Biologia Serbica

JUNE 2021
Vol. 43 - No. 1 Special Edition

Biologia Serbica is formerly Review of Research, Faculty of Sciences, Biology Series (1971-2004), published by Department of Biology and Ecology, Faculty of Sciences, University of Novi Sad, Serbia

Aim and Scope

Biologia Serbica (BS) is an international scientific, peer-reviewed, open access journal that publishes original research articles, review articles, and short communications in all areas of biology.

Publisher

Department of Biology and Ecology
Faculty of Sciences
University of Novi Sad
Trg Dositeja Obradovića 2
21000 Novi Sad, Serbia
: +381 21 485 26 59
: +381 21 450 620
www.dbe.uns.ac.rs

Biologia Serbica is published biannually.

Printed by

"Sajnos"
Momčila Tapavice 2,
21000 Novi Sad
+381/21/499-461, +381/21/499-088
sajnosns@gmail.com

Date od publication: June 2018.

Subscription rates

Instructions available at
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Imidazolines: *In silico* off-target fishing in the class A of G protein-coupled receptors

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Abstract

Centrally acting hypotensive imidazoline derivatives are agonists of α_2-adrenoceptors and non-adrenergic I1-imidazoline receptors. Based on the finding that a central antihypertensive agent with high affinity for I1-type imidazoline receptors – rilmenidine, shows cytotoxic effects on cultured cancer cell lines, it has been suggested that imidazoline receptors agonists might have a therapeutic potential in cancer therapy. Nevertheless, rilmenidine itself does not represent a suitable candidate because of possible side effect caused by activation of α_2-adrenergic receptors. In our previous work, several novel rilmenidine-derived compounds with anticancer potential and without an agonistic activity on α_2-adrenoceptor were identified. Taking into consideration that human α_2-adrenergic receptors belong to the rhodopsin-like class A of G protein-coupled receptors (GPCRs), the biggest group of drug targets, that share structure similarity, it is reasonable to assume that these ligands might have the affinity on some other receptors from the same class.

To investigate potential additional targets for novel imidazoline I1 agonists a reverse docking protocol on 107 GPCRs, using 63 imidazoline ligands and their 670 decoys was prepared. Unlike typical molecular docking protocol, where series of small molecules are docked in one macromolecular target, in case of reverse docking a small-molecule is docked in the set of potential target proteins. Due to the availability of crystal structures all of the included GPCRs, were in inactive state, and therefore suitable for identification of the receptors antagonized by imidazoline ligands. Based on ROC curves and Enrichment Factors, 20 potential off-target GPCRs were selected. To better assess the affinity of imidazoline derivatives for chosen receptors, an additional docking study was performed, and docking scores of imidazolines were compared with docking scores of known antagonists. Finally, to verify *in silico* results, three ligands with high scores and tree ligands with low scores were tested for antagonistic activity on α_2-adrenergic receptors.

The protocol described here could be applied on all the small molecules, for the detection of potential interactions with GPCRs of class A, in the early stage of drug design process. Additionally, this protocol is easily expandable, by adding novel receptors/subfamily of receptors as soon as the crystal structures and/or 3D models become available.

Keywords:

off-target, cross-docking, GPCRs, imidazolines, adrenoceptors

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