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Synthesis, Characterization And Study Of Antifungal And Antioxidant Activities Of Some Thiazolidinone Derivatives

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Abstract: In this work, the synthetic part involves the formation of acid hydrazides from the from the ester of Indole 2- carboxylic acid with hydrazine hydrate. This derivative on treatment with various substituted aldehydes to form corresponding schiffs base. The above titled compounds were synthesised by the cyclization of the schiff base with thioglycollic acid in presence of zinc chloride. The structures of the final compounds were established on the basis of IR, 1H-NMR and MASS spectral data. The synthesized compounds were evaluated for their antioxidant activity and antifungal activity. Out of the above synthesised compounds , TZ2, and TZ4 showed a significant activity towards the antioxidant activity. All the compounds were screened for their Antifungal activity against Candida albicans and Aspergillus niger. Among the synthesized compounds TZ_1, TZ_2 and TZ_4 were found to be moderately active against *Candida albicans at* 500 µg/disc. concentration.
Key words: Indole 2- carboxylic acid, Thiazolidinone, Antioxidant activity, Anti fungal activity.

Introduction

The wide range of biological activities exhibited by thiazolidin-4-ones and indole, it was our aim is to prepare derivatives of thiazolidin-4-ones incorporated with indole ring system in a molecular frame work and to explore the therapeutic advantage of this combination. Indole derivatives constitute an important class of therapeuticagents in medicinal chemistry including anticancer[1],antioxidant[2], antirheumatoidal[3] and anti-HIV[4] and also play a vital role in the immune system[5] and potent scavenger of free radicals[6]. Thiazolidinones are well famed for their
Anticonvulsant activity[7], Hypnotic[8], Antitubercular[9], Anticancer[10] and Antiviral activity[11]. The literature review shown enough biological profile on the above these moieties. With these consideration our research was concentate to synthesise some novel derivatives which have these nucleus.

Experimental

Melting points were determined by using melting point apparatus MP-DS TID 2000 V and the values were uncorrected. Reactions were monitored by thin layer chromatography (TLC) on pre coated silica gel G plates using iodine vapour as visualizing agent. UV spectra were recorded on JASCO V-530 UV/Vis spectrophotometer .IR spectra were recorded on JASCO FT/IR-140 spectrophotometer by using KBr pellets technique. PMR spectra were recorded using BRUCKER FT-NMR-300MHz FT spectrophoto meter by using DMSO as solvent and TMS as internal standard. The chemical shift was expressed in δ ppm.Mass spectra were recorded on

Finnigan MAT 8230 Mass spectometer. The physical characterization of the synthesized compounds were shown in table no:1.

Step I

Synthesis of Indole-2-carboxylic acid ester12

A mixture of 20.4 gm, (0.1 mole) of indole-2-carboxylic acid,6.4mlof methanol, 100 ml of dichloromethane and 5drops of concentrated sulphuric acid was refluxed for 5 hrs and cooled to 5°C. The contents were poured into 100ml of ice cold water. The organic layer at the bottom was separated and dichloromethane was distilled off to get the crude product. The high vacuum distillation of this crude product afforded the pure compound which is crystallized from methanol. The purity of the ester was established by single spot on the TLC plate. The solvent system used was methanol : chloroform (3:1).

Step II

Synthesis of Indole-2-carbohydrazide13

To 21.7g,(0.1mol)of Indole-2-carboxylicacidesterin 20 ml ethanol, 2 ml of 99% hydrazine hydrate was added in drops with constant stirring and themixturewasrefluxed for 4 hrs . After cooling, the solution was poured on to crushed ice. The solid separated was filtered, dried and recrystallised from methanol. The purity of the compound was established by single spot on the TLC plate. The solvent system used was methanol : chloroform (3:1).

Step III

Synthesis of Schiff's Base14

Indole-2-acid hydrazide (1mol) and arylaldhyde (1mol) were dissolved in 15 ml of ethanol in a 100 ml beaker and the mixture was refluxed for 2 hrs. The reaction mixture was cooled and the solid formed was separated by filtration, washed with cold ethanol and recrystalised from ethanol. Purity of the product was established by single spot on the TLC plate. The solvent system used was methanol : chloroform (3:1).

Step IV

Synthesis of substituted thiazolidinone 15

A mixture of Schiff base (1mM) in DMF and 0.92 ml of thioglycolic acid with a pinch of Zinc chloride was taken in a 100 ml beaker and the reaction mixture was zapped inside a microwave oven at 20% for 3 min. The solution was then diluted with ice cold water and solid formed was separated and recrystallized from ethanol.

Compound. TZ1

IR (KBr,cm-1): 3343.96 (N-H str),1716.34 (C=O str),667.25 (C-S-C str),1187.94(C-N str), 1H NMR (DMSO):11.92 (s,1H,indole NH),10.2(s,1H,Ar OH), 8.22 (s, 1H, CONH), 7.84 (s, 1H, N-CH, cyclic), 7.23-7.59(m, 7H, ArH), 2.50 (s, 2H, N-CH2). lmax: 286.

Compound. TZ2

IR (KBr,cm-1): 3340.10 (N-H str),1716.23 (C=O str),663.39 (C-S-C str),1189.94(C-N str), 740.53(C-Cl str). 1H NMR(DMSO):11.54 (s,1H,indole NH), 8.32 (s, 1H, CONH), 7.8 (s, 1H, N-CH, cyclic), 7.2-7.6(m, 7H, ArH), 2.50 (s, 2H, N-CH2). lmax: 312.

Compound. TZ3

IR (KBr,cm-1): 3337.10 (N-H str),1718.3 (C=O str),668.39 (C-S-C str),1186.94(C-N str), 2850.56, (N-CH3 str). MS(m/z+)- 381.(M+1), 222.178,161. lmax: 306.

Compound. TZ4

IR (KBr,cm-1): 3343.10 (N-H str),1718.23 (C=O str),673.39 (C-S-C str),1191.94(C-N str), 1098.53 (0- CH3 str). lmax: 321

Compound. TZ5

IR (KBr,cm-1): 3345.6 (N-H str),1719.4 (C=O str),668.25 (C-S-C str),1188.94(C-N str), 1099.3(0-CH3 str). lmax: 36

Screening For Antifungal Activity:

Antifungal Screening

The organisms *Candida albicans* NCIM 3471, *Aspergillus niger* NCIM 596 were inoculated in separate plates prepared earlier by adopting the following procedure. A sterile swab was dipped in the medium and the excess of inoculum was removed by pressing and rotating the swab firmly against the sides of the culture tube above the level of the liquid. Then the swab was streaked all over the surface of the medium three times, rotating the plates through an angle of 60° after each application. Finally the swabbing was done around the edges of the agar surface. The inoculum was left to dry at room temperature with the lid closed. Sterile discs containing the test, standard and blank were placed aseptically on the medium in the petridish. 10µL/disc of saturated solutions of the synthesized compounds were used by transferring the drug solution carefully over the discs using micro pipette. The petridishes were placed in a refrigerator for one hour to facilitate uniform diffusion. Then they were incubated at 25°C for 24-48 hours. Observations

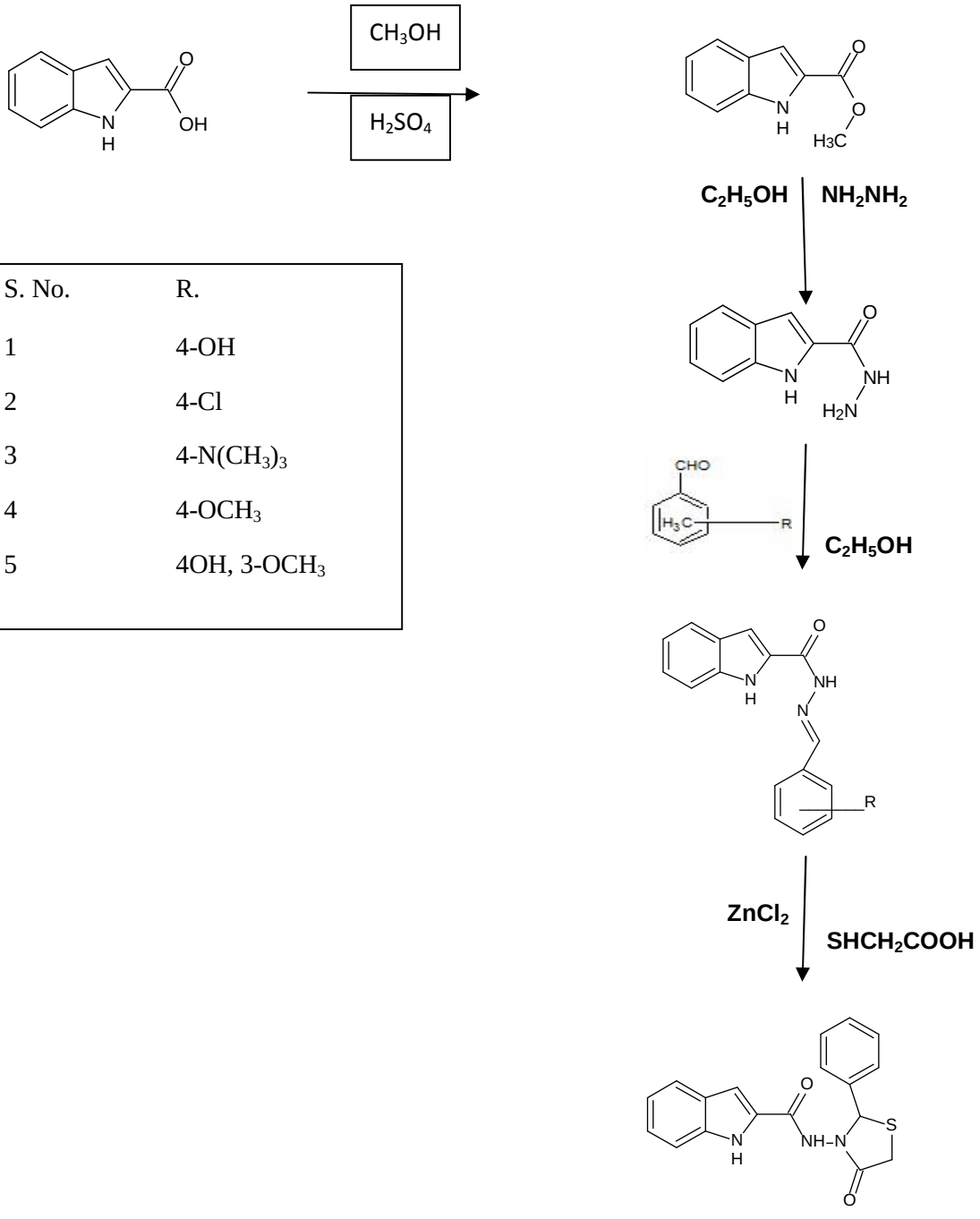
were made for zone of inhibition around the discs and their diameters were measured and compared with that of the standard. All the synthesized compounds were tested for antifungal activity.

The details of the zone of inhibition of the compounds at 500 μg/disc concentrations were shown in table no:2.

Drugs Used

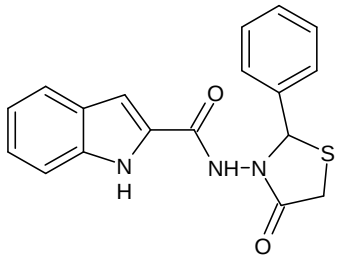
Test drug derivatives : Synthesized thiazolidinone
Standard used : Fluconazole (25 μg/disc)
Vehicle used(as blank): Dimethyl sulfoxide.

Scheme:



S. No.	R.
1	4-OH
2	4-Cl
3	4-$N(CH_3)_3$
4	4-OCH_3
5	4OH, 3-OCH_3

Table No: 1: Physical Characterization Of Newly Synthesized Compounds



S.No.	Compound Code	R	Molecular Formula	Molecular Weight	Melting Point	R_f value	% yield
1	TZ_1	4-hydroxy	$C_{18}H_{15}N_3O_3S$	353.40	79.9°C	0.69	82%
2	TZ_2	4-chloro	$C_{18}H_{14}ClN_3O_2S$	371.84	75.7°C	0.68	87%
3	TZ_3	4-dimethyl amino	$C_{20}H_{20}N_4O_2S$	380.47	82°C	0.72	84%
4	TZ_4	4-methoxy	$C_{19}H_{17}N_3O_3S$	367.43	78.9°C	0.78	73%
5	TZ_5	4-hydroxy-3-methoxy	$C_{19}H_{17}N_{30}O_4S$	383.42	77.9°C	0.74	72%

Solvent System = Methanol : Chloroform

Table No:2: Screening Of Test Compounds For Antifungal Activity

Compound Code	Diameter of Zone of inhibition in mm	
	Candida albicans NCIM 3471 (500 «g/disc) (mm)	***Aspergillus niger NCIM 596 (500 «g/disc) (mm)***
TZ_1	14	-
TZ_2	15	-
TZ_3	-	-
TZ_4	16	-
TZ_5	-	-
DMSO (Blank)	-	-
Fluconazole (25µg/disc)	26	20

(–) indicates no zone of inhibition

Antioxidant activity (using DPPH Method)

1.5 ml of 0.2 mM of DPPH solution was added to 1.5 ml of different concentrations of drug solutions and 1.5 ml of methanol. The above solutions were allowed to react at room temperature for 30 min. After 30 min the absorbance values were measured at 517nm and converted to percentage of scavenging activity which was calculated by using the following formula. The details of the percentage of scavenging of the compounds at different concentrations were shown in table no:3

% of Scavenging activity=

$$\left[\frac{(Ab+As)-Am}{Ab}\right] X\,100$$

Ab =Absorbance of 1.5 ml DPPH + 1.5 ml methanol
Am=Absorbance of 1.5 ml DPPH + 1.5 ml drug solution
As =Absorbance of 1.5 drug + 1.5 ml methanol solution

Table No:3 :Screening For Antioxidant Activity By Dpph Assay Method

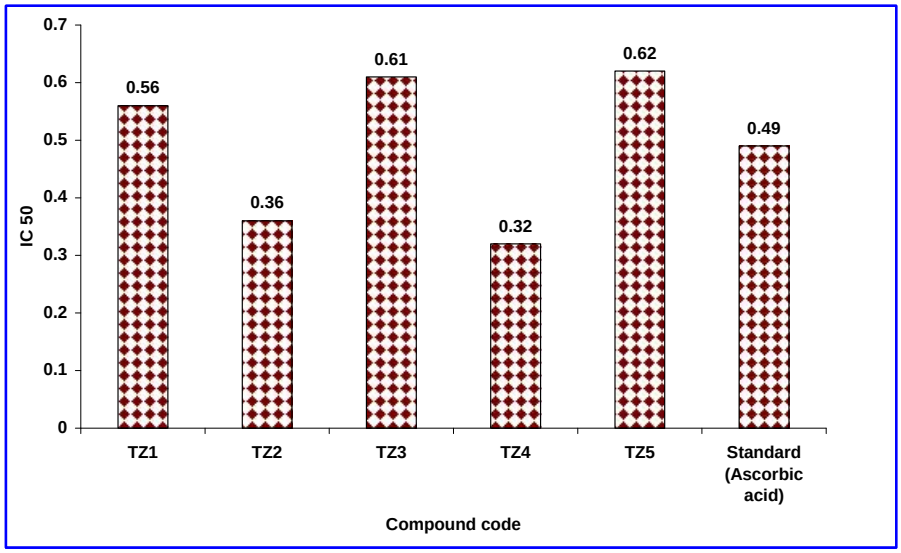
Compound Code	Absorbance at 517nm						
	Absorbance	**0.1mM**	**0.2mM**	**0.5mM**	**0.7 mM**	**1mM**	**IC_{50} (mM)**
TZ_1	Drug + DPPH	0.9359	0.8555	0.4814	0.3715	0.3212	0.56
	Drug + Methanol	0.0089	0.0072	0.0032	0.0025	0.0018	
	% of activity	13.90	20.30	55.07	65.33	70.02	
TZ_2	Drug + DPPH	0.9213	0.5697	0.4328	0.3050	0.2132	**0.36**
	Drug + Methanol	0.0022	0.0347	0.0029	0.0024	0.0015	
	% of activity	13.06	49.73	59.28	71.49	80.11	
TZ_3	Drug + DPPH	1.0380	1.0171	0.7047	0.6147	0.5223	0.61
	Drug + Methanol	0.0089	0.0022	0.0113	0.0092	0.0083	
	% of activity	3.32	4.65	34.85	43.11	51.70	
TZ_4	Drug + DPPH	0.9215	0.5935	0.4750	0.3435	0.2395	**0.32**
	Drug + Methanol	0.0048	0.0043	0.0006	0.0005	0.0003	
	% of activity	13.87	43.83	55.35	67.77	77.49	
TZ_5	Drug + DPPH	0.9218	0.8795	0.768	0.624	0.512	0.62
	Drug + Methanol	0.0036	0.0130	0.0046	0.0034	0.0026	
	% of activity	13.05	18.59	31.21	41.69	52.14	
Standard absorbic acid	Absorbance	0.0039	0.028	0.005	0.003	0.002	**0.49**
	% of activity	70.28	84.29	96.45	97.75	98.17	

Absorbance of negative control (DPPH + Methanol = 1.0644)

Result and Discussion

All the synthesized compounds were characterized by recrystallization, TLC, Melting point, UV, IR, 1HNMR analysis,and Mass fragmentation pattern. All the synthesized structures showed satisfactory result. The chemical shift values of the synthesised compounds were full agreement with the number of protons present in it.

All the newly synthesized thiazolidinone derivatives of indole were evaluated for their antioxidant activity. Among the newly synthesized compounds, compound TZ2 and TZ4 showed lowest IC50 value of 0.36 and 0.32 mM respectively compared to the standard drug Ascorbic acid which showed. IC50 value of 0.49 mM. Thecompound TZ2 and TZ4 showed maximum inhibitory activity compared to the standard drug ascorbic acid.



Among the synthesized compounds TZ_1, TZ_2 and TZ_4 were found to be moderately active against *Candida albicans at* 500 μg/disc. concentration. They were not active against *Aspergillus niger*. All the other compounds were found to be inactive against both *Candida albicans* and *Aspergillus niger* at concentration 500μg/ disc. concentration. From the research work we found the indole ring incorporated with a thiazolidinone moiety have significant role in the anti oxidant activity.

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