Journal of the Taiwan Institute of Chemical Engineers 46 (2015) 15–29

Contents lists available at ScienceDirect

Journal of the Taiwan Institute of Chemical Engineers

journal homepage: www.elsevier.com/locate/jtice

Pharmacophore modeling, drug design and virtual screening on multi-targeting procognitive agents approaching histaminergic pathways

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ARTICLE INFO

Article history:
Received 27 March 2014
Received in revised form 8 August 2014
Accepted 21 September 2014
Available online 16 October 2014

Keywords:
Drug design
3D-QSAR
Histamine H_3 receptor
Histamine *N*-methyltransferase
Pharmacophore
Virtual screening

ABSTRACT

In an effort to design dual acting compounds enhancing histaminergic neurotransmission in the central nervous system, a novel class of 35 non-imidazole histamine H_3 receptor (H_3R) antagonists that simultaneously possess strong inhibitory potency on catabolic histamine *N*-methyltransferase (HMT), have been examined by 3D-QSAR study.

For improved understanding, the crucial chemical functionalities for combined H_3R/HMT activities 3D-QSAR pharmacophore models (H_3R: R^2 (0.98), Q^2 (0.94), RMSE (0.171); and HMT: R^2 (0.80), Q^2 (0.60), RMSE (0.159) were developed.

Pharmacophore for H_3R antagonistic activity mainly differs from pharmacophore for HMT inhibiting activity in presence of specific lipophilic/steric components of the H_3R pharmacophore, H-bond accepting components of the H_3R pharmacophore, H-bond donating components of the HMT pharmacophore, and longer optimal distance between H-bond donor and steric hot spots in the H_3R pharmacophore than in the HMT pharmacophore.

Formed 3D-QSAR models were applied for design of novel piperidino-aminoquinoline hybrids as multitarget H_3R/HMT ligands with potential impact in therapy of sleep-wake disorders and cognitive impairment. Designed compounds with 3D-QSAR predicted p*K*i (H_3R) > 9.6 and (p*K*i (H_3R) + pIC_{50}(HMT)) > 16.8 were selected for further profiling.

Virtual screening of ZINC database is performed against the most promising H_3R/HMT ligand and top ranked compounds are tested by both 3D-QSAR models.

1. Introduction

Histamine is a well-known chemical mediator in the immediate allergic response, regulation of gastric acid secretion, and also plays a role as a neurotransmitter in the central nervous system (CNS) [1]. In the CNS neurons, histamine is synthesized from L-histidine by cytoplasmatic L-histidine decarboxylase enzyme (HDC, E.C. 4.1.1.22) and then stored in the vesicles and released from the axon terminals in a calcium-dependent rapid-turnover mechanism [1,2]. The main inactivation procedure in the CNS is an enzymatic catabolic process occurring in the nearest glia cells [2]. In the brain histamine is mainly inactivated by methylation of the imidazole ring in the N^t-position, catalyzed by histamine *N*-methyltransferase enzyme (HMT, E.C. 2.1.1.8) [2,3]. Histamine mediated its main biological activities by interaction with four distinct histamine receptors (H_1R–H_4R, which are members of the class A family of G-protein coupled receptors (GPCRs) [1,3]. Pharmacological studies of frontocortical histaminergic pathways confirmed that antagonism of negative feed-back mechanism presynaptic histamine H_3 autoreceptors reinforces histaminergic transmission, while blockade of histamine H_3 heteroreceptors accelerates the corticolimbic liberation of different neurotransmitters like dopamine, acetylcholine, glutamate, norepinephrine, GABA, and serotonin [4–7].

Recent pharmacological studies and clinical trials demonstrated that H_3R play an essential role in regulation of the sleep-wake cycle and cognition. H_3R antagonists assumed to have therapeutic effectiveness in the treatment of a sleep disorders (narcolepsy), cognitive impairment, pain/itch, stroke, depression, attention deficit hyperactivity disorder (ADHD), schizophrenia, dementia and neurodegenerative disorders (*e.g.* Parkinson's disease, Alzheimer's disease) [8–18].

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http://dx.doi.org/10.1016/j.jtice.2014.09.017
1876-1070/

Multitarget ligands displaying dual H_3R antagonist/histamine *N*-methyltransferase (HMT) inhibiting properties are able to greatly enhance histaminergic neurotransmission by simultaneously combining histamine-releasing properties (*via* H_3 autoreceptor blockade), release of other neurotransmitters by complex receptor cross talk, and reduced catabolic rate for inactivation (*via* HMT inhibition) [19–23]. This novel approach of hybrid compounds targeting both H_3R and HMT could contribute to the elevation of intersynaptic histamine levels in the CNS and might have therapeutic applications in psychiatric and neurodegenerative diseases [10,19–23].

In contrast to the early work on H_3R [24], almost all chemical series of current clinical interest are non-imidazoles [25]. Major potential disadvantages of the imidazole derivatives are poor brain penetration, CYP450 inhibition, drug–drug interactions, liver toxicity, extrapyramidal symptoms, and inhibition of adrenal steroid synthesis [26–30].

Recently developed set of 35 multipotent ligands [19,20] containing a piperidinoalkyl group, as a key structural feature for human H_3R antagonism, connected by different spacer lengths to an aminoquinoline moiety, as pharmacophoric moiety for HMT inhibiting activity, have been studied. The new class of non-imidazole derivatives [19,20] exerted moderate ($Ki(H_3R)$:1–100 nM) to very high ($Ki(H_3R)$: 0.09–1.80 nM) affinity at human H_3R and simultaneously possess strong (IC_{50}: 20–100 nM) inhibiting activity on the HMT enzyme.

Based on our previous work in the synthesis and biological evaluation of the multipotent H_3R/HMT inhibitors [19,20] and other multiple targeting ligands we have applied 3D-QSAR approach for design of novel dual H_3R antagonists and HMR inhibitors as potential procognitive agents which may have additional properties on other precognitive targets, such as acetylcholinesterase (AChE) and butyrylcholinesterase (BChE).

The main aims of the 3D-QSAR study were to define specific molecular determinants for H_3R antagonism and HMT inhibition of the 35 piperidino-aminoquinoline hybrids, design novel H_3R/HMT ligands, and use 3D-QSAR models for evaluation of H_3R antagonistic and HMT inhibiting activities of the newly designed compounds.

2. Materials and methods

2.1. 3D-QSAR study

The antagonist binding at H_3R (*Ki*) and inhibitory potency on HMT (IC_{50}) of 35 aminoquinoline derivatives were used for the 3D-QSAR study [19,20]. Negative decadic logarithm of determined *Ki* and IC_{50}, *i.e.* (p*Ki* ($\log(1/Ki)$) and pIC_{50} ($\log(1/IC_{50})$) values were calculated and used for the QSAR modeling. The p*Ka* calculation and selection of dominant molecules/cations at physiological pH 7.4 for the 35 examined compounds was performed by the MarvinSketch 5.5.1.0 program [31]. Dominant forms at physiological pH were further used for geometry optimization and for the 3D-QSAR study. Geometry optimization for the aminoquinoline derivatives was performed by *ab initio* Hartree–Fock/3–21G (HF/3–21) method [32] included in the Gaussian 98 program [33]. The selected HF/3–21 method was proven as very good choice for geometry optimization of related imidazoline, pyridine, piperidine derivatives and aromatic compounds [34–38]. Suitability of the HF/3–21 method for geometry optimization of the aminoquinolines was tested by comparing experimental and HF/3–21 tacrine conformations. Histamine methyltransferase (Natural Variant I105) complexed with the acetylcholinesterase Inhibitor and Altzheimer's disease drug tacrine (PDB: 2AOW) was used to obtain tacrine conformation in the enzyme active site. The experimental tacrine conformation was then superimposed with tacrine conformation obtained by use of the (HF/3–21) method. Results of the overlay study (RMS error: 0.065) confirmed very high structural similarities between experimental and HF/3–21 tacrine conformations (Supplement material). Since tacrine and all examined ligands are aminoquinoline derivatives was concluded that the HF/3–21 is suitable method for geometry optimization of the data set.

The 3D-QSAR studies of the aminoquinoline derivatives were performed by use of the Pentacle 1.0.6 program [39] and Schrödinger–Phase software included in Maestro 2011 program [40,41]. The Pentacle 1.0.6 program [39] is advanced software tool for obtaining alignment-independent 3D quantitative structure–activity relationships. The 3D-QSAR starts from computing highly relevant 3D maps of interaction energies (GRID based Molecular Interaction Fields-MIFs) between the examined molecule and four chemical probes: DRY (which represent hydrophobic interactions), O (sp^2 carbonyl oxygen, representing H-bond acceptor), N1 (neutral flat NH, like in amide, H-bond donor), and the TIP probe (molecular shape descriptor). The grid spacing was set to 0.5 Å and the CLACC (for 3D-QSAR (H_3R))/or MACC2(for 3D-QSAR (HMT)) encoding with smoothing window to 0.8. The number of filtered nodes was set to 100 with 50% relative weights within the ALMOND discretization.

The interaction energy between the probe and the target molecule was calculated at each point as the sum of Lennard-Jones (E_{lj}), hydrogen bond (E_{hb}), electrostatic interactions (E_{el}), and an entropic term: $E_{xyz} = \sum E_{ij} + \sum E_{el} + \sum E_{hb} + S$ [42].

Geometry and calculated electronic properties of the target molecule have mutual impact on the interaction energy between the probe and the target molecule and consequently on the developed pharmacophore model.

The obtained maps were encoded into GRID Independent Descriptors (GRIND and GRIND2 descriptors). The GRIND and GRIND2 descriptors were independent of the alignment of the series [42]. The GRIND approach was aimed to extract the information enclosed in the MIFs and compress it into new types of variables whose values were independent of the spatial position of the molecule studied by using an optimization algorithm with the intensity of the field at a node and the mutual node–node distances between the chosen nodes as a scoring function. Such variables constituted a matrix of descriptors that were analyzed using multivariate techniques, such as principal component analysis (PCA) and partial least squares (PLS) regression analysis. The principal component analysis was used for inspection of our series and for obtaining a heatmap of our compounds describing their similarities and differences. Variables were used for development of 3D-QSAR models by use of the PLS regression [43].

Based on the PCA plots (t1 *vs.* t2 and t1 *vs.* u1) the data set of 35 aminoquinoline derivatives was divided on training set (**27–28** compounds for QSAR models building) and verification set (**7–8** compounds for QSAR models validation) [44]. The most important pharmacophores (GRID descriptors), responsible for the H_3R and HMT inhibition, were selected by the PLS regression and used for the 3D-QSAR (H_3R and HMT) models building (Pentacle 1.0.6 program). The formed 3D-QSAR (H_3R and HMT) models and corresponding 3D-pharmacophores were used for design and selection of novel aminoquinoline derivatives as promising multipotent ligands. Quality of the obtained 3D-QSAR (H_3R and HMT) models was examined by use of: leave-one-out cross-validation (Q^2), correlation coefficient (R^2 observed *vs.* predicted), root main squared error of estimation (RMSEE), and external validation (root main squared error of prediction (RMSEP)) [43,44].

Predictive power of the model was determined by Q^2, which is leave-one-out cross-validated version of R^2. A model was fitted to the data leaving one compound out, selected the best variables, and predicted *Y* for the left—out compound. This procedure was repeated until all compounds have been left out, which resulted in