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ANTIBACTERIAL ACTIVITY OF HYDROXYIMIDAZOLE DERIVATIVES

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ABSTRACT

The imidazole ring is containing one of the important heterocyclic compounds found in endogenous biomolecules and pharmaceutical preparations. Different methods have been reported for the synthesis of 1-Hydroxyimidazoles and a number of them reported to possess significant biological activity, thus synthesis of some new derivatives are introduced for better antibacterial activity.

KEYWORDS

Imidazole, Hydroxyimidazole derivatives and Antibacterial activity.

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INTRODUCTION

The imidazole ring is containing five membered ring systems have been described for their biological activity against various micro organisms[1,2]. It is commonly found as a part of structure substances such as histamine and purine, also in a number of pharmaceutical drugs, such as antifungal agent[1] (ketoconazole), antiprotozoal agentsmetronidazole[3] (1) and antihistamine cimetidine[4] (2). *N*-hydroxyimidazoles are analogous of imidazole, have been prepared and tested biologically. Besides this, apesticidal screening was carried out by Allan[5] on a series of *N*-hydroxyimidazoles (3) and found them to have herbicide and insecticide activities. Antihypertensive[6] activity was observed in some

N-hydroxyimidazole-5-methanamine derivatives such as (4). (Figure No.1). They have been also applied to coloring materials[7].

1-Hydroxyimidazoles were prepared by condensation reaction of monoximes of 1, 2-diketones with an aldehyde in presence of ammonia[5] (Scheme No.1). They were prepared by reduction of 3-hydroxy-imidazole-1-oxide, and by cyclization of a 1, 2-diketone, and an aldehyde in the presence ofhydroxyl-amine[7,8]. *N*-hydroxyimidazole has also been synthesized by *N*-oxidation of imidazole with 3-chloroperbenzoic acid[7] or peroxyphethalic acid[8,9]. The compounds in the present work have been synthesized by using Akagane method[7] (Table No.1). The reproduced compounds and the new derivatives (10, 11) were identified by means of physical and spectrophotometric analysis and evaluated *in vitro* for their antimicrobial activity.

MATERIAL AND METHODS

All solvents and reagents were used as received from various vendors. Infrared spectra were recorded by using KBr disc in the region 4000-400cm^{-1} on a Nicolet FT-IR Impact 400D infrared spectrometer. ^{1}H NMR and ^{13}C NMR spectra were run as solutions in $CDCl_3$ or DMSO-d_6 on a Bruker Advance 300 MHz instrument. Mass spectra were carried out on a Kratos Profile mass spectrometer. The melting points were determined by open capillary method and were uncorrected.

General procedure for preparation of *1H-imidazole-1-ol 4, 5-Dimethyl-2-(pyridine-2-yl)-1H-imidazole-1-ol*[5] (5)

The general procedure of Akagane and coworkers was used. A 250-mL, round-bottomed flask, equipped with a magnetic stirrer was charged with diacethylmonoxime (1.5g, 15mmol) dissolved in a mixture of ammonia and water (1:1). Picolinaldehyde (1.5g, 14mmol) was added and the mixture was stirred overnight a room temperature. The solvent was removed under reduced pressure and the product was extracted with chloroform. The chloroform extract was dried over magnesium sulphate, filtered and evaporated under vacuum. The residue was crystallised from toluene to give (1) as yellow crystals (1g, 30%), mp = 139-141°C.

^{1}H NMR ($CDCl_3$): 2.22 (6H, s), 7.21-7.16 (1H, m), 7.82-7.76 (1H, dt, J = 7.8, 1.7 Hz), 8.19 (1H, s), 8.38 (1H, d, J = 7.5 Hz).

^{13}C NMR ($CDCl_3$): 7.6, 13.0, 119.7, 122.2, 122.8, 131.0, 138.4, 146.5, 149.3.

IR (KBr): 3382, 2421, 1639, 1588, 1524, 1488, 1310, 1231, 1154, 1115, 964, 794, 742, 610, 505 cm^{-1}.

m/z: 189 (M^+, 16%), 172 (64), 105 (56), 95 (8), 79 (100), 69 (28), 51 (58).

***4, 5-Diphenyl-2-(pyridine-2-yl)-1H-imidazole-1-ol*[5] (6)**

The product was prepared in a similar method to (1) using α-benzilmonoxime (2g, 8.8mmol) and picolinaldehyde (1g, 9mmol). The product was crystallised from toluene giving (2) as yellow crystals (2.5g, 89%), mp = 163-164°C.

^{1}H NMR ($CDCl_3$): 7.30-7.19 (4H, m), 7.52-7.38 (3H, m), 7.61-7.56 (4H, m), 7.92-7.86 (1H, dt, J = 7.8 Hz), 8.27 (1H, d, J = 8 Hz), 8.44 (1H, d, J = 5 Hz).

^{13}C NMR ($CDCl_3$): 120 2, 122.5, 125.8, 126.9, 127.4, 128.2, 128.30, 128.37, 128.4, 129.9, 132.2, 134.6, 134.9, 138.4, 145.7, 149.8.

IR (KBr): 3063, 1606, 1562, 1531, 1476, 1439, 1402, 1309, 1148, 959, 783, 730, 700cm^{-1}.

m/z: 313 (M^+, 26%), 296 (28), 284 (18), 193 (22), 176 (8), 165 (36), 148 (14), 105 (58), 89 (58), 79 (92), 63 (54), 51 (100).

***4, 5-Dimethyl-1H, 3'H-[2, 4'-biimidazol]-1-ol*[10] (7)**

The white solid was prepared in a similar method to (1) using diacethylmonoxime (0.5g, 5mmol) and 4 (5)-imidazole carboxaldehyde (0.5g, 5mmol). The solid was crystallised from ethyl acetate to afford (3) as white crystals (0.75g, 80%), mp 155°C.

^{1}H NMR (DMSO-d_6): 1.91 (3H, s), 2.01 (3H, s), 7.64 (2H, s).

^{13}C NMR (DMSO-d_6): 7.2, 10.9, 118.5, 121.9, 123.2, 126.2, 131.3, 135.9.

IR (KBr): 3079, 1646, 1461, 1295, 1221, 1172, 1129, 1086, 1006, 870, 704, 633cm^{-1}.

m/z: 178 (M^+, 28%), 161 (82), 147 (4), 120 (18), 94 (100), 81 (10), 68 (66), 64 (26), 60 (10), 55 (48).

2-(2, 4-Dimethoxyphenyl)-4, 5-diphenyl-1H-imidazol-1-ol[11] **(8)**

This solid was prepared in a similar method of (1) using 2, 4-dimethoxybenzaldehyde (1.47g, 8.84mmol) and α-benzilmonoxime (2.0g, 8.88mmol). The product was crystallised from toluene giving a white solid (2.1g, 63%), mp 196-197°C.

^{1}H NMR ($CDCl_3$): 3.75 (3H, s), 3.85 (3H, s), 6.50-6.47 (2H, d, J = 8.9 Hz), 7.38-7.25 (11H, m).

^{13}C NMR ($CDCl_3$): 27.3, 55.8, 56.55, 99.3, 105.6, 127.3, 128.5, 129.4, 130.7, 162.0.

IR (KBr): 3413, 3070, 2943, 2845, 1619, 1585, 1541, 1468, 1302, 1214, 1165, 1136, 1034, 973, 919, 835, 804, 764, 701, 654, 517 cm^{-1}.

m/z: 372 (M^+, 10%), 355 (18), 178 (1), 165 (2), 103 (4), 91 (100), 84 (26), 77 (6), 65 (14), 56 (36).

2-(2-Hydroxyphenyl)-4, 5-dimethyl-1H-imidazol-1-ol[5] **(9)**

This solid was prepared in a similar way to (1) using diacetylmonoxime (1.0g, 10mmol) and salicyladehyde (1.2g, 10mmol). The solid was crystallised from ethanol/acetonitrile giving colourless crystals (1.3g, 64%), mp 245°C.

^{1}H NMR (DMSO-d_6): 2.10 (3H, s), 2.20 (3H, s), 6.82-6.88 (2H, m), 7.27-7.33 (1H, dt, J = 7.7 Hz), 7.46 (1H, d, J = 7.5 Hz).

^{13}C NMR (DMSO-d_6): 7.25, 10.0, 113.3, 118.4, 119.8, 122.5, 124.1, 127.6, 131.7, 134.2, 158.6.

IR (KBr): 2927, 1646, 1609, 1436, 1307, 1276, 1166, 972, 910, 849, 753, 541 cm^{-1}.

m/z: 204 (M^+, 60%), 187 (100), 159 (68), 145 (16), 121 (40), 105 (16), 91 (14), 80 (20), 77 (38), 68 (28), 51 (52).

4, 5-Dimethyl-2-[(E)-2-phenylvinyl]-1H-imidazol-1-ol **(10)**

The yellow solid was prepared in a similar way to (1) using cinnamaldehyde (0.26g, 1.96mmol) and diacetylmonoxime (0.2g, 1.97mmol). The solid was crystallised from acetonitrile/ethanol giving yellow crystals (0.36g, 85%), mp 94-95°C.

^{1}H NMR (DMSO-d_6): 1.82 (6H, s), 6.73 (1H, d, J = 16.4 Hz), 7.05 (2H, m), 7.14 (2H, t, J = 7.4 Hz), 7.26 (2H, d, J = 7.4 Hz).

^{13}C NMR (DMSO-d_6): 7.6, 126.6, 128.1, 128.2, 129.1, 136.9, 162.8.

IR (KBr): 3035, 1648, 1477, 1320, 1199, 1138, 1024, 966, 891, 748, 689, 561, cm^{-1}. m/z: 214 (M^+, 34%), 197 (100), 182 (26), 128 (26), 115 (42), 103 (30), 98 (12), 89 (14), 77 (42), 68 (12), 63 (26), 58 (14), 51 (42).

4, 5-Bis(4-fluorophenyl)-2-pyridin-2-yl-1H-imidazol-1-ol **(11)**

This solid was prepared in a similar way to (1) using pyridine-2-carboxaldehyde (0.15g, 1.40mmol) and 4, 4′-difluorobenzilmonoxime (0.24g, 0.91mmol). The solid was recrystallised from cyclohexane/ethylacetate giving yellow crystals (0.3g, 74%), mp 163-164°C.

^{1}H NMR ($CDCl_3$): 6.99 (2H, t, J = 8.7 Hz), 7.13 (2H, t, J = 8.7 Hz), 7.33 (1H, t, J = 6 Hz), 7.51-7.56 (4H, m), 7.92 (1H, t, J = 9 Hz), 8.24 (1H, d, J = 8 Hz), 8.46 (1H, d, J = 5 Hz).

^{13}C NMR ($CDCl_3$): 115.1, 115.4, 115.6, 115.9, 120.2, 122.7, 124.0, 124.1, 124.6, 129.0, 129.1, 130.6, 131.6, 131.7, 132.2, 134.1, 138.5, 145.7, 149.6, 160.4, 161.0163.7, 164.3.

IR (KBr): 3075, 1603, 1516, 1480, 1393, 1233, 1160, 1092, 956, 836, 815, 778, 735, 670, 578cm^{-1}.

m/z: 349 (M+, 44%), 332 (22), 211 (28), 201 (12), 150 (10), 123 (20), 107 (48), 95 (28), 79 (100), 69 (22), 57 (58).

4, 5-Dimethyl-2-(4-nitrophenyl)-1H-imidazole-1-ol[5] **(12)**

The yellow solid was prepared in a similar way to (1) using *p*-nitrobenzaldehyde (1.0g, 6.6mmol) and diacetylmonoxime (1.0g, 10mmol). The solid was crystallised from acetonitrile/ ethanol giving yellow crystals (1.2 g, 55%), mp 221°C.

^{1}H NMR ($CDCl_3$): 2.25 (3H, s), 2.55 (3H, s), 8.05 (2H, d, J = 9.1 Hz), 8.27 (2H, d, J = 9.1Hz).

IR (KBr): 3325, 2420, 1633, 1600, 1544, 1355, 1310, 1231, 1154, 1115, 855cm^{-1}.

RESULTS AND DISCUSSION

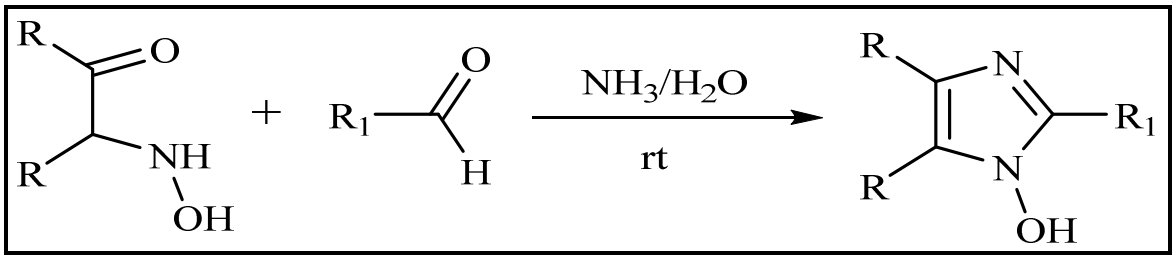
The Akagane[7] method was followed for the synthesis of new derivatives (10, 11) and other hydroxyimidazole compounds. A diacethylmonoxime or benzilmonoxime was reacted

with an appropriate aldehyde as shown in Scheme No.1. The reaction was carried out in aqueous media using ammonia and water mixture (1:1) in a stoppard flask at room temperature. The products are formed in solid form with good yields. The reactions were monitored by TLC, using silica gel as an adsorbent and ethyl acetate-hexane in different ratios as eluent, and they were characterized by spectroscopic techniques (Table No.1).

Biological Evaluation

The antimicrobial activities were determined using agar–cup method by measuring the zone of inhibition in mm. All newly synthesized compounds were screened *in vitro* for their antibacterial activity against gram positive bacteria such as *B.sub: bacillus subtilis, St.aur: Staphylococcus aureus, MRSA*: *Metacillin-Resistant Staphylococcus Aureus* and gram negative bacteria such as *K.P: Klebsiella pneumoniae, E.Coli*: *Escherichia coli*, *P.aeru: Pseudomonas aeruginosa* by agar plate method. Nitrofurantoin (F, 300µg) is a standard reference antibiotic used for antibacterial comparison activity with tested synthesized compounds (5-12, Table No.1).

DMSO 5% was used as solvent to enhance the solubility of the compounds. The zone of inhibition was recorded in mm after incubation of plates of agar medium for 24 hrs at 37ºC. The results of antibacterial activity indicated that compounds 10, 12 have a good antibacterial activity compared to the standard drug as shown in Table No.2. Compound 10 has moderate activity on gram-positive bacteria and have similar activity with same concentration on *P. aeru* and *B. sub* compared to nitrofurantoin, while compound 12 has exhibited good activity on *St.aur* and *MRSA* and showed no effect on the other species. The results did not show any antibacterial activity of the other prepared compounds (Table No.2). Structurally the imidazole ring of the prepared compounds is multi-substituted, these substituents make the ring unable to move freely and bind with function groups of bacterial proteins. The activity of compound 10 on some species of gram positive and gram negative may due to the double bond and phenyl group at position two. Substitution of phenyl group at *para*- position with nitro group provides compound 12 some moderate activity compared with compound 9.



Scheme No.1: General synthetic reaction for 1-hydroxyimidazole derivatives

Table No.1: Products of 1-Hydroxyimidazole derivatives

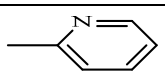
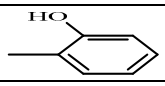
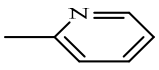
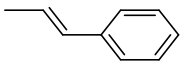
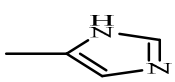
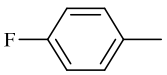
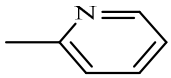
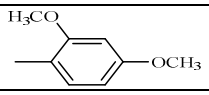
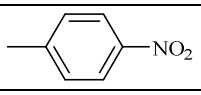
S.No	Entry	R	R1	Entry	R	R1
1	5	CH_3		9	CH_3	
2	6	Ph		10	CH_3	
3	7	CH_3		11		
4	8	Ph		12	CH_3	

Table No.2: Antibacterial activity of tested compounds 5-12

S.No		Zone of inhibition (mm)					
		Gram negative bacteria			Gram positive bacteria		
	Compound	*K.p*	*E. coli*	*P.aeru*	*B.sub*	*St.aur*	*MRSA*
1	5	6	6	6	6	9	6
2	6	6	6	6	6	6	6
3	7	6	6	6	6	6	6
4	8	6	6	6	6	6	6
5	9	6	6	6	6	6	6
6	10	6	6	11	12	14	14
7	11	6	6	6	6	6	6
8	12	6	6	6	6	12	13
9	DMSO	6	6	6	6	6	6
10	F	18	18	11	11	20	21

The concentration of each tested compounds and nitrofurantoin F is 300µg

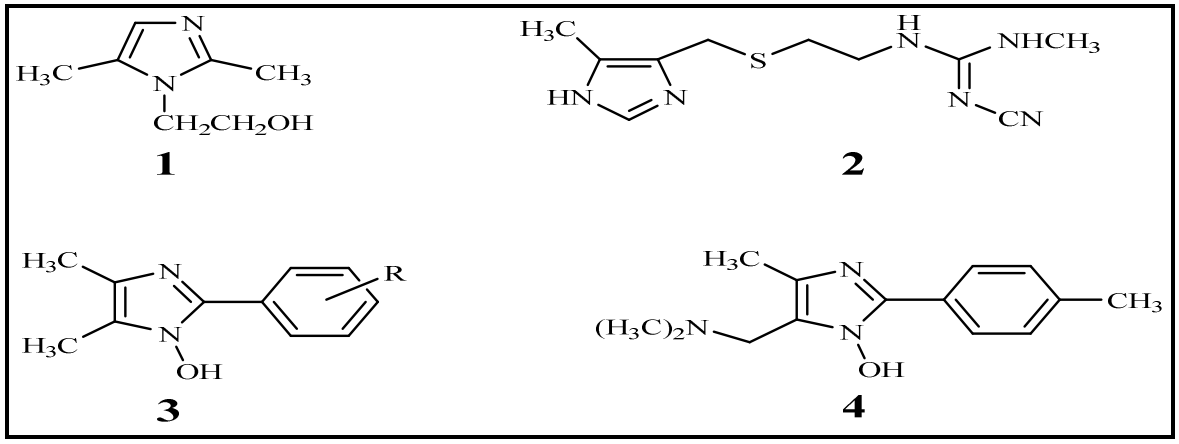


Figure No.1: Biologically active imidazole derivative

CONCLUSION

In general most of the prepared 1-hydroxyimidazole compounds have low or no activity against different species of bacteria, therefore, some structural modifications on imidazole ring are necessary to improve their activity.

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CONFLICT OF INTEREST

We declare that we have no conflict of interest.

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