A NOVEL SERIES OF METABOTROPIC GLUTamate RECEPTOR 5 (mGluR5) NEGATIVE ALLOSTERIC MODULATORS


* Addex Pharmaceuticals, 12 Chemin des Aulx, CH-1228, Plan Les Ouates, Geneva, Switzerland

** Nikem Research s.r.l., Via Zambeletti, 25, 20021, Baranzate (MI), Italy

Introduction

- mGluR5 is a member of the group 1 mGluRs (along with mGluR1). It is expressed in the CNS both pre-synaptically and post-synaptically and is involved in both regulation of neurotransmitter release and post-synaptic responses.
- Inhibition of mGluR5, for example through the use of negative allosteric modulators (NAMs), has been predicted to be of use across a range of therapeutic indications including migraine, GERD, Fragile X syndrome and treatment of L-DOCA-induced sickness in Parkinson’s Disease patients.
- A number of companies are involved in mGluR5 NAM research, the most advanced of which are currently engaged in Phase II and Phase III clinical trials across a variety of therapeutic areas (see fig. 1.). Addex are currently engaged in a Phase II PO-LO trial with our lead mGluR5 NAM program.

Further profiling - Representative Compounds

- In rat PK at 3 mg/kg i.v. Compound 25 demonstrated high clearance and moderate volume of distribution, resulting in a short half-life.
- 30 mg/kg s.c. dosing of compound 24 followed by continuous plasma and CSF sampling demonstrated that compound 24 is readily brain penetrant with a high CSF/plasma ratio (AUC) similar to the observed plasma free fraction in vivo (rat PFR 1% = 32%) suggesting blood and CSF behave as one compartment.

Figure 1: examples of mGluR5 NAMs

Identification of Hit

- HTS screening of the Addex Corporate Library using a Ca2+ flux assay (FLIPR) resulted in identification of the following HT based on a bicyclic furoxpyrazole core.

Fig 1. examples of mGluR5 NAMs

A series of structurally differentiated mGluR5 Negative Allosteric Modulators have been identified from a HTS screening hit. Elaboration around the core scaffold has demonstrated a number of divergent SARs distinguished by the nature of the linking group. The most advanced molecules are brain penetrant with low molecular weight and IC50 below 100 nM. Optimisation of in vivo clearance through improvement of metabolic stability is required to progress this series further.

For further information on diaphragmat or the mGluR5 NAM programme at Addex, please contact our business development: chris.moggis@addexpharma.com