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Synthesis Of 3-[3-Chloro-4-Hydroxy-2(4-Hydroxy Phenyl)-2h-Azetidene-1-Yl]-5-(4-Hydroxy Benzylidene)-2-Phenyl-3,5-Dihydro-Imidazol-4-One As Possible Antimicrobial Agents

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Abstract: A series of 3-[3-Chloro-4-Hydroxy-2(4-hydroxy phenyl)-2H-Azetidene-1-yl]-5-(4-hydroxy benzylidene)-2-phenyl-3,5-Dihydro-imidazol-4-one were synthesized. All these compound have been screened for their antimicrobial activity against three microorganism *Staphylococcus aureus, Enterococcus faecalis & Escherichia coli*.
Keywords: Synthesis, 3-[3-Chloro-4-Hydroxy-2(4-Hydroxy Phenyl)-2h-Azetidene-1-Yl]-5-(4-Hydroxy Benzylidene)-2-Phenyl-3,5-Dihydro-Imidazol-4-One, Antimicrobial Agents.

Introduction:

A variety of synthetic bio-dynamic agents contain imidazolone-5-one residues[1,2]. Some of them have shown pronounced antimicrobial[3] and antifungal[l4] spectrum and other antimicrobial activities[5,6]. A large number of 2-azetidinone-containing β-lactam moiety[7], have also shown considerable antimicrobial activity, also its activity is greatly influenced by difference substitutent[8,9]. Keeping in mind these fact we decided to incorporate the azetidinone moiety with the imidazole active pharmacophore and study their combined effect as potential antimicrobial agent on the micro organism *Staphylococcus aureus, Enterococcus faecalis & Escherichia coli*.

Reaction of 4-Arylidene-2-phenyl-4-H-oxazol-5-one(1) with hydrazine hydrate gave the – corresponding 3-amino-5-Arylidene-2-phenyl-3,5-dihydro-imidazol-4-one(2) which on further treatment of different substituted aromatic aldehyde gave the corresponding 5,4-substituted arylidene-3-[(4-hydroxy-benzylidene)-amino]-2-phenyl-3,5-dihydro-imidazol-4-one(3) which on further treatment with chloro acetyl chloride yielded the corresponding 3-[3-Chloro-4-Hydroxy-2(4-hydroxy phenyl)-2H-Azetidene-1-yl]-5-(4-hydroxy benzylidene)-2-phenyl-3,5-Dihydro-imidazol-4-one(4) the title compound.

The structure of the title compound have been characterised by their elemental analysis and spectral data (IR & PMR) comparison of the spectral data showed the complete disappearance of band at ν max 3440 cm^{-1} in the IR spectrum of the latter indicating the absence of $–NH_2$ group. The PMR spectrum of compound (4b) in $CDCl_3$ showed signal at-

(4b) ^{1}HNMR δ 7.5-7.8 (5H Benzylidene H), δ 7.5-8.2 (9H Ar-H), δ 9.9792 (-OH). δ 6.7121 (=CH), δ 4.8172 (ArOH), δ 4.7095 (-CH Azetidene H)

Experimental

Melting point were taken in open capillaries and were uncorrected. IR spectra were recorded on IR spectrophotometer. Simadazu 8201 Pc (4000-350 cm^{-1} in KBr and PMR spectra on NMR spectrometer. Bruker DRX 300 (300 MHZ FT NMR) in $CDCl_3$ (Chemical shift in ppm). The purity of the compounds were checked by TLC on Silica gel-G plates and spot were visualised by iodine vapours.

4-(substituted benzylidene)-2-phenyl-4H-oxazol-5-one(1).

These were prepared by the literature method[10].

3-Amino-5-(substituted benzylidene)-2-phenyl-3,5-dihydro imidazole-4-one. (2)

It was synthesized following the procedure described by Ned D. Heindel[11]

5-(Substituted Benzylidene-3-[(4-hydroxy-benzylidene)-amino]2-phenyl-3,5-dihydro-imidazole-4-one. (3)

It was synthesized following the procedure described by A.K. Sengupta etal[12].

3-[3-Chloro-4-Hydroxy-2(4-hydroxyphenyl)-2H-Azetidene-1-yl]-5-(4-hydroxy benzylidene)-2-phenyl-3,5-Dihydro-imidazole-4-one. (4)

5-substituted Benzylidene-3-(4-hydroxy benzylidene)-amino]-2-phenyl-3,5-dihydro-imidazol-4-one (0.01 mole) was taken in 20 ml dry benzene and 0.02 mole of anhydrous K_2CO_3 was added slowly to a solution of 0.01 mole of chloroacetyl chloride in 15 ml dry benzene. The solution was stirred for 30 minute and then refluxed on a water bath for 4 to 5 hour. Benzene was then removed by distillation under reduced pressure and residue was washed several time with cold water and dried in vacuum. It was recrystallised from ethanol. The title compound obtained are characterised with their spectral and analytical data given in Table I.

(4b) IR in ν cm^{-1} (ICBr) 3033 (C=CH), 1396 (S Ar-OH) 1118 (OH) (Secondary OH), 1662 (C=N), 1899 (C=O).

^{1}HNMR δ 7.5 – 7.8 (5H Benzylidene H), δ 7.5 – 8.2 (9H ArH), δ 9.9792 (-OH) δ 6.7121 (=CH),

δ 4.8172 (Ar-OH), δ 4.7095 (-CH Azetidene H)

Mass Fragmentation peaks are (m/z) 443/445, 408, 426/428, 366/368, 313/315, 247, 340/342, 196/198, 161, 107, 367, 120, 157, 395.

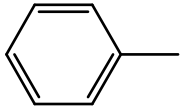
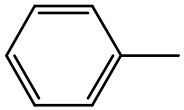
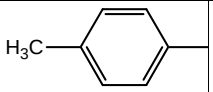
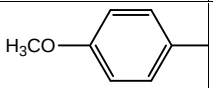
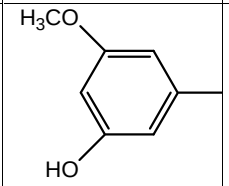
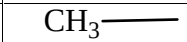
Base peak appeared at m/z = 157.

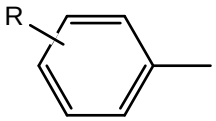
The NMR spectra indicates that the compound (4) shows Kelo-enol tautomerism and exist in enol form.

Biological activity

Six compound belonging to the category 3-[3-chloro-4-hydroxy-2-(4-hydroxyphenyl)-2H-azetidine-1-yl]-5-arylidene-2-phoryl-3,5-dihydro-imidazol-4-ones were evaluated against three bacteria viz. *Staphylococcus aureus (Sa), Enterococcus faecalis (Ef) & Escherichia coli (Ec)* involving two strains (Sa) and (Ef) and only one ol (EC) as recommended by NCCLS, Moxifloxacin and Linezolid were taken as the reference standard. The results are summarised in Table II.

Table I

Compd.	Ar	R_1	Molecular formula	MW	MP °C	Yield %	Elemental Analysis Found (Cal) (%)		
							C	H	N
4a		H	$C_{25}H_{18}ClN_3O_2$	427.88	140	65	70.14 (70.18)	4.28 (4.24)	9.78 (9.82)
4b		OH	$C_{25}H_{18}ClN_3O_3$	443.88	155	68	67.64 (67.65)	4.05 (4.09)	9.43 (9.47)
4c		OH	$C_{26}H_2OClN_3O_4$	473.91	115	70	65.85 (65.89)	4.20 (4.25)	8.94 (8.87)
4d		OH	$C_{26}H_2OClN_3O_3$	457.91	120	60	68.24 (68.20)	4.36 (4.40)	9.14 (9.18)
4e		OH	$C_{26}H_2OClN_3O_5$	489.91	138	75	63.70 (63.74)	4.08 (4.11)	8.50 (8.54)
4f		OH	$C_{20}H_{16}ClN_3O_3$	381.5	98	55	62.94 (62.90)	4.17 (4.19)	11.04 (11.00)

 = Ar

SCHEME ROUT

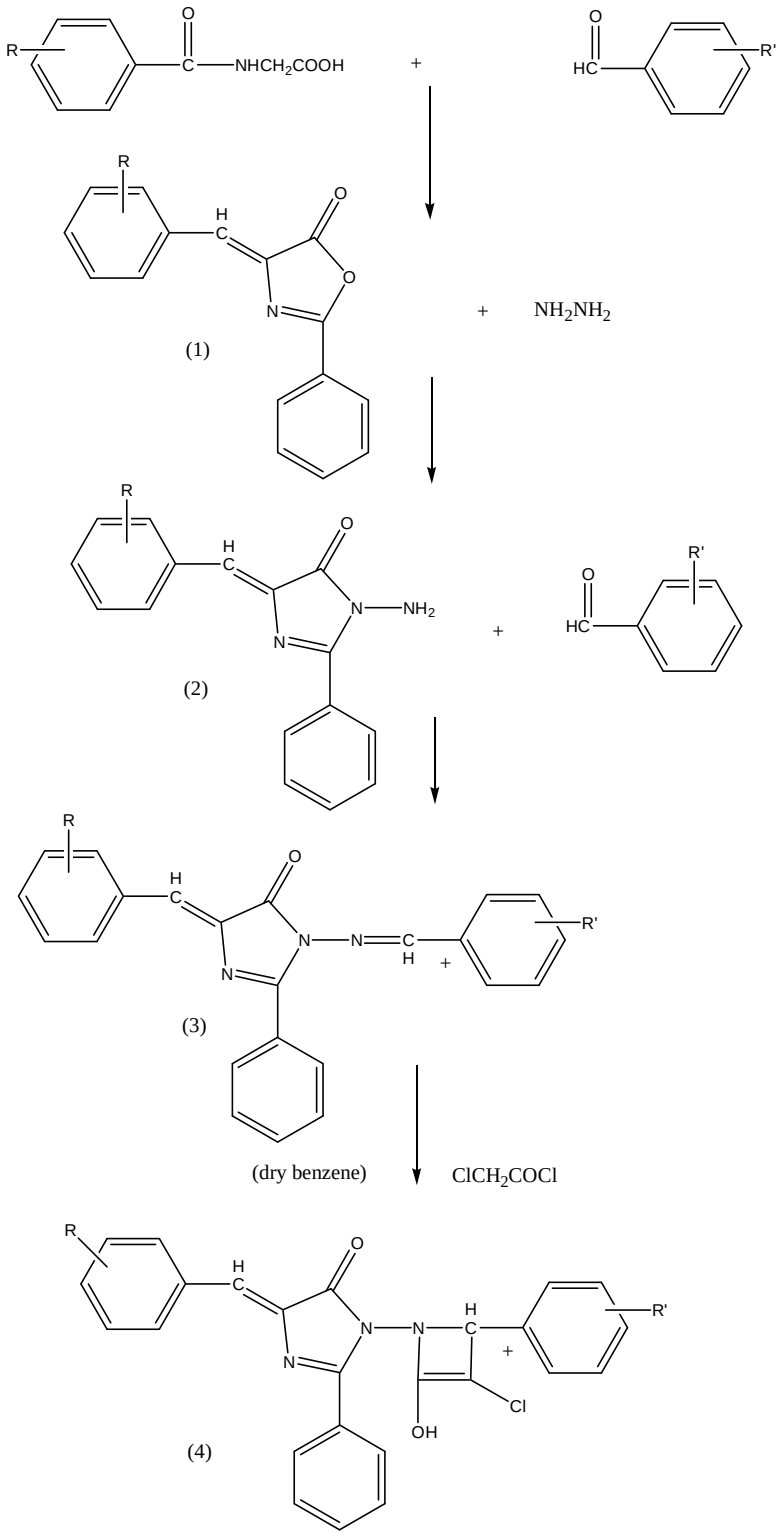


Table II: Antimicrobial Activity of Compound (4a-f)
Method : Broth micro dilution **

Compound No.	MIC (ug/ml)				
	S. aureus		E. faecalis		E. coli
	DRCC 035 MISSA	DRCC 019 MRSA	DRCC 034 VSE	DRCC 153 VRE	DRCC 018
4a*	>256	>256	>256	>256	>256
4b*	>256	>256	>256	>256	>256
4c*	>256	>256	>256	>256	>256
4d*	>256	>256	>256	>256	>256
4e*	>256	>256	>256	>256	>256
4f*	>256	>256	>256	>256	>256
Moxifloxacin	0.06	0.06	0.25	0.25	0.03
Linezolid	2 (2-4)	1 (1-2)	2 (2-4)	1 (2-4)	>32

Note : * Compound precipitated after diluting with water in test system.
Value ( ) indicated standard range.
** As per the recommended protocol from.

National Committee for Clinical Laboratory Standard (NCCLS), Vol. 20 No. 2(2000). Method for dilution antimicrobial susceptibility test for bacteria that grows aerobically.

Method and Materials

The test bacteria were maintained on nutrient agar slants. Testing was done in nutrient broth. After incubation with a loopful of culture from the slant, the broth were incubated at 37± 1^{o}C for 24 hours. Fresh broth (20 ml) was seed with 0.25 ml of 24 hours broth culture and two fold dilution method was followed. The test sample was dissolve in dimethyl sulfoxide (DMSO) to obtain a 10 ml solution and 0.2 ml solution of the test material was added to 1.8 ml of the seeded broth and this formed the first dilution. One ml of this was diluted with a further 1 ml of the seeded broth to prepare the second dilution and so on till six such dilutions were obtained. A set of tubes containing only seeded broth was kept as control and suitable solvent controls were also maintained. After incubation for 24 hours the last tube with no visible growth of the micro organism was taken to represent the minimum inhibitory concentration (MIC) of the test sample expressed in ug/ml. The antibacterial data of the tested compounds are recorded in Table II.

Result and Discussion

Six compounds belonging to the type 3-[3-chloro-4-hydroxy-2-(4-substituted phenyl)-2H-azetidene-1-yl]-5-arylidene-2-phenyl-3,4-dihydro-imidazol-4-one.

None of the six compounds incorporated in table was found to show better antimicrobial activity against bacterial strains employed for investigation. It was anticipated that such compound having a β–lactam ring joined with imidazole group at one end would provoke better and more satisfactory antimicrobial activity. Azetidinone (β-lactam) is the integral part of penicillins and cephalosporins which marked the beginning of an era leading to the development of clinically useful antibacterial drugs. Although these agents often have a high level of intrinsic activity in nitro, the success or failure may depend on a number of factors such as distribution and metabolism of resistance factors and the ability of the patient's host defence mechanism to respond to bacterial infections.

There may be two factors responsible for the absence or decreased order of activity of these compounds. One important reason for diminished level of antibacterial activity of these β–lactam derivatives may be due to their differential arrangement. In penicillin, and cephalosporins, β-lactam ring is in fused form with thiazole or thiazine ring while in these compounds it is not in fused state with imidazolone ring system. This state of arrangement of

two main nuclei viz., β-lactam and imidazolone in one molecular union seems unsuitable with the antimicrobial activity point of view because such an arrangement most probably does not find a suitable and better fit at the receptor site of the bacteria and thus can not penetrate the bacterial cell in order to block the biosynthesis of the peptidoglycan layer. A second reason may be that here a free oxo group is not present but it is in the enolised form. In penicillin and cephalosporins enolization is not possible because of the absence of an adjacent hydrogen atom while a hydrogen atom is present adjacent to the carbonyl function in the present compounds and the spectral studies have shown an enol rather than a carbonyl function. This enolized form of the system may be responsible for the loss of activity. However, other factors which contribute for the loss of activity of such compounds against all the bacterial strains may not be ruled out. In conclusion, it can be postulated that the synthesis of such compounds should be encouraged provided the two main biologically active nuclei. Viz. β-lactam and imidazole bearing substituents are infused form.

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