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Effect of newly synthesized 1,2,4-triazino[5,6-b]indole-3-thione derivatives on olfactory bulbectomy induced depression in rats

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PEER REVIEW

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Comments

This is a good article which has taken into account the various behavioral parameters of chronic depression the article provides an insight into development of newer synthetic analogs with indole-3-thione derivatives.
(Details on Page)

ABSTRACT

Objective: To study the derivatives of 1,2,4-triazino[5,6-b]indole-3-thione for antidepressant activity in olfactory bulbectomized (OBX) rats. Out of various derivatives tested for acute tail suspension test, the two derivatives showing prominent action were selected for bilateral olfactory bulbectomy model of chronic depression in rats. **Methods:** The sub acute effects of 14-day oral pretreatment of two derivatives labeled as 3a (70 mg/kg) and 3r (70 mg/kg), imipramine (20 mg/kg), fluoxetine (30 mg/kg) and moclobemide (15 mg/kg) were evaluated on bilateral bulbectomy induced rise in body weight, hyperphagia, hyperactivity, and on sexual dysfunction. The serum sodium concentration, body temperature, and heart rate were also recorded. **Results:** The derivatives 3a and 3r showed reversal of drop in body weight, reversed OBX induced hyperactivity, normalized body temperature, heart rate, and serum sodium concentration. In elevated maze test, moclobemide, 3a, 3r treatment significantly reduced time spent in open arm as compared to OBX rats. 3a and 3r also improved sexual behavior parameters. **Conclusions:** The present study shows promising antidepressant action and provides a proof of concept for the chronic treatment of 3a, 3r to treat depression.

KEYWORDS

1,2,4 -triazino-[5,6-b]indole-3-thione, Olfactory bulbectomy, Antidepressant activity

1. Introduction

Depression is projected to become the second leading cause of disability in the coming decades[1], producing large economic burdens. According to the World Health Organization, depression is currently the second cause of disability adjusted life years in the age category 15-44 years for both sexes combined, affecting 121 million people worldwide, and it will be at the second place by 2020 calculated for all ages[2]. It is thought to be a heterogeneous illness that can result from the dysfunction of several neurotransmitters on metabolic system[3]. Depression also could result from an inability to make the appropriate adaptive responses to stress or other aversive stimuli. This could be attributed to dysfunction of the neuronal mechanisms underlying neural plasticity[4]. Depressive illness is associated with mental illness and physical changes. Mental illness is characterized by symptoms like feeling of intense sadness, despair, mental slowing, loss of concentration, and variable agitation[5]. Physical changes are characterized by insomnia, hypersomnia, altered eating pattern, weight loss/over eating, and disruption of normal circadian and ultradian rhythms and alteration in body temperature and many endocrine functions[6,7].

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Most antidepressants exert actions on metabolism of monoamine neurotransmitters and their receptors particularly nor-adrenaline and serotonin[8,9]. Current treatment for depression includes drugs such as selective serotonin reuptake inhibitors, tricyclic antidepressants and monoamine oxidase inhibitors. They are effective and tolerated well but noncompliance due to slow action, low response, and plethora of side effects are generally observed[10-17]. Also they inhibit sexual behavior[18]. Therefore, there is need to develop efficacious and safer antidepressant drug.

Derivatives of 1,2,4-triazino[5,6-b]indole-3-thione are known to possess diverse biological activities such as actoprotector, antiviral, antihypoxic, anti-inflammatory, antimalarial, antimicrobial, antitumor, and hepatoprotective. Importantly, this tricyclic structure is comparable to β-carboline (9H-pyrido[3,4-b]indole), an endogenous monoamine oxidase inhibitor. The 18 derivatives of 1, 2, 4-triazino[5, 6-b]indole-3-thione were synthesized and evaluated using tail suspension test in the dose of 30 mg/kg *i.p.*, twice a day. The effects of derivatives were compared with that of standard drugs meclobemide and fluoxetine. The compounds 3a and 3r showed maximum to moderate decrease in immobility duration (% DID) (70.62% and 47.51% DID, respectively)[19].

As depression is a chronic disorder, and it takes several days and weeks for achievement of therapeutic effect of antidepressants[20]. Therefore, it is necessary to study the antidepressant agents in a chronic model of depression with good face validity with human depressive disorder. olfactory bulbectomized (OBX) model in rats is well validated animal model and resembles clinical depression. So we conceived it interesting to evaluate the effects of 3a and 3r in chronic model of depression using OBX rats. As current antidepressants affects libido, an attempt has been made to study the effects of 3a and 3r on sexual behavior in OBX rats (Figures 1 and 2).

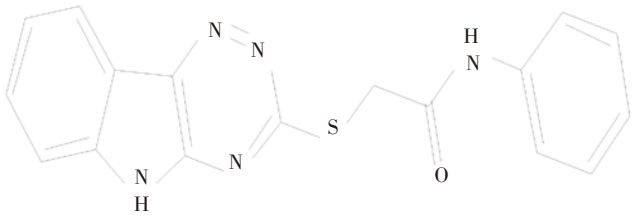

Figure 1. {2-(5H-[1,2,4]triazino[5,6-b]indol-3-ylthio)-N-phenylacetamide}(3a).

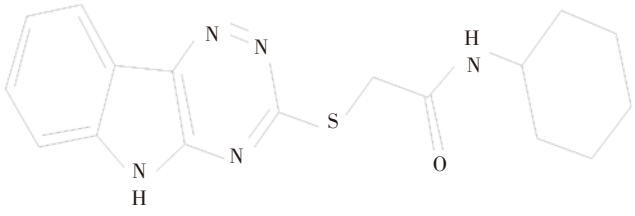

Figure 2. {2-(5H-[1,2,4]triazino[5,6-b]indol-3-ylthio)-N-cyclohexylacetamide} (3r).

2. Materials and methods

2.1. Animals

Male Sprague Dawley rats (250-270 g) were purchased from National Toxicology Centre (NTC), Pune. The animals were housed at (25±1) °C and relative humidity of 44%-45% under 12:12 light: dark cycle. The animals had free access to feed pellets (Chakan Oil Mills Ltd., Sangli, Maharashtra, India) and tap water *ad libitum*. The experimental protocol was approved by Institutional Animal Ethics Committee of Poona College of Pharmacy, Pune, as per norms of Committee for the Purpose of Control and Supervision of Experiments on Animals, Government of India, New Delhi. All observations were recorded between 8.00 a.m. and 15.00 p.m., and each animal was used only once. To avoid subjective bias, the observer was not aware about the given treatment. Each experimental group consisted of six animals unless otherwise stated. Rats were transported from the housing room to the testing area in their own cages and were allowed to adapt to the new environment for 3 h before testing.

2.2. Drugs and chemicals

Imipramine hydrochloride (Imipramine) and Fluoxetine hydrochloride (fluoxetine) were obtained as gift samples from Torrent Pharmaceuticals Ltd., India and Cadila Pharmaceuticals, India, respectively. Moclobemide was obtained from Sigma-aldrich, USA.

2.3. Synthesis of 3a and 3r

Substituted acetamides were prepared as per routine procedure which involved reaction of primary amines with chloroacetyl chloride in glacial acetic acid containing saturated solution of sodium acetate. The tricyclic compound 1,2,4-triazino[5,6-b]indole-3-thione was prepared. Isatin was condensed with thiosemicarbazide by refluxing in aqueous solution of potassium carbonate. The solution so formed was filtered and acidified with glacial acetic acid to yield condensed product. Synthesis of title compounds 3a and 3r was accomplished by stirring overnight solution of in dry DMSO containing anhydrous milled potassium carbonate with appropriate acetamides. Yields of final compounds were in the range of 66%-78% after recrystallization from N, N-dimethylformamide-water. Structure conformation of synthesized compounds was done by IR, 1H NMR, 13C NMR, 13C DEPT, MS, and elemental analysis[19].

The drug solution was used as the suspension of test drugs in 2% CMC, and the dose corresponding to 70 mg/kg was administered according to body weight of animals. The dose was selected on the basis of previous study carried out in mice[19].

2.4. Bilateral olfactory bulbectomy surgery

The male Sprague Dawley rat was anaesthetized with ketamine (80 mg/kg *i.p*). The animal was placed in stereotaxic frame. Head was shaven and 1 cm midline scalp sagittal incision was made, and bilateral 2 mm burr holes were drilled 8 mm anterior to bregma and 2 mm from midline. Both main and accessory olfactory bulbs were aspirated through the both burr hole using a blunt hypodermic needle attached to water pump without damaging frontal cortex. The burr holes were then plugged with a haemostatic sponge to control bleeding. Povidone iodine solution was applied to the wounds and allowed to recover for 14 d[21]. The rats undergone olfactory bulbectomy surgeries were henceforth called as OBX rats.

2.5. Treatment schedule in OBX rats

After recovery period of 14 d, OBX rats were divided into following groups of six rats each and administered with drug treatments as follows. Group I was sham control and was administered with saline. Group II was OBX control rat without any treatment. Group III, IV, and V were OBX rats and treated with imipramine (20 mg/kg), fluoxetine (30 mg/kg) and moclobemide (15 mg/kg), respectively, and Group VI and VII were treated with 3a and 3r, 70 mg/kg each. All the treatments were given orally for 14 d.

2.6. Effect on body weight and food intake in OBX rats

The rats in all the groups were weighed before olfactory bulbectomy and were placed individually in polypropylene cages. During the study period, the animal's body weight and food intake were measured 1 h of drug administration on Day 1, 7 and 14 after treatment to OBX rats.

2.7. Effect on behavioral and physiological parameters during open field activity in OBX rats

The animals were placed in the centre of open field apparatus, the animals were observed for the period of 3 min. Number of ambulation, rearing, and grooming during the 3-minute observation period was counted[22]. The heart rate and serum sodium concentration were measured immediately after open field activity.

2.8. Effect on behavioral and physiological parameters

Female wistar rats (200-250 g) previously experienced in sexual behavior were used for the study. The rectangular wooden box with Plexiglass front and wire mesh top was used as a apparatus. One male rat was placed 5 minutes before introduction of female. The observations were made for 15 minutes. The study was carried out at 2 200-2 400 h under dim white light (30 lux). Sexual behavior in male rats was studied by the methods described by Tyagi *et al*[23].

2.9. Effect on behavioral parameters in elevated plus maze in OBX rats

The OBX rats were tested in the elevated plus maze for anxiety. Thirty minutes after administration of respective treatment, each rat was placed individually in the center of maze, facing one of the closed arms. During a 5-minute test period, number of open arm entries, number of closed arm entries, and time spent in open arm were measured[24,25].

2.10. Statistical analysis

All data were expressed as mean±SEM and analyzed with the help of software Prism version 5.0.3 (GraphPad Inc., California, USA). All the data was analyzed by One-way ANOVA followed by Dunnett's t test except food intake and body weight which were analyzed by Two-way ANOVA followed by Bonferroni's *post hoc* test.

3. Results

3.1. Effect of 3a and 3r on food intake

Food intake in OBX rats was significantly (P<0.001)

Table 1
Effects of 3a and 3r on food intake and body weight in OBX rats.

Treatment	Daily food intake (g/day)			Body weight (g)		
	Day 1	Day 7	Day 14	Day 1	Day 7	Day 14
Sham control	15.25±0.75	17.83±0.87	17.00±1.26	262.34±14.98	266.34±13.57	279.67±14.18
OBX control	25.28±0.64[a]	26.90±0.90[a]	27.66±0.21[a]	306.00±3.59[a]	333.00±7.27[a]	351.00±4.24[a]
OBX+ Imp (20)	11.35±1.02[d]	11.05±0.35[d]	13.50±0.56[d]	300.00±5.05	282.50±7.80[b]	286.83±3.65[b]
OBX+ Flx (30)	13.95±0.27[d]	12.28±0.42[d]	9.45±1.62[d]	298.00±7.10	277.60±9.93[b]	271.00±9.48[d]
OBX+ Moclo (15)	24.34±0.67	19.84±0.45[d]	15.34±0.67[d]	289.67±6.49	299.50±10.08	255.83±15.88[d]
OBX+3a (70)	22.16±0.57	19.17±0.46	18.58±0.34[d]	291.83±5.67	279.67±5.54[c]	261.84±5.69[d]
OBX+ 3r (70)	21.25±0.65	17.17±0.92[d]	15.25±1.20[d]	293.67±3.36	284.67±4.29[b]	279.00±4.30[c]

The values are expressed as the mean±SEM (n=6). The drug/vehicle treatments were administered once a day for 14 d. Figures in the bracket indicate dose in mg/kg, *p.o*. Data was analyzed by Two-way repeated measures ANOVA followed by Bonferroni posttests. [a]P<0.001 as compared to sham control, [b]P<0.05, and [c]P<0.01, [d]P<0.001 when compared to the OBX control. Imp-Imipramine, Flx-Fluoxetine, Moclo-Moclobemide.

increased on Day 1, 7, and 14. Imipramine, fluoxetine reduced the food intake at all the time intervals significantly (P<0.001). Moclobemide reduced food intake on Day 7 and 14 significantly (P<0.001). Treatment with 3a significantly (P<0.001) reduced food intake on Day 14 where as 3r reduced it significantly on Day 7 and 14 as shown in Table 1.

3.2. Effect of 3a and 3r on body weight

OBX increased food intake which was well correlated with increase in body weight. Body weight in OBX group was significantly increased as compared to sham group on Day 0 (P<0.001), on Day 7 (P<0.001) and on Day 14 (P<0.001). Treatment with imipramine (20 mg/kg) as well as with fluoxetine (30 mg/kg) significantly reduced body weight on Day 7 (P<0.05) and Day 14 (P<0.05, P<0.001) as compared to OBX rats. Moclobemide (15 mg/kg) significantly reduced food intake on Day14 (P<0.05) as compared to OBX rats. 3a and 3r treatment significantly reduced body weight on Day 7 (P<0.01, P<0.05) as well as on Day 14 (P<0.001, P<0.01) as compared to OBX rats (Table 1).

3.3. Effect of 3a and 3r on explorative behavior

The exploratory behavior is shown in Table 2. Olfactory bulbectomy increased the ambulation significantly (P<0.001) as compared to sham group. Imipramine, fluoxetine as well as moclobemide treatment significantly (P<0.001) reduced the ambulation score. 3a, 3r treatment also significantly (P<0.001, P<0.001) diminished the ambulation score.

Olfactory bulbectomy significantly (P<0.001) increased the rearing score as compared to sham group. Imipramine, fluoxetine, moclobemide and 3r treatment significantly (P<0.001, P<0.01) reduced the rearing scores when compared with OBX group. 3a treatment did not have any significant effect.

Grooming score was increased significantly (P<0.001) as compared to sham operated animals. All the treatments reduced the grooming score significantly (P<0.001, P<0.01) as compared with OBX group.

3.4. Effect of 3a and 3r on cardiovascular parameters

The normal heart rate in sham group was found to be (365.0 ±4.8) BPM. Olfactory bulbectomy significantly (P<0.001) reduced the heart rate to (288.70±8.28) BPM. Imipramine, fluoxetine and 3r administration to rats significantly (P<0.001) increased the heart rate (Table 2).

3.5. Effect of 3a and 3r on serum sodium concentration

The serum sodium concentration in sham group was found to be (130.44±8.20) mmol/L. Olfactory bulbectomy significantly (P<0.001) increased the serum sodium concentration as shown in Table 2 as compared to sham group. Fluoxetine, 3a and 3r treatment significantly reduced

Table 2

Effects of 14-day administration of 3a and 3r on behavioral and physiological parameters during open field activity in OBX rats.

Treatment	Ambulation (score)	Rearing (score)	Grooming (score)	Heartrate (beats/min)	Serum sodium concentration (mmol/L)
Sham control	29.67±0.91	13.00±0.73	18.83±0.6	365.00±4.86	130.44±8.20
OBX control	80.50±4.40[a]	32.50±3.43[a]	31.67±2.36[a]	288.70±8.28[a]	390.59±6.07[a]
OBX+Imp (20)	33.67±2.66[d]	16.00±1.65[d]	17.00±0.81[d]	433.80±7.62[d]	320.65±29.31
OBX+Flx (30)	41.83±3.89[d]	24.17±2.53	16.83±2.31[d]	376.80±5.64[d]	235.50±15.47[c]
OBX+Moclo (15)	36.50±2.44[d]	20.17±2.84[c]	16.50±1.76[d]	313.80±20.93	328.90±38.62
OBX+3a (70)	43.00±2.25[d]	24.67±1.56	16.83±0.98[d]	322.40±7.62	174.80±25.25[d]
OBX+3r (70)	40.83±2.20[c]	23.17±1.40[b]	16.17±1.44[d]	346.30±12.37[c]	241.00±48.89[b]

The values are expressed as the mean±SEM (n=6). The drug/vehicle treatments were administered once a day for 14 d. Figures in the bracket indicate dose in mg/kg, $p.o$. Data was analyzed by Two-way repeated measures ANOVA followed by Bonferroni posttests. [a]P<0.001 as compared to sham control, [b]P<0.05, and [c]P<0.01, [d]P<0.001 when compared to the OBX control. Imp-Imipramine, Flx-Fluoxetine, Moclo-Moclobemide.

Table 3

Effects of 14-day administration of 3a and 3r on sexual behavior in OBX rats.

Treatment	Mounting latency (s)	Monuting frequency (N)	Intromission latency (s)	Intromission frequency (N)
Sham control	74.10±7.44	10.00±0.86	191.40±34.55	6.17±0.61
OBX control	669.00±52.16[a]	3.84±0.55[a]	805.20±31.08[a]	1.33±0.20[a]
OBX+Imp (20)	717.00±45.00	2.50±0.35	777.60±39.79	1.67±0.33
OBX+Flx (30)	780.00±21.91	2.67±0.33	840.60±11.57	1.50±0.23
OBX+Moclo (15)	272.00±17.37[c]	5.84±0.41	395.00±5.94[c]	3.00±0.26[c]
OBX+ 3a (70)	518.00±19.64[b]	4.33±0.50	587.00±20.81[c]	2.00±0.26
OBX+3r (70)	394.00±22.80[c]	5.00±0.37	434.00±21.73[c]	2.50±0.23

The values are expressed as the mean±SEM (n=6). The drug/vehicle treatments were administered once a day for 14 d. Figures in the bracket indicate dose in mg/kg, $p.o$. Data was analyzed by Two-way repeated measures ANOVA followed by Bonferroni posttests. [a]P<0.001 as compared to sham control, [b]P<0.01, and [c]P<0.001 when compared to the OBX control. Imp-Imipramine, Flx-Fluoxetine, Moclo-Moclobemide.

(P<0.05, P<0.001, P<0.05) the serum sodium concentration as compared to OBX rats (Table 2).

3.6. Effect of 3a and 3r on sexual behavior parameters

The sexual behavior parameters are gathered in Table 3. Mounting latency (ML) in sham operated animals was found to be 74.10±7.44 seconds. Olfactory bulbectomy significantly (P<0.001) increased the ML to 669.00±52.16 seconds. Moclobemide, 3a and 3r exhibited significant (P<0.01, P<0.001) reduction in the ML. On the other hand imipramine, fluoxetine had no effects.

Mounting frequency (MF) in sham operated animals was found to be 10.00±0.85. OBX group showed significant (P<0.001) reduction in MF to 3.83±0.54. Treatment with imipramine, fluoxetine, moclobemide did not improve MF. 3a and 3r treatment showed non significant increase in MF.

Intromission latency (IL) in sham group was found to be 191.40±34.55 seconds. OBX rats showed significant (P<0.001) increase in IL as compared to sham operated animals. Treatment with Imipramine, fluoxetine did not show any effect on IL. Moclobemide, 3a and 3r significantly restored IL (P<0.001) to normal.

Intromission frequency (IF) in sham group was found to be 6.16±0.60. OBX rats significantly reduced (P<0.001) IF (1.33± 0.22). Treatment with moclobemide significantly increased IF (P<0.001) compared to OBX. Imipramine, fluoxetine, 3a and 3r failed to restore IF.

3.7. Effect of 3a and 3r on elevated plus maze

3.7.1. Open arm entries

Table 4 shows the effect of test drug treatment on elevated plus maze activity in OBX rats. In sham operated animals, the mean open arm entries were found to be 1.50±0.42.

Table 4
Effects of 14-day administration of 3a and 3r on elevated plus maze activity in OBX rats.

Treatment	Open arm entries	Closed arm entries	Time spent in open arm
Sham control	1.50±0.43	4.50±0.56	1.15±0.35
OBX control	13.33±1.36[a]	8.33±0.55[a]	2.81±0.22[a]
OBX+Imp (20)	1.83±0.60[d]	3.50±0.42[d]	1.71±0.41
OBX+Flx (30)	1.83±0.61[d]	3.66±0.42[d]	1.15±0.27[b]
OBX+Moclo (15)	14.00±0.37	3.66±0.42[d]	3.08±0.08[d]
OBX+3a (70)	13.83±0.31	4.17±0.47[d]	8.63±0.33[c]
OBX+3r (70)	13.83±0.31	4.33±0.49[d]	6.56±0.39[d]

The values are expressed as the mean±SEM (n=6). The drug/vehicle treatments were administered once a day for 14 d. Figures in the bracket indicate dose in mg/kg, *p.o.* Data was analyzed by Two-way repeated measures ANOVA followed by Bonferroni posttests. [a]P<0.001 as compared to sham control, [b]P<0.01, and [c]P<0.001 when compared to the OBX control. Imp-Imipramine, Flx-Fluoxetine, Moclo-Moclobemide.

OBX significantly (P<0.001) increased the open arm entries as compared to control OBX group as shown in Table 2. Fluoxetine treatment significantly (P<0.001) reduced the open arm entries. While moclobemide, 3a and 3r did not show any significant effect on open arm entries.

3.7.2. Closed arm entries

Closed arm entries in sham operated animals were found to be 4.50±0.56. OBX significantly increased (P<0.001) the closed arm entries to 8.33±0.55 as compared sham operated animals. All the treatment groups showed significant (P<0.001) reduction in closed arm entries as compared to control group.

3.7.3. Time spent in open arm

In sham operated animals the time spent in open arm was found to be 1.15±0.35 min. OBX significantly (P<0.001) increased the time spent in open arm as compared to sham operated animals. Animals treated with fluoxetine remained for longer duration in open arm as compared to OBX rats (P<0.05). Moclobemide, 3a, 3r treatment significantly (P<0.001) reduced time spent in open arm as compared to OBX rats.

4. Discussion

The results of this behavioral investigation divulge the antidepressant-like effects of 3a and 3r derivatives of 1,2,4-triazino[5,6-b]indole-3-thione. Bilateral olfactory bulbectomy in the rat is associated with behavioral changes in exploratory behavior and passive avoidance conditioning that are largely reversed by chronic, but not acute, treatment with antidepressant drugs[26,27]. The present study reveals the use of derivatives of 2,4-triazino[5,6-b]indole-3-thione in chronic model of depression. The 3a is the phenyl substitution. In the earlier study made, phenyl substitution showed 70.62% DID in acute model of depression[19]. Any substitution of phenyl ring diminished antidepressant activity of parent compound 3a from small to considerable extent depending upon its type and position. In OBX model, 3a phenyl substitution showed maximum antidepressant activity in mostly all of the paradigms tested. 3r showed 47.5% DID in acute model, but when tested in chronic model of depression, it showed significant antidepressant activity. The antidepressant paradigms were carried out on last day of dosing *i.e.* Day 28 of surgery. Thus it is difficult to remark on onset of action of 3a and 3r. Delayed action of 3r could be responsible for low DID in acute test.

In the present study, OBX rats displayed a wide range of behavioral abnormalities, such as (i) increased horizontal and vertical activities and defecation in modified open field exploration paradigm, (ii) decreased active interaction and increased crossing in social interaction paradigm, and (iii) increased hyperemotionality scores as reported

earlier[25]. The chronic treatment of OBX rats with 3a and 3r compounds chronically reversed the above mentioned parameters. This result is in line with previous reports on reversal of bulbectomy induced behaviour by tricyclic antidepressants[28]. OBX rats showed hyper motility (activity) as seen by increase in open and closed arm entries. Fluoxetine and imipramine reduced open arm and close arm entries indicating decrease in hyperactivity. This effect was absent with moclobemide as well as with the test compounds. Measurement of total time spent in open arm showed OBX rats could not differentiate the threat and protected environment and thus spent more time in open arms. This was not the case with moclobemide, 3a, 3r treatments while fluoxetine failed to normalize this behavior.

Our study showed that fluoxetine exhibited sexual dysfunction which is in parallel with many reports[29]. 3a and 3r on the other hand improved sexual dysfunction associated with OBX[30]. OBX is associated with increased HPA axis activity[11]. Depression associated with stress has shown to have over expression of CRF[31]. This leads to increased cortisol in blood further increasing serum sodium concentration. Treatment with 3a, 3r, fluoxetine as well moclobemide normalized serum sodium concentration indicating normalization of dysfunctional HPA axis activity. Exposure of normal rats to novel environment increases heart rate[32]. Similar effects were seen in the present study. OBX rats showed reduced BPM indicating loss of vagus control[33]. Imipramine and fluoxetine significantly increased heart rate as reported earlier[33]. 3a and 3r also showed normalization of heart rate demonstrating its effect on monoaminergic system as seen with imipramine and fluoxetine.

Thus in conclusion the above studies revealed that synthesized 1,2,4-triazino[5,6-b]indole-3-thione derivatives 3a-{2-(5H-[1,2,4]triazino[5,6-b]indol-3-ylthio)-N-phenylacetamide} and 3r-{2-(5H-[1,2,4]triazino[5,6-b]indol-3-ylthio)-N-cyclohexylacetamide} exhibited significant antidepressant activity in chronic model of depression. The study also indicated that 3a and 3r improved sexual behavior in OBX rats.

Conflict of interest statement

We declare that we have no conflict of interest.

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Comments

Background

Depression can be long-lasting or recurrent, substantially impairing an individual's ability to function at work or cope with daily life. One of the important factor causing depression is stress, which stimulate the HPA axis activity leading to increase in serum corticosterone as shown by number of experiments. The present study has made an attempt to assess the newly synthesized antidepressants using olfactory bulbectomy induced depression model. The OBX model has been reported to mimic clinical depression moreover it also stimulates HPA axis (as seen in stress induced depression). The research also involves the study of test molecules on sexual dysfunction and their comparison with the std treatments.

Research frontiers

This present study has undertaken the effect of derivatives of indole-3-thione. The derivatives (3a and 3r) on OBX model of chronic depression. The molecules have shown to exhibit significant antidepressant activity.

Related reports

The results show that 3a derivative exhibited maximum antidepressant activity in all paradigms of depression. Sexual dysfunction is one of the major side effects of Fluoxetine. The study has made an attempt to evaluate the effects of indole-3-thione derivatives on sexual dysfunction. The results shows 3a and 3r improved all the parameters of sexual dysfunction. The reports are in accordance with Hoon *et al.*, 1997.

Innovations and breakthroughs

The research article involves the development of newer antidepressants with fewer side effects.

Applications

Major depressive disorder is highly rampant psychological illness with 9%-18% prevalence and ranking fourth among the causes of death or injury worldwide. There is the need to develop efficacious and safer antidepressant.

Peer review

This is a good article which has taken into account the various behavioral parameters of chronic depression the article provides an insight into development of newer synthetic analogs with indole-3-thione derivatives.

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