SYNTHESIS AND CHARACTERIZATION OF SOME NOVEL THIAZOLIDINE DERIVATIEVES AND ITS BIOLOGICAL EVALUATION

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ABSTRACT

Thiazolidine derivatives TZ-1 to TZ-6 were synthesized, characterized by the spectral analysis and screened for anti anti-helminthic activity and anti oxidant .*in vitro* method using piperazin citrate as standard. *In vitro* anti ulcer activity by acid neutralizing capacity(ANC).

0.1 mol of crude drug was added with various aromatic aldehydes was dissolved in 25 ml of ethanol and stirred for 25 mins, after which it was filtered and recrystallized with ethanol, and 0.1 mol of crude product was added into 0.1 mol of thaioglycolic acid in 40 ml of N,N-dimethylformide to the above mixture pinch of zinc chloride is added. After another 4 hours of magnetic stirring at 60 degrees Celsius, this reaction was filtered and recrystallized with ethanol.

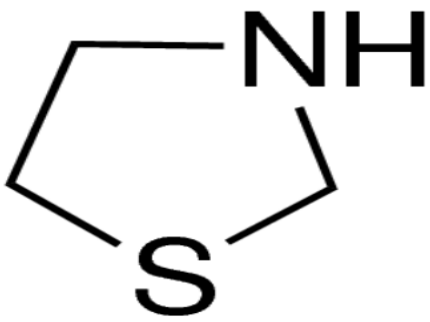
IR, NMR, and mass spectroscopy are used in the spectroscopical approach to characterize the freshly synthesized derivatives. Using piperazine citrate as a benchmark, the selective derivatives of the title chemical are tested for in-vitro anthelmentic activity. The chemical (TZ6,TZ4) exhibits stronger anthelmentic action and more potent activity. anti-ulcer activity by acid-neutralizing capacity method. It displays more powerful activity in (TZ1,TZ3).

KEY WORDS: thiazolidine, anti-helmenthic activity, anti ulcer activity,

INTRODUCTION

Thiazolidine is a five-membered heterocyclic compound containing a sulfur atom (S) and a nitrogen atom (N) in the ring. It has gained significant interest in medicinal chemistry and pharmaceutical research due to its versatile chemical properties and wide potential applications[1]. Thiazolidine derivatives have shown promise in various therapeutic areas, including anti-inflammatory, antimicrobial, anticancer, and antioxidant activities[2,3].

The historical background and discovery of thiazolidine date back to the early 20th century. They discovered thiazolidine during their studies on the reaction between hydrazine and ketones[4]. The name "thiazolidine" is derived from the fusion of two terms: "thio" (indicating the sulfur atom) and "azolidine" (referring to the five-membered heterocyclic ring)[5]. Gabriel and Colman initially named the compound "hydrazinobenzoylthiazolidine," emphasizing its relationship to hydrazine and its benzoyl derivative[6,7].



MATERIALS AND METHODS

All the chemicals and solvents used were of synthetic grade from finer chemicals melting point were determined in open capillary tubes using melting point appratus .purity of the compounds was verified by single spot in TLC , 0.25mm aluminium plates with mobile phase benzene and acetone (7:3) .The IR spectra were recorded on SCHIMADZU FT-IR by using 1% potassium bromide discs.

Experimental methodology[13-20]

Step:1 Synthesis of 4- amino benzhydrazide

Take para amino benzoic acid (PABA) (3.mmol) was grind with Hydrazine hydrate (80% 3.75 mmol) by motor and pestle for 3-5 minutes and left for digestion for (10min) when the reaction mixture set into a solid mass the completion of the reaction was checked by a thin layer chromatography .the solid mass was crystalized from ethanol to give hydrazides[8].

Step: 2 Preparation of 2-methyl-6 nitro-1H-thyazolidine

A mixture of 0.01 mole of step 1 product , different aromatic aldehydes mentioned above in table no.(0.01 moles) was dissolved absolute ethanol (25ml) and magnetic stirred for 15-20 min. the reaction mixture was poured onto crushed ice , the solid thus filtered off and washed with water and recrystallized with ethanol[9.]

Step: 3 Preparation of thiozolidine derivatives

0.01mol of step 2 product and 0.01mol of thioglycolic acid in 40ml of N, N-Dimethyl formamide to the above mixture a pinch of Zncl2 was added and the reaction mixture was undergone for continuous stirring with the constant maintenance of temperature of 60^0 C for 4 hours, after the completion of reaction the reaction mixture was poured into crushed ice and the solid obtained was filtered, dried and recrystallized from ethanol[10,11].

Biological activities:

Anthelmentic activity

For all of the newly synthesised derivatives, adult earthworms measuring 4-5 cm in length and 0.1-0.2 cm in width were utilised. All of the earthworms were gathered in the AP Indian district of Anantapur. Six worms were placed in each of the groups that were formed from the worms. To assemble the concentrations of 5, 10, and 20 mg/ml, all of the recently synthesised derivatives were dissolved in a minimum of 2% v/v Tween 80 and the volume was increased to 10 ml with normal saline. All of the

derivatives and standard medication solutions were newly made prior to the start of the tests. Before being discharged into 10 ml of the appropriate formulation, each earthworm was thoroughly cleaned in normal saline solution[12]. The formulations were as follows: vehicle (2% v/v Tween 80 in normal saline), albendazole (20 mg/ml), and derivatives (5,10,20 mg/ml). Six observations were made for each petri dish containing six worms of the same size in order to determine the anthelmintic activity. They were practical since they moved naturally and elicited reactions. Individual worms' paralysis and deaths were tracked in terms of timing[13]. When the worms failed to awaken even in regular saline, paralysis was thought to have occurred. Worms were said to have died when they stopped moving, which was followed by the fading of their body colour.

Anti-ulcer activity

The typical antacid, AHMH (aluminium hydroxide + magnesium hydroxide - 500mg/ml), was compared to freshly synthesised prototypes at different concentrations (10 mg/ml, 20 mg/ml, 40 mg/ml, 60 mg/ml, 80 mg/ml, and 100 mg/ml) for acid neutralising capacity[14]. Water was added and well mixed with the 5ml amount of each extract to get the 70 ml total volume. Following the addition of 30 ml of 1N HCL and 15 minutes of stirring the standard and test preparation, 2–3 drops of phenolphthalein solution were added and combined[15]. The excess HCL was immediately titrated with 0.5N sodium hydroxide solution dropwise until a pink colour appeared. The moles of acid neutralized is calculated by[16.]

Moles of acid neutralized = (vol. of HCL ×normality of HCL) – (vol. of NaOH × normality of NaOH)

Acid neutralizing capacity (ANC) per gram of antacid = moles of HCL neutralized / grams of antacid

Synthetic scheme :

SCHEME:

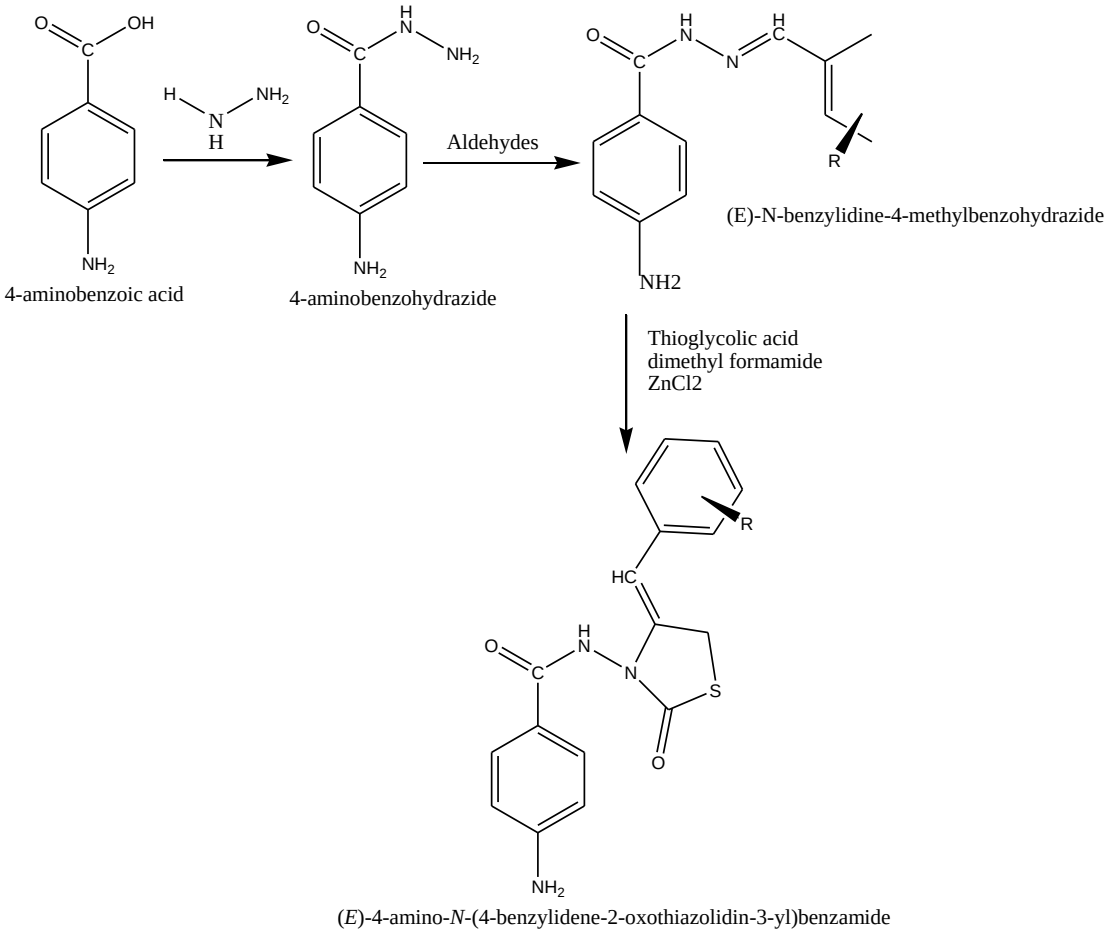


Fig:1 scheme for thiozolidine

RESULTS AND DISCUSSION

Characterization:

Compound (TZ_1):

IR (KBr in cm^{-1}): C=C stretch 2523.06, C-C Stretch 1610.37, Aromatic 1810.2, C-NH Stretch 3273.4, C-Cl Stretch 746.16

NMR chemical shift (δ, ppm): 2.2 (S,1H, CH, ArCH),7.2-7.8 (M, Ar CH,14H),8,4 (S, NH,1H)

Mass: Base peak 79.20000, molecular ion peak 368.71

Compound (TZ_2):

IR (KBr in cm^{-1}): N-H Stretch 3419.3, C=C Stretch 1632.2, C-O Stretch 1133.1, C-N Stretch 1316.1, Aromatic Stretch 1600.6

NMR chemical shift (δ, ppm): 1.3 (S, CH,1H, Ar CH), 7.3-7.8 (M, Ar-H, 12H),8.6 (S,1H, NH)

Mass: Base peak 384.00, Molecular ion peak 341.29

Compound (TZ_3):

IR (KBr in cm^{-1}): N-H Stretch 3319.3, C=C Stretch 1702.2**,** C=N Stretch 1543.1, C-HStretch1412.1, Aromatic 1612.6

NMR chemical shift (δ, ppm): 1.3 (S,1H, CH),1 (solvent peak),7.3-7.8 (M,12H), 7(S,1H, NH)

Mass: Base peak 79.30000, Molecular ion peak 343.38

Compound (TZ_4):

IR (KBr in cm^{-1}): Aromatic1642.3, C=CStretch 1602.2 **,**C-H Stretch 1153.1, C-N Stretch 1206.1 ,O-H Stretch 3043.6

NMR chemical shift (δ, ppm): 1(S,1H, CH) , 5.5 (S,OH, 1H), 7-7.7 (M, Ar-H,12H), 8.6 (S,NH, 1H, Ar-CH).

Mass: Base peak 79.2500, Molecular ion peak 359.83

Compound (TZ_5):

IR (KBr in cm^{-1}): N-H Stretch 3312.3, C=CStretch 1602.2, C-O Stretch1103.1, C=NStretch 1646.1, Aromatic C-H Stretch1602.6

Compound (TZ_6):

IR (KBr in cm^{-1}): N-H Stretch 3329.3, C=CStretch 1622.2, C=N Stretch1516.1, Aromatic C-H Stretch 1623.6

In-vitro anthelmentic activity

The synthetic derivatives of antihelmintic activity were performed by using the adult earth worms 4-5 cm in length and 0.1-0.2 cm in width against the standard drug Albendazole , the results as shown in the table.

Table no 2: In vitro anthelminthic activity

COMPOUNDS	Time taken for Paralysis (min)			Time taken for death (min)		
	25mg/ml	**50mg/ml**	**100mg/ml**	**25mg/ml**	**50mg/ml**	**100mg/ml**
TZ_1	39.09±1.25	20.47±1.04	15.24±1.5	70.21±2.74	34.13±1,17	26.41±1.10
TZ_2	37±2.50	27.43±1.87	17.01±2,46	63.09±1.03	23.33±2.57	18.25±1,62
TZ_3	28.19±2.34	22.58±2.03	19.46±2.37	48.18±2.47	20.06±1.84	17.53±2.07
TZ_4	29.17±2.23	23.32±2.46	14.32±1.74	41.29±2.35	15.42±2.78	13.34±1.31
TZ_5	43.52±1.08	36.56±1.98	18.33±1.09	69.45±1.35	36.28±1.76	28.36±2.88
TZ_6	23 .02±1.87	14.35±2.47	11.42±2.05	12.38±0.98	9.54±2.88	9.36±1.87
Standard(piperazine citrate(20mg/ml)	25.26±1.5			59±6.8		

In- vitro anti-ulcer activity

The synthesized compounds were evaluated for their in vitro anti-ulcer activity by Acid Neutralizing Capacity (ANC) method.

The synthesized derivatives of benzimidazole are performed the antiulcer activity against the standard aluninium hydroxide and magnesuim hydroxide.

Table no 2: In-vitro antiulcer activity by Acid Neutralizing Capacity (ANC) Method

CONCENTRATION Mg/ml	ANC per gram of drug					
	BI_1	BI_2	BI_3	BI_4	BI_5	BI_6
50	190	200	160	182	130	202
100	70	90	110	65	78.5	64
150	81	80	56.6	39.3	42.5	46.3
200	51.25	53.25	32.25	34.25	50.25	50.5
250	26	32	34.4	41	36.4	32.2
500	15.5	21.5	17.9	18.8	19.7	20.1
$Al(OH)_2$ &$Mg(OH)_2$ (500mg/ml)	10.7					

Discussion

The present research work, involves the synthesis of series of 6 novel substituted compounds of thiazolidine. This compound is treated with various aldehydes to form thiazolidine derivatives. Purification was done by recrystallization. Characterization of all derivatives were done by FT-IR.

All derivatives were screened for their *in-vitro* anthelminthic and anti-ulcer activities.

Anthelminthic activity

In-vitro anthelminthic activity was performed by using earthworms, and Albendazole as the reference standard. All the titled compounds (TZ_1-TZ_6) were evaluated for *in-vitro* anti helminthic activity. The effect of the synthesized titled compounds was tested with different concentrations (25, 50, and 100 mg/ml). All derivatives were able to inhibit anti-helminthic activity. The most effective was TZ_6, TZ_4 shows more potent activity. The results were tabulated in table no.2 The order of anthelminthic activity of synthesized compounds as follows.

$$TZ_6 > TZ_4 > TZ_3 > TZ_2 > TZ_1 > TZ_5$$

Anti ulcer activity

In-vitro anti-ulcer activity was performed by using Acid neutralizing capacity (ANC), were compared with the standard antacid AHMH (aluminum hydroxide + magnesium hydroxide. All the titled compounds (TZ_1-TZ_6) were evaluated for *in-vitro* anti -ulcer activity. The effect of the synthesized titled compounds was tested with different concentrations (50, 100, 150, 200, 250, and 500 mg/ml). All derivatives were able to show anti-ulcer activity. The most effective was TZ_1, TZ_3 shows more potent activity. The results were tabulated in table no. 3 The order of anti-ulcer activity of synthesized compounds as follows.

$$TZ_1 > TZ_3 > TZ_4 > TZ_5 > TZ_6 > TZ_2$$

CONCLUSION

Six substituted thiazolidine derivatives were synthesized and characterized by using physical data (solubility, melting point and TLC monitoring) and spectral data (FT-IR).

All the derivatives were evaluated for biological studies like in-vitro anthelminthic activity and invitro anti ulcer activity. The electron withdrawing groups such as amino, Nitro, containing compounds (TZ_1, TZ_6) has shown the highest activity and the rest of compounds having electron donating groups (TZ_2 TZ_3, TZ_4 TZ_5) shows mild to moderate activity. In brief electron withdrawing groups containing compounds possess potent activity than that of compounds containing electron donating groups.

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