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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.

## History

It was not until the late 1950's that dopamine was recognised as a neurotransmitter in its own right but the demonstration of its non uniform distribution in the brain suggested a specific functional role for dopamine.<sup>1</sup> Interest in dopamine was intensified by the realisation that dopamine had an important role in the pathogenesis or drug treatment of certain brain diseases e.g. Parkinson's disease, schizophrenia.<sup>2</sup> This led to much research on the sites of action of dopamine and the dopamine receptors. A 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.<sup>3</sup> Biochemical studies on dopamine receptors in the 1970's, based on second messenger assays e.g. stimulation of cAMP production and ligand binding assays, supported the idea of more than one kind of dopamine receptor. This idea was given a firm foundation by Keabian and Calne in their 1979 review.<sup>4</sup> They extended an earlier suggestion by Spano,<sup>5</sup> and proposed that there were two classes of dopamine receptor, D<sub>1</sub> and D<sub>2</sub>, with different

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

	<b>D<sub>1</sub> Receptors</b>	<b>D<sub>2</sub> Receptors</b>
<b>Physiological functions</b>	Aspects of motor function (brain), cardiovascular function	Aspects of motor function and behaviour (brain), control of prolactin and $\alpha$ MSH secretion from pituitary, cardiovascular function
<b>Biochemical responses</b>	Adenylyl cyclase $\uparrow$ Phospholipase C $\uparrow$	Adenylyl cyclase $\downarrow$ K <sup>+</sup> channel $\uparrow$ Ca <sup>2+</sup> channel $\downarrow$
<b>Localisation</b>	Caudate nucleus, putamen, nucleus accumbens, olfactory tubercle, cerebral cortex (brain), cardiovascular system	Caudate nucleus, putamen, nucleus accumbens, olfactory tubercle, cerebral cortex (brain) anterior and neurointermediate lobes of pituitary gland, cardiovascular system
<b>Selective antagonists</b>	<b>SCH 23390</b> <b>SCH 39166</b> <b>SKF 83566</b>	<b>Domperidone</b> <b>Nemonapride</b> <b>Raclopride</b> <b>(-)-Sulpiride</b>
<b>Selective agonists</b>	<b>A 77636</b> <b>R-(+)-SKF 38393<sup>†</sup></b> <b>R-(+)-SKF 81297<sup>†</sup></b> <b>Dihydroxidine</b>	PHNO <b>Quinpirole</b> N-0437
<b>Specific radioligands</b>	[ <sup>3</sup> H]-SCH 23390* [ <sup>125</sup> I]-SCH 23982	[ <sup>3</sup> H]-Nemonapride [ <sup>3</sup> H]-Raclopride [ <sup>3</sup> H]-Spiperone**

(Bold Text Denotes Compounds Available From Tocris)

With the advent of molecular biological studies (Table 2), these subtypes should be termed D<sub>1</sub>-like and D<sub>2</sub>-like receptors. The localisation data are from functional and ligand-binding studies on dispersed tissues and tissue slices. \* [<sup>3</sup>H]SCH23390 can also bind to 5-HT<sub>2</sub> receptors if present ; \*\* [<sup>3</sup>H]Spiperone can also bind to 5-HT<sub>1A</sub>, 5-HT<sub>2</sub> receptors, and  $\alpha_1$ -adrenoceptors if present. <sup>†</sup>Racemate available from Tocris

biochemical and pharmacological properties, mediating different physiological functions. The properties of these two subtypes are summarised 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), however different G proteins and effectors are involved in their signalling 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 1980's that the true extent of this was revealed with the application of gene cloning techniques. This has 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.<sup>6,7</sup> The two subfamilies are often termed  $D_1$ -like ( $D_1$ ,  $D_5$ ) and  $D_2$ -like ( $D_2$ ,  $D_3$ ,  $D_4$ ) and some of their key properties are summarised in Tables 2 and 3.

In subsequent discussion I shall 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 I shall use the  $D_1$ -like and  $D_2$ -like nomenclature.

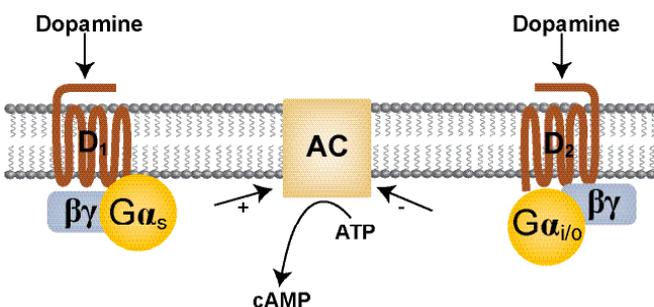
## Properties of the Dopamine Receptor Subtypes

### 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.<sup>6,7</sup> 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

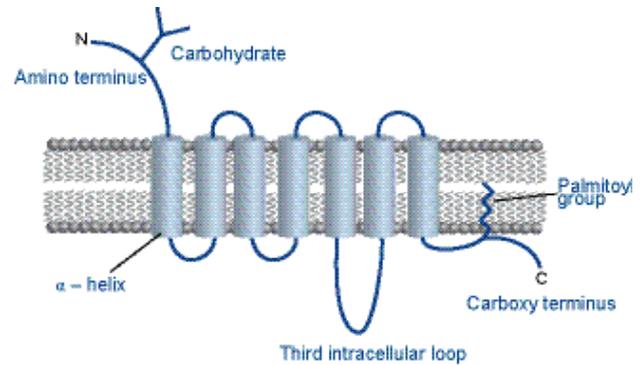
**Figure 1 | Regulation of adenylyl cyclase by  $D_1$  and  $D_2$  dopamine receptors**

The diagram shows the effects of dopamine to stimulate or inhibit adenylyl cyclase (AC) via the  $D_1$  receptor and G protein  $G\alpha_s$  or the  $D_2$  receptor and G protein  $G\alpha_{i/o}$  respectively.



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

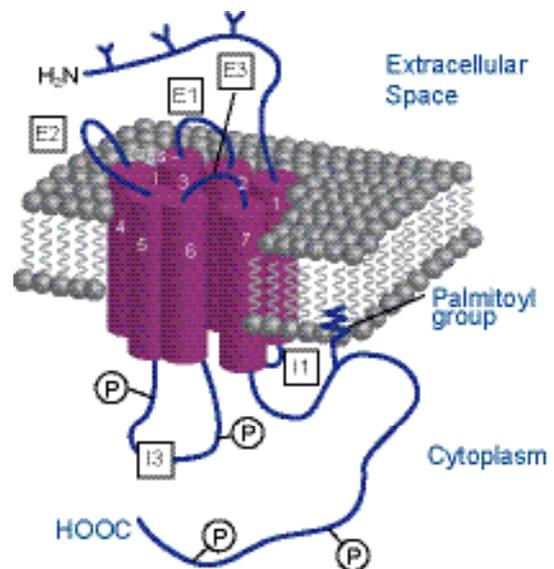
The diagram shows the arrangement of the seven transmembrane spanning  $\alpha$ -helices and their associated loops.



receptors conforms to the general structural model for a G-protein-coupled receptor,<sup>8-10</sup> with an extracellular amino terminus and seven putative membrane spanning  $\alpha$ -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

**Figure 3 | Bundling of the helices to form the ligand binding site**

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 disulphide 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.



to form the ligand binding site (Figure 3) and some information is available on the residues that make contact with ligands.<sup>10,11</sup> There is an intracellular carboxyl terminus probably bearing a palmitoyl group which may form a further link to the membrane. The D<sub>1</sub>-like receptors have short third intracellular loops and long carboxyl terminal tails whereas the D<sub>2</sub>-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 (I3) is thought to be important for the interaction of the receptor and G protein. For the D<sub>2</sub>-like receptors variants of the subtypes exist based on this loop. For example there are short and long variants of the D<sub>2</sub> and D<sub>3</sub> receptors with the long forms having an insertion (29 amino acids for D<sub>2</sub> long) in this loop.<sup>12,13</sup> Polymorphic variants of the D<sub>2</sub> receptor have been described with single amino acid changes in I3.<sup>14</sup> The D<sub>4</sub> receptor is highly polymorphic in the human population with

variants containing different length insertions in I3.<sup>15,16</sup> In some cases these D<sub>2</sub>-like receptor variants may have differential abilities to couple to or activate G proteins<sup>17,18</sup> and may also exhibit slightly different pharmacological properties.<sup>15,19,20</sup> The variants of the D<sub>4</sub> receptor have not been found to exhibit any differences in agonist signalling or in coupling to G proteins.<sup>21</sup>

The individual properties of the different subtypes have been probed by expressing the receptors in recombinant cells and by examining the localisation of the subtypes at the mRNA and protein level.

### Individual Receptor Properties

The dopamine receptor subtypes exhibit different properties in terms of their pharmacological profiles, localisations and mechanisms of action, these differences will be briefly summarised below.

#### D<sub>1</sub>-like receptors

Both the D<sub>1</sub> and D<sub>5</sub> receptors show pharmacological properties similar to those of the original pharmacologically defined D<sub>1</sub> receptor i.e. a high affinity for the benzazepine ligands SCH 23390,

**Table 2 | Dopamine receptor subtypes from molecular biological studies**

The properties of the principal dopamine receptor subtypes identified by gene cloning are shown. They are divided into 'D<sub>1</sub>-like' and 'D<sub>2</sub>-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 I). D<sub>2short</sub> and D<sub>2long</sub> refer to different alternatively spliced forms of the D<sub>2</sub> receptor gene. The homology values are for the transmembrane-spanning regions.<sup>50</sup> The localisations shown are the principal ones known at present from in-situ hybridisation and use of the polymerase chain reaction. Some pharmacological data for the different receptor subtypes is given in Table 3. For further information consult reference.<sup>7</sup>

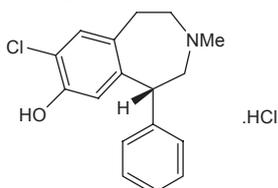
	'D <sub>1</sub> -like'		'D <sub>2</sub> -like'		
	D <sub>1</sub>	D <sub>5</sub>	D <sub>2short/long</sub>	D <sub>3</sub>	D <sub>4</sub>
<b>Amino acids</b>	446 (human, rat)	477 (human) 475 (rat)	414/443 (human) 415/444 (rat)	400 (human) 446 (rat)	387 (human, rat)
<b>Homology</b> with D <sub>1</sub> with D <sub>2</sub> (short)	100 44	82 49	44 100	44 76	42 54
<b>Localisation</b>	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
<b>Response</b>	Adenylyl cyclase↑	Adenylyl cyclase↑	Adenylyl cyclase↓	Adenylyl cyclase↓	Adenylyl cyclase↓
<b>Introns in gene</b>	None	None	Yes	Yes	Yes
<b>Organisation of amino acid sequence</b> Putative third intracellular loop Carboxyl terminal tail	Short Long	Short Long	Long Short	Long Short	Long Short
<b>Reference examples</b>	51	22,52	53	33	54

SCH 39166 and SKF 83566 which are selective antagonists for these subtypes. Thioxanthines e.g. flupentixol and phenothiazines e.g. fluphenazine also show high affinity but are not selective for D<sub>1</sub>-like over D<sub>2</sub>-like receptors. The D<sub>1</sub>-like receptors show moderate affinities for typical dopamine agonists such as apomorphine and selective agonists such as A 77636, SKF 38393, SKF 82526, SKF 81297 and dihydrexidine are now available. There are differences in the affinities of some compounds for the D<sub>1</sub> and D<sub>5</sub> receptors (higher agonist and lower antagonist affinities<sup>22,23</sup>) but no truly selective compounds are as yet available.

D<sub>1</sub> receptors are found at high levels in the typical dopamine regions of brain such as the neostriatum, substantia nigra, nucleus accumbens, olfactory tubercle whereas the distribution of the D<sub>5</sub> receptors is much more restricted (Table 2) and this subtype is

### SCH 23390, Standard Selective D<sub>1</sub>-like Antagonist

**SCH 23390**  
Cat. No. 0925



SCH 23390 is a potent D<sub>1</sub> antagonist (K<sub>i</sub> values are ~ 0.2, 0.3, ~ 1100, ~ 800 and ~ 3000 nM at D<sub>1</sub>, D<sub>5</sub>, D<sub>2</sub>, D<sub>3</sub> and D<sub>4</sub> receptors respectively). The compound is also an agonist at 5-HT<sub>2C</sub> receptors (K<sub>i</sub> = 6.3 nM) *in vitro*.

**Barnett et al** (1986) Relative activities of SCH 23390 and its analogs in three tests for D<sub>1</sub>/D<sub>1A</sub> dopamine receptor antagonism. *Eur.J.Pharmacol.* **128** 249.

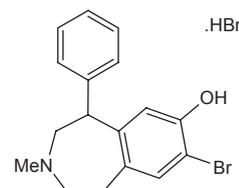
**Briggs et al** (1991) Activation of the 5-HT<sub>1C</sub> receptor expressed in Xenopus oocytes by the benzazepines SCH 23390 and SKF 38393. *Br.J.Pharmacol.* **104** 1038. **Seeman and Van Tol** (1994) Dopamine receptor pharmacology. *TIPS.* **15** 264.

found generally at much lower levels. Both receptors are able to stimulate adenylyl cyclase (Figure 1) and the D<sub>5</sub> receptor shows some constitutive activity for this response.<sup>23</sup> Inverse agonist activity at the D<sub>1</sub> and D<sub>5</sub> receptors is seen in recombinant systems for some compounds such as butaclamol<sup>23</sup> which were previously considered to be antagonists. It has been established for some time that stimulation of the D<sub>1</sub> dopamine receptor leads to activation of phospholipase C<sup>24</sup> and recently this response has been linked to the D<sub>1</sub>/D<sub>2</sub> receptor heterodimer<sup>25</sup> providing a function for heterodimer formation (see below). Agonists selective for the cAMP response (SKF 83822) or the phospholipase C response (SKF 83959) associated with D<sub>1</sub> receptors have been described.<sup>26</sup>

The function of the D<sub>5</sub> receptor is not understood although roles in brain function have been proposed.<sup>27</sup> The D<sub>1</sub> receptor seems to mediate important actions of dopamine to control movement, cognitive function and cardiovascular function. Direct interactions

### SKF 83566, Potent, Selective D<sub>1</sub>-like Antagonist

**SKF 83566**  
Cat. No. 1586



SKF 83566 is a potent and selective D<sub>1</sub>-like dopamine receptor antagonist (K<sub>i</sub> values are 0.3 and 0.4 nM for D<sub>1</sub> and D<sub>5</sub> receptors respectively). Also antagonist at the vascular 5-HT<sub>2</sub> receptor (K<sub>i</sub> = 11 nM). The antagonist is centrally active following systemic administration *in vivo*.

**Ohlstein and Berkowitz** (1985) SCH 23390 and SK&F 83566 are antagonists at vascular dopamine and serotonin receptors. *Eur.J.Pharmacol.* **108** 205.

**Sunahara et al** (1991) Cloning of the gene for a human dopamine D<sub>5</sub> receptor with higher affinity for dopamine than D<sub>1</sub>. *Nature* **350** 614. **Meyer et al** (1993) Effects of dopamine D<sub>1</sub> antagonists SCH23390 and SK&F83566 on locomotor activities in rats. *Pharmacol.Biochem.Behav.* **44** 429.

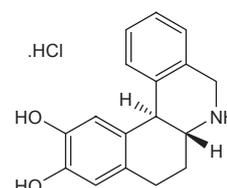
between D<sub>1</sub>-like receptors and ion channel-linked receptors have been described (D<sub>1</sub>/NMDA, D<sub>5</sub>/GABA<sub>A</sub>)<sup>28</sup> leading to modulation of receptor function. These interactions provide for cross talk between fast and slow neurotransmitter systems and may point towards a further functional role for the D<sub>5</sub> receptor.

### D<sub>2</sub>-like receptors

Overall the D<sub>2</sub>, D<sub>3</sub> and D<sub>4</sub> receptors exhibit pharmacological properties similar to those of the originally defined D<sub>2</sub> receptor i.e. they all show high affinities for drugs such as the butyrophenones e.g. haloperidol and substituted benzamides e.g. sulpiride and these classes of drugs provide selective antagonists for the D<sub>2</sub>-like receptors over D<sub>1</sub>-like receptors (Table 3). As indicated above,

### Dihydrexidine, Selective D<sub>1</sub>-like Agonist

**Dihydrexidine**  
Cat. No. 0884

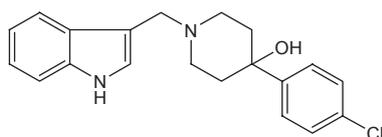


Dihydrexidine is a potent, full efficacy dopamine D<sub>1</sub> agonist which shows no agonist activity at peripheral D<sub>2</sub> receptors or adrenoceptors at doses which cause maximal stimulation of D<sub>1</sub> sites. The compound appears to be fully bioavailable in the brain and exhibits profound anti-Parkinsonism effects *in vivo*.

**Lovenberg et al** (1989) Dihydrexidine, a novel selective high potency, full dopamine D-1 receptor agonist. *Eur.J.Pharmacol.* **166** 111. **Brewster et al** (1990) *Trans*-10,11-dihydroxy-5,6,6a,7,8,12b-hexahydrobenzo[a]phenanthridine: a highly potent selective dopamine full agonist. *J.Med.Chem.* **33** 1756. **Taylor et al** (1991) Dihydrexidine, a full dopamine D<sub>1</sub> agonist, reduces MPTP-induced parkinsonism in monkeys. *Eur.J.Pharmacol.* **199** 389. **Kholi et al** (1993) Dihydrexidine: a new potent peripheral dopamine D<sub>1</sub> receptor agonist. *Eur. J.Pharmacol.* **235** 31.

## L-741,626, High Affinity D<sub>2</sub> Antagonist

**L-741,626**  
Cat. No. 1003



L-741,626 is a potent D<sub>2</sub> dopamine receptor selective antagonist, with affinities of 2.4, 100 and 220 nM for D<sub>2</sub>, D<sub>3</sub> and D<sub>4</sub> receptors respectively. The antagonist is centrally active following systemic administration *in vivo*.

**Kulagowski et al** (1996) 3-[[4-(4-Chlorophenyl)piperazin-1-yl]methyl]-1H-pyrrolo[2,3-b]pyridine: an antagonist with high affinity and selectivity for the human dopamine D<sub>4</sub> receptor. *J.Med.Chem.* **39** 1941. **Bowery et al** (1996) Antagonism of the effects of (+)-PD 128907 on midbrain dopamine neurones in rat brain slices by a selective D<sub>2</sub> receptor antagonist L-741,626. *Br.J.Pharmacol.* **119** 1491. **Pillai et al** (1998) Human D<sub>2</sub> and D<sub>4</sub> dopamine receptors couple through βγ G-protein subunits to inwardly rectifying K<sup>+</sup> channels (GIRK1) in a *Xenopus* oocyte expression system: selective antagonism by L-741,626 and L-745,870 respectively. *Neuropharmacology* **37** 983. **Millan et al** (2000) S33084, a novel, potent, selective, and competitive antagonist at dopamine D<sub>3</sub>-receptors: II. Functional and behavioral profile compared with GR218,231 and L741,626. *J.Pharmacol.Exp.Ther.* **293** 1063.

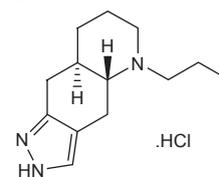
the D<sub>2</sub>-like receptors also show high affinities for phenothiazines and thioxanthenes. Each D<sub>2</sub>-like receptor has its own pharmacological signature so there are some differences in affinities of drugs for the individual D<sub>2</sub>-like receptors (Table 3). For example, the substituted benzamides sulpiride and raclopride show high affinity for the D<sub>2</sub> and D<sub>3</sub> receptors but a lower affinity for the D<sub>4</sub> receptor. Clozapine shows a slight selectivity for the D<sub>4</sub> receptor. More selective antagonists have been synthesised and these will be invaluable in determining the functions of these subtypes. For example L-741,626, GR 103691 and L-745,870 are D<sub>2</sub> selective (~40 fold), D<sub>3</sub> selective (~100 fold) and D<sub>4</sub> selective (~2000 fold) antagonists respectively.<sup>29-31</sup> The aminotetralins UH 232 and AJ 76 have been reported to be selective D<sub>2</sub>-like

autoreceptor antagonists<sup>32</sup> but they also possess some selectivity for the D<sub>3</sub> receptor<sup>33</sup> where UH 232 is a partial agonist.<sup>34</sup> Most antagonists show a higher affinity for the D<sub>2</sub> receptor compared with the D<sub>3</sub> and D<sub>4</sub> receptors. The D<sub>2</sub>-like subtypes show moderate affinities for typical dopamine agonists with the D<sub>3</sub> receptor generally showing higher affinities for agonists than the other subtypes. There are compounds available that are selective agonists for the D<sub>2</sub>-like receptors relative to the D<sub>1</sub>-like receptors e.g. N-0437, PHNO, quinpirole. There are no highly selective agonists for the individual D<sub>2</sub>-like subtypes as yet.

The D<sub>2</sub> receptor is the predominant D<sub>2</sub>-like subtype in the brain, located at high levels in typical dopamine rich brain areas. D<sub>3</sub> and D<sub>4</sub> 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<sub>3</sub> receptors are

## (-)-Quinpirole, Selective D<sub>2</sub>-like Agonist

**(-)-Quinpirole**  
Cat. No. 1061



(-)-Quinpirole is a selective dopamine D<sub>2</sub> receptor agonist. K<sub>i</sub> values are 4.8, ~ 24, ~ 30 and 1900 nM for D<sub>2</sub>, D<sub>3</sub>, D<sub>4</sub> and D<sub>1</sub> receptors respectively.

**Clark and White** (1987) Review: D<sub>1</sub> dopamine receptor - the search for a function: a critical evaluation of the D<sub>1</sub>/D<sub>2</sub> dopamine receptor classification and its functional significance. *Synapse* **1** 347. **Levant et al** (1996) Modulation of [<sup>3</sup>H]quinpirole binding in brain by monoamine oxidase inhibitors: evidence for a potential novel binding site. *J.Pharmacol.Exp.Ther.* **278** 145. **Sullivan et al** (1998) Effects of quinpirole on central dopamine systems in sensitized and non-sensitized rats. *Neuroscience* **83** 781.

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

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.<sup>43</sup> Data taken from <sup>7,20,22,43,55</sup>. Data for dopamine are obtained in the presence of Gpp(NH)p and so are for the free receptor uncoupled from G proteins.

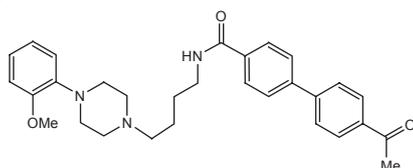
Drug	K <sub>i</sub> (nM)				
	D <sub>1</sub>	D <sub>5</sub>	D <sub>2</sub>	D <sub>3</sub>	D <sub>4</sub>
Dopamine	2340	228	1705	27	450
Chlorpromazine	73	133	0.55	1.2	9.7
<b>Clozapine</b>	141	250	35	83	22
<b>Haloperidol</b>	27	48	0.53	2.7	2.3
<b>Raclopride</b>	>72000	–	1	1.8	2400
<b>(-)-Sulpiride</b>	36000	77000	2.5	8	1000
<b>SCH 23390</b>	0.35	0.3	267	314	3560
<b>SCH 39166</b>	1.2	2	980	–	5520
<b>SKF 83566</b>	0.3	0.4	2000	–	–

(Bold Text Denotes Compounds Available From Tocris)

## GR 103691, Highly Selective D<sub>3</sub> Antagonist

### GR 103691

Cat. No. 1109



GR 103691 is a potent and selective dopamine D<sub>3</sub> receptor antagonist, with a K<sub>i</sub> value of 0.3 nM and > 100-fold selectivity over D<sub>2</sub> and D<sub>4</sub> sites.

**Murray et al** (1995) A novel series of arylpiperazines with high affinity and selectivity for the dopamine D<sub>3</sub> receptor. *Bioorg.Med.Chem.Lett.* **5** 219. **Hurley et al** (1996) Dopamine D<sub>3</sub> receptors are not involved in the induction of c-fos mRNA by neuroleptic drugs: comparison of the dopamine D<sub>3</sub> receptor antagonist GR 103691 with the typical and atypical neuroleptics. *Eur.J.Pharmacol.* **318** 283. **Audinot et al** (1998) A comparative *in vitro* and *in vivo* pharmacological characterization of the novel dopamine D<sub>3</sub> receptor antagonists (+)-S 14297, nafadotride, GR 103,691 and U 99194. *J.Pharmacol.Exp.Ther.* **287** 187

also found in regions associated with motor function such as the putamen. The D<sub>2</sub>-like receptor subtypes have each been shown to inhibit adenylyl cyclase (Figure 1) when expressed in recombinant cells,<sup>35-38</sup> although the signal via the D<sub>3</sub> 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<sub>3</sub> receptor to specific adenylyl cyclase isoforms.<sup>39</sup>

The D<sub>2</sub>-like receptors will, upon activation, stimulate a range of processes including acute signalling events (inhibition of adenylyl cyclase, stimulation of K<sup>+</sup> channels, inhibition of Ca<sup>2+</sup> channels, stimulation of arachidonic acid release) and longer term events (MAP kinase, mitogenesis, β-arrestin-2/Akt/GSK-3).<sup>7,40</sup> D<sub>3</sub> receptor-mediated signalling events are often of lower magnitude than for the other D<sub>2</sub>-like receptors. The relation of these signalling events to *in vivo* responses is only beginning to be clarified. Many compounds that were thought to be antagonists at D<sub>2</sub>-like receptors such as the antipsychotic drugs e.g. haloperidol, chlorpromazine, clozapine have been shown to possess inverse agonist activity at D<sub>2</sub> and D<sub>3</sub> receptors.<sup>36,41,42</sup> This inverse agonism may be associated with the increases in D<sub>2</sub> receptor number seen in the brain when experimental animals are treated chronically with these drugs.

The D<sub>2</sub> receptor is important for mediating the effects of dopamine to control movement, certain aspects of behaviour in the brain and prolactin secretion from the anterior pituitary gland. The functions of the D<sub>3</sub> and D<sub>4</sub> receptors are currently unknown although their localisations in limbic areas of brain suggest roles in cognitive, emotional and behavioural function. The D<sub>2</sub>-like receptors show high affinities for most of the drugs used to treat schizophrenia (antipsychotics) and Parkinson's disease ( e.g. bromocriptine).<sup>43</sup> The D<sub>3</sub>

and D<sub>4</sub> receptors are located predominantly in limbic brain regions and this has made them particularly attractive targets for the design of potential selective antipsychotic drugs. L-745,870 was the first highly selective D<sub>4</sub> antagonist synthesised but it proved to be inactive against the psychosis of schizophrenia.<sup>30</sup>

## Future Directions

### Understanding the Role of the Dopamine Receptor Subtypes

We are still a long way away from understanding the role of the different subtypes. Although partially selective antagonists are available for some of the subtypes and transgenic "receptor knock out" animals are available, much is still to be done here (see for example<sup>26</sup>).

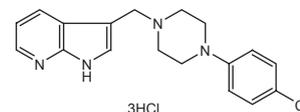
### Dopamine Receptor Subtypes in Drug Discovery

Because of 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. This continues to be the case and indications have expanded in to 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<sub>2</sub>-like partial agonists such as aripiprazole.<sup>44</sup> It had been thought that antipsychotics had to be antagonists/inverse agonists at the D<sub>2</sub> receptor<sup>43</sup> and the effective use of partial agonists as antipsychotics raises questions about mechanism that need to be addressed.<sup>45</sup> It will be important, for example, to understand the relationship between the efficacy of the ligands in signalling assays and their therapeutic effects.

## L-745,870, Highly Selective D<sub>4</sub> Antagonist

### L-745,870

Cat. No. 1002



L-745,870 is a highly potent and selective D<sub>4</sub> dopamine receptor antagonist. The antagonist has K<sub>i</sub> values of 0.51, 2300 and 960 nM for D<sub>4</sub>, D<sub>3</sub> and D<sub>2</sub> subtypes respectively and > 1000-fold selectivity over 5-HT<sub>2</sub>, D<sub>1</sub> and D<sub>5</sub> receptors.

**Kulagowski et al** (1996) 3-[[4-(4-Chlorophenyl)piperazin-1-yl]methyl-1H-pyrrolo[2,3-b]pyridine: an antagonist with high affinity and selectivity for the human D<sub>4</sub> receptor. *J.Med.Chem.* **39** 1941. **Bristow et al** (1997) Schizophrenia and L-745, 870 a novel dopamine D<sub>4</sub> receptor antagonist. *TIPS* **18** 186. **Patel et al** (1997) Biological profile of L-745,870, a selective antagonist with high affinity for the dopamine D<sub>4</sub> receptor. *J.Pharmacol.Exp.Ther.* **283** 636. **Pillai et al** (1998) Human D<sub>2</sub> and D<sub>4</sub> dopamine receptors couple through β<sub>γ</sub> G-protein subunits to inwardly rectifying K<sup>+</sup> channels (GIRK1) in a *Xenopus* oocyte expression system: selective antagonism by L-741,626 and L-745,870 respectively. *Neuropharmacology* **37** 983.

## 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 phospho protein 32 kD). DARPP-32 seems to be a key protein in striatal neuronal function.<sup>46</sup> Important progress has also been made in understanding temporal aspects of signalling 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  $\beta$ -arrestin-2/Akt/GSK-3 signalling.<sup>40</sup>

## 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 and this will be an active field of research in the future. One class of cytoskeletal, adapter and signalling proteins that interact with dopamine receptors has been termed DRIPs (dopamine receptor interacting proteins).<sup>47,48</sup> An example includes the neuronal  $\text{Ca}^{2+}$  sensor-1 (NCS-1) which interacts with  $\text{D}_2$ . In this case the interacting proteins may mediate the effects of  $\text{Ca}^{2+}$  on the  $\text{D}_2$  dopamine receptor. Interactions also occur with other receptors including ligand-gated ion channels (see above) and GPCRs leading to homo- and heterodimer formation. A role for  $\text{D}_1/\text{D}_2$  heterodimer formation has been suggested above,<sup>25</sup> roles for homodimer formation e.g.  $\text{D}_2$  homodimers<sup>49</sup> are being actively pursued.

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# Dopamine Receptor Compounds Available from Tocris

## D<sub>1</sub>-like Receptors

- 1534 A 68930**  
Potent, selective D<sub>1</sub>-like agonist
- 1701 A 77636**  
Potent, selective D<sub>1</sub>-like agonist. Orally active
- 2073 (R)-(-)-Apomorphine**  
Dopamine agonist; non-subtype-selective
- 1249 CY 208-243**  
Selective D<sub>1</sub>-like agonist
- 0884 Dihydraxidine**  
Selective D<sub>1</sub>-like agonist
- 1659 Fenoldopam**  
Selective D<sub>1</sub>-like partial agonist
- 1674 LE 300**  
Potent and selective dopamine D<sub>1</sub> antagonist
- 0925 SCH 23390**  
Standard selective D<sub>1</sub>-like antagonist
- 2299 SCH 39166**  
High affinity D<sub>1</sub>/D<sub>5</sub> receptor antagonist
- 0922 SKF 38393**  
Selective D<sub>1</sub>-like agonist
- 1662 SKF 77434**  
Selective D<sub>1</sub>-like partial agonist
- 1447 SKF 81297**  
D<sub>1</sub> agonist
- 1586 SKF 83566**  
Potent, selective D<sub>1</sub>-like antagonist
- 2075 SKF 83822**  
Selective D<sub>1</sub>-like agonist
- 2074 SKF 83959**  
D<sub>1</sub>-like partial agonist

## D<sub>2</sub>-like Receptors

### Agonists

- 2073 (R)-(-)-Apomorphine**  
Dopamine agonist; non-subtype-selective
- 0427 Bromocriptine**  
Selective D<sub>2</sub>-like agonist
- 2664 Cabergoline**  
Selective D<sub>2</sub>-like agonist
- 2193 Carmoxirole**  
Selective, peripherally acting D<sub>2</sub>-like agonist
- 0474 Dihydroergocristine**  
Partial dopamine receptor agonist
- 0475 Dihydroergotamine**  
Partial D<sub>2</sub>-like agonist
- 1031 Piribedil**  
Dopamine agonist
- 1519 Quinelorane**  
D<sub>2</sub> and D<sub>3</sub> agonist
- 1061 (-)-Quinpirole**  
Selective D<sub>2</sub>-like agonist
- 1559 Roxindole**  
Dopamine D<sub>2</sub> autoreceptor agonist. Also has affinity for D<sub>3</sub> and D<sub>4</sub> receptors

### Antagonists

- 0678 (+)-AJ 76**  
Antagonist; preferential action at D<sub>2</sub>-like autoreceptors
- 0524 AMI-193**  
D<sub>2</sub>-like receptor antagonist
- 2132 Amisulpride**  
Selective D<sub>2</sub>/D<sub>3</sub> receptor antagonist; atypical antipsychotic agent
- 0782 2-Chloro-11-(4-methylpiperazino)dibenz[b,f]oxepin**  
D<sub>2</sub>-like antagonist. Displays some D<sub>4</sub> selectivity
- 0444 Clozapine**  
Dopamine antagonist with some D<sub>4</sub> selectivity
- 2536 Domperidone**  
Peripheral D<sub>2</sub>-like antagonist
- 1847 Eticlopride**  
Selective D<sub>2</sub>/D<sub>3</sub> antagonist
- 0701 3'-Fluorobenzylspiperone**  
D<sub>2</sub>-like receptor ligand
- 0931 Haloperidol**  
Antagonist, partly D<sub>2</sub> selective
- 1746 Nemonapride**  
Highly potent D<sub>2</sub>-like antagonist
- 0937 Pimozide**  
D<sub>2</sub>-like antagonist
- 1810 Raclopride**  
Potent, selective D<sub>2</sub>/D<sub>3</sub> antagonist
- 0916 Remoxipride**  
Selective D<sub>2</sub>-like antagonist

- 0995 Spiperone**  
D<sub>2</sub>-like antagonist
- 0894 (RS)-(±)-Sulpiride**  
Standard selective D<sub>2</sub>-like antagonist
- 0895 (S)-(-)-Sulpiride**  
Standard selective D<sub>2</sub>-like antagonist
- 0775 (+)-UH 232**  
D<sub>2</sub>-like autoreceptor antagonist. D<sub>3</sub> partial agonist.

### D<sub>2</sub>-selective

- 2759 B-HT 920**  
D<sub>2</sub> receptor agonist
- 1003 L-741,626**  
High affinity D<sub>2</sub> antagonist
- 2495 Melperone**  
D<sub>2</sub>/5-HT<sub>2A</sub> receptor antagonist; neuroleptic
- 2865 Risperidone**  
D<sub>2</sub> antagonist
- 3085 Ziprasidone**  
5-HT<sub>2A</sub>/D<sub>2</sub> antagonist; atypical antipsychotic

### D<sub>3</sub>-selective

- 1847 Eticlopride**  
D<sub>3</sub> antagonist (D<sub>3</sub> > D<sub>2</sub>)
- 1109 GR 103691**  
Highly selective D<sub>3</sub> antagonist
- 0706 7-Hydroxy-DPAT**  
Dopamine agonist (D<sub>3</sub> ≥ D<sub>2</sub> > D<sub>4</sub>)
- 0719 7-Hydroxy-PIPAT**  
D<sub>3</sub> agonist (D<sub>3</sub> > D<sub>2</sub>)
- 1347 Nafadotride**  
Highly potent, preferential D<sub>3</sub> antagonist
- 2635 NGB 2904**  
Potent and selective D<sub>3</sub> antagonist
- 1243 (+)-PD 128907**  
D<sub>3</sub> agonist (D<sub>3</sub> ≥ D<sub>2</sub> > D<sub>4</sub>)
- 1357 U 99194**  
Potent, selective D<sub>3</sub> antagonist

### D<sub>4</sub>-selective

- 2214 ABT 724**  
Potent, selective D<sub>4</sub> partial agonist; prorectile
- 2645 Fananserin**  
D<sub>4</sub> antagonist
- 1004 L-741,742**  
Highly selective D<sub>4</sub> antagonist
- 1002 L-745,870**  
Highly selective D<sub>4</sub> antagonist
- 1065 PD 168077**  
High affinity, selective D<sub>4</sub> agonist
- 2735 PNU 96415E**  
D<sub>4</sub> and 5-HT<sub>2A</sub> antagonist; antipsychotic
- 2329 Ro 10-5824**  
Selective D<sub>4</sub> receptor partial agonist

### Dopamine Transporters

- 0918 3 $\alpha$ -Bis-(4-fluorophenyl) methoxytropane**  
Potent dopamine uptake inhibitor
- 0702 BTCP**  
Potent dopamine uptake inhibitor
- 2831 Bupropion**  
Non-selective inhibitor of dopamine and noradrenalin transporters
- 0917 3 $\alpha$ -[[4-Chlorophenyl]phenylmethoxy] tropane**  
Dopamine uptake inhibitor
- 2833 Cocaine**  
Inhibitor of monoamine transporters
- 0513 GBR 12783**  
Potent, selective dopamine uptake inhibitor
- 0421 GBR 12909**  
Selective DA uptake inhibitor
- 0514 GBR 12935**  
Selective dopamine uptake inhibitor
- 0420 GBR 13069**  
Potent dopamine uptake inhibitor
- 1588 Indatraline**  
Potent dopamine uptake inhibitor
- 2148 (±)-McN 5652**  
Dopamine uptake inhibitor
- 2742 Reserpine**  
Inhibitor of vesicular monoamine transport
- 1497 Rimcazole**  
DAT inhibitor
- 2175 Tetrabenazine**  
Potent inhibitor of vesicular monoamine transport; depletes dopamine stores

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