ABSTRACT OF THE THESIS

The research work reported in this dissertation consists of synthesis of pharmacologically active compounds and the modification of their structure according to the result of pharmacological screening. All these synthesized compounds were characterized by satisfactory spectroscopic data. These compounds belong to the classes of 1,3,4-oxadiazole-2(3H)-thione and 1,2,4-triazole-3(4H)-thione. All these compounds were screened for different biological activities including bactericidal, fungicidal, analgesic, anti-inflammatory, anxiolytic and anticonvulsant activities and as expected most of them had exhibited moderate to good activities.

Scheme I & Scheme II: Here focus was made mainly on the synthesis of 1,2,4-triazoline-3-thione as the essential pharmacophore and investigation of its combination with various N-substituted carboxamidoalkylthio moiety through sulfur atom and converting them to corresponding sulfoxides and sulfones selectively by solid state green oxidation method using Oxone®.

Analgesic and Anti-inflammatory activity: All the synthesized triazole derivatives (11a-k) were found to exhibit potent anti-inflammatory activity but lower analgesic activity as compared to (6a-k). It might be due to increase in distance between aromatic nucleus and side chain nitrogen by one carbon atom as to exhibit analgesic activity, molecule should contain one aromatic nucleus attached to quaternary carbon then ethylene bridge and tertiary nitrogen. N-Phenyl carboxamidoethylthio-(4H)-1,2,4-triazole (11a) had exhibited equipotent anti-inflammatory and analgesic activity as compared to standard drug.

Anxiolytic Activity: All the compounds (6a-k and 11a-k) were tested for their Anxiolytic activity. There was increase in percent time spent and number of entries in the open arm but the Anxiolytic activity was found to be very less as compared to diazepam.

Antimicrobial Activity: Among the compounds 6a-k and 11a-k, particularly, compounds having chloro substituent on phenyl ring exhibited more activity at MIC value of 125 µg/ml. All compounds of the series have shown less activity against the tested fungi.

Molecular Docking Study: In order to investigate mechanism involved in anti-inflammatory activity we have carried out molecular docking of compounds 11a which had shown comparable inhibition as that of Diclofenac Sodium. Stereochemistry of 11a revealed characteristic ring chain and amide-amidic tautomerism. We have derived six principal neutral possible tautomeric forms for compounds 11a and carried out docking study. The lowest conformational energy tautomer 2 might be the best conformation for compounds 11a to interact with COX-1 receptor. In mapping, it was observed that compounds 11a docked near the gate of COX-1. Finally, we concluded that interference in arachidonic acid binding channel might be possible mode of action of compound 11a, wherein tautomerism plays vital role in selective inhibition of COX-1.

Scheme III: In this study we have prepared biheterocycle wherein biologically interesting pyridine heterocycle has been linked to triazole. All the compounds (7a-e) were found to displayed betted antibacterial activity compared with their antifungal activity. It was found that compound 7d and 7c showed good inhibition with MIC value 16µg/ml against tested bacteria.

Scheme IV and Scheme V: The results obtained for antimicrobial activity revealed
that in general, the inhibitory activity against the gram-positive bacteria was higher than that of the gram-negative bacteria. In regard to structure the most important variable affecting the activity was the oxidation of sulfur to sulfoxides and sulfones. In each case the sulfoxides and sulfones proved to be more potent than corresponding sulfides. Moreover, little distinction and no discernable trends were observed in comparing the sulfoxides with corresponding sulfones and both exhibit the said activities to the same extent. In the sulfide series, compounds 8k and 8l, in which side chain nitrogen was incorporated into pyrrolidine and morpholine ring respectively were more active than other compounds in the series. The same trend was observed in case of sulfoxides and sulfones. Among the substituents on the phenyl ring 4-chloro has shown greater influence on biological activity in each series. Oxone® is proved as an excellent green oxidant promoting highly chemo selective and fast oxidation of sulfide to sulfoxide and sulfone. We conclude that this solid state oxidation method meets the need to contemporary “green chemistry” and is suitable for practical synthesis.

**Scheme VI:** The existence of a hydrophobic unit, an electron donor group and H-bonding domain was essential for anticonvulsant activity as depicted by the models and also evidenced by active drug Phenytoin and Hibicon. Anticonvulsant data of MES and PTZ screening revealed that compounds 8a, 8c, 8d and 9d had significant activity (P< 0.01) compared to standard drug Phenytoin and control group, respectively. Compound 9h was found to be significant but with P< 0.05.

a) In both sulfide and sulfoxides series, compounds (8d and 9d) having 2-furyl substituent at 5th position of oxadiazole ring had significant activity compared to other substituents.

b) In general all sulfides were found more active than their corresponding sulfoxides.

c) Activity decreases by increasing the carbon chain by one –CH₂ group.

**Docking analysis of 8d into the active site of GABA receptor revealed that**

a) Presence of aromatic ring vital for the drug to act as potent anticonvulsant agent.

b) Presence of amide moiety and hydrophobic group adjacent to each other is favorable for activity and further substitution of aromatic nucleus with any bulky substituent may enhance hydrophobic interaction with receptor.

c) Substitution of oxadiazole nitrogen with any electronegative functional group enhances the electrostatic interaction with receptor which in turn beneficial for anticonvulsant activity.

d) Presence of furan ring enhances the hydrophobicity of the scaffold and further substitution of furan ring with any bulky group may increase the affinity of scaffold towards GABA receptor.

Receptor based pharmacophore modeling of 8d revealed that

a) Aromatic ring facing the hydrophobic surface of the receptor signifies that presence of aromatic ring is beneficial for anticonvulsant activity.

b) Ortho position of aromatic ring facing hydrogen bonding area revealed that substitution of H-bond acceptor at ortho position of aromatic ring enhances the electrostatic interaction, whereas para position is directing towards hydrophobic surface of GABA receptor and there might be requirement of any bulky group that impart hydrophobicity to the scaffold.

c) The carbon chain imparts excellent flexibility to the structure to acquire desired conformation into the GABA receptor pocket.
From this study four compounds (8a, 8c, 8d and 9d) have emerged as lead molecules, further structural modification might lead to the discovery of more potent anticonvulsant agents.

Scheme VII: In this we have prepared hybrid compounds that comprise both the pyridine and oxadiazole heterocycle by one-pot synthesis from malononitrile, aromatic aldehyde, ketone derivative and ammonium acetate under MW irradiation without solvent. The antimicrobial screening results revealed that inhibitory activity against the bacterial species was higher than that of fungal species. Compound 6c showed good antibacterial activity while all the tested compounds showed weak to moderate activity towards the selected pathogenic fungi.

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