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Synthesis, Antimicrobial and Insecticidal Activity Studies of 5-Nitro N' -[Arylidenhydrazidomethyl Indole] 2-(Substituted Aryl) -3-(N'-Indolyl Acetamiddyl)-4-Oxothiazolidines

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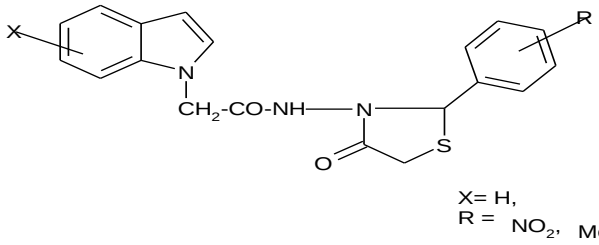
Abstract

Several 5nitro N'-(arylidine hydrazidomethyl) indole were prepared by condensing N'-indolyl acetyl hydrazine with different type of aromatic aldehydes. 2-(substituted aryl)-3-(N'-5-nitro indole acetamiddyl)-4-oxo-thiazolidines were prepared by condensing N'-(arylidine hydrazidomethyl)-indoles with thioglycollic acid.The IR and ^{1}HNMR spectral studies have confirmed the structures of these synthesized compounds.The synthesized compounds which have also been tested for their antimicrobial activity against S. aureus, B.megaterium and A. niger and A. Paraciticus.

Keywords: synthesis of 2-(substituted aryl)-3-(N'-5-nitro indole acetamiddyl)-4-oxo-thiazolidines derivatives, characterization IR and NMR spectral data, biological activity.

Introduction

Indole, as the important heterocyclic ring present in a large number of biologically active molecules of different pharmacological classes[1] is known to have fungicidal, bactericidal, herbicidal, antitubercular, anticonvulsant, analgesic, antithyroid and antiparkinson activity[2-9]. Recently, the synthesis and antimicrobial activity of thiazolidinones (A) has been reported[10].



X= H,
R = NO_2, Me, Cl

In the present investigations we describe the synthesis of some new indole derivatives and their antimicrobial and insecticidal properties.

Material and Methods

Melting points were determined in an open capillary tube with a Buchi melting point apparatus and are uncorrected. Elemental analysis was obtained using Perkin-Elmer 240C CNH analyzer, I.R. spectra were recorded on FTIR 8400S Simandzu spectrophotometer, ^{1}HNMR spectra in $CDCl_3$ at 300MHz on a Bruker DRX 300 spectrometer. The purity of the compounds has been checked by TLC.

Synthesis of 5-nitroindole (I): It was prepared by the Vogel's method[11].

Synthesis of N'-indolyl acetate (II): An equimolar solution of indole (0.01 mol) and ethyl chloroacetate (0.01 mol) in dry acetone (10 mol) in the presence of anhydrous K_2CO_3 (2.3 g) was stirred on magnetic stirrer for 22 hr. The progress the reaction was monitored by T.L.C. The reaction mixture was poured into 100 ml ice cold water and the above formed ester was extracted with ether. Upon removing the ether, the final ester product was obtained in 87% yield.

Synthesis of N'-indole acetyl hydrazine (III) : A mixture of indole ester (0.01 mol) and hydrazine hydrate (0.01 mol) was refluxed on a waterbath for 13 hr. The time of refluxion monitored by T.L.C. The mixture was poured into a beaker containing ice-cold water and kept in the fridge overnight. The product was filtered, washed with ice cold water and recrystallized from ethanol with 85% yield.

Synthesis of N'-(substituted benzylidine hydrazido methyl)-indoles (IV) : Equimolar quantity of **(III)** (0.01 mol) and substituted aromatic aldehyde (0.01 mol) was taken in ethanol (50 ml) and refluxed for 11 hrs. The time of refluxion monitored byT.L.C. The reaction mixture was then cooled to room temperature and poured under stirring into a beaker containing ice cold water and triturated sodium bisulfite solution. The product was isolated and then recrystallized from aqueous ethanol with 86% yield.

Synthesis of 2-(substituted phenyl)-3-(N'-5-nitro indoleacetamidyl)-4-oxo-thiazolidines (V) : An equimolar solution of **(IV)** (0.0 mol) dissolved in dry benzene and thioglycollic acid (0.01 mol) containing a pinch of fused zinc chloride was refluxed for 21 hr. The time of refluxion monitored byT.L.C. Excess benzene was removed by vacuum distillation. The above mixture was then cooled at room temperature and poured in to a beaker containing ice cold water. The reaction mixture was then treated with sodium carbonate solution to remove the unreacted thioglycollic acid. The separated product was then recrystallized from ethanol in 80% yield.

Antimicrobial activity of the synthesized compounds (Va-Vf) : In the present study, the filter paper disc diffusion plate method has been employed to evaluate the antimicrobial activity in vitro.

Preparation of media[12]: In the present study, the filter paper disc diffusion plate method has been employed to evaluate the antimicrobial activity in vitro.

Table-1
Physical data of synthesized compounds (Va – Vf)

No.	mol. formula	M.W.	m.p.range (°C)	Yield (%)	elemental analysis (%)		
					C Cal.(found)	N, Cal.(found)	H Cal.(found)
Va	$C_{19}H_{16}N_4O_4S$	396.37	128-129	80	57.52 (57.50)	14.12 (14.10)	4.03 (4.01)
Vb	$C_{19}H_{15}N_4O_4SCl$	430.86	135- 136	76	52.96 (52.94)	12.97 (12.97)	3.48 (3.47)
Vc	$C_{19}H_{15}N_4O_4SCl$	430.86	138 - 139	78	52.96 (52.93)	12.97 (12.95)	3.48 (3.46)
Vd	$C_{20}H_{18}N_4O_5S$	426.38	134 – 135	82	56.33 (56.31)	13.13 (13.11)	4.22 (4.21)
Ve	$C_{20}H_{18}N_4O_6S$	442.37	142 - 143	80	54.29 (54.27)	12.66 (12.64)	4.06 (4.06)
Vf	$C_{19}H_{16}N_4O_5S$	412.36	131- 132	79	55.34 (55.32)	13.58 (13.56)	3.88 (3.86)

Table-2
I.R spectral data of synthesized compounds (Va – Vf)

Comp. No.	Type Vibration Mode and Frequency cm^{-1}
Va	1604 (C=C str), 3045 (C-H str ring), 1325 (C-N str ring), 1453 (C-H deformation-CH_2), 1625 (C=N str), 1665 (N =O str) 3442 (N-H str), 624 (C-S-C str),
Vb	1608 (C=C str), 3040 (C-H str ring), 1335 (C-N str ring), 1458 (C-H deformation-CH_2), 1620 (C=N str), 1662 (N=O str) 3448 (N-H str), 628 (C-S-C str),725 (C-Cl str),
Vc	1602 (C=C str), 3042 (C-H str ring), 1326 (C-N str in ring), 1480 (C-H deformation -CH_2), 1622 (C=N str), 1667 (N=O str), 3440 (N-H str), 632 (C-S-C str), 727 (C-Cl str)
Vd	1610 (C=C str), 3038 (C-H str in ring), 1322 (C-N str in ring), 1450 (C-H deformation -CH_2), 1629 (C=N str), 1672 (N=O str), 3440 (N-H str), 625 (C-S-C str), 1240 (C-O-C str), 2883 (C-H str in -CH_3), 1339 bending (in -CH_3)
Ve	1612 (C=C str), 3035 (C-H str in ring), 1325 (C-N str in ring), 1448 (C-H deformation-CH_2), 1626 (C=N str), 1670 (N=O str), 3452 (N-H str), 1256 (C-O-C str), 635 (C-S-C str), 3652 (-OH str), 2876 (C-H str in -CH_3), 1236 bending (in -CH_3)
Vf	1606 (C=C str), 3030 (C-H str in ring), 1327 (C-N str in ring), 1440 (C-H deformation -CH_2-), 1629 (C=N str), 1672 (N=O str), 3438 (N-H str), 632 (C-S-C str), 3658 (-OH str)

Table-3
^{1}HNMR spectral data ($CDCl_3$)of synthesized compounds (Va – Vf)

Comp. No.	Relative protons and signal position in δ ppm .
Va	3.72 [s, 2H, -N-CH_2], 3.40 [s, 2H, -CH_2-S-], 3.21 [s, 1H, -CH-N], 8.10 [s, 1H, -CN-H], 7.28-7.90 [m, 10 H, Ar-H],
Vb	3.69 [s, 2H -N-CH_2], 2.67 [s ,2H, -CH_2-S-], 3.70 [s, 1H, -CH-N], 8.60 [s, 1H, -CN-H], 6.97-7.27 [m 7 H, Ar-H], 6.4-6.7 [d 2H Pyrrole ring]
Vc	3.60 [s, 2H, -N-CH_2], 2.54 [s, 2H, -CH_2-S-], 3.65 [s, 1H, -CH-N], 8.73 [s, 1H, -CN-H], 6.93-7.23 [m 7H, Ar-H], 6.46-6.72 [d 2H, Pyrrole ring],
Vd	3.63 [s, 2H, -N-CH_2], 2.58 [s, 2H, -CH_2-S-], 3.72 [s, 1H, -CH-N], 8.32 [s, 1H, -N-H], 3.73 [s, 3H, –O-CH_3], 6.67-7.13 [s, 7H, Ar-H], 6.48-6.80 [d, 2H, Pyrrole ring],
Ve	3.58 [s, 2H, -N-CH_2], 2.56 [s, 2H, -CH_2-S-], 3.70 [s, 1H -CH-N], 8.17 [s, 1H -N-H], 3.72 [s, 3H –O-CH_3], 4.87 [s, 1H, -OH], 6.58-7.02 [m, 6H, Ar-H], 6.42-6.72 [d, 2H, Pyrrole ring],
Vf	3.55 [s, 2H, -N-CH_2], 2.54 [s, 2H, -CH_2-S-], 3.67 [s, 1H, -CH-N], 8.27 [s,1H, -N-H], 4.82 [s, 1H, -OH], 6.72-7.06 [m, 6H, Ar-H], 6.42-6.69 [d, 2H, Pyrrole ring],

Table- 4
Inhibitory effects of the synthesized compounds (Va-Vf) against Bacteria and Fungi

S. No.	Bacteria		Fungi	
	B. megaterium	**S. aureus**	**A. niger**	**A. paraciticus**
Va	**18**	**18**	**8**	**12**
Vb	**17**	**17**	**10**	**14**
Vc	**16**	**15**	**9**	**13**
Vd	**18**	**19**	**11**	**16**
Ve	**14**	**12**	**10**	**14**
Vf	**16**	**14**	**10**	**10**
Standard drug	**20**	**16**	**12**	**15**

Zone of inhibition measured in mm.

Table-5
Insecticidal activity of the synthesized compounds (Va-Vf)

S. No. compounds	Va	Vb	Vc	Vd	Ve	Vf	Control
K.D. Value in minutes	7	6	4	5	6	8	5

Reaction sequences as follows : RH,H,Vb,o-Cl,Vc,p-Cl,Vd,p-OCH3,Ve, 3-OCH3. 4-OH,Vf o-OH

Preparation of paper discs: Discs of 6 mm in diameter prepared from very pure and highly absorbent filter paper have been sterilized in screw capped bottles by dry heat at 140°C. These discs are soaked in sample solution and transferred to sterile Petri dishes with sterile forceps when required. The Petri dishes were sterilized by heating in an oven at 140°C. On cooling the melted sterilized medium was poured into them, under laminar floor.

Determination of activity:- Antibacterial activity: Antibacterial activity of all the synthesized compounds was

determined by the diffusion method against the gram - positive organisms Staphylococcus aureus and B. megaterium at 500 µg/ml concentration .the bacteria were subcultured on Mellar Hintol Agar medium. The petridishes were incubated at 37°C for 48 hr. standard antibacterial drugs were also screened under similar conditions for comparison .streptomycin (1000 unit/ml) was used as standard for other microorganisms. The results were in table no. 2.

Antifungal activity: The antifungal activity of all the synthesized compounds were carried out against the fungi, Aspergillus niger and aspergillus paracitica 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 Griseofulvin (1000 unit/ml) as standard .

The petridishes were incubated for 24 hr. at 22 to 25°C. The results were presented in table no. 2. petridishes were sterilized by heating in an oven at 140°C. On cooling the melted sterilized medium was poured into them, under laminar floor.

Determination of activity: Filter paper disc diffusion method was used. The medium was first inoculated with loopful of broth culture of the organism and shacked for uniform distribution. It was poured into Petridis. Discs soaked in test sample solution were placed over the seeded medium and pressed so that all parts of disc come in contact with the medium. The seeded plates were incubated at 28°C for 32 hours in case of bacteria and 37°C for 72 hours in case of fungi.

The same procedure was adopted for the standard drugs. The activity was determined by using 4% solution of prepared of synthesized compounds and 4% solution of standard drugs, Griseofulvin (for fungi) and streptomycin (for bacteria) were also prepared. The filter paper discs were soaked in the standard drug solution and the activity was determined.

Insecticidal activity of the synthesized compounds (Va-Vf): Cockroaches were selected for the present investigation. 4% (w/v) solutions of synthesized compounds have been prepared in acetone. 1 to 2 ml solution of synthesized compounds has been injected in to the abdominal region of the cockroach with the help of micro syringe. The time of death was noted as KD value (knockdown value). At the time of death, the antennae became motionless, the appendages shrunk and folded towards the ventral side and cockroach lay dorsally. The KD values have been compared with the control cypermethrin activity reported in table 7.

Results and Discussion

The synthesized compounds (Va-Vf) have shown inhibitory action against all the tested microorganisms used in the present investigation (table 6). The synthesized compounds Va, Vb and Vd have, however, been found to be more effective than the antibiotic streptomycin against S.

Aureus and can thus serve better for its inhibition. The synthesized compound Vd has, however been found to be more effective than the antifungal Griseofulvin against A. paraciticus and can thus serve better for its inhibition. Regarding insecticidal activity on comparing the KD values of the synthesized compounds (Va-Vf, table 7), all the synthesized compounds (except Vc and Vd) have shown better insecticidal activity than the control, and can thus serve as better antiinsecticidal agents.

The synthetic protocol, followed here, is out line in scheme (i). The 5-nitroindole was prepared by Vogel's the method.[11] The ethyl chloroacetate reacts with 5-nitro indole as an active methylene group to form an ester (ii). The synthesis of the N'-indole-acetylhydrazine (iii) by a addition reaction. In this step nitrogen atom donates lone pair electrons to the carbonyl carbon atom.

The synthesis of compounds (IVa-IVf) : N'-Indole acetyl hydrazine reacts with different type of aromatic aldehydes like a schiff base reaction. In the last N'-(substituted benzylidine hydrazidomethyl) indole (IVa-IVf) reacts with thioglycollic acid in the presence of zinc chloride to form the final products (Va-Vf) the structure of synthesized compounds have been characterized by IR ^{1}HNMR and elemental analysis.

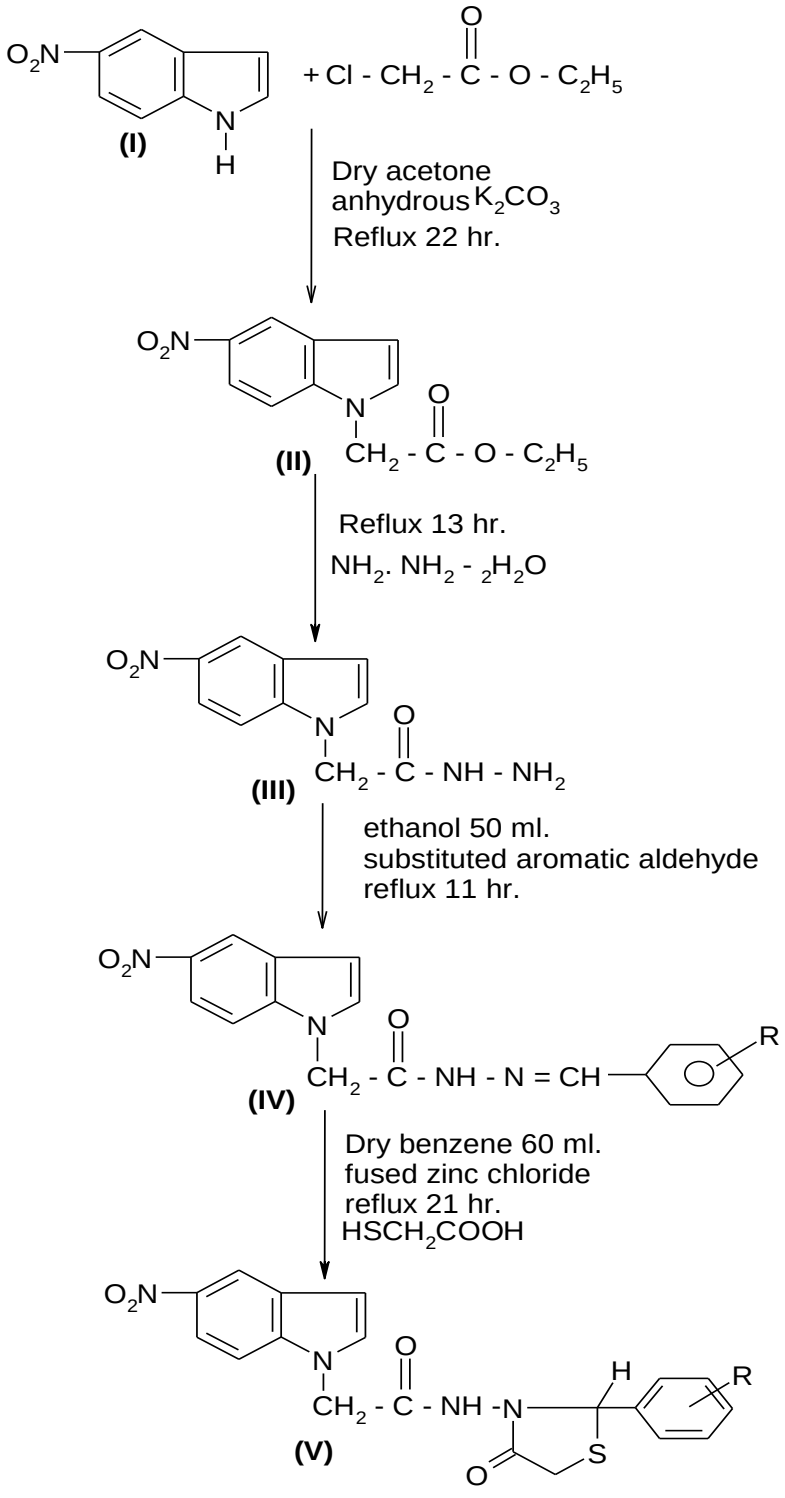
Conclusion

The present investigation reveals that the synthesized compounds Va, Vb and Vd have greater activity than that of the antibiotic streptomycin against S. aureus and can thus serve better for its inhibition. The above said synthesized compounds possess more potential than streptomycin to combat the harmful effect of the bacteria S.

aureus at a cheaper rate to the farmers in the fields. Similarly the synthesized compound Vd has shown greater efficacy than Griseofulvin against the fungi A. paraciticus. Hence the above said compound may prove a better antifungal agent to combat the harmful effects of the *A. paraciticus.*

Regarding the insecticidal activity, the synthesized compounds (Va-Vf) have exhibited better insecticidal efficacy than cypermethrin (control) and can thus serve as better antiinsecticidal agents.

Keeping in mind the above discussed facts regarding antimicrobial and insecticidal activity of the synthesized compounds. We may conclude that they can prove very beneficial to man to mankind in the era of 21st century.


+ Cl - CH2 - C - O - C2H5
(I)
Dry acetone
anhydrous K2CO3
Reflux 22 hr.
(II)
Reflux 13 hr.
NH2. NH2 - 2H2O
(III)
ethanol 50 ml.
substituted aromatic aldehyde
reflux 11 hr.
(IV)
Dry benzene 60 ml.
fused zinc chloride
reflux 21 hr.
HSCH2COOH
(V)

Scheme 1

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