SYNTHESIS OF SOME NOVEL 1,3,4-OXADIAZOLES AND 5-OXO-IMIDAZOLINES AS POTENT BIOLOGICALLY ACTIVE AGENTS.

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ABSTRACT : 1,3,4-Oxadiazoles ***2*** have been synthesised by the cyclocondensation of acid hydrazide of 5-nitro-o-benzoylene-2,1-benzimidazole ***1*** with different aromatic acids in presence of $POCl_3$, the same acid hydrazide ***1*** was made to react with different azlactones in dry pyridine which yielded 5-oxo-imidazolines ***3***. All the products were screened for their antimicrobial activity against several microbes and antitubercular activity against ***Mycobacterium tuberculosis H37 Rv***.

INTRODUCTION

During the past years, considerable evidence has been accumulated to demonstrate the efficacy of substituted 1,3,4 - oxadiazole and 5 - oxo - imidazoline derivatives in including antiinflammatory (1,2), antitubercular (3,4), antimalarial (5), antifungal (6,7), and antibacterial (8) activities. Moreover, benzimidazoles have aquired a special place in the heterocyclic field because of their diversified activities such as antiinflammatory (9) and antimicrobial activity (10). To further assess the pharmacological profile of such a class of compounds, the titled compounds bearing benzimidazole moiety have been synthesised.

The starting compound 5 - Nitro - o - benzoylene - 2,1 - benzimidazole is synthesised by the condensation of 3,4 - diamino nitro benzene with phthalic anhydride and acetic anhydride. The acid hydrazide ***1*** was obtained by treating 5 - nitro - o benzoylene - 2,1 - benzimidazole with hydrazine hydrate. 2-Aryl-5-(5'-nitro- benzimidazol -2'-yl-o-phenyl)-1,3,4-oxadiazoles ***2a-o*** have been prepared by the cyclocondensation of 5-nitro- benzimidazol-2-yl-o-benzoyl hydrazide ***1*** with different aromatic acids in presence of $POCl_3$ (scheme). 4-Arylidine-5-(5'-nitro benzimidazol -2'-yl-benzamido)-2-phenyl-5-oxo-imidazolines ***3a-m*** have been synthesised by reacting ***1*** with different azlactones in the presence of dry pyridine (scheme). The azlactones were prepared by the condensation of araldehydes with benzoyl glycine in presence of sodium acetate and acetic anhydride (11).

The constitution of all the products was established by elemental analyses like IR and PMR spectral study. All the compounds were screened for their antimicrobial activity against different strains of bacteria and fungi. Moreover, 1,3,4-oxadiazoles ***2a-o*** were also tested ***in vitro*** for their antitubercular activity towards a strain of ***Mycobacterium tuberculosis H37 Rv.*** Further work is under progress for 5 - oxo - imdazoline derivatives ***3a-m***.

RESULTS AND DISCUSSION

All the compounds reported in Table-2 were tested ***in vitro*** for their antimicrobial activity against various microbes. Under identical condition, the standard antibiotics showed zones of inhibition like Ampicillin 18-29 mm, Chloramphenicol 21 - 27 mm, Norfloxacin 20 - 28 mm against bacterial strains and Greseofulvin showed zones of inhibition of 15-25 mm against ***A. awamori***.

It can be concluded from the Table - 2 that the compounds **2c, 2g, 2h, 2i, 3c, 3g, 3i** and **3h** were highly active against ***B. megaterium***. The compounds **2b, 2e, 2l, 3b** and **3c, 3i, 3m 3g, 3l** showed significant activity against ***Ps. flourescens*** and ***A. awamori***. In case of ***E.coli*** all the compounds have displayed maximum activity.

The antitubercular activity of the compounds 2a-o have been evaluated against ***Mycobacterium tuberculosis H37 Rv***. The antitubercular activity data showed that some of the 1,3,4 - oxadiazoles exhibited various degree of activity (**0** to **79%**) except **2a, 2m, 2n** showed (**62, 58, 79%**) inhibition. The results are presented in Table-2. The compounds **2e** and **3d** have been selected for their agrochemical screening by Dupont Agricultural Products, USA and MERCK Pharmaceuticals, USA, respectively.

IN VITRO EVALUATION OF PHARMACOLOGICAL STUDIES

The antitubercular evaluation of the compounds was carried out at Tuberculosis Antimicrobial Acquisition Coordinating Facility (TAACF) U.S.A. Primary screening of the compounds for antitubercular activity have been conducted at 12.5 μg/ml against ***Mycobacterium tuberculosis H37 Rv*** in BACTEC 12B medium Using the BACTEC 460 radiometric system.

The antimicrobial activity was assayed by using the cup-plate agar diffusion method (**12**) by measuring the inhibition zones in mm. All the compounds were screened ***in vitro*** for their antimicrobial activity against a variety of bacterial strains such as ***Bacillus megaterium***, ***Escherichia coli***, ***Bacillus subtilis***, ***Pseudomonas flourescens*** and fungi such as ***Aspergillus awamori*** at a concentration of 50 μg. Known antibiotics like Chloramphenicol, Ampicillin, Norfloxacin and Greseofulvin were used for comparison purpose.

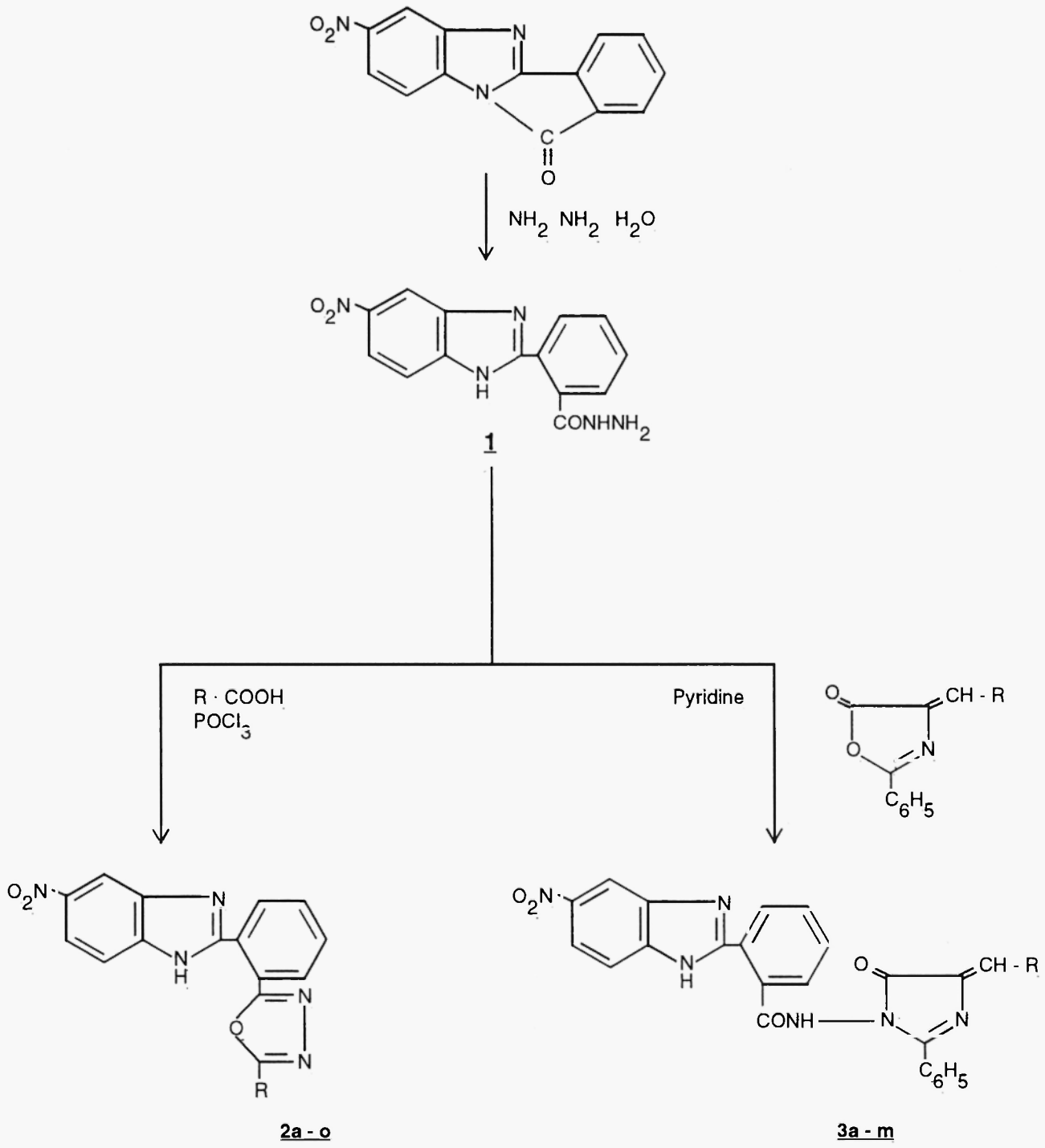
EXPERIMENTAL

All the melting points are uncorrected. Infrared spectra (KBr) were recorded on a Shimadzu-435-IR spectrophotometer and ^{1}H-PMR spectra on Brucker - 300 F MHz using TMS as an internal standard.

Preparation of 5-Nitro benzimidazol-2-yl-o-benzoyl hydrazide.

5-Nitro-o-benzoylene-2,1-benzimidazole (2.65 gm, 0.01 mol) was refluxed with hydrazine hydrate (0.5 ml, 0.01 mol) in oil bath for 4 hrs. The reaction was poured onto crushed ice. The

SCHEME



R=Aryl

Table - 1 : Physical constants of the compounds 2a-o and 3a-m.

compd.	R	Molecular Formula	M.P. (°C)	Yield (%)	%of N Found	%of N Calcd.
2a	C_6H_5-	$C_{21}H_{13}N_5O_3$	107	72	18.25	18.27
2b	-OCH_2-C_6H_5-	$C_{22}H_{15}N_5O_4$	150	63	14.85	14.89
2c	4-Br-C_6H_4-	$C_{21}H_{12}BrN_5O_3$	175	59	15.10	15.15
2d	2-Cl-C_6H_4-	$C_{21}H_{12}ClN_5O_3$	220	65	16.73	16.76
2e	3-Cl-C_6H_4-	$C_{21}H_{12}ClN_5O_3$	140	69	16.78	16.76
2f	4-Cl-C_6H_4-	$C_{21}H_{12}ClN_5O_3$	196	64	16.74	16.76
2g	2,4-$(OH)_2$-C_6H_3-	$C_{21}H_{13}N_5O_5$	220	60	16.88	16.86
2h	2-OH-C_6H_4-	$C_{21}H_{13}N_5O_4$	100	65	17.50	17.54
2i	2-OCH_3 C_6H_4-	$C_{22}H_{15}N_5O_4$	90	67	16.92	16.94
2j	4-OCH_3-C_6H_4-	$C_{22}H_{15}N_5O_4$	102	62	16.99	16.94
2k	2-CH_3-C_6H_4-	$C_{22}H_{15}N_5O_3$	80	62	17.60	17.63
2l	3-CH_3-C_6H_4-	$C_{22}H_{15}N_5O_3$	115	64	17.61	17.63
2m	3-NO_2-C_6H_4-	$C_{21}H_{12}N_6O_5$	254	70	16.31	16.35
2n	4-NO_2-C_6H_4-	$C_{21}H_{12}N_6O_5$	216	73	16.32	16.35
2o	-CH=CH-C_6H_5-	$C_{23}H_{15}N_5O_3$	108	60	17.10	17.11
3a	C_6H_5-	$C_{30}H_{20}N_6O_4$	270	75	15.85	15.90
3b	2-Cl-C_6H_4-	$C_{30}H_{19}ClN_6O_4$	140	67	14.90	14.93
3c	4-Cl-C_6H_4-	$C_{30}H_{19}ClN_6O_4$	123	69	14.91	14.93
3d	3,4-$(OCH_3)_2$-C_6H_3-	$C_{32}H_{24}N_6O_6$	140	62	14.26	14.28
3e	4-N,N-$(CH_3)_2$-C_6H_4-	$C_{32}H_{25}N_7O_4$	196	65	17.13	17.16
3f	-C_4H_3O-	$C_{28}H_{18}N_6O_5$	164	60	16.25	16.21
3g	2-OH-C_6H_4-	$C_{30}H_{20}N_6O_5$	170	69	15.49	15.44
3h	4-OH-C_6H_4-	$C_{30}H_{20}N_6O_5$	175	61	15.40	15.44
3l	4-OCH_3-C_6H_4-	$C_{31}H_{22}N_6O_5$	178	65	15.01	15.05
3j	2-NO_2-C_6H_4-	$C_{30}H_{19}N_7O_6$	155	70	17.05	17.10
3k	3-NO_2-C_6H_4-	$C_{30}H_{19}N_7O_6$	140	71	17.08	17.10
3l	-CH=CH-C_6H_5-	$C_{32}H_{22}N_6O_4$	188	59	15.13	15.16
3m	3,4,5-$(OCH_3)_3$-C_6H_2-	$C_{33}H_{26}N_6O_7$	165	60	13.55	13.59

product was isolated and crystallised from methanol. yield : 75 % ; m.p. : 220° C. Calcd. for $C_{14}H_{11}O_3N_5$: C 56.56, H 3.70, N 23.56 %. Found : C 56.45, H 3.65, N 23.58 % .

Preparation of 2-Aryl-5-(5'-nitro benzimidazol-2'-yl-o-phenyl)-1,3,4-oxadiazoles *2a-o*.

5-Nitro benzimidazol-2'-yl-o-benzoyl hydrazine (*1*, 0.01 mol) and aromatic acid (0.01 mol) was refluxed in $POCl_3$ (5ml) for 6 hrs. The content was cooled, poured onto crushed ice and neutralized with sodium bicarbonate solution. The separated solid was filtered, dried and crystallised from methanol. **2j** ; yield : 62%, M.P. 102° C, Calcd. for $C_{22}H_{15}O_4N_5$: C 63.92, H 3.63, N 16.94 %. Found : C 63.81, H 3.67, N 16.99 % IRυ_{max} (KBr) : 3300 (N-H str.), 1610 (C=N str.), 1350 (N=O str.), 1250 (C-O-C str.) cm^{-1} , ^{1}H-PMR δppm (TFA) : 3.9 (s, 3H, $-OCH_3$), 7.2 - 8.5 (m, 11H, Ar-H).

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

Preparation of 4-Arylidine - 5- (5'-nitro benzimidazol-2'-yl-benzamido)-2-phenyl-5-oxo-imidazolines *3a-m*.

5-Nitro-benzimidazol-2-yl-o-benzoyl hydrazide (*1*, 0.01 mol) and 4-arylidine-2-phenyl-5-oxazolinone (0.02mol) was refluxed in dry pyridine (20 ml) for 6 hrs. The excess of solvent was removed under reduced pressure. The reaction mixture was poured onto crushed ice. The solid mass was filtered, dried and crystallised from methanol. **3i** ; yield : 65%, M.P. 178° C, Calcd. for $C_{31}H_{22}O_5N_6$: C 66.66, H 3.94, N 15.05 %. Found : C 66.56, H 3.99, N 15.08 % IRυ_{max} (KBr) : 3300 (N-H str.), 1710 (C=O str.), 1680 (-CONH str.), 1600 (C=N str.) cm^{-1} ; ^{1}H-PMR δppm (TFA) : 3.91 (s,3H, $-OCH_3$), 7.2 - 8.5 (m, 16H, Ar-H + = CH-R).

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

Table - 2 : Antimicrobial data (inhibition zone 18-25 mm) and Antitubercular data (% inhibition > 50%) of some selected compounds which exhibited higest activity.

Standard Antibiotics	B.megaterium	B.subtilis	E.coli	Ps. flourescens	Mycobacterium tuberculosis H37 RV % inhi.
Chloramphenicol 21-27mm	2b,2c,2h,2i	2d,2h,2l 3c,3g,3i,3h	2b,2c,2e,2g	2f,2l,2o 2h,2i,2m,2o	2a, 2k,2m,2n
Ampicillin 18-29 mm					
Norfloxacin 20-28 mm					
Griseofulvin 15-25 mm					

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