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A Novel Series of Hybrid Compounds Derived by Combining 2-Aminotetralin and Piperazine Fragments: Binding Activity at D_2 and D_3 Receptors

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Abstract—A series of 7-hydroxy-2-[*N*-alkyl-(*N*-(4-phenylpiperazine)-alkyl)amino]tetralins was developed based on a novel hybrid approach that combined 2-aminotetralin and arylpiperazine pharmacophoric moieties. Our preliminary study revealed that a four-methylene butyl linker produced very potent compounds for both the D_2 and D_3 receptors. Further structure–activity studies led to a novel template showing 50- to 100-fold selectivity for the D_3 receptor.

Enormous progress has been made over the last three decades in the development of drugs specific for dopamine receptor subtypes and at the same time novel pharmacology for the characterization of these drugs has also been developed.[1–3] In addition, in 1990 a new subtype of dopamine receptor was discovered which is now known as D_3 receptor, cloned from rat complementary DNA library using probes derived from the D_2 receptor.[4,5] This dopamine D_3 receptor possesses a high degree of primary structural homology with the D_2 receptor subtype and exhibits similar pharmacological properties.[4] Subsequently, the human version of this receptor was also cloned.[5]

The problems associated with therapies of neurological disorders involving D_2-specific drugs are the production of extrapyramidal side effects. These undesirable side effects are believed to originate in the blockade of D_2 receptors in the striatal region of the brain.[6] Importantly, studies showed that the localization of D_3 receptors in the brain is different from D_2 receptors. In situ D_3 hybridization studies of human brain showed its dominant presence in the nucleus accumbens area and islands of Calleja, along with moderate expression in the caudate and putamen.[7] Due to the predominant limbic location of D_3 receptor in the central nervous system, selective D_3-specific antagonists and agonists are expected to have therapeutic applications in the treatment of psychiatric disorders and neurodegenerative diseases with much less undesirable side effects.[8,9] In recent studies, it has been shown that D_3-specific compounds might have a therapeutic use in the treatment of cocaine addiction.[10–12]

Since the discovery of the D_3 receptor, substantial efforts have been directed towards the development of molecules selective for D_3 versus D_2 receptors.[4] Historically 2-aminotetralins have been regarded as potent and selective agonists for D_2-type receptors.[13,14] Recently, 7-OH-DPAT and PD 128907 (Fig. 1) were

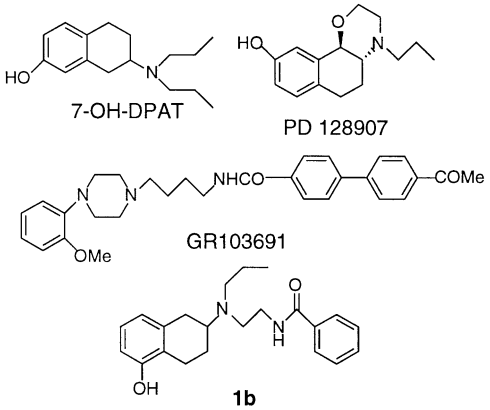

Figure 1. Chemical structures of D_3 receptor preferring ligands.

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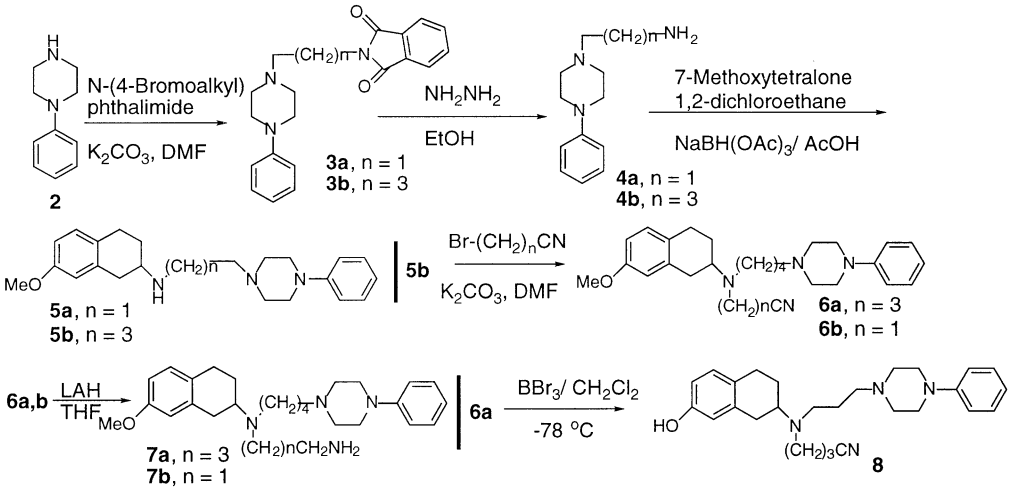
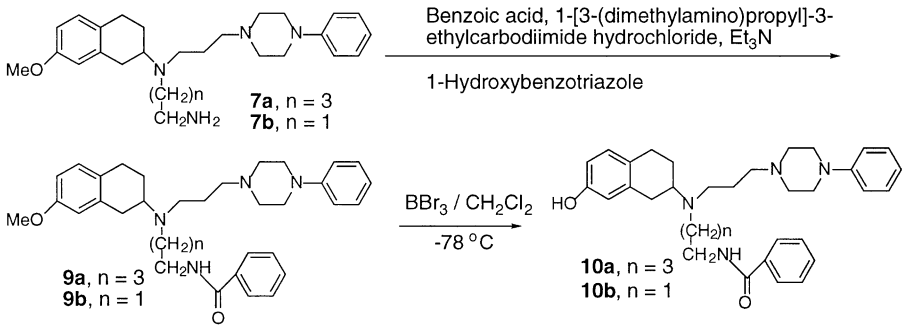


Scheme 1.



Scheme 2.

evaluated in binding studies for D_2 and D_3 receptor subtypes by a number of authors. In general they were shown to have preferential affinity at the D_3 receptor and the degree of selectivity was dependent upon the assay conditions, transfected cell lines or tissue used and the radioligands employed.[9,15] Recently a novel series of arylpiperazine compounds was developed and evaluated for D_2/D_3 receptors binding.[16,17] Some of these compounds were found to have a high affinity and selectivity for the D_3 receptor. GR103691 was identified as one of the compounds in this class with high affinity for the D_3 receptor.[16] In another recent study, a highly selective ligand **1b** (Fig. 1) was developed by incorporating aminotetralin and benzamide moieties together.[18]

In our ongoing effort to develop selective and novel ligands for D_2/D_3 receptors, we decided to proceed with a hybrid structure strategy. Thus, we combined the aminotetralin pharmacophoric fragment with the aryl-substituted piperazine moiety with varying substitutions on the N-atom. It was envisioned that incorporation of the substituted piperazine molecular fragment into the aminotetralin moiety, as represented in Figure 2, should produce a novel template for the generation of compounds with selective affinity for dopaminergic receptor subtypes. One of our goals was to determine the effect of different methylene linker size, different aromatic substitutions, and different substitutions on the N-atom, upon binding affinity and selectivity for the D_3 receptor. Such structural optimization in these hybrid molecules may allow interactions with accessory binding sites in these receptors to impart selectivity. In this report, we describe the design, synthesis and biological characterization of such analogues.

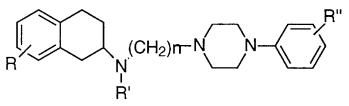
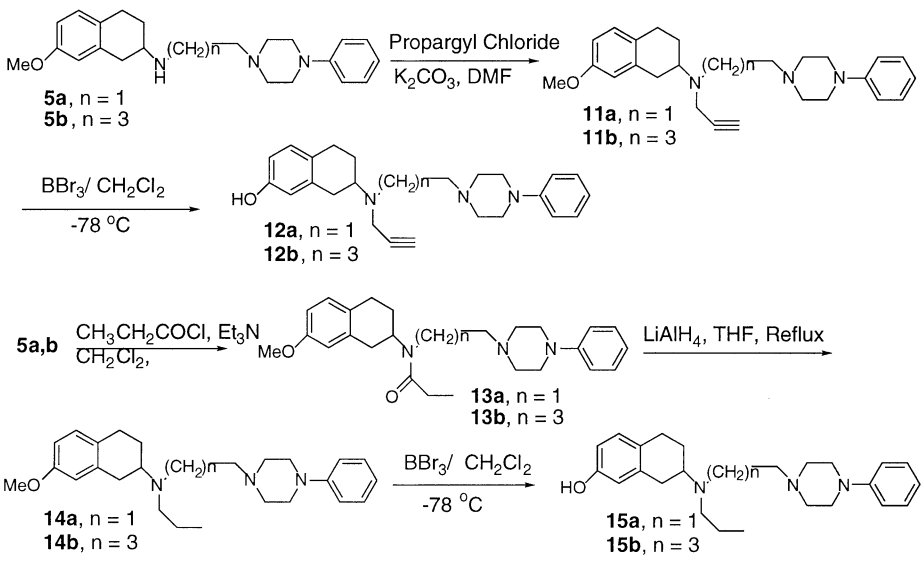


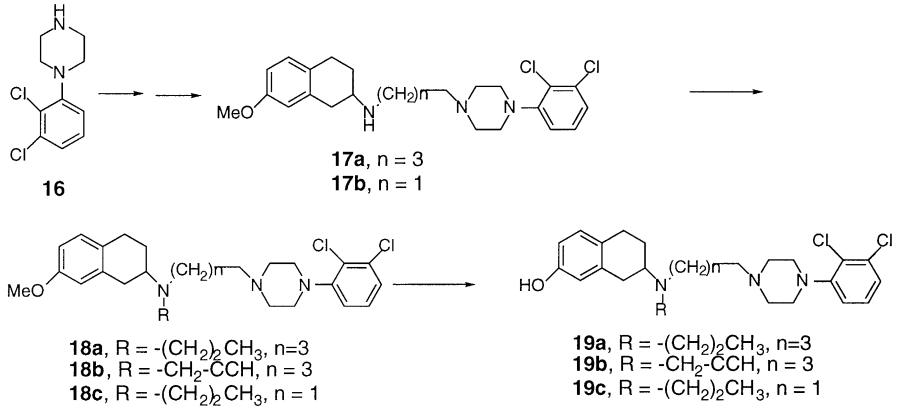
Figure 2. General structures of the novel molecular template.

The syntheses of our target compounds are described in Schemes 1–4.

N-Alkylation of phenylpiperazine with *N*-(4-bromoalkyl)phthalimide in the presence of a base furnished **3a**,**b** which on reaction with hydrazine produced amines **4a**,**b**. Reductive amination reaction of amine **4a**,**b** with 7-methoxytetralone under standard conditions furnished amines **5a**,**b** in 80–85% yield. *N*-Alkylation with different bromoalkylcyanides resulted in cyano compounds **6a**,**b** which were converted into amines **7a**,**b** by reaction with lithium aluminum hydride (Scheme 1). Demethylation of **6a** with BBr_3 produced the final compound **8**. Conversion of amines **7a,b** to benzamide derivatives followed by demethylation produced the final targets **10a**,**b** (Scheme 2). Similarly, alkylation of **5a**,**b** with propargyl bromide produced *N*-alkylated derivatives which on demethylation produced the final target compounds **12a**,**b**. *N*-Acetylation of **5a**,**b** followed by



Scheme 3.



Scheme 4.

reduction with lithium aluminum hydride furnished **14a,b**. Demethylation of **14a**,**b** produced the final **15a**,**b** (Scheme 3).[19] The dichloro compounds **19a**,**c** were synthesized using the methods described in Schemes 1 and 3 (Scheme 4).

The activity of the 2-aminotetralin class of compounds for D_2/D_3 receptors has been known for some time. Recently, a novel series of piperazine and modified 2-aminotetralins was shown to have preferential activity at the D_3 receptor. In our effort to design and develop new analogues for D_2/D_3 receptors, we decided to combine the pharmacophoric elements of 2-aminotetralins with piperazine derivatives by a linker to design a novel series of piperazine moiety derived aminotetralin compounds. Our initial effort resulted in the design and synthesis of two novel compounds, **12b** and **15b**. In designing **10a**,**b** we decided to incorporate an additional benzamide moiety into our structural base. In a recently reported work, it has been demonstrated that the benzamide derivatives of 2-aminotetralin compounds exhibit preferential affinity for the D_3 receptor.[18] Thus, it was perceived that an additional amide linkage should enhance the binding of these novel analogues for D_3 receptors by accessing the additional binding domains in the receptor, potentially playing a role in selectivity as well. The design of compound **8** originated from our own results, which demonstrated that the presence of a cyanopropyl substituent led to an increase in selectivity for the D_3 receptor.[20]

These compounds were characterized for their binding at the cloned human dopamine D_2 and D_3 receptor subtypes.[21] Compounds **15b** and **12b**, which contained a 4-methylene-long linker, exhibited weak potency for the D_2 and high affinity for the D_3 receptors (Table 1) while exhibiting moderate selectivity for the D_3 receptor. On the other hand, compound **15a**, which contained the 2-methylene linked carbon chain length, was more selective and potent at the D_3 receptor. As such, **15a** was the most selective compound in its racemic form in this series. The replacement of the phenyl group in **12b** and **15b** by a 2,3-dichlorophenyl moiety resulted in **19a**,**b**, which showed improved potency for the D_2 receptor compared to their unsubstituted phenyl counterparts. At the same time their potency for the D_3 receptor was unaffected, resulting in lowered selectivity for the D_3 receptor. However, compound **19c**, which had the two

Table 1. Inhibition constants for binding to the cloned D_{2L} and D_3 receptors expressed in HEK cells by displacing [^{3}H]spiperone. Results are means ± SEM for three experiments each performed in triplicate

Compd	D_{2L} HEK Cells [^{3}H]spiperone K_i (nM)	D_3 HEK Cells [^{3}H]spiperone K_i (nM)	D_{2L}/D_3
8	622 ± 102	50.2 ± 7.1	12.4
10a	782 ± 42	756 ± 48	1
10b	354 ± 2	55.7 ± 5.5	6.3
12a	245 ± 26	14.2 ± 1.7	17.2
12b	68.4 ± 7.6	1.40 ± 0.14	48.9
15a	213 ± 26	1.75 ± 0.34	121.7
15b	114 ± 8	3.79 ± 0.40	30
19a	8.78 ± 0.81	2.26 ± 0.50	3.8
19b	7.37 ± 0.27	3.59 ± 0.58	2.0
19c	27.4 ± 1.0	1.13 ± 0.04	24.2

methylene linker chain, was more potent and selective at the D_3 receptor compared to **19a**,**b**. These results are different from previous observations in a different series of compounds, indicating that the presence of the 2,3-dichlorophenyl moiety imparted more selectivity for D_3 receptors previously.[22]

The amide piperazines **10a**,**b** had a weak binding affinity for the dopamine receptor subtypes, while the cyano compound **8** showed some modest binding activity (Table 1).

In this report, we have carried out a brief SAR study with hybrid piperazine–aminotetralin molecules. Our results indicated that the compounds with a 2-methylene linker as in racemic **15a** showed high binding activity at the D_3 receptor while being more selective for D_3 over D_2 receptors. It is evident from our results that the length of methylene chain linker played an important role in selectivity. This might indicate subtle differences in molecular structures between these two receptor subtypes, which could have been exploited for more favorable interactions by the shorter 2-methylene linker compound with the D_3 receptor. We plan to carry out the functional activities in the future to evaluate for agonist, antagonist, and partial agonist properties of these compounds for D_2/D_3 receptors. We are now currently exploring this newly developed template to generate further analogues for selective action at dopamine receptor subtypes.

Acknowledgements

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19. All new compounds exhibited satisfactory spectral and elemental analysis data. 7-Hydroxyl-2-[*N*-propyl-(*N*-(4-phenylpiperazin-1-yl)-ethyl)amino]tetralin **15a**. ^{1}H NMR ($CDCl_3$) 0.86–0.91 (t, J = 7.2 Hz, 3H, $CH_3CH_2CH_2N$), 1.43–1.50 (m, 4H), 1.89–1.93 (m, 2H), 2.46–2.51 (t, J = 7.5 Hz, 2H, NCH_2), 2.53–2.68 (m, 6H), 2.70–2.74 (t, J = 4.8 Hz, $4HN(CH_2)_2$), 2.83–2.88 (m, 1H), 3.23–3.26 (t, J = 4.8 Hz, 4H, $N(CH_2)_2$), 6.45–6.56 (m, 2H, Ar-H), 6.83–6.93 (m, 4H, Ar-H), 7.23–7.26 (m, 2H, Ar-H). Free base was converted into its HCl salt, mp 143–146 °C. Anal. ($C_{27}H_{35}N_3O \cdot 3HCl \cdot 0.9H_2O$) calcd: C, 57.83; H, 7.72; N, 8.09; Found: C, 57.88; H, 7.52; N, 7.90.
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