ACS Medicinal Chemistry Letters

Letter

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ACS Med. Chem. Lett., **Just Accepted Manuscript** • DOI: 10.1021/acsmedchemlett.9b00050 • Publication Date (Web): 05 Apr 2019

Just Accepted

ACS Publications

is published by the American Chemical Society. 1155 Sixteenth Street N.W., Washington, DC 20036

Synthesis and pharmacological evaluation of non-catechol G protein biased and unbiased dopamine D1 receptor agonists

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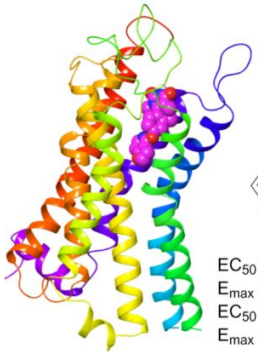
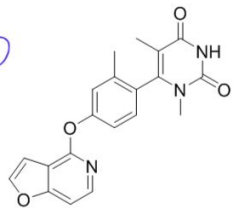
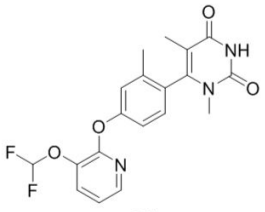
ABSTRACT: Non-catechol heterocycles have recently been discovered as potent and selective G protein biased dopamine 1 receptor (D1R) agonists with superior pharmacokinetic (PK) properties. To determine the structure-activity relationships (SARs) centered on G protein or β-arrestin signaling bias, systematic medicinal chemistry was employed around three aromatic pharmacophores of the lead compound **5** (PF2334), generating a series of new molecules that were evaluated at both D1R G_s-dependent cAMP signaling and β-arrestin recruitment in HEK293 cells. Here we report the chemical synthesis, pharmacological evaluation and molecular docking studies leading to the identification of two novel non-catechol D1R agonists that are a sub-nanomolar potent unbiased ligand **19** (PW0441) and a nanomolar potent complete G protein biased ligand **24** (PW0464), respectively. These novel D1R agonists provide important tools to study D1R activation and signaling bias in both health and disease.





19

EC_{50} = 0.3 ± 0.1 nM (Gs-cAMP)
E_{max} = 107 ± 6 %DA (Gs-cAMP)
EC_{50} = 35 ± 4 nM (Arrestin-TANGO)
E_{max} = 86 ± 14 %DA (Arrestin-TANGO)



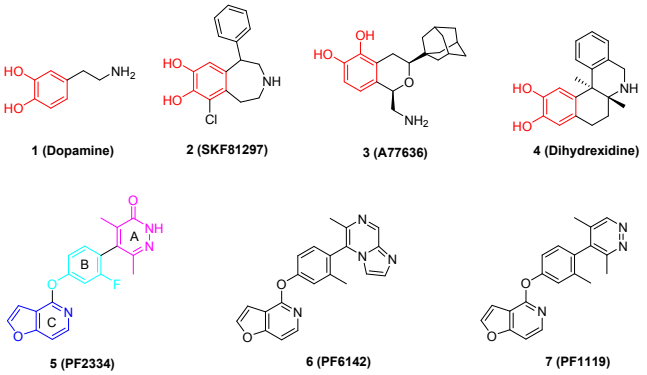
24

EC_{50} = 5.8 ± 1.0 nM (Gs-cAMP)
E_{max} = 104 ± 2 %DA (Gs-cAMP)
EC_{50} = No effect (Arrestin-TANGO)
E_{max} = No effect (Arrestin-TANGO)

KEYWORDS: *dopamine 1 receptor, biased agonism, functional selectivity, non-catechol, cAMP, β-arrestin*

The dopamine (DA) (**1**, **Figure 1**) receptor family consists of five G protein-coupled receptors (GPCRs) which play a critical role in central nervous system (CNS) signaling.[1] Numerous studies have revealed that dopamine receptors are involved in the pathophysiology of human diseases including neurologic and psychiatric illnesses,[2, 3] addiction,[4] cardiovascular and endocrine diseases.[5] Based on their structure, biochemical and pharmacological characteristics, the dopamine receptor family are divided into two subfamilies: the D1-like family (D1 and D5) or the D2-like family (D2, D3 and D4).[6] Canonical dopamine signaling by D1-like receptors occurs via heterotrimeric $G_{s/olf}$ proteins which activate adenylyl cyclase to increase production of cyclic adenosine monophosphate (cAMP).[1, 6] In addition, D1-like receptors can engage and couple to β-arrestin proteins, which control receptor trafficking, desensitization and promote G protein-independent signaling.[1, 6] Agonists that activate receptors to signal primarily via G proteins versus β-arrestin are known as biased agonists,[7] which may improve agonist efficacy and/or reduce side effects induced by receptor ligands.[8]

The dopamine 1 receptor (D1R) is the most abundant dopamine receptor in mammalian brain, with particularly high expression in the striatum (caudate, putamen and nucleus accumbens) and the frontal cortex.[9] The D1R enables DA neurotransmission to control working memory and attention,[10, 11] voluntary movement,[12, 13] reward,[14, 15] and other physiological processes. Hypofunction of the D1R has also been observed in a variety of neurologic and psychiatric disorders including Parkinson's disease (PD),[16] Alzheimer's disease (AD),[17] attention deficit hyperactivity disorder (ADHD),[18] cognitive impairment in schizophrenia[19] and addiction.[20] This suggests that selective activation of the D1R is a promising therapeutic avenue for developing CNS therapeutics.



1 (Dopamine) **2 (SKF81297)** **3 (A77636)** **4 (Dihydrexidine)**

5 (PF2334) **6 (PF6142)** **7 (PF1119)**

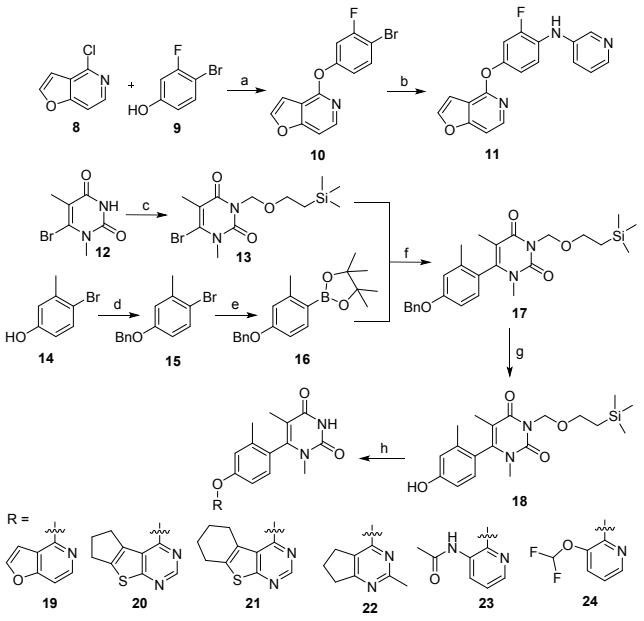
Figure 1. Structures of previous representative catechol (shown in red) and non-catechol D1R selective agonists.

Due to the fundamental role of the D1R in the CNS function and disease, tremendous efforts for over 40 years have been devoted to the discovery of selective D1R agonists for clinical use.[2, 21-23] While several selective D1R ligands have been identified, none are currently FDA approved for the treatment of CNS disorders, and development of clinically viable, drug-like D1R selective agonists for CNS diseases remains elusive. This is primarily due to the chemistry of all previous D1R agonists, which possess a dihydroxyphenyl catechol or catechol-like scaffolds, for example compounds **2**, **3**, and **4** (highlighted in red, **Figure 1**). Catechol-based D1R agonists suffer from poor CNS penetration, negligible oral bioavailability, rapid metabolism and therefore insufficient *in vivo* efficacy.[22] Most recently, a new generation of D1R non-catechol agonists (compounds **5-7**, **Figure 1**) with high affinity, selectivity and superior PK (pharmacokinetic) profiles were reported by Pfizer.[24, 25] In addition, previous catechol D1R agonists typically display activation of both G protein-

mediated and β-arrestin recruitment; however, a recent report suggested select benzazepine derivatives exhibit G protein bias;[26] while non-catechol D1R agonists show minimal β-arrestin recruitment (G protein biased agonists).[22, 26] Accumulated studies suggest that the D1R-mediated β-arrestin recruitment pathway may be involved in memory related functions and cognitive processes.[27-30] In addition, D1R-mediated β-arrestin recruitment can cause D1R desensitization that may limit the efficacy of some D1R agonists.[22, 24, 31] To accurately address the impact of D1R-mediated signaling by β-arrestins versus G proteins, novel D1R chemical probes that are biased and unbiased at these pathways are needed. Here we report the synthesis, biological activity and docking studies of novel non-catechol D1R ligands leading to our discovery of G protein biased and the first unbiased non-catechol agonist. These novel chemical probes provide important tools to study D1R signaling mechanisms in health and disease and to evaluate if balanced or biased D1R agonist activity is preferred for the treatment of neurological and psychiatric disorders.

The general premise of this report was to apply the scaffold of the selective, high affinity, non-catechol G protein-biased D1R agonist, compound **5**,[24] as the lead compound for further structure−activity relationship (SAR) studies. We employed systematic medicinal chemistry around three aromatic substituents of compound **5**: (**A**) head pyridazinone, (**B**) middle phenyl, and (**C**) lower furopyridine (**Figure 1**; Ring C highlighted in blue, ring B highlighted in cyan and ring A highlighted in pink). The synthetic procedures of these newly synthesized D1R agonists are depicted in **Schemes 1-3**.

Scheme 1. Synthesis of compounds **11** and **19 - 24**[a]

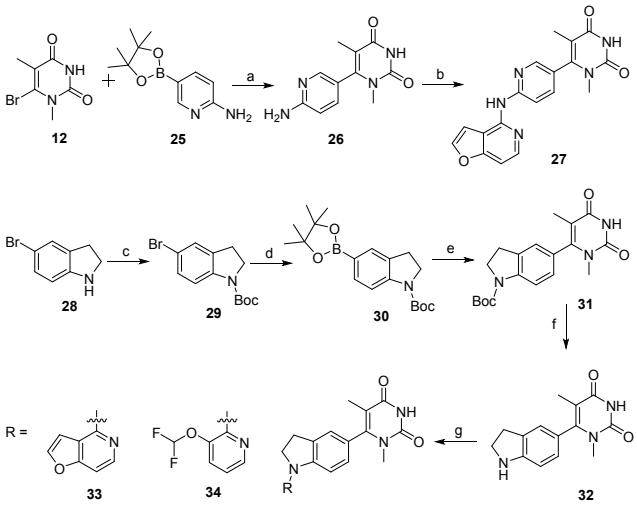


[a]Reagents and conditions: (a) Cs_2CO_3, DMSO, 18 h, 86%; (b) Tris(dibenzylideneacetone)dipalladium(0), pyridin-3-amine, K_2CO_3, XantPhos, 1,4-dioxane, 100 °C, 12 h, 67%; (c) 2-(trimethylsilyl)ethoxymethyl chloride, 1,8-Diazabicyclo[5.4.0]undec-7-ene, MeCN, 60 °C, 18 h, 64%; (d) BnBr, K_2CO_3, DMF, rt, 12 h, 80%; (e) bis(pinacolato)diboron, [1,1'-Bis(diphenylphosphino)ferrocene]dichloropalladium(II), KOAc, 1,4-dioxane, 85 °C, 16 h, 71%; (f) [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II), K_2CO_3, 1,4-dioxane, 100 °C, 12 h, 41%; (g) H_2, $Pd(OH)_2$/C, EtOH, 60 °C, 12 h, 94%; (h) (i) Cs_2CO_3, corresponding Cl-R, 120 °C, 12 h. (ii) CF_3COOH, CH_2Cl_2, rt, 1 h; (iii) K_2CO_3, MeOH, rt, 12 h, 37-69% (three steps).

First, we modified the pyridazin-3(2*H*)-one moiety of compound **5** leading to compound **11**, and its synthetic route is described in **Scheme 1**. With starting material 4-chlorofuro[3,2-*c*]pyridine (**8**) and 4-bromo-3-fluorophenol (**9**), the intermediate **10** was obtained in the presence of Cs_2CO_3.[24] Compound **11** was produced via C-N coupling reaction of **10** with pyridin-3-amine in a yield of 67%.[32] Replacement the pyridazin-3(2*H*)-one moiety of compound **5** with pyrimidine-2,4(1*H*,3*H*)-dione led to compound **19**. Further modification of compound **19** by replacement of the furo[3,2-*c*]pyridine with tricyclic ring, bicyclic ring and pyridine ring generated compounds **20-24** (**Scheme 1**). Protection of compound **12**[33] with 2-(trimethylsilyl)ethoxymethyl group resulted in key intermediate **13**. The intermediate **15** was obtained by protection of the starting material 4-bromo-3-methylphenol (**14**) with a benzyl group. Treatment of intermediate **15** with bis(pinacolato)diboron under palladium catalysis produced the intermediate **16**. Coupling of the intermediate **13** with **16** under the condition of Suzuki reaction provided the intermediate **17**. Deprotection of the benzyl group of **17** led to intermediate **18**. Compounds **19** ~ **24** were obtained by reaction of intermediate **18** with corresponding heterocyclic halides[34-36] in the presence of Cs_2CO_3, followed by deprotection of the 2-(trimethylsilyl)ethoxymethyl group.

As outlined in **Scheme 2**, compound **27** was designed by substituting the phenoxyl group of compound **19** with aminopyridine ring. The intermediate **26** was produced via C-N coupling reaction of **12** with compound **25** in a yield of 67%. Further, the C-N coupling reaction of intermediate **26** with compound **8** afforded compound **27**. Replacement of the phenoxyl scaffold of compound **19** with indoline led to compounds **33** and **34**. The intermediate **29** was obtained by protection of the starting material 5-bromoindoline (**28**) with a Boc group. Treatment of intermediate **29** with bis(pinacolato)diboron under palladium catalysis produced the intermediate **30**. Coupling of the intermediate **30** with **12** under the condition of Suzuki reaction provided the intermediate **31**, followed by Boc-deprotection leading to intermediate **32**. Coupling of **32** with corresponding heterocyclic halides under the C-N condition produced compounds **33** and **34**, respectively.

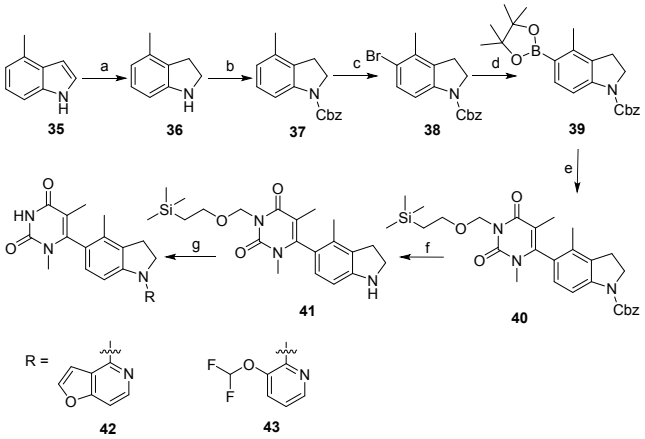
Scheme 2. Synthesis of compounds **27**, **33** and **34** [a]



[a]Reagents and conditions: (a) [1,1'-bis(diphenylphosphino)ferrocene]tdichloropalladium(II), K_2CO_3, 1,4-dioxane, 100 °C, 12 h, 67%; (b) compound **8**, tris(dibenzylideneacetone)dipalladium(0), 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene, K_2CO_3, 1,4-dioxane, 100 °C, 12 h, 59%; (c) $(Boc)_2O$, Et_3N, CH_2Cl_2, rt, 12 h, 91%; (d) bis(pinacolato)diboron, bis(diphenylphosphino) ferrocene]tdichloropalladium(II), KOAc, 1,4-dioxane, 85 °C, 16 h, 81%; (e) $Pd(PPh_3)_4$, Na_2CO_3, 1,4-dioxane, water, 100 °C, 12 h, 77%; (f) i) CF_3COOH, CH_2Cl_2, rt, 1 h; ii) K_2CO_3, MeOH, rt, 12 h, 92%; (g) $Pd(OAc)_2$, 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene, Cs_2CO_3, 1,4-dioxane, 100 °C, 12 h, 50-73%.

Compounds **42** and **43** were designed by adding a methyl group on the compounds **33** and **34**, respectively, and the synthetic procedures are outlined in **Scheme 3**. 4-Methylindoline (**36**) was obtained by hydrogenation of the starting material 4-methyl-1*H*-indole (**35**). Protection of intermediate **36** by CbzCl in the presence of Et_3N led to intermediate **37**. Compound **38** was prepared by reacting intermediate **37** with NBS. The boronate intermediate **39** was synthesized from compound **38** under the palladium catalysis condition, and was further converted into compound **40** under palladium catalyzed cross-coupling reaction conditions. Cbz-deprotection of compound **40** gave intermediate **41.** Coupling of **41** with corresponding heterocyclic halides under the palladium catalyzed C-N condition led to the compounds **42** and **43**. The detailed synthetic procedures and structural characterization data are provided in the **Supporting Information** (SI).

Scheme 3. Synthesis of compounds **42** and **43**[a]



[a]Reagents and conditions: (a) $NaBH_3CN$, AcOH, 0 °C - rt, 4 h, 68%; (b) CbzCl, Et_3N, CH_2Cl_2, 0 °C - rt , 12 h, 74%; (c) *N*-bromosuccinimide, CH_2Cl_2, 0 °C ~ rt , 12 h, 94%; (d) bis(pinacolato)diboron, [1,1'-Bis(diphenylphosphino) ferrocene]dichloropalladium(II), KOAc, 1,4-dioxane, 70 °C, 48 h, 46%; (e) **13**, [1,1'-Bis(diphenylphosphino)ferrocene] dichloropalladium(II), K_2CO_3, 1,4-dioxane, 100 °C, 12 h, 38%; (f) Pd/C, H_2, rt, 12 h, 96%; (g) (i) $Pd(OAc)_2$, 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene, Cs_2CO_3, 1,4-dioxane, 100 °C, 12 h. (ii) CF_3COOH, CH_2Cl_2, rt, 1 h; (iii) K_2CO_3, MeOH, rt, 12 h, 17-24% (three steps).

Previous studies of non-catechol D1R agonists suggested that the head group (**A**) might interact with residues S188 and L190 in ECL2 to influence the potency of G protein-mediated cAMP signaling.[24] To probe the steric availability and flexibility around this region of the molecule, we introduced a nitrogen linker to yield compound **11**, which was found to drastically decrease the cAMP potency (> 1,000 nM). However, replacement of pyridazin-3(2*H*)-one moiety of compound **5** with pyrimidine-2,4(1*H*,3*H*)-dione to yield compound **19** resulted in a dramatically increased cAMP potency from 10.3 ± 2.8 nM to 0.3 ± 0.1 nM, and retained efficacy in the cAMP assay (**Figure 3** and **Table 1**). Interestingly, this substitution led to the restoration of β-arrestin recruitment, which increased the potency from 485 ± 102 nM to 35 ± 4 nM, and efficacy from 45 ± 4 to 86 ± 14 % DA, in comparison to the lead compound (**Figure 4** and **Table 2**). The reversal of G protein cAMP bias from compound **5** to **19** suggests that ECL2 interactions with this head group may affect both potency and signaling bias.

Table 1. EC_{50} values and E_{max} (Gs-cAMP) of D1R agonists

Compounds	cLogP[a]	Gs-cAMP EC_{50} (nM)[b]	E_{max} (% DA)[b]
1	-0.40	44 ± 14	100
2	3.03	4.7 ± 2.8	100 ± 3
5	3.28	10 ± 3	90 ± 4
6	4.13	11 ± 3	78 ± 6
7	4.13	81 ± 38	66 ± 5
11	4.14	>1,000	63 ± 1
19	3.02	0.3 ± 0.1	107 ± 6
20	3.51	>1,000	30 ± 2
21	3.75	>1,000	7 ± 1

22	2.83	580 ± 60	5 ± 1
23	2.37	610 ± 86	106 ± 17
24	2.97	5.3 ± 1.0	104 ± 2
27	2.27	450 ± 100	89 ± 2
33	3.18	410 ± 70	61 ± 8
34	3.01	>1,000	77 ± 2
42	3.23	360 ± 120	96 ± 9
43	3.28	950 ± 190	92 ± 4

[a]cLogP: http://biosig.unimelb.edu.au/pkcsm/prediction. [b]The values are the mean ± S.E.M. of at least three independent experiments.

Table 2. EC_{50} values and E_{max} (Arrestin-TANGO) of selected D1R agonists

Compounds	Arrestin-TANGO	
	EC_{50} (nM)[a]	E_{max} (% DA)[a]
1	1,400 ± 190	100
2	360 ±70	76 ± 6
5	490 ± 100	45 ± 4
6	320 ± 50	21 ± 2
7	1,100 ± 300	9 ± 2
19	35 ± 4	86 ± 14
24	N.A.[b]	N.A.[b]

[a]The values are the mean ± S.E.M. of at least three independent experiments. [b]N.A. is no activity

Gray and Allen et al. previously suggested the lower heterocycle (**C**) in compound **5** orients the compound into a unique binding mode, responsible for enabling G protein bias.[24] Thus, we further probed the steric and electronic components around the lower scaffold of the molecule to probe the SAR influencing signaling bias of these non-catechol agonists. Increasing the size and/or aromaticity of the heterocycle, i.e. compounds **20-22**, detrimentally affected both cAMP potency (> 500 nM) and efficacy (< 30% DA), suggesting that the space in the orthosteric binding pocket for the heterocycle is sterically limited (**Table 1**). In addition, all of the newly synthesized compounds exhibit cLogP < 5, similar to compound **5**, suggesting these novel ligands may have a favorable PK profile (**Table 1**). Interestingly, when we broke the furan ring into a linear substituted amide, or difluoroether moiety yielding compounds **23** and **24**, these molecules retained their cAMP full agonism, and compound **24** was similarly potent (5.3 ± 1.0 nM) to compound **5** (10.3 ± 2.8 nM). Additionally, compound **24** was found to elicit complete G protein bias, showing no activity for D1R-mediated β-arrestin recruitment (**Figure 4** and **Table 2**).

Compounds **27**, **33**, **34**, **42** and **43** were synthesized to probe the impact of flexibility and aromaticity of the middle aromatic ring (**B**). Unfortunately, all five compounds substantially lost potency in the cAMP assay (decreased ≥ 500 nM) (**Table 1**), suggesting that modifications on this portion of the molecule are neither amenable for D1R G protein activation, nor β-arrestin recruitment.

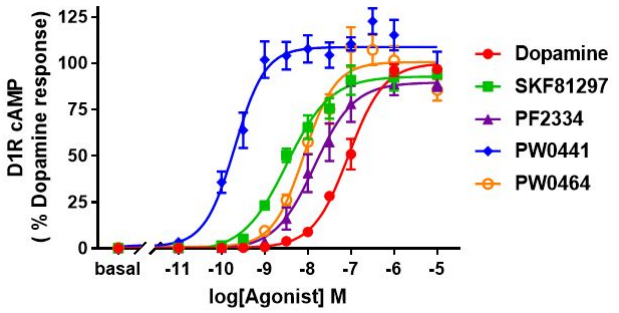


Figure 3. Representative dose-response curve for D1R-mediated cAMP increase from **1** (red), **2** (green), **5** (purple), **19** (PW0441, blue), **24** (PW0464, orange). Luminescence counts/sec were normalized to 100% DA response (10 μM DA).

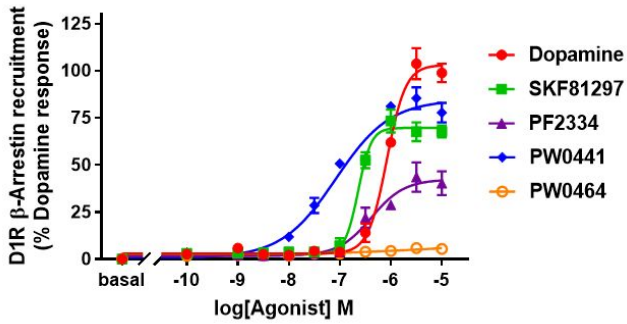


Figure 4. Representative dose-response curve for D1R-mediated β-arrestin recruitment from **1** (red), **2** (green), **5** (purple), **19** (PW0441, blue), **24** (PW0464, orange). Luminescence counts/sec were normalized to 100% DA response (10 μM DA).

Table 3. D1R affinity values of selected D1R agonists

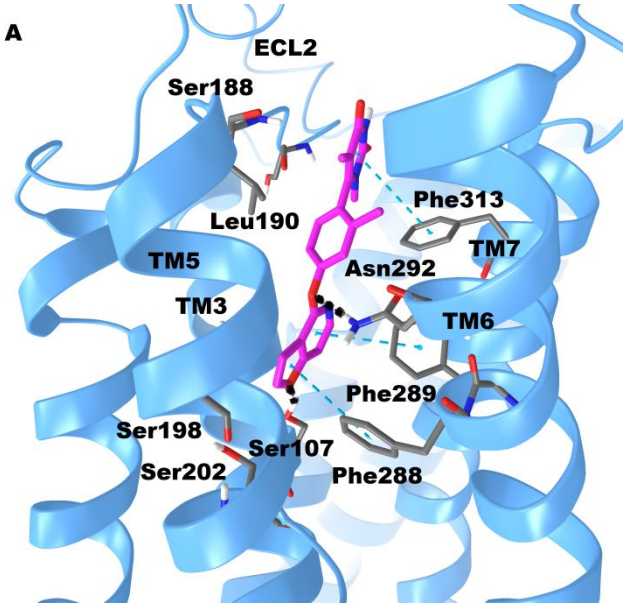
Compounds	K_i (nM)[a]
2	15 ± 2
5	51 ± 13[b]
19	2.4 ± 0.1
24	51 ± 4

[a]The values are the mean ± S.E.M. of at least three independent experiments. [b]Data are taken from reference.[24]

Following the discovery of the potent unbiased agonist **19** and complete G protein biased ligand **24**, we formally determined binding affinities at the orthosteric D1R binding pocket using competition radioligand binding (see SI). Both compounds **19** and **24** displayed relevant affinities of 2.4 ± 0.1 nM and 51 ± 4 nM, respectively (**Table 3**) indicating the ligands are high affinity orthosteric site D1R agonists. In addition, we further confirmed G protein signaling bias of select molecules using the method of Kenakin, resulting in bias factors of 1.0 for **2**, 0.94 for **5** and 1.28 for **19,** indicating these ligands are not biased. Bias factors could not be calculated for **24** due to the complete inactivity of this agonist for D1R-mediated β-arrestin recruitment, consistent with its complete G protein bias. Lastly, the selectivity of **19** and **24** for G protein-mediated cAMP activity at other DA receptors was performed (**Figure S1**, **Table S1**). Neither ligand had detectable activity at D2R or D4R, but both showed similar

potency and efficacy at the D5R and D1R, consistent with the dual D1R/D5R agonist activity of non-catechol ligands.[24]

To probe which amino acid residues our leads are mostly likely to interact with, we docked compounds **19** and **24** in an established D1R homology model based on the β2-adrenergic receptor[24, 37] using the Schrödinger Drug Discovery Suite program (**Figures 5A** & **5B**). The docking results indicated that the new compounds have energetically favorable interactions and readily dock into the orthosteric ligand-binding site. To further characterize the binding pose, compounds **19** and **24** were compared in our theoretical investigation. As shown in **Figures 5A** and **5B**, both compounds **19** and **24** do not form significant interactions with D1R Ser198 or Ser202 in the transmembrane 5 (TM5). These TM5 residues are known to form hydrogen bonds with catechol-based ligands and the lack of such interactions suggest non-catechol agonists form a unique binding mode versus catechols.[24] Interestingly, residue Ser107 in the TM3 does form a hydrogen bond interaction with the O atom on the furo[3,2-*c*]pyridine ring of **19**. The furo[3,2-*c*]pyridine ring of **19** forms π-π stacking interactions with residues Phe288 and Phe289 in the TM6. Moreover, the O atom between benzene ring and furo[3,2-*c*]pyridine ring of **19** forms a hydrogen bond with Asn292 in the TM6. This binding mode may explain the significant activity loss when changing phenoxyl into the aminopyridine ring or indoline ring. In addition, another similar π-π stacking interaction between pyrimidinedione ring and Phe313 is also formed. Meanwhile, the pyrimidinedione ring points into the ECL2 chain, leading to hydrophobic interactions with the hydrophobic residues of Leu190, Ser189, Ser188 and Asp187 in the ECL2 (**Figures S2** and **S3**). Its analog **24** displayed a similar binding pose as **19**, but notably without a π-π interaction with Phe288 and no H-bond with Ser107 in TM3 due to lack of the aromatic furan ring. This may explain the decreased binding affinity of **24** with D1R compared to **19**.



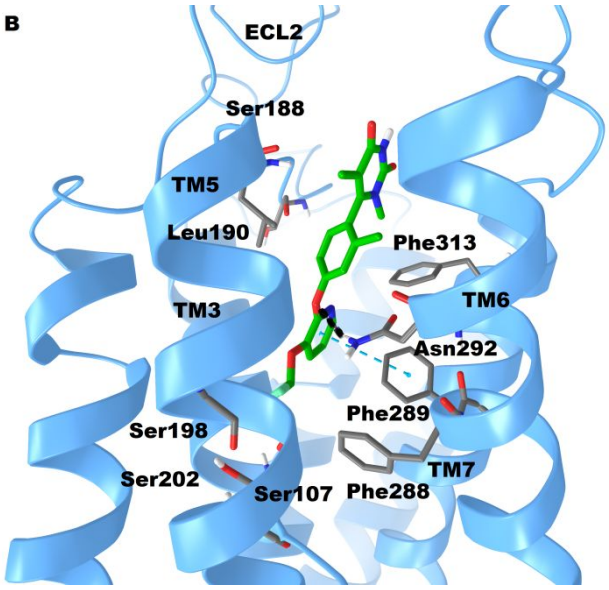


Figure 5. Putative binding modes and molecular docking of compound **19** and **24** with D1R. (A) Docking of compound **19** (purple) into the binding pocket of D1R. Important residues are drawn in sticks. Hydrogen bonds are shown as dashed black lines, while π-π interactions are shown in dashed cyan lines. (B) Docking of compound **24** (green) into the binding pocket of D1R. Important residues and key interactions are presented in a similar fashion.

As shown in **Figures 5A** and **5B**, compound **19** forms a hydrogen bond with Ser107 on the TM3 and it displays both G protein and β-arrestin activities (unbiased D1R agonist). However, compound **24** without that Ser107 TM3 hydrogen bond shows no β-arrestin activity (biased D1R agonist). This suggests non-catechol ligands which engage Ser107 in TM3 of the D1R may be important for β-arrestin activity. Interestingly, recent studies by McCorvy et al. indicate ligand interactions with TM5 serine residues and ECL2 are very important for G protein and β-arrestin signaling activity at related GPCRs.[38, 39] **19** and **24** do not form significant interactions with D1R Ser198 or Ser202 in the transmembrane 5 (TM5) but are in close proximity to form hydrophobic interactions with ECL2 residues, further supporting the concept that ligand interactions with ECL2 and TMs drive D1R biased signaling. However, to mechanistically understand the key ligand-D1R interactions and receptor conformations controlling biased signaling, future D1R biochemical (e.g. receptor mutagenesis) and biophysical studies are required. Taken together, the radioligand binding and ligand docking studies indicate **19** and **24** are both orthosteric site agonists at the D1R. These modeling studies also provide a foundation to further study structural mechanisms by which **19** and **24** promote D1R biased and balanced signaling.

In summary, a series of non-catechol heterocycles have been designed, synthesized, and pharmacologically evaluated as D1R orthosteric agonists. We probed the steric and electronic components around three aromatic regions of the lead compound **5**. The findings demonstrate that both the head (**A**) and lower (**C**) aromatic regions have significant impact on the potency and efficacy of G protein cAMP signaling and β-arrestin recruitment; these regions are amenable for further medicinal chemistry efforts. However, changing the middle

(B) aromatic ring into the indoline ring is not tolerated. These studies culminated with the discovery of the first potent non-catechol D1R unbiased agonist **19** (PW0441) and a complete G protein biased agonist **24** (PW0464). Further studies to discover a D1R β-arrestin biased agonist and testing of lead molecules **19** and **24** for *in vivo* efficacy in preclinical models of neurological and neuropsychiatric diseases are currently underway.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

Synthetic procedures for the preparation of new compounds, analytical data, and experimental procedures for *in vitro* assays as well as molecular docking studies (PDF).

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Funding

This work was supported by grants from the National Institutes of Health (P50 DA033935, P30 DA028821), and T32 DA07287 (to DEF), Pharmaceutical Research and Manufacturers of America Foundation (PhRMA Research Starter Grant RSGPT18) (to JAA), and the Center for Addiction Research at the University of Texas Medical Branch.

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENT

We sincerely thank Dr. Scot Mente for the assistance with and for providing the D1R homology model.

ABBREVIATIONS

AD, Alzheimer's disease; ADHD, attention deficit hyperactivity disorder; CNS, central nervous system; cAMP, cyclic adenosine monophosphate; D1R, dopamine 1 receptor; DA, dopamine; GPCR, G protein-coupled receptor; PD, Parkinson's disease; PK, pharmacokinetic; SAR, structure-activity relationship; TM, transmembrane.

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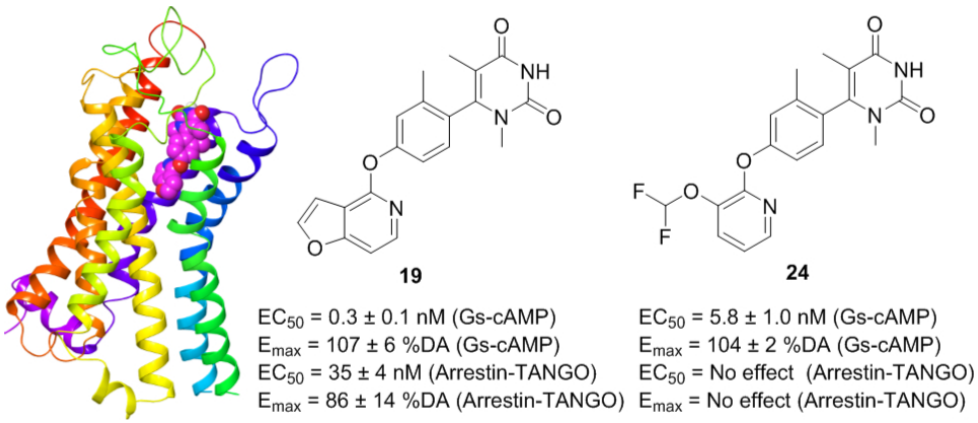

TOC

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