RESEARCH PAPER

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Synthesis And Biological Screening of Imidazolyl Bisbenzimidazoles and Bisbenzimidazolyl Azetidinones

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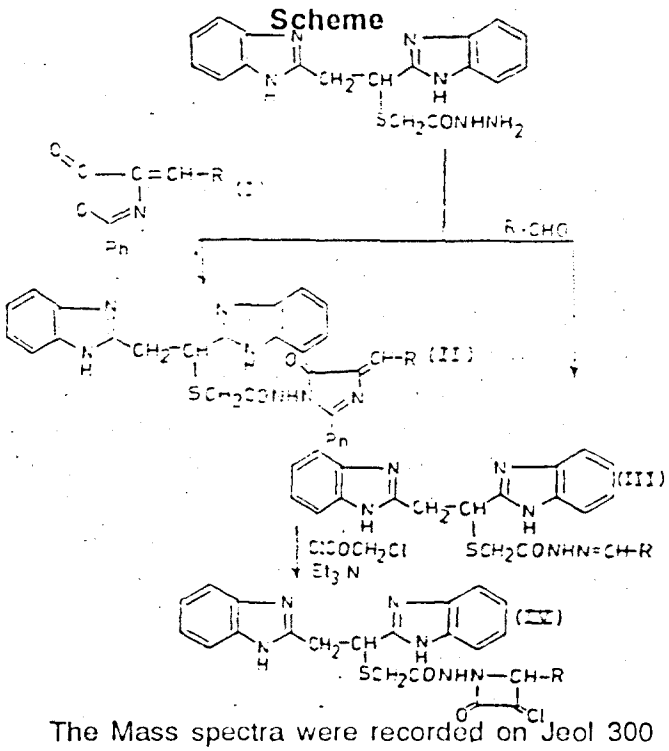
Some new α-(2-phenyl-4-arylidene-5-imidazolinon- l-yl-amino carbonylmethyl thio)- α,β-bisbenzimidazol-2', 2'- ethane and α-(4-aryl-3-chloro-2-azetidinon-l-yl- amino-carbonylmethyl thio) - α,β-bisbenzimidazol-2,2'-yl- ethane were synthesised. The products have been characterised by IR, PMR, Mass spectra and elemental analyses. The products have been screened for antimicrobial activity. Some of the products exhibited comparable activity with standard drugs at same concentration.

IMIDAZOLINONES[1-4], benzimidazoles[5-7] and a large number of antibiotics containing β-lactam heterocylic moiety[8-11] are known to exhibit wide spectrum of biodynemic properites. In view of these facts and with the aspiration of achieving pharmacological compounds of high potency, reaction of preformed azlactone with α- hydrazino carbonylmethyl thio-α, β-bisbenzimidazol-2, 2-yl-ethane in molar ratio in pyridine afforded compound (II) **(Table-I).** The compound (IV) was synthesised by condensing chloroacetyl chloride in presence of triethyl amine with α-(substituted benzal hydrazino carbonyl methyl thio)-α, β-bisbenzimidazole (III) obtained by the reaction of α-hydrazino carbonylmethyl thio- α, β-bisbenzimidazol-2-yl- ethane (I) with different aromatic aldehydes. The structural assignments of the products are based on their elemental analysis, IR, PMR and Mass spectral data.

Scheme



EXPERIMENTAL

All the melting points were uncorrected. The IR(KBr) spectra were recorded on shimadzu 435 infrared spectrophotometer. The PMR spectra were recorded in trifluoro acetic acid on Jeol (90 MHz) using TMS as internal reference; chemical shifts are expressed in δ (ppm).

The Mass spectra were recorded on Jeol 300 at 70 ev. Elemental analyses are quite comparable with their structures.

α-Mercapto-α, β-bisbenzimidazol-2,2-yl-ethane (A)

A mixture of thiomalic acid (0.01 M) and thionyl-chloride (5 ml) was refluxed on water bath for eight hrs. o-phenylenediamine (0.02 M) and pyridine

Table -1: Phsical data and Antimicrobial Activity of Benzimidazolyl azetidinones

Sr. No.	R	M.P. O°C	Antibacterial Activity Zone of inhibition in mm.				Antifungal Activity Zone of inhibition in mm.	
			B. subtilis	S. pyogens	E.coli	K.pneumoniae	A.niger	S.cerevisiae
IVa	4-Cl C_6H_4	149	17	10	20	12	10	11
IVb	2-OH C_6H_4	173	20	18	14	13	12	13
IVc	4-OH C_6H_4	220	20	17	11	13	14	13
IVd	2-NO_2 C_6H_4	161	12	10	21	12	14	15
	Ampicillin		22	26	24	25	—	—
	Chloramphenicol		28	22	21	22	—	—
	Norfloxacin		21	27	25	27	—	—
	Griseofulvin		—	—	—	—	24	22

% yield varied from 58 to 70

(2 ml) was added. The mixture was further refluxed on water bath for six hrs. The products was suspended in HCl (2N) solution and filtered. The products was washed with cold water and crystallised from ethanol. (yield 70% m.p. 165°C). IR : 3200 (NH-N str. Benzimidazole moiety), 2550 (S-H str), 710 (C-S str.) Cms^{-1} PMR : δ: 3.3-3.41 (d, 2H, CH.$_2$-CH), 4.1 (S, IH, SH), 4.4-5.2 (t, IH, CH_2, -CH.), 7.3-8.1 (m, 8H, Ar-H), 9.2 (S, (br), IH, NH Benzi. ring) M/z = 294(M^+), 259 (B.P).

α-Carbethoxy methylthio- α, β-bisbenzimidazol-2,2-yl- ethane (B)

A mixture of (A) (0.01 M) ethyl chloroacetate (0.01 M) and anhydrous K_2CO_3 (2 gm) in dry acetone (30 ml) was refluxed for eight hrs. The product was poured in ice cold water, filtered and crystallised from ethanol. (Yiled 72%, m.p. 183°C).

α-Hydrazinocarbonyl methylthio- α, β-bisbenzimidazol^2-2-yl- ethane (I)

A mixture of (B) (0.01 M) and hydrazine hydrate (0.01 M) in ethanol (10 ml) was refluxed slowly on a water bath for five hrs. The product was isolated and crystallised from ethanol. (Yield 80 % m.p. 203°C).

α-(2-phenyl-4-benzylidene-5-imidazolinon-1-yl- amino carbonyl methylthio)-α, β-bisbenzimidazol-2',2'-yl-ethane (II)

A mixture of (I) (0.01 M) and 3-phenyl—4-benzylidene-5-oxazolone (0.01 M) in pyridine (10 ml) was refluxed on oil bath for nine hrs.at 120°C. The product was isolated and crystallised from methanol : water (3:2), (yiled 59% m.p. 201°C), IR : 3180 (NH-N str), 3300 (NH str. Amide), 1650 (C=O str. Imidazolinone ring), 1595 (C-N str. Imidazolinone

ring), 710 (C-S str) M/z = 278, 252, 206, 178, 131, 149, 105, 103, 76 (B.P.).

Similarly other derivatives were prepared.

α-[(p)-Methoxybenzal hydrazinocarbonyl-methylthio]-α, β-bisbenzimidazol-2, 2-yl-ethane (III)

A mixture of (I) (0.01 M), p-methoxy benzaldehyde (0.011m) and ethanol (25 ml) was refluxed on a water bath for three hrs. using two to three drops of, pyridine as catalyst. The product was poured into ice cold water, filtered and crystallised from ethanol. (yiled 78 % m.p. 145°C). IR : 3200 (NH ... N str. Benz. ring), 1660 (CH = N str), 710 (C-S-C str). PMR : δ : 1.2-1.6 (d, 2H, CH_2-CH), 4.O (S, 3H, OCH_3), 4.9-5.2 (t, IH, CH_2-CH.), 7.3 (S, IH, CH =N) 7.5-8.O (m, I2H, ArH), 8.9 (S, IH, NH Benz. ring).

Similarly other azomethines were synthesised.

α-(4-(p)-Methoxyphenyl-3-chloro-2-azetidinon-1-yl-aminocarbonylmethylthio)-α, β-bisbenzimidazol-2',2'-yl-ethane (IV)

To a well stirred solution of (III) (0.01 M) and triethylamine (0.02 M) in dioxane (25 ml), chloro acetylchloride (0.011 M) was added dropwise at room temperature. The mixture was stirred for five hrs. and left at room temperature for three days. The contents were poured on crushed ice and filtered, washed with water and the isolated product was recrystallised from methanol : water (3:1) (yiled 68 % m.p. 180°C). IR : 3300- 2800 (NH-N str overlapped), 3440 (N-H str amide), 1655 (C=O str β-Lactam), 1610 (C=O str amide), 730 (C-S-C str), 750 (C-Cl str). PMR : δ:1.4-1.8 (d, 2H, CH_2-CH), 3.89 (S, 3H, OCH_3), 4.7-5.0 (t, IH, CH_2-CH.), 5.62(S, IH, S-CH_2), 6.21 (d, IH, CH- Cl), 7.1-7.9 (m, 12, Ar-H), 8.8(d, IH, CH-N), 9.1 (S, IH, NH Benz. ring). M/z = 530.5 (M^+), 269.5, 233, 194, 179, 166.5, 153.5, 138.5, 135, 119 (B.P.), 105, 101.5, 91, 65.

Similarly other 2-azetidinones were synthesised. The physical data recorded in **Table-1**

ANTIMICROBIAL ACTIVITY

All the products (II), (III), and (IV) were screened for their antibacterial and antifungal activity by the agar cup-plate method[12] at a concentration of 50 μδ using DMF as a solvent against gram positive bacteria **Staphylococcus pyogens, Bacillus subtilis,** gram negative Escherichia coli, **Klebsiella pheumonia** (antibacterial activity) and **Aspergillus niger, Sacheromyces cerevisiae**(antifungal activity). The zones of inhibition of each strain are recorded in table-1. The activity has been compared with known standard drugs such as, Ampicillin, Chloramphanicol, Norfloxacin and Griseofulvin at the same concentration.

From the screening results, it has been observed that in case of antibacterial and antifungal activity, imidazolinones (II), azomethines (III) and azetidinones (IV) were found to be moderately active against **B. subtilis, S.pyogens, E.coli, K.pneumoniae** and **A.niger, S. cerevisiae.** 2-Azetidinones (IV) were found to be more active than azomethines(III). However, compounds IVa, IVd exhibited comparable activity with known standard drug Chloramphenicol against gram negative bacteria **E.coli** and IVd, IVb showed comparable activity with standard Norfloxacin against **B.subtilis.** Compounds (III) and (IV) exhibited low to moderate antifungal activity when compared to Griseofulvin.

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