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Structure based evolution of a novel series of positive modulators of the AMPA receptor

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ABSTRACT

Starting from compound **1**, we utilized biostructural data to successfully evolve an existing series into a new chemotype with a promising overall profile, exemplified by **19**.

The α-amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid (AMPA) receptors belong to the family of ionotropic glutamate ion channels. These receptor complexes are widely expressed in the central nervous system and are considered to mediate the majority of fast excitatory amino acid neurotransmission.[1] AMPA receptors appear to be crucial to facilitating synaptic plasticity and long-term potentiation (LTP), the use dependent enhancement in synaptic efficacy which is believed to underlie various forms of learning and memory. AMPA receptor modulators have been shown to enhance LTP and are, therefore, under serious consideration as therapeutic agents for a range of neurological disorders including schizophrenia, Alzheimer's Disease, Parkinson's disease and ADHD.[2,3]

Our earlier work described the identification of **1** through optimization of an HTS-derived hit.[4,5] Figure 1 depicts key properties of compound **1** alongside the X-ray co-crystal structure of **1** in complex with the GluA2 S1S2 Ligand Binding Domain (LBD) construct.[6]

In order to identify a new chemotype as a potential back-up series to that exemplified by **1**, we sought to leverage literature data through exploiting our knowledge of the binding mode of our existing leads. The basic strategy adopted is delineated in Figure 2.

Compound **2**, a hydroxyl containing analogue of **1,** was considered to be a synthetically more expedient starting point and was shown to have similar potency[7] and solubility (GluA1 pEC_{50} = 6.4, solubility = 20 mg/L). We proposed to hybridize **2** with LY404187 (**3**), an AMPA receptor modulator which had previously been reported in the literature.[8] In addition, the X-ray co-crystal structure of **3** was known,[9] thus providing detailed knowledge of how the compound interacted with the receptor. Preparation and subsequent characterization of **4** indicated that the hybridized compound retained an acceptable balance of potency and solubility.

In vitro, compound **4** was shown to have excellent microsomal stability (rat Cli <12 μL/min/mg protein, human Cli <12 μL/min/mg protein) and reasonable permeability in a CaCo-2 assay, with no evidence of efflux (A–B = 206 nm/s, B–A = 287 nm/s). However, in vivo pharmacokinetic data was less promising (Cl_p = 49.7 mL/min/kg; $T_{1/2}$ = 1.0 h; *F*% = 3.2; 1 mg/kg dose (iv), 5 mg/kg (po) using Wistar BRL rats). We hypothesized that the oral bioavailability of **4** could be improved by lowering clearance. Therefore, we considered conformational constraint of **4** with the expectation of being able to negate conformations predisposed to metabolism by CYP P450 enzymes. At the same time, we became aware of a related series of AMPA receptor modulators represented by **5** (Fig. 3)[10] and thus sought to leverage those in our ligand constraint strategies.

Disappointingly, evaluation of **6** in the GluA2 functional assay indicated that the compound had only weak activity as an AMPA

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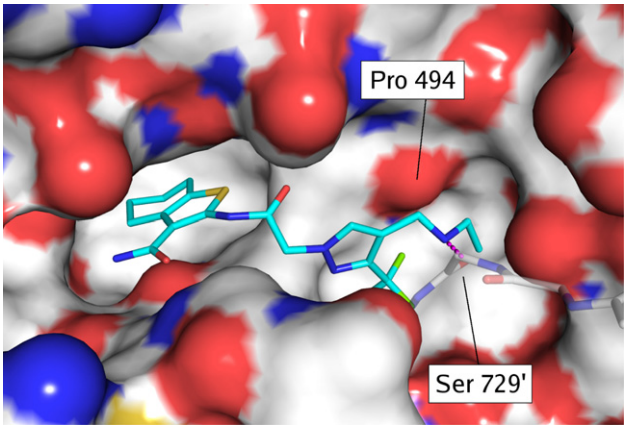

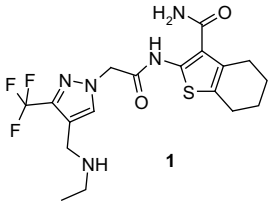

GluA1 pEC_{50} = 6.1
Solubility = 107 mg/L
$T_{1/2}$ = 1.1 h
F% = 43

Figure 1. Lead compound **1**, summary property data and structure in complex with the GluA2 S1S2 LBD. As the binding site spans an intramolecular two-axis, two orientations of **1** are observed in the crystal structure, but only one is shown here. In this and subsequent figures,[18] some residues are omitted for clarity, but main-chain atoms of residues 727–730 are here shown as sticks to illustrate the hydrogen bond between **1** and Ser 729′.

receptor modulator (pEC_{50} <4.5). We then determined the X-ray structure of **4** in complex with the GluA2 S1S2 LBD,[11] which made it clear that the pyrazole moiety did not interact with the receptor in the same way as we anticipated from the structures of progenitor compounds [4,5] such as **1** (Fig. 4). In particular, the pendant trifluoromethyl group, whose location in a hydrophobic pocket appeared a key binding element within other chemical series,[12–14] was instead oriented away from the binding site. Modeling and conformational analysis suggested that insertion of a methylene spacer between the pyrazole group and central phenyl ring of **6** would be sufficient to alter the pyrazole orientation and restore this preferred interaction. Preparation and testing of compound **7** (GluA1 pEC_{50} = 6.3) confirmed our hypothesis and the X-ray co-complex of **7** with the GluA2 S1S2 LBD (Fig. 4) demonstrated the binding mode was as anticipated from modeling.

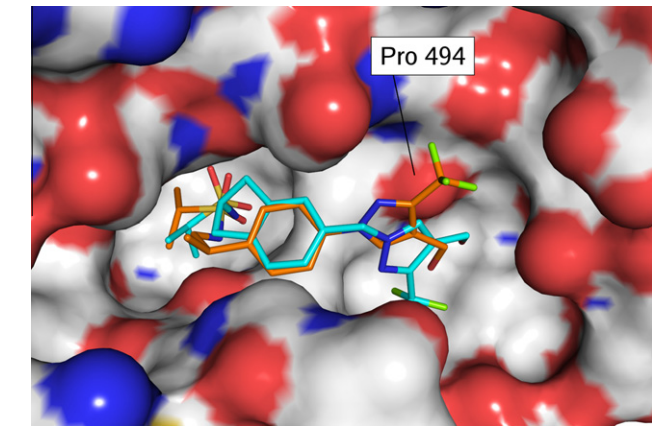

Figure 4. Overlaid X-ray structures of compounds **4** (carbons shown in orange) and **7** (carbons in cyan) in complex with the GluA2 S1S2 LBD. While the central phenyl rings overlay well, the orientations of the pyrazole fragments are very different. For **4**, the environment of the trifluoromethyl substituent is different to that observed for a related series [4,5], but the additional methylene in **7** allows the trifluoromethyl to return to the expected position.

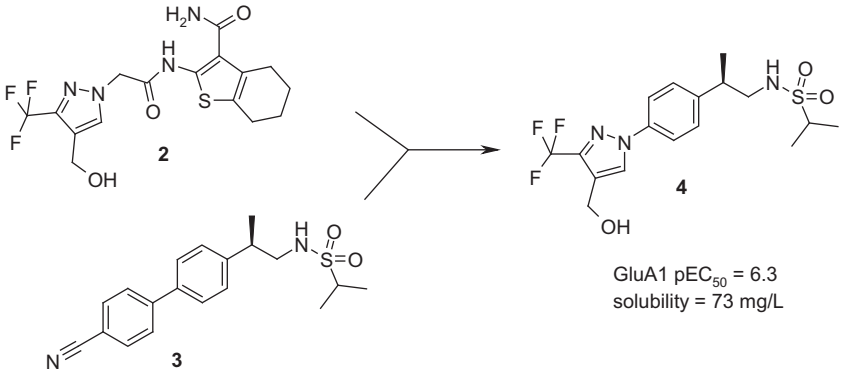

Figure 2. Lead series evolution through hybridization with literature compounds.

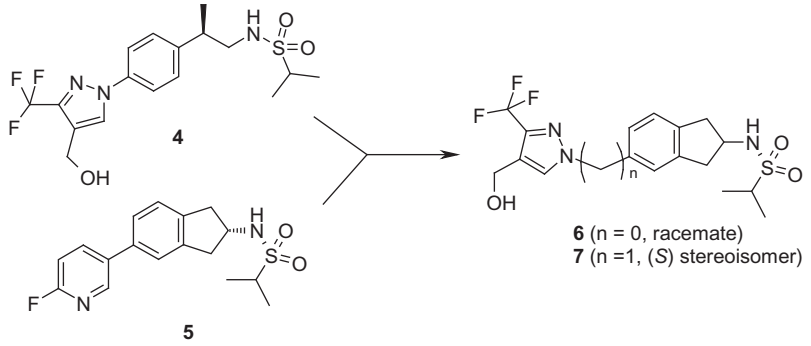

Figure 3. Introduction of conformational restraint.