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SYNTHESIS AND EVALUATION OF DERIVATIVES OF THIAZOLIDINE-4-ONE FOR POTENTIAL BIOLOGICAL ACTIVITY

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ABSTRACT

The aim of present study was to synthesize a new series ofthiazolidine-4-one from schiff bases of Indole-3-carboxaldehyde,reaction with different Anilines. The structure of synthesized compounds was established by IR and ^{1}H-NMR method. The antimicrobial activity of the synthesized compounds was checked in which the compounds TZ_1, TZ_4 and TZ_6showed good activity against, gram positive bacteria Bacillus subtilis and compounds TZ_2, TZ_3 and TZ_5 showed good activity againstgram-negative bacteria *Escherichia-coli*, as compared to standard drug, ampicillin.

Keywords: Thiazolidine-4-one, antimicrobial activity, Schiff base

INTRODUCTION

It is well known that a number of heterocyclic compounds containing nitrogen, oxygen and sulphur, exhibits a wide variety of biological activity. Thiazolidinediones are the derivatives of thiazolidine which belongs to an important group of heterocyclic compounds containing sulphur and nitrogen in a five-member ring. The derivatives of these compounds possess different types of biological activities**.** In the presence of various reagents, thiazolidinones undergoes different types of reactions to yield other heterocyclic compounds. e.g. Thiazole, benzimidazole, thiopyranothiazolone, benzodiazepine triazoles, benzothiophenes etc. Thiazolidin-4- one has been considered as a magic moiety which possess almost all types of biological activities. This diversity in the biological activity profile has

attracted the attention of several researchers to explore this skeleton to its multiple potential against several activities. Thiazolidin-4- ones or 4-thiazolidinones are the derivatives of thiazolidine with a carbonyl group at the 4th position andsubstitution is feasible at 2, 3 and 5 positions. The carbonyl group of thiazolidn-4- one is highly unreactive. But in a few cases, thiazolidin-4-one on reaction with Lawson's reagent gives corresponding 4-thione derivatives. The thiazolidine ring system represents a very important structural unit in drug discovery. From the recent studies its revealed that extensive researchhave been carried out on the synthesis of thiazolidines. These compounds are known to exhibits interesting biological activity such as antimicrobial **[2-3, 6-8]**, antitubercular **[6-8]**, anti-cancer **[5, 8-9]**, antiviral **[4, 8]**, anti-HIV **[9]**, anti-inflammatory **[3, 12]** and anti-hyperglycemic effects **[1, 10-11]**. The presence of electron-withdrawing substitution on aromatic ring on C-2 position of 4-thiazolinone presenting varied degrees of inhibition against gram-positive and gram-negative bacteria, showing inhibition as good as to the standard drugs.

MATERIAL AND METHODS

Analytical grade material and reagents were used for the study. The reactions were checked by TLC, using Silica-G as stationary phase and spots were detected by Iodine chamber. Melting point was determined by Decibel melting point apparatus and are uncorrected. The I.R. spectra were recorded on, Perkin Elmer BX II FTIR spectrophotometer using KBr disks. The ^{1}H nuclear magnetic resonance spectra were recorded on Bruker AVANCE (400MHz) NMR instrument. Chemical shift is expressed as δ values (ppm) downfield from tetramethyl silane (TMS) used as internal standard. Splitting patterns are presented as s, singlet; d, doublet; t, triplet; and m, multiplet.

Experimental procedure

The schematic representation of synthesized compounds (TZ1-TZ9) was summarized in **Figure 1**. The physical data of synthesized compounds were given in **Table 1**.

Synthesis of Indole-3-carboxaldehyde

A three necked round bottom flask fitted with a mechanical stirrer, a drying tube containingcalciumsulphateand a 125ml dropping funnel is placed. 2 ml of freshly distilled Dimethylformamide (DMF) were added in flask. The flask was cooled in an ice bath for about 0.5 hours and 0.8 ml of freshly distilled, Phosphorus oxychloride were added into flask with stirring over a period of 0.5 hours. The pinkish colourwas observed during this step. The 125ml dropping funnel is replaced with a 200ml dropping funnel and a solution of 0.1gm Indole were prepared in 1.8ml of DMF.

This solution was added into the pinkish solution of the flask over a period of one hour with continuous stirring, in which temperature of the solution was not allowed above 10ºC. Once the solution is well mixed the dropping funnel was replaced with a thermometer and the temperature of the viscous solution brought to 35ºC. The solution was stirred effectively at35ºCtemperature for one hour, after which an opaque, canary-yellow paste was obtained. At the end of the reaction 300gm crushed ice was added to the paste carefully with stirring, which produced aclear, cherry-red solution. This solution was transferred with 10ml of water to the three necked round bottom flasks contained 200gm crushed ice, fitted with a mechanical stirrer and a separation funnel contained a solution of 3.7gm sodium hydroxide in water. The one third aqueous base solution were added drop wise into the flask with stirring and remaining were added rapidly with stirring. The resulted suspension was heated rapidly to boiling point and were allowed to cooled at room temperature. This suspension was placed in a refrigerator overnight. The precipitates were collected on filter paper and resuspended in the water. Most of inorganic materials were dissolved in the water and the product were collected on filter paper and air dried.

Synthesis of the Schiff bases

The Indole-3-carboxaldehyde, were taken in round bottom flask, contained ethanol. The aniline, were added into the flask and few drops of glacial acetic acid were added. The solution was refluxed for about 4-8 hours. Then content was cooled, filtered and dried.

Synthesis of Thiazolidine-4-ones

The synthesis of Thiazolidine-4-ones, were carried as follow: -

A well stirred solution of schiff base were added in round bottom flask in the dry DMF, contained pinch of anhydrous Zinc chloride. The thioglycolic acid were added into this solution. The solution was refluxed for about 8-10 hours. After that the solution were cooled and poured in cold water. Then solution was filtered, washed with water and recrystallized to rectified spirit.

5-(1H-indol-3yl)-3-(4-nitrophenyl)-thiazolidine-4-one

Yield: 80.2%, m.p: 220-223 0C, IR (KBr,Vmax, cm-1): 3296.46 (N-H str.), 1749.49 (C=O of β-lactum), 1664.62 (C=O of coumarin), 1292.35 cm-1(Ar-OCH3**);** 1H -NMR (400 MHz, DMSO- *d6*) δ 6.40-7.70 (m,11H, Ar-H); 3.76 (s,1H, C-NH); 8.19 (d, 1H, H at C-5 of coumarin), 5.75 (s, 1H, H at C-3of coumarin), 3.38 (S,3H,-OCH3), 4.10 (s,2H,CH2); C, 60.17; H, 3.86; N, 12.38; O, 14.14; S, 9.45.

5-(1H-indol-3yl)-3-(2-nitrophenyl)-thiazolidine-4-one

Yield: 82.1%, m.p: 210-212 0C, IR (KBr, cm-1): 3296.46 (N-H str.), 1749.49 (C=O of β-lactum), 1664.62 (C=O of coumarin), 1292.35 cm-1(Ar-OCH3**);** 1H -NMR (400 MHz, DMSO- *d6*) δ 6.40-7.70 (m,11H, Ar-H); 3.76 (s,1H, C-NH); 8.19 (d, 1H, H at C-5 of coumarin), 5.75 (s, 1H, H at C-3 of coumarin), 3.38 (S,3H, -OCH3), 4.10 (s,2H, CH2); C, 74.13; H, 4.26; N, 12.88; O, 14.6; S, 9.12.

5-(1H-indol-3yl)-3-(4-chlorophenyl)-thiazolidine-4- one

Yield: 77.4%, m.p: 222-2260C, IR (KBr, cm-1): 3296.46 (N-H str.), 1749.49 (C=O of β-lactum), 1664.62 (C=O of coumarin), 1292.35 cm-1(Ar-OCH3**);** 1H -NMR (400 MHz, DMSO- *d6*) δ 6.40-7.70 (m,11H, Ar-H); 3.76 (s,1H,C-NH); 8.19 (d, 1H, H at C-5 of coumarin), 5.75 (s, 1H, H at C-3of coumarin), 3.38 (S,3H,-OCH3), 4.10 (s,2H,CH2); C, 62.10; H, 3.98; N, 8.52; O, 4.87; S, 9.75; Cl,10.78

5-(1H-indol-3yl)-3-(2-chloro-4-nitrophenyl)-thiazolidine-4-one

Yield: 74.6%, m.p: 230-2340C, IR (KBr, cm-1): 3296.46 (N-H str.), 1749.49 (C=O of β-lactum), 1664.62 (C=O of coumarin), 1292.35 cm-1(Ar-OCH3**);** 1H -NMR (400 MHz, DMSO- *d6*) δ 6.40-7.70 (m,11H, Ar-H); 3.76 (s,1H, C-NH); 8.19 (d, 1H, H at C-5 of coumarin), 5.75 (s, 1H, H at C-3of coumarin), 3.38 (S,3H, -OCH3), 4.10 (s,2H, CH2); C, 66.70; H, 5.16; N, 12.29; O, 11.58; S, 9.49.

5-(1H-indol-3yl)-3-(2, 3-dimethylphenyl)-thiazolidine- 4-one

Yield: 79.2%, m.p: 225-2290C, IR (KBr, cm-1): 3296.46 (N-H str.), 1749.49 (C=O of β-lactum), 1664.62 (C=O of coumarin), 1292.35 cm-1(Ar-OCH3**);** 1H -NMR (400 MHz, DMSO- *d6*) δ 6.40-7.70 (m,11H, Ar-H); 3.76 (s,1H, C-NH); 8.19 (d, 1H, H at C-5 of coumarin), 5.75 (s, 1H, H at C-3of coumarin), 3.38 (S,3H, -OCH3), 4.10 (s,2H, CH2); C, 70.78; H, 5.63; N, 8.69; O, 4.96; S, 9.94.

5-(1H-indol-3yl)-3-(3-nitrophenyl)-thiazolidine-4-one

Yield: 62.3%, m.p: 180-1920C, IR (KBr, cm-1): 3296.46 (N-H str.), 1749.49 (C=O of β-lactum), 1664.62 (C=O of coumarin), 1292.35 cm-1(Ar-OCH3**);** 1H -NMR (400 MHz, DMSO- *d6*) δ 6.40-7.70 (m,11H, Ar-H); 3.76 (s,1H, C-NH); 8.19 (d, 1H, H at C-5 of coumarin), 5.75 (s, 1H, H at C-3of coumarin), 3.38 (S,3H, -OCH3), 4.10 (s,2H, CH2); C, 63.19; H, 3.64; N, 12.44; O, 12.11; S, 9.48.

5-(1H-indol-3yl)-3-(2- fluorophenyl)-thiazolidine-4-one

Yield: 67.8%, m.p: 195-1980C, IR (KBr, cm-1): 3296.46 (N-H str.), 1749.49 (C=O of β-lactum), 1664.62 (C=O of coumarin), 1292.35 cm-1(Ar-OCH3**);** 1H -NMR (400 MHz, DMSO- *d6*) δ 6.40-7.70 (m,11H, Ar-H); 3.76 (s,1H, C-NH); 8.19 (d, 1H, H at C-5 of coumarin), 5.75 (s, 1H, H at C-3of coumarin), 3.38 (S,3H, -OCH3), 4.10

(s,2H, CH2); C, 61.14; H, 2.94; N, 13.21; O, 13.07; S, 8.47.

5-(1H-indol-3yl)-3-(3-chloro-2-fluorophenyl)-thiazolidine-4-one

Yield: 74.4%, m.p: 226-2300C, IR (KBr, cm-1): 3296.46 (N-H str.), 1749.49 (C=O of β-lactum), 1664.62 (C=O of coumarin), 1292.35 cm-1(Ar-OCH3**);** 1H -NMR (400 MHz, DMSO- *d6*) δ 6.40-7.70 (m,11H, Ar-H); 3.76 (s,1H, C-NH); 8.19 (d, 1H, H at C-5 of coumarin), 5.75 (s, 1H, H at C-3of coumarin), 3.38 (S,3H, -OCH3), 4.10 (s,2H, CH2); C, 55.08; H, 3.70; N, 11.23; O, 10.02; S, 7.38.

5-(1H-indol-3yl)-3-phenylthiazolidine-4-one

Yield: 72.6%, m.p: 218-2210C, IR (KBr,cm-1) : 3296.46 (N-H str.), 1749.49 (C=O of β-lactum),1664.62 (C=O of coumarin), 1292.35 cm-1(Ar-OCH3**)** ; 1H -NMR (400 MHz, DMSO- *d6*) δ 6.40-7.70 (m,11H,Ar-H); 3.76 (s,1H,CNH); 8.19 (d, 1H, H at C-5 of coumarin), 5.75 (s, 1H, H at C-3of coumarin), 3.38 (S,3H,-OCH3), 4.10 (s,2H,CH2); C, 69.36; H, 4.79; N, 9.52; O, 5.44; S, 10.89.

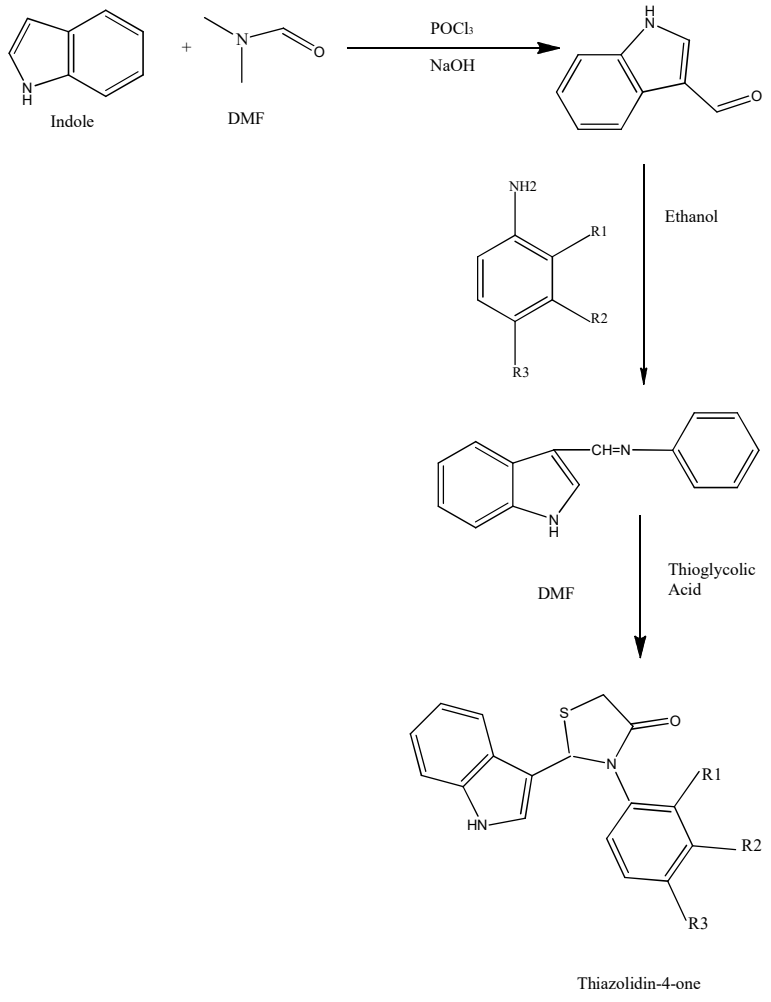

Figure 1: Schematic representation of derivatives of thiazolidine-4-one

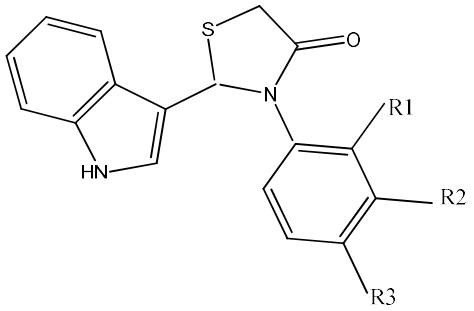

Table 1: Physical data of synthesized compounds (TZ1-TZ9)

Compound	R1	R2	R3	m.p.(°C)	%Yield	Rf value	Molecular Formula	Molecular Weight
TZ1	H	H	NO2	220-223	80.2	0.75	C17H13N3O3S	339.37
TZ2	NO2	H	H	210-212	82.1	0.70	C17H13N3O3S	339.37
TZ3	H	H	Cl	222-226	77.4	0.77	C17H13ClN2OS	328.82
TZ4	Cl	H	NO2	230-234	74.6	0.69	C17H13ClN3O3S	374.82
TZ5	CH3	CH3	H	225-229	79.2	0.89	C19H18N2OS	322.42
TZ6	H	NO2	H	180-192	62.3	0.76	C17H13N3O3S	339.37
TZ7	F	H	H	195-198	67.8	0.64	C17H13FN2OS	312.36
TZ8	H	Cl	F	226-230	74.4	0.67	C17H13ClFN2OS	347.81
TZ9	H	H	H	218-221	72.6	0.82	C17H14N2OS	294.37

m.p: Melting point; % yield: Percentage yield; Rf value: Retention factor

Table-2: Antibacterial activity of synthesized compounds (TZ1-TZ9)

Minimum Inhibitory Concentration (ug\ml.)		
Compound No.	*B.subtilis* (MTCC 10)	*E.coli* (MTCC 15)
TZ1	0.65	0.60
TZ2	0.79	0.72
TZ3	0.70	0.69
TZ4	0.60	0.52
TZ5	0.70	0.72
TZ6	0.55	0.62
TZ7	0.73	0.79
TZ8	0.69	0.63
TZ9	0.72	0.68
Ampicillin	0.22	0.26

***B. subtilis: Bacillus subtilis; E. coli: Escherichia coli*; MTCC: Microbial Type Culture Collection**

Biological Evaluation of Antimicrobial activity

All the synthesized compounds were evaluated for their antibacterial activity by serial tube dilution method by measuring minimum inhibitory concentration (MIC), is the lowest concentration of an antimicrobial agent that inhibit the growth of test organism. The MIC were determined at different concentrations of the synthesized compounds against gram positive, *Bacillus subtilis* and gram negative, *Escherichia coli*. The Ampicillin was used as standard drug.

Tube Dilution Method

Antibacterial activity, were evaluated by the tube dilution method in which, the different concentrations of target antibacterial agent were prepared in tubes, inoculated with population of the test organism, incubated and examined for the bacterial growth. Muller Hinton agar media for strain was used as culture medium and dimethyl sulfoxide (DMSO)

was used as solvent control. The test organisms were inoculated in nutrient broth and were incubated at 37 ºC for 48 hours, it was stored in refrigerator. The bacterial culture was harvested by using sterilized saline. The stock solution of the target compounds and the standard drug having concentration 5ug/mg were prepared. The stock solution was serially diluted by nutrient broth media aseptically to concentration of 1.0 ug/mg to 0.5 ug/mg. A control tube was prepared by transferring aseptically the 0.5 ml of sterilized nutrient broth media and 0.5 ml of the solvent (DMSO). All the culture tubes were inoculated by 0.1 ml of bacterial culture in the sterilized saline solution. The inoculated tubes were incubated at 37 ºC for 24 hours. After 24 hours the culture tubes were examined for turbidity. The culture tube showing turbidity and no turbidity, gave the MIC of the synthesized compounds.

RESULT AND DISCUSSION

Chemistry

The synthetic pathway of Thiazolidine-4-one derivatives is demonstrated in Figure-1. The indole-3-carboxaldehyde was synthesized by the reaction between indole, phosphorous oxychloride, dimethyl sulfoxide and sodium hydroxide. The Schiff baseof indole-3-carboxaldehyde was synthesized by reactions with different anilines and the addition of thioglycolic acid in the Schiff baseof indole-3-carboxaldehydegave, Thiazolidine-4-one derivatives. The structure of the synthesized compound was identified by I.R. spectroscopy and 1H -NMR. The melting points were matched with reported ones. Physiochemical data of the synthesized compounds is given in Table-1. The purity of the synthesized compounds was checked by TLC.

Antimicrobial activity

The compounds (TZ1-TZ9) were evaluated for their invitro antimicrobial activity by the tube dilution method by measuring minimum inhibitory concentration (MIC). The results of antimicrobial activity showed (Table-2) that some of the compounds showed moderate to good bacterial inhibition. The compounds, TZ1, TZ4 and TZ6 were more active against *B. Subtilis*and the compound TZ2, TZ3 and TZ5 were more active against *E. coli*.

CONCLUSION

To synthesize and evaluation of derivatives Thiazolidine-4-one. To carry out this task the work was planned as follows-:

1. Literature survey of new chemical entities of existing drugs.
2. Design of compounds.
3. Designing the synthetic scheme of the designed compounds.
4. Synthesis of designed compounds.

5. Physiochemical and Spectral characterization of synthesized compounds.
6. In-vitro antibacterial evaluation of synthesized compounds.

The antibacterial activity was, carried out by the tube dilution method against, bacterial strain *B.Subtilis* and *E.coli*. The result of antibacterial activity was showed in table-2. The result showed that the compounds TZ1, TZ4 and TZ6 were more active against *B. subtilis*. The compound TZ2, TZ3 and TZ5 were more active against the *E. coli* comparable to the standard drug. The present work focuses on the synthesis of nine compounds (TZ1-TZ9) using conventional procedures. So, these synthesized compounds could be selected as a lead compounds for further development of antimicrobial agents.

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