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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

Urmila M Aswar[1], Padmaja P Kalshetti[3], Suhas M Shelke[2], Sharad H Bhosale[2], Subhash L Bodhankar[2*]

[1]*Department of Pharmacology, STES's Sinhgad Institute of Pharmacy, Narhe, Pune-411041,India*
[2]*Department of Pharmacology, Poona College of Pharmacy, Bharati Vidyapeeth Deemed University, Erandwane, Paud road, Pune-411038, India*
[3]*Department of Pharmacology, Maharashtra Institute of Pharmacy, Paud Road, Pune-411038, India*

## PEER REVIEW

**Peer reviewer**

Dr. Prashant Murumkar, Professor, Department of Pharmaceutical Chemistry, Sinhgad Institute of Pharmacy, S. No. 49/2, 53/2, Off Westerly Bypass, Mumbai-Pune Expressway, Narhe, Pune - 411 041.
Tel: +91-20-66831811, 8793265140
Fax: +91-20- 66831816
E-mail: prashant_murumkar@yahoo.com.

**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 997)**

## 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].

*Corresponding author: Dr. SL Bodhankar, Professor and Head, Department of Pharmacology, Poona College of Pharmacy, Bharati Vidyapeeth University, Erandwane-411038, Pune, India.
Tel: +91-20-24537237
Fax: +91-20 25439386
E-mail: bodhankarsl@gmail.com

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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).

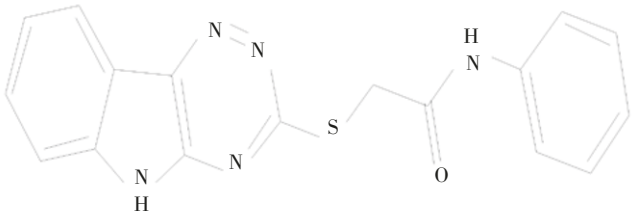


**Figure 1.** {2-(5H-[1,2,4]triazino[5,6-b]indol-3-ylthio)-N-phenylacetamide}(3a).

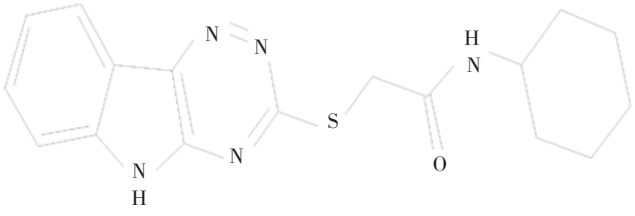


**Figure 2.** {2-(5H-[1,2,4]triazino[5,6-b]indol-3-ylthio)-N-cyclohexylacetamide} (3r).

## 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].