CHAPTER SEVEN

NMDA Antagonists of GluN2B Subtype and Modulators of GluN2A, GluN2C, and GluN2D Subtypes—Recent Results and Developments

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1. INTRODUCTION

N-methyl-D-aspartate (NMDA) receptors are members of a family of ionotropic glutamate receptors (iGluR).[1–10] They are widely expressed in the brain with specific anatomical localization and populations for different subunit types and thought to be involved in numerous physiological and pathological processes.[5] A common feature of iGluRs is

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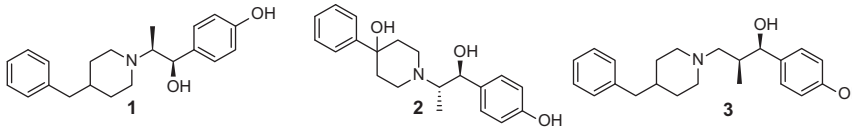
their construction as tetrameric assemblies of subunits. NMDA tetramers are assembled from two subunits of glycine-binding GluN1 and two subunits of glutamate-binding GluN2 (GluN2A, GluN2B, GluN2C, or GluN2D), or in some cases GluN3 subunits (GluN3A or GluN3B). NMDA receptor ligand-gated channels are normally blocked by extracellular Mg^{2+} at resting membrane potential. They are activated upon binding to two coagonists, glycine or D-serine, at the GluN1 subunit ligand-binding domain (LBD), and glutamate at the GluN2 subunit LBD, resulting in the opening of the ion channel and permitting passage of Na^{+}, K^{+}, and Ca^{2+} ions in a nonselective manner. Overactivation of NMDA receptors generates an uncontrolled influx of calcium ions, which then activates a cascade of excitotoxic processes leading to neurodegeneration. Accordingly, NMDA antagonism is thought to be useful in the treatment of many CNS disorders including ischemic stroke, Parkinson's disease, Alzheimer's disease, neuropathic pain, and depression, among many others.[11–13]

Among the NMDA receptor subtypes, it is known that the GluN2B subunit can be allosterically regulated by the binding of ligands at multiple sites. These allosteric binding sites recognize ions (H^{+}, Mg^{2+}, Zn^{2+}), small molecules (ifenprodil-like ligands), or polyamines. Thus, the function of NMDA receptors could be altered by blocking or interacting with one of the following binding sites, (i) glycine agonist site, (ii) glutamate agonist site, (iii) ion channel pore, and (iv) allosteric sites on the amino terminal domain (ATD). The ATD, being distinct for subunit types, currently offers the greatest advantage for designing highly subunit selective antagonists.

The major focus of this review is to summarize recent medicinal chemistry advances in the area of GluN2B receptors, and emerging antagonists and modulators of other NMDA receptor subtypes.

2. X-RAY STRUCTURAL STUDIES AND HOMOLOGY MODELING OF NMDA RECEPTORS

Many reports have appeared describing the structural features and function of NMDA receptors.[14–23] Based on mutagenesis studies and molecular modeling, it has generally been accepted that the mechanism of action of phenylethanolamine ligands such as ifenprodil (**1**), traxoprodil (CP-101,606, **2**), and Ro 25-6981 (**3**) is exerted *via* allosteric binding to the ATD of GluN2B.[14–16]



These studies, though, have only provided limited direct evidence regarding the detailed structure of the phenylethanolamine binding site.[15,16] A major step forward was recently made by Karakas *et al.*[17] with the publication of cocrystal structures of ifenprodil and Ro 25-6981 bound to a GluN1b–GluN2B ATD complex. The ATDs of GluN1b from *Xenopus laevis* and GluN2B from *Rattus norvegicus* form a unique heterodimer whose secondary structure is characterized by an asymmetrical set of interactions between the R1 and R2 domains of the GluN1b and GluN2B ATDs. The GluN1b R2 domain is not directly involved in the GluN1b–GluN2B interaction, leaving sufficient room for conformational flexibility in the opposing GluN2B R2 domain. Movement of the GluN2B R2 domain is thought to be important in mediating the allosteric regulation observed for this receptor.[18,19]

Ifenprodil and Ro 25-6981 were shown to bind at the GluN1b–GluN2B subunit interface through an induced-fit mechanism. The binding pocket is defined by residues from GluN1b R1, GluN2B R1, and GluN2B R2, with no overlap of the Zn^{2+} binding site located in the GluN2B ATD cleft. Furthermore, binding is characterized by three distinct types of interactions in the complex (Fig. 7.1): (1) hydrophobic interactions between the benzylpiperidine group common to both molecules and a cluster of hydrophobic residues from the GluN1b α2 and α3 helices and the GluN2B α1′ and α2′ helices, (2) hydrophobic interactions between the phenol groups and GluN1b Leu135, GluN2B Phe176, and GluN2B Pro177, and (3) direct polar interactions with Ser132 of GluN1b, Gln110 of GluN2B, and Asp236 of GluN2B. Although the benzylpiperidine groups of ifenprodil and Ro 25-6981 orient in a similar fashion, the methyl and hydroxyl groups in the propanol moiety face opposite directions, which may account for the difference in their binding affinities (Fig. 7.1C). In support of the physiological relevance of the identified binding site, the authors used a set of mutagenesis studies to show that critical residues in the site not only impart crucial binding interactions but also are important in producing the functional effect. The information contained in these cocrystal structures will undoubtedly serve as a molecular

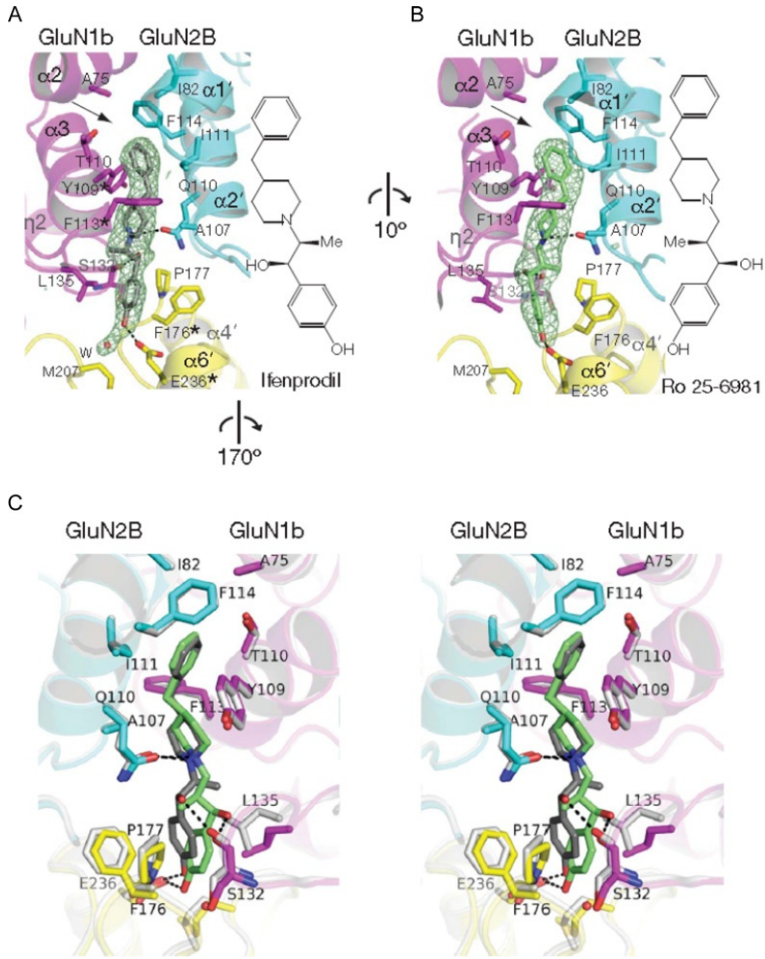


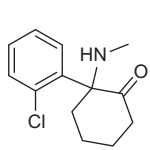
Figure 7.1 Binding of ifenprodil (A) and Ro 25-6981 (B) at the binding pocket; (C) comparison of binding patterns of ifenprodil (gray) and Ro 25-6981 (lime) in stereoview (reproduced with permission from Ref. 17 Nature Publishing Group).

blueprint for the design of improved compounds which target the ATD of NMDA receptors.[17]

Vance *et al.* reported the crystal structures of isolated GluN2D LBD in complex with four different agonist ligands (L-glutamate, D-glutamate, L-aspartate, and NMDA).[23] This study reveals that the binding of L-glutamate induces a unique conformation at the backside of the ligand-binding site. These data suggest that the activity of the GluN1/GluN2D NMDA receptor is controlled distinctively by the endogenous neurotransmitter L-glutamate.

3. CHANNEL BLOCKERS

NMDA channel blockers are noncompetitive antagonists and generally lack subunit selectivity. In addition, known channel blockers have a wide range of off-target activities (e.g., D_2, 5-HT, GABA, μ-, κ-opioid, σ, mAChR) and block channels other than NMDA (Na, nAChR, HCN1, and K_{ATP}). Examples of high-affinity blockers are ketamine (**4**), phenylcyclidine (PCP, **5**), and MK-801 (**6**), while memantine (**7**) and amantadine (**8**) are low-affinity blockers ($K_i > 1$ μM).



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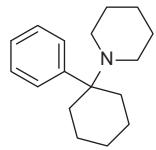

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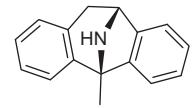

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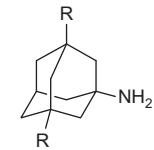
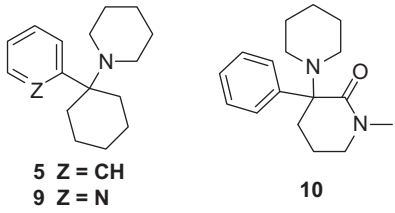


7 R = H
8 R = CH_3

Both ketamine and PCP produce psychotomimetic effects and are abused as recreational drugs. Subanaesthetic doses of ketamine are reported to cause a rapid and sustained antidepressant effect.[24] Related to this clinical finding, Duman et al., reported that the mTOR cellular signaling pathway in the prefrontal cortex (PFC) of the rat brain is activated as a response to ketamine. This leads to increased synaptic signaling proteins and a reversal of atrophy of spine synapses in the PFC.[24] The authors suggest that the functional reconnection of neurons resulting from this process underlies the rapid behavioral responses which are observed.[24] While channel blockers represent an interesting pharmacological class for the treatment of depression, ample opportunities remain for the development of drugs with a better tolerability profile.

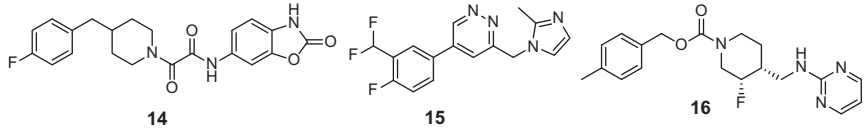
A recent study described the identification of analogs of ketamine and PCP with reduced lipophilicity.[25] A heteroatom was introduced into the phenyl ring of PCP as in **9** and a novel lactam scaffold was employed as in ketamine analog **10**, and functional activity was tested in a Ca^{2+} flux FLIPR assay. Both ketamine and PCP showed moderate potencies at both GluN2A and GluN2B receptors, whereas **9** and **10** were 2- to 10-fold less potent. Dexoxadrol (**11**) is a high-affinity channel blocker ($K_i = 11$ nM), which like MK-801 ($K_i = 3$ nM) has PCP-like dissociative properties.[26] Since the severe side effects are attributed to high NMDA receptor affinity, analogs with moderate affinities between those of **11** and memantine ($K_i = 1.2$ μM) may display desired pharmacological activity with an

improved side effect profile. Fluorinated analogs **12** and **13** were indeed two- and sevenfold less potent than **11** as evaluated in a [^{3}H]-MK-801 binding assay. Additionally, **12** and **13** showed reduced affinities at σ_1 and σ_2 receptors relative to **11**.



4. INHIBITORS OF GLUN2B SUBTYPE RECEPTOR

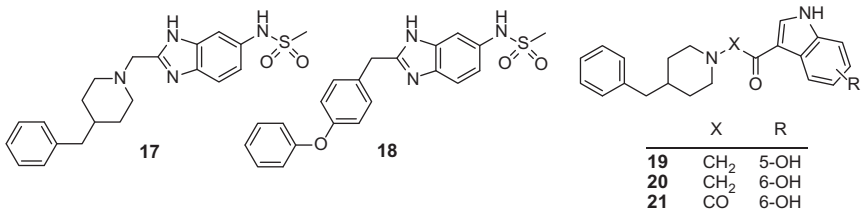
A number of GluN2B antagonists, such as ifenprodil (**1**), CP-101,606 (**2**), Ro 25-6981 (**3**), RGH-896 (radiprodil, **14**), EVT-101 (**15**), MK-0657 (**16**), have progressed as far as Phase II clinical trials; however, progress beyond this point has been hindered by the presence of undesirable CNS and other off-target side effects. Despite early setbacks, there still remains a high interest in developing orally administered, subtype selective NMDA antagonists with an acceptable side effect profile. Allosteric inhibitors of GluN2B have been hypothesized to have the highest potential to offer an improved therapeutic index. With the recent identification of the allosteric binding site of ifenprodil and Ro 25-6981,[17] a detailed template for the design of highly refined allosteric inhibitors of GluN2B now exists.



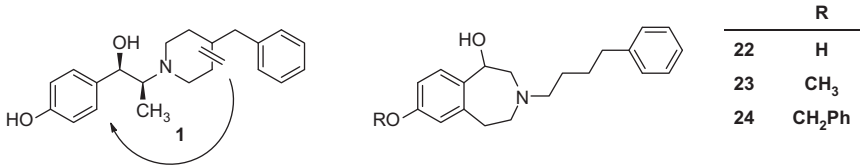
Early allosteric inhibitors such as the phenylethanolamines, ifenprodil and CP-101,606, required a terminal phenol group. In later compounds, phenol bioisosteres were employed. Additional studies focused on removing the metabolically labile OH group in the chain, while others transformed the basic tertiary amine center to a less basic ionizable form or to an amide center to minimize prominent off-target side effects at hERG and α_1-adrenergic receptors.

4.1. Phenylethanolamines and related compounds

The themes continue to be explored in recent examples. Wee and coworkers characterized the high-affinity protein binding domain of the 5-substituted benzimidazoles **17** and **18**.[27] Compounds **17** and **18**, subnanomolar inhibitors of GluN2B, were shown to bind directly to the ATD of the GluN2B subunit. In a series bearing some resemblance to **17**, an indole scaffold was identified by a molecular modeling strategy.[28] Optimum members of the series (**19–21**) showed potent GluN2B binding (K_i = 17–25 nM). Compound **19** reduced NMDA receptor-mediated current in CA1 pyramidal neurons from rat hippocampus, suggesting that it might be useful as a neuroprotective agent.

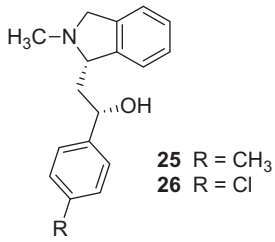


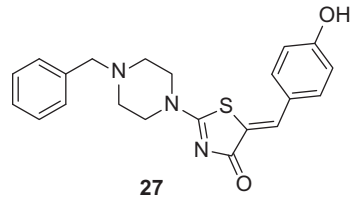
Cyclic analogs of ifenprodil, **22** and **23**, based on a tetrahydro-3-benzazepine scaffold, had high GluN2B affinities in a [^{3}H]-ifenprodil-binding assay (K_i = 14 and 5.5 nM, respectively).[29,30] Benzyl ether **24** had a loss of GluN2B affinity (K_i = 187 nM). Despite its higher GluN2B binding affinity, the methyl ether **23** (IC_{50} = 360 nM) was substantially less potent in an excitotoxicity assay than the phenol **22** (IC_{50} = 18.4 nM), suggesting that the phenol group is necessary for efficient functional inhibition.



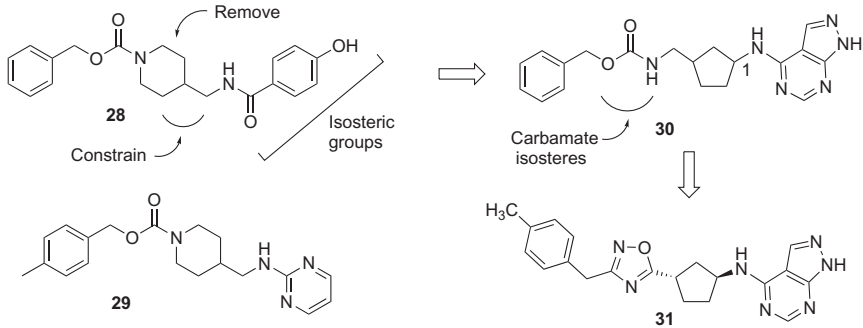
A series of isomeric *N*-methyl isoindolines was unique in lacking a phenol or bioisostere typically found in ifenprodil-like molecules.[31] Compounds **25** and **26**, both [1*S*, 1′*S*] configuration, were only moderately potent in a competitive binding assay with [^{3}H]-ifenprodil (430 and 270 nM, respectively) and also displayed functional inhibition of [^{3}H] MK-801 binding at the channel pore (210 and 500 nM, respectively).

A commercial database was evaluated in a virtual screening approach for GluN2B selective antagonists.[32] The primary hit compound **27** (IC_{50} 2.7 μM) was only 10-fold less potent than ifenprodil. Further, refinement of this chemotype will be necessary in order to decrease the potential for formation of covalent intermediates *in vivo*.





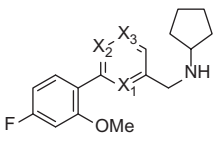
Members of a series of novel 3-substituted aminocyclopentanes were identified as orally bioavailable, highly potent and selective GluN2B receptor antagonists.[33] Starting from the initially identified carbamate **28** (similar to benchmark **29**), **30** was conceived by successively introducing ring constraints and isosteric groups for the benzamide and phenol. Two diastereomers of **30** (*SR*- and *SS*-) were as potent (K_i = 2.8 and 3.6 nM, respectively) against GluN2B as compound **29** and had low hERG potency (> 1000-fold vs. GluN2B) but were susceptible to human P_{gp} efflux *in vitro*. Replacement of the carbamate with an isosteric 1,2,4-oxadiazole and optimization of the phenyl group substitution pattern then yielded **31** (K_i = 0.88 nM) with low hERG potency (> 20,000-fold over GluN2B) and an acceptable P_{gp} liability. Compound **31** was active in a spinal nerve ligation model of neuropathic pain in rats (Chung model) and was efficacious in the haloperidol-induced catalepsy model as an acute rodent model of Parkinson's disease. In addition, **31** showed no measurable effect on motor coordination when dosed orally at 100 mg/kg in the rotarod assay, suggestive of a significant therapeutic margin.



In addition to the established efficacy of GluN2B antagonists in models of depression and other CNS disorders, Smith *et al.* have reported that Ro 25-6981 and CP-101,606 reverse cognitive deficits induced by PCP and MK-801 in rats, using standard models of visual attention and working memory. Altogether, these data suggest that cognitive benefits might be achieved by selective blockade of GluN2B receptors.[34] Moreover, Ro 25-6981 preserved the beneficial effects of general NMDA antagonists on the expression of conditioned fear in comparison to fluoxetine.[35]

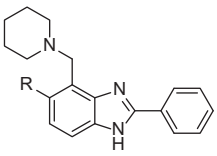
4.2. Atypical selective inhibitors of GluN2B

EVT-101 is a selective antagonist of GluN2B, but because its structure is more compact and it lacks a classic phenol bioisostere, it falls outside the typical motif of the phenylethanolamines and related isosteric compounds. Likewise, the 2,6-disubstituted pyrazines and corresponding matched pyridines **32**–**36** reported by Brown *et al.* are atypical GluN2B antagonists.[36] Although several compounds with different substituents on the phenyl group were identified, 4-F-2-OMePh was the optimum group for GluN2B potency. A cyclopentylaminomethyl group was optimal *meta*- to the phenyl substituent. To optimize GluN2B and decrease hERG potencies, pyridine (**33**, **35**, and **36**) and phenyl (**34**) moieties were substituted in place of the pyrazine (**32**). Pyridine isomer **33** was found to have the highest binding affinity for GluN2B, with an adequate safety index relative to hERG. Evaluated in the mouse forced swim test model of depression, **33** was active at 60 mg/kg. The brain/plasma ratio at 30 min post-dose was >10 with a dose-proportional exposure.



	X_1	X_2	X_3	GluN2B[a] K_i, nM	hERG[b] IC_{50}, μM
32	N	C	N	54	16.0
33	C	C	N	12	1.89
34	C	C	C	48	2.15
35	N	C	C	66	6.23
36	C	N	C	8900	3.85

[a] Inhibition of binding of [^{3}H]CP-101,606 to rat brain membranes
[b] IC_{50} values determined in CHOK1-hERG cells using EP measurements



	R	IC_{50}[c], nM
37	H	398.1
38	OH	7.9
39	F	79.4

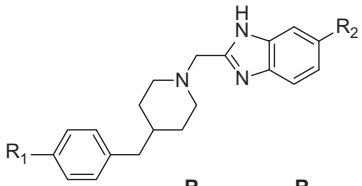
[c] [^{3}H]-Ro 25-6981 binding assay

Another compact scaffold identified by HTS as GluN2B-selective NMDA receptor antagonists had a benzimidazole core.[37] Although the potent molecule **38** had a phenolic OH group, the structure does not resemble

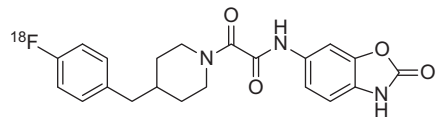
the typical framework of phenylethanolamines. The replacement of the OH group in **38** with fluorine as in compound **39** resulted in retention of GluN2B potency (IC_{50} < 100 nM). In contrast, the H-analog **37** lost 50-fold potency.

4.3. Radioligands and imaging tool compounds

Several radioligands for the GluN2B subunit have been developed (e.g., [^{11}C]-CP-101,606, [^{11}C]-benzylamidine derivative, [^{11}C]-EMD-95885), but these ligands have only proven useful *in vitro* probably due to nonspecific binding.[38] A new study reports the development of high-affinity benzimidazole derivatives **40** and **41** as new SPECT ligands for GluN2B subunits. *In vitro* autoradiography experiments demonstrated that **40** and **41** bind selectively to GluN2B in rat brain slices.



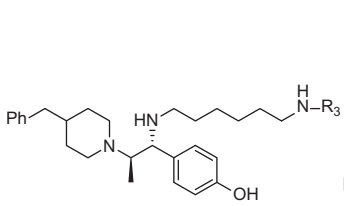
	R_1	R_2
40	^{125}I	OH
41	^{125}I	$NHSO_2Me$
42	^{18}F	OH

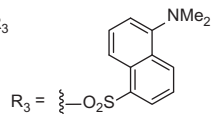


[^{18}F]-14

Recently, Labas *et al.* have reported the radiotracers [^{18}F]-**42** and [^{18}F]-RGH-896 ([^{18}F]-**14**) for PET imaging.[39] Both have demonstrated identical *in vivo* properties in rats. However, lower brain uptake and high accumulation of radioactivity in bone and cartilage were noticed.

Ifenprodil scaffold conjugates **43** and **44** were reported as fluorescent probes for confocal microscopy imaging of the GluN2B receptor.[40] Both **43** and **44** showed moderate GluN2B affinity (IC_{50} 1.4 and 1.8 μM, respectively).





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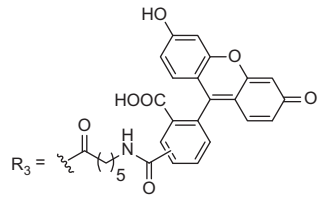
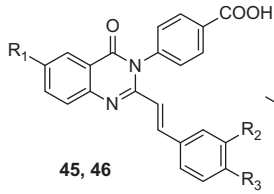


44 (mixture of isomers)

5. INHIBITORS AND MODULATORS OF GLUN2A, GLUN2C, AND GLUN2D SUBTYPE RECEPTORS

In contrast to the abundance of molecules reported to modulate GluN2B subtype selective NMDA receptors, selective ligands for GluN2A, GluN2C, and GluN2D have only recently begun to emerge. The inhibition of both GluN2C and GluN2D by quinazolin-4-ones **45** and **46**,[41,42] and quinolone **47** have been reported recently.[43] A homology modeling study of chimeric NMDA receptors identified two key residues Gln701 and Leu705 in the lower lobe (membrane-proximal portion) of the GluN2 agonist binding domain that control the selectivity of **47**.[43]



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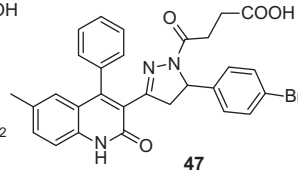

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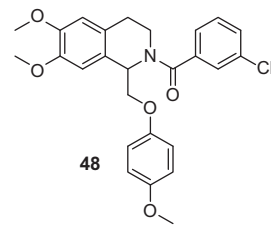
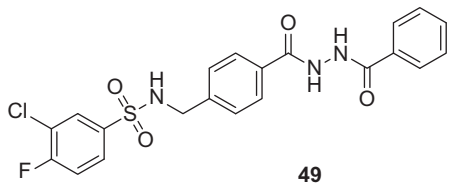


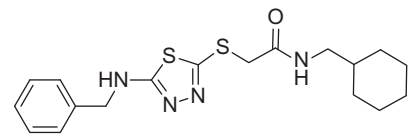
48

	R_1	R_2	R_3	GluN2C IC_{50} (μM)	GluN2D IC_{50} (μM)
45	I	H	NO_2	2.0	1.0
46	OMe	NO_2	H	7.1	3.9
47	-	-	-	7.0	2.7

Mullasseril *et al.* reported a novel subunit-selective potentiator of GluN2C and GluN2D of tetrahydroisoquinoline derivatives.[44] Compound **48** enhances by ~twofold the NMDA receptor responses of GluN2C (233% potentiation, $EC_{50} = 2.7$ μM) and GluN2D (205% potentiation, $EC_{50} = 2.8$ μM) activated by the partial agonists NMDA and glycine.



49



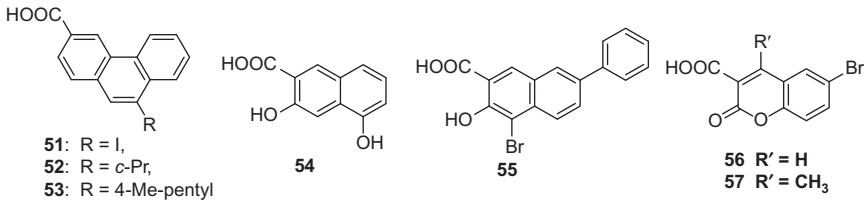
50

	49	**50**
IC_{50} GluN2A* (μM)	0.158	3.98

* FLIPR/Ca^{2+} assays. Corresponding IC_{50} for GluN2B were >50 μM

Sulfonamide **49** and thiadiazole **50** represent a new class of GluN2A antagonists identified through a HTS campaign.[45] Compound **49** was the most

potent among the reported list of analogues. The replacement of the right side phenyl group with furanyl, pyridinyl, or cyclohexyl groups resulted in loss of potency. However, the displacement of glutamate site antagonist [^{3}H]CGP 39653 by **49** implies partial interaction with an agonist binding site.



Costa *et al.* and Irvine *et al.*, reported the identification of both negative and positive allosteric modulators and inhibitors of subtype specific GluN2A/2C/2D NMDA receptors of polycyclic aryl carboxylic acid derivatives **51–57** and their related analogues.[46,47] The IC_{50}s were in the range of ≥ 2 μM but the observed effects in *X. laevis* oocyte two-electrode voltage clamp studies were significant with minor variations of substituent groups.

6. CLINICAL TRIALS

Among subtype selective NMDA antagonists, CP-101,606 alone has achieved proof of concept in human clinical trials of depression.[11] The non-selective antagonist ketamine has also been reported to demonstrate rapid clinical efficacy in treatment-resistant depression (TRD).[24] Together, this body of work serves to highlight the potential for developing GluN2B antagonists with an improved CNS side effect profile.

AZD6765, which is described as a low-trapping, mixed GluN2A/2B antagonist, is currently in multiple Phase IIb trials as an i.v. formulation for treatment-resistant major depressive disorder. Neither the structure of this compound nor the study results have been made public.[48]

Another GluN2B subtype selective antagonist, radiprodil (RGH-896), has been evaluated by Gedeon Richter and Forest Laboratories in a phase IIb study for neuropathic pain associated with diabetic peripheral neuropathy. In 2010, radiprodil failed to meet the primary endpoint of reducing mean daily pain scores compared with placebo, and no further development has been reported.[49] The Merck GluN2B antagonist, MK-0657, has been evaluated in Phase I trials for the treatment of both Parkinson's disease[50] and depression. It was reported that blood pressure effects were observed in some patients and that efficacy had not been achieved. Neither trial is

ongoing.[51] The Evotec drug EVT-101, also a GluN2B-specific antagonist, has recently been evaluated as an oral agent in a Phase II proof-of-concept study for TRD. Following difficulties in the enrollment of the patients under the study protocol, clinical development was terminated during 2011. The company announcement also cited the need to improve "sharpen" the toxicology profile of EVT-101 and the potential need for an adjustment to the dosage scheme.[52] A follow-up compound EVT-103, also reported to be a GluN2B-specific antagonist, completed a Phase I study for TRD and was found to be safe and well tolerated.[53] The structure of EVT-103 has not been released.

7. CONCLUSIONS

Improvements to existing treatments for CNS diseases represent an unmet medical need, and NMDA receptors have become an important target for new therapeutic approaches. Complicating the development of new drugs has been the requirement that therapies target aberrant NMDA function while preserving normal CNS function across other glutamate or excitatory receptors. Progress in this area has been largely driven by the discovery of subtype selective GluN2B NMDA antagonists which act at an allosteric site of the ATD without direct block of the ion channel pore. With the determination of the structure and the molecular contacts of selective antagonists bound within that allosteric site, a template now exists for the design of molecules with improved potency and selectivity. Recent advances have not been limited to subtype selective GluN2B receptors. For the first time, subunit selectivity has been achieved with the development of novel antagonists and modulators of GluN2A/2C/2D receptors. It is generally accepted that these ligands do not bind within the ATD, LBD, or ion channel pore, but instead at a novel site on the NMDA receptor complex. Though improvements in potency, selectivity, and drug-like properties are still needed, this class presents new opportunities to improve our understanding of NMDA receptors and their pharmacology. With these new tools in hand, the potential for medicinal chemists to address the limitations of current therapies in a number of CNS diseases is greater than ever.

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