***Short communication***

# NEW PHENOTHIAZINE DERIVATIVE DESIGNED ACCORDING TO LIPINSKI'S RULE OF FIVE AND ITS VARIANTS

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## ABSRACT

Some of the new 10H phenothiazine derivatives had been synthesized for their anti psychotic activity as dopamine antagonists. They had been synthesized with the help of software Marvin sketch. 10 parameters were analyzed for each of them which could make them drug like molecule. All parameters were found to be within range. Newly designed structures justify all the aspects of anti psychotic activity by satisfying Lipinski's Rule. Three carbon distance from two amine atoms keeps the polar surface area within range (>10). Log P value and conformational energy of these derivatives shows that they are structurally constrained molecules. They have also satisfied the stereo chemistry and hence safer derivatives. The limit for total numbers of atoms and H-bond donor and Acceptor are also seem to be fulfilled. So these derivatives have maximum chances that they could be drug like molecules which may have valuable anti psychotic activity. They could be investigated further for clinical use in conditions like schizophrenia, mania and other psychotic disorders.

***Keywords*:** Drug designing, Therapeutic derivative, Phenothiazine

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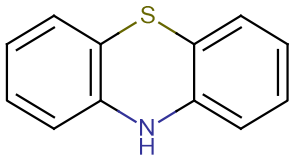
## INTRODUCTION:

Phenothiazine is a group of anti psychotic drugs. Synthesis of phenothiazine was started in 1883. In early era phenothiazine dyes were discovered like in 1877. These dyes were used to dye cellulose and fibers. But this drug is of pharmacological importance because its activities as therapeutic agent came to be known when phenothiazines were synthesized in 1950s, a 10-substituted drug. Phenothiazine has anti septic, anti helminthes, and insecticidal effect. Most prominent use of this drug is as tranquilizer because it has defused anti psychotic effects. [1] Also reports to have anti cancer and antiviral effects [2]




10H-phenothiazine

Chemically phenothiazine can interact with many physiological processes in body and for treatment of number of medical conditions. Its chemical structure gives an important base for developing new drug like molecules. New 10 H phenothiazines were synthesized previously with different biological activities due to heterocyclic structure. [2] Phenothiazines structurally consist of two benzene rings connected in tri cyclic system with the help of nitrogen and sulphur. [2] Phenothiazine also acts against many bacteria like *Mycobacterium tuberculosis* [3]. Many derivatives of phenothiazine inhibits the cleavage activity noncompetitively of MALT-1 (mucosa associated lymphoid tissues) hence showing anti cancer activity [4]. Phenothiazine as amino alkyl molecules has anti histaminic action by antagonizing H1 receptor. [5]. This drug has affinity for dopaminergic D1 and D2 receptor acting as anti psychotic drugs. [6]

Phenothiazine is structurally stable crystalline solid having melting point 185.1°C. It is a semi solid having activation energy 1.6 e.V. It is 10-(2-pyridyl)-5H-pyrido [3,2-b][1,4]benzothiazine. Its molecular configuration depicts that it has sp-3 hybridization and arrangement is planar or tetragonal.[1] Structures of phenothiazines can be analyzed by NMR, mass spectroscopy[7] and partitioning through HPLC [1]

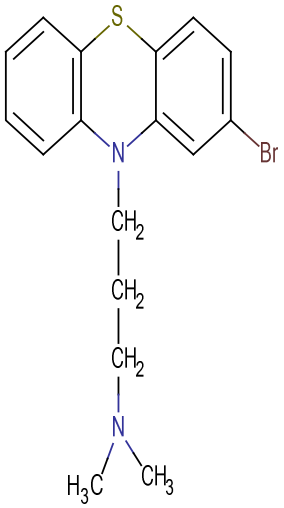
## METHODOLOGY

The methodology used in this study was software named as MarvinSketch 5.12.1, build date 19th March, 2013. Internal build ID 5.12.1_b94. Its maximum memory is 247.5M. It runs on JAVA (oracle corporation java 1.7.0_09). This software was used during study and different aspects were analyzed. The software has greatly helped in drug designing process due to its accuracy in structure naming and placing of functional groups was done very effectively. The IUPAC naming system of this software prevents wrong structure forming i.e if any moiety is placed wrongly then the naming system clearly indicates that the structure is not desired one. Placing of desired bond on desired place is so simple that there is no chance of error.

The major important aspect of this software is that the designer can easily study the properties of drug and structures like polarity, log P, No. of atoms, Stereo chemistry, Tautomerism, Refractivity, partitioning, NMR, Geometry etc. We had studied these properties according to Lipinski's Rule. This software has structure checker system that can identify the errors and recommend for change.

## RESULTS AND DISCUSSION

The final results obtained from Marvin Sketch are being examined and found appropriate for further pharmaco-therapeutical evaluation. The new derivatives qualify all the parameters of Llipinski's rule of five and its variants.



[3-(2-bromo-10H-phenothiazin-10-yl)propyl]dimethylamine

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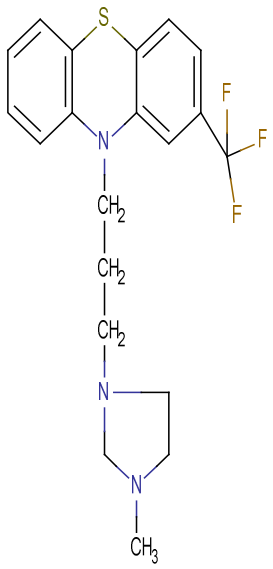
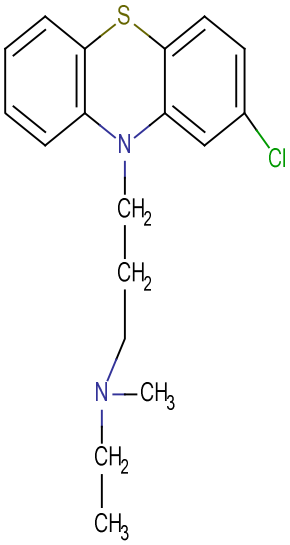
Fig 1.



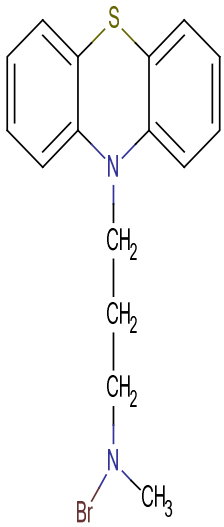
10-[3-(3-methylimidazolidin-1-yl)propyl]-2-(trifluoromethyl)-10H-phenothiazine

Fig 2.



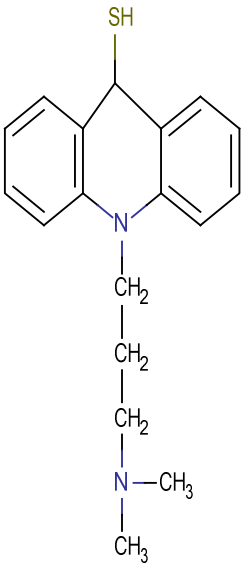
[3-(2-chloro-10H-phenothiazin-10-yl)propyl](ethyl)methylamine

Fig 3



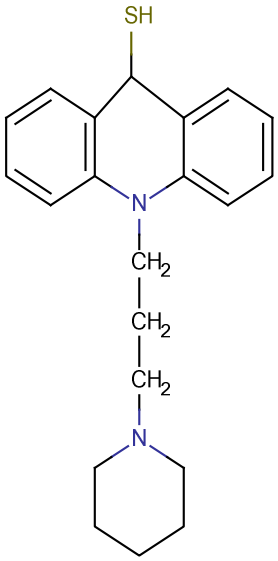
bromo(methyl)[3-(10H-phenothiazin-10-yl)propyl]amine

Fig 4



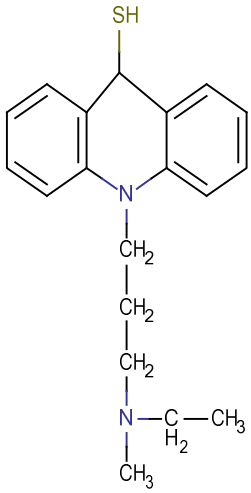

10-[3-(dimethylamino)propyl]-9,10-dihydroacridine-9-thiol

Fig 5



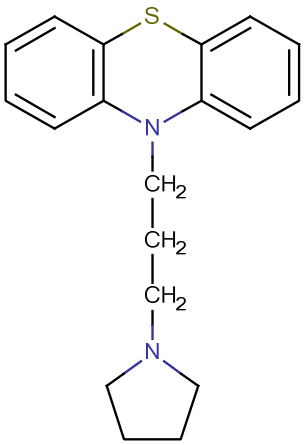

10-[3-(piperidin-1-yl)propyl]-9,10-dihydroacridine-9-thiol

Fig 6



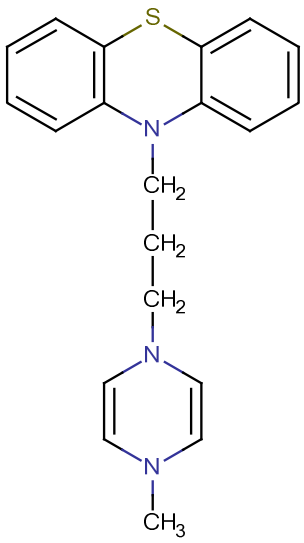

10-{3-[ethyl(methyl)amino]propyl}-9,10-dihydroacridine-9-thiol

Fig 7




10-[3-(pyrrolidin-1-yl)propyl]-10H-phenothiazine

Fig 8




10-[3-(4-methyl-1,4-dihydropyrazin-1-yl)propyl]-10H-phenothiazine

Fig 9

**PROPERTIES OF DRUG LIKE MOLECULE ACCORDING TO LIPINSKI RULE AND ITS VARIANTS**

| *No* | *Molecular Mass* | *No. of atom* | *Log P* | *Polar surface area* | *Conformat-ional Energy Kcal/mol* | *H-bond acceptor* | *Isotope formula* | *H bond Donor* | *Stereo Chemistry* | *Refractivity Kjoule* |
|---|---|---|---|---|---|---|---|---|---|---|
| **1** | 363.3 | 40 | 4.7 | 6.48 | 67.7-74.8 | 2 | C17H19Br2S | 0 | Isomer=1 | 96.5 |
| **2** | 393.4 | 49 | 4.7 | 9.72 | 86.0-96.5 | 3 | C20H22F3S | 0 | Isomer=1 | 105.7 |
| **3** | 332.8 | 43 | 4.8 | 6.48 | 73.7-81.0 | 2 | C18H21ClNS | 0 | Isomer=1 | 98.5 |
| **4** | 349.2 | 37 | 4.0 | 6.48 | 62.5-66.5 | 2 | C16H17N2S | 0 | Isomer=1 | 91.59 |
| **5** | 298.4 | 43 | 3.9 | 6.48 | 67.3-75.5 | 2 | C18H22N2S | 1 | Isomer=2 | 101.07 |
| **6** | 338.5 | 50 | 4.7 | 6.48 | 74.9-82.9 | 2 | C21H26N2S | 1 | Isomer=1 | 105.5 |
| **7** | 312.4 | 46 | 4.2 | 6.48 | 71.7-81.0 | 2 | C19H24N2S | 1 | Isomer=1 | 98.1 |
| **8** | 310.4 | 44 | 4.3 | 6.48 | 73.5-85.3 | 2 | C19H22N2S | 0 | Isomer=1 | 96.4 |
| **9** | 335.4 | 45 | 3.9 | 9.72 | 90.3-95.4 | 3 | C20H21N3S | 0 | Isomer=1 | 103.7 |

We tried to design new phenothiazines derivatives which have potential to become drug like molecule and ultimately clinically useful drug. For each of the newly designed drug the 10 parameters which are necessary for an organic molecule to become drug like molecule were studied. All newly designed phenothiazine was found to have the properties which could make them clinically useful drug. The parameter tested was basically the Lipinski's rule and its variants by using the software like Marvin Sketch. These compounds are drug like molecules which could become clinically useful anti psychotic drug.

Jack [6] reported Phenothiazine carry lipophilic specificity. In structure 3-C molecules from one nitrogen to second nitrogen is very important for psychotic treatment as its binding with dopamine receptor becomes easy and antagonizes them [6]. Two amine (N) present in structure

have their importance in receptor affinity. [6] The basic structure of phenothiazine necessary for anti psychotic activity keeping in view SAR of drug was maintained during the study. In literature only basic structure was explained for dopamine antagonizing activity but here new moieties were actually applied and their properties were studied.

Sinha *et al.,* [2] reported about antiviral, anti cancer and other biological activities of phenothiazine derivatives, according to her small change in moieties may cause greater change in pharmacological and therapeutic performance. Her worked was focused mainly on antimicrobial, anti inflammatory, antiviral and anti histaminic activity of phenothiazine, but no discussion on anti psychotic activity of this drug. Keeping in view this study the therapeutic work of phenothiazines derivatives were screened by making small manipulations to main structure and main focus was their antipsychotic activity.

Upendra *et al.,* [7] reported the analgesic activity of new derivatives of phenothiazine by adding azetidinyl thiazolyl and azetidinyl oxazolyl moieties on phenothiazine nucleus thus proving that substitution on phenothiazine aggravates its therapeutic properties. However this was a complex study and synthesis was difficult because anti inflammatory and ulcerogenic activity was also studied. Focusing on this literature new drug like molecules designed with therapeutic effect as anti psychotic but simple and basic study was carried out by adding basic functional groups on nucleus.

## CONCLUSION:

Newly designed structures justify all the aspects of anti psychotic activity by satisfying Lipinski's Rule. Three carbon distance from two amine atoms keeps the polar surface area within range (>10). Log P value and conformational energy of these derivatives shows that they are structurally constrained molecules. They have also satisfied the stereo chemistry and hence safer derivatives. The limit for total numbers of atoms and H-bond donor and Acceptor are also seem to be fulfilled. So these derivatives have maximum chances that they could be drug like molecules which may have valuable anti psychotic activity. They could be investigated further for schizophrenia, mania and psychotic disorders in clinical practice.

## FURTHER STUDY

In the next research work we will try to study them on animal models for anti psychotic activity.

## RECOMMENDATION

1. These drugs like molecules may be synthesized and formulated appropriately.
2. Their pharmacological and toxicological activities could be performed on animal models before clinical trials.

## ACKNOWLEDGEMENT

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