Dual Nicotinic Acetylcholine Receptor α4β2 Antagonists/α7 Agonists: Synthesis, Docking Studies, and Pharmacological Evaluation of Tetrahydroisoquinolines and Tetrahydroisoquinolinium Salts - DTU Orbit (01/04/2018)

Dual Nicotinic Acetylcholine Receptor α4β2 Antagonists/α7 Agonists: Synthesis, Docking Studies, and Pharmacological Evaluation of Tetrahydroisoquinolines and Tetrahydroisoquinolinium Salts

We describe the synthesis of tetrahydroisoquinolines and tetrahydroisoquinolinium salts together with their pharmacological properties at various nicotinic acetylcholine receptors. In general, the compounds were α4β2 nAChR antagonists, with the tetrahydroisoquinolinium salts being more potent than the parent tetrahydroisoquinoline derivatives. The most potent α4β2 antagonist, 6c, exhibited submicromolar binding Ki and functional IC50 values and high selectivity for this receptor over the α4β4 and α3β4 nAChRs. Whereas the (S)-6c enantiomer was essentially inactive at α4β2, (R)-6c was a slightly more potent α4β2 antagonist than the reference β2-nAChR antagonist DHβE. The observation that the α4β2 activity resided exclusively in the (R)-enantiomer was in full agreement with docking studies. Several of the tetrahydroisoquinolinium salts also displayed agonist activity at the α7 nAChR. Preliminary in vivo evaluation revealed antidepressant-like effects of both (R)-5c and (R)-6c in the mouse forced swim test, supporting the therapeutic potential of α4β2 nAChR antagonists for this indication.

General information
State: Accepted/In press
Organisations: Center for Nuclear Technologies, The Hevesy Laboratory, Department of Chemistry, University of Copenhagen, Technical University of Denmark
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Number of pages: 11
Publication date: 2018
Main Research Area: Technical/natural sciences

Publication information
Journal: Journal of Medicinal Chemistry
ISSN (Print): 0022-2623
Ratings:
BFI (2018): BFI-level 2
Web of Science (2018): Indexed yes
BFI (2017): BFI-level 2
Web of Science (2017): Indexed yes
BFI (2016): BFI-level 2
Scopus rating (2016): CiteScore 6.06
BFI (2015): BFI-level 2
Scopus rating (2015): SJR 2.529 SNIP 1.631 CiteScore 5.66
Web of Science (2015): Indexed yes
BFI (2014): BFI-level 2
Scopus rating (2014): SJR 2.259 SNIP 1.693 CiteScore 5.55
Web of Science (2014): Indexed yes
BFI (2013): BFI-level 2
Scopus rating (2013): SJR 2.293 SNIP 1.78 CiteScore 5.65
ISI indexed (2013): ISI indexed yes
Web of Science (2013): Indexed yes
BFI (2012): BFI-level 2
Scopus rating (2012): SJR 2.33 SNIP 1.756 CiteScore 5.52
ISI indexed (2012): ISI indexed yes
Web of Science (2012): Indexed yes
BFI (2011): BFI-level 2
Scopus rating (2011): SJR 2.259 SNIP 1.706 CiteScore 5.48
ISI indexed (2011): ISI indexed yes
BFI (2010): BFI-level 2
Scopus rating (2010): SJR 1.99 SNIP 1.586
Web of Science (2010): Indexed yes
BFI (2009): BFI-level 2
Scopus rating (2009): SJR 2.012 SNIP 1.636