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Positive Allosteric Modulators of the α-Amino-3-hydroxy-5-methyl-4-isoxazolepropionic Acid (AMPA) Receptor

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1. Introduction

L-glutamate is the major excitatory neurotransmitter in the mammalian central nervous system (CNS[a]) and plays a fundamental role in the control of motor function, cognition, and mood. The physiological effects of glutamate are mediated through two functionally distinct receptor families. While activation of metabotropic (G-protein-coupled) glutamate receptors results in modulation of neuronal excitability and transmission, the ionotropic glutamate receptors (ligand-gated ion channels) are responsible for mediating the fast synaptic response to extracellular glutamate. The ionotropic glutamate receptors are divided into three subclasses on the basis of molecular and pharmacological differences and are named after the agonists that were originally identified to selectively activate them: AMPA (α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid), NMDA (*N*-methyl-D-aspartate), and kainate (2-carboxy-3-carboxymethyl-4-isopropenylpyrrolidine).[1,2] AMPA receptors are ubiquitous in the CNS and mediate the majority of fast amino acid neurotransmission. They are also critical to synaptic plasticity and the induction of long-term potentiation (LTP), the use-dependent increase in synaptic efficacy widely considered a substrate for learning and memory. Given the key role of AMPA receptors in brain physiology, a lot of early effort in terms of pharmaceutical drug development focused on the identification of AMPA receptor antagonists as a means of ameliorating the excitotoxic effects of excessive glutamate such as occurs during brain injury or ischemia. However, these compounds have failed to progress because of a variety of side effects including psychotomimetic-like effects and memory impairment. More recently, there has been a growing appreciation of the therapeutic potential of positive allosteric modulators of the AMPA receptor as a means of potentiating glutamatergic function while avoiding the attendant excitotoxic effects of direct agonists. A number of distinct classes of AMPA receptor positive allosteric modulators have been described in recent years that have been demonstrated to modulate key functional properties of AMPA receptors such as desensitization (the process of ion channel closure with agonist remaining bound to the receptor) and deactivation (the process of channel inactivation following the dissociation of agonist) which in turn modulate the amplitude and duration of synaptic responses to glutamate. These molecules have been shown to enhance synaptic transmission and LTP and increase the expression of neurotrophic factors. As such, the potential therapeutic utility of these molecules is being investigated for a variety of clinical indications such as schizophrenia, depression, Alzheimer's disease, Parkinson's disease, ADHD, and respiratory depression. Clinical data, however, are still quite limited with only **4** (CX516, Ampalex), **43** (CX717, structure not disclosed), **9** (CX691/Org 24448, farampator), and **21** (LY451395) having progressed to phase II trials. Despite concerns over potential toxicity issues with these compounds, given the link with excitotoxicity that has been associated with excessive activation of ionotropic glutamate receptors, clinical studies carried out to date have demonstrated that they are tolerated more than would be expected. In fact, positive allosteric modulators of the AMPA receptor appear to have relatively few adverse effects at therapeutically relevant doses and indeed have been shown to protect neurons against neurotoxic insults.[3] These seemingly paradoxical findings have been linked to the induction (by AMPA receptor positive modulators) of growth factors, such as BDNF which is known to possess neuroprotective properties.[4]

The basic pharmacology and clinical potential of positive allosteric modulators of the AMPA receptor have been the subject of a number of extensive reviews[5−10] which provide a broad perspective on AMPA receptors, including the mechanisms of action of various classes of modulator, the clinical, and emerging clinical evidence supporting their use in the aforementioned indications. In this article we will focus briefly on the recent developments in elucidating receptor structure and its relation to channel biophysics, followed by an overview of the various chemotypes known to modulate the channel.

2. Receptor Structure and Function

AMPA receptor subunits are encoded by four distinct genes labeled GluA1 to GluA4, which are known synonymously as GluR1 to GluR4.[11] Each of the four subunits exists as two splice variants termed "flip" (i) or "flop" (o) which differ by less than 10 amino acids in their extracellular domain. In particular, the Asn residue at position 754 is mutated to Ser in the "flip" isoform. Additional complexity in the receptor

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[a]Abbreviations: AMPA, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; ADHD, attention deficit hyperactivity disorder; BDNF, brain derived neutrotrophic factor; CNS, central nervous system; CTZ, cyclothiazide; FW, fluorowillardine; GluR, glutamate receptor; LBD, ligand binding domain; HEK, human embryonic kidney; KcsA, K^+ channel from *Streptomyces lividans*; LIVbp, leucine−isoleucine−valine binding protein; LTP, long-term potentiation; NMDA, *N*-methyl-D-aspartate; TM, transmembrane.

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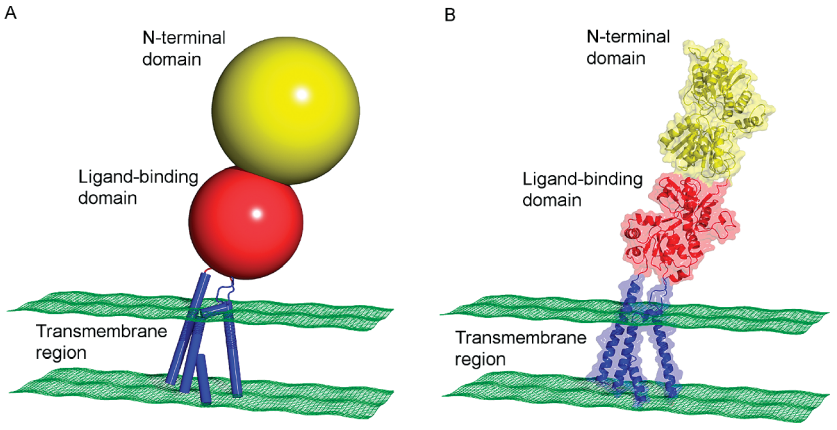


Figure 1. (A) Schematic of the domain structure of an iGluR monomer comprising the large N-terminal domain (yellow), the ligand-binding domain (red) which bears the agonist site, and the transmembrane region (blue). (B) Cartoon depiction of one monomer from the GluA2 crystal structure.[12,23]

stems from RNA editing, the most well characterized variant being a Gln/Arg site within the ion-channel pore of GluA2, resulting in reduced calcium permeability. An additional Arg/Gly editing site has been identified in the extracellular domains of GluA2−4.

The AMPA receptor is tetrameric, each monomer having a modular structure (Figure 1) comprising two large extracellular domains; the N-terminal domain (NTD) and the ligand-binding domain (LBD), both of which show homology to LIVbp; a transmembrane (TM) domain showing homology to potassium channels such as KcsA; and a C-terminal domain which varies greatly in size. The structure of the intact rat GluA2 receptor has recently been determined[12,13] and provides fascinating insights into the architecture and function of these receptors. Although the intact receptor is notionally a tetramer, this usually comprises heteromeric subunits GluA1−4. The precise composition of the functional heterotetramer is variable; however, each generally contains at least one GluA2 subunit which is believed to be important in controlling Ca^{2+} permeability. The structure demonstrates a symmetry mismatch, with 4-fold symmetry in the transmembrane regions but a 2-fold, dimer-of-dimer arrangement in the extracellular regions, which appears integral to the gating mechanism of all ionotropic glutamate receptors. Crystal structures of individual GluA2, GluA3, GluA4 receptor domains have also been determined,[14−16] and there have been extensive studies of the GluA2 LBD and its interactions with modulators of various pharmacologies.[14,17−19]

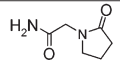
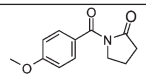
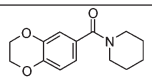
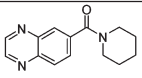
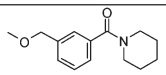
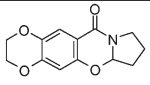
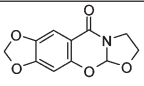
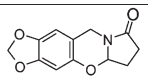
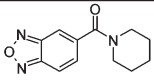
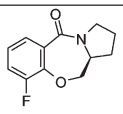
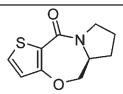
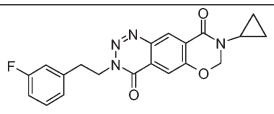
2.1. Allosteric Binding Site and Functional Relevance. Crystal structures have shown that within a tetrameric AMPA receptor the LBD is a functional dimer and have revealed multiple sites at which ligands can bind to influence function. The orthosteric glutamate-binding site is located within the clamshell structure of an individual LBD, and it is clear[12,20,21] that binding of ligands at this site induces conformational changes that are propagated to the transmembrane region to facilitate gating. Specifically, binding of an agonist induces closure of the clamshell and the force exerted by this domain movement is mechanically transmitted into opening of the pore. Receptor desensitization occurs when the interface between two closed, agonist-bound clamshells within a functional dimer becomes disrupted, removing the leverage required to force the channel open. Knowledge of the structural changes underlying receptor function has focused the design and development of allosteric AMPA modulators toward this interface because compounds that bind to and stabilize it can reduce both desensitization and deactivation[17,19,22] and thereby enhance AMPA currents.

2.2. Ligand Binding. Crystal structures have been reported for several of the modulators shown in Tables 1, 2, and 3 bound to the LBD of GluA2. Specifically, protein−ligand structures have been reported for benzothiadiazines such as **13** (cyclothiazide),[14] the benzamides **2** (aniracetam),[17] and **6** (CX614)[17] and the sulfonamides **20**,[12] **22**[19] and **31**.[68] The different classes of modulator share distinct but overlapping binding sites, as detailed in Figure 2. In each case, the allosteric modulator sits at the interface between two LBD clamshells and modulates the protein−protein interaction between the two subunits, preventing the conformational changes required to move the receptor to the desensitized state.

The binding mode of **2** is shown in Figure 2a. Compound **2** makes no hydrophilic interactions with protein atoms and forms just one hydrogen bond with a network of solvent molecules occupying the buried hydrophobic pocket. Figure 2b shows the binding mode of **13** which forms a network of hydrogen bonds with the side chains of Ser497 and Ser754 and with main chain atoms of Pro494 and Ser497. The norbornyl moiety is buried within the hydrophobic pocket. Figure 2c shows the binding mode of **20** (LY404187). The isopropylsulfonamide occupies the hydrophobic pocket and forms a single hydrogen bond with Pro494. Considered together, these three structural classes map out the surface properties and explore much of the available volume within the allosteric site. The binding site is symmetrical, with two deep, mainly hydrophobic pockets separated by a hydrophobic saddle. Opportunities for hydrophilic interactions occur toward the extremities of the binding site, as demonstrated by the structure of **13** in Figure 2b. The hydrophobic pockets accommodate a network of solvent molecules, which can form interactions with lower potency modulators (e.g., **2**) but can also be displaced by higher potency modulators such as **13** and **20**. Compounds that occupy one or both of these pockets appear to be advantageous, presumably as they both inhibit the conformational changes associated with desensitization and simultaneously interact with the LBD monomers comprising the allosteric site to increase the stability of the activated state of the receptor.

Biostructural data have greatly enhanced understanding of the mechanisms underlying both the normal function and the pharmacological modulation of AMPA receptors and are certain to remain a key factor in the identification of novel modulators of AMPA receptor function.

Table 1. Benzamide Derivatives[e]

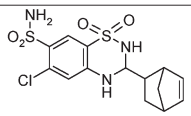
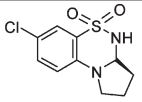
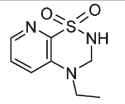
Compound	Structure	EC_{50} (μM)
1		ND
2		>1000[a]
3		1600 (est)[b]
4		95[b] 156[c] >1000[c]
5		ND
6		43.7[b] 21[d]
7		ND
8		ND
9		14
10		ND
11		ND
12		ND

[a] Measured at GluR 3/4o expressed in *Xenopus oocytes*. [b] Measured at rat hippocampal CA1 pyramidal neurons. [c] GluA4(i) in HEK-293 cells. [d] GluA1(o) expressed in human HEK cells. [e] ND = data not disclosed.

3. Chemical Classes of AMPA Receptor Positive Modulators

Over the years, a growing body of compounds spanning a variety of chemotypes has emerged from both the chemical and patent literature, with that number burgeoning considerably in recent times. Reporting of biological data has been complicated by the use of different cell and assay formats as well as differing measures of efficacy. The main emphasis of this article is to provide an overarching view of the established and emerging chemotypes in the area of AMPA receptor modulators as well as to give some measure of the associated SAR. The review will focus on four predominant chemical classes as well as summarize other significant compounds of interest.

Table 2. Cyclothiazide and Related Species

Compound	Structure	EC_{2X} (μM)
13		1.6[a]
14		60[a]
15		8.8[a]

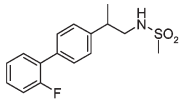
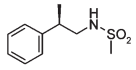
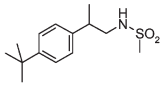
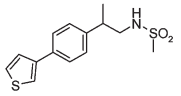
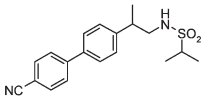
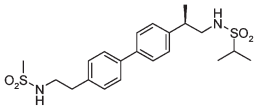
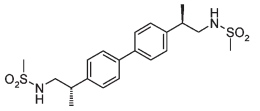
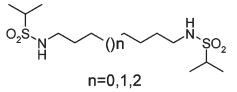
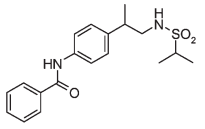
[a] Measured in *Xenopus* oocytes.

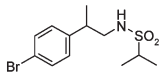
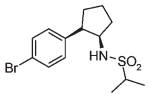
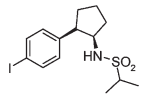
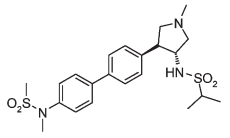
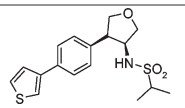
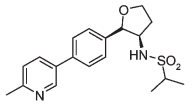
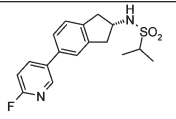
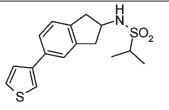
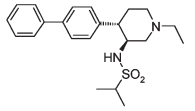
3.1. Benzamide Derivatives. The benzamides were one of the first series of AMPA receptor positive modulators. This series was discovered by researchers at the University of California following chemical modification of the putative nootropic compounds **1** (piracetam)[24] and **2**.[25] In early work **1** had been shown to potentiate AMPA-induced $^{45}Ca^{2+}$ uptake into neuronal cultures at 10 μM. Compound **2** has been shown to potentiate the L-glutamate evoked steady state currents at rat AMPA receptors with a low (≳1 mM) potency with selectivity for flop over flip receptors.

Early members of the benzamide series include **3** (CX546)[26−28] and **4**.[26−29] These analogues, like compound **2**, are weak potentiators of agonist evoked steady state currents with EC_{50} values greater than 100 μM. Much of the electrophysiology data on these compounds have been performed using fast applications of agonists and the measurements of deactivation time constants (as opposed to long agonist applications and measuring inhibition of desensitized currents). Whole system ex vivo slice electrophysiology has also been reported extensively for benzamide series compounds, measuring so-called excitatory postsynaptic current or EPSCs. The effects of the positive modulator on the binding of the agonist have been reported in several publications. Compounds **3** and **4** have been shown to slow the deactivation time constant 10-fold and 3.2-fold (rat native membranes), respectively, and the slice electrophysiology data for compound **4** is reported as showing increases in EPSC half-width of 28% and amplitude of 68% at 2 μM. Compound **4** is reported as showing no effect on 5-fluorowillardine binding (FW, an AMPA receptor agonist) up to 20 μM. Even more simplified analogues of **3** have been claimed by researchers at Cortex. Compound **5** is claimed to increase the slice EPSC amplitude by 25% at 300 μM.[30]

Conformationally constraining **3** has given the more potent analogue **6**.[31,32] By use of slice electrophysiology, a 30 μM concentration of **3** is reported to increase the slice EPSC amplitude and half-width by approximately 40% and 80%, respectively, to slow the deactivation time constant by

Table 3. Sulfonamide Derived Systems[g]

Compound	Structure	EC_{50} (μM)
16		19.6[a]
17		1980[b]
18		1.2[a]
19		4.5[a]
20		0.29[a]
21		0.15[a]
22		0.87[c]
23	 n=0,1,2	a(n=0) 2.88[d] b(n=1) 0.91[d] c(n=2) 0.66[d]
24		0.52[a]

Compound	Structure	EC_{50} (μM)
25		26%@3μM[a]
26		0.52[a]
27		0.023[a]
28		1.6[e]
29		ND
30		ND
31		2.5[e]
32		10[e]
33		<10[f]

[a]Recombinant human GluA4(i) expressed in HEK-293. [b] Recombinant rat GluA2(i) flip expressed in *Xenopus oocytes*. [c] Recombinant rat GluA4(i) flip expressed in *X. laevis oocytes*. [d] Recombinant human GluA1(i) expressed in HEK-293. [e] Recombinant human GluA2. [f] AMPA ES Cell FLIPR assay. [g] ND = data not disclosed.

a factor of 8.4 and to enhance FW binding to rat native receptors with an EC_{50} of 64 μM.

Related conformationally constrained analogues include **7**[33] and **8**[34] that are claimed to increase the slice EPSC amplitude by 25% at 30 and 300 μM, respectively.

Structural modifications of **4** have led Cortex workers to the more potent analogue **9**.[35,29] This compound has been licensed to Organon (now Merck). Patch clamp electrophysiology indicates that **9** is approximately 10-fold more potent than **4**. Compound **9** is claimed to increase the slice EPSC amplitude by 10% (3 μM).

The benz- and pyrido/thienyloxazepinone series of compounds have been disclosed by workers at Organon (now Merck). Compounds **10**[36] and **11**[37] are claimed to increase steady state currents in rat hippocampal neurones by 20% and 32%, respectively, with no EC_{50} values reported.

Recent work from the Servier−Cortex collaboration has resulted in the disclosure of compounds such as **12**[38] which is claimed to have a 2-fold potentiation of the AMPA current ($EC_{2\times}$) of 0.1 μM in rat cortical cells by patch clamp electrophysiology.

The only compounds from this class to have progressed to the clinic are **4**, **43** (structure not disclosed), and **9**. Although **4** showed some early promise with modest effects on cognition being reported in studies with healthy human volunteers,[39,40] subsequent double-blind studies in schizophrenics failed to show any beneficial therapeutic effect, either as a monotherapy[41] or as an add-on[42] to standard antipsychotic drugs. Following up on the demonstration that **43** was able to improve cognitive performance in sleep-deprived monkeys, Cortex Pharmaceuticals reported that **43** had an alerting effect on sleep deprivation trials in healthy young men and produced some attenuation of

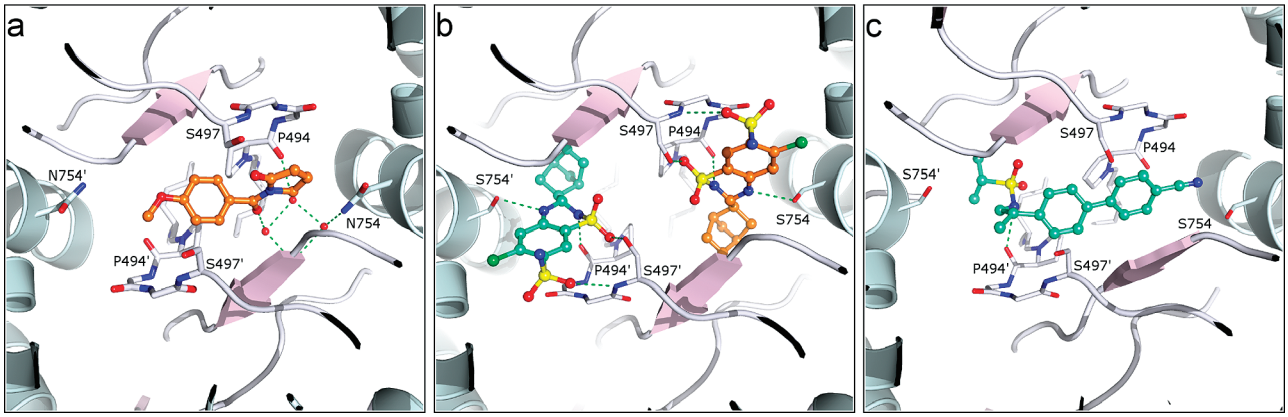


Figure 2. Binding modes of diverse AMPA positive allosteric modulators. Each of these structures was determined using a variant of the GluA2 LBD. The view is down the 2-fold axis relating monomers within the LBD dimer. (a) Crystal structure of **2** (aniracetam) bound to the GluA2 flop LBD, showing **2** spanning the central 2-fold axis. As a result, there are two overlapping binding sites related by the 2-fold symmetry, though only one molecule is shown here for clarity. (b) Crystal structure of **13** (cyclothiazide) bound to the GluA2 flop (N754S mutant) LBD. In contrast to the other examples shown, **13** does not coincide with the central 2-fold axis, and therefore, two independent molecules can be accommodated within the same binding pocket, as observed in the crystal structure depicted. (c) Crystal structure of **20** (LY404187) bound to the GluA2 flip LBD. Again, only one molecule is shown for clarity, as **20** also spans the central 2-fold axis.

cognitive deficits. However, that finding failed to be replicated in a double-blind placebo-controlled trial in volunteers undergoing simulated night shift work.[43] Other more promising clinical data reported by Cortex include a phase IIa study in subjects with ADHD where **43** had a statistically significant effect on the hyperactivity subscale. Further phase IIa studies with **43** have demonstrated that it is able to prevent the onset of respiratory depression induced by an opioid while preserving the opioid's pain-relieving effects.[44] To date, there has yet to be any clinical data reported for **9**.

3.2. Cyclothiazide and Related Compounds. Another significant class of AMPA positive allosteric modulator that has emerged are the benzothiadiazine derivatives. Such compounds are generally derived from **13** (cyclothiazide, CTZ), which was originally designed as a diuretic but has since been profiled extensively as a positive modulator of the AMPA receptor (data in Table 2).[45] Biostructural data detailing the binding mode of **13** to the AMPA ligand binding domain are discussed above. Perhaps the most advanced member of this class is the Servier compound **14** (S-18986), which exhibited an $EC_{2\times}$ of 60 μM[46] in the current induced by AMPA when added to *Xenopus oocytes*. The Servier group demonstrated that only the (*S*)-enantiomer was effective as an AMPA positive allosteric modulator. In spite of its relatively lower potency compared to **13**, compound **14** is able to penetrate the blood−brain barrier, thus enabling in vivo investigation.[47] In vivo pharmacological studies using the object recognition test in rat showed that **14** when dosed from 0.3 to 3 mg/kg po improved the retention of memory and at the 0.3 mg/kg dose counteracted the effect of age-related memory deficits.[48]

Subsequent studies have shown that analogues derived from **14** have been shown to have superior levels of potency (e.g., **15** $EC_{2\times}$ = 8.8 μM).[45] It remains to be seen if this enhanced potency leads to improved in vivo efficacy in, for example, cognition models.

3.3. Sulfonamide Derivatives. The first examples in this class of AMPA positive modulators were reported by Lilly in 2000.[49] The progenitor alkylsulfonamide **16** was derived from high throughput screening using a recombinant assay in which compounds were assessed for their ability to potentiate the response mediated by 100 μM L-glutamate in a stable cell line expressing homomeric GluA4 flip receptors.[28] In this assay compound **16** displayed potency (EC_{50} = 19.6 μM) only 5-fold lower than **13** and significantly higher than that for previously reported benzamide modulators such as **4**. Initial efforts by the Lilly group to further improve the potency of the modulator **16** established relatively tight SAR around the alkylsulfonamide region. For example, ethyl and isopropyl analogues showed around 4-fold improved modulation compared to the parent methylsulfonamide **16**, whereas derivatives with slightly larger *n*-butyl and benzyl groups displayed complete loss of activity in the AMPA assay (EC_{50} > 100 μM).[28] Similarly, a progressive increase in size of the benzylic group showed the methyl to be the most optimal in this position. The region around the distal aromatic ring also proved important for AMPA potency but more tolerant to structural changes. For instance, whereas deletion analogue **17** showed a significant loss of activity (EC_{50} = 1980 μM),[19] replacement of the *o*-fluorophenyl group in **16** with structurally diverse groups such as a *tert*-butyl **18** and 3-thiophenyl **19** resulted in a 5- to 10-fold jump in the potency (EC_{50} = 1.2 μM and EC_{50} = 4.5 μM, respectively). Studying the effect of substitution around the distal aryl ring in combination with the most optimal isopropylsulfonamide functionality, Lilly scientists observed a 2 orders of magnitude enhancement in potency for analogues containing methyl, formyl, amino, or nitrile groups in the 4′ position.

As one of the most potent AMPA modulators reported in the literature (GluA4 EC_{50} = 0.29 μM), the nitrile analogue (±)-**20** was extensively profiled both in vitro and in vivo and became an important and widely applied tool for further elucidation of the role of AMPA receptors in neurological disorders.[50] Equipotent at GluA2 (EC_{50} = 0.15 μM), **20** was shown to be moderately selective over the other two isoforms, GluA1 (EC_{50} = 5.65 μM) and GluA3 (EC_{50} = 1.66 μM),[51] and essentially inactive at a range of ion channels, including other ionotropic glutamate receptors such as kainate or NMDA and voltage gated potassium, sodium, or calcium channels.[52] In addition, **20** was shown to have around 10-fold selectivity for flip (i) versus flop (o) receptors (GluA2(o) EC_{50} = 1.44 μM). In terms of its mechanism of action, whole-cell voltage clamp using rat prefrontal cortex neurons studies revealed that **20** potentiates AMPA receptors by blocking the channel desensitization and therefore favoring an agonist-bound open state.[50]

The observed high potency in the recombinant GluA4 assay translated into robust potentiation of AMPA receptors in in vitro preparations, as well as efficacy in relevant in vivo models. For example, electrophysiology studies in Purkinje neurons have shown **20** to be around 1000-fold more potent than benzamide modulators such as **4**.[53] In vivo electrophysiological studies of **20** indicated a dose dependent increase in firing rate on rat hippocampal neurones with an ED_{50} of 12 μg/kg.[54] Preclinical studies with **20** demonstrated improvements in models of working memory such as water maze and passive avoidance,[50] providing further evidence for the link between glutamatergic hypofunction and cognitive deficits in schizophrenia. It has also been reported that subchronic treatment of rats with **20** produced an increase in expression of BDNF, a neural growth factor for which reduced levels have been associated with depression, suggesting that this compound could also have utility as an antidepressant.[8]

Building on the promising preclinical data, Lilly scientists continued optimization efforts around **20**, which resulted in the discovery of a bis-sulfonamide series, from which compound **21** has progressed into clinical studies.[55,56] Very little preclinical data have been reported for this compound. It has been disclosed that compound **21** showed efficacy in preclinical cognitive models, such as the water maze and acquisition and retention in the radial arm maze, thus having a similar profile to compound **20**.[8] In the clinic, **21** was found to be safe and well tolerated in human volunteers at doses of up to 5 mg.[57] However, in a phase II clinical study on 181 patients with Alzheimer's disease, **21** failed to show any effect on cognition.[58] The authors of the study suggested that this could potentially be due to a suboptimal dosing regime (0.2 mg b.i.d. for 28 days followed by 1.0 mg b.i.d. thereafter up to a maximum of 8 weeks).

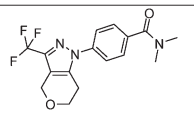
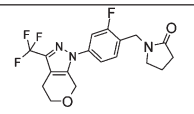
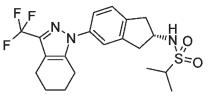
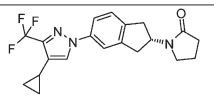
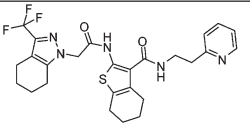
A recently published X-ray structure of compound **22**, a closely related symmetrical analogue of **21**, cocrystallized with a soluble GluA2 construct revealed an interesting binding mode with the bis-sulfonamide imbedded into the GluA2 homodimeric interface.[19] The two sulfonamide moieties of **22** were shown to form an identical hydrogen-bonding pattern within the same allosteric site on the two dimerized GluA2 subunits, whereas the biaryl linker makes hydrophobic contacts with a saddle-like formation in the central part of the binding site created by Pro494 and Pro494′ residues. The fact that bis-sulfonamides with greatly simplified structure such as **23a**−**c**[59] still maintained high potency[60] (Table 3) suggests that the isopropylsulfonamide moiety is responsible for most of the ligand binding in this series. Flexibility in the SAR of the linker region has been further demonstrated by insertion of an amide spacer resulting in compound **24**, with potency similar to the most active potentiators in the biarylsulfonamide series (GluA2 EC_{50} = 0.52 μM).[61]

Further optimization efforts around this chemotype led scientists at Lilly to produce a range of constrained analogues, which generally showed at least an order of magnitude greater potency than the related open-chain ligands.[62] For instance, a 4-bromo derivative in the 2-arylpropylsulfonamide series (±) **25** showed significantly lower potency in the GluA2 assay (26% at 3 μM) than the corresponding cyclopentane derivative (±)-**26** (EC_{50} = 0.52 μM). With an EC_{50} value of 23 nM, iodo derivative (*R*,*R*)-**27** was the most potent AMPA modulator among 29 examples reported in this series.

A series of related constrained analogues have also been disclosed by GlaxoSmithKline. Their work around this chemotype focused on insertion of heteroatoms into the molecule, possibly to optimize physicochemical properties, resulting in AMPA potentiators such as **28** (EC_{50} = 1.6 μM), **29**, and **30**.[63−65] In their earlier efforts the GlaxoSmithKline group took an alternative constraining approach, which led to discovery of indane series, typified by **31** (EC_{50} = 3 μM) and **32** (EC_{50} = 10 μM).[66,67] Limited SAR data disclosed by GlaxoSmithKline suggest generally lower AMPA potency of their constrained analogues when compared to those claimed by the Lilly group. A recent report describes how **31** had promising PK, and further profiling enabled the compound to reach phase I clinical trials for cognitive impairment associated with schizophrenia.[68]

Most recently Pfizer has also disclosed its interest in AMPA modulators, with a patent application around a constrained sulfonamide series, exemplified by **33**.[69] To date, no information on the stage in development of this series has been reported.

Table 4. Indazole Derived Modulators

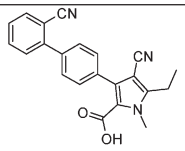
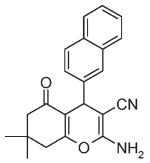
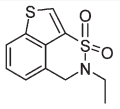
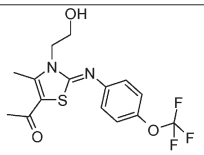
Compound	Structure	EC_{50} (μM)
34		<300[a]
35		<300[a]
36		<300[a]
37		<300[a]
38		<10[b]

[a] Measured at GluA2. [b] Measured at GluA1.

3.4. Indazole Based Derivatives. Workers at GlaxoSmithKline have shown an interest in the tetrahydroindazole type compounds as evidenced in some recent patent applications.[70] Compounds typified by **34** (Table 4) have been claimed as positive allosteric modulators of the AMPA receptor, with subsequent patent applications demonstrating that modification of both the fused ring system and the amide portion is also feasible.[71] Characterization by whole cell patch-clamp electrophysiology indicated that compounds from this class applied at 10 nM showed a potentiation of between 14% and 79% of the current evoked by 30 μM AMPA.

Compounds such as **35** have been disclosed by GSK as clinical candidates for the treatment of cognitive defects in schizophrenia.[71] In vitro characterization by electrophysiology indicates that compounds show similar levels of efficacy to the progenitor series. Subsequent work has shown that replacement of the fused ring system substituent with

Table 5. Miscellaneous AMPA Modulators[d]

Compound	Structure	EC_{50} (μM)
39		0.056[a]
40		1.6[b]
41		ND
42		<200[c]

[a]Measured in GluA4. [b]Measured in *X. laevis* oocytes. [c]Measured in GluA2. [d]ND = data not disclosed.

5-pyridyl or 5-cyclopropyl moieties is tolerated.[72] Most recently, a hybridization approach was applied to furnish compounds of the type **36** and **37** through combination of SAR from the pyrazole series with the previously disclosed indane based derivatives.[73]

A 2008 patent application from Organon (now Merck) revealed a further series of pyrazole derivatives exemplified by compound **38**.[74] Variation of both the pyrazole ring and peripheral amide moiety is also presented in the same patent application.

3.5. Other Chemotypes of Interest. Lastly, a number of more structurally diverse compounds have appeared in the literature over the past few years, each representing a unique chemotype.

Further efforts from Lilly[75] have disclosed the biarylpyrrole acid compounds exemplified by **39** (Table 5). This compound evolved through a hits to leads program and is believed to be the most potent compound in the series. The compound exhibited similar potencies against both flip and flop forms of two different subunits (GluA4(i) = 56 nM, GluA4(o) = 53 nM, GluA2(i) = 82 nM, GluA2(o) = 73 nM) and has been selected for further biological studies. The results of these studies will undoubtedly provide insight into the utility or otherwise of high potency AMPA receptor modulators as cognition enhancers.

Workers from CoCensys (now Purdue) have disclosed a series of benzopyran derived analogues[76] typified by **40** ($EC_{2\times}$ = 1.6 μM), and Boehringer Ingleheim has published a patent application on a class of benzothiazine analogues[77] (**41**, no data reported).

More recently, GSK have consolidated their efforts in the area of AMPA receptor modulators through the publication of a patent application concerning a series of (arylimino)dihydrothiazoles typified by compound **42**.[78] When characterized by whole cell patch-clamp electrophysiology, compounds from this class applied at 10 nM showed a potentiation of between 15% and 42% of the current evoked by 30 μM AMPA.

4. Summary and Outlook

The past few years have witnessed a marked expansion in activity in the area of positive allosteric modulators of the AMPA receptor, and this review has aimed to provide an overview of the major chemotypes developed thus far. Significant advances have been made in our understanding of the molecular basis of how many of these emerging templates exert their biological effect at the receptor, and this will undoubtedly facilitate the discovery of new templates as well as enable the optimization of existing lead series. We anticipate that in the next few years the results from ongoing clinical efforts in the area will come to fruition and are likely to ignite further interest in AMPA receptor modulators for the treatment of a number of debilitating neurological disorders.

Biographies

Simon J. A. Grove completed his doctoral studies at the University of Cambridge, U.K. (1995), before moving to Organon Laboratories (now Merck Research Laboratories) where he is currently a Group Leader in the Department of Medicinal Chemistry working on ion channel, GPCR, and nuclear receptor targets, mostly in the CNS area.

Craig Jamieson completed his doctoral studies at the University of Edinburgh, U.K. (1999). After postdoctoral work at the University of Cambridge, U.K., he joined GlaxoSmithKline as a Principal Scientist before moving to Organon Laboratories in 2004 (now Merck Research Laboratories) where he is currently a Group Leader in the Department of Medicinal Chemistry and has continued his interest in the chemical biology of ion channels, particularly in the CNS area.

John K. F. Maclean obtained his Ph.D. from Glasgow University, U.K. (1997). He applied X-ray crystallography and structural biology to numerous research projects while with Pantherix and Evotec before joining Organon Laboratories (now Merck Research Laboratories) in 2004. He works in the Chemistry, Modelling, and Informatics group, providing molecular modeling support to various neuroscience and cardiovascular research projects, with a particular interest in the structure and function of ion channels.

John. A. Morrow completed his doctoral studies at the University of Glasgow, U.K. (1992). Following postdoctoral work at the MRC Brain Metabolism Unit in Edinburgh, U.K., he joined Organon Laboratories in 1993 (now Merck Research Laboratories) where he is currently a Group Leader in the Department of Molecular Pharmacology. His main interest lies in ion channels and transporters as therapeutic targets for CNS indications.

Zoran Rankovic received his Ph.D. degree in Organic Chemistry from the University of Leeds, U.K. In 1995 he joined Organon Laboratories (now Merck Research Laboratories) were he is currently a Medicinal Chemistry Section Head in the CNS area.

References

(1) Kew, J. N. C.; Kemp, J. A. Ionotropic and metabotropic glutamate receptor structure and pharmacology. *Psychopharmacology* **2005**, *179*, 4–29.
(2) Mayer, M. L.; Armstrong, N. Structure and function of glutamate receptor ion channels. *Annu. Rev. Physiol.* **2004**, *66*, 161–181.
(3) Dicou, E.; Rangon, C. M.; Guimiot, F.; Spedding, M.; Gressens, P. Positive allosteric modulators of AMPA receptors are neuroprotective against lesions induced by an NMDA agonist in neonatal mouse brain. *Brain Res.* **2003**, *970*, 221–225.
(4) Siegel, G. J.; Chauhan, N. B. Neurotrophic factors in Alzheimer's and Parkinson's disease brain. *Brain Res. Rev.* **2000**, *33*, 199–227.

(5) Morrow, J. A.; Maclean, J. K.F.; Jamieson, C. Recent advances in positive allosteric modulators of the AMPA receptor. *Curr. Opin. Drug Discovery Dev.* **2006**, *9*, 571–579.
(6) Marenco, S.; Weinberger, D. R. Therapeutic potential of positive AMPA receptor modulators in the treatment of neuropsychiatric disorders. *CNS Drugs* **2006**, *20*, 173–185.
(7) O'Neill, M. J.; Dix, S. AMPA receptor potentiators as cognitive enhancers. *IDrugs* **2007**, *10*, 185–192.
(8) O'Neill, M. J.; Witkin, J. M. AMPA receptor potentiators: application for depression and Parkinson's disease. *Curr. Drug Targets* **2007**, *8*, 603–620.
(9) Ren, J.; Poon, B. Y.; Tang, Y.; Funk, G. D.; Greer, J. J. Ampakines alleviate respiratory depression in rats. *Am. J. Respir. Crit. Care Med.* **2006**, *174*, 1384–1391.
(10) Zarate, J.; Manji, H. K. The role of AMPA receptor modulation in the treatment of neuropsychiatric diseases. *Exp. Neurol.* **2008**, *211*, 7–10.
(11) Palmer, C. L.; Cotton, L.; Henley, J. M. The molecular pharmacology and cell biology of α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptors. *Pharmacol. Rev.* **2005**, *57*, 253–277.
(12) Sobolevsky, A. I.; Rosconi, M. P.; Gouaux, E. X-ray structure, symmetry and mechanism of an AMPA-subtype glutamate receptor. *Nature* **2009**, *462*, 745–756.
(13) Figures were generated using Protein Data Bank entry 3KG2.
(14) Sun, Y.; Olson, R.; Horning, M.; Armstrong, N.; Mayer, M.; Gouaux, E. Mechanism of glutamate receptor desensitization. *Nature* **2002**, *417*, 245–253.
(15) Jin, R.; Singh, S. K.; Gu, S.; Furukawa, H.; Sobolevsky, A. I.; Zhou, J.; Jin, Y.; Gouaux, E. Crystal structure and association behaviour of the GluR2 amino-terminal domain. *EMBO J.* **2009**, *28*, 1812–1823.
(16) Clayton, A.; Siebold, C.; Gilbert, R. J. C.; Sutton, G. C.; Harlos, K.; McIlhinney, R. A. J.; Jones, E. Y.; Aricescu, A. R. Crystal structure of the GluR2 amino-terminal domain provides insights into the architecture and assembly of ionotropic glutamate receptors. *J. Mol. Biol.* **2009**, *392*, 1125–1132.
(17) Jin, R.; Clark, S.; Weeks, A. M.; Dudman, J. T.; Gouaux, E.; Partin, K. M. Mechanism of positive allosteric modulators acting on AMPA receptors. *J. Neurosci.* **2005**, *25*, 9027–9036.
(18) Armstrong, N.; Sun, Y.; Chen, G. Q.; Gouaux, E. Structure of a glutamate-receptor ligand-binding core in complex with kainate. *Nature* **1998**, *395*, 913–917.
(19) Kaae, B. H.; Harpsøe, K.; Kastrup, J. S.; Sanz, A. C.; Pickering, D. S.; Metzler, B.; Clausen, R. P.; Gajhede, M.; Sauerberg, P.; Liljefors, T.; Madsen, U. Structural proof of a dimeric positive modulator bridging two identical AMPA receptor-binding sites. *Chem. Biol.* **2007**, *14*, 1294–1303.
(20) Frandsen, A.; Pickering, D. S.; Vestergaard, B.; Kasper, C.; Nielsen, B. B.; Greenwood, J. R.; Campiani, G.; Fattorusso, C.; Gajhede, M.; Schousboe, A.; Kastrup, J. S. Tyr702 is an important determinant of agonist binding and domain closure of the ligand-binding core of GluR2. *Mol. Pharmacol.* **2005**, *67*, 703–713.
(21) Jin, R.; Banke, T. G.; Mayer, M. L.; Traynelis, S. F.; Gouaux, E. Structural basis for partial agonist action at ionotropic glutamate receptors. *Nat. Neurosci.* **2003**, *6*, 803–810.
(22) Ptak, C. P.; Ahmed, A. H.; Oswald, R. E. Probing the allosteric modulator binding site of GluR2 with thiazide derivatives. *Biochemistry* **2009**, *48*, 8594–8602.
(23) DeLano, W. L. *The PyMOL Molecular Graphics System*; DeLano Scientific: Palo Alto, CA, 2002.
(24) Johansen, T. H.; Chaudhary, A.; Verdoorn, T. A. Interactions among GYKI-52466, cyclothiazide and aniracetam at recombinant AMPA and kainate receptors. *Mol. Pharmacol.* **1995**, *48*, 946–955.
(25) Copani, A.; Genazzani, A. A.; Aleppo, G.; Casabona, G.; Canonico, P. L.; Scapagnini, U.; Nicoletti, F. Nootropic drugs positively modulate α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid-sensitive glutamate receptors in neuronal cultures. *J. Neurochem.* **1992**, *58*, 1199–1204.
(26) Arai, A. C.; Xia, Y.-F.; Rogers, G.; Lynch, G.; Kessler, M. Benzamide-type AMPA receptor modulators form two subfamilies with distinct modes of action. *J. Pharmacol. Exp. Ther.* **2002**, *303*, 1075–1085.
(27) Lynch, G. S.; Rogers, G. A. Drugs That Enhance Synaptic Responses Mediated by AMPA Receptors. WO/1994/02475, 1994.
(28) Ornstein, P. L.; Zimmerman, D. M.; Arnold, M. B.; Bleisch, T. J.; Cantrel, B.; Simon, R.; Zarrinmayeh, H.; Baker, S. R.; Gates, M.; Tizzano, J. P.; Bleakman, D. Biarylpropylsulfonamides as novel, potent potentiators of 2-amino-3-(5-methyl-3-hydroxyisoxzol-4-yl)-propanoic acid (AMPA) receptors. *J. Med. Chem.* **2000**, *43*, 4354–4354.
(29) Wezenberg, E.; Verkes, R. J.; Ruigt, G. S. F.; Hulstijn, W.; Sabbe, B. G. C. Acute effects of the ampakine farampator on memory and information processing in healthy elderly volunteers. *Neuropsychopharmacology* **2007**, *32*, 1272–1283.
(30) Rogers, G. A.; Nilssen, L. Benzoyl Piperidines/Pyrrolidines for Enhancing Synaptic Response. WO/1996/38414, 1996.
(31) Arai, A. C.; Kessler, M.; Rogers, G.; Lynch, G. Effects of the potent ampakine CX614 on hippocampal and recombinant AMPA receptors: interactions with cyclothiazide and GYKI 52466. *Mol. Pharmacol.* **2000**, *58*, 802–803.
(32) Rogers, G. A.; Lynch, G. S. Benzoxazines for Enhancing Synaptic Response. WO/1997/36907, 1997.
(33) Rogers, G. A.; Marrs, C. Benzoxazine Compounds for Enhancing Synaptic Response. WO/1999/33469, 1999.
(34) Rogers, G. A.; Johnstrom, P. Acylbenzoxazines for Enhancing Synaptic Response. WO/1999/51240, 1999.
(35) Rogers, G. A.; Marrs, C. M. Benzofurazan Compounds Which Enhance AMPA Receptor Activity. WO/1998/35950, 1998.
(36) Grove, S. J. A.; Zhang, M.; Shahid, M. Benzoxazapine Derivatives and Their Use as AMPA Receptor Stimulators. WO/2002/100865, 2002.
(37) Grove, S. J. A.; Adam-Worrall, J.; Zhang, M.; Gilfillan, R. Pyrido/Thieno-[*f*]-oxazipine-5-one Derivatives as Positive Modulators of the AMPA Receptor. WO/2002/102808, 2002.
(38) Cordi, A.; Rogers, G.; Mueller, R. 3-Substituted-[1,2,3]-Benzotriazinone Compounds for Enhancing Glutamategic Synaptic Response. WO/2008/085506, 2008.
(39) Lynch, G.; Granger, R.; Ambros-Ingerson, J.; Davis, C. M.; Kessler, M.; Schehr, R. Evidence That a Positive Modulator of AMPA-Type Glutamate Receptors Improves Delayed Recall in Aged Humans. *Exp. Neurol.* **1997**, *145*, 89–92.
(40) Lynch, G.; Kessler, M.; Rogers, G.; Ambros-Ingerson, J.; Granger, R.; Schehr, R. S. Psychological effects of a drug that facilitates brain AMPA receptors. *Int. Clin. Psychopharmacol.* **1996**, *11*, 13–19.
(41) Marenco, S.; Weinberger, D. R. Therapeutic potential of positive AMPA receptor modulators in the treatment of neuropsychiatric disorders. *CNS Drugs* **2006**, *20*, 173–185.
(42) Goff, D. C.; Lamberti, J. S.; Leon, A. C.; Green, M. F.; Miller, A. L.; Patel, J.; Manschreck, T.; Freudenreich, O.; Johnson, S. A. A placebo-controlled add-on trial of the ampakine, CX516, for cognitive deficits in schizophrenia. *Neuropsychopharmacology* **2008**, *33*, 465–472.
(43) Wesensten, N. J.; Reichardt, R. M.; Balkin, T. J. Ampakine (CX717) effects on performance and alertness during simulated night shift work. *Aviat., Space Environ. Med.* **2007**, *78*, 937–943.
(44) Oertel, B. G.; Felden, L.; Tran, P. V; Bradshaw, M. H.; Angst, M. S.; Schmidt, H.; Johnson, S.; Greer, J. J.; Geisslinger, G.; Varney, M. A.; Lötsch, J. Selective antagonism of opioid-induced ventilatory depression by an ampakine molecule in humans without loss of opioid analgesia. *Clin. Pharmacol. Ther.* **2010**, *87*, 204–211.
(45) Pirotte, B.; Podona, T.; Diouf, O.; de Tullio, P.; Lebrun, P.; Dupont, L.; Somers, F.; Delarge, J.; Morain, P.; Lestage, P.; Lepagnol, J.; Spedding, M. 4*H*-1,2,4-Pyridothiadiazine 1,1-dioxides and 2,3-dihydro-4*H*-1,2,4-pyridothiadiazine 1,1-dioxides chemically related to diazoxide and cyclothiazide as powerful positive allosteric modulators of (*R*/*S*)-2-amino-3-(3-hydroxy-5-methylisoxazol-4-yl)propionic acid receptors: design, synthesis, pharmacology, and structure−activity relationships. *J. Med. Chem.* **1998**, *41*, 2946–2959.
(46) Desos, P.; Cordi, A.; Lestage, P. Derivatives of Benzothiazine and Benzothiadiazine, Process for Their Preparation, and Pharmaceutical Compositions Containing Them as AMPA Receptor Modulators. EP/1486503, 2004.
(47) Bourasset, F.; Bernard, K.; Munoz, C.; Genissel, P.; Scherrmann, J. M. Neuropharmacokinetics of a new {alpha}-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA) modulator, S18986 [(*S*)-2,3-dihydro-[3,4]cyclopentano-1,2,4-benzothiadiazine-1,1-dioxide] in the rat. *Drug Metab. Dispos.* **2005**, *33*, 1137–1143.
(48) Lestage, P.; Danober, L.; Lockhart, B.; Roger, A.; Lebrun, C.; Robin, J.-L.; Desos, P.; Cordi, A. 48 S-18986, positive allosteric modulator of AMPA receptors as a novel cognition enhancer in rodents. *Res. Pract. Alzheimer's Dis.* **2002**, *6*, 253–259.
(49) Arnold, M. B.; Jones, W. D.; Ornstein, P. L.; Zarrinmayeh, H.; Zimmerman, D. M. Preparation of N-Substituted Sulfonamide Derivatives for Potentiating Glutamate Receptor Function. WO/2000/006537, 2000.
(50) Quirk, J. C.; Nisenbaum, E. S. LY404187: a novel positive allosteric modulator of AMPA receptors. *CNS Drug Rev.* **2002**, *8*, 255–282.

(51) Miu, P.; Jarvie, K. R.; Radhakrishnan, V.; Gates, M. R.; Ogden, A.; Ornstein, P. L.; Zarrinmayeh, H.; Ho, K.; Peters, D.; Grabell, J.; Gupta, A.; Zimmerman, D. M.; Bleakman, D. Novel AMPA receptor potentiators LY392098 and LY404187: effects on recombinant human AMPA receptors in vitro. *Neuropharmacology* **2001**, *40*, 976–983.
(52) Baumbarger, P. J.; Muhlhauser, M.; Zhai, J.; Yang, C. R.; Nisenbaum, E. S. Positive modulation of alpha-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA) receptors in prefrontal cortical pyramidal neurons by a novel allosteric potentiator. *J. Pharmacol. Exp. Ther.* **2001**, *298*, 86–102.
(53) Arundine, M.; Tymianski, M. Molecular mechanisms of glutamate-dependent neurodegeneration in ischemia and traumatic brain injury. *Cell. Mol. Life Sci.* **2004**, *61*, 657–668.
(54) Vandergriff, J.; Huff, K.; Bond, A.; Lodge, D. Potentiation of responses to AMPA on central neurones by LY392098 and LY404187 in vivo. *Neuropharmacology* **2001**, *40*, 1003–1009.
(55) Arnold, M. B.; Bleisch, T. J.; Cuff, G. W.; Ornstein, P. L.; Zimmerman, D. M. Preparation of [[[(Methylsulfonamido)ethyl]phenyl]-phenyl]propyl Sulfonamide Derivatives with Glutamate Receptor Function Potentiating Activity. WO/2001/090057, 2001.
(56) Miller, W. D.; Fray, A. H.; Quatroche, J. T.; Sturgill, C. D. Suppression of a Palladium-Mediated Homocoupling in a Suzuki Cross-Coupling Reaction. Development of an Impurity Control Strategy Supporting Synthesis of LY451395. *Org. Process Res. Dev.* **2007**, *11*, 359–364.
(57) Jhee, S. S.; Chappell, A. S.; Zarotsky, V.; Moran, S. V.; Rosenthal, M.; Kim, E.; Chalon, S.; Toublanc, N.; Brandt, J.; Coutant, D. E.; Ereshefsky, L. Multiple-dose plasma pharmacokinetic and safety study of LY450108 and LY451395 (AMPA receptor potentiators) and their concentration in cerebrospinal fluid in healthy human subjects. *J. Clin. Pharmacol.* **2006**, *46*, 424–432.
(58) Chappell, A. S.; Gonzales, C.; Williams, J.; Witte, M. M.; Mohs, R. C.; Sperling, R.; Chappell, A. S.; Gonzales, C.; Williams, J.; Witte, M. M.; Mohs, R. C.; Sperling, R. AMPA potentiator treatment of cognitive deficits in Alzheimer disease. *Neurology* **2007**, *68*, 1008–1012.
(59) Knobelsdorf, J. A.; Zarrinmayeh, H. Preparation and Formulation of (Bis)sulfonamides for Pharmaceutical Use Potentiating Glutamate Receptor Function and Treating a Wide Variety of Conditions, Such as Psychiatric and Neurological Disorders. WO/2001/094306, 2001.
(60) Merck internal data.
(61) Zarrinmayeh, H.; Bleakman, D.; Gates, M. R.; Yu, H.; Zimmerman, D. M.; Ornstein, P. L.; McKennon, T.; Arnold, M. B.; Wheeler, W. J.; Skolnick, P. [^{3}H]*N*-2-(4-(*N*-Benzamido)phenyl)propyl-2-propanesulfonamide: a novel AMPA receptor potentiator and radioligand. *J. Med. Chem.* **2001**, *44*, 302–304.
(62) Shepherd, T. A.; Aikins, J. A.; Bleakman, D.; Cantrell, B. E.; Rearick, J. P.; Simon, R. L.; Smith, E. C.; Stephenson, G. A.; Zimmerman, D. M.; Mandelzys, A.; Jarvie, K. R.; Ho, K.; Deverill, M.; Kamboj, R. K. Design and synthesis of a novel series of 1,2-disubstituted cyclopentanes as small, potent potentiators of 2-amino-3-(3-hydroxy-5-methyl-isoxazol-4-yl)propanoic acid (AMPA) receptors. *J. Med. Chem.* **2002**, *45*, 2101–2111.
(63) Bradley, D. M.; Thewlis, K. M.; Ward, S. E. Preparation of *N*-Indan-2-yl and Related Sulfonamides That Potentiate Glutamate Receptor for Use against Schizophrenia. WO/2006/015828, 2006.
(64) Andreotti, D.; Ward, S. E. Preparation of *N*-[2-Phenyltetrahydrofuran-3-yl]-2-propanesulfonamide Derivatives as Glutamate Receptor Modulators. WO/2007/090841, 2007.
(65) Thewlis, K. M.; Ward, S. E. Preparation of 4-Phenyl-3-(isopropylsulfonylamino)tetrahydrofuran Derivatives as Glutamate Receptor Modulators for Treatment of Schizophrenia. WO/2007/090840, 2007.
(66) Ward, S. E.; Thewlis, K. M. Preparation of *N*-Indan-2-yl and Related Sulfonamides That Potentiate Glutamate Receptor for Use against Schizophrenia. WO/2006/015829, 2007.
(67) Thewlis, K. M.; Ward, S. E. Preparation of *N*-Pyrrolidinyl Sulfonamides That Potentiate Glutamate Receptor for Use against Schizophrenia. WO/2006/015827, 2006.
(68) Ward, S. E.; Harries, M.; Aldegheri, L.; Andreotti, D.; Ballantine, S.; Bax, B. D.; Harries, A. J.; Harker, A. J.; Lund, J.; Melarange, R.; Mingardi, A.; Mookherjee, C.; Mosley, J.; Neve, M.; Oliosi, B.; Profeta, R.; Smith, K. J.; Smith, P. W.; Spada, S.; Thewlis, K. M.; Yusaf, S. P. Discovery of *N*-[(2S)-5-(6-Fluoro-3pyridinyl)-2,3-dihydro-1*H*-indenyl]-2-propane sulfonamide, a Novel Clinical AMPA Receptor Positive Modulator. *J. Med. Chem.* **2010**, *53*, 5801–5812.
(69) Estep, K. G.; Fliri, A. F. J.; O'Donnell, C. J. Sulfonamides and Pharmaceutical Compositions Thereof. WO/2008/120093, 2008.
(70) Bradley, D. M.; Chan, W. N.; Harrison, S.; Thatcher, R.; Thewlis, K. M.; Ward, S. E. Compounds Which Potentiate AMPA Receptor and Uses Thereof in Medicine. WO/2007/107539, 2007.
(71) Bradley, D. M.; Chan, W. N.; Thewlis, K. M.; Ward, S. E. Compounds Which Potentiate AMPA Receptor and Uses Thereof in Medicine. WO/2008/053031, 2008.
(72) Bradley, D. M.; Chan, W. N.; Ward, S. E. Compounds Which Potentiate AMPA Receptor and Uses Thereof in Medicine.WO/2008/148836, 2008
(73) Bertheleme, N.; Bradley, D. M.; Cardullo, F.; Merlo, G.; Pozzan, A.; Scott, J. S.; Thewlis, K. M.; Ward, S. E. Compounds Which Potentiate AMPA Receptor and Uses Thereof in Medicine. WO/2008/113795, 2008.
(74) Bertheleme, N.; Bradley, D. M.; Cardullo, F.; Merlo, G.; Pozzan, A.; Scott, J. S.; Thewlis, K. M.; Ward, S. E. Compounds Which Potentiate AMPA Receptor and Uses Thereof in Medicine. WO/2008/003452, 2008.
(75) Zarrinmayeh, H,; Tromiczak, E.; Zimmerman, D. M.; Rankl, N.; Ho, K. H.; Dominguez, E.; Castano, A.; Escribano, A.; Fernandez, C.; Jimenez, A.; Hornback, W. J.; Nisenbaum, E. S. A novel class of positive allosteric modulators of AMPA receptors: design, synthesis, and structure−activity relationships of 3-biphenyl-4-yl-4-cyano-5-ethyl-1-methyl-1*H*-pyrrole-2-carboxylic acid, LY2059346. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 5203–5206.
(76) Konkoy, C. S.; Fick, D. B.; Cai, S. X.; Lan, N. C.; Keana, J. F. W. Substituted 5-Oxo-5,6,7,8-tetrahydro-4*H*-1-benzopyrans and Benzothiopyrans and Their Use as Potentiators of AMPA. WO/2000/075123, 2000.
(77) Winter, K.; Weiser, T.; Blech, S. M.; Ceci, A. Preparation of Azaacenaphthylene Dioxides and Related Compounds as Positive Allosteric AMPA Receptor Modulators (PAARM). WO/2001/057045, 2001.
(78) Bradley, D. M.; Chan, W. N.; Harrison, S.; Hughes, O.; Miller, D. D.; Neesom, J.; Thewlis, K. M.; Ward, S. E. Compounds Which Potentiate AMPA Receptor and Uses Thereof in Medicine. WO/2007/122241, 2007.