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SYNTHESIS AND ANTIMICROBIAL ACTIVITY OF NEW INDOLE DERIVATIVES

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ABSTRACT

Twenty one new 2-{(benzalamino-4-hydroxybenzyl) (1, 3, 4)-oxadiazino[6, 5-b]} indole derivatives (**V**) have been synthesized by condensing 2-amino-4-[(1, 3, 4)oxadiazino[6,5-b]indole-3-yl]-phenol (**IV**) with various aromatic aldehydes. The intermediates, on the other hand, have been synthesized by the cyclization of 3-amino-4-hydroxy-benzoic acid (2-oxo-1, 2-dihydro-indol-3-ylidene)-hydrazide (**III**) in presence of concentrated H_2SO_4. The title compounds have been purified and characterized by their analytical and spectral data and screened for their antimicrobial activity.

Key words: (1, 3, 4)Oxadiazino-[5, 6-b] indole, Isatin derivatives, Antimicrobial activity.

INTRODUCTION

It is known from the literature that indole derivatives exhibit varied biological and pharmacological properties[1-7] viz. antimicrobial, antiviral, anti-neoplastic, analgesic, CNS activities etc. In view of these observations, the synthesis of some new (1, 3, 4)oxadiazino-[5, 6-b]- indole derivatives **(V)** has been carried out (**Scheme 1**)

EXPERIMENTAL

Methods

The melting points (^{0}C) were recorded in open capillaries using Toshniwal melting point apparatus and are uncorrected. The purity of the compounds were checked by TLC using ethyl acetate and chloroform (0.5 mL : 1.5 mL) as solvent system and iodine vapours as visualizing agents. The IR spectra were recorded on Perkin-Elmer Infracord-283

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spectrophotometer. PMR spectra were recorded on OMEGA-500 MHz spectrophotometer using TMS as an internal standard. Mass spectra were recorded by the direct inlet method on FINNINIGAN MAT -90 in the EI mode.

General procedure

Isatins **(I)**, 3-amino-4-hydroxybenzoic acid hydrazide **(II)** were synthesized by the methods available in literature.

3-Amino-4-hydroxy-benzoic acid (2-oxo-1,2-dihydro-indol-3-ylidene)-hydrazide (III)

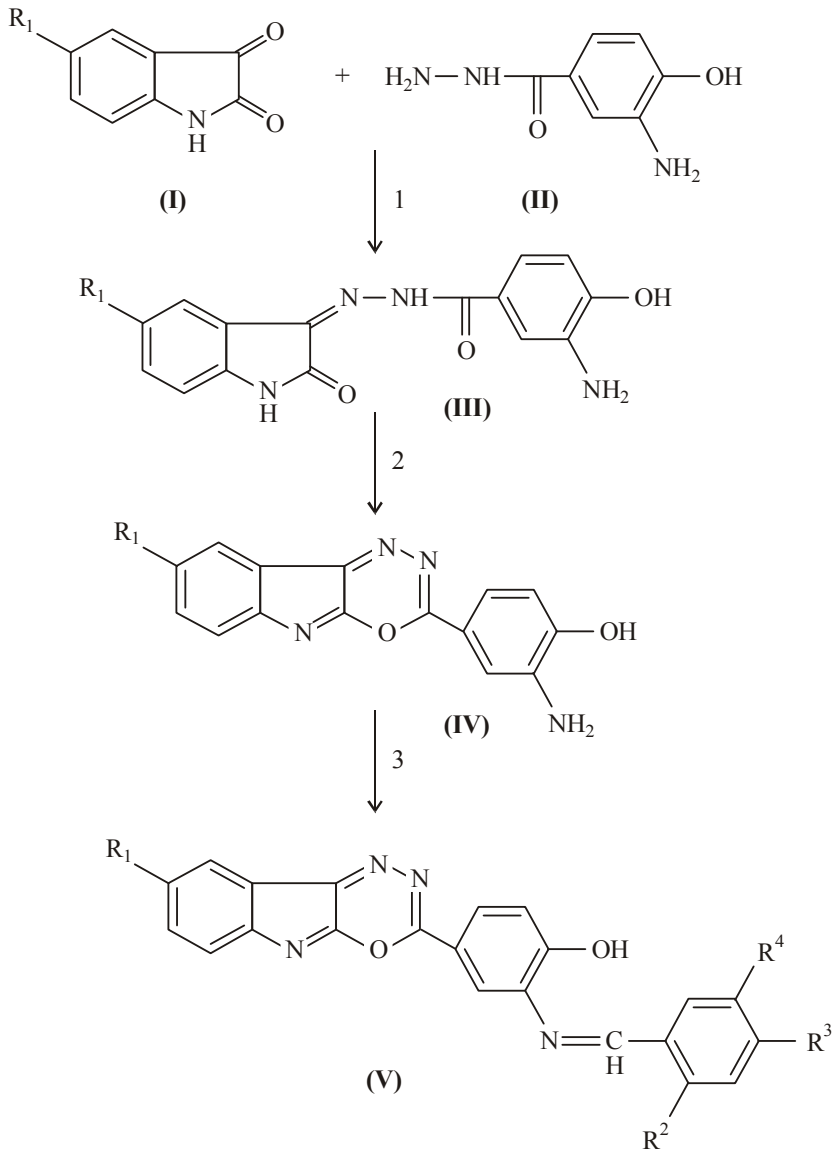
An appropriate isatin (**I**, 0.01 mol) was heated under reflux, in ethanol (50 mL) with 3-amino-4-hydroxybenzoic acid hydrazide (**II**, 0.01 mol) for 1.5 hrs. The product thus separated was filtered and purified by recrystallization from suitable solvents. The physical constants were compared with the literature values.

2-Amino-4-[(1, 3, 4)oxadiazino[6, 5-b]indole-3-yl]-phenol (IV)

An appropriate 3-amino-4-hydroxybenzoic acid (2-oxo-1,2-dihydro-indol-3-ylidene)-hydrazide (**III**, 0.0.1 mol) was dissolved in 10 mL of concentrated sulphuric acid. The reaction mixture was kept aside for 2 hours, poured onto crushed ice and neutralized with sodium bicarbonate solution. The product **(IV)** thus separated was filtered and recrystallized from suitable solvents.

2-[(Benzalamino-4-hydroxybenzyl) (1, 3,4)-oxadiazino(6,5-b)]indole (V)

Each of the 2-amino-4-([1, 3, 4]oxadiazino[6, 5-b]indole-3-yl)-phenol (**IV**, 0.01 mol) was heated with an aromatic aldehyde (benzaldehyde, *p*-chlorobenzaldehyde, salicylaldehyde, anisaldehyde, veratraldehyde, *p*-dimethylaminobenzaldehyde and vanilaldehyde) in ethanol (20 mL) and few drops of acetic acid, under reflux on water bath for 3 hours. The solvent was removed to the possible extent by distillation under reduced pressure. The product thus obtained was filtered, washed with water and purified by recrystallization from suitable solvent (Table 1), for example, 2-amino-4-(8-fluoro-[1, 3, 4]oxadiazino[6, 5-b]indol-3-yl)phenol (**IV**, R^1 = F) was condensed with benzaldehyde to get a single product. This on purification by recrystallization from methanol and DMF (1 : 1) has resulted in yellow solid, m.p. 286^0C. It was characterized as 2-(benzylideneamino)-4-(8-fluoro-[1, 3, 4]oxadiazino-[6, 5-b]indol-3-yl)phenol (**V(1)**). Its IR spectrum (in KBr) showed characteristics absorption bands (in cm^1) at 1610 (C=N) and 1100 (C-O-C). PMR spectrum (in DMSO-d_6) showed characteristic signals (in δ ppm) at 12.5 (s, 1H, -OH) and 7.1 -8.9 (m, 11H, Ar-H). The mass spectrum of the compound showed its molecular ion peak (M^+) at m/z 386. It exhibited the fragmentation pattern characteristic of the compound.



1. Ethanol; 2. Con. H_2SO_4; 3. Aromatic aldehyde/Ethanol/few drops of acetic acid
R^1 = H, Br, NO_2; R^2 = H, OH; R^3 = H, OH, OCH_3, $N(CH_3)_2$; R^4 = H, OCH_3

Scheme 1

Antimicrobial Activity

The antibacterial activity of the test compounds was assayed against *Bacillus subtilis, Staphylococcus aureus* (gram – positive) and *Escherichia coli* and *Proteus vulgaris* (gram –

negative) by CUP-plate method[8]. The antifungal activity of test compounds was determined against *A. niger, C. verticulata, F. oxysporum and A. flavus* by the cup-plate method[9]. The results are presented in Table 3.

RESULTS AND DISCUSSION

The required indole-2, 3-diones **(I)** were prepared and condensed with 3-amino-4-hydroxybenzoicacidhydrazide **(II)** in ethanol to get the respective 3-amino-4-hydroxy-benzoic acid (2-oxo-1, 2-dihydro-indol-3-ylidene)-hydrazide **(III)**. These compounds were cyclized using concentrated sulfuric acid to get respective 2-amino-4-[(1, 3, 4)oxadiazino[6, 5-b]indole-3-yl]-phenol **(IV)**. These compounds were refluxed with aromatic aldehyde, ethanol and few drops of acetic acid to get the title compounds as shown in **Scheme 1**. The compounds were characterized by their physical, analytical and spectral data (IR, PMR and MASS). The physical and analytical data are presented in Tables 1 and 2 and data on antimicrobial activities are presented in Table 3.

Table 1: Physical and analytical data of new (1, 3, 4)oxadiazino-[5, 6-b]indole (V) derivatives

Compd.	Substituents				Molecular formula	M.P. (^{0}C)	R_f Value	Yield (%)
	R^1	R^2	R^3	R^4				
V(1)	F	H	H	H	$C_{22}H_{13}N_4O_2F$	268	0.659	88
V(2)	F	H	Cl	H	$C_{22}H_{12}N_4O_2ClF$	256	0.557	86
V(3)	F	OH	H	H	$C_{23}H_{13}N_4O_3F$	296	0.501	85
V(4)	F	H	OCH_3	H	$C_{23}H_{15}N_4O_3F$	233	0.780	89
V(5)	F	H	OCH_3	OCH_3	$C_{24}H_{17}N_4O_4F$	262	0.670	90
V(6)	F	H	$N(CH_3)_2$	H	$C_{24}H_{18}N_5O_2F$	>300	0.739	86
V(7)	F	H	OH	OCH_3	$C_{23}H_{15}N_4O_4F$	239	0.697	87
V(8)	Cl	H	H	H	$C_{22}H_{13}N_4O_2Cl$	284	0.698	90
V(9)	Cl	H	Cl	H	$C_{22}H_{12}N_4O_2Cl_2$	298	0.721	91
V(10)	Cl	OH	H	H	$C_{23}H_{13}N_4O_3Cl$	261	0.540	83

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Compd.	Substituents				Molecular formula	M.P. (^{0}C)	R_f Value	Yield (%)
	R^1	R^2	R^3	R^4				
V(11)	Cl	H	OCH_3	H	$C_{23}H_{15}N_4O_3Cl$	240	0.668	81
V(12)	Cl	H	OCH_3	OCH_3	$C_{24}H_{17}N_4O_4Cl$	298	0.820	85
V(13)	Cl	H	$N(CH_3)_2$	H	$C_{24}H_{18}N_5O_2Cl$	276	0.932	81
V(14)	Cl	H	OH	OCH_3	$C_{23}H_{15}N_4O_4Cl$	293	0.912	83
V(15)	CH_3	H	H	H	$C_{23}H_{16}N_4O_2$	>300	0.721	79
V(16)	CH_3	H	Cl	H	$C_{23}H_{15}N_4O_2Cl$	234	0.742	81
V(17)	CH_3	OH	H	H	$C_{24}H_{16}N_4O_3$	256	0.554	80
V(18)	CH_3	H	OCH_3	H	$C_{24}H_{18}N_4O_3$	269	0.829	81
V(19)	CH_3	H	OCH_3	OCH_3	$C_{25}H_{20}N_4O_4$	225	0.876	88
V(20)	CH_3	H	$N(CH_3)_2$	H	$C_{25}H_{21}N_5O_2$	298	0.901	81
V(21)	CH_3	H	OH	OCH_3	$C_{24}H_{18}N_4O$	256	0.889	81

Table 2: Analytical data of new (1, 3, 4)oxadiazino-[5, 6-b]indole (V) derivatives

Compd.	Calculated						Found					
	C%	**H%**	**N%**	**O%**	**Cl%**	**F%**	**C%**	**H%**	**N%**	**O%**	**Cl%**	**F%**
V(1)	68.75	3.41	14.58	8.33	-	4.94	69.01	3.23	14.65	8.78	-	4.78
V(2)	63.09	2.89	13.38	7.64	8.47	4.54	63.21	2.98	13.78	7.90	8.89	4.98
V(3)	66.00	3.27	13.99	11.99	-	4.75	69.90	3.78	13.89	11.09	-	4.56
V(4)	66.66	3.65	13.58	11.58	-	4.58	67	3.98	13.09	11.56	-	4.43
V(5)	64.86	3.86	12.61	14.40	-	4.27	64.36	3.90	12.78	14.36	-	4.23
V(6)	67.44	4.24	16.38	7.49	-	4.44	67.13	4.65	16.93	7.47	-	4.67
V(7)	64.19	3.51	13.02	14.87	-	4.41	64.57	3.87	13.90	14.97	-	4.25
V(8)	65.92	3.27	13.98	7.98	8.85	-	65.87	3.56	13.78	7.45	8.66	-

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Compd.	Calculated						Found					
	C%	H%	N%	O%	Cl%	F%	C%	H%	N%	O%	Cl%	F%
V(9)	60.71	2.78	12.87	7.35	16.29	-	61.07	2.90	12.13	7.24	16.87	-
V(10)	63.39	3.14	13.44	11.52	8.51	-	64.30	3.23	13.45	11192	8.66	-
V(11)	64.12	3.51	13.00	11.14	8.23	-	64.32	3.45	13.56	11294	8.45	-
V(12)	62.55	3.72	12.16	13.89	7.69	-	63.01	3.89	12.167	13999	7.25	-
V(13)	69.94	4.09	15.78	7.21	7.99	-	70.00	4.21	15.34	7.46	7.76	-
V(14)	61.82	3.38	12.54	14.32	7.93	-	61.89	3.46	12.09	14.89	7.87	-
V(15)	72.62	4.24	14.73	8.41	-	-	72.87	4.56	14.24	8.67	-	-
V(16)	66.59	3.64	13.51	7.71	8.55	-	66.56	3.89	13.56	7.89	8.23	-
V(17)	69.99	4.07	14.13	12.11	-	-	69.90	4.01	14.46	12.67	-	-
V(18)	70.23	4.42	13.65	11.69	-	-	70.48	4.56	13.98	11.86	-	-
V(19)	68.17	4.58	12.72	14.53	-	-	68.99	4.78	12.90	14.90	-	-
V(20)	70.91	5.00	16.54	7.56	-	-	71.09	5.05	16.34	7.54	-	-
V(21)	67.60	4.25	13.14	15.01	-	-	67.98	4.56	13.14	15.89	-	-

Table 3: Antimicrobial activity of new (1, 3, 4)oxadiazino-[5, 6-b]indole (V) derivatives

Compd.	Antibacterial activity (Zone of inhibition in mm)				Antifungal activity (Zone of inhibition in mm)			
	B. Subtillis	***S. Aureus***	***E. coli***	***P. vulgaris***	***A. niger***	***C. verticulata***	***F. oxysporum***	***A. flavus***
V(1)	15	13	12	10	17	14	10	09
V(2)	17	15	13	12	15	16	13	11
V(3)	15	12	10	10	13	14	10	09
V(4)	13	10	13	09	11	12	07	09
V(5)	14	13	14	12	11	10	08	08

Cont…

Compd.	Antibacterial activity (Zone of inhibition in mm)				Antifungal activity (Zone of inhibition in mm)			
	B. Subtillis	***S. Aureus***	***E. coli***	***P. vulgaris***	***A. niger***	***C. verticulata***	***F. oxysporum***	***A. flavus***
V(6)	15	12	10	11	13	12	11	10
V(7)	10	12	09	11	14	13	11	06
V(8)	17	16	13	13	13	14	08	09
V(9)	19	17	15	14	17	16	13	11
V(10)	15	12	13	12	14	14	06	10
V(11)	13	14	14	13	12	11	12	09
V(12)	15	12	12	10	13	12	13	10
V(13)	16	15	14	13	16	13	12	08
V(14)	14	13	13	11	12	10	09	09
V(15)	12	11	12	11	14	09	07	04
V(16)	13	14	14	10	10	13	06	07
V(17)	10	10	09	11	12	10	10	06
V(18)	09	13	12	13	10	13	08	09
V(19)	11	11	08	12	10	11	10	05
V(20)	12	09	13	11	12	10	07	08
V(21)	11	08	11	13	13	12	10	06
Ampicillin (10 µg/cup)	22	20	18	17	-	-	-	-
Clotrimazole (10 µg/cup)	-	-	-	-	21	22	23	15

*Concentration of test compound:100 µg/cup

The title compounds were characterized by their physical, analytical and spectral data. The details of the compounds have been given in the experimental section. The

antibacterial data of 2-[(benzalamine-4-hydroxybenzyl) (1, 3, 4)-oxadiazino[6, 5-b]]indole **(V)** indicate that these compounds exhibited a marginal antibacterial activity, interestingly, against all the fours strains of bacterial and almost to the same extent. The compounds exhibit antifungal activity against all the four strains fungi employed but of course with a degree of variation. These compounds were found to be relatively more effective against *A. niger* and *C. verticulata.*

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