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Design, synthesis, and evaluation of hexahydrobenz[*f*]isoquinolines as a novel class of dopamine 3 receptor ligands

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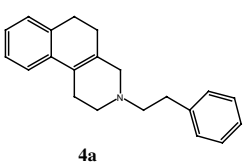
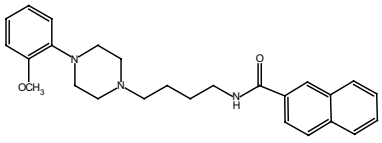
Abstract—We previously identified hexahydrobenz[*f*]isoquinoline (**4a**) as a new class of dopamine 3 receptor (D_3) ligand. Herein, we described the design, synthesis, and preliminary structure–activity relationships of new analogues of **4a** as a novel class of D_3 ligands. Among these new analogues, compound **4h** is a potent D_3 ligand (K_i = 6.1 nM) and has a selectivity of 133-fold between D_3- and D_2-like receptors, and of 163-fold between D_3- and D_1-like receptors, respectively. Thus, compound **4h** represents a promising new lead compound for further design and optimization toward achieving highly potent and selective D_3 ligands.

Dopamine receptors belong to the G-protein coupled receptors (GPCR). The dopamine 3 (D_3) subtype receptor has been implicated in several neurological conditions, and potent and selective D_3 ligands may have the therapeutic potential for the treatment of drug addiction, Parkinson's disease, and schizophrenia.[1–3] Accordingly, there has been an enormous research interest in the design and development of novel, potent, and selective D_3 ligands in recent years.[3–10]



4a



BP897

Although several classes of D_3 ligands have been discovered in the last decade, many of the previously reported D_3 ligands were derived from the very limited number of basic core structures.[4] Indeed, the majority of those recently reported selective D_3 ligands were based upon the core structure of BP897.[6–9] Accordingly, D_3 ligands with novel chemical core structures or scaffolds would have considerable value to increase the chemical diversity in D_3 ligand design and may lead to the development of highly potent and selective D_3 ligands with different in vitro and in vivo pharmacological properties. Potent and highly selective D_3 ligands with novel chemical scaffolds may serve as additional pharmacological tools to investigate the potential role of the D_3 receptor in several neurological conditions and may be developed as potentially useful therapeutic agents for the treatment of drug addiction, Parkinson's disease, and schizophrenia. To this end, we have employed a novel computational three-dimensional database screening strategy to discover novel D_3 ligands.[10]

Compound **4a** was identified as a novel D_3 ligand using a computational three-dimensional database searching strategy.[10] This compound has a novel tricyclic hexahydrobenz[*f*]isoquinoline core structure that is not found in other known D_3 ligands.[4] In our in vitro binding assays, **4a** has a K_i value of 84 nM for its binding affinity to the D_3 receptor and a moderate selectivity over the D_1- and D_2-like receptors, being 10- and 39-fold, respectively (Table 1). Compound **4a** represents a

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Table 1. Binding affinities of novel and reference compounds at D_1-, D_2-, and D_3-like receptors in binding assays using rat brain

Ligands	K_i (nM)[a]			Selectivity	
	D_1-like [^{3}H]SCH 23390[b]	D_2-like [^{3}H]spiperone[c]	D_3 [^{3}H]PD 128907[d]	D_1-like/D_3	D_2-like/D_3
4a	819 ± 96	3290 ± 441	84 ± 13	10	39
4b	n.t.[e]	n.t.	103	—	—
4c	696 ± 58	59 ± 4	74 ± 5	9	1
4d	n.t.	n.t.	183	—	—
4e	1117 ± 120	84 ± 8	63 ± 10	18	1
4f	1566 ± 155	122 ± 11	25 ± 5	62	5
4g	1055 ± 83	46 ± 11	38 ± 13	28	1
4h	993 ± 123	811 ± 43	6.1 ± 1.3	163	133
BP897	636 ± 103	162 ± 48	1.1 ± 0.2	578	147

[a] Data represent the mean ± SEM of 3–5 independent determinations.

[b] [^{3}H]SCH 23390 binding assays for D_1-like dopamine receptors were performed as previously described in detail[20] using membranes prepared from the caudate-putamen of adult male Sprague–Dawley rats (Harlan, Indianapolis, IN). All compounds were dissolved in 100% EtOH at a concentration of 5 mM. The assay buffer was 50 mM Tris–HCl, 5 mM KCl, 2 mM $MgCl_2$, and 2 mM $CaCl_2$, pH 7.4 at 23 °C; the concentration of [^{3}H]SCH 23390 (73 Ci/mmol; Amersham) was 0.3 nM; and nonspecific binding was determined in the presence of 1 μM (+)-butaclamol. Assay tubes were incubated at 23 °C for 90 min followed by rapid vacuum filtration. Data were analyzed using SigmaPlot 8.0.2 to determine K_i values using the K_D value for [^{3}H]SCH 23390 of 0.3 nM.[20]

[c] [^{3}H]spiperone binding assays were performed as previously described in detail[20,21] and as described for [^{3}H]SCH 23390 except the concentration of [^{3}H]spiperone (24 Ci/mmol; Amersham) was 0.2 nM. K_i values were determined using the K_D value for [^{3}H]spiperone of 0.1 nM.[21]

[d] [^{3}H]PD 128907 binding assays were performed as previously described in detail[20,22] using ventral striatal (nucleus accumbens and olfactory tubercles) membranes prepared in assay buffer (50 mM Tris, 1 mM EDTA; pH 7.4 at 23 °C). The concentration of [^{3}H]PD 128907 (116 Ci/mmol; Amersham, Arlington Heights, IL) was 0.3 nM; nonspecific binding was defined by 1 μM spiperone; and the incubation time was 3 h. K_i values were determined using the K_D value for [^{3}H]PD 128907 of 0.3 nM.[22]

[e] n.t.—not tested due to low affinity in the D_3 binding assay.

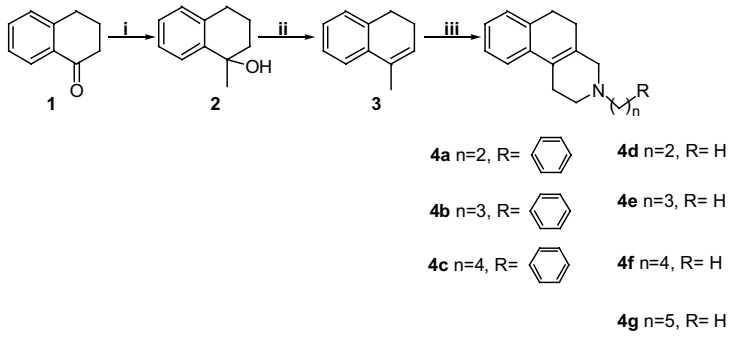
promising starting point for further optimization to improve its binding affinity to the D_3 receptor and its selectivity over the closely related D_1- and D_2-like receptors. In this paper, we wish to report the design, synthesis, and preliminary structure–activity relationship studies of a series of new analogues of **4a** as new ligands for the D_3 receptors and their selectivity over D_1- and D_2-like subtype receptors.

Compound **4a** may be divided into three segments, the tricyclic hexahydrobenz[*f*]isoquinoline core structure as the 'head', the phenyl ring as the 'tail', and the linker between the head and the tail. Compounds **4b** and **4c** were designed to test the influence of the length of the linker to the binding affinity and selectivity. Although **4a**, **4b**, and **4c** have similar affinities to the D_3 receptor, the selectivity of **4c** over the D_2-like receptor is significantly decreased as compared to **4a**, primarily due to its increased binding affinity at D_2-like receptors (K_i value changed from 3290 nM for **4a** to 59 nM for **4c** at D_2-like receptors).

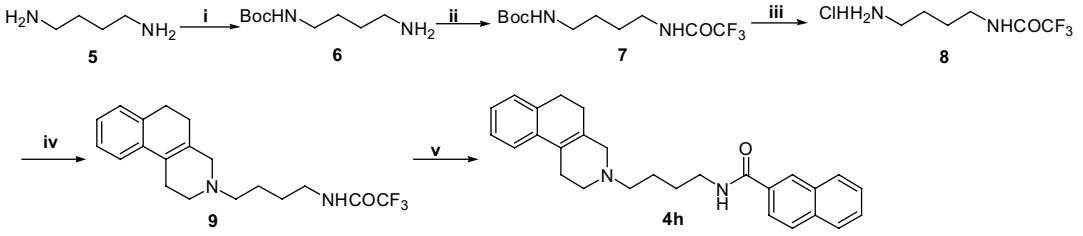
The diminished selectivity from **4a** to **4c** could be due to the change either in the direct interactions between the linker and the receptors, or in the interactions between the phenyl ring and the receptors, or in both. To clarify this point, several new analogues (**4d**–**g**) with different lengths of the linker but without the phenyl ring 'tail' were designed and synthesized. While compound **4d** is approximately two times less potent than **4a** to the D_3 receptor, compound **4e** is as potent as **4a**, and compounds **4f** and **4g** are three- and two times more potent than **4a**, respectively. Compound **4f** is also the most selective ligand among **4d**–**g**. These data suggest that the 'tail' primarily contributes to the selectivity by diminishing the binding of the ligands to D_2-like receptors.

To further test this idea, compound **4h** with a 2-naphthyl tail was designed and synthesized. Compound **4h** has a K_i value of 6.1 nM to the D_3 receptor. Furthermore, its binding affinity to the D_2 receptor is decreased by seven times as compared to **4f**, and 18 times as compared to **4g**. Interestingly, its binding affinity at D_1-like receptors remained virtually the same as compared to compounds **4f** and **4g**. As a result, compound **4h** has a selectivity of 163- and 133-fold over D_1- and D_2-like receptors, respectively. Hence, **4h** represents a novel, potent D_3 ligand with a good selectivity over D_1- and D_2-like receptors.

To directly compare **4h** with other known D_3 ligands, we have evaluated BP897, a known selective D_3 ligand,[3] in our assay conditions and the results are provided in Table 1. As can be seen, BP897 has K_i values of 1.1 nM at the D_3 receptor, 162 nM at the D_2-like receptors, and 636 nM at the D_1-like receptors, respectively. These values are in good agreement with the reported K_i values of 0.92 nM at the D_3 receptor, 61 nM at the D_2 receptor, and 3 μM at the D_1 receptor, respectively, using the CHO cells expressing recombinant human D_1, D_2, and D_3 receptors.[3] Of note, although it is known that assay conditions can have a significant influence on the binding affinity of a ligand at the D_3 receptor and the selectivity over other dopamine subtype receptors,[11] our results on BP897 show our assays using membranes prepared from rat brains and assays using CHO cells expressing recombinant human D_1, D_2, and D_3 appear to produce quite consistent results. Furthermore, our data indicate that BP897 and compound **4h** have a similar selectivity between the D_3 and D_2 receptors



Scheme 1. Synthesis of new analogues **4b–g**. Reagents and conditions: (i) 1.2 equiv MeMgBr, Et_2O, 0 °C then reflux for 0.5 h; (ii) *p*-toluenesulfonic acid, toluene, reflux, 4 h, yield 72% in two steps; (iii) CH_2O, RNH_3Cl, AcOH, H_2O, 6 h, yield 18–28%.



Scheme 2. Synthesis of compound **4h**. Reagents and conditions: (i) **5**/Boc_2O = 7:1, dioxane, room temperature (rt), overnight; (ii) 1.2 equiv trifluoroacetic anhydride, Et_3N, CH_2Cl_2, rt, overnight, yield 88% in two steps; (iii) AcCl, MeOH, rt, 10 h, quantitative; (iv) **3**, CH_2O, AcOH, H_2O, 6 h, yield 38%; (v) (a) K_2CO_3, MeOH, rt, overnight; (b) 1.2 equiv 2-naphthoyl chloride, Et_3N, CH_2Cl_2, 0° C, rt, 1 h, yield 83% in two steps.

(147-fold vs 133-fold) but BP897 is four times more selective than **4h** between the D_3 and D_1 receptors (578-fold vs 163-fold) under our assay conditions.

The synthesis of compounds **4a–g** is shown in Scheme 1.[12–14] Briefly, treatment of the 1-tetralone **1** with methylmagnesium bromide, followed by dehydration with *p*-toluenesulfonic acid in refluxing toluene, generated the corresponding 1-methyl-3,4-dihydronaphthalene **3**. Aminomethylation of **3** with the appropriate amine hydrochloride salt and formaldehyde in aqueous acetic acid afforded the hexahydrobenz[*f*]isoquinolines **4a–g**.

The synthesis of compound **4h** is provided in Scheme 2. Monoprotection of 1,4-diaminobutane was achieved by reacting an excess of the amine with Boc_2O in dioxane.[15] Upon protection of the primary amine in **6** with a trifluoroacetyl group,[16] the protected amine **7** was converted to the amine hydrochloride salt **8** using AcCl/MeOH.[17] Reaction of **8**, **3**, and formaldehyde in acetic acid yielded the hexahydrobenz[*f*]isoquinoline **9** using the same procedure as described in Scheme 1. The target compound **4h**[18] was obtained by treatment of **9** first with K_2CO_3 in MeOH[19] and then with 2-naphthoyl chloride.

In summary, starting from a novel D_3 ligand **4a** with a good affinity (K_i = 84 nM) to the D_3 receptor and moderate selectivity over D_1- and D_2-like receptors, several new analogues have been designed, synthesized, and tested for their binding affinity at the D_1-, D_2-, and D_3-like receptors. Among them, compound **4h** is a very potent D_3 ligand (K_i = 6.1 nM) and has a good selectivity of 163- and 133-fold between D_3- and D_1-like receptors, and between D_3- and D_2-like receptors, respectively. Hence, compound **4h** represents a promising lead compound for further optimization toward obtaining novel, highly potent, and selective D_3 ligands.

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