SYNOPSIS OF

STUDIES ON THE SYNTHESIS, CHARACTERIZATION AND BIOLOGICAL ACTIVITIES OF SOME NOVEL PIPERAZINE AND TRIAZOLE DERIVATIVES

A thesis
submitted
In fulfilment of the requirement for the award of the Degree of Doctor of Philosophy (Engineering)

Jadavpur University
2017

By

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- **INTRODUCTION:**

Various biologically active synthetic compounds have nitrogen containing heterocyclic ring in their structures. Two such important heterocycles are piperazine & triazoles.

In our present work we have synthesized some new chemical entities containing the triazole and piperazine nucleus. These new chemical entities were screened for their anticonvulsant and antibacterial activity based on their design and chemical structure.

Piperazine is an organic compound that consists of a six-member ring containing two nitrogen atoms at opposite positions in the ring. The piperazines are a broad class of chemical compounds, many with important pharmacological properties.

Table 1: Few examples of common drugs containing the piperazine nucleus

Serial number	Name of the drug	Uses	Reference
1.	Ziprasidone	Atypical antipsychotic	Hagop S *et al*. [1]
2.	Ciprofloxacin	Antibiotic	Drusano GL *et al*. [2]
3.	Levofloxacin	Antibiotic	Nelson JM *et al*. [3]
4.	Flunarizine	Anticonvulsant	Fischer W *et al*. [4]
5.	Cinnarizine	Anticonvulsant	L K Desmedt *et al*. [5]

Triazoles are five member aromatic systems with hetero atoms at symmetrical positions. Their biological activity has been studied extensively.

Table 2: Few examples of common drugs containing the triazole nucleus

Serial number	Name of the drug	Uses	Reference
1.	Rufinamide	Anticonvulsant	Hakimian S *et al*. [6]
2.	Fluconazole	Antifungal	"WHO Model List of EssentialMedicines". World Health Organization. October 2013. Retrieved 22 April 2014 (a) [7]
3.	Ribavirin	Antiviral	"WHO Model List of EssentialMedicines". World Health Organization. October 2013. Retrieved 22 April 2014 (b) [8]
4.	Dapiprazole	An alpha blocker	Doughty *et al*. [9]

Considering the importance of these two heterocyclic compounds in medicinal chemistry, the present work was designed on piperazines and triazoles.

- **MOTIVATION**

We have tried to synthesize new compounds containing the triazole ring, the piperazine ring or both. The synthetic work is categorized into two main divisions based on the biological activity of the synthesized molecules. Those are:

1) Compounds which are supposed to act as anticonvulsant/ antiepileptic agents and

2) Compounds which are supposed to act as antibacterial agents

Anticonvulsant/ Antiepileptic

Epilepsy, which is a devastating neurological disease, affects more than 50 million people in the world. The cost of treatment and loss of productivity to the society are also staggering.

With the motivation of finding suitable anticonvulsant agents, some novel compounds were synthesized and were screened for their anticonvulsant activity by subcutaneous Pentylenetetrazole method.

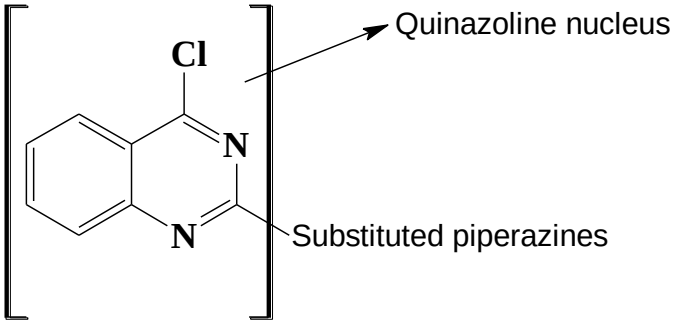
Antibacterial

An antibacterial is an agent that interferes with the growth and reproduction of bacteria. The rampant use of antibiotics for the last 10 years by doctors as well as due to over-the-counter sale has led to a serious health care crisis. Therapy to bacterial infections is getting difficult because bacteria is evolving and becoming more immune to existing antibiotics. With the motivation of finding new antibacterial agents, eight novel fluoroquinolones were synthesized, characterised and tested for their antibacterial activity.

The fluoroquinolones are a family of broad spectrum, systemic antibacterial agents that have been used widely as therapy of respiratory and urinary tract infections. Fluoroquinolones are active against a wide range of aerobic Gram-positive and Gram-negative organisms.

- **OBJECTIVE OF THE PRESENT WORK**

- To synthesize and characterize new 4-chloro-2-(4-substituted-piperazin-1-yl) quinazoline derivatives and screen them for their anticonvulsant activity by subcutaneous Pentylenetetrazole method.



Schematic representation of 4-chloro-2-(4-substituted-piperazin-1-yl) quinazoline derivatives

- To synthesize and characterize new compounds by incorporating modifications on the 1-(2, 6-difluorobenzyl)-1H-1, 2, 3-triazole nucleus. Listed below are the four groups of compounds synthesized in line with the stated objective

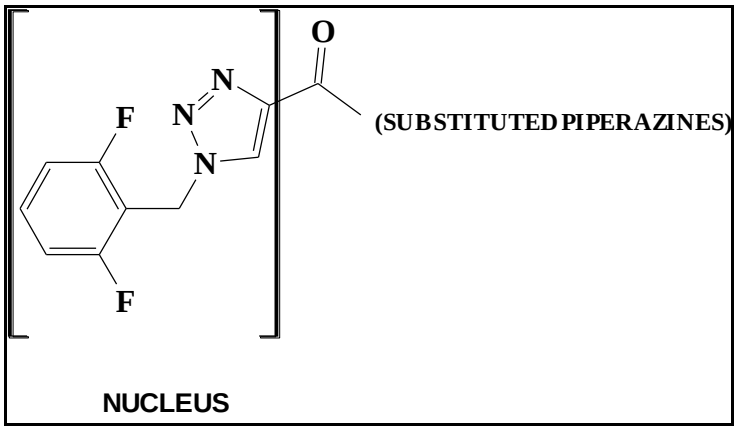
✓ 1-(2, 6-difluorobenzyl)-1H-1, 2, 3-triazol-4-yl] (4- substituted piperazin-1-yl) methanones

✓ [5-chloro-1-(2, 6-difluorobenzyl)-1H-1, 2, 3-triazol-4-yl] (4-substituted piperazin-1-yl) methanones

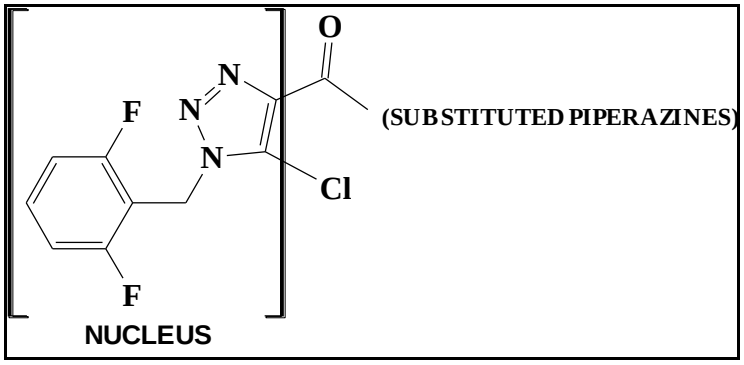
✓ Substituted 2-[5-chloro-1-(2, 6-difluorobenzyl)-1H-1, 2, 3-triazol-4-yl]-1, 3, 4-oxadiazoles

✓ Substituted 2-[1-(2, 6-difluorobenzyl)-1H-1, 2, 3-triazol-4-yl]-1, 3, 4-oxadiazoles

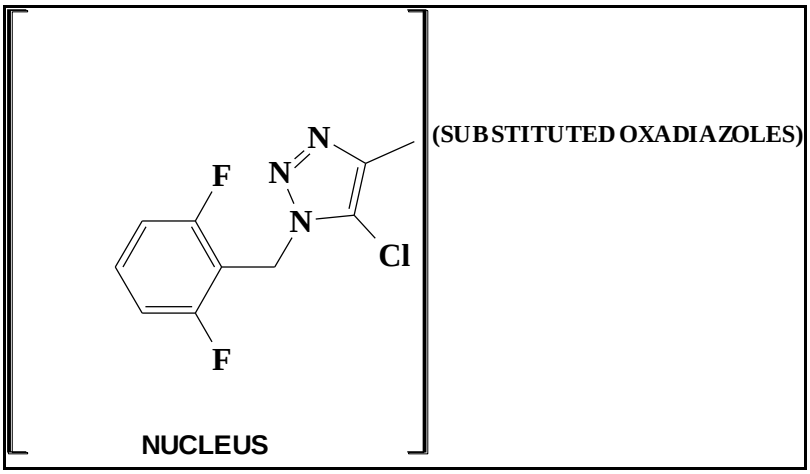
All the compounds were screened for their anticonvulsant activity by subcutaneous Pentylenetetrazole induced seizures/ convulsions.



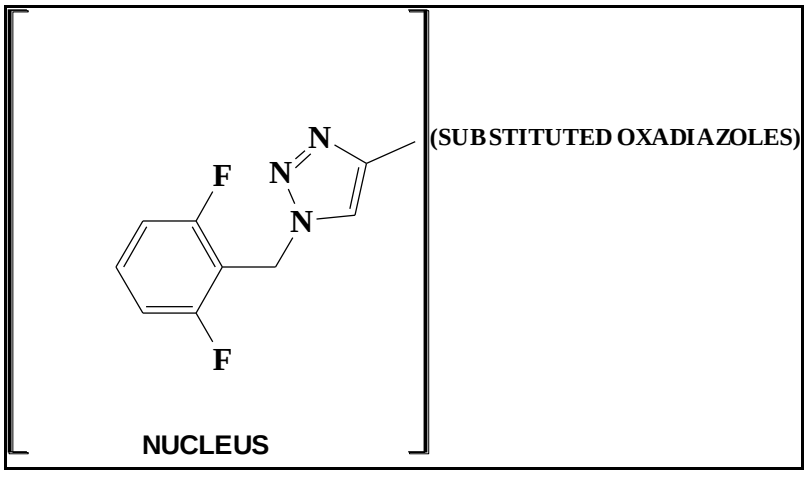
Schematic representation of 1-(2, 6-difluorobenzyl)-1H-1, 2, 3-triazol-4-yl] (4-substituted piperazin-1-yl) methanones



Schematic representation of [5-chloro-1-(2, 6-difluorobenzyl)-1H-1, 2, 3-triazol-4-yl] (4-substituted piperazin-1-yl) methanones

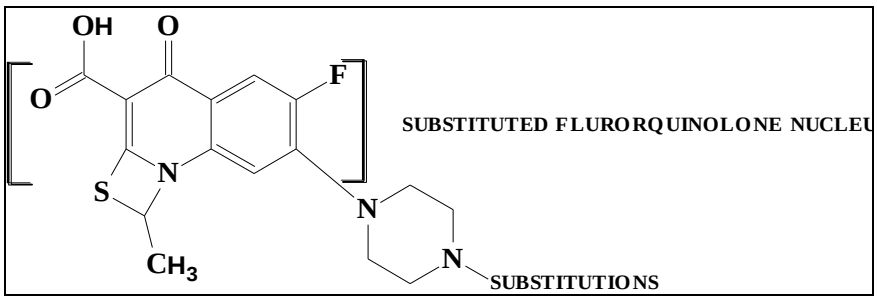


Schematic representation of substituted 2-[5-chloro-1-(2, 6-difluorobenzyl)-1H-1, 2, 3-triazol-4-yl]-1, 3, 4-oxadiazoles



Schematic representation of substituted 2-[1-(2, 6-difluorobenzyl)-1H-1, 2, 3-triazol-4-yl]-1, 3, 4-oxadiazoles

- To synthesize and characterize new compounds by incorporating modifications on the piperazine nucleus of the 6-fluoro-1-methyl-4-oxo-7-(piperazin-1-yl)-4H- [1, 3] thiazeto [3, 2-a] quinoline-3-carboxylic acid and evaluating them on their antibacterial activity.



Schematic representation of substitutions on the piperazine nucleus of 6-fluoro-1-methyl-4-oxo-7-(piperazin-1-yl)-4H- [1, 3] thiazeto [3, 2-a] quinoline-3-carboxylic acid

The synthesized compounds were tested against Gram-positive and Gram-negative bacteria in order to access their potential as antibacterial agents.

- **DESCRIPTION OF THE RESEARCH WORK**

Anticonvulsant/Antiepileptic

The first category of synthesized molecules was designed to act as anticonvulsant/ antiepileptic drugs.

In this category five different types of molecules were synthesized based on the structural pattern. Each group of molecules has a piperazine or a triazole or both the moieties.

The five categories involve the synthesis, characterization and anticonvulsant activity of:

I. 4-chloro-2-(4-substituted-piperazin-1-yl) quinazoline derivatives
II. 1-(2, 6-difluorobenzyl)-1H-1, 2, 3-triazol-4-yl] (4- substituted piperazin-1-yl) methanones
III. [5-chloro-1-(2, 6-difluorobenzyl)-1H-1, 2, 3-triazol-4-yl] (4-substituted piperazin-1-yl) methanones
IV. Substituted 2-[5-chloro-1-(2, 6-difluorobenzyl)-1H-1, 2, 3-triazol-4-yl]-1, 3, 4-oxadiazoles
V. Substituted 2-[1-(2, 6-difluorobenzyl)-1H-1, 2, 3-triazol-4-yl]-1, 3, 4-oxadiazoles

The synthesis and isolation was carried out.

The synthesized new compounds were characterized.

All the compounds were screened for anticonvulsant activity.

The molecules were accessed on their anticonvulsant/ antiepileptic activity based on protection against subcutaneous Pentylenetetrazole induced seizures/ convulsions.

Antibacterial Activity

In our work we have tried to explore the effect of the substituted phenyl, biphenyl, quinoline and pyrazole substitutions at the piperazine ring of the fluoroquinolone nucleus in 6-fluoro-1-methyl-4-oxo-7-(piperazin-1-yl)-4*H*-[1,3]thiazeto[3,2-*a*]quinoline-3-carboxylic acid. The synthesized molecules were characterized and checked for antibacterial activity.
Evaluation of antibacterial activity and determination of minimum inhibitory concentration of the synthesized molecules was done by disk diffusion method.

- **SUMMARY AND CONCLUSIONS:**

Anticonvulsant /Antiepileptic Activity

- Studies on the synthesis, characterization and anticonvulsant activity of 4-chloro-2-(4-substituted-piperazin-1-yl) quinazoline derivatives yielded following results and related conclusions were derived.
    - ✓ The synthesized new compounds were characterized.
    - ✓ All the compounds were screened for anticonvulsant activity.
    - ✓ The molecules were accessed on their anticonvulsant/ antiepileptic activity based on protection against subcutaneous Pentylenetetrazole induced seizures/ convulsions.
    - ✓ The effect of the compounds was measured by the latency of tonic convulsion and the duration of clonus. The mortality ratio and the recovery were calculated.
    - ✓ The molecules with aryl substituted and alkyl substituted piperazines showed better protection against subcutaneous Pentylenetetrazole induced seizures/ convulsions than un-substituted piperazines.

- ✓ The active compounds prevented tonic convulsions and no clonus was observed. 100% of the animals recovered from the induced seizure and no deaths were recorded.

- In the study on synthesis, characterization and anticonvulsant activity of 1-(2, 6-difluorobenzyl)-1H-1, 2, 3-triazol-4-yl] (4- substituted piperazin-1-yl) methanones and [5-chloro-1-(2, 6-difluorobenzyl)-1H-1, 2, 3-triazol-4-yl] (4-substituted piperazin-1-yl) methanones the following results were achieved and related conclusions derived.

  - ✓ The synthesized new compounds were characterized.
  - ✓ All the compounds were screened for anticonvulsant activity.
  - ✓ The molecules were accessed on their anticonvulsant/ antiepileptic activity based on protection against subcutaneous Pentylenetetrazole induced seizures/ convulsions.
  - ✓ The molecules with aryl substituted and alkyl substituted piperazines showed better protection against subcutaneous Pentylenetetrazole induced seizures/ convulsions than un- substituted and methyl substituted piperazines.
  - ✓ The effect of the compounds was measured by the latency of tonic convulsion and the duration of clonus. The mortality ratio and the recovery were calculated.
  - ✓ The active compounds prevented tonic convulsions and no clonus was observed. 100% of the animals recovered from the induced seizure and no deaths were recorded.

VI. In the study on synthesis, characterization and anticonvulsant activity of substituted 2-[5-chloro-1-(2, 6-difluorobenzyl)-1H-1, 2, 3-triazol-4-yl]-1, 3, 4-oxadiazoles and substituted 2-[1-(2, 6-difluorobenzyl)-1H-1, 2, 3-triazol-4-yl]-1, 3, 4-oxadiazoles the following results were achieved and related conclusions derived.

- ✓ The synthesized new compounds were characterized.
- ✓ All the compounds were screened for anticonvulsant activity.
- ✓ Protection was offered by all the synthesized compounds against subcutaneous Pentylenetetrazole induced threshold seizure.

- ✓ All the compounds prevented tonic convulsions and no clonus was observed. 100% of the animals recovered from the induced seizure and no deaths were recorded.

Antibacterial Activity

- The results and conclusions from the synthesis, characterization and antibacterial activity of some N-substituted derivatives of 6-fluoro-1-methyl-4-oxo-7-(piperazin-1-yl)-4H-[1,3]thiazeto[3,2-a]quinoline-3-carboxylic acid are listed below.
  - ✓ The synthesized new compounds were characterized.
  - ✓ All the eight derivatives were subjected to antibacterial activity. Among the tested compounds seven compounds showed antibacterial activity against *Bacillus subtilis* (Gram-positive bacteria). None of the compounds showed zone of inhibition against *Escherichia coli* (Gram-negative bacteria).
  - ✓ Some of the active compounds showed higher zone of inhibition for *Bacillus subtilis* at a concentration of 1024 (µg/ml) with respect to the standard.

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