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SAR determination and preliminary modelling studies for a new mGluR4 positive allosteric modulators

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Metabotropic glutamate receptors (mGluRs) are members of the group C family of GPCRs and play important roles in a broad range of central nervous system functions having therapeutic potential in a variety of neurological and psychiatric disorders [1]. Due to the lack of receptor subtype selectivity and physiochemical properties of mGluR orthosteric ligands (poor bioavailability and low potential of blood-brain barrier penetration) a significant effort has been made to identify compounds that can act as allosteric modulators which potentiate the response of endogenous glutamate [2]. A number of reviews are available summarizing recent progress in developing new allosteric ligands of mGluRs [3]. Among all, the group III subtypes: mGluR4, mGluR7 and mGluR8 still remains the least explored but with mighty potential for future development of clinical drugs [4].
Herein structures of a recently discovered mGluR4 PAM's are disclosed together with the results of in vitro and in vivo experiments. The developed mGluR4 homology models were used to rationalize the observed structure-activity relationships.

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