Pergamon

Bioorganic & Medicinal Chemistry Letters 9 (1999) 2715–2720

BIOORGANIC & MEDICINAL CHEMISTRY LETTERS

HETEROCYCLIC ANALOGUES OF 2-AMINOTETRALINS WITH HIGH AFFINITY AND SELECTIVITY FOR THE DOPAMINE D_3 RECEPTOR

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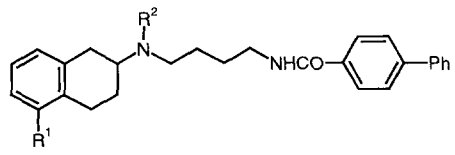
Received 25 May 1999; accepted 13 August 1999

Abstract: A novel series of 5,6,7,8-tetrahydroquinazolines, 4,5,6,7-tetrahydroindazoles and 4,5,6,7-tetrahydrobenzothiazoles has been prepared, having high affinity and selectivity for the dopamine D_3 receptor. The 4-methoxy-5,6,7,8-tetrahydroquinazoline **6i** and 2-amino-4,5,6,7-tetrahydrobenzothiazole **8** proved to be agonists with among the highest D_3 receptor affinities and selectivities reported to date.

All clinically effective antipsychotic agents share the property of dopamine D_2 and D_3 receptor antagonism. At clinical doses these drugs occupy D_3 as well as D_2 receptors and their antipsychotic effects could therefore be mediated *via* D_2 and/or D_3 receptors. Blockade of D_2 receptors in the striatum leads to serious extrapyramidal side-effects, which result in poor patient compliance and consequently poor control of the disease. Dopamine D_3 receptors are preferentially located in limbic brain regions, such as the nucleus accumbens, where dopamine receptor blockade has been associated with antipsychotic activity. A selective dopamine D_3 receptor antagonist therefore offers the potential for an effective antipsychotic therapy, free of the serious side-effects of currently available drugs.[1-3] As an aid to the discovery of such a selective antagonist, there is a need for a selective dopamine D_3 receptor agonist as a pharmacological tool for the further characterisation of the D_3 receptor and its physiological role. In this regard, the Parke-Davis dopamine D_3 agonist PD128907[4] reportedly has high selectivity for the D_3 over the D_2 receptor.

Recently, we described a series of agonist and antagonist 2-aminotetralins **1** with high affinity for the dopamine D_3 receptor and selectivity over the D_2 receptor.[5] These compounds were formally derived from the known dopamine D_3 agonist 5-OH-DPAT **2**.[6,7] We reasoned that by using alternative agonists as a starting point, such as quinelorane **3**,[8] quinpirole **4**,[9] or pramipexole **5**,[10] whose pKi values at the dopamine D_3 receptor we determined as 9.0, 7.0 and 8.0 respectively, corresponding novel series of heterocyclic derivatives **6**, **7** and **8** bearing the same 4-(4-phenylbenzoylamino)butyl side-chain would be obtained, having high affinity for the dopamine D_3 receptor. This *Letter* reports our key findings regarding the D_3 affinity and selectivity of **6**,**7** and **8** and describes the functional influence of the substituent R^1 in the heterocyclic ring of **6** (see **Table 1**).



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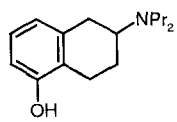

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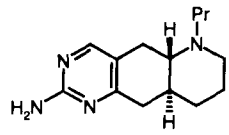

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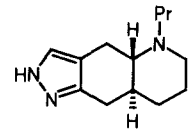

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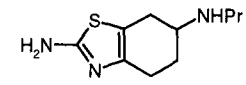

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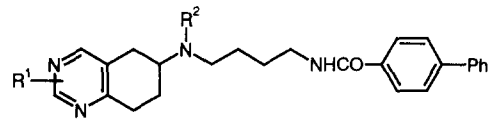

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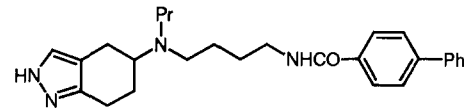

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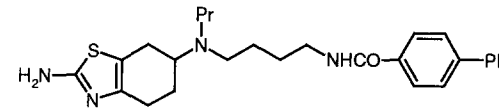

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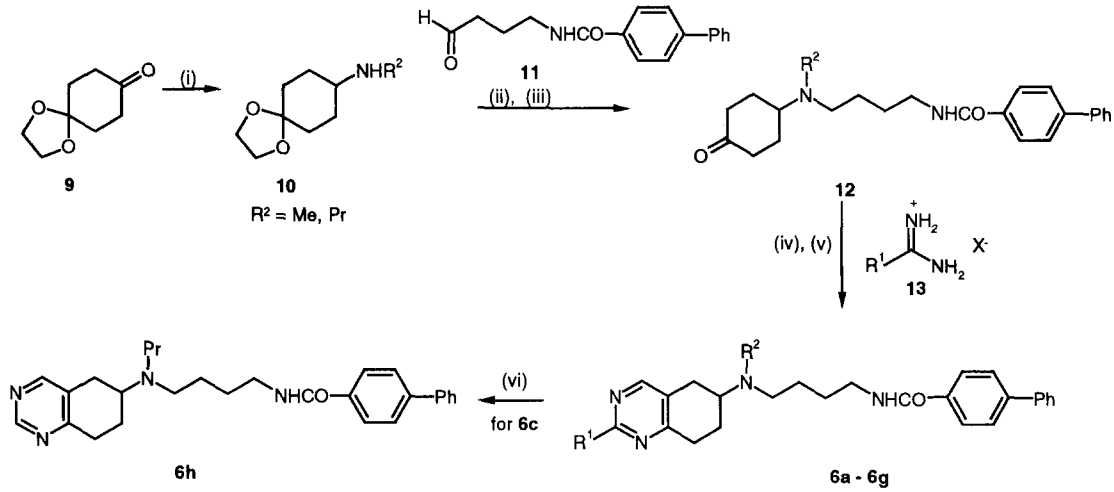
Novel 2-substituted 5,6,7,8-tetrahydroquinazolines **6a** - **6h** (**Table 1**) could be prepared from common intermediate **12**, which was itself readily synthesised from the previously described aldehyde **11**[5] (**Scheme 1**). Thus, reductive amination of **9** with either methylamine or *n*-propylamine in the presence of sodium triacetoxyborohydride gave the secondary amines **10** in high yield, and a second reductive amination using **11** under similar conditions, followed by hydrolysis with aqueous hydrochloric acid, gave key intermediates **12**. Condensation of **12** with *tris*-dimethylaminomethane in toluene at reflux gave the corresponding enaminoketones which could be condensed with a range of guanidines, amidines and thiouronium salts (**13**, R^1 = amino, alkyl and alkythio, respectively) in the presence of either sodium ethoxide or sodium bicarbonate as base, to give final compounds **6a** - **6g** in 27-74% yield. For the synthesis of unsubstituted compound **6h**, the condensation step with formamidine (**13**, R^1 = H) gave only intractable materials. However **6h** could be prepared by Raney nickel reduction of thioether **6c** in 60% yield.

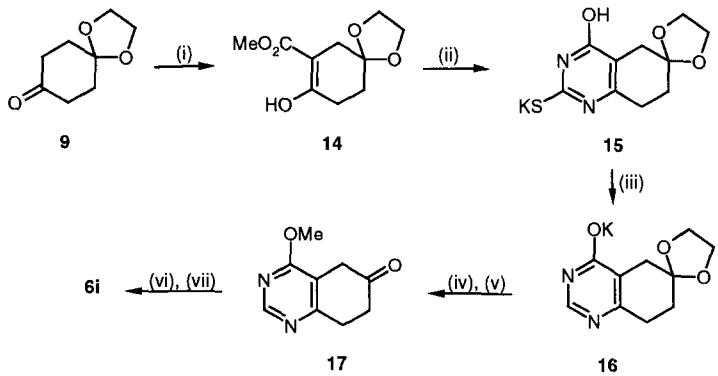
Our previous studies on 2-aminotetralins **1** had shown that hydrogen bonding capability in the aryl ring substituent R^1 was required for **1** to be an agonist.[5] We anticipated that addition of a 4-methoxy substituent into the tetrahydroquinazoline moiety would increase the electron density around the pyrimidine nitrogens and thus enhance the H-bond accepting ability of the system, which would in turn lead to potent agonism. The 4-substituted tetrahydroquinazoline **6i** (**Table 1**) was therefore targeted. Approaches to **6i** involving carboxylation of **12** proved unsuccessful, so the strategy of **Scheme 2** was adopted. Carboxylation of **9** to give **14** was effected using dimethyl carbonate in the presence of sodium hydride, and this was followed by condensation with thiourea under basic conditions to give **15**, which was desulfurised with Raney nickel to give the 4-hydroxy intermediate as the potassium salt **16**. Attempts to methylate **16** gave solely *N*-alkylated products, so conversion to the 4-methoxy **17** was accomplished by reaction with phosphorus oxychloride followed by workup with excess sodium methoxide. Reductive amination of **17** with *n*-propylamine using sodium triacetoxyborohydride, followed by reaction of the resulting amine with aldehyde **11**, gave target **6i**.

Scheme 1



Reagents: (i) R^2NH_2, $NaBH(OAc)_3$, $ClCH_2CH_2Cl$; (ii) **11**, $NaBH(OAc)_3$, $ClCH_2CH_2Cl$; (iii) HCl, H_2O; (iv) $(Me_2N)_3CH$, toluene, Δ; (v) **13**, NaOEt or $NaHCO_3$, EtOH; (vi) Raney Ni, EtOH

Scheme 2



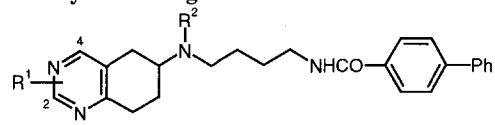
Reagents: (i) NaH, $(MeO)_2CO$, benzene, Δ; (ii) KOBu^t, thiourea, MeOH; (iii) Raney Ni, 20 M aqueous ammonia, Δ; (iv) $POCl_3$, then excess NaOMe, MeOH; (v) H_2SO_4, H_2O; (vi) $PrNH_2$, $NaBH(OAc)_3$, $ClCH_2CH_2Cl$; (vii) **11**, $NaBH(OAc)_3$, $ClCH_2CH_2Cl$.

Compounds **6a – 6i** were evaluated using displacement of ^{125}I-iodosulpride from human cloned D_3 and D_2 receptors, expressed in CHO cells, and results (together with those for PD128907) are shown in **Table 1**. The dopamine D_3 receptor has been shown to be weakly coupled to adenylate cyclase in CHO cells.[11] Functional activity of the compounds was therefore determined *in vitro* using microphysiometry.[12]

The initial compounds prepared in this series, **6a** and **6b**, showed high D_3 affinity and selectivity over D_2. Our previous work with 2-aminotetralins **1**[5] had demonstrated the beneficial effect on D_3 affinity and selectivity of an *N*-propyl compared to an *N*-methyl substituent, and the same effect operates in this new series of compounds although the selectivity difference between **6a** and **6b** is less than for the corresponding 2-aminotetralins.[5] Both

6a and **6b** displayed agonist activity, presumably as a result of activation of the dopamine D_3 receptor by the 2-amino group *via* hydrogen bond donation to a serine residue on trans-membrane helix 5.[6,13] In this respect the 2-amino group can be considered to function as a mimic of a phenolic hydroxyl in the aminotetralins. Removal of this hydrogen bonding potential, as in **6c, 6e** and **6g**, switched the functional activity to antagonism in line with previous findings with 2-aminotetralins, albeit with significant cost in terms of D_3 receptor affinity and selectivity against the D_2 receptor. The 2-methylamino analogue **6d** retained agonist activity, although with reduced D_3 receptor affinity relative to **6b**. Removal of the substituent at C-2 altogether, as in **6h**, caused a significant further loss in D_3 affinity and selectivity relative to **6c, 6e** and **6g**, suggesting the presence in the D_3 receptor of a lipophilic pocket capable of accommodating a methylthio, dimethylamino or *t*-butyl group. This implies that substituents at C-2 having hydrogen bonding capability are binding in a different area of the receptor from that accessed by C-2 substituents without hydrogen bonding capability. These observations are suppported by molecular modelling studies, involving the docking of **6b** and **6c** into dopamine D_3 receptor models.[13] The loss of affinity with **6h** is particularly dramatic when seen in the context of the 2-methyl analogue **6f**. However, the agonism observed with **6f** is interesting in the light of the antagonism found for **6c, 6e** and **6g**. A possible explanation for these observations is that in the case of **6f**, one or other pyrimidine nitrogen can interact with a serine on helix 5 as a hydrogen bond acceptor, and this interaction is prevented on steric grounds in the case of **6c, 6e** and **6g**. Alternatively, **6f** may adopt a different binding mode in the D_3 receptor relative to that of **6c, 6e** and **6g**.

Table 1. Affinities of Novel Heterocyclic Analogues of 2-Aminotetralins at Dopamine D_3 and D_2 Receptors



Compound[a]	R^1	R^2	D_3[b]	D_2[b]	Selectivity[c]	D_3 Function[d]
6a	2-NH_2	Me	8.0	5.8	150	Agonist
6b	2-NH_2	Pr	9.1	6.8	200	Agonist
6c	2-SMe	Pr	7.8	5.9	80	Antagonist
6d	2-NHMe	Pr	7.8	5.6	160	Agonist
6e	2-NMe_2	Pr	7.6	5.8	70	Antagonist
6f	2-Me	Pr	8.1	5.6	310	Agonist
6g	2-^{t}Bu	Pr	7.9	5.8	110	Antagonist
6h	H	Pr	6.9	5.9	10	NT
6i	4-OMe	Pr	8.5	5.8	490	Agonist
PD128907	-	-	7.6	5.6	100	NT

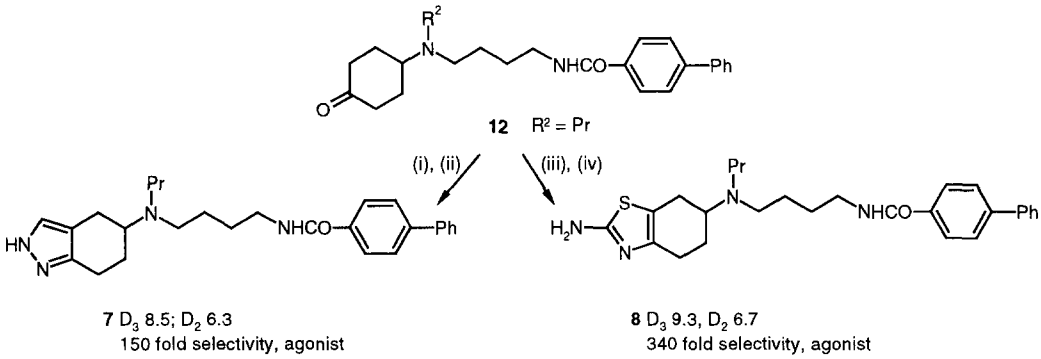
[a]All new compounds gave satisfactory analytical and/or mass spectral data.[14] [b]Affinities are pKi values. All values represent the mean of at least 2 experiments. [c]Selectivity ratio is defined as the antilogarithm of the difference between D_3 and D_2 pKi values. [d]Microphysiometer.[12] NT = not tested.

The 4-methoxy analogue **6i** showed very high D_3 affinity (pKi 8.5) and selectivity (490 fold) despite lacking a substituent at C-2. In agreement with our hypothesis that addition of a 4-methoxy substituent would enhance the hydrogen bond accepting ability of the pyrimidine nitrogens, **6i** is an agonist. The postulated hydrogen bond

interaction with the serine residue on helix 5 may involve either of the pyrimidine nitrogens, or the 4-methoxy substituent may act as a hydrogen bond acceptor in its own right.

The quinpirole- and pramipexole-derived analogues, **7** and **8** respectively, were also synthesised from the common intermediate ketone **12** (**Scheme 3**). Base-mediated condensation of **12** with ethyl formate followed by *in situ* reaction with hydrazine gave pyrazole **7**, while treatment of **12** with bromine in acetic acid and subsequent reaction with thiourea gave thiazole **8**.

Scheme 3



Reagents: (i) $KOBu^t$, THF, HCO_2Et; (ii) N_2H_4. H_2O, HCl; (iii) Br_2, HOAc; (iv) thiourea.

Data for compounds **7** and **8** are summarised in **Scheme 3.** In agreement with our hypothesis, both **7** and **8** were found to possess high D_3 affinity and selectivity over the D_2 receptor. Interestingly, aminothiazole **8** (D_3 pKi 9.3, selectivity 340 fold) had nearly 10 fold higher D_3 affinity and twice the selectivity against D_2 compared to pyrazole **7**. The former reflects the difference in D_3 affinity of quinpirole **4** and pramipexole **5**, from which **7** and **8**, respectively, are formally derived. In line with the presence of hydrogen bonding capable residues in both **7** and **8**, potent agonism was observed in each case.

In conclusion, using the selective D_3 agonists quinelorane, quinpirole and pramipexole as agonist starting points, in conjunction with a 4-(4-phenylbenzoylamino)butyl side-chain, a series of agonists and antagonists has been obtained with high affinity and selectivity for the dopamine D_3 receptor. In particular, the agonists **6b**, **6i** and **8** show improved selectivity compared with the related series of 2-aminotetralins previously reported,[5] together with 10 - 50 fold higher D_3 affinity than that determined by us for PD128907 (pKi 7.6), and may prove to be useful tools for further characterising the dopamine D_3 receptor and its physiological role.

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14. ^{1}H NMR spectra were recorded at 250 MHz in $CDCl_3$ as solvent. Compound **6b**, ^{1}H: δ 0.88 (t, J = 7 Hz, 3H), 1.36 - 1.77 (m, 7H), 2.04 (m, 1H), 2.48 (dd, J = 8,7 Hz, 2H), 2.57 (t, J = 7 Hz, 2H), 2.49 - 3.00 (m, 5H), 3.50 (m, 2H), 4.88 (br s, 2H), 6.45 (m, 1H), 7.33 - 7.52 (m, 3H), 7.62 (m, 4H), 7.83 (d, J = 9 Hz, 2H), 7.99 (s, 1H). Compound **6i**, mpt 136-140 °C (.HCl salt); ^{1}H: δ 0.89 (t, J = 7 Hz, 3H), 1.36 - 1.80 (m, 7H), 2.08 (m, 1H), 2.42 (dd, J = 18,10 Hz, 1H), 2.50 (m, 2H), 2.59 (t, J = 7 Hz, 2H), 2.64 - 3.07 (m, 4H), 3.50 (m, 2H), 3.97 (s, 3H), 6.54 (m, 1H), 7.32 - 7.53 (m, 3H), 7.63 (m, 4H), 7.85 (d, J = 9 Hz, 2H), 8.54 (s, 1H) (free base). Compound **7**, mpt 121 – 125 °C (oxalate salt); ^{1}H: δ 0.88 (t, J = 7 Hz, 3H), 1.34 - 1.71 (m, 7H), 2.02 (m, 1H), 2.32 - 3.06 (m, 9H), 3.50 (m, 2H), 5.50 - 7.20 (br s, 1H), 6.61 (m, 1H), 7.27 (s, 1H), 7.32 - 7.53 (m, 3H), 7.63 (m, 4H), 7.73 (d, J = 9 Hz, 2H) (free base). Compound **8**, mpt 130 – 134 °C (oxalate salt), ^{1}H: δ 0.87 (t, J = 7 Hz, 3H), 1.35 - 1.83 (m, 7H), 1.97 (m, 1H), 2.30 - 2.77 (m, 8H), 3.05 (m, 1H), 3.49 (m, 2H), 4.89 (br s, 2H), 6.60 (m, 1H), 7.32 - 7.52 (m, 3H), 7.62 (m, 4H), 7.85 (d, J = 9 Hz, 2H) (free base).