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Aromatic ring functionalization of benzolactam derivatives: New potent dopamine D_3 receptor ligands

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ABSTRACT

Since the discovery of the dopamine D_3 receptor, an intensive effort has been directed toward the development of potent and selective ligands in order to elucidate the function and potential therapeutic advantages of targeting D_3 receptors. As a part of our efforts, a novel series of substituted benzolactams derivatives was synthesized mostly through palladium-catalyzed reactions. Their affinities on D_1–D_4 receptors were evaluated and the data led us to highly potent D_3 ligands, some of them highly selective for D_3 receptor, compared to the related dopamine receptor subtypes. Functional D_3 activity assays of the most relevant compounds have been carried out revealing antagonist as well as partial agonist activity.
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The D_3 dopamine receptor was first identified and cloned by Sokoloff et al.[1] in 1990 and has been shown to be an interesting target for different CNS diseases. Although its structure and pharmacology are very similar to dopamine D_2, the D_3 receptor is generally less abundant than the D_2 receptor, and the difference is particularly striking in the caudate putamen, where D_2 receptors are displayed at high density, whereas D_3 receptors are poorly represented.[2] Moreover, D_3-binding sites and mRNA encoding D_3 receptors are concentrated in the limbic brain areas known to be associated with cognitive and emotional functions.[3] Due to this observation, the D_3 receptor has been suggested to be a potential target in the treatment of neurological disorders such as schizophrenia,[4,5] Parkinson's disease,[6] drug-induced dyskinesia,[7] and drug abuse.[8] Moreover, recent studies have shown that proerectile effects of dopamine D_2-like agonists are mediated by the D_3 receptor in rats and mice.[9]

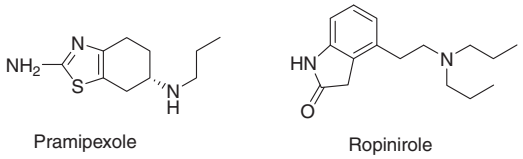
In an attempt to prove these hypotheses, an intensive effort has been directed toward the development of selective ligands for dopamine D_3 receptors.[8,10] A large number of compounds with various selectivities for the D_3 receptor have been developed. Some of the well known D_3 agonists include pramipexole and ropinirole (Fig. 1), and these agonists were shown to exhibit a 4–10-fold higher affinity for the D_3 than D_2 receptor.[11]

On the other hand, numerous ligands as antagonists have been developed so far with a number of lead compounds showing high selectivity for the D_3 receptor (Fig. 2). Most of these compounds contain a piperazine ring connected to a suitable benzamide-type moiety via variable linker size.[10,12]

Today there is an urgent need for more selective molecular tools to facilitate a relevant differentiation between D_3 actions and those mediated by the D_2 receptors, in order to elucidate the function and potential therapeutic advantages of targeting D_3 receptors.

We have previously reported the synthesis and binding affinity of a new series of DA D_2/D_3 receptor ligands (Fig. 3) based on the benzolactam scaffold.[13]

These compounds maintain three characteristic elements of many dopamine D_3 receptor antagonists: (1) an amine moiety, (2) a spacer, usually a linear alkyl chain, and (3) a hydrophobic residue, often connected through an amide bond. The size of the lactam cycle varied from a six to eight-membered ring, the length of the alkyl spacer, from propyl to pentyl, and the aryl substituent of the piperazine ring was varied to achieve a set of compounds that allows us to evaluate some of the structural requirements for high binding affinity and selectivity on the D_3 receptor. One of our long-term objectives in this project is to develop a reliable



Pramipexole Ropinirole

Figure 1. Structures of the D_3 dopamine agonists pramipexole and ropinirole.

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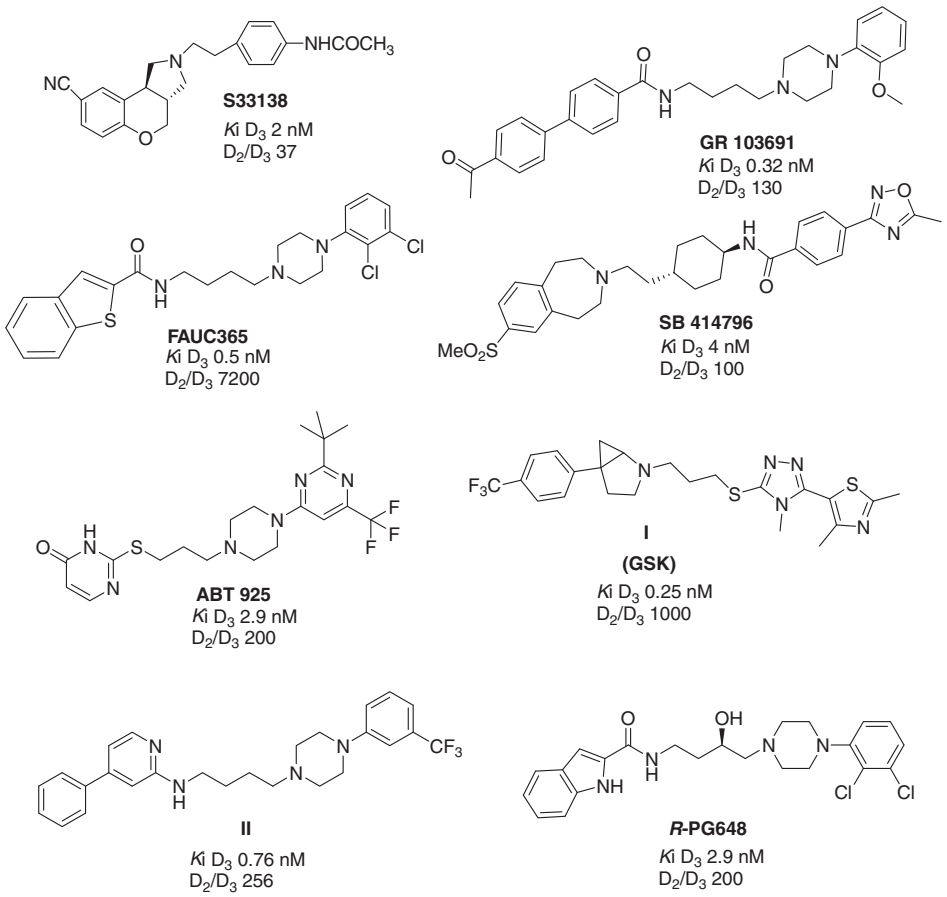


Figure 2. Structures of selective D_3 receptor ligands.

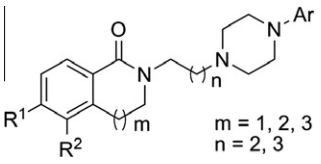


Figure 3. General structure of benzolactam derivatives.

pharmacophore model for these compounds with which we would be able to rationalize the observed DA D_2/D_3 binding affinities and selectivities of our compounds.

In our further quest to understand the role of the benzolactam ring and the effect of different substitutions in the fused-benzene ring, we have designed a new series of compounds where the benzene ring of the benzolactam motif has been functionalized by the introduction of different substituents, mostly through a palladium-catalyzed reaction.

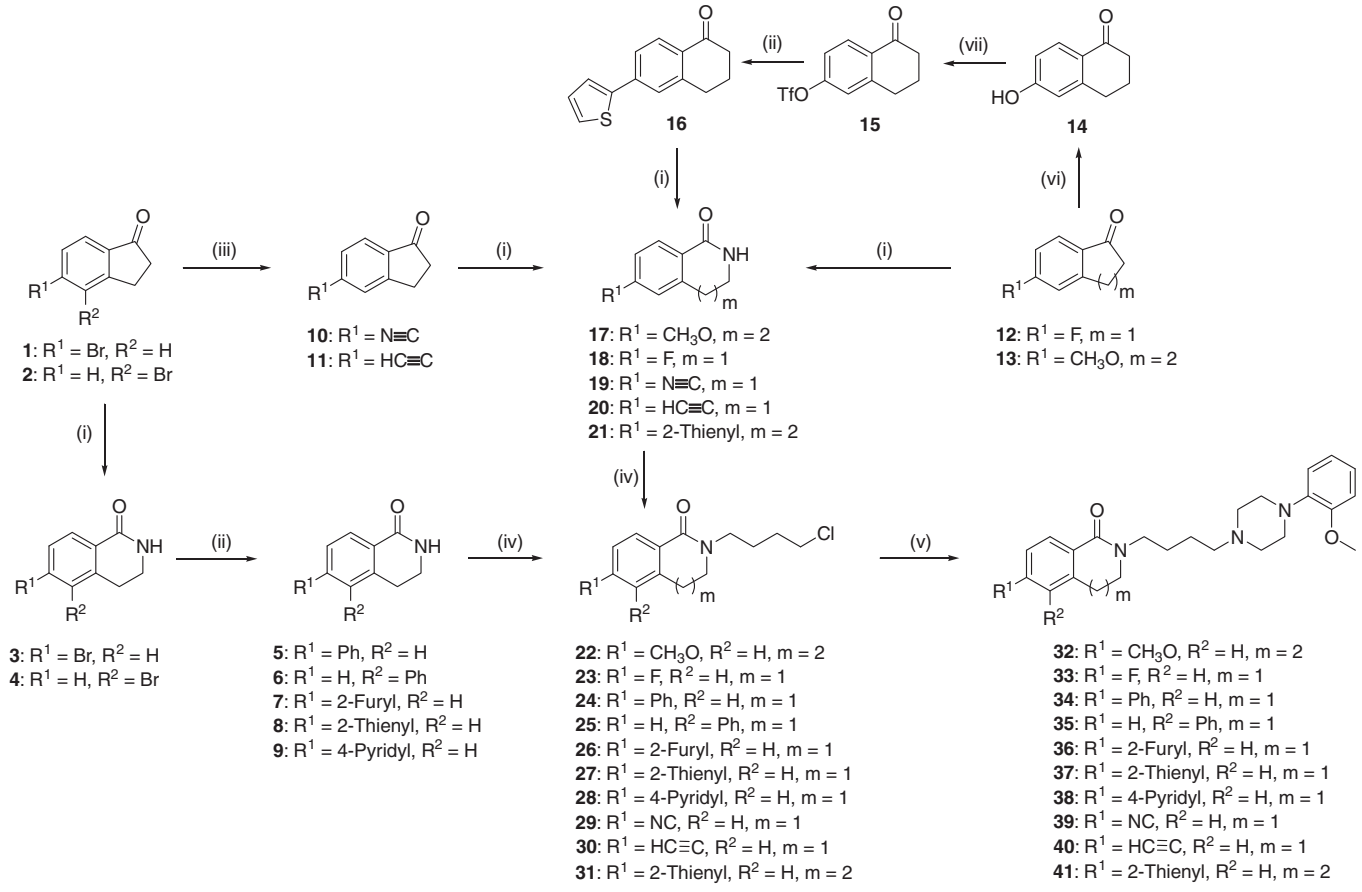
The expansion of the substituted benzocycloalkanones **1**, **2**, **10**–**13**, and **16** (Scheme 1) for obtaining the corresponding 1-oxo-2*H*-benzolactams **3**, **4**, and **17**–**21** was carried out by means of Schmidt reaction. The success of this reaction is dependent of several variables such as the solvent, the acid, or the starting material. In our case, the best results were achieved when a 1:1 mixture of CH_2Cl_2 and methanesulfonic acid as solvent, and 2 equiv of NaN_3 were used. In the case of 6-methoxytetralone (**13**) the expansion was carried out more productively in concentrated HCl (Table 1). In all cases, the corresponding isomeric 2-oxo-1*H*-benzolactams were also isolated in lower quantity.

The substitution of the bromine atom in arylbromides for different boronic acids using Pd(0) as catalyst (Suzuki reaction) has been widely described. Nevertheless, the particular reaction conditions had to be optimized depending on the starting compounds. In our case, the best results were obtained when **3**, or **4** were coupled with phenyl-, 2-thienyl-, or 2-furylboronic acid in deionized water using $Pd(AcO)_2$ as catalyst in the presence of K_2CO_3 and Bu_4NBr.[14] Under these conditions, the 6-arylbenzolactams (**5**–**8**) were obtained in 75–96% yield. Coupling the more deactivated 4-pyridylboronic acid required $Pd(Ph_3P)_4$ as catalyst[15] yielding **9** in 79% yield (Table 2, entry 5).

Cyanation reaction of bromide **3** was also performed with $Zn(CN)_2$ and $Pd(PPh_3)_4$ in DMF to obtain the corresponding aromatic nitrile (Table 2, entry 6). However, repeated assays where cyanide sources, catalysts, or solvents were varied afforded poor yields (<10%) of the 6-cyanobenzolactam **19**. Alternatively, for obtaining this compound, we decided to reverse the order of the steps: cyanation of 5-bromoindanone (**1**) with CuCN in DMF yielded 5-cyanoindanone (**10**, 52%), which was transformed in the corresponding lactam **19** by Schmidt rearrangement in 55% yield, providing better overall yield and a more efficient purification.

The same problems were found for palladium-catalyzed ethynylation of bromolactame **3** (Table 2, entry 7), where ethynylbenzolactam **20** was isolated in a poor 5% yield. Therefore, Sonogashira coupling between bromoindanone **1** and TMS–acetylene was attempted using $Pd(PPh_3)_2Cl_2$ as the catalyst and CuI in 3:1 triethylamine/DMF. 5-(Trimethylsilylethynyl)-2,3-dihydroinden-1-one was obtained in 46% yield, which upon alkaline hydrolysis with K_2CO_3 in MeOH gave 5-ethynyl-2,3-dihydroinden-1-one **(11)** in 56% yield.

Due to the better pharmacological outcomes demonstrated in previous studies[13] by compounds bearing a 7-membered lactam, the 2,3,4,5-tetrahydro-7-(2-thienyl)benzo[*c*]azepin-1-one **(21)**



Scheme 1. Reagents and conditions: (i) NaN_3 (2 equiv), 1:1 CH_3SO_3H/CH_2Cl_2 (or HCl for **17**), 0 °C 1 h, rt, 12 h; (ii) for **5–8,** and **16**: boronic acid, Bu_4NBr, K_2CO_3, $Pd(AcO)_2$, H_2O, 70 °C, 2–4 h; for **9**: 4-pyridylboronic acid, 2 M K_2CO_3 (aq), $Pd(Ph_3P)4$, 1:1 EtOH/toluene, 90 °C, 5 h; (iii) for **10**: CuCN, DMF, reflux, 24 h; for **11**: (a) TMS-C≡CH, $Pd(PPh_3)_2Cl_2$, CuI, 3:1 Et_3N/DMF; (b) K_2CO_3, MeOH; (iv) 1-bromo-4-chlorobutane, NaH, benzene, reflux, 24–48 h; (v) 1-(2-methoxyphenyl)piperazine, K_2CO_3, KI, methylisobutylketone, reflux, 48 h; (vi) **13**, $AlCl_3$, CH_2Cl_2, reflux, 24 h; (vii) **14**, trifluoromethane sulfonic anhydride, anhydrous pyridine, 0 °C 10 min, rt 40 h.

Table 1
Reaction conditions of Schmidt reaction for the preparation of substituted benzolactams

Ketone	Reagent (equiv)	Solvent	Temp (°C)	Time (h)	Product (yield)	R^1	R^2	*N*
1	NaN_3	Methanesulfonic acid:CH_2Cl_2	rt	12	3 (47%)	Br	H	1
2	NaN_3	Methanesulfonic acid:CH_2Cl_2	rt	12	4 (46%)	H	Br	1
10	NaN_3	Methanesulfonic acid:CH_2Cl_2	rt	12	19 (55%)	NC	H	1
11	NaN_3	Methanesulfonic acid:CH_2Cl_2	rt	12	20 (37%)	HC≡C	H	1
12	NaN_3	Methanesulfonic acid:CH_2Cl_2	rt	12	18 (48%)	F	H	1
13	NaN_3	HCl (c)	rt	12	17 (60%)	CH_3O	H	2
16	NaN_3	Methanesulfonic acid:CH_2Cl_2	rt	12	21 (35%)	2-Furyl	H	2

Table 2
Reaction conditions of palladium-catalyzed cross-coupling reaction for the synthesis of new substituted benzolactams

Entry	Reactant	Reagent	Catalyst system (equiv)	Base	Additives	Solvent	Temp (°C)	Time (h)	Product (yield)	R^1	R^2
1	**3**	$PhB(OH)_2$	$Pd(AcO)_2$ (1%)	K_2CO_3	Bu_4NBr	H_2O	70	2.5	**5** (75%)	Ph	H
2	**4**	$PhB(OH)_2$	$Pd(AcO)_2$ (1%)	K_2CO_3	Bu_4NBr	H_2O	70	2.5	**6** (96%)	H	Ph
3	**3**	(2-Furyl)$B(OH)_2$	$Pd(AcO)_2$ (1%)	K_2CO_3	Bu_4NBr	H_2O	70	2.5	**7** (81%)	2-Furyl	H
4	**3**	(2-Thienyl)$B(OH)_2$	$Pd(AcO)_2$ (1%)	K_2CO_3	Bu_4NBr	H_2O	70	2.5	**8** (83%)	2-Thienyl	H
5	**3**	(4-Pyridyl)$B(OH)_2$	$Pd(PPh_3)_4$ (6%)	K_2CO_3	—	EtOH/toluene	90	5	**9** (79%)	4-Pyridyl	H
6	**3**	$Zn(CN)_2$	$Pd(PPh_3)_4$ (10%)	—	—	DMF	100	6	**19** (7%)	N≡C	H
7	**3**	$(HC{\equiv}C)SiMe_3$	$(PPh_3)_2PdCl_2$ (4%)	Et_3N	CuI	Et_3N/THF	rt	15	**20** (5%)	HC≡C	H
8	**1**	$(HC{\equiv}C)SiMe_3$	$(PPh_3)_2PdCl_2$ (4%)	Et_3N	CuI	Et_3N/DMF	80	16	**11** (44%)	HC≡C	H
9	**15**	(2-Thienyl)$B(OH)_2$	$Pd(AcO)_2$ (1%)	K_2CO_3	Bu_4NBr	H_2O	70	2.5	**16** (65%)	2-Furyl	H

was synthesized in four steps from **13.** Starting with the cleavage of the methoxy group with $AlCl_3$ (5 equiv) in CH_2Cl_2, the alcohol **14** was obtained in 83% yield. Then, triflate **15** was generated in 74% yield by treating **14** with trifluoromethanesulfonic anhydride in pyridine. Substitution of the triflate group in **15** for 2-thienyl was carried out by Suzuki reaction using the same conditions as for compound **8** (Table 2, entry 4): 2-thienylboronic acid, $Pd(AcO)_2$, K_2CO_3 and Bu_4NBr, affording the desired ketone **16** in 65% yield

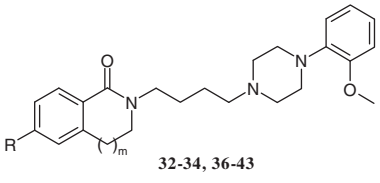
(Table 2, entry 9). Subsequently, lactam **21** was synthesized from ketone **16** by Schmidt rearrangement in 35% yield (Table 1).

The differently substituted benzolactams **5–9**, and **17–21** were alkylated with 1-bromo-4-chlorobutane in anhydrous benzene using NaH as a base to give the corresponding 4-chlorobutylamides 22–**31** in good yields (62–90%). Finally, subsequent displacement of the chlorine atom by *o*-methoxyphenylpiperazine in methylisobutylketone with K_2CO_3 as a base and KI in catalytic amount furnished the final products (**32–41**) in 35–80% yield.

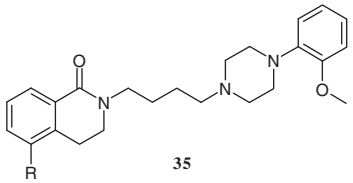
Receptor binding experiments were established to evaluate the binding properties of the newly synthesized lactams **32–41** in comparison to the recently described compounds **42** and **43** (Table 3). The binding data was generated by measuring their ability to compete with [^{3}H]spiperone for the cloned human dopamine receptor subtypes D_{2long}, D_{2short},[16] D_3[17] and $D_{4.4}$[18] stably expressed in Chinese hamster ovary cells (CHO).[19] D_1 receptor affinities were determined utilizing porcine striatal membranes and the D_1 selective radioligand [^{3}H]SCH23390. The ligands were also investigated for their potency to displace [^{3}H]WAY100635, [^{3}H]ketanserin and [^{3}H]prazosin when employing porcine 5-HT_{1A}, 5-HT_2 and α_1 receptors, respectively.[20] While all test compounds show only moderate affinities to the D_1 and 5-HT_2 receptor, binding in the two digit and one digit nanomolar range was determined for the subtypes of D_2 and D_4, the serotonergic 5-HT_{1A} and the adrenergic α_1 receptor. For all compounds best receptor recognition could be observed for the D_3 receptor, when K_i values in the range form 0.12 to 1.7 nM could be measured. Analyzing the impact of the ring size of the benzolactams on the binding properties the seven-membered ligand **43** showed a K_i of 0.27 nM and a more than sixfold increase of D_3 affinity compared to the tetrahydroisoquinolinone **42**, but a similar selectivity pattern. Introduction of small residues like methoxy (in **32**) or fluoro (in **33**) as well as the unsaturated moieties like cyano (in **39**) or ethynyl (in **40**) at position 6 of the six-membered benzolactam revealed no or only a less distinct improvement of D_3 binding and selectivity in relation to the unsubstituted analogue **42**. In contrast, the extension of the aromatic system of the benzolactam with aromatic or heteroaromatic appendages like phenyl, furyl, thienyl or pyridyl yielded in a 7- to 14-fold increase of D_3 affinity and at the same time a clear enhancement of D_3 selectivity over D_2 (5- to 27-fold) and D_4 (13- to 25-fold). Best D_3 affinity could be determined for the 2-thienyl derivative **37** and the 4-pyridyl analogue **38** both showing a K_i value of 0.12 nM with compound **38** displaying the best selectivity pattern of D_3 over D_{2long}, D_{2short} and D_4 with ratios of 59, 110 and 28, respectively. While for the unsubstituted compounds **42** and **43** a better D_3 affinity could be shown for the seven-membered benzolactam **43** with a K_i value of 0.27 nM, this effect could not be observed for the 2-thienyl substituted analogues **37** and **41**, when the seven-membered derivative **41** displayed a slightly reduced K_i value of 0.29 nM compared to the K_i of 0.12 nM measured for the six-membered congener **37** and an attenuation of D_3 selectivity over D_2 (18- and 7-fold for **41** vs 92- and 58-fold for **37**). Interestingly, when shifting the aromatic appendage of the benzolactam from position 6 to position 5 creating a more bended unsaturated carboxamide system the binding profile clearly changes. For the more linearly oriented 6-phenyl benzolactam **34** a subnanomolar K_i value of 0.25 nM was measured for D_3, whereas the 5-phenyl analogue **35** showed an 48-fold decrease of D_3 binding (K_i = 12 nM) and a change of the selectivity pattern towards a slightly D_4 preference.

As a measure of functional D_3 activity, ligand efficacy of representative benzolactams **34**, **36–38**, **42** and **43** was determined by a mitogenesis assay measuring the rate of [^{3}H]thymidine incorporation into a CHO dhfr$^-$ cell line stably expressing the human D_3 receptor when the full agonist quinpirole was used as a reference agent[17,21,22] (Table 4). While all tested compounds showed partial agonist activity with 27–40% of the full agonist effect of the reference only the 4-pyridyl substituted derivative **38** displayed a neutral antagonist activity. This observation might be explained by the fact that the introduction of a basic nitrogen in the heteroaromatic appendage of the benzolactam substructure might let to a distinct interaction of the ligand with the receptor protein inferring the conformational change, which is considered to be necessary during receptor activation.[23] Future SAR investigations with compounds bearing different basic substructures are necessary to confirm this observation.

Table 3
Receptor binding data and selectivity pattern for the test compounds **31–43** at the human dopamine D_2, D_3 and D_4 subtypes as well as the porcine D_1, the serotonergic 5-HT_{1A}, 5-HT_2 and adrenergic α_1 receptor (K_i values in nM)[a]



32-34, 36-43



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Compound (code)	Structure		Binding affinity (K_i values in [nM])											
			[^{3}H]SCH 23390	[^{3}H]spiperone				[^{3}H]WAY 600135	[^{3}H]ketan-serin	[^{3}H]prazo-sin	Selectivity			
	R	*m*	pD_1	hD_{2long}	hD_{2short}	hD_3	hD_4	p5-HT_{1A}	p5-HT_2	pα_1	D_1/D_3	D_{2long}/D_3	D_{2short}/D_3	D_4/D_3
42 (USC-A401)[b]	H	1	2500	21	7.0	1.7	1.9	2.4	990	2.3	1500	12	4.1	1.1
43 (USC-B401)[b]	H	2	2900	3.9	1.5	0.27	1.3	1.7	1100	5.7	11,000	14	5.6	4.8
32 (USC-J401)	CH_3O	2	2100	3.2	0.93	0.27	3.0	2.5	810	3.7	7800	12	3.4	11
33 (USC-G401)	F	1	2300	26	9.2	1.6	2.8	1.7	840	3.1	1400	16	5.8	1.8
34 (USC-H401)	Ph	1	640	38	15	0.25	3.4	38	330	5.4	2600	150	60	14
35 (USC-N401)	Ph	—	220	52	63	12	9.8	47	230	1.3	18	4.3	5.3	0.82
36 (USC-I401)	2-Furyl	1	580	16	4.8	0.21	3.3	19	330	1.6	2800	77	23	16
37 (USC-K401)	2-Thienyl	1	480	11	6.9	0.12	2.3	6.2	190	3.7	4000	92	58	19
41 (USC-P401)	2-Thienyl	2	920	5.1	2.1	0.29	2.9	68	530	9.7	3200	18	7.2	10
38 (USC-M401)	4-Pyridyl	1	380	7.1	13	0.12	3.4	13	160	2.2	3200	59	110	28
39 (USC-L401)	N≡C	1	3200	38	22	1.3	6.1	3.8	430	3.8	2500	29	17	4.7
40 (USC-O401)	HC≡C	1	1900	24	8.8	0.50	4.1	14	920	2.4	3800	48	17	8.2

[a] All values are means of two to four individual competition experiments each done in triplicate.
[b] See Ref. 13.

Table 4
Intrinsic activities of the representative test compounds **34, 36–38, 42** and **43** and the reference compound quinpirole derived from the stimulating effect on mitogenesis of D_3 receptor expressing cells[a]

[3H]Thymidine uptake (mitogenesis)		
Compound	Agonist effect[b] (%)	EC_{50}[c] (nM)
42 (USC-A401)	36	3.3
43 (USC-B401)	34	0.33
34 (USC-H401)	41	3.3
36 (USC-I401)	27	2.3
37 (USC-K401)	40	2.8
38 (USC-M401)	0	–
Quinpirole	100	1.4

[a] Determined with CHO dhfr$^-$ mutant cells stably expressing the human D_3 receptor.
[b] Rate of incorporation of [^{3}H]thymidine as evidence for mitogenesis activity relative to the maximal effect of the full agonist quinpirole (=100%) used as a reference.
[c] EC_{50} values derived from a mean curve of four or six independent experiments.

In summary, based on the chemical structure of the benzolactam derivative **43**, a compound with high affinity for D_3 receptor, and maintaining the *N*-(*o*-methoxyphenyl)piperazine residue, new benzolactam-containing derivatives have been synthesized with good overall yields (40–60%). Their affinities on D_1–D_4 receptors were evaluated to elucidate how substitutions in the benzolactam part of the pharmacophore affect to the affinity or selectivity for these receptors. The best results were found when H-6 was substituted by bulky groups, especially aromatic heterocycles. In this regard, higher D_3 affinity could be determined for the 2-thienyl derivative **37** and the 4-pyridyl analogue **38** both showing a K_i value of 0.12 nM, with compound **38** displaying the best selectivity pattern of D_3 over D_{2long}, D_{2short} and D_4 receptors, with ratios of 59, 110 and 28, respectively. Functional D_3 activity assays showed that while all tested compounds exhibited partial agonist activity with 27–40% of the full agonist effect of the reference, the 4-pyridyl substituted derivative **38** was displayed as a neutral antagonist, which might be explained by the fact that the introduction of a basic nitrogen in the heteroaromatic appendage might infer the conformational change within the receptor protein, which is necessary for receptor activation.

As these compounds show very promising properties to be used as pharmacological tools for the investigation of the function of the D_3 receptor, further optimization of this series of compounds has to be done considering drug development. In this sense, the improvement of selectivity over the α_1 receptor which is considered as an anti-target as well as the investigation of the influence on a probable inhibition of the hERG channel which is described for drugs bearing a phenylpiperzine substructure must be achieved.

Acknowledgements

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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.2010.12.083.

References and notes

1. Sokoloff, P.; Giros, B.; Martres, M. P.; Bouthenet, M. L.; Schwartz, J. C. *Nature* **1990**, *347*, 146.
2. Levant, B. *Pharmacol. Rev.* **1997**, *49*, 231.
3. (a) Joyce, J. N.; Miador-Woodruff, J. H. *Neuropsychopharmacology* **1997**, *16*, 375; (b) Shafer, R. A.; Levant, B. *Psychopharmacology* **1998**, *135*, 1; (c) Joyce, J. N. *Pharmacol. Ther.* **2001**, *90*, 231.
4. Joyce, J. N.; Millan, M. J. *Drug Discovery Today* **2005**, *10*, 917.
5. Richtand, N. M.; Woods, S. C.; Berger, S. P.; Strakowski, S. M. *Neurosci. Biobehav. Rev.* **2001**, *25*, 427.
6. Joyce, J. N.; Ryoo, H. L.; Beach, T. B.; Caviness, J. N.; Stacy, M.; Gurevich, E. V.; Reiser, M.; Adler, C. H. *Brain Res.* **2002**, *955*, 138.
7. Bezard, E.; Ferry, S.; Mach, U.; Stark, H.; Leriche, L.; Boraud, T.; Gross, C.; Sokoloff, P. *Nat. Med.* **2003**, *9*, 762.
8. Heidbreder, C. A.; Newman, A. H. *Ann. N. Y. Acad. Sci.* **2010**, *1187*, 4.
9. Collins, G. T.; Truccone, A.; Haji-Abdi, F.; Newman, A. H.; Grundt, P.; Rice, K. C.; Husbands, S. M.; Greedy, B. M.; Enguehard-Gueiffier, C.; Gueiffier, A.; Chen, J.; Wang, S.; Katz, J. L.; Grandy, D. K.; Sunahara, R. K.; Woods, J. H. *J. Pharmacol. Exp. Ther.* **2009**, *329*, 210.
10. (a) Jean, M.; Renault, J.; Levoin, N.; Danvy, D.; Calmels, T.; Berrebi-Bertrand, I.; Robert, P.; Schwartz, J. C.; Lecomte, J. M.; Uriac, P.; Capet, M. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 5376; (b) Micheli, F.; Arista, L.; Bonanomi, G.; Blaney, F. E.; Braggio, S.; Capelli, A. M.; Checchia, A.; Damiani, F.; Di-Fabio, R.; Fontana, S.; Gentile, G.; Griffante, C.; Hamprecht, D.; Marchioro, C.; Mugnaini, M.; Piner, J.; Ratti, E.; Tedesco, G.; Tarsi, L.; Terreni, S.; Worby, A.; Ashby, C. R.; Heidbreder, C. *J. Med. Chem.* **2010**, *53*, 374; (c) Newman, A. H.; Grundt, P.; Cyriac, G.; Deschamps, J. R.; Taylor, M.; Kumar, R.; Ho, D.; Luedtk, R. R. *J. Med. Chem.* **2009**, *52*, 2559; (d) Micheli, F.; Heidbreder, C. *Expert Opin. Ther. Patents* **2008**, *18*, 821; (e) Zahng, A. *Chem. Rev.* **2007**, *107*, 274; (f) Boeckler, F.; Gmeiner, P. *Pharmacol. Ther.* **2006**, *112*, 281.
11. Perachon, S.; Schwartz, J. C.; Sokoloff, P. *Eur. J. Pharmacol.* **1999**, *366*, 293.
12. Elsner, J.; Boeckler, F.; Heinemann, F. W.; Hubner, H.; Gmeiner, P. *J. Med. Chem.* **2005**, *48*, 5771.
13. Ortega, R.; Raviña, E.; Masaguer, C. F.; Areias, F.; Brea, J.; Loza, M. I.; López, L.; Selent, J.; Pastor, M.; Sanz, F. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 1773.
14. Chordia, M. D.; Zigler, M.; Murphree, L. J.; Figler, H.; Macdonald, T. L.; Olsson, R. A.; Linden, J. *J. Med. Chem.* **2005**, *48*, 5131.
15. Jenkins, P. R.; Wilson, J.; Emmerson, D.; Garcia, M. D.; Smith, M. R.; Gray, S. J.; Britton, R. G.; Mahale, S.; Chaudhuri, B. *Bioorg. Med. Chem.* **2008**, *16*, 7728.
16. Hayes, G.; Biden, T. J.; Selbie, L. A.; Shine, J. *Mol. Endocrinol.* **1992**, *6*, 920.
17. Sokoloff, P.; Andrieux, M.; Besançon, R.; Pilon, C.; Martres, M.-P.; Giros, B.; Schwartz, J.-C. *Eur. J. Pharmacol.* **1992**, *225*, 331.
18. Asghari, V.; Sanyal, S.; Buchwaldt, S.; Paterson, A.; Jovanovic, V.; Van Tol, H. H. M. *J. Neurochem.* **1995**, *65*, 1157.
19. Hübner, H.; Haubmann, C.; Utz, W.; Gmeiner, P. *J. Med. Chem.* **2000**, *43*, 756.
20. Schlotter, K.; Boeckler, F.; Hübner, H.; Gmeiner, P. *J. Med. Chem.* **2005**, *48*, 3696.
21. Mierau, J.; Schneider, F. J.; Ensinger, H. A.; Chio, C. L.; Lajiness, M. E.; Huff, R. M. *Eur. J. Pharmacol.* **1995**, *290*, 29.
22. Bettinetti, L.; Schlotter, K.; Hübner, H.; Gmeiner, P. *J. Med. Chem.* **2002**, *45*, 4594.
23. (a) Wess, J.; Han, S.-J.; Kim, S.-K.; Jacobson, K. A.; Li, J. H. *Trends Pharmacol. Sci.* **2008**, *29*, 616; (b) Nygaard, R.; Frimurer, T. M.; Holst, B.; Rosenkilde, M. M.; Schwartz, T. W. *Trends Pharmacol. Sci.* **2009**, *30*, 249.