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Advances and Challenges in the Search for D₂ and D₃ Dopamine Receptor-Selective Compounds

Amy E. Moritz¹, R. Benjamin Free¹, and David R. Sibley^{1,*}

¹Molecular Neuropharmacology Section, National Institute of Neurological Disorders and Stroke, National Institutes of Health, 35 Convent Drive, MSC-3723, Bethesda, MD 20892-3723

Abstract

Compounds that target D₂-like dopamine receptors (DRs) are currently used as therapeutics for several neuropsychiatric disorders including schizophrenia (antagonists) and Parkinson's disease (agonists). However, as the D₂R and D₃R subtypes are highly homologous, creating compounds with sufficient subtype-selectivity as well as drug-like properties for therapeutic use has proved challenging. This review summarizes the progress that has been made in developing D₂R- or D₃R-selective antagonists and agonists, and also describes the experimental conditions that need to be considered when determining the selectivity of a given compound, as apparent selectivity can vary widely depending on assay conditions. Future advances in this field may take advantage of currently available structural data to target alternative secondary binding sites through creating bivalent or bitopic chemical structures. Alternatively, the use of high-throughput screening techniques to identify novel scaffolds that might bind to the D₂R or D₃R in areas other than the highly conserved orthosteric site, such as allosteric sites, followed by iterative medicinal chemistry will likely lead to exceptionally selective compounds in the future. More selective compounds will provide a better understanding of the normal and pathological functioning of each receptor subtype, as well as offer the potential for improved therapeutics.

1. Introduction

Dopamine receptors (DRs) belong to the G-protein coupled receptor (GPCR) super-family and are divided into two subcategories based on their structure, pharmacology, and signaling preferences. The D₁-like receptors, consisting of the D₁R and D₅R, promote intracellular cAMP accumulation through activating G_s or G_{olf} proteins [1]. In contrast, D₂-like receptors, consisting of the D₂R, D₃R, and D₄R, activate G_{i/o} proteins to diminish cAMP levels as well as modulate select ion channels [1]. D₂Rs are also known to signal through G protein-independent pathways involving the recruitment of the scaffolding protein β -arrestin and downstream activation of glycogen synthase kinase-3 (GSK-3) [2, 3]. Importantly,

*to whom correspondence should be addressed: David R. Sibley, Ph.D., Molecular Neuropharmacology Section, National Institute of Neurological Disorders & Stroke/NIH, 35 Convent Drive, Room 3A201, MSC 3723, Bethesda, MD 20892-3723, Phone: 301-496-9316, Fax: 301-480-3726, sibleyd@ninds.nih.gov.

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aberrant DR signaling is linked to the etiology and/or therapy of a number of neuropsychiatric disorders including Parkinson's disease and schizophrenia (Table 1) [1, 2]. Most therapeutics that target these disorders are known to be selective for the D₂-like receptor subfamily, however, these drugs, as well as related research tool compounds, lack complete selectivity and can modulate multiple members of this subfamily. This is particularly true for the structurally-related D₂R and D₃R subtypes where most clinically used compounds modulate both of these two receptors to varying degrees [4].

Since the ascertainment of the D₂R as the “antipsychotic receptor” (reviewed in [5]) and the subsequent cloning of the closely related D₃R [6] there has been a drive to understand the physiological and pharmacological differences between the D₂R and D₃R. The D₂R and D₃R share 78% amino acid homology within their transmembrane-spanning domains [7], and are nearly identical in their orthosteric binding sites where the majority of dopaminergic ligands bind [8, 9]. Studies using mRNA *in situ* hybridization and receptor autoradiography [6, 10-12] have localized the D₃R mainly to the “limbic” regions of the brain including the ventral striatum, with the highest densities in the Islands of Calleja and the olfactory bulb [13]. The D₂R has a significantly wider distribution throughout the brain, and displays expression levels several orders of magnitude higher than that of the D₃R [6, 10], with the highest expression seen in the striatum (particularly the dorsal striatum), nucleus accumbens, and olfactory tubercle. The D₂R and D₃R appear to couple to similar signaling pathways including activation of Gi/o proteins to inhibit cAMP accumulation, Gβ/γ proteins to activate GIRK channels, and the recruitment of β-arrestin following agonist stimulation. Notably, however, when compared in parallel, the strength or degree of D₃R signaling through these pathways appears to be less efficacious than that of the D₂R [14-17].

While it is generally agreed that blockade of D₂R-mediated signaling is the primary mechanism of action of all antipsychotics [18], these drugs also interact with the D₃R to varying degrees at therapeutic doses. In fact, most antipsychotics are known to interact with a broad array of GPCRs and these off-target activities are responsible for a number of observed side effects such as weight gain and metabolic syndrome [19]. Clearly, the identification of more D₂R-selective agents for the treatment of schizophrenia is highly desirable. Notably, the D₃R has also become a drug target in its own right for such diverse conditions as addiction (antagonists) and neuroprotection in Parkinson's disease (agonists). Thus, there is a desire to develop compounds that selectively target the D₂R or the D₃R with minimal subtype cross-reactivity, not only to ascertain the physiological and pathological functions governed by these individual subtypes, but also because such compounds will likely exhibit significant clinical utility.

Three primary approaches have been used to identify and develop D₂R or D₃R subtype-selective small molecules: 1) synthesis of structural analogs of known compounds to generate structure-activity relationship (SAR) information for determining how chemical structure can lead to increased subtype selectivity; 2) high-throughput screening of large (thousands to millions) compound libraries to identify novel chemical scaffolds with promising selectivity profiles, followed by chemical optimization; and 3) use of molecular (crystal) structures of the receptors, or corresponding homology models, to rationally design new compounds, or structure-based virtual (*in silico*) screening to identify unique chemical

scaffolds. Each approach has benefits and pitfalls and some have been more successful than others – several groups have used a combination of these approaches. Taken together, these studies have resulted in novel compounds capable of targeting the D₂R and D₃R subtypes selectively. This review will discuss several of these compounds, focusing on those that show the highest selectivity. It will also highlight caution that is needed in interpretations of selectivity, and difficulties in determining if a given compound will be selective in all cases.

2. D₂R-Selective Antagonists

As noted above, selective antagonists of the D₂R can be useful for treating psychosis and schizophrenia, but can also be useful as therapeutics for other neuropsychiatric disorders such as Tourette's syndrome and Huntington's chorea [20, 21], and some cancers such as glioblastomas [22-24]. However, despite the clear therapeutic indications, the successful development of truly selective D₂R antagonists has proven difficult. A few compounds have been developed using multiple approaches that show moderately high selectivity, and this pursuit remains an active area of investigation.

Robert Mach's group has developed several D₂R-preferring antagonists based on previously known structures. These include derivatives of the D₂-like antagonist haloperidol and the Merck compound L741,626, which shows moderate D₂R selectivity [25-27] (Fig. 1). Using *in vitro* radioligand binding and *in situ* functional assays, the derivatives from Mach's group exhibit between 10-100-fold selectivity for the D₂R vs. the D₃R [25-27]. The most promising of these compounds displays over 100-fold D₂R vs. D₃R selectivity in radioligand binding assays [25] (Fig. 1 compound **58**). Follow-up studies, however, found the compound to be less selective in functional assays (60-fold D₂R vs. D₃R selective), and it exhibited a very short half-life of 2.4 min in a liver microsomal test of metabolic stability [27]. Compound 58 was also found to be quite promiscuous as revealed in a panel screen of 168 GPCRs [27], which may limit its utility as a therapeutic lead. It is likely that other compounds in this series will suffer from similar GPCR promiscuity as they share structural similarities.

The novel antipsychotic aripiprazole (Fig. 1) has also served as a scaffold for the development of D₂R-selective compounds [28, 29]. Aripiprazole is a low efficacy partial agonist of the D₂R and some of these derivatives have demonstrated biased or functionally-selective agonist stimulation of the D₂R [28, 30-32]. Interestingly, one aripiprazole derivative, SV-III-130s (Fig. 1) demonstrates 50-fold D₂R vs. D₃R selectivity, but also exhibits partial agonist activity in some signaling assays [33]. It was also found to bind to the sigma receptor with high affinity [29]. SV-III-130s has found great utility as a PET ligand for imaging the D₂R *in vivo* [34], but its agonist activity may complicate its utility as a D₂R antagonist probe compound. A recent group of publications has also highlighted a series of N-(1-benzylpiperidin-4-yl)pyridazin-3-amines, exemplified by the antipsychotic candidate JNJ-37822681 (Fig. 1), as effective D₂R antagonists [35]. However, JNJ-37822681 is only around 10-fold selective for the D₂R vs. the D₃R.

Our group has also attempted to identify novel D₂R-selective antagonists through employing a high throughput functional screen of nearly half a million diverse chemical compounds.

Not surprisingly, most of the compounds identified as D₂R antagonists from the screen were active at both the D₂R and D₃R; however, there was a small pool of compounds that exhibited significant D₂R selectivity. One of the most promising D₂R-selective scaffolds, NCGC00109414, was subjected to iterative chemical modifications leading to the probe compound ML321 (Fig 1.) [27]; an antagonist with a D₂R vs. D₃R selectivity of >50-fold, and even higher selectivity against the other dopamine receptor subtypes. ML321 also demonstrates high global selectivity against other GPCRs and select transporters and ion channels as demonstrated using radioligand-binding assays [27]. In fact, other than high affinity interactions with the D₂R, only the D₃R, 5-HT_{2C} and 5-HT₇ serotonin receptors were found to exhibit even low-moderate affinity for ML321. Moreover, a functional screen using a panel of 168 different GPCRs demonstrated little to no functional interactions of ML321 with receptors other than the D₂R and, to a lesser extent, the D₃R [27]. The molecular mechanisms underlying this remarkably high level of selectivity of ML321 among GPCRs is currently under investigation.

As mentioned above, current FDA-approved medications that are used to block D₂Rs are rather non-selective and they typically interact with other GPCRs such as adrenergic, serotonergic, histaminergic, and cholinergic receptors. Therefore, it is not surprising that such drugs have multiple adverse effects including sedative, locomotor, endocrine, metabolic, and hypotensive properties. It is anticipated that a compound with more selectivity at the D₂R would have fewer off-target side effects. Although ML321 (and members of its chemical series) is less potent than comparator D₂R antagonists, it demonstrates good D₂R vs. D₃R and, importantly, global GPCR selectivity, and also positive ADME and PK properties [36]. ML321 may therefore prove to be a useful *in vitro* and *in vivo* chemical probe compound and a promising therapeutic lead.

3. D₃R Selective Antagonists

There has been considerable interest in developing D₃R-selective antagonists/partial agonists primarily for the treatment of substance abuse disorders, but also potentially for psychosis-related syndromes. As the D₃R shows a distribution more restricted to the limbic system as compared to the D₂R [6], D₃R-selective antagonists/partial agonists could, in theory, attenuate psychotic symptoms and/or drug-seeking behavior and relapse without inducing the motor side effects frequently associated with currently available D₂-like antagonists. There are several excellent reviews covering the recent development and characterization of D₃R-selective antagonists [37-43]. Notably, while some of these D₃R-selective compounds exhibit reasonably high selectivity towards the D₃R (>100-fold), their global selectivity towards other GPCRs is either poor or untested. While the above-mentioned reviews cover the majority of the D₃R-selective compounds described to-date, some unique approaches to the discovery/development of D₃R-selective compounds will be mentioned here.

While most D₃R-selective antagonists have been found through iterative medicinal chemistry of known chemical scaffolds (GSK598,809 as an example [44] (Fig. 1.), several studies have taken advantage of the recently elucidated D₃R crystal structure [9] in an attempt to use structure-guided ligand discovery [41, 45, 46]. As an example, one study used the D₃R crystal structure for a virtual *in silico* screen and found compounds that bound to

the orthosteric site as well a secondary binding pocket [45] within the D₃R. While these compounds exhibited modest selectivity and potency, the study demonstrated that novel D₃R-selective compounds can be discovered through structure-guided virtual screening. Another approach has used D₃R crystal structure information, coupled with SAR knowledge from leading D₃R-selective antagonists, like eticlopride [46] and PG648 (Fig. 1) [47] and related synthons [48], to synthesize novel compounds with D₃R vs. D₂R selectivities reported to be >1,000-fold (see Fig 1. compound **19**) [46]. The global selectivity of this series has not yet been fully established, but these data highlight the usefulness of structure-guided medicinal chemistry efforts in finding selective compounds; particularly focusing on elongated bivalent compounds that engage secondary binding pockets in the D₃R as a bitopic mechanism of engendering selectivity [49].

4. D₂R and D₃R Selective Agonists

While antagonists primarily need sufficient affinity to bind to the receptor and block agonist activation, agonists must also have intrinsic efficacy to stabilize an active signaling conformation of the receptor. This raises the bar for an agonist compound, which may be one reason why identifying and developing D₂-like selective agonists has been met with only limited success. Further, the assessment of agonist selectivity and efficacy can be confounded by issues such as receptor reserve within a given receptor expression/assay system. In fact, numerous studies have found that subtype selectivity can vary based on assay conditions, expression system used, and functional output tested [50-53]. Despite these challenges, some moderately selective D₂R and D₃R agonists have been developed and their improvement remains an important research goal.

Sumanitrole (((*R*)-5,6-dihydro-5-(methylamino)-4*H*-imidazo[4,5,1-*ij*]quinolin-2(1*H*)-one (*Z*)-2-butenedioate) (Fig. 2) has been reported as a D₂R-selective agonist and shown to be an effective and well-tolerated adjunctive therapy for the treatment of PD when compared to another D₂-like receptor agonist, ropinirole [54] (Fig. 1). However, a separate study found that ropinirole was more effective [55], and Pfizer stopped development of sumanitrole as a treatment for PD. Initial studies determined sumanitrole to have a high affinity (K_i) of 9 nM for the D₂R and to be >200-fold selective vs. other dopamine receptor subtypes. This was determined using radioligand binding assays [56], but the study used an agonist ligand, [³H]U-86170, for D₂R binding and an antagonist ligand, [³H]spiperone, for D₃R binding. This mixed use of agonist/antagonist radioligands potentially biased the results as [³H]agonists label the high-affinity G protein-coupled state of the D₂R receptor, which exhibits higher affinity for agonists [57-60]. In contrast, [³H]antagonists label both the coupled and uncoupled states of the D₃R receptor, the latter of which exhibits lower affinity for agonists.

A subsequent study using the antagonist radioligand [³H]*N*-methylspiperone to label both the D₂R and D₃R found that sumanitrole displayed much lower affinity (K_i) for the D₂R (16 μM) and was actually 2.5-fold selective for the D₃R [61]. When yet another radiolabeled agonist, [³H]7-OH-DPAT (Fig. 1), was used, sumanitrole's affinity (K_i) for the D₂R was 17 nM, which was 32-fold selective vs. the D₃R [61]. Functional assays conducted in this study found that sumanitrole was a full agonist at both the D₂R and D₃R with low nM potency, but

the D₂R-selectivity was only 3-10 fold [61]. This latter study also conducted an SAR analysis of the sumanirole scaffold [61]. While some compounds showed full agonist activity, with higher D₂R affinity than the parent compound, D₃R affinity was similarly increased leading to compounds with only moderate D₂R selectivity. However, molecular dynamic simulations indicated that amino acid sequence differences between the D₂R and D₃R in their second extracellular loops and N-terminal segments of their fifth transmembrane domains may contribute to the D₂R-preference of sumanirole and its analogs [61], potentially opening the door for the development of more D₂R selective agonists. Recently, further investigations using sumanirole as a scaffold for creating elongated, potentially bivalent, compounds did not result in greater D₂R selectivity, but did result in agonists that might be biased for G-protein-mediated vs. β -arrestin-mediated signaling [62].

The development of D₃R-selective agonists has been more successful than D₂R-selective agonists, although not without several challenges. One important reason for developing D₃R-selective agonists is that they exhibit neuroprotective and neurorestorative properties. In fact, preclinical animal models suggest that D₃R-preferring agonists are efficacious in protecting against 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-induced neurodegeneration in mice [63, 64] and primates [65], and against 6-hydroxydopamine (6-OHDA)-induced lesions in rats [66] – both toxins destroy dopaminergic neurons in the substantia nigra in the brain resulting in the symptoms of PD. Importantly, studies with D₃R knockout mice support that the neuroprotective effects are mediated directly by the D₃R. [67-69] In clinical trials, the D₃R-preferring agonist pramipexole (Fig. 2) was shown to protect against the loss of dopaminergic neurons vs. treatment with L-DOPA in a 46-month long study utilizing [¹²³I] β -CIT SPECT imaging of dopamine transporter (DAT) levels [70], and a 2-year study found that treatment with ropinirole (also D₃R preferring, Fig. 2) was associated with a slower progression of PD vs. L-DOPA treatment as assessed by [¹⁸F]-DOPA PET [71]. As the protective effects found in both studies could have been skewed by a difference in the regulation of DAT or [¹⁸F]-DOPA metabolism induced by treatment, a short-term study in patients was conducted that found no difference in either measure [72]. The findings of these studies are somewhat controversial, as a later study found no difference in DAT levels or clinical improvements when comparing an early vs. delayed treatment with pramipexole. However, this study design may not have been able to detect a disease-modifying effect needing longer than 6-9 months to develop [73]. Regardless, the development of D₃R-selective agonists as potential neuroprotective agents remains an important therapeutic goal.

Several agonists have been identified that display a preference for D₃R vs the D₂R, including the endogenous agonist dopamine, pergolide, quinpirole, pramipexole, quinlorane, ropinirole, 7-OH-DPAT, and PD128907 [6, 11, 74-80] (Fig. 2). However, reported potency and D₃R/D₂R selectivity values vary considerably depending on specific assay conditions, and whether radioligand binding or functional assays are used as the readout. This may be due to the fact that, while there are large differences in affinity for the high affinity (G-protein coupled) agonist binding state of the D₂R versus the low affinity uncoupled state, there is little difference observed between these two states for the D₃R [74, 76]. Given that the high affinity agonist binding state will depend on receptor-G protein expression ratios (typically driven by receptor levels), when comparing agonist affinity

across receptor subtypes using radioligand binding assays, it is important to use conditions (absence of divalent cations and presence of guanine nucleotides [57]) that favor the low affinity state of the receptors, so as not to bias the results [78, 81]. This may explain why some D₂-like receptor agonists display “apparent” D₃R selectivity when assessed using radioligand binding assays in contrast to results obtained using functional assays [82].

The identification of novel D₃R-selective agonists was initially hampered by a dearth of functional outputs available for this receptor subtype. The D₃R displays weak or no agonist-induced [³⁵S]GTPγS binding or inhibition of adenylyl cyclase when compared to the D₂R in a number of expression systems [6, 14, 15, 75, 83, 84], although more robust effects are seen in cell lines with a more neuronal phenotype or if the “correct” signal transduction components are co-expressed with the D₃R, such as adenylyl cyclase type V [16, 85]. Recent reports have also implicated the D₃R in the modulation of Na⁺/H⁺ exchange, Ca²⁺ and K⁺ flux, mitogenesis, and β-arrestin recruitment [17, 75, 86-88], although there is a general trend in these assays that the observed functional effects are less robust than those induced by the D₂R. In addition, there are few behavioral responses that can be used to differentiate between D₂R and D₃R agonist effects *in vivo*. Studies utilizing an array of D₂R/D₃R agonists and antagonists indicate that the induction of yawning in rats and primates is mediated by activation of the D₃R. This yawning effect displays a characteristic inverted U-shape, such that higher agonist doses result in the inhibition of this yawning effect. This inhibition appears to be the result of D₂R activation [53, 89]. D₂R activation has also been shown to be responsible for hypothermia induced by D₂R/D₃R agonists [90]. Therefore, the dose at which an agonist induces yawning vs. the dose needed to induce hypothermia can be used as a measure of D₃R/D₂R selectivity *in vivo* [53]. The most D₃R-selective agonist identified in these studies was pramipexole, with a D₃R/D₂R selectivity of 32-fold [53], which has become a lead scaffold in the search for D₃R selective agonists.

Several groups have conducted medicinal chemistry efforts using the putatively D₃R-preferring agonists mentioned above in order to generate more highly-selective D₃R agonists [91-94]. The majority of this work has focused on the pramipexole scaffold because of its high affinity for the D₃R (nM range) [77, 78, 93, 95, 96], favorable solubility, and being an FDA-approved [97] medication whose analogs are likely to be well tolerated. These efforts have generally involved a hybrid drug design in which the agonist compound is linked to a known D₂R/D₃R antagonist fragment via a linker region. The theory being that the agonist headgroup would interact with the primary orthosteric binding pocket while the antagonist fragment would interact with a secondary binding pocket of the D₃R, conferring D₃R selectivity [98]. Through this method, several compounds have been synthesized and evaluated for both binding affinity and functional activity. CJ-703 (Fig. 2) displayed 18-fold higher affinity for the D₃R compared to pramipexole and 62-fold D₃R/D₂R selectivity [93]. However, the binding assays used the agonist radioligand [³H]PD128,907 (Fig. 2) for D₃R binding while the antagonist radioligand [³H]spiperone was used for the D₂R binding, thus possibly skewing the selectivity (see above discussion). In addition, ventral striatal tissue from rat brain was used for the D₃R binding, while tissue from the caudate and putamen were used for the D₂R binding. However, while the ventral striatum is enriched in D₃R, it also contains a large amount of D₂R [99], further clouding the interpretation of these results. This compound was also evaluated using *in vivo* yawning and hypothermia studies. CJ-703

produced yawning, but at higher doses than pramipexole despite its higher affinity for the D₃R. It also induced hypothermia at high doses, suggesting that it mimics the D₃R/D₂R selectivity of pramipexole, albeit with lower potency [93].

Follow-up studies produced more pramipexole-related compounds including CJ-1598, CJ-1600, CJ-1638, and CJ-1639 [100] (Fig. 2). These compounds were found to have similar D₃R affinity as pramipexole, but were claimed to exhibit >1,000-fold D₃R/D₂R selectivity using similar binding assays as the previous study with the exception that the agonist radioligand [³H]7-OH-DPAT was used in place of [³H]PD128,907 - thus raising the caveat mentioned above about using mixed agonist/antagonist radioligands to assess D₃R/D₂R selectivity in binding assays. CJ-1638 and CJ-1639 produced yawning over a wider range of doses as compared to pramipexole, indicating that they may display greater *in vivo* D₃R/D₂R selectivity [100]. Although they were shown to be active *in vivo*, metabolic stability tests showed that CJ-1638 and CJ-1639 were rapidly metabolized using human liver microsomes. As a result, modifications have produced further analogs with better microsomal stability and similar D₃R affinities as the parent compounds [101]. The global GPCR selectivity of this D₃R-selective agonist series remains unknown, but represents a promising lead to be further investigated.

Dutta et al. have also investigated the pramipexole scaffold as a source of D₃R-selective agonists [98, 102-116]. The compound D-264 (Fig. 2) displays nanomolar affinity for the D₃R and is 253-fold D₃R/D₂R selective as assessed using [³H]spiperone binding in HEK cells expressing cloned D₂R or D₃R [117]. Similar selectivity values were found in [³⁵S]GTPγS binding assays using CHO cells expressing D₂R and ATt-20 cells expressing the D₃R [117]. However, the fold-selectivity decreased to 22-fold when tested in CHO cells expressing either human D₂R or D₃R [107]. In fact, D-264 stimulated [³⁵S]GTPγS binding to brain membranes prepared from wild-type mice, but had no efficacy in membranes from D₂R KO mice, indicating that D-264 has little efficacy *in vivo* at the D₃R, and that its functional effects are probably mediated by activation of the D₂R, or possibly the D₄R as it also displays significant affinity for the latter receptor subtype [113]. This study also found that the D₂R and D₃R expression levels in the heterologous CHO cells used were 2-fold and 135-fold, respectively, higher than those in rodent striatum, and the expression of the D₃R was 10 times higher than that of the D₂R in their cell model. These factors could lead to artificially inflated D₃R/D₂R selectivity values, and the authors proposed the cautious interpretation of their results obtained from a single model system [113]. Treatment with D-264 improved movement in acute MPTP and lactacystin mouse models of PD [104]. The D-264 treatment also increased BDNF and GDNF production and attenuated the loss of both DA levels and dopaminergic neurons in the substantia nigra, although only 50% of this effect was blocked by the D₃-preferring inhibitor U99194 [104]. The effects of D-264 could partially be due to the antioxidant effects of this compound, as the neuroprotective effects of pramipexole are known to be mediated by both dopaminergic and antioxidant mechanisms [67]. Other pramipexole-based compounds produced by this group display similar effects [106].

5. Conclusions

While advances have been made in finding compounds with significant selectivity for either the D₂R or D₃R, much remains to be accomplished to identify compounds with both sufficient selectivity *in vivo* and drug-like attributes for therapeutic use. While recent work has focused on alterations of known orthosteric structures leading to compounds with modest selectivity, the very high conservation of the orthosteric binding sites may place a limit on the level of selectivity that can be achieved. Future advances may take advantage of structural data and the subsequent targeting of alternative secondary binding sites through creating bivalent or bitopic-type chemical structures. Appropriate functional assays using side-by-side comparisons in systems with similar receptor expression levels, as well as the use of appropriate radioligands, are necessary to fully and correctly characterize the selectivity of any given compound. Novel scaffolds identified through high-throughput screening that might bind to the D₂R or D₃R in areas other than the orthosteric site, such as allosteric sites, coupled with structural biology and molecular modeling, followed by iterative medicinal chemistry will likely lead to exceptionally selective compounds in the future and a better understanding of the contributions and therapeutic potential of these receptors.

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Figure 1.
Examples of D2R-like antagonists.

Figure 2.
Examples of D2R-like agonists.

Table 1
Roles of Dopamine Receptor Subtypes with Regard to Disease and Therapeutics

Receptor Subtype	Potential Role in Disease	Potential Therapeutic
D₁R * caudate-putamen, nucleus accumbens, substantia nigra, olfactory bulb, amygdala, frontal cortex	Cognitive Decline (Aging/Stress) Obesity Sexual Disorders Hypertension	Agonist[118] Antagonist[119] Agonist[120] Partial Agonist[121]
D₂R * dorsal striatum, nucleus accumbens, olfactory tubercle	Schizophrenia Parkinson's Disease Huntington's Disease Restless Legs Syndrome Depression Tourette's Syndrome ADHD Type 2 Diabetes Sexual Disorders Hyperprolactinemia Cancers	Antagonist[18] Agonist[122] Partial Agonist/Stabilizer[123] Agonist[124] Agonist[125] Antagonist[20] Agonist/Antagonist[126] Agonist[127] Agonist[120] Agonist[128] Antagonist[22-24]
D₃R * ventral striatum, Islands of Calleja, olfactory bulb	Schizophrenia Parkinson's Disease Huntington's Disease Restless Legs Syndrome Depression Tourette's Syndrome Substance Use Disorders ADHD Sexual Disorders	Antagonist[38] Agonist[98] Partial Agonist/Stabilizer[123] Agonist[124] Agonist[125] Antagonist[20] Antagonist[42] Agonist/Antagonist[126] Agonist[120]
D₄R * Low levels in frontal cortex, amygdala, hippocampus, hypothalamus, globus pallidus substantia nigra pars reticulata, thalamus	ADHD [?] Schizophrenia Substance Use Disorders Sexual Disorders	Agonist/Antagonist[129] Agonist[130] Antagonist[131] Agonist[120]
D₅R * Low levels throughout cortex, substantia nigra, Hypothalamus, Hippocampus, dentate gyrus	Cognitive Decline (Aging/Stress) Obesity Sexual Disorders Hypertension	Agonist[118] Antagonist[119] Agonist[120, 132] Partial Agonist[121]

* Primary areas of localization

[?]Unclear role/genetic linkage