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A novel series of metabotropic glutamate receptor 5 negative allosteric modulators based on a 4,5,6,7-tetrahydropyrazolo [1,5-*a*]pyridine core

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ABSTRACT

A series of potent non-acetylinic negative allosteric modulators of the metabotropic glutamate receptor 5 (mGlu5 NAMs) was developed starting from HTS screening hit **1**. Potency was improved via iterative SAR, and physicochemical properties were optimized to deliver orally bioavailable compounds acceptable for in vivo testing. A lead molecule from the series demonstrated dose-dependent activity in the second phase of the rat formalin test from 30 mg/kg, and a preliminary PK/PD relationship was established.

mGlu5 is a family I G_q-coupled metabotropic glutamate receptor expressed both peripherally and within the CNS, primarily postsynaptically in the limbic cortex, hippocampus, amygdala, basal ganglia, thalamus and olfactory tubercule.[1] mGlu5 has been the target of significant drug discovery efforts due to its implications in numerous, varied indications such as migraine, Fragile X syndrome, chronic pain, gastroesophageal reflux disease (GERD) and Parkinson's disease.[2] The majority of this work has focused on negative allosteric modulators (NAMs) of mGlu5 receptor such as MTEP, mavoglurant and dipraglurant (Fig. 1).[3–5] With the intention of identifying novel mGlu5 receptor NAM pharmacophores, a high throughput screen of the Addex corporate library was performed (ca. 70,000 molecules) using a FLIPR-based Ca^{2+} release assay.[6] Amongst the hits identified was 4,5,6,7-tetrahydropyrazolo[1,5-*a*]pyridine **1**, which afforded full inhibitory modulation with an IC_{50} of 1.3 μM. Subsequent validation of this molecule in an mGlu5 receptor rat cortex binding assay (^{3}H-MPEP) showed a binding IC_{50} of 1.2 μM. Further profiling showed this hit compound to have a good solubility in kinetic solubility assays (0.17 and 0.18 mg/mL at pH 1.0 and 7.4 respectively), no major issue in CYP inhibition (no inhibitory IC_{50} >10 μM on 4 major CYP isoforms), however the compound suffered high intrinsic clearance in both human and rat microsomes (97 and 118 μL/min/mg prot. respectively). As such, it was decided to further investigate this chemotype with view to identifying compounds displaying improved potency and in vitro microsomal stability.

Initial investigation focused on the nature of the link between the pyridine ring and 4,5,6,7-tetrahydropyrazolo[1,5-*a*]pyridine core, in order to find the optimal distance between these two motifs in terms of potency. Various linkers were investigated in this position, the majority of which were inactive. Those that were found active are shown in Table 1; these optimal linkers were of 2-atom lengths bearing either a carbonyl or ether functionality at the linking position with the 4,5,6,7-tetrahydropyrazolo[1,5-*a*]pyridine core (ether **2**, ketone **3** and amide **4**). Reversing the amide or ether resulted in inactive compounds, as did extending or reducing chain length. It is postulated that an element of conjugation between the two aromatic systems due to linker tautomerism may be a significant potency driver; amide **4**, capable of a tautomeric form where the linker is a double bond, is active whereas substituted amide **5** is inactive. Likewise ketone **3**, which is observed as a 2:3 mixture between tautomeric enol ether and ketone in 1D ^{1}H NMR, is rather potent. It is plausible that these pseudo-conjugated linkers may be occupying the same area of the mGlu5 receptor NAM pharmacophore as the classic acetylene linker

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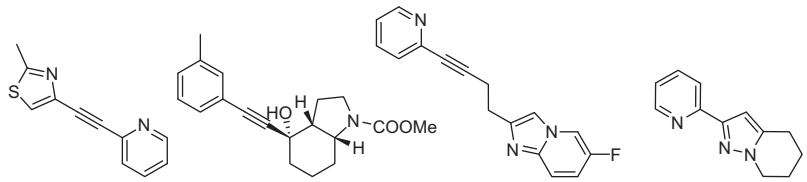
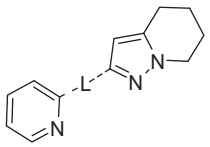


Figure 1. Known mGlu5 NAMs and HTS screening hit **1**.

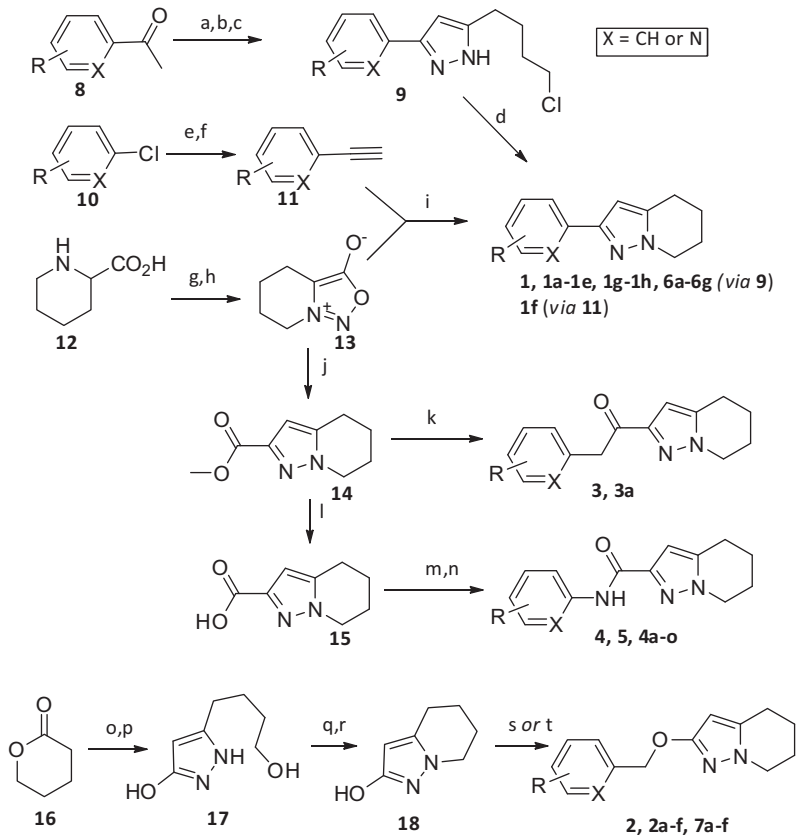
Table 1
Investigation of the linker space between aromatic rings



Compound	1	2	3	4	5
Linker					
FLIPR rmGlu5 IC_{50} (nM)	1292	2498	390	364	NA

present in many of the known mGlu5 receptor NAMs. It should be noted that only one stereoisomer of the enol was observed by 1D ^{1}H NMR (*E*/*Z* stereochemistry not determined).

Representative synthesis of the various linked compounds is shown in Scheme 1. Direct-linked analogues **1**, **1a–e** and **6a–g** can be synthesized in 4 steps from substituted 2-acetylpyridines or acetylbenzenes via pyrazoles **9** followed by ring closure. In an alternative route to generate **1f**, key intermediate 4,5,6,7-tetrahydro-[1,2,3]oxadiazolo[3,4-*a*]pyridin-8-ium-3-olate (**13**) is generated in two steps from piperidine-2- carboxcylic acid **12**.[7] Reaction of this intermediate with various 2-acetylinyl-pyridines or phenylacetylenes generates the direct-linked compounds via a [3+2]cycloaddition. Reaction of key intermediate **13** with methyl propiolate generates ester **14**, which can either be reacted with methylpyridines under basic conditions to give ketone-linked **3** and **3a**, or saponified and coupled with amines to generate amides **4, 5** and **4a–o**. Ester-linked compounds are generated using an



Scheme 1. Reagents and conditions: (a) Me_2NNH_2, EtOH, reflux, 37–92%; (b) LDA, THF, −78 °C then 5-chlorovaleroylchloride, −78 to 0 °C; (c) hydrazine mono-hydrate, EtOH; reflux 35–66% over 2 steps; (d) NaH, THF, 0 °C, 30–51%; (e) TMSCCH, $Pd(PPh_3))_2Cl_2$, CuI, TEA, DCM, 80 °C, 84%; (f) KOH, MeOH, DCM, rt, 34%; (g) $NaNO_2$, HCl, 0 °C; (h) TFAA, THF, rt; 63% over 2 steps (i) xylene, reflux, 67%; (j) methyl propiolate, xylene, reflux, 85%; (k) substituted 2-methyl pyridine, KHMDS, THF, −78 °C to rt, 64–88%; (l) KOH, MeOH, RT, 78%; (m) $(COCl)_2$, DMF, DCM, RT; (n) substituted 2-aminopyridine, pyridine, RT, 60–80% over 2 steps; (o) EtOAc, Na, EtOH, RT; (p) hydrazine mono-hydrate, EtOH, 40 °C, 77% over 2 steps; (q) HBr, H_2SO_4, reflux; (r) NaOH, rt, 57% over 2 steps; (s) substituted 2-halomethylpyridine/benzyl halide, NaH, DMF, 0 °C to rt 5–51%; (t) substituted 2-hyroxymethyl pyridine/benzyl alcohol, PBu_3, THF, $(pipCON)_2$.