European Journal of Medicinal Chemistry 115 (2016) 94–108

Contents lists available at ScienceDirect

European Journal of Medicinal Chemistry

journal homepage: http://www.elsevier.com/locate/ejmech

Research paper

Synthesis and biological activities of indolizine derivatives as alpha-7 nAChR agonists

Yu Xue [a], Jingshu Tang [b], Xiaozhuo Ma [a], Qing Li [a], Bingxue Xie [a], Yuchen Hao [b], Hongwei Jin [a], Kewei Wang [b, **], Guisen Zhang [c], Liangren Zhang [a, *], Lihe Zhang [a]

[a] State Key Laboratory of Natural and Biomimetic Drugs, School of Pharmaceutical Sciences, Peking University, Beijing, 100191, PR China
[b] Department of Molecular and Cellular Pharmacology, PKU-IDG/McGovern Institute for Brain Research, School of Pharmaceutical Sciences, Peking University, Beijing, 100191, PR China
[c] Jiangsu Nhwa Pharmaceutical Co. Ltd. 69 Minzhu South Road, Xuzhou, Jiangsu, 221116, PR China

ARTICLE INFO

Article history:
Received 30 September 2015
Received in revised form
3 March 2016
Accepted 4 March 2016
Available online 8 March 2016

Keywords:
α7 nAChR
Indolizine
Agonists
SAR
Schizophrenia

ABSTRACT

Human α7 nicotinic acetylcholine receptor (nAChR) is a promising therapeutic target for the treatment of schizophrenia accompanied with cognitive impairment. Herein, we report the synthesis and agonistic activities of a series of indolizine derivatives targeting to α7 nAChR. The results show that all synthesized compounds have affinity to α7 nAChR and some give strong agonistic activity, particularly most active agonists show higher potency than control EVP-6124. The docking and structure–activity relationship studies provide insights to develop more potent novel α7 nAChR agonists.

1. Introduction

Schizophrenia is one of the most important diseases in psychiatry. As a chronic psychiatric disorder, it severely afflicts approximately 1% of the general population around the world [1]. Schizophrenia was characterized by three distinct symptoms respectively, i.e. positive (increased in normal function delusion, agitation, hallucination, and paranoia), negative (reduced affect, low motivation and social withdrawal), and cognitive (impairment in attention, executive functioning, working memory, the ability to learn and to process information) symptoms [2]. Although significant therapeutic advances have been made in the treatment of positive and negative symptoms, the vast majority of schizophrenia patients (over 85%) also suffer from the cognitive impairment that is poorly addressed with current agents [3,4]. Accordingly, cognitive disorders represent a still unmet medical need in the psychiatric and neurology therapeutic area.

There are many known targets relevant with schizophrenia, such as acetylcholine (ACh), dopamine (DA), 5-hydroxytryptamine (5-HT), glutamate (Glu), GABA and other neuropathic receptors, which were activated to release corresponding neurotransmitters functioned in the nervous system [5–8]. At present, most of clinical therapeutics in the field of anti-psychiatry are multi-target therapeutic agents, which make easy to bring about some adverse effects. Hence, a highly selective and effective potential drug is fairly meaningful.

Over the past three decades, neuronal nicotinic acetylcholine receptors (nAChRs) which belong to the Cys-loop super family of ligand-gated ion channels have been regarded as targets for drug discovery primarily for central nervous system (CNS) indications [9,10]. They comprise of heterogeneous subtypes of receptors with individual pharmacological nature and specific functional profiles, which are widely distributed in the human brain [11]. Among them, homomeric α7 and heteromeric α4β2 are identified as primary

Abbreviations: ACh, acetylcholine; THF, tetrahydrofuran; DMSO, dimethylsulfoxide; CNS, central nervous system; HRMS, high resolution mass; DIPEA, diisopropylethylamine; AChBP, acetylcholine binding protein; SAR, structure–activity relationship; nAChR, nicotinic acetylcholine receptor; DABCO, 1, 4-Diaza[2.2.2]bicyclooctane; HATU, 2-(7-Aza-1*H*-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate.

* Corresponding author.
** Corresponding author.
E-mail addresses: wangkw@bjmu.edu.cn (K. Wang), liangren@bjmu.edu.cn (L. Zhang).

http://dx.doi.org/10.1016/j.ejmech.2016.03.016
0223-5234/

interests from the drug discovery perspectives [12–14]. A plentiful of experimental evidences have supported the involvement of α7 nAChR in CNS diseases like Schizophrenia and Alzheimer's disease as well as in inflammatory disorders [15–17]. It was found that decreased expression of α7 nAChR appeared in brain tissue of Schizophrenia [18]. The analysis of families of Schizophrenia patients which displayed a P50 sensory gating deficit [19,20] clearly indicated that the defect is linked to chromosome 15q14, the site of the gene of α7 nAChR [21]. According to the report of epidemiology, in addition, highly nicotine-seeking behavior was observed from Schizophrenia patients for the reason that nicotine, which is contained in cigarette as an endogenous agonist of α7 nAChR, can improve symptoms including cognitive dysfunction [22–24]. Besides, typical α7 nAChR agonists have demonstrated improved cognition in animal models and normalized sensory gating deficits, which are believed to implicate in the cognitive fragmentation in Schizophrenia. Consequently, human α7 nAChR is a promising therapeutic target for the treatment of Schizophrenia accompanied with cognitive impairment [25–28].

Human α7 nAChR has a homomeric and pentameric structure composed of five membrane spanning subunits, each of which is comprised of three regions: transmembrane spanning domain, extracellular C-terminal and N-terminal. The interface of two adjacent α7 subunits of extra-membrane region contributes to the binding site of α7 nAChR agonists [29,30]. Recent studies showed that α7 nAChR agonists improved cognitive performance in both animal models and clinical trials [30–32], out of which, quinuclidine containing compounds exhibited outstanding behaviors in clinical or preclinical studies, such as EVP-6124, JN403, PHA-543613 and RG3487 (Fig. 1). EVP-6124, a selective α7 nAChR agonist, is in phase III clinical trials for the treatments of Schizophrenia and Alzheimer's diseases [33]. JN403 displayed unique potency and selectivity in preclinical studies [34]. PHA-543613 [35] and RG3487 [36] also showed high potencies for the improvements of cognitive deficits, but were discontinued in phase I and II clinical trials, respectively, due to the occurrences of adverse events related to cardiovascular and gastrointestinal functions [37–39].

Based on the structural characteristics of the reported α7 nAChR agonists, the structure of α7 nAChR agonist is generally composed of three moieties, i.e., a basic fragment, an aromatic part, and a linker [40]. Quinuclidine, piperidine and azabicyclic tropane are often used as basic parts, which can be protonated at physiological pH and participate in a cation–π interaction with acceptor [31]. The aromatic part provides hydrophobic and π–π interaction with acceptor. Amide and carbamate are frequently used as linkers which also play roles as hydrogen-bond acceptors.

Indolizine, also named pyrrolo[1,2-a]pyridine, is an isomeride of indole. It belongs to a class of azabicyclic compound with ten peripheral π electrons and is a bioisostere of indole [41]. Indolizine derivatives have shown various biological activities, such as antitumor [42], antiarrhythmic [43], antihypertensive [44], anti-inflammatory [45], antiviral [46] and antimicrobial activities [47]. Indolizine-3-carboxylic acid derivatives were also reported to be a potent 5-HT_3 receptor antagonist [48]. Based on the diverse biological activities and our previous research on indolizine derivatives [46], in this study, indolizine is employed as the aromatic moiety for the discovery of novel α7 nAChR agonist. Meanwhile, owing to the extensive utilization of quinuclidine in various synthetic nAChR ligands, it was used as the basic moiety [49]. To elucidate the structure–activity relationship (SAR) and discover active α7 nAChR agonist, a variety of indolizine derivatives have been designed in which the chemical modification was focused on the indolizine moiety either by changing the substituted group or substituted position (Fig. 2) along with agonistic activity assay.

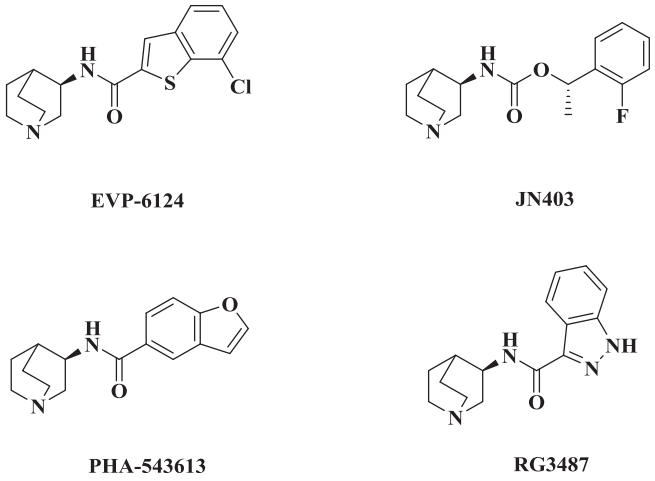

Fig. 1. Chemical structures of some α7 nAChR agonists.

2. Results and discussion

2.1. Docking analysis

To investigate the information on the orthosteric binding pocket and the detailed ligand–receptor interaction, docking studies of the representative compounds into the binding site of homologous model for human α7 nAChR were conducted. Although the three-dimensional structure of α7 nAChR has not been characterized, several structures of the extracellular region of the homologous acetylcholine binding protein (AChBP) or chimera are available, which shares 64% sequence identity and 71% similarity with native α7 nAChR [50]. So, an α7 nAChR model generated from AChBP template was used for docking study [51].

Compound **D3** was docked into the binding site of α7 nAChR model. The agonist binding site was located at the interface between two adjacent subunits in the extracellular domain of the receptor and was mainly defined by an aromatic cage composed of TRP53, TYR89, TRP143, TYR185, TYR192 and a disulfide-bridged loop (Cys-loop, CYS187 and CYS188) [50]. The indolizine aromatic

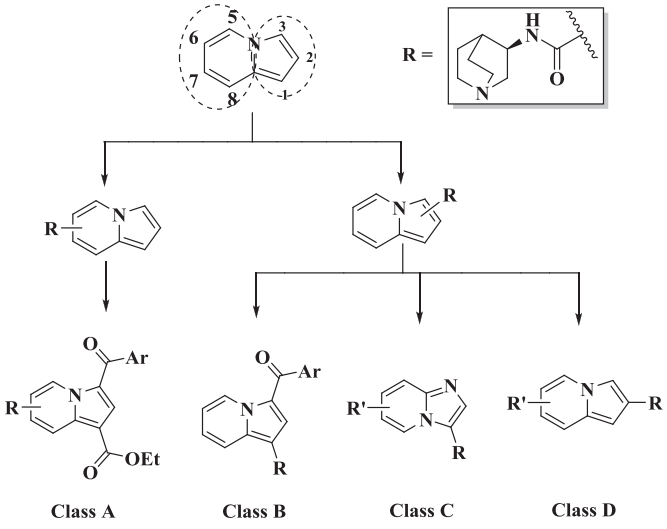

Fig. 2. Design of indolizine derivatives for α7 nAChR agonists.