Antidepressant and anxiolytic-like effects of 4n, a novel 5-HT₃ receptor antagonist using behaviour based rodent models

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The present study was designed to investigate the putative antidepressant and anxiolytic-like effects of N-n-Butylquinoxalin-2-carboxamide (4n), a novel 5-HT₃ receptor antagonist, with an optimal log P (2.01) and pA₂ value (7.3) greater than ondansetron (6.9) using rodent behavioural models of depression and anxiety. Acute treatment of 4n (1-4 mg/kg, ip) in mice produced antidepressant-like effect in forced swim test (FST) without affecting the baseline locomotion in actophotometer test in mice. 4n (2-4 mg/kg, ip) treatment also potentiated the 5-hydroxytryptophan (5-HTP) induced head twitch response in mice. Further, 4n (1-4 mg/kg, ip) treatment antagonized reserpine induced hypothermia in rats. Chronic treatment (14 days) with 4n (1-4 mg/kg) and paroxetine (10 mg/kg) significantly attenuated the behavioural anomalies induced by bilateral olfactory bulbectomy in rats in modified open field paradigm. An anxiogenic-like behaviour was induced by light alone as the stimulus using light-dark aversion test. 4n (2-4 mg/kg, ip) treatment significantly increased no. of transitions between dark and lit area and the time spent in the lit area. In conclusion, these preliminary investigations confirm that 4n exhibited antidepressant and anxiolytic-like effects in rodent models of depression and anxiety.

Keywords: 5-HT₃ receptor antagonist, Depression, Forced swim test, Light-dark aversion test, N-n-butylquinoxalin-2-carboxamide, Olfactory bulbectomy

Depression is a severe psychiatric disorder with lifetime prevalence as high as 20%¹. According to World Health Organization by the year 2020, it will be the second largest global burden of disease, illustrating the severity and impact of the disorder¹². Depression is not a unitary disorder and most experts agree that it should be considered a syndrome comprised of a spectrum of various symptoms, making animal research into the underlying mechanisms difficult but feasible⁵. Serotonin type-3 (5-HT₃) receptor antagonists are currently used in the management of nausea and vomiting associated with cancer chemotherapy⁴. Interestingly, in the last decade, these molecules have been extensively evaluated for their neuro-psychopharmacological potentials in various pre-clinical and few clinical studies⁵. Several pre-clinical (behavioural, neurochemical and genetic) studies have provided evidences linking 5-HT₃ receptors and depression. It has been well demonstrated that 5-HT₃ receptor antagonists reverse escape deficits in rat learned helplessness test, a sensitive antidepressant screening method⁷. Selective 5-HT₃ receptor antagonist, ondansetron (OND) alters local cerebral glucose utilization in the rat median raphe and also potentiated anti-immobility effects of selective serotonin reuptake inhibitors (SSRI’s)⁸,⁹ indicating the role played by 5-HT₃ receptors in depression.

A study with 5-HT₃ receptor antagonist, ICS 205-930 has been shown to decrease the duration of immobility in forced swim test¹⁰. The hypothesis of the antidepressant effects of 5-HT₃ receptor antagonists and the role of 5-HT₃ receptors in the neurobiology of depression is strengthened by recent preclinical reports. MDL72222 (bemesetron) and tropisetron, selective 5-HT₃ receptor antagonists, have been shown to reduce the duration of immobility in the mouse tail suspension test (TST)¹¹ and forced swim test respectively¹². Further, commercially available antidepressants like fluoxetine, imipramine, phenelzine and iproniazid also showed antidepressant-like activity by blocking 5HT₃ receptors¹³. Moreover, it is also well documented that the 5-HT₃ receptor antagonists ondansetron, bemesetron, tropisetron, zacopride and itasetron also produce anxiolytic effects¹⁴.

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The pharmacophoric elements of 5-HT\(_3\) receptor antagonists consist of an aromatic residue, a linking carbonyl unit and a basic nitrogen atom. As per this pharmacophore, a series of quinoxalin-2-carboxamides were designed and synthesized as 5-HT\(_3\) receptor antagonists\(^5\). Of the designed molecules, quinoxaline nucleus is serving as a source of basic nitrogen atom, carboxamide as a linking carbonyl unit and phenyl ring as an aromatic residue. In compounds 4m to 4p and 5, the phenyl ring is replaced with aliphatic hydrophobic group, to mimic the role of aromatic residue for the interaction with 5-HT\(_3\) receptor. The 5-HT\(_3\) receptor antagonism was expressed in the form of \(pA_2\) value, using isolated guinea pig ileum, against 2-methyl-5-hydroxytryptamine\(^4,16\). The \(\log P\) and \(pA_2\) value of the compounds are depicted in Table 1.

Animal models of depression and anxiety have been utilized vigorously to screen novel compounds and were originally designed as screening tests to assess the efficacy of various antidepressants and anxiolytics\(^17\). Hence, a battery of behavioural tests viz. forced swim test\(^18\), 5-hydroxytryptophan (5-HTP) induced head twitch response in mice, reserpine induced hypothermia\(^19\) and olfactory bulbectomy\(^20\) were utilized in rats to provide significant information about antidepressant-like activity of 4n. However, light-dark aversion test was used to explore the anxiolytic activity of 4n\(^21\).

In the present study, compound 4n has been selected from a series of compounds\(^15\) for preliminary antidepressant and anxiolytic-like potential based on the optimal \(\log p\) (2.01) and \(pA_2\) value (7.3) greater than 5-HT\(_3\) receptor antagonist, ondansetron (6.9) using rodent behavioural models of depression and anxiety.

### Materials and Methods

**Animals**—Swiss Albino mice (25-30 g) and Wistar rats (225-300 g) were obtained from Agricultural University, Hisar, Haryana, India. All procedures were in adherence to Institutional Animal Ethics Committee (IAEC) of Birla Institute of Technology & Science (BITS), Pilani, India (Protocol No. IAEC/RES/14/4). The animals were housed in laboratory cages and maintained under standard light/dark cycle (light on 06:00–18:00 hrs), temperature (23 ± 2 °C) and humidity conditions (50-60 %). The animal were given free access to food (standard food pellets) and filtered water. Behavioural studies were carried out during the light phase (09.00 – 14.00 hrs).

**Chemistry of N-n-butylquinoxalin-2-carboxamide (4n)**—The target carboxamide (4n) was synthesized from the key intermediate quinoxalin-2-carboxylic acid, by coupling with n-butylamine in presence of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDC.HCl) and 1-hydroxybenzotriazole (HOBt) under nitrogen atmosphere\(^15\). The key intermediate was synthesized from the starting material o-phenylenediamine in a sequence of reaction as per the method shown in the scheme 1. The structure of the synthesized compound was confirmed by the spectral data; yield: 58%; mp: 45-50 °C; IR (KBr, \(v_{\text{max}}\) cm\(^{-1}\)): 3285 (sharp N-H str.), 3080, 3060 (aromatic C-H str.), 2980, 2953 (aliphatic C-H str.), 1645 (C=O str.), 1590, 1490 (C=C, C=N ring str.), 1560 (N-H bend); \(^1\)H NMR (CDCl\(_3\)); \(\delta\) 9.68 (s, 1H, quinoxaline), 8.19 (dd, 1H, quinoxaline), 8.02 (d, 1H, quinoxaline), 7.88 (m, 2H, quinoxaline) ppm.

<table>
<thead>
<tr>
<th>Compound</th>
<th>R</th>
<th>(\log P)</th>
<th>Antagonism to 2-Me--5-HT((pA_2))</th>
</tr>
</thead>
<tbody>
<tr>
<td>4a</td>
<td>(\text{C}_6\text{H}_5)</td>
<td>2.43</td>
<td>6.8</td>
</tr>
<tr>
<td>4b</td>
<td>4--Me-(\text{C}_6\text{H}_4)</td>
<td>2.92</td>
<td>5.2</td>
</tr>
<tr>
<td>4c</td>
<td>4-MeO-(\text{C}_6\text{H}_4)</td>
<td>2.31</td>
<td>5.0</td>
</tr>
<tr>
<td>4d</td>
<td>(\text{C}_6\text{H}_5)-(\text{CH}_2)</td>
<td>2.50</td>
<td>5.7</td>
</tr>
<tr>
<td>4e</td>
<td>(\text{C}_6\text{H}_5)-(\text{NH})</td>
<td>1.95</td>
<td>5.8</td>
</tr>
<tr>
<td>4f</td>
<td>3-Ac-(\text{C}_6\text{H}_5)</td>
<td>1.75</td>
<td>6.1</td>
</tr>
<tr>
<td>4g</td>
<td>3-Cl-(\text{C}_6\text{H}_5)</td>
<td>2.99</td>
<td>5.8</td>
</tr>
<tr>
<td>4h</td>
<td>4-NO(_2)-(\text{C}_6\text{H}_5)</td>
<td>2.40</td>
<td>5.0</td>
</tr>
<tr>
<td>4i</td>
<td>3-Cl-2-(\text{CH}_3)-(\text{C}_6\text{H}_5)</td>
<td>3.48</td>
<td>7.6</td>
</tr>
<tr>
<td>4j</td>
<td>Benzothiazol-2-yl-</td>
<td>3.63</td>
<td>4.5</td>
</tr>
<tr>
<td>4k</td>
<td>4-Benzamido-phenyl-</td>
<td>3.24</td>
<td>4.9</td>
</tr>
<tr>
<td>4l</td>
<td>2-Benzamido-phenyl-</td>
<td>3.24</td>
<td>4.0</td>
</tr>
<tr>
<td>4m</td>
<td>(\text{CH}_3\text{CH}_2\text{CH}_2)</td>
<td>1.59</td>
<td>6.7</td>
</tr>
<tr>
<td>4n(^*)</td>
<td>(\text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2)</td>
<td>2.01</td>
<td>7.3</td>
</tr>
<tr>
<td>5</td>
<td>Pyrrolidine</td>
<td>1.32</td>
<td>6.4</td>
</tr>
<tr>
<td>4o</td>
<td>Cyclopentyl-</td>
<td>1.90</td>
<td>6.5</td>
</tr>
<tr>
<td>4p</td>
<td>Cyclohexyl-</td>
<td>2.32</td>
<td>6.0</td>
</tr>
<tr>
<td>Ondansetron</td>
<td></td>
<td>2.58</td>
<td>6.9</td>
</tr>
</tbody>
</table>

\(^a\) \(\log P\) values were calculated using Chem BioDraw Ultra 11 (Cambridge Software).

\(^b\) \(pA_2\) values are the means of two separate experiments.

\(^c\) Screened for antidepressant and anxiolytic-activity.
KUMAR et al.: ANTIDEPRESSANT & ANXIOLYTIC-LIKE EFFECTS OF 5-HT₃ RECEPTOR ANTAGONIST

1.73 (quin, 2H, NHCH₂CH₂CH₃), 1.52 (sex, NHCH₂CH₂CH₂CH₃) 1.01 (t, 3H,NHCH₂CH₂CH₂CH₃); Mass spectra (ESI) of the compound exhibited the molecular ion peak at m/z 231(M+1)+.

Drugs and chemicals—Fluoxetine and paroxetine were obtained from Sun Pharmaceuticals and IPCA Laboratories, India, respectively as generous gift samples. Pargyline and 5-hydroxtryptophan (5-HTP) were procured from Sigma Chemicals, USA. Reserpine was purchased from Sisco Research Laboratories, India. Diazepam was obtained from Nitin Life Sciences Ltd, India. Ketamine and xylazine were purchased from Neon Laboratories Ltd. and Indian Immunologicals, India, respectively. Haemostatic sponge was purchased from Sri Gopal Krishan Lab Pvt. Ltd, India.

Behavioural screening

Spontaneous locomotor activity—The spontaneous locomotor activity of mice was assessed using actophotometer. The photocells of the actophotometer were checked before use and the mice were individually placed in the centre of the square arena (30 cm x 30 cm) of actophotometer. After an initial familiarization period (2 min), the digital locomotor scores were recorded for the next 8 min in a dimly lit room. The arena was cleaned with dilute alcohol and dried between trials. The animals were kept in the procedure room for 30 min before experiment. 4n (0.5-4 mg/kg, ip) was administered 30 min prior to testing.

Forced swim test (FST)—The FST was performed with slightly modifications from the originally described method. The mice were forced to swim for 6 min duration. The total duration of immobility during the last 4 min of a single 6 min test session was recorded. An animal was judged to be immobile whenever it remains floating passively in water in a slightly hunched but upright position, keeping its head just above the water level. Water was changed between trials and temperature was maintained at 22–23 °C. 4n (0.5-4 mg/kg, ip) and fluoxetine (10 mg/kg, ip) were administered 30 min prior to testing.

5-Hydroxytryptophan (5-HTP)-induced head twitch response—The method mentioned elsewhere was adopted with slight modifications. Briefly, the mice were treated with a monoamine oxidase inhibitor, pargyline (75 mg/kg, ip) 30 min before 5-HTP (5 mg/kg, ip) treatment. 4n (2-4 mg/kg, ip) and fluoxetine (10 mg/kg, ip) were injected 15 min prior 5-HTP administration. After 15 min of 5-HTP administration, the number of head twitches exhibited by the mice (vehicle or drug treated) during the next 30 min were recorded as head twitch score. The head twitch response was characterized by abrupt lateral movements, which may or may not be accompanied by body twitches and hind limb retraction.

Reserpine-induced hypothermia (RIH)—RIH was performed in rats as per Devadoss et al. Briefly, rats were treated with 4n (1-4 mg/kg, ip) and reserpine (1 mg/kg, ip) 30 and 15 min prior to testing, respectively. The animals were gently hand-restrained, while inserting the probe rectally. The effect of 4n (1-4 mg/kg, ip) and fluoxetine (10 mg/kg, ip) treatment on reserpine induced hypothermia (measured with digital thermometer) was recorded by measuring temperature at 0, 30, 60, 90 and 120 min following reserpine administration. Hypothermia was measured by calculating temperature difference between 0 min and 60th min.

Olfactory bulbectomy

Surgery—Bilateral olfactory bulbectomy was performed according to previously described methods. Briefly, rats were anaesthetized with the cocktail of xylazine and ketamine (5 and 75 mg/kg, ip) respectively. The animals were fixed in a stereotactic frame (Inco, India) and the skull was exposed by a midline incision. The burr holes (2 mm in diameter) were drilled 8 mm anterior to bregma and 2 mm on either side of the midline at a point corresponding to the posterior margin of the orbit of an eye. The olfactory bulbs were removed by suction,
the holes were then filled with haemostatic sponge to control excessive bleeding and the scalp was sutured. Sham-operated rats were subjected to the same surgical procedure, including piercing of the dura mater but their bulbs were left intact. To prevent post surgical infection, the animals were given Sulprim injection (each mL containing 200 and 40 mg of sulphadiazine and trimethoprim respectively), intramuscularly (0.2 mL/300 g), once a day for 3 days. Following a rehabilitation period of 14 days, olfactory bulbectomized/sham operated rats were treated orally with 4n (1-4 mg/kg), paroxetine (10 mg/kg) or the vehicle once daily between 09:00-12:00 hrs for 14 days (15th-28th day). The detail of surgical and treatment schedule is given in the Table 2.

Modified open field behaviour—The olfactory bulbectomized (OBX)/sham rats were subjected to an open field exploration test on 29th post surgery and 15th day of chronic drug treatment according to the method described by Kelly et al., with slight modifications. The apparatus consisted of a circular (diameter: 90 cm) arena with 75 cm high aluminum walls and floor equally divided into 10 cm squares. A 60 W light bulb was positioned 90 cm above the base of the arena, which was the only source of illumination in the testing room. On 29th day, each animal was individually placed in the center of the open field apparatus and the ambulation scores (number of squares crossed), rearing and fecal pellets were counted for 5 min.

Light-dark aversion test—The test was performed according to Belzung et al., with slight modifications. The apparatus consisted of two polycarbonate boxes (27×21×14 cm) with an interconnecting tunnel (73×10 cm). One of these boxes was darkened by black paint and covered with a black cover. The other box was lit by a 60 W desk lamp 30 cm above the box, which provided the only laboratory illumination. The apparatus was positioned on a bench, 1 meter above the floor. The 4n (2-4 mg/kg, ip) and diazepam (2 mg/kg, ip) were given 30 min before the light-dark aversion test. Each mouse was placed into the center of the lit box. During 5 min test, the number of transitions between the lit and dark area and the time spent in the lit area were determined by an observer. A mouse was considered to have entered the new area when all four legs were in the area.

Statistical analysis—Results are expressed as a mean ± SE. The single treatment studies were analysed using one-way analysis of variance followed by Dunnett’s test in Graph pad prism 3.

Results

Spontaneous locomotor activity—Acute 4n (0.5-4 mg/kg, ip) treatment had no significant effect on the baseline locomotor activity of mice when compared to the control group (Fig. 1).

Forced swim test—One-way analysis of variance showed that acute treatment with 4n (1-4 mg/kg, ip) produced a significant [F (5, 42) = 34.81, P<0.05] reduction of immobility time as compared to the control group in mouse FST (Fig. 2). The positive

![Fig. 1](image1)

![Fig. 2](image2)

Table 2—Surgery and treatment schedule to assess the effect of 4n on OBX/sham rats

<table>
<thead>
<tr>
<th>Day 0</th>
<th>0 – 1st day</th>
<th>1st – 14th</th>
<th>15th – 28th</th>
<th>29th day</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surgery</td>
<td>Recovery from surgery (Continuous care)</td>
<td>Rehabilitation period (Daily handling and Observation)</td>
<td>Drug/vehicle treatment (once daily p.o. administration for 14 days)</td>
<td>Behavioural assessments (Modified open field exploration)</td>
</tr>
</tbody>
</table>

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![Table 2](image3)
control fluoxetine (10 mg/kg, ip), also significantly reduced the immobility duration (P<0.05) as compared to the control group. However, 4n at 0.5 mg/kg dose failed to reach the level of significance in comparison to control group in FST.

**5-HTP-induced head twitches response**—The co-administration of pargyline (75 mg/kg, ip) and 5-HTP (5 mg/kg, ip) induced the characteristic head twitch response. 4n (2-4 mg/kg, ip) and fluoxetine (10 mg/kg, ip) treatment significantly [F (3, 28) = 26.96, P<0.05] potentiated the head twitch response as compared to combination of pargyline and 5-HTP treatment alone (Fig. 3).

**Reserpine-induced hypothermia**—Administration of reserpine (1 mg/kg, ip) elicited a pronounced decrease (P<0.05) in core body temperature of control group’s rats. This effect was significantly antagonized by 4n (1-4 mg/kg, ip) treatment [F (4, 35) = 17.79, P<0.05]. Similarly, fluoxetine (10 mg/kg, ip) also attenuated the hypothermic response induced by reserpine treatment (Fig. 4).

**Olfactory bulbectomy**

**Modified open field behaviour**—The effects of chronic 4n treatment on the behaviour of olfactory bulbectomized (OBX)/sham rats were analyzed in the modified open field paradigm (Table 3). Removal of the olfactory bulbs produced a characteristic hyperactivity in the OBX rats when compared to sham rats in the modified open field test. Chronic treatment (14 days) with 4n (1-4 mg/kg, po) significantly [F (9,70) = 21.24, P<0.05] reduced the ambulation (Table 3) but a saturation effect was observed at 4 mg/kg dose, rearing (Table 3) [F (9,70) = 5.8, P<0.05] and fecal pellets at 1-2 mg/kg dose but not at 4 mg/kg dose (Table 3) in olfactory bulbectomized rats [F(9,70) = 5.8, P<0.05] as compared to the vehicle treated olfactory bulbectomized rats. Paroxetine treatment (10 mg/kg) also significantly (P<0.05) attenuated all of the effects of bilateral olfactory bulbectomy.

**Light-dark aversion test**—The effects of 4n (2-4 mg/kg, ip) and diazepam (2 mg/kg, ip) on the number of transitions and time spent in the lit area in the light-dark aversion test are presented in Figs 5 and 6 respectively. Analysis of the data in one way ANOVA revealed that 4n and diazepam treatment significantly increased the no. of transitions [F (3, 28) = 25.60, P<0.001] when compared with vehicle treated sham control group.

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**Table 3**—The effect of 4n and paroxetine on the behaviour of OBX/sham rats in modified open field test

<table>
<thead>
<tr>
<th>Groups and Dose (mg/kg)</th>
<th>Ambulation (F)</th>
<th>Rearing (°F)</th>
<th>Fecal Pellets (F)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sham control 0</td>
<td>92.5±5.8</td>
<td>9.6±0.6</td>
<td>2.75±0.15</td>
</tr>
<tr>
<td>Sham + 4n 1</td>
<td>98±6.1</td>
<td>9±0.7</td>
<td>2.6±0.12</td>
</tr>
<tr>
<td>2</td>
<td>103±5.8</td>
<td>8.6±0.7</td>
<td>2.5±0.14</td>
</tr>
<tr>
<td>4</td>
<td>102±7.0</td>
<td>9.3±0.6</td>
<td>2.6±0.13</td>
</tr>
<tr>
<td>Sham + paroxetine 10</td>
<td>100±6.3</td>
<td>8.5±0.6</td>
<td>2.5±0.16</td>
</tr>
<tr>
<td>OBX control 0</td>
<td>207±13.5*</td>
<td>36±2.5*</td>
<td>4.8±0.26*</td>
</tr>
<tr>
<td>OBX + 4n 1</td>
<td>166±10.5#</td>
<td>28.2±2.3#</td>
<td>4.3±0.22#</td>
</tr>
<tr>
<td>2</td>
<td>130±9.2#</td>
<td>22.4±2.1#</td>
<td>3.2±0.16#</td>
</tr>
<tr>
<td>4</td>
<td>125±8.8#</td>
<td>17.0±2.0#</td>
<td>5.0±0.28</td>
</tr>
<tr>
<td>OBX + paroxetine 10</td>
<td>113±7.2#</td>
<td>11.8±1.5#</td>
<td>2.4±0.18#</td>
</tr>
</tbody>
</table>

Drugs/vehicle were administered once a day for 14 days * P < 0.05 when compared to the sham control, # P < 0.05 when compared to the vehicle treated OBX group.

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Fig. 3—The effect of 4n (2-4 mg/kg, ip) and fluoxetine (FLX) (10 mg/kg, ip) on the 5-HTP and Pargyline induced head twitch response in mice. Each column represents the mean number of head twitches over 30 min. Control group animals were administered 5-HTP (5 mg/kg, ip) and pargyline (75 mg/kg, ip). Error bars represent the SEM, *P < 0.05 when compared to the control group, n = 8/ group.

Fig. 4—The effect of 4n (1-4 mg/kg, ip) and fluoxetine (FLX) (10 mg/kg, ip) treatment on reserpine induced hypothermia in rats. Each column represents the mean decrease in rectal temperature (°F). Error bars represent the SEM, * P < 0.05 when compared to the 1st hr value of vehicle treated group, n = 8/ group.
control (Fig. 5). Furthermore, 4n and diazepam treatment significantly increased time spent in the lit area [F (3, 28) = 76.93, P <0.001] when compared with vehicle control (Fig. 6).

Discussion

The results obtained in the present work indicate that 4n, a novel 5-HT3 antagonist is active in rodent models predictive of antidepressant and anxiolytic activity. The preliminary attributes of 4n namely (i) Log P value of 2.01, which is optimum for blood brain barrier permeability 27, (ii) pA2 value (7.3) greater than selective 5-HT3 receptor antagonist ondansetron (6.9), (iii) antidepressant-like effects observed in mouse FST, incentivised the present study which comprised a series of standardized antidepressant assays. In spite of differences between laboratories, predictive assays of antidepressant activity such as FST and TST in mice are responsive to major classes of antidepressants including tricyclics, SSRIs and serotonin-norepinephrine reuptake inhibitors (SNRIs)28,29. Assessment of antidepressant potential is interfered by possible hyper-locomotive property of a test substance leading to false positive results30. 4n treatment (1-4 mg/kg) exhibited significant antidepressant-like effects in FST and the tested dose range did not alter the basal spontaneous locomotor activity (Fig. 1). Hence, the antidepressant-like effects of 4n in the FST is not due to hyper-locomotive effects as indicated by the spontaneous locomotor activity test.

The enhancement of synaptic concentrations of monoamine, particularly serotonin is considered as the well known mechanism of several antidepressants. The serotonergic property of 4n was confirmed by in vivo study in mice. The potentiation of 5-HTP induced behaviour has previously been related to serotonergic mechanisms24. In the present study, the pargyline (MAO inhibitor) and 5-HTP-induced head twitch response was significantly potentiated by 4n and fluoxetine. The depletion of brain biogenic amines induced by biogenic amine depletors such as reserpine is reported to induce hypothermia and ptosis response in rodents31. The decrease in body temperature induced by reserpine treatment has been reported to be antagonized by antidepressants19,31. Both 4n and fluoxetine significantly antagonized the hypothermic response induced by reserpine.

The rat olfactory bulbectomy model of chronic depression (with adequate face and predictive validity) was proposed as a model for agitated hypoperotoninergic model of depression and is used to explore the antidepressant potential of novel agents22,33. The OBX rats exhibited a specific abnormal behavioural pattern in the brightly lit, circular, open field arena characterized by increased ambulation,28 rearing28 and fecal pellets34. Such changes are attenuated by antidepressants of many pharmacological classes35. In the present investigation, 4n and paroxetine significantly attenuated the behavioural abnormalities exhibited by OBX rats which strongly support the clinical potential of 4n as an antidepressant agent.

The light/dark aversion test is based on the aversive properties of light21,26 and uses as its index of anxiety the time spent in the lit area as opposed to the time spent in the dark area. In fact, consistent with the present data, studies36 showed that, in mice, the best way of measuring the effect of anxiolytic agents is the time spent in the lit area, while a decrease in the time...
spent in the lit area as well as in the number of transitions are characteristic of an anxiogenic response. A novel 5-HT3 receptor antagonist, could be responsible for the antidepressant-like effect of 14 as many conventional antidepressants also possess affinity for central 5-HT3 binding sites. Hopefully, further studies will provide a better understanding of the promiscuous nature of novel 5-HT3 antagonists that could also be useful for management depression and anxiety. Though no abnormal behaviour was observed at the tested dose levels, assessment of the safety profile of the molecule is essential.

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References


