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N-Substituted pyrrolidines and tetrahydrofurans as novel AMPAR positive modulators

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ABSTRACT

A series of novel AMPA receptor positive modulators displaying CNS penetration have been discovered with sub-micromolar activity and good selectivity over the cardiac channel receptor, hERG. We describe here the synthesis of these compounds which are biaryl pyrrolidine and tetrahydrofuran sulfonamides and disclose their activities against the human GluA2 flip isoform homotetrameric receptor.

AMPA receptors (α-amino-3-hydroxyl-5-methyl-4-isoxazole-propionic acid (AMPA)) belong to the ligand-gated, ionotropic glutamatergic receptor family. They are widely distributed in the mammalian central nervous system and mediate the vast majority of fast excitatory neurotransmission in the CNS.[1,2] The glutamatergic neurotransmitter system has been a recent focus for the advancement of innovative treatments for psychiatric and neurodegenerative conditions as its dysfunction underlies the pathophysiology of diseases such as schizophrenia, Alzheimer's disease, Parkinson's disease and mood disorders.[3,4] Preclinical studies have identified modulators of the AMPAR which slow the rate of receptor deactivation and/or desensitization leading to enhanced synaptic activity and efficacy in cognition models.[5–7]

There are a number of molecules exemplified by a variety of chemotypes that have been described as AMPAR positive modulators.[8,9] This can be highlighted by describing three major, well-established, classes that have been investigated clinically which exist alongside a number of less extensively exemplified structures (Fig. 1). The first group was derived from the nootropic agent **1** (Aniracetam) which was shown to improve different phases of learning and memory impairment in rats and mice.[10] This molecule was subsequently developed into a range of benzamide derivatives by Cortex which included **2** (CX-516) and **3** (CX-691). The second major class, known as the benzothiadiazines, can be exemplified by the diuretic agent **4** (cyclothiazide) and was developed into **5** (S-18986) by Servier. Thirdly, there are the phenethylsulfonamides discovered by Lilly, which include molecules that have been clinically investigated, such as **6** (LY450108) and **7** (LY451395). In broad terms the molecules have generally displayed higher affinities for the AMPAR over time, with the Lilly phenethylsulfonamides being considerably more potent than the original benzamide class.[11]

From evaluation of these chemical chemotypes, we proposed a medicinal chemistry strategy with the purpose of creating our own series of CNS-penetrant AMPAR positive modulators, with the focus of combining high potency with desirable physicochemical and pharmacokinetic properties.

One area of exploration was to build on existing literature for the phenethylsulfonamide series of molecules, and seek to modulate the physicochemical properties such as solubility and lipophilicity by introduction of heteroatoms into the phenethyl linker. This led to the synthesis and evaluation of a set of 3,4-disubstituted pyrrolidines and 3,4-disubstituted tetrahydrofurans with *trans* and *cis* relative stereochemistry, respectively. These targets were chosen for their synthetic tractability and, although structurally similar, should be considered as two distinct series. It was anticipated that the introduction of a heteroatom into the linker would reduce the lipophilicity and hence improve the physicochemical profile of the series. Furthermore, we sought to discover compounds with reduced polar surface area allowing for a greater probability of achieving CNS penetration.[12]

Molecules with a pyrrolidine linker were prepared by the route described in Scheme 1. The *trans*-N-substituted pyrrolidine skeletons (**10a–d**) were constructed via a paraformaldehyde mediated [3+2] cycloaddition reaction on commercially available *trans*-4-bromonitrostyrene (**8**) with the equivalent N-substituted glycines (**9a–d**). The nitro group was then reduced using indium

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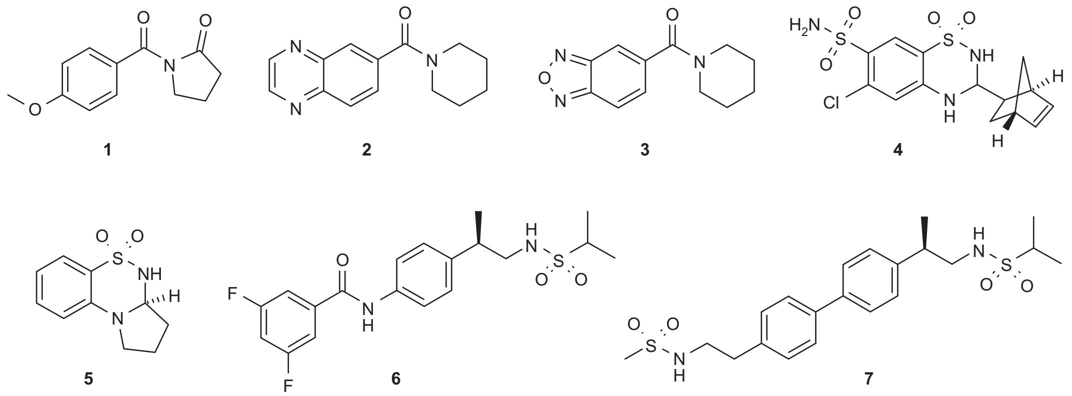
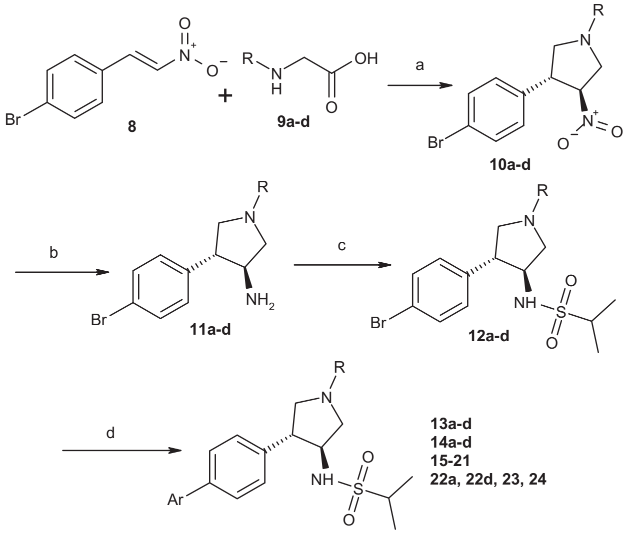


Figure 1. Clinically evaluated AMPAR positive modulators.

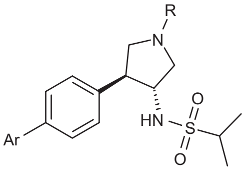


Scheme 1. General procedure for the synthesis of pyrrolidine analogues. Reagents and conditions:[13] (a) paraformaldehyde, toluene, reflux, Dean–Stark; (b) indium metal, concd HCl, THF, rt; (c) $^{i}PrSO_2Cl$, DBU, CH_2Cl_2; (d) $ArB(OH)_2$, $Pd(OAc)_2$, PPh_3, Cs_2CO_3, dioxane, water, reflux.

powder in concentrated hydrochloric acid to give the corresponding amines (**11a–d**) which were functionalized to form the sulfonamides (**12a–d**). However, this seemingly simple transformation was difficult to optimise, the best results were obtained when using two equivalents of isopropylsulfonyl chloride at 0 °C in the presence of DBU (1,8-diazabicyclo[5.4.0]undec-7-ene) as base. These key intermediates were reacted under standard Suzuki coupling conditions affording a range of analogues (**13–24**).

As detailed in Table 1, initial lead **13a** remained the most potent compound in this series. However, activity at the human GluA2 flip isoform homotetrameric receptor (hGluA2) can be achieved with a range of substituted phenyl and heterocyclic groups (Ar) some of which were aimed at lowering the polar surface area of the molecule in a bid to improve CNS penetration. Sulfonamide **13a** is over 10-fold more active at hGluA2 than the amide equivalent (**16**). Furthermore, the sulfone (**15**) and ketone (**17**) equivalents are equipotent with **16**. Switching to other electron withdrawing substituents such as trifluoromethyl (**18**) sees a dramatic loss in activity. Pyridines offered no advantage in terms of hGluA2 activity versus phenyl as compounds **19** and **21** are equipotent, but **21** has the higher maximal response relative to the maximal response of the cyclothiazide (**4**) [defined as 100%] standard used in the assay.

Table 1
Biological activity of *trans*-3,4-disubstituted pyrrolidine analogues[a,b]



Compds	Ar	R	EC_{50} (μM)	Asym max	hERG[c] IC_{50} (μM)
13a	(3-$NHSO_2$Me)Ph	Me	0.3	124	31.6
13b	(3-$NHSO_2$Me)Ph	Et	1.6	111	2.5
13c	(3-$NHSO_2$Me)Ph	^{i}Pr	6.3	89	6.3
13d	(3-$NHSO_2$Me)Ph	Ph	5.0	38	1.3
14a	(4-CN)Ph	Me	5.0	109	2.0
14b	(4-CN)Ph	Et	7.9	90	0.4
14c	(4-CN)Ph	^{i}Pr	20.0	30	ND
14d	(4-CN)Ph	Ph	6.2	48	0.8
15	(3-SO_2Me)Ph	Me	5.0	75	>63
16	(3-NHCOMe)Ph	Me	4.0	79	12.6
17	(3-COMe)Ph	Me	6.3	73	7.9
18	(3-CF_3)Ph	Me	79.4	26	4.0
19	(2-F)Ph	Me	2.5	20	ND
20	3-Pyridyl	Me	4.0	100	31.6
21	3-(2-F)pyridyl	Me	2.5	101	6.3
22a	3-(6-F)pyridyl	Me	5.0	117	1.0
22d	3-(6-F)pyridyl	Ph	4.0	74	0.08
23	2-Thiophene	Me	20.0	29	>63
24	3-Thiophene	Me	3.2	106	4.0

[a] Drawn with relative stereochemistry.

[b] FLIPR generated EC_{50} against hGluA2. Asym max is the fitted maximum response, relative to 100% defined as the maximal response of cyclothiazide standard.

[c] hERG affinity from ^{3}H-dofetilide displacement assay.

Moving the fluorine from the 2-position to the 6-position of the pyridyl ring, as in **22a**, saw a reduction in hGluA2 potency as well as an increase in hERG (KCNH$_2$ voltage-sensitive potassium channel) affinity. But removing the fluorine altogether as in compound **20** reduced hERG affinity whilst maintaining hGluA2 activity. Other heterocycles such as thiophenes **23** and **24** showed a contrast between 2- and 3-substitution with compound **24** being the more active.

Activity is also possible with a range of substituents on the nitrogen of the pyrrolidine ring (R). However, the trend is that activity decreases with increasing alkyl steric bulk on the pyrrolidine nitrogen, that is, Me > Et > ^{i}Pr. This trend is demonstrated by compounds **13a–c** and **14a–c**. Interestingly, when R was phenyl (**13d** and **14d**) it was found that the activity was greater than when R was isopropyl (**13c** and **14c**), and the activities were equipotent in the case of **22a** (R = Me) and **22d**.