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Exploring the NMDAR antagonists as potential therapeutic agents in the treatment of Alzheimer's disease- A Review

Neeru Dugar [1], Jinu Mathew [1], Nagarjuna Palathoti [1], Gomathi Swaminathan [1], Srikanth Jupudi [1,*], MohammedAfzal Azam [2]

[1] Department of Pharmaceutical Chemistry, JSS College of Pharmacy, JSS Academy of Higher Education & Research, Ooty, Nilgiris, Tamil Nadu, India
[2] Principal, College of Pharmacy, JSS Academy of Technical Education, Noida, Uttar Pradesh, India
* Correspondence: sjphd@jssuni.edu;

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Abstract: Alzheimer's disease is the prevailing and irreversible degenerative disorder affecting approximately around 44 million people worldwide. A chronic neurological disorder that causes by atypical processing or misfolding of the neurological proteins persilin1, persilin2, and amyloid beta precursor protein. The hallmark of Alzheimer's disease is the cleavage of amyloid-beta in the hippocampal area of the brain followed by phosphorylation of tau proteins. Recent studies have revealed that excitatory glutamatergic neurotransmission via syn-NMDAR is critical for synaptic plasticity and the survival of neurons. However, the increased ex-NMDAR activity causes excitotoxicity and promotes cell death, leading to neurodegeneration in Alzheimer's disease. Until now, there are only six drugs approved by Food and Drug Administration for Alzheimer's Disease among which one was recently approved in 2021. This review's updated information on NMDAR antagonists and the importance of these antagonists stated structural characteristics were underlined. This review will be a valuable resource for structural information that could be used to create more effective inhibitors for this enzyme.

Keywords: Alzheimer's disease, NMDA antagonist, memantine, MK-801.

1. Introduction

Neurodegenerative disorder (ND) is an umbrella term for a span of conditions that predominantly influence the neurons in the human brain. ND was characterized by progressive neuronal deprivation because of metabolic or toxic disorders. The most common cause of neuronal loss is protein abnormalities [1]. Alzheimer's disease (AD) is a type of neurodegenerative disorder that progresses slowly, involving chronic dementia integrated with the decrease in the neurotransmitter acetylcholine (AcH) and oxidative stress caused by the aggravation of glutaminergic transmission [2]. It is primarily caused by the atypical processing and misfolding of normally soluble neuronal proteins ascribable to genetic mutations, external factors, or aging leading to unusual neuronal function and loss [3]. The hallmark pathways for AD are amyloid β (Aβ) cleavage, Aβ degeneration, Apolipoprotein E cholesterol pathway, and neurofibrillary tangles amassment,-; these are the crucial pathophysiological pathways of AD [4]. A study on biomarkers suggests that Aβ amassment is followed by increased phosphorylation and synaptic dysfunction and the production of tau. This microtubule-binding

axonal protein is expressed highly in cortical neurons [5]. Plasma $A\beta_{42}/A\beta_{40}$ is an accurate predictor for the presence of amyloid plaques and can be used to diagnose AD, identify people who may develop dementia in the future as a result of AD, and increase the diversity of populations included in AD studies and therapeutic trials. [6]. Neuroinflammation, as well as stimulation of microglial cells and astrocytes, are salient features of neurodegenerative dementias. During the past years, it has been discussed whether neuroinflammation and astrogliosis are chief drivers of neurodegeneration or downstream effects of the amassment of Aβ and tau [7]. Misfolding of TAR DNA-binding protein 43 (TDP-43) are usually seen with classical AD pathogenesis [8]. Biometals like zinc, copper, and iron have been involved in ADS pathology for over 25 years. Although these metal ions are physically necessary, a genetic (or nutritional) imbalance causes neurotoxicity and brain impairment. Zinc ions rapidly cause histopathological amyloid formation in soluble Aβ. Copper and iron ions were also discovered to aid in the accumulation of Aβ and to catalyze the generation of reactive oxygen species from ternary complexes [9-15]. Premature centromere division (PCD), a genetic mechanism connected with increased aneuploidy, is found to be strongly associated with aging and AD. On the X chromosome, the mean frequency of PCD in frontal cortical neurons of patients with AD is nearly higher thrice than in control subjects [16]. Animal and human studies suggest the practical role of sex hormones such as estrogens, progesterone, and androgens in cognition and behavior [17, 18]. Previous studies have observed cognitive decline and AD development associated with polymorphisms of estrogen receptors in females, particularly GPER1 [19]. Only 31% of 184 AD9 patients had AD pathology, 17.5% had AD pathology plus α-synuclein and TDP43 pathology, 29.5 % had AD pathology plus TDP43 pathology (TDP43 inclusions in hippocampi), and 22% had AD pathology plus α-synuclein pathology (Lewy bodies outside the brainstem). There were multiple infarcts in between 29% and 52% of individuals (micro infarct, lacunar infarct, or large infarct) [20].

The recognized AD pathways are acetylcholine production, cholesterol synthesis, Wnt signaling pathway, Notch signaling pathway, Ubiquitin mediated proteolysis, calcium signaling pathway, apoptosis, ER stress, insulin pathway, abnormal ceramide accumulation, MAPK signaling pathway, cell cycle, ceramide synthesis, reactive oxidation process, neurotrophin signaling pathway, regulation of autophagy, arachidonic acid cascade, lipid pathway, mTOR signaling pathway, lipid raft, inflammation pathway, and CREB pathway [4]. Primary advancements to improve the amyloid-instigated cascade include immunotherapy, β-secretase 1 (BACE1) inhibitors, and vaccines [21-23]. Despite the lack of success of more than

30 phase 3 trials, clinical trials for Aβ-lowering agents proceed to manifest apparent concentrative benefits to AD patients or occasionally unfavorable, even when amyloid plaques are successfully removed [24-29]. The therapy modalities employed in treating AD's pathogenesis are primarily symptomatic and ineffective [30]. Aducanumab was submitted to the Food and Drug Administration (FDA) for approval based on questionable benefits seen in one of the 2-phase 3 trials and was approved recently [29]. Despite the fact that patient inclusion in the trial and drug approval were based on the presence and subsequent removal of amyloid plaques, aducanumab has been approved for patients with Alzheimer's disease without specifying whether demonstration of Aβ pathology by cerebrospinal Fluid (CSF) analysis or positron emission tomography (PET) scan is required [31]. AD was the first and most prevalent disease to be recognized as implicating the pathological aggregation of tau protein [32]. Dementia is anticipated to grow from 0.05 billion people in 2010 to 0.113 billion by 2050 globally [33]. With advancing age, the prevalence of cognitive impairment is increasing

rapidly. The incidence of dementia grows abruptly by age 65 and continues to increase subsequently [34]. One of the major risk factors for dementia is age. For developing AD, genetic factors like rare, dominantly inherited mutations in presenilin-1 (PSEN1), amyloid beta protein precursor (APP), and presenilin-2 (PSEN2) play a major role [35]. Alzpathway is the first diverse map of intracellular, intercellular, and extracellular signaling pathways for AD. It contains 129 phenotypes, 34 canonical pathways, 134 species, and 1070 reactions [4].

The N-Methyl-D-aspartate receptor (NMDAR) is one of the 3 primary glutamate receptor subtypes [36]. The molecular infrastructure and functional properties of NMDAR depend on the brain region and developmental stages [37,38]. There are seven genes that encode NMDA receptor subunits: a GRIN1 gene encodes GluN1, four GRIN2 genes encodes GluN2A-D, and two GRIN3 genes encode GluN3A-B. As depicted in Figure 1, the 3D structure of NMDA subunits is composed of four domains: a large extracellular amino-terminal domain (ATD), a bifunctional agonist binding domain (ABD), a pore-forming transmembrane domain (TMD), and an intracellular carboxy-terminal domain. (CTD). The TMDs consist of a reentrant loop (M2) and three transmembrane helices M1, M3, and M4. The ABDs are formed by the S1 and S2 segments of the polypeptide chain, which are distinguished by the M1, M2, and M3 segments, and it forms kidney-shaped bilobed structures that contain an upper lobe (D1) and a lower lobe (D2). The phosphorylation sites and binding sites for intracellular proteins involved in the regulation of membrane trafficking and receptor function vary significantly among the various ionotropic glutamate receptor subunits in the intracellular CTD. Co-expression of at least one NR1 and one NR2 subtype is required to express NMDARs in mammals. NR3 subunit reduces conductance by single-channel, Ca^{2+} permeability, and Mg^{2+} blockage. They are permeable to sodium, potassium, and calcium ions [39-41]. Non-NMDAR and NMDAR channels differ in physiological functions. Permeability for Ca^{2+} ions to NMDAR channels is high when compared to non-NMDAR. The NMDAR channel is gated distinctively both by ligands and by voltage [42-45]. Mg^{2+} ions block the NMDAR channel via the intracellular compartment [46]. Because of intrinsic permeability to Ca^{2+} ions, NMDARs play a pivotal part in neuronal apoptosis and synaptic plasticity in excitotoxicity pathophysiological conditions [47]. Excessive NMDAR activity leads to an overload of intracellular Ca^{2+}, which is directly linked to the activation of intracellular events responsible for apoptosis [48]. GluN3A (NR3A) is a subunit that inhibits NMDAR. Zong *et al*., hypothesized that GluN3A is essential for sustained Ca^{2+} homeostasis, and its deficiency is pathogenic for AD. [49]. NMDARs are targeted to synaptic (syn- NMDARs) and extra-synaptic (ex-NMDARs) sites. The syn-NMDARs are present on the plasma membrane at 200-300nm of the postsynaptic density and the ex-NMDARs are situated on the spine, neck, dendrite shafts, or somas [50,51]. The ex-NMDARs regulate glutamate excitotoxicity. Sattler *et al*. proved a reduced number of syn-NMDARs decrease the oxygen-glucose deprivation-induced apoptosis [52]. Extracellular AβOs are observed over neuronal soma and neurites and colocalize with NMDA GluN1 and GluN2B subunits and ionotropic glutamate receptor 1 (mGluR1), but not with NMDA GluN2A subunits and mGluR5. This was observed by dual immunofluorescence staining of AβO-treated neurons without permeabilization pretreatment [53]. Aβ toxicity is regulated by NMDARs. Consequently, Aβ can influence NMDAR expression. Back *et al*., investigated whether distinct NMDAR expression profiles or specific Aβ -mediated regulation of NMDAR expression may contribute to the elevated susceptibility of neocortical neurons to Aβ-toxicity [54]. The development and accumulation of Aβ were studied in 5XFAD mice, and the results indicated that NMDAR antagonists had a significant impact on lowering Aβ deposition and the amount

and size of Thioflavin-S positive plaques. Additionally, GSK3 active form and phosphorylated tau (AT8) levels decreased after UB-ALT-EV treatment, indicating an improvement in tau pathology [55]. Degrading synaptic glutamate with glutamate pyruvate transaminase or blocking the syn-NMDARs with Dizocilpine (MK-801,1) can mediate excitotoxicity [56]. The ex-NMDAR toxicity hypothesis posits that synaptic receptors trigger trophic pathways while ex-NMDARs selectively trigger cell death pathways [57]. Cognitive impairments can result from NMDAR hypofunction, and excitotoxicity and eventual neurodegeneration can be brought on by NMDAR overactivity. NMDARs are significant therapeutic targets for treating various central nervous system disorders, including schizophrenia, mood disorders, alcoholism, epilepsy, head trauma, hypoxia, ischemia, Huntington's, Parkinson's, and Alzheimer's diseases [58].

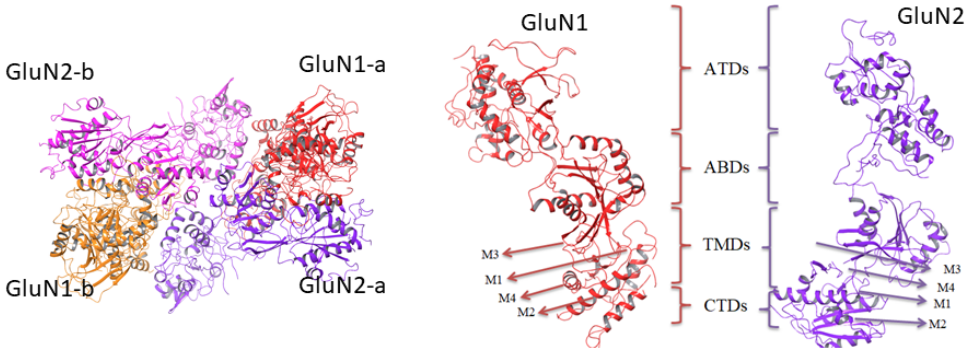


Figure 1. The figure depicts the different domains of NMDA receptor (PDB ID: 5IPV).

2. NMDA Receptor antagonists

In 1991, Clements and Westbrook proved that the opening of NMDAR channelrequires the cording of two glycine components and two glutamate components [59]. The binding rates estimated for glutamate (4.9 μM^{-1} s^{-1}) and glycine (8.3 $\mu M^{-1}s^{-1}$) to NMDARs areat the bottom of the scale (1-100 $\mu M^{-1}s^{-1}$), distinctive in their capability to bind enzymes to substrates with substrate specificity [60]. The binding rates are observed to be lagging than NMDAR channel blockers Mg^{2+} (16-18 $\mu M^{-1}s^{-1}$) and MK-801 (1) (30 $\mu M^{-1}s^{-1}$) [61-63].

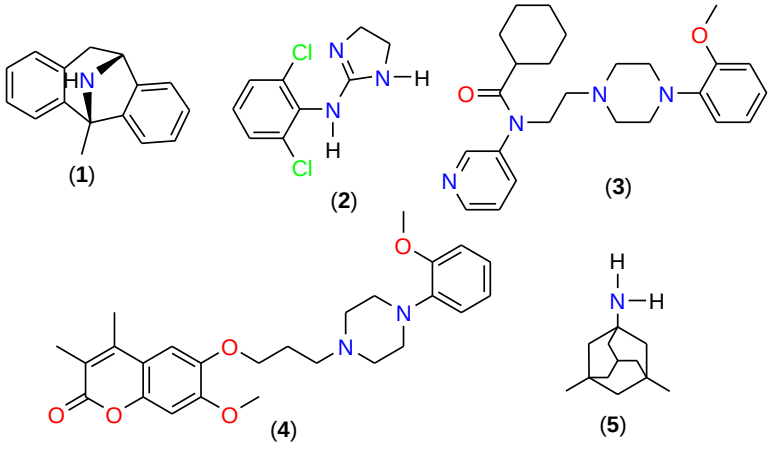


Figure 2. Chemical structures of compounds **1-5** as NMDA receptor antagonists.

NMDA receptor antagonist MK-801 (1) effectively blocks all NMDARs at 0.5 nmol and 5 nmol in the retrosplenial cortex (RSC), which indicates that it interacts with NMDARs

in non-RSC brain regions, and it produces RSC neurotoxic reaction. The mechanism of NMDA receptor hypo-function (NRHypo)-neurotoxicity, according to the author, involves a polysynaptic chain of events and is indirect in which blocking NMDARs in multiple non-RSC brain regions causes excessive release of ACh and glutamate at muscarinic (most likely M3) and α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA)/Kainate (kA) receptor. It was proposed that these two neurotransmitters have a role in neuronal injury that takes place by increased stimulation of RSC neurons. Clonidine (2) did not effectively reverse the AcH release when injected directly into clonidine (2) by interacting with alpha 2 adrenergic receptors present outside RSC to suppress the ACh release in RSC [64].

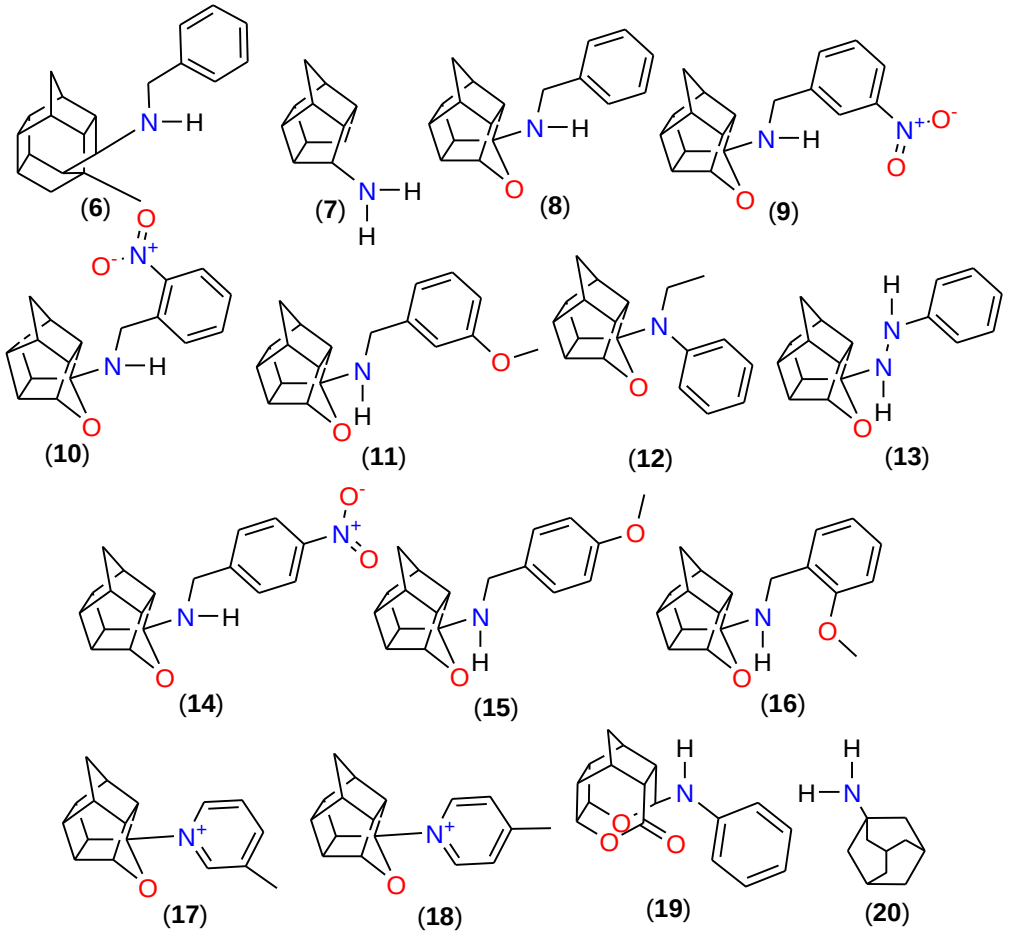


Figure 3. Chemical structures of compounds **6-20** as NMDA receptor antagonists.

Piperazine derivative WAY 100635 (3) (a 5HT 1A receptor antagonist) does not itself affect the accuracy of choice in a spatial challenge when administered subcutaneously, however, it helped to lessen the disability caused by 3 and 10 ng /µl 3-((R)-2-carboxypiperazin-4-yl) propyl-1-phosphonic acid (CPP) administered into the dorsal hippocampus to block NMDARs [65]. Ensaculin (KA-672, 4) showed blocking effects at a concentration of 10 µM for the NMDAR, but the degree of blockage was the same at 5 min and 5s. KA-672 (4) has a voltage-dependent blocking effect that decreases with depolarization. It expressed blocking action at the membrane potential between -80 mV and -20 mV. IC_{50} for KA-672 (4) is 20 µM when measured at a -90 mV holding potential [66]. In Xenopus oocytes, memantine (5) blocked NMDAR in a voltage and concentration-dependent way in the extracellular compartment and blocked currents induced by NR1a/2A L-glutamate receptors at -70 mV to +70 mV potential with an IC_{50} of 1.05 µM, hill coefficient close to one and voltage-dependent site (δ) 0.77.

Memantine (5) at the same concentration (0.1 to 100 μM) was unable to block the NMDAR from the intracellular compartment [67].

Compounds 6 and 7 showed notable antagonism for NMDAR-mediated 45Ca influx, while absolute antagonism was acquired by compounds 8-12 and reference compounds memantine (5), and MK-801 (1) but NMDAR driven 45Ca influx into synaptoneurosomes was gently blocked by compounds 13-19 and the reference compound amantadine (20). Moderate inhibition of background 45Ca influx was shown with all the pentacycloundacylamines only MK-801 (1) had a statistically significant antagonism. All selected compounds had r2 values, not below 0.94 and mostly near 0.99. the threshold for NMDAR stimulated influx into synaptoneurosomes was about 10 μM, and a maximal effect was observed at 1 μM. Compound 8 (2 μM) was selected as representative, and it reduced the maximal effect of NMDA-driven 45Ca influx from 113.4% to 108.9% of control [68].

After a 24-hour intertrial interval, animals given memantine (5) dosages of 10 and 20, not 3 mg/kg, were able to distinguish familiar and novel objects. After administrating memantine (5) the time required for exploring the familiar object was reduced during the choice trial, which prevented retention drop. In the recognition test for objects, rats' performance was enhanced by co-administration of subliminal dosages of memantine (5) and molsidomine (21) that, suggests a functional relation between memantine (5) and the nitrergic system. In this recognition memory example, neither memantine (5) (3 mg/kg) nor molsidomine (21) (1 mg/kg) alone reduced delay-dependent shortfall [69].

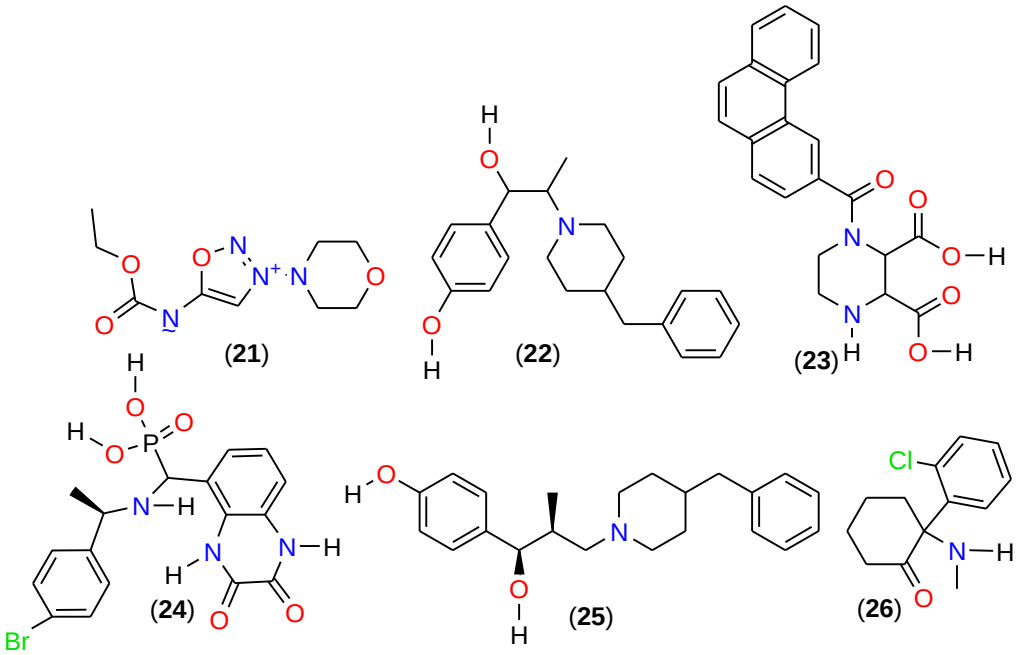
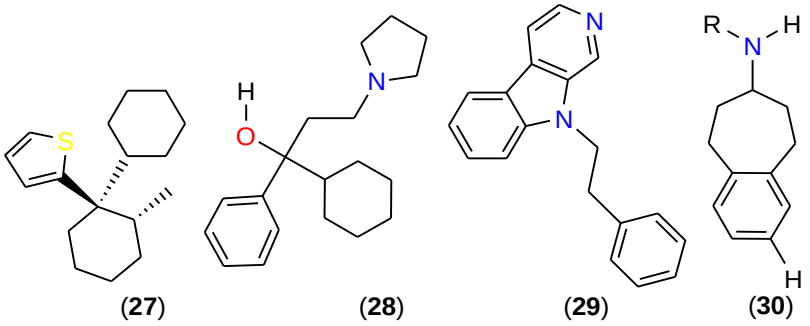


Figure 4. Chemical structures of compounds **21-26** as NMDA receptor antagonists.

In an average adult male C57BL/6J mouse, oral administration of memantine (5) at dosages of 10, 30, and 100 mg/kg per day reduced isolation-induced aggressiveness and improved navigation in the water maze. Daily treatment of 100 mg/kg produced a steady state plasma level of 6 μM memantine (5) which is about 12 times higher than the normal therapeutic level in AD patients. The raised plus maze test displayed outstanding anxiolytic effects without eliciting any noticeable motor adverse effects. The invaders were assaulted by around half of the memantine (5)-medicated resident mice (memantine 10: 4/10, memantine 30: 5/10, memantine 100: 5/10) [70].

PEAQX (NVP-APMO77, 24) intracerebroventricular (i.c.v) injections, [25 pmol, 129.5% pre-high frequency stimulation (HFS) mean baseline excitatory postsynaptic potential (EPSP) amplitude, at 3 h post-HFS, n=5], ifenprodil (22) a GLuN2B-selective agent (3 nmol, 133.9%, n=5) or UBP141 (23) a GluN2D antagonist (6.25 nmol, 133.8%, n = 4) alone had no notable effect on long term potentiation (LTP) induction. Ifenprodil (22) averted the inhibition of LTP by soluble Aβ 1–4. NVP-AAM077 (24) (125 pmol i.c.v.) (98.6, n = 6;) or UBP141 (6.25 nmol i.c.v.) (106.0, n = 4;) entirely inhibited LTP. Systemic injection of Ro 25-6981 (25) a piperidine derivative (6 mg/kg i.p) prevented the inhibition of LTP 60 min before the HFS caused by Aβ 1–42. LTP was inhibited by TNF α in a GLuN2B-dependent manner. The fact that the Aβ's inhibitory effect requires TNFa action presents a shred of strong evidence that TNF α stimulation of GLuN2B containing NMDARs plays a critical role in mediating the disruption of mechanisms underlying cognition by Aβ [71]. Kotermanski and Johnson compared memantine (5) antagonism of whole-cell currents documented at -66 mV from HEK293T cells cultured with cDNAs encoding the NR1 and either the NR2A, NR2B, NR2C, or NR2D subunitin 0 or 1 mM Mg^{2+}. The results confirmed that memantine (5) has little selectivity for NMDAR subtypes. Memantine (5) IC_{50} was found to be between 0.5 and 1 μM for all NMDAR subtypes. IC_{50} for NR1/2A was slightly higher than the other receptor subtypes. At voltages near rest, 1mM Mg^{2+} firmly inhibits NMDAR responses, particularly responses mediated by NR1/2A or NR1/2B receptor subtypes. 1 mM Mg^{2+} extremely influenced the IC_{50} of memantine (5) in a subtype selective manner. The effect of Mg^{2+} NMDAR inhibition by ketamine (26) was studied. It had a similar effect as memantine (5) inhibition on ketamine (26) IC_{50} [72].



(**27**) (**28**) (**29**) (**30**)

Figure 5. Chemical structures of compounds **27-30** as NMDA receptor antagonists.

Ring *et al*., [73] employed two different concentrations of each drug in the experiment. First low concentration of each drug was used, followed by a high concentration. Cell death was estimated in slices that were either treated with 10 μM NMDA in conjunction with each of the protective drugs or treated with 10 μM NMDA alone or untreated. In low drug concentrations of 0.25 μM gacyclidine (GK11, 27), 3 μM memantine (5), and 3 μM procyclidine (28), only GK11 (27) showed protection in the CA1 region, and no significant drug protection in the CA3 and DG regions was found. Concentration was increased by 10 fold for each drug, 30 μM memantine (5) 2.5 μM GK11 (27), and 30 μM procyclidine (28) cell death was again estimated in the DG CA1, and CA3 regions, and it was found that NMDAR toxicity was more in the CA1 region. For discriminating between neuroprotectants the organotypic hippocampal slice culture gives a valuable in vitro model, and it can be used to analogize the efficacies and toxicities of drugs in a pre-clinical trial setting [73].

The antagonistic characteristics of quaternate bivalent β-carboline against NMDAR were compared with memantine (5). Still interestingly its activity vanished upon hydration

(partial) of the pyridine ring or abstinence of the pyrido-N-methyl group. Otto *et al*., found that pyrido-N- quaternate compound 29 displayed significant activity against the NMDA receptor. Compound 29 showed 7-fold higher activity on NMDAR with NR2B subunit than NR2A subunit (IC_{50} values 5.1 μM vs 34.8 μM) [74].

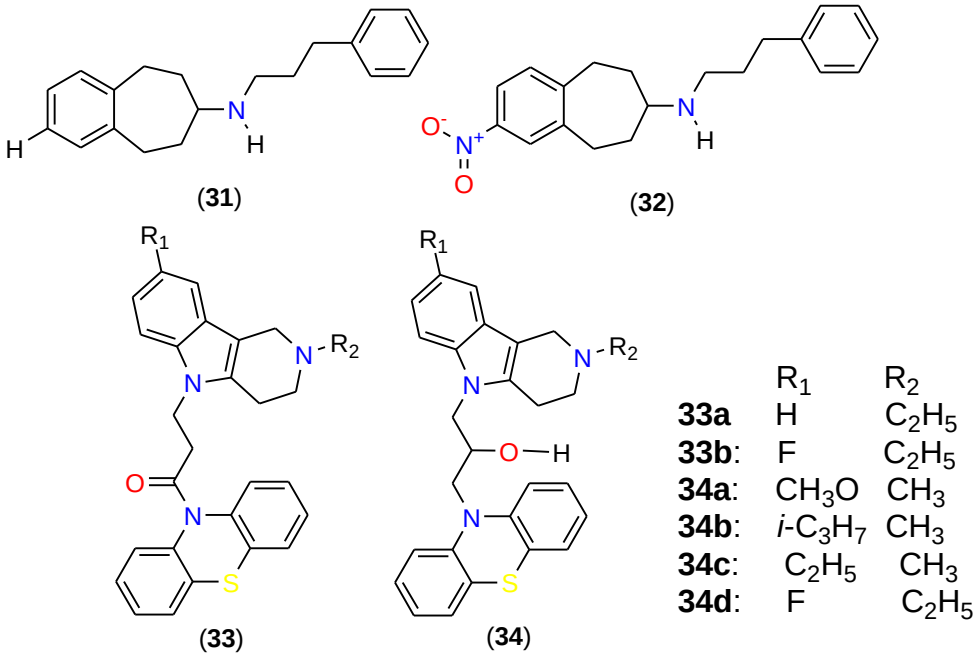


Figure 6. Chemical structures of compounds **31-34** as NMDA receptor antagonists.

The polar OH moieties were removed from the potent GluN2B ligand Ro 25-6981 (25), resulting in unsubstituted benzo [7] annulen-7-amines (30) having GluN2B affinities within the limits of 16–57 nM, indicating that the polar substituents of Ro 25-6981 (25) are not essential for robust interaction with NMDAR containing GluN2B. By introducing a nitro group at the 2-position of the benzo [7] annulene (30) scaffold, the GluN2B affinity is enhanced by 5 to 10 fold. The phenylpropylamines derivatives 31 and 32, with equilibrium dissociation constant (Ki) values of 16 nM and 1.6 nM, respectively, are the most potent ligands. Docking studies of the phenylpropylamines compounds 31 and 32 showed a prime H-bond interactivity between the protonated central amino moiety of compounds 31 and 32 and the carbamoyl moiety of Gln110. Because the aromatic system lacks an anchoring group, the unsubstituted benzo[7]annulen-7-amine (31) can acquire within the binding site two different binding modes. The secondary -NO2 moiety of compound 32 can generate H-bonds with a water molecule bound in the receptor's ifenprodil (22) binding site [75].

The results showed that the conjugates with both types of spacers 1-oxo propylene in compounds 33a and 33b and 2-hydroxy propylene in compounds 34a-34d resulted in very weak inhibition of acetylcholinesterase (AChE) and carboxylesterase (CaE) but butyrylcholinesterase (BChE) inhibitory activity was high. Compounds 33a and 33b showed the maximum inhibitory activity with IC_{50} of 0.52 and 0.58 μM, respectively, against BChE. The most active compound with a 2-hydroxy propylene spacer was 34a, it had an IC_{50} value of 0.39 M. Compound 34c with IC_{50} of 1.36 μM was twice more active than compound 34b with bulky isopropyl substituent with IC_{50} 2.79 μM. Higher inhibitory activity by 3.5 times was observed for compounds with 2-hydroxy propylene spacers than compounds with 1-oxo propylene spacer when the IC_{50} values for the conjugates 33b and 34d, which have 1-oxo- and 2-hydroxy propylene spacers and similar substituents at R1 and R2 were compared. Methylene

blue (35), phenothiazine (36), and dimebon (Latrepirdine is an antihistamine drug) (37) were used as reference compounds. γ -carboline phenothiazine derivatives had very low inhibitory activity against AcHE and CAE but high inhibitory activity towards BChE. When compounds binding to the MK-801 (1) and ifenprodil (22) NMDAR binding sites were studied, it was discovered that conjugates containing a 1-oxo propylene spacer exhibited higher affinity towards both NMDAR binding sites compared to dimebon (37) conjugates [76].

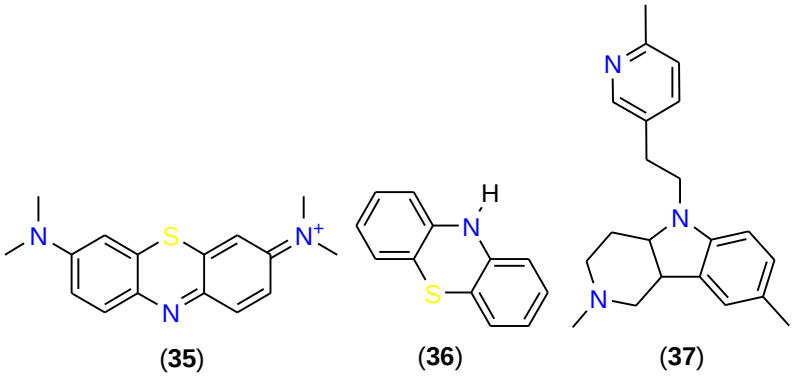


Figure 7. Chemical structures of compounds **35-37** as NMDA receptor antagonists.

To study the binding of isothiourea compounds 38 and 39 with NMDAR and 40-48 with AMPA receptor radio-labeled ligand and electrophysiological patch-clamp method were used. The result revealed at most compounds ability to block NMDAR was pertuated, and they procured their ability to concurrently activate AMPA receptors. By introducing the isothiuronium group in the dibenzyl amine AMPA activating properties could be observed. The ethyl-substituent at the sulfur atom is preferable to the methyl one [77].

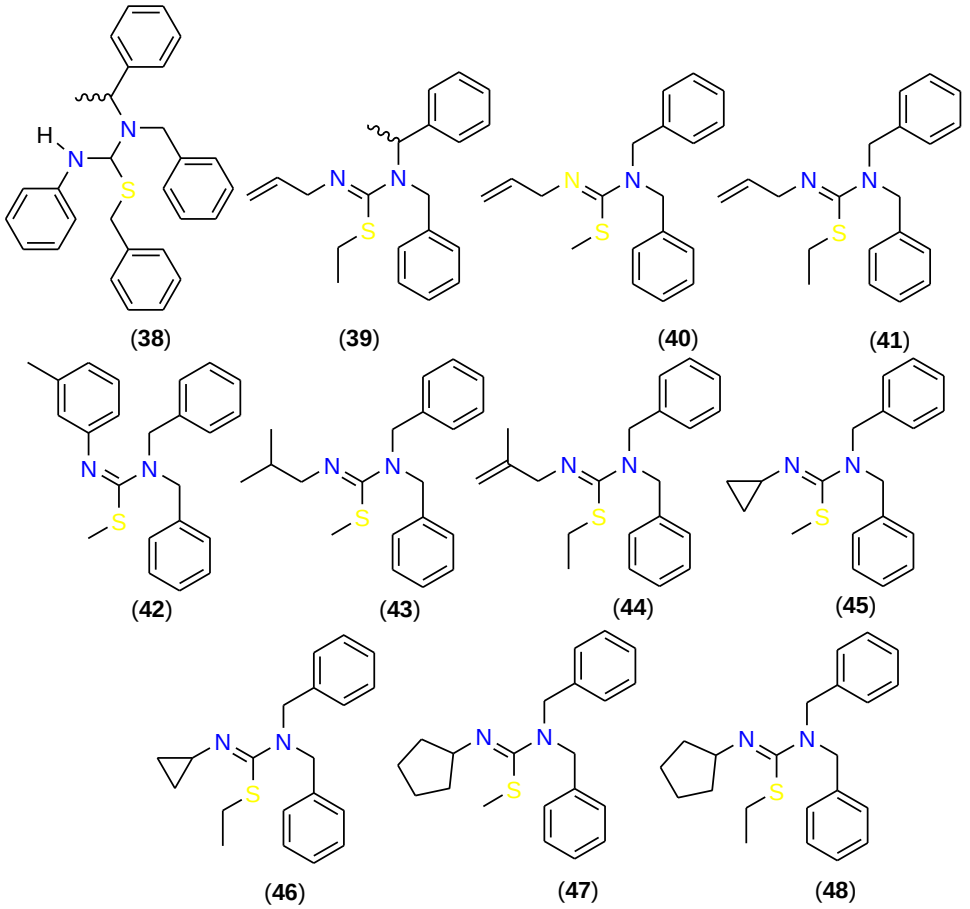


Figure 8. Chemical structures of compounds 38-48 as NMDA receptor antagonists.

A Sandwich ELISA kit was used for Aβ estimation in mice brains, and it showed that the Aβ levels were markedly higher in the hippocampal sample than in cortex samples. When treated with the tetracyclic analog, Aβ1-42 levels were reduced by 80% in the hippocampus in sodium dodecyl sulfate (SDS) and folic acid samples. Still, no significant reduction was seen in cortex samples. The basal level of total tau proteins was not affected by the tetracyclic analog, which was recognized by Tau 5 antibody. AT270 and HT7 antibodies detected a notable decline of phosphorylation at the 181 and 159/163 residues, respectively. An antibody that recognizes total GSK-3β (tGSK3-β) and another for the inert homolog of the enzyme phosphorylated at Ser9 (pGSK-3β) were used. In the hippocampal samples ratio of pGSK-3β/tGSK-3β was distinctly amplified, but no changes were observed in the cortex samples. The data obtained pointed out that expression of the inactive isoform of GSK-3β was enhanced in the hippocampus of the animals when treated with the gambierol analog (marine polycyclic ether), and the treatment with the tetracyclic analog produced a decreased expression of the NMDAR subunit N2A by 56.5 in the cortical samples but did not affect N2B subunit [78].

Phenylalaninol-derived bicyclic lactams 49a-49h and 50a-50h were evaluated at the concentration of 100 μM in the first screening. Ca^{2+} entry was significantly decreased by most compounds. In particular, 70% of the Ca^{2+} influx was blocked by bicyclic lactams 49c-49d and 50c-50d and were found to be more active than memantine (5). The results suggest that at the phenyl group's para position, a halogen atom (chlorine or bromine atom) is important for the activity. The fluorinated analog of 49a, that is 49b, exerts a similar blockade as 49a, whilst chlorine or bromine, present in 49c and 49d, enhanced the blockade. Because the methoxy group (-OCH_3) is present in 49f and 50f, which are isosteres of the bromine atom, the binding pocket is hydrophobic, and when compared to its bromine isosteres derivative or the non-substituted head compound 49a, it has a weaker blocking effect. Derivative 50e, possessing a methyl group (-CH3) at the para position, generates a blocking effect better than 50a, confirming the residence of a hydrophobic binding pocket. The chlorinated derivative 49c showed more activity than the corresponding enantiomer 50c. To block Ca^{2+} entry pyrrolidone ring is required. As (R)-phenylalaninol derivative 51 contains an indole moiety it is much less active compared to the (R)-tryptophanol derivative 52, which contains a phenyl group. Compounds 49c and 49d are the most promising antagonists, and NMDA receptor blockade was significantly decreased by compound 53. The presence of a hydroxyl moiety (-OH) and the chlorine atom at the oxazolopyrrolidone in compound 55 significantly increased Ca^{2+} influx. Compounds 49d and 49c have almost the same IC_{50} values as memantine (5), and they were found to be 2.5 and 2.3 times more active than the hit compound 49a with IC_{50} values of 36 and 39 μM, respectively. In in vitro cytotoxicity of compounds 49c, 49d, and 54 in the human hepatocellular carcinoma HepG2 cell line, no reduction in cell viability was observed, showing that these chemicals are non-hepatotoxic at this dose [79].

The author found that induction of LTP can be abolished by GluN2A antagonist PEAQX (24), but ifenprodil (22) had little effect on LTP. LTP induction can be prevented by NMDA, and NMDA-induced LTP deficits were reserved by ifenprodil (22), which suggests that NMDA can induce excitotoxicity via GluN2B477-containing receptors. It was found ifenprodil (22) had no protective effect on LTP in slices against Aβ, and these results are not in agreement with previous studies. Experimental data show that Aβ can also induce LTP deficit with little influence on PPF, suggesting that Aβ-induced LTP disruption does not occur via presynaptic hypo function [80].

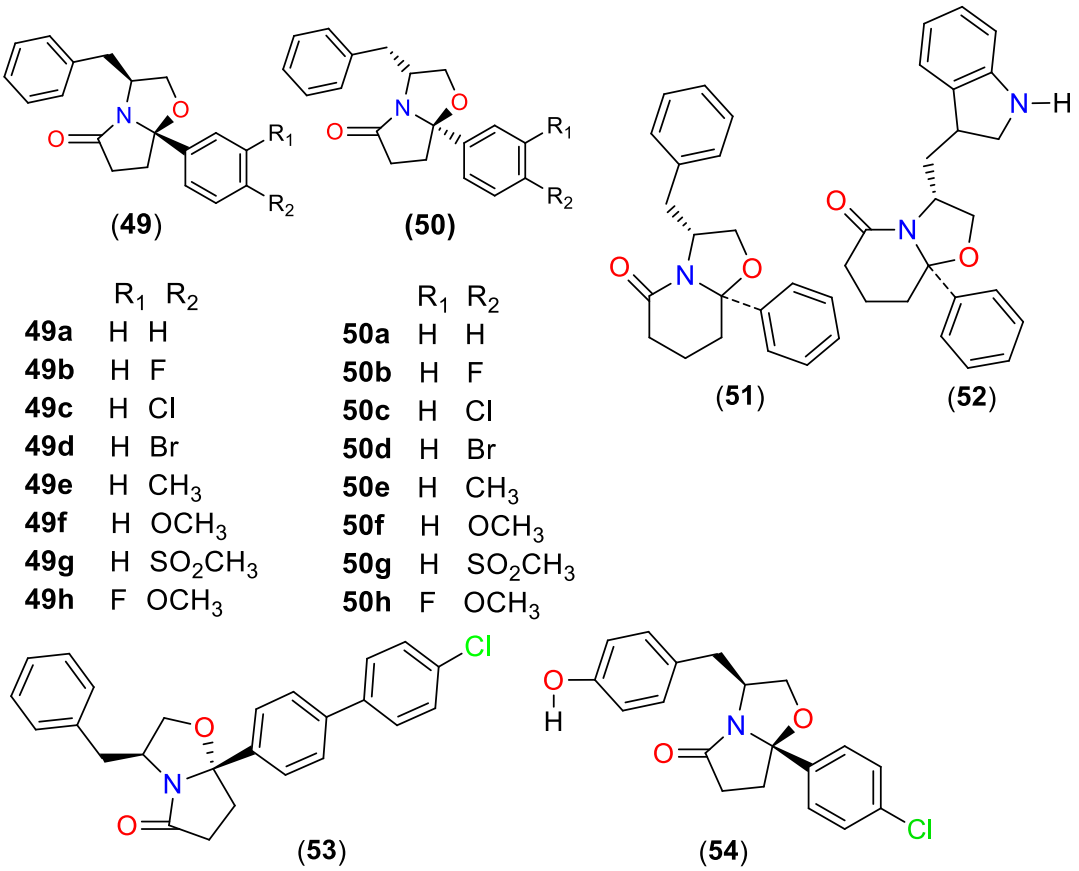


Figure 9. Chemical structures of compounds **49-54** as NMDA receptor antagonists.

At 0.1-3.0 mM memantine (5) in a concentration-dependent manner inhibited the formation of Aβ agglomeration. However, Aβ agglomeration was not affected by amantadine at the same concentration range. It was proposed that memantine (5) reduces brain Aβ levels by directly affecting the Aβ aggregates. Memantine (5) inhibited not only human Aβ1-42 aggregates but also other Aβ peptides, including mouse Aβ, [Pyr3]- Aβ (3-42) (found in AD patients), Aβs with distinct N- or C-terminal lengths, and Aβs carrying amino acid substitutions linked to early-onset Familial Alzheimer's disease (FAD). These data imply that memantine (5) reduces Aβ accumulation independent of the amino acid sequence surrounding the mutation site in Aβ. Memantine (5) had just a low influence on [Pyr3]-Aβ (3-42) and the Aβ mutant D23N. This shows that the N-terminus of Aβ and residue D23 may be involved in the interaction of memantine (5) with Aβ and/or its effect on Aβ oligomerization [81].

A study by Rammes *et al.*, [82] in 2018 clearly showed amyloid peptides synaptotoxicity which was assessed using three distinct ways, that is NMDA receptor-mediated excitatory postsynaptic potential (EPSCs), changes in synaptic spine density and LTP of AMPA receptor-induced field excitatory postsynaptic potential (fEPSP) mediated via NMDA receptors. However, as stated in a study by Kummer *et al.*, in 2011 [83], it was not verified that nitrated Aβ (3NTyr10-Aβ) or pyroglutamate-modified Aβ-(AbpE3) species demonstrated greater neurotoxic effects in this investigation. A clear difference in the acute effects of Aβ was observed on baseline synaptic reactions mediated by AMPA and NMDA receptors. Tested Aβ species, despite blocking LTP of the responses, did not influence the baseline of AMPA-receptor-mediated fEPSPs,-; however, most of the tested Aβ species had a negative influence

on baseline NMDA receptor-mediated EPSCs. These data support their hypothesis that Aβ reduces the "differential" synaptic calcium signal (EPSC) by producing tonic synaptic background Ca^{2+} "noise" via NMDA receptor activation. Radiprodil (55), which restores Aβ-induced impairments in LTP and synaptic density, contributes to the growing evidence supporting the efficacy of several GLUN2B selective antagonists [84]. Radiprodil (55) showed negative effects on LTP with high concentrations; however, Aβ-induced deficits in LTP were reversed with the lowest radiprodil (55) concentration tested (10 nM) though it did not affect baseline responses. $Aβ_{1-42}$ was more toxic than Aβ pE3-42. Radiprodil (55) was unable to counteract the effects of Aβ pE3-42, implying that the synaptotoxicity mediated by target receptors/subunits may differ between Aβ species [82].

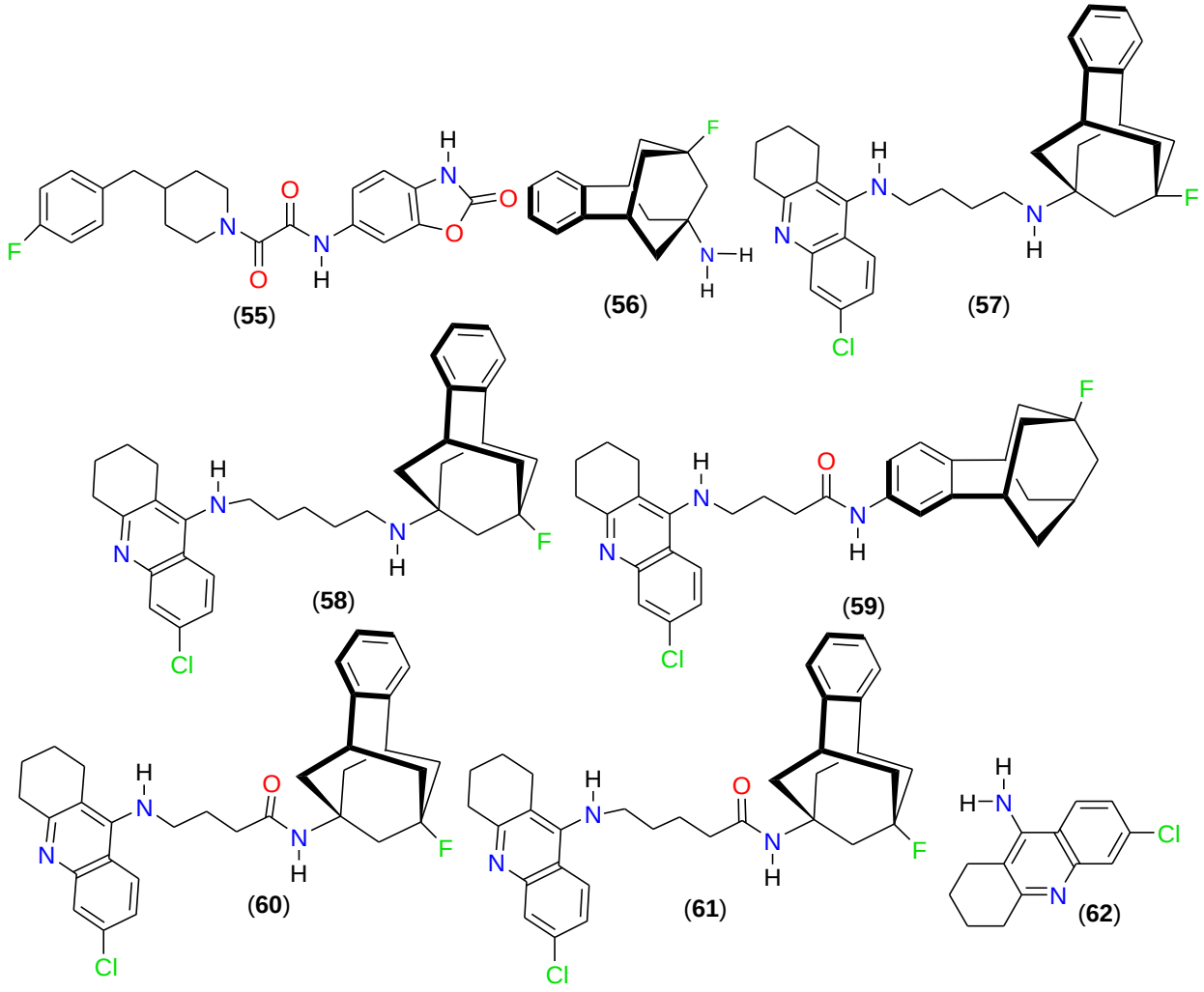


Figure 10. Chemical structures of compounds 55-62 as NMDA receptor antagonists.

Amino group alkylation of the parent benzohomoadamantane (56) core induced a two-fold reduction of NMDA antagonistic activity in compound 57 and an enhancement in activity by two-fold in compound 58. It was found that the activity depends on the linker length,-; the longer homolog 58 is 4-fold more potent than the shorter homolog 57. Indeed, the activity of the most potent NMDA antagonist 58, is equipotent to 59, which is the most potent hybrid with an unsubstituted primary amino group. Monoalkylation of the polycyclic amino group can be tolerated by this class of compound without losing NMDA antagonistic activity but, NMDA antagonistic activity was reduced by acylation of this amino group in 60 and 61. Furthermore, these novel hybrids are slightly more potent (1.7-fold) or equipotent to memantine (5).

By utilizing a 4- and 5-carbon-atom restrained chain at the bridgehead amino group or an extra amino group on the benzene ring of the benzohomoadamantane core, molecular hybridization of the NMDA antagonist 56 with the powerful AChE inhibitor 62 resulted in multitarget compounds. These compounds are 2-fold more potent NMDA antagonists than the parent compound 56 (IC_{50}, 1.93 mM) and memantine (5) (IC_{50}, 1.50 mM) [85].

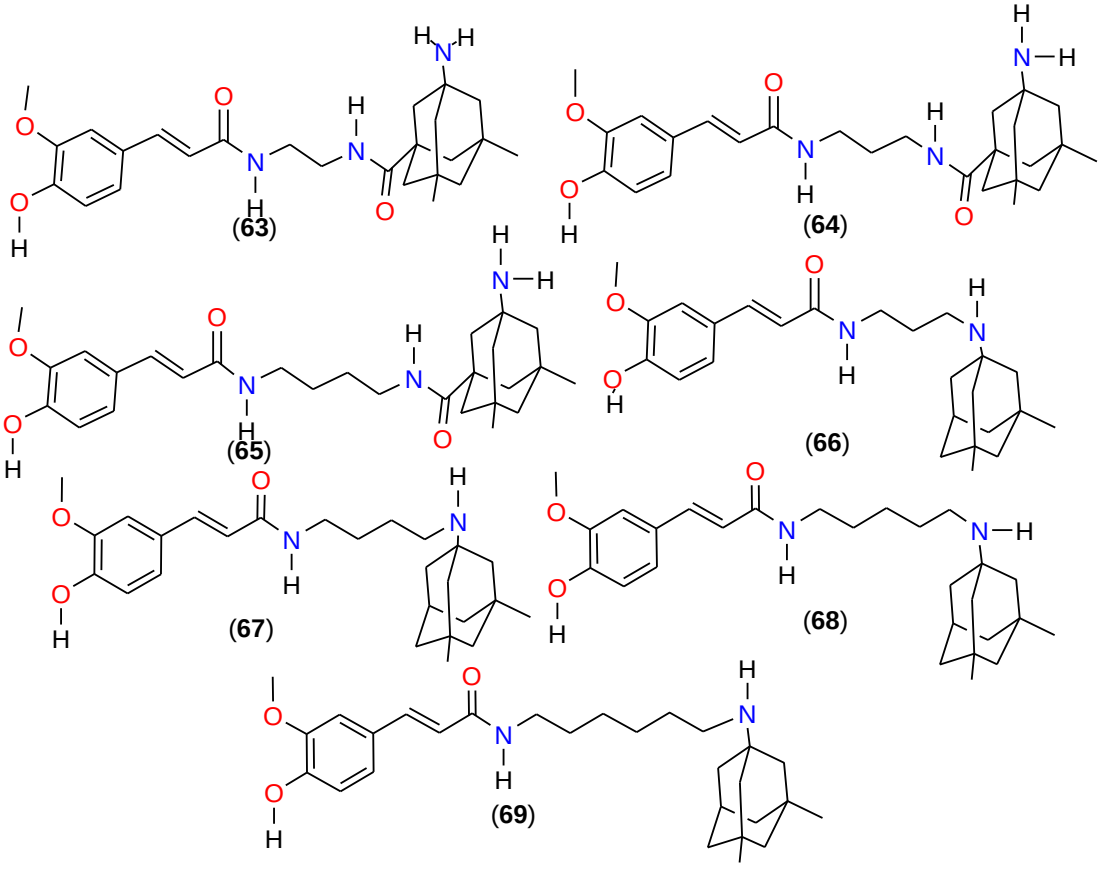


Figure 11. Chemical structures of compounds 63-69 as NMDA receptor antagonists.

To measure the antagonism on NMDA and glycine with compounds 63 – 69, voltage-clamp recordings applied in tenfold increments in the range of 0.01 to 100 mM were used on GluN1-1a/GluN2A NMDAR expressed in Xenopus laevis oocytes. Compounds 63 -65, which have primary amine function as of memantine showed very low or no potency to block NMDAR. The Shorter compound 66 has an IC_{50} value greater than 100 mM, and compounds 67 -69 have IC_{50} values ranging from 6.9 to 23.9 mM. Compounds 67-69 showed δ values (fraction of the membrane electric field crossed by the blocking compound) slightly higher than memantine (5) (δ, 0.39) in the range between δ 0.43 to 0.51. NMDAR blocking properties were shown by compounds 67 -69. They were selected because they were able to improve the antioxidant profile of SH-SY5Y human neuroblastoma cells. All the compounds at a concentration of up to 50 mM, retained good tolerability, and at a concentration, of up to 20 mM, were devoid of any toxicity except the shorter derivative 63 like ferulic acid (FA). No toxicity was observed in compound 66. H_2O_2-induced intracellular ROS formation was reduced by all compounds, at a concentration of 10 mM, however, it was less effective than FA. The ability of the compounds to modulate the mRNA levels of Nrf2 was assessed by real-time PCR using 10 mM of each compound incubated for 6 h. It was observed that only compound 69 determined a considerable increase in Nrf2 mRNA expression, while cells treated with compounds 67 and 68 or FA behaved like untreated cells. In a dose-dependent manner, HO-1

expression was increased by compound 69, and it almost doubled HO-1 protein levels of control with cells treated with 20 mM. Compound 69 is a multimodal antioxidant is confirmed by these results. Compounds 67, 68, and FA carry the α, β-unsaturated carbonyl features and lack antioxidant efficacy. It reveals that for activating redox sensor proteins, an electrophilic moiety is not adequate, and shape complementarity may play a crucial role in this respect [86].

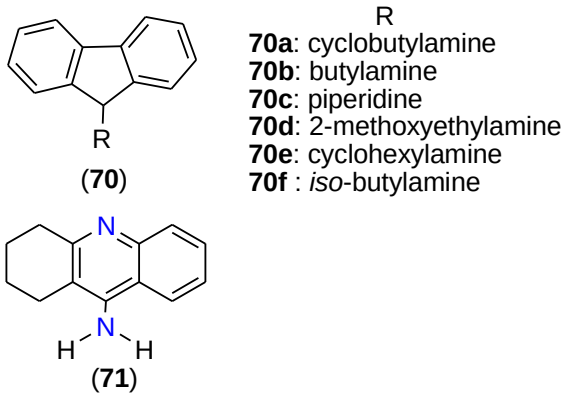


Figure 12. Chemical structures of compounds 70 and 71 as NMDA receptor antagonists.

An inhibitory effect was exhibited by all fluoren-9-amines (70) compounds ranging from ~7% to ~52%. 70a is highly effective at the GluN1/GluN2A receptors, while 70b is most effective at the GluN1/GluN2B receptors. Concentration-response curves for 70a and 70b (1–300 M) at membrane potentials of -60 mV and 40 mV for both the GluN1/GluN2A and GluN1/GluN2B subunits were constructed. Both derivatives had a stronger inhibitory effect at negative membrane potentials (IC_{50} values ranged from 9 to 15 μM) but were less active at positive membrane potentials (IC_{50} values ranged from 83 to 221 μM). Under the studied conditions, memantine (5) is more potent than 70a and 70b. During toxicity studies, it was found that the most lipophilic compound 70c, and hydrophilic compound 70d showed low toxicity. 70a, 70b, and 70e were the most cytotoxic agents, and some new derivatives were less cytotoxic than tacrine (THA, 71). At 50 μM, it was observed that the cell viability was not decreased by tested compounds except 70b, which decreased the cell viability to 82%. So, for the blood-brain barrier (BBB) permeation test, a concentration of 30 μM was used for 70b. Compounds 70a, 70e, and 70f have a low ability to pass the BBB ideally. In this experiment, to investigate the BBB permeability of the compounds, a panel of reference drugs or drugs with BBB permeability in vivo is known was used to correlate the Papp values. The Papp value for 70b correlates with standard drugs having high CNS permeability [87].

Cytotoxicity and fluctuating morphological changes in Purkinje cells/dendrites of the hippocampal CA1 region and cerebellum were observed with Vanadium (NMDA antagonist,72) exposure in this study which was characterized by loss of apical dendrites, cell clustering, cytoplasmic vacuolation and loss of layering pattern. This suggests that retrogression of cell function leads to leveling of cellular structures and cell death. Reduction and impairment of Purkinje cells were seen with Calbindin immunolabeling of the hippocampus and cerebellum. Variations were observed in the morphology of Purkinje cells, including pyknosis and cytoplasmic vacuolation, and a paucity of dendritic staining in the hippocampus and the cerebellum in the vanadium-treated brains compared with control. This study shows that Compounds 73,74 and 75 administration improves vanadium (72)-induced neurotoxicity. Present study findings support a potential use of the compounds as a protective agent against vanadium (72) neurotoxicity. The compounds 73, 74, and 75 rectified the trend,

least likely through maintaining and regulating Ca^{2+} ion channel homeostasis, as well as antioxidative and anti-inflammatory mechanisms [88].

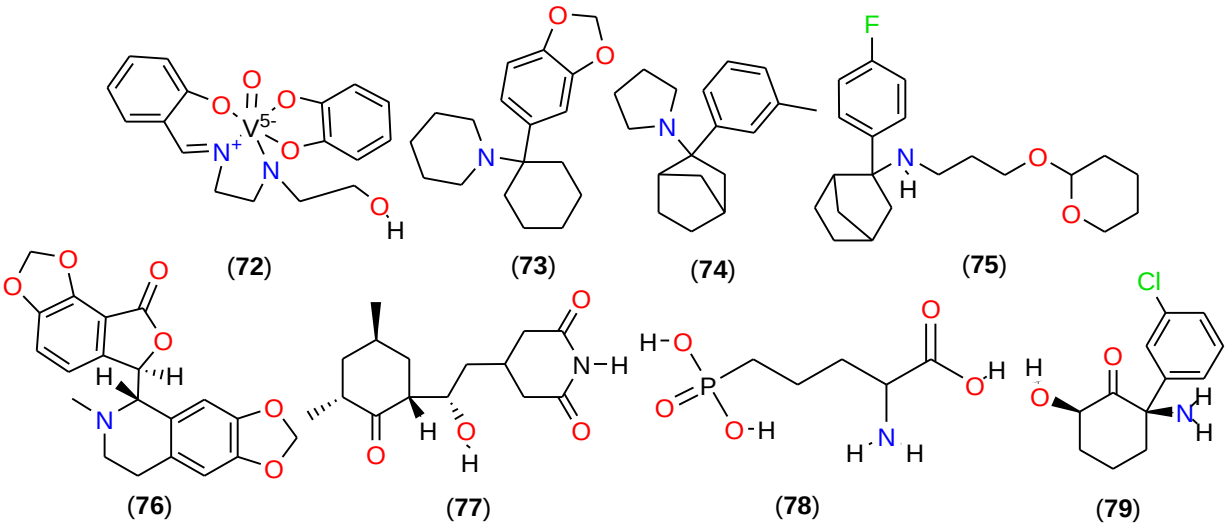


Figure 13. Chemical structures of compounds 72-79 as NMDA receptor antagonists.

There was an increase in prefrontal neurons' stimulus selectivity when the excitatory glutamatergic synapses were obstructed with MK-801 (1), as well as the deactivation of inhibitory synapses by bicuculline (Bic, GABA(A)-receptor antagonist (76) during the delay period, although only delicate for NMDA receptors. The author investigated individual neurons with both of the receptor antagonists, and observed most neurons (both putative pyramidal cells as well as inhibitory interneurons) with one of the medications, and they enhanced their signal-to-noise ratio while improving selectivity with the other. From this, it may be concluded that both major classes of cortical neurons consist of glutamatergic NMDA and GABA receptors. The experiment shows a significant, although mild, reduction of spontaneous firing rate after administration of MK-801 (1) in awake-behaving monkeys [89].

In this study, it was observed that deterioration of agglomeration of conditioned food antagonizes memory by NMDAR antagonists or protein synthesis inhibitors, initiating the evolution of amnesia. Differences in latency period (LP) of amnestic effects were shown by tested substances. 2.5 hour post injecting cycloheximide (CH, 77) LP of conditioning stimuli (CS)-evoked reactions decreased, while MK-80 (1) or DL-2-amino-5-phosphonopentanoic acid, (APV, 78) in less than 20 min reduced LP of these reactions. LP marginally exceeded the correlated values in reactions to the food observed in entire snails at minute 60. NMDAR antagonists provoked down-regulation of aversive reactions to CS that critically depend on protein synthesis. Thus, it can be hypothesized that the synthesis of amnesia proteins may be a key step in the processes that lead to a decrease in AMPA receptors in the postsynaptic membrane [90].

Different animal groups, with each group comprising of 3 females and 3 male animals, were administered with (2R,6R)-Hydroxynorketamine (2R,6R-HNK, 79), and ketamine (26), at a dose of 10 mg/kg, and WAY 100635 (1) was administered at a dose of 0.5 mg/kg. In both males and females, hyperactivity was observed with intravenous (IV) administration of ketamine (26), which resolved within 1 h whereas it had no effects by subcutaneous (SC) administration at the same dose. Ataxia was observed in male animals with IV and IP administration of MK-801 (1) that resolved within 6-7 h of administration. At the same dose of MK-801 (1) female also became severely ataxic and non-responsive by 4-6 h. Ketamine had

no behavioral effects on animals by subcutaneous (SC) administration, whereas by SC administration of MK-806 (1), both males and females became ataxic. Neurotoxicity was not observed after IP administration of ketamine (26) dose up to 60 mg/kg or after IV administration of (2R, 6R)-HNK (79) dose up to 160 mg/kg. After administration of MK-801 (1), Olney's lesions and neurotoxicity were observed in a dose-dependent manner. In females, ataxia lasted till 8h, which resolved after 24 h. In contradiction to MK-801 (1), ketamine (26) did not cause any measurable neurotoxicity via any routes of administration or doses examined. Safety of (2R,6R)-HNK (79) over a wide range of doses (up to 160 mg/kg) with zero neurotoxicity was confirmed in the study. The findings of this study indicate that ketamine-induced Olney's lesion-type neurotoxicity depends on the administration route in acute and repeat-dose paradigms, and correlative pharmacokinetic exposure of ketamine [91].

A reliable method for the quick identification of NMDA-2A ligands from natural products was developed in the present study by Yuan-Yuan Chen *et al*., [93]. This study used an NMDA-2A column for screening NMDA-2A ligands from *G. jasminoides Ellis*. Furthermore, the EGFR-tag and its inhibitor ibrutinib undergo a highly specific covalent interaction to create the affinity stationary phase. Compared to affinity stationary phases developed by physical adsorption, it was more active and stable. Crocetin was extracted from *G. jasminoides Ellis* and screened using this NMDA-2A column. Using an *in vitro* model of AD, researchers observed that crocetin elevated the NMDA-2A protein level, implying that crocetin may also attenuate AD via mediating NMDA-2A, which is consistent with other research [92].

As part of the current study by Chinthaa *et al*.,[94] 11 acetylcholinesterase (AChE) and 4 N-methyl-D-aspartate receptors (NMDAR) proteins were taken into consideration for docking with rivastigmine and riluzole, respectively. Selected notable binding was seen for AChE with 5FPQ and NMDA receptors with 5I2K amongst 15 proteins. In contrast to the 5I2K/Riluzole complex, which demonstrated a binding score of 9.6 kcal/mol and an inhibitory concentration (Ki) of 21 nM, the molecular docking simulations of the 5FPQ/Rivastigmine complex showed a binding score of 8.6 kcal/mol. Riluzole formed π-alkyl interactions with Pro129, π-stacking interactions with Tyr144, and conventional hydrogen bonds with Phe130 when it was in complex with 5I2K. In contrast, rivastigmine and 5FPQ established a hydrogen bond in their complex [93].

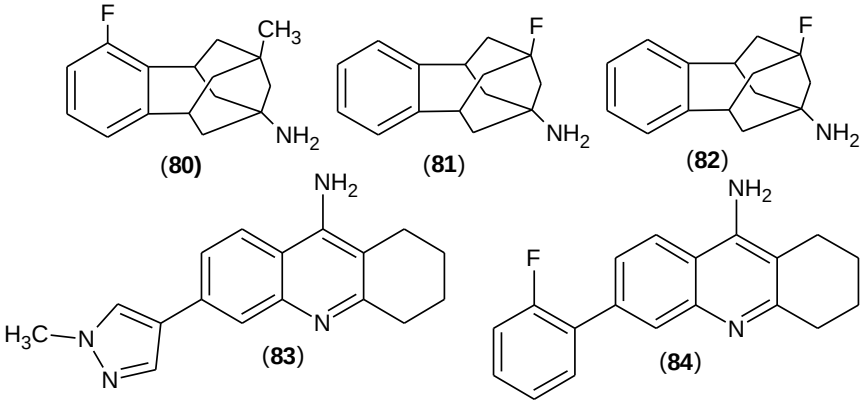


Figure 14. Chemical structures of compounds 80-84 as NMDA receptor antagonists.

Turcu *et al*., synthesized a series of memantine analogs and measured their effect on increases in intracellular calcium evoked by 100 mM NMDA (in the presence of 10 mM of

glycine) on rat cultured cerebellar granule neurons using a Fura 2 assay. With varying substitutions, it was found that the aromatic substitution, is having highly deleterious properties for the compound's NMDAR chaneel-blocking potency, regardless of the electron donor or acceptor character of the substituent. Small-size substituents such as chlorine and fluorine at C2 had less deleterious properties for potency than bigger substituents such as nitro or an acetyl group. Compound 80, with its fluorine atom at C1, and a methyl group at C9 emerged as the most intriguing derivative from this collection of new amines. It was found that the replacement of methyl group at C9 with a fluorine atom resulted in a remarkable increase in potency. Unexpectedly, compound 81 (IC_{50} ¼ 29.0 ± 11.9 mM) was a less potent NMDAR channel blocker than compound 82 (IC_{50} ¼ 1.93 ± 0.21 mM) [94].

In silico studies revealed that both 83 and 84 can bind to AChE and NMDAR much stronger than tacrine, and they bind in a similar way as tacrine. Hydrophobic contacts with residues in the M3 helices of both GluN1 and GluN2B strongly favor the interactions of these molecules. The in vitro studies revealed that aromatic or hetero aromatic ring substitutions at R4 position in group 2 favored the inhibitory activity against NMDAR and AChE. Additionally, phenyl ring R4 substitutions with halogens favored inhibitory efficacy against AChE and NMDAR. However, compounds substituting at R1 and R4 positions in group 3 showed reduced inhibitory activity towards NMDAR and AChE. Group-1 compounds showed reduced inhibitory activity to NMDAR, but towards AChE the activity was promising [95].

NMDA receptor antagonists are a class of drugs that not are not only used for the treatment of AD but to treat other diseases as well. These are used for the treatment of stroke and traumatic brain injury, alcoholism, PTSD, vascular dementia, and Parkinson's disease. Drugs such as selfotel, aptiganel, eliprodil, licostinel, and gavestinel antagonizing NMDA receptors have entered clinical trials for treating different diseases, but they failed to show efficacy in clinical trials in different stages. One reason for the drug's failure is that blockade of synaptic transmission mediated by NMDA receptors hinders neuronal survival [96, 97].

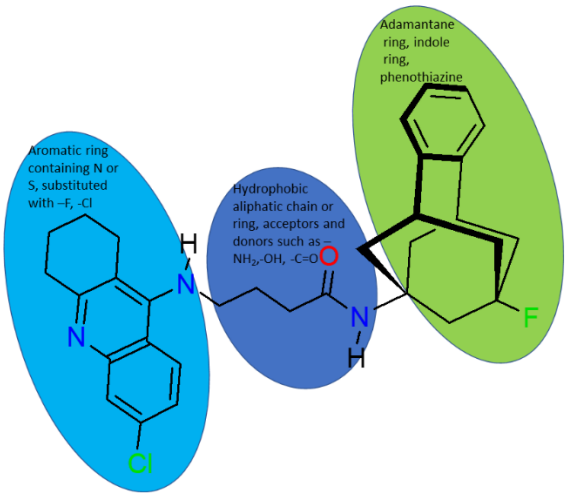


Figure 15. SAR of NMDA receptor antagonists.

Conclusions

Alzheimer's disease is a progressive neurological disorder that is caused by misfolding of proteins persilin1, persilin2, and APP. AD is associated with a decrease in the neurotransmitter acetylcholine in the brain and cleavage of amyloid beta in the hippocampal region of the brain. There has been an investigation going on into the involvement of the

neurotransmitter glutamate and its receptor NMDA in the function of synaptic plasticity and the etiology of AD for many years. The syn-NMDARs are important for neuronal protection but the ex-NMDARs are responsible for neurodegeneration. Among the different antagonists mentioned, compound 34a was observed to be potent with the lowest IC_{50} value of 0.39 μM which is lower than the standard drug memantine (1.05 μM). The Amine group is important for the activity against NMDAR. Several scaffolds like piperazine derivative, pentacycloundacylamines, benzo[7]annulen-7-amines, γ-Carbolines and phenothiazine, isothiourea, dibenzylamine, phenylalaninol-derived bicyclic lactams, benzohomoadamantane chlorotacrine hybrids, fluoren-9-amines have been investigated as NMDAR antagonists. Moreover, aducanumab, Donepezil, Rivastigmine, Galantamine, Memantine, and, Suvorexant were approved by FDA for the treatment of AD. Among these, only memantine is used NMDAR antagonist. Based on the reported literature, the SAR analysis (figure 15) indicated that the presence of two ring systems attached by a hydrophobic linker moiety was crucial for NMDA antagonistic activity. The two-ring system constituted of one adamantane ring and other rings may be phenothiazine, indole or benzene rings, showed better NMDA inhibitory activity. Also, the linkers containing C3-C7 carbons with acceptor and donor groups such as -OH, $-NH_2$ and -C=O groups showed potent activity. In addition to this, fluoro and chloro-substituted benzene rings exhibited better inhibitory activity when compared to alkyl-substituted benzene rings. This review's updated information on NMDAR antagonists highlights the SAR properties responsible for NMDAR inhibitory properties. It provides a valuable resource for structural information that could be incorporated into the design of more effective inhibitors.

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Conflicts of Interest

On behalf of all authors, the corresponding author states that there is no conflict of interest.

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