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Anxiolytic and Antidepressant Like Effects of a Novel Synthetic Compound in Animal Models

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Abstract

A significant number of people suffer from anxiety and depression, which are two of the most common mental health conditions. Even while first-line anxiolytic and antidepressant medicines have been shown to be effective, their serious side effects frequently lead people to look for alternative therapies due to their potential therapeutic profile. The potency, efficacy, wide pharmacological activity, and reduced side effects of trisamine-based medications have attracted attention in the modern medicine. Because of their potential therapeutic characteristics, they are a safer, more effective, and more economical option for treating mental health concerns. This study evaluated the neuropharmacological potential of trisamine derivatives, emphasizing its sedative, anxiolytic, and antidepressant qualities.Several behavioral models were used to screen the selectedcompound, and the results were noteworthy.In an open field test, compound Z-1 demonstrated potent sedative action at every tested dosage.In behavioral tests, it also showed quite significant (***P<0.001) anxiolytic effects. Compound Z-1 demonstrated potent antidepressant effect in the forced swimming test (FST).Strong neuropharmacological effects were shown by the chosen compound.

KEYWORDS:
Trisamine compound, Anxiolytic, Antidepressant, Neuropharmacological effects.

1.0 INTRODUCTION

Anxiety and depression are two of the most common mental illnesses that have a significant negative impact on both patient well-being and global healthcare resources [1]. Pharmacological medication, particularly selective serotonin reuptake inhibitors (SSRIs) and serotonin –norepineprine reuptake inhibitors (SNRIs), is given priority as primary therapy in current clinical guidelines.

[2]. By altering serotonergic pathways, drugs like escitalopram and citalopram enhance mood, but they also have certain negative side effects include withdrawal, delayed onset of action, and emotional blunting. These disadvantages demonstrate the need for innovative treatments with increased safety and efficacy.

[3]. Nitrogen-containing heterocyclic compounds have drawn more attention in research because of their wide range of biological activities, including neuropharmacological effects. compounds of tris(2-aminoethyl)amine (TREN), in

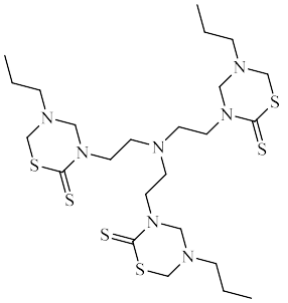
particular, have gained attention due to their strong metal chelation properties, neuroprotective potential, and ability to modulate serotonin and GABA pathways. The heterocyclic compounds having nitrogen in their moiety are of great attention nowadays for diverse pharmacological potentials [4-5]. In medicinal chemistry, various TREN derivatives have shown promise in diverse therapeutic applications, including antimicrobial, anticancer, and anti-inflammatory properties [6]. 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 [7-8]. 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.**

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

Sample Code	Structure of Compound	Molecular Formula	Mass	Solubility
Z-1		$C_{24}H_{45}N_7S_6$	**624.03**	**DMSO (1%)**

2.1 Experimental 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 different 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. Standard drug-treated groups were given clinically relevant dosages of fluoxetine (SSRI) and diazepam (benzodiazepine) as reference antidepressants and anxiolytics, while the control group was given 1% DMSO in normal saline/distilled water as a vehicle control. To reduce stress and guarantee accurate results, the animals were acclimated to the typical laboratory conditions prior to research, which included a controlled temperature of 25°C and a 12-hour light-dark cycle. To ensure uniformity, doses were given once daily at the same time every day. The length of drug exposure varied according to the particular behavioral and biochemical evaluations carried out in the study.

2.2 *Invivo* Studies

2.2.1 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 [9-10].

2.2.2 Sedative Activity

For the assessment of sedative activity, the

mice's crossings of squares in the apparatus were counted [11].

2.2.3 Anxiolytic Activity

For anxiolytic activity, the frequency of rearing behavior and the number of steps ascended were tracked for three minutes [12].

2.2.4 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 [13].

2.3 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 [14].

3.0 RESULTS

3.1 Acute toxicity result

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

Table 2 Acute Toxicity

Compound	Dose(mg/kg)	Mortality
Z-1	50	_
	100	_
	200	_
	400	_
	600	_
	800	_
	1000	_

3.2 *Invivo* Pharmacological potential of compound Z-1

The number of lines crossed by mice when treated with the test compound **Z-1** were observed to be decreased. Significant sedative activity (***P< 0.001) was observed at 5 and 2.5 mg/kg, and 1.25mg/kg which shows the sedative activity of the compound at all the tested doses. Compound **Z-1** showed highly significant (***P< 0.001) effect across all tested doses (5, 2.5, and 1.25 mg/kg), demonstrating strong anxiolytic property. The decline in number of rearing and steps showed that the test compound has anxiolytic potential at these tested doses. At a dose of 5 and 2.5mg/kg, demonstrated a significant (***P<0.001) reduction in immobility time,however at the tested dose of 1.25mg/kg, a significance of (*P<0.01) was noted; The statistical data indicate that this compound's antidepressant action is dose dependent.These activities are tabulated in **Table 3.**

Table 3 Sedative, Anxiolytic and Antidepressant Activity of the compound Z-1

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***	
Z-1	5 (mg/kg)	16.67 ± 4.05***	
	2.5 (mg/kg)	34.67 ± 4.97***	
	1.25 (mg/kg)	39.62 ± 2.72***	
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***
Z-1	5 (mg/kg)	0.6667 ± 0.57***	0.667 ± 0.54***
	2.5 (mg/kg)	0.6667 ± 0.54***	0.0 ± 0.0***
	1.25 (mg/kg)	0.6667 ± 1.15***	0.333 ± 0.57***
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***	
Z-1	5 (mg/kg)	33.33 ± 1.78***	
	2.5 (mg/kg)	40.00 ± 2.87***	
	1.25 (mg/kg)	41.33 ± 1.33***	

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 **Z-1** reveals a promising therapeutic profile characterized by potent CNS activity and a high safety margin [15]. The absence of mortality at all the administered doses suggests that the compound is well-tolerated within the tested range. The number of lines that the animal crossed after treatment with **Z-1** compound were decreased at all the tested doses.The compound showed a significant ($P <$ 0.001) throughout. The decline in number of steps was observed to be (P<0.001) significant at all the tested doses,which shows strong anxiolytic activity of this compound. Compound **Z-1** had a (P<0.001) significance at all the test doses. It showed that the compound has antidepressant effect even at low doses. The larger propyl group present in the compound is advantageous for optimal binding within a specific binding pocket or active site. Propyl groups increase a compound's lipophilicity, which improves its capacity to interact with lipid-based structures or pass through cell membranes. The compound's overall lipophilicity, which in turn affects its bioavailability, distribution, and metabolism, can be influenced by the side chain's size. Increased resistance to enzymatic degradation is often provided by the larger propyl group. The propyl group may change the compound's orientation or add more hydrophobic interactions , which could affect the compound's binding affinity.

5.0 CONCLUSION

This study demonstrates that compound Z-1 is a promising candidate for the management of anxiety and depression, exhibiting dose-dependent efficacy along with a favorable safety profile. The findings further suggest that TREN derivatives may serve as valuable scaffolds for the development of a novel class of dose-dependent sedative psychotherapeutic agents. Continued optimization and pharmacological refinement of these compounds could lead to more effective and better-tolerated therapeutic alternatives to currently available treatments for anxiety and depressive disorders.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

6.0 REFERENCES

1. Søvold, L.E., et al., Prioritizing the mental health and well-being of healthcare workers: an urgent global public health priority. Frontiers in public health, 2021. **9**: p. 679397.
2. Locher, C., et al., Efficacy and safety of selective serotonin reuptake inhibitors, serotonin-norepinephrine reuptake inhibitors, and placebo for common psychiatric disorders among children and adolescents: a systematic review and meta-analysis. JAMA psychiatry, 2017. **74**(10): p. 1011-1020.
3. (- 1768-3254 (Electronic)).
4. Shah, M., et al., SAR and lead optimization of (Z)-5-(4-hydroxy-3-methoxybenzylidene)-3-(2-morpholinoacetyl) thiazolidine-2, 4-dione as a potential multi-target antidiabetic agent. European Journal of Medicinal Chemistry, 2023. **258**: p. 115591.
5. Sadiq, A., et al., 3-(((1 S, 3 S)-3-((R)-Hydroxy (4-(trifluoromethyl) phenyl) methyl)-4-oxocyclohexyl) methyl) pentane-2, 4-dione: Design and Synthesis of New Stereopure Multi-Target Antidiabetic Agent. Molecules, 2022. **27**(10): p. 3265.
6. Alessio, E., Bioinorganic medicinal chemistry. 2011: John Wiley & Sons.
7. Ledonne, A., et al., Trace amines depress D(2)-autoreceptor-mediated responses on midbrain dopaminergic cells. Br J Pharmacol, 2010. **160**(6): p. 1509-20.
8. Alam, W., et al., Synthesis, in-vitro inhibition of cyclooxygenases and in silico studies of new isoxazole derivatives. Frontiers in chemistry, 2023. **11**: p. 1222047.
9. Jan, M.S., et al., Synthesis of pyrrolidine-2, 5-dione based anti-inflammatory drug: in vitro COX-2, 5-LOX inhibition and in vivo anti-inflammatory studies. Latin Am J Pharm, 2019. **38**(11): p. 2287-2294.
10. Hussain, F., et al., Screening of Abenaria plantaginea Lindl for anti-alzheimer potential. Phytopharmacology Research Journal, 2025. **4**(3): p. 101-107.
11. Akkol, E.K., et al., Sedative and anxiolytic activities of Opuntia ficus indica (L.) Mill.: An experimental assessment in mice. Molecules, 2020. **25**(8): p. 1844.
12. Seibenhener, M.L. and M.C. Wooten, Use of the open field maze to measure locomotor and anxiety-like behavior in mice. Journal of visualized experiments: JoVE, 2015(96): p. 52434.
13. Saviluoto, T., Chronic antidepressant administration and validation of automatized analysis of forced swim test on mice. 2022, Itä-Suomen yliopisto.
14. Ejaz, I., et al., Rational design, synthesis, antiproliferative activity against MCF-7, MDA-MB-231 cells, estrogen receptors binding affinity, and computational study of indenopyrimidine-2, 5-dione analogs for the treatment of breast cancer. Bioorganic & Medicinal Chemistry Letters, 2022. **64**: p. 128668.
15. Khan, A., et al., Phytochemical profiling, anti-inflammatory, anti-oxidant and in-silico approach of cornus macrophylla bioss (Bark). Molecules, 2022. **27**(13): p. 4081.
16. Shah, L., et al., Phytochemical Profiling and Bioactive Potential of Rhizoclonium hookeri, Antioxidant, Antidiabetic, and Neuroprotective Effects. Chemistry & biodiversity, 2025. **22**(11): p. e00947.
17. Fong, C.W., Statins in therapy: understanding their hydrophilicity, lipophilicity, binding to 3-hydroxy-3-methylglutaryl-CoA reductase, ability to cross the blood brain barrier and metabolic stability based on electrostatic molecular orbital studies. European Journal of Medicinal

Chemistry, 2014. **85**: p. 661-674.
18. Ullah, Z., et al., Dual-Action Compounds for Glycemic Control: N-Benzyl-2, 5-Dioxopyrrolidin-3-yl-Methanesulfonamide and 2-Benzylsuccinimide mimic α-Amylase and α-Glucosidase activities to regulate blood glucose levels. 2025.