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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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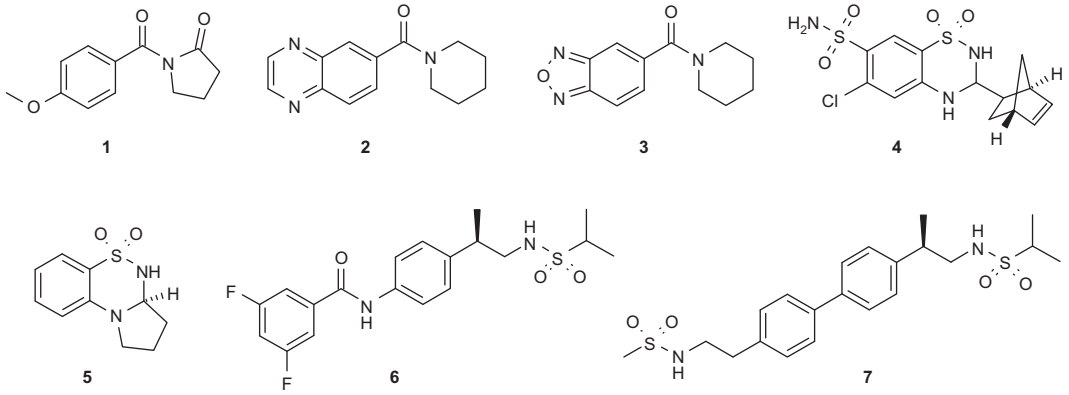
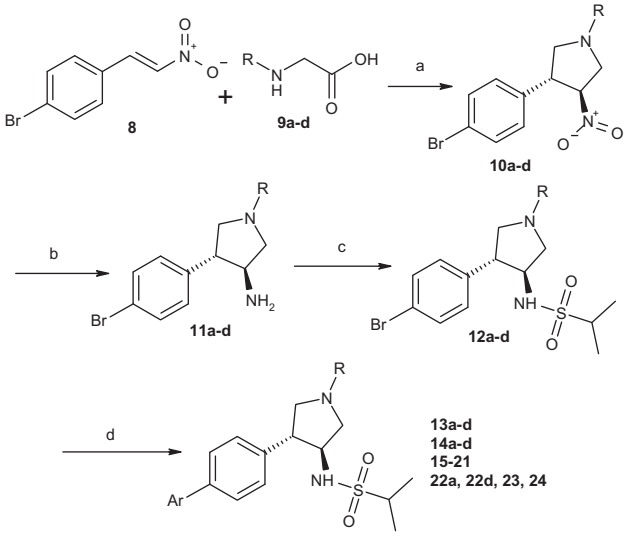


Figure 1. Clinically evaluated AMPAR positive modulators.

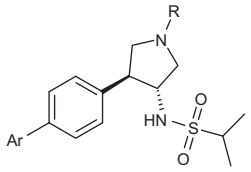


Scheme 1. General procedure for the synthesis of pyrrolidine analogues. Reagents and conditions:[13] (a) paraformaldehyde, toluene, reflux, Dean–Stark; (b) indium metal, concd HCl, THF, rt; (c) $^{i}PrSO_2Cl$, DBU, CH_2Cl_2; (d) $ArB(OH)_2$, $Pd(OAc)_2$, PPh_3, Cs_2CO_3, dioxane, water, reflux.

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-$NHSO_2Me$)Ph	Me	0.3	124	31.6
13b	(3-$NHSO_2Me$)Ph	Et	1.6	111	2.5
13c	(3-$NHSO_2Me$)Ph	^{i}Pr	6.3	89	6.3
13d	(3-$NHSO_2Me$)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.

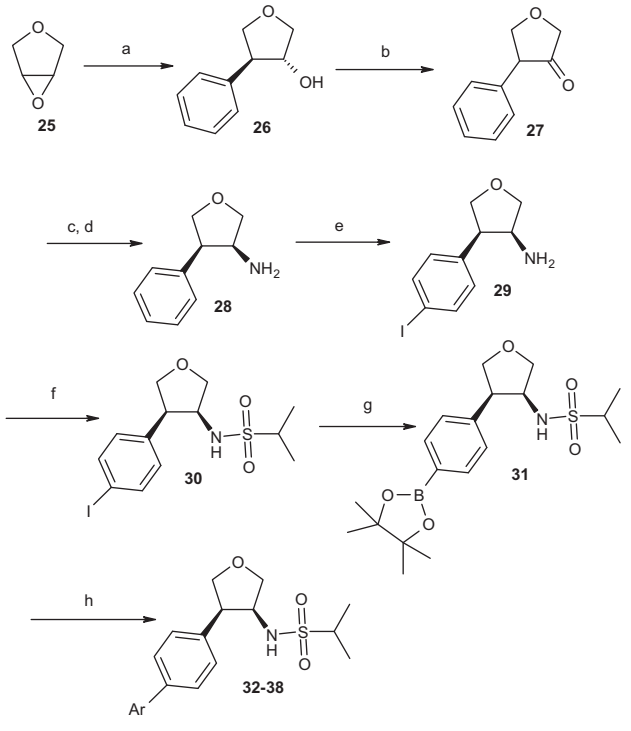
Moving the fluorine from the 2-position to the 6-position of the pyridyl ring, as in **22a**, saw a reduction in hGluA2 potency as well as an increase in hERG ($KCNH_2$ voltage-sensitive potassium channel) affinity. But removing the fluorine altogether as in compound **20** reduced hERG affinity whilst 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**.

This series of compounds whilst active also produced many examples with significant affinity in the hERG cardiac channel binding assay. For example, a comparison of the N–R substitution showed that when R is methyl the level of hERG affinity is lower than with other, larger, groups. Interestingly, when R is the more lipophilic phenyl substituent hERG affinity is at a significantly higher level than hGluA2 activity; in particular compound **22d** (daylight *c* log *P* of 4.20) has approximately 50-fold more affinity for hERG. Therefore when R is a small, less lipophilic, group such as methyl improved potency at hGluA2 was possible with greater selectivity over hERG. Furthermore, compounds **13a** and **14a** have favourable aqueous solubility achieving levels of >9 mg/mL and >2.7 mg/mL, respectively.

It was also seen with many examples that the *N*-methylated pyrrolidines had high intrinsic clearance in both human and rat liver microsomes. A metabolite identification study was performed confirming that the major metabolite of compound **13a** in rat liver microsomes was the anticipated *N*-demethylated analogue. A trace of a +16 Da metabolite was also detected, but not characterised further, which would indicate oxidation has occurred somewhere in the molecule. We therefore needed to identify a series of molecules free of hERG affinity as well as exhibiting improved metabolic stability. It was proposed to synthesise a series of tetrahydrofurans where the NR of the pyrrolidine was replaced with oxygen.

Molecules with a tetrahydrofuran (THF) linker were prepared by the route described in Scheme 2. Commercially available 3,6-dioxabicyclo[3.1.0]hexane (**25**) underwent epoxide ring opening by way of a Grignard reaction with phenylmagnesium bromide to form the *trans*-THF product (**26**). This material was oxidised to the ketone (**27**) followed by a reductive amination reaction with benzylamine with subsequent debenzylation under hydrogenation conditions to give the *cis*-THF amine intermediate (**28**). The *cis*-product is obtained presumably because the hydride is delivered from the least hindered face during the reduction of the intermediate imine complex. Subsequent iodination using *N*-iodo-succinimide predominantly affords the 4-iodo regioisomer to give intermediate **29**. Sulfonylation is carried out using the same conditions as described above for intermediates **12a–d** to make compound **30**. Subsequent conversion of the iodo into the pinacolato boronate ester (**31**) under Suzuki style conditions with bis(pinacolato)diboron and [1,1-bis(diphenylphosphino)ferrocene] palladium (II) chloride dichloromethane complex as catalyst, before standard Suzuki conditions using polymer supported tetrakis(triphenylphosphine)palladium(0) are employed to form a range of targets (**32–38**).

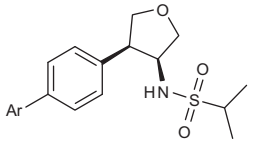


Scheme 2. General procedure for the synthesis of THF analogues. Reagents and conditions:[14] (a) PhMgBr, CuI, THF 0 °C; (b) trichloroisocyanuric acid, TEMPO, CH_2Cl_2, 0 °C; (c) $PhCH_2NH_2$ $NaBH(OAc)_3$, acetic acid, CH_2Cl_2; (d) $Pd(OH)_2/C$, H_2, MeOH; (e) CF_3SO_3H, NIS, MeCN; (f) $^iPrSO_2Cl$, DBU, CH_2Cl_2; (g) [1,1-bis(diphenylphosphino)ferrocene]dichloropalladium(II) CH_2Cl_2 complex, bis(pinacolato)diboron, KOAc, DMSO; (h) ArBr, polymer supported $Pd(PPh_3)_4$, Na_2CO_3, dioxane, water.

It is evident from Table 2 that the THF analogues are more active at hGluA2 than their *N*-methyl pyrrolidine equivalents. This could be due to steric effects, consistent with the trend observed in the pyrrolidine series. The THF series is generally less lipophilic, for example, the daylight *c* log *P* of **32** is 3.03, whereas the *N*-methyl pyrrolidine analogue **14a** has a daylight *c* log *P* value of 3.30. The THF series also has low polar surface area and would also be free from the metabolic issues associated with an *N*-methyl pyrrolidine as highlighted above. Therefore, it could be predicted that these compounds would be more soluble and more CNS penetrant. These molecules were also free from significant hERG affinity, with only **32** and **34** showing <100-fold selectivity. This could be attributed to the non-basic nature of the THF.

Table 3 gives a summary of key physicochemical properties and metabolic data collected for some of these compounds. In the pyrrolidine series, when the amino substituent is larger than methyl, low intrinsic clearances can be achieved, but these molecules have higher lipophilicities which potentially contributes to poorer selectivity versus hERG. Compound **22a** represents a pyrrolidine of lower lipophilicity with a daylight *c* log *P* of 2.60 (although hERG affinity is still high). PSA is lower also due to the use of a fluorinated pyridine as the Ar group. Unfortunately this compound had high rat intrinsic clearance (5.6 mL/min/g) and so was not evaluated in vivo. Similarly, THF compounds **35** and **36** also displayed lower PSA and lipophilicity (daylight *c* log *P* 2.33 and 2.54, respectively) but had high intrinsic clearance in rat liver microsomes, whereas in human liver microsomes both had a clearance of <1 ml/min/g. However, compound **14a** had a rat intrinsic clearance of <0.5 mL/min/g despite being a methylated pyrrolidine and a PSA of 73 which gave us confidence to test this compound in a rat

Table 2
Biological activity of *cis*-3,4-disubstituted tetrahydrofuran analogues[a,b]



Compds	Ar	EC_{50} (μM)	Asym max	hERG[c] IC_{50} (μM)
32	(4-CN)Ph	0.5	112	12.6
33	(3-COMe)Ph	0.1	124	>63
34	3-(6-F)pyridyl	0.3	125	12.6
35	3-(5-F)pyridyl	0.3	131	>63
36	2-(5-F)pyridyl	0.3	117	>63
37	2-Thiophene	0.3	117	>63
38	3-Thiophene	0.4	120	>63

[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.

Table 3
Physicochemical properties and intrinsic clearance of selected molecules

Compds	PSA (Å^2)	*c* log *P*[a]	hCLi (mL/min/g)	rCLi (mL/min/g)
13b	96	3.33	0.7	0.5
13c	96	3.64	0.7	0.6
14a	73	3.30	0.8	<0.5
14b	73	3.96	1.2	0.9
22a	62	2.60	0.8	5.6
35	62	2.33	0.6	3.6
36	68	2.54	0.8	5.1

[a] *c* log *P* Daylight Chemical Information Systems Inc., Aliso Viejo, CA, http://www.daylight.com.

PK model. The results showed that **14a** did indeed show good levels of brain exposure with CNS penetration (brain to blood ratio of 1.8), it also exhibited a half-life of over 2 h.

It is difficult to make direct comparisons between the pyrrolidines and THFs as they have *trans* and *cis* regioisomerism, respectively. For example, the selectivity that the THFs have over hERG may be due in part to the *cis* configuration rather than the THF itself, although a reduction in the lipophilicity and basicity may also add to a reduction in hERG affinity. Furthermore, the *cis* and *trans* isomers may have differing solubilities and lipophilicities. These isomers discussed above were made due to the tractability of their synthesis but it may be useful to make a *cis*-pyrrolidine and a *trans*-THF to be able to make a full SAR comparison.

We have demonstrated that a series of pyrrolidines and tetrahydrofurans display high activity against the AMPA receptor, with some molecules showing sub-micromolar potencies. We have also successfully developed this series to afford molecules with a good selectivity profile, in particular against hERG.

Moreover, we identified examples which show a good in vitro pharmacokinetic profile with low intrinsic clearance in both rat and human liver microsomes and for the example tested, good CNS penetration. Further studies are ongoing.

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