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α-Amino-3-hydroxy-5-methyl-4-isoxazolepropionic Acid (AMPA) Antagonists: From Bench to Bedside

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Introduction

Glutamate, the major excitatory neurotransmitter in the central nervous system (CNS[a]), is essential for numerous brain functions, including learning and memory. Yet excess glutamate, released after acute CNS injury or during chronic disease, causes massive cell death in gray and white matter. Both the physiological and pathological effects of glutamate are mediated by a large family of glutamate receptors consisting of ionotropic [*N*-methyl-D-aspartate (NMDA), AMPA, and kainate (KA) receptors] and G-protein-coupled metabotropic glutamate receptors. AMPA receptors (AMPAR) are essential for numerous physiological functions in the mammalian nervous system. They are involved in basal excitatory synaptic transmission and forms of synaptic plasticity, which are thought to be necessary for learning and memory. AMPARs present in the spinal cord play a pivotal role in pain transmission and seem to be involved in neuronal plasticity that accompanies sensitization to pain. AMPARs antagonists therefore possess potential as therapeutic drugs for the treatment of neurological disorders (e.g., epilepsy, schizophrenia, and pain). In addition, it has been well established that overstimulation of AMPARs can induce Ca^{2+} overload in cells, which potentially can lead to cell damage and death. These processes are relevant for a larger number of acute and chronic neurodegenerative pathologies such as cerebral ischemia, amyotrophic lateral sclerosis, and Parkinson's disease. AMPA receptor subtypes therefore represent potential targets for therapeutic intervention in many neurological diseases. The present Perspective deals with drugs that act as inhibitors of AMPA receptors and cites evidence for their therapeutic effectiveness in clinical trials. It will also discuss the proposed mechanisms of action and the implications thereof for our current understanding of the biomolecular basis of these pathologies.

AMPA Receptors Description

On the basis of pharmacology and amino acid sequence homology, the ionotropic glutamate receptors are subdivided in families that are classified as kainate, AMPA, and NMDA receptor subtypes. In rodents and humans there are four AMPA receptor subunit (GluR1−4) genes, five kainate receptor subunit (GluR5−7, KA1, KA2) genes, and seven NMDA receptor subunits (NR1, NR2A−D, NR3A,B) genes (for comprehensive reviews, see refs 1−3). These genes were originally identified by molecular cloning. The four AMPA receptor subunits share 68−73% amino acid sequence identity. There is also substantial sequence homology between members of the kainate and AMPA subtypes, while both are clearly distinct from members of the NMDA class.[2,3] Owing to the availability of whole genomes of mice, rats, and humans, it is not expected that further subtypes will be discovered.[3]

AMPA receptors are tetramers composed of the four homologous subunits GluR1−4, assembled as either homomeric or heteromeric complexes that form a cation channel. Upon binding of two molecules of the neurotransmitter glutamate, AMPA receptors undergo conformational changes leading to rapid activation of the channel, allowing an influx of cations into cells. This activation is followed by a rapid desensitization.

Functional diversity in ionotropic glutamate receptors is produced via alternative splicing of exons and by editing of pre-mRNAtranscripts.[2] C-Terminus splice variants are found in the GluR2 and GluR4 subunits. Each subunit exists in a "flip" and "flop" form due to alternative splicing before the transmembranal TM4 segment. The AMPA receptor subunits consist of a long extracellular amino terminus and a short intracellular C-terminus. Both termini are joined via three transmembrane spanning domains (TM1, TM3, and TM4) and a re-entry loop (M2) that links TM1 and TM3. The glutamate binding site where both competitive agonists and antagonists bind is composed of two disconnected extracellular domains S1 and S2 as illustrated in Figure 1. A proportion of

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[a]Abbreviations: 5-HT1B, serotonin receptor 1B; 5-HT2A, serotonin receptor 2A; ADAR2, adenosine deaminase acting on RNA-2; ALS, amyotrophic lateral sclerosis; AMPA, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; AMPAR, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptors; ATPA, 2-amino-3-(5-*tert*-butyl-3-hydroxy-4-isoxazolyl)propionic acid; CA1, cornu Ammonis area 1; CNS, central nervous system; CSF, cerebrospinal fluid; DBA2, dilute brown nonagouti; DOI, 1-[2,5-dimethoxy-4-iodophenyl]-2-aminopropane; EAE, experimental autoimmune encephalomyelitis; GABA, γ-aminobutyric acid; GAD67, glutamic acid decarboxylase; GluR1−4, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor subunit genes 1−4; GluR5−7, kainate receptor subunit (GluR5−7, KA1, KA2) genes 5−7; HEK293, human embryonic kidney 293; hOAT1−4, human organic anion transporters 1−4; KA, kainate; M2, re-entry loop; MCAO, middle cerebral artery occlusion; MES, maximal electroshock seizure; MTD, maximum tolerated dose; NIHSS, National Institutes of Health Stroke Scale; NR1, *N*-methyl-D-aspartate receptor subunit gene 1; NR2A−D, *N*-methyl-D-aspartate receptor subunit genes 2A−D; NR3A,B, *N*-methyl-D-aspartate receptor subunit genes 3A,B; PTZ, pentylenetetrazol; MS, multiple sclerosis; NMDA, *N*-methyl-D-aspartate; PDN, painful diabetic neuropathy; PHN, postherpetic neuralgia; SAR, structure−activity relationship; S1,2, extracellular domains 1 and 2; TBI, traumatic brain injury; TM1−4 transmembrane spanning domains 1−4; VH, ventral hippocampus.

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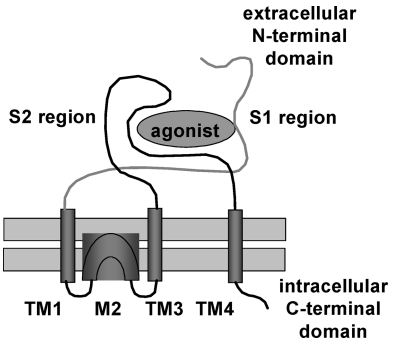


Figure 1. Schematic drawing of the AMPA receptor.

GluR2 subunits have a long C-terminus, and some GluR4 subunits have a shorter C-terminus.

The mRNA coding for the GluR2 subunit is subject to enzymatic modification by the enzyme adenosine deaminase acting on RNA-2 (ADAR2[4,5]). This RNA editing process alters the amino acid sequence around the ionic pore and thereby affects Ca^{2+} permeability.[2,5] As a consequence of the RNA editing, the GluR2 subunit occurs in two versions, termed Q/R, depending on whether glutamine (Q) or arginine (R) is inserted. The unedited, original Q form of the GluR2 receptor is expressed in embryos and allows Ca^{2+} passage, whereas the R version of the GluR2 subunit, expressed in the postembryonic stage, is Ca^{2+} impermeable. While heteromeric AMPA receptor channels lacking GluR2 are Ca^{2+} permeable, channels containing the dominant GluR2-R form do not conduct Ca^{2+} (for review, see ref 6). The subunit composition thus strongly influences the functional properties. Absence of the GluR2 subunit in the heteromeric channel complex, or its presence in the unedited form, may have pathophysiological consequences because high intracellular levels of Ca^{2+} can lead to cell death.

The kinetic properties of the channels also depend on the subunit composition. Among the homomeric receptors, the GluR4 flop channel shows the fastest desensitization and the GluR3 flip channel the slowest one. Desensitization is also effected by RNA editing at an R/G (arginine/glycine) site. Furthermore, AMPA receptors are dynamically regulated by phosphorylation.[7−10]

AMPA Receptors Distribution

AMPA receptors are abundantly expressed in human brain.[11] High levels GluR2-containing AMPA receptor complexes are found in rat and human cortex and hippocampus and in cerebellar granule cells, thalamic nuclei, brain stem, and retina. Conversely, in certain basal ganglia-related structures (subthalamic nucleus, lateral habenula, Purkinje cells in the cerebellum) GluR1 is the predominant subtype.[11,12] AMPA receptors are expressed on pyramidal neurons, interneurons, oligodendrocytes, and glial cells. Subsets of cortical and hippocampal interneurons and pyramidal cells express AMPA receptor complexes that lack the GluR2 subunit and thus are particularly vulnerable to excitotoxicity.[13,14] Similarly, Ca^{2+}-permeable AMPA and kainate receptors expressed in oligodendrocytes may contribute to excitotoxicity of white matter.[15]

Biological Functions of AMPA Receptors

A good overview of what happens if AMPA/KA receptors are overstimulated is provided by accounts of domoic acid intoxication. Domoic acid is a potent agonist at KA and AMPA receptors[16] and was identified as the toxin responsible for an outbreak of human poisoning that occurred in Canada in 1987 following consumption of contaminated blue mussels.[17] In the acute phase of intoxication patients had headache, seizures, hemiparesis, ophtalmoplegia, and abnormalities in arousal. Several months later the patients suffered from neuronopathy and anterograde memory deficits. Autopsy of patients who died within a few months after intoxication demonstrated neuronal necrosis and loss of hippocampus and amygdala.[17] Similar patterns were seen experimentally in animals after administration of domoic or kainic acid.[18] Experiments in rodents and nonhuman primates indicate that the area postrema is a target for domoic acid.[18,19] Consistent with the presence of AMPA receptors in the retina, retinal lesions were noted in sea lions that died from shellfish intoxication. In monkeys, emesis, neuronal, and glial cell toxicity, degeneration of the limbic system, and degeneration of the retina were described.[19]

Psychosis and Schizophrenia

Rats that were administered domoic acid displayed behaviors like head twitching, scratching, and wet dog shakes and went on to develop full tonic−clonic convulsions.[20] This is interesting, since head twitching, scratching, and wet dog shake behavior is also seen in rodents following administration of hallucinogenic 5-HT2A receptor agonists like mescaline, psylocibin, or 1-[2,5-dimethoxy-4-iodophenyl]-2-aminopropane (DOI). In a study in rats, DOI increased FOS expression in the somatosensory cortex (an area involved in visual hallucinations) via an indirect mechanism involving activation of thalamocortical glutamatergic neurons, with subsequent stimulation of postsynaptic AMPA/KA receptors. The DOI-induced FOS response was blocked by the AMPA/KA receptor antagonist **21**,[21] suggesting that visual hallucinations provoked by 5HT2A receptor agonists might involve AMPA/KA receptors. Also, NMDA channel blockers (e.g., ketamine, phencyclidine) provoke psychotic effects in humans,[22−24] and this response again may involve AMPA receptor activation. Two very similar mechanisms are proposed for acute and chronic psychotic responses to NMDA blockade.[25] Acute NMDA blockade silences the activation of GABAergic interneurons, leading to a disinhibition of pyramidal neurons with increased glutamate release and activation of non-NMDA glutamate receptors.[26] Chronic administration with NMDA antagonists interrupts a feedback mechanism via NMDA-NR2A receptors, leading to suppression of parvalbumin and glutamic acid decarboxylase (GAD67) gene transcription in a crucial group of interneurons.[25,27] Down-regulation of GAD67, a major γ-aminobutyric acid (GABA) synthesizing enzyme, will suppress the GABAergic tone upon pyramidal cells, leading to hyperexcitation with increased glutamate release.[28] Indeed, chronic NMDA blockade in rodents was shown to induce neurotoxicity via AMPA/KA receptor activation.[29,30] Although not identical, there is a remarkable similarity between ketamine-induced effects and the positive, negative, and cognitive symptoms of schizophrenia. This has led to the hypothesis that in schizophrenia neurotransmission at NMDA receptors might be impaired. There are indeed several strong hints for a NMDA receptor hypofunction in schizophrenia. For instance, expression of the NR2A subunit is diminished for up to 50% in a subset of parvalbumin-positive interneurons,[31]

while diminished expression of GAD67 and parvalbumin is one of the most replicated observations in schizophrenia literature.[32−34] When the clinical and preclinical data sets are combined, it is conceivable that excessive glutamate release with subsequent activation of AMPA/KA receptors could be involved in the induction of psychoses in schizophrenia. In this respect, it is also worth mentioning that schizophrenia patients are more prone to seizures, whereas patients with temporal lobe epilepsy often suffer from psychoses that are almost indistinguishable from those in schizophrenia.[35]

Epilepsy

AMPA receptor antagonists are currently in clinical development as antiepileptic drugs (AEDs), and there is evidence from various sources that this mechanism of action is likely to be of therapeutic use in epilepsy. First, AMPA receptor antagonists prevent the excessive neuronal activation leading to epileptic seizures.[36] Second, they potently and efficiently block seizures in animal models of seizures and epilepsy.[37] Third, changes in the distribution, expression, and editing of AMPA receptors have been reported in human epileptic hippocampal tissue.[38] Fourth, in Rasmussen's encephalitis, an autoimmune disease, one of the autoantigens causing the disease, is directed against the AMPA GluR3 receptor.[39] By use of radioligand binding assays, it was shown that AMPA receptors were up-regulated in neocortical tissue removed during surgery for treatment of pharmacoresistant focal epilepsy. In contrast, binding sites to **42** (NMDA receptor, MK-801) (Figure 15), kainate (KA receptor), and muscimol ($GABA_A$ receptor) were not changed.[40] In tissue resectioned from children with intractable epilepsy, dense immunostaining for the GluR1 and GluR2/3 was found in patients with medial temporal lobe epilepsy in comparison to patients with lateral temporal lobe epilepsy. It was suggested that changes in the expression of AMPA receptors appear early in temporal lobe epilepsy and that these changes contribute to synaptic rearrangement (mossy fiber sprouting) in the hippocampus. These pre- and postsynaptic changes could be the basis for hyperexcitability in temporal lobe epilepsy.[41] Furthermore, in patients with temporal lobe epilepsy, editing at the GluR2 R/G site is altered. The relative amount of edited RNA in epileptic hippocampal tissue was increased by 20% while the flip-flop ratio was unaffected. The G-form of the AMPA receptor has an effect on the desensitization kinetics and a faster recovery rate from desensitization compared to the R form. Therefore, a higher proportion of the G-form could result in enhanced synaptic transmission.[38]

Cytoprotection of Oligodendrocytes

Experiments with oligodendrocytes from mouse forebrain, rat optic nerve, or rat spinal cord show that AMPA and kainate receptors are involved in glutamate-induced excitotoxicity. The main AMPA receptor subunits expressed in oligodendrocytes cultured from optic nerve and spinal cord were GluR3 and GluR4.[42,43] Oligodendrocyte cell death was prevented by incubation with AMPA/KA antagonists like **1** (CNQX), **2** (NBQX) (Figure 2), 7*H*-1,3-dioxolo[4,5-*h*][2,3]benzodiazepine-7-carboxamide, or 5-(4-aminophenyl)-8,9-dihydro-*N*,8-dimethyl-, monohydrochloride (GYKI53655).[15,43,44] In animal experiments AMPA/KA antagonists reduced white matter loss caused by middle cerebral artery occlusion (a model for stroke) and spinal cord injury.[45,46]

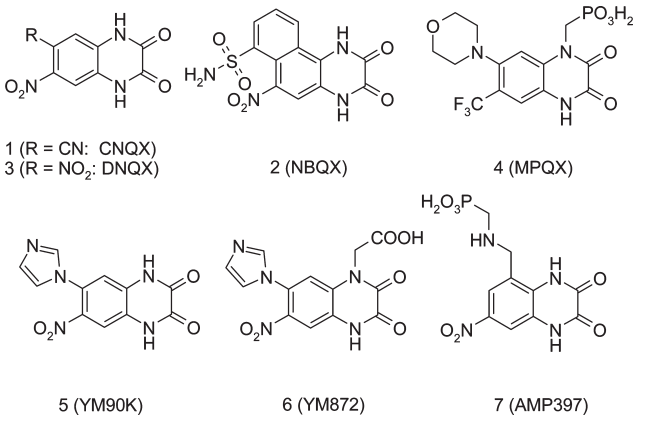


Figure 2. Structures of representative quinoxalinediones.

AMPA receptor activation may play a role in inflammatory demyelinating disease such as multiple sclerosis. In inflammatory demyelinating lesions glutamate could be present because of liberation from activated microglia, lymphocytes, and macrophages.[47,48] Several reports have shown that blockade of AMPA/KA receptors reduced synaptic, axonal, and oligodendrocyte pathology in the experimental autoimmune encephalomyelitis (EAE) rodent model of multiple sclerosis.[49−51] Given these results and the fact that the pharmacotherapy of multiple sclerosis is at best only partially effective, safe AMPA antagonists might represent a useful extension to the therapeutic arsenal.

Cytoprotection of Neurons

Amyotrophic lateral sclerosis (ALS) appears in two forms: the sporadic form, which accounts for about 95% of all cases, and the familiar form.[52] The fALS mouse, carrying mutations in the superoxide dismutase gene, is used to study the hereditary form of ALS, whereas there is no animal model for the sporadic form of ALS. Recent evidence suggests that altered GluR2 editing plays a role in motor neuron death in the sporadic form of ALS.[53] By use of laser microdissection technologies, single motor neurons were isolated from five ALS patients and the GluR2 editing status was analyzed. In motor neurons of ALS patients, the GluR2 editing efficiency was incomplete in comparison to normal control subjects. Incomplete GluR2 editing could result in an increased Ca^{2+} load of the motor neurons and may contribute to the motor neuron loss in ALS patients. This hypothesis is supported by results obtained with mice, transgenic for GluR2 receptors that are permeable to Ca^{2+}. These mice develop a motor neuron disease late in life.[54]

There is evidence that glutamate induces massive Ca^{2+} flow into neurons under pathological conditions such as ischemia which lead to cell death.[55] Glutamate induced Ca^{2+} entry could be mediated by NMDA receptors, Ca^{2+}-permeable AMPA receptors, and voltage gated Ca^{2+} channels. As mentioned before, heteromeric AMPA receptors containing the GluR2 subunit are Ca^{2+} impermeable. However, following transient forebrain ischemia, the expression of the GluR2 subunits is reduced in hippocampal CA1 neurons at a time that precedes their degeneration.[56] This change in the expression pattern of AMPA receptor subunits could be the mechanism of delayed cell death in the cornu Ammonis area 1 (CA1) area.[57]

Pain

There are at least two kinds of pain in which AMPA/KA receptors may be involved. Injury of peripheral nerves can give rise to chronic pain. In rats, this neuropathic pain is blocked by AMPA inhibitors, alone or in combination with NMDA inhibitors. The relevant AMPA subunit involved is likely the GluR2, since sciatic nerve ligation in rats caused an up-regulation of GluR2 AMPA receptor subunits in primary afferent synapses in the spinal cord.[58,59] Involvement of spinal AMPA receptors in pain transmission is also indicated by two reports where intrathecally applied AMPA antagonists, ACEA 2085 (structure not disclosed), the butanediamide, *N*1-[5-[[3-[[4-[(3-aminopropyl)amino]butyl]amino]-1-oxopropyl]amino]pentyl]-2-[2-[(2,4-dihydroxyphenyl)acetyl]-amino]-, (2*S*)- (Joro spider toxin, JSTx), inhibited thermally induced pain.[60,61]

The second kind of pain in which non-NMDA ionotropic glutamate receptors play a role involves activation of sensory nerves by central or peripheral inflammatory processes. In rat models of migraine, trigeminal nerves innervating meningeal blood vessels are activated by electrical, chemical, or immunological stimuli, creating a local inflammatory response, release of neurokinins and calcitonin-gene related peptide, plasma extravasation, and activation of the trigeminal nucleus caudalis (e.g., measured by c-fos expression).[62] Ionotropic glutamate receptor subtypes present on trigeminal ganglia have been identified as heteromeric GluR5/KA2 kainate receptors.[63] Consistent with the notion that kainate receptors are involved in trigeminal nerve excitation is the finding that AMPA/KA antagonists with relative selectivity toward the GluR5 subunit were efficacious in blocking dural plasma extravasation or c-fos expression in the trigeminal ganglion.[64] A further hint that GluR5 containing kainate receptors are relevant for inflammatory pain is provided by a report that formalin-induced pain in rats was inhibited by compounds preferentially blocking kainate receptors, nonselective AMPA/KA blockers, but not by selective AMPA inhibitors.[65] From motivation by these data, AMPA/KA antagonists are now being developed for analgesia in humans.

AMPA Receptor Antagonists

Quinoxalinediones. The quinoxalinediones represent an important class of AMPA antagonists, introduced 1988 with the two compounds **1** and **3** (Figure 2).[66] Many academic institutions and pharmaceutical companies embarked on this scaffold, searching for derivatives endowed with drug-like properties. A milestone was achieved with the discovery of **2**, the first quinoxalinedione derivative with high affinity at the AMPA receptor and a more than 30-fold selectivity for AMPA versus kainate receptors. **2**, initially planned for clinical studies, was only given to healthy volunteers for the investigation of its pharmacokinetic profile, but it was not further pursued to therapeutic studies, at least in part because of its preclinically assessed nephrotoxicity.

First, clinical data from patients were obtained with the quinoxalinediones **4** (ZK 200775),[83] **5**,[76] **6** (YM872, zonampanel),[77] and **7**[85] (Figure 2). As shown by the data in Table 1, these four compounds, together with **1**, **2**, and **3**, are high affinity, competitive AMPA receptor antagonists with some lower affinity to kainate receptors and no or only marginal affinity to the NMDA receptor complex.

NBQX (2). Although not developed for humans, **2** was and still is an important tool and reference compound. It was tested by numerous research groups in a variety of animal models for different indications, e.g., epilepsy, pain, head trauma, or brain ischemia. In particular, models for neuroprotection were extensively used and the compound was investigated with variation of many parameters such as the animal species, mode of occlusion, onset of reperfusion, dose, and regimen of drug administration, and survival time.[67] **2** was shown to be protective in some paradigms even when given with a delay of several hours after the induction of cerebral ischemia, a key factor for the therapeutic usefulness of neuroprotective drugs. Thus, in the transient two-vessel occlusion model in Mongolian gerbils, statistically significant protection of the CA1 subfield of the hippocampus was observed.[68,69] Similar findings were observed in the four-vessel occlusion model in rats.[70] Further support for the neuroprotective effects of **2** in a clinically relevant situation was obtained by using spontaneously hypertensive rats in the transient focal ischemia paradigm. When infused over a period of 4 h starting 1 h after occlusion, 30% of protection was attained.[71] On the other hand, in a dog model of transient ischemia, **2** when given as an intravenous infusion 5 min after ischemia (1 mg/kg bolus, followed by 3 (mg/kg)/h for 4 h) did not improve neurological functions and did not reduce histological damage in parietal cortex and hippocampus.[72]

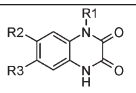
Whereas the anticonvulsant activity of competitive NMDA antagonists in a wide range of seizure models was already known in the early 1980s of the past century, because of the lack of selective AMPA antagonists, it was not clear whether cerebral seizures would also be suppressed by inhibition of AMPA receptor mediated neurotransmission. This was positively shown with **2** which inhibited sound-induced clonic seizures in DBA2 mice with an ED_{50} of 27.8 mg/kg ip.[73] In the maximal electroshock seizures in mice, a more translational anticonvulsant model for humans, **2** with 25 mg/kg iv administration prevented convulsions for 10 s to 3 min, but no anticonvulsant action was seen 10 min or more after dosing. Interestingly, pretreatment of the animals with the organic anion transport inhibitor probenecid extended the protective effect of **2** to 120 min. This result suggests that **2** is rapidly cleared from plasma by transporters sensitive to probenecid.[74] In the amygdala kindling paradigm in rats, a model for human complex partial seizures with secondary generalization, **2** with 40 mg/kg ip administration reduced the after-discharge duration of previously kindled rats 0.5−2 h after injection. It is of interest that **2**, applied at similar doses, has much weaker effects in hippocampus kindled rats. Given the higher density of AMPA

Table 1. Affinities of Quinoxalinediones at Ionotropic Glutamate Receptors in Rat Cortical Membranes

	K_i or IC_{50} (μM)			
	receptor, radioligand		NMDA receptor complex	
	AMPA, [^{3}H]AMPA	kainate, [^{3}H]kainate	glutamate site	glycine site
1[f]	IC_{50} = 0.30	IC_{50} = 1.5	IC_{50} = 25[a]	IC_{50} = 14[d]
3[f]	IC_{50} = 0.50	IC_{50} = 2.0	IC_{50} = 40[a]	IC_{50} = 9.5[d]
2[f]	IC_{50} = 0.15	IC_{50} = 4.8	IC_{50} > 90[a]	IC_{50} > 100[d]
4[g]	IC_{50} = 0.12	IC_{50} = 2.5	IC_{50} = 2.8[a]	IC_{50} = 5.15[d]
5[h]	K_i = 0.084	K_i = 2.2	K_i > 100[b]	K_i = 37[d]
6[i]	K_i = 0.096	IC_{50} = 4.6	IC_{50} > 100[b]	IC_{50} > 100[d]
7[j]	IC_{50} = 0.29	IC_{50} = 4.2	IC_{50} = 0.49[c]	IC_{50} = 1.16[e]

[a] Tritiated ligand CPP. [b] Tritiated ligand glutamate. [c] Tritiated ligand 3-heptenoic acid, 2-amino-4-(phosphonomethyl)-, (3*E*)-(CGP39653). [d] Tritiated ligand glycine. [e] Tritiated ligand **43** (MDL105519, Figure 15). [f] See ref 68. [g] See ref 83. [h] See ref 76. [i] See ref 77. [j] See ref 85.

Table 2. Influence of Substituents on the Affinity of Quinoxalinediones to the AMPA Receptor

				
Compd	**R1**	**R2**	**R3**	**[^{3}H]AMPA Ki [μM]**
8	H	H	H	>100
9	H	NO_2	H	2.0
10	H	CN	H	5.0
11	H		H	1.6
5	H		NO_2	0.084
12	H			0.82

receptors in the hippocampus, larger doses of **2** would probably be required to reduce seizure stage scores and after-discharge durations in this paradigm.[75]

YM90K (5).[76] In an attempt to find a replacement for the cyano and nitro groups of **1** and **3** (Figure 2), researchers at Yamanouchi found imidazolyl as a viable bioisostere, as shown by the comparison of the receptor affinity of compounds **5** and **8**−**12** (Table 2). All three groups led to a similar enhancement of affinity, starting from the virtually inactive, unsubstituted **8**. The imidazole group, however, did not improve solubility, one of the main drawbacks of this compound class. By further attachment of a nitro group in position 6, **5** was obtained with greatly enhanced binding affinity at the AMPA receptor.[76]

5 showed a similar spectrum of anticonvulsant and neuroprotective properties as **2**. In the sound induced seizures in DBA2 mice both compounds were equipotent by icv injection, in line with their almost identical affinity for the AMPA receptor. The duration of action, however, was short in this model, not exceeding 30 min.[77] **5** markedly suppressed duration of after-discharges in amygdala kindled rats (15 and 30 mg/kg ip). Similar to **2**, **5** retarded the development of kindling seizures after pretreatment with 7.5−30 mg/kg ip over 8 days, when administered 60 min before the daily stimulation of the amygdala.[78] In the global ischemia model in gerbils, **5** showed a significant therapeutic time window; it inhibited delayed neuronal death when intraperitoneally administered 6 h after ischemia. In a rat focal ischemia paradigm (permanent occlusion of the left middle cerebral artery) the compound reduced the volume of ischemic damage in the hemispheres and cortex after a bolus injection of 30 mg/kg immediately after the occlusion, followed by infusion at 10 (mg/kg)/h for 4 h. No protective effect against striatal damage was found.[77]

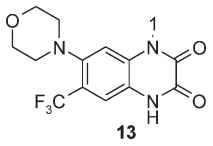
A common property of the first generation of quinoxalinediones, **1**, **2**, and **5**, is their low water solubility around neutral pH (~0.1 mg/mL). In the case of **2** this prevented further development since, after iv infusion at therapeutically effective doses, drug precipitation in the medullary tubules of the kidney occurred. To overcome this issue, quinoxalinediones were prepared carrying acidic chains at different positions of the framework. With this rationale compounds **4**, **6**, and **7** were prepared and found to retain strong affinity to the AMPA receptor with decent selectivity (Table 1).

YM872 (Zonampanel, 6).[77] Attachment of an acetic acid side chain in position 1 of **5** delivers **6** (Figure 2). The binding data (Table 1) show that this side chain very likely does not interact with the AMPA receptor whereas it further enhances selectivity against the NMDA associated glycine site. A high impact is seen on solubility around neutral pH which increases from 0.096 mg/mL (**5**) to 83 mg/mL for **6**.[78] With its excellent potency, selectivity, and solubility, **6** is a good drug candidate for testing in various acute and chronic brain ischemic and antiepileptic paradigms.

The neuroprotective effects have been demonstrated in rats with transient middle cerebral artery occlusion, when **6** was infused immediately after occlusion for 4 h at 20 (mg/kg)/h (55% reduction of infarct volume). Delayed administration was still effective when infusion was started 2 or 3 h after the occlusion (45% and 35% protection, respectively). The drug treated animals showed a better neurological score and a faster improvement from neurological deficits than the control group.[79] **6** also proved to be strongly protective after permanent focal cerebral ischemia in cats (61% protection in the cerebral hemisphere, 63% in the cerebral cortex). The cortical protection obtained in this study is relatively high for an AMPA antagonist and is more typical for NMDA receptor antagonists. However, determination of the cerebrospinal fluid (CSF) concentration of **6** in the protected cats resulted in a value of about 0.22 μM, a concentration at which the drug in vitro blocks AMPA but not NMDA receptors. The efficacy of **6** in a "gyrencephalic" species provides further support for a therapeutic potential of AMPA antagonists in the treatment of acute stroke in humans.[80]

The antiepileptic potential of **6** was assessed in the audiogenic seizure model in DBA2 mice where it had a minimal effective dose of 3 mg/kg after intraperitoneal administration.[80] The antiepileptogenic effect of **6** in amygdala kindled rats was further corroborated by its effects in a rekindling protocol. Whereas there was no difference in the number of stimulations required to reach the first generalized seizures, the after-discharge duration was significantly shortened.[81] On the basis of the observation that **6** after intravenous infusion in humans is rapidly cleared by renal excretion as the unchanged parent compound, a detailed study was performed to identify possible transport mechanisms. In cells from the second portion of the proximal tubule, expressing human organic anion and cation transporters, it was found that **6** competitively inhibits substrate uptake of the organic anion transporters, hOAT1, hOAT3, and hOAT4 with IC_{50} values of 3.0, 6.6 and 300−1000 μM, respectively, thereby binding at the same sites as probenecid and cimetidine. Interestingly, **5**, lacking the acetic acid side chain, showed a very similar profile (IC_{50} values of 3.8 and 4.4 μM for hOAT1 and hOAT3, respectively) but with a noncompetitive interaction to hOAT1.[82]

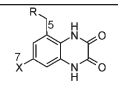
MPQX (ZK 200775, 4).[83] Introduction of a phosphonomethyl side chain at position 1 (**4**, R = $CH_2PO_3H_2$) of

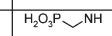
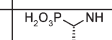
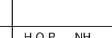


13

Figure 3. Structure of scaffold **13**.

Table 3. Influence of Substituents on Selectivity at AMPA/NMDA-(Gly) Receptors[a]



Compd.	X	R	IC_{50} [μM] [^{3}H]AMPA	IC_{50} [μM] [^{3}H]**43**
7	NO_2		0.29	1.0
14	NO_2		0.17	0.032
15	Br		2.4	0.1

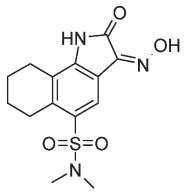
[a] Rat cortical membranes.

quinoxalinedione **13** (Figure 3) has a 2-fold effect: it increases the affinity to the AMPA receptor by a factor of 33 (IC_{50} = 0.12 μM) when compared to the unsubstituted compound (R = H), and it ensures a comfortable solubility of 25 mg/mL at pH 7.35.[83]

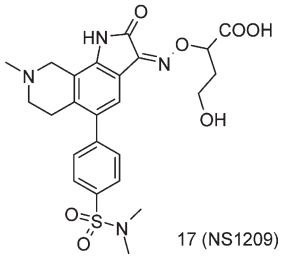
In a model for global ischemia in Mongolian gerbils, **4** showed good protection of the CA1 hippocampal subfield after repeated intraperitoneal injections of 10 mg/kg at 30−210 min postocclusion. It also protected mice and rats after permanent focal ischemia induced by middle cerebral artery occlusion (MCAO). **4** was still active in the permanent focal ischemia model in rats when delayed 1−5 h after the occlusion (19−29% protection, assessed by reduction of whole brain infarct volume). **4** is considered to have a favorable safety profile compared with **2** or **5**, since no major deleterious effects on motor behavior, cardiovascular status, or respiratory system were detected in rats treated with doses up to 10 (mg/kg)/h iv over 6 h.[83] **4** was also shown to be anticonvulsive and analgesic. It inhibited, after iv injection 5 min before electroshock, tonic convulsions in mice with an ED_{50} of 13 mg/kg. In the hot plate test in mice, testing for analgesic effects, **4** after subcutaneous injection was comparable to morphine sulfate.[84]

AMP397 (7).[85] A different series of water-soluble quinoxalinediones was created at Novartis by attaching amino acid side chains in position 5 of the quinoxalinedione scaffold. This resulted in potent dual or selective AMPA/NMDA(glycine) receptor antagonists.[85] The selectivity is influenced by the character of the side chain and even more by the substituent at position 7. For example, **7** with a phosphonoglycine side chain favors the AMPA receptor whereas the closely related compound **14** bearing a phosphonoalanine chain favors the glycine receptor. Even more pronounced, compound **15** with a bromo atom in place of the nitro group has much higher affinity at the glycine than at the AMPA receptor (Table 3).

As expected, **7** display excellent water solubility (6.6 g/L at pH 7.4). As a great exception among the quinoxalinediones, it exhibits oral activity in the maximal E-shock test in mice (ED_{50} of 5 mg/kg at 2 h pretreatment time) as well as in the audiogenic seizure model in DBA2 mice, thereby demonstrating sufficient brain penetration, despite its high polarity (polar surface area of 181 Å^2) and its high ionized fraction at physiological pH.



16



17 (NS1209)

Figure 4. Structures of isatine oximes.

On the basis of the oral activity, **7** was selected for development as an antiepileptic drug. Initially the aromatic nitro group raised concerns about mutagenicity, supported by a weakly positive AMES test in *Salmonella typhimurium*. However, mammalian liver enzymes and in particular mammalian nitroreductases do not metabolize **7** into mutagenic intermediates under conditions of the Ames test. Furthermore, in an extensive in vivo genotoxicity screen in mice and rats, performed after oral administration, **7** behaved cleanly, indicating that no genotoxic metabolites are formed in mammalian cells. The absence of effects in assay testing for gene mutation, for the formation of micronuclei, and for DNA binding on jejunum, colon, and liver confirmed that no reactive intermediates are released into the adjacent intestinal tissue.[86]

Isatin Oximes: NS1209 (SPD502, 17).[87,88] In an attempt to replace the rather insoluble quinoxalinedione scaffold by better soluble variants, Wätjen and Drejer from Neurosearch A/S disclosed a series of isatine oximes as AMPA receptor antagonists.[87] With compound **16** (Figure 4) they reported the first AMPA antagonist with oral activity, blocking AMPA induced seizures in mice with an ED_{50} of 30 mg/kg (30 min pretreatment).

From this class the clinical candidate **17** emerged,[88] a water-soluble isatine oxime carboxylic acid that currently undergoes profiling as an antiepileptic drug after intravenous administration. **17** is highly selective for AMPA receptors, displacing [^{3}H]AMPA in cortical neurons from rats with an IC_{50} of 0.043 μM. No discrimination is seen between the two enantiomers ((*R*)-enantiomer of NS1219, IC_{50} = 0.070 μM; (*S*)-enantiomer of NS1220, IC_{50} = 0.063 μM). In terms of selectivity, **16** shows very weak affinity to kainate receptors (IC_{50} = 81 μM) but is inactive at NMDA receptors and its glycine site, as it does not displace [^{3}H]**44** ([^{3}H]CGS19755, Figure 15) or [^{3}H]glycine up to 30 μM. In an in vitro electrophysiological assay using cultured mouse cortical neurons, **16** inhibited AMPA triggered spikes in the presence of cyclothiazide with an IC_{50} of 0.15 μM. The reduction of AMPA induced neutrotransmission by **17** was also confirmed in vivo. In rats an intravenous bolus injection of **17** reduced the AMPA-evoked spikes by 86% with an ED_{50} of 6.1 mg/kg and a duration of action of about 2 h. In the maximal E-shock test in mice a single intravenous injection of 60 mg/kg of **17** resulted in full protection from tonic convulsions for a duration of up to 90 min. The potential of **17** for use as an antiepileptic was further supported by the finding that status epilepticus in rats was interrupted by bolus injection (30 mg/kg ip) followed by

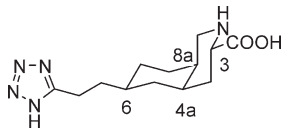


Figure 5. Structure of **18** (LY293558, tezampanel).

infusion of 5 (mg/kg)/h for 2 h. Within the first 30 min the disruption of status epilepticus was faster and more complete than with diazepam.[89]

17 was shown to be neuroprotective in several animal models of brain ischemia. In the transient two-vessel occlusion assay in gerbils, a model for global cerebral ischemia, a highly significant protection of hippocampal neurons was observed with a 10 mg/kg intravenous bolus of **17** when applied immediately after reperfusion and followed by a 2 h infusion. Neuroprotection was obtained even when the treatment was started 2 h after the insult. In a model of transient focal ischemia in rats, **17** protected axons, oligodendrocytes, and percaryal neurons in the cerebral cortex after intravenous administration 15 min before occlusion of the middle cerebral arteria. However, as observed with many other glutamate receptor antagonists in neuroprotective paradigms, no protection of subcortical regions was obtained.[90]

AMPA receptors are known to play a role in the central sensitization and nociceptive transmission after noxious and allodynic stimuli. **17** was tested in rat pain models for acute, persistent, and neuropathic pain and was found in all three paradigms to be an effective analgesic after intraperitoneal and subcutaneous administration.[91]

LY-293558 (Tezampanel, 18).[92] In the course of a program aimed at the identification of potent NMDA receptor antagonists, investigators at Eli Lilly published a series of 6-substituted decahydroisoquinoline-3-carboxylic acids that are mixed antagonists at NMDA, AMPA, and kainate receptors. The most interesting compound of the series in terms of potency and selectivity at AMPA receptors is the systemically active, water-soluble **18** (Figure 5), a pure enantiomer with a tetrazoleethyl group in position 6 of the perhydroisoquinoline scaffold.[92]

Many analogues were prepared and tested for affinity and potency at glutamate receptors with the result that **18** appears to be rather optimized for binding at AMPA receptors. Trans fusion of the decahydroisoquinoline ring system leads to inactive compounds, while the 6-epimer has reduced AMPA affinity. The (*R*)-configuration at the stereocenter 3 abolishes all activity. The tetrazole group was the best selection among a variety of polar groups such as carboxylic, phosphonic, and sulfonic acids or other five-membered heterocyclic ring acids.[93] A striking feature of the structure−activity relationship (SAR) is the influence of the chain linking the tetrazole ring to the bicyclic nucleus. Elongation of the chain (to propyl, butyl, thiomethyl, or methoxymethyl) as well as its shortening to a single methylene group or direct attachment of the tetrazole to the scaffold reduces AMPA affinity and/or diminishes the selectivity over the NMDA receptor. Oxygen or nitrogen substitution in the ethylene spacer at the position adjacent to the bicyclic ring system increases NMDA receptor affinity, whereas compounds with alkyl or phenyl substitution on either carbon atom have similar activity and selectivity as **18**.[94,95] The simple ethyl linker was also shown to be superior to aromatic rings, although a phenyl ring para-substituted by the tetrazole and the bicyclic nucleus leads to the same AMPA receptor affinity as with **18**. The functional potency, however, is 10 times weaker.[96] **18** displaced the binding of [^{3}H]AMPA, [^{3}H]kainate, and the NMDA receptor ligand [^{3}H]**44** in rat brain membranes with IC_{50} values of 1.3, 28.1, and 12.1 μM, respectively, whereas the enantiomer of **18** was inactive up to 100 μM.[97] Binding affinities for the AMPA and kainate receptor subtypes, expressed as K_i values, are reported to be 9.2, 3.2, 32, 50.5, 4.2, > 100, and > 100 μM for GluR1, GluR2, GluR3, GluR4, GluR5, GluR6, and GluR7, respectively.[98] Functional potencies of **18** for inhibition of glutamate-induced calcium influx in human embryonic kidney (HEK293) cells expressing recombinant AMPA and kainate receptors demonstrated significant differences: the highest potency was found at GluR5 (K_b = 0.2 μM), the lowest at GluR6 (< 20% inhibition at 100 μM), and for the AMPA subtypes K_b values of approximately 1, 0.7, 1, and 17 μM were determined for GluR1, -2, -3, and -4, respectively.[99] In addition, the affinity of **18** to GluR5 receptors is corroborated by the fact that it inhibited kainate induced currents in dorsal root ganglions of young rats (pK_B = 6.24), a region predominantly expressing GluR5 receptors. The same pK_B value is reported for inhibition of kainate evoked currents in human GluR5 receptors stably expressed in HEK293 cells.[100] The 10-fold selectivity of **18** for AMPA over NMDA receptors was confirmed in the rat cortical wedge preparation. Submicromolar potency of **18** was also shown in whole cell voltage clamp recordings from cerebellar Purkinje neurons where currents evoked by AMPA were inhibited with an inhibition constant (K_i) of 0.68 μM.[97] The in vitro profile of **18** as a mixed AMPA/kainate but only weak NMDA antagonist is consistent with the observation that relatively high doses of **18** do not block NMDA lethality in mice, whereas lower doses prevent rigidity in mice induced by the selective GluR5 agonist 2-amino-3-(5-*tert*-butyl-3-hydroxy-4-isoxazolyl)propionic acid (ATPA, structure not shown).[92]

The therapeutic potential of **18** was tested in several animal models. The compound inhibited E-shock convulsions in mice with an ED_{50} of 2.9 mg/kg ip. No activity was found after oral dosing of up to 320 mg/kg.[97] Neuroprotective effectiveness was assessed in focal ischemia in rats with the racemate **19** and, using the enantiomer **18**, in focal ischemia in cats and in global ischemia in gerbils. In the first paradigm, significant reduction of infarct volume was achieved (25% and 31%) in hemisphere and cortex, but caudate was not protected.[101] In the cat focal ischemia model a lower but still significant degree of protection (18% in the cerebral hemisphere and 19% in the cerebral cortex) was obtained, whereby a direct comparison is not easy because of the subtle differences in experimental design.[102] In the global ischemia model where gerbils were made ischemic by transient occlusion of both carotid arteries, **18** provided 56% protection of the CA1 subfield of the hippocampus. The dose regimen consisted of intraperitoneal administration of 20 mg/kg 30 min before occlusion, followed by four further injections of 10 mg/kg at 3 h intervals. No protection was obtained when **18** was injected 90 min after the occlusion, followed by four further injections.[95]

Because of its dual mechanism as an AMPA/kainate antagonist, it was of particular interest to test **18** in animal models of pain, as there is increasing evidence that inhibition of GluR5 receptors produces antinociception.[103] In fact, **18** proved to be very efficacious in the capsaicin induced mechanical hyperalgesia test in rats, as it increased latency

for withdrawal of hind paw from light touch with an IC_{50} of 4 mg/kg after subcutaneous administration. The role of kainate receptors to the analgesic effect in this test was supported by testing structurally closely related but kainate receptor selective analogues of **18** which, after intracisternal administration, showed inhibition of allodynia with the same rank order of potencies as for the inhibition of GluR5 receptors in vitro.[104] In rat models of evoked postoperative pain, **18** was active after intrathecal and epidural injection. AMPA/kainate receptor antagonists might therefore have the potential to extend the medicinal armamentarium against evoked postoperative pain, a condition resistant to opioid treatment.[105] Consistent with the postulated role of kainate receptors in pain transmission, **18** was also effective in preventing plasma protein extravasation in the rat dura, a putative preclinical model of migraine. In a direct comparison with selective kainate antagonists of the same compound class, the rank order of potency followed the affinity for GluR5 receptors, emphasizing their role in migraine.[106]

On the basis of the hypothesis that AMPA and kainate receptors may play an important role in mediating the psychotomimetic effects of NMDA antagonists, **18** was also tested in rats containing a ventral hippocampus (VH) lesion that was induced by local administration of ibotenic acid at the age of 7 days. This animal model reflects dopamine dependent behaviors such as hyperlocomotion after D-amphetamine or **42**, enhanced stereotypy after apomorphine, or deficits in prepulse inhibition of startle. Subcutaneous administration of **42** significantly increases locomotion and stereotypies in these animals, which both can be prevented by pretreatment with neuroleptic drugs. Whereas **18** did not affect **42**-induced locomotor activity in the sham operated rats, the compound significantly reduced **42**-induced hyperlocomotion as well as stereotypies in the lesioned rats. These findings indicate that VH lesion in rats, causing symptoms reminiscent of schizophrenia, may modulate AMPA/kainate receptors, suggesting an important role of these receptors in psychoses.[107] Soon after the discovery of **18** its anxiolytic-like activity was demonstrated in a punished responding paradigm in pigeons, a species particularly sensitive to certain anxiolytic agents.[108] The findings were further corroborated in rats, where 10 mg/kg **18** after intraperitoneal administration increased punished responding to about the same degree as chlordiazepoxide. The data show that non-NMDA receptors might be a drug target for anxiolytics, but more selective drugs would be required to sort out the relevance of each receptor subtype.[109]

Furthermore, a contribution of AMPA receptors to opiate dependence is also well established. Recently it was shown that naloxone-precipitated jumping of heroin dependent mice (considered as readout for withdrawal symptoms) was attenuated by continuous subcutaneous infusion of **18**. The compound was active under the same delivery protocols as the NMDA channel blocker **42**, and it is conceivable that the reduction of the heroin dependence by this AMPA antagonist is eventually caused by an AMPA-mediated decrease in NMDA receptor activity. More detailed animal studies are needed to allow an estimation of the prospects for AMPA antagonists as potential treatments of drug abuse and dependence.[110]

Quinazolinediones. Researchers at Novartis introduced substituted 2,4-quinazolinediones as a novel class of orally active, competitive AMPA receptor antagonists. Some of the compounds are also antagonists at the NMDA receptor associated glycine site. The ring system is substituted in position 3 by an alkylsulfonamido group, resulting in a pK_a of about 6.9. The chloro-substituted compound **20** (R = H, R′ = Cl, Figure 6) has low micromolar affinity at both receptors and inhibits E-shock induced tonic seizures in mice after oral administration with an ED_{50} of 40 mg/kg after 60 min of pretreatment time.[111] Two follow-up patents[112,113] describe a wide range of derivatives with substituents in positions 6 and 7 of the scaffold and claim high potency at AMPA receptors among the enclosed examples. Selected compounds are currently in development.

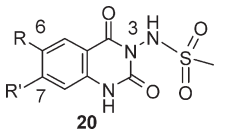


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Figure 6. Substituted 2,4-quinazolinediones.

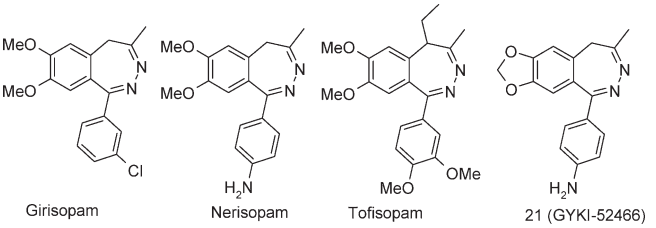


Figure 7. 2,3-Benzodiazepine analogues with various pharmacology.

Noncompetitive AMPA Antagonists

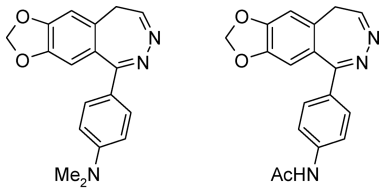
In addition to the competitive AMPA antagonists, another class of compounds that blocks the AMPA receptors via an allosteric binding site was first described in the early 1990s.[114] For certain indications, where the endogenous glutamate level is very high, such noncompetitive AMPA antagonists may have the advantage of retaining good efficacy.[115] Furthermore, the structure of this class of compounds suggested that this novel allosteric binding site might be less hydrophilic than its orthosteric counterpart, providing an opportunity to develop orally active AMPA antagonists with more favorable physicochemical properties and better brain exposure.

2,3-Benzodiazepine Derivatives. The discovery of **21** (GYKI52466),[116] the first noncompetitive AMPA antagonist reported in the literature, is remarkable. Investigations at Institute for Drug Research (IDR, Budapest, Hungary) aiming at identifying new papaverine derivatives with enhanced cardiovascular activity led to the discovery of 5*H*-2,3-benzodiazepine compounds with considerable CNS activity. Initial pharmacological profiling demonstrated that such compounds act as tranquilizing agent without any muscle relaxant or anticonvulsant character in rodent.[116] Subsequent optimization led to identification of several clinical candidates such as girisopam, nerisopam, and tofisopam; the last being launched as a highly active nonsedative anxiolytic in 1986 (Figure 7). The clinical success of this new class of compound triggered further investigations resulting in the preparation of analogues bearing a 2,3-methylenedioxy substituent on the fused aromatic ring and a 4-amino group on the exo-phenyl substituent, which were shown to have anticonvulsant and muscle relaxant effects of central origin.[117] Later, electrophysiological experiments in vitro revealed that compounds such as **21** acted as specific AMPA

antagonist.[118] The AMPA-mediated effect was confirmed in vivo shortly after, and the noncompetitive mode of action of these compounds was subsequently disclosed in 1993.[119] The low in vitro efficacy of **21** prevented its development as an anticonvulsant drug; however, this compound has been a very valuable tool compound and its discovery triggered extensive research to identify analogues with improved pharmacological profiles.

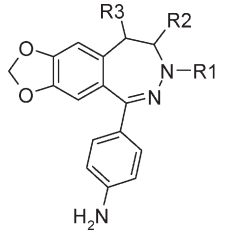
A brief and nonexhaustive overview of the progress made around this 2,3-benzodiazepine scaffold will be discussed hereafter. A more detailed review covering the pharmacology of this class of compound is published elsewhere.[119,120]

Structure−activity studies around **21** shed light on a narrow SAR around the exo-phenyl ring. In addition to the critical 2,3-methylenedioxy group, the 4-amino group was shown to enhance both in vitro and in vivo effects and to be crucial for the antiepileptic effects.[121] Acylation or alkylation of the aniline led to significant loss of biological activity in vitro (e.g., **22** and **23**)[122] (Figure 8).



22 23

Figure 8. N-Substituted 2,3-benzodiazepine derivatives.



	R1	R2	R3
24	H	Me	H
25	Ac	Me	H
26*	Ac	(R)-Me	H
27	CONHMe	(R)-Me	H
28	Ac	Me,CN	H
29	Ac	H	Me
30	CONHMe	H	Me

* Talampanel

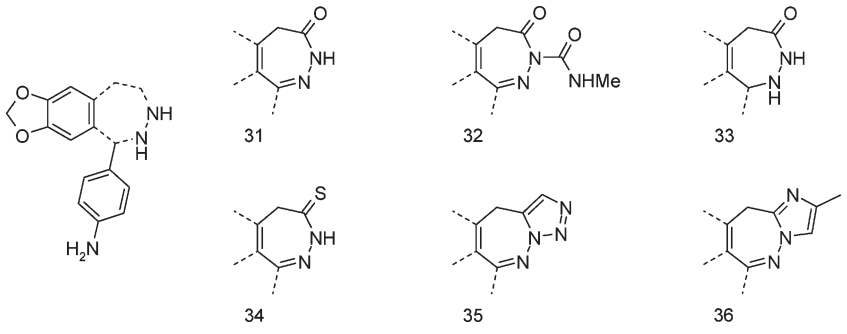
Figure 9. Various 2,3-benzodiazepine analogues.

Replacement of the methylenedioxy with two methoxy groups led to a compound known as nerisopam, which lacks anticonvulsant activity but has remarkable anxiolytic and antipsychotic properties.[123] Interestingly, saturation of the 3,4-double bond in **21** provided 3,4-dihydro-2,3-benzodiazepine **24** which is a selective dopamine uptake inhibitor,[124] whereas subsequent substitution of the N-3 position (**25**) restores AMPA antagonism.[125] The racemic 3-acetyl analogue **25** demonstrated good in vitro potency and in vivo efficacy in the maximal electroshock (MES) model. Optical resolution and pharmacological profiling of the enantiomers permitted identification of the 4-(*R*) eutomer **26**, which was later chosen for clinical development with a main indication in epilepsy.[126,127] Further exploration of the N-3 substitution and replacement of the *N*-acetyl with a *N*-methylcarbamoyl led to **27**, the most potent derivative in this series.[127] Quaternization of the 4-position with a nitrile gave **28**, which has significant neuroprotective and anticonvulsant properties.[128] Attempts to shift the 4-methyl group to the 5-position led to significantly lower biological activity, as exemplified by compounds **29** and **30**[129] (Figure 9).

The scope of this class of compounds was further expanded when 2,3-benzodiazepin-4-one **31** was reported to have improved anticonvulsant activity with respect to the reference compound.[130,131] By analogy to the 3,4-dihydro-2,3-benzodiazepine scaffold, functionalization of the N-3 position proved to be a positive structural modification, i.e., **32**.[132] Reduction of the 1,2-azomethine functionality in the seven-ring was well tolerated, and derivative **33** retains potent anticonvulsant activity.[133] An interesting observation was made with the thio derivative **34**, where the oxygen atom of the carbonyl group has been replaced with a sulfur atom. This compound presents an improved pharmacological profile, which has been attributed to a better permeation across the blood−brain barrier.[134]

Structure−activity studies were taken one step further with derivatives such as **35** and **36**, where the hydrazide functionality has been replaced bioisoterically with various azole rings while retaining good in vitro potency (Figure 10). The imidazole analogue **37**, decorated with a 8-chloro substituent, showed a broad spectrum of anticonvulsant activity (Figure 11).[135]

Finally, the field of 2,3-benzodiazepine as a noncompetitive AMPA antagonist was further expanded with the discovery of dihydrophthalazines exhibiting AMPA antagonistic activity such as **38**.[136] By analogy, it was also demonstrated that the 2,3-benzodiazepin-4-one scaffold can also be contracted to compounds such as **39**, which were



31 32 33 34 35 36

Figure 10. Variations around the central seven-ring system.

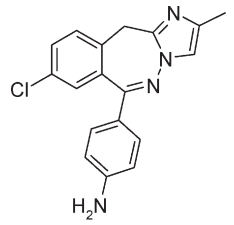


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Figure 11. 7-Chloro analogue with broad spectrum of anticonvulsant activity.

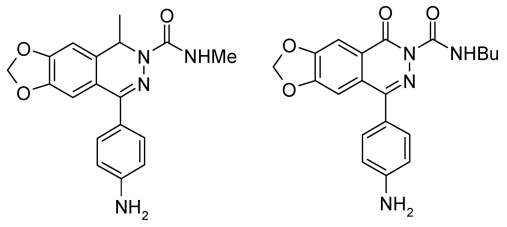


Figure 12. Phthalazine analogues.

Table 4. Oral Efficacy of **26** in Various Mouse Seizure Models

seizure model	ED_{50} (mg/kg, po)
maximal electroshock	8.6
metrazole	16.8
strychnine	17.4
bemegride	23.9
bicuculline	14.6
nicotine	22.7
4-AP[a]	8.4
3-MPA[b]	17.1

[a] 4-AP = 4-aminopyridine. [b] 3-MPA = 3-mercaptopropionic acid.

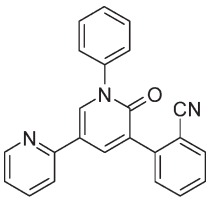
shown to be 11-fold more potent than **21** in animal models of epilepsy (Figure 12).[137]

However, despite all the pharmacological progress made with this class of 2,3-benzodiazepine compounds, **26** remains, to the best of our knowledge, the only candidate that is in active clinical development.

Talampanel (26).[138] The in vitro pharmacological profiling showed that **26** is a noncompetitive and selective AMPA antagonist in functional assays. In cerebellar Purkinje neurons, **26** inhibited the AMPA receptor-mediated response with an IC_{50} of 2.5 μM. In another assay, **26** inhibited AMPA-induced chicken retinal spreading depression with an IC_{50} of 1.7 μM.[138] **26** also exhibited a broad spectrum anticonvulsant activity in various mice epilepsy models, as summarized in Table 4.[138]

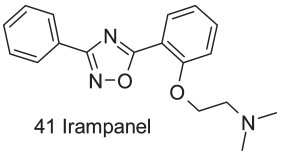
The neuroprotective effects of **26** have also been evaluated in a variety of models. In the Mongolian gerbil carotid artery occlusion model **26** demonstrated efficacy, providing survival of up to 25% of hippocampal CA1 neurons. In a model of transient cerebral ischemia in rats, **26** provided protection against cell death induced by middle cerebral artery occlusion. At a dose of 6 × 2 mg/kg iv, the infracted area was decreased by 47% compared to control animals.[139] In addition, **26** was also shown to inhibit tremors induced by harmaline (no structure) or oxotremorine (no structure) in mice with ED_{50} values of 9.0 and 5.6 mg/kg, respectively.[139]

Perampanel (E-2007, 40).[140,141] More recently, several interesting notes have been disclosed about a novel noncompetitive AMPA antagonist, **40**, developed by Eisai for



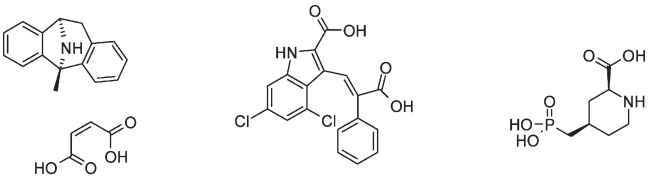
40 Perampanel

Figure 13. Structure of **40** (perampanel, E-2007).



41 Irampanel

Figure 14. Structure of **41** (Irampanel).



42 (MK-801) 43 (MDL105519) 44 (CGS19755)

Figure 15. Structures of reference compounds **42**, **43**, and **44**.

the treatment of epilepsy, treatment of pain from diabetic peripheral neuropathy and postherpetic neuralgia, and treatment of migraine and multiple sclerosis. The development of **40** for the treatment of Parkinson's disease was terminated in 2008.[140] However, despite the recent disclosure of the structure of **40**, very little information has been released by Eisai about its development compound (Figure 13).

In rat cortical neurons, **40** demonstrated potent inhibition of the AMPA-induced Ca^{2+} accumulation with an IC_{50} of 93 nM and had no meaningful effect on the radioligand binding assays used, suggesting a noncompetitive mechanism of action. Patch-clamp studies showed a distinct effect of **40** (10 μM) on AMPA-induced current, comparable with **26** (10 μM). The compound displayed high selectivity for the AMPA receptor.[141]

In rodent, **40** significantly and dose-dependently prolonged the time to onset of AMPA-induced seizures at oral doses of 2.5 mg/kg and above. In additional seizure models, **40** protected mice from audiogenic seizures, maximal electroshock, and pentylenetetrazol (PTZ)-induced seizures with ED_{50} values of 0.47, 1.6, and 0.94 mg/kg, respectively. In amygdala-kindled rats, a dose of 10 mg/kg significantly elevated the after-discharge threshold.[142] **40** was also shown to have antitermor effects at a dose of 2 mg/kg in oxotremorine- and harmaline-treated animals.[142]

Irampanel (41).[143,144] In the late 1990s, scientists at Boehringer-Ingelheim reported a novel class of 3,5-disubstituted [1,2,4]oxadiazole, which combines AMPA-receptor-blocking and Na^+-channel-blocking properties. According to a company's press release, a representative of this class, **41**, entered phase I clinical trials for stroke in October 1999 (Figure 14). However, no additional data are currently available and the drug no longer appeared on the company's research and development pipeline.[143]

In the absence of detailed information about the synthesis and SAR in this series and because of **41**'s dual mode of action, which lies outside the scope of this article, the pharmacology of **41** on AMPA receptors will only be briefly covered in the next section.

In cultured rat cortical neurons, **41** inhibited AMPA-receptor-mediated membrane currents with an IC_{50} of 8.5 μM and was shown to act noncompetitively. The effect of **41** ex vivo was also investigated in cortical wedges; **41** reduced the depolarization in response to 5 μM AMPA with an IC_{50} of 10.8 μM.[144]

41 dose-dependently protected mice from AMPA-induced lethality with an ED_{50} value of 4.5 mg/kg. The compound was shown to induce dose- and time-dependent protection against tonic seizures after electrical stimulation with an ED_{50} of 23.4 mg/kg, following oral application, in the MES test in mice. Finally, in amygdala-kindled rats, a dose of 11.2 mg/kg administered ip led to a significant increase of the after-discharge threshold.[145]

Clinical Results with AMPA Receptor Antagonists

Epilepsy. Testing in various established animal seizure models (MES, WAG/Rij rat, PTZ, audiogenic, and kindling seizure models) has suggested that AMPA antagonists have a potential antiepileptic effect. From the group of AMPA antagonists that have reached the clinic, three (**26**, **40** and **7**) were tested for efficacy against epilepsy.

In a double-blind, placebo-controlled, crossover study in 49 patients with refractory partial seizures, **26** was efficacious in reducing seizure frequency with a median seizure reduction of 21%. Three doses of **26** were investigated on the basis of differences in patients' concomitant antiepileptic drug usage. Eighty percent of patients had fewer seizures on **26** than on placebo. Dizziness (52%) and ataxia (26%) were the only significant adverse events.[146] Three phase II studies, which include doses to be used in phase III, suggest that **40** is generally well tolerated with a dose-dependent efficacy in patients with refractory partial seizures. The most recently completed phase II study evaluated maximum tolerated dose (MTD) and safety of **40** as adjunctive therapy in subjects with refractory partial seizures. This was a 16-week, placebo-controlled, dose-escalation (to a maximum of 12 mg/day), and parallel-group study. **40** showed an increasing trend in activity up to 12 mg/day in epilepsy patients with refractory partial seizures. There was a 40% median seizure reduction in the **40** arm and a 2% median seizure increase in the placebo arm. The responder rate, defined as a proportion of patients with more than 50% seizure reduction, was 40% in the **40** arm and 22% in the placebo arm.[147] **7** has a broad-spectrum anticonvulsant profile in preclinical seizure models and therefore may be clinically efficacious against partial, generalized tonic−clonic, and myoclonic/absence type seizures. In a double-blind, randomized, placebo-controlled study in patients with refractory partial seizures, all 22 **7**-treated patients remained seizure-free upon completion of the 7-day treatment, compared to 40% of the 19 patients on placebo treatment.[148]

Migraine. In migraine patients, the number of AMPA/kainate receptors increases in the trigeminal ganglion. AMPA/GluR5 antagonism may provide a novel target for migraine therapy that circumvents the vasoconstrictive liability of 5-HT1B agonism, a property shared by triptans and ergots. In the absence of vasoconstrictive effects, this potential therapy is quite attractive, as it could be extended to patients with coronary artery risk factors, a group whom current migraine-specific therapies are contraindicated.

Efficacy of **18** in a small migraine proof of concept trial has been reported. Patients with acute migraine were given 1.2 mg/kg **18** intravenously, 6 mg of sumatriptan subcutaneously, or placebo. More than two-thirds of patients who received iv **18** reported a reduction of headache pain from moderate/severe to mild/no pain at 2 h, and more than half were pain-free at 2 h without headache recurrence or need for rescue therapy. Also, **18** was effective in relieving nausea, photophobia, and phonophobia, complaints that impart significant disability during migraine.[149] **18** also met the primary end point in a 306-patient, phase IIb clinical trial for the treatment of a single, acute migraine attack. A 40 mg sc dose demonstrated statistically significant improvement on headache pain response at 2 h postdose compared to placebo (78.2% versus 58.7%), and the response was sustained through 24 h postdose. Improvement in key secondary measures at 40 mg were either statistically significant ($p < 0.050$) or trending ($p < 0.100$) when compared to placebo and corroborated the results for the primary end point of the study. These key secondary measures included nausea or vomiting, photophobia, a sum of pain intensity scores at 3 and 4 h postdose, sustained headache response at 24 h, functional disability, and a composite score of core migraine symptoms at 2 and 4 h postdose that included measures of headache severity, nausea, vomiting, photophobia, phonophobia, and functional disability. At baseline, 58% of the patients in the group receiving **18** had cutaneous allodynia compared with 56% in the placebo group. After treatment with **18**, 83.3% of the patients with cutaneous allodynia had pain relief, compared with 59.5% on placebo. Effectiveness of **18** in the presence of cutaneous allodynia is important because many of these patients are refractory to triptan treatment.[150]

Neuroprotection. Despite several demonstrations of neuroprotective efficacy of AMPA antagonists in experimental models of stroke or traumatic brain injury (TBI), clinical results in stroke patients are rather disappointing. In a multicenter, double-blind, randomized, placebo-controlled phase II trial, the AMPA antagonist **4** reversibly worsened the neurological condition in patients with acute ischemic stroke. Following a total dose of 262.5 mg in 48 h, there was a significant transient worsening in the mean National Institutes of Health Stroke Scale (NIHSS) score. This was due to reduction of consciousness (stupor and coma) in 8 of 13 patients. The trial was stopped prematurely for safety reasons.[151,152] Second-generation noncompetitive AMPA receptor antagonists such as **26** have been shown to be neuroprotective in experimental TBI or stroke models but failed to advance successfully in clinical trials. A new competitive AMPA antagonist **6**, which is also neuroprotective in rats,[79] was in phase II clinical trial for treating stroke patients. This study was abandoned after failing an interim futility analysis.[153]

Pain. Considerable preclinical evidence has demonstrated that AMPA receptors play an important role in the central mechanisms of pain processing. Central sensitization in the brain and spinal cord appears to play a role in neuropathic pain, migraine headache, chronic diabetic neuropathy, herpetic, and HIV neuropathy, some types of chronic cancer pain, and evoked pain in postoperative patients. Infusions of **18** (100% maximally tolerated dose vs 33% maximally tolerated dose vs placebo) after intradermal injection of

250 μg of capsaicin in the volar forearm significantly reduced pain intensity, pain unpleasantness, and the area in which light brush evoked pain, in a phase II study . There were no significant changes in electrical or warm−cool detection and pain thresholds or heat pain thresholds. **18** had little effect on brief pain sensations in normal skin. Reported dose-limiting side effects were hazy vision in 95% of volunteers and sedation in 40%.[154] Analgesic efficacy of intravenous **18** (0.4 or 1.2 mg/kg) was demonstrated in a randomized, double-blind, parallel group study after oral surgery. Study drugs were administered at the onset of moderate pain; pain intensity and relief were measured for 240 min. High-dose **18** and ketorolac tromethamine (30 mg, iv) were superior to placebo for pain evoked by mouth opening and one of several measures of spontaneous pain. The summed pain intensity difference over 240 min for pain evoked by mouth opening was highest for ketorolac tromethamine (151 ± 58), intermediate for high-dose **18** (−45 ± 35), and least for low-dose **18** (−151 ± 39) and placebo (−162 ± 50). High-dose **18** was superior to placebo at individual time points (45−240 min) for pain evoked by mouth opening but not for spontaneous pain. **18** was well tolerated, with dose-dependent and reversible side effects including hazy vision in 20% of patients and sedation in 15%.[155] Oral administration of **45** (NGX426, structure not disclosed),[146] an ester prodrug of **18**, was recently demonstrated to significantly reduce spontaneous pain, hyperalgesia (abnormally increased pain state), and allodynia (pain resulting from normally nonpainful stimuli to the skin) compared to placebo following intradermal injections of capsaicin in a human experimental model of cutaneous pain, hyperalgesia, and allodynia. The randomized, double-blinded study enrolled a total of 18 healthy male subjects. Subjects received two intradermal injections of capsaicin at 30 and 120 min after administration of a single, oral dose of 90 mg or 150 mg of **45** or placebo. Pain assessments were determined at specified intervals after each injection of capsaicin and measured by visual analog scale. The 150 mg dose was statistically significant compared to placebo on all three measures: reduction in spontaneous pain, hyperalgesia, and allodynia. The 90 mg dose also showed statistical significance on reduction of hyperalgesia and allodynia. In addition, a statistically significant pain-reducing effect was observed for the 150 mg dose through 4.5 h postdosing.[156] Several preclinical models have also suggested that **40** may be effective in treating neuropathic pain. A phase II proof of concept study in painful diabetic neuropathy (PDN) is expected to provide results soon. A phase II study in a second neuropathic pain indication, postherpetic neuralgia (PHN), was initiated in January 2008.[147] **17** was evaluated for efficacy, safety, and tolerability in comparison with placebo and lidocaine for the treatment of chronic neuropathic pain and allodynia in a randomized, double-blind, placebo-controlled, three-way crossover study in patients with peripheral nerve injury. Patients were treated iv with **17** (322 mg), lidocaine (5 mg/kg), or placebo. Measures of spontaneous current pain and pain evoked by brush, pinprick, cold, and heat stimulation were performed at screening and at 0, 2, 4, 6, 8, and 24 h after the start of the treatment session. While **17** did not demonstrate a significant change in spontaneous current pain compared with placebo, it was superior to placebo in alleviating key symptoms of neuropathic pain, including evoked mechanical and cold allodynia. The patients' ratings of overall pain were also statistically significantly improved compared with placebo at a level similar to lidocaine. **17** was safe and significantly better tolerated than lidocaine.[157]

Summary and Perspectives

Ligands showing competitive antagonistic action at the AMPA type of glutamate receptors were first reported in 1988, and 2,3-dihydroxy-6-nitro-7-sulfamoylbenzo[*f*]quinoxaline (**2**) was first shown to have useful therapeutic effects in animal models of neurological disease in 1990. Over the ensuing years there have been many interesting developments in the study of these antagonists, including the identification of diverse new chemical series, increased understanding of receptor pharmacology, and reports of in vivo studies both in preclinical animal models of disease and in early clinical trials. Compounds that present improved pharmacokinetic properties and less serious adverse effects have yielded positive results in early clinical evaluations. In the near future, the most important clinical applications for the AMPA receptor antagonists will probably be as neuroprotectant in neurodegenerative diseases and treatment resistant epilepsy, for the treatment of patients not responding to current therapies. Pioneer studies using experimental allergic encephalomyelitis (EAE) as a model of multiple sclerosis (MS) suggested that excitotoxic processes could induce axonal damage and may represent a key element in the pathogenesis of MS. Blockade of excessive, excitotoxic AMPA transmission with AMPARs in various animal models of MS led to a reduction in clinical signs and axonal damage in the spinal cord and may be a promising strategy for the treatment of chronic neurodegenerative diseases such as MS. Recent reports of analgesic efficacy and migraine reducing activity in clinical trials will undoubtly open the way to new therapies with AMPAR antagonists for various types of pain.

Finally, while preclinical studies with AMPA receptor antagonists strongly suggest that dysfunctional glutamatergic neurotransmission may play a role in psychiatric disorders, conclusive clinical data to support or reject this hypothesis are still awaited.

Biographies

Henri Mattes received his Ph.D. in Organic Chemistry in 1987 from the University of Strasbourg, France, under the direction of Professor Claude Benezra. Following postdoctoral tenure with Professor R. E. Ireland at the University of Virginia, Charlottesville, VA, Henri moved to Sandoz, which over the years turned into Novartis, as Lab Head. Over the past 22 years he was engaged in drug discovery projects in the areas of endocrinology, combinatorial chemistry, ophthalmology, neuroscience, and inflammation which resulted in multiple clinical candidates. Henri is a co-inventor of Tegaserod.

David A. Carcache received his chemistry degree from the University of Neuchâtel, Switzerland, in 1998. He then completed a Ph.D. at the Swiss Federal Institute of Technology in Zurich (ETHZ) under the direction of Prof. François Diederich in 2002. After conducting postdoctoral studies with Prof. Samuel J. Danishefsky at the Memorial Sloan-Kettering Cancer Center in New York, he joined the Global Discovery Chemistry group at Novartis in 2004. He has contributed to various research projects in disease areas such as CNS and immunology.

Hans O. Kalkman studied pharmacy and pharmacology at the University of Groningen (The Netherlands) and obtained his Ph.D. at the University of Amsterdam in 1983. From that year on, he worked in the preclinical research department of Sandoz-Novartis. He has been preclinical representative in numerous drug-development teams.

Manuel Koller studied chemistry at the University of Zurich and completed his Ph.D. in 1985 under the direction of Prof. A. S. Dreiding. He then worked as a postdoctoral fellow on the synthesis of β-lactams in the group of Prof. L. Ghosez in Louvain-La-Neuve, Belgium. In 1987 he joined the preclinical department of Neuroscience at Sandoz-Novartis as a medicinal chemist, working, among other projects, in the field of excitatory amino acids.

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