Identification and Optimization of a Series of Tetrahydrobenzotriazoles as Metabotropic Glutamate Receptor 5-Selective Positive Allosteric Modulators that Improve Performance in a Preclinical Model of Cognition

○Tomoyuki SHIBUGUCHI[1], John M ELLARD[2], Andrew MADIN[2], Oliver PHILPS[2], Mark HOPKIN[2], Scott HENDERSON[2], Louise BIRCH[2], Desmond O'CONNOR[2], Tohru ARAI[1], Kazuma TAKASE[1], Louise MORGAN[2], David REYNOLDS[2], Sonia TALMA[2], Eimear HOWLEY[2], Ben POWNEY[2], Jane E GARTLON[2], Lee A DAWSON[2], Luis CASTRO[2], Peter J ATKINSON[2]

[1]Eisai Co., Ltd, Tsukuba Research Laboratories, [2]Eisai Limited, European Knowledge Centre

Herein we describe a series of tetrahydrobenzotriazoles as novel, potent metabotropic glutamate receptor subtype 5 (mGlu5) positive allosteric modulators (PAMs). Exploration of the SAR surrounding the tetrahydrobenzotriazole core ultimately led to the identification of a potent mGlu5 PAM with a low maximal glutamate potency fold shift, acceptable in vitro DMPK parameters and in vivo PK profile and efficacy in the rat novel object recognition (NOR) assay. As a result it was identified as a suitable compound for progression to in vivo safety evaluation.