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Review Article

The search for AMPA/Gly_N receptor antagonists

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Introduction

Glutamate is the major excitatory neurotransmitter in the central nervous system (CNS) and plays an important role in neuronal activity via different receptor systems. Overexcitation or loss of homeostasis of glutamate receptors may contribute to several neurological disorders and neurodegenerative diseases. This has resulted in major efforts aimed at developing antagonists of glutamate receptors as neuroprotective agents and for the treatment of a variety of neurodegenerative diseases such as epilepsy, Huntington's disease, Alzheimer's disease and Parkinson's disease. The molecular biology of glutamate receptors and their functions in the CNS have been reviewed extensively (1-12).

Excitatory amino acid (EAA) receptors are characterized as ionotropic or metabotropic glutamate receptors (Fig. 1). The ionotropic receptors are ligand-gated ion channels, whereas the metabotropic receptors are G-protein-linked receptors coupled to secondary messengers such as adenylate cyclase and phospholipase C systems. The ionotropic receptors are further subdivided into two major subgroups based on the agonists used to characterize them, *i.e.*, the *N*-methyl D-aspartate (NMDA) and non-NMDA receptors. The NMDA receptor requires

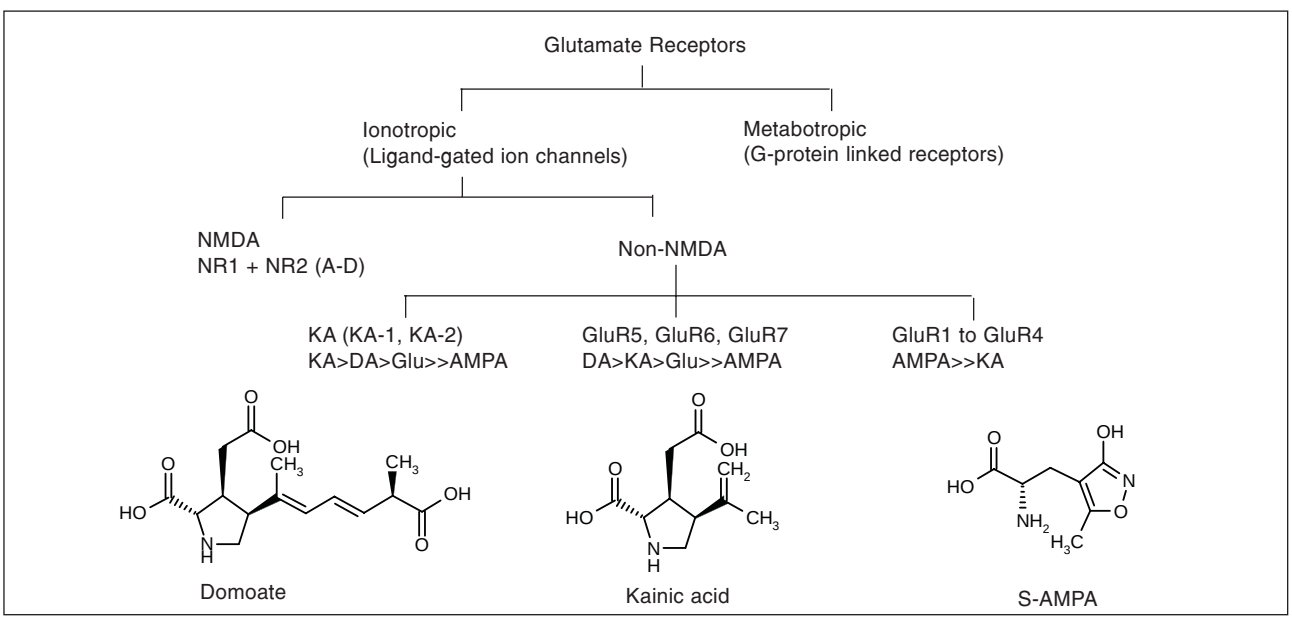


Fig. 1. Classification of glutamate receptors.

activation by the coagonists glutamate and glycine. The glycine site (Gly_N) of the NMDA receptor is different than the glycine receptor, which is a glycine-gated chloride ion channel localized in the brain stem and spinal cord. The glycine binding site of the NMDA receptor was proposed in 1987 after glycine was observed to increase the frequency of channel opening, while strychnine had no effect (13). Potentially important residues of the glycine coagonist site of the NMDA receptor were revealed through site-directed mutagenesis studies. Phe substitution at 735 and 736 in the M3-M4 loop with Ala resulted in >100-fold decrease in glycine affinity (1). Extensive reports have been published on the biology of these receptors and will not be discussed in this review (14-17).

Non-NMDA receptors are comprised of the α-amino-3-hydroxy-5-methyl-4-isoxazole propionate (**1**, AMPA) and kainate receptors. The AMPA and kainate receptors were originally grouped together because of their molecular biology and commonality of their agonists. However, more specific ligands and distinct pharmacological actions (18-20) have been identified for kainate receptors separating them as a distinct class of receptors. This review focuses on the recent developments in the area of AMPA and Gly_N (glycine recognition site of NMDA receptor) receptor antagonists. The AMPA and Gly_N receptor antagonists are discussed together due to the similarities in their pharmacophore models and in the commonality of the assays used to evaluate their potential as anticonvulsants and neuroprotectants (21-23).

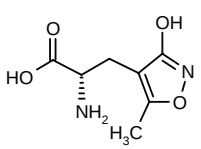
In recent years more information has become available regarding the structure and mechanism of action of AMPA receptors. Kinetic data from single-channel recordings using patch-clamp techniques implies that AMPA receptors exist as a tetrameric complex of subunits (24) instead of the pentameric complex that has been the dogma. High concentrations of antagonist were applied to the receptor complex and then switched rapidly to a high concentration of agonist in a flowing stream. Within a few 100 ms, the antagonist was displaced. Kinetics revealed that the ion channel opens in 3 steps observed as discrete substrate conductances (S – small), (M – middle) and fully open (L – large). Two glutamate (agonist) molecules are required for binding to initiate the first transition from the closed state to S. One additional glutamate is required for each of the other transitions, namely one to go to M and another to go to L.

Additional structural studies of the extracellular and ion channel domains have helped describe mechanisms through which the ion channel is opened (25). Models suggest new potential interactions in the extracellular domain between protein and the agonists. The ion channel domain has been modeled with a central antiparallel β-barrel that partially crosses the membrane and against which two α-helices from each subunit are packed. A third α-helix packs against these two helices in each subunit. The transition from the closed to an open state may involve the movement of a conserved positive residue away from and two negative residues into the extracellular entrance to the pore upon agonist binding.

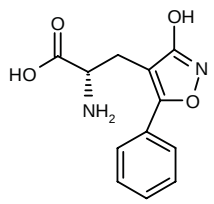
Several AMPA agonists and antagonists have been reported in the literature and will be described based on their structural properties. AMPA agonists and antagonists designed from agonist-like structures will be discussed separately because the three-dimensional organization of amino acids in the active site of the receptor has not yet been reported in adequate detail to permit a traditional structure-based design approach, and they do not readily fit the AMPA pharmacophore model derived from compact heterocyclic antagonists. Other sections include the AMPA/Gly_N receptor pharmacophore model, quinoxaline-2,3-dione-antagonists and Gly_N receptor antagonists.

Amino acids as AMPA agonists/antagonists

Several AMPA and Gly_N receptor antagonists were designed from modifications of agonist structures. Minor changes in AMPA-like structures gave important information regarding the conformational requirements for activity at the AMPA receptor. This resulted in the synthesis of a variety of amino acid derivatives with a large spread of activity that could not be easily interpreted by the three-dimensional fitting at the active site. Krogsgaard-Larsen's group has actively investigated novel amino acid derivatives as EAA receptor ligands. One fruitful area of research was the preparation of 5-substituted AMPA derivatives. The 5-phenyl derivative (**2**) was first thought to be a partial agonist but later studies showed that the (*S*)-enantiomer (5 μM) was a full AMPA agonist while the (*R*)-enantiomer was a weak antagonist (26). The 5-heteroaryl derivatives are particularly interesting since they retain affinity comparable to AMPA itself (**1**, R = Me). Three of the more potent examples are the 5-(2-thienyl) (**3**) (27), 5-(2-pyridyl) (**4**, 0.19 μM) (28) and 5-(2-furanyl) (**5**, 0.11 μM) (29) derivatives of AMPA. These and other analogs support stereospecific binding sites for the



1 S-AMPA



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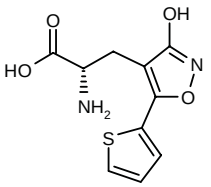

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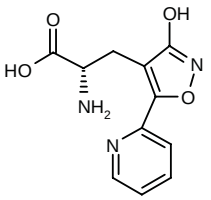

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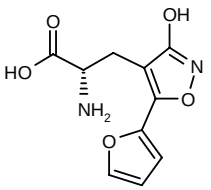

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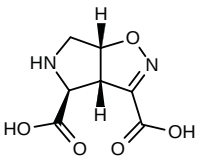
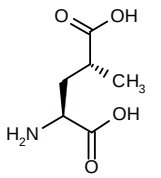


6 CIP-A



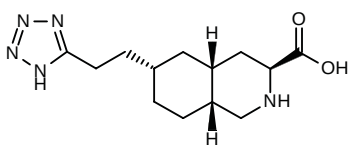
7 SYM-2081

charged groups in addition to a lipophilic cavity of limited size. The 2-position heteroatom of the 5-substituent heterocycle enhances AMPA receptor agonist activity. An intramolecular hydrogen bond between the amino group and the heteroatom may stabilize a receptor active conformation (30). The clinical potential of the 2-thienyl derivative is currently being investigated by H. Lundbeck A/S. Agonists such as AMPA have previously demonstrated both neurotoxicity and convulsant activity which may prevent establishment of an acceptable therapeutic index.

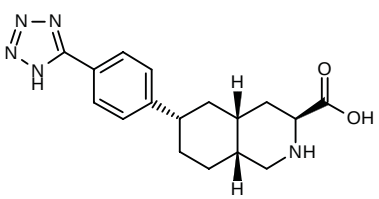
A bicyclic hybrid (**6**, CIP-A) of AMPA and kainic acid was prepared (31). This conformationally constrained molecule showed activity in both AMPA and kainate binding assays. It was also found to have potent convulsant activity. SYM-2081 (**7**, 2-(*S*),4-(*R*)-4-methyl glutamate) is a high affinity and selective kainate agonist. It is a prototype molecule to probe for novel kainic acid receptor ligands (32). Molecules such as these are more likely to be used as pharmacological tools rather than as drugs.

Decahydroisoquinoline antagonists

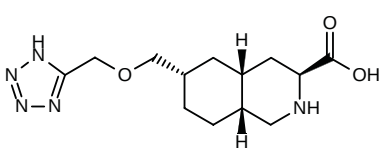
Various 6-substituted decahydroisoquinolines (**8-11**) have distinct profiles of activity at the NMDA, AMPA and kainate receptors. Decahydroisoquinoline amino acids have four stereocenters and eight possible diastereomers. Investigation of these possibilities has demonstrated that these analogs have unique conformational preference for EAA receptors. LY-293558 (**8**) is a moderately potent AMPA receptor antagonist that demonstrated activity in the CNS following parenteral administration (33). Analogs of **8** illustrated the demanding conformational requirements of NMDA and AMPA receptors: 1) the C-6 epimer was 12-fold less potent as an AMPA antagonist; 2) the C-3 epimer was inactive; 3) a *trans* ring juncture or transformation into the tetrahydroisoquinoline template gave inactive derivatives (34). The length of the side chain (A = $(CH_2)_n$) altered receptor selectivity. The n = 1 derivative is a selective NMDA receptor antagonist, n = 2 (**8**) is a selective AMPA antagonist and n = 0 has mixed NMDA/AMPA activity and is weaker than the other two.



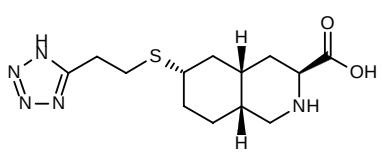
8 LY-293558



9 LY-301199



10 LY-377770



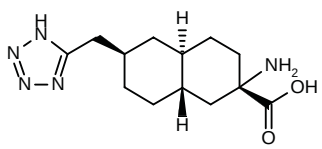
11 LY-292025

When n = 3 or 4, there is a decrease in potency and selectivity for EAA receptors. Although LY-293558 has anticonvulsant activity, it has a marginal therapeutic index (impaired motor function on horizontal screen) and lacks oral bioavailability, thus preventing development as an anticonvulsant. Analog **6** was neuroprotective in both rat and cat cerebral ischemia models. Parenteral administration would be required for the treatment of acute neuronal injury (*i.e.*, stroke) in humans (35). LY-293558 has demonstrated selective antagonist action of iGluR5 kainate receptors compared to their inactivity of iGluR6 kainate receptors, and thus is a useful tool for elucidating the role of kainate receptors in synaptic function (36).

Current information from the Investigational Drugs Database indicates that LY-293558 (**8**) and LY-301199 (**9**) are candidates for development for neurological disorders. Compounds **8** and **9** were approximately equipotent in AMPA binding assays, but **8** was twice as potent in functional studies in a rat cortical slice preparation (37).

A recent report discusses the neuroprotective potential of LY-377770 (**10**) (38). This compound has a mixed pharmacological profile with moderate AMPA antagonist activity and selective activity for the iGluR5 kainate receptor. In a gerbil model of global cerebral ischemia, LY-377770 showed neuroprotection (17%) in the CA1 region of the hippocampus when administration was initiated 2 h after 5 min of bilateral carotid artery occlusion. Thus, this compound showed very good neuroprotection in the gerbil model with only mild side effects. LY-292025 (**11**) is 10-fold more potent than LY-377770 at iGluR5. Apparently, AMPA receptor antagonist activity is required for neuroprotection since a selective iGluR5 antagonist from the decahydroisoquinoline series (A = 4-Ph, COOH for tetrazole; no significant AMPA receptor activity) was not neuroprotective. LY-377770 is considered a potential clinical candidate as a neuroprotectant for the treatment of acute stroke.

Lilly has reported other amino acid-based derivatives as AMPA receptor antagonists that meet threshold requirements for consideration as drug candidates. These include the *trans*-decalin derivative **12** and the tyrosine derivative **13** (39). However, it is unlikely that either of these derivatives will meet the rigorous standards for potency, safety and efficacy established to progress to clinical development.



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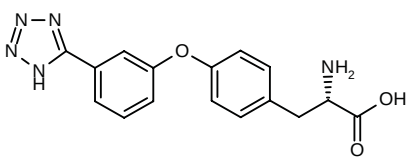

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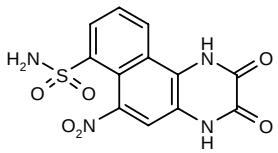
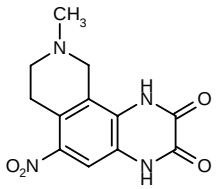
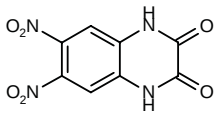


14 NBQX



15 PNQX



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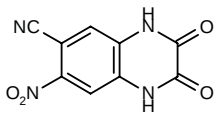

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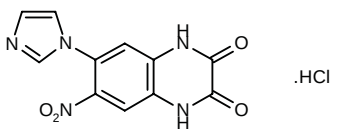
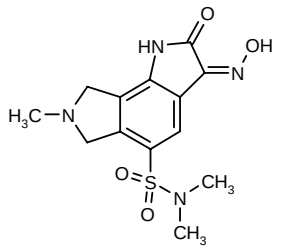


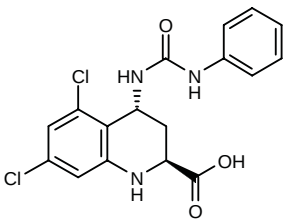
18 YM-90K

AMPA/Gly$_N$ pharmacophore model

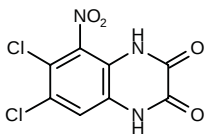
In recent years, most of the work in the area of competitive AMPA/Gly$_N$ receptor antagonists has focused on quinoxaline-2,3-diones and other heterocycles that can mimic this heterocyclic template. Several reviews have discussed the design, synthesis and therapeutic utility of AMPA/Gly$_N$ receptor antagonists (40-43). Therefore, this review will emphasize only the most recent advances, highlighting the important classes of compounds in terms of their *in vitro* and *in vivo* potencies. Quinoxaline-2,3-diones such as NBQX (**14**) (44), PNQX (**15**)(45), DNQX (**16**) (46), CNQX (**17**) (47) and YM-90K (**18**) (48) have been used extensively as reference standards. An AMPA pharmacophore model was constructed based on the high receptor affinity of these agents. Other heterocyclic compounds which fit the quinoxaline-2,3-dione template, such as the isatin compounds NS-257 (**19**) (49) and NS-1209 (**22**) (50), were also used to generate this model. Quinoxaline-2,3-diones have been used to build both the



19 NS-257



20 L-689560



21 ACEA-1021

AMPA and Gly_N pharmacophore models. Therefore, there is a remarkable similarity between the ligands which fit them and they are defined by very subtle differences. The Gly_N pharmacophore model is based on compounds such as the Merck quinoline-2-carboxylic acid urea (**20**) (51) and the quinoxaline-2,3-dione derivative ACEA-1021 (**21**) (52). These models have been used to design new AMPA and Gly_N receptor antagonists with improved physical properties including increased aqueous solubility compared to the highly polar quinoxaline-2,3-diones and other heterocyclic lactams.

In the AMPA pharmacophore model (Fig. 2), the quinoxaline-2,3-dione template can be divided into two halves. The most important receptor interaction sites are located in the southern half of the molecule and the C-3 carbonyl functionality at the northeastern corner of the molecule. These essential elements must be conserved for the successful design of new antagonists. The northern half, especially the northwestern corner, is amenable to modifications that can be used to increase selectivity and potency and to improve the physicochemical properties of the second and third generation of compounds. The model highlights several major factors that are required in the quinoxaline-2,3-dione template for activity at the AMPA receptor, which are as follows.

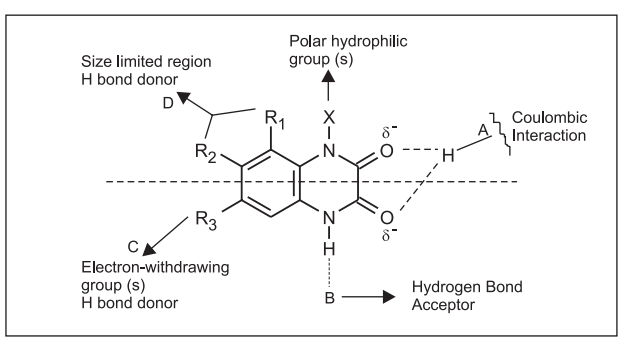


Fig. 2. Pharmacophore model for AMPA antagonists.

A) The primary interaction is the Coulombic interaction between the C-2 and C-3 carbonyl group oxygens and the receptor. This interaction is rather unique in the quinoxaline-2,3-dione template because there is a considerable double bond or keto character at the carbonyl oxygen resulting in significant negative charge at this eastern interface of the heterocyclic template. This effect is further amplified by the out-of-plane conformation of the carbonyl groups especially in the 6,7-disubstituted quinoxaline-2,3-dione derivatives. These observations have been confirmed by ^{17}O and ^{14}N NMR studies of quinoxaline-2,3-diones (53, 54). Similar Coulombic interaction is also possible with other heterocyclic lactams such as indole-2-ones and quinoline-2-ones that are appropriately substituted at C-3 with polar groups such as the nitro or oxime.

B) The N-H bond at N-1 is an essential proton donor. Methylation of this nitrogen results in total loss in activity.

C) A strong electron withdrawing group such as a nitro, trifluoromethyl or halo atom such as Br or Cl is required at C-7 and enhances the Coulombic interaction at the C-3 carbonyl by making the proton at N-4 more acidic. In particular, the nitro group seems to be preferred, indicating a weak hydrogen bond interaction with the receptor. The requirement of an acidic functionality at N-4 can also be satisfied by H-bond donating groups such as carboxylic acid, phosphonic and hydroxamic acids. These groups can also significantly enhance the aqueous solubility of the quinoxaline-2,3-diones and is a prominent feature in some of the newer AMPA antagonists.

D) The northwestern region of the molecule can accommodate substituents of limited size and polarity. The various groups incorporated in this region can be utilized to modulate the physical properties, especially the aqueous solubility and lipophilicity of these molecules. Smaller and weakly polar groups are well tolerated at C-5 and C-6 positions, suggesting a defined volume in this region and a weak electropositive hydrogen bonding interaction with the receptor. The spatial direction of these groups is also important. The northwest orientation is preferred for AMPA binding affinity. Thus, substitutions at C-6 have greater affinity for the AMPA receptor than substitutions at C-5. Polar groups of limited size such as the amides, ureas, sulfonamides, amines and amino acids are well tolerated in this region. Thus, this region is very important in terms of the design of selective AMPA/Gly_N receptor antagonists.

The Gly_N pharmacophore model is shown in Figure 3. The major differences that distinguish it from AMPA are as follows.

A) In the southwest portion of the heterocyclic template, *i.e.*, at C-7, halogen substituents are preferred. Even though polar electron withdrawing groups such as a nitro functionality are tolerated, they can be substituted

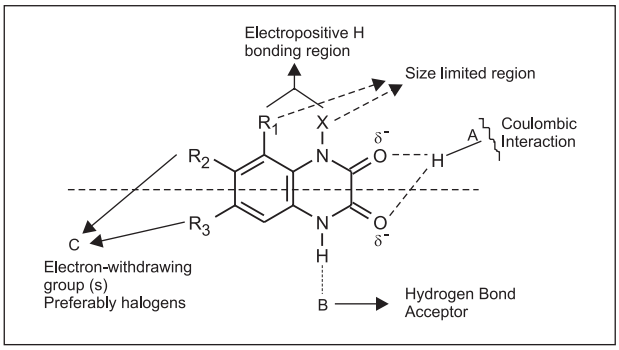


Fig. 3. Pharmacophore model for Gly_N antagonists.

by halogens with minimal loss in activity for the Gly_N receptor.

B) In the northwestern region of the molecule, especially at the C-5 and C-6 positions, a halogen (preferably chlorine) is well tolerated. No substitution is required in this area to enhance the affinity for the Gly_N receptor. The substituent at C-5 has been utilized to orient the polar groups at the C-5 and N-4 positions in the northeast direction. This weak electropositive hydrogen bonding interaction site is very important for the selectivity at the Gly_N receptor. More northern orientation of this interaction leads to balanced AMPA/Gly_N receptor antagonists such as PNQX.

Thus, a comprehensive study of these pharmacophore models should enable chemists to design selective AMPA or Gly_N receptor antagonists. In the last few years, several new selective, balanced and potent AMPA/Gly_N receptor antagonists have been reported and they are discussed below based on their structural motifs.

Quinoxaline-2,3-dione antagonists

As mentioned previously, the quinoxaline-2,3-dione template was the primary heterocyclic motif for several AMPA/Gly_N receptor antagonists. In the last few years, new analogs have been synthesized in this area and are grouped according to their structural subtypes based on the structural motif and substitution patterns as shown in Figure 4. The numbering system used to designate positions in the quinoxaline-2,3-dione ring system throughout the manuscript is shown in Figure 4.

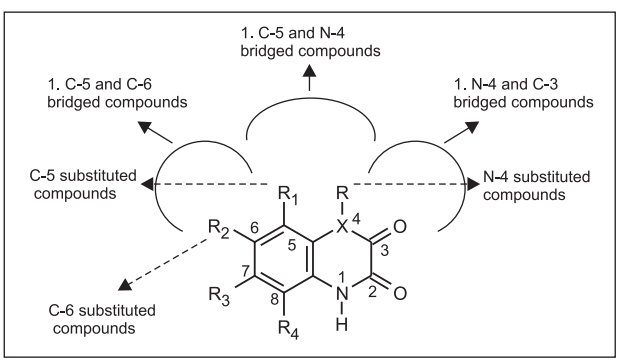


Fig. 4. Structural motifs of AMPA/Gly_N antagonists.

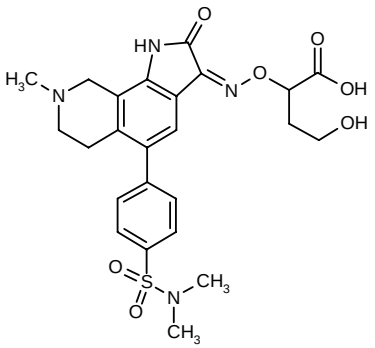
Tricyclic compounds

Tricyclic quinoxaline-2,3-diones have been reported with the tricycle formed by a bridge between C-5 and C-6 or C-5 and N-4 and or N-4 and C-3. Each of these tricyclic compounds are discussed separately in the following.

1) C-5 and C-6 bridged compounds

This group of tricyclic compounds contains some of the most potent AMPA antagonists reported and therefore have been a topic of intense study. In this group, NBQX (**14**) was one of the first selective AMPA antagonists (AMPA, IC_{50} = 52 nM, Gly_N, IC_{50} = >100 μM) reported (44) and demonstrated good *in vivo* activity in global and focal ischemia models. NBQX effectively demonstrated that a compact heterocycle with an acidic functionality (N-1 hydrogen) can effectively replace the traditional amino acid motif of AMPA/Gly_N receptor antagonists. As discussed, the orientation of the substituents in the *c* ring determined the selectivity of these compounds for the AMPA or Gly_N receptors. The AMPA selectivity of NBQX can be attributed to the northwestern orientation of the polar sulfonamide moiety. NBQX was reported by Novo Nordisk (44) and was subsequently being codeveloped with Schering AG for the treatment of cerebrovascular ischemia, epilepsy, psychosis and other neurodegenerative diseases. However, this compound suffered from poor aqueous solubility, which rendered it a poor drug candidate. This prompted chemists to design the next generation of compounds such as NS-257 (**19**), which has an indole-2-one, or an isatin-oxime, template (49). The compound was being jointly developed for the treatment of stroke by NeuroSearch and Warner-Lambert but was dropped to pursue more potent candidates.

PNQX (**15**) was designed in our laboratories at Warner-Lambert as a hybrid structure between NBQX and NS-257 (45). In this compound, the quinoxaline-2,3-dione template from NBQX was retained, whereas the aromatic *c* ring was replaced with an *N*-methyl-tetrahydropyridinyl ring, which was similar to the pyrrolidine ring in NS-257. These structural changes led to a balanced antagonist, in that the AMPA activity was greater (IC_{50} = 62 nM) and Gly_N affinity was significantly higher (IC_{50} = 370 nM). This balanced profile of PNQX is attributed to the orientation of the amine functionality in the northern direction, which interacts with the electropositive hydrogen bonding interaction site. Several other analogs of PNQX (**15**) were synthesized by changing the position of the nitrogen in the ring, alkyl substitutions at the nitrogen to replace the methyl group, and other substituents at C-7 to replace the nitro functionality. However, none of these analogs showed better affinity for the AMPA receptor and it became evident that bulk tolerance is limited at the basic nitrogen and that the nitro



22 SPD-502

group is optimum at C-7 of the quinoxaline ring. In addition to the excellent *in vitro* activity, PNQX showed good neuroprotection in the focal ischemia models, such as the middle carotid artery occlusion (MCAO) model in rats (2.5 mg/kg i.v.). It was a development candidate for stroke at Warner-Lambert. Similar to NBQX, PNQX has poor aqueous solubility and several new analogs were synthesized in recent years to alleviate this problem. Schering (55) and BASF (56) have reported other compounds with the 5,6-bridged tricyclic motif in the patent literature. The *c* ring in the Schering compounds is a phenyl ring similar to NBQX, whereas BASF compounds have a cyclohexyl ring. Complete SAR on these compounds has yet to be published.

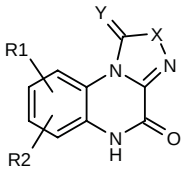
Recently, an amino acid analog of NS-257 (**19**), NS-1209 or SPD-502 (**22**), was reported as a second-generation isatin oxime (49, 57). It is obvious that the hydroxy acid side chain was added to improve the aqueous solubility compared to NS-257 and PNQX and may also contribute to increased AMPA activity. SPD-502 (**22**) has demonstrated efficacy in a rat permanent MCAO model with a 2-h window of treatment. It is currently a clinical candidate for neuroprotection following stroke and other neurodegenerative diseases.

2) C-5 and N-4 bridged compounds

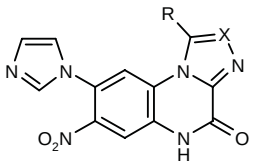
The compounds in this class were initially reported by the Sumitomo group (58) and later by other companies such as Schering (59), Ciba-Geigy (60) and Acea (61). However, the compounds from Sumitomo appear to be the most extensively studied in this class and their selectivity for Gly_N receptor was expected based upon the pharmacophore models described earlier in the review. These will be discussed more extensively in a latter part of the review in the section on Gly_N receptor antagonists.

3) N-4 and C-3 bridged compounds

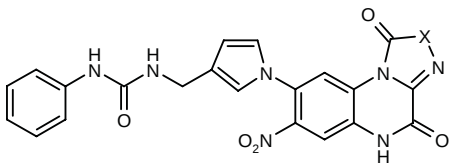
Efforts to improve the aqueous solubility of the quinoxaline-2,3-diones were directed at replacing the C-3 amide with a bioisosteric replacement such as an N-4/



23 X = NH
24 X = CH

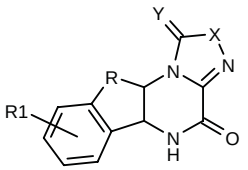


25 X = CH, R = H or alkyl
26 X = N, R = H or alkyl

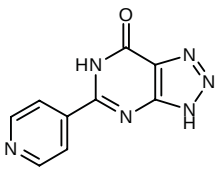


27 X = CH or N

C-3 bridged nitrogen heterocycle. These compounds retained good AMPA binding affinity, but the effect on their physical properties and *in vitro* and *in vivo* efficacy cannot be included here since it was not disclosed in the general literature. Most of the work in this area has appeared in the patent literature and several compounds with a triazolo(4,3-a)-quinoxaline-2-ones (**23**) ring system were reported by Novo Nordisk followed by the imidazo(1,2-a)-quinoxaline-2-one derivatives (**24**) that were disclosed by Novo Nordisk (62, 63), Yamanouchi (65) and BASF (66). Yamanouchi compounds have the N-imidazolyl substitution at C-6 (**25** and **26**), whereas the BASF compounds have appropriately substituted N-pyrrolidinyl ring (**27**). Scientists at Yamanouchi have done a comprehensive SAR with both the imidazo[1,2-a] and [1,2,4]triazolo-[4,3-a]quinoxalinones motifs. They observed that both the imidazo[1,2-a] and [1,2,4]triazolo[4,3-a] (**25**, R = H, K_i = 0.057 μM; R = Et, K_i = 0.020 μM; and **26**, R = H, K_i = 0.19 μM; R = Et, K_i = 0.048 μM) quinoxaline-2,3-diones were comparable in AMPA binding affinity, indicating that the extra nitrogen in the ring does not play a significant role in any hydrogen bonding interaction in the eastern portion of the molecule. Additionally, the replacement of the lactam carbonyl at C-3 with the heterocyclic bioisosteres did not diminish the AMPA binding affinity (YM-90K, **18**, AMPA, K_i = 0.084 μM), indicating possible participation of the nitrogen of the imidazo or the triazolo ring in the Coulombic interaction with the receptor. It would be interesting to compare the *in vivo* profiles of these compounds with the highly potent YM-90K and YM-872, that do not have the C-3 and N-4 bridged heterocycle.



28 X = NH or CH
R = CH



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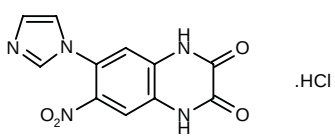
Two new classes of compounds with similar bioisosteric replacements and a novel ring system were also reported in the patent literature. Rhône-Poulenc Rorer (67-69) have reported the imidazo[1,2-a]indeno[1,2-*e*]-pyrazine-4-ones and the 1,2,4-triazolo[4,3]pyrazine-4-ones represented by structure **28** as AMPA/Gly$_N$ receptor antagonist. The highlight of this work was the absence of a strongly electron withdrawing group in the aromatic ring attached to the pyrazine ring. Efforts to change the template completely with 6-(4-pyridinyl)-1*H*-1,2,3-triazolo-[4,5-d]pyrimidin-4(5*H*)-one analogs (**29**) were not very successful (70). Compound **29**, the best compound in this series, had an IC_{50} of 1.8 μM.

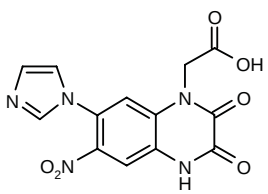
5- and 6-substituted compounds

Substitutions at C-5 and C-6 positions of quinoxaline-2,3-diones have provided chemists a handle to modulate the physical properties and selectivity for AMPA or Gly$_N$ receptors. This class of compounds includes 5- and or 6-substituted quinoxaline-2,3-diones bearing an electron withdrawing group at C-7. The initial forays in this area were based on the structures of CNQX (**17**, AMPA, K_i = 0.27 μM) (47) and DNQX (AMPA, K_i = 0.27 μM) (46). In the second and third generation of these quinoxaline-2,3-diones, substitutions with limited polarity were incorporated at C-5 and C-6 with significant success. In the 6-substituted compounds, Yamanouchi chemists designed an important class of 6-*N*-imidazolyl compounds. Of these, YM-90K (**18**, AMPA, K_i = 0.084 μM) was most promising with an imidazoline ring at C-6 as a bioisosteric replacement for the cyano group in CNQX (48, 71, 72). This was a very successful modification in that the new analog was at least 3-fold more active than CNQX. This drug also demonstrated an excellent *in vivo* profile in the DBA/2 model (mice, ED_{50} = 2.54 mg/kg i.p.) and in focal ischemia models such as MCAO in cats (0.5 mg/kg/h i.v. for 6 h) and in rats (20 mg/kg/h i.v.) (71, 73, 74). In rats, YM-90K was efficacious in reducing the size of the lesion volume even 3 h post-MCAO, which gives a significant time window for effective treatment of stroke patients. Other analogs of YM-90K have been synthesized with the goal of improving the aqueous solubility of these compounds, particularly by substituting the hydrogen at N-4 with a polar side chain or replacing the C-3 amide carbonyl by a heterocyclic bioisostere discussed in the N-4 and C-3 bridged heterocycles (65, 76). Of these compounds, YM-872 (**30**, AMPA, K_i = 95 nM) has shown the most promise with significant neuroprotection in rats in MCAO assay at 40 mg/kg/h for 4 h (77-80). However, unlike YM-90K, the compound was not neuroprotective at 20 mg/kg/h and had to be infused for 24 h to show significant neuroprotection under this dosing protocol. Indeed, 24 h infusion was possible with YM-872 because it has 62-fold increased solubility compared to YM-90K (78). Of the 6-*N*-imidazolyl compounds, the hydroxamic acid derivative has the best AMPA receptor affinity with a K_i of 21 nM (75). The effect of the *N*-4 hydroxyl on the AMPA binding affinity is not well understood even though several hypotheses regarding hydrogen bonding interactions in the N-4 region have been proposed by several groups, including Yamanouchi.

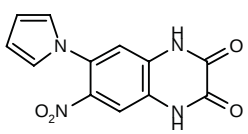
Other 6-substituted-quinoxaline-2,3-diones that have made significant impact in the field of AMPA antagonists were reported by BASF (81). The two series of compounds reported had an unsubstituted N-pyrrolyl (**31**) (81) or a N-pyrrolyl ring with a urea functionality (**32**) (82) at the C-6 position of the quinoxaline-2,3-dione. Some of the compounds reported in these series are distinguished as some of the most potent AMPA antagonists (K_i = 4 nM) hitherto reported in the receptor binding assay. It is important for the compounds to have the acetic acid side chain at N-4 for good AMPA receptor binding (83). For example, the analog with a hydrogen at N-4 (**18**, K_i = 0.4 μM) has



18 YM-90K



30 YM-872



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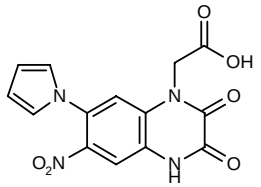

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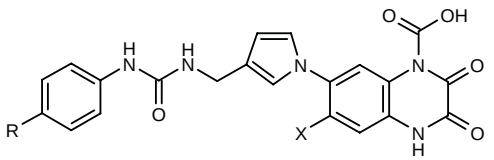

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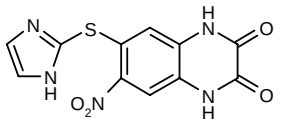

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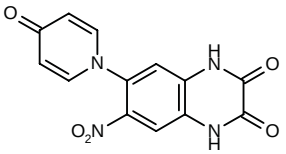

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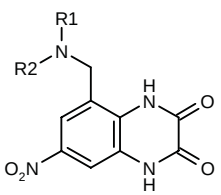
about 4-fold less affinity for the AMPA receptor than the corresponding compound (**32**, K_i = 0.07 μM) with an acetic acid side chain. The compounds which had the best affinity for the AMPA receptor require the presence of both an acetic acid side chain at N-4 and a substituted N-phenyl urea side chain at C-3 of the pyrrole ring and are represented by the compounds of general structure **33**. Compounds with an electron withdrawing group in the urea phenyl group (**33,** R = NO_2, Br or CF_3) and a trifluoromethyl at C-7 (**33**, X = CF_3) had the best affinity for the AMPA receptor (<5 nM). The compound lacking the electron withdrawing group in the urea phenyl ring (**33**, R = H, K_i = 15 nM) was 3-fold less active, whereas the compound with the nitro group (**33**, R = H, X = NO_2) was about 5-fold less active than the corresponding trifluoromethyl analog (**33**, R = H, X = CF_3). The SAR in these series illustrates the requirements of the AMPA pharmacophore model in that the C-7 trifluoromethyl group is preferred over the nitro group. Additionally, the pocket in the northwestern region of the molecule appears to hold much more bulk in the form of substituted phenyl urea side chain attached to the C-3 of the pyrrolidinyl ring, further indicating the need for optimization of substituents in other C-5 and C-6 substituted quinoxaline-2,3-diones series. The importance of the acidic functions in the N-4 side chain was further emphasized, as evidenced earlier, in the Yamanouchi imidazolyl series (71, 75). In the BASF series, the compound without an acetic acid side chain at N-4 was about 100-fold less active at the AMPA receptor. Also, the weak H-bonding interaction in the northwestern region of the molecule, proposed by our group at Warner-Lambert in the PNQX series, is important in this series as the compounds without the acid or ester functionality in the pyrrolidine ring were significantly less active at the AMPA receptor (45). All the BASF compounds had significantly less affinity for the Gly_N receptor. This confirms the observation that side chains with a northwest orientation rather than north or northeast, favors good AMPA selectivity. The compounds with high AMPA affinity (**33**, R = NO_2, Br or CF_3, X = CF_3) also showed good neuroprotection against AMPA-induced seizures (ED_{50} = 4.1-14 mg/kg i.p.). Additional data on the efficacy of these compounds in the stroke models has yet to be reported.

Several other polar groups attached to the side chains at C-6 position of the quinoxaline-2,3-dione template have been disclosed in the patent literature. They are the arylthio (**34**) and 4-oxo-pyridinyl (**35**) analogs by Shionogi (84, 85). Complete biological profiles of these compounds have not yet been disclosed and hence are not discussed here in detail.

5-substituted compounds

This class of analogs has seen tremendous activity in the last few years with Novartis, Pfizer and Warner-Lambert groups leading the way. The main focus has been to synthesize compounds substituted with aminoalkyl groups at C-5. The groups at Novartis (86-89), Pfizer (90) and Warner-Lambert (91-95) have reported a variety of substituted amines, amino acids, amides, ureas and sulfonamides at C-5 of the quinoxaline-2,3-dione template via a methylene linker. The amino acid compounds reported by Novartis, shown in Table I, and by Warner-Lambert, shown in Table II, were the most potent

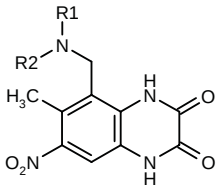
Table I: Novartis C-5 substituted AMPA antagonists.



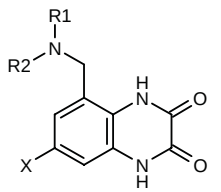
Compd	R_1	R_2	IC_{50} (μM) AMPA	Gly_N*
36a	Pyrrolidinyl		0.28	NA
36b	Piperidinyl		0.29	41%
36c	CH_2CO_2H	H	0.16	0.76
36d	CH_2CO_2H	CH_3	0.34	22%
36e	$CH_2CH_2CO_2H$	H	0.38	19%
36f	$(CH_2)_3CO_2H$	H	0.61	9

*% inhibition at 1 μM.

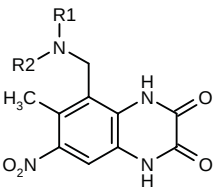
Table II: Warner-Lambert C-5 substituted AMPA antagonists.



Compd	R_1	R_2	IC_{50} (μM) AMPA	Gly_N
37a	Pyrrolidinyl		0.23	>1
37b	Piperidinyl		0.28	>1
37c	CH_2CO_2H	H	0.5	0.02
37d	CH_2CO_2H	CH_3	0.12	0.47
37e	$CH_2CH_2CO_2H$	H	0.03	0.2
37f	$(CH_2)_3CO_2H$	H	0.12	1.8



36 X = Br, CF_3 or NO_2



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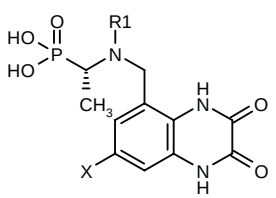
compounds at the AMPA receptor and have good affinity for the Gly_N receptor. The major difference between the analogs appears to be the orientation of the amino acid functionality in the northern region of the molecule. Novartis compounds represented by the general structure **36** do not have any substitution at the C-6 position, whereas the Warner-Lambert compounds have an alkyl group that constrains the conformation of the amine functionality. In the Warner-Lambert compounds represented by the general structure **37**, the aminomethyl side chain assumes an out-of-plane conformation by virtue of its being held between the C-6 alkyl and the N-4 hydrogen (96). This difference in conformation results in some unique differences in affinities for the AMPA and Gly_N receptors. For example, the glycine, sarcosine and β-alanine derivatives had much better affinity for the AMPA receptor in both sets of compounds, with Novartis compounds (89) in general being slightly weaker than the Warner-Lambert compounds (96). The exceptions were the Novartis glycine side chain analog, which was about 3-fold more active than the Warner-Lambert compound and the Warner-Lambert β-alanine analog was about 12-fold more active than the corresponding Novartis compound. The affinity for the Gly_N receptor cannot be directly compared since different ligands were used for the binding assay, but the Warner-Lambert compounds appeared to have much better affinity for this receptor than the Novartis compounds. Other aminoalkyl analogs such as the alkyl and cyclic amines (Table II) did not show significant differences in the affinity for both receptors. Polar side chains such as the amides, ureas and sulfonamides altered the selectivity profile with the analogs being more active at the Gly_N receptor than the AMPA receptor. The exception was the 3,4,5-trimethoxy or the 3,4,5-trihydroxy phenyl amides which showed very good affinity for the AMPA receptor. Selectivity for the Gly_N receptor could once again be attributed to the orientation of these side chains in the northeastern portion of the molecule.

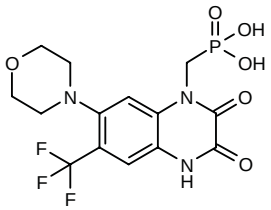
It was interesting to note that the amino phosphonic acid derivatives (**38**) were similar in their binding affinities to the amino acids. The activity was dependent on the substitution pattern on the amine nitrogen, chirality of the amino phosphonic acid and the substitution at C-7. The analogs (38) with D-phosphoalanine side chain and a trifluoromethyl group or a bromine at C-7 had significantly better binding affinity for the Gly_N receptor (IC_{50} = 6 nM) compared to the AMPA receptor (IC_{50} = >1 μM) and was also active in the MES assay (ED_{50} = <12 mg/kg i.p.) with a longer duration of action (2 h). The same compound with a nitro group at C-7 showed much better binding affinity for the AMPA receptor (IC_{50} = 0.17 μM) and was about 5-fold less active at the Gly_N receptor (IC_{50} = 0.032 mcM). The selectivity for the AMPA/Gly_N receptors could be switched by adding an ethyl group on to the nitrogen of the amino phosphonic acid nitrogen. With the trifluoromethyl group at C-7, the compound had excellent binding affinity for the AMPA receptor (IC_{50} = 0.068 μM). However, with the nitro group at C-7, affinity for both the receptors dropped considerably (AMPA, IC_{50} = 0.31 μM; Gly_N, 25% with 1 μM), indicating that the R stereochemistry in the amino phosphonic acid side chain gave the preferred conformation for binding to either receptors, and N-ethylation significantly changed the conformation to enhance the selectivity of these compounds for the AMPA receptor.

The role of different electron withdrawing groups such as bromine, trifluoromethyl and nitro at C-7 on the selectivity are not well understood in these series of



38 X = Br, CF_3, NO_2
R1 = H or Et

compounds. The major advantage of these compounds was the enhanced aqueous solubility over the tricyclic compounds and improved MES activity in terms of longer duration of action. The Warner-Lambert C-5 substituted acyclic aminomethyl compounds (Table II) were indeed designed to disrupt the planarity of the PNQX template and prevent the formation of the zwitterionic dimers that pack to form strong crystal lattice (91). The strategy of having polar groups such as carboxylic acid in the side chain at C-5 has provided medicinal chemists with several benefits: increased aqueous solubility, additional tools to study the AMPA/Gly_N pharmacophore model and a means to improve potency and selectivity of new analogs. In both the C-5 and C-6 substituted quinoxaline-2,3-diones, several compounds continue to show promise as possible drug candidates, although no development candidates have been clearly identified.



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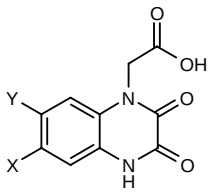
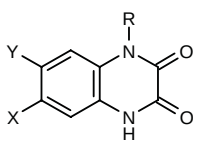


41 X = Y = CH3 or Cl

N-4 substituted compounds

The N-4 position in various quinoxaline-2,3-diones has been invariably substituted with polar and hydrophilic groups such as carboxyalkyl and phosphonoalkyl groups. In general, these groups have significantly improved the binding affinity and aqueous solubility of these analogs as demonstrated by the Yamanouchi compounds discussed earlier (71, 77-80). The systematic SAR done on the 4-phosphonomethyl quinoxaline-2,3-diones by Turski *et al.* (97) has been of great value in understanding the binding interactions of various functionalities at the AMPA/Gly_N receptors. They confirmed that the unsubstituted quinoxaline-2,3-dione (**39**, R = X = Y = H) was very weak at the AMPA receptor (IC_{50} = 204 μM). The 7-trifluoromethyl substitution enhanced AMPA binding affinity about 16-fold (**39**, R = Y = H, X = CF_3, IC_{50} = 13 μM) and the incorporation of a morpholino moiety at C-6 further increased the binding affinity 51-fold (**39**, X =CF_3, R = H, Y = N-morpholinyl, IC_{50} = 4 μM). Initial substitution of the hydrogen at N-4 with a methyl group gave an equipotent compound (IC_{50} = 4 μM), indicating that the role of this hydrogen is not significant in AMPA binding. However, replacement of the hydrogen with a phosphonomethyl group (**40**, ZK-200775) enhanced receptor binding 34-fold (IC_{50} = 0.12 μM) over the 4-N-methyl analogs and 1700-fold over the unsubstituted quinoxaline-2,3-dione. The compound ZK-200775 showed excellent efficacy in the MCAO model in rodents (10 mg/kg/h i.v. for 6 h). A complete time-course study was done with **40** in the MCAO model that confirmed its efficacy and established a long therapeutic time window (>4 h). No renal toxicity due to kidney crystallization of the drug was observed in any of the long-term infusion studies, thus providing a definite advantage over several other classes of quinoxaline-2,3-diones. Therefore, ZK-200775 (**40**) has an excellent profile for a selective AMPA receptor antagonist (Gly_N, IC_{50} = 5.15 μM) with *in vivo* efficacy in the permanent focal ischemia model in rodents and excellent aqueous solubility (25 mg/ml at pH 7.35). The compound is reported to be in clinical trials for the treatment of stroke patients.

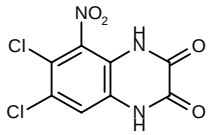


39 R = H or Me
X = H or CF3
Y = N-morpholinyl

Several other N-4 acetic acid quinoxaline-2,3-dione analogs (**41**) were synthesized by Bristol-Myers Squibb (98) that have a methyl or chloro disubstitution at C-6 and C-7. The most active compound in this series at the AMPA receptor (**41**, X = Y = Me, K_i = 0.70 μM) was the 6,7-dimethyl substituted compound and the most potent at the Gly_N receptor (**41**, X = Y = Cl, K_i = 0.11 μM) was the corresponding 6,7-dichloro substituted analog. The affinity for both receptors was diminished by increasing or branching the alkyl chain length between the carboxylic acid moiety, by replacing the carboxylic acid moiety with a phosphonic acid group or by bioisosteric replacement of the carboxylic acid moiety.

Gly_N receptor antagonists

An overview of glycine site antagonists was recently published (43). A glycine site antagonist that has good pharmacokinetic and pharmacodynamic properties and is able to penetrate the blood-brain barrier is likely to have clinical utility for a number of therapeutic indications. Several parameters have been investigated that affect CNS penetration and *in vivo* activity. High plasma protein binding limits brain penetration and is directly correlated to LogP and affected by the compound's pK_a (99). Design information based upon these physicochemical requirements and an understanding of published glycine

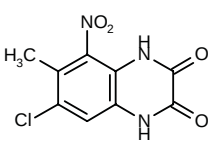


42 ACEA-1021

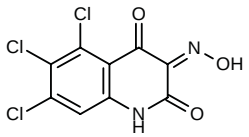
recognition site pharmacophore models may lead to therapeutically useful agents. A few important Gly_N antagonists are described in detail below.

ACEA-1021 (**42**) is a prototypical quinoxaline 2,3-dione glycine site antagonist which fits the Gly_N pharmacophore model described earlier. ACEA-1021 (licostinel) has low nanomolar affinity for NMDA receptors. *In vitro* studies showed that ACEA-1021 has 120- to 250-fold greater selectivity for NMDA receptors as compared to non-NMDA receptors (52, 100). However, the compound exhibits both NMDA and non-NMDA-mediated effects *in vivo* (101). ACEA-1021 has consistently demonstrated neuroprotective effects in several models of cerebral ischemia following parenteral administration (102, 103); neuroprotection may be partially due to its action at AMPA receptors. Evidence indicates that Gly_N antagonists do not result in substantial adverse central behavioral effects. ACEA-1021 had little or no effect on regional cerebral glucose metabolic rate and cerebral blood flow (104) and did not precipitate the psychotomimetic effects that are associated with other classes of NMDA receptor antagonists such as PCP (105). Administration of ACEA-1021 caused a reversible alteration in cingulate and retrosplenal cortical neurons, but did not cause lethal neurotoxicity (106). ACEA-1021 underwent human safety trials in healthy volunteers and stroke patients (107). There were no dose-limiting CNS side effects observed, but crystals in the urine were seen. The compound is currently in phase II clinical trials for stroke and has been dropped from clinical trials for head trauma. Like other quinoxaline-2,3-dione derivatives, the coadministration of probenecid has been shown to reduce tubular excretion and protect the kidneys from crystallization. The combination also increases plasma and brain concentrations of the drug. This coadministration strategy is being pursued preclinically. The complexity of developing the combination therapy of ACEA-1021 and probenecid is likely to delay its rapid advancement through clinical trials.

Replacement of the 6-chloro substituent of ACEA-1021 with a methyl group gave ACEA-1416 (**43**) (108). This derivative is described as having the best combination of *in vitro* and *in vivo* potency of this type of compound. ACEA-1416 was neuroprotective in a model of focal cerebral ischemia (109). Alternative templates have generated novel and potent Gly_N antagonists. The tetrahydroquinolin-2,3,4-trione 3-oxime series (**44**) gave compounds 5- to 10-fold more potent than the quinoxaline-2,3-diones. The 5,6,7-trichloro analog **44** has low nanomolar affinity as a Gly_N antagonist (110). The 3-hydroxy benzazepinedione **45** is also potent as a Gly_N antagonist, showing *in vivo* anticonvulsant activity (111). Each of these alternative templates fits predictably into known glycine site pharmacophore models.



43 ACEA-1416



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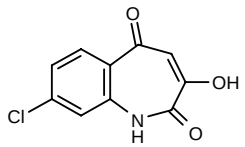

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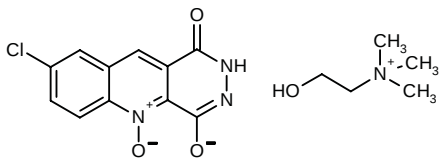
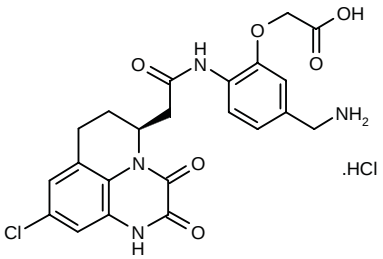


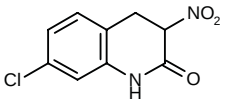
46 X = Br MRZ 2/570
X = Cl MRZ 2/571

Merz has prepared a series of quinolinophthalazine derivatives, MRZ 2/570 and MRZ 2/571 (**46**), that present a more novel template for glycine site antagonists. They compared the activity of these derivatives to L-701324 (**54**). They claimed that glycine site antagonists are relatively safe and have substantial potential for the treatment of morphine addiction and neuroprotection with less utility for parkinsonism or anxiety (112).

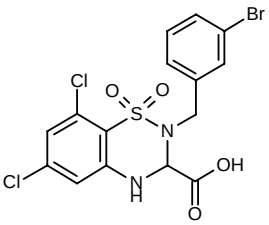
SM-18400 (**47**) is a potent, selective, third-generation glycine site antagonist that is derived from a series of C-5 and N-4 bridged tricyclic quinoxaline-2,3-diones being developed by Sumitomo (113). The side chain emanating from the tricyclic ring system was clearly added to improve aqueous solubility and physicochemical properties. The aryl side chain does not interfere with critical binding domains of the glycine site model. SM-18400 demonstrated activity in MCAO with a 2 h window of administration. Generally, it has no effect on locomotor



47 SM-18400



48 L-698544



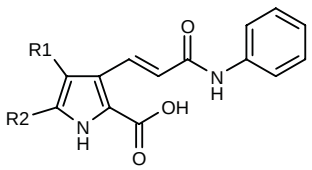
49 RPR-104632

function at efficacious doses. A compound with these characteristics has a reasonable chance of being successfully developed, although it is unlikely that SM-18400 will be orally active and have a long duration of effect.

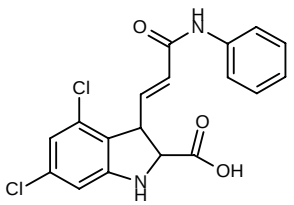
The 3-nitroquinolone derivative, L-698544 (**48**), has modest potency as a mixed AMPA and Gly_N antagonist. The simple structure easily fits into either pharmacophore model. Earlier reports had identified this compound as a potential development candidate for the treatment of convulsive disorders and stroke. It now appears that development has been discontinued (114).

A highly potent series of glycine site antagonists was identified by Rhône-Poulenc Rorer that are based upon a benzothiadiazine template. Substitution patterns are consistent with previously understood requirements for potent Gly_N receptor activity. RPR-104632 (**49**) is a racemate with 8 nM affinity for the glycine site (115). The (*S*)-(-)enantiomer is the active enantiomer, whereas the (*R*)-(+)-enantiomer is about 500-fold less active. Although this compound has demonstrated neuroprotective activity *in vitro* (116), its limited CNS penetration is the greatest liability for this class of compound. Since i.c.v. administration was required to produce *in vivo* anticonvulsant activity, it is unlikely that this compound will be a drug candidate.

A novel series of pyrrole 2-carboxylic acids (**50**) offers a structural alternative to previous glycine site antagonist templates (117). In this instance, the structure-activity relationships parallel those of an indole series (**52**), and demonstrate that the fused benzo ring system such as quinoxaline is not required. A QSAR describes a negative



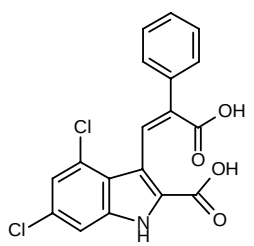
50 generic
51 R_1,R_2 = Br



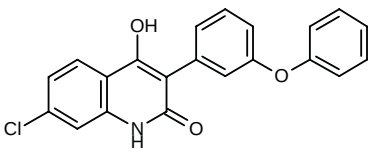
52

correlation between the bulk at C-4 and C-5 and affinity enhanced by halo substituents. Electron withdrawing groups at C-4 and C-5 enhanced activity. The pyrrole analog **51** was the most potent analog at the Gly_N receptor (pK_i = 7.95). Interestingly, **51** showed *in vivo* activity when administered either i.v. or p.o. Compound **52** was a development candidate for Glaxo-Wellcome at one time (118). Pharmacological characterization of MDL-105519 (**53**), a related indole-based NMDA receptor glycine site antagonist, showed anticonvulsant and anxiolytic effects *in vivo* (119). As with other glycine site antagonists, no effect on mesolimbic dopamine turnover was observed, limiting the possibility that it will cause psychotomimetic side effects.

Extensive studies yielded potent Gly_N antagonists related to L-701324 (**54**) (120-122). These compounds have promising effects as neuroprotectants, anticonvulsants and antipsychotics. From a design perspective, they have the ability to widely distribute the incipient



53 MDL-105,519



54 L-701324

negative charge through resonance and, thus, facilitate penetration of the blood-brain barrier. A pharmacophore model was developed based upon this series of compounds. There is compelling evidence that a ligand/receptor hydrogen bond interaction exists between an acceptor attached to the 4-position of the ligand and a hydrogen bond donor attached to the receptor. Analogs related to L-701324 have been shown to have very low nanomolar affinity for the glycine site, and are anticonvulsants with oral activity *in vivo*. However, it is unclear whether clinical development will be aggressively pursued for any of the compounds in this series.

Conclusions

A variety of AMPA and Gly_N receptor antagonists have been synthesized and tested successfully in various *in vitro* and *in vivo* models. Several of these compounds, such as ZK-200775, PNQX, YM-90K, ACEA-1021 and L-701324, show promise in terms of their therapeutic potential and are being evaluated for the treatment of stroke, head trauma and convulsions. However, most of these compounds need to have better physical properties to show good development potential, especially for oral administration. The design and evaluation of compounds with better pharmacodynamic properties, such as solubility and LogP values, is imperative. The area of noncompetitive AMPA and NMDA antagonists also needs to be further developed with the expectation that other molecular templates with the desired physical properties will emerge from that class and also present newer opportunities in terms of other pathophysiological indications.

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