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Short Communication

Synthesis and preliminary pharmacological investigations of 1-(1,2-dihydro-2-acenaphthylenyl)piperazine derivatives as potential atypical antipsychotic agents in mice

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Abstract

In research towards the development of new atypical antipsychotic agents, one strategy is that the dopaminergic system can be modulated through manipulation of the serotonergic system. The synthesis and preliminary pharmacological evaluation of a series of potential atypical antipsychotic agents based on the structure of 1-(1,2-dihydro-2-acenaphthylenyl)piperazine (**7**) is described. Compound **7e**, 5-{2-[4-(1,2-dihydro-2-acenaphthylenyl)piperazinyl]ethyl}-2,3-dihydro-1*H*-indol-2-one, from this series showed significant affinities at the 5-HT_{1A} and 5-HT_{2A} receptors and moderate affinity at the D_2 receptor. **7e** exhibits a high reversal of catalepsy induced by haloperidol indicating its atypical antipsychotic nature.

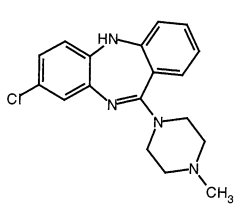
Keywords: 1-(1,2-Dihydro-2-acenaphthylenyl)piperazine; 5-Hydroxytryptamine; Catechol mimics; Dopamine; Atypical antipsychotics

1. Introduction

The inhibition of post-synaptic dopaminergic neurotransmission is traditionally assumed to be the mode of action of clinically effective antipsychotic agents [1]. Treatment with these agents is accompanied by the development of extrapyramidal side effects (EPS) and tardive dyskinesia [2].

During the past few years, a second generation of antipsychotic agents, the atypical antipsychotic agents has emerged from the observation that these agents exhibit antipsychotic activity without EPS and tardive dyskinesia [3].

In research towards the development of such atypical antipsychotic agents, one strategy is that the dopaminergic system can be modulated through pharmacological manipulation of the serotonergic system. The reported atypical antipsychotics, clozapine (**1**) [4] and ziprasidone (**2**) [5] possess 5-HT_2 receptor antagonist properties in addition to D_2 antagonism.



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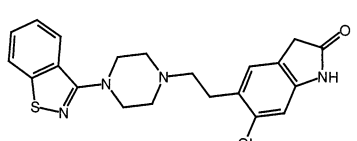

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The utility and potential of arylpiperazines as the pharmacophore in developing a serotonergic is well documented [6]. Incorporation of suitable substituents on the arylpiperazines can result in compounds with selectivity for a particular serotonergic receptor subtype and exhibit the pharmacological profile displayed by the substituent. Consistent with this observation,

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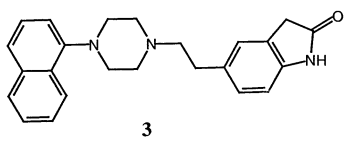
5 - {2 - [4 - (1 - naphthyl)piperazinyl]ethyl} - 2,3 - dihydro-indol-2-one (**3**), a derivative of 1-naphthyl piperazine has been developed as an atypical antipsychotic [7].



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We have recently communicated the synthesis and binding affinities of 1-(1,2-dihydro-2-acenaphthylenyl)-piperazine (**7**) as a new arylpiperazine with slight affinity at the 5-HT_{1A} receptor and moderate affinity at the 5-HT_{2A} receptor. Though **7** does not possess affinity at the dopaminergic receptor, it is more amenable for the structural variation necessary for incorporation of this activity. The strategy to achieve incorporation of the requisite dopamine–antagonist activity into an arylpiperazine is well documented and was achieved for **7**, using various heterocyclic surrogates, which are reported to mimic the catechol moiety of dopamine [7].

This article describes the synthesis and pharmacological evaluation of derivatives of an arylpiperazine-1-(1,2-dihydro-2-acenaphthylenyl)piperazine (**7**), as potential atypical antipsychotics. Some of the compounds have shown potential antipsychotic activity with an atypical profile, in accordance with Meltzer's classification [8].

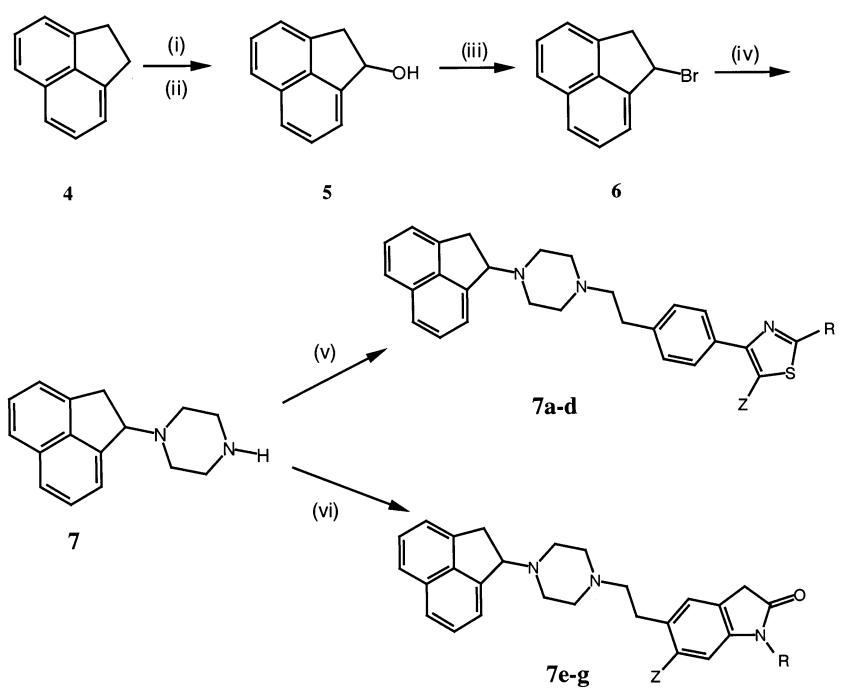
2. Chemistry

1,2-Dihydro-2-acenaphthylenol (**5**) was synthesized according to a literature procedure [9] from acenaphthylene (**4**) using lead oxide (red) in the presence of glacial acetic acid to give 1,2-dihydro-2-acenaphthylenyl acetate which was hydrolyzed using methanolic sodium hydroxide. Compound **5** on bromination gave 2-bromo-1,2-dihydroacenaphthylene (**6**) [10], which was reacted with anhydrous piperazine to give 1-(1,2-dihydro-2-acenaphthylenyl)piperazine (**7**). Compounds **7a**–**d** were obtained by alkylation of **7** with 2- and 5-substituted thiazoles appended to a phenethyl side-chain and compounds **7e**–**g** were obtained using 5-(2-chloroethyl)-1- and 6-substituted-2,3-dihydro-1*H*-indol-2-ones via base-catalysis using diisopropylethylamine (DIPEA) in methyl isobutyl ketone (MIBK). (Scheme 1).

3. Experimental

3.1. Chemistry

Melting points were determined on a Büchi model 530 melting point apparatus and are uncorrected. IR spectra were recorded on JASCO IR Report-100 spectrometer and are given in cm^{-1} and were recorded as a mull, unless specified. The ^1H NMR spectra, were



Scheme 1. Reagents (i) Pb_3O_4/CH_3COOH; (ii) $NaOH/CH_3OH$; (iii) PBr_3/anhydrous ether; (iv) anhydrous piperazine; (v) 4-[4-(2-chloroethyl)phenyl]-2- and 5-substituted thiazoles, Na_2CO_3, NaI, DIPEA, MIBK; (vi) 5-(2-chloroethyl)-1- and 6-substituted-2,3-dihydro-1*H*-indol-2-ones, Na_2CO_3, NaI, DIPEA, MIBK R = H/OH/CH_3/NH_2/NH–allyl; Z = H/CH_3/F.

recorded using Bruker AC 300F NMR spectrometer or Jeol GSX 400 NMR spectrometer and are reported in δ units (ppm) relative to TMS as internal standard. Mass spectra were recorded on a Finnigan MAT 8230 spectrometer. The results of the elemental analyses (C, H, N) were within $\pm 0.4\%$ of the theoretical values.

*3.1.1. 1-(1,2-Dihydro-2-acenaphthylenyl)piperazine (**7**)*

A mixture of **6** (0.1 mol) and anhydrous piperazine (0.2 mol) was heated at 110°C for 6 h. The mixture after cooling to room temperature (r.t.), basification with 2N NaOH, extraction with ether, removal of solvent under reduced pressure, chromatographed on silica gel using 9:1 $CHCl_3$–CH_3OH as eluent, gave **7** as pale yellow crystals. Yield 65%, m.p. 66°C (diisopropyl ether). IR (cm^{-1}): 1600 (aromatic), 1560 (C–N), 800, 775 (1,2,3-trisubstituted benzene). MS: 238 (M^+, $C_{16}H_{18}N_2$), 223 ($C_{16}H_{17}N$), 182 ($C_{14}H_{14}$), 153 ($C_{12}H_9$), 127 ($C_{10}H_7$), 85 ($C_4H_9N_2$), 56 ($C_2H_4N_2$). ^1H NMR ($CDCl_3$): 7.79–7.30 (m, 6H, Ar–H), 5.16 (s, 1H, C–H), 3.55–3.23 (m, 10H, methylenes), 3.01 (s, 1H, N–H).

*3.1.2. 4-(4-{2-[4-(1,2-Dihydro-2-acenaphthylenyl)-piperazinyl]ethyl}phenyl-2-amino thiazole trihydrochloride (**7a**)*

Literature procedure [7] was adopted for this synthesis. In a 50 ml round-bottomed flask equipped with a reflux condenser and N_2 inlet were placed 4-[4-(2-chloroethyl)phenyl]-2-amino thiazole (0.952 g, 3.46 mmol), **7** (0.825 g, 3.46 mmol), anhydrous Na_2CO_3 (0.733 g, 10.3 mmol), NaI (2 mg), DIPEA (1.79 ml, 10.3 mmol) in 15 ml of MIBK. The reaction mixture was refluxed for 2 days, cooled, filtered and the solvent was removed under reduced pressure to give light yellow oil, which was converted into its hydrochloride in acetone–ether mixture. Yield 0.990 g (52%), m.p. 227°C (methanol). IR (cm^{-1}): 3400 (amino), 2395 ($^+NHCl^-$), 1700, 1300 (C–S), 1620 (aromatic).^1H NMR (DMSO-d_6): 8.05–7.31 (m, 11H, Ar–H), 5.33 (d, 1H, CH), 3.84 (s, 2H, CH_2), 3.70–3.33 (m, 8H, piperazinyl methylenes), 3.12–2.97 (q, 4H, methylenes).

*3.1.3. 4-(4-{2-[4-(1,2-Dihydro-2-acenaphthylenyl)-piperazinyl]ethyl}phenyl)-2-amino-5-methylthiazole trihydrochloride (**7b**)*

Synthesized according to the method for **7a** using 4-[4-(2-chloroethyl)phenyl]-2-amino-5-methylthiazole. Yield 62%, m.p. 258°C (ethanol–ether). IR (cm^{-1}): 3400 (amino), 2415 ($^+NHCl^-$), 1700, 1300 (C–S), 1615, 1600 (aromatic). ^1H NMR (DMSO-d_6): 7.35–6.76 (m, 10H, Ar–H), 5.62 (d, 1H, CH), 4.24 (d, 2H, CH_2), 3.51 (s, 2H, NH_2), 3.47–3.45 (q, 4H, CH_2), 3.42–3.03 (m, 8H, piperazinyl methylenes), 1.97 (s, 3H, CH_3).

*3.1.4. 4-(4-{2-[4-(1,2-Dihydro-2-acenaphthylenyl)-piperazinyl]ethyl}phenyl)-2-allylaminothiazole trihydrochloride (**7c**)*

Synthesized according to the method for **7a** using 4-[4-(2-chloroethyl)phenyl]-2-allylaminothiazole. Yield 30%, m.p. 278°C (methanol–ether). IR (cm^{-1}): 2505, 2380 ($^+NHCl^-$), 1690 (C–S), 1600 (aromatic), 1075 (C–N), 925 (vinyl). ^1H NMR (DMSO-d_6): 8.07–7.26 (m, 11H, Ar–H), 5.37 (d, 1H, CH), 5.35 (q, 2H, CH_2), 5.15 (m, 1H, CH–vinyl), 4.76–4.10 (m, 8H, CH_2), 3.91–3.73 (m, 8H, piperazinyl methylenes), 3.48 (t, 1H, NH).

*3.1.5. 4-(4-{2-[4-(1,2-Dihydro-2-acenaphthylenyl)-piperazinyl]ethyl}phenyl)thiazole-2(3H)-one dihydrochloride (**7d**)*

Synthesized according to the method for **7a** using 4-[4-(2-chloroethyl)phenyl] thiazole-2-one (synthesized according to the literature procedure [11]. Yield 32%, m.p. 218°C (methanol). IR (cm^{-1}): 3400 (OH), 2395 ($^+NHCl^-$), 1680 (C–S), 1600 (aromatic). ^1H NMR (DMSO-d_6): 11.74 [d, 1H, OH (enolised)], 8.21–7.26 (m, 11, Ar–H), 5.44 (d, 1H, CH), 4.16–3.74 (m, 8H, piperazinyl methylenes), 3.35 (d, 2H, CH_2), 3.15 (t, 2H, CH_2), 3.06 (t, 2H, CH_2).

*3.1.6. 5-{2-[4-(1,2-Dihydro-2-acenaphthylenyl)-piperazinyl]ethyl}-2,3-dihydro-1H-indol-2-one dihydrochloride (**7e**)*

Synthesized according to the method for **7a** using 5-(2-chloroethyl)-2,3-dihydro-1*H*-indol-2-one (synthesized according to the literature procedure [7]). Yield 64%, m.p. 236°C (ethanol–ether). IR (cm^{-1}): 3200 (N–H), 2400 ($^+NHCl^-$), 1695 (C=O: amide), 1620 (aromatic), 1482 (C–N). ^1H NMR (DMSO-d_6): 8.14–7.79 (m, 3H, Ar–H), 7.68–6.79 (m, 6H, Ar–H), 5.42 (d, 1H, CH), 4.07 (s, 2H, CH_2), 3.94–3.75 (m, 8H, piperazinyl methylenes), 3.47 (t, 4H, CH_2), 3.16 (bs, 2H, CH_2).

*3.1.7. 5-{2-[4-(1,2-Dihydro-2-acenaphthylenyl)-piperazinyl]ethyl}-1-methyl-2,3-dihydro-1H-indol-2-one dihydrochloride (**7f**)*

Synthesized according to the method for **7a** using 5-(2-chloroethyl)-1-methyl-2,3-dihydro-1*H*-indol-2-one (synthesized according to the literature procedure [7]). Yield 54%, m.p. 247°C (methanol–ether). IR (cm^{-1}): 2400 ($^+NHCl^-$), 1695 (C=O, amide), 1610 (aromatic). ^1H NMR (DMSO-d_6): 8.15–7.86 (m, 3H, Ar–H), 7.72–6.82 (m, 6H, Ar–H), 5.62 (d, 1H, CH), 3.78–3.60 (m, 8H, piperazinyl methylenes), 3.46 (s, 3H, N–CH_3), 3.38 (t, 2H, CH_2), 3.15–3.06 (q, 4H, methylenes).

*3.1.8. 6-Fluoro-5-{2-[4-(1,2-dihydro-2-acenaphthylenyl)piperazinyl]ethyl}-2,3-dihydro-1H-indol-2-one dihydrochloride (**7g**)*

Synthesized according to the method for **7a** using 5-(2-chloroethyl)-6-fluoro-2,3-dihydro-1*H*-indol-2-one (synthesized according to the literature procedure [5]). Yield 45%, m.p. 248°C (ethanol–ether). IR (cm^{-1}): 3190 (N–H), 2400 ($^{+}NHCl^{-}$), 1700 (C=O), 1622 (aromatic), 1480 (C–N). ^{1}H NMR (DMSO-d_6): 8.11–7.78 (m, 2H, Ar–H), 7.68–6.60 (m, 6H, Ar–H), 5.47 (d, 1H, CH), 3.92–3.72 (m, 8H, piperazinyl methylenes), 3.25 (t, 2H, CH_2), 3.55–3.30 (m, 4H, CH_2), 3.19 (q, 2H, CH_2).

3.2. Pharmacology

3.2.1. Evaluation of apomorphine-induced cage climbing behaviour in mice

The effect of pretreatment with 30 mg/kg doses of the test compounds on apomorphine 0.5 mg/kg (s.c.) induced cage climbing behaviour was studied by the literature method [12]. Haloperidol 1.0 mg/kg (i.p.) was used as control as it completely inhibited the climbing induced by apomorphine.

3.2.2. Evaluation of reversal of haloperidol-induced catalepsy in mice

Catalepsy was evaluated by the literature method [13] and scoring was done as per literature [14]. The test compounds 30 mg/kg (i.p.) were injected 30 min before the injection of haloperidol 0.25 mg/kg (i.p.). The catalepsy score was recorded at 30, 60, 120 and 180 min after haloperidol administration. The percentage reversal is calculated as a percentage of the difference between the total points obtained between control and test drugs.

3.2.3. Reversal of apomorphine-induced stereotypy in mice

The animals were observed for stereotypic behaviour by the literature method [5]. The effect of the test compound 60 mg/kg (i.p.) was studied using haloperidol 0.5 mg/kg (i.p.) and apomorphine 5 mg/kg (s.c.) as control.

3.3. Receptor binding studies

3.3.1. 5-HT_{2A} receptor binding assay

The cortex of the rat brain was homogenized in 10 volumes of ice-cold buffer (50 mM Tris–HCl, pH 7.6) with an Ultra-Turrax T 25. The homogenate was centrifuged at $20\,000 \times g$ for 10 min. The resulting pellet was resuspended with the Ultra-Turrax and centrifuged again at $20\,000 \times g$ for 10 min. After repeating the same procedure the pellet was resuspended in 10 volumes of buffer and stored at −20°C until used in binding studies. [^{3}H]Ketanserin (3148.7 GBq/mmol from NEN) was used as a radioligand for 5-HT_2 receptor binding. The binding assay was carried out in a final volume of 5 ml Tris–HCl buffer, pH 7.6, containing 0.12 nM [^{3}H]ketanserin, membrane homogenate (about 20 g/ml protein), and various concentrations of the drugs. The drugs were dissolved in DMSO up to 1 mM, then diluted with buffer. Nonspecific binding was defined as the amount of [^{3}H]ketanserin bound in the presence of 1 μM mianserin (Sigma), and ranged from 17 to 24% of total binding. The samples were incubated in triplicates at 20°C for 60 min. The incubation was terminated by rapid filtration through GF/B glass fiber filters (Whatman) using a 30-port Brandel Cell Harvester. The filters were rapidly washed with four 4 ml portions of ice-cold buffer, transferred into 10 ml scintillation fluid (Ultima-Gold, Packard) and analyzed for radioactivity.

3.3.2. 5-HT_{1A} receptor binding assay

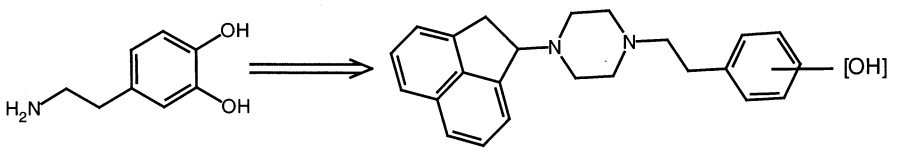
The hippocampus of rat brain was prepared as described above and stored at −20°C until used in binding studies. [^{3}H]8-OH-DPAT, membrane homogenate (about 20 μg/ml protein), and various concentrations of the drugs dissolved and diluted as described above. Non-specific binding was defined as the amount of [^{3}H]8-OH DPAT bound in the presence of 10 μM serotonin (Sigma), and ranged from 5 to 9% of the total binding. The samples were incubated in triplicates at 20°C for 120 min. Filtration and counting of the samples were the same as described above.

3.3.3. D_2 receptor binding assay

[^{3}H]Spiperone (684.5 GBq/mmol, NEN) was used as the radioligand. The binding assay was carried out in a final volume of 5 ml Tris–HCl buffer, pH 7.4, containing 10 mM $MgCl_2$, 1 mM EDTA, 0.27 nM [^{3}H]spiperone bound in the presence of 10 μM haloperidol and ranged from 8 to 12% of total binding. The samples were incubated in triplicates for 20°C for 60 min. Filtration and counting of the samples were the same as described above.

4. Results and discussion

In recent years, renewed attention has been paid to the possible benefit of combined serotonin (5-HT_2) and dopamine (D_2) receptor antagonism for the treatment of disorders like schizophrenia. Potent 5-HT_2 antagonism in combination with neuroleptics (D_2 antagonists) has been reported to reduce catalepsy in rats, increase neuroleptic induced dopamine turnover and also to reduce EPS in patients. Studies on the binding affinities of 1-(1,2-dihydro-2-acenaphthylenyl)piperazine (**7**) re-



Dopamine, agonist Dopamine antagonist

Fig. 1.

vealed, that it lacks affinity for the dopamine D_2 receptor but has moderate affinity for the $5HT_{2A}$ receptor.

The chemical strategy designed to afford the desired antipsychotic activity onto **7** was based on previously reported literature using heterocyclic surrogates to mimic the catechol and indole portions of dopamine and serotonin [5,7]. With 1-(1,2-dihydro-2-acenaphthylenyl)piperazine as the lipophilic group, the receptor agonist was modified into an antagonist as shown in Fig. 1.

We could envisage an interaction as reported for **3** [7] for 1-(1,2-dihydro-2-acenaphthylenyl)piperazine, binding to the accessory binding site of the D_2 receptor and held by a phenethyl side-chain to reach the serine residues as shown in Fig. 2.

The physical properties of 1-(1,2-dihydro-2-acenaphthylenyl)piperazine derivatives are shown in Table 1. These compounds were subjected to a preliminary in vivo evaluation in mice predictive of atypical antipsychotic activity and the results are shown in Table 1.

In the in vivo evaluation, **7b–g** afforded behavioural activity of antipsychotic efficacy consistent with dopamine antagonism in reversing apomorphine induced climbing behaviour as shown in Table 1. Among these compounds, **7e** has shown maximal reversal of haloperidol induced catalepsy, indicating its impressive atypical character.

Compound **7e**, comprising the indolone moiety appended through an ethyl chain to 1-(1,2-dihydro-2-acenaphthylenyl)piperazine, has shown minimal dopamine

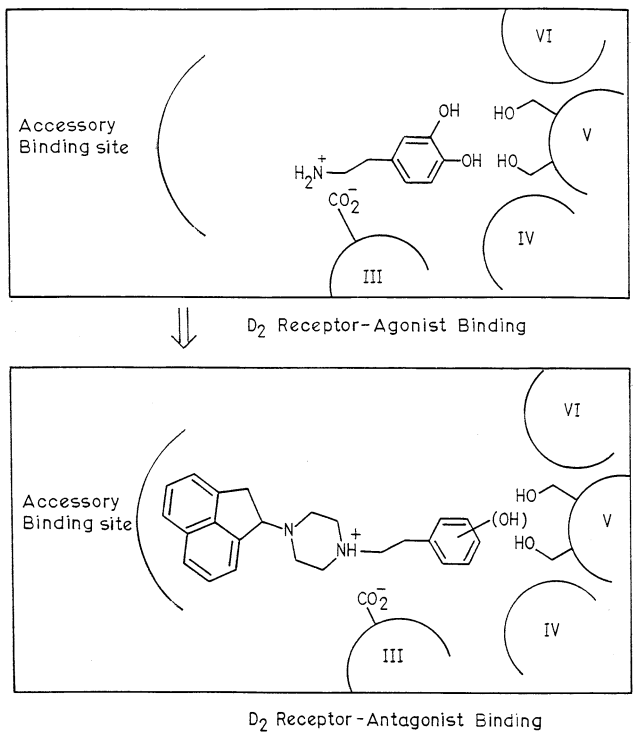


Fig. 2. Model of D_2 receptor, incorporating D_2 receptor affinity onto 1-(1,2-dihydro-2-acenaphthylenyl)piperazine (proposed interaction as reported for 1-naphthyl piperazine [7]).

(D_1/D_2) antagonism and maximal 5-HT_2 antagonism indicative of a potential antipsychotic with an atypical profile. Further, **7e** had shown minimal inhibition of the stereotypic behaviour induced by apomorphine

Table 1
Physical properties and in vivo evaluation of 1-(1,2-dihydro-2-acenaphthylenyl)piperazine derivatives [a]

Comp.	R	Z	M.p. (°C)	Yield (%)	Solvent	Anal.	D_1/D_2 [b]	5-HT_2 [c]
7			66	65	A	$C_{16}H_{18}N_2$	#	75.40 ± 7.3
7a	NH_2	H	227	52	B	$C_{27}H_{31}N_4SCl_3$	#	#
7b	NH_2	CH_3	258	62	C–D	$C_{28}H_{33}N_4SCl_3$	61.1 ± 6.4	6.25 ± 2.4
7c	NH–allyl	H	278	30	B–D	$C_{30}H_{35}N_4SCl_3$	41.6 ± 7.9	39.16 ± 6.4
7d	OH	H	218	32	B	$C_{27}H_{30}N_4OSCl_3$	52.4 ± 4.8	39.58 ± 5.7
7e	H	H	236	64	C–D	$C_{26}H_{29}N_3OCl_2$	16.6 ± 7.8	83.30 ± 7.4
7f	CH_3	H	247	54	B–D	$C_{27}H_{31}N_3OCl_2$	22.2 ± 5.6	6.25 ± 3.4
7g	H	F	248	45	C–D	$C_{26}H_{28}N_3OFCl_2$	27.7 ± 7.3	64.58 ± 8.9

[a] A, diisopropyl ether; B, MeOH; C, EtOH; D, Et_2O; #, not significant <5%.
[b] % Inhibition of apomorphine induced climbing behaviour in mice. Values are mean ± SE ($n = 5$).
[c] % Reversal of haloperidol induced catalepsy. Values are mean ± SE ($n = 5$).

Table 2
IC_{50} values (nM) [a]

Comp.	5-HT_{1A}	5-HT_{2A}	D_2
7	4800 ± 320	780 ± 179	>20 000
7e	34 ± 8	82 ± 44	222 ± 94
Clozapine	37 ± 4	8.9 ± 1.6	128 ± 2
Ketanserin	n.d.	1.00 ± 0.08	n.d.
Mianserin	n.d.	0.42 ± 0.10	n.d.
8-OH-DPAT	0.52 ± 0.10	n.d.	n.d.
Spiperone	n.d.	13 ± 4	0.49 ± 0.24
Haloperidol	n.d.	n.d.	13 ± 2

[a] n.d., not determined.

even at a dose of 60 mg/kg, indicating a minimal D_2 antagonism.

In vitro evaluation of **7e** was carried out by receptor binding studies. The results are given as IC_{50} values (nM) as shown in Table 2. High affinity was observed for the 5-HT_{1A} and 5-HT_{2A} receptor and moderate affinity at the D_2 receptor for this compound. This is in agreement with reported putative atypical antipsychotic agents which possess greater affinity for the 5-HT_{2A} receptor than the D_2 receptor [5].

In fact, the most potent affinity for **7e** was found at the 5-HT_{1A} receptor followed by that at the 5-HT_{2A} and D_2 receptors. It was observed that the introduction of D_2 receptor affinity into the 1-(1,2-dihydro-2-acenaphthylenyl)piperazine has also improved the affinity for 5-HT_{1A} and 5-HT_{2A} receptor, suggesting that the strategy of mimicking a phenolic group, present in both dopamine and serotonin can succeed at more than one receptor simultaneously, which is consistent with literature reports [7].

Mixed affinities at 5-HT_{1A}/D_2 or 5-HT_{2A}/D_2 receptors has been reported to be indicative of antipsychotic activity with an atypical profile [15]. Compound **7e** has shown affinities for both 5-HT_{1A} and 5-HT_{2A} receptors, in addition to the minimal D_2 receptor affinity confirming its atypical character. Further characterization of these compounds, would result in development of effective antipsychotics with low EPS liabilities.

Acknowledgements

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