INTRODUCTION
1. INTRODUCTION

The chance of discovering a new drug is 1 in 10,000 and development costs about 40 million dollars per new drug. This gives the emphasis on the development of new scientific approaches in discovery of new drugs, “Drug design”. It involves the study of effects of biologically active compounds on the basis of molecular interactions in terms of molecular structure or its physiochemical properties.

The current trend in drug design is to develop new clinically effective agents through the structural modification of lead nucleus which is a prototype compound that has the desired pharmacological activity but may have many undesirable characteristics. Identification of such lead compounds and optimum bioactive position on basic skeleton is the area of drug design. Lead can be identified by following methods:
(a) random screening (b) non random screening (c) drug metabolism studies (d) chemical observations (e) rational approaches of drug design. The knowledge about receptors and the mode of interaction with drug molecules plays an important role in drug design, to develop conformationally bioactive skeletons having exact three dimensional complementarily to a receptor.

Optimization of the lead: Various approaches are employed in order to improve the desired pharmacological properties of the lead nucleus. (a) identification of active part (pharmacophore) (b) functional group optimization (c) structure activity relationship studies (SAR) (d) homologation (e) cyclization of side chain (d) bioisosterism (These are substituents or groups that have similar physical or chemical properties and hence similar biological activity pattern.

Prodrug design defined as the chemical modification of biologically active compound to form a new compound which upon in vivo enzymatic attack will liberate the present compound.

Soft drugs defined as therapeutically beneficial agents characterized by predictable and controllable in vivo metabolism to non toxic moieties, after they achieve their therapeutic role.

Combinatorial chemistry: It deals with the goal of synthesizing very large number of chemical entities by condensing a small number of reagents together in all combinations defined by a given reaction sequence. Compound libraries need to serve two distinct
functions in the drug discovery process, lead identification and lead optimization. Pfizer has reported an analog synthesis of an antiatherosclerotic drug with 100 fold increase in potency, while Lilly has described the optimization of a 5-HT agonist, for development of a new antimigraine drug. A most promising new approach to drug discovery concerns the synthesis in one-pot reaction without isolation or purification and reaction mixture in screened using a competitive binding assay based on pulsed ultrafiltration electro spray mass spectroscopy (PUF/ESMS), which tentatively identify those derivatives having the highest affinity for target receptors. An important feature of combinatorial chemistry is the synthesis of compounds on solid support.

It has been observed that almost every active drug possess the heterocyclic nucleus in which nitrogen is the most abundant atom present. It means that nitrogen atom plays an important role in the constitution of many of the natural products as well as synthetic compounds. It is a vital element present in the many of the biomolecules present in our bio-system like proteins, nucleic acids (RNA and DNA), vitamins, etc...

From the medicinal point of view, alkaloids are the best examples for containing nitrogen atom as a principal element. The alkaloids are more important for their varied biological activities like antihypertensive (reserpine), vasodilator (papaverine), analgesic (morphine), antimalarial (quinine), anesthetic (cocaine), antitussive (codeine), antineoplastic (vincristine and vinblastine), oxytocic (ergotoxine), antimitotic (colchicine), stimulant (strychnine), antiarrhythmic (ajmalicine), antispasmodic (atropine), antiasthmatic (ephedrine), respiratory stimulant (lobeline), etc.

Next in the order, Xanthine bases (caffeine, theophyline and theobromine) are also naturally available compounds and having varied biological activities such as CNS stimulant, antiasthmatic and diuretic activities. Similarly, neurotransmitters present in our body and essential for life, contains nitrogen atom in acyclic or cyclic form in adrenaline, nor-adrenaline, dopamine, acetylcholine, gamma amino butyric acid, 5-Hydroxytryptamine.

Inspired by the importance of nitrogen atom in therapeutic area many researchers synthesized 'n' number of nitrogen containing compounds. Some of them lead to attain the stage of drugs after succeeded in clinical trials.
Nitrogen is a major atom present in many of biologically active heterocycles like pyrimidines, quinazolines, oxadiazoles. Azetidinones, indoles etc...which paved way for the discovery of novel compounds with therapeutic significance.

Table 1.1 summarizes a few of the nitrogen containing compounds, which are clinically used or running under trial.

**Table 1 Clinically Useful Heterocyclic Drugs Containing Nitrogen Atom**

1. **Pyrimethamine**
   - Antimalarial
   - ![Pyrimethamine](image)

2. **Oxyphencyclimine hydrochloride**
   - Antispasmodic
   - ![Oxyphencyclimine](image)

3. **Thiotepa**
   - Antineoplastic
   - ![Thiotepa](image)
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4. Captopril

\[
\text{HSCH}_2\text{CH-CH}_3 \quad \text{CO} \quad \text{N} \quad \text{COOH}
\]
Antihypertensive

5. Sulphinpyrazole

\[
\text{C}_6\text{H}_5 \quad \text{N} \quad \text{O} \quad \text{CH}_2\text{CH}_2 \text{SO} \quad \text{Ph}
\]
Antigout

6. Azathioprine

\[
\text{H}_3\text{C} \quad \text{N} \quad \text{NO}_2 \quad \text{S} \quad \text{N} \quad \text{N}
\]
Immunomodulator

7. Isoniazid

\[
\text{CONHNH}_2
\]
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8. Haloperidol²¹

\[
\text{F-COCH}_2\text{CH}_2\text{CH}_2-N\text{H}_{\text{one}}\text{phenyl-Cl}
\]

Antipsychotic

9. Sulphamethoxypyrazine²²

\[
\text{H}_2\text{N-SO}_2\text{NH-pyrazin-OMe}
\]

Antibacterial

10. Hydralazine²³

\[
\text{NHNH}_2
\]

Antihypertensive

11. Pyrimethamine²⁴

\[
\text{H}_2\text{N-N=C-CON=NH}
\]

Antimalarial

12. Pyrazinamide²⁵

\[
\text{CONH}_2
\]

Antitubercular

13. Amiloride²⁶

\[
\text{Cl-CON=C-NH}_2
\]

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14. Indomethacin\textsuperscript{27}  
Anti-inflammatory  
Anti-gout

\[
\text{CH}_3\text{O} - \text{CO}_2\text{H}
\]

15. Chloroquine\textsuperscript{28}  
Antimalarial

\[
\text{Cl} - \text{N} - \text{CH(CH}_2\text{)}_2\text{N(CH}_3\text{)}_2
\]

16. Bemoradan\textsuperscript{29}  
Positive  
inotropic agent

\[
\text{CH}_3
\]

17. Clofazimine\textsuperscript{30}  
Antileprotic

\[
\text{Cl} - \text{N} - \text{CH(CH}_3\text{)}_2
\]
Prompted by the role of nitrogen in all diversities and in continuation of our work on the biologically active heterocycles like triazole, pyrazinone and oxadiazoles, it was considered worthwhile to work on the same molecules containing nitrogen as a principal atom. Hence, some novel nitrogen atom containing molecules were synthesized and attempted to explore some of their biological activities.
REFERENCES

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