SYNTHESIS OF SOME ARYLAMIDES, SULPHONAMIDES AND 5-OXO-IMIDAZOLINES AS NOVEL BIOACTIVE COMPOUNDS DERIVED FROM BENZIMIDAZOLE

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ABSTRACT

A number of new arylamides ***(2a-o)***, sulphonamides ***(3a-p)*** and 5-oxo imidazolines ***(4a-o)*** have been synthesised by the condensation of acid hydrazide of o-benzoylene-2,1-benzimidazole ***1*** with different aromatic acid chlorides, aryl carboxy sulphonylchlorides and azlactones in dry pyridine. All the products were evaluated ***invitro*** for their antimicrobial activity against several microbes and antitubercular activity against ***Mycobacterium tuberculosis H37Rv***.

INTRODUCTION

Although a large number of benzimidazole analogs have been synthesised, there still exists much scope for the synthesis of benzimidazole derivatives possessing different pharmacophores. (1-5).

Literature survey reveals that various arylamides, sulphonamides and 5-oxo-imidazolines have resulted in many potential drugs. This observation prompted us to synthesise some new aryl amides (6,7), sulphonamides (8,9) and 5-oxo-imidazolines (10,11) derivatives bearing benzimidazole moiety, with a view to studying their pharmacological profile.

The starting compound o-benzoylene-2,1-benzimidazole is prepared by the condensation of o-phenylenediamine with phthalic anhydride in presence of acetic anhydride. The acid hydrazide ***1*** was synthesised by reaction of o-benzoylene-2,1-benzimidazole with hydrazine hydrate. Benzoyl-(benzimidazol-2'-yl-o-benzoyl) hydrazines ***(2a-o)*** and 2-Arylsulphonyl (benzimidazol-2'-yl-o-benzoyl) hydrazines ***(3a-p)*** have been prepared by the condensation of Benzimidazol-2-yl-o-benzoyl hydrazide ***1*** with different aromatic acid chlorides and arylcarboxy sulphonyl chloride in presence of dry pyridine (scheme). Preparation of aryl carboxy sulphonyl chloride has been undertaken as described by Cremlyn (12). 4-Arylidene-(benzimidazol-2'-yl-o-benzamido)-2-phenyl-5-oxo-imidazolines ***(4a-o)*** have been synthesised by refluxing ***1*** with different azlactones in few drops of dry pyridine (Scheme). The azlactone were prepared by the condensation of arylaldehyde with phenyl glycine in presence of sodium acetate and acetic anhydride. (13).

The constitution of all the products was characterised by elemental analyses like IR and PMR spectral study. Arylamides ***(2a-o)*** and 5-oxo-imidazolines ***(4a-o)*** are evaluated ***in vitro*** for their antimicrobial activity against different strains of bacteria and fungi. Moreover all the compounds were also screened ***in vitro*** for their antitubercular activity towards a strain of ***Mycobacterium tuberculosis H37Rv***.

RESULTS AND DISCUSSION

Arylamides ***(2a-o)*** and 5-oxo-imidazolines ***(4a-o)*** were tested ***invitro*** for antimicrobial activity against Gram-positive bacteria ***Bacillus megaterium***, and ***Bacillus subtilis***, Gram-negative bacteria ***Escherichia coli*** and ***Pseudomonas fluorescens*** and fungi ***Aspergillus awamori***. Activity of the compounds was compared with known antibiotics at the same concentration level. Under the identical condition the known standard antibiotics showed zones of inhibition like Ampicillin

(16-25 mm), Chloramphenicol (20-30 mm), Norfloxacin (15-30), against bacterial strains and Greseofulvin showed zones of inhibition (15-25 mm) against ***A. awamori***.

From the table-2, it can be concluded that the compounds ***2h, 2i, 2l, 4d, 4j, 4i*** were highly active against ***B. megaterium***. The compounds ***2b, 2c, 2k, 2m, 2l, 4a, 4m, 4o*** showed significant activity against ***B. subtilis, P. fluorescens*** and ***A. awamori***. In case of ***E. coli,*** all the compounds have exhibited highest activity.

All the new synthesised compounds reported in Table-1 were screened ***in vitro*** for their antitubercular activity against ***Mycobacterium Tuberculosis H37Rv***. The activity exhibited by reference standard drug Rifampin (which showed 97% inhibition) was compared.

The antitubercular activity data showed that some of the compounds exhibited significant activity against ***H37Rv*** strain. It has been observed from the Table-2, that compounds ***2b, 2f, 4d, 3d, 3i, 4f*** showed good activity (>50% inhibition). The compounds ***2k, 3a, 4o*** have been selected for their pharmaceutical screening by E. MERCK Ltd. USA.

INVITRO EVALUATION OF BIOLOGICAL STUDIES

The antitubercular evaluation of the compounds was carried out at "Tuberculosis Antimicrobial Acquisition And Coordinating Facility" (TAACF) USA. Primary screening of the compounds for antitubercular activity have been conducted at 12.5 ug/ml against ***Mycobacterium tuberculosis H37Rv***, in BACTEC 12B medium using BACTEC 460 radiometric system. Antitubercular activity data were compared with standard drug Rifampin at 0.031µg/ml concentration which showed 97% inhibition.

Compounds ***(2a-o)*** and ***(4a-o)*** were screened ***in vitro*** for antibacterial and antifungal activities at 50µg / ml concentrations. The test organisms chosen were ***Bacillus megaterium, Bacillus Subtilis, Escherichia coli, Pseudomonas flourescens*** and fungi ***Aspergillus awamori.*** Cup-plate agar diffusion method (14) was used to measure the activity. Known antibiotics like Ampicillin, Chloramphenicol, Norfloxacin and Greseofulvin were used for comparison purpose.

EXPERIMENTAL

All the melting points are taken in open capillary in a liquid paraffin bath and are uncorrected. Purity of all compounds were checked by TLC. Infra red spectra (KBr) were recorded on Shimadzu-435-IR Spectrophotometer and ^{1}H-PMR Spectra on Brucker-300F MHz using TMS as an internal standard.

Preparation of Benzimidazol-2-yl-o-benzoyl hydrazide *1*

A mixture of o-benzoylene-2, 1-benzimidazole (1.68g, 0.01 mol) and hydrazine hydrate (0.5 ml, 0.01 mol) was refluxed for 3 hrs in oil bath at 120^{o}C. The reaction mixture was poured on to crushed ice. The product was isolated and crystallised from DMF. Yield : 80%, m.p. Above 300^{o}C, Calcd. for $C_{14}H_{12}ON_4$: C, 66.66, H, 4.76, N, 22.22%. Found : C 65.00, H 4.50, N 21.40%.

Preparation of Benzoyl-(benzimidazol-2'-yl-o-benzoyl) hydrazines *(2a-o)*.

A mixture of aromatic acid (1 gm) and thionyl chloride (5ml) was refluxed for 6 hrs. in water bath. Excess of thionyl chloride was distilled off. The acid chloride obtained was refluxed for additional 3 hrs with benzimidazol-2-yl-o-benzoyl hydrazide *1* in pyridine. Excess of solvent was removed under reduced pressure. The reaction mixture was poured on to crused ice. The solid mass

was filtered, dried, and crystallised from DMF. ***2h*** Yield : 69%,m.p. 170°C, Calcd for $C_{22}H_{18}O_3N_4$: C 74.57, H 5.80, N 14.50 %. Found : C 74.12, H 5.0, N 13.85 % $IR_{\upsilon max}$ (KBr) : 3400 (N-H Str.), 1680 (C=O Str.), 1650 (-CO-NH Str.), 1610(C=N Str.), 1250 (C-O-C Str.), 1160 (C-N Str.), cm^{-1}; ^{1}H-PMR δppm. (TFA) : 4.03 (s, 3H, $-OCH_3$), 7.0-7.9 (m, 12H, Ar-H), 8.09 (s, 2H, $(-CONH)_2$). TLC solvent system-benzene : acetone (9:1)

Similarly other members of ***2*** were synthesised. The physical constants are recorded in Table -1.

Preparation of Aryl sulphonyl-(benzimidazol-2'-yl-o-benzoyl) hydrazines *(3a-p)*.

Benzimidazol-2-yl-o-benzoyl hydrazide ***1*** (0.01 mol) and aryl carboxy sulphonyl chloride (0.01 mol) was refluxed in dry pyridine (10 ml) for 4-5 hours. The content was poured on to crushed ice. The seperated solid was filtered, dried and crystallised from dioxane : dimethyl formamide mixture ***3h*** Yield 70% m.p. 290°C, Calcd for $C_{22}H_{18}O_6N_4S$: C 56.65, H 3.86, N 12.01 %. Found : C 55.59, H 3.13, N 11.10 % IRυmax (KBr) :3395 (N-H Str.), 1657 (C=O Str.), 1621 (S=O Str.(asym)), 1595(C=N Str.),1200 (C-O-C Str.), 1178 (S=O Str.(sym)),1118 (C-N Str.), 891 ($N-SO_2$ Str.)cm^{-1} ; ^{1}H-PMR δppm. (TFA) : 3.99 (s, 3H, $-OCH_3$), 7.0-7.9 (m, 12H, Ar-H), 8.1 (s, 1H, -CONH),8.4 (s, 1H, NH-H), TLC solvent system benzene : acetone (7:3).

Similarly other members of ***3*** were synthesised. The physical constants are recorded in Table -1.

Preparation of 4-Arylidene-(benzimidazol-2'-yl-o-benzamido)-2-phenyl-5-oxo-imidazolines *(4a-o)*.

Benzimidazol-2-yl-o-benzoyl hydrazide ***1*** (0.01 mol) and 4-arylidene-2-phenyl-5-oxazolinone (0.02 mol) was refluxed in dry pyridine (20 ml) for 6 hrs. The excess of solvent was removed under reduced pressure. The resulting mass was poured on to crushed ice. The solid mass was filtered, dried and crystallised from DMF. ***4k***, Yield : 72%, m.p. 181°C, Calcd for $C_{31}H_{23}O_3N_5$: C 73.14, H 4.38, N 13.64 %. Found : C 73.00, H 4.20, N 13.29 % IR_{υ}max (KBr) : 3250 (N-H Str.), 1695(C=O Str.), 1650 (-CONH Str.), 1600 (C=N Str.),1200 (C-O-C Str.), 1011 (C-N Str.) cm^{-1} ; ^{1}H-PMR δppm. (TFA) : 3.89 (s, 3H, $-O\underline{CH}_3$), 6.9 (s, 1H, =CH-Ar),7.3-7.9 (m, 17H, Ar-H), 8.05 (S, 1H, NH-N), TLC solvent system benzene : acetone (7:3).

SCHEME

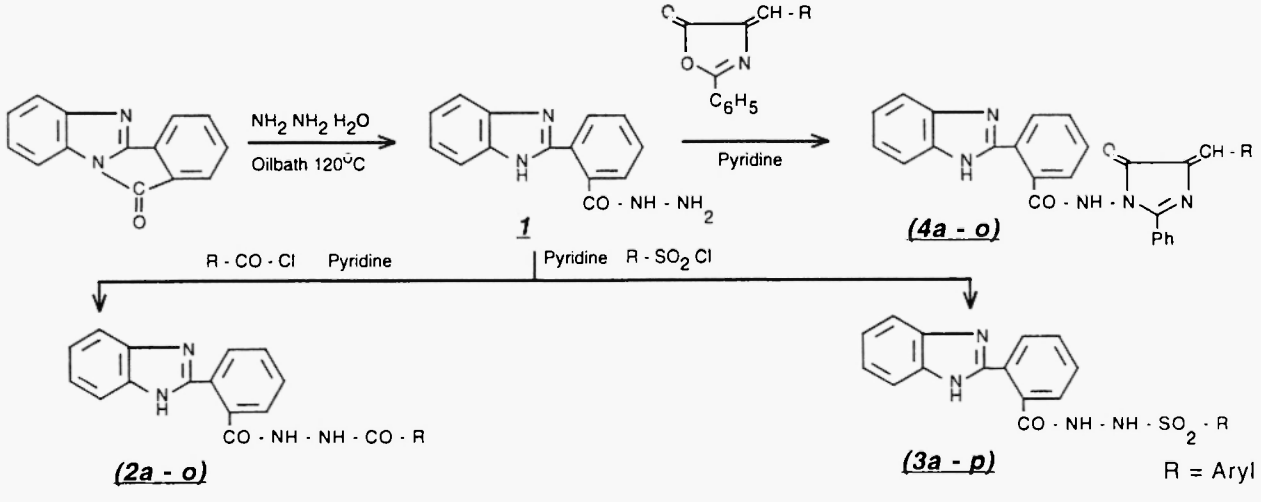

Table - 1 : Physical constants of the compounds (2a-o), (3a-p) and (4a-o).

Compd.	R	Molecular Formula	M.P. °C	Yield %	Nitrogen %	
					Calcd.	Found
1	2	3	4	5	6	7
2a	$-C_6H_5$	$C_{21}H_{16}O_2N_4$	155	69	15.73	15.09
2b	$4\text{-Br-}C_6H_4$	$C_{21}H_{15}O_2N_4Br$	171	77	12.90	11.99
2c	$2\text{-Cl-}C_6H_4$	$C_{21}H_{15}O_2N_4Cl$	193	76	14.35	14.10
2d	$4\text{-Cl-}C_6H_4$	$C_{21}H_{15}O_2N_4Cl$	199	79	14.35	13.76
2e	$3,4\text{-}(OCH_3)_2\text{-}C_6H_3$	$C_{23}H_{20}O_4N_4$	165	73	13.46	12.89
2f	$2\text{-OH-}C_6H_4$	$C_{21}H_{16}O_3N_4$	169	71	15.05	14.02
2g	$2\text{-}OCH_3\text{-}C_6H_4$	$C_{22}H_{18}O_3N_4$	179	68	14.50	14.00
2h	$4\text{-}OCH_3\text{-}C_6H_4$	$C_{22}H_{18}O_3N_4$	170	69	14.50	13.85
2i	$2\text{-}CH_3\text{-}C_6H_4$	$C_{22}H_{18}O_2N_4$	191	71	15.13	14.03
2j	$3\text{-}CH_3\text{-}C_6H_3$	$C_{22}H_{18}O_3N_4$	175	70	15.13	14.60
2k	$4\text{-}CH_3\text{-}C_6H_4$	$C_{22}H_{18}O_3N_4$	170	69	15.13	14.96
2l	$2\text{-}NO_2\text{-}C_6H_4$	$C_{21}H_{15}O_4N_5$	160	71	17.45	16.40
2m	$3\text{-}NO_2\text{-}C_6H_4$	$C_{21}H_{15}O_4N_5$	216	77	17.45	16.76
2n	$-CH{=}CH\text{-}C_6H_5$	$C_{23}H_{18}O_2N_4$	205	79	14.65	14.03
2o	$3,4,5\text{-}(OCH)_3\text{-}C_6H_2$	$C_{23}H_{18}O_3N_4$	215	74	14.62	13.21
3a	$-C_6H_5$	$C_{20}H_{16}O_3N_4S$	260	69	14.28	14.39
3b	$4\text{-}NHCOCH_3\text{-}C_6H_4$	$C_{22}H_{16}O_4N_5S$	249	67	15.59	15.09
3c	$3\text{-COOH-4-}NHCOCH_3\text{-}C_6H_3$	$C_{23}H_{19}O_6N_5S$	215	61	14.19	13.20
3d	$4\text{-Br-}C_6H_4$	$C_{20}H_{15}O_3N_4SBr$	245	67	11.91	10.20
3e	$3\text{-COOH-}C_6H_4$	$C_{21}H_{16}O_5N_4S$	210	69	12.84	11.93
3f	$3\text{-COOH-4-OH-}C_6H_3$	$C_{21}H_{16}O_6N_4S$	195	66	12.38	11.49
3g	$3\text{-COOH-4-}OCH_3\text{-}C_6H_3$	$C_{22}H_{18}O_6N_4S$	300	71	12.01	11.63
3h	$3\text{-COOH-6-}OCH_3\text{-}C_6H_3$	$C_{22}H_{18}O_6N_4S$	290	70	12.01	11.10
3i	$3\text{-COOH-4-}CH_3\text{-}C_6H_3$	$C_{22}H_{18}O_5N_4S$	180	71	12.94	11.50
3j	$3\text{-COOH-6-}CH_3\text{-}C_6H_3$	$C_{22}H_{18}O_5N_4S$	220	63	12.44	11.93
3k	$2\text{-Cl-}C_6H_4$	$C_{20}H_{15}O_3N_4SCl$	250	63	13.13	12.45
3l	$4\text{-Cl-}C_6H_4$	$C_{20}H_{15}O_3N_4SCl$	269	71	13.13	12.93
3m	$2,5\text{-}Br_2\text{-}C_6H_3$	$C_{20}H_{14}O_3N_4SBr_2$	235	70	10.21	9.45
3n	$2,5\text{-}Cl_2\text{-}C_6H_3$	$C_{20}H_{14}O_3N_4SCl_2$	290	61	12.14	12.43
3o	$4\text{-}CH_3\text{-}C_6H_5$	$C_{21}H_{18}O_3N_4S$	239	72	13.79	12.99
3p	$3\text{-COOH-CH=CH-}C_6H_4$	$C_{22}H_{18}O_5N_4S$	245	72	12.12	11.03

Compd.	R	Molecular Formula	M.P.°C	Yield %	Nitrogen %	
					Calcd.	Found
1	2	3	4	5	6	7
4a	$-C_6H_5$	$C_{30}H_{21}O_2N_5$	196	71	14.49	14.40
4b	$2\text{-Cl-}C_6H_4$	$C_{30}H_{20}O_2N_5Cl$	203	79	13.53	13.21
4c	$4\text{-Cl-}C_6H_4$	$C_{30}H_{20}O_2N_5Cl$	210	63	13.53	13.41
4d	$3,4\text{-}(OCH_3)_2\text{-}C_6H_3$	$C_{32}H_{25}O_4N_5$	190	77	12.89	11.99
4e	$4\text{-N,N-}(CH_3)_2\text{-}C_6H_4$	$C_{32}H_{26}O_2N_6$	215	69	15.96	15.45
4f	$-C_4H_3O$	$C_{28}H_{19}O_3N_5$	210	69	14.79	14.20
4g	$2\text{-OH-}C_6H_4$	$C_{30}H_{21}O_3N_5$	180	69	14.02	13.21
4h	$4\text{-OH-}C_6H_4$	$C_{30}H_{21}O_3N_5$	191	72	14.02	13.63
4i	$3\text{-OCH}_3\text{4-OH-}C_6H_3$	$C_{31}H_{23}O_4N_5$	193	79	13.23	12.74
4j	$2\text{-OCH}_3\text{-}C_6H_4$	$C_{31}H_{23}O_3N_5$	175	72	13.64	13.03
4k	$4\text{-OCH}_3\text{-}C_6H_4$	$C_{31}H_{23}O_3N_5$	181	72	13.64	13.29
4l	$2\text{-NO}_2\text{-}C_6H_4$	$C_{30}H_{20}O_4N_6$	165	71	15.90	15.64
4m	$3\text{-NO}_2\text{-}C_6H_4$	$C_{30}H_{20}O_4N_6$	169	73	15.90	15.02
4n	$-CH{=}CH\text{-}C_6H_5$	$C_{32}H_{23}O_2N_5$	205	75	13.75	12.83
4o	$3,4,5\text{-}(OCH)_3\text{-}C_6H_2$	$C_{33}H_{27}O_5N_5$	223	71	12.21	11.47

Table - 2 : Antimicrobial data (inhibition zone = 18-24 mm) and Antitubercular data (% inhibition > 50%) of some selected compounds which exhibited highest activity.

Standard *antibiotics*	*B.megaterium*	*B.subtilis*	*E.coli*	*Psflourescens*	*A.awamori*	*Mycobacterium tuberculosis H37 Rv* % inhi.
Chloramphenicol, (20-30 mm)	*2h, 2i, 2l, 4d, 4j, 3i*	*2k, 2m 4a, 4m*	*2o, 2c, 2a, 2d, 2m, 4c,*	*2k, 4k*	*2b, 2m, 2c 2c, 2l,*	*2b, 2f, 3d, 3i, 4f*
Ampicillin (16-25 mm)			*4b, 4d 4k, 4m*		*4m, 4o*	
Norfloxacin (15-30 mm)			*4n*			
Greseofulvin (15-25 mm)						
Rifampin 97% inhibition						

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