Bioorganic & Medicinal Chemistry Letters 26 (2016) 2610–2615

Contents lists available at ScienceDirect

Bioorganic & Medicinal Chemistry Letters

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

1-Sulfonyl-6-Piperazinyl-7-Azaindoles as potent and pseudo-selective 5-HT$_6$ receptor antagonists

Charles-Henry Fabritius [a], Ullamari Pesonen [b], Josef Messinger [b], Raymond Horvath [a], Harri Salo [b], Michał Gałęzowski [a], Mariusz Galek [a], Klaudia Stefańska [a], Joanna Szeremeta-Spisak [a], Marta Olszak-Płachta [a], Anna Buda [a], Justyna Adamczyk [a], Marcin Król [a], Peteris Prusis [b], Magdalena Sieprawska-Lupa [a], Maciej Mikulski [a], Katja Kuokkanen [b], Hugh Chapman [b], Radosław Obuchowicz [a], Timo Korjamo [b], Niina Jalava [b], Mateusz Nowak [a,*]

[a] Selvita S.A., Ul. Bobrzyńskiego 14, 30-348 Krakow, Poland
[b] Orion Corporation, Orion Pharma, Orionintie 1A, 02200 Espoo, Finland

ARTICLE INFO

Article history:
Received 19 February 2016
Revised 7 April 2016
Accepted 10 April 2016
Available online 23 April 2016

Keywords:
Serotonin receptor
5-HT$_6$ receptor
Antagonists
Azaindole
Cognitive impairment

ABSTRACT

A series of 1-Sulfonyl-6-Piperazinyl-7-Azaindoles, showing strong antagonistic activity to 5-HT$_6$ receptor (5-HT$_6$R) was synthesized and characterized. The series was optimized to reduce activity on D$_2$ receptor. Based on the selectivity against this off-target and the analysis of the ADME-tox profile, compound **1c** was selected for in vivo efficacy assessment, which demonstrated procognitive effects as shown in reversal of scopolamine induced amnesia in an elevated plus maze test in mice. Compound **3**, the demethylated version of compound **1c**, was profiled against a panel of 106 receptors, channels and transporters, indicating only D$_3$ receptor as a major off-target. Compound **3** has been selected for this study over compound **1c** because of the higher 5-HT$_6$R/D$_2$R binding ratio. These results have defined a new direction for the design of our pseudo-selective 5-HT$_6$R antagonists.

Novel therapies against dementias and in particular Alzheimer's disease (AD) constitute one of the biggest medical needs in developed countries. With the morbidity reaching over 35 million cases worldwide[1] and the annual worldwide cost of above US$315 billion[2] this group of diseases remains in the center of interest of pharmaceutical industry and drug research around the world. Disease modifying treatments do not yet exist, and disadvantages of current standard symptomatic medications, namely inhibitors of acetyl cholinesterase (e.g., donepezil, rivastigmine, galantamine) and NMDA receptors (e.g., memantine) have poor tolerability, low efficacy and present challenges with patient compliance because of suboptimal dosing regimens and side effects (mainly gastrointestinal). These shortcomings result in symptomatic therapies which benefit the patient for only about one year on average,[3] whereas the potential need for therapy for AD patients can last for even 8.5 years (considering the duration from the onset of the disease to the severe stage).[4] Due to the above mentioned reasons an innovative approach to enhance cognition in AD patients is desirable.

One of the approaches to cognitive improvement is blocking the serotonin 5-HT$_6$ receptor with an antagonist. 5-HT$_6$R is expressed almost exclusively in the central nervous system in humans, mainly in hippocampus, striatum and nucleus accumbens. 5-HTRs couple to Gs-protein and stimulate adenylyl cyclase activity. Antagonism of 5-HT$_6$R was shown to improve cognitive performance in rodents in numerous memory related tasks.[5–9] Importantly, these effects seem to be translated to humans—Lundbeck has recently announced positive results from a Phase II clinical trial of its selective 5-HT$_6$R antagonist (idalopirdine; Lu AE58054) in improving cognitive performance in mild to moderate AD patients[10] and initiated Phase III.[11] Additionally, antagonizing 5-HT$_6$R provides a potential therapeutic strategy for cognitive symptoms of schizophrenia[12] and obesity.[13] The mode of action of 5-HT$_6$R antagonists has been elucidated in vivo by means of electrophysiology[14] and microdialysis[15] where it was shown that antagonizing 5-HT$_6$R enhances glutamatergic, cholinergic and monoaminergic neurotransmission.

Comprehensive reviews of 5-HT$_6$R related medicinal chemistry were published in recent years by Holenz,[16] Liu,[17] Ivachtchenko[18] and Lopez-Rodriguez.[19] According to Lopez-Rodriguez most of the known 5-HT$_6$R ligands can be clustered into four structural families taking into account the groups that occupy the main

* Corresponding author. Tel.: +48 12 297 47 00; fax: +48 12 297 47 01.
E-mail address: mateusz.nowak@selvita.com (M. Nowak).

http://dx.doi.org/10.1016/j.bmcl.2016.04.024
0960-894X/

pharmacophoric features: bisarylsulfonamides, indoles, indole-like derivatives and non-sulfonyl compounds. Those key structural elements for 5-HT6 antagonism can be modeled into a simplified pharmacophore:[19,20] a positive ionizable atom, an aromatic ring-hydrophobic site, a hydrogen bond acceptor and a hydrophobic site. Some diversified atypical compounds have also been reported, although they share common structural part of those 4 main families. According to the recent review of Ivachtchenko, which is focused mainly on the selectivity profile of 5-HT_6 ligands, these can be further classified into three categories: multimodal/multi target, pseudo-selective and selective.

Here we report the discovery and pharmacological characterization of a series of 6-piperazinyl-7-azaindoles bearing an alkyl or hetero alkyl sulfone in position 1 and an aryl or hetero aryl in position 4 (compounds **1a**–**p**, **2a**–**f** and **3** represented in Scheme 1). Those compounds could be assigned to the indole-like family: azaindole is used here as a bioisostere of the typical indole core. We also synthesized the bisarylsulfonamides derivatives on this azaindole core[21] but those compounds were not selected for further studies due to the superior results obtained for the aliphatic analogs (results not reported) and tolerance of this new chemical series for non-lipophilic moieties. Furthermore, the removal of the sulfonyl group is not tolerated and results in losing the potency for 5-HT_6 receptor.

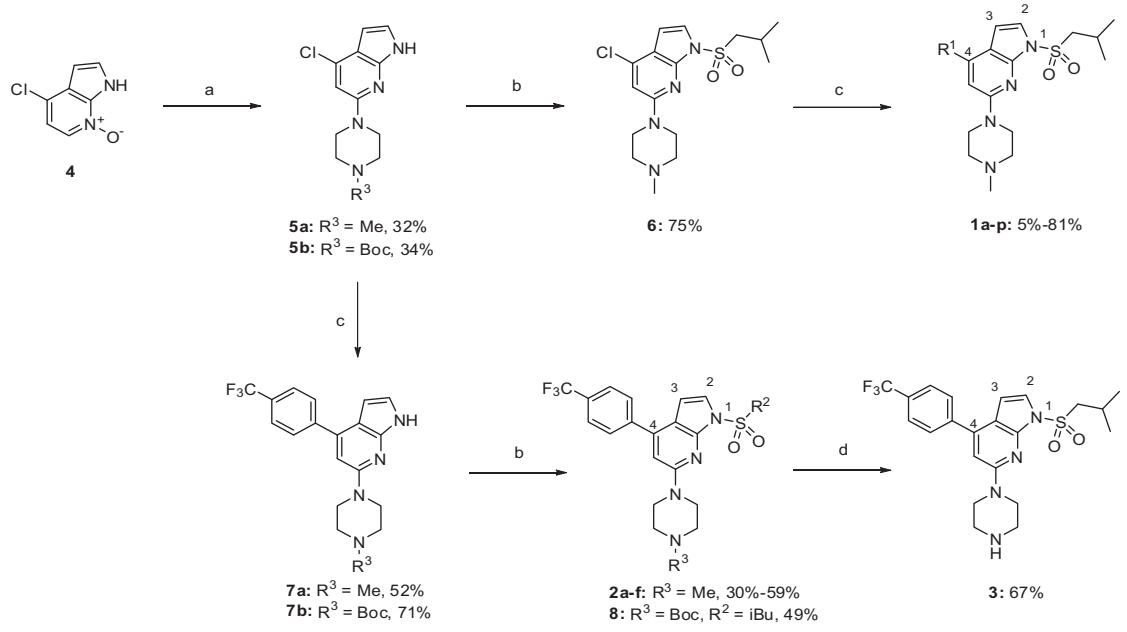
Most compounds from these series are potent and pseudo-selective according to the classification of Ivachtchenko. In our project we have defined D_2 receptor as an antitarget. This receptor is connected to extrapyramidal symptoms most commonly caused by typical antipsychotics. Additionally, the selectivity against a broad panel of diverse targets was checked for the selected representative example **3**. Full SAR for the series is available for 5-HT_6 and D_2 receptors.

As shown in Scheme 1, the lead structure template was divided into two structural regions for analog optimization, the aryl group R^1 and the pendant alkyl R^2. The synthesis of the proposed compounds was achieved as described in Scheme 1. 4-Chloro-7-azaindole **4** was transformed into *N*-oxide with *m*-CPBA.[22] *N*-Oxide **4** was alkylated with dimethyl sulfate and the obtained intermediate was treated with commercially available *N*-substituted piperazines in the presence of *N*,*N*-Diisopropylethylamine to afford 4-chloro-6-(*N*-substituted-piperazynyl)-1*H*-7-azaindoles **5** using the procedure of Reissert-Henze reaction.[22] In order to study the influence of the aryl group R^1, compound **5** was reacted with isobutyl sulfonyl chloride in the presence of sodium hydride, followed by a Suzuki coupling with the corresponding boronic acid to give compounds **1a**–**p**. Similarly to understand the role of R^2 on the sulfone, compounds **2a**–**f** were synthesized by exchanging the two previous steps. First, the Suzuki coupling was performed with 4-trifluoromethylphenyl boronic acid and then sulfonylation reaction was performed with the appropriate sulfonyl chloride. Demethylated compound **3** was obtained by following the same synthetic pathway using *N*-Boc-piperazine. An additional deprotection step with trifluoroacetic acid was needed to obtain the final compound.

All compounds were screened in search of high affinity ($K_i \leqslant 20$ nM) on the 5-HT_6R and low to negligible affinity to the dopamine D_2 receptor ($K_i \geqslant 200$ nM) in a radioligand binding assay. The affinities (K_i) of the studied compounds for the 5-HT_6R and D_2R were determined indirectly by displacement of [^{3}H]-LSD and [^{3}H]-NMSP, respectively. Results are displayed in Tables 1 and 2.

Our first compound **1a** (R^1 = Ph and R^2 = isobutyl) was found to have potent in vitro binding affinity toward 5-HT_6R (K_i = 16 nM) and an acceptable 5-HT_6R/D_2R binding ratio of 35. Initially, we were interested to know if R^1 = Ph was the optimal group in this chemical series. So we investigated the influence of the group R^1 (compounds **1a**–**p**, Table 1). A scan through various substitutions on the phenyl was initially tested (compounds **1a–j**, Table 1). Compound **1b** with an ethyl substituent in position 4 was shown to have similar potency and 5-HT_6R/D_2R binding ratio to **1a**. When ethyl was replaced with –CF_3, compound **1c** was 3 times more potent. Although the compound had higher affinity for D_2R, the 5-HT_6R/D_2R binding ratio was the best one among the three aforementioned compounds.

Next, we have tested effect of polar substituents on 5-HT_6R and D_2R affinities of the compounds. Interestingly, compound **1f** with –OMe was the most potent 5-HT_6R binder (K_i = 2nM). However, the 5-HT_6R/D_2R binding ratio was 10 fold lower than our prototype compound **1c**. Replacement of –OMe by –OBn (compound **1g**) reversed the binding ratio toward D_2R by a factor of 30. Compound



Scheme 1. Reagents and conditions: (a) Me_2SO_4, MeCN, piperazine derivatives; 60 °C, 6 days; (b) R_2SO_2Cl, NaH, dry DMF; 0 °C, 90 min; (c) boronic acid or boronic ester, Pd $(OAc)_2$, S-Phos, K_3PO_4, toluene; 130 °C, 24 h; (d) CF_3CO_2H, DCM; RT, 1 h. For the definition of R1 and R2, see Tables 1 and 2.