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Synthesis, Characterization, Lethal dose (LD_{50}) and *In vivo* Acute Oral Toxicity Studies of a Novel 1,5-Benzothiazepine Derivatives

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KEYWORDS

Synthesis,Acute toxicity, LD_{50}, OECD.

ABSTRACT:

Background: Since they've numerous bioactivities, the 1, 5-benzothiazepines are enormous seven-member heterocyclic nitrogen and sulphur compounds in healing improvement. The maximum famous sort of 1,4-thiazepines are 1,5-benzothiazepines. The 1,5-benzothiazepine derivatives are of specific relevance for lead discovery because it has been located that they may be lively towards numerous objectives from numerous families.A benzene ring and a diazepine ring integrate to shape benzodiazepines (BZD, BDZ, BZs), a own circle of relatives of depressive drugs now and again stated as "benzos" or "benzos". They are advertised as a remedy for seizures, sleeplessness, and tension problems. 1,5-Benzothiazepines have inspired the improvement of some of artificial strategies for his or her synthesis and chemical changes because of their usefulness in pharmacological research.

Aim of Study: With the use of different dosages (10, 100, 1000, 1600, 2900, and 5000 mg/kg p.o. route), an unique series of the chosen 1,5-benzothiazepine derivatives were produced and tested for in vivo safety pharmacological tests (acute toxicity LD50).

Materials and methods: Completion of chemical response become monitored with the aid of using skinny layer chromatography on silica gel G covered plates and very last compounds had been purified with the aid of using recrystallisation with methanol. The chemical shape of synthesized had been prominent with the aid of using FTIR, 1H-NMR, Mass and elemental analysis. The LD50 of novel 1,5-benzothiazepine derivatives decided with the aid of using acute poisonous magnificence approach as consistent with OECD 423 guidelines.

Results and discussion: In the results of the spectral study, all the compounds showed characteristic peak in FTIR and ^{1}H-NMR spectroscopy. Compounds containing chlorine moiety show $[M+2]^+$ peak in mass spectrum. The result of in *vivo* acute oral toxicity studies showed that the compounds 6c1, 6e2 and 6e3 were toxic to mice and cause death at dose of 1600 and 2900 mg/kg body weight of live mice and LD50 of compounds 6c1: 4786 mg/Kg, 6e2: 2542 mg/kg and 6e3: 2039 mg/kg respectively.

1. INTRODUCTION

Discovering and creating novel drugs to treat diseases is the focus of the field of medicinal chemistry. The majority of this activity is focused on novel synthetic or natural medicines [1]. In order to help the frame heal and resume wholesome function, herbal remedy examines the frame`s everyday physiological techniques and digs deep to discover the underlying motives of illness.The pharmaceutical zone finds, creates, manufactures, and sells prescription drugs or pharmaceutical pills which are used as remedies for patients. Every year, hundreds of thousands of new pharmaceuticals are developed around the world, and many of them are put through pharmacological tests to see if they have any beneficial biological activity [2]. According to an intensive assessment of the literature and facts series at the 1,5-benzothiazepine nucleus, it became found that the moiety reveals a number of organic activities, consisting of antimicrobial [3], anti-inflammatory [4], anti-lung cancer [5], anti-malarials [6], anti-bacterial [7], anti-HIV [8], anti-angiogenic and antioxidant [9], anti-diabetic [10], anti-ulcer [11], anti Numerous commercially to be had medications, consisting of Clentiazem, Clothiapine, Diltiazem,

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Quetiapine, Siratiazem, etc., encompass the 1,5-benzothiazepine nucleus as their number one pharmacophore [14–16]. The target of present research was development and synthesis of new 1,5-benzothiazepine derivatives with minimum toxic effect. In 1,5-benzothiazepine the nucleus comprises of two fused ring system one ring is 6-membered and second one is 7-membered [14]. A cautious evaluation of the literature located that exceptional substitutions on the three and five places bring about a clinically applicable molecule. Studies at the substation had already been performed at numerous factors withinside the ring system. Our consciousness is totally on positions three and five. The alternative is made at function range three`s facet chain, and at function range five's H atom, a exceptional suitable substituent is utilized in its stead.Acute toxicity is usually described because the negative change(s) going on proper away or inside a brief time period after being uncovered to a substance or organization of substances, or as negative consequences going on inside a brief time period after administering a unmarried dose of a substance or more than one doses inside a 24-hour period.Testing for acute toxicity has primary goals: to examine extra approximately a chemical`s biologic interest and its mode of action. Typically, long-time period research start with a dose-locating workout in an acute setting. Additionally, the information on acute systemic toxicity produced through the take a look at is utilisedwithinside the context of chemical manufacture, handling, and utilization to perceive risks and manipulate risks.

Toxicological screening is crucial for both the identification of novel therapeutic agents and the improvement of the therapeutic potential of already known compounds [17]. Most frequently, toxicology assessments are achieved to have a look at unique quit desires or facet results, consisting of cancer, cardiotoxicity, and pores and skin and eye irritation. For medical studies, toxicity evaluation is beneficial in figuring out the no discovered unfavourable impact level (NOAEL) dosage [18]. The blessings of hazard ratio calculation and healing index prediction, which might be produced as a ratio of most tolerated dosage and minimum healing dose and are said with the aid of using the subsequent equation, are vital for toxicological research.

The dose that effects in a "acceptable" degree of toxicity or that, if surpassed, could situation animals or humans to a "unacceptable" threat of toxicity is called the "most tolerable dose" (MTD), additionally referred to as the "most tolerated dose" or the "maximally tolerated dose". Maximum tolerable dose divided with the aid of using healing index (Minimum healing dose).Toxicology checks are a methodical evaluation of the damaging consequences that a substance may also have; they can't show a substance is absolutely harmless. It takes a lot of computational, cell-primarily based totally, and animal-primarily based totally strategies to derive this expertise a good way to expect human reactions without the usage of human subjects.

The more secure the drugs are, the decrease the ratio has to be [17]. The purpose of the modern in vivo protection pharmacology research became to decide how the unfavourable results of 1,5-benzothiazepine derivatives reply to dosage. In the present study selected 1,5-benzothiazepine derivatives under research have been given at diverse dosages, and the effects have been tracked after 14 days. Throughout the trial period, all deaths introduced on through 1,5-benzothiazepine derivatives have been documented. Animal behavioural abnormalities have been additionally checked out and documented.

2. EXPERIMENTAL SECTION

2.1. Materials and Methods

All the solvents and reagents used for the synthesis of novel compounds were purchased from S.D. Fine Chemicals and E. Merck. The melting point ranges of all the novel synthesized compounds were determined by open tube capillary method[20] by melting point test apparatus (Medicraft Pharmaceutical Pvt. Ltd.). TLC become used to examine the stop product and intermediate merchandise of chemical processes, the usage of the cell segment using methanol and chloroform (9:1). The infrared spectrometer at the Perkin-Elmer FTIR-8400S (synthetic through SHIMADZU, Japan) hired KBr pressed pellet processes to validate the chemical systems of newly produced substances. Molecular mass become decided the usage of the Micromass ESI-MS the usage of ESI technique and proton NMR spectra on a Bruker DRX300 in DMSO-d6 at 300MHz. Carlo Erba`s EA 1108 defines elemental analysis.

2.2 General procedure for synthesis of lead compound: The basic nucleus i.e. the lead compound of 1, 5-Benzothiazepine was synthesized in three steps-

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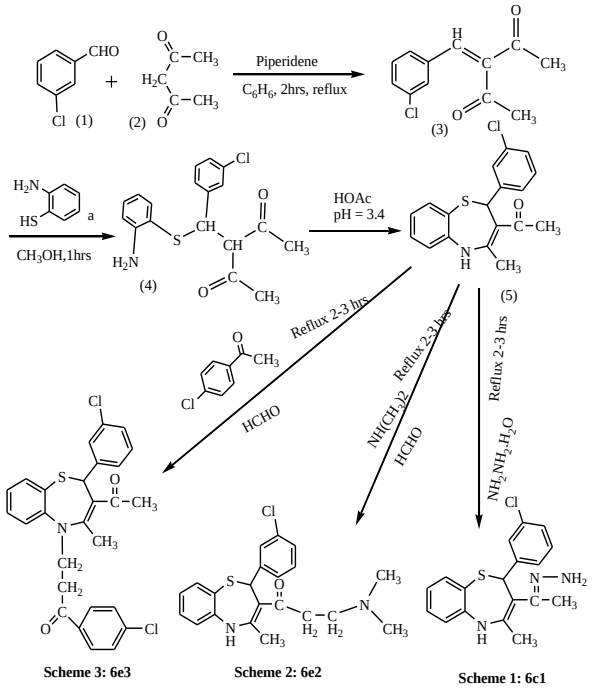
Step-1: Knoevenagel condensation of aromatic aldehydes (1) with 2, 5-pentadione (2) in dry benzene catalyzed by piperidine.

Step-2: The Michal addition of *o*-aminothiophenol (a) to the above compound yielded the corresponding pentadione derivative (4).

Step-3: Intramolecular cyclization followed by dehydration in strong acid yielded 1, 5-Benzothiazepine (5).

Step-4:

- Scheme-1: Schiff's base (compound 6c1) was synthesized by reacting compound (5) withhydrazine hydrate.
- Scheme-2: Compound (5) become reacted with dimethyl amine withinside the presence of formaldehyde to create a 3-substituted mannich base (compound 6e2).
- Scheme-3:Compound (5) and p-chloroacetophenone had been mixed to create compound (6e3), a 5-substituted mannich base, even as formaldehyde turned into gift withinside the reaction.



Schemes: Synthesis of 1,5-Benzothiazepine derivatives

2.3 Animals and Environment condition

Swiss albino mice of both sex, weighing 20–25g, had been bought from the Lucknow-primarily based totally Central Drug Research Institute`s Laboratory Animal Facility. For every week earlier than and after the trials, they had been housed in an animal housing with well-crossed ventilation, a room temperature of 25°C, a relative humidity of 44-56%, and mild and darkish cycles of 10 and 14 hours, respectively. Animals had been given a ordinary mouse pellet eating regimen from Bharat Ansh Scientific Industries, with meals eliminated 18–24 hours earlier than to the test and limitless get right of entry to to water. The Institutional Animal Care Committee, CPCSEA, India, followed and posted the steering for the care and use of laboratory animals (Reg. No. 1957/PO/Re/S/17CPCSEA), that is observed through all investigations.

2.4 *In vivo* acute toxicity (LD_{50}) studies

In the acute oral toxicity study as per OECD 423 guidelines [21], To take a look at the toxicity consequences of positive 1,5-benzothiazepine derivatives, fifty four Swiss albino mice had been used. According to the findings, fatalities had been recorded and intense toxicological signs and symptoms had been observed within side the examined mice as early because the decrease dosage. The bodily traits of the animals, together with their hair, expanded tails, salivation, and paw licking, confirmed that the selected 1,5-benzothiazepine derivatives did impact them [17–19]. In steps, the albino mice had been coded, weighed, and randomly divided into 3 agencies with 3 mice in every group. Phase I worried the oral management of 10, 100, and one thousand mg/kg frame weight of the produced materials 6c1, 6e2, and 6e3 in 30% v/v PEG400 aqueous approach to 9 mice randomly divided into 3 agencies of 3 animals every.

In phase II, a brand new batch of 9 mice turned into randomly divided into 3 organizations of 3 animals, and 1600, 2900, and 5000 mg/kg of frame weight of the artificial compounds 6c1, 6e2, and 6e3 had been administered orally in a 30% v/v PEG400 aqueous solution. Following the management of the check substance, get entry to foods and drinks turned into halted for round hours. Clinical symptoms and symptoms and signs and symptoms for the primary 24 hours, with unique attention starting four hours later and persevering with each day for the subsequent 14 days after the check medicinal drug management. Additionally, elements which includes righting reflux,

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gripping, pupils, ache response, tremors, convulsion, pores and skin colour, corneal reflex, salivation, torch response, water intake, meals intake, sleep, diarrhoea, grooming, urination, alertness, lethargy, contact response, coma, and mortality had been determined according with OECD guidelines. Dose/Log10 dose and % mortality of compounds 6c1, 6e2 and 6e3 were presented in table 1-3. The geometric suggest of the successive doses for which 0% and 100% survival charges have been recorded with inside the 2nd section turned into used to calculate the geometric suggest of the oral median deadly dose, and the LD50 turned into then calculated because the rectangular root of the made from the bottom deadly dose and maximum non-deadly dose:

$LD_{50}=\sqrt{}$(Minimum toxic dose × maximum toxic dose)

Verified through a graph displaying the connection among the loss of life charge as a percent and the wide variety of doses given. The acute poisonous elegance technique (OECD TG 423) take a look at standards of the Organization for Economic Cooperation and Development (OECD) had been well followed.

Table 1: Dose/Log10 dose and % mortality of compound 6c1

Dose (mg/kg)	Log10 Dose	% Mortality	Sign of Toxicity
10	1	0	none
100	2	0	none
1000	3	0	none
1600	3.2	0	none
2900	3.5	33.3	sleep
5000	3.7	66.7	salivation

Table 2: Dose /Log10 dose and % mortality of compound 6e2

Dose (mg/kg)	Log10 Dose	% Mortality	Sign of Toxicity
10	1	0	none
100	2	0	none
1000	3	0	none
1600	3.2	33.3	coma
2900	3.5	66.7	erect fur
5000	3.7	66.7	coma

Table 3: Dose /Log10 dose and % mortality of compound 6e3

Dose (mg/kg)	Log10 Dose	% Mortality	Sign of Toxicity
10	1	0	none
100	2	0	none
1000	3	0	none
1600	3.2	66.7	sleep
2900	3.5	66.7	coma
5000	3.7	100	convulsion

2.5 Statistical analysis

The ANOVA became used to assess all of the values that have been stated as Mean Standard mistakess mean (SEM), and the a couple of contrast checks have been implemented the usage of the Dunnett`s test. Graph Pad Prism five model software programs became used to assess and gather all the statistical data.

3. RESULTS AND DISCUSSION

3.1. Chemistry

A novel series of schiff bases and mannich bases were synthesized in satisfactory yield (49-84%). The physicochemical properties, m.p. $R_f$and % yield and characterization of chemical structure by spectroscopic (FTIR, ^{1}H-NMR, MASS) and elemental methods.

3.1.1 Compounds Details

{1-[3-Chlorophenyl-4-methyl-2,5-dihydro-1,5-benzothiazepin-3-yl]-ethylidene} hydrazine(6c1): Molecular formula $C_{18}H_{18}ClN_3S$; Molecular weight 343; Yield 49%; FTIR (KBr) ν, cm^{-1}): 3414 (N-H_{str}), 3093 (Ar. C-H_{str}), 2977 (Ali. C-H_{str}), 1618 (Ar. C⋯C$_{str}$), 1548 (C=N_{str}), 1461 (Ar. C-C_{str}), 1274 (Ar. C-N_{str}), 1074 (Ar. C-Cl_{str}), 721 (C-H *m*-disub. benzene), 645 (C-S_{str}); ^{1}H NMR, δ ppm: 1.220 (s, 3H, CH_3), 2.200 (s, 3H, CH_3), 4.122 (s, 2H, NH_2, D_2O exchange), 6.167 (s, 1H, Ar-H), 7.123-7.169 (t, 2H, Ar-H), 7.363-7.367 (d, 1H, Ar-H), 7.500-7.534 (t, 1H, Ar-H), 7.705-7.721 (d, 2H, Ar-H), 7.902 (s, 1H, Ar-H), 7.910-8.032 (d, 1H, Ar-H), 9.140 (s, 1H, N-H, D_2O exchange); MS (m/z): 344 $[M+1]^+$; 345 $[M+2]^+$; Elemental analysis: C, 62.82, H, 5.31, N, 13.83, S, 10.22, Cl, 10.21 %. Atypical antipsychotic clotiapine (Entumine) belongs to the dibenzothiazepine chemical family.

3-(Dimethylamino)-{1-[3-chlorophenyl-4-methyl-2, 5-dihydro-1,5-benzothiazepin-3-yl]}propan-1-one(6e2): Molecular formula $C_{21}H_{23}ClN_2OS$; Molecular

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weight 386; Yield 53%; FTIR (KBr) ν, cm^{-1}): 3419 (N-H_{str}), 2996 (Ar. C-H_{str}), 2909 (Ali. C-H_{str}), 1799 (C=O_{str}), 1674 (Ar. C⋯C$_{str}$), 1583 (Ar. C-C_{str}), 1313 (Ar. C-N_{str}), 1174 (Al. C-N_{str}), 1074 (Ar. C-Cl_{str}), 756 (C-H *m*-disub. benzene), 678 (C-S_{str}); ^{1}H NMR, δ ppm: 1.423-1.483 (m, 6H, CH_3), 2.142 (s, 3H, CH_3), 2.410-2.427 (t, 2H, CH_2), 2.616-2.665 (t, 2H, CH_2), 6.213 (s, 1H, Ar-H), 7.680-7.727 (m, 8H, Ar-H), 8.427 (s, 1H, N-H, D_2O exchange); MS (m/z): 387 $[M+1]^+$; 388 $[M+2]^+$; Elemental analysis: C, 65.18, H, 5.99, N, 7.24, S, 8.29, Cl, 9.16 %. This own circle of relatives of indole alkaloids is maximum usually composed of the hapalindoles, which account for as a minimum 31 molecules.

3-Acetyl-2-(3-chlorophenyl)-4-methylbenzo[b][1,4]thiazepin-5(2H)-yl)-1-(4-chlorophenyl)propan-1-one (6e3) Molecular formula $C_{27}H_{23}Cl_2NO_2S$; Molecular weight 495; Yield 84%; FTIR (KBr) ν, cm^{-1}): 3082 (Ar. C-H_{str}), 2977 (Ali. C-H_{str}), 1809 (C=O_{str}), 1604 (Ar. C⋯C$_{str}$), 1284 (Ar. C-N_{str}), 1174 (Al. C-N_{str}), 833 (C-H p-disub. benzene), 754 (C-H m-disub. benzene), 644 (C-S_{str}), 603 (Ar. C-Cl_{str}); ^{1}H NMR, δ ppm: 1.329 (s, 3H, CH_3), 2.089 (s, 3H, CH_3), 2.821-2.983 (m, 4H, CH_2), 6.239 (s, 1H, Ar-H), 7.740-7.961 (m, 12H, Ar-H); MS (m/z): 497 $[M+1]^+$, 498 $[M+2]^+$; Elemental analysis: C, 64.64, H, 4.24, N, 2.48, S, 5.67, Cl, 13.**27** %.Loratadine is a member of the elegance of medication referred to as antihistamines. Various allergic reaction issues are dealt with with it. It eases symptoms and symptoms consisting of rashes, swelling, and itching.

3.2 *In vivo* acute toxicity (LD_{50}) studies

Traditional in vivo toxicology researches encompass administering a chemical to businesses of animals-generally rats and mice-at numerous dosages and tracking their reactions. Table 1-three summarises the findings of the Phase I and II in vivo acute toxicity (LD50) exams. To make sure the protection and efficacy of the selected 1,5-benzothiazepine derivatives, the in vivo acute toxicity (LD50) research of these compounds have been screened. The in vivo exams located proof of toxicity withinside the shape of physical changes, discomfort, distress, allergic responses, and different signs and symptoms withinside the studied animals.The 1,5-benzothiazepine derivatives have caused acute toxicity effects and cause death at dose of 1600 and 2900 mg/kg body weight of live mice.The lethal dose for half of the animal number (LD_{50}) values of compounds 6c1: 4786 mg/Kg, 6e2: 2542 mg/kg and 6e3: 2039 mg/Kg respectively. **Fig. 1-3** suggests the mortality percent vs log 10 dose graph for compounds 6c1, 6e2, and 6e3. The findings mean that the excessive LD50 values of unique compounds might also additionally function a supply for the advent of prescription drugs that can be used to deal with quite a few illnesses.

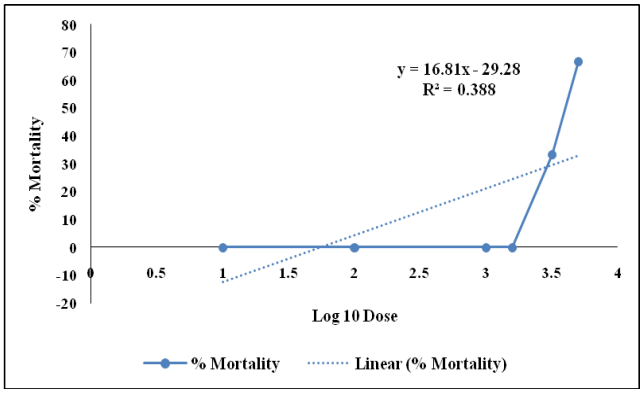

Figure 1: Graph of % mortality versus log 10 Dose of compound 6c1

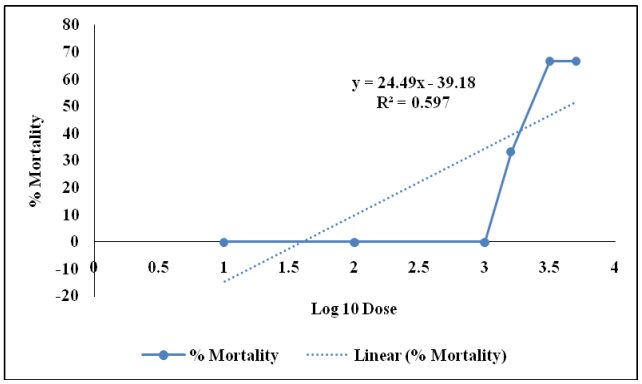

Figure 2: Graph of % mortality versus log 10 Dose of compound 6e2

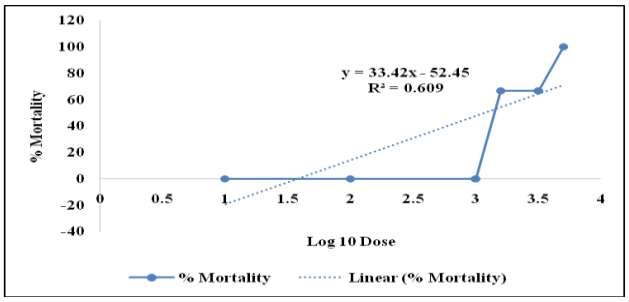

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Figure 3: Graph of % mortality versus log 10 Dose of compound 6e3

4. CONCLUSION

This examine covers a number of of recent 1,5-benzothiazepine compounds that had been correctly synthesised with perfect yield. Various spectroscopic methods, which include chromatography, 1H-NMR, FTIR, MS, and elemental analysis, had been used to explain the brand new compounds. In order to evaluate the steadiness and solubility of the synthesised derivatives, physicochemical traits had been studied. The selected 1,5-benzothiazepine compounds had LD50 values of 4786, 2542, and 2039 mg/kg, respectively, of the animal`s weight.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The Institutional Animal Care Committee, CPCSEA, India, followed and posted the steering for the care and use of laboratory animals (Reg. No. 1957/PO/Re/S/17CPCSEA),

HUMAN AND ANIMAL RIGHTS

CPCSEAR guidelines were followed for animal experimentation.

CONFLICT OF INTEREST

None.

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