ISSN: 2319-5967
ISO 9001:2008 Certified
International Journal of Engineering Science and Innovative Technology (IJESIT)
Volume 3, Issue 4, July 2014

Synthesis and Characterization of Some New N, O and S Containing Chlorosubstituted Heterocycles and Their Antimicrobial Screening against Some Common Causative Organisms

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Abstract*—Some new nitrogen, oxygen and sulfur containing heterocyclic systems such as pyrazoles, isoxazoles and 1,3-thiazoles were synthesized via cyclization of 1-(2-hydroxy-3,5-dichlorophenyl)-3'-ethyl-1,3-dione and 1-(2-hydroxy-3,5-dichlorophenyl)-4-bromo-3-ethyl-1,3-dione by using suitable reagents. Structures of the newly synthesized compounds were established by molecular weight determinations, elemental analysis and spectral data. All the products were also screened in vitro for their antimicrobial activity against the bacteria P. vulgaris and B. subtilis spp. and antifungal activity against Aspergillusn niger , Curvularia lunata by disc diffusion method.

***Index Terms*—Antimicrobial activity, Isoxazoles, Pyrazoles and 1, 3-Thiazoles..**

I. INTRODUCTION

The N, O and S containing chlorosubstituted heterocycles viz. pyrazoles, isoxazoles and 1, 3-thiazoles, is an important class of heterocyclic compounds. These are reported to have a broad spectrum of biological and medicinal activities, such as Anticonvalsant [1], cytotoxic, herbicidal [2], antiinflammatory [3], antifungal [4], antimicrobial [5], antioxidant [6] activities.

Pyrazole ring is incorporated into many of the commercially available pharmaceuticals, agrochemicals [7]. Isoxazole derivatives [8] have been in commercial use for many years. Thiazole being an integral part of many potent biologically active molecules [9] plays an important role as antifungal and antibacterial agent.

In view of the above mentioned findings, we decided to synthesize some new pyrazoles, isoxazoles and 1,3-thiazoles and investigate their antimicrobial activities.

II. EXPERIMENTAL

Preparation of 2-hydroxy-3,5-dichloro-4'-ethylchalcone (3a):

To the boiling solution of the 2-hydroxy-3,5-dichloroacetophenone (2b) (0.01 mol) and propanaldehyde (0.01 mol) in ethanol (20ml), 40% solution of NaOH was added gradually. The reaction mixture was stirred mechanically at room temperature for 1 hr. and kept it at room temperature for 6 to 8 h. followed by decomposition with ice-cold HCl (1:1). The yellow granules thus obtained were filtered and washed with 10% $NaHCO_3$ solution and then crystallized from ethanol to obtain compound (3a) m.p.94^{o}C, yield: 75%**.**

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Preparation of Chalconedibromide (3b)

2-Hydroxy-3,5-dichlorophenyl-4'-ethylchalcone (3a) was suspended in bromine-glacial acetic acid reagent. The reagent was added drop by drop with constant stirring and reaction mixture was kept at room temperature for about 30 minutes. The solid product thus separated was filtered and washed with a little petroleum ether to get the compound (3b). M.P. 75^{o}C, Yield 82%.

Preparation of 6,8-dicloroflavone (4a).

Compound (3b) was dissolved in ethanol (25ml) containing a little piperidine. To this aqueous KOH solution (25 ml) was added. The reaction mixture was then refluxed for 1 hour, cooled and diluted with water. The product thus separated was filtered and crystallized from ethanol to get the compound (4a). M.P. 147^{o}C, Yield 60 %.

Preparation of 1-(2-hydroxy-3,5-dichlorophenyl)-3'-ethyl-1,3-dione (5a).

1-Ethyl-6,8-dichloroflavone (4a) was dissolved in ethanol containing a little piperidine. To this aqueous HCl solution (25 ml) was added. The reaction mixture was then refluxed for 1 hour, cooled and diluted with water. The product thus separated was filtered and crystallized from ethanol to get the compound (5a). M.P. 110^{o}C, Yield 65 %.

Preparation of 1-(2-hydroxy-3,5-dichlorophenyl)-4-bromo-3-ethyl-1,3-dione (5b).

1-(2-Hydroxy-5-chlorophenyl)-3-ethyl-1,3-dione(5a) was dissolved in ethanol (10 ml) containing a little piperidine. To this, liquid bromine (0.5 ml) was added and allowed it to stand for 1 hour. It was then diluted and washed several times with water and finally extracted with ether to get the compound (5b), M.P. 78^{o}C, Yield 60 %.

Preparation of pyrazole 3-(2-hydroxy-3,5-dichlorophenyl)-5 –ethylpyrazole (6a).

1-(2-Hydroxy-3,5-chlorophenyl)-3'-ethyl-1,3-dione (5a) and phenylhydrazine hydrochloride were dissolved in ethanol (25 ml) containing a little piperidine refluxed for 1.5 hours, cooled and diluted with water and acidified with conc. HCl. The product thus separated was filtered and crystallized from ethanol to get the compound (6a). M.P. 167^{o}C, Yield 75 %. Elemental analysis: % **C** 60.21/ 61.23; % **H** 4.39/ 5.40; % **O** 7.75/ 8.16; % **Cl** 17.86/ 18.07; % **N** 6.82/ 7.14; UV spectrum (dioxane) $\lambda_{max,}$ 395.0 nm (n—›π*). IR (KBr,): 3600 (-OH stret.), 3038 (Aromatic stret.), 3200 (-NH stret.), 2850 (Ali. C-CH stret.), 1431 (-CH_2 bend.), 1304 (-CH_3 bend.), 825.57(C-Cl Stret.), ^{1}H NMR: δ 1.28 (t, 3H, -CH_2-C**H**$_3$), δ 2.05 (q, 2H, -C**H**$_2$-CH_3), δ 6.91 to 8.11 (m, 3H, Ar-H), 11.2 (s, H, -O**H**), 4.6 (s, 1H, -N**H**).

Preparation of isoxazole 3-(2-hydroxy-3,5-dichlorophenyl)-5-ethylisoxazole (6b).

1-(2-Hydroxy-3,5-chlorophenyl)-3'-ethyl-1,3-dione (5a) and hydroxylamine hydrochloride were dissolved in ethanol (25 ml) contains few drops of piperidine refluxed for 2.5 hours, cooled and diluted with water and acidified with conc. HCl. The product thus separated was filtered and crystallized from ethanol to get the compound (6a). M.P. 185^{o}C, Yield 75 %. Elemental analysis: % **C** 52.00/ 52.02; % **H** 3.59/ 3.69; % **O** 15.66/ 15.99 % **Cl** 23.44/ 23.62 % **N** 4.55/ 4.67; UV spectrum (dioxane) $\lambda_{max,}$ 402.0 nm (n—›π*). IR (KBr): 3500 (-OH stret.), 3084 (Aromatic stret.), 3359 (-NH stret.), 2861(Ali. C-CH stret.), 1451(-CH_2 bending), 1338, (CH_3 bending), 819 (C-Cl Stret.), ^{1}H NMR: δ 1.26 (t, 3H, -CH_2-C**H**$_3$), δ 2.4, (s, 2H, -C**H**$_2$-CH_3), δ 6.67 to 7.83 (m, 3H, Ar-H), 11.3 (s, H, -O**H**).

Preparation of 5-(2-hydroxy-3,5-dichlorophenyl)-4'-ethyl-2'-amino-1,3-thiazole (6c).

1-(2-Hydroxy-3,5-chlorophenyl)-2-bromo-3-ethyl-1,3-dione (5b) and thiourea were dissolved in ethanol (25 ml) contains few drops of piperidine. To this reaction mixture aqueous KOH solution (10ml) was added and refluxed for 2.5 hours, cooled and diluted with water and acidified with conc. HCl. The product thus separated was filtered and crystallized from ethanol to get the compound (6a). M.P. 102^{o}C, Yield 64 %. Elemental analysis: %**C** 46.79/ 46.89; %**H** 2.39/ 2.46; %**O** 7.75/ 7.82; %**Cl** 8.56/ 8.65; %**N** 6.82/ 6.89; %**S** 7.73/ 7.82.; UV spectrum (dioxane) $\lambda_{max,}$ 401.0 nm (n—›π*). IR (KBr): 3500, (-OH stret.), 3038 (Aromatic stret.), 3300 (-NH stret.), 2850 (Ali. C-CH stret.), 1434 (-CH_2 bend.), 1338, (-CH_3 bend.) 1022 (C-S stret.), 829.39 (C-Cl Stret.), ^{1}H NMR: δ 2.7 (s, 3H, -C**H**$_3$), δ 7-8 (m, 12H, Ar-**H**), δ 6.2 (s, 1H, -N**H**), δ 12.5 (s, 2H, Ar-O**H**), 11.2 (s, H, -O**H**), 4.7 (s, 1H, -N**H**).

Preparation of 5-(2-hydroxy-3,5-dichlorophenyl)-4'-ethyl-2'-aminophenyl-1,3-thiazole (6d).

1-(2-Hydroxy-3,5-chlorophenyl)-4'-bromo-3'-ethyl-1,3-dione (5b)and phenylthiourea were dissolved in ethanol

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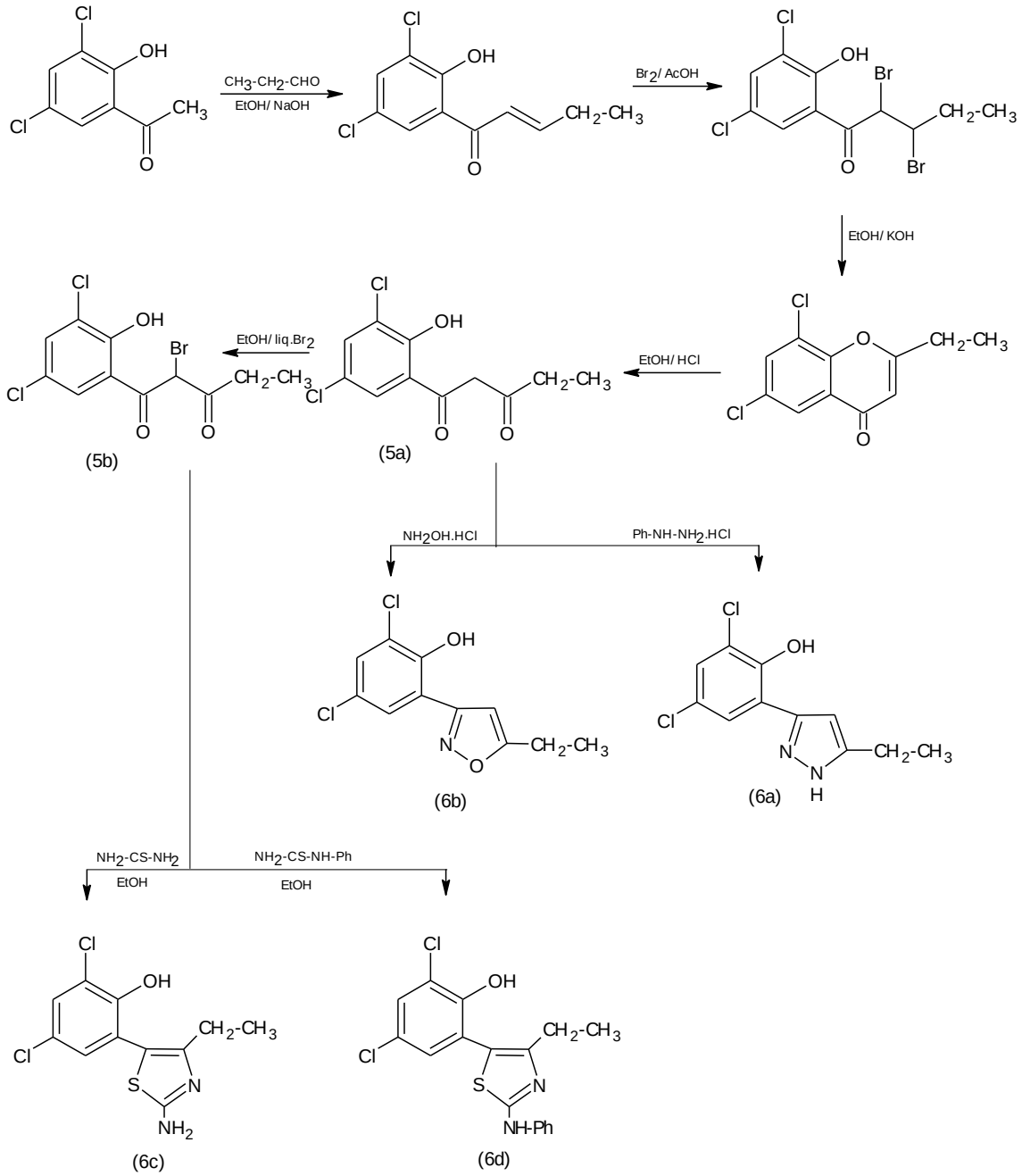
(25 ml) contains few drops of piperidine. To this reaction mixture aqueous KOH solution (10ml) was added and refluxed for 2.5 hours, cooled and diluted with water and acidified with conc. HCl. The product thus separated was filtered and crystallized from ethanol to get the compound (6b). M.P. 130^{o}C, Yield 70 %. Elemental analysis: %**C** 56.02/ 56.74; %**H** 3.98/ 4.76 %**O** 15.78/ 16.75 %**Cl** 6.09/ 6.62; %**N** 7.12/ 7.56; %**S** 6.98/ 7.57.; UV spectrum (dioxane) $\lambda_{max,}$ 395 nm (n—›π*). IR (KBr): 3300, (-OH stret.), 3035 (Aromatic stret.), 3300 (-NH stret.), 2839 (Ali. C-CH stret.), 1431 (-CH_2 bend.), 1338, (-CH_3 bend.) 1022 (C-S stret.), 830 (C-Cl Stret.), ^{1}H NMR: δ 2.7 (s, 3H, -C**H**$_3$), δ 7-8 (m, 12H, Ar-**H**), δ 6.2 (s, 1H, -N**H**), δ 12.75, (s, 8H, Ar-O**H**), 11.5 (s, H, -O**H**), 5.0 (s, 1H, -N**H**).

SCHEME



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III. ANTIMICROBIAL ACTIVITY

All the compounds synthesized in the first part of the study were screened *in vitro* for their antibacterial activity against the bacteria *P. vulgaris* and *B. subtilis spp.* and antifungal activity against *Aspergillus niger*, *Curvularia lunata* by disc diffusion method.

The efficacy of the test compounds were determined by measuring the visible clear area of growth free zones i.e. *zone of inhibition* produced by diffusion of the antibiotics in to media from the discs by callipers in mm. The results are tabulated in the table given below:

Table I: Antimicrobial activity of test compounds

Test compounds	Zone of inhibition (mm)							
	P. vulgaris		***B. subtilis spp.***		***Aspergillus niger***		***Curvularia lunata***	
	10 ug/ disc	500 ug/ disc	10 ug/ Disc	500 ug/ disc	10 ug/ disc	500 ug/ disc	10 ug/ disc	500 ug/ disc
3a	4	18	2.4-2.3	16	3.3-4.0	12	3-5	13
5a	3	20	2-3	19	4	16	4.0-4.3	17
5b	3	17	2-3	18	5	15	8	17
6a	5	22	6	20	7	23	6	21
6b	5	21	8	23	4	24	7	18
6c	3	19	2-3	16	3.4-3.7	19	5.9-6.5	25
6d	5	21	8	22	6	16	5	22
Gentamicine	-	-	-	-	-	-	-	-

The results depicted in Table-I revealed that most of the synthesized compounds were found to possess various antimicrobial activities towards the test organisms. In general, most of the synthesized compounds have better activities against the microbial strains in comparison with the starting material (3a). Compounds **6a, 6b, 6c** and **6d** were found to possess high inhibitory activities at 500 ug/disc concentration against the test organisms. In this context it has also been observed that the antimicrobial activities of newly synthesized heterocycles increases with increased structural complexity.

ACKNOWLEDGMENT

The authors are thankful to SAIF, CDRI, Lucknow for providing the spectral data and also grateful to Department of Microbiology, Shankarlal Khandelwal College, Akola for providing the help in carrying out the antimicrobial activities.

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ISO 9001:2008 Certified
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Volume 3, Issue 4, July 2014

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