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## Update 1 of: Recent Progress in Development of Dopamine Receptor Subtype-Selective Agents: Potential Therapeutics for Neurological and Psychiatric Disorders

Na Ye,<sup>†</sup> John L. Neumeyer,<sup>‡</sup> Ross J. Baldessarini,<sup>§</sup> Xuechu Zhen,<sup>||</sup> and Ao Zhang<sup>\*,†</sup>

<sup>†</sup>CAS Key Laboratory of Receptor Research, and Synthetic Organic & Medicinal Chemistry Laboratory (SOMCL), Shanghai Institute of Materia Medica (SIMM), Chinese Academy of Sciences, Shanghai, China 201203

<sup>‡</sup>Medicinal Chemistry Laboratory, McLean Hospital, Harvard Medical School, Massachusetts 02478, United States

<sup>§</sup>Psychopharmacology Program, McLean Hospital, Massachusetts 02478, United States

<sup>||</sup>Department of Pharmacology, College of Pharmaceutical Sciences, Soochow University, Suzhou, China 215123

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### 1. INTRODUCTION

Dopamine (DA) is a critical neurotransmitter in the mammalian central nervous system (CNS). The cerebral dopaminergic system is implicated in the pathophysiology of several neurobehavioral disorders, including Parkinson's disease and other movement and hyperactivity disorders, schizophrenia, mania, depression, substance abuse, and eating disorders, and it is involved in the neuropharmacology of drugs proven

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effective in the treatment of most of these neuropsychiatric disorders. DA contributes importantly to the neurophysiological control of arousal and attention, initiation of movement, perception, motivation, and emotion. Its actions are mediated by five major DA receptor subtypes ( $D_1$ – $D_5$ ) with distinct differences in their gene and peptide composition, molecular functions, and neuropharmacology. These receptors represent rational targets for development of both drugs and radioligands. In recent years, substantial efforts have been directed at the more recently described DA receptor types,  $D_3$ ,  $D_4$ , and  $D_5$ , as well as the longer-known and more abundant  $D_1$  and  $D_2$  receptors. Current trends in medicinal chemistry and neuropharmacology include development of  $D_1$  full agonists and  $D_2$  partial agonists as well as agents with dopaminergic activity combined with effects at CNS serotonergic, muscarinic, adrenergic, and histaminic receptors. This review focuses on progress during 2006–2011 on the development of selective ligands targeting mainly to the five main DA receptors.

### 1.1. Dopaminergic System: Synthesis, Function, and Degeneration

Dopamine (DA) is one of the naturally occurring catecholamines biosynthesized in dopaminergic neuron terminals via enzymatic pathways from the essential amino acid L-tyrosine (Tyr). Enzymes responsible for this biosynthetic pathway include the cytosolic enzyme tyrosine hydroxylase (TH), which converts tyrosine into L-dihydroxyphenylalanine (L-DOPA), and aromatic L-amino acid decarboxylase (AADC), which decarboxylates L-DOPA to DA. TH is the rate-limiting enzyme that controls the overall synthetic process of DA. Activation of this enzyme by phosphorylation via protein kinases can enhance DA synthesis<sup>1–3</sup>.

In the axon terminals of dopaminergic neurons, after synthesis in the cytoplasm, DA is packaged into presynaptic, membrane-enclosed storage vesicles by a vesicular membrane transporter where it is stored in a complex involving  $\text{Ca}^{2+}$ , ATP, and chromogranins.<sup>2–4</sup> By a process of exocytosis, the storage vesicle and cell membranes fuse to release DA and other vesicular contents into the extracellular synaptic cleft in response to depolarization and a large influx of calcium ( $\text{Ca}^{2+}$ ) into the nerve terminal. In the synaptic space, DA acts on its  $D_2$ -like presynaptic autoreceptors, which regulate the synthesis and release of DA, as well as at  $D_1$ -like and  $D_2$ -like postsynaptic receptors.<sup>3,4</sup> Dopaminergic actions at DA receptors are terminated principally by active transport of the amine back into the presynaptic neurons, in exchange for  $\text{Na}^+$ . This crucial physiological inactivation process is mediated by a selective DA transporter (DAT) membrane protein that is specifically expressed by DA neurons, particularly at their terminals. There is some metabolic inactivation by largely extraneuronal O-methylation by catechol-O-methyltransferase (COMT). DA transported back into presynaptic neuronal terminals and not restored in presynaptic vesicles can be oxidatively catabolized to an acidic byproduct (3,4-dihydroxyphenylacetaldehyde [DHPA], which is rapidly oxidized to 3,4-dihydroxyphenylacetic acid [DOPAC]) by intraneuronal mitochondrial monoamine oxidase (MAO), and secondarily O-methylated to 3-methoxy-4-hydroxyphenylacetic acid (MHPA) to end up predominantly as the 3-O-methylated and deaminated acidic metabolite homovanillic acid (HVA). Lesser amounts of 3-methoxytyramine (3-MT) are also formed and subsequently deaminated by MAO and aldehyde reductase to produce additional HVA. Some DA taken into presynaptic

dopaminergic nerve terminals is stored again in vesicles and reutilized. DOPAC and HVA are the major metabolites of DA that diffuse into the cerebrospinal fluid (CSF) and blood and are eventually excreted through the kidneys. Concentrations of DOPAC and HVA have been assayed in plasma or CSF to monitor DA metabolism and as indices of dopaminergic dysfunction.<sup>4</sup>

### 1.2. Dopamine-Containing Neuronal Pathways

There are four major DA pathways in the mammalian CNS, including the mesocortical, mesolimbic, nigrostriatal, and tuberoinfundibular pathways.<sup>5,6</sup>

The mesocortical system is a neural pathway connecting the ventral tegmentum of midbrain to the cerebral cortex, particularly the mesioprefrontal lobes. It is essential to the normal cognitive function of the dorsolateral prefrontal cortex and involved in motivation and emotional response. The mesolimbic system is one of the neural pathways in the brain linking the ventral tegmental area (VTA) to the nucleus accumbens septi (NAS) in the limbic system. It is involved in producing pleasurable effects associated with reward and desire, particularly owing to the connection to the nucleus accumbens.<sup>7</sup> The nigrostriatal pathway is a neural circuit connecting the substantia nigra pars compacta with the caudate-putamen in the striatum. This system contains 70% of the DA in brain tissue. Idiopathic loss of DA neurons in the caudate-putamen is a major pathological feature of Parkinson's disease. The tuberoinfundibular pathway runs between the hypothalamus (arcuate nucleus) and the median eminence of hypothalamus to deliver DA to the anterior pituitary as a regulatory neurohormone. Some antipsychotic drugs block  $D_2$ -like DA receptors on lactotrophic cells of the anterior pituitary to increase blood prolactin levels.

### 1.3. Dopamine Receptor Subtypes

DA receptors belong to a superfamily of large proteins characterized by having seven relatively hydrophobic segments that are assumed to be cell-membrane spanning. They are coupled to G proteins that interact with several membrane or cytoplasmic effector molecules (usually enzymes, transporters, or ion channels) that regulate neuronal functions. In 1979, Kebabian and Calne<sup>8</sup> proposed that DA exerts its effects by binding to two hypothetical major receptor types, designated as  $D_1$  and  $D_2$  receptors. These receptors were hypothesized based primarily on molecular neuropharmacological evidence, long before their anatomical localization by receptor-selective radioligands and eventual cloning and chemical characterization by the methods of molecular genetics.<sup>9</sup> The  $D_1$  receptor was identified initially as mediating the stimulation of adenylyl cyclase by DA to increase production of cyclic-AMP. Later, it was characterized by selective labeling with the radiolabeled  $D_1$  antagonist SCH-23390. A second DA receptor type was suspected, based principally on the ability of some antipsychotic drugs, such as haloperidol and spiperone, to antagonize metabolic and behavioral actions of DA and effects of DA agonists, including R-(–)-apomorphine, without blocking production of cyclic-AMP by DA. Selective radiolabeling of these ligands further stimulated identification of the  $D_2$  receptor and characterization of its anatomical distribution in brain tissue.<sup>10</sup>

Both types of DA receptors exert their biological actions by coupling to and activating different G protein complexes. The  $D_1$  receptor interacts with guanosine-triphosphate (GTP)

binding proteins of the G<sub>s</sub> type to activate adenylyl cyclase and stimulate synthesis of the intracellular second-messenger cyclic-AMP, whereas the D<sub>2</sub> receptor is now known to interact with G<sub>i</sub> or G<sub>o</sub> proteins to inhibit adenylyl cyclase and also to suppress Ca<sup>2+</sup> currents and activate receptor-gated K<sup>+</sup> currents.<sup>11</sup> The anatomical distribution of these two DA receptors in the CNS overlap in quantitative ratios that differ among particular anatomical areas.

In the late 1980s, application of gene cloning and recombinant DNA techniques revealed that there were at least five distinct DA receptors (D<sub>1</sub>–D<sub>5</sub>) and their molecular variants. This family of DA receptors bears many similarities to receptor proteins for other monoamine neurotransmitters (norepinephrine, serotonin, and acetylcholine). In humans, DA receptors range in peptide length from 414 (D<sub>2short</sub>) to 515 amino acids (D<sub>4,10</sub> with 10 repeats of a 16-amino acid sequence in intracellular peptide loop-3), with 446 in D<sub>1</sub>, and 443 in D<sub>2-long</sub>, the two most abundant DA receptors. The original classification of DA receptors into two basic types, now considered D<sub>1</sub>-like and D<sub>2</sub>-like, still stands.<sup>12</sup> The D<sub>1</sub>-like receptors include D<sub>1</sub> (or D<sub>1A</sub>) and a low-abundance D<sub>5</sub> (or D<sub>1B</sub>) subtype. The D<sub>2</sub>-like receptors include three main types: the most abundant D<sub>2</sub> as well as less common D<sub>3</sub> and D<sub>4</sub> types, which comprise a D<sub>2</sub>-like family. The D<sub>2</sub> receptor in some species also has two gene-splice variants, an abundant D<sub>2-long</sub> type and a far less common D<sub>2-short</sub> form.<sup>13,14</sup> The endogenous ligand DA is more effective in stimulating the D<sub>2-short</sub> form by stimulating the binding of GTP to the receptor-associated G<sub>i</sub> and G<sub>o</sub> proteins.<sup>15,16</sup> In man, nonhuman primates, and some other species, D<sub>4</sub> receptors also vary in their molecular composition, based on the number of repeats of a 16-amino acid sequence found in the third intracellular loop of the receptor peptide sequence. This sequence as well as the intracytoplasmic C-terminal segment are thought to be particularly critical for DA-stimulated interactions with G-proteins and effectors and so for DA receptor functioning.

## 2. PHARMACOLOGY OF DOPAMINE RECEPTOR SUBTYPES

Compounds targeted to these several DA receptor membrane proteins can activate or inhibit their biological functions as well as provide a rational treatment for several neuropsychiatric disorders. The D<sub>1</sub> receptor is the most abundant DA receptor type in mammalian forebrain. Its mRNA in human brain tissue has been found primarily in neurons of the corpus striatum (caudate-putamen), olfactory tubercle, and nucleus accumbens but with highest total quantities in the cerebral cortex.<sup>4</sup> Although SCH-23390 was introduced as the first selective D<sub>1</sub> antagonist three decades ago, extensive efforts to develop additional pure D<sub>1</sub> antagonists and full agonists, as well as to apply them to clinical neurotherapeutics, have met limited success. Since the D<sub>1</sub> receptor requires more DA to be activated than does the D<sub>2</sub> receptor, it may be that disorders involving a deficiency of DA, such as Parkinson's disease, have a particularly great impact on D<sub>1</sub> functioning. Early D<sub>1</sub> agonists, including SKF-38393 and CY-208243, are now considered "partial agonists", with limited intrinsic activity.<sup>17</sup> They may occupy available D<sub>1</sub> receptors but fail to produce full agonism in comparison with relatively high concentrations of DA. Available D<sub>1</sub> partial agonists have not proved useful in the treatment of Parkinson's disease.<sup>17</sup> Clarification of their partial-agonist characteristics has stimulated efforts to identify D<sub>1</sub> agonists with full intrinsic activity.

The D<sub>1</sub> (or D<sub>1A</sub>) and D<sub>5</sub> (or D<sub>1B</sub>) receptors share about 80% sequence homology within the highly conserved seven transmembrane spanning domains but only 50% homology of amino acid content in other regions of their peptide sequences. The relative abundance or tissue density of D<sub>5</sub> receptors is remarkably low and less widely distributed than the far more abundant D<sub>1</sub> receptors. Outside of the CNS, both D<sub>1</sub> and D<sub>5</sub> receptors are expressed in the kidney in the proximal and distal tubules, the cortical collecting ducts, and the tunica media of renal arterioles, and the thick ascending limbs of the loops of Henle. These receptors appear to contribute to the potent effects of DA on renal functioning and blood pressure.<sup>18,19</sup> Further localization of the D<sub>5</sub> receptor subtype is difficult, since there are no ligands available that can distinguish this receptor from the D<sub>1</sub> receptor subtype.<sup>14,18</sup>

The D<sub>2</sub>-like receptor family (D<sub>2</sub>, D<sub>3</sub>, and D<sub>4</sub>) is currently of great therapeutic interest, including their identification as primary sites of action of most anti-Parkinsonian and antipsychotic drugs. The D<sub>2</sub> receptor is the second most abundant DA receptor type in mammalian forebrain. It is highly concentrated in the corpus striatum, pituitary, and olfactory tubercle, with lower levels in thalamus, anterior cingulate, and retrosplenial cortex. The D<sub>2</sub> receptor has been targeted successfully by a growing number of agonists that reduce the bradykinesia, rigidity, and tremor characteristic of Parkinson's disease, as well as symptoms of other movement disorders, including Ekbom's restless legs syndrome.<sup>20–22</sup> In addition to the immediate precursor of DA, L-DOPA, D<sub>2</sub> full or partial agonists, including R-(–)-apomorphine, pramipexole, and ropinirole, are widely used as treatments of Parkinson's disease.

D<sub>2</sub> receptors also are believed to mediate the reinforcing, dependency-producing effects of a variety of dissimilar drugs of abuse. Reinforcing effects of alcohol and morphine self-administration are diminished in D<sub>2</sub> receptor gene knockout mice and by pretreatment with D<sub>2</sub> antagonists.<sup>23–26</sup> Treatments of psychotic disorders such as schizophrenia include traditional neuroleptics (e.g., chlorpromazine, fluphenazine, haloperidol) introduced in the 1950s and modern, atypical, or "second-generation" antipsychotics (e.g., aripiprazole, clozapine, iloperidone, lurasidone, olanzapine, paliperidone, quetiapine, risperidone, ziprasidone).<sup>27–30</sup> Both types of antipsychotics have broad utility in the treatment of mania, schizophrenia, and other psychotic disorders, but the modern agents are generally less potent D<sub>2</sub> antagonists and more potent antagonists of serotonin 5-HT<sub>2A</sub> (5-hydroxytryptamine) receptors, and they pose less risk of adverse acute and late extrapyramidal neurological effects. Modern antipsychotic drugs are approximately as effective as the classic neuroleptics but with limited or different safety concerns. Clozapine is exceptional in having superior efficacy and greater potential toxicity. Many of these drugs also have effects on serotonin 5-HT<sub>1A</sub> receptors as well as on adrenergic, glutaminergic, histaminergic, and acetylcholinergic neurotransmission.<sup>31–33</sup>

The D<sub>3</sub> receptor is the first of three relatively recently cloned DA receptors (D<sub>3</sub>, D<sub>4</sub>, and D<sub>5</sub>). Its mRNA has been localized by *in situ* hybridization and radiolabeling, mainly in limbic regions of the basal forebrain, including the islands of Calleja, the olfactory tubercle, and the shell of nucleus accumbens septi. It is also found sparingly on some midbrain DA neurons and in the cerebellum. Functions of the D<sub>3</sub> receptor remain uncertain. Its effects have been inconsistent on standard effector mechanisms (e.g., adenylyl cyclase, phospholipase, ion channels) in cultured cell preparations genetically transfected

to express D<sub>3</sub> receptor proteins selectively. D<sub>3</sub> agonists appear to have inhibitory actions on behavior that contrast to arousal and motor-activating effects of D<sub>2</sub> agonists.<sup>4</sup> The selective anatomical distribution of the D<sub>3</sub> receptor in limbic brain areas known to be associated with cognitive and emotional functions suggests potential involvement of this receptor in neurological and psychiatric disorders and strongly encourages development of D<sub>3</sub> receptor-selective ligands.<sup>34–37</sup>

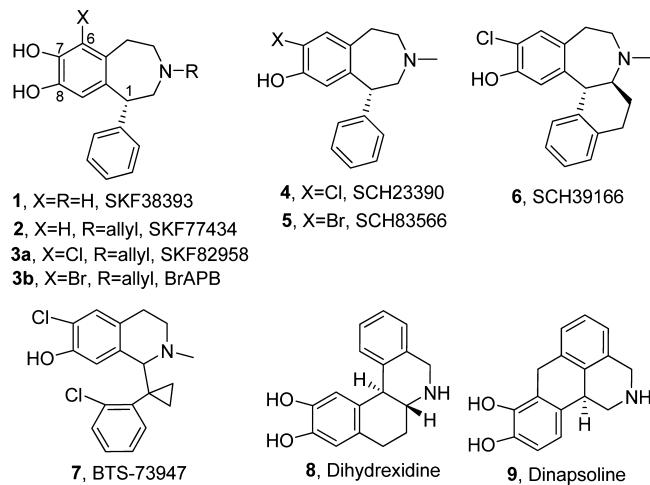
D<sub>4</sub> receptors are the third members of the D<sub>2</sub>-like receptor family. Their mRNA is detected primarily in the hippocampus and frontal cerebral cortex, with lesser expression in D<sub>2</sub>-rich areas, including the corpus striatum and midbrain. Some D<sub>4</sub> receptors may arise on terminals of corticostriatal projections innervating the striatum.<sup>4</sup> D<sub>4</sub> receptors mediate a wide range of neuronal signal transduction cascades, generally resembling the effects of D<sub>2</sub> receptors. **Several preclinical studies confirm the functions of D<sub>4</sub> receptors, including effects on motor activity, initiation and inhibition of behavior, and contributions to working memory.** Some clinical genetic studies associate D<sub>4</sub> receptors with attention deficit-hyperactivity disorder (ADHD). However, the few selective D<sub>4</sub> antagonists tested have been ineffective as antipsychotic drugs, although they also lack adverse extrapyramidal effects.<sup>38,39</sup>

### 3. DEVELOPMENT OF DOPAMINE RECEPTOR SUBTYPE LIGANDS: RECENT PROGRESS

During the last several decades, dopaminergic ligands have remained a very active area in the development of CNS drugs. Several core molecular structures have been established to be associated with dopaminergic properties and led to development of a number of clinically useful pharmaceutical and radiopharmaceutical products. They include ergolines, aporphines, benzazepines, aminotetralins, arylpiperazines, and arylpiperidines.<sup>40–46</sup> Substituted indoles, thiazoles, quinolines, and indan fragments are frequently incorporated into these molecules in efforts to enhance interactions with receptor binding sites or promote particular pharmacological properties. There is no generally accepted system of classifying such molecules, and this review relies on broad structural similarity in considering recent advances through the end of December 2011 in developing compounds that selectively target dopaminergic receptors.

#### 3.1. D<sub>1</sub> Receptor-Selective Ligands

Since the discovery of the prototype agent SCH-23390 (compound 4, Figure 1) as a D<sub>1</sub> antagonist,<sup>47</sup> other 1-phenylbenzazepines were developed that also possessed selective D<sub>1</sub> agonist or antagonist properties. This unique pharmacological profile is ascribed to the  $\beta$ -catechol-substituted ethylamine template, which mimics the structure of the catecholamine DA and is widely recognized for predictable association with D<sub>1</sub> receptor activity. In contrast, replacing this  $\beta$ -catechol component with a  $\beta$ -(3-hydroxyphenyl)-substituted ethylamine unit usually yields D<sub>2</sub> receptor activity. In general, catechol-benzazepines are D<sub>1</sub> agonists (compounds 1–3),<sup>48,49</sup> and some substitutions on the N-3, C-6, or C-1 phenyl ring can modulate affinity and selectivity for D<sub>1</sub> versus D<sub>2</sub> receptors. Notably, the C-7 substituent can control pharmacological agonism versus antagonism at D<sub>1</sub> receptors. For example, halogen replacement of the 7-OH group (analogous to the *meta*-OH of DA) results in benzazepines with D<sub>1</sub> antagonist activity (4 and 5).<sup>50–52</sup> Following these principles, a large number of even more potent and selective D<sub>1</sub> receptor ligands



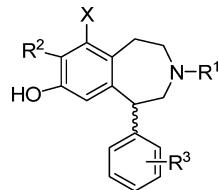
**Figure 1.** Dopamine D<sub>1</sub> receptor ligands.

(SCH and SKF series) have been identified as D<sub>1</sub> agonists or antagonists, **with variable D<sub>1</sub> versus D<sub>2</sub> selectivity and usually with little D<sub>1</sub> versus D<sub>5</sub> selectivity.**<sup>53</sup>

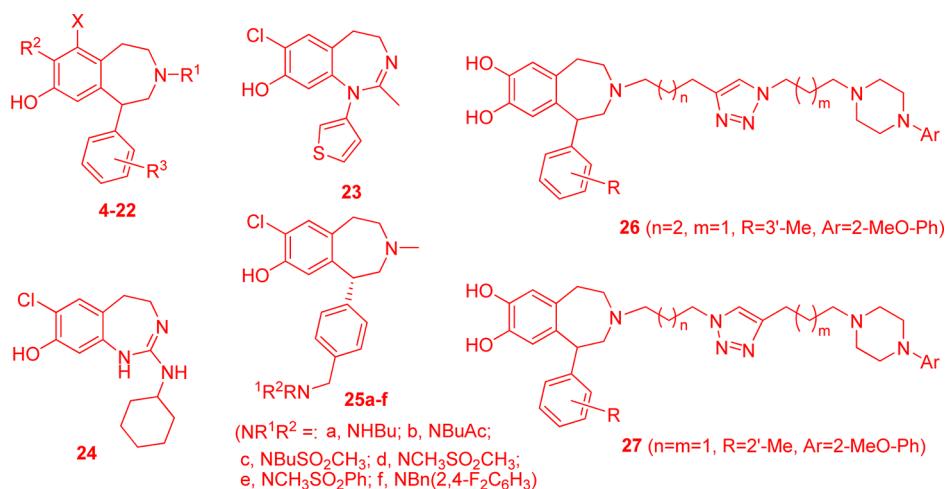
Efforts to enhance the intrinsic efficacy and their metabolic stability **as well as to improve the D<sub>1</sub> versus D<sub>2</sub> receptor selectivity** of these ligands resulted in several series of novel compounds represented by structures 6–9 (Figure 1). The conformationally restricted compound 6 (SCH-39166, also known as ecopipam) was developed by Berger et al.<sup>54</sup> in 1989 with the aim of improving the D<sub>1</sub> over D<sub>2</sub> receptor selectivity. **This D<sub>1</sub> antagonist was proposed, but not tested, as a potential antipsychotic drug, but was developed for the treatment of self-injurious behaviors in patients with Lesch–Nyhan Disease (LND).**<sup>55,56</sup> The D<sub>1</sub> antagonist 7, containing a cyclopropane unit between the C-1 and the phenyl group in the 1-phenyltetrahydroisoquinoline component, **designed to reduce the flexibility of the phenyl group**, was patented by Kozlik et al. in 1993.<sup>57</sup> Its high D<sub>1</sub> affinity is unexpected, since the  $\beta$ -(3-substituted phenyl)-ethylamine pharmacophore is not satisfied in this structure. Compounds 8 and 9 are newer D<sub>1</sub> agonists, reported by Brewster et al.<sup>58</sup> and Ghosh et al.<sup>59</sup> in the 1990s. They showed full D<sub>1</sub> intrinsic efficacy, comparable to that of DA itself, and have exceptional anti-Parkinsonism effects in monkeys treated with the selective DA-neurotoxin 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) as a laboratory model for Parkinson's disease. **However, dihydrexidine (8) is an unfavorable agent for the treatment of Parkinson's disease, in having poor oral bioavailability, a short half-life, and adverse effects, although it has been tolerated in patients with schizophrenia, even if not effective.**<sup>60–62</sup> More recent efforts to develop D<sub>1</sub> receptor ligands have continued to focus on structural optimization of the preceding molecular models with more limited exploration of novel structural scaffolds.

**3.1.1. Multiple Substituted Phenylbenzazepines.** Neumeyer and co-workers<sup>63</sup> recently reported a series of multi-substituted arylbenzazepine derivatives. In general, these compounds bear a halogen atom at the C-6 and a 3-methyl group on the C-1 phenyl ring of the benzazepine skeleton. These substitution patterns had been found previously to be beneficial for D<sub>1</sub> receptor interactions. A chloro- or bromo-substituent at C-6, a methyl or allyl substituent at N-3, and a 2'- or 3'-methyl-substituted phenyl at C-1 gave the best D<sub>1</sub> affinity and selectivity, as exemplified by compounds 11–18 in Table 1.

Table 1. Binding Affinity of Multisubstituted Benzazepines



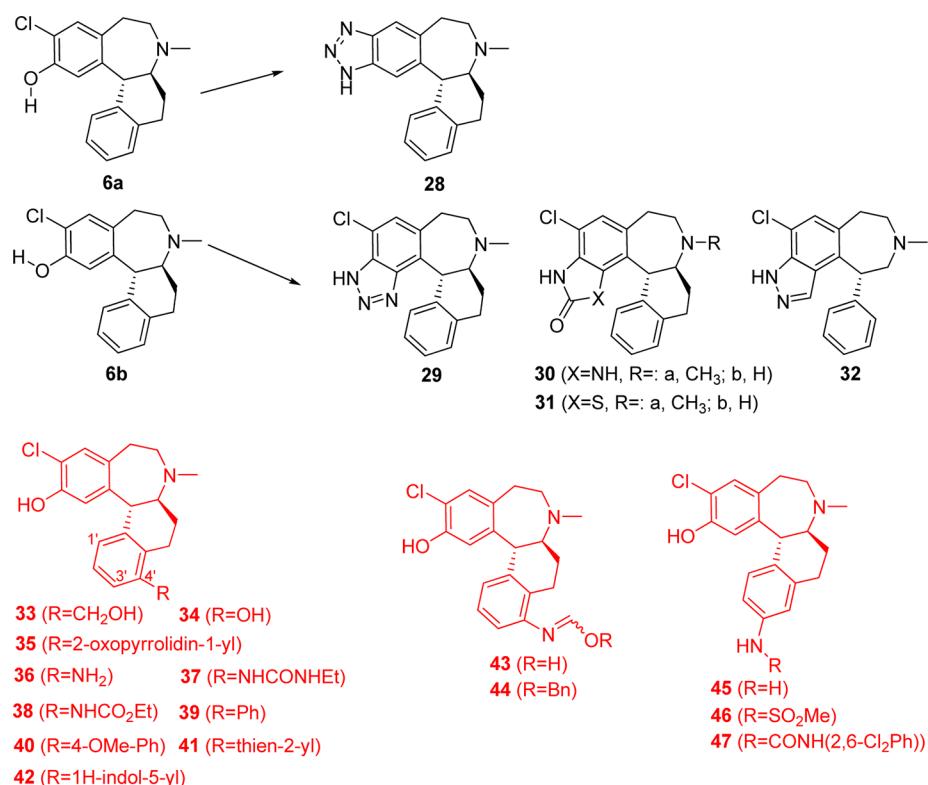
| compd        | isomer | X          | R<sup>1</sup>                      | R<sup>2</sup> | R<sup>3</sup>      | K<sub>i</sub> (nM) |               |
|--------------|--------|------------|------------------------------------|---------------|--------------------|--------------------|---------------|
|              |        |            |                                    |               |                    | D<sub>1</sub>      | D<sub>2</sub> |
| 4(SCH23390)  | R-(+)  | H          | CH <sub>3</sub>                    | Cl            | H                  | 0.12               | 1210          |
| 10(SKF83959) | RS-(±) | Cl         | CH <sub>3</sub>                    | OH            | 3'-CH <sub>3</sub> | 1.18               | 920           |
| 3b(BrAPB)    | R-(+)  | Br         | CH <sub>2</sub> CH=CH <sub>2</sub> | OH            | H                  | 2.29               | 2.09          |
| 11           | RS-(±) | Cl         | CH <sub>3</sub>                    | OH            | 2'-CH <sub>3</sub> | 0.46               | 226           |
| 12           | RS-(±) | Cl         | H                                  | OH            | 3'-CH <sub>3</sub> | 0.60               | ≥5000         |
| 13           | R-(+)  | Cl         | CH <sub>3</sub>                    | OH            | 3'-CH <sub>3</sub> | 0.49               | 515           |
| 14           | RS-(±) | Br         | CH <sub>3</sub>                    | OH            | 3'-CH <sub>3</sub> | 0.19               | 440           |
| 15           | RS-(±) | Br         | CH <sub>3</sub>                    | OH            | 2'-CH <sub>3</sub> | 1.10               | 409           |
| 16           | RS-(±) | Br         | H                                  | OH            | 2'-CH <sub>3</sub> | 1.81               | 19.5          |
| 17           | RS-(±) | Cl         | CH <sub>2</sub> CH=CH <sub>2</sub> | OH            | 3'-CH <sub>3</sub> | 0.52               | 119           |
| 18           | RS-(±) | Br         | CH <sub>2</sub> CH=CH <sub>2</sub> | OH            | 3'-CH <sub>3</sub> | 0.11               | 83.8          |
| 19           | RS-(±) | 3-tolyl    | H                                  | OH            | H                  | 39                 | >10000        |
| 20           | RS-(±) | 2-naphthyl | H                                  | OH            | H                  | 56                 | >10000        |
| 21           | RS-(±) | 3-tolyl    | H                                  | OH            | 3'-CH <sub>3</sub> | 6.81               | >10000        |
| 22           | RS-(±) | 2-naphthyl | H                                  | OH            | 3'-CH <sub>3</sub> | 4.88               | >10000        |
| 23           |        |            |                                    |               |                    | 87                 | 2800          |
| 24           |        |            |                                    |               |                    | 129                | 1550          |
| 25a          | R-(+)  |            |                                    |               |                    | 0.9                | 2000          |
| 25b          | R-(+)  |            |                                    |               |                    | 0.2                | 159           |
| 25c          | R-(+)  |            |                                    |               |                    | 0.5                | 2000          |
| 25d          | R-(+)  |            |                                    |               |                    | 0.5                | 6000          |
| 25e          | R-(+)  |            |                                    |               |                    | 0.6                | 331           |
| 25f          | R-(+)  |            |                                    |               |                    | 0.7                | 552           |
| 26           | RS-(±) |            |                                    |               |                    | 144                | 80            |
| 27           | RS-(±) |            |                                    |               |                    | 551                | 19.1          |

Figure 2. Newer dopamine D<sub>1</sub> selective benzazepine ligands.

Most of these agents possess subnanomolar affinity for the D<sub>1</sub> receptor and ≥100-fold selectivity over the D<sub>2</sub> receptor.

Benzazepine **10** (SKF-83959) is an atypical dopamine D<sub>1</sub> receptor ligand in that it can activate the phosphatidylinositol (PI)-linked pathway.<sup>53,64,65</sup> This compound possesses anti-Parkinsonian and antidyskinesia actions in animal models; the latter may be derived from the neuroprotective mechanism

associated with this agent.<sup>66,67</sup> On the basis of the structure of **10**, Zhang et al. reported a series of 6-aryl substituted 1-phenylbenzazepines.<sup>68</sup> Steric hindrance was well tolerated at position-6, suggesting a relatively large lipophilic pocket on the D<sub>1</sub> receptor around the 6-position of the benzazepine scaffold (Figure 2). Among the various analogs tested, 6-tolyl- and 6-β-naphthyl-substituted compounds **19** and **20** showed high D<sub>1</sub>



**Figure 3.** Conformationally constrained D<sub>1</sub> antagonists.

receptor affinity, with respective  $K_i$  values of 39 and 56 nM (Table 1). Much higher affinity was observed with compounds **21** (3-tolyl) and **22** (2-naphthyl), with  $D_1$  receptor  $K_i$  values of 6.31 and 4.88 nM, respectively. Low or no activity at the  $D_2$  receptor was observed for compounds **19** and **20**, which had low affinity for  $D_2$  sites, but compounds **21** and **22** showed moderate affinity at the  $D_2$  receptor, suggesting that a 3'-methyl substituent on the 1-phenyl ring is beneficial to both DA  $D_1$  and  $D_2$  receptors, but with a loss of  $D_1$ -selectivity.

In addition, functionalizing the *N*-3 substituent of benzazepine (**1**) also was explored by the same investigators with the aim of developing dual-activity agents with affinity at both dopamine D<sub>1</sub> and serotonin 5-HT<sub>1A</sub> receptors (Figure 2).<sup>69</sup> A series of novel 1-aryl-3-benzazepine derivatives containing an arylpiperazinyl function as the *N*-3 substituent was synthesized by combining a D<sub>1</sub> receptor agonistic pharmacophore and a 5-HT<sub>1A</sub> receptor pharmacophore through Click procedures. Interestingly, these compounds generally had limited or poor binding affinity at the D<sub>1</sub> receptor but were potent at both D<sub>2</sub> and 5-HT<sub>1A</sub> receptors (Table 1). Compound **26**, containing a 1-(*m*-tolyl)benzazepine scaffold and a (2-methoxyphenyl)piperazine core, exhibited good affinity at D<sub>2</sub>, 5-HT<sub>1A</sub>, and D<sub>1</sub> receptors, with respective K<sub>i</sub> values of 80, 133, and 144 nM. Compound **27**, with a triazole moiety formed differently from that in **26**, had the highest D<sub>2</sub> affinity (K<sub>i</sub>, 19 nM). This compound also showed moderate affinity at 5-HT<sub>1A</sub> (K<sub>i</sub>, 105 nM) and D<sub>1</sub> (K<sub>i</sub>, 551 nM) receptors. Functional assays indicated that compounds **27** and **26** are both antagonists at D<sub>1</sub> and D<sub>2</sub> receptors, with full agonistic activity at the 5-HT<sub>1A</sub> receptor. In accord with the binding affinity of this series, compound **27** is a high efficacy D<sub>2</sub> antagonist and 5-HT<sub>1A</sub> agonist.<sup>69</sup>

In an effort to identify novel D<sub>1</sub> antagonists, Zhu et al.<sup>70</sup> examined the 1,3-benzodiazepine core structure found in

compounds 23 and 24 (Figure 2) as a replacement for the benzazepine scaffold. This approach was encouraged by the  $pK_a$  values of *N*-aryl amidine ( $pK_a \sim 8-9$ ; e.g. 23) and *N*-guanidine ( $pK_a 10-11$ ; e.g., 24) model systems, which match the basicity of the *tert*-azepine nitrogen center in the D<sub>1</sub> receptor antagonist 4 (SCH-23390). However, the more basic cyclic *N*-aryl guanidine did not improve the binding affinity compared to the cyclic *N*-aryl amidine. The representative compounds 23 and 24 display D<sub>1</sub>  $K_i$  values of 87 and 129 nM (Table 1).

A series of substituents also have been introduced at the 4'-position of the pendent phenyl ring in compound 4 (Figure 2).<sup>71</sup> Both D<sub>1</sub> affinity and selectivity over D<sub>2</sub> were maintained or improved. Most of these compounds (**25a–f**) displayed subnanomolar D<sub>1</sub> affinity ( $K_p$ , 0.5–0.9 nM), indicating a wide tolerance of sterically bulky substituents at this position (Table 1).

**3.1.2. Bioisosteres of Conformationally Constrained Benzazepines.** Wu et al.<sup>72</sup> improved the metabolic stability

and bioavailability of conformationally constrained benzazepines with a series of phenol bioisosteres, including indole, triazole, benzimidazolone, and benzothiazolone (Figure 3). In compound 6, the preferred orientation of the hydrogen bond is the conformation of **6b** not **6a**. This conclusion is supported by the observation that the triazole **29** is 4 times more potent at the D<sub>1</sub> receptor than its congener **28** (Table 2). Nevertheless, the absence of a C-6 chloro group also may contribute to the low D<sub>1</sub> affinity of compound **28**. Further optimization aimed at increasing the acidity of the NH group as a hydrogen-bond donor led to the discovery of very potent benzimidazolones **30a,b** and benzothiazolone analogs **31a,b**. The N-CH<sub>3</sub> analogs **30a** and **31a** are 2- to 3-fold more potent at D<sub>1</sub> receptors than the corresponding nor-analogs **30b** and **31b**. The most potent compound of this type, **31a**, has an affinity ( $K_i$ ) of 2.1 nM for the D<sub>1</sub> receptor, comparable to parent compound **6** ( $K_i$ , 1.2

**Table 2. In Vitro Binding Data of Conformationally Constrained D<sub>1</sub> Antagonists**

| compd        | K <sub>i</sub> (nM) |                |                |                |
|--------------|---------------------|----------------|----------------|----------------|
|              | D <sub>1</sub>      | D <sub>2</sub> | D <sub>4</sub> | D <sub>5</sub> |
| 4 (SCH23390) | 1.4                 | 100            |                | 2.8            |
| 6 (SCH39166) | 1.2                 | 980            |                | 2.0            |
| 28           | 583                 | 3000           |                |                |
| 29           | 146                 | 1530           |                |                |
| 30a          | 7.0                 | 1023           |                | 4.2            |
| 30b          | 16.5                | 3270           |                | 2.4            |
| 31a          | 2.1                 | 257            |                | 2.8            |
| 31b          | 6.5                 | 661            |                | 1.7            |
| 32           | 14                  | 3550           |                | 30             |
| 33           | 2.0                 | 1647           | 6281           | 7.4            |
| 34           | 0.6                 | 440            | 3987           | 1.4            |
| 35           | 3.1                 | >10000         | 1370           | 26.9           |
| 36           | 2.8                 | 2100           | >10000         | 7.0            |
| 37           | 2.4                 | 900            |                |                |
| 38           | 2.3                 | 500            |                |                |
| 39           | 0.2                 | 79             |                |                |
| 40           | 0.7                 | 550            |                | 6.2            |
| 41           | 0.9                 | 93             |                | 1.9            |
| 42           | 0.6                 | 51             |                | 10.5           |
| 43           | 1.6                 | 882            | 4370           | 3.3            |
| 44           | 0.2                 | 69             | 8344           | 2.5            |
| 45           | 7.0                 | 5400           | >10000         | 8.3            |
| 46           | 0.5                 | 3000           | >10000         | 5.8            |
| 47           | 0.7                 | 1093           |                |                |

nM). Compound 31a also has improved metabolic stability and so is worthy of further investigation. In contrast, similar phenolic replacements in SCH-23390 (4) greatly decreased D<sub>1</sub> affinity, with the exception of the indazole 32, which had moderate D<sub>1</sub> affinity ( $K_i = 14$  nM) and was only 10-times less potent than its parent SCH-23390 but with a 3-fold gain in selectivity for D<sub>1</sub> over D<sub>2</sub> receptors.

In 2010, researchers at Merck reported several series of benzazepine analogs of 6 (SCH-39166) by introducing a range of substituents to the 3' or 4' -position of the pendent phenyl ring.<sup>71,73</sup> A wide variety of functionality (Br, CHO, CN, CO<sub>2</sub>H, amino, aryl, etc.) were tolerated in the 4'-position, and all these analogs displayed nanomolar to subnanomolar D<sub>1</sub> affinity, similar to that of parent compound 6. Representative compounds 33–42 showed K<sub>i</sub> values of 0.2–3.1 nM at the D<sub>1</sub> receptor (Table 2, Figure 3). The steric and electronic properties of the substituents did not affect D<sub>1</sub> affinity appreciably. Interestingly, the oxime analogs 43 and 44 also exhibited good D<sub>1</sub> receptor affinity, with the O-benzyl oxime 44 showing the highest potency ( $K_i$ , 0.2 nM). The pharmacokinetic (PK) properties of these compounds also were evaluated.<sup>73</sup> The prototypical compound 6 (SCH-39166) showed a reasonable area under the plasma concentration–time curve (AUC), but the T<sub>max</sub> (time of maximum concentration (T<sub>max</sub>) was 30 min, and the elimination half-life (T<sub>1/2</sub>) was only 2.5 h. Introduction of a 2-thienyl group at C-4 (compound 41) in the D-ring of compound 6 considerably increased AUC and maximum plasma concentration (C<sub>max</sub>) and prolonged T<sub>1/2</sub>. On the other hand, 4-methoxyphenyl or 4-pyridinyl substitution (40 and 42) did not improve the PK profile.

In a similar strategy, a series of amino substituents were introduced to the 3'-position of the pendent phenyl ring in

compound 6.<sup>71</sup> These analogs also displayed high affinity at the D<sub>1</sub> receptor that was similar to, or even more potent than, parent compound 6 (Table 2). Compared to the unprotected amino analog 45, the methylsulfonamide 46 and 3-phenylurea 47 displayed more than 1-fold higher D<sub>1</sub> affinity, with K<sub>i</sub> values of 0.5 and 0.7 nM, respectively. Further exploration of these compounds disclosed that 47 not only has subnanomolar D<sub>1</sub> affinity but also shows nearly 10-fold improvement in D<sub>1</sub>-selectivity over D<sub>2</sub>, D<sub>4</sub>, and D<sub>5</sub> receptors. In comparison to parent compound 6, selectivity for D<sub>1</sub> over 5-HT<sub>2A</sub> and α<sub>2a</sub> receptors was also improved in compound 47. Further, there was a significant improvement of PK properties and oral bioavailability (29% for 47 versus 0.6% for 6).<sup>71</sup>

### 3.1.3. Derivatives of Dinapsoline and Dihydrexidine.

Advances in understanding the structure–activity relationships (SAR; Figure 1) of dinapsoline (9) have clarified the effects of its stereochemistry on pharmacological properties and guided further development of derivatives. Stereoselective preparation of the *trans* conformation of dihydrexidine (8) used an asymmetric conjugate-addition technique.<sup>74,75</sup> Similarly, an improved synthesis of dinapsoline (9) has been reported that used a free-radical initiated cyclization as the key step.<sup>76</sup> Half of the synthetic steps in earlier procedures are eliminated, and the enantiomers of 9 produced are readily separated. R-(+)-9 is the active enantiomer with similar potencies (IC<sub>50</sub>) at D<sub>1</sub> and D<sub>2</sub> receptors (33 and 38 nM, respectively), whereas the S-(−)-9 enantiomer is 161- and 39-fold less potent (IC<sub>50</sub> at D<sub>1</sub> and D<sub>2</sub> sites, 5.3 and 1.5 μM), and racemic 9 is approximately half as potent as the R-(+)-9 enantiomer, as expected (D<sub>1</sub> and D<sub>2</sub> IC<sub>50</sub> = 67 and 56 nM). In rats with unilateral 6-hydroxydopamine (6-OHDA) lesions of DA neurons, S-(−)-9 but not R-(+)-9 was virtually inactive. N-Alkylation of racemic 9 with an allyl- or n-propyl group, or introducing a 4-methyl group, decreases D<sub>1</sub> receptor affinity. However, the 6-methyl-substituted derivative retains reasonable D<sub>1</sub> affinity at D<sub>1</sub> receptor (1.5-fold less potent than dinapsoline 9) with a substantial gain in D<sub>1</sub> over D<sub>2</sub> receptor selectivity of 20-fold.<sup>77</sup>

Another bioisostere of 9 (dinapsoline; Figure 1) is compound 48 (dinoxyline; Figure 4), which was prepared by replacing the methylene tether in 9 with an ether linkage (oxygen atom). Since the presumably required pharmacophoric element for D<sub>1</sub> receptor binding (β-phenyldopamine) was well conserved, this novel compound exhibited high affinity at cloned D<sub>1</sub> receptors (K<sub>i</sub>, 3.9 nM, comparable to 5.5 nM for dinapsoline) and showed 22-fold greater selectivity for D<sub>1</sub> over

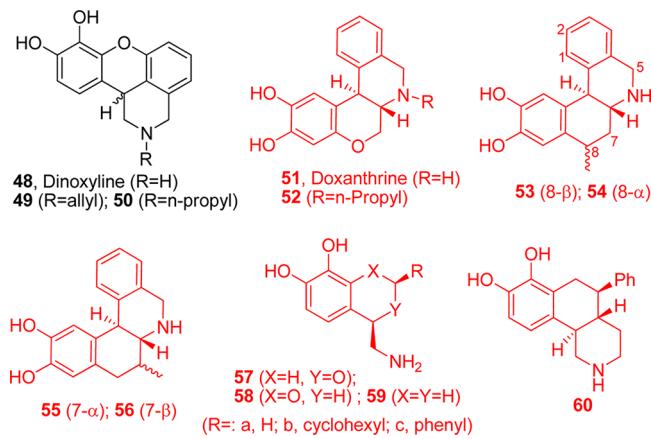


Figure 4. Derivatives of dihydrexidine (8) and dinapsoline (9)..

**Table 3.** *In Vitro Binding Data of Derivatives of Dinapsoline and Dihydrexidine<sup>a,b</sup>*

| compd                          | D <sub>1</sub>                     | K <sub>i</sub> (nM)                    |                  |                 |                |
|--------------------------------|------------------------------------|--|------------------|-----------------|----------------|
|                                |                                    | D <sub>2</sub>                         | D <sub>3</sub>   | D <sub>4</sub>  | D <sub>5</sub> |
| 8 (dihydrexidine) <sup>b</sup> | 2.2 (21 <sup>a</sup> )             | 180 (240 <sup>a</sup> )                | 15               | 14              | 14             |
| 9 (dinapsoline) <sup>b</sup>   | 5.5                                | 140                                    | 10               | 60              | 10             |
| 48(dinoxyline) <sup>b</sup>    | 3.9                                | 86                                     | 1.0              | 1.1             | 3.8            |
| 49 <sup>b</sup>                | 110                                | 290                                    | 9.0              | 6.3             | 1500           |
| 50 <sup>b</sup>                | 190                                | 98                                     | 0.93             | 2.6             | 570            |
| 51 (doxanthrine)               | 22 <sup>a</sup> (98 <sup>b</sup> ) | 3700 <sup>a</sup> (1910 <sup>b</sup> ) | 390 <sup>b</sup> | 90 <sup>b</sup> | 7 <sup>b</sup> |
| (+)-51 <sup>b</sup>            | 8                                  | 2500                                   |                  |                 |                |
| (-)-51 <sup>b</sup>            | 270                                | 6800                                   |                  |                 |                |
| 52 <sup>b</sup>                | 330                                | 340                                    |                  |                 |                |
| 53 <sup>a</sup>                | 270                                | 5530                                   |                  |                 |                |
| 54 <sup>a</sup>                | 920                                | 3630                                   |                  |                 |                |
| 55 <sup>a</sup>                | >10000                             | 7380                                   |                  |                 |                |
| 56 <sup>a</sup>                | 6540                               | 8670                                   |                  |                 |                |
| 57a <sup>a</sup>               | 80                                 | 1960                                   |                  |                 |                |
| 57b <sup>a</sup>               | 3.4                                | 920                                    |                  |                 |                |
| 57c <sup>a</sup>               | 2.6                                | 240                                    |                  |                 |                |
| 58a <sup>a</sup>               | 9100                               | 290                                    |                  |                 |                |
| 58b <sup>a</sup>               | 770                                | 4600                                   |                  |                 |                |
| 59a <sup>a</sup>               | 1100                               | 2000                                   |                  |                 |                |
| 59b <sup>a</sup>               | 40                                 | 3500                                   |                  |                 |                |
| 59c <sup>a</sup>               | 23                                 | 770                                    |                  |                 |                |
| 60 <sup>a</sup>                | 6                                  | 440                                    |                  |                 |                |

<sup>a</sup>Binding data for porcine striatal homogenates. <sup>b</sup>Binding data for cloned human receptor subtypes.

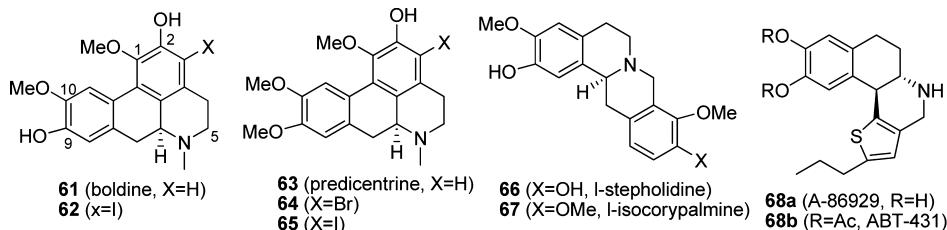
D<sub>2</sub> ( $K_i$ , 86 nM) receptors (Table 3).<sup>78</sup> Dinoxyline (48) also showed high affinity for D<sub>1</sub>-like D<sub>5</sub> receptors ( $K_i$  = 1.0 nM) and was slightly less potent for the D<sub>3</sub> receptor ( $K_i$  = 6.6 nM). N-Alkylation of 48 remarkably decreased D<sub>1</sub> affinity (49, 50). In functional assays, 48 showed higher potency and intrinsic activity than the earlier full D<sub>1</sub> agonists dihydrexidine (8) and dinapsoline (9), equal to that of DA itself. Dinoxyline (48) is undergoing further evaluation for the treatment of Parkinson's disease.<sup>78</sup>

Since replacement of the methylene linkage in 9 resulted in improved D<sub>1</sub> affinity in 48, a similar strategy was pursued with the polycyclic DA agonist 8, where the ethylamine side chain is held in the “trans-β” rotameric orientation by a tetracyclic ring system containing the catechol and β-phenyl moieties.<sup>58,79,80</sup> Therefore, the ethyl tether between the catechol and tetrahydroisoquinoline substructures in 8 was replaced with an oxymethylene ether bridge, to result in compound 51 (doxanthrine), *trans*-2,3-dihydroxy-6*a*,7,8,12*b*-tetrahydro-6*H*-chromeno[3,4-*c*]isoquinoline (Figure 4). In competition binding assays using porcine striatal preparations, racemic 51 had high affinity ( $K_i$ , 22 nM) at D<sub>1</sub>-like receptors, similar to that of parent compound 8 (Table 3). Surprisingly however, compound 51 showed negligible binding affinity ( $K_i$ , 3.0 μM) at D<sub>2</sub>-like receptors, in sharp contrast to the more potent carbocyclic parent compound 8 (D<sub>2</sub>-like  $K_i$ , 240 nM). A similar stereochemical profile was observed in the enantiomers of 51: 6*aS*,12*bR*-(+)-51 showed high D<sub>1</sub> affinity ( $K_i$ , 7 nM) and 2- and 50-fold greater potency than that of racemic 51 (22 nM) or (-)-51 (290 nM). Compared to compound 51, the *N*-propyl analog 52 exhibited 15-fold lower D<sub>1</sub> potency, but this compound had somewhat higher affinity at D<sub>2</sub>-like receptors. Functional assays revealed that racemic 51 was a potent and full D<sub>1</sub> agonist, comparable to DA. The (+)-isomer was slightly more potent than the racemate (EC<sub>50</sub>, 29 nM), whereas (-)-51

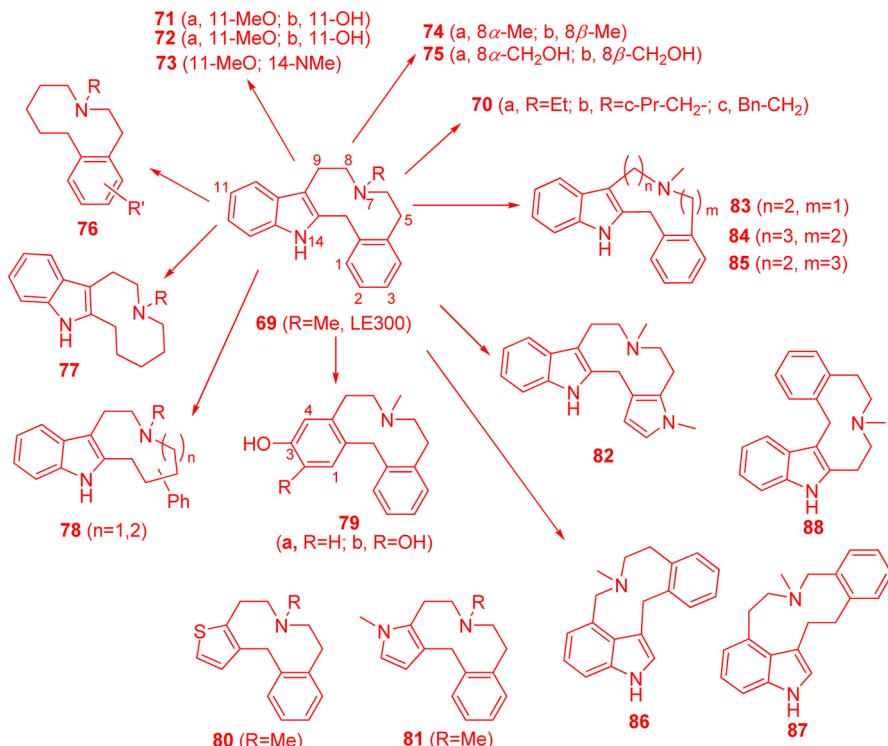
was a much weaker agonist (EC<sub>50</sub>, 1.1 μM). The potency of 51 and its enantiomers at D<sub>2</sub> receptors was negligible.<sup>80</sup>

As a continuation of the SAR pertaining to the D<sub>1</sub> agonist 8, four methyl-substituted analogs were synthesized with substitutions at the 7- and 8-positions (53–56, Figure 4) through strategies involving photochemical cyclization or the intramolecular Henry reaction.<sup>81</sup> However, all of the methylated analogs 53–56 displayed only moderate or low D<sub>1</sub> affinity (270 nM to 10.0 μM). Molecular modeling studies suggested that disruption of an aromatic interaction between Phe203<sup>5,47</sup> and Phe288<sup>6,51</sup> is likely the cause of the 14-fold loss in affinity associated with 8β-axial substitution (53), whereas unfavorable steric interactions with Ser107<sup>3,36</sup> may be responsible for the even more dramatic decreases in D<sub>1</sub> binding affinity suffered by analogs 54–56.

The same research group recently explored a series of isochroman analogs.<sup>82</sup> The earlier isochroman compounds (57a–c) generally had good affinity and selectivity for the D<sub>1</sub> receptor. The new analogs 58–59 were designed to reposition the oxygen atom in the heterocyclic ring (Figure 4). However, significant reduction in D<sub>1</sub> potency resulted. The low D<sub>1</sub> affinity of compounds 58a,b was rationalized by *in silico* modeling, which found evidence of potential intramolecular hydrogen bonding between the oxygen in the chroman ring and the *meta*-hydroxyl group of the catechol moiety. This hypothesis was supported by the fact that carbocyclic compound 59b, which lacks a potential for intramolecular hydrogen bonding, retained reasonable D<sub>1</sub>-like receptor potency and selectivity (Table 3). In addition, 7,8-dihydroxyoctahydrobenzo[*h*]isoquinoline (60) was synthesized as a tricyclic analog of 8 and 9.<sup>83</sup> It showed D<sub>1</sub> full-agonist activity with high affinity and potency, with a  $K_i$  value as high as 0.6 nM with cloned D<sub>1</sub> human receptors. Surprisingly, further screening of compound 60 against other brain receptors disclosed that it showed high potency for targets including α<sub>2A</sub>, α<sub>2B</sub>, α<sub>2C</sub>, and D<sub>5</sub> receptors, with respective



**Figure 5.** Boldine, predicentrine, and tetracyclic analogs.



**Figure 6.** Benz[d]indolo[2,3-g]azecines derivatives.

$K_i$  values of 3.5, 6.4, 1.1, and 2.8 nM.<sup>83</sup> In view of its high affinity at D<sub>1</sub> and D<sub>5</sub> DA receptors, and the reportedly beneficial effects of stimulating prefrontal cerebrocortical  $\alpha_2$  adrenergic receptors on spatial working memory, the interesting neuropharmacology of compound 60 encourages its further development as a potential drug.

**3.1.4. Boldine, Predicentrine, and Related Derivatives.** The aporphine alkaloids boldine (61) and predicentrine (63) possess similar, moderate affinity at both D<sub>1</sub> and D<sub>2</sub> receptors and exhibit neuroleptic-like behavioral effects in mice, suggesting that they act as DA antagonists (Figure 5).<sup>84,85</sup> It should be noted that the stereochemistry at the 6 $\alpha$ -carbon is S in these compounds, whereas it is R in apomorphine and its congeners. Substitution patterns at the 1-, 2-, 9-, and 10-carbon positions are responsible for the DA antagonist properties and differ from those of R-(–)-apomorphine and its derivatives, which are DA agonists. SAR analyses indicate that halogenation of these alkaloids 61 and 63 at C-3 yields new compounds (62, 64, 65; Figure 5) with enhanced affinity and selectivity for the D<sub>1</sub> receptor.<sup>86</sup> The 3-iodinated analog (62) of boldine (61) has the highest D<sub>1</sub> affinity ( $K_i = 2$  nM) among the halogenated boldine derivatives and is 150-fold more potent than boldine itself. In addition, 3-iodoboldine (62) has a 34-fold D<sub>1</sub>/D<sub>2</sub> receptor selectivity. Similarly, 3-iodination of predicentrine

(63) gave compound 65, which is 40-times more potent ( $K_i = 6$  nM) at the D<sub>1</sub> receptor than parent compound 63, with 139-fold D<sub>1</sub>/D<sub>2</sub> selectivity.<sup>87</sup> 3-Bromo-predicentrine (64) also is quite potent and selective at the D<sub>1</sub> receptor but only about one-half as potent as the 3-iodo congener 65.

*l*-Stepholidine (66, Figure 5) is a tetrahydroprotoberberine alkaloid isolated from the Chinese herb Stephonia.<sup>88</sup> It is a mixed D<sub>1</sub> agonist/D<sub>2</sub> antagonist with D<sub>1</sub> and D<sub>2</sub>  $K_i$  values of 13 and 82 nM, respectively. Preliminary clinical trials indicate that this compound improves both positive and negative symptoms of schizophrenia without producing significant extrapyramidal side effects.<sup>88</sup> Like the classic atypical (with low risk of adverse extrapyramidal neurological effects) antipsychotic agent clozapine, *l*-stepholidine increases expression of the immediate early gene *c-fos* preferentially in corticolimbic areas of animal forebrain tissue, including the medial prefrontal cortex, although it is uncertain if this effect is mediated by DA.<sup>89</sup> Oral administration of 66 showed rapid absorption from the gastrointestinal tract, followed by dose-dependent occupancy of D<sub>1</sub> and D<sub>2</sub> receptors (9% to 77% at 0.3 to 30 mg/kg for D<sub>1</sub>; 44% to 94% at 1 to 30 mg/kg for D<sub>2</sub>). However, rapid elimination and extensive initial metabolism of this compound led to low oral bioavailability (<2%).<sup>90,91</sup> The MeO-analog 67 was recently isolated from *Corydalis yanhusuo* by a bioactivity-

Table 4. Binding Data at Human Cloned Dopamine Receptors

| compd                      | hD <sub>1</sub> | hD <sub>2L</sub> | K <sub>i</sub> (nM) |                |                |
|----------------------------|-----------------|------------------|---------------------|----------------|----------------|
|                            |                 |                  | D <sub>3</sub>      | D <sub>4</sub> | D <sub>5</sub> |
| 69 (LE300)                 | 1.9             | 44.7             |                     | 109            | 7.5            |
| 70a                        | 16.4            | 253              |                     | 378            | 14.7           |
| 70b                        | 767             | >5000            |                     | >5000          | 893            |
| 71a <sup>a</sup>           | 0.82            | 11.9             | 475                 | 266            | 3.6            |
| 71b <sup>a</sup>           | 0.56            | 38.4             | 944                 | 398            | 0.39           |
| 72a <sup>a</sup>           | 19              | 22.8             | 1135                | 92.6           | 31.5           |
| 72b <sup>a</sup>           | 3.7             | 74.7             | 2070                | 1359           | 5.4            |
| 73 <sup>a</sup>            | 2.0             | 1.7              | 3.78                | 21.5           | 0.23           |
| 74a                        | 6.1             | 85.3             | 304                 | 64.1           | 4.4            |
| 74b                        | 640             | >10000           | >10000              | >10000         | 389            |
| 75a                        | 10.3            | 268              | 681                 | 408            | 11.4           |
| 75b                        | 114             | 2923             | 4676                | 4861           | 91.4           |
| 79a                        | 0.39            | 17.5             |                     | 11.3           | 1.5            |
| 79b <sup>a</sup>           | 341             | >5000            |                     | 165            | 1078           |
| 80                         | 10.7            | 198              |                     | 299            | 79.1           |
| 81                         | 61              | 712              |                     | 1647           | 361            |
| 84(LE-CE-580) <sup>a</sup> | 163             | 143              | 521                 | 184            | 92             |
| 85(LE-CE-560) <sup>a</sup> | 2.2             | 14.5             | 277                 | 98.4           | 0.61           |
| 86 <sup>a</sup>            | >10000          | >10000           | >10000              | >10000         | >10000         |
| 87 <sup>a</sup>            | 4.2             | 4.0              | 42.9                | 39.1           | 2.5            |
| 88 <sup>a</sup>            | 28.5            | 55.1             | 513                 | 225            | 10.3           |

<sup>a</sup>The data for the D<sub>1</sub> receptor was on HEK 293 cells, and CHO cells were used for the rest of DA cells.

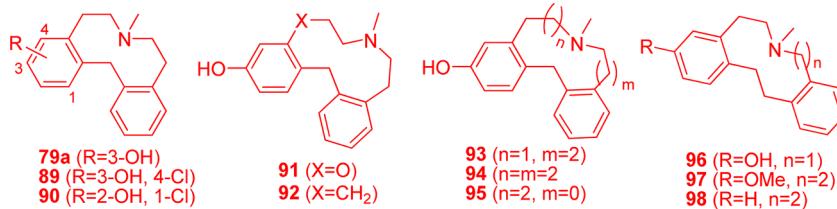
guided fractionation;<sup>92</sup> it showed high binding affinity at the D<sub>1</sub> receptor ( $K_i$ , 83 nM) expressed in transfected HEK-T cells.<sup>92</sup>

**3.1.5. Hexahydrobenzo[f]thieno[c]quinolines.** Tetracyclic **68a** (A-86929) is an important D<sub>1</sub> agonist bearing a chiral arene-fused hexahydrobenzoquinoline structural motif (Figure 5).<sup>93,94</sup> This compound has high potency and selectivity at the D<sub>1</sub> receptor ( $K_i$ , 39 nM). It elicits a full agonist response relative to DA in stimulating adenylyl cyclase (EC<sub>50</sub>, 7 nM) and induces contralateral rotation in rodents with the unilateral lesions of the DA system, as well as antibradykinetic effects in primate models of Parkinson's disease.<sup>93</sup> However, this compound has poor oral bioavailability and metabolic stability. The diacetyl prodrug derivative **68b** (ABT-431, DAS-431, adigolide)<sup>95</sup> is also a high affinity, full D<sub>1</sub> agonist with improved PK properties that has been found to be effective in Parkinson's disease and several other CNS disorders.<sup>95</sup>

**3.1.6. Benz[d]indolo[2,3-g]azecines.** The benz[d]indolo[2,3-g]azecine skeleton represents another novel molecular format for D<sub>1</sub> receptor antagonists, prepared by incorporating the substructures of tryptamine and  $\beta$ -phenylethylamine into a moderately constrained 10-membered azecine ring.<sup>96</sup> The key elements for high D<sub>1</sub> receptor activity include the indole, the benzene ring, the central azecine ring, and the N-Me substituent. Lead compound **69** (LE300, 7-methyl-6,7,8,9,14,15-hexahydro-5H-benz[d]indolo[2,3-g]azecine; Figure 6, Table 4) displayed high affinity at cloned human D<sub>1</sub> receptors and 24-fold D<sub>1</sub>/D<sub>2</sub> selectivity (D<sub>1</sub> versus D<sub>2</sub>  $K_i$ : 1.9 nM versus 44.7 nM). Other analogs with an *ortho*-dihydroxy function on the phenyl ring (a typical DA-like profile) have lower D<sub>1</sub> affinity.<sup>96–98</sup> Further, compound **69** acts like DA-antagonistic antipsychotic drugs by inhibiting conditioned avoidance responses in mice and also shows nanomolar affinity at 5-HT<sub>2A</sub> and 5-HT<sub>2C</sub> receptors.<sup>97</sup> In addition, compound **69** showed slightly higher D<sub>5</sub> than D<sub>1</sub> affinity ( $K_i$ , 7.5 versus 9.1 nM; Table 4). Compound **69** opens a novel avenue in the search for D<sub>1</sub> and D<sub>5</sub> agonists or antagonists.

Replacement of the N-methyl in **69** with other alkyl groups (e.g., in **70a–c**) reduced D<sub>1</sub> affinity, indicating that only small alkyl groups were tolerated.<sup>98</sup> Modification on the indole-phenyl ring led to methoxylated, hydroxylated, and indole-N methylated derivatives **71–73** (Figure 6, Table 4).<sup>99</sup> The 11-MeO and 11-OH analogs **71a,b** retained high affinity for both D<sub>1</sub> and D<sub>5</sub> receptors, compatible with that of lead compound **69**. Similar substitution on the second benzene ring retained good affinity for D<sub>1</sub> and D<sub>5</sub> receptors as well, although compounds **72a,b** were slightly less potent than **71a,b**. Notably, 11-methoxy-7,14-dimethyl-6,7,8,9,14,15-hexahydro-5H-indolo[3,2-f][3]benzazecine (**73**) was potent at all DA receptor types (D<sub>1</sub>–D<sub>5</sub>), with very high affinity and 9-fold selectivity, for D<sub>5</sub> over D<sub>1</sub> receptors ( $K_i$ , 0.23 versus 2.00 nM). Substitution on the central azecine ring was explored in both racemic and enantiopure forms of **73**.<sup>100</sup>  $\alpha$ -Configured **74a** and **75a** showed moderately high D<sub>1</sub> affinity ( $K_i$ , 6.1 and 10.3 nM) that was only slightly less potent than the lead compound **69** but much more potent than corresponding  $\beta$ -enantiomers **74b** and **75b**.

Similar trends were observed with the D<sub>5</sub> receptor, at which the  $\alpha$ -configured isomers were much more potent than the corresponding  $\beta$ -enantiomers. The two aromatic rings, separated by a methylene carbon in these compounds, were critical for the D<sub>1</sub> receptor binding. Their absence (**76**, **77**) or substitution or replacement by other ring systems (**76–78**, **80–82**) resulted in marked decrease in D<sub>1</sub> affinity.<sup>98</sup> Replacing the indole component in **69** with a benzene ring was tolerated, especially for the phenol **79a** (D<sub>1</sub> and D<sub>5</sub>  $K_i$ , 0.39 and 1.5 nM). However, compound **79b**, bearing a dopamine like catechol function, showed much lower affinity (D<sub>1</sub> and D<sub>5</sub>  $K_i$ , 341 and 1078 nM). The dihydroxylated compound **79b** had much higher inhibitory activities than **79a** in assays involving calcium transport. In summary, **79a** (LE404) and lead compound **69** turn out to be potent D<sub>1</sub> receptor antagonists with nanomolar to subnanomolar affinity for all DA receptor subtypes and selectivity for the D<sub>1</sub> receptor.<sup>98</sup>

**Figure 7.** Dibenzazecine analogs..**Table 5.** Binding Data of Dibenzazecine Derivatives at Human Cloned Dopamine Receptors

| compd                    | hD <sub>1</sub> | hD <sub>2L</sub> | D <sub>3</sub> | D <sub>4</sub> | D <sub>5</sub> |
|--------------------------|-----------------|------------------|----------------|----------------|----------------|
| 69 (LE300) <sup>a</sup>  | 1.9             | 44.7             |                | 109            | 7.5            |
| 79a (LE404) <sup>a</sup> | 0.39            | 17.5             |                | 11.3           | 1.5            |
| 89 <sup>a</sup>          | 0.83            | 4.0              | 24.6           | 5.2            | 0.057          |
| 90 <sup>a</sup>          | 0.46            | 0.99             | 1.88           |                | 0.98           |
| 91 <sup>a</sup>          | 3.2             | 274              | 1384           | 375            | 0.57           |
| 92                       | 13.9            | 518              | 6122           | 2258           | 17             |
| 93                       | 3.2             | 74               | 100            | 60             | 9.8            |
| 94                       | 83              | 382              | 3964           | 422            | 95             |
| 95                       | 2070            | >10000           | >10000         | >10000         | 1810           |
| 96                       | >10000          | >10000           | >10000         | >10000         | >10000         |
| 97                       | 119             | 1502             | 3120           | 726            | 492            |
| 98                       | 118             | 917              | 3045           | 475            | 97.5           |

<sup>a</sup>The data for the D<sub>1</sub> receptor was on HEK 293 cells, and CHO cells were used for the rest of the DA cells.

Changing the central azecine ring of compound **69** led to compound **83**, which was inactive at DA receptors, whereas enlarging the 10-membered azecine ring yielded homologous compounds **84** and **85**, showing high D<sub>1</sub> affinity.<sup>101</sup> Compared to **69**, the phenylpropyl homologue **85** (LE-CE-560) was superior in selectivity and binding affinity for D<sub>5</sub> receptors ( $K_i$ , 0.6 nM), whereas the affinity of the indolylpropyl homologue **84** was lower for all DA receptor types. Such D<sub>5</sub> over D<sub>1</sub> receptor selectivity of compound **85** was not observed in functional assays involving calcium transport, where the compound was a similarly potent inverse agonist at both sites.<sup>101</sup>

Changing the annulation pattern of the azecine system led to compounds **86–88**, which showed quite different profiles (Figure 6, Table 4).<sup>102</sup> Between the two homologues **86** and **87**, where the alicycle is fused at the 3-, 3a-, and 4-positions of the indole system, indolo[4,3a,3-ef]benzazecine **86** showed low affinity at all DA receptors, whereas the ring-expanded compound **87** (indolo[4,3a,3-f]benzazacycloundecene) displayed high D<sub>1</sub>, D<sub>2</sub>, and D<sub>5</sub> affinity (respective  $K_i$  values, 4.2, 4.0, and 2.5 nM), which were similar to those of lead compound **69**. Similar selectivity was observed with the indolo[2,3-f]benzazecine **88**, but with noticeable reduction in affinity for all DA receptors. The significant discrepancy in receptor affinities for compounds **86** and **87** may be due to the steric effects produced by their different annulation patterns. Compound **86** is much more constrained, compared to lead **69**, whereas the expanded ring structure of compound **87** possesses higher structural flexibility.

On the basis of the extensive SAR on analogs of the “azecine-type” D<sub>1</sub>- and D<sub>5</sub>-selective antagonist **69**, as described above, hexahydro-dibenzo[d,g]azecine **79a** was identified as another new, highly potent, D<sub>1</sub>, D<sub>5</sub> antagonist which serves as an additional lead for further structural modifications.<sup>98,103</sup> Since a chloro-substituent is generally beneficial for strengthening the

interaction of the D<sub>1</sub> receptor with antagonists, especially in the benzepine series,<sup>46,53,63</sup> chlorinated analogs of **79a** were developed. As shown in Figure 7 and Table 5, hydroxylation and chlorination of the dibenzazecines generally increased D<sub>1</sub>-like affinity significantly, by varying the substitution sites.<sup>104</sup> 4-Chloro-3-hydroxy-7-methyl-substituted dibenz[d,g]azecine (**89**) was the most potent of such compounds at cloned human DA receptors (D<sub>1</sub>, D<sub>2L</sub>, D<sub>3</sub>, D<sub>4</sub>, and D<sub>5</sub> receptor  $K_i$ : 0.83, 4.0, 24.6, 5.2, 0.06 nM). 1-Chloro-2-hydroxyhexahydrodibenzo[d,g]azecine (**90**) was a slightly less potent antagonist at both D<sub>1</sub>-like and D<sub>2</sub>-like DA receptors. Compound **89** (LE-PM-36), with 14-fold selectivity for D<sub>5</sub> over D<sub>1</sub> receptors, may facilitate study of the physiology of the D<sub>5</sub> receptor.

High affinity at the D<sub>1</sub> receptor was retained in the oxazacycloundecene **91** ( $K_i$ , 3.2 nM), with nearly 6-fold higher affinity for the D<sub>5</sub> receptor ( $K_i$ , 0.57 nM).<sup>105</sup> The corresponding carbocyclic analog **92** displayed 4- (D<sub>1</sub>) and 30-fold (D<sub>5</sub>) less affinity than **91**. Further expansion of the central N-heterocycle was also conducted similar to the case of the benzindoloazecine series, leading to analogs **93–98** (Figure 7).<sup>106–108</sup> Enlarging the dibenzazecines to the corresponding dibenzazacycloundecenes **92** and **93** and dibenzazacyclododecene **94** generally yielded lower but still substantial affinity for D<sub>1</sub> and D<sub>5</sub> receptors (3.2–95 nM; Table 5). The position of the nitrogen in relation to the substituted benzene ring appeared to be crucial. Compound **93**, with the nitrogen closer to the substituted benzene ring, was more active than other regioisomers.<sup>106</sup>

In addition, several potent D<sub>1</sub>–D<sub>5</sub> antagonists derived from the lead indolobenzazecine **69** were evaluated at the serotonin 5-HT<sub>2A</sub> receptor. Most of these compounds were highly potent and likely to be 5-HT<sub>2A</sub> receptor antagonists,<sup>109,110</sup> especially compounds **69**, **71b**, **79a**, and **89** (with 5-HT<sub>2A</sub>  $K_i$  values of 0.16, 0.11, 0.64, and 0.89 nM).

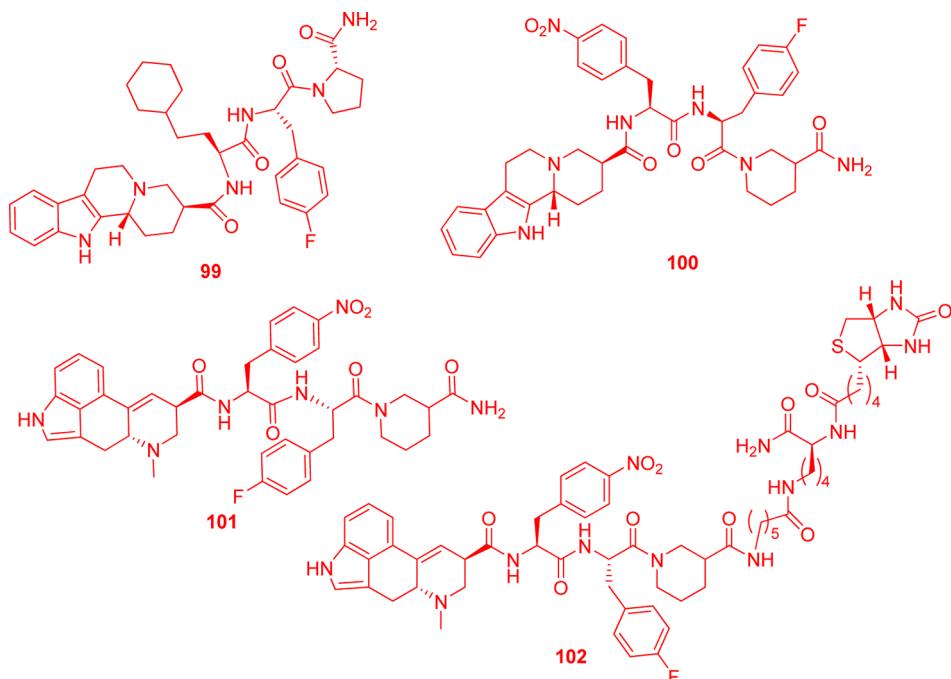


Figure 8. Indoloquinolizidine- and ergolene-peptide hybrid analogs.

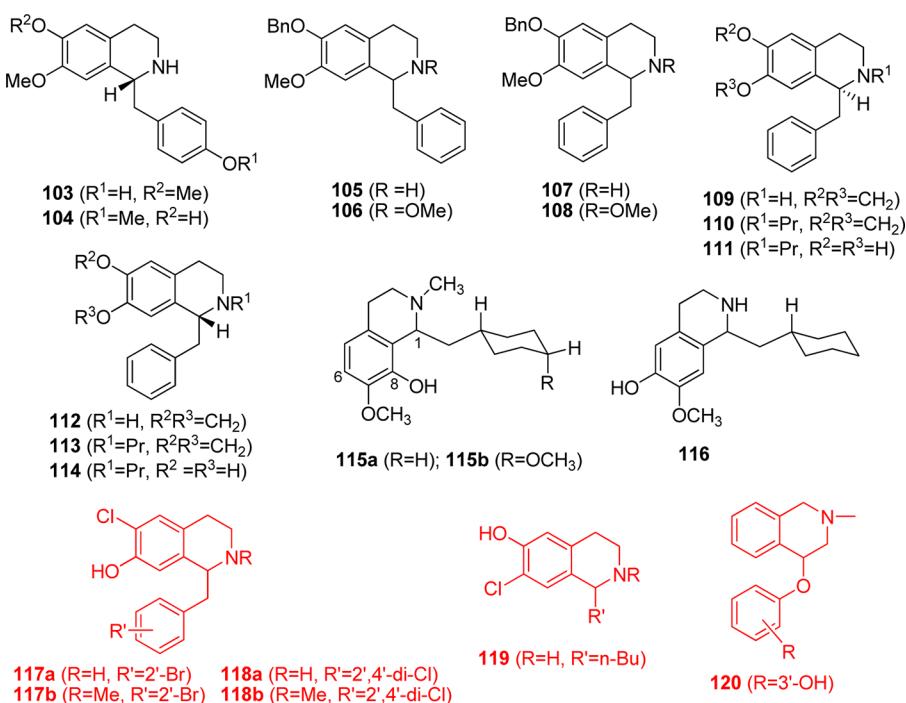
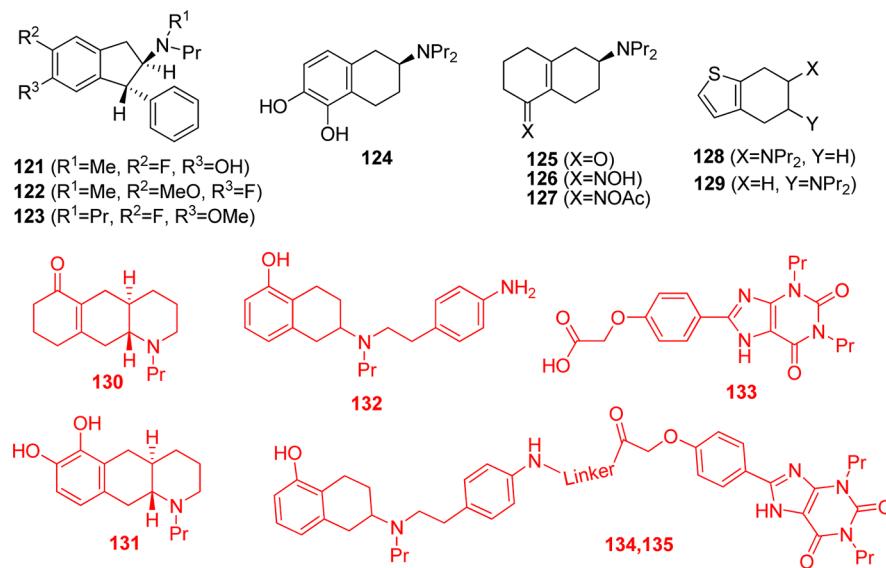


Figure 9. Isoquinoline and thieno[c]quinoline analogs.

Vendrell and co-workers<sup>111,112</sup> recently reported several series of multiple-specificity hybrids by introducing a linear tripeptide to the indolo[2,3-*a*]quinolizidine core, as represented by compounds **99** and **100**. These new compounds showed greater affinity for D<sub>1</sub> and D<sub>2</sub> receptors than their unmodified heterocyclic analogs. Among these compounds, compounds **99** and **100** were the most potent (D<sub>1</sub>  $K_{\text{d}}$ , 350 and 510 nM; D<sub>2</sub>  $K_{\text{d}}$ , 1.5 and 3.7  $\mu\text{M}$ ), with respective D<sub>1</sub>/D<sub>5</sub> selectivity of 4.3- and 7.3-fold.<sup>111</sup> Compound **99** was found to be a weak allosteric modulator without significant impact on the partial or full D<sub>1</sub> agonist-mediated effect on cAMP synthesis.<sup>112</sup> Hybrids

with a linear tripeptide included in the structures of typical D<sub>1</sub> and D<sub>2</sub> agonist ergolenes also were reported (Figure 8).<sup>113,114</sup> These compounds generally retained DA agonist activity with low ( $\mu\text{M}$ ) affinity, together with antagonistic effects at adenosine A<sub>2A</sub> receptors. The representative compound **101** displayed moderate affinity at D<sub>1</sub> and D<sub>2</sub> receptors ( $K_{\text{d}}$ , 0.7 and 0.02  $\mu\text{M}$ ). Although these compounds lack high binding potency at these receptors, they may serve as novel leads for generating more potent ligands with effects at both DA and adenosine receptors that may have value for the treatment of Parkinson's disease.<sup>113</sup> Biotin also was connected to the



**Figure 10.** 2-Amino-1-phenyl-2,3-dihydroindenes and aminotetralin analogs.

ergolene scaffold through various linkers. After optimization of the length and nature of the linker, ergopeptide **102** was identified, possessing high affinity and agonist behavior at D<sub>1</sub> and D<sub>2</sub> receptors ( $K_i$ , 56 and 17 nM, respectively); this lead compound may be a useful tool for the study of heteromers involving D<sub>1</sub>, D<sub>2</sub>, or D<sub>3</sub> receptors.<sup>114</sup>

### 3.2. D<sub>2</sub> Receptor-Selective Ligands

**3.2.1. Isoquinoline Analogs.** Tetrahydroisoquinolines are among the most numerous naturally occurring alkaloids and possess a wide range of biological activities. They include 1-benzyltetrahydro-isoquinolines and aporphines, both of which have structural similarities to DA and interact at DA receptors. Several 1-benzyl-1,2,3,4-tetrahydroisoquinoline alkaloids, including nor-armepavine (**103**) and nor-roefractine (**104**, Figure 9), have affinity for both D<sub>1</sub>- and D<sub>2</sub>-type receptors.<sup>115,116</sup> However, the stereochemistry and optimal substitutions of these structures relevant to their biological activities are still not clear.

Andreu et al.<sup>117</sup> developed a “one-pot” procedure including cyclization, reduction, and N-alkylation, starting from N-phenylethylphenacetamide, to prepare the *trans*-1-benzyltetrahydro-isoquinolines **105** and **106** as well as the *cis*-rotamers **107** and **108** (*trans* and *cis* refer to the relative conformation of the two phenyl groups, Figure 9). These compounds show rather low potency at both D<sub>1</sub> and D<sub>2</sub> receptors ( $IC_{50}$  = 3–57  $\mu$ M) and poor D<sub>2</sub>/D<sub>1</sub> selectivity. For N-methyl isoquinolines, the *cis*-rotamer **108** is 2.5-fold more potent than *trans*-rotamer **106** at the D<sub>2</sub> receptor, and for norisoquinolines, the *cis*-rotamer **107** is 8-fold more potent than *trans*-rotamer **105**. The *cis*-rotamer **108** has the highest affinity and selectivity for the D<sub>2</sub> receptor ( $IC_{50}$  = 3, 40  $\mu$ M at D<sub>2</sub> and D<sub>1</sub> receptors, respectively).

Recently, Cabedo et al.<sup>118</sup> prepared the enantiomers of several 6,7-dioxygenated 1-benzyl-1,2,3,4-tetrahydroisoquinolines (**109–114**) by a chiral auxiliary-induced asymmetric synthesis strategy. The S-enantiomers (**109–111**) show poor  $IC_{50}$ 's at both D<sub>1</sub> (17–52  $\mu$ M) and D<sub>2</sub> (4–22  $\mu$ M) receptors. The corresponding R-enantiomers (**112–114**) are even less potent. The S-isomer **109** shows the highest D<sub>2</sub> affinity ( $IC_{50}$  = 4  $\mu$ M), with 6-fold D<sub>2</sub>/D<sub>1</sub> selectivity. This compound weakly

inhibited the DA transporter (DAT;  $IC_{50}$  = 4  $\mu$ M), and its *N*-n-propyl analog **110** and catechol **111** show even lower D<sub>2</sub> and D<sub>1</sub> affinities.

To explore the role of the 1-benzyl group in the tetrahydroisoquinolines, Andreu et al.<sup>119</sup> prepared compounds with a cyclohexylmethyl group at the C-1 position to replace the benzyl substituent (**115a,b**, **116**; Figure 9). These novel compounds, like their benzyl congeners, retained substantial D<sub>2</sub> receptor binding. A free hydroxyl group at the C-8 (**115a,b**) or C-6 (**116**) position did not contribute appreciably to affinity at any DA receptor type, although compound **116** was 60% more potent at the D<sub>2</sub> receptor ( $IC_{50}$  = 6.4  $\mu$ M) than at D<sub>1</sub> sites.

Several C-1 substituted tetrahydroisoquinoline analogs also have been reported (Figure 9). The 1-benzyl analogs **117** and **118**, with one or two halogen substituents, displayed high affinity for the D<sub>2</sub>-like or D<sub>1</sub>-like DA receptors in striatal membranes from mammalian brain, with D<sub>2</sub>  $K_i$  values of 46–300 nM, and D<sub>1</sub>  $K_i$  values of 65–240 nM, together with slight D<sub>2</sub>/D<sub>1</sub> selectivity.<sup>120</sup> 1-Butyl- and 1-phenyl-substituted tetrahydroisoquinolines displayed good D<sub>2</sub> affinity as well. Among these derivatives, compound **119** showed the highest affinity at D<sub>2</sub>-like receptors in striatal membranes ( $K_i$ , 66 nM), and 49-fold selectivity over D<sub>1</sub>-like receptors.<sup>121</sup> Compound **119** was found to act as a D<sub>2</sub> agonist and increase spontaneous activity in the forced swimming test in injected doses of 0.04–25 mg/kg. Several 1-aryloxy-substituted tetrahydroisoquinolines also were evaluated, but these compounds (e.g., **120**) had only micromolar D<sub>2</sub> affinity.<sup>122</sup>

**3.2.2. 2-Amino-1-phenyl-2,3-dihydroindenes and Their Analogs.** A series of *trans*-2-amino-5[6]-fluoro-6[5]-hydroxy-1-phenyl-2,3-dihydro-1*H*-indenes (**121–123**, Figure 10) were reported through further structural modifications of tetrahydroisoquinolines with the aim to developing metabolically stable DA receptor agonists.<sup>123,124</sup> The *trans* conformation of the amino group relative to the phenyl moiety in these compounds was essential for DA receptor activity, whereas selectivity between D<sub>2</sub> and D<sub>1</sub> receptors was dependent on substitutions on the indene core. Unsubstituted amines had low affinity at both D<sub>1</sub> and D<sub>2</sub> receptors. However, the *N,N*-di-*n*-propyl-, *N*-methyl-*N*-*n*-propyl-, and *N*-allyl-*N*-methyl-substituted indenes had somewhat greater affinity and D<sub>2</sub>/D<sub>1</sub>

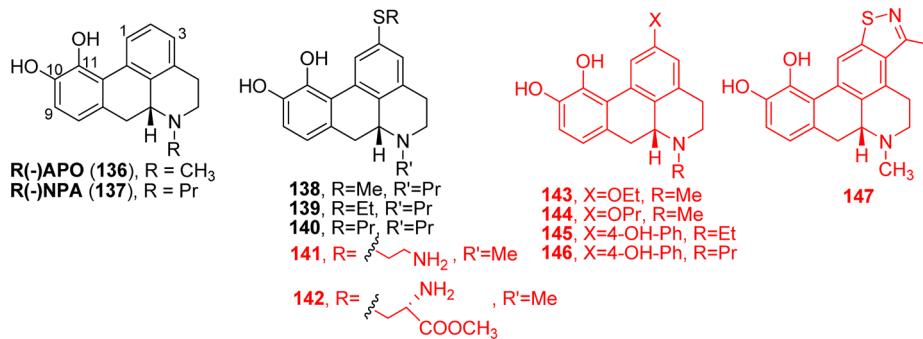


Figure 11. Apomorphine and catechol analogs.

selectivity. In this series, compounds 121–123 (Figure 10) exhibited the highest  $D_2$  affinity ( $K_i = 650, 270$ , and  $170\text{ nM}$ , respectively). Compounds 121 and 122 had  $D_2$ -like agonist activity, as supported by their ability to reduce striatal adenylyl cyclase activity.<sup>123,124</sup>

A series of racemic and enantiomerically pure oxime derivatives of the 6-(*N,N*-di-*n*-propylamino)-3,4,5,6,7,8-hexahydro-2*H*-naphthalen-1-one (125) were prepared as prodrugs of aminotetralin 124.<sup>125</sup> The oximes can induce rotational behavior **contralaterally to the unilateral 6-OHDA DA-lesioning model for Parkinson's disease in the rat**, and they are orally active. Both the unsubstituted oxime ([−]-126) and the acetyl-oxime ([−]-127) induced particularly pronounced and long-lasting dopaminergic effects in this behavioral model. Though less potent than the parent prodrug 125, the oxime derivatives [−]-126 and [−]-127 may be used as orally active prodrugs.

Another approach to DA agonists is to develop bioisosteres of DA itself. Since compounds with a thienylethylamine moiety possess affinity for DA receptors, Dijkstra et al. reported a series of compounds such as 128 and 129 in which the classical phenethylamine pharmacophore was replaced by a thienylethylamine moiety.<sup>126</sup> These compounds generally showed only moderate affinity at DA receptors ( $D_2$  and  $D_3$   $K_i = 27$  and  $28\text{ nM}$  for 128;  $20$  and  $40\text{ nM}$  for 129), but they had improved oral bioavailability. Similarly, decahydro-1*H*-benzo[*g*]quinoline-6-one (130) also is an enone prodrug, whose active form, octahydrobenzo[*g*]quinoline-6,7-diol (131) has potent dopaminergic agonist activity at very low oral as well as injected doses, based on cerebral microdialysis.<sup>127,128</sup> Therefore, prodrug 131 represents an interesting lead compound for potential development of anti-Parkinson agents.

In view of the therapeutic potentials of adenosine A<sub>2A</sub> and dopamine D<sub>2</sub> receptor bivalent ligands in the treatment of Parkinson's disease, a family of heterobivalent ligands containing a D<sub>2</sub> agonist (aminotetralin 132) and an A<sub>2A</sub> antagonist (xanthine amine 133) pharmacophore linked through a spacer of variable size was designed.<sup>129</sup> The spacer features a central PEG–polyamine oligomer flanked by adjacent trifunctional amino acid moieties (Figure 10). These compounds (134, 135) displayed nanomolar binding affinity at both D<sub>2</sub> and A<sub>2A</sub> receptors. The agonistic property of these compounds at the D<sub>2</sub> receptor was confirmed by the significant decrease in the forskolin-induced cAMP levels.

**3.2.3. Aporphine Analogs.** Aporphines constitute one of the largest groups of isoquinoline alkaloids. R(-)-Apomorphine (136; Figure 11), an acid-catalyzed rearrangement product of morphine, is the prototype of aporphine DA agonists. Apomorphine, known since the 19th century, and some of its derivatives were among the earliest pharmacological

tools used to characterize DA receptors.<sup>130</sup> Clinically, subcutaneously injected R(-)-apomorphine (Apokyn) is used as an anti-Parkinsonism drug, and its sublingual preparation (Uprima) has been marketed as a treatment of male erectile dysfunction. As an agonist for both D<sub>2</sub> and D<sub>1</sub> receptors, apomorphine can limit the commonly fluctuating responses to the treatment with L-Dopa or potent direct D<sub>2</sub> agonists (the so-called “on–off” effect). However, its utility is greatly limited by poor bioavailability and short duration of action. SAR studies involving newer synthetic aporphines have focused mainly on improving the pharmacokinetic and pharmacodynamic properties of apomorphine.<sup>20,21,131</sup>

Although the catechol, tertiary amine, and 6a- $\alpha$ -configuration are generally recognized as critical pharmacophore characteristics of apomorphine (136), an additional binding site was proposed at the C-2 position of this molecule. Therefore, introducing a 2-alkylthio function retained high D<sub>2</sub> affinity (138–140).<sup>132</sup> Compared to the C-2 unsubstituted parent aporphine 136, these 2-alkylthio-substituted aporphines showed slightly higher (2-methylthio- [138] and 2-ethylthio- [139]) or lower (2-propylthio, 140) D<sub>2</sub> affinity. In this series, the R(-)-2-methylthio analog 138 had the highest D<sub>2</sub> affinity ( $K_i = 3.7\text{ nM}$ ), but without improvement of poor oral bioavailability (Table 6). Alkylthio functions bearing amino or carboxylic moieties also were explored. Compounds 141 and 142 were found to be D<sub>2</sub> full agonists and similarly potent ( $K_i \sim 10\text{ nM}$ ) as the parent compound 136.<sup>133</sup> Furthermore, studies of 2-alkyloxy substituents with different lengths and various functionalities indicated that the lipophilicity of the substituents was more important than the spatial parameters. Compared to the parent compound 136 or 137, the 2-alkyloxy aporphines 143 and 144 were 4- to 8-fold less potent,<sup>134</sup> whereas compounds 145 and 146, with a more hydrophilic substituent 4-hydroxyphenyl, displayed more than a 5-fold increase in binding potency, with  $K_i$  values of  $1.5$  and  $2.0\text{ nM}$  at the D<sub>2</sub> receptor.<sup>135</sup> The isothiazole-fused aporphine 147 was much less potent than the parent 136 (Figure 11).<sup>136</sup>

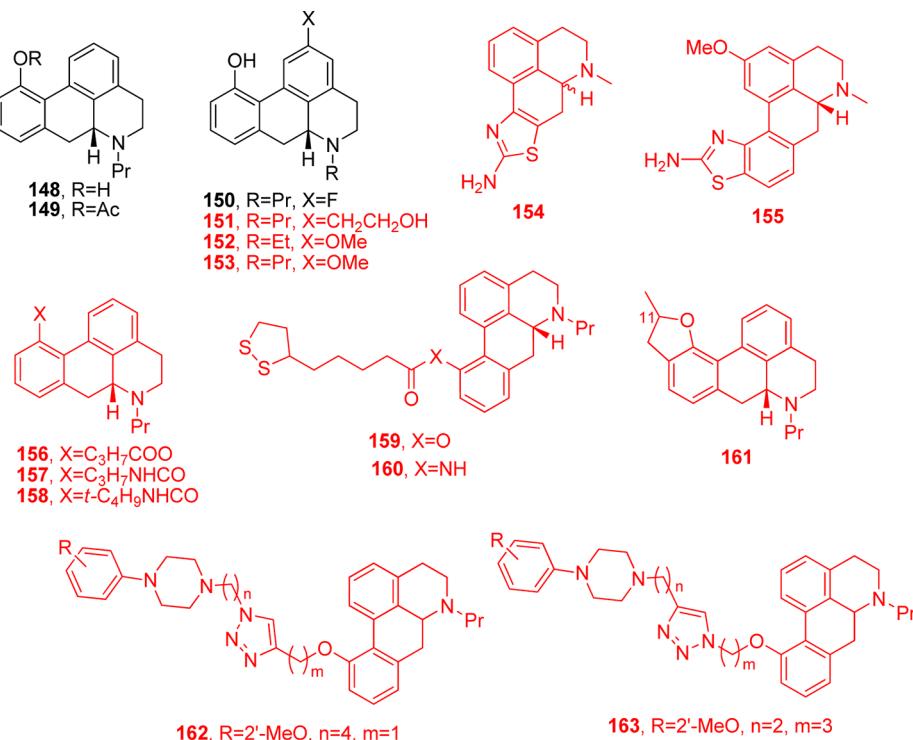
The *in vivo* metabolism of apomorphine (136) is complex due to its interactions with proteins and other tissue components affecting its pharmacokinetics, as well as its tendency to be oxidized spontaneously to quinones<sup>137</sup> and its susceptibility to both O-methylation and conjugation. However, the short duration of *in vivo* activity and lack of oral bioavailability appear to stem from the 10,11-catechol substructure as well as the tertiary-amino moiety of apomorphine. One approach to enhancing its chemical stability is to eliminate or occlude one or both of its hydroxyl groups or to develop prodrugs that mask these phenolic moieties. In this regard, Neumeyer et al.<sup>138</sup> developed a series of monohydroxy

**Table 6. Affinity of Aporphine Derivatives**

| aporphine | D <sub>1</sub> | K <sub>i</sub> (nM) |                |                    |                    |
|-----------|----------------|---------------------|----------------|--------------------|--------------------|
|           |                | D <sub>2</sub>      | D <sub>3</sub> | 5-HT <sub>1A</sub> | 5-HT <sub>2A</sub> |
| 136 (APO) | 214            | 13.2                |                |                    |                    |
| 137 (NPA) | 733            | 9.9                 |                |                    |                    |
| 138       |                | 3.73                |                |                    |                    |
| 139       |                | 7.8                 |                |                    |                    |
| 140       |                | 15.6                |                |                    |                    |
| 141       | 1300           | 9.6                 |                |                    |                    |
| 142       | 380            | 10                  |                |                    |                    |
| 143       | 2900           | 44                  |                |                    |                    |
| 144       | 3500           | 75                  |                |                    |                    |
| 145       | 124            | 1.5                 |                |                    |                    |
| 146       | 94             | 2.0                 |                |                    |                    |
| 147       | 1027           | 197                 | 1874           |                    |                    |
| 148       | 699            | 28.5                |                |                    |                    |
| 149       | >10000         | 72.3                |                |                    |                    |
| 150       | 800            | 39                  |                |                    |                    |
| 151       | >10000         | 97                  |                |                    |                    |
| 152       | 130            | 28.0                |                |                    |                    |
| 153       | 1690           | 44.0                |                |                    |                    |
| 154       | >10000         | >10000              |                |                    |                    |
| 155       | >10000         | >10000              |                |                    |                    |
| 156       | >10000         | 56                  | 12             | >10000             |                    |
| 157       | >10000         | >10000              | 87             | >10000             |                    |
| 158       | >10000         | 871                 | 96             | >10000             |                    |
| 159       | >10000         | 174                 | 66             | >10000             |                    |
| 160       | >10000         | >10000              | 249            | >10000             |                    |
| 161       | >10000         | >10000              |                | 6.7                |                    |
| S-161     | >10000         | >10000              |                | 45.3               |                    |
| R-161     | >10000         | >10000              |                | 3.1                |                    |
| 162       | 2700           | 661                 | 2.67           |                    |                    |
| 163       | >10000         | 7384                | 1.14           |                    |                    |

aporphines and found that the 11-hydroxy group (analogous to the physiologically critical *meta*-hydroxyl of DA and the catecholamines norepinephrine and epinephrine) is crucial for the D<sub>2</sub> receptor affinity and activity in aporphines and that the 10-hydroxy group is less important. To this end, in a series of monohydroxy aporphines, the D<sub>2</sub> receptor affinity of *R*-(−)-11-hydroxyaporphine (**148**) (D<sub>2</sub>, K<sub>i</sub> = 28.5 nM) was only 2- to 3-times less than that of its catechol congeners, *R*-(−)-apomorphine (**136**; D<sub>2</sub>, K<sub>i</sub> = 13 nM) or its *N*-*n*-propyl analog **137** (D<sub>2</sub>, K<sub>i</sub> = 9.9 nM; Table 6, Figure 12). Compound **148** also showed nearly 25-fold selectivity (K<sub>i</sub> ratio = 699/28.5 nM) for D<sub>2</sub> over D<sub>1</sub> receptors, compared to D<sub>2</sub>/D<sub>1</sub> potency ratios of 16 for **136** and 74 for **137**. Introduction of a 2-fluoro group (**150**) to the 11-hydroxyaporphine had little effect on D<sub>2</sub> receptor affinity, suggesting that the binding site at the C-2 position, as in catechol **136**, can tolerate a substituent with different properties.<sup>139</sup> Therefore, varied functionalities were introduced to the C-2 site of the monohydroxy-aporphine skeleton. Compound **151**, containing a 2-(β-hydroxyethyl) group, showed ~100 nM affinity at the D<sub>2</sub> receptor,<sup>140</sup> and 2-methoxy analogs **152** and **153** were 2- or 3-times more potent.<sup>141,142</sup>

Zhang et al. explored the potential of direct bioisosteric replacement of the catechol component of **136** or **137** with a metabolically stable heterocycle; however, such compounds (e.g., **154** and **155**) were inactive at the D<sub>2</sub> receptor (Figure 12, Table 6).<sup>143</sup> Alternatively, a prodrug strategy was used to generate new and stable aporphine analogs. 11-Esterified aporphines retained high affinity at the D<sub>2</sub> receptor, especially the butyryl ester **156** (D<sub>2</sub>, K<sub>i</sub> = 56 nM). Interestingly, this compound had high affinity (K<sub>i</sub> = 12 nM) at the 5-HT<sub>1A</sub> receptor as well.<sup>144</sup> Such dual binding profile of these monoesters at D<sub>2</sub> and 5-HT<sub>1A</sub> receptors may be useful for the treatment of neuropsychiatric disorders. The chemically more stable carbamates **157** and **158** lost D<sub>2</sub> binding affinity

**Figure 12.** Mono- and nonhydroxyaporphine analogs.

but retained reasonable affinity at the 5-HT<sub>1A</sub> receptor.<sup>145</sup> A more thorough investigation of aporphine analogs bearing a C-, N-, or O-linkage at the C-11 position led to identification of the lipoic ester (−)-159 as a full agonist at both D<sub>2</sub> and 5-HT<sub>1A</sub> receptors (respective K<sub>i</sub> values, 174 and 66 nM).<sup>145</sup> This compound elicited anti-Parkinson-like effects in rodent models of Parkinson's disease with minor adverse, dyskinetic effects. Repeated administration of (−)-159 reduced L-DOPA-induced dyskinesia without attenuating the anti-Parkinsonian effects.<sup>145</sup> These findings suggested that 5-HT<sub>1A</sub> and D<sub>2</sub> receptor dual agonists such as (−)-159 may represent novel candidates for the treatment of Parkinson's disease and DA-agonist induced dyskinesias. It is intriguing that the amido analog 160 lost activity at the D<sub>2</sub> receptor but retained some 5-HT<sub>1A</sub> affinity, a profile similar to that of carbamates 157 and 158. These relationships indicated that the D<sub>2</sub> receptor is more sensitive to C-11 substituents than is the 5-HT<sub>1A</sub> receptor.<sup>145</sup> Following this principle, further exploration of the nature of the 5-HT<sub>1A</sub> receptor binding site around the C-11 of aporphines revealed that 11-allyloxy-, 11-propargyloxy-, and dihydrofuroaporphines displayed high 5-HT<sub>1A</sub> affinity, especially the dihydrofuroaporphine 161 (5-HT<sub>1A</sub> K<sub>i</sub> = 6.7 nM).<sup>146</sup> The high binding potential of the diastereomeric mixture of aporphine 161 was found to reside in the *cis*-diastereomer (*cis*-161). [<sup>35</sup>S]GTPyS assays of 5-HT<sub>1A</sub> receptor functioning indicated that *trans*-161 behaved as a high efficacy full antagonist whereas *cis*-161 was a full agonist.<sup>146</sup> The agonistic property of *cis*-161 at the 5-HT<sub>1A</sub> receptor was further supported by additional *in vitro* and *in vivo* findings, and this compound may represent a potential treatment for anxiety.<sup>146</sup>

Additional aporphine analogs have been prepared from appropriate aporphine and arylpiperazine precursors using the Click reaction protocol.<sup>147</sup> Interestingly, these compounds displayed good to high affinity at the D<sub>3</sub> receptor, with very low affinity at D<sub>1</sub> and D<sub>2</sub> receptors. Compounds 162 and 163 were the most potent at the D<sub>3</sub> receptors (K<sub>i</sub> = 2.67 and 1.14 nM), with high 5-HT<sub>1A</sub> affinity (K<sub>i</sub> = 9.68 and 7.59 nM) and with 3.6- and 6.6-fold D<sub>3</sub>-over-5-HT<sub>1A</sub> selectivity, respectively.<sup>147</sup> Such compounds may be useful in the treatment of several brain disorders.

By comparison of DA receptor binding affinities of 1-benzyltetrahydroisoquinolines and aporphines, it is clear that rigidifying the flexible benzyl group of benzyltetrahydroisoquinolines into tetracyclic aporphines causes a remarkable increase in D<sub>2</sub> receptor affinity. To this end, two series of analogs of aporphines (164–177; Figure 13) with an oxygen bridge between the two phenyl moieties were prepared with the aim of clarifying the role of the biphenyl component in the aporphine molecular skeleton in DA receptor interactions.<sup>148</sup> All of the biphenyl ethers 164–169 have low D<sub>2</sub> and D<sub>1</sub> affinity. Only the N-methyl-5-hydroxy- (164) and N-methyl-10-hydroxy- (167)

2,3,12,12α-tetrahydro-1H-[1]benzoxepino[2,3,4-*ij*]-isoquinolines show at least weak D<sub>2</sub> affinity (K<sub>i</sub> = 270 and 720 nM). Analysis of the influence of Na<sup>+</sup> on [<sup>3</sup>H]spiperone binding as a proposed index of DA agonist-like activity shows that 164 displayed a potential D<sub>2</sub> agonist profile whereas 167 is predicted to be a D<sub>2</sub> antagonist. The D<sub>2</sub> agonist activity of 164 is further supported by its ability to inhibit release of prolactin from primary cultures of rat anterior pituitary cells.<sup>148</sup>

In the series of aporphines where a methylene unit is the linker (170–177) (Figure 13), lower affinities at D<sub>2</sub> and D<sub>1</sub> receptors are also observed.<sup>149</sup> Only the 5-hydroxy-1-methyl-2,3,12,12a-hexahydrobenzo[5,6]cyclohepta[1,2,3-*ij*]-isoquinoline 174 and its 5,6-dihydroxy analog 170 exhibited limited D<sub>2</sub> affinity (K<sub>i</sub> = 8.9 and 8.2 μM, respectively) with similarly low D<sub>1</sub> potency. Slightly higher affinity at the D<sub>2</sub> receptor is observed with the methylenedioxy N-benzyl analog 173 (K<sub>i</sub> = 4.9 μM) and 12-fold D<sub>2</sub>/D<sub>1</sub> selectivity. Molecular modeling indicates that the geometric parameters of the supposed dopaminergic pharmacophore, including the distance from the *meta*- and *para*-hydroxyl oxygens to the nitrogen, and the height of nitrogen from the hydroxylated phenyl ring plane, have lower values in these compounds than in ligands that are more potent and selective for D<sub>1</sub> or D<sub>2</sub> receptors.<sup>149</sup>

**3.2.4. Aryl/Heteroaryl-Substituted Piperidines/Piperazines.** Aryl- or heteroaryl-substituted piperazines or piperidines represent one of the largest categories of chemical structures with dopaminergic properties. A number of current widely used antipsychotics with potent D<sub>2</sub> antagonist activity, such as haloperidol, risperidone, and others, belong to this family. In these molecules, an additional functional group generally is attached to a presumed primary pharmacophore (piperidine or piperazine) via a linker and is believed to provide accessory interactions at DA receptors. Such accessory functions may contribute to additional nondopaminergic activities of these compounds at other neurotransmitter receptors, including serotonergic, muscarinic, α-adrenergic, and H<sub>1</sub>-histaminic receptors. Some of these interactions also may be relevant to the relatively low risk of adverse extrapyramidal neurological effects observed in modern antipsychotic drugs, such as olanzapine and risperidone, which are potent D<sub>2</sub> and 5-HT<sub>2A</sub> receptor dual antagonists. Recent efforts in developing D<sub>2</sub> antagonists with limited adverse neurological effects have focused on agents with only moderate D<sub>2</sub> antagonist activity or with D<sub>2</sub> partial-agonist effects, combined with interactions at other DA receptors (D<sub>1</sub>, D<sub>3</sub>, or D<sub>4</sub>) and serotonin (5-HT<sub>1A</sub>, 5-HT<sub>2A</sub>, or 5-HT<sub>3A</sub>) or α<sub>1</sub>-adrenergic receptors.<sup>31,32</sup>

**3.2.4.1. Aryl Piperazines/Piperidines with Dual D<sub>2</sub> and D<sub>3</sub> or D<sub>4</sub> Activities.** On the basis of bioisosteric replacement of the highly effective, atypical antipsychotic agent, clozapine, a small series of phenylpiperazines combined with phenyl-substituted pyrazole or triazole via a methylene linkage (178–180; Figure 14) were developed. Binding studies with brain homogenates indicated that all these compounds bind selectively to D<sub>2</sub> receptors. Electrophysiological studies of cultured hippocampal neurons suggest that a chloro substituent on the pyrazole/triazole-attached phenyl ring is crucial to either D<sub>2</sub> agonist (178, 180) or antagonist (179) properties of these compounds.<sup>150</sup>

Compounds 181–186 represent another series of phenylpiperidines with an indole or furan moiety as the accessory function (Figure 14). Both share similar structural elements with the classical D<sub>2</sub>-like receptor antagonist-neuroleptics,

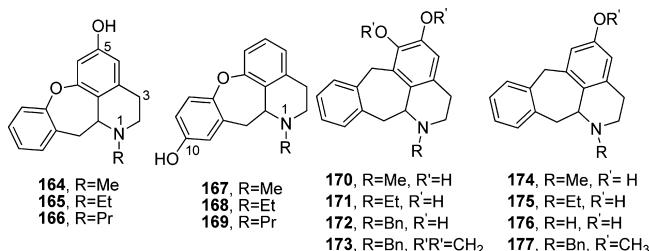


Figure 13. Aporphine-like homologues.

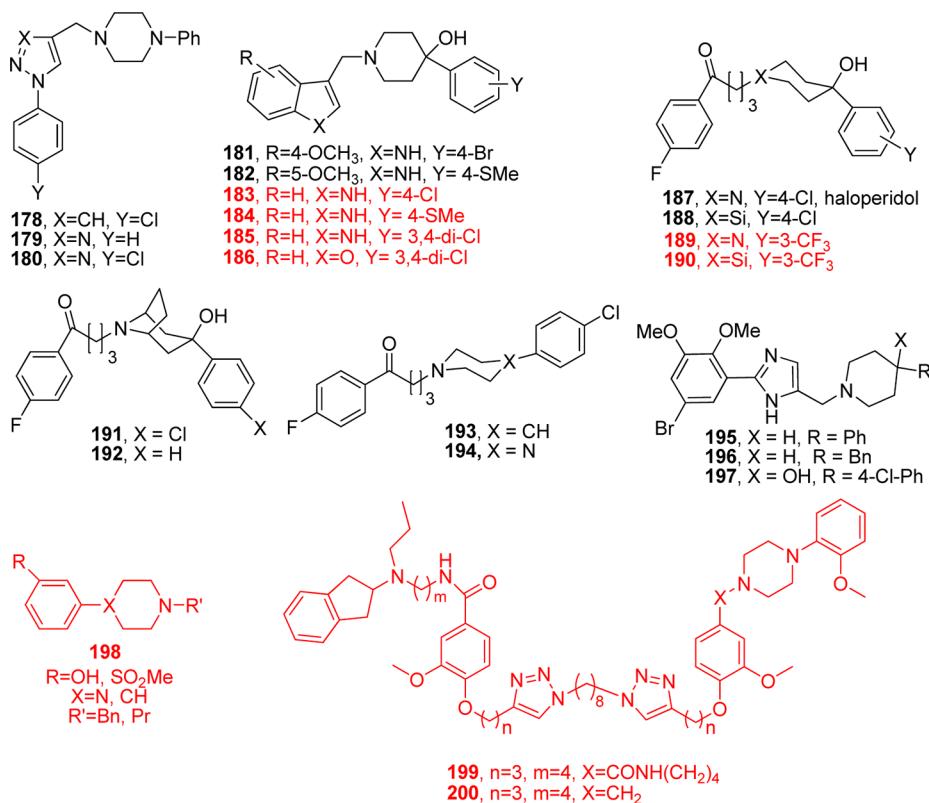


Figure 14. Aryl-/heteroaryl-substituted piperazines and piperidines.

including haloperidol (**187**). Compounds **181** and **182** bind at cloned human D<sub>2</sub> receptors with high affinity ( $K_i = 2.3$  and  $5.5$  nM) with  $>50$ -fold D<sub>2</sub>/D<sub>3</sub> and D<sub>2</sub>/D<sub>4</sub> selectivity and no intrinsic DA-agonist-like adenylyl cyclase stimulating activity.<sup>151,152</sup> Compounds **183–185** also are high affinity, D<sub>2</sub>-selective antagonists that are being investigated in animal models of drug abuse.<sup>152</sup> Compound **182** demonstrated more than 100-fold selectivity for D<sub>2</sub> over D<sub>3</sub> and D<sub>4</sub> receptors that may be related to a 5-OCH<sub>3</sub> in its indolyl system. Replacement of the indole fragment with a benzofuran moiety led to compound **186**, showing moderate D<sub>2</sub> affinity and selectivity.<sup>153</sup>

Another approach to developing bioisosteres of haloperidol (**187**) is nitrogen/silicon exchange at the C-4 position of the piperidinyl ring. This approach led to sila-haloperidol **188** and sila-trifluperidol **190**, prepared by Tacke et al.<sup>154–156</sup> in multiple steps and characterized by single-crystal X-ray diffraction and solution NMR spectroscopy. Two analogous chair conformations (2:1) are observed in the crystal of the 4-silapiperidinium (**188-HCl**), which differ substantially from the conformation of haloperidol (13:1). Compound **188** shows moderate affinity at recombinant human D<sub>4</sub>, D<sub>5</sub>, and D<sub>1</sub> receptors ( $K_i = 10$ , 21, and 94 nM, respectively) and nearly 3-fold higher affinity at D<sub>2</sub> receptors than is found with haloperidol ( $K_i = 0.85$  vs  $4.0$  nM). The trifluoromethyl analogs **189** and **190** retained high D<sub>2</sub> receptor affinity. However, similar improvement was not observed with sila-trifluperidol **190** in a functional assay, as **190** was 10-times less potent than the parent compound **189**.<sup>156</sup>

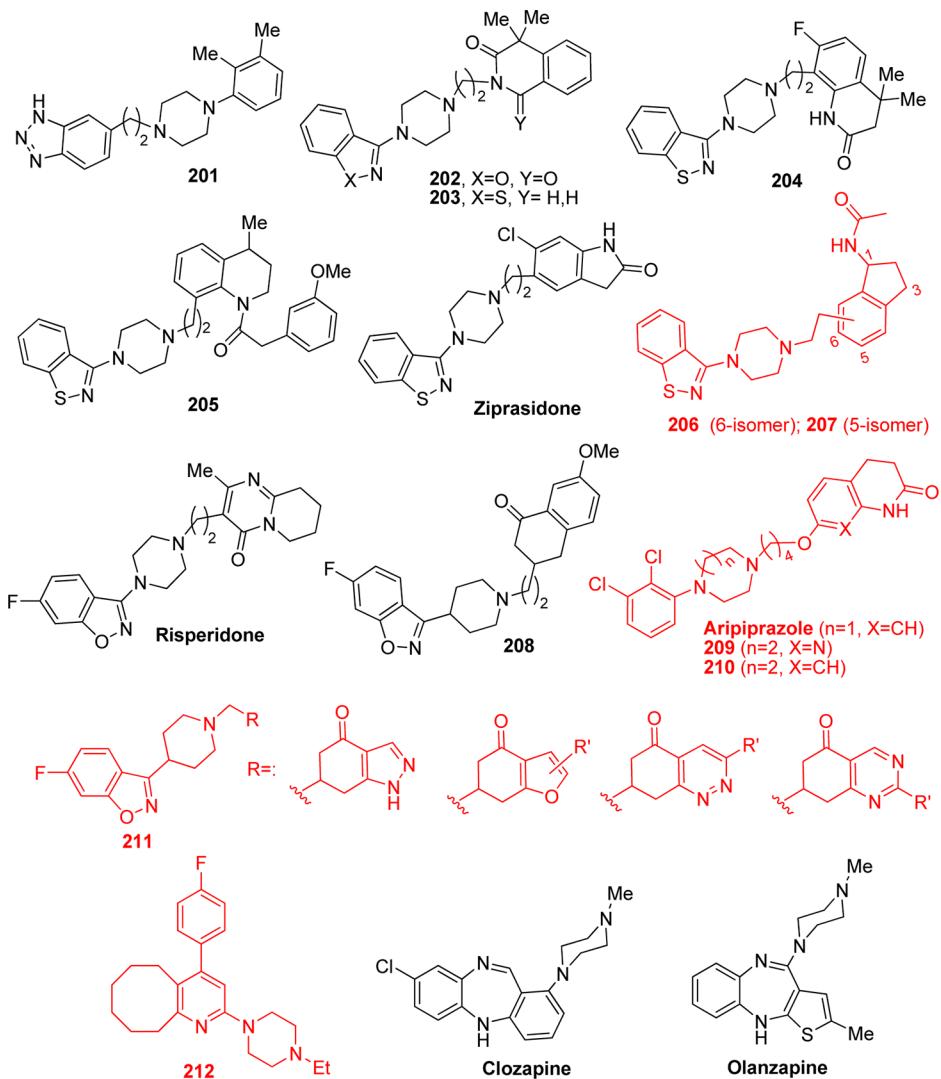
Compounds **191–194** also are haloperidol isosteres aimed at probing the role of the hydroxyl group and other features. These compounds have substantial affinity at all three D<sub>2</sub>-like receptors (D<sub>2</sub>, D<sub>3</sub>, D<sub>4</sub>) with some selectivity for the D<sub>2</sub>

receptor. The hydroxyl group is not essential for DA receptor activity, but the axial orientation of the hydroxyl group seems to enhance D<sub>2</sub> binding. In this series, the structurally rigid tropanes **191** and **192** display the highest D<sub>2</sub> affinity ( $K_i = 0.31$  and  $2.3$  nM, respectively; Table 7), with similar potency at D<sub>3</sub> and slightly lower affinity at D<sub>4</sub> receptors. The piperazine **194**

Table 7. Binding Property of Compounds at DA Receptors

| compd                      | D <sub>2</sub>            | K <sub>i</sub> (nM) |                |
|----------------------------|---------------------------|---------------------|----------------|
|                            |                           | D <sub>3</sub>      | D <sub>4</sub> |
| <b>181</b>                 | 2.3                       | 190                 | 840            |
| <b>182</b>                 | 5.5                       | 580                 | 567            |
| <b>183</b>                 | 10                        | 104                 | 449            |
| <b>184</b>                 | 23.9                      | 638                 | 319            |
| <b>185</b>                 | 6.9                       | 111                 | 1100           |
| <b>186</b>                 | 21.0                      | 28.0                | 167            |
| haloperidol ( <b>187</b> ) | 1.1                       | 5.5                 | 12.7           |
| <b>188</b>                 | 3.0                       | <i>a</i>            |                |
| <b>189</b>                 | 15.0                      |                     |                |
| <b>190</b>                 | 1.5                       |                     |                |
| <b>191</b>                 | 0.31                      | 0.81                | 12.1           |
| <b>192</b>                 | 2.3                       | 3.2                 | 19.1           |
| <b>193</b>                 | 16.3                      | 46.0                | 25.9           |
| <b>194</b>                 | 254                       | 403                 | 17.5           |
| <b>195</b>                 | 11.9                      | 10.8                |                |
| <b>196</b>                 | 15.7                      | 40.5                |                |
| <b>197</b>                 | 13.8                      | 36.6                |                |
| <b>199</b>                 | 25 (hD <sub>2long</sub> ) | 2.0                 | 40             |
| <b>120</b>                 | 14 (hD <sub>2long</sub> ) | 1.2                 | 22             |

<sup>a</sup>Data is not available.



**Figure 15.** Aryl- or heteroaryl-substituted piperazines and piperidines with high D<sub>2</sub> and 5-HT<sub>2A</sub> affinity.

has remarkably low affinity at both D<sub>2</sub> and D<sub>3</sub> receptors but good affinity and selectivity at the D<sub>4</sub> receptor.<sup>157–159</sup>

Yet another series that employs the phenyl-substituted imidazole fragment as the accessory function connected to the phenylpiperidine component (presumed primary pharmacophore) of haloperidol has been reported (195–197; Figure 14). They all show good D<sub>2</sub> affinity ( $K_i = 12\text{--}16 \text{ nM}$ ) and similar D<sub>3</sub> potency. Unlike haloperidol, these novel compounds are devoid of  $\alpha_1$  adrenergic receptor affinity, indicating that the accessory group and not the phenylpiperidine moiety is responsible for the  $\alpha_1$  receptor activity in haloperidol.<sup>160,161</sup>

D<sub>2</sub> receptor partial agonists have been proposed to stabilize aberrant DA pathways by normalizing excessive or deficient D<sub>2</sub> receptor stimulation and thereby facilitating more physiological levels of activity in DA neurons.<sup>162</sup> Pettersson recently modified the D<sub>2</sub> partial agonist 3-(1-benzylpiperidin-4-yl)phenol to generate a series of novel D<sub>2</sub> antagonists (e.g., 198). These compounds bound competitively with low affinity to D<sub>2</sub> receptors *in vitro*. *In vivo*, they showed neurochemical effects similar to those of known D<sub>2</sub> antagonists. The “agonist-like” kinetic profile of these compounds, combined with their lack of intrinsic agonist activity, supported the proposal that they may represent “dopaminergic stabilizers.”<sup>163</sup>

To explore D<sub>2</sub> receptor dimerization, several series of bivalent D<sub>2</sub> receptor ligands were designed by incorporating the privileged structure of 1,4-disubstituted aromatic piperidines or piperazines (1,4-DAPs), and triazolyl-linkers of various lengths.<sup>164,165</sup> The representative compounds 199 and 200 showed high affinity for both D<sub>2long</sub> and D<sub>2short</sub> receptors ( $K_i = 14\text{--}25 \text{ nM}$ ) and higher affinity ( $K_i = 1.2\text{--}2 \text{ nM}$ ) for the D<sub>3</sub> receptor. Further investigation of these ligands revealed their antagonist or weak partial agonist properties in cAMP inhibition and receptor internalization assays, indicating functional crosstalk between two physically interacting D<sub>2</sub> protomers.<sup>164,165</sup>

**3.2.4.2. Heteroaryl-Substituted Piperazines or Piperidines with Mixed D<sub>2</sub> and 5-HT Receptor Activity.** The rationale of dual antagonism at DA D<sub>2</sub> and serotonin receptors, especially 5-HT<sub>2A</sub> as clinically effective antipsychotics arises from the presence of such properties in several modern or “atypical” antipsychotic drugs with a low risk of adverse extrapyramidal neurological effects, including clozapine, olanzapine, and risperidone (Figure 15). Pure D<sub>2</sub> antagonists, such as haloperidol (187), are effective antipsychotics but have prominent adverse extrapyramidal neurological effects, whereas selective 5-HT<sub>2A</sub> antagonists lack antipsychotic efficacy but have less risk of extrapyramidal effects.<sup>166–170</sup> A widely held

proposal is that relatively potent 5-HT<sub>2A</sub> antagonists combined with weaker D<sub>2</sub> antagonism may be more effective, or at least better-tolerated antipsychotics, although the optimal balance between these two actions remains to be defined.<sup>171</sup>

Some benzotriazole analogs connected with a phenyl-piperazine function through an ethylene unit have shown characteristics of atypical antipsychotic agents. For example, the [4-(2,3-dimethylphenyl)piperazin-1-yl]ethyl-substituted benzotriazole **201** (Figure 15) possesses nearly 10-fold higher 5-HT<sub>2A</sub> ( $K_i = 5.1$  nM) than D<sub>2</sub> ( $K_i = 51$  nM) receptor affinity, along with moderate  $\alpha_1$  affinity. Like clozapine and other atypical or second-generation antipsychotics, benzotriazole **201** also lacked motor-inhibitory (cataleptic) behavioral effects but inhibited d-amphetamine-induced locomotor behavioral arousal in rats.<sup>172</sup> Compounds **202–205** are bioisosteres of the atypical antipsychotics risperidone and ziprasidone, with benzoisoxazolylpiperazine and benzoisothiazolylpiperazine frameworks (Figure 15). They all have high 5-HT<sub>2A</sub>, and moderate D<sub>2</sub> affinity. For example, compounds **202** and **203** showed 5-HT<sub>2A</sub>/D<sub>2</sub> potency ratios of 35 ( $K_i = 0.73$  versus 25 nM) and 225 ( $K_i = 0.12$  versus 27 nM), profiles similar to that of risperidone and clozapine (Figure 15).<sup>173</sup> Furthermore, quinolinones **204** and **205** exhibited 5-HT<sub>2A</sub>/D<sub>2</sub> potency ( $K_i$ ) ratios of 88 (15/0.17 nM) and 4 (4.0/1.1 nM), respectively, again favoring the serotonin sites.<sup>174</sup> In addition, compounds **202–205** all are very weak in inducing catalepsy in rodents (minimum effective dose  $\geq 30$  mg/kg, i.v.), but **204**, at least, is active in blocking d-amphetamine-stimulated locomotor activity.<sup>175</sup>

Other structural modifications of the accessory heterocyclic function further affected 5-HT<sub>2A</sub>/D<sub>2</sub> selectivity. With the benzoisothiazolylpiperazine component in ziprasidone intact, replacing the indolinone moiety with a 6- or 5-linked 1-aminoindane system resulted in analogs **206** and **207** (Figure 15; Table 8).<sup>176</sup> They showed  $K_i$  values of 22 and 15 nM at D<sub>2</sub> receptors, but of 0.01 and 0.33 nM at 5-HT<sub>2A</sub> receptors, as well as high affinity at 5-HT<sub>1A</sub> and  $\alpha_{1A}$  receptors. Similarly, with the benzoisoxazolylpiperazine component in risperidone intact, replacing the tetrahydropyrido[1,2-a]pyrimidin-4-one moiety

with a tetralone function yielded analog **208**, which has similarly high potency at both 5-HT<sub>2A</sub> and D<sub>2</sub> receptors.<sup>175</sup>

Aripiprazole is an FDA-approved atypical antipsychotic drug that behaves, variably, as a full or partial agonist, or an antagonist at the D<sub>2</sub> receptor, depending on the assay method involved.<sup>177,178</sup> Enlarging the piperazine ring or replacing the dihydroquinolinone moiety with dihydro-1,8-naphthyridin-2-one skeleton provided analogs **209** and **210** (Figure 15).<sup>179</sup> Compared to the parent aripiprazole, these compounds showed higher binding affinity at D<sub>2</sub> ( $K_i = 2.6$  and 5.0 nM) and 5-HT<sub>2A</sub> receptors ( $K_i = 7.4$  and 16 nM). It was found that these compounds also represent unprecedented  $\beta$ -arrestin-biased ligands for a G<sub>i</sub>-coupled G protein-coupled receptor (GPCR). They are simultaneously antagonists of G<sub>i</sub>-regulated cAMP production and partial agonists for D<sub>2</sub>- $\beta$ -arrestin-2 interactions. Importantly, compound **209** displayed potent antipsychotic-like activity without inducing adverse motor effects in inbred C57BL/6 mice. Such functionally selective,  $\beta$ -arrestin-biased D<sub>2</sub> receptor ligands provide valuable chemical probes for further investigations of D<sub>2</sub> receptor signaling in health and disease conditions.<sup>179</sup> In addition, Loza et al. reported several series of risperidone derivatives prepared by incorporating a benzofuranone, quinazoline, cinnoline, indazolone, or quinazolinone motif connected to the benzoisoxazolylpiperazine component (e.g., compound **211**; Figure 15).<sup>180–183</sup> Although these compounds interacted with both D<sub>2</sub> and 5-HT<sub>2A</sub> receptors, their affinities were significantly low.

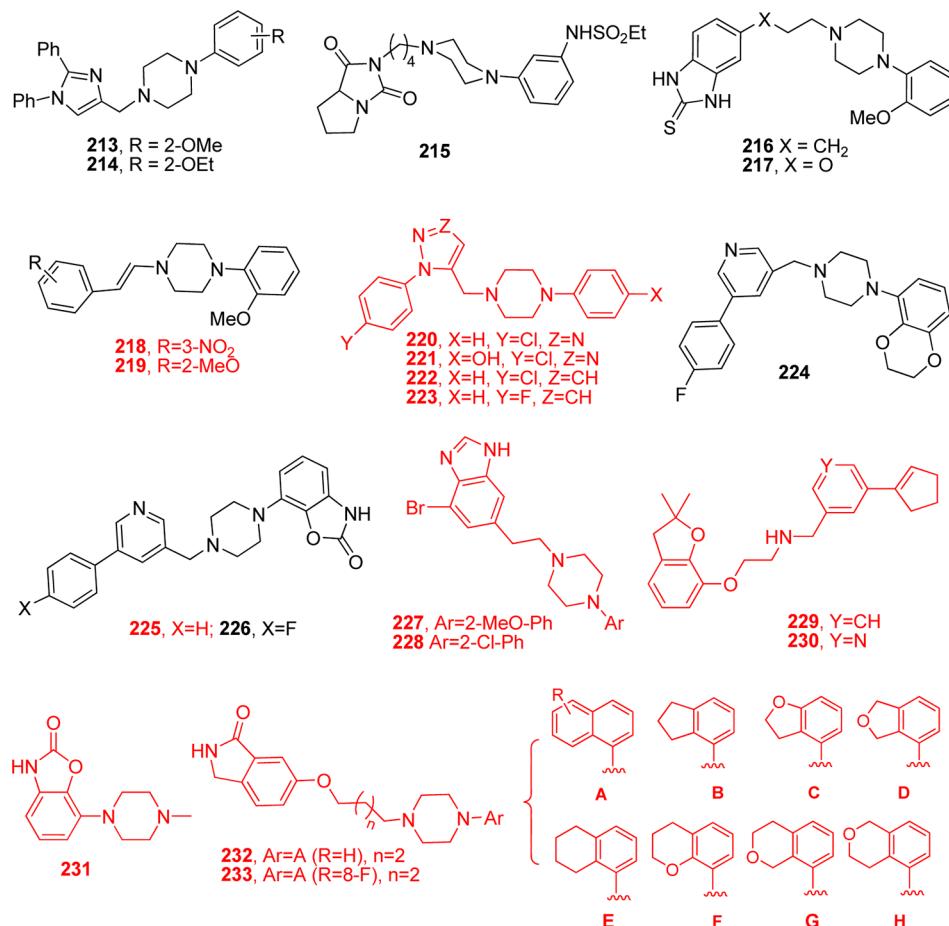
Interestingly, compound **212** (also known as blonanserin; Figure 15), 2-(4-ethylpiperazin-1-yl)-4-(4-fluorophenyl)-5,6,7,8,9,10-hexahydrocycloocta[b]pyridine, is a dual D<sub>2</sub> and 5-HT<sub>2A</sub> receptor ligand, structurally distinct from current known antipsychotics.<sup>184</sup> It has high binding potency for both D<sub>2</sub> and 5-HT<sub>2A</sub> receptors ( $K_i = 0.14$  and 0.81 nM). Blonanserin was well tolerated by laboratory animals but has similar risks of prolactin-elevation and extrapyramidal effects as haloperidol, particularly with respect to prolactin elevation and EPS frequency. It has also been found effective in the short term treatment of schizophrenia, with greater efficacy against negative symptoms (emotional withdrawal) than either placebo or haloperidol.<sup>185</sup>

The serotonin 5-HT<sub>1A</sub> receptor also has been recognized as an important target in the development of psychotropic drugs, and agents that combine D<sub>2</sub>-antagonist and 5-HT<sub>1A</sub>-agonist effects are in clinical trials for the treatment of schizophrenia, mania, and cognitive disorders.<sup>186–192</sup> Compounds **213–215** (Figure 16) were developed to probe the optimal ratios of these two receptor interactions. Compounds **213** and **214** are 1,2-biphenylimidazoles connected to phenylpiperazine via a methylene unit. They have similar affinities at D<sub>2</sub> and 5-HT<sub>1A</sub> sites but are much weaker at the 5-HT<sub>2A</sub> receptor. The IC<sub>50</sub> values of these compounds are 70 and 35 nM at D<sub>2</sub>, and 74 and 57 nM at 5-HT<sub>1A</sub> receptors, respectively. Compound **213**, injected intraperitoneally, induced increased extracellular concentrations of DA in rat medial prefrontal cortex. Like clozapine, compound **213** also inhibited Cl<sup>−</sup> currents evoked by the inhibitory amino acid transmitter  $\gamma$ -aminobutyric acid (GABA) at human GABA<sub>A</sub> receptors expressed in cultured cells. This compound appears to have similar properties as the atypical antipsychotics.<sup>193</sup> Compound **215**, containing an electronically poor amide function connected to the phenylpiperazine pharmacophore via a four-methylene unit, shows similar D<sub>2</sub> and 5-HT<sub>1A</sub> affinity ( $K_i = 22$  and 27 nM) with weak interactions at 5-HT<sub>2A</sub>, 5-HT<sub>3</sub>, 5-HT<sub>4</sub>, and  $\alpha_1$  receptors. It acts

**Table 8. D<sub>2</sub> and 5-HT Receptor Binding Affinities of Aryl/Heteraryl Piperazines/Piperidines**

| aporphine              | D <sub>2</sub> | K <sub>i</sub> (nM) |                |                    |                    |
|------------------------|----------------|---------------------|----------------|--------------------|--------------------|
|                        |                | D <sub>3</sub>      | D <sub>4</sub> | 5-HT <sub>1A</sub> | 5-HT <sub>2A</sub> |
| <b>201</b>             | 51             |                     |                | 7.08               | 5.1                |
| <b>202</b>             | 25.2           |                     |                | >1000              | 0.73               |
| <b>203</b>             | 27.7           |                     |                | 84.9               | 0.12               |
| <b>204</b>             | 15             |                     |                |                    | 0.17               |
| <b>205</b>             | 4.0            |                     |                |                    | 1.07               |
| <b>206</b>             | 22             |                     |                | 7.5                | 0.01               |
| <b>207</b>             | 15             |                     |                | 1.1                | 0.33               |
| <b>208<sup>b</sup></b> | 7.04           |                     |                |                    | 8.23               |
| <b>209</b>             | 2.6            | 11                  | 178            | 29                 | 7.4                |
| <b>210</b>             | 5.0            | 16                  | 200            | 60                 | 16                 |
| <b>212</b>             | 0.14           |                     |                |                    | 0.81               |
| ziprasidone            | 4.6            |                     |                | 12                 | 1.4                |
| risperidone            | 5.65           |                     |                | 217                | 0.22               |
| aripiprazole           | 8.0            | 19                  | 251            | 18                 | 40                 |
| clozapine              | 120            |                     |                | 380                | 14                 |
| olanzapine             | 11             |                     | 27             |                    | 4                  |

<sup>b</sup>pK<sub>i</sub> values.



**Figure 16.** Substituted piperidines/piperazines with  $D_2$  and  $5-HT_{1A}$  affinity.

as a  $D_2$  antagonist *in vivo*, as well as at pre- and postsynaptic  $5-HT_{1A}$  sites; therefore, it can be considered a dual  $5-HT_{1A}$ - $D_2$  antagonist.<sup>194</sup>

A large number of arylpiperazines connected to benzimidazole-2-thiones or benzimidazole-2-ones via a linker show dual  $D_2$  and  $5-HT_{1A}$  receptor affinity as well. However, in contrast to the selectivity profile of compounds described in Figure 15, affinity at the  $D_2$  receptor in this series is much higher than that at the  $5-HT_{1A}$  receptor. Favorable compounds of this type are benzimidazole-2-thiones 216 and 217 (Figure 16) that showed  $D_2$ / $5-HT_{1A}$  affinities ( $K_i$ ) of 0.4/8.6 nM and 0.19/308 nM, respectively. Compound 216 is 21.5-fold and 217 is 1620-times more potent at the  $D_2$  than at the  $5-HT_{1A}$  receptors.<sup>195–198</sup>

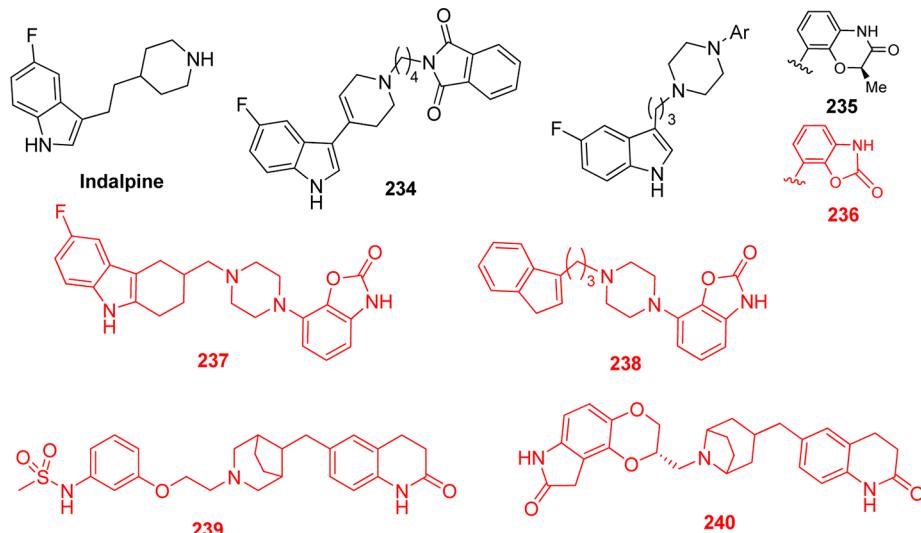
Arylpiperazines connected with a simple 1-cinnamyl component also have shown relatively high affinity at the  $D_2$  receptor and moderate affinity at  $5-HT_{1A}$  or  $5-HT_{2A}$  receptors. The representative compounds 218 and 219 of this type have display  $D_2$   $K_i$  values of 16.9 and 14.2 nM, respectively (Table 9). Interactions of these compounds at  $D_2$  sites probably are related to H-bonding between their  $NO_2^-$  or  $MeO$ -substituents and amino acid residues Ser<sup>122</sup> or His<sup>189</sup> in the  $D_2$  receptor peptide chain.<sup>199</sup>

Triazole 220, containing a *para*-chlorophenyl in the arylpiperazine component, was designed as a selective  $D_2$  receptor agonist.<sup>200</sup> Despite its moderate  $D_2$  affinity, this compound has shown some effects similar to those of clozapine, supporting its potential candidacy as a lead for development of novel atypical antipsychotics. Binding studies with brain homogenates revealed a gain in  $D_2$ / $5-HT_{1A}$

**Table 9.  $D_2$  and  $5-HT$  Receptor Binding Affinity of Arylpiperazines/Piperidines**

| aporphine        | $D_2$ | $K_i$ (nM) |       |             |             |
|------------------|-------|------------|-------|-------------|-------------|
|                  |       | $D_3$      | $D_4$ | $5-HT_{1A}$ | $5-HT_{2A}$ |
| 213 <sup>a</sup> | 70    |            |       | 74          | 131         |
| 214 <sup>a</sup> | 35    |            |       | 57          | 171         |
| 215 <sup>a</sup> | 22    |            |       | 27          | -           |
| 216              | 0.4   |            |       | 8.6         | -           |
| 217              | 0.19  |            |       | 308         | -           |
| 218              | 16.9  |            |       | 225         | 204         |
| 219              | 14.2  |            |       | 181         | 120         |
| 220              | 950   |            |       | 1200        | 11000       |
| 221              | 1700  |            |       | 8000        | >10000      |
| 222              | 110   |            |       | 90          | 2300        |
| 223              | 70    |            |       | 60          | 920         |
| 224              | 3.6   |            |       | 3.2         | -           |
| 225              | 9.3   |            |       | 2.2         | -           |
| 226              | 1.6   |            |       | 2.1         | -           |
| 227              | 0.56  |            |       | 1.4         | -           |
| 228              | 5.77  |            |       | 0.14        | -           |
| 229              | 0.42  |            |       | 5.75        | -           |
| 230              | 0.27  |            |       | 0.95        | -           |
| 231              | 3.16  |            |       | 7.94        | -           |
| 232              | 7.39  |            |       | 0.151       | 4.95        |
| 233              | 3.18  |            |       | 0.050       | 1.83        |

<sup>a</sup> $IC_{50}$  values for  $D_2$  and  $5-HT_{1A}$  receptors.



**Figure 17.** Substituted piperidines/piperazines with  $D_2$  and SERT affinity.

selectivity in the *p*-hydroxyphenyl metabolite (221).<sup>200</sup> Higher  $D_2$  affinity but a loss in  $D_2$ -selectivity followed replacement of the triazole component in 220 with an imidazole moiety in compounds 222 ( $D_2 K_i = 110$  nM;  $5\text{-HT}_{1A} K_i = 90$  nM) and 223 ( $D_2 K_i = 70$  nM;  $5\text{-HT}_{1A} K_i = 60$  nM; Figure 16, Table 9). These two compounds inhibited apomorphine-induced climbing behavior in mice without cataleptic effects, suggesting their potential as atypical antipsychotic agents.<sup>201</sup>

Dual  $D_2$ -antagonist and  $5\text{-HT}_{1A}$ -agonist activity was found in compounds 224–226 (Figure 16, Table 9).<sup>202–204</sup> These heteroaryl-substituted piperazines are connected to a 3-phenylpyridine moiety via a methylene linker and are structurally related to risperidone. Compound 224 has similar  $D_2$  and  $5\text{-HT}_{1A}$  receptor affinity, with evidence of full  $D_2$  antagonism and full  $5\text{-HT}_{1A}$  agonism. *In vivo*, 224 antagonized apomorphine-induced climbing and induced hypothermia and behavioral symptoms, suggestive of excessive central serotonergic activity (“serotonin syndrome”).<sup>204</sup> Moreover, this compound did not produce catalepsy predictive of adverse extrapyramidal effects, at oral doses up to 60 mg/kg.<sup>204</sup> Compound 225 was 4-fold  $D_2/5\text{-HT}_{1A}$ -selective ( $5\text{-HT}_{1A}/D_2, K_i = 9.3/2.2$  nM). This compound also inhibited apomorphine-induced climbing behavior in mice at doses of 0.1–10 mg/kg ( $\text{ED}_{50} < 1$  mg/kg) and was active in a rat model of  $5\text{-HT}_{1A}$  agonism based on a lip-retraction response.<sup>204</sup>

Arylpiperazines connected with a benzimidazole moiety also displayed high affinity at both  $D_2$  and  $5\text{-HT}_{1A}$  receptors. For example, the 2-methoxyphenyl analog 227 was 10-times more potent than the 2-chlorophenyl analog 228 and had a  $D_2 K_i$  of 0.56 nM. Analog 226 was 10-times more potent ( $D_2 K_i = 1.6$  nM) than 228.<sup>205</sup> Compounds with (5-cyclopentenylpyridin-3-yl)methanamine or (3-cyclopentenyl phenyl)methanamine as the replacement of arylpiperazine component retained high affinity at both  $D_2$  and  $5\text{-HT}_{1A}$  receptors.<sup>206</sup> Among these compounds, 229 and 230 showed subnanomolar  $D_2$  affinity ( $D_2 K_i = 0.42$  and 0.27 nM) and up to 14-fold selectivity over  $5\text{-HT}_{1A}$  receptor. In cellular models of signal transduction, 229 turned out to be an antagonist at rat  $D_2$  receptors but activated human  $5\text{-HT}_{1A}$  receptors with an efficacy at least equivalent to that of the prototypical  $5\text{-HT}_{1A}$  agonist ( $\pm$ )-8-OH-DPAT.<sup>207</sup> In a behavioral model predictive of antipsychotic effects, 229 was comparably active to the typical neuroleptic haloperidol, but

without cataleptic effects. The observed antagonist actions of this compound at DA receptors may contribute to its antipsychotic-like effects.<sup>207</sup> Additionally, 229 activated both  $5\text{-HT}_{1A}$  and  $D_4$  receptors—effects that may predict beneficial effects on negative symptoms and cognitive impairment in schizophrenia.<sup>207</sup> Therefore, compound 229 has shown several characteristics that make it promising for further development.

Arylpiperazine 231 (pardoprunox) lacks additional remote accessory functionality but binds potently to  $D_2$  and  $5\text{-HT}_{1A}$  receptors. It appears to be a  $D_2$  partial agonist and full  $5\text{-HT}_{1A}$  agonist with additional activity at  $D_3$  and  $D_4$  receptors.<sup>208,209</sup> In rats with unilateral 6-hydroxydopamine-induced lesions of nigrostriatal DA projections and supersensitive ipsilateral  $D_2$  receptors, 231 induced contralateral turning behavior.<sup>208</sup> In nonhuman primates (marmosets) given the DA-neurotoxic 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), 231 potently and dose-dependently increased locomotor activity and decreased motor disability at oral doses of 30  $\mu\text{g}/\text{kg}$ .<sup>208</sup> It also attenuated novelty-induced locomotor activity, (+)-amphetamine-induced hyperlocomotion, and apomorphine-induced climbing behavior in mice (all at oral doses of 300–600  $\mu\text{g}/\text{kg}$ ). Collectively, these findings have supported clinical development of pardoprunox as a treatment of Parkinson’s disease.<sup>208</sup>

In addition, Favor et al. reported a series of 6-alkoxyisoindolin-1-ones with various arylpiperazine substituents (Figure 16, Table 9). These compounds displayed *in vitro* activity indicative of potent  $D_2$  partial agonism (30%–55%),  $5\text{-HT}_{1A}$  partial agonism (60%–90%), and  $5\text{-HT}_{2A}$  antagonism.<sup>210</sup> Compounds 232 and 233 in this series showed good *in vivo* activity and were potent in an *ex vivo*  $D_2$  binding assay.<sup>210</sup>

Compounds with combined  $D_2$  antagonism and serotonin transporter (SERT) inhibitory effects also have been proposed as innovative antipsychotics. This includes agents with a piperazine function as the  $D_2$  pharmacophore, and an indalpine moiety (Figure 17) as the anti-SERT pharmacophore (Figure 17). After optimizing the linker and substitution pattern of these pharmacophores, compounds 234 and 235 were identified as potent  $D_2$  antagonists and highly active SERT inhibitors with SERT/ $D_2$  potency ratios of 2.0 and 34.5 ( $D_2/\text{SERT } K_i = 5.0/2.5$  and 6.9/0.2 nM).<sup>211,212</sup> Compound 235 has shown favorable PK properties and a high brain/plasma

concentration ratio.<sup>213</sup> Molecular modeling analysis indicated that this compound can adopt two different conformations fitting either D<sub>2</sub> receptor or SERT binding sites.<sup>213</sup> In addition, the benzo[d]oxazol-2(3H)-one analog 236 displayed a SERT K<sub>i</sub> value of 0.63 nM in rat frontal cortex, and D<sub>2</sub> K<sub>i</sub> of 3.2 nM in transfected CHO cells. It is a D<sub>2</sub> partial agonist and selective serotonin transporter reuptake inhibitor. Moreover, this compound has shown promising effects in a chronic stress animal model of depression at oral doses of 1–10 mg/kg/day, suggesting potential value as a novel treatment for major depression.<sup>214</sup> Replacing the indole component in 236 with a tetrahydrocarbazole moiety yielded compound 237, having D<sub>2</sub> and SERT K<sub>i</sub> values of 17 and 22 nM, respectively. It is active in the apomorphine-induced climbing mouse model and is devoid of cataleptic effects at injected doses up to 10 mg/kg.<sup>215</sup> Replacing the indole component in 236 with an indene functionality retained the dual D<sub>2</sub>-SERT profile. Compound 238 is representative of such indene analogs; it showed moderately high affinity at both sites (D<sub>2</sub> K<sub>i</sub> = 4.0 nM; SERT K<sub>i</sub> = 7.1 nM) and somewhat lower affinity at 5-HT<sub>1A</sub>, 5-HT<sub>2A</sub>, 5-HT<sub>2B</sub>, α<sub>1</sub>, and H<sub>1</sub> receptors.<sup>216</sup> This compound showed efficacy similar to that of aripiprazole in animal behavioral models of antipsychotic and antidepressant effects.

Compounds 239 and 240 represent a series of dihydroquinolinone analogs bearing a conformationally constrained linker. These compounds also displayed high binding affinity at the same two sites (D<sub>2</sub> K<sub>i</sub> = 11 and 16 nM; SERT K<sub>i</sub> = 1.7 and 0.26 nM), and the sulfonamide 239 was almost inactive at α<sub>1</sub> adrenergic receptors.<sup>217</sup>

**3.2.4.3. Heteroarylpiriperidines with Mixed D<sub>2</sub> and α<sub>1</sub> Receptor Antagonist Activities.** Another approach to developing novel antipsychotics is to seek compounds with dual D<sub>2</sub> and α<sub>1</sub> receptor activities. An anti-α<sub>1</sub> adrenergic component may contribute to therapeutic effects of some antipsychotic agents, including clozapine, olanzapine, quetiapine, and sertindole,<sup>218–222</sup> although such an effect, by itself, does not appear to be sufficient to produce antipsychotic benefits. For example, the selective α<sub>1</sub> antagonist prazosin, though showing activity in some laboratory models predictive of antipsychotic activity,<sup>223–226</sup> was ineffective in clinical trials in schizophrenia.<sup>227–230</sup>

Compounds 237–240 (Figure 17) displayed nanomolar affinity at the α<sub>1</sub> receptor, in addition to having potency at D<sub>2</sub> receptor and the 5-HT transporter.<sup>215–217</sup> Balle et al. developed an additional series of dual D<sub>2</sub> and α<sub>1</sub> antagonists derived from the putative antipsychotic drug sertindole (Figure 18).<sup>231</sup> These compounds have similar D<sub>2</sub> and α<sub>1</sub> affinity as sertindole, as well as moderate affinity at 5-HT<sub>1B</sub>, 5-HT<sub>2A</sub>, and 5-HT<sub>2C</sub> receptors.<sup>231</sup> The most potent α<sub>1</sub> adrenergic receptor agent, 1-(2-{4-[5-aminomethyl-1-(4-fluorophenyl)-1H-indol-3-yl]-1-piperidinyl}ethyl)-2-imidazolidinone (241a), bound with high

affinity (K<sub>i</sub> = 0.50 nM) at α<sub>1</sub> receptors, and at least 44-times lower affinity for D<sub>2</sub>, D<sub>3</sub>, D<sub>4</sub>, 5-HT<sub>1A</sub>, 5-HT<sub>1B</sub>, 5-HT<sub>2A</sub>, and 5-HT<sub>2C</sub> receptors. Compound 241b was even more potent at α<sub>1</sub> receptors (K<sub>i</sub> = 0.28 nM) and also potent at D<sub>2</sub> receptors (K<sub>i</sub> = 1.9 nM). The indole and imidazole-2-one functions are essential for high affinity at the α<sub>1</sub> receptor, whereas the size and electronic characteristics of substituents on the indoles determine the affinity of the D<sub>2</sub> receptor. Larger substituents out of the indole plane result in compounds with high affinity for both D<sub>2</sub> and α<sub>1</sub> receptors.<sup>231</sup>

**3.2.4.4. Biphenylpiperidines with Mixed D<sub>2</sub> and Ion Channel Blockade Activities.** Annoura et al.<sup>232</sup> reported a series of novel 4-arylpiperidines and 4-aryl-4-piperidinols that block the effects of DA on neuronal Na<sup>+</sup> and Ca<sup>2+</sup> channels as well as at D<sub>2</sub> receptors, usually with only moderate affinity for both D<sub>2</sub> receptors and ion channels. Representative compounds 242–244 (Figure 19) displayed IC<sub>50</sub> values of 0.3 μM for

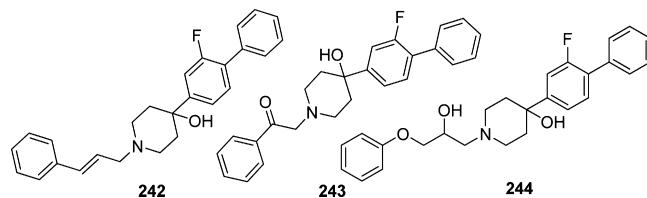


Figure 19. Biphenylpiperazines.

inhibition of veratridine-induced Na<sup>+</sup> channel activity, 0.6–3.0 μM for T-type Ca<sup>2+</sup> channel inhibitory effects, and 0.16–0.71 μM for D<sub>2</sub> receptors. These compounds also exhibited anticonvulsant effects against audiogenic seizures in mice following intraperitoneal injection, indicating access to the brain *in vivo*, and they can limit neuronal damage induced by ischemia in laboratory models of stroke.<sup>232</sup> Conformational analysis indicated that cinnamyl, phenacyl, and phenoxypropanol groups are likely to be structurally and biologically equivalent in this series.

**3.2.5. Dibenzazepine Antipsychotic Analogs.** In addition to the aryl/heteroaryl-substituted piperazines or piperidines, dibenzo(di)azepines are another major structural theme found in several atypical antipsychotic agents, including clozapine, olanzapine, quetiapine, sertindole, and zotepine. These drugs generally have moderate D<sub>2</sub> antagonist activity with high 5-HT<sub>2A</sub> potency and a range of affinity at other neurotransmitter receptors.<sup>233</sup> Adverse effects of these drugs include weight gain (ascribed to serotonin 5-HT<sub>2C</sub> and histamine H<sub>1</sub> blockade), dry mouth (muscarinic M<sub>1</sub> receptor blockade), postural hypotension (α<sub>1</sub> adrenoceptor blockade), and sedation (histamine H<sub>1</sub> and α<sub>1</sub> receptor blockade). In addition, sertindole and, to a lesser extent, ziprasidone interact with voltage-gated K<sup>+</sup> channels involved in the control of heart rhythm<sup>234</sup> and can prolong cardiac repolarization (QTc interval in the electrocardiogram) so as to risk potentially lethal cardiac arrhythmias, including *torsades de pointes*.<sup>234–236</sup> Extensive efforts have been made to optimize the structures of such compounds at the dibenzo(di)azepine core and the piperazine side chain.<sup>237</sup>

A major clinical advantage of this group of agents is the low risk of adverse extrapyramidal neurological effects on posture and motility, including bradykinesia, dystonia, and dyskinesia. Replacement of the N-methyl group in clozapine with a N-2-(2-hydroxyethoxy)ethyl group yielded compounds with adverse extrapyramidal effects.<sup>238</sup> Such distinctions have encouraged

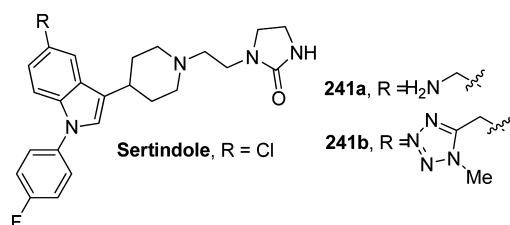


Figure 18. Heteroarylpiriperidines with mixed D<sub>2</sub> and α<sub>1</sub> Receptor Activity.

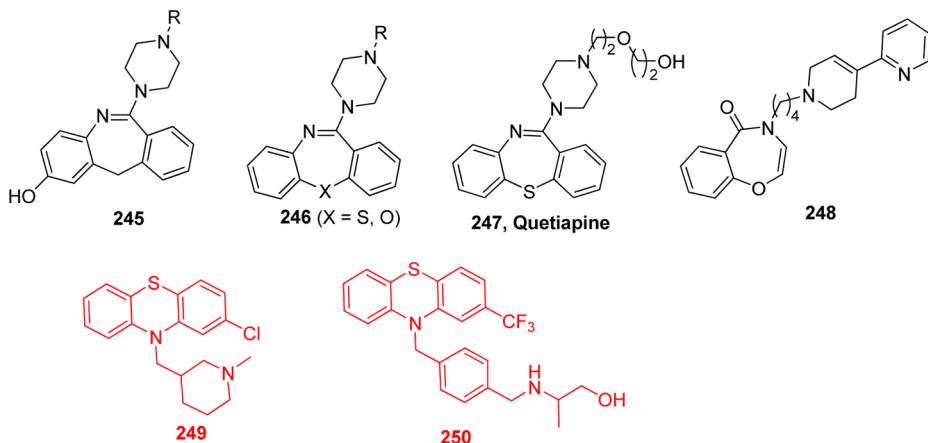


Figure 20. Dibenzo(di)azepine analogs.

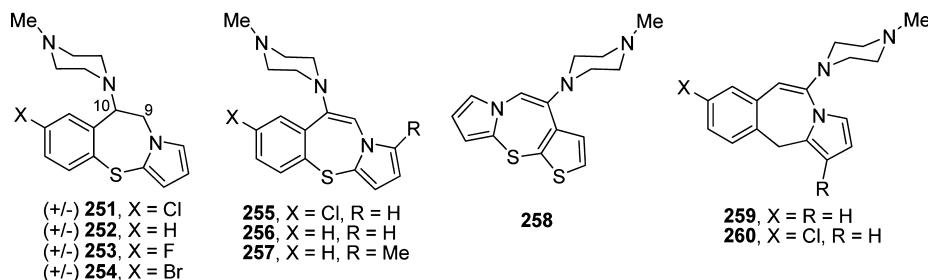


Figure 21. Pyrrolo[1,3]benzothiazepine and pyrrolobenzazepine derivatives.

development of a series of clozapine analogs, including 6-(piperazin-1-yl)-11*H*-dibenzo[*b,e*]azepines (e.g., 245) and 11-(piperazin-1-yl)dibenzo[*b,f*][1,4]thiazepines and -oxazepines (e.g., 246; Figure 20). Most of these compounds were effective D<sub>2</sub> antagonists and exerted adverse extrapyramidal effects. A notable exception is quetiapine (247; 11-(4-[2-(2-hydroxyethoxy)ethyl]piperazin-1-yl)dibenzo[*b,f*][1,4]-thiazepine). Like clozapine, quetiapine lacks extrapyramidal and prolactin-elevating effects in animal models while still exerting antiapomorphine behavioral activity.<sup>173,239</sup> Such *atypicality* of quetiapine leads to improvement of psychotic symptoms in Parkinson's disease patients without worsening the motor symptoms.<sup>240</sup>

Kamei et al.<sup>241</sup> reported a novel class of 1,4-benzoxazepine-5-one derivatives characterized as having high potency at the 5-HT<sub>1A</sub> receptor but low D<sub>2</sub> affinity. The representative compound 248 is 179-fold selective for 5-HT<sub>1A</sub> over D<sub>2</sub> sites (*K<sub>i</sub>* ratio, 84/0.47 nM). The electron-withdrawing property of the carbonyl group in the benzoxazepine core probably is responsible for the limited D<sub>2</sub> affinity of 248, and the 4-(2-pyridinyl)-1,2,3,6-tetrahydropyridinyl side chain may contribute to the high 5-HT<sub>1A</sub> affinity. This compound has neuroprotective effects *in vivo* and requires evaluation for potential clinical utility in degenerative neurological disorders and in limiting neuronal damage in stroke.

Some analogs of the psychotropic phenothiazines were reported to have weak binding potency at the D<sub>2</sub> receptor. These compounds (e.g., 249 and 250) showed some activity at 5-HT<sub>2A</sub> or 5-HT<sub>2C</sub> receptors as well.<sup>242</sup>

A series of pyrrolo[1,3]benzothiazepines and pyrrolobenzazepines (Figure 21) have been developed and appear to have improved safety profile compared to olanzapine. An earlier dual DA and 5-HT antagonist, ( $\pm$ )-9,10-dihydropyrrolo[2,1-*b*][1,3]-

benzothiazepine (251), was resolved into its enantiomers by crystallization of the diastereomeric tartaric acid salts.<sup>243</sup> The R-( $-$ )-enantiomer was 24-times more potent than the S-(+)-enantiomer as a D<sub>2</sub> antagonist (*K<sub>i</sub>* = 2.1 vs 50 nM), whereas both enantiomers have similar 5-HT<sub>2A</sub> affinities, and the S-(+)-251 also has high affinity at H<sub>1</sub> and  $\alpha_1$  receptors, moderate affinity for  $\alpha_2$  and D<sub>3</sub> receptors, as well as low affinity for muscarinic M<sub>1</sub> acetylcholine receptors. Meanwhile, this compound has shown low propensity to induce catalepsy in the rat and minimal effects on serum prolactin levels, presumably owing to its moderate D<sub>2</sub> affinity. The congeners 252–254 have similar receptor affinity and other neuropharmacological properties.<sup>244</sup> Substitution on the pyrrole ring decreased affinity for both D<sub>2</sub> and 5-HT<sub>2A</sub> receptors. However, introducing a double bond at C-9, C-10 in S-(+)-252 provided compound 255, having similarly high D<sub>2</sub> and 5-HT<sub>2A</sub> affinity. Additional modification of substitution patterns on the tricyclic system led to compounds 256 and 257 (Figure 21), which had greater 5-HT<sub>2A</sub> than D<sub>2</sub> affinity, as well as affinity at other receptors. Compound 256 was much more potent in the conditioned avoidance response test, a model predictive of antipsychotic activity ( $ED_{50}$  = 1.1 mg/kg), than in producing catalepsy ( $ED_{50}$  >90 mg/kg), which predicts adverse extrapyramidal effects. It also did not produce hyperprolactinemia at behaviorally effective doses, but antagonized models of cognitive impairment induced by phencyclidine. These properties suggest that 256 is an attractive candidate as an atypical antipsychotic drug.<sup>245</sup>

A similar series of compounds, including the pyrro[1,2-*b*][2]thieno[3,2-*f*][1,3]thiazepine 258 and pyrro[1,2-*b*][2]benzazepines (259,260; Figure 21), also have been reported.<sup>245</sup> Compound 258 is potent at D<sub>1</sub>, D<sub>2</sub>, D<sub>4</sub>, and 5-HT<sub>2A</sub> receptors, and congeners 259 and 260 are more potent and more selective

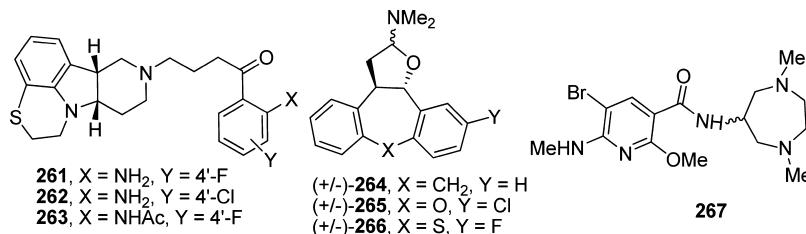


Figure 22. Tetracyclic butyrophenone and benzodiazepine analogs.

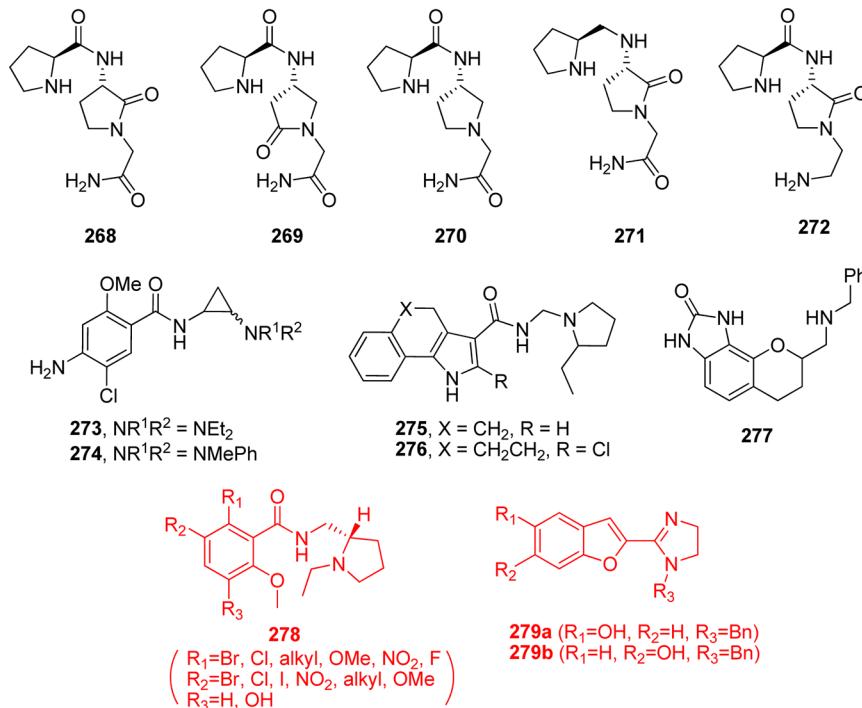


Figure 23. Amide analogs.

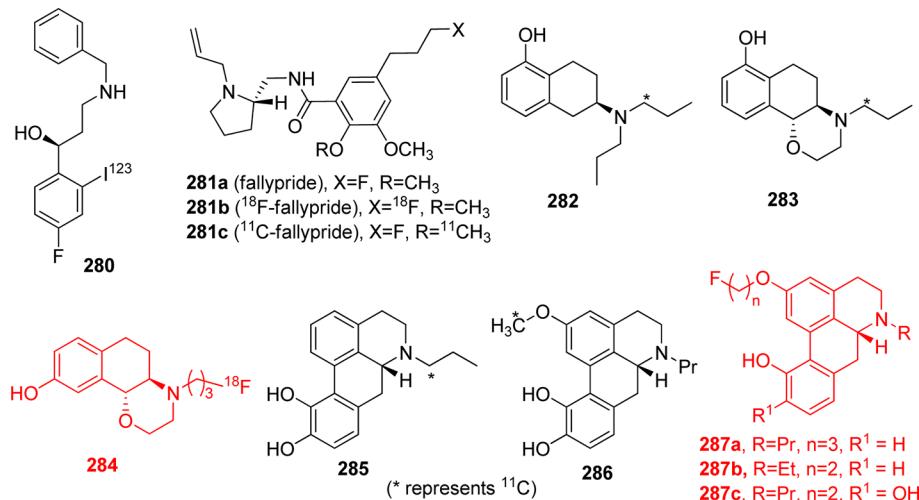
than 258 for 5-HT<sub>2A</sub> than D<sub>2</sub> receptors. Effects of compound 259 resemble those of clozapine and olanzapine in several behavioral screening tests believed to predict antipsychotic activity, and showed high potency (oral ED<sub>50</sub> ca. 0.6 mg/kg).<sup>245</sup>

Several novel tetracyclic butyrophenones and related analogs also have shown potential atypical antipsychotic properties. In these compounds, a tetracyclic *cis*-(8a,12a)-6,7,8a,9,10,11,12,12a-octahydro-5*H*-pyrido[4,3-*b*][1,4]-thiazepino[2,3,4-*hi*]indole core is connected with a phenylbutyrophenone moiety containing different substitutions. These compounds have similar D<sub>2</sub> affinity but various potency at 5-HT<sub>2A</sub> receptors. Compounds 261–263 (Figure 22) display D<sub>2</sub> K<sub>i</sub> of 2–6 nM and 5-HT<sub>2A</sub> K<sub>i</sub> of 0.7, 70, and 0.8 nM, respectively, and are potent and orally active *in vivo*.<sup>246</sup>

Compounds with major structural changes to the benzodiazepine pharmacophore include a series of tetrahydrodibenzocyclohepta[1,2-*b*]furans and tetrahydronbenzo[*b**f*]furo[2,3-*d*]oxepins (Figure 22).<sup>247,248</sup> Compound (-)-264 was a potent 5-HT<sub>2A/2C</sub> antagonist and may have antianxiety effects. Further modifications include incorporating an oxygen or sulfur in the seven-membered ring, such as in compound 265, a dibenzo[*b**f*]furo[2,3-*d*]oxepine, and 266, a ( $\pm$ )-dibenzo[*b**f*]furo[2,3-*d*]tiepine, which are moderately potent at the D<sub>2</sub> receptor (K<sub>i</sub> = 5.9 and 2.3 nM). The enantiomer (-)-266 has higher D<sub>2</sub> potency than (+)-266

or (-)-264 and greater activity in behavioral screening tests predictive of antipsychotic activity, as well as greater potency in behavioral tests of 5-HT<sub>2A</sub> than of D<sub>2</sub> effects.<sup>249</sup> Compounds (-)-264, (+)-266, and (-)-266 thus represent a new family of tetracyclic tetrahydrofuran derivatives with neuropharmacological activities of potential clinical interest.<sup>249</sup>

Hirokawa et al. reported another strategy to develop compounds with dual DA and 5-HT receptor activities.<sup>250</sup> Compound 267, *N*-(1,4-dimethylhexahydro-1,4-diazepin-6-yl)pyridine-3-carboxamide (Figure 22), and other substituted pyridine-3-carboxamides exhibited moderate D<sub>2</sub> and high 5-HT<sub>3</sub> receptor affinity. Introduction of the more lipophilic bromine atom or methylamino group at the 5- and 6-positions of the pyridine ring, respectively, led to enhanced affinity for the D<sub>2</sub> receptor while retaining potent 5-HT<sub>3</sub> affinity. Racemic 267 shows 24-fold selectivity for 5-HT<sub>3</sub> versus D<sub>2</sub> receptors (IC<sub>50</sub> ratio, 23.3/0.97 nM). Optical resolution provided the enantiomers R-267 and S-267. R-267 has moderate affinity for both D<sub>2</sub> (IC<sub>50</sub> = 6.9 nM) and 5-HT<sub>3</sub> receptors (IC<sub>50</sub> = 1.2 nM), whereas S-135 is 94-fold selective for 5-HT<sub>3</sub> versus D<sub>2</sub> receptors (IC<sub>50</sub> ratio, 122/1.3 nM). X-ray crystallographic study of (R)-267 revealed two energetically stable conformers of mirror images. This characteristic property may account for its high affinity for both D<sub>2</sub> and 5-HT<sub>3</sub> receptors. Pharmacologically, R-267 shows potent antagonistic



**Figure 24.**  $\text{D}_2$  receptor imaging ligands.

activity for both receptors based on *in vivo* tests as well as potent inhibition of emesis induced by the cancer chemotherapy agent cisplatin or by morphine (oral  $\text{ID}_{50} = 27.1$  and  $136 \mu\text{g}/\text{kg}$ , respectively).

**3.2.6. Amides.** Amides with various substitution patterns are a unique category of structures that lack known DA pharmacophores but have DA agonist or antagonist properties.

Dolbeare et al.<sup>251</sup> reported a series of analogs of the  $\text{D}_2$ -receptor active and highly potent  $\gamma$ -lactam Pro-Leu-Gly-NH<sub>2</sub> peptidomimetic, 3*R*-[(2*S*-pyrrolidinylcarbonyl)amino]-2-oxo-1-pyrrolidineacetamide (**268**, Figure 23). In the assay to test the ability to enhance the binding of [<sup>3</sup>H]-*N*-*n*-propylnoraporphine (NPA) to DA receptors in bovine striatal membranes, compound **269** (in which the lactam carbonyl moiety is located in a different position with respect to the 3-amino group), was more potent than **268** ( $\text{IC}_{100}$ , 1 nM). Reduction of one of the three carboxamido functions of **268** and **269** led to compounds **270**–**272**. Compounds **270** and **271** are much less potent than **268** at the  $\text{D}_2$  receptor, whereas the peptidomimetic compound **272** has a pharmacological profile similar to that of **268**. The carboxamide groups in these compounds may form important hydrogen-bonding interactions with the  $\text{D}_2$  receptor. Retention of  $\text{D}_2$ -receptor activity in **272** suggests that the reduced amide bond can substitute for the carboxamide moiety present in **268**. This characteristic may be due to the amino group in **272**, in either the protonated or unprotonated form, possessing the ability to participate in hydrogen-bonding interactions either intramolecularly or intermolecularly, as does the amide NH<sub>2</sub> group in **268**.

Benzamides **273** and **274** (Figure 23), derived from 4-amino-5-chloro-2-methoxybenzoic acid and *cis*- or *trans*-1,2-diaminocyclopropane, also were active at bovine striatal  $\text{D}_2$  receptors, recombinant human  $\text{D}_2$  and  $\text{D}_3$  receptors expressed in CHO cells, and rat cortical 5-HT<sub>3</sub> and striatal 5-HT<sub>4</sub> receptors. These compounds showed superiority of the *cis*-over *trans*-conformers in DA receptor binding assays. The *cis*-**273** and *cis*-**274** isomers show  $K_i$  of 13.4 and 6.9 nM at transfected human  $\text{D}_2$  receptors and 17.7 and 4.5 nM at human  $\text{D}_3$  receptors. In contrast, *trans*-**273** and *trans*-**274** have  $K_i$ s of 816 nM and >1.0  $\mu\text{M}$  for the  $\text{D}_2$  and 469 nM and >1.0  $\mu\text{M}$  for  $\text{D}_3$  receptor. It may be important that the *cis* compounds were probably folded, so that the benzamide group and the basic nitrogen atom were in a *syn* relationship.<sup>252</sup>

Pinna et al.<sup>253</sup> reported another series of heteroarylamides with moderate  $\text{D}_2$ -like affinity. 1*H*-Benzo[*g*]indole-3-carboxamide **275** is representative of a series of 2-aminomethylpyrrolidinyl-derived 4,5-dihydrobenzo[*g*]indol-carboxamides. It shows moderate  $\text{D}_2$  affinity ( $\text{IC}_{50} = 160 \text{ nM}$ ), and compound **276**, 2-chloro-*N*-(1-ethyl-2-pyrrolidinylmethyl)-5,6-dihydro-4*H*-benzo-6,7-cyclohepta[*b*]pyrrole-3-carboxamide, is somewhat more potent ( $\text{IC}_{50} = 30 \text{ nM}$ ). Like most antipsychotic drugs, compound **276** reduced motor hyperactivity that was induced by *d*-amphetamine in rat at doses that do not induce catalepsy, a predictor of adverse extrapyramidal effects.

Another interesting structure is compound **277**, prepared by heterocyclic isosteric replacement of the  $\text{D}_2$  template, 7-hydroxy-2-(aminomethyl)chroman (Figure 23).<sup>254</sup> Resolution of  $(\pm)$ -**277** indicated that the eutomer is the  $(-)$ -isomer, with an eudismic ratio (50–80) similar to other resolved chromans. Both  $(\pm)$ -**277** ( $\text{ED}_{50}$ , 40  $\mu\text{g}/\text{kg}$ ) and  $(-)$ -**277** ( $\text{ED}_{50}$ , 30  $\mu\text{g}/\text{kg}$ , both injected subcutaneously) reduced spontaneous locomotor activity in mice, but  $(+)$ -**277** had no effect at doses up to 3 mg/kg. Compound **277** was a DA partial agonist, showing reduction of locomotor activity at low doses (possibly by selectively stimulating presynaptic receptors) followed by a return to baseline levels of activity or hyperactivity as doses were increased.<sup>254</sup>

6-Methoxy benzamides such as **278** were predicted to have moderate  $\text{D}_2$  antagonistic activity,<sup>255</sup> while the cyclized compounds **279a,b**, derived from an imidazoline nucleus, showed  $\text{D}_2$ -like properties (Figure 23). All these compounds have low affinity at the  $\text{D}_2$  receptor ( $K_i$  values of  $\sim 5.0 \mu\text{M}$ ), but compounds **279a,b** showed nearly full  $\text{D}_2$  agonistic activity.<sup>256</sup>

**3.2.7. Imaging Ligands.** Positron emission tomography (PET) and single-photon emission computed tomography (SPECT) imaging of DA receptors is based on use of both DA antagonists, such as [<sup>11</sup>C]raclopride, [<sup>11</sup>C]*N*-methylspiperone, and [<sup>123</sup>I]IBZM, and agonist radioligands. DA agonists bind selectively to the functionally crucial high-affinity state of DA receptors and are believed to be more sensitive to competition by changing concentrations of endogenous DA than antagonist tracers, which bind equipotently to the high- and low-DA receptor affinity states. Relatively recently developed DA-receptor radioligands are considered here.

Radiolabeled [<sup>125</sup>I]-3-benzylamino-1-(4-fluoro-2-iodophenyl)propan-1-ol (**280**; Figure 24) has shown relatively

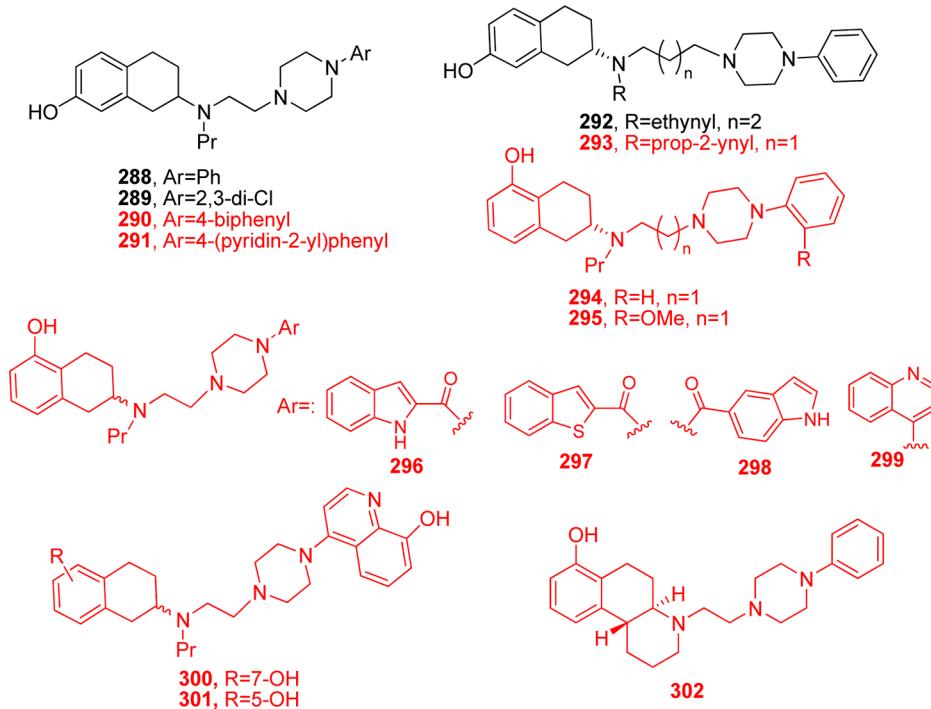


Figure 25. 2-Tetralin derivatives.

low ( $\mu\text{M}$ ) affinity for both  $\text{D}_2$  and  $5\text{-HT}_{2A}$  receptors but readily crossed the blood–brain barrier; approximately 50% was extracted during first-pass cerebral extraction at normal blood flow.<sup>257</sup> Autoradiographic distribution of [ $^{125}\text{I}$ ]-**280** in rat brain slices showed preferential localization in striatum and other cerebral regions rich in DA and 5-HT receptors, though with high levels of nonspecific binding.<sup>258</sup>

Fallypride (**281a**), 5-(3-fluoropropyl)-2,3-dimethoxy-*N*[(2*S*)-1-(2-propenyl)-2-pyrrolidinyl]methylbenzamide, is a selective  $\text{D}_2/\text{D}_3$  receptor antagonist. Its fluorine-18 radiolabeled tracer derivative **281b** ( $^{18}\text{F}$ -fallypride) can be used in PET to visualize both striatal and extrastratal  $\text{D}_2$  and  $\text{D}_3$  receptors. *In vitro* and *in vivo* experiments have demonstrated its relatively selective binding to striatal and several extrastratal  $\text{D}_2$  receptor-rich regions in rat brain. PET experiments in rhesus monkeys indicated its binding to extrastratal regions as well.<sup>259</sup> In addition, radiolabeled [ $^{11}\text{C}$ ]-fallypride (**281c**) has been prepared as well.<sup>260</sup> PET imaging studies with this tracer in nonhuman primates showed its selective localization in relatively DA-rich brain regions, including caudate, putamen, thalamus, and cerebral cortex. The similar regional localization of **281b** and **281c** suggests that radiolabeled fallypride may be useful for PET-imaging of  $\text{D}_2$  and  $\text{D}_3$  receptors.<sup>260</sup>

Autoradiographic binding properties as well as *in vivo* imaging characteristics of the  $\text{D}_2$  receptor agonist (*R,S*)-2-(*N*-1-[ $^{11}\text{C}$ ]-*n*-propyl)amino-5-hydroxytetralin (**282**, [ $^{11}\text{C}$ ]-5-OH-DPAT) include selective binding to dopaminergic regions in striatum that are displaced by the  $\text{D}_2$  antagonist sulpiride.<sup>261</sup> Selective binding to striatum was blocked in the presence of the GTP analog, 5'-guanylylimidodiphosphate, indicating that [ $^{11}\text{C}$ ]-5-OH-DPAT (**282**) binds to the high-affinity state of  $\text{D}_2$  receptors. *Ex vivo* autoradiographic studies in rats also show selective binding of **282** to striatum. A PET study in monkeys confirmed selective localization on **282** in corpus striatum with a striatum/cerebellum selectivity ratio of nearly 2 at 40 min postinjection.

Wilson et al.<sup>262</sup> reported a modified 2-aminotetralin tracer, (+)-[ $^{11}\text{C}$ ]-4-propyl-3,4,4a,5,6,10b-hexahydro-2*H*-naphtho[1,2-*b*][1,4]oxazin-9-ol ([+]-**283**), as a potential  $\text{D}_2$ -agonist radiotracer for PET imaging of the high-affinity state of  $\text{D}_2$  receptors. This compound crossed the rat blood–brain barrier readily and distributed selectively to brain regions rich in  $\text{D}_2$  receptors. Binding of [ $^{11}\text{C}$ ]-(+)-**283** is saturable and stereospecific, with a favorable striatum/cerebellum distribution ratio and selective displacement by unlabeled  $\text{D}_2$  ligands. This  $\text{D}_2$ -agonist radioligand also showed high sensitivity to altered levels of endogenous DA. [ $^{11}\text{C}$ ]-Labeled (+)-**283**, therefore, is a promising candidate for PET imaging of the  $\text{D}_2$  high-affinity state in human subjects. Wilson et al. also prepared a series of fluorinated analogs of **283**. Most of these compounds inhibited binding of  $\text{D}_2$  antagonist [ $^3\text{H}$ ]domperidone and agonist [ $^3\text{H}$ ]-(+)-PHNO to the low- and high-affinity states of  $\text{D}_2$  receptors, respectively, consistent with  $\text{D}_2$  receptor agonist behavior. However, [ $^{18}\text{F}$ ]-labeled **284** did not show *in vivo* characteristics suitable for imaging  $\text{D}_2$  receptors with PET.<sup>263</sup>

Hwang et al.<sup>264–269</sup> found that [ $^{11}\text{C}$ ]-radiolabeled *N*-*n*-propylnorapomorphine ([ $^{11}\text{C}$ ]NPA (**285**) fulfilled most requirements of a potential radiotracer for imaging the high-affinity state of the  $\text{D}_2$  receptor, including good brain penetration and at least moderate regional selectivity in rat brain tissue *ex vivo* and in primate PET studies. When the  $\text{D}_2$  agonist [ $^{11}\text{C}$ ]NPA (**285**) and  $\text{D}_2$  antagonist [ $^{11}\text{C}$ ]raclopride were compared for responsiveness to changes in extraneuronal concentrations of endogenous DA elicited by *d*-amphetamine, the  $\text{D}_2$  agonist ligand was 47% more sensitive than the antagonist in primates, but such studies have not been reported in human subjects. Another [ $^{11}\text{C}$ ]-radiolabeled aporphine analog, 2-[ $^{11}\text{C}$ ]-methoxy-*N*-*n*-propylnorapomorphine ([ $^{11}\text{C}$ ]MNPA; **286**), also is a potential  $\text{D}_2$ -agonist radioligand for *in vivo* imaging of the high-affinity state of the  $\text{D}_2$  receptor that requires further study.<sup>270</sup>

Monohydroxy aporphines have better metabolic stability and retain similar high affinity at the D<sub>2</sub> receptor as the catechol aporphine.<sup>271</sup> Neumeyer et al. reported a series of fluorinated monohydroxyaporphines to examine their potential as PET tracers.<sup>271b</sup> These compounds showed high affinity and selectivity at the D<sub>2</sub> receptor, especially compounds 287a–c ( $K_i = 0.5, 0.8$ , and  $3.7\text{ nM}$  for D<sub>2</sub><sup>high</sup> respectively, Figure 24). In view of the more facile preparation of the corresponding [<sup>18</sup>F]-derivatives (287a, 287b) than the catechol 287c, these hydroxyaporphines have potential value for DA receptor imaging.<sup>271b</sup>

### 3.3. D<sub>3</sub> Receptor-Selective Ligands

#### 3.3.1. 2-Tetralin Derivatives as Potential D<sub>3</sub> Agonists.

By using a strategy of hybridizing pharmacophoric amino-tetralin and piperazine fragments, a series of novel D<sub>2</sub> and D<sub>3</sub> receptor ligands were developed.<sup>272,273</sup> In this series, compounds 288, 289, and 292 (Figure 25, Table 10) exhibit

**Table 10. Binding Affinity of the Aminotetraline Derivatives**

| compd   | D <sub>2</sub> | K <sub>i</sub> (nM) |                |
|---------|----------------|---------------------|----------------|
|         |                | D <sub>3</sub>      | D <sub>4</sub> |
| 288     | 213            | 1.75                |                |
| 289     | 27.4           | 1.13                |                |
| 290     | 64.1           | 5.22                |                |
| 291     | 103            | 1.96                |                |
| 292     | 68.4           | 1.40                |                |
| (−)-293 | 25.2           | 0.35                |                |
| 294     | 58.6           | 0.8                 |                |
| (−)-295 | 9.56           | 0.46                |                |
| (−)-296 | 47.5           | 0.57                |                |
| 297     | 76.9           | 1.69                |                |
| (−)-298 | 157            | 2.27                |                |
| (−)-299 | 4.89           | 0.40                |                |
| 300     | 15.9           | 0.818               |                |
| 301     | 13.8           | 1.35                |                |
| 302     | 23.6           | 4.95                |                |
| 303     | 110            | 9.1                 | 250            |
| 304     | 54             | 3.2                 | 6.3            |
| S-305   | 90             | 6.0                 |                |
| S-306   | 180            | 4.0                 | 58             |
| 307     | 85             | 0.54                | 50             |
| 308     | 230            | 16                  | 87             |
| 309     | 40             | 0.21                | 4.3            |
| 310     | 610            | 1.3                 | 190            |
| 311     | 150            | 0.71                | 59             |
| S-311   | 5.3            | 0.027               |                |
| 312     | 270            | 0.55                | 230            |
| 313     | 330            | 0.41                |                |
| 314     | 2568           | 0.50                |                |
| 315     | 264            | 0.92                |                |

high affinity at the D<sub>3</sub> receptor with  $K_i$ s of 1.75, 1.13, and 1.40 nM, respectively. Compound 288 has the highest D<sub>3</sub>/D<sub>2</sub> selectivity (122-fold). On the basis of mitogenesis assays, this compound showed the most potent D<sub>3</sub> agonistic activity: 10-times more potent than quinpirole. It is the most selective compound for the D<sub>3</sub> receptor in this series. Resolution of 288 produces little separation of activity between the two enantiomers, and only marginally greater activity in the (−)-288 isomer.<sup>273</sup> In the unilaterally 6-OH-DA-lesioned rat turing model, (−)-288 was quite potent in inducing

contralateral rotations and had a longer duration of action than apomorphine.

Incorporation of a larger substituent to the arylpiperazine fragment retained high D<sub>3</sub> affinity, but one such compound 291 was much more D<sub>3</sub>/D<sub>2</sub>-selective than other analogs.<sup>274</sup> To investigate the effects of the length of the linker and regiochemistry of the phenolic hydroxyl group, compounds 293–295 were designed and showed subnanomolar affinity ( $K_i = 0.35–0.8\text{ nM}$ ) at the D<sub>3</sub> receptor, together with >20-fold D<sub>3</sub>/D<sub>2</sub> selectivity.<sup>275</sup> Interestingly, the S-hydroxy analogs (±)-294 and (−)-295 showed similarly high D<sub>3</sub> affinity. Notably, (−)-295 was 6-times more potent than the racemate (294) and 40-times more potent than its (+)-isomer.

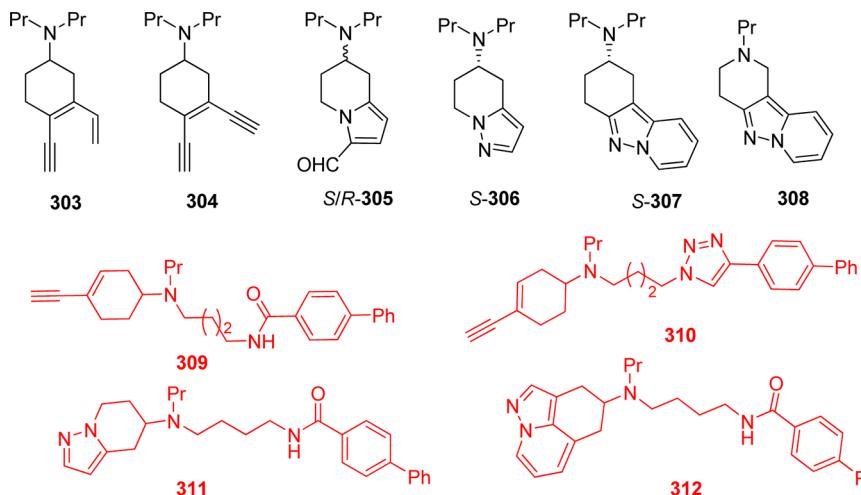
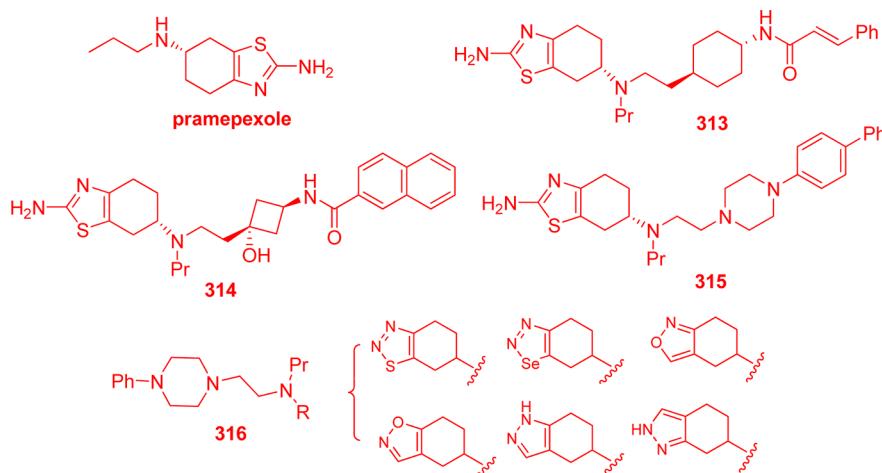
Replacement of the aryl in the arylpiperazine fragment with indole, benzothiophene, benzofuran, quinoline, or 1*H*-indazole moieties yielded a large series of analogs,<sup>276–279</sup> with high D<sub>3</sub> affinity, especially compounds 296–301. N-Substitution on the piperazine ring could accommodate various substituted indole rings, and the heterocyclic ring did not need to connect directly with the piperazine ring. The enantiomers of compound 296 exhibited differential activity: the (−)-isomer (D<sub>2</sub>  $K_i = 47.5\text{ nM}$ , D<sub>3</sub>  $K_i = 0.57\text{ nM}$ ) displayed 2.4–6.5-times higher affinity at both D<sub>2</sub> and D<sub>3</sub> receptors than the (+)-enantiomer (D<sub>2</sub>  $K_i = 113\text{ nM}$ , D<sub>3</sub>  $K_i = 3.73\text{ nM}$ ), with D<sub>3</sub>/D<sub>2</sub> selectivity of 30–83-fold. In the functional GTP $\gamma$ S binding assay, (−)-296 exhibited potent agonist activity at both D<sub>2</sub> and D<sub>3</sub> receptors with preferential D<sub>3</sub> affinity at the D<sub>3</sub> receptor.<sup>276</sup>

The 8-hydroxyquinoline analogs 300 and 301 were designed as multifunctional agents possessing D<sub>2</sub> and D<sub>3</sub> receptor agonism and iron chelating properties.<sup>278</sup> Compounds (+)-300 and (−)-301 had ~1.0 nM affinity ( $K_i$ ) at D<sub>3</sub> and ~15 nM at D<sub>2</sub> receptors, with potent agonistic actions at both DA receptors. The S-hydroxyl isomer 301 had efficient iron chelating effects shown in *in vitro* complexation studies. Antioxidant activity also was observed with this compound. In animal models of Parkinson's disease, (−)-301 exhibited potent *in vivo* activity in reversing locomotor activity in reserpine-treated rats and in producing contralateral rotational activity in 6-OHDA lesioned rats.

*trans*-Octahydrobenzo[*f*]quinolin-7-ol (302) represents a structurally constrained analog bearing an octahydrobenzo[*g* or *f*]quinoline scaffold. It exhibited high affinity for D<sub>2</sub> and D<sub>3</sub> receptors, and the (−)-isomer was found to be the eutomer. Although the affinity of 302 and its congeners was slightly lower than the 8-hydroxyquinoline analogs 300 and 301, such constrained derivatives have provided a unique pharmacophore model for further structure modification.<sup>279</sup>

Another strategy for generating potent and selective D<sub>3</sub> ligands is to modify isosteres of 2-aminotetralins. Gmeiner et al. reported that the phenol component in 2-aminotetralins can be replaced by conjugated enyne (303) or endiyne (304) moieties (Figure 26).<sup>280–282</sup> These novel, nonaromatic tetralin analogs have high D<sub>3</sub> affinity and selectivity, with  $K_i$ s of 9.1 and 3.2 nM for compounds 303 and 304. The endiyne 304 also has high D<sub>4</sub> and moderate D<sub>2</sub> affinity as well as 75% D<sub>3</sub> agonistic efficacy, compared to only 26% for 303, and full (100%) efficacy in the standard comparator quinpirole.

Further modifications of the phenol fragment of tetralins result in compounds 305–308 (Figure 26).<sup>283–285</sup> The 3-formyl-substituted aminoindolizine S-305 has a  $K_i$  of 6.0 nM for the high-affinity D<sub>3</sub> binding site; its R-isomer was much less potent. Similarly, the S-enantiomer of 5-aminotetrahydropyrazolo[1,5-*a*]pyridine (S-306) is also highly

**Figure 26.** Bioisosteres of 2-aminotetralin.**Figure 27.** Hybrids of pramipexole and arylpiperazines.

selective for high affinity D<sub>3</sub> binding ( $K_i = 4.0$  nM). These observations indicate that the sp<sup>2</sup>-nitrogens of the pyrazole in S-306 and the thiazole in pramipexole are important pharmacophoric elements. Computational studies based on the similarity of molecular electrostatic potential maps suggested synthesis of the tricyclics 307 and 308. The azaindole 307 has very high D<sub>3</sub> affinity ( $K_i = 0.54$  nM) and considerable selectivity over D<sub>2</sub> and D<sub>4</sub> receptors as well as substantial intrinsic agonist activity in mitogenesis assays, whereas 308 lacks D<sub>3</sub> interactions.<sup>285</sup>

Since enyne derivatives of 2-aminotetralins retained high D<sub>3</sub> affinity, this pharmacophore was introduced to the hybrids of 2-aminotetralines and arylpiperazines as described in Figure 25. Representative compounds 309 and 310 (Figure 26, Table 10) showed very high D<sub>3</sub> affinity ( $K_i = 0.21$  and 1.3 nM) and high selectivity over related other GPCRs.<sup>286</sup> According to mitogenesis experiments and bioluminescence-based cAMP assays, biphenylcarboxamide 309 and its Click chemistry derived triazole analog 310 behaved as D<sub>3</sub> partial agonists, but their relative efficacy was dependent on the type of functional assay. Heterocyclic DA surrogates of types 311 and 312 also have shown high D<sub>3</sub> receptor activity.<sup>287</sup> The enantiomerically pure biphenylcarboxamide (S)-311 displayed an unusually low  $K_i$  value of 27 pM at the agonist-labeled D<sub>3</sub> receptor, together with a significant D<sub>3</sub>/D<sub>2</sub> selectivity. Measurement of [<sup>35</sup>S]GTPyS incorporation in the presence of a coexpressed PTX-insensitive

G<sub>α0-1</sub> subunit confirmed the highly efficient G-protein coupling of (S)-311. It is also likely that the superior D<sub>3</sub> affinity of the eutomer 311 is caused by favorable binding energy resulting from interaction between the ligand's central ammonium unit and the aspartate residue in position 3.32 of the receptor peptide chain.<sup>287</sup>

Pramipexole is a D<sub>3</sub>-preferring DA agonist with limited D<sub>3</sub>/D<sub>2</sub> selectivity *in vitro* or *in vivo*. A series of hybrids of pramipexole and arylpiperazines were designed to improve D<sub>3</sub> receptor selectivity. Compound 313 has a  $K_i$  value of 0.41 nM at D<sub>3</sub> and selectivity of >30,000- and 800-fold over the D<sub>1</sub>-like and D<sub>2</sub> receptors (Figure 27, Table 10).<sup>288</sup> *In vivo* functional assays indicated that 313 was a D<sub>3</sub> partial agonist with no detectable D<sub>2</sub> activity.

Meanwhile, Wang et al.<sup>289</sup> reported several such hybrids with high D<sub>3</sub> affinity and excellent selectivity over D<sub>2</sub> and D<sub>1</sub> receptors. Compound 314 bound with a D<sub>3</sub>  $K_i$  of 0.50 nM and selectivity of >5000 over D<sub>2</sub> and D<sub>1</sub> receptors in rat brain tissue. In assays with human D<sub>3</sub> receptors, this compound showed a  $K_i$  value of 3.61 nM, and >1000-fold selectivity over human D<sub>1</sub> and D<sub>2</sub> receptors. This agent was active in behavioral assays in rat at doses of only 10 µg/kg.<sup>289</sup> Further modification<sup>290,291</sup> of the pramipexole or arylpiperazine moieties led to compounds 315 and 316, but only 315 had high affinity and selectivity for the D<sub>3</sub> receptor (D<sub>3</sub>  $K_i = 0.92$

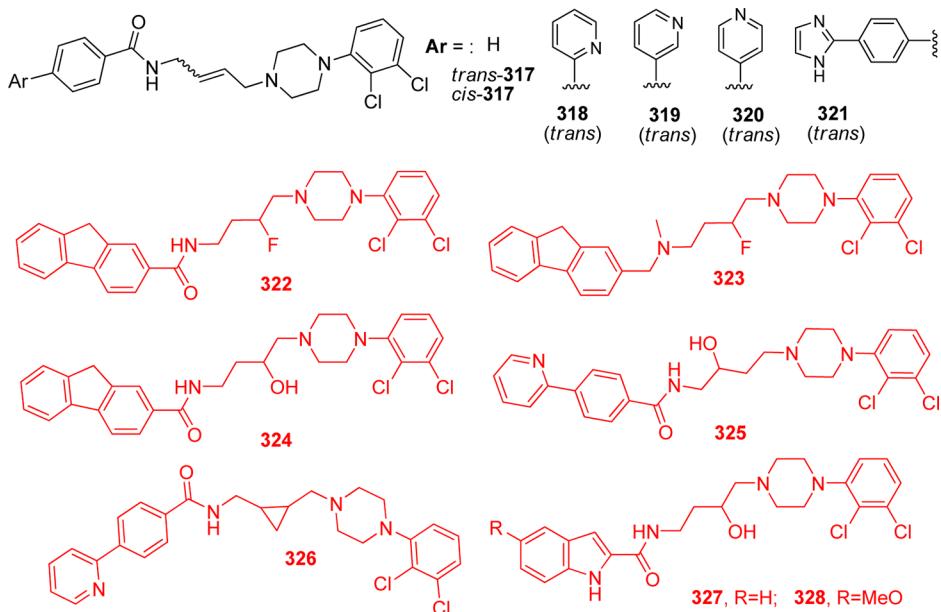


Figure 28. Hybrids of 2,3-dichlorophenylpiperazines with benzamides bearing different linkers.

nM;  $D_2/D_3 K_i$  ratio, 253). This compound exhibited potent  $D_3$  full agonist activity in *in vitro* assays ( $\text{EC}_{50}$ , 0.08 nM).<sup>290</sup> *In vivo*, 315 showed potent rotational activity in unilaterally 6-OH-DA lesioned rats with prolonged action, suggesting its potential value for the treatment of Parkinson's disease.

**3.3.2. Arylpiperazines/Piperidines.** 3.3.2.1. *2,3-Dichlorophenylpiperazines.* Newman et al.<sup>292</sup> reported a series of 2,3-dichlorophenylpiperazines connected with an arylcarboxamido residue through a but-2-ene linker. The *trans* isomer of 317 is potent and selective for the  $D_3$  receptor ( $D_3 K_i = 1.3$  nM;  $D_2 K_i = 50$  nM), and *cis*-317 is only slightly less potent and less  $D_3$ -selective ( $D_3 K_i = 4.9$  nM;  $D_2 K_i = 20$  nM). A related biaryl series, compounds 318–321 (Figure 28, Table 11), has high affinity for both  $D_2$  and  $D_3$  receptors with variable selectivity. The 2-pyridinylphenylamide 318 has the highest affinity and selectivity of the series ( $D_3 K_i = 0.7$  nM;  $D_2 K_i = 93$  nM). This compound shows  $D_3$  antagonist activity by inhibiting quinpirole-induced stimulation of mitogenesis by human  $D_3$  receptors in transfected cells ( $\text{EC}_{50}$ , 3.0 nM).<sup>293</sup>

Further modification on either the linker or the aryl component of the arylpiperazine portion led to several potent  $D_3$  receptor agents. For example, compounds 322–328 represent hybrids of arylpiperazines with arylcarboxamides connected by a fluoro- or hydroxyl-substituted butylene linker (Figure 28). Compounds 322 and 323, with a fluoro-substituted butylene linker, had  $D_3 K_i$  values of 2.6 and 393 nM, and 322 showed high  $D_3/D_2$  selectivity of 1640-fold.<sup>294</sup> The marked difference in  $D_3$  affinity of these two compounds indicates that the carbonyl moiety of the carboxamide component is essential for high affinity binding at the  $D_3$ , but not the  $D_2$  receptors. Incorporation of a hydroxyl group in the butylene linker was tolerated. The regiochemistry of the hydroxyl group in the linker did not impact  $D_3$  binding affinity appreciably, and compounds 324 and 325 had similar high  $D_3 K_i$  values (1.8 and 0.5 nM, respectively).<sup>295</sup> Compared to derivatives with an olefinic linker (e.g., 318), which acted as antagonists in quinpirole-stimulated mitogenesis at human  $D_3$  receptors, the hydroxybutyl-linked analogs 324 and 325 showed  $D_3$  partial agonist activity.

Table 11. Binding Affinities of 2,3-Dichlorophenylpiperazines

| compd             | $D_2$  | $K_i$ (nM) |        |
|-------------------|--------|------------|--------|
|                   |        | $D_3$      | $D_4$  |
| <i>trans</i> -317 | 50     | 1.3        |        |
| <i>cis</i> -317   | 20     | 4.9        |        |
| 318               | 93     | 0.7        | 375    |
| 319               | 54     | 0.9        | 520    |
| 320               | 44     | 0.9        |        |
| 321               | 46     | 1.3        |        |
| 322               | 4260   | 2.6        |        |
| 323               | 2060   | 393        |        |
| 324               | 319    | 1.8        | 16400  |
| 325               | 28     | 0.5        |        |
| 326               | 54     | 1.0        |        |
| 327               | 502    | 1.39       | 4900   |
| 328               | 489    | 1.2        | >10000 |
| 329               | 89.6   | 1.4        | 1850   |
| 330               | >10000 | 0.18       | >10000 |
| 331               | >10000 | 0.38       | >10000 |
| 332               | 3200   | 5.7        | 2200   |
| 333               | 450    | 4.5        | 550    |
| 334               | 170    | 0.14       | 800    |
| 335               | 373    | 0.13       | 720    |
| 336               | 77     | 0.17       | 64     |
| 337               | 830    | 0.6        | 720    |
| 338               | 17     | 0.53       | 44     |
| 339               | 21     | 1.1        | 100    |
| 340               | 15     | 0.31       | 120    |
| 341               | 15     | 0.83       | 40     |
| 342               | 49     | 1.0        | 280    |
| 343               | 122    | 0.105      |        |
| 344               | 75     | 0.14       |        |

Replacing the biaryl fragment in 325 with an indole moiety provided compounds 327 and 328 (Figure 28), showing high  $D_3$  affinity ( $K_i = 1.39$  and 1.20 nM). Resolution of compound 327 led to *R*- ( $D_3 K_i = 1.39$  nM) and *S*-327 ( $D_3 K_i = 16.6$  nM).

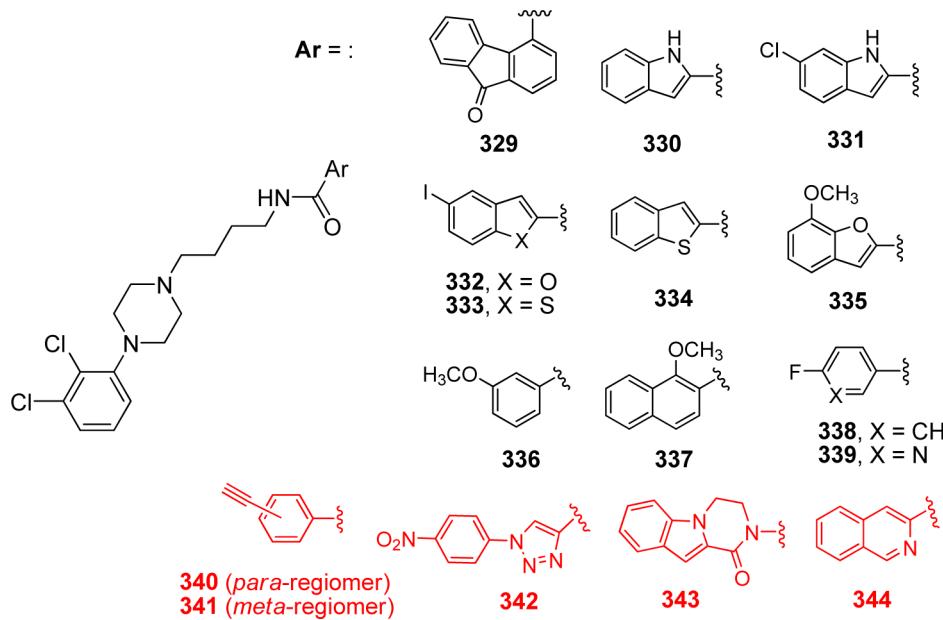


Figure 29. Hybrids of 2,3-dichlorophenylpiperazines with variant arylcarboxamides.

A binding region in the second extracellular loop (E2) of the D<sub>3</sub> receptor peptide chain appears to play a role in both enantioselectivity and D<sub>3</sub> receptor selectivity.<sup>296</sup> Compound 326, containing a cyclopropyl substitution on the butylene linkage, also showed high D<sub>3</sub> affinity ( $K_i = 1.0 \text{ nM}$ ).<sup>295,296</sup>

In a series of 2,3-dichlorophenylpiperazines 329–331 (Figure 29, Table 11), a flexible butylene linker connects the piperazinyl and carboxyamido components. Compound 329 has a D<sub>3</sub>  $K_i$  of 1.4 nM with moderate D<sub>3</sub>/D<sub>2</sub> selectivity (64-fold) and high D<sub>3</sub>/D<sub>4</sub> selectivity (1300-fold). However, 329 is very lipophilic, and this property may limit its pharmacokinetic utility as a D<sub>3</sub> ligand.<sup>297</sup> The indolylcarboxamides 330 and 331 also have high D<sub>3</sub> affinity ( $K_i = 0.18$  and 0.38 nM) as well as minimal interaction at D<sub>1</sub>, D<sub>2</sub>, and 5-HT<sub>1A</sub> receptors. Compound 330 proved to be a potent and selective D<sub>3</sub> antagonist based on its ability to reduce lever pressing in rats for cocaine. Congener 331 is a potent and selective D<sub>3</sub> partial agonist and lacks effects on cocaine-seeking behavior.<sup>298</sup>

Two additional [<sup>131</sup>I]-radiolabeled 2,3-dichlorophenylpiperazinyl-substituted derivatives, 332 and 333, exhibit good D<sub>3</sub> affinity ( $K_i = 5.7$  and 4.5 nM) and substantial selectivity over D<sub>2long</sub>, D<sub>2short</sub>, and D<sub>4</sub> receptors, making them potential SPECT radioligands for imaging the D<sub>3</sub> receptor.<sup>299</sup> The amides 334–337 (Figure 29, Table 11) had D<sub>3</sub>  $K_i$  values of 0.14, 0.13, 0.60, and 0.17 nM, respectively, together with substantially lower affinity at D<sub>2</sub>, D<sub>4</sub>, 5-HT<sub>1A</sub>, and  $\alpha_1$  receptors.<sup>300</sup> The 3-methoxyphenyl- or 1-methoxy-2-naphthyl carboxamides 336 and 337 as well as the 7-methoxy-2-benzofuran-carboxamide 335 are candidate PET ligands, owing to their high D<sub>3</sub> affinity, selectivity, and lipophilicity.<sup>300</sup> [<sup>11</sup>C]-Radiolabeled 335 and 337 were reported to cross the blood–brain barrier and to be regionally localized in rat brain tissue but not in the expected distribution of D<sub>3</sub> receptors. They are, therefore, unlikely candidates as useful D<sub>3</sub> ligands.<sup>301</sup>

In addition, high D<sub>3</sub> affinity was also observed in fluorosubstituted arylcarboxamides, including 338 and 339, showing K<sub>i</sub> values of 0.53 and 1.1 nM, respectively.<sup>302,303</sup> Autoradiography with [<sup>18</sup>F]-339 failed to follow the distribution of D<sub>3</sub> receptors and showed high nonspecific labeling, marking it as an improbable D<sub>3</sub> radioligand.

Propargyl-substituted benzamides 340 and 341 had similar high affinity at the D<sub>3</sub> receptor, with partial agonistic activity.<sup>304</sup> The Click chemistry product N-phenyltriazole carboxamide 342 had a K<sub>i</sub> of 1.0 nM at the human D<sub>3</sub> receptor and substantial D<sub>3</sub>-selectivity over D<sub>2</sub> and  $\alpha_1$  receptors.<sup>305</sup> Further modification on the aryl component of the arylcarboxamide moiety led to analogs 343 and 344, which both had high D<sub>3</sub> affinity ( $K_i = \sim 0.1 \text{ nM}$ ). These also had moderate 5-HT<sub>1A</sub> and 5-HT<sub>2A</sub> affinity, making them useful as multitargeted ligands for possible development as antipsychotics.<sup>306</sup>

**3.3.2.2. 2-Methoxyphenylpiperazines.** With an N-(2-methoxyphenyl)piperazine component as the major pharmacophore, various aryl and heteroaryl amide derivatives have been prepared with four-methylene as the linker. Examples include compounds 345–349 (Figure 30, Table 12). They had

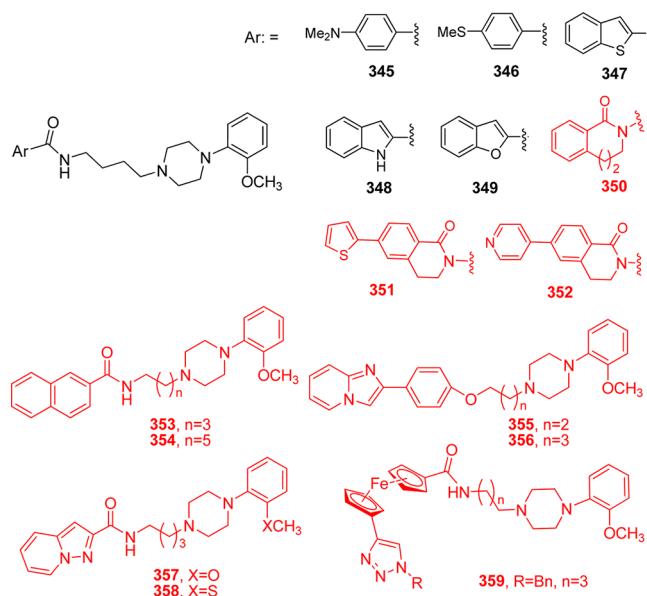


Figure 30. 2-Methoxyphenylpiperazines.

**Table 12. Binding Affinities of 2-Methoxyphenylpiperazines**

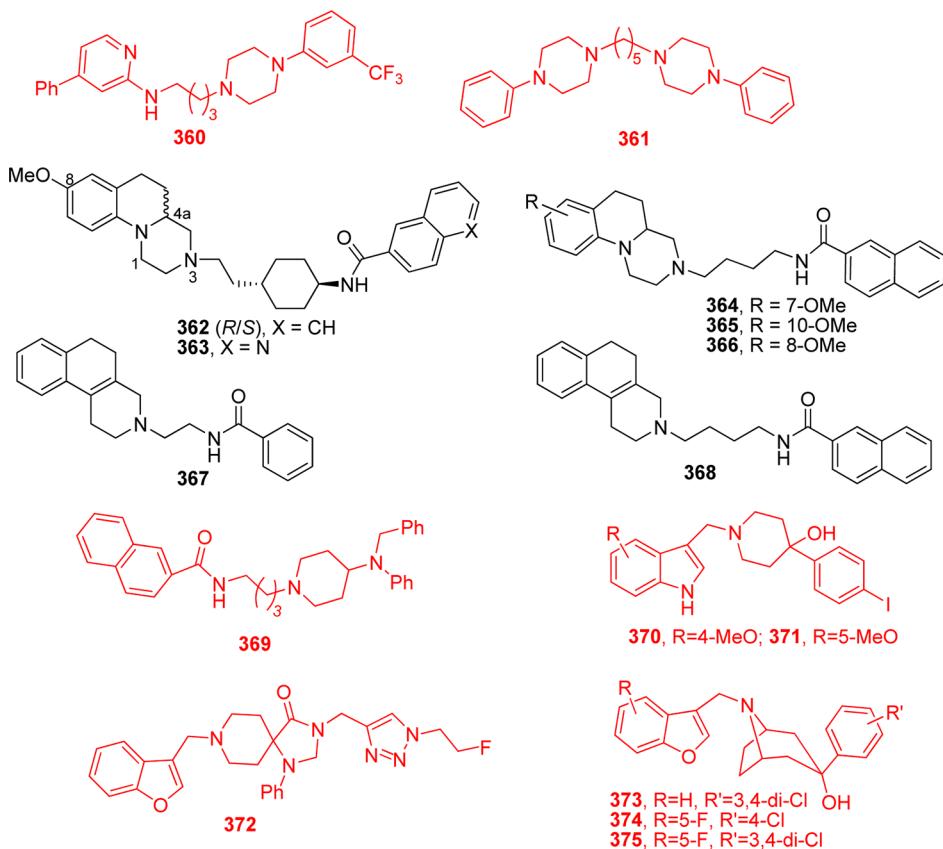
| compd | D <sub>2</sub> | K <sub>i</sub> (nM) |                |
|-------|----------------|---------------------|----------------|
|       |                | D <sub>3</sub>      | D <sub>4</sub> |
| 345   | 34.4           | 0.8                 | 896            |
| 346   | 31.7           | 0.6                 | 674            |
| 347   | 21.5           | 0.2                 | 305            |
| 348   | 37.4           | 0.3                 | 476            |
| 349   | 36.5           | 0.9                 | 868            |
| 350   | 8.44           | 8.80 <sup>a</sup>   |                |
| 351   | 11             | 0.12                | 2.3            |
| 352   | 7.1            | 0.12                | 3.4            |
| 353   | 30             | 0.77                | 174            |
| 354   | 121            | 0.56                | 102            |
| 355   | 49             | 1.6                 |                |
| 356   | 179            | 0.72                |                |
| 357   | 310            | 4.3                 | 130            |
| 358   | 16             | 0.35                | 65             |
| 359   | 3.7            | 0.34                | 5.4            |

<sup>a</sup>pK<sub>i</sub> value.

high D<sub>3</sub> affinity ( $K_i = 0.3\text{--}0.9$  nM) and moderate D<sub>2</sub> affinity ( $K_i = 40\text{--}53$  nM), together with high 5-HT<sub>1A</sub> affinity. Their lipophilicity ( $\log P = 2.6\text{--}3.5$ ) indicates that they should readily cross the blood–brain barrier. The analogous benzothiophene derivative 347 had a D<sub>3</sub>  $K_i$  of 0.23 nM and was selective over D<sub>2long</sub> (380-) D<sub>2short</sub> (230-) and D<sub>4</sub> receptors (65-fold). This compound, and its oxa-analog (furan) 349, had D<sub>3</sub> partial-agonist properties.<sup>307,308</sup>

In addition, a series of 2-methoxyphenylpiperazines connected to a benzolactam derivative were reported to have high D<sub>3</sub> receptor binding potency as well. The benzo[c]azepin-1-ones were slightly more potent than corresponding isoquinolin-1-ones. The representative compound 350 had the highest D<sub>3</sub> potency in this series ( $K_i = 1.58$  nM).<sup>309,310</sup> Even higher binding affinity was observed from 6-substituted benzolactam derivatives. For example, compounds 351 and 352 had identical D<sub>3</sub>  $K_i$  values of 0.12 nM, and 352 displayed the greatest selectivity (110-fold) for D<sub>3</sub> over D<sub>2long</sub>, D<sub>2short</sub>, and D<sub>4</sub> receptors, compared to ratios of 59- and 28-fold for 350 and 351. Compound 352 appears to be a D<sub>3</sub> antagonist.<sup>311</sup> Further modifications with a focus on the aryl component of the arylcarboxamide moiety and the nature and length of the linker led to naphthamides 353 and 354. These compounds contain linkers of different lengths but showed similarly high affinity at D<sub>3</sub> ( $K_i = 0.77$  and 0.56 nM) and 5-HT<sub>1A</sub> ( $K_i = 2.75$  and 6.15 nM), along with moderate affinity at  $\alpha_{2A}$  ( $K_i = 20$  and 96 nM) receptors.<sup>312</sup>

2-Methoxyphenylpiperazines bearing the fluorescent moiety phenylimidazo[1,2-*a*]pyridine also were designed as D<sub>3</sub> ligands.<sup>313</sup> The most potent compounds 355 and 356 ( $K_i = 1.6$  and 0.72 nM, respectively) showed good Stokes wavelength-shift properties and high quantum yield in ethanol ( $\Phi = 0.74$  and 0.66, respectively). However, preliminary experiments indicated that compound 355 was unable to visualize D<sub>3</sub> receptors expressed in CHO cells, based on epifluorescence microscopy. High D<sub>3</sub> affinity was observed on the pyrazolo[1,5-*a*]pyridine-2-carboxamides 357 and 358. The methylthio analog 358 was 10-fold more potent than the methoxy analog 357 ( $K_i = 0.35$  versus 4.30 nM).<sup>314</sup>

**Figure 31.** Other piperazine/piperidine derivatives.

Meanwhile, disubstituted ferrocenes were developed as bioisosteres of the aryl moiety in the benzamide component of the preceding compounds. Triazole derived appendages were used for the attachment of linker units (Figure 30).<sup>315</sup> High D<sub>3</sub> affinity was obtained with several compounds of this type (Table 12), for example, 359 (D<sub>3</sub> K<sub>i</sub> = 0.34 nM). In contrast to other D<sub>3</sub> ligands, this compound also showed good affinity at human D<sub>2long</sub> (K<sub>i</sub> = 3.7 nM) and D<sub>4</sub> receptors (K<sub>i</sub> = 5.4 nM). Compound 359 appears to be an antagonist at D<sub>3</sub> and D<sub>4</sub> receptors and a potent partial agonist at the D<sub>2</sub> receptor *in vitro* (intrinsic activity, 57%; EC<sub>50</sub>, 2.5 nM).

**3.3.2.3. Other Piperazine/Piperidine Derivatives.** Isosteric replacement of the amide function and modulation of the arylpiperazine moiety of known D<sub>3</sub> receptor ligands led to (*meta*-trifluorophenyl)piperazine 360, possessing high affinity at D<sub>3</sub> receptors (K<sub>i</sub> = 0.76 nM) and 255-fold selectivity over D<sub>2</sub> receptors (Figure 31).<sup>316</sup> This compound has superior oral bioavailability and preferential brain distribution, which make it a good candidate for further pharmacological and clinical evaluation. Several bis-hetero (or -homo) arylpiperazines without connecting to a carboxamide moiety also were reported to be active at multiple G-protein associated targets.<sup>317</sup> A representative compound of this type, 361, had K<sub>i</sub> values of 1.0, 3.0, 31, and 1000 nM at D<sub>3</sub>, 5-HT<sub>1A</sub>, 5-HT<sub>2A</sub>, and D<sub>2</sub> receptors, together with a 1000-fold D<sub>3</sub>/D<sub>2</sub> selectivity.

Wang et al.<sup>318</sup> developed a series of conformationally constrained phenylpiperazines based on a novel tricyclic core (Figure 31). These include the hexahydropyrazinoquinolines 362–366, all of which displayed high D<sub>3</sub> affinity and selectivity. The racemate and enantiomers of 362 all had D<sub>3</sub> K<sub>i</sub> values of 5–10 nM. R-362 had a D<sub>3</sub> K<sub>i</sub> of 5.7 nM, with D<sub>3</sub>/D<sub>2</sub> selectivity of 1600-fold and D<sub>3</sub>/D<sub>1</sub> selectivity of >10,000-fold, but with low aqueous solubility.<sup>318</sup> Replacement of the 2-naphthyl residue with a 6-quinolinyl ring yielded compound 363, with a D<sub>3</sub> K<sub>i</sub> of 9.7 nM, D<sub>3</sub>/D<sub>2</sub> selectivity of >400-fold, and D<sub>3</sub>/D<sub>1</sub> selectivity of >5000-fold. Importantly, the hydrochloride salt of this compound 363 had substantial aqueous solubility (>50 mg/mL) and is a promising D<sub>3</sub> ligand for further evaluation.<sup>319</sup>

Replacing the *trans*-cyclohexylethyl linker in compound 362 with a four-methylene unit resulted in compounds 364–366 (Figure 31). Compound 365 had a D<sub>3</sub> K<sub>i</sub> of 2.6 nM, 99-fold of D<sub>3</sub>/D<sub>2</sub>, and >2000-fold of D<sub>3</sub>/D<sub>1</sub> selectivity. The location of the methoxy group affects D<sub>3</sub> affinity. Notably, the regioisomers 364 and 366 had markedly different D<sub>3</sub> K<sub>i</sub> values (5.8 versus 244 nM).<sup>320</sup> Modeling studies suggest that the D<sub>3</sub> potency and selectivity of these compounds may be influenced by interactions between the methoxy group and amino acid Ser192 of the D<sub>3</sub> peptide chain, as well as van der Waals contacts of the linker with amino acids Tyr373 and Thr369, and hydrophobic contacts of the naphthyl moiety with Leu89 and Phe106. These modeling considerations guided later synthesis of the hexahydrobenz[f]isoquinolines 367 and 368. Compound 367 has a D<sub>3</sub> K<sub>i</sub> of 84 nM, and 10- and 39-fold selectivity over the D<sub>1</sub>- and D<sub>2</sub>-like receptors.<sup>320</sup> Compound 368 has a higher D<sub>3</sub> affinity (K<sub>i</sub> = 6.1 nM), 133-fold D<sub>3</sub>/D<sub>2</sub> selectivity, and 163-fold D<sub>3</sub>/D<sub>1</sub> selectivity. These findings make compound 368 a promising lead for further structural optimization.<sup>321,322</sup>

Hybrid structures containing scaffolds of known histamine H<sub>1</sub> receptor antagonists and fragments of the D<sub>3</sub> receptor-prefering ligands have been reported. One of the most promising compounds, the naphthylamide 369, has a K<sub>i</sub> of 0.3 nM at the human D<sub>3</sub> receptor, with 2343-fold D<sub>3</sub>/D<sub>2</sub>-

selectivity.<sup>323</sup> Mach et al. reported a series of 4-aryl-substituted piperidin-4-ols bearing an indole, 7-azaindole, benzofuran, or benzothiophene fragment.<sup>324</sup> These compounds have structural similarities to classical D<sub>2</sub>-like receptor antagonists such as haloperidol, N-methylspiperone, and benperidol. Two new compounds, 4-methoxy-1*H*-indole (370) and 5-methoxy-1*H*-indole (371), had high D<sub>2</sub> affinity and D<sub>2</sub>/D<sub>3</sub> selectivity. Changing the aromatic ring system from an indole to benzofuran reversed the selectivity to D<sub>3</sub>/D<sub>2</sub>. Further optimization led to the potent (D<sub>3</sub> K<sub>i</sub> = 0.9 nM) and 2.2-fold D<sub>3</sub>/D<sub>2</sub>-selective compound 372. Replacement of the central piperidine moiety with a tropane framework produced the highly potent D<sub>3</sub> receptor ligands 373–375 (Figure 31; Table 13), with K<sub>i</sub> values of 0.34–0.53 nM, though with only about 5-fold D<sub>3</sub>/D<sub>2</sub>-selectivity.<sup>325</sup>

**Table 13. Binding Affinities of Piperazine/Piperidine Derivatives**

| compd | D <sub>2</sub> | K <sub>i</sub> (nM) |                |
|-------|----------------|---------------------|----------------|
|       |                | D <sub>3</sub>      | D <sub>4</sub> |
| 360   | 194            | 0.76                |                |
| 361   | >1000          | 1.0                 |                |
| R-362 | >1000          | 5.7                 |                |
| 363   | 4500           | 9.7                 |                |
| 364   | 762            | 5.8                 |                |
| 365   | 258            | 2.6                 |                |
| 366   | >20000         | 244                 |                |
| 367   | >3000          | 84                  |                |
| 368   | 811            | 6.1                 |                |
| 369   | 703            | 0.3                 |                |
| 370   | 0.9            | 122                 | 60.4           |
| 371   | 0.9            | 100                 | 129            |
| 372   | 2.0            | 0.9                 | 978            |
| 373   | 1.7            | 0.34                |                |
| 374   | 1.2            | 0.37                |                |
| 375   | 1.4            | 0.53                |                |

**3.3.3. Benzazepines, Tetrahydroisoquinolines, and Their Derivatives.** Tetrahydroisoquinoline and benzazepine skeletons can be viewed as conformationally constrained N-benzylamine analogs (Figure 32). Compound 376 has relatively low D<sub>3</sub>, but high  $\alpha_1$  affinity.<sup>326</sup> Compounds 377 and 378, containing a conformationally constrained cyclohexylethyl linker, are potent and selective D<sub>3</sub> receptor antagonists (K<sub>i</sub> = 4.0 and 10 nM). Compound 377 reverses quinelorane-induced reduction in DA efflux, in accord with the regional distribution of cerebral D<sub>3</sub> receptors. Even at high doses, 377 lacks induction of catalepsy or elevation of serum prolactin.<sup>327</sup> Compound 378 is 100-fold D<sub>3</sub>/D<sub>2</sub>-selective,  $\geq$ 60-fold selective for D<sub>3</sub> receptors over other DA receptors and ion channels, and 30-fold D<sub>3</sub>/M<sub>2</sub> selective.<sup>327</sup> This compound lacks intrinsic agonist activity and appears to be a potent D<sub>3</sub> antagonist; it also blocks conditioned place-preference in response to cocaine in male rats, suggesting its potential utility for the treatment of cue-induced relapse in drug-free cocaine addicts.<sup>328</sup>

Further efforts are directed to removing the cyclohexyl ether linker, the sulfone, and the amide moieties to improve the PK properties and hERG (human K<sup>+</sup> ion channel protein) activity of the preceding compounds. One of these compounds, pyrazolyl substituted 1,2,4-triazol-3-yl-thiopropyltetrahydrobenzazepine (379), had a K<sub>i</sub> value of 1.0 nM in the functional GTP $\gamma$ S assay, with cell membranes expressing human D<sub>3</sub>

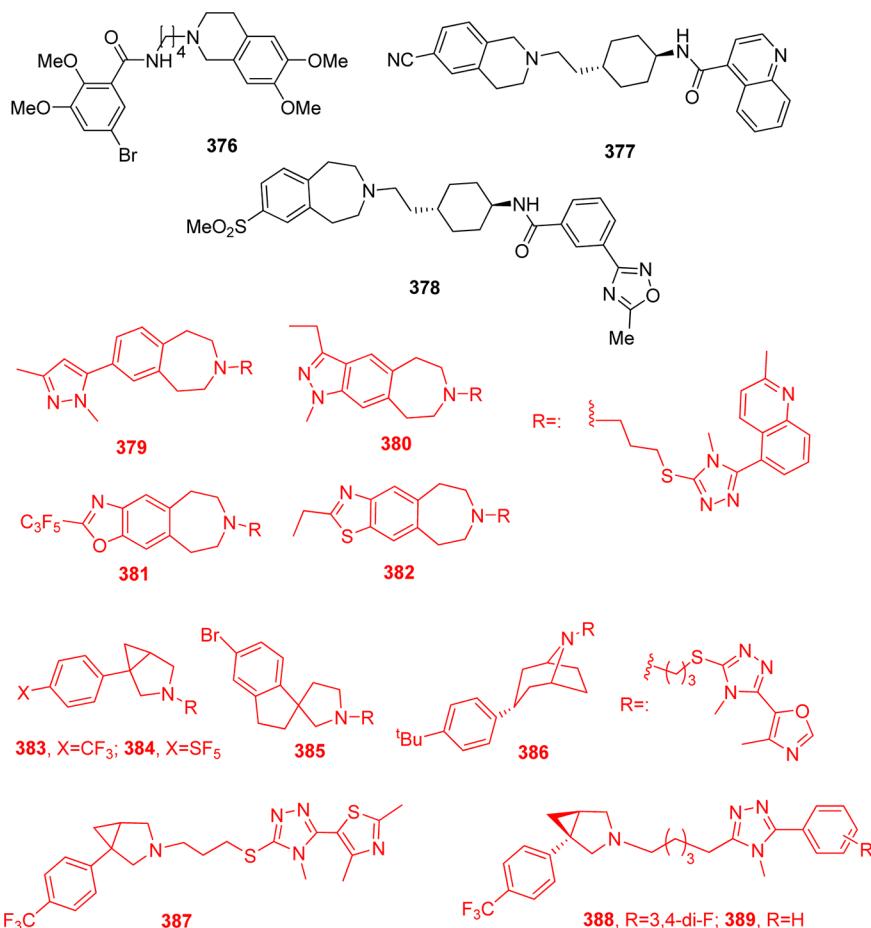


Figure 32. Benzazepines, tetrahydroisoquinolines, and their derivatives..

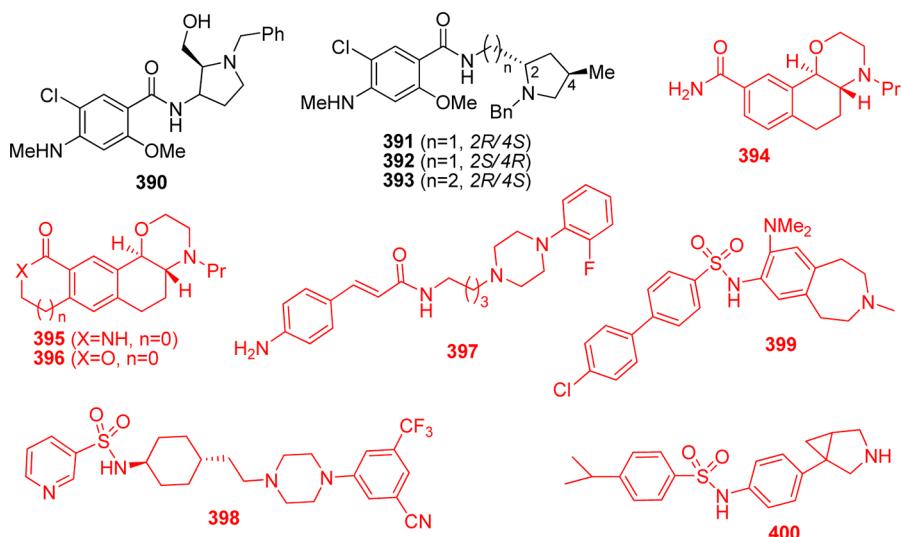


Figure 33. Benzamides and sulfonamides.

receptors. As expected, it showed good oral bioavailability and brain penetration, associated with its high potency and  $D_3$  selectivity *in vitro*. *In vivo*, this compound blocked the expression of nicotine- and cocaine-conditioned place preference in rat.<sup>329</sup>

Fusing the pendant heterocycle to the benzazepine template led to tricyclic[*h*]-fused benzazepines 380–382, possessing  $K_i$  values of 1.0–2.5 nM in the GTP $\gamma$ S assay with cells expressing

human  $D_3$  receptors. The  $D_3$  selectivity of these compounds over  $D_2$  and  $H_1$  receptors, and the hERG channel also are improved over compound 379.<sup>330,331</sup>

Additional scaffolds are explored as well to replace the benzazepine moiety, and several compounds are identified retaining high  $D_3$  receptor affinity and activity.<sup>332–334,335a,b</sup> Compounds 383 and 384, bearing an azabicyclo[3.1.0]hexane moiety, had  $D_3$   $K_i$  values of 0.79 and 0.50 nM. Both compounds

had relatively low distribution volumes, high bioavailability, long half-life, and high brain penetration.<sup>334</sup> Additional bi- or tricyclic templates also were explored as replacements for the benzazepine moiety. Notably, the 2,3-dihydropyro[*indene-1,3'-pyrrolidine*] 385 and 8-azabicyclo[3.2.1]octane 386 had D<sub>3</sub> K<sub>i</sub> values of 2.5 and 0.63 nM in the [<sup>35</sup>S]GTPγS functional assay.<sup>333</sup>

As one of the earlier lead compounds bearing the azabicyclo[3.1.0]hexane moiety, compound 387 has a low K<sub>i</sub> value in the same functional assay, along with good oral bioavailability and brain penetration, as well as *in vitro* potency as an antagonist at the D<sub>3</sub> receptor. This compound attenuated expression of conditioned place preference to nicotine and cocaine.<sup>332</sup>

To explore the role of the sulfur atom in the previously reported thiotriazole derivatives, “C-linked” 1,2,4-triazolylazabicyclo[3.1.0]hexanes were designed and were found to retain high activity and selectivity at the human D<sub>3</sub> receptor. The representative compounds 388 and 389 have D<sub>3</sub> K<sub>i</sub> values of 3.2 and 2.5 nM in the [<sup>35</sup>S]GTPγS assay. These agents also show high (>100-fold) human D<sub>3</sub>/D<sub>2</sub>- and D<sub>3</sub>/hERG-channel-selectivity (>500-fold). The IC<sub>50</sub> values for all major P450 isoforms are >10 μM, and clearance values in both human and rat are low. In addition, both compounds show high distribution volumes (10.2 L/kg), long half-life (≥6 h), and high oral bioavailability (84%), which make them attractive lead compounds for further assessment.<sup>335a</sup>

**3.3.4. Benzamides and Sulfonamides.** Gmeiner et al.<sup>336,337</sup> developed a series of *N*-pyrrolidinyl(alkyl)benzamides derived from 4-hydroxyproline showing variable affinity and selectivity at D<sub>2</sub>, D<sub>3</sub>, and D<sub>4</sub> receptors. Their neuropharmacological properties depended on the substituents on the pyrrolidine ring, chirality, and the length of the alkyl chain between the pyrrolidine and carboxamido residues. Compounds with no linker (390) or with a two-methylene linker (393) displayed high D<sub>4</sub> affinity and selectivity (Figure 33). However, compounds 391 and 392, with a single-methylene linker, exhibit D<sub>3</sub> affinity and selectivity.<sup>338</sup> The *trans*-4-methyl-substituted 392 D<sub>3</sub> K<sub>i</sub> is 20 nM, with D<sub>3</sub>-selectivity of 700-, 17-, 14-, 73-, 37-, and 150-fold over D<sub>1</sub> (K<sub>i</sub> = 14,000 nM), D<sub>2long</sub> (K<sub>i</sub> = 330 nM), D<sub>2short</sub> (K<sub>i</sub> = 280 nM), D<sub>4</sub> (K<sub>i</sub> = 1500 nM), 5-HT<sub>1A</sub> (K<sub>i</sub> = 740 nM), and 5-HT<sub>2A</sub> (K<sub>i</sub> = 3000 nM).

The naphtoxazine derivative 394 represents another series of D<sub>3</sub> receptor agonists, with high potency and efficacy in several functional models of coupling to the cloned human D<sub>3</sub> receptor. It also is a potent agonist at both the presynaptic and postsynaptic D<sub>3</sub> receptors and a less potent D<sub>2</sub> agonist in both rodents and primates. In the studies of receptor discriminative stimulus substitution or antagonism, dose-dependent and stereospecific activity is observed in the *R,R*-isomer of 394, whereas the racemate was less active, and *S,S*-394 was inactive.<sup>339</sup>

Further efforts were made to improve D<sub>3</sub> potency and selectivity. However, bioisosteric replacement of the carboxamido moiety with *N*-mono or *N*-bis substituted carboxamido, cyano, acetyl, tetrazolo, or alkoxy carbonyl moieties decreased D<sub>3</sub> affinity substantially. Conversely, integration of the carboxamido moiety into a five-membered ring yielded enhancement of both D<sub>3</sub> affinity and selectivity. Compared to the moderate K<sub>i</sub> value of 14.8 nM for (*R,R*)-394, the (*R,R*)-lactam 395 and (*R,R*)-lactone 396 (Figure 33) had lower K<sub>i</sub> values of 4.2 and 7.6 nM, respectively. The corresponding six-membered analogs were less potent. It was found that the five-

membered ring system was necessary for maximal D<sub>3</sub> agonistic efficacy.<sup>340</sup> Cinnamoyl amides (Figure 33) were reported as well, having D<sub>3</sub> agonistic potency. The representative compound 397 had a human D<sub>3</sub> K<sub>i</sub> of 0.9 nM, 19-fold D<sub>3</sub>/D<sub>2</sub>-selectivity, and full D<sub>3</sub>-agonist activity.<sup>341</sup>

Several sulfonamides had dual D<sub>3</sub> and D<sub>2</sub> receptor affinity. One of the most potent was the pyridine-3-sulfonamide 398 (Figure 33), possessing rat D<sub>3</sub> K<sub>i</sub> values of 0.4 nM and 60-fold D<sub>3</sub>/D<sub>2</sub>-selectivity. This compound showed favorable PK properties (rat %F, 55%; brain T<sub>max</sub> 1 h; C<sub>max</sub> 921 ng/mL) and *in vivo* antipsychotic-like animal behavioral activity comparable to that of aripiprazole and olanzapine.<sup>342</sup>

SAR study on the receptor interaction profiles of marketed antipsychotics led to identification of the sulfonamide 399 as a candidate antipsychotic agent (Figure 33). It showed antagonistic activity at D<sub>2</sub>, D<sub>3</sub>, 5-HT<sub>2A</sub>, 5-HT<sub>2C</sub>, and 5-HT<sub>6</sub> receptors.<sup>343</sup> The K<sub>i</sub> values for the last four receptors were 1.6–7.9 nM, with lower affinity at D<sub>2</sub> receptors (K<sub>i</sub> = 501 nM). In functional assays, compound 399 did not show agonist activity at any of these five receptors. *In vivo* pharmacodynamic activity occurred with an ED<sub>50</sub> of approximately 20 mg/kg following oral dosing. Moreover, compound 399 did not show any propensity to induce catalepsy in rats at oral doses up to 100 mg/kg, indicating a substantial therapeutic index.

The sulfonamide 400 represents another series of potent D<sub>3</sub> receptor antagonists, showing a human D<sub>3</sub> K<sub>i</sub> value of 0.50 nM, 100-fold human D<sub>3</sub>/D<sub>2</sub>-selectivity, and approximately 400-fold human D<sub>3</sub>/ERG selectivity.<sup>344</sup>

**3.3.5. Conformationally Constrained Amides as Potential D<sub>3</sub> Antagonists.** **3.3.5.1. Cyclic Bioisosteres of Amides.** Geneste et al.<sup>345,346</sup> reported a series of pyrimidinylpiperazines coupled with various conformationally constrained cyclic carboxamido appendages through a four-methylene linker (401–404; Figure 34). The 1*H*-pyrimidin-

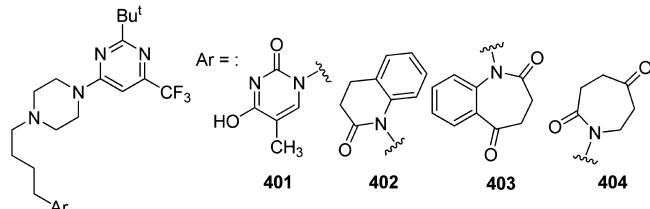


Figure 34. Cyclic bioisosteres of amides.

2-one 401 had a D<sub>3</sub> K<sub>i</sub> value of 1.3 nM, 246-fold D<sub>3</sub>-over-D<sub>2</sub> selectivity. It was a potent antagonist in reversing behavioral effects (huddling deficits) induced by the D<sub>3</sub> agonist PD-128907 in the rat (oral ED<sub>50</sub>, 6.1 mg/kg).<sup>345</sup> Quinolinone 402, benzazepinedione 403, and azepinedione 404 also displayed a good D<sub>3</sub> affinity. In this series, the benzazepinedione 403 had the highest D<sub>3</sub> affinity (K<sub>i</sub> = 0.8 nM), along with 300-fold of D<sub>3</sub>/D<sub>2</sub>-selectivity, and was a potent antagonist reversing the behavioral effects of PD-128907 in rat (ED<sub>50</sub>, 2.2 mg/kg).<sup>346</sup>

The molecular structure of imidazole can be viewed as a masked, conformationally constrained carboxamido fragment. Compound 405, 2-(5-bromo-2,3-dimethoxyphenyl)-4-(6,7-dimethoxy-1,2,3,4-tetrahydroisoquinolinomethyl)imidazole (Figure 35), has moderately high D<sub>3</sub> affinity (K<sub>i</sub> = 21 nM) and 7-fold D<sub>3</sub>/D<sub>2</sub>-selectivity, indicating that masking the carboxamido function between the phenyl ring and the basic nitrogen with an imidazole moiety did not enhance D<sub>3</sub> receptor selectivity.<sup>347</sup> Replacing the imidazole moiety with a pyrrole ring provides 2-

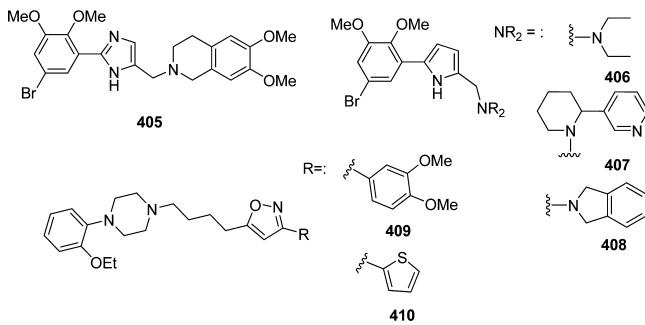


Figure 35. Imidazole, pyrrole, and isoxazoline analogs.

(5-bromo-2,3-dimethoxyphenyl)-5-(aminomethyl)-1*H*-pyrroles (**406–408**; Figure 35) with somewhat greater  $D_3$  affinity than the preceding imidazoles. The most selective pyrrole compound was 2-(5-bromo-2,3-dimethoxyphenyl)-5-(2-[3-pyridyl]piperidinyl)methyl-1*H*-pyrrole (**407**), having a  $D_3 K_i$  value of 4.3 nM, 20-fold  $D_3/D_2$  selectivity, and 300-fold  $D_3/D_4$  selectivity, as well as *in vivo* neuropharmacological activity.<sup>348</sup> The isoxazoline fragment is another carboxamido bioisostere. Coupling isoxazoline and arylpiperazine components has yielded several piperazinylalkylisoxazoles (Figure 35).<sup>349</sup> Of these, compounds **409** and **410** had  $D_3 K_i$  values of 2.6 and 3.9 nM with 46- and 50-fold of  $D_3/D_2$  selectivity.<sup>350</sup>

**3.3.5.2. Aryl Acrylamides.** The aryl acrylamide moiety is another scaffold of structurally rigid amides (**411–414**; Figure 36). Molecular modeling revealed that the steric inflexibility of the aromatic amidic residue, as found in this series of  $D_3$  partial-agonist acrylamides, enhanced  $D_3$  affinity and selectivity. An extended and more linear conformation in the aliphatic or aryl spacers was crucial for the  $D_3$  selectivity, whereas structural diversity in the aryl moiety (benzamides, heteroaryl amides, arylimides) had a major influence on the  $D_3$  receptor affinity.<sup>351</sup> Among such compounds, (*E*)-4-iodo-N-(4-(4-(2-methoxyphenyl)piperazin-1-yl)butyl)cinnamoylamide (**411**) had a promising pharmacological profile that included high  $D_3$  potency ( $K_i = 0.5$  nM) and 149-fold  $D_3/D_2$ -selectivity. It showed  $D_3$  partial agonist activity in a mitogenesis test.<sup>351</sup>

Gao et al.<sup>352</sup> developed [<sup>11</sup>C]-radiolabeled forms of the acrylamide **412** and its regioisomers (**415–417**; Figure 36) as potential PET imaging agents for brain  $D_3$  receptors. These

new tracers have been prepared with 40–65% radiochemical yields, decay-corrected to end of bombardment, and a synthesis time of 15–20 min. Dynamic PET studies of these tracers in rats indicate that the brain uptake ranks 4-[<sup>11</sup>C]MMC (**415**) > 3-[<sup>11</sup>C]MMC (**416**) > 2-[<sup>11</sup>C]MMC (**417**), consistent with their *in vitro* neuropharmacological properties. However, the cerebral binding of all three tracers (**415–417**) was not blocked by competing, unlabeled  $D_3$ -selective agents, suggesting non-selective labeling *in vivo*.<sup>352</sup>

The cinnamide derivatives **418** and **419** (Figure 36)<sup>353,354</sup> are additional acrylamides with high  $D_3$  affinity ( $K_i = 5.0$  and 4.0 nM) and  $D_3/D_2$  selectivity (100- and 130-fold). Therefore, there is nearly no difference on the  $D_3$  affinity between the tetrahydroisoquinoline **418** and benzazepine **419**. It was further found that these compounds are ≥100-fold  $D_3$ -selective over more than 60 other receptors and ion channels. Compound **418** readily entered the CNS *in vivo* and showed favorable PK properties (e.g., **418** is 77% orally bioavailable with an elimination half-life of 5.2 h).

**3.3.6. [<sup>18</sup>F]- and [<sup>11</sup>C]-Containing  $D_3$  Receptor Radiotracers.** As described in Figure 36, earlier developed radioligands for imaging  $D_3$  receptors lacked sufficient  $D_3$  receptor selectivity and brain penetration; therefore, bioavailable  $D_3$  subtype selective tracers are highly needed to elucidate its physiological role.<sup>270b</sup>

Gmeiner et al. developed several fluorine-containing  $D_3$  receptor ligands (Figure 37), among which 2-fluoropyridine-substituted benzamides **420** and **421** displayed high  $D_3$  affinity ( $K_i = 0.37$  and 0.45 nM) and  $D_3/D_2$  (73- and 30-fold) selectivity.<sup>355</sup> This profile makes their corresponding [<sup>18</sup>F]-radiolabeled compounds useful for imaging study. In addition, similar fluorinated pyridinylphenyl amides (e.g., **422** and **423**) were designed using CoMFA and CoMSIA methods. These biphenyl amides had high  $D_3$  potency ( $K_i = 0.52$ –1.6 nM), with good  $D_3/D_2$  selectivity (110- and 210-fold).<sup>356</sup> However, biodistribution studies of the radiolabeled tracers [<sup>18</sup>F]-**422** and [<sup>18</sup>F]-**423** based on autoradiography of rat brain revealed accumulation in the cerebral ventricles that suggested inadequate distributional characteristics for their use as tracers for  $D_3$  receptor imaging *in vivo*.

Introducing a fluorine atom to the arylpiperazine portion, instead of the aryl amide component, as in compounds **420**–

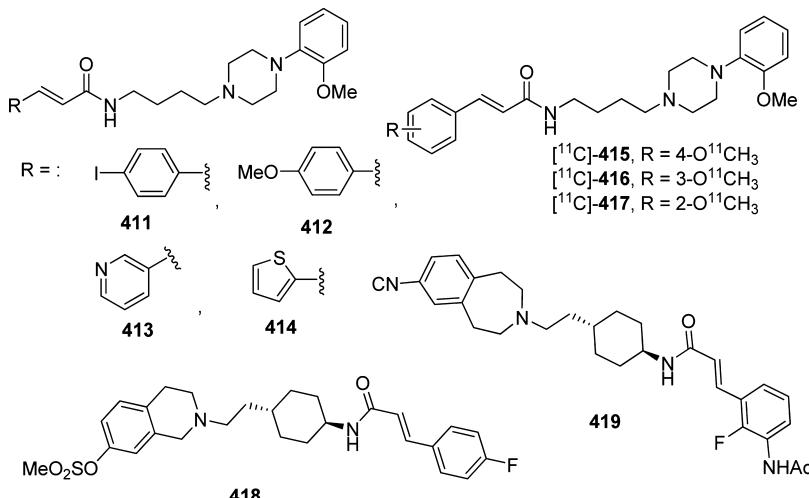


Figure 36. Aryl acrylamide analogs.

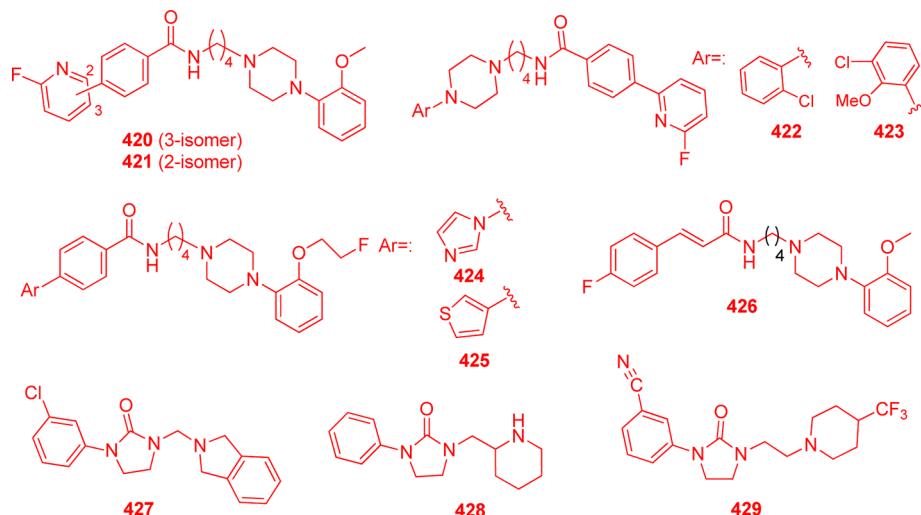


Figure 37.  $[^{18}\text{F}]$ - and  $[^{11}\text{C}]$ -containing  $\text{D}_3$  receptor radiotracers.

423, provided novel fluorinated compounds 424 and 425 (Figure 37).<sup>357–359</sup> Compound 424 had a  $\text{D}_3 K_i$  of 2.95 nM, but with only 2-fold  $\text{D}_3/\text{D}_2$ -selectivity.<sup>357</sup> Compound 425 also had high  $\text{D}_3$  affinity ( $K_i = 0.17$  nM) as well as greater  $\text{D}_3/\text{D}_2$ -selectivity (163-fold). Corresponding radiolabeled  $[^{18}\text{F}]\text{-425}$  was prepared as a potential candidate for *in vivo* PET imaging studies; however, it showed high lipophilicity ( $\log P, 4.67$ ), low brain uptake, and relatively high nonspecific binding.<sup>358</sup> The cinnamoyl carboxamide 426 had high  $\text{D}_3$  affinity ( $K_i = 0.34$  nM) and >60-fold  $\text{D}_3/\text{D}_2$  selectivity, as well as 15-fold  $\text{D}_3/\alpha_1$  selectivity.<sup>360</sup> The lipophilicity ( $\log P$ ) of  $[^{18}\text{F}]\text{-426}$  as a measure of blood–brain barrier permeability was 2.07, suggesting sufficient brain uptake when applied *in vivo*. Preliminary CNS distribution studies with  $[^{18}\text{F}]\text{-426}$  based on autoradiography of rat brain after intravenous injection revealed selective uptake in striatum and cortex, but not in other  $\text{D}_3$ -rich receptor regions, such as the nucleus accumbens or islands of Calleja. The *in vivo* PK characteristics of this ligand need to be elucidated further.<sup>360</sup>

Meanwhile, several potential  $[^{11}\text{C}]$ -radiotracers bearing an *N*-phenylimidazolidin-2-one scaffold have been explored (Figure 37).<sup>361–364</sup> Compound 427 showed a  $K_i$  value of 2.5 nM,  $\text{D}_3/\text{D}_2$ -selectivity of 40-fold, and human  $\text{D}_3/\text{hERG}$ -selectivity of ≥100-fold in a functional assay. In assays of intrinsic clearance in human and rat liver microsomes, this compound showed potency values of 8.9 and 36.9 mL/(min kg), indicating its tendency of rapid metabolic clearance.<sup>361</sup> These promising profiles led to further structural optimization, and two new analogs (428 and 429; Figure 37) with improved affinity and selectivity were identified. Despite their structural similarity, compound 428 was more potent than 429 at the  $\text{D}_2$  receptor and acted as a  $\text{D}_2$  partial agonist and  $\text{D}_3$  antagonist, with much lower affinity at  $\alpha_{1\text{B}}$  ( $K_i = 316$  nM) and  $\text{D}_1$  receptors ( $K_i = 5.0 \mu\text{M}$ ) and the hERG  $\text{K}^+$  transporter protein ( $\text{IC}_{50} = 15.8 \mu\text{M}$ ). PK analyses of compound 428 have shown a high brain/blood ratio of 5.5, with substantial brain concentrations (667 ng/g) after a single subcutaneously injected dose of 3 mg/kg, together with a  $T_{\text{max}}$  of 0.5 h, making it suitable for further testing in behavioral models.<sup>362</sup> The nitrile 429 had high human  $\text{D}_3$  potency ( $K_i = 1.0$  nM) and 100-fold  $\text{D}_3/\text{D}_2$ - and 1000-fold  $\text{D}_3/\text{hERG}$ -selectivity. This compound showed a high brain/blood ratio (6.4), with substantial concentrations in brain tissue (258 ng/g) after a dose of 1 mg/kg (i.v.), with a moderate

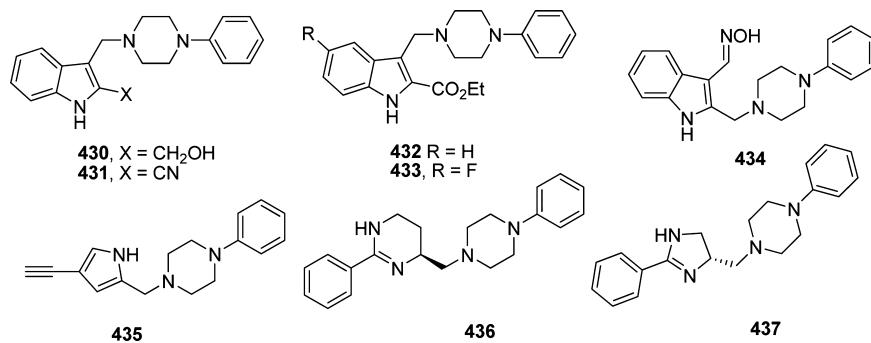
distribution volume ( $V_d, 5.4 \text{ L/kg}$ ), together with a reasonable half-life ( $T_{1/2}, 1.7 \text{ h}$ ). These characteristics supported consideration of this compound as a potential PET  $\text{D}_3$  radioligand. To this end, the radiolabeled derivative, [*cyanato* $^{11}\text{C}$ ]-429, was prepared for *in vivo* imaging; however, it failed to produce an anatomically coherent PET signal in pig or monkey.<sup>364</sup>

### 3.4. $\text{D}_4$ Receptor-Selective Ligands

Similar to the study of agents selective for  $\text{D}_2$  and  $\text{D}_3$  receptors, substantial efforts toward  $\text{D}_4$  receptor have also progressed on the basis of the hypothesis that the  $\text{D}_4$  receptor is likely involved in a number of diseases, including schizophrenia, ADHD, and erectile dysfunction (ED). As mentioned earlier, apomorphine is a pan-DA receptor agonist and is efficacious in ED. However, it showed an adverse PK profile and unwanted effects (particularly nausea, emesis, and hypotension). To explore the hypothesis that erectile and adverse effects may be mediated by receptor targets of this drug other than the  $\text{D}_4$  receptor, selective  $\text{D}_4$  receptor agonists and antagonists are highly needed. As highlighted by Gueiffier and Gmeiner,<sup>365,366</sup> the major structural pharmacophores for reported  $\text{D}_4$  receptor-selective ligands include arylpiperazines or arylpiperidines (connected to a lipophilic appendage through an appropriate linkage) and benzodiazepines.

**3.4.1. Piperazines, Piperidines, and Their Derivatives.** Molecular modeling studies of  $\text{D}_4$ -selective ligands indicate that pharmacologically effective  $\text{D}_4$  ligands should contain a pharmacophore with two aromatic rings and a basic nitrogen with optimal separation by a linker.<sup>367–370</sup> This conclusion, supported by other SAR analyses of earlier  $\text{D}_4$  ligands, has effectively guided the design of new  $\text{D}_4$ -selective ligands with a wide range of selectivity profiles. It has to be noted that such a structural feature can be found in many  $\text{D}_2$  and  $\text{D}_3$  receptor ligands as well, but the linker between the aromatic appendage and basic nitrogen in  $\text{D}_4$  receptor ligands appears to be shorter, usually one or three carbon atoms long.<sup>366</sup>

**3.4.1.1. Phenylpiperazines Connected with an Arylmethyl Appendage.** This series of compounds feature a nonsubstituted phenylpiperazine connected to an indole or its analogs through a methylene linker. The electrostatic property of the indole component was evaluated by introducing electropositive (430) or electronegative (431) groups at C-2 of the indole moiety

**Figure 38.** Phenylpiperazinylmethylindole analogs.

(Figure 38). Interestingly, these modifications had little effect on D<sub>4</sub> affinity ( $K_i = 0.66$  and  $0.76$  nM, respectively) or selectivity over other DA receptors (micromolar  $K_i$  at D<sub>1</sub>, D<sub>2</sub>, and D<sub>3</sub>). The carboxylate 433, with two electronegative substituents on the indole, also had only slightly reduced D<sub>4</sub> affinity. The regioisomer 434, with an oxime group on the indole C-3 position, also displayed high D<sub>4</sub> affinity ( $K_i = 0.50$  nM) and selectivity. All of these indoles have D<sub>4</sub> partial-agonist effects, yielding 32%–53% of the activity of the full D<sub>4</sub> agonist quinpirole in a mitogenesis assay.<sup>371–373</sup>

It was found that replacing the indole moiety of compounds 430 and 431 with a pyrrole element retained D<sub>4</sub> receptor activity (Figure 38, Table 14). The representative ethynylpyrrole

**Table 14. Binding Properties of Compounds at DA Receptors**

| compd | $K_i$ (nM)          |                 |                                      |
|-------|---------------------|-----------------|--------------------------------------|
|       | hD <sub>2long</sub> | hD <sub>3</sub> | hD <sub>4,4</sub>                    |
| 430   | 2100                | 3300            | 0.66                                 |
| 431   | 4900                | 2500            | 0.76                                 |
| 432   | 5000                | 3800            | 1.9                                  |
| 433   | 22000               | 15000           | 1.5                                  |
| 434   | 8800                | 3700            | 0.50                                 |
| 435   |                     | 850             | 5.9 (EC <sub>50</sub> <sup>a</sup> ) |
| 436   | 25000               | 13000           | 1.5                                  |
| 437   | 10000               | 7100            | 0.95                                 |

<sup>a</sup>EC<sub>50</sub> for agonists measured in FLIPR assays using HEK-293 cells cotransfected with human D<sub>4,4</sub> receptor and G-protein G<sub>q/5</sub>.

role 435 exerted selective D<sub>4</sub> binding and substantial *in vitro* partial agonistic efficacy (66%; EC<sub>50</sub>, 5.9 nM). The acetylene substructure may compensate the impact of the lower electronic property of the pyrrole moiety, compared to benzimidazoles and indoles.<sup>374</sup> Tetrahydropyrimidine 436 and dihydroimidazole 437 can be viewed as bioisosteres of conformationally restricted benzamides; their D<sub>4</sub> affinity and activity were dependent on their stereochemistry. The dihydroimidazole 437 and tetrahydropyrimidine 436 had high D<sub>4</sub> affinity ( $K_i = 0.95$  and  $1.5$  nM) with 42% and 83% intrinsic partial agonist activity, respectively.<sup>375,376</sup>

**3.4.1.2. Methoxyphenylpiperazines Connected with an Arylmethyl Appendage.** Steward and co-workers recently prepared several series of phenyl- or heteroaryl-piperazines connected to the benzimidazole or acetamide moieties via a linker. In the benzimidazole series (438–440, Figure 39), a variety of substituted phenyl or heteroaryl groups are used as the aryl component in the critical arylpiperazine pharmacophore. Most of these compounds have good affinity and

selectivity at the D<sub>4</sub> receptor, suggesting that the aryl or heteroaryl groups in the aryl/heteroarylpirperazine component do not play an important role in receptor binding. However, the EC<sub>50</sub>s of high affinity do not correlate well with the intrinsic affinity for these ligands. For example, the *o*-chloro analog 438 produces a partial response (43% of 10 μM DA) with a potent EC<sub>50</sub> of 1 nM in an assay using HEK-293 cells cotransfected with human D<sub>4,4</sub> receptor and G<sub>q/5</sub>, and the 2-methoxy analog 439, with an EC<sub>50</sub> of 5.6 nM, is also a potent D<sub>4</sub> partial agonist, producing approximately 50% of the response of DA.<sup>377</sup>

Shifting one of the nitrogen atoms in the imidazole fragment attached to the fused phenyl ring led to compounds 441–443 (Figure 39, Table 15).<sup>378</sup> These compounds retained high D<sub>4</sub> potency (human D<sub>4</sub>  $K_i = 3.6, 1.4, 4.7$ , and  $1.9$  nM, respectively) and showed D<sub>4</sub> antagonist activity. Further, replacement of the benzimidazole component in compound 439 with pyrro[2,3]-pyrimidine, imidazo[1,2-*c*]-, pyrrolo[2,3-*d*]-, or pyrrolo[3,2-*d*]-pyrimidine moieties generated several additional analogs (Figure 39). Among them, the pyrrolo[2,3-*d*]pyrimidine 444 and pyrrolo[2,3-*d*]pyrimidin-4-one 445 showed high D<sub>4</sub> affinity ( $K_i = 1.9$  and  $2.4$  nM).<sup>379</sup> Even higher affinity was found in compounds 446–449, where one nitrogen atom was shifted to the bridge of the appendage component. The D<sub>4</sub>  $K_i$  values of these compounds were  $2.8, 0.25, 0.33$ , and  $0.94$  nM, respectively, and all were nearly inactive at D<sub>3</sub> receptors.<sup>380</sup> These compounds were further found to be D<sub>4</sub> antagonists or weak partial agonists. The 2-methoxyphenyl substituted analog 446 showed substantial agonist efficacy in a mitogenesis model and in a GTP $\gamma$ S binding test, with EC<sub>50</sub> values of  $3.0$  and  $4.5$  nM, respectively. This compound also induced penile erection *in vivo* when administered to rats.<sup>380</sup>

With an N-phenyl or a pyridinyl substituted pyrazole moiety as the appendage, instead of the previously described bicyclic congeners (Figure 39, Table 15), compounds 450 and 451 were potent and selective as well at the D<sub>4</sub> receptor ( $K_i = 0.44$  and  $0.28$  nM). Other N-substituents, or changing the pyrazole ring to a triazole moiety, reduced D<sub>4</sub> affinity.<sup>381</sup> These compounds all were D<sub>4</sub> partial agonists with only moderate intrinsic activity.

Compound 452, bearing a non-N-containing framework, retained high D<sub>4</sub> affinity ( $K_i = 0.40$  nM).<sup>382</sup> Compared to full agonist quinpirole, compound 452, showed partial agonist efficacy in both the mitogenesis model and GTP $\gamma$ S binding and induced penile erection in male rats over a wide range of doses ( $0.1$ – $50$  μg intracerebroventricularly or  $1$ – $200$  μg/kg subcutaneously). These findings suggested advantages of such azulene derivatives over apomorphine.<sup>382</sup>

As described earlier,<sup>315</sup> bisubstituted ferrocenes were used to develop bivalent D<sub>3</sub> receptor ligands through a Click

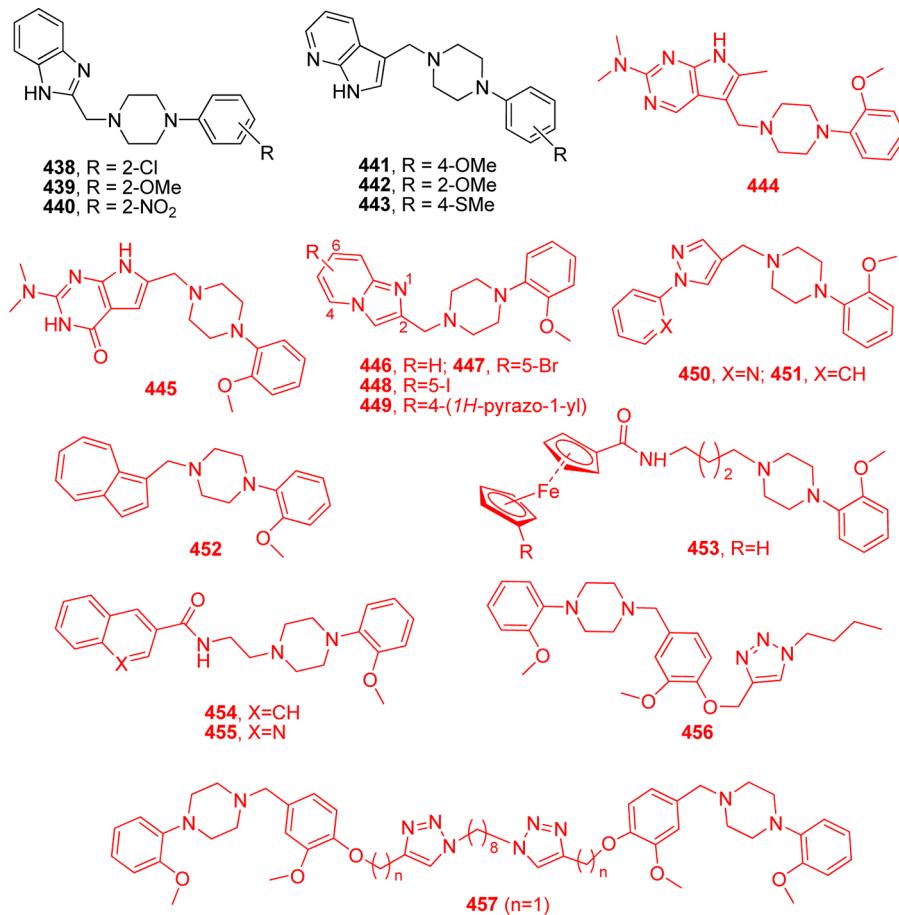


Figure 39. Methoxyphenylpiperazine analogs..

Table 15. Binding Properties of Compounds at DA Receptors

| compd | hD <sub>2long</sub> | K <sub>i</sub> (nM) |                                       |
|-------|---------------------|---------------------|---------------------------------------|
|       |                     | hD <sub>3</sub>     | hD <sub>4,4</sub>                     |
| 438   |                     |                     | 7.2 (EC <sub>50</sub> <sup>a</sup> )  |
| 439   |                     |                     | 12.4 (EC <sub>50</sub> <sup>a</sup> ) |
| 440   |                     |                     | 3.9 (EC <sub>50</sub> <sup>a</sup> )  |
| 441   | 10000               | 10000               | 3.6                                   |
| 442   | 438                 | 668                 | 1.4                                   |
| 443   | 10000               | 4507                | 4.7                                   |
| 444   | 190                 | 20000               | 1.9                                   |
| 445   | 130                 | 960                 | 2.4                                   |
| 446   | 990                 | 3900                | 2.8                                   |
| 447   | 130                 | 800                 | 0.25                                  |
| 448   | 73                  | 72                  | 0.33                                  |
| 449   | 590                 | 1000                | 0.94                                  |
| 450   | 40                  | 72                  | 0.44                                  |
| 451   | 11                  | 35                  | 0.28                                  |
| 452   | 33                  | 82                  | 0.40                                  |
| 453   | 110                 | 6.5                 | 0.52                                  |
| 454   | 890                 | 66                  | 2.32                                  |
| 455   |                     |                     | 25                                    |
| 456   | 16                  | 31                  | 5.4                                   |
| 457   | 63                  | 320                 | 3.3                                   |

<sup>a</sup>EC<sub>50</sub> for agonists measured in FLIPR assays using HEK-293 cells cotransfected with human D<sub>4,4</sub> receptor and G-protein G<sub>q/11</sub>.

chemistry protocol. The monomer 453 showed high D<sub>4</sub> affinity and selectivity (human D<sub>4</sub> K<sub>i</sub> = 0.52 nM), with 12.5- and 212-fold D<sub>4</sub>/D<sub>3</sub> and D<sub>4</sub>/D<sub>2long</sub> selectivity.

Naphthalylcarboxamides or naphthylsulphonamides connected to 2-methoxy phenylpiperazine through an ethylene linker also are potent D<sub>4</sub> receptor ligands. Representative compound 454 had a D<sub>4</sub> K<sub>i</sub> value of 2.3 nM, with a D<sub>4</sub>/D<sub>3</sub>-selectivity of 29-fold. The D<sub>4</sub>/D<sub>3</sub> selectivity was highly dependent on the length of the linker, and compounds with a butylene linker were generally D<sub>3</sub>-selective.<sup>383</sup> The quinoxaline analog 455 was 11-fold less potent than 454 (D<sub>4</sub> K<sub>i</sub> 25 nM). Compound 455 behaved as an inverse agonist,<sup>384</sup> and both compounds 454 and 455 were nearly equipotent at the 5-HT<sub>1A</sub> receptor (K<sub>i</sub> = 1.69 and 1.5 nM).

During development of D<sub>2</sub> receptor bivalent ligands such as 457 through a Click procedure, it was found that the length of the linker connecting triazole and trisubstituted phenyl moieties was crucial for the receptor affinity and selectivity within the D<sub>2</sub>-like family. Only the short linker preferred the D<sub>4</sub> receptor; for example, compound 457 with a one-methylene unit linker displayed a K<sub>i</sub> value of 3.3 nM at the human D<sub>4</sub> receptor and K<sub>i</sub> values of 63 and 320 nM, respectively, at the D<sub>2long</sub> and D<sub>3</sub> receptors. Interestingly, the monomer 456 showed moderate D<sub>4</sub> potency (K<sub>i</sub> = 5.4 nM) and selectivity.<sup>165</sup>

**3.4.1.3. Chlorophenyl Piperazine Derivatives Connected with an Arylalkyl Appendage.** Several 4-chloro- or 2,3-dichloro-substituted phenylpiperazine derivatives also were potent and selective at the D<sub>4</sub> receptor. The pyrazolo[1,5-*a*]pyridines 458–461 (Figure 40) had high D<sub>4</sub> affinity and

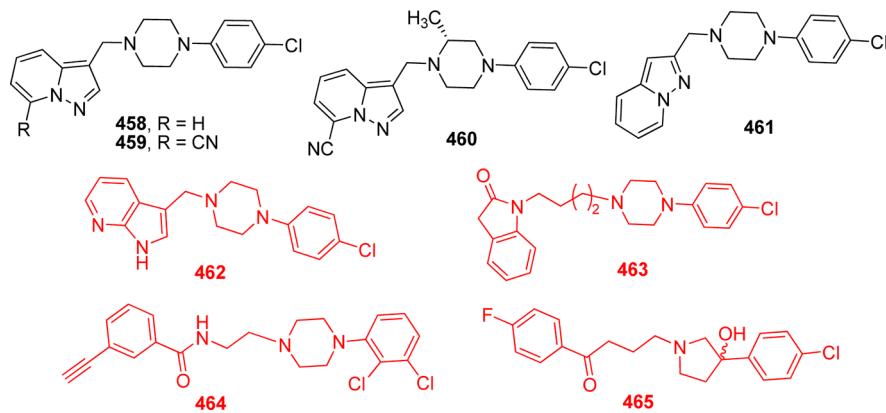


Figure 40. Chlorophenyl piperazine analogs..

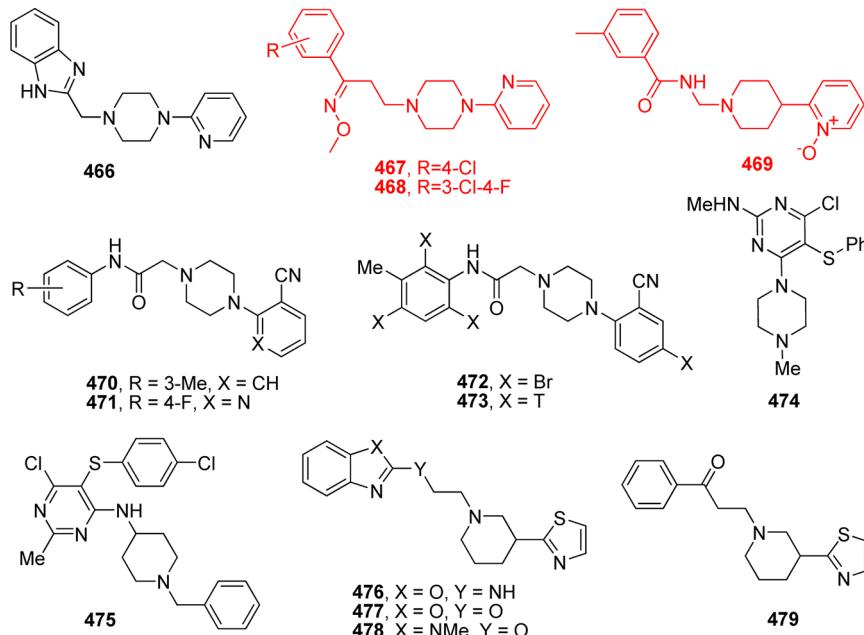


Figure 41. Heteroaryl piperazine analogs..

functional potency.<sup>385,386</sup> It was suggested that substitution patterns on the pyrazolo[1,5-a]pyridine component or the piperazine core in these agents contributed to their efficacy as D<sub>4</sub> agonists.<sup>385</sup> Compound 458 was a potent D<sub>4</sub> partial agonist possessing a K<sub>i</sub> value of 3.1 nM). Introduction of a cyano substituent at C-7 of the pyrazolo[1,5-a]pyridine component provided compound 459 with even greater D<sub>4</sub> affinity and intrinsic agonistic efficacy, making it the most potent D<sub>4</sub> partial-agonist ligand in this series.<sup>385</sup> Bearing a methyl group in the piperazine core, the R-isomer of 460 (D<sub>4</sub> IC<sub>50</sub> = 6.2 nM) was 5-fold more potent than the S-isomer.<sup>386</sup> Compound 461, a regioisomer of the partial agonist 458 (Figure 40), also was potent and selective at the D<sub>4</sub> receptor, but it acted as a pure antagonist.<sup>387,388</sup> Relocation of the bridge nitrogen atom in the pyrazolo[1,5-a]pyridine subcomponent generated the azaindole 462, which had excellent PK properties and showed low risk of adverse effects. However, this compound was ineffective clinically for the treatment of acutely psychotic patients,<sup>389</sup> although it may have the potential to treat amyotrophic lateral sclerosis (ALS).<sup>390</sup>

Several lactam (cyclic amide) derivatives bearing various phenylpiperazinylbutyl side chains attached to the amide

nitrogen showed variant affinity and selectivity within the D<sub>2</sub>-like receptor family.<sup>391</sup> For example, compound 463 exhibited extraordinarily high affinity to human D<sub>4</sub> receptors, with a K<sub>i</sub> value of 40 pM, and acted as a D<sub>4</sub> antagonist. This compound has high selectivity of 43,000-fold for D<sub>4</sub> over D<sub>3</sub> receptors.

In the course of development of D<sub>3</sub>-selective compounds, substituted benzamides connecting to 2,3-dichlorophenylpiperazine through an alkyl linker with variant lengths were developed (Figure 40). Those with a relatively long alkyl linking chain (especially with four methylene units) showed high D<sub>3</sub> affinity and selectivity, whereas short linkers led to D<sub>4</sub> receptor potency and selectivity. Representative compound 464, bearing a two-methylene chain, had K<sub>i</sub> values of 0.97, 50, and 120 nM at the D<sub>4</sub>, D<sub>3</sub>, and D<sub>2long</sub> receptors and acted as a D<sub>4</sub> partial agonist.<sup>394</sup>

The pyrrolidine 465 is an analog of haloperidol with moderate D<sub>2</sub> affinity and low risk of adverse extrapyramidal effects in laboratory animals. Enantiomeric separation of racemic 465 revealed that most of the binding affinity at DA and 5-HT receptors resides in the (+)-isomer, which showed 14-fold higher affinity for D<sub>4</sub> (K<sub>i</sub> = 3.6 nM) than for D<sub>2</sub> receptors. In animal models of antipsychotic efficacy, (+)-465

was efficacious, with an  $ED_{50}$  of approximately 1.6 mg/kg, intraperitoneally, without inducing catalepsy in rats at doses of 3–4 mg/kg.<sup>392</sup>

#### 3.4.1.4. Heteroaryl Piperazine or Piperidine Derivatives.

Replacement of the phenylpiperazine moiety with a 2-pyridinylpiperazine component led to several novel compounds that retained  $D_4$  receptor affinity and selectivity. The benzimidazole **466** (Figure 41) was a  $D_4$  partial agonist of moderate potency ( $EC_{50}$ , 12 nM), showing 61% of the intrinsic activity of 10  $\mu$ M DA. This compound also elicited penile erection in rat ( $ED_{75}$  = 30 nmol/kg) without inducing abnormal behaviors or emesis in this or other species.<sup>393</sup> Bioisosteric substitution of the benzimidazole moiety with a methylene-oxime component yielded analogs **467** and **468** (Figure 41), which had favorable PK profiles and good oral bioavailability in rat and dog. Compound **467** induced a rat penile erection model similar to that induced by apomorphine.<sup>394</sup> *N*-Oxidation of the pyridine ring in the (2-pyridinyl)piperidine fragment of these compounds provided an alternative pharmacophore that retained structural requirements for  $D_4$  receptor activation.<sup>395</sup> The representative compound **469** (ABT-670) exhibited nearly full  $D_4$  agonist activity and had oral bioavailability of 68%–91% in rat, dog, and monkey. It induced erections in rats without emesis or adverse cardiovascular effects and, thereafter, was selected for further toxicological assessment evaluation as a candidate treatment for erectile dysfunction.<sup>395</sup>

Substitution on the pyridine ring or replacing such component with substituted phenyl moieties led to new  $D_4$ -active compounds **470** and **471**, which retained high  $D_4$  affinity but with decreased intrinsic agonist activity.<sup>396</sup> Compound **470** induced penile erection and showed improvement in cognitive functioning in rats.<sup>397</sup> As its close analog, compound **473** showed similar high  $D_4$  affinity. Its radiolabeled version [<sup>3</sup>H] **473** was prepared by reaction of its brominated precursor **472** with tritium gas and has been explored as a selective  $D_4$  agonist radiotracer.<sup>398</sup> It performed well in a saturation binding assay with human  $D_4$  receptor transfected HEK-293 cells ( $K_d$ , 4.0 nM).

Nishimura et al.<sup>399</sup> investigated the effect of the conformations of several structurally rigid pyrimidinylpiperazines on  $D_4$  receptor affinity. Representative compounds **474** and **475** differed 109-fold in  $D_4$  affinity ( $K_i$  = 250 versus 2.3 nM). The pyrimidine moiety can be viewed as a cyclic derivative of the amide component in compounds **470**–**473**. The major difference in potency between compounds **474** and **475** emphasizes the importance of free-rotation of the exocyclic amide moiety for  $D_4$  receptor interactions. Replacing the phenylpiperazine pharmacophore with a 3-(2-thiazoyl)-piperazinyl moiety as in **476** (Figure 41) had little effect on  $D_4$  affinity but increased intrinsic activity. Replacement of the benzimidazole function by a benzoxazole ring connecting to the piperidine template via a heteroatom linker yielded compounds **477** and **478** with high  $D_4$  potency (Table 16) and full agonism. The spatial orientation between the primary piperidine pharmacophore and the benzoxazole or benzimidazole accessory element thus appears to be crucial for  $D_4$  agonist potency and efficacy. Of note, **479**, with a benzoyl accessory component, also showed high  $D_4$  potency and efficacy.<sup>400</sup>

**3.4.1.5. Arylmethylpiperazine/Piperidine Derivatives.** Benzyl- or arylmethyl piperazines or piperidines connected to an amido moiety or its cyclic bioisosteres through a short linker showed good  $D_4$  potency and selectivity as well. Compounds

**Table 16. Binding Properties of Compounds at DA Receptors**

| compd           | hD <sub>2long</sub> | $K_i$ (nM)      |                      |
|-----------------|---------------------|-----------------|----------------------|
|                 |                     | hD <sub>3</sub> | hD <sub>4,4</sub>    |
| <b>458</b>      | 32000               | 5000            | 3.1                  |
| <b>459</b>      | 44000               | 26000           | 1.5                  |
| <b>460</b>      | 40000               | 11000           | 6.2                  |
| <b>461</b>      | 3400                | 5300            | 2.2                  |
| <b>462</b>      | 6100                | 29000           | 0.61                 |
| <b>463</b>      | 1747                | 1204            | 0.04                 |
| <b>464</b>      | 120                 | 50              | 0.97                 |
| (+)- <b>465</b> | 51.1                | 1069            | 3.6                  |
| <b>466</b>      |                     |                 | 12.4 ( $EC_{50}^a$ ) |
| <b>467</b>      |                     |                 | 37.6 ( $EC_{50}^a$ ) |
| <b>468</b>      |                     |                 | 148 ( $EC_{50}^a$ )  |
| <b>469</b>      |                     |                 | 89 ( $EC_{50}^a$ )   |
| <b>470</b>      |                     |                 | 7.5 ( $EC_{50}^a$ )  |
| <b>471</b>      |                     |                 | 3.8 ( $EC_{50}^a$ )  |
| <b>472</b>      |                     |                 | 113                  |
| <b>473</b>      |                     |                 | 4.0                  |
| <b>474</b>      |                     |                 | 250                  |
| <b>475</b>      |                     |                 | 2.3                  |
| <b>476</b>      |                     |                 | 15 ( $EC_{50}^a$ )   |
| <b>477</b>      |                     |                 | 24 ( $EC_{50}^a$ )   |
| <b>478</b>      |                     |                 | 28 ( $EC_{50}^a$ )   |
| <b>479</b>      |                     |                 | 7.5 ( $EC_{50}^a$ )  |

<sup>a</sup> $EC_{50}$  for agonists measured in FLIPR assays using HEK-293 cells cotransfected with human  $D_{4,4}$  receptor and G-protein  $G_{q\beta 5}$ .

**480**–**487** (Figure 42) are benzylpiperazin-ylsubstituted, conformationally constrained acetamides with high  $D_4$  affinity and selectivity. A variety of C-2 substituents in the indoline moiety are tolerant, and the  $D_4$  affinity is retained. 2-Methyl-substituted analogs give the best results. High  $D_4$  affinity is also observed on compounds **480**–**483**, possessing  $K_i$  values of 2–5 nM at the  $D_4$  receptor.<sup>401</sup> The R-isomers of **481** and **483** are potent at  $D_4$  receptors, but both lack agonist properties up to 10  $\mu$ M concentrations and, instead, showed dose-dependent reduction of *d*-amphetamine-induced locomotor activity in rats at doses of about 4 mg/kg and did not induce catalepsy.<sup>402</sup> Among tricyclic and bicyclic analogs designed to further rigidify the carboxamido moiety, compounds **484** and **485** were potent at  $D_4$  receptors ( $K_i$  = 5 and 4 nM) and showed 29- and 42-fold of  $D_4/D_2$  selectivity.<sup>403</sup> Similar  $D_4$  affinity and  $D_4/D_2$  selectivity were found on the conformationally constrained bicyclic acetamides **486** and **487**.<sup>404</sup> These mixed  $D_4/D_2$  profiles are similar to that of clozapine but the  $\alpha_1$  affinity was not observed. None of the preceding compounds showed  $D_4$  agonist activity in concentrations up to 10  $\mu$ M.<sup>404</sup>

Compounds **488** and **489** are pyrrolo[2,3-*b*]pyridine-derived benzylpiperazines (Figure 42) with high  $D_4$  affinity ( $K_i$  = 4.1 and 1.5 nM).<sup>405</sup> Compound **489** has also been radiolabeled with [<sup>18</sup>F]- and was found to be an inappropriate  $D_4$  receptor imaging agent by showing uniform regional brain distribution and a rapid washout in mice. The benzodioxanes **490** and **491** also have high  $D_4$  affinity (both  $K_i$  = 2 nM) and selectivity and show antagonist properties. They were inactive at the 5-HT<sub>2A</sub> receptor and have low affinities at  $\alpha_1$  and  $\alpha_2$  receptors.<sup>406</sup> Using a morpholine fragment as an isostere of the piperazine core, the resulting compounds **492**–**495** were prepared as potent  $D_4$  ligands ( $K_i$  = 2.9, 2.8, 2.0, and 4.5 nM).<sup>407</sup> Different substituents on the phenyl rings have little effect on  $D_4$  affinity.

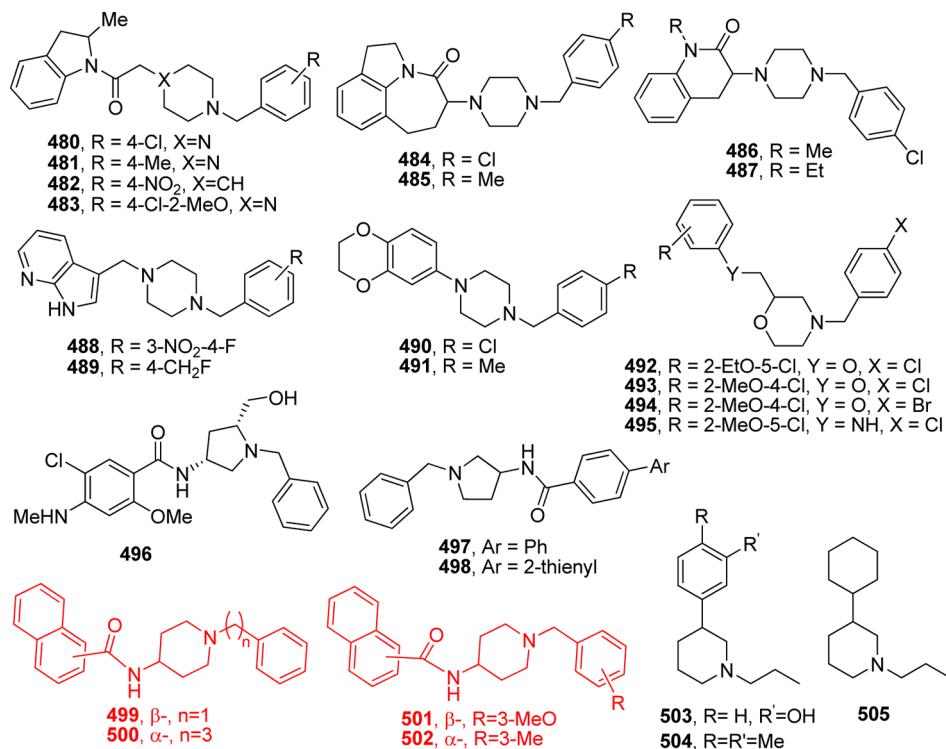


Figure 42. Arylmethyl piperazine/piperidine analogs.

The S-stereoisomer of **493** is slightly more potent than the racemate, and the *R*-isomer is inactive. Structural features of this series should be helpful in further development of D<sub>4</sub>-selective compounds.

Other compounds with major modifications on the primary piperazine core pharmacophore include **496–498** (Figure 42). Among these compounds, a benzylpiperazine template is replaced by a benzylpyrrolidine element. They had at least moderate potency at D<sub>2</sub>, D<sub>3</sub>, and D<sub>4</sub> receptors (Table 17). Compound **496** (*cis* isomer) had the highest D<sub>4</sub> affinity ( $K_i$  = 3.4 nM), as well as 10- and 16-fold selectivity over D<sub>2</sub> and D<sub>3</sub> receptors.<sup>408</sup> The N-biphenyl- (**497**) or 4-thienylphenyl- (**498**) amides had high D<sub>4</sub> potency (both  $K_i$  = 3 nM) and 280- and 327-fold D<sub>4</sub>/D<sub>2</sub> selectivity. They had even higher 5-HT<sub>2A</sub> affinity ( $K_i$  = 1.8 nM).<sup>409</sup> These properties suggest potential utility for the treatment of psychotic disorders.

A series of novel 1- and 2-naphthamides showed varied selectivity for D<sub>4</sub> and 5-HT<sub>2A</sub> over D<sub>2</sub> receptors.<sup>410,411</sup> In general, *N*-(1-aryalkylpiperidin-4-yl) carboxamides had higher affinity than corresponding *N*-(4-aryalkylaminopiperidin-1-yl)carboxamide analogs (Figure 42). A benzyl moiety in position 1 of the piperidine ring in 2-naphthamide-containing compounds appears to be the best choice for interaction with D<sub>4</sub> and 5-HT<sub>2A</sub> receptors; for example, representative compound **499** had  $K_i$  values of 11 and 44 nM for D<sub>4</sub> and 5-HT<sub>2A</sub> receptors, respectively. Increasing the linker length between the phenyl ring and the basic nitrogen led to decreased affinity for both receptors. The most potent D<sub>4</sub> ligand of the 1-naphthamide series is compound **500**, containing a phenylpropyl moiety and possessing moderate D<sub>4</sub> ( $K_i$  = 63 nM) and lower 5-HT<sub>2A</sub> affinity ( $K_i$  = 50 nM).<sup>410</sup>

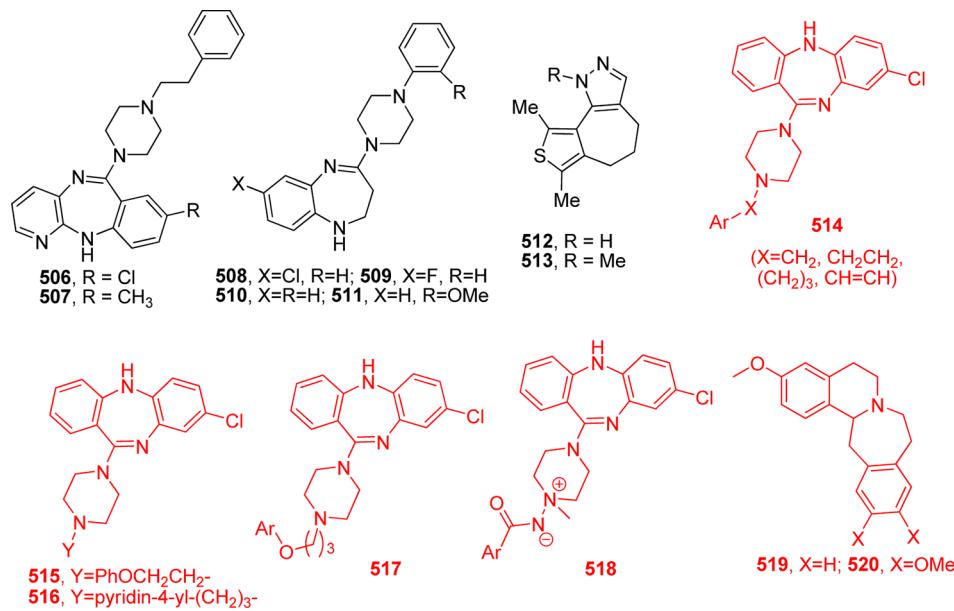
In addition, the effect of substituted benzyl groups on D<sub>2</sub>, D<sub>4</sub>, and 5-HT<sub>2A</sub> receptor affinity was evaluated. A halogen, methoxy, or methyl substituent in position 3 or 4 of the benzyl group enhanced D<sub>4</sub> affinity.<sup>411</sup> Such compounds as **501**

Table 17. Binding Properties of Compounds at DA Receptors

| compd         | hD <sub>2long</sub> | $K_i$ (nM)      |                   |
|---------------|---------------------|-----------------|-------------------|
|               |                     | hD <sub>3</sub> | hD <sub>4,4</sub> |
| <b>480</b>    | 209                 | <i>a</i>        | 5.4               |
| <b>481</b>    | 188                 |                 | 3                 |
| <b>482</b>    | >10000              |                 | 2                 |
| <b>483</b>    | 273                 |                 | 3                 |
| <b>484</b>    | 116                 |                 | 5                 |
| <b>485</b>    | 209                 |                 | 4                 |
| <b>486</b>    | 133                 |                 | 4                 |
| <b>487</b>    | 21                  |                 | 4                 |
| <b>488</b>    | >10000              | 3283            | 4.10              |
| <b>489</b>    | >10000              | 990             | 1.48              |
| <b>490</b>    | 526                 | 1396            | 2                 |
| <b>491</b>    | 1212                | 2388            | 2                 |
| <b>492</b>    |                     |                 | 2.9               |
| <b>493</b>    |                     |                 | 2.8               |
| <b>494</b>    |                     |                 | 2.0               |
| <b>495</b>    |                     |                 | 4.5               |
| <b>496</b>    | 59                  | 37              | 3.4               |
| <b>497</b>    | 600                 |                 | 3                 |
| <b>498</b>    | 840                 |                 | 3                 |
| <b>499</b>    | >1000               |                 | 11                |
| <b>500</b>    |                     |                 | 63                |
| <b>501</b>    |                     |                 | 16                |
| <b>502</b>    |                     |                 | 11                |
| R- <b>503</b> |                     |                 | 397               |
| R- <b>504</b> |                     |                 | 4                 |

<sup>a</sup>Data is not available.

and **502** had D<sub>4</sub>  $K_i$  values of 16 and 11 nM, and 5-HT<sub>2A</sub>  $K_i$  values of 158 and 87 nM. Compounds **499–502** all were antagonists at both receptors.



**Figure 43.** Dibenzodiazepine analogs.

A series of novel *N*-*n*-propyl-3-(3-hydroxyphenyl)piperidine (3PPP) derivatives including compound **503** were found as the first  $D_3$  autoreceptor-selective agonist (Figure 42).<sup>412</sup> Its 3,4-dimethylated congener **504** had moderate  $D_4$  affinity ( $K_i = 10$  nM) and selectivity. *R*-**504** ( $K_i = 4$  nM) was 5-fold more potent than the *S*-isomer.<sup>413</sup> Interestingly, cyclohexylpiperidines (e.g., **505**) contained no aromatic rings, but displayed even higher  $D_4$  affinity than their aromatic analogs **503** and **504**, both of which acted as  $D_4$  partial agonists. The unique structures of these compounds indicate that  $\pi$ - $\pi$ -type interactions between the aromatic ring of the arylpiperidine ligands and the  $D_4$  receptor may not be essential for  $D_4$  affinity, whereas a simple hydrophobic attraction of the cyclohexyl ring, as in compound **505**, was beneficial to  $D_4$  receptor binding.<sup>414</sup>

**3.4.2. Dibenzodiazepines with  $D_4$  Agonist/Antagonist Activity.** Development of dibenzodiazepine analogs as  $D_4$  ligands has been stimulated by properties of the atypical and highly effective antipsychotic drug, clozapine, which has a dibenzodiazepine core structure and preferentially blocks the  $D_4$  receptor with somewhat greater potency than for the  $D_2$  receptor. Structural modifications of the clozapine molecule might yield compounds with improved  $D_4$  receptor activity, combined with specifically altered activities at other receptors. Replacing one of the phenyl groups in the dibenzodiazepine component of clozapine with a pyridinyl moiety yielded compounds **506** and **507** (Figure 43).<sup>415</sup> These compounds showed high  $D_4$  ( $K_i = 40$  and 37 nM), 17–22-times less  $D_2$  ( $K_i = 892$  and 635 nM), and moderate 5-HT<sub>2A</sub> ( $K_i = 103$  and 36 nM) affinities. It was found that compound **506** lacked cataleptic effects in rat but reduced immobility in the porsolt forced swimming test, suggestive of potential antidepressant activity.<sup>415</sup>

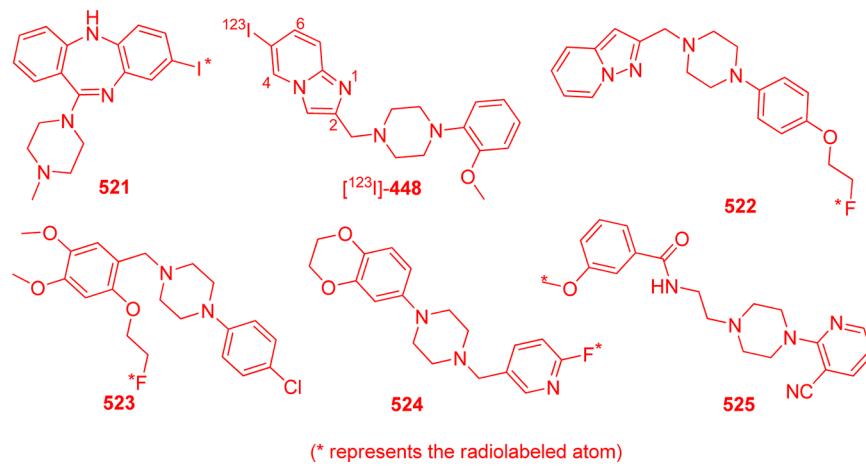
Benzodiazepines **508**–**511** were designed as debenzoclozapine analogs (Figure 43).<sup>416</sup> They have moderate  $D_4$  affinity ( $K_i = 10$ –30 nM) and selectivity and appear to be  $D_4$  partial agonists, in contrast to the antagonist properties of clozapine. In addition, compound **508** was inactive at 5-HT<sub>1A</sub> and 5-HT<sub>2A</sub> receptors; however, the fluoro-substituted analog **509** had moderate affinity at both the serotonin receptors ( $K_i = 48$  and 58 nM). Compound **510** showed some 5-HT<sub>2A</sub>/5-HT<sub>1A</sub>

selectivity ( $K_i = 52$  nM versus 105 nM), whereas compound **511** favored 5-HT<sub>1A</sub> over 5-HT<sub>2A</sub> receptors ( $K_i = 250$  versus 2250 nM).<sup>416</sup> Apparently, the affinity of these compounds at serotonin receptors is sensitive to substitution patterns on the phenyl rings.

Tricyclic compounds **512** and **513** (Figure 43) are additional novel clozapine analogs containing a cycloheptyl ring coupled with a pyrazole moiety to replace the diazepine unit of clozapine.<sup>417</sup> Notably, the phenyl group, which is fused to the diazepine core in clozapine and its analogs, also is replaced by a thiophenyl ring. These analogs can be viewed as denitrogenated clozapine derivatives and retained high  $D_4$  affinity ( $K_i = 12$  and 2 nM). Compound **512** was  $\geq 100$ -fold selective for  $D_4$  over several other cerebral receptors, whereas the *N*-methyl congener **513** had moderate  $D_2$  affinity ( $K_i = 176$  nM). It was further found that compound **512** lacked agonist activity at the human  $D_4$  receptor and acted as an antagonist in attenuating DA agonist-induced [<sup>35</sup>S]GTP $\gamma$ S binding.<sup>417</sup>

In addition, Taylor et al. also conducted extensive structural modifications on clozapine, with a focus on optimizing the *N*-methylpiperazine component.<sup>418</sup>–<sup>422</sup> They first modified the linkage of the piperazinyl-4-methyl to arylalkyl moieties with various alkyl chains. The resulting analogs, represented by **514**, were much less potent than clozapine at either  $D_4$  or 5-HT<sub>2A</sub> receptors.<sup>418</sup> However, compounds **515** and **516**, bearing a phenoxypropyl or pyridine-4-ylbutyl tail group attached to the piperazine component, displayed good affinity at both  $D_4$  or 5-HT<sub>2A</sub> receptors, similar to that of clozapine.<sup>419</sup> A similar profile was observed on analogs such as **517**, bearing various substituted phenoxypropyl tail groups.<sup>420</sup> Like clozapine, compounds **515**–**517** strongly blocked apomorphine-induced climbing in mice.<sup>419</sup>–<sup>421</sup> Aminimides such as **518** proved to be much less potent at  $D_4$  and 5-HT<sub>2A</sub> receptors than clozapine.<sup>422</sup> As analogs of  $D_1$ – $D_2$  agonist tetrahydroprotoberberines, the homo-C-congeners **519** and **520** showed moderate affinity but substantial selectivity for the  $D_4$  receptor. They had  $D_4$   $K_i$  values of 224 and 282 nM, and  $>10$   $\mu$ M at  $D_2$  and  $D_3$  receptors, respectively.<sup>108</sup>

**3.4.3. Imaging Ligands with  $D_4$  Receptor Selectivity.** The  $D_4$  receptor has drawn considerable attention due to being



**Figure 44.** Imaging ligands with D<sub>4</sub> receptor selectivity.

implicated in schizophrenia and erectile dysfunction. However, the lack of specific D<sub>4</sub>-receptor SPECT or PET radioligands for *in vivo* imaging limits understanding of its involvement in those disorders.<sup>385,386,270b</sup>

8-Iodo-11-(4-methylpiperazino)-5H-dibenzo[*b,e*][1,4]-diazepine (**521**, iozapine, Figure 44) was a reported potential D<sub>4</sub>-receptor ligand.<sup>423</sup> Its radiolabeled congeners [<sup>125</sup>I]-**521** and [<sup>123</sup>I]-**521** were prepared using an oxidative iodo-destannylation reaction. Biodistribution studies in male mice with 0.1 mL of [<sup>125</sup>I]-**521** (7–8 KBq) showed that there was no preferential uptake (per gram of tissue) in any brain region.<sup>423</sup> Studies in rabbits using [<sup>123</sup>I]-**521** injected 20 MBq showed that the brain retained the radioligand (75% of material initially taken up by brain remained at 3 h) longer than that in mice. Such results suggested that iozapine (**521**) might have the potential as brain imaging agent and as an experimental antipsychotic agent.<sup>423</sup> The iodide **448** was a highly potent D<sub>4</sub> receptor antagonist that could be tested as an antipsychotic agent.<sup>380</sup> Its radiolabeled derivative [<sup>123</sup>I]-**448** was prepared with a radiochemical purity exceeding 99%. However, *in vivo* evaluation of this SPECT ligand in baboon showed no brain uptake after intravenous injection (7.6 mCi) during 120 min scan acquisition.<sup>424</sup>

A series of fluoro-substituted analogs structurally derived from the aminomethyl-substituted pyrazolo[1,5-*a*]pyridine lead compound **458** (FAUC-113; Figure 44)<sup>385,386</sup> were synthesized and evaluated as high-affinity D<sub>4</sub> receptor ligands.<sup>425</sup> The *para*-(2-fluoroethoxy)phenylpiperazine derivative **522** had a D<sub>4</sub> K<sub>i</sub> of 13 nM and showed properties of inverse D<sub>4</sub>-agonism, with ≥1,000-fold selectivity for D<sub>4</sub> over D<sub>2</sub> and D<sub>3</sub> receptors.<sup>386</sup> The corresponding radioligand [<sup>18</sup>F]-**522** had high stability *in vitro* in human serum and log P values of 2–3. *In vitro* rat brain autoradiography showed that it bound selectively in distinct brain regions, including the dentate gyrus of hippocampus and other D<sub>4</sub>-rich areas. These findings supported [<sup>18</sup>F]-**522** as a potential PET radioligand for D<sub>4</sub> receptors.<sup>425</sup> Compound **523** is another fluorine-containing ligand that was potent and selective for D<sub>4</sub> receptors (K<sub>i</sub> = 1.7 nM).<sup>426</sup> Its radiolabeled derivative [<sup>18</sup>F]-**523** had an optimal log D<sub>7,4</sub> of 2.8 and was highly stable in human serum. It represents an additional promising D<sub>4</sub>-selective PET radioligand.

A series of 1-(2,3-dihydrobenzo[1,4]dioxin-6-yl)-4-(arylmethyl)piperazines also showed high D<sub>4</sub> affinity (K<sub>i</sub> = 1.1–15 nM) and selectivity.<sup>427</sup> The 2-fluoropyridine **524** was radiolabeled as [<sup>18</sup>F]-**524**; it showed an excellent binding pattern with a high selectivity and limited nonspecific binding in

*vitro*. Meanwhile, it also had a high stability and very high brain uptake *in vivo* with selective accumulation in hippocampus, cortex, colliculus, and cerebellum, as determined by *ex vivo* autoradiography. Therefore, this radiotracer might be a suitable D<sub>4</sub> radioligand for further *in vivo* imaging.<sup>427</sup>

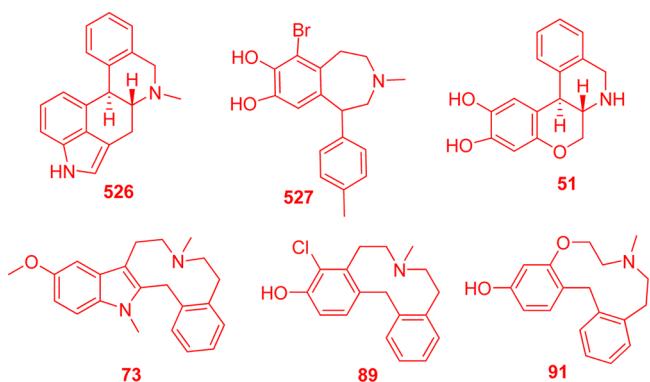
Alternatively, a series of aryl- and heteroarylpirperazines connected to an arylamide component through a two-methylene linker were developed with the potential of [<sup>11</sup>C]- or [<sup>18</sup>F]-radiolabeling. The 3-methoxybenzamide **525** showed a D<sub>4</sub> K<sub>i</sub> value of 1.52 nM and ≥100-fold selectivity over several off-target receptors.<sup>428</sup> [<sup>11</sup>C]-radiolabeling of the phenol precursor resulted in the 3-methoxybenzamide derivative [<sup>11</sup>C]-**525** (Figure 44). When the radiotracer was injected into Rhesus monkey, brain penetration as well as fast washout were observed, but with no evidence of selective labeling of D<sub>4</sub>-rich brain regions, except some accumulation in the retina, a CNS tissue that is rich in D<sub>4</sub> receptors. On the basis of these results, [<sup>11</sup>C]-**525** might yet have utility as a radioligand for studying the distribution and density of the D<sub>4</sub> receptor both *ex vivo* and *in vitro*.<sup>428</sup>

### 3.5. D<sub>5</sub> Receptor-Selective Ligands

A few studies have implicated the D<sub>5</sub> receptor in the pathophysiology of hypertension and drug abuse, making it of pharmacological interest.<sup>429–431</sup> However, discrimination between D<sub>1</sub> and D<sub>5</sub> receptors remains largely unexplored due to lack of highly selective ligands and of specific methods of biological characterization. Both D<sub>1</sub> and D<sub>5</sub> receptors belong to the same D<sub>1</sub>-like receptor family, but most of the few reported D<sub>5</sub> ligands are structurally similar to or originally born from known D<sub>1</sub> receptor agonists or antagonists.<sup>46,53,432</sup>

Most structural derivatives bearing typical D<sub>1</sub> receptor pharmacophores, such as arylbenzazepine, aporphine, dihydrexidine, and isoquinoline, displayed high D<sub>5</sub> receptor potency as well.<sup>46,53,432</sup> However, subtle structural adjustments in these D<sub>1</sub>-prototypes have led at least to slight D<sub>5</sub> preference (Figure 45).

Ergolines (e.g., cabergoline, lisuride, pergolide) are among the earliest anti-Parkinsonism drugs; they interact with both D<sub>2</sub>-like and D<sub>1</sub>-like receptors. The ergoline CY-208243 (**526**; Figure 45) had good D<sub>5</sub> affinity and 10-fold D<sub>5</sub>/D<sub>1</sub>-selectivity, but with similar D<sub>5</sub> and D<sub>4</sub> affinity.<sup>433</sup> Arylbenzazepines are typical, potent D<sub>1</sub>-like receptor ligands with similar high affinity at both D<sub>1</sub> and D<sub>5</sub> receptors. Some D<sub>5</sub> selectivity has been achieved in arylbenzazepines containing 1-(4-tolyl) and 6-



**Figure 45.** Dopamine D<sub>5</sub> receptor ligands.

bromo substituents. Among them, the best compound, **527**, had a D<sub>5</sub>  $K_i$  of 4.3 nM and was 4.4-fold D<sub>5</sub>/D<sub>1</sub>-selective.<sup>63</sup>

Among conformationally constrained D<sub>1</sub> receptor agonists derived from the tetracyclic dihydrexidine (compound **8**), doxanthrine (**51**) bearing an oxymethylene ether bridge had high D<sub>1</sub> affinity ( $K_i = 22$  nM), similar to that of the parent compound **8**. Surprisingly, racemic **51** was 14-fold D<sub>5</sub>/D<sub>1</sub>-selective and quite potent at D<sub>5</sub> receptors ( $K_i = 7.0$  nM; Tables 3 and 18). Functionally, (±)-**51** was a potent and full D<sub>1</sub>-like agonist at the cloned human DA receptors.<sup>80</sup>

**Table 18.** *In Vitro* Binding Data for Cloned Human Receptor Subtypes

| compd                      | D <sub>1</sub> | K <sub>i</sub> (nM) |                 |                 |                |  |
|----------------------------|----------------|---------------------|-----------------|-----------------|----------------|--|
|                            |                | D <sub>2</sub>      | D <sub>3</sub>  | D <sub>4</sub>  | D <sub>5</sub> |  |
| <b>526</b>                 | 417            | 92 <sup>a</sup>     | 92 <sup>a</sup> | 92 <sup>a</sup> | 40             |  |
| <b>527</b>                 | 19.3           | 1031                | >10000          | >10000          | 4.36           |  |
| <b>51</b><br>(doxanthrine) | 98             | 1910                | 390             | 90              | 7              |  |
| (+)- <b>51b</b>            | 8              | 2500                | <i>b</i>        |                 |                |  |
| (-)- <b>51b</b>            | 270            | 6800                |                 |                 |                |  |
| <b>73<sup>a</sup></b>      | 2.0            | 1.7                 | 3.78            | 21.5            | 0.23           |  |
| <b>89</b>                  | 0.83           | 4.0                 | 24.6            | 5.2             | 0.057          |  |
| <b>91</b>                  | 3.2            | 274                 | 1384            | 375             | 0.57           |  |

<sup>a</sup>For D<sub>2</sub>-like. <sup>b</sup>Data is not available.

The benz[d]indolo[2,3-g]azecine skeleton represents a novel structure that has yielded high binding affinity and antagonistic activity at D<sub>1</sub>-like receptors.<sup>96</sup> The benzazecine **73** with 11-methoxy and indole-N-methyl substituents was highly potent for all DA receptor types, but the highest affinity was found at the D<sub>5</sub> receptor ( $K_i = 0.23$  nM), which was 8.7-fold D<sub>5</sub>/D<sub>1</sub>-selective.<sup>100</sup> Replacement of the indole fragment in this compound with a phenyl or substituted phenyl retained high D<sub>1</sub>-like receptor affinity. Among such derivatives, dibenz[d,g]-azecine analogs **89** and **91** stood out, having high D<sub>5</sub> affinity, in addition to their high D<sub>1</sub> affinity. 4-Chloro-3-hydroxydibenz-[d,g]azecine (**89**) appears to be the most potent D<sub>5</sub> ligand reported so far, with a  $K_i$  value of 57 pM. It has 15-fold of D<sub>5</sub>/D<sub>1</sub> selectivity, and lower affinity at D<sub>2</sub>-like receptors ( $K_i = 4.0\text{--}25$  nM).<sup>104</sup> Compared to compound **89**, the oxa-azacycloundecene **91** was slightly less potent ( $K_i = 0.57$  nM). It was 5.5-fold D<sub>5</sub>/D<sub>1</sub> selective, and ≥50-fold selective over D<sub>2</sub>-like receptors.<sup>105</sup>

#### 4. CONCLUSION AND PERSPECTIVES

Recent years have brought remarkable developments in the chemistry, pharmacology, and neurobiology of DA systems in mammalian brain and particularly rapid gains of information about the molecular genetics and neuropharmacology of DA receptors. Despite these advances, many details of the three-dimensional structures of DA receptors at the atomic, electron-density, and molecular levels remain to be worked out. Moreover, the design and development of DA receptor-selective ligands remains largely empirical, quite conservative in following molecular precedents, somewhat unpredictable, and not ready for routine application of such techniques as computer-aided drug design. Nevertheless, current knowledge of the five major types of DA receptor peptides, including their genetic and molecular subtypes, and relatively selective neuroanatomical localization and dissimilar functions, has greatly stimulated interest in designing growing numbers of novel DA receptor agonists, partial agonists, and antagonists. Many of these novel molecules are aimed at basic scientific applications as experimental receptor probes or as imaging radiotracers. Many are also being considered for potential clinical applications to treat a remarkable range of neurological, psychiatric, and substance abuse disorders. These include Parkinson's disease, schizophrenia, mania and depression, alcohol and drug abuse, as well as attention and eating disorders, and sexual dysfunctions.

D<sub>1</sub> agonists have been investigated as potential treatments for Parkinson's disease and hypertension, and D<sub>1</sub> antagonists have been tested in the treatment of psychotic disorders, including schizophrenia, though both efforts have yielded only limited success.<sup>434,435</sup> *Fenoldopam*, a benzazepine analog, remains the only D<sub>1</sub>-selective compound to reach the pharmaceutical market in the US (1998) for short-term management of severe hypertension with or without deteriorating end-organ function.<sup>53</sup> Recent efforts to develop novel D<sub>1</sub> agonists and antagonists have focused mainly on the conformationally rigid benzazepine analogs and their polycyclic derivatives, leading to several agents in clinical development. These include *ecopipam* (SCH-39166; **6**), developed by Schering-Plough (now Merck) for management of obesity in 2000, and *dihydrexidine* (**8**), developed by Purdue University to treat drug dependence, Parkinson's disease, and schizophrenia; its polycyclic derivatives of interest include *dinapsoline* (**9**), *dinoxyline* (**48**), and *doxanthrine* (**51**). Dihydrexidine had advanced to phase II trials for treating moderate-to-severe Parkinson's disease, but poor pharmacokinetic profiles and adverse effects of the agent are likely to limit its clinical value.

The search for D<sub>2</sub> receptor agonists and antagonists continues to represent a major effort in DA drug development.<sup>434,435</sup> D<sub>2</sub> receptor agonists have been used to treat disorders that include Parkinson's disease, drug abuse, sexual dysfunction, restless leg syndrome, and other conditions. These drugs include the earlier ergoline family (e.g., *bromocriptine*, *cabergoline*, *lisuride*, and *pergolide*), and several nonergoline agonists (e.g., *apomorphine*, *piribedil*, *ropinirole*, and *rotigotine*). Newer D<sub>2</sub> agonists include novel aporphines, including monohydroxy- or catechol-protected congeners with improved oral bioavailability and longer duration than apomorphine. D<sub>2</sub> partial agonists have recently been pursued as potentially safer anti-Parkinsonian drugs; two such compounds, *pardoprunox* (**231**) and *aplindore*, are currently in phase II clinical trials. D<sub>2</sub> antagonists have long been applied successfully in the treatment

of schizophrenia, mania, and other major psychiatric disorders. Newer D<sub>2</sub> antagonists include structurally modified benzazepines and piperazines, some of which have proved to be useful antipsychotic agents with limited risk of adverse extrapyramidal neurological effects, typical of older neuroleptics. Clinically successful drugs of these types include *amisulpride*, *clozapine*, *iloperidone*, *lurasidone*, *olanzapine*, *paliperidone*, *quetiapine*, *risperidone*, and *ziprasidone* as well as the D<sub>2</sub> partial-agonist *ariPIPrazole*. In addition to the primary D<sub>2</sub> target, most of these agents also interact potently with serotonin, especially 5-HT<sub>2A</sub> and 5-HT<sub>1A</sub> receptors, and variably with muscarinic acetylcholine receptors, histamine H<sub>1</sub> receptors, or adrenergic α<sub>1</sub> receptors. Owing to their lower risk of adverse neurological effects on posture and movement as well as inconsistently demonstrated or marginal antipsychotic superiority, these agents have largely replaced older neuroleptics, including *chlorpromazine*, *fluphenazine*, and *haloperidol*. However, some of these agents (especially clozapine, olanzapine, and quetiapine) strongly promote weight gain and result in adverse metabolic effects, including type 2 diabetes mellitus, hyperlipidemia, and hypertension, with potentially severe long-term health consequences. Therefore, a more rational combination of activities at these various receptors needs to be addressed. Several compounds including *cariprazine* (in phase III), *ondansetron* (phase II), and *AM-831* (phase I), with more diversified receptor selectivity and potency are now in clinical trials.

Beyond the mixed D<sub>2</sub> and D<sub>3</sub> agonists, *pergolide*, *pramipexole*, *ropinirole*, and *rotigotine*, selective high-potency D<sub>3</sub> agonists entering clinical trials are rare; therefore, the net therapeutic benefit of D<sub>3</sub> receptor agonists/antagonists is still unclear.<sup>434,435</sup> The most studied D<sub>3</sub> partial agonist *BP-897* had entered clinical trials for the treatment of drug addiction, but the results are not promising. Another D<sub>3</sub> receptor partial agonist, *cariprazine*, also has antagonistic activity at the D<sub>2</sub> receptors and partial agonist effects at 5-HT<sub>1A</sub> receptors, and it is now in phase III trials sponsored by Gedeon Richter, Ltd. for the treatment of schizophrenia and bipolar disorders.

The most promising indication for D<sub>4</sub>-receptor activation is an impact on sexual arousal. D<sub>4</sub> receptor agonists, such as apomorphine, have been proposed as an alternative treatment of erectile dysfunction. Several D<sub>4</sub> receptor agonists (e.g., *ABT-724*, *CP-226269*) have been in clinical trials for this indication, but the results are not promising.<sup>434,435</sup>

A growing number of new antagonists of D<sub>3</sub> or D<sub>4</sub> receptors have been developed. Most share similar structural elements comprised of arylpiperazine or its analogs as the headgroup, a lipophilic appendage as the tail group, and an alkyl linker to connect them. These compounds show variable selectivity among D<sub>3</sub>, D<sub>4</sub>, and D<sub>2</sub> receptors, which appears to be related to the structures of the lipophilic appendage and the connecting linkage. Several such D<sub>3</sub> or D<sub>4</sub> receptor antagonists have advanced to clinical trials as potential antipsychotic drugs with low risk of extrapyramidal effects, including *abaperidone* (phase I), *ABT-925* (phase II), and *GSK-598809*.<sup>434,435</sup>

In general, recent efforts in medicinal chemistry and neuropharmacology have yielded substantial numbers of compounds with activity and selectivity at each of the major DA receptors. Benzazepine and piperazine or piperidine structural elements have remained dominant pharmacophores in these efforts, based on successful precedents dating back several decades. These pharmacophoric elements are usually connected with other functional groups, often heteroaryl

fragments, through a linker, based on the general concept of providing additional or accessory binding sites to improve selectivity for specific receptor proteins. However, remarkably few truly innovative chemical entities or new pharmacophoric principles can be identified among recently developed DA receptor-directed compounds. It has also been difficult to design compounds that lack interactions with other monoaminergic receptors, most of which bear considerable molecular homology to DA receptors. These interactions often include serotonergic, muscarinic, adrenergic, and histaminic receptors.<sup>436</sup>

Recent determination of the crystal structure of the human D<sub>3</sub> receptor complexed with the D<sub>2</sub>–D<sub>3</sub> antagonist eticlopride has revealed important features of the extracellular loops and probable binding pockets of the receptor proteins.<sup>437</sup> In particular, identification of an extracellular binding pocket that may interact with bitopic or allosteric ligands highlights the possibility of designing selective D<sub>2</sub> and D<sub>3</sub> receptor ligands.<sup>438,439</sup> However, in addition to the D<sub>3</sub> receptor, structural information of other receptors with which the reported ligands are likely to interact—especially D<sub>2</sub>, D<sub>4</sub>, 5-HT<sub>1A</sub>, and 5-HT<sub>2A</sub>—also is much-needed.

Another major challenge is to clarify the rationale for developing potent ligands selective at one DA receptor, since no currently available DA drug is so selective. Moreover, the hard-to-avoid secondary interactions of most dopaminergic agents may actually be desirable for disease treatment. Therefore, further efforts in both neurobiology and medicinal chemistry campaigns should focus on defining sites that are essential for primary therapeutic actions and for undesired effects. It is hoped that such knowledge will contribute to the more rational design of novel agents with improved efficacy and safety.

## AUTHOR INFORMATION

### Corresponding Author

\*E-mail: aozhang@simm.ac.cn. Tel: 86-21-50806035. Fax: 86-21-50806035.

### Notes

The authors declare no competing financial interest.

### Biographies



Na Ye was born in Wuhan, China in 1987. She graduated in Medicinal Chemistry from Shenyang Pharmaceutical University in 2008 and then became a graduate student under the supervision of Professor Ao Zhang at the Shanghai Institute of Materia Medica, Chinese Academy of Sciences. Her research topics focus on the design and synthesis of

novel benzazepines and aporphines with activities at dopamine receptors (D<sub>1</sub>, D<sub>2</sub>) and/or serotonin receptors (5-HT<sub>1A</sub>, 5-HT<sub>2A</sub>).



John L. Neumeyer received his B.S. degree from Columbia University and his Ph.D. degree in Medicinal Chemistry from the University of Wisconsin, Madison, in 1961. He began his career as a Research Scientist at Ethicon, Inc., a division of Johnson and Johnson, FMC Corp, and Arthur D. Little, Inc., joined the faculty at Northeastern University in 1969 as Professor of Medicinal Chemistry and Chemistry, and was appointed Matthews Distinguished Professor in 1980. He was the Co-Founder, Chairman, and Scientific Director of Research Biochemicals International (RBI) from 1980 to 1997, when the company was sold to Sigma/Aldrich. He has had a long and creative career in Medicinal Chemistry that is summarized in more than 280 refereed scientific publications and 20 U.S. Patents. In 2008 he was elected to the Hall of Fame of the Division of Medicinal Chemistry, ACS. At present, he continues his research activities at Harvard Medical School, the Alcohol and Drug Abuse Research Center at McLean Hospital, where he is a Lecturer in Psychiatry (Neuroscience) and Director of the Medicinal Chemistry Program. His current research interests include development of novel aporphines and benzazepines as D<sub>2</sub> and D<sub>1</sub> agonists and antagonists for the treatment of Parkinson's Disease, development of opioid ligands with mixed kappa/mu activity as potential medications for treatment of drug abuse, and development of brain imaging agents for PET, SPECT, and MRI.



Ross J. Baldessarini was born in western Massachusetts and graduated from Williams College in Chemistry in 1959. He completed his medical education at Johns Hopkins University in 1963 and continued his training in internal medicine, neuroscience, neuropharmacology, and psychiatry at Boston City Hospital, the National Institutes of Health, and Johns Hopkins Hospital. He holds honorary M.A. and D.Sc. degrees. In 1969, he moved to Massachusetts General Hospital (MGH) to found the Neuropharmacology Laboratory and directed

the Laboratories for Psychiatric Research (LPR) from 1983; he was named permanent Director of the LPR as well as the founding Director of a new Bipolar & Psychotic Disorders Program in 1988. He continued to direct the Neuropharmacology Laboratory at McLean Hospital's Mailman Research Center from 1977 to 2007. He has collaborated closely with Professor Neumeyer since the 1980s. In 1989 he also became Co-Director of Psychopharmacology and Psycho-pharmacology Training at the McLean Psychiatric Division of MGH, and he has directed that program since 1996. He founded the International Consortium for Bipolar Disorder Research in 1995 with colleagues from the United States, Canada, and Europe. Currently, he is Director of the Psychopharmacology Program at the McLean Division of Massachusetts General Hospital. He is also a tenured Professor of Psychiatry and Neuroscience at Harvard Medical School and Senior Consulting Psychiatrist at MGH.



Xuechu Zhen, Professor of Neuropharmacology at Shanghai Institute of Materia Medica (SIMM), Chinese Academy of Sciences, was formerly Associate Professor of the Department of Physiology and Pharmacology at the City University of New York. He received his doctoral degree in 1996 at University of Geneva, and then he moved to Medical College of Pennsylvania and Pennsylvania State University Medical School for postdoctoral training. He was appointed as a faculty member in 1999 at Drexel University Medical School prior to moving to City University of New York as an Associate Professor. Since 2006, he has had the position of Principal Investigator and Professor in SIMM and has headed the Laboratory of Neurotransmitter and related CNS diseases. Dr. Zhen's research interests include the following: (1) neurotransmitter receptor functional regulation and signaling transduction; (2) dopamine system and related disorders, such as Parkinson's disease and schizophrenia; (3) preclinical study of tetrahydroprotoberberine (THPBs) and derivative compounds in schizophrenia and drug abuse.



Ao Zhang was born in Sichuan, China, in 1969. He received his B.S. degree in Chemistry in 1992 from Sichuan Normal College, now Xihua Normal University. He was awarded his M.S. degree in Organic Chemistry in 1995 from Nankai University. He worked at the Shanghai Institute of Organic Chemistry for 2 years and then joined the predoctoral program of the same Institute in 1997 under the supervision of Professor Biao Jiang. After he was awarded his Ph.D. diploma in Organic Chemistry in 2000, he joined Professor Alan P. Kozikowski's Drug Discovery Group at Georgetown University Medical Center as a Postdoctoral Fellow. In 2002, he joined Professor John L. Neumeyer's Medicinal Chemistry Program as a Research Investigator at McLean Hospital, Harvard Medical School. He was promoted to Instructor at Harvard Medical School in 2003 and Assistant Director of the Medicinal Chemistry Program at McLean Hospital in 2004. He was awarded an *Alfred Pope Young Investigator Award* in 2004 and an *Adam Corneel Young Investigator Award* in 2005 from Harvard Medical School. In 2006 he received the *Hundred Talent Project* award from the Chinese Academy of Sciences and became a Professor of Medicinal Chemistry at Shanghai Institute of Materia Medica (SIMM). In 2011, he was awarded the *Distinguished Young Investigator Award* from the Chinese Natural Science Foundation. His research interests include the design and synthesis of novel small molecules as structural and functional probes for the diagnosis and treatment of brain disorders and cancers.

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