Research Paper

Antidepressant-like effect of a novel 5-HT_3 receptor antagonist *N*-(benzo[*d*] thiazol-2-yl)-3-ethoxyquinoxalin-2-carboxamide 6k using rodents behavioral battery tests

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ABSTRACT

Objective: To investigate the antidepressant-like effect of *N*-(benzo[*d*] thiazol-2-yl)-3-ethoxyquinoxalin-2-carboxamide 6k, a 5-hydroxytryptamine type 3 (5-HT_3) receptor antagonist using rodents behavioral battery tests. **Materials and Methods:** 6k screening was performed with behavioral assays for depression-like forced swim test (FST) at several single doses (0.25-4 mg/kg, intraperitoneal injection (i.p.)) to test the potency of 6k, in which 2 and 4 mg/kg doses were found to be most effective and hence, in further behavioral assays including mechanistic model like 5-hydroxytryptophan (5-HTP)-induced head twitches was performed in mice at acute doses of 6k (2 and 4 mg/kg, i.p.). Furthermore, olfactory bulbectomy (OBX), a surgical model-induced behavioral alterations was performed in rats, and the effect of 6k administered orally (2 and 4 mg/kg, p.o.) after subchronic treatment for 14 days starting from day 15 of postsurgery was examined by percent sucrose preference test and modified open field test (OFT). **Results:** 6k (1, 2, and 4 mg/kg, i.p.) reduced the immobility time and increased the swimming behavior in FST without affecting the baseline locomotor score showing antidepressant-like effect. 5-HTP-induced head twitch response was potentiated by 6k (2 and 4 mg/kg, i.p.), which indicated rise in the serotonergic neurotransmission in the brain. 6k (2 and 4 mg/kg, p.o.) showed anti-anhedonia effect by increasing the sucrose consumption and reversed the behavioral alterations when exposed to modified open field in OBX rats after subchronic treatment for 14 days, thus exhibiting antidepressant-like effect. **Conclusion:** 6k attenuated the behavioral derangement in rodents-based behavioral battery tests for depression, indicating antidepressant-like potential.

Key words: 5-HT_3 receptor antagonists, depression, forced swim test, head twitches, *N*-(benzo[*d*] thiazol-2-yl)-3-ethoxyquinoxalin-2-carboxamide 6k, sucrose preference

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INTRODUCTION

Depression is a psychiatric disorder having serious impact on socioeconomic status and quality of life.[1] World Health Organization predicts that depression would be second most prevalent cause of illness-induced disability by 2020.[2] Several promising evidences from preclinical studies in understanding the

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neurobiology of depression suggests serotonergic neurotransmitter system as one of the potential target for depression.[3]

5-HT_3 receptors, the only ligand-gated ion channel receptors in the serotonergic system, are highly expressed in area postrema, hippocampus, and amygdala.[4] 5-HT_3 receptor antagonists are currently recommended for chemotherapy-induced emesis.[5] Earlier, ondansetron, a 5-HT_3 receptor antagonist, has been reported for antidepressant-like effect[6] and it potentiated the swimming behavior of selective serotonin reuptake inhibitors (SSRIs), suggesting the role of 5-HT_3 receptor antagonist in depression.[7] Furthermore, other 5-HT_3 receptor antagonists like tropisetron[8] and MDL 72222[9] are reported for antidepressant-like effect in rodents behavioral battery tests by modulation of serotonergic system. Interestingly, one of the study suggested antidepressant effect through functional antagonism of 5-HT_3 receptors by SSRIs, currently most prescribed class of antidepressants.[10]

There are various preclinical models developed originally to screen the potential efficacy of various antidepressants. Hence, we utilized a battery of behavioral tests, namely, forced swim test (FST),[11] 5-hydroxytryptophan (5-HTP)-induced head twitch response in mice,[12] and olfactory bulbectomy (OBX)[13] a surgical model in rats to investigate antidepressant-like effect of *N*-(benzo[*d*] thiazol-2-yl)-3-ethoxyquinoxalin-2-carboxamide 6k.

From a series of structurally novel compounds, 6k was selected on the basis of optimal log *P* (4.56) and pA2 value (6.8), which is comparable with that of standard ondansetron (pA2 6.9). 5-HT_3 receptor antagonist potential of 6k was performed on guinea pig ileum against 2-methyl 5-hydroxytryptamine (5-HT agonist).[14] In the earlier report, compound (6p) with pA2 value (7.6) and log *P* (2.94) has been reported for antidepressant effect.[15] In the present study, 6k was selected from the series of compounds as it has superior log *P* value as compared with that of (6p) because log *P* value ultimately indicates the ability of a compound to cross the blood-brain barrier and in addition to this 6k also possesses comparable pA2 value with that of standard ondansetron (6.9), suggesting the antagonism potency at 5-HT_3 receptors. Our previous finding dealt with the anxiolytic potential of 6k in mice behavioral tests battery for anxiety.[16] Taking into consideration the optimum pA2 value and good log *P* value, the present investigation was designed to assess the antidepressant-like potential of a novel 5-HT_3 receptor antagonist 6k using *in vivo* behavioral battery tests and to assess the possible implications of serotonergic neurotransmitter system in depression.

MATERIALS AND METHODS

Animals

Male Swiss albino mice (20-25 g) and Wistar rats (280-320 g) were procured from Chaudhary Charan Singh Haryana Agricultural University, Hisar, India (Reg. No. 417/01/a/CPCSEA). The animals were housed under standard laboratory conditions (temperature 23 ± 2ºC and room humidity 60 ± 10%) and maintained on 12:12 h light-dark cycle. Standard diet and filtered water was provided *ad libitum*. Animals were acclimatized to laboratory conditions 24 h before the commencement of experiment. Each group consisted of six animals. All the experiments were carried out between 9:00 am and 12:00 pm. The experimental protocol was approved by Institutional Animal Ethics Committee (IAEC) of Birla Institute of Technology and Science, Pilani, India (Protocol No. IAEC/RES/16/06). The groupings of mice for FST and 5-HTP-induced head twitch response included vehicle control, treatment groups with 6k at cumulative doses (FST at 0.25-4 mg/kg, i.p.) (5-HTP at 2 and 4 mg/kg, i.p.), and escitalopram (10 mg/kg, i.p.). Whereas the rats in the surgical OBX model were divided into two sections comprising sham and OBX, respectively, which included sham control, sham+6k (2 mg/kg, p.o.), sham+6k (4 mg/kg, p.o.), sham + escitalopram (10 mg/kg, p.o.), OBX control, OBX+6k (2 mg/kg, p.o.), OBX+6k (4 mg/kg, p.o.), and OBX + escitalopram (10 mg/kg, p.o.).

Drugs and chemicals

Sources: 6k was synthesized in-house by the medicinal chemistry group of the Birla Institute of Technology and Science (BITS)-Pilani Institute. Escitalopram (10 mg/kg, i.p.) was procured from Ranbaxy Research Laboratory (Gurgaon, India) as generous gift sample. 6k and escitalopram were prepared freshly in distilled water (vehicle) and administered at a dose volume of 10 ml/kg in mice and 2 ml/kg in rats, respectively.

Chemistry and synthesis of 6k

Our earlier study has reported the anxiolytic potential of 6k where the structure [Figure 1] and chemistry of 6k is described in details.[16,17]

Dose selection of 6k

On the basis of preliminary studies using FST in mice, the active doses of 6k were found to be 1, 2, and 4 mg/kg, i.p. Doses less than 1 mg/kg, i.p. were not effective, whereas doses

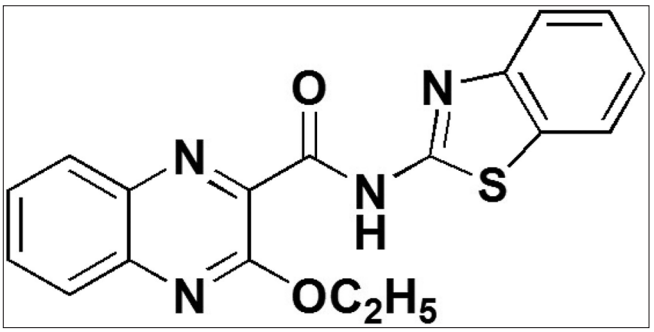

Figure 1: Structure of 6k. 6k = *N*-(benzo[*d*]thiazol-2-yl)-3-ethoxyquinoxalin-2-carboxamide

above 4 mg/kg, i.p. exhibited saturation effect. As 6k showed better results at 2 and 4 mg/kg, i.p. in FST, furthermore in the mechanistic model of 5-HTP-induced head twitch response, doses selected for 6k were 2 and 4 mg/kg, i.p. In the surgical OBX model of depression in rats, subchronic (14 days) treatment with 6k was performed at 2 and 4 mg/kg, p.o. doses.

Behavioral tests

Spontaneous locomotor activity

The spontaneous locomotor score in mice was recorded using actophotometer, (INCO-India) as described earlier.[18] Mice were introduced centrally in actophotometer 30 min post 6k single time administration at different doses (0.25-8 mg/kg, i.p.) for 10 min, consisting 2 min of acclimatization and remaining 8 min of test duration.

FST

FST was performed as described previously[11] with slight modification. One day before proceeding for the actual test, mice were trained for swimming for 15 min in a glass cylinder 25 × 12 × 25 cm (L × B × H) filled with water of temperature 23 ± 2°C up to 15 cm of height. On next day, 30 min post acute treatment with 6k (0.5-4 mg/kg, i.p.)/escitalopram (10 mg/kg, i.p.)/vehicle (10 ml/kg, i.p.), the animals were individually subjected for swimming for 6 min of which initial 2 min were for acclimatization. Immobility was recorded for 4 min.

5-HTP induced head twitch response

The method described by Martin *et al*.,[12] was adopted with slight modifications. Briefly, the mice were administered once with a monoamine oxidase inhibitor, pargyline (75 mg/kg i.p.). 5-HTP (5 mg/kg i.p.) was injected 30 min later. Acute treatment with 6k (2 and 4 mg/kg, i.p.)/escitalopram (10 mg/kg, i.p.)/vehicle (10 ml/kg, i.p.) was scheduled 15 min before 5-HTP injection. The number of head twitch response shown by the animals were recorded for 15 min post 5-HTP administration for a period of 30 min.

OBX surgery

The rats were bulbectomized at the age of 7-8 weeks. Bilateral OBX was performed according to the previously described method.[13] Briefly, rats were anesthetized with ketamine (75 mg/kg, i.p.) and xylazine (5 mg/kg, i.p.). The skull of the animals was dissected using a stereotactic frame (INCO, India) and drilled burr holes (2 mm in diameter), 8 mm anterior to bregma and 2 mm on either side of the midline incision. The olfactory bulbs were removed by suction using the syringe and long steel gauge. Sham-operated rats were subjected to the same surgical procedure, but their bulbs were left undisturbed. Following a rehabilitation period of 14 days, OBX/sham-operated rats were treated orally with 6k (2 and 4 mg/kg)/escitalopram (10 mg/kg)/vehicle (2 ml/kg) once daily between 09:00-11:00 a.m. for 2 weeks as mentioned in Table 1.

Sucrose preference test

The sucrose preference test was conducted in OBX/sham-operated rats after subchronic treatment with 6k (2 and 4 mg/kg, p.o.)/escitalopram (10 mg/kg, p.o.)/vehicle (2 ml/kg, p.o.) for 14 days on day 29 to day 32. The test was performed as described earlier with minor modifications.[19] Briefly, before the test, mice were trained to adapt to sucrose solution (1% w/v). Two bottles of sucrose solution were placed in each cage for 24 h and then one bottle of sucrose solution was replaced with water for the next 24 h followed by deprivation of water and food for another 24 h. Sucrose preference test was conducted at 9:30 a.m. in which mice were housed in individual cages and were free to access two bottles containing 100 ml of sucrose solution (1% w/v) and 100 ml of water, respectively. After 24 h of exposure, the volumes of sucrose solution and water consumed were recorded and the percent sucrose preference was calculated by using the formula described in following equation.

% Sucrose preference = [sucrose consumption in ml/(water + sucrose consumption in ml)] × 100

Modified open field behavior

OFT was performed in OBX/sham-operated rats on day 35 postsurgery as described earlier[20] with minor modifications after subchronic treatment with 6k (2 and 4 mg/kg, p.o.)/escitalopram (10 mg/kg, p.o.)/vehicle (2 ml/kg, p.o.) for 14 days. The apparatus designed for OFT consisted of a circular (90 cm in diameter) area, with aluminum walls of 75 cm height and white floor that was divided equally into 10-cm squares. The apparatus was suspended 90 cm above the base with a 60 W light bulb remaining the only source of light in the experimental room. The parameters measured during the 5-min test were number of ambulation scored, number of rearing episodes, and fecal pellets. After each test, the apparatus was wiped with 70% (v/v) alcohol to get rid of the residual odor.

Statistical analysis

Data were analyzed using Graphpad Prism software version 2.01 (GraphPad Software, La Jolla, USA). One specific group of mice was assigned to one specific drug treatment condition. All the values were expressed as mean ± standard error of mean (SEM). The significance of differences between groups for behavioral assays was analyzed using

Table 1: Schematic representation of OBX study protocol

Days	0-14th day	15-28th day	29-35th day	
Study protocol	Rehabilitation time (after surgery)	Treatment with 6k/ escitalopram/ vehicle	Behavioral assays	
			29th to 33rd	35th
			Sucrose preference test	Modified OFT

OBX=Olfactory bulbectomy, OFT=Open field test, 6k =*N*-(benzo[*d*] thiazol-2-yl)-3-ethoxyquinoxalin-2-carboxamide

one-way analysis of variance (ANOVA) followed by post hoc Dunnett's test. For statistical analysis, $P < 0.05$ was considered statistically significant.

RESULTS

Effect of 6k on spontaneous locomotor activity in mice

Acute 6k (0.25-4 mg/kg, i.p.) treatment exhibited no significant ($F = 1.20$; $P > 0.05$) effect on the baseline locomotor activity of mice as compared with vehicle control group [Figure 2].

Effect of 6k on FST in mice

Figure 3 represents the results of FST. Acute administration of 6k (0.25-4 mg/kg, i.p.) significantly reduced the immobility time ($F = 44.42$; $P < 0.05$; $P < 0.01$) as compared with vehicle control group in FST, thus showing the antidepressant-like activity of 6k. 6k at (0.25 and 0.5 mg/kg, i.p.) exhibited no significant ($P > 0.05$) effect on immobility time in FST when compared with vehicle control group. Whereas in comparison with escitalopram group (10 mg/kg, i.p.), 6k at 0.25, 0.5, and 1 mg/kg, i.p. showed significantly ($P < 0.01$) higher duration of immobility.

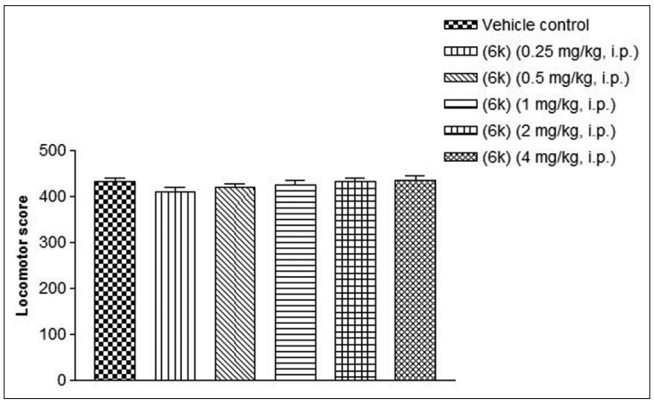

Figure 2: Effect of 6k on locomotor score in mice. All the values are expressed as mean ± SEM. No significant statistical difference was observed in 6k treatment groups when compared with vehicle control group; *n* = 6/group. SEM = standard error of mean, 6k = *N*-(benzo[*d*]thiazol-2-yl)-3-ethoxyquinoxalin-2-carboxamide

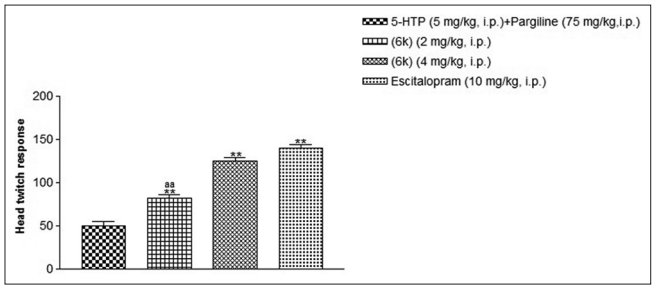

Figure 4: Effect of 6k on 5-HTP-induced head twitch response in mice. All the values are expressed as mean ± SEM. $^{**}P < 0.01$ as compared with vehicle control group; $^{aa}P < 0.01$ as compared with escitalopram group; *n* = 6/group. SEM = standard error of mean, 5-HTP = 5-hydroxytryptophan, 6k = *N*-(benzo[*d*]thiazol-2-yl)-3-ethoxyquinoxalin-2-carboxamide

Effect of 6k on 5-HTP-induced head twitches in mice

Figure 4 showed that systemic treatment with 6k at 2 and 4 mg/kg, i.p. and reference standard escitalopram (10 mg/kg, i.p.), significantly ($F = 99.89$; $P < 0.01$) potentiated the 5-HTP (5 mg/kg, i.p.) induced head twitch response in mice when compared with vehicle control. 6k at 2 mg/kg, i.p., in comparison with escitalopram (10 mg/kg, i.p.) showed significantly ($P < 0.01$) lesser number of head twitches.

Effect of 6k on sucrose preference test in OBX-operated rats

Figure 5 represents that 6k (2 and 4 mg/kg, p.o.) and reference standard escitalopram (10 mg/kg, p.o.) significantly ($F = 210.7$; $P < 0.01$) increased the sucrose consumption in OBX-operated rats when compared with OBX control group. OBX control rats showed significant reduction ($P < 0.01$) in sucrose consumption when compared with sham control group. In comparison with escitalopram group (10 mg/kg, p.o.), 6k

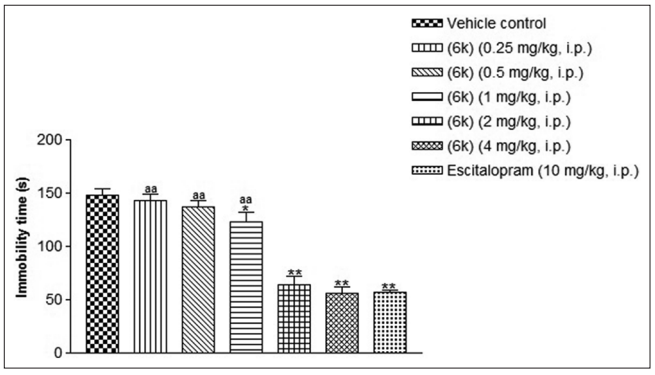

Figure 3: Effect of 6k on immobility time in FST in mice. All the values are expressed as mean ±SEM. $^{*}P < 0.05$ and $^{**}P < 0.01$ as compared with vehicle control group; $^{aa}P < 0.01$ as compared with escitalopram group; *n* = 6/group. SEM = standard error of mean, FST = forced swim test, 6k = *N*-(benzo[*d*]thiazol-2-yl)-3-ethoxyquinoxalin-2-carboxamide

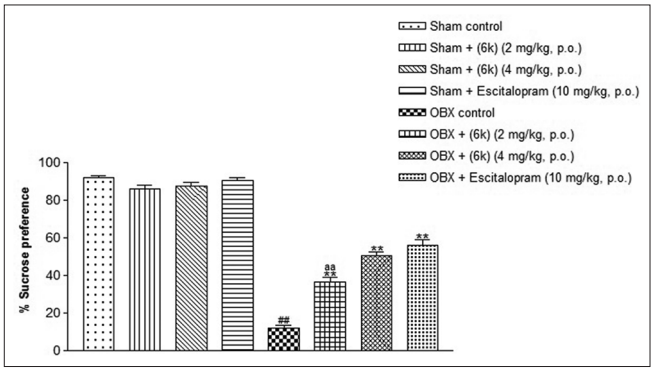

Figure 5: Effect of 6k on sucrose preference test in OBX-operated rats. All the values are expressed as mean ± SEM. $^{##}P < 0.01$ as compared with sham control group, $^{**}P < 0.01$ as compared with OBX control group; $^{aa}P < 0.01$ as compared with escitalopram group; *n* = 6/group. SEM = standard error of mean, OBX = olfactory bulbectomy, 6k = *N*-(benzo[*d*]thiazol-2-yl)-3-ethoxyquinoxalin-2-carboxamide

at (2 mg/kg, p.o.) showed significantly ($P < 0.01$) reduced sucrose consumption.

Effect of 6k on modified OFT in OBX-operated rats

Table 2 showed that 6k (2 and 4 mg/kg, p.o.) and reference standard escitalopram (10 mg/kg, p.o.), significantly decreased the number of ambulation ($F = 85.60$; $P < 0.01$), fecal pellets ($F = 10.70$; $P < 0.01$), and rearing ($F = 10.83$; $P < 0.05$) in OBX-operated rats when compared with hyperactive OBX control group. OBX control group showed significantly ($P < 0.01$) increased the number of ambulation, fecal pellets, and rearings when compared with sham control group. In comparison with escitalopram (10 mg/kg, p.o.) 6k at (2 mg/kg, p.o.) showed significantly ($P < 0.01$) higher number of ambulations.

DISCUSSION

The results of the present study suggest that 6k exhibits antidepressant-like effect in rodents behavioral battery tests of depression. The preliminary attributes of 6k in terms of i) log *P* (4.56) that is optimal to cross blood-brain barrier,[21] ii) pA2 (6.8) value indicating antagonistic potential against 5-HT agonist on guinea pig ileum[22] that is comparable with that of standard ondansetron (6.9), and iii) the results of preliminary behavioral tests taken together indicates the potential antidepressant-like effect of 6k.

Despite variations in FST level, the test has high predictive validity and is responsive to most commonly used antidepressant drugs.[23]

Table 2: Effect of 6k (2 and 4 mg/kg, p.o.) on ambulatory, fecal pellets, and rearing score in modified OFT in OBX-operated rats

Groups	Ambulations	Fecal pellets	Rearings
Sham control	97.67±5.30	3.17±0.54	15.00±1.48
Sham+ 6k (2 mg/kg, p.o.)	100.17±5.64	3.00±0.26	16.00±2.03
Sham+ 6k (4 mg/kg, p.o.)	105.00±5.14	3.33±0.42	16.83±1.80
Sham+escitalopram (10 mg/kg, p.o.)	108.83±4.87	2.83±0.31	16.67±1.05
OBX control	233.67±3.82##	6.83±0.48##	35.50±2.92##
OBX+ 6k (2 mg/kg, p.o.)	165.83±2.74**aa	4.50±0.43**	25.67±2.12*
OBX+ 6k (4 mg/kg, p.o.)	140.50±4.72**	3.50±0.43**	20.33±2.85**
OBX+escitalopram (10 mg/kg, p.o.)	132.17±6.69**	3.17±0.31**	19.17±1.80**

All the values are expressed as mean±SEM. For statistical significance, ##$P<0.01$ as compared with the sham control group, *$P<0.05$, **$P<0.01$ as compared with the OBX control group, aa$P<0.01$ as compared with escitalopram group; (*n*=6/group), SEM=Standard error of mean, OBX=Olfactory bulbectomy, 6k = *N*-(benzo[*d*] thiazol-2-yl)-3-ethoxyquinoxalin-2-carboxamide, OFT=Open field test

However, FST may produce "false positive" results for drugs enhancing the motor activity and "false negative" for drugs reducing the motor activity, which remain as major drawbacks of the test.[24] 6k treatment produced an antidepressant-like effect reflected by various standard antidepressants in clinical use[11] and also by other 5-HT_3 receptor antagonist.[25] Moreover, the dose range used in the present study for 6k does not alter the basal spontaneous locomotor activity score in mice, and hence showing no sheer central nervous system (CNS) effect of 6k.

Furthermore, serotonin is considered as one of the most important monoamines involved in depression. In 5-HTP-induced head twitches, pargyline (MAO inhibitor) and 5-HTP-induced head twitch response was potentiated significantly by 6k showing the mechanism pathway through increasing the synaptic levels of serotonin in depression.[26] These findings have clinical relevance and one of the studies reported that 5-HT3 antagonists produced serotonin syndrome in patients taking antidepressants.[27]

The OBX-induced depression is one of the most prominent model of depression, in which the depressive-like symptoms are reversed by subchronic but not acute treatment with antidepressants.[20] The OBX rats exhibit severe depressive-like behavior as indicated by anhedonia indicating loss of interest or pleasure.[28] Though the exact mechanism for anhedonia in OBX rats is not clear, it is thought to be because of damage to serotonergic and dopaminergic systems leading to depression-like symptom of inability to experience the pleasure or happiness.[29] The reduction in sucrose consumption in OBX animals was reversed by subchronic treatment with 6k showing antidepressant-like activity. In another behavioral assay, the OBX rats exhibited a specific abnormal behavioral pattern when exposed to the brightly lit, circular, open field arena characterized by increased ambulation, rearing, and fecal pellets.[13] These behavioral alterations were reversed by sub-chronic treatment with 6k.

Earlier studies dealing with antidepressant action of 5-HT_3 antagonists like (6p)[15] and (6n)[30] has been reported. Furthermore, we selected 6k based on the pA2 and log *P* values indicating the antagonism potential and ability to cross blood-brain barrier. In the present study, antidepressant-like effect of 6k was observed with single treatment in preliminary behavioral models of depression because the proposed mechanism for antidepressant-like effect of 6k suggests that 6k antagonizes the ion channel coupled post-synaptic 5-HT_3 receptors and thereby raising the synaptic serotonergic neurotransmission that leads to allosteric modulation of serotonin.[31] The results of the present investigation examines that 6k significantly attenuated the behavioral alterations exhibited by OBX rats, which suggests the potential antidepressant-like effect of 6k. As depression is a major psychiatric disorder[32] studies dealing with selectivity, biochemical and molecular pathways, and

signal transduction of 6k are likely to reveal the mechanism antidepressant-like action.

CONCLUSION

Based on the results obtained from preliminary studies, 6k exhibits potential antidepressant-like effect in rodents behavioral tests battery of depression. However, further studies dealing with the selectivity toward 5-HT_3 receptors and molecular mechanisms for antidepressant-like effect of 6k will enlight the present findings with respect to clinical potency.

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