Section I

Chapter 2: Review of Literature

2. Review of Literature

Seven-membered nitrogen containing heterocycles are constituents of a number of compounds with interesting and diversified pharmacological properties.[119,122] The tetrahydro-3-benzazepine ring system is of particular interest from medicinal chemistry point of view because it contains the phenethylamine nucleus, an essential part of several neurotransmitters and corresponding drugs, embedded in its structure.

Benzazepine moiety is attracting a lot of attention due to its wide spectrum of biological activity mostly on central nervous system (CNS). Synthesis of benzazepine scaffold is reported by a number of researchers and its presence is noticed in nature as a basic structure in some alkaloids. Different pharmacological actions associated with benzazepine ring-containing compounds are reviewed and majority of these actions are on CNS disorders. Not limited to CNS, benzazepine derivatives are involved in a multitude of biological activities.[121] Therefore, development of new and efficient synthetic routes for these compounds is of high interest in heterocyclic chemistry.[122] Hence, a number of research articles devoted to the chemistry, stereochemistry and biological activity of benzazepine and its derivatives are available in literature.[123]

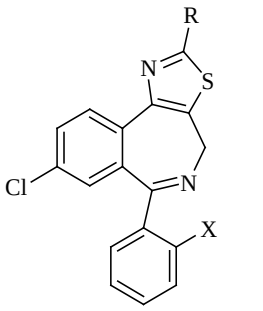
2.1 Benzazepine – a biologically active scaffold

Benzazepine is a biologically active scaffold having multifarious pharmacological activities. Substitution at various positions of the benzazepine ring has resulted in compounds with diversified activities like antiobesity, neuroleptic, anticancer, anti-ischemic etc. Among the benzazepines, the *3H*-benzazepine derivatives have been shown to be affecting mainly the dopaminergic and serotonergic system. Reports exist for the use of medicinal compounds bearing this moiety for schizophrenia and sexual disorders.

Novel benzazepine derivatives have been claimed to be useful in neurological as well as psychiatric disorders. They show narcotic antagonistic activity. The GPR12/14 activity of these compounds is claimed to be useful in the treatment of attention deficit disorder, narcolepsy or anxiety, hypertension, atherosclerosis and cardiac infarction. These are effective agents in the preparation of cells for transplantation in addition to the inhibition of diseases such as diabetes. Some of the benzazepine analogs show urotensin II receptor antagonist activity and are claimed to be useful in the treatment of neurodegenerative disorders.[124]

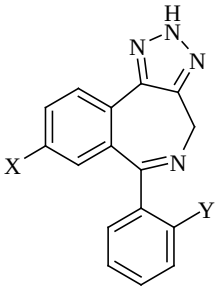
2.1.1 Role of benzazepines in anxiety and other neurological disorders: Benjamin L.E. *et al*.[125] reported certain thiazolo[5,4-d] [2]benzazepines (**2.1**) having CNS activity similar to diazepam and other 1,4-benzodiazepines. They show their activity by binding with

benzodiazepine-receptors. Trybulsky *et al.*[126] reported a series of triazolobenzazepines (**2.2**), resembling diazepam in activity in anti-PTZ (pentylenetetrazole induced seizures) test and were weaker than diazepam in rota rod and inclined screen procedures, suggesting antianxiety property of these compounds. One of the compounds in the series (where X=Y=Cl) has been found to be a diazepam antagonist. Trybulsky E.J. *et al.*[127] studied pyrimidobenzazepines, 2-benzazepine, 9-chloro-7-(2-chlorophenyl)-5*H*-pyrimido[5,4-*d*] [2]benzazepine (**2.3**) and its metabolites for antianxiety activity. This compound (**2.3**) and two of its metabolites, (**2.4** and **2.5**) which were formed by hydroxylation at the 3rd position of benzazepine ring and N-oxidation at 3 position of pyrimido ring respectively, had shown promising anxiolytic activity in various pharmacological tests.



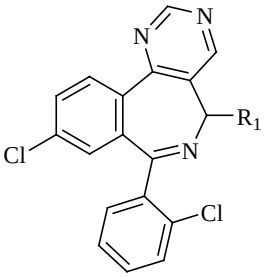
(2.1)

R = CH_3 or NH_2
X = H, Cl, or F

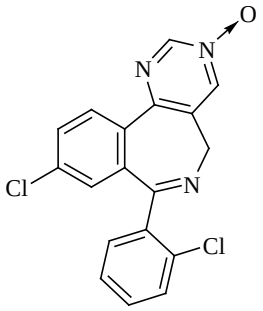


(2.2)

X = H or Cl
Y = H, Cl, or F



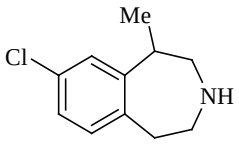
(2.3) R_1 = H
(2.4) R_1 = OH



(2.5)

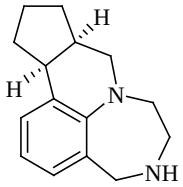
2.1.2 Role of benzazepines as 5-HT receptor modulators: The neurotransmitter serotonin (5-HT) mediates its effects through at least 14 different receptor subtypes that are classified into seven major families, 5-HT_{1-7}.[128] The 5-HT_2 family has three members 5-HT_{2A}, 5-HT_{2B} and 5-HT_{2C}. Unlike 5-HT_{2A} and 5-HT_{2B} receptors, the expression of 5-HT_{2C} receptors is restricted to the central nervous system (CNS).[129] Hence, 5-HT_{2C} receptor agonists have been implicated to be of potential use for the treatment of a number of abnormalities like obesity, schizophrenia, sexual dysfunction, and urinary

incontinence.[130] During the past 30 years, some 3-benzazepines have been reported to be selective 5-HT_{2C} receptor agonists and one of the good agonists, Lorcaserin (**2.6**) developed by Arena Pharma is used for the treatment of obesity.[131] Vabicaserin (**2.7**) was found to have antipsychotic and anorectic activity which is under development by Wyeth.



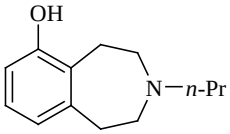
Lorcaserin

(2.6)

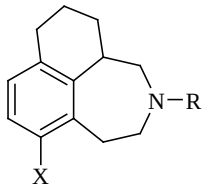


Vabicaserin

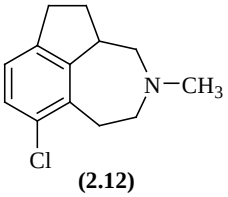
(2.7)



(2.8)



(2.9) X = Cl, R = CH_3
(2.10) X = Cl, R = $CH_2CH{=}CH_2$
(2.11) X = OCH_3, R = $CH_2CH{=}CH_2$



(2.12)

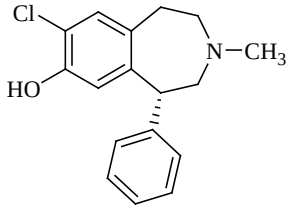
Wikstrom H. *et al*.[132] reported 6-hydroxy-3-*n*-propyl-2,3,4,5-tetrahydro-l*H*-3-benzazepine (**2.8**) and other N-alkyl analog as 5-HT_{1A} receptor agonists of moderate potency, as per *in vivo* biochemical and *in vitro* binding data. A series of 1,9-alkane bridged 2,3,4,5-tetrahydro-1*H*-3-benzazepines were explored for 5-HT_{1A} and α_2 adrenoceptor affinity. Greater affinity towards 5-HT_{1A} receptors was achieved by Clark[133] and his group by some modifications in the benzazepine ring e.g. *N*-alkyl-, *N*-allyl-5-chloro-, and 5-methoxy-l,2,3,4,8,9,10,10a-octahydronaphth[1,8-cd]azapines (**2.9, 2.10, 2.11**), while 5-chloro-2-methyl-2,3,4,8,9,9a-hexahydro-l*H*-indeno[1,7-cd]azepine (**2.12**) shows greater affinity for both the α_2 adrenoceptor and 5-HT_{1A} receptors.

2.1.3 Role of benzazepines as dopaminergic receptors modulators: Shah *et al*. reported that central dopamine receptors were the target for pharmacotherapy in Parkinson's disease, Huntington's disease, and psychosis.[134,135] Dopamine receptors are classified into two major subclasses, D_1 and D_2, and the functions of these receptor subtypes have largely been discerned through ligands that selectively bind to each site.[136,137] These receptor subtypes have been cloned, and their pattern of expression in the central nervous system has been characterized.[138]

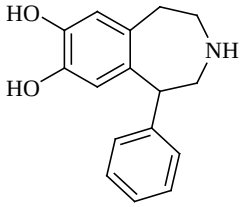
Chemical entities based on the 1-phenyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine nucleus has been shown to bind with the dopaminergic family of G-protein-coupled

receptors (GPCRs).[139] The binding profile of SCH23390 (**2.13**) is similar in both amygdala and hippocampus, to the high affinity site (K_D ~0.4 nM) consistent with D_1/D_5 receptors.[140]

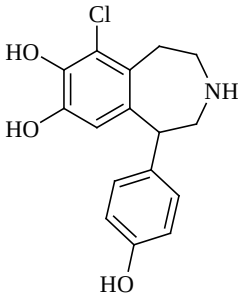
7,8-Dihydroxy-3-benzazepines have been reported to be active on dopaminergic system. SK&F 38393 (**2.14**), a potential anti-Parkinsonism agent reported by Setler *et al*.[141] had shown D_1 agonistic activity with some mixed antagonist effects. Weinstock *et al*.[142] and Hahn *et al*.[143] have reported SK&F 82526 (**2.15**) (FENOLDOPAM), a potent and selective D_1 agonist which mainly acts peripherally, and exerts its effects greatly on the kidney vasculature and causes potent vasodilation with increased renal blood flow. The confirmation of this pharmacological finding was done by clinical experimentation by Stote *et al*.[144] Further finding on the compounds related to **2.15** resulted in a new subgroup of the compounds extending their activity to D_2 receptor agonistic activity with retention of D_1 agonistic activity. The lead compound of this subseries is N-allyl derivative SK&F 85174 (**2.16**).[145]



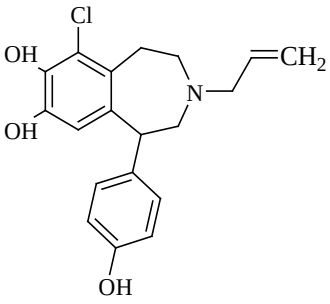
SCH 23390
(2.13)



SK&F 38393
(2.14)



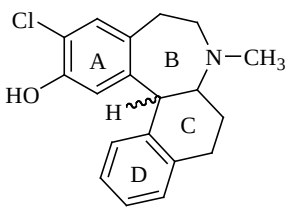
SK&F 82526
(2.15)



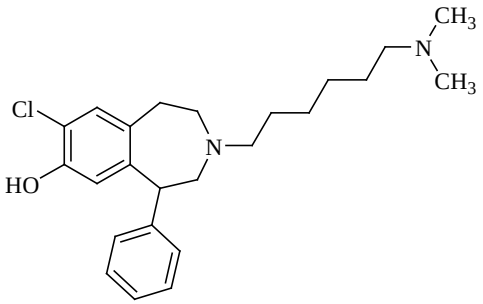
SK&F 85174
(2.16)

A series of conformationally restricted analogs hexahydro-5*H*-benzo[*d*]naphtho[2,l-*b*]azepines (**2.17** and **2.18**) have also shown similar activity. Compounds with B/C-trans ring junction (**2.18**) show considerably higher D_1 receptor affinity and selectivity as compared to the cis stereoisomer (**2.17**) which has higher selectivity for D_2 receptor.[146] Shah *et al*.[147] prepared (*N*-alky-1-amino)benzazepine analogs as dopamine D_1 receptor antagonists. Among them 7-chloro-8-hydroxy-3-[6-(*N*,*N*-dimethylamino)hexyl-l-phenyl-2,3,4,5-tetrahydro-l*H*-3-benzazepine (**2.19**) showed the

highest affinity and subtype-selectivity for dopamine D_1 over dopamine D_2, 5-HT2a, and 5-HT2c receptors.

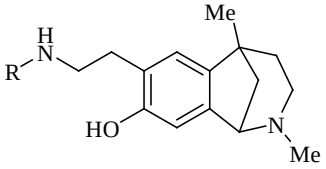


(2.17) B/C-cis
(2.18) B/C-trans

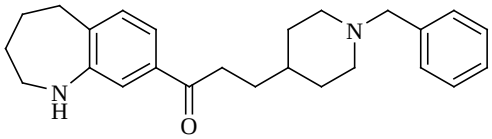


(2.19)

2.1.4 Role of benzazepines as acetylcholinesterase (AChE) inhibitors: A series of alkylcarbamates of 1,5-methano-2,3,4,5-tetrahydro-l*H*-2-benzazepin-7-ol (**2.20**) was reported as potent acetylcholinesterase (AChE) inhibitor by Chen *et al.*[148] 3-[l-(Phenylmethyl)-4-piperidinyll-1-(2,3,4,5-tetrahydro-l*H*-l-benzazepin-8-yl)-l-propanone (**2.21**) and its analogs were studied by Ishiharaet Y *et al.*[149] for central selective acetylcholinesterase (AChE) inhibitory activity. Among them (**2.21**) has shown satisfactory central selectivity.

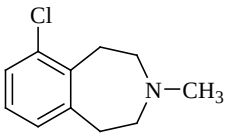


(2.20)

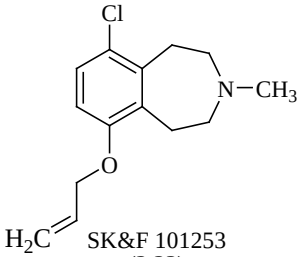


(2.21)

2.1.5 Role of benzazepines as α-adrenoreceptor modulators: During the last decade much evidence has accumulated that supports the concept that in addition to the classical postsynaptic α-adrenoceptors that mediate the responses of effector organs to norepinephrine, there are also α_2-receptors located presynaptically on noradrenergic nerve terminals.[150] These receptors are part of a negative feedback mechanism that modulate the release of norepinephrine in the periphery and the central nervous system. Moreover these α_2-receptors can be differentiated from the α_1-receptors by their specificity towards a series of agonists and antagonists. This pharmacological classification is independent of anatomical distribution.[151,152] Such a sub-classification of α-adrenoceptors opens up new possibilities for drug discovery through the development of agonists or antagonists having a high degree of selectivity for each receptor subtype.



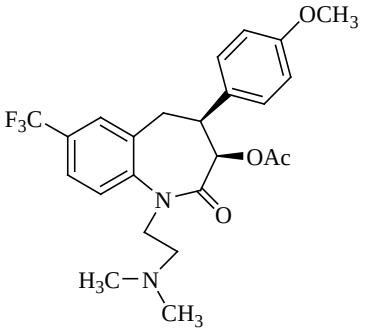
SK&F 86466
(2.22)



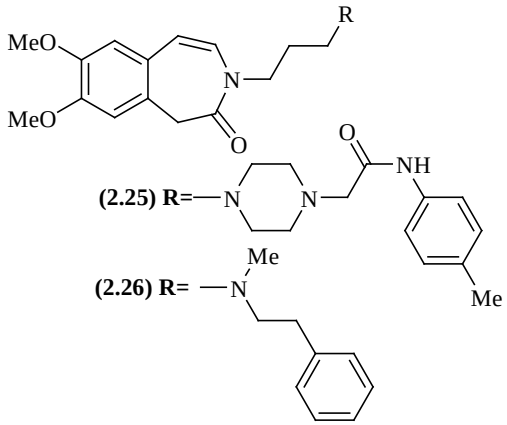
SK&F 101253
(2.23)

DeMarinis *et al.*[153] reported the synthesis and preliminary characterization of a novel and selective α-adrenoceptor antagonist, 6-chloro-2,3,4,5-tetrahydro-3-methyl-*1H*-3-benzazepine (SK&F 86466, **2.22**). DeMarinis modified its structure in another report to 9-allyloxy-6-chloro-3-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine (SK&F 101253, **2.23**) which had also shown α_2-adrenoceptor antagonistic activity.[154] It was used for the purification of the α_2 adrenoreceptors from human platelet membranes, as an affinity ligand.

2.1.6 Role of benzazepines in cardiovascular disorders: Benzazepine derivative (**2.24**) was found to be a calcium antagonist selectively blocking the voltage dependent calcium channel hence showing protecting effects for ischemic myocardium.[155] Some other benzazepine analogs (**2.25** and **2.26**) also found to be specific bradycardiac agents (sinus node inhibitors) show higher potency, selectivity and prolonged duration of action.[156]

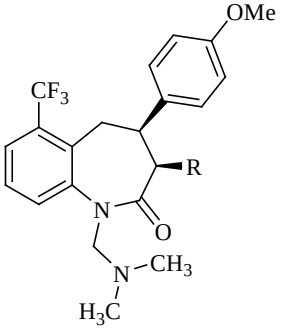


SQ 31,486
(2.24)

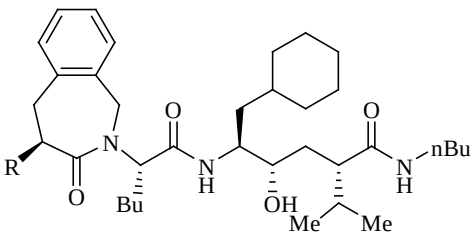


(2.25) R=

(2.26) R=



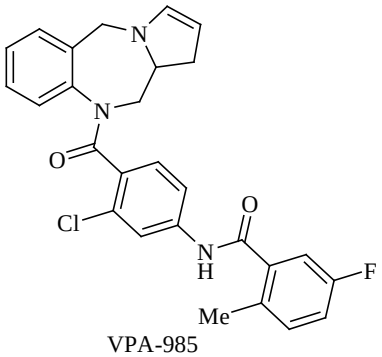
(2.27) R = Me
(2.28) R = Et
(2.29) R = Allyl



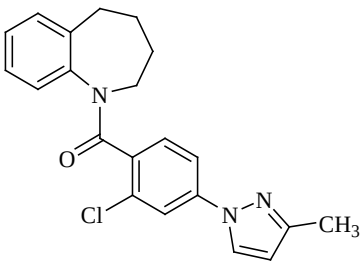
R = N-Phthlimide or NH_2 or BocNH or AcNH
(2.30)

Das *et al*.[157] have reported several analogs of 3-alkyl benzazepinones as potent calcium channel blocking agents, both *in vitro* and *in vivo*. Analogs (**2.27** and **2.28**) containing a 6-trifluoromethyl substituent have shown the highest vasorelaxant activity *in vitro*. The oral antihypertensive activity of these compounds was comparable to 8-chlorodiltiazem. The 3-allyl analog (**2.29**) was a more potent antihypertensive agent as compared to **2.27**, **2.28** and 8-chlorodiltiazem with a longer duration of action *in vivo*. De Laszlo S. E. *et al*.[158] have reported certain 4(*S*)-amino-2-benzazepinones (**2.30**) to show renin inhibitory action although with low potency.

2.1.7 Role of benzazepines as arginine vasopressin (AVP) receptor modulators: Fuk-Wah Sum *et al*.[159] had reported that arginine vasopressin (AVP) is a cyclic nonapeptide hormone released from the posterior pituitary in response to increased plasma osmolality, or decreased blood volume and blood pressure. AVP binds to three known receptor subtypes: vascular V1a, hormone releasing V1b, and renal V2 receptors, and regulates osmotic water permeability of water channels in the kidney through the V2 receptors.[160-162] These mechanisms help to maintain normal plasma osmolality, blood volume, and blood pressure. Antagonists of the V2 receptor are potentially useful for treating diseases characterized by excess renal re-absorption of free water, such as congestive heart failure, liver cirrhosis, nephrotic syndrome, and hyponatremia.[163] They have reported compound (**2.31**) as orally active AVP antagonist with selectivity for the V2 receptor. Recently, nonpeptide agonists for the seven trans-membrane G-protein-coupled receptors have been reported in the angiotensin system[164] and the cholecystokinin system.[165] Kondo *et al*.[166] synthesized a number of 1-benzazepine derivatives in which substituted benzoly group was attached to the azepine nitrogen showing good V_2 agonist acivity and the compound (**2.32**) showed potent activity as per *in vivo* characterization on the cloned angiotensin AT1 receptor. This may be the first report indicating that the insertion of methyl group produces agonist action.

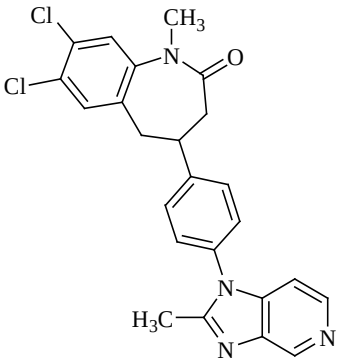


VPA-985
(2.31)



(2.32)

2.1.8 Role of benzazepines on different other disorders: Fray *et al.*[167] reported 7,8-dichloro-l-methyl-4-[4-(2-methyl-1*H*-imidazo[4,5-c]pyridin-l-yl)phenyl]-1*H*-benzo[*b*]azepin-2(3*H*)-one (**2.33**) as potent PAF (Platelet-activating factor) antagonist. Some of the 7,8-dihydroxy-2-benzazepines (e.g. **2.34**) have been reported as anti-platelet aggregatory agents. Clark *et al.*[168] reported analogs of **2.34** and **2.35** as inhibitors of phospholipase C.



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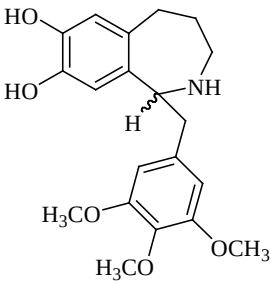

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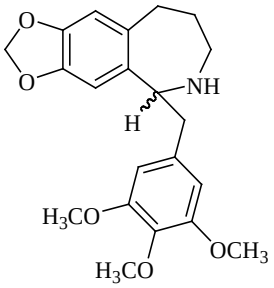
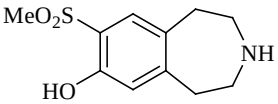


(2.35)

Sulfinyl and sulfonyl substituted 3-benzazepines have been reported to treat gastric motility disorders. In particular, 8-hydroxy-7-methylsulfonyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine (**2.36**) has been reported to be useful to treat gastrointestinal motility related disorders including gastro-easophageal reflux disease, disorders of upper GI motility, anorexia nervosa, early satiety, aspiration, disorders of delayed gastric emptying of various etiologies, etc. and in diagnostic radiology.[169]



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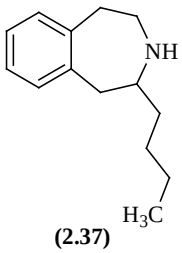

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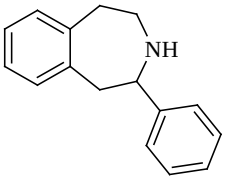
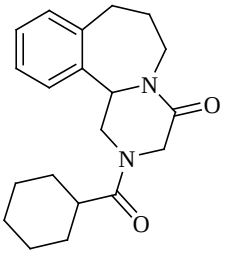


(2.38)



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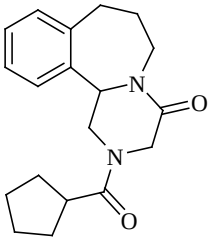

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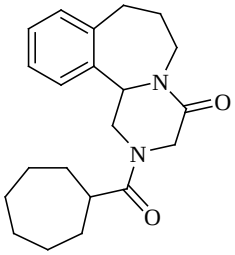

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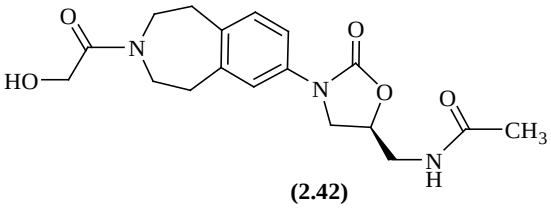


(2.42)

Recently, high σ-receptor affinity of enantio pure 2-substituted 3-benzazepines (**2.37** and **2.38**) was reported by Husain *et al.*[170] This prompted the study of binding of

enantio pure 2-substituted 3-benzazepines at σ-receptors as viable targets. The σ-receptors are well established as non-opioid, non-phencyclidine, and haloperidol sensitive receptor family with their own binding profile and a characteristic distribution in the CNS and some peripheral tissues like kidney, liver, lung, and heart.[171,172] The class of σ-receptors comprises of two subtypes, termed as σ1 and σ2 receptors. The σ1-receptor plays an important role in several physiological and pathophysiological processes. In particular, σ1 antagonists can be used for the treatment of psychosis representing a new approach for the treatment of neuropathic pain. Furthermore, σ binding ligands are investigated in clinical studies for the treatment of depression, cocaine abuse, and epilepsy.[173-175] The structures of σ1 binding ligands are quite diverse. In order to gain more information about the σ1 binding site, it is necessary to develop stereochemically defined, conformationally restricted ligands with high σ1 affinity and high selectivity.

Anderson *et al.*[176] reported certain pyrrole fused 1- or 2-benzazepine derivatives as antileukemic agents. Analogs of **2.39** and **2.40** show *in vivo* activity against P388 lymphocytic leukemia. Brewer *et al.*[177] reported a group of 1,2,3,4,6,7,8,12b-octahydropyrazino[2,1-a][2]benzazepine derivatives as anthelmintics. These compounds were tested for the cestocidal activity in an *in vitro Taenia crassiceps* screen. Many of these derivatives including **2.41** proved to be highly active.

Johnson *et al.*[178] reported SAR studies of the oxazolidinones demonstrating that the phenyloxazolidinone core structure (e.g. **2.42**), is important for antibacterial activity. However, analogs with a variety of substituents including nitrogen and carbon-linked heterocycles with benzazepine attached to the 4-position of the phenyl ring demonstrate antibacterial activity.[179,180]

Owing to the pharmacological importance of benzazepines, several synthetic methods are reported for the benzazepine ring and its derivatives. The intermediates or final targets containing benzazepine core were used in the synthesis of antipyretics, diuretics, sedatives and anticancer agents.[181-185]

2.2 Benzazepines as NMDA receptor modulators`

NMDA receptors in particular have received much attention over the last few decades, due to their key role in many types of neuronal plasticity on the one hand, and their involvement in neuronal excitotoxicity on the other hand. An important goal of recent research interest is to identify clinically relevant NMDA receptor antagonists capable of preferentially blocking excitotoxic NMDA receptor activation without

interfering with the NMDA receptor functions needed for normal synaptic transmission and plasticity.[186,187]

Synaptic transmission is central to the ability of the nervous system to process and store information. Synapses are specialized contacts between neurons, where the release of neurotransmitter by the presynaptic neuron activates receptors on the membrane of the postsynaptic neuron. Excitatory synaptic transmission in the mammalian brain is mediated primarily by the amino acid glutamate, activating two different groups of glutamate receptors: ionotropic and metabotropic. Ionotropic glutamate receptors[188] are ligand-gated ion channels further divided with respect to their pharmacological properties into the following sub-groups: GluA (AMPA, 2-amino-3,3-hydroxy-5-methylisoxazol-4-ylpropanoic acid), GluK (kainate), GluN (NMDA, *N*-Methyl-*D*-aspartic acid), and GluD (δ) receptors.

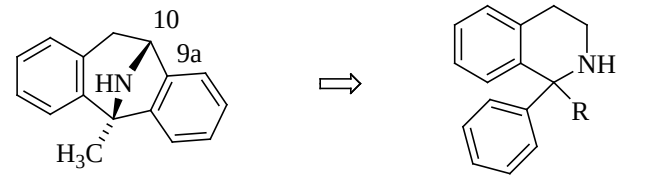
The NMDA receptor is significant for the growth of neurons and therefore for developments like learning and memory. However, a number of acute and chronic neurodegenerative disorders occur due to an overstimulation of the NMDA receptor by an uncontrolled release of (*S*)-glutamate. Actually, the excitotoxic processes caused by cerebral ischemia (stroke), epilepsy and trauma (brain injury), are based on huge inflow of Ca^{2+}-ions through the NMDA receptor linked ion channels. The role of the NMDA receptors in the development of Parkinson's disease, Alzheimer's disease,[189] amyotrophic lateral sclerosis[190] and alcohol dependency has been well established. Therefore, the NMDA receptor can be an interesting target for the therapeutic exploitation of these neurological diseases.

Ligands interacting with the phencyclidine (PCP) binding site, located within the NMDA receptor associated ion channels, block the influx of Ca^{2+}-ions and therefore function as NMDA receptor antagonists.

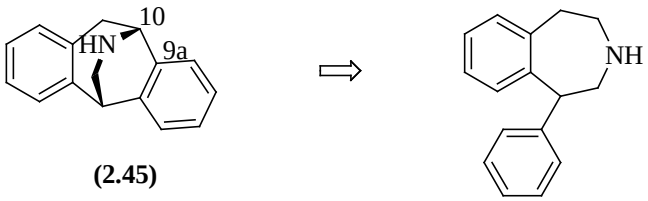
The NMDA receptor is an ionotropic receptor that allows the transfer of electrical signals between neurons in the brain and in the spinal column. For electrical signals to pass, the NMDA receptor must be open. To remain open, glutamate and glycine must bind to the NMDA receptor. An NMDA receptor that has glycine and glutamate bound to it and has an open ion channel is called "activated". NMDAR antagonists fall into four categories: competitive antagonists, which bind to and block the binding site of the neurotransmitter glutamate; glycine antagonists, which bind to and block the glycine site; noncompetitive antagonists, which inhibit NMDARs by binding to allosteric sites; and uncompetitive antagonists, which block the ion channel by binding to a site within it.

Among them glycine site shows good NMDA receptor antagonistic properties with fewer side effects as glycine is the main co-agonist for NMDA receptor activation. Basically NMDA antagonists or blockers help in NMDA related excitotoxicity. Some reports on the NMDA receptor antagonists acting specifically on gycine site are discussed below.

The tetracyclic MK-801 (**2.43**) is a non-competitive NMDA receptor antagonist, that binds with high affinity (Ki=1.26 nM)[191] to the PCP-binding site of the NMDA receptor. The cleavage of the C9a/C10- bond of MK-801 (**2.43**) results in tetrahydroisoquinolines (**2.44**), which also interact with the PCP-binding site.[192-194] Extension of the amino bridge of **2.43** leads to the constitutional isomer (**2.45**)[195,196] which also binds with high affinity to the PCP-binding site of the NMDA receptor. The opened ring (cleavage of the C9a/C10-bond) analog of **2.45**, the racemic 1-phenyltetrahydro-3-benzazepine **(2.46)** exhibits considerable interaction with the NMDA receptor.[197] In some other reports 3-benzazepine heterocycles with a one-atomic spacer between the parent ring and the phenyl residue in position 1 display most promising NMDA receptor affinity.[198]



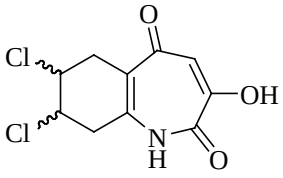
(2.43) **(2.44)**



(2.45) **(2.46)**

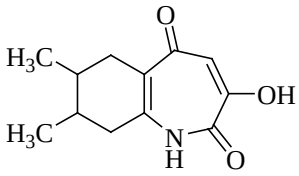
Receptor overstimulation, caused by excessive glutamate concentration in the synaptic region, is believed to contribute to the symptomatology of many neurological disorders. In addition to glutamate, the amino acid glycine is a necessary co-agonist for activation of NMDA receptors. Glycine site of NMDA receptor is composed of non-planar hydrophobic region which is responsible for binding. A number of compounds were synthesized in search for NMDA receptor antagonists through glycine site of the receptor. 3-Benzazepines were investigated by Guzikowski and their group and developed a number of compounds. Their research on the glycine site shows that 6,7,8,9-tetrahydro-3-hydroxy-1*H*-1-benzazepine-2,5-diones substituted at C7 and C8 positions with different groups

offer potent antagonists at NMDA receptor glycine site as shown by IC_{50} values of compounds (**2.47, 2.48** and **2.49**).[199]



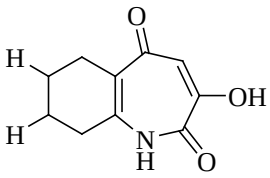
I (IC_{50}= 131 nM)

(2.47)



II (IC_{50}=2281 nM)

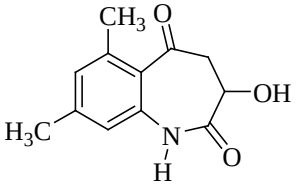
(2.48)



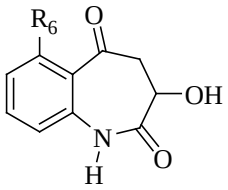
III (IC_{50}= 3205 nM)

(2.49)

Analogs of 3-hydroxy-1*H*-1-benzazepine-2,5-dione also showed their role to antagonize glycine site of NMDA receptor. 6,8-Dimethyl analog (**2.50**)[200] is the most potent derivative having ED_{50} value of 3.9 mg/kg. Changes in aryl side chain with different substituents offer analogs having different potencies and affinities.



(2.50)

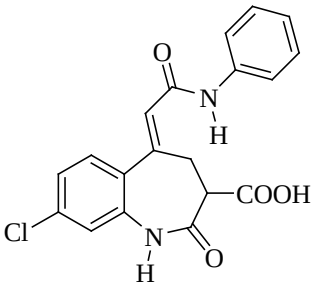


R_6= Me, Et

(2.51)

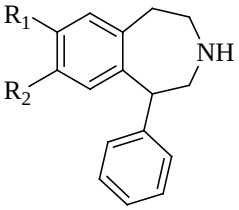
Further research on NMDA receptor glycine site has been carried out by Guzikowski *et al.*[201] through substitution at C-6 position with smaller alkyl groups. Structures having 1-benzazepine substituted at C-6 position (**2.51**) with methyl or ethyl show better activity on NMDA receptor glycine site compared to AMPA-glutamate site.

Studies carried out by Fabio *et al.*[202] claim that 1-benzazepine structure having carboxylic acid at C-3, CH=CH-CONH-Ph at fifth position and chloro group at 8th position offered a very effective compound **(2.52)** which acts mainly through gycine site having an IC_{50} value of about 0.09 mg/kg i.v. and excellent affinity for the receptor with k_i value of 32 nM.



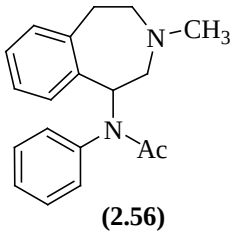
(2.52)

Wunsch have made significant contribution in exploring tetrahydro-3-benzazepine derivatives as NR2B selective NMDA receptor antagonist. Research carried out on 1-phenyltetrahydro-3-benzazepines (**2.53**) by Wunsch *et al*.[203] defined the compound as non-competitive antagonist of PCB binding site and the SAR showed that un-substituted benzo fused benzazepine moiety with phenyl at C-1 position (**2.53**) offered good binding affinity with k_i value of 6.41 µM. Donor substituents on the aryl moiety (**2.54** and **2.55**) reduced the affinity for the receptor.

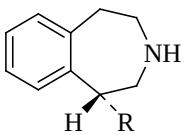


	R_1	R_2
(2.53)	-H	-H
(2.54)	$-OCH_3$	-OBn
(2.55)	$-OCH_3$	-OH

Charge distribution and H-bond forming abilities with the protein structure is essential for the affinity for the receptor, so substituted groups having charge distribution or H-bond forming capacity show good affinity for the receptor. Krull and Wunsch[204] synthesized novel tetrahydro-3-benzazepine derivatives by introducing various substituents at position 1 of the 3-benzazepine heterocycle and concluded that ligands with a one-atomic spacer between the 3-benzazepine heterocycle and the phenyl residue at position 1 displayed the most promising NMDA receptor affinity. The 3-benzazepine ring system substituted at position 1 with acetanilide **(2.56)**, makes the most potent NMDA antagonist because due to charge distribution capacity of acetamide moiety it takes part in H-bond formation while interacting with the receptor. Hence substituents like ether, amide, amine, and imine at position 1 offer promising biological activity.



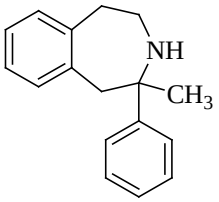
(2.56)



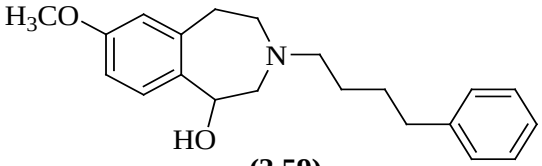
(2.57)

In one of the findings reported by Wirt in association with Wunsch[205] suggested that (*R*) configured 2-methylbenzyl substituent if attached at first position of tetrahydro-3-benzazepines (**2.57**) offered the highest NMDA receptor affinity with k_i value of 1.66 µM as a very good NMDA receptor binding ligand to the PCP site.

Husain *et al.*[206] synthesized benzazepine derivatives as NMDA receptor antagonists and found that enantiomerically pure 2-methyl-2-phenyltetrahydro-3-benzazepine (**2.58**) showed a moderate affinity (Ki = 496 nM) for the PCP binding site of the NMDA receptor.



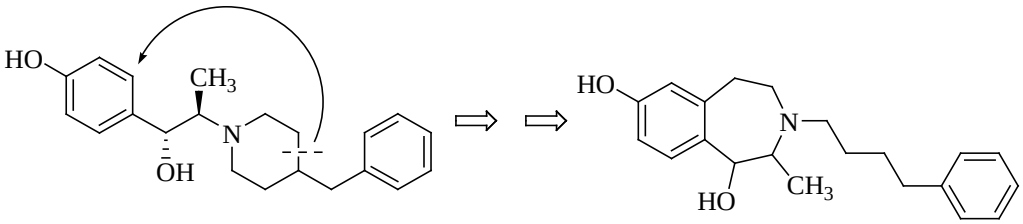
(2.58)



(2.59)

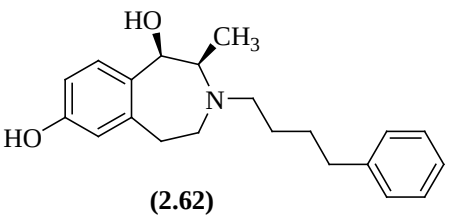
Bernhard and their group synthesized and evaluated different 3-benzazepine ring analogs for NMDA receptor antagonistic properties.[207] Substitutions were carried out on the secondary amine of the heterocyclic seven membered ring with 4-phenylbutyl group, in which butyl side chain acted as spacer between the core structure and the phenyl group. It was observed that unexpected high GluN2B affinity was seen when C7 site of 3-benzazepine structure (**2.59**) was substituted by ether. The most promising compound was 7-methoxy-3-(4-phenylbutyl)-2,3,4,5,-tetrahydro-1*H*-3-benzazepin-1-ol (**2.59**) showing high affinity (Ki=5.4 nm) for the NR2B receptors.

Another work on 3-benzazepines for NMDA receptors modulatory activity was reported by Wünsch and coworkers. They considered ifenprodil (**2.60**) as the lead molecule and suggested that proper cleavage and rebuilding of a bond of the piperidine ring of **2.60** led to tetrahydro-3-benzazepine (**2.61**).[208] From among more than 25 compounds they had synthesized, compound (**2.61**) represented the most promising NR2B antagonist of the series showing a Ki-value of 14 nM.

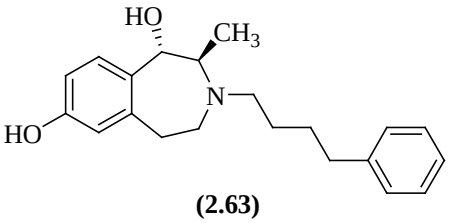


(2.60) **(2.61)**

One of the studies by Wünsch focused on stereochemical configuration of substituents on the core structure displaying their role in receptor binding. The study suggested that the (*R, R*) and (*S, R*) isomers (**2.62** and **2.63**) showed good affinity for GluN2B site.[209]

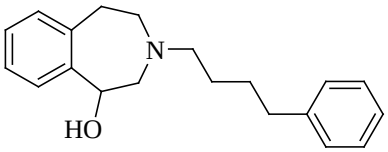


(2.62)



(2.63)

Later on, to analyze the role of the phenolic OH group of ifenprodil (**2.60**) and 3-benzazepin-1,7-diol (**2.61**) for the affinity and selectivity at GluN2B subunit of NMDA receptors, 3-benzazepin-1-ol (**2.64**) was designed, synthesized and pharmacologically evaluated by Wünsch *et al*.[210] Molecular interactions of the derivative (**2.64**) were investigated with the GluN2B receptor. In receptor binding studies using radioligand [^{3}H]ifenprodil (Ki-value of 10 nM), 3-benzazepin-1-ol (**2.64**) revealed a high GluN2B affinity (Ki-value of 73 nM) indicating that the phenolic OH group of **2.60** and **2.61** is not essential but favorable for high GluN2B affinity. In docking studies 3-benzazepin-1-ol (**2.64**) shows the same binding pose as ifenprodil in the X-ray crystal structure. H-Bond interactions and lipophilic interactions of **2.64** and ifenprodil (**2.60**) are very similar.



(2.64)

Pharmacological activity of benzazepines is restricted to CNS mainly because of their similarity in structure to dopamine and other neurotransmitters in the CNS. Hence, researchers across the world are engaged in the development of benzazepine-based CNS-responsive drugs. In order to investigate the structure-affinity relationships within the 3-benzazepine class of NMDA receptor antagonists, it is needed to develop new methods for the synthesis of tetrahydro-3-benzazepines with various substituents in position 1.