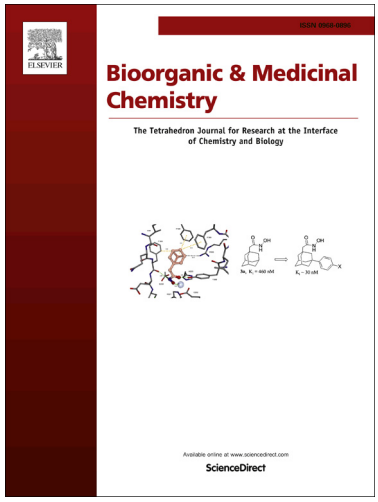

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The twin drug approach for novel nicotinic acetylcholine receptor ligands

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ABSTRACT

The association of two pharmacophoric entities generates so-called "twin drugs" or dimer derivatives. We applied this approach for the design of a small compound library for the interaction with α4β2* nicotinic acetylcholine receptors (nAChRs). In this compound series, the nAChR ligand *N,N*-dimethyl-2-(pyridin-3-yloxy)ethan-1-amine **9** served as one pharmacological entity and it was initially kept constant as one part of the "twin" compound. "Twin" compounds with identical or non-identical entities using the "no linker mode" or "overlap" mode were synthesized and evaluated for their nAChR affinities. Compound **17a** showed the highest affinity for the α4β2* nAChR subtype (K_i = 0.188 nM) and its (di)fluoro analogs could retain nanomolar affinities, when replacing pyridine as the hydrogen bond acceptor system by mono- or difluoro-phenyls. The "twin drug" approach proved to provide compounds with high affinity and subtype selectivity for α4β2* nAChRs.

Keywords:
Twin drugs
Nicotinic acetylcholine receptor
nAChR
Structure-activity relationship
3D QSAR pharmacophore

Abbreviations: ADME, absorption/distribution/metabolism/excretion; BBB, blood-brain barrier; CD_3OD, tetradeuteromethanol; $CDCl_3$, deuterochloroform; CH_2Cl_2, dichloromethane; ClogD, distribution coefficient; ClogP, calculated partition coefficient; CNS, central nervous system; DAT, dopamine transporter; DCC, N,N'-dicyclohexylcarbodiimide; DIAD, diisopropyl