Dopamine D_1 Receptor Ligands: Where Are We Now and Where Are We Going

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Abstract: The dopamine (DA) D_1 receptor is the most highly expressed DA receptor subtype among the DA receptor family. Although the first DA D_1 receptor selective ligand SCH-23390 (**1**) was introduced more than two decades ago, clinically useful D_1 receptor selective ligands are rare. A renewed interest was ignited in the early 1990s by Nichols and Mailman who developed dihydrexidine (**27a**), the first high affinity full efficacy agonist for the D_1 receptor. Since then, a number of D_1 receptor agonists with full intrinsic activity, including A-86929 (**31a**), dinapsoline (**32a**), dinoxyline (**34a**), and doxanthrine (**35a**) were identified. These compounds all contain a conformationally rigid structure. However, the fate of such ligands for clinical use as treatments of Parkinson's disease and other related CNS disorders is not optimistic since the clinical trial with dihydrexidine (**27a**) was not successful. Further investigations on other compounds which are currently in the discovery stage will be crucial for determining the future of the D_1 receptor agonists. Med Res Rev, 29, No. 2, 272–294, 2009

Key words: dopamine; dopamine receptor; benzazepine; dihydrexidine; Parkinson's disease

1. DOPAMINE AND DOPAMINE RECEPTORS

Dopamine (DA) is one of the most important neurotransmitters in the central nervous system (CNS). It is involved in almost every aspect of brain functions, including control of movement, cognition,

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emotion, and regulation of the endocrine system. Dysfunctions of CNS dopaminergic neurotransmission account for a number of neurodegenerative and psychiatric disorders, including Parkinson's disease (PD), bipolar disorder, and schizophrenia.[1,2] In addition, all drugs of abuse influence directly or indirectly DA neurotransmission. Clinical and experimental studies clearly indicated that the positive reinforcement of the drugs of abuse is mediated primarily through the activation of the mesocorticolimbic DA system.[3–5] In the peripheral systems, DA also plays an important role in the functional regulation of cardiovascular and endocrinal systems.[6]

Dopamine (DA) exerts its actions mainly through DA receptors. These receptors exist both in mammalian CNS and peripheral tissues. They belong to a superfamily of large proteins containing seven relatively hydrophobic α-helical transmembrane spanning segments linked to more hydrophilic segments with an extracellular amino terminus. This is the typical conformation for G-protein-coupled receptors (GPCRs) that interact with many membrane or cytoplasmic effector molecules and regulate corresponding brain functions. The five cloned DA receptors (D_1–D_5) are classified on the basis of their cDNA/gene sequence, as well as their pharmacological and biochemical characteristics. The D_1 and D_5 subtypes preferentially bind to phenylbenzazepines and activate G_s proteins (G proteins that stimulate adenylate cyclase). Members of the D_2-like DA receptor family (D_2, D_3, and D_4), recognize the butyrophenones and benzamides, and are coupled to G_i proteins (G proteins that inhibit adenylate cyclase formation). Activation of these D_2-like receptors results in the inhibition of adenylate cyclase.[7,8]

Regulation of adenylate cyclase results in the change of cAMP that had been considered to be the major responsible secondary messenger system for DA receptor functions. However, recent information indicates that other intracellular signaling pathways (e.g., phospholipase C, protein kinase C and so on) are also involved in transducing DA signals.[9–11] In addition, DA receptors have also been shown to regulate mitogen-activated protein kinase (MAPK) pathways, a central pathway in the regulation of cell proliferation, differentiation, and survival. It was shown that stimulation of the D_2, D_3, and D_4 DA receptors activates extracellular signal-regulated kinase (ERK),[9,10] whereas D_1 DA receptor stimulation activates the p38 MAPK.[12] Interestingly, there are some reports indicating that differential regulation of DA receptors on these signaling pathways may underlie the functional differences of D_1 and D_2 DA receptors.

2. DA D_1 RECEPTOR AND ITS THERAPEUTIC POTENTIAL

The D_1 receptor is the most highly expressed DA receptor subtype with high levels in the DA rich areas of the mammalian forebrain, such as the caudate nucleus, putamen, substantia nigra, nucleus accumbens, hypothalamus, thalamus, frontal cortex, and olfactory bulb. It plays a crucial role in a variety of cognitive functions and is implicated in substance abuse disorders. The importance of the D_1 receptor in the treatment of PD was only appreciated until the 1990s when dihydrexidine (DHX), the first high affinity D_1 agonist with full intrinsic activity, was developed.[13,14] The pathology of PD is the progressive loss of nigrostriatal dopaminergic neurons. Degeneration of these neurons causes depletion of striatal DA. It is known that dopaminergic projections from the substantia nigra to the striatum are vital to motor control. Depletion of DA leads to motor symptoms clinically characterized by tremor, bradykinesia, rigidity and a late appearing loss of postural reflexes.[15] Thus, DA replacement is the most common therapeutic approach for relieving the PD symptoms. L-3,4-dihydroxy-phenylalanine (L-DOPA, levodopa) remains the most potent therapeutic drug for PD, and often produces dramatic effects in *de novo* patients.[16] Unfortunately, long-term use of levodopa is commonly associated with motor complications such as dyskinesia. Selective DA receptor agonists gained popularity because of their long-lasting and somewhat less severe adverse effects.[17] Another important advantage for using DA receptor agonists in PD therapy is the potential neuroprotective actions. The protective effects of DA agonists on DA neurons, however, seemingly do not involve DA

receptors.[18] It has been believed for quite a long time, that the therapeutic anti-parkinsonian effects of levodopa is primarily attributed to its stimulation of DA D_2 receptor whereas dyskinesias might be mediated by the over-stimulation of the D_1 receptor. As a result, D_2 receptor agonists were first introduced for the PD treatment.[19] The ergoline bromocriptine is the first DA receptor agonist that has been approved for anti-parkinsonian therapy since 1974. It was used initially as adjunct therapy to levodopa in patients experiencing motor fluctuations but was later recommended as mono-therapy for early PD patients.[20]

Little attention was paid to the anti-parkinson potential of D_1 receptor agonists at the beginning of their development. Part of the reasons was due to the lack of ideal D_1 receptor agonists which limited the effort in exploring the role of the D_1 receptor in PD treatment. Selective D_1 agonists of the first generation, such as SKF-38393 (compound **6**, Fig. 1), possess high affinity and selectivity, but have relative low intrinsic activities.[21,22] However, recent information indicates that D_1 receptor may play even greater role in motor control. DHX (**27a**), discovered in the late 1980s, was the first full D_1 DA receptor agonist.[23] DHX has high affinity for the D_1 receptor, with a relative low selectivity ($\sim$10-fold) for D_1 versus D_2 receptors.[24] The initial clinical trial with DHX failed due to severe adverse effects.[25] In fact, many clinically approved dopaminergic agents, such as α-dihydroergocryptine, lisuride, pergolide, pramipexole, and ropinirole, all have multiple actions at many of DA receptor subtypes (including D_1, D_2, or D_3 receptors) indicating that a more complex mechanism may be involved. It is therefore reasonable to hypothesize that each of these DA receptors contributes to the therapeutic effects in a unique manner and stimulation of one particular DA receptor may not be sufficient.[26] Although selectivity of DA agonists for DA receptors have been demonstrated to have some benefits for PD patients, the overall advantage of this type of drugs remains uncertain. In terms of the high selective D_1 receptor agonists, it is far from clear to classify their role in PD, simply because there is no such drug available in clinical trial for the time being. A combination therapy with L-DOPA according the stage of PD and therapeutic responses may be a better approach.

Schizophrenia is a devastating mental illness affecting approximately 1% of the population worldwide. It is generally believed that abnormal neurotransmission, especially in DA and glutamate (NMDA) system, plays a critical role in the pathophysiology of schizophrenia. The hyperactivity of DA in subcortical structure is thought to associate with the positive symptoms, whereas D_1 receptor hypoactivity in the frontal cortical area has recently been suggested to attribute to the negative symptom and impaired cognitive function.[27] Indeed, D_1 receptor in frontal cortex is involved in the working memory expression.[28] Low doses of selective D_1 receptor agonists (e.g., DHX, A77636, and SKF-81297) have been shown to enhance the cognitive function in primates.[27,29] Recently, preliminary human studies indicated that DHX is safe and well tolerated with no serious adverse events at a single dose of 20 mg.[30,31] It is now suggested that combined activation of D_1 receptor along with α_7 nicotonic receptor, may be the most promising therapeutic mechanisms for improving cognitive deficits and negative symptoms in schizophrenia.[30,31] Thus, D_1 receptor selective agonists may represent an exciting direction for the treatment of schizophrenia in the future.[32]

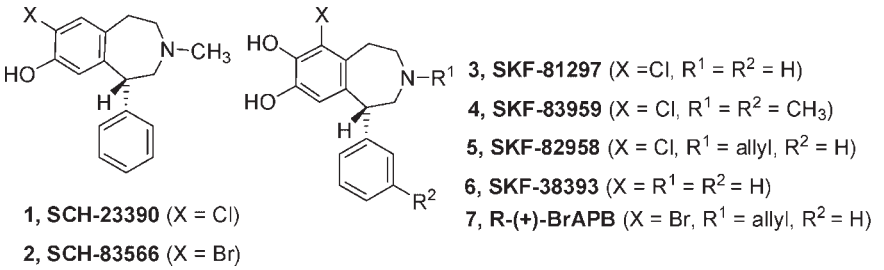


Figure 1. Representative D_1 benzazepines.

3. HISTORICAL REVIEW ON DA D_1 RECEPTOR SELECTIVE LIGANDS

The therapeutic potentials of DA D_1 receptor ligands were re-kindled in 1990s. Studies since then have provided a wealth of information on the structure–activity relationship (SAR) at the D_1 receptor. However, lack of information on the exact three-dimensional orientation of amino acid residues at the binding sites of the DA receptors, together with the limited understanding on interactions between the D_1 receptor and selective ligands still hampers the rational design and development of potent and selective D_1 receptor agents. Current knowledge on D_1 agonist and antagonist pharmacophores, and the intrinsic SAR, remains largely empirical. Most recently, computer-aided analysis on the conformations of the current available full agonists and quantitative structure–activity relationship (QSAR) characterizing D_1 antagonists has greatly stimulated the advances in this field.[33–37]

A number of ligands with high affinity for the D_1 receptor had been developed in 1980s. Most of those research work was limited on a single chemical class: phenyltetrahydrobenzazepines. Therefore, many useful D_1 receptor selective agents possessing partial agonist or antagonist properties with high D_1 affinity, for example, SCH-23390 (**1**), SKF-83959 (**4**) were derived from this group (Fig. 1). Ironically, the high D_1 receptor binding profile of these ligands was poorly relevant to their intrinsic activity. As a result, few D_1 full agonists were available for further investigation.[22,36]

In 1990s, led by Nichols et al.,[22,33–35] the search of DA D_1 full agonists was switched to the development of structurally rigid analogs of β-phenyldopamines. Thus, several compounds with novel structures distinguished from traditional phenylbenzazepines were found possessing exceptional anti-parkinsonian effects in the MPTP-treated monkey model.[33,34,38] Such breakthrough has largely spurred the interests of developing D_1 agonists as potential treatment of PD. Thus, a tentative SAR was established for typical high affinity D_1 full agonists, based on Nichols and Mailman's conceptual model of the agonist state on the D_1 receptor (Fig. 2). They generally contain the following principles:

(i) A phenylethylamine moiety. It would be optimal for D_1 receptor intrinsic activity if this moiety is in a *trans* extended conformation. An aspartate residue of the D_1 receptor may bind with its protonated amino group and the substituent on the nitrogen atom may greatly influence its D_1 selectivity over the D_2 receptor.[7,39]

(ii) A catechol moiety, or a catechol ring with halogen replacement of the two hydroxyl groups is necessary. It is believed that such catecholic function would serve as a hydrogen-bond donor to the serine residues in the active site of the D_1 receptor, although D_1 receptor agents without a catechol ring do exist.[40–44]

(iii) A hydrophobic substituent (e.g., phenyl) attached to the β-carbon of the ethylamine side chain. Such a component is postulated to interact with the hydrophobic binding domain of the

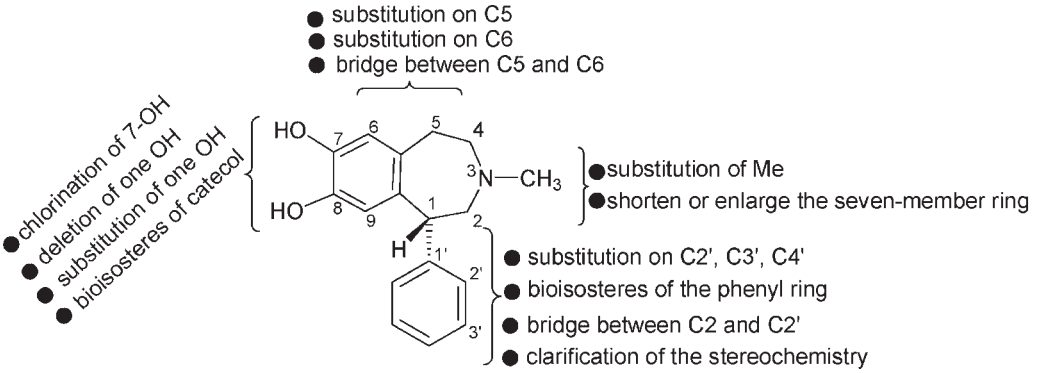


Figure 2. Structural modification on benzazepines.

D_1 receptor active site, and is crucial to the agent's affinity and potency as well as selectivity over other DA subtypes. However, whether the coplanar orientation of the β-phenyl moiety with the catechol ring is the optimal conformation remains controversial.[45]

Part of the advances described above has been discussed in several recent articles.[18,46] This review, therefore, will focus on progress of two major categories of D_1 receptor ligands: conformationally constrained benzazepine derivatives and dihydrexidine tetracyclic analogues.

4. RECENT DEVELOPMENT OF DA D_1 RECEPTOR SELECTIVE LIGANDS

A. Conformationally Constrained Arylbenzazepine Analogues

The family of phenylbenzazepines represents a unique class of compounds possessing high binding affinity for the D_1 receptors and high selectivity over the D_2 receptors. Considerable efforts have been devoted to this category of compounds in the past several decades, mainly because of its therapeutic application as anti-psychotics and anti-stimulant medications. Although full D_1 agonists with high affinity are rare, a large number of partial agonists and antagonists have been discovered (see Fig. 1), including the first high-affinity and selective D_1/D_5 antagonist SCH-23390 (**1**) and its conformationally restricted analogue SCH-39166 (**9**, Fig. 3).

The SAR of benzazepine analogues has been studied extensively using fruitful structural modifications (Fig. 2). In general, a chiral center exists on the C1-position where the receptor affinity resides primarily in the R enantiomer.[47] These compounds possess a considerable degree of conformational mobility, and the optimum position of the phenyl ring for interaction with the proposed accessory binding site of the D_1 receptor (e.g., SCH-23390, **1**) is likely to be equatorially.[48,49] There was a hypothesis that the preferred binding of benzazepine analogues to the D_1 receptor might be the consequence of a π–π non-bonded interaction between the C1-aromatic ring and a complementary residue of Phe, Tyr, or Trp on the receptor surface.[50] To probe the validity of such a concept, conformationally constrained benzazepines **8**–**10** were developed (Fig. 3).

Insertion of an ethylene bridge between C5 and C6 into the molecule of benzazepine **6** (SKF-38393) resulted in compound **8**, with either a *cis*-, or *trans*-conformation.[49] Compound *cis*-**8** has a high affinity at the D_1 receptor with a K_{bind} of 24 nM, whereas the *trans*-**8** is inactive. However, similar to other benzazepine derivatives, this compound also shows partial agonist activity with only

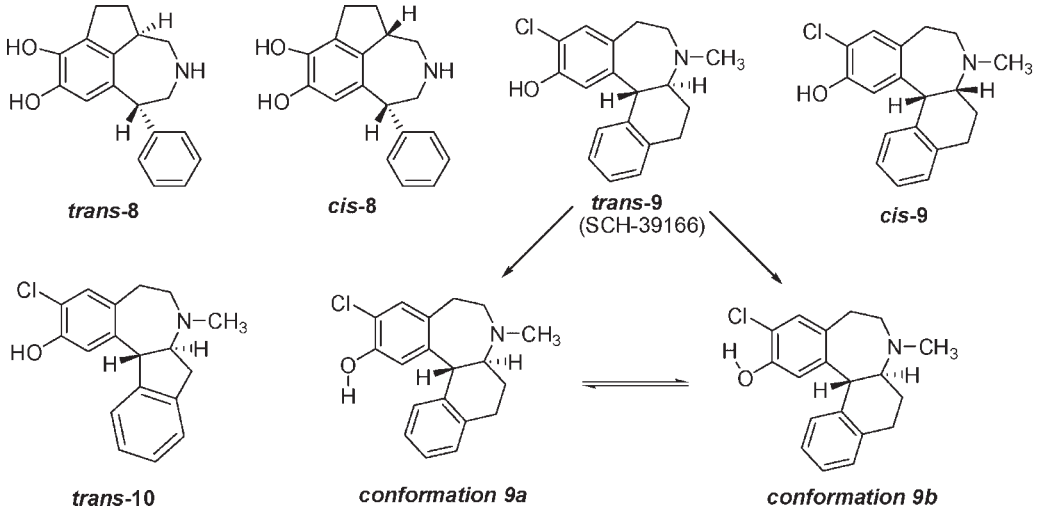


Figure 3. Conformationally restrained benzazepine analogues.

62% of DA response. The high affinity of *cis*-isomer may be rationalized by the fact that the side-chain nitrogen of *cis*-isomer is nearly in the plane of the catechol nucleus which is required for dopaminergic pharmacophore and D_1 receptor binding, and *trans*-isomer **8** is unable to reach the D_1 receptor binding site (Table I).

Insertion of an ethylene bridge between C2 and C2′ into the molecule of benzazepine **1** (SCH-23390) yielded compounds **9** where the additional ring C was fused in *cis* or *trans* form.[48] Binding studies on both the *cis* and *trans* isomers disclosed that the *trans*-**9** has a K_i of 3.3 nM and is 143-fold more potent than *cis*-**9**. Resolution of the racemic *trans*-**9** indicated that the *R*-(−)-*trans*-**9** has a significantly greater D_1 affinity and selectivity (K_i, 1.9 nM). This phenomenon is consistent with the fact that the D_1 receptor affinity in the 1-phenyl-1H-3-benzazepine family is associated specifically with the *R*-enantiomers. Similarly, the C2 and C2′ methylene-bridged benzazepine **10** also favors its affinity and selectivity for the D_1 receptor in its *trans* form *R*-enantiomer.[51] Further investigation on *trans*-**9** (SCH-39166) disclosed that in comparison to the prototype SCH-23390, it is a selective DA D_1 receptor antagonist, with reduced affinity for serotonin receptors and with a longer duration of actions in a conditioned avoidance paradigm in primates.[52]

Conformational analysis was also conducted to clarify the exact mode of binding of these conformationally constrained compounds to the D_1 receptors, without reaching a solid conclusion.[53] One additional question raised from these studies is the exact orientation of the C8 hydroxyl group in these compounds. For example, compound **9** has two possible orientations when approaching the receptors, conformation **9a** and conformation **9b** (Fig. 3). The C8 hydroxyl group was recognized a prerequisite for binging to the DA receptors. In 2005, Wu and his colleagues indirectly addressed this question by carefully designing a series of heterocycle-fused compounds **11**–**16** (Fig. 4).[54] They concluded that a suitably arranged heterocycle with an NH group would be able to mimick the prototypic OH group to probe its binding direction, and more importantly, to serve as metabolically stable bioisosteres.

The triazole compound **11** can roughly represent a rigid analog of conformation A, and the triazole NH is sufficiently acidic to form a hydrogen bond as its prototypic OH. However, the affinity of this compound at the D_1 receptor is disappointing with a K_i of 583 nM. With proposed hydrogen bonding in opposite orientation, compound **12** represents the conformation B. This methyl substituted pyrrole analog displayed a K_i of 24.7 nM for binding to the D_1 receptor, which is much higher than that of compound **11**, where the proposed hydrogen bonding is oppositely oriented. Based on these findings, it was concluded that conformation B (similar to conformation A and B for compound **9** in Fig. 3) might be the active binding conformer, while the conformation A is not. According to this hypothesis, benzimidazole **13** and benzotriazole **14** were prepared with proper hydrogen bonding orientation, but the binding affinity of these two analogues at the D_1 receptor turned out to be poor (K_i, 248 and 146 nM, respectively). The unexpected poor affinity of compounds **13** and **14** may be ascribed to the possible tautomerization of the imidazole and triazole functions in these two compounds, thus the N–H can switch from N1-position to N3 position. This analysis prompted the design and synthesis of benzimidazolone **15**, where two NHs exist in different chemical and magnetic environments. As expected, compounds **15a,b** display a significant enhancement in binding affinity to the D_1 receptor with K_is of 7 and 16.5 nM, respectively. Further, compounds **16a,b**, with a stronger acidic NH and without the additional unnecessary NH, give remarkably high D_1 receptor binding affinity. The K_is of **16a,b** are 2.1 and 6.5 nM, respectively, threefold higher than that of compound **15a,b**.

To further explore the potential of the conformationally rigid 2,2′-bridged benzazepines, a large series of substituted analogues **17** and **18** were synthesized (Fig. 5).[55] Variant substitution patterns (3′-, 4′-, 5′-), substituent nature and size were investigated. High binding affinity for the D_1 receptor was observed in compounds **17a–k**, and **18a–l**. All these compounds have K_is of less than 5 nM, with the highest affinity of 0.45 nM for compound **18g** which contains a 4′-methanesulfonylamino

Table I. Binding Affinity at the Dopamine D_1, D_2 and Serotonin 5-HT_{2A} Receptors of Benzazepine Analogues (K_i/IC_{50}, nM)[a]

Compound	D_1	D_2	D_5	5-HT_{2A}	Reference
1 (SCH23390)	0.12	83.8	12	596	36
3 (SKF81297)	1.90	1272	-	398	36
4 (SKF83959)	1.18	920	7.56	266	36
5 (SKF82958)	4.56	264	-	1612	36
6 (SKF38393)	26.6	>10000	-	>10000	36
7 (BrAPB)	2.29	209	-	-	36
trans-**8**	1220	>10000	-	-	49
cis-**8**	24	>10000	-	-	49
cis-**9**	473	9073	-	-	48
trans-**9**	3.3	4115	-	-	48
R-(-)-trans-**9**	1.9	514	-	-	48
S-(+)-trans-**9**	531	3046	-	-	48
10	7	-	-	-	51
11	583	3000	-	-	54
12	24.7	232	-	-	54
13	248	984	-	-	54
14	146	1530	-	-	54
15a	7	1023	-	-	54
15b	16.5	3270	-	-	54
16a	2.1	257	-	-	54
16b	6.5	661	-	-	54
18g	0.45	>10000	-	-	55
19[b]	12	-	-	-	56

[a]Data were taken directly from the corresponding literature.
[b]IC_{50} value.

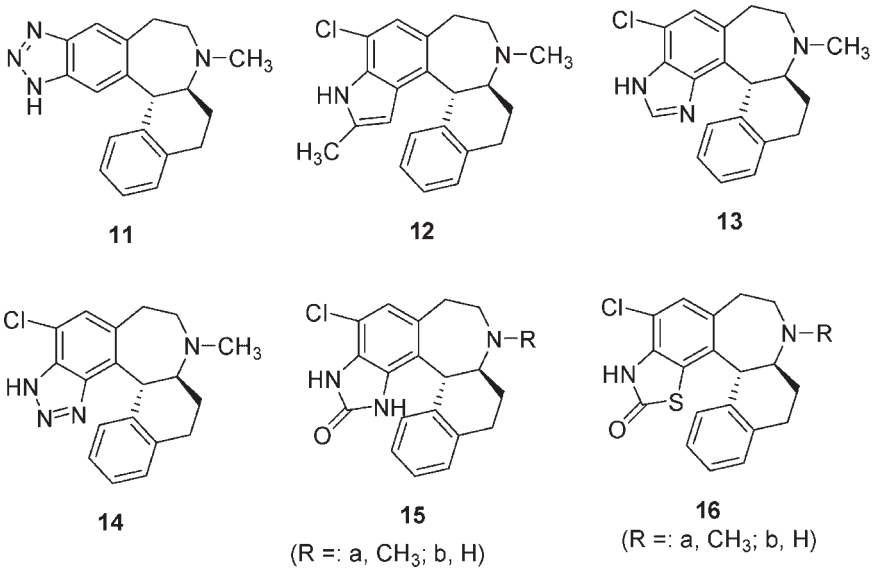


Figure 4. 2,2′-Bridged conformationally restrained benzazepine analogues.

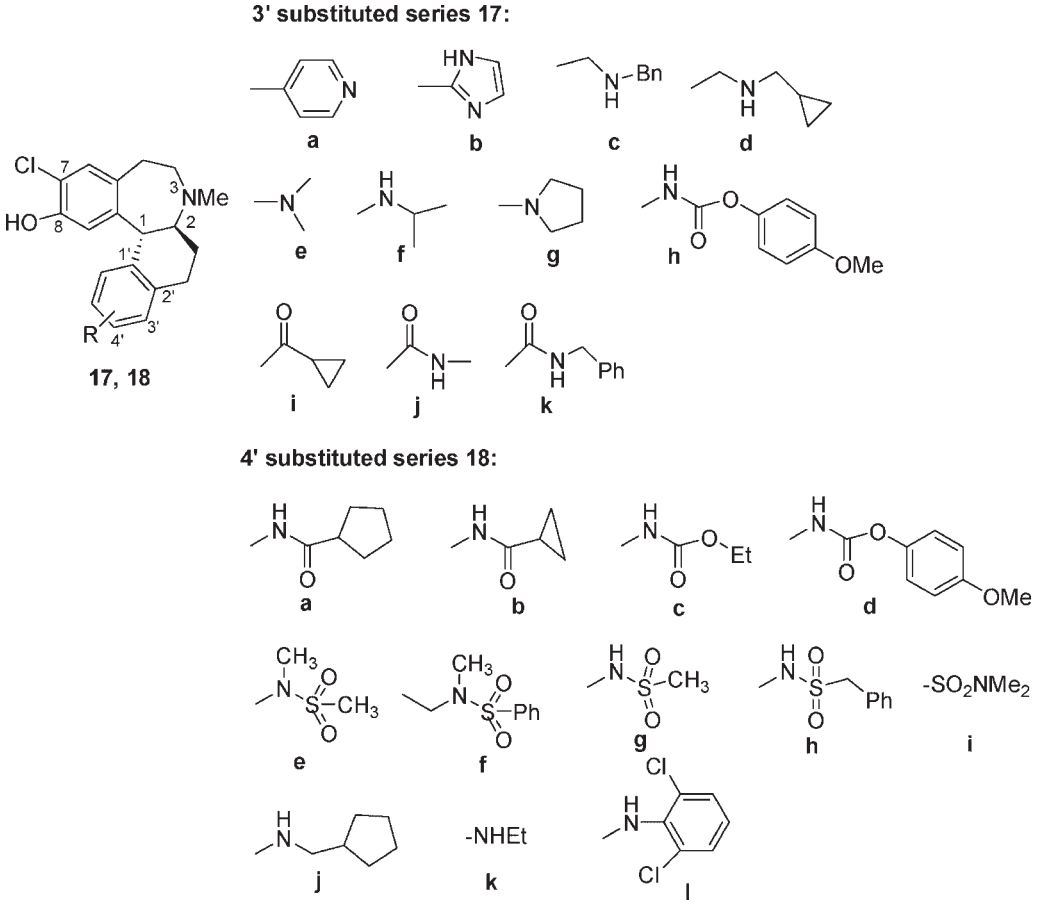


Figure 5. Substituted 2,2′-bridged benzazepine analogues.

substituent. The selectivity of this compound for the D_1 receptor over the D_2 receptor is more than 6,000-fold.

Another series of compounds is 6,7-heterocycle-fused benzazepines with a general formula **I** (Fig. 6).[56] In these compounds, a furan-, pentane-, hexane-, thiophene-, or 1,3-dioxopentane-, was fused to the C6 and C7 of the benzazepine ring system (**19–25**). In several cases, the C1-phenyl group of benzazepine core was generally substituted with a benzofuran-7-yl, or a 2,3-dihydrobenzofuran-7-yl moiety that has been previously reported to be a good bioisostere of phenyl functionality. These compounds generally retain high affinity at the DA D_1 receptor. Among this series, compound **19** has the highest binding affinity with an IC_{50} of 12 nM at this receptor.

B. Dihydrexidine and Its Polycyclic Analogues

Compound **26** represents a series of 4-phenyl substituted tetrahydroisoquinolines,[34,37,57,58] which has moderate, but selective affinity for the DA D_1 receptors. Rigidification of this template by insertion of an ethylene-bridge yielded a series of novel tetracyclic compounds **27a–c** (Fig. 7).[59,60] These compounds can be viewed as a B-ring modification of the conformationally constrained benzazepine analogue **9** (SCH-39166). The *trans*-configured 10,11-dihydroxy-5,6,6a,7,8,12b-hexahydrobenzo[a]phenanthridine **27a** (dihydrexidine, DHX) is a highly potent and selective D_1 receptor agonist in rat brain. It competes for [^{3}H]SCH-23390 binding sites in rat striatal homogenate with an IC_{50} of 12 nM. EC_{50} of DHX in activating DA-sensitive rat striatal adenylate cyclase is 70 nM. The maximal stimulation is equal to or slightly greater than that produced by DA itself. More importantly, compound **27a** is a full DA D_1 agonist, different from the previously available agents which show only partial agonism. The *N*-methyl-(**27b**), *N*-propyl-(**27c**) analogues give a much lower potency in binding to the D_1 receptor, with IC_{50}s of 91 and 651 nM, respectively, and their intrinsic activity is substantially reduced. Compound **28**, reported much earlier by Wei and Teitel[61] with a 9,10-dihydroxy substituted catechol moiety is inactive at the D_1 receptor. The *cis*-isomer **29** is also found neither stimulating cAMP synthesis nor inhibiting the cAMP synthesis induced by DA itself.

The discovery of DHX (**27a**) was a breakthrough in the development of DA D_1 receptor full agonists. It was the first high-potency, full efficacy, bioavailable agonist selective for the D_1 receptor, and represents a new conformationally rigid structural scaffold of D_1 receptor ligands. The racemate **27a** has impressive anti-parkinsonian actions in the MPTP primate model and was studied in several clinic trials.[24] Resolution of racemic **27a** resulted in two isomers (+)-**27a** (6a*R*,12b*S*) and (−)-**27a**

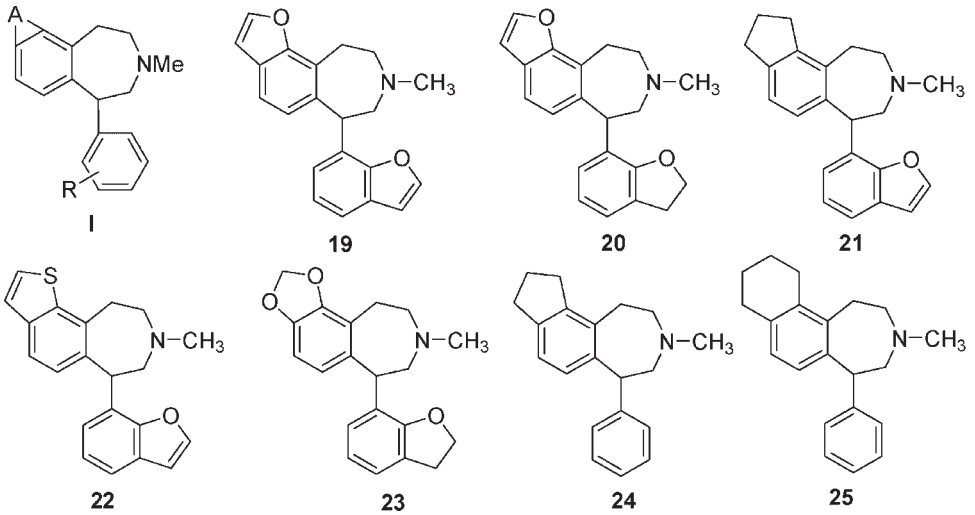


Figure 6. Tricyclic benzazepine analogues.

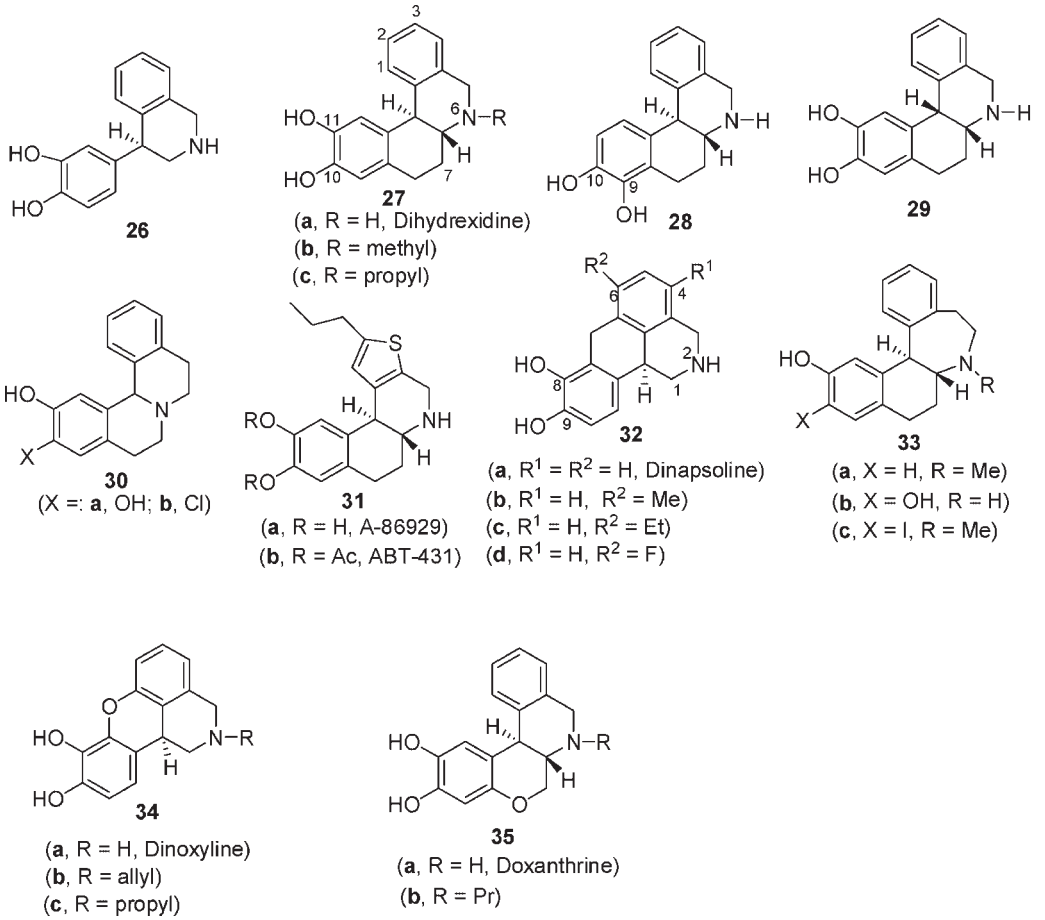


Figure 7. Dihydrexidine and its tetracyclic analogues.

(6a*S*,12b*R*).[62] (+)-**27a** is 2-, and 25-fold more potent than the racemate and (−)-**27a**, respectively. Functionally, (+)-**27a** is a full agonist, with an EC_{50} of 51 nM in activating striatal DA-sensitive adenylate cyclase versus 2.15 μM for the (−)-isomer (−)-**27a**. Thus, it is likely that the DA receptor activity of DHX resides principally in the (6a*R*,12b*S*)-(+)-enantiomer conformation (Table II).

An approach to explore the N-atom location was conducted yielding compounds **30a,b**.[63] Such structurally rigid tetrahydroisoquinolines are poor D_1 receptor ligands, with K_i values at 2700 nM and 830 nM, respectively for compounds **30a** and **30b** in competition for [^{3}H]SCH-23390 binding sites in rat striatal homogenate. Thus, the nitrogen position has a crucial pharmacophoric importance in modulating D_1 receptor binding affinity and functionality.

Thiophenes **31a,b** can be viewed as bioisosteres of the A-ring phenyl group of DHX (**27a**).[64] The NH compound **31a** (A-86929) possess high affinity for the cloned human D_1 receptor with a K_i of 49 nM. Similar to **27a**, this compound also has full intrinsic activity relative to DA in stimulating adenylate cyclase (EC_{50}, 9 nM). Resolving this racemic compound showed that (+)-**31a** is approximately 60-fold weaker in both binding affinity and functional activity. In addition, compound **31a** produces robust rotation in the unilaterally lesioned rat after both acute and repeated administration. However, this compound is very unstable, and readily undergoes air-oxidation. As a result, it is generally prepared and used as its diacetate precursor **31b** (ABT-431). This prodrug offers greater solid-state stability and can be easily converted to its parent compound **31a** both *in vitro* and *in vivo*.[64]

Table II. Dopamine D_1, D_2 Receptor Binding affinity of Conformationally Constrained Tetracyclic Ligands[a]

Compound	K_i /$K_{0.5}$/ IC_{50} (nM)	D_1	D_2	Reference
27a (dihydrexidine)	IC_{50}	12	120	59
(+)-27a	$K_{0.5}$(IC_{50})	4.59 (5.6)	43	62, 65
(-)-27a	IC_{50}	149	1250	62
27b	IC_{50}	91	136	59
27c	IC_{50}	651	53	59
28	-	NA[b]	NA[b]	59
29	IC_{50}	> 5000	>5000	59
30a	K_i	830	>5000	63
30b	K_i	2700	>5000	63
31a (A-86929)	K_i	49	710	64
32a (dinapsoline)	$K_{0.5}$(IC_{50})	5.93(67)	31.3	65
(+)-32a	IC_{50}	33	38	66
(-)-32a	IC_{50}	5300	1500	66
32b	$K_{0.5}$	11	57	67
32c	$K_{0.5}$	14	-	68
(-)-32d	$K_{0.5}$	>3000	-	68
(+)-32d	$K_{0.5}$	71	7	68
33a	$K_{0.5}$	3950	>10000	69
33b	$K_{0.5}$	2850	2220	69
33c	$K_{0.5}$	1380	2960	69
34a (dinoxyline)	$K_{0.5}$	8.3	6.2	70
34b	$K_{0.5}$	260	54	70
34c	$K_{0.5}$	250	17	70
35a (doxanthrine)	K_i	22	3700	71
(+)-35a	K_i	8	2500	71
(-)-35a	K_i	270	6800	71
35b	K_i	330	340	71

[a]Data were taken directly from the corresponding reference, the dash lines indicate no data available.
[b]No activity.

Following the original idea to rigidify the tetrahydroisoquinolines (e.g., **26**), and encouraged by successful development of the full D_1 agonist **27a**, Nichols and colleagues introduced a bridge to the structure **26** and its analogues.[65] Thus, a series of 8,9-dihydroxy-2,3,7,11*b*-tetrahydro-1*H*-naph[1,2,3-*de*]isoquinolines **32a–d** were developed (Fig. 7). This approach involves taking the backbone of DHX (**27a**), the first high-affinity full D_1 agonist, and tethering the two phenyl rings

through a methylene-bridge followed by removal of the C(7)-C(8) ethyloxy-bridge. Preliminary molecular modeling studies demonstrated that these modifications conserved the essential elements of the pharmacophore required for D_1 receptor activity.[35] Compound **32a** (dinapsoline) has almost identical affinity ($K_i = 5.9$ nM) to **27a** at the rat striatal D_1 receptors and displays a shallow competition curve ($n_H = 0.66$) that suggests agonist properties. In both the rat striatum and C-6-mD_1 cells, dinapsoline **32a** is a full agonist with an EC_{50} of ca. 30 nM in stimulating cAMP synthesis via the D_1 receptor. Resolution of **32a** into a pair of enantiomers showed that the (*R*)-(+)-**32a** is the active enantiomer.[66] In unilateral 6-hydroxydopamine (6-OHDA)-lesioned rats (+)-dinapsoline **32a** induces robust rotational behavior comparable to that of an external benchmark, **31a**. The C6-methyl (**32b**) and C6-ethyl (**32c**) analogues have almost identical binding affinity to the D_1 receptor with K_is of 11 and 14 nM, respectively.[67,68] Other C6 or C4 substitutions led to a decay in D_1 receptor affinity. It is of note that the active D-ring analog, 6-fluorodinapsoline **32d**, resides its biological activity in the (+)-enantiomer which is consistent with the activity of (+)-dinapsoline **32a**.

trans-6,6a,7,8,9,13b-Hexahydro-5*H*-benzo[*d*]naphth[2,1-*b*]azepines **33a–c** were designed as conformationally restricted homologues of the potent benzophenanthridine D_1 agonist DHX **27a**.[69] Based on previously knowledge, the dihydroxy secondary amine **33b** was predicted to be a D_1 receptor agonist, whereas the *N*-methyl compounds **33a** and **33c** were predicted to be D_1 receptor antagonists. Surprisingly, none of the three compounds shows appreciable affinity for the D_1 receptor ($K_{0.5}$: 3.9, 2.8, and 1.38 μM, respectively). A comparison of the low-energy conformations of these molecules shows that the pendant phenyl ring of **33b** is twisted for approximately 28° relative to that of the corresponding ring of **27a**. Further, the additional methylene unit used to expand the C ring of **33b** projects toward the α-face of the molecule, suggesting that steric protrusion in this region of the molecule is not well tolerated.[69]

Different from the approach in designing dihydrexidine (**27a**) and dinapsoline (**32a**), 8,9-dihydroxy-1,2,3,11b-tetrahydrochromeno[4,3,2,-*de*] isoquinolines **34a–c** were developed by tethering the two phenyl rings of β-phenyldopamine D_1 pharmacophore using an ether linkage.[70] The resulting compound **34a** (dinoxyline) is found to be a potent full D_1 agonist ($K_{0.5} = 8.3$ nM; $EC_{50} = 87$ nM) for striatal D_1 receptors, but also has high affinity for brain D_2-like and cloned D_2 and D_3 receptors. The *N*-allyl (**34b**) and *N*-*n*-propyl (**34c**) derivatives have much reduced affinity for the D_1 receptor with $K_{0.5}$ of 260 and 250 nM, respectively. However, increased D_2-like receptor binding affinity is observed. Therefore, this represents the first example of ligands with high affinity for all DA receptors, yet with functional characteristics similar to DA itself.

Tethering the two phenyl rings of β-phenyldopamine D_1 pharmacophore by a $–CH_2O–$ linkage produced *trans*-2,3-dihydroxy-6a,7,8,12b-tetrahydro-6*H*-chromeno [3,4-*c*]-isoquinolines **35a,b**.[71] These compounds can be viewed as heterocyclic bioisosteres of the potent DA D_1-selective full agonist DHX (**27a**). Compound **35a** (doxanthrine) possesses high affinity ($K_i = 20–30$ nM) for the porcine D_1-like receptors in native striatal tissue and full intrinsic activity at cloned human DA D_1 receptors with much lower affinity at the D_2-like receptors ($K_i = 3000$ nM). Again (+)-**35a** gives much higher potency ($K_i = 8$ nM) in binding to the D_1 receptor than (−)-**35a** ($K_i = 270$ nM). The binding and functional properties of this compound highlights the effectiveness of constructing DA D_1 agonist ligands using the β-phenyldopamine pharmacophore template. The *N*-propyl analogue **35b** has a substantially weaker affinity at the D_1 receptor ($K_i = 330$ nM).

C. Computational Modeling of DA D_1 Receptor

Computer-aided drug design plays an important role in the development of new drugs that target GPCRs. As in the efforts for targeting D_1 DA receptors, many computational modeling methods have been utilized with the aim to investigate the SARs mostly lying in the agonists. However, due to the difficulty in crystallizing GPCRs, and the limitation in obtaining the three-dimensional structures, early investigations mostly used the ligand-based approaches, such as pharmacophore detection and

Quantitive-SAR (QSAR).[35,72–78] In 1996, following the conformational analyses of dihydrexidine (DHX) and other active D_1 agonists, Mottola et al.[79] applied the active analog approach with the help of a SYBYL software package, and built a pharmacophoric model of the DA D_1 receptor. In this model, two distances constraints and one angle constraint are included, namely the distance between the positively charged nitrogen and oxygen of *m*-hydroxyl group of the catechol ring in a range of 7.1–8.0 Å, the distance between the nitrogen and oxygen of *p*-hydroxyl group in a range of 7.1–7.4 Å, and the angle between the planes defined by the catechol ring and the pendent aromatic ring in a range of 50–80°. In comparison to the inactive compounds of several DHX analogs, it is clearly indicated that additional bulk group attached to the nitrogen atom in DHX is intolerable and sterically clashes with binding site residues of the D_1 receptor. Similarly, Wilcox et al.[80,81] also conducted an analysis of a series of D_1 receptor agonists, and summarized a pharmacophore model and a CoMFA based QSAR model. In this model, the distance constraints from the positively charged nitrogen to *m*-hydroxyl and to *p*-hydroxyl groups are slightly shorter than that in Mottola's model, at 5.9–7.8 Å and 5.1–7.5 Å, respectively. In addition to these distance constraints, Wilcox detected a pharmacophoric pattern that modeled how high the nitrogen above the plane defined by the catechol ring. According to their model, the ideal N-plane height is within 0.5–2.0 Å. They also found that the distance between the nitrogen atom and the oxygen atom of the *m*-hydroxyl-, and *p*-hydroxyl is at 7.0 Å, and the N-plane height of 1.2 Å would give agonists with greatest D_1/D_2 selectivity.

Apart from ligand-based studies on D_1 agonist design, numerous attempts have been done toward modeling the interactions between D_1 receptor ligands and the binding sites of the receptor.[82–90] Kalani et al.[88] performed a structure prediction for D_2 DA receptors, which also shed lights on D_1 agonist interaction mechanism on D_1 receptors. Based on the model they built, they successfully incorporated the structure information with large volume of data from biochemical and pharmacological studies. From the interaction patterns between the D_2 receptor and its endogenous ligand DA, it is apparent that the two hydroxyl groups in the catechol ring form several hydrogen bonds with serine residues (Ser5.42, Ser5.43, Ser5.47, numbered according to the Ballesteros–Weinstein designation) in transmembrane (TM) helix 5, whereas the positively charged amino group forms a tight salt bridge with the carboxyl group of Asp3.32. The studies also revealed that certain hydrophobic residues located at TM3, TM4 TM5, and TM6 form a hydrophobic pocket to accommodate the aromatic ring in several agonists. Since the breakthrough in determining the high-resolution crystal structure of bovine rhodopsin,[89] building the homology model of the D_1 receptor is feasible by utilizing this crystal structure as the 3D template. Recently Xhaard et al.[91] investigated the binding modes of catecholamines in the frame of homology models of adrenoceptors and DA receptors constructed from the crystal structure of bovine rhodopsin (PDB access code 1U19). This study clearly demonstrated the important amino acid residues in the receptor binding site that interact with DA receptor ligands, which are similar to the findings by Kalani et al.[88] They also highlighted that several residues may be responsible for the subtype selectivity among DA receptors, such as the SerXl2.52 in the D_1-like receptors and HisXl2.52 in the D_2-like receptors. In the D_1-like receptors, a more bulky side chain of Ile3.33 (Val3.33 in D_2-like receptor) may explain why a slightly smaller hydrophobic group is favorable for selective D_1-like ligands. Recently, a higher homology GPCR, β-adrenergic receptor was determined[90] at 2.4 Å resolution by X-ray crystallography. A comparison with the bovine rhodopsin structures revealed that these two proteins have large deviation on several TM helices, especially in TM3 and TM5, which in turn cause the different orientations of certain residues at the binding sites. These differences raised the question that how accurate the homology models would be. But as demonstrated by many homology structure-based virtual screening studies,[88–94] these models are relatively useful in lead identification and lead optimization if the model was built within the proper constraints provided by experiments. Nevertheless, additional high-resolution structure of GPCR is needed to clarify the agonist-binding conformational states in the activation process.

In summary, the development of computational model of DA receptors has provided extensive useful information and greatly assisted the explanation and prediction of ligand activity and selectivity at the DA receptors. However, a major obstacle in this field is the lack of exact 3D structures of DA receptors at an atomic level that extremely hinders the effective design and development of DA receptor-selective ligands. Current design of DA receptor (D_1, D_2) selective ligands still remains largely empirical and somewhat unpredictable. However, the rapid progress in structural genomics[95–97] of membrane proteins and methodology development in structure prediction[98,99] will gradually shift the way to structure-based drug design for developing high selective D_1 agonist as well as for other GPCR modulators. The efforts of attaining the GPCR 3D structure models will eventually provide an interaction map for finding novel scaffolds of D_1 agonists and optimizing the potency and selectivity of lead compounds. Another exciting strategy in GPCR drug development is the emergence of chemogenomics method that aims to construct the drug-target networks. This will sequentially provide additional clues for lead identification and off-target prediction.[100–105]

5. DISCOVERY OF NEW D_1 RECEPTOR (PI-D_1) AND ITS SPECIFIC LIGANDS

In addition to the well-characterized D_1- and D_2-like DA receptors, recent evidence suggests that there may be a new type of D_1-like DA receptors. Unlike the classical D_{1A} or D_5 receptors that couple to Gs proteins and stimulate cAMP formation, this novel D_1 receptor selectively couples to G_q protein and stimulates the hydrolysis of phosphoinositide (PI) to diacetylglycerol (DAG) and inositol 1,4,5-trisphosphate (IP_3) via the activation of PLCβ.[106–115] DAG activates protein kinase C (PKC) whereas IP_3 induces release of calcium from intracellular stores. The putative PI-linked D_1 receptor (PI-D_1) is widely distributed in the brain.[113] The functional role of PI-D_1 receptor was completely unknown until the recent identification of a selective agonist (SKF-83959, **4**) for this receptor.

SKF-83959 (compound **4**), as described above, belongs to the benzazepine family, and has been characterized early as an agonist for the classic D_1 receptor but producing a novel behavioral profile in rodents.[116,117] It was recently identified that this drug is a selective agonist for the putative PI-linked DA D_1 receptor (PI-D_1).[113,118] Previous studies have shown that this compound has excellent anti-parkinsonian effects in the MTTP-treated monkey model or 6-OHDA-lesioned rat model of PD.[119,120] The anti-parkinsonian action of this compound exhibits unique features, including: (1) it is effective in L-DOPA-insensitive animals; (2) side effects, such as dyskinesias that are sometimes severe during L-DOPA treatment,[121] disappear with time during SKF-83959 treatment, and (3) the anti-parkinsonian effects are stable over time of treatment, unlike the case with the L-DOPA treatment. Biochemical and pharmacological studies clearly indicate that the action of SKF-83959 is independent of cAMP/PKA pathway.[117–119,122] It was further demonstrated that the anti-parkinsonian action of SKF-83959 appears to be mediated via the PI-D_1 receptor in the 6-OHDA lesioned PD rat model,[115] indicating that stimulation of striatal PLC/IP3 pathway by the PI-D_1 receptor may be the underlying mechanism for the drug's anti-parkinsonian action. Moreover, it was found that chronic SKF-83959 produced less severe dyskinesia, and attenuated the development of L-DOPA-induced dyskinesia.[123] In addition, the anti-dyskinesia effect of the PI-D_1 receptor agonist appears to be associated with the neuroprotective effect of SKF-83959.[124] In addition to the role of PI-D_1 receptors in the anti-parkinsonian effects, it was also found that SKF-83959 alters the sensoring-motor gating response of rats, and stimulation of this receptor induces activation of CaMKII in brain tissues.[125–128] In view of the importance of CaMKII in neuroplasticity associated with learning and memory, this observation raised a potential interest in exploring the role of PI-D_1 receptor in brain cognitive function. Taken together, all this indicates that the putative PI-D_1 receptor could be a potential target for PD or other neuropsychotic diseases. However, the existence of a novel PI-linked DA receptor is hampered by the failure in the effort to identify the specific gene for this

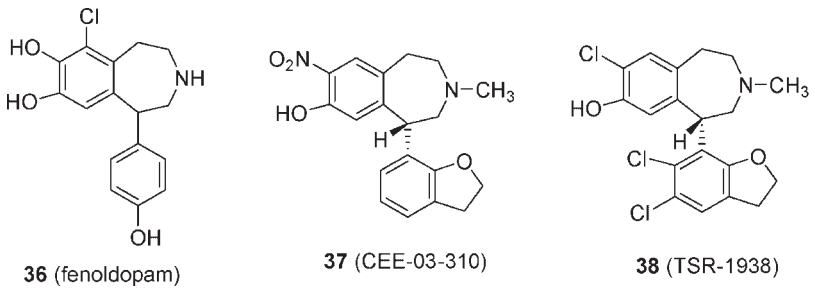
receptor, and by other controversial reports.[129–132] The discrepancy could be attributed to the differences in cellular contents or partners that requires for DA-mediated Gq/11 activation. Interestingly, Susan George et al.[133] recently provided evidence in support of their proposal that D_1 and D_2 receptor interaction (hetero-oligomeric association of GPCRs) may underlie the DA receptor-coupled Gq/11 pathway. This is an attractive proposal since it could explain the failure of heterologously expressed D_1 receptor cells to activate Gq/11 pathway.

6. CLINICAL DEVELOPMENT ON DA D_1 RECEPTOR LIGANDS

As stated above, development of DA D_1 receptor ligands was started much earlier than for other DA receptors. The classical benzazepine analogues, for example, **1** (SCH-23390) and **6** (SKF-38393), were widely used as pharmacological tools for probing the D_1 receptor functions. Several compounds, with high binding affinity and selectivity for the D_1 receptor had even entered clinical trials as anti-parkinsonian or anti-psychotic drugs, but were discontinued later or no development information reported for several years.[134–137] These ligands include conformationally flexible benzazepines, for example, SKF-83566 (**2**), SKF-81297 (**3**), SKF-82958 (**5**), SKF-38393 (**6**), SKF-77434, SKF-87516, SKF-80273, SKF-83565, A-86929 (**31a**), LY-270411, NNC-112, and NNC-22-0010. In addition to their low intrinsic partial agonist activity, the failure of these compounds was largely due to poor oral bioavailability and rapid tolerance.

The only compound that reached the market is fenoldopam (**36**). Benzazepine **36** is a potent D_1 receptor agonist which acts peripherally and selectively produces systemic vasodilation.[137] It was developed by GlaxoSmithKline and was launched as Corlopam in the US in 1998 for short-term management of severe hypertension with or without deteriorating end-organ function. It was licensed to Abbott in the US in 2001 (Figure 8).

The conformationally rigid benzazepine analogues and the polycyclic derivatives have spurred new interests in exploration of the therapeutic potentials of the D_1 receptor agents.[138–143] Several compounds have already been under development. These include: (1) benzazepine analogues: **CEE-03-310** (**37**) by Addex for the treatment of drug abuse in 2002, **TSR-1938** (**38**) by CeNes for the treatment of substance abuse and sleep disorders in 2003, **Ecopipam** (**9**, SCH-39166) by Schering-Plough for the management of obesity in 2000, and (2) polycyclic derivatives: **DHX** (**27a**) by Purdue University for drug dependence, PD and schizophrenia, **DAR-201** (dinapsoline, **32a**) by DarPharm Inc as treatment for PD, schizophrenia (+)-**32a** by Bristol-Myers Squibb under development for treatment of PD, and **Doxanthrine** (**35a**) by Purdue University as anti-psychotics and as anti-parkinsonian agent. Among these agents, DHX (**27a**) was in Phase I trials with moderate-to-severe PD in 1995 and was pushed to phase II trials. However, negative results, especially poor pharmacokinetic profiles and adverse effects, have been observed in the development process, which make this compound less likely to be used clinically.



36 (fenoldopam) **37** (CEE-03-310) **38** (TSR-1938)

Figure 8. Benzazepine analogues launched or under development.

7. CONCLUSION AND PROSPECTIVE

Dopamine D_1 receptor is the most abundant DA receptor subtype among the DA receptor family. Although the first DA D_1 receptor selective ligands SCH-23390 (**1**) was introduced more than two decades ago, clinically useful D_1 receptor selective ligands remain rare. The conformationally flexible 1-phenylbenzazepine analogues have served as the major D_1 receptor agonists and antagonists for many years only resulting in several research tools. The therapeutic utility of D_1 receptor agents was largely suspended for years in 1980s, primarily due to the early hypothesis that D_1 receptor agonists are more or less likely to be associated with dyskinesia than levodopa, and due to the lack of a D_1 full efficacy agonists.[143–148] A renewed interest has not been initiated until the development of polycyclic derivatives, for example, DHX (**27a**) by David E Nichols and Roth B Mailman in the early 1990s. Since then, the development of DA D_1 receptor ligands has fallen in two major categories, dihydrexidine analogues and conformationally rigid benzazepine derivatives with exception of a few others (e.g., isochromans). The former category has opened a new avenue for the development of high affinity full efficacy D_1 receptor agonists, including **31a** (A-86929), **32a** (dinapsoline), **34** (dinoxyline), **35** (doxanthrine). The latter approach has also provided several new benzazepines with D_1 receptor high binding and selectivity, including SCH-39166 (compound **9**).

These advances have highlighted several crucial principles for drug designers to develop full D_1 receptor agonists, and several such agonists have indeed shown full anti-parkinsonian responses that is not supportive of the previous D_1-induced-dyskinesia hypothesis (e.g., ABT0431).[145,148] Despite of these advances, the chance for any given compound as a treatment of PD or any other CNS disorder is not optimistic because of the many obstacles in pharmacokinetics and toxicity, as evidenced by the example of DHX (**27a**). Further investigations on compounds **9**, **32a**, **34**, and **35**, which are currently in the discovery stage, will be crucial for determining the future of the D_1 receptor agonists or antagonists.

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