with hydrazines **102** has been developed by Yu *et al*. The reaction can be carried out in tert-butanol at 120 °C to synthesize 3-pyrazolyl indoles **103** in excellent yields (**Scheme 1.32**).[51]



Scheme 1.32. Synthesis of indole–pyrazole hybrids by catalyst free cyclocondensation reaction.

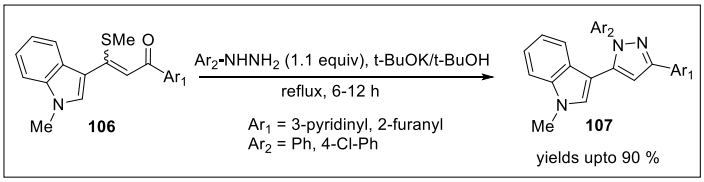
Rangappa[52] *et al*. devised a cyclocondensation strategy for achieving indolyl-*N*-arylpyrazole derivatives **105** from 1,3-bisheteroaryl-monothio-1,3-diketones **104**. under neutral conditions, the precursors **104** were condensed with arylhydrazine in refluxing ethanol to produce indolyl-



Scheme 1.33. Regioselective synthesis of indole–pyrazole hybrids.

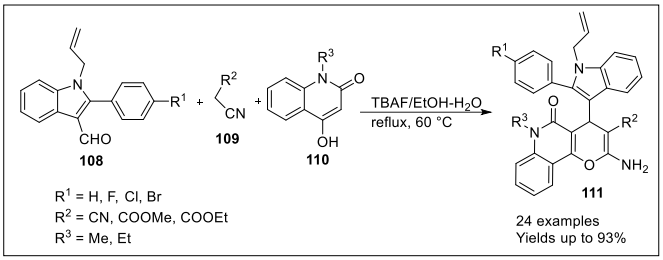
N-arylpyrazole derivatives **105** (**Scheme 1.33**). The sharp difference in reactivity between carbonyl and thiocarbonyl groups enables high regioselectivity. The reactions are usually high yielding and perfect regioselectivity has been observed. In most of the product the thioketone moiety is inserted at C3 position of pyrazole.

In the same report, another indolyl-*N*-arylpyrazoles **107** was synthesized with complementary regioselectivity by reacting of S-methylated monothio-1,3-diketones **106** with arylhydrazine in presence of *t*-BuOK in *t*-BuOH (**Scheme 1.34**). Interestingly, all examples displayed reverse regioselectivity with thioenolether group insertion at pyrazole C5 position. Furthermore, this strategy is adaptable to a one-pot three component reaction staring from ketone.



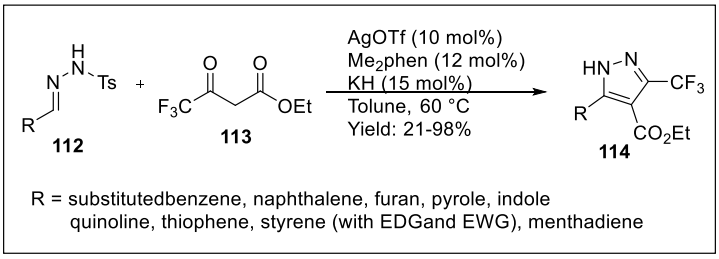
Scheme 1.34. Synthesis of regioisomeric indole–pyrazole moiety from 3-methylthiopropenones.

In 2017, the group of Prasad conceived a one-pot cyclocondensation protocol for the synthesis of indole–based pyranoquinoline hybrid compounds. Reaction of indole-3-carbaldehyde deriavtives **108**, and active methylenes **109**, with 4-hydroxy-2-quinolinone derivatives **110** in the presence of tetra-n-butylammonium fluoride (TBAF) as organocatalyst in water–ethanol (2:8) mixture solvent afforded indole-pyranoquinoline hybrids **111** in moderate to good yields (**Scheme 1.35**).[53] After that, the synthesized compounds were examined for antimicrobial activity. Most of the products showed promising effectiveness against a range of human infection compared to traditional drugs.



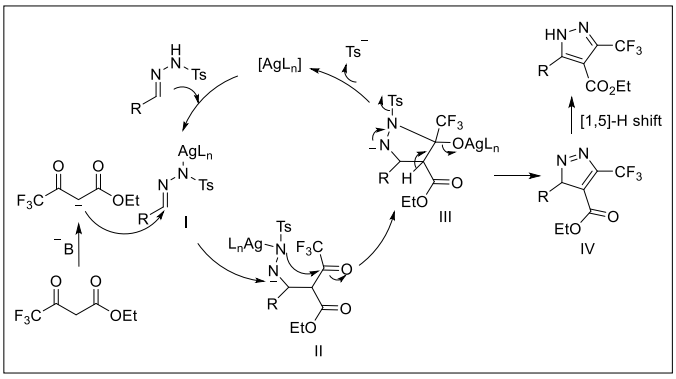
Scheme 1.35. Organocatalyzed synthesis of biologically valuable indole–pyaranoquinolinone hybrids.

Bi-heteroaryl structural fragments are prevalent in pharmaceuticals, agrochemicals, natural products, and organic functional material. Among them indole containing bi-heteroaryls have received significant interest due to their board spectrum of biological activities.[54] Therefore, greater attention to their synthesis has been directed by the synthetic chemists.[55] In 2020, Xu et al. developed a silver-catalyzed synthesis of 5-aryl-3-trifluoromethyl pyrazoles **114** using readily available *N*′-benzylidene tolylsulfonohydrazides **112** and ethyl 4,4,4-trifluoro-3-oxobutanoate **113** under basic conditions. To broaden the scope of the reaction, an indole-linked pyrazole derivative was synthesized. But the yield of this indole-pyrazole hybrid is very low (**Scheme 1.36**).[56]



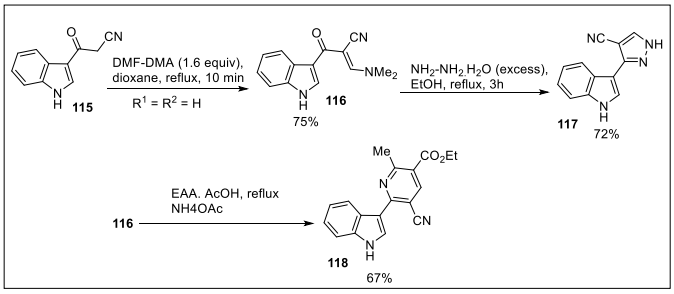
Scheme 1.36. Silver-catalyzed synthesis of pyrazole containing hybrid molecules.

The group also proposed a plausible mechanism for this transformation as shown in scheme 1.37. Initially, silver forms complexation with tosyl hydrazone. Then, the nucleophile ethyl 4,4,4-trifluoro-3- oxobutanoate added with the activated tosyl hydrazone, followed by intramolecular cyclisation, elimination of *p*-toluenesulfonyl group and 1,5-H shift led to the formation of the desired product (**Scheme 1.37**).



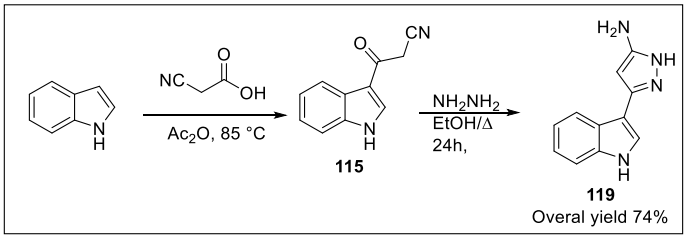
Scheme 1.37. Proposed mechanism for the formation of pyrazole hybrids.

Abdallah reported the synthesis of 3-indolylpyrazole-4-carbonitrile **117** via two-step process. Initially, the compound **115** was reacted with dimethylformamide dimethylacetal (DMF-DMA) in refluxing dioxane, followed by cyclization with hydrazine hydrate in ethanol. Starting from the compound **116**, the group also synthesized indolylpyridine derivative **118** by reaction of **116** with ethyl acetoacetate (EAA) in refluxing acetic acid and in presence of ammonium acetate (**Scheme 1.38**).[57]



Scheme 1.38. Synthesis of 3-indolylpyrazole-4-carbonitrile and indole–pyridine hybrid.

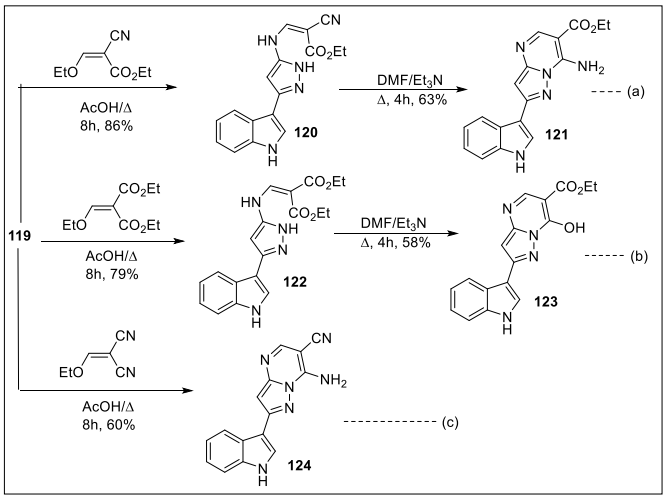
In 2018, El-Mekabaty and co-workers demonstrated the construction of 5-amino-3-indolyl-pyrazole **119** in 74% overall yield by treating indole with cycnoacetic acid in acetic anhydride to form the unsubstituted 3- cyanoacetylindole **115**, then cyclizing it with hydrazine hydrate in EtOH at the refluxing condition (**Scheme 1.39**).[58]



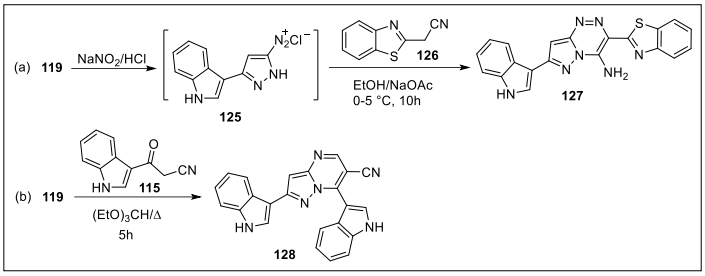
Scheme 1.39. Synthesis of 5-amino-3-indolylpyrazole.

This group used the obtained 5-amino-3-indolylpyrazole **119** as intermediate for the synthesis of a wide variety of indole containing hybrid heterocycles. Some of them were summarized in scheme 1.40. The compound **119** on reaction with ethyl-2-cyano-3-ethoxyacrylate in acetic acid under reflux condition yielded *N*-substituted derivative **120** in step one. In second step, cyclisation of **120** proceeded by the addition of catalytic Et_3N in DMF afforded compound **121** (**Scheme 1.40a**). Again, the reaction of **119** with diethyl 2-(ethoxymethylene) malonate by following the similar condition to provide indole-based hybrid **123** via intermediate **122** (**Scheme 1.40b**). When 5-aminopyrazole **119** was reacted with 2-(ethoxymethylene) malononitrile in boiling acetic acid, it produced indolyl pyrazolopyrimidine derivative **124** directly (**Scheme 1.40c**).

This group also explored the synthetic utility of **119** for the synthesis of indole linked pyrazolotriazines **127** via coupling of diazonium salt **125** of **119** with active methylene compounds **126** in the presence of ethanol and sodium acetate (**Scheme 1.41a**). Furthermore the two indole ring containing pyrazolo[1,5-*a*]pyrimidine that is compound **128** was achieved by a multicomponent condensation reaction between 5-aminopyrazole **119**, 3-cyanoacetyl indole **115**, and triethyl orthoformate under solvent-free conditions. The synthetic compounds were screened for antioxidant activity and compound **127** and **128** exhibited a promising efficacy (**Scheme 1.41b**).

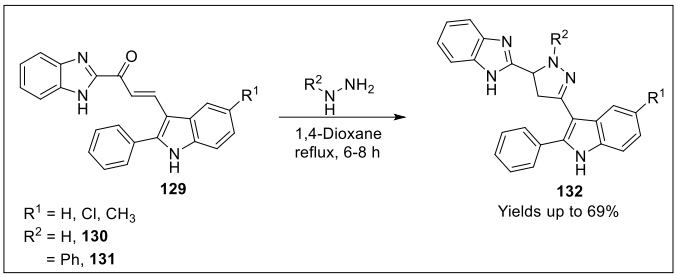


Scheme 1.40. Synthesis of various indole containing hybrids from 5-amino-3-indolylpyrazole.



Scheme 1.41. Synthesis of antioxidant active indole hybrids from 5-amino-3-indolylpyrazole.

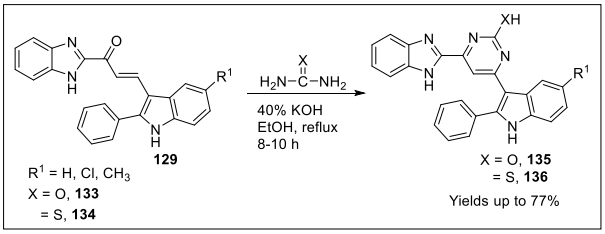
Mathada *et al*. designed and synthesized a library of novel benzimidazole-attached indole-



Scheme 1.42. Synthesis of biologically active indolylpyrazole derivatives.

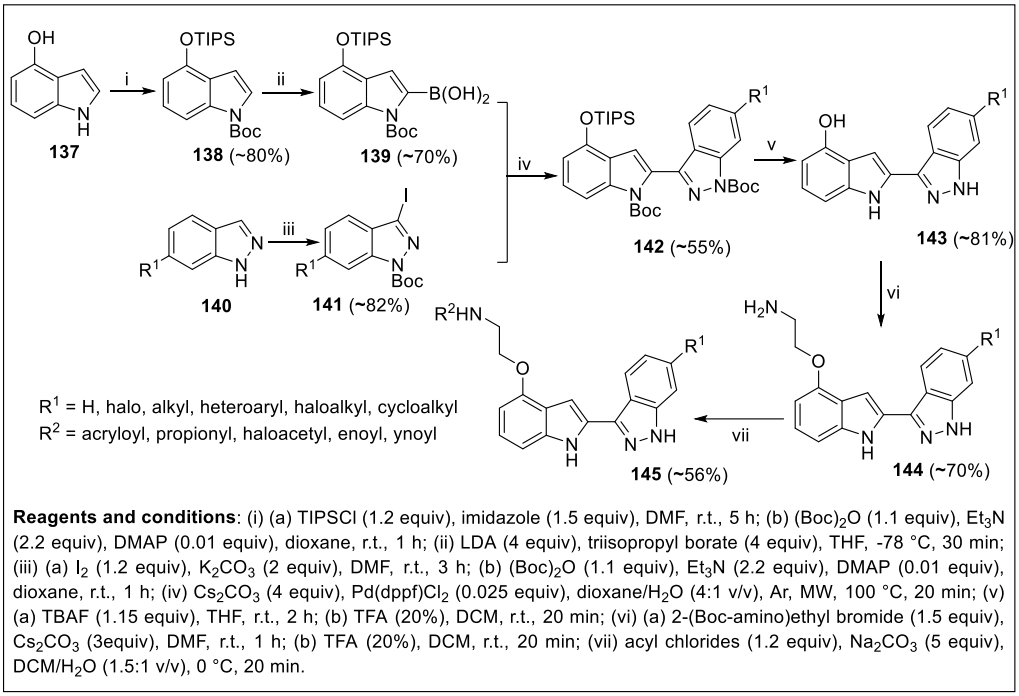
C-3 pyrazoline hybrids **132** and investigated their antioxidant and antimicrobial activities. The cyclization of indole chalcones **129** were done using hydrazine hydrate **130** and phenylhydrazine **131** in refluxing dioxane to access the desired hybrid molecules **132** in good yields (**Scheme 1.42**).[59]

The group also reported the reactivity of the same substrate with other coupling partners. For example, the obtained chalcones **129** were cyclized with urea **133** (or thiourea **134**) and 40 % KOH to afford the desired compound **135** and **136** respectively (**Scheme 1.43**).



Scheme 1.43. Synthesis of biologically active benzimidazole-attached indole derivatives.

Pan *et al*. described a synthetic route for the formation of a series of indolylindazole derivatives **145** and recognized some of them as potent and selective covalent inhibitors for interleukin-2 inducible T-cell kinase (ITK). The intermediate **139** was synthesized through successive -OH

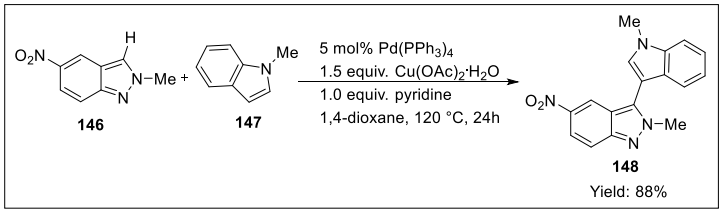


Reagents and conditions: (i) (a) TIPSCl (1.2 equiv), imidazole (1.5 equiv), DMF, r.t., 5 h; (b) $(Boc)_2O$ (1.1 equiv), Et_3N (2.2 equiv), DMAP (0.01 equiv), dioxane, r.t., 1 h; (ii) LDA (4 equiv), triisopropyl borate (4 equiv), THF, -78 °C, 30 min; (iii) (a) I_2 (1.2 equiv), K_2CO_3 (2 equiv), DMF, r.t., 3 h; (b) $(Boc)_2O$ (1.1 equiv), Et_3N (2.2 equiv), DMAP (0.01 equiv), dioxane, r.t., 1 h; (iv) Cs_2CO_3 (4 equiv), $Pd(dppf)Cl_2$ (0.025 equiv), dioxane/H_2O (4:1 v/v), Ar, MW, 100 °C, 20 min; (v) (a) TBAF (1.15 equiv), THF, r.t., 2 h; (b) TFA (20%), DCM, r.t., 20 min; (vi) (a) 2-(Boc-amino)ethyl bromide (1.5 equiv), Cs_2CO_3 (3equiv), DMF, r.t., 1 h; (b) TFA (20%), DCM, r.t., 20 min; (vii) acyl chlorides (1.2 equiv), Na_2CO_3 (5 equiv), DCM/H_2O (1.5:1 v/v), 0 °C, 20 min.

Scheme 1.44. Synthesis of biologically active indole–indazole hybrids.

and -NH protection of 1*H*-indol-4-ol **137** using triisopropylsilyl chloride (TIPSCl) and $(Boc)_2O$, respectively, then borylated employing triisopropyl borate. Regioselective iodination of 1*H*-indazole derivative **140** followed by the selective Boc protection resulted the another intermediate **141**. The Suzuki coupling of intermediates **139** and **141** formed hybrid **142** in around 55% yield. Deprotection of TIPS and Boc groups of **142** led to the formation of hybrid **143**. Alkylation of hybrid **143** with 2-(Boc-amino)ethyl bromide and elimination of Boc in 20% TFA afforded the hybrid **144** in a good yield. Finally, the desired indole–indazole hybrid **145** was obtained by *N*-acylation of **144** with acryloyl chloride in only about 56% yield (**Scheme 1.44**).[60]

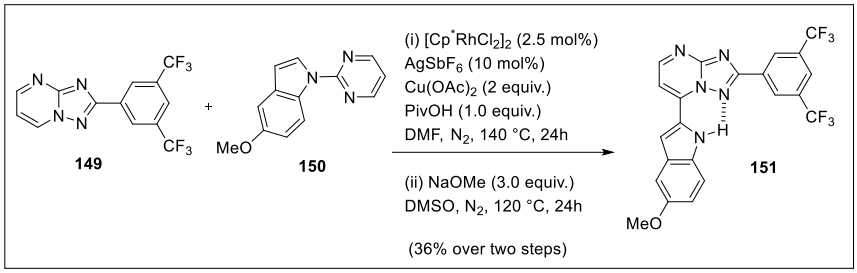
a straightforward strategy to construct a large library of donor−acceptor-type biheteroaryls **148** via the palladium-catalyzed oxidative C−H/C−H cross-coupling of electron-deficient 2*H*-indazoles **146** with electron-rich heteroarenes such as indole **147**,



Scheme 1.45. Palladium catalyzed oxidative cross-coupling reaction of indole with indazole.

pyrrole, furan, thiophene etc. has been developed by You and co-workers. They proposed that 5 mol % $Pd(PPh_3)_4$, 1.5 equiv. $Cu(OAc)_2 \cdot H_2O$, and 1.0 equiv. pyridine in 1,4-dioxane at 120 °C for 24 h was the best reaction condition (**Scheme 1.45**).[61] The group synthesized a series of near-infrared (NIR) fluorophores with tunable full-color emission and excellent fluorescence quantum yields udder the optimized condition.

The same group later reported the Rh(III)-catalyzed oxidative C−H/C−H cross-coupling of [1,2,4]triazolo[1,5-*a*]pyrimidines (TAP) **149** with indoles **150** for the synthesis of indole–triazolopyrimidine hybrids **151**. The coupling of **149** with pyrrole was also achieved under the same condition. The application of a directing group technique leads

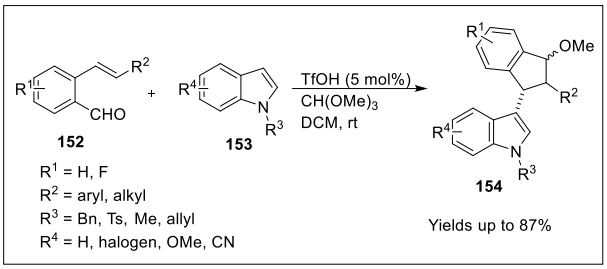


Scheme 1.46. Oxidative C−H/C−H cross-coupling to synthesis indole–triazolopyrimidines hybrids.

to excellent site selectivity. After removing the pyrimidyl directing group under basic condition, the photophysical characteristics of the resulting fluorophores **151** were studied, revealing excited-state intramolecular proton transfer (ESIPT). Although, the strategy is efficient, the yield of most of the desired product over two steps is not satisfactory (**Scheme 1.46**).[62]

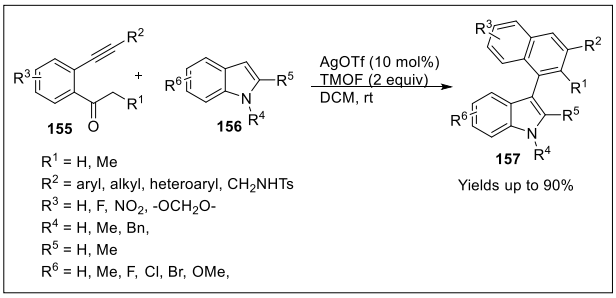
Indole linked carbocycles have numerous applications in the development of biologically active molecules.[63] In this context, efficient strategies to make C-3 arylated indoles are of great interest. In 2021, Ramesh *et al*. developed a TfOH catalyzed method for the synthesis of indole-substituted indanes **154** from *o*-alkenylbenzaldehydes **152** and indoles **153** under acetalization condition (**Scheme 1.47**).[64] The reaction yielded the desired products as an inseparable mixture of diastereomers in most of the cases. Although, this protocol provided the final product with good yield and high diastereoselectivity, the yield considerably fallen when tosylated indole was used. Halogen containing substrates also afforded a lower yield of the desired product. The reaction proceeded through *in situ* generated acetal-facilitated nucleophilic addition of indole followed by a conrotatory 4π-electrocyclization reaction, which ensures the exclusive diastereoselectivity seen in the cyclization step. Having different steric environments the two

geometrical isomers of *o*-alkenylbenzaldehyde exhibit different reactivity.



Scheme 1.47. Triflic acid-catalyzed synthesis of indole-indane hybrid compounds.

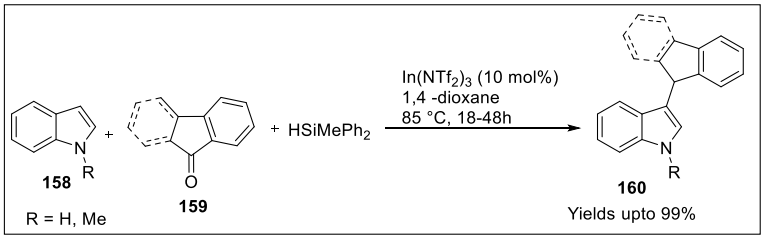
In the next year, the group of Ramesh taken a very similar approach to synthesize C-3-naphthyl indole hybrids **157** from *o*-alkynylacetophenones **155** and indoles **156**. The reaction involves acetalization using trimethyl orthoformate (TMOF) in the presence of AgOTf catalyst. The acetal formation in the presence of TMOF have a significant role to promote the reaction under ambient condition (**Scheme 1.48**).[65] They synthesized a series of C-3-naphthyl indole



Scheme 1.48. Ag(I)-catalyzed cyclization of *o*-alkynylacetophenones to synthesize C-3-naphthyl indole derivatives.

derivatives in moderate to good yields. Furthermore, a gram scale reaction offered the indole–naphthyl hybrid along with a by-product.

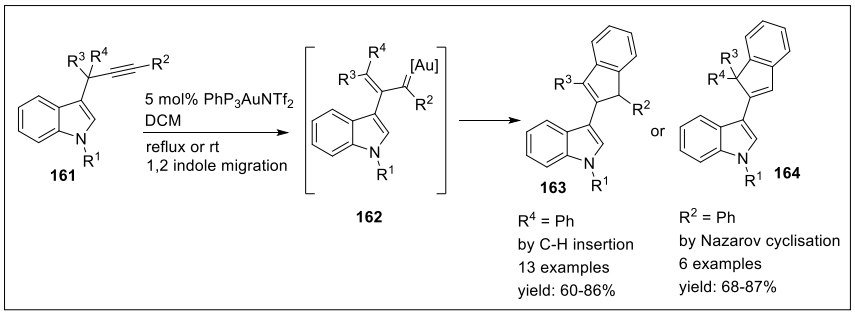
Tsuchimoto and Co-workers described a reliable and practical method towards the synthesis of indole–carbocycle hybrids **160** via indium-catalyzed reductive alkylation of indoles **158**. In this reaction, the carbonyl compounds **159** were applied as sources of alkyl groups (**Scheme 1.49**).[66]



Scheme 1.49. Indium-catalyzed reductive alkylation of indoles with carbonyl compounds and hydrosilanes.

This strategy could also allow to react indole with a wide range of acyclic aldehydes or ketone, making it a useful tool for producing alkylindoles with structural diversity.

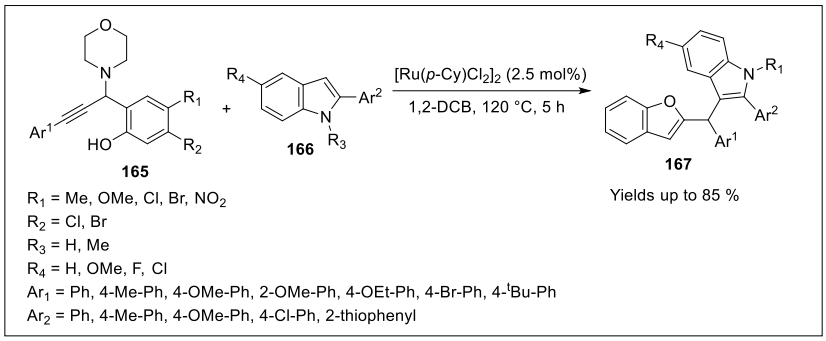
We have already described in introduction, why tandem reactions are so popular for the construction of complex organic scaffolds. Now we will introduce the examples of some indole containing hybrid molecules, where tandem reactions are employed to execute their synthesis. In 2008, Sanz *et al.* have reported for the synthesis of various indene-containing indole scaffolds **163** and **164** involving Au(I)-catalyzed tandem reaction of C-3- propargylated indoles **161** in moderate to good yields as a regioisomeric mixture. The reaction was initiated by 1,2-indole migration of **161** to furnish complex **162**. Depending on the substituents on both the propargylic and terminal position of alkyne **161**, either 1,2-indole migration/C–H insertion or 1,2-indole migration/Nazarov cyclization occurred. When R^4 = Ph, 1,2-indole migration/C–H insertion to



Scheme 1.50. Synthesis of indene–indole hybrids by tandem 1,2-indole migration/C–H insertion reactions.

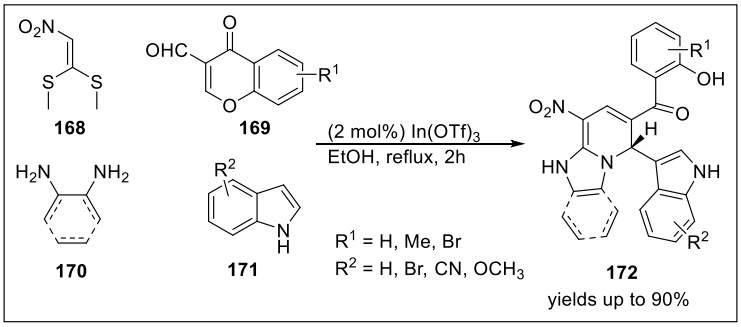
3-indenyl-indoles **163** was observed. When R^2 = Ph, 1,2-indole migration followed by Nazarov cyclisation occurred to give desired indole–indene hybrid **164** (**Scheme 1.50**).[67]

Recently, a facile Ru-catalyzed tandem annulation/arylation of 2-hydroxyphenyl propargylic alcohols **165** with C2-substituted indoles **166** to furnish a series of unsymmetrical bis(heteroaryl)methane derivatives **167** with high yield has been developed by the group of Hajra (**Scheme 1.51**).[68] The reaction involves furan annulation, followed by nucleophilic addition of indole. The annulation technique is also effective for the synthesis of bisimidazopyridinylindolylmethanes in moderate to high yield.



Scheme 1.51. Synthesis of indole based bis(heteroaryl) methanes through ruthenium-catalyzed tandem annulation/arylation reaction.

In 2022, Jayabal *et al*. synthesized 3-substituted indole (or 2- substituted pyrrole)-based 1,2-dihydropyridine derivatives **172** from nitroketene S,S-acetal (NKA) **168**, diamines **170**, 3-formylchromone **169**, and indole **171** (or pyrrole) using indium triflate as a green and reusable catalyst in ethanol (**Scheme 1.52**).[69] The reaction proceeded through a domino condensation-Henry reaction-intramolecular Michael addition-cyclization-ring opening-nucleophilic addition sequence. Control experiments and computational studies all supported the regioselectivity of the product formation. The molecular docking studies exhibited that some of the synthesized

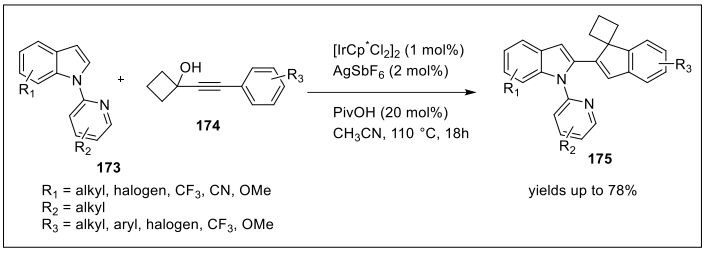


Scheme 1.52. Indium-catalyzed tandem strategy for the synthesis of antiviral active indole-dihydropyridine hybrids.

compounds for the main protease (Mpro) of SARS-CoV-2 and 7NX7 spike glycoprotein's A chain of the Delta plus K417N mutant have better biding ability than remdesivir that is an FDA-approved drug for the treatment of COVID-19. Notable features of the reaction are high regioselectivity, easy separation, excellent yield, simple execution, high atom economy, eco-friendly solvents, and avoidance of chromatographic purification.

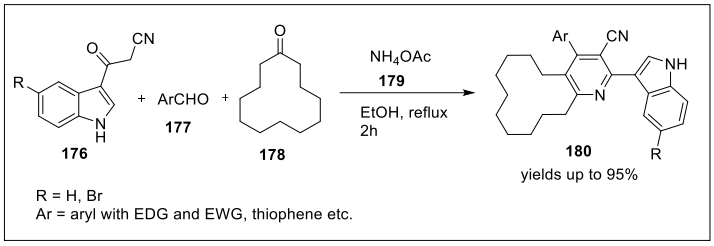
Fan *et al*. reported an efficient synthesis of indolyl-tethered spiro[cyclobutane-1,1′-indenes] **175** through the cascade reaction of pyridinyl–indoles **173** with alkynyl cyclobutanols **174** using

$[IrCp^*Cl_2]_2$ as catalyst and $AgSbF_6$ in the presence of PivOH as additives (**Scheme 1.53**).[70] Mechanistic studies show a sequential process in which pyridinyl–indole is alkenylated using alkynyl cyclobutanol followed by an intramolecular Friedel−Crafts reaction to give the target products. this novel protocol is useful due to its broad substrate scope, high chemo- and regioselectivity, removable directing group, and scalable preparation process.



Scheme 1.53. Synthesis of indolyl-tethered spiro[cyclobutanylindenes] *via* cascade reaction.

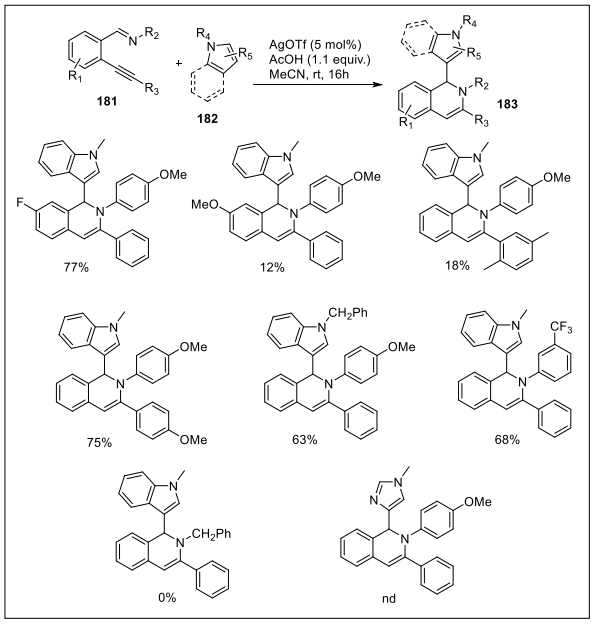
Muthu and Co-workers have developed a one-pot four-component reaction of indolyl-oxopropanenitriles **176**, aromatic aldehydes **177**, cycloalkanones **178** and ammonium acetate **179** to synthesize structurally intriguing indole–cycloalkylpyridine hybrid **180** in excellent



Scheme 1.54. Synthesis of indole–cycloalkylpyridine hybrids through a four-component six-step tandem reaction.

yields (**Scheme 1.54**).[71] The reaction proceeded through a six-step tandem Knoevenagel condensation–nucleophilic addition to carbonyl–Michael addition–N-cyclization–elimination–air oxidation sequence.

Belmont *et al*. synthesized a series of indole–dihydroisoquinoline hybrids **183** using silver catalyzed cascade hydroarylation/cycloisomerization processes. The *ortho*-alkynyl arylaldimines **181** and indoles **182** were reacted in MeCN for 16 h at room temperature under the synergistic association of a 5 mol% AgOTf as catalyst with 1.1 equiv. acetic acid additive.

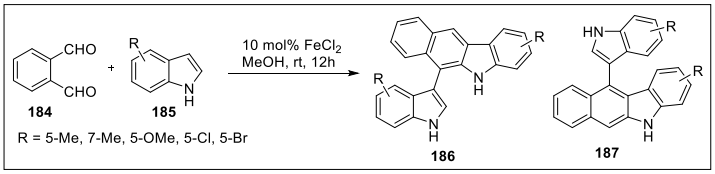


Scheme 1.55. Silver-catalyzed tandem cycloisomerization/ hydroarylation reactions for the synthesis of indole-dihydroisoquinoline hybrids.

This method synthesized and developed a novel heterocyclic pharmacophore that merges the biological activities of isoquinolines with various nitrogen-containing heterocycles like indoles, pyrroles through a tandem reaction. Substrate scope investigations reveled that alkyne connected ring with electron-donating substituents have lower reaction yields than those with electron-withdrawing substituents. The steric effects of ortho-substituents on the alkyne decreased the yield of the product. Also, the aliphatic imine obtained from benzylamine does not yield the desired product. This research group also investigated the protocol's applicability to a variety of nitrogen-containing heterocycles as nucleophiles (**Scheme 1.55**).[72] Unfortunately, the heterocyclic nucleophiles containing O and S did not produced the target product due to their lower nucleophilicity. The role of the acetic acid additive was discovered to be significant in the reaction, since it encouraged the final protodesilveration step leading to the product synthesis.

Presently, economic depression and environmental degradation are the major issue for the development of metal-based catalysts in organic synthesis. Due to cheap and environmentally benign, iron catalysts are well known for its application in synthesizing valuable organic compounds[73], examples of which will be discussed right now. In 2014, Xu et al. have reported a one-pot iron-catalyzed cycloaddition of indole **185** with *o*-phthalaldehyde **184** to afford

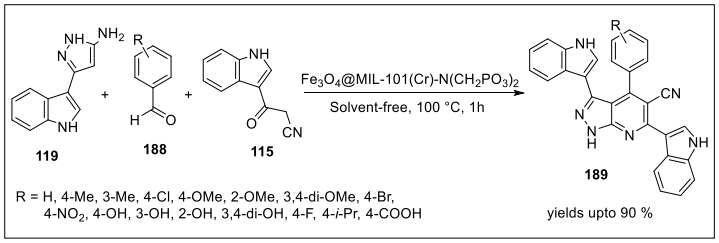
indolyl benzo[*b*]carbazoles **186** and **187**. The desired product was achieved via sequential carbon-carbon bond-forming addition, cyclization involving intramolecular alkylation and aromatization. Having extended π-conjugation, the indolyl benzo[*b*]carbazole derivatives **186** and **187** showed strong fluorescence intensity. The group also performed the reaction under different catalysts and solvents, but mixture of two products were obtained. During optimization, $FeCl_2$ in MeOH exhibited better chemoselectivity for the product of **186** over **187** (91:9) (**Scheme 1.56**).[74]



Scheme 1.56. Synthesis of indole–benzocarbazole hybrids by iron-catalyzed cycloaddition.

Furthermore, 3-substituted indole derivatives did not react under this condition. 5-substituted indole derivatives improved the yield (79-85%) of this reaction whereas 7-substituted indole derivatives decreased it (48%).

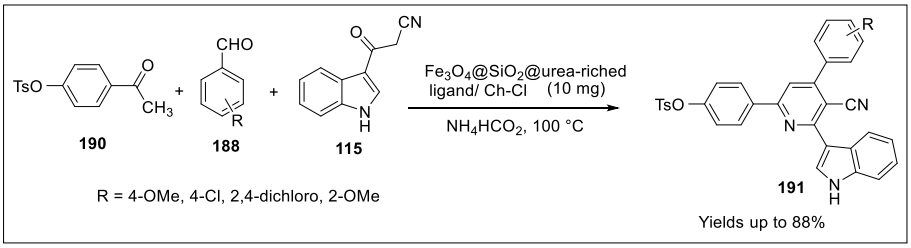
In 2022 Sepehrmansourie and Co-workers designed and synthesized a magnetic metal–organic frameworks Fe_3O_4@MIL-101(Cr)-$N(CH_2PO_3)_2$ as nano-catalyst. The group examined this catalyst for the synthesis of indolyl–pyrazolopyridines **189** as convenient medicine by condensation reaction of benzalaldehydes **188**, 5-amino-3-indolyl-pyrazole **119** and 3-(cyanoacetyl)indole **115** via a cooperative vinylogous anomeric-based oxidation (CVABO). The products **189** were gained with high yields at 100 °C and without the use of solvents (**Scheme 1.57**).[75]



Scheme 1.57. Harnessing iron nanocatalyst for the synthesis of indole linked pyrazolopyridine derivatives.

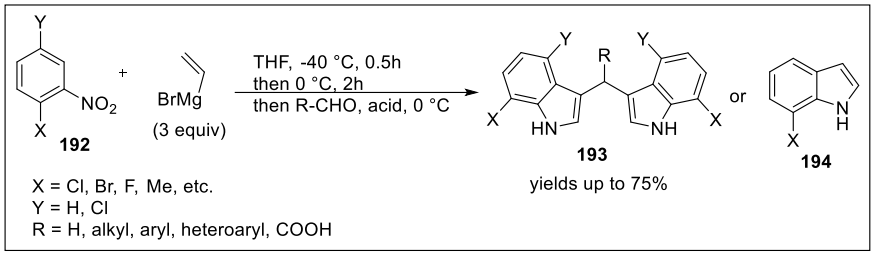
Later, the group of Zarei reported the design, synthesis and characterization of a heterogeneous catalytic system namely [Fe_3O_4@SiO_2@urea-riched ligand/Ch-Cl]. Then this catalyst was

tested for the synthesis of hybrid pyridines with sulfonate and indole moieties **191** by the condensation of same indole **115** and benzaldehyde **188** with acetophenone **190**. This method offers diverse indole–pyridine hybrids **191** from several starting materials under mild condition (**Scheme 1.58**).[76] Additionally, a CVABO pathway was proposed as plausible mechanism for the synthesis of indole–pyridine hybrid compound.



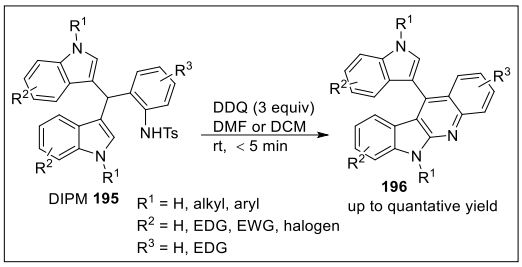
Scheme 1.58. Synthesis of indole–pyridine hybrids using iron as nano catalyst.

Ishikura *et al.* demonstrated a one-pot approach to construct 3,3′-bisindolylmethane derivatives **193** from nitrobenzene derivatives **192** through the Bartoli indole synthesis. The acid employed to quench the reaction, significantly affected the formation of product **193** and **194**. Quenching the reaction with concentrated HCL produced 3,3′-bisindolylmethane derivatives **193** as opposed to the formation of 7-substituted indole **194** by quenching with NH_4Cl (**Scheme 1.59**).[77] Several natural products were synthesized starting from desired product **193.**



Scheme 1.59. One-pot assembly of bisindolylmethane derivatives by Bartoli Indole Synthesis.

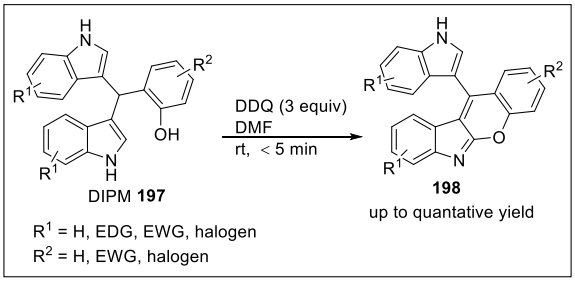
In 2017, Challa and Co-workers reported the wide utilization of easily accessible 3,3′-diindolylphenylmethanes (DIPMs) under DDQ-mediated oxidative conditions to form biologically relevant molecules. All the synthesized compounds were examined *in-vitro* for their antibacterial activity against a panel of Gram positive and negative bacterial strains including methicillin-resistant Staphylococcus aureus (MRSA) (**Scheme 1.60, Scheme 1.61 and Scheme 1.62**).[78] DIPM **195** generated from *N*-methylindole or 1*H*-indole appended to *ortho*-NHTs phenyl group furnished indoloquinoline–indole hybrids **196** with excellent yield in the presence of DDQ (**Scheme 1.60**).



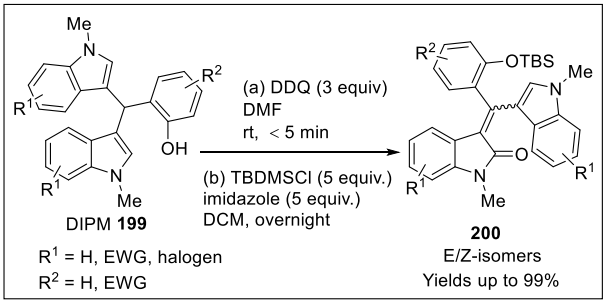
Scheme 1.60. DDQ-mediated construction of indole tethered indoloquinoline derivatives.

The group also synthesized chromenoindole–indole hybrids **198** with high yield from DIPMs with 1*H*-indole appended to *ortho*-hydroxy phenyl group **197** using the same oxidizing agent DDQ under mild condition within 5 min (**Scheme 1.61**).

Furthermore, DIPM **199** created from *N*-methylindole and salicylaldehyde under DDQ-mediated oxidative conditions afforded an inseparable mixture of products **200** up to 99% yield. Protecting the -OH group of resulting crude mixture with silyl (TBDMS) facilitated the separation of mixture by column chromatography (**Scheme 1.62**).



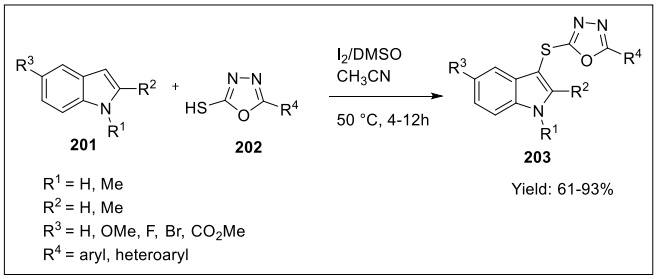
Scheme 1.61. Synthesis of biologically active indole–chromenoindole hybrids.



Scheme 1.62. DDQ-mediated synthesis of antibiotic active indole–oxindole hybrids.

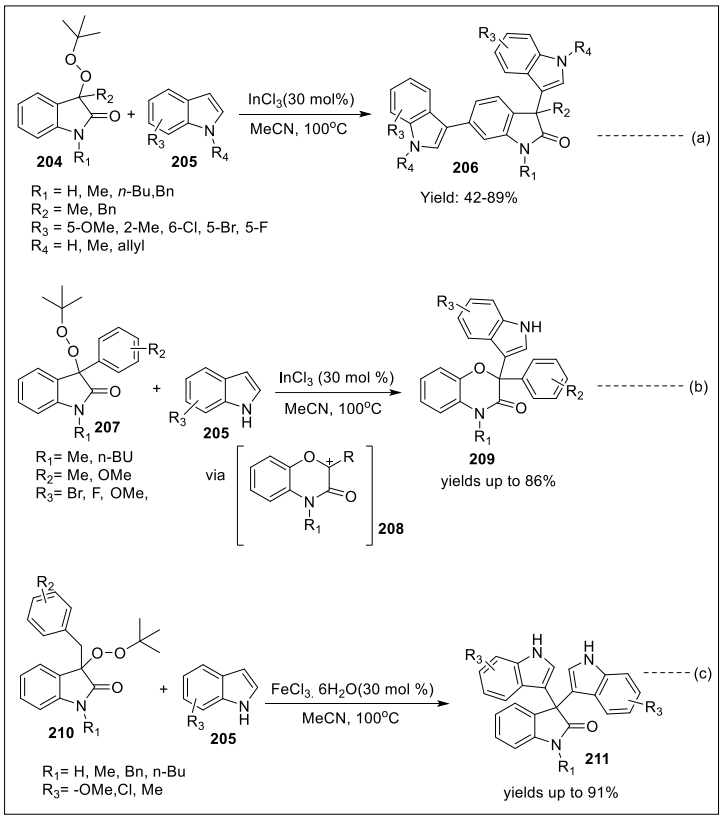
Ghosh *et al.* have described a simple approach towards the synthesis of indole–oxadiazole molecular hybrids **203** from easily available indole **201**. The reaction involves regioselective C-3 sulfenylation of indoles **201** with 1,3,4-oxadiazole-2-thiols **202** using iodine as a catalyst

and DMSO as a co-oxidant **(Scheme 1.63)**.[79] Although the yields of the product are high, a heteroaryl substituent at oxadiazole unit somewhat reduced the yield. Biological studies revealed the promising antiproliferative activities of some of these molecular hybrids against human breast carcinoma cell line MCF-7**.**



Scheme 1.63. Iodine-dimethyl sulfoxide mediated synthesis of indole–oxadiazole molecular hybrids.

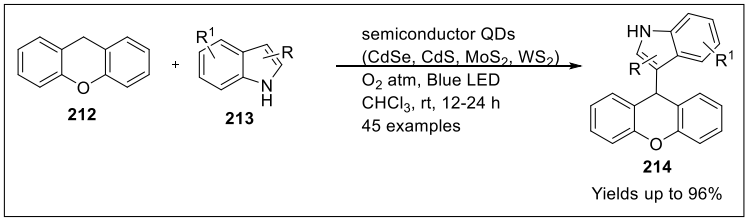
The group of Gnanaprakasam synthesized a series of indole linked hybrid compounds from peroxyoxindole using indole as nucleophile. The substituents on peroxyoxindole furnished Lewis acid catalyzed diverse reaction with indole **(Scheme 1.64)**.[80] Thus, a



Scheme 1.64. Sequential remote C–H indolylation and rearrangement reaction of peroxyoxindole.

consecutive double indolylation of peroxyoxindole **204** via remote C–H functionalization and C3-peroxy substitution for the construction of terindolinone **206** was obtained using indole **205** as nucleophile and $InCl_3$ as a catalyst **(Scheme 1.64a**). Whereas N-H protected 3-pnenyl peroxyoxindole **207** underwent a sequential skeleton rearrangement, generating a transient carbocation **208** which was trapped by an indole **205** to afford indolyl-benzooxazinone **209 (Scheme 1.64b**). Moreover, unlike $InCl_3$, $FeCl_3 \cdot 6H_2O$ allowed the oxidative cleavage of peroxyoxindole **210** (Hock cleavage), followed by reaction with indole **205** delivered biologically active trisindoline derivatives **211 (Scheme 1.64c**). All the reactions were supported by a significant number of instances, yielding the products in range 42-91%.

Very recently, De *et al.* have developed a visible-light-mediated process for selective functionalization of the xanthene-9*H* position through carbon−carbon bond formation. Reaction of xanthenes **212** with indoles **213** in the presence of semiconductor quantum dots (QDs) as photocatalysts afforded indole–xanthene hybrids **214** with excellent yields **(Scheme 1.65**).[81] This method could also allow the reaction of xanthenes with aza-indoles, or pyrroles, or carbonyls under the optimized condition. Their mechanistic investigation provided important insights into the energy-transfer and electron-transfer pathways involved in reactions, as well as the radical polar crossover (RPC) and triplet-to-triplet energy transfer (TTEnT) processes. This strategy offers mild reaction conditions, affordable catalysis, a wide substrate scope, avoidance of pre-functionalization, and suitability for gram-scale synthesis.



Scheme 1.65. Photo-catalyzed C–C coupling reaction between Xanthene and Indole.

1.2 OBJECTIVES OF THE WORK IN THIS THESIS

Today, in organic synthesis, sanitization and waste disposal are the primary focus. It is essential to develop an efficient atom and step economical protocol which minimized the use of organic solvents, hazardous reagents and formation of side products. Bearing these in mind, we devised a tandem approach to execute the synthesis of indole-based hybrid molecules. This

research aims to demonstrate the transformative potential of tandem reactions in modern synthetic chemistry.

Inspired by indole chemistry and the role of their hybrid molecules in biologically and pharmacologically influential compounds, we sought to design and synthesize indole containing hybrid molecules. The main motive of this research was to develop synthetic method for the integration of indole moiety with another carbocyclic or heterocyclic compound. So that, the target indole-based hybrid molecules may exhibit unique pharmacological and photophysical capabilities.

To be honest, the earlier works of my research group served as a foundation for new ideas to emerge. The work in chapter 2 was initially based on DDQ-mediated allylic C-H oxidation strategy, previously developed by our research group.[82] This newly developed process was used to synthesize indole-fluorene hybrids, demonstrating its versatility and applicability. The work presents in chapter 3 is the synthesis of indole-xanthydrol hybrid, which is strategically the extension of previous work described in chapter 2. Unfortunately, the similar DDQ-mediated oxidation strategy did not work well for this purpose. Therefore, we focused on developing a new reaction condition for the synthesis of indole-xanthydrol hybrid. Chapter 4 demonstrates a synthetic method to generate the indole-indazole hybrids. This work is motivated from the earlier development of iron-catalyzed 1,5-enyne cycloisomerization[28], we hypothesized that replacement of -C≡C- unit with its nitrogenous analog, -N≡N$^+$ (diazo) may undergo a similar type of cycloisomerisation to generate the indole-indazole hybrids.

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Chapter 2

DDQ/$FeCl_3$-Mediated Tandem Oxidative Carbon-Carbon Bond Formation for The Synthesis of Indole-Fluorene Hybrid Molecules

2.1. INTRODUCTION

Indole derivatives have garnered much attention due to the occurrence of indole motif in many natural products,[1] drug molecules[2] and many functional materials,[3] e.g., in OLED devices. Consequently, the synthesis of functionalized indoles, especially those with C-3 substitution has received significant attention due to their potential use as drugs in treating many diseases.[4] Recently, the hybrid compounds of indole with various heterocycles and carbocycles have also been exhibited as promising pharmacological agents.[5] Some of the pharmaceutically important hybrid compounds containing indole scaffolds are depicted in figure 2.1. While compound **(A)** has proved their efficacy in the treatment and prevention of diabetes.[5e] Naphthyl-indole **(B)** and phenyl-indole **(C)** exhibit as an antioxidant agents and HCV NS5B polymerase inhibitors respectively.[5g] Meridianin G **(D)** shows anti-proliferative activity against HCT-116 cell line. Compound **(E)** has exhibited effective inhibition of GSK-3a/β.[5j] Also compound **(F)** was found to resist unwanted cell growth in case of breast cancer (**Figure 2.1**).[5h] Therefore, the development of new indole-based hybrid structures can open up new avenues for application.

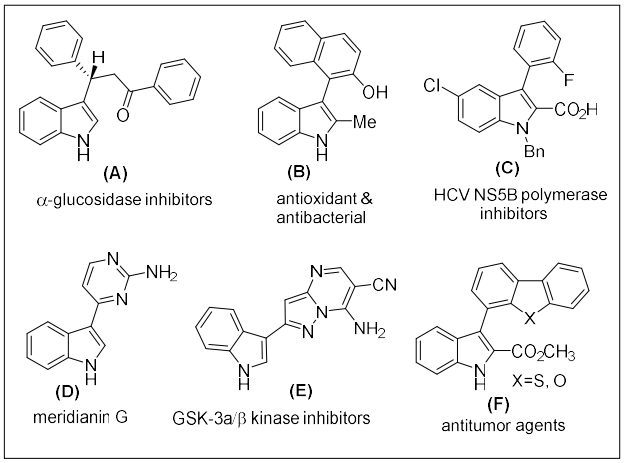


Figure 2.1 Some important examples of bioactive indole based-hybrid molecules.

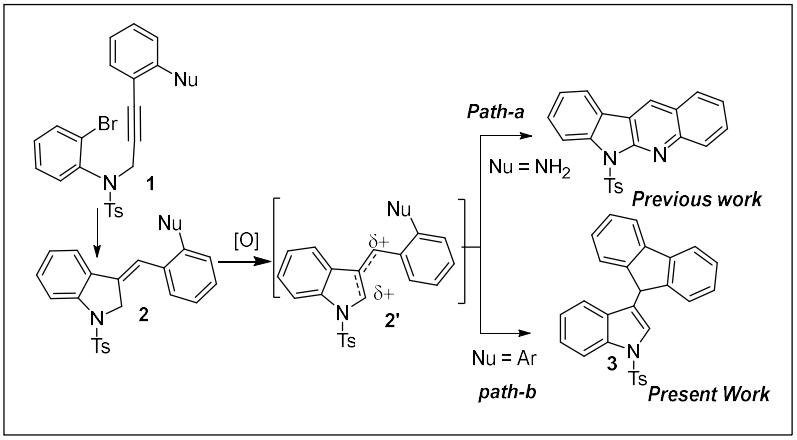
The tricyclic fluorene motif is also very essential to synthetic chemists and plenty of synthetic methods have been developed because of its presence in natural products, and its exceptional biological and pharmaceutical activities and optoelectronic properties.[6] Moreover, carbazole/fluorene hybrid compounds have been extensively utilized in the designing of optoelectronic devices such as organic light emitting diodes (OLED) and organic field effect transistors (OFET).[7] Considering the significance of 3-substituted indoles and fluorene derivatives, we anticipated that their hybrid, might exhibit unique medicinal and photophysical

properties. Although, a limited reports were found in literature[8]. Some of these reports were already discussed in Chapter 1. (**see chapter 1, Scheme 1.16, Scheme 1.17, Scheme 1.49**)

Therefore, developing an efficient and new strategy to synthesize indole–fluorene hybrid molecules from simply prepared starting materials in a single step is highly desirable.

Recently, we have developed a novel and efficient method for synthesizing C-3 substituted indoles and fused indoles *via* palladium-catalyzed tandem intramolecular carbopalladation/cross coupling of 2-halo-*N*-propargylhalides (**1**) and isomerisation/cyclisation under several reaction conditions.[5a, 9] For example, we have shown that under the conditions of oxidative coupling, the reductive Heck-coupling product, 3-(methylene)indoline (**2**), acted as an electrophile in the presence of DDQ by generating allylic carbocation **2′** through allylic Csp3 –H activation which could be efficiently trapped by a nucleophilic amine (**Scheme 2.1**, path-a).[9d]

Our continuing efforts along these lines have led us to present in this chapter a novel strategy for the synthesis of indole–fluorene hybrid molecules **3** (**Scheme 2.1**, path-b) in high yields from readily available starting material. The strategy involves

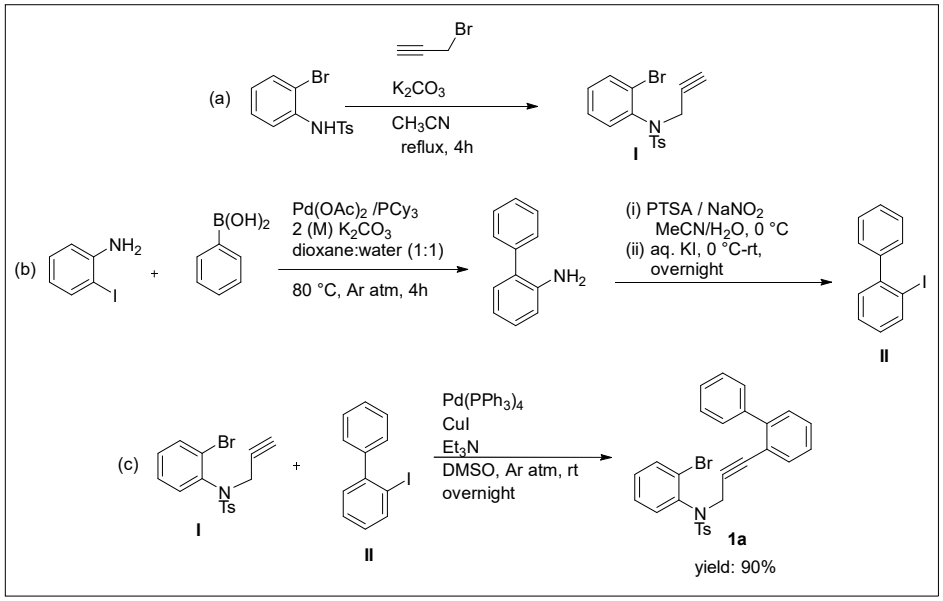


Scheme 2.1 conceptual development of the present strategy.

intramolecular reductive Heck coupling with biphenyl tethered *N*-propargyl-2-haloanilide **1** (Nu = Ar) and subsequent oxidative cyclisation of the resultant biphenyl tethered 3-(methylene)indoline **2** (Nu = Ar) through the generation and intramolecular trapping of allylic/benzylic carbocation **2′** by the appropriate disposition of the biphenyl unit. Although a few DDQ-mediated oxidative intramolecular C–C bond formation methods have been reported.[10] Additionally, the construction of indole–fluorene hybrid molecules employing the present strategy is highly attractive due to its high efficiency and environmentally benign nature

as it does not need prefunctionalization of substrates.

2.2. RESULTS AND DISCUSSION

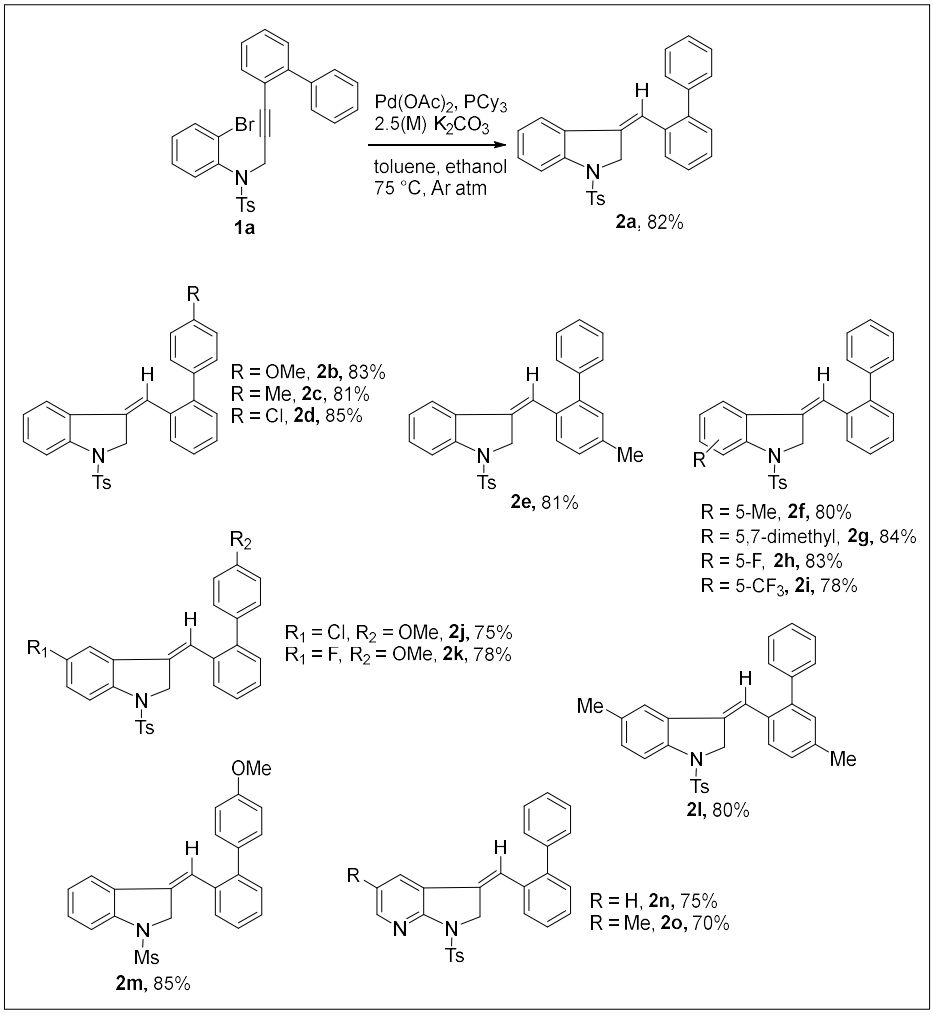


Scheme 2.2 Preparation of compounds **I, II** and starting materials **1a**

To established the above idea (**Scheme 2.1**, path-b), we first attempted to synthesize required compounds 2-bromo-*N*-propergyl-*N*-tosylbenzenamine **I** and 2-iodo biphenyl **II** for the construction of starting material 2-bromo-*N*-(3-(1,1$^{/}$-biphenyl)prop-2-ynyl)-*N*-tosylbenzenamine **1a** (**Scheme 2.2**). First of all, a simple nucleophilic substitution reaction was performed b/w 2-bromo-*N*-tosylaniline and propargyl bromide using K_2CO_3 as base to achieve 2-bromo-*N*-propergylaniline I (**Scheme 2.2** (a)). Then we moved our attention to prepare 2-iodo biphenyl **II** from 2-iodoaniline by two steps, that is Suzuki coupling reaction and diazotization reaction followed by iodination (**Scheme 2.2** (b)). The two-step yield was 75%. After that, the starting material **1a** for the reductive Heck coupling reaction was synthesized using a selective Sonogashira coupling reaction, presented in **Scheme 2.2** (c). The 2-bromo-N-propergyl-N-tosylbenzenamine **I** reacted with 2-iodo biphenyl **II** using catalytic $Pd(PPh_3)_4$ in the presence of catalytic CuI and Et_3N as base in DMSO solvent at rt to furnish the starting material **1a** in 90% yield.

After preparing **1a**, we then focused to prepare our final precursor biphenyl tethered 3-(methylene)indoline **2a** *via* the reductive Heck cyclisation of **1a** according to our previously developed method[9c,d] (**Scheme 2.3**). This cyclisation reaction proceeds through an

intramolecular *syn*-carbopalladation via a 5-*exo-dig* cyclisation process instead of a 6-*endo-dig* cyclisation with the alkyne unit to give a σ-alkylpalladium(II) intermediate, and subsequent reductive elimination of Csp^2–[Pd]–H species, gave the reductive heck product **2a** in 82% yield. Presumably, ethanol serves as a hydrogen source for the reduction of intermediate carbopalladation. Following similar method, a various biphenyl tethered 3-(methylene)indoline derivatives **2b-2o** were prepared in good yields, the results are shown in **Scheme 2.3**. For instance, 2-haloaniline nucleus possessing both electron-donating groups such as -Me and electron withdrawing groups like -Cl, -F, $-CF_3$ (**Scheme 2.3**, entries **2f-2l**) underwent smooth

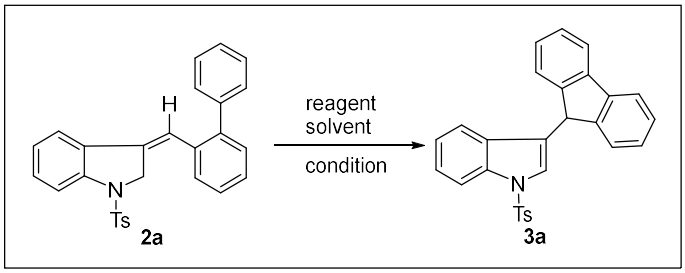


Scheme 2.3 Preparation of final substrates **2a-2o.**

reductive Heck coupling under standard condition in high yields (80−85%). Similarly, different substituents on biphenyl rings at alkyne terminus like -Me, -OMe, and -Cl (**Scheme 2.3,** entries **2b-2e** and **2j-2m**) were also tolerated and gave the reductive Heck products in high yields (75-85). Simultaneous presence of electronically similar and opposing substituents on both 2-

haloaniline and biphenyl unit (**Scheme 2.3, 2j, 2k, 2l**) did not hamper the coupling reaction and yielded the desired indoline derivatives in good yields (75-80%). Moreover, this process was applicable to achieve 7-azaindoline derivatives **2n**, **2o** in 75%, 70% yields respectively (**Scheme 2.3, 2n, 2o**).

After synthesizing the series of final substrates **2b**-**2o**, we began to optimize the



Entry	Oxidant	Catalyst	Solvent	Temp (°C)	Time (h)	Yield (%)
1	DDQ		CH_3NO_2	rt	2	38
2	DDQ		CH_3NO_2	rt	2	20
3	DDQ		CH_3NO_2	60	2	40
4	DDQ		CH_3NO_2	60	2	68
5	DDQ	$FeCl_3$	CH_3NO_2	rt	3	58
6	DDQ	$FeCl_3$	CH_3NO_2	60	3	74
7	**DDQ**	**$FeCl_3$**	**CH_3NO_2**	**60**	**3**	**85**
8	DDQ	$FeCl_3$	DCE	60	3	50
9	DDQ	$FeCl_3$	DMF	60	3	nr
10	DDQ	$FeCl_3$	toluene	60	3	46
11	DDQ	$Fe(OTf)_3$	CH_3NO_2	60	3	35
12	DDQ	AgOTf	CH_3NO_2	60	3	30
13	DDQ	$InCl_3$	CH_3NO_2	60	3	65
14	DDQ	$In(OTf)_3$	CH_3NO_2	60	3	76
15	DDQ	PTSA	CH_3NO_2	60	3	42
16	CAN		CH_3NO_2	60	3	trace
17	PIDA		CH_3NO_2	60	3	0
18		$FeCl_3$	CH_3NO_2	60	3	nr

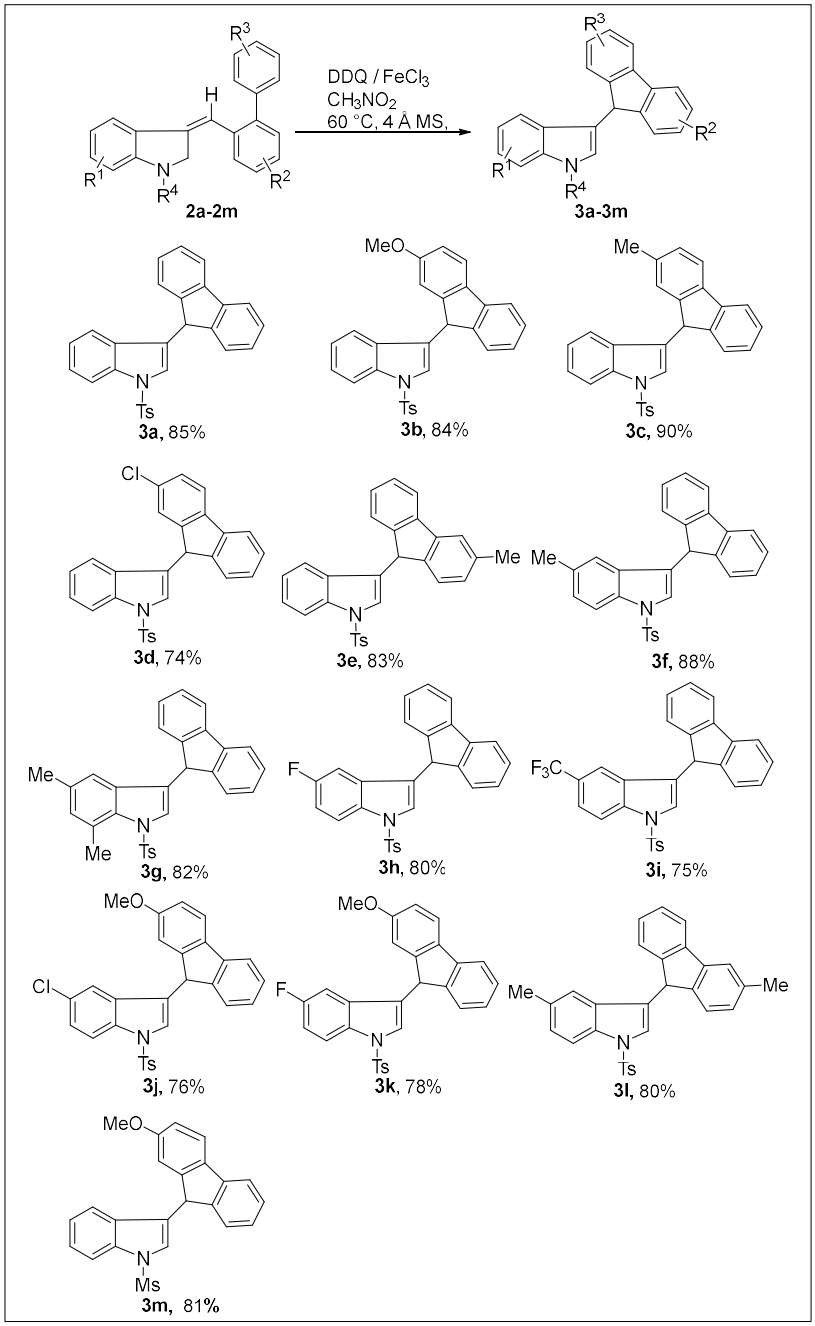
Table 2.1 Optimization of Reaction Conditions.

reaction conditions for the formation of 3-(fluoren-9-yl)indole **3a** from **2a** in the presence of various oxidants, catalysts, and solvents at different temperatures. The results are summarized in **Table 2.1**. Initially, the substrate **2a** was allowed to react with 1.0 equiv. of DDQ in nitromethane at room temperature. We observed that our strategy worked and the target product **3a** was obtained in 38% yield in 2h (**Table 2.1**, entry 1) along with the mixture of unwanted

products. Interestingly, increasing the amount of DDQ (2.0 equiv.) led to a gradual decrease in the yield of the desired product (**Table 2.1**, entry 2). From these results, we inferred that the oxidation/cyclisation process was quite sensitive to the amount of oxidizing agent used. Although, the yield slightly increased when the reaction was carried out at 60 ^{o}C, the formation of undesired products could not be inhibited (**Table 2.1**, entry 3). However, during the later stage of investigations using the substrate **2a,** we could isolate and characterize one of the byproducts, 3-indolyl biphenyl ketone under identical conditions (**see section 2.4.7**). We thought that the ketone was formed through an in situ generated 3-indolylalcohol *via* nucleophilic attack on indolyl cation by small amount of moisture present in the reaction mixture. Therefore, we inferred that because of the formation of some amount of alcohol/ketone, the amount of intermediate carbocation and hence the target product is reduced. So, to further improve the yield, we examined the reaction in the presence of 4Å molecular sieves as an additive. Gratifyingly, the yield of the desired product was enhanced to 68% (**Table 2.1**, entry 4) at 60 °C. We continued with our trials to check whether Lewis acids could provide better results by minimizing the formation of unwanted products. When the said reaction was conducted with 1equiv. of DDQ in combination with 0.2 equiv. of $FeCl_3$ at rt and at 60°C, the yields were increased up to 58% and 74%, respectively, (**Table 2.1**, entries 5 and 6) even in the absence of molecular sieve.

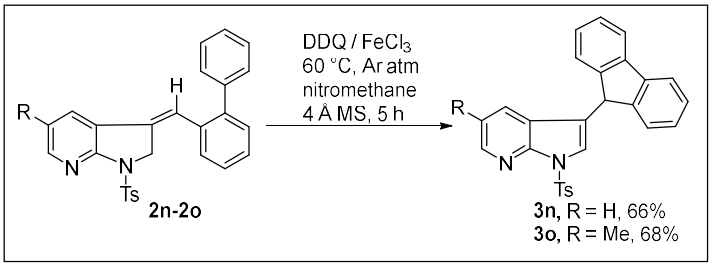
Logical interpolation of the superior effects of both $FeCl_3$ and molecular sieves prompted us to investigate the combination of two additives for even better results. We were delighted to observe that the substrate **2a** fruitfully converted to **3a** within 3 hours in presence of 0.2 equiv. $FeCl_3$ and 4Å molecular sieves with 1.0 equiv. DDQ as oxidizing agent in $MeNO_2$ (1.5 ml) at 60 °C, with an excellent yield of 85% (**Table 2.1**, entry 7). Initially, the product **3a** was characterised by assigning the peak at δ 5.24 (s, 1H) for 9H of fluorene moiety in ^{1}H and at δ 45.8 for 9C of fluorene in ^{13}C NMR (see section 2.4.6, **3a**). Switching to solvents such as dichloroethane, DMF and toluene yielded inferior results; for example, both DCE and toluene generated **3a** in 50% and 46% yields, respectively, whereas, no reaction occurred in DMF (**Table 2.1**, entries 8-10). Further screening of a series of Fe, Ag, In salts and PTSA (*p*-toluenesulphonic acid) as catalyst, proved to be far less efficient and **3a** could be obtained in 35%, 30%, 65%, 76% and 42% yields, respectively (**Table 2.1**, entries 11-15). In addition, the other oxidizing agents such as Ceric ammonium nitrate (CAN) and phenyliodine(III) diacetate

(PIDA) were also studied for this transformation. Unfortunately, the trace amount of **3a** could be seen in the presence of 1.0 equiv. CAN at 60ºC for 3 h, while PIDA (1.0 equiv.) failed to conduct any transformation (**Table 2.1**, entries 16 and 17). 20 mol% $FeCl_3$ alone could not initiate the reaction (**Table 2.1**, entry 18). Therefore, DDQ (1.0 equiv.) in combination with $FeCl_3$ (0.2 equiv.) and 4Å molecular sieves in $MeNO_2$ at 60 °C was set up as the optimum condition for the tandem cross dehydrogenative coupling reaction.



Scheme 2.4 Substrate scopes for the synthesis of indole–fluorene hybrids.

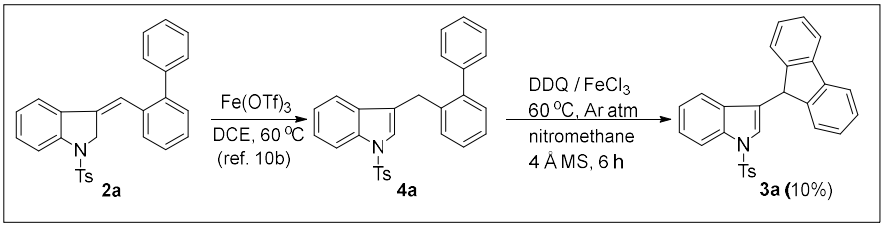
Having optimized the best conditions, we then intended to synthesize a series of indole-fluorene hybrid by reacting **2** (0.15 mmol) with 0.15 mmol of DDQ in combination with 0.03 mmol $FeCl_3$ and molecular sieve (4Å) using 1.5 mL nitromethane as solvent under Ar atm. at 60 °C. The reaction was not notably affected by the electronic effects of the various substituents on each of the aryl rings. The results are summarized in **Scheme 2.4**. The reaction performed well with electron-donating groups such as *o*-Me, *p*-Me and *p*-OMe, and led to product formation in high yields (82-90%, **Scheme 2.4**, entries **3b, 3c,** and **3e-3g**). Similarly, introductions of electron-withdrawing groups such as *p*-Cl and *p*-F were also compatible and produced 74% and 80% of the desired products, respectively (**Scheme 2.4**, entries **3d** and **3h**). Incorporation of -CF_3 group on indoline ring did not impede the reaction and resulted the desired product **3i** in 75% yield (**Scheme 2.4**, **3i**). Furthermore, the reaction could also provide the desired 3-(fluoren-9-yl)indole derivatives in 76%, 78% and 80% yields respectively, when indoline and biphenyl moiety had electronically opposing and similar substituents (**Scheme 2.4**, **3j**, **3k** and **3l**).
Moreover, electron-donating group such as *p*-Me on the aryl group directly attached to alkene was well accommodated and furnished good yields of the desired products, 83% and 80% (**Scheme 2.4**, **3e** and **3l**), respectively. Compounds with electron-donating *p*-Me, *p*-OMe groups and electron-withdrawing *p*-Cl group on aryl motif of biphenyl unit which directly engaged in the nucleophilic attack also underwent the DDQ mediated oxidative intramolecular coupling, affording the hybrid products in good to excellent yields (**Scheme 2.4**, entries **3b**, **3c**, **3d**, **3j** and **3k**). Along this line, it is worth mentioning that the tosyl protecting group on nitrogen, when substituted with mesyl group, also delivered 81% yield (**Scheme 2.4**, **3m**).



Scheme 2.5 Synthesis of 7-Azaindole-fluorene hybrid.

Due to the growing interests in the synthesis and potential pharmaceutical application of aza-indole compounds, we next explored our present tandem method for the synthesis of 3-(fluoren-9-yl)-7-azaindolederivatives. The results are summarized in **Scheme 2.5**. The precursor molecules, **2n** and **2o** were synthesized in 75% and 70% yields through reductive

carbopalladation from corresponding *N*-propargyl derivative of 2-amino-3-bromo pyridine in the presence of $Pd(OAc)_2/PCy_3$ and K_2CO_3 in toluene-ethanol mixture at 75 °C. Pleasantly, the compounds **2n** and **2o** were smoothly transformed to 7-azaindole tethered fluorene derivatives, **3n** and **3o** in 66% and 68% yields, respectively, in 5 hours at 60 °C (**Scheme 2.5**). All the structures were characterized by ^1H, ^{13}C NMR and HRMS spectra (see section 2.4.6) and one of the structures, **3a** was confirmed by X-ray diffraction (See section 2.7, **Figure 2.2**).

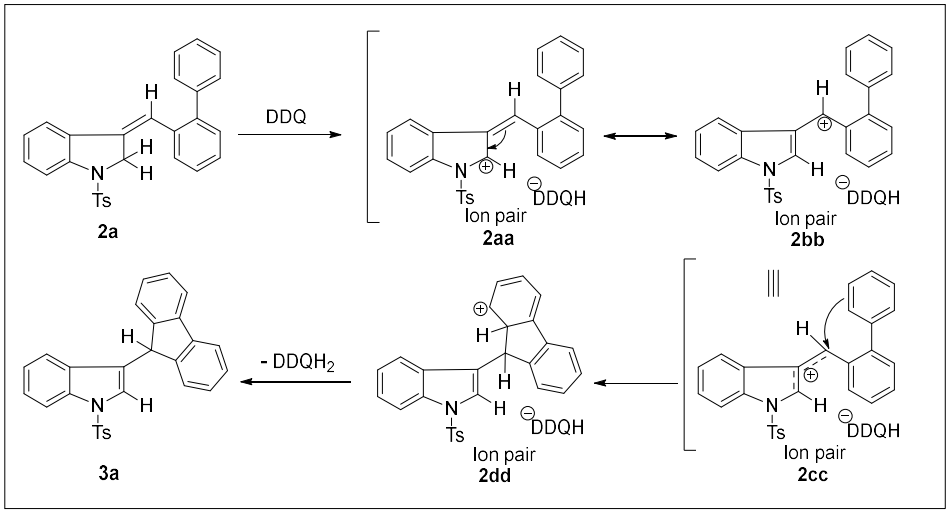


Scheme 2.6 A comparative study for the tandem oxidative isomerization/cyclisation.

To better understand the reaction mechanism, we synthesized the substrate **4a** by the isomerization of **2a** according to our previous report[9b] using $Fe(OTf)_3$ as catalyst and dichloroethane as solvent. Then, we performed the present cyclization reaction with the isomerized product **4a** according to our present strategy (**Scheme 2.6**). It was observed that the reaction was sluggish and most of the starting material **4a** unreacted even after 6 hours. only 10% of the desired product **3a** was obtained. It is evident that simple generation of benzylic cation by the DDQ mediated oxidation is inefficient for this smooth cyclization. Rather, aromatization of the substrate **2a** via allylic Csp^3–H oxidation serves as the driving force for the aforementioned tandem cyclization process.

Based on our experimental results and earlier literature reports, a plausible mechanism for the DDQ mediated oxidative cyclisation is depicted in **Scheme 2.7**. In literature, both ionic and radical mechanism has been described for DDQ mediated oxidations, depending on substrates and reaction conditions.[11] Generally, DDQ mediated radical pathway is established by the inhibition of reaction in the presence of radical scavenger.[12] However, we noticed that in the present transformation the radical scavenger, TEMPO could not suppress the yield of the desired products, implying that a cationic pathway must be involved in the initial oxidative step. Therefore, we proposed the formation of an ion-pair **2aa**/$DDQH^-$ by a hydride ion transfer from the allylic Csp^3–H of **2a** to DDQ. The allylic carbocation intermediate **2aa** is stabilized by resonance and driven to form a benzylic cation **2bb** due to the aromatic stabilization. Then, intramolecular electrophilic substitution took place by the *o*-aryl group with the indolyl cation

2cc. Finally, aromatization was accomplished through removal of proton by $DDQH^-$ leading to the formation of desired 3-fluorenyl indole derivatives **3a**. The exact roles of $FeCl_3$ and molecular sieve have not yet been determined. But we conclude that the yield of the target products was improved in the presence of 4Å



Scheme 2.7 The plausible mechanistic pathway for the tandem synthesis.

molecular sieve/$FeCl_3$ by increasing the availability of indolyl cation **2cc** for the intramolecular aromatic electrophilic cyclisation. While, molecular sieves can prevent the *in-situ* generation of alcohols by removing water from the reaction medium, $FeCl_3$ can revert the alcohol, if generated, back to the indolyl cation.[9e, 13] $FeCl_3$ also had a role in preventing the formation of unwanted by-products.

2.3. CONCLUSION

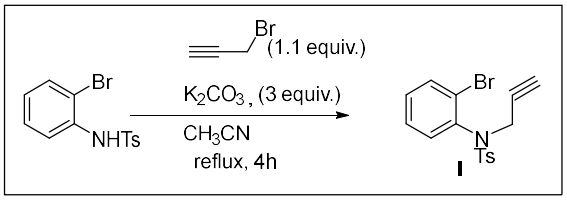
In conclusion, we have developed a novel, efficient and highly regioselective synthesis of 3-fluorenyl-indoles/azaindoles *via* tandem allylic Csp^3–H oxidation/intramolecular C–C bond formation, in the presence of DDQ/$FeCl_3$. The strategy is widely applicable and delivers moderate to high yields. The yield of the product was dramatically improved in the presence of additives such as $FeCl_3$ and molecular sieves (4 Å). The utilisation of reductive Heck coupling reaction for the synthesis of precursor substrates makes this strategy appealing for easy access to complex and diverse indole–fluorene hybrid molecules.

2.4 EXPERIMENTAL PROCEDURE

2.4.1 General Information

All ^{1}H NMR spectral data were recorded by Bruker 300, 400, 500 (300, 400, 500 MHz) spectrometer in $CDCl_3$ solutions expressing chemical shifts in parts per million (ppm, δ) and are referenced to $CHCl_3$ (δ = 7.26 ppm) as an internal standard. All coupling constants are absolute values and are expressed in Hz. The description of the signals include: s = singlet, d = doublet, t = triplet, m = multiplet, dd = doublet of doublets and brs = broad singlet, td = triplet of doublet. ^{13}C NMR spectra were recorded with a Bruker 300, 400, 500 (75, 100, 125 respectively MHz) spectrometer as solutions in $CDCl_3$ with complete proton decoupling. Chemical shifts are expressed in parts per million (ppm, δ) and are referenced to $CDCl_3$ (δ = 77.0 ppm) as an internal standard. High-Resolution Mass Spectra (HRMS) were performed with a Q-tof Micro YA263 spectrometer in trichloromethane solvent. The molecular fragments are quoted as the relation between mass and charge (m/z). The routine monitoring of reactions was performed with silica gel coated glass slides (Merck, silica gel G for TLC), and pre-coated Al plate, which were analyzed with iodine and uv light respectively. Solvents, reagents and chemicals were purchased from Aldrich, Fluka, Merck, SRL, Spectrochem and Process Chemicals. All reactions involving moisture sensitive reactants were executed with oven-dried glassware.

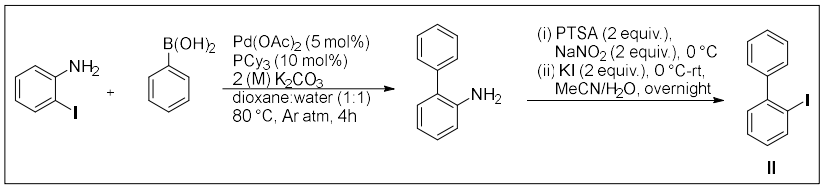
2.4.2 Representative Experimental Procedure for the Synthesis of *N*-(2-bromophenyl)-4-methyl-*N*-(prop-2-yn-1-yl)benzenesulfonamide (I)



In an oven-dried 50 mL round-bottomed flask fitted under Ar gas, *N*-(2-bromophenyl)-4-methylbenzenesulfonamide (600 mg, 1.84 mmol), K_2CO_3 (761 mg, 5.52 mmol) and propargyl bromide (240 mg, 2.02 mmol) were taken in CH_3CN (20 mL) and the mixture was refluxed. The reaction was complete after 4 hours (monitored by TLC). The reaction mixture was extracted with ethyl acetate and washed with water. After separation from the aqueous layer, the

combined organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by silica gel (60-120 mesh) column chromatography, eluted by petroleum ether/ ethyl acetate (90:10 v/v), to afford the substitution product **I** (602 mg, 90%) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76 – 7.70 (m, 2H), 7.66 (dd, *J* = 7.7, 1.6 Hz, 1H), 7.33 – 7.22 (m, 5H), 4.79 (d, *J* = 18.2 Hz, 1H), 4.17 (d, *J* = 18.4 Hz, 1H), 2.46 (s, 3H), 2.19 (t, *J* = 2.5 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 143.88, 137.25, 136.83, 133.88, 132.45, 130.35, 129.48, 128.09, 127.91, 125.58, 77.82, 73.83, 40.26, 21.63.

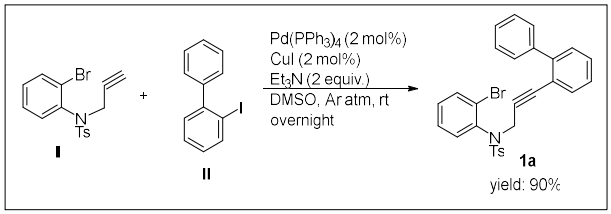
2.4.3 Representative Experimental Procedure for the Synthesis of 2-iodo-1,1'-biphenyl (II)



In an 50 mL round-bottomed flask, 2-iodoaniline (500 mg, 2.28 mmol), phenylboronic acid (362 mg, 2.96 mmol) 2.5 M aqueous K_2CO_3 solution (7 mL), $Pd(OAc)_2$ (25 mg, 0.114 mmol) and PCy_3 (64 mg, 0.23 mmol) were taken in dioxane solvent (7 mL) and the mixture was heated at 80 °C under Ar atm. The substrate was fully reacted after 4 hours (monitored by TLC). The reaction mixture was extracted with ethyl acetate and washed with brine solution. After separation from the aqueous layer, the combined organic layer was dried over anhydrous Na_2SO_4 and concentrated under pressure. The crude product was purified by silica gel (60-120 mesh) column chromatography, eluted by petroleum ether/ ethyl acetate (90:10 v/v), to afford [1,1'-biphenyl]-2-amine (339 mg, 88%) as a brown solid. The purified product [1,1'-biphenyl]-2-amine (335 mg, 1.98 mmol) was taken in a 100 mL round-bottom flask. PTSA (681 mg, 3.96 mmol) and a mixture of MeCN (5 mL) and water (10 mL) were added to it. The mixture was placed in an ice bath and stirred for 5 minutes. Then, $NaNO_2$ (273 mg, 3.96 mmol) in water (10 mL) was added drop wise at 0-5 °C. Then, aqueous KI (657 mg, 3.96 mmol) solution (10 mL) was poured into the mixture after formation of a clear greenish solution. After the addition was complete, the reaction was allowed to run at room temperature overnight. Next day, the reaction mixture was quenched by $Na_2S_2O_3{\cdot}5H_2O$ and neutralized by $NaHCO_3$ successively. Then, the reaction mixture was extracted with DCM. After separation from the aqueous layer, the combined organic layer was dried over anhydrous Na_2SO_4 and concentrated under pressure.

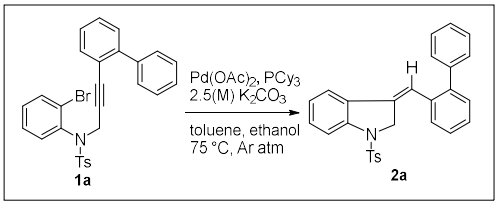
After that, column chromatography on silica gel (60-120 mesh) was performed to purify the 2-iodo-1,1'-biphenyl **II**. The desired 2-iodo-1,1'-biphenyl **II** (479 mg, 1.71 mmol) was eluted as a white liquid with petroleum ether to get a two-step yield of 75%.

2.4.4 Representative Experimental Procedure for the Synthesis of *N*-(3-([1,1'-biphenyl]-2-yl)prop-2-yn-1-yl)-*N*-(2-bromophenyl)-4-methylbenzenesulfonamide (1a)



To a solution of *N*-(2-bromophenyl)-4-methyl-*N*-(prop-2-yn-1-yl)benzenesulfonamide **I** (363 mg, 1 mmol) in dimethyl sulfoxide (2 mL) and 2-phenyliodobenzene **II** (308 mg, 1.1 mmol), triethylamine (202 mg, 2 mmol), CuI (4 mg, 0.02 mmol) and $Pd(PPh_3)_4$ (12 mg, 0.02 mmol) were added successively. The resulting solution was stirred at room temperature under argon atmosphere for overnight. After the completion of the reaction (monitored by TLC), the crude reaction mixture was extracted with ethyl acetate. The organic extract was washed with brine solution, dried over anhydrous Na_2SO_4 and concentrated. The product was subjected to column chromatography (silica gel, 60-120 mesh), eluting with pet ether/EtOAc 90:10 (v/v) to afford the product **1a** as a yellow semisolid (463 mg, 0.90 mmol, 90%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.42 (s, 3H), 4.28 (d, J = 18.0 Hz, 1H), 4.93 (d, J = 18.0 Hz, 1H), 6.99 (d, J = 6.3 Hz, 1H), 7.13 (d, J = 6.6 Hz, 1H), 7.18–7.26 (m, 4H), 7.29–7.36 (m, 6H), 7.42 (t, J = 4.2 Hz, 2H), 7.64 (d, J =8.7 Hz, 1H), 7.70 (d, J =8.1 Hz, 2H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz) δ 21.7, 41.4, 85.3, 85.9, 120.7, 125.8, 127.0, 127.5, 127.9, 128.1, 128.8, 129.1, 129.5, 129.6, 130.2, 132.3, 133.6, 133.8, 137.2, 137.6, 140.3, 143.7, 143.8 ppm. Compounds **1b-1o** were synthesised by the above similar procedure.

2.4.5 Representative Experimental Procedure for the Synthesis of (*Z*)-3-([1,1'-biphenyl]-2-ylmethylene)-1-tosylindoline (2a)



To a solution of *N*-(3-([1,1'-biphenyl]-2-yl)prop-2-yn-1-yl)-*N*-(2-bromophenyl)-4-methylbenzenesulfonamide **1a** (155 mg, 0.3 mmol) in 2.5 M K_2CO_3 (2 mL) and 2 mL ethanol-toluene (1:1), PCy_3 (8 mg, 0.03 mmol) and $Pd(OAc)_2$ (4 mg, 0.015 mmol) were added successively. The resulting solution was stirred at 75 °C under argon atmosphere for 3 h. After the completion of the reaction (monitored by TLC), the crude reaction mixture was extracted with ethyl acetate. The organic extract was washed with brine solution, dried over anhydrous Na_2SO_4 and concentrated. The product was subjected to column chromatography (silica gel, 60-120 mesh), eluting with pet ether/EtOAc 95:5 (v/v) to afford the product **2a** as a greenish white solid (109 mg, 0.25 mmol, 82%); m. p. 116-118 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.37 (s, 3H), 4.80 (d, *J*= 2.8 Hz, 2H) , 6.70 (d, *J* = 2.8 Hz, 1H), 6.96 (t, *J*= 7.6 Hz,1H), 7.16 (d, *J*= 7.6 Hz, 1H), 7.20–7.27 (m, 5H), 7.29–7.44 (m, 7H), 7.72 (t, *J*= 8.0 Hz,3H)ppm. ^{13}C NMR ($CDCl_3$, 100MHz) δ 21.7, 54.5, 115.0, 118.2, 120.6, 123.9, 127.3, 127.4, 127.5, 127.6, 127.7, 128.2, 129.8, 129.9, 130.6, 131.4, 132.8, 134.0, 134.2, 140.9, 141.9, 143.4, 144.4, ppm.

(*z*)-2-(1-(1-tosylindolin-3-ylidene)methyl)-4'-methoxybiphenyl (2b): To a solution of *N*-(2-bromophenyl)-*N*-(3-(4'-methoxy-[1,1'-biphenyl]-2-yl)prop-2-yn-1-yl)-4-methylbenzenesulfonamide **1b** (164 mg, 0.3 mmol) in 2.5 M K_2CO_3(2 mL) and 2 mL ethanol-toluene (1:1), PCy_3(8 mg, 0.03 mmol) and $Pd(OAc)_2$ (4 mg, 0.015 mmol) were added successively. The resulting solution was stirred at 75 °C under argon atmosphere for 4 h. After the completion of the reaction (monitored by TLC), the crude reaction mixture was extracted with ethyl acetate. The organic extract was washed with brine solution, dried over anhydrous $Na_2SO_4$and concentrated. The product was subjected to column chromatography (silica gel, 60-120 mesh), eluting with pet ether/EtOAc 95:5 (v/v) to afford the product **2b** as a greenish white solid (117 mg, 0.25 mmol, 83%); m. p. 130-132°C. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 2.39 (s, 3H), 3.84 (s, 3H) 4.78 (d, *J*= 3.0 Hz, 2H) , 6.72 (t, *J* = 3.0Hz, 1H), 6.90 (d, *J*= 8.5 Hz,2H), 6.97 (t, *J*= 7.5 Hz, 1H), 7.16–7.25 (m, 4H), 7.31–7.41 (m, 6H), 7.72 (dd, *J*= 8.5, 12.0, Hz,3H) ppm. ^{13}C NMR (CDC_{l3}, 100 MHz) δ 21.6, 54.5, 55.4 113.7, 115.0, 118.4, 120.5, 123.9, 127.2, 127.3, 127.5, 127.6, 129.7, 129.9, 130.6, 130.9, 131.4, 132.6, 133.2, 134.1, 134.2, 141.5, 143.4, 144.3, 159.0 ppm.

(*z*)-2-((1-tosylindolin-3-ylidene)methyl)-4'-methylbiphenyl (2c): To a solution of *N*-(2-bromophenyl)-4-methyl-*N*-(3-(4'-methyl-[1,1'-biphenyl]-2-yl)prop-2-yn-1-

yl)benzenesulfonamide **1c** (159 mg, 0.3 mmol) in 2.5 M K_2CO_3(2 mL) and 2 mL ethanol-toluene (1:1), PCy_3 (8 mg, 0.03 mmol) and $Pd(OAc)_2$ (4 mg, 0.015 mmol) were added successively. The resulting solution was stirred at 70-75 °C under argon atmosphere for 4 h. After the completion of the reaction (monitored by TLC), the crude reaction mixture was extracted with ethyl acetate. The organic extract was washed with brine solution, dried over anhydrous Na_2SO_4 and concentrated. The product was subjected to column chromatography (silica gel, 60-120 mesh), eluting with pet ether/EtOAc 95:5 (v/v) to afford the product **2c** as a greenish white solid (106 mg, 0.24mmol, 81%); m. p. 138-140 °C.^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.28 (s, 3H), 2.30 (s, 3H), 4.72 (d, *J*= 3.2 Hz, 2H), 6.63 (t, *J* = 3.2Hz, 1H), 6.88 (t, *J*= 7.6 Hz, 1H), 7.07–7.11 (m, 5H), 7.14–7.17 (m, 3H), 7.22-7.31 (m, 4H), 7.63 (t, *J*= 8.4 Hz,3H). ppm. ^{13}C NMR ($CDCl_3$, 100 MHz) δ 21.3, 21.6, 54.5, 114.9, 118.4, 120.6, 123.9, 127.3, 127.4, 127.6, 128.9, 129.7, 129.9, 130.6, 131.4, 132.5, 134.0, 134.1, 137.0, 137.8, 141.8, 143.3, 144.4 ppm.

(*z*)-2-((1-tosylindolin-3-ylidene)methyl)-4'-chlorobiphenyl (2d): To a solution of *N*-(2-bromophenyl)-*N*-(3-(4'-chloro-[1,1'-biphenyl]-2-yl)prop-2-yn-1-yl)-4-methylbenzenesulfonamide **1d** (165 mg, 0.3 mmol) in 2.5 M K_2CO_3(2 mL) and 2 mL ethanol-toluene (1:1), PCy_3 (8 mg, 0.03 mmol) and $Pd(OAc)_2$ (4 mg, 0.015 mmol) were added successively. The resulting solution was stirred at 70-75 °C under argon atmosphere for 4 h. After the completion of the reaction (monitored by TLC), the crude reaction mixture was extracted with ethyl acetate. The organic extract was washed with brine solution, dried over anhydrous Na_2SO_4 and concentrated. The product was subjected to column chromatography (silica gel, 60-120 mesh), eluting with pet ether/EtOAc 95:5 (v/v) to afford the product **2d** as a greenish white solid (118 mg, 0.25mmol, 85%); m. p. 142-144 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.26 (s, 3H), 4.66 (d, *J*= 2.8 Hz, 2H), 6.55 (t, *J* = 2.8Hz, 1H), 6.88 (t, *J* = 7.6 Hz, 1H), 7.09 (d, *J*= 8.8 Hz, 3H), 7.15 (t, *J* = 8.0 Hz, 3H), 7.21–7.27 (m, 5H), 7.32 (dd, *J*= 7.6, 2.4 Hz, 1H), 7.62 (dd, *J*= 11.2, 8.4 Hz, 3H). ppm. ^{13}C NMR ($CDCl_3$, 100 MHz) δ21.6, 54.3, 114.9, 117.6, 120.5, 123.9, 127.2, 127.5, 127.7, 127.9, 128.4, 129.9, 130.4, 131.0, 133.2, 133.4, 134.0, 139.2, 140.3, 143.3, 144.4. ppm.

(*z*)-2-((1-tosylindolin-3-ylidene)methyl)-5-methylbiphenyl (2e): To a solution of *N*-(2-bromophenyl)-4-methyl-*N*-(3-(5-methyl-[1,1'-biphenyl]-2-yl)prop-2-yn-1-yl)benzenesulfonamide **1e** (159 mg, 0.3 mmol) in 2.5 M K_2CO_3(2 mL) and 2 mL ethanol-

toluene (1:1), PCy_3 (8 mg, 0.03 mmol) and $Pd(OAc)_2$ (4 mg, 0.015 mmol) were added successively. The resulting solution was stirred at 70-75 °C under argon atmosphere for 4 h. After the completion of the reaction (monitored by TLC), the crude reaction mixture was extracted with ethyl acetate. The organic extract was washed with brine solution, dried over anhydrous Na_2SO_4 and concentrated. The product was subjected to column chromatography (silica gel, 60-120 mesh), eluting with pet ether/EtOAc 95:5 (v/v) to afford the product **2e** as a yellowish white solid (108 mg, 0.24mmol, 81%); m. p. 126-128 °C.^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.37 (s, 3H), 2.42 (s, 3H), 4.80 (d, *J*= 3.0 Hz, 2H), 6.68 (bs, 1H), 6.95 (t, *J* = 7.5 Hz, 1H), 7.14 (d, *J*= 7.5 Hz, 1H), 7.19–7.26 (m, 8H), 7.32-7.36 (m, 3H), 7.70 (dd, *J*= 7.8, 4.5 Hz, 3H). ppm. ^{13}C NMR ($CDCl_3$, 75 MHz) δ21.4, 21.7, 54.6, 114.9, 118.1, 120.5, 123.9, 127.4, 128.2, 128.4, 129.6, 129.8, 129.9, 131.2, 131.4, 131.6, 131.9, 134.2, 137.5, 141.0, 141.9, 143.3, 144.4. ppm.

(*z*)-2-((5-methyl-1-tosylindolin-3-ylidene)methyl)biphenyl (2f): To a solution of*N*-(3-([1,1'-biphenyl]-2-yl)prop-2-yn-1-yl)-*N*-(2-bromo-4-methylphenyl)-4-methylbenzenesulfonamide **1f** (159 mg, 0.3 mmol) in 2.5 M K_2CO_3(2 mL) and 2 mL ethanol-toluene (1:1), PCy_3 (8 mg, 0.03 mmol) and $Pd(OAc)_2$ (4 mg, 0.015 mmol) were added successively. The resulting solution was stirred at 75 °C under argon atmosphere for 4 h. After the completion of the reaction (monitored by TLC), the crude reaction mixture was extracted with ethyl acetate. The organic extract was washed with brine solution, dried over anhydrous Na_2SO_4 and concentrated. The product was subjected to column chromatography (silica gel, 60-120 mesh), eluting with pet ether/EtOAc 95:5 (v/v) to afford the product **2f** as a yellowish white solid (108 mg, 0.24 mmol, 80%); m. p. 136-138 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.24 (s, 3H), 2.37 (s, 3H), 4.76 (d, *J*= 2.8 Hz, 2H) , 6.65 (t, *J* = 2.8 Hz, 1H), 6.96 (s,1H), 7.05 (d, *J*= 8.4 Hz, 1H), 7.22–7.29 (m, 4H), 7.30–7.44 (m, 7H), 7.62 (d, *J*= 8.0 Hz,1H), 7.68 (d, *J*= 8.4 Hz,2H). ppm. ^{13}C NMR ($CDCl_3$, 100 MHz) δ 21.1, 21.7, 54.7, 114.98, 117.94, 120.9, 127.3, 127.4, 127.5, 127.5, 127.6, 128.2, 129.8, 129.9, 130.7, 131.5, 133.1, 133.7, 134.1, 134.2, 140.9, 141.3, 141.7, 144.3 ppm.

(*z*)-2-((5,7-dimethyl-1-tosylindolin-3-ylidene)methyl)biphenyl (2g): To a solution of *N*-(3-([1,1'-biphenyl]-2-yl)prop-2-yn-1-yl)-*N*-(2-bromo-4,6-dimethylphenyl)-4-methylbenzenesulfonamide **1g** (163 mg, 0.3 mmol) in 2.5 M K_2CO_3(2 mL) and 2 mL ethanol-toluene (1:1), PCy_3 (8 mg, 0.03 mmol) and $Pd(OAc)_2$ (4 mg, 0.015 mmol) were added successively. The resulting solution was stirred at 75 °C under argon atmosphere for 5 h. After

the completion of the reaction (monitored by TLC), the crude reaction mixture was extracted with ethyl acetate. The organic extract was washed with brine solution, dried over anhydrous Na_2SO_4 and concentrated. The product was subjected to column chromatography (silica gel, 60-120 mesh), eluting with pet ether/EtOAc 95:5 (v/v) to afford the product **2g** as a greenish white solid (116 mg, 0.25 mmol, 84%); m. p. 138-140 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.25 (s, 3H), 2.34 (s, 3H), 2.58 (s, 3H), 4.70 (d, *J*= 2.4 Hz, 2H) , 6.32 (d, *J* = 2.4Hz, 1H), 6.71 (s,1H),6.96 (s, 1H),7.00-7.05 (m, 4H), 7.15 (d, *J*= 6.8 Hz,1H), 7.20–7.29 (m, 2H), 7.31 (dd, *J*= 2.0, 4.8 Hz,3H), 7.35-7.38 (m, 3H). ppm. ^{13}C NMR ($CDCl_3$, 100 MHz) δ 19.8, 21.2, 21.8, 56.8, 118.3, 118.6, 125.0, 127.2, 127.5, 127.6, 127.7, 128.1, 128.2, 129.2, 129.8, 130.4, 132.3, 133.0, 133.2, 134.1, 135.1, 136.4, 137.7, 140.8, 141.1, 141.4, 143.8 ppm.

(*z*)-2-((5-fluoro-1-tosylindolin-3-ylidene)methyl)biphenyl (2h): To a solution of *N*-(3-([1,1'-biphenyl]-2-yl)prop-2-yn-1-yl)-*N*-(2-bromo-4-fluorophenyl)-4-methylbenzenesulfonamide **1h** (160 mg, 0.3 mmol) in 2.5 M K_2CO_3(2 mL) and 2 mL ethanol-toluene (1:1), PCy_3 (8 mg, 0.03 mmol) and $Pd(OAc)_2$ (4 mg, 0.015 mmol) were added successively. The resulting solution was stirred at 70-75 °C under argon atmosphere for 4 h. After the completion of the reaction (monitored by TLC), the crude reaction mixture was extracted with ethyl acetate. The organic extract was washed with brine solution, dried over anhydrous Na_2SO_4 and concentrated. The product was subjected to column chromatography (silica gel, 60-120 mesh), eluting with pet ether/EtOAc 95:5 (v/v) to afford the product **2h** as a greenish white solid (114 mg, 0.25mmol, 83%); m. p. 152-154 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.29 (s, 3H), 4.72 (d, *J*= 2.8 Hz, 2H), 6.54 (t, *J* = 2.8 Hz, 1H), 6.71 (dd, *J* = 8.0, 2.4Hz, 1H), 6.84 (td, *J*= 9.2, 2.8 Hz, 1H), 7.14 (dd, *J* = 7.6, 2.0Hz, 3H), 7.16 (s, 1H), 7.21 (d, *J*= 7.2 Hz, 1H) 7.25–7.30 (m, 5H), 7.32–7.34 (m, 1H), 7.56–7.61 (m, 3H). ppm. ^{13}C NMR ($CDCl_3$, 100 MHz) δ21.7, 54.9, 107.2 (d, $J_{C\text{-}F}$ = 24.0 Hz), 116.4 (d, $J_{C\text{-}F}$ = 9.0 Hz), 116.5, 119.5, 127.3, 127.4, 127.4, 127.6, 127.9, 128.2, 129.7, 129.9, 130.6, 132.0 (d, , $J_{C\text{-}F}$ = 3.0 Hz), 133.3, 133.4, 133.5, 133.7, 139.4, 140.6, 142.0, 144.5, 160.0 (d, , $J_{C\text{-}F}$ = 241.0 Hz). ppm.

(*z*)-2-((5-trifluoromethyl-1-tosylindolin-3-ylidene)methyl)biphenyl (2i): To a solution of *N*-(3-([1,1'-biphenyl]-2-yl)prop-2-yn-1-yl)-*N*-(2-bromo-4-(trifluoromethyl)phenyl)-4-methylbenzenesulfonamide **1i** (175 mg, 0.3 mmol) in 2.5 M K_2CO_3(2 mL) and 2 mL ethanol-toluene (1:1), PCy_3 (8 mg, 0.03 mmol) and $Pd(OAc)_2$ (4 mg, 0.015 mmol) were added successively. The resulting solution was stirred at 70-75 °C under argon atmosphere for 5 h.

After the completion of the reaction (monitored by TLC), the crude reaction mixture was extracted with ethyl acetate. The organic extract was washed with brine solution, dried over anhydrous Na_2SO_4 and concentrated. The product was subjected to column chromatography (silica gel, 60-120 mesh), eluting with pet ether/EtOAc 95:5 (v/v) to afford the product **2i** as a pale greenish solid (116 mg, 0.23mmol, 78%); m. p. 124-126 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.40 (s, 3H), 4.80 (d, *J*= 3.2 Hz, 2H), 6.80 (t, *J* = 3.2Hz, 1H), 7.25–7.29 (m, 4H), 7.32 (d, *J*= 7.2 Hz, 1H), 7.35–7.43 (m, 7H), 7.47 (d, *J*= 8.8 Hz, 1H), 7.72 (d, *J*= 8.0 Hz, 2H), 7.77 (d, *J*= 8.4 Hz, 1H). ppm. ^{13}C NMR ($CDCl_3$, 100 MHz) δ21.7, 54.8, 114.4, 117.7, 120.1, 126.8, 127.2, 127.6, 127.6, 128.1, 128.3, 129.7, 130.1, 130.8, 131.2, 133.5, 134.0, 140.5, 142.0, 144.9, 145.8. ppm.

(*z*)-2-((5-chloro-1-tosylindolin-3-ylidene)methyl)-4'-methoxybiphenyl (2j): To a solution of *N*-(2-bromo-4-chlorophenyl)-*N*-(3-(4'-methoxy-[1,1'-biphenyl]-2-yl)prop-2-yn-1-yl)-4-methylbenzenesulfonamide **1j** (175 mg, 0.3 mmol) in 2.5 M K_2CO_3(2 mL) and 2 mL ethanol-toluene (1:1), PCy_3 (8 mg, 0.03 mmol) and $Pd(OAc)_2$ (4 mg, 0.015 mmol) were added successively. The resulting solution was stirred at 70-75 °C under argon atmosphere for 4 h. After the completion of the reaction (monitored by TLC), the crude reaction mixture was extracted with ethyl acetate. The organic extract was washed with brine solution, dried over anhydrous Na_2SO_4 and concentrated. The product was subjected to column chromatography (silica gel, 60-120 mesh), eluting with pet ether/EtOAc 95:5 (v/v) to afford the product **2j** as a white solid (116 mg, 0.23mmol, 75%)as a mixture of non-separable isomers (E:Z=1:1.2); m. p. 144-146 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.28 (s, 3.6H), 2.30 (s, 3H), 3.75 (s, 3.6H), 3.76 (s, 3H), 4.67 (d, *J*= 2.8 Hz, 2H), 4.70 (d, *J*= 3.2 Hz, 2.4H), 6.62 (dt, *J* = 12.0, 3.2 Hz, 2H), 6.80–6.83 (m, 4H), 6.88 (td, *J*= 8.0, 1.0Hz, 1H), 7.05–7.16 (m, 14H), 7.18–7.23 (m, 2H), 7.26–7.30 (m, 6H),7.60 (dt, *J*= 21.6, 9.6Hz, 6H). ppm. ^{13}C NMR ($CDCl_3$, 100 MHz) δ21.6, 54.4. 54.8, 55.3, 113.6, 113.8, 114.9, 116.0, 118.4, 119.9, 120.5, 120.5, 123.9, 127.2, 127.3, 127.4, 127.5, 127.6, 128.0, 129.4, 129.5, 129.7, 129.9, 130.0, 130.6, 130.7, 130.8, 130.9, 131.4, 132.5, 133.2, 133.6, 133.7, 134.0, 134.1, 141.4, 141.6, 141.9, 144.3, 144.3, 144.6, 158.9, 159.0. ppm.

(*z*)-2-((5-fluoro-1-tosylindolin-3-ylidene)methyl)-4'-methoxybiphenyl (2k): To a solution of *N*-(2-bromo-4-fluorophenyl)-*N*-(3-(4'-methoxy-[1,1'-biphenyl]-2-yl)prop-2-yn-1-yl)-4-methylbenzenesulfonamide **1k** (169 mg, 0.3 mmol) in 2.5 M K_2CO_3(2 mL) and 2 mL ethanol-toluene (1:1), PCy_3 (8 mg, 0.03 mmol) and $Pd(OAc)_2$ (4 mg, 0.015 mmol) were added

successively. The resulting solution was stirred at 70-75 °C under argon atmosphere for 4 h. After the completion of the reaction (monitored by TLC), the crude reaction mixture was extracted with ethyl acetate. The organic extract was washed with brine solution, dried over anhydrous Na_2SO_4 and concentrated. The product was subjected to column chromatography (silica gel, 60-120 mesh), eluting with pet ether/EtOAc 95:5 (v/v) to afford the product **2k** as a greenish white solid (112 mg, 0.23mmol, 78%); m. p. 158-160 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.28 (s, 3H), 3.75 (s, 3H), 4.69 (d, *J*= 3.2 Hz, 2H), 6.56 (t, *J* = 3.2 Hz, 1H), 6.75 (dd, *J*= 8.0, 2.4Hz, 1H), 6.78–6.86 (m, 3H), 7.06 (dt, *J*= 6.8, 2.0 Hz, 2H) 7.14–7.18 (m, 3H), 7.20–7.30 (m, 3H), 7.55–7.60 (m, 3H). ppm. ^{13}C NMR ($CDCl_3$, 100 MHz) δ21.6, 54.3, 54.9, 107.2 (d, , J_{C-F} = 24.0 Hz), 113.7, 116.3 (d, , J_{C-F} = 7.0 Hz), 116.4 (d, , J_{C-F} = 9.0 Hz), 119.8, 127.2, 127.3, 127.4, 127.9, 129.9, 130.6, 130.8, 131.8 (d, , J_{C-F} = 2.0 Hz), 132.9, 133.3, 133.4, 133.5, 133.6, 139.4, 141.6, 144.5, 159.0, 160.0 (d, , J_{C-F} = 241.0 Hz), ppm.

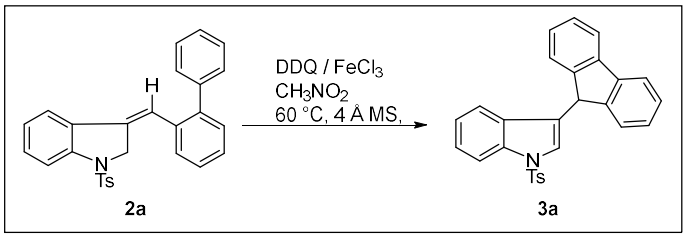
(*z*)-2-((5-methyl-1-tosylindolin-3-ylidene)methyl)-5-methylbiphenyl (2l): To a solution of *N*-(2-bromo-4-methylphenyl)-4-methyl-*N*-(3-(5-methyl-[1,1'-biphenyl]-2-yl)prop-2-yn-1-yl)benzenesulfonamide **1l** (164 mg, 0.3 mmol) in 2.5 M K_2CO_3(2 mL) and 2 mL ethanol-toluene (1:1), PCy_3 (8 mg, 0.03 mmol) and $Pd(OAc)_2$ (4 mg, 0.015 mmol) were added successively. The resulting solution was stirred at 70-75 °C under argon atmosphere for 5 h. After the completion of the reaction (monitored by TLC), the crude reaction mixture was extracted with ethyl acetate. The organic extract was washed with brine solution, dried over anhydrous Na_2SO_4 and concentrated. The product was subjected to column chromatography (silica gel, 60-120 mesh), eluting with pet ether/EtOAc 95:5 (v/v) to afford the product **2l** as a greenish solid (112 mg, 0.24mmol, 80%); m. p. 162-164 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.23 (s, 3H), 2.36 (s, 3H),2.41 (s, 3H), 4.76 (d, *J*= 2.8 Hz, 2H), 6.62 (t, *J* = 3.2Hz, 1H), 6.94 (s, 1H), 7.03 (d, *J*= 8.0 Hz, 1H), 7.18–7.26 (m, 7H), 7.32-7.38 (m, 3H), 7.61 (d, *J*= 8.0 Hz, 1H), 7.67 (d, *J*= 8.0 Hz, 2H). ppm. ^{13}C NMR ($CDCl_3$, 100 MHz) δ21.0, 21.3, 21.6, 54.7, 114.9, 117.8, 120.8, 127.2, 127.3, 127.4, 128.2, 128.3, 129.8, 129.8, 130.4, 131.3, 131.4, 131.6, 132.2, 133.6, 134.1, 137.4, 141.0, 141.2, 141.7, 144.2. ppm.

(*z*)-2-((1-mesylindolin-3-ylidene)methyl)-4'-methoxybiphenyl (2m): To a solution of *N*-(2-bromophenyl)-*N*-(3-(4'-methoxy-[1,1'-biphenyl]-2-yl)prop-2-yn-1-yl)methanesulfonamide **1m** (141 mg, 0.3 mmol) in 2.5 M K_2CO_3(2 mL) and 2 mL ethanol-toluene (1:1), PCy_3(8 mg, 0.03 mmol) and $Pd(OAc)_2$ (4 mg, 0.015 mmol) were added successively. The resulting solution

was stirred at 75 °C under argon atmosphere for 3 h. After the completion of the reaction (monitored by TLC), the crude reaction mixture was extracted with ethyl acetate. The organic extract was washed with brine solution, dried over anhydrous Na_2SO_4 and concentrated. The product was subjected to column chromatography (silica gel, 60-120 mesh), eluting with pet ether/EtOAc 95:5 (v/v) to afford the product **2m** as a white solid (102 mg, 0.26 mmol, 85%); m. p. 146-148 °C. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 2.88 (s, 3H), 3.85 (s, 3H) 4.83 (d, *J*= 3.0 Hz, 2H) , 6.88 (t, *J* = 3.5 Hz, 1H), 6.95 (dd, *J*= 7.0, 2.0 Hz,2H), 7.04 (td, *J*= 7.5, 0.5 Hz, 1H), 7.24 (d, *J*= 7.5 Hz, 1H), 7.27 (dd, *J*= 5.0, 4.5 Hz, 2H), 7.29 (dd, *J*= 6.5, 2.0 Hz, 1H), 7.33 (d, *J*= 7.5 Hz, 1H) 7.34–7.39 (m, 3H), 7.51 (d, *J*= 8.5 Hz,1H) ppm. ^{13}C NMR (CDC_{l3}, 125 MHz) δ 35.3, 54.8, 55.4, 113.7, 113.8, 114.2, 118.8, 120.8, 124.1, 127.3, 127.5, 127.8, 129.9, 130.5, 130.6, 131.0, 131.2, 132.3, 133.3, 134.0, 141.6, 143.2, 159.0 ppm.

(*z*)-2-((1-tosyl-7-azaindolin-3-ylidene)methyl)biphenyl (2n): To a solution of *N*-(3-([1,1'-biphenyl]-2-yl)prop-2-yn-1-yl)-*N*-(3-bromo-5-methylpyridin-2-yl)-4-methylbenzenesulfonamide **1o** (159 mg, 0.3 mmol) in 2.5 M K_2CO_3(2 mL) and 2 mL ethanol-toluene (1:1), PCy_3 (8 mg, 0.03 mmol) and $Pd(OAc)_2$ (4 mg, 0.015 mmol) were added successively. The resulting solution was stirred at 75 °C under argon atmosphere for 5 h. After the completion of the reaction (monitored by TLC), the crude reaction mixture was extracted with ethyl acetate. The organic extract was washed with brine solution, dried over anhydrous Na_2SO_4 and concentrated. The product was subjected to column chromatography (silica gel, 60-120 mesh), eluting with pet ether/EtOAc 90:10 (v/v) to afford the product **2o** as a yellow solid (95 mg, 0.21 mmol, 70%); m. p. 156-158 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.21 (s, 3H), 2.40 (s, 3H), 4.94 (d, *J*= 3.2 Hz, 2H) , 6.77 (t, *J* = 3.2Hz, 1H), 7.22 (d, *J*= 1.6 Hz,1H), 7.29 (d, *J*= 8.0 Hz, 2H),7.32–7.35 (m, 2H), 7.38–7.40 (m, 6H),7.42 (dd, *J*= 5.6, 1.6 Hz, 1H), 8.00 (d, *J*= 8.0 Hz, 2H), 8.03 (d, *J*= 1.0 Hz, 1H). ppm. ^{13}C NMR ($CDCl_3$, 100 MHz) δ 18.0, 21.7, 53.5, 120.4, 127.4, 127.6, 127.7, 127.9, 128.0, 128.3, 128.9, 129.6, 129.8, 129.8, 130.7, 133.5, 140.8, 141.9, 144.3, 148.8, 154.8 ppm.

2.4.6 Representative Experimental Procedure for the Synthesis of 3-(9*H*-fluoren-9-yl)-1-tosyl-1*H*-indole (3a)



To a solution of **2a** (66 mg, 0.15 mmol) in dry nitromethane (1.5 mL) was added DDQ (0.15 mmol) in presence of anhydrous $FeCl_3$ (5 mg, 0.03 mmol) and 4Å molecular sieves as additive. The reaction mixture was stirred at 60 ºC temperature under an argon atmosphere for 3 h. After the completion of the reaction (monitored by TLC), the crude reaction mixture was extracted with DCM. The organic extract was dried over anhydrous Na_2SO_4 and product was purified by column chromatography (silica gel, 60-120 mesh), eluting with pet ether/EtOAc 97:3 (v/v) to afford the product **3a** as a white solid (56 mg, 0.13 mmol, 85%), m. p. 166-168 °C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.37 (s, 3H), 5.24 (s, 1H), 6.70 (d, *J*= 7.8 Hz, 1H), 6.95 (t, *J*= 8.1 Hz,1H), 7.17–7.23 (m, 5H), 7.24–7.29 (m, 2H), 7.40 (t, *J*= 7.2 Hz,2H), 7.57 (s, 1H), 7.76 (d, *J*= 8.1 Hz, 2H),7.84 (d, *J*= 6.9 Hz, 2H), 7.93 (d, *J*= 8.1 Hz, 1H). ppm. ^{13}C NMR ($CDCl_3$, 75MHz) δ 21.7, 45.8, 113.9, 120.2, 120.3, 122.3, 123.2, 124.5, 124.8, 125.1, 126.9, 127.5, 127.7, 129.8, 130.0, 135.3, 135.9, 141.0, 145.0, 146.0 ppm. HRMS: cacld for $C_{28}H_{21}NO_2S$ $[M]^+$ 435.1293; found 435.1292.

3-(2-methoxy-9*H*-fluoren-9-yl)-1-tosyl-1*H*-indole (3b): Compound **2b** (70 mg, 0.15 mmol) was treated with DDQ (0.15 mmol) in combination with anhydrous $FeCl_3$ (5 mg, 0.03 mmol) and 4Å molecular sieves under argon atmosphere at 60 ºC temperature as described for the synthesis of **3a** for 2 h to afford **3b** as an off white solid (60 mg, 0.13 mmol, 84%), m. p. 147-149 °C.^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.39 (s, 3H), 3.77 (s, 3H), 5.20 (s, 1H), 6.71 (d, *J*= 7.2 Hz, 1H), 6.82 (s, 1H), 6.95 (d, *J*= 7.2 Hz, 2H), 7.15–7.19 (m, 2H),7.22–7.28 (m, 3H), 7.38 (t, *J*= 7.2 Hz, 1H), 7.60 (s, 1H), 7.77 (t, *J*= 8.7 Hz, 4H), 7.95 (d, *J*= 8.4 Hz, 1H). ppm. ^{13}C NMR ($CDCl_3$, 75 MHz) δ 21.7, 45.8, 55.5, 110.6, 113.8, 119.3, 120.3, 122.4, 123.2, 124.5, 124.8, 124.9, 126.3, 126.9, 127.7, 129.7, 129.9, 133.9, 135.3, 135.9, 141.0, 145.0, 145.5, 147.8, 159.7 ppm. HRMS: cacld for $C_{29}H_{23}NO_3S$ $[M+H]^+$ 466.1432; found 466.1478.

3-(2-methyl-9*H*-fluoren-9-yl)-1-tosyl-1*H*-indole (3c): Compound **2c** (68 mg, 0.15 mmol) was treated with DDQ(0.15 mmol) in combination with anhydrous $FeCl_3$ (5 mg, 0.03 mmol)and 4Å molecular sieves under argon atmosphere at 60 ºC temperature as described for the synthesis of **3a** for 2.5 h to afford **3c** as a white solid (58 mg, 0.13 mmol, 90%), m. p. 168-170 °C.^{1}H NMR

($CDCl_3$, 400 MHz) δ 2.32 (s, 3H), 2.37 (s, 3H), 5.20 (s, 1H), 6.70 (d, *J*= 6.0 Hz,1H), 6.95 (t, *J*= 7.2 Hz,1H), 7.08 (s, 1H), 7.17–7.26 (m, 6H), 7.39 (t, *J*= 7.2 Hz, 1H), 7.59 (s, 1H), 7.72–7.81 (m, 4H), 7.96 (d, *J*= 8.4 Hz, 1H). ppm. ^{13}C NMR ($CDCl_3$, 100 MHz) δ 21.4, 21.6, 21.7, 45.6, 113.9, 119.8, 120.3, 122.6, 123.2, 124.5, 124.7, 125.0, 125.7, 126.8, 126.9, 127.7, 128.6, 129.0, 129.8, 129.9, 135.3, 135.9, 137.3, 138.3, 141.1, 144.9, 145.8, 146.2 ppm. HRMS: cacld for $C_{29}H_{23}NO_2SNa$ $[M+Na]^+$ 472.1347; found 472.1350.

3-(2-chloro-9*H*-fluoren-9-yl)-1-tosyl-1*H*-indole (3d): Compound **2d** (71 mg, 0.15 mmol) was treated with DDQ (0.15 mmol) in combination with anhydrous $FeCl_3$ (5 mg, 0.03 mmol) and 4Å molecular sieves under argon atmosphere at 60 °C temperature as described for the synthesis of **3a** for 2 h to afford **3d** as an off white solid (52 mg, 0.11 mmol, 74%), m. p. 158-160 °C.^1H NMR ($CDCl_3$, 400 MHz) δ 2.37 (s, 3H), 5.22 (s, 1H), 6.66 (d, *J*= 5.6 Hz,1H), 6.96 (t, *J*= 7.6 Hz,1H),7.21–7.30 (m, 6H), 7.36–7.42 (m, 2H),7.59 (s, 1H), 7.78 (td, *J*= 8.4, 13.2 Hz, 4H), 7.98 (d, *J*= 8.4 Hz,1H). ppm. ^{13}C NMR ($CDCl_3$, 100 MHz) δ 21.6, 45.7, 114.0, 120.0, 120.2, 121.0, 121.6, 123.3, 124.7, 124.9, 125.1, 125.3, 126.9, 127.8, 128.1, 129.5, 130.0, 133.1, 135.1, 135.9, 139.5, 139.9, 145.1, 145.8, 147.8ppm. HRMS: cacld for $C_{28}H_{20}ClNO_2SNa$ $[M+Na]^+$ 492.0801; found 492.0800.

3-(3-methyl-9*H*-fluoren-9-yl)-1-tosyl-1*H*-indole (3e): Compound **2e** (68 mg, 0.15 mmol) was treated with DDQ (0.15 mmol) in combination with anhydrous $FeCl_3$ (5 mg, 0.03 mmol) and 4Å molecular sieves under argon atmosphere at 60 °C temperature as described for the synthesis of **3a** for 2 h to afford **3e** as an off white solid (54 mg, 0.12 mmol, 83%), m. p. 156-158 °C.^1H NMR ($CDCl_3$, 300 MHz) δ 2.37 (s, 3H), 2.46 (s, 3H), 5.20 (s, 1H), 6.71 (d, *J*= 7.8 Hz,1H), 6.95 (t, *J*= 7.8 Hz,1H),7.04 (d, *J*= 7.8 Hz,1H), 7.19 (dd, *J*= 7.8, 15.6 Hz,2H), 7.25–7.41 (m, 4H), 7.38 (t, *J*= 7.5 Hz, 1H), 7.55 (s, 1H), 7.65 (s, 1H), 7.79 (dd, *J*= 8.4, 15.6 Hz, 3H), 7.93 (d, *J*= 8.4 Hz,1H). ppm. ^{13}C NMR ($CDCl_3$, 125MHz) δ 21.6, 45.4, 113.9, 120.0, 120.3, 120.7, 122.7, 123.2, 124.8, 125.1, 126.9, 127.3, 127.7, 128.4, 129.9, 135.6, 136.0, 137.5, 141.1, 141.2, 143.2, 144.9, 146.5ppm. HRMS: cacld for $C_{29}H_{23}NO_2SNa$ $[M+Na]^+$ 472.1347; found 472.1385.

3-(9*H*-fluoren-9-yl)-5-methyl-1-tosyl-1*H*-indole (3f): Compound **2f** (68 mg, 0.15 mmol) was treated with DDQ(0.15 mmol) in combination with anhydrous $FeCl_3$ (5 mg, 0.03 mmol) and 4Å molecular sieves under argon atmosphere at 60 °C temperature as described for the synthesis of **3a** for 2 h to afford **3f** as an off white solid (59 mg, 0.13 mmol, 88%), m. p. 183-185 °C.^1H NMR ($CDCl_3$, 400 MHz) δ 2.20 (s, 3H), 2.36 (s, 3H), 5.23 (s, 1H), 6.60 (bs, 1H), 7.05 (d, *J*=

8.4 Hz,1H), 7.21–7.26 (m, 4H), 7.29 (d, *J*= 7.2 Hz, 2H), 7.41 (t, *J*= 7.6 Hz, 2H),7.46 (s, 1H), 7.74 (d, *J*= 8.4 Hz, 2H), 7.84 (t, *J*= 8.4 Hz, 3H). ppm. ^{13}C NMR ($CDCl_3$, 100 MHz) δ 21.4, 21.6, 45.6, 113.6, 120.0, 120.2, 122.3, 124.5, 125.0, 126.3, 126.9, 127.4, 127.7, 128.3, 129.9, 130.2, 132.9, 134.1, 135.3, 141.0, 144.9, 146.0 ppm. HRMS: cacld for $C_{29}H_{23}NO_2SNa$ $[M+Na]^+$ 472.1347; found 472.1385.

3-(9*H*-fluoren-9-yl)-5,7-dimethyl-1-tosyl-1*H*-indole (3g): Compound **2g** (70 mg, 0.15 mmol) was treated with DDQ(0.15 mmol) in combination with anhydrous $FeCl_3$ (5 mg, 0.03 mmol)and 4Å molecular sieves under argon atmosphere at 60 °C temperature as described for the synthesis of **3a** for 3.5 h to afford **3g** as an off white solid (57 mg, 0.12 mmol, 82%), m. p. 152-154 °C.^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.16 (s, 3H), 2.37 (s, 3H), 2.54 (s, 3H), 5.21 (s, 1H), 6.51 (bs, 1H), 6.80 (s, 1H), 7.16–7.25 (m, 4H), 7.26–7.28 (m, 2H),7.38–7.53 (m, 5H),7.84 (d, *J*= 7.5 Hz, 2H). ppm. ^{13}C NMR ($CDCl_3$, 75MHz) δ 21.1, 21.7, 21.7, 45.4, 117.7, 120.1, 122.6, 124.9, 125.6, 126.6, 127.4, 127.6, 128.2, 129.7, 130.0, 132.7, 133.5, 134.5, 136.3, 141.0, 144.4, 146.1 ppm. HRMS: cacld for $C_{30}H_{25}NO_2SNa$ $[M+Na]^+$ 486.1504; found 486.1502.

3-(9*H*-fluoren-9-yl)-5-fluoro-1-tosyl-1*H*-indole (3h): Compound **2h** (68 mg, 0.15 mmol) was treated with DDQ (0.15 mmol) in combination with anhydrous $FeCl_3$ (5 mg, 0.03 mmol) and 4Å molecular sieves under argon atmosphere at 60 °C temperature as described for the synthesis of **3a** for 3 h to afford **3h** as a white solid (54 mg, 0.12 mmol, 80%), m. p. 208-210 °C.^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.38 (s, 3H), 5.20 (s, 1H), 6.25 (d, *J*= 8.0 Hz,1H), 6.93 (t, *J*= 8.0 Hz, 1H), 7.24–7.28 (m, 6H),7.43 (t, *J*= 8.0 Hz, 2H), 7.66 (s, 1H), 7.76 (d, *J*= 8.8 Hz,2H), 7.88 (dd, *J*= 8.0, 8.0 Hz, 3H). ppm. ^{13}C NMR ($CDCl_3$, 100 MHz) δ 21.7, 45.7,106.0 (d, $J_{C\text{-}F}$ = 24.0 Hz), 112.9 (d, , $J_{C\text{-}F}$ = 26.0 Hz),114.9 (d, , $J_{C\text{-}F}$ = 9.0 Hz), 122.2 (d, , $J_{C\text{-}F}$ = 4.0 Hz), 125.0, 126.8, 126.9, 127.5, 127.9, 128.3, 129.1, 129.9, 130.0, 130.6, 130.7, 132.3, 135.1, 141.0, 145.2, 145.5, 159.3 (d, , $J_{C\text{-}F}$ = 239.0 Hz),ppm. HRMS: cacld for $C_{28}H_{20}FNO_2SNa$ $[M+Na]^+$ 476.1096; found 476.1091.

3-(9*H*-fluoren-9-yl)-5-(trifluoromethyl)-1-tosyl-1*H*-indole (3i): Compound **2i** (76 mg, 0.15 mmol) was treated with DDQ (0.15 mmol) in combination with anhydrous $FeCl_3$ (5 mg, 0.03 mmol) and 4Å molecular sieves under argon atmosphere at 60 °C temperature as described for the synthesis of **3a** for 3.5 h to afford **3i** as an off white solid (55 mg, 0.11 mmol, 75%), m. p. 170-172 °C.^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.38 (s, 3H), 5.27 (s, 1H), 7.06 (s, 1H), 7.22–7.28 (m, 6H), 7.41–7.47 (m, 3H), 7.62 (s, 1H), 7.77 (d, *J*= 8.4 Hz, 2H), 7.86 (d, *J*= 7.6 Hz, 2H), 8.04

(d, *J*= 8.8 Hz, 1H). ppm. ^{13}C NMR ($CDCl_3$, 100 MHz) δ 21.7, 45.3, 114.2, 117.7 (q, $J_{C\text{-}F}$ = 4.0 Hz), 120.3, 121.6 (q, , $J_{C\text{-}F}$ = 4.0 Hz), 122.6, 123.0, 124.9, 125.1, 125.4, 125.7 (d, , $J_{C\text{-}F}$ = 5.0 Hz), 126.9, 127.6, 128.0, 128.4, 129.6, 130.2, 135.0, 137.2, 141.0, 145.5 (d, , $J_{C\text{-}F}$ = 8.0 Hz).ppm. HRMS: cacld for $C_{29}H_{20}F_3NO_2SNa$ $[M+Na]^+$ 526.1065; found 526.1068.

5-chloro-3-(2-methoxy-9*H*-fluoren-9-yl)-1-tosyl-1*H*-indole (3j): Compound **2j** (75 mg, 0.15 mmol) was treated with DDQ (0.15 mmol) in combination with anhydrous $FeCl_3$ (5 mg, 0.03 mmol) and 4Å molecular sieves under argon atmosphere at 60 ºC temperature as described for the synthesis of **3a** for 3 h to afford **3j** as a pale yellow solid (57 mg, 0.11 mmol, 76%, 1:1.7 dr), m. p. 120-122 °C.^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.36 (s, 3H), 2.37 (s, 5H), 3.74 (s, 3H) 3.75 (s, 5H), 5.13 (s, 1.7H), 5.18 (s, 1H)6.63 (s, 1H), 6.70 (d, *J*= 7.8 Hz,1H), 6.79 (dd, *J*= 1.8, 10.8 Hz,3H), 6.95 (dt, *J*= 2.1, 8.4 Hz,3H), 7.11–7.26 (m, 14H),7.33–7.40 (m, 3H), 7.58 (s, 3H), 7.60–7.61 (m, 10H), 7.72 (d, *J*= 3.3 Hz, 2H), 7.75 (d, *J*= 3.3 Hz, 1H). ppm. ^{13}C NMR ($CDCl_3$, 100 MHz) δ 21.6, 21.7, 45.5, 45.8, 55.5, 55.5, 110.6, 110.7, 113.8, 114.9, 119.3, 119.5, 119.9, 120.3, 120.8, 121.0, 122.0, 123.2, 124.5, 124.7, 124.8, 124.9, 125.2, 125.8, 126.3, 126.4, 126.9, 126.9, 127.7, 127.9, 129.1, 129.8, 130.0, 130.9, 133.9, 134.0, 134.3, 135.0, 140.9, 145.0, 145.0, 145.3, 145.5, 147.4, 147.9, 159.8, 159.8 ppm. HRMS: cacld for $C_{29}H_{22}ClNO_3SNa$ $[M+Na]^+$ 522.0907; found 522.0908.

5-fluoro-3-(2-methoxy-9*H*-fluoren-9-yl)-1-tosyl-1*H*-indole (3k): Compound **2k** (73 mg, 0.15 mmol) was treated with DDQ (0.15 mmol) in combination with anhydrous $FeCl_3$ (5 mg, 0.03 mmol) and 4Å molecular sieves under argon atmosphere at 60 ºC temperature as described for the synthesis of **3a** for 3 h to afford **3k** as a white solid (58 mg, 0.12 mmol, 78%), m. p. 138-140°C.^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.37 (s, 3H), 3.74 (s, 3H), 5.11 (s, 1H), 6.21 (d, *J*= 8.0 Hz,1H), 6.22 (s, 1H), 6.89–6.95 (m, 2H), 7.16 (dd, *J*= 7.6, 13.2 Hz,2H), 7.23–7.25 (m, 2H) 7.36 (t, *J*= 7.2 Hz, 1H), 7.64 (s, 1H), 7.71–7.75 (m, 4H) 7.86 (dd, *J*= 4.4, 8.8 Hz,1H). ppm. ^{13}C NMR ($CDCl_3$, 125MHz) δ 21.7, 45.7, 55.5, 106.0 (d, , $J_{C\text{-}F}$ = 23.7 Hz), 110.7, 112.9 (d, , $J_{C\text{-}F}$ = 25.0 Hz), 113.8, 114.9 (d, , $J_{C\text{-}F}$ = 8.7 Hz), 119.5, 121.0, 122.4 (d, , $J_{C\text{-}F}$ = 3.7 Hz), 124.8, 126.3 (d, , $J_{C\text{-}F}$ = 8.7 Hz), 126.9, 127.4, 127.9, 129.9 (d, , $J_{C\text{-}F}$ = 26.2 Hz), 130.6 (d, , $J_{C\text{-}F}$ = 8.7 Hz), 132.3, 133.9, 135.0, 141.0, 145.1 (d, , $J_{C\text{-}F}$ = 26.2 Hz),147.4, 159.8 159.4 (d, , $J_{C\text{-}F}$ = 238.7 Hz),ppm. HRMS: cacld for $C_{29}H_{22}FNO_3S$ $[M+H]^+$ 484.1383; found 484.1374.

5-methyl-3-(3-methyl-9*H*-fluoren-9-yl)-1-tosyl-1*H*-indole (3l): Compound **2l** (70 mg, 0.15 mmol) was treated with DDQ(0.15 mmol) in combination with anhydrous $FeCl_3$ (5 mg, 0.03

mmol) and 4Å molecular sieves under argon atmosphere at 60 ºC temperature as described for the synthesis of **3a** for 3 h to afford **3l** as an off white solid (56 mg, 0.12 mmol, 80%), m. p. 168-170 °C.^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.20 (s, 3H), 2.35 (s, 3H), 2.46 (s, 3H), 5.17 (s, 1H), 6.61 (bs, 1H), 7.03–7.05 (m, 2H), 7.15–7.26 (m, 5H), 7.39 (dd, *J*= 8.8 , 15.6 Hz, 2H), 7.65 (s, 1H), 7.72 (d, *J*= 8.0 Hz, 2H), 7.81 (d, *J*= 8.4 Hz, 2H). ppm. ^{13}C NMR ($CDCl_3$, 100MHz) δ 21.4, 21.7, 5.2, 113.6, 120.0, 120.0, 120.7, 122.6, 124.4, 124.7, 125.0, 126.2, 126.9, 127.3, 127.6, 128.4, 129.9, 132.8, 134.1, 135.3, 137.4, 141.1, 143.2, 144.8, 146.4ppm. HRMS: cacld for $C_{30}H_{25}NO_2SNa$ $[M+Na]^+$ 486.1504; found 486.1506.

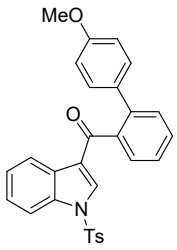
3-(2-methoxy-9*H*-fluoren-9-yl)-1-mesyl-1*H*-indole (3m): Compound **2m** (59 mg, 0.15 mmol) was treated with DDQ (0.15 mmol) in combination with anhydrous $FeCl_3$ (5 mg, 0.03 mmol) and 4Å molecular sieves under argon atmosphere at 60 ºC temperature as described for the synthesis of **3a** for 2 h to afford **3m** as a white solid (47 mg, 0.12 mmol, 81%), m. p. 160-162 °C.^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.13 (s, 3H), 3.80 (s, 3H), 5.26 (s, 1H), 6.91 (d, *J*= 7.6 Hz,1H), 6.95 (s, 1H), 6.99 (d, *J*= 8.4 Hz, 1H), 7.08 (t, *J*= 7.6 Hz, 1H), 7.20 (t, *J*= 7.2 Hz, 1H), 7.28–7.42 (m, 3H), 7.46 (s, 1H), 7.78 (d, *J*= 8.0 Hz, 2H), 7.89 (d, *J*= 8.4 Hz, 1H) .ppm. ^{13}C NMR ($CDCl_3$, 75MHz) δ 40.7, 45.7, 55.6, 110.9, 113.2, 113.7, 119.4, 120.6, 120.9, 122.2, 123.4, 123.9, 125.0, 125.1, 126.4, 127.8, 129.7, 134.0, 135.8, 141.0, 145.5, 147.8, 159.8 ppm. HRMS: cacld for $C_{23}H_{19}NO_3SNa$ $[M+Na]^+$ 412.0983; found 412.0985.

3-(9*H*-fluoren-9-yl)-1-tosyl-1*H*-pyrrolo[2,3-b]pyridine (3n): Compound **2n** (66 mg, 0.15 mmol) was treated with DDQ (0.19 mmol) in combination with anhydrous $FeCl_3$ (5 mg, 0.03 mmol) and 4Å molecular sieves under argon atmosphere at 60 ºC temperature for 5 h to afford **3n** as an off white solid (44 mg, 0.10 mmol, 66%),The organic extract was dried over anhydrous Na_2SO_4 and product was purified by column chromatography (silica gel, 60-120 mesh), eluting with pet ether/EtOAc 97:5 (v/v),m. p. 176-178 °C.^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.38 (s, 3H), 5.21 (s, 1H), 6.75–6.84 (m, 2H), 7.20–7.31 (m, 6H), 7.38–7.43 (m, 2H), 7.84 (t, *J*= 4.2 Hz, 3H), 8.08–8.12 (m, 2H), 8.27 (dd, *J*= 1.8, 4.5 Hz, 1H). ppm. ^{13}C NMR ($CDCl_3$, 100 MHz) δ 21.7, 46.0, 118.5, 118.6, 120.2, 121.7, 124.2, 125.2, 127.5, 127.9, 128.2, 128.7, 129.7, 135.6, 140.9, 145.0, 145.2, 145.6, 147.9 ppm. HRMS: cacld for $C_{27}H_{20}N_2O_2S$ $[M+H]^+$ 437.1324; found 437.1322.

3-(9*H*-fluoren-9-yl)-5-methyl-1-tosyl-1*H*-pyrrolo[2,3-b]pyridine (3o): Compound **2o** (68 mg, 0.15 mmol) was treated with DDQ (0.19 mmol) in combination with anhydrous $FeCl_3$ (5

mg, 0.03 mmol) and 4Å molecular sieves under argon atmosphere at 60 ºC temperature for 5 h to afford **3o** as a white solid (45 mg, 0.10 mmol, 68%),The organic extract was dried over anhydrous Na_2SO_4 and product was purified by column chromatography (silica gel, 60-120 mesh), eluting with pet ether/EtOAc 97:5 (v/v),m. p. 194-196 °C.^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.03 (s, 3H), 2.31 (s, 3H), 5.11 (s, 1H), 6.52 (s, 1H), 7.15–7.24 (m, 6H), 7.34 (t, *J*= 7.6 Hz, 2H), 7.68 (s, 1H), 7.77 (d, *J*= 7.6 Hz, 2H), 7.98–8.05 (m, 3H). ppm. ^{13}C NMR ($CDCl_3$, 100 MHz) δ 18.4, 21.7, 46.0, 118.3, 120.2, 121.7, 124.4, 125.1, 127.5, 127.9, 128.0, 128.1, 128.6, 129.7, 135.7, 141.0, 145.0, 145.7, 145.9, 146.5 ppm. HRMS: cacld for $C_{28}H_{23}N_2O_2SNa$ $[M+Na]^+$ 473.1300; found 473.1303.

2.4.7 NMR data of compound 3-indolyl biphenyl ketone:



^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.37 (s, 3H), 3.69 (s, 3H), 6.75 (d, *J*= 8.0 Hz, 2H), 7.24 (t, *J*= 8.0 Hz, 3H), 7.31 (d, *J*= 8.0 Hz, 3H), 7.45 (t, *J*= 8.0 Hz, 1H), 7.53 (t, *J*= 8.0 Hz, 2H), 7.54–7.58 (m, 3H), 7.61 (s, 1H), 7.74 (t, *J*= 8.0 Hz, 1H), 8.28 (t, *J*= 8.0 Hz, 1H). ppm. ^{13}C NMR ($CDCl_3$, 75 MHz) δ 21.8, 55.2, 113.0, 114.2, 123.1, 124.8, 125.7, 127.2, 127.8, 128.6, 130.0, 130.2, 130.4, 130.5, 133.0, 134.5, 134.7, 135.2, 139.6, 145.8, 159.8, 193.9 ppm. HRMS: cacld for $C_{29}H_{23}NO_4SNa$ $[M+Na]^+$ 504.1245; found 504.1241.

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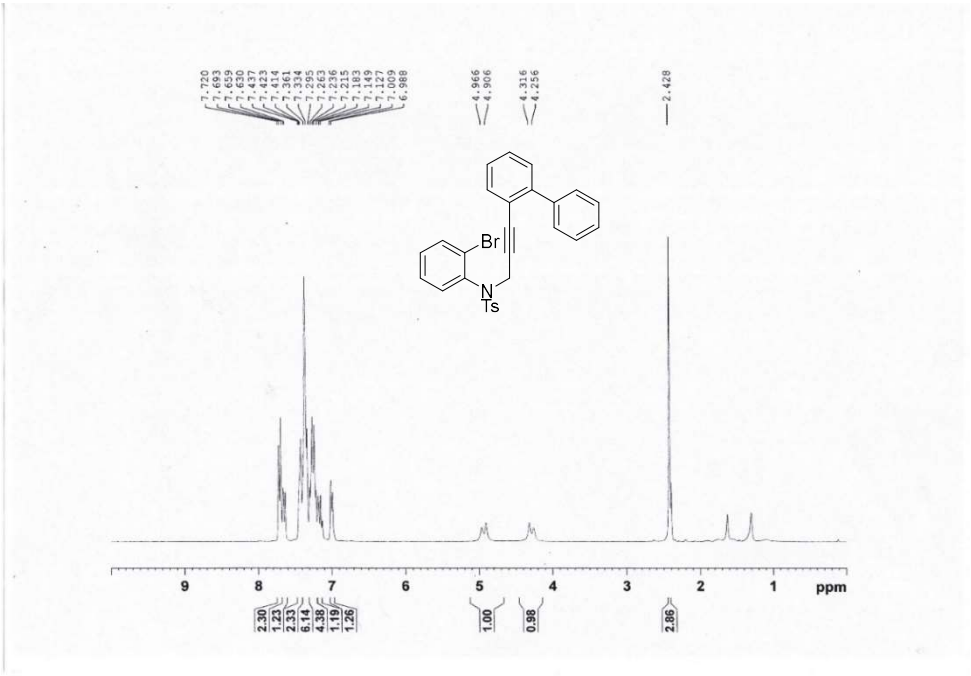
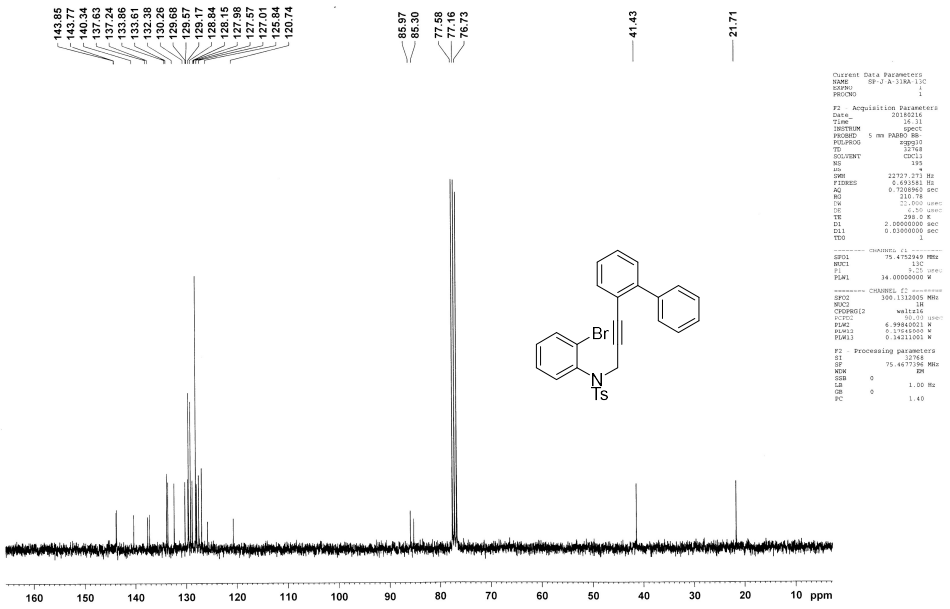
2.6 ^{1}H AND ^{13}C NMR SPECTRA OF SOME SYNTHESIZED COMPOUNDS

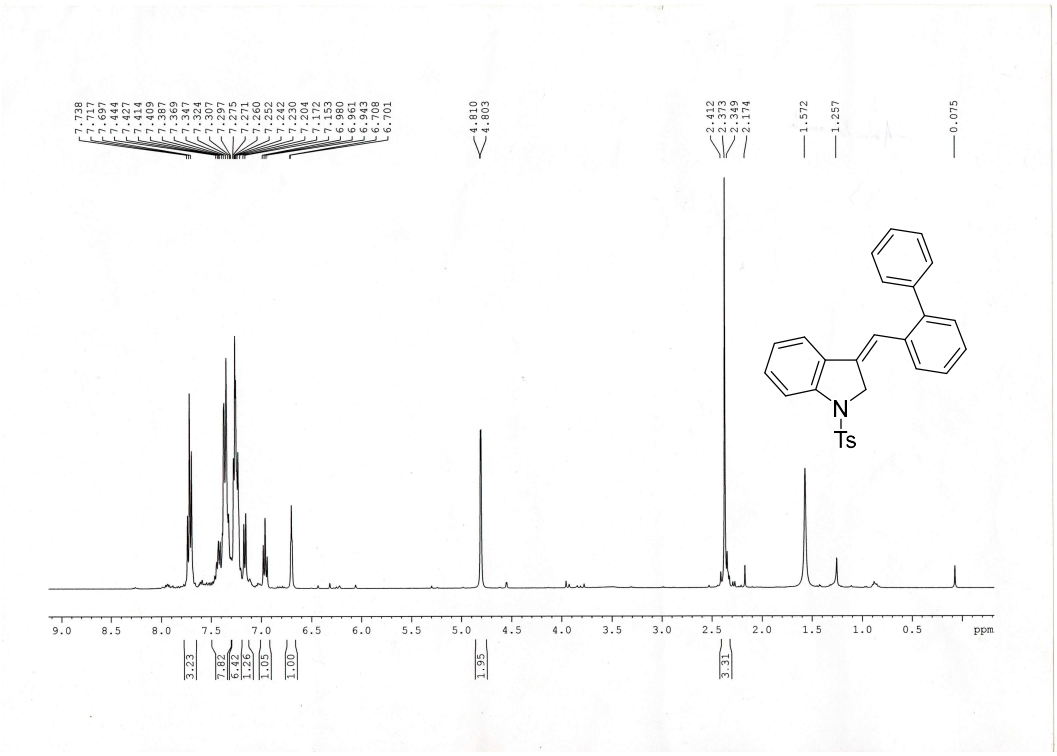
^{1}H NMR of 1a, $CDCl_3$, 300 MHz



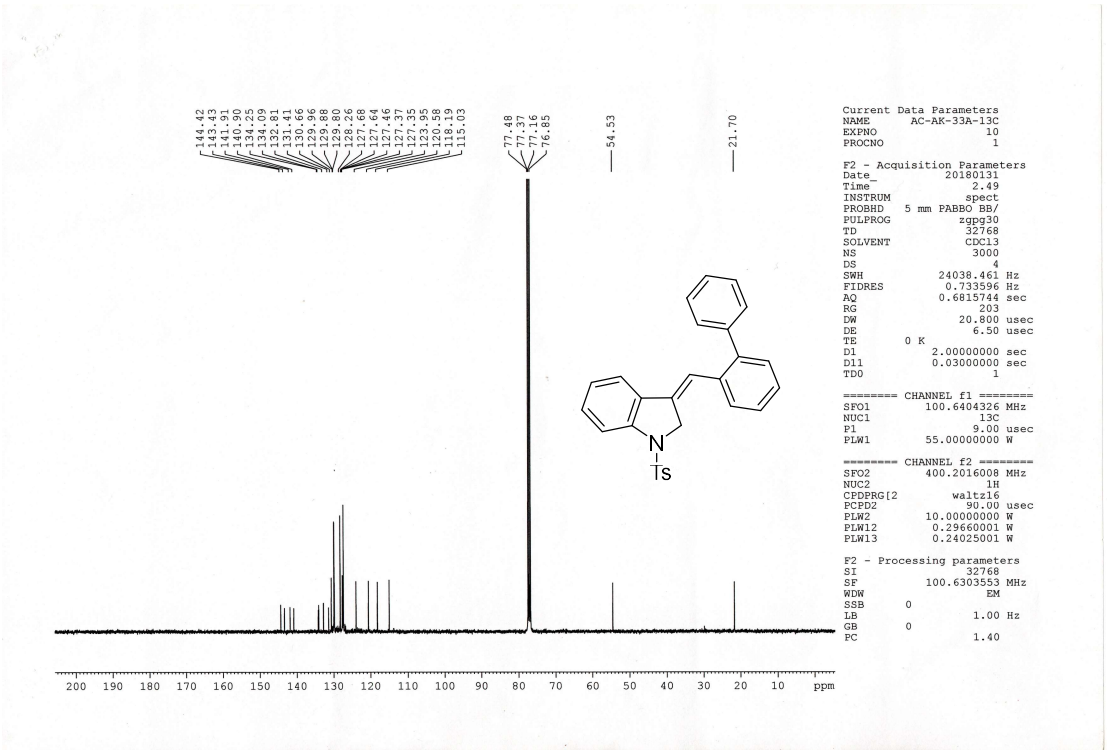
^{13}C NMR of 1a, $CDCl_3$, 75 MHz



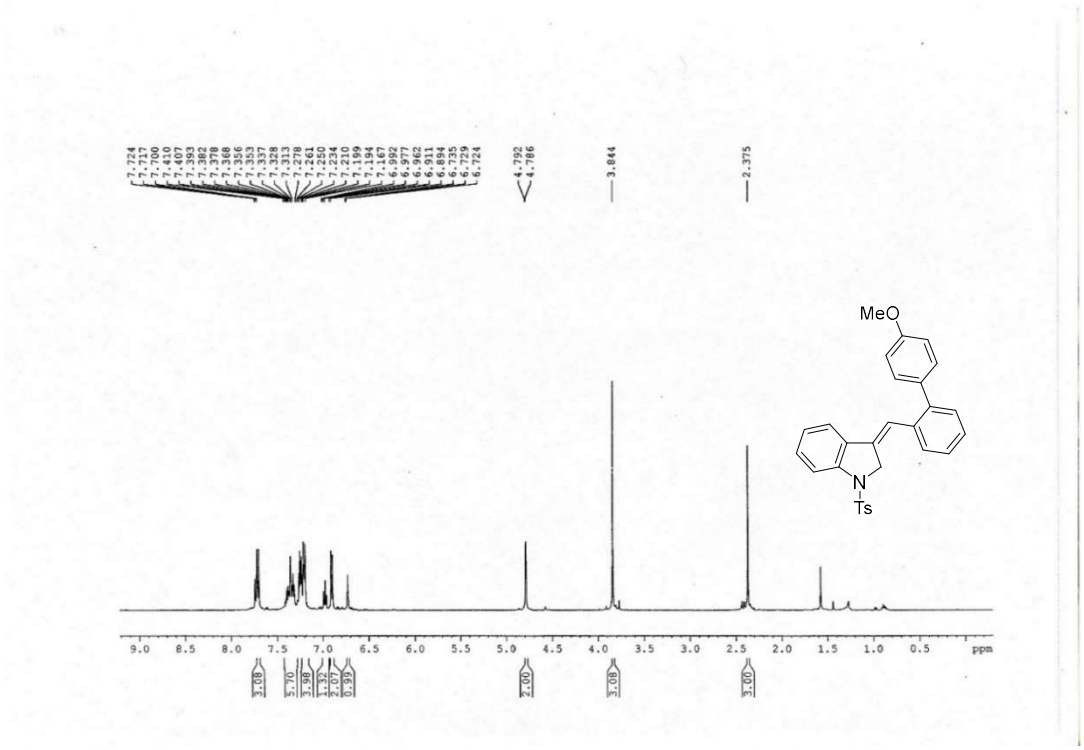
^{1}H NMR of 2a, $CDCl_3$, 400 MHz



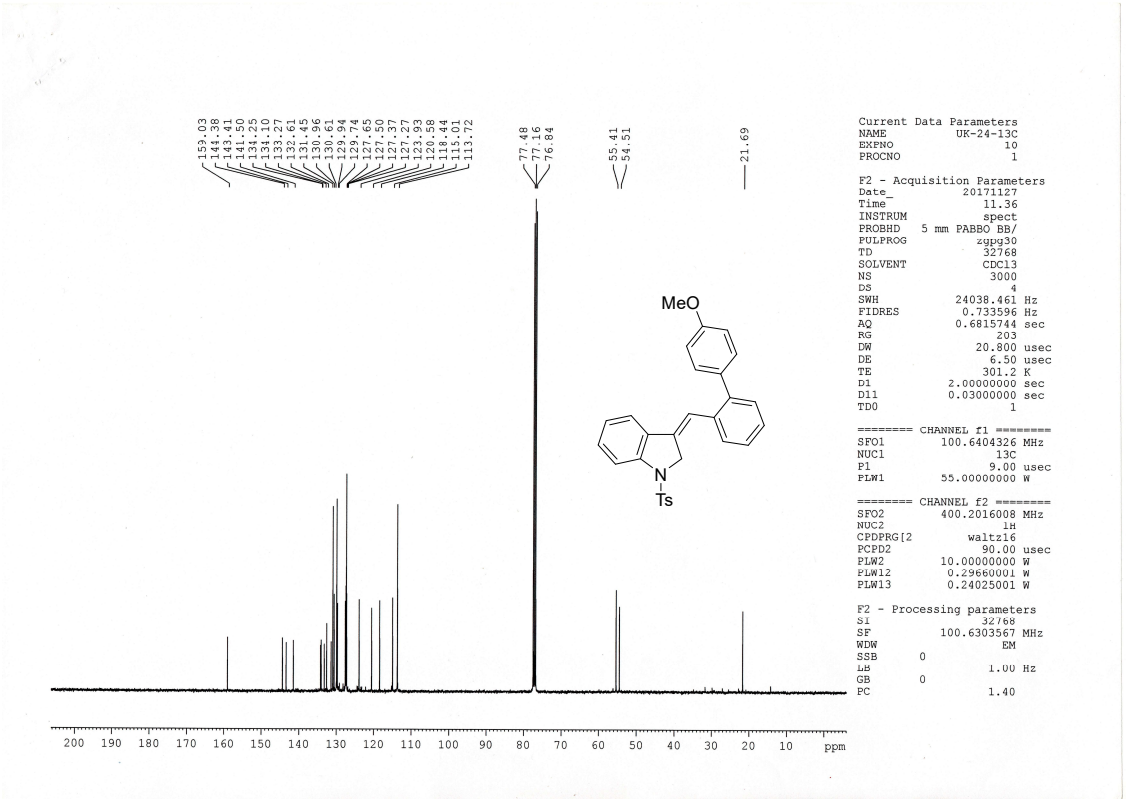
^{13}C NMR of 2a, $CDCl_3$, 100 MHz



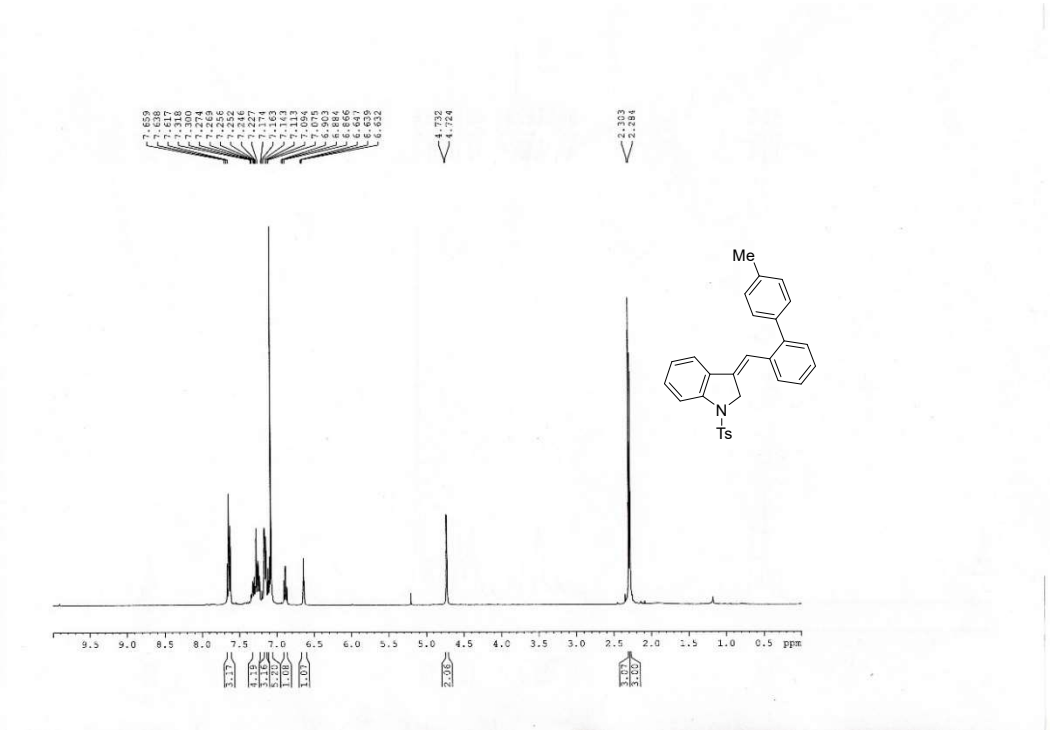
^{1}H NMR of 2b, $CDCl_3$, 500 MHz



^{13}C NMR of 2b, $CDCl_3$, 100 MHz



^{1}H NMR of 2c, $CDCl_3$, 400 MHz



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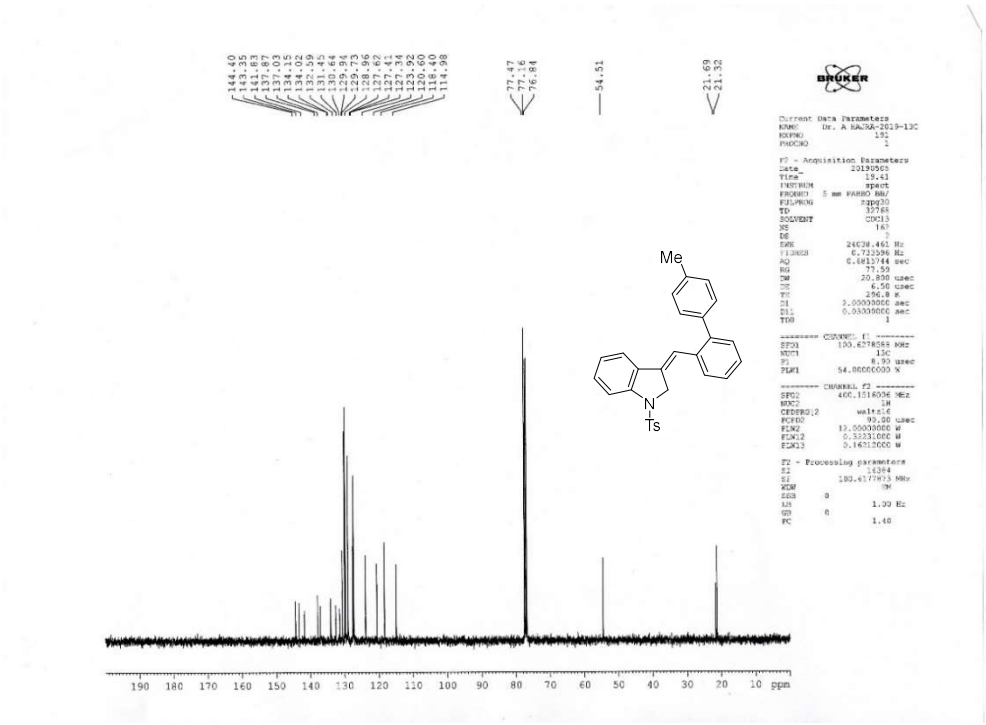

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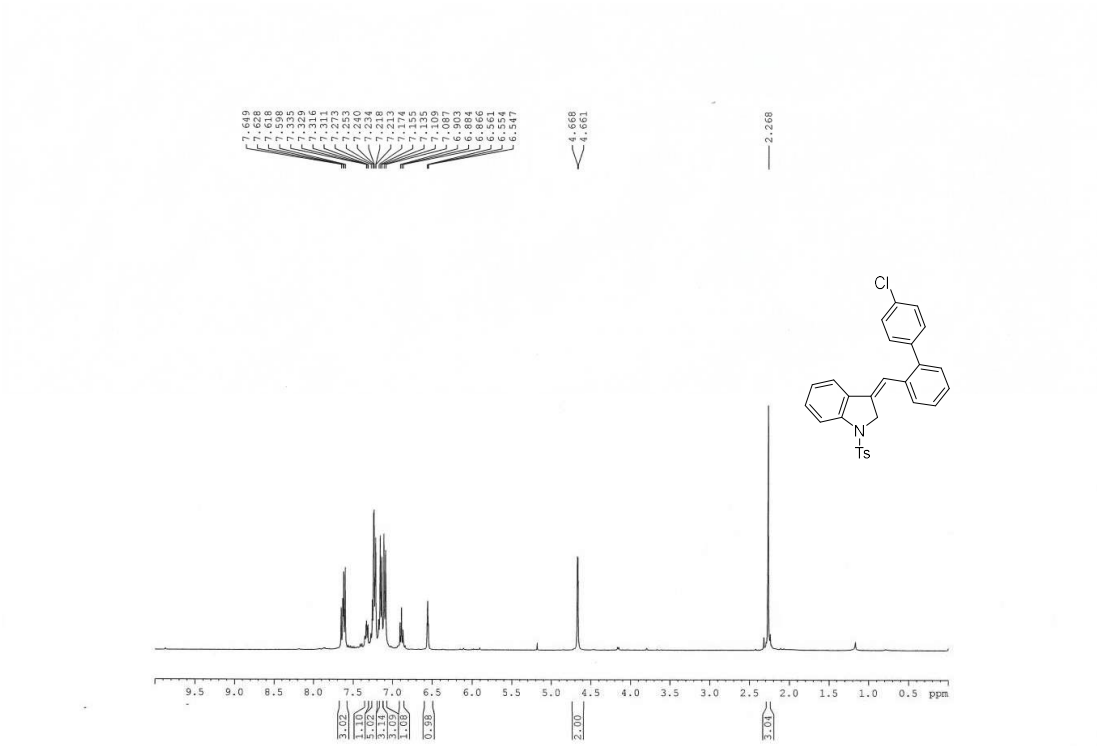

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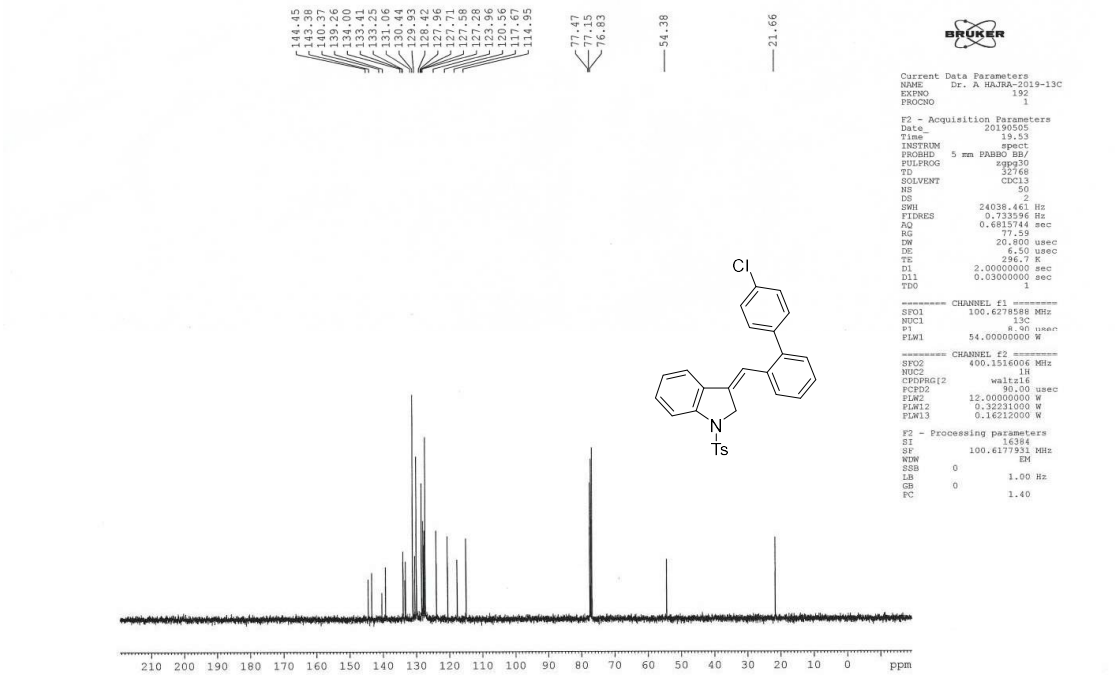
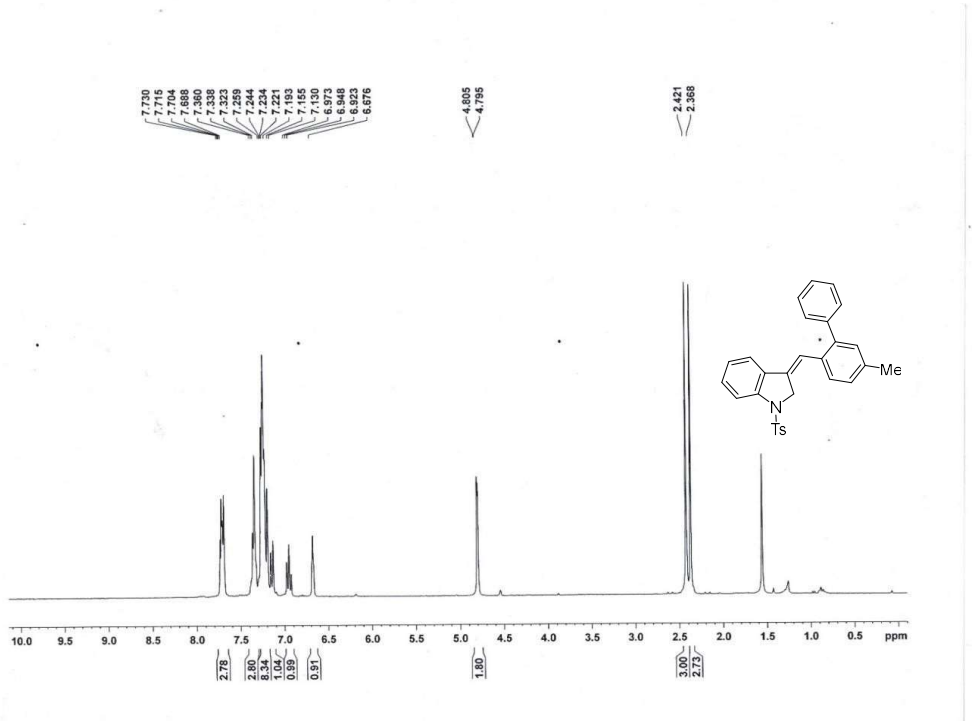
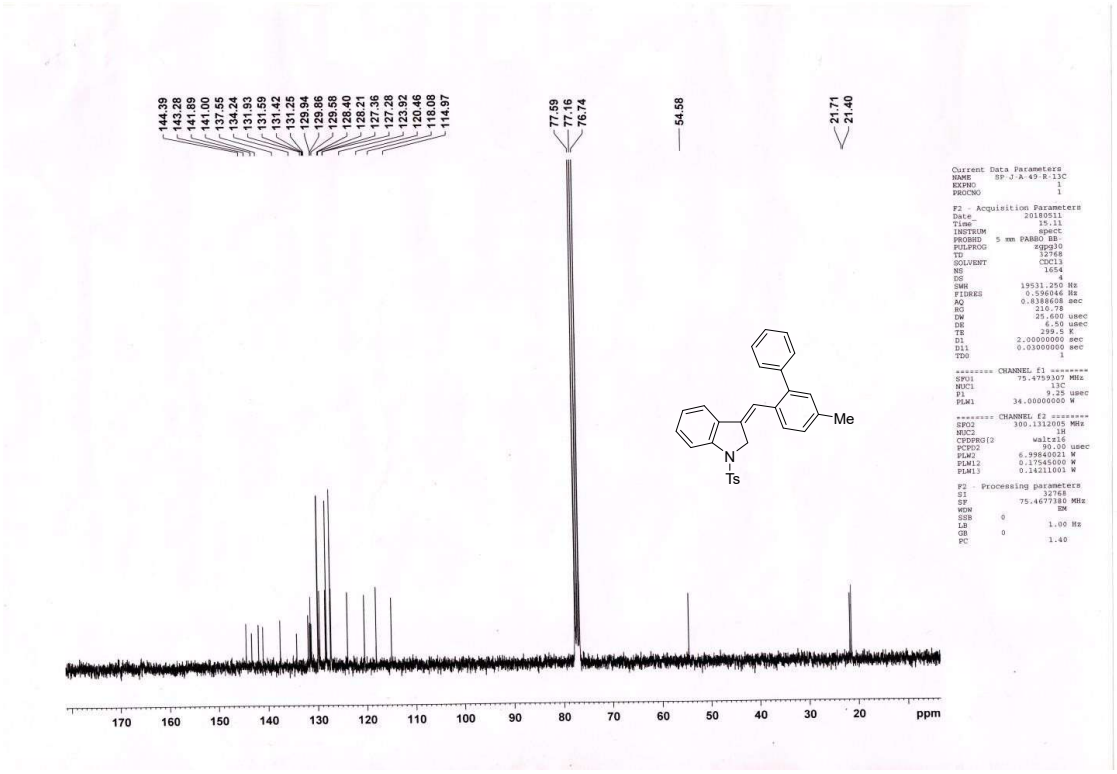


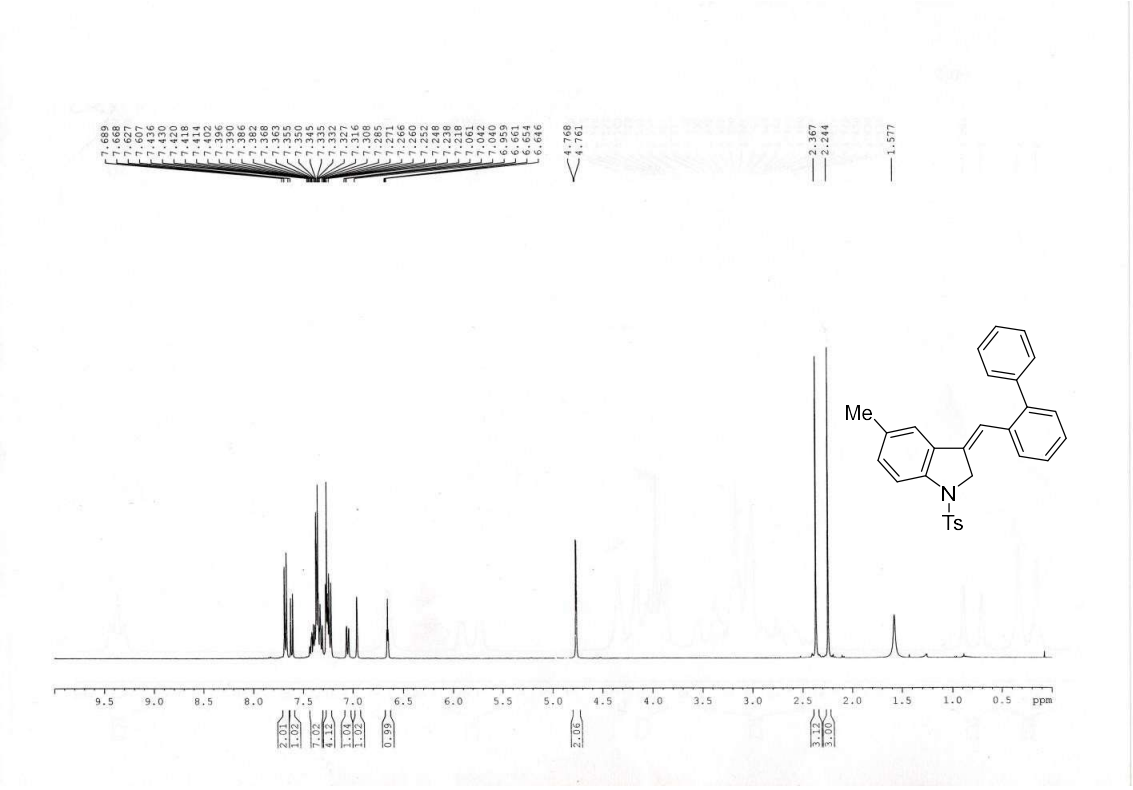
^{1}H NMR of 2e, $CDCl_3$, 300 MHz



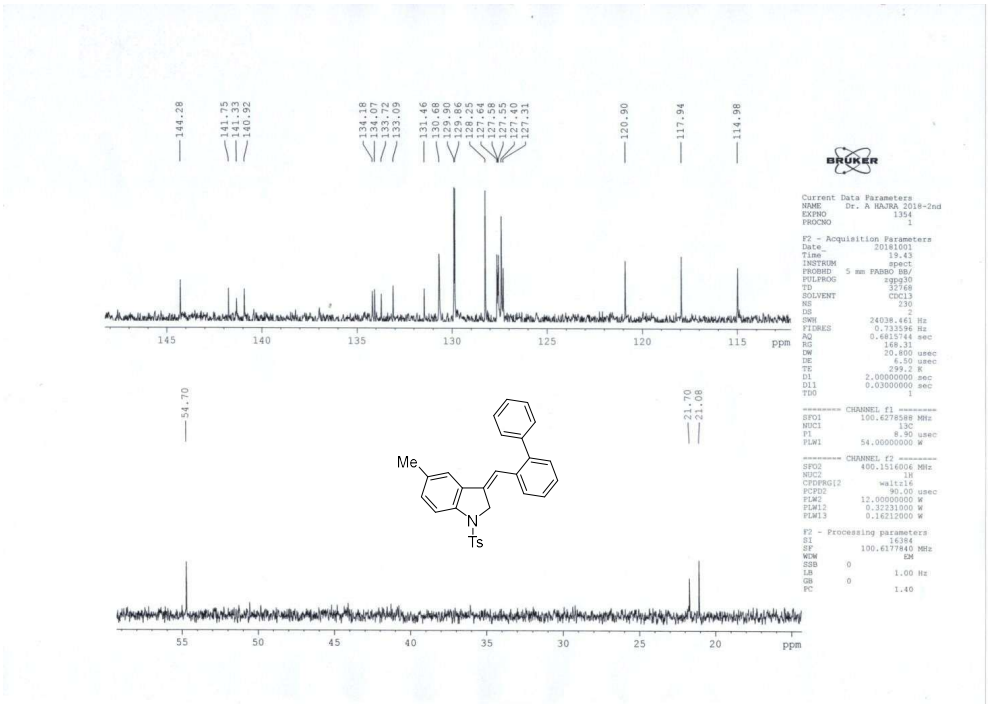
^{13}C NMR of 2e, $CDCl_3$, 75 MHz



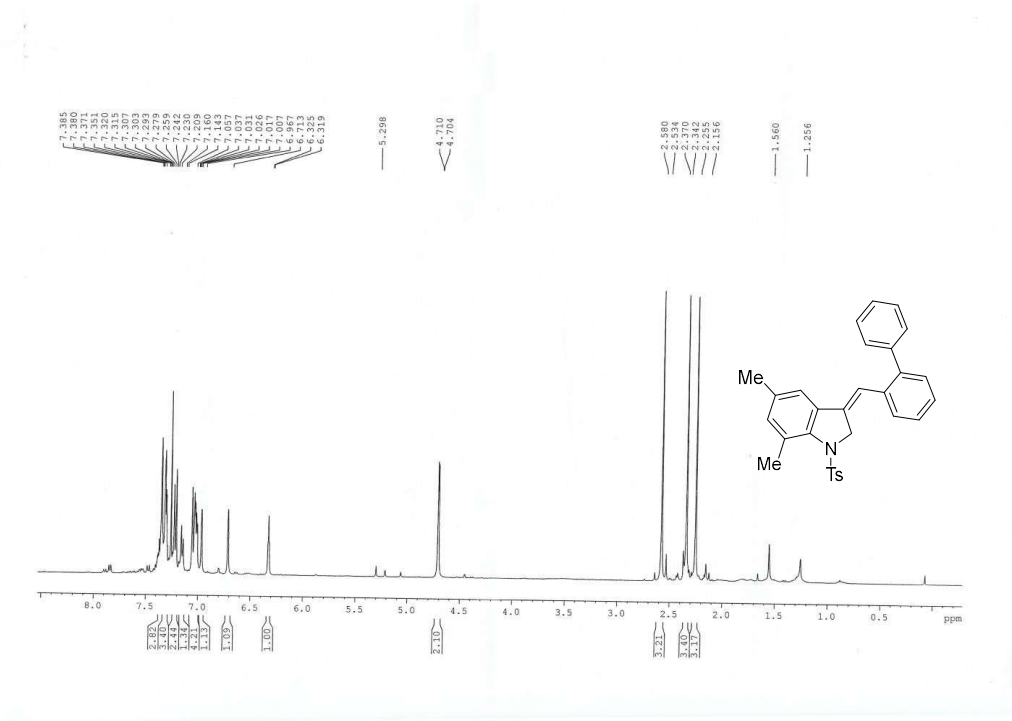
^{1}H NMR of 2f, $CDCl_3$, 400 MHz



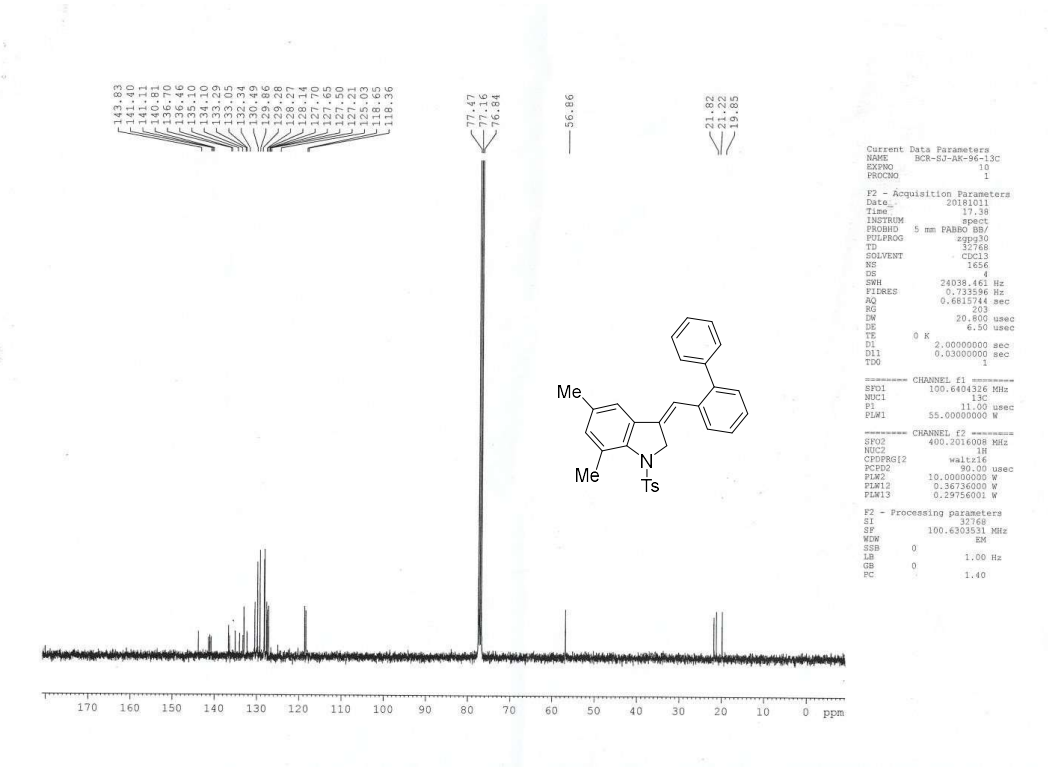
^{13}C NMR of 2f, $CDCl_3$, 100 MHz



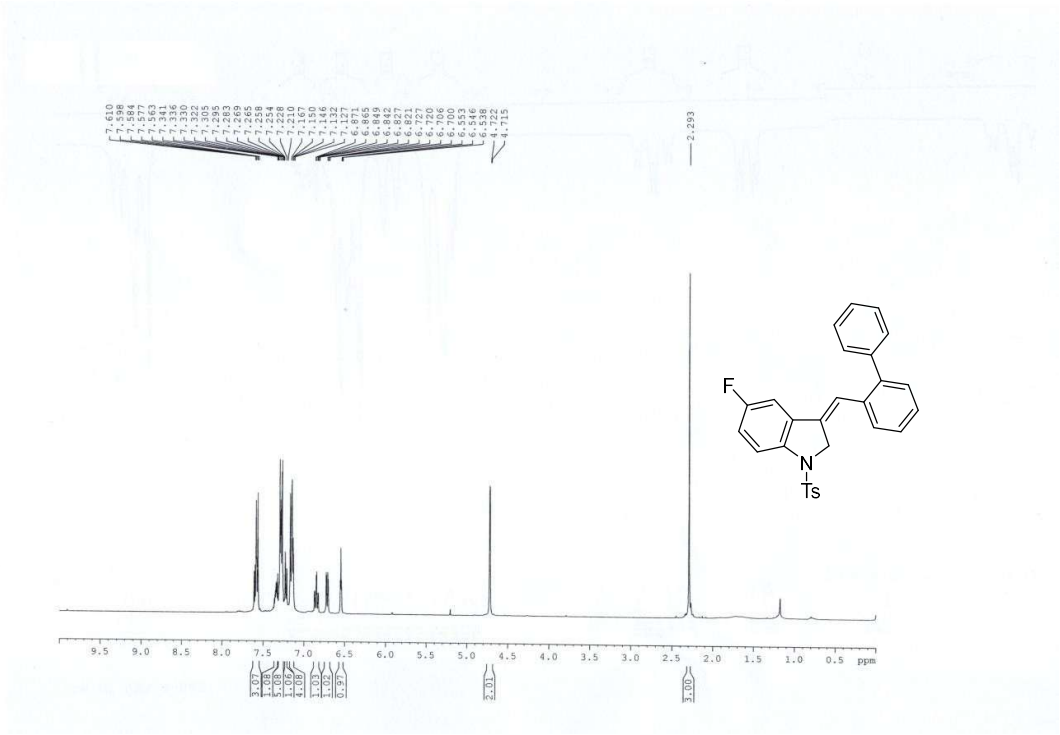
^{1}H NMR of 2g, $CDCl_3$, 400 MHz



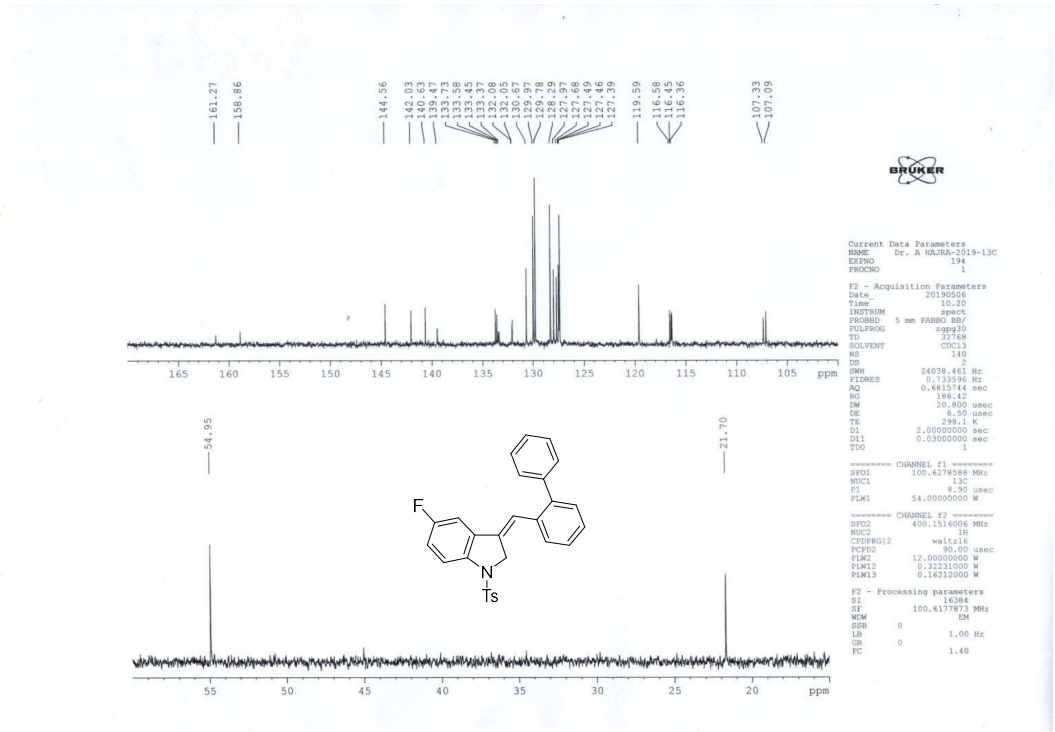
^{13}C NMR of 2g, $CDCl_3$, 100 MHz



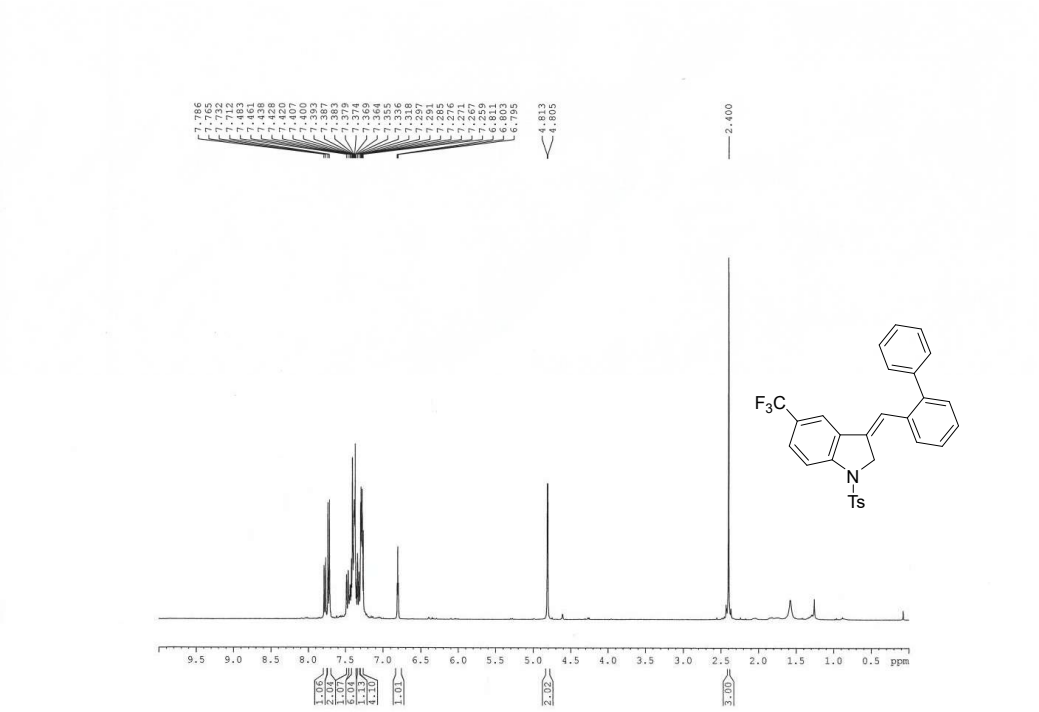
^{1}H NMR of 2h, $CDCl_3$, 400 MHz



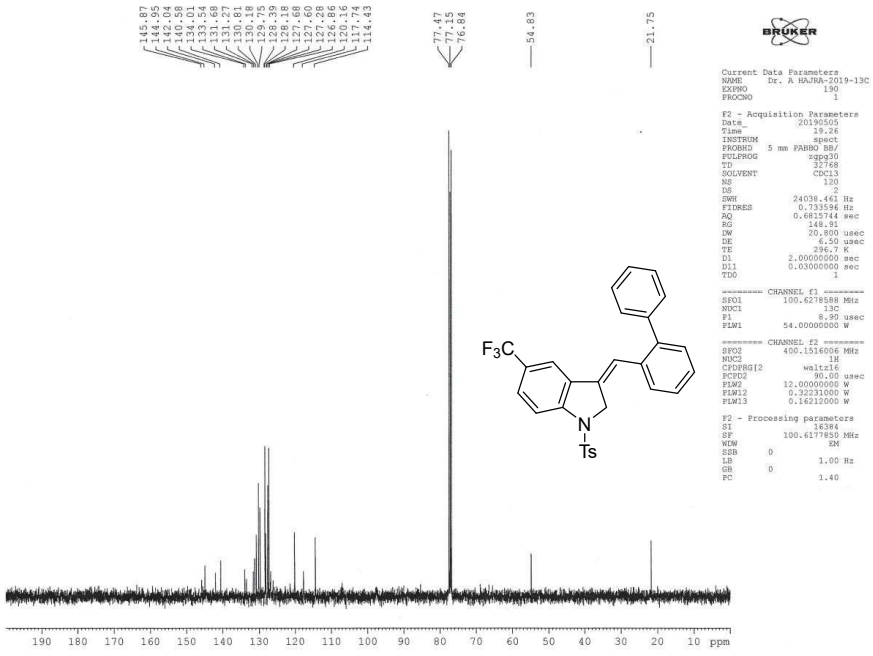
^{13}C NMR of 2h, $CDCl_3$, 100 MHz



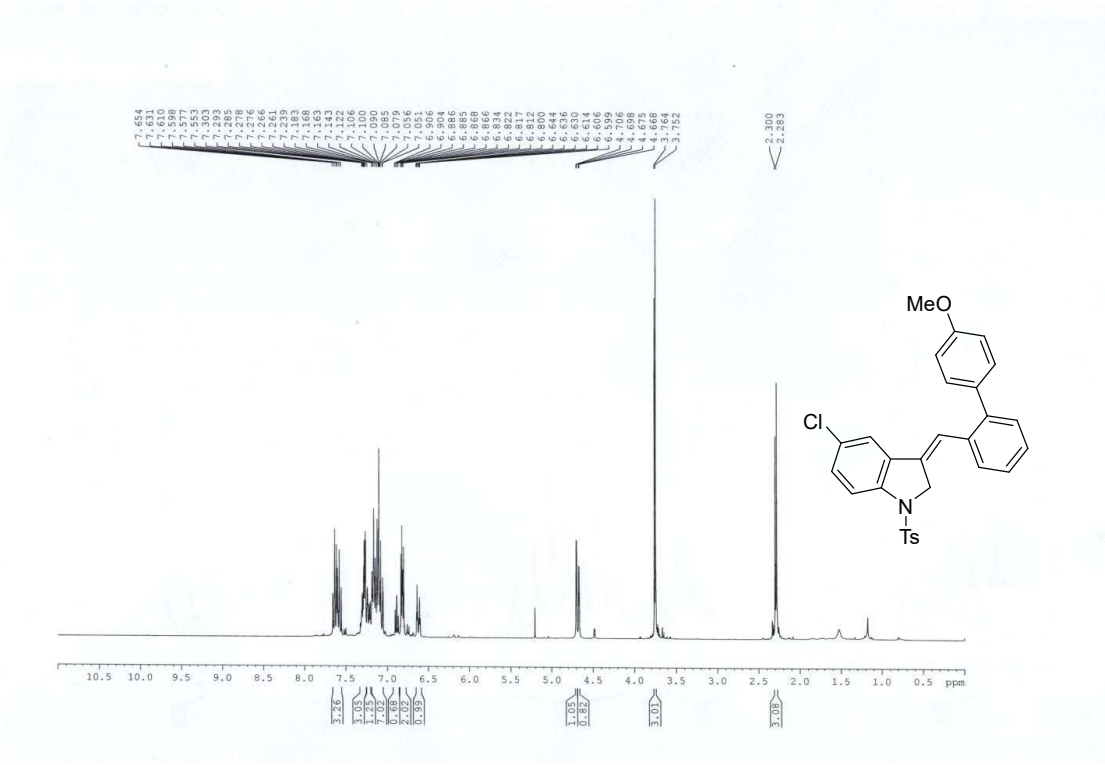
^{1}H NMR of 2i, $CDCl_3$, 400 MHz



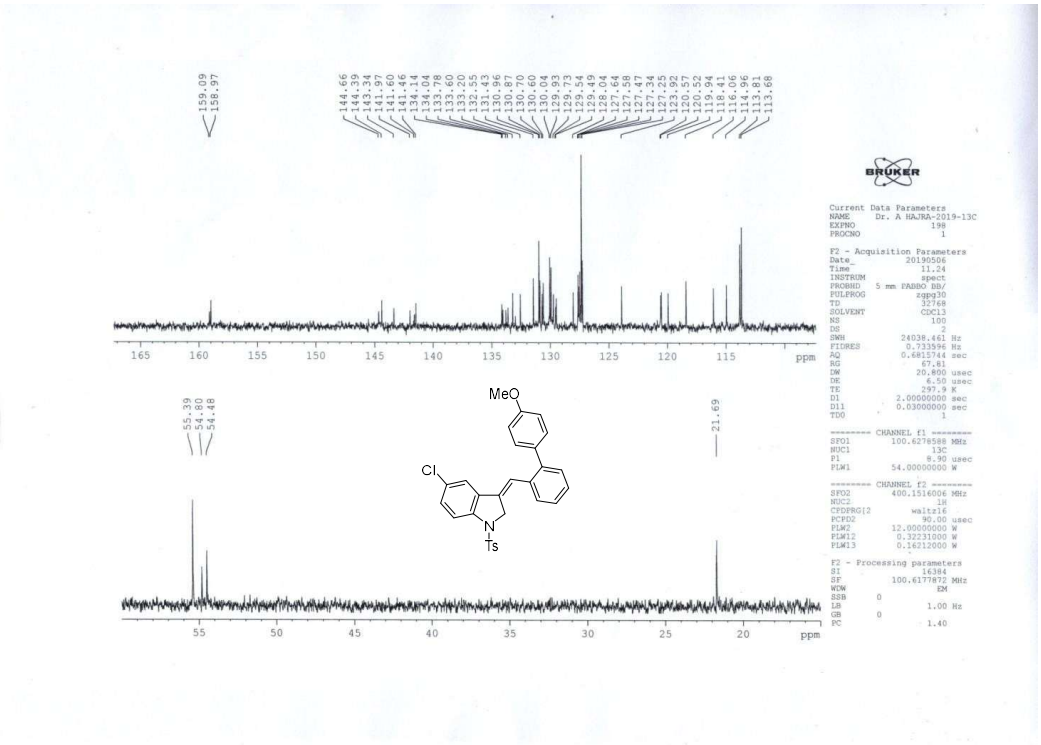
^{13}C NMR of 2i, $CDCl_3$, 100 MHz



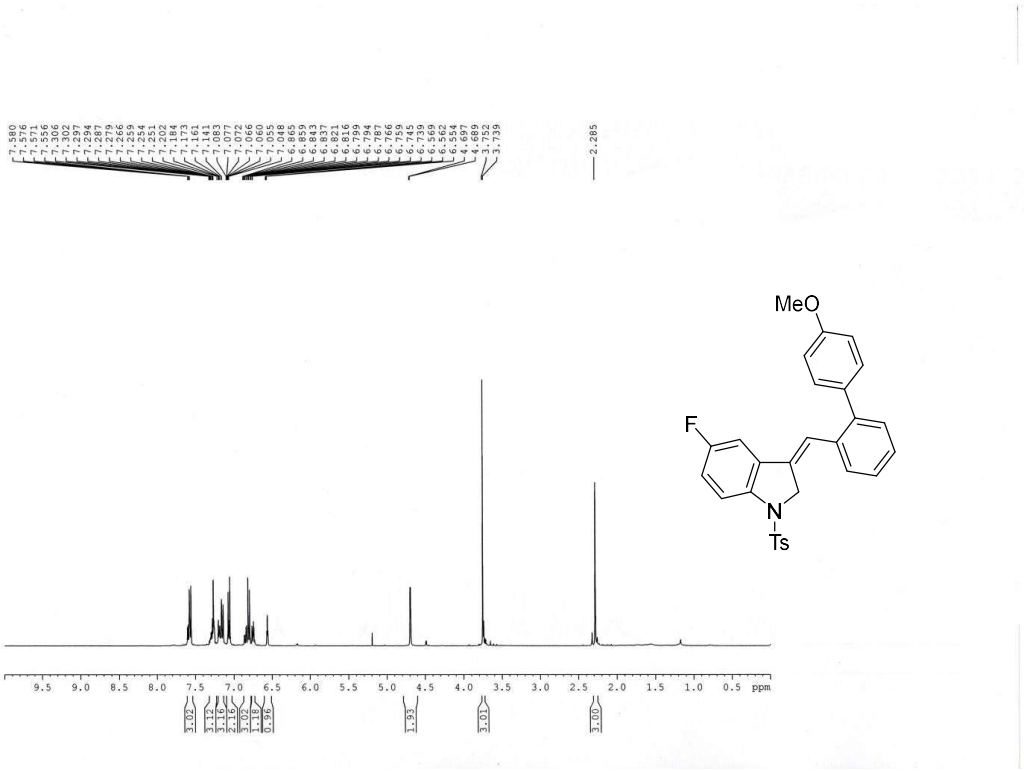
^{1}H NMR of 2j, $CDCl_3$, 400 MHz



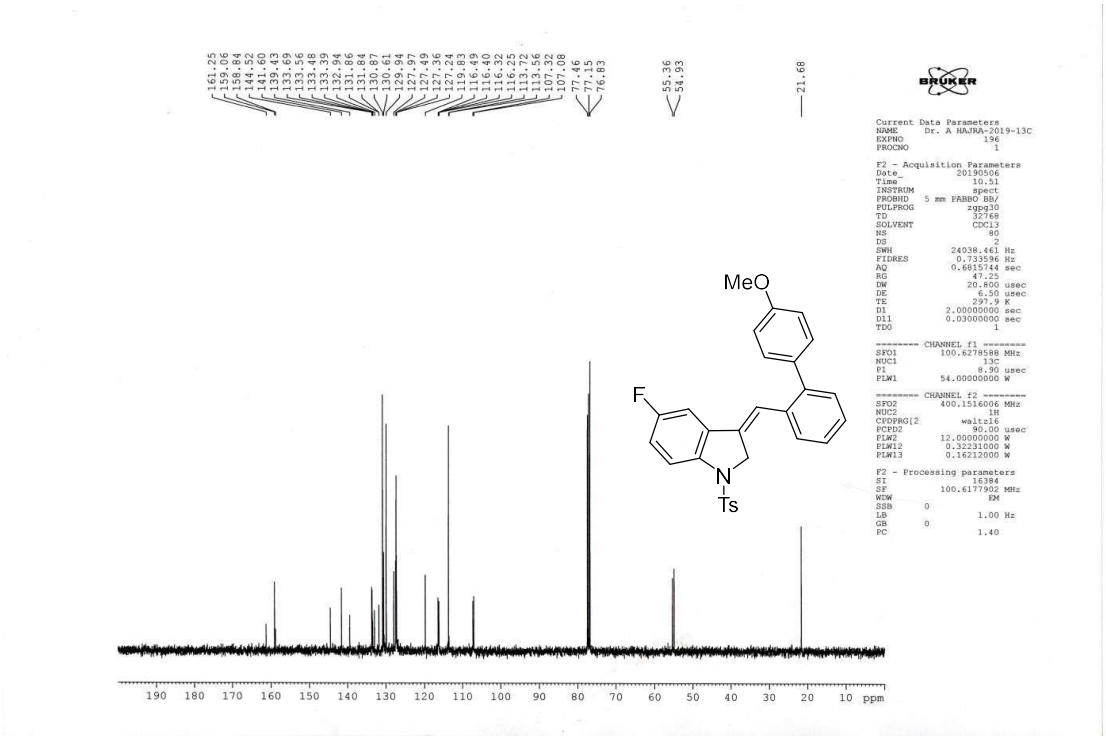
^{13}C NMR of 2j, $CDCl_3$, 100 MHz



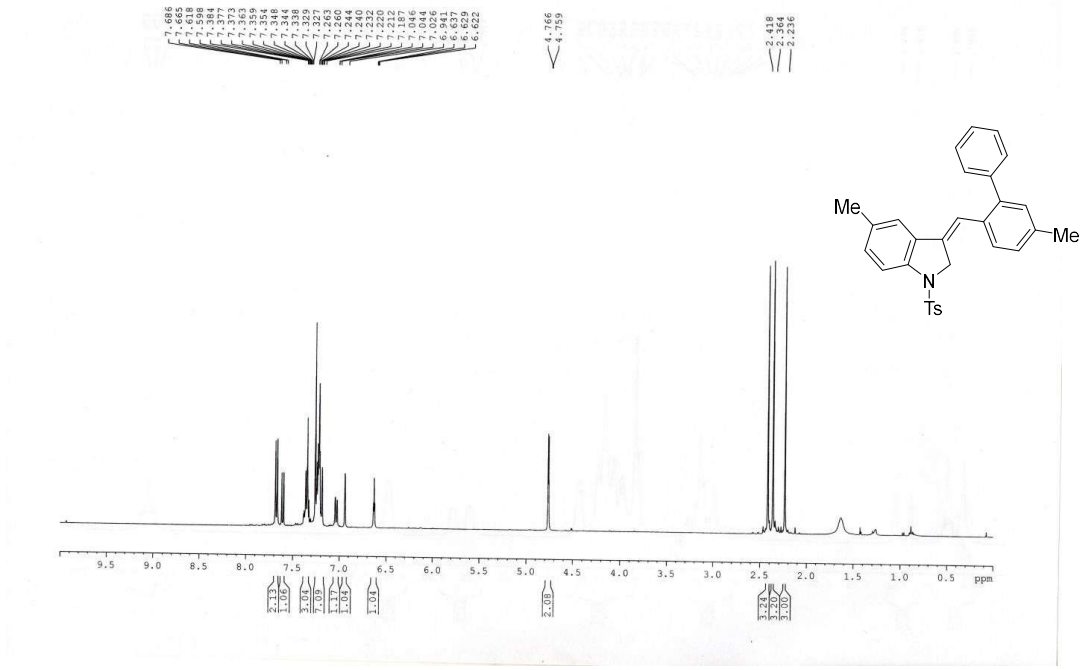
^{1}H NMR of 2k, $CDCl_3$, 400 MHz



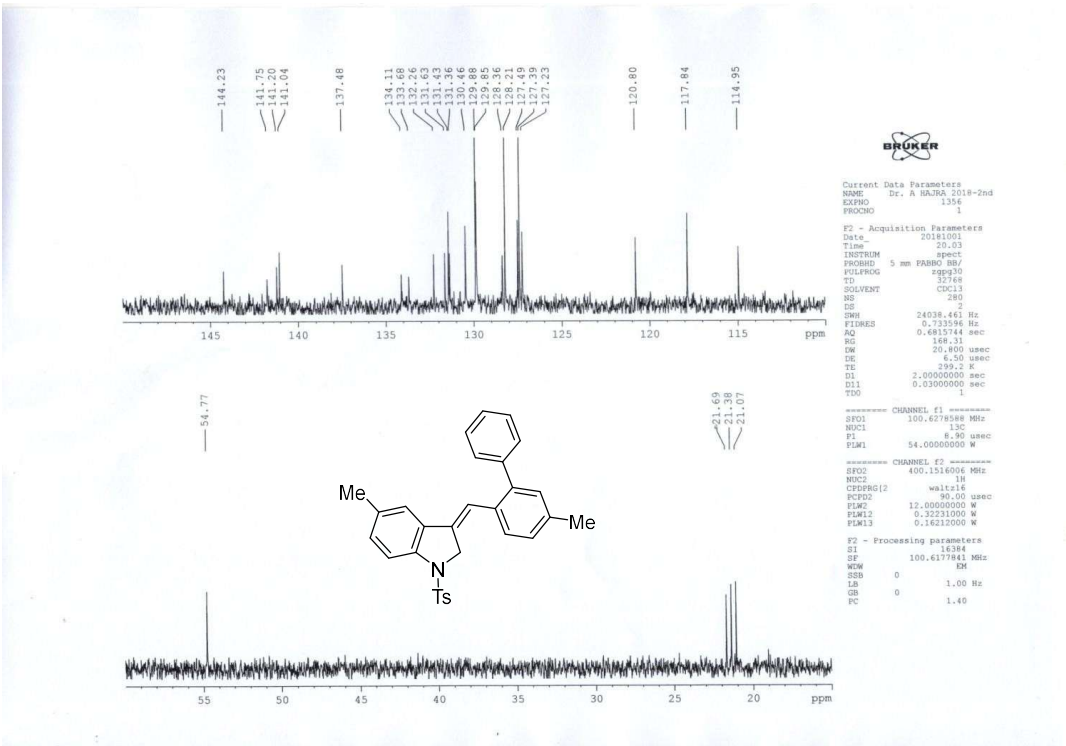
^{13}C NMR of 2k, $CDCl_3$, 100 MHz



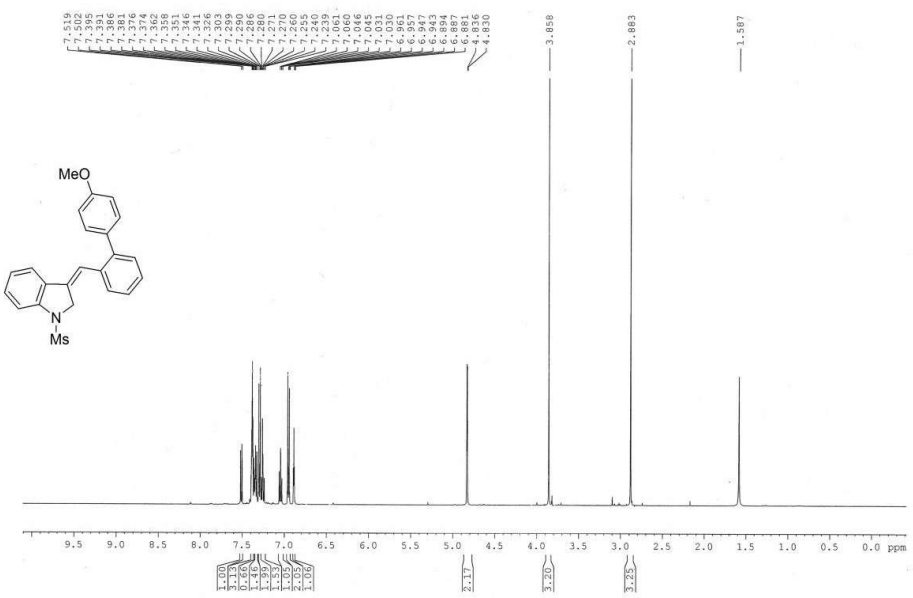
^{1}H NMR of 2l, $CDCl_3$, 400 MHz



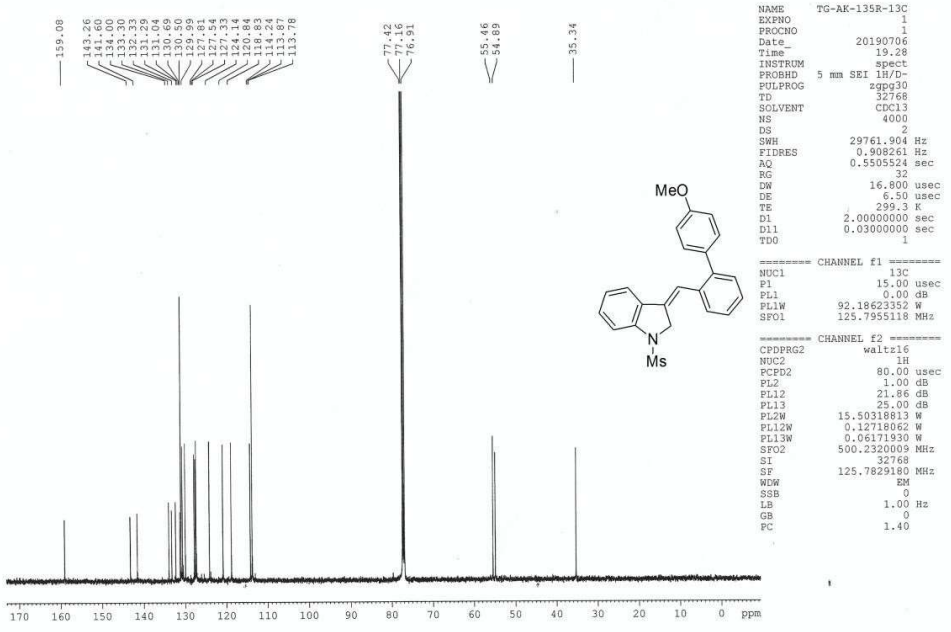
^{13}C NMR of 2l, $CDCl_3$, 100 MHz



^{1}H NMR of 2m, $CDCl_3$, 500 MHz



^{13}CNMR of 2m, $CDCl_3$, 125 MHz



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FIDRES	0.908261 Hz
AQ	0.5505524 sec
RG	32
DW	16.800 usec
DE	6.50 usec
TE	299.3 K
D1	2.00000000 sec
D11	0.03000000 sec
TD0	1
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NUC1	13C
P1	15.00 usec
PL1	0.00 dB
PL1W	92.18623352 W
SFO1	125.7955118 MHz
======== CHANNEL f2 ========	
CPDPRG2	waltz16
NUC2	1H
PCPD2	80.00 usec
PL2	1.00 dB
PL12	21.86 dB
PL13	25.00 dB
PL2W	15.50318813 W
PL12W	0.12718062 W
PL13W	0.06171930 W
SFO2	500.2320009 MHz
SI	32768
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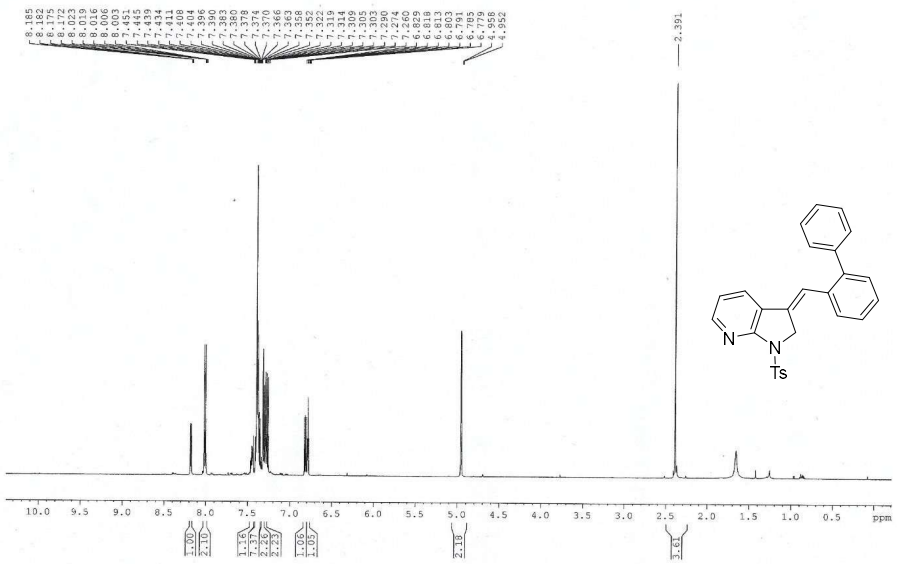
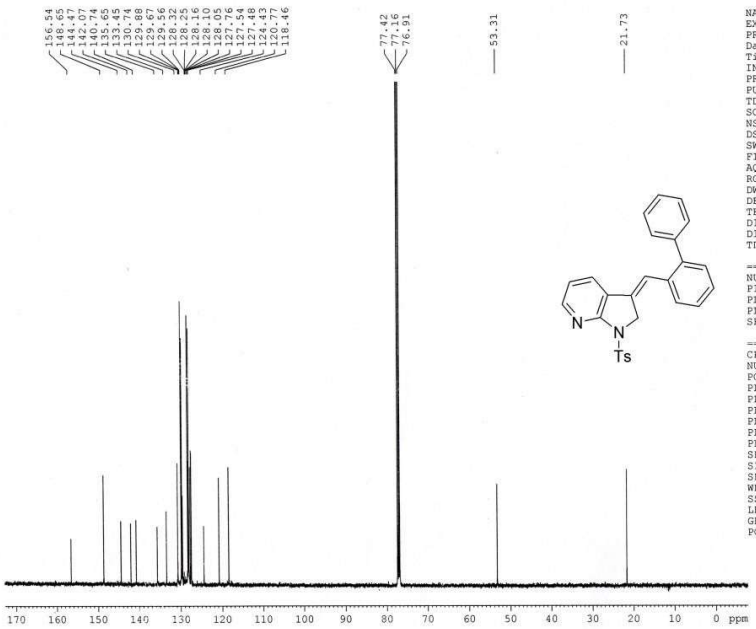
WDW	EM
SSB	0
LB	1.00 Hz
GB	0
PC	1.40

^{1}H NMR of 2n, $CDCl_3$, 500 MHz



^{13}C NMR of 2n, $CDCl_3$, 125 MHz

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SOLVENT               CDCl3
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SWH               29761.904 Hz
FIDRES            0.908261 Hz
AQ                0.5505524 sec
RG                       32
DW                   16.800 usec
DE                    6.50 usec
TE                   298.7 K
D1                2.00000000 sec
D11               0.03000000 sec
TD0                       1

======== CHANNEL f1 ========
NUC1                    13C
P1                   15.00 usec
PL1                   0.00 dB
PL1W          92.18623352 W
SFO1         125.7955118 MHz

======== CHANNEL f2 ========
CPDPRG2              waltz16
NUC2                    1H
PCPD2                80.00 usec
PL2                   1.00 dB
PL12                 21.86 dB
PL13                 25.00 dB
PL2W          15.50318813 W
PL12W          0.12718062 W
PL13W          0.06171930 W
SFO2         500.2320009 MHz
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SF           125.7829193 MHz
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GB                       0
PC                    1.40
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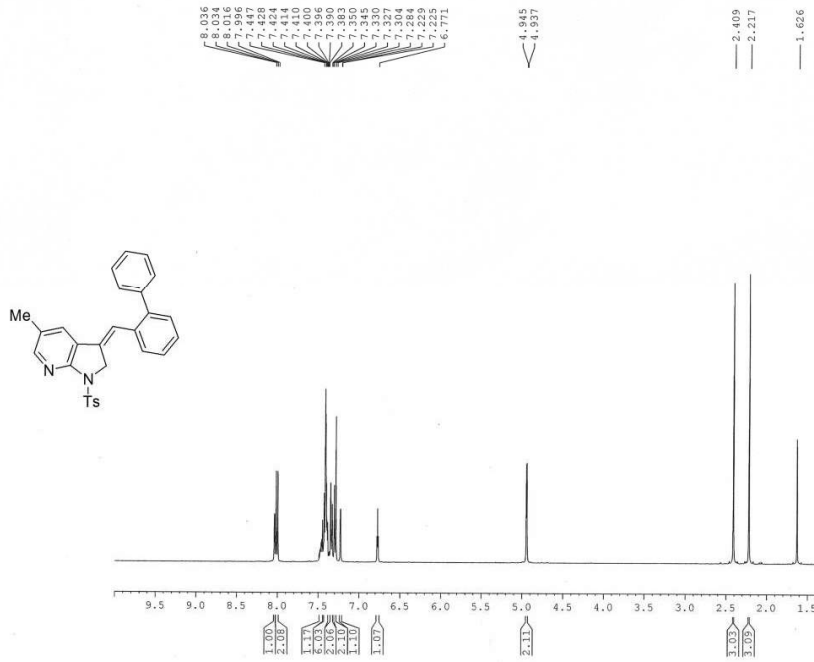
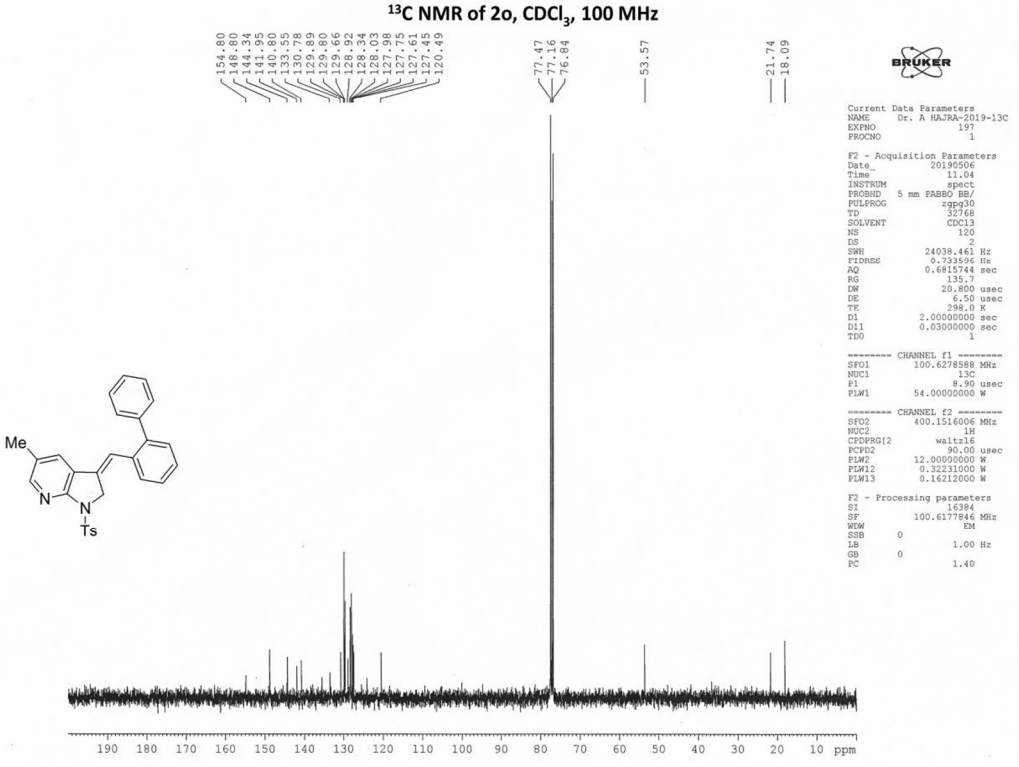
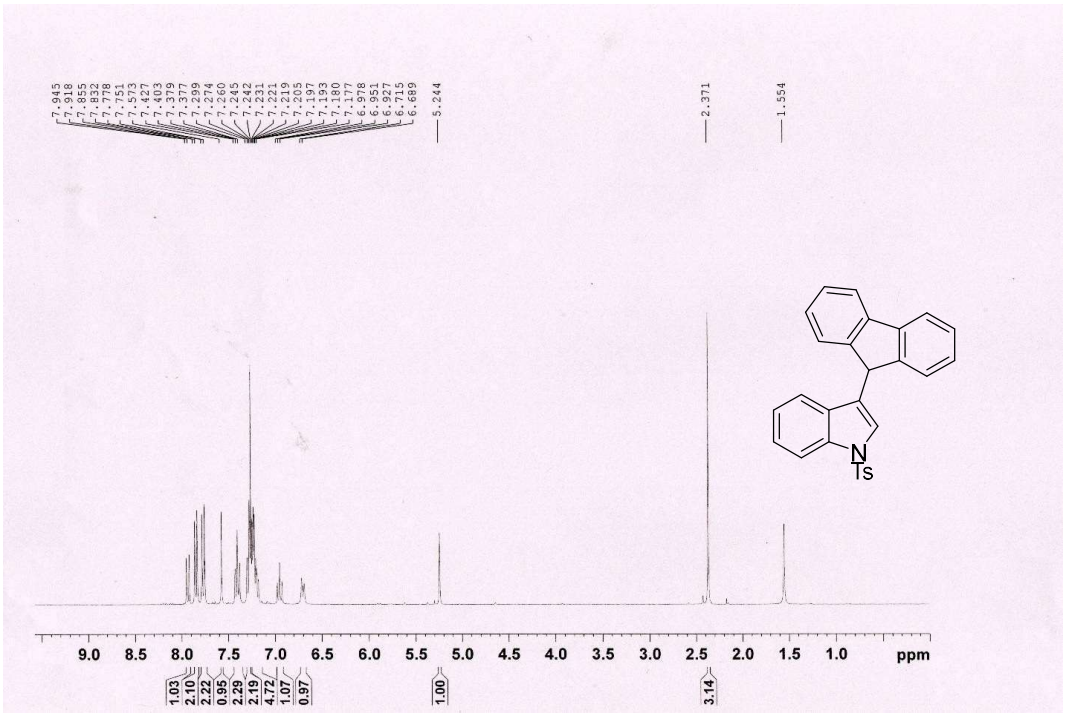
^{1}H NMR of 2o, $CDCl_3$, 400 MHz



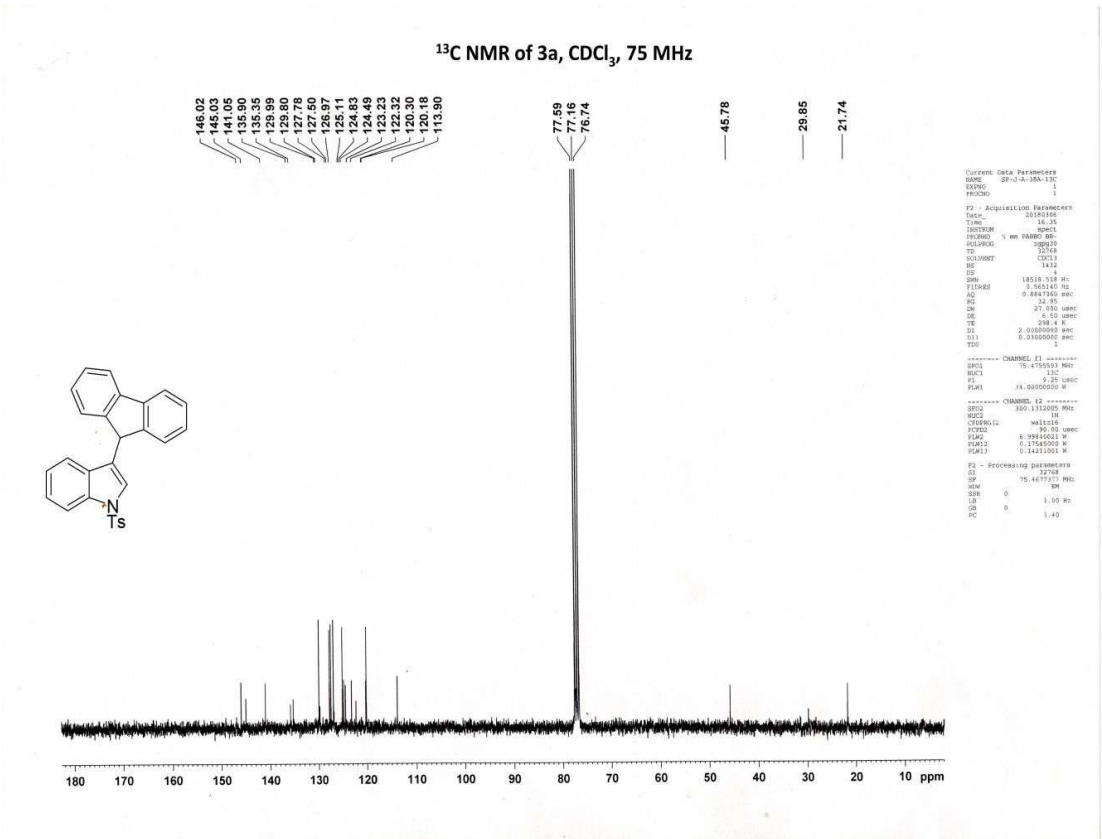
^{13}C NMR of 2o, $CDCl_3$, 100 MHz



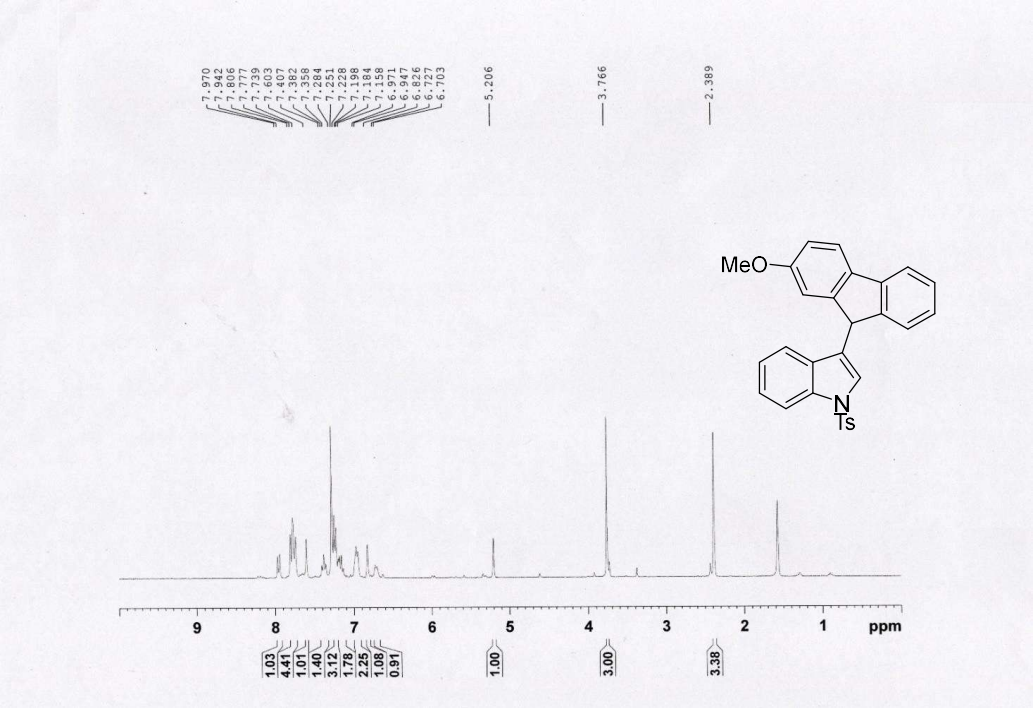
^{1}H NMR of 3a, $CDCl_3$, 300 MHz



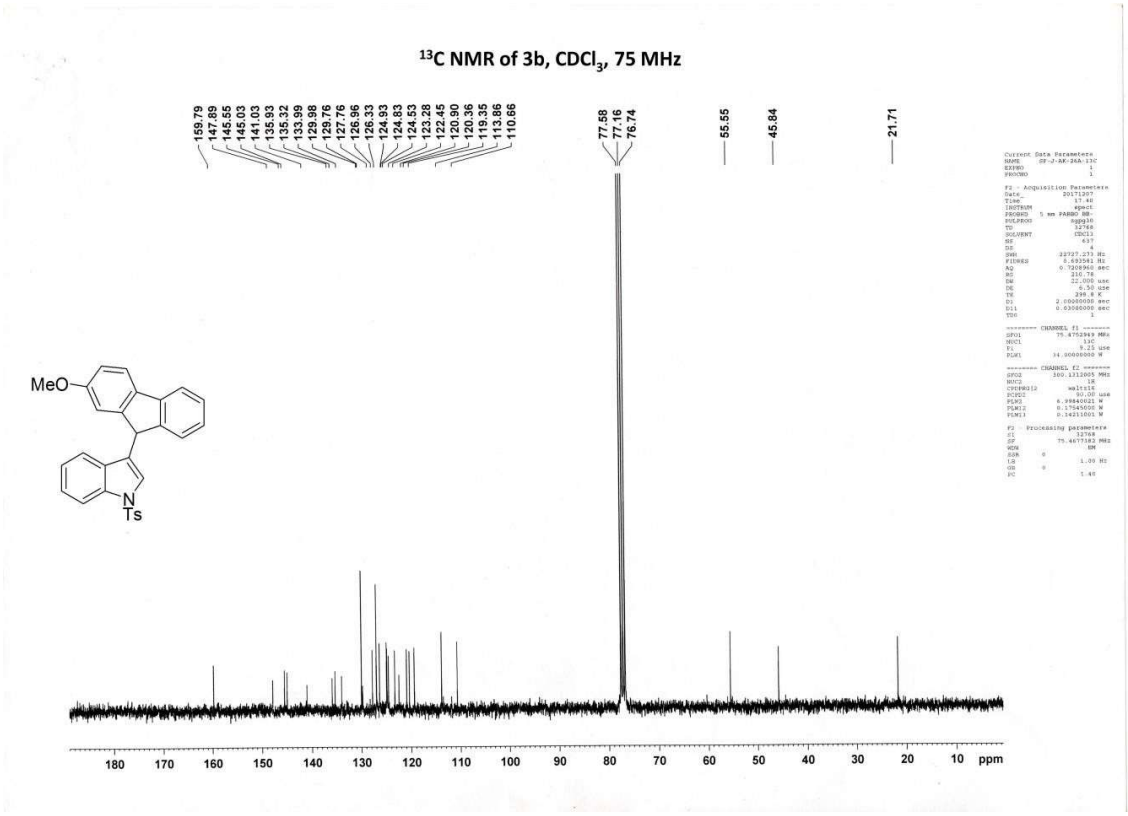
^{13}C NMR of 3a, $CDCl_3$, 75 MHz



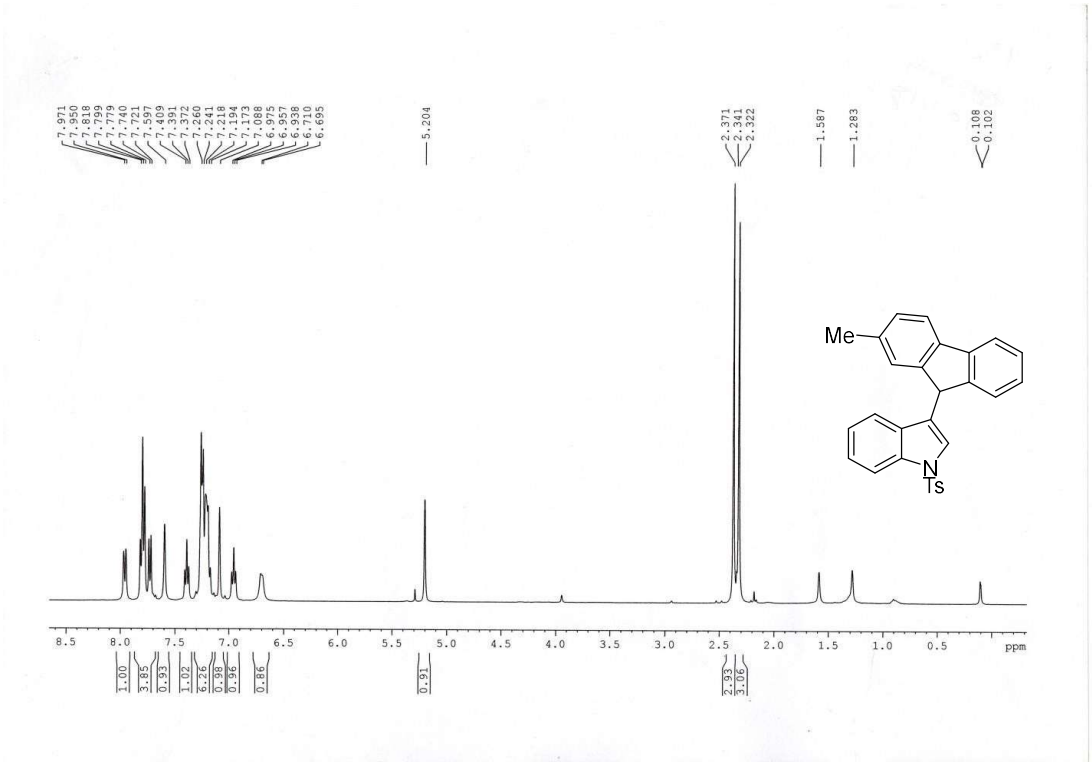
^{1}H NMR of 3b, $CDCl_3$, 300 MHz



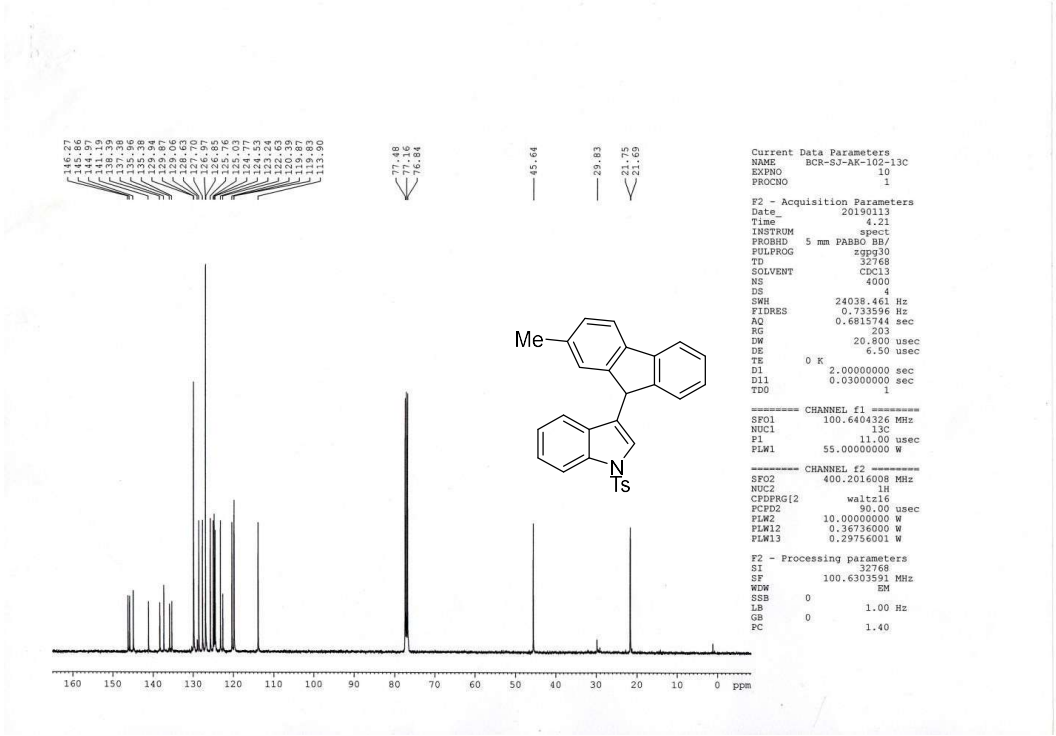
^{13}C NMR of 3b, $CDCl_3$, 75 MHz



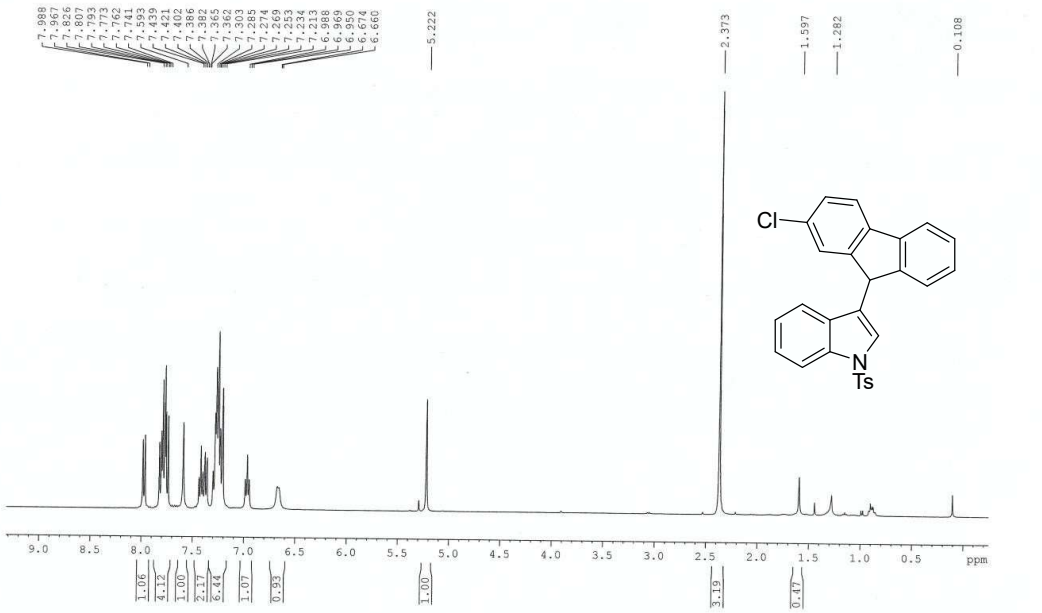
^{1}H NMR of 3c, $CDCl_3$, 400 MHz



^{13}C NMR of 3c, $CDCl_3$, 100 MHz



^{1}H NMR of 3d, $CDCl_3$, 400 MHz



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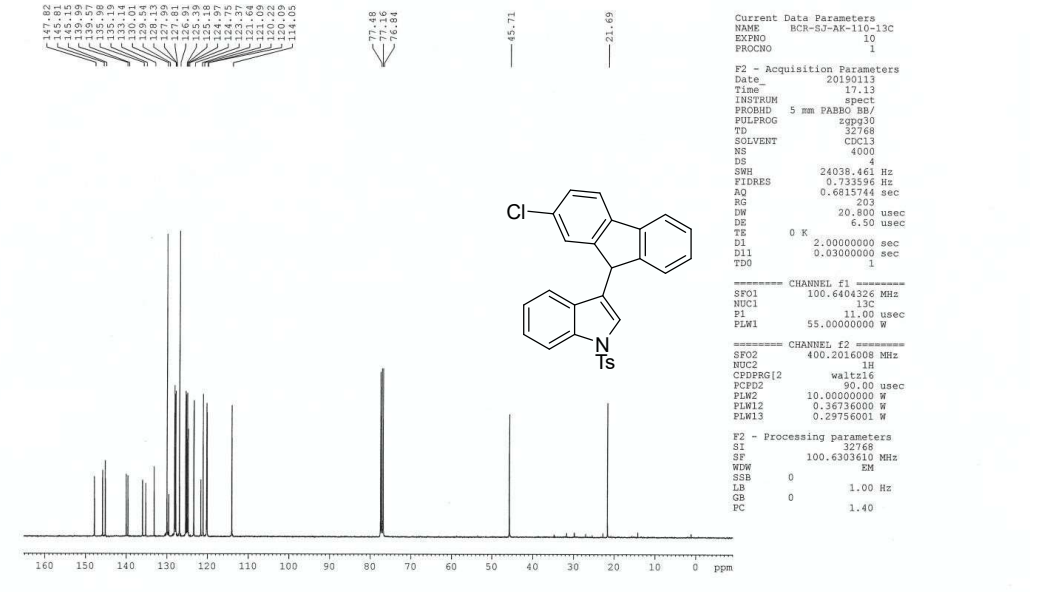
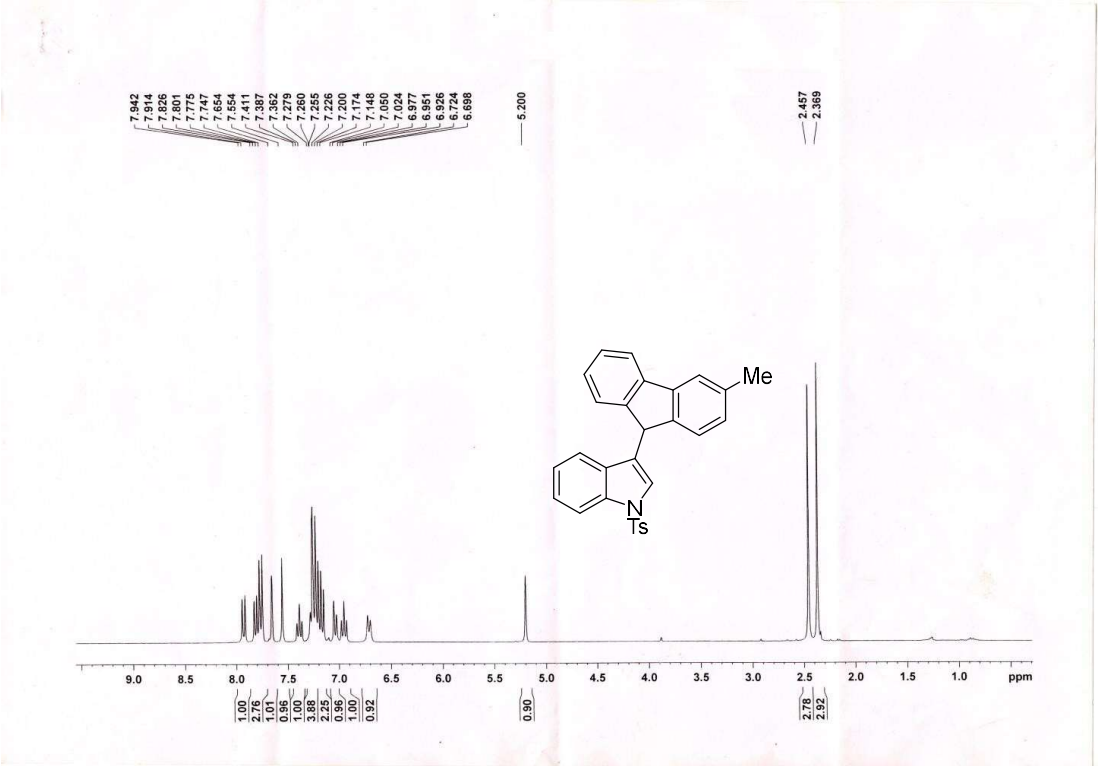
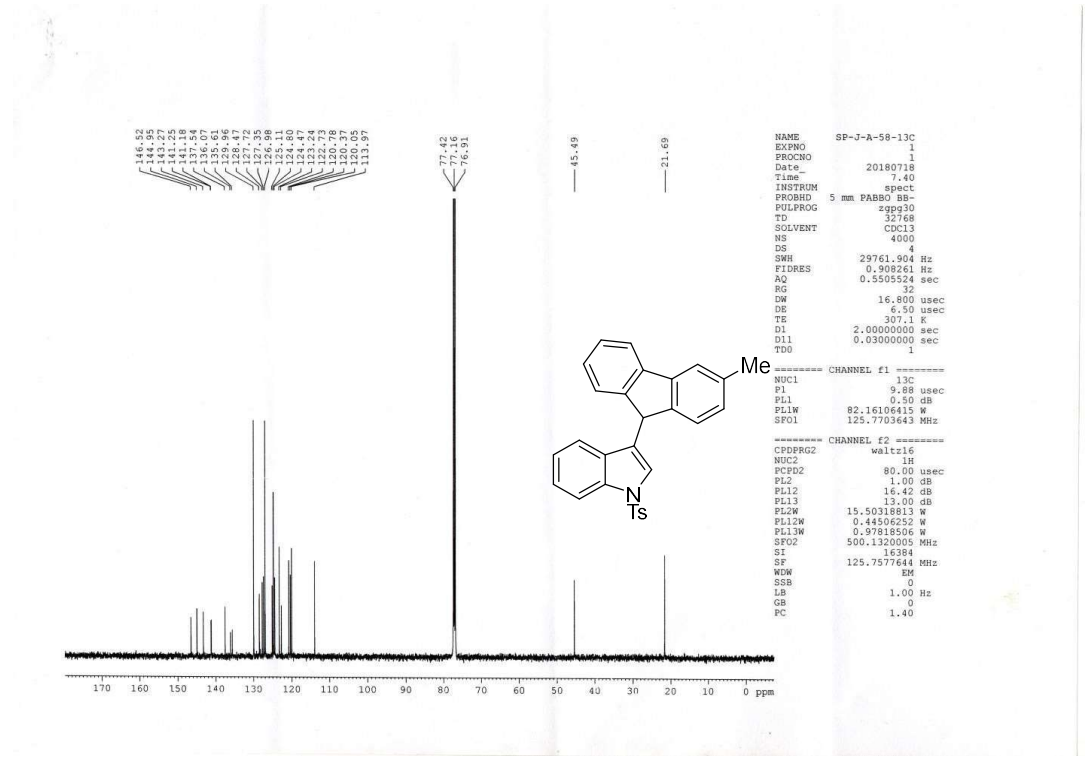


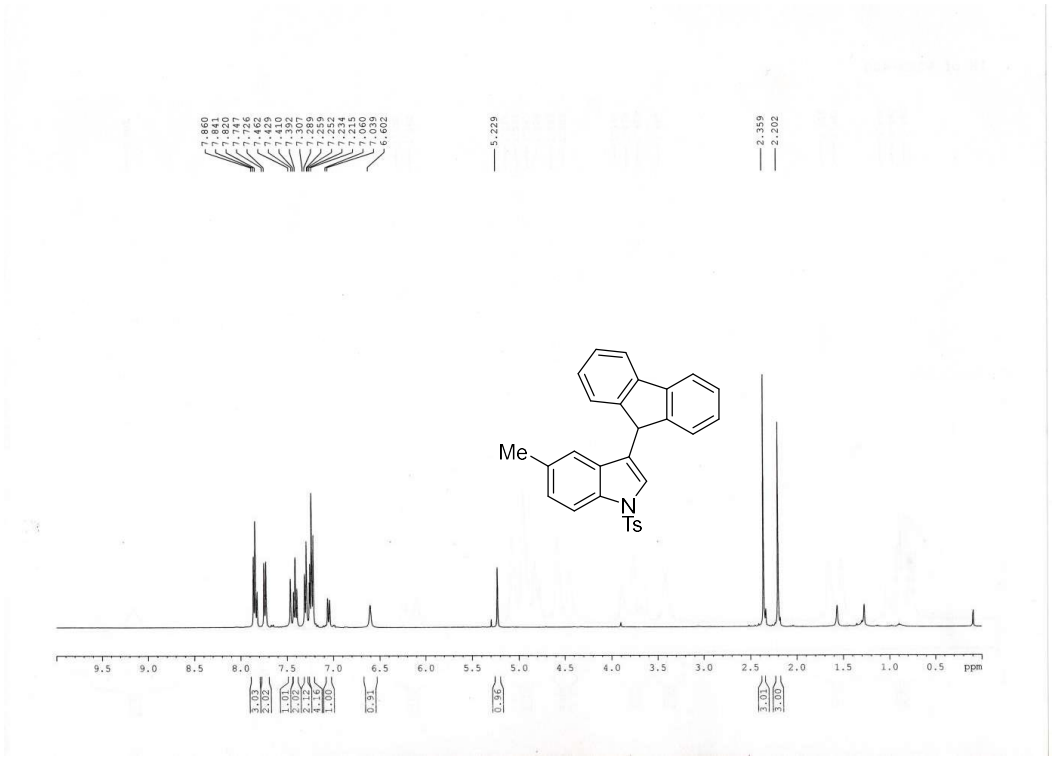
^{1}H NMR of 3e, $CDCl_3$, 300 MHz



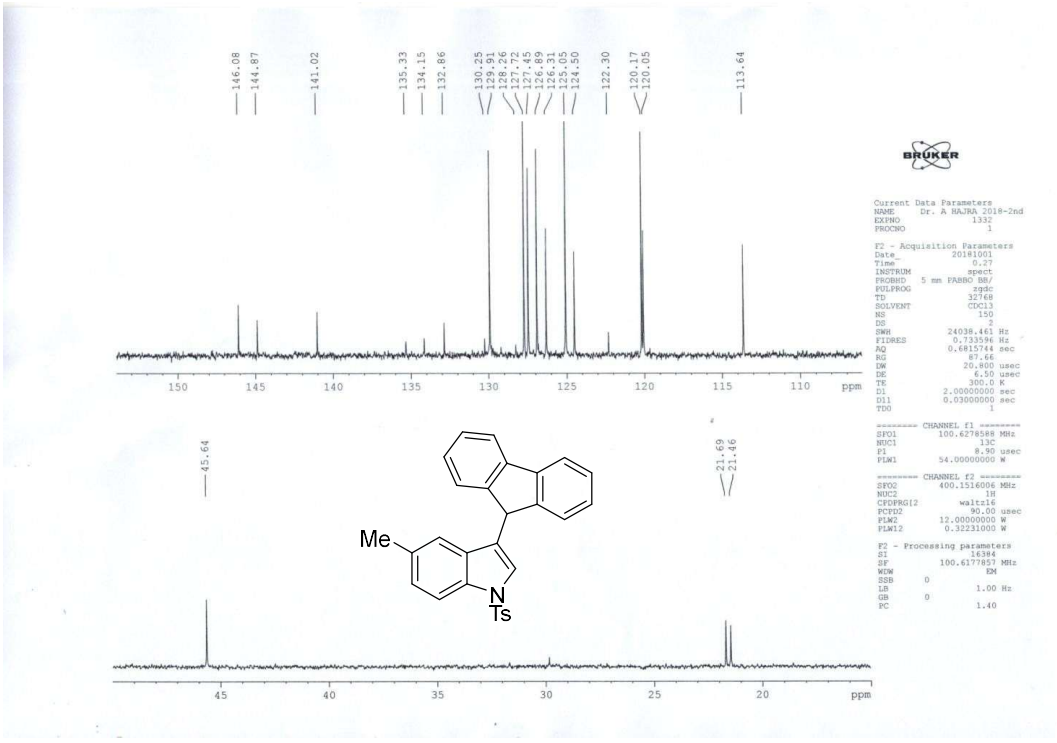
^{13}C NMR of 3e, $CDCl_3$, 125 MHz



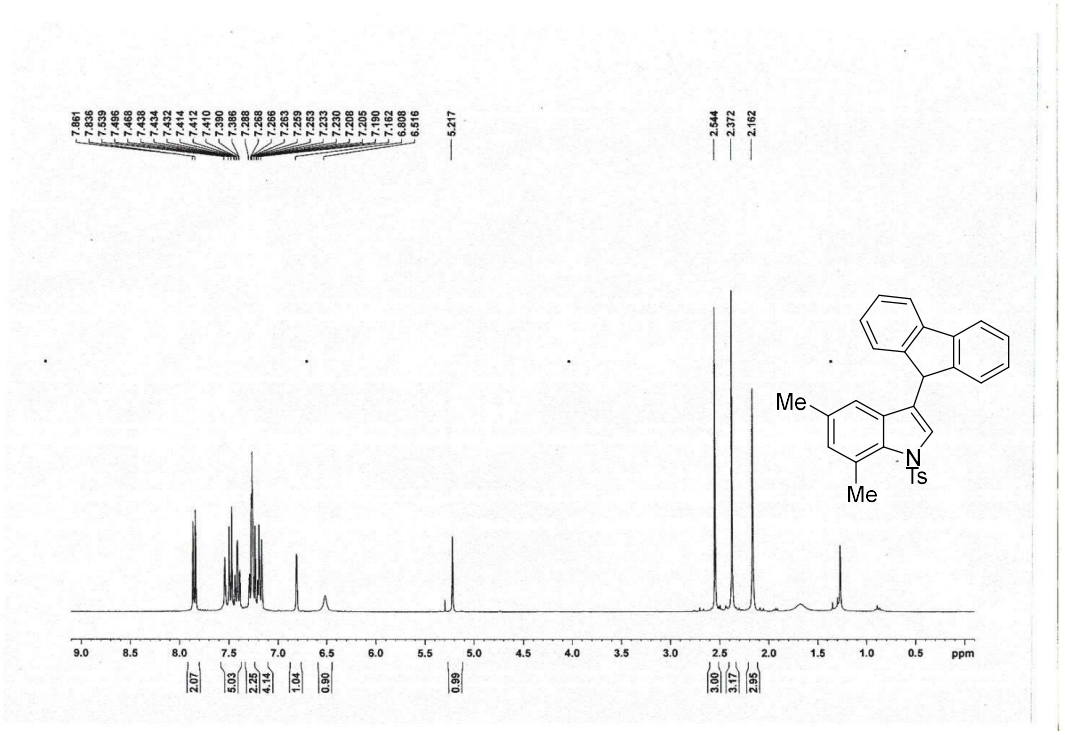
^{1}H NMR of 3f, $CDCl_3$, 400 MHz



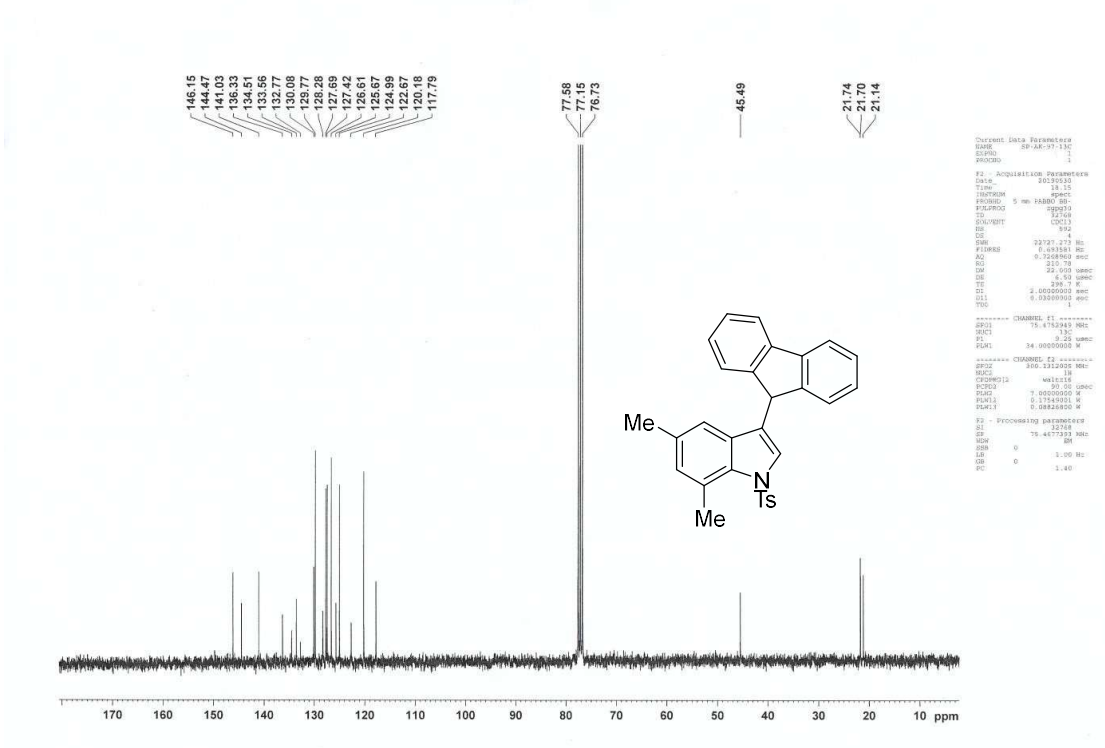
^{13}C NMR of 3f, $CDCl_3$, 100 MHz



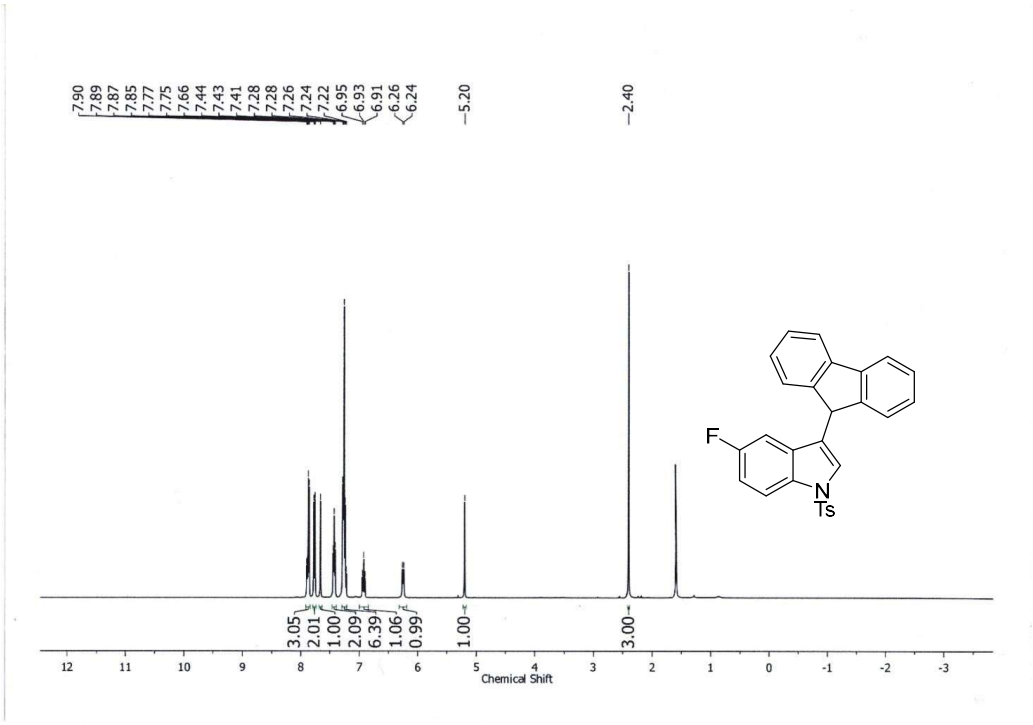
^{1}H NMR of 3g, $CDCl_3$, 300 MHz



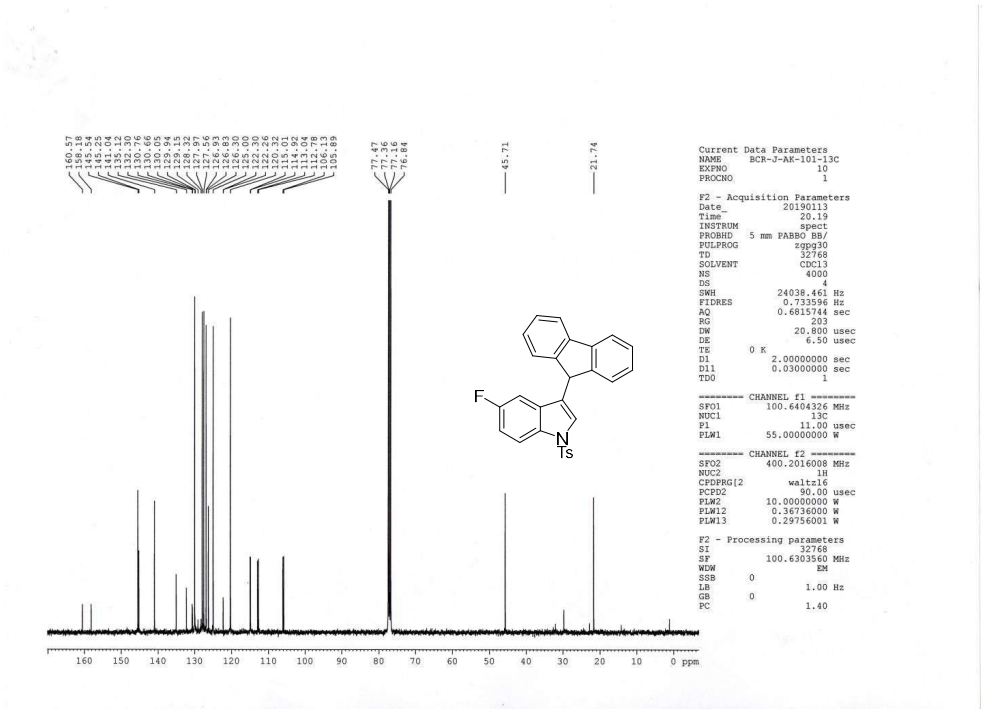
^{13}C NMR of 3g, $CDCl_3$, 75 MHz



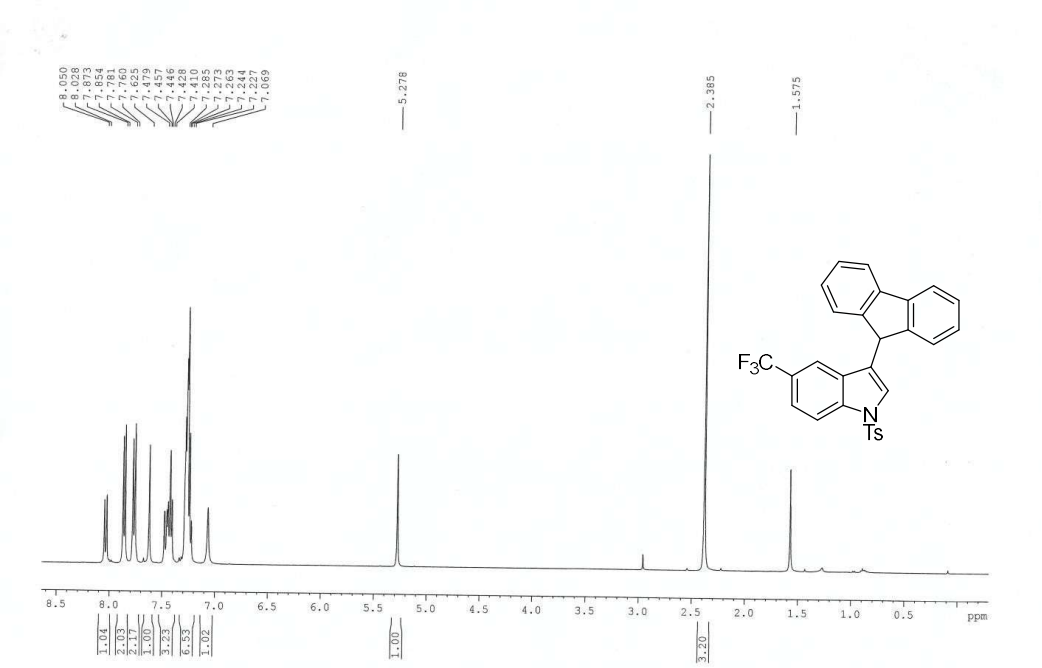
^{1}H NMR of 3h, $CDCl_3$, 400 MHz



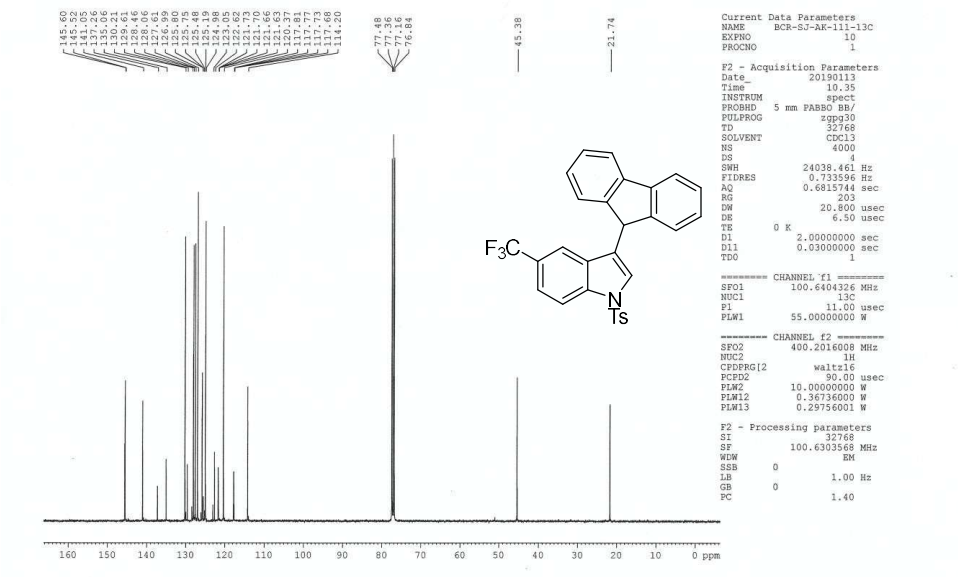
^{13}C NMR of 3h, $CDCl_3$, 100 MHz



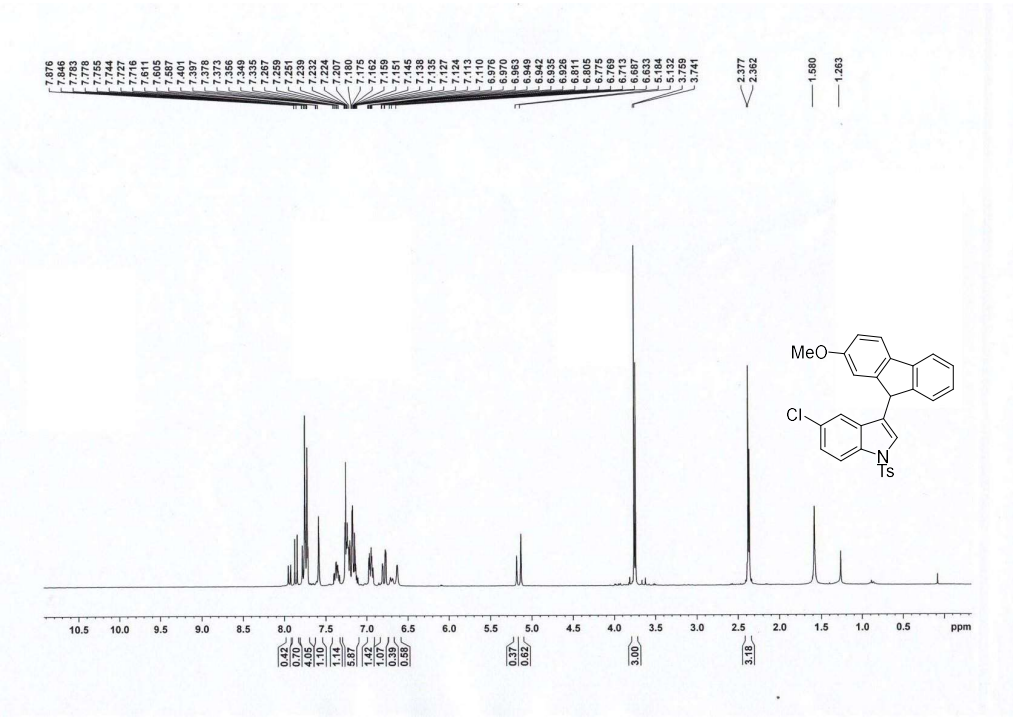
^{1}H NMR of 3i, $CDCl_3$, 400 MHz



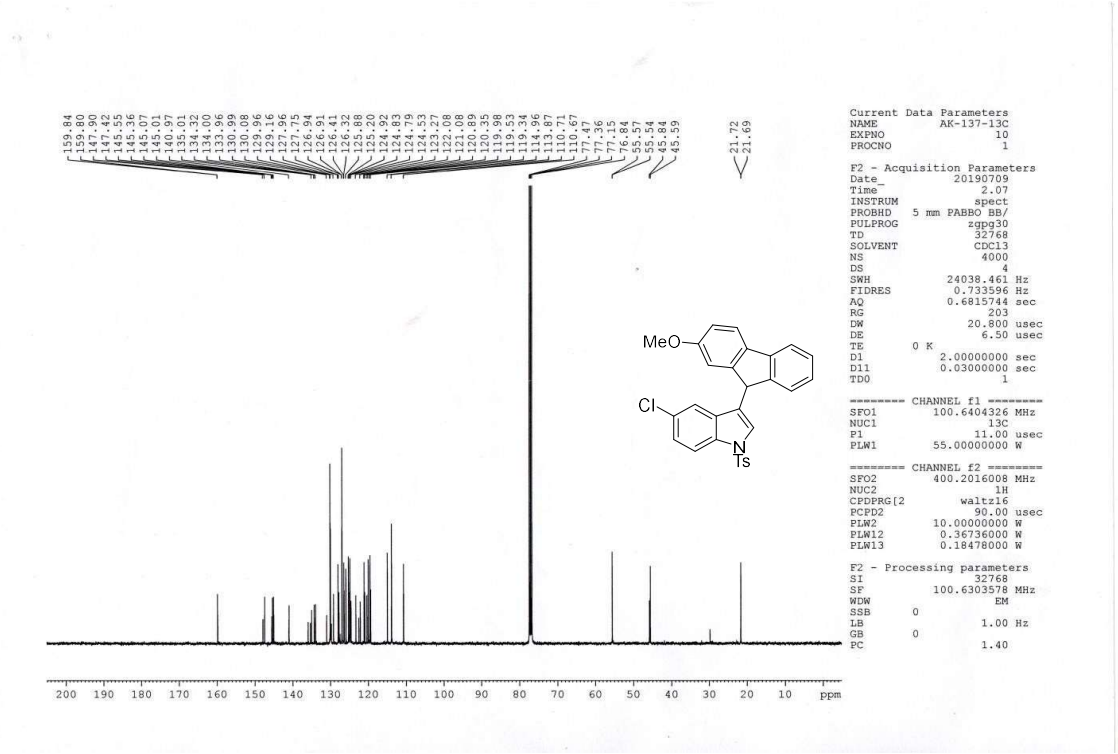
^{13}C NMR of 3i, $CDCl_3$, 100 MHz



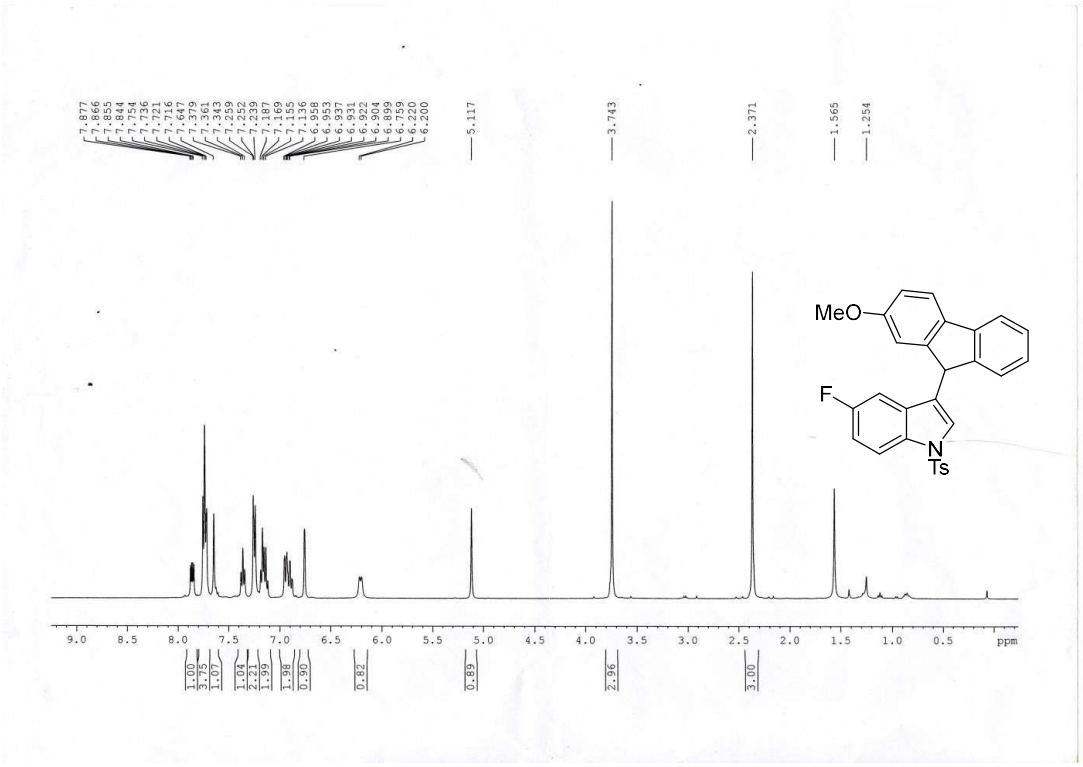
^{1}H NMR of 3j, $CDCl_3$, 300 MHz



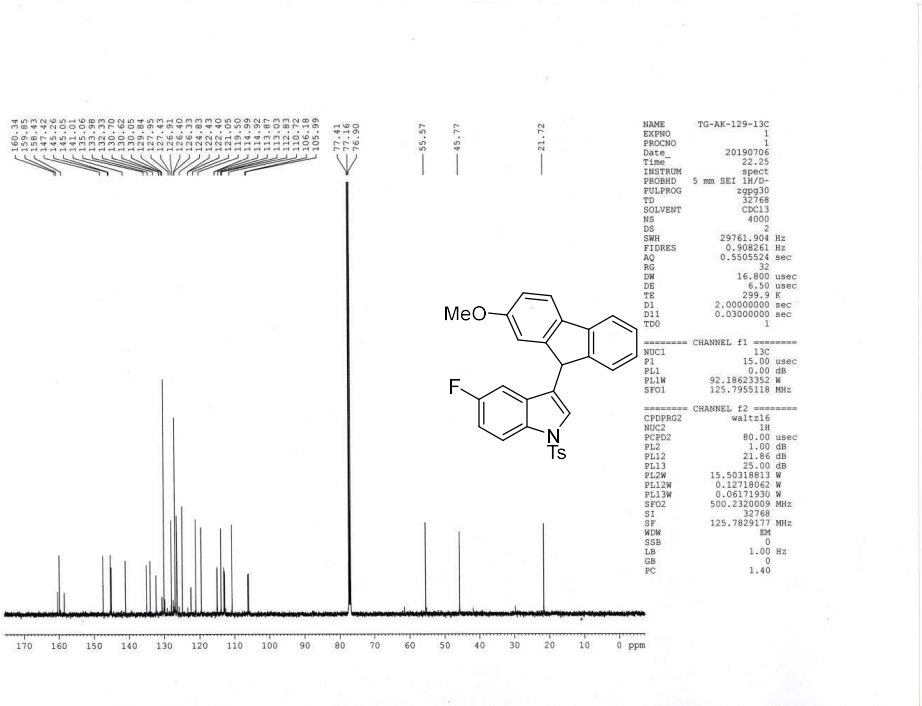
^{13}C NMR of 3j, $CDCl_3$, 100 MHz



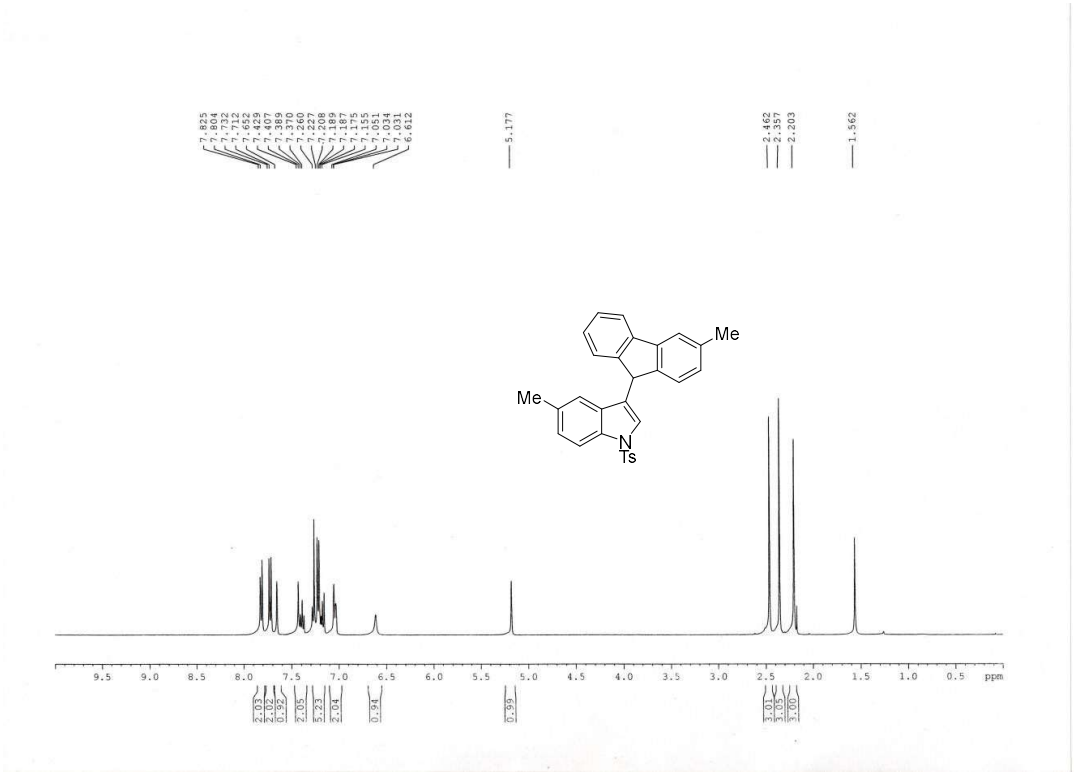
^{1}H NMR of 3k, $CDCl_3$, 400 MHz



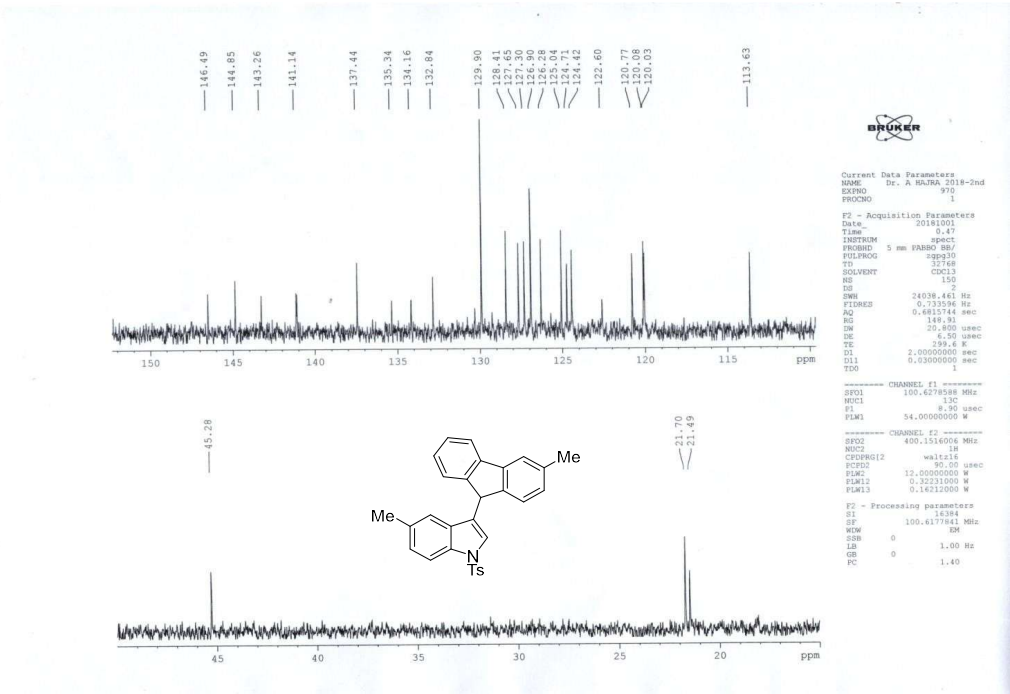
^{13}C NMR of 3k, $CDCl_3$, 125 MHz



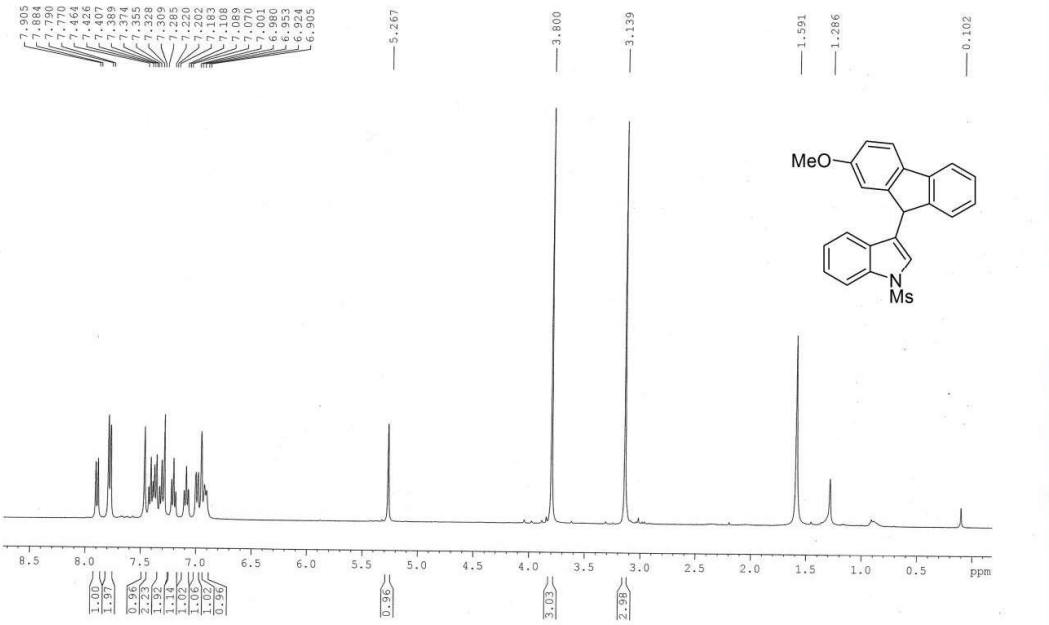
^{1}H NMR of 3l, $CDCl_3$, 400 MHz



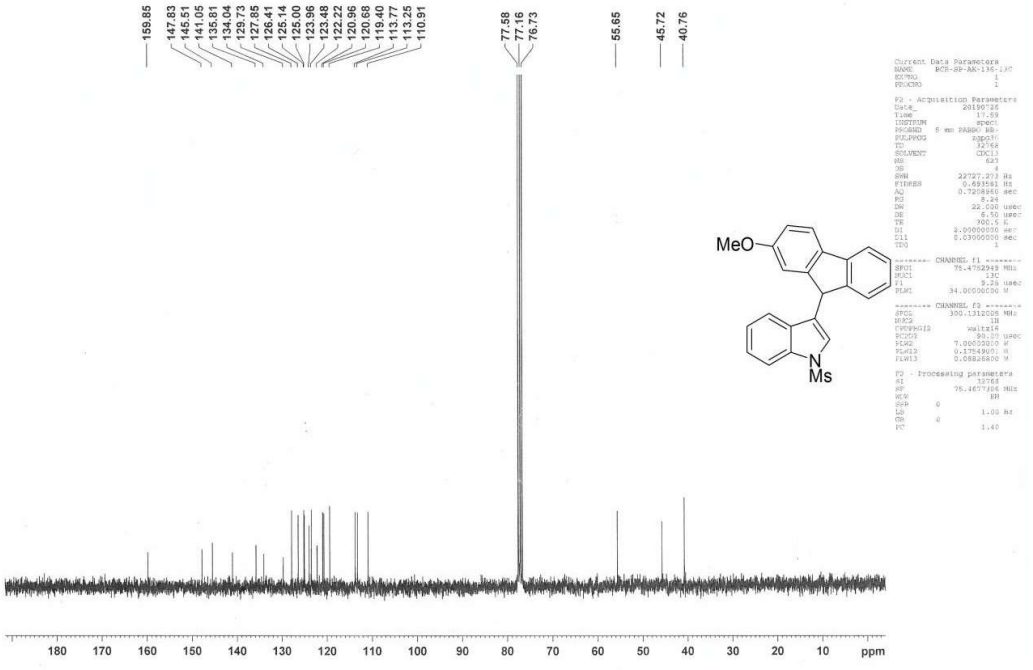
^{13}C NMR of 3l, $CDCl_3$, 100 MHz



^{1}H NMR of 3m, $CDCl_3$, 400 MHz



^{13}C NMR of 3m, $CDCl_3$, 75 MHz



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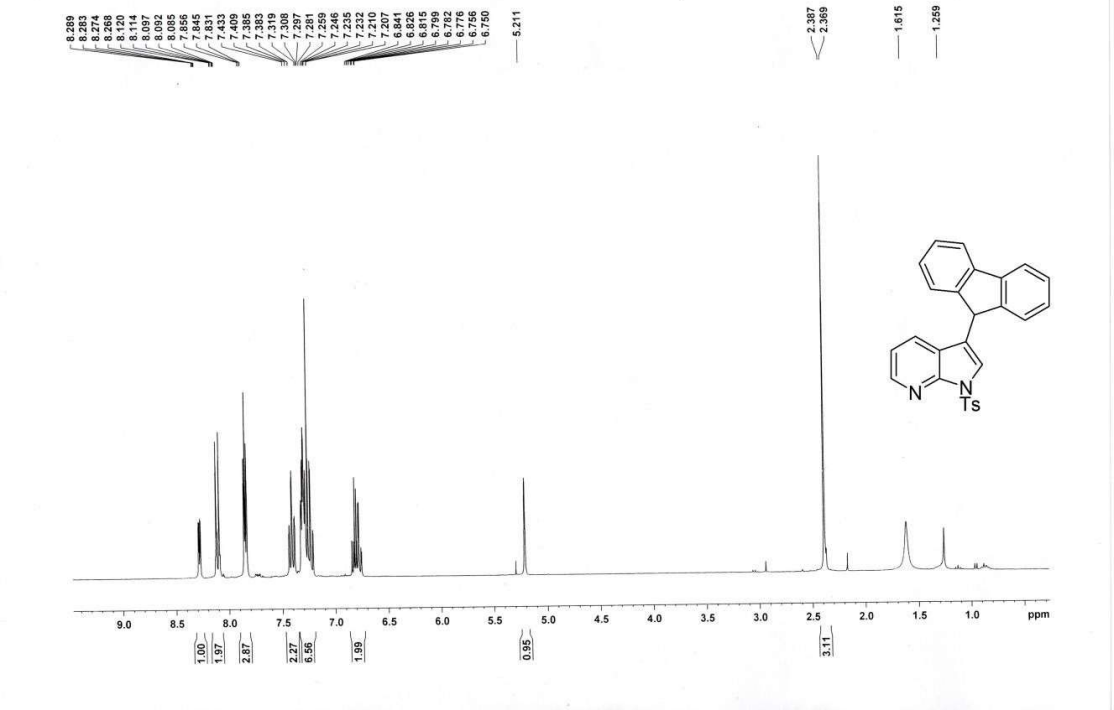
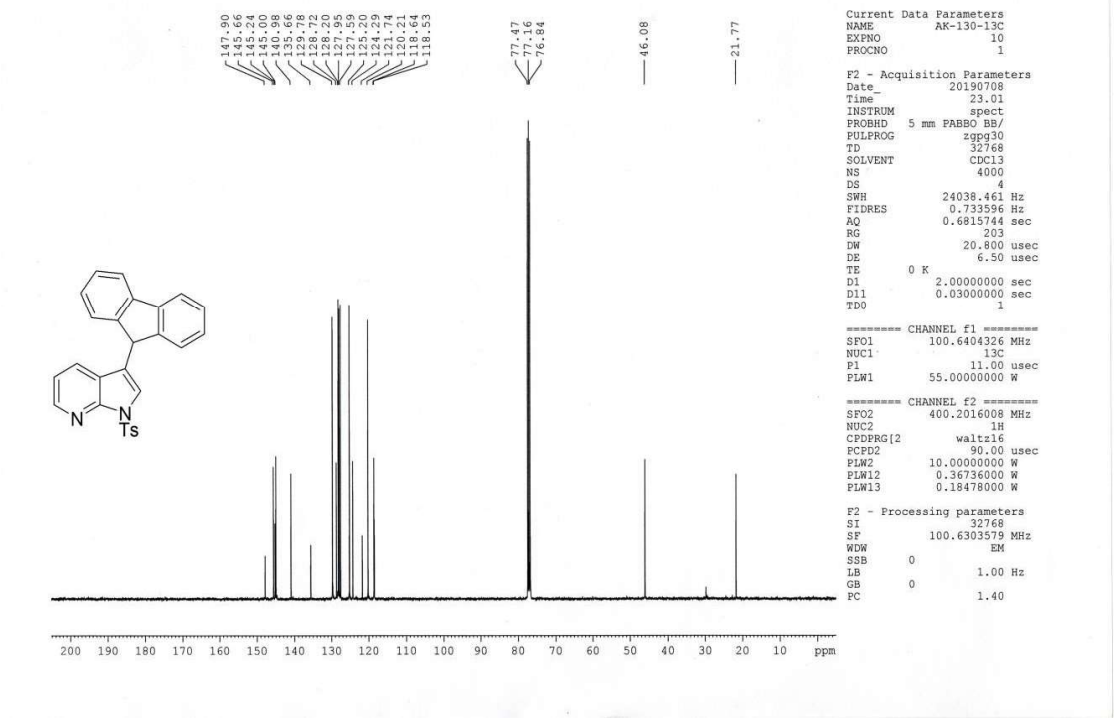


^{13}C NMR of 3n, $CDCl_3$, 100 MHz

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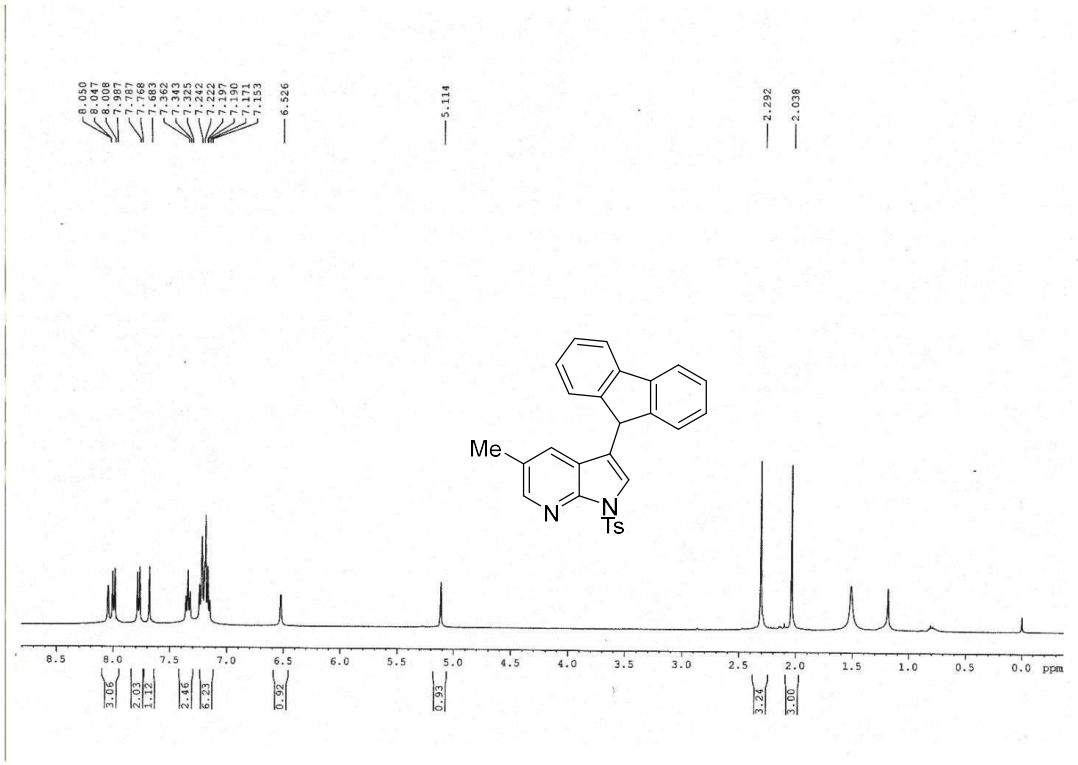
FIDRES               0.733596 Hz
AQ                   0.6815744 sec
RG                        203
DW                     20.800 usec
DE                      6.50 usec
TE                  0 K
D1                   2.00000000 sec
D11                  0.03000000 sec
TD0                           1

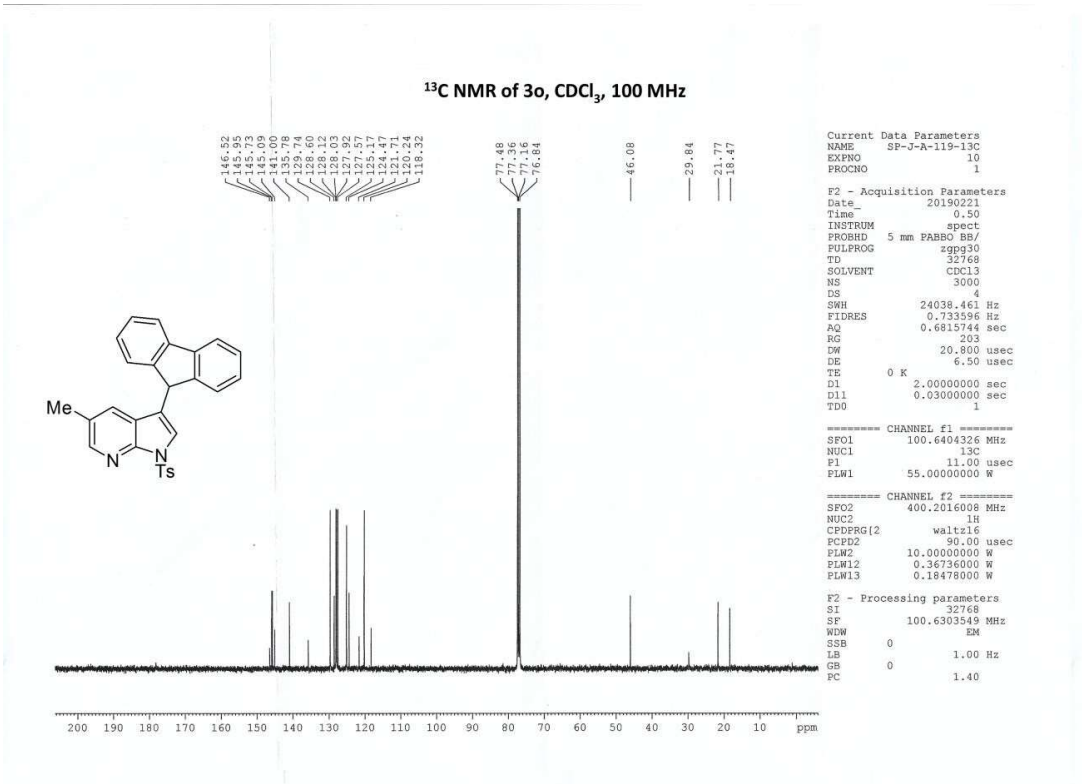
======== CHANNEL f1 ========
SFO1               100.6404326 MHz
NUC1                       13C
P1                      11.00 usec
PLW1                55.00000000 W

======== CHANNEL f2 ========
SFO2               400.2016008 MHz
NUC2                        1H
CPDPRG[2                waltz16
PCPD2                   90.00 usec
PLW2                10.00000000 W
PLW12                0.36736000 W
PLW13                0.18478000 W

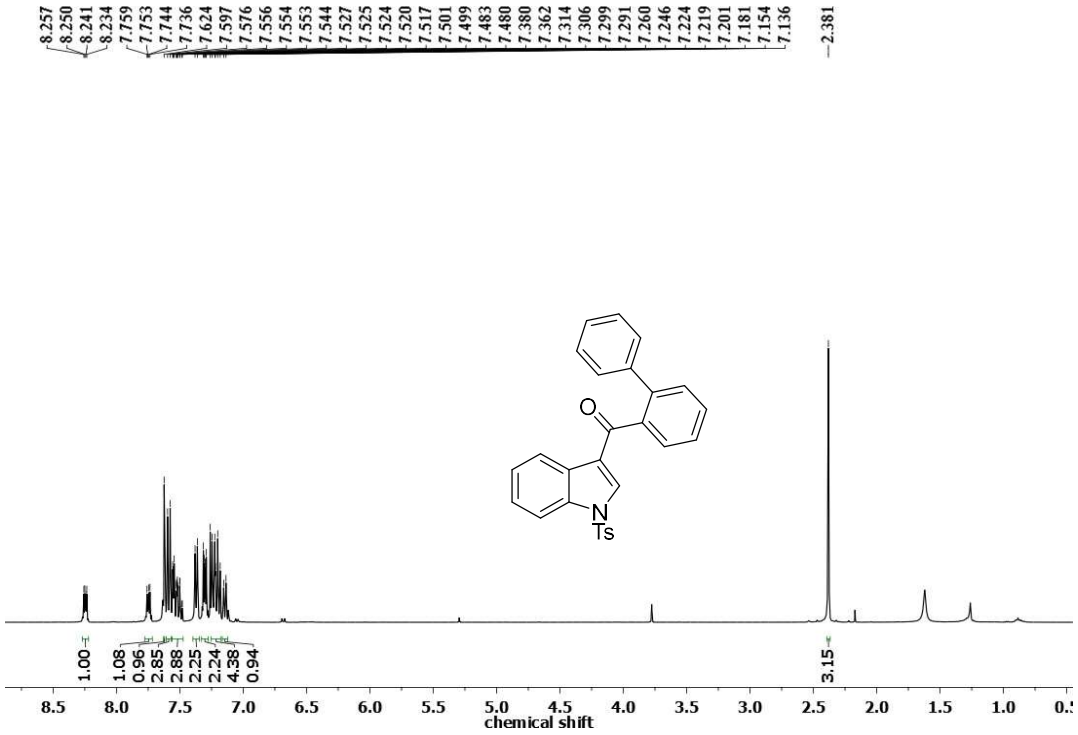
F2 - Processing parameters
SI                          32768
SF                 100.6303579 MHz
WDW                            EM
SSB                 0
LB                           1.00 Hz
GB                  0
PC                           1.40
```

^{1}NMR of 3o, $CDCl_3$, 400 MHz

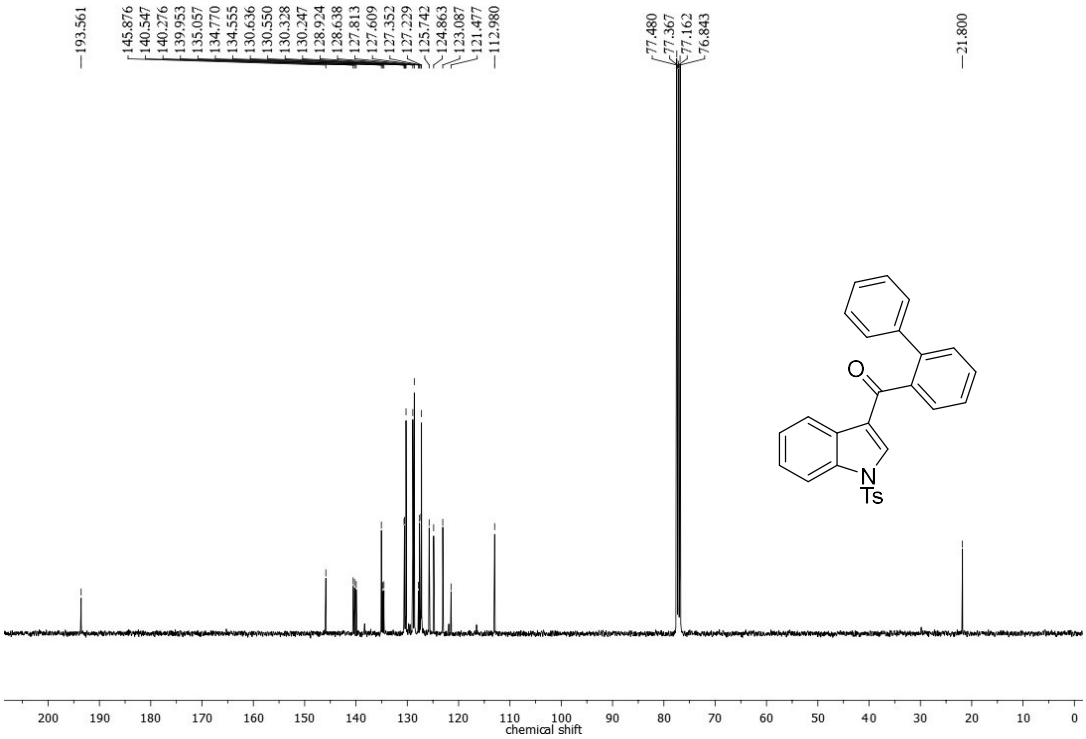




^{1}H NMR of 3-Indolyl biphenyl ketone, $CDCl_3$, 400 MHz



^{13}C NMR of 3-Indolyl biphenyl ketone, $CDCl_3$, 100 MHz



2.7 X-RAY CRYSTALLOGRAPHIC DATA AND STRUCTURE

	3a
Formula	$C_{28}H_{21}NO_2S$
M_r	435.52
Crystal system	monoclinic
Space group	P 21/n
a / Å	9.730(2)
b / Å	20.980(4)
c / Å	11.450(2)
α /°	90
β /°	104.39(3)
γ /°	90
V /Å^3	2264.0(8)
Z	4
D_{calcd} /g cm^{-3}	1.278
μ /mm^{-1}	0.168
θ/°	1.94 - 27.46
T /K	293

Table 2.2 Crystallographic data and structural refinement parameters for **3a** (**CCDC NO. – 1964540**)

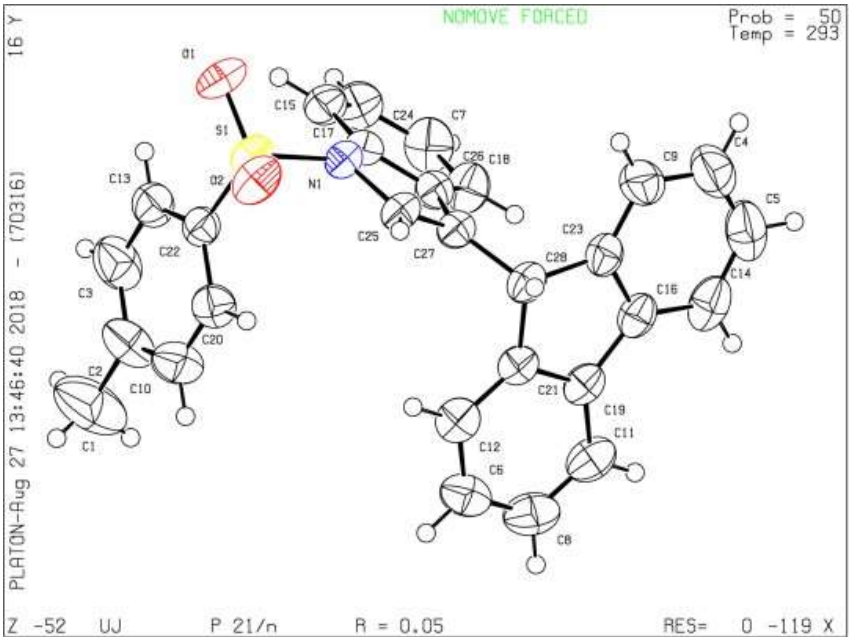


Figure 2.2. ORTEP diagram of the crystal structure of **3a** (thermal ellipsoid contour at 50% probability level).

Chapter 3

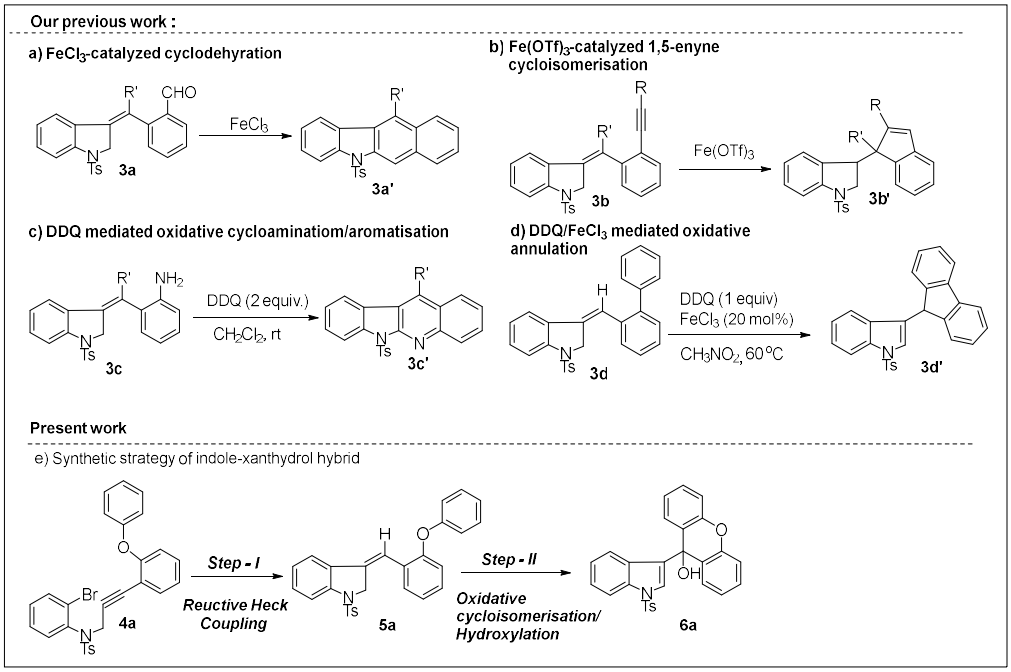
Iron(III)-Catalyzed Synthesis of Indole-Xanthydrol Hybrid Through Oxidative Cycloisomerization/ Hydroxylation Reaction

3.1 INTRODUCTION

Xanthene and its derivatives are considered to be an important core structure, appearing in a variety of natural products, synthetic drug candidates,[1] photodynamic therapeutic agents[2] and in optoelectronic devices.[3] Additionally, xanthene based hybrid molecules are particularly attractive due to their pharmaceutical activities, as shown by their use as anti-breast cancer agents, selective estrogen receptor modulators and so on.[4] It is noteworthy that xanthene-9-ol derivatives have also been shown to be potent cancer cell cytotoxic agents because of their 9-OH functionality.[5a–c] Therefore, the synthesis of functionalized xanthene has received a lot of interest in recent years.[6] Similarly, C-3 substituted indoles, are of great importance for their wide range of applications in natural/non-natural products, synthetic drugs, agrochemicals and in materials chemistry.[7]

We anticipated that hybrids of xanthene and indole subunits with a methylene group may exhibit good biological and photophysical activities. To date, only a few methods have been developed to synthesize indole tethered xanthene molecules,[8] that include intermolecular electrochemical cross-dehydrogenative coupling of indole with xanthene,[8a] (see chapter 1, **Scheme 1.7**) intermolecular nucleophilic substitution of xanthen-9-ol with indole[8b] (see chapter 1, **Scheme 1.24** and **Scheme 1.25**) and visible-light-mediated process for selective functionalization of the xanthene-9*H* position through carbon−carbon bond formation using quantum dots (QDs) as photocatalysts[8c] (see chapter 1, **Scheme 1.65**). Therefore, the development of new and environmentally benign protocols for constructing indole tethered xanthene derivatives is highly desirable.

Recently, we have established that 3-benzylidineindoline derivatives could be smoothly accessible by intramolecular carbopalladation of alkyne tethered 2-haloarene, serving as versatile building blocks in the efficient construction of C-3 substituted indoles and fused indoles etc.[9] For example, 3-benzylidineindolines **3a** and **3b** were transformed to substituted benzo [*b*]carbazole **3a′** derivatives (**Scheme 3.1** a) and 3-(1-indenyl) indoles **3b′** (**Scheme 3.1**



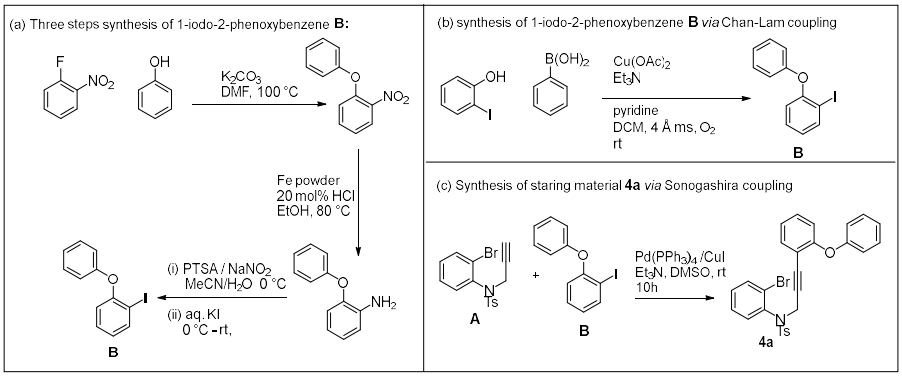
Scheme 3.1 Reactions of 3-benzylideneindoline derivatives

b) in good yields by iron(III)-catalyzed cycloisomerisation. We have also demonstrated the effective synthesis of important compounds such as indoloquinoline **3c′** (**Scheme 3.1** c) and indolylfluorene **3d′** derivatives (**Scheme 3.1** d) via DDQ mediated allylic oxidation and subsequent cyclization of 3-benzylidineindoline **3c** and **3d**, respectively. In continuation of our investigation exploring methods for the synthesis of varieties of heterocyclic scaffolds from 3-benzylidineindoline, in this chapter, we described an iron-catalyzed tandem oxidative cycloisomerization/hydroxylation strategy for the construction of indole–xanthydrol hybrid **6a** in good yields (**Scheme 3.1,** e).

3.2 RESULTS AND DISCUSSION

Prior to the implementation of this two-step protocol (**Scheme 3.1**, e), the first work was to prepare the starting material **4a** from easily available chemicals. Initially, we separately prepared the necessary fragments 2-bromo-*N*-propergyl-*N*-tosylbenzenamine **A** (see **scheme 2.2** (a) in chapter 2 for its synthesis) and 1-iodo-2-phenoxybenzene **B** for the synthesis of **4a** (**Scheme 3.2**). The compound *o*-phenoxy iodobenzene **B** was prepared through two different routes. Route (a) simple three steps involving *ipso*-substitution of 2-fluoro nitrobenzene with phenol, iron powder reduction of nitro group and subsequent Sandmeyer-type iodination (**Scheme 3.2,** a) and in route (b) a Chan-Lam coupling reaction between 2-iodophenol with

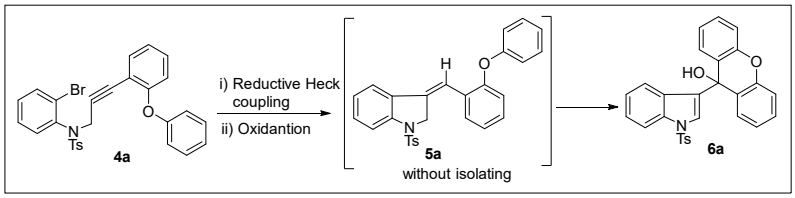
boronic acids (**Scheme 3.2,** b) was performed. We then, synthesized **4a** *via* a selective Sonogashira cross-coupling reaction of alkyne **A** with aryl iodide **B** using catalytic amounts of $Pd(PPh_3)_4$ and CuI in presence of triethylamine as base and DMSO as solvent (**Scheme 3.2,** c).



Scheme 3.2 Synthesis of starting material **4a** from easily available rack chemicals.

Then, to execute the above two-steps strategy (**Scheme 3.1**, e), we attempted to construct the substrate **5a** via the reductive Heck coupling of 2-bromo-*N*-(3-(2-phenoxyphenyl)prop-2-ynyl)-*N*-tosylbenzenamine **4a**, following the previous report.[10a] We observed that $Pd(OAc)_2$ (5 mol%), tricyclohexylphosphine (10 mol%), and 2.5 M aqueous K_2CO_3 (2.0 mL) in combination with ethanol (2.0 mL) and toluene (2.0 mL) at 75 °C for 2 hours gave the best result. However, we also noticed that during the separation of the crude products over silica gel column chromatography, a part of the reductive product **5a** was isomerized to produce C-3 alkylated indoles.[10b] To avoid this isomerization and unnecessary tedious separation, we decided to execute the second stage reaction with the crude product **5a**.

Next, we aimed to optimize the second step reaction for the synthesis of indole–xanthene derivative by employing various oxidants, co-catalysts, solvents and reaction temperature. The results are summarized in **Table 3.1**. Initially, we probed our model substrate **5a** with 1 equiv. of DDQ in combination with 20 mol% $FeCl_3$ and 4 Å molecular sieves in 1.5 mL $MeNO_2$ at 60 °C under Ar atm, as per our previous work.[9c] Unfortunately, this strategy did not perform well and the desired product **6a** was obtained in 5% yield in 3 h along with mixture of unwanted products (**Table 3.1**, entry 1). Next, we switch our thought from the stoichiometric use of oxidants and decide to build a catalytic transformation of the current model substrate **5a** into desired product **6a** under environmentally benign condition. As part of our research program in the development of affordable, nontoxic and ecologically friendly iron-catalysis[9a,9e-f,10]



Entry	Oxidant	Catalyst	Solvent	Temp (°C)	Yield (%)
1	DDQ	$FeCl_3$	CH_3NO_2	60	5
2	$Fe(NO_3)_3{\cdot}9H_2O$		DCE	rt	nr
3	$Fe(NO_3)_3{\cdot}9H_2O$		DCE	70	nr
4	$Fe(NO_3)_3{\cdot}9H_2O$		CH_3NO_2	rt	30
5	$Fe(NO_3)_3{\cdot}9H_2O$		CH_3NO_2	70	56
6	$Fe(NO_3)_3{\cdot}9H_2O$		CH_3NO_2	85	44
7	$Fe(NO_3)_3{\cdot}9H_2O$	$FeCl_3$	CH_3NO_2	70	70
8	$Fe(NO_3)_3{\cdot}9H_2O$	$FeCl_3$	CH_3CN	70	78
9	$Fe(NO_3)_3{\cdot}9H_2O$	$FeCl_3$	THF	70	10
10	$Fe(NO_3)_3{\cdot}9H_2O$	$FeCl_3$	DMF	70	nr
11	$Fe(NO_3)_3{\cdot}9H_2O$	$FeCl_3$	toluene	70	24
12	$Fe(NO_3)_3{\cdot}9H_2O$	$Fe(OTf)_3$	CH_3CN	70	74
13	$Fe(NO_3)_3{\cdot}9H_2O$	$InCl_3$	CH_3CN	70	65
14	$Fe(NO_3)_3{\cdot}9H_2O$	$In(OTf)_3$	CH_3CN	70	62
15	$Fe(NO_3)_3{\cdot}9H_2O$	PTSA	CH_3CN	70	53
16	$Fe(NO_3)_3{\cdot}9H_2O$	TfOH	CH_3CN	70	45
17	-	$FeCl_3$	CH_3CN	70	15
18	-	$FeCl_3{\cdot}6H_2O$	CH_3CN	70	20
19	$Al(NO_3)_3{\cdot}9H_2O$	$FeCl_3$	CH_3CN	70	59
20	$Ce(NO_3)_3{\cdot}6H_2O$	$FeCl_3$	CH_3CN	70	51
21	$Cu(NO_3)_2{\cdot}3H_2O$	$FeCl_3$	CH_3CN	70	64
22	$Fe(NO_3)_3{\cdot}9H_2O$	$FeCl_3$	CH_3CN	70	60

Table 3.1 Optimization of Reaction Condition.

herein, we opted to use iron-salts as oxidant. So, when the reaction was carried out with 30 mol% $Fe(NO_3)_3.9H_2O$ as oxidizing agent in 1,2-dichloroethane (DCE) (3.0 mL) at room temperature under O_2. Regrettably, the reaction did not proceed even after rising the

temperature to 70 °C (**Table 3.1**, entries 2-3). But, when the reaction was conducted with 30 mol% $Fe(NO_3)_3.9H_2O$ in the presence of 3.0 mL $MeNO_2$ at varying temperature under O_2 for 3 hours (**Table 3.1**, entries 4-6). To our delight, when the reaction afforded the desired indole-xanthene-9-ol **6a** in 30% yield at room temperature, but at 70 °C the desired **6a** was produced in 56% overall yield in two steps along with the few by-products (**Table 3.1**, entry 5). However, further increasing the temperature to 85 °C lowered the yield to 44% (**Table 3.1**, entry 6). In our previous DDQ mediated oxidative cycloisomerisation process,[10c] we observed that the yield of the product increased in the presence of the catalytic combination of $FeCl_3$.

Similarly, in the present study, when the similar reaction was performed in combination with 30 mol% $FeCl_3$ as co-catalyst at 70 °C under O_2, the overall yield of the desired product **6a** was increased up to 70% (**Table 3.1**, entry 7). To further improve the yield, a series of solvents such as MeCN, THF, DMF and toluene were examined in the second step of the reaction (**Table 3.1**, entries 8-11). Pleasantly, the yield of the desired product **6a**, was further improved up to 78%, (**Table 3.1**, entry 8) in MeCN (3.0 ml). Whereas, the yield was even lower in both THF and toluene, produced **6a** in 10% and 24% yields, respectively (**Table 3.1**, entry 9 and 11). However, in DMF the substrate **5a** remains unreacted (**Table 3.1**, entry 10). Further screening with a series of Fe(III), In(III), PTSA and TfOH as co-catalyst reveled that, with exception of $Fe(OTf)_3$, no remarkable change in the yield was noticed (**Table 3.1**, entries 12-16). Surprisingly, 15% and 20% yield of the product **6a** were obtained on exposing the reactant **5a** individually with 30 mol% $FeCl_3$ and 30 mol% $FeCl_3.6H_2O$ alone in 3.0 mL CH_3CN respectively (**Table 3.1**, entries 17-18). Switching to other metal nitrates such as $Al(NO_3)_3.9H_2O$, $Ce(NO_3)_3.6H_2O$, $Cu(NO_3)_2.3H_2O$ in combination with $FeCl_3$ under similar reaction conditions were less successful, compare to $Fe(NO_3)_3.9H_2O$ (**Table 3.1**, entries 19-21). Furthermore, we have also investigated the reaction without molecular oxygen (**Table 3.1**, entry 22), and found that the yield of the product was reduced to 60%. Therefore, the molecular oxygen was essential for this sequential oxidative cyclisation/hydroxylation process as a terminal oxidant. Hence, the fruitful transformation of the substrate **5a** into desired product **6a** in the presence of 30 mol% $Fe(NO_3)_3.9H_2O$ in combination with 30 mol% $FeCl_3$ in acetonitrile (3.0 mL) at 70 °C under O_2 for 3 hours gave the optimal reaction condition.

It is worth noting that a common hydroxyl unit between indole and xanthene scaffolds in **6a** make this hybrid molecule a more appealing substructure for both xanthene-9-ol[5b] and indole-

3-carbinol[5d-e] in biomedical research relevance.

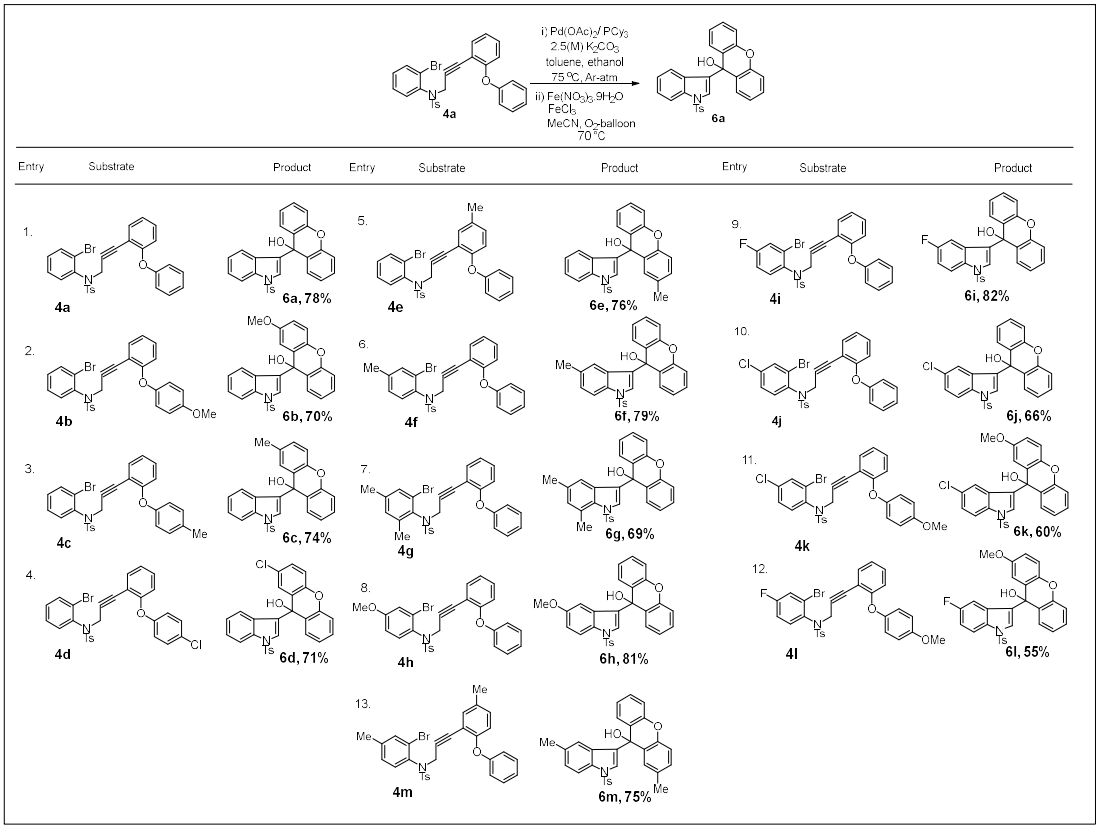
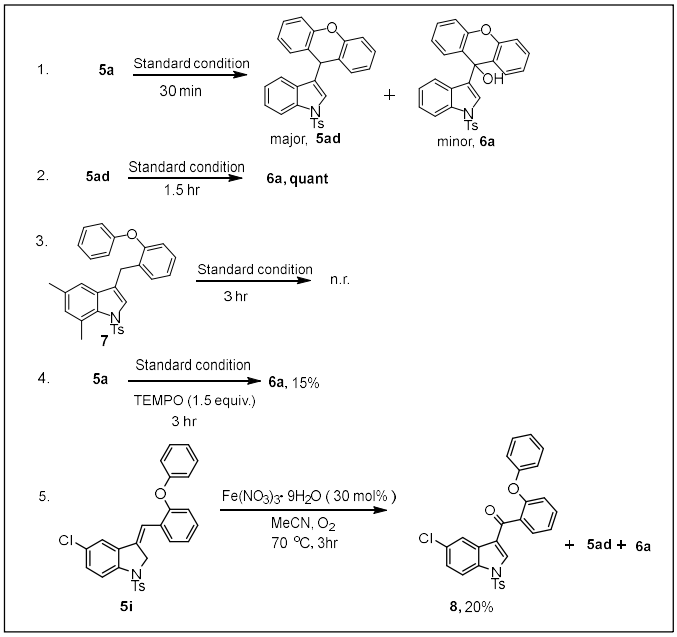


Table 3.2 Synthesis of indole bearing xanthene-9-ol hybrid molecules.

Following the optimum reaction condition, we decided to explore the robustness of this methodology using a variety of crude substrates and the results are summarized in **Table 3.2**. The substrate without any substituent on each aryl ring was reacted smoothly to produce the corresponding product **6a** in 78% yield (**Table 3.2**, entry 1). The electronic effect on both the phenyl ring of biaryl ether unit was studied. The experimental results showed that the reaction worked well with different electron donating groups such as *p*-OMe and *p*-Me, and also electron-withdrawing group such as *p*-Cl to afford the desired product in high yields of 70%, 74%, 76% and 71%, respectively (**Table 3.2**, entries 2-5). Next, we examined the effect of different substituents at the 2-haloaniline nucleus. The 2-haloaniline moiety bearing electron-donating groups such as *p*-Me, *o*-Me and *p*-OMe were well tolerated under the present reaction condition, yielding the indole–xanthydrol hybrid in 79%, 69% and 81% respectively (Table 3.2, entries 6-8). Halogens like –F, -Cl at *para*-position of this 2-haloaniline scaffold underwent the $Fe(NO_3)_3.9H_2O/FeCl_3$ catalyzed sequential oxidative C-C coupling and hydroxylation without

any difficulties and furnished the hydroxylated product in 82% and 66% yield respectively (**Table 3.2**, entries 9 and 10). Furthermore, the simultaneous installation of electronically opposing and similar substituents on both the alkyne connected 2-haloaniline and biaryl ether unit were also survived for reductive heck coupling and subsequent iron catalyzed oxidative cycloisomerization/hydroxylation and delivered the target products in moderate to good yields over the two steps (Table 3.2, entries 11-13). Moreover, our designed compounds, having more than one –Me substituents were also successfully converted into desired products, **6g** and **6m** in 69% and 75% yields, respectively (**Table 3.2**, entries 7 and 13). All the structures were characterized by ^{1}H NMR, ^{13}C NMR and HRMS data (see section 3.4.4 in this chapter). The structure of **6a** was further confirmed by X-ray structure (see section 3.7, **Figure 3.2**).

To shed light on the mechanistic pathway for this transformation, a several control experiments were carried out under different reaction condition as shown in **Scheme 3.3**. First of all, when the reaction was quenched just after 30 min following TLC, then we were able to isolate an intermediate indole-xanthene hybrid, **5ad** (**Scheme 3.3**, 1) as a major product along with the

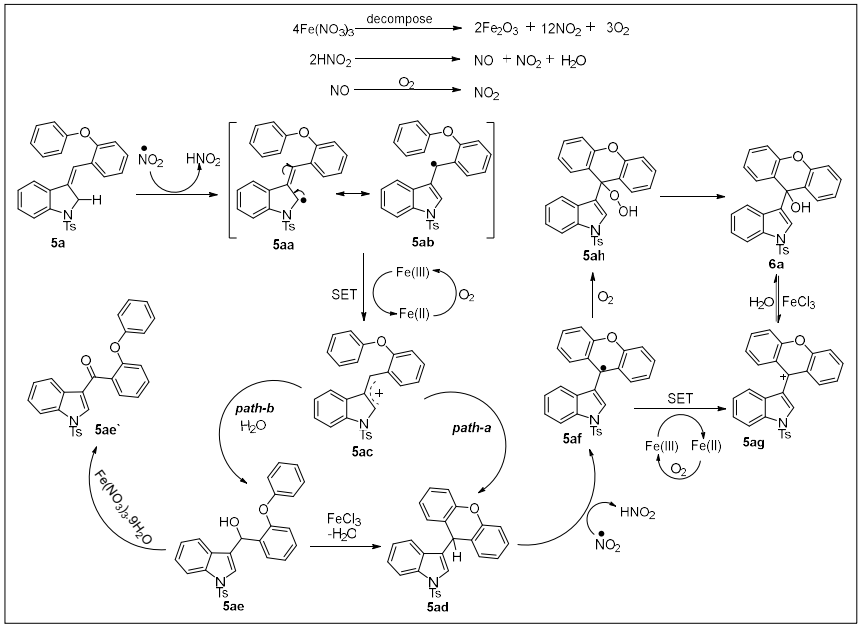


Scheme 3.3 Control experiments.

minor amount of desired product **6a**. Furthermore, when **5ad** was allowed to react under the standard reaction condition, then it converted quantitatively into the desired product **6a** within 1.5 hr in 99% yield (**Scheme 3.3**, 2). This finding indicated that the reaction goes through the intermediate **5ad** (as characterized by XRD and NMR spectroscopy; see section 3.7, **Figure 3.1**

and section 3.4.6 (a)). There are possibilities that the reaction could proceed through oxidation followed by isomerisation or vice-versa. To check this, we synthesized the isomerized substrate **7** using our earlier method[10b] (see section 3.4.6 (b)) and performed the reaction by employing presently developed procedure, but no reaction occurred (**Scheme 3.3**, 3). This experiment implies that the reaction does not proceed through isomerisation followed by oxidation of the substrate. Therefore, aromatization of the substrate **5a** is the driving force for the allylic C–H oxidation/isomerisation. Moreover, the yield of the product **6a** was reduced to 15% when the reaction was conducted in the presence of radical scavenger 1.5 equiv. TEMPO (**Scheme 3.3**, 4). This result indicated that the reaction proceeds through a radical pathway. To further understand the mechanistic investigations, we allowed the substrate **5i** to react with 30 mol% $Fe(NO_3)_3.9H_2O$ in absence of $FeCl_3$, one of the byproducts, acylated indole **8** was isolated and characterized (**Scheme 3.3**, 5) (see section 3.4.6 (c)). This experimental observation suggests that the ketone **8** was produced via in situ generated intermediate 3-indolyl alcohol.

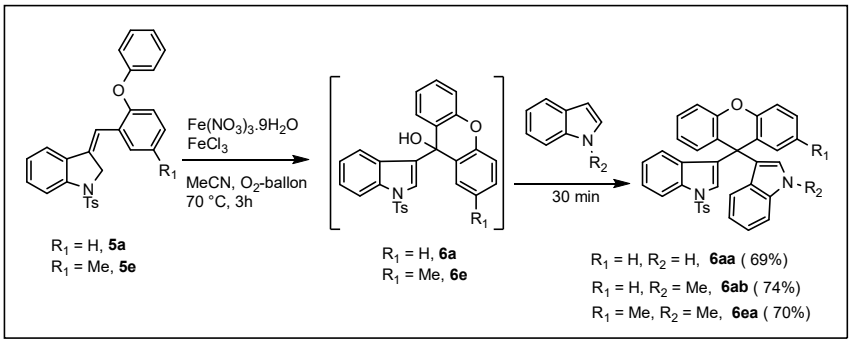
Based on our control experiments and previous literature reports[11], **Scheme-3.4** depicts a tentative mechanism for sequential oxidative cyclisation and hydroxylation.



Scheme 3.4 Plausible mechanism for iron catalyzed sequential aerobic oxidation of **5a.**

Initially, NO_2 radical was generated from the partial decomposition of $Fe(NO_3)_3.9H_2O$, which abstracted allylic Csp^3–H of **5a** to form allylic radical **5aa**, which was then isomerized to a benzyl radical **5ab**. Subsequently, this resonance stabilized radical reacts with Fe(III) salts to form a indolyl cation intermediate **5ac** *via* a single electron transfer (SET) process. This is

followed by electrophilic attack by *ortho* –OPh ring (path-a, **Scheme 3.4**) to give intermediate indole–xanthene hybrid **5ad**. The cationic intermediate **5ac** could be trapped by H_2O (path-b, **Scheme 3.4**) present in the reaction medium to form indolylalcohol **5ae**. $FeCl_3$ can also activate this π-activated alcohol[9a] **5ae** to increase the availability of indolyl cationic intermediate **5ac** for electrophilic substitution by *ortho*-aryl ether ring. In the absence of $FeCl_3$ this benzylic alcohol **5ae** could be further oxidized by $Fe(NO_3)_3.9H_2O$ to produce biphenyl etheryl 3-indolyl ketone **5ae`** as by-product. Being HNO_2 an unstable compound, its rapid decomposition generats NO and NO_2, where NO can reoxidised to NO_2 by molecular O_2. Finally, NO_2 radical again may abstract the highly labile tertiary benzylic H-atom from the intermediate **5ad,** resulting in a resonance stabilized tertiary indolyl radical **5af**. Which is easily transformed into benzylic cation **5ag** by oxidation with Fe(III) salts and reversibly trapping of water leading to alcohol **6a**. Although, we have shown that the molecular oxygen serves as terminal oxidant, but the trapping of **5af** with molecular oxygen to corresponding hydroperoxide intermediate **5ah** and subsequent hydrolysis to **6a** cannot be ruled out as the reaction yields increased significantly in the presence of molecular oxygen.



Scheme 3.5 Synthesis of xanthene containing bis-indolylmethane derivatives.

The existence of carbocation in the presence of Fe(III)-salt under the reaction conditions was further demonstrated by the addition of another nucleophile such as indole. After the formation of **6a** (monitored by TLC), adding indole directly to the reaction mixture led to an interesting xanthene fused bis-indolylmethane derivative **6aa** with a 69% overal yield (**Scheme 3.5**). Using this one-pot method, we were also synthesized substituted 3-(9-indol-3-yl-9*H*-xanthen-9-yl)-indole deivatives **6ab** and **6ea** in overall good yields, (**Scheme 3.5**, 74% and 70%) by employing *N*-methyl indole as nucleophile.

3.3 CONCLUSION

In conclusion, a novel and efficient $Fe(NO_3)_3/FeCl_3$-catalyzed synthesis of indole-xanthydrol hybrid scaffold in the presence of molecular oxygen as terminal oxidant has been developed. The present strategy proceeds through a series of reactions such as allylic oxidation, isomerization, cyclisation and hydroxylation in tandem manner. The preliminary mechanistic investigation revealed that the reaction is initiated by the generation of radical in the presence of iron(III)-salts. This method could be used to synthesize a variety of indole-xanthydrol hybrids in high yields. The notable features of this reaction are mild reaction conditions, operational simplicity, ease of preparation of starting materials, and environmentally benign reaction conditions. The synthetic utility of this strategy was demonstrated by the one-pot synthesis of xanthene tethered bis indolylmethane derivatives. We believe that both synthetic and medicinal chemist will find this chemistry interesting and this newly developed method will open up a new avenue for the synthesis of diverse indole containing hybrid compounds.

3.4 EXPERIMENTAL PROCEDURE

3.4.1 Representative Experimental Procedure for the Synthesis of 1-iodo-2-phenoxybenzene (B)

As shown in Scheme 3.2 (a) the compound **B** has been synthesized in three steps.

Step 1 To an oven-dried 50 mL round-bottomed flask, 2-fluoronitrobenzene (500 mg, 3.55 mmol) phenol (334 mg, 3.55 mmol) and K_2CO_3 (980 mg, 7.1 mmol) were added in DMF (20 mL) under Ar atmosphere. The reaction mixture was stirred for 3 hours at 100 °C. After completion of the reaction (monitored by TLC), the reaction mixture was extracted with ethyl acetate and washed with water. The combined organic layer was separated and dried over anhydrous Na_2SO_4. It was then concentrated under reduced pressur, and the resulting crude mixture was purified by column chromatography on silica gel (60-120 mesh), eluted by solvent Petroleum ether/ethyl acetate (95:5) to afford the product of the substitution reaction, 1-nitro-2-phenoxybenzene (610 mg, 80%) as a brown color liquid.

Step 2 The product of Step 1, 1-nitro-2-phenoxybenzene (600 mg, 2.79 mmol) was taken in ethanol (15 mL) in a 50 mL round-bottomed flask. To this mixture, iron powder (624 mg, 11.16 mmol), 20 mol% HCl (17 µL). The reaction mixture was stirred at 80 °C for 4 hours. After the reaction was complete (monitored by TLC), the reaction mixture was subjected for filtration

through celite pad. Then, the filtrate was extracted with ethyl acetate and the combined organic layer was washed with water, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The crude material was purified by silica gel (60-120 mesh) column chromatography, eluted by mixed solvent petroleum ether/ethyl acetate (90:10 v/v), to afford 2-phenoxyaniline (387 mg, 75%) as a brown sticky liquid.

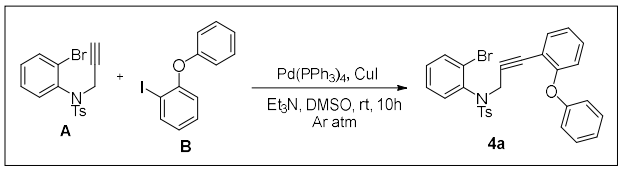
Step 3 The purified product of step 2, 2-phenoxyaniline (380 mg, 2.05 mmol) was taken in a 100 mL round-bottom flask. PTSA (706 mg, 4.11 mmol) and a mixture of MeCN (5 mL) and water (10 mL) were added to it. The mixture was placed in an ice bath and stirred for 5 minutes. Then, saturated aqueous $NaNO_2$ (283 mg, 4.11 mmol) was added drop wise at 0-5 °C. Then, aqueous KI (657 mg, 4.11 mmol) solution was poured into the mixture after formation of a clear greenish solution. After the addition was complete, the reaction was allowed to run at room temperature overnight. Next day, the reaction mixture was quenched by $Na_2S_2O_3{\cdot}5H_2O$ and neutralized by $NaHCO_3$ successively. Then, the reaction mixture was extracted with DCM. After separation from the aqueous layer, the combined organic layer was dried over anhydrous Na_2SO_4 and concentrated under pressure. After that, column chromatography on silica gel (60-120 mesh) was performed to purify the 1-iodo-2-phenoxybenzene **B**. The desired 1-iodo-2-phenoxybenzene **B** (424 mg, 70%) was eluted as a white liquid with petroleum ether.

3.4.2 Another Experimental Procedure for the Synthesis of 1-iodo-2-phenoxybenzene (B)

As shown in Scheme 3.2 (b) the compound B has been synthesized by Chan-Lam coupling

To a solution of 2-iodophenol (220 mg, 1.0 mmol), phenylboronic acid (146 mg, 1.2 mmol) in DCM (10 ml) were added Et_3N (505 mg, 5 mmol), pyridine (395 mg, 5 mmol) and $Cu(OAc)_2$ (217 mg, 1.2 mmol) successively. The resulting mixture was stirred at room temperature for 18 h under molecular oxygen atmosphere. After the completion of the reaction (monitored by TLC), the crude reaction mixture was extracted with DCM. The combined organic extracts were washed with brine solution, dried over anhydrous Na_2SO_4 and concentrated. The product was subjected to column chromatography (silica gel, 60-120 mesh), eluting with petroleum ether to afford the product **B** as a colorless liquid (192 mg, 65%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.91 (dd, J = 7.8, 1.6 Hz, 1H), 7.43 – 7.34 (m, 2H), 7.33 – 7.29 (m, 1H), 7.20 – 7.13 (m, 1H), 7.06 – 6.98 (m, 2H), 6.96 – 6.92 (m, 1H), 6.90 (dd, J = 7.6, 1.5 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.90, 156.55, 139.93, 129.88, 129.70, 125.39, 123.54, 119.51, 118.48, 89.00.

3.4.3 Representative experimental procedure for the synthesis of 2-bromo-*N*-(3-(2-phenoxyphenyl)prop-2-ynyl)-*N*-tosylbenzenamine (4a)



To a solution of 2-bromo-*N*-(prop-2-ynyl)-*N*-tosylbenzenamine **A** (109 mg, 0.3 mmol), 1-iodo-2-phenoxybenzene **B** (98 mg, 0.33 mmol) and triethyl amine (91 mg, 0.9 mmol) in DMSO (2 mL) were added CuI (3 mg, 0.015 mmol) and $Pd(PPh_3)_4$ (17 mg, 0.015 mmol) successively. The resulting mixture was stirred at room temperature for 10 h under argon atmosphere. After the completion of the reaction (monitored by TLC), the crude reaction mixture was extracted with EtOAc. The organic extract was washed with brine solution, dried over anhydrous Na_2SO_4 and concentrated. The product was subjected to column chromatography (silica gel, 60-120 mesh), eluting with Hexane/EtOAc 97:3 (v/v) to afford the product **4a** as a light yellow viscous liquid (135 mg, 0.225 mmol, 85%).

Compounds **4b-4m** were synthesized by the above similar procedure.

2-bromo-*N*-(3-(2-phenoxyphenyl)prop-2-ynyl)-*N*-tosylbenzenamine (4a): light yellow viscous liquid (135 mg, 85%), ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89 – 7.83 (m, 2H), 7.72 (dd, *J* = 8.0, 1.5 Hz, 1H) 7.48 – 7.32 (m, 6H), 7.30 – 7.21 (m, 3H), 7.14 (td, *J* = 7.5, 1.1 Hz, 1H), 7.07 – 6.97 (m, 3H), 6.92 (dd, *J* = 8.4, 1.1 Hz, 1H), 5.14 (d, *J* = 18.3 Hz, 1H), 4.43 (d, *J* = 18.3 Hz, 1H), 2.49 (s, 3H), ^{13}C NMR (101 MHz, $CDCl_3$) δ 157.95, 156.85, 143.64, 137.52, 137.05, 133.71, 133.62, 132.20, 130.18, 129.83, 129.78, 129.41, 128.19, 127.79, 125.95, 123.61, 123.03, 118.93, 118.25, 114.53, 87.66, 81.60, 41.45, 21.57.

***N*-(3-(2-(4-methoxyphenoxy)phenyl)prop-2-ynyl)-2-bromo-*N*-tosylbenzenamine (4b)**: yellow viscous liquid (152 mg, 90%), ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.77 – 7.71 (m, 2H), 7.61 (dd, *J* = 8.0, 1.5 Hz, 1H), 7.24 (d, *J* = 1.7 Hz, 1H), 7.23 – 7.21 (m, 2H), 7.20 (d, *J* = 1.4 Hz, 1H), 7.18 – 7.09 (m, 2H), 7.00 – 6.96 (m, 1H), 6.95 – 6.83 (m, 5H), 6.67 (dd, *J* = 8.4, 1.1 Hz, 1H), 5.04 (d, *J* = 18.3 Hz, 1H), 4.34 (d, *J* = 17.7 Hz, 1H), 3.82 (s, 3H), 2.36 (s, 3H), ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.13, 155.11, 148.73, 142.54, 136.52, 136.06, 132.68, 132.48, 131.28, 129.14, 128.65, 128.35, 127.18, 126.73, 124.97, 121.16, 119.80, 115.53, 113.84, 112.47, 86.46,

80.77, 54.66, 40.48, 20.52.

***N*-(3-(2-(p-tolyloxy)phenyl)prop-2-ynyl)-2-bromo-*N*-tosylbenzenamine (4c)**: yellow viscous liquid (144 mg, 88%), ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.74 (d, *J* = 7.9 Hz, 2H), 7.61 (d, *J* = 8.0 Hz, 1H), 7.26 – 7.09 (m, 8H), 7.03 – 6.89 (m, 2H), 6.76 (dd, *J* = 15.8, 8.4 Hz, 3H), 5.04 (d, *J* = 18.4 Hz, 1H), 4.31 (d, *J* = 18.4 Hz, 1H), 2.36 (s, 3H), 2.35 (s, 3H), ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.54, 154.29, 143.59, 137.54, 137.07, 133.70, 133.53, 133.33, 132.25, 130.27, 130.17, 129.72, 129.39, 128.20, 127.78, 125.99, 122.54, 119.20, 117.44, 114.02, 87.50, 81.75, 41.49, 21.55, 20.77.

***N*-(3-(2-(4-chlorophenoxy)phenyl)prop-2-ynyl)-2-bromo-*N*-tosylbenzenamine (4d)**: colourless viscous liquid (139 mg, 82%), ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.78 – 7.71 (m, 2H), 7.62 (dd, *J* = 8.3, 1.4 Hz, 1H), 7.29 (td, *J* = 5.1, 4.5, 2.5 Hz, 3H), 7.26 – 7.19 (m, 3H), 7.17 (d, *J* = 1.6 Hz, 1H), 7.15 (s, 1H), 7.05 (dtd, *J* = 12.6, 8.6, 8.1, 1.4 Hz, 2H), 6.87 – 6.81 (m, 2H), 6.80 (d, *J* = 2.2 Hz, 1H), 4.99 (d, *J* = 18.2 Hz, 1H), 4.33 (d, *J* = 18.3 Hz, 1H), 2.40 (s, 3H), ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.30, 155.67, 143.72, 137.46, 136.98, 133.82, 133.77, 132.14, 130.25, 130.02, 129.73, 129.45, 128.42, 128.15, 127.79, 125.89, 123.67, 119.82, 118.72, 114.86, 88.03, 81.26, 41.38, 21.60.

2-bromo-*N*-(3-(5-methyl-2-phenoxyphenyl)prop-2-ynyl)-*N*-tosylbenzenamine (4e): yellow viscous liquid (138 mg, 84%), ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.77 – 7.68 (m, 2H), 7.59 (dd, *J* = 8.3, 1.5 Hz, 1H), 7.33 – 7.26 (m, 2H), 7.22 (d, *J* = 8.0 Hz, 2H), 7.16 – 7.00 (m, 5H), 6.92 (td, *J* = 7.6, 1.5 Hz, 1H), 6.87 – 6.80 (m, 2H), 6.73 (d, *J* = 8.3 Hz, 1H), 5.00 (d, *J* = 18.4 Hz, 1H), 4.27 (d, *J* = 18.4 Hz, 1H), 2.38 (s, 3H), 2.29 (s, 3H), ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.39, 155.50, 143.59, 137.51, 137.09, 133.87, 133.69, 132.81, 132.19, 130.60, 130.16, 129.68, 129.41, 128.19, 127.80, 125.92, 123.16, 118.77, 118.39, 114.52, 87.29, 81.69, 41.43, 21.60, 20.53.

2-bromo-4-methyl-*N*-(3-(2-phenoxyphenyl)prop-2-ynyl)-*N*-tosylbenzenamine (4f): pale yellow viscous liquid (141 mg, 86%), **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.76 – 7.68 (m, 2H), 7.42 – 7.27 (m, 4H), 7.23 – 7.17 (m, 3H), 7.16 – 7.08 (m, 1H), 7.01 (dd, *J* = 8.2, 6.6 Hz, 2H), 6.92 – 6.84 (m, 2H), 6.79 (dd, *J* = 8.3, 1.1 Hz, 1H), 6.69 (dd, *J* = 8.3, 2.0 Hz, 1H), 4.99 (d, *J* = 18.4 Hz, 1H), 4.28 (d, *J* = 18.3 Hz, 1H), 2.37 (s, 3H), 2.24 (s, 3H), ^{13}C NMR (75 MHz, $CDCl_3$) δ

157.95, 156.86, 143.50, 140.62, 137.15, 134.70, 134.11, 133.62, 131.66, 129.75, 129.35, 128.56, 128.16, 125.45, 123.56, 122.97, 118.98, 118.20, 114.58, 87.81, 81.42, 41.47, 21.55, 20.85.

2-bromo-4,6-dimethyl-*N*-(3-(2-phenoxyphenyl)prop-2-ynyl)-*N*-tosylbenzenamine (4g): pale yellow viscous liquid (134 mg, 80%), ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.80 – 7.71 (m, 2H), 7.43 – 7.23 (m, 6H), 7.19 (d, *J* = 3.0 Hz, 1H), 7.14 (d, *J* = 8.3 Hz, 1H), 7.03 (d, *J* = 8.8 Hz, 1H), 6.92 (d, *J* = 7.8 Hz, 3H), 6.81 (d, *J* = 8.4 Hz, 1H), 4.88 (dd, *J* = 18.0, 3.6 Hz, 1H), 4.48 (dd, *J* = 17.8, 3.5 Hz, 1H), 2.42 (s, 3H), 2.39 (s, 3H), 2.25 (s, 3H), ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.94, 156.81, 143.40, 143.28, 139.96, 138.14, 134.10, 133.72, 131.78, 131.75, 131.25, 129.93, 129.67, 129.65, 129.44, 129.42, 127.88, 124.81, 123.48, 122.94, 119.54, 119.02, 118.19, 114.61, 88.00, 80.96, 40.88, 21.57, 20.72, 20.18.

***N*-(2-bromo-4-methoxyphenyl)-4-methyl-*N*-(3-(2-phenoxyphenyl)prop-2-yn-1-yl)benzenesulfonamide (4h)**: pale yellow viscous liquid (145 mg, 86%), ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.39 (s, 3H), 3.71 (s, 3H), 4.28 (d, *J* = 18.3 Hz, 1H), 5.04 (d, *J* = 18.3 Hz, 1H), 6.38 (dd, *J* = 8.8, 2.9 Hz, 1H), 6.82 (d, *J* = 8.3 Hz, 1H), 6.91 (dd, *J* = 8.0, 1.8 Hz, 2H), 6.99 – 7.09 (m, 2H), 7.15 (td, *J* = 6.7, 5.8, 1.9 Hz, 2H), 7.23 (d, *J* = 8.3 Hz, 3H), 7.28 – 7.40 (m, 3H), 7.75 (d, *J* = 8.0 Hz, 2H), ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.56, 41.64, 55.63, 81.50, 87.87, 113.27, 114.59, 118.19, 118.83, 119.00, 123.03, 123.60, 126.50, 128.19, 129.36, 129.78, 129.80, 130.01, 132.45, 133.60, 137.08, 143.51, 156.89, 157.97, 159.98.

2-bromo-4-fluoro-*N*-(3-(2-phenoxyphenyl)prop-2-ynyl)-*N*-tosylbenzenamine(4i): yellow viscous liquid (135 mg, 82%), ^{1}H NMR (300 MHz, $CDCl_3$) 7.74 (d, *J* = 8.1 Hz, 2H), 7.38 – 7.30 (m, 5H), 7.23 (S, 2H), 7.18 – 7.12 (m, 2H), 7.04 (t, *J* = 7.5 Hz, 1H), 6.89 (d, *J* = 7.5 Hz, 2H), 6.82 (d, *J* = 8.1 Hz, 1H), 6.58 (td, *J* = 8.1, 2.7 Hz, 1H), 5.04 (d, *J* = 18.3 Hz, 1H), 4.29 (d, *J* = 18.3 Hz, 1H), 2.39 (s, 3H), ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.62, 160.26, 157.96, 156.82, 143.83 , 136.73, 133.77, 133.72, 133.56, 133.17, 133.05, 129.96, 129.86, 129.49, 128.16, 126.81, 123.69, 123.10, 121.05, 120.72, 118.86, 118.28, 114.99, 114.70, 114.40, 87.34, 81.84, 41.48, 21.58.

2-bromo-4-chloro-*N*-(3-(2-phenoxyphenyl)prop-2-ynyl)-*N*-tosylbenzenamine (4j): yellow viscous liquid (131 mg, 77%), ^{1}H NMR (300 MHz, $CDCl_3$) 7.72 (d, *J* = 8.4 Hz, 2H), 7.60 (d, *J*

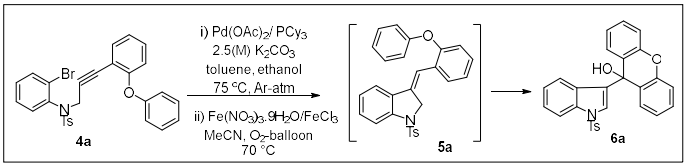
= 2.1 Hz, 1H), 7.38 – 7.31 (m, 3H), 7.28 – 7.22 (m, 3H), 7.16 (t, *J* = 7.5 Hz, 1H), 7.09 – 6.98 (m, 2H), 6.89 (d, *J* = 7.8 Hz, 2H), 6.85 – 6.80 (m, 2H), 5.01 (d, *J* = 17.7 Hz, 1H), 4.29 (d, *J* = 18.3 Hz, 1H), 2.39 (s, 3H), ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.95, 156.81, 143.86 , 136.69, 136.12, 135.61, 133.55, 133.36, 132.82, 129.94, 129.85, 129.81, 128.79, 128.14, 128.08, 127.32, 126.58, 123.67, 123.07, 118.85, 118.29, 114.37, 87.23, 81.84, 41.36, 21.58.

***N*-(3-(2-(4-methoxyphenoxy)phenyl)prop-2-ynyl)-2-bromo-4-chloro-*N*-tosylbenzenamine (4k)**: light yellow viscous liquid (141 mg, 79%), **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.79 – 7.70 (m, 2H), 7.62 (d, *J* = 2.4 Hz, 1H), 7.30 – 7.19 (m, 4H), 7.16 (d, *J* = 8.5 Hz, 1H), 6.98 (td, *J* = 7.5, 1.1 Hz, 1H), 6.94 – 6.85 (m, 5H), 6.70 (dd, *J* = 8.3, 1.1 Hz, 1H), 5.05 (d, *J* = 18.3 Hz, 1H), 4.34 (d, *J* = 18.3 Hz, 1H), 3.85 (s, 3H), 2.39 (s, 3H), ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.18, 156.19, 149.69, 143.87, 136.69, 136.17, 135.39, 133.43, 133.37, 132.91, 129.85, 129.51, 128.16, 128.09, 126.67, 122.27, 120.77, 116.60, 114.96, 113.31, 87.04, 82.11, 55.73, 41.44, 21.59.

***N*-(3-(2-(4-methoxyphenoxy)phenyl)prop-2-ynyl)-2-bromo-4-fluoro-*N*-tosylbenzenamine (4l)**: light yellow viscous liquid (132 mg, 76%), ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.75 – 7.69 (m, 2H), 7.32 (dd, *J* = 8.0, 2.9 Hz, 1H), 7.23 (dd, *J* = 2.7, 1.6 Hz, 2H), 7.21 – 7.14 (m, 3H), 6.96 (td, *J* = 7.5, 1.1 Hz, 1H), 6.91 – 6.83 (m, 4H), 6.67 (dd, *J* = 8.4, 1.1 Hz, 1H), 6.62 (ddd, *J* = 8.8, 7.7, 2.9 Hz, 1H), 5.04 (d, *J* = 18.3 Hz, 1H), 4.31 (d, *J* = 18.3 Hz, 1H), 3.82 (s, 3H), 2.37 (s, 3H), ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.64, 160.28, 159.19, 156.20, 149.67, 143.78, 136.74, 133.78, 133.73, 133.42, 133.27, 133.15, 129.80, 129.71, 129.46, 128.18, 127.34, 126.85, 126.72, 122.25, 121.06, 120.77, 120.72, 116.55, 114.97, 114.94, 114.68, 113.33, 87.16, 82.05, 55.70, 41.53, 21.56.

2-bromo-4-methyl-*N*-(3-(5-methyl-2-phenoxyphenyl)prop-2-ynyl)-*N*-tosylbenzenamine (4m): colorless viscous liquid (144 mg, 86%), ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.75 (d, *J* = 8.0 Hz, 2H), 7.43 (d, *J* = 1.9 Hz, 1H), 7.32 (t, *J* = 7.8 Hz, 2H), 7.24 (d, *J* = 7.9 Hz, 2H), 7.15 – 7.03 (m, 3H), 6.99 (d, *J* = 8.1 Hz, 1H), 6.91 – 6.82 (m, 2H), 6.79 – 6.67 (m, 2H), 5.00 (d, *J* = 18.3 Hz, 1H), 4.27 (d, *J* = 18.3 Hz, 1H), 2.40 (s, 3H), 2.31 (s, 3H), 2.27 (s, 3H), ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.41, 155.51, 143.46, 140.60, 137.19, 134.72, 134.10, 133.88, 132.76, 131.65, 130.53, 129.65, 129.62, 129.37, 128.58, 128.17, 127.36, 125.44, 123.13, 118.73, 118.44, 114.57, 87.44, 81.55, 41.46, 21.58, 20.86, 20.52.

3.4.4 Representative experimental procedure and characterization data for the synthesis of 9-(1-tosyl-1H-indol-3-yl)-9H-xanthen-9-ol (6a) without isolation of precursor (5a)



To a solution of **4a** (106 mg, 0.2 mmol) in toluene (2 mL) and ethanol (2 mL) were added aq. K_2CO_3 solution (2.5 M, 2 mL), PCy_3 (6 mg, 0.02 mmol) and $Pd(OAc)_2$ (2 mg, 0.01 mmol) successively. The resulting solution was stirred at 75 °C under argon atmosphere for 2 h. After the completion of the reaction (monitored by TLC), the crude reaction mixture was extracted with EtOAc. The organic extract was washed with brine solution, dried over anhydrous Na_2SO_4 and concentrated. The crude product **5a** was dissolved in acetonitrile (3 mL) and $Fe(NO_3)_3 \cdot 9H_2O$ (24 mg, 30 mol%) and $FeCl_3$ (10 mg, 30 mol%) were added to it. The reaction was continued at 70 °C for 3 h under oxygen atmosphere. After the completion of the reaction (monitored by TLC) the crude reaction mixture was extracted with DCM. The organic extract was washed with brine solution, dried over anhydrous Na_2SO_4 and concentrated. The product was subjected to column chromatography (silica gel, 60-120 mesh), eluting with Hexane/EtOAc 93:7 (v/v) to afford the product **6a** as a white solid (73 mg, 0.16 mmol, 78%). Compounds **6b**-**6m** were synthesized following the same procedure.

9-(1-tosyl-1*H*-indol-3-yl)-9*H*-xanthen-9-ol (6a): 73 mg (78%); white crystalline solid; m. p. 176 – 180 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.09 (s, 1H), 7.98 (d, *J* = 8.4 Hz, 1H), 7.87 (d, *J* = 8.0 Hz, 2H), 7.39 – 7.27 (m, 8H), 7.20 (t, *J* = 7.8 Hz, 1H), 7.01 (t, *J* = 7.4 Hz, 2H), 6.92 (t, *J* = 7.6 Hz, 1H), 6.66 (d, *J* = 8.0 Hz, 1H), 2.69 (s, 1H), 2.43 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 149.81, 144.95, 136.05, 135.22, 129.87, 129.73, 128.92, 128.74, 128.32, 126.90, 124.50, 124.44, 123.75, 123.62, 123.24, 120.43, 116.65, 113.78, 67.83, 21.60; HRMS: m/z calcd for $C_{28}H_{21}NO_4S$: $[M+H]^+$ 468.1270, found 468.1273.

2-methoxy-9-(1-tosyl-1*H*-indol-3-yl)-9*H*-xanthen-9-ol (6b): 70 mg (70%); white solid; m. p. 108 – 110 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.02 (s, 1H), 7.94 (dt, *J* = 8.4, 0.9 Hz, 1H), 7.84

– 7.78 (m, 2H), 7.29 (d, *J* = 1.5 Hz, 1H), 7.26 – 7.22 (m, 3H), 7.20 (d, *J* = 1.3 Hz, 1H), 7.19 – 7.12 (m, 2H), 6.98 – 6.83 (m, 3H), 6.73 (d, *J* = 3.0 Hz, 1H), 6.65 (dt, *J* = 8.0, 1.0 Hz, 1H), 3.56 (s, 3H), 2.64 (s, 1H), 2.36 (s, 3H); ^{13}C NMR (101 MHz, CHLOROFORM-*D*) δ 155.58, 149.97, 144.97, 144.01, 136.10, 135.31, 129.92, 129.80, 129.73, 129.15, 128.79, 128.35, 126.91, 124.89, 124.60, 123.87, 123.53, 123.43, 123.36, 120.45, 117.71, 117.08, 116.62, 113.83, 111.60, 68.20, 55.50, 21.66; HRMS: m/z calcd for $C_{29}H_{23}NO_5S$: $[M+H]^+$ 498.1375, found 498.1370.

2-methyl-9-(1-tosyl-1*H*-indol-3-yl)-9*H*-xanthen-9-ol (6c): 71 mg (74%); white solid; m. p. 108 – 112 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.05 (s, 1H), 7.94 (dt, *J* = 8.4, 0.9 Hz, 1H), 7.85 – 7.80 (m, 2H), 7.30 (dd, *J* = 8.4, 1.6 Hz, 1H), 7.27 (d, *J* = 1.1 Hz, 1H), 7.25 (d, *J* = 1.7 Hz, 1H), 7.23 – 7.21 (m, 1H), 7.20 – 7.11 (m, 2H), 7.10 (dd, *J* = 2.2, 1.3 Hz, 2H), 7.01 (dt, *J* = 1.8, 0.9 Hz, 1H), 6.94 (ddd, *J* = 8.0, 7.0, 1.4 Hz, 1H), 6.87 (ddd, *J* = 8.1, 7.2, 1.0 Hz, 1H), 6.60 (dt, *J* = 8.0, 1.0 Hz, 1H), 2.61 (s, 1H), 2.37 (s, 3H), 2.14 (s, 3H); ^{13}C NMR (101 MHz, CHLOROFORM-*D*) δ 149.92, 147.76, 144.97, 136.17, 135.29, 133.04, 130.76, 130.09, 129.91, 129.73, 129.28, 128.86, 128.65, 128.49, 126.94, 124.55, 124.38, 123.92, 123.65, 123.49, 123.33, 120.50, 116.67, 116.45, 113.86, 67.90, 21.67, 20.81; HRMS: m/z calcd for $C_{29}H_{23}NO_4S$: $[M+H]^+$ 482.1426, found 482.1244.

2-chloro-9-(1-tosyl-1*H*-indol-3-yl)-9*H*-xanthen-9-ol (6d): 71 mg (71%); white solid; m. p. 103 – 105 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.04 (s, 1H), 7.95 (d, J = 8.4 Hz, 1H), 7.83 – 7.78 (m, 2H), 7.36 – 7.28 (m, 3H), 7.25 – 7.19 (m, 3H), 7.18 – 7.16 (m, 2H), 7.15 (d, J = 1.4 Hz, 1H), 7.00 (ddd, J = 8.2, 7.0, 1.4 Hz, 1H), 6.89 (td, J = 7.6, 1.0 Hz, 1H), 6.59 (d, J = 8.0 Hz, 1H), 240(s, 1H), 2.37 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 149.45, 148.29, 145.11, 136.15, 134.95, 130.02, 129.97, 128.79, 128.66, 128.43, 128.36, 128.07, 126.76, 125.94, 124.69, 124.04, 123.81, 123.78, 123.40, 120.14, 118.24, 116.66, 113.97, 67.65, 21.65; HRMS: m/z calcd for $C_{28}H_{20}ClNO_4S$: $[M+H]^+$ 502.0880, found 502.0891.

2-methyl-9-(1-tosyl-1*H*-indol-3-yl)-9*H*-xanthen-9-ol (6e): 71 mg (76%); white solid; m. p. 105 – 109 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.07 (s, 1H), 7.96 (d, *J* = 8.4 Hz, 1H), 7.84 (d, *J* = 8.1 Hz, 2H), 7.34 – 7.27 (m, 3H), 7.24 (d, *J* = 2.3 Hz, 1H), 7.22 – 7.07 (m, 4H), 7.03 (s, 1H), 6.95 (dd, *J* = 8.1, 6.8 Hz, 1H), 6.89 (t, *J* = 7.6 Hz, 1H), 6.63 (d, *J* = 7.9 Hz, 1H), 2.39 (s, 3H),

2.16 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 149.85, 147.69, 144.93, 136.11, 135.20, 132.98, 130.69, 129.86, 129.66, 129.24, 128.81, 128.59, 128.42, 126.88, 124.49, 124.31, 123.85, 123.58, 123.43, 123.28, 120.44, 116.60, 116.39, 113.80, 67.82, 21.60, 20.75; HRMS: m/z calcd for $C_{29}H_{23}NO_4S$: $[M+H]^+$ 482.1426, found 482.1428.

9-(5-methyl-1-tosyl-1*H*-indol-3-yl)-9*H*-xanthen-9-ol (6f): 76 mg (79%); white crystalline solid; m. p. 184 – 186 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99 (s, 1H), 7.83 (dd, J = 8.3, 5.7 Hz, 3H), 7.36 – 7.31 (m, 2H), 7.29 – 7.25 (m, 6H), 6.99 (ddd, J = 8.0, 4.9, 2.4 Hz, 3H), 6.41 (s, 1H), 2.64 (s, 1H), 2.40 (s, 3H), 2.11 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.84, 144.83, 135.17, 134.32, 132.85, 129.82, 129.71, 128.69, 128.65, 128.56, 126.86, 126.03, 124.49, 124.10, 123.62, 120.34, 116.65, 113.48, 67.89, 21.61, 21.34; HRMS: m/z calcd for $C_{29}H_{23}NO_4S$: $[M+H]^+$ 482.1426, found 482.1431.

9-(5,7-dimethyl-1-tosyl-1*H*-indol-3-yl)-9*H*-xanthen-9-ol (6g): 68 mg (69%); white solid; m. p. 177 – 179 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.15 (s, 1H), 7.66 – 7.60 (m, 2H), 7.35 (ddd, *J* = 8.5, 7.0, 1.6 Hz, 3H), 7.30 – 7.28 (m, 3H), 7.20 (dd, *J* = 7.9, 1.6 Hz, 2H), 7.03 – 6.97 (m, 2H), 6.76 (s, 1H), 6.22 (s, 1H), 2.60 (s, 3H), 2.44 (s, 3H), 2.05 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 149.92, 144.40, 136.18, 134.81, 133.45, 130.99, 129.80, 129.73, 129.68, 128.71, 128.64, 128.04, 126.68, 125.57, 124.45, 123.55, 118.23, 116.64, 67.83, 21.74, 21.62, 20.97; HRMS: m/z calcd for $C_{30}H_{25}NO_4S$: $[M+H]^+$ 496.1583, found 496.1593.

9-(5-methoxy-1-tosyl-1*H*-indol-3-yl)-9*H*-xanthen-9-ol (6h): 80 mg (81%); white solid; m. p. 160-165 °C; ^{1}H NMR (400 MHz, CHLOROFORM-*D*) δ 2.37 (s, 3H), 2.67 (s, 1H), 3.44 (s, 3H), 6.05 (d, *J* = 2.5 Hz, 1H), 6.73 (dd, *J* = 9.0, 2.5 Hz, 1H), 6.96 (ddd, *J* = 8.2, 7.1, 1.3 Hz, 2H), 7.18 – 7.23 (m, 3H), 7.24 (dd, *J* = 2.5, 1.0 Hz, 2H), 7.26 – 7.31 (m, 3H), 7.73 – 7.82 (m, 3H), 7.96 (s, 1H); ^{13}C NMR (101 MHz, CHLOROFORM-*D*) δ 21.68, 55.27, 67.76, 103.16, 113.13, 114.74, 116.61, 123.73, 124.39, 124.43, 126.88, 128.81, 129.33, 129.46, 129.81, 129.87, 130.80, 135.14, 144.90, 149.87, 156.03.; HRMS: m/z calcd for $C_{29}H_{23}NO_5S$: $[M]^+$ 497.1297, found 497.1294.

9-(5-fluoro-1-tosyl-1*H*-indol-3-yl)-9*H*-xanthen-9-ol (6i): 79 mg (82%); white solid; m. p. 170 – 174 °C; ^{1}H NMR (400 MHz, CHLOROFORM-*D*) δ 8.02 (s, 1H), 7.85 (dd, *J* = 9.0, 4.4 Hz, 1H), 7.79 – 7.75 (m, 2H), 7.32 (d, *J* = 1.7 Hz, 1H), 7.30 (t, *J* = 1.4 Hz, 1H), 7.28 (d, *J* = 1.7 Hz,

1H), 7.24 (s, 1H), 7.22 (d, *J* = 1.5 Hz, 2H), 7.20 (d, *J* = 1.6 Hz, 2H), 6.96 (ddd, *J* = 8.0, 7.1, 1.3 Hz, 2H), 6.86 (td, *J* = 9.0, 2.6 Hz, 1H), 6.27 (dd, *J* = 9.1, 2.5 Hz, 1H), 2.37 (s, 3H); ^{13}C NMR (101 MHz, CHLOROFORM-*D*) δ 160.50, 158.11, 149.84, 145.25, 134.98, 132.45, 130.01, 129.97, 129.50, 129.40, 129.08, 129.03, 128.66, 126.93, 125.49, 124.14, 123.75, 116.88, 115.02, 114.93, 112.85, 112.60, 106.37, 106.12, 67.75, 21.71; HRMS: m/z calcd for $C_{28}H_{20}FNO_4S$: $[M+H]^+$ 486.1175, found 486.1195.

9-(5-chloro-1-tosyl-1*H*-indol-3-yl)-9*H*-xanthen-9-ol (6j): 66 mg (66%); white solid; m. p. 202 – 206 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00 (s, 1H), 7.85 (d, *J* = 8.9 Hz, 1H), 7.80 – 7.75 (m, 2H), 7.36 – 7.26 (m, 4H), 7.26 – 7.23 (m, 3H), 7.21 (d, *J* = 1.6 Hz, 1H), 7.12 (dd, *J* = 8.8, 2.1 Hz, 1H), 6.99 (ddd, *J* = 8.2, 7.1, 1.3 Hz, 2H), 6.62 (d, *J* = 2.0 Hz, 1H), 2.66 (s, 1H), 2.40 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 149.77, 145.29, 134.86, 134.41, 129.98, 129.95, 129.52, 129.12, 128.52, 128.46, 126.86, 125.28, 124.93, 124.12, 123.71, 120.16, 116.86, 114.86, 67.74, 21.65; HRMS: m/z calcd for $C_{28}H_{20}ClNO_4S$: $[M+H]^+$ 502.0880, found 502.0884.

9-(5-chloro-1-tosyl-1*H*-indol-3-yl)-2-methoxy-9*H*-xanthen-9-ol (6k): 64 mg (60%); off white solid; m. p. 150 – 152 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.99 (s, 1H), 7.86 (d, *J* = 8.9 Hz, 1H), 7.80 – 7.76 (m, 2H), 7.31 (ddd, *J* = 8.5, 7.0, 1.6 Hz, 2H), 7.24 (d, *J* = 1.3 Hz, 1H), 7.22 (dd, *J* = 3.0, 1.5 Hz, 1H), 7.19 (d, *J* = 1.1 Hz, 1H), 7.16 (s, 1H), 7.12 (dd, *J* = 8.9, 2.1 Hz, 1H), 6.97 (ddd, *J* = 8.0, 7.0, 1.3 Hz, 1H), 6.89 (dd, *J* = 9.0, 3.0 Hz, 1H), 6.67 (dd, *J* = 15.8, 2.5 Hz, 2H), 3.59 (s, 3H), 2.59 (s, 1H), 2.38 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.55, 149.86, 145.24, 143.89, 134.87, 134.38, 129.96, 129.88, 129.47, 129.15, 128.57, 128.49, 126.80, 124.99, 124.96, 124.49, 123.45, 120.10, 117.85, 117.07, 116.76, 114.84, 111.43, 68.02, 55.46, 21.62; HRMS: m/z calcd for $C_{29}H_{22}ClNO_5S$: $[M+H]^+$ 532.0985, found 532.0978.

9-(5-fluoro-1-tosyl-1*H*-indol-3-yl)-2-methoxy-9*H*-xanthen-9-ol (6l): 56 mg (55%); brownish semi solid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.03 (s, 1H), 7.88 (dd, *J* = 9.1, 4.5 Hz, 1H), 7.78 (d, *J* = 8.4 Hz, 2H), 7.35 – 7.30 (m, 1H), 7.28 (d, *J* = 1.7 Hz, 1H), 7.26 – 7.20 (m, 3H), 7.17 (d, *J* = 9.1 Hz, 1H), 6.96 (ddd, *J* = 8.2, 7.0, 1.4 Hz, 1H), 6.92 – 6.84 (m, 2H), 6.70 (d, *J* = 3.0 Hz, 1H), 6.31 (dd, *J* = 9.1, 2.5 Hz, 1H), 3.59 (s, 3H), 2.65 (s, 1H), 2.38 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.65, 155.55, 149.86, 145.13, 143.89, 134.92, 132.35, 129.91, 129.84, 129.08, 128.55, 126.79, 125.13, 124.43, 123.41, 117.81, 117.06, 116.72, 114.94, 114.81, 112.86,

112.52, 111.45, 106.29, 105.96, 100.00, 67.98, 55.45, 21.62; HRMS: m/z calcd for $C_{29}H_{22}FNO_5S$: $[M+H]^+$ 516.1281, found 516.1286.

2-methyl-9-(5-methyl-1-tosyl-1*H*-indol-3-yl)-9*H*-xanthen-9-ol (6m): 74 mg (75%); white solid; m. p. 184 – 188 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.98 (s, 1H), 7.84 – 7.78 (m, 3H), 7.33 – 7.26 (m, 2H), 7.25 – 7.22 (m, 2H), 7.20 (dd, *J* = 3.9, 1.5 Hz, 1H), 7.15 – 7.07 (m, 2H), 7.03 – 6.90 (m, 3H), 6.38 (dt, *J* = 1.7, 0.8 Hz, 1H), 2.59 (s, 1H), 2.37 (s, 3H), 2.15 (s, 3H), 2.09 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 149.87, 147.72, 144.79, 135.20, 134.38, 132.94, 132.83, 130.66, 129.80, 129.63, 128.97, 128.76, 128.66, 128.55, 126.84, 126.00, 124.37, 123.90, 123.42, 120.35, 116.59, 116.38, 113.48, 67.87, 21.59, 21.36, 20.77; HRMS: m/z calcd for $C_{30}H_{25}NO_4S$: $[M+H]^+$ 496.1583, found 496.1573.

3.4.5 Representative experimental procedure and characterization data for the synthesis of 3-(9-(1*H*-indol-3-yl)-9*H*-xanthen-9-yl)-1-tosyl-1*H*-indole (6aa) without isolation of precursor (5a) and (6a)

To an oven-dried 25 ml round bottom flask charged with 4**a** (106 mg, 0.2 mmol) in toluene (2 mL) and ethanol (2 mL) were added aq. K_2CO_3 solution (2.5 M, 2 mL), PCy_3 (6 mg, 0.02 mmol) and $Pd(OAc)_2$ (2 mg, 0.01 mmol) successively. The resulting solution was stirred at 75 °C under argon atmosphere for 2 h. After the completion of the reaction (monitored by TLC), the crude reaction mixture was extracted with EtOAc. The organic extract was washed with brine solution, dried over anhydrous Na_2SO_4 and concentrated. In a 10 ml round bottom flask, the crude product **5a** was dissolved in acetonitrile (3 mL) and $Fe(NO_3)_3 \cdot 9H_2O$ (24 mg, 30 mol%) and $FeCl_3$ (10 mg, 30 mol%) were added to it. The reaction was continued at 70 °C for 3 h under oxygen atmosphere. After the complete formation of **6a** (monitored by TLC) we added Indole (23 mg, 0.2 mmol) directly to the reaction mixture and The reaction was continued at 70 °C for 30 min under ambient atmosphere. the crude reaction mixture was extracted with DCM. The organic extract was washed with brine solution, dried over anhydrous Na_2SO_4 and concentrated. The product was subjected to column chromatography (silica gel, 60-120 mesh), eluting with Hexane/EtOAc 95:5 (v/v) to afford the product **6aa** as a white solid (78 mg, 0.14 mmol, 69%). Compounds **6ab** and **6ea** were synthesized following the similar procure.

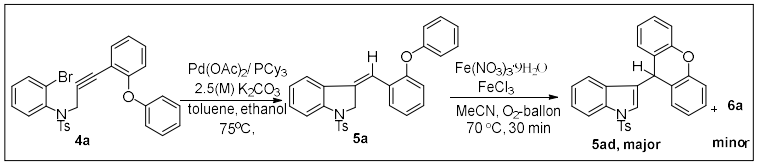
3-(9-(1*H*-indol-3-yl)-9*H*-xanthen-9-yl)-1-tosyl-1*H*-indole (6aa): 78 mg (69%); off white solid; m. p. 242 – 245 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.44 (s, 3H), 6.33 (d, *J* = 2.6 Hz, 1H), 6.88 – 7.01 (m, 7H), 7.12 (s, 1H), 7.14 – 7.27 (m, 7H), 7.31 – 7.39 (m, 2H), 7.72 (d, *J* = 8.2 Hz, 2H), 7.98 – 8.08 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.67, 44.27, 111.49, 113.96, 116.61, 119.27, 119.88, 121.54, 122.05, 122.79, 122.92, 122.96, 124.40, 125.02, 125.10, 126.14, 126.98, 127.54, 128.11, 128.20, 128.72, 129.26, 129.82, 134.96, 136.40, 137.36, 144.92, 152.67; HRMS: m/z calcd for $C_{36}H_{27}N_2O_3S$: $[M+H]^+$ 567.1742, found 567.1744.

1-methyl-3-(9-(1-tosyl-1*H*-indol-3-yl)-9*H*-xanthen-9-yl)-1*H*-indole (6ab): 86 mg (74%); white solid; m. p. 248 – 255 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.45 (s, 3H), 3.66 (s, 3H), 6.11 (s, 1H), 6.84 (d, J = 8.0 Hz, 1H), 6.89 – 7.00 (m, 6H), 7.16 (s, 1H), 7.17 – 7.27 (m, 8H), 7.31 (d, J = 8.2 Hz, 2H), 7.73 (d, J = 8.3 Hz, 2H), 8.05 (d, J = 8.4 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 21.68, 32.80, 44.18, 109.59, 113.94, 116.60, 118.40, 118.72, 121.54, 121.56, 122.80, 122.92, 122.94, 124.37, 125.46, 126.11, 127.01, 127.65, 128.03, 128.43, 128.71, 129.30, 129.37, 129.81, 134.97, 136.39, 138.09, 144.91, 152.59; HRMS: m/z calcd for $C_{37}H_{29}N_2O_3S$: $[M+H]^+$ 581.1899, found 581.1896.

1-methyl-3-(2-methyl-9-(1-tosyl-1*H*-indol-3-yl)-9*H*-xanthen-9-yl)-1*H*-indole (6ea): 83 mg (70%); off white solid; m. p. 230 – 235 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.12 (s, 3H), 2.44 (s, 3H), 3.65 (s, 3H), 6.12 (s, 1H), 6.70 (d, *J* = 2.1 Hz, 1H), 6.80 – 7.01 (m, 5H), 7.02 – 7.13 (m, 2H), 7.15 – 7.33 (m, 9H), 7.71 – 7.78 (m, 2H), 8.07 (d, *J* = 8.4 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 20.95, 21.66, 32.79, 44.18, 109.57, 113.96, 116.18, 116.58, 118.62, 118.69, 121.48, 121.59, 122.67, 122.90, 122.94, 124.36, 125.47, 126.35, 127.00, 127.19, 127.53, 127.91, 128.43, 128.72, 128.80, 128.83, 129.36, 129.43, 129.79, 132.16, 135.00, 136.47, 138.08, 144.89, 150.48, 152.63; HRMS: m/z calcd for $C_{38}H_{30}N_2O_3S$: $[M]^+$ 594.1977, found 594.1972.

3.4.6 Control experiments:

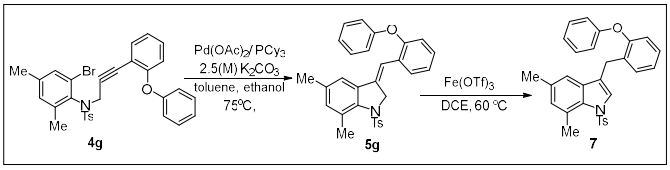
(a) Synthesis and characterization data of intermediate 5ad:



To a solution of **4a** (106 mg, 0.2 mmol) in toluene (2 mL) and ethanol (2 mL) were added aq. K_2CO_3 solution (2.5 M, 2 mL), PCy_3 (6 mg, 0.02 mmol) and $Pd(OAc)_2$ (2 mg, 0.01 mmol)

successively. The resulting solution was stirred at 75 °C under argon atmosphere for 2 h. After the completion of the reaction (monitored by TLC), the crude reaction mixture was extracted with EtOAc. The organic extract was washed with brine solution, dried over anhydrous Na_2SO_4 and concentrated. The solid crude reaction mixture **5a** was dissolved in acetonitrile (3 mL) and $Fe(NO_3)_3 \cdot 9H_2O$ (24 mg, 30 mol%) and $FeCl_3$ (10 mg, 30 mol%) were added to it. The reaction was continued at 70 °C for 30 min under oxygen atmosphere. After that, the crude reaction mixture was extracted with EtOAc. The organic extract was washed with brine solution, dried over anhydrous Na_2SO_4 and concentrated. The product was subjected to column chromatography (silica gel, 60-120 mesh), eluting with Hexane/EtOAc 97:3 (v/v) to afford the product **5ad** majorly as a white crystalline solid.^{1}H NMR (300 MHz, $CDCl_3$) δ 7.96 (d, *J* = 8.4 Hz, 1H), 7.77 (d, *J* = 8.0 Hz, 2H), 7.61 (s, 1H), 7.23 (dd, *J* = 12.3, 7.5 Hz, 5H), 7.18 – 7.10 (m, 3H), 7.03 (d, *J* = 7.5 Hz, 1H), 6.97 (s, 1H), 6.95 – 6.87 (m, 3H), 5.50 (s, 1H), 2.39 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 151.13, 144.92, 136.15, 135.11, 129.83, 129.12, 128.96, 128.24, 126.79, 126.08, 124.74, 124.44, 123.29, 123.17, 122.16, 120.56, 116.57, 113.93, 35.42, 21.58. HRMS: m/z calcd for $C_{28}H_{21}NO_3S$: 451.1242 $[M]^+$; found: 451.1244

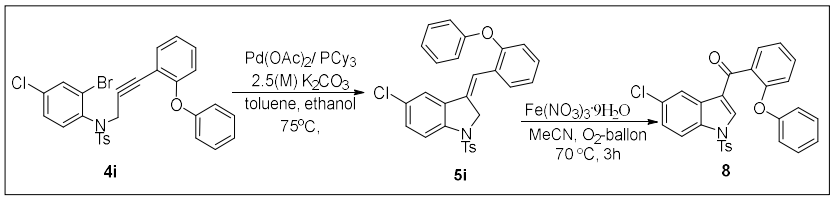
(b) Experimental procedure and characterization data for the synthesis of isomerized product 7:



Compound **4g** (112 mg, 0.2 mmol) in toluene and ethanol was treated with aq. K_2CO_3 solution (2.5 M, 2 mL), $Pd(OAc)_2$ (2 mg, 0.01 mmol), PCy_3 (6 mg, 0.02 mmol) similarly to the procedure for the synthesis of **5a** during synthesis of **6a** for 2 h at 75 °C. After the completion of the reaction (monitored by TLC), the crude reaction mixture was extracted with EtOAc. The organic extract was washed with brine solution, dried over anhydrous Na_2SO_4 and concentrated. Then $Fe(OTf)_3$ (10 mg, 10 mol%) was added to the solution of crude product **5g** in 1,2-dichloroethane as described earlier repport[11b] for 1 h to afford **7** as a off white solid (91 mg, 0.19 mmol, 95%) by using column chromatography (silica gel, 60-120 mesh), eluting with Hexane/EtOAc 95:5 (v/v) .^{1}H NMR (300 MHz, $CDCl_3$) δ 7.47 (d, *J* = 8.1 Hz, 2H), 7.42 (s, 1H), 7.34 (dd, *J* = 5.4, 5.7 Hz, 1H),7.19 – 7.25 (m, 1H), 7.09 – 7.16 (m, 4H), 6.99 – 7.06 (m, 2H), 6.90 – 6.97 (m, 4H), 6.85 (s, 1H), 4.00 (s, 2H), 2.55 (s, 3H), 2.39 (s, 3H), 2.21 (s, 3H).

If, we attempt to isolate **5g** in the reductive Heck step, then the substrate **5g** was prone to isomerize for the synthesis of **7** during column chromatography (silica gel, 60-120 mesh) separation. After the completion of the reductive Heck reaction (monitored by TLC), the solvent was evaporated and the product was purified by column chromatography using silica gel (60-120 mesh), eluting with Hexane/EtOAc 90:10 (v/v) to afford the mixture of **5g** and **7** as products**.** ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.52 – 7.41 (m, 1H), 7.36 (t, *J* = 7.7 Hz, 2H), 7.29 (d, *J* = 2.6 Hz, 1H), 7.27 – 7.18 (m, 1H), 7.18 – 7.11 (m, 5H), 7.08 (d, *J* = 11.1 Hz, 1H), 6.94 (q, *J* = 10.2, 9.1 Hz, 8H), 6.60 (t, *J* = 2.6 Hz, 1H), 4.76 (d, *J* = 2.7 Hz, 2H), 4.00 (s, 0.6H), 2.60 (s, 3H), 2.55 (s, 1H), 2.36 (s, 1H), 2.31 (s, 7H).^{13}C NMR (75 MHz, $CDCl_3$) δ 157.45, 154.31, 143.84, 141.16, 136.62, 136.61, 136.28, 133.30, 132.86, 132.25, 131.95, 130.63, 129.82, 129.77, 129.65, 129.04, 128.62, 128.59, 128.30, 128.05, 127.90, 127.84, 126.46, 125.21, 123.91, 123.60, 123.15, 122.80, 121.40, 119.39, 119.24, 118.51, 118.34, 117.85, 117.41, 113.59, 57.29, 25.14, 21.60, 21.56, 21.12, 20.96, 19.51.

(c) Synthesis and characterization data of by-product biphenyl etheryl 3-indolyl ketone 8:



Compound **4i** (113 mg, 0.2 mmol) in toluene and ethanol was treated with aq. K_2CO_3 solution (2.5 M, 2 mL), $Pd(OAc)_2$ (2 mg, 0.01 mmol), PCy_3 (6 mg, 0.02 mmol) as described for the synthesis of **5a** during synthesis of **6a** for 2 hours at 75 °C. After the completion of the reductive Heck reaction (monitored by TLC), the crude reaction mixture was extracted with EtOAc. The organic extract was washed with brine solution, dried over anhydrous Na_2SO_4 and concentrated. The solid crude reaction mixture **5i** was dissolved in acetonitrile (3 mL) and $Fe(NO_3)_3 \cdot 9H_2O$ (24 mg, 30 mol%) was added to it. The reaction was continued at 70 °C for 3 h under oxygen atmosphere. After the completion of the reaction (monitored by TLC) the crude reaction mixture was extracted with EtOAc. The organic extract was washed with brine solution, dried over anhydrous Na_2SO_4 and concentrated. Along with the desired product **6a** and intermediate **5ad**, one of the byproducts, biphenyl etheryl 3-indolyl ketone **8** (20 mg, 0.04 mmol, 20%) was isolated by column chromatography using silica gel (60-120 mesh), eluting with Hexane/EtOAc 95:5 (v/v).NMR Characterized data of **8** : ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.36

(d, *J* = 2.1 Hz, 1H), 8.08 (s, 1H), 7.83 (d, *J* = 8.9 Hz, 1H), 7.70 – 7.65 (m, 2H), 7.57 (dd, *J* = 7.6, 1.8 Hz, 1H), 7.50 (ddd, *J* = 8.3, 7.4, 1.8 Hz, 1H), 7.32 (ddt, *J* = 11.1, 7.5, 2.3 Hz, 3H), 7.26 (dd, *J* = 7.5, 1.1 Hz, 1H), 7.23 – 7.19 (m, 2H), 7.14 – 7.09 (m, 1H), 7.04 (dd, *J* = 8.4, 1.0 Hz, 1H), 6.98 – 6.93 (m, 2H), 2.37 (s, 3H).^{13}C NMR (101 MHz, $CDCl_3$) δ 189.46, 156.41, 154.42, 146.14, 135.71, 134.17, 133.15, 132.18, 131.53, 131.04, 130.28, 129.96, 129.90, 129.05, 127.13, 126.09, 123.84, 123.53, 122.82, 120.85, 119.09, 118.81, 114.05, 21.67.HRMS: m/z calcd for $C_{28}H_{20}ClNO_4S$: 502.0880 [M + H]+ ; found: 502.0891.

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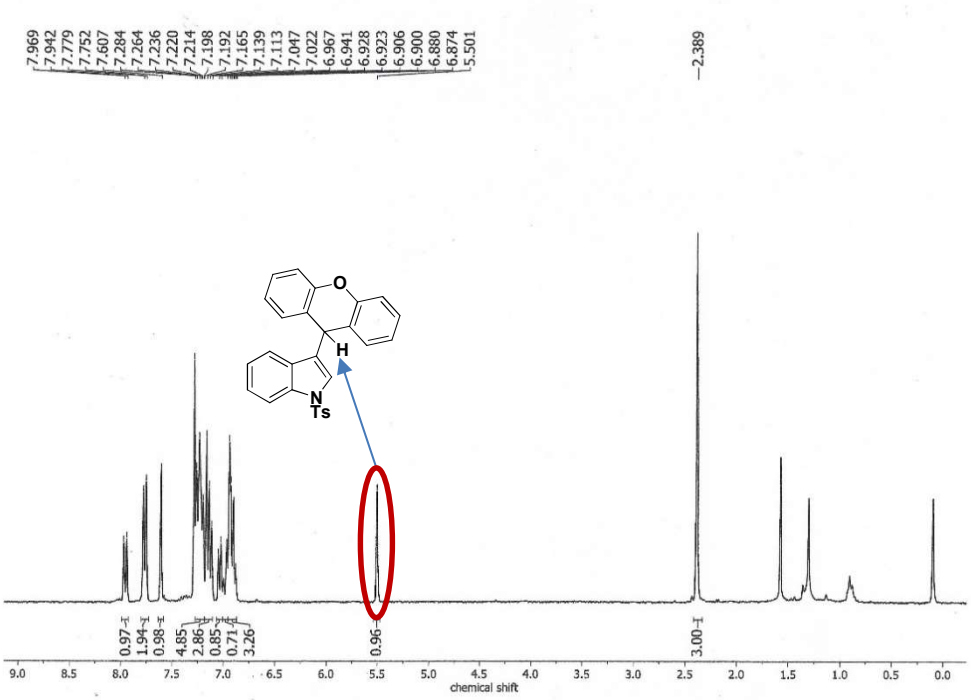
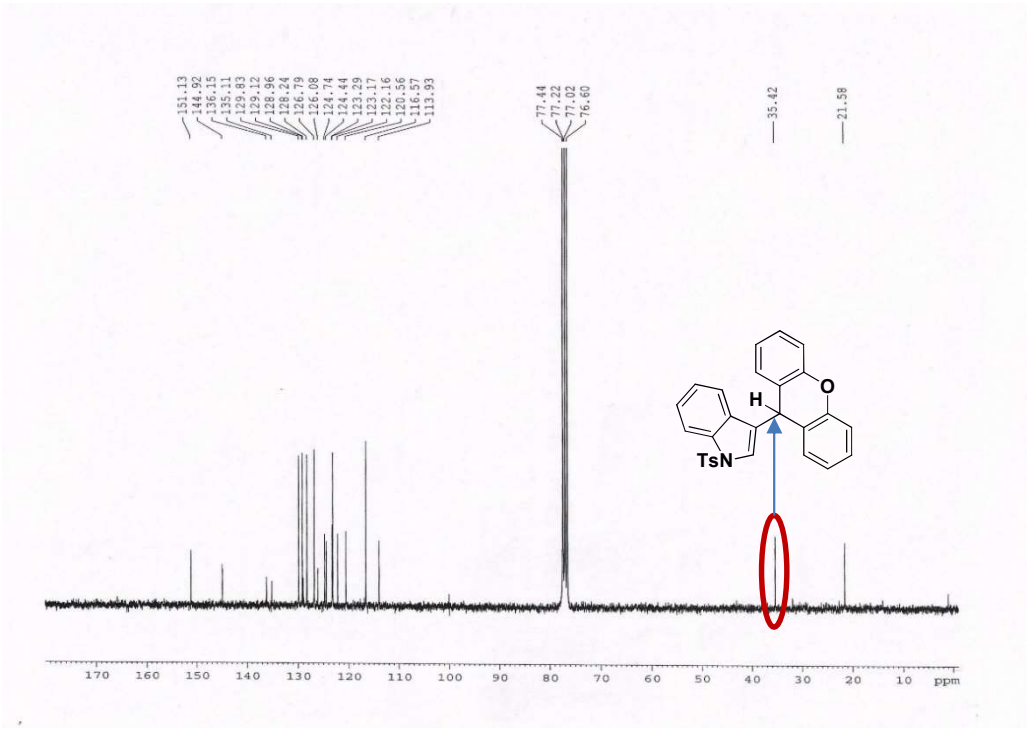
3.6 ^{1}H AND ^{13}C NMR SPECTRA OF SOME IMPORTANT COMPOUNDS

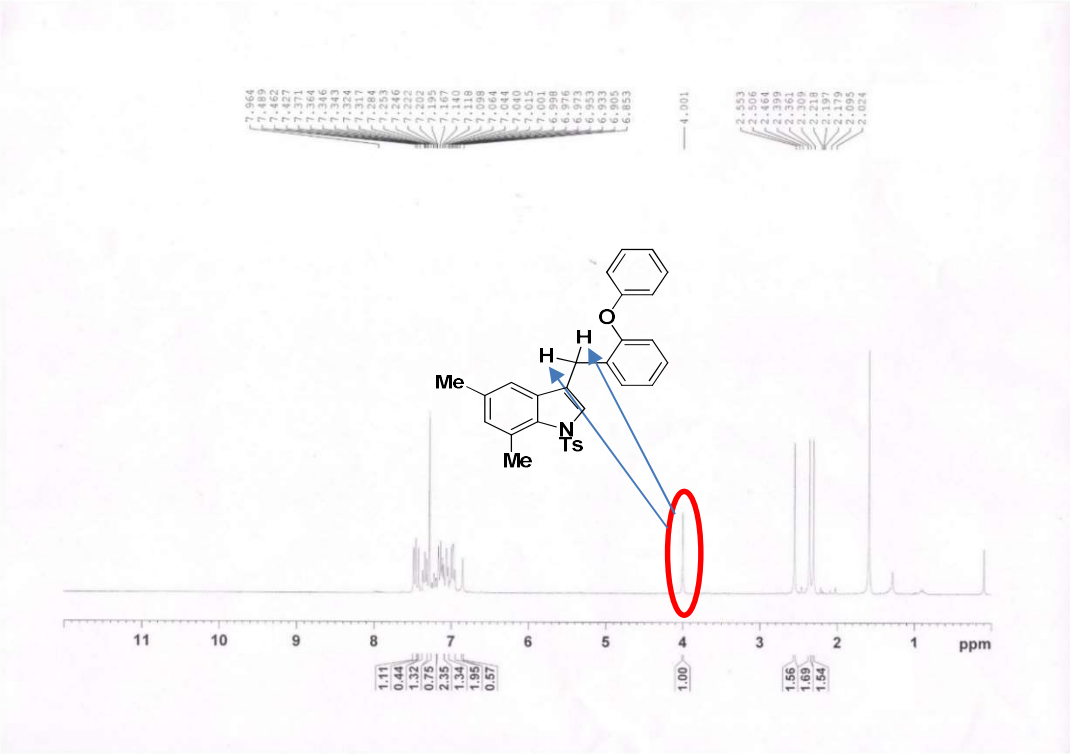
^{1}H NMR (300 MHz, $CDCl_3$) of intermediate 5ad



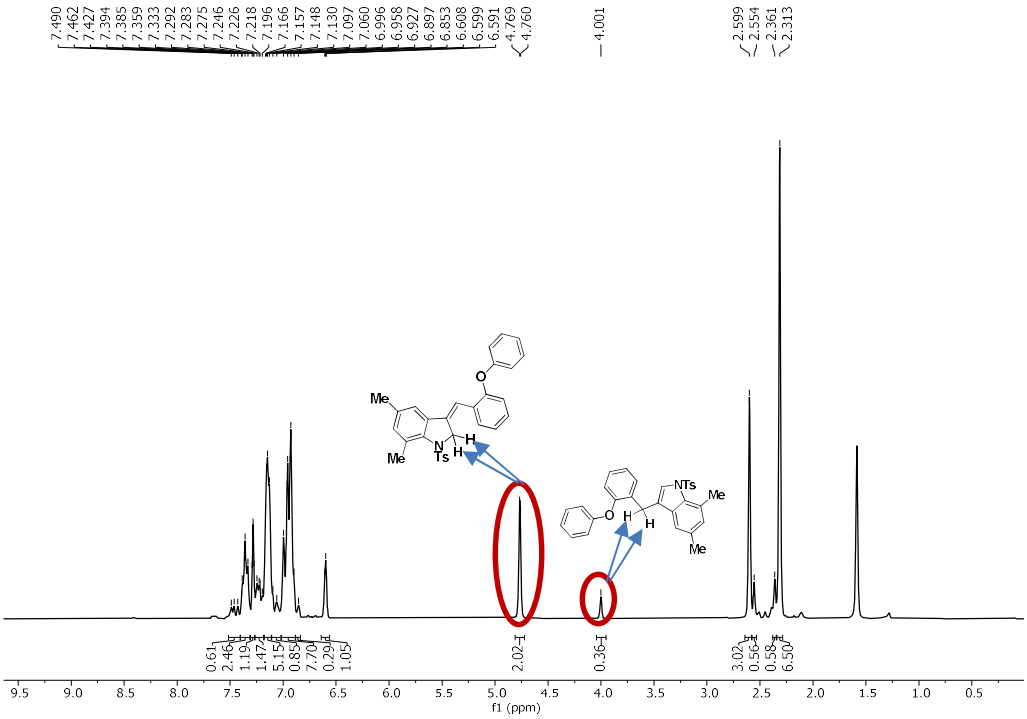
^{13}C NMR (75 MHz, $CDCl_3$) of intermediate 5ad



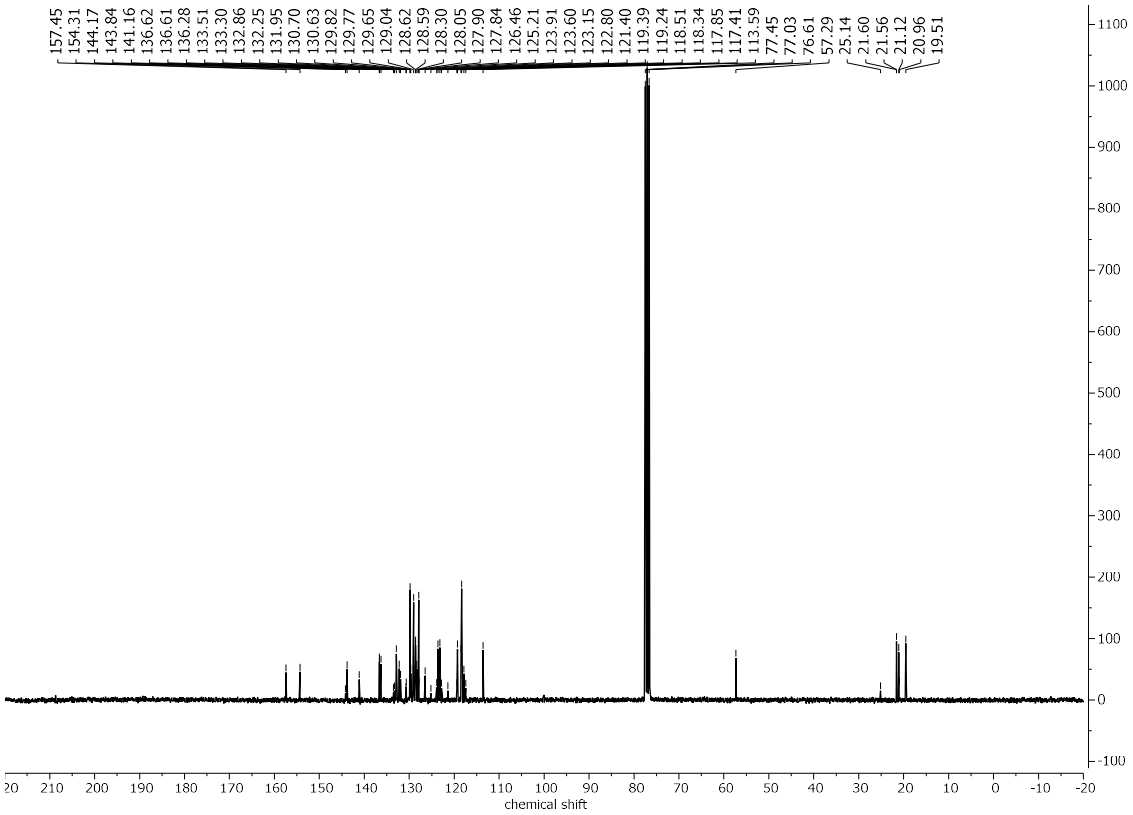
^{1}H NMR (300 MHz, $CDCl_3$) of 7



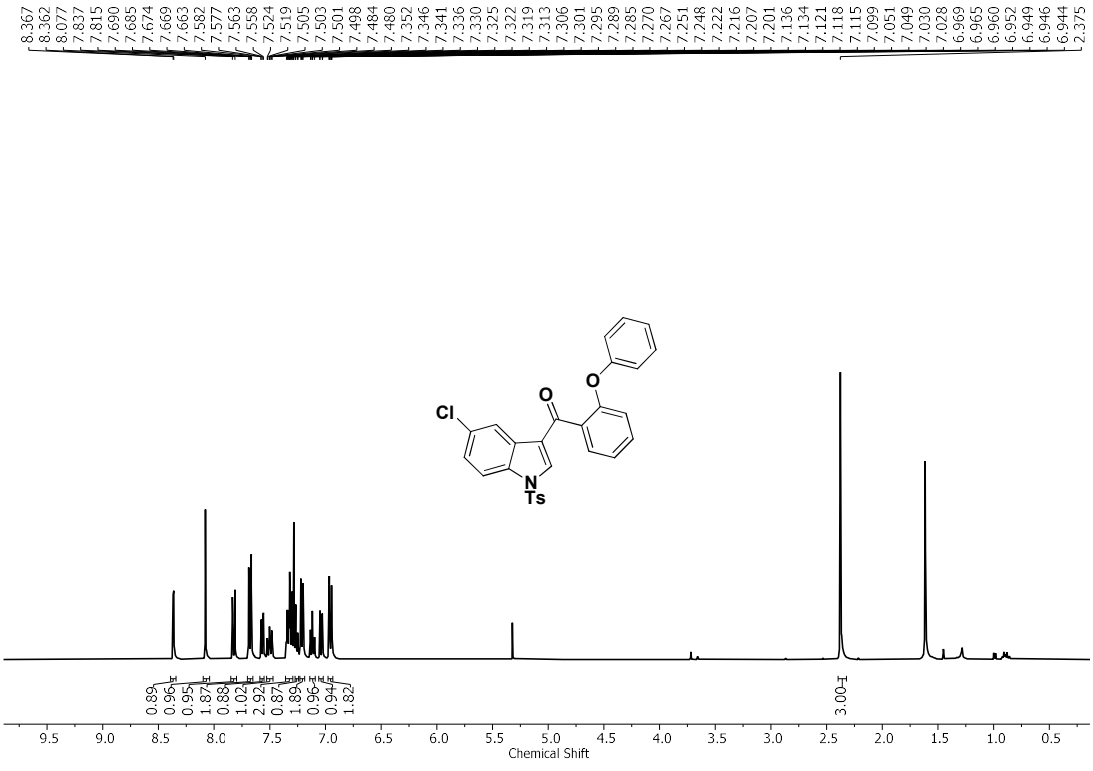
^{1}H NMR (300 MHz, $CDCl_3$) of 5g with 7 as by-product



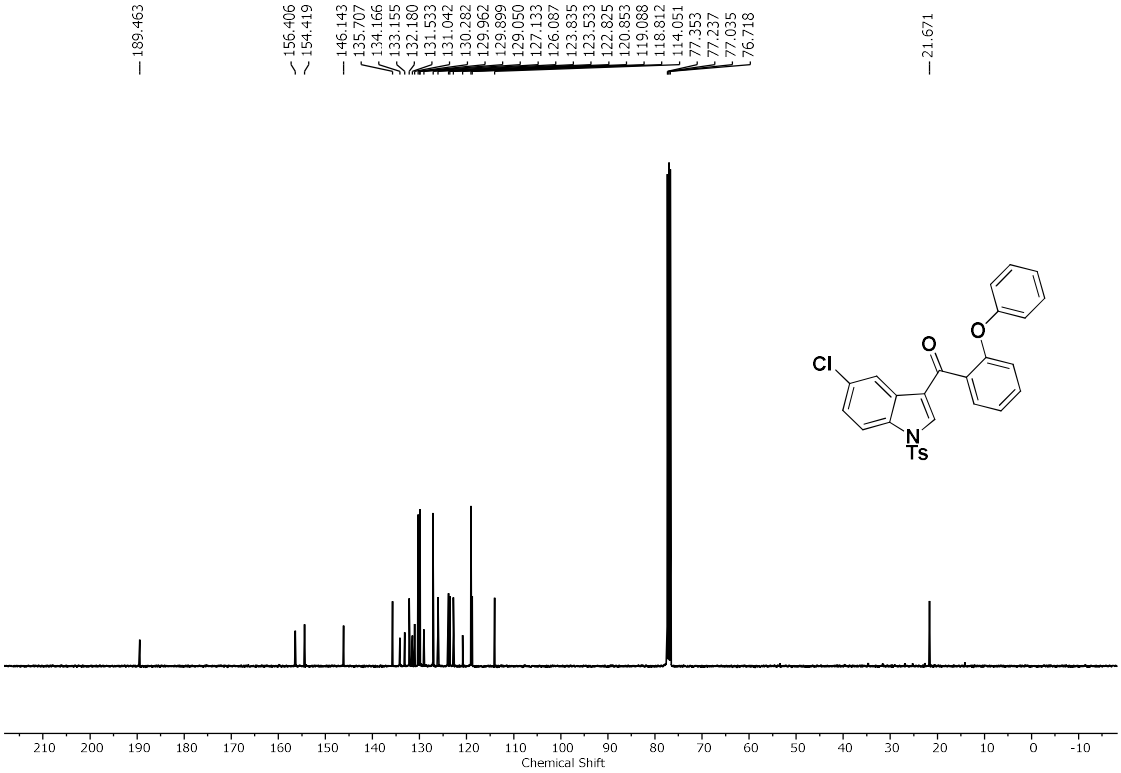
^{13}C NMR (75 MHz, $CDCl_3$) of 5g with 7 as by-product



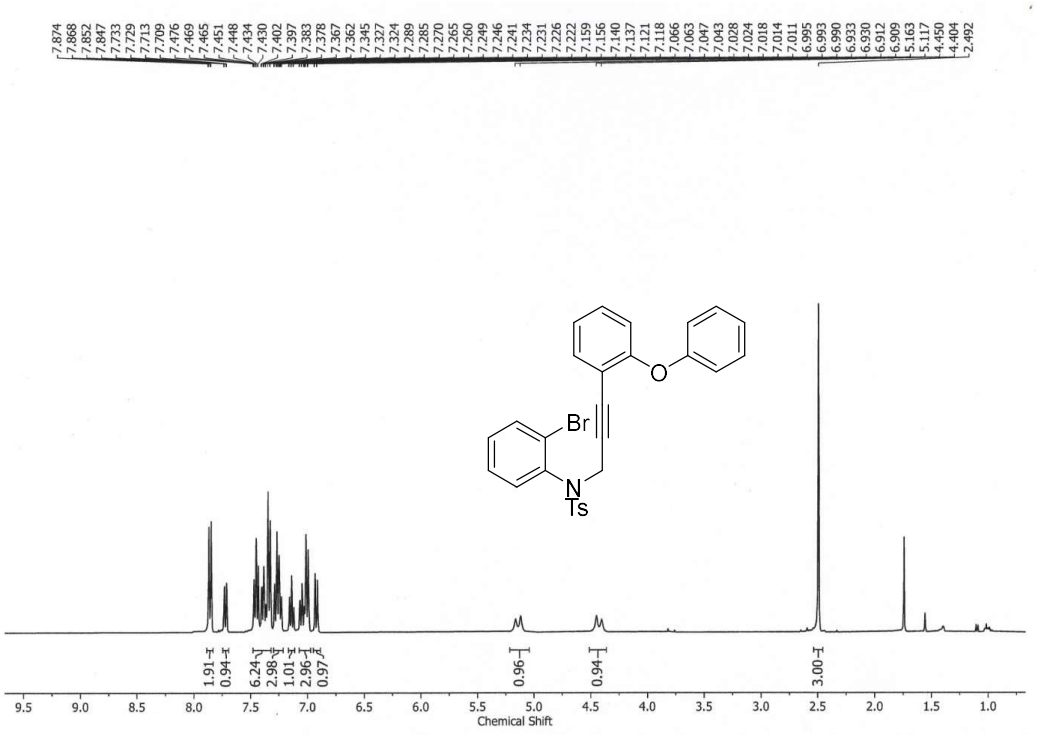
^{1}H NMR (300 MHz, $CDCl_3$) of 8



^{13}C NMR (101 MHz, $CDCl_3$) of 8



^{1}H NMR (400 MHz, $CDCl_3$) of 4a



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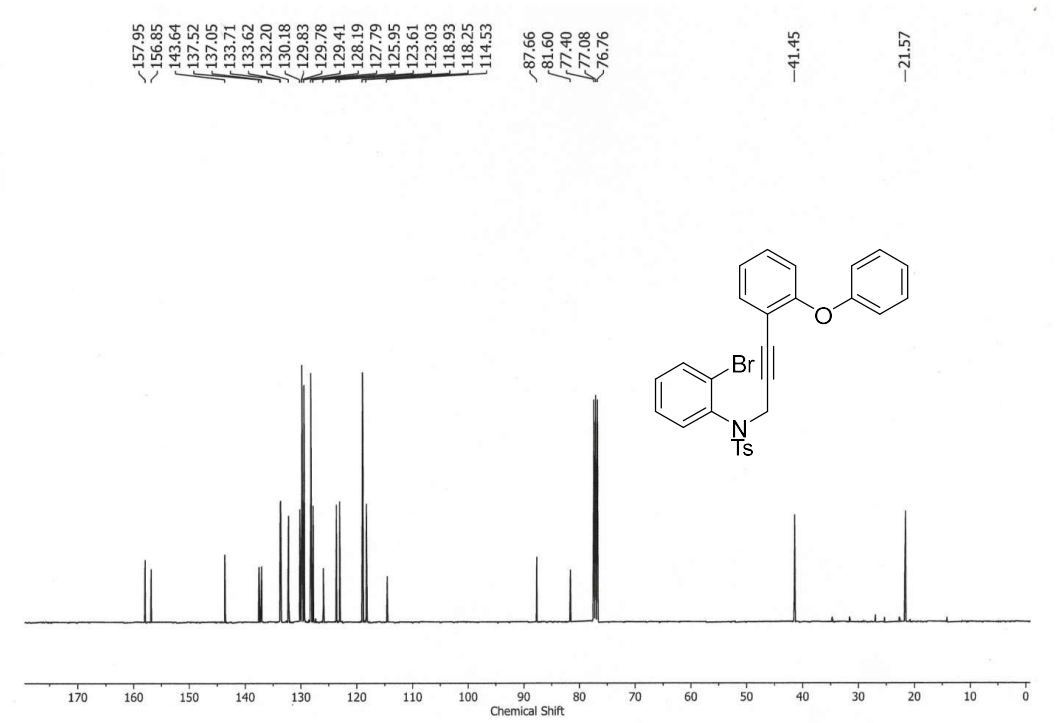
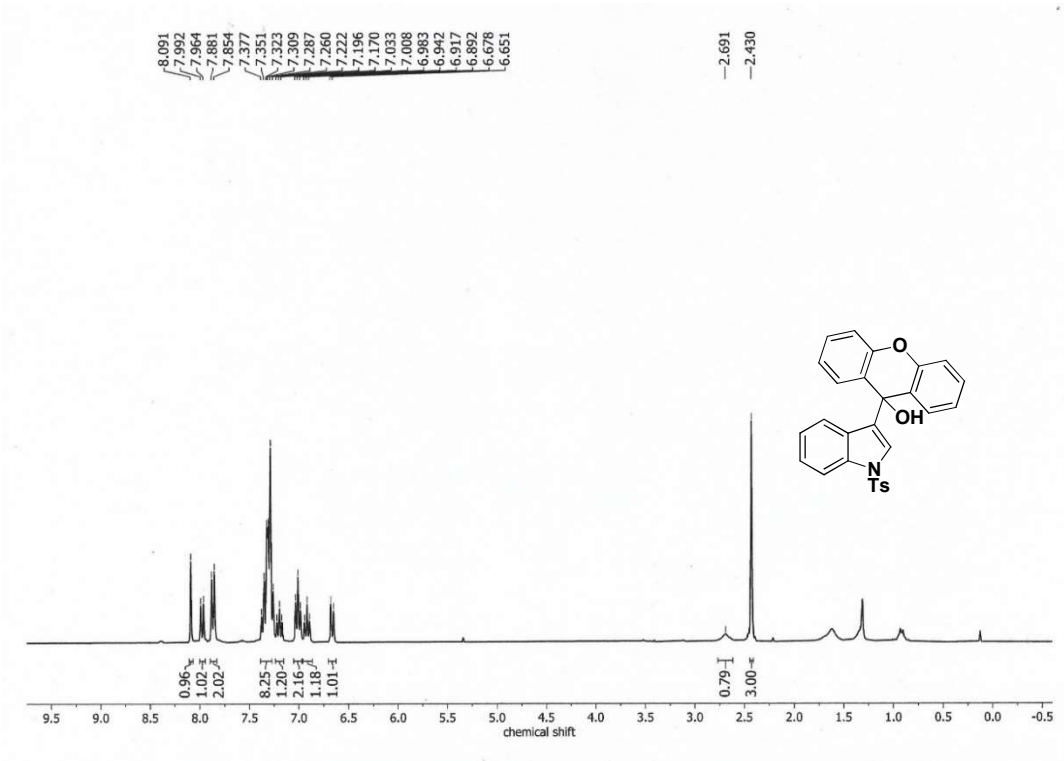
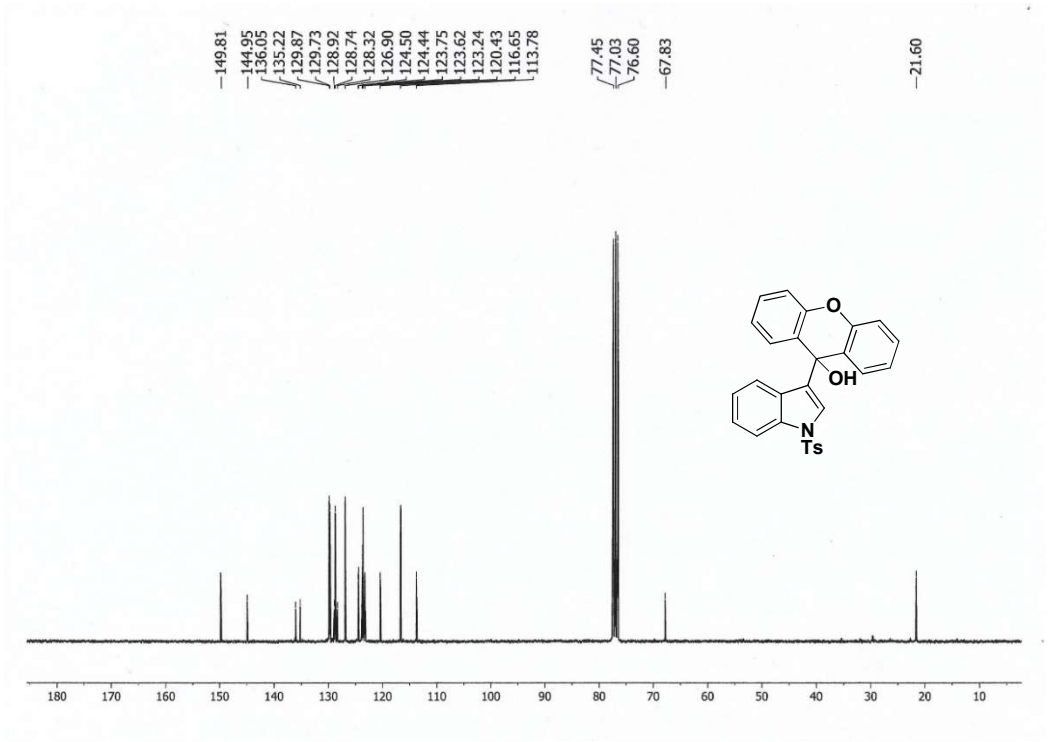


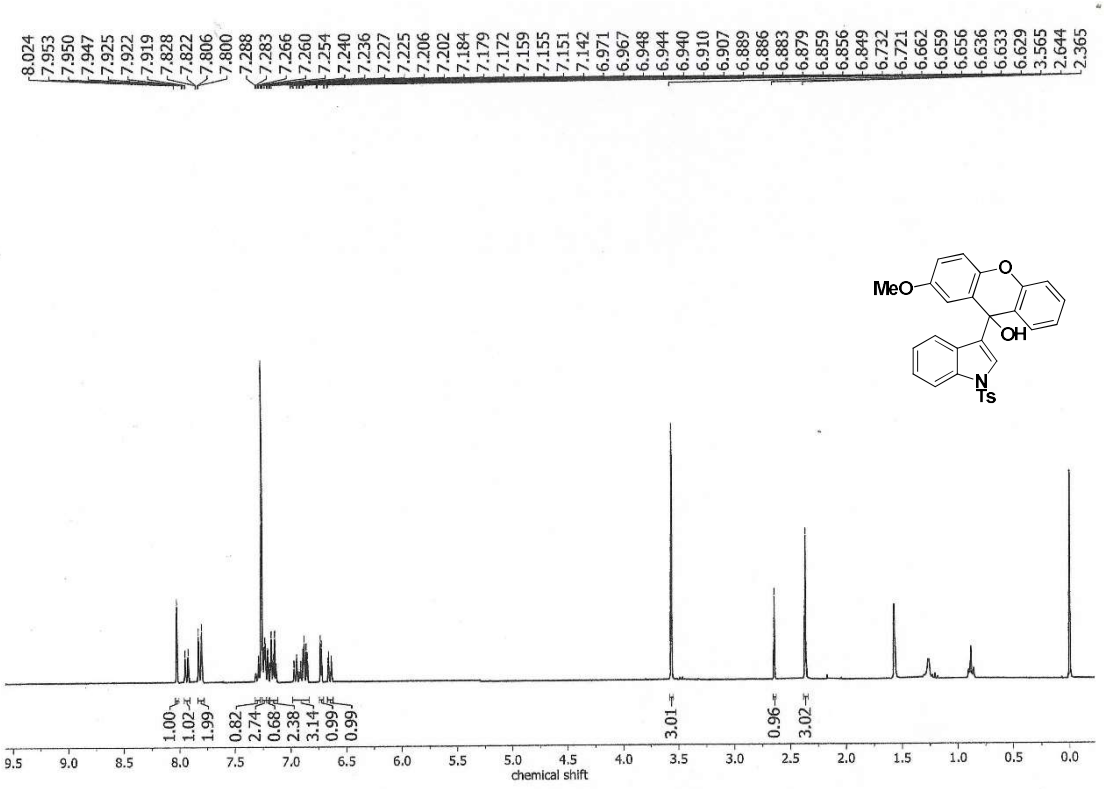
^{1}H NMR (300 MHz, $CDCl_3$) of 6a



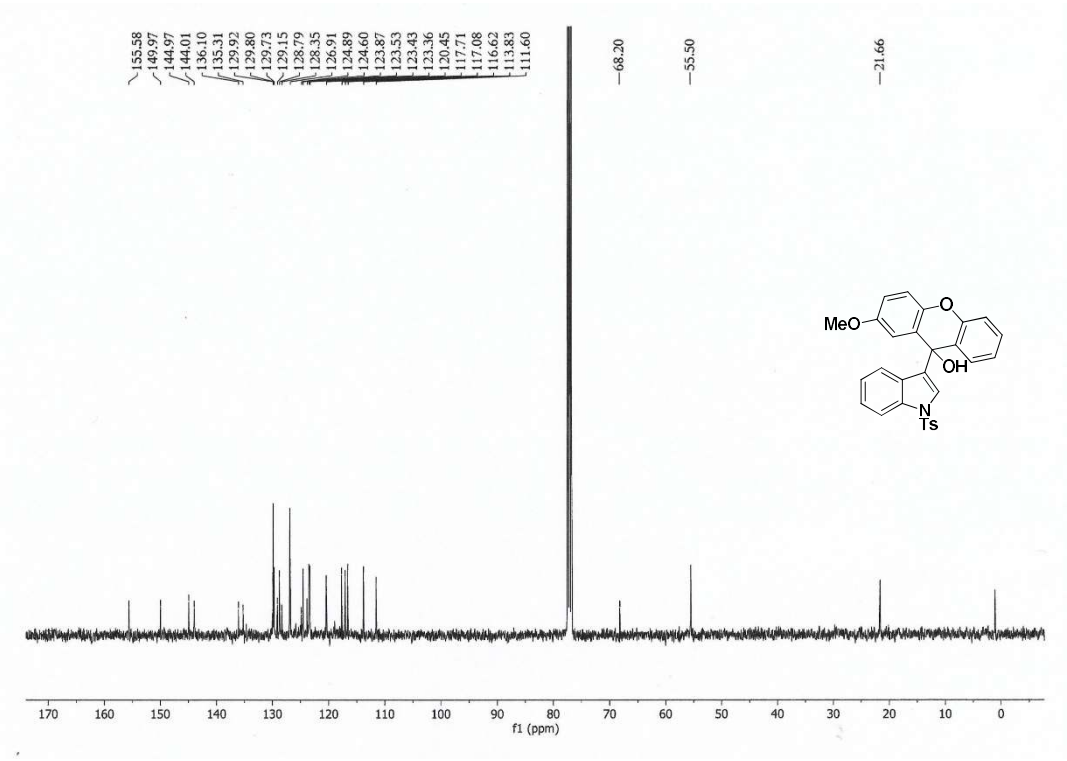
^{13}C NMR (75 MHz, $CDCl_3$) of 6a



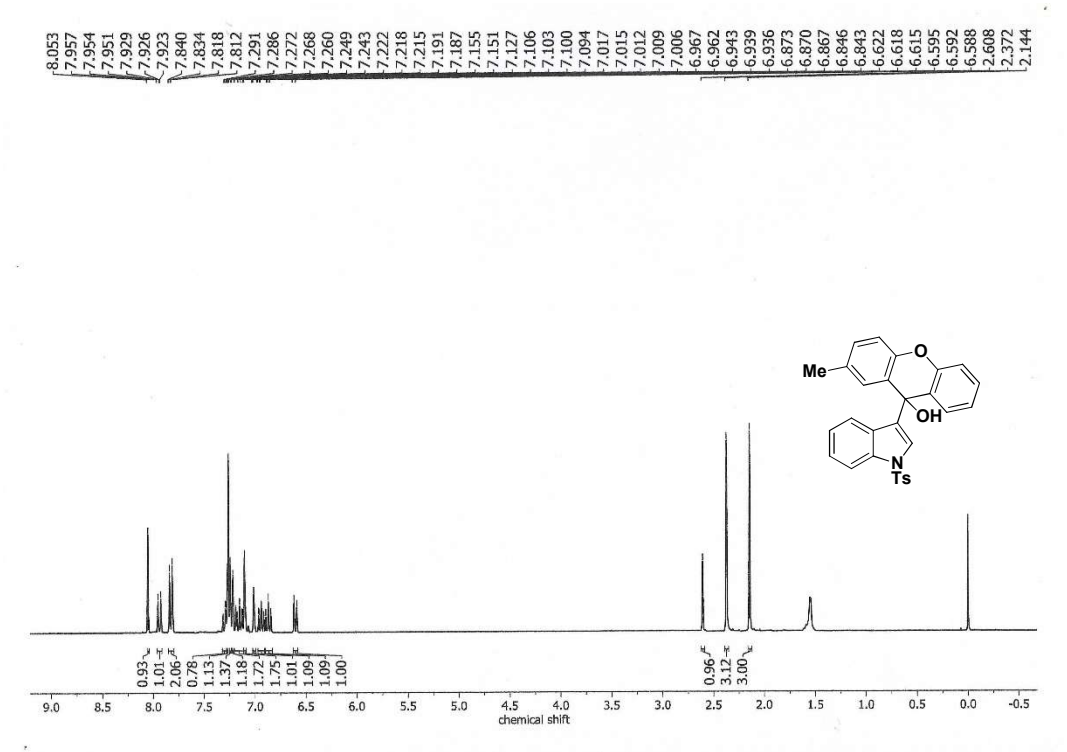
^{1}H NMR (300 MHz, $CDCl_3$) of 6b



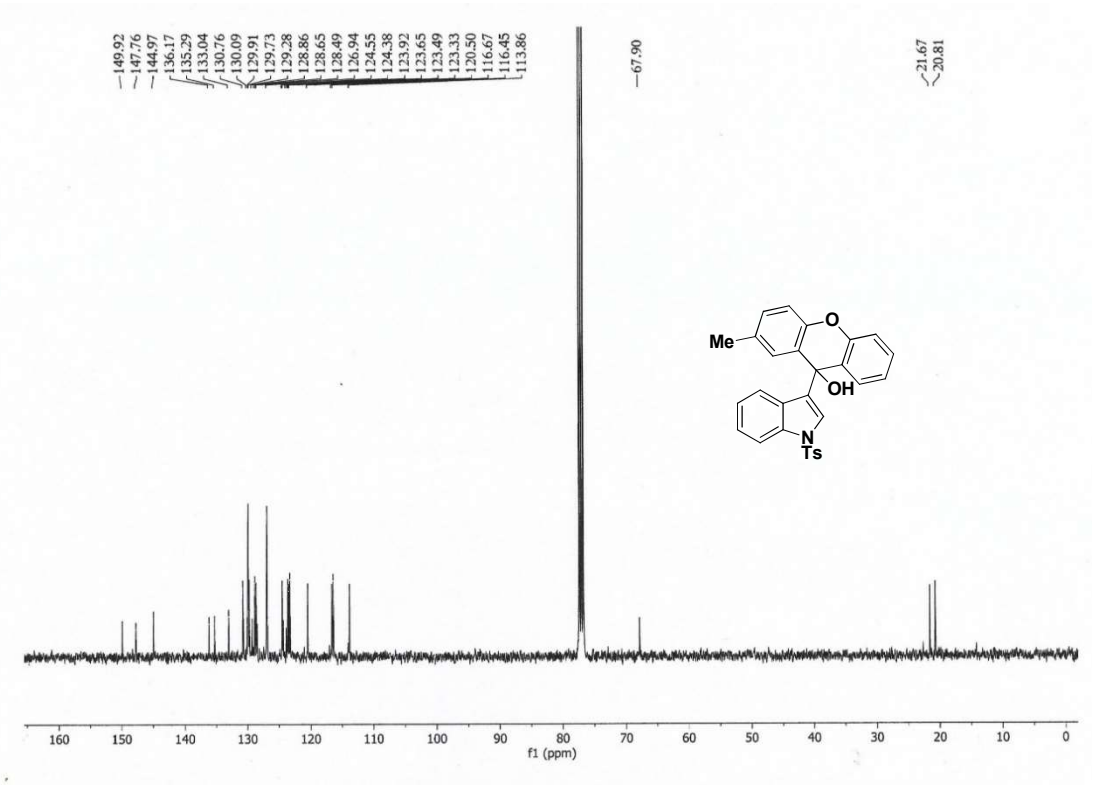
^{13}C NMR (101 MHz, $CDCl_3$) of 6b



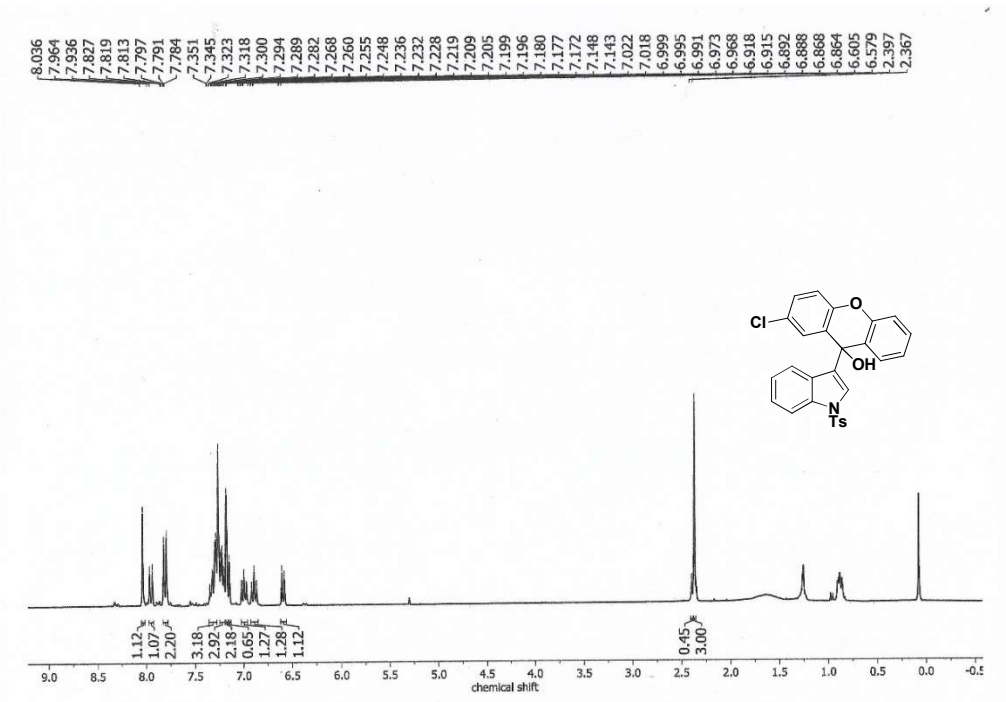
^{1}H NMR (300 MHz, $CDCl_3$) of 6c



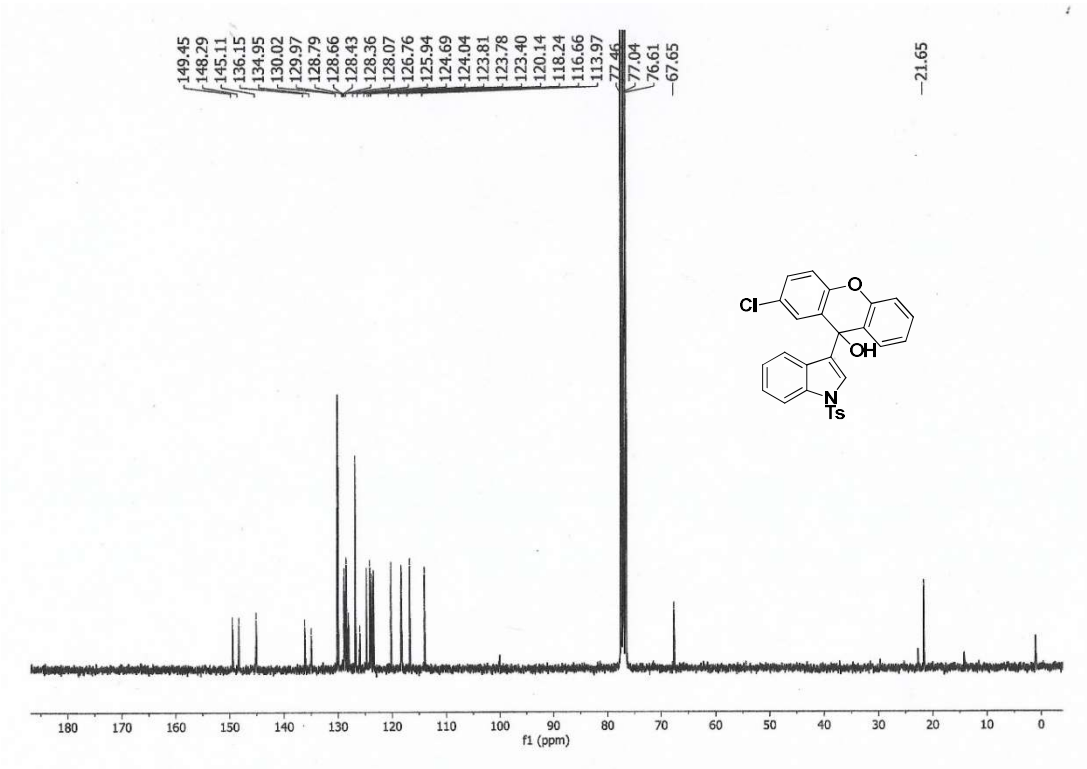
^{13}C NMR (101 MHz, $CDCl_3$) of 6c



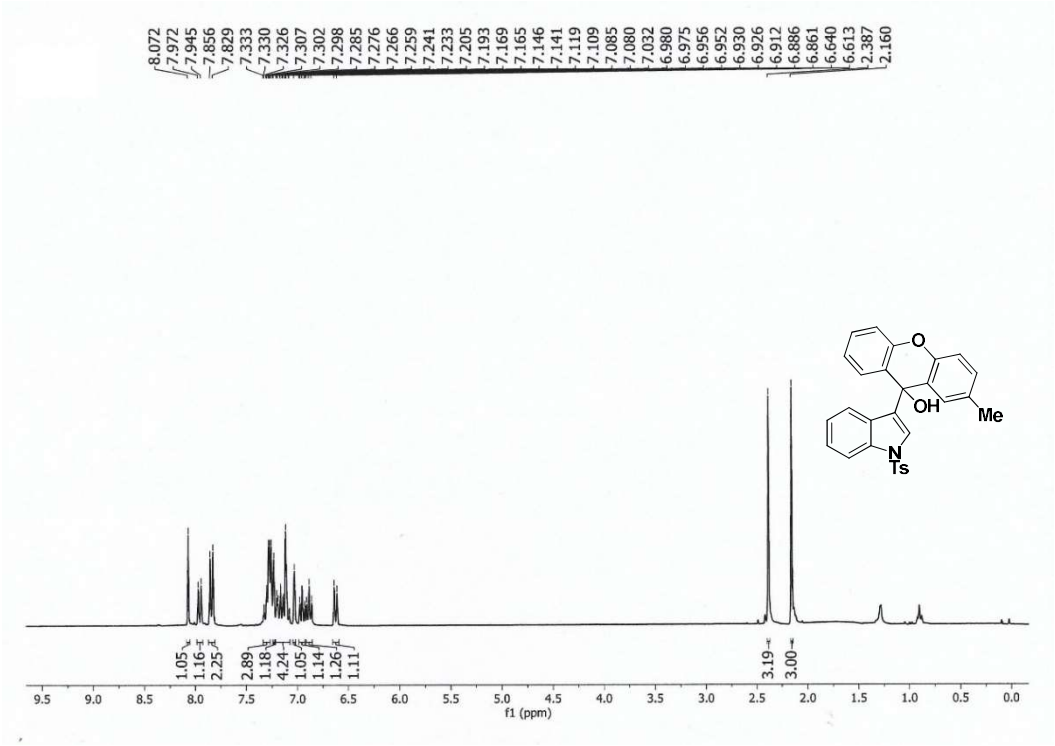
^{1}H NMR (300 MHz, $CDCl_3$) of 6d



^{13}C NMR (75 MHz, $CDCl_3$) of 6d



^{1}H NMR (300 MHz, $CDCl_3$) of 6e



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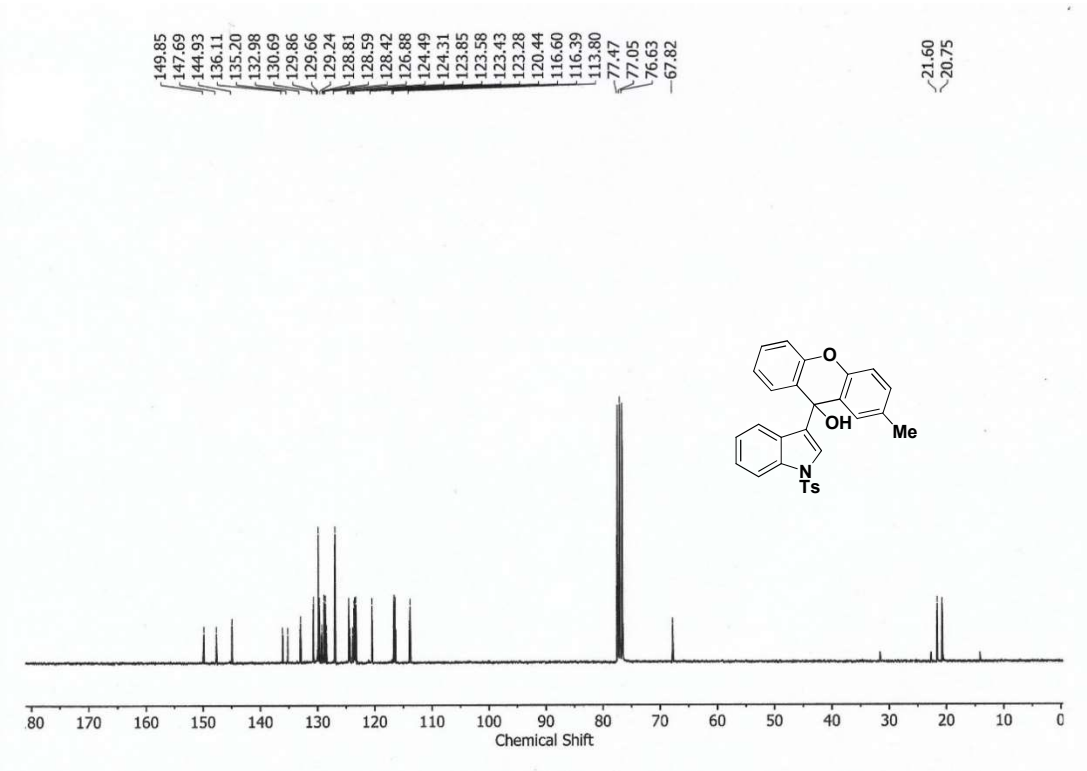
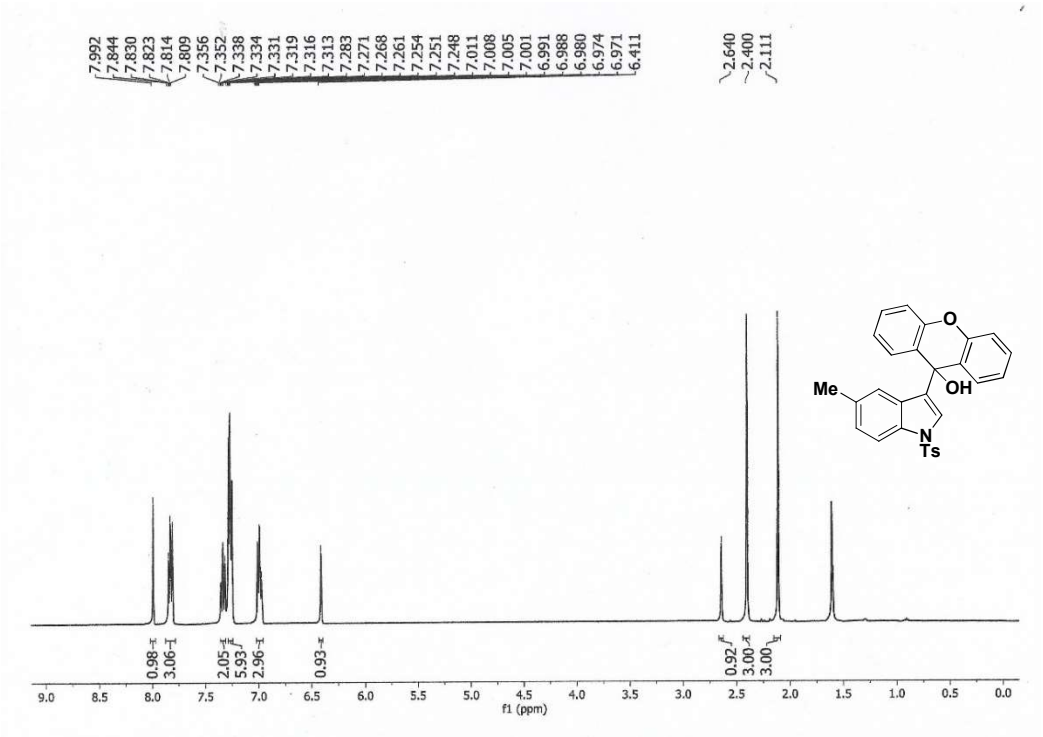
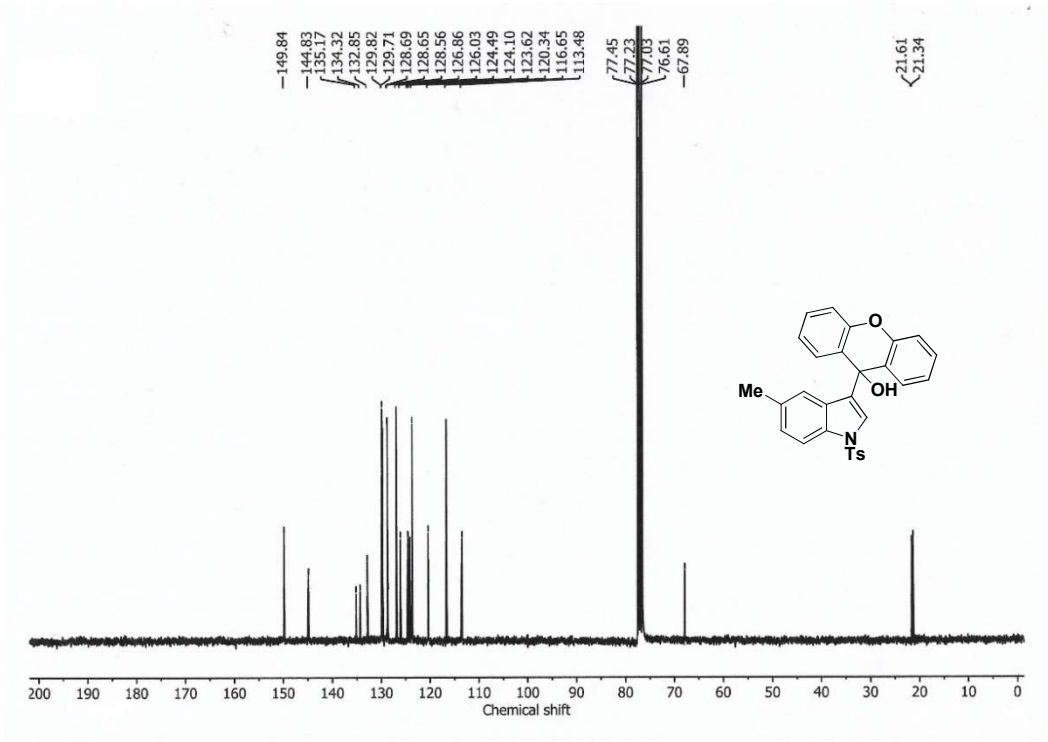


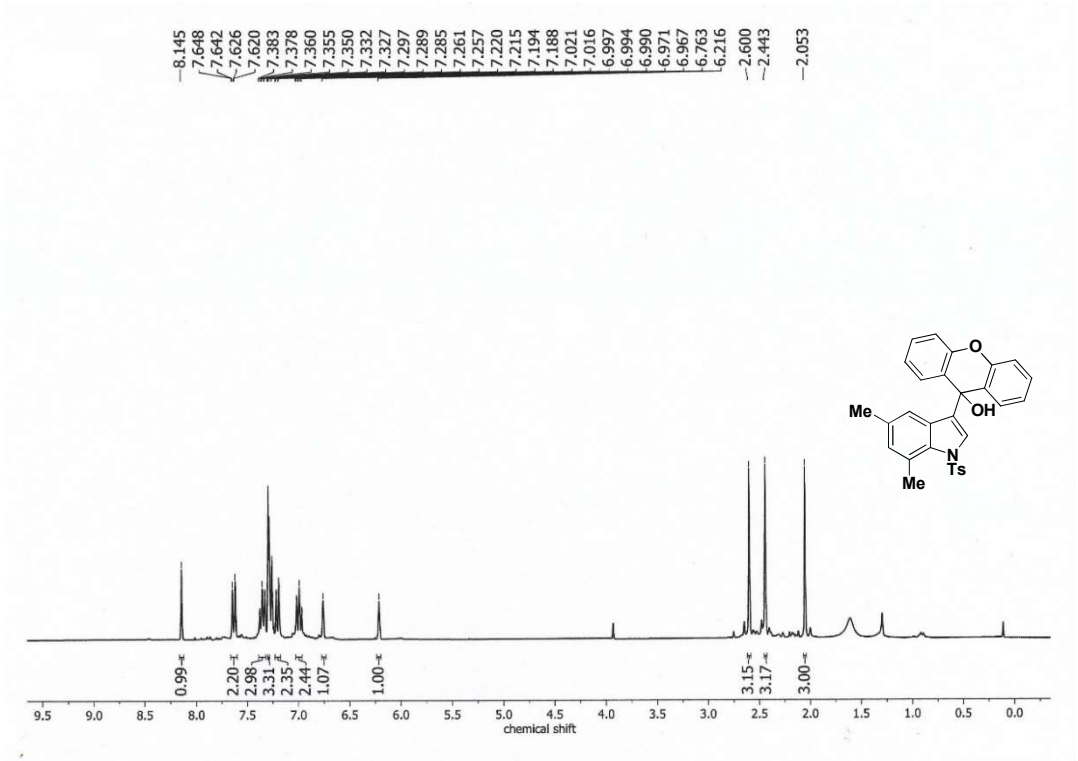
^{1}H NMR (400 MHz, $CDCl_3$) of 6f



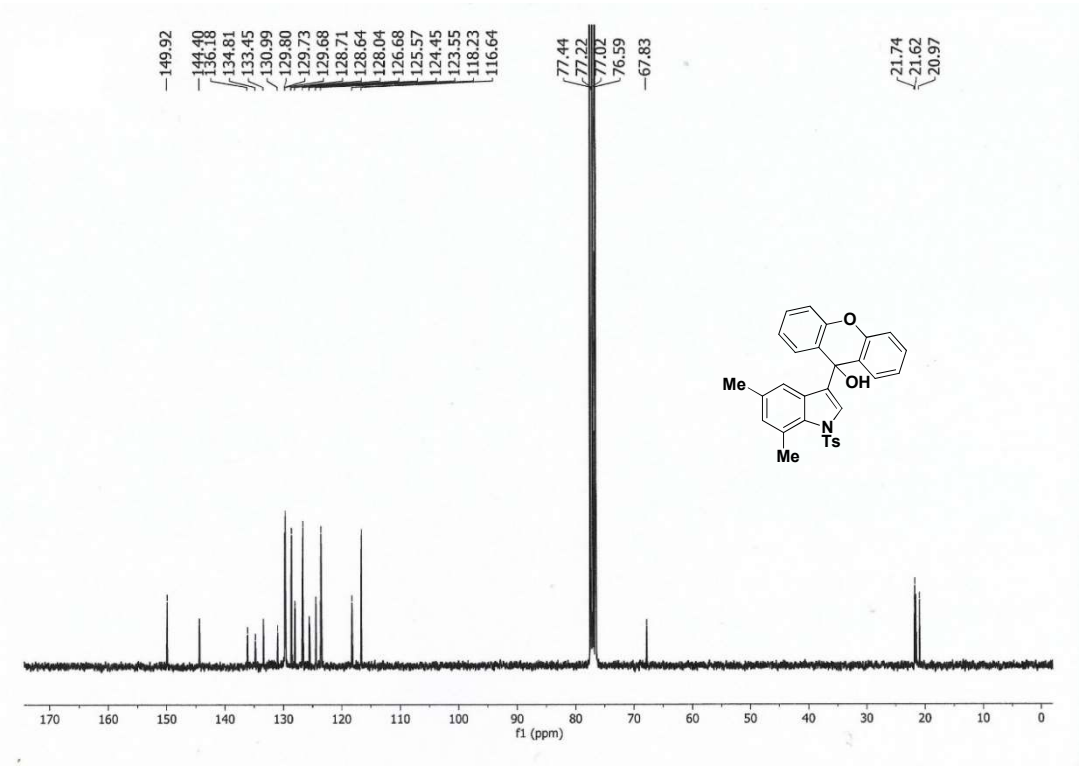
^{13}C NMR (100 MHz, $CDCl_3$) of 6f



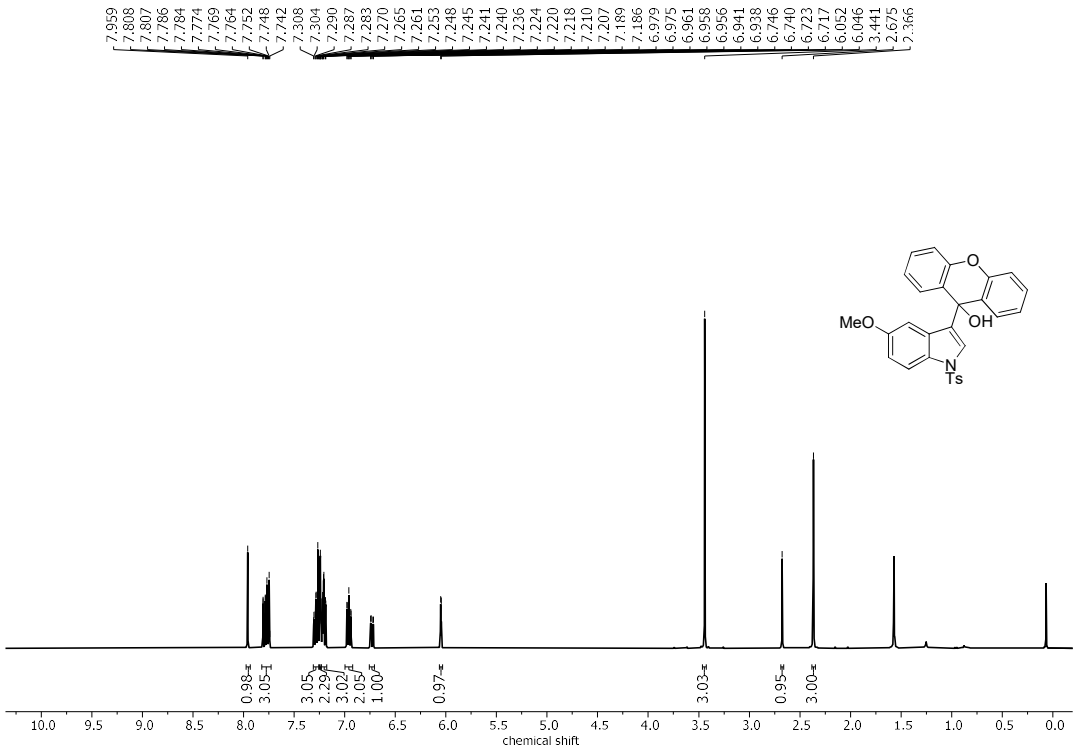
^{1}H NMR (300 MHz, $CDCl_3$) of 6g



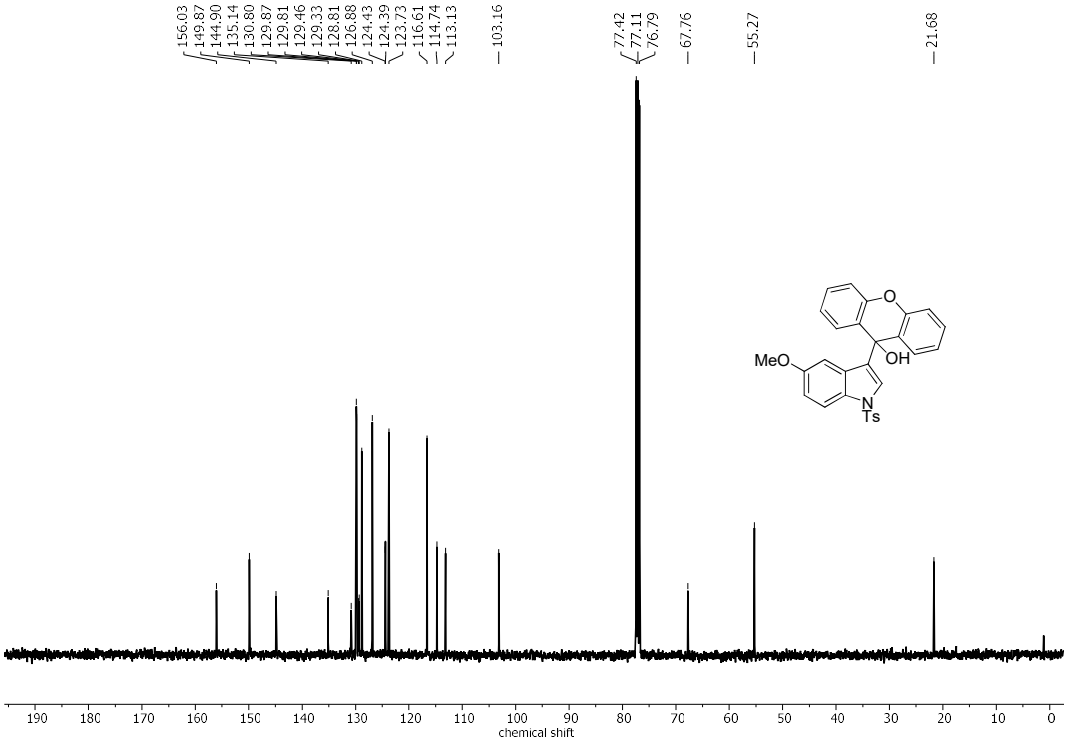
^{13}C NMR (100 MHz, $CDCl_3$) of 6g



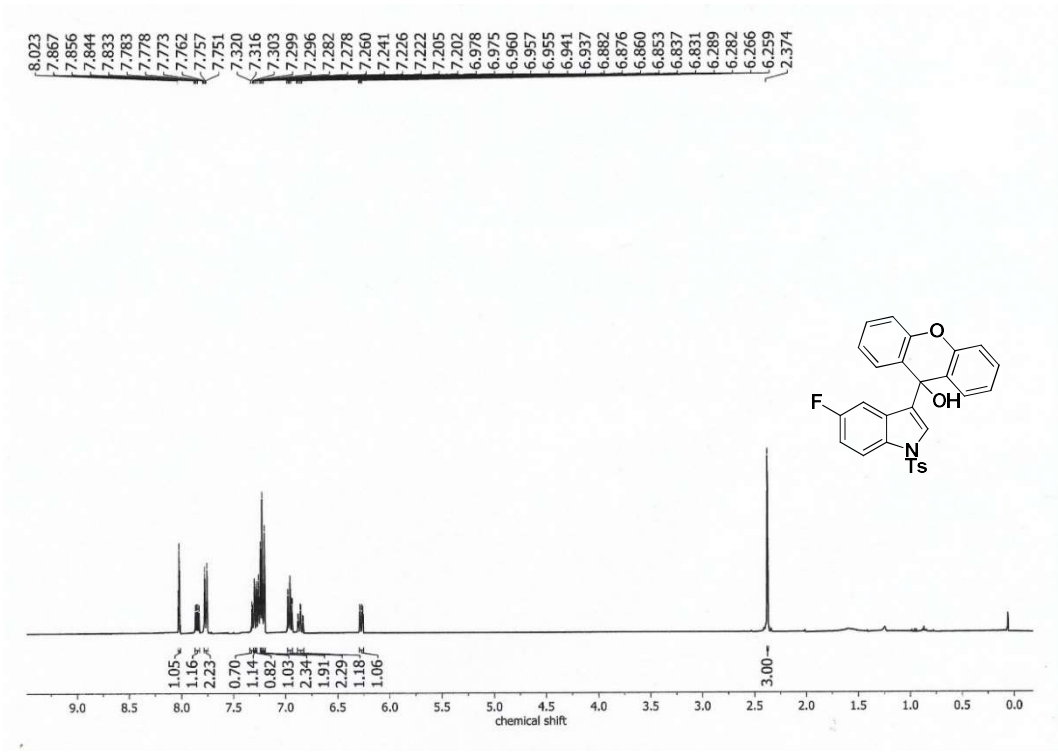
^{1}H NMR (400 MHz, $CDCl_3$) of 6h



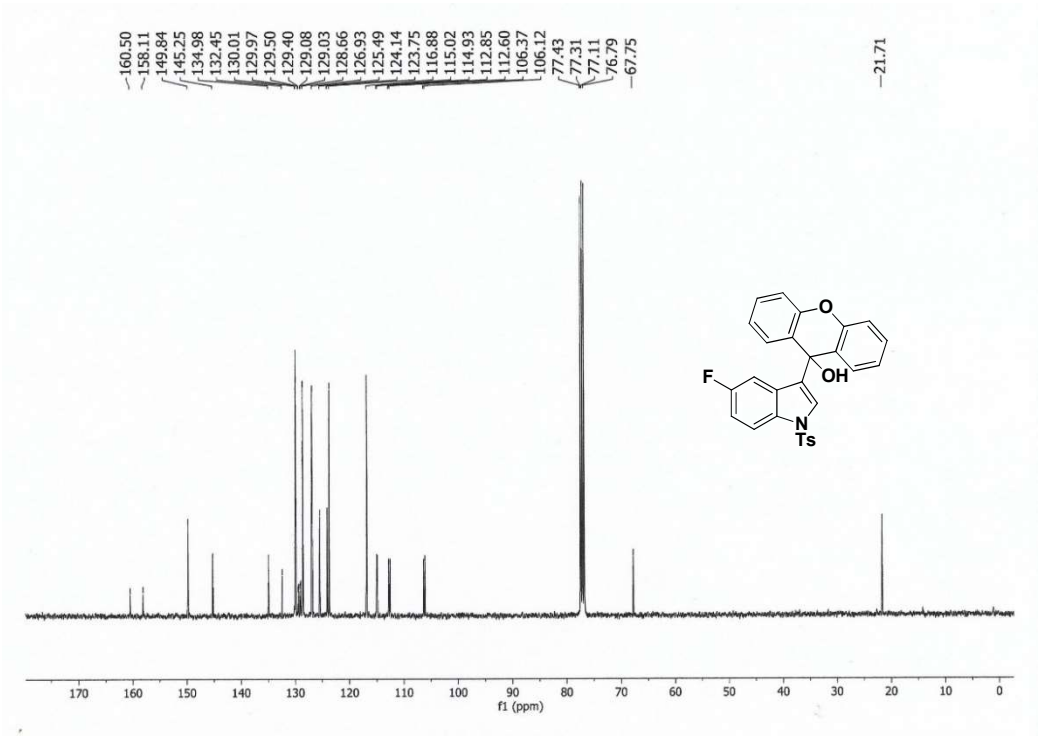
^{13}C NMR (100 MHz, $CDCl_3$) of 6h



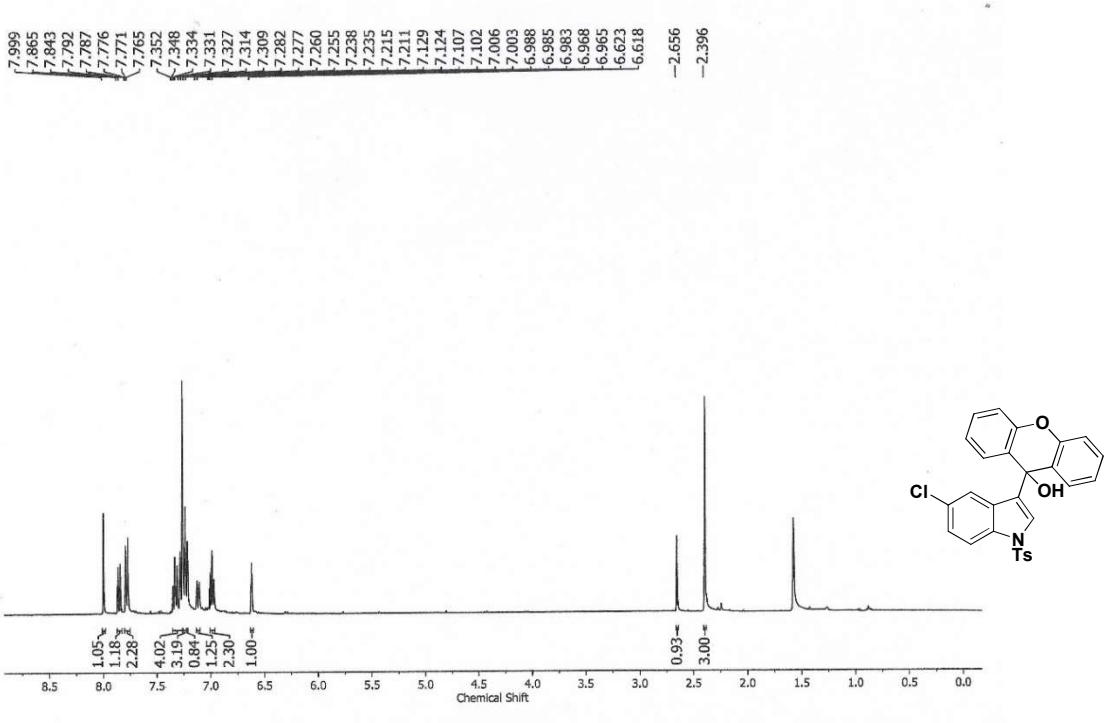
^{1}H NMR (400 MHz, $CDCl_3$) of 6i



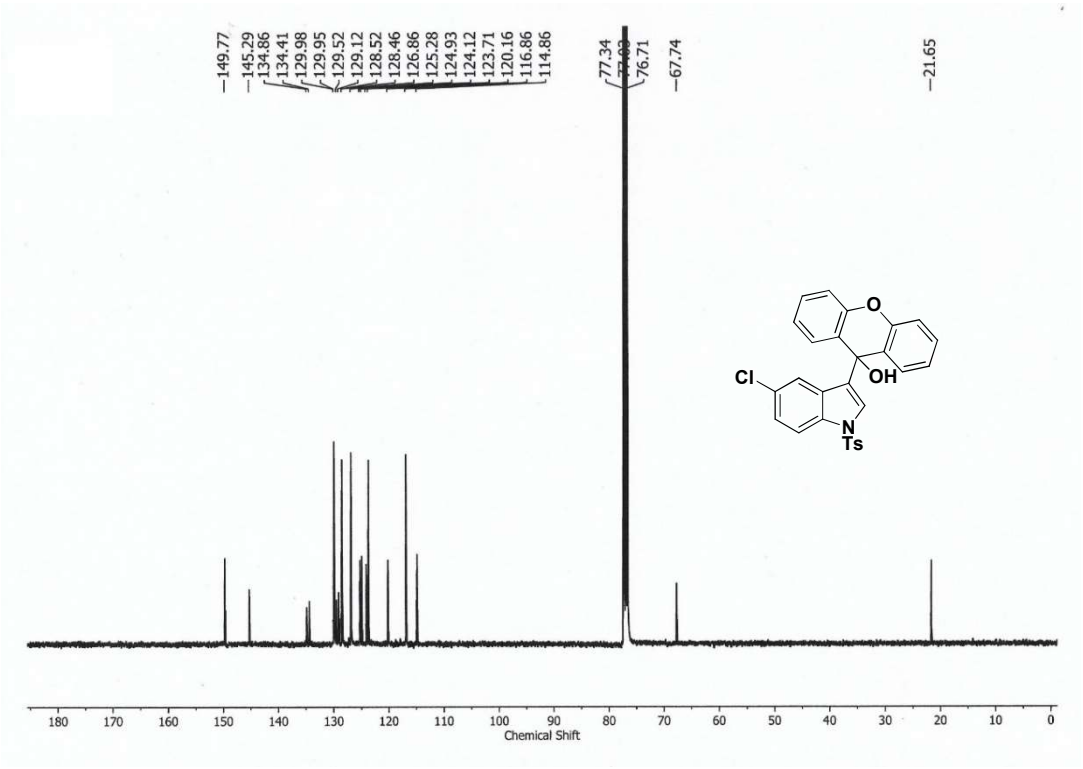
^{13}C NMR (101 MHz, $CDCl_3$) of 6i



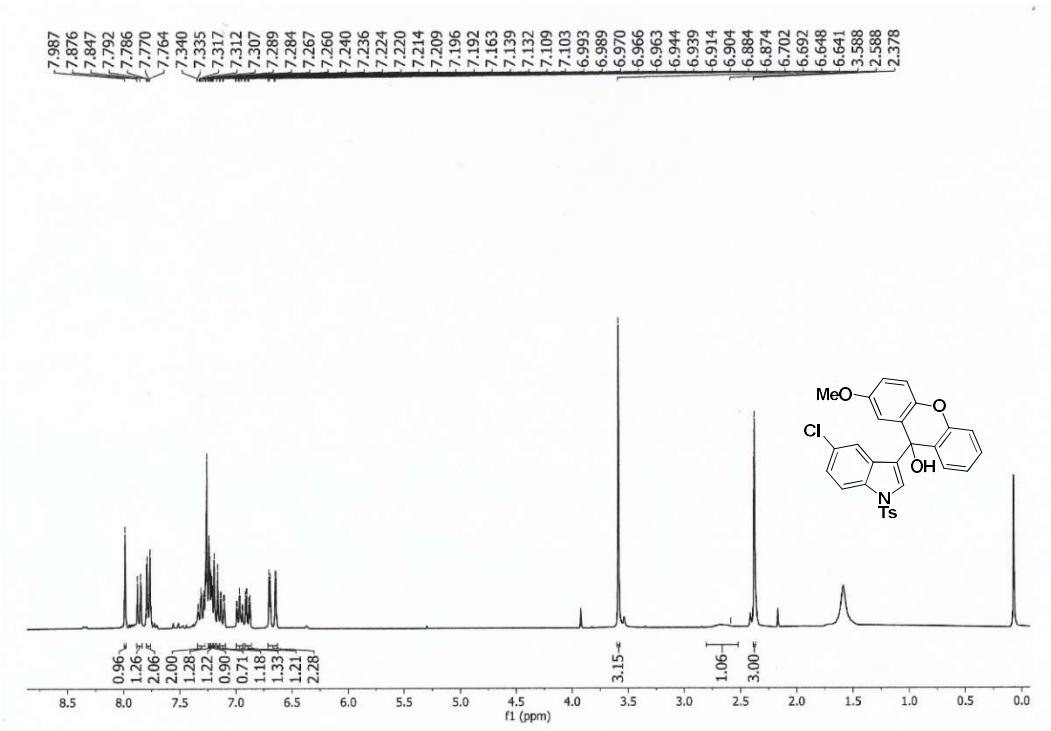
^{1}H NMR (400 MHz, $CDCl_3$) of 6j



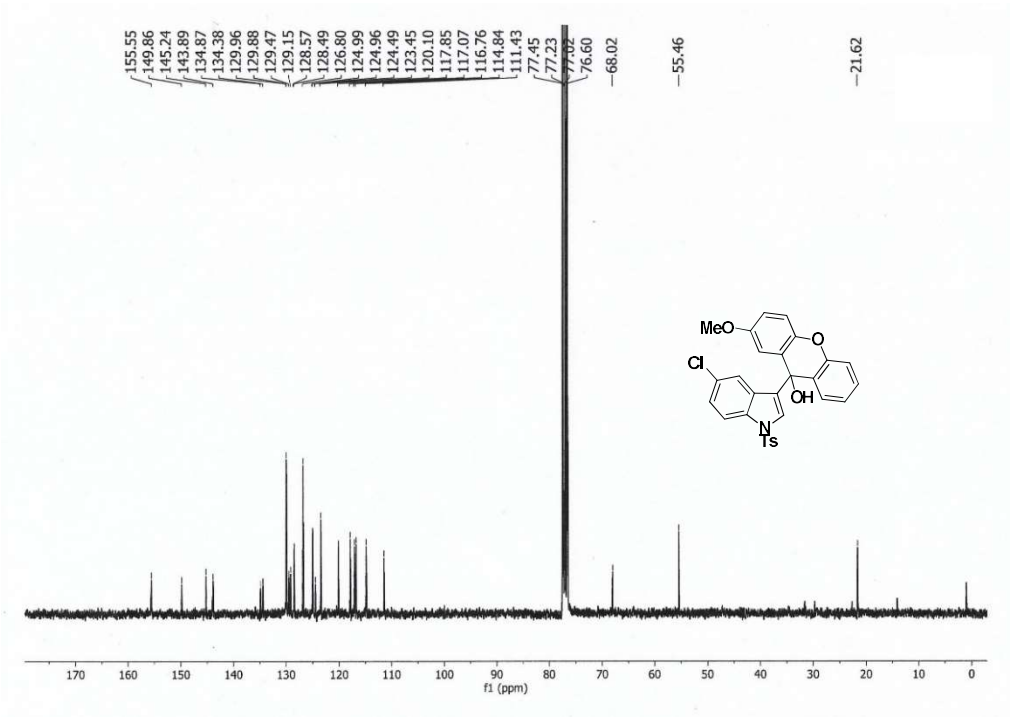
^{13}C NMR (101 MHz, $CDCl_3$) of 6j



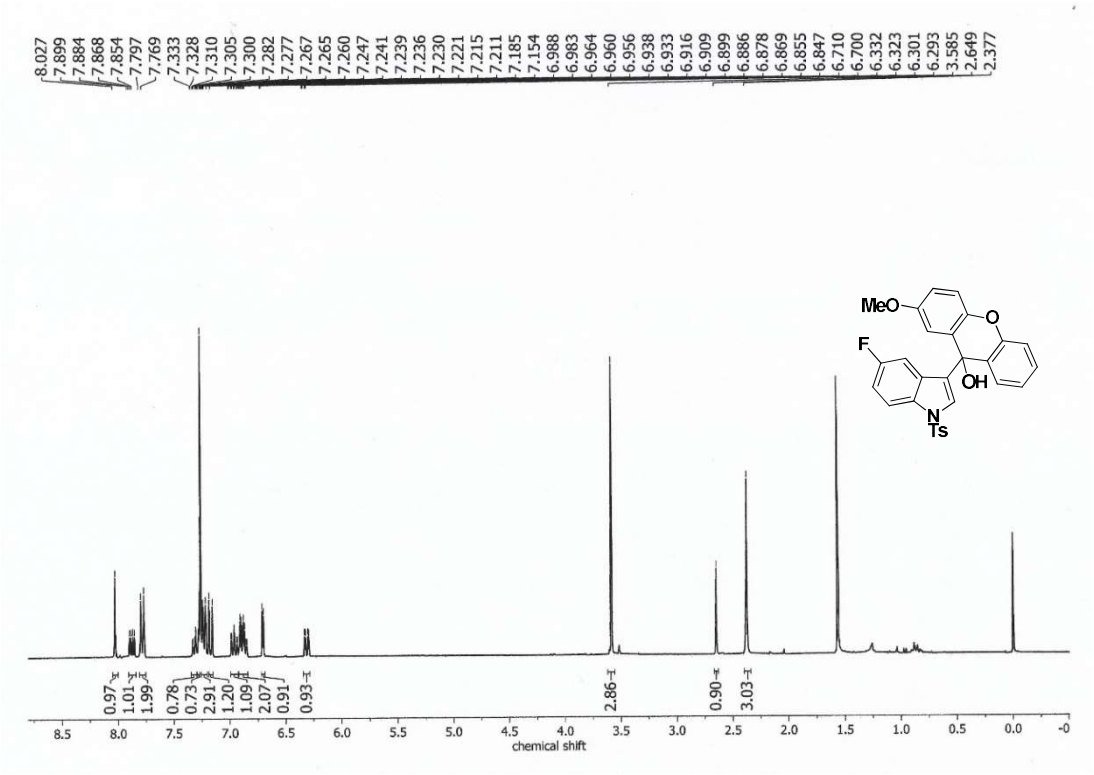
^{1}H NMR (300 MHz, $CDCl_3$) of 6k



^{13}C NMR (75 MHz, $CDCl_3$) of 6k



^{1}H NMR (300 MHz, $CDCl_3$) of 6l



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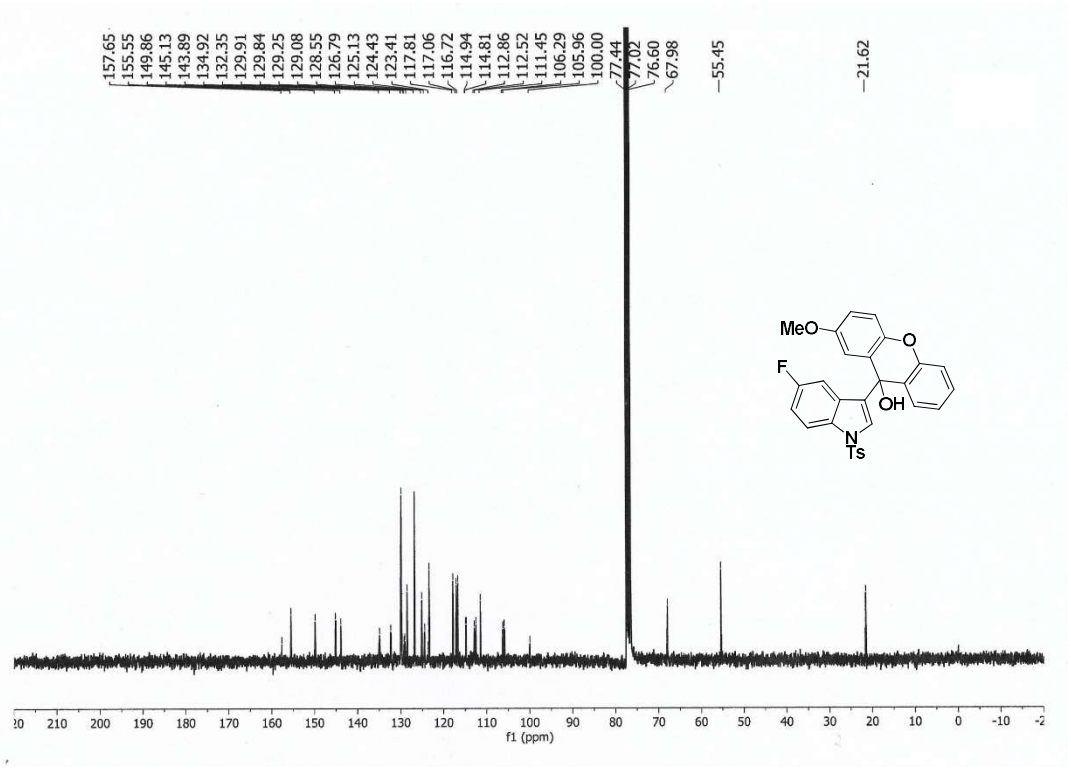
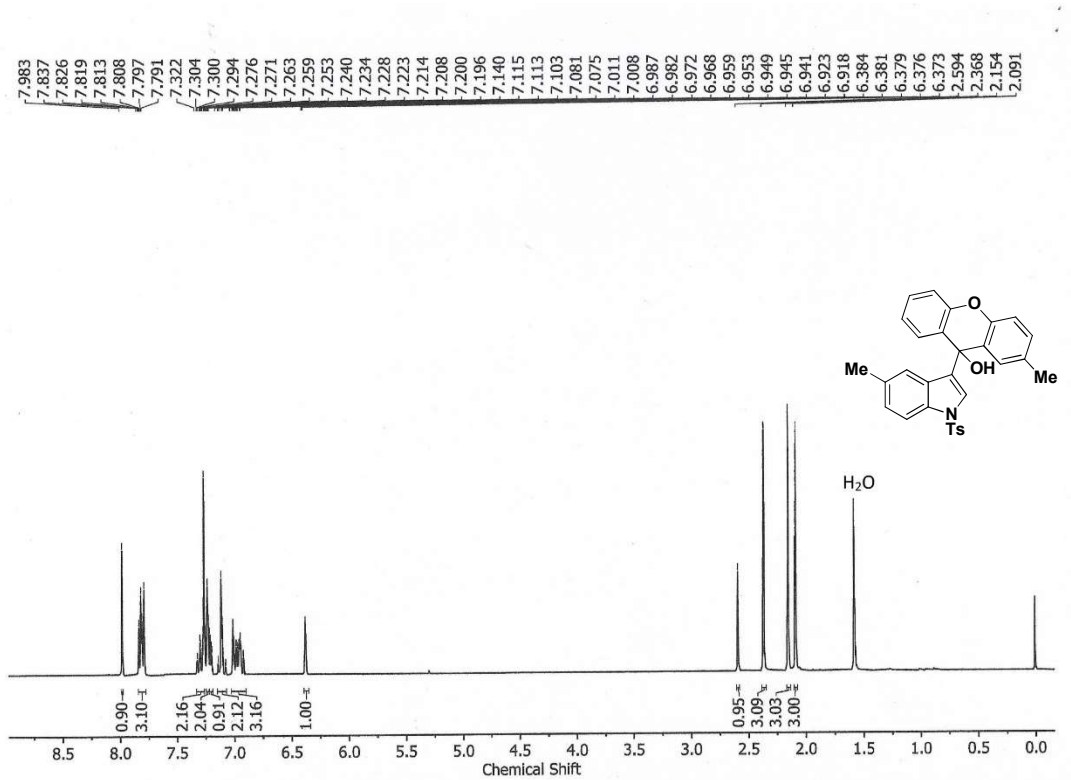
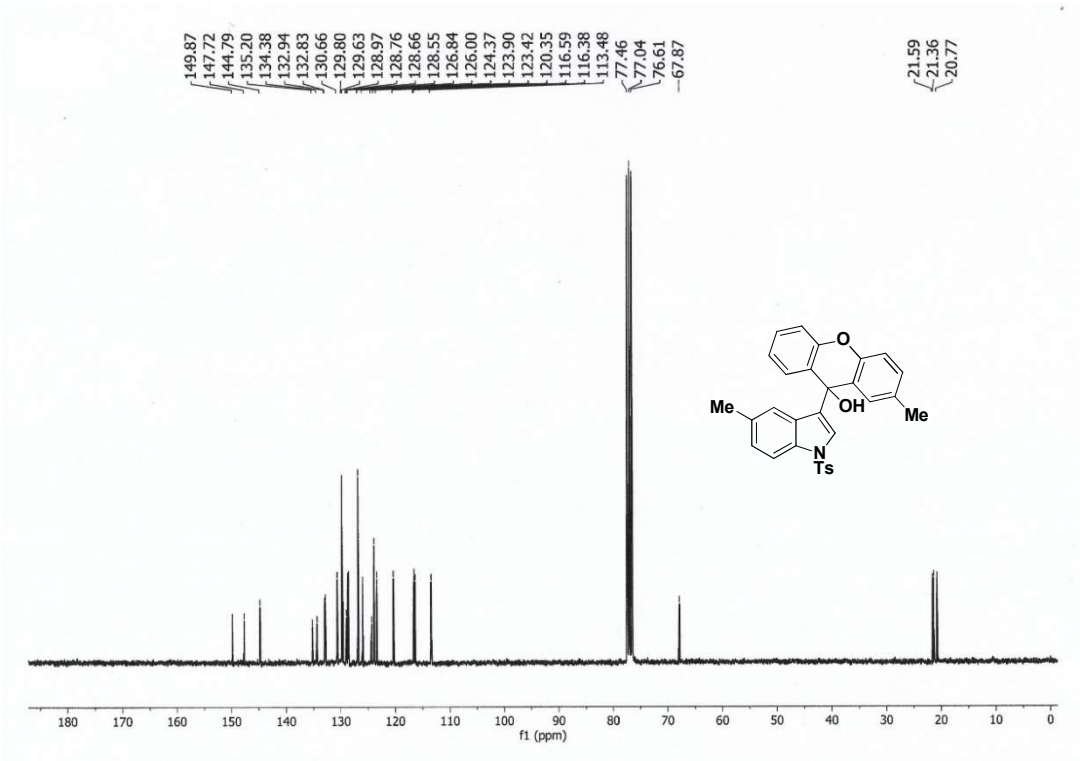


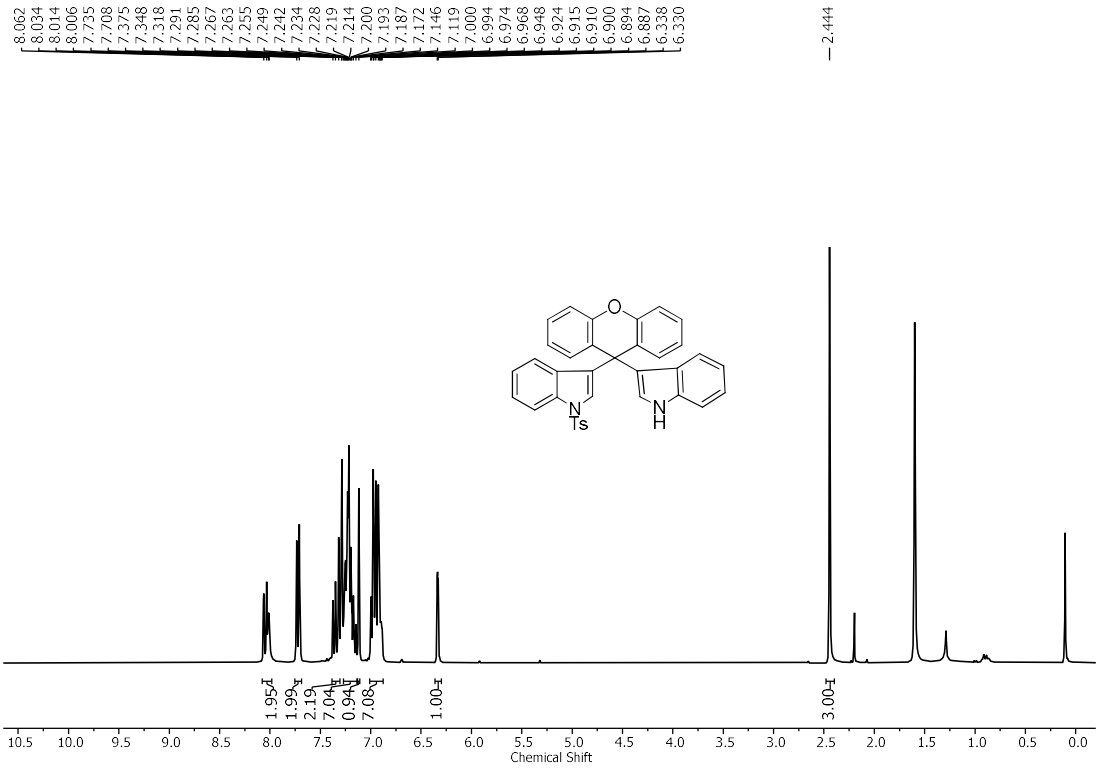
^{1}H NMR (300 MHz, $CDCl_3$) of 6m



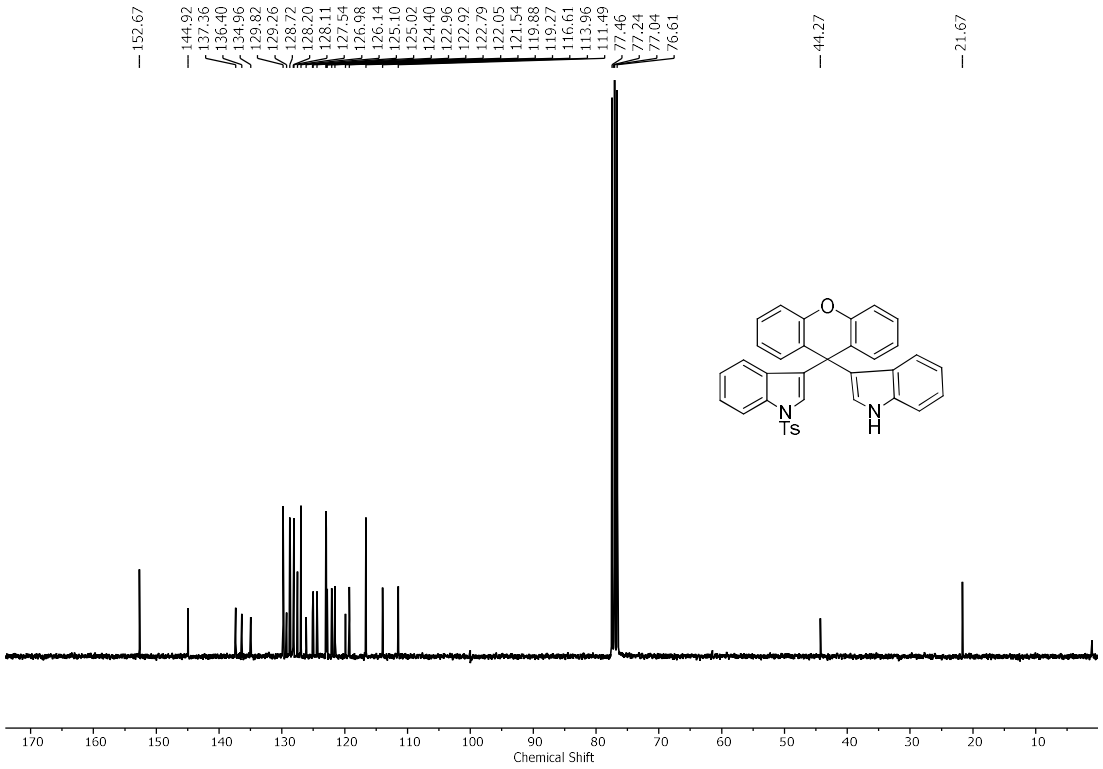
^{13}C NMR (75 MHz, $CDCl_3$) of 6m



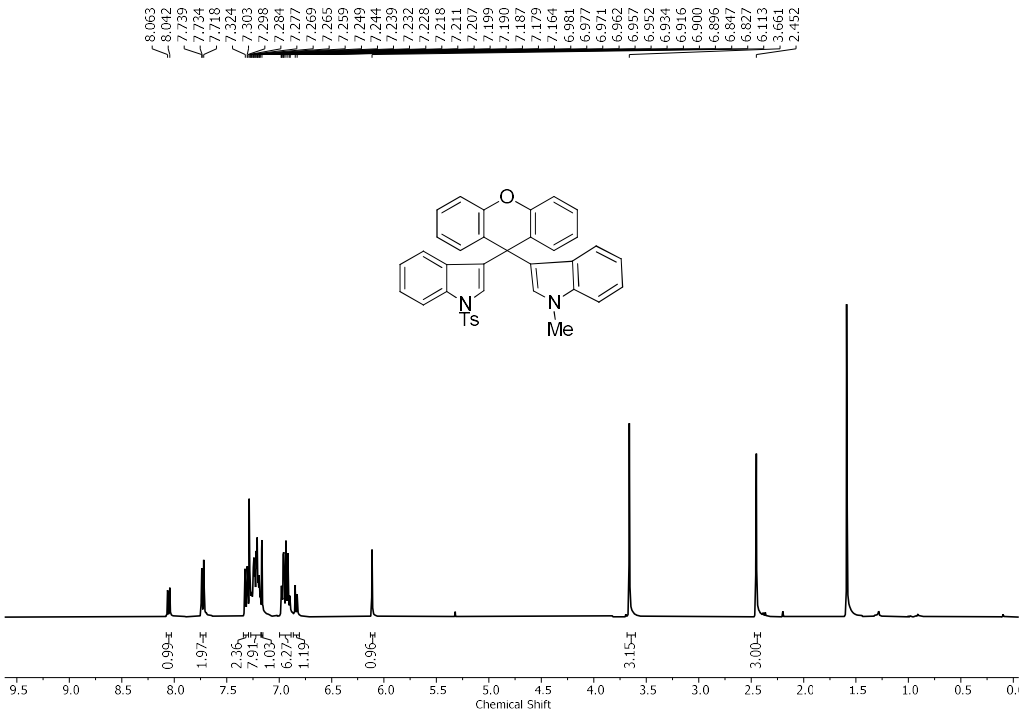
^{1}H NMR (300 MHz, $CDCl_3$) of 6aa



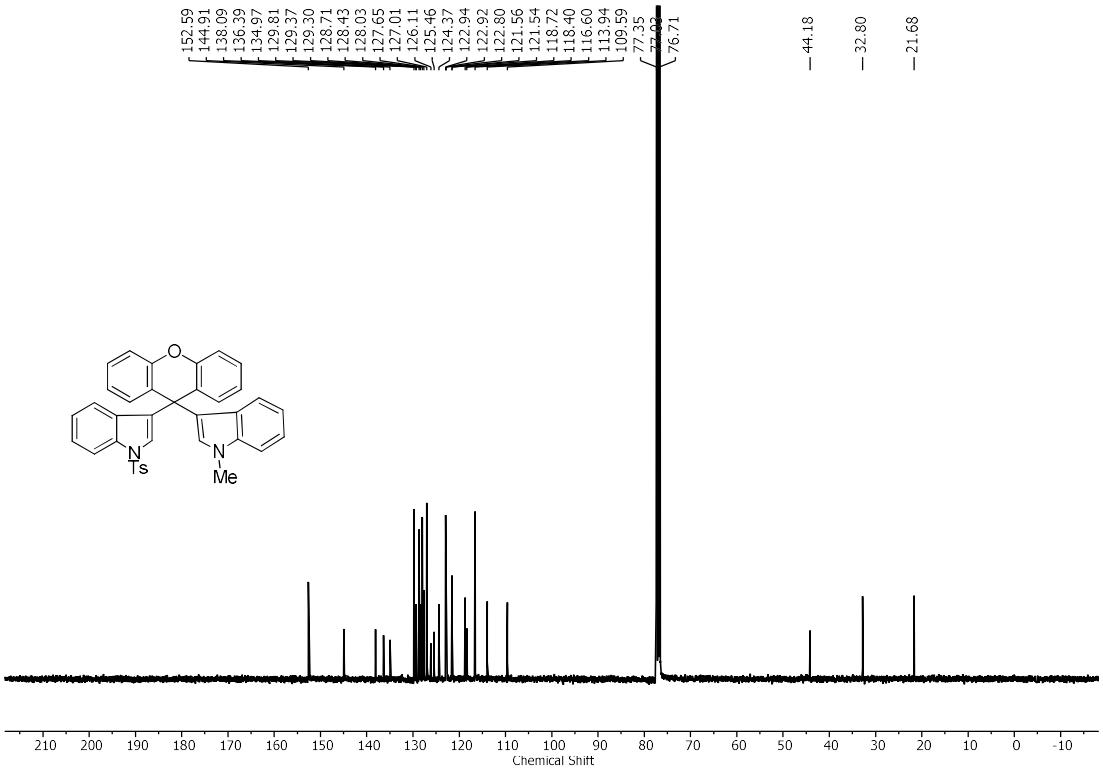
^{13}C NMR (75 MHz, $CDCl_3$) of 6aa



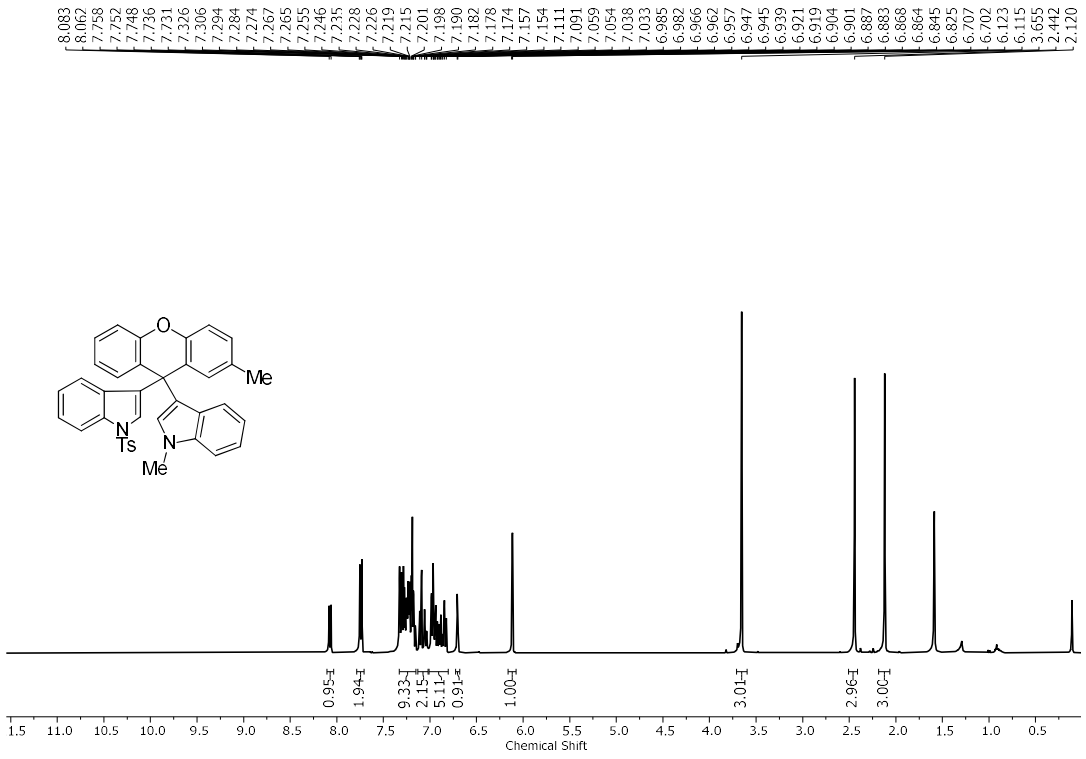
^{1}H NMR (400 MHz, $CDCl_3$) of 6ab



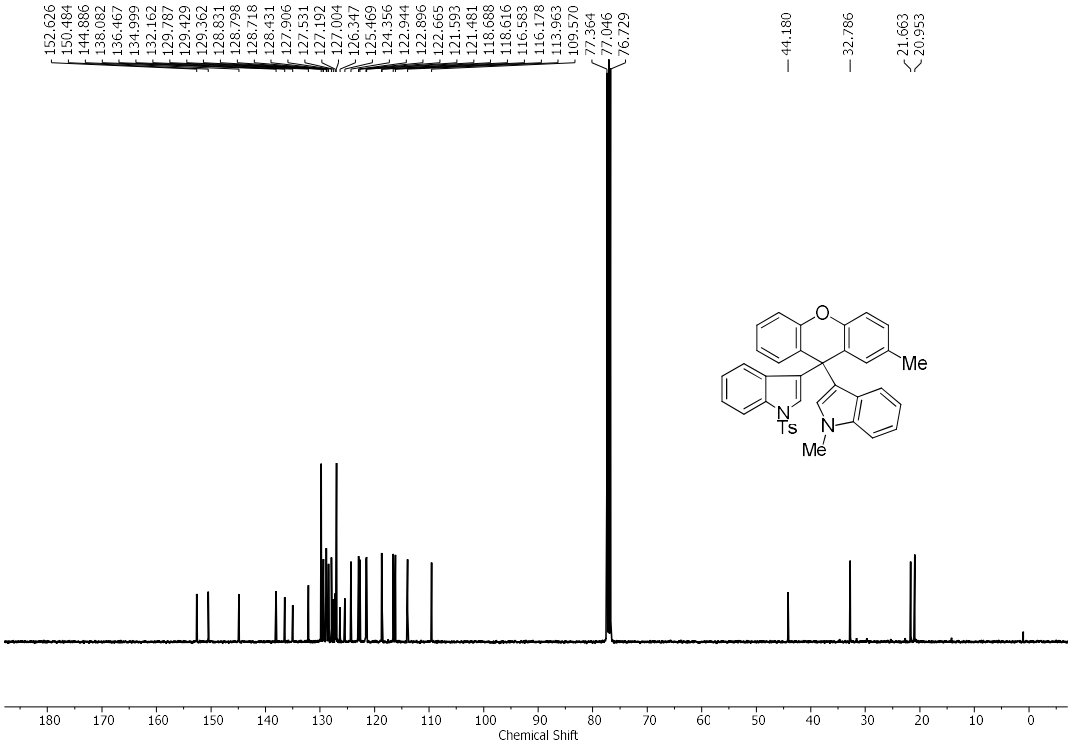
^{13}C NMR (100 MHz, $CDCl_3$) of 6ab



^{1}H NMR (400 MHz, $CDCl_3$) of 6ea



^{13}C NMR (100 MHz, $CDCl_3$) of 6ea



3.7 X-RAY CRYSTALLOGRAPHIC DATA AND STRUCTURE

	5ad
Formula	$C_{28}\ H_{21}\ N\ O_3\ S$
M_r	451.52
Crystal system	Triclinic
Space group	P -1
a / Å	9.5860(8)
b / Å	11.0980(9)
c / Å	11.1110(9)
α /°	72.424(2)
β /°	86.594(3)
γ /°	83.803(2)
V /Å^3	1119.83(16)
Z	2
D_{calcd} /mg m^{-3}	1.339
μ /mm^{-1}	0.176
θ/°	1.923– 24.837
T /K	273

Table 3.3 Crystallographic data and structural refinement parameters for **5ad** (**CCDC NO. – 2190255**)

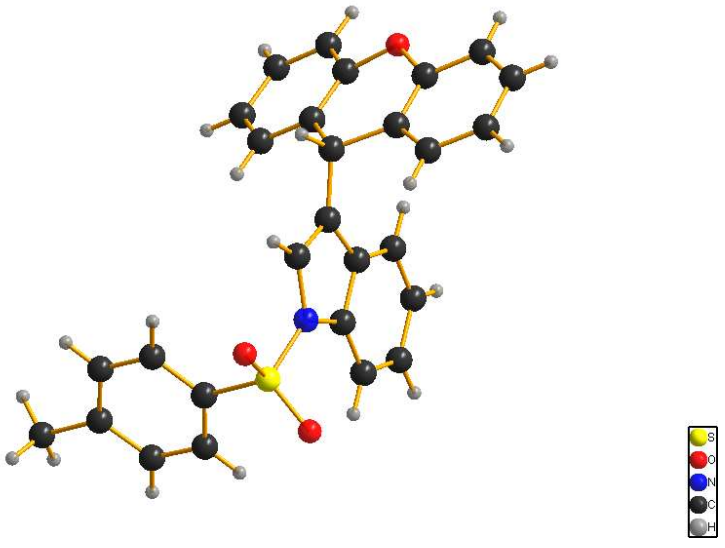


Figure 3.1 SXRD structure of **5ad** (ball and stick model). Thermal ellipsoids are given at the 50% probability level.

	6a
Formula	$C_{28}\ H_{21}\ N\ O_4\ S$
M_r	467.52
Crystal system	Triclinic
Space group	P -1
a / Å	9.3059(8)
b / Å	11.2684(10)
c / Å	11.5922(10)
α /°	71.398(3)
β /°	86.047(3)
γ /°	86.349(3)
V /Å^3	1148.22(17)
Z	2
D_{calcd} /mg m^{-3}	1.352
μ /mm^{-1}	0.177
θ/°	1.909– 27.190
T /K	273

Table 3.4 Crystallographic data and structural refinement parameters for **6a** (**CCDC NO. – 2190254**)

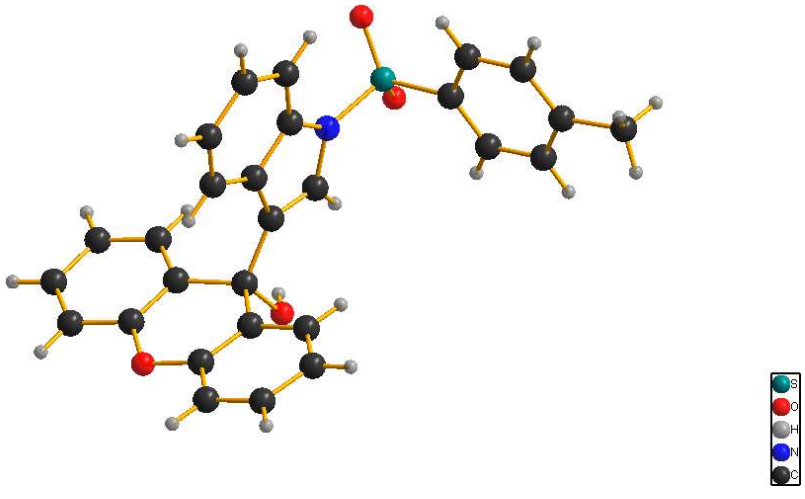


Figure 3.2 SXRD structure of **6a** (ball and stick model). Thermal ellipsoids are given at the 50% probability level.

Chapter 4

Design and Synthesis of Indazole-Indole Hybrid *via tert*-Butyl Nitrite Mediated Cascade Diazotization/Isomerization/Cyclisation

4.1 INTRODUCTION

Nitrogen-containing heterocycles are valuable building blocks in a wide range of bioactive natural products, commercially available drugs, and material science applications.[1] Among them, indazoles[2] are privileged structural motifs in the fields of drug discovery and material chemistry. For example, indazole scaffold has a wide range of pharmacological activities, such as the therapy of respiratory diseases, central nervous system (CNS) disorders, Parkinson's disease, and multi-kinase inhibitory activities.[3] These significant and broad-spectrum activities have prompted synthetic chemists to continue developing new methods for the construction of functionalized indazoles.[4] Similarly, indoles are another valuable structural scaffold. In particular, C-3 functionalized 1H-indazoles[5] and indoles[6] have gained significant interest over the past decades, as they are commonly found in commercial drug candidates and have been the focus of great research in medicinal chemistry. Namely, MLi-2[5a] is a very much selective leucine-rich repeat kinase 2 (LRRK2) inhibitor and has potential for Parkinson's disease; NSR is a norepinephrine/serotonin reuptake inhibitor for the treatment of fibromyalgia[5c]; Cerlapirdine[5d] (SAM-531) is a potent antagonist of 5-HT6R that is undergoing in clinical trials for the treatment of Alzheimer's disease; YC-1[5b] (lificiguat) activates guanylyl cyclase and is identified for its outstanding anticancer properties (**Figiure 4.1**, A); similarly, **Figure 4.1** (B) depicts the structures of selected C-3 substituted indole derivatives along with their corresponding pharmacological activities.[6b]

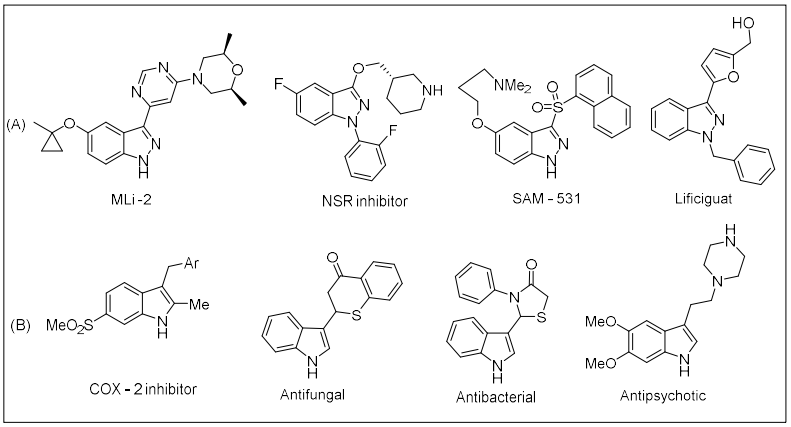
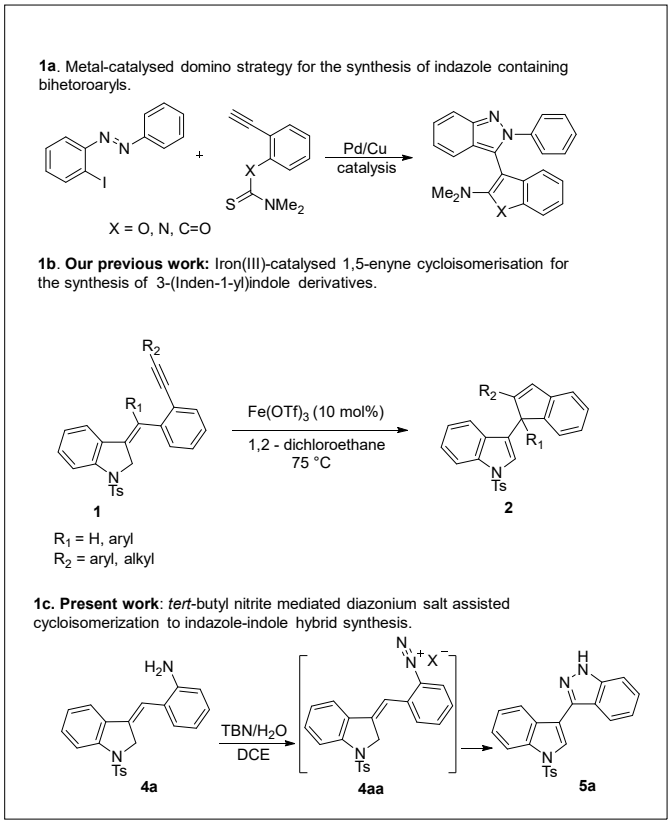


Figure 4.1 Some examples of C-3 substituted indazole and C-3 substituted indole containing bioactive molecules.

Recognizing the significant applicability in the drug discovery of these two structural scaffolds, we perceived that the hybrid of these two *N*-heterocyclic motifs at their C-3 position

could potentially intensify their performance in their application compared to their individual components. Nevertheless, to the best of our knowledge, the synthesis of indazole linked indole hybrid is barely reported.[7] Very recently, Mai *et al.* described a method for the construction of indazole-containing biheteroaryls *via* a tandem Sonogashira coupling/azaenyne cycloisomerization/Barton–Kellogg reaction (**Scheme 4.1**, 1a).[7a] Consequently, the development of a new synthetic method that synthesizes structurally diverse C-3-linked indazole–indole hybrid in a sequential manner rather than a direct coupling of individual components is highly desirable.

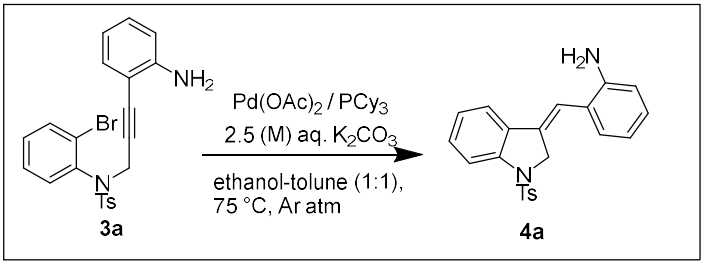


Scheme 4.1 Overview of the work.

In recent years, transition metal-catalyzed cycloisomerization of alkyne *via* 5-*endo-dig* cyclisation has been consciously evolving as it allows for the efficient formulation of structurally diverse and complex 5-membered carbo- and heterocycles with high atom economy.[8] In this regard, we have recently developed an iron catalyzed 1,5-enyne cycloisomerization of 3-(methylene)indoline derivative **1** *via* 5-*endo-dig* cyclization to synthesize substituted 3-(1-indenyl)indole **2** (**Scheme 4.1**, 1b).[9] Inspired by this result, we speculated that replacing -C≡C- unit with its nitrogen analog **-**N≡N$^+$ may go through a similar

type of cycloisomerisation to accomplish the C-3 linked indole-indazole hybrid in a sequential way. Herein, we demonstrate a *ter*t-butyl nitrite (TBN)-mediated metal-free strategy for the synthesis of indazole-indole biheteroaryl **5a** in excellent yield (**Scheme 4.1**, 1c) from 2-(1-tosylindolin-3-ylidenemethyl)aniline **4a**. The present protocol proceeds through *in-situ* generated diazonium salt triggered allylic isomerization, intramolecular C-N bond formation *via* 5-*endo-dig* cyclisation, and tautomerization.

4.2 RESULTS AND DISCUSSION

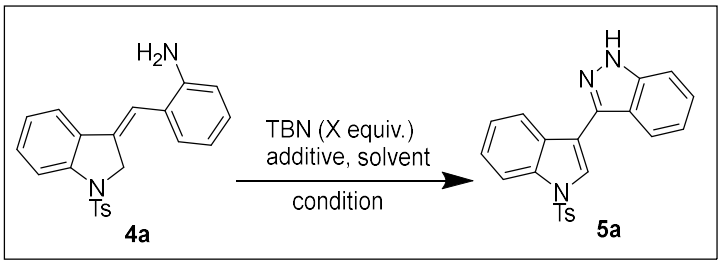


Scheme 4.2 Preparation of substrate **4a**

To probe the viability of this strategy, 2-(1-tosylindolin-3-ylidenemethyl)aniline **4a** was first synthesized through intramolecular reductive Heck coupling reaction of 2-halo-*N*-propargylanilide derivative **3a**, guided by the previously developed method,[10] using 5 mol% of $Pd(OAc)_2$, and 10 mol% of tricyclohexylphosphine (PCy_3) at 75 °C in the presence of 2.5 M K_2CO_3 (**Scheme 4.2**) (see section 4.4.2).

Next, the inquiry began for finding a suitable reaction condition for the cascade diazotization/cycloisomerization of model substrate **4a** to synthesize 3-(1-tosyl-1H-indol-3-yl)-1H-indazole **5a**. the results are summarized in **Table 4.1**. Initially, the transformation was carried out with **4a** and 1.0 equiv. TBN in 3.0 mL DCE (1,2-dichloroethane) at 50 °C for 10 min. Pleasantly, the desired C-3 linked indazole-indole **5a** was isolated in 53% yield with excellent regioselectivity (**Table 4.1**, entry 1). Notably, increasing temperature to 75 °C while using the same amount of TBN in DCE for 10 minutes, without any additives, significantly improved the yield of the desired product **5a** to 76% (**Table 4.1**, entry 2). However, when the similar reaction was performed with 4 Å molecular sieves, the yield of the product **5a** was reduced to 32% in 60 min (**Table 4.1**, entry 3). From this result, we understood that moist condition is necessary to accelerate the diazotization process and subsequent cyclisation of substrate **4a**. However, when the reaction was conducted in the presence of H_2O (5µl) the yield

of the desired indazole–indole **5a** was increased up to 90% (Table 1, entry 4).

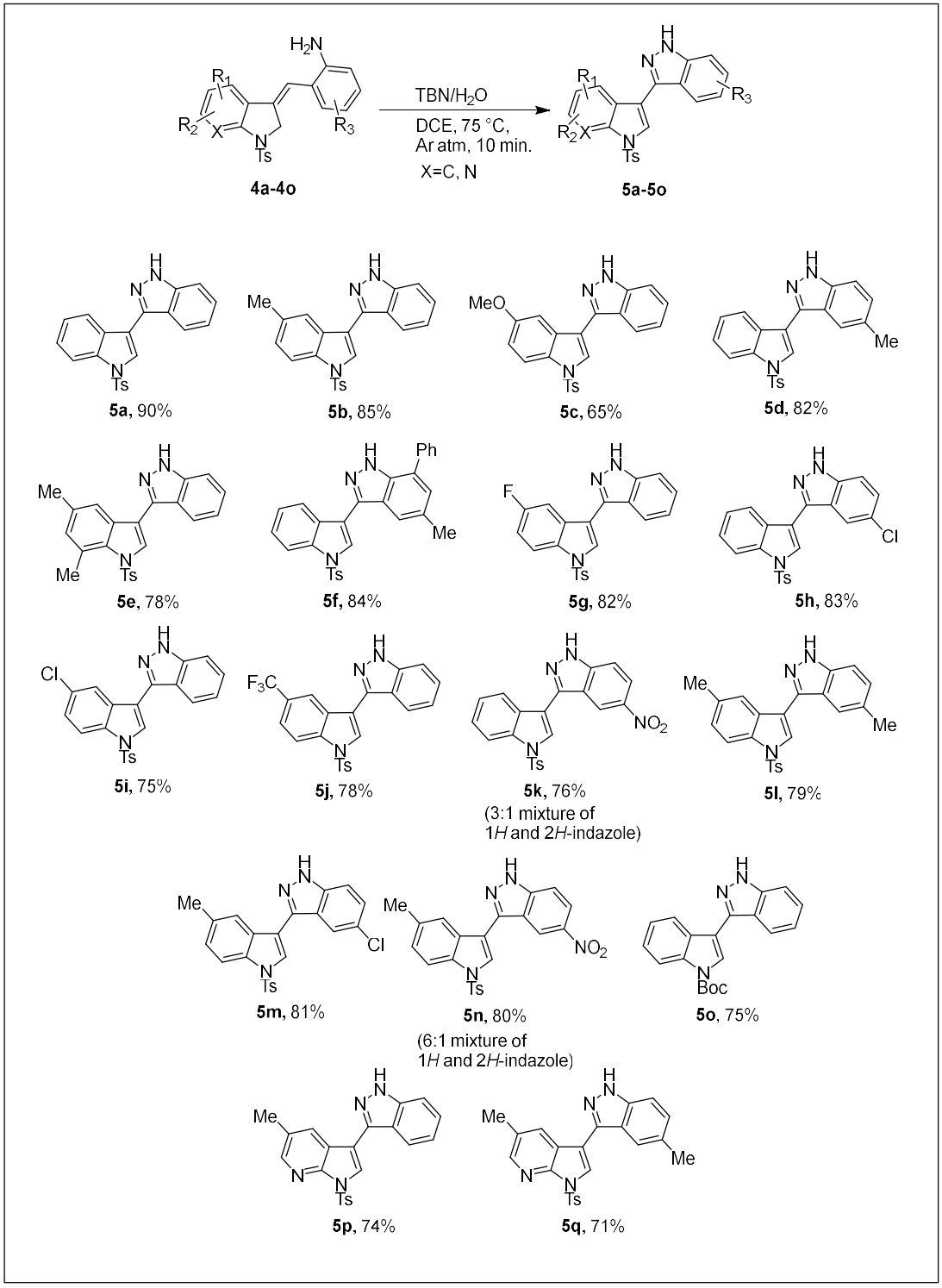


Entry	X equiv.	Additive	Solvent	T/° C	t/ min.	Yield (%)
1	1	-	DCE	50	10	53
2	1	-	DCE	75	10	76
3	1	4 Å ms	DCE	75	60	32
4	1	H_2O (5 µl)	DCE	75	10	90
5	1.5	H_2O (5 µl)	DCE	75	10	44
6	1	$Fe(OTf)_3$	DCE	75	10	48
7	1	PTSA	DCE	75	10	86
8	1	TfOH	DCE	75	10	41
9	1	H_2O (5 µl)	EtOH	75	10	39
10	1	H_2O (5 µl)	MeCN	75	10	36
11	1	H_2O (5 µl)	CH_3NO_2	75	10	32
12	1	H_2O (5 µl)	tolune	75	10	20
13	1	H_2O (5 µl)	DMF	75	10	ND

Table 4.1 Optimization of Reaction Condition.

Moreover, increasing the amount of TBN to 1.5 equiv. resulted in a lower yield of **5a** (**Table 4.1**, entry 5). Furthermore, the reaction was also examined in the presence of Lewis acid or Brønsted acid as additives. It was observed that the reaction progressed smoothly in the presence of 0.2 equiv. *p*-toluenesulfonic acid (PTSA) to afford the target product in 86% yield, while $Fe(OTf)_3$ and TfOH gave inferior results (**Table 4.1**, entries 6-8). A series of other common solvents, including EtOH, MeCN, CH_3NO_2, toluene, and DMF were also screened to check the solvents effect. However, in most cases, relatively lower yields were obtained compared to the yields gained in DCE. For example, in EtOH, MeCN, CH_3NO_2, and toluene, the yield of **5a** is drastically reduced to 39%, 36%, 32%, and 20%, respectively (**Table 4.1**, entries 9-12) and in DMF (**Table 4.1**, entry 13), no desired product was isolated. Thus, 1.0

equiv. of TBN in 3 mL 1, 2-dichloroethane at 75 °C for 10 min under an Ar atmosphere in the presence of 5 µl of H_2O was defined as the standard reaction condition for additional study.



Scheme 4.3 Substrate scope of 1*H*-indazole-indole and 1*H*-indazole-azaindole hybrids.

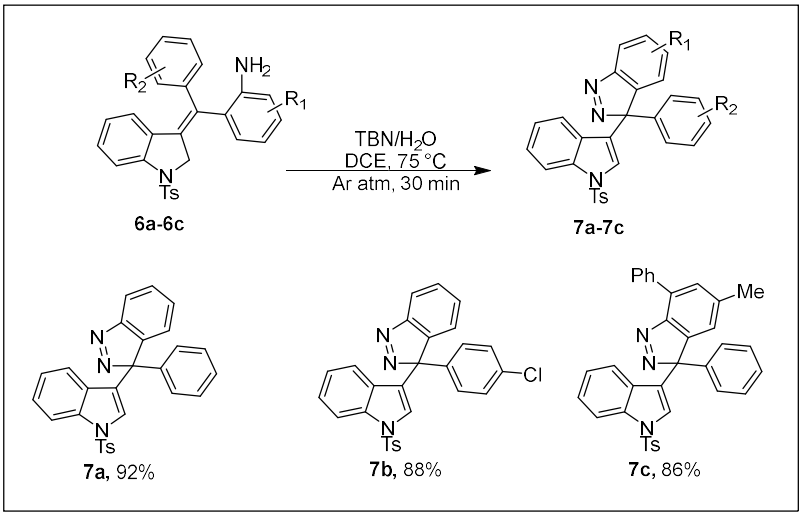
Following the optimal reaction conditions, a series of indole-indazole hybrids were synthesised

by reacting substrate **4** (0.13 mmol) with tert-butyl nitrite (TBN) (0.13 mmol) in the presence of 5 µl H_2O in 3.0 mL of 1,2- DCE solvent under Ar atmosphere at 75 °C for 10 minutes. The reaction was accomplished on both unsubstituted and substituted aryl groups of 3-indoline unit, and the findings are summarized in **Scheme 4.3**. Unsubstituted 2-amino aryl ring such as **5a** were Successfully achieved with a high yield of **5a** (90%, **Scheme 4.3**, **5a**). The substrate containing *o*-Me, *p*-Me, and strong electron donating compound such as p-OMe substituted derivative were well tolerated in diazonium triggered intramolecular cyclisation and furnished the final cyclisation products in 85%, 65%, 82%, 78%, and 84% yields, respectively **(Scheme 4.3, 5b, 5c, 5d, 5e, 5f**). Similarly, electron withdrawing groups, viz. –F, –Cl, $–CF_3$ containing substrates, reacted efficiently to construct the desired products in 82%, 83%, 75%, and 78% yields, respectively (**Scheme 4.3, 5g, 5h, 5i, 5j**). However, we also examined the electronic effects of *p*-NO_2 on the aryl ring of 2-alkenyl aniline moiety, which could have a direct impact on diazonium assisted cyclization. It was observed that these compounds underwent smooth cycloisomerisation reactions in 76% and 80% yields with non-separable tautomeric forms of 1*H*- and *2H*- indazoles in 3:1 and 6:1 (**Scheme 4.3, 5k, 5n**)[11]. There was no such steric influence of *ortho*-phenyl group on the aryl ring of 2-alkenyl aniline moiety (**Scheme 4.3, 5f**). The precursors, containing both electronically similar and opposing substituents simultaneously, exhibited fruitful transformations to the desired **5l, 5m, 5n** products in 79%, 81% and 80% yields, respectively, (**Scheme 4.3**, **5l**, **5m**, **5n**). Moreover, it is noteworthy that the *tert*-butoxycarbonyl group, which function as an amine protector also survived under the reaction conditions, and formed

Similarly, 7-azaindoles, an important bioisoster of indole, are frequently found in several commercially available drug candidates.[12] However, there are no reports of the synthesis of indazole-azaindole hybrid in the literature. In order to explore the further benefits of this developed strategy, the biheteroaryls containing 7-azaindole and indazole was also constructed using 7-azaindolines, **4p** and **4q**. Gratifyingly, the products **5p** and **5q** were also achieved in 74% and 71% yields, respectively (**Scheme 4.3**, **5p**, **5q**).

To further broaden the substrates scope, we also investigated the synthesis of 3*H*-indazole-indole hybrid. The synthesis of 3*H*-indazoles has been limited because of their instability.[13] Therefore, it would be intriguing to synthesize the 3*H*-indazole-indole hybrid. First, the substrates **6a**, **6b,** and **6c** were prepared following our earlier method[13]. When these 3-

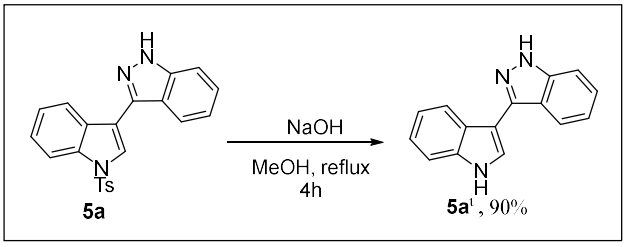
substituted indolines **6a**, **6b,** and **6c** were subjected to the present reaction conditions, pleasantly, the desired products **7a, 7b,** and **7c** were afforded in 92%, 88%, and 86% yields, respectively (**Scheme 4.4**, **7a, 7b, 7c**).



Scheme 4.4 Substrate scope of 3*H*-indazole-indole hybrids.

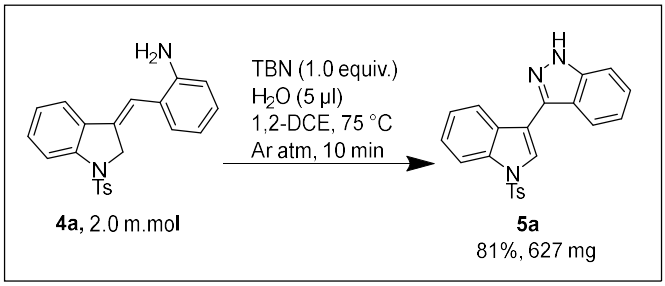
Therefore, this new strategy is quite general. All of the substrates could successfully be converted into the desired C-3 substituted indazole-indole hybrids in high yields via 5-*endo-dig* cyclization. All the hybrid structures were characterized using ^{1}H, ^{13}C NMR, and HRMS spectra (see section 4.4.3 and 4.4.4). Structure **5m** was further confirmed through X-ray diffraction (see section 4.7, **Figure 4.2**, CCDC no. 2297939).

It was reported[14] that *N*-sulfonamide indole derivatives have interesting pharmaceutical activities such as antibacterial, antioxidant, property etc., and hence *N*-tosyl indole–indazole will have substantial pharmaceutical properties. However, because natural occurring indoles lack protecting groups, we also performed the detosylation of **5a** using a solution of 50 mol% sodium hydroxide (NaOH) in methanol-water (1:1) under reflux conditions to obtain the detosylated product **5a′** in 90% yield (**Scheme 4.5**, **5a′**) (see section 4.4.5).



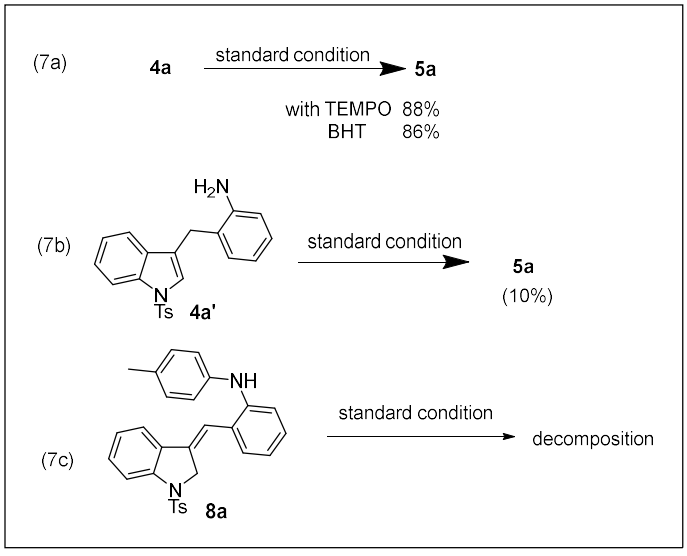
Scheme 4.5 Detosylation of 1*H*-indazole tethered indole derivative **5a.**

To explore the practical applicability of the present methodology, we carried out semi large-scale diazotization/cyclization reaction of **4a** in the usual laboratory set up. Under our standard condition the indazole-indole hybrid **5a** was achieved in 81% yield (**Scheme 4.6**).



Scheme 4.6 Scale-up synthesis of 3-(1-tosyl-1H-indol-3-yl)-1H-indazole **(5a)**.

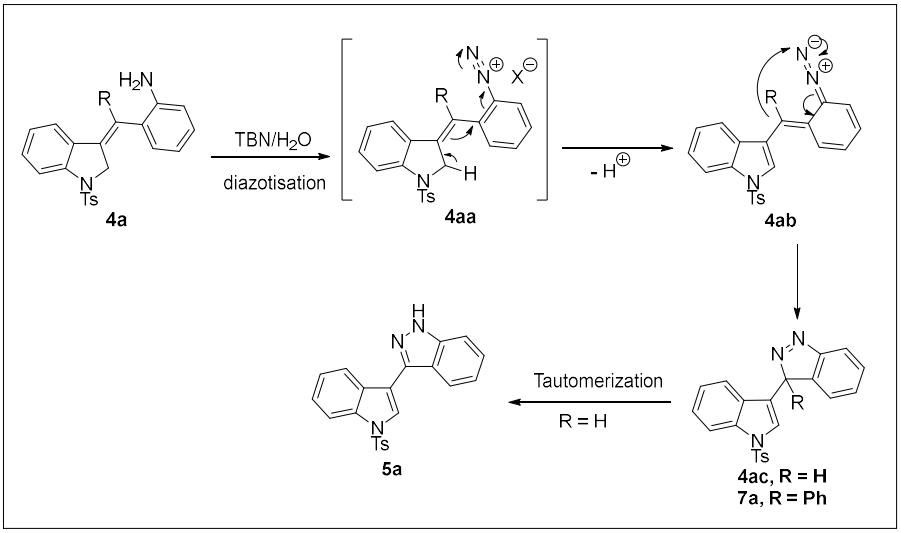
Finally, to gain insight into the reaction mechanism, a few control experiments were conducted, as depicted in **Scheme 4.7**. First, we carried out the reaction of **4a** with TBN in the presence of



Scheme 4.7 Control experiments.

radical scavengers, TEMPO and BHT separately to understand whether the reaction proceeds through a radical intermediate. It was observed that the yields of the desired product **5a** did not decrease considerably in both cases, which implies the ionic pathway for this transformation (**Scheme 4.7**, 7a). We also thought that this reaction could begin with isomerization to furnish **4a′**, followed by diazotization, and cyclisation to afford **5a**.[15] In order to ascertain that we first prepared **4a′** through the isomerization of **4a** according to our modified previous method[16] (see section 4.4.7 (b)), and then the final reaction was set out under the optimized conditions, just a

trace amount of the desired product **5a** was formed (**Scheme 4.7**, 7b). This observation revealed that diazotization/isomerization/cyclisation occurred in a cascade manner. Additionally, the reaction of secondary amine **8a** did not give any product under our present protocol (**Scheme 4.7**, 7c). This finding indicates that C-N bond formation step follows a diazotization pathway.



Scheme 4.8 Plausible mechanistic pathway.

Based on the above experimental results, control experiments, and related works,[17] we have defined the process of TBN-mediated diazotisation/cycloisomerization/tautomerization of **4a,** as shown in **Scheme 4.8**. Initially, TBN in the presence of H_2O reacts with **4a** to form a diazonium salt **4aa**. Diazonium salt **4aa** is stabilized by a push-pull mechanism through aromatization of the indole nucleus and generates a betaine like intermediate **4ab**. Subsequently, the intermediate **4ab** was smooth cyclized to furnish **4ac** (R = H) either through 6π-electrocyclisation reaction or through direct intramolecular C-N bond formation via 5-*endo-dig* cyclization. Finally, a rapid tautomerization of **4ac** produces the desired **5a**. However, when R = Ph, the reaction stopped after the formation of **7a**.

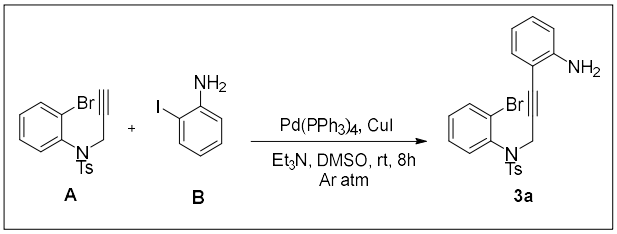
4.3 CONCLUSION

In conclusion, a *tert*-butyl nitrite (TBN) mediated straightforward metal free approach has been developed for the synthesis of a diverse range of C-3-substituted indazole-indole hybrids using readily accessible 2-(indolin-3-ylidenemethyl)aniline derivatives. This approach is proposed to occur *via* a diazonium salt intermediate that is capable of cascade isomerization and intramolecular C-N bond formation though a *5-endo-dig* cyclisation to achieve indazole-indole hybrids. In the present strategy many substituents are well tolerated and furnished desired

product with high yields. Moreover, this versatile and flexible approach allows to synthesize 7-azaindole-indazole as well as 3*H*-indazole-indole hybrids. Additionally, this novel reaction has several notable features including the straightforward preparation of substrates, a high degree of atom economy, high regioselectivity, and mild reaction conditions. We believe this strategy may be of interest in the synthesis of pharmaceuticals and natural products.

4.4 EXPERIMENTAL PROCEDURE

4.4.1 Representative experimental procedure for the synthesis of *N*-(3-(2-aminophenyl)prop-2-yn-1-yl)-*N*-(2-bromophenyl)-4-methylbenzenes ulfonamide (3a).

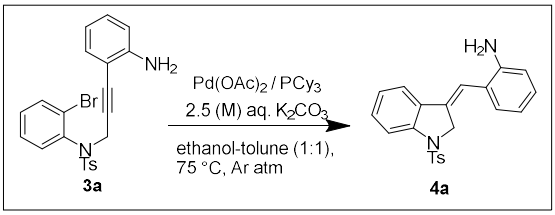


Compound **3a** was synthesized by following our previous reported procedure[10] with modification of reaction time.

To a solution of **A** (250 mg, 0.69 mmol) in dimethylsulfoxide (DMSO) (2 mL), 2-iodoaniline (**B**) (165 mg, 0.75mmol), triethylamine (139 mg, 1.38 mmol), CuI (3 mg, 0.014 mmol) and $Pd(PPh_3)_4$ (8 mg, 0.01 mmol) were added successively. The resulting solution was stirred at room temperature under argon atmosphere for 8 h. After the completion of the reaction (monitored by TLC), the crude reaction mixture was extracted with ethyl acetate. The organic extract was washed with brine solution, dried over anhydrous Na_2SO_4 and concentrated. The product was subjected to column chromatography (silica gel, 60-120 mesh), eluting with hexane/EtOAc 95:5 (v/v) to afford the product **3a** as a yellow semisolid (235 mg, 0.52 mmol, 75%).

Compounds **3b-3q** were synthesized by following the above method.

4.4.2 Representative experimental procedure for the synthesis of 2 -(1-tosylindolin-3-ylidenemethyl)aniline (4a)



Compound **4a** was synthesized by following our previous reported procedure[10]

To a well-stirred solution of **3a** (130 mg, 0.3 mmol) in in toluene (2 mL) and ethanol (2 mL), aq. K_2CO_3 solution (2.5 M, 1 mL), PCy_3 (8 mg, 0.03 mmol) and $Pd(OAc)_2$ (3 mg, 0.015 mmol) were added successively. The resulting solution was stirred on a silicone-oil bath at 70-75 °C under argon atmosphere for 3 h. After the completion of the reaction (monitored by TLC), the crude reaction mixture was extracted with ethyl acetate. The organic extract was subjected to a washing with brine solution, then, drying using anhydrous Na_2SO_4 and finally, the solvent was concentrated. The crude product was subjected to column chromatography (silica gel, 60-120 mesh), eluting with hexane/EtOAc 95:5 (v/v) to afford the product **4a** as a yellow solid (100 mg, 0.27 mmol, 89%). Compound **4h** and **8a** were synthesized following the above procedure.

Compounds **4b**-**4g** and **4i**-**4q** were synthesized by following the above procedure. Due to mixtures of inseparable isomers, we could not get good NMR spectra of these compounds. So, final step reaction was performed directly with those substrates after some purification through column chromatography (silica gel, 60-120 mesh).

Compounds **6a**, **6b** and **6c** were synthesized according to our previous method[10].

(*Z*)-5-methyl-3-(phenyl(1-tosylindolin-3-ylidene)methyl)-[1,1'-biphenyl]-2-amine (6c): Yield: 78%, yellow solid, m. p. – 161-166, ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.76 (dt, *J* = 8.2, 0.9 Hz, 1H), 7.72 – 7.66 (m, 2H), 7.54 – 7.46 (m, 4H), 7.43 – 7.31 (m, 4H), 7.28 – 7.22 (m, 4H), 7.22 – 7.17 (m, 1H), 6.93 (dd, *J* = 2.1, 0.8 Hz, 1H), 6.79 – 6.66 (m, 3H), 4.59 (d, *J* = 26.4 Hz, 2H), 3.70 (s, 2H), 2.40 (s, 3H), 2.27 (s, 3H), ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 145.9, 144.3, 140.2, 139.7, 137.4, 133.9, 132.3, 131.8, 130.9, 129.75, 129.64, 129.37, 129.28, 129.04, 128.89, 128.71, 128.68, 128.57, 127.96, 127.89, 127.61, 127.34, 124.4, 123.4, 115.7, 56.0, 21.6, 20.5.

(*Z*)-N-(p-tolyl)-2-((1-tosylindolin-3-ylidene)methyl)aniline (8a): Yield: 82% grey solid, m. p. 160 – 165 °C , ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 (d, *J* = 8.2 Hz, 1H), 7.72 – 7.66 (m, 2H),

7.48 (dd, *J* = 7.8, 1.3 Hz, 1H), 7.34 – 7.30 (m, 1H), 7.27 (d, *J* = 1.5 Hz, 1H), 7.20 (ddt, *J* = 8.8, 4.3, 1.8 Hz, 4H), 7.12 (d, *J* = 8.2 Hz, 2H), 7.06 (td, *J* = 7.5, 1.0 Hz, 1H), 7.00 (dd, *J* = 7.3, 1.3 Hz, 1H), 6.98 – 6.94 (m, 2H), 6.84 (t, *J* = 3.1 Hz, 1H), 4.75 (d, *J* = 3.1 Hz, 2H), 2.38 (s, 3H), 2.34 (s, 3H), $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) δ 144.2, 143.7, 141.7, 140.2, 134.8, 133.9, 131.1, 130.6, 129.98, 129.96, 129.81, 129.68, 129.60, 128.51, 128.21, 127.2, 125.90, 125.83, 123.7, 120.86, 120.55, 119.1, 117.1, 114.89, 114.02, 54.2, 21.5, 20.7.

4.4.3 Representative experimental procedure for the synthesis of 3-(1-tosyl-1-*H*-indol-3-yl)-1*H*-indazole (5a).

In a 10 ml round bottom flask, compound **4a** (50 mg, 0.13 mmol) was dissolved in 3 mL 1, 2-dichloroethane (DCE). Then, 5 µL H_2O and *tert*-butyl nitrite (TBN) (1 equiv, 15.4 µL) were added to the solution successively. The resulting solution was set on a silicone-oil bath preheated to 75 °C and continued under argon atmosphere for 10 min. After the completion of the reaction (monitored by TLC), the crude reaction mixture was subjected to extract with ethyl acetate. After that, the organic extract was washed with brine solution, dried over anhydrous Na_2SO_4 and finally, the solvent was evaporated. The crude product was subjected to column chromatography (silica gel, 60-120 mesh), eluting with hexane/EtOAc 92:8 (v/v) to afford the product **5a** as an off white solid (46mg, 0.12 mmol, 90%).

Compounds **5b-5q** were synthesized by following the above procedure.

3-(1-tosyl-1*H*-indol-3-yl)-1*H*-indazole (5a): off white solid (46 mg, 90%); m. p. 150 – 155 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.34 (bs, 1H), 8.32 (d, *J* = 6.4 Hz, 1H), 8.13 (s, 1H), 8.08 (d, *J* = 6.4 Hz, 1H), 8.00 (d, *J* = 6.4 Hz, 1H), 7.83 (d, *J* = 6.8 Hz, 2H), 7.52 – 7.35 (m, 2H), 7.33 (t, *J* = 6.0 Hz, 1H), 7.31 (d, *J* = 6.8 Hz, 1H), 7.29 (t, *J* = 6.0 Hz, 1H), 7.23 (dd, *J* = 22.0, 6.8 Hz, 2H), 2.32 (s, 3H); $^{13}C\{^{1}H\}$ NMR (75 MHz, $CDCl_3$) δ 145.2, 141.0, 139.7, 135.2, 135.1, 129.9, 129.3, 127.2, 126.9, 125.3, 123.97, 123.92, 122.6, 121.52, 121.45, 120.8, 116.0, 113.5, 110.0, 21.5; HRMS: m/z calcd for $C_{22}H_{17}N_3O_2S$: 388.1120 $[M + H]^+$, found: 388.1128.

3-(5-methyl-1-tosyl-1*H*-indol-3-yl)-1*H*-indazole (5b): This compound was synthesized according to the representative procedure as described previously and purified through column chromatography (silica gel, 60-120 mesh), eluting with hexane/EtOAc 92:8 (v/v), to afford the

product **5b** as a white solid (44 mg, 85%); m. p. 100 – 105 °C; ^{1}H NMR (400 MHz, DMSO) δ 13.30 (s, 1H), 8.30 (s, 1H), 8.24 – 8.15 (m, 2H), 8.01 – 7.96 (m, 2H), 7.93 (d, *J* = 8.5 Hz, 1H), 7.63 (d, *J* = 8.3 Hz, 1H), 7.46 (dd, *J* = 8.2, 7.0 Hz, 1H), 7.35 (d, *J* = 8.2 Hz, 2H), 7.32 – 7.20 (m, 2H), 2.42 (s, 3H), 2.27 (s, 3H); ^{13}C{^{1}H} NMR (75 MHz, DMSO) δ 145.9, 141.2, 138.2, 134.4, 133.60, 133.25, 130.7, 129.4, 127.36, 127.21, 126.9, 123.92, 123.09, 121.50, 121.24, 120.9, 116.4, 113.4, 110.9, 21.53, 21.45; HRMS: m/z calcd for $C_{23}H_{19}N_3O_2S$: 402.1276 [M + H]$^{+}$, found: 402.1276.

3-(5-methoxy-1-tosyl-1*H*-indol-3-yl)-1*H*-indazole (5c): This compound was synthesized according to the representative procedure as described previously and purified through column chromatography (silica gel, 60-120 mesh), eluting with hexane/EtOAc 90:10 (v/v), to afford the product **5c** as a yellow viscous liquid (35 mg, 65%); ^{1}H NMR (400 MHz, DMSO) δ 13.33 (s, 1H), 8.30 (s, 1H), 8.18 (d, *J* = 8.2 Hz, 1H), 8.00 – 7.92 (m, 3H), 7.90 (d, *J* = 2.6 Hz, 1H), 7.62 (d, *J* = 8.4 Hz, 1H), 7.49 – 7.43 (m, 1H), 7.37 (d, *J* = 8.1 Hz, 2H), 7.28 (t, *J* = 7.5 Hz, 1H), 7.07 (dd, *J* = 9.1, 2.6 Hz, 1H), 3.80 (s, 3H), 2.29 (s, 3H); ^{13}C{^{1}H} NMR (101 MHz, DMSO) δ 156.9, 145.9, 141.1, 138.1, 134.3, 130.69, 130.28, 129.5, 127.35, 127.02, 124.5, 121.53, 121.25, 120.9, 116.6, 114.78, 114.65, 110.8, 105.6, 55.8, 21.4; HRMS: m/z calcd for $C_{23}H_{19}N_3O_3S$: 418.1225 [M + H]$^{+}$, found: 418.1225.

5-methyl-3-(1-tosyl-1*H*-indol-3-yl)-1*H*-indazole (5d): This compound was synthesized according to the representative procedure as described previously and purified through column chromatography (silica gel, 60-120 mesh), eluting with hexane/EtOAc 92:8 (v/v), to afford the product **5d** as a white solid (43 mg, 82%); m. p. 190 – 195 °C; ^{1}H NMR (300 MHz, DMSO) δ 13.20 (s, 1H), 8.41 (d, *J* = 7.8 Hz, 1H), 8.34 (s, 1H), 8.03 (dd, *J* = 8.3, 6.6 Hz, 3H), 7.95 (s, 1H), 7.52 (d, *J* = 8.5 Hz, 1H), 7.41 (dq, *J* = 15.2, 7.4 Hz, 4H), 7.29 (d, *J* = 8.5 Hz, 1H), 2.53 (s, 3H), 2.30 (s, 3H); ^{13}C{^{1}H} NMR (75 MHz, DMSO) δ 145.6, 139.5, 136.9, 134.5, 133.9, 130.29, 130.12, 128.80, 128.54, 126.9, 125.4, 123.93, 123.13, 123.02, 120.8, 119.6, 116.3, 113.2, 110.2, 21.11, 21.03; HRMS: m/z calcd for $C_{23}H_{19}N_3O_2S$: 402.1276 [M + H]$^{+}$, found: 402.1276.

3-(5,7-dimethyl-1-tosyl-1*H*-indol-3-yl)-1*H*-indazole (5e): This compound was synthesized according to the representative procedure as described previously and purified through column chromatography (silica gel, 60-120 mesh), eluting with hexane/EtOAc 91:9 (v/v), to afford the

product **5e** as a white viscous liquid (42 mg, 78%); ^{1}H NMR (300 MHz, DMSO) δ 13.31 (s, 1H), 8.30 (s, 1H), 8.13 – 8.01 (m, 2H), 7.77 – 7.69 (m, 2H), 7.68 – 7.61 (m, 1H), 7.47 (ddd, *J* = 8.3, 6.8, 1.0 Hz, 1H), 7.37 (d, *J* = 8.3 Hz, 2H), 7.29 (ddd, *J* = 7.9, 6.8, 1.0 Hz, 1H), 7.04 – 6.98 (m, 1H), 2.55 (s, 3H), 2.36 (s, 3H), 2.32 (s, 3H); ^{13}C{^{1}H} NMR (101 MHz, DMSO) δ 145.6, 141.2, 137.9, 135.7, 133.99, 133.54, 131.7, 130.7, 127.5, 126.98, 126.96, 124.5, 121.59, 121.16, 120.93, 120.83, 116.2, 111.0, 21.74, 21.48, 21.17; HRMS: m/z calcd for $C_{24}H_{21}N_3O_2S$: 416.1433 $[M + H]^+$, found: 416.1433.

5-methyl-7-phenyl-3-(1-tosyl-1*H*-indol-3-yl)-1*H*-indazole (5f): This compound was synthesized according to the representative procedure as described previously and purified through column chromatography (silica gel, 60-120 mesh), eluting with hexane/EtOAc 91:9 (v/v), to afford the product **5f** as a gummy liquid (52 mg, 84%); ^{1}H NMR (400 MHz, DMSO) δ 13.30 (s, 1H), 8.40 (d, *J* = 10.4 Hz, 2H), 8.08 – 8.03 (m, 2H), 8.02 (d, *J* = 2.0 Hz, 1H), 7.94 (s, 1H), 7.74 (d, *J* = 7.0 Hz, 2H), 7.60 – 7.53 (m, 2H), 7.50 – 7.43 (m, 2H), 7.42 – 7.32 (m, 4H), 2.59 (s, 3H), 2.30 (s, 3H); ^{13}C{^{1}H} NMR (101 MHz, DMSO) δ 146.1, 137.99, 137.86, 137.81, 134.95, 134.45, 131.3, 130.7, 129.53, 129.31, 128.68, 128.60, 128.28, 127.4, 125.9, 124.81, 124.39, 123.79, 123.33, 122.4, 119.3, 116.5, 113.7, 21.4; HRMS: m/z calcd for $C_{29}H_{23}N_3O_2S$: 478.1589 $[M + H]^+$; found: 478.1590.

3-(5-fluoro-1-tosyl-1*H*-indol-3-yl)-1*H*-indazole (5g): This compound was synthesized according to the representative procedure as described previously and purified through column chromatography (silica gel, 60-120 mesh), eluting with hexane/EtOAc 92:8 (v/v), to afford the product **5g** as a white solid (43 mg, 82%); m. p. 210 – 215 °C; ^{1}H NMR (300 MHz, DMSO) δ 13.36 (s, 1H), 8.46 (s, 1H), 8.23 (d, *J* = 8.2 Hz, 1H), 8.13 (dd, *J* = 9.6, 2.7 Hz, 1H), 8.10 – 8.00 (m, 3H), 7.63 (d, *J* = 8.4 Hz, 1H), 7.47 (t, *J* = 7.6 Hz, 1H), 7.40 (d, *J* = 8.1 Hz, 2H), 7.38 – 7.24 (m, 2H), 2.31 (s, 3H); ^{13}C{^{1}H} NMR (75 MHz, DMSO) δ 159.6 (d, $J_{C\text{-}F}$ = 237 Hz), 146.3, 141.2, 137.7, 134.24, 131.4, 130.82, 130.29, 127.49, 127.09, 125.4, 121.60, 121.29, 120.7, 115.3, 114.0, 110.9, 108.92, 108.58, 21.5; ^{19}F NMR (282 MHz, DMSO) δ -118.68; HRMS: m/z calcd for $C_{22}H_{16}FN_3O_2S$: 406.1026 $[M + H]^+$, found: 406.1026.

5-chloro-3-(1-tosyl-1*H*-indol-3-yl)-1*H*-indazole (5h): This compound was synthesized according to the representative procedure as described previously and purified through column

chromatography (silica gel, 60-120 mesh), eluting with hexane/EtOAc 93:7 (v/v), to afford the product **5h** as an off white solid (45 mg, 83%); m. p. 208 – 212 °C; ^{1}H NMR (400 MHz, DMSO) δ 13.51 (s, 1H), 8.51 (s, 1H), 8.40 (d, *J* = 7.9 Hz, 1H), 8.32 (d, *J* = 1.9 Hz, 1H), 8.12 – 8.00 (m, 3H), 7.66 (d, *J* = 8.8 Hz, 1H), 7.53 – 7.31 (m, 5H), 2.30 (s, 3H); ^{13}C{^{1}H} NMR (101 MHz, DMSO) δ 146.0, 139.8, 138.0, 134.86, 134.49, 130.7, 129.0, 127.52, 127.41, 126.0, 125.9, 124.40, 124.34, 123.3, 121.6, 120.5, 115.6, 113.6, 112.6, 21.4; HRMS: m/z calcd for $C_{22}H_{16}ClN_3O_2S$: 421.0652 $[M]^+$, found: 421.0652.

3-(5-chloro-1-tosyl-1*H*-indol-3-yl)-1*H*-indazole (5i): This compound was synthesized according to the representative procedure as described previously and purified through column chromatography (silica gel, 60-120 mesh), eluting with hexane/EtOAc 93:7 (v/v), to afford the product **5i** as a white solid (41 mg, 75%); m. p. 105 – 110 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.29 (d, *J* = 1.6 Hz, 1H), 8.14 (s, 1H), 7.97 (d, *J* = 8.8 Hz, 2H), 7.81 (d, *J* = 8.4 Hz, 2H), 7.55 (d, *J* = 8.4 Hz, 1H), 7.48 (t, *J* = 8.0 Hz, 1H), 7.35 – 7.29 (m, 2H), 7.23 (d, *J* = 8.4 Hz, 2H), 2.35 (s, 3H); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 145.5, 140.8, 138.4, 134.7, 133.4, 130.1, 129.9, 128.1, 126.9, 125.7, 125.54, 122.19, 122.05, 120.91, 120.79, 114.59, 114.41, 110.5, 21.6; HRMS: m/z calcd for $C_{22}H_{16}ClN_3O_2S$: 422.0730 $[M+H]^+$, found: 422.0730.

3-(1-tosyl-5-(trifluoromethyl)-1*H*-indol-3-yl)-1*H*-indazole (5j): This compound was synthesized according to the representative procedure as described previously and purified through column chromatography (silica gel, 60-120 mesh), eluting with hexane/EtOAc 91:9 (v/v), to afford the product **5j** as an off white solid (46 mg, 78%); m. p. 206 – 209 °C; ^{1}H NMR (300 MHz, DMSO) δ 13.42 (s, 1H), 8.83 (s, 1H), 8.59 (s, 1H), 8.28 (d, *J* = 8.5 Hz, 2H), 8.10 (d, *J* = 8.1 Hz, 2H), 7.80 (dd, *J* = 8.9, 1.9 Hz, 1H), 7.65 (d, *J* = 8.4 Hz, 1H), 7.53 – 7.38 (m, 3H), 7.31 (t, *J* = 7.5 Hz, 1H), 2.32 (s, 3H); ^{13}C{^{1}H} NMR (75 MHz, DMSO) δ 146.6, 141.1, 137.6, 136.5, 134.1, 130.9, 128.8, 127.59, 127.1, 126.9, 125.52, 125.33, 124.9, 123.3, 122.5, 121.70, 121.34, 120.7, 116.2, 114.7, 111.0, 21.5; ^{19}F NMR (282 MHz, DMSO) δ -59.70; HRMS: m/z calcd for $C_{23}H_{16}F_3N_3O_2S$: 455.0915$[M]^+$, found: 455.0915.

5-nitro-3-(1-tosyl-1*H*-indol-3-yl)-1*H*-indazole (5k): This compound was synthesized according to the representative procedure as described previously and purified through column chromatography (silica gel, 60-120 mesh), eluting with hexane/EtOAc 90:10 (v/v), to afford

the product **5k** as a yellow solid (43 mg, 76%); m. p. 190 – 195 °C; ^{1}H NMR (400 MHz, DMSO) δ 13.97 (s, 1H), 9.08 (d, *J* = 2.0 Hz, 1H), 8.68 (s, 1H), 8.36 – 8.21 (m, 3H), 8.05 (d, *J* = 7.6 Hz, 3H), 7.81 (d, *J* = 9.1 Hz, 1H), 7.47 (dd, *J* = 9.9, 7.9 Hz, 2H), 7.41 (dd, *J* = 8.0, 2.7 Hz, 3H), 7.12 (d, *J* = 7.8 Hz, 1H), 2.31 (s, 3H), 2.29 (s, 1H); ^{13}C{^{1}H} NMR (101 MHz, DMSO) δ 146.2, 143.2, 142.5, 141.3, 138.0, 136.9, 134.91, 134.45, 130.7, 128.80, 128.49, 127.5, 126.0, 125.98, 125.51, 124.5, 123.0, 122.3, 121.9, 120.1, 119.4, 114.8, 113.7, 111.8, 21.50, 21.24; HRMS: m/z calcd for $C_{22}H_{16}N_4O_4S$: 433.0971 $[M + H]^+$, found: 433.0971.

5-methyl-3-(5-methyl-1-tosyl-1*H*-indol-3-yl)-1*H*-indazole (5l): This compound was synthesized according to the representative procedure as described previously and purified through column chromatography (silica gel, 60-120 mesh), eluting with hexane/EtOAc 92:8 (v/v), to afford the product **5l** as an off white solid (42 mg, 79%); m. p. 153 – 158 °C; ^{1}H NMR (300 MHz, DMSO) δ 13.16 (s, 1H), 8.28 (s, 1H), 8.21 (s, 1H), 7.95 (dd, *J* = 19.2, 8.5 Hz, 4H), 7.52 (d, *J* = 8.5 Hz, 1H), 7.38 (d, *J* = 8.1 Hz, 2H), 7.32 – 7.24 (m, 2H), 2.53 (s, 3H), 2.42 (s, 3H), 2.30 (s, 3H); ^{13}C{^{1}H} NMR (75 MHz, DMSO) δ 145.9, 139.8, 137.5, 134.4, 133.56, 133.25, 130.68, 130.54, 129.5, 128.9, 127.35, 127.16, 123.73, 123.22, 121.2, 120.0, 116.6, 113.4, 110.6, 21.56, 21.55, 21.48; HRMS: m/z calcd for $C_{24}H_{21}N_3O_2S$: 438.1252 $[M + Na]^+$, found: 438.1252.

5-chloro-3-(5-methyl-1-tosyl-1*H*-indol-3-yl)-1*H*-indazole (5m): This compound was synthesized according to the representative procedure as described previously and purified through column chromatography (silica gel, 60-120 mesh), eluting with hexane/EtOAc 92:8 (v/v), to afford the product **5m** as a white crystal solid (46 mg, 81%); m. p. 225 °C; ^{1}H NMR (300 MHz, DMSO) δ 13.48 (s, 1H), 8.44 (s, 1H), 8.30 (d, *J* = 1.9 Hz, 1H), 8.20 (s, 1H), 8.02 (d, *J* = 8.2 Hz, 2H), 7.92 (d, *J* = 8.5 Hz, 1H), 7.66 (d, *J* = 8.8 Hz, 1H), 7.47 (dd, *J* = 8.8, 1.8 Hz, 1H), 7.38 (d, *J* = 8.1 Hz, 2H), 7.26 (dd, *J* = 8.5, 1.7 Hz, 1H), 2.42 (s, 3H), 2.30 (s, 3H); ^{13}C{^{1}H} NMR (75 MHz, DMSO) δ 145.9, 139.7, 138.0, 134.4, 133.61, 133.18, 130.6, 129.2, 127.44, 127.40, 127.20, 126.0, 124.4, 123.0, 121.6, 120.5, 115.5, 113.4, 112.6, 21.54, 21.48; HRMS: m/z calcd for $C_{23}H_{18}ClN_3O_2S$: 436.0887 $[M + H]^+$, found: 436.0887.

3-(5-methyl-1-tosyl-1*H*-indol-3-yl)-5-nitro-1*H*-indazole (5n): This compound was synthesized according to the representative procedure as described previously and purified

through column chromatography (silica gel, 60-120 mesh), eluting with hexane/EtOAc 90:10 (v/v), to afford the product **5n** as a yellow solid (46 mg, 80%); m. p. 192 – 196 °C; ^{1}H NMR (300 MHz, DMSO) δ 13.93 (s, 1H), 9.09 – 9.00 (m, 1H), 8.62 (s, 1H), 8.31-8.22 (m, 1.45H), 8.13 – 8.09 (m, 1H), 8.01 (dd, *J* = 6.6, 1.8 Hz, 2H), 7.93 (d, *J* = 8.5 Hz, 1H), 7.81 (d, *J* = 9.2 Hz, 1H), 7.73 (d, *J* = 9.3 Hz, 0.37H) 7.49-7.37 (m, 3H), 7.29 (dd, *J* = 8.6, 1.8 Hz, 1H), 7.19 – 7.01 (m, 1H), 6.88 (d, *J* = 8.4 Hz, 0.27H) 2.45 (s, 0.5H), 2.43 (s, 3H), 2.31 (s, 3H), 2.29 (s, 0.5H); ^{13}C{^{1}H} NMR (75 MHz, DMSO) δ 146.1, 143.1, 142.4, 134.3, 133.86, 133.21, 130.7, 129.0, 128.5, 127.46, 127.38, 125.6, 122.72, 122.00, 120.1, 119.5, 114.7, 113.5, 21.53, 21.50; HRMS: m/z calcd for $C_{23}H_{18}N_4O_4S$: 447.1127 $[M + H]^+$, found: 447.1127.

tert-butyl 3-(1*H*-indazol-3-yl)-1*H*-indole-1-carboxylate (5o): This compound was synthesized according to the representative procedure as described previously and purified through column chromatography (silica gel, 60-120 mesh), eluting with hexane/EtOAc 91:9 (v/v), to afford the product **5o** as a brown liquid (32 mg, 75%); ^{1}H NMR (300 MHz, DMSO) δ 13.29 (s, 1H), 8.44 (dd, *J* = 7.4, 1.5 Hz, 1H), 8.23 (s, 1H), 8.17 (d, *J* = 8.1 Hz, 1H), 8.04 (d, *J* = 8.2 Hz, 1H), 7.63 (d, *J* = 8.4 Hz, 1H), 7.48 – 7.35 (m, 3H), 7.26 (ddd, *J* = 8.0, 6.9, 1.0 Hz, 1H), 1.70 (s, 9H); ^{13}C{^{1}H} NMR (101 MHz, DMSO) δ 149.0, 140.8, 138.1, 134.8, 128.3, 126.4, 125.0, 123.1, 122.84, 122.39, 120.96, 120.53, 120.42, 114.73, 114.13, 110.5, 84.2, 27.7; HRMS: m/z calcd for $C_{20}H_{19}N_3O_2$: 334.1556 $[M + H]^+$; found: 334.1554.

3-(5-methyl-1-tosyl-1*H*-pyrrolo[2,3-b]pyridin-3-yl)-1*H*-indazole (5p): This compound was synthesized according to the representative procedure as described previously and purified through column chromatography (silica gel, 60-120 mesh), eluting with hexane/EtOAc 88:12 (v/v), to afford the product **5p** as a grey solid (39 mg, 74%); m. p. 182 – 187 °C; ^{1}H NMR (300 MHz, DMSO) δ 13.32 (s, 1H), 8.52 (dd, *J* = 2.2, 0.9 Hz, 1H), 8.39 (s, 1H), 8.32 (d, *J* = 2.3 Hz, 1H), 8.19 (dd, *J* = 8.2, 1.0 Hz, 1H), 8.14 – 8.05 (m, 2H), 7.64 (dt, *J* = 8.4, 1.0 Hz, 1H), 7.51 – 7.38 (m, 3H), 7.29 (ddd, *J* = 8.0, 6.8, 0.9 Hz, 1H), 2.43 (s, 3H), 2.33 (s, 3H); ^{13}C{^{1}H} NMR (75 MHz, DMSO) δ 146.57, 146.03, 145.8, 141.3, 137.9, 135.0, 131.7, 130.4, 129.5, 128.1, 127.0, 123.4, 121.60, 121.19, 121.14, 120.6, 113.2, 111.0, 21.5, 18.4; HRMS: m/z calcd for $C_{22}H_{18}N_4O_2S$: 402.1150 $[M]^+$, found: 402.1150.

5-methyl-3-(5-methyl-1-tosyl-1*H*-pyrrolo[2,3-b]pyridin-3-yl)-1*H*-indazole (5q): This compound was synthesized according to the representative procedure as described previously and purified through column chromatography (silica gel, 60-120 mesh), eluting with hexane/EtOAc 88:12 (v/v), to afford the product **5q** as a grey solid (38 mg, 71%); m. p. 180 – 185 °C; ^{1}H NMR (400 MHz, DMSO) δ 8.56 – 8.51 (m, 1H), 8.38 (s, 1H), 8.31 (d, *J* = 2.1 Hz, 1H), 8.08 (d, *J* = 8.1 Hz, 2H), 7.96 (s, 1H), 7.52 (d, *J* = 8.5 Hz, 1H), 7.42 (d, *J* = 8.2 Hz, 2H), 7.30 (d, *J* = 8.5 Hz, 1H), 2.53 (s, 3H), 2.43 (s, 3H), 2.34 (s, 3H); ^{13}C{^{1}H} NMR (101 MHz, DMSO) δ 146.51, 146.00, 145.8, 140.0, 137.3, 135.0, 131.8, 130.67, 130.44, 129.75, 129.48, 129.06, 128.1, 126.0, 123.2, 121.2, 120.9, 119.9, 113.4, 110.7, 21.5, 18.4; HRMS: m/z calcd for $C_{23}H_{20}N_4O_2S$: 417.1385 $[M + H]^+$, found: 417.1385.

4.4.4 Representative experimental procedure for the synthesis of 3-phenyl-3-(1-tosyl-1*H*-indol-3-yl)-3*H*-indazole (7a).

In a 10 ml round bottom flask, compound **6a** (50 mg, 0.11 mmol) was dissolved in 3 mL 1, 2-dichloroethane (DCE). Then, 5 µL H_2O and *tert*-butyl nitrite (TBN) (1 equiv. 13.07 µL) were added to the solution successively. The resulting solution was set on a silicone-oil bath preheated to 75 °C and continued under argon atmosphere for 30 min. After the completion of the reaction (monitored by TLC), the crude reaction mixture was subjected to extract with ethyl acetate. After that, the organic extract was washed with brine solution, dried over anhydrous Na_2SO_4 and finally, the solvent was evaporated. The crude product was subjected to column chromatography (silica gel, 60-120 mesh), eluting with hexane/EtOAc 92:5 (v/v), to afford the product **7a** as a grey solid (47mg, 0.12 mmol, 92%).

Compounds **7b** and **7c** were synthesized by following the above procedure.

3-phenyl-3-(1-tosyl-1*H*-indol-3-yl)-3*H*-indazole (7a): grey solid (47 mg, 92%); m. p. 85 – 90 °C; ^{1}H NMR (300 MHz, DMSO) δ 8.35 (dd, *J* = 5.9, 2.3 Hz, 1H), 7.97 (dd, *J* = 5.9, 2.8 Hz, 1H), 7.90 (d, *J* = 8.5 Hz, 3H), 7.76 – 7.63 (m, 2H), 7.39 (d, *J* = 7.9 Hz, 2H), 7.37 – 7.29 (m, 6H), 7.20 – 7.11 (m, 3H), 2.32 (s, 3H); ^{13}C{^{1}H} NMR (75 MHz, DMSO) δ 156.1, 146.3, 142.9, 136.4, 135.2, 134.0, 131.5, 130.84, 130.50, 129.54, 129.18, 128.9, 127.4, 126.6, 125.8, 124.73, 124.37, 124.09, 122.89, 122.32, 119.2, 113.8, 96.7, 21.5; HRMS: m/z calcd for $C_{28}H_{21}N_3O_2S$: 464.1433 $[M + H]^+$; found: 464.1433.

3-(4-chlorophenyl)-3-(1-tosyl-1*H*-indol-3-yl)-3*H*-indazole (7b): This compound was synthesized according to the representative procedure as described previously and purified through column chromatography (silica gel, 60-120 mesh), eluting with hexane/EtOAc 95:5 (v/v), to afford the product **7b** as a white liquid (48 mg, 88%); ^{1}H NMR (400 MHz, DMSO) δ 8.36 (dd, *J* = 6.8, 1.9 Hz, 1H), 8.00 – 7.95 (m, 1H), 7.89 (d, *J* = 8.2 Hz, 3H), 7.71 (ddd, *J* = 6.6, 4.7, 1.4 Hz, 2H), 7.43 – 7.37 (m, 4H), 7.37 – 7.31 (m, 3H), 7.22 – 7.15 (m, 3H), 2.32 (s, 3H); ^{13}C{^{1}H} NMR (101 MHz, DMSO) δ 156.1, 146.3, 142.5, 135.35, 135.18, 134.0, 133.7, 131.7, 130.85, 130.67, 129.6, 128.95, 128.63, 127.4, 125.8, 124.87, 124.34, 124.16, 123.0, 122.1, 118.6, 113.8, 96.1, 21.5; HRMS: m/z calcd for $C_{28}H_{20}ClN_3O_2S$: 498.1043 $[M + H]^+$; found: 498.1034.

5-methyl-3,7-diphenyl-3-(1-tosyl-1*H*-indol-3-yl)-3*H*-indazole (7c): This compound was synthesized according to the representative procedure as described previously and purified through column chromatography (silica gel, 60-120 mesh), eluting with hexane/EtOAc 94:6 (v/v), to afford the product **7c** as a white solid (52 mg, 86%); m. p. 192 – 197 °C; ^{1}H NMR (400 MHz, DMSO) δ 8.01 (d, *J* = 1.4 Hz, 1H), 7.99 (d, *J* = 1.5 Hz, 1H), 7.92 (d, *J* = 2.0 Hz, 1H), 7.91 – 7.88 (m, 2H), 7.71 (d, *J* = 1.5 Hz, 1H), 7.66 (d, *J* = 0.8 Hz, 1H), 7.60 – 7.55 (m, 2H), 7.53 – 7.47 (m, 1H), 7.41 (d, *J* = 8.6 Hz, 2H), 7.39 (s, 1H), 7.36 – 7.31 (m, 5H), 7.21 – 7.14 (m, 3H), 2.53 (s, 3H), 2.33 (s, 3H); ^{13}C{^{1}H} NMR (75 MHz, DMSO) δ 151.7, 146.3, 144.6, 142.5, 136.66, 136.63, 135.40, 135.23, 134.0, 130.84, 130.66, 130.25, 129.54, 129.26, 129.13, 128.97, 128.90, 127.5, 126.7, 125.7, 124.88, 124.08, 123.7, 122.3, 119.4, 113.8, 96.2, 21.74, 21.53; HRMS: m/z calcd for $C_{35}H_{27}N_3O_2S$: 554.1902 $[M + H]^+$; found: 554.1901.

4.4.5 Experimental procedure for the synthesis of 3-(1H-indol-3-yl)-1H-indazole (5a′).

In a 10 ml round bottom flask, compound **5a** (50 mg, 0.13 mmol) was dissolved in 1 mL each of methanol and water. Then, 50 mol% NaOH was added to the solution. The resulting solution was refluxed on a silicone-oil bath under argon atmosphere for 4h. After the completion of the reaction (monitored by TLC), the crude reaction mixture was subjected to extract with ethyl acetate. After that, the organic extract was washed with brine solution, dried over anhydrous Na_2SO_4 and finally, the solvent was evaporated. The crude product was subjected to column chromatography (silica gel, 60-120 mesh), eluting with hexane/EtOAc 92:5 (v/v), to afford the product **5a′** as a white solid (27 mg, 0.12 mmol, 90%).

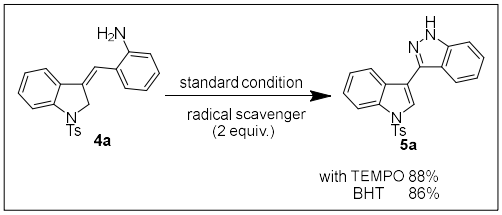
3-(1*H*-indol-3-yl)-1*H*-indazole (5a′): white solid (27 mg, 90%); m. p. 245 – 250 °C; ^{1}H NMR (300 MHz, $CDCl_3$/methanol-d_4) δ 8.04 (dd, *J* = 7.6, 3.3 Hz, 1H), 7.96 – 7.87 (m, 1H), 7.71 (d, *J* = 5.4 Hz, 1H), 7.50 (dd, *J* = 8.5, 5.6 Hz, 1H), 7.47 – 7.35 (m, 2H), 7.31 (s, 1H), 7.25 – 7.08 (m, 3H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$/ methanol-d_4) δ 141.1, 136.5, 127.6, 124.1, 122.5, 121.65, 121.05, 120.7, 111.5, 110.4; HRMS: m/z calcd for $C_{15}H_{11}N_3$: 234.1031 $[M + H]^+$; found: 234.1031.

4.4.6 Scale-up synthesis of 3-(1-tosyl-1*H*-indol-3-yl)-1*H*-indazole (5a).

In a 100 ml round bottom flask, compound **4a** (752 mg, 2.0 mmol) was dissolved in 50 mL 1, 2-dichloroethane (DCE). Then, 80 µL H_2O and *tert*-butyl nitrite (TBN) (2.0 mmol, 237 µL) were added to the solution successively. The resulting solution was set on a silicone-oil bath preheated to 75 °C and continued under argon atmosphere for 10 min. After the completion of the reaction (monitored by TLC), the crude reaction mixture was subjected to extract with ethyl acetate. After that, the organic extract was washed with brine solution, dried over anhydrous Na_2SO_4 and finally, the solvent was evaporated. The crude product was subjected to column chromatography (silica gel, 60-120 mesh), eluting with hexane/EtOAc 92:8 (v/v) to afford the product **5a** as an off white solid (627 mg, 1.62 mmol, 81%).

4.4.7 Control experiment

(a) Radical trapping experimental procedure:

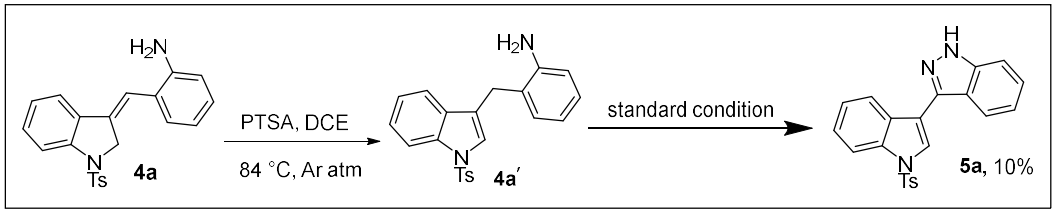


Compound **4a** (50 mg, 0.13 mmol) in DCE was added with *tert*-butylnitrite (TBN) (1 equiv, 15.4 µL), TEMPO (41 mg, 2 equiv.) and 5 µL H_2O. The reaction mixture was stirred on a silicone-oil bath at 75 °C under argon atmosphere for 10 min. After the completion of the reaction (monitored by TLC), the crude reaction mixture was subjected to extract with ethyl acetate. Then, the organic extract was washed with brine solution, dried over anhydrous Na_2SO_4 and finally, the solvent was evaporated. The crude product was subjected to column

chromatography (silica gel, 60-120 mesh), eluting with hexane/EtOAc 92:8 (v/v) to afford the product **5a** as an off white solid (41 mg, 0.11 mmol, 88%).

Following the similar process, When the standard reaction was performed in presence of BHT (2 equiv.), we get **5a** in 86% yield.

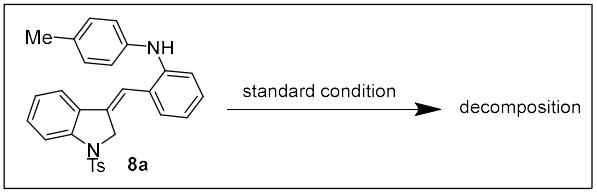
(b) Experimental procedure for the Synthesis of 2-((1-tosyl-1*H*-indol-3-yl)methyl)aniline (4a′) and comparative Study:



At first, Compound **4a′** was synthesized using p-Toluenesulfonic acid (PTSA) in DCE on a silicone-oil bath at 84 °C under argon atm. Then, the reaction of isolated product **4a′** was set out following the standard procedure. Compound **4a′** (50 mg, 0.13 mmol) in DCE was treated with *tert*-butylnitrite (TBN), in the presence of H_2O under argon atmosphere at 75 °C as described for the synthesis of **5a** for 10 min. to afford **5a** as an off white solid (5 mg, 0.013 mmol, 10%).

2-((1-tosyl-1*H*-indol-3-yl)methyl)aniline (4a′): yellow solid, m. p. 149 – 154 °C
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00 (d, *J* = 8.3 Hz, 1H), 7.74 (d, *J* = 7.8 Hz, 2H), 7.46 (d, *J* = 7.9 Hz, 1H), 7.33 (t, *J* = 7.9 Hz, 1H), 7.26 – 7.18 (m, 4H), 7.13 (t, *J* = 7.6 Hz, 1H), 7.04 (d, *J* = 7.6 Hz, 1H), 6.81 (dd, *J* = 7.6, 2.5 Hz, 2H), 3.95 (s, 2H), 2.35 (s, 3H); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 144.8, 135.60, 135.18, 130.75, 130.34, 129.8, 127.9, 126.8, 124.91, 124.03, 123.2, 120.4, 119.96, 119.78, 116.8, 113.8, 27.7, 21.5.

(c) Experimental procedure to understand the diazotization pathway:



Compound **8a** underwent decomposition when it was reacted under standard reaction condition as described for the synthesis of **5a**.

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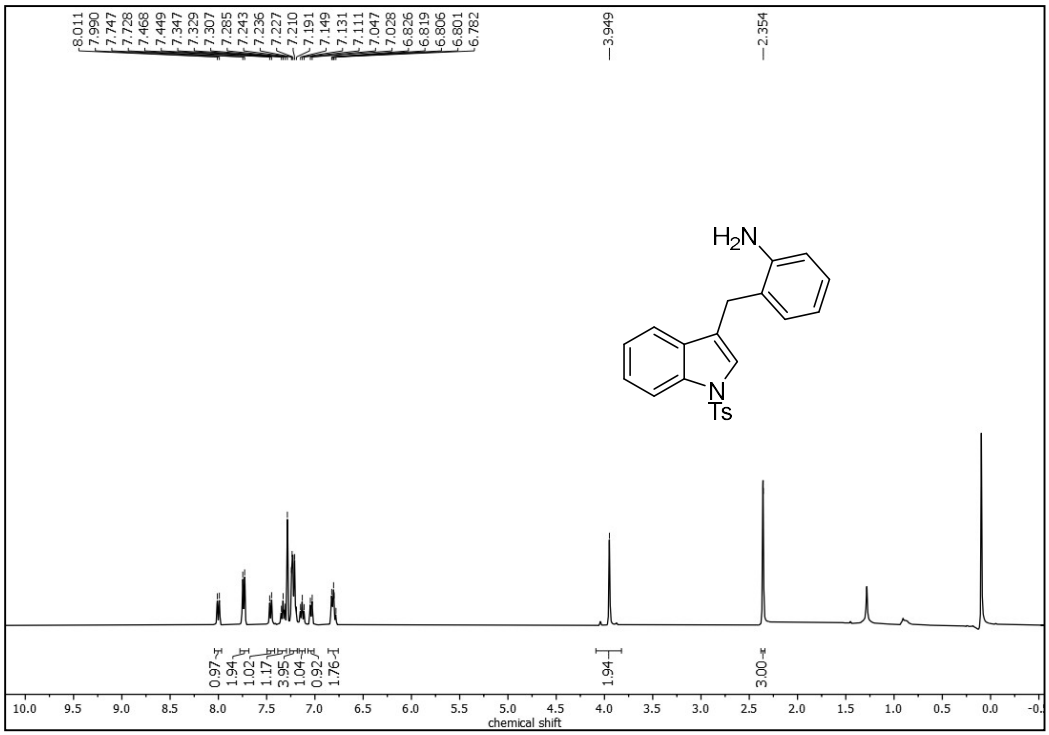
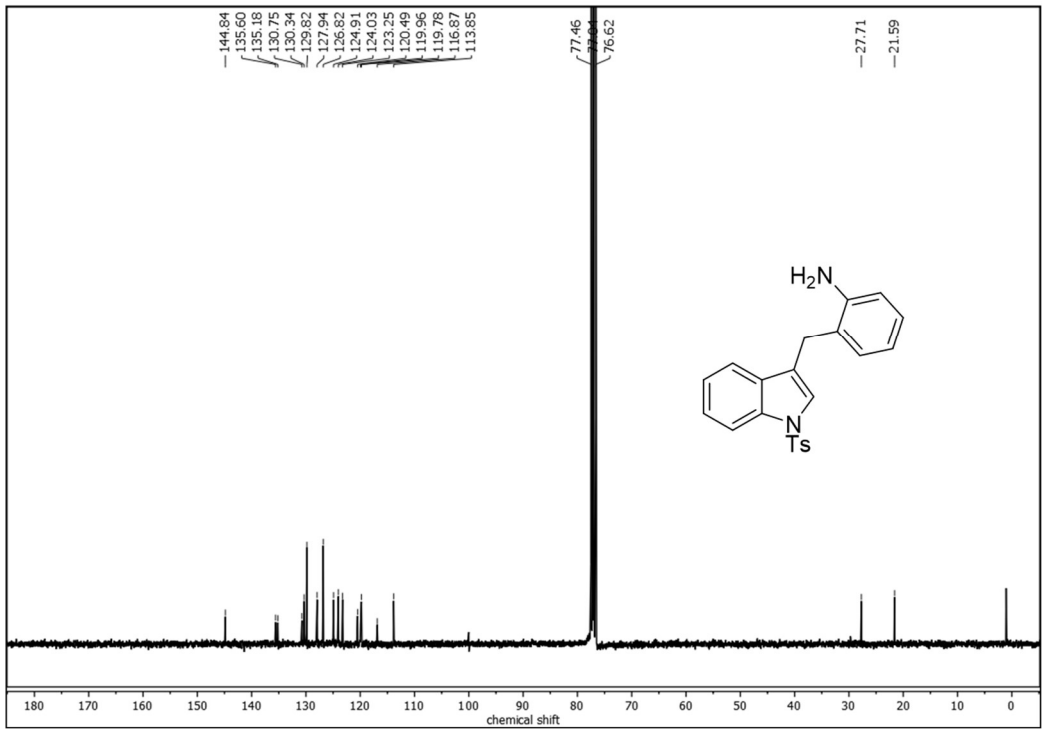
4.6 ^{1}H, $^{13}C\{^{1}H\}$ AND ^{19}F NMR SPECTRA OF RELEVENT COMPOUNDS

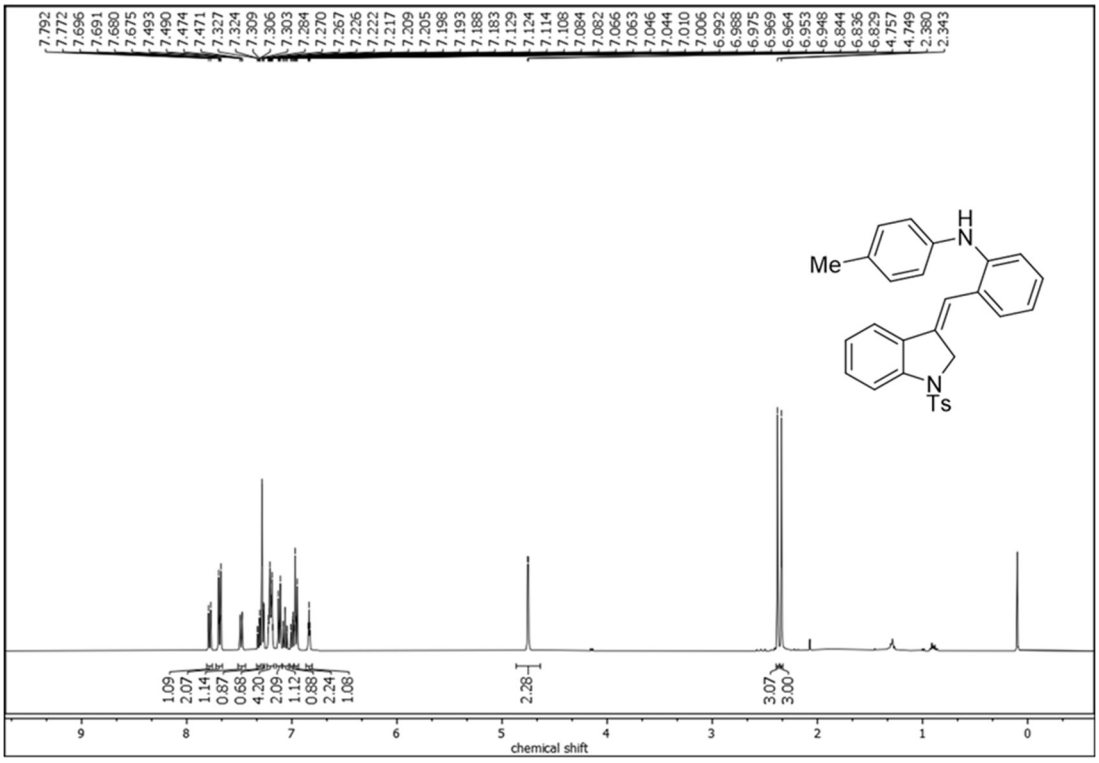
^{1}H NMR (400 MHz, $CDCl_3$) of 4a′



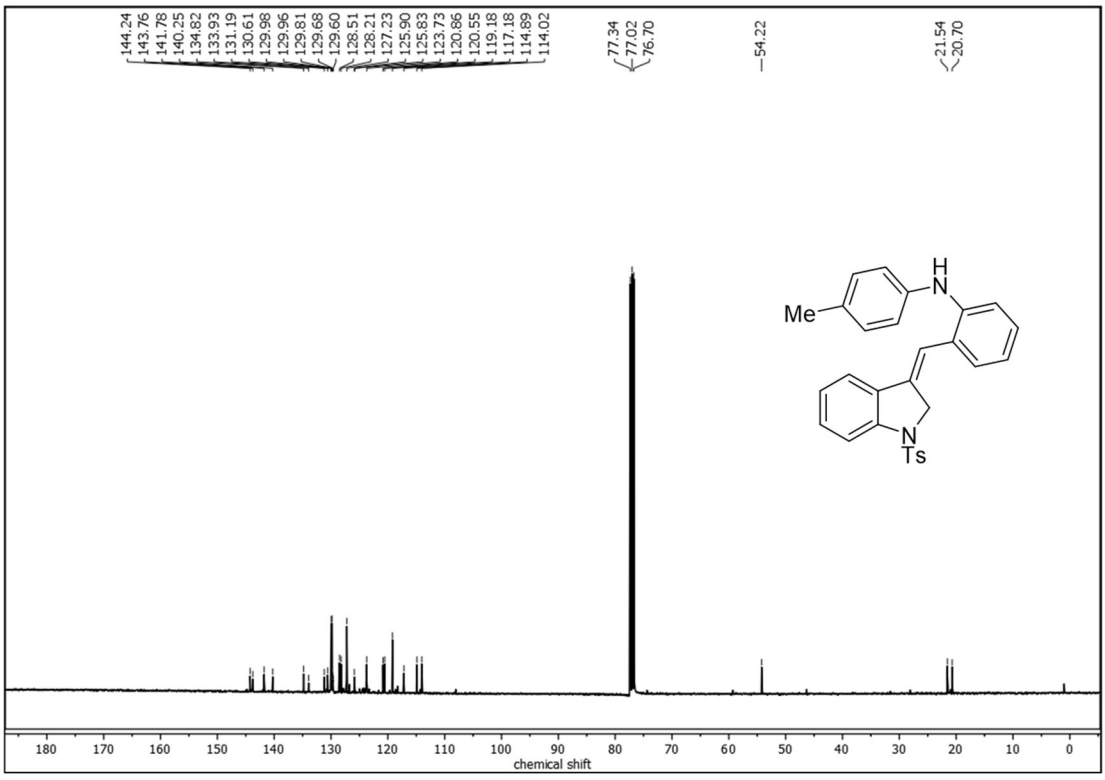
$^{13}C\{^{1}H\}$ NMR (75 MHz, $CDCl_3$) of 4a′



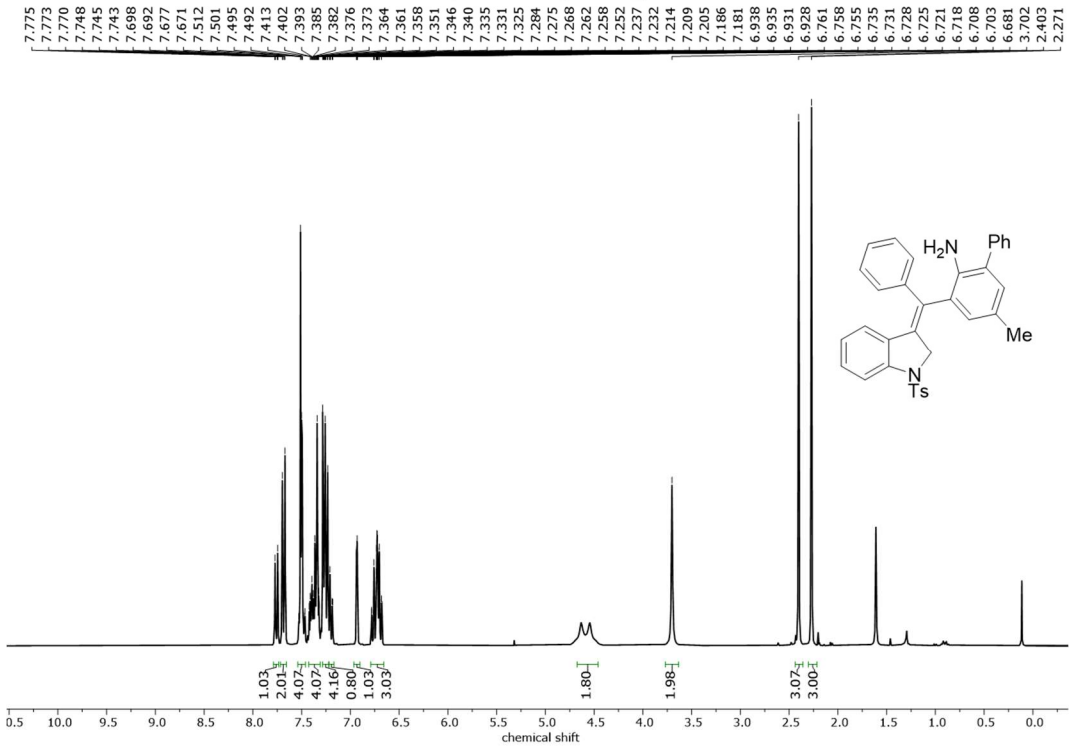
^{1}H NMR (400 MHz, $CDCl_3$) of 8a



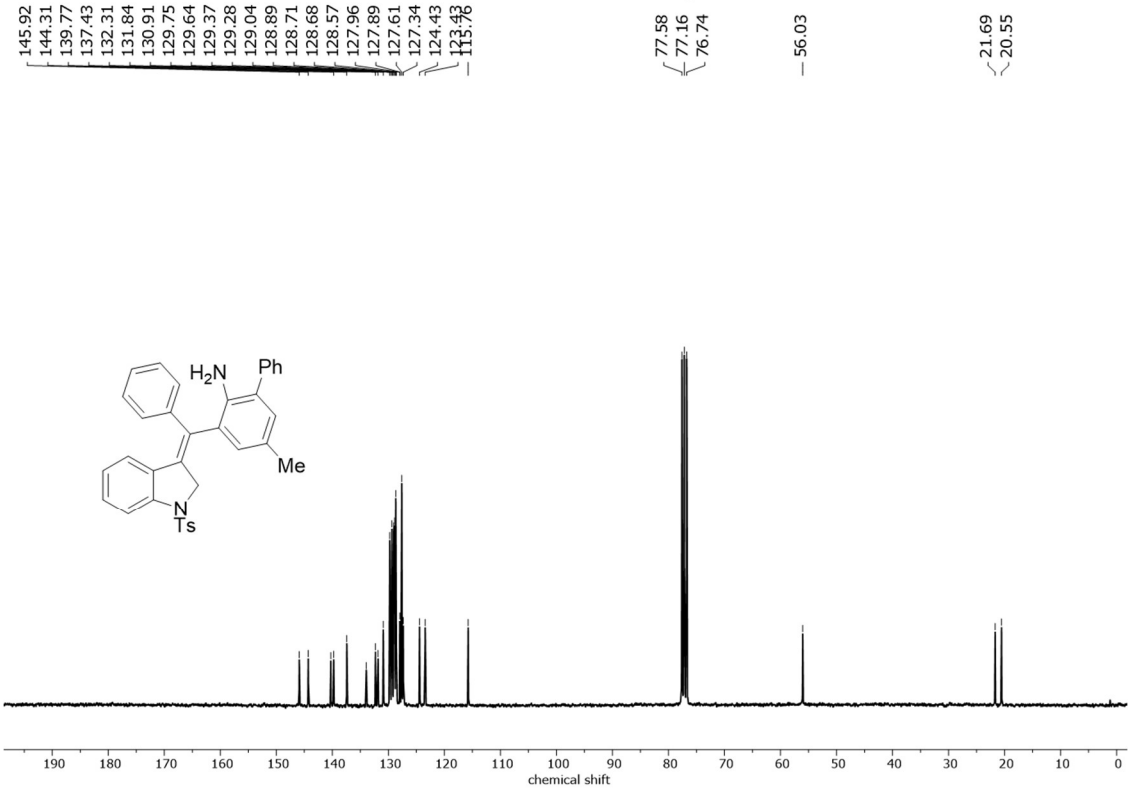
^{13}C {^{1}H} NMR (101 MHz, $CDCl_3$) of 8a



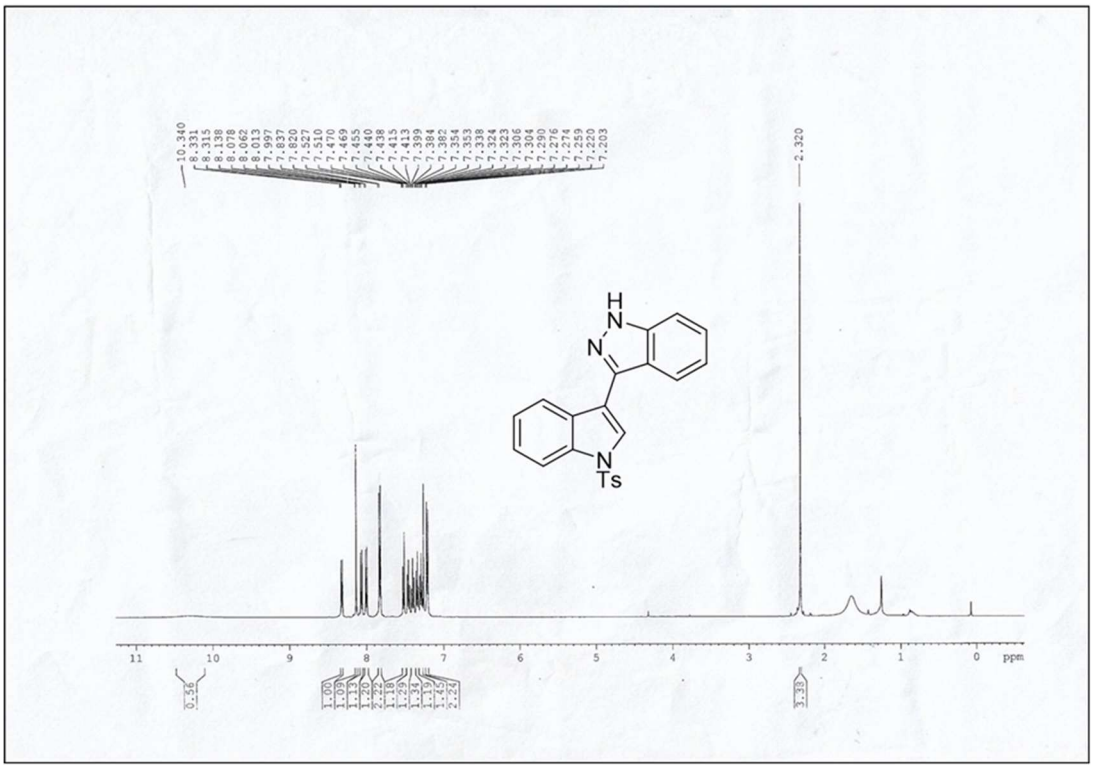
^{1}H NMR (300 MHz, $CDCl_3$) of **6c**



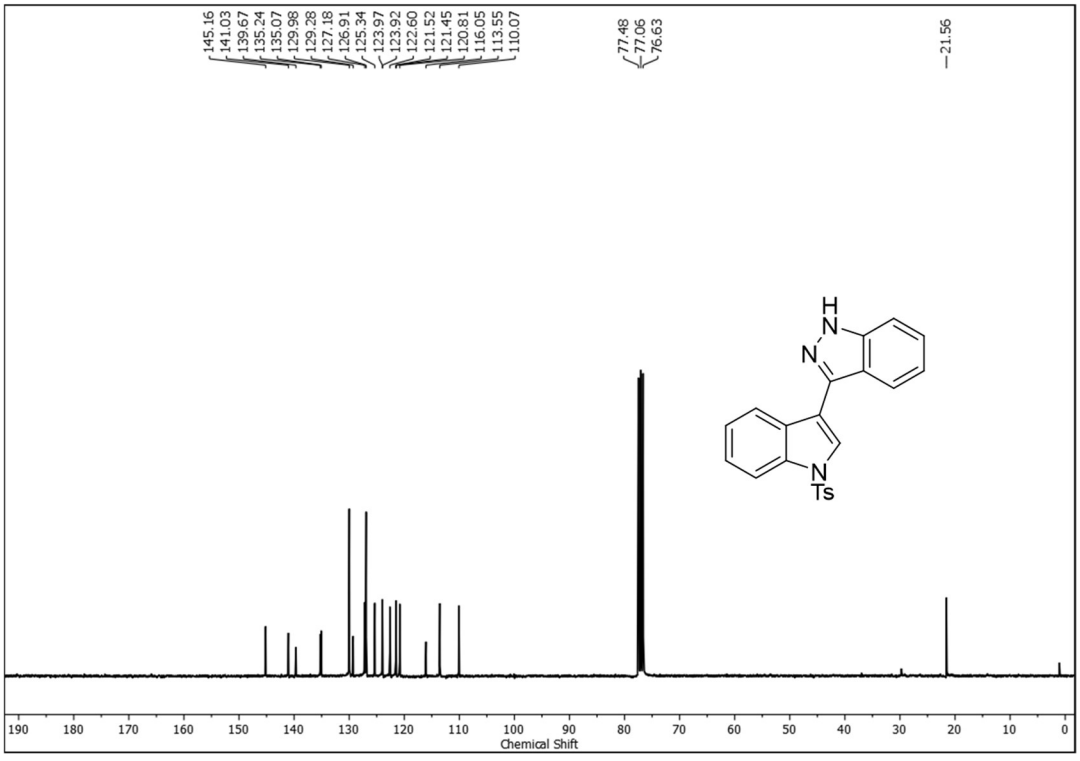
^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) of **6c**



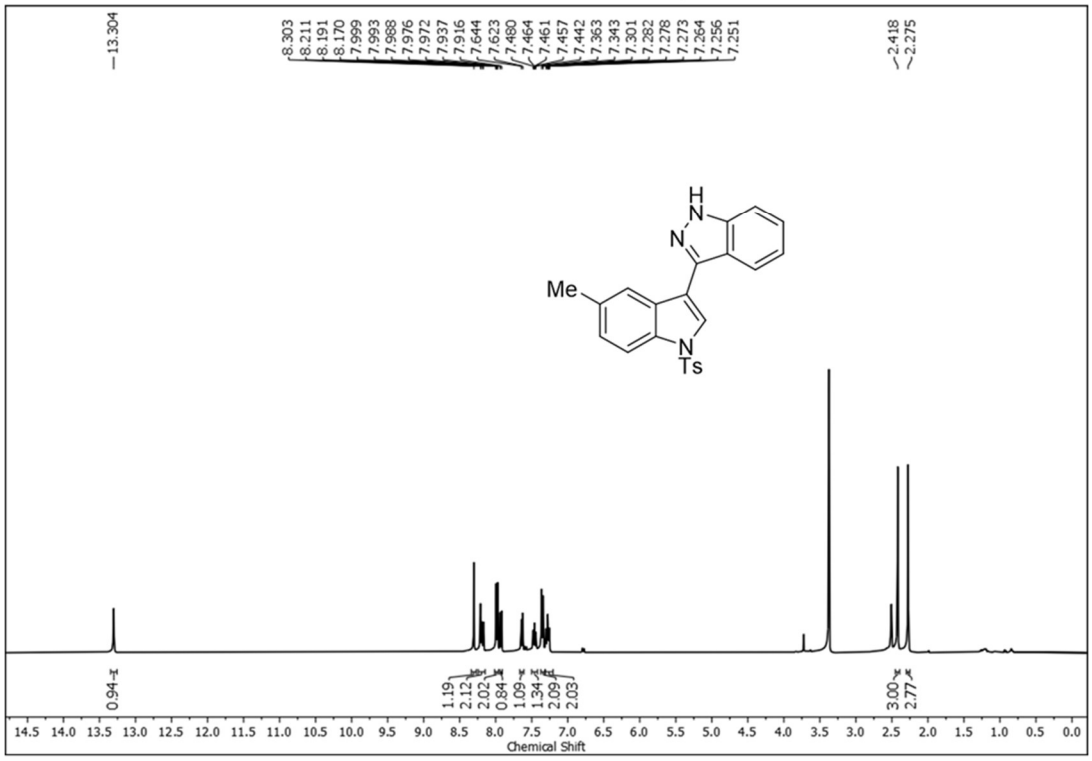
^{1}H NMR (400 MHz, $CDCl_3$) of 5a



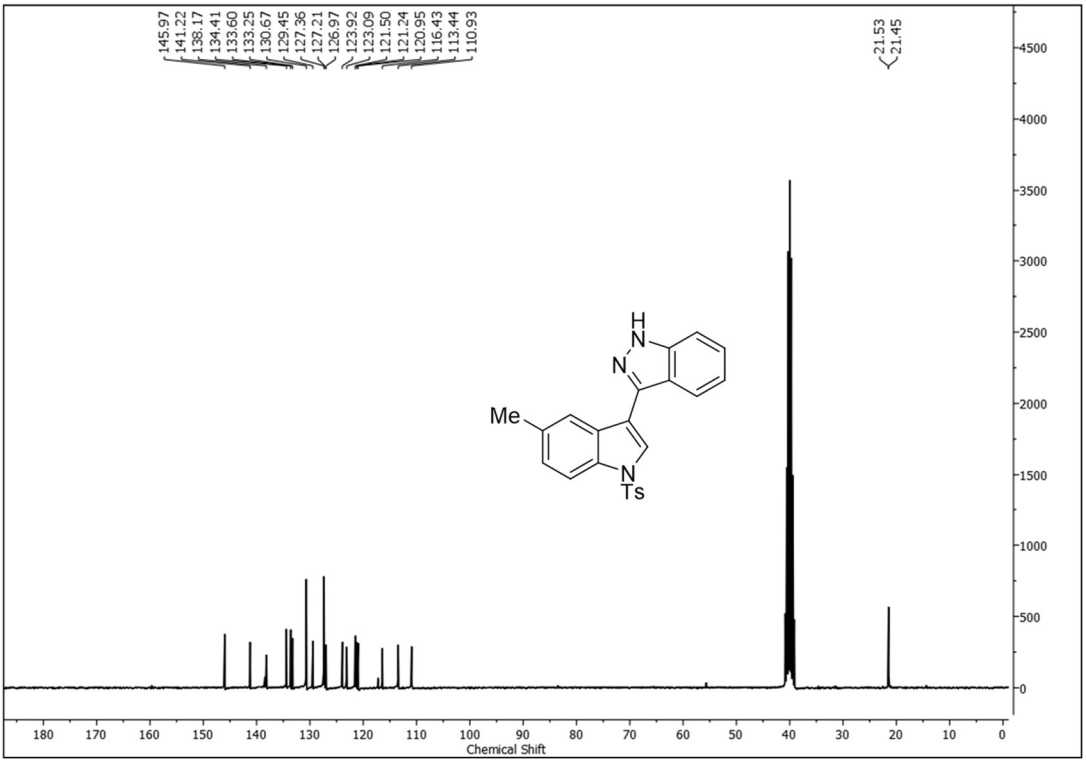
^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) of 5a



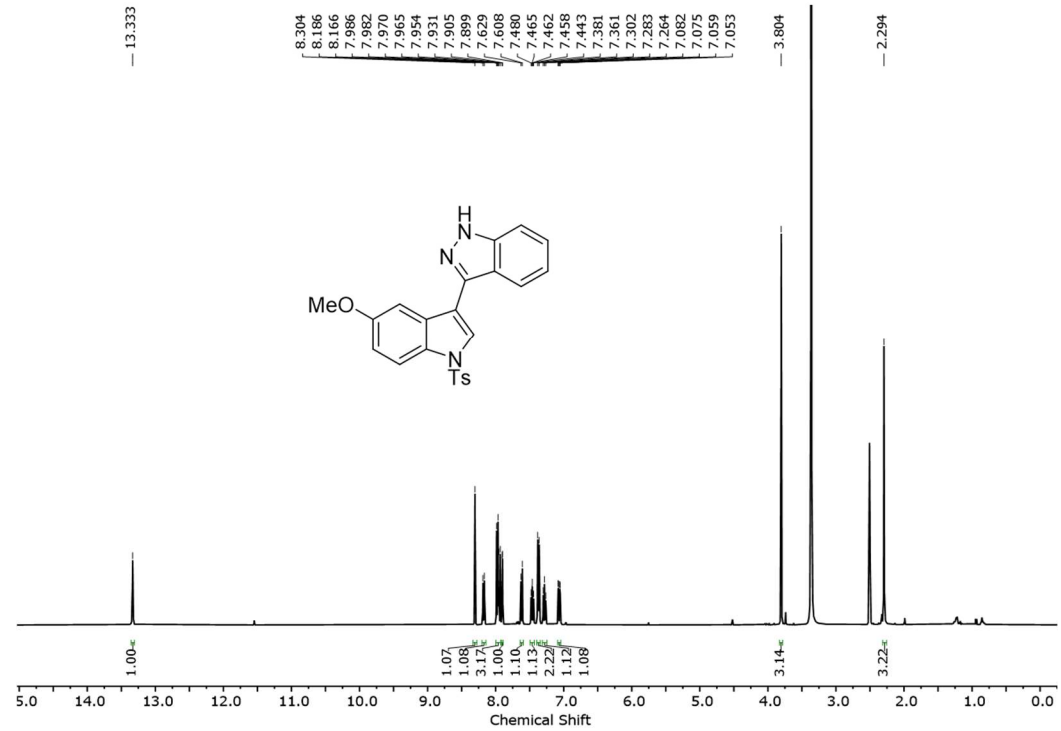
^{1}H NMR (400 MHz, DMSO-d_6) of 5b



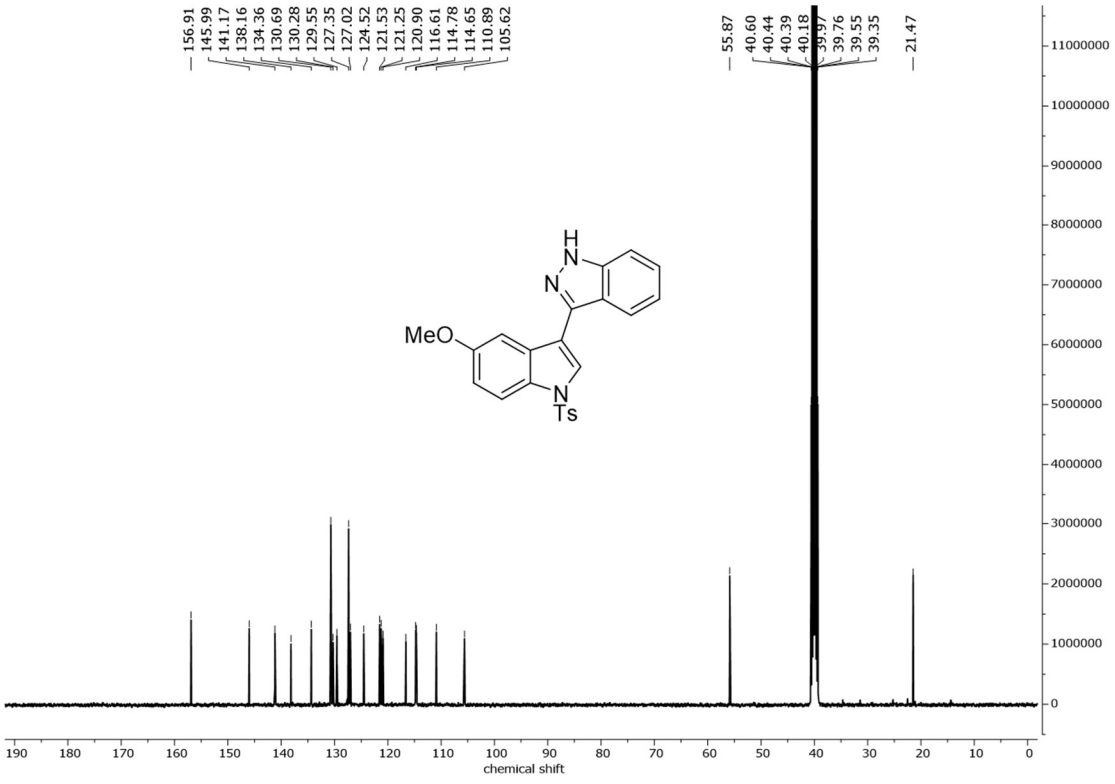
^{13}C{^{1}H} NMR (75 MHz, DMSO-d_6) of 5b



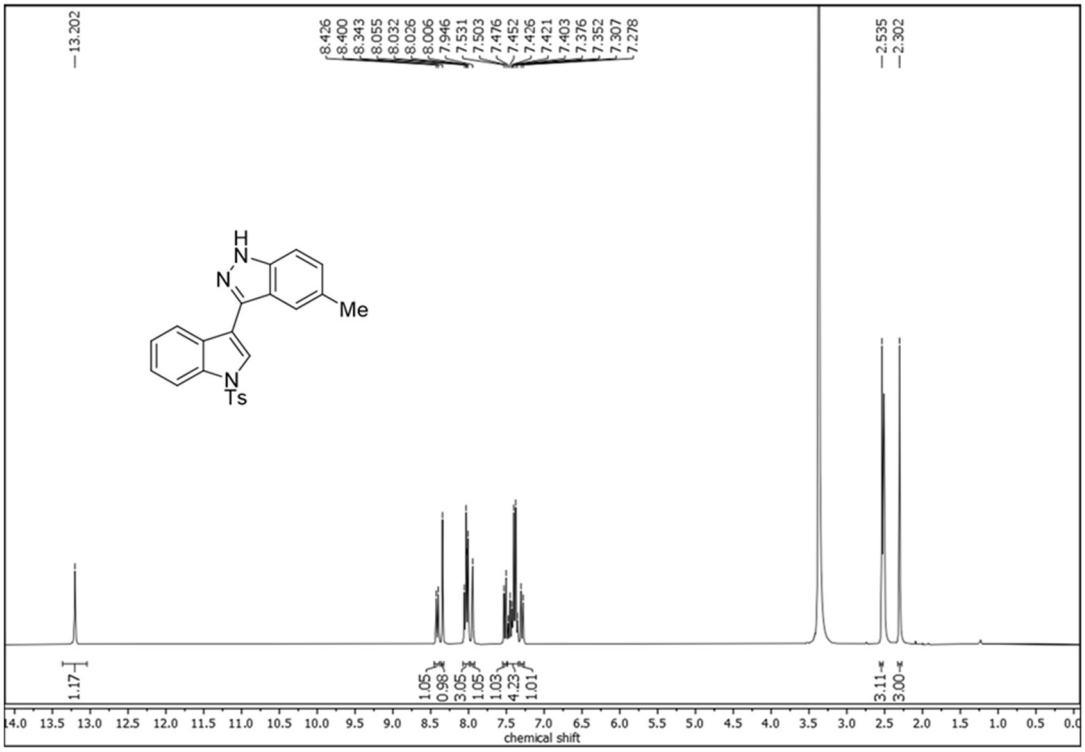
^{1}H NMR (400 MHz, DMSO-d_6) of 5c



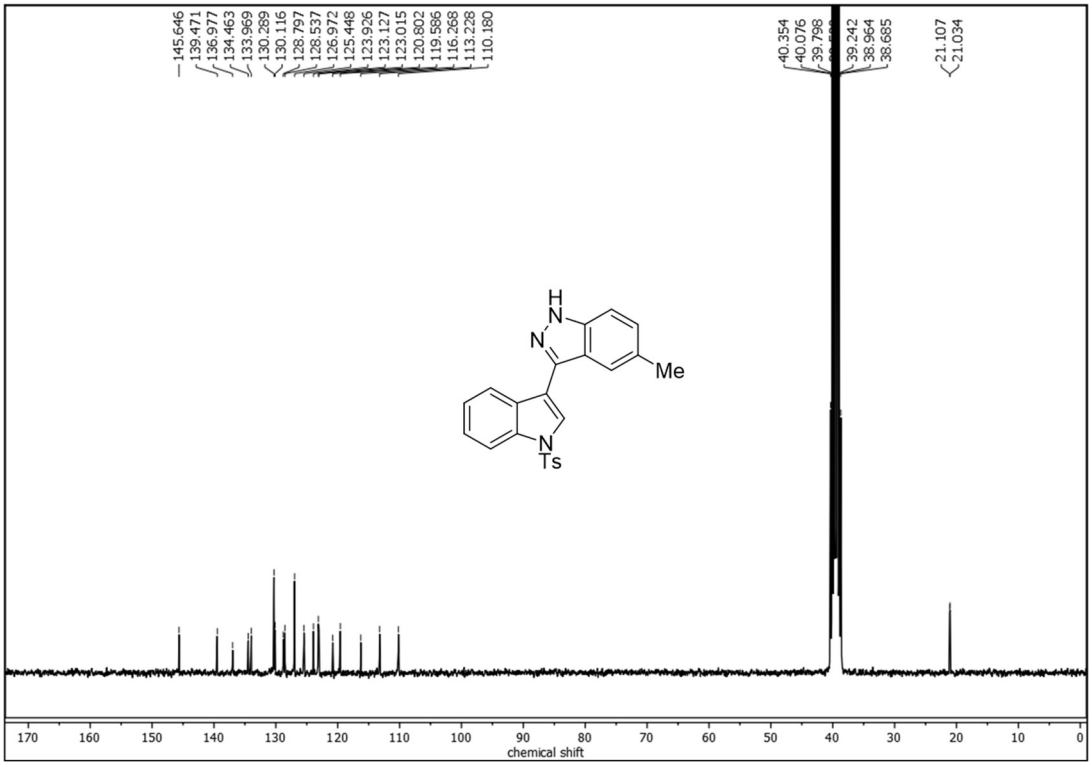
^{13}C{^{1}H} NMR (75 MHz, DMSO-d_6) of 5c



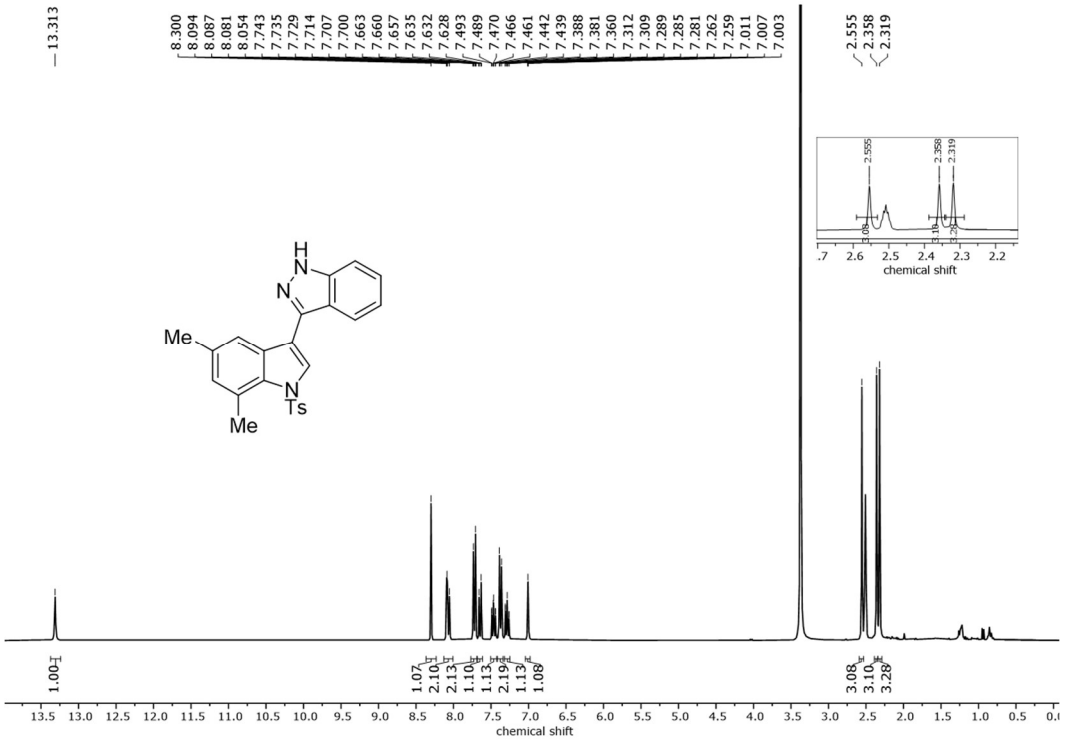
^{1}H NMR (300 MHz, DMSO-d_6) of 5d



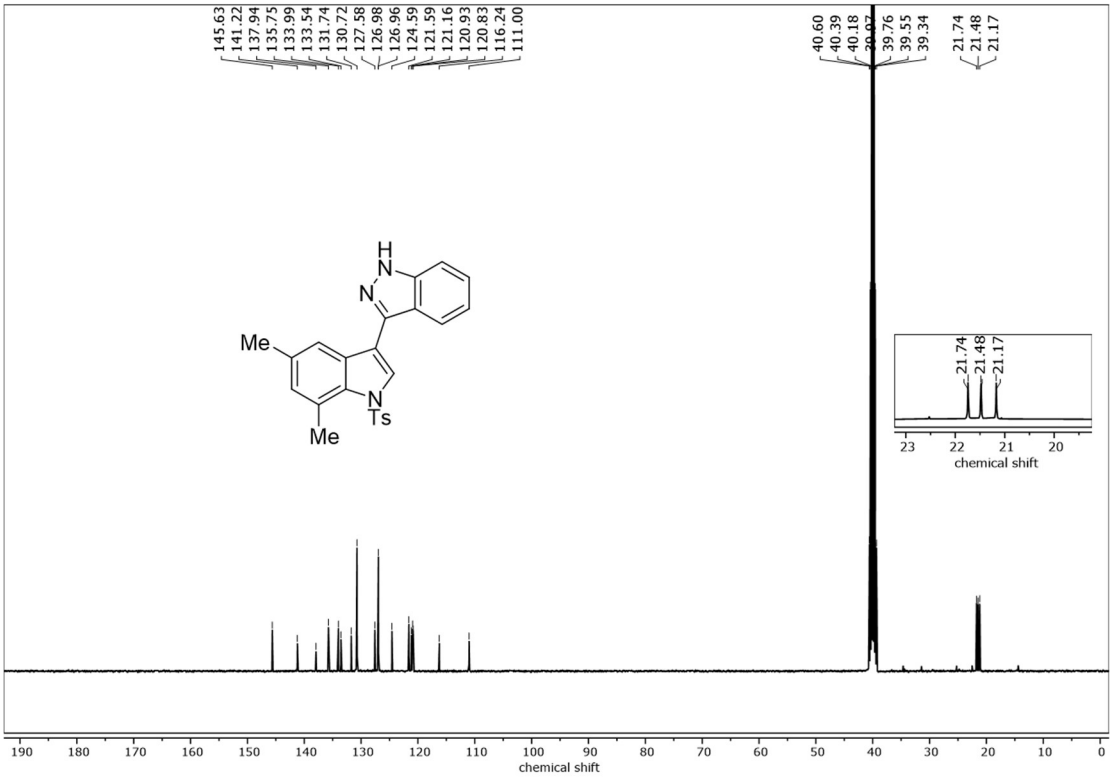
^{13}C{^{1}H} NMR (75 MHz, DMSO-d_6) of 5d



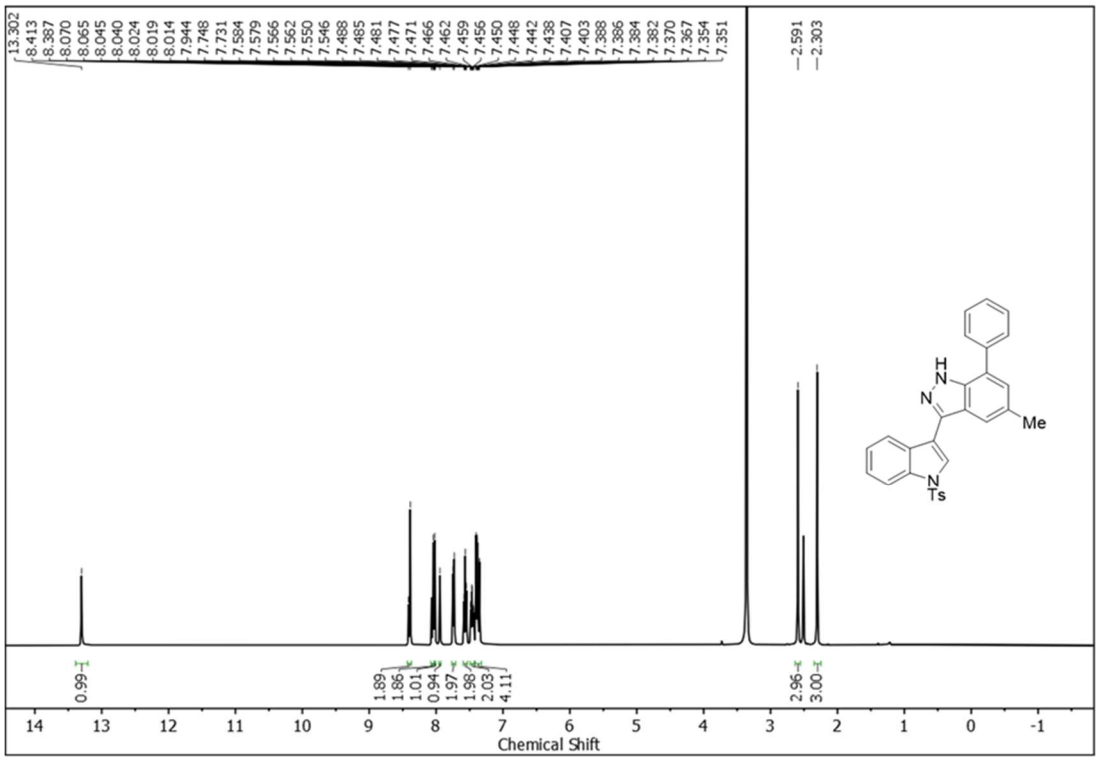
^{1}H NMR (300 MHz, DMSO-d_6) of 5e



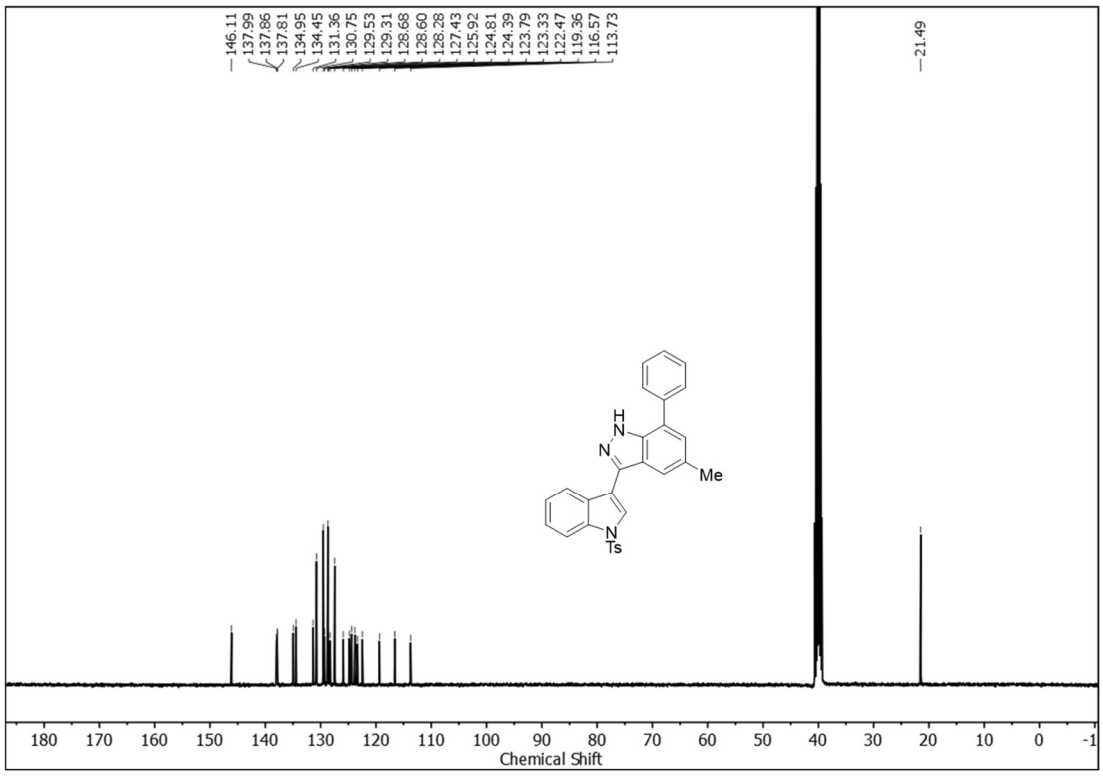
^{13}C{^{1}H} NMR (75 MHz, DMSO-d_6) of 5e



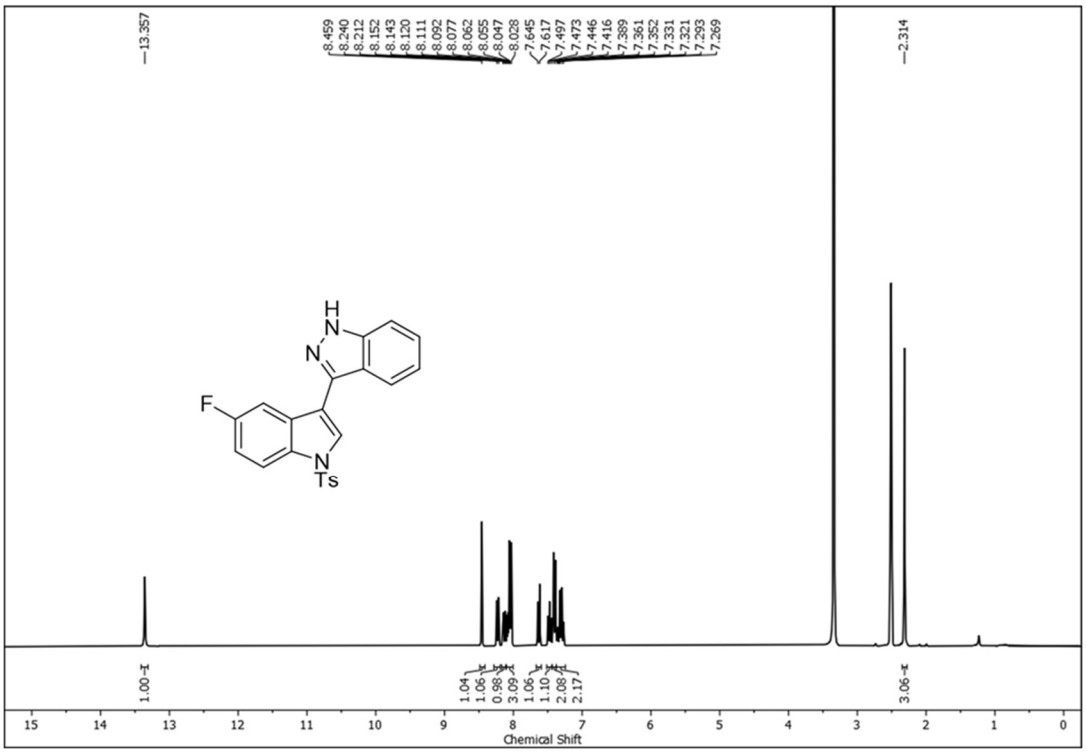
^{1}H NMR (400 MHz, DMSO) of 5f



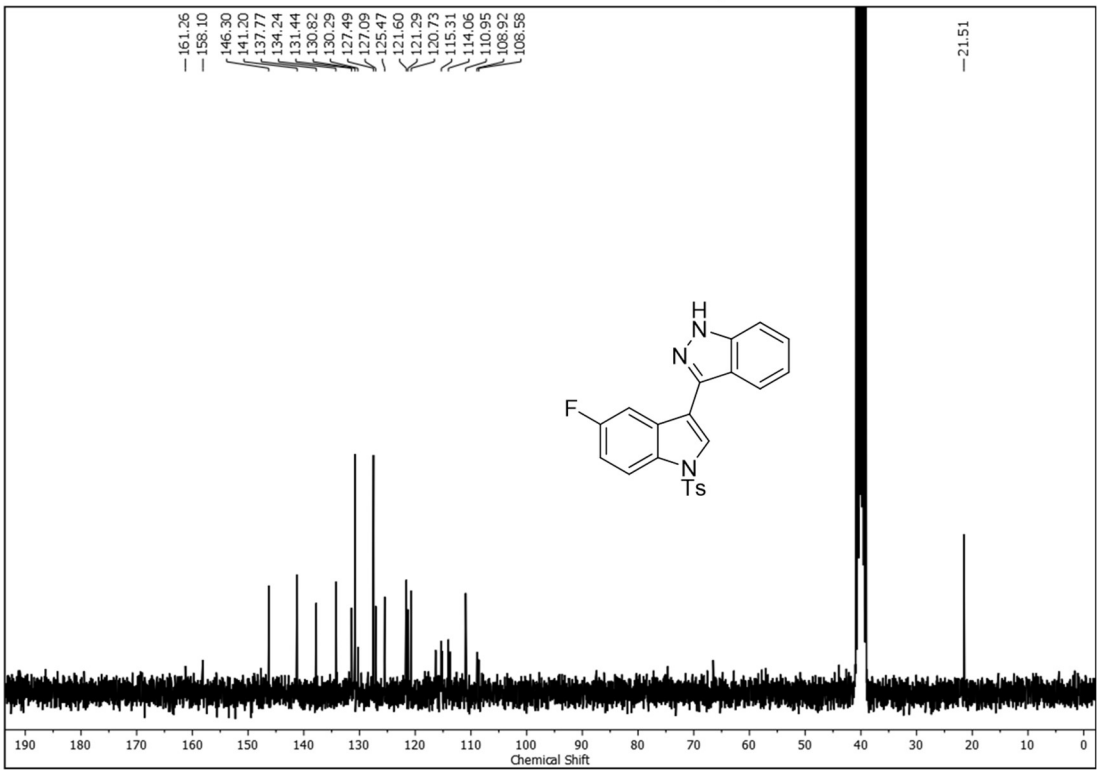
^{13}C{^{1}H} NMR (101 MHz, DMSO) of 5f



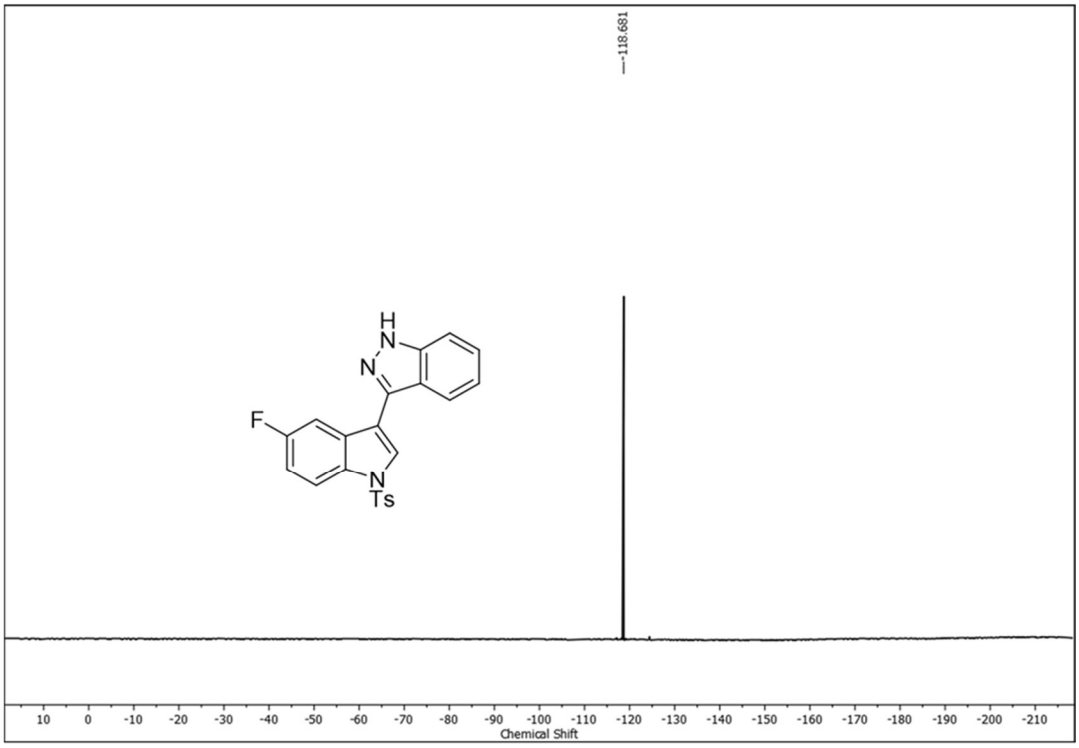
^{1}H NMR (300 MHz, DMSO-d_6) of 5g



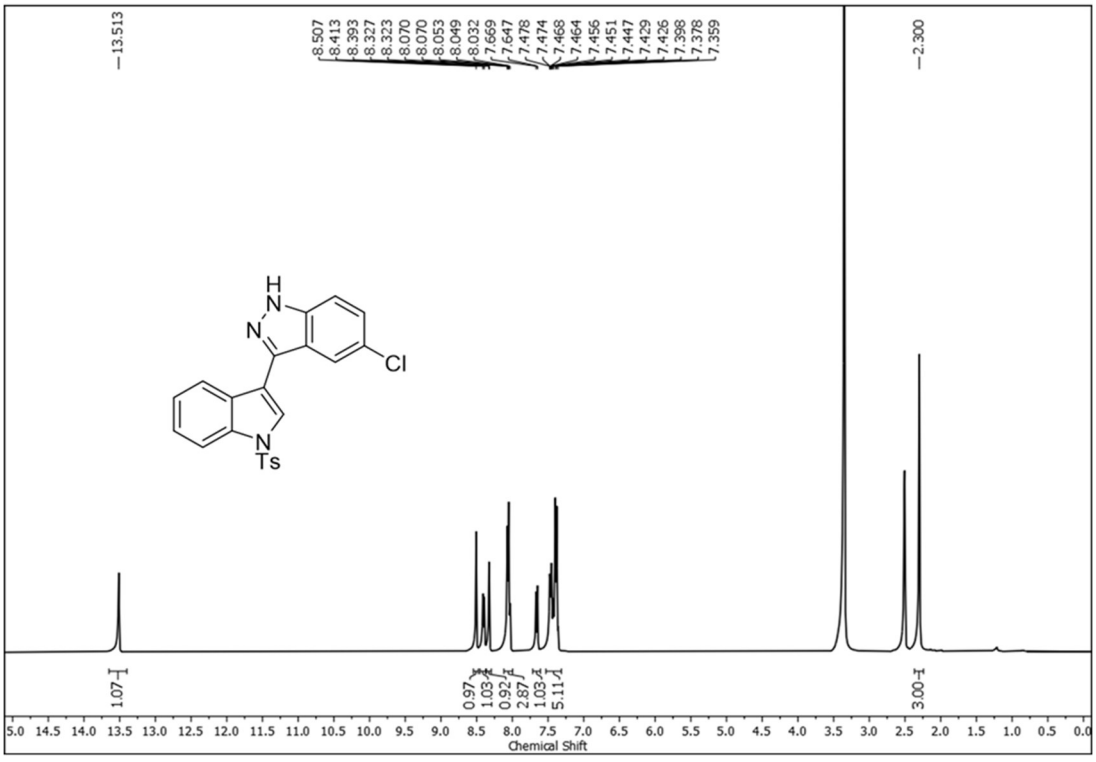
^{13}C{^{1}H} NMR (75 MHz, DMSO-d_6) of 5g



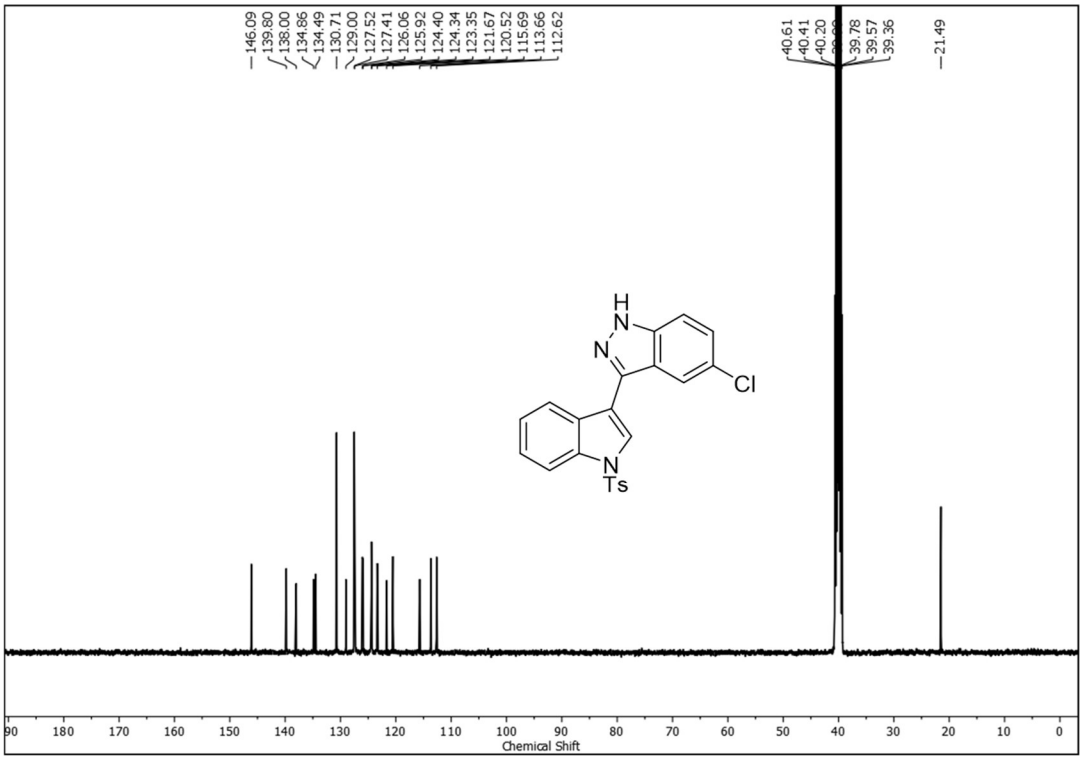
^{19}F NMR (282 MHz, DMSO-d_6) of 5g



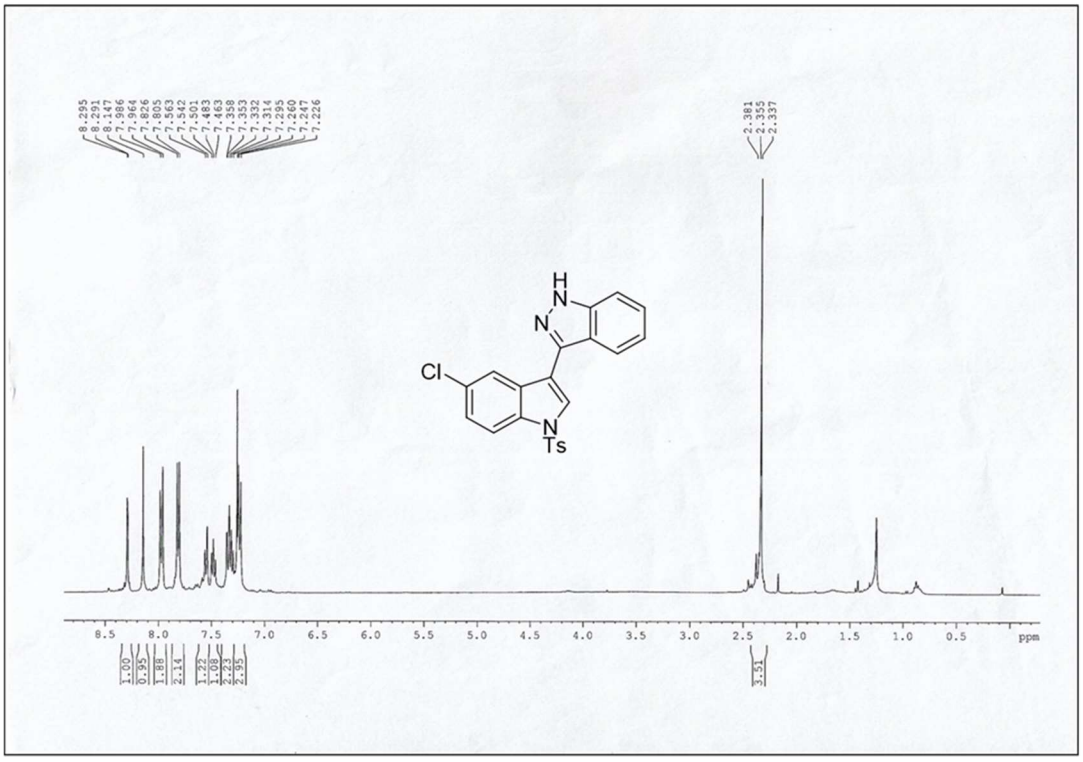
^{1}H NMR (400 MHz, DMSO-d_6) of 5h



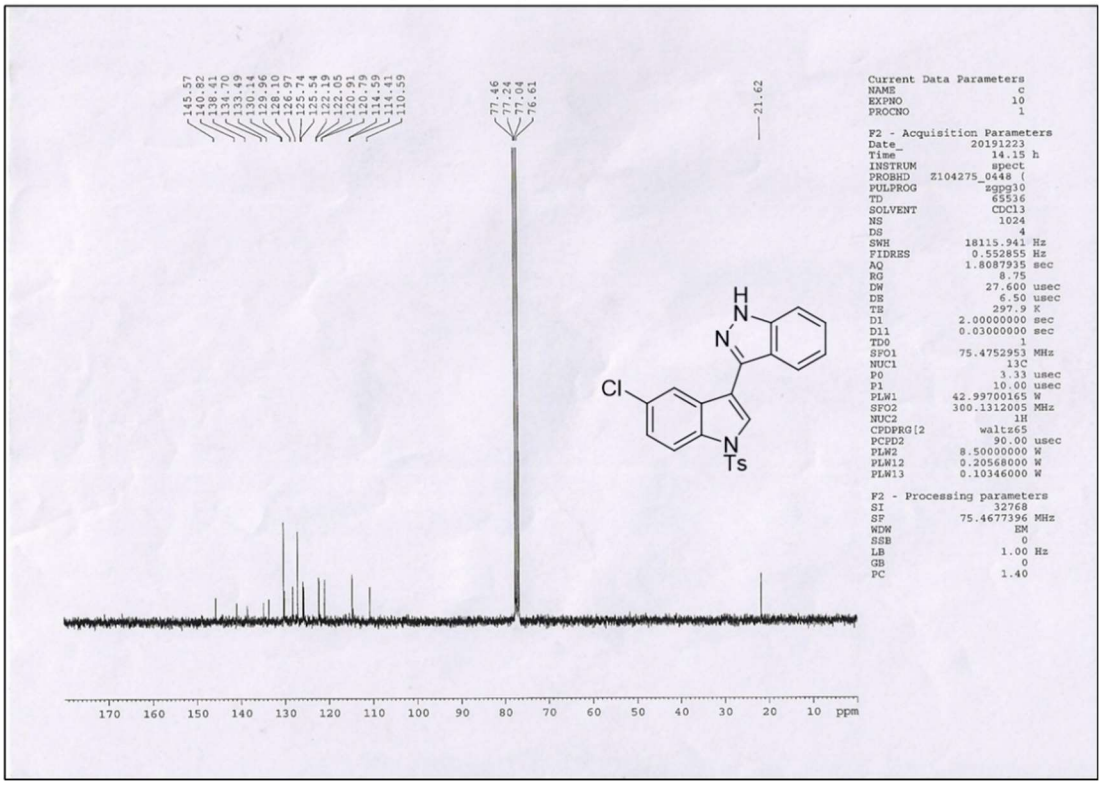
$^{13}C\{^{1}H\}$ NMR (101 MHz, DMSO-d_6) of 5h



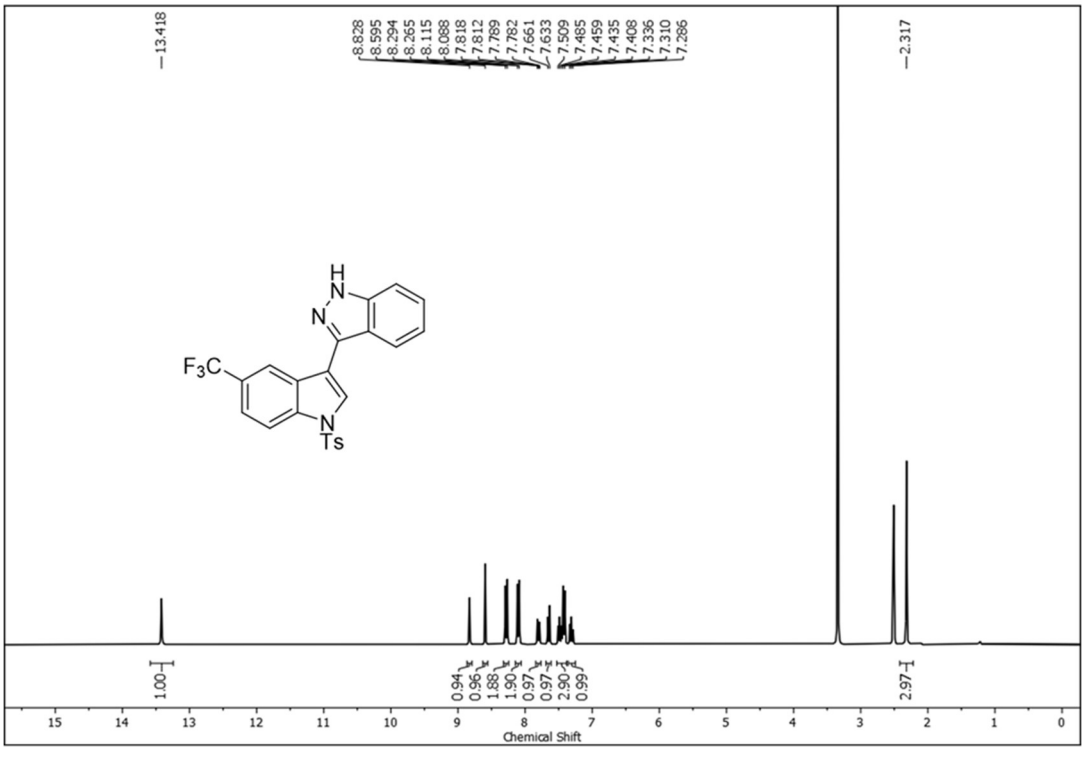
^{1}H NMR (300 MHz, $CDCl_3$) of 5i



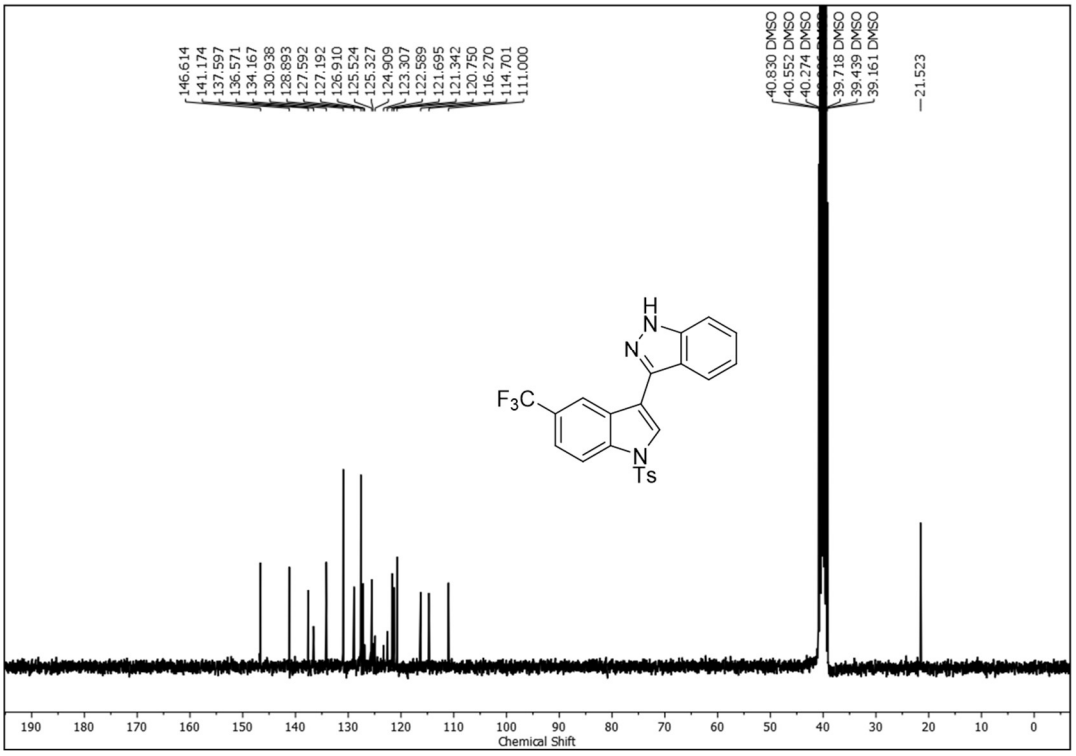
$^{13}C\{^{1}H\}$ NMR (75 MHz, $CDCl_3$) of 5i



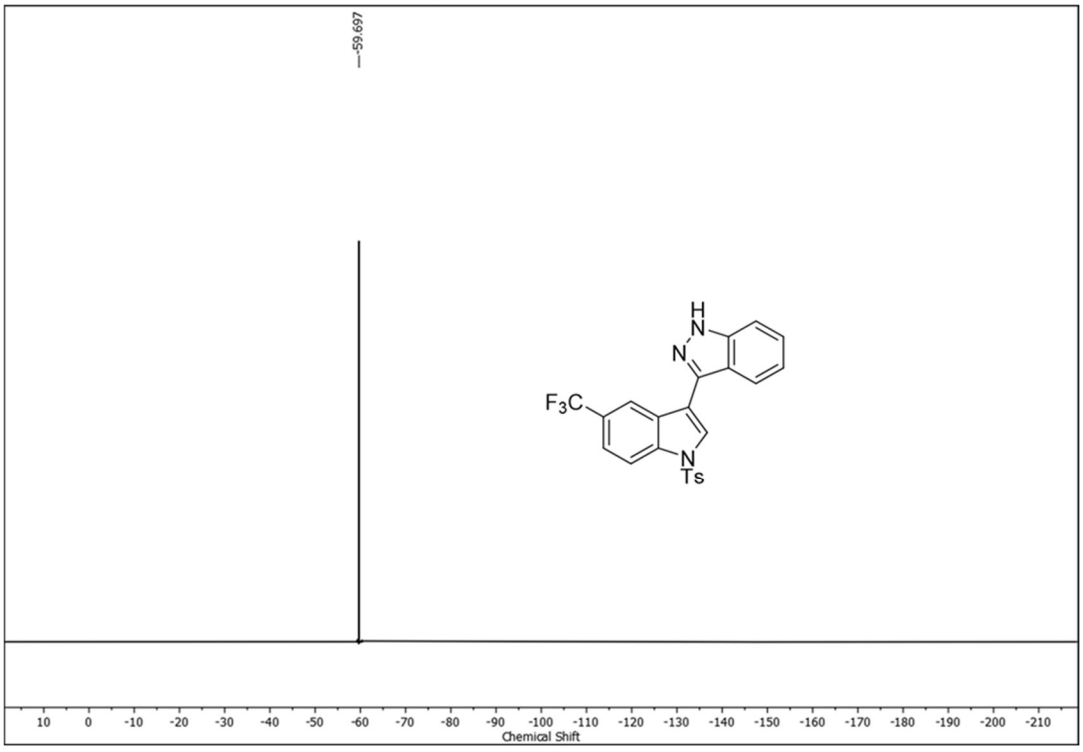
^{1}H NMR (300 MHz, DMSO-d_6) of 5j



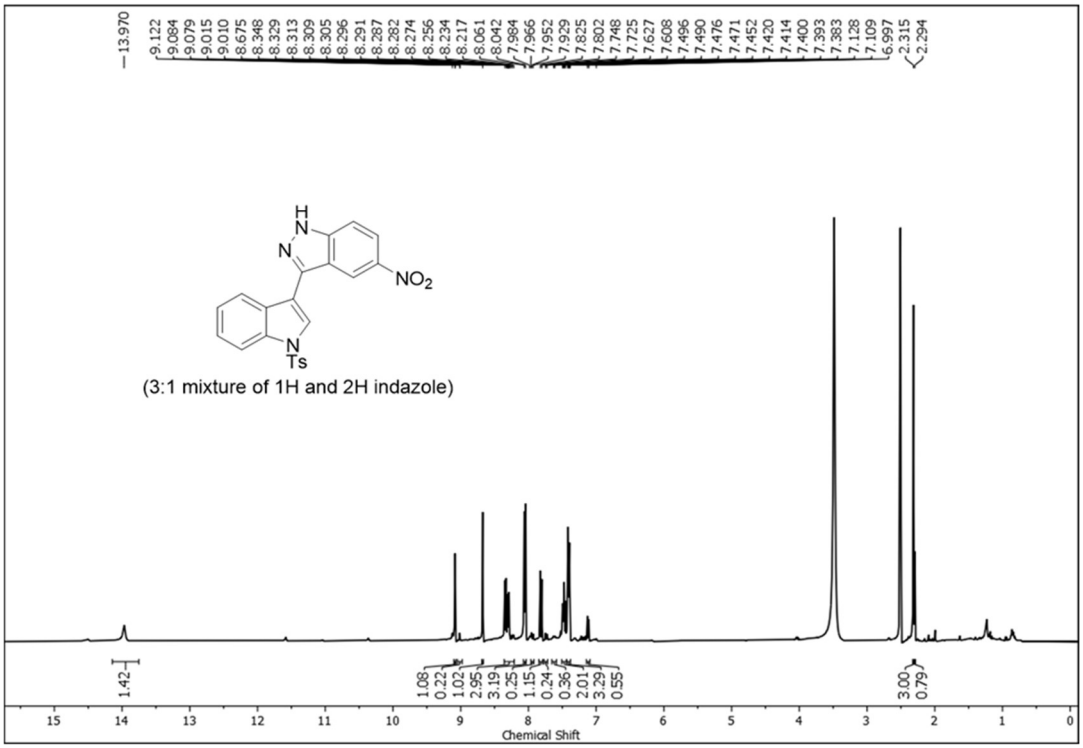
$^{13}C\{^{1}H\}$ NMR (75 MHz, DMSO-d_6) of 5j



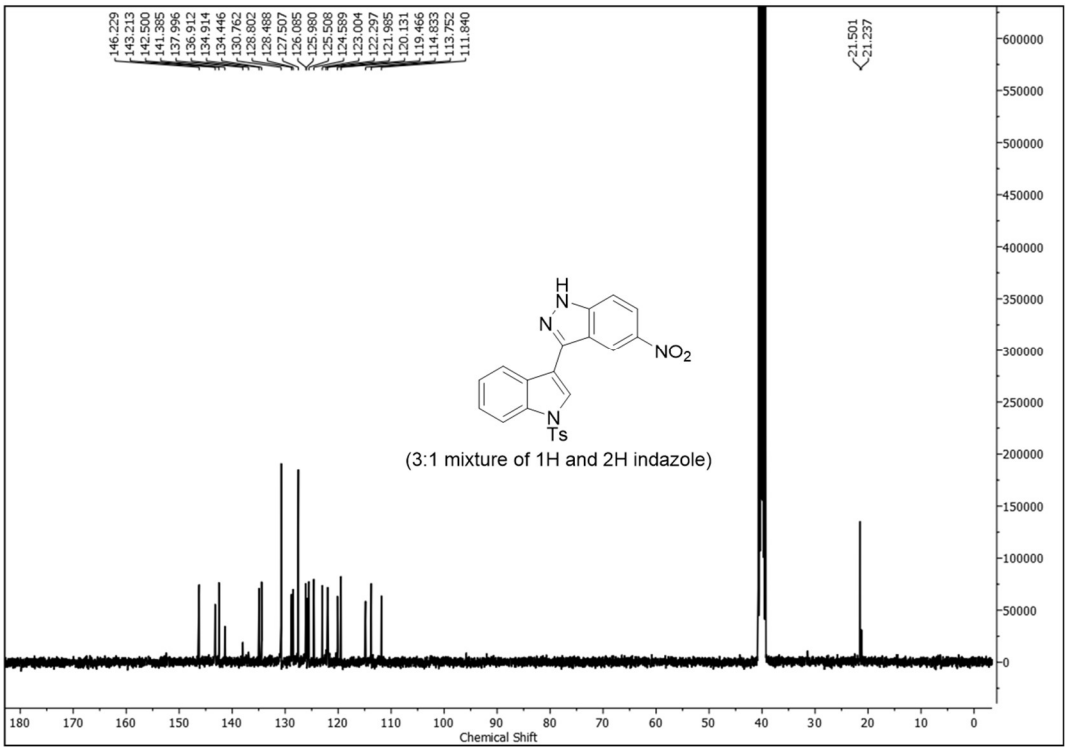
^{19}F NMR (282 MHz, DMSO-d_6) of 5j



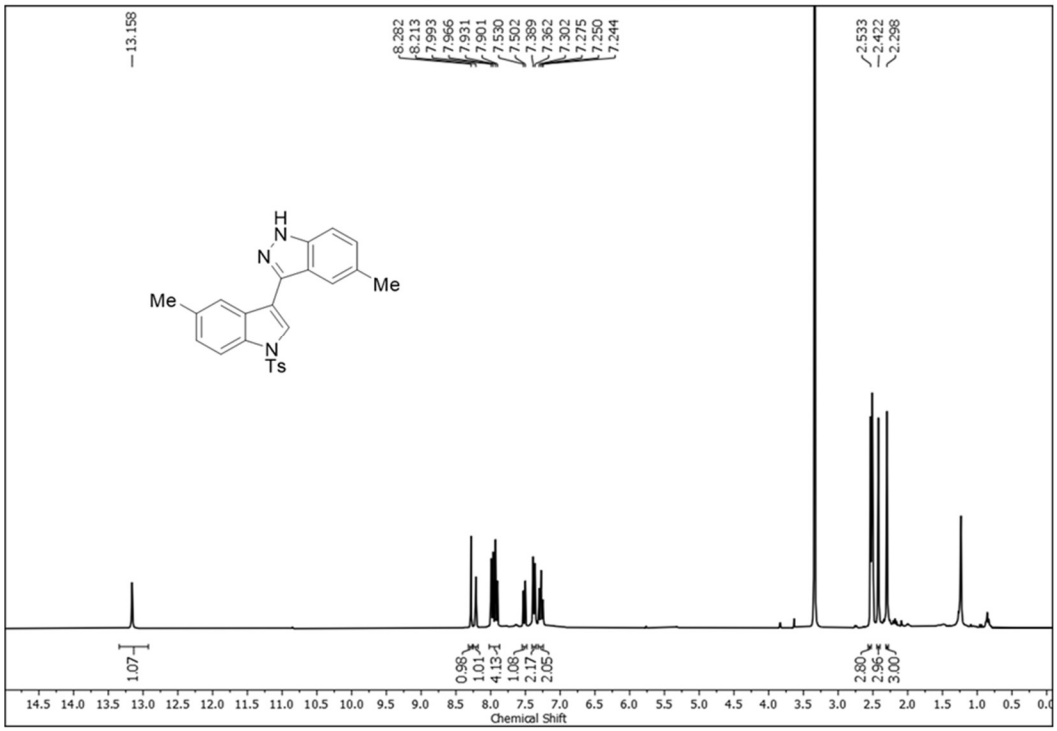
^{1}H NMR (400 MHz, DMSO-d_6) of 5k



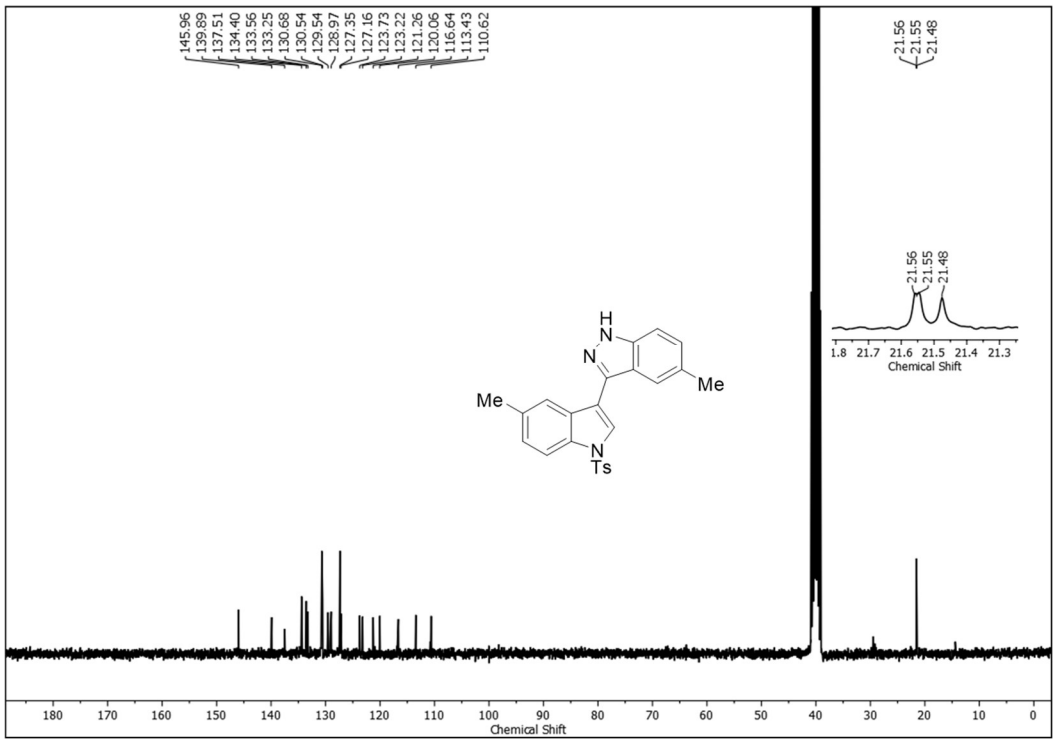
^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6) of 5k



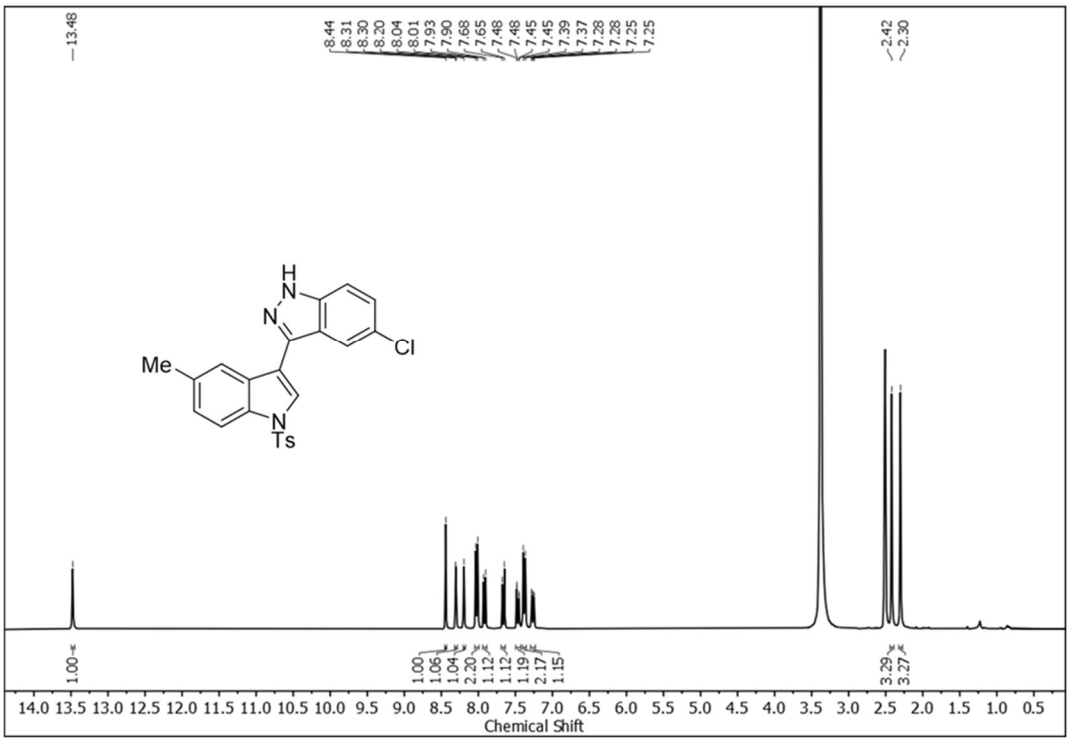
^{1}H NMR (300 MHz, DMSO-d_6) of 5l



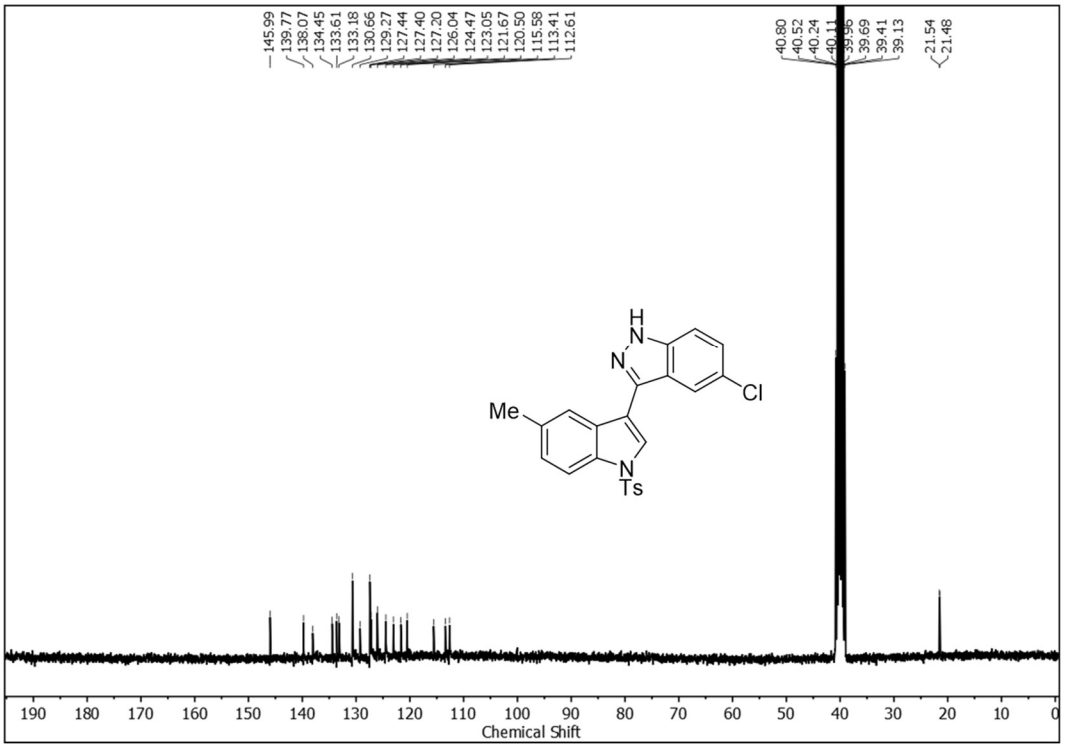
^{13}C{^{1}H} NMR (75 MHz, DMSO-d_6) of 5l



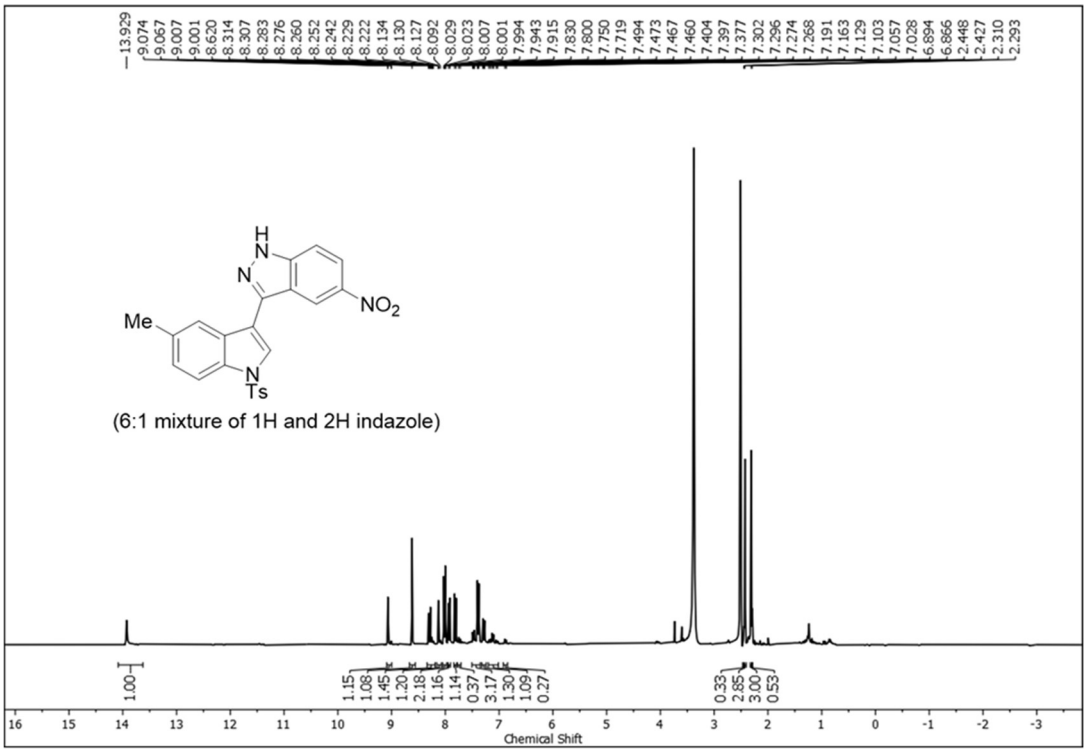
^{1}H NMR (300 MHz, DMSO-d_6) of 5m



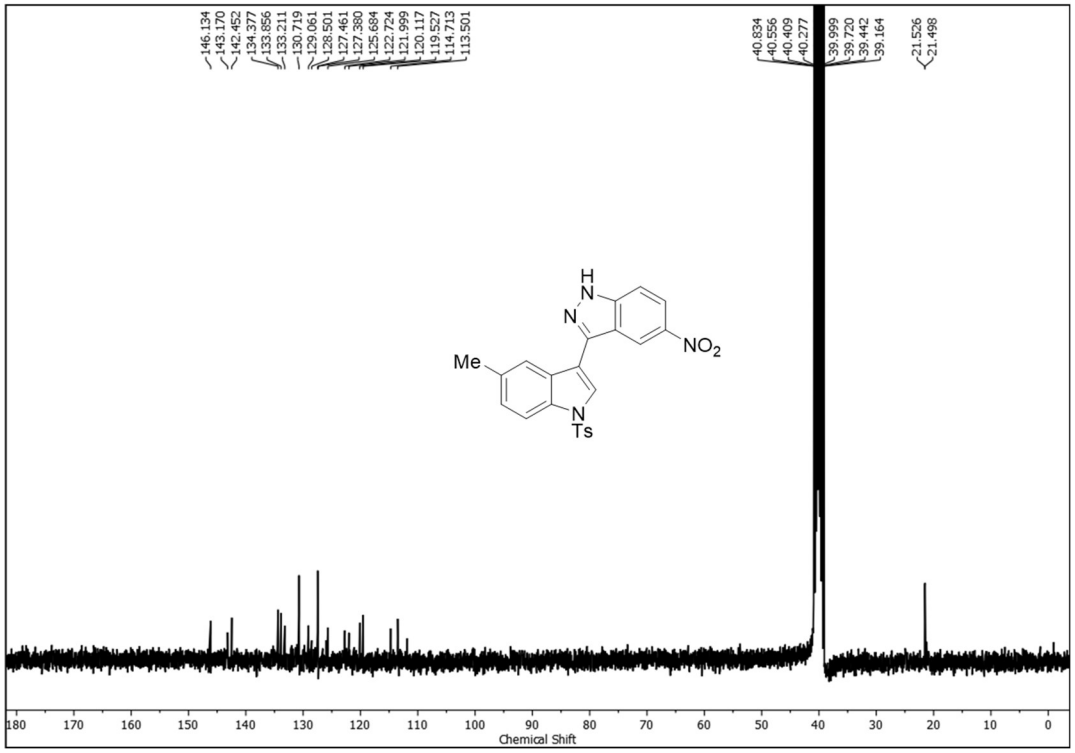
^{13}C{^{1}H} NMR (75 MHz, DMSO-d_6) of 5m



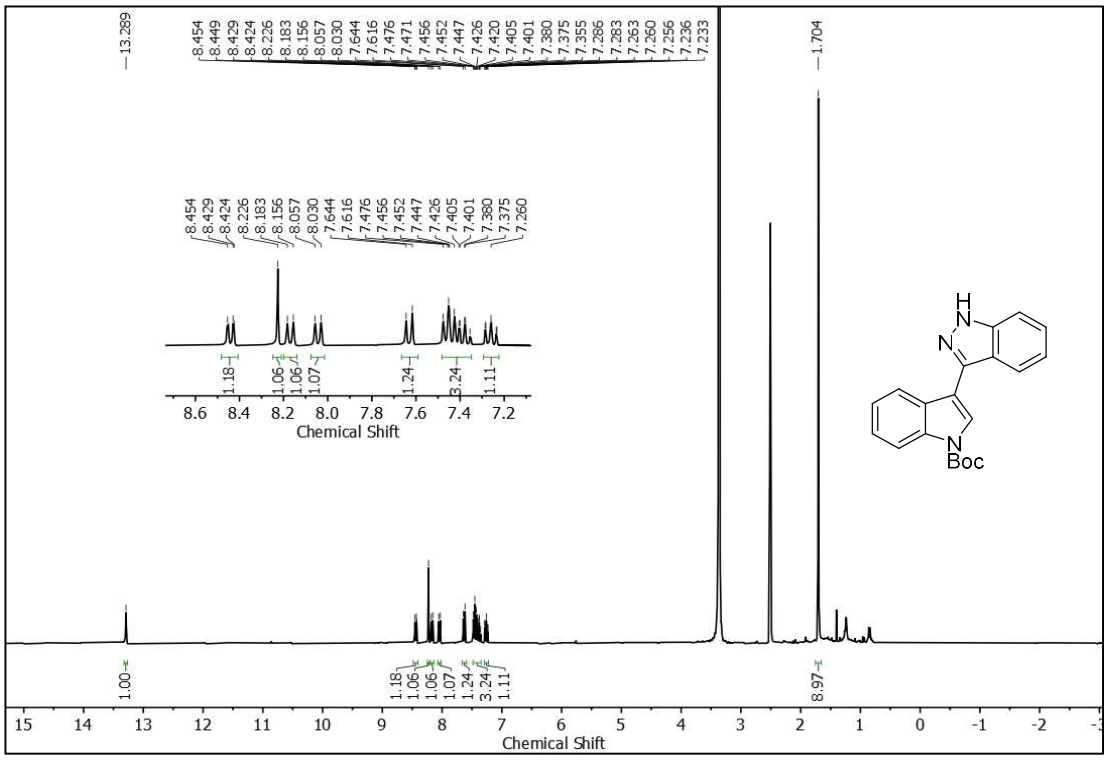
^{1}H NMR (300 MHz, DMSO-d_6) of 5n



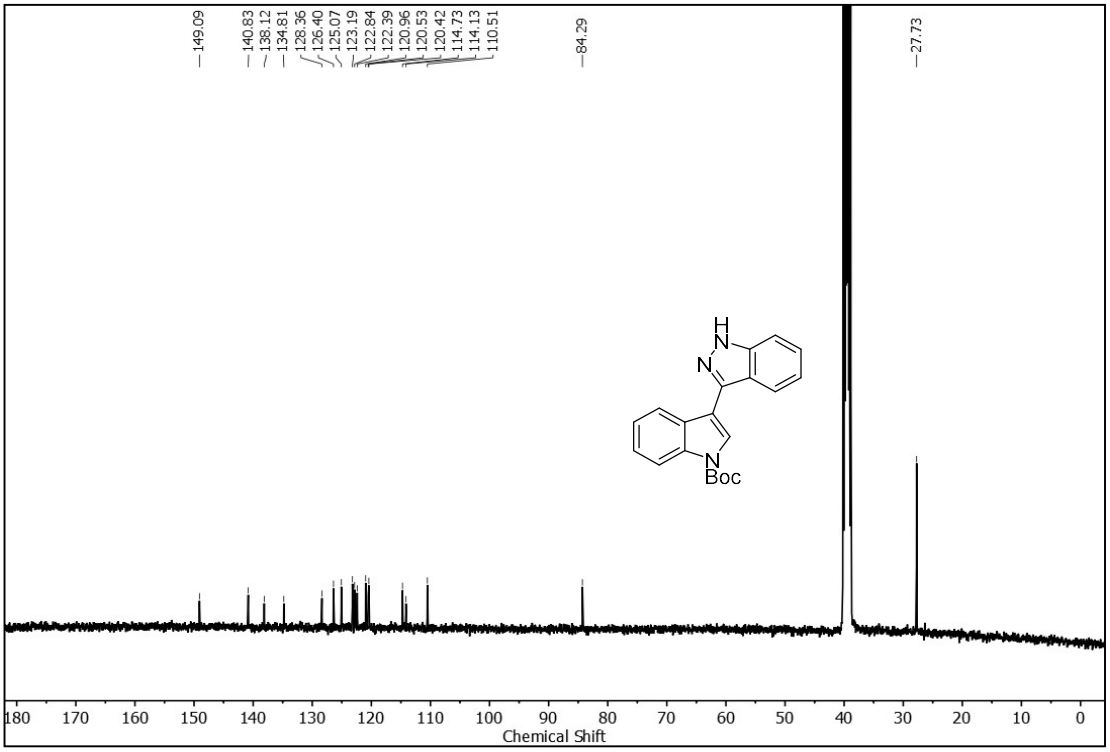
^{13}C{^{1}H} NMR (75 MHz, DMSO-d_6) of 5n



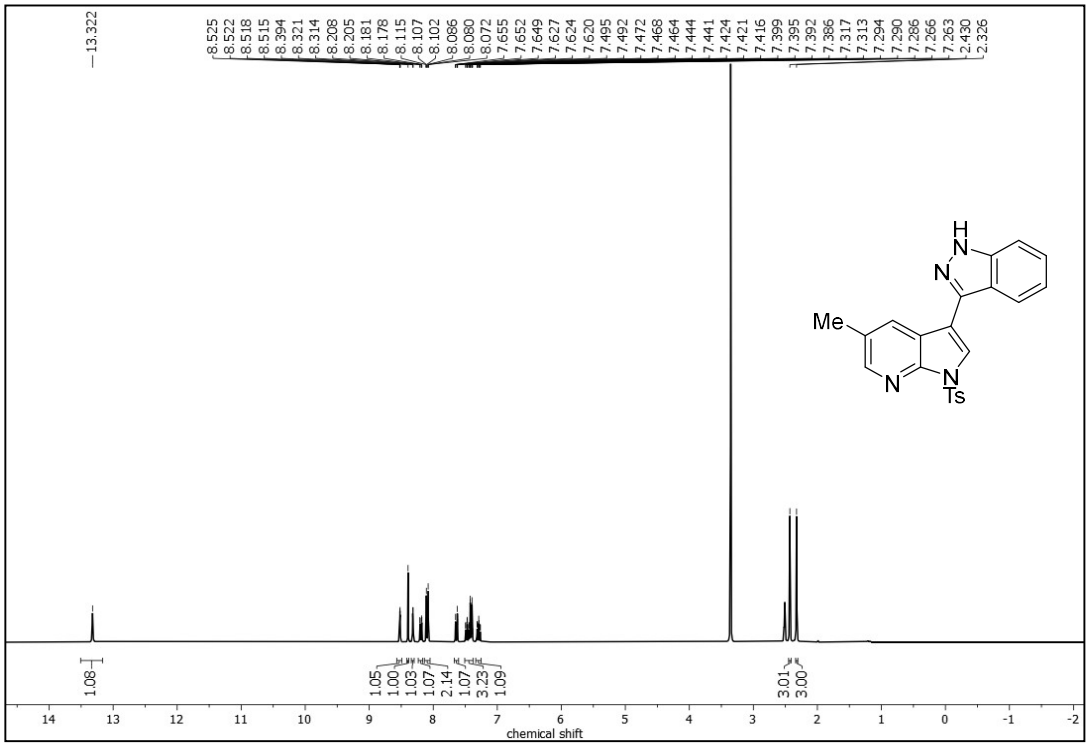
^{1}H NMR (300 MHz, DMSO) of 5o



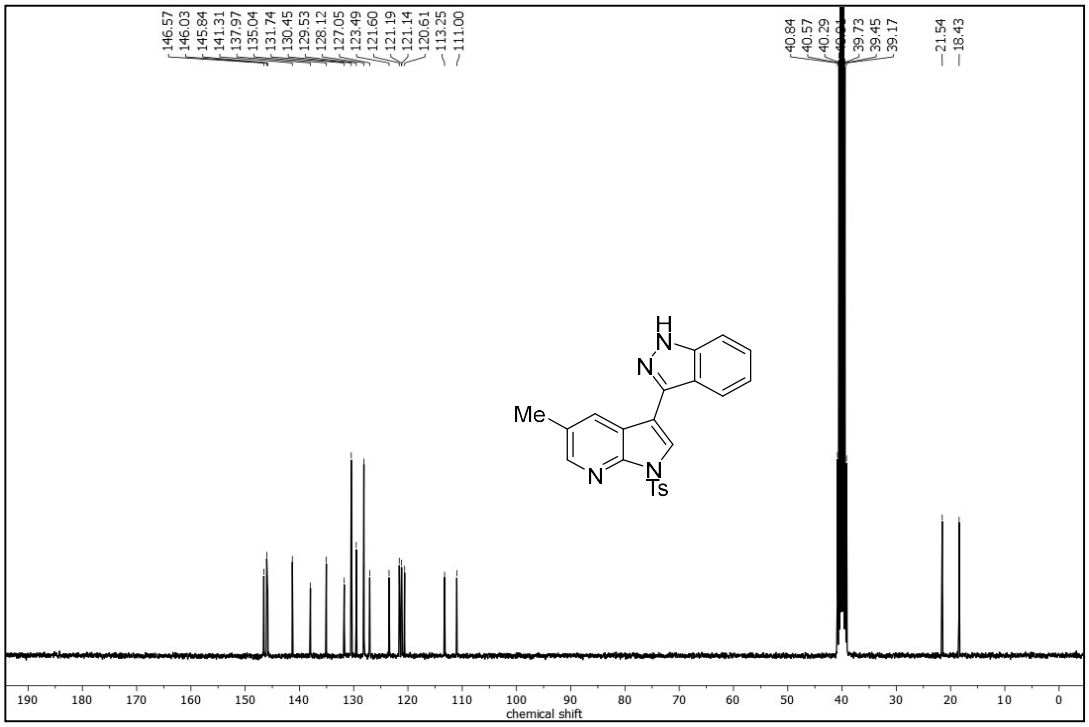
^{13}C{^{1}H} NMR (101 MHz, DMSO) of 5o



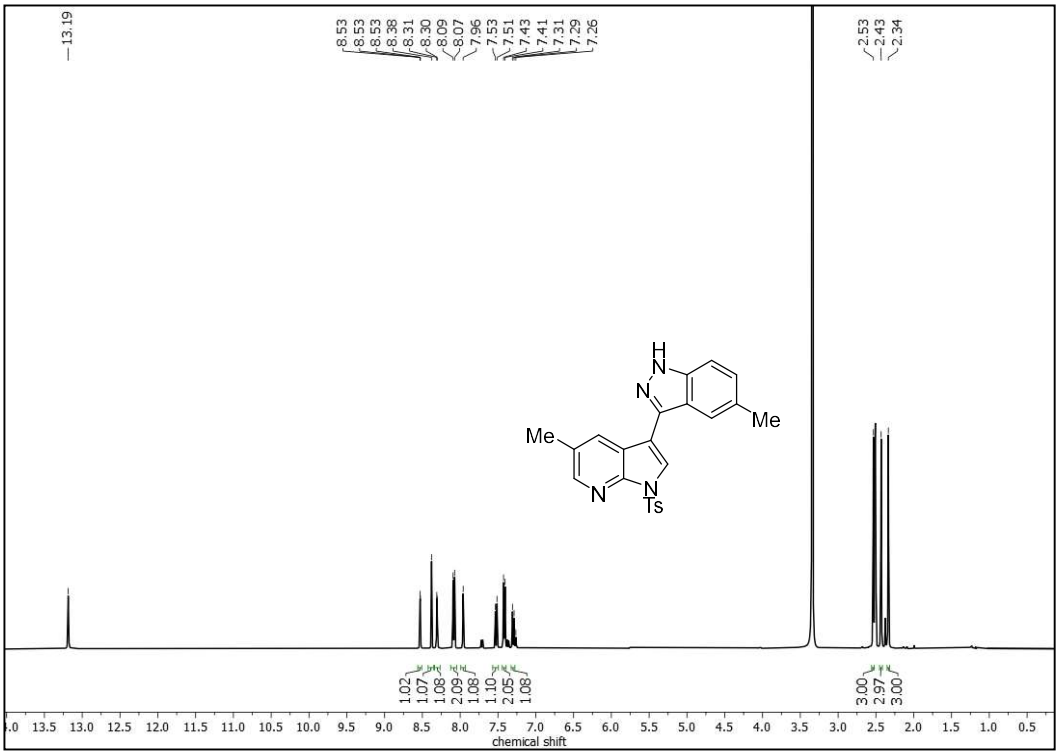
^{1}H NMR (300 MHz, DMSO-d$_6$) of 5p



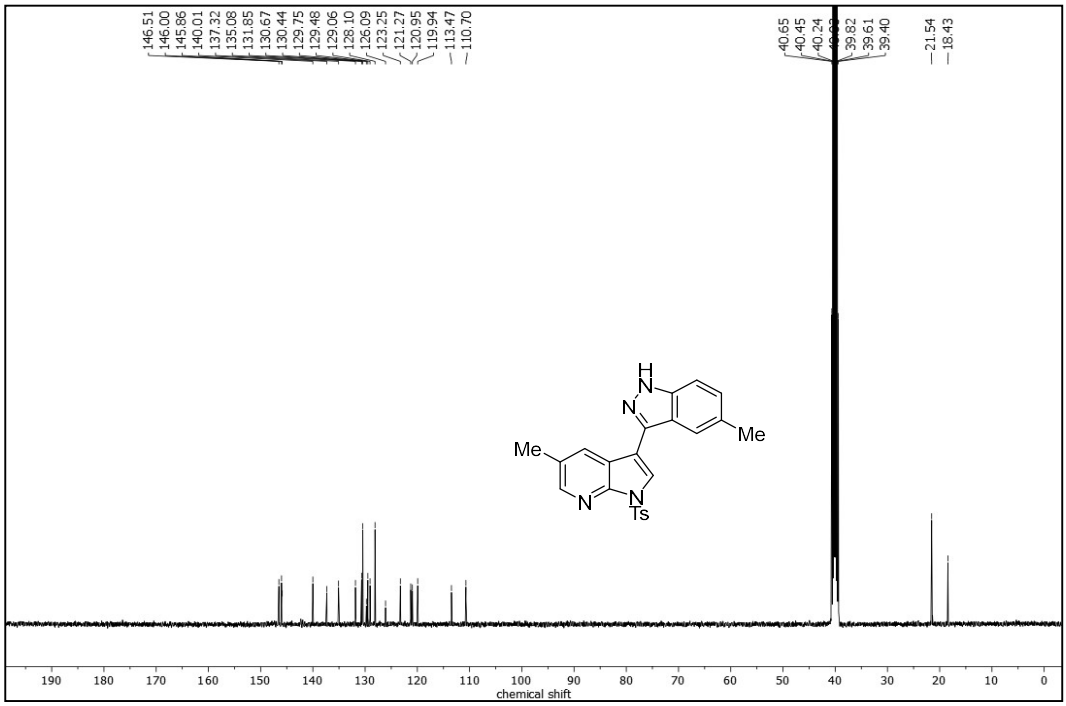
^{13}C{^{1}H} NMR (75 MHz, DMSO-d$_6$) of 5p



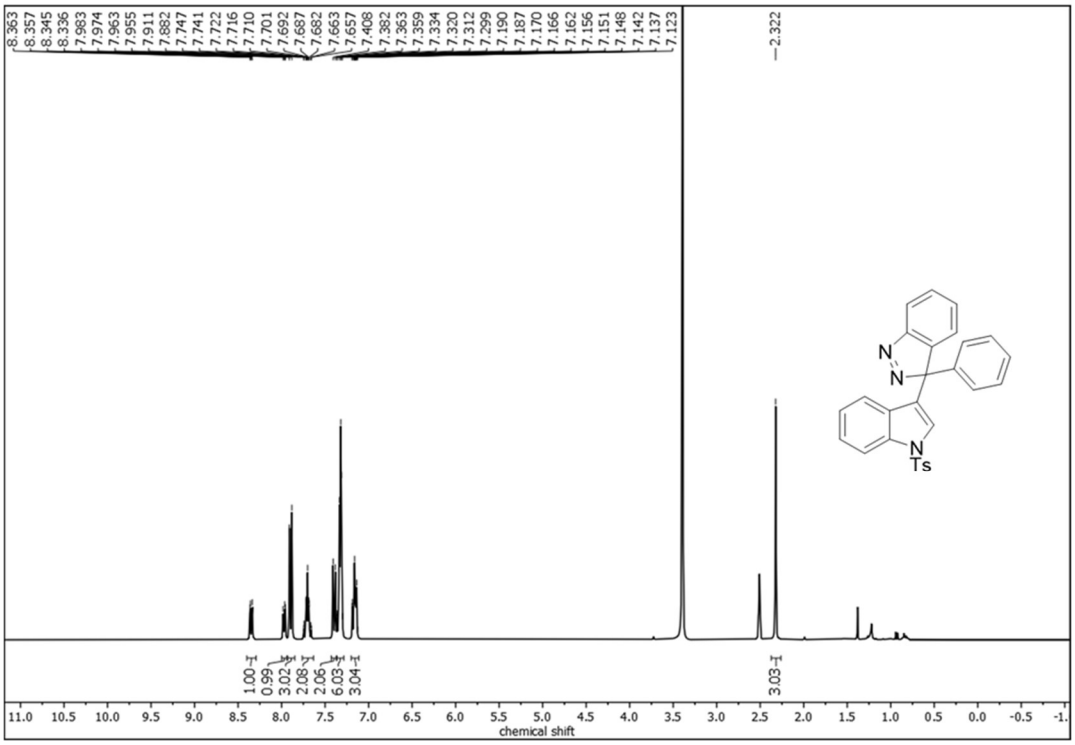
^{1}H NMR (400 MHz, DMSO-d$_6$) of 5q



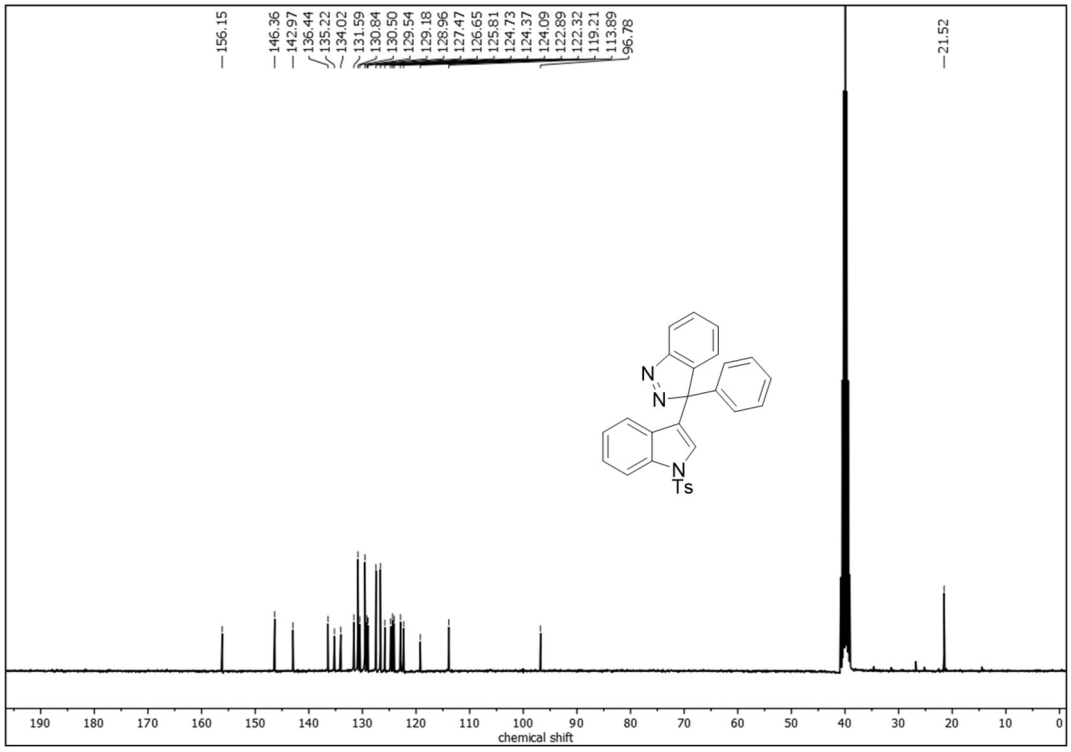
^{13}C{^{1}H} NMR (101 MHz, DMSO-d$_6$) of 5q



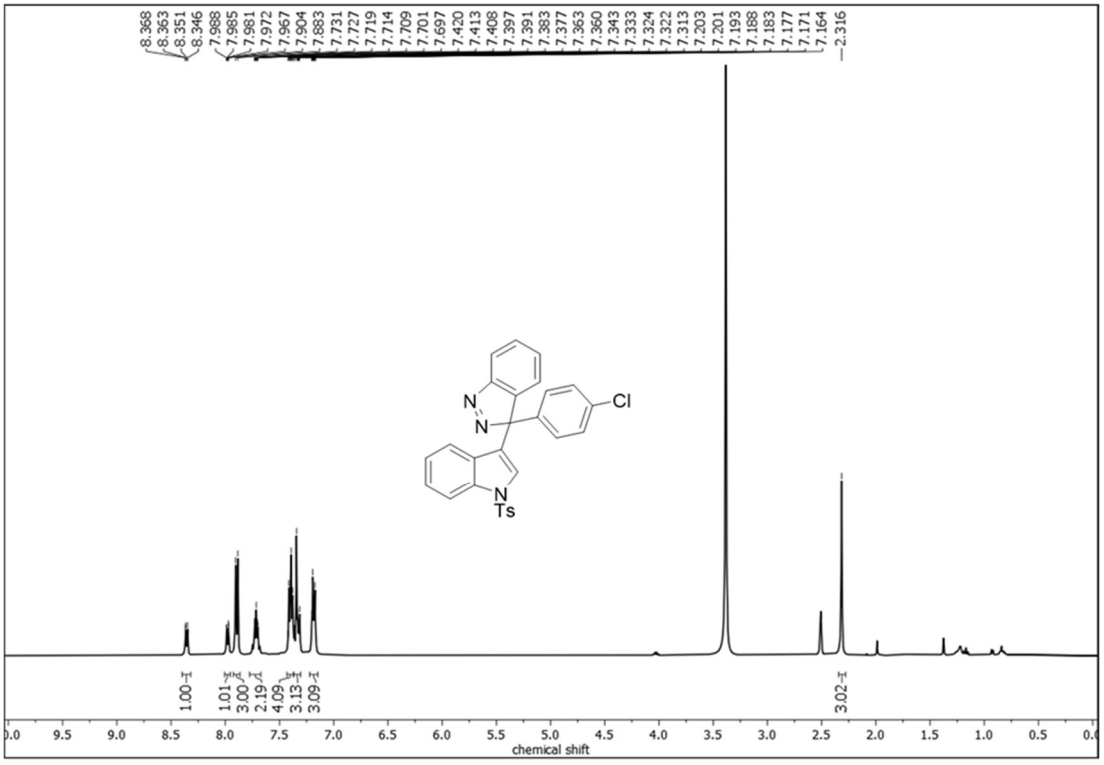
^{1}H NMR (300 MHz, DMSO) of 7a



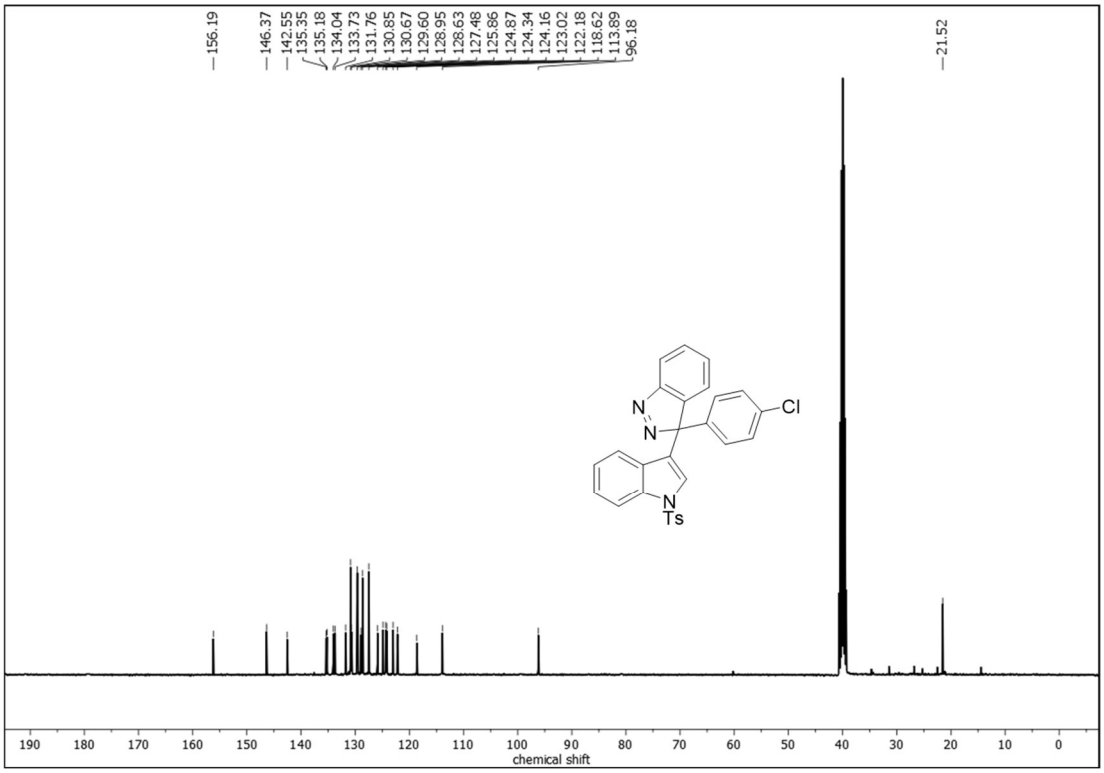
^{13}C{^{1}H} NMR (75 MHz, DMSO) of 7a



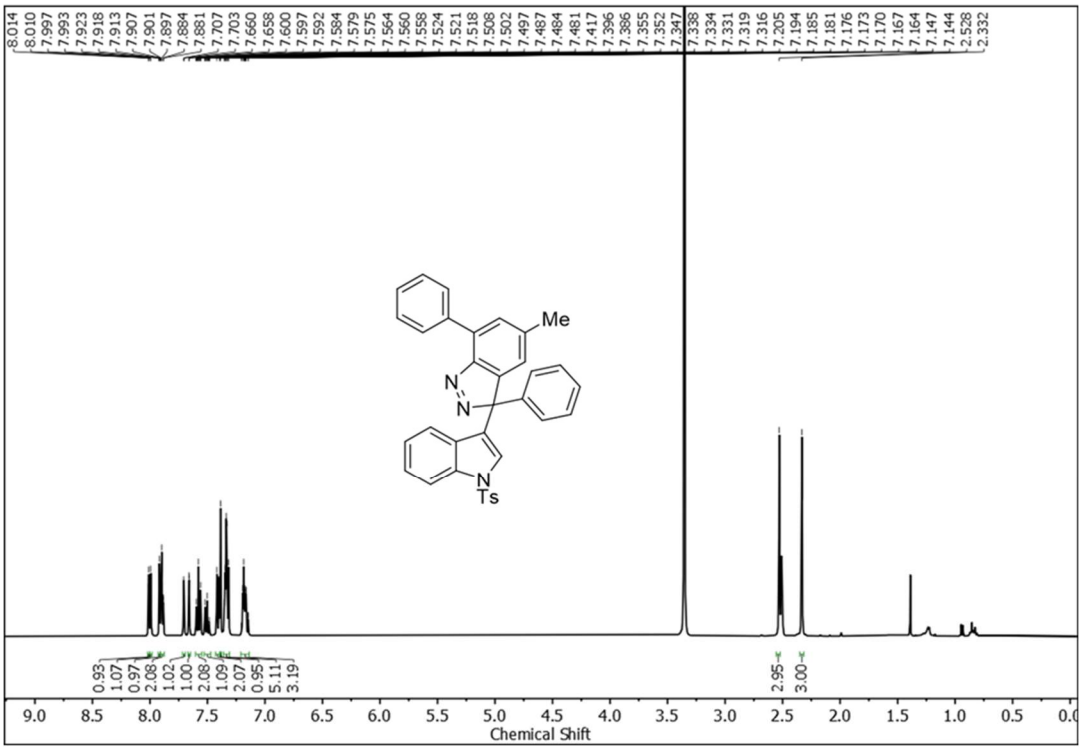
^{1}H NMR (400 MHz, DMSO) of 7b



^{13}C{^{1}H} NMR (101 MHz, DMSO) of 7b



^{1}H NMR (400 MHz, DMSO) of 7c



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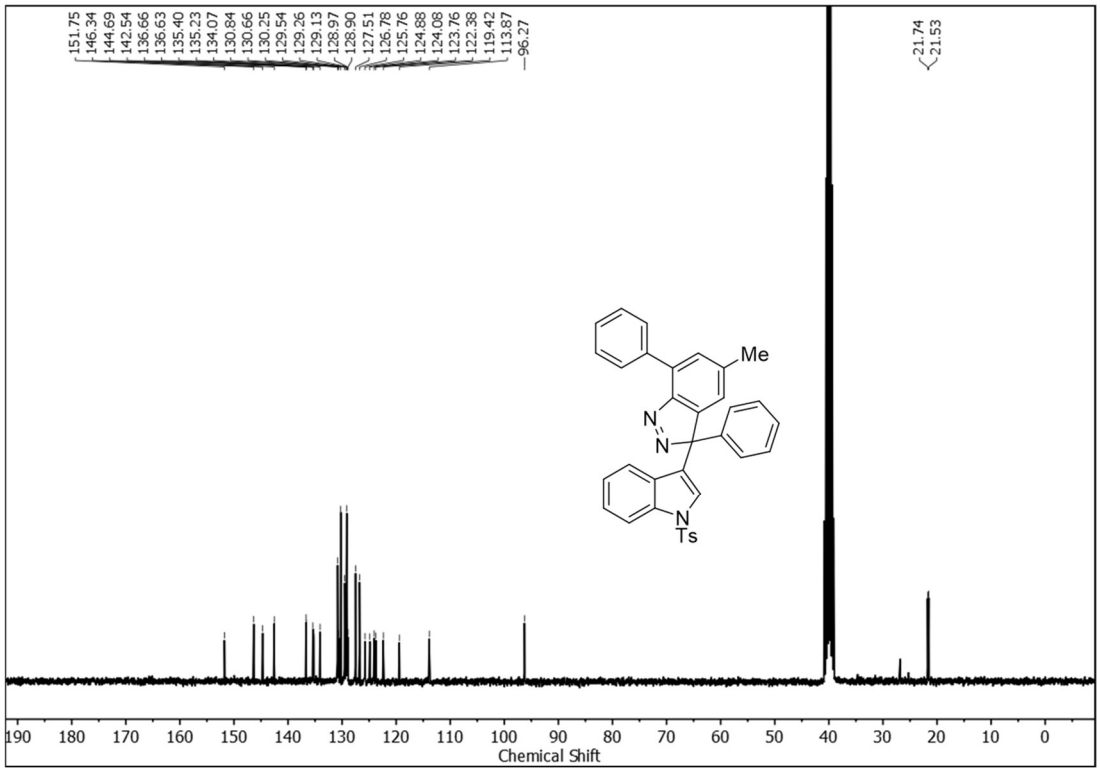
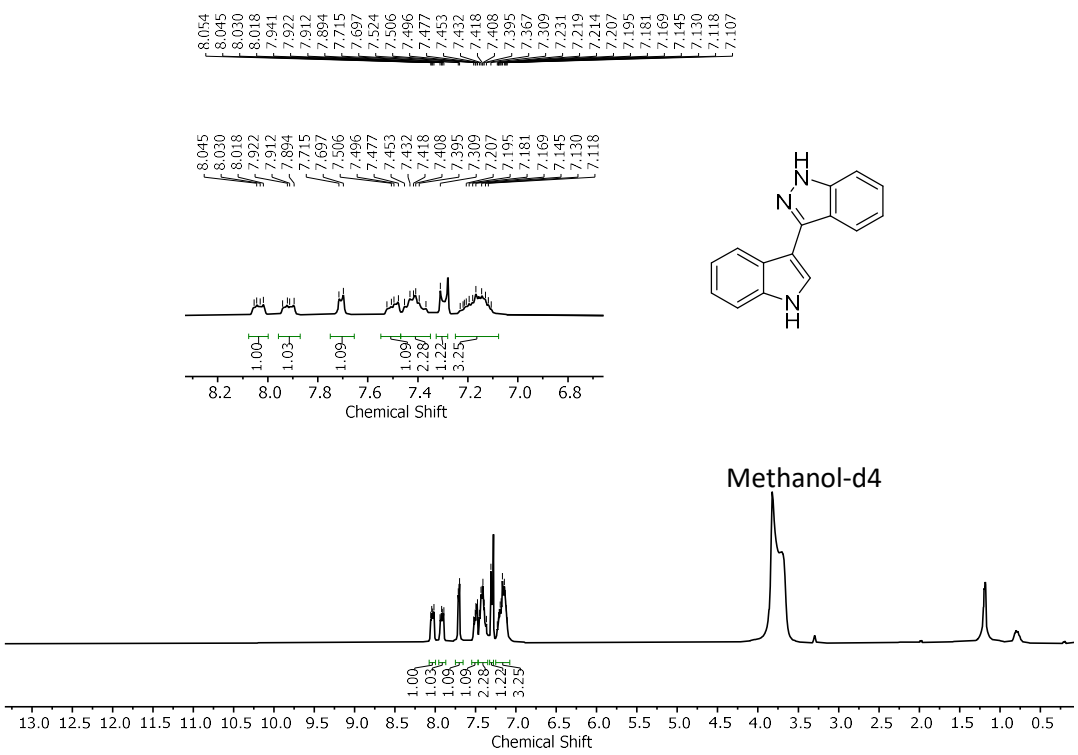
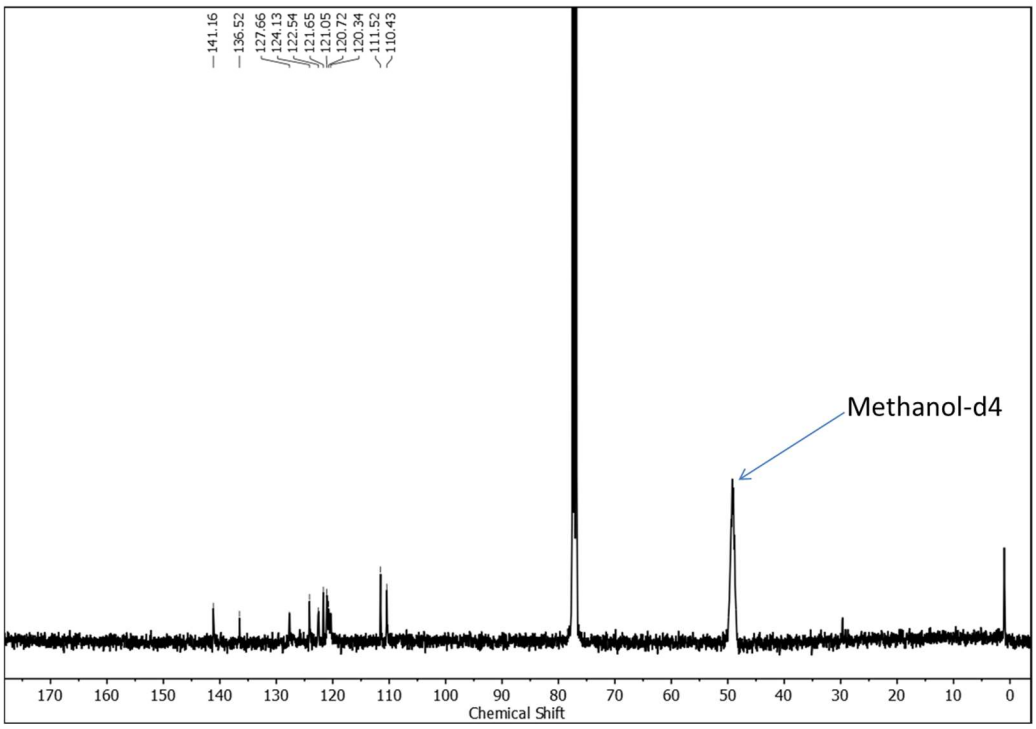


^{1}H NMR (300 MHz, $CDCl_3$ / CD_3OD) of 5a′



^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$ / CD_3OD) of 5a′



4.7 X-RAY CRYSTALLOGRAPHIC DATA AND STRUCTURE

	5m
Formula	C_{23} H_{18} Cl N_3 O_2 S
M_r	435.91
Crystal system	Triclinic
Space group	P -1
a / Å	8.4446(8)
b / Å	10.9035(10)
c / Å	11.1690(10)
α /°	91.912(3)
β /°	90.356(3)
γ /°	97.116(3)
V /Å^3	1019.85(16)
Z	2
D_{calcd} /mg m^{-3}	1.420
μ /mm^{-1}	0.316
θ/°	2.431– 25.740
T /K	273

Table 4.2 Crystallographic data and structural refinement parameters for **5m** (**CCDC NO. – 2297939**)

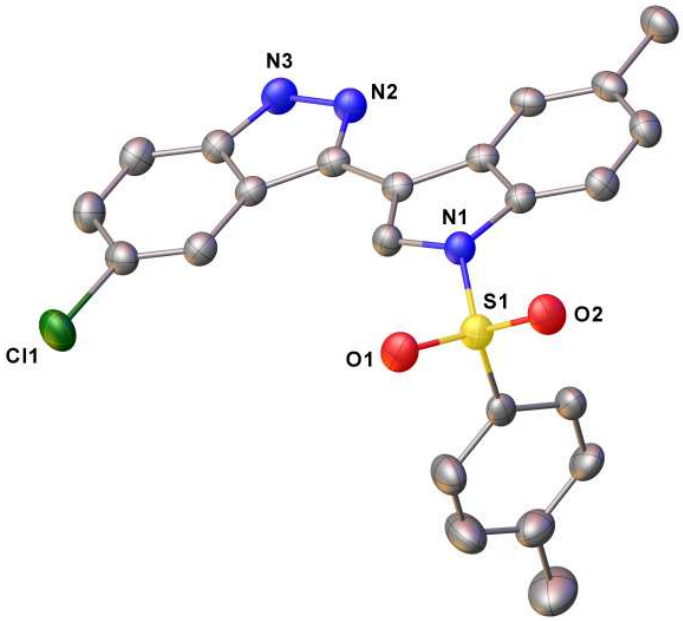


Figure 4.2. SXRD structure of **5m** (*ball and stick* model). Thermal ellipsoids are given at the 50% probability level.

APPENDICES

LIST OF PUBLICATIONS

1. DDQ/$FeCl_3$-Mediated Tandem Oxidative Carbon–Carbon Bond Formation for the Synthesis of Indole–fluorene Hybrid Molecules. **Abhishek Kar**, Baitan Chakraborty, Sandip Kundal, Gopal Rana and Umasish Jana*. *Org. Biomol. Chem.*, **2021**, *19*, 906-910.

2. Iron(iii)-Catalyzed Synthesis of Indole–xanthydrol Hybrid Through Oxidative Cycloisomerization/hydroxylation Reaction. **Abhishek Kar**, Gopal Rana, Rupsa Chanda and Umasish Jana*. *Org. Biomol. Chem.*, **2022**, *20*, 8545-8553.

3. Design and Synthesis of Indazole-Indole Hybrid *via* tert-Butyl nitrite Mediated Cascade Diazotization/Isomerisation/Cyclisation. **Abhishek Kar**, Gopal Rana, Rajkamal Sahoo, Sourav Ghosh and Umasish Jana*. *J. Org. Chem.* **2024**, *89*, 7295–7302.

4. Application of the Povarov Reaction in Biaryls under Iron Catalysis for the General Synthesis of Dibenzo[*a*,*c*]Acridines. Baitan Chakraborty, **Abhishek Kar**, Rupsa Chanda and Umasish Jana*. *J. Org. Chem.,* **2020**, *85*, 14, 9281–9289.

5. DDQ/$Fe(NO_3)_3$-Catalyzed Aerobic Synthesis of 3-Acyl Indoles and an In Silico Study for the Binding Affinity of *N*-Tosyl-3-acyl Indoles toward RdRp against SARS-CoV-2. Gopal Rana, **Abhishek Kar,** Sandip Kundal, Dulal Musib and Umasish Jana*. *J. Org. Chem.,* **2023**, *88*, 838–851.

6. Iron-Catalyzed Carboarylation of Alkynes *via* Activation of π-activated Alcohols: Rapid Synthesis of Substituted Benzofused six-membered Heterocycles. Rupsa Chanda, **Abhishek Kar**, Aniruddha Das, Baitan Chakraborty and Umasish Jana*. *Org. Biomol. Chem.,* **2021**, *19*, 5155-5160.

7. The Synthesis of Indole-3-carbinols (I3C) and Their Application to Access Unsymmetrical bis(3-indolyl)methanes (BIMs) Bearing a Quaternary sp^3-Carbon. Sandip Kundal, Gopal Rana, **Abhishek Kar** and Umasish Jana*. *Org. Biomol. Chem.*, 2022, *20*, 5234-5238.

8. Catalytic Alkyne/Alkene-Carbonyl Metathesis: Towards the Development of Green Organic Synthesis. Aniruddha Das, Soumen Sarkar, Baitan Chakraborty, **Abhishek Kar** and Umasish Jana*. *Curr. Green Chem.* **2020**, *7,* 5–39.

9. Iron(III)-Catalysed Povarov Cyclisation for the Synthesis of Fused Dibenzo[*b*,*f*][1,7]naphthyridine Embedded Arylpyrrolo Scaffolds. Rajkamal Sahoo, Gopal Rana, **Abhishek Kar,** Sourav Ghosh and Umasish Jana*. *Synthesis*, **2025**, *57*, 147–153.

10. Visible-Light-Triggered Organophotoredox-Catalyzed Oxidation of 3-(benzylidine)indoline to Access Indole-3-carbinols and 3-acyl indoles. Sourav Ghosh, Gopal Rana, **Abhishek Kar**, Rajkamal Sahoo and UmasishJana*. (Communicated)

Reprints of the Papers Included in the Thesis

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DDQ/$FeCl_3$-mediated tandem oxidative carbon–carbon bond formation for the Synthesis of indole–fluorene hybrid molecules†

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A series of diverse and complex hybrid structures of indole bearing fluorene were obtained in the presence of DDQ with high regioselectivity under mild conditions from biaryl tethered 3-(methylene)indoline in good to excellent yields. The strategy involves tandem allylic Csp^3–H oxidation and subsequent intramolecular carbon–carbon bond formation. The yield of the product was dramatically improved in the presence of additives such as $FeCl_3$ and molecular sieves (4 Å). A possible mechanism is proposed for this tandem process.

Introduction

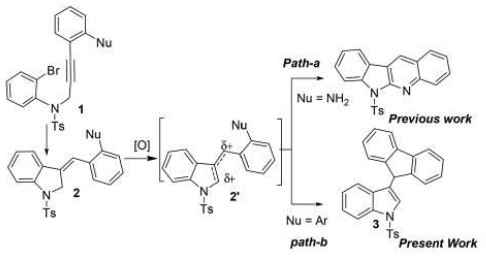
The synthesis of hybrid molecules composed of biologically and photophysically different structural motifs is pertinent in the rational designing and development of new drugs and materials.[1] Indole derivatives have gained much attention as the indole motif is found in many natural products,[2] drug molecules[3] and many functional materials,[4] *e.g.*, in OLED devices. Consequently, the synthesis of functionalized indoles, especially with C-3 substitution, has received considerable attention due to their potential use as drugs for many diseases.[5] Recently, the hybrid structures of indole with various heterocycles and carbocycles have also been developed as promising pharmaceutical agents.[6] Therefore, the development of new indole-based hybrid structures can lead us to newer avenues of application.

The tricyclic fluorene motif is also important to synthetic chemists and plenty of synthetic methods have been developed due to its presence in natural products, extraordinary biological and pharmaceutical activities and optical and electronic properties.[7] Moreover, carbazole/fluorene hybrid derivatives have been widely used in the designing of optoelectronic devices such as organic light emitting diodes (OLED) and organic field effect transistors (OFET).[8] Considering the significance of 3-substituted indoles and fluorene derivatives, we perceive that their hybrid, although barely reported,[9] could appear to possess unique medicinal and photophysical properties.

Therefore, the development of an efficient and new strategy to synthesize indole–fluorene hybrid molecules from easily prepared starting materials in one step is highly desirable.

Recently, we have developed a novel and efficient strategy for the synthesis of C-3 substituted indoles and fused indoles through palladium-catalyzed tandem intramolecular carbopalladation/cross coupling of 2-halo-*N*-propargylhalides (**1**) and isomerisation/cyclisation under various reaction conditions.[6a,10] For example, we have reported that under the conditions of oxidative coupling,[11] the reductive Heck-coupling product, 3-(methylene)indoline (**2**), behaved as an electrophile in the presence of DDQ by the generation of allylic carbocation **2′** through allylic Csp^3–H activation which could be efficiently trapped by a nucleophilic amine (Scheme 1, path-a).[10d]

Our continuing efforts along these lines allow us to report herein a novel access to indole–fluorene hybrid molecules **3** (Scheme 1, path-b) in high yields from easily available starting



Scheme 1 Strategy to access indole–fluorene hybrid molecules.

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†Electronic supplementary information (ESI) available. CCDC 1964540. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/d0ob00413h

materials, which consists of intramolecular reductive Heck coupling with biphenyl tethered *N*-propargyl-2-haloanilide **1** (Nu = Ar) and subsequent oxidative cyclisation of the resultant biphenyl tethered 3-(methylene)indoline **2** (Nu = Ar) through the generation and intramolecular trapping of allylic/benzylic carbocation **2′** by the suitable disposition of the biphenyl unit. Although a few DDQ-mediated oxidative intramolecular C–C bond formation processes have been reported,[12] to the best of our knowledge, the synthesis of fluorene/indolyl-fluorene molecules has not been reported yet. Moreover, the construction of indole–fluorene hybrid molecules in the present strategy is highly attractive due to its high efficiency and environmentally benign nature as no prefunctionalization of substrates is required.

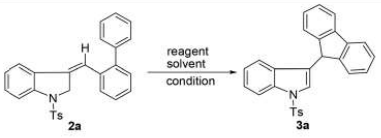
Results and discussion

To accomplish the above idea, we first prepared biphenyl tethered 3-(methylene)indoline **2a** through the reductive Heck cyclisation of **1a** according to our previously developed method[10c,d] (Scheme 2). This cyclisation reaction proceeds through an intramolecular *syn*-carbopalladation *via* a 5-*exo-dig* cyclisation process in preference to 6-*endo-dig* cyclisation with the alkyne unit to give a σ-alkylpalladium(II) intermediate, and subsequent reductive elimination of the Csp^2–[Pd]–H species produces the reductive Heck product **2a** in 82% yield. Presumably, ethanol acts as a hydrogen source for the reductive Heck coupling of substrate **1a**. Following a similar method, a series of biphenyl tethered 3-(methylene)indolines **2b–2o** were prepared in good yields (see the ESI†).

After preparing the series of substrates, we set out to optimize the reaction conditions for the construction of 3-(fluoren-9-yl)indole **3a** from **2a** in the presence of various oxidants, catalysts, and solvents at different temperatures. The results are presented in Table 1. Initially, substrate **2a** was allowed to react with DDQ (1 equiv.) in nitromethane at room temperature. We observed that our strategy worked and the desired product **3a** was obtained in 38% yield in 2 h (Table 1, entry 1) along with a mixture of undesired products. Interestingly, it was also found that upon increasing the amount of DDQ, the yield of the desired product gradually decreased (Table 1, entry 2). From these results, we inferred that the oxidation/cyclisation process was quite sensitive to the amount of the oxidizing agent. Although the yield slightly increased when the reaction was conducted at 60 °C, the formation of undesired products could not be inhibited (Table 1, entry 3). Although we could not isolate any unwanted byproducts for substrate **2a**, however, during the later stage of investigations using substrate **2b**, we were able to isolate and characterise one of the byproducts, 3-indolyl biphenyl ketone, under similar conditions (see the ESI†). We thought that the ketone was formed through an *in situ* generated 3-indolylalcohol *via* nucleophilic attack on the indolyl cation by a little amount of moisture present in the reaction mixture. Therefore, we concluded that due to the formation of some amount of alcohol/ketone, the amount of the intermediate carbocation and hence the final product is reduced. So, to further improve the yield, we studied the reaction in the presence of 4 Å molecular sieves as an additive. Gratifyingly, the yield of the desired product was increased to 68% (Table 1, entry 4) at 60 °C. We proceeded with our trials to check whether Lewis acids could provide better results by reducing the formation of unwanted products. When the said reaction was carried out with 1 equiv. of DDQ in combination with 0.2 equiv. of $FeCl_3$ at rt and at 60 °C, the yields were increased up to 58% and 74%, respectively (Table 1, entries 5 and 6) even in the absence of molecular sieves.

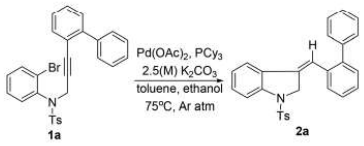
Logical interpolation of the superior effects of both $FeCl_3$ and molecular sieves prompted us to investigate the combination of two additives for even better results. We were delighted to observe that substrate **2a** fruitfully converted to **3a** within 3 hours in the presence of catalytic $FeCl_3$ and 4 Å mole-

Table 1 Optimization of reaction conditions[a]



Entry	Oxidant	Catalyst	Solvent	Temp. (°C)	Time (h)	Yield[b] (%)
1	DDQ		CH_3NO_2	Rt	2	38
2	DDQ[c]		CH_3NO_2	Rt	2	20
3	DDQ		CH_3NO_2	60	2	40
4	DDQ		CH_3NO_2	60	2	68[d]
5	DDQ	$FeCl_3$	CH_3NO_2	Rt	3	58
6	DDQ	$FeCl_3$	CH_3NO_2	60	3	74[e]
7	**DDQ**	**$FeCl_3$**	**CH_3NO_2**	**60**	**3**	**85**[d]
8	DDQ	$FeCl_3$	DCE	60	3	50
9	DDQ	$FeCl_3$	DMF	60	3	nr
10	DDQ	$FeCl_3$	Toluene	60	3	46
11	DDQ	$Fe(OTf)_3$	CH_3NO_2	60	3	35
12	DDQ	AgOTf	CH_3NO_2	60	3	30
13	DDQ	$InCl_3$	CH_3NO_2	60	3	65
14	DDQ	$In(OTf)_3$	CH_3NO_2	60	3	76
15	DDQ	PTSA	CH_3NO_2	60	3	42
16	CAN		CH_3NO_2	60	3	Trace
17	PIDA		CH_3NO_2	60	3	0
18		$FeCl_3$	CH_3NO_2	60	3	nr

[a] Reaction conditions: **2a** (1.0 equiv.), oxidant (1.0 equiv.), catalyst (0.2 equiv.), solvent (2 mL). [b] Isolated pure yield. [c] DDQ (2.0 equiv.). [d] Molecular sieves (4 Å). [e] Without molecular sieves. CAN = Ceric ammonium nitrate, PIDA = phenyliodine(III) diacetate.



Scheme 2 Preparation of substrate **2a**.

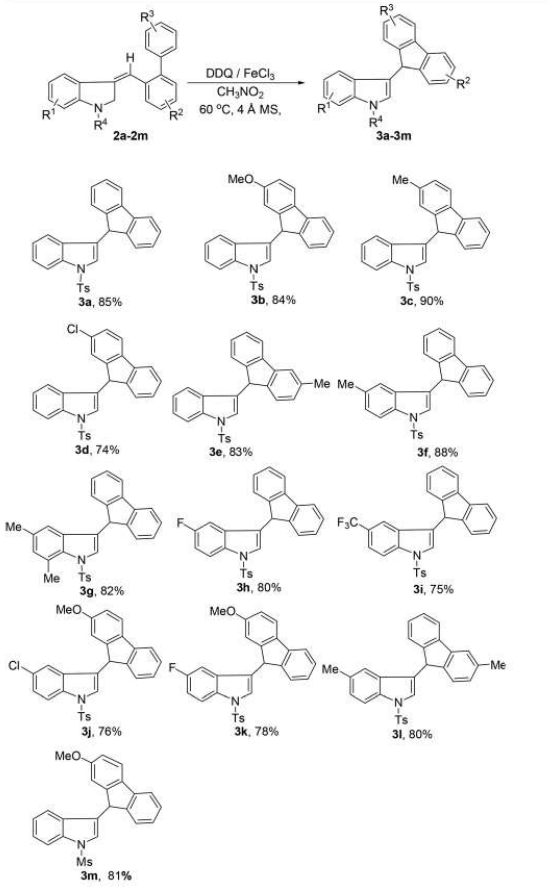
cular sieves with DDQ as an oxidizing agent in $MeNO_2$ at 60 °C, with an excellent yield of 85% (Table 1, entry 7). Switching to solvents such as dichloroethane, DMF and toluene gave inferior results; for example, both DCE and toluene produced **3a** in 50% and 46% yields, respectively, whereas no reaction took place in DMF (Table 1, entries 8–10). Further screening of a series of Fe, Ag and In salts and PTSA (*p*-toluenesulphonic acid) as the catalyst turned out to be far less efficient and **3a** could be obtained in 35%, 30%, 65%, 76% and 42% yields (Table 1, entries 11–15). In addition, other oxidizing agents such as ceric ammonium nitrate (CAN) and phenyliodine(III) diacetate (PIDA) were also examined for this transformation. Unfortunately, a trace amount of **3a** could be observed in the presence of CAN at 60 °C for 3 h, while PIDA failed to execute any transformation (Table 1, entries 16 and 17). $FeCl_3$ alone could not initiate the reaction (Table 1, entry 18). Therefore, DDQ (1.0 equiv.) in combination with $FeCl_3$ (0.2 equiv.) and 4 Å molecular sieves in $MeNO_2$ at 60 °C were established as the optimum conditions for the tandem cross dehydrogenative coupling reaction.

Having optimized the best conditions, we then wanted to expand the substrate scope. The reaction was not significantly affected by the electronic effects of various substituents on each of the aryl rings.

The results are presented in Table 2. The reaction proceeded well with electron-donating groups such as *o*-Me, *p*-Me and *p*-OMe, and led to product formation in high yields (82–90%, Table 2, **3b**, **3c**, and **3e–3g**). Similarly, the introduction of electron-withdrawing groups such as *p*-Cl and *p*-F was also compatible and yielded 74% and 80% of the desired products, respectively (Table 2, **3d** and **3h**). Incorporation of the $-CF_3$ group on the indoline ring did not hamper the reaction and gave the desired product **3i** in a good yield (Table 2, **3i**). Furthermore, the reaction could also furnish the desired 3-(fluoren-9-yl)indole derivatives in very good yields when the indoline and biphenyl moieties contained electronically opposing and similar substituents (Table 2, **3j**, **3k** and **3l**). Moreover, electron-donating groups such as *p*-Me on the aryl group directly attached to alkene were well accommodated and furnished good yields of the desired products, 83% and 80% (Table 2, **3e** and **3l**), respectively. Compounds having electron-donating *p*-Me and *p*-OMe groups and the electron-withdrawing *p*-Cl group on the aryl motif of the biphenyl unit which were directly involved in the nucleophilic attack also underwent the DDQ-mediated oxidative intramolecular coupling and afforded the hybrid products in good to excellent yields (Table 2, **3b**, **3c**, **3d**, **3j** and **3k**). Along this line, it is worth mentioning that the tosyl protecting group on nitrogen, when replaced with the mesyl group, gave an impressive result as well (Table 2, **3m**).

Due to the growing interest in the synthesis and potential pharmacological applications of azaindole molecules, we next explored our present tandem strategy for the synthesis of 3-(fluoren-9-yl)-7-azaindole derivatives. The results are presented in Scheme 3. The precursor molecules, **2n** and **2o**, were prepared in 75% and 70% yields through reductive carbopalladation from the corresponding *N*-propargyl derivative of 2-amino-3-bromo pyridine in the presence of $Pd(OAc)_2/PCy_3$ and K_2CO_3 in a toluene–ethanol mixture at 75 °C. Pleasantly, the compounds **2n** and **2o** were smoothly converted to 7-azain-

Table 2 Scope of substrates[a,b]



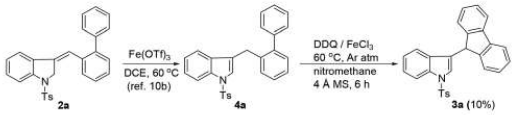
[a] Reaction conditions: **2** (0.15 mmol), DDQ (0.15 mmol), $FeCl_3$ (0.03 mmol), molecular sieves (4 Å), $MeNO_2$ (1.5 mL), 60 °C, Ar atm. [b] Isolated yields.

Scheme 3 Synthesis of 7-azaindole–fluorene derivatives.

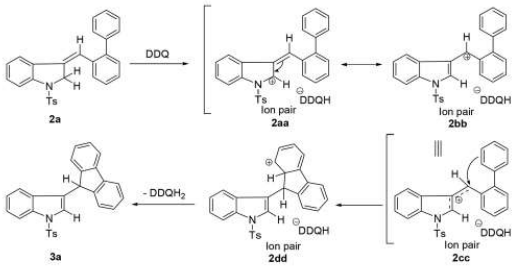
dole tethered fluorene derivatives, **3n** and **3o**, in 66% and 68% yields, respectively, in 5 h at 60 °C. All the structures were characterized by ^{1}H and ^{13}C NMR and HRMS and one of the structures, **3a**, was confirmed by X-ray diffraction (see the ESI†).

For a better understanding the reaction mechanism, we prepared substrate **4a** by the isomerisation of **2a** according to our earlier report.[10b] Then, we performed the present cyclization strategy with the isomerised product **4a** according to our present protocol (Scheme 4). It was noticed that the reaction was sluggish and most of the starting material **4a** remained even after 6 hours. Merely 10% of the desired product **3a** was obtained. It is evident that simple generation of the benzylic cation by the DDQ-mediated oxidation is not efficient for this smooth cyclization. Rather, aromatization of substrate **2a** *via* allylic Csp^3–H oxidation is the driving force for the aforementioned tandem cyclization process.

Based on our experimental results and previous literature reports, a tentative mechanism for the DDQ-mediated oxidative cyclisation is outlined in Scheme 5. In the literature, both ionic and radical mechanisms have been reported for DDQ-mediated oxidations, depending on the substrates and reaction conditions.[13] Generally, the DDQ-mediated radical pathway is established by the inhibition of the reaction in the presence of a radical scavenger.[14] However, we noticed that in the present transformation, the radical scavenger, TEMPO, could not suppress the yield of the desired products, which implies that a cationic pathway must be involved in the initial oxidative step. Therefore, we proposed the formation of an ion pair **2aa**/DDQH$^-$ through a hydride ion transfer from the allylic Csp^3–H site of substrate **2a** to DDQ. The allylic carbocation intermediate **2aa** is stabilized by resonance and driven to furnish benzylic cation **2bb** due to aromatic stabilization. Then, intramolecular electrophilic substitution took place by the *o*-aryl group of biphenyl unit with the indolyl cation **2cc**. Finally, aromatization was achieved by the removal of a proton by DDQH$^-$ leading to the desired 3-fluorenyl indole derivative **3a**. The exact roles of $FeCl_3$ and molecular sieves have not yet been ascertained. But we conclude that the yield of the products was increased in the presence of 4 Å molecular sieves/$FeCl_3$ by increasing the availability of indolyl cation **2cc** for intramolecular aromatic electrophilic cyclisation. While molecular sieves can prevent the *in situ* generation of alcohols through the removal of water from the reaction mixture, $FeCl_3$ can revert the alcohol, if generated, back to the indolyl cation.[10e,15] The role of $FeCl_3$ was also evident in restricting the formation of unwanted by-products.



Scheme 4 A comparative study.



Scheme 5 Plausible mechanistic pathway.

Conclusions

In summary, we have developed a new, efficient and highly regioselective synthesis of 3-fluorenyl-indoles/azaindoles involving tandem allylic Csp^3–H oxidation/intramolecular C–C bond formation in the presence of DDQ/$FeCl_3$ in high yields. The use of the reductive Heck coupling reaction for the preparation of precursor substrates makes this strategy attractive for an easy access to complex and diverse indole–fluorene hybrid molecules. Our efforts for the development of new hybrid molecules based on this strategy are currently in progress.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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Notes and references

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Iron(III)-catalyzed synthesis of indole–xanthydrol hybrid through oxidative cycloisomerization/hydroxylation reaction†

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An efficient one-pot synthesis of an indole–xanthydrol hybrid is described in the presence of catalytic combinations of $Fe(NO_3)_3$/$FeCl_3$. This strategy involves a series of reactions such as allylic oxidation, isomerisation, cyclisation and hydroxylation reactions in a tandem manner. This protocol offers several advantages including mild reaction conditions, operational simplicity, high selectivity, good yields and easily accessible starting materials. The synthetic utility of this protocol was further demonstrated by the one-pot synthesis of the highly substituted xanthene containing bis-indolylmethane derivative. The preliminary mechanistic studies reveal that the reaction is initiated by the generation of radicals in the presence of catalytic iron(III)-salts.

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Introduction

Hybrid molecules with two different structural domains of biological interest exhibit better performance in terms of biological and photophysical activities compared to their individual units. Therefore, the design and development of efficient synthetic routes for easy access to such complex hybrid molecular scaffolds is an important area of research in modern organic synthesis and medicinal chemistry.[1] In this regard, xanthene and its derivatives are found to be an important core, present in numerous natural products, synthetic drug candidates,[2] photodynamic therapeutic agents[3] and in optoelectronic devices.[4] In addition, xanthene based hybrid molecules are also attractive because of their pharmaceutical activities, exemplified by their use as anti-breast cancer agents, selective estrogen receptor modulators *etc*.[5] It is noteworthy that xanthene-9-ol derivatives have also been proven as prominent cancer cell cytotoxic agents because of their 9-OH functionality.[6a–c] Therefore, the synthesis of functionalized xanthene has received much attention in recent years.[7]

Similarly, functionalized indoles, especially substitution at the C-3 position, are of enormous importance for their wide array of applications in natural/non-natural products, synthetic drugs, agrochemicals and in materials chemistry.[8a–f] Most biologically relevant indole alkaloids are C-3-substituted, for example, natural amino acid tryptophan and the neurotransmitter serotonin.[8g] Therefore, the development of newer methodologies and reactions for the construction of varieties of C-3 substituted indoles has received much attention.[8h]

We believe that hybrids of xanthene and indole subunits with a methylene group may have good biological and photophysical activities. To date, only a few methods have been established to construct indole tethered xanthene molecules,[9] including intermolecular electrochemical cross-dehydrogenative coupling of indole with xanthene,[9a] intermolecular nucleophilic substitution of xanthen-9-ol with indole[9b] and iron(III)-catalyzed cascade arene–aldehyde addition/cyclisation of 2-aryloxybenzaldehyde with indole.[9c] Therefore, the development of new and environmentally friendly protocols to construct indole tethered xanthene derivatives is highly desirable.

In recent years, we have demonstrated that 3-benzylidineindoline derivatives could be easily accessible *via* intramolecular carbopalladation of alkyne tethered 2-haloarene, serving as versatile building blocks in the efficient synthesis of C-3 substituted indoles and fused indoles *etc*.[10] For example, 3-benzylidineindolines **3a** and **3b** were converted to substituted benzo[*b*]carbazole **3a′** derivatives (Scheme 1a) and 3-(1-indenyl) indoles **3b′** (Scheme 1b) in good yields *via* iron(III)-catalyzed cycloisomerisation. We have also reported the efficient synthesis of important molecules such as indoloquinoline **3c′** (Scheme 1c) and indolylfluorene **3d′** derivatives (Scheme 1d) *via* DDQ mediated allylic oxidation and subsequent cyclisation of 3-benzylidineindoline **3c** and **3d**, respectively. In continuation of our investigation exploring methods for the construction of varieties of heterocyclic scaffolds from 3-benzylidineindoline, we herein report an iron-catalyzed tandem oxidative

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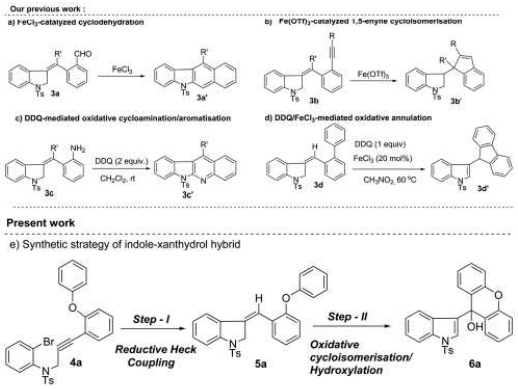


Scheme 1 Reactions of 3-benzylideneindoline derivatives.

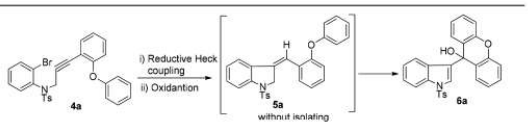
cycloisomerization/hydroxylation protocol for the synthesis of indole–xanthydrol hybrid (**6a**) in good yields (Scheme 1e).

Results and discussion

To establish the above two-step protocol (Scheme 1e), we first attempted to prepare the substrate **5a** *via* reductive Heck coupling of substituted 2-bromo-*N*-(3-(2-phenoxyphenyl)prop-2-ynyl)-*N*-tosylbenzenamine **4a** according to our previous work.[11a] We observed that of $Pd(OAc)_2$ (5 mol%), tricyclohexylphosphine (10 mol%), and 2.5 M aqueous K_2CO_3 in combination with ethanol and toluene at 75 °C for 2 hours gave the best result. However, we noticed that during the separation of the crude products over silica gel column chromatography, a part of the reductive product **5a** was isomerized to produce C-3 alkylated indoles.[11b] To avoid this isomerization and unnecessary tedious separation, we decided to execute the second stage reaction with the crude product **5a**.

Next, we focused on the optimization of the second step reaction to obtain the indole–xanthene derivative by employing various oxidants, co-catalysts, solvents and reaction temperature. The results are summarized in Table 1. Initially, we probed our model substrate **5a** with 1 equiv. of DDQ in combination with 20 mol% $FeCl_3$ and 4 Å molecular sieves in $MeNO_2$ at 60 °C under Ar atm, according to our previous work.[10c] Unfortunately, this strategy did not work well and the desired product **6a** was obtained in 5% yield after 3 h, along with a mixture of unwanted products (Table 1, entry 1). Next, we switched our thoughts from the stoichiometric use of oxidants and decided to develop a catalytic transformation of the present model substrate **5a** into desired product **6a** under environmentally benign conditions. As part of our research program in the development of cheap, nontoxic and environmentally benign iron-catalysis,[10a,e,f,11] herein, we decided to use iron-salts as the oxidant. So, when the reaction was conducted with 30 mol% $Fe(NO_3)_3{\cdot}9H_2O$ as the oxidizing agent in

Table 1 Optimization of the 2nd step's reaction condition[a(i)]



Entry	Oxidant	Catalyst	Solvent	Temp. (°C)	Yield[b] (%)
1	DDQ[c]	$FeCl_3$ [d]	CH_3NO_2	60	5[e]
2	$Fe(NO_3)_3{\cdot}9H_2O$		DCE	rt	nr
3	$Fe(NO_3)_3{\cdot}9H_2O$		DCE	70	nr
4	$Fe(NO_3)_3{\cdot}9H_2O$		CH_3NO_2	rt	30
5	$Fe(NO_3)_3{\cdot}9H_2O$		CH_3NO_2	70	56
6	$Fe(NO_3)_3{\cdot}9H_2O$		CH_3NO_2	85	44
7	$Fe(NO_3)_3{\cdot}9H_2O$	$FeCl_3$	CH_3NO_2	70	70
8	$Fe(NO_3)_3{\cdot}9H_2O$	$FeCl_3$	CH_3CN	70	78
9	$Fe(NO_3)_3{\cdot}9H_2O$	$FeCl_3$	THF	70	10
10	$Fe(NO_3)_3{\cdot}9H_2O$	$FeCl_3$	DMF	70	nr
11	$Fe(NO_3)_3{\cdot}9H_2O$	$FeCl_3$	Toluene	70	24
12	$Fe(NO_3)_3{\cdot}9H_2O$	$Fe(OTf)_3$	CH_3CN	70	74
13	$Fe(NO_3)_3{\cdot}9H_2O$	$InCl_3$	CH_3CN	70	65
14	$Fe(NO_3)_3{\cdot}9H_2O$	$In(OTf)_3$	CH_3CN	70	62
15	$Fe(NO_3)_3{\cdot}9H_2O$	PTSA	CH_3CN	70	53
16	$Fe(NO_3)_3{\cdot}9H_2O$	TfOH	CH_3CN	70	45
17	—	$FeCl_3$	CH_3CN	70	15
18	—	$FeCl_3{\cdot}6H_2O$	CH_3CN	70	20
19	$Al(NO_3)_3{\cdot}9H_2O$	$FeCl_3$	CH_3CN	70	59
20	$Ce(NO_3)_3{\cdot}6H_2O$	$FeCl_3$	CH_3CN	70	51
21	$Cu(NO_3)_2{\cdot}3H_2O$	$FeCl_3$	CH_3CN	70	64
22	$Fe(NO_3)_3{\cdot}9H_2O$	$FeCl_3$	CH_3CN	70	60[f]

[a] Reaction conditions: (i) **4a** (1.0 equiv.), $Pd(OAc)_2$ (0.05 equiv.), PCy_3 (0.1 equiv.), toluene (2 mL), EtOH (2 mL), aq. K_2CO_3 (2.5 M, 2 mL), 75 °C, Ar atm, 2 h; (ii) oxidant (0.3 equiv.), catalyst (0.3 equiv.), solvent (3 mL), O_2 atm. [b] Isolated yield. [c] 1 equiv. used. [d] 20 mol% used. [e] Ar atm. [f] Without molecular oxygen.

1,2-dichloroethane (DCE) at room temperature under O_2, regrettably the reaction did not proceed even after raising the temperature to 70 °C (Table 1, entries 2 and 3). However, when the reaction was performed in $MeNO_2$ in the presence of 30 mol% $Fe(NO_3)_3{\cdot}9H_2O$ at various temperatures under O_2 for 3 hours (Table 1, entries 4–6), the reaction afforded the desired indole-xanthene-9-ol, **6a** at 30% yield even at room temperature. At 70 °C the desired **6a** was formed in 56% overall yield in two steps along with a few by-products (Table 1, entry 5). However, further increasing the temperature to 85 °C reduced the yield to 44% (Table 1, entry 6). In our previous DDQ mediated oxidative cycloisomerisation process,[10c] we reported that the yield of the product improved in the presence of the catalytic combination of $FeCl_3$.

Similarly, in the present study, when the reaction was carried out in combination with 30 mol% $FeCl_3$ as co-catalyst at 70 °C under O_2, the overall yield of the desired product **6a** was increased up to 70% (Table 1, entry 7). To further improve the yield, a series of solvents such as MeCN, THF, DMF and toluene were screened in the second step of the reaction (Table 1, entries 8–11). Encouragingly, the yield of the desired product **6a**, was further improved up to 78%, (Table 1, entry 8) in MeCN. Whereas, the yield was lower in both THF and toluene, producing **6a** in 10% and 24% yields, respectively

(Table 1, entries 9 and 11). However, in DMF substrate **5a** remains unreacted (Table 1, entry 10). Further screening with the series of Fe(III), In(III), PTSA and TfOH as co-catalysts, provided no remarkable change in the yield – except for $Fe(OTf)_3$ (Table 1, entries 12–16). Surprisingly, 15% and 20% yields of **6a** were obtained upon exposing reactant **5a** individually to 30 mol% $FeCl_3$ and 30 mol% $FeCl_3{\cdot}6H_2O$ in CH_3CN, respectively (Table 1, entries 17 and 18). Switching to other metal nitrates such as $Al(NO_3)_3{\cdot}9H_2O$, $Ce(NO_3)_3{\cdot}6H_2O$, $Cu(NO_3)_2{\cdot}3H_2O$ in combination with $FeCl_3$ was less effective, compared to $Fe(NO_3)_3{\cdot}9H_2O$ (Table 1, entries 19–21). In addition, we have also studied the reaction without molecular oxygen (Table 1, entry 22), it was observed that the yield of the product was reduced. Therefore, molecular oxygen is essential for this sequential oxidative cyclisation/hydroxylation process as a terminal oxidant. Hence, the successful transformation of substrate **5a** into desired product **6a** in the presence of 30 mol% $Fe(NO_3)_3{\cdot}9H_2O$ in combination with 30 mol% $FeCl_3$ in CH_3CN at 70 °C under O_2 for 3 hours, provided the optimum reaction conditions.

It is noteworthy to mention that a common hydroxyl unit between the indole and xanthene scaffold in **6a** make this hybrid molecule a more attractive substructure of both xanthene-9-ol [6b] and indole-3-carbinol [6d,e] in biomedical research.

After elucidating the optimum reaction conditions, we decided to explore the robustness of this methodology with a series of crude substrates and the results are summarized in Table 2. The substrate without any substituent on each aryl ring was reacted smoothly to afford the corresponding product **6a** in 78% yield (Table 2, entry 1). The electronic effect on both the phenyl ring of the biaryl ether unit was investigated. The experimental results show that the reaction worked well with different electron-donating groups such as *p*-OMe and *p*-Me, but also with electron-withdrawing groups such as *p*-Cl, to give the desired product in high yields of 70%, 74%, 76% and 71% (Table 2, entries 2–5). Next, we examined the effect of different substituents at the 2-haloaniline nucleus. The 2-haloaniline moiety bearing electron-donating groups such as *p*-Me, *o*-Me and *p*-OMe were well tolerated under the present reaction conditions, providing the indole–xanthydrol hybrid in 79%, 69% and 81% yield, respectively (Table 2, entries 6–8). Halogens like –F, –Cl at the *para*-position of this 2-haloaniline scaffold underwent $Fe(NO_3)_3{\cdot}9H_2O/FeCl_3$ catalyzed sequential oxidative C–C coupling and hydroxylation without any difficulties, and offered the hydroxylated product in 82% and 66% yield, respectively (Table 2, entries 9 and 10). Furthermore, the simultaneous installation of electronically opposing and similar substituents on both the alkyne connected 2-haloaniline and biaryl ether unit were also retained for reductive heck coupling and subsequent iron catalyzed oxidative cycloisomerization/hydroxylation, and delivered the final products in moderate to good yields over the two steps (Table 2, entries 11–13). Moreover, our designed compounds, having more than one –Me substituent, were also successfully transformed into desired products, **6g** and **6m** in 69% and 75% yields, respectively (Table 2, entries 7 and 13).

All the structures were characterized by ^1H NMR, ^{13}C NMR and HRMS data (see ESI†). The structure of **6a** was further confirmed by X-ray structure analysis (Fig. 1).

To shed light on the mechanistic pathway for this transformation, several control experiments were conducted under different reaction conditions as depicted in Scheme 2. First of all when the reaction was quenched just after 30 min following TLC, we were able to isolate an intermediate indole–xanthene hybrid, **5ad** (Scheme 2, 1) as a major product along with the minor amount of desired product **6a**. Furthermore, when **5ad** was allowed to react under the standard reaction conditions, quantitative conversion of **5ad** into the desired product **6a** within 1.5 h in 99% yield (Scheme 2, 2). This result indicates that the reaction proceeds through the intermediate **5ad** (characterized by XRD and NMR spectroscopy; see ESI†). There are possibilities that the reaction could proceed through oxidation followed by isomerisation or *vice versa*. To verify this we prepared the isomerized substrate **7** by employing our previous method [11b] (see ESI†) and performed the reaction using the currently developed procedure, but no reaction took place (Scheme 2, 3). This experiment implies that the reaction does not proceed through isomerisation followed by oxidation of the substrate. Therefore, aromatization of the substrate **5a** is the driving force for the allylic C–H oxidation/isomerisation. Moreover, the yield of product **6a** was reduced to 15% when the reaction was carried out in the presence of radical scavenger 1.5 equiv. TEMPO (Scheme 2, 4). This result suggests that the reaction proceeds through a radical pathway. To further elucidate the mechanism, we allowed substrate **5i** to react with catalytic $Fe(NO_3)_3{\cdot}9H_2O$ in the absence of $FeCl_3$, one of the by-products, acylated indole **8**, was isolated and characterized (Scheme 2, 5) (see ESI†). This experimental observation suggests that ketone **8** was formed *via in situ* generated intermediate 3-indolyl alcohol.

Based on our control experiments and previous literature reports,[12] a tentative mechanism for sequential oxidative cyclisation and hydroxylation is depicted in Scheme 3. Initially, a NO_2 radical was formed by partial decomposition of $Fe(NO_3)_3{\cdot}9H_2O$, which abstracted the allylic Csp^3–H of **5a** to form allylic radical **5aa**, which subsequently isomerized to a benzyl radical **5ab**. Then, this resonance stabilized radical reacts with Fe(III) salt to form indolyl cation intermediate **5ac** *via* a single electron transfer (SET) process followed by electrophilic attack by *ortho*-OPh ring (path-a, Scheme 3) to give intermediate indole–xanthene hybrid **5ad**. The cationic intermediate **5ac** could be trapped by H_2O (path-b, Scheme 3) as present in the reaction medium to give indolylalcohol **5ae**. $FeCl_3$ can also activate this π-activated alcohol [10a] **5ae** to increase the availability of indolyl cationic intermediate **5ac** for electrophilic substitution by the *ortho*-aryl ether ring. In the absence of $FeCl_3$ this benzylic alcohol **5ae** could be further oxidized by $Fe(NO_3)_3{\cdot}9H_2O$ to form biphenyl etheryl 3-indolyl ketone **5ae′** as the by-product. As HNO_2 is an unstable compound, its rapid decomposition gives NO and NO_2, where NO can reoxidise to NO_2 by molecular O_2. Finally, the NO_2 radical again may abstract the highly labile tertiary benzylic H-atom from the

Table 2 Synthesis of complex hybrid structure of indole bearing xanthene-9-ol molecules[a]

Entry	Substrate	Product	Entry	Substrate	Product	Entry	Substrate	Product
1.	4a	6a, 78%	5.	4e	6e, 76%	9.	4i	6i, 82%
2.	4b	6b, 70%	6.	4f	6f, 79%	10.	4j	6j, 66%
3.	4c	6c, 74%	7.	4g	6g, 69%	11.	4k	6k, 60%
4.	4d	6d, 71%	8.	4h	6h, 81%	12.	4l	6l, 55%
			13.	4m	6m, 75%			

[a] Reaction conditions: (i) **4a** (0.2 mmol), $Pd(OAc)_2$ (0.01 mmol), PCy_3 (0.02 mmol), toluene (2 mL), EtOH (2 mL), aq. K_2CO_3 (2.5 M, 2 mL), 75 °C, Ar atm, 2 h; (ii) $Fe(NO_3)_3{\cdot}9H_2O$ (0.06 mmol), $FeCl_3$ (0.06 mmol), MeCN (3 mL), 70 °C, O_2 atm, 3 h.

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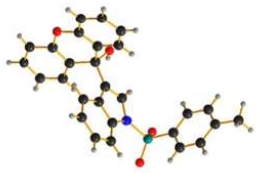
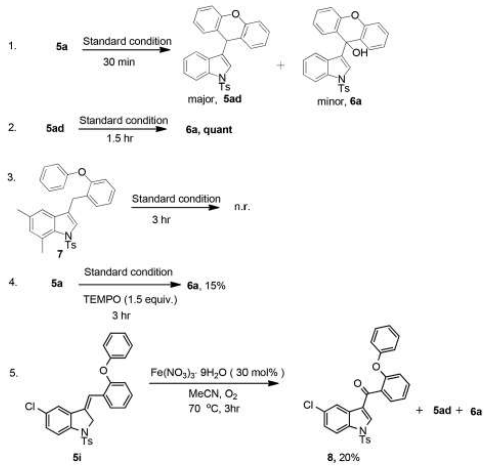
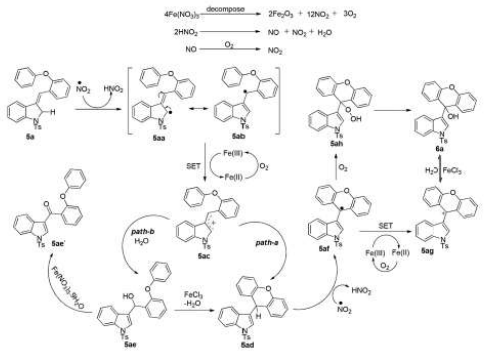


Fig. 1 X-ray crystallographic structure of **6a** (CCDC no. 2190254†).

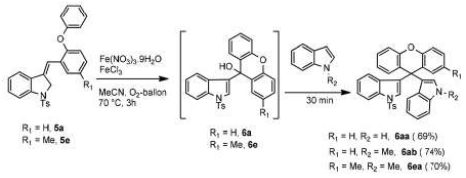


Scheme 2 Control experiments.



Scheme 3 Plausible mechanism for iron catalyzed sequential aerobic oxidation of **5a**.

intermediate **5ad** to generate a resonance stabilized tertiary indolyl radical **5af**. This is readily converted into benzylic cation **5ag** through oxidation with Fe(III) salts and reversible trapping of water leading to alcohol **6a**. Although, we have shown that molecular oxygen acts as the terminal oxidant, the trapping of **5af** with molecular oxygen to the corresponding



Scheme 4 Synthesis of xanthene containing bis-indolylmethane derivatives.

hydroperoxide intermediate **5ah** and subsequent hydrolysis to **6a**, cannot be ruled out as the reaction yield increased significantly in the presence of molecular oxygen.

The existence of a carbocation in the presence of Fe(III)-salt under the reaction conditions was further demonstrated by trapping the carbocation with the other nucleophiles – indole and *N*-methyl indole. When indole was added directly to the reaction mixture after the formation of **6a** (monitored by TLC), an interesting xanthene fused bis-indolylmethane derivative **6aa** was afforded in 69% overall yield (Scheme 4). Following this one-pot method, we were also able to synthesise substituted 3-(9-indol-3-yl-9*H*-xanthen-9-yl)-indole derivatives **6ab** and **6ea** in overall good yields, (Scheme 4, 74% and 70%) using *N*-methyl indole as the nucleophile.

Conclusions

In conclusion, we have developed a novel and efficient Fe$(NO_3)_3$/$FeCl_3$-catalyzed synthesis of indole–xanthydrol hybrid scaffold in the presence of molecular oxygen as the terminal oxidant. The present strategy involves Fe$(NO_3)_3$ catalyzed allylic oxidation/isomerisation/cyclisation/hydoxylation *via* a radical intermediate. A variety of indole–xanthydrol hybrids could easily be synthesised by this method in high yields. The important features of this reaction are mild reaction conditions, operational simplicity, ease of preparation of starting materials, and environmentally benign reaction conditions. The synthetic utility of this protocol was demonstrated by the one-pot synthesis of the xanthene tethered bis-indolylmethane derivative. We believe that synthetic chemists, as well as medicinal chemists will find this chemistry interesting and this newly developed strategy will open up new avenues for the synthesis of various indole containing hybrid molecules.

Experimental

General information

All ^{1}H NMR spectral data were recorded using a Bruker 300 and 400 (300 and 400 MHz) spectrometer in $CDCl_3$ solutions expressing chemical shifts in parts per million (ppm, δ), and are referenced to $CHCl_3$ (δ = 7.26 ppm) as an internal standard. All coupling constants are absolute values and are expressed in Hz. The description of the signals include: s = singlet, d =

doublet, t = triplet, m = multiplet, dd = doublet of doublets and brs = broad singlet, td = triplet of doublet. ^{13}C NMR spectra were recorded with a Bruker 300 and 400 (75 and 100 MHz, respectively) spectrometer as solutions in $CDCl_3$ with complete proton decoupling. Chemical shifts are expressed in parts per million (ppm, δ) and are referenced to $CDCl_3$ (δ = 77.0 ppm) as the internal standard. High-resolution mass spectra (HRMS) were performed with a Q-tof Micro YA263 spectrometer in acetonitrile solvent. The molecular fragments are quoted as the relation between mass and charge (m/z). The routine monitoring of reactions was performed with silica gel coated glass slides (Merck, silica gel G for TLC), and pre-coated Al plate, which were analyzed with iodine and UV light, respectively. Solvents, reagents and chemicals were purchased from Aldrich, Fluka, Merck, SRL, Spectrochem and Process Chemicals. All reactions involving moisture sensitive reactants were executed with oven-dried glassware.

Representative experimental procedure and characterization data for the synthesis of 9-(1-tosyl-1*H*-indol-3-yl)-9*H*-xanthen-9-ol (6a) without isolation of precursor (5a). To a solution of **4a** (106 mg, 0.2 mmol) in toluene (2 mL) and ethanol (2 mL), we added aq. K_2CO_3 solution (2.5 M, 2 mL), PCy_3 (6 mg, 0.02 mmol) and $Pd(OAc)_2$ (2 mg, 0.01 mmol) successively. The resulting solution was stirred at 75 °C under an argon atmosphere for 2 h. After the completion of the reaction (monitored by TLC), the crude reaction mixture was extracted with EtOAc. The organic extract was washed with brine solution, dried over anhydrous Na_2SO_4 and concentrated. The crude product **5a** was dissolved in acetonitrile (3 mL), and $Fe(NO_3)_3{\cdot}9H_2O$ (24 mg, 30 mol%) and $FeCl_3$ (10 mg, 30 mol%) were added. The reaction was continued at 70 °C for 3 h under an oxygen atmosphere. After the completion of the reaction (monitored by TLC) the crude reaction mixture was extracted with DCM. The organic extract was washed with a brine solution, dried over anhydrous Na_2SO_4 and concentrated. The product was subjected to column chromatography (silica gel, 60–120 mesh), eluting with hexane/EtOAc 93 : 7 (v/v) to afford product **6a** as a white solid (73 mg, 0.16 mmol, 78%).

9-(1-Tosyl-1*H*-indol-3-yl)-9*H*-xanthen-9-ol (6a). 73 mg (78%); white crystalline solid; m.p. 176–180 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.09 (s, 1H), 7.98 (d, J = 8.4 Hz, 1H), 7.87 (d, J = 8.0 Hz, 2H), 7.39–7.27 (m, 8H), 7.20 (t, J = 7.8 Hz, 1H), 7.01 (t, J = 7.4 Hz, 2H), 6.92 (t, J = 7.6 Hz, 1H), 6.66 (d, J = 8.0 Hz, 1H), 2.69 (s, 1H), 2.43 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 149.81, 144.95, 136.05, 135.22, 129.87, 129.73, 128.92, 128.74, 128.32, 126.90, 124.50, 124.44, 123.75, 123.62, 123.24, 120.43, 116.65, 113.78, 67.83, 21.60; HRMS: m/z calcd for $C_{28}H_{21}NO_4S$: $[M + H]^+$ 468.1270, found 468.1273.

Compounds **6b** to **6m** were synthesized following the above experimental method.

2-Methoxy-9-(1-tosyl-1*H*-indol-3-yl)-9*H*-xanthen-9-ol (6b). 70 mg (70%); white solid; m.p. 108–110 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.02 (s, 1H), 7.94 (dt, J = 8.4, 0.9 Hz, 1H), 7.84–7.78 (m, 2H), 7.29 (d, J = 1.5 Hz, 1H), 7.26–7.22 (m, 3H), 7.20 (d, J = 1.3 Hz, 1H), 7.19–7.12 (m, 2H), 6.98–6.83 (m, 3H), 6.73 (d, J = 3.0 Hz, 1H), 6.65 (dt, J = 8.0, 1.0 Hz, 1H), 3.56 (s, 3H), 2.64 (s, 1H), 2.36 (s, 3H); ^{13}C NMR (101 MHz, chloroform-D) δ 155.58, 149.97, 144.97, 144.01, 136.10, 135.31, 129.92, 129.80, 129.73, 129.15, 128.79, 128.35, 126.91, 124.89, 124.60, 123.87, 123.53, 123.43, 123.36, 120.45, 117.71, 117.08, 116.62, 113.83, 111.60, 68.20, 55.50, 21.66; HRMS: m/z calcd for $C_{29}H_{23}NO_5S$: $[M + H]^+$ 498.1375, found 498.1370.

2-Methyl-9-(1-tosyl-1*H*-indol-3-yl)-9*H*-xanthen-9-ol (6c). 71 mg (74%); white solid; m.p. 108–112 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.05 (s, 1H), 7.94 (dt, J = 8.4, 0.9 Hz, 1H), 7.85–7.80 (m, 2H), 7.30 (dd, J = 8.4, 1.6 Hz, 1H), 7.27 (d, J = 1.1 Hz, 1H), 7.25 (d, J = 1.7 Hz, 1H), 7.23–7.21 (m, 1H), 7.20–7.11 (m, 2H), 7.10 (dd, J = 2.2, 1.3 Hz, 2H), 7.01 (dt, J = 1.8, 0.9 Hz, 1H), 6.94 (ddd, J = 8.0, 7.0, 1.4 Hz, 1H), 6.87 (ddd, J = 8.1, 7.2, 1.0 Hz, 1H), 6.60 (dt, J = 8.0, 1.0 Hz, 1H), 2.61 (s, 1H), 2.37 (s, 3H), 2.14 (s, 3H); ^{13}C NMR (101 MHz, chloroform-D) δ 149.92, 147.76, 144.97, 136.17, 135.29, 133.04, 130.76, 130.09, 129.91, 129.73, 129.28, 128.86, 128.65, 128.49, 126.94, 124.55, 124.38, 123.92, 123.65, 123.49, 123.33, 120.50, 116.67, 116.45, 113.86, 67.90, 21.67, 20.81; HRMS: m/z calcd for $C_{29}H_{23}NO_4S$: $[M + H]^+$ 482.1426, found 482.1244.

2-Chloro-9-(1-tosyl-1*H*-indol-3-yl)-9*H*-xanthen-9-ol (6d). 71 mg (71%); white solid; m.p. 103–105 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.04 (s, 1H), 7.95 (d, J = 8.4 Hz, 1H), 7.83–7.78 (m, 2H), 7.36–7.28 (m, 3H), 7.25–7.19 (m, 3H), 7.18–7.16 (m, 2H), 7.15 (d, J = 1.4 Hz, 1H), 7.00 (ddd, J = 8.2, 7.0, 1.4 Hz, 1H), 6.89 (td, J = 7.6, 1.0 Hz, 1H), 6.59 (d, J = 8.0 Hz, 1H), 2.40 (s, 1H), 2.37 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 149.45, 148.29, 145.11, 136.15, 134.95, 130.02, 129.97, 128.79, 128.66, 128.43, 128.36, 128.07, 126.76, 125.94, 124.69, 124.04, 123.81, 123.78, 123.40, 120.14, 118.24, 116.66, 113.97, 67.65, 21.65; HRMS: m/z calcd for $C_{28}H_{20}ClNO_4S$: $[M + H]^+$ 502.0880, found 502.0891.

2-Methyl-9-(1-tosyl-1*H*-indol-3-yl)-9*H*-xanthen-9-ol (6e). 71 mg (76%); white solid; m.p. 105–109 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.07 (s, 1H), 7.96 (d, J = 8.4 Hz, 1H), 7.84 (d, J = 8.1 Hz, 2H), 7.34–7.27 (m, 3H), 7.24 (d, J = 2.3 Hz, 1H), 7.22–7.07 (m, 4H), 7.03 (s, 1H), 6.95 (dd, J = 8.1, 6.8 Hz, 1H), 6.89 (t, J = 7.6 Hz, 1H), 6.63 (d, J = 7.9 Hz, 1H), 2.39 (s, 3H), 2.16 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 149.85, 147.69, 144.93, 136.11, 135.20, 132.98, 130.69, 129.86, 129.66, 129.24, 128.81, 128.59, 128.42, 126.88, 124.49, 124.31, 123.85, 123.58, 123.43, 123.28, 120.44, 116.60, 116.39, 113.80, 67.82, 21.60, 20.75; HRMS: m/z calcd for $C_{29}H_{23}NO_4S$: $[M + H]^+$ 482.1426, found 482.1428.

9-(5-Methyl-1-tosyl-1*H*-indol-3-yl)-9*H*-xanthen-9-ol (6f). 76 mg (79%); white crystalline solid; m.p. 184–186 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99 (s, 1H), 7.83 (dd, J = 8.3, 5.7 Hz, 3H), 7.36–7.31 (m, 2H), 7.29–7.25 (m, 6H), 6.99 (ddd, J = 8.0, 4.9, 2.4 Hz, 3H), 6.41 (s, 1H), 2.64 (s, 1H), 2.40 (s, 3H), 2.11 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.84, 144.83, 135.17, 134.32, 132.85, 129.82, 129.71, 128.69, 128.65, 128.56, 126.86, 126.03, 124.49, 124.10, 123.62, 120.34, 116.65, 113.48, 67.89, 21.61, 21.34; HRMS: m/z calcd for $C_{29}H_{23}NO_4S$: $[M + H]^+$ 482.1426, found 482.1431.

9-(5,7-Dimethyl-1-tosyl-1*H*-indol-3-yl)-9*H*-xanthen-9-ol (6g). 68 mg (69%); white solid; m.p. 177–179 °C; ^{1}H NMR

(300 MHz, $CDCl_3$) δ 8.15 (s, 1H), 7.66–7.60 (m, 2H), 7.35 (ddd, J = 8.5, 7.0, 1.6 Hz, 3H), 7.30–7.28 (m, 3H), 7.20 (dd, J = 7.9, 1.6 Hz, 2H), 7.03–6.97 (m, 2H), 6.76 (s, 1H), 6.22 (s, 1H), 2.60 (s, 3H), 2.44 (s, 3H), 2.05 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 149.92, 144.40, 136.18, 134.81, 133.45, 130.99, 129.80, 129.73, 129.68, 128.71, 128.64, 128.04, 126.68, 125.57, 124.45, 123.55, 118.23, 116.64, 67.83, 21.74, 21.62, 20.97; HRMS: m/z calcd for $C_{30}H_{25}NO_4S$: $[M + H]^+$ 496.1583, found 496.1593.

9-(5-Methoxy-1-tosyl-1*H*-indol-3-yl)-9*H*-xanthen-9-ol (6h). 80 mg (81%); white solid; m.p. 160–165 °C; ^{1}H NMR (400 MHz, chloroform-*D*) δ 2.37 (s, 3H), 2.67 (s, 1H), 3.44 (s, 3H), 6.05 (d, J = 2.5 Hz, 1H), 6.73 (dd, J = 9.0, 2.5 Hz, 1H), 6.96 (ddd, J = 8.2, 7.1, 1.3 Hz, 2H), 7.18–7.23 (m, 3H), 7.24 (dd, J = 2.5, 1.0 Hz, 2H), 7.26–7.31 (m, 3H), 7.73–7.82 (m, 3H), 7.96 (s, 1H); ^{13}C NMR (101 MHz, chloroform-*D*) δ 21.68, 55.27, 67.76, 103.16, 113.13, 114.74, 116.61, 123.73, 124.39, 124.43, 126.88, 128.81, 129.33, 129.46, 129.81, 129.87, 130.80, 135.14, 144.90, 149.87, 156.03; HRMS: m/z calcd for $C_{29}H_{23}NO_5S$: $[M]^+$ 497.1297, found 497.1294.

9-(5-Fluoro-1-tosyl-1*H*-indol-3-yl)-9*H*-xanthen-9-ol (6i). 79 mg (82%); white solid; m.p. 170–174 °C; ^{1}H NMR (400 MHz, chloroform-*D*) δ 8.02 (s, 1H), 7.85 (dd, J = 9.0, 4.4 Hz, 1H), 7.79–7.75 (m, 2H), 7.32 (d, J = 1.7 Hz, 1H), 7.30 (t, J = 1.4 Hz, 1H), 7.28 (d, J = 1.7 Hz, 1H), 7.24 (s, 1H), 7.22 (d, J = 1.5 Hz, 2H), 7.20 (d, J = 1.6 Hz, 2H), 6.96 (ddd, J = 8.0, 7.1, 1.3 Hz, 2H), 6.86 (td, J = 9.0, 2.6 Hz, 1H), 6.27 (dd, J = 9.1, 2.5 Hz, 1H), 2.37 (s, 3H); ^{13}C NMR (101 MHz, chloroform-*D*) δ 160.50, 158.11, 149.84, 145.25, 134.98, 132.45, 130.01, 129.97, 129.50, 129.40, 129.08, 129.03, 128.66, 126.93, 125.49, 124.14, 123.75, 116.88, 115.02, 114.93, 112.85, 112.60, 106.37, 106.12, 67.75, 21.71; HRMS: m/z calcd for $C_{28}H_{20}FNO_4S$: $[M + H]^+$ 486.1175, found 486.1195.

9-(5-Chloro-1-tosyl-1*H*-indol-3-yl)-9*H*-xanthen-9-ol (6j). 66 mg (66%); white solid; m.p. 202–206 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00 (s, 1H), 7.85 (d, J = 8.9 Hz, 1H), 7.80–7.75 (m, 2H), 7.36–7.26 (m, 4H), 7.26–7.23 (m, 3H), 7.21 (d, J = 1.6 Hz, 1H), 7.12 (dd, J = 8.8, 2.1 Hz, 1H), 6.99 (ddd, J = 8.2, 7.1, 1.3 Hz, 2H), 6.62 (d, J = 2.0 Hz, 1H), 2.66 (s, 1H), 2.40 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 149.77, 145.29, 134.86, 134.41, 129.98, 129.95, 129.52, 129.12, 128.52, 128.46, 126.86, 125.28, 124.93, 124.12, 123.71, 120.16, 116.86, 114.86, 67.74, 21.65; HRMS: m/z calcd for $C_{28}H_{20}ClNO_4S$: $[M + H]^+$ 502.0880, found 502.0884.

9-(5-Chloro-1-tosyl-1*H*-indol-3-yl)-2-methoxy-9*H*-xanthen-9-ol (6k). 64 mg (60%); off white solid; m.p. 150–152 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.99 (s, 1H), 7.86 (d, J = 8.9 Hz, 1H), 7.80–7.76 (m, 2H), 7.31 (ddd, J = 8.5, 7.0, 1.6 Hz, 2H), 7.24 (d, J = 1.3 Hz, 1H), 7.22 (dd, J = 3.0, 1.5 Hz, 1H), 7.19 (d, J = 1.1 Hz, 1H), 7.16 (s, 1H), 7.12 (dd, J = 8.9, 2.1 Hz, 1H), 6.97 (ddd, J = 8.0, 7.0, 1.3 Hz, 1H), 6.89 (dd, J = 9.0, 3.0 Hz, 1H), 6.67 (dd, J = 15.8, 2.5 Hz, 2H), 3.59 (s, 3H), 2.59 (s, 1H), 2.38 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.55, 149.86, 145.24, 143.89, 134.87, 134.38, 129.96, 129.88, 129.47, 129.15, 128.57, 128.49, 126.80, 124.99, 124.96, 124.49, 123.45, 120.10, 117.85, 117.07, 116.76, 114.84, 111.43, 68.02, 55.46, 21.62; HRMS: m/z calcd for $C_{29}H_{22}ClNO_5S$: $[M + H]^+$ 532.0985, found 532.0978.

9-(5-Fluoro-1-tosyl-1*H*-indol-3-yl)-2-methoxy-9*H*-xanthen-9-ol (6l). 56 mg (55%); brownish semi solid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.03 (s, 1H), 7.88 (dd, J = 9.1, 4.5 Hz, 1H), 7.78 (d, J = 8.4 Hz, 2H), 7.35–7.30 (m, 1H), 7.28 (d, J = 1.7 Hz, 1H), 7.26–7.20 (m, 3H), 7.17 (d, J = 9.1 Hz, 1H), 6.96 (ddd, J = 8.2, 7.0, 1.4 Hz, 1H), 6.92–6.84 (m, 2H), 6.70 (d, J = 3.0 Hz, 1H), 6.31 (dd, J = 9.1, 2.5 Hz, 1H), 3.59 (s, 3H), 2.65 (s, 1H), 2.38 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.65, 155.55, 149.86, 145.13, 143.89, 134.92, 132.35, 129.91, 129.84, 129.08, 128.55, 126.79, 125.13, 124.43, 123.41, 117.81, 117.06, 116.72, 114.94, 114.81, 112.86, 112.52, 111.45, 106.29, 105.96, 100.00, 67.98, 55.45, 21.62; HRMS: m/z calcd for $C_{29}H_{22}FNO_5S$: $[M + H]^+$ 516.1281, found 516.1286.

2-Methyl-9-(5-methyl-1-tosyl-1*H*-indol-3-yl)-9*H*-xanthen-9-ol (6m). 74 mg (75%); white solid; m.p. 184–188 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.98 (s, 1H), 7.84–7.78 (m, 3H), 7.33–7.26 (m, 2H), 7.25–7.22 (m, 2H), 7.20 (dd, J = 3.9, 1.5 Hz, 1H), 7.15–7.07 (m, 2H), 7.03–6.90 (m, 3H), 6.38 (dt, J = 1.7, 0.8 Hz, 1H), 2.59 (s, 1H), 2.37 (s, 3H), 2.15 (s, 3H), 2.09 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 149.87, 147.72, 144.79, 135.20, 134.38, 132.94, 132.83, 130.66, 129.80, 129.63, 128.97, 128.76, 128.66, 128.55, 126.84, 126.00, 124.37, 123.90, 123.42, 120.35, 116.59, 116.38, 113.48, 67.87, 21.59, 21.36, 20.77; HRMS: m/z calcd for $C_{30}H_{25}NO_4S$: $[M + H]^+$ 496.1583, found 496.1573.

Representative experimental procedure and characterization data for the synthesis of 3-(9-(1*H*-indol-3-yl)-9*H*-xanthen-9-yl)-1-tosyl-1*H*-indole (6aa) without isolation of precursor (5a) and (6a). IN an oven-dried 25 ml round bottom flask charged with **4a** (106 mg, 0.2 mmol) in toluene (2 mL) and ethanol (2 mL), we added aq. K_2CO_3 solution (2.5 M, 2 mL), PCy_3 (6 mg, 0.02 mmol) and $Pd(OAc)_2$ (2 mg, 0.01 mmol) successively. The resulting solution was stirred at 75 °C under an argon atmosphere for 2 h. After the completion of the reaction (monitored by TLC), the crude reaction mixture was extracted with EtOAc. The organic extract was washed with a brine solution, dried over anhydrous Na_2SO_4 and concentrated. In a 10 ml round bottom flask, the crude product **5a** was dissolved in acetonitrile (3 mL) and $Fe(NO_3)_3{\cdot}9H_2O$ (24 mg, 30 mol%) and $FeCl_3$ (10 mg, 30 mol%) were added to it. The reaction was continued at 70 °C for 3 h under an oxygen atmosphere. After the complete formation of **6a** (monitored by TLC) we added indole (23 mg, 0.2 mmol) directly to the reaction mixture and the reaction was continued at 70 °C for 30 min under ambient atmosphere. The crude reaction mixture was extracted with DCM. The organic extract was washed with brine solution, dried over anhydrous Na_2SO_4 and concentrated. The product was subjected to column chromatography (silica gel, 60–120 mesh), eluting with hexane/EtOAc 95 : 5 (v/v) to afford the product **6aa** as a white solid (78 mg, 0.14 mmol, 69%).

3-(9-(1*H*-Indol-3-yl)-9*H*-xanthen-9-yl)-1-tosyl-1*H*-indole (6aa). 78 mg (69%); off white solid; m.p. 242–245 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.44 (s, 3H), 6.33 (d, J = 2.6 Hz, 1H), 6.88–7.01 (m, 7H), 7.12 (s, 1H), 7.14–7.27 (m, 7H), 7.31–7.39 (m, 2H), 7.72 (d, J = 8.2 Hz, 2H), 7.98–8.08 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.67, 44.27, 111.49, 113.96, 116.61, 119.27, 119.88, 121.54, 122.05, 122.79, 122.92, 122.96, 124.40, 125.02,

125.10, 126.14, 126.98, 127.54, 128.11, 128.20, 128.72, 129.26, 129.82, 134.96, 136.40, 137.36, 144.92, 152.67; HRMS: *m*/*z* calcd for $C_{36}H_{27}N_2O_3S$: $[M + H]^+$ 567.1742, found 567.1744.

1-Methyl-3-(9-(1-tosyl-1*H*-indol-3-yl)-9*H*-xanthen-9-yl)-1*H*-indole (6ab). 86 mg (74%); white solid; m.p. 248–255 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.45 (s, 3H), 3.66 (s, 3H), 6.11 (s, 1H), 6.84 (d, J = 8.0 Hz, 1H), 6.89–7.00 (m, 6H), 7.16 (s, 1H), 7.17–7.27 (m, 8H), 7.31 (d, J = 8.2 Hz, 2H), 7.73 (d, J = 8.3 Hz, 2H), 8.05 (d, J = 8.4 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 21.68, 32.80, 44.18, 109.59, 113.94, 116.60, 118.40, 118.72, 121.54, 121.56, 122.80, 122.92, 122.94, 124.37, 125.46, 126.11, 127.01, 127.65, 128.03, 128.43, 128.71, 129.30, 129.37, 129.81, 134.97, 136.39, 138.09, 144.91, 152.59; HRMS: *m*/*z* calcd for $C_{37}H_{29}N_2O_3S$: $[M + H]^+$ 581.1899, found 581.1896.

1-Methyl-3-(2-methyl-9-(1-tosyl-1*H*-indol-3-yl)-9*H*-xanthen-9-yl)-1*H*-indole (6ea). 83 mg (70%); off white solid; m.p. 230–235 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.12 (s, 3H), 2.44 (s, 3H), 3.65 (s, 3H), 6.12 (s, 1H), 6.70 (d, J = 2.1 Hz, 1H), 6.80–7.01 (m, 5H), 7.02–7.13 (m, 2H), 7.15–7.33 (m, 9H), 7.71–7.78 (m, 2H), 8.07 (d, J = 8.4 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 20.95, 21.66, 32.79, 44.18, 109.57, 113.96, 116.18, 116.58, 118.62, 118.69, 121.48, 121.59, 122.67, 122.90, 122.94, 124.36, 125.47, 126.35, 127.00, 127.19, 127.53, 127.91, 128.43, 128.72, 128.80, 128.83, 129.36, 129.43, 129.79, 132.16, 135.00, 136.47, 138.08, 144.89, 150.48, 152.63; HRMS: *m*/*z* calcd for $C_{38}H_{30}N_2O_3S$: $[M]^+$ 594.1977, found 594.1972.

Conflicts of interest

There are no conflicts to declare.

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Design and Synthesis of Indazole–Indole Hybrid via *tert*-Butyl Nitrite Mediated Cascade Diazotization/Isomerization/Cyclization

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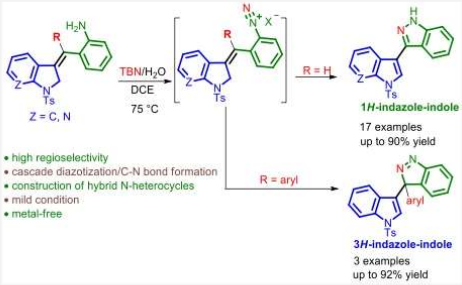
ABSTRACT: In this report, a *tert*-butyl nitrite (TBN)-mediated straightforward metal-free approach has been presented for the synthesis of a diverse range of C-3-substituted indazole–indole hybrids using readily accessible 2-(indolin-3-ylidenemethyl)aniline derivatives. This strategy is proposed to occur via a diazonium salt intermediate that is capable of cascade isomerization and intramolecular C–N bond formation through a *5-endo-dig* cyclization to achieve a wide variety of indazole–indole hybrids in good yields.



Nitrogen-containing heterocycles are important building blocks in numerous bioactive natural products, commercially available drugs, and material science.[1] Among them, indazole[2] and indole[3] are privileged scaffolds in the fields of drug discovery and material chemistry. For example, the indazole scaffold possesses a wide range of pharmacological activities, such as treatment of respiratory disease, central nervous system (CNS) disorders, Parkinson's disease, and multikinase inhibitory activities.[4] These important and broad-spectrum activities have inspired synthetic chemists to continue to develop new methods for the synthesis of functionalized indazoles.[5] Similarly, indoles are another important structural motif found in many biologically active compounds, including alkaloids, agrochemicals, functional materials, and drug candidates.[6] Consequently, numerous methods have been devised to synthesize and functionalize indole[7] scaffolds. In particular, C-3-functionalized 1*H*-indazoles[8] and indoles[9] have received significant interest over the past decades, as they are commonly found in commercial drugs and have been the subject of great interest in medicinal chemistry. Namely, MLi-2[8a] is a highly selective leucine-rich repeat kinase 2 (LRRK2) inhibitor and has potential for Parkinson's disease; NSR is a norepinephrine/serotonin reuptake inhibitor for the treatment of fibromyalgia;[8c] cerlapirdine[8d] (SAM-531) is a potent antagonist of 5-HT6R, undergoing clinical evaluation for Alzheimer's disease treatment; YC-1[8b] (lificiguat) activates guanylyl cyclase and is recognized for its outstanding anticancer properties (Figure 1, A); similarly, Figure 1(B) displays the structures of selected C-3-substituted indole derivatives along with their corresponding pharmacological activities.[9b]

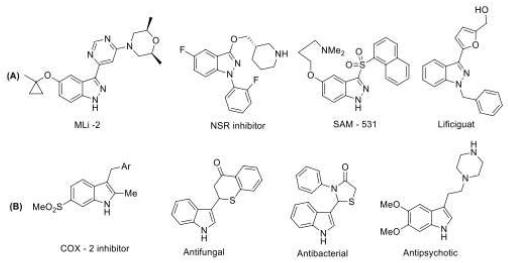


Figure 1. Some examples of C-3-substituted indazole and C-3-substituted indole containing bioactive molecules.

Recognizing the significant relevance in the drug discovery of these two structural motifs, we envisioned that the hybrid of these two N-heterocyclic scaffolds at their C-3 position could potentially enhance their performance in their application compared with their individual counterparts. Nevertheless, to the best of our knowledge, the synthesis of an indazole-containing indole hybrid is scarcely reported.[10] Very recently, Mai et al. demonstrated a method for the synthesis of indazole-containing biheteroaryls via a domino Sonogashira coupling/

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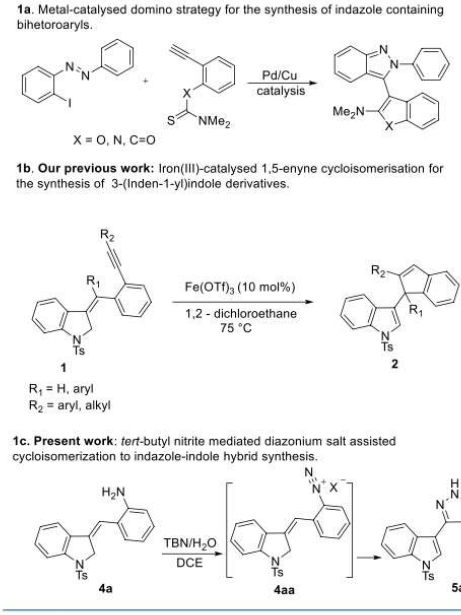
azaenyne cycloisomerization/Barton−Kellogg reaction (Scheme 1, **1a**).[10a] Consequently, designing a new synthetic

Scheme 1. Overview of the Work



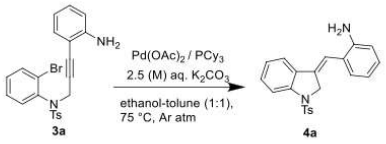
strategy that accesses a structurally diverse C-3-linked indazole−indole hybrid in a sequential manner rather than a direct coupling of individual components is highly desirable.

In recent years, transition metal-catalyzed cycloisomerization of alkyne via 5-*endo-dig* cyclization has been continuously developing, as it enables the creation of structurally diverse and complex five-membered carbo- and heterocycles with high atom economy.[11] In this connection, we have recently reported an iron-catalyzed 1,5-enyne cycloisomerization of a 3-(methylene)indoline derivative (**1**) via 5-*endo-dig* cyclization for the synthesis of substituted 3-(1-indenyl)indole (**2**) (Scheme 1, **1b**).[12] Inspired by this result, we speculated that the replacement of the −C≡C− unit with its nitrogen analogue $-N{\equiv}N^{+}$ may undergo a similar type of cycloisomerization to achieve the C-3-linked indole−indazole hybrid in a sequential manner. Herein, we report a *tert*-butyl nitrite (TBN)-mediated metal-free approach for the synthesis of a indazole−indole biheteroaryl (**5a**) in excellent yield (Scheme 1, **1c**) from 2-(1-tosylindolin-3-ylidenemethyl)aniline (**4a**). The present strategy goes through in situ generated diazonium salt triggered allylic isomerization, intramolecular C−N bond formation via 5-*endo-dig* cyclization, and tautomerization.

To probe the viability of this strategy, 2-(1-tosylindolin-3-ylidenemethyl)aniline **4a** was first prepared via intramolecular reductive Heck coupling reaction of 2-halo-*N*-propargylanilide derivative **3a** according to our previously developed method,[13] using 5 mol % of $Pd(OAc)_2$ and 10 mol % of tricyclohexylphosphine (PCy_3) at 75 °C in the presence of 2.5 M K_2CO_3 (Scheme 2) (see Supporting Information).

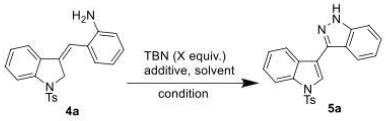
Next, we commenced our investigation to optimize the reaction conditions for the cascade diazotization/cycloisome-

Scheme 2. Preparation of Substrate 4a



rization of model substrate **4a** (Table 1). Initially, the transformation was conducted with **4a** and 1.0 equiv of TBN

Table 1. Optimization of Reaction Condition[a]



entry	*X* equiv	additive	solvent	T/°C	*t*/min	yield/%[b]
1	1		DCE	50	10	53
2	1		DCE	75	10	76
3	1	4 Å ms	DCE	75	60	32
4	1	H_2O (5 μL)	DCE	75	10	90
5	1.5	H_2O (5 μL)	DCE	75	10	44
6	1	$Fe(OTf)_3$	DCE	75	10	48
7	1	PTSA	DCE	75	10	86
8	1	TfOH	DCE	75	10	41
9	1	H_2O (5 μL)	EtOH	75	10	39
10	1	H_2O (5 μL)	MeCN	75	10	36
11	1	H_2O (5 μL)	CH_3NO_2	75	10	32
12	1	H_2O (5 μL)	tolune	75	10	20
13	1	H_2O (5 μL)	DMF	75	10	ND

[a]Reaction conditions: **4a** (0.13 mmol), *tert*-butyl nitrite (TBN), and additive in 3 mL of solvent under an Ar atmosphere. [b]Isolated yield; ND, not desired.

in DCE (1,2-dichloroethane) at 50 °C for 10 min. Pleasantly, the desired C-3-linked indazole−indole **5a** was isolated in 53% yield with excellent regioselectivity (Table 1, entry 1). Notably, the steep increase in yield of desired product **5a** (76%) was observed by reacting 1.0 equiv of TBN at 75 °C in DCE within 10 min without any additives (Table 1, entry 2). However, when a similar reaction was attempted with 4 Å molecular sieves, the yield of the product **5a** was reduced to 32% in 60 min (Table 1, entry 3). From this result, we understood that moist conditions are required to accelerate the diazotization process and subsequent cyclization of substrate **4a**. However, when the reaction was conducted in the presence of H_2O (5 μL), the yield of the desired indazole−indole **5a** was increased up to 90% (Table 1, entry 4).

Moreover, increasing the amount of TBN to 1.5 equiv led to a lower yield of **5a** (Table 1, entry 5). Furthermore, the reaction was also screened in the presence of a Lewis acid or Brønsted acid as additive. It was noticed that the reaction proceeded smoothly in the presence of *p*-toluenesulfonic acid (PTSA) to afford the target product in 86% yield, while $Fe(OTf)_3$ and TfOH gave inferior results (Table 1, entries 6−8). A series of other common solvents, like EtOH, MeCN, CH_3NO_2, toluene, and DMF, were also examined to check the solvents' effect. However, in most cases, relatively lower yields were obtained compared to the yields obtained in DCE. For example, in EtOH, MeCN, CH_3NO_2, and toluene, the yield of

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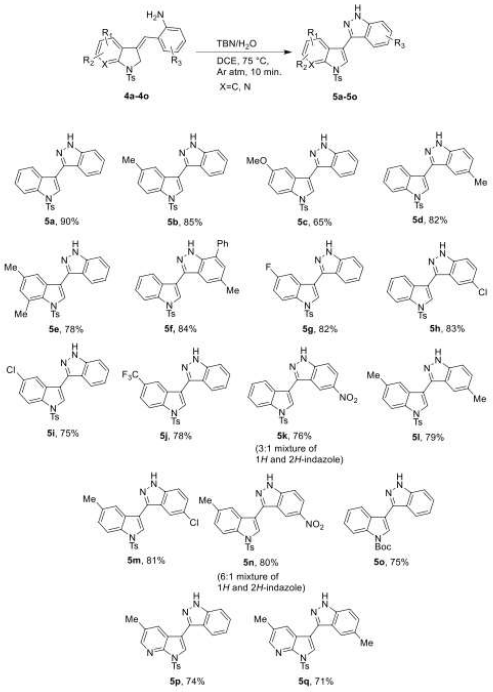
5a is significantly reduced to 39%, 36%, 32%, and 20%, respectively (Table 1, entries 9−12), and in dimethylformamide (DMF) (Table 1, entry 13), no desired product was isolated. Thus, 1.0 equiv of TBN in 3 mL of 1,2-dichloroethane at 75 °C for 10 min under an Ar atmosphere in the presence of 5 μL of H_2O was determined as the optimum reaction condition.

Having established the optimal reaction conditions, we further explored the substrate scope and functional group tolerance of this newly developed strategy. The reaction was carried out on both unsubstituted and substituted aryl groups of the 3-indoline unit, and the results are summarized in Scheme 3. Unsubstituted desired product such as **5a** was

Scheme 3. Substrate Scope of 1*H*-Indazole−Indole and 1*H*-Indazole−Azaindole Hybrids[a]



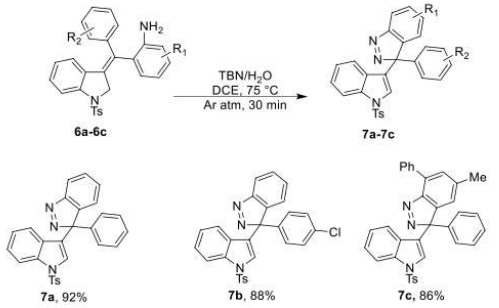
[a]Reaction conditions: **4a** (0.13 mmol), *tert*-butyl nitrite (TBN) (0.13 mmol), and H_2O (5 μL) in 3 mL of 1,2-DCE solvent under an Ar atmosphere at 75 °C. [b]Isolated yield after 10 min.

fruitfully achieved with a high yield of **5a** of 90% (Scheme 3, **5a**). The substrates containing *o*-Me, *p*-Me, and a strong electron-donating compound like a *p*-OMe-substituted derivative were well tolerated in diazonium-triggered intramolecular cyclization and afforded the final cyclization products in 85%, 65%, 82%, 78%, and 84% yields, respectively (Scheme 3, **5b**, **5c**, **5d**, **5e**, **5f**). Similarly, electron-withdrawing groups, viz., −F, −Cl, and $-CF_3$ containing substrates, reacted efficiently to produce the desired products in 82%, 83%, 75%, and 78% yields, respectively (Scheme 3, **5g**, **5h**, **5i**, **5j**). However, we also studied the electronic effects of *p*-NO_2 on the aryl ring of the 2-alkenyl aniline moiety, which could directly affect the diazonium-assisted cyclization. It was observed that these compounds underwent smooth cycloisomerization reactions in 76% and 80% yields with nonseparable tautomeric forms of 1*H*- and 2*H*-indazoles in 3:1 and 6:1 ratios (Scheme 3, **5k**, **5n**).[14] There was no such steric influence of the *ortho*-phenyl group on the aryl ring of the 2-alkenyl aniline moiety (Scheme 3, **5f**). The precursors with the simultaneous presence of electronically similar and opposing substituents exhibited successful transformations to the desired **5l**, **5m**, and **5n** products in 79%, 81%, and 80% yields, respectively, (Scheme 3, **5l**, **5m**, **5n**). Moreover, it is noteworthy that the *tert*-butoxycarbonyl group as an amine protector also survived under the reaction conditions and produced the desired product in high yield (Scheme 3, **5o**).

Similarly, 7-azaindoles, important bioisosters of indole, are often found in many commercially available drug candidates.[15] However, there are no reports of the construction of the indazole−azaindole hybrid in the literature. In order to explore the further advantages of this developed protocol, the construction of biheteroaryls containing 7-azaindole and indazole was also performed using 7-azaindolines, **4p** and **4q**. Gratifyingly, products **5p** and **5q** were also afforded in 74% and 71% yields, respectively (Scheme 3, **5p**, **5q**).

To further expand the substrate scope, we also studied the synthesis of the 3*H*-indazole−indole hybrid. The synthesis of 3*H*-indazoles has been limited because of their instability.[16] Therefore, it would be interesting to synthesize the 3*H*-indazole−indole hybrid. First, the substrates **6a**, **6b**, and **6c** were prepared according to our previous method.[13] When these 3-substituted indolines **6a**, **6b**, and **6c** were subjected to the present reaction conditions, pleasantly, the desired products **7a**, **7b**, and **7c** were afforded in 92%, 88%, and 86% yields, respectively (Scheme 4, **7a**, **7b**, **7c**).

Scheme 4. Substrate Scope of 3*H*-Indazole−Indole Hybrids



Therefore, this new strategy is quite general. All of the reactions could fruitfully transform into the desired C-3-substituted indazole−indole hybrids in high yields via 5-*endo*-*dig* cyclization. All of the structures were characterized using ^1H and ^{13}C NMR and HRMS spectra (see Supporting Information). Structure **5m** was further confirmed through X-ray diffraction (Figure 2, CCDC no. 2297939).

It was reported[17] that *N*-sulfonamide indole derivatives possess interesting pharmaceutical activities such as antibacterial and antioxidant, properties, and hence *N*-tosyl indole−indazole will have significant pharmaceutical properties. However, since naturally occurring indoles lack protecting groups, we also carried out the detosylation of **5a** using a

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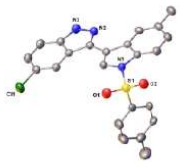
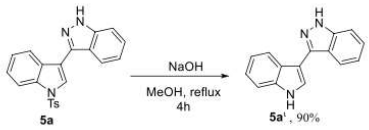


Figure 2. ORTEP diagram of **5m** (H atoms have been omitted for the sake of clarity). Thermal ellipsoids are given at the 50% probability level.

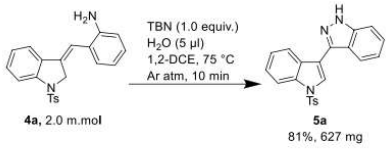
solution of 50 mol % sodium hydroxide (NaOH) in methanol−water (1:1) under reflux conditions to obtain the detosylated product **5a′** in 90% yield (Scheme 5, **5a′**).

Scheme 5. Detosylation of 1*H*-Indazole-Tethered Indole Derivative 5a



To explore the practical applicability of the present methodology, we performed a semi large-scale diazotization/cyclization reaction of **4a** in the usual laboratory setup. Under our optimized conditions, the indazole−indole hybrid **5a** was obtained in 81% yield (Scheme 6).

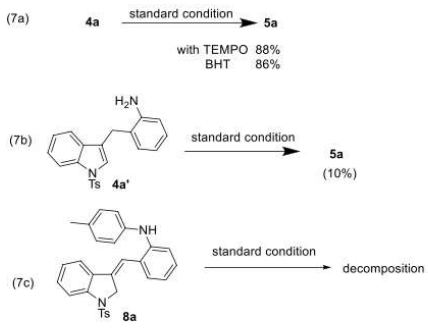
Scheme 6. Scale-up Synthesis of 3-(1-Tosyl-1*H*-indol-3-yl)-1*H*-indazole (5a)



Finally, to gain insight into the reaction mechanism, a few control experiments were carried out, as depicted in Scheme 7.

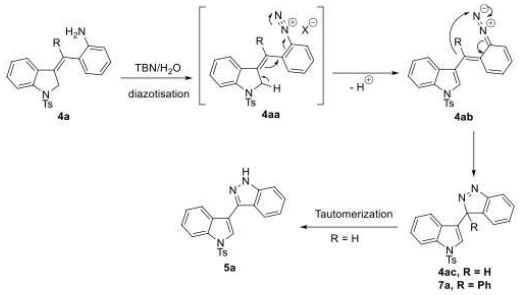
First, we conducted the reaction of **4a** with TBN in the presence of radical scavengers TEMPO and BHT separately to understand whether the reaction proceeds through a radical intermediate. It was observed that the yields of the desired product **5a** did not decrease significantly in both cases, which implies the ionic pathway for this conversion (Scheme 7, 7a). We also thought that this reaction may also proceed through isomerization as a first step to furnish **4a′**, then diazotization, and subsequent cyclization to furnish **5a**.[18] In order to ascertain that, we first prepared **4a′** by the isomerization of **4a** according to our modified previous method[19] (see Supporting Information), and then the final reaction was set out under the standard condition; only a trace amount of the desired product **5a** was obtained (Scheme 7, 7b). This observation revealed that diazotization/isomerization/cyclization occurred in a cascade manner. Additionally, the reaction of secondary amine **8a** did not give any product under our present protocol (Scheme 7, 7c). This finding indicates that the C−N bond formation step follows a diazotization pathway.

Scheme 7. Control Experiments



Based on the above experimental results, control experiments, and related works,[20] we have delineated the process of TBN-mediated diazotization/cycloisomerization/tautomerization of **4a**, as illustrated in Scheme 8. Initially, TBN in the presence of H_2O reacts with **4a** to form diazonium salt **4aa**. Diazonium salt **4aa** is stabilized by a push−pull mechanism through aromatization of the indole nucleus and generates a betaine-like intermediate **4ab**. Subsequently, the intermediate **4ab** underwent smooth cyclization to furnish **4ac** (R = H) either through 6π-electrocyclization reaction or through direct intramolecular C−N bond formation via 5-*endo-dig* cyclization. Finally, rapid tautomerization of **4ac** furnishes the desired **5a**. However, when R = Ph, the reaction stopped after the formation of **7a**.

Scheme 8. Plausible Mechanistic Pathway



In conclusion, we have successfully developed a TBN-mediated cascade diazotization/cycloisomerization/tatutomerization to access the indazole−indole hybrid. In the present metal-free approach many substituents are well compatible and furnished the desired product with high yields. Moreover, with this versatile and flexible approach, it is possible to synthesize 7-azaindole−indazole as well as 3*H*-indazole−indole hybrids. Notable advantages of this novel reaction include the straightforward preparation of substrates, a high degree of atom economy, high regioselectivity, and mild reaction conditions. We believe that this strategy could find interest in the synthesis of pharmaceuticals and natural products.

EXPERIMENTAL SECTION

General Procedures. ^{1}H NMR spectral data were recorded by Bruker 300 and 400 (300 and 400 MHz) spectrometers using $CDCl_3$

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and d_6-DMSO as deuterated solvents. All chemical shifts are expressed in parts per million (ppm, δ). All coupling constants are absolute values and are expressed in Hz. The description of the signals include the following: s = singlet, d = doublet, t = triplet, m = multiplet, dd = doublet of doublets, brs = broad singlet, td = triplet of doublets. ^{13}C NMR spectra were recorded with Bruker 300 and 400 (75 and 100 MHz, respectively) spectrometers as solutions in $CDCl_3$ and d_6-DMSO with complete proton decoupling. Chemical shifts are expressed in ppm (δ). High-resolution mass spectra (HRMS) were performed with a Q-tof Micro YA263 spectrometer in an acetonitrile solvent. The molecular fragments are quoted as the relation between mass and charge (m/z). The routine monitoring of reactions was performed with silica gel coated glass slides (Merck, silica gel G for TLC) and precoated Al plates, which were analyzed with iodine and UV light, respectively. Solvents, reagents, and chemicals were purchased from Aldrich, Fluka, Merck, SRL, Spectrochem, and Process Chemicals. All reactions involving moisture-sensitive reactants were executed with oven-dried glassware.

Representative Experimental Procedure for the Synthesis of 3-(1-Tosyl-1*H*-indol-3-yl)-1*H*-indazole (5a). In a 10 mL round-bottom flask, compound **4a** (50 mg, 0.13 mmol) was dissolved in 3 mL of DCE. Then, 5 μL of H_2O and TBN (1 equiv, 15.4 μL) were added to the solution successively. The resulting solution was set on a silicone-oil bath preheated to 75 °C and continued under an argon atmosphere for 10 min. After the completion of the reaction (monitored by TLC), the crude reaction mixture was subjected to extraction with ethyl acetate. After that, the organic extract was washed with brine solution and dried over anhydrous Na_2SO_4, and finally, the solvent was evaporated. The crude product was subjected to column chromatography (silica gel, 60−120 mesh), eluting with hexane−EtOAc, 92:8 (v/v), to afford the product **5a** as an off-white solid (46 mg, 0.12 mmol, 90%).

Compounds **5b**−**5q** were synthesized by following the procedure described above.

Representative Experimental Procedure for the Synthesis of 3-Phenyl-3-(1-tosyl-1*H*-indol-3-yl)-3*H*-indazole (7a). In a 10 mL round-bottom flask, compound **6a** (50 mg, 0.11 mmol) was dissolved in 3 mL of DCE. Then, 5 μL of H_2O and TBN (1 equiv, 13.07 μL) were added to the solution successively. The resulting solution was set on a silicone-oil bath preheated to 75 °C and continued under an argon atmosphere for 30 min. After the completion of the reaction (monitored by TLC), the crude reaction mixture was subjected to extraction with ethyl acetate. After that, the organic extract was washed with brine solution and dried over anhydrous Na_2SO_4, and finally, the solvent was evaporated. The crude product was subjected to column chromatography (silica gel, 60−120 mesh), eluting with hexane−EtOAc, 92:5 (v/v), to afford the product **7a** as a gray solid (47 mg, 0.12 mmol, 92%).

Compounds **7b** and **7c** were synthesized by following the above procedure.

Experimental Procedure for the Synthesis of 3-(1*H*-Indol-3-yl)-1*H*-indazole (5a′). In a 10 mL round-bottom flask, compound **5a** (50 mg, 0.13 mmol) was dissolved in 1 mL each of methanol and water. Then, 50 mol % NaOH was added to the solution. The resulting solution was refluxed on a silicone-oil bath under an argon atmosphere for 4 h. After the completion of the reaction (monitored by TLC), the crude reaction mixture was subjected to extraction with ethyl acetate. After that, the organic extract was washed with brine solution and dried over anhydrous Na_2SO_4, and finally, the solvent was evaporated. The crude product was subjected to column chromatography (silica gel, 60−120 mesh), eluting with hexane−EtOAc, 92:5 (v/v), to afford product **5a′** as a white solid (27 mg, 0.12 mmol, 90%).

3-(1-Tosyl-1*H*-indol-3-yl)-1*H*-indazole (5a): off-white solid (46 mg, 90%); mp 150−155 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 10.34 (brs, 1H), 8.32 (d, J = 6.4 Hz, 1H), 8.13 (s, 1H), 8.08 (d, J = 6.4 Hz, 1H), 8.00 (d, J = 6.4 Hz, 1H), 7.83 (d, J = 6.8 Hz, 2H), 7.52−7.35 (m, 2H), 7.33 (t, J = 6.0 Hz, 1H), 7.31 (d, J = 6.8 Hz, 1H), 7.29 (t, J = 6.0 Hz, 1H), 7.23 (dd, J = 22.0, 6.8 Hz, 2H), 2.32 (s, 3H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 145.2, 141.0, 139.7, 135.2, 135.1, 129.9, 129.3, 127.2, 126.9, 125.3, 123.97, 123.92, 122.6, 121.52, 121.45, 120.8, 116.0, 113.5, 110.0, 21.5; HRMS m/z calcd for $C_{22}H_{17}N_3O_2S$ 388.1120 $[M + H]^+$, found 388.1128.

3-(5-Methyl-1-tosyl-1*H*-indol-3-yl)-1*H*-indazole (5b). This compound was synthesized according to the representative procedure as described previously and purified through column chromatography (silica gel, 60−120 mesh), eluting with hexane−EtOAc, 92:8 (v/v), to afford the product **5b** as a white solid (44 mg, 85%): mp 100−105 °C; ^1H NMR (400 MHz, DMSO) δ 13.30 (s, 1H), 8.30 (s, 1H), 8.24−8.15 (m, 2H), 8.01−7.96 (m, 2H), 7.93 (d, J = 8.5 Hz, 1H), 7.63 (d, J = 8.3 Hz, 1H), 7.46 (dd, J = 8.2, 7.0 Hz, 1H), 7.35 (d, J = 8.2 Hz, 2H), 7.32−7.20 (m, 2H), 2.42 (s, 3H), 2.27 (s, 3H); $^{13}C\{^1H\}$ NMR (75 MHz, DMSO) δ 145.9, 141.2, 138.2, 134.4, 133.60, 133.25, 130.7, 129.4, 127.36, 127.21, 126.9, 123.92, 123.09, 121.50, 121.24, 120.9, 116.4, 113.4, 110.9, 21.53, 21.45; HRMS m/z calcd for $C_{23}H_{19}N_3O_2S$ 402.1276 $[M + H]^+$, found 402.1276.

3-(5-Methoxy-1-tosyl-1*H*-indol-3-yl)-1*H*-indazole (5c). This compound was synthesized according to the representative procedure as described previously and purified through column chromatography (silica gel, 60−120 mesh), eluting with hexane−EtOAc, 90:10 (v/v), to afford the product **5c** as a yellow viscous liquid (35 mg, 65%); ^1H NMR (400 MHz, DMSO) δ 13.33 (s, 1H), 8.30 (s, 1H), 8.18 (d, J = 8.2 Hz, 1H), 8.00−7.92 (m, 3H), 7.90 (d, J = 2.6 Hz, 1H), 7.62 (d, J = 8.4 Hz, 1H), 7.49−7.43 (m, 1H), 7.37 (d, J = 8.1 Hz, 2H), 7.28 (t, J = 7.5 Hz, 1H), 7.07 (dd, J = 9.1, 2.6 Hz, 1H), 3.80 (s, 3H), 2.29 (s, 3H); $^{13}C\{^1H\}$ NMR (101 MHz, DMSO) δ 156.9, 145.9, 141.1, 138.1, 134.3, 130.69, 130.28, 129.5, 127.35, 127.02, 124.5, 121.53, 121.25, 120.9, 116.6, 114.78, 114.65, 110.8, 105.6, 55.8, 21.4; HRMS m/z calcd for $C_{23}H_{19}N_3O_3S$ 418.1225 $[M + H]^+$, found 418.1225.

5-Methyl-3-(1-tosyl-1*H*-indol-3-yl)-1*H*-indazole (5d). This compound was synthesized according to the representative procedure as described previously and purified through column chromatography (silica gel, 60−120 mesh), eluting with hexane−EtOAc, 92:8 (v/v), to afford the product **5d** as a white solid (43 mg, 82%): mp 190−195 °C; ^1H NMR (300 MHz, DMSO) δ 13.20 (s, 1H), 8.41 (d, J = 7.8 Hz, 1H), 8.34 (s, 1H), 8.03 (dd, J = 8.3, 6.6 Hz, 3H), 7.95 (s, 1H), 7.52 (d, J = 8.5 Hz, 1H), 7.41 (dq, J = 15.2, 7.4 Hz, 4H), 7.29 (d, J = 8.5 Hz, 1H), 2.53 (s, 3H), 2.30 (s, 3H); $^{13}C\{^1H\}$ NMR (75 MHz, DMSO) δ 145.6, 139.5, 136.9, 134.5, 133.9, 130.29, 130.12, 128.80, 128.54, 126.9, 125.4, 123.93, 123.13, 123.02, 120.8, 119.6, 116.3, 113.2, 110.2, 21.11, 21.03; HRMS m/z calcd for $C_{23}H_{19}N_3O_2S$ 402.1276 $[M + H]^+$, found 402.1276.

3-(5,7-Dimethyl-1-tosyl-1*H*-indol-3-yl)-1*H*-indazole (5e). This compound was synthesized according to the representative procedure as described previously and purified through column chromatography (silica gel, 60−120 mesh), eluting with hexane−EtOAc, 91:9 (v/v), to afford the product **5e** as a white viscous liquid (42 mg, 78%): ^1H NMR (300 MHz, DMSO) δ 13.31 (s, 1H), 8.30 (s, 1H), 8.13−8.01 (m, 2H), 7.77−7.69 (m, 2H), 7.68−7.61 (m, 1H), 7.47 (ddd, J = 8.3, 6.8, 1.0 Hz, 1H), 7.37 (d, J = 8.3 Hz, 2H), 7.29 (ddd, J = 7.9, 6.8, 1.0 Hz, 1H), 7.04−6.98 (m, 1H), 2.55 (s, 3H), 2.36 (s, 3H), 2.32 (s, 3H); $^{13}C\{^1H\}$ NMR (101 MHz, DMSO) δ 145.6, 141.2, 137.9, 135.7, 133.99, 133.54, 131.7, 130.7, 127.5, 126.98, 126.96, 124.5, 121.59, 121.16, 120.93, 120.83, 116.2, 111.0, 21.74, 21.48, 21.17; HRMS m/z calcd for $C_{24}H_{21}N_3O_2S$ 416.1433 $[M + H]^+$, found 416.1433.

5-Methyl-7-phenyl-3-(1-tosyl-1*H*-indol-3-yl)-1*H*-indazole (5f). This compound was synthesized according to the representative procedure as described previously and purified through column chromatography (silica gel, 60−120 mesh), eluting with hexane−EtOAc, 91:9 (v/v), to afford the product **5f** as a gummy liquid (52 mg, 84%): ^1H NMR (400 MHz, DMSO) δ 13.30 (s, 1H), 8.40 (d, J = 10.4 Hz, 2H), 8.08−8.03 (m, 2H), 8.02 (d, J = 2.0 Hz, 1H), 7.94 (s, 1H), 7.74 (d, J = 7.0 Hz, 2H), 7.60−7.53 (m, 2H), 7.50−7.43 (m, 2H), 7.42−7.32 (m, 4H), 2.59 (s, 3H), 2.30 (s, 3H); $^{13}C\{^1H\}$ NMR (101 MHz, DMSO) δ 146.1, 137.99, 137.86, 137.81, 134.95, 134.45, 131.3, 130.7, 129.53, 129.31, 128.68, 128.60, 128.28, 127.4, 125.9, 124.81, 124.39, 123.79, 123.33, 122.4, 119.3, 116.5, 113.7, 21.4; HRMS m/z calcd for $C_{29}H_{23}N_3O_2S$ 478.1589 $[M + H]^+$; found 478.1590.

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3-(5-Fluoro-1-tosyl-1*H*-indol-3-yl)-1*H*-indazole (5g). This compound was synthesized according to the representative procedure as described previously and purified through column chromatography (silica gel, 60−120 mesh), eluting with hexane−EtOAc, 92:8 (v/v), to afford the product **5g** as a white solid (43 mg, 82%): mp 210−215 °C; ^{1}H NMR (300 MHz, DMSO) δ 13.36 (s, 1H), 8.46 (s, 1H), 8.23 (d, J = 8.2 Hz, 1H), 8.13 (dd, J = 9.6, 2.7 Hz, 1H), 8.10−8.00 (m, 3H), 7.63 (d, J = 8.4 Hz, 1H), 7.47 (t, J = 7.6 Hz, 1H), 7.40 (d, J = 8.1 Hz, 2H), 7.38−7.24 (m, 2H), 2.31 (s, 3H); ^{13}C{^{1}H} NMR (75 MHz, DMSO) δ 159.6 (d, J_{C-F} = 237 Hz), 146.3, 141.2, 137.7, 134.24, 131.4, 130.82, 130.29, 127.49, 127.09, 125.4, 121.60, 121.29, 120.7, 115.3, 114.0, 110.9, 108.92, 108.58, 21.5; ^{19}F NMR (282 MHz, DMSO) δ −118.68; HRMS m/z calcd for $C_{22}H_{16}FN_3O_2S$ 406.1026 $[M + H]^+$, found 406.1026.

5-Chloro-3-(1-tosyl-1*H*-indol-3-yl)-1*H*-indazole (5h). This compound was synthesized according to the representative procedure as described previously and purified through column chromatography (silica gel, 60−120 mesh), eluting with hexane−EtOAc, 93:7 (v/v), to afford the product **5h** as an off-white solid (45 mg, 83%): mp 208−212 °C; ^{1}H NMR (400 MHz, DMSO) δ 13.51 (s, 1H), 8.51 (s, 1H), 8.40 (d, J = 7.9 Hz, 1H), 8.32 (d, J = 1.9 Hz, 1H), 8.12−8.00 (m, 3H), 7.66 (d, J = 8.8 Hz, 1H), 7.53−7.31 (m, 5H), 2.30 (s, 3H); ^{13}C{^{1}H} NMR (101 MHz, DMSO) δ 146.0, 139.8, 138.0, 134.86, 134.49, 130.7, 129.0, 127.52, 127.41, 126.0, 125.9, 124.40, 124.34, 123.3, 121.6, 120.5, 115.6, 113.6, 112.6, 21.4; HRMS m/z calcd for $C_{22}H_{16}ClN_3O_2S$ 421.0652 $[M]^+$, found 421.0652.

3-(5-Chloro-1-tosyl-1*H*-indol-3-yl)-1*H*-indazole (5i). This compound was synthesized according to the representative procedure as described previously and purified through column chromatography (silica gel, 60−120 mesh), eluting with hexane−EtOAc, 93:7 (v/v), to afford the product **5i** as a white solid (41 mg, 75%); mp 105−110 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.29 (d, J = 1.6 Hz, 1H), 8.14 (s, 1H), 7.97 (d, J = 8.8 Hz, 2H), 7.81 (d, J = 8.4 Hz, 2H), 7.55 (d, J = 8.4 Hz, 1H), 7.48 (t, J = 8.0 Hz, 1H), 7.35−7.29 (m, 2H), 7.23 (d, J = 8.4 Hz, 2H), 2.35 (s, 3H); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 145.5, 140.8, 138.4, 134.7, 133.4, 130.1, 129.9, 128.1, 126.9, 125.7, 125.54, 122.19, 122.05, 120.91, 120.79, 114.59, 114.41, 110.5, 21.6; HRMS m/z calcd for $C_{22}H_{16}ClN_3O_2S$ 422.0730 $[M + H]^+$, found 422.0730.

3-(1-Tosyl-5-(trifluoromethyl)-1*H*-indol-3-yl)-1*H*-indazole (5j). This compound was synthesized according to the representative procedure as described previously and purified through column chromatography (silica gel, 60−120 mesh), eluting with hexane−EtOAc, 91:9 (v/v), to afford the product **5j** as an off-white solid (46 mg, 78%); mp 206−209 °C; ^{1}H NMR (300 MHz, DMSO) δ 13.42 (s, 1H), 8.83 (s, 1H), 8.59 (s, 1H), 8.28 (d, J = 8.5 Hz, 2H), 8.10 (d, J = 8.1 Hz, 2H), 7.80 (dd, J = 8.9, 1.9 Hz, 1H), 7.65 (d, J = 8.4 Hz, 1H), 7.53−7.38 (m, 3H), 7.31 (t, J = 7.5 Hz, 1H), 2.32 (s, 3H); ^{13}C{^{1}H} NMR (75 MHz, DMSO) δ 146.6, 141.1, 137.6, 136.5, 134.1, 130.9, 128.8, 127.59, 127.1, 126.9, 125.52, 125.33, 124.9, 123.3, 122.5, 121.70, 121.34, 120.7, 116.2, 114.7, 111.0, 21.5; ^{19}F NMR (282 MHz, DMSO) δ −59.70; HRMS m/z calcd for $C_{23}H_{16}F_3N_3O_2S$ 455.0915$[M]^+$, found 455.0915.

5-Nitro-3-(1-tosyl-1*H*-indol-3-yl)-1*H*-indazole (5k). This compound was synthesized according to the representative procedure as described previously and purified through column chromatography (silica gel, 60−120 mesh), eluting with hexane−EtOAc, 90:10 (v/v), to afford the product **5k** as a yellow solid (43 mg, 76%): mp 190−195 °C; ^{1}H NMR (400 MHz, DMSO) δ 13.97 (s, 1H), 9.08 (d, J = 2.0 Hz, 1H), 8.68 (s, 1H), 8.36−8.21 (m, 3H), 8.05 (d, J = 7.6 Hz, 3H), 7.81 (d, J = 9.1 Hz, 1H), 7.47 (dd, J = 9.9, 7.9 Hz, 2H), 7.41 (dd, J = 8.0, 2.7 Hz, 3H), 7.12 (d, J = 7.8 Hz, 1H), 2.31 (s, 3H), 2.29 (s, 1H); ^{13}C{^{1}H} NMR (101 MHz, DMSO) δ 146.2, 143.2, 142.5, 141.3, 138.0, 136.9, 134.91, 134.45, 130.7, 128.80, 128.49, 127.5, 126.0, 125.98, 125.51, 124.5, 123.0, 122.3, 121.9, 120.1, 119.4, 114.8, 113.7, 111.8, 21.50, 21.24; HRMS m/z calcd for $C_{22}H_{16}N_4O_4S$ 433.0971 $[M + H]^+$, found 433.0971.

5-Methyl-3-(5-methyl-1-tosyl-1*H*-indol-3-yl)-1*H*-indazole (5l). This compound was synthesized according to the representative procedure as described previously and purified through column chromatography (silica gel, 60−120 mesh), eluting with hexane−EtOAc, 92:8 (v/v), to afford the product **5l** as an off-white solid (42 mg, 79%): mp 153−158 °C; ^{1}H NMR (300 MHz, DMSO) δ 13.16 (s, 1H), 8.28 (s, 1H), 8.21 (s, 1H), 7.95 (dd, J = 19.2, 8.5 Hz, 4H), 7.52 (d, J = 8.5 Hz, 1H), 7.38 (d, J = 8.1 Hz, 2H), 7.32−7.24 (m, 2H), 2.53 (s, 3H), 2.42 (s, 3H), 2.30 (s, 3H); ^{13}C{^{1}H} NMR (75 MHz, DMSO) δ 145.9, 139.8, 137.5, 134.4, 133.56, 133.25, 130.68, 130.54, 129.5, 128.9, 127.35, 127.16, 123.73, 123.22, 121.2, 120.0, 116.6, 113.4, 110.6, 21.56, 21.55, 21.48; HRMS m/z calcd for $C_{24}H_{21}N_3O_2S$ 438.1252 $[M + Na]^+$, found 438.1252.

5-Chloro-3-(5-methyl-1-tosyl-1*H*-indol-3-yl)-1*H*-indazole (5m). This compound was synthesized according to the representative procedure as described previously and purified through column chromatography (silica gel, 60−120 mesh), eluting with hexane−EtOAc, 92:8 (v/v), to afford the product **5m** as a white crystal solid (46 mg, 81%): mp 225 °C; ^{1}H NMR (300 MHz, DMSO) δ 13.48 (s, 1H), 8.44 (s, 1H), 8.30 (d, J = 1.9 Hz, 1H), 8.20 (s, 1H), 8.02 (d, J = 8.2 Hz, 2H), 7.92 (d, J = 8.5 Hz, 1H), 7.66 (d, J = 8.8 Hz, 1H), 7.47 (dd, J = 8.8, 1.8 Hz, 1H), 7.38 (d, J = 8.1 Hz, 2H), 7.26 (dd, J = 8.5, 1.7 Hz, 1H), 2.42 (s, 3H), 2.30 (s, 3H); ^{13}C{^{1}H} NMR (75 MHz, DMSO) δ 145.9, 139.7, 138.0, 134.4, 133.61, 133.18, 130.6, 129.2, 127.44, 127.40, 127.20, 126.0, 124.4, 123.0, 121.6, 120.5, 115.5, 113.4, 112.6, 21.54, 21.48; HRMS m/z calcd for $C_{23}H_{18}ClN_3O_2S$ 436.0887 $[M + H]^+$, found 436.0887.

3-(5-Methyl-1-tosyl-1*H*-indol-3-yl)-5-nitro-1*H*-indazole (5n). This compound was synthesized according to the representative procedure as described previously and purified through column chromatography (silica gel, 60−120 mesh), eluting with hexane−EtOAc, 90:10 (v/v), to afford the product **5n** as a yellow solid (46 mg, 80%); mp 192−196 °C; ^{1}H NMR (300 MHz, DMSO) δ 13.93 (s, 1H), 9.09−9.00 (m, 1H), 8.62 (s, 1H), 8.31−8.22 (m, 1.45H), 8.13−8.09 (m, 1H), 8.01 (dd, J = 6.6, 1.8 Hz, 2H), 7.93 (d, J = 8.5 Hz, 1H), 7.81 (d, J = 9.2 Hz, 1H), 7.73 (d, J = 9.3 Hz, 0.37H), 7.49−7.37 (m, 3H), 7.29 (dd, J = 8.6, 1.8 Hz, 1H), 7.19−7.01 (m, 1H), 6.88 (d, J = 8.4 Hz, 0.27H), 2.45 (s, 0.5H), 2.43 (s, 3H), 2.31 (s, 3H), 2.29 (s, 0.5H); ^{13}C{^{1}H} NMR (75 MHz, DMSO) δ 146.1, 143.1, 142.4, 134.3, 133.86, 133.21, 130.7, 129.0, 128.5, 127.46, 127.38, 125.6, 122.72, 122.00, 120.1, 119.5, 114.7, 113.5, 21.53, 21.50; HRMS m/z calcd for $C_{23}H_{18}N_4O_4S$ 447.1127 $[M + H]^+$, found 447.1127.

***tert*-Butyl 3-(1*H*-indazol-3-yl)-1*H*-indole-1-carboxylate (5o).** This compound was synthesized according to the representative procedure as described previously and purified through column chromatography (silica gel, 60−120 mesh), eluting with hexane−EtOAc, 91:9 (v/v), to afford the product **5o** as a brown liquid (32 mg, 75%): ^{1}H NMR (300 MHz, DMSO) δ 13.29 (s, 1H), 8.44 (dd, J = 7.4, 1.5 Hz, 1H), 8.23 (s, 1H), 8.17 (d, J = 8.1 Hz, 1H), 8.04 (d, J = 8.2 Hz, 1H), 7.63 (d, J = 8.4 Hz, 1H), 7.48−7.35 (m, 3H), 7.26 (ddd, J = 8.0, 6.9, 1.0 Hz, 1H), 1.70 (s, 9H); ^{13}C{^{1}H} NMR (101 MHz, DMSO) δ 149.0, 140.8, 138.1, 134.8, 128.3, 126.4, 125.0, 123.1, 122.84, 122.39, 120.96, 120.53, 120.42, 114.73, 114.13, 110.5, 84.2, 27.7; HRMS m/z calcd for $C_{20}H_{19}N_3O_2$ 334.1556 $[M + H]^+$; found 334.1554.

3-(5-Methyl-1-tosyl-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)-1*H*-indazole (5p). This compound was synthesized according to the representative procedure as described previously and purified through column chromatography (silica gel, 60−120 mesh), eluting with hexane−EtOAc, 88:12 (v/v), to afford the product **5p** as a gray solid (39 mg, 74%): mp 182−187 °C; ^{1}H NMR (300 MHz, DMSO) δ 13.32 (s, 1H), 8.52 (dd, J = 2.2, 0.9 Hz, 1H), 8.39 (s, 1H), 8.32 (d, J = 2.3 Hz, 1H), 8.19 (dd, J = 8.2, 1.0 Hz, 1H), 8.14−8.05 (m, 2H), 7.64 (dt, J = 8.4, 1.0 Hz, 1H), 7.51−7.38 (m, 3H), 7.29 (ddd, J = 8.0, 6.8, 0.9 Hz, 1H), 2.43 (s, 3H), 2.33 (s, 3H); ^{13}C{^{1}H} NMR (75 MHz, DMSO) δ 146.57, 146.03, 145.8, 141.3, 137.9, 135.0, 131.7, 130.4, 129.5, 128.1, 127.0, 123.4, 121.60, 121.19, 121.14, 120.6, 113.2, 111.0, 21.5, 18.4; HRMS m/z calcd for $C_{22}H_{18}N_4O_2S$ 402.1150 $[M]^+$, found 402.1150.

5-Methyl-3-(5-methyl-1-tosyl-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)-1*H*-indazole (5q). This compound was synthesized according to the representative procedure as described previously and purified through column chromatography (silica gel, 60−120 mesh), eluting with hexane−EtOAc, 88:12 (v/v), to afford the product **5q** as a gray

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solid (38 mg, 71%): mp 180–185 °C; ^{1}H NMR (400 MHz, DMSO) δ 8.56–8.51 (m, 1H), 8.38 (s, 1H), 8.31 (d, J = 2.1 Hz, 1H), 8.08 (d, J = 8.1 Hz, 2H), 7.96 (s, 1H), 7.52 (d, J = 8.5 Hz, 1H), 7.42 (d, J = 8.2 Hz, 2H), 7.30 (d, J = 8.5 Hz, 1H), 2.53 (s, 3H), 2.43 (s, 3H), 2.34 (s, 3H); ^{13}C{^{1}H} NMR (101 MHz, DMSO) δ 146.51, 146.00, 145.8, 140.0, 137.3, 135.0, 131.8, 130.67, 130.44, 129.75, 129.48, 129.06, 128.1, 126.0, 123.2, 121.2, 120.9, 119.9, 113.4, 110.7, 21.5, 18.4; HRMS m/z calcd for $C_{23}H_{20}N_4O_2S$ 417.1385 [M + H]$^+$, found 417.1385.

3-Phenyl-3-(1-tosyl-1*H*-indol-3-yl)-3*H*-indazole (7a): gray solid (47 mg, 92%); mp 85–90 °C; ^{1}H NMR (300 MHz, DMSO) δ 8.35 (dd, J = 5.9, 2.3 Hz, 1H), 7.97 (dd, J = 5.9, 2.8 Hz, 1H), 7.90 (d, J = 8.5 Hz, 3H), 7.76–7.63 (m, 2H), 7.39 (d, J = 7.9 Hz, 2H), 7.37–7.29 (m, 6H), 7.20–7.11 (m, 3H), 2.32 (s, 3H); ^{13}C{^{1}H} NMR (75 MHz, DMSO) δ 156.1, 146.3, 142.9, 136.4, 135.2, 134.0, 131.5, 130.84, 130.50, 129.54, 129.18, 128.9, 127.4, 126.6, 125.8, 124.73, 124.37, 124.09, 122.89, 122.32, 119.2, 113.8, 96.7, 21.5; HRMS m/z calcd for $C_{28}H_{21}N_3O_2S$ 464.1433 [M + H]$^+$; found 464.1433.

3-(4-Chlorophenyl)-3-(1-tosyl-1*H*-indol-3-yl)-3*H*-indazole (7b). This compound was synthesized according to the representative procedure as described previously and purified through column chromatography (silica gel, 60–120 mesh), eluting with hexane–EtOAc, 95:5 (v/v), to afford the product **7b** as a white liquid (48 mg, 88%): ^{1}H NMR (400 MHz, DMSO) δ 8.36 (dd, J = 6.8, 1.9 Hz, 1H), 8.00–7.95 (m, 1H), 7.89 (d, J = 8.2 Hz, 3H), 7.71 (ddd, J = 6.6, 4.7, 1.4 Hz, 2H), 7.43–7.37 (m, 4H), 7.37–7.31 (m, 3H), 7.22–7.15 (m, 3H), 2.32 (s, 3H); ^{13}C{^{1}H} NMR (101 MHz, DMSO) δ 156.1, 146.3, 142.5, 135.35, 135.18, 134.0, 133.7, 131.7, 130.85, 130.67, 129.6, 128.95, 128.63, 127.4, 125.8, 124.87, 124.34, 124.16, 123.0, 122.1, 118.6, 113.8, 96.1, 21.5; HRMS m/z calcd for $C_{28}H_{20}ClN_3O_2S$ 498.1043 [M + H]$^+$; found 498.1034.

5-Methyl-3,7-diphenyl-3-(1-tosyl-1*H*-indol-3-yl)-3*H*-indazole (7c). This compound was synthesized according to the representative procedure as described previously and purified through column chromatography (silica gel, 60–120 mesh), eluting with hexane–EtOAc, 94:6 (v/v), to afford the product **7c** as a white solid (52 mg, 86%); mp 192–197 °C; ^{1}H NMR (400 MHz, DMSO) δ 8.01 (d, J = 1.4 Hz, 1H), 7.99 (d, J = 1.5 Hz, 1H), 7.92 (d, J = 2.0 Hz, 1H), 7.91–7.88 (m, 2H), 7.71 (d, J = 1.5 Hz, 1H), 7.66 (d, J = 0.8 Hz, 1H), 7.60–7.55 (m, 2H), 7.53–7.47 (m, 1H), 7.41 (d, J = 8.6 Hz, 2H), 7.39 (s, 1H), 7.36–7.31 (m, 5H), 7.21–7.14 (m, 3H), 2.53 (s, 3H), 2.33 (s, 3H); ^{13}C{^{1}H} NMR (75 MHz, DMSO) δ 151.7, 146.3, 144.6, 142.5, 136.66, 136.63, 135.40, 135.23, 134.0, 130.84, 130.66, 130.25, 129.54, 129.26, 129.13, 128.97, 128.90, 127.5, 126.7, 125.7, 124.88, 124.08, 123.7, 122.3, 119.4, 113.8, 96.2, 21.74, 21.53; HRMS m/z calcd for $C_{35}H_{27}N_3O_2S$ 554.1902 [M + H]$^+$; found 554.1901.

3-(1*H*-Indol-3-yl)-1*H*-indazole (5a′): white solid (27 mg, 90%); mp 245–250 °C; ^{1}H NMR (300 MHz, $CDCl_3$–methanol-d_4) δ 8.04 (dd, J = 7.6, 3.3 Hz, 1H), 7.96–7.87 (m, 1H), 7.71 (d, J = 5.4 Hz, 1H), 7.50 (dd, J = 8.5, 5.6 Hz, 1H), 7.47–7.35 (m, 2H), 7.31 (s, 1H), 7.25–7.08 (m, 3H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$–methanol-d_4) δ 141.1, 136.5, 127.6, 124.1, 122.5, 121.65, 121.05, 120.7, 111.5, 110.4; HRMS m/z calcd for $C_{15}H_{11}N_3$ 234.1031 [M + H]$^+$; found 234.1031.

■ ASSOCIATED CONTENT

Data Availability Statement

The data underlying this study are available in the published article and its Supporting Information.

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.joc.4c00377.

General information, experimental procedure, control experiment, physical data of synthesized compounds, copies of NMR spectra, HRMS spectra of final products, and X-ray crystallographic data and structure of **5m** (PDF)

Accession Codes

CCDC 2297939 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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