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Exploring the *In vivo* Neuropsychopharmacological Potential of Polyamine Scaffolds

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Abstract

Anxiety and depression are among the most prevalent mental health disorders, affecting a vast portion of the population. Despite the well-established efficacy of first-line anxiolytic and antidepressant treatments, their significant side effects often drive individuals to seek alternative therapies. Trisamine-based drugs have drawn interest in the modern age because of their potency, efficacy, broad pharmacological activity, and decreased adverse effects. They are a safer, more effective, and more affordable option for treating mental health issues because of their promising therapeutic profile. Trisamine derivatives' neuropharmacological potential was assessed in this study, with a focus on their sedative, anxiolytic, and antidepressant properties. The chosen compound was screened using a variety of behavioral models, and the results were significant. Although Compound T10 showed no sedative activity in open field test, however it demonstrated highly significant ($^{***}P< 0.001$) anxiolytic effects in behavioral assessments. Similarly the Compounds displayed significant ($^{***}P< 0.001$) antidepressant activity in the forced swimming test (FST). The selected compounds exhibited strong neuropharmacological effects.

KEYWORDS

Trisamine compounds, Anxiolytic, Antidepressant, Neuropharmacologicaleffects.

1.0 INTRODUCTION

Depression and anxiety are among the most prevalent mental health disorders, significantly impacting quality of life and increasing the burden on healthcare systems. Pharmacological treatments such as selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs) remain first-line therapies [1]. SSRIs, including citalopram and escitalopram, enhance serotonergic neurotransmission but have limitations such as delayed onset of action, emotional blunting, and withdrawal. These drawbacks highlight the need for novel therapeutics with improved efficacy and safety. Research has increasingly focused on nitrogen-containing heterocyclic compounds due to their diverse biological activities, including neuropharmacological effects. Tris(2-aminoethyl)amine (TREN) derivatives, in particular, have gained attention due to their strong metal chelation properties, neuroprotective potential, and ability to modulate serotonin and GABA pathways. The heterocyclic compounds having nitrogen in their moiety are of great attention nowadays for diverse pharmacological potentials [2-4]. In medicinal chemistry, various TREN derivatives have shown promise in diverse therapeutic applications, including antimicrobial, anticancer, and anti-inflammatory properties [5]. However, limited research has been conducted on their potential role as anxiolytic and antidepressant agents. Some studies indicate that modifications in TREN structures enhance their ability to interact with central nervous system (CNS) receptors, particularly those involved in monoamine regulation [6-7]. Recent advancements in synthetic chemistry have enabled the development of novel TREN-based compounds with improved pharmacokinetic properties. The current study aims in the development of Tris amine derivatives. Through these investigations, the study aims to contribute to the development of novel anxiolytic and antidepressant compounds with improved therapeutic potential and minimal adverse effects.

2.0 MATERIALS AND METHODS

The compound was donated by the Institute of Chemical Sciences, University of Peshawar. The structure, molecular formula, Mass and solubility of the compounds are displayed in **Table 1.**

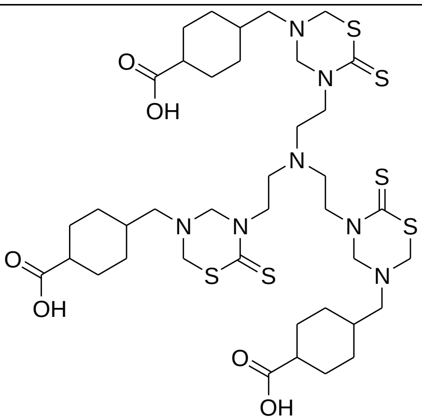
Sample Code	Structure of Compound	Molecular Formula	Mass	Solubility
T10		**$C_{39}H_{63}N_7O_6S_6$**	**918.39**	**DMSO (1%)**

Table 1: Chemical characteristics of the tested polyamine derivative (T10).

2.1Experimental Animals and Treatment Regimen

BALB mice weighing 18–22 grams, both male and female, were acquired from the National Institute of Health (NIH), located in Islamabad. The test compound, Tris(2-aminoethyl)amine (TREN) derivatives, was administered via the peritoneal (p.o.) route. The doses were selected based on preliminary toxicity studies and previous literature on structurally related compounds. Intraperitoneal administration was performed using freshly prepared solutions, maintaining sterile conditions to prevent contamination. The experimental animals were divided into groups, having (n=6), which consisted of an equal number of mice of both sexes. They were administered various doses of the compound in mg/kg, adjusted according to their body weights. The tested concentration range included 5, 2.5, and 1.25 mg/kg, i.p. The control group received 1% DMSO in normal saline/distilled water, serving as the vehicle control, while standard drug-treated groups received clinically relevant doses of fluoxetine (SSRI) and diazepam (benzodiazepine) as reference antidepressant and anxiolytic agents. Before experimentation, the animals were acclimatized to the laboratory environment under standard conditions, including a controlled temperature of 25°C and a 12/12-hour light-dark cycle to minimize stress and ensure reliable results. Doses were administered once daily at the same time each day to maintain consistency, and the duration of drug exposure varied based on the specific behavioral and biochemical assessments conducted in the study.

2.3 *Invivo* Studies

2.3.1 Acute Toxicity

To determine acute toxicity, various doses were delivered to groups of six mice of both sexes. The observation protocol consisted of an initial 2-hour period of constant monitoring, intermittent checks for an additional 4 hours, and a final evaluation after 72 hours to record any delayed physiological responses [8].

2.3.2 Sedative Activity

For the assessment of sedative activity, the mice's crossings of squares in the apparatus were counted [9].

2.3.3 Anxiolytic Activity

For anxiolytic activity, the frequency of rearing behavior and the number of steps ascended were tracked for three minutes [10].

2.3.4 Antidepressant Activity

Similarly, for antidepressant activity, each mouse was submerged in water and given 360 seconds to swim for 30 minutes following treatment. In order to assess depressive-like behavior, the time of immobility during the final 240 seconds of the test was recorded [11].

2.4 STATISTICAL ANALYSIS

All tests were performed in triplicate and values were represented as mean ± standard deviation. Results were interpreted based on concentration-dependent activity patterns [12].

3.0 RESULTS

3.1 Acute toxicity result

No mortality was observed during the observation period, which indicates that the compounds are well tolerated, as shown in **Table 2** at various concentrations ranging from 50-1000 mg/kg body weight.

Table 2 Acute Toxicity of the compound T10

Compound	Dose (mg/kg)	Mortality
T10	50	_
	100	_
	200	_
	400	_
	600	_
	800	_
	1000	_

3.2 *Invivo* Pharmacological potential of compound T10

The compound T10 exhibited a lack of sedative properties, notably, mice demonstrated a dose-dependent increase in the frequency of line crossing, suggesting enhanced locomotor activity across all tested concentrations. The decreased number of steps and rearing showed that the test compound has anxiolytic potential at these tested doses. A compound was observed showing a significance of (P<0.001) at the tested dose of the compound, i.e., 5 and 2.5mg/kg, IP. However, at low dose, i.e.,1.25mg/kg, no sedative activity was shown by the compound. Further, there was a (P<0.001) significant decline in the number of rearing. Similarly, the Compound was showing (P<0.001) significance, the immobility time became reduced at all of the examined doses, which were 5, 2.5, and 1.25mg/kg. These statistical parameters indicate that there was a decline in the immobility time of the animal, which is an indication of antidepressant activity. These activities are tabulated in **Table 3.**

Table 3 Sedative, Anxiolytic and Antidepressant Activity of the compound T10

Sedative activity			
Groups	Dose(mg/kg)	Number of lines crossed by mice in 10 min	
Normal Saline	10 ml/kg	121 ± 0.56	
Diazepam	0.5 mg/kg	5.01 ± 0.67***	
T10	5 (mg/kg)	117.7 ± 3.3	
	2.5 (mg/kg)	123.3 ± 6.17	
	1.25 (mg/kg)	165.3 ± 6.88	
Anxiolytic activity			
Groups	Dose (mg/kg)	Number of steps	Number of rearing
Normal Saline	10 ml/kg	23.566 ± 2.1	10.3 ± 0.32
Diazepam	0.5 (mg/kg)	2.54 ± 0.22***	1.667 ± 0.32***
T10	5 (mg/kg)	2.000 ± 0.54***	1.333 ± 0.33***
	2.5 (mg/kg)	3.667 ± 0.67***	2.667 ± 0.89***
	1.25 (mg/kg)	27.66 ± 2.028ns	2.000 ± 1.00***
Antidepressant Activity			
Groups	Dose(mg/kg)	Immobility Time of Animal in Seconds	
Normal saline	10 ml/kg	100.00 ± 0.55	
Fluoxetine	0.5 (mg/kg)	25.66 ± 0.31***	
T10	5 (mg/kg)	42.67 ± 2.91***	
	2.5 (mg/kg)	46.00±2.31***	
	1.25 (mg/kg)	53.33±1.67***	

Experiments were performed in triplicate and results were represented as the mean ± standard deviation. The analysis of results focused on identifying dose-dependent activity patterns. The values were compared to the normal saline group. ***P < 0.001, **P < 0.01, ***P < 0.05, P > 0.05 = ns (not significant) to that of the control group.

4.0 DISCUSSION

The pharmacological evaluation of Compound **T10** reveals a promising therapeutic profile characterized by potent CNS activity and a high safety margin, which is related to inflammation [13]. The absence of mortality at all the administered doses suggests that the compound is well-tolerated within the tested range. However, **T10** demonstrated a non-sedative activity. The significant reduction in rearing and stepping of the mice at all the tested doses strongly indicates an anxiolytic effect. Interestingly, even at the lowest dose of 1.25mg/kg, while no sedative activity was present, a significant decrease in rearing was maintained, which suggests that the compound's anxiolytic property is robust even at low doses. Furthermore, the dose-dependent reduction in immobility time across all test groups suggests significant antidepressant potential. In behavioral models, a decrease in immobility is often interpreted as a reduction in behavioral despair. Collectively, these statistical parameters suggest that Compound **T10** acts as a dual-action candidate, offering both anxiolytic and antidepressant benefits without the confounding side effect of sedation. In **T10**, the carboxylic acid group of cyclohexanoic acid is joined to a cyclohexane ring. Cyclohexanoic acid has a more aliphatic structure. Its ability to interact with biological targets and its lipophilicity are both impacted by this structural variation, as well as the cytotoxicity [14] of the compound T10. It can pass through cell membranes because of its lipophilicity, which is facilitated by the benzene ring. In addition to increasing a drug's potency, high lipid solubility allows for quick diffusion through cell membranes [15]. These substituents' type and location can affect a compound's solubility, potency, and selectivity for particular targets. The substituents affixed to the central core are the reason why T10 is more active.

5.0 CONCLUSION

This study demonstrates that compound T10 is are promising candidate for the treatment of anxiety and depression, exhibiting dose-dependent efficacy and a favorable safety profile. These results suggest that TREN derivatives could serve as scaffolds for a novel class of non-sedative psychotherapeutic agents. Further development and optimization of these compounds may provide more effective and better-tolerated alternatives to existing treatments for depression and anxiety.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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