Rational design, synthesis, SAR study of N-napthalen-1-yl-2-[4-(substituted phenyl)-piperazin-1-yl]-acetamides as atypical antipsychotic agents

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Design and synthesis of various N-napthalen-1-yl-2-[4-(substituted phenyl)-piperazin-1-yl]-acetamides have been carried out on the basis of structural information available for dopamine D2 and serotonin receptor and screened for antagonist activity at the target receptors and atypical antipsychotic profile. The series synthesized affords compounds having varying degree of affinity for target receptors. N-napthalen-1-yl-2-[4-(2-methoxy phenyl)-piperazin-1-yl]-acetamide 1 is found to be the most potent atypical antipsychotic compound synthesized.

Keywords: N-Napthalen-1-yl acetamide, serotonin antagonists, arylpiperazines, dopamine antagonists, atypical antipsychotic

Schizophrenia is one of the most common psychiatric disorders that affect about 1.5% of the world population. Conventional antipsychotic drugs like haloperidol and chlorpromazine were antagonists of the dopamine D2 receptor but were associated with serious extrapyramidal side effects. The development of a new era of antipsychotic drugs began with the discovery of clozapine which produced no extrapyramidal side effects and thus was the prototype of a new category of antipsychotic drugs and called as ‘atypical antipsychotic’. Antagonism at dopamine D2 and serotonin 5-HT2 receptor is one of the most accepted theories for atypical antipsychotic action.

Dopamine and serotonin receptors belong to the family of G-protein coupled receptors whose structures are characterized by seven transmembrane helices (TM1-TM7). Accurate three-dimensional structural information is not available for dopamine D2 receptor. However, dopamine D2 receptor has more than 50% sequence homology to the dopamine D3 receptor. Recently, on the basis of docking studies on D3 receptor, it has been suggested that there are five important pharmacophoric features in binding of ligands to the dopamine receptor. These features are: salt bridge interaction via a protonated amine, an aromatic and a non-aromatic pharmacophoric site and three hydrogen bond donor/acceptors. Similar homology modeling and docking studies of serotonin 5-HT1 receptor revealed that arylpiperazine moiety is located between TM3 and TM7. The aromatic portion of the ligand may interact with Phe 3.28, Trp 7.40 and Tyr 7.43, while the substituents in the aryl ring interact with Asn 7.39 (Ref 8). In view of these observations, the molecules are designed so as to have the required features and thus imparting affinity at both the target receptors. This led to synthesis of various N-napthalen-1-yl-2-[4-(substituted phenyl)-piperazin-1-yl]-acetamides and screening for antagonist activity at dopamine D2 and serotonin 5-HT2 receptor, and evaluate their propensity to produce catalepsy as an indication of atypical antipsychotic profile.

Results and Discussion

The compounds were prepared as reported in Scheme I. Napthalen-1-yl amine was treated with chloroacetyl chloride to afford the acetamide (compound 1). The acetamide was then coupled with various phenyl piperazines to yield the target compounds 1a-k respectively, in yields varying from minimum 38% to maximum 70%. All the target compounds were obtained in solid state. The physical and spectral characterization data of the synthesized compounds are given in Tables I and II respectively.

Compound 1 showed IR absorption at 1678 cm⁻¹ corresponding to C=O stretching in secondary amides. ¹H NMR spectral studies showed peaks at δ 7.26-7.98, 8.78 and 4.36, assigned respectively to protons of naphthalene, -NH and methylene protons. The ESMS of the compound 1 showed its molecular ion peak at 219 and (M+H)⁺ peak at 220. All these details confirmed the structure of compound 1.

Similarly the spectral details of the final compounds also confirmed their structures, for example: ¹H NMR spectrum of compound 1e in addition to showing peaks characteristic to compound...
1. showed signals at δ 3.89, 3.28-3.35 and 2.88-2.91 corresponding to methoxyl; 3′ and 5′ protons in piperazine; and 2′, 6′ protons in piperazine. Peaks at m/z 375, 376 and 248 were observed in the MS, corresponding to molecular ion peak, (M+H)+ and the fragmentation peak respectively. The above mentioned spectral details confirmed the structure of 1e and indicate the formation of product. Similar characterization was used to confirm the structures of other title compounds 1a-k.

**Scheme I**

In the series synthesized, a representative electron withdrawing group (chloro) and electron donating groups (methyl and methoxyl) were introduced as a single substituent at each of the three available positions. Di-substituted compound with an electron withdrawing group (chloro) was also synthesized. The novel compounds were biologically evaluated and the results obtained are shown in the Figures 1, 2 and 3. The SAR study reveals that ortho substitution by electron donating group (methoxyl) yielded most potent member of the series (1e). Electron withdrawing/donating groups at other positions yielded derivatives with varying affinity at the target receptors. Di-substitution with chlorine at 2 and 3 position did not produce much effect on the affinity towards the receptors.

**Experimental Section**

Melting points were determined in open capillaries and are uncorrected. IR spectra were recorded in KBr on a Perkin-Elmer FTIR-1600 spectrophotometer. 1H NMR spectra were recorded in CDCl3 using TMS as an internal standard (chemical shift in δ, ppm). The electrospray mass spectra (ESMS) were recorded on a Micromass Quattro II triple quadrupole mass spectrometer. The FAB mass spectra were recorded on a Jeol SX 102/DA-6000 mass spectrometer using Argon/Xenon (6 kV, 10 mA) as the FAB gas. Elemental analyses were performed for C, H and N. All the compounds gave satisfactory elemental analysis. TLC were run on silica gel G plates and spots were visualized by iodine vapours/UV light. All the test compounds and the reference drug Olanzapine were orally administered.

**Preparation of N-napthalen-1-yl-2-chloroacetamide, 1**

To a solution of napthalen-1-yl amine (0.01 mol) in acetonitrile, chloroacetyl chloride (0.011 mol) was added dropwise in the presence of anhydrous K2CO3. The reaction mixture was refluxed for 8 hr and then allowed to cool to RT. The solvent was removed under reduced pressure to afford crude solid. The solid obtained was dissolved in dichloromethane and filtered. The filtrate was put into separating funnel and extracted successively with sodium bicarbonate (5%) and water. The organic layer was separated and dried over anhydrous Na2SO4. The dried organic layer was concentrated under reduced pressure and allowed to cool to afford the product 1 which was recrystallized using methanol. Yield 74%; m.p. 120-22°C; Rf 0.49 (50% Benzene- EtOAc); IR (KBr): 3449, 3028, 3049, 2929, 2851, 1727, 1629, 1595, 1440, 1373, 1327, 1249, 1167, 1095, 984, 816, 753, 695, 632 cm⁻¹.
Table I — Physical characterization data for compound 1a-k

<table>
<thead>
<tr>
<th>Compd</th>
<th>R_1</th>
<th>R_2</th>
<th>R_3</th>
<th>Mol. formula</th>
<th>m.p.</th>
<th>Yield</th>
<th>R_f</th>
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<td>1a</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>C_{22}H_{23}N_{10}O</td>
<td>172-74</td>
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<tr>
<td>1b</td>
<td>CH_3</td>
<td>H</td>
<td>H</td>
<td>C_{22}H_{23}N_{10}O</td>
<td>181-83</td>
<td>54</td>
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<tr>
<td>1c</td>
<td>H</td>
<td>CH_3</td>
<td>H</td>
<td>C_{22}H_{23}N_{10}O</td>
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<td>59</td>
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<tr>
<td>1d</td>
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<td>H</td>
<td>CH_3</td>
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<tr>
<td>1e</td>
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<td>H</td>
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<tr>
<td>1f</td>
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<td>H</td>
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<td>55</td>
<td>0.41</td>
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Elemental analyses were within ± 0.4% of theoretical values, Melting point are uncorrected, Solvent for recrystallization is methanol, Mobile phase is benzene:ethylacetate-3:2

Table II — Spectral characterization data for compounds 1a-k

<table>
<thead>
<tr>
<th>Compd</th>
<th>IR (cm⁻¹)</th>
<th>¹H NMR (CDCl₃, δ)</th>
<th>MS (m/z)</th>
</tr>
</thead>
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<tr>
<td>1a</td>
<td>3443, 3033, 1680</td>
<td>7.22-7.89 (m, 7H, ArH naphthalene), 6.73-6.91 (m, 5H, ArH phenyl), 3.46 (s, 2H, -CH₂), 3.28-3.35 (t, 4H, 3' and 5' H piperazine), 2.88-2.91 (t, 4H, 2' and 6' H piperazine)</td>
<td>345, 346, 219</td>
</tr>
<tr>
<td>1b</td>
<td>3440, 3038, 1676</td>
<td>7.27-7.91 (m, 7H, ArH naphthalene), 6.70-6.88 (m, 4H, ArH phenyl), 9.87 (bs, 1H, -NH), 3.42 (s, 2H, -CH₂), 3.26-3.35 (t, 4H, 3' and 5' H piperazine), 2.58-2.62 (t, 4H, 2' and 6' H piperazine), 2.31 (s, 3H, -CH₃ of phenyl)</td>
<td>—</td>
</tr>
<tr>
<td>1c</td>
<td>3443, 3040, 1679</td>
<td>7.25-7.90 (m, 7H, ArH naphthalene), 6.75-6.89 (m, 4H, ArH phenyl), 9.97 (bs, 1H, -NH), 3.47 (s, 2H, -CH₂), 3.25-3.33 (t, 4H, 3' and 5' H piperazine), 2.86-2.90 (t, 4H, 2' and 6' H piperazine), 2.35 (s, 3H, -CH₃ of phenyl)</td>
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</tr>
<tr>
<td>1d</td>
<td>3445, 3048, 1683</td>
<td>7.26-7.98 (m, 7H, ArH naphthalene), 6.75-6.91 (m, 4H, ArH phenyl), 9.92 (bs, 1H, -NH), 3.42 (s, 2H, -CH₂), 3.24-3.30 (t, 4H, 3' and 5' H piperazine), 2.82-2.89 (t, 4H, 2' and 6' H piperazine) and 2.33 (s, 3H, -CH₃ of phenyl)</td>
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<tr>
<td>1e</td>
<td>3448, 3051, 1679</td>
<td>7.25-7.95 (m, 7H, ArH naphthalene), 6.76-6.89 (m, 4H, ArH phenyl), 10.00 (bs, 1H, -NH), 3.84 (s, 3H, -OCH₃), 3.39 (s, 2H, -CH₂), 3.28-3.35 (t, 4H, 3' and 5' H piperazine) and 2.88-2.92 (t, 4H, 2' and 6' H piperazine)</td>
<td>375, 376, 205 (M+H)</td>
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<tr>
<td>1f</td>
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<td>7.29-7.89 (m, 7H, ArH naphthalene), 6.78-6.86 (m, 4H, ArH phenyl), 9.92 (bs, 1H, -NH), 3.85 (s, 3H, -OCH₃), 3.37 (s, 2H, -CH₂), 3.27-3.36 (t, 4H, 3' and 5' H piperazine) and 2.85-2.89 (t, 4H, 2' and 6' H piperazine)</td>
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<tr>
<td>1g</td>
<td>3445, 3049, 1676</td>
<td>7.26-7.98 (m, 7H, ArH naphthalene), 6.89-6.91 (m, 4H, ArH phenyl), 8.97 (bs, 1H, -NH), 3.81 (s, 3H, -OCH₃), 3.43 (s, 2H, -CH₂), 3.28-3.37 (t, 4H, 3' and 5' H piperazine) and 2.89-2.95 (t, 4H, 2' and 6' H piperazine)</td>
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<tr>
<td>1h</td>
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<td>7.25-7.95 (m, 7H, ArH naphthalene), 6.84-6.92 (m, 4H, ArH phenyl), 9.94 (bs, 1H, -NH), 3.43 (s, 2H, -CH₂), 3.27-3.36 (t, 4H, 3' and 5' H piperazine) and 2.56-2.68 (t, 4H, 2' and 6' H piperazine)</td>
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<td>1i</td>
<td>3439, 3060, 1676</td>
<td>7.22-7.95 (m, 7H, ArH naphthalene), 6.87-6.95 (m, 4H, ArH phenyl), 9.89 (bs, 1H, -NH), 3.39 (s, 2H, -CH₂), 3.28-3.35 (t, 4H, 3' and 5' H piperazine) and 2.87-2.95 (t, 4H, 2' and 6' H piperazine)</td>
<td>—</td>
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<tr>
<td>1j</td>
<td>3443, 3058, 1679</td>
<td>7.22-7.89 (m, 7H, ArH naphthalene), 6.87-6.96 (m, 4H, ArH phenyl), 9.96 (bs, 1H, -NH), 3.41 (s, 2H, -CH₂), 3.28-3.37 (t, 4H, 3' and 5' H piperazine) and 2.89-2.96 (t, 4H, 2' and 6' H piperazine)</td>
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<tr>
<td>1k</td>
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<td>7.27-7.86 (m, 7H, ArH naphthalene), 6.83-6.94 (m, 3H, ArH phenyl), 9.89 (bs, 1H, -NH), 3.40 (s, 2H, -CH₂), 3.29-3.37 (t, 4H, 3' and 5' H piperazine) and 2.89-2.93 (b, 4H, 2' and 6' H piperazine)</td>
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</table>
$^{1}H$ NMR (CDCl$_3$): $\delta$ 7.26-7.98 (m, 7H, ArH napthalene), 8.78 (bs, 1H, -NH proton), 4.36 (s, 2H, -CH$_2$- protons); MS (FAB): $m/z$ 219 (M)$^+$, 220(M+H)$^+$, 184

General procedure for preparation of N-naphthalen-1-yl-2-[4-(substituted phenyl)-piperazin-1-yl]-acetamides, 1a-k

Compound 1 (0.01 mol) was dissolved in toluene and substituted phenyl piperazine (0.012 mol) was added in the presence of triethylamine. The reaction was refluxed for 24 hr. The reaction mixture was allowed to cool to RT, transferred to separating funnel and washed with water. The organic phase was separated, dried (anhydrous Na$_2$SO$_4$) and concentrated under reduced pressure to afford the target compounds 1a-k as crude solids which were later recrystallized from methanol.

Pharmacological evaluation

The novel compounds were pharmacologically evaluated for antagonist activity at dopamine D$_2$
receptor by studying inhibition of apomorphine induced climbing behaviour\textsuperscript{9}. Inhibition of the 5-
hydroxy tryptophan induced head twitch behaviour
served as a measure of antagonist activity at serotonin
5-HT\textsubscript{2} receptor\textsuperscript{9} and finally the catalepsy induction
test as a measure of extrapyramidal side effects and
thus atypical antipsychotic profile\textsuperscript{9,10}. All the
compounds were tested at a dose of 10 mg/kg for
studying inhibition of head twitch behaviour.

Conclusion
Various N-naphthalen-1-yl acetamides have been
synthesized and characterized by spectroscopic and
elemental analysis. The compounds were screened for
atypical antipsychotic activity. The series synthesized
afforded compounds having varying degree of affinity
for the target receptors. As is evident from the
Figures 1 and 2, all the compounds synthesized were
able to antagonize the target receptors, but their
potency was found to be less than the standard drug
Olanzapine. Compound N-naphthalen-1-yl-2-[4-(2-
methoxy phenyl)-piperazin-1-yl]-acetamide, 1e
was found to be the most potent member of the series
synthesized. The propensity of the compounds to
produce catalepsy was comparable with Olanzapine
as indicated in Figure 3. This study provides an
insight into rational designing of molecules and the
results may be used to aid the design of better atypical
antipsychotics.

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