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A specific and direct comparison of the trifluoromethyl and pentafluoro sulfanyl groups on the selective dopamine D_3 antagonist 3-(3-{[4-methyl-5-(4-methyl-1,3-oxazol-5-yl)-4*H*-1,2,4-triazol-3-yl]thio}propyl)-1-phenyl-3-azabicyclo[3.1.0]-hexane template

Fabrizio Micheli *, Daniele Andreotti, Simone Braggio, Anna Checchia

Neurosciences Centre of Excellence, GlaxoSmithKline Medicines Research Centre, Via Fleming 4, 37135 Verona, Italy

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ABSTRACT

A direct and specific comparison of a trifluoromethyl group with the corresponding pentafluorosulfanyl group is made in terms of primary affinity and pharmacokinetic properties.

Following the isolation and characterization of the cDNA for the dopamine D_3 receptor,[1] a number of non selective and selective dopamine D_3 receptor antagonists have been reported.[2] GSK showed a long-standing interest in this field and contributed to the discovery of selective D_3 receptor antagonists.[3–7] Some of these derivatives are drawn in Figure 1. We have recently reported[6] a class 1,2,4-triazol-3-ylthiopropyl)-1-[4-phenyl]-3-azabicyclo[3.1.0]-hexanes (**1**, Fig. 1) as potent and selective compounds endowed with excellent pharmacokinetic (PK) properties and strong in vivo efficacy in preclinical animal models.[8] In this specific series, when the 4-methyl-1,3-oxazol-5-yl was present as right-handside portion of the scaffold, a specific comparison was made between the trifluoromethyl group and the pentafluoro sulfanyl derivatives as substituents of the 1-phenyl group.

In the last few years, the pentafluoro sulfanyl group has not received major attention in the medicinal chemistry field and SAR information is poorly reported. On the other side, a number of patents, especially related to biocides, are present. Considering the continuous quest of the medicinal chemists to obey to Lipinski's rules and to work in well defined physico-chemical spaces, the high molecular weight and the potential increase of the overall lipophilicity associated to this specific fragment might have probably limited it exploitation in drug discovery.

Considering the careful exploration made on the 1,2,4-triazol-3-yl-thiopropyl)-1-phenyl-3-azabicyclo[3.1.0] hexane template, it was decided to test the behaviour of such group on derivative **1**.

Moreover, this substitution was performed also on its close derivative where the group on the phenyl substituent was located in *meta* rather than in *para* position. The compounds were prepared in accordance to previously described[6] chemical procedures as racemates and single enantiomers were separated with chiral HPLC techniques.

The results of this work are reported in Table 1. Racemic mixtures of the *p*- and *m*-CF_3 derivatives are directly compared with the corresponding racemic mixtures of $-SF_5$ compounds (**1** vs **6** and **9** vs **10**). Results obtained on the single $-SF_5$ enantiomers are also reported (**7**, **8** and **11**, **12**).

The first step in the comparison of the two different groups was the evaluation of the physico-chemical data.

The difference in molecular weight was 58 Da with the replacement of the $-CF_3$ (MW = 464) by the $-SF_5$ (MW = 522). Assuming a correct computational parametrization of the $-SF_5$ group, the calculated molar refractivity (cmr) slightly increased for the compound bringing this new substituent, while the polar surface area (PSA) was identical on the two resulting molecules. As expected with the introduction of a sulfur and 5 fluorine atoms, also the *C*log *D* increased for this molecule.

A second step in the characterization was related to the comparison of the biological results. The direct comparison between

* Corresponding author. Tel.: +39 045 8218515; fax: +39 045 8218196.
E-mail addresses: fm20244@gsk.com, cfjvb1943@alice.it (F. Micheli).

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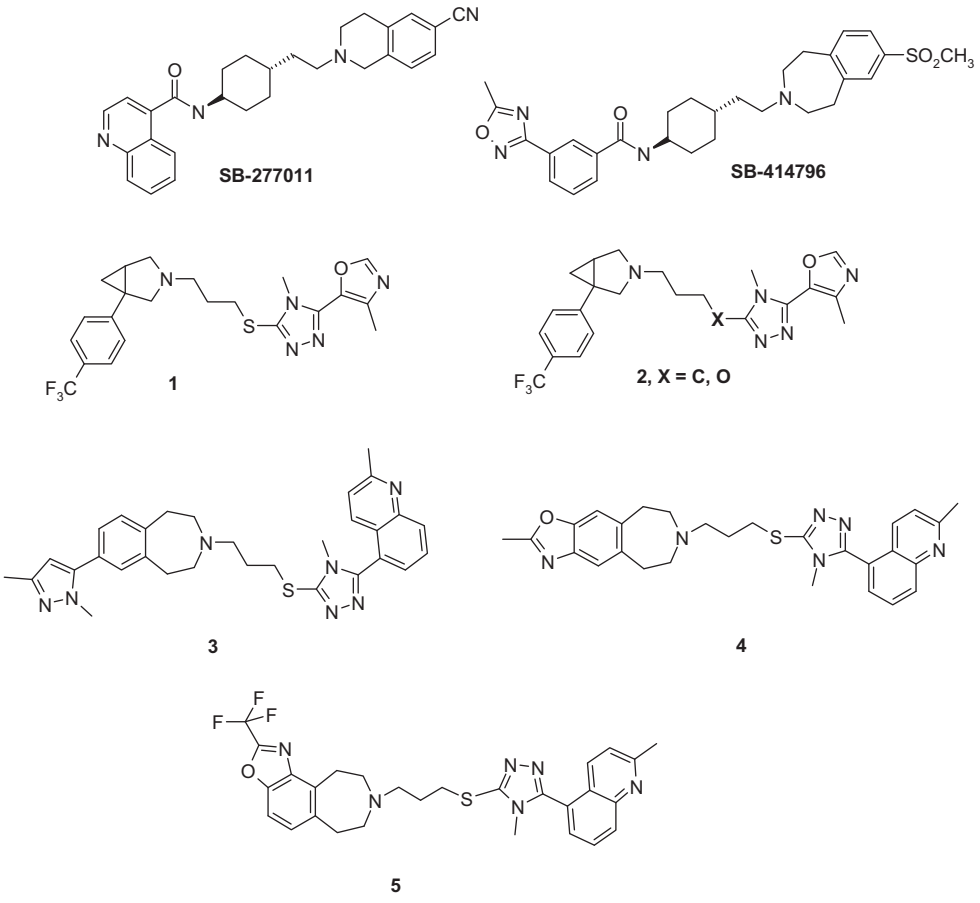
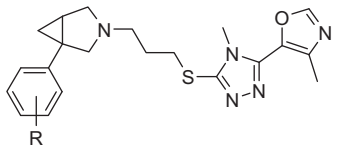


Figure 1. GSK selective D_3 antagonist.

the two groups is reported in Table 1 and it was made comparing the racemates. This was done because, while for the $-CF_3$ substituted molecules the stereochemistry of each enantiomer was known (by VCD and X-ray data), the characterization of the $-SF_5$ single enantiomers was not yet completed at the time of the biological assay. In both specific cases (**1** vs **6** and **9** vs **10**), the affinity at the DA D_3 primary target was slightly inferior for the $-SF_5$ substituted derivatives and significative only in the latter case. This decrease might potentially be considered related to the slightly higher volume occupied in the limited space of the binding region of the receptor. A similar trend was observed also for the DA D_2 receptor, with the *m*-substitution more affected by the change. On the hERG channel, a slight increased for the $-SF_5$ bearing template was observed for each of the two couples being compared. This increase might be linked to the higher lipophilicity of the scaffold. Despite all that, both molecules (**6** and **10**) showed a remarkable 100-fold selectivity over the DA D_2 receptors and a 1000-fold selectivity over the hERG channel. After separation of the racemates in the specific enantiomers by chiral HPLC, a similar trend was observed on the most active enantiomer. Consequently, it might be stated that, when used in this specific context and with this pattern of substitution of these two selective DA D_3 antago-

Table 1
Affinity results



Entry	R	D_3 fpKi	D_2 fpKi	hERG pIC_{50}	cmr	PSA ($Å^2$)	ACD log D[a]
1	4-CF_3	9.3	6.9	6.0	11.6	60	2.1
6	4-SF_5	9.1	6.8	6.3	12.7	60	2.5
7	4-SF_5	7.9	6.6	6.4	12.7	60	2.5
8	4-SF_5	9.0	6.8	6.1	12.7	60	2.5
9	3-CF_3	9.3	7.5	5.5	11.6	60	1.8
10	3-SF_5	8.9	6.9	6.0	12.7	60	2.5
11	3-SF_5	7.8	<5.5	5.7	12.7	60	2.5
12	3-SF_5	9.2	7.5	5.9	12.7	60	2.5

SEM for D_3 GTPγS, H_1 FLIPR and hERG data sets is ±0.1 and for the D_2 GTPγS data is ±0.2.

[*] ACD_logD_ Version 11. fpKi = functional pK_i obtained from the GTPγS functional assay.

Table 2
Cli (ml/min/g of protein) and P450 (μM) data for selected derivatives

Entry	hCli	rCli	1A2	2C9	2C19	2D6	3A4[a] DEF	3A4[a] 7BQ
1	1.6	<0.5	5	>10	>10	>10	NA	>10
6	2.3	1.0	>10	9.0	>10	8.0	>10	>10
7	2.0	1.1	7.0	9.0	>10	>10	>10	>10
8	1.7	1.4	8.0	9.0	>10	>10	>10	>10
9	3.2	1.5	>10	>10	5.0	>10	>10	>10
10	3.9	1.9	>10	4.0	9.0	3.0	>10	>10
11	2.7	12.6	>10	2.0	4.0	5.0	>10	>10
12	3.3	1.2	>10	2.0	3.0	2.0	>10	>10

hCli = human intrinsic clearance. rCli = rat intrinsic clearance. NA = not available.

[a] 3A4 DEF assay uses diethoxyfluorescein as CYP 3A4 substrate. The 3A4 7BQ assay uses 7-benzyloxyquinoline.

Table 3
Pharmacokinetic properties of derivatives **1** and **6**

Entry	Clb (ml/min/kg)	$T_{1/2}$ (h)	Vd (l/kg)	*F*%	T_{max} (h)	B/B
1	14	3.2	3.5	85	1.5	2.3
6	8	4.4	2.8	87	2.7	2.2

B/B = brain/blood ratio.

nists, the $-SF_5$ group produced similar results to a –CF3 moiety from the fpKi point of view.

These results elicited the interest to progress these molecules in the screening cascade; accordingly, the CYPEX bactosome P450 inhibition and rat and human in vitro clearance in liver microsomes were performed to further evaluate their developability potential. For the *p*-derivative **6**, IC_{50} values for all major P450 isoforms tested (CYP1A2, CYP2C9, CYP2C19, CYP2D6 and CYP3A4) were greater than 5 μM and intrinsic clearance (Cli) values both in human and in rat resulted moderately low (2.3 and 1.0) ml/min/g of protein. For the *m*-derivative **10**, IC_{50} values for the P450 isoforms were greater than 3 μM; Cli values for human and rat were, respectively 3.9 and 1.9 ml/min/g of protein. Single Cli and P450 values for the products mentioned in Table 1 are reported in Table 2. In both cases, these results were in agreement with the very good developability properties previously reported for the corresponding specific $-CF_3$ derivatives.

Accordingly, when used in this particular context and with the substitution pattern reported, the $-SF_5$ group seem to be well tolerated from the in vitro PK point of view.

The next step was related to their in vivo evaluation.[8] Derivatives **1** and **6** were selected for this specific task and were administered in rats. The results of this head to head comparison are reported in Table 3. It is evident that, under these specific conditions, the profile of the two compounds resulted completely superimposable. Both compounds were endowed with relatively low distribution volumes, high bioavailability and long half-life. Brain penetration, measured as brain to blood ratio (B/B) was also high.

Accordingly, it can be stated that under these specific conditions, from the in vivo PK point of view, no major differences between a $-CF_3$ and a $-SF_5$ groups emerged.

No toxicological data are currently available to compare derivative **6** with **1** and determine if, also in this event, the two molecules might show a comparable behavior.

Nonetheless, with this specific pattern of substitution where the 4-methyl-1,3-oxazol-5-yl was chosen as the substituent on the right part of the scaffold, it can be reported that for the in vitro affinity, the in vitro PK properties and the in vivo PK profile, the $-SF_5$ moiety represented a valid alternative to the $-CF_3$ group.

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8. 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.