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DESIGN AND SYNTHESIS OF SOME IMIDAZOLE DERIVATIVES CONTAINING 4-(3,5-DICHLORO-2-HYDROXYPHENYL) IMIDAZOLE MOIETY AS ANTIBACTERIAL AGENTS

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Abstract
In the last few decades, the compounds bearing heterocyclic nuclei have received much attention due to their chemotherapeutic values in the development of novel antimicrobials. The literature survey is enriched with the synthesis and pharmacological evaluation of fused heterocycles containing imidazole moieties. Due to their vital role in biological activities, it was thought interesting to synthesize some imidazole derivatives containing 4-(3,5-dichloro-2-hydroxyphenyl) moiety. The newly synthesized compounds were screened for antibacterial activities against some plant pathogens.
Keywords- chlorosubstituted, fused heterocycles, imidazole, antibacterial activity, plant pathogens.

I. INTRODUCTION

Certain small fused heterocyclic[1] molecules act as highly functionalized scaffolds and are known pharmacophores of a number of biologically[2,3] active and medicinally useful molecules. The literature contains several reports on the incorporation of imidazole moiety[4,5] with substituted pyrazole[6-12] ring resulting in compounds with potent bioactivities[13-15]. The five-membered imidazole[16-19] ring is a structural unit found in many biologically active[20,21] compounds. The strong therapeutic properties of imidazole containing drugs have encouraged medicinal chemists to synthesize a large number of novel chemotherapeutic agents comprising this entity. Amongst others, imidazole core structures are found in different carboxypeptidase, hemeoxygenase and lactamase inhibitors showing anti-inflammatory[22-24], anticancer[25], antifungal[26], antibacterial[27,28], antitubercular[29], anti-diabetic, anticonvulsant[30], antiamoebial[31,32], anti-hyperlipidemic[33], antiviral, antiasthmatic, cardioprotective, alpha-blocker, CNS-depressants, antiprotozoal and antihelmintics [34] activities. Keeping in view the advantages of imidazole and pyrazole moieties, we had planned for synthesis of some imidazole derivatives containing 4-(3,5-dichloro-2-hydroxyphenyl) moiety and assayed them for antibacterial activity.

II. MATERIALS AND METHODS

The synthetic routes which furnished the target compounds are as under along with their IR and NMR data.

Preparation of 2,4-dichlorophenyl acetate (1a): 2,4-Dichlorophenol (0.01M) was mixed with acetic anhydride (0.01M) and anhydrous sodium acetate (5g). The mixture was refluxed for about an hour. It was then cooled and poured into cold water. Acetate layer thus separated was washed with water for several times. Finally it was purified by distillation and the distillate of compound (1a) was collected at about 221^{o}C; yield: 75%, b.p: 221^{o}C.

Preparation of 1-(3,5-dichloro-2-hydroxyphenyl)ethanone (2a): The compound (1a) (50ml) was mixed with anhydrous aluminum trichloride (120 g) and heated at 120^{o}C for 45 minutes on sand bath. The reaction mixture was decomposed by ice cold water containing a little HCl to get the crude product. It was then purified by recrystalization using ethanol to get a greenish white solid as compound(2a); yield:74% ; m.p.:53^{o}C.

IR(KBr ν_{max})=3423cm^{-1}(-OH str),1664cm^{-1}(C=Ostr), 1300cm^{-1}(C-Ostr), 766cm^{-1}(C-Clstr)

NMR: δ12.69(s,1H,Ar-OH) , δ7.25 to 7.63 (m,2H,Ar-H) , δ2.60,(s,3H,-CH_3).

Preparation of 1-(2-hydroxy-3,5-dichlorophenyl)-2-bromoethanone (3a): 1-(3,5-dichloro-2-hydroxypheny d…….l)ethanone (2a) (0.01M) dissolved in acetic acid (0.02M) treated with bromine in acetic acid (0.02M) reagent in cold condition with occasional shaking for 30 minutes. It was then poured into ice cold water. The solid thus separated was filtered, washed with sodium bisulphate and finally with water to get the crude product. It was then recrystallised from ethanol to get the compound (3a); yield:65%; m.p.:97^{0}C.

IR(KBr ν_{max})=3336cm^{-1}(-OH str),1692cm^{-1}(C=O str), 756cm^{-1}(C-Br str), 732cm^{-1}(C-Cl str).

NMR: δ12.34(s,1H,Ar-OH) , δ7.7 to 7.4 (m,2H,Ar-H) , δ3.9,(s,2H,-CH_2Br).

Preparation of 1H-2-one-4-(2-hydroxy-3,5-dichlorophenyl)-5*H*-imidazole (4a) and **1-H-2-imine-4-(2-hydroxy-3,5-dichloro-phenyl)-5*H*-imidazole (4b):**

1-(2-Hydroxy-3,5-dichlorophenyl)-2-bromoethanone (3a)(0.01M) dissolved in ethanol refluxed with aqueous urea (0.01M) and aqueous guanidine(0.01M) independently for 3 h. using TEBA (Triethyl Benzyl Ammonium Chloride) catalyst. After cooling the reaction mixtures were diluted with water to get the compound (4a); yield:65%; m.p.:110^{o}C and the compound (4b) yield:63%; m.pt.:115^{o}C respectively.

IR(KBr ν_{max})=3522cm^{-1}(-OH str),3423cm^{-1}(N-H str), 1610cm^{-1}(C=O str),1568cm^{-1}(C=N str).

NMR: δ12.59(s,1H,Ar-OH) , δ7.7 to 7.9(m,2H,Ar-H) , δ3.3,(s,1H,-NH), δ2.7,(s,2H,-CH_2).

Preparation of 6-(2-hydroxy-3,5-dichlorophenyl)-2,5-dihydro-imidazo[1,2-a]imidazol-3-one (5a) and **6-(2-hydroxy-3,5-dichlorophenyl)-2,5-dihydro-imidazo[1,2-a]imidazol-3-one (5b):**

The compound (4a) (0.01) dissolved in ethanol (5 ml) refluxed with aqueous glycine (0.02 M) and aqueous alanine (0.02 M) separately in presence of TEBA (0.05 M) catalyst for 2 h. After cooling the reaction mixtures were triturated until the solid gets separated. The products thus obtained were filtered, washed with water and recrystallized from ethanol to get the compound (5a); yield:73%; m.p.: 95^{o}C and the compound (5b); yield:71%; m.pt.:83^{0}C.

IR(KBr ν_{max})=3366cm^{-1}(-OH str),1600cm^{-1}(C=O str),1522cm^{-1}(C=N str).

NMR: δ12.32(s,1H,Ar-OH) , δ7.7 to 7.3(m,2H,Ar-H) , δ3.3,(s,1H,-NH), δ2.9,(s,2H,-CH_2).

Preparation of 1-acetyl-4-(3,5-dichloro-2-hydroxyphenyl)-1,5-dihydro-2H-imidazol-2-one (6a): A mixture of compound (5a)(0.01M) and acetyl chloride(0.01M) dissolved in THF (5 ml) refluxed with aqueous NaOH (0.03M) for 2 h. After cooling the reaction mixture was triturated until the solid gets separated. The product thus obtained was filtered, washed with water and recrystallized from ethanol to get the compound (6a);yield:65%; m.p.:102^{o}C.

IR(KBr ν_{max})=3367cm^{-1}(-OH str),1692cm^{-1}(C=O str),1649cm^{-1}(C=O str),1588cm^{-1}(C=N str).

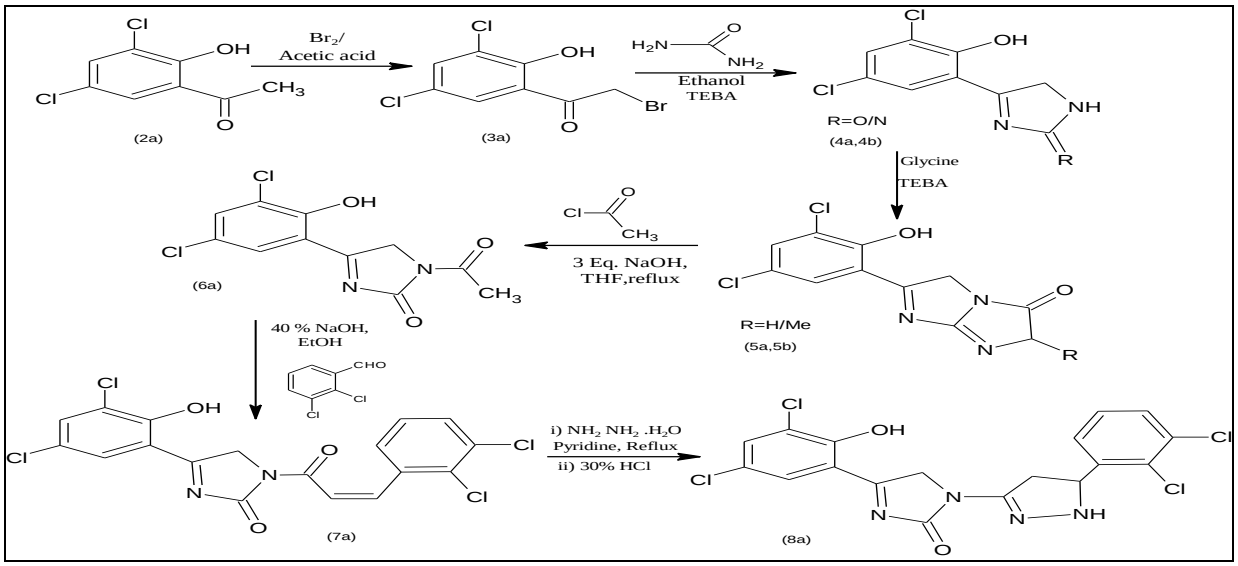
NMR: δ12.11(s,1H,Ar-OH) , δ7.7 to 7.3(m,2H,Ar-H) , δ2.8,(s,3H,-CH_3), δ2.3,(s,2H,-CH_2).

Preparation of 4-(3,5-dichloro-2-hydroxyphenyl)-3-(2,3-dichlorophenyl)prop-2-enoyl]-1,5-dihydro-2*H*-imidazol-2-one (7a): The compound (6a) (0.01M) dissolved in ethanol treated with 2,3-dichlorobenzaldehyde (0.01M) at its boiling temperature. Aqueous sodium hydroxide solution 40% (10ml) was added to it dropwise with constant stirring. The mixture was mechanically stirred for 30 minutes at room temperature and kept for overnight. It was then acidified with HCl (10%). The solid product thus obtained was filtered, washed with sodium bicarbonate (10%) followed by washing with water to get the crude product. It was crystallized from ethanol to get the compound (7a); yield:75%; m.p.:124^{o}C.

IR(KBr ν_{max})=3367cm^{-1}(-OH str),1693cm^{-1}(C=O str),1650cm^{-1}(C=C-H str),1563cm^{-1}(C=N str).
NMR: δ12.65(s,1H,Ar-OH) , δ7.7 to 7.3(m,2H,Ar-H) , δ7.6,(dd,2H,CH-CH), δ2.7,(s,2H,-CH_2).

Preparation of 4-(3,5-dichloro-2-hydroxyphenyl)-1-[5-(2,3-dichloro-phenyl)-4,5-dihydro-1*H*-pyrazol-3-yl]-1,5-dihydro-2*H*-imidazol-2-one (8a): A reaction mixture of the compound (7a) (0.01M) and hydrazine hydrate (0.01M) in pyridine (10ml) was refluxed on oil bath using magnetic stirrer for 2.5h. On cooling the reaction mixture was acidified with HCl (30%). The solid product thus obtained was filtered, washed with sodium bicarbonate (10%) followed by washing with water to get the crude product. It was crystallized from ethanol to get the compound (XaIII); yield: 64%; m.p.:103^{o}C.
IR(KBr ν_{max})=3550cm^{-1}(-OH str),3423cm^{-1}(C-N str),1693cm^{-1}(C=Ostr),1588cm^{-1}(C=N str).
NMR: δ12.23(s,1H,Ar-OH) , δ7.8 to 7.3(m,5H,Ar-H) , δ6.1,(s,1H,N-H), δ3.9,(s,1H,N-C-H), δ3.0,(s,2H,-CH_2), δ1.7,(dd,1H,-C-H), δ1.4,(dd,1H,-C-H).

Scheme-



III. ANTIBACTERIAL ACTIVITY

The test compounds showed good to excellent antiabacterial activities when screened against some ornamental plant pathogens viz. Staphylococcus aureus, Staphylococcus epidermis, Pseudomonas aeruginosa and Salmonella typhi by using Agar disc diffusion method. The zones of inhibition formed were measured in mm and are shown in table-1.

"Table No.1- Impact of test compounds against plant pathogens"

	Pseudomonas aeruginosa MTCC-424 (Gram Negative)				*Salmonella typhi* ATCC-25812 (Gram Negative)				*Staphylococcus aureus* ATCC-33591 (Gram Positive)				*Staphylococcus epidermidis* MTCC-3086 (Gram Positive)			
Sample Code	AB	SP	ABSP	CL	AB	SP	ABSP	CL	AB	SP	ABSP	CL	AB	SP	ABSP	CL
4a	23	16	26	00	26	19	32	00	16	18	18	00	27	16	28	00
4b	23	16	26	00	27	18	33	00	17	19	17	00	27	15	29	00
5a	23	17	26	00	27	17	33	00	17	20	18	00	27	15	29	00
5b	23	16	25	00	27	18	32	00	17	20	18	00	27	16	28	00
6a	23	12	24	00	27	16	29	00	17	17	18	00	27	15	28	00
7a	22	11	23	00	27	16	30	00	17	16	19	00	27	13	27	00
8a	22	10	23	00	27	15	28	00	16	15	16	00	27	12	28	00

Diameter of inhibition zone (mm) AB-Antibiotic Disc (Chloramphenicol-10), SP- Sample, ABSP- Antibiotic+Sample, CL-Control (DMSO),Values were represented as the mean.

IV. RESULTS AND DISCUSSION

The newly synthesized compounds (4a-8a) showed good to excellent activity against test pathogens. A further detailed study in the light of Plant pathology is advised.

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