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New fused benzazepine as selective D_3 receptor antagonists. Synthesis and biological evaluation. Part 2: [*g*]-Fused and hetero-fused systems

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Abstract—The synthesis and the SAR of a new series of potent and selective dopamine D_3 receptor antagonists is reported. The new scaffolds of the [*g*]-fused and the hetero-fused tricyclic benzazepine are here reported together with their pharmacokinetic profile.

A growing body of evidence indicates that dopamine D_3 receptors are implicated in the control of drug-seeking behaviour, and may play an important role in both the physiology and pathology of impulse control disorders, drug addiction and schizophrenia. This hypothesis has been difficult to prove due to the lack of compounds with the appropriately high selectivity for the D_3 receptors. Recently, however, the synthesis and characterization of new potent and selective DA D_3 receptor antagonists[1] has allowed the characterization of the D_3 receptor in a wide range of preclinical animal models. GSK showed a long-standing interest in this field and contributed to the discovery of selective D_3 receptor antagonists.[2–5] As described in the first part of this manuscript,[5] the possibility to increase the complexity in the benzazepine (BAZ) portion of derivative **2** (Fig. 1) was investigated. The introduction of [*h*]-fused BAZ led to new chemical entities (NCE) endowed with promising properties in terms of potency, selectivity and pharmacokinetic (PK) properties. To further expand the exploration of the new class, [*g*]-fused tricyclics and anellated systems were prepared and are described in the following paragraphs (Scheme 1).

Considering that in the [*h*]-fused system series, the oxazolyl moiety gave rise to a new template that was endowed with good potency and promising rat PK properties, it was attempted to introduce this fragment in the new [*g*]-fused template to probe potential analogies between the series. In contrast with the [*h*] bond of the BAZ, the [*g*] one is no more intersected by a C_2 symmetry axis and, therefore, the introduction of the new fragment generated two different templates on unsubstituted systems. In agreement with previous reports,[5] each NCE prepared was assayed for agonistic versus antagonistic properties using a functional GTPγS assay expressing the human dopamine D_3 receptor. All the compounds here reported proved to be antagonists at the D_3 receptor.[5] A 100-fold selectivity versus dopamine D_2 and histamine H_1 receptors (functional assays) was set as a primary criterion for further progression along the screening cascade of this specific series. In addition, a 100-fold selectivity versus the hERG ion channel (Dofetilide binding assay) was also required.

Keywords: Rat; Dopamine; D_3 antagonists; Selective; Drug dependence.
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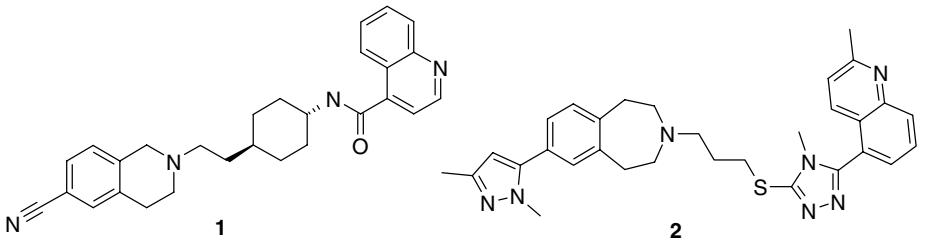
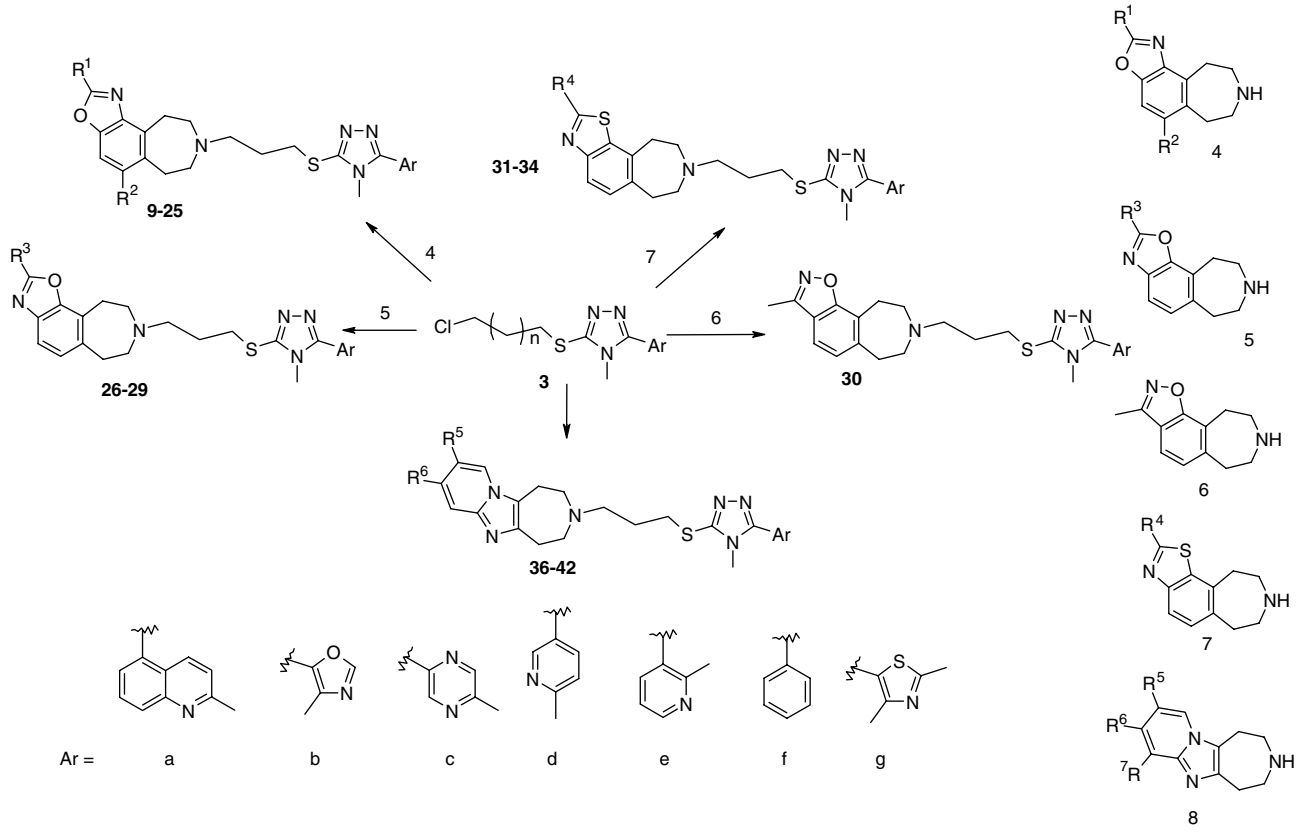


Figure 1. GSK selective D_3 antagonist.



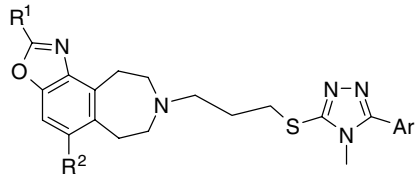
Scheme 1. Reagents and condition: K_2CO_3, DMF 60 °C, cat NaI and appropriate tricyclic **4**–**8**, overnight, $n = 0, 1, 2$. R as defined in each Table.

Generic developability screens such as CYPEX bactosome P450 inhibition and rat and human in vitro clearance in liver microsomes (Cli) were included early in the screening cascade.

The first derivative prepared (**9**, Table 1) belonged to the 7,8,9,10-tetrahydro-6H-[1,3]oxazolo[4,5-*g*][3]benzazepine series and showed a comparable potency to its [*h*]-fused derivative. Also the PK properties (both in vitro and in vivo[6]) were comparable showing rat blood clearance (Clb) of 48 ml/min/kg, a relatively high distribution volume (V_d) of 6.3 l/kg, with moderate half-life ($T_{1/2}$) of 1.7 h and bioavailability (F) of 15%. More importantly for a potential central nervous system (CNS) drug, this compound had a good brain to blood ratio (B/B) (2.5), measured through sampling of the blood and brain[6] 1 h after iv administration. The replacement of the quinolinyl fragment with an oxazolyl one (**10**) led to a slight decrease in D_3 affinity, which was paralleled, as for the previous [*h*]-fused system, by a decrease in the hERG affinity. The introduction of the ethyl group in derivatives **11** and **12** led to the increase in potency as suggested by receptor modelling; as both H_1 and hERG values were significantly below the screening cascade's selectivity threshold it was decided to further progress derivative **12** to in vivo assays which provided favourable in vitro PK properties. The PK profile, probably controlled by both the polar surface area (PSA)[7] (86 vs 73 Å^2 for **12** vs **9**) and the lower clog D[8] (3.5 vs 5.1), showed a much reduced Clb (5 ml/min/kg) with low V_d (0.6 l/kg), and a similar $T_{1/2}$ (1.9 h), but a much higher F (73%).

Not too surprisingly, given the above-reported PK data, the B/B ratio was only 0.1. The introduction of a lipophilic trifluoromethyl moiety in the tricyclic system (**13**

Table 1. Affinity results



Entry	R^1	R^2	Ar	D_3 fpKi	D_2 fpKi	H_1 fpKi	hERG pIC_{50}	PSA (Å^2)	ACD log *D*
1	Not applicable			8.4	6.4	6.2	5.7	69	3.8
2	Not applicable			8.8	6.5	6.1	5.7	65	5.3
9	Me	H	a	7.2	<6.2	<6.1	5.6	73	5.1
10	Me	H	b	7.0	<6.3	<5.5	4.9	86	3.0
11	Et	H	a	8.1	<6.3	6.3	5.2	73	5.6
12	Et	H	b	7.9	<6.4	<5.5	5.3	86	3.5
13	CF_3	H	a	8.4	<6.1	6.3	5.7	73	6.3
14	CF_3	H	b	8.8	<6.0	<5.6	5.9	86	4.1
15	CF_2CH_3	H	b	9.1	7.8	5.8	5.6	86	3.9
16	CF_2CF_3	H	a	9.0	<6.5	5.7	6.6	73	8.3
17	CF_2CF_3	H	b	9.1	<6.5	<5.7	6.5	86	6.2
18	CF_3	H	c	8.2	<6.4	5.8	5.9	86	4.7
19	CF_3	H	d	8.4	<6.4	5.7	5.8	73	5.3
20	CF_3	H	e	7.8	<6.4	<5.5	5.4	73	5.3
21	CF_3	H	f	8.5	<6.3	5.9	6.6	60	5.9
22	CF_3	H	g	8.3	<6.4	6.0	6.1	73	5.3
23	Me	Cl	a	6.5	<6.2	<5.8	5.8	73	6.0
24	pir*	H	a	8.4	<6.4	6.0	6.1	91	6.0
25	pir*	H	b	7.6	<6.4	<5.5	6.1	104	3.8

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. pir* = 1,3-dimethyl-1H-pyrazol-5-yl.

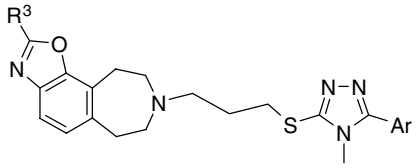
and **14**) led to increased D_3 affinity which was paralleled by the hERG value for compound **13** only, while derivative **14** showed an almost 1000-fold selectivity. Derivative **13** (clog *D* = 6.3) showed relatively high Clb (60 ml/min/kg), with V_d equal to 5.8 l/kg, $T_{1/2}$ = 1.3 h and *F* = 36%. The B/B was back to high values (7.3). The reduction in clog *D* shown by **14** (4.1) once again led to a lower V_d (1.6 l/kg), accompanied by lower Clb (35 ml/min/kg); *F* was high (63%) and $T_{1/2}$ was of 0.6 h. The B/B ratio was 0.8 with a relatively high concentration of compound in the brain, making this compound a promising molecule to be further progressed. The introduction of the CF_2CH_3 portion (**15**), with an almost unchanged clog *D* value with respect to derivative **14**, led to nanomolar affinity at the D_3 receptor, but raised unexpected activity at H_1 and D_2 receptors. The unexpected profile was also seen in vivo, where, despite a comparable PK profile to **14** (V_d = 0.8 l/kg; $T_{1/2}$ = 1.2 h; Clb = 9 ml/min/kg; *F* = 54%), the B/B ratio was reduced to 0.2. A further increase in lipophilicity with the introduction of the CF_2CF_3 group (**16** and **17**) maintained nanomolar affinity at the D_3 receptor, but this time with more than 1000-fold selectivity over the D_2 receptor; selectivity over hERG and H_1 was also good. The exploration of this series continued with the decoration of the thiotriazole moiety showing that both basic (**18**–**20**) and neutral (**21** and **22**) derivatives were well tolerated in terms of D_3 affinity and selectivity, while the presence of basic moieties was beneficial to achieve lower hERG values. The introduction of a chlorine atom on position 5 of the tricyclic moiety (**23**) had a greater impact on the D_3 receptor than on the hERG channel, the introduction of a further heterocycle into the system was well tolerated by the quinolinyl derivative (**24**), but showed a higher decrease in D_3 affinity in the oxazolyl one (**25**), probably due to the much lower clog *D* achieved by this latter derivative (clog *D* = 3.8 vs 6.0 for **24**).

The 7,8,9,10-tetrahydro-6H-[1,3]oxazolo[5,4-*g*][3]benzazepine template (Table 2) gave similar results to its regioisomer previously described (Table 1) in terms of in vitro affinity, even if slightly lower D_3 affinity was achieved when the same substituents (**26**–**29**) were compared. From the PK point of view, however, it is important to note that derivative **28** showed a clearly different profile with higher Clb (43 ml/min/kg) than corresponding compound **15**, leading to lower *F* (8%); however, its higher V_d (3.3 l/kg) led to a much better brain penetration (B/B = 4.0).

To further investigate the role of the relative positions of the oxygen and nitrogen in the tricyclic template, the synthesis of one of the isomeric 3-methyl-7,8,9,10-tetrahydro-6H-isoxazolo[5,4-*g*][3]benzazepines was completed. Specifically, when the compound was coupled with the pyrazine fragment (c) on the thiotriazolyl moiety (**30**), minimal residual activity at the D_3 receptor was observed (Table 3).

The synthesis of the 7,8,9,10-tetrahydro-6H-[1,3]thiazolo[5,4-*g*][3]benzazepine was completed to analyze the role of the replacement of the oxygen with a sulfur atom. Similar, but not completely superimposable, results

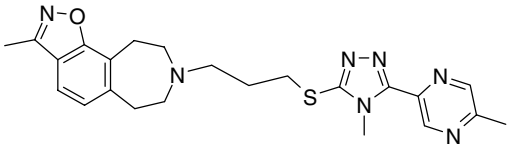
Table 2. Affinity results



Entry	R^3	Ar	D_3 fpKi	D_2 fpKi	H_1 fpKi	hERG pIC_{50}	PSA (Å^2)	ACD log *D*
26	CF_3	a	8.3	<5.8	5.4	6.0	73	6.2
27	CF_3	b	7.7	<5.8	<5.5	5.3	86	4.0
28	CF_2CH_3	a	8.7	<6.1	5.8	5.6	73	6.0
29	CF_2CH_3	b	8.6	<6.7	<5.7	5.3	86	3.8

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.

Table 3. Affinity results



Entry	D_3 fpKi	D_2 fpKi	H_1 fpKi	hERG pIC_{50}	PSA (Å^2)	ACD log *D*
30	6.1	<6.1	5.6	nt	86	4.1

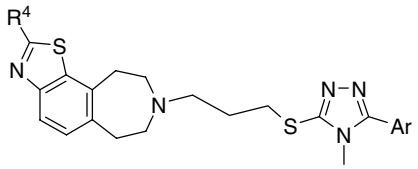
SEM for D_3 GTPγS, H_1 FLIPR and HERG data sets is ±0.1 and for the D_2 GTPγS data is ±0.2. nt, not tested.

(Table 4) to the ones achieved on the [*h*]-fused system[5] were observed. Compounds with similar shape, bulkiness and c log *D* (**31**–**32** vs **26**–**27**), but with a slightly different electronic component showed slightly lower affinity values in this series with respect to their oxygenated counterparts.

Further exploration on this template was performed with the introduction of more hydrophilic derivatives in the tricyclic moiety. The 2,3,4,5-tetrahydro-1H-pyrido[1′,2′:1,2]imidazo[4,5-d]azepine was chosen as a probe for two main reasons. The first reason was 'geometric' in nature, providing this structure a shape which is positioned between a [*h*]-fused and a [*g*]-fused system; the second reason was physicochemical to have PSA values ranging from 60 to 80 Å^2, while maintaining c log *D* values between 4 and 6. The results are clearly reported in Table 5, and while the affinity at the hERG channel was only marginally modified by this new substitution pattern, the affinity at the D_3 receptor was significantly affected.

In summary, substitution of an isolated BAZ ring with a more complex tricyclic structure can be tolerated in terms of D_3 affinity, and remarkable examples of selectivity versus D_2, H_1 receptors and hERG channel were identified. Promising rat PK profiles were also achieved, showing balanced properties and generally high brain penetration values. Overall, the exploration work of [*h*]-fused, [*g*]-fused and anellated tricyclic scaffolds contributed to shed further light into the nature of the D_3 receptor and has enriched the portfolio of selective D_3 receptor antagonists. Some of these have been used in in vivo animal models belonging to different therapeutic areas and will be the subject of future communications.

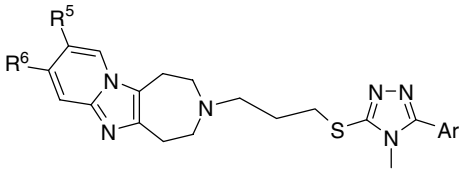
Table 4. Affinity results



Entry	R^4	Ar	D_3 fpKi	D_2 fpKi	H_1 fpKi	hERG pIC_{50}	PSA (Å^2)	ACD log *D*
31	Me	a	7.5	<6.0	6.6	5.5	60	5.6
32	Me	b	<6.9	<6.0	<5.6	4.9	73	3.4
33	Et	a	8.7	<6.5	6.4	6.8	60	6.1
34	Et	b	8.2	<6.4	<5.6	5.5	73	3.9

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.

Table 5. Affinity results



Entry	R^5	R^6	Ar	D_3 fpKi	D_2 fpKi	H_1 fpKi	hERG pIC_{50}	PSA (Å^2)	ACD log *D*
35	H	Me	a	6.8	<5.9	<5.5	6.6	64	4.4
36	Me	H	a	<6.6	<5.9	<5.5	5.6	64	4.7
37	Cl	H	a	<6.6	<5.9	6.0	5.8	64	5.3
38	H	H	a	<6.6	<5.9	5.7	5.6	64	4.3
39	H	CF_3	a	6.6	<6.1	6.1	6.6	64	5.6
40	H	CF_3	b	6.7	<6.1	<5.5	6.1	77	3.7
41	CF_3	H	a	6.8	<6.1	<5.5	5.3	64	5.2
42	CF_3	H	b	6.4	<6.1	<5.5	5.7	77	3.3

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.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.bmcl.2007.12.042.

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