European Journal of Medicinal Chemistry 108 (2016) 334–346

Contents lists available at ScienceDirect

European Journal of Medicinal Chemistry

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

Research paper

Towards new 5-HT$_7$ antagonists among arylsulfonamide derivatives of (aryloxy)ethyl-alkyl amines: Multiobjective based design, synthesis, and antidepressant and anxiolytic properties

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ARTICLE INFO

Article history:
Received 29 July 2015
Received in revised form
23 November 2015
Accepted 24 November 2015
Available online 30 November 2015

Keywords:
Screening of combinatorial library
Molecular docking
5-HT$_7$ antagonist
SB-269970
Forced swim test
Tail suspension test
Four plate test
Depression
Anxiety

ABSTRACT

A series of 39 arylsulfonamide/amide derivatives of (aryloxy)ethyl alkyl amines, was designed with the support of the Virtual Combinatorial Library-Virtual Screening protocol, and synthesized using solid-phase methodologies. Representative compounds were biologically evaluated for their affinity for 5-HT$_7$Rs and for their selectivity over related 5-HTRs (5-HT$_{1A}$Rs, 5-HT$_{2A}$Rs, 5-HT$_6$Rs), dopamine D$_2$Rs and adrenergic α_1Rs. The study identified the derivatives **27** (3-fluoro-N-{1-[2-(2-cyclopentylphenoxy) ethyl]piperidin-4-yl}-benzenesulfonamide; PZ-1417) and **35** (4-fluoro-N-(1-{2-[(propan-2-yl)phenoxy] ethyl}-8-azabicyclo[3.2.1]octan-3-yl)-benzenesulfonamide; PZ-1150) as being potent 5-HT$_7$R antagonists with antidepressant and anxiolytic properties in the forced swim test (0.625–5 mg/kg and 0.625 mg/kg, respectively), the tail suspension test (0.625 mg/kg and 0.625 mg/kg, respectively), and in four plate test (0.625 mg/kg and 1.25–2.5 mg/kg, respectively) in mice. It has to be stressed that new compounds displayed higher activity than that of SB-269970, a reference 5-HT$_7$R antagonist. Finally, the study provided valuable insight into the development of potential therapeutic agents for the treatment of CNS disorders.

1. Introduction

The 5-HT$_7$ receptors (5-HT$_7$Rs) are the most recently described members of the serotonin family [1]. These receptors are typical metabotropic receptors (GPCRs) positively coupled with adenylyl cyclase through the stimulatory Gα12 proteins [2]. Correlations between the distribution of 5-HT$_7$Rs (e.g. thalamus, suprachiasmatic nuclei, and hippocampus) and their function in the central nervous system (CNS), have suggested their involvement in physiological functions including the circadian rhythm, learning and memory as well as in mood disorders, schizophrenia, anxiety or in cognitive decline processes [3]. Cognitive impairment observed in CNS disorders such as schizophrenia have in several studies shown to be addressed by 5-HT$_7$Rs antagonists [4]. Moreover, many piece of evidences have confirmed that the pharmacological blockade of 5-HT$_7$Rs produced an antidepressant-like behavior in animal models [5], suggesting 5-HT$_7$R antagonists may be clinically relevant for the treatment of depression [6,7]. Finally, the antidepressant effects of atypical antipsychotics – amisulpride and lurasidone, could be related to the antagonism at the 5-HT$_7$Rs [8,9].

Initially, the quest for selective 5-HT$_7$R ligands led to arylsulfonamide derivatives of alkylamines (e.g., SB-269970 and SB-656104) [10,11]. Soon after long-chain arylpiperazines/piperidines

Abbreviations: BAL, Backbone amide linker; Boc, Di-tert-butyl-dicarbonate; TEA, Trimethylamine; DBU, 1,8-diazabicyclo [5,4,0]udec-7-ene; DMF, Dimethylformamide; TFA, Trifluoroacetic acid; AcOH, Acetic acid; TMSOtf, Trimethylsilyl trifluoromethanesulfonate; CHO, Chinese Hamster Ovary; HEK, Human Embryonic Kidney; FST, forced swim test; TST, tail suspension test; FPT, four-plates test.

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http://dx.doi.org/10.1016/j.ejmech.2015.11.040
0223-5234/

functionalized with different terminal fragments (e.g., tetrahydrobenzindoles, oxindoles, benzothiophenes, biphenyl, benzoimidazolones) [12–21] and their bioisosteres (i.e., tetrahydroisoquinoline) [22] have emerged as an important class of 5-HT$_7$R agents. Further efforts resulted in the identification of JNJ-18038683 with efficacy confirmed in preclinical models, which has been recently evaluated in a clinical trial (phase II) for the treatment of major depression [23]. These findings indicated the significant interest in the development of 5-HT$_7$R antagonists with appropriate drug-like properties for pre-clinical and clinical validation.

Our research group has recently reported the design of a new class of 5-HT$_7$R antagonists, namely arylsulfonamide derivatives of (aryloxy)ethyl alicyclic amines, and identified several compounds (e.g., PZ-766 and PZ-1404) that displayed distinct antidepressant-like and anxiolytic-like properties in the forced swim test (FST) and the four plate test (FPT) in mice, respectively, and pro-cognitive activity in the novel object recognition (NOR) test in rats (Fig. 1) [24,25].

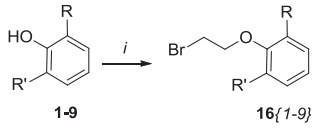
Encouraged by those promising results, we decided to further explore the group of 5-HT$_7$Rs antagonists with PZ-766 and PZ-1404 lead structures, expanding chemical diversity of central amine part to identify other high affinity scaffolds, and to improve their overall pharmacological profile by modifications in both aryloxy and arylsulfonamide fragments. For this purpose we adapted the approach of Virtual Combinatorial Library-Virtual Screening (VCL-VS), consisting of construction of VCL and its subsequent filtration by physicochemical descriptors, pharmacophore model, and molecular docking with SVM-SIFt based post-docking ranking scheme, to prioritize the synthesis [24]. Structural modifications of the finally synthesized compounds comprised the introduction of new alicyclic amine scaffolds (3-amino-azetidine, 3-amino-8-azabicyclo [3.2.1]octane and 2,5-diazabicyclo[2.2.1]heptane), small and sterically encumbered substituents in position-2 of aryloxy fragment, and replacement of the arylsulfonamide group with arylamide and arylurea moieties.

We further report on the extensive structure–activity relationships among the synthesized analogs regarding their activity for 5-HT$_7$ and 5-HT$_{1A}$Rs, an extended evaluation of the selected compounds for serotoninergic, dopaminergic and adrenergic receptors (5-HT$_{2A}$, 5-HT$_6$, D$_2$ and α_1Rs), as well as for off-targets, i.e. adrenergic β_1, histamine H$_1$, muscarinic M$_1$ receptors, *in vitro* functional signaling, and *in vivo* behavioral evaluation in rodents models of depression and anxiety.

2. Results and discussion

2.1. Chemistry

The designed compounds **18**–**52** were synthesized according to a multistep procedure. In the first step, commercially available phenols **1**–**9** were treated with 1,2-dibromoethane in the presence of potassium carbonate in refluxing acetone, yielding (aryloxy) ethyl bromides **16**{*1–9*} (Scheme 1). These building blocks were subsequently used for a solid-phase approach.



Scheme 1. Synthesis of (aryloxy)ethyl bromides **16**{*1–9*}. Reagents and conditions: (*i*) 1,2-dibromoethane, K_2CO_3, KI, $(CH_3)_2CO$, 60 °C, 48–72 h.

Next, a solid-supported synthesis protocol was performed on a commercially available BAL-functionalized polystyrene resin **10** (Scheme 2). The initial step consisted of one-pot reductive amination to anchor the Boc-protected secondary amine **11**{*1–3*} (Table 1) onto the solid support.

The obtained secondary amines were further treated with different arylsulfonyl chlorides **13**{*1–8*}, arylacyl chlorides **13** {*9–10*} and arylisocyanates **13**{*11–12*} (Table 2) in the presence of TEA and CH_2Cl_2.

After Boc removal, the obtained resin-bound compounds **15** were further alkylated with different (aryloxy)ethyl bromides **16** {*1–9*} (Table 3) under the DBU promoted reaction in DMF. The final step involved cleavage from the resin of the final compounds **18**–**52** under acidic conditions.

Compounds containing the 2,5-diazabicyclo[2.2.1]heptane core **11**{*4*} were synthesized in alternative way (Scheme 3). After alkylation of the Boc-protected secondary amine with (aryloxy) ethyl bromides **16**{*6*} and **16**{*9*}, final arylsulfonamides **55**–**58** were obtained upon treatment of the deprotected intermediates **53**–**54** with the selected arylsulfonyl chlorides.

2.2. Molecular modeling

To explore available chemical space around central amine part of PZ-766 a set of 680 cyclic secondary amine reagents of different ring size and additional primary or secondary amine group was selected from MolPort database. Next, Virtual Combinatorial Library based on the elaborated synthetic protocol (Scheme 2) was generated by the in-house script for iterative combination of the above mentioned set of central amine scaffolds and small sets of acylating and alkylating agents (Tables 2 and 3). Acylating and alkylating agents were selected on a basis of our previous reports [24,25]; to further explore an impact of the sp^2 configuration, a set of acylating agents was extended to isocyanates (Table 2). The obtained VCL of PZ-766 derivatives (680 cores × 9 alkylating agents × 12 acylating agents = 73,440 cmpds) was processed by the hierarchical multistep virtual screening protocol including: physico-chemical filter (the strongest basic pK_a < 10, logP < 6, logD < 5), ADMET filter (QPPCaco – gut-blood barrier): <25 poor, >500 great, solubility in water at 25 °C (QPlogS: −6.5 – 0.5) and the

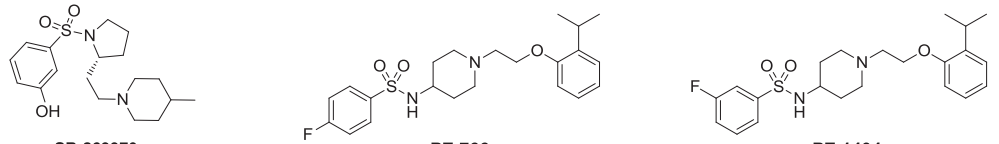


Fig. 1. 5-HT$_7$ receptor antagonists – SB-269970 [10] and arylsulfonamide derivative of (2-isopropylphenoxy)ethyl piperidine.