ACS Medicinal Chemistry Letters
Cite This: ACS Med. Chem. Lett. 2018, 9, 990−995
Letter
pubs.acs.org/acsmedchemlett

New Dopamine D3-Selective Receptor Ligands Containing a 6-Methoxy-1,2,3,4-tetrahydroisoquinolin-7-ol Motif

Satishkumar Gadhiya,[†,‡] Pierpaolo Cordone,[†,∥] Rajat K. Pal,[§,∥] Emilio Gallicchio,[§,‡,∥] Lauren Wickstrom,[#] Tom Kurtzman,[⊥,‡,∥] Steven Ramsey,[⊥,∥] and Wayne W. Harding*[,†,‡,∥,⊥]

[†]Department of Chemistry, Hunter College, City University of New York, 695 Park Avenue, New York, New York 10065, United States

[‡]Ph.D. Program in Chemistry, CUNY Graduate Center, 365 Fifth Avenue, New York, New York 10016, United States

[∥]Ph.D. Program in Biochemistry, CUNY Graduate Center, 365 Fifth Avenue, New York, New York 10016, United States

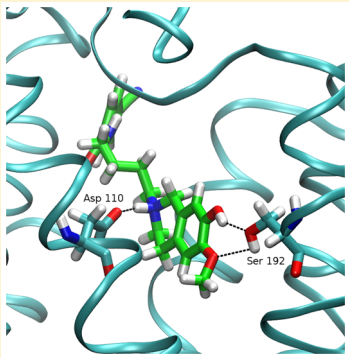
[§]Department of Chemistry, Brooklyn College, 2900 Bedford Avenue, Brooklyn, New York 11210, United States

[⊥]Department of Chemistry, Lehman College, The City University of New York, Bronx, New York 10468, United States

[#]Department of Science, Borough of Manhattan Community College, 199 Chambers Street, New York, New York 10007, United States

Supporting Information

ABSTRACT: A series of analogues featuring a 6-methoxy-1,2,3,4-tetrahydroisoquinolin-7-ol unit as the arylamine "head" group of a classical D3 antagonist core structure were synthesized and evaluated for affinity at dopamine D1, D2, and D3 receptors (D1R, D2R, D3R). The compounds generally displayed strong affinity for D3R with very good D3R selectivity. Docking studies at D2R and D3R crystal structures revealed that the molecules are oriented such that their arylamine units are positioned in the orthosteric binding pocket of D3R, with the arylamide "tail" units residing in the secondary binding pocket. Hydrogen bonding between Ser 182 and Tyr 365 at D3R stabilize extracellular loop 2 (ECL2), which in turn contributes to ligand binding by interacting with the "tail" units of the ligands in the secondary binding pocket. Similar interactions between ECL2 and the "tail" units were absent at D2R due to different positioning of the D2R loop region. The presence of multiple H-bonds with the phenol moiety of the headgroup of 7 and Ser192 accounts for its stronger D3R affinity as compared to the 6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline-containing analogue **8**.



KEYWORDS: *D3, D3R, D2R, D1R, antagonist, dopamine receptor, docking, 3PBL, 6CM4*

The dopaminergic system plays a significant role in the control of a variety of brain functions such as emotion, cognition, and movement.[1−3] The neurotransmitter dopamine is a key endogenous player in the dopaminergic system and exerts its pharmacological effects via interacting with dopamine receptors. There are five dopamine receptor subtypes (D1−D5), and these are classified into two families based on their pharmacological, genetic, and structural properties as D1-like (D1 and D5) and D2-like (D2, D3, and D4) receptors.[4,5] All five dopamine receptor subtypes are G-protein coupled receptors (GPCRs), characterized by the presence of seven transmembrane helical domains. Because dopaminergic dysfunction is implicated in a range of neurological and psychiatric disorders, ligands that selectively interact with each of the dopamine receptor subtypes are sought after as such compounds may serve as useful tools and therapeutics relevant to such disorders.

Antagonists at the dopamine D3 receptor (D3R) in particular have received considerable attention as potential therapeutics to treat schizophrenia and stimulant abuse.[6−14] Although numerous D3R antagonists are known, problems with selectivity of the compounds especially with respect to the closely related D2R has been an issue of concern.[15] Furthermore, the majority of D3R antagonists that are selective display poor pharmacokinetic properties (in some cases related to high lipophilicity), which has largely precluded their successful clinical translation.[16] Thus, the identification of D3R antagonist leads that are selective and that feature promising or favorable pharmacokinetic properties continues to be of interest.

Several selective D3R antagonists (e.g., BP 897, NGB 2904, YQA 14, and SB 277011A, Figure 1) share a common "classical" pharmacophore that consists of an arylamine-containing "head" group and an arylamide "tail" unit connected via an alkyl group linker (Figure 1). Previous investigations suggest that the aromatic ring of the head portion of these molecules interacts with the orthosteric binding pocket of D3R

Received: May 17, 2018
Accepted: September 10, 2018
Published: September 10, 2018

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DOI: 10.1021/acsmedchemlett.8b00229
ACS Med. Chem. Lett. 2018, 9, 990−995

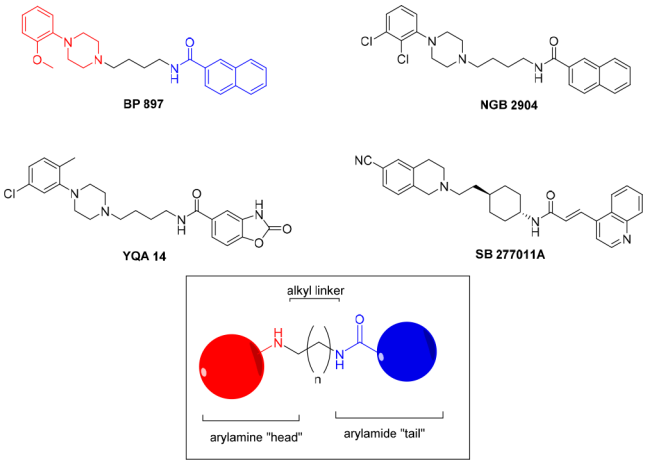


Figure 1. Structures of selective D3R antagonists: BP 897, NGB 2904, YQA 14, and SB 277011A and D3R antagonist pharmacophore (inset; color scheme exemplified with BP 897).

and are key for D3R affinity, while the arylamide tail units reside in the secondary binding pocket of D3R and appear to be important for promoting selectivity versus D2R.[16−20]

In a separate SAR study on the nonselective D3R antagonist stepholidine (unpublished results), we discovered that 6-methoxy-1,2,3,4-tetrahydroisoquinolin-7-ol (Figure 2), a fragment of stepholidine, possessed good affinity and D3R selectivity (K_i values at D1R, D2R, and D3R were 6479, 1593, and 92 nM, respectively). Therefore, we decided to incorporate the 6-methoxy-1,2,3,4-tetrahydroisoquinolin-7-ol motif into a series of compounds that are based on the classical D3R pharmacophore with the expectation that the presence of this D3R preferring structural motif would allow for strong D3R affinity and selectivity. Furthermore, this headgroup seemed to offer some advantage in terms of favorably lowering lipophilicity/clogP as compared to other commonly employed head groups, due to presence of a phenolic functionality.

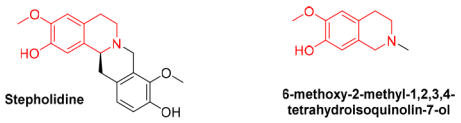
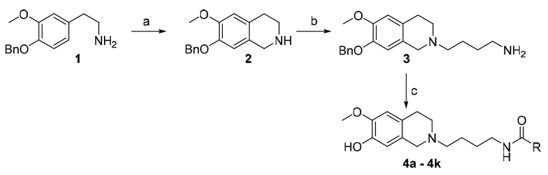


Figure 2. Structures of stepholidine and tetrahydroisoquinolin-ol unit used as "head" group.

Synthesis of the analogues was readily accomplished as depicted in Scheme 1. We chose to use arylamide tail units that were present in known selective D3 antagonists to promote the binding and selectivity of the compounds. We also investigated a variety of predominantly *p*-substituted phenyl tail groups to probe steric and electronic structure−affinity effects in the tail unit within the series.

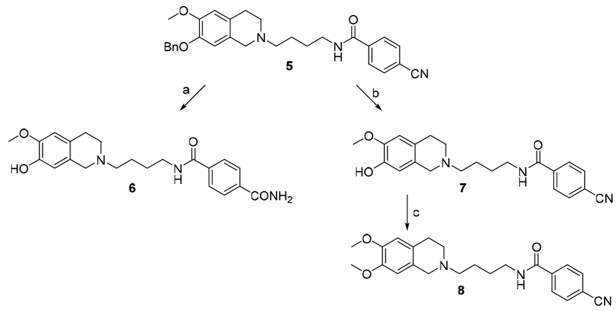
Scheme 1. Synthesis of Analogues 4a−4k[a]



[a]Reagents and conditions: (a) paragomaldehyde, HCOOH, 50 °C, 87%; (b) (i) 4-bromobutyronitrile, K_2CO_3, CH_3CN, reflux; (ii) LAH,THF, rt; 76% over two steps; (c) (i) RCOOH, EDC, DC, rt; (ii) conc. HCl, EtOH, reflux, 65−83% over two steps.

Readily available amine **1** underwent Pictet−Spengler cyclization to produce the tetrahydroisoquinoline **2**. Subsequently, compound **2** was reacted with 4-bromobutyronitrile, and the nitrile thus produced was reduced to primary amine **3** with lithium aluminum hydride. Amine **3** was then condensed with various acids via coupling with EDC to afford amide derivatives that were subsequently subjected to acidic conditions to unmask the phenolic group in analogues. In the synthesis of analogues **4a−4k**, refluxing in acidic ethanol was successful in achieving *O*-debenzylation from the corresponding benzylated precursors. However, similar attempts to prepare compound **7** by *O*-debenzylation of **5** with HCl/EtOH resulted in concomitant hydrolysis of the arylnitrile group, yielding **6** (Scheme 2). Alternatively, treatment of **5** with TFA at room temperature allowed for selective removal of the benzyl protecting group to give **7**. Thereafter, Williamson ether methylation of the phenolic group in **7** gave compound **8**.

Scheme 2. Synthesis of Analogues 6−8[a]

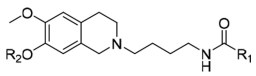


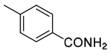
[a]Reagents and conditions: (a) conc. HCl, EtOH, reflux; (b) TFA, DCM, 48 h, reflux; (c) MeI, K_2CO_3, acetone.

Compounds **4a−4k** and **6−8** were submitted to the Psychoactive Drug Screening Program (PDSP)[21] for evaluation of binding affinity at dopamine D1R, D2R, and D3R. Table 1 summarizes the data gathered from this evaluation. In line with our design rationale, the compounds were all selective for D3R. Compounds **4a** and **4b**, containing biphenyl and naphthyl arylamide units, displayed similar affinities at D1R, D2R, and D3R, with the highest affinity being for D3R (2.7 nM for both compounds). Both compounds showed good selectivity for D3R versus D1R and D2R in an approximately 300-fold range. As compared to **4a** and **4b**, the 4-quinolinyl containing analogue **4c** had lower affinity at all three receptors; no affinity was observed at D2R. Compound **4c** maintained D3R selectivity but had D3R affinity that was approximately 8-fold lower than that for **4a** and **4b**. With the 4-pyridyl analogue **4d**, no affinity was observed at D1R and D2R, and the analogue had moderate D3R affinity similar to **4c** (24 nM). The 4-hydroxyphenyl analogue (**4e**) lacked D1R and D2R affinity and possessed strong D3R affinity (8.7 nM). A similar affinity profile was seen for the 4-methoxy phenyl analogue (**4f**), albeit with slightly lower D3R affinity (5.9 nM). For the 3-methoxyphenyl analogue **4g**, there was a 2-fold decrease in D3R affinity, indicating better tolerance for a methoxy substituent in the 4-position of the phenyl ring. Among the halogenated phenyl analogues **4h−4k**, the 4-fluorophenyl

DOI: 10.1021/acsmedchemlett.8b00229
ACS Med. Chem. Lett. 2018, 9, 990−995

Table 1. D1, D2, and D3 Binding Affinity, Selectivity, and clogP Data for Analogues 4a−4k and 6−8



			K_i ± SEM (nM)[a]				Selectivity		
Cmpd.	R_1	R_2	D1[b]	D2[c]	D3[d]	D4[e]	D1/D	D2/D	clogP[f]
4a		H	800 ± 100	800 ± 100	2.7 ± 0.4	720 ± 93	296	296	4.6
4b		H	800 ± 100	700 ± 100	2.7 ± 0.4	170 ± 22	296	260	3.8
4c		H	1810 ± 230	na	22 ± 3.0	410 ± 54	82	nd	3.3
4d		H	na	na	24 ± 3.1	1400 ± 180	nd	nd	1.9
4e		H	na	na	8.7 ± 1.1	660 ± 85	nd	nd	2.3
4f		H	na	na	5.9 ± 0.8	560 ± 73	nd	nd	2.6
4g		H	na	na	12 ± 1.5	150 ± 20	nd	nd	2.6
4h		H	na	na	4.4 ± 0.6	95 ± 12	nd	nd	3.0
4i		H	680 ± 90	1100 ± 100	2.1 ± 0.3	140 ± 18	323	524	3.6
4j		H	500 ± 60	>10,000	3.4 ± 0.4	350 ± 45	147	>2941	3.7
4k		H	1600 ± 200	na	10 ± 1.3	1500 ± 19	160	nd	4.0
6		H	na	860 ± 110	28 ± 4.0	na	nd	31	1.6
7		H	na	na	6.3 ± 0.8	na	nd	nd	2.6
8		Me	na	na	410 ± 53	na	nd	nd	3.0

[a]Experiments carried out in triplicate. [b][3H]SCH23390 used as radioligand. [c][3H]*N*-Methylspiperone used as radioligand. [d][3H]*N*-Methylspiperone used as radioligand. [e][3H]*N*-Methylspiperone used as radioligand. [f]Calculated with ChemBioDraw Ultra version 13.02; na, not active (<50% inhibition in a primary assay when tested at 10 μM); nd, not determined.

analogue **4h** was superior in terms of D3R selectivity and showed strong D3R affinity (4.4 nM). D3R selectivity was maintained in the **4h−4k** haloaryl subset, but no particular trend was detected with respect to the impact of steric and electronic effects of the halogen substituent for binding at the various receptors. The 4-cyanophenyl analogue **7** displayed strong D3R affinity (6.3 nM) and lacked affinity for D1R and D2R. D3R affinity of **6** decreased 4-fold as compared to **7**, and low D2R affinity was observed (860 nM).

A number of D3R ligands are known that contain a 6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline motif as the headgroup.[22,23] As our compounds contained a slight variation in this motif in containing a 6-methoxy-1,2,3,4-tetrahydroisoquinolin-7-ol unit, we were motivated to evaluate compound **8** for comparison to compound **7**. In this manner, we could determine to what extent the phenolic replacement for the methoxy group in the head unit impacts D3R affinity. Interestingly, compound **8** showed 65-fold lower D3R affinity than its phenol counterpart **7**, indicating better tolerance for the 7-hydroxy substituent than the 7-methoxy substituent in the headgroup. It will be interesting to determine the extent to which a similar change would affect the D3R affinity of the other phenol-containing analogues in the series. Nevertheless, the presence of the phenol moiety diminishes clogP as compared to the analogous methoxy counterparts, and this in combination with the presence of one less rotatable bond and a slightly lower molecular weight may engender improved pharmacokinetic performance of the analogues. Compounds **4a−4k** and **6−8** were also evaluated for affinity at D4R, D5R, and σ2 receptors (see Table 1 for D4R data; Supporting Information for D5R and σ2R data). We found that the compounds had no or very low affinity (K_i > 1500 nM) at D5 receptors. In general, affinity of the compounds at D4R was moderate with all compounds maintaining D3R versus D4R selectivity. In that regard, the analogues were at least 10-fold selective for D3R versus D4R. Except for compound **8**, all of the analogues were also selective for D3 versus σ2 with selectivities ranging from 3-fold (compound **4a**) to 84-fold (compound **4d**). The result from the σ2R screening of the compounds tends to suggest that the 6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline motif (seen in compound **8**) promotes a reversal in the D3R versus σ2R selectivity noted for the other compounds. Thus, the 6-methoxy-1,2,3,4-tetrahydroisoquinolin-7-ol unit may be advantageous for D3R versus σ2R selectivity as compared to the 6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline motif. Compound **7** is particularly promising

DOI: 10.1021/acsmedchemlett.8b00229
ACS Med. Chem. Lett. 2018, 9, 990−995

given its high D3R affinity, lack of affinity at D1R, D2R, D4R, and D5R, and its >40-fold selectivity versus σ2R.

Compounds **4e**, **4f**, **4h**, and **7** were then evaluated for D3R agonist and D3R antagonist activity in G-protein-independent β-arrestin recruitment Tango assays. In agonist mode, none of the compounds displayed β-arrestin recruitment activity. However, when run in antagonist mode, all compounds showed antagonist activity in the Tango assay and inhibited quinpirole-induced β-arrestin recruitment, with EC_{50} values of 0.42, 0.36, 0.49, and 1.4 μM being recorded for **4e**, **4f**, **4h**, and **7**, respectively.

To understand the structural basis for the D3R versus D2R selectivity of the analogues and to rationalize the significant difference in D3R affinity between compounds **7** and **8**, we conducted docking studies on the compounds with an available D3R crystal structure (PDB code 3PBL)[24] and the recently published D2R crystal structure (PDB code 6CM4).[25] Glide Standard Precision (SP) as part of the Schrodinger Suite version 2016−3 was employed for molecular docking. Structural refinement of the bound poses were performed using the IMPACT program.[26] The details of the docking and refinement procedures are provided as Supporting Information.

The extracellular loop 2 (ECL2) region found in the secondary binding pocket of D3R is known to be important for the binding and selectivity of D3R antagonists.[24] The analogues are oriented differently at D2R and D3R (Figure 3). We found that the arylamine head units of the analogues

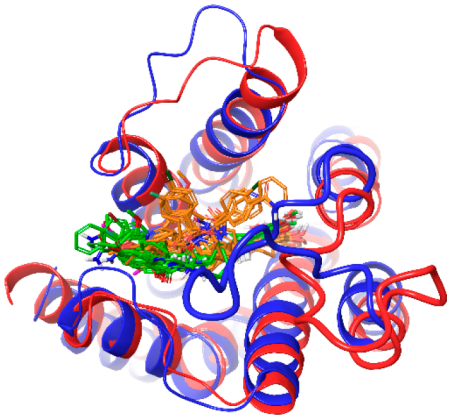


Figure 3. Comparison of the binding modes of the analogues docked at D2R and D3R. Docked orientation of the analogues are shown in orange and green at D2R and D3R, respectively. The D2R and D3R structures are represented in red and blue, respectively. The ECL2 in D2R and D3R are shown in tube representation in its respective receptor color codes.

occupied the orthosteric binding pocket of D3R, with the arylamide tail units projecting extracellularly in proximity to ECL2. The headgroup of the ligands makes H-bonding contacts in the orthosteric binding site with Ser 192 of D3R and Ser 193 or Ser197 of D2R. The position of the extracellular loop ECL2 is stabilized by the interaction between Tyr 365 of helix VII and Ser 182 of ECL2 in D3R. The arylamide tail units of the ligands are observed to make frequent contacts with the ECL2 loop in D3R. The capabilities for these interactions are lost in the case of the D2R due to the different positioning of the D2R loop region. The presence of interactions of the analogues with ECL2 likely contributes to the binding preference of the compounds for D3R, a result in congruence with previous docking studies with the selective D3R antagonist R-22.[27]

Concerning the higher D3R affinity of compound **7** with respect to compound **8**, our docking studies provided some interesting revelations. The compounds had similar binding orientations at D3R (Figure 4a,b). However, interactions with

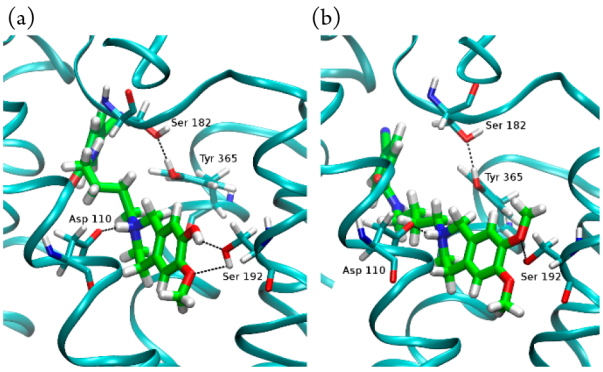


Figure 4. (a) Compound **7** docked at D3R showing two key H-bond interactions with Ser 192. (b) Compound **8** docked at D3R showing single H-bond interaction with Ser 192. The interaction between Tyr 365 and Ser 182 is indicated.

the headgroup regions were slightly different between the two compounds. In that regard, within the orthosteric pocket, compound **7** forms two simultaneous hydrogen bonds to Ser 192: one via the oxygen atom of the methoxy group and the second via the phenolic hydrogen atom (Figure 4a) in the headgroup; in contrast, compound **8** is observed to form only one hydrogen bond at a time to Ser 192 either via the oxygen atom of the C7 methoxy group (Figure 4b) or the oxygen atom of the methoxy group at position 7. Similar to **7**, the analogues with a phenolic moiety formed two H-bonding interactions between the phenol and Ser 192. Thus, this interaction seems to also contribute to the high D3R affinity of this series of ligands.

In conclusion, this study has identified new selective D3R antagonists based on a classical D3R pharmacophore. The 6-methoxy-1,2,3,4-tetrahydroisoquinolin-7-ol head motif is well tolerated for D3R affinity and selectivity in this series. Docking studies reveal that the D3R versus D2R selectivity of the analogues is due to strong interactions between ECL2 of D3R and the arylamide motifs. The presence of an additional hydrogen bond interaction with Ser192 in the orthosteric binding site may account for the higher D3R affinity of compound **7** as compared to compound **8**. Given its D3R affinity and selectivity as well as its favorable clogP characteristics, the 6-methoxy-1,2,3,4-tetrahydroisoquinolin-7-ol fragment is expected to find utility in the design of future generations of selective D3R antagonists.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acsmedchemlett.8b00229.

Experimental procedures for analogue synthesis and docking procedures on analogues; ^{1}HNMR and ^{13}CNMR data for analogues (PDF)

DOI: 10.1021/acsmedchemlett.8b00229
ACS Med. Chem. Lett. 2018, 9, 990−995

AUTHOR INFORMATION

Corresponding Author

*Phone: 212 772 5359. E-mail: whardi@hunter.cuny.edu.

ORCID

Emilio Gallicchio: 0000-0002-2606-4913

Steven Ramsey: 0000-0001-7441-3228

Wayne W. Harding: 0000-0002-1866-3553

Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

K_i determinations and receptor binding profiles were generously provided by the National Institute of Mental Health's Psychoactive Drug Screening Program, Contract # HHSN-271-2008-00025-C (NIMH PDSP). The NIMH PDSP is directed by Bryan L. Roth MD, PhD at the University of North Carolina at Chapel Hill and Project Officer Jamie Driscol at NIMH, Bethesda MD, USA. For experimental details please refer to the PDSP website https://pdspdb.unc.edu/pdspWeb/?site=assays.

ABBREVIATIONS

D1R, dopamine D1 receptor; D2R, dopamine D2 receptor; D3R, dopamine D3 receptor; ECL2, extracellular loop 2; LAH, lithium aluminum hydride; EDC, 1-ethyl-3-(3-(dimethylamino)propyl)carbodiimide; DCM, dichloromethane; TFA, trifluoroacetic acid; PDB, Protein Data Bank

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