FAR-PO-29 Novel Bifunctional Compounds Targeting Nicotine and Dopamine Receptor Subtypes: Synthesis and Pharmacological Investigation

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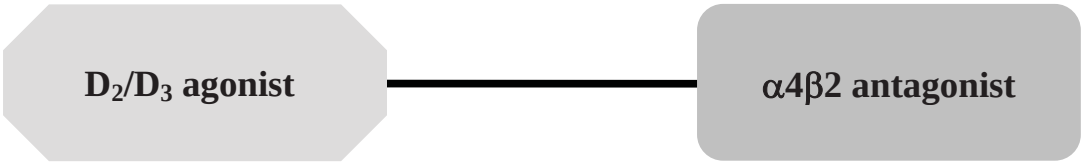
Future therapies for diseases associated with altered dopaminergic signaling, including Parkinson's disease, schizophrenia and drug addiction or drug dependence, may be substantially built on the existence of intramembrane receptor-receptor interactions within receptor mosaics where it is believed that the D_2 receptor may operate as the "hub receptor" [1]. In particular, it has been proposed that striatal dopaminergic neurotransmission could be under the control of receptor heteromers containing D_2 autoreceptors and non-α7 nicotinic acetylcholine heteroreceptors [2].

In an attempt to investigate the biochemical and functional interactions between dopaminergic autoreceptors and nAChRs containing the β2 subunit, we designed and prepared a group of potential bifunctional derivatives incorporating a D_2/D_3 *agonist* moiety and a nicotinic $\alpha4\beta2$ *antagonist* fragment, linked by polymethylene spacers of different length.



The new compounds have been biologically characterized for their affinity/specificity/functional profile at the target nACh and D_2 receptor subtypes. The synthesis of the designed derivatives and the results of their pharmacological investigation will be presented and discussed.

[1] K.Fuxe, D.Marcellino, A.Rivera, Z.Diaz-Cabiale, M.Filip, B.Gago, D.C.S.Roberts, U.Langel, S.Genedani, L.Ferraro, A.de la Calle, J.Narvaez, S.Tanganelli, A.Woods, L.F.Agnati, *Brain Res.Rev.*, *58*, **2008**, 415-452.

[2] D.Quarta, F.Ciruela, K.Patkar, J.Borycz, M.Solinas, C.Lluis, R.Franco, R.A.Wise, S.R.Goldberg, B.T.Hope, A.Woods, S.Ferré, *Neuropsychopharmacol.*, *32*, **2007**, 35-42.