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Synthesis, binding affinity and SAR of new benzolactam derivatives as dopamine D_3 receptor ligands

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ABSTRACT

A series of new benzolactam derivatives was synthesized and the derivatives were evaluated for their affinities at the dopamine D_1, D_2, and D_3 receptors. Some of these compounds showed high D_2 and/or D_3 affinity and selectivity over the D_1 receptor. The SAR study of these compounds revealed structural characteristics that decisively influenced their D_2 and D_3 affinities. Structural models of the complexes between some of the most representative compounds of this series and the D_2 and D_3 receptors were obtained with the aim of rationalizing the observed experimental results. Moreover, selected compounds showed moderate binding affinity on 5-HT_{2A} which could contribute to reducing the occurrence of extrapyramidal side effects as potential antipsychotics.

Dopamine (DA) is a major neurotransmitter in the central nervous system (CNS) that plays important roles in behaviour and cognition, ranging from movement to emotion, sensitization to addiction, and development to plasticity. All DA receptors belong to a superfamily of large peptides that are coupled to G-proteins and modified by attached carbohydrate, lipid–ester or phosphate groups. They are characterized by having seven hydrophobic transmembrane-spanning regions, as well as a functionally critical third intracytoplasmic loop that interacts with G-proteins and other effector molecules to mediate the physiological and neurochemical effects of the receptors. Based on their pharmacological profiles, including their effects on different signal transduction cascades, these receptors are currently divided into two families: the D_1-like family or adenylyl-cyclase stimulators, which includes D_1 and D_5 receptors, and the D_2-like family or adenylyl-cyclase inhibitors, which includes D_2, D_3 and D_4 receptors.[1]

The D_3 dopamine receptor was first identified and clonated by Sokoloff et al.[2] 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 densest and D_3 receptors are poorly represented.[3] 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.[4] Due to this, the D_3 receptor has been suggested to be a potential target in the treatment of neurological disorders such as schizophrenia, and drug abuse.[5] In schizophrenia, a blockade of D_2 receptors has been considered to be the main mechanism responsible for the efficacy of antipsychotics,[6] but the complex profiles of some atypical drugs challenged this assumption, that is, clozapine exhibits activity at multiple receptors.[7] Now there is an increasing body of clinical evidence that supports the notion that multi-target ligands may be more efficacious than strictly selective agents in the treatment of schizophrenia and other CNS disorders.[8] Among multiple receptor subtypes, D_3 receptors have been proposed as putative targets for atypical antipsychotic drugs, and thus, some works suggest that D_3 antagonism may cause cognitive enhancement[9] and a lack of catalepsy.[10]

In an attempt to prove these hypotheses, an intensive effort has been directed toward the development of selective ligands for dopamine D_3 receptors.[11] Some of these D_3 ligands are now in ongoing clinical development as potential therapeutics for the aforementioned disorders. The compound BP 897 (Fig. 1), which was initially identified as a partial agonist but later displayed an antagonist property in other experiments, could reduce cocaine-seeking behaviour in rats.[12] The superpotent benzothiophene derivate FAUC 365 displays neutral antagonistic behaviour and a 7200-fold selectivity over the D_2 subtype.[13] Another D_3 versus D_2

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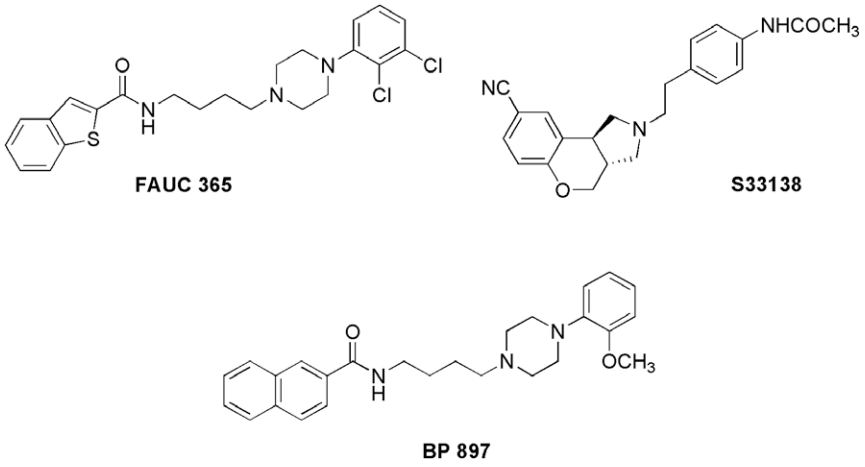


Figure 1. Structures of the D_3 receptor ligands BP 897, FAUC 365 and S33138.

receptor antagonist is S33138, which is now in Phase IIb clinical trials for schizophrenia.[14]

Today there is an urgent need for more selective molecular tools to help definitively separate D_3 actions from those mediated by the D_2 receptors, in order to elucidate the function and potential therapeutic advantages of targeting D_3 receptors.

In an attempt to design a novel class of D_3 ligands to study this receptor system, we report herein the synthesis and binding affinity of a new series of potential D_3 receptor ligands (Fig. 2). This novel series is based on the benzolactam scaffold and maintains 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.[15] 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.

The synthetic route for the preparation of the target arylpiperazinylalkylbenzolactams started from a commercially available benzocycloalkanone (indanone, tetralone or benzosuberone), with the aim of achieving the corresponding benzolactam by a Schmidt rearrangement (Scheme 1). The Schmidt reaction, according to the literature, gives benzolactam **3** as the major product; however, by changing the reaction medium from trichloroacetic acid,[16] polyphosphoric acid[17] or sulfuric acid[18] to concentrated hydrochloric acid,[19] the desired benzolactams **2** can be obtained in moderate yields (42%). This reaction was optimized by adding two equivalents of the sodium azide,[20] and it resulted in a 75–85% yield of the benzolactam type **2**. Nevertheless, this technique was not useful in case the of the benzosuberone, where the benzolactam **2c** was obtained in only a 7% yield, whereas **3c** was obtained in an 87% yield.

Depending on the length of the spacer, one of two synthetic routes was used starting from the benzolactams **2a–c**, as shown

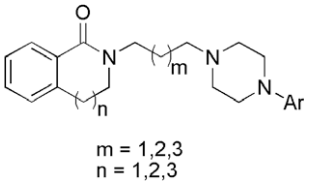
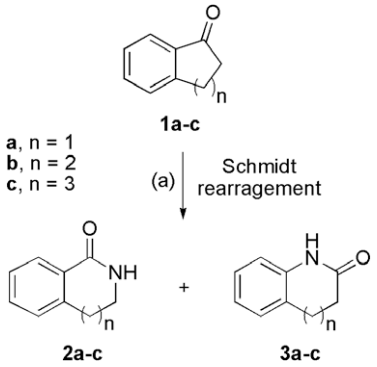


Figure 2. General structure of new benzolactam derivatives.

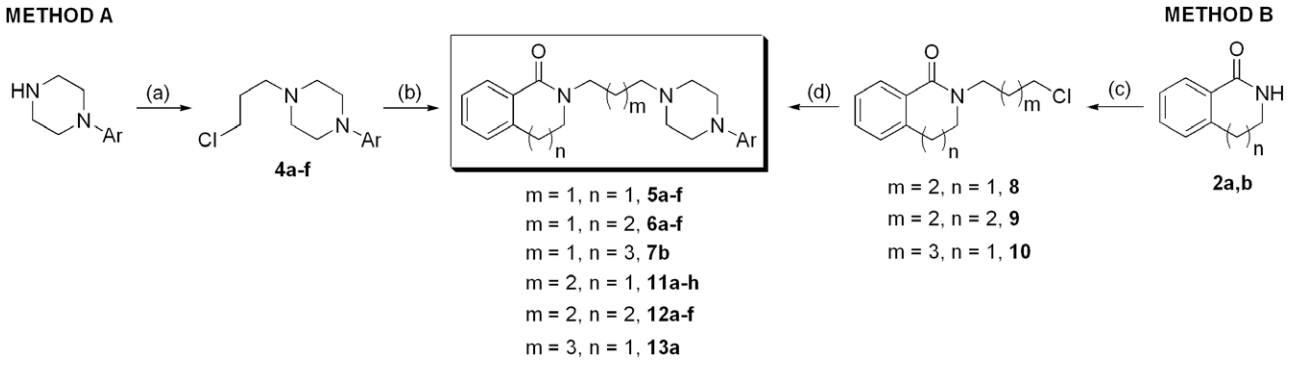


Scheme 1. Reagents and conditions: (a) 2 equiv NaN_3, HCl conc.

in Scheme 2. In the case of a propyl spacer (method A), chlorides **4a–f** were prepared from commercially available piperazines by alkylation with 1-bromo-3-chloropropane in acetone using 25% aqueous NaOH as a base. The corresponding *N*-(3-chloropropyl)piperazines **4a–f** were obtained with 60–80% yields. Alkylation of the benzolactams **2a–c** was achieved when they were treated with the different chloropropylpiperazines **4a–f** in anhydrous benzene after deprotonation with NaH, resulting in the final compounds **5a–f**, **6a–f** and **7b** in a 60–85% yield.

Alkylation of piperazines with 1-bromo-4-chlorobutane or 1-bromo-5-chloropentane, following method A (Scheme 2), produced an azaspiroazonium salt. Although the reaction of this salt with imides has been described in the literature,[21] in our case the desired products were obtained in very low yields. Consequently, method B (Scheme 2) was applied for the synthesis of *N*-arylpiperazinylbutyl- and pentyl-benzolactams. Alkylation of the benzolactams **2a,b** with 1-bromo-4-chlorobutane or 1-bromo-5-chloropentane in anhydrous benzene using sodium hydride as a base gave the corresponding amides **8–10** in acceptable yields, depending on the size of the benzolactam ring. Higher yields were obtained with the six-membered benzolactams **8**[22] (62%) and **10** (75%), and lower yields with the seven-membered benzolactam **9**[22] (50%). For alkylation of piperazines, the best results were obtained by reacting the arylpiperazine and chloroalkylbenzolactam with potassium carbonate as a base and potassium iodide as a catalyst in methylisobutylketone. The alkylated benzolactams **11a–h**, **12a–f** and **13a** were obtained in a 30–75% yield.

The affinity of the new compounds for cloned human D_1, D_2 and D_3 receptors was evaluated in in vitro binding assays using



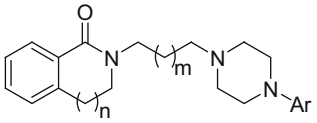
Scheme 2. Reaction conditions: (a) 1-bromo-3-chloropropane, NaOH, acetone; (b) **2a**–**c**, NaH, benzene, reflux; (c) 1-bromo-4-chlorobutane or 1-bromo-5-chloropentane, NaH, benzene, reflux; and (d) arylpiperazine, K_2CO_3, IK, methyl isobutylketone, reflux.

[^{3}H]SCH23390 for labelling D_1 receptors and [^{3}H]spiperone for labelling D_2 and D_3 receptors, according to our previously described procedures.[23] K_i values (expressed as pK_i) were calculated according to the Cheng–Prusoff equation.[24] For the compounds that showed little affinity, a percentage of inhibition at the highest concentration tested (10 μM) is reported. The in vitro receptor binding data are summarized in Table 1.

With the aim of rationalizing the observed experimental results, structural models of the complexes between some of the most representative compounds of this series and the D_2 and D_3 receptors were obtained. It must be stressed that such models were built using computational methods and therefore do not have the value of an experimental result (e.g., a crystallographic structure). Even so, the inspection of such structures allows us to formulate an interesting hypothesis about the physicochemical justifications for the observed pharmacological results. A full description of the methods used for the building of such models is provided as Supplementary data and can also be found in Selent et al.[25] For the description of these models here, the residues in the transmembrane domains (TM) will be named using the Ballesteros and Weinstein indexing system.[26]

One of the points studied here is the length of the linker between the lactam and the piperazine ring. Available data indicate that the length of this bridge decisively influences the affinity of these compounds to the D_2 and D_3 receptors, whereas on the D_1 receptor the length of the bridge seems to have little influence. Lengthening the bridge from propyl to butyl resulted in a beneficial effect on the affinity at the D_2 and D_3 receptors. Propyl derivatives such as **5a** or **6a**, with modest D_2 and D_3 affinities became high affinity ligands when transformed into their butyl analogues **11a**

Table 1
Human D_1–D_3 receptor binding affinities of new compounds (pK_i or percent displacement at 10 μM)[a]



Compound	Code	*m*	*n*	Ar	D_1	D_2	D_3
5a	USC-A301	1	1	2-Methoxyphenyl	59.47% ± 6.87	50.42% ± 2.80	5.80 ± 0.15
5b	USC-A302	1	1	4-Methoxyphenyl	43.45% ± 5.89	1.35% ± 6.95	5.00 ± 0.37
5c	USC-A303	1	1	2-Pyridyl	5.77 ± 0.37	12.40% ± 0.52	5.08 ± 0.11
5d	USC-A304	1	1	2-Pyrimidyl	40.82% ± 0.79	0.36% ± 6.95	4.61 ± 0.20
5e	USC-A305	1	1	3-Trifluoromethylphenyl	5.76 ± 0.29	52.38% ± 0.73	5.62 ± 0.24
5f	USC-A306	1	1	2,3-Dichlorophenyl	5.84 ± 0.17	59.87% ± 4.77	6.68 ± 0.49
6a	USC-B301	1	2	2-Methoxyphenyl	5.60 ± 0.10	6.10 ± 0.07	6.68 ± 0.16
6b	USC-B302	1	2	4-Methoxyphenyl	42.83% ± 3.40	1.10% ± 1.51	5.96 ± 0.34
6c	USC-B303	1	2	2-Pyridyl	57.00% ± 9.75	26.26% ± 0.00	5.38 ± 0.32
6d	USC-B304	1	2	2-Pyrimidyl	46.01% ± 6.74	36.44% ± 0.31	5.08 ± 0.32
6e	USC-B305	1	2	3-Trifluoromethylphenyl	5.31 ± 0.50	55.46% ± 0.62	5.98 ± 0.18
6f	USC-B306	1	2	2,3-Dichlorophenyl	5.62 ± 0.13	6.66 ± 0.05	6.41 ± 0.14
7b	USC-C302	1	3	4-Methoxyphenyl	58.85% ± 4.65	13.13% ± 1.35	5.05 ± 0.14
11a	USC-A401	2	1	2-Methoxyphenyl	61.10% ± 5.76	7.91 ± 0.30	8.58 ± 0.16
11b	USC-A402	2	1	4-Methoxyphenyl	34.16% ± 0.79	33.25% ± 2.59	6.31 ± 0.19
11c	USC-A403	2	1	2-Pyridyl	5.69 ± 0.10	57.54% ± 0.31	7.92 ± 0.21
11d	USC-A404	2	1	2-Pyrimidyl	31.56% ± 0.12	60.51% ± 0.12	5.82 ± 0.12
11f	USC-A406	2	1	2,3-Dichlorophenyl	5.75 ± 0.19	7.94 ± 0.52	6.79 ± 0.26
11g	USC-A407	2	1	2-Chlorophenyl	6.46 ± 0.22	7.45 ± 0.10	8.17 ± 0.16
11h	USC-A408	2	1	3-Methoxyphenyl	6.37 ± 0.30	6.80 ± 0.11	7.39 ± 0.14
12a	USC-B401	2	2	2-Methoxyphenyl	5.57 ± 0.26	8.44 ± 0.17	8.80 ± 0.35
12b	USC-B402	2	2	4-Methoxyphenyl	47.47% ± 5.10	59.02% ± 0.73	7.39 ± 0.08
12c	USC-B403	2	2	2-Pyridyl	6.55 ± 0.34	6.64 ± 0.05	6.40 ± 0.21
12d	USC-B404	2	2	2-Pyrimidyl	5.06 ± 0.14	6.82 ± 0.24	6.20 ± 0.16
12f	USC-B406	2	2	2,3-Dichlorophenyl	5.76 ± 0.31	7.44 ± 0.07	7.84 ± 0.17
13a	USC-A501	3	1	2-Methoxyphenyl	6.01 ± 0.12	7.69 ± 0.09	7.49 ± 0.18

[a] All values are means of two or three separate competition experiments.

or **12a**, respectively. While the affinity for D_2 receptors increased with the linker extension, selectivity by the D_3 receptors decreased. In the only pentyl case studied (**13a**), the use of a five carbon bridge produced a decrease in the affinity for the D_3 receptors and a moderate increase in the affinity for the D_1 receptor, when compared with the butyl compound **11a**.

The analysis of the structural models obtained for the complexes between ligands of the propyl and butyl series and the D_2 and D_3 receptors suggests an explanation for the experimental results observed. In all of the structures obtained, the same key interactions were observed: besides the well-known salt bridge (D3.32), which is essential for ligand binding, the aryl ring is fixed in a hydrophobic sandwich consisting of V3.33 and F6.52 and the polar aryl substituents interact with the Ser residues in TM5. The benzolactam ring is directed towards the TM 2, 1, 7 regions and is laterally stabilized by a hydrophobic interaction with L2.64 and Y7.35 in both sides of the pocket. In the ligands with a butyl linker (like **11a** in Fig. 3, in grey), the benzolactam ring can establish a H-bond between the carbonyl oxygen of the benzolactam and the side chain of H-bond donor residues in TM7 (T7.39 in D_2 and S7.36 in D_3). On the other hand, the compounds with a propyl linker (like **5a** in Fig. 3, in green) orient the benzolactam carbonyl oxygen in a different position from which it is not possible to establish an equivalent H-bond neither in the D_2 nor in the D_3 receptor. As a consequence of this lack of polar anchorage, the docking simulation results suggest alternate poses for some propyl compounds, in which the lactam moiety is directed either upwards or downwards and out of the common binding pocket.

Another aim of this work was to study the influence of the lactam ring size on the affinity of the dopamine receptors and the selectivity of these compounds. On D_3 receptors, increasing the size of the lactam ring from 6 to 7 members produced, in all cases of available data (except **11c** → **12c**), a slightly positive effect on affinity. In addition, the series **5b** → **6b** → **7b** seems to indicate that the optimum size of the lactam ring for affinity to the D_3 receptors would be 7 members. On D_2 receptors, the effect is similar to the previous case: increasing the size of the lactam ring from 6 to 7 produces an advantageous effect on affinity. One exception is the compound **11f**, where the expansion of its lactam ring from 6 to 7 members resulted in a drop in the affinity. As for the effect on the D_1 receptors, we can say that, in most cases, there was no significant change in the affinity. As regards the selectivity, the compounds bearing a six-membered lactam were generally more D_3 selective than derivatives with a lactam of seven members. The exception was found in the derivative **12b**, which has a relatively high affinity for D_3 (K_i = 40 nM, pK_i = 7.39) while lacking an affinity for D_1 or D_2 receptors.

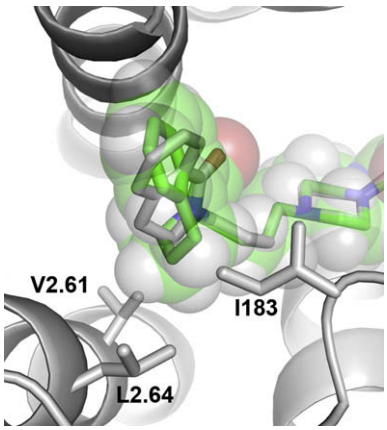


Figure 4. Complex of D_2 receptor with **11a** (in grey) and **12a** (in green, with a CPK representation superimposed). The seven member lactam ring present in **12a** interacts better with the hydrophobic residues shown in the figure (V2.61, L2.64 and I183).

An observation of the structural models obtained for the complexes suggested that the minor positive effect of the lactam ring size (six- or seven-membered ring) on the D_2 and D_3 receptor affinity could be explained by the slightly more favourable contacts of the seven-membered lactam ring compounds with the nearby hydrophobic residues than the equivalent six-membered ring compounds. This is illustrated in Figure 4, the structure of **11a** (grey) and **12a** (green) in complex with D_2. The aliphatic carbons of the seven-membered ring are located closer to the V2.61, L2.64 and the I1.83, located in the extracellular loop 2 (the residue of the binding site not conserved between the D_2 and D_3 receptors). Interestingly, the effect on the antagonist affinity of V2.61F[27] and L2.64S[27] mutations in the D_2 receptor supports our finding. Furthermore, mutational studies of the I1.83 indicate that, due to the observed impact on the ligand binding, this residue should be close to the core of the binding pocket.[28]

In looking at the influence of the phenylpiperazine moiety, we have analysed eight *N*-substituted piperazines with aryl or heteroaryl groups: 2-methoxyphenyl, 3-methoxyphenyl, 4-methoxyphenyl, 2-pyridyl, 2-pyrimidyl, 3-trifluoromethylphenyl, 2-chlorophenyl, and 2,3-dichlorophenyl. The aryl groups that produced a greater affinity for the D_3 receptor were the 2-methoxyphenyl, 2-chlorophenyl and 2,3-dichlorophenyl. Moreover, the substituents of the piperazine ring that led to a greater selectivity of the D_3 over D_2 were 2-pymimidyl, and especially 4-methoxyphenyl.

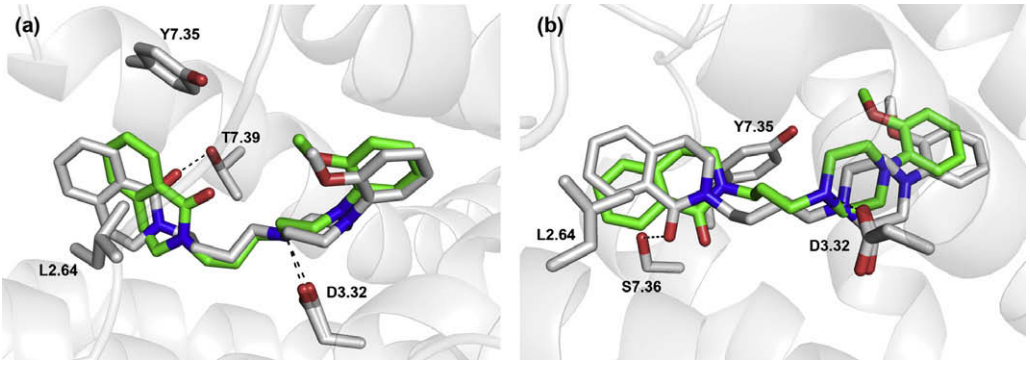


Figure 3. (a) Complexes of the D_2 receptor with **11a** (in grey) and **5a** (in green). (b) Complex of the D_3 receptor with **11a** (in grey) and **5a** (in green). The figure illustrates how compounds with a butyl linker (like **11a**) are able to establish H-bonds with polar residues of the seventh helix in both the D_2 (T7.39) and the D_3 receptors (S7.36), which are not observed in complexes of compounds with a propyl linker (like **5a**). The position of the residue D3.32 is shown as reference.

In the compounds bearing a methoxyphenylpiperazine, the position of the methoxy group in the aromatic group critically influences the selectivity and affinity for dopamine receptors. For example, on the D_2 receptor, the pK_i values of the 2-methoxyphenylpiperazines **11a** and **12a** were 7.91 and 8.44, respectively, while its position isomers, the 4-methoxyphenylpiperazines **11b** and **12b**, showed no affinity for this receptor. The same can be said for the isomers **6a** (pK_i = 6.10) and **6b** (pK_i < 4), which carry a propyl bridge. Displacement of the methoxy group in the aromatic ring from position 2 to 4 produced, in all cases, a decrease in the affinity for the three receptors, though selectivity of the D_3 receptors increased significantly. This indicates that the change of the location of the methoxy group is far more detrimental for D_1 and D_2 than for D_3 receptor binding.[29] Thus, the compound that was most selective for D_3 was **12b**, as it had an affinity for this receptor more than 1000-fold higher than it had for D_1 or D_2. The location of the methoxy in position 3 leads to a compound (**11h**) with D_2 and D_3 affinities that are intermediate between those of its position 2 (**11a**) and position 4 (**11b**) isomers.

Considering that serotonin antagonism at 5-HT_{2A} receptors has been reported to improve the negative symptoms of schizophrenia and to reduce the occurrence of extrapyramidal side effects[30] and bearing in mind that a preferential blockade of D_3 versus D_2 receptors is associated with a relatively benign effect upon motor function as compared with drugs possessing D_2/D_3 or principally D_2 antagonist properties,[5,31] compounds **11a**, **11g**, **12a** and **12f**[32] were selected among the new compounds. This is because (a) their K_i values <50 nM (or pK_i > 7.30) at both D_2 and D_3 receptors, and (b) they have a higher affinity to D_3 than to D_2 receptors (2.2- to 5.2-fold). These chosen compounds were examined further for binding affinity toward 5-HT_{2A} receptors by competing against [^{3}H]ketanserin (Table 2).

Compound **12f** showed the highest affinity for the 5-HT_{2A} receptors (pK_i = 7.98, K_i = 10 nM), followed by **11g** and the 2-methoxyphenyl derivatives **11a** and **12a**. Although the set of compounds is small and limits the conclusions we may draw, it can be said that the presence of chlorine atoms in the aromatic ring and a larger size of the lactam favour the affinity at this receptor. It is noteworthy that those compounds with higher affinities for D_2 and D_3 receptors (**11a** and **12a**) have the smallest affinities for the 5-HT_{2A} receptor, and vice versa. As far as their potential as antipsychotics, the 5-HT_{2A} affinity, even though not high, may help to reduce the occurrence of extrapyramidal side effects, especially for the compound **12f**. This compound is also the only one that shows greater affinity for 5-HT_{2A} than for the D_2 receptors (K_i ratio 5-HT_{2A}/D_2 = 3.4), a profile that has been related to a potential behaviour as atypical antipsychotic.[33] A multi-target binding profile of these compounds and in vivo pharmacological assays to determine their antipsychotic activity and potential side effects are in progress, and will be reported in due course.

In summary, we have synthesized a series of 26 new compounds with two fragments, a benzolactam and an arylpiperazine, linked by a propyl or butyl chain, and determined their affinities at the D_1, D_2, and D_3 receptors. Some of these compounds, for example **11a** and **12a**, showed a high D_2 and D_3 affinity and good selectivity over the D_1 receptor. Moreover, **12b** displayed a D_3 affinity in the nanomolar range and a high selectivity over D_1 and D_2. The SAR study on these compounds revealed that both the length of the bridge between the benzolactam and the piperazine and the size of the lactam ring decisively influenced their D_2 and D_3 affinities. Selected compounds showed moderate 5-HT_{2A} binding affinity, which could help to reduce the occurrence of extrapyramidal side effects should the compounds be used as antipsychotics. These data significantly improve our understanding of the D_3 pharmacophore and are expected to lead to novel approaches for the treatment of schizophrenia. Further optimization of this series will be reported in due course.

Table 2
Human D_2, D_3 and 5-HT_{2A} receptor binding affinities (pK_i) of compounds **11a**, **11g**, **12g**, and **12f**[a]

Compound	D_2	D_3	D_2/D_3 K_i ratio	5-HT_{2A}
11a	7.91 ± 0.30	8.58 ± 0.16	4.7	6.32 ± 0.07
11g	7.45 ± 0.10	8.17 ± 0.16	5.2	7.02 ± 0.05
12a	8.44 ± 0.17	8.80 ± 0.35	2.2	6.75 ± 0.27
12f	7.44 ± 0.07	7.84 ± 0.17	2.5	7.98 ± 0.06

[a] All values are means of two or three separate competition experiments.

Acknowledgments

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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.2009.01.067.

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32. Data for selected compounds: Compound **11a**: Yellow solid, mp 107–108 °C (cyclohexane); IR (KBr) 2933, 2817, 1647, 1499, 1307, 1240: ^{1}H NMR ($CDCl_3$) δ 8.06 (dd, 1H, J = 7.6, 1.5), 7.41–7.31 (m, 2H), 7.15 (dd, 1H, J = 7.4, 0.6), 6.98–6.82 (m, 4H), 3.84 (s, 3H), 3.61–3.52 (m, 4H), 3.07 (b.s., 4H), 2.96 (t, 2H, J = 6.6), 2.63 (b.s., 4H), 2.47–2.42 (m, 2H), 1.70–1.58 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 164.7, 152.7, 141.7, 138.3, 131.9, 130.0, 128.6, 127.4, 127.2, 123.3, 121.4, 118.6, 111.6, 58.8, 55.7, 53.8, 51.0, 47.7, 46.5, 28.6, 26.2, 24.3; APEI-MS *m/z* 393 (M^+, 14), 378 (36), 231 (100), 205 (82), 180 (35), 160 (19).Compound **11g**: Yellow-orange oil; IR (film) 2938, 2818, 1708, 1646, 1586, 1481, 1448, 1341, 1307, 1231; ^{1}H NMR ($CDCl_3$) δ 8.04 (dd, 1H, J = 7.6, 1.2), 7.38–7.28 (m, 3H), 7.19–1.11 (m, 2H), 6.99 (dd, 1H, J = 8.1, 1.4), 6.91 (td, 1H, J = 7.6, 1.4), 3.59–3.55 (m, 4H), 3.53–3.48 (m, 2H), 3.04 (s, 4H), 2.94 (t, 2H, J = 6.6), 2.61 (s, 4H), 2.45–2.41 (m, 2H), 1.68–1.53 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 164.0, 149.0, 137.7, 131.2, 130.3, 129.4, 128.4, 127.9, 127.3, 126.7, 123.4, 120.1, 58.0, 53.1, 51.2, 50.9, 46.9, 45.8, 27.9, 25.5, 24.0; APEI-MS *m/z* 397 (M^+, 5), 382 (16), 257 (57), 231 (100), 209 (84), 160 (34).Compound **12a**: Yellow solid, mp 107–108 °C; IR (KBr) 2929, 1626, 1475, 1362, 1240; ^{1}H NMR ($CDCl_3$) δ 7.22 (dd, 1H, J = 7.2, 1.8), 7.38–7.28 (m, 2H), 7.14–7.11 (m, 1H), 7.02–6.88 (m, 3H), 6.87–6.84 (m, 1H), 3.86 (s, 3H), 3.63–3.58 (m, 2H), 3.21 (t, 2H, J = 6.4), 3.11 (b.s., 4H), 2.79 (t, 2H, J = 7.1), 2.67 (b.s., 4H), 2.50–2.46 (m, 2H), 2.03 (q, 2H, J = 6.8), 1.75–1.50 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 171.1, 153.1, 140.1, 136.0, 137.5, 131.2, 128.9, 128.7, 127.4, 124.1, 121.5, 119.1, 111.7, 58.1, 55.8, 53.3, 49.2, 46.9, 46.7, 30.7, 30.3, 26.9, 25.9; APEI-MS *m/z* 407 (M^+, 8), 392 (33), 245 (100), 205 (92), 162 (20), 128 (40), 91 (30).Compound **12f**: Brownish oil; IR (film) 2938, 2821, 1635, 1574, 1451; ^{1}H NMR ($CDCl_3$) δ 7.65 (dd, 1H, J = 7.21, 1.8), 7.37–7.28 (m, 2H), 7.14–7.10 (m, 3H), 6.95 (dd, 1H, J = 6.2, 3.3), 3.59 (t, 2H, J = 7.1), 3.20 (t, 2H, J = 6.4), 3.09 (d., 4H, J = 4.5), 2.78 (t, 2H, J = 7.1), 2.67 (b.s., 4H), 2.53–2.48 (m, 2H), 2.02 (q, 2H, J = 6.8), 1.70–1.61 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 162.0, 151.5, 137.6, 136.5, 134.5, 131.1, 128.9, 128.7, 128.5, 127.8, 127.3, 125.0, 119.0, 58.62, 53.7, 51.8, 51.6, 47.5, 46.6, 30.7, 30.4, 24.6; APEI-MS *m/z* 445 (M^+, 0.28), 245 (100), 174 (20).
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