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New fused benzazepine as selective D_3 receptor antagonists. Synthesis and biological evaluation. Part one: [h]-fused tricyclic systems

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Abstract—The synthesis and SAR of a new series of potent and selective dopamine D_3 receptor antagonists is reported. The introduction of a tricyclic [h]-fused benzazepine moiety on the recently disclosed scaffold of 1,2,4-triazol-3-yl-thiopropyl-tetrahydrobenzazepines is reported. A full rat pharmacokinetic characterization is also reported.

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] Growing evidence suggests that selective antagonists at dopamine D_3 receptor can reduce the reinforcing efficacy of drugs of abuse, reverse cognitive deficits, and show efficacy in animal models of schizophrenia.[2a] GSK showed a long-standing interest in this field and contributed to the discovery of selective D_3 receptor antagonists.[3–5] While SB-277011[3] (**1**, Fig. 1) represented an excellent tool to the purpose of target validation, the recently disclosed benzazepine derivative **2**[5–10] (Fig. 1) represents a more balanced molecule with improved developability criteria. In the present study we investigated the possibility to 'fuse' the pendant heterocycles attached to the benzazepine (BAZ) template of the series to which **2**[5–10] belongs with the BAZ moiety itself to develop tricyclic derivatives. Depending on the bond on which the fusion is achieved, this task can lead to [h]-fused or [g]-fused derivatives. This manuscript deals with the former class, while the latter one will be the topic of the second part.

Each new chemical entity (NCE) prepared was assayed for its agonistic versus antagonistic properties using a functional GTPγS assay expressing the human dopamine D_3 receptor.[5] All the compounds here reported proved to be antagonists at the D_3 receptor.[5] The objective of the screening cascade for this specific series was to identify molecules having at least 100-fold selectivity versus dopamine D_2 and histamine H_1 receptors (functional assays), and being endowed with 100-fold selectivity versus the hERG ion channel (Dofetilide binding assay).[5] 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. Substituted 3-[(3-chloropropyl)thio]-4-methyl-5-aryl-4 *H*-1,2,4-triazoles

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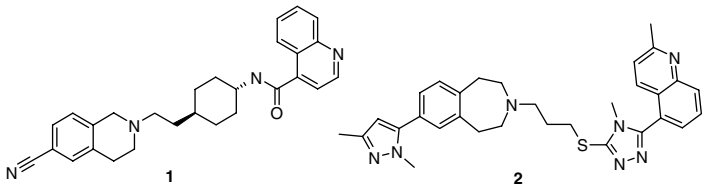


Figure 1. GSK selective D_3 antagonist.

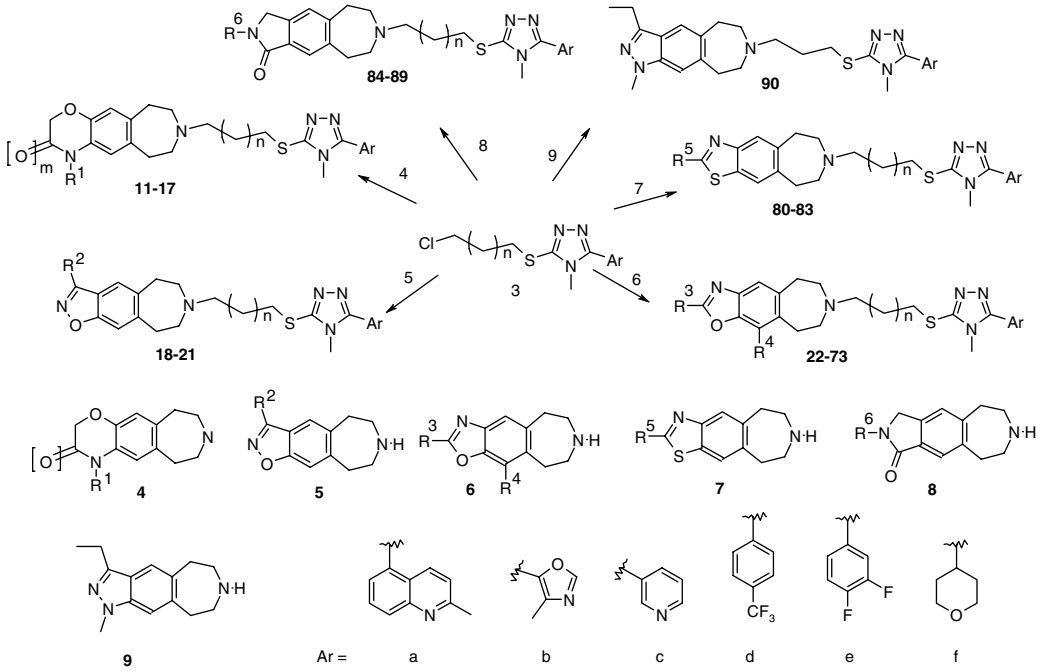
were reacted[5–10] with tricyclic derivatives, according to the general Scheme 1, at 60 °C in DMF using K_2CO_3 overnight and purified through column chromatography to obtain the products described in Tables 1–7.

For the preparation of the alpha-substituted derivatives, reductive ammination was used as depicted in Scheme 2. The introduction of an oxazinone system (**4**) on the thiotriazole scaffold (**11**, **12**) led to a marked increase in PSA[11] (values > 90 $\AA^2$ with respect to 65 $\AA^2$ for derivative **2**) and was detrimental both to the desired D_3 affinity and to the selectivity of the molecule, leading to an increased unwanted interaction with the hERG channel (Table 1). This could have been due to either a potential detrimental effect of a hydrogen bond (HB) donor (morpholinone N–H) or to the presence of an additional HB acceptor (morpholinone C=O). The first hypothesis may find some support in the fact that N-methylation (**13**, **14**) allowed some recovery in terms of D_3 affinity and significantly reduced hERG affinity. On the other hand, while the sulfonamide (**15**) further increased the desired affinity with the removal of both features, the acetamide (**16**) had a similar profile to **11** in terms of D_3 affinity having introduced again a carbonyl group into the system. However, the [1,4]oxazino[2,3-h][3]benzazepine derivative (**17**), where none of the features (i.e., carbonyl group and acidic NH) were present, showed an excellent D_3 potency and selectivity versus D_2 receptor.

Unfortunately, the hERG value did not match the selectivity criteria described in the screening cascade.

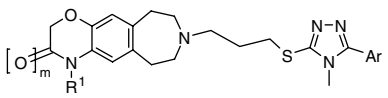
In this series it is important to highlight that the heterocyclic decoration on the thiotriazole moiety can be modified with no significant loss in terms of D_3 affinity (**12** vs. **11**, **14** vs. **13**). Taking into account the high PSA values displayed by derivatives **11**–**17** (ranging from 90 to 130 $\AA^2$), the pharmacokinetic (PK) properties of **15** were assessed in vivo in the rat.[12] The compound showed low blood clearance (Clb = 32 ml/min/kg), moderate half life ($T_{1/2}$ = 1.2 h), and low distribution volume (V_d = 2.4 l/kg). One may assume that this parameter (V_d), coupled with the high PSA value mentioned above, led to low brain penetration: the brain to blood (B/B) ratio, measured through sampling of the blood and brain[12] 1 h after i.v. administration, was actually equal to 0.2.

Consequently, it was decided to move from 6-membered anellated BAZ to 5-membered anellated BAZ to modulate the PSA parameter and the isoxazolo[4,5-h][3]benzazepine scaffold was designed (Table 2).



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

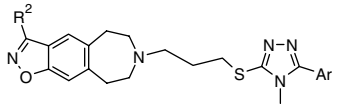
Table 1. Affinity results



Compound	R^1	m	Ar	D_3 fpKi	D_2 fpKi	H_1 fpKi	hERG pIC_{50}	PSA ($\widehat{A}^2$)	ACD log*D*
1	N.A.			8.4	6.4	6.2	5.7	69	3.8
2	N.A.			8.8	6.5	6.1	5.7	65	5.3
11	H	1	a	6.6	<5.6	6.8	8.2	110	3.5
12	H	1	b	5.6	<5.0	5.7	7.2	124	1.3
13	Me	1	a	7.4	<5.6	6.6	5.3	102	4.2
14	Me	1	b	7.2	<6.7	5.7	4.6	115	2.1
15	$MeSO_2$	0	a	7.9	<5.6	nt	5.1	127	2.9
16	Ac	0	a	6.8	<5.6	6.0	5.0	102	4.7
17	H	0	a	8.1	<5.9	nt	6.4	93	4.2

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. N.A., not applicable; nt, not tested.

Table 2. Affinity results



Compound	R^2	Ar	D_3 fpKi	D_2 fpKi	H_1 fpKi	hERG pIC_{50}	PSA ($\widehat{A}^2$)	ACD log*D*
18	Me	a	7.7	<6.2	7.0	6.1	98	5.5
19	Me	b	6.8	<5.9	nt	5.2	86	3.4
20	Et	a	7.6	<6.1	6.9	6.0	73	6.1
21	Me	d	7.9	<6.9	6.2	6.9	60	6.2

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.

The first derivative prepared (**18**) had actually a lower (98 $\widehat{A}^2$) PSA value compared to the majority of the scaffold reported above, but it was still higher than our reference compound **2** (65 $\widehat{A}^2$). The in vivo rat PK profiling was therefore put forward in the screening cascade to assess the brain penetration of the series.

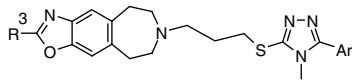
Compound **18** showed acceptable bioavailability (*F*) and half life ($F = 22\%$; $T_{1/2} = 1.3$ h) with acceptable V_d and Clb (3.3 l/kg and 40 ml/min/kg, respectively), but more importantly, it demonstrated high B/B (7.7) with a large amount of compound in the brain. The introduction of the oxazolyl moiety on the thiotriazole (**19**) contributed to a further reduction of PSA (86 $\widehat{A}2$). This had a positive impact on hERG, but also the desired D_3 affinity was 10-fold reduced. The introduction of an Et substituent (**20**) in the tricyclic portion did not substantially change the affinity, as well as the presence of a *para*-CF_3 Ph substituent (**21**) on the thiotriazole moiety which, however, was detrimental both for hERG activity and for some in vitro PK properties.

Based on receptor modeling[5] results analysis, the isoxazolyl portion in the tricyclic scaffold was rearranged to an oxazolyl one, to maintain similar PSA values, reduce the favorable interactions within the hERG channel (Fig. 2) because of the position of R^3 substituent, and have a better interaction with key features in the D_3 receptor pocket (Fig. 3).

The first compound prepared, **22**, was slightly less potent than the corresponding isoxazolyl derivative **18**, but it was much more selective and devoid of any hERG activity. Also for this compound, the rat PK profile was immediately performed, showing a relatively high Clb (47 ml/min/kg), $T_{1/2} = 1.7$ h and $F = 34\%$. One may assume that because of its V_d (4.3 l/kg), its brain penetration was very good showing a B/B ratio = 5.4. A slight increase in the clog*D*[13] value shown by compound **26** (5.6 vs. 5.0 for **22**) led to a 10-fold increase in the D_3 affinity, in agreement with the analysis deriving from the D_3 receptor model (Fig. 3). In order to assess whether or not the increased lipophilicity was detrimental to the in vivo PK properties, the profile of this derivative was studied. The compound was endowed with a relatively higher Clb and V_d (57 ml/min/kg and 5.1 l/kg, respectively) with respect to **22**, but both *F* (31%) and $T_{1/2}$ (1.6 h) were almost identical. A further increase in the lipophilicity of the *n*-Pr derivative (**28**, clog*D* = 6.1) led to an improvement in D_3 affinity, but was also paralleled by an increase in hERG affinity; moreover the overall PK parameters were much more affected leading to low *F* (6%), probably because of high Clb (62 ml/min/kg).

As predicted by the SAR developed so far, the introduction of the *i*-Pr substituent (**29**, **30** vs. **22**, **23**) was positive in terms of desired D_3 affinity; while both molecules demonstrated similar and positive in vitro

Table 3. Affinity results



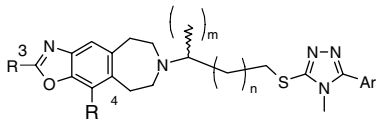
Compound	R^3	Ar	D_3 fpKi	D_2 fpKi	H_1 fpKi	hERG pIC_{50}	PSA ($\AA^2$)	ACD log*D*
22	Me	a	7.2	<5.6	<5.7	<5.0	98	5.0
23	Me	b	6.8	<5.6	5.6	4.5	111	2.9
24	H	b	6.7	<5.6	<5.3	5.2	86	2.6
25	H	a	7.3	<5.6	5.6	5.4	73	4.8
26	Et	a	7.9	<6.3	<5.9	5.3	73	5.6
27	Et	b	7.5	<6.3	<5.5	5.2	86	3.4
28	Pr	a	8.4	<6.2	<5.6	6.2	73	6.1
29	*i*-Pr	a	8.5	<5.9	<5.5	5.7	73	5.9
30	*i*-Pr	b	8.0	<6.1	<5.5	5.4	86	3.8
31	CyPr	a	7.3	<6.2	<5.8	6.0	73	5.0
32	CyPr	b	6.7	<6.2	<5.5	<5.4	86	2.9
33	*t*-Bu	a	9.1	<6.0	<5.3	6.1	73	6.2
34	Me	c	6.9	<6.1	<5.4	4.3	73	3.6
35	Me	d	7.6	<6.1	<5.4	5.4	60	5.7
36	Me	e	7.5	<6.1	<5.4	5.0	60	5.1
37	Me	f	7.0	<6.3	<5.5	<4.2	69	2.7
38	Et	c	7.0	<6.2	<5.6	4.8	73	4.2
39	Et	d	8.1	<6.2	<5.5	6.6	60	6.2
40	Et	e	7.6	<6.3	<5.6	5.9	60	5.6
41	CF_3	a	7.3	<6.2	<5.8	6.0	73	6.2
42	CH_2CF_3	a	7.4	<6.2	<5.5	5.6	73	6.4
43	CF_2Me	a	8.2	<6.1	<5.7	5.9	73	6.0
44	CF_2Me	b	7.7	<6.1	<5.7	nt	86	3.8
45	CH_2OMe	a	6.6	<6.2	<5.5	<4.8	82	4.9
46	CH_2CyPr	a	7.9	<6.2	<5.5	5.9	73	5.9
47	CH_2CyPr	b	7.4	<6.2	<5.5	6.0	86	3.8
48	Piperidyl	a	8.3	<6.2	<5.5	5.3	76	2.1
49	Me2N	a	9.0	<6.3	<5.5	4.7	76	4.9
50	CF_2CF_3	a	8.3	<6.4	<5.6	7.0	73	8.2
51	CF_2CF_3	b	8.5	<6.2	<5.6	6.7	86	6.1
52	pir*	a	8.1	<6.3	<5.6	6.3	91	5.9
53	pir*	b	8.4	<6.4	<5.5	6.0	104	3.7

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

PK parameters (P450 and rat Cli), their in vivo properties were sub-optimal probably due to high Clb (81 and 152 ml/min/kg, respectively). Actually very low *F*% and $T_{1/2}$ values were achieved. An attempt to slow down the potential metabolic degradation of the *i*-Pr substituent was undertaken with the introduction of the cyclopropyl derivative (**31**, **32**), but the outcome was not positive in terms of D_3 affinity. The introduction of the *t*-Bu moiety (**33**), on the other hand, led to a very high D_3 affinity with 1000-fold selectivity over the D_2, and H_1 receptors and the hERG channel. Unfortunately, the rat Clb of this derivative was too high (137 ml/min/kg) to make it progressable down the screening cascade. At the same time, the exploration of the right-hand side of the molecule introducing different aromatic or heterocyclic groups was performed. The introduction of a 3-pyridyl derivative (**34**) had a positive effect on the hERG side, but was detrimental to the main target, while a *p*-CF_3 Ph (**35**) was well balanced in terms of affinity profile. Its PK properties showed a Clb equal to 62 ml/min/kg, with a relatively good $T_{1/2}$ (1.5 h), a moderate V_d (5.4 l/kg), while F was 17%. Brain penetration was also good, with a B/B ratio = 2.9. In accordance with the SAR developed for this series, the introduction of an Et group (**39**) was positive for the primary affinity and had no major effect on the PK parameters (Clb = 48 ml/min/kg; V_d = 3.4 l/kg; $T_{1/2}$ = 1.1 h; *F* = 17% ; B/B = 3.1).

The introduction of groups less prone to metabolic degradation, like the $-CF_3$, in the tricyclic scaffold, (**41**) led to a much reduced Clb (20 ml/min/kg) and to a relatively balanced PK profile (V_d = 5.0 l/kg; $T_{1/2}$ = 3.3 h; *F* = 31%; B/B = 2.8), while the introduction of spaced cyclopropyl derivatives (**46**, **47**) maintained reasonable affinity and a relatively good PK profile (*F* = 25%, V_d = 4.3 l/kg, Clb = 50 ml/min/kg; and *F* = 32%, V_d = 1.7 l/kg; Clb = 26 ml/min/kg for **46** and **47**, respectively). The introduction of amine moieties was positive from the affinity point of view and the piperidine derivative **48** showed a 1000-fold selectivity versus hERG with an excellent B/B ratio (5.1); its Clb was unfortunately relatively high (76 ml/min/kg) leading to poor *F* data (3%). More promising was the dimethyl amino derivative **49** that not only achieved nanomolar potency and excellent selectivity, but was also endowed with a

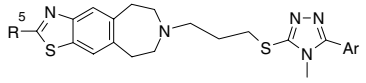
Table 4. Affinity results



Compound	R^3	R^4	m	n	Ar	D_3 fpKi	D_2 fpKi	H_1 fpKi	hERG pIC_{50}	PSA ($\widehat{A}^2$)	ACD log*D*
54	Me	Br	0	1	a	7.6	<6.2	<5.9	5.6	73	5.8
55	Et	Br	0	1	a	<7.2	<6.2	<6.3	5.9	73	6.4
56	*t*-Bu	Br	0	1	a	7.9	<6.2	6.0	6.4	73	7.0
57	Me	Me	0	1	a	7.4	<6.0	<5.7	5.3	73	5.5
58	Et	Me	0	1	a	7.5	<6.0	<5.7	6.3	73	6.0
59	*t*-Bu	Me	0	1	a	7.4	<6.0	5.8	6.6	73	6.6
60	Me	H	0	2	b	6.5	<6.2	<5.6	4.3	86	2.9
61	Me	Br	0	2	a	7.4	<6.1	<5.7	5.3	73	5.9
62	Et	Br	0	2	a	7.4	6.4	5.7	5.8	73	6.4
63	CF_3	Br	0	2	a	7.7	6.0	5.9	6.6	73	7.0
64	Me	Me	0	2	a	8.2	6.8	<5.6	5.8	73	5.5
65	Et	Me	0	2	a	7.6	6.2	<5.6	5.8	73	6.0
66	CF_3	Me	0	2	a	7.2	6.2	5.6	6.6	73	6.7
67	Me	H	0	0	a	7.5	<6.1	<5.5	4.3	73	5.3
68	Me	Br	0	0	a	6.5	<6.0	<5.8	5.2	73	6.1
69	Et	Br	0	0	a	6.7	<6.0	<5.6	5.6	73	6.6
70	CF_3	Br	0	0	a	6.5	<6.1	<5.6	6.2	73	7.2
71	Me	Me	0	0	a	6.5	<6.0	<5.6	4.9	73	5.8
72	Et	Me	0	0	a	6.6	<6.0	<5.6	5.6	73	6.3
73	CF_3	Me	0	0	a	6.9	<5.8	<5.6	6.4	73	6.9
74	Me	Me	1	1	a	6.6	<6.0	<5.6	4.9	73	5.8
75	Et	Me	1	1	a	6.9	<6.0	<5.6	5.4	73	6.3
76	CF_3	Me	1	1	a	7.1	<6.0	<5.7	6.0	73	6.9
77	Me	Br	1	1	a	7.3	<5.8	6.0	5.0	73	6.1
78	Et	Br	1	1	a	7.0	<6.0	<5.6	5.5	73	6.6
79	CF_3	Br	1	1	a	7.0	<5.8	<6.3	5.7	73	7.3

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.

Table 5. Affinity results



Compound	R^5	Ar	D_3 fpKi	D_2 fpKi	H_1 fpKi	hERG pIC_{50}	PSA ($\widehat{A}^2$)	ACD log*D*
80	Me	a	7.7	<6.1	6.0	5.6	60	5.6
81	Me	b	7.1	<6.0	5.8	5.5	73	3.4
82	Et	a	8.6	<6.3	<5.7	6.6	60	6.1
83	Et	b	8.4	<6.5	<5.6	5.9	73	3.9

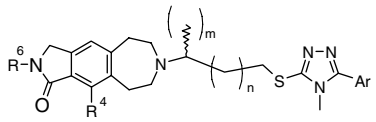
SEM for D_3 GTPγS, H_1 FLIPR and HERG data sets is ±0.1 and for the D_2 GTPγS data is ±0.2.

good PK profile (Clb = 29 ml/min/kg; $T_{1/2}$ = 1.6 h; V_d = 2.8 l/kg; F = 45%; B/B = 1.1). The compound was therefore progressed along the screening cascade to in vivo animal disease models and the exploration was further continued for better understanding of the SAR around this series.

The tolerance of the D_3 receptor versus the introduction of relatively basic groups in the tricyclic template was further confirmed by the introduction of a substituted pyrazole (**52**, **53**) in the system, while the introduction of a Bromine atom or of a Methyl group on the tricyclic portions was almost neutral (**54**–**59**). The increase in the spacer length (**60**–**66** vs. **54**–**59**) was relatively well tolerated, as well as its reduction in nonsubstituted systems (**67**). The introduction of a substitution alpha to the basic nitrogen in the system led to a general decrease in hERG activity, with no significant effect on D_3 affinity (**74**–**79**).

The modification of the tricyclic portion with the replacement of the oxazolyl moiety with a thiazolyl one was well tolerated from the D_3 affinity point of view (**80**–**83**, Table 5) and showed a similar trend for the hERG profile. From the PK point of view, derivative **80** showed no major issues in terms of P450 or Cli and

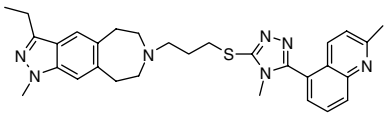
Table 6. Affinity results



Compound	R^6	m	n	Ar	D_3 fpKi	D_2 fpKi	H_1 fpKi	hERG pIC_{50}	PSA ($\widehat{A}^2$)	ACD log *D*
84	Me	0	1	a	6.2	<6.0	5.5	nt	67	3.1
85	*i*-Pr	0	1	a	7.6	<5.8	<5.7	5.4	67	4.0
86	Me	0	2	a	6.6	<6.0	<5.6	4.5	67	3.2
87	*i*-Pr	0	2	a	7.4	<6.0	<5.6	5.4	67	4.0
88	Me	1	1	a	<6.3	<6.0	<5.6	4.4	67	3.4
89	*i*-Pr	1	1	a	6.9	<6.0	<5.6	5.6	67	4.3

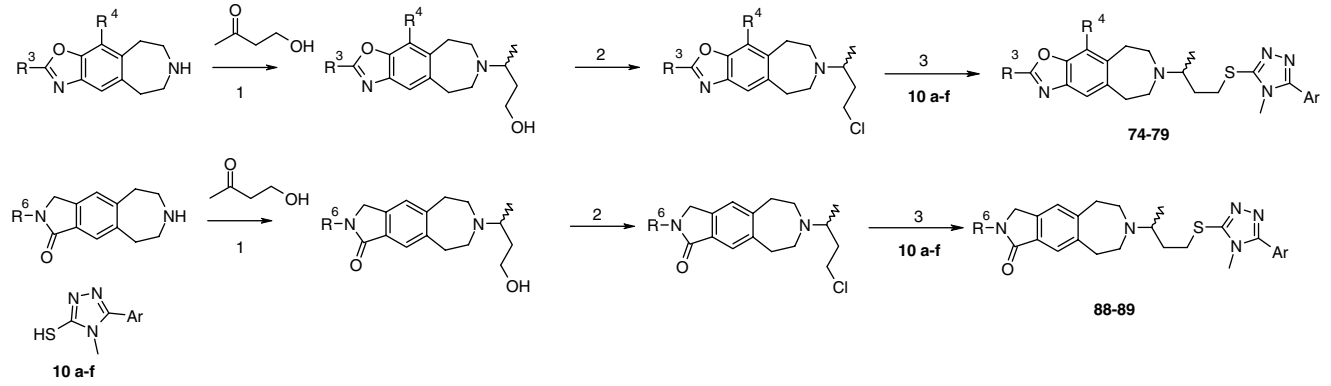
SEM for D_3 GTPγS, H_1 FLIPR and HERG data sets is ±0.1 and for the D_2 GTPγS data is ±0.2. nt, not tested.

Table 7. Affinity results



Compound	D_3 fpKi	D_2 fpKi	H_1 fpKi	hERG pIC_{50}	PSA ($\widehat{A}^2$)	ACD log *D*
90	8.6	6.4	6.2	6.0	65	5.8

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.



Scheme 2. Reagents and conditions: (1) 4-hydroxy-butan-2-one, $NaBH(OAc)_3$, THF 0 °C, rt; (2) $SOCl_2$, $CHCl_3$, 0 °C, rt; 3 h; (3) Et_3N, NaI, DMF 70 °C, 24 h.

its profile was comparable to derivative **22** showing a Clb = 34 ml/min/kg, a $T_{1/2}$ = 2.2 h, a V_d = 4.3 l/kg, and F = 25%. The brain penetration was also excellent, with a B/B ratio equal to 4.4.

Further modifications, balancing the slight increase in lipophilicity due to the ethyl substituent on the left-hand side with the oxazolyl moiety on the right portion of the molecule (**83**), led to a very balanced profile also in terms of hERG affinity.

The introduction of a more hydrophilic lactam portion led to a more significant modification of the tricyclic system, and the first derivative prepared (**84**) showed poor affinity at the desired receptor, probably due to the very high polarity of the new left-hand side. To counterbalance the reduction in clog *D* in the new scaffold, a higher degree of lipophilicity in the substitution pattern was introduced to improve the D_3 affinity (e.g., **85** vs. **84**). Nonetheless, the much reduced PSA (67 $\widehat{A}^2$ for **85**) was probably the reason for low B/B (0.2) showed by the NCE, while the remaining parameters were similar to previously tested compounds (V_d = 3.5 l/kg; Clb = 36 ml/min/kg; $T_{1/2}$ = 1.5 h; F = 10%).

Finally, using the same chemistry described in Scheme 1, the pyrazolyl derivative **90** was prepared to complete the analysis of the pattern of substitution in the h-fused scaffold. From the in vitro point of view this led to excellent affinity and selectivity profile as reported below in Table 7.

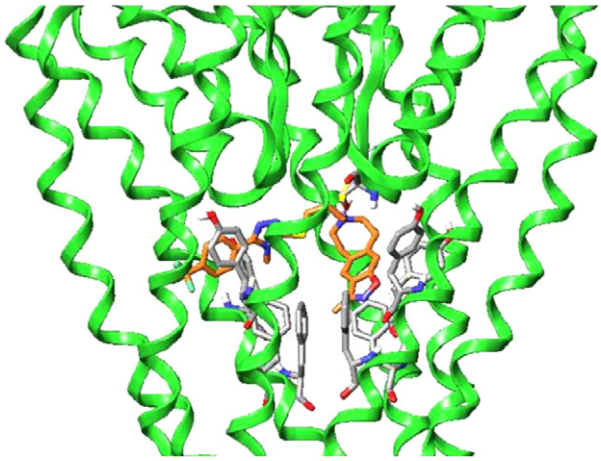


Figure 2. An energetically favorable docking solution of **21** in the closed state of the hERG receptor model. This solution suggests that this ligand can establish hydrophobic interactions with Phe656 and Tyr652 while its protonated nitrogen can make an HB interaction with Ser624 in the pore helix.

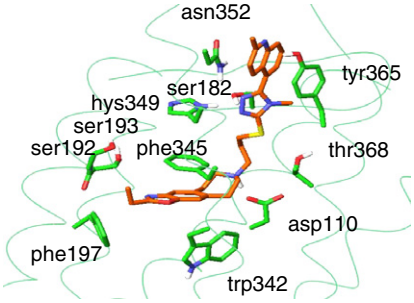


Figure 3. Derivative **26** was probed for its ability to bind a dopamine D_3 receptor model based on the bovine rhodopsin crystal structure. Using a docking approach based on Macromodel, a possible binding mode shows a strong interaction of the basic benzazepine nitrogen with Asp110 on transmembrane helix 3 (TM3). Hydrogen bond interactions can also be observed between the triazole ring and Asn352 (to a lesser extent, also to Hys349 and Ser182). The fused oxazolo-benzazepine scaffold extends through the 'classic' agonist binding pocket toward TM5, with the Et group (R^3) positively fitting in the available space. Two aromatic residues, Phe345 and Tyr365, can form π-stacking interactions, respectively, with the oxazolo-benzazepine ring and the quinoline mojety.

In summary, substitution of a simple benzazepine ring with a more complex tricyclic structure was well tolerated by the D_3 receptor and some NCEs here described showed remarkable selectivity versus D_2, H_1 receptors and the hERG channel. Among this new class of selective D_3 receptor antagonists, a number of derivatives with balanced rat PK profiles were also discovered. These will be very useful in the continuation of the screening cascade to further validate the concept of selective D_3 receptor antagonism in different therapeutic areas.

The exploration of the new tricyclic scaffold was to be completed probing the sensitivity of the D_3 receptor to the [g]-fusion and to the introduction of much more polar systems into the new template. This exploration will be the topic of the following Part 2 of this manuscript.

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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.2007.12.066.

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12. The research complied with national legislation and with company policy on the Care and Use of Animals and with related codes of practice.
13. ACD Labs suite is available from http://www.acdlabs.com.