REVIEW ON THE MEDICINAL IMPORTANCE OF PIPERAZINE DERIVATIVES*

BY

Kaur Anoopjeet♣
Assistant Professor, School of Pharmacy, Desh Bhagat University, Mandi Gobindgarh.

Gulati Puja♣
Professor, School of Pharmacy, Desh Bhagat University, Mandi Gobindgarh.

Kaur Sapreet♣
Student of B.Pharmacy, School of Pharmacy, Desh Bhagat University, Mandi Gobindgarh.

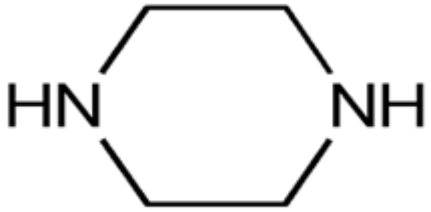
Abstract
Piperazine and its derivatives are the important chemical compounds with tremendous applications in the various fields. In this review we have summarized the medicinal and non-medicinal uses of number of piperazine derivatives. Piperazine derivatives have been reported for variety of biological activities and numbers of the compounds are in clinical uses. Piperazine derivatives also have increasing importance for modern medicinal applications.
Key words: Piperazine Derivatives, Medicinal Use, Synthesis of Piperazines, Characterization of Piperazines.

Received 06May 2021, Accepted 27May 2021, Published 15June 2021
♣ Correspondence Author: Kaur Anoopjeet

Introduction
Piperazine (hexahydropyrazine diethylenediamine) is an organic, heterocyclic compound with a six-membered ring containing two nitrogen heteroatoms at the C-1 and C-4 positions.[1]Piperazines were initially named for their chemical similarity with piperidine, part of the structure of piperine in the black pepper plant (Piper nigrum).[2]Piperazine derivatives are a broad class of chemical compounds, many with important pharmacological properties, which contain a core piperazine heterocyclic nucleus. A minor change in the substitution pattern in the piperazine nucleus causes distinguishable difference in their pharmacological activities.[3]Nitrogen in piperazine ring plays an important role in biological research and drug manufacturing industry including the proportion of Anthelmintic, Antiallergic Antibacterial[4], Antihistaminic[5] , Antiemetic and Antimigrainic agent.

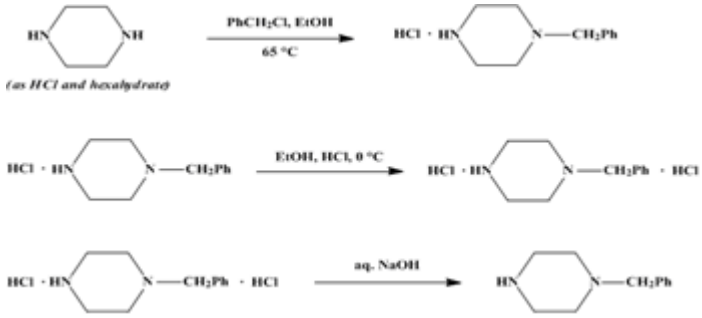
HISTORICAL BACKGROUND
Piperazines were originally named because of their chemical similarity with piperidine, a constituent of piperine in the black pepper plant (Piper nigrum). Piperazine is an organic compound that consists of a six-membered ring containing two nitrogen atoms at opposite positions in the ring. Piperazine exists as small alkaline deliquescent crystals with a saline taste. The -az- infix added to "piperazine" refers to the extra nitrogen atom, compared to piperidine. It is important to note, however, that

piperazines are not derived from plants in the Piper genus. Piperazine was marketed by Bayer as an anthelmintic in the early 20th century, was first introduced as an anthelmintic in 1953.Their mode of action is generally by paralysing parasites, action is mediated by its agonist effects upon the inhibitory GABA (γ-aminobutyric acid) receptor. Piperazine was introduced to medicine as a solvent for uric acid.[6]

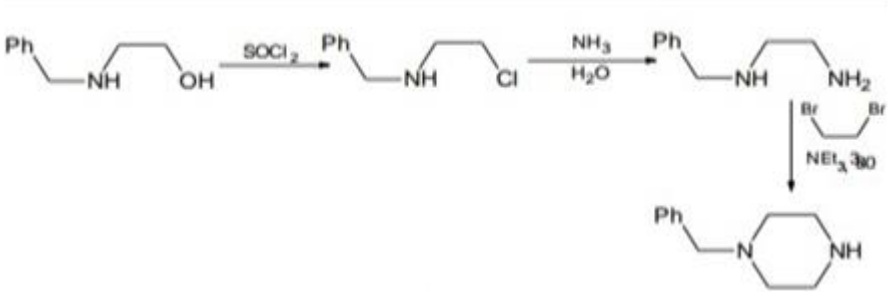


General Synthesis of Piperazine:

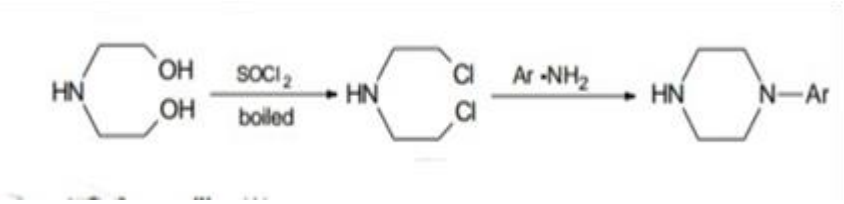
1-Benzylpiperazine has been prepared by the reaction of piperazine and benzyl chloride, followed by fractionation of piperazine, and the mono- and dibenzyl derivatives. It has also been obtained4 by alkaline hydrolysis of 1-benzyl-4- carbethoxypiperazine. The present method, which is a modification of that first reported by Cymerman Craig, Rogers, and Tate,is simple and yields an easily purified product.[7,8,9,10]



Formation from n-benzylaminoethanol:

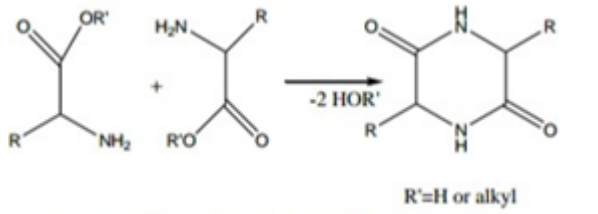


Formation from diethanolamine:



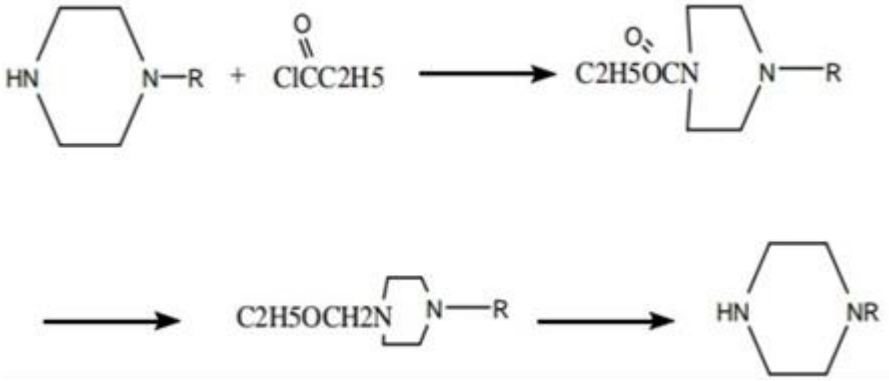
Synthesis of Dioxopiperazine:

2, 5-Dioxopiperazines (Diketopiperazines) are formed by a dimerizing cyclo condensation of anamino acids or their esters.[11]

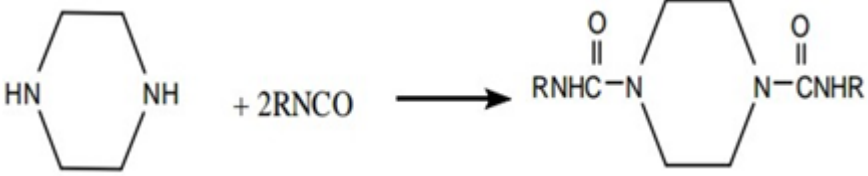


Dioxopiperazine

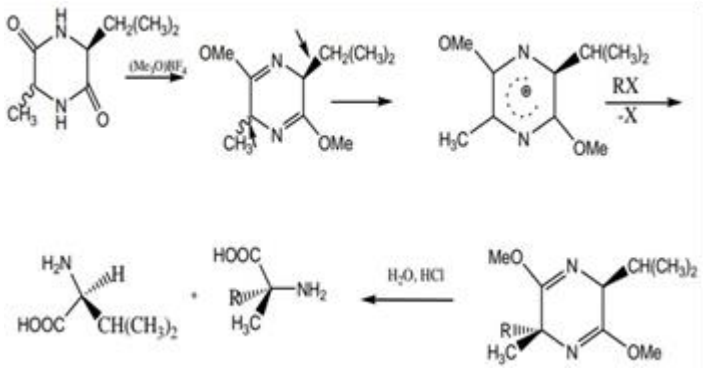
Alkylation of Piperazine: Piperazine is generally alkylated to yield the N, N'-disubstituted compounds. It is possible to prepare monoalkylated piperazine by first blocking one nitrogen with ethyl chloroformate, reaction of the other nitrogen with an alkyl halide, and hydrolyzing to liberate the monoalkylated compound.[12]



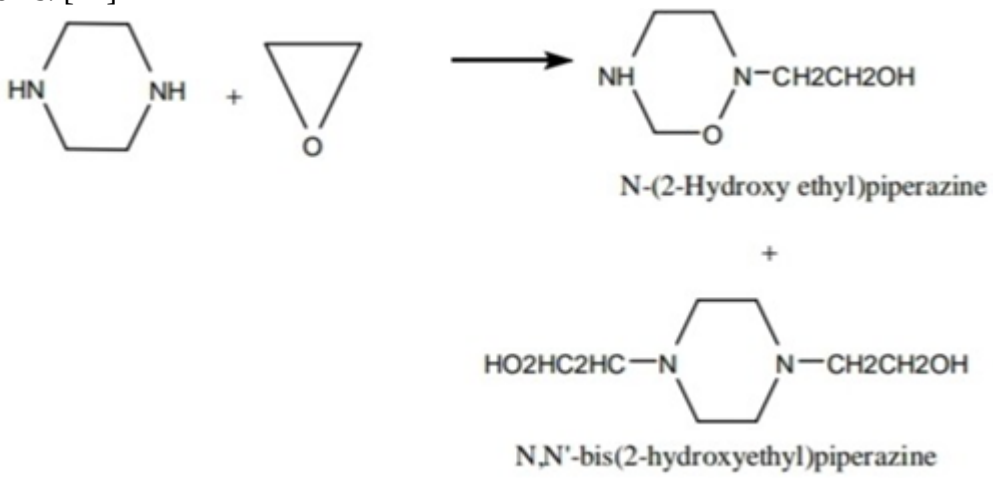
Reaction of Piperazine with Isocyanates: Substituted urea's can be prepared by the reaction of piperazine with isocyanates or isothiocyanates.



O-Alkylation: O-Alkylation of dioxopiperazines with oxonium salts yields bislactim ethers which are used as reagents for the asymmetric synthesis of amino acids.[13]



Reaction with Ethylene oxide: Ethylene oxide and propylene oxide react to form the corresponding amine alcohols.These alcohols can be further alkoxylated to form longer polyalkoxy chains on the nitrogen atoms. [14]



Characterization of Piperazine Derivatives:

Infra red (IR): Infrared spectrometry is often used as a confirmatory method for drug identification in forensic drug analysis. Gas-chromatography with infrared detection (GC-IRD) was evaluated for differentiation among the regioisomeric trifluoromethylphenylpiperazines (TFMPP).Infrared detection should provide compound specificity without the need for chemical modification of the drug molecule.[15]

Gas chromatography-mass spectrometry (GC-MS): Gas chromatography-mass spectrometry (GC-MS) is the main tool used for the detection and identification of unknown drugs in forensic and other drug screening laboratories reported the electron impact (EI) mass spectrometric fragmentation pathway for some underivatized and acetylated benzyl and phenylpiperazines. The ions of significant relative abundance common to the BZP likely arise from fragmentation of the piperazine ring.[16]

Nuclear magnetic resonance (NMR): NMR is a nondestructive flexible technique that can be used for the simultaneous identification of pure compounds and even mixtures of compounds in one sample. Its advantages, compared to GC-MS techniques, include Stereochemical differentiation and the capability to analyze nonvolatile compounds. However, the lack of use in forensic laboratories can be attributed to the high cost of instrumentation and the poor sensitivity of NMR. Solid state NMR also can be used for analytical purposes in much the same way as solution NMR. The observed chemical

shifts however differ in the solution and solid states because of conformational freezing and packing effects. NMR was utilized in the analytical structure elucidation of a new designer benzyl piperazine (4-bromo-2, 5-dimethoxybenzylpiperazine) that was seized in Germany in 2006.[17]

Liquid chromatography- electrospray ionization mass spectrometric detection (LC MS) and liquid chromatography- ultraviolet detection (HPLC-UV): LC-MS is a non-destructive exact mass determination technique. It utilizes chemical ionization to identify the molecular ion of drugs or their metabolites. Analytical aspects and profiles of some designer piperazine-derived drugs of abuse.e.g. 1-benzylpiperazine, 1 - [4 - methoxyPhenyl] piperazine and TFMPP using both Liquid chromatography- electrospray ionization mass spectrometric detection (LC-MS) and liquid chromatography- ultraviolet detection (HPLC-UV) have been reported by [de Boer et al, 2001]. Development of simultaneous gas chromatography mass spectrometric and liquid chromatographic electrospray ionization mass spectrometric determination method for the new designer drugs, N-benzylpiperazine (BZP), 1-(3-trifluoromethylphenyl) piperazine (TFMPP) and their main metabolites in urine was also reported.[18]

Biological Applications of Piperazine Derivatives

Antibacterial agents: Coumarin-piperazine derivatives are used as antibacterial agents. The treatment of infectious diseases has become a major problem in the world. Therefore, it is important to overcome this problem for a better life. Antibacterial activity of N-[2-(coumarin-3- yl)ethyl]piperazinyl quinolones have been first shown in 2008 by the Emami's group (Emami et al., 2008). The compounds were designed as analogs of ciprofloxacin, norfloxacin and enoxacin, modifying their struc ture by inserting new substituents into the piperazine ring located at the C- 7 quinolones position.[19]

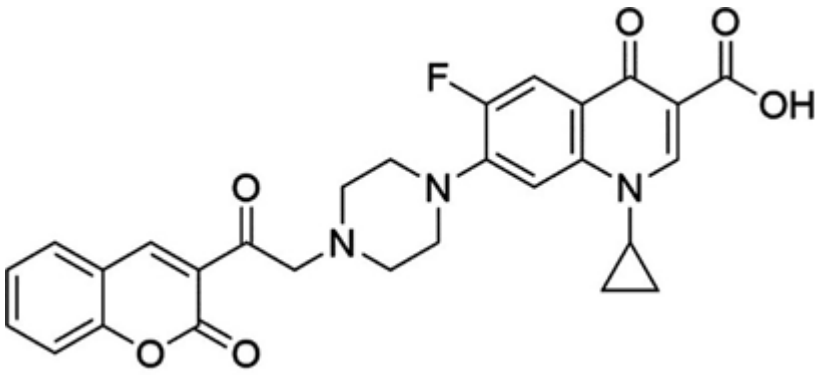


Fig. Coumarin derivative synthesized by the Emami's group.(N-[2-(coumarin-3yl)ethyl]piperazinyl quinolones)

As an Antialzheimer: 18 Rangappa et al. (2006) worked on the 1-[bis(4-flurophenyl)methyl]piperazine derivatives(Fig.) synthesis and there efficacy for acetylcholinestrase inhibition as a stimulant of central cholinergic neurotramission in Alzheimer's disease [20]

Fig.1-[bis(4-flurophenyl)methyl]piperazine derivatives

As an Antimicrobial: 30Lin-Ling Gan et al (2010) have been designed and synthesized series of azole-containing piperazine derivatives. The obtained compounds were investigated in vitro for their antibacterial, antifungal and cytotoxic activities. The preliminary results showed that most compounds exhibited moderate to significant antibacterial and antifungal activities in vitro. 1-(4- ((4-

chlorophenyl) (phenyl)methyl)piperazin-1-yl)-2-(1H-imidazol-1-yl)ethanone and 1-(4-((4-Chlorophenyl) (phenyl)methyl)piperazin-1- yl)-2-(2-phenyl-1H-imidazol-1-yl) ethanone gave remarkable and broad-spectrum antimicrobial effects.[21]

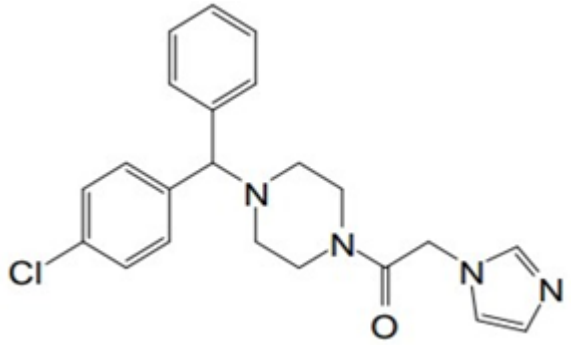


Fig.1-(4-((4-chlorophenyl)(phenyl)methyl)piperazin-1-yl)-2-(1H imidazol-1-yl)ethanone

As an antipsychotic: Sushil et al (2011) synthesize 2-[4-(aryl substituted) piperazin-1-yl]-N-phenylacetamides and evaluate for the anti psychotic activity. All the 10 new arylpipeazines showed variable antipsychotic activity with compound 3h being the least effective in the induction of catalepsy. Their effect may involve interaction with 5-HT2A and D2 receptors.[22]

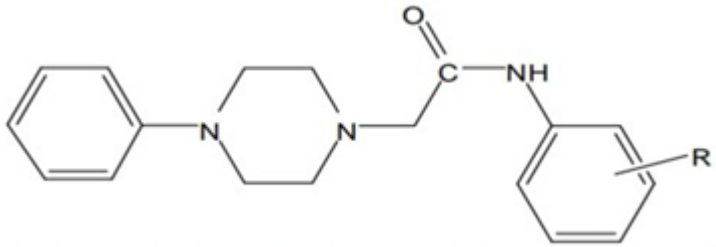


Fig. R=H, 3-CH3, 4- CH3, 3- CH3, 2- OCH3 , 3- OCH3, 2-Cl, 3-Cl

As an anticonvulsant and antidepressant: Dauzonne et al. (1995) had reported the synthesis and some CNS activities of new benzofuranyl acryloylpiperazine. This literature describes our attempts to explore the pharmacological properties related to chemical modifications carried on a new series of (E)-4-[3-(2-benzofuranyl) acryloyl] piperazine (fig), obtained as their hydrochloride, substituted at N-1 and benzofuran ring in various ways.[23]

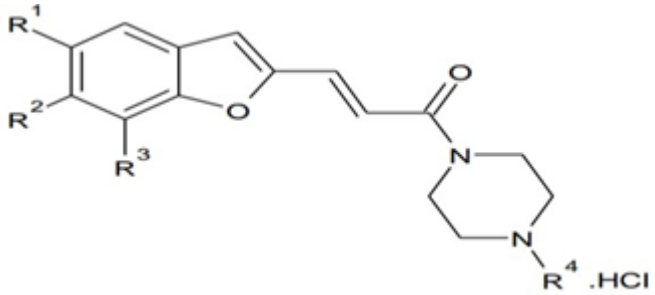
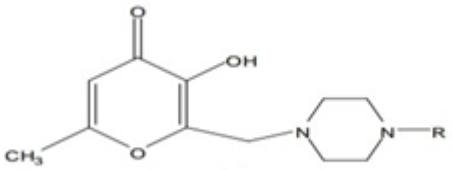


Fig. (E)-4-[3-(2-benzofuranyl) acryloyl] piperazine

Mutlu Dilsiz aytmir et al (2010) also reported the synthesis and evaluation of anticonvulsant activity of 3-hydroxy-6-methyl-2-substituted 4H pyran-4-one derivatives. Among the compounds 4-(3-trifluoromethyl phenyl) piperazine -1-yl methyl group at position 2 on the pyranone ring.[24]



As an Antihistaminic: Piperazines are known to show their action on histamine receptors. Britta C. Sasse, Ulrich R. Mach et al (2006) synthesize a series of compounds containing privileged scaffolds of the known histamine H1 receptor antagonists Cetirizine, Mianserin, Ketotifen, Loratadine, and Bamipine were synthesized for further optimization as ligands for the related biogenic amine binding dopamine D3 receptor. A pharmacological screening was carried out at dopamine D2 and D3 receptor.[25]

Conclusion:

This review has fulfilled significant information about piperazine and its various derivatives based on medicinal importance . Piperazine, Piperazine hydrate, piperazine adipate and piperazine citrate used to treat ascariasis and enterobiasis are the most common anthelmintic piperazine compounds. These are used as antimicrobial agents, antibacterial and antifungal agents, act as histaminics and so on.

References

1. Martin, R.J., 1997. Modes of action of anthelmintic drugs. Vet. J. 154, 11–34. https://doi.org/10.1016/S1090-0233(05)80005-X.
2. Admin in pharmacy. Comments Off on Introduction to Central Nervous System Pharmacology. Basic medical KeyFastest Basicmedical Insight Engine Jan 1
3. Rajeev Kharb, Kushal Bansal, Anil Kumar Sharma. A valuable insight into recent advances on antimicrobial activity of piperazine derivatives. Scholars Research LibraryDer Pharma Chemica. 2012; 4(6):2470-2488.
4. Lien,J C, Huang L J, Wang JP and Teng CM: Synthesis and antiplatelet, anti-inflammatory and antiallergic activities of 2-substituted --3-chloro-1,4-napthoquinone derivatives. Bioorganic & Medicinal Chemistry. 1997;5:2111-2120
5. Shishoo C J, Shirsath VS and Rathod I S: Design, synthesis and antihistaminic (H1) activity of some condensed 3-aminopyrimidin-4(3H)-ones Eur. J. Med. Chem. 2000; 35: 351−358.
6. Merck Index, 11th Edition, 7431.
7.1.R. Baltzly, J. S. Buck, E. Lorz, and W. Schon, J. Am. Chem. Soc., 66, 263 (1944).
8.R. E. Lutz and N. H. Shearer, J. Org. Chem., 12, 771 (1947).
9.B. W. Horrom, M. Freifelder, and G. R. Stone, J. Am. Chem. Soc., 77, 753 (1955).
10.J. Cymerman Craig, W. P. Rogers, and M. E. Tate, Australian J. Chem., 9, 397 (1956).
11. Capasso S, Vergara A and Mazzarella L: Mechanism of 2,5-Dioxopiperazine Formation J. Am. Chem. Soc., 1998; 120 (9):1990–1995.
12. Brown D A, Mishra M and Zhang S: Investigation of various N-heterocyclic substituted piperazine versions of 5/ 7-{[2-(4-Aryl-piperazin-1-yl)-ethyl]-propyl-amino}-5,6,7,8-tetrahydro-naphthalen-2-ol: Effect on affinity and selectivity for dopamine D3 receptor Bioorg Med Chem. 2009

;17(11): 3923–3933.
13. Leków Z C, Medyczna A and Wrocław: Evaluation of the synthesis and action of O- and N-aryl
-piperazine propyl derivatives of ethyl ester acid 3-cyano-2-hydroxy-6-methylpyridine-4-carboxyl Acta Pol Pharm. 1992; 49(1-2):61-5.
14. Zaugg HE and Raymond J: Michaels Tertiary Carbinols of the Piperazine Series. III. Reaction of 1, 1-Diphenylethylene Oxide with Piperazines and Other Polyamine J. Am. Chem. Soc., 1958; 80 (11): 2770–2773.
15. Maher H M, Awad T and Clark C R: Differentiation of the regioisomeric 2-, 3-, and 4-trifluoromethylphenylpiperazines (TFMPP) by GC-IRD and GC-MS. Forensic Science International, 2009; 188: 31-39.16.Tsutsumi, H, Katagi M, Miki A, Shima N, Kamata T and Nishikawa M: Development of simultaneous gas chromatography-mass spectrometric and liquid chromatography-electrospray ionization mass spectrometric determination method for the new designer drugs, N-benzylpiperazine (BZP), 1-(3-trifluoromethylphenyl)piperazine (TFMPP) and their main metabolites in urine. J Chromatogr B Analyt Technol Biomed Life Sci. 2005; 25: 315-22.
18.De Boer I J, Bosman E, Hidvégi C and Manzoni A A: Piperazine-like compounds: a new group of designer drug of-abuse on the European Market, Forensic Science International. 2001; 121: 47-56.
17.Alver O: Complete experimental and theoretical proton and carbon nuclear magnetic resonance spectral assignments, molecular structure and conformational study of 1-cyclo hexylpiperazine and 1-(4-pyridyl)piperazine" Magn Reson Chem. 2010 ;48(1):53-60.19.Emami, S., Foroumadi, A., Faramarzi, M.A., Samadi, N., 2008. Synthesis and antibacterial activity of quinolone-based compounds containing a coumarin moiety. Arch. Pharm. Chem. Life Sci. 341, 42–48. https://doi.org/10.1002/ardp.200700090.
20. Malviya M, Sunil Kumar Y C, Mythri R B and Venkateshappa C: Muscarinic receptor 1 agonist activity of novel N-aryl carboxamide substituted 3-morpholino arecoline derivatives in Alzheimer's presenile dementia models". Bioorg. Med. Chem., 17, 5526 –5534.
21. Ling Gan L, Fang B and Zhou C H: Synthesis of Azole containing Piperazine Derivatives and Evaluation of their Antibacterial, Antifungal and Cytotoxic Activities Bull. Korean Chem. Soc201; 31:12.
22. Kumar S and Wahi A.K: Tropical journal of medicinal chemistry. 2011,10(3), 265-272 .
23. Dauzonne D, Gillardin J M, Lepage F and Pointet R: Synthesis and some CNS activities of new benzofuranylacryloylpiperazines, Eur.J.Med.Chem. 1995; 30: 53-59.
24. Aytmir M D: Synthesis and anticonvulsant activity of new kojic acid derivatives. Arzennimittal forschung, 2010; 60 (1): 22-29.
25. Sasse B C, Ulrich R Mach and Leppaenen J: Hybrid approach for the design of highly affine and selective dopamine D(3) receptor ligands using privileged scaffolds of biogenic amine GPCR ligands Bioorg Med Chem. 2007; (23):7258-73.