Recent Advances in the Development of Dopamine D_3 Receptor Agonists and Antagonists

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Abstract: Advances in molecular cloning techniques have allowed the characterization of five subtypes (D_1-D_5) of dopamine (DA) receptors. The limbic location of the D_3 receptor has led to speculation about its possible role in schizophrenia and drug abuse. Since the D_3 receptor is localized in the limbic region rather than the striatum, antipsychotics with D_3 receptor selectivity could be devoid of extrapyramidal side effects commonly seen with D_2 receptor antagonists. Recent work in our laboratory revealed that the benz[e]indole cis-(±)-**44b** demonstrated high selectivity for the D_3 receptor. This compound exhibits a typical antipsychotic profile without the motor effects found in commonly used antipsychotic agents. This mini-review will give a brief introduction on D_3 receptors and a detailed description of selectively-acting D_3 agonists and antagonists which have recently appeared in the literature.

INTRODUCTION

Advances in molecular techniques have facilitated the design and development of novel ligands with selectivity at dopamine (DA) receptor subtypes. Compounds with selectivity for DA receptors in the limbic region of the brain have been suggested as novel agents in the treatment of schizophrenia and drug abuse [1]. The limbic regions such as the nucleus accumbens, olfactory tubercles, and the islets of Calleja are believed to be involved in thought and emotional processes, whereas the caudate may effect motor control [2]. Thus, compounds that have a selective limbic site of action may lack extrapyramidal side effects of currently available antipsychotic agents [3].

Presently, at least five DA receptor subtypes are known [4]. On the basis of similarities in functional and pharmacological properties, ligand binding, and sequence homologies, these receptors can be divided into two major classes: the D_1-family (D_1 and D_5) and the D_2-family (D_2, D_3, and D_4) [3-5]. Analyses of the amino acid sequences of the DA receptor subtypes reveal that a great deal of receptor homology exists, particularly between members of the same family of DA receptors. The rat and human D_3 receptors contain 400 and 446 amino acids, and the D_3 receptor has overall homologies of 52 % and 41 % with the D_2 and D_4 receptors, respectively. The DA receptor subtypes have been shown to contain seven regions of hydrophobic amino acids fully capable of spanning the cell membrane. Thus, the DA receptors appear to fit the general model of a G-protein coupled receptor with seven membrane spanning α-helical regions with extracellular and intracellular loops. The D_1-family of receptors do not contain introns, whereas the D_2-family of receptors are interrupted by introns in the gene sequences. The D_2-family also differs from the D_1-family with the presence of a long third intracellular loop and a short carboxyl terminal end. The third intracellular loop is believed to be important in the interaction of the G-protein and the receptor. Variants in the D_2 receptor subtype are due to insertion of the 29 amino acids into the third loop to give D_{2S} and D_{2L} receptor variants [1,5,6]. Variable length polymorphic forms of the D_4 receptor are also known, formed by insertion of repeats of a 48 base pair sequence into the predicted third intracellular loop of the receptor [7].

The D_1 and D_2 receptor subtypes were initially distinguished on the basis of coupling to adenylate cyclase leading to increased and decreased cAMP synthesis, respectively [4]. While D_3 receptors were not initially observed to regulate adenylate cyclase activity, a variety of other cellular responses mediated by this receptor have been observed in heterologous expression systems. These responses include a D_3 receptor-mediated increase in mitogenesis in NG108-15 cells [8] and Na^+-dependent extracellular acidification in CHO cells [4]. DA agonist-mediated changes in *c-fos* expression have also been seen in NG108-15 cells [9]. Robinson and Caron [10] subsequently showed that the D_3 receptor is able to negatively regulate the type V variant of adenylate cyclase. Several studies have shown that the transmembrane segments (TM) play a critical role in the formation of the ligand binding pocket of catecholamine receptors. The aspartate residue (D110) on TMIII of D_3 receptors probably forms an ionic attraction with the protonated amine group of DA. Using site-directed mutagenesis, the cysteine residue (C114) in TMIII of D_3 receptors was shown to be important in receptor binding of

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ligands containing *N*-propyl substitution. This cysteine residue is believed to play an important role in maintaining the key "propyl cleft" of the receptor [11].

Although the use of gene knockout and antisense strategies have been utilized, the development of selectively-acting ligands at D_3 receptors is critically important to study the significance and function of this receptor [12]. Depending on the assay conditions, transfected cell line or tissue employed, and radioligand used, the reported affinities and selectivities have varied widely [6]. The binding affinities of a number of DA receptor ligands were recently evaluated at hD_3, hD_2, and rat D_2 receptors using several different radioligands [12]. In this study, (+)-7-OH-DPAT exhibited D_2/D_3 selectivities ranging from 47-302-fold, depending upon the radioligand utilized.

Several functional assays have been utilized to determine agonist or antagonist activity at D_3 receptors. Agonists at D_3 receptors have been shown to enhance mitogenesis in NG108-15 cells [8}, increase extracellular acidification in CHO cells [4], and mediate changes in *c-fos* expression in NG108-15 cells [9]. Antagonists at D_3 receptors have been shown to block these effects. However, a number of agonists exhibit higher D_2/D_3 selectivities in binding studies than in functional tests [4].

Several investigators [6,13,14] have proposed the existence of pre- and postsynaptic D3 receptors, due to anatomical evidence of postsynaptic receptor expression in the nucleus accumbens and studies suggesting the presynaptic expression of functional receptors in terminals projecting from the substantia nigra. A number of methods have been utilized to assess pre- and postsynaptic activity including measurement of locomotor activity in normal and reserpinized mice, evaluation of contralateral turning in 6-hydroxydopamine (6-OH-DA)-lesioned rats, and determination of intrastitial dopamine levels in rats [15]. The role of DA D_3 receptors in spontaneous locomotor activity has been extensively studied. The work of several groups to profile the activity of selective dopaminergic agents has suggested that agonist action at D_3 receptors inhibits locomotor activity. This is in contrast to the opinion that stimulation of D_2 receptors increases locomotor activity [6,16]. The DA agonists 7-OH-DPAT and PD 128907 were shown to produce a biphasic effect on rat locomotor activity. The inhibition of locomotor activity at lower doses was attributed to D_3 receptor stimulation. At higher doses, however, 7-OH-DPAT leads to an increase in rat locomotor activity, apparently due to D_2 receptor stimulation [16]. In contrast, the D_3 receptor antagonist U99194A was shown to increase spontaneous locomotor activity in mice [13,15]. DA agonists produce contralateral turning in unilateral 6-hydroxydopamine-lesioned rats. This effect is mediated by stimulation of postsynaptic DA receptors. DA D_2 antagonists such as haloperidol block the contralateral turning behavior in rats induced by the D_3 agonist 7-OH-DPAT [3,17]. Maj *et al.* [18] showed that 7-OH-DPAT antagonized catalepsy induced by reserpine, haloperidol, and fluphenazine. The D_3 antagonist nafadotride was shown to antagonize the effect of 7-OH-DPAT was due to its action at D_3 receptors. In contrast, Boulay *et al*. [19] used D_3 receptor knock-out mice to show that the D_2 receptor is necessary for haloperidol-induced catalepsy. These workers postulated that D1-like, D2-like, and D1/D2 antagonists do not involve the D3 receptor in the production of catalepsy. These studies with receptor-selective ligands and receptor knockout animals suggesting a selective D_3 receptor involvement in regulating cognition and awareness states, and not generalized motor coordination, have suggested a possible therapeutic utility of D_3 agonists in treating Attention Deficit Disorders. However, an initial clinical study examining association with polymorphisms in the D_3 receptor gene has failed to establish a genetic linkage to this disease [20].

DA D_3 RECEPTOR LIGANDS

The aminotetralin 7-hydroxy-2-(*N,N*-di-*n*-propylamino) tetralin (**1,** 7-OH-DPAT) was the first compound to show preference for the DA D_3 receptor [21,22]. Most of the D_3 receptor binding affinity is found in the *R*-(+)-enantiomer [21]. The apparent selectivity of *R*-(+)-7-OH-DPAT in radioligand binding studies is greatly decreased when in vivo functional tests are employed to evaluate D_3 receptor activation [23,24]. In fact, several in vivo effects of 7-OH-DPAT are believed to be mediated by D_2 receptors [1]. Receptor binding was initially studied in CHO-K1 cells using [^{3}H]spiperone as the radioligand; however, these studies were carried out using conditions which favor binding to GTP-insensitive D_{2L} receptor sites with low affinity for agonists. When these studies were performed using the agonist ligand [^{3}H]N-0437, only binding to the high affinity site of the D_{2L} receptor was measured. Under these conditions, the D_3 versus D_2 selectivity of 7-OH-DPAT was only 24-fold [2]. A recent report showed that 7-OH-DPAT-induced hypothermia and penile erections (PE) were inhibited by D_3-selective antagonists [25]. Another recent study [26] demonstrated that 7-OH-DPAT decreased intraocular pressure (IOP) in sympathetically-denervated rabbits. This effect was inhibited by D_3 receptor antagonists. These workers suggest that the IOP-lowering effect of 7-OH-DPAT is due to stimulation of postsynaptic D_3 receptors located on sympathetic nerve endings in the ciliary body.

An iodinated analog of 7-OH-DPAT, (*R,S*-2'-*trans*-7-hydroxy-2-[*N*-*n*-propyl-*N*-(3'-iodo-2'-propenyl)amino]tetralin (*trans*-7-OH-PIPAT, **2**) was reported to exhibit a 143-fold D_3 versus D_2 selectivity [27]. Binding studies using membrane preparations containing D_3 receptors expressed in *Spodoptera frugiperda* (Sf9) cells showed that the activity resides with the *R*-enantiomer [28]. Further studies demonstrated that 7-OH-PIPAT additionally binds with high affinity at $5HT_{1A}$ [28] and σ-receptors [29].

The 5-methoxy-2-aminotetralin (**3,** (+)-UH 232) was shown to bind with a 4-fold D_3 versus D_2 selectivity [30]. The pharmacological profile of compound **3** and the related *n*-propyl derivative (**4,** (+)-AJ 76) suggests that both of these compounds act as DA autoreceptor antagonists [31,32]. However, more recent reports indicate that UH 232 may be acting as a partial agonist [8].

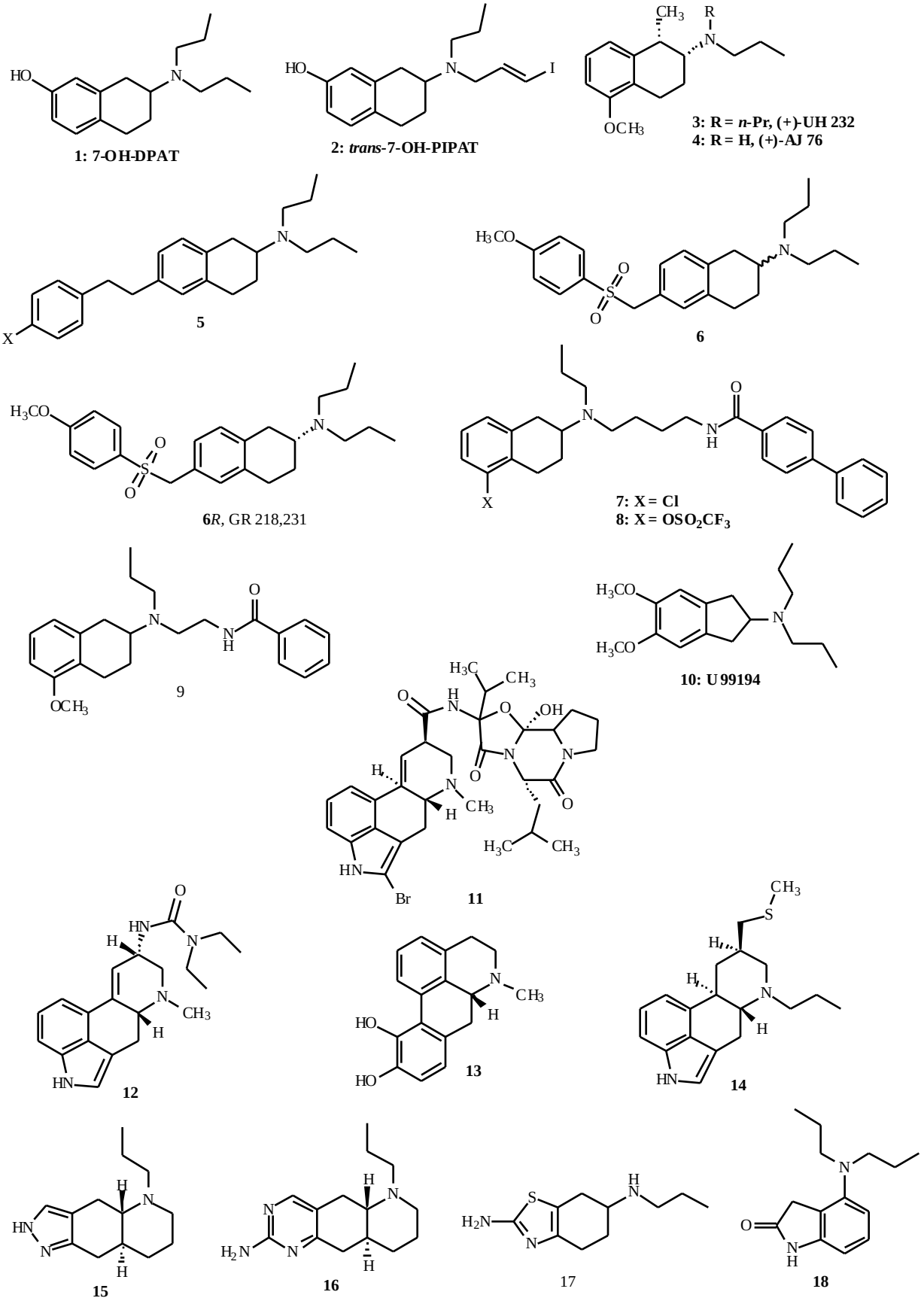


Fig. (1). Structures of D_3 ligands (**1**-**18**).

Using (+)-UH 232 as a structural lead, Murray *et al.* [33] prepared a series of 6-hydroxy-2-aminotetralins with high binding affinity for D_3 receptors. A number of compounds of general structure **5**, in which the 5-methoxy group of (+)-UH 232 was removed, exhibited high binding affinity for the D_3 receptor with greater than 100-fold D_3 versus D_2 selectivity. The high lipophilicity of the aminotetralins **5** make clinical development of these compounds unlikely due to rapid in vivo clearance. As a result, several derivatives with decreased lipophilicity were prepared. The sulfone **6** exhibited high binding affinity and favorable D_3/D_2 selectivity. The *R*-enantiomer (*R*-**6,** GR 218,231) was shown to be the active isomer, and the compound demonstrated D_3/D_2 selectivity of 400-fold and about 10,000-fold D_3 versus D_1 or D_4 selectivity. A report by Cussac et al [34] showed that GR 218,231 displaced [^{3}H]7-OH-DPAT with similar affinities at cloned and native rat D_3 receptors. The affinity of GR 218,231 at these sites was much higher than at D_2 receptors in the striatum. GR 218,231 dose-dependently reduced 7-OH-DPAT-induced PE and hypothermia, but was inactive against 7-OH-DPAT-induced yawning and hypothermia. Furthermore, GR 218,231 did not block contralateral turning behavior caused by quinpirole. These workers also demonstrated that GR 218,231 was inactive in models to predict antipsychotic and extrapyramidal activity. This study further confirms the need for development of selectively-acting ligands to determine the role of D_2 and D_3 receptors in the study and treatment of schizophrenia.

A series of 5-substituted-*N*-*n*-propyl-2-aminotetralins were recently described by Boyfield *et al.* [35]. Compounds **7** and **8** demonstrated high binding affinity for the DA D_3 receptor (K_i = 2.2 nM) with about 200-fold D_3 versus D_2 selectivity. These compounds were shown, however, to undergo rapid clearance due to *N*-depropylation.

Homan *et al.* [36] prepared a series of compounds which were structural hybrids of the aminotetralins and the 2-pyrrolidinylmethylbenzamides. The lead compound (5-methoxy-2-[*N*-(2-benzamidoethyl)-*N*-(*n*-propyl)amino]tetralin, **9**) exhibited binding affinities at $5HT_{1A}$, D_{2A}, and D_3 receptors of 0.82 nM, 3.2 nM, and 0.58 nM, respectively. These workers postulated that the benzamidoethyl side chain binds to an accessory site at all three receptors, and this site may be identical to that occupied by the 2-pyrrolidinylmethylbenzamide D_2/D_3 antagonists. Furthermore, these workers speculated that these antagonists at $5\text{-}HT_{1A}$ and D_2/D_3 receptors may have a reduced tendency to produce extrapyramidal side effects (EPS).

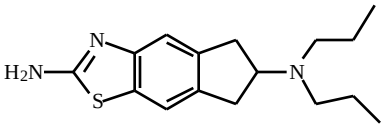
The preferential D_3 antagonist U 99194 (**10,** U 99194) was shown to increase rat locomotor activity through postsynaptic D_3 receptor stimulation [37]. Using various radioligands to label the D_3 receptor, Audinot *et al.* [12] reported K_i values for U 99194 of between 160-223 nM with D_3/D_2 selectivity of 10 to 14-fold. Additionally, these workers showed that U 99194 antagonized the induction of hypothermia by (+)-7-OH-DPAT and did not induce catalepsy in rats.

In displacement studies and functional tests based on the mitogenic response to D_3 or D_2 receptor stimulation, Griffon *et al.* [30] showed that the ergolines, bromocriptine (**11**) and lisuride (**12**), and apomorphine (**13**) exhibited high binding affinities at both subtypes with no apparent D_3/D_2 selectivity. Pergolide (**14**), an ergoline with antiparkinsonian activity, exhibited high binding affinities at both D_2 and D_3 receptors with about an 8-fold selectivity at D_3 receptors. Pergolide was also shown to be a full agonist in the mitogenic assay [38].

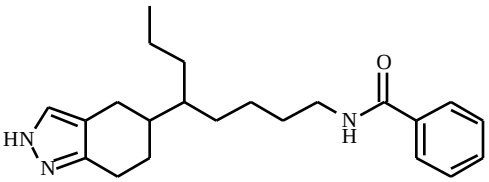
The tricyclic analogs quinpirole (**15**) and quinelorane (**16**) show selectivities at D_3 versus D_2 receptors in radioligand binding experiments of 36- and 95-fold, respectively [4]. However, in the mitogenic assay to measure functional activity only quinelorane exhibited some selectivity (approximately 20-fold). The related bicyclic aminothiazole derivative pramipexole (**17**) binds with high affinity at both D_2 and D_3 receptors with about a 70-fold selectivity for D_3 receptors. In the mitogenic response in cells expressing D_2 or D_3 receptors, pramipexole demonstrated over 80-fold D_3 selectivity [38]. Pramipexole inhibits DA synthesis and release and neuronal firing by acting on DA autoreceptors [39]. The 2-indolone ropinirole (**18**) demonstrated a 16-fold D_3/D_2 selectivity with full agonist activity in the mitogenic functional assay [38]. Both pramipexole and ropinirole have been used as monotherapy and in combination with levodopa in the treatment of parkinsonism [40,41]. The efficacy of these compounds may be related to their high D_3 binding affinity [38]. However, several studies have suggested action via activation of D_2 autoreceptors as a likely mechanism of drug action [42,43]. This would be consistent with the high D_2 receptor expression and relative paucity of D_3 receptors in motoric regions of the brain, and D_2 agonist activity of these compounds [44].

Incorporation of the 2-aminothiazole moiety into the 2-aminoindane nucleus led to the discovery that (**19**, GMC 1111) had high affinity for D_3 receptors. This compound caused rotation in 6-hydroxydopamine (6-OH-DA)-lesioned rats and an increase in DA turnover in the striatum. In the mitogenic assay to assess functional activity, GMC 1111 was shown to be a partial agonist at D_2 receptors and an antagonist at D_3 receptors. Additionally, GMC 1111 demonstrated good oral bioavailability in rats [45]. These workers suggested that GMC 1111 may have potential therapeutic utility in the treatment of Parkinson's disease, as suggested by the combined D_3 antagonist and D_2 agonist activity of the compound.

Incorporation of the 4-(4-phenylbenzoylamino)butyl side-chain, found in compounds **7** and **8**, into structural fragments of quinpirole, quinelorane, and pramipexole led to the synthesis of the corresponding bicyclic derivatives (**20-22**) [46]. These compounds were evaluated in displacement studies using [^{125}I]iodosulpride for D_2 and D_3 receptors expressed in CHO cells. Functional activity was determined by microphysiometry. The quinelorane analog (**21**, R_2 = 4-OCH_3, R_1 = *n*-Pr) showed high D_3 receptor affinity with 490-fold D_3/D_2 selectivity. The quinpirole (**20**) and pramipexole derivative (**22**) analogs also demostrated high D_3 binding affinities and D_3 versus D_2 selectivities of 150-fold and 340-fold, respectively. These derivatives were shown to act as agonists in the functional assay.



19: GMC1111



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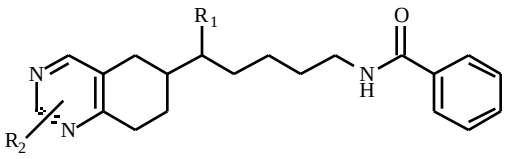

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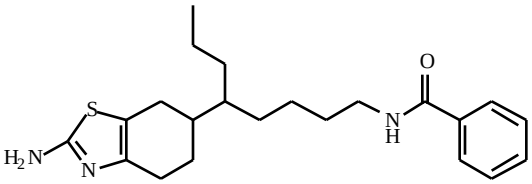

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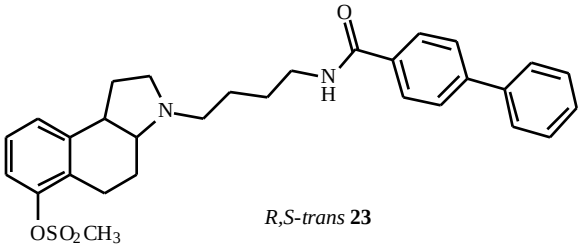
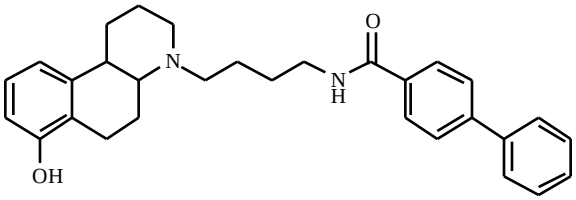
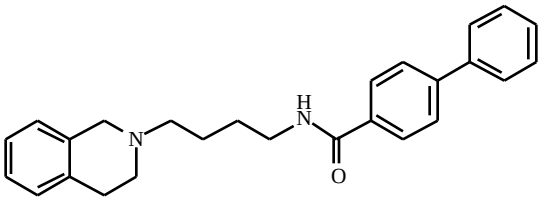


R,S-trans **23**



R,S-trans-**24**



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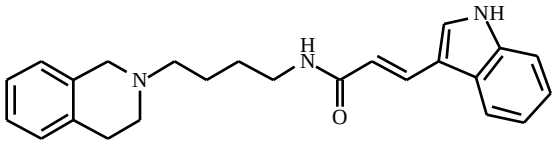

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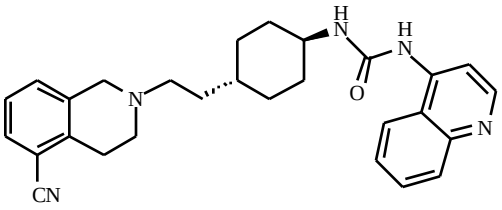
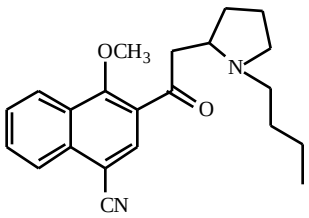


27: SB-277011-A



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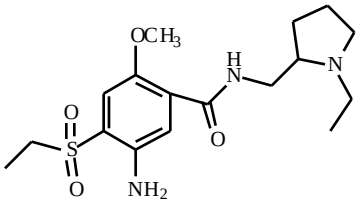

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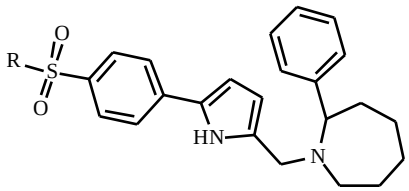


30: R = Et
31: R = PhN(CH_3)-
32: R = PhCH_2N(Et)-
33: R = 1,2,3,4-tetrahydroquinolin-1-yl
34: R = 1,2,3,4-tetrahydroisoquinolin-2-yl

Fig. (2). Structures of D_3 ligands (**19**-**34**).

The aminotetralins, as typified by compounds **7** and **8**, were shown to be metabolized by *N*-dealkylation of the *n*-propyl group and undergo rapid clearance. In an attempt to improve the metabolic stability of these analogs, the *N*-*n*-propyl group was incorporated into either a benz[*e*]indole or benzo[*f*]quinoline nucleus. The (±)-*trans*-benz[*e*]indole **23** and the (±)-benzo[*f*]quinoline **24** were shown to bind with high affinity at D_3 receptors with D_3/D_2 selectivities of 65-fold and 72-fold, respectively. Using microphysiometry, compounds **23** and **24** acted as antagonists at D_3 receptors. These tricyclic analogs had improved in vivo stability compared to the aminotetralins [47]. These same workers used brain penetration and clearance studies to develop a novel isoquinoline **25** with high D_3 affinity and good in vivo stability. Modification of compound **25** led to the *N*-(3-indolylpropenamido) derivative **26**, a compound with high affinity for the D_3 receptor (K_i = 4 nM) and 150-fold D_3/D_2 selectivity. Similar to the isoquinoline **25**, compound **26** demonstrated a low blood clearance and CNS penetration following IV administration. The plasma half-life of compound **26** was 2.5 hours [48]. Further studies on compound **26** demonstrated oral bioavailability of only 7 % and modest affinity for the $5HT_{1B}$ and $5HT_{1D}$ receptors. Replacement of the 7-trifluorosulfonyl group with a cyano-substituent slightly improved oral bioavailability, but reduced D_3 receptor affinity. Molecular modeling studies suggested that the flexible butyl spacer in compound **26** may impart $5HT_{1B}$ and $5HT_{1D}$ receptor binding affinity. Using this information, a number of conformationally constrained linkers were investigated. Further structural modification yielded the 4-quinolinyl derivative (**27,** SB-277011). This compound exhibited high D_3 receptor affinity with over 100-fold selectivity against D_2, $5HT_{1B}$, and $5HT_{1D}$ receptors. Additionally, this analog demonstrated D_3 antagonist activity, good oral bioavailability (43 %), low blood clearance, and high CNS activity. The compound does not induce catalepsy or elevate prolactin levels. Additional studies using microphysiometry revealed that SB-277011-A antagonized the effect of quinpirole-induced extracellular acidification rates with over 80-fold D_3/D_2 selectivity in CHO cells. Additionally, SB-277011-A did not alter spontaneous locomotion or enhance amphetamine or phencyclidine-induced hyperactivity per se, and significantly reversed a prepulse inhibition deficit in isolation-reared rats [49]. Thus, this novel isoquinoline may have a reduced tendency to produce extrapyramidal side effects which are typical of classical antipsychotics such as haloperidol [50].

Sautel *et al.* [51] recently described the pharmacological profile of nafadotride (**28**) and its enantiomers. In displacement studies, the (-)-isomer displays about 20-fold greater affinity for the D_3 receptor (K_i = 0.3 nM) than the (+)-isomer. The (+)-isomer shows only 2-fold D_3/D_2 selectivity; however, the (-)-isomer exhibits about 10-fold D_3 selectivity. Nafadotride failed to show any efficacy in the mitogenic response of the DA agonist quinpirole. At low doses (0.1-l.0 mg/kg) nafadotride, unlike haloperidol, increased rat spontaneous locomotor activity and climbing behavior in mice. Similar to haloperidol, nafadotride induced catalepsy at high doses (1-100 mg/kg). These researchers suggested that the increase in motor activity was due to D_3 receptor blockade. Griffon *et al.* [30] postulated that activation of a subpopulation of mesolimbic D_3 receptors inhibits rat locomotor activity. Thus, the increae in locomotor activity elicited by nafadotride is consistent with prefential D_3 receptor antagonism. Similar to haloperidol, nafadotride induced catalepsy at high doses (1-100 mg/kg). These researchers suggested that the increase in motor activity was due to D_3 receptor blockade, although this result may reflect D_2 receptor antagonism at the doses employed in this study.

Amisulpride (**29**) is a benzamide derivative that exhibits high binding affinity at D_2 (K_i = 2.8 nm) and D_3 (K_i = 3.2 nM) receptors. In the rat, amisulpride exhibits an antagonist action at pre- and postsynaptic D_2 receptors. At low doses, the compound selectively blocks DA autoreceptors that regulate synthesis and release. This unique pharmacological profile has been suggested to be responsible for the use of amisulpride for the negative symptoms of schizophrenia at low doses and the positive symptoms at high doses. Due to the low incidence of EPS, the clinical use of amisulpride is of considerable interest [52].

The 2,5-disubstituted-1*H*-pyrrole (**30**) was shown to bind with high affinity at D_3 receptors with about a 30-fold selectivity over D_2 receptors [53]. Modification of the ethylsulfone group of **30** yielded several derivatives (**31**-**34**) with high affinities and D_3 versus D_2 selectivities of over 100-fold [54]. Little enantiomeric selectivity was noted with the isomers of compound **31**, although the *R*-isomer showed higher binding affinities at both D_2 and D_3 receptors.

The tricyclic 1,4-oxazine (**35,** (+)-PD 128,907) was reported by Patel *et al.* [55] to exhibit high binding affinity (K_i= 1.7 nM) and over 100-fold D_3/D_2 selectivity. Using a mitogenic assay to assess functional activity, (+)-PD 128,907 was found to act as an agonist with approximately 50-fold selectivity at D_3 receptors [4]. Studies by Whetzel *et al.* [56] demonstrated that (+)-PD 128,907 decreased striatal and mesolimbic L-dihydroxyphenylalanine (L-DOPA) levels in rats pretreated with the L-aromatic amino acid decarboxylase inhibitor NSD 1015. This study adds further evidence for the regulatory role of D_3 receptors on the synthesis and release of DA. Millan *et al.* [57] demonstrated that the decrease in rectal temperature in rats induced by 7-OH-DPAT could be modulated by (+)-PD 128,907. These workers suggested that the modulation of hyperthermia in rats involves D_3 receptor activation. Witkin *et al.* [58] used stereotypic behaviors in mice induced by either the DA agonist, apomorphine, or the NMDA antagonist, dizocilpine, to compare the differences among haloperidol, (+)-PD 128,907, and clozapine. Similar to clozapine, (+)-PD 128,907 blocked stereotyped behavior produced by dizocilpine at about a 12-fold lower dose than stereotypy induced by apomorphine. Also, (+)-PD 128,907 failed to produce catalepsy. The authors suggested that the ability of (+)-PD 128,907 to inhibit dizocilpine-induced stereotypic behaviors may be related to its effect on neuronal pathways involving both DA and glutamate. Recent studies have shown that rats can be trained to discriminate (+)-PD 128,907 from saline [59]. However, the use of subtype selective antagonists suggests the involvement of presynaptic D_2 receptors in this response. Thus, these results indicate that the in vivo selectivity of (+)-PD 128,907 is much less than its in vitro selectivity. The thiopyran isostere (**36**) of (+)-PD 128,907 was recently reported by van Vliet *et al.*

[60]. The highest binding affinity in the *trans*-series resided with the (-)-isomer. Unlike (+)-PD 128,907, *trans*-**36** did not exhibit any DA receptor selectivity, but demonstrated agonist activity at $5HT_{1A}$ receptors. The *cis*-isomer acted as a full agonist at D_2 receptors and a partial agonist at D_3 receptors with about a 20-fold D_3/D_2 selectivity.

The benzofuran (±)-S 11566 exhibited preferential affinity for D_3 receptors in displacement studies using [^{125}I]iodosulpride as the radioligand. The active isomer was shown to be the (+)-isomer (**37,** S 14297) with D_3/D_2 K_i values of 13 nM and 297 nM and over 20-fold D_3/D_2 selectivity [61]. Additionally, (+)-S 14297 inhibited hypothermia induced by a variety of D_3 agonists including 7-OH-DPAT and (-)-quinpirole. In this study, potency for inhibition of 7-OH-DPAT-induced hypothermia correlated well with D_3 receptor binding affinity. Unlike nonselective DA antagonists such as haloperidol, (+)-S 14297 did not produce catalepsy or stimulate prolactin release. However, (+)-S 14297 demonstrated partial agonist activity in stimulation of D_3-coupled mitogen-activated protein kinase (MAPK) [62].

The chromanopyrrole (**38,** S 33084) was shown to act as preferential D_3 antagonist with greater than 100-fold D_3/D_2 selectivity and greater that 100-fold selectivities at over 30 other receptors evaluated [63]. Although S 33084 inhibited hypothermia and PE induced by 7-OH-DPAT and (+)-PD 128,907, the compound was inactive in several models used to predict antipsychotic or extrapyramidal activities.

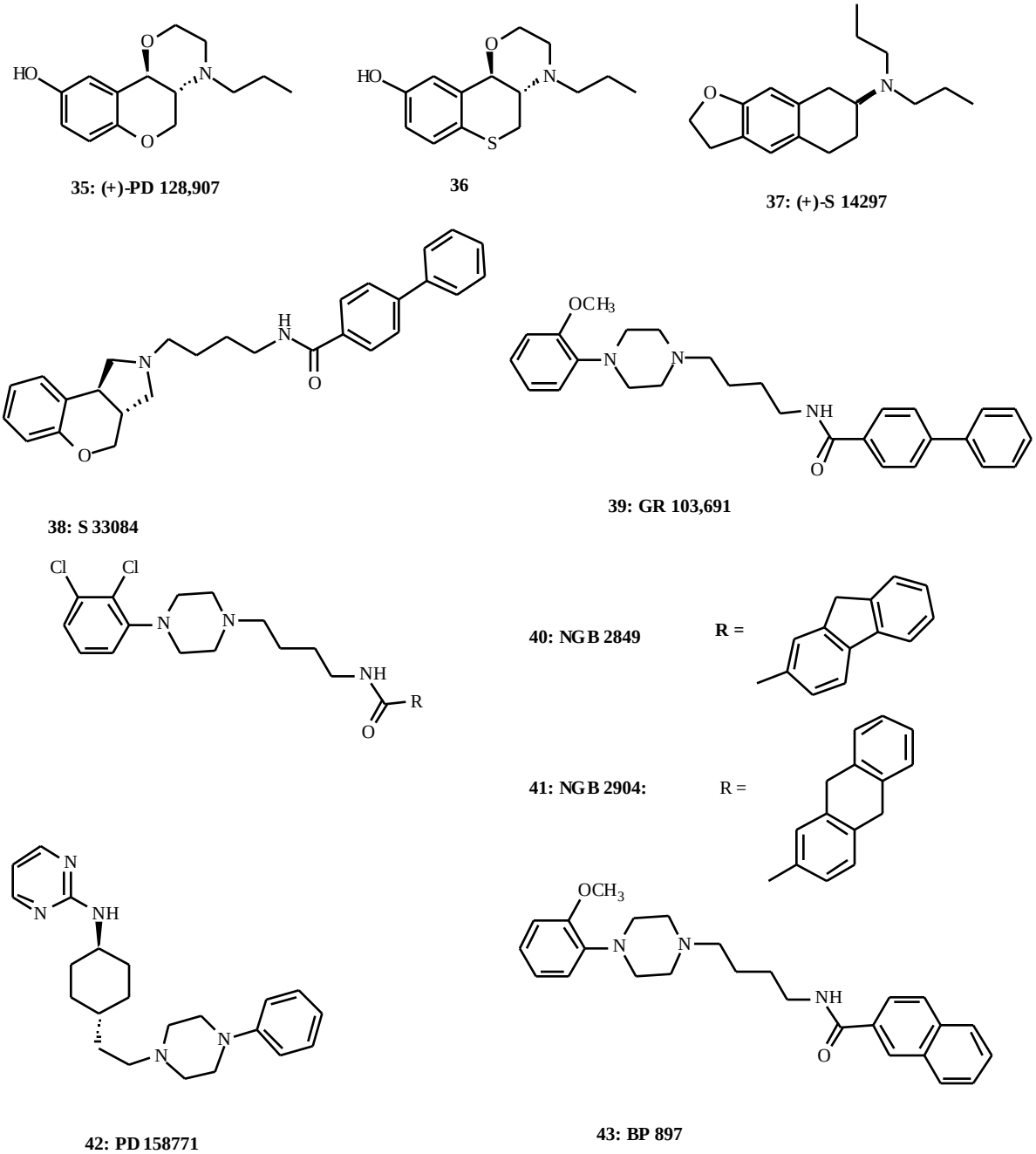
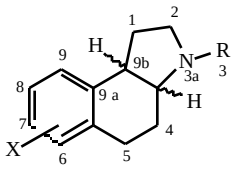


Fig. (3). Structures of D_3 ligands (**19**-**34**).

Table 1. In Vitro Binding at D_{2S} and D_3 Receptors[a,b]



Compound	R	X	B/C Ring Junction	D_{2S}[c]	D_3[d]	D_{2S}/D_3[e]
(±)-44a	*n*-Pr	8-OCH_3	*cis*	5070± 357	1500± 158	3
(±)-**44b**	*n*-Pr	8-OH	***cis***	1576± 237	39.2 ± 3.0	40
(+)-**44b**	*n*-Pr	8-OH	***cis***[f]	5476± 1194	296± 12	19
(-)-**44b**	*n*-Pr	8-OH	*cis*[g]	1007± 45	14.7± 4.3	69
(±)-**44c**	**allyl**	8-OCH_3	***cis***	3630± 201	553± 0.5	7
(±)-**44d**	allyl	8-OH	*cis*	2907± 34	10± 1	290
(±)-**44e**	*n*-Pr	8-OCH_3	***trans***	8417± 1338	368± 66	23
(±)-**44f**	*n*-Pr	8-OH	***trans***	147± 21	2.1± 1.9	73
(+)-**44f**	*n*-Pr	8-OH	***trans***[h]	105± 21	2.3± 1.9	46
(-)-**44f**	*n*-Pr	8-OH	***trans***[i]	2100± 569	156± 2.5	14
(±)-**44g**	allyl	8-OCH_3	***trans***	2760± 429	158± 43	18
(±)-**44h**	allyl	8-OH	***trans***	57± 4	1.7± 0.2	34
34				202± 123	0.4± 0.3	505
14				80± 42	1.2± 0.8	67

[a]Competitive displacement studies were performed using membrane preparations from clonal cells expressing D_{2S} (LtK$^-$ cells) and D_3 (BHK 21tK$^-$ cells) receptors, respectively. [b]K_i values were reported earlier [65,66]. [c][^{3}H]Spiperone (0.1 nM) was used to label D_3 receptors. [d][^{3}H]*R*-(+)-7-OH-DPAT (0.1 nM) was used to label D_3 receptors. [e]D_3 selectivity, $D_{2S}(K_i)/D_3$ (K_i). [f]Absolute configuration (3a*S*,9b*R*). [g]Absolute configuration (3a*R*,9b*S*). [h]Absolute configuration (3a*R*,9b*R*). [i]Absolute configuration (3a*S*,9b*S*).

Furthermore, S 33084 did not enhance locomotor activity or inhibit yawning behavior induced by 7-OH-DPAT. These authors concluded that only the induction of hypothermia and PE involve D_3 receptors [25].

The arylpiperazine (**39,** GR 103,691) was shown to bind with high affinity at the D_3 receptor [64]. In comparison studies with (+)-S 14297, nafadotride, U 99194, and GR 103,691 exhibited a K_i= 0.40 nM and a D_3/D_2 selectivity of 60-fold. However, GR 103,691 exhibits significant affinity for $5HT_{1A}$ and α_1-adrenergic receptors. Furthermore, GR 103,691 demonstrates little in vivo bioavailability and appears to only be useful as an in vitro pharmacological tool [12]. Yuan *et al.* [65] showed that the 2,3-dichlorophenylpiperazines (**40,** NGB 2849) and (**41,** NGB 2904) demonstrated high D_3 receptor binding affinities (K_i = 0.9 nM and 1.4 nM, respectively) and selectivities of over 150-fold versus other DA receptor subtypes. In a mitogenic assay to evaluate functional activity, NGB 2849 and NGB 2904 inhibited quinpirole-stimulated mitogenesis with IC_{50} values of 8.8 and 6.8 nM, respectively. The aminopyrimidine (**42,** PD 158771) was found to possess high affinity for D_2, D_3, and $5HT_{1A}$ receptors [66]. Further evaluation of this compound revealed partial agonism at DA receptors and agonist activity at $5HT_{1A}$ receptors [67,68]. Pilla *et al.* [69] reported that the D_3 partial agonist (**43,** BP 897) inhibited cocaine-seeking behavior in rats. These workers suggested that BP 897 could be potentially useful for inhibiting cocaine craving and relapse susceptibility produced by drug-related environmental stimuli.

Scheideler *et al.* [70] reported that the benz[*e*]indole (**44b,** *cis*-(±)-8-OH-PBZI) binds with high affinity for D_3 receptors with selectivities of 775-fold, 550-fold, 90-fold, and 10-fold at D_{1A}, D_5, D_{2S}, and D_4 receptors. The compound demonstrated agonist activity at D_3 receptors with a selective limbic site of action. Additonal behavioral and neurochemical studies were performed to fully characterize the pharmacological profile of *cis*-(±)-8-OH-PBZI [15]. This compound decreased spontaneous locomotor activity in mice, inhibited conditioned avoidance responding in rats, and failed to elicit catalepsy. At doses which inhibited spontaneous locomotor activity in rats, *cis*-(±)-8-OH-PBZI did not alter interstitial levels of DA or DOPAC in the nucleus accumbens or dorsolateral striatum. The pharmacological profile of *cis*-(±)-8-OH-PBZI suggests an action at postsynaptic D_3 receptors with possible antipsychotic potential devoid of undesirable motor side effects. Using *cis*-(±)-8-OH-PBZI as the structural lead, a detailed structure-activity relationship (SAR) study was

performed (**Table 1**) [71]. The *trans*-diastereoisomers exhibited greater binding affinities for DA D_3 receptors than the corresponding *cis*-isomers. In both series, the greatest binding affinities were found with compounds substituted with either *n*-propyl or allyl groups at the 3-position of the benz[*e*]indole nucleus. The allyl derivative *cis*-(±)-**44d** exhibited the greatest D_3/D_2 selectivity (290-fold) of any benz[*e*]indole evaluated in this study. Resolution of *cis*-(±)-**44b** or *trans*-(±)-**44f** into individual isomers showed that in both series the more active isomer had 3a*R* absolute configuration.

SUMMARY

In about one decade since its discovery, a vast amount of research has occurred on the study of the D_3 receptor and the development of selectively-acting D_3 agonists and antagonists. Potential therapeutic targets for these novel agents include Parkinson's disease, schizophrenia, and cocaine abuse. The continued development of selectively-acting ligands will greatly assist in determining the functional role for this novel receptor and its significance in numerous disease states.

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