# Dopamine Receptors

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Professor Philip Strange has worked on the structure and function of G protein-coupled receptors for many years. A major focus of his work has been the receptors for the neurotransmitter dopamine, with particular emphasis on their role as targets for drugs and understanding the mechanisms of agonism and inverse agonism at these receptors.

Professor Kim Neve has studied dopamine receptors for most of his scientific career, with an emphasis on relating structural features of the receptors to specific functions and assessing how receptor responsiveness is altered by denervation or prolonged treatment with agonists.
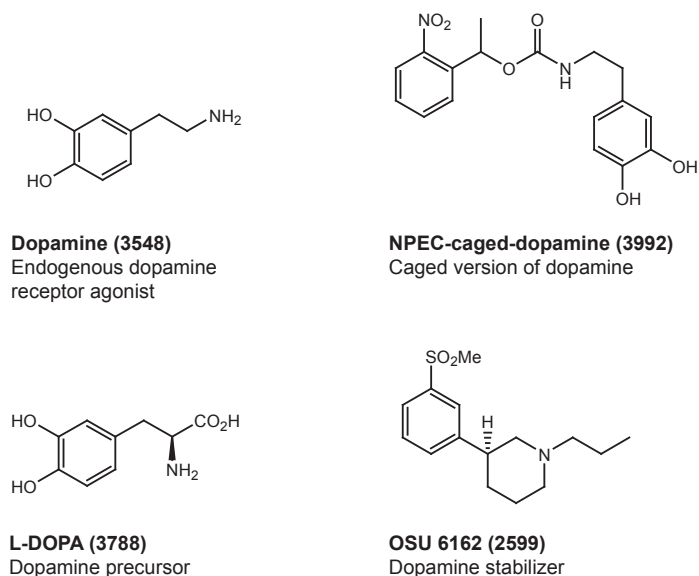
## Contents

## History

It was not until the late 1950s that dopamine was recognized as a neurotransmitter in its own right, but the demonstration of its non-uniform distribution in the brain, distinct from the distribution of noradrenaline, suggested a specific functional role for dopamine.[1] Interest in dopamine was intensified by the realization that dopamine had an important role in the pathogenesis or drug treatment of certain neurological disorders, e.g. Parkinson's disease and schizophrenia.[2,3] This led to much research on the sites of action of dopamine and the dopamine receptors (Box 1). One milestone was the suggestion by Cools and van Rossum, based on anatomical, electrophysiological and pharmacological studies, that there might be more than one kind of receptor for dopamine in the brain.[4] Biochemical studies on dopamine receptors in the 1970s based on second messenger assays (e.g. stimulation of cAMP production and ligand binding assays) supported the idea, and it was given a firm foundation by Kebabian and Calne in their 1979 review.[5] They extended an earlier suggestion by Spano *et al*,[6] and proposed that there were two classes of dopamine receptor, $D_1$ and $D_2$, with different biochemical and pharmacological properties, mediating different physiological functions. The properties of these two subtypes are summarized in Table 1. Selective agonists and antagonists exist to define the two subtypes in functional assays and some of these are shown in Table 1. Both the $D_1$ and $D_2$ subtypes are G protein-coupled receptors (GPCRs), yet different G proteins and effectors are involved in their signaling pathways (Figure 1, Table 1).

Although there were some indications of further heterogeneity of these dopamine receptor subtypes in biochemical studies, it was not until the late 1980s that the true extent of this was revealed with the application of gene cloning techniques. These studies have shown that there are at least five dopamine receptors ($D_1$-$D_5$) that may be divided into two subfamilies whose properties resemble the original $D_1$ and $D_2$ receptors.[7,8] The $D_1$-like receptor family, which comprises $D_1$ and $D_5$, corresponds to the original $D_1$ receptors whilst the $D_2$-like receptor family ($D_2$, $D_3$ and $D_4$ receptors) corresponds to the original $D_2$ receptors. A selection of the key properties of the receptor subtypes are summarized in Tables 2 and 3.

In subsequent discussion we refer to receptor subtypes defined from cloned genes as $D_1$, $D_2$, $D_3$, $D_4$, $D_5$, and where only the subfamily of receptor has been defined pharmacologically we use the $D_1$-like and $D_2$-like nomenclature.

## Box 1 │ Dopamine synthesis and metabolism

**Dopamine (3548)**
Endogenous dopamine
receptor agonist

**NPEC-caged-dopamine (3992)**
Caged version of dopamine

**L-DOPA (3788)**
Dopamine precursor

**OSU 6162 (2599)**
Dopamine stabilizer

# Properties of the Dopamine Receptor Subtypes

## Common receptor properties

Analysis of the amino acid sequences of the dopamine receptor subtypes has shown that significant homologies exist among the subtypes, with the greatest being found between members of either subfamily.[7,8] Each receptor has been shown to contain seven stretches of amino acids that are hydrophobic and long enough to span the membrane. It seems therefore that each of the dopamine receptors conforms to the general structural model for a GPCR,[9-11] with an extracellular amino terminus and seven putative membrane spanning α-helices linked by intracellular and extracellular protein loops (Figure 2). One or more potential sites for glycosylation are found on the amino terminus and second extracellular loop. The helices are bundled together in the membrane to form the ligand binding site (Figure 2); some information is available on the residues that make contact with ligands.[11,12] There is an intracellular carboxyl terminus, probably bearing a palmitoyl group, which may form a further link to the membrane. The $D_1$-like receptors have short third intracellular loops and long carboxyl terminal tails, whereas the $D_2$-like receptors have long third intracellular loops and short carboxyl terminal tails. This provides a structural basis for the division of the receptors into two subfamilies but is also likely to have a functional significance, possibly related to the specificity of receptor/G protein interaction.

The third intracellular loop, termed 'I3', is important for the interaction of the receptor and G protein. For the $D_2$-like receptors, variants of the subtypes exist based on this loop. For example, there are short and long splice variants of the $D_2$ and $D_3$ receptors with the long forms having an insertion (29 amino acids for the long $D_2$, $D_{2L}$) in this loop.[13,14] Polymorphic variants of the $D_2$ receptor have been described with single amino acid changes in I3.[15] The $D_4$ receptor is highly polymorphic

in the human population with variants containing different length insertions in I3.[16,17] In some cases, these $D_2$-like receptor variants may have differential abilities to couple to or activate G proteins,[18,19] and may also exhibit slightly different pharmacological properties.[16,20,21] Lines of mice have been developed in which the I3 insertion that produces the long $D_2$ receptor variant ($D_{2L}$) is deleted, resulting in the expression of only the short variant ($D_{2S}$). Characterization of these mice suggests that the splice variants are not fully interchangeable; some $D_2$ receptor responses are not observed in mice that express only $D_{2S}$.[22-24] The variants of the $D_4$ receptor have not been found to exhibit any substantive differences in agonist signaling or in coupling to G proteins.[25]

The individual properties of the different subtypes were initially probed by expressing the receptors in recombinant cells and examining the localization of the subtypes at the mRNA and protein level. More recently, the use of subtype-selective drugs and transgenic mice with one or more receptor subtypes genetically deleted has enabled further study of these receptors.

## Individual receptor properties

The dopamine receptor subtypes exhibit different properties in terms of their pharmacological profile, localization, and mechanism of action; these differences will be briefly summarized below.

### $D_1$-like receptors

Both the $D_1$ and $D_5$ receptors show pharmacological properties similar to those of the original pharmacologically defined $D_1$ receptor, that is, a high affinity for the benzazepine ligands SCH 23390, SCH 39166, and SKF 83566, which are selective antagonists for these subtypes. Although not as selective for $D_1$ over $D_2$ as the benzazepine antagonists, LE 300 is a potent $D_1$-like antagonist that is useful because it is structurally distinct from the benzazepines. Thioxanthines such as flupentixol and

## Figure 1 │ Regulation of adenylyl cyclase by $D_1$ and $D_2$ dopamine receptors
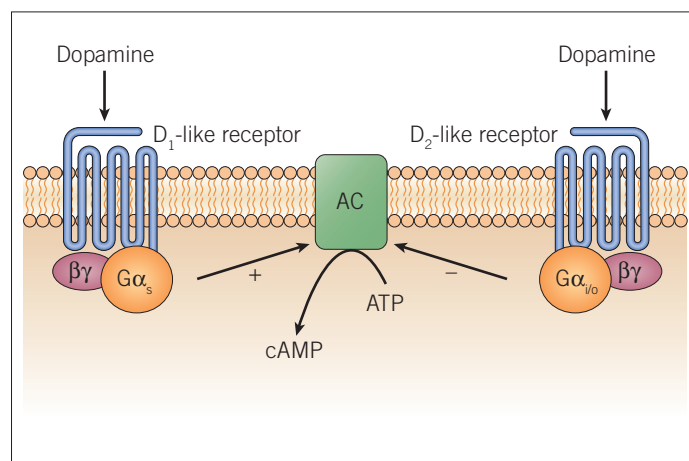
The diagram shows the effects of dopamine to stimulate or inhibit adenylyl cyclase (AC) via the $D_1$-like receptor and G protein $G\alpha_s$ or the $D_2$-like receptor and G protein $G\alpha_{i/o}$, respectively.

**Table 1 | Dopamine receptor subtypes defined from physiological, pharmacological, and biochemical studies**

| | $D_1$-like Receptors | $D_2$-like Receptors |
|---|---|---|
| **Physiological Functions** | Aspects of motor and cognitive function (brain), cardiovascular function | Aspects of motor function and behavior (brain), control of prolactin and α-MSH secretion from pituitary, cardiovascular function |
| **Biochemical Responses** | Adenylyl cyclase↑<br>Phospholipase C↑ | Adenylyl cyclase↓<br>$K^+$ channel activity↑<br>$Ca^{2+}$ channel activity↓<br>GSK-3β↑ |
| **Localization** | Caudate nucleus, putamen, nucleus accumbens, olfactory tubercle, cerebral cortex, cardiovascular system | Caudate nucleus, putamen, nucleus accumbens, olfactory tubercle, cerebral cortex, anterior and neurointermediate lobes of pituitary gland, cardiovascular system |
| **Receptor Antagonists** | **SCH 23390**<br>**SCH 39166**<br>**SKF 83566**<br>**LE 300** | **Domperidone**<br>**Nemonapride**<br>**Raclopride**<br>**(*S*)-(-)-Sulpiride** |
| **Receptor Agonists** | **A 77636**<br>SKF 38393<br>SKF 81297<br>**A 68930**<br>**SKF 81297**<br>Doxanthrine | PHNO<br>**Quinpirole**<br>N-0437<br>**Rotigotine**<br>**Sumanirole** |
| **Radioligands** | [³H]-SCH 23390*<br>[¹²⁵I]-SCH 23982 | [³H]-Nemonapride (YM-09151-2)<br>[³H]-Raclopride<br>[³H]-Spiperone** |

(Bold text denotes compounds available from Tocris at time of publication)

The localization data are from functional and ligand-binding studies on dispersed tissues and tissue slices. *[³H]-SCH 23390 can also bind to 5-HT₂ receptors if present; **[³H]-Spiperone can also bind to 5-HT₁ₐ, 5-HT₂ receptors, and α₁-adrenoceptors if present.

phenothiazines such as fluphenazine also show high affinity but are not selective for $D_1$-like over $D_2$-like receptors. The development of the first $D_1$-like receptor agonist, SKF 38393, was important for differentiating between activation of $D_1$-like and $D_2$-like receptors, although it was later realized that the partial agonist nature of SKF 38393 produced an under-appreciation of the contribution of $D_1$-like receptors to behavior.[26] The $D_1$-like receptors show moderate affinities for typical dopamine agonists such as apomorphine; full and/or selective $D_1$-like receptor agonists such as such as A 77636, A 68930, SKF 81297, dihydrexidine, and doxanthrine are now available (Box 2). There are minor differences in the affinities of some compounds for the $D_1$ and $D_5$ receptors (higher agonist and lower antagonist affinities for $D_5$), but no compounds that effectively distinguish between those subtypes are as yet available.[27,28]

$D_1$ receptors are found at high levels in the typical dopamine-rich regions of brain such as the neostriatum, substantia nigra, nucleus accumbens, and olfactory tubercle, whereas the distribution of the $D_5$ receptors is much more restricted (Table 2); this subtype is found generally at much lower levels. Both receptors are able to stimulate adenylyl cyclase (Figure 1), with the $D_5$ receptor showing some constitutive activity for this response.[28] Inverse agonist activity at the $D_1$ and $D_5$ receptors is seen in recombinant systems for some compounds such as butaclamol,[28] which were previously considered to be antagonists. It has been known for some time that stimulation of a $D_1$-like receptor leads to activation of phospholipase C[29] and recently this response has been linked to the $D_1/D_2$ receptor heterodimer, providing a function for heterodimer formation.[30] Agonists that preferentially stimulate the cAMP response

(SKF 83822) or the phospholipase C response (SKF 83959) associated with $D_1$-like receptors have been described.[31]

The $D_1$ receptor seems to mediate important actions of dopamine to control movement, cognitive function, and cardiovascular function. Direct interactions between $D_1$-like receptors and ion channel-linked receptors have been described ($D_1$/NMDA, $D_5$/GABA$_A$),[32] leading to modulation of receptor function. These interactions provide for cross talk between fast and slow neurotransmitter systems and may point towards a further functional role for the $D_5$ receptor, which is not well understood. Studies with null mutant 'knock-out' mice have suggested that in some respects, the functions of the $D_1$ and $D_5$ receptors are reciprocal – for example, with respect to spontaneous locomotion – and in other respects similar, for example with respect to grooming or psychostimulant-induced locomotion.[33,34]

### $D_2$-like receptors

Overall, the $D_2$, $D_3$ and $D_4$ receptors exhibit pharmacological properties similar to those of the originally defined $D_2$ receptor; that is, they all show high affinities for drugs such as the butyrophenones (haloperidol, spiperone) and substituted benzamides (sulpiride, raclopride), and these classes of drugs provide selective antagonists for $D_2$-like receptors over $D_1$-like receptors (Table 3). As indicated above, the $D_2$-like receptors also show high affinities for phenothiazines and thioxanthines. Each $D_2$-like receptor has its own pharmacological signature, so there are some differences in affinities of drugs for the individual $D_2$-like receptors (Box 3). For example, sulpiride and raclopride show high affinity for the $D_2$ and $D_3$ receptors but

## Figure 2 | Schematic representation of a G protein-coupled dopamine receptor
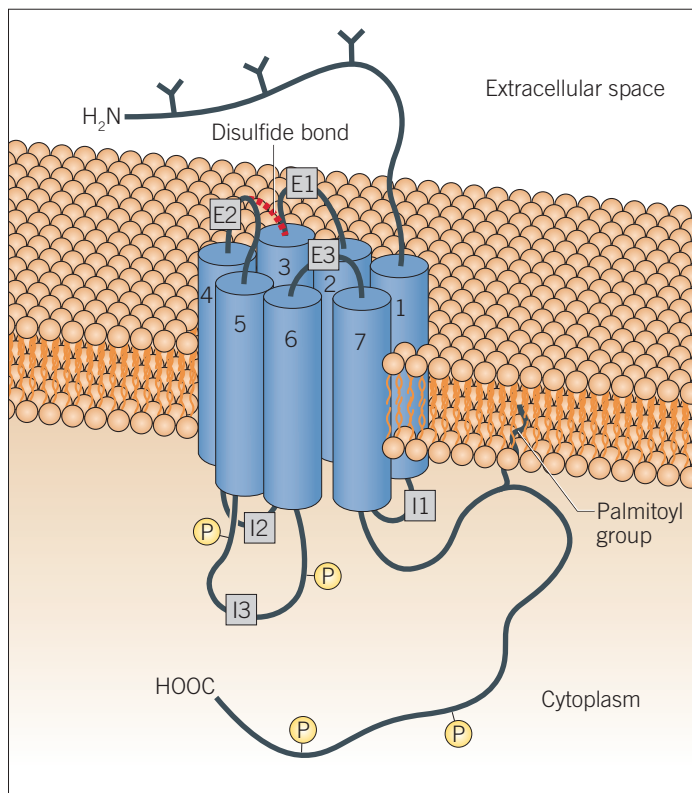


The diagram shows the seven helices bundled together in the membrane and the intra- (I1, I2, I3) and extracellular (E1, E2, E3) loops. The ligand binding site is contained in the cavity formed between the helices. There may be an eighth helix formed in the carboxyl terminus parallel to the membrane (not shown). There is also a disulfide bond between E2 and the top of helix 3. The helices have been drawn parallel to one another for clarity but in fact there are kinks in the helices and they are not fully parallel. I3 and the carboxyl terminus contain multiple sites for phosphorylation that are involved in regulation of receptor responsiveness and interactions with adapter proteins.

a lower affinity for the $D_4$ receptor (Box 4). Clozapine displays moderate selectivity for the $D_4$ receptor. Most $D_2$ antagonists show a higher affinity for the $D_2$ receptor compared with the $D_3$ and $D_4$ receptors; this is because the $D_2$ receptor, being overall much more abundant in brain than the other $D_2$-like receptors, corresponds to the pharmacologically defined $D_2$-like receptor for which these drugs were developed. The molecular cloning of additional $D_2$-like receptors enabled the development of more selective antagonists that are invaluable in determining the functions of these subtypes. For example, L-741,626, NGB 2904, and L-745,870 are $D_2$ selective (~40-fold), $D_3$ selective (~200-fold) and $D_4$ selective (~2000-fold) antagonists respectively.[35,36]

Selective agonists for the $D_2$-like receptors relative to the $D_1$-like receptors, e.g. N-0437, PHNO, and quinpirole, have been developed. Sumanirole is a full-efficacy agonist that is highly selective for the $D_2$ receptor over other dopamine receptors.[37] There are a number of $D_4$ agonists of varying efficacy and selectivity, with A 412997 being an example of a highly selective full

## Box 2 | $D_1/D_5$ receptors
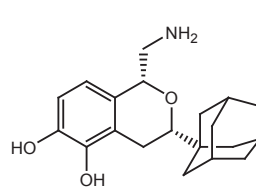
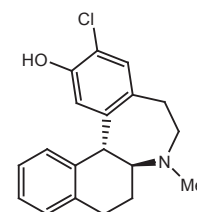

**A 77636 (1701)**
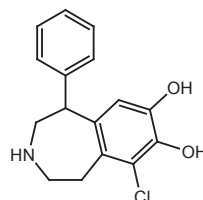Potent, selective $D_1$-like agonist; orally active
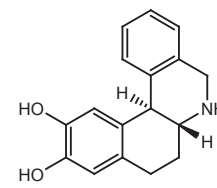
**Dihydrexidine (0884)**
Full $D_1$-like agonist
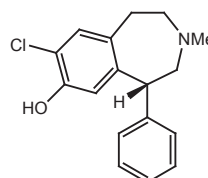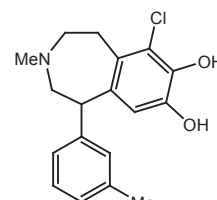
**SCH 23390 (0925)**
Standard selective $D_1$-like antagonist. Also 5-HT$_{2C}$ agonist

**SCH 39166 (2299)**
High affinity $D_1/D_5$ receptor antagonist

**SKF 81297 (1447)**
$D_1$-like agonist

**SKF 83959 (2074)**
$D_1$-like partial agonist

$D_4$ agonist (Box 5).[38] Many agonists appear to be highly selective for the $D_3$ receptor over other $D_2$-like receptors in radioligand binding assays, but this frequently reflects an invalid comparison between a mixed population of agonist high- and low-affinity $D_2$ receptors, and the $D_3$ receptor that is apparently constrained in an agonist-high affinity conformation,[39] rather than a difference in drug concentrations capable of activating the two subtypes.[40] When care is taken to compare functional responses or binding to the agonist high-affinity state of the receptors, dopamine and some agonists such as pramipexole are determined to be modestly $D_3$ selective.[41]

The $D_2$ receptor is the predominant $D_2$-like subtype in the brain, located at high levels in typical dopamine rich brain areas. $D_3$ and $D_4$ receptors are found at much lower levels and in a more restricted distribution pattern, located predominantly in limbic areas of the brain (Table 2). Some $D_3$ receptors are also found in regions associated with motor function such as the putamen. The $D_2$-like receptor subtypes have each been shown to inhibit adenylyl cyclase (Figure 1) when expressed in recombinant cells,[40,42,43] although the signal via the $D_3$ receptor has proven more difficult to demonstrate and is generally lower than for the other two subtypes. This may relate to preferential coupling of the $D_3$ receptor to specific adenylyl cyclase isoforms.[44]

**Table 2 | Dopamine receptor subtypes identified by molecular biological studies**

| | $D_1$-like | | $D_2$-like | | |
|---|---|---|---|---|---|
| | $D_1$ | $D_5$ | $D_{2S/L}$ | $D_3$ | $D_4$ |
| **Amino Acids** | 446 (human, rat) | 477 (human) 475 (rat) | 414/443 (human) 415/444 (rat) | 400 (human) 446 (rat) | 387 (human*, rat) |
| **Homology** | | | | | |
| with $D_1$ | 100% | 82% | 44% | 44% | 42% |
| with $D_2$ (short) | 44% | 49% | 100% | 76% | 54% |
| **Localization** | Caudate/putamen, nucleus accumbens, olfactory tubercle, hypothalamus, thalamus, frontal cortex | Hippocampus, thalamus, lateral mamillary nucleus, striatum, cerebral cortex (all low) | Caudate/putamen, nucleus accumbens, olfactory tubercle, cerebral cortex (low) | Nucleus accumbens, olfactory tubercle, islands of Calleja, putamen (low), cerebral cortex (low) | Frontal cortex, midbrain, amygdala, hippocampus, hypothalamus, medulla (all low), retina |
| **Response** | Adenylyl cyclase↑ | Adenylyl cyclase↑ | Adenylyl cyclase↓ | Adenylyl cyclase↓ | Adenylyl cyclase↓ |
| **Introns in Gene** | None | None | Yes | Yes | Yes |
| **Organization of Amino Acid Sequence** | | | | | |
| Third intracellular loop | Short | Short | Long | Long | Long |
| Carboxyl terminal tail | Long | Long | Short | Short | Short |
| Reference | 65 | 27 | 66 | 67 | 68 |

The properties of the principal dopamine receptor subtypes identified by gene cloning are shown. They are divided into '$D_1$-like' and '$D_2$-like' groups to reflect amino acid homology, functional similarity, structural similarity, and pharmacological properties. This grouping conforms with a previous classification based on pharmacological and biochemical properties (Table 1). $D_{2S}$ and $D_{2L}$ refer to different alternatively spliced forms of the $D_2$ receptor gene. The homology values are for the transmembrane-spanning regions.[69] The localizations and relative expression levels shown are the principal ones known at present from *in-situ* hybridization and use of the polymerase chain reaction. Some pharmacological data for the different receptor subtypes is given in Table 3. *The human $D_4$ receptor has many longer allelic variants. For further information on the properties of the dopamine receptor subtypes, please consult reference 8.

The $D_2$-like receptors will, upon activation, stimulate a range of processes including acute signaling events (inhibition of adenylyl cyclase, stimulation of $K^+$ channels, inhibition of $Ca^{2+}$ channels, stimulation of arachidonic acid release) and longer term events (MAP kinase and β-arrestin-2/Akt/GSK-3 signaling, and mitogenesis).[45,46] $D_3$ receptor-mediated signaling events are often of lower magnitude than for the other $D_2$-like receptors. The relation of these signaling events to *in vivo* responses is only beginning to be clarified. Many compounds that were thought to be antagonists at $D_2$-like receptors – such as the antipsychotic drugs haloperidol, chlorpromazine, and clozapine – have been shown to possess inverse agonist activity at $D_2$ and $D_3$ receptors.[47-49] This inverse agonism may contribute to the increases in $D_2$ receptor number seen in the brain when experimental animals are treated chronically with these drugs.

The $D_2$ receptor is important for mediating the effects of dopamine to control movement, certain aspects of behavior in the brain and prolactin secretion from the anterior pituitary

**Table 3 | Pharmacological properties of the dopamine receptor subtypes**

| Drug | Receptor Affinity, $K_i$ (nM) | | | | |
|---|---|---|---|---|---|
| | $D_1$ | $D_5$ | $D_2$ | $D_3$ | $D_4$ |
| **Chlorpromazine** | 73 | 133 | 0.55 | 1.2 | 9.7 |
| **Clozapine** | 141 | 250 | 35 | 83 | 22 |
| **Dopamine**† | 2340 | 228 | 1705 | 27 | 450 |
| **Haloperidol** | 27 | 48 | 0.53 | 2.7 | 2.3 |
| **Raclopride** | >72000 | – | 1 | 1.8 | 2400 |
| **SCH 23390** | 0.35 | 0.3 | 267 | 314 | 3560 |
| **SCH 39166** | 1.2 | 2 | 980 | – | 5520 |
| **SKF 83566** | 0.3 | 0.4 | 2000 | – | – |
| **(S)-(-)-Sulpiride** | 36000 | 77000 | 2.5 | 8 | 1000 |

Values for the dissociation constants are given for ligands, determined using ligand binding assays for the five dopamine receptor subtypes. As far as possible, values are given that avoid artefacts present in ligand binding assays with high affinity radioligands.[3] †Data for dopamine were obtained in the presence of Gpp(NH)p and therefore represent the agonist low-affinity state. Data taken from references 3, 8, 21, 27 and 70.
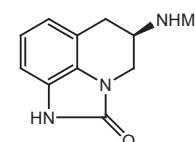
**Box 3 | $D_2$ receptors**

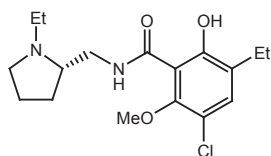**L-741,626 (1003)**
High affinity $D_2$ antagonist
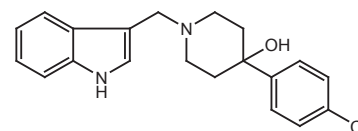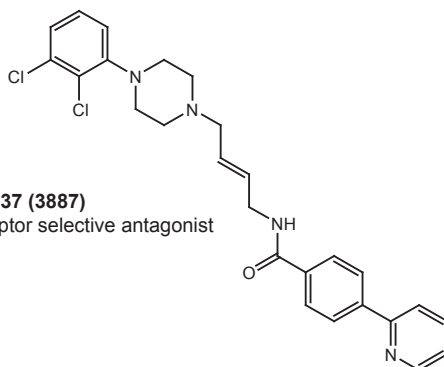
**(-)-Quinpirole (1061)**
Selective $D_{2-4}$ agonist
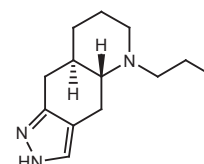
**Sumanirole (2773)**
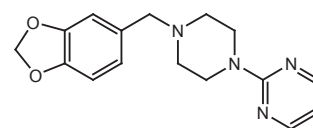$D_2$-selective agonist
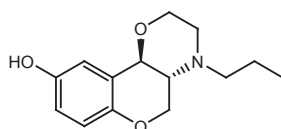
**Box 4 | D$_3$ receptors**

**Eticlopride (1847)**
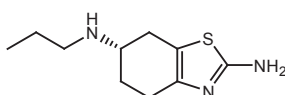Selective D$_2$/D$_3$ antagonist (D$_3$ > D$_2$)

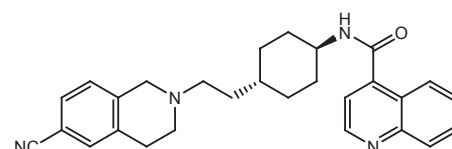**PG 01037 (3887)**
D$_3$ receptor selective antagonist

**Piribedil (1031)**
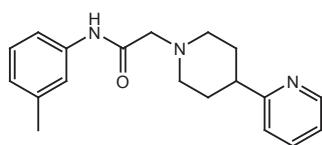D$_2$/D$_3$ receptor agonist (D$_3$ > D$_2$)

**(+)-PD 128907 (1243)**
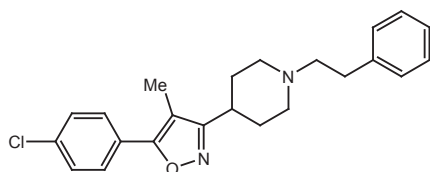D$_3$ agonist (D$_3$ ≥ D$_2$ > D$_4$)

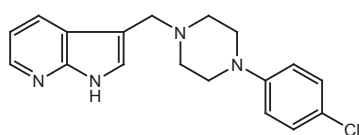**Pramipexole (4174)**
Selective D$_3$ agonist

**SB 277011A (4207)**
Selective D$_3$ antagonist
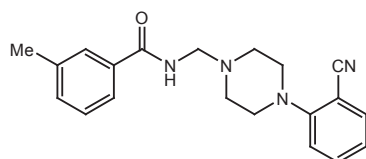
**Box 5 | D$_4$ receptors**

**A 412997 (4552)**
Selective D$_4$ agonist

**L-741,742 (1004)**
Highly selective D$_4$ antagonist

**L-745,870 (1002)**
Highly selective D$_4$ antagonist

**PD 168077 (1065)**
High affinity, selective D$_4$ agonist

gland. The functions of the D$_3$ and D$_4$ receptors are currently unknown, although their localizations in limbic areas of brain suggest roles in cognitive, emotional, and behavioral function. These properties have made them attractive targets for the design of potential selective antipsychotic drugs. The D$_2$-like receptors show high affinities for most of the drugs used to treat schizophrenia (antipsychotics) and Parkinson's disease (e.g. bromocriptine).[3] L-745,870 was the first highly selective D$_4$ antagonist synthesized, but it proved to be inactive against the psychosis of schizophrenia.[50]

## Future Directions

### Understanding the role of the dopamine receptor subtypes
We are still a long way away from understanding the role of the different receptor subtypes. Although partially selective antagonists and transgenic 'receptor knock out' animals are available for some of the subtypes, much is still to be done here (see for example Waddington *et al* (2005)[31]).

### Dopamine receptor subtypes in drug discovery
Due to the importance of dopamine for the pathogenesis or drug treatment of several important disorders e.g. Parkinson's disease, schizophrenia and pituitary prolactin dysfunction, dopamine receptors have been very popular as targets for drug discovery campaigns (Box 6). This continues to be the case and indications have expanded into areas such as drug dependence and penile erectile dysfunction. A new development in the search for effective antipsychotics has been the development of dopamine D$_2$-like partial agonists such as aripiprazole.[51] It had been thought that antipsychotics had to be antagonists/inverse agonists at the D$_2$ receptor,[3] yet the effective use of D$_2$ partial agonists as antipsychotics raises questions about the mechanism of D$_2$ receptor-mediated antipsychotic activity that need

**Box 6 | Atypical antipsychotics**

**Quetiapine (4735)**
5-HT$_2$/D$_2$ antagonist;
atypical antipsychotic
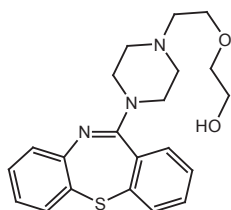
**Paliperidone (4493)**
5-HT$_{2A}$ and D$_2$ antagonist;
atypical antipsychotic
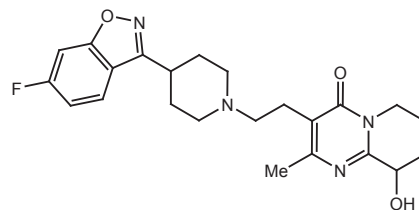
**Remoxipride (0916)**
Selective D$_2$ antagonist;
atypical antipsychotic

**Risperidone (2865)**
5-HT$_{2A}$/D$_2$ antagonist;
atypical antipsychotic

to be addressed.[52] It will be important, for example, to understand the relationship between the efficacy of the ligands in signaling assays and their therapeutic effects.
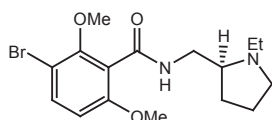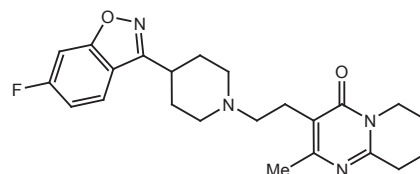
An important new tool for the rational design of subtype-selective drugs is the availability of crystal structures for the D$_3$ receptor and the β$_2$-adrenoceptor.[10,11] These structures and the precise models that can be constructed on the basis of their close homology with other D$_2$-like receptors and the D$_1$-like receptor, respectively, make it possible to predict the affinity of a receptor for molecules that may be novel scaffolds.[53,54]

**Biochemical mechanisms underlying the effects of dopamine receptor activation**
It will be very important to define clearly how activation of dopamine receptors leads to changes in the function of cells such as neurons. In time, this will lead to a better understanding of how drugs act on the brain. Important progress has been made in this area. For example, in striatal neurons it has been shown that a protein strongly regulated by dopamine receptors is DARPP-32 (dopamine and cAMP-regulated phosphoprotein 32 kD). DARPP-32 seems to be a key protein in striatal neuronal function.[55] Important progress has also been made in understanding temporal aspects of signaling processes in the brain. It has been suggested that there may be two waves of dopamine-mediated responses: one set of faster responses associated with changes in cAMP and DARPP-32 phosphorylation, and another slower set of non-cAMP mediated processes associated with β-arrestin-2/Akt/GSK-3 signaling.[46]

**Interactions of dopamine receptors with other proteins**
It is becoming clear that interactions of the dopamine receptors with other proteins are very important in determining their function; this will be an active field of research in the future. As a group, the cytoskeletal, adapter, and signaling proteins that interact with dopamine receptors have been termed DRIPs (dopamine receptor-interacting proteins).[56] An example includes the neuronal Ca$^{2+}$ sensor-I (NCS-1) which interacts

with D$_2$.[57] In this case, the interacting proteins may mediate the effects of Ca$^{2+}$ on the D$_2$ receptor. Interactions also occur with other receptors including ligand-gated ion channels, and GPCRs leading to homo- and heterodimer formation. A role for D$_1$/D$_2$ heterodimer formation has been suggested,[58] and roles for homodimer formation, e.g. D$_2$ homodimers,[59,60] are being actively pursued.

**Development and characterization of biased ligands**
A promising new avenue for drug development is based on the observation that many ligands do not engage, to the same extent, all of the mechanisms that are consequences of activation of a receptor; activation of a receptor by its endogenous agonist may activate G protein- and β-arrestin-mediated signaling, phosphorylation of the receptor by one or more protein kinases, desensitization, and receptor internalization followed by either recycling or degradation of the receptor. A given ligand may be fully efficacious (i.e., a full agonist) for some of these responses, and a partial agonist or an antagonist at other responses mediated by the same receptor.[61,62] This phenomenon is referred to as functional selectivity, and a ligand that engages only some of the repertoire of responses available to a receptor is a functionally selective (or 'biased') ligand.

The D$_1$ receptor is a promising target for treatment of Parkinson's disease, with two impediments to the use of D$_1$ agonists being rapid development of tolerance and the side effects of hypotension and seizures.[63] Both of these impediments could potentially be addressed through the development of biased agonists. For example, SKF 83822 is a functionally selective ligand biased towards D$_1$-mediated signaling via adenylyl cyclase that also induces seizures at high doses,[64] while SKF 83959 preferentially activates the D$_1$/D$_2$ receptor heteromer and the associated phospholipase C response.[30] Ligands biased towards either G protein- or β-arrestin-mediated signaling pathways modulated by the D$_2$ receptor are also of considerable interest as pharmacological tools and as potential antipsychotic drugs that may be more efficacious or have fewer side effects.

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# Dopamine Compounds Available from Tocris

| Cat. No. | Product Name | Primary Action |
| --- | --- | --- |
| **$D_1$ and $D_5$ Receptors** | | |
| 1534 | A 68930 | Potent, selective $D_1$-like agonist |
| 1701 | A 77636 | Potent, selective $D_1$-like agonist; orally active |
| 1249 | CY 208-243 | Selective $D_1$-like agonist |
| 0884 | Dihydrexidine | Selective $D_1$-like agonist |
| 1659 | Fenoldopam | Selective $D_1$-like partial agonist |
| 1674 | LE 300 | Potent and selective dopamine $D_1$ antagonist |
| 0925 | SCH 23390 | Standard selective $D_1$-like antagonist. Also 5-$HT_{2C}$ agonist |
| 2299 | SCH 39166 | High affinity $D_1/D_5$ receptor antagonist |
| 0922 | SKF 38393 | Selective $D_1$-like agonist |
| 1662 | SKF 77434 | Selective $D_1$-like partial agonist |
| 1447 | SKF 81297 | $D_1$ agonist |
| 1586 | SKF 83566 | Potent, selective $D_1$-like antagonist |
| 2075 | SKF 83822 | Selective $D_1$-like agonist |
| 2074 | SKF 83959 | $D_1$-like partial agonist |
| **$D_2$ Receptors** | | |
| 0524 | AMI-193 | 5-$HT_2/D_2$ antagonist |
| 2132 | Amisulpride | Selective $D_2/D_3$ receptor antagonist; atypical antipsychotic agent |
| 2759 | B-HT 920 | $D_2$ receptor agonist. Also $\alpha_2$ agonist and 5-$HT_3$ antagonist |
| 2664 | Cabergoline | $D_2/D_3$ agonist |
| 2193 | Carmoxirole | Selective, peripherally acting $D_2$ agonist |
| 0475 | Dihydroergotamine | Partial $D_2$ agonist. Also partial $\alpha$ agonist and 5-HT antagonist |
| 2536 | Domperidone | Peripheral $D_2/D_3$ antagonist |
| 0701 | 3'-Fluorobenzylspiperone | Potent $D_2$ receptor ligand |
| 3940 | GSK 789472 | $D_2$ partial agonist; $D_3$ antagonist |
| 0931 | Haloperidol | High affinity dopamine receptor antagonist; displays some $D_2$ selectivity |
| 1003 | L-741,626 | High affinity $D_2$ antagonist |
| 2495 | Melperone | $D_2/5$-$HT_{2A}$ receptor antagonist; neuroleptic |
| 1746 | Nemonapride | Highly potent, selective $D_2$-like antagonist. Also 5-$HT_{1A}$ agonist |
| 4349 | Olanzapine | 5-$HT_{2A}/D_2$ antagonist; atypical antipsychotic |
| 4493 | Paliperidone | 5-$HT_{2A}$ and $D_2$ antagonist; atypical antipsychotic |
| 3287 | Prochlorperazine | $D_2$ receptor antagonist. Also 5-$HT_3$ and nAChR antagonist |
| 4735 | Quetiapine | 5-$HT_2/D_2$ antagonist; atypical antipsychotic |
| 1519 | Quinelorane | $D_2$ and $D_3$ agonist |
| 1061 | (-)-Quinpirole | Selective $D_{2-4}$ agonist |
| 1810 | Raclopride | Potent, selective $D_2/D_3$ antagonist |
| 0916 | Remoxipride | Selective $D_2$ antagonist; atypical antipsychotic |
| 2865 | Risperidone | $D_2/5$-$HT_{2A}$ antagonist; atypical antipsychotic |
| 3896 | Rotigotine | Dopamine $D_2/D_3$ agonist |
| 0995 | Spiperone | $D_2$-like antagonist ($D_2 > D_4 > D_3$). Also 5-$HT_{2A}$ antagonist |
| 0894 | (*RS*)-(±)-Sulpiride | Selective $D_2/D_3$ receptor antagonist |
| 2773 | Sumanirole | $D_2$-selective agonist |
| 0775 | (+)-UH 232 | $D_2$ autoreceptor antagonist. Also $D_3$ partial agonist |
| 3085 | Ziprasidone | 5-$HT_{2A}/D_2$ antagonist; atypical antipsychotic |
| 3996 | Zotepine | 5-$HT_{2A}/D_2$ antagonist; atypical antipsychotic |

| Cat. No. | Product Name | Primary Action |
|---|---|---|
| **$D_3$ Receptors** | | |
| 2132 | Amisulpride | Selective $D_2$/$D_3$ receptor antagonist; atypical antipsychotic agent |
| 0427 | Bromocriptine | Selective $D_2$/$D_3$ agonist ($D_3$ > $D_2$) |
| 0706 | 7-Hydroxy-DPAT | Dopamine agonist ($D_3 \geq D_2 = D_4$) |
| 1847 | Eticlopride | Selective $D_2$/$D_3$ antagonist ($D_3$ > $D_2$) |
| 1109 | GR 103691 | Highly selective $D_3$ antagonist |
| 3940 | GSK 789472 | $D_3$ antagonist. Also $D_2$ partial agonist |
| 1347 | Nafadotride | Highly potent, preferential $D_3$ antagonist |
| 2635 | NGB 2904 | Potent and selective $D_3$ antagonist |
| 1243 | (+)-PD 128907 | $D_3$ agonist ($D_3 \geq D_2 > D_4$) |
| 3887 | PG 01037 | $D_3$ receptor selective antagonist |
| 0719 | 7-Hydroxy-PIPAT | $D_3$ agonist ($D_3$ > $D_2$) |
| 1031 | Piribedil | $D_2$/$D_3$ receptor agonist ($D_3$ > $D_2$) |
| 3355 | PNU 177864 | Highly selective $D_3$ antagonist |
| 4174 | Pramipexole | Selective $D_3$ agonist |
| 1519 | Quinelorane | $D_2$ and $D_3$ agonist |
| 1061 | (-)-Quinpirole | Selective $D_{2-4}$ agonist |
| 1810 | Raclopride | Potent, selective $D_2$/$D_3$ antagonist |
| 3680 | Ropinirole | Selective $D_2$-like agonist ($D_3 > D_2 > D_4$) |
| 3896 | Rotigotine | Dopamine $D_2$/$D_3$ agonist |
| 4207 | SB 277011A | Selective $D_3$ antagonist |
| 0895 | (S)-(-)-Sulpiride | Selective $D_2$-like receptor antagonist ($D_3 > D_2 > D_4$) |
| 1357 | U 99194 | Potent, selective $D_3$ antagonist |
| **$D_4$ Receptors** | | |
| 4552 | A 412997 | Selective $D_4$ agonist |
| 2214 | ABT 724 | Potent, selective $D_4$ partial agonist; proerectile |
| 0444 | Clozapine | Dopamine antagonist with some $D_4$ selectivity. Also 5-$HT_{2A/2C}$ antagonist |
| 0782 | 2-CMDO | $D_4$/$D_2$ antagonist |
| 2645 | Fananserin | $D_4$ antagonist. Also 5-$HT_{2A}$ antagonist |
| 1004 | L-741,742 | Highly selective $D_4$ antagonist |
| 1002 | L-745,870 | Highly selective $D_4$ antagonist |
| 3298 | NGD 94-1 | Selective $D_4$ receptor ligand |
| 1065 | PD 168077 | High affinity, selective $D_4$ agonist |
| 3529 | PD 168568 | Potent and selective $D_4$ antagonist |
| 2735 | PNU 96415E | $D_4$ and 5-$HT_{2A}$ antagonist; antipsychotic |
| 1061 | (-)-Quinpirole | Selective $D_{2-4}$ agonist |
| 2329 | Ro 10-5824 | Selective $D_4$ receptor partial agonist |
| 4185 | Sonepiprazole | Selective $D_4$ receptor antagonist |
| **Dopamine Receptors (Non-selective)** | | |
| 0678 | (+)-AJ 76 | Dopamine receptor antagonist; displays preferential action at $D_2$-like autoreceptors |
| 2073 | (R)-(-)-Apomorphine | Dopamine receptor agonist; non-subtype-selective |
| 3737 | Asenapine | Novel antipsychotic agent; dopamine receptor antagonist |
| 0474 | Dihydroergocristine | Partial dopamine receptor agonist. Also partial adrenergic agonist and 5-HT antagonist |
| 3548 | Dopamine | Endogenous agonist at dopamine $D_{1-5}$ receptors |
| 4057 | Flupenthixol | Dopamine receptor antagonist |
| 4052 | Lisuride | Dopamine receptor agonist; antiparkinson's agent |

| Cat. No. | Product Name | Primary Action |
|---|---|---|
| 1644 | Mesulergine | Dopamine receptor partial agonist. Also 5-HT$_{2A}$ and 5-HT$_{2C}$ antagonist |
| 0937 | Pimozide | D$_2$-like antagonist. Also binds with high affinity to 5-HT$_7$ receptor. Ca$^{2+}$ channel blocker |
| 1559 | Roxindole | Dopamine D$_2$ autoreceptor agonist. Also displays affinity for D$_3$, D$_4$, 5-HT$_{1A}$ receptors and 5-HT transporters |
| 3070 | Thioridazine | Dopamine receptor antagonist; antipsychotic |
| **Dopamine Transporters** | | |
| 4357 | Bicifadine | Noradrenaline, 5-HT and dopamine re-uptake inhibitor |
| 4798 | (*S*)-Duloxetine | Potent 5-HT and noradrenaline reuptake inhibitor; also blocks dopamine reuptake |
| 0513 | GBR 12783 | Potent, selective dopamine uptake inhibitor |
| 0421 | GBR 12909 | Selective dopamine uptake inhibitor. Also σ ligand |
| 4351 | JHW 007 | High affinity dopamine uptake inhibitor |
| 2742 | Reserpine | Inhibitor of vesicular monoamine transport |
| 2175 | Tetrabenazine | Potent inhibitor of vesicular monoamine transport; depletes dopamine stores |
| **Related Products** | | |
| 2813 | D-Amphetamine | Induces dopamine, 5-HT and noradrenaline release |
| 3788 | L-DOPA | Dopamine precursor |
| 2547 | 6-Hydroxydopamine | Selective catecholaminergic neurotoxin |
| 3992 | NPEC-caged-dopamine | Caged version of dopamine (Cat. No. 3548) |
| 2599 | OSU 6162 | Dopamine stabilizer |
| 0730 | 4-Phenyl-1,2,3,4-tetrahydroisoquinolone | Dopamine release inhibitor |

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