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*Review Article*

# Piperazine Derivatives: A Review of Activity on Neurotransmitter Receptors

**Seba M C, Dr. S M Sandhya, Dr. Prasobh G R**

Department of Pharmaceutical Chemistry, Sree Krishna College of Pharmacy and Research Centre, Parassala, Kerala, India

Corresponding Author: Seba M C

## ABSTRACT

Piperazine is a vital organic scaffold that consists of a six-membered ring containing two nitrogen atoms at opposite positions in the ring and also posse's four carbon atoms. This moiety can be found in surplus of well-known drugs with pharmacophoric activities on various receptors. Piperazine derivatives have been the subject of research for activity primarily on neurotransmitter receptors. This review focused on the activity of piperazine pharmacophore on diverse neurotransmitter receptors.

***Key Words:*** Piperazine, Pharmacophoric activities, Neurotransmitter receptors.

## INTRODUCTION

Piperazines were initially named for their chemical similarity with piperidine, part of the structure of piperine in the black pepper plant (*Piper nigrum*). Medicinal chemists have been extremely successful in the recent years in redesigning this scaffold which is vital for an exact pharmacological activity. [1]

Piperazine derivatives are a broad class of chemical compounds, many with important pharmacological properties, which contain a core piperazine heterocyclic nucleus. A trivial change in the substitution pattern in the piperazine nucleus causes distinguishable difference in their pharmacological activities. Literature survey of the recent studies done on piperazine derivatives point out that they have activities on neurotransmitter receptors, which have been summarized as given below.

A neurotransmitter receptor is a membrane receptor protein, that is triggered by a neurotransmitter. [2] NTs are synthesized from precursors accumulated or synthesized in the neurons. Neurotransmitters can evoke either an excitatory or an inhibitory synaptic membrane potential and trigger effects at presynaptic and postsynaptic sites on target neurons. [3]

The major classes of neurotransmitter are Acetyl choline, Amino acids (GABA, Glutamate, Glycine), Biogenic Amines (Dopamine, Norepinephrine, Serotonin, and Histamine) and Neuropeptides (Opioid peptides and Tachykinins). Acetyl choline receptors are Muscarinic receptors ($M_1$, $M_2$, $M_3$, and $M_4$) and Nicotinicreceptors. Amino acid, GABA receptors are $GABA_A$ and $GABA_B$. Amino acid, Glutamate receptors are NMDA, AMPA and KA receptors. Biogenic Amine, Dopamine receptors are $D_1$, $D_2$, $D_3$, $D_4$ and $D_5$receptors.Biogenic Amine Norepinephrine receptors are $\alpha_1$, $\alpha_2$, $\beta_1$, $\beta_2$receptors. Biogenic Amine, Serotonin receptors are 5-$HT_I$, 5-$HT_2$,5-$HT_3$,5-$HT_4$. Biogenic Amine, Histamine receptors are $H_1$, $H_2$, $H_3$. Neuropeptide, Opioid peptides receptors are Mu, delta and kappa receptors.

Neuropeptide, Tachykinin receptors are $NK_1$, $NK_2$, and $NK_3$. [3]

## PIPERAZINE DERIVATIVES: ACTION ON CHOLINERGIC RECEPTORS

Roger B. Clark, et.al designed and synthesized derivatives of novel 2-((Pyridin-3-yloxy)methyl) piperazines scaffold as α7 Nicotinic Acetylcholine Receptor Modulators for the Treatment of Inflammatory Disorders. The oxazolo[4,5-b]pyridine,1a, and 4-methoxyphenylurea, 1b, were identified as potent and selective modulators of the α7 nAChR with favorable in vitro safety profiles and good oral bioavailability in mouse. Both compounds were shown to significantly inhibit cellular infiltration in a murine model of allergic lung inflammation. Despite the structural and in vivo functional similarities in the compounds, only 1a was shown to be antagonist. He concluded selective agonist of the receptor may be useful in the treatment of inflammatory conditions. [4]

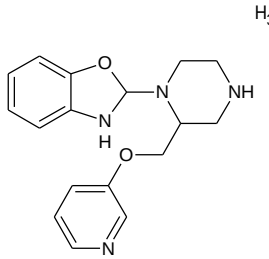


**Figure 1a**

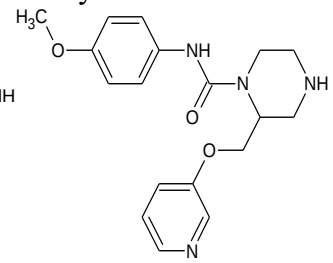


**Figure 1b**

Yan-qing He et.al, described 1,1 Dimethyl 4-phenyl piperazine iodide is a synthetic nicotinic acetylcholine receptor agonist that could decrease airway inflammation. Yan-qing and his co-workers further demonstrated that 1,1-Dimethyl 4-phenyl piperazine iodide could dramatically inhibit glioma size maintained on the chick embryonic chorioallantoic membrane. [5]

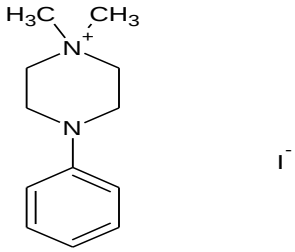


**Figure 2**

Jianhong Chen et.al, prepared and evalulated a series of N,N-disubstituted piperazines for binding to a4$\beta_2$ and α7 neuronal nicotinic acetylcholine receptors by means of rat striatum and whole brain membrane preparations, respectively. This sequence of compounds displayed selectivity for a4$\beta_2$nAChRs. Thus, connecting together a pyridine p-system and a cyclic amine moiety through a piperazine ring affords compounds with low affinity, but worthy selectivity for a4$\beta_2$ nicotinic receptors. [6]

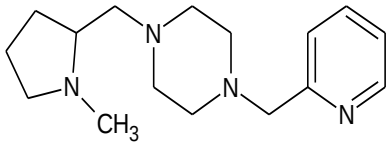


**Figure 3**

Debra J. Post-Munsona et.al, described 3-(3,4-difluorophenyl)-N-(1-(6-(4-(pyridin-2-yl) piperazin-1-yl)pyrazin-2-yl)ethyl) propanamide (B-973), a novel piperazine-containing compound that acts as a positive allosteric modulator of the α7 receptor. They characterized the action of B-973 on the α7 receptor by means of electrophysiology and radio-ligand binding and they established that B-973 will be a suitable probe for scrutinizing the biological consequences of increasing α7 receptor activity via allosteric modulation. [7]

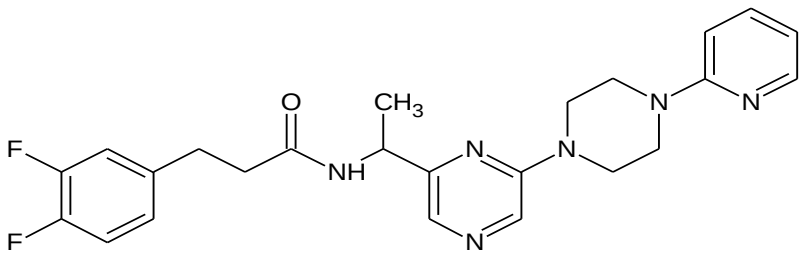


**Figure 4**

## PIPERAZINE DERIVATIVES: ACTION ON GABA RECEPTORS

Richard F. Squires and Else Saederup described about the GABA receptor blocking ability of piperazine derivatives and their effects in psychiatry. They have been used 35S-TBPS binding method to characterize the GABA receptor blocking properties of several compounds not known to be GABA antagonist. Several N-aryl piperazines, such as clinical antidepressants (Amoxapine, Mianserine) and antipsychotic drugs (Clothiapine, Loxapine, Metiapine, Clo- zapine, Fluperlapine) exhibiting GABA antagonistic activity. [8]

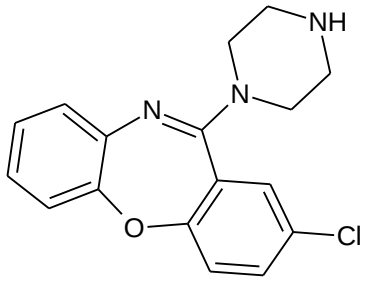



**Figure 5**

Frank Nicolay et.al, described the synergistic effects of the cyclic desipeptide BAY 44-4400 and piperazine in the treatment against the nematodes Trichinella spiralis, Heligmosomoides polygyrus, and Hetrakinspumosa. The in vitro anthelmintic activity of a combination of the two compounds shows 1.7 motility unit against T.spiralis larvae was significantly higher than the sum of the individual drug effect, 1.3 motility units. He also reported that this activity is due to GABAergic action of piperazine and BAY 44-4400. [9]

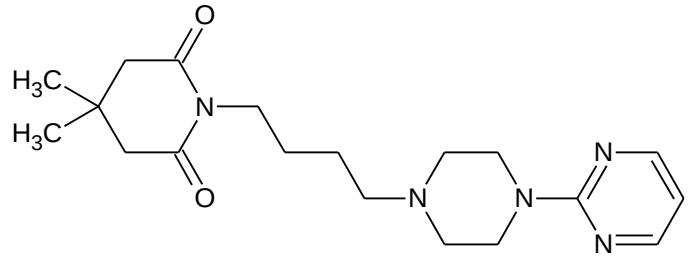



**Figure 6**

## PIPERAZINE DERIVATIVES: ACTION ON SEROTONIN RECEPTORS

Brian A. McMillen et.al, determined effects of gepirone, and aryl-piperazine anxiolytic drug, on aggressive behavior and brain monoaminergic neurotransmission. It was found that gepirone potentially attacked against group housed intruder mice (ED50=4.5 Mg/Kg i.p) without causing sedation or ataxia and it was concluded that potentiation of the antiaggressive effect is by blocking 5-HT receptor caused by gepirone. [10]

EnzaLacivita et.al, reported the design, synthesis, and 5HT7 receptor affinity of a set of 1-(3-biphenyl)- and 1-(2biphenyl) piperazines. The effect on 5-HT7 binding of different substituents on the second (distal) phenyl ring was investigated. Several compounds revealed 5-HT7 affinities in the nanomolar range and >100-times selectivity for 5-HT1A and adrenergic α1 receptors. 1-[2-(4-Methoxyphenyl) phenyl] piperazine displayed 5-HT7 agonist properties in a guinea pig ileum assay but inhibited 5-HT-mediated cAMP accumulation in 5-HT7expressing HeLa cells. [11]

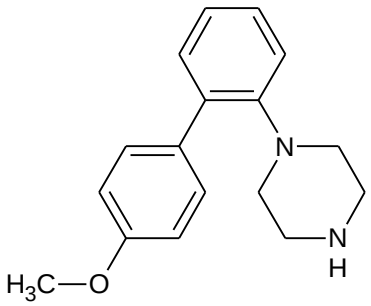



**Figure 7**

Andrew C McCreary et.al were synthesized new 2-

(methoxypheny1)piperazine derivatives 1 and 2 containing a terminal heteroaryl or cycloaklyl amide fragment and their 5-HT1.4 binding ability was evaluated by radioligand binding assays. They found that a four-carbon chain seems to be optimal activity when the amide fragment is a heteroaryl group. Derivatives with a cycloalkyl moiety exhibited maximum affinity in the two methylene chain series. Replacement of the heteroaryl moiety by a cycloalkyl group directed to compounds with enhanced affinity. Increasing the lipophilicity of the cycloalkyl derivatives by annelation and/or saturation increased their affinity for the 5-HT1.4 sites. [12]

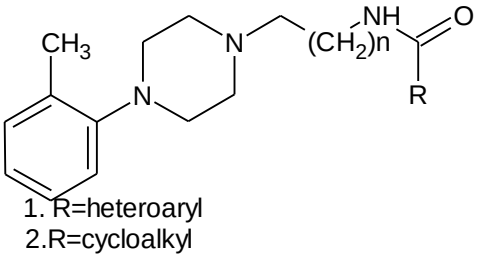



**Figure 8**

Frances H et.al, studied the effect of l-(m-(trifluoromethyl) phenyl) piperazine (TFMPP). TFMPP, an agonist of the 5-HTlb receptors, in mice on numerous psychopharmacological parameters. They have been found that, TFMPP antagonized oxotremorine-induced hypothermia and was active in the behavioural despair test. In addition, TFMPP normalized a social behavioural deficit induced by isolation. It is concluded that TFMPP seems to possess psychotropic activity resembling only in part that of imipramine-like drugs and that these actions may be mediated through 5-HT~b receptors. [13]

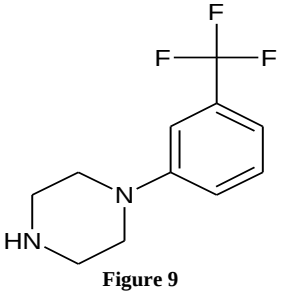



**Figure 9**

Douglas J.Pettibonde et.al were evaluated the effects of various piperazine-containing compounds on the release of endogenous serotonin (5-HT) from rat hypothalamic slices. Incubation of hypothalamic slices with m-chlorophenylpiperazine (mCPP) or m-trifluoromethylphenylpiperazine (mTFMPP) induced a potent, dose-dependent release of endogeous 5-HT. In the presence of the 5-HT uptake blockers fluoxetine or chlorimipramine, this release was reduced intensely. Furthermore, elimination of calcium from the incubation medium had slight effect on the drug-induced release, proposing that the release mechanism involved displacement of 5-HT stores. These resultss prove that numerouspiperazine-containing compounds can induce a potent release of endogenous stores of hypothalamic 5-HT in vitro, actions which should be considered along with their direct agonist activity when interpreting the CNS properties in vivo. [14]

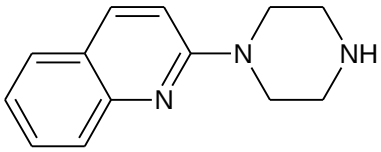



**Figure 10**

Linda D.Simmler et.al characterized the pharmacological properties of aminoindanes, piperazines and piperadol derivatives. Among this they have characterized the piperazine derivatives such as meta-chlorophenylpiperazine, trifluoromethylphenylpiperazine, and 1-benzylpiperazine. They investigated serotonin reuptake inhibition using human embryonic kidney 293 cells that express the respective human monoamine transporters (SERT). Among these piperazine derivatives meta-chloropiperazine showed interaction with serotonergic receptors. [15]

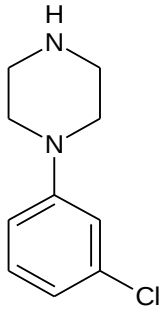



**Figure 11**

## PIPERAZINE DERIVATIVES: ACTION ON HISTAMINE RECEPTORS

AOrjales, et.al, synthesized and evaluated new 4-(diphenylmethyl)-1-piperazine derivatives with a terminal heteroaryl or cycloalkyl amide fragment for their antihistaminic, anticholinergic and antiallergic activities. Tested compounds demonstrated moderate to potent in vitro(in vitro) histamine H1-receptor antagonistic activity. [16]

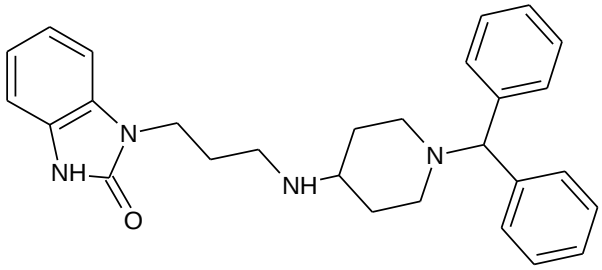



**Figure 12**

NalanTerzioglu et.al described the synthesis and structure activity relationships for a series of ligands structurally related to (5-chloro-1-H-indol-2-yl)-(4-methyl-piperazin-1-yl) methanone as antihistamine H4 receptor antagonist. [17]

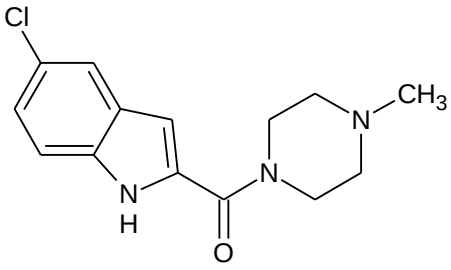



**Figure 13**

Jennifer D.Venable et.al, have been synthesized and evaluated structure activity relationship for activity at theH4 receptor using competitive binding and functional assays of three series of H4 receptor ligands, derived from indoly-2-yl-(4-methyl-piperazin-1-yl) methanones. They have been found that Inallcases, substitution of small lipophilic groups in the 4 and 5-positions led to increased activity in a [3H]histamine. [18]

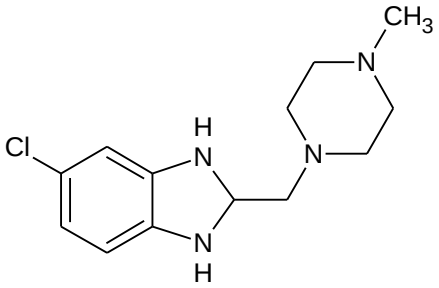



**Figure 14**

John P.Arlette described cetirizine, (2-(2-(4-(4-chlorophenyl)phenyl- methyl)-l-piperazinyl) ethoxy)acetic acid di-hydrochloride) is the principal human metabolite of hydroxyzine, a member of the piperazine class of antihistamines. It is a selective Hl histamine receptor antagonist, which has been shown to be effective in the treatment of urticaria and allergic rhinitis. [19]

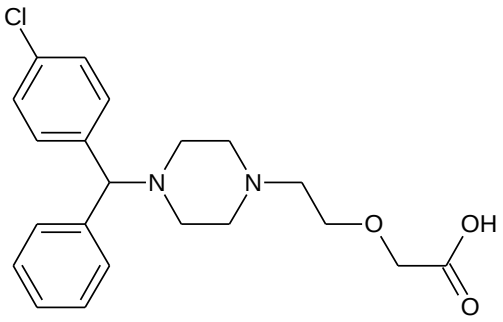



**Figure 15**

## PIPERAZINE DERIVATIVES: ACTION ON DOPAMINE RECEPTORS

Andrew C McCreary et.al, conducted a study which describes the in vitro and in vivo depiction of 1-(2,3-dihydrobenzo[1,4]dioxin-5-yl)-4-[5-(4-fluoro-phenyl)-pyridin-3-ylmethyl]-piperazine monohydrochloride (SLV313), a D2/3 antagonist and 5-HT1A agonist. They have been found that SLV313 possessed high affinity at human recombinant D2,D 3,D 4, 5-HT2B, and 5-HT1A receptors, moderate affinity at 5-HT7 and weak affinity at 5-HT2A receptors, with little-no affinity at 5-HT4, 5-HT6, a1, and a2 (rat), H1 (guinea pig), M1,M 4, 5-HT3 receptors, and the 5-HT transporter. SLV313 had full agonist activity at cloned h5-HT1A receptors (pEC50¼9.0) and full antagonist activity at hD2 (pA2¼9.3) and hD3 (pA2¼8.9) receptors. In vivo, SLV313 antagonized apomorphine-induced climbing and induced 5-HT1A syndrome behaviors and hypothermia. These results suggest that SLV313 is a full 5-HT1A receptor agonist and full D2/3 receptor antagonist possessing characteristics of an atypical antipsychotic, representing a potential novel treatment for schizophrenia. [12]

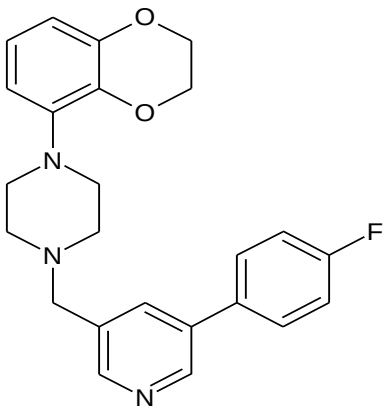
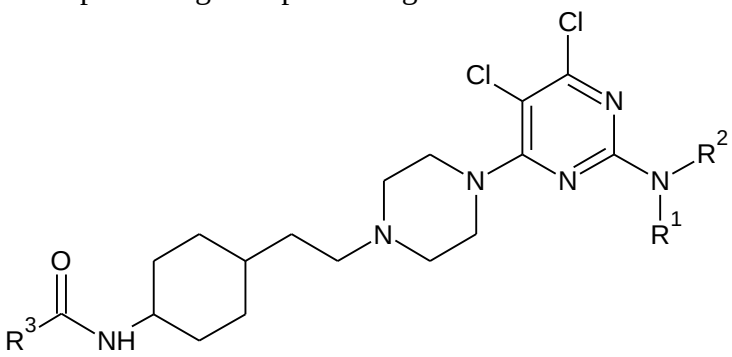



**Figure 16**

Szalai et.al, described the invention relates to new dopamine D3 and D2 ligands. Wherein R1, R2 and R3 may be alkyl, phenyl or substituted phenyl group. The invention similarly relates to processes for pre paring the same, to compositions containing the similar and to their use in the management and/or avoidance of conditions which needs modulation of dopamine receptors. [20]




$R^1$,$R^2$,$R^3$=alkyl, phenyl or substituted phenyl group

**Figure 17**

## PIPERAZINE DERIVATIVES: ACTION ON GLUTAMATE RECEPTORS

Bihua Feng et.al synthesized, a series of 1-(phenanthrene-2-carbonyl) piperazine-2,3-dicarboxylic acid (PBPD) derivatives with structural variations in the biphenyl group and tested to probe the shape of the hydrophobic pocket of NMDA receptor and to determine if such modifications alter subunit specificity. NMDA receptor selectivity was evaluated at native NMDA receptors with the use of quantitative autoradiography and at recombinant NMDA receptors expressed in

Xenopus oocytes using two electrode voltage clamp electrophysiology. [21]

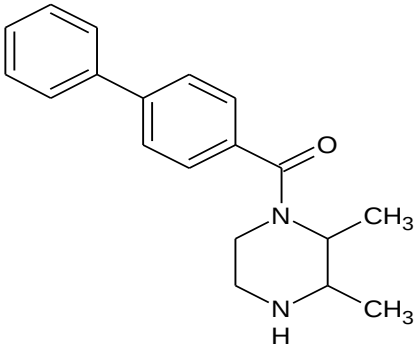


**Figure 18**

Mark W. Irvineet.al have been reported a Modeling study which shown structural features required for activity at GluK1 subunits and proposed that N1-substituted derivatives of cispiperazine-2,3-dicarboxylic acid was essential for antagonist activity. Reliable with this hypothesis, replacing the equivalent residue in GluK3 (alanine) with a serine provide antagonist activity. Antagonists with dual GluN2D and GluK1 antagonist activity may have beneficial effects in various neurological disorders. [22]

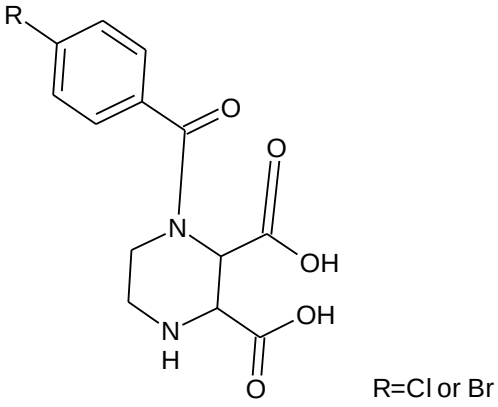



**Figure 19**

K.J. Gregory et.al described the characterization of two innovative N-aryl piperazine mGlu5 positive allosteric modulators (PAMs): 2-(4-(2-(benzyloxy) acetyl) piperazin1-yl)benzonitrile (VU0364289) and 1-(4-(2,4-difluorophenyl) piperazin-1-yl)-2-((4-fluorobenzyl)oxy) ethanone (DPFE). VU0364289 and DPFE induced robust leftward shifts in the glutamate concentration-response curves for Ca21 mobilization and extracellular signal-regulated kinases 1 and 2 phosphorylation. Both PAMs displayed micromolar affinity for the common mGlu5 allosteric binding site and high selectivity for mGlu5. Collectively, these data support and extend the development of novel mGlu5 PAMs for the treatment of psychosis and cognitive deficits observed in individuals with schizophrenia. [23]

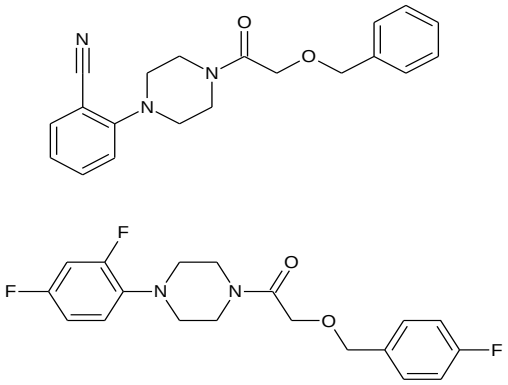


**Figure 20**

## PIPERAZINE DERIVATIVES: ACTION ON GLYCINERGIC RECEPTORS

Robert J. Harvey et.al described, glycine transporters are endogenous regulators of the dual functions of glycine, which acts as a classical inhibitory neurotransmitter at glycinergic synapses and as a modulator of neuronal excitation mediated by NMDA (N-methyl-d-aspartate) receptors at glutamatergic synapses. They have been examined the rationale for the therapeutic potential of GlyT1 and GlyT2 inhibition, and surveys the latest advances in the biology of glycine reuptake and transport as well as the drug discovery and clinical development of compounds that block glycine transporters. [24]

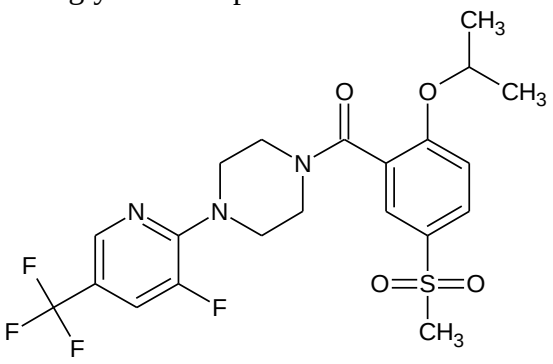


**Figure 21**

## PIPERAZINE DERIVATIVES: ACTION ON OPIOID RECEPTORS

NiklasPlobek et.al, reported a simplified pharmacophore, N,N-diethyl-4-[phenyl(1-piperazinyl)methyl] benzamide, which reserved potent binding affinity and selectivity to the human δ receptor and potency as a pure agonist. They also described, from this compound, the key pharmacophore groups for δ receptor activity and activation were more clearly defined by SAR and mutagenesis studies. Other structural modifications on the basis of this compound proven the importance of the N,N-diethylbenzamide group and the piperazine lower basic nitrogen for δ binding, in agreement with mutagenesis data. A number of piperazine N-alkyl substituents were accepted. In contrast, alterations of the phenyl group led to the finding of a series of diarylmethylpiperazines revealed by N,N-diethyl-4-[1-piperazinyl(8-quinolinyl) methyl] benzamide which had an enhanced in vitro binding profile (IC50 ) 0.5 nM, μ/δ ) 1239, EC50 ) 3.6 nM) and upgraded in vitro metabolic stability. [25]

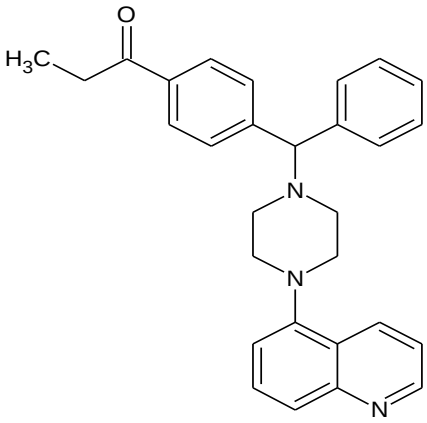



**Figure 22**

Aaron M. Bender et. al described a series of 4-substituted piperazine compounds a compound that displays balanced, low nanomolar binding affinity for the mu opioid receptor (MOR) and the delta opioid receptor (DOR). They further found that, by changing the length and flexibility profile of the side chain in this location, binding affinity is better at both receptors by a significant degree. Also a number of the compounds exhibited good efficacy at MOR, while concurrently showing DOR antagonism. The MOR agonist/DOR antagonist has shown potential in the decrease of negative side effects exhibited by selective MOR agonists, specifically the development of dependence and tolerance. [26]

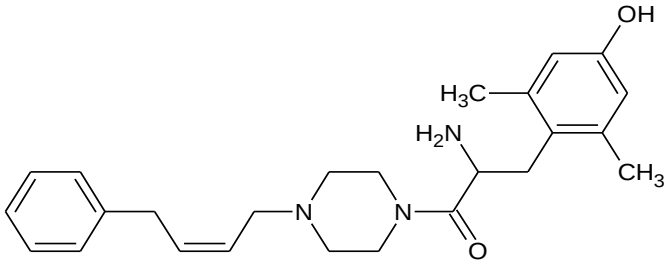



**Figure 23**

John P.McCauley et.al, synthesized a series of piperazine derivatives exhibits sub-nanomolar binding and improved subtype selectivity as delta opioid agonists. They also described the SAR and application of computational models to increase ADME and safety properties suitable for CNS indications, permeability, specifically microsomal clearance, and Herg channel inhibition. [27]

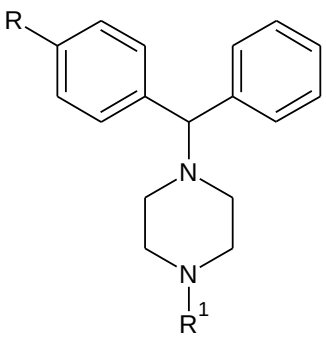



**Figure 24**

F.IvyCarroll described the discovery that 1-substituted 4-(3-hydroxypohenyl) piperazines are best opioid receptor antagonists. Molecules in this new series include N-Pheny propyl (3S)-3-methyl-4-(3-hydroxyphenyl)piperazine and (3R)-4—(3-hydroxyphenyl)piperazine together of which display low nanomolar potencies at μ,δ,and κ receptor and better antagonist properties in a [35S]GTPγS assay. [28]

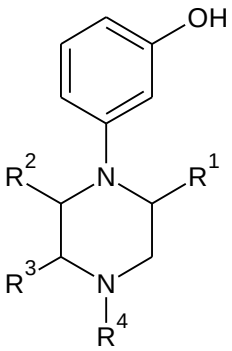
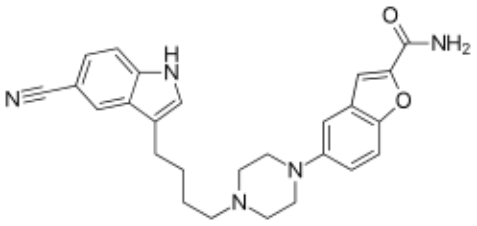
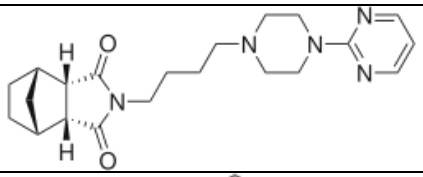
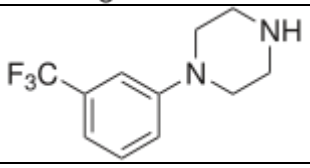
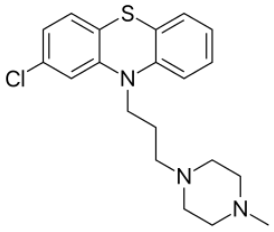
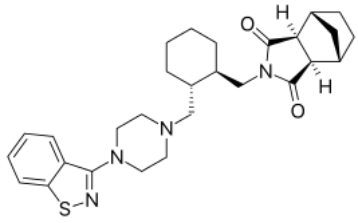



**Figure 25**

**Table 1: Piperazine Nucleus Based Clinically Used Drugs. [29-33]**

| Drug and receptor | Structure | Use |
|---|---|---|
| Vilazidone<br>(activator of the 5-$HT_{1A}$ receptor) |  | Antidepressant |
| Tandospirone<br>(5HT1A receptor partial agonist) |  | Anxiety and depressive disorder |
| Trifluoromethyl phenyl piperazine<br>(5HT1A agonist) |  | Atypical antipsychotic |
| Prochlorperazine<br>(Blocking dopamine receptors) |  | schizophrenia, migraines, and anxiety |
| Lurasidone<br>Antagonist of the dopamine D2 and D3 receptors |  | schizophrenia and bipolar disorder |

## CONCLUSION

This review has fulfilled significant information about neurotransmitter receptor activities of various derivatives based on piperazine moiety and also some drugs having piperazine nucleus. It may be concluded that piperazine scaffold is a resourceful and vital nuclei possessing medicinal importance and is a promising lead compound for the drug design and development of potent therapeutic agents related to neurotransmitter receptors for future.

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