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Synthesis and Antimicrobial activities of 1,2-Disubstituted-4- [(Benzimidazole-2-yl) Methylene] Imidazolin-5 (4H) - ones

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Fourteen new 1,2-disubstituted-4- [(benzimidazole-2-yl) methylene] - imidazolin-5 (4H) - ones - (4-17) were synthesized by reacting 2-substituted-4-[(benzimidazole-2-yl) methylene] oxazolin -5 (4H) - ones (2 & 3) with different primary amines. These compounds were characterized by their analytical and spectral data. A few of them were found to be efficient antibacterial and antifungal agents on evaluation.

In view of the significant biological and pharmacological activities associated with both imidazolin - 5 (4H) - ones[1-3] and benzimidazoles[4-6] and in continuation of our studies on imidazolin-5 (4H) - ones connected to other heterocyclic systems through a methylene group[7,8], we report herein the synthesis and antimicrobial activities of 1, 2- disubstituted - 4 [(benzimidazole - 2 - yl) methylene] imidazolin - 5 (4H) - ones. The title compounds were synthesized as outlined in Scheme - 1.

2-Benzimidazolecarboxaldehyde(1)[9] and N-acetylglycine or N-benzoylglycine[10] were condensed by heating with anhydrous sodium acetate and acetic anhydride to afford a single product in each case. The products were purified and characterized by analytical and spectral data. For instance, the condensation of 1 with N-acetylglycine in presence of freshly fused sodium acetate and acetic anhydride gave a pale yellow solid. It was purified by recrystallization from ethanol and characterized as 2 - methyl -4 -[(benzimidazole - 2 yl) methylene] oxazolin - 5(4H) - one(2). Its IR (KBr) spectrum showed characteristic peaks at 3325 (NH), 1715 (C=0), 1650 (CH=C), 1620 (C=N) and 1230 (C-O-C) cm^{-1}, PMR ($CDCl_3$) spectrum exhibited signals for aromatic CH_3, aromatic-H, CH=C and benzimidazole-NH protons, respectively (Table-2), while its mass spectrum showed molecular ion peak at m/z 227 (68%).

Each of these two oxazolin - 5(4H) - ones (2 & 3) were reacted with primary amines in dry pyridine using phosphorus oxychloride (5 ml), which facilitates the cyclization of possible N-aryl derivative as a result of ring cleavage on reacting corresponding oxazolin-5 (4H) - one with appropriate primary amine, under anhydrous conditions[11] to get crystalline solids which were recrystallized from chloroform and characterized as the corresponding imidazolin - 5(4H) - ones (4-17). For example, compound 3 on reaction with o-toluidine gave an yellow crystalline solid characterized as 1-(2-methylphenyl) - 2 - phenyl - 4-[(benzimidazole - 2 - yl) methylene] imidazolin - 5 (4H) - one (14). Its IR(KBr) spectrum showed peaks at 3310(NH), 1700(C=O), 1650 (CH=C) and 1630(C=N)cm^{-1}, PMR ($CDCl_3$) spectrum displayed signals assignable for aromatic -CH_3, aromatic -H, CH=C and benzimidazole -NH groups, respectively (Table-2) and the mass spectrum exhibited strong molecular ion peak at m/z 378 (100%). All the

*For Correspondence

Table 1 : Physical, analytical and antimicrobial data of compounds 2-17

Compd.	R	R^1	Mol. Formula	M.P. °C	Nitrogen analysis obs. (Calc)	Antibacterial Activity				Antifungal Activity*	
						B.s.	S.a	E.c	P.v	A.n	C.l
2.	methyl	-	$C_{12}H_9O_2N_3$	246	18.42(18.50)	-	-	-	-	-	-
3.	phenyl	-	$C_{17}H_{11}O_2N_3$	239	14.39 (14.53)	-	-	-	-	-	-
4.	methyl	ethyl	$C_{14}H_{14}ON_4$	181	21.90 (22.05)	5	9	7	4	8	10
5.	methyl	benzyl	$C_{19}H_{16}ON_4$	188	17.66 (17.72)	9	8	NA	NA	13	17
6.	methyl	phenyl	$C_{18}H_{14}ON_4$	147	18.46 (18.54)	6	3	5	4	4	4
7.	methyl	2-methylphenyl	$C_{19}H_{16}ON_4$	167	17.64 (17.72)	4	NA	NA	NA	9	4
8.	methyl	4-methylphenyl	$C_{19}H_{16}ON_4$	169	17.60 (17.72)	12	NA	NA	NA	8	5
9.	methyl	2-methoxyphenyl	$C_{19}H_{16}O_2N_4$	216	16.72 (16.87)	8	NA	6	9	10	3
10.	methyl	4-methoxyphenyl	$C_{19}H_{16}O_2N_4$	221	16.70 (16.87)	6	NA	4	5	15	12
11.	phenyl	ethyl	$C_{19}H_{16}ON_4$	211	17.65 (17.72)	4	3	5	NA	11	14
12.	phenyl	benzyl	$C_{24}H_{18}ON_4$	139	14.75 (14.81)	7	15	18	13	18	25
13.	phenyl	phenyl	$C_{23}H_{16}ON_4$	162	15.31 (15.38)	5	7	5	5	8	3
14.	phenyl	2-methylphenyl	$C_{24}H_{18}ON_4$	189	14.79 (14.81)	5	3	NA	NA	9	9
15.	phenyl	4-methylphenyl	$C_{24}H_{18}ON_4$	181	14.72 (14.81)	NA	NA	NA	NA	11	14
16.	phenyl	2-methoxyphenyl	$C_{24}H_{18}O_2N_4$	260	14.12 (14.21)	3	6	8	8	10	12
17.	phenyl	4-methoxyphenyl	$C_{24}H_{18}O_2N_4$	295	14.13 (14.21)	NA	3	4	4	16	9
Benzylpenicillin			-	-	-	14	17	-	-	-	-
Streptomycin sulphate		-	-	-	-	-	21	17	-	-	
Clotrimazole			-	-	-	-	-	-	-	16	24

Yields were between 50-80%. Satisfactory C&H analayses were also obtained. Compounds 4, 5, 11 & 12 were colourless while the rest of the compounds were pale yellow. IR (KBr) spectra of all the compounds showed characteristic peaks in cm^{-1} for NH (3270-3350), C=O (1690-1725), CH = C (1645-1655), C = N (1610-1630) and in addition compounds 2 & 3 exhibited peaks for C-O-C (1220-1235).

*Zone of inhibition in mm; B.s.=*B subtilis*; S.a=*S. aureus;* E.c=*E. coli;* P.v.=P. *vulgar is;* A.n= *A. niger;* C.l = *C. lunata*; NA = Not active.

Table 2 : ^{1}H NMR data of representative compounds

Compd.	^{1}H NMR ($CDCl_3$) in δ ppm.
2	2.45 (s, 3H, Ar-CH_3), 7.20-7.85 (m, 4H, Ar-H), 9.25 (s, 1H, CH=C, 11.32 (bs, 1H, NH, D_2O exchangeable).
3.	7.25-8.70 (m, 9H, Ar-H), 9.35 (s, 1H, CH=C), 11.62 (bs, 1H, NH, D_2O exchangeable).
10.	2.40 (s, 3H, Ar-CH_3), 3.27 (s, 3H, OCH_3), 6.76-7.42 (m, 8H, Ar-H), 7.95 (s, 1H, CH=C), 11.50 (bs, 1H, NH, D_2O exchangeable)
14.	2.48 (s, 3H, Ar-CH_3), 6.95-7.55 (m, 13H, Ar-H), 7.92 (s, 1H, CH=C), 12.80 (br, 1H, NH, D_2O exchangeable).
16.	3.15 (s, 3H, OCH_3), 6.85-7.60 (m, 13H, Ar-H), 8.25 (s, 1H, CH=C), 12.65 (br, 1H, NH, D_2O exchangeable).

compounds were screened for their antibacterial and antifungal properties by standard method[12].

EXPERIMENTAL

Melting points were determined in open capillaries and are uncorrected. IR spectra were recorded on Perkin-Elmer model-1600 spectrophotometer, PMR spectra on Perkin-Elmer EM 390 90 MHz spectrophotometer using TMS as internal standard and mass spectra on Jeol-D 300 double spectrophotometer.

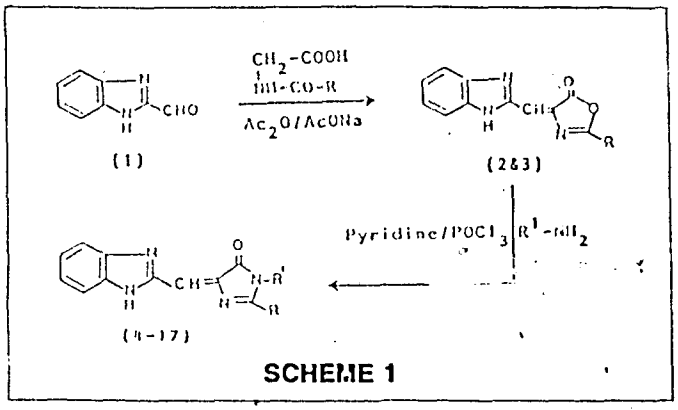
2- Substituted - 4 - [(benzimidazole - 2 - yl) methylene] oxazolin - 5 (4H) - ones (2 & 3) : An equimolar (0.01 mol) mixture of 2-benzimidazole- carboxaldehyde(1)[9], N-acetylglycine/ N- benzoylglycine[10] and freshly fused sodium acetate was heated in acetic anhydride (40 ml) for 20 minutes at 60° under anhydrous conditions, while shaking the contents intermittently. Excess acetic anhydride was distilled off. Pale yellow solid thus resulted was filtered, washed with cold water, dried and recrystallized from ethanol. Physical and analytical data of these compounds are given in Table-1 and Table-2.

1, 2-Disubstituted - 4 -[benzimidazole-2-yl) methylene] imidazolin - 5 (4H) - ones (4-17) : An equimolar (0.01 mol) mixture of corresponding oxazolin-5(4H)- one (2 or 3) and appropriate primary amine in dry pyridine (25ml), was refluxed for 2 hr. in presence of phosphorus oxychloride (5 ml) under anhydrous conditions[11]. Excess pyridine was distilled off under reduced pressure. The residue was poured onto crushed ice and the solid separated out was filtered, washed with cold water, dried and recrystallized from chloroform. Pertinent physical and analytical parameters of all the compounds prepared in similar way, are presented in Table-1 and Table-2.

Antibacterial activity of the compounds (in DMF) was determined by aggar cup-plate method[12] at a concentration of 100 μg/ml against two gram - positive bacteria, *Bacillus subtilis* and *Staphylococcus aureus* and two gram-negative bacteria, *Escherichia coli* and *Proteus vulgaris* employing benzylpenicillin (100 units/ml) and streptomycin sulphate (700 units/ml) as reference standards, respectively. Antifungal activity was also determined in similar way against *Aspergillus niger, Fusarium oxysporum, Rhizopus stolonifer* and *Curvularia lunata* using clotrimazole (100 μg/ml) as the standard. The results are presented in Table-1.

RESULTS AND DISCUSSION

It is interesting to note that many of the test compounds were effective against all the four strains



SCHEME 1

of bacteria, however with a degree of variation. *B. subtilis* was relatively more sensitive to the compounds. Compound 8 exhibited better antibacterial profile against *B. subtilis* which was comparable to that of benzylpenicillin, while no activity was seen against the remaining strains. Compound 12, possessing considerable action against all the bacteria employed except against *B. subtilis,* was however not equipotent with the standards, benzylpenicillin and streptomycin sulphate. Compound 15 was inactive against all the bacteria employed while the rest of the compounds found to possess moderate to mild activity.

It could be noted that all the compounds were found to exhibit appreciable antifungal action only against *A. niger* and *C. lunata,* 2-phenyl series being relatively more potent. Compound 12 was superior in its action over the rest of the compounds, and also over the standard, clotrimazole. But, these compounds were inactive against *F. oxysporum* and *R. stolonifer.*

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