New AMPA antagonists in epilepsy

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EXPERT OPINION

New AMPA antagonists in epilepsy

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Introduction: Epilepsy is a common neurological disorder; however, its therapy is not satisfactory because a large number of patients suffer from refractory seizures and/or has a low quality of life due to antiepileptic drug (AED) side effects. Glutamate is the major excitatory neurotransmitter in the brain, AMPA receptors (AMPARs) represent a validated target for AEDs' development. Evidences support their role during seizures and neurodegeneration. Development of AMPAR ligands has led to two different branches of research, with the identification of competitive and noncompetitive antagonists.
Areas covered: We herein describe the architecture of AMPAR and the main structure–activity relationships of antagonists. Finally, we report the effects of AMPAR antagonists in preclinical models and clinical trials in epileptic patients. We reviewed the most relevant research in the field, focusing on research advances for the oldest AMPA antagonists and the new most promising molecules identified.
Expert opinion: Overall, the development of AMPAR antagonists confirms their great clinical potential; their arrival to clinical practice has been slowed down by their unfavorable pharmacokinetic profile and tolerability; however, their clinical use might be justified by their efficacy and the new drugs developed such as perampanel have been greatly ameliorated from both points of view.

Keywords: AMPA antagonists, AMPA receptors, IKM, NS1209, perampanel, talampanel

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1. Introduction

Glutamic acid (Glu) is the major excitatory neurotransmitter in the mammalian central nervous system (CNS) where it plays a pivotal role in regulating neuronal activity [1]. It has been well established that overstimulation of AMPA receptors (AMPARs) is one of the major causes of Ca^{2+} overload in cells, producing cell damage and death [2]. These processes are strictly related to a large number of acute and chronic neurodegenerative pathologies such as cerebral ischemia, epilepsy, amyotrophic lateral sclerosis and Parkinson's disease [3-6].

In recent years, extensive research has been directed towards the clarification of glutamate receptor (GluR) functions in the CNS [7,8]. In particular, extensive work was addressed towards the development of AMPA antagonists, which proved to be particularly useful in the prevention and treatment of these neurological pathologies [9,10]. AMPAR antagonists have been investigated for antiseizure activity both preclinically and clinically, and different studies demonstrated that activation of AMPARs plays a critical role into the generation and propagation of seizures [3,5,11-15]. Agents that inhibit or decrease AMPAR activity have the potential to reduce excessive excitatory responses providing neuroprotection and seizure suppression [12,16]. Furthermore, both lamotrigine and topiramate, two marketed antiepileptic drugs, have been reported to act also on AMPARs [17-19]; and also

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Article highlights.

- Description of AMPA receptor structure and functioning.
- Chemical structure and SARs of AMPA antagonists.
- Definition and identification of the most promising chemical scaffolds as AMPA antagonists.
- Preclinical efficacy of AMPA antagonists.
- Clinical efficacy of AMPA antagonist.

This box summarizes key points contained in the article.

leptin, a peptidergic hormone, has shown anticonvulsant effects in preclinical models through a block of AMPA-mediated excitatory synaptic transmission; although this effect was mediated by the activation of the JAK2/PI3K pathway and not a direct action on the AMPA receptor complex [20]. Our actual knowledge, therefore, indicates that AMPAR antagonists have a great potentiality as suitable antiepileptic drugs, so the present review deals with drugs that act as competitive and noncompetitive antagonists on the AMPA receptor complex considering the new most relevant results in the field of epilepsy. We provide a brief description of the AMPA receptor complex, the chemical scaffolds with potential antagonistic effects on this receptor and the results obtained in both preclinical models of epilepsy and during clinical trials.

2. AMPA receptors (AMPARs)

In the mammalian CNS fast excitatory neurotransmission is mainly mediated by ionotropic glutamate receptors (iGluRs) [21] that are a superfamily of ligand-gated cation channels comprising three receptor families named on the basis of selectivity to exogenous agonists: α-amino-3-hydroxyl-5-methyl-4-isoxazole-propionate (AMPA), *N*-methyl-D-aspartate (NMDA) and kainate (KA) (**Figure 1**).

Like other classes of iGluRs, the AMPARs are composed of a combination of four pore-lining α-subunits GluA1–4 (formerly GluR1-4 or GluRA-D) each encoded by a different gene. Each subunit consists of approximately 900 aminoacidic residues exhibiting high-sequence homology to other subunits. Significantly, the GluA1–4 are differentially distributed in the mammalian brain and their expression is developmentally regulated. Through the combination of GluA1–4 subunits, AMPARs assemble as tetrameric complexes of homo/heteromeric dimer of dimers [22]. Schematically the tetrameric structure can be subdivided in amino-terminal domain (NTD), ligand binding domain (LBD), transmembrane domain (TMD, forming the channel pore area) and carboxy terminal domain (CTD) [23]. The pair of NTD dimers lines the area located much distal from the membrane, the pair of LBD dimers forms a middle area and the tetrameric TMD area is embedded in a lipid bilayer forming the core of the ion channel. By means of crystallographic data, the structure of membrane-spanning tetrameric glutamate receptor was described as well as discrete NTDs and LBDs in complex with agonists, antagonists and modulators, thus furnishing relevant suggestions about interaction binding modes for these different classes of ligands [23,24]. **Figure 2** represents the architecture of GluA2 subunit and the different ligand binding sites. Notably, it was observed that the LBD cleft can display different organization according to the nature of interaction with full agonists, partial agonists or antagonists. The LBD, defined by two polypeptide segments named D1 and D2, adopts a clamshell-like conformation and contains the competitive agonist/antagonist recognition site [25].

Glu activates AMPARs by binding the cleft between domains D1 and D2 of the LBD inducing domain closure and creating conformational events that induce the opening of the ion channel. It was demonstrated that the Glu binding happens via a network of interactions with specific aminoacidic residues Tyr 450, Pro478, Thr480, Arg485, Thr 655 and Glu705 within the ligand binding agonist pocket [23]. Competitive AMPAR antagonists generally possess specific chemical features generating contacts within D1/D2 domains thus preventing cleft closure [26-28]. The TMD area consists of three transmembrane helices (M1, M3 and M4) and a re-entrant loop (M2); this area is connected to LBD through short linkers surrounding the channel pore. Experimental evidence suggested that positive and negative allosteric modulators (PAMs and NAMs) interact with several specific modulator binding sites that are located in LBD dimer interface, LBD–TMD linkers, and ion channel pore [29]. Particularly, NAMs seem to interact with the above-mentioned short linkers D1–M1 or D2–M4. Moreover, several toxic polyamines (Joro spider toxins and philanthotoxin-433) exert open-channel blockade interacting with M2 re-entrant pore-lining loop [30]. Finally, the intracellular CTD domain may contain different phosphorylation sites and binding sites for intracellular proteins involved in regulation of membrane trafficking [31,32]. Recently it was demonstrated that AMPARs are also associated with auxiliary subunits called transmembrane AMPA regulatory proteins (TARPs) controlling receptor trafficking and channel gating [33].

3. AMPA receptor antagonists

Distinct classes of ligands targeting AMPARs have been developed and can be classified as competitive agonists and antagonists, positive and negative allosteric modulators (also known as noncompetitive antagonists) and channel pore blockers [4,34-38]. In this section, we will report an overview of the main structure–activity relationships (SARs) for several different chemical classes of antagonists as promising anticonvulsant agents.

3.1 Competitive AMPAR antagonists

The quinoxalinedione derivatives 6-cyano-7-nitroquinoxaline-2,3-dione (CNQX) and the 6,7-dinitroquinoxaline-2,3-dione (DNQX) (**Figure 3**) were the prototype compounds of

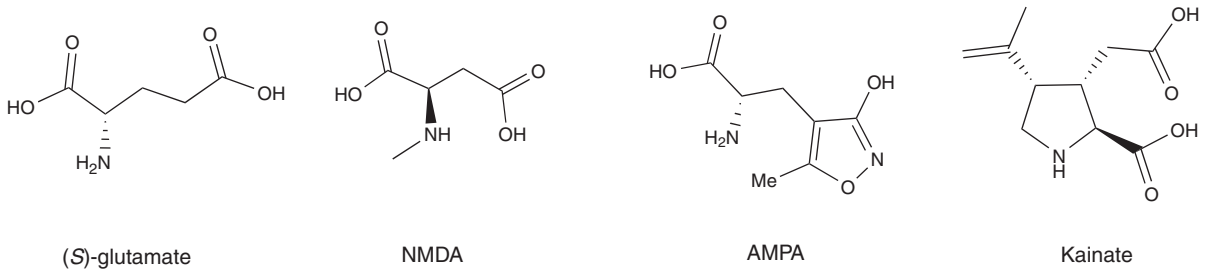

Figure 1. iGluR ligands.

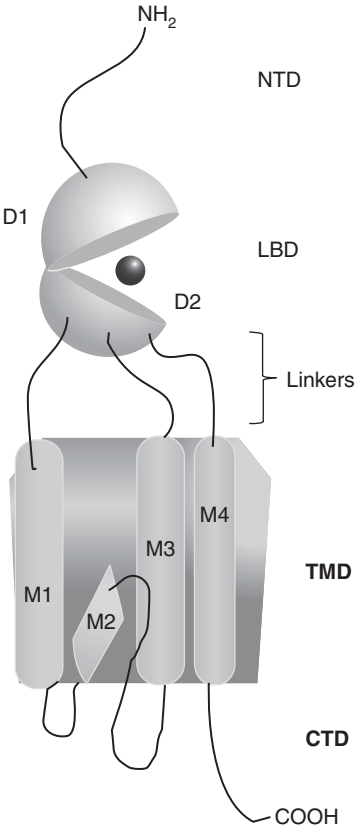

Figure 2. Schematic representation of GluA2 subunit and ligand binding sites.

competitive antagonists for AMPARs [34]. However, their clinical trials were stopped due to the lack of selectivity, thus they represented the starting point in searching for derivatives endowed with drug-like properties. Then 2, 3-dioxo-6-nitro-1,2,3,4-tetrahydrobenzo[f]quinoxaline-7-sulfonamide (NBQX) demonstrated an improved AMPAR selectivity with respect to CNQX and it was used as antagonist of choice in many *in vitro* and *in vivo* models. The replacement of cyano and nitro group of CNQX and DNQX with the imidazolyl moiety furnished the 1,4-dihydro-6-(1*H*-imidazol-1-yl)-7-nitro-2,3-quinoxalinedione (YM90K) as potent and selective AMPAR antagonist [39]. Then, the synthesis of different derivatives highlighted the main SARs to develop an AMPAR pharmacophore model for the first-generation of quinoxalinediones [34]: i) a NH proton donor that binds to a proton acceptor site of the receptor; ii) the 2,3-dione moiety, which serves as potent hydrogen bond acceptor; iii) a strong electron withdrawing group (EWG) at C-7 position able to increase the acidity of the NH at position 1 as well as providing a weak hydrogen bond interaction. To obtain water-soluble quinoxalinediones, the synthesis of new analogues containing a phosphono- or carboxymethyl side chain as acidic fragment has been planned, thus developing the [[3,4-dihydro-7-(4-morpholinyl)-2,3-dioxo-6-(trifluoromethyl)-1(2*H*)-quinoxali-nyl]methyl]phosphonic acid (MPQX, also known as ZK200775) [40], the [2.3-dioxo-7-(1*H*-imidazol-1-yl)-6-nitro-1,2,3,4-tetrahydro-1-quinoxalinyl]acetic acid (YM872, Zonampanel) [41,42] and the [(7-nitro-2,3-dioxo-1,2,3,4-tetrahydroquinoxalin-5-ylmethyl) amino]methyl-phosphonic acid (AMP397) [43].

Further structural modifications were explored and compounds bearing (hetero)cyclic bridge between C5 and C6 have been studied and the 1,4,7,8,9,10-hexahydro-9-methyl-6-nitropyrido[3,4-f]quinoxaline-2,3-dione (PNQX) [44] represents one of the most interesting compound. Moreover, different C3-N4 (hetero)cyclic bridged compounds containing an imidazo- or a triazole cycle have been developed thus confirming the possibility to introduce a bioisosteric substitution of the oxygen of the quinoxalinonic system with a nitrogen atom of the heterocycle ring [34].

Several 2-(1H)-oxoquinolines have also been reported; the 6,7-dichloro-2-(1H)-oxoquinoline-3-phosphonic acid (S17625, **Figure 3**) [45] was demonstrated to be a potent AMPAR antagonist efficacious as anticonvulsant. Although S17625 displays activity after oral administration, at therapeutically effective doses, it is nephrotoxic. So new analogues of S17625 incorporating some specific features were synthesized. The replacement of the chlorine in position 6 by a sulfonamide moiety led to very potent AMPAR antagonists (e.g., **1**) lacking of nephrotoxicity and endowed with significant anticonvulsant activity in preclinical models [46].

In the course of a program aimed at the identification of new competitive AMPAR antagonists, researchers at Novartis recently disclosed several substituted 2,4-quinazolinediones

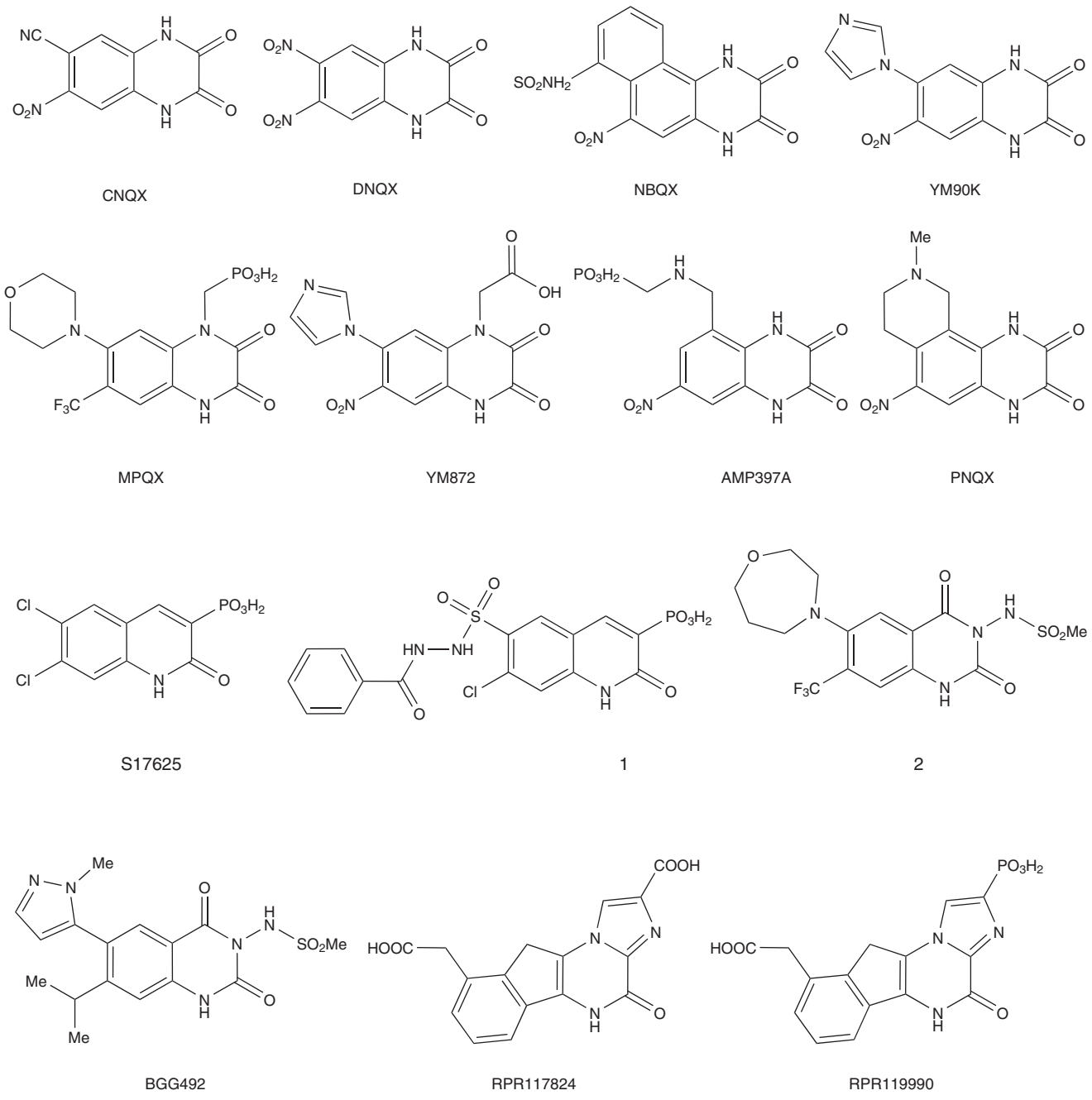

Figure 3. Competitive AMPAR antagonists.

(e.g., **2** and BGG492, **Figure 3**) as a novel class of orally active anticonvulsants [47,48]. Crystallographic studies described the binding mode of the most active 2,4-quinazolinediones within the LBD of GluA2 subunit (extracellular domain) thus drawing the network of interactions between aminoacidic residues and specific chemical moieties on quinazoline scaffold [48]. These findings clarified the SAR for this class of compounds thus justifying the role of alkylsulfonamide group as well as 6,7-substituents.

A series of AMPAR antagonists containing a 4,5-dihydro-4-oxo-10H-imidazo[1,2a]indeno[1,2-e]pyrazine system (**Figure 3**) has been explored by researchers at Aventis Pharma. The 9-carboxymethyl-imidazo[1-2a]indeno[1-2e]pyrazin-4-one-2-carboxylic acid (RPR117824) [49] and the 9-carboxymethyl-4-oxo-5H,10H-imidazo[1,2-a]indeno[1,2-e]pyrazin-2-phosphonic acid (RPR119990) [50] were the first two compounds of this class showing high selectivity for AMPAR and good *in vivo* activity. By bioisosteric

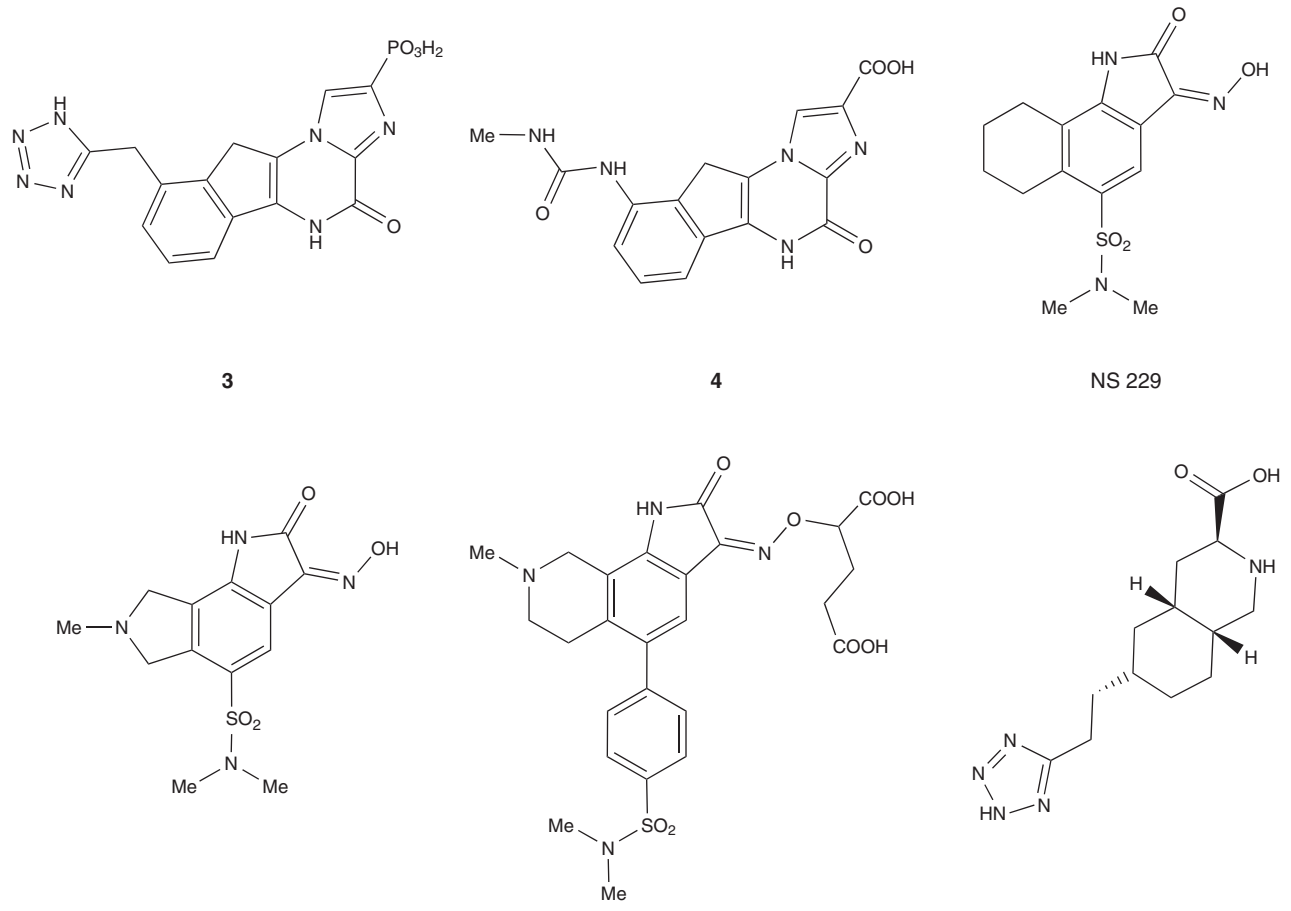

Figure 3. Competitive AMPAR antagonists (continued).

replacement of the carboxylic moiety in position 9 with a (tetrazol-5-yl)methyl substituent, the corresponding derivative **3** has been prepared and it demonstrated a similar pharmacological profile. Following a further structural modification by the introduction of a 8-methylureido-fragment, a water-soluble analogue **4** was obtained [38].

Figure 3 also displays the chemical structure of the two prototypes of the series of isatinoximes [51] demonstrating anticonvulsant activity: (3*Z*)-3-(hydroxyimino)-*N*,*N*-dimethyl-2-oxo-2,3,6,7,8,9-hexahydro-1*H*-benzo[*g*]indole-5-sulfonamide (NS229) and the 1,2,3,6,7,8-hexahydro-3(hydroxymino)-*N,N*-7-trimethyl-2-oxobenzo[2,1-b:3,4-c]dipyrrole-5-sulfonamide (NS257). Further developments on this class of AMPAR antagonists brought to the second-generation derivative (8-methyl-5-(4-(*N*,*N*-dimethylsulfamoyl)phenyl)-6,7,8,9-tetrahydro-1H-pyrrolo[3,2-*h*]-iso-quinoline-2,3-dione-3-*O*-(4-hydroxybutyric acid-2-yl)oxime (NS1209), characterized by a hydrophylic side chain linked to the oxime oxygen and then a higher water solubility.

Among the decahydroisoquinoline derivatives, the (3*S*,4a*R*,6*R*,8a*R*)-6-[2-(1*H*-tetrazol-5-yl)ethyl]decahydroisoquinoline-3-carboxylic acid (LY293558, Tezampanel, **Figure 3**) [52] was the most interesting competitive AMPA/KA receptor antagonist showing systemic activity as well as water solubility. Tezampanel belongs to a class of iGluR ligands bearing the 6-substituted decahydroisoquinoline-3-carboxylic acid group. The main feature of this class of compounds is the influence of the chain linking tetrazole ring to bicyclic nucleus in terms of iGluR selectivity. Particularly, elongation of the chain as well as its shortening reduces AMPA/KA affinity and selectivity over NMDA receptor.

3.2 Noncompetitive AMPA receptor antagonists (negative allosteric modulators)

The first generation of noncompetitive AMPAR antagonists were 2,3-benzodiazepine derivatives (**Figure 4**) [53]. Some of these compounds act through negative modulation by binding to an allosteric site and present the advantage of retaining good efficacy independently of the level of glutamate. The 1-(4'-aminophenyl)-4-methyl-7,8-methylenedioxy-5*H*-2,3-benzodiazepine (GYKI 52466, **Figure 4**) was the first inhibitor of this class of compounds [54]. Then, the synthesis

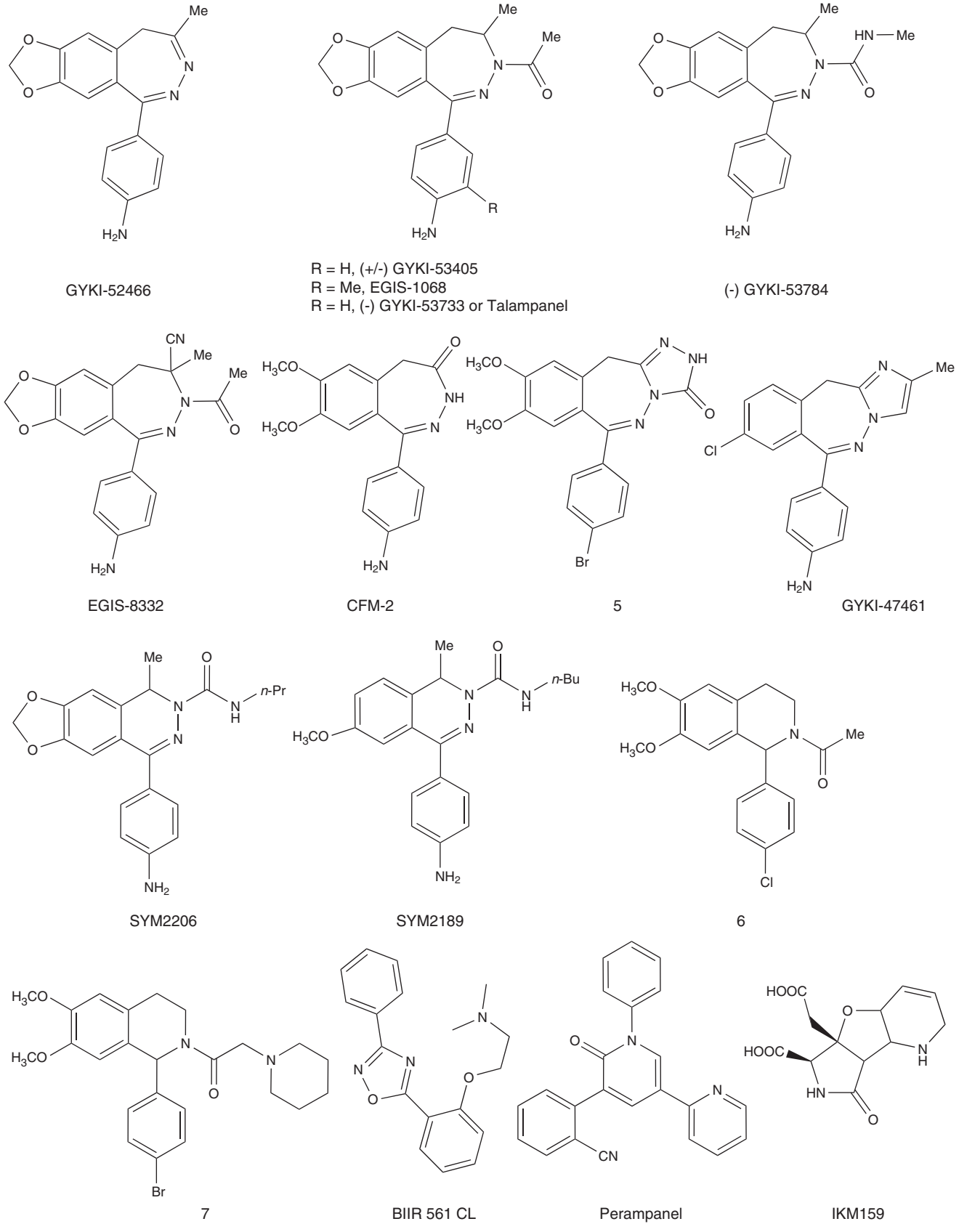

Figure 4. Noncompetitive AMPAR antagonists.

of a great number of other 2,3-benzodiazepines has been carried out and some SARs were highlighted [55-64], Several 3-*N*-substituted-3,4-dihydro-2,3-benzodiazepine analogues have been developed and the racemic derivatives (GYKI 53405 and EGIS 1068) demonstrated good *in vitro* potency and *in vivo* efficacy. Pharmacological profiling of the two enantiomers clarified that the highest activity corresponds to the *R*-(-)-enantiomer GYKI 53733 (LY300164, also named talampanel). The role of stereoselectivity in AMPAR inhibition was also confirmed by the (-)1-(4'-aminophenyl)-4-methyl-7,8-methylenedioxy-4,5-dihydro-3-methylcarbamoyl-2,3-benzodiazepine (GYKI 53784) in which the *N*-acetyl group was replaced with a *N*-methylcarbamoyl moiety. In an attempt to obtain more active, less toxic and longer lasting anticonvulsant agents, different functionalities were introduced on the 2,3-benzodiazepine system (**Figure 4**). It was shown that a chlorine or a methoxy substituent at C-7 position or C-7,8 dimethoxy/methylenedioxy moiety need to be present on the benzodiazepine system. The 1-(4'-aminophenyl)-3,5-dihydro-7,8-dimethoxy-4*H*-2,3-benzodiazepin-4-one (CFM-2) [55], characterized by a lactam functionality and a modification of the methylendioxy moiety, has shown positive results in *in vivo* studies. As displayed for 6-(4'-bromophenyl)-8,9-dimethoxy-11*H*-[1,2,4]triazolo[4,5-c][2,3]benzodiazepine-3 (2H)-one [62] (**5**) and GYKI-47621 [59] the introduction of a heterocyclic nucleus was well tolerated for AMPA receptor recognition process.

Starting from the 2,3-benzodiazepine scaffold, the contraction of the heptatomic nucleus to a six-member ring brought to discover a series of 1,2-dihydrophthalazines exhibiting AMPAR antagonistic activity [65]. In this context, it was demonstrated that the 4-(4'-aminophenyl)-1-methyl-6,7-methylenedioxy-*N*-propyl-1,2-dihydrophthalazine-2-carboxamide (SYM2206) and the 4-(4'-aminophenyl)-6-methoxy-1-methyl-*N*-butyl-1,2-dihydrophthalazine-2-carboxamide (SYM2189) proved to be very active compounds.

By means of ligand-based approach and using the HipHop module within catalyst, a qualitative pharmacophore model was generated in order to identify the 3D structural requirements to interact with AMPAR in a noncompetitive manner [66-68]. Then the obtained common-features hypothesis was successfully used as query for virtual screening, which led to the identification of a new class of potent antagonists such as 1-aryl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinolines (**6**-7, **Figure 4**) [68,69]. The same authors proposed a refined pharmacophore model able to predict the rank order of pharmacological activity of noncompetitive AMPAR antagonists [69]. Moreover, for this class of ligands quantitative structure–activity relationship (QSAR) studies were performed and the obtained results showed good statistics in regression revealing high correlation between anticonvulsant activity and some electrotopological descriptors [70]. The enantiomeric resolution of the racemic mixture of derivative **6** showed that the anticonvulsant effects as well as AMPAR antagonism reside mainly in the (*R*)-enantiomer whose absolute configuration has been confirmed by crystallography [71]. The 5'-(2-cyanophenyl)-1'-phenyl-2,3'-bipyridinyl-6'(1'*H*)-one (E-2007, Perampanel) and the hexahydro-2H-furo[2,3-c]pyrroledicarboxylic acid derivative, IKM 159, were recently identified as emerging new chemical entities for the development of AMPAR antagonists (**Figure 4**). Particularly, Perampanel [72] has been discovered at Eisai research laboratories by means of a high throughput screening campaign to assess inhibition of AMPA-induced current in cortical neuron. IKM159 [73] belongs to a small class of tricyclic compounds structurally related to naturally occurring toxins KA and neoDH showing convulsant effects. Oikawa *et al.* synthesized a small series of IKM compounds; they obtained SARs useful to optimize AMPA antagonistic effects as well as receptor selectivity over other iGluRs.

4. AMPA antagonists' effectiveness in preclinical models of epilepsy

AMPA receptor antagonists have been demonstrated to possess a broad-spectrum of anticonvulsant activity in animal models of both focal and generalized epilepsies [3,9,41,61,72]. The first generation of selective, competitive AMPA receptor antagonists with quinoxaline-2,3-dione chemical structures are NBQX, PNQX and YM-90K [3,36]. The prototypical competitive AMPA receptor antagonist (NBQX) showed activity in both the maximal electroshock (MES) and pentylenetetrazole (PTZ)-induced seizure models [74]. Furthermore, some of these compounds (NBQX, YM872 and YM-90K) are potent anticonvulsants against experimentally kindled seizures and have been suggested to possess antiepileptogenic properties and a possible efficacy in partial seizures [13,41,75-80]. It has also been reported that AMPA receptor antagonists could be effective in the acute treatment of status epilepticus, even in cases of benzodiazepine resistance, and that they may provide a means to avoid the cardiovascular toxicity of benzodiazepines [81,82]. Another study demonstrated that intrahippocampal injection of the competitive AMPA receptor antagonist CNQX transiently suppressed seizures in the rat self-sustaining status epilepticus model [83]. Several studies demonstrated that systemic administration of AMPA antagonists exert neuroprotective effects [81,84-87], however, in the 4-aminopyridine seizure model, it was demonstrated that AMPA receptor blockade does not prevent astrocyte swelling [88]. Moreover, the effects of NBQX in a kindling model are increased by pretreatment with low doses of NMDA antagonists, suggesting that both non-NMDA and NMDA receptors are critically involved in the kindled state [89]. Also NMDA receptor antagonists (in subthreshold doses) considerably potentiate the protective activity of AMPA receptor antagonists against MES and vice versa. The interaction between NMDA and AMPA receptor antagonists may occur in both directions against electroconvulsions, that is, NMDA receptor blockers enhance the protective effects of AMPA/kainate receptor antagonists and,

Table 1. Overview of the *in vivo* effects of AMPA antagonists in preclinical models of epilepsy.

Compound	Seizure test ED_{50} (mg/kg)				Ref.
	Audiogenic seizures		MES	PTZ	
	Clonus	Tonus			
NBQX	6.96	4.52	38	32.66	[61,80]
GYKI 52466	4.3	3.6	6.9	22.5	[61,91]
Talampanel (GYKI 53773, LY-300164)	4.5	3,27	8.6	16.8	[61,100,103]
BIIR 561 CL (Irampanel)	ND	ND	2.8-3	ND	[116,119]
NS1209 (SPD 502)	ND	ND	6.1	ND	[86,123]
EGIS-8332	2.4	1.4	5.3	3	[125,126]
Perampanel (E2007)	ND	0.47	1.6	0.94	[72]
Quinazolinedione sulfonamides (29)	ND	5.5	23	ND	[47,48]

This table reports the effects of the main AMPA antagonists against audiogenic seizures, in the MES test and PTZ models of epilepsy. Molecules not reported in the table were not tested in these models. For other models refer to the test. Values represent ED_{50} expressed as mg/kg. 29 refers to compound 29 of the quinazolinedione sulfonamides series.
MES: Maximal electroshock; ND: Not determined in any available study; PTZ: Pentylenetetrazole.

additionally, AMPA/kainate receptor antagonists potentiate the anticonvulsive action of NMDA receptor antagonists. Thus, a simultaneous blockade of glutamate-mediated excitation, at more than one subtype of its ionotropic receptors, leads to a pronounced anticonvulsive effect, with no further increase in the adverse effects suggesting that combinations of AMPA and NMDA receptor antagonists might also provide a new strategy for treatment of epileptic seizures [90].

GYKI 52466, and its 3-N substituted 3,4-reduced analogue (GYKI 53405), are the best-known AMPA receptor antagonists from the 2,3-benzodiazepine chemical structure, which selectively antagonizes AMPA receptors in a noncompetitive manner [91,92]. These compounds, termed as negative allosteric modulators of AMPA receptors, can terminate ongoing status epilepticus, providing long-lasting inhibition of electrographic and behavioral seizure activity [74,82,91,93]. GYKI 52466, like other structurally related 2,3-benzodiazepine selective AMPA receptor antagonists, exhibits excellent bioavailability and blood–brain barrier penetration [92]. Noncompetitive AMPA receptor antagonists have shown weak *in vitro* efficacy but a wider anticonvulsant spectrum in seizure models than competitive antagonists possibly because their blocking action cannot be overcome by high synaptic glutamate levels [74,94]. Equivalent protection would require higher doses of a competitive antagonist, but these higher doses would be more likely to induce side effects. Competitive AMPA receptor antagonists had poor water solubility at physiological pH and, combined with rapid kidney excretion, caused nephrotoxicity due to precipitation in the kidneys [94]. Finally, AMPA receptor antagonists have weak activity in genetic models of absence epilepsy indicating that they will not be of use in the treatment of absence seizures in humans [95-98], although, low doses of **6** (**Figure 4**), a highly potent noncompetitive AMPA receptor antagonist) potentiate the effects of ethosuximide against absence seizures in WAG/Rij rats [68,99]. Overall, AMPA receptor antagonists show a great potentiality in preclinical models of epilepsy with effects on a wide range of generalized and partial seizures with a potential neuroprotective effect, which might be accompanied by antiepileptogenic properties. Despite this promising scenario, only few compounds did undergo a comprehensive preclinical screening or reach clinical trials; the main difficulties encountered during development are represented by their low water solubility and the incidence of side effects such as sedation, dizziness and ataxia (see also Section 5). The next part of this section will review the most recent results in preclinical models of the latest AMPA receptor antagonists, ED_{50} values are reported in **Table 1**.

4.1 Talampanel

Talampanel (GYKI 53773, LY-300164), the active enantiomer of GYKI 53405 [100], is a stereoselective and noncompetitive AMPA receptor antagonist, which also weakly inhibits kainate receptors [101]. It has been shown to be anticonvulsant in various experimental models of seizures such as the MES (ED_{50} = 4.6 mg/kg) and PTZ tests (ED_{50} = 16.8 mg/kg) [100,102-105]. Furthermore, talampanel is effective in amygdala-kindled rats [106,107], chemically kindled seizures in mice [103,105,108] and arrests seizures in a phenytoin-resistant model of status epilepticus in mice [103,109]. In the WAG/Rij rat model of absence epilepsy, it showed only modest effects. When used in combination studies, it was found to potentiate the effects of various classical antiepileptic drugs (i.e., valproic acid and phenobarbital), however, in some cases, tolerability was lower [105,108] similarly to GYKI 52466 [110,111]. Moreover, talampanel shows neuroprotective effects in a model of focal cerebral ischemia [112], attenuates AMPA-induced hippocampal injury in neonatal

rodents [113] and improves functional deficit in rats after transient ischemia also improving survival rate [114]. Finally, it was recently demonstrated, in a model of early hypoxia-related seizures, that talampanel both reduces seizures dose-dependently at doses of 7.5 – 10 mg/kg and given as a pretreatment it prevents seizure-related neuronal damage in rats [115]. Talampanel has undergone several preclinical studies and after completing early clinical studies has been involved in many clinical trials regarding epilepsy but also Parkinson's disease and recurrent glioma (see Section 5).

4.2 BIIR 561 CL

BIIR 561 CL (Dimethyl-(2-[2-(3-phenyl-[1,2,4]oxadiazol-5-yl)-phenoxyl]-ethyl)-amine hydrochloride), also known as irampanel, is a compound combining blocking effects on both AMPA receptors and Na^+ channels [116]. This compound was developed on the suggestion that this particular combination of effects may offer protection in various diseases of the CNS such as epilepsy or ischemia [87,117]. BIIR 561 CL reduces AMPA currents as a noncompetitive antagonist, binding on the same receptor site of GYKI 53655, with an IC_{50} value of 10.8 μM [116,118], furthermore, it suppresses kainate responses in cultured neurons with an IC_{50} of 9.5 μM [118]. *In vivo*, BIIR 561 CL protects against AMPA-induced lethality in mice with an ED_{50} of 4.5 mg/kg [119]. This compound induces dose- and time-dependent protection against tonic seizures in the MES test with an ED_{50} value of 3.0 mg/kg and showed an anticonvulsant effect in the amygdala-kindling model at doses comprised between 3 and 11 mg/kg [116,119]. These protective effects make BIIR 561 CL an attractive candidate for neuroprotective therapy of diseases of the CNS such as epilepsy and ischemia [119,120]; however, its development seems to be blocked in the epilepsy field [121].

4.3 NS1209

NS1209 (SPD 502) is a competitive AMPA receptor antagonist with high affinity, which selectively inhibits AMPA receptor currents with little effect on NMDA receptor currents [86]. Furthermore, NS1209 also blocks GluR5 kainate receptors with similar potency to its action on AMPA receptors [122]. It shows potent and dose-dependent anticonvulsant activity in a variety of preclinical models [123]; NS1209 increases the threshold for electroconvulsive tonic seizures in mice at a dose of 40 mg/kg [86] and it has been reported to protect against audiogenic seizures in mice [123]. As competitive AMPA antagonists are very likely to develop sedation and other unbearable side effects in patients, attention for this compound has been focused on status epilepticus and neuroprotection. It was early reported that NS1209 was able to prevent ischemic damage in the hippocampus of gerbils [86], and reduced cell death after transient brain ischemia in rats protecting several cell lines [124]. Based on this observation, NS1209 was tested against electrically and chemically induced status epilepticus and it was found to be effective in both models [81]. In the same study, its neuroprotective effects were compared with dose of diazepam and despite it showed some effects in protecting from neuronal damage after kainic acid status epilepticus, it was less effective than diazepam; it was concluded that this water-soluble AMPA antagonist might be added to the armamentarium of drugs used in human status epilepticus [81]. Finally, it was recently demonstrated that NS1209 has neuroprotective effects comparable with those of valproic acid in the status epilepticus model obtained by sustained electrical stimulation of the basolateral amygdala in rats concluding that it is powerfully neuroprotective, and may possess disease-modifying effects following brain insult [84]. In conclusion, NS1209, even if it might be effective against seizures, suffers from its own mechanism of action that is expected to lead to sedation and ataxia; however, its anticonvulsant efficacy is accompanied by an unexpected neuroprotective action in comparison to other anticonvulsant drugs, which might in turn be very important.

4.4 EGIS-8332

EGIS-8332 is a newly developed potent selective noncompetitive AMPA antagonist with 2,3-benzodiazepine chemical structure [107]. EGIS-8332 and its analogue EGIS-10608 have favorable pharmacokinetic and toxicological profiles with a prolonged duration of action compared with their related first-generation compounds [125]. EGIS-8332 has demonstrated anticonvulsant effects in a range of animal models [125]. EGIS-8332 also demonstrated effective neuroprotective action in experimental models of global and focal cerebral ischemia [125-127] and it may be useful as a potential therapeutic agent for the treatment of stroke, if treatment is initiated shortly after the beginning of ischemia [128]. Patch clamp studies and neuroprotection tests *in vitro* demonstrated the inhibitory potency of EGIS-8332 on AMPA/kainate currents in cerebellar Purkinje cells and in telencephalon neuronal cell cultures [129]. The inhibitory action of EGIS-8332 is stereospecific and follows a noncompetitive mechanism [129]. Through the temporary inhibition of AMPA receptors, it significantly improves the motor skills in a mouse model of the incurable juvenile Batten disease, a neurodegenerative disorder in children in which the deficit and progressive neurological decline of the disease are associated to an abnormally increased AMPA receptor activity in the cerebellum [130-132]. EGIS-8332 possesses anticonvulsant actions in the MES test with an ED_{50} of 5.3 mg/kg [126]. Good anticonvulsant actions of EGIS-8332 were also demonstrated against sound-induced seizures in DBA/2 mice (ED_{50} = 1.4 and 2.4 mg/kg for tonus and clonus, respectively) and chemically induced seizures in mice (nicotine, bicuculline, pentylenetetrazole, picrotoxin), however, the anticonvulsant effect of GYKI 53405 was superior than that of EGIS-8332 indicating that it is potentially useful for the treatment of epilepsy but this may not be a preferred therapeutic indication for this compound [125]. Indeed, EGIS-8332 is a better anti-ischemic agent than GYKI 53405 [125].

4.5 Perampanel

Perampanel (E2007) is a potent, noncompetitive and selective AMPA receptor antagonist with broad spectrum anticonvulsant activity in preclinical models of both partial (amygdala-kindling model of temporal lobe epilepsy) and generalized seizures (audiogenic, PTZ- and MES-induced seizure tests) [72]. It is known to reduce calcium flux mediated by AMPA but not NMDA-receptors in cultured cortical neurons [72] and selectively reduces AMPA receptor-mediated synaptic transmission at similar concentrations to those in plasma following anticonvulsant doses [133]. Perampanel protects from audiogenic seizures in DBA/2 mice with an ED_{50} of 0.47 mg/kg, tonic extension in the MES test (ED_{50} = 1.6 mg/kg) and PTZ-induced seizures (ED_{50} = 0.94 mg/kg) with a higher potency than carbamazepine and valproic acid [72]. Furthermore, perampanel also showed efficacy in the rat amygdala-kindling model of temporal lobe epilepsy increasing the afterdischarge threshold at 10 mg/kg and decreasing motor seizure duration at 5 mg/kg [72]. Moreover, perampanel, also acting synergistically with other AEDs, completely inhibited the 6Hz 'psycomotor seizures' (ED_{50} between 2.1 and 2.8 mg/kg depending on stimulus intensity), suggesting that AMPA receptor antagonists may be promising candidates for combination therapy [72,134]. The therapeutic window for antiseizure effects of perampanel in rodents appears small due to significant effects on motor coordination. In both the mouse and rat rotarod tests, perampanel showed significant effects on motor coordination (TD_{50} = 1.8 in mice and 9.14 in rats) close to the concentrations required to reduce seizure activity [72]. In preclinical animal studies, perampanel pharmacokinetic was evaluated in rats, dogs and primates and it was shown to have a good oral bioavailability across species, and notably a half-life of 7.55 h in primates [72].

4.6 IKM-159

A novel series of heterotricyclic glutamate analogues (named IKM's) acting as AMPA receptor-selective antagonist demonstrates partial subunit specificity for GluA2-, GluA3- and GluA4-containing receptors [135,136]. The IKM molecules are all heterotricyclic hexahydro-2H-furo[2,3-c]pyrrole-dicarboxylic acids with variable third ring components [135,136]. IKM-159 (tetrahydropyridine derivative) is the most potent molecule of this series acting as an AMPA receptor-selective antagonist; it was shown to reduce neuronal hyperexcitability in an *in vitro* model of SE through inhibition of AMPA receptors suggesting that this compound could serve as a useful starting point for the development of potentially clinically relevant subunit-selective antagonists [73]. IKM-159, at a fixed concentration of 30 μM, reduced charge transfer during spontaneously occurring, polysynaptic bursts of EPSCs mediated by AMPA receptors in cultured hippocampal neurons [73]. It was then tested on hippocampal slices, where IKM-159 was able to inhibit AMPA receptor-mediated EPSCs but not KA or NMDA receptor-mediated events [73]. The selectivity for glutamate receptor subunits was also tested in transfected HEK-293 cells; IKM-159 (30 μM) inhibited heteromeric GluA1/GluA2 receptors and GluA4 homomeric AMPA receptors, it had weaker activity on homomeric GluA3 receptors and did not inhibit activation of homomeric GluA1 receptors. Therefore, at this concentration, it has preferential activity for GluA1/GluA2 AMPA receptors. Finally, it was able to reduce spontaneous action potential firing frequency in cultured hippocampal neurons and neuronal hyperactivity under 0-Mg^{2+} conditions, an *in vitro* model of status epilepticus [73]. As IKM's molecules fail to displace AMPA, a noncompetitive mechanism of action has been suggested [135,136], however, it was later demonstrated that the interaction of IKM-159 with AMPA receptors might be more complex as it was not consistent with either simple competitive or state-independent allosteric inhibition [73].

4.7 Quinazolinedione sulfonamides

Quinazoline-2,4-diones with a sulfonamide group attached to the N(3) ring atom constitute a novel class of competitive AMPA receptor antagonists [47,48]. This class of molecules shows nanomolar affinity for the AMPA receptor and anticonvulsant activity against electrically induced seizures and audiogenic seizures in DBA/2 mice [48]. However, receptor affinity is not directly correlated with their ED_{50}, which might be explained by the chemical properties of these compounds. In a subsequent study, these derivatives were optimized for oral activity with the identification of a molecule (compound **29**) with an oral ED_{50} of 5.5 mg/kg against audiogenic seizures and an affinity of 360 nM [47].

5. AMPA antagonists' effectiveness in clinical trials

Competitive AMPA antagonists can be considered anticonvulsant agents with clinical potential, and even some currently used anticonvulsant drugs have antagonist action at AMPA receptors [137]. AMPA receptor antagonists may be particularly beneficial in combination with other treatments [138] and have been shown to be effective in add-on studies in humans with a limited side effect profile (see **Table 2**) [139].

Despite the rationale and the preclinical evidence, no compound developed as a glutamate receptor antagonist has yet become a clinically accepted therapy for the treatment of epilepsy.

Clinical trials in adults demonstrated the anticonvulsant efficacy of talampanel as monotherapy in refractory epilepsy [139] and as an add-on drug for partial complex seizures therapy [100,140]; however, its use was associated with adverse events including mild-to-moderate ataxia and dizziness occurring around plasma peak concentration. Furthermore, talampanel has a relatively short half-life, which may limit its utility in the clinical setting [139]. In the first trial available [140], talampanel was used in a double-blind, placebo-controlled, crossover study in 49 patients with refractory partial seizures

Table 2. Overview of clinical trials utilizing AMPA receptor antagonists.

Drugs	Dose	Efficacy	Safety	Ref.
Talampanel	35-mg single dose Concomitant AEDs (CBZ, CLB, CZP, LTG, PRM, TPM, VPA, VGB)	Intractable Epilepsy	Dizziness, Ataxia, Drowsiness, Headaches	[139]
	25, 60 or 75 mg, t.i.d.	Refractory Partial Seizures	Dizziness, Ataxia	[140]
Perampanel	2 – 12 mg/day	Refractory partial-onset Seizures	Nausea, Gait Disturbance, Dysarthria, Insomnia. Severe Dizziness	[144]
BGG492	50 – 150 mg/day	Photosensitive Epilepsy Refractory Partial Seizures		clinicaltrials.gov

AED: Antiepileptic drug; CBZ: Carbamazepine; CLB: Clobazam; CZP: Clonazepam; LTG: Lamotrigine; PRM: Primidone; TPM: Topiramate; VGB: Vigabatrin; VPA: Valproate.

at three doses (25, 60 or 75 mg, t.i.d.). It was effective in reducing seizure frequency with a median seizure reduction of 21% [140]; however, various confounding elements were not evaluated and were not considered to invalidate the overall results [123]. According to this study, dizziness (52%) and ataxia (26%) were the only significant adverse events reported by the patients, however, talampanel was reported to increase carbamazepine plasmatic concentration and its serum levels were reduced by their enzyme inducers. In 2003, the single- and multiple-dose pharmacokinetics, safety, and tolerability of talampanel in patients with intractable epilepsy together with the potential for pharmacokinetic interaction was assessed in 14 patients [139]. When data obtained were also compared with these available from healthy volunteers, authors found that peak plasma concentrations was achieved between 1 and 3 h after oral ingestion, mean half-life was 3 h, which was lower than healthy volunteers and after multiple doses at steady state it was 5.6 h. Furthermore, it was evidenced that in patients taking enzyme inducers, plasma concentration were 50% lower and talampanel itself inhibited valproic acid metabolism. No serious adverse events were reported; the most frequently reported (about 40% of patients) being dizziness, ataxia, drowsiness, and headaches even though these side effects appeared at lower doses than in healthy volunteers, it was suggested that this might depend on the concomitant use of other AEDs [139]. Finally, talampanel has recently been used in other clinical trials of CNS pathologies different from epilepsy such as glioblastoma [141,142], amyotrophic lateral sclerosis [143].

Perampanel, a novel orally active, is a prospective antiepileptic agent currently in Phase III clinical studies for refractory partial-onset seizures. Two Phase II, dose-escalation, placebo-controlled studies demonstrated that perampanel was safe and well-tolerated when given as adjunctive therapy in patients with refractory partial-onset seizures [134,144]. Selective non-competitive AMPA receptor antagonism has been associated with a low side effect profile [9,140,145] and the lack of effect of perampanel on synaptic NMDA receptor-mediated responses suggests that psychotomimetic issues are less likely to arise [12,146,147]. Recent reports have indicated that perampanel, at doses of up to 12 mg/day, is well tolerated in humans [148], and from 4 mg/day is effective as an add-on antiepileptic treatment in double-blind trials in patients with refractory partial onset seizures [148]. Perampanel was much more stable in the presence of human liver microsomes than in the presence of microsomes from non-human animal species, suggesting that the half-life of perampanel may be even longer in humans. This may offer advantages for perampanel over talampanel, because a less frequent dosing regimen may be possible, with a consequently smoother drug concentration profile and potentially fewer adverse events [144]. Perampanel has potential as a treatment in patients whose seizures are refractory to other AEDs, and may be effective either alone or as add-on therapy with other AEDs [148]. These studies show also evidence of safety and tolerability of this novel selective AMPA antagonist with the most frequent and dose-dependent side effect being dizziness and headache [148]. Finally, also perampanel is currently undergoing or has finished other clinical trials regarding Parkinson [149,150] and patients with painful diabetic neuropathy or post-herpetic neuralgia (Study NCT00592904; clinicaltrials.gov).

Another AMPAR antagonist that is undergoing clinical trials for epilepsy is BGG492 (selurampanel; N-[6-(1-methyl-1H-pyrazol-5-yl)-7-(prpan-2-yl)-2,4-dioxo-1,4-di hydroquinazolin-3(2H)-yl]methanesulfonamide). Very few information are available about this compound, from the clinicaltrials.gov website, it appears that BGG492 completed a first Phase II clinical trial in patients with photosensitive epilepsy (NCT00784212; EudraCT number: 2007-005418-38) and then two studies in patients with partial seizures. The first was carried out in monotherapy in patients with refractory partial seizures undergoing inpatient evaluation for epilepsy surgery (EudraCT number: 2008-005065-64) and the second as an add-on therapy (EudraCT number: 2010-018766-23); all these studies result completed (clinicaltrials.gov), however, the results are not available. At this moment, patients are being recruited for an extension study of safety and tolerability of

BGG492 adjunctive therapy in patients with partial onset seizures (NCT01338805). Finally, BGG492 has also been studied in a Phase II clinical trial against migraine (EudraCT number: 2008-005392-10) and in patients with chronic subjective tinnitus (EudraCT number: 2010-022166-27).

Despite their considerable clinical potential, the use of AMPAR antagonists in humans should be contemplated with high caution due to their widespread actions in the CNS. It has to be noted that only few clinical trials have been reported till now [151] in fact, the low-water solubility of most currently available AMPAR antagonists limits their entry as drug candidates. Fortunately, as reported above, recent breakthroughs in the development of water-soluble derivatives have been made. Preliminary studies in humans did not evidence any serious adverse effect at therapeutic doses with the exception of lack of motor coordination. However, the principal problem of most of the AMPA antagonists reported till now is the short duration of action and the absence of any oral activity, both properties being essential for treatment of chronic diseases.

6. Conclusions

We are giving an overview of the most relevant results in the research of AMPA antagonists to be used in the epilepsy field. The first part of our review focalizes on the structure of AMPAR; many advances have been achieved since their discovery and the actual knowledge of its biochemical structure is very detailed. The most relevant results are the identification and characterization of the binding sites for both glutamate and allosteric modulators, which together with QSAR studies greatly improve the capability of researchers in the field; we are presenting a brief description of the main characteristics. These latter studies have brought to the development of several ligands including different chemical classes of antagonists. Starting from the discovery of the first competitive antagonists with quinoxalinedione scaffold, a description of all QSAR studies and pharmaceutical development has been reported; the most relevant chemical scaffolds are represented by oxoquinolines, the quinazolinedione sulfonamide derivatives by Novartis, the dihydroimidazoindenopyrazine derivatives by Aventis Pharma, isatinoximes and decahydroisoquinoline derivatives. However, most of these competitive AMPA antagonists will have to be studied from a pharmacokinetic and toxicological point of view. On the other side, also the development of non-competitive AMPA antagonists has been greatly improved with several drugs also reaching clinical trials. From a chemical point of view, we have reported the most relevant studies starting from the first generation of 2,3-benzodiazepine derivatives reporting the main chemical modifications that have led to the discovery of talampanel and other very potent and selective negative allosteric antagonists. 2,3-Benzodiazepine together with the series of 1,2-dihydrophthalazines, obtained by contraction of the former, have been used to determine a tridimensional quali-quantitative pharmacophore model with the requirements to interact with AMPAR in a noncompetitive manner. New chemical entities are represented by the chemical scaffold of perampanel, developed by Eisai, and IKM159. The former has already faced several clinical trials, whereas the latter is still undergoing SARs to optimize effects. The most important SARs and chemical identities have been reported, being useful for future studies to both optimize the pharmacological profile and identify new chemical scaffolds. The second part of the review focalizes on preclinical and clinical studies of the most relevant researches on the effects of AMPAR antagonists in the field of epilepsy. We give a brief general description of the effectiveness of AMPAR antagonists in various animal models of epilepsy also considering their potential neuroprotective action. Generally, AMPAR antagonists have a broad spectrum of anticonvulsant action on both models of partial and generalized seizures with the exception of absence seizures. Due to their neuroprotective action, it has also been suggested that AMPAR antagonists possess antiepileptogenic properties and efficacy against status epilepticus; they might be helpful in the prevention of the development of epilepsy following brain injury. In the same section, we analyze in details the efficacy of the most important new derivatives in the various models where they have been tested; in particular, we discuss the effects of talampanel, NS1209, EGIS-8332, perampanel, IKM-159 and quinazolinedione sulfonamides derivatives by Novartis. Overall, these compounds show an excellent activity in preclinical models of epilepsy and neurodegeneration. Finally, we have reviewed the available data obtained in clinical trials in the field of epilepsy. Only talampanel, perampanel and BGG492 have been studied in humans for epilepsy but also other neurological diseases. We reported for every drug the available results relatively to their efficacy and tolerability. Talampanel has been used as an add-on drug for partial complex seizures and in monotherapy in refractory patients; despite results are encouraging, its short half-life and drug–drug interaction profile remain the major problem. Perampanel is currently undergoing Phase III trials for patients with refractory partial seizures and has already completed Phase II trials as adjunctive therapy obtaining good results. The last AMPAR antagonist under clinical studies is BGG492, unfortunately, the results obtained in the clinical trials have not been published and therefore, it is not possible to draw any definitive conclusion on its effectiveness. However, as it has already completed three trials on partial seizures while a fourth one is recruiting, we can suppose that the drug is worth to be studied. Overall, clinical trials have confirmed the effectiveness of AMPAR antagonists also indicating the possible tolerability in therapeutic use.

7. Expert opinion

The development of AMPAR antagonists has recently gained new interest as their potential use in several neurological pathologies such as Amyotrophic Lateral Sclerosis (ALS),

Parkinson Disease (PD), glioblastoma multiforme and gliomas seems to be therapeutically useful. Research in epilepsy is still a very productive and exciting field both from a preclinical and clinical point of view. The major challenges that are still under extensive study are represented by: i) effective drugs in refractory patients; ii) effective drugs against epileptogenesis; iii) safer drugs. In this light, AMPAR antagonists are indeed of interest relatively to the first two points, although their tolerability has slowed down their clinical development. The key findings are represented by different aspects: i) The possibility of modulating AMPAR both competitively and noncompetitively; this has apparently differentiated their potential application: competitive antagonists are investigated mainly for their suppressive action against status epilepticus also in accordance with their neuroprotective/antiepileptogenic potential effects, whereas noncompetitive antagonists are considered for their potential antiepileptic effects.

1) The possibility of creating different chemical entities retaining effects on AMPAR, that in the next few years might bring some new compounds to clinical trials. Very exciting is the possibility that IKM derivatives might have a unique mechanism of action on these receptors as suggested in these earlier studies, indeed they are not competitive antagonists, neither their mechanism is consistent with allosteric antagonism.
2) The excellent activity of NS1209 against status epilepticus and its neuroprotective effects might represent a very excellent achievement. It remains to be better defined, if the drug is suitable for clinical use; it has been used in a Phase II clinical trial for peripheral neuropathic pain [152].
3) The main weakness of this research field is that a high number of promising molecules reaches clinical trials, but in most of the case they display low tolerability and unfavorable pharmacokinetic profiles.

AMPAR antagonists represent indeed very promising drugs against epilepsy and the recent excellent clinical results obtained by perampanel confirm that this area of research holds a great potential. Extremely important will be to understand if these drugs possess antiepileptogenic and neuroprotective properties in humans; this represents the biggest challenge of the future, which is very much complicated by the difficulties to define it in clinical settings.

We believe that in the near future, the new chemical structures identified (i.e., IKM derivatives and quinazolinedione sulfonamides) will turn out to be very promising scaffolds leading to some effective compounds; talampanel and perampanel should be soon marketed for their use in epileptic patients and possibly in other diseases, this more than anything else will definitively determine if all the efforts in the field were worthwhile as they really should be. The most promising molecule seems to be perampanel, however, our lack of knowledge on BGG492 can raise some doubt; furthermore, the most recent synthetized agents still need a lot of investigation but all of them have the potentiality to obtain significant results. In conclusion, great progresses have been achieved and the recent results focus again attention on these compounds to develop new anticonvulsants targeting AMPA receptor complex.

Declaration of interest

The authors state no conflict of interest and have received no payment in preparation of this manuscript.

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