Published in final edited form as:

Bioorg Med Chem Lett. 2012 September 1; 22(17): 5612–5617. doi:10.1016/j.bmcl.2012.07.003.

High-affinity and selective dopamine D₃ receptor full agonists

Jianyong Chen^a, Beth Levant^d, and Shaomeng Wang^{a,b,c,*}

^aDepartment of Internal Medicine, University of Michigan, 1500 East Medical Center Drive, Ann Arbor, Michigan 48109, USA

^bDepartment of Pharmacology, University of Michigan, 1500 East Medical Center Drive, Ann Arbor, Michigan 48109, USA

^cDepartment of Medicinal Chemistry, University of Michigan, 1500 East Medical Center Drive, Ann Arbor, Michigan 48109, USA

^dDepartment of Pharmacology, Toxicology, and Therapeutics, University of Kansas Medical Center, Kansas City, Kansas 66160-7417, USA

Abstract

We have designed, synthesized and evaluated a series of new compounds with the goal to identify potent and selective D₃ ligands. The two most potent and selective new D₃ ligands are compounds **38** and **52**, which bind to the D₃ receptors with a K_i value of <1 nM and display a selectivity of 450–494 times over the D₂ receptors and >10,000 times over the D₁ receptors. Both **38** and **52** are full agonists with high potency at the D₃ receptor in a D₃ functional assay.

Keywords

Dopamine 3 receptor; Full agonists; Structure-activity-relationships

Dopaminergic neurotransmission is mediated by five dopamine receptors (D₁–D₅), which can be grouped into the D₁-like (D₁ and D₅) and D₂-like (D₂, D₃, and D₄) receptor subtypes. The dopamine 3 (D₃) subtype receptor has been identified as an important target for agents currently used clinically for the treatment of schizophrenia, Parkinson's disease, depression, and other neurological diseases^{1–4} and a number of studies have provided strong evidence that potent and selective D₃ ligands may have therapeutic potential as novel therapies for the treatment of drug abuse.^{5–8} Hence, considerable effort has been devoted to the discovery and development of potent and selective D₃ ligands.^{7–32}

A number of known potent and selective D₃ ligands, including antagonists, partial agonists and full agonists, are shown in Figure 1. Evaluated in *in vitro* binding assays either using cloned human dopamine receptors or rat brain,^{7,8} these ligands were shown to bind to the D₃ receptor with high affinities and selectivities of 100–500 fold over the D₂ receptor and >1,000 over the D₁-like receptors. SB-277011A (**1**) is a potent and selective D₃ antagonist⁹ which has been extensively used in animals to investigate the role of the D₃ receptor in drug abuse.⁸ A shortcoming of SB-277011A is that relatively high doses are needed to produce an

© 2012 Elsevier Ltd. All rights reserved.

*Corresponding author. Tel.: +1 734 615 0362; fax: +1 734 647 9647; shaomeng@umich.edu.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

in vivo effect, suggesting only moderate CNS penetration. Subsequent optimization efforts led to the identification of SB-414796 (**2**), which is a potent and selective D₃ antagonist with excellent bioavailability in the rat, and good CNS penetration.¹⁶ However, SB-414796 was not advanced into clinical development because it inhibits p450 and has potential cardiotoxicity due to its strong binding to the hERG potassium channel.^{8,32} Very recently, compound **3** was designed as a highly potent and selective D₃ antagonist.³² This compound has excellent oral bioavailability and good CNS penetration, shows weak inhibition on all the P450 isoforms and at the hERG channel, thus defusing the major issues associated with compound **2**. BP 897 (**4**) was initially described as a potent D₃ partial agonist with a modest selectivity of < 100 over D₂,⁶ but subsequent studies have shown that it may behave as a D₃ antagonist.^{33,34} NGB 2904 (**5**) is a potent and selective D₃ antagonist¹⁰ and has been extensively evaluated *in vivo*.⁸ A large number of new analogues, including compounds **6**,¹⁸ **7**³⁰ and **8**,³⁰ have been designed and synthesized in an effort to improve D₃ selectivity and solubility. Among them, compound **8** is the most potent and selective D₃ antagonist and displays a selectivity of >400-fold over D₂ in *in vitro* binding assays.³⁰ Significantly, compound **8** is also more soluble than compound **5**.³⁰

Pramipexole (**9**) is a highly potent D₃ full agonist but with only modest selectivity for the D₃ receptor over the D₂ receptor.^{25,28} Pramipexole has been approved for the treatment of Parkinson's disease and restless legs syndrome and has excellent safety and pharmacological properties in humans. Hence, Pramipexole serves as an excellent leading compound for the design of potent and selective D₃ ligands. In an effort to improve its selectivity for D₃ over D₂, we have previously designed and synthesized a series of compounds based upon the core structure of pramipexole.²⁵ Our study led to the identification of several potent D₃ ligands such as compounds **10** and **11**, which are much more selective for D₃ over D₂ than pramipexole. Unfortunately, notwithstanding their high binding affinity to the D₃ receptor (K_i < 1nM) and excellent aqueous solubility, compounds **10** and **11** were found to be active at the D₃ receptor only at 32 mg/kg in the yawning assay in the rat, indicating that these compounds have poor bioavailability in the brain.²⁵

In the present study, we have performed additional chemical modifications based upon the chemical structures of compounds **10** and **11** with the goal of identifying new D₃ ligands with high affinity and excellent selectivity.

Since the D₃ radioligand [³H]PD128907 used previously in our D₃ binding assays recently became unavailable, it became necessary to switch to another radioligand [³H]-*R*(+)-7-hydroxy-*N,N*-di-*n*-propyl-2-aminotetralin ([³H]-*R*(+)-7-OH-DPAT) for our D₃ receptor binding assay. Accordingly, we re-evaluated compounds **10** and **11** in both D₃ and D₂ binding assays using this new D₃ radioligand. Compounds **10** and **11** were found to bind to the D₃ receptor with K_i values of 1.0 ± 0.04 nM (Table 1) and 1.1 ± 0.3 nM (Table 2), respectively, as compared to 0.41 ± 0.031 nM and 0.40 ± 0.057 nM, respectively, in our previous D₃ assay²⁵ using [³H]PD128907. Compounds **10** and **11** were found to bind to the D₂ receptor with K_i values of 239 ± 60 nM (Table 1) and 185 ± 61 nM (Table 2), respectively, as compared to 330 ± 69 nM and 307 ± 38 nM, respectively, as we previously reported.²⁵ The selectivity of compounds **10** and **11** for D₃ over D₂ are 239- and 168-times, respectively, as compared to 800- and 763-times, respectively, in our previous report.²⁵ This is due primarily to the 2.5-fold increase in K_i values in the D₃ receptor binding assay.

We first performed modifications on **10** by installation of an F, Cl or CH₃O group in the *para*-, *meta*- or *ortho*-positions in the phenyl ring to yield compounds **15–23** (Table 1). Compounds **15–23** were tested for their binding affinities to the dopamine D₁, D₂ and D₃ receptors and the results are summarized in Table 1. Our binding data showed that

substitution of the phenyl ring in compound **10** with F, Cl or OCH₃ improves neither the potency to D₃ nor the selectivity for D₃ over D₂.

We next synthesized compounds **24–26** to investigate the effect of replacing a carbon atom in the naphthyl group with a nitrogen atom at each of three different positions in compound **11** (Table 2). These three compounds bind to D₃ with K_i values of 1.6, 1.6 and 5.9 nM, respectively, and are somewhat less potent than **11**. They are also less selective than **11** for D₃ over D₂.

A series of compounds (**27–32**) in which a phenyl group connected to different 2–3 nitrogen-containing hetero-cyclic systems replaces the naphthyl group in **11** (Table 2) was synthesized. These compounds bind to D₃ with K_i values of 1.1 to 3.0 nM and have a modest selectivity of 12–29 times for D₃ over D₂.

We synthesized compound **33**, in which the naphthyl group is replaced by a 4-(5-methyl-1,2,4-oxadiazol-3-yl)phenyl group, which had been used in the design of compound **2** (Table 2). Compound **33**, binds to D₃ with the same high affinity (K_i = 1.3 nM) as **11**, but its selectivity over the D₂ receptor is improved to 345-fold due to its decreased binding affinity to D₂. Encouraged by this promising binding and selectivity data, we further modified **33** with different 1,2,4-oxadiazol-3-yl-phenyl groups, to obtain compounds **34–38** (Table 2). Replacement of the methyl group in **33** with ethyl (**34**), isopropyl (**35**) or cyclopropyl (**36**) decreased the binding affinity to D₃ and also the selectivity for D₃ over D₂ by factors of 2–3 as compared to **33**. Compounds **37** and **38**, in which the 4-(5-methyl-1,2,4-oxadiazol-3-yl)phenyl group in **33**, has been replaced by either 3-(5-ethyl-1,2,4-oxadiazol-3-yl)phenyl or 3-(5-methyl-1,2,4-oxadiazol-3-yl)phenyl, bind to D₃ with K_i values of 1.5 nM and 0.73 nM, respectively and their selectivity for D₃ over D₂ is 339 and 494, respectively.

Compounds **39–53**, which all contain a sulfonamide group in place of the amide group in the linker region (Table 3), were made. Compound **39**, in which a sulfonamide group was used to replace the amide group in **11**, binds to D₃ with a similar affinity (1.5 nM) as **11**, but its selectivity over D₂ is decreased due to its increased binding affinity to D₂. Compound **40**, in which the naphthyl group is connected to the sulfonamide group *via* its alpha position instead of the beta position in **39**, binds to D₃ with a K_i value of 1.5 nM and has a selectivity of 21-times for D₃ over D₂. Compound **41**, in which the naphthyl group in **39** is replaced by a phenyl group, binds to the D₃ receptor with a K_i of 0.79 nM, and due to its decreased binding affinity to D₂, its selectivity over D₂ is improved to 72-fold, 8 times more selective than **39**. Compound **42**, in which the naphthyl group in **39** is replaced by a biphenyl group, binds to D₃ with a K_i value of 41 nM, much weaker than compound **39**.

Compound **41** has a high binding affinity to D₃ but a modest selectivity for D₃ over D₂. We next modified the phenyl ring of **41** using different substituents, which yielded compounds **43–50**. Compound **43**, which has a *meta*-F substituent, has a high binding affinity to D₃ (K_i = 0.72 nM) and displays 190-fold selectivity over D₂. Compound **44**, which has a methoxyl group at the *para* position of the phenyl ring, binds to D₃ with a high affinity (K_i = 0.78 nM), but its selectivity over D₂ is decreased to 49-fold due to its improved binding affinity to D₂. Compounds **45–47** with a Cl substituent at three different positions in the phenyl ring have high binding affinities (K_i = 0.68–1.1 nM) to D₃ and 100-fold selectivity over D₂. Compound **48** with a *meta* methyl substituent binds to D₃ with a high affinity (0.89 nM) and has a selectivity of 70-fold over D₂. However, an isopropyl (**49**) or a tert-butyl (**50**) substituent at the *para* position of the phenyl ring decreases the binding affinity to the D₃ receptor by a factor of 6 as compared to **41**. These two compounds also have a modest selectivity of 20–30 times over D₂.

Both **46** and **47** have a high affinity to D₃ but a modest selectivity for D₃ over D₂. We replaced one carbon atom with a nitrogen atom in the phenyl ring in **46** and **47** to investigate the effect on binding and selectivity. Compound **51**, in which a nitrogen atom was inserted into the *meta* position of the phenyl ring in **46**, binds to D₃ with the same affinity as **46** but is slightly less selective than **46** over D₂. Compound **52**, in which a nitrogen atom was inserted into the *ortho* position with respect to the Cl substituent in the phenyl ring in **47**, binds to D₃ with a K_i value of 0.38 nM and has a selectivity of 451 times over D₂. Compound **53**, in which a nitrogen atom was inserted into the *para* position with respect to the Cl substituent in the phenyl ring in **47**, binds to D₃ with a K_i value of 0.93 nM and has a selectivity of 229 times over D₂.

Hence, our chemical modifications of compound **11** have identified a number of new ligands with high affinities to D₃ and an excellent selectivity for D₃ over D₂. Of these, **38** (UM-206) and **52** (UM-226) bind to D₃ with K_i values of 0.73 nM and 0.38 nM, respectively, and have a selectivity of 494 and 451 times, respectively, over D₂. These two compounds also display a selectivity of >10,000 times for D₃ over the D₁-like receptors.

We evaluated **38** and **52** in the D₃ functional mitogenesis assay using CHO cells transfected with the human D₃ receptor. The functional data showed that both **38** and **52** function as full agonists with EC₅₀ values of 4.3 ± 1.2 nM and 1.5 ± 0.5 nM, respectively.

The synthesis of compounds **15–23** is shown in Scheme 1. Pramipexole **9** was allowed to react with commercially available *tert*-butyl trans-4-(2-oxoethyl)cyclohexylcarbamate to give key intermediate **13** which was treated with TFA to afford the amine **14**. Compound **14**, when reacted with different cinnamoyl chlorides, gave compounds **15–23**. The synthesis of compounds **24–38** is straightforward and is shown in Scheme 2. Compound **14** was condensed with the appropriate carboxylic acid to give the designed compounds, **24–38**. The synthesis of compounds **39–53** is described in Scheme 3. Compound **14** was reacted with appropriate sulfonyl chloride in the presence of diisopropylethylamine (DIPEA) to give compounds **39–53**.

In summary, through chemical modifications of our previously reported two D₃ ligands, compound **10** and **11**, we have identified a number of new D₃ ligands with high binding affinities to the D₃ receptor and an excellent selectivity over the D₂ and D₁ receptors based upon our *in vitro* binding data. Compounds **38** and **52** are the two most potent and selective D₃ ligands among these new analogues. Both compounds bind to D₃ with a K_i value of <1 nM and display a selectivity of 450–494 times over D₂ and >10,000 selectivity over D₁. Both **38** and **52** are full agonists with a high potency at the D₃ receptor in a D₃ functional assay. Further *in vivo* characterizations of these compounds are in progress and will be reported in due course.

Acknowledgments

This work was supported by a grant from the National Institute on Drug Abuse, National Institutes of Health (R01DA020669). We are grateful to the Addiction Treatment Discovery Programs at the NIDA, NIH, for evaluation of compounds **38** and **52** for their functional activity in cells transfected with cloned human dopamine receptors under the contract NIDA Y1-DA-0101-02, performed by Dr. Aaron Janowsky at the Oregon Health & Science University (Portland, Oregon).

References and notes

1. Joyce JN. Pharmacol Ther. 2001; 90:231. [PubMed: 11578658]
2. Prasad S, Semwal P, Deshpande S, Bhatia T, Nimgaonkar VL, Thelma BK. J Biosci. 2002; 27:35. [PubMed: 11927776]

3. Shimohama S, Sawada H, Kitamura Y, Taniguchi T. Trends Mol Med. 2003; 9:360. [PubMed: 12928038]
4. Volkow ND, Fowler JS, Wang GJ. Behav Pharmacol. 2002; 13:355. [PubMed: 12394411]
5. Luedtke RR, Mach RH. Curr Pharm Des. 2003; 9:643. [PubMed: 12570797]
6. Pilla M, Perachon S, Sautel F, Garrido F, Mann A, Wermuth CG, Schwartz JC, Everitt BJ, Sokoloff P. Nature. 1999; 400:371. [PubMed: 10432116]
7. Newman AH, Grundt P, Nader MA. J Med Chem. 2005; 48:3663. [PubMed: 15916415]
8. Heidbreder CA, Newman AH. Ann N Y Acad Sci. 2010; 1187:4. [PubMed: 20201845]
9. Reavill C, Taylor SG, Wood MD, Ashmeade T, Austin NE, Avenell KY, Boyfield I, Branch CL, Cilia J, Coldwell MC, Hadley MS, Hunter AJ, Jeffrey P, Jewitt F, Johnson CN, Jones DN, Medhurst AD, Middlemiss DN, Nash DJ, Riley GJ, Routledge C, Stemp G, Thewlis KM, Trail B, Vong AK, Hagan JJ. J Pharmacol Exp Ther. 2000; 294:1154. [PubMed: 10945872]
10. Yuan J, Chen X, Brodbeck R, Primus R, Braun J, Wasley JW, Thurkauf A. Bioorg Med Chem Lett. 1998; 8:2715. [PubMed: 9873609]
11. Robarge MJ, Husbands SM, Kieltyka A, Brodbeck R, Thurkauf A, Newman AH. J Med Chem. 2001; 44:3175. [PubMed: 11543687]
12. Bettinetti L, Schlotter K, Hubner H, Gmeiner P. J Med Chem. 2002; 45:4594. [PubMed: 12361386]
13. Hackling A, Ghosh R, Perachon S, Mann A, Holtje HD, Wermuth CG, Schwartz JC, Sippl W, Sokoloff P, Stark H. J Med Chem. 2003; 46:3883. [PubMed: 12930150]
14. Leopoldo M, Berardi F, Colabufo NA, De Giorgio P, Lacivita E, Perrone R, Tortorella V. J Med Chem. 2002; 45:5727. [PubMed: 12477356]
15. Campiani G, Butini S, Trotta F, Fattorusso C, Catalanotti B, Aiello F, Gemma S, Nacci V, Novellino E, Stark JA, Cagnotto A, Fumagalli E, Carnovali F, Cervo L, Mennini T. J Med Chem. 2003; 46:3822. [PubMed: 12930145]
16. Macdonald GJ, Branch CL, Hadley MS, Johnson CN, Nash DJ, Smith AB, Stemp G, Thewlis KM, Vong AK, Austin NE, Jeffrey P, Winborn KY, Boyfield I, Hagan JJ, Middlemiss DN, Reavill C, Riley GJ, Watson JM, Wood M, Parker SG, Ashby CR Jr. J Med Chem. 2003; 46:4952. [PubMed: 14584946]
17. Campiani G, Butini S, Fattorusso C, Catalanotti B, Gemma S, Nacci V, Morelli E, Cagnotto A, Mereghetti I, Mennini T, Carli M, Minetti P, Di Cesare MA, Mastroianni D, Scafetta N, Galletti B, Stasi MA, Castorina M, Pacifici L, Vertechy M, Di Serio S, Ghirardi O, Tinti O, Carminati P. J Med Chem. 2004; 47:143. [PubMed: 14695828]
18. Grundt P, Carlson EE, Cao J, Bennett CJ, McElveen E, Taylor M, Luedtke RR, Newman AH. J Med Chem. 2005; 48:839. [PubMed: 15689168]
19. Varady J, Wu X, Fang X, Min J, Hu Z, Levant B, Wang S. J Med Chem. 2003; 46:4377. [PubMed: 14521403]
20. Haadsma-Svensson SR, Cleek KA, Dinh DM, Duncan JN, Haber CL, Huff RM, Lajiness ME, Nichols NF, Smith MW, Svensson KA, Zaya MJ, Carlsson A, Lin CH. J Med Chem. 2001; 44:4716. [PubMed: 11741489]
21. Ji M, Chen J, Ding K, Wu X, Varady J, Levant B, Wang S. Bioorg Med Chem Lett. 2005; 15:1701. [PubMed: 15745825]
22. Ding K, Chen J, Ji M, Wu X, Varady J, Yang CY, Lu Y, Deschamps JR, Levant B, Wang S. J Med Chem. 2005; 48:3171. [PubMed: 15857123]
23. Chen J, Ding K, Levant B, Wang S. Bioorg Med Chem Lett. 2006; 16:443. [PubMed: 16290142]
24. Ehrlich K, Gotz A, Bollinger S, Tschammer N, Bettinetti L, Harterich S, Hubner H, Lanig H, Gmeiner P. J Med Chem. 2009; 52:4923. [PubMed: 19606869]
25. Chen J, Collins GT, Zhang J, Yang CY, Levant B, Woods J, Wang S. J Med Chem. 2008; 51:5905. [PubMed: 18785726]
26. Micheli F, Arista L, Bertani B, Braggio S, Capelli AM, Cremonesi S, Di-Fabio R, Gelardi G, Gentile G, Marchioro C, Pasquarello A, Provera S, Tedesco G, Tarsi L, Terreni S, Worby A, Heidbreder C. J Med Chem. 2010; 53:7129. [PubMed: 20839775]

27. Biswas S, Hazeldine S, Ghosh B, Parrington I, Kuzhikandathil E, Reith ME, Dutta AK. *J Med Chem.* 2008; 51:3005. [PubMed: 18410082]
28. Brown DA, Kharkar PS, Parrington I, Reith ME, Dutta AK. *J Med Chem.* 2008; 51:7806. [PubMed: 19053758]
29. Ghosh B, Antonio T, Reith ME, Dutta AK. *J Med Chem.* 2010; 53:2114. [PubMed: 20146482]
30. Grundt P, Prevatt KM, Cao J, Taylor M, Floresca CZ, Choi JK, Jenkins BG, Luedtke RR, Newman AH. *J Med Chem.* 2007; 50:4135. [PubMed: 17672446]
31. Newman AH, Grundt P, Cyriac G, Deschamps JR, Taylor M, Kumar R, Ho D, Luedtke RR. *J Med Chem.* 2009; 52:2559. [PubMed: 19331412]
32. Micheli F, Arista L, Bonanomi G, Blaney FE, Braggio S, Capelli AM, Checchia A, Damiani F, Di-Fabio R, Fontana S, Gentile G, Griffante C, Hamprecht D, Marchioro C, Mugnaini M, Piner J, Ratti E, Tedesco G, Tarsi L, Terreni S, Worby A, Ashby CR Jr, Heidebreder C. *J Med Chem.* 2010; 53:374. [PubMed: 19891474]
33. Wood MD, Boyfield I, Nash DJ, Jewitt FR, Avenell KY, Riley GJ. *Eur J Pharmacol.* 2000; 407:47. [PubMed: 11050289]
34. Wicke K, Garcia-Ladona J. *Eur J Pharmacol.* 2001; 424:85. [PubMed: 11476753]

Figure 1.
Chemical structures of representative known D3 ligands.

Scheme 1.

Synthesis of compounds **15–23**. Conditions and reagents: (i) tert-butyl trans-4-(2-oxoethyl)cyclohexyl carbamate, NaBH(OAc)₃, MOAc, DCM, 75%; (ii) TFA, DCM, RT, 12 h, 90%; (iii) respective cinnamoyl chloride, DIPEA, DCM, RT, 2 h, 50–76%.

Scheme 2.

Synthesis of compounds **24–38**. Conditions and reagents: (i) RCO_2H , EDCI, HOBt, DIPEA, DCM, 55–78%.

Scheme 3.

Synthesis of compounds **39-53**. Conditions and reagents: (i) RSO_2Cl , DIPEA, DCM, RT, 2 h, 60–75%.

Table 1

Binding Affinities at the D₁-like, D₂-like, and D₃ Receptors in Binding Assays Using Rat Brain.

ligand	R	$K_{\pm}$ SEM (nM)				Selectivity	
		D ₃ ([³ H]-R(+)-7-OH-DPAT)	D ₂ -like ([³ H]Spiperone)	D ₁ -like ([³ H]SCH23390)	D ₂ -like/D ₃	D ₁ -like/D ₃	
9		0.78	3.1±0.3	>100,000	4.0	>100,000	
10	H	1.0±0.04	239±60	NT	239	NT	
15	4-F	1.0±0.2	66±10	4,674±466	66	71	
16	3-F	9.9±2.4	80±2	6,606±556	8	666	
17	2-F	2.9±0.3	92±32	10,022±1692	32	3,513	
18	4-Cl	2.5±0.7	27±4	4,032±394	11	1,596	
19	3-Cl	1.2±0.3	52±7	5,766±508	43	4,644	
20	2-Cl	1.2±0.2	30±5	5,436±389	26	4,646	
21	4-OMe	6.7±1.5	94±9	8,026±776	14	1,196	
22	3-OMe	9.3±1.7	122±23	8,890±928	13	953	
23	2-OMe	8.1±0.8	102±10	7,916±712	13	983

Table 2

Binding Affinities at the D₁-like, D₂-like, and D₃ Receptors in Binding Assays Using Rat Brain.

ligand	$K_i \pm \text{SEM}$ (nM)				Selectivity	
	R	D ₃ ([³ H]-R(+)-7-OH-DPAT)	D ₂ -like ([³ H]Spiperone)	D ₁ -like ([³ H]SCH23390)	D ₂ -like/D ₃	D ₁ -like/D ₃
11		1.1±0.3	185±61	NT	168	NT
24		1.6±0.24	88±4.8	11,305±864	55	6,054
25		1.6±0.25	72±5.7	44,047±2,317	45	27,106
26		5.9±1.4	64±16	26,450±2,782	11	4,503
27		2.0±0.55	45±3.3	46,877±5,199	23	23,755
28		1.9±0.03	23±2.6	37,163±2,354	12	19,909

ligand	R	$K_{\pm}$ SEM (nM)			Selectivity	
		D ₃ ([³ H]-R(+)-7-OH-DPAT)	D ₂ -like ([³ H]Spiperone)	D ₁ -like ([³ H]SCH23390)	D ₂ -like/D ₃	D ₁ -like/D ₃
29		3.0±0.69	43±5.9	59,660±5,488	14	19,877
30		1.1±0.26	32±2.3	24,667±1,894	29	21,790
31		3.0±0.29	52±0.43	14,407±1,184	18	4,867
32		2.4±0.51	56±5.2	14,033±1,691	23	5,959
33		1.3±0.12	442±41	34,613±3,625	345	27,041
34		2.1±0.15	328±53	17,748±921	155	8,381
35		2.0±0.19	470±53	10,912±756	231	5,366

ligand	R	K_i SEM (nM)			Selectivity	
		D ₃ ([³ H]-R(+)-7-OH-DPAT)	D ₂ -like ([³ H]Spiperone)	D ₁ -like ([³ H]SCH23390)	D ₂ -like/D ₃	D ₁ -like/D ₃
36		3.5±0.57	633±100	11,410±765	180	3,245
37		1.5±0.23	491±70	5,000±495	339	3,448
38		0.73±0.028	359±58	9,937±888	494	13,678

Table 3

Binding Affinities at the D₁-like, D₂-like, and D₃ Receptors in Binding Assays Using Rat Brain.

ligand	$K_i \pm \text{SEM}$ (nM)					Selectivity	
	R	D ₃ ([³ H]-R(+)-7-OH-DPAT)	D ₂ -like ([³ H]Spiperone)	D ₁ -like ([³ H]SCH23390)	D ₂ -like/D ₃	D ₁ -like/D ₃	
39		1.5 ± 0.2	14 ± 2	3,689 ± 366	9	2,427	
40		1.5 ± 0.4	31 ± 3	4,667 ± 476	21	3,164	
41		0.79 ± 0.08	57 ± 8	23,370 ± 1,331	72	29,686	
42		41 ± 3	75 ± 10	1,800 ± 168	2	44	
43		0.72 ± 0.11	136 ± 17	10,359 ± 805	190	14,467	
44		0.78 ± 0.11	38 ± 3	21,330 ± 1,006	49	27,487	
45		1.1 ± 0.1	127 ± 15	5,552 ± 231	117	5,094

ligand	R	$K_i \pm \text{SEM}$ (nM)				Selectivity	
		D_3 ([^3H]-R(+)-7-OH-DPAT)	D_2 -like ([^3H]-Spiperone)	D_1 -like ([^3H]-SCH23390)	D_2 -like/ D_3	D_1 -like/ D_3	
46		0.95 ± 0.01		71 ± 5	$8,287 \pm 257$	75	8,754
47		0.68 ± 0.06		66 ± 11	$9,484 \pm 630$	98	14,015
48		0.89 ± 0.04		62 ± 8	$8,399 \pm 672$	70	9,472
49		4.5 ± 0.1		133 ± 16	$8,147 \pm 836$	30	1,810
50		5.0 ± 0.4		101 ± 12	$3,149 \pm 263$	20	626
51		0.63 ± 0.04		28 ± 3	$8,191 \pm 937$	44	12,933
52		0.38 ± 0.05		170 ± 19	$17,443 \pm 1,727$	451	46,310
53		0.93 ± 0.10		213 ± 11	$10,716 \pm 623$	229	11,523