IJPSR (2015), Vol. 6, Issue 10 (Review Article)

INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES AND RESEARCH

Received on 25 March, 2015; received in revised form, 10 May, 2015; accepted, 30 July, 2015; published 01 October, 2015

PIPERAZINE – A BIOLOGICALLY ACTIVE SCAFFOLD

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Keywords:

Piperazine, synthesis, Spectral studies, Stereochemistry, Biological activity

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ABSTRACT: The broad and potent activity of piperazine has established it as one of the biologically important scaffolds. This article is an effort to highlight the importance of the piperazine in the present context and promise they hold for the future. This review mainly focused the updated information on the most active piperazine derivatives that have been reported to show significant biological actions for instance anti-microbial, anti-depressant, anticonvulsant, anti-parkinson, anti-inflammatory, antipsychotic, antioxidant, antidiabetic, antiarrhythmic, antiproliferative, anxiolytic, antialzheimer, antimalarial, antihypertensive, antiplatelet aggression and anti-histaminic activity. This review would take on benzylpiperazine (BZP) and trifluoromethylpiperazine (TFMPP), benzhydryl piperazine, diphenylalkyl piperazine, phenyl piperazine as the most popular member of the piperazines, focusing the discussion on their origins, pharmacokinetics and pharmacodynamics, and their effects on the human body. From these outcomes, information for future molecular modifications leading to compounds with greater positive pharmacological properties may be derived.

INTRODUCTION: One of the main objectives of organic and medicinal chemistry is the design, synthesis and production of molecules having value as human therapeutic agents. During the past decade, Combinatorial chemistry has provided access to chemical libraries based on privileged structures [1], with heterocyclic structures receiving special attention as they belong to a class of compounds with proven utility in medicinal chemistry [2]. Piperazine which arrived in the 1950 was the first modification with broad spectrum activity. Useful in the ascarides, small strongyles and pinworms. It still wasn't effective against the large strongyles. [3]

QUICK RESPONSE CODE

DOI: 10.13040/IJPSR.0975-8232.6(10).4145-58

Article can be accessed online on: www.ijpsr.com

DOI link: http://dx.doi.org/10.13040/IJPSR.0975-8232.6(10).4145-58

There are numerous biologically active molecules with six membered rings, containing two hetero atoms. Piperazine (A) is an important scaffold known to be associated with several biological activities **(Fig. 1**)

2. Piperazine:

2.1 Chemistry of piperazine:

Piperazine is a heterocyclic compound containing four carbon atoms and two nitrogen at 1 and 4 position (as called 1, 4-hexahydropyrazine). The Piperazines or Cyclizines can also be considered as ethylenediamine derivatives or cyclic ethylenediamines (cyclizines); Piperazines are a broad class of chemical compounds with many important pharmacological properties. This dinitrogen moiety has been an inseparable component of plethora of drugs. Piperazine has the chemical similarity with piperidine, a constituent of piperazine in the black piper plant (*Piper nigrum*). Piperazine introduced into the medicine as a

solvent for uric acid. Nitrogen in piperazine ring plays an important role in biological research and drug manufacturing industry including the proportion of Anthelmintic, Antiallergic [4] Antibacterial, Antihistaminic [5], Antiemetic and Antimigrainic agent.

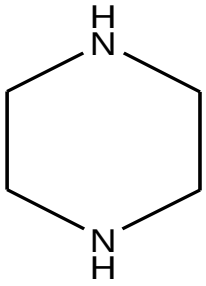


FIG. 1

2.2 General Synthetic Methods of Piperazine derivatives:

The piperazines may be regarded as *N, N'*–disubstituted ethylenediamine derivatives.

2.2.1 Formation from n-benzylaminoethanol:

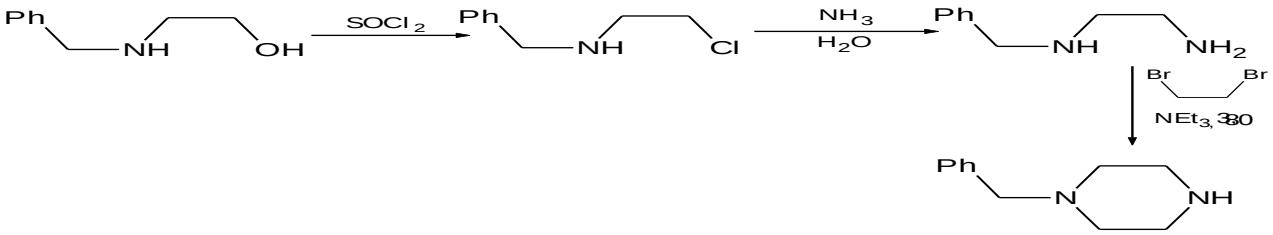


FIG.2

2.2.2 Formation from diethanolamine:

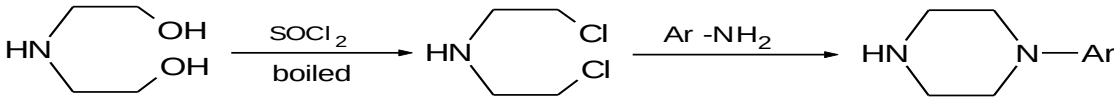


FIG.3

2.2.3 Formation from aniline (A):

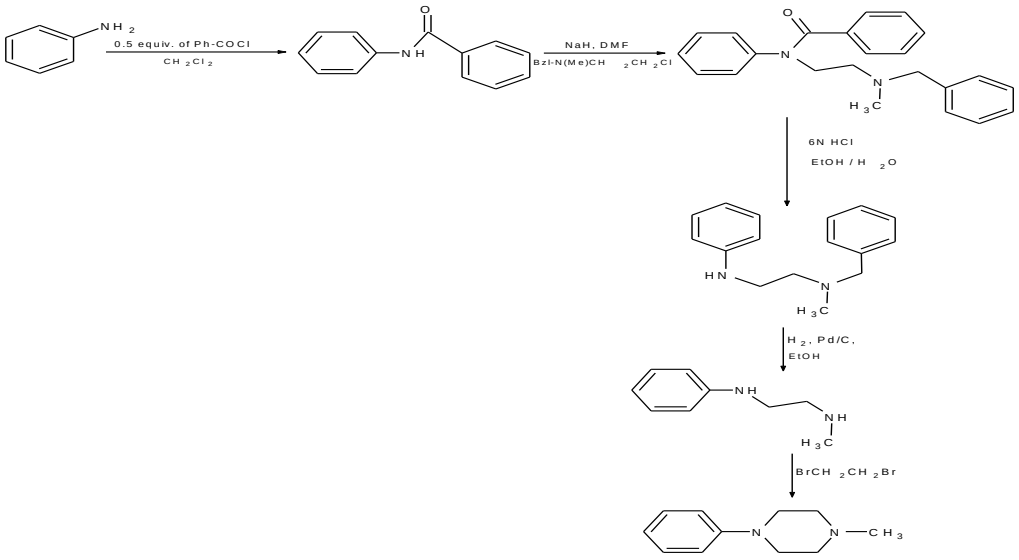


FIG.4

2.2.4 Formation from *N*-phenyl Ethanolamine:

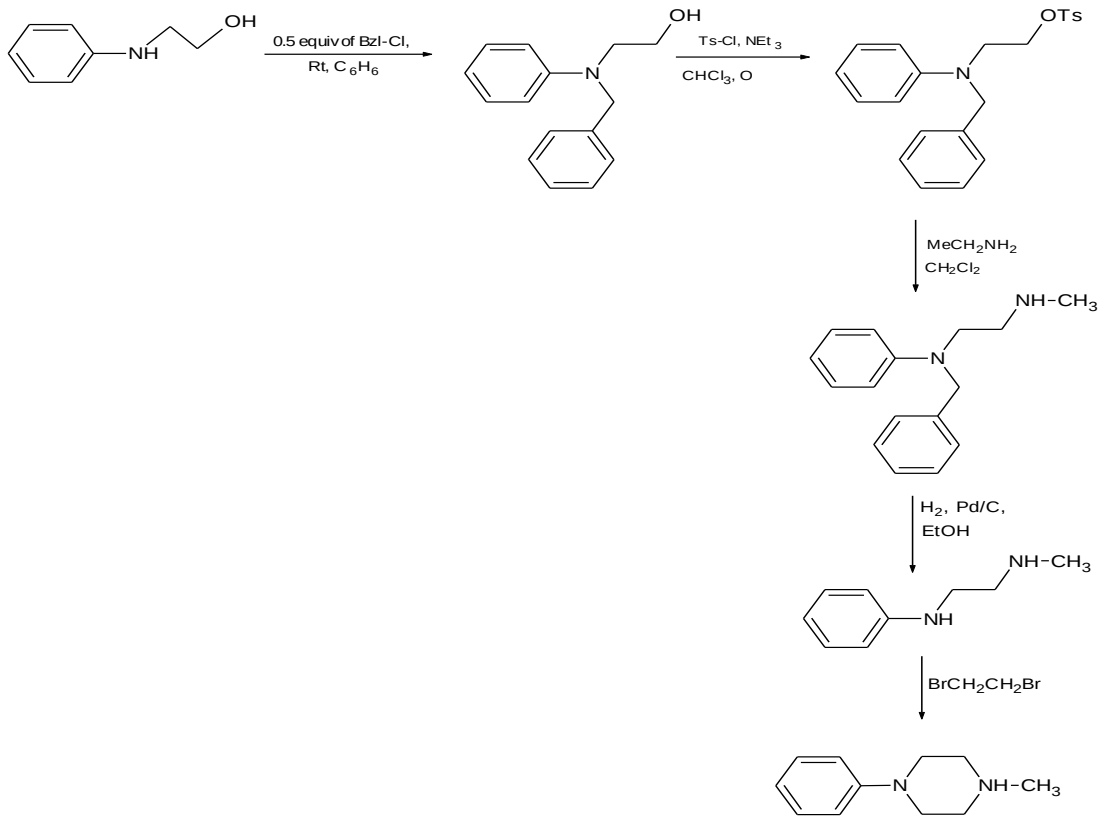


FIG.5

2.3 Spectral studies on piperazine:

2.3.1 Infrared and mass spectral studies: [6]

The vibration spectrum and FAB mass spectrum of (+/-)-1-[3-(2-methoxyphenoxy)-2-hydroxy propyl]-4-[(2,6-dimethylphenyl) aminocarbonylmethyl] piperazine dihydrochloride salt was studied. By comparing with the spectra of free base, different bands of IR were found in the NH+ stretching, the NH+ deformation motion, the CH_2 of NCH_2 group symmetric stretching, the CH_2 of N-CH_2 group twisting and the CN stretching. FAB shows the basic peak is M + H. Other m/e peaks are consistent with the structure.

2.3.2 Gas chromatography-mass spectrometry (GC-MS): [7]

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. The mass spectrum of BZP shows the fragment ions at m/z 134, 120, and 91 as well as other ions of low relative abundance.

2.3.3 Nuclear magnetic resonance (NMR): [8]

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.

2.3.4 Liquid chromatography- electrospray ionization mass spectrometric detection (LC-MS) and liquid chromatography- ultraviolet detection (HPLC-UV): [9]

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 - methoxy Phenyl] 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.

2.3.5 Infra red (IR): [10]

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.

2.3.6 X-ray crystal structure: [11]

The title compound 1-benzhydryl-4-(4-chloro-2-fluoro - benzenesulfonyl) - piperazine was synthesized, and structure of the product obtained was confirmed by the X-ray diffraction study. The compound $C_{23}H_{22}ClFN_2O_2S$ crystallizes in the monoclinic crystal class in the space group $P2_1/c$ with cell parameters a = 9.6180(7) Å, b = 12.9670(10) Å, c = 19.4020(12) Å, β = 114.716(3)°, and Z = 4. The structure has been solved by direct methods and refined to $R_1 = 0.0440$ for 3877 observed reflections with $I > 2\sigma(I)$. The structure reveals that the piperazine ring is in a chair conformation. The geometry around the S atom is distorted tetrahedral.

2.3.7 Stereochemistry: [12]

Cyclohexane is a prototype of saturated six-member ring, as well as of the molecules with one or two heteroatom inserted in the ring molecules, and it has been widely investigated both theoretically and experimentally. Piperazine plays an important role as a unit present in more complex molecules studied in several fields. Piperazine in crystals has a chair conformation with the N–H bonds in the equatorial positions and resides at the crystallographic inversion center.

However, the experimentally determined dipole moment is 1.47 D and the rotational spectra suggest the existence of piperazine as a mixture of the three conformers: axial–axial, equatorial– equatorial and axial–equatorial. The conversion process of six-membered saturated heterocycles is more complex than that in cyclohexane. Their molecules can perform three different types of intermolecular motion:

(i) Rotation about single bonds of the ring substituent's

(ii) Pyramidal nitrogen inversion and

(iii) Ring inversion, responsible for the whole conformational dynamic processes for the six-membered aza-cycles**.** The axial substituent's in six-membered rings are less stable than the equatorial ones, in which the electronic effect does not play a direct role, because of the repulsion between 1,3-diaxial protons and the axial substituent's. The effect of substituent's is broadly subdivided into electronic (polar or inductive) and steric components. However, it has been also demonstrated that in a number of cases the axial isomers are favored, even though either steric or dipolar considerations lead to the opposite prediction.

2.4 Reactions of Piperazine:

2.4.1 2, 5-Dioxopiperazines: [13]

2, 5-Dioxopiperazines (Diketopiperazines) are formed by a dimerizing cyclo condensation of an amino acids or their esters **Fig. 6.**

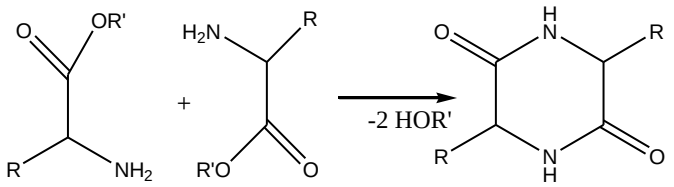


FIG.6: SYNTHESIS OF DIOXOPIPERAZINE

or by cyclization of dipeptide esters resulting in unsymmetrical substitution (**Fig. 7**):

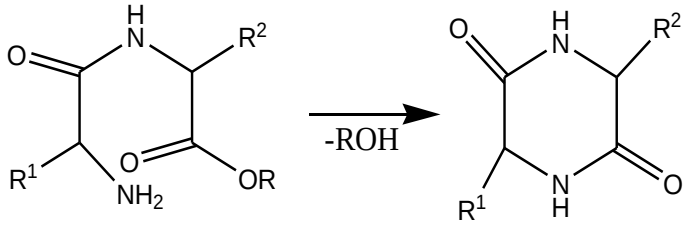


FIG.7: SYNTHESIS OF DIKETOPIPERAZINE BY CYCLIZATION

N-Acylated dioxopiperazines undergo base-catalyzed C-3 alkylation, (**Fig. 8**) e.g.:

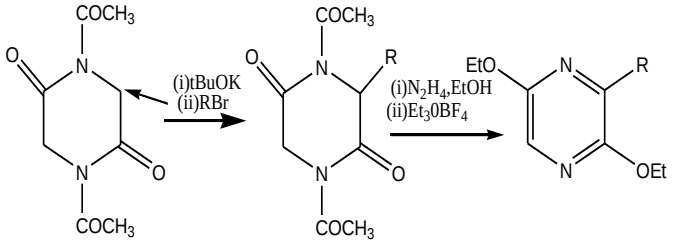


FIG.8: BASE-CATALYZED ALKYLATION OF DIKETOPIPERAZINE

This reaction, when applied to dioxopiperazines, can lead to the synthesis of 2,5 dialkoxypiperazine.

2.4.2 O-Alkylation [14] O-Alkylation of dioxopiperazines with oxonium salts yields bislactim ethers which are used as reagents for the asymmetric synthesis of amino acids (**Fig. 9**).

Method: The chiral bislactim ether is converted into the anion (under kinetic control) by rc-butyllithium. Alkylation proceeds with high stereoselectivity (greater than 95%). Acid hydrolysis of the alkylation leads to (unnatural) (R)-amino acids and recovery of the chiral auxiliary valine, from which the start dioxopiperazine was derived.

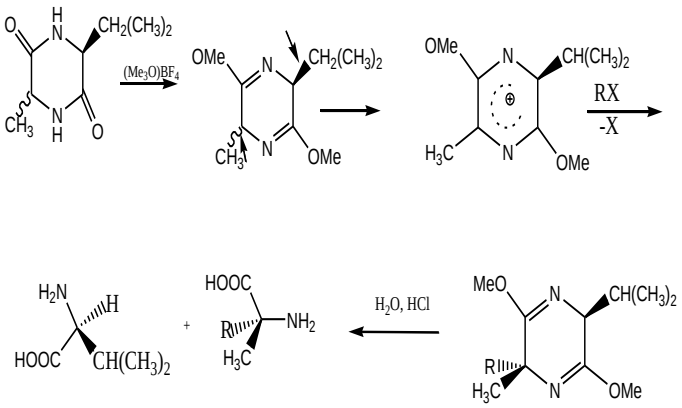


FIG.9: O-ALKYLATION OF DIOXOPIPERAZINES

Both amines can be alkylated on the nitrogen atom. Alkyl halides, dialkyl sulfates and a combination of aldehyde and formic acid (Leuckart-wallach reaction) have all been used.

In one useful method the alkylation is effected by a primary or secondary alcohol in the presence of hydrogen and a catalyst containing nickel, copper, and chromium oxides.

2.4.3 Alkylation of Piperazine: [15] 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.

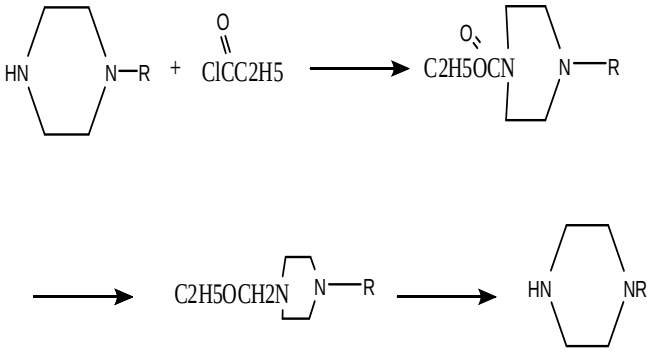


FIG.10: ALKYLATION OF PIPERAZINE

Benzoyl chloride may also be used as a blocking agent (in this case, the agent is removed by catalytic hydrogenation).

2.4.4 Reaction with Ethylene oxide: [16]
Ethylene oxide and propylene oxide react to form the corresponding amine alcohols.

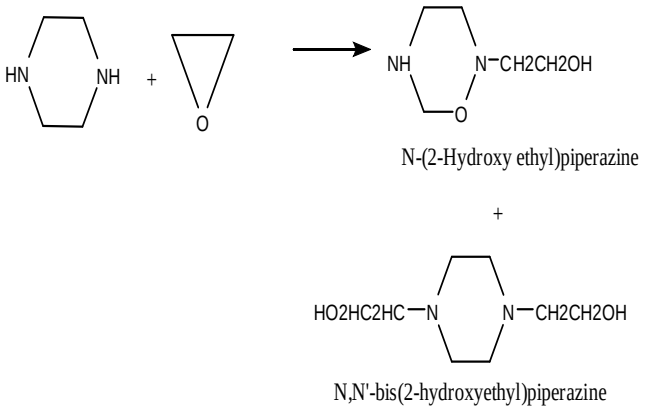


FIG.11: REACTION WITH ETHYLENE OXIDE

These alcohols can be further alkoxylated to form longer polyalkoxy chains on the nitrogen atoms.

2.4.5 Reaction of Piperazine with Isocyanates:

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

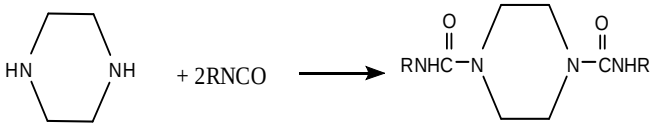


FIG.12: REACTION OF PIPERAZINE WITH ISOCYANATES

2.4.6 Nucleophilic reaction:

In many reactions the simple saturated nitrogen heterocyclics (piperazine) behave simply as secondary amines that happen to be cyclic. They do the sorts of things that other amines do, acting as nucleophiles in addition and substitution reactions.

N-methyl piperazine can be alkylated in an S_N1 reaction with diphenylmethyl chloride to give cyclizines (**Fig. 13)**

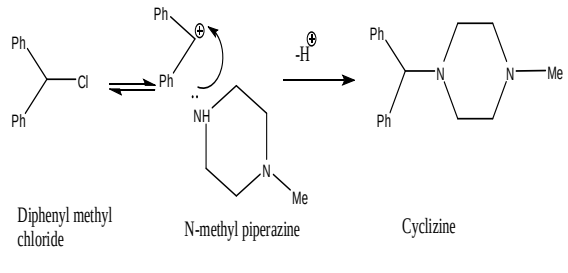
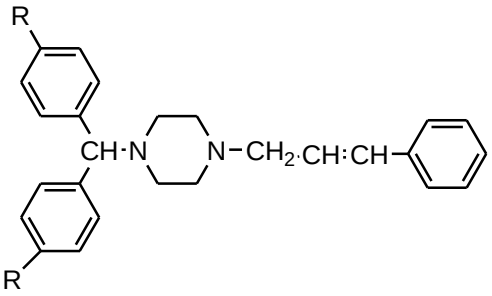


FIG.13: NUCLEOPHILIC REACTION

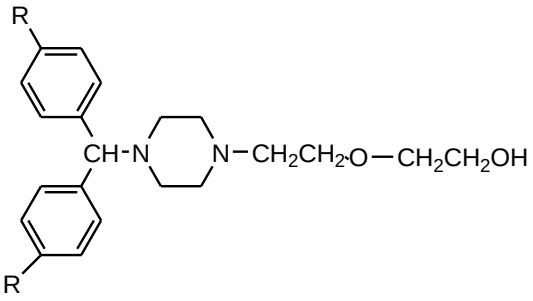
Salts of piperazine (citrate, phosphate, adipate) or its hexahydrate are used as anthelmintics. The piperazine ring is frequently used as a building block for pharmaceutical industries.

Benzhydrylpiperazines, such as cinnarizine (**Fig.14**) and its difluoro analogue flunarizine (**Fig.15**), possess considerable activity as peripheral and cerebral vasodilators. Hydroxyzine is used as a tranquilizering material**.**



(Structure of Cinnarizine)
R=H

FIG.14



R=F
(Structure of Flunarizine)

FIG.15

3. Biological Activity of Piperazine:

3.1 As antidepressant and anxiolytic: [17]

Kossakowski et al. (2006) described the preparation of a no. of cyclic imide 5-HT_{1A} receptor ligand derivatives. Their structures were conformationally constrained by introducing rigid linkers containing unsaturated bonds or aromatic benzene ring. These compounds are expected to possess anxiolytic and antidepressant activity. Linkers are cis- and trans-1,4-dichloro-2-butene, 1,2 – bis (chloromethyl)benzene, 1 - (2-methoxy phenyl) piperazine.

3.2 As an Antialzheimer: [18]

Rangappa et al. (2006) worked on the 1-[bis(4-flurophenyl)methyl]piperazine derivatives(**Fig.17**) synthesis and there efficacy for acetylcholinestrase inhibition as a stimulant of central cholinergic neurotramission in Alzheimer's disease.

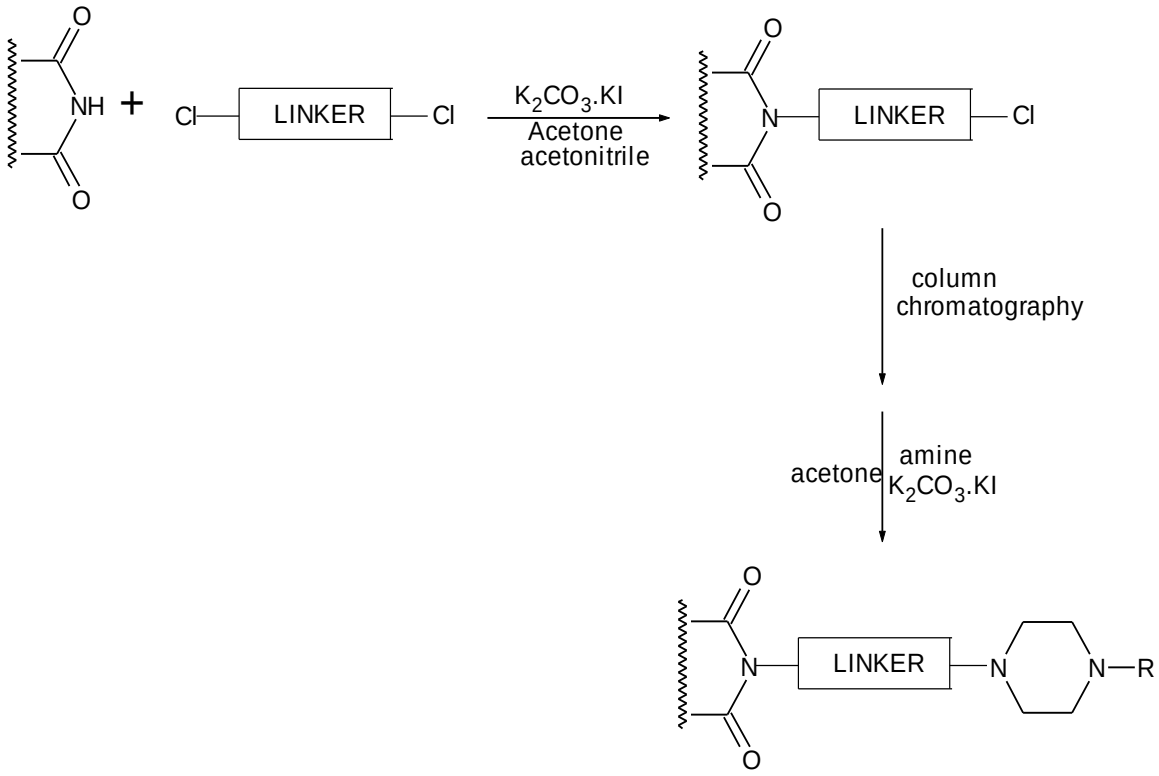


FIG. 16

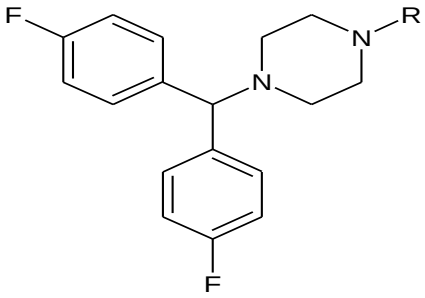
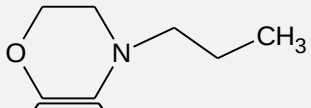
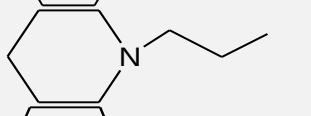
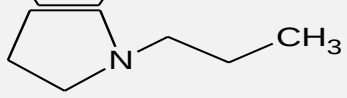
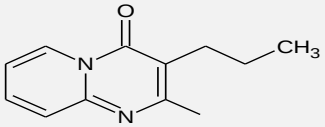
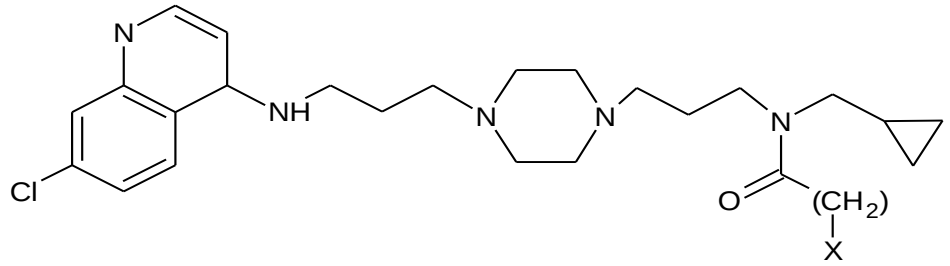


FIG.17

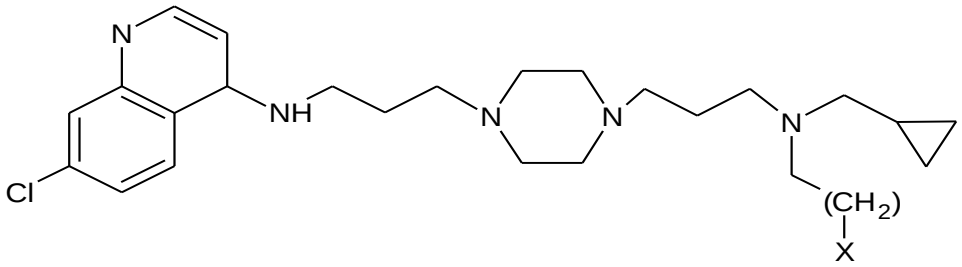
COMPOUND	R
28a	
28b	
28c	
28d	

3.3 As an Antimalarial: [19]

Ryckebusch et al. (2005) reported the synthesis and antimalarial evaluation of new *N*'-(7-chloro-4-quinolyl)-1,4-bis(3-aminopropyl) piperazine derivatives.



1. n = 0 ; X = Cyclopropyl 2. n = 3 ; X = OH
3. n = 2 ; X = COOH 4. n = 0 ; X = $CONH_2$



5. n = 3 ; X = CN 6. n = 2 ; X = NHBoc
7. n = 2 ; X = NH_2

FIG.18

Wilson Cunico et al reported (*2R, 3S*)-4-(aryl methyl)-1-(4- phenyl-3-amino-2-hydroxy butyl) piperazine derivatives as potential antimalarial agents**.** [20]

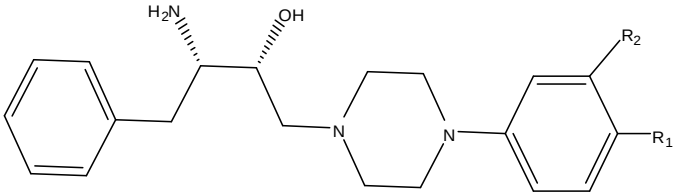


FIG. 19

3.4 As an Antioxidant: [21]

Kimura et al. (2004) reported the antioxidant activities of novel diphenylalkyl piperazine derivatives with high affinities for the dopamine transporter.

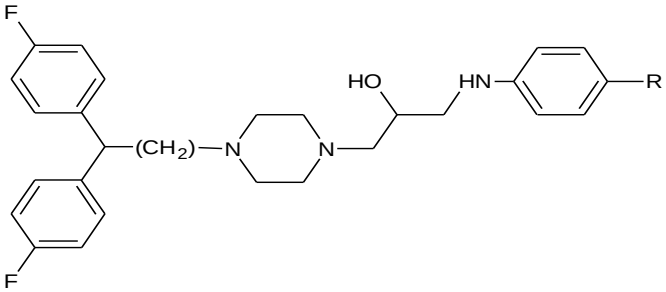


FIG.20

COMPOUND	N	R_1
23a	0	H
23b	1	H
23c	2	H
23d	3	H
23e	4	H
23f	3	3,4-diCl
23g	3	4-Cl
23h	3	4-Me
23i	3	4-OMe

3.5 As an Antiparkinson: [22]

Acri JB et al (1996) saw the behavioral effects of cocaine that are relevant to its abuse have been associated with pharmacological actions at the dopamine uptake carrier. Benztropine (Cogentin) is an antiparkinson agent that has limited abuse despite its ability to block dopamine uptake, and has been suggested as a candidate for the treatment of cocaine dependence. Preclinical studies were conducted to assess the behavioral and toxic effects of benztropine alone and in conjunction with cocaine. Because of the mixed pharmacology of benztropine which includes antimuscarinic as well as dopaminergic actions, results obtained from parallel experiments with atropine and the selective dopamine uptake inhibitor, GBR 12935 (1-[2-(diphenylmethoxy) ethyl]- 4 - (3-phenyl-propyl)-piperazine), were performed. All of the drugs stimulated locomotor activity of mice, but atropine

and benztropine had much lower efficacy. Nonstimulatory doses of GBR 12935 enhanced the locomotor stimulant effects of cocaine, whereas benztropine and atropine did not share this effect. GBR 12935, benztropine and cocaine increased fixed-interval responding, whereas atropine decreased fixed-interval response rates in rats. Only GBR 12935 and cocaine increased responding during timeout periods. GBR 12935, but not benztropine or atropine, fully reproduced the discriminative stimulus effects of cocaine (10 mg/kg). GBR 12935 and atropine augmented the discriminative stimulus effects of lower cocaine doses in rats. Only GBR 12935 and cocaine had convulsant effects and only GBR 12935 significantly enhanced the convulsant effects of cocaine in mice.

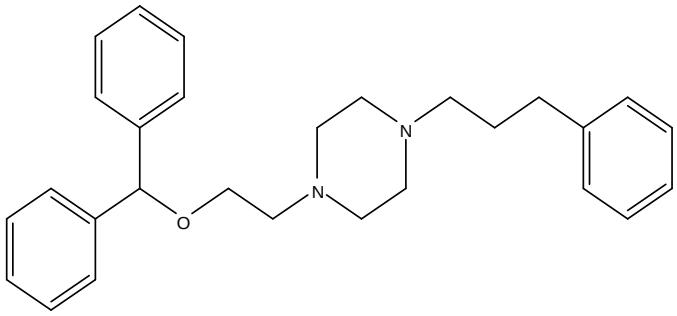


FIG.21

3.6 As an Antihypertensive: [23]

Cecchetti et al. (2000) identified the (1,4-benzothiazinyloxy)alkyl piperazine derivatives as potential antihypertensive agents.

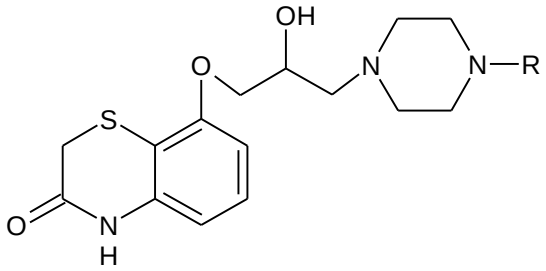


FIG.22

COMPOUND	POSITION	R
13a	6	2-MeOC$_6$H$_4$
13b	7	2-MeOC$_6$H$_4$
13c	8	2-MeOC$_6$H$_4$
13d	6	4-FC$_6$H$_4$
13e	7	4-FC$_6$H$_4$
13f	6	CO(4-FC$_6$H$_4$)

3.7 As an Anti-diabetic:[24]

Bihan et al. (1999) identified the piperazine derivatives as new anti-diabetic compounds, by the substituting both piperazine N-atom using various alkyl groups, branched or not, and benzyl groups; some modification of the Imidazoline ring. Through this work some of the compounds reported areas.

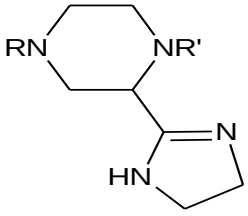
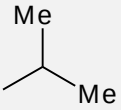
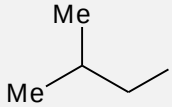
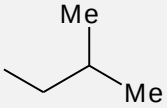
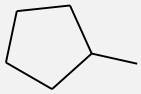
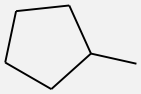
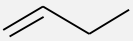
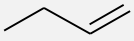
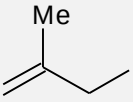
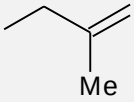


FIG.23

COMPOUND	R	R’
11a		
11b		
11c		
11d		
11e		

3.8 As an anticonvulsant and antidepressant: [25]

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.24), obtained as their hydrochloride, substituted at N-1 and benzofuran ring in various ways.

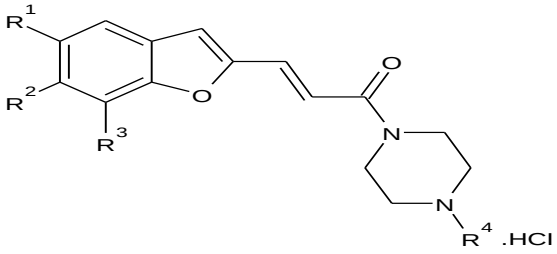


FIG.24

COMPOUND	R^1	R^2	R^3	R^4
7a	H	H	H	Phenyl
7b	H	H	H	2-CH_3CH_2O-Phenyl
7c	H	H	H	3-CF_3-Phenyl
7d	H	H	H	2-Pyridinyl
7e	H	H	H	2-Pyrimidinyl

Biological testing of these compounds proved that these have the anticonvulsant and antidepressant activities. 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. [26]

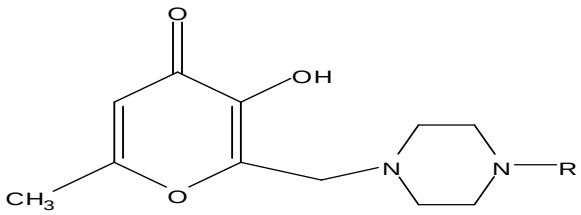


FIG.25

3.9 As an Antihistaminic: [27]

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.

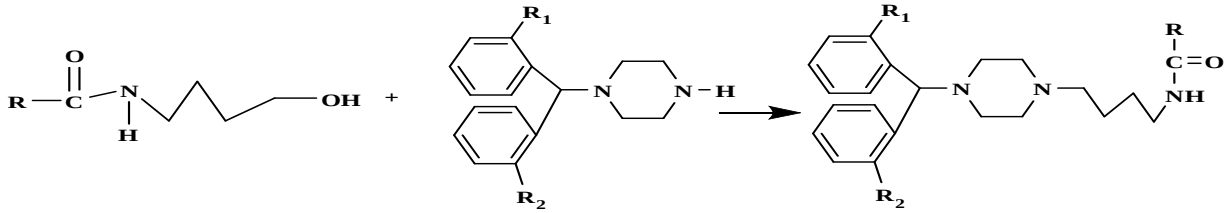


FIG.26

3.10 Antiproliferative activity: [28]

C.S. Ananda Kumar, S.B. Benaka Prasad et al (2009) explore the antiproliferative effect associated with the piperazine framework, several 1-benzhydrylpiperazine derivatives were synthesized. Variation in the functional group at *N*-terminal of the piperazine led to three sets of compounds, bearing the sulfonyl, amide and thiourea, respectively.

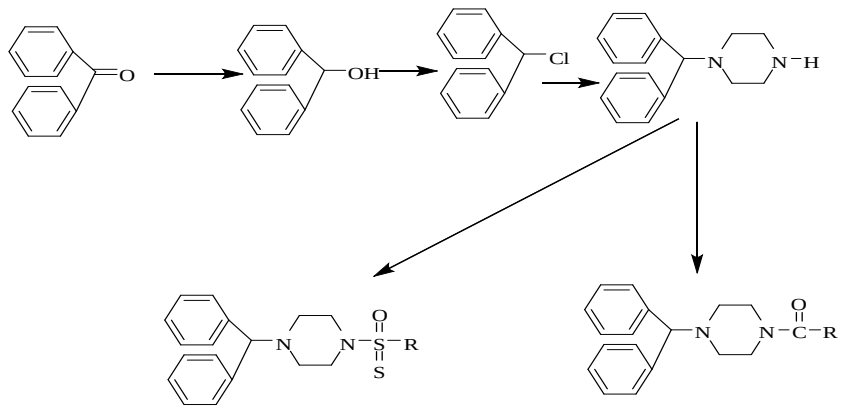
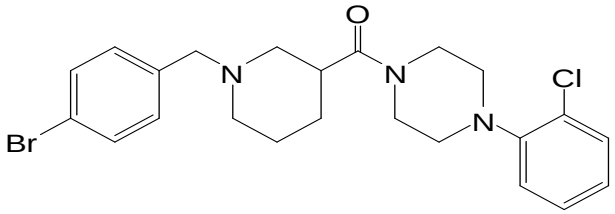


FIG.27

3.11 As an antiplatelet aggression activity: [29]

Khairia M. Youssef et al (2011) design and synthesized new carbamoylpyridine and carbamoyl piperidine analogues containing nipecotic acid scaffold and evaluated for their platelet aggregation inhibitory activity. Molecular modeling investigation was performed and the impact of lipophilicity on activity was also discussed. Structure activity relationship among this Series was obtained.

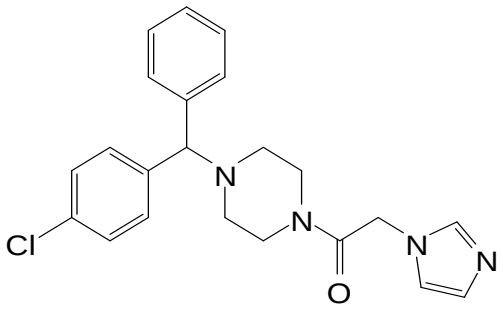
*N*1-[1-(4-bromobenzyl)-3-piperidinocarbonyl]- N^4-(2-chlorophenyl)-piperazine hydrobromide, and 1,4-bis-[3-[N^4-(2-chlorophenyl) - N^1 - (piperazino carbonyl)]-piperidin - 1 - yl-methyl] - benzene dibromide is the most active antiplatelet aggregating compounds in this study, both at concentration of 0.06 µM.



(1-(4-bromobenzyl) piperidin-3-yl)(4-(2-chlorophenyl) piperazin-1-yl) methanone

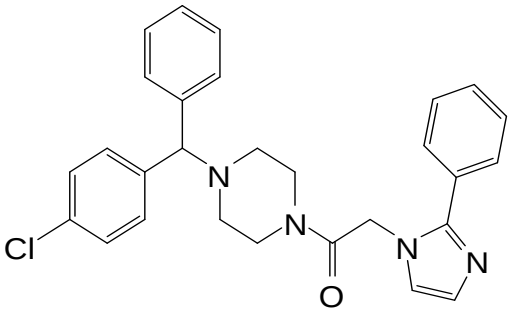
FIG.28

PC-3 cell line, reaching growth inhibition values (36.4, 60.1 and 76.5%) for each tested concentration: 25 µM, 50 µM and 100 µM in dose-dependent manner.



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

FIG.29



1-(4-(4-Chlorophenyl) (phenyl) methyl) piperazin-1- yl)-2-(2-phenyl-1*H*-imidazol-1-yl) ethanone

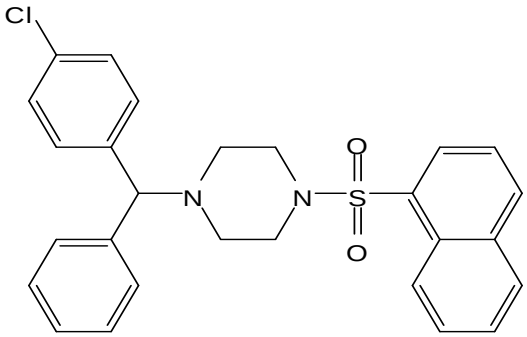
FIG.30

3.12 As an Antimicrobial: [30]

Lin-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*.

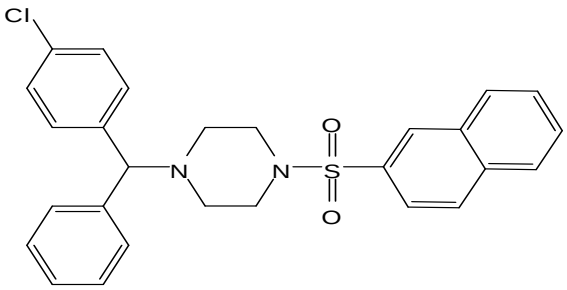
1-(4-((4-chlorophenyl) (phenyl)methyl)piperazin-1-yl)-2-(1*H*-imidazol-1-yl)ethanone and 1-(4-((4-Chlorophenyl) (phenyl)methyl)piperazin-1- yl)-2-(2-phenyl-1*H*-imidazol-1-yl) ethanone gave remarkable and broad-spectrum antimicrobial efficacy against all tested strains with MIC values ranging from 3.1 to 25 µg/mL, and exhibited comparable activities to the standard drugs chloramphenicol and fluconazole in clinic. Moreover, 2-(4-(4-chlorophenyl)(phenyl) methyl) piperazin-1-yl) methyl)-1*H*-benzo[d]imidazole was found to be the most effective *in vitro* against the

A. Dayalan, P.gurumurthy, et al (2007) synthesized [31] isomeric naphthalene sulphonyl compounds *viz.*, 1-and 2-[4-{(4-chloro phenyl) phenyl methyl}-1-piperazinyl] sulphonyl naphthalene's were synthesized from p-chloro benzophenone and naphthalene as the main starting materials with piperazine bridge and characterized by spectral methods. Their antimicrobial activities were also studied.



1-(4-chlorophenyl) (phenyl) methyl)-4-(naphthalen-1-ylsulfonyl) piperazine

FIG.31

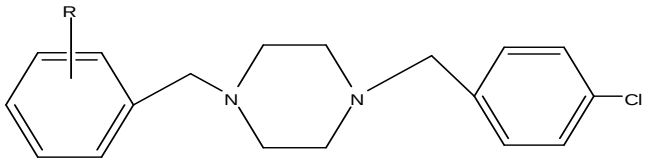


1-(4-chlorophenyl) (phenyl) methyl)-4-(naphthalen-2-ylsulfonyl) piperazine

FIG.32

3.13 As an antipsychotic: [32]

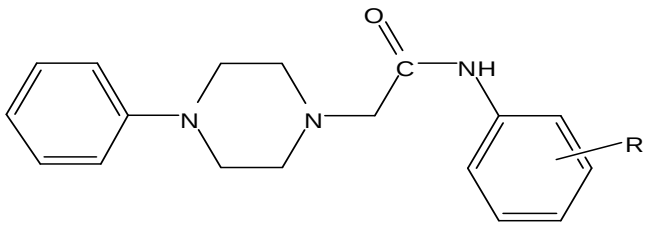
Alka Bali et al (2010) synthesized a series of acetophenone based 1-(Aryloxy propyl) -4-(chloro aryl) piperazine. All the synthesized compounds were evaluated for anti psychotic activity. All the targeted compounds were subjected to preliminary pharmacological evaluation to determine their ability to antagonize Apomorphine induced mesh climbing behavior and apomorphine induced stereotype in mice. Compound a1-4 and b1 and b2 shows positive result for reversal of Apomorphine induced mesh climbing and compound a5-8 shows negative response. Apomorphine used as a standard drug.



R= Cl

FIG.33

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. [33]

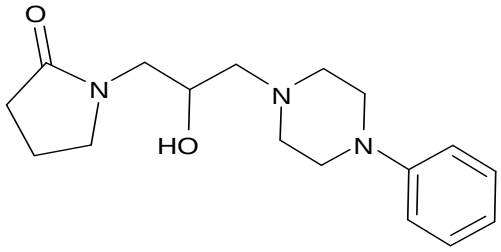


R=H, 3-CH_3, 4- CH_3, 3- CH_3, 2- OCH_3 , 3- OCH_3, 2-Cl, 3-Cl

FIG.34

3.14 As an anti arrhythmic: [34]

Jacek sapa et al (2011 synthesized a series of novel pyrrolidin-2-one derivatives (17 compounds) with adrenolytic properties were evaluated for antiarrhythmic, electrocardiographic and antioxidant activity. Some of them displayed antiarrhythmic activity in barium chloride-induced arrhythmia and in the rat coronary artery ligation-reperfusion model, and slightly decreased the heart rate, prolonged P–Q, Q–T intervals and QRS complex. Among them, compound EP-40 (1-[2-hydroxy-3-[4-[(2-hydroxyphenyl) piperazin-1-yl] propyl] pyrrolidin-2-one showed excellent antiarrhythmic activity



1-(2-hydroxy-3-(4-phenylpiperazin-1-yl) propyl) pyrrolidin-2-one

FIG. 35

CONCLUSION: The article has outlined the chemistry and biological activities of the piperazine scaffold. The synthetic methodologies indicate the simplicity, maneuverability and versatility, which offer the medicinal chemist a complete range of novel derivatives. The stereochemical orientation provides a further variety of products. The high degree of protection against seizures can be positive signs for further investigation of piperazine derivatives as anticonvulsants. The activity of piperazine as antihistaminic and their potent anthelmintic activity are promising. The broad spectrum antibacterial and antifungal activity of these compounds could lead to a new series of antimicrobials. The piperazine derivatives have demonstrated significant antidiabetic and antiproliferative activities. Thus piperazine scaffold is not only synthetically important but also possesses a wide range of promising biological activities.

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How to cite this article:
Singh K, Siddiqui HH, Shakya P, Bagga P, Kumar A, Khalid M, Arif M and Alok S: Piperazine – A Biologically Active Scaffold . Int J Pharm Sci Res 2015; 6(10): 4145-58.doi: 10.13040/IJPSR.0975-8232.6(10).4145-58.