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Synthesis and Antimicrobial Activity of some new 1'–[1–Methyl–{(N–alkyl Phthalyl)–benzimidazolo}]–4'–(3''/4''/3'', 4''–substituted Benzylidene)–4', 5'–dihydro–2'–alkyl–imidazol–5'–ones

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Abstract

1'–[1–methyl–{(N–alkyl phthalyl)–benzimidazolo}]–4'–(3''/4''/3'', 4''–substituted benzylidene)–4', 5'–dihydro–2'–alkyl–imidazol–5'–ones were synthesized by treating Equimolar mixture of 4–(3'/4'/3',4'–substituted benzylidene)–2–alkyl–oxazol–5–one (II) and N–methyl phthalyl–1–amino methyl benzimidazole(III).Chemical structures were elucidated by the spectral technique of IR and ^{1}H NMR. These compounds were screened for their antibacterial and antifungal activity in vitro. Some of the imidazolones were found to be active.

Keywords: Benzimidazoles, imidazoles, antimicrobial agents.

Introduction

Benzimidazole nucleus has a broad spectrum of biological activities[1-8] i.e. antibacterial, antifungal, anticancer, antitumor, HIV reverse transcriptase inhibitory activities. Heterocycles having two nitrogen atom oriented at 1,3–position in the ring show potent biological activity. Modification of the imidazole nucleus have resulted in a large number of compounds having diverse pharmacological activity[9-16] such as antimicrobial, anticancer, analgesic, anti-inflammatory, antiepileptic and in the field of medicinal chemistry. Some novel imidazolone derivatives are inhibitors of the HIV reverse transcriptase enzyme which is involved in virus replication. These compounds can be used as therapeutic agents against HIV infection. Imidazolinones are also associated with a wide range of therapeutic activity. Similarly imidazolin–5–ones, which are the nitrogen analogs of azalactones, are also useful as antimicrobial agents

and in drugs. This prompted us to synthesize some new imidazolone derivatives and study their biological action.

Experimental

Melting points were taken in open capillaries in a simple 'neolab'electrical apparatus and are uncorrected.IR were recorded on a Schimadzu 8101A soectrophotometer.^{1}H NMR spectrometer in DMSO with chemical shift in δ ppm.

N-protected amino acid (I) and oxazole-5-ones (II) were synthesized by the reported method[17].N-methyl-1-aminomethyl Benzimidazoles (III) were prepared by earlier published method[3].

Synthesis of 1'–[1–methyl–{(N–methyl phthalyl)–benzimidazolo}]–4'–(4''–hydroxybenzylidene)–4', 5'–dihydro–2'–methyl–imidazol–5'–one (IVb)

Equimolar mixture (0.01 mole) of 4–(4'–hydroxy benzylidene)–2–methyl–oxazol–5–one (IIb) and N–methyl phthalyl–1–amino methyl benzimidazole (III) were heated on a sand bath for 5–6 hours in DMF (10 ml.) in the presence of few drops of glacial acetic acid. The contents were cooled and poured into crushed ice. A solid separated out which was then removed by filtrations, dried and recrystallized from ethanol.

IR (cm-1): 1775, 1715(>C=O, phthalimido), 1623(C=N), 3012(CH=C).

^{1}HNMR (δ):2.65(s,2H,N-CH_2-C),2.38(s,3H,CH_3),3.15(s,2H,N-CH_2-N),5.35(s,1H,CH=C),7.27-8.15(m,12H,ArH).

IVg; IR (cm-1): 1775, 1710(>C=O, phthalimido), 1625(C=N), 3012(CH=C), 2345,2348(C-H str.,OCH_3).

^{1}HNMR (δ):2.73(s,2H,N-CH_2-C), 3.21(s,2H,N-CH_2-N),5.41(s,1H,CH=C),7.29-7.89(m,17H,ArH).

The other derivatives were synthesized following same procedure. The physical and analytical data are given in Table1.

Table 1: Characterization data.

Compound No.	R_1	R_2	R_3	M.P.(°C)	Molecular Formula	Nitrogen Calculated	Nitrogen Found
IVa	CH_3	H	OH	>250	$C_{28}H_{21}O_4N_5$	14.25	14.30
IVb	CH_3	OCH_3	OH	250	$C_{29}H_{23}O_5N_5$	13.43	13.40
IVc	CH_3	H	Cl	245	$C_{28}H_{20}O_3N_5Cl$	13.74	13.80
IVd	CH_3	NO_2	H	>250	$C_{28}H_{20}O_5N_6$	16.15	16.12
IVe	C_6H_5	OCH_3	OH	230	$C_{34}H_{25}O_5N_5$	12.00	12.04
IVf	C_6H_5	H	OH	>250	$C_{33}H_{23}O_4N_5$	12.65	12.62
IVg	C_6H_5	H	Cl	240	$C_{33}H_{22}O_3N_5Cl$	12.25	12.20
IVh	C_6H_5	NO_2	H	225	$C_{33}H_{22}O_5N_6$	14.43	14.42

Antibacterial and Antifungal activity

1'–[1–methyl–{(N–alkylphthalyl)–benzimidazolo}]–4'–(3''/4''/3'',4''–substitutedbenzylidene)– 4', 5'–dihydro–2'–alkyl–imidazol–5'–ones (IV_a – IV_h) were screened for their antibacterial activity against five different strains of bacteria at a concentration of 250 µg/disc by Disc Diffusion Technique.(Table2). The dilution method was followed for the two fungal strains at a concentration of 500 µg/ml for antifungal activity (Table3).

Results and Discussion

The antibacterial screening data have revealed that all the compounds except IV_c and IV_g showed remarkable activity against *B. subtilis*. Compounds IV_b, IV_d, IV_e, IV_f and IV_h were active against *S. mutans* and *E. coli* while rests of the compounds were found to be inactive. Against *A. tumifaciens* only two compounds IV_d and IV_h showed significant activity while against *S. aureus* compounds IV_a, IV_d and IV_h displayed zone of inhibition between 8–12 mm.

Among the imidazol–5'–ones (Table 1) compounds IV_c, IV_d, IV_g and IV_h showed some activity with the development of just 2–3 fungal colonies of the *Penicillium species* after 72 hours incubation. The other derivatives were inactive.

Against *A. nizer*, two derivatives IV_d and IV_h were active with the growth of only one fungal colony while the other derivatives i.e. IV_b, IV_c, IV_e, IV_f and IV_g were moderately active. Only one derivative IV_a was found to be inactive against *A. niger*.

Antibacterial Activity

Table 2: 1'–[1–methyl–{(N–alkylphthalyl)–benzimidazolo}]–4'–(3''/4''/3'', 4''–substitutedbenzylidene) – 4', 5'–dihydro–2'–alkyl–imidazol–5'–ones (IV_a – IV_h).

Compound No.	S. aureus	S. mutans	E. coli	B. subtilis	A. tumifaciens
IVa	±	–	–	±	–
IVb	–	±	±	±	–
IVc	–	–	–	–	–
IVd	±	±	±	±	±
IVe	–	±	±	±	–
IVf	–	±	±	±	–
IVg	–	–	–	–	–
IVh	±	±	±	±	±

Concentration : 500 µg/ml Duration : 72 hours

Standard: Griseofulvin, Gentamycin Control : DMF

Medium: PDA (Potato Dextrose Agar)

–: Inactive (heavy fungal colony)

±: Moderately active (two–three fungal colony)

+: Active (one fungal colony)

++: Highly active (no fungal colony)

Antifungal Activity

Table 3: 1'–[1–methyl–{(N–alkylphthalyl)–benzimidazolo}]–4'–(3''/4''/3'', 4''–substitutedbenzylidene)– 4', 5'–dihydro–2'–alkyl–imidazol–5'–ones (IV_a – IV_h).

Compound No.	Penicillium sp.	Aspergillus niger
IV_a	–	–
IV_b	–	±
IV_c	±	±
IV_d	±	+
IV_e	–	±
IV_f	–	±
IV_g	±	±
IV_h	±	+

Concentration : 500 µg/ml Duration : 72 hours

Standard: Griseofulvin, Gentamycin Control : DMF

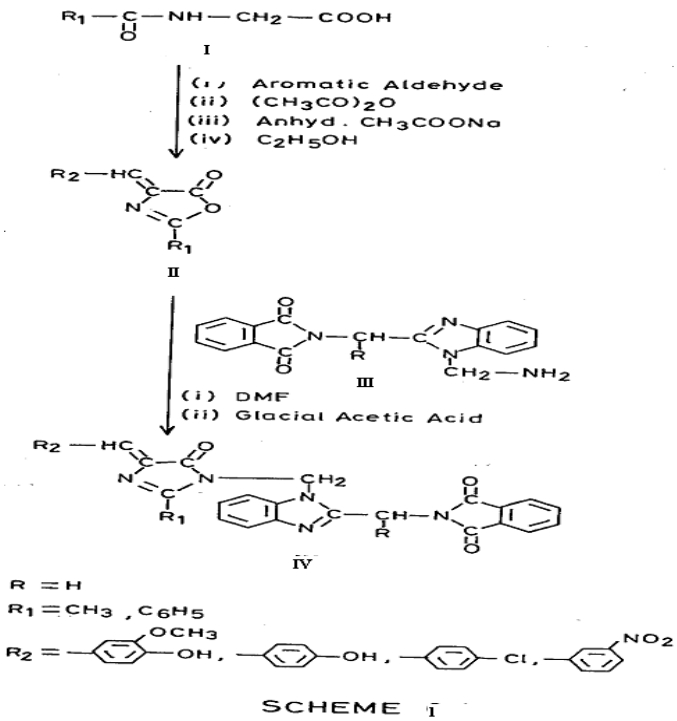
Medium: PDA (Potato Dextrose Agar)

–: Inactive (heavy fungal colony)

±: Moderately active (two–three fungal colony)

+: Active (one fungal colony)

++: Highly active (no fungal colony)



SCHEME I

Conclusion

On the basis of structure activity relationship it has been observed that among substituent presence of a nitro group played a significant role in determining the antibacterial and antifungal activity of the compounds as compared to the other substituent.

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