Bioorganic & Medicinal Chemistry Letters xxx (2018) xxx–xxx

Contents lists available at ScienceDirect

Bioorganic & Medicinal Chemistry Letters

journal homepage: www.elsevier.com/locate/bmcl

Synthesis of 3-(3-hydroxyphenyl)pyrrolidine dopamine D_3 receptor ligands with extended functionality for probing the secondary binding pocket

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ARTICLE INFO

Article history:
Received 17 January 2018
Revised 14 March 2018
Accepted 29 March 2018
Available online xxxx

Keywords:
Dopamine receptors
Dopamine D_3 receptor selectivity
D_3 secondary binding pocket
Homologous series
Structure-activity relationships

ABSTRACT

A series of 3-(3-hydroxyphenyl)pyrrolidine analogues which incorporate *N*-alkyl groups and *N*-butylamide-linked benzamide functionality have been synthesized and their in vitro binding affinities at human dopamine receptors have been evaluated. Our ligand design strategy was to take the 3-(3-hydroxyphenyl)pyrrolidine scaffold and extend functionality from the orthosteric binding site to the secondary binding pocket for enhancing affinity and selectivity for the D_3 receptor. The *N*-alkyl analogues constitute a homologous series from *N*-pentyl to *N*-decyl to probe the length/bulk tolerance of the secondary binding pocket of the D_3 receptor. Enantiomeric 3-(3-hydroxyphenyl)pyrrolidine analogues were also prepared in order to test the chirality preference of the orthosteric binding site for this scaffold. Benzamide analogues were prepared to enhance affinity and/or selectivity based upon the results of the homologous series.

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Since its discovery and cloning in the early 1990 s, the dopamine D_3 receptor (D_3R) has emerged as a key target for the development of selective dopamine agonists for treating Parkinson's disease (PD).[1] While dopamine D_2 receptor (D_2R) stimulation has long been thought to be necessary for the attenuation of motor dysfunction in PD, a number of the currently important dopamine agonists (e.g. pramipexole **1**) actually have greater affinity for the D_3R subtype.[1b,2] In addition to the relief of PD motor symptoms, D_3R activation is directly associated with downstream neuroprotective and neurorestorative signaling.[3] Accordingly, D_3R selective agonists may also enforce a disease-modifying mode of action by the partial restoration of the function of the damaged nigrostriatal neuronal connections in PD. In addition, recent studies have determined that D_3R antagonists and partial agonists may also be used to treat schizophrenia and substance abuse disorders.[4] Thus, the D_3R has emerged as a key biological target for the therapeutic manipulation of a variety of neurological conditions associated with an imbalance in dopamine levels.

With these considerations in mind, we have been working to reinvestigate the known 3-(3-hydroxyphenyl)pyrrolidine scaffold and extend structure–activity relationship (SAR) studies for this basic core structure for the purpose of developing novel D_3R binding ligands. 3-(3-Hydroxyphenyl)pyrrolidines were first reported by Hacksell[5] and later investigated by Crider[6] as potential alternatives to the well-known 3-(3- hydroxyphenyl)piperidine dopaminergics, such as (*S*)-3-(1-propylpiperidin-3-yl)phenol (3-PPP) **(2)**. Elegant studies which characterized the D_1R and D_2R binding activity of a number of 3-(3-hydroxyphenyl)piperidine and 3-(3-hydroxyphenyl)-pyrrolidine derivatives, through in vivo pharmacological methods (biochemical, motor function, and behavioral assays), were reported several decades ago.[5,7] As such, many of these important lead molecules were evaluated prior to the cloning of the D_3R.[1a] Remarkably, more recent studies have shown that 3-PPP **(2)** and the related *N*-propyl-3-(3-hydroxyphenyl)pyrrolidine **(3)** show significant affinity for the D_3R (Fig. 1).[8,9] While the clinical development of D_3R-preferring agonists like pramipexole (from an alternative structural class) overshadowed the earlier interest in analogues like **2** and **3**, we feel that there is still significant opportunity for further discovery of new selective D_3R agonists through extending SAR studies of the 3-(3-hydroxyphenyl)pyrrolidine scaffold.

The nearly identical orthosteric binding site (OBS) and the high sequence identity (78%) in the transmembrane domain has been viewed as an impetus to look beyond the primary catecholamine pharmacophore for achieving selectivity for the D_3R over the D_2R.[1d–f,10] Analysis of the D_3R crystal structure (in complex with the selective D_2/D_3 antagonist eticlopride)[11] and recent homology modeling studies have identified differences in a secondary

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https://doi.org/10.1016/j.bmcl.2018.03.084
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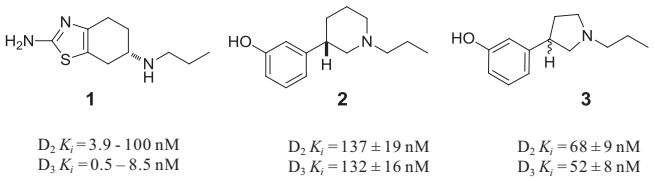


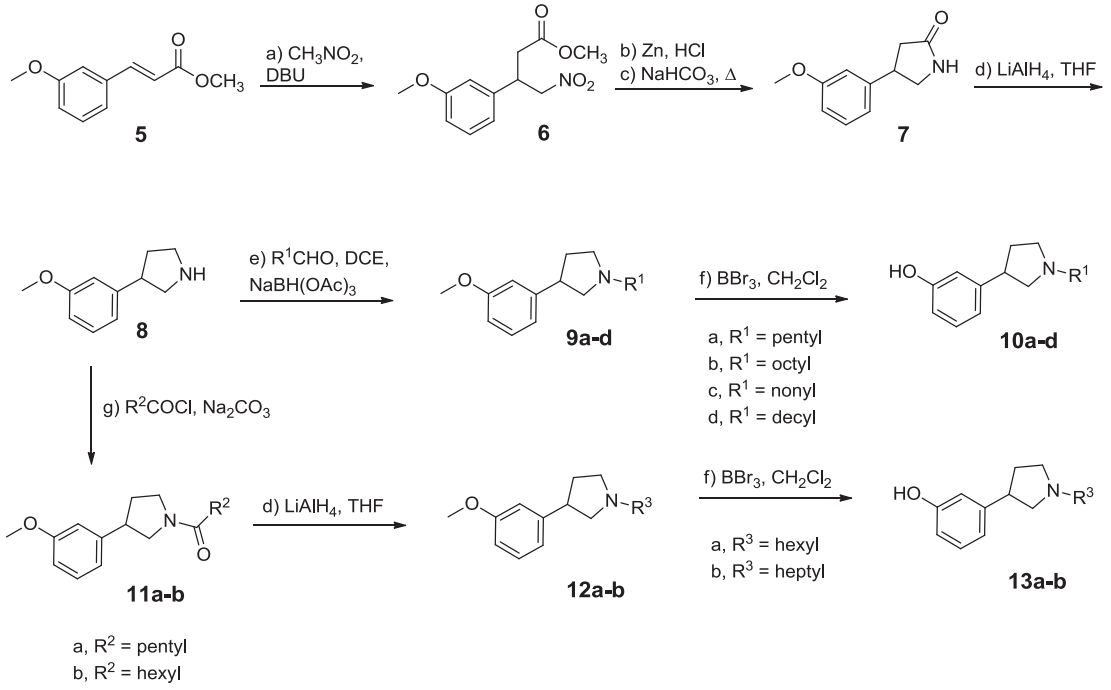
Fig. 1. Dopamine D_2/D_3 receptor ligands. Pramipexole1(Ref. 1f), 3-PPP 2(Ref. 8d), Pyrrolidineanalogue 3(Ref. 9).

binding pocket (SBP) which has attracted the attention of a number of groups for generating selectivity over the D_2R.[10] The D_3R SBP connects to the orthosteric site through a largely hydrophobic region (near transmembrane helices 1, 2, and 7) and extends out toward extracellular loops I and II (which open to the outer aqueous space). These structural studies along with comparative ligand docking analyses, molecular dynamics simulations, and SAR studies from several groups using the privileged 4-phenylpiperazine class of selective D_3 ligands to occupy the OBS while extending functionality into the SBP, suggest a longer, linear OBS-SBP orientation in the D_3R compared to a bent orientation in the D_2R.[10,12]

To further investigate the 3-(3-hydroxyphenyl)pyrrolidine scaffold for targeting the D_3R we envisioned a ligand design based upon extending functionality from the OBS-binding scaffold into the SBP to enhance both D_3R affinity and selectivity over D_2R. This type of bitopic ligand design has been employed by a number of groups to afford D_3R antagonists and partial agonists with other core templates.[12,13] In addition, there is some literature evidence that relates allosteric interactions within the SBP via the bitopic ligand approach to biased signaling.[14] Biased signaling leading to functional selectivity has been shown to govern the tolerance and slow response termination properties of the D_3R[15] and new bitopic ligands maybe particularly useful to more fully investigate these pathways.

To probe the carbon chain-length tolerance of the hydrophobic region of the SBP we have synthesized a homologous series of racemic *N*-alkyl analogues (5–10 carbons in length) for comparison to the known *N*-propyl **3** and *N*-butyl **4** analogues.[6a,9] While the *N*-alkyl substituents of the homologous series of may not be considered true secondary pharmacophores, we hoped this study would determine the optimal chain length from this specific pyrrolidine scaffold into the SBP. In addition, since the D_3R SBP is predominantly hydrophobic, we chose this lipophilic *N*-alkyl series with the hope of potentially gaining some increase in D_3R affinity and selectivity though resulting hydrophobic interactions with the alkyl chains. Target compounds were synthesized according to the reductive alkylation or amide reduction chemistries outlined in Scheme 1.

Thus, cinnamate **5**[16] was converted to nitro-ester analogue **6** by a literature method involving the conjugate addition of nitromethane mediated by DBU.[17] Compound **6** was converted to the lactam **7** in one pot by sequential reduction of the nitro-group with Zn powder in 1 N HCl followed by neutralization and heating to effect cyclization. The lactam **7** underwent smooth reduction with lithium aluminum hydride to afford the key 3-(3-methoxyphenyl) pyrrolidine **8**. Reductive alkylation of **8** with pentanal, octanal, nonanal, and decanal afforded compounds **9a-d**. Methyl deprotection of each of the compounds using boron tribromide afforded the corresponding phenol analogues **10a-d**. The amide reduction route was devised for derivatives for which the precursor acid chloride was more economical to purchase than the corresponding aldehyde required for the reductive amination route. Thus, for the amide reduction route key intermediate **8** was acylated under Schotten-Baumann conditions with hexanoyl and heptanoyl chlorides to afford amides **11a** (R^2 = pentyl) and **11b** (R^2 = hexyl), respectively. These amide derivatives were then converted to analogues **12a** and **12b** by reduction with lithium aluminum hydride. Finally, compounds **12a** and **12b** were deprotected by treatment



Scheme 1. Synthesis of *N*-alkyl-3-(hydroxyphenyl)pyrrolidinehomologous series, reductive amination route. Reagents and conditions: (a) nitromethane (18 equiv), DBU (5 equiv), 0 °C, 1 h, 20 °C, 16 h, 91%; (b) Zn (23 equiv), 1 N HCl, IPA, 2 h; (c) $NaHCO_3$(to pH ~ 7.5), 70 °C, 1 h, 79% over 2 steps; (d) $LiAlH_4$(2 equiv), THF, 0 °C, 1 h, then heated at 65 0 °C, 2 h, 77%; (e) aldehyde (1 equiv), $NaBH(OAc)_3$(1.5 equiv), 20 °C, 16 h, R = *n*-pentyl, 97%, R = *n*-octyl, 53%, R = *n*-nonyl, 58%, R = *n*-decyl, 59%; (f) BBr_3, (2 equiv), CH_2Cl_2, 0 °C, 1 h, 20 °C, 2 h, R = *n*-pentyl, 12%, R = *n*-octyl, 98%, R = *n*-nonyl, 36%, R = *n*-decyl, 61%. Amide reduction route. Reagents and conditions: (g) acid chloride (1.1 equiv), Na_2CO_3(1.75 equiv), H_2O, CH_2Cl_2, 20 °C, 2 h, R = *n*-pentyl(hexanoylchloride), 84%, R = *n*-hexyl (heptanoylchloride), 77%; (d) $LiAlH_4$(2.2 equiv), THF, 0 °C, 1 h, 65 0 °C, 2 h, R = *n*-hexyl, 62%, R = *n*-heptyl, 77%; (f) BBr_3, (2.3 equiv), CH_2Cl_2, 0 °C, 1 h, 20 °C, 2 h, R = *n*-hexyl, 39%, R = *n*-heptyl, 44%.

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with boron tribromide to afford analogues **13a** and **13b**, respectively.

Compounds **10a-d**, **13a**, and **13b** were evaluated in receptor binding assays using stably transfected or transiently transfected cloned human receptors. Radioligand competition assays were conducted with [^{3}H]*N*-methylspiperone for D_2R, D_3R, and D_4R and [^{3}H]SCH23390 for D_1R and D_5R. Full experimental details for binding measurements at these and all other receptors can be found at the NIMH Psychoactive Drug Screening Program website: (http://pdspdb.unc.edu/pdspWeb/).[18]

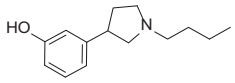
Analysis of the data from the radioligand binding studies for the homologous series (*N*-pentyl through *N*-decyl) of analogues of the 3-(3-hydroxyphenyl)pyrrolidine scaffold (**10a-d**, **13a** and **13b**) showed several interesting trends (Table 1). The *N*-butyl analogue[6a] was included as well. As expected for *N*-alkyl derivatives of this scaffold, low affinity for the D_1-like receptors (D_1R and D_5R) was observed. However, a modest increase in affinity for the D_1R and the D_5R was observed in longer chain analogues **10b-d**. For the D_2-like receptors (D_2R, D_3R and D_4R), a similar trend of increasing binding affinity with increasing chain length was observed for all three receptors. However, this series of analogues shows very low affinity for the D_2R in general with the exception of the *N*-nonyl analogue **10c** affording a modest K_i = 98 nM.

We were gratified to observe that the series shows much higher overall affinity for the D_3R and D_4R over the other dopamine receptors. For both receptors, the *N*-octyl and *N*-nonyl analogues, **10b** and **10c** show the highest affinity, both converging on single-digit nanomolar K_i values. Thus, there is no selectivity for D_3R over D_4R. However, the best D_3R ligand, *N*-nonyl compound **10c** shows a 20-fold selectivity over the D_1R, and 11-fold selectivity over both the D_2R and the D_5R. D_2/D_3 ratios indicate significant selectivity for the D_3R over the D_2R for all members of the series.

A similar trend of increasing affinity with increasing chain length was observed for the $5HT_{1A}$ receptor. High affinity is first observed in the *N*-heptyl analogue **13a** (K_i = 19 nM) and continues through the *N*-octyl, *N*-nonyl, and *N*-decyl series (compounds **10b-d**).

Since the *N*-nonyl compound **10c** showed the highest affinity of the series for the D_3R (K_i = 9 nM), we selected this compound for preparation of the enantiomeric pyrrolidine analogues (−)-**19** and (+)-**20**. Our goal was to probe the chirality-dependence of the 3-(3-hydroxyphenyl)pyrrolidine scaffold within the OBS while maintaining the optimal lipophilic tail length for hydrophobic

Table 1
Homologous study: Binding affinities for dopamine and $5HT_{1A}$ receptors (K_i, nM).

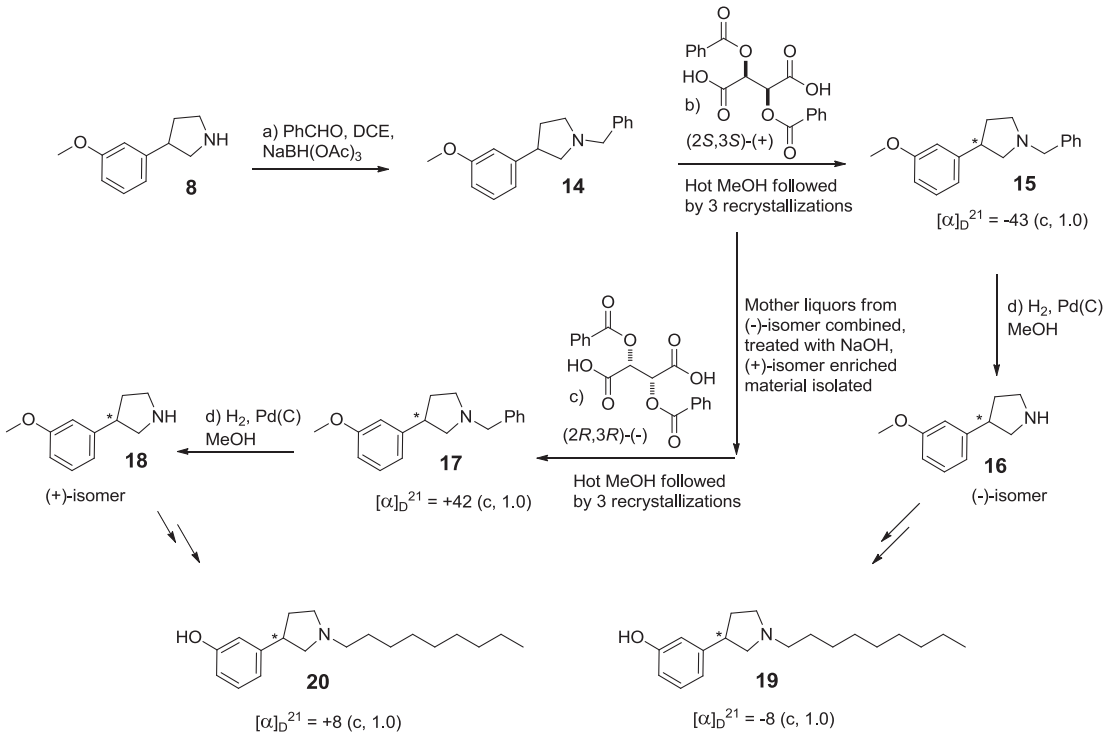
Compound	D_1	D_2	D_3	D_4	D_5	D_2/D_3	$5HT_{1A}$
	861 ± 323 (5 4 0)[b]	2877 ± 602(2 4 1)[a]	324 ± 119	1174 ± 247	1613 ± 884	8.9	1805 ± 210
4	542 ± 75	>10,000	131 ± 15	164 ± 23	605 ± 107	>76	326 ± 53
10a	1278 ± 272	3555 ± 741	162 ± 26	114 ± 5	640 ± 147	21.9	272 ± 31
13a	597 ± 98	369 ± 52	49 ± 5.5	11 ± 0.9	438 ± 93	7.5	19 ± 2
13b	170 ± 37	368 ± 68	19 ± 2.5	5.1 ± 2.5	286 ± 60	19.4	9.4 ± 0.9
10b	174 ± 29	98 ± 21	9 ± 1.2	5.8 ± 0.7	101 ± 21	10.9	15 ± 1.0
10c	128 ± 38	464 ± 87	41 ± 4.8	14 ± 1.0	143 ± 31	11.3	12 ± 6.3
10d							

[a] Radioligand binding measurements were performed by the NIMH Psychoactive Drug Screening Program (Ref. 18).
[b] (Ref. 6a).

interaction with the SBP. To prepare the chiral *N*-nonyl analogues **19** and **20** we chose to resolve the racemic key intermediate **8** using a modification of the methodology reported for the resolution of the related phenylpiperidine analogues (Scheme 2).[7a] Thus, pyrrolidine **8** was converted to the *N*-benzyl analogue **14** by reductive amination. Treatment of a hot methanolic solution of (+)-dibenzoyl-d-tartaric acid with a solution of **14** in methanol afforded crystalline material after cooling. Two additional recrystallizations afforded the (−)-isomer **15** in enantiomerically pure form after isolation as the free base ($[\alpha]_D^{21} = -43$ (c, 1.0)). Similarly, enantomerically pure (+)-isomer **17** was obtained through treatment of the free base isolated from the previous mother liquor with (−)-dibenzoyl-l-tartaric acid ($[\alpha]_D^{21} = +42$ (c, 1.0)). Compounds **15** and **17** were hydrogenated using 5% palladium on carbon in methanol to remove the *N*-benzyl groups affording pyrrolidines **16** and **18**, respectively. These key chiral intermediates were then converted to the *N*-Nonyl analogues **19** and **20**, respectively, using the reductive amination route described in Scheme 1. To confirm optical purity, compound **16** was reacted with (*S*)-(1-isothiocyanatoethyl)benzene (**S1**) to afford a single diastereomeric thiourea **S2** derivative. In addition, racemic compound **8** was also reacted with (*S*)-(1-isothiocyanatoethyl)benzene (**S1**) to afford a 50:50 mixture of diastereomeric thioureas (**S2-diastereomeric mixture)** for comparison (see Supplementary material for characterization data and NMR analyses for these compounds).

Using the information obtained from the homologous series we also became interested in preparing 3-(3-hydroxyphenyl)-pyrrolidine *N*-substituents with similar overall penetration into the SBP but further functionalized for increased interactions. To this end we were drawn to a report from the Mach group describing D_3R ligands with benzamide-based secondary pharmacophores.[12a] Compounds in this series such as WC10 (Table 2) showed very high affinity and selectivity for the D_3R over the D_2R. To account for the high affinity, it was proposed that the benzamide-NH of WC10 engages in a hydrogen bond with Cys-181 on extracellular loop 2 of the D_3R. In addition, since Cys-181 participates in a disulfide bond between extracellular loop 2 and the third transmembrane domain, and therefore plays a role in stabilizing the GPCR structure, a hydrogen bond interaction with the backbone carbonyl of Cys-181 may be useful in altering receptor conformation via the SBP. With these considerations in mind, our next goal was to determine if this benzamide-Cys-181 interaction could be extended to the 3-(3-hydroxyphenyl) pyrrolidine scaffold. Thus, we designed compounds **28**, **29** and **30** in order incorporate the Mach benzamide secondary pharmacophore with an overall length similar to WC10 and our best analogue from the homologous series. Remarkably, inspection of molecular models indicates that the *N*-nonyl compound **10c**, the compound from the homologous series with the highest affinity for the D3R, has an overall length which is closest to compounds **28**, **29** and **30**, as well as WC10. In order to bridge the 3-(3-hydroxyphenyl)pyrrolidine scaffold with the Mach secondary pharmacophore effectively in this new series the compounds needed to employ a 4-carbon linker from the pyrrolidine nitrogen to the benzamide. It is interesting to note that this linkage length has been found to offer optimal results with the phenylpiperazine scaffold and other secondary pharmacophores for D_3R affinity.[13b]

Synthesis of the benzamide analogues is presented in Scheme 3. The commercially available 4-aminobutyraldehyde diethyl acetal **21** was Boc-protected to afford compound **22**. Deprotection of the acetal under mild acidic hydrolysis afforded the Boc-protected cyclic hemi-aminal **23**. Reductive amination of key pyrrolidines **8**, **16**, and **18** using **23** as the aldehyde source (formed in situ), followed by acidic deprotection of the Boc- group afforded the *N*-(4-aminobutyl)pyrrolidine derivatives, **24**, **25** and **26**. EDC coupling of these intermediates with 4- dimethylaminobenzoic acid **27** followed by cleavage of the methyl group with boron tribromide afforded compounds **28**, **29** and **30**.



Scheme 2. Synthesis of chiral *N*-alkyl-3-(hydroxyphenyl)pyrrolidineanalogues, resolution and reductive amination route. Reagents and conditions: (a) benzaldehyde (1 equiv), $NaBH(OAc)_3$(1.5 equiv), 20 °C, 16 h, 81%; (b) (2*S*, 3*S*)-(+)-dibenzoyl-D-tartaric acid, MeOH, then NaOH, 42%; (c) (2*R*, 3*R*)-(−)-dibenzoyl-L-tartaric acid, MeOH, then NaOH, 35%; (d) H_2(balloon), 5% Pdon carbon, MeOH, 95% for 16, 89% for 18.

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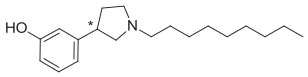
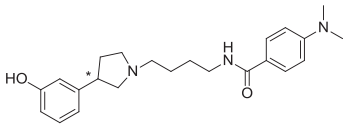
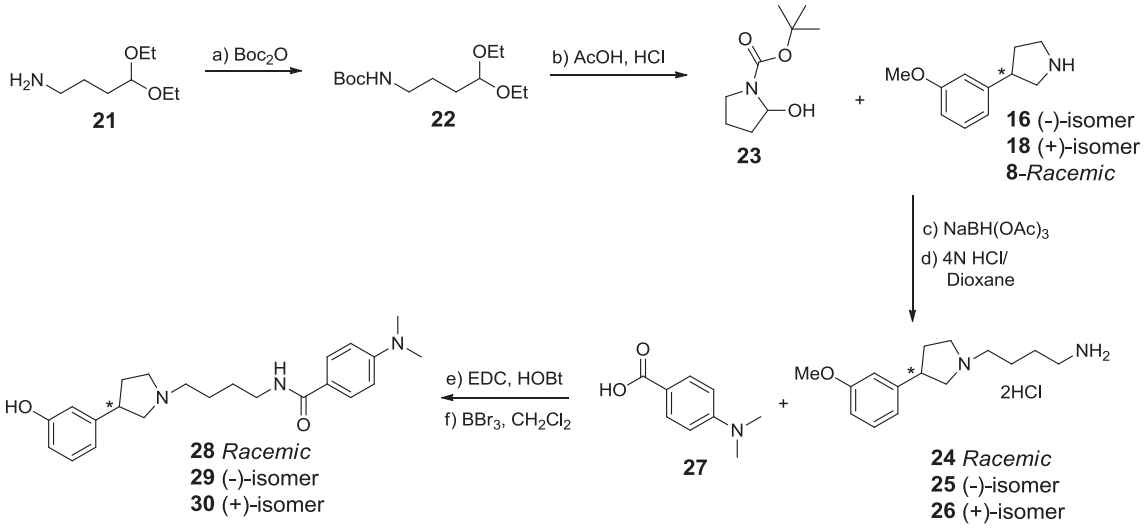
Table 2
Chiral and *N*-functionalized ligands: Binding affinities for dopamine and 5HT1A (K_i, nM).

Compound	Compound	D_1	D_2	D_3	D_4	D_5	$5HT_{1A}$
	**Rac-10c**	174 ± 29	98 ± 21	9 ± 1.2	5.8 ± 0.7	101 ± 21	15 ± 1.0
	(−)-**19**	181 ± 47	42 ± 7.7	2.4 ± 0.33	5.5 ± 23	227 ± 59	48 ± 6.7
	(+)-**20**	>10,000	62 ± 11	12 ± 1.6	27 ± 15	639 ± 120	115 ± 16
	**Rac-28**	831 ± 116	343 ± 63	14 ± 2.2	54 ± 10	312 ± 74	110 ± 23
	(−)-**29**	4589 ± 847	360 ± 68	14 ± 2.6	135 ± 60	955 ± 477	160 ± 27
	(+)-**30**	>10,000	345 ± 72	27 ± 4.4	>10,000	>10,000	328 ± 74

[a]Radioligand binding measurements were performed by the NIMH Psychoactive Drug Screening Program (Ref. 18).



Scheme 3. Synthesis of racemic and chiral *N*-benzamidobutyl-3-(hydroxyphenyl)pyrrolidineanalogues. Reagents and conditions: (a) Bocanhydride (1 equiv), TEA, THF, 0–5 °C then RT, 3.5 h, 95%; (b) AcOH, H_2O, HCl, 26 h, 81%; (c) $NaBH(OAc)_3$(1.5 equiv), 20 °C, 16 h; (d) 4 N HClin dioxane, CH_2Cl_2, 51% for 24 from8, 90% for 25 from16, 91% for 26 from18(for 2 steps); (e) EDC.HCl, HOBt·H_2O, TEA, DMF 16 h; (f) BBr_3, (2.3 equiv), CH_2Cl_2, 0 °C, 1 h, 20 °C, 21% for 28from 24, 29% for 29from 25, 35% for 30from 26(for 2 steps).

Radioligand binding data for the racemic and chiral *N*-nonyl and benzamide analogues are presented in Table 2. Both series show a strong preference for the (−)-enantiomer for high affinity toward the D_3R and the D_4R. For the *N*-nonyl series, the (−)-enantiomer **19** shows high affinity for the D_3R (K_i = 2.4 nM) with a 75-fold selectivity over the D_1R, 17.5-fold selectivity over the D_2R, and a 95-fold selectivity over the D_5R. A modest 2-fold selectivity over the D_4R was also observed. Similarly, for the $5HT_{1A}$ receptor, higher affinity appears to lie in the (−)-enantiomer **19**. Unfortunately, the potential additional interaction of the benzamide N—H with the carbonyl of Cys-181 was not achieved and/or did not contribute to further enhanced binding affinity over the *N*-nonyl-probe analogues. Thus, the (−)-enantiomer **29** afforded a K_i = 14 nM whereas the (+)-enantiomer **30** showed a K_i = 27 nM for the D_3R.

While the OBS for all dopamine receptors appears to have some preference for binding the (−)-enantiomer of the 3-(3-hydroxyphenyl)pyrrolidine scaffold, the (+)-isomers in both the *N*-nonyl and benzamide series still afford significant binding affinity for the D_3R in particular. In fact, while the (−)-enantiomers are higher affinity ligands, the (+)-enantiomers are considerably more selective for the D_3R. Remarkably, the (+)-benzamide analogue **30** shows good binding affinity for the D_3R (Ki = 27 nM), with a 13-fold selectivity over D_2R, and > 370-fold selectivity over the D_1R, D_4R and D_5R.

In summary, we have synthesized a homologous series of *N*-alkyl-3-(3-hydroxyphenyl)pyrrolidine analogues to probe the chain-length requirements of functionality extending from the pyrrolidine scaffold in the OBS to the SBP of the D_3R. From this series we have identified the *N*-nonyl analogue as having the highest binding affinity for the D_3R. Key scaffold intermediate **8** was resolved and the *N*-nonyl enantiomers were prepared following the information gained by the homologous series work. The (−)-isomer **19** afforded the highest affinity for the D_3R with good selectivity over the D_1R, D_2R and D_5R and slight selectivity over D_4R. *N*-Benzamidobutyl analogues **28**–**30** were also prepared to attempt to engage Cys-181 in the SBP to enhance affinity and selectivity for the D_3R. Unfortunately, no gain in affinity was observed for this series but selectivity for the D_3R was further improved. For the benzamide series the highest affinity for the D_3R was also found in the (−)-isomer, compound **29**. This study reinvestigates and further expands the SAR of the 3-(3-hydroxyphenyl)pyrrolidine scaffold for dopaminergic activity. Future studies will involve the development of new *N*-functionality for further probing the SBP of the D_3R.

Acknowledgments

This work was supported by the SIUE School of Pharmacy Research Grant (2016). Radioligand binding measurements were conducted by the NIMH Psychoactive Drug Screening Program website: (http://pdspdb.unc.edu/pdspWeb/). High Resolution Mass Spectrometry was performed by the University of Notre Dame Mass Spectrometry and Proteomics Facility.

A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.bmcl.2018.03.084.

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