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Design and Synthesis of Selurampanel, a Novel Orally Active and Competitive AMPA Receptor Antagonist

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A series of potent quinazolinedione sulfonamide antagonists of the α-amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid (AMPA) receptor were designed and synthesized. The structure–activity relationships (SAR) and in vivo activity of the series were investigated. In particular, compound **1S** (selurampanel; *N*-[7-isopropyl-6-(2-methylpyrazol-3-yl)-2,4-dioxo-1*H*-quinazolin-3-yl]methanesulfonamide) has shown excellent oral potency against maximal electroshock seizure (MES)-induced generalized tonic–clonic seizures in rodents as well as significant activity in patients suffering from various forms of epilepsy. The X-ray crystal structure of selurampanel bound to the AMPA receptor hGluA was also obtained.

Despite the fact that several antiepileptic drugs (AEDs) are on the market, there is still a high medical need for improved treatments of epilepsy, as about 40% of patients are inadequately controlled[1] or suffer from adverse events.[2,3] Current treatment strategies focus on three main biological targets: the γ-aminobutyric acid (GABA) system, voltage-gated sodium channels, and calcium channels.[4]

Based on this information, AEDs with new mechanisms of action are of interest. Because glutamate is the principal excitatory neurotransmitter of the central nervous system where it acts at both ionotropic and metabotropic receptors, a novel approach to treat epilepsy could be by modulation of the glutamatergic system and in particular the AMPA receptor. Metabotropic glutamate receptors (mGluRs) are G-protein-coupled receptors and, to date, eight subtypes, subdivided into three groups, are described. Ionotropic glutamate receptors (iGluRs) are classified according to their agonist selectivity toward *N*-methyl-D-aspartate (NMDA), kainic acid, and α-amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid (AMPA) receptors. For every class of iGluR several subunits are known: NR1, NR2A–D, NR3A,B for NMDA receptors, GluK1–5 for kainate receptors, and GluA1–4 for AMPA receptors. iGluRs mediate rapid excitatory neurotransmission and are linked to a variety of neurodegenerative and psychiatric diseases such as ischemic brain damage, amyotrophic lateral sclerosis, schizophrenia, and, most significantly, epilepsy.[5] Overstimulation of the glutamatergic system plays a role in triggering seizures associated with epilepsy.[6]

AMPA receptor antagonists are currently in clinical development as 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 excessive neuronal activation leading to epileptic seizures.[7,8,9] Second, they potently and efficiently block seizures in animal models of seizures and epilepsy. Third, changes in the distribution, expression, and editing of AMPA receptors have been reported in human epileptic hippocampal tissue.[10–16] Fourth, in Rasmussen's encephalitis, an autoimmune disease, one of the autoantigens causing the disease is directed against the AMPA GluA3 receptor.[17–19] And finally, there is direct clinical evidence that the non-competitive AMPA receptor antagonist perampanel, which has been approved for clinical use, is effective in patients with partial-onset seizures.[9]

The quinazolinedione-sulfonamide structural class presented herein was designed as hybrid between two well-known classes of AMPA antagonists, namely kynurenic acids and quinoxalinediones (Figure 1).[20,23–25] Herein we report the preparation and biological activity of a set of novel quinazolinedione-sulfonamides as potent and orally bioavailable AMPA antagonists.

The synthesis of quinazolinedione-sulfonamides **1** was accomplished by following the general procedure highlighted for the 6-isopropyl derivatives (Scheme 1). Starting from commercially available 4-isopropyl-1-methyl-2-nitrobenzene, Vilsmaier

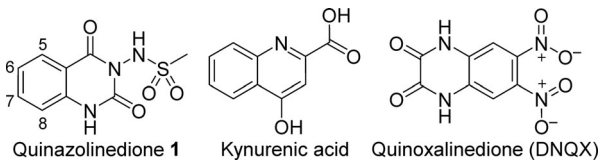

Figure 1. AMPA antagonists.

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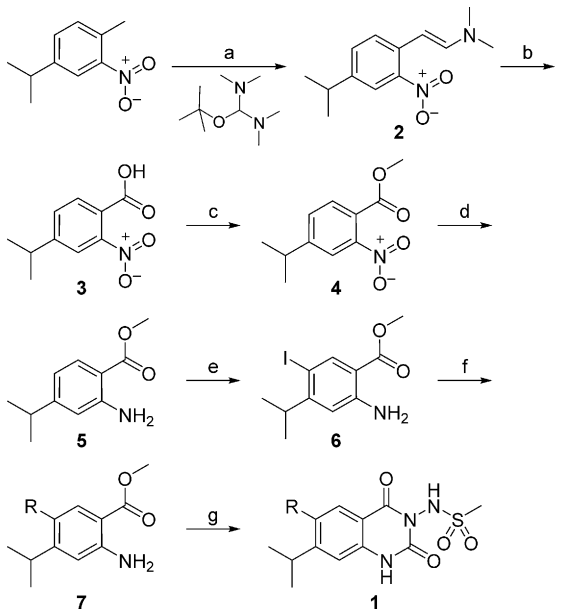


Scheme 1. Representative synthesis of quinazolinedione-sulfonamide. *Reagents and conditions*: a) reflux (150 °C oil bath), 20 h, 95%; b) $KMnO_4$, KOAc, *t*BuOH/H_2O, 25 °C 1.5 h, quant. (crude); c) 1. $SOCl_2$, reflux, 2. MeOH, 86%; d) H_2, MeOH, 10% Pd/C, 97%; e) I_2, Ag_2SO_4, EtOH, 60%; f) [bistriphenylphosphine]dichloropalladium dioxane (0.1 equiv), R–$SnBu_3$ (1.2 equiv), 85 °C, 18 h; g) 1. 4-chlorophenylchloroformate (1 equiv), Et_3N (2 equiv), CH_2Cl_2, RT, 4 h, then evaporation, 2. methanesulfonyl hydrazide (1.2 equiv), THF, RT, 30 min, then 1 M NaOH (1 equiv), RT, 30 min.

reaction yielded enamine intermediate **2**,[21] which was oxidatively cleaved to carboxylic acid **3** using potassium permanganate. Esterification of the carboxylic acid followed by reduction of the nitro group yielded compound **5**. Regioselective iodination with iodine and silver sulfate afforded **6**.[22] Subsequent palladium-mediated carbon–carbon couplings of this intermediate with various heteroaryl stannane reagents provided the required 4-isopropyl-5-heteroaryl-disubstituted 2-aminobenzoates **7**. Final ring closure of **7** was effected by treatment with 4-chlorophenylchloroformate to generate the activated carbamate derivative, which was then allowed to undergo reaction with methanesulfonyl hydrazide to furnish the expected products **1** after base-catalyzed cyclization. The 6-chloro, 6-methyl, and 6-trifluoromethyl analogues were synthesized in a similar manner by starting from the corresponding commercially available 2-aminobenzoates.

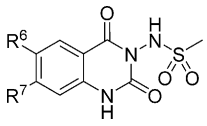
Compound **1F** was prepared similarly from the appropriate 2-aminobenzoate derivative. It was synthesized by starting from commercially available methyl 2-nitro-4-trifluoromethyl-5-fluorobenzoate by nucleophilic aromatic substitution with methanesulfonylacetic acid benzyl ester followed by reduction of the nitro group with concomitant decarboxylation. Finally, the 2-aminobenzoate derivative required for the preparation of compound **1G** was synthesized by starting from commercially available methyl 2-nitro-4-trifluoromethyl-5-fluorobenzoate by nucleophilic aromatic substitution with methylamine. Following reduction of the nitro group, the bis-aniline was treated with acetyl chloride to yield a mixture of mono- and bis-acetylated anilines, from which 5-(acetylmethylamino)-2-amino-4-trifluoromethylbenzoic acid methyl was separated.[23] Detailed experimental procedures can be found in Allgeier et al.[23]

The affinity of new compounds (Tables 1 and 2) at the AMPA receptor was assessed by measuring the inhibition of the binding of [^{3}H]CNQX at the AMPA receptor according to previously described methods.[26] The in vivo activity of the compounds was assessed in the audiogenic seizure test in DBA/2 (Dilute Brown Agouti) mice which is a model of reflex epilepsy.[27–29] As this model does not discriminate between different drug mechanisms and because seizures cannot be provoked in humans by auditory stimulation, best compounds were also assessed in the maximal electroshock seizure (MES) test in rodents, which is highly predictive for the activity of drugs against generalized tonic–clonic seizures in humans.[30,31]

It was found that various substituents at position 7 imparted moderate affinity and oral activity to the corresponding analogues, as shown in Table 1. In a first optimization cycle, 6-imidazolyl and 6-triazolyl derivatives were synthesized.[23,24] These substituents were reported to substantially increase affinity of related scaffolds, for example, quinoxalinedione, for the AMPA receptor.[32] In line with published data, the new analogues embedding these 6-substituents showed high affinity for the AMPA receptor. However, despite good improvement in binding affinity, the resulting products showed no in vivo activity, following oral administration of the drug, as shown in Table 1. Pharmacokinetic profiling of **1E**[25] indicated a very low bioavailability of this compound (10%), which may explain its lack of oral activity.

The next challenge was thus to prepare quinazolinedione derivatives which would show oral activity in animal models of epilepsy. The availability of a number of in-house X-ray crystal structures in conjunction with molecular modelling efforts were important assets to assist the selection of new substituents which would potentially interact with the receptor, keeping in mind that the ultimate goal was to influence the pharmacokinetic properties of the molecules in order to gain in vivo activity.

Table 1. Binding affinity, in vivo activity of selected quinazolinediones **1**.



Compd	R^6	R^7	IC_{50} [μM][a]	AS p.o. ED_{50} [mg kg^{-1}][b]
1A	H	*t*Bu	4.9 ± 0.1	9.7
1B	H	Cl	3.6 ± 0.2	15
1C	H	CF_3	0.7 ± 0.1	24
1D	H	NO_2	1.2 ± 0.1	0% @ 30 mg kg^{-1}
1E		CF_3	0.046 ± 0.01	0% @ 30 mg kg^{-1}

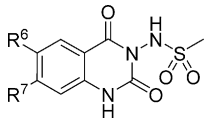
[a] Rat AMPA [^{3}H]CNQX binding. [b] Audiogenic seizure in DBA/2 mice. Values are the geometric mean of at least three independent experiments.

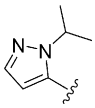
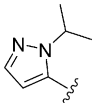
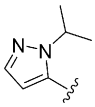
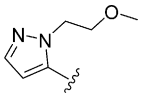
X-ray analysis of hGluA2 complexes with a number of close analogues of **1E**[24,25,40] allowed us to identify important ligand–receptor interactions. The 3D structure highlights the exquisite complementarity of the quinazolinedione scaffold for the AMPA binding site. The sulfonamide nitrogen atom accepts a hydrogen bond from NH_2-Arg485 and is thus possibly negatively charged in the complex. The quinazolinedione ring system makes favorable π–π stacking interactions with Tyr450 and establishes a network of hydrogen bonds with CO-Pro478, NH-Thr480, and NH1-Arg485. An interaction is observed between the 3-nitrogen atom of the imidazolyl substituent and Thr686. The importance of this interaction correlates with improved binding affinity. Moreover, the five-membered heterocycle establishes favorable hydrophobic contacts with Met708.

With the aim to restore oral activity, novel molecules were designed according to the following strategy. To preserve strong interactions with Thr686, substituents at position 6 containing good hydrogen bond acceptors (high pK_β), in a topology similar to that found in **1E**, were introduced in the quinazolinedione scaffold. Preference was given to moieties bearing non-basic hydrogen bond acceptors in order to avoid the formation of zwitterionic species at physiological pH. In addition, substitution patterns the could possibly increase lipophilicity (increase cLog*P*) without having detrimental effects on solubility were selected, because a delicate balance between these two parameters was thought to be required for good oral absorption and brain penetration. Special attention was given to the identification of substitution patterns bringing the pK_a of the sulfonamide moiety as close as possible to physiological pH in order to achieve a percentage, as high as possible, of neutral species in solution at physiological pH. Finally, the overall size of the analogues was kept small, with $M_r < 450$ Da.

A set of compounds potentially fulfilling these criteria were synthesized and allowed the discovery of a number of potent and orally active compounds which are highlighted in Table 2. As exemplified in the 6-trifluoromethyl series, introducing a flexibly linked hydrogen bond acceptor at position 6 yielded at most a threefold improvement in affinity for the sulfone analogue **1G** relative to the naked trifluoromethyl analogue **1C**. It is well accepted that hydrogen bonds are sensitive to the local chemical environment[33,34] and may offer limited binding energy gains when located in polar and hydrated surface regions of a protein. Introducing tetrahydrofuran at position 6 (in **1H**) yielded a compound equipotent to the sulfone analogue and displaying moderate oral activity. Embedding the hydrogen bond acceptor into a five- or six-membered heteroaromatic ring as in **1I**–**1K** led again to a twofold improvement in affinity. This result may reflect the favorable hydrophobic contacts with Met708 and/or the increased hydrophobic shielding of the aforementioned hydrogen bond. These compounds, however, lack oral activity in the MES model. To further increase the hydrophobic character near the hydrogen bond acceptor, the size or number of alkyl substituents on the heterocycles was increased as exemplified by **1L** and **1M**. This led to fairly potent AMPA antagonists displaying good oral activity: **1O**. In parallel, to increase the pK_a of the sulfonamide, the 6-trifluoromethyl group was replaced with monofluoro-

Table 2. Binding affinity, in vivo activity of selected quinazolinediones **1**.



Compd	R^6	R^7	IC_{50} [μM][a]	MES p.o. ED_{50} [mg kg^{-1}][b]
1F		CF_3	0.20 ± 0.05	NE
1G		CF_3	0.36 ± 0.05	NT
1H		CF_3	0.23 ± 0.05	20 %[c]
1I		CF_3	0.14 ± 0.02	NE
1J		CF_3	0.12 ± 0.02	NE
1K		CF_3	0.12 ± 0.02	NE
1L		CF_3	0.96 ± 0.1	NT
1M		CF_3	0.086 ± 0.03	18
1N		CH_2F	0.57 ± 0.1	NT
1O		CHF_2	0.25 ± 0.05	7.4
1P		CHF_2	0.095 ± 0.03	20
1Q		*i*Pr	2 ± 0.3	NT
1R		Cl	0.32 ± 0.05	20 %[c]
1S		*i*Pr	0.19 ± 0.05	7
1T		*i*Pr	0.36 ± 0.05	40 %[c]
1U		*i*Pr	0.31 ± 0.05	40 %[c]

[a] Rat AMPA [^{3}H]CNQX binding. [b] Maximal electroshock seizure test in mice (1 h). Values are the geometric mean of at least three independent experiments. NT: not tested. NE: not effective at 50 mg kg^{-1} p.o. [c] Percent inhibition at 50 mg kg^{-1} p.o.

methyl, difluoromethyl, chloro, and various alkyl groups as exemplified in **1N**–**1S**. These variations led to the most potent orally active AMPA antagonists **1O** and **1S** of this series. Increasing the heterocycle substituent size further and/or incorporating various weak hydrogen bond acceptor functionalities as exemplified by **1T** or **1U** did not further improve overall activity.

An X-ray structure (Figure 2) was obtained for **1S** co-crystallized with a construct of the human receptor hGluA2 (SwissProt P42262), similar to that reported by Koller et al.,[24] but with the mutation Y702.[38] The central scaffold of **1S** forms a favorable π–π stacking interaction with Tyr450, as well as a hydrogen bond network with residues Pro478, Thr480, and Arg485. An additional hydrogen bond with Thr686 was also identified. The methyl group on the pyrazole of **1S** points toward a water-filled cavity (containing for example, Glu705), and the isopropyl group makes van der Waals interactions with hydrophobic parts of E402, Y405, P478, and M708.

Compounds **1M**, **1O**, and **1S** potently and dose-dependently antagonized MES-induced generalized tonic–clonic seizures in mice with ED_{50} values around 7 mg kg^{-1} after 1 h pre-treatment. When pretreatment time was extended, clear differences appeared between these compounds. While the 7-CF_3 derivatives, **1M** and the 7-CHF_2 derivative **1O** suppressed generalized tonic–clonic seizures as induced by MES using 1 h pre-treatment, their activity dropped considerably following 4 h pre-treatment and disappeared following 8 h pre-treatment (Table 3). The 7-*i*Pr derivative **1S**, on the other hand, potently suppressed generalized tonic–clonic seizures, at peak oral ED_{50} values of 6.1 mg kg^{-1} and 8.4 mg kg^{-1} in mice and rats, respectively. As shown in Table 3, this effect lasted for at least 8 h in mice. Seizure suppression in these tests is indicative of anticonvulsant efficacy against generalized as well as partial seizures.

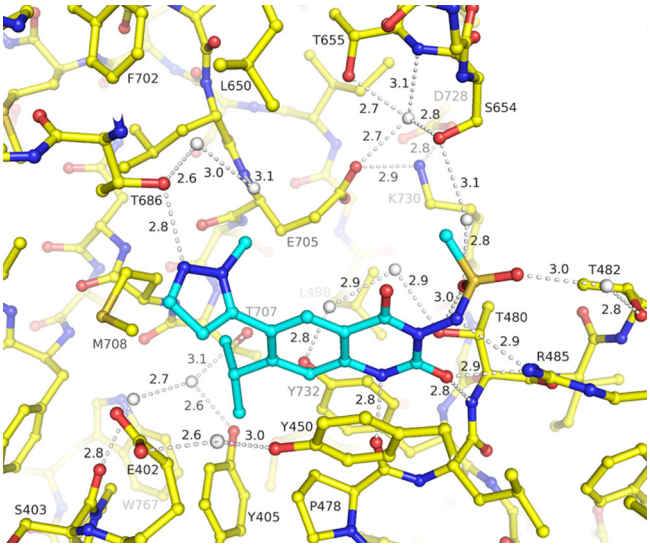


Figure 2. X-ray crystal structure at 1.65 Å resolution of the ligand binding domain of an hGluA construct (carbon atoms in yellow, nitrogen atoms in blue, oxygen atoms in red, and sulfur atoms in brown) bound to **1S** (carbon atoms in cyan). Selected water molecules and interactions (distances in Å) are shown in white. Details of this X-ray structure determination will be published elsewhere.

Table 3. In vivo activity and properties of selected quinazolinediones **1**.

Compd	MES p.o. ED_{50} [mg kg^{-1}][a] 1 h	4 h	8 h	log *D*	pK_a	Solubility [g L^{-1}] pH 1/pH 7.4
1M	18	28	NE	2.6	6.2	0.1/1.6
1O	7.4	20%[b]	NE	1.4	6.4	0.5/5.5
1S	7	11	25.5	1.3	6.7	0.016/0.11
selurampanel						

[a] Maximal electroshock seizure test in mice; values are the geometric mean of at least three independent experiments; NE: not effective at 50 mg kg^{-1} p.o. [b] Percent inhibition at 50 mg kg^{-1} p.o.

The oral absolute bioavailability and disposition pharmacokinetics of **1S**, as well as its in vivo brain penetration, corroborated these findings. When tested in mice (30 mg kg^{-1} p.o.), **1S** exhibited good pharmacokinetic properties with reasonable AUC (208 116 pmol mL^{-1} h) although with a low brain/plasma ratio of <0.1. In a study with a 3 mg kg^{-1} i.v. dose, a mouse plasma half-life of 3.3 h was determined, with a moderate volume of distribution ($V_{dss}=1.3$ L kg^{-1}) and a low clearance of 5.4 mL min^{-1} kg. Compound **1S** has a good selectivity profile with no apparent binding to a panel of over 60 receptors and enzymes. The compound shows a low risk of hERG interaction with an IC_{50} value of >30 μM in the hERG cell-based assay. It also showed no substantial inhibition of all tested cytochromes P450 up to 10 μM. It should finally be pointed out that not all possibilities to interfere with the glutamatergic system seem well suited for chronic treatment purposes in patients. As most classes of NMDA antagonists have been associated with severe psychotomimetic effects,[35] cardiovascular side effects,[36] impairment of learning and memory,[37] and neurotoxicity,[38] selectivity of **1S** for the AMPA receptor versus the other ionotropic receptors was assessed (Table 4). Compound **1S** inhibited the binding of radioligands to the glutamate ([^{3}H]CGP39653) or glycine ([^{3}H]MD L105519) sites of the NMDA receptor only at much higher concentrations. Similarly,

Table 4. Binding of **1S** and reference compounds to iGluRs.

Compd	AMPA C_{50} [μM]	NMDA glu IC_{50} [μM]	SR[b]	NMDA gly IC_{50} [μM]	SR[b]	Kainate IC_{50} [μM]	SR[b]
DNQX	0.5	40	80	9.5	19	2.3	4
kynurenic acid	101	184	1.8	20	0.2	>1000	>10
1S	0.186	>100	>540	27	145	>100	>540

[a] Radioligand binding experiments were carried out using rat whole-brain membranes; GraphPad Prism software was used for the analysis of radioligand binding data. [b] Selectivity ratio: (IC_{50} receptor X)/(IC_{50} AMPA); values are the geometric mean of at least three independent experiments.

[^{3}H]kainate binding to the kainic acid receptor was only marginally displaced by **1S**.

In summary, the present work provides a new class of orally active AMPA antagonists. We demonstrated that 6- and 7-position-substituted quinazolinedione-sulfonamide analogues display potent AMPA antagonistic activity in vitro. *N*-[7-Isopropyl-6-(2-methyl-2*H*-pyrazol-3-yl)-2,4-dioxo-1,4-dihydro-2*H*-quinazolin-3-yl]methanesulfonamide (**1S**) described herein is a highly selective and competitive AMPA receptor antagonist. Moreover, **1S** has a good mouse pharmacokinetic profile, low human microsomal clearance, and has been shown to antagonize, when given orally, MES-induced generalized tonic–clonic seizures in mice for at least 8 h with an ED_{50} value of ~25 mg kg^{-1}.

The favorable pharmacological profile and adequate pharmacokinetic properties led to the selection of **1S** (selurampanel) as a clinical candidate. In a proof-of-concept (POC) study, selurampanel significantly decreased the sensitivity of patients with photosensitive epilepsy to flashing lights.[39] Results of further POC studies in patients with therapy-refractory partial seizures, in patients with migraine pain, and in patients with chronic subjective tinnitus have been or will be reported shortly.[40,41] Finally, a phase 2 multicenter, randomized, double-blind, placebo-controlled, crossover study in patients with partial-onset seizures was run, and results will be reported in due course.

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Keywords: AMPA · antagonists · epilepsy · glutamate · quinazolinediones · selurampanel

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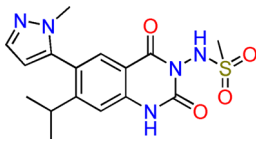
Design and Synthesis of Selurampanel, a Novel Orally Active and Competitive AMPA Receptor Antagonist



Strong anticonvulsant: We report the design and synthesis of the AMPA receptor antagonist selurampanel. The X-ray crystal structure of selurampanel bound to the AMPA receptor hGluA, which is also described, highlights the interactions of the compound with hGluA. This compound has shown excellent oral potency against MES-induced generalized tonic–clonic seizures in rodents as well as significant activity in patients suffering from various forms of epilepsy.