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Synthesis and Antimicrobial Activity of N^1-(Arylidine hydrazidomethyl)-Indoles, 2-(Substituted aryl)-3-(N^1-Indolyl acetamidyl)-4-Oxo-Thiazolidines and 5-Benzylidine Derivatives of Thiazolidinones

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Several N^1-(arylidine hydrazidomethyl)-indoles were prepared by condensing N^1-indolyl acetyl hydrazine with different substituted benzaldehydes. 2-(substituted aryl)-3-(N^1-indolyl acetamidyl)-4-oxo-thiazolidines were prepared by condensing N^1-(arylidine hydrazidomethyl)-indoles with mercaptoacetic acid followed by the Knoevanagel condensation with benzaldehyde leading to the 5-benzylidine derivatives. The IR, ^{1}HNMR and mass spectral studies confirmed the structures of these compounds. The synthesized compounds were tested *in vitro* against *Staphylococcus aureus, Bacillus subtilis, Escherichia coli, Salmonella typhi, Pseudomonas aeruginosa, Proteus vulgaris, Candida albicans* and *Aspergillus niger.* The zones of inhibition were compared with the standard drugs under the identical conditions.

The molecular manipulation of promising lead compounds is still a major line of approach to new drugs. Molecular manipulation involves the efforts to combine the separate groups of similar activity into one compound, thus making structural changes into the compound leading to changes in the biological activity. Indole as the important heterocyclic ring present in a large number of biologically active molecules of different pharmacological classes[1,2] is known to have fungicidal, bactericidal and herbicidal activities. The historical importance of thiazolidine derivatives was emphasized during the period 1941-1945, when work on the structure of penicillin showed the presence of thiazolidine ring in it. Compounds carrying the thiazolidinone ring have been reported to demonstrate a wide range of pharmacological activities[5-12], which include antibacterial, antifungal, antitubercular, anticonvulsant, analgesic, antihistaminic, anaesthetic, antithyroid and antiparkinson activity. Joining of two different biologically active chemical moieties i.e. indole and thiazolidinone may enhance the antibacterial, antifungal activities. Schiff's bases of different heterocyclic compounds were also found to be having antibacterial and antifungal activities[3,4]. The N^1-(arylidine hydrazidomethyl)-indoles (Schiff's bases) were prepared by the condensation of N^1-indolyl acetyl hydrazine with different substituted benzaldehydes. The 2-(substituted aryl)-3-(N^1-indolyl acetamidyl)-4-oxo-thiazolidines were prepared by the condensation of Schiff's bases with mercaptoacetic acid. The 2-(substituted aryl)-3-(N^1-indolyl acetamidyl)-4-oxo-thiazolidines on Knoevanagel condensation with benzaldehyde yielded the 5-benzylidine derivatives of thiazolidinones as shown in Scheme 1. The structures of the synthesized compounds have been established by IR, ^{1}HNMR, mass spectral data. All the synthesized compounds were screened for antimicrobial activity.

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MATERIAL AND METHODS

Melting points of the synthesized compounds were determined on a scientific melting point apparatus and are uncorrected. IR absorption spectra of synthesized compounds were determined on FTIR-8300, KBr Press, Shimadzu at

COPS, Manipal. ^{1}HNMR spectra were determined on the Jeol GSX 400 6OMHz Spectrometer at RSIC, IIT, Chennai. Mass spectra were recorded on the Jeol 300 Spectrometer at 70 eV at RSIC, IIT, Chennai.

Method of preparation of ethyl- N^1-indolyl acetate (1):

An equimolar solution of indole (0.01 mol) and ethyl chloro acetate (0.01 mol) in dry acetone (10 ml) in the presence of anhydrous K_2CO_3 (2.3 g) was stirred over a magnetic stirrer for a period of 24 h. The mixture was poured into about 100 ml of ice-cold water. The above-formed ester was extracted with ether and ester was obtained on removing the ether. Yield:90%.

Method of preparation of N^1-indolyl acetyl hydrazine (2):

A mixture of indolyl ester (0.01 mol) and hydrazine hydrate (0.01 mol) was refluxed over a water bath for a period of 12 to 16 h. The mixture was poured into a beaker containing ice-cold water and kept in the fridge overnight. The product was filtered at pump and washed repeatedly with ice-cold water and recrystallized with a suitable solvent (absolute alcohol). Yield: 90%, melting point: 39°, IR (KBr): 3300 (-NH-NH_2), 1650 (C=O, amido), ^{1}HNMR (DMSO): 2.50 (s, 2H, $-NH_2$), 3.65 (s, 2H, -N-CH_2), 7.70 (s, 1H, CONH) 7.20-7.40 (m, 6H, Ar-H),

Method of preparation of N^1- (4-methyl benzylidine hydrazidomethyl)-Indole (3e):

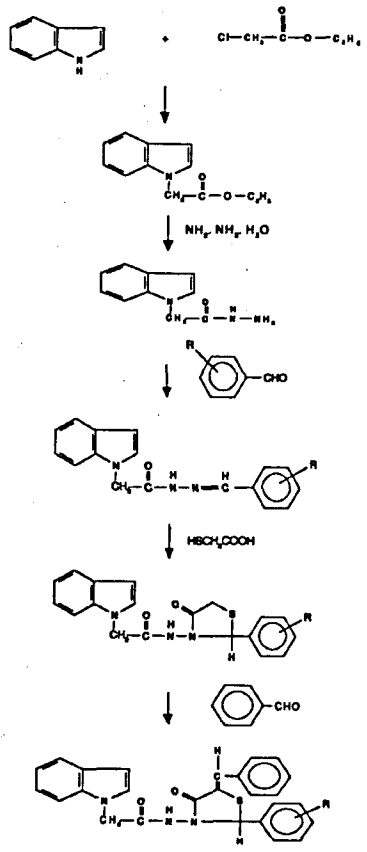
An equimolar quantity of 2 (0.01 mol) and 4-methylbenzaldehyde (0.01 mol) was refluxed in absolute alcohol for a period of 10-12 h. The reaction mixture was cooled and poured into a beaker with stirring containing ice-cold water and triturated with sodium bisulfite solution. The product was isolated and then recrystallized with aqueous ethanol. Solvent system used for TLC was benzene:petroleum ether (60: 40), 6:4, Yield:80%, m.p. 123°, IR (KBr): 3408 cm^{-1} (-NH-), 1610 (>C=O, CONH), 1544.9 (-HC=N-), ^{1}HNMR (DMSO): 3.70 (s, 2H, -N-CH_2), 4.50 (s, 1H, -N=CH-), 7.90 (s, 1H, CONH), 7.30-7.90 (m, 10H, Ar-H), MS: 291(M^+), 161 $(C_9H_9N_2O)^+$, 130 $(C_9H_8N)^+$. Likewise other N^1-(arylidine hydrazidomethyl)-Indoles were prepared by treating N^1-Indolyl acetyl hydrazine with various benzaldehydes and their physical data are given in Table 1.

Method of preparation of 2-(4-methyl phenyl)-3-(N^1-indolyl acetamidyl)-4-oxo-thiazolidine (4e):

An equimolar solution of 3e (0.01 mol) dissolved in dry benzene and thioglycollic acid (0.01 mol) containing a pinch of fused zinc chloride was refluxed for 20 h. The removal of benzene was carried out using the Dean-stark water separator till no more water separated with benzene i. e. the turbidity of benzene was removed. The excess of benzene was removed by vaccum distillation. The above mixture was then cooled to room temperature and poured into a beaker containing ice-cold water. The reaction mixture was then treated with ice-cold water containing Sodium bicarbonate to remove the unreacted thioglycollic acid. The separated product was then recrystallized from absolute ethanol. Solvent system used for TLC was benzene:chloroform:ethanol (absolute), 5:3:2, Yield:60%, m.p.110°, IR (KBr): 3408 cm^{-1} (-NH-), 1610 (>C=O, CONH), 1718 (>C=O, cyclic), ^{1}HNMR (DMSO): 3.70 (s, 2H, -N-CH_2), 3.40 (s, 2H, CH_2S), 3.20 (s, 1H, -CHN-), 8.10 (s, 1H, CONH), 7.30-7.90 (m, 10H, Ar-H), MS: 192 $(C_{10}H_{10}NSO)^+$, 144 $(C_4H_4N_2O_2S)^+$, 130 $(C_9H_8N)^+$. Likewise other 2-(substituted aryl)-3-(N^1-indolyl acetamidyl)-4-oxo-thiazolidines were prepared by treating (3a-d) with thioglycollic acid and their physical data are given in Table 1.

Method of preparation of 2-(4-methoxy phenyl) -3-(N^1-indolyl acetamidyl)-5-benzylidine-4-oxo-thiazolidine (5b):

Metallic sodium (0.005 mol) was added to ethanol (99%, 25 ml) with external cooling. After 30 min, thiazolidinone 4d



(0.005 mol) was added and the mixture was refluxed for 5 min followed by the addition of benzaldehyde (0.005 mol) in ethanol (99%, 30 ml). The contents were then refluxed for 8 h, cooled, poured into ice water and acidified with glacial acetic acid. The solid thus obtained was filtered and recrystallized from absolute ethanol. Solvent system used for TLC was benzene:chloroform:ethanol (absolute), 5:3:2, Yield 85%, m.p.130°, IR (KBr): 3408 cm^{-1} (-NH-), 1658.7 (>C=CH-), 1610 (>C=O, CONH), 1718 (>C=O, cyclic), ^{1}HNMR (DMSO): 3.70 (s, 2H, -N-CH_2), 3.40 (s, 2H, CH_2S), 3.20 (s, 1H, -CHN-), 8.10 (s, 1H, CONH), 5.2 (s, 1H, C=CH-Ar), 7.00-8.00(m, 15H, Ar-H). Likewise other 2-(substituted aryl)-3-(N^1-Indolyl acetamidyl)- 5-benzylidine-4-oxo-thiazolidines were prepared by treating (3a,c) with benzaldehyde and their physical data are given in Table 1.

Antibacterial activity:

Antibacterial activity of all the synthesized compounds was determined by the disc diffusion method against the gram-positive organisms *Staphylococcus aureus* and *Bacillus subtilis* and gram-negative organisms *Escherichia coli, Salmonella typhi, Pseudomonas aeruginosa* and *Proteus vulgaris* at 500 µg/ml concentration. The bacteria were subcultured on Mueller Hinton Agar medium. The petridishes were incubated at 37° for 48 h. Standard antibacterial drugs were also screened under similar conditions for comparison. Penicillin (1000 units/ml) was used as a standard for *Staphylococcus aureus*. Streptomycin (1000 units/ml) was used as a standard for other microorganisms. The results were presented in Table 2.

Antifungal activity:

The antifungal activity of all the synthesized compounds was carried out against the fungi *Candida albicans* and *Aspergillus niger* at 500 µg/ml concentration. The fungi were subcultured in Sabourad's Dextrose Agar medium. The fungal susceptibility testing was done by disc diffusion method using amphotericin B (1000 units/ml) as standard. The petridishes were incubated for 24 h at 22° to 25°. The results were presented in Table 2.

RESULTS AND DISCUSSION

All compounds were in conformity with the structures envisaged. The structures were proved on the basis of spectral data. The synthesized Schiff's bases 3a, 3c, 3e showed higher antibacterial activity against gram-positive organism *S. aureus* in comparison to that of standard penicillin. All the synthesized schiff's bases showed moderate activity against *B. subtilis* when compared with the standard streptomycin. The gram-negative bacteria were found to be resistant to

TABLE 1: PHYSICAL DATA OF THE SYNTHESIZED COMPOUNDS.

Compd.	R	Molecular formula	%Yield	Rf	M.P.
3a	H	$C_{17}H_{15}N_3O$	80	0.85	123°
3b	o-Cl	$C_{17}H_{14}N_3OCl$	75	0.81	120°
3c	m-NO_2	$C_{17}H_{14}N_4O_3$	85	0.73	115°
3d	p-OCH_3	$C_{18}H_{17}N_3O_2$	80	0.80	130°
3e	p-CH_3	$C_{18}H_{17}N_3O$	70	0.86	125°
4a	H	$C_{19}H_{17}N_3O_2S$	70	0.81	114°
4b	o-Cl	$C_{19}H_{16}N_3O_2SCl$	65	0.78	106°
4c	m-NO_2	$C_{19}H_{16}N_4O_4S$	75	0.80	102°
4d	p-OCH_3	$C_{20}H_{19}N_3O_3S$	70	0.82	145°
4e	p-CH_3	$C_{20}H_{19}N_3O_2S$	60	0.77	110°
5a	H	$C_{26}H_{21}N_3SO_2$	80	0.76	107°
5b	p-OCH_3	$C_{27}H_{23}N_3SO_3$	85	0.80	130°
5c	m-NO_2	$C_{26}H_{23}N_4O_4$	70	0.82	110°

Rf- Retention factor, M.P.- Melting point.

TABLE 2: BIOLOGICAL ACTIVITY DATA OF THE SYNTHESIZED COMPOUNDS.

Compd.	*S. typhi*	*P. vulgaris*	*E. coli*	*P. aeruginosa*	*S. aureus*	*B. Subtilis*	*C. albicans*	*A. niger*
3a	-	-	-	-	17	18	-	-
3b	-	-	-	-	16	17	-	-
3c	-	-	-	-	20	19	-	-
3d	-	-	-	-	15	17	-	-
3e	-	-	-	-	18	20	-	-
4a	-	-	-	-	-	-	-	-
4b	-	-	-	-	-	-	9	8
4c	10	-	10	-	-	-	-	-
4d	-	-	8	-	-	-	-	-
4e	-	-	10	-	-	-	8	-
5a	-	-	-	-	-	-	8	-
5b	-	-	-	-	-	-	-	-
5c	-	-	-	-	-	-	-	-
Std.	15	25	15	25	16	25	15	12

S. typhi- Salmonella typhi, P. vulgaris- Proteus vulgaris, E. coli- Escherichia coli, P. aeruginosa- Pseudomonas aeruginosa, S. aureus- Staphylococcus aureus, B. subtilis- Bacillus subtilis, C. albicans- Candida albicans, A. niger- Aspergillus niger. Zone of inhibition in mm.

most of the compounds. Only the thiazolidinones having R=m-NO_2, p-OCH_3 (i.e. electron withdrawing groups) showed moderate inhibitory action against the gram-negative bacterium *E. coli*. Schiff's bases having the p-CH_3 and o-Cl groups (electron donating groups) were found to exhibit a higher order of activity.

The synthesized benzylidines (5a-c) were found to be inactive against the bacterial as well as the fungal strains. The results show that there is a loss in the antibacterial activity against the gram-positive microorganisms on cyclization to the thiazolidinones. Results also show that the incorporation of the electron-withdrawing groups may increase the biological activity of the 4-thiazoldinones against the gram-negative bacteria.

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