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SYNTHESIS OF SOME CHLOROSUBSTITUTED THIAZOLES, IMIDAZOLO-THIAZOLES-AS EFFICIENT ANTIBACTERIAL AGENTS

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ABSTRACT
In the past 2,3 decades, the literature survey is enriched with progressive finding about the synthesis and pharmacological evaluation of fused heterocycles containing imidazole and thiazole moeities. Due to their vital role in biological activities, it was thought interesting to synthesize some chlorosubstitutedthiazoles and their imidazole containing derivatives. The newly synthesized compounds when screened for antibacterial activities against some plant pathogens showed good to excellent activity.

KEYWORDS: thioureas, thiazoles, imidazolo-thiazoles, antibacterial agent.

INTRODUCTION

Literature survey reveals that many heterocyclic[1] compounds containing fused ring system have a broad spectrum of biological[2-3] as well as physiological activities. It is also revealed that thiazole moieties have attracted considerable attention of medicinal chemists as they are endowed with a wide range of diverse biological activities[4] such as anti-inflammatory[5], analgesic, antifungal[6], antimicrobial[7], anti-oxidant activity.[8] Imidazole is also one of the most fascinating classes of compounds possessing variety of biological activities[9-14] such as anti-HIV, anti-histamine, antibacterial, tranquillizer *etc*. Morever imidazole[15] motif is found in number of chemo-therapeutic agents such as etomidate, zolpidem, nafimidone, cimetidine, clodine, pilocarpine and metronidazole. Encouraged by the earlier reports, we have designed and synthesized some new chlorosubstituted thiazoles and their imidazolo-thiazole blends. These titled compounds were screened for their antibacterial[16-19] assay against some *ornamental plant pathogens* viz. *Staphylococcus aureus, Staphylococcus epidermis, Pseudomonas aeruginosa and Salmonella typhi* by using Agar disc diffusion method.

EXPERIMENTAL

Physical characterization data of all the compounds are given in Table-1.

TABLE-1: Characterization data of newly synthesized compounds

Compound	Molecular Formula	Melting Point (^oC)	Yield (%)	R_f
1a	$C_8H_6Cl_2O_2$	221(B.P)	75	0.81
2a	$C_8H_6Cl_2O_2$	53	74	0.84
3a	$C_{15}H_8Cl_4O_2$	130	78	0.74
4a	$C_{15}H_6Cl_4O_2$	122	75	0.86
5a	$C_{15}H_8Cl_4O_3$	141	59	0.77
6a	$C_{15}H_7BrCl_4O_3$	100	60	0.79
7a	$C_{16}H_8Cl_4N_2O_2S$	150	59	0.88
7b	$C_{22}H_{12}Cl_4N_2O_2S$	141	56	0.86
8a	$C_{24}H_{12}Cl_4N_2O_4S$	111	65	0.80
9a	$C_{25}H_{11}Cl_6N_3O_3S_2$	103	70	0.75

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

Scheme-I

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-H) , δ7.25 to 7.63 (m,2H,Ar-H) , δ2.60,(s,3H,-CH_3).

Preparation of 1-(3,5-dichloro-2-hydroxyphenyl)-3-(2,3-dichlorophenyl)prop-2-en-1-one (3a): The compound (2a)(0.01M) dissolved in ethanol and 2,3-dichloro benzaldehyde (0.01M) was added to it, the mixture was heated to boiling, 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 overnight. Then the mixture was 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-acetic acid mixture to get the compound (3a); yield:78%; m.p.:130^{0}C.

IR(KBr ν_{max})=3445cm^{-1}(O-Hstr),1649(C=Ostr),3068cm^{-1}(ArC-Hstr),1608cm^{-1} (C=Cstr), 780cm^{-1}(C-Clstr).

NMR: δ13.16(s,1H,Ar-OH),δ8.39(d,1H,-CH), δ8.35(d,1H,-CH), δ7.26-7.78(m,5H,Ar-H).

Preparation of 6,8-dichloro-2-(2,3-dichlorophenyl)-4*H*-chromen-4-one(4a): The compound (3a)(0.01) suspended in 10 ml DMSO refluxed with crystals of iodine for 45 minutes. After cooling the reaction mixture was diluted with water. The solid thus obtained was filtered, washed with 20% sodium thiosulphate solution and finally crystallised from ethyl alcohol to get the compound (4a);yield:75%, m.p.:122^{o}C.

IR(KBr ν_{max})=1664cm (C=Ostr), 1176cm^{-1} (C-Osrt), 780cm^{-1} (C-Clstr).

NMR: δ7.8-8.1(m,5H,Ar-H), δ6.7(s,1H,=CH).

Preparation of 1-(3,5-dichloro-2-hydroxyphenyl)-3-(2,3-dichlorophenyl)propane-1,3-dione (5a): The compound (4a) (0.01M) dissolved in ethanol (25ml) treated with HCl solution (25ml) (20%). The reaction mixture was then refluxed for 45 minutes, cooled and diluted with cold water. The product thus separated was filtered and washed with water and finally recrystallised from ethanol to get the compound (5a); yield:59%, m. p.:141^{o}C.

IR(KBr ν_{max})=3364cm^{-1}(O-Hstr),1690cm^{-1} (C=Ostr),1310cm^{-1}(C-Osrt),798cm^{-1}(C-Clstr).

NMR: δ10.45(s,1H,Ar-OH), δ7.2-7.9(m,5H,Ar-H), δ3,9(s,2H,CH_2).

Preparation of 2-bromo-1-(3,5-dichloro-2-hydroxyphenyl)-3-(2,3-dichlorophenyl)propane-1,3-dione (6a): The compound (5a) (0.01M) dissolved in acetic acid (10 ml), treated with bromine in acetic acid reagent (0.01M) (0.5ml). The mixture was allowed to stand for 1 h. at room temperature. The reaction mixture was decomposed with ice cold water to get the compound 6a; yield:60%, m.p.:100^{o}C.

IR(KBr ν_{max})= 3367cm^{-1}(O-Hstr),1692cm^{-1} (C=Ostr),1162cm^{-1}(C-Osrt),782cm^{-1}(C-Clstr), 630cm^{-1} (C-Br str).

NMR: δ12.9(s,1H,Ar-OH), δ7.2-7.9(m,5H,Ar-H), δ3.3(s,1H,C-H).

Preparation of 2-amino-4-(2,3-dichlorobenzoyl)-5-(2-hydroxy-3,5-dichlorophenyl)-1,3-thiazole (7a) and **2-aminophenyl-4-(2,3-dichlorobenzoyl)-5-(2-hydroxy-3,5-dichlorophenyl)-1,3-thiazole (7b):** The compound (6a) (0.01M) refluxed separately with thiourea (0.01M) and phenyl thiourea(0.01M) in presence of aqueous KOH solution (25ml, 0.02M) in ethanol (25ml) to obtain the compounds (7a); yield 59%; m.p. 150^{o}C and (7b); yield 56%; m.p. 141^{o}C respectively.

IR(KBr ν_{max})= 3510cm^{-1} (O-Hstr), 3340cm^{-1} (sharp,NH_2str), 1660cm^{-1} (C=Nstr), 1600cm^{-1} (C=Ostr),1310cm^{-1} (C-Ostr),780cm^{-1}(C-Clstr).

NMR: δ10.20(s,1H,Ar-OH), δ7.2-7.9(m,5H, Ar-H), δ4.0(s,2H,-NH_2).

Preparation of 2-({5-(3,5-dichloro-2-hydroxyphenyl)-4-[(2,3-dichlorophenyl)carbonyl]-1,3-thiazol-2-yl}amino)-1-(2,3-dichlorophenyl) ethanone (8a)

The compound (7a) (0.01M) was refluxed with 2-bromo-1-(3,5-dichloro-2-hydroxyphenyl) ethanone (0.01M) in absolute alcohol for 1 h. On cooling, the mixture was decomposed in ice cold water. The product thus separated was filtered and crystallized from alcohol to get the compound (8a); yield:65%; m.p.:111^{o}C.

IR(KBr ν_{max})=3460cm^{-1} (O-Hstr), 3367cm^{-1} (sharp,NH_2str), 1622cm^{-1} (C=Ostr), 1583cm^{-1} (C=Nstr),1310cm^{-1} (C-Ostr),796cm^{-1}(C-Clstr).

NMR: δ12.72(s,2H,Ar-OH), δ7.25-7.65(m,7H, Ar-H), δ2.65(s,2H,-CH_2), δ1.8(s,2H,-NH_2).

Preparation of 2-[2-mercapto-4-(2-hydroxy-3,5-dichlorophenyl) imidazolo]-4-(2,3-dichlorobenzoyl)-5-(2-hydroxy-2,3-dichlorophenyl)-1,3-thiazol (9a)

The compound (8a) (0.01M) was refluxed with KSCN in glacial acetic acid (20 ml) for about 4 h. On cooling, the reaction mixture was poured into ice cold water. The product thus separated was filtered and recrystallised from ethanol to get the compound (9a); yield:70%; m.pt.:103^{o}C.

IR(KBr ν_{max})=3341cm^{-1} (O-Hstr), 3068cm^{-1} (sharp,NH_2str), 2548cm^{-1} (S-Hstr), 1662cm^{-1} (C=Ostr),1641cm^{-1} (C=Nstr),796cm^{-1}(C-Clstr).

NMR: Δ12.61-13.0(S,2H,AR-OH), Δ7.25-7.92(M,8H, AR-H), Δ2.5(S,1H,-SH).

ANTIBACTERIAL ACTIVITY

The test compounds were screened for their antibacterial assay against *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-2.

Table No.2: Impact of newly synthesized chlorosubstituted heterocycles against plant pathogens.

Sample Code	*Pseudomonas aeruginosa* MTCC-424 (Gram Negative)				*Salmonella typhi* ATCC-25812 (Gram Negative)				*Staphylococcus aureus* ATCC-33591 (Gram Positive)				*Staphylococcus epidermidis* MTCC-3086 (Gram Positive)			
	AB	SP	ABSP	CL	AB	SP	ABSP	CL	AB	SP	ABSP	CL	AB	SP	ABSP	CL
7a	23	16	25	00	27	22	31	00	15	17	17	00	26	16	27	00
7b	23	16	25	00	26	21	32	00	14	18	16	00	26	17	27	00
8a	23	17	24	00	26	19	33	00	14	21	17	00	28	16	28	00
9a	23	16	24	00	27	18	31	00	13	21	17	00	27	16	27	00

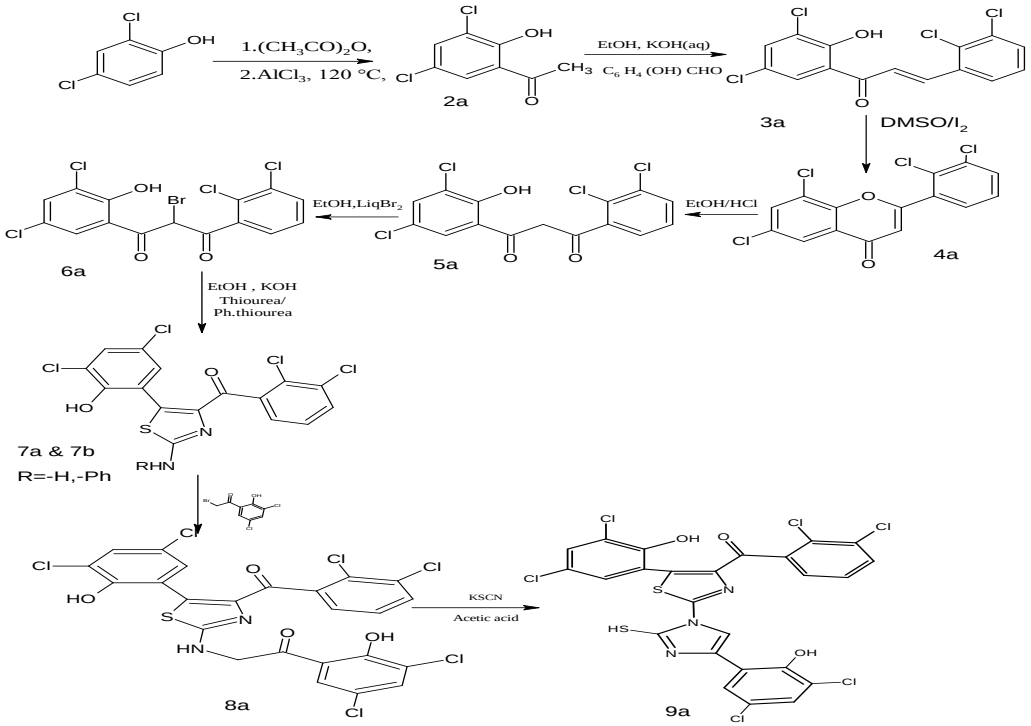
Diameter of inhibition zone (mm)

AB- Antibiotic Disc (Chloramphenicol-10), SP- Sample, ABSP- Antibiotic+Sample, CL- Control (DMSO).

RESULTS AND DISCUSSION

The newly synthesized compounds (7a,7b,8a and 9a) showed good to excellent activity against test pathogens. A further detailed study in the light of Plant pathology is advised.

Scheme-1



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