Bioorganic & Medicinal Chemistry Letters 20 (2010) 5491–5494

Contents lists available at ScienceDirect

Bioorganic & Medicinal Chemistry Letters

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

[3-Azabicyclo[3.1.0]hex-1-yl]phenyl-benzenesulfonamides as selective dopamine D_3 antagonists

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ARTICLE INFO

Article history:
Received 28 June 2010
Revised 15 July 2010
Accepted 16 July 2010
Available online 21 July 2010

Keywords:
Dopamine
Selective
Dopamine D3
Antagonist

ABSTRACT

A new class of azabicyclo[3.1.0]benzenesulfonamides is presented as selective dopamine D_3 antagonists together with SAR and selectivity data.

Following the isolation and characterization of the cDNA for the dopamine (DA) D_3 receptor,[1] a number of non-selective and selective DA D_3 receptor antagonists have been reported.[2] GlaxoSmithKline (GSK) has shown a long-standing interest in this field and has contributed to the discovery of selective DA D_3 receptor antagonists.[3–7] Some of these derivatives are illustrated in Figure 1.

Growing evidence suggests that selective antagonists of the DA D_3 receptor can reduce the reinforcing efficacy of drugs of abuse, reverse cognitive deficits, and show efficacy in animal models of schizophrenia. Accordingly, potential manifold therapeutic applications (e.g., Parkinson's disease, schizophrenia, drug addiction) exist for selective DA D_3 antagonists and they have recently been the subject of a comprehensive review.[8]

In our quest to identify small molecules in the field of selective DA D_3 antagonists, we recently reported a new structural template (**6**, Fig. 1) endowed with low molecular weight and described its potential applications.[9] Such a template is slightly smaller, in terms of size and molecular weight, with respect to the other derivatives reported in Figure 1.

To identify another alternative small template beyond derivative **6**, it was decided to investigate a series of azabicyclo[3.1.0]benzensufonamides. The working hypothesis behind this choice was related to the identification of three potentially distinct and specific regions in derivative **6**: an aromatic region (the cyanophenyl group), a hydrogen bond acceptor (the imidazolinone), and a basic region (the trifluoromethyl piperidine).

To test such a theory, a first derivative compound **7**[10,11] was prepared where the hydrogen bond acceptor was represented by a sulfonamide, a phenyl-3-azabicyclo[3.1.0]hexane was introduced as a basic side chain, and the aromatic region was represented by an additional benzene ring attached to the sulfonamide moiety (the one with the *i*-Pr group in compound **7**).

The compounds were tested according to the screening cascade previously reported[5–7] and the results are reported in Table 1.

Derivative **7** showed high DA D_3 activity coupled with a 100-fold selectivity versus the DA D_2 receptor and about 400-fold selectivity versus the hERG (human ether-a go–go K^+ channel) ion channel, a liability target potentially associated with cardiovascular adverse events.

The presence of a hydrogen bond donor, not present in derivative **6**, was not detrimental to DA D_3 activity and constituted a further point of interest in the exploration of this new series.

Accordingly, a minimal synthetic activity was performed to identify the existence of a potential SAR around this original starting point. The introduction of a *N*-methyl group on the [3.1.0] portion (derivative **8**) slightly decreased the activity at the DA D_3 receptor, while a minimal increase at the DA D_2 receptor reduced

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doi:10.1016/j.bmcl.2010.07.073

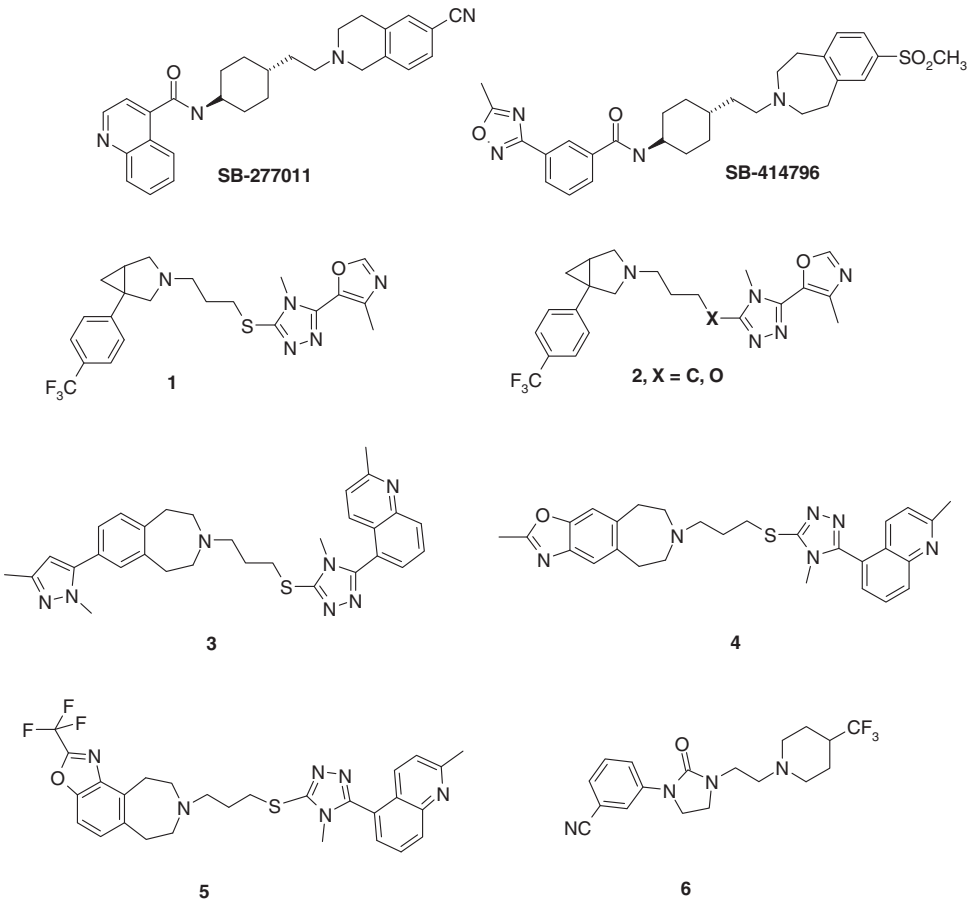


Figure 1. GSK selective DA D_3 antagonists.

the selectivity to just 10-fold. No major consequence was observed on the hERG channel. The *N*-ethyl derivative (**9**) was almost equipotent to derivative **8**, while the introduction of a *N*-allyl moiety (**10**) fully restored the affinity at the primary target. This may have been related, in this specific case, to the increased *clogD* which was the highest achieved in this mini-series. The selectivity towards the DA D_2 receptor was slightly reduced, while the affinity at the hERG channel was unexpectedly high. Once again a potential relation to the increased *clogD* might be considered.

The introduction of a methoxy group (**11**) in a position able to stabilize the sulfonamide further increased the activity at both dopaminergic targets, leading to a 40-fold selectivity window. The replacement of the *i*-Pr group with a $-CF_3$ group (**12**) determined a 100-fold loss of potency at the D_3 receptor. This might have been explained by the significant drop in *clogD*. However, derivative **13**, the $-OCF_3$ substituted compound also demonstrated a low activity at the primary target despite a similar *clogD* to derivative **7**. Considering that the polar surface area was also similar in these three derivatives, the presence of a specific lipophilic pocket able to fit the isopropyl group of this specific series might be theorized.

To better understand the role of the acidic sulfonamide hydrogen, the NH moiety was appropriately modified. In derivative **14**, it was replaced by a $-CH_2-$ leading to a sulfone, while in **15** it was N-methylated. The presence of the 'acid' benzylic methylene of compound **14** whilst retaining some DA D_3 activity led to a 10-fold drop of potency, while the N-methylation (**15**) of the system determined a larger drop in activity. The latter result might potentially be due to the lack of the NH group, but a full conformational change of the system cannot be ruled out. In fact, this was the only derivative to completely abolish the hERG affinity and this might also find an explanation in a completely different conformational pose able to prevent access to the hERG channel.

The isomeric sulfone **16** was also prepared; no major difference with respect to derivative **14** was noticed as far as DA D_3 activity was concerned, while a complete deletion of the activity at the DA D_2 receptor was observed.

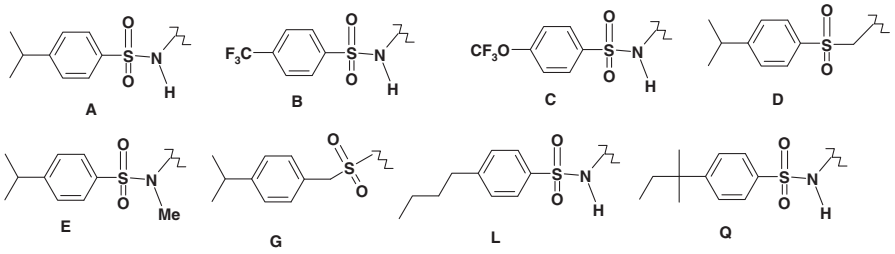
To explore further the hypothesis of the presence of a lipophilic pocket able to fit the *i*-Pr substituent, derivatives **17** and **18** were prepared. Both compounds showed excellent activity at the DA D_3 receptor, but a slightly inferior selectivity with respect to the DA D_2 target. This might be related to the specific spatial orientation of the *i*-Pr group with respect to the butyl and neopentyl moieties.

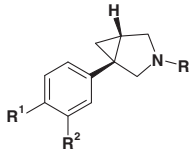
Finally, a new preparation of racemate **7** was used to separate[12] the two enantiomers and evaluate their individual activities (**19**, **20** Table 1). It may be noticed that one enantiomer demonstrated a significant greater activity than the other, suggesting an enantiospecific mode of binding within the receptor.

To complete their characterization, derivatives **19** and **8** were tested for their ability to cross the blood/brain barrier in rat.[13] While the presence of two acidic NH moieties hampered this task for compound **19** (brain/blood ratio = 0.6), the presence of a single sulfonamide NH had no negative effect on derivative **8** (brain/blood ratio = 7.3), suggesting a high potential for this derivative to achieve CNS distribution.

In summary, a new and selective class of DA D_3 antagonists was reported. Derivative **7** demonstrated excellent potency and selectivity versus the DA D_2 receptor and the hERG channel. The synthetic activities performed around this scaffold demonstrated the existence of a SAR and critical interaction points were identified

Table 1
Activity (fpKi) results for derivatives **1**–**20**





Entry	R	R^1	R^2	D_3 fpK_i	D_2 fpK_i	hERG pIC_{50}	PSA (Å^2)	ACD log D^*
1	NA	NA	NA	9.3	6.9	6.0	60	2.1
7	H	A	H	8.6	6.6	6.0	58	1.5
8	Me	A	H	8.2	7.2	5.8	49	1.8
9	Et	A	H	8.1	7.0	5.9	49	2.3
10	Allyl	A	H	8.6	7.2	7.0	49	3.1
11	H	A	OMe	8.9	7.3	5.9	67	1.4
12	H	B	H	6.6	<5.5	6.1	58	0.7
13	H	C	H	6.2	6.0	5.0	55	1.6
14	H	D	H	7.6	6.5	5.9	46	0.9
15	H	E	H	7.1	6.3	<4.2	49	−0.8
16	H	G	H	7.6	<5.5	5.5	46	1.0
17	H	L	H	8.3	6.9	5.7	58	1.6
18	H	Q	H	8.2	7.3	5.9	58	1.6
19 (enant. 1)	H	A	H	8.4	6.3	5.3	58	1.5
20 (enant. 2)	H	A	H	6.7	6.1	5.8	58	1.5

SEM for D_3 GTPγS and hERG data sets is ±0.1 and for the D_2 GTPγS data is ±0.2.
* ACD_log *D*_ Version 11. fpK_i = functional pK_i obtained from the GTPγS functional assay.

in these new scaffolds. Enantioselective preference for one of the isomers was also demonstrated as well as the presence of good brain penetration for a selected derivative. Further aspects of the medicinal chemistry have to be evaluated to fully exploit the potential of this new series.

Acknowledgments

We thank Dr. C. Marchioro and her analytical group, and Dr. A. Worby for screening activities. We thank Dr. S. Braggio and his DMPK group for the support received. Finally, we thank Dr. T. Rossi and Dr. J. Hagan for the proactive discussions in the progression of the program activities and Dr. C. P. Leslie for careful proofreading of the manuscript.

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11. *N-{4-[3-Azabicyclo[3.1.0]hex-1-yl]phenyl}-4-(1-methylethyl)benzenesulfonamide hydrochloride*. To a stirred solution of racemic-1-(4-bromophenyl) -3-azabicyclo[3.1.0]hexane in CH_2Cl_2 at rt, Et_3N and bis(1,1-dimethylethyl) dicarbonate were added. Stirring was continued for 6 h; after work up and purification, 1,1-dimethylethyl-1-(4-bromophenyl)-3-azabicyclo[3.1.0]hexane -3-carboxylate was dissolved in dry toluene and lithium bis(trimethylsilyl) amide was added. Subsequently, tributylphosphine and tris (dibenzylideneacetone)dipalladium(0) was added and the reaction mixture stirred at room temperature for 5 h. After work up and purification the resulting compound was reacted with 4-(1-methylethyl)benzenesulfonamide in *N*-methylpyrrolidinone in a vial where potassium carbonate and copper iodide were added. The vial was sealed and heated by microwave irradiation at 195 °C for 2.5 h. After work up and chromatography, the resulting derivative was dissolved in CH_2Cl_2 and HCl (1 M in Et_2O) was added to give the title compound after appropriate work up and purification.
12. Derivative **7** was submitted to semipreparative HPLC to give the separated enantiomers by using a chiral column chiralpak AD-H 5 μm, 250 × 21 mm, eluent A: *n*-hexane; B: ethanol + 1% isopropylamine. Gradient isocratic 40% B. Flow rate 6 mL/min. Detection UV at 254 nm.
13. All the works involving animals were carried out in accordance with European directive 86/609/EEC governing animal welfare and protection, which is acknowledged by Italian Legislative Decree no. 116, 27 January 1992, and according to internal review performed by the GlaxoSmithKline Committee on Animal Research & Ethics (CARE) and to the company Policy on the Care and Use of Laboratory Animals.