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EVALUATION OF SOME NOVEL 5-IMIDAZOLONES AND THEIR ANTIBACTERIAL STUDY

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Abstract: **The target compounds were prepared by the reaction between different azalactones (1a-j) and thiophene-2-ethylamine (2). The constitution of all the synthesized compounds was established by their physical properties, elemental analysis and special analysis (IR and ^{1}H NMR spectra). All the synthesized compounds were screened for their in vitro antibacterial activity by using Gram positive and Gram negative bacteria.**

Keywords: **Azalactone, thiophene-2-elthylamine, 2-imidazolones, antibacterial activity.**

I. INTRODUCTION

Unsaturated imidazolin-5-ones, which are the nitrogen analogues of azalactones, form an important class of heterocyclic compounds because they can be converted into amino acid[1, 2] and used in drugs[3], pigments and electrodes[4] etc. Literature survey reveals that 5-imidazolones have exhibited promising biological and pharmacological activities[5] such as CNS depressant[6], anthelmintic[7], antifungal[8], anticaner[9] *etc*. Different methods have been documented for the synthesis of imidazolones in literature[10, 11].

Prompted by these observations and in continuation of the work[12, 13] on 5-imidazolones, it was contemplated to synthesize a new series of 5-imidzaolones by the interactions of thiophene-2-ethylamine with 2-phenyl-4-1(benzylidene/substituted benzylidene)-2-oxazol-5-one (different azalactones) which were prepared by well known Erlemeyer azalactone synthesis[14] (**Scheme I)**. The structure of all the synthesized compounds has been established on the basis of physical characterization data, elemental analysis and spectral characterization data. The synthesized compounds were screened for their *in vitro* antibacterial activity against three different strains *viz S. aureus* (MTCC 96), *B. subtilis* (MTCC 441) [Gram-postive bacteria] and *E. coli* (MTCC 443) [Gram-negative bacteria] by agar diffusion method (**Table I**).

II. RESULT AND DISCUSSION

The products **3a-j** were obtained by the treatment of **1a-j** with thiophene-2-ethylamine 2 and were characterized from their spectral and analytical data. The IR Spectra revealed the presence of –C=O group (imidazolone moiety) by exhibiting strong absorption band in the region between 1760-1655 cm^{-1}. The ^{1}H NMR spectra of compounds **3a-j** (in $CDCl_3$) showed multiplet at δ 2.8-2.9 due to $–CH_2$-CH_2 and another multiplet at δ 3.4-3.6 due to –CH_2-CH_2. The ^{1}H NMR spectra of compounds **3a-j** showed the complex multiplet of aromatic protons at δ 6.70-7.9. The physical and analytical characterization data also confirmed the synthesis of compound **3a-j**.

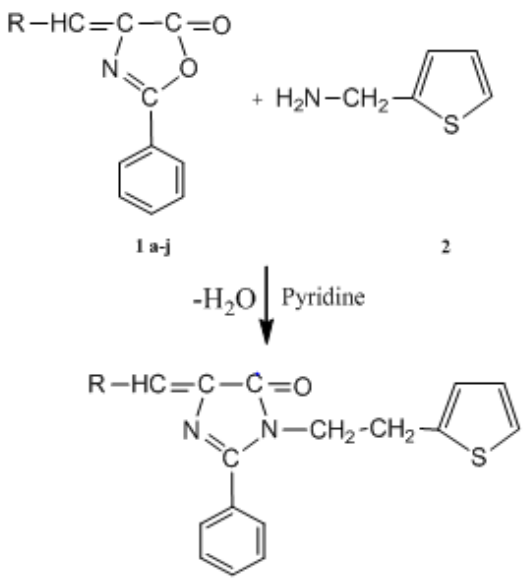
III. ANTIBACTERIAL ACTIVITY

All the synthesized compound were screened for their antibacterial activity by using agar diffusion method[15] against *S. aureus* and *B. subtilis* (Gram positive bacteria) and *E. coli* (Gram negative bacteria) in nutrient agar medium. Ciprofloxacin was used as standard drug for the comparison of antibacterial activity.

Compound **1a** containing R= phenyl was found to be active for all bacterial strains. Subsitution of a chloro group at 2nd position decreases the antibacterial activity of the compound for all bacterial strains. Substitution of chloro group at 3rd and 4th position gives satisfactory results. In case of Gram-positive bacteria, substitution of methoxy group at 4th position increases antibacterial activity of the compounds. In case of Gram-negative bacteria, substitution of methoxy group at 4th position decreases the antibacterial activity of compounds.

IV. EXPERIMENTAL SECTION

All melting points were determined in open capillary and are uncorrected. The IR spectra were recorded on a Perkin-Elmer 237 spectrometer. ^{1}H NMR spectra were recorded on a Bruker Advance DPX 400 MHz spectrometer with $CDCl_3$ as a solvent and tetramethylsilane (TMS) as internal standard. The chemical shifts are expressed in parts per million (ppm) downfield from the internal standard and signals are quoted as *s* (singlet) and *m* (multiplet).



R= phenyl **3a,** 2-chlorophenyl **3b,** 3-chlorophenyl **3c,** 4-chlorophenyl **3d,** 2-methoxyphenyl **3e,** 4-methoyphenyl **3f,** 2-nitrophenyl **3g,** 4-nitrophenyl **3h,** 3-bromophenyl **3i,** 4-bromophenyl **3j**

Scheme I

Analytical separation was conducted on silica gel 60 F-254 (Merck) plates of 0.25 mm thickness and eluted with toluene : acetone (10 : 2 v/v). They were visualized with UV (254 nm) or iodine vapours to check the homogeneity of the synthesized compounds.

General procedure for the preparation different azalactones

2-Phenyl-4-(benzylidene/substituted benzylidene)-oxazol-5-ones were prepared by the reported method[14].

General procedure for the preparation of 1-(2'-ethylthiophene)-2-phenyl-4-(benzylidene/substitute-d benzylidene)-5-imidazolones 3a-j

A mixture of 2-Phenyl-4-(benzylidene/ substituted benzylidene)-oxazole-5-one **1a-j** (0.01 mole), thiophene-2-ethyl amine **2** (0.01 mole) and pyridine 15 ml) were taken in a round bottom flask and refluxed for 13 hrs in the presence of a few drops of glacial acetic acid. Heating was continued till reaction was completed. The progress of reaction was monitored on TLC plate. Thereafter, the reaction

Table I – Antibacterial activity data of compounds **3a-j**

No.	Compound	Antibacterial Activity Diameter of zone of inhibition (in mm)		
		S. aureus (MTCC-96)	***B. subtilis*** (MTCC-441)	***E. coli*** (MTCC-443)
1	**3a**	22	21	23
2	**3b**	17	17	19
3	**3c**	22	18	16
4	**3d**	21	18	15
5	**3e**	21	17	14
6	**3f**	21	20	20
7	**3g**	-	20	19
8	**3h**	-	16	18
9	**3i**	20	13	19
10	**3j**	-	18	17
	Ciprofloxacin	22	24	26

mixture was poured into crushed ice and neutralized with conc. HCl. The solid separated out was filtered, washed with water, dried and purified by recrystallization from ethyl alcohol which furnished the target compounds **3a-j.**

1-(2'-Ethylthiophene)-2-phenyl-4-benzylidine-5-imidazolone 3a. m.P.139ºC, yield 80%, IR (KRr): 3064 (=CH str.), 1635 (C=C str.), 1768 (-C=O, imidazolone moiety), 607(C=N str.), 1260 (C-O-C str., asym), 1035 (C-O-C str., sym.), 666cm^{-1} (C-S-C, thiophene ring); ^{1}H NMR ($CDCl_3$): δ 2.90 (t, 2H, - CH_2-CH_2), 3.20 (t, 2H, - CH_2-CH_2), 6.70-7.80 (m,13H, Ar-H+ Ar-CH= + CH of thiophene). Anal. Calcd for $C_{22}H_{18}N_2OS$:
C, 73.72; H, 5.06; N, 7.86%

1-(2'-Ethylthiophene)-2-phenyl-4-2(2'-chlorobenzylidine)-5-imidazolone 3b. m.p. 87ºC, yield 72%; IR (KBr); 3050 (=CH str.), 1638 (C=C str.), 749 (-CH bending, 1,2 disubstitution), 1761 (-C=O, imidazolone moiety), 1600 (C=N str.), 1260 (C-O-C str., asym), 1033 (C-O-C str., sym.), 615 (C-S-C, thiophene ring), 785 cm^{-1} (C-C1); ^{1}H NMR ($CDCl_3$): δ 2.80 (t, 2H, -CH_2-CH_2), 3.27 (t, 2H, - CH_2-CH_2), 6.72-7.80 (m, 12H, Ar-H+ Ar-CH= + CH of thiophene). Anal. Calcd for $C_{22}H_{17}N_2OSCl$: C, 67.26; H, 4.36; N, 7.13. Found: C, 67.20; H, 4.42; N, 7.19%.

1-(2'-Ethylthiophene)-2-phenyl-4-(3'-chlorobenzylidine)-5-imidazolone 3c. m.p. 122ºC, yield 74%; IR (KBr); 3060 (=CH str.), 1633 (C=C str.), 755 (-CH bending, 1,3 disubsitution), 1769 (-C=O, imidazolone moiety), 1610 (C=N str.), 1263 (C-O-C str., asym), 1031 (C-O-C str., sym.), 618 (C-S-C, thiophene ring), 780 cm^{-1} (C-Cl); ^{1}H NMR ($CDCl_3$): δ 2.82 (t, 2H, -CH_2-CH_2), 3.18 (t, 2H, - CH_2-CH_2), 6.70-7.83 (m, 12H, Ar-H+ Ar-CH= + CH of thiophene). Anal. Calcd for $C_{22}H_{17}N_2OSCl$; C, 67.26; H, 4.36; N, 7.13. Found: C, 67.19; H, 4.43; N, 7.16%.

1-(2'-Ethylthiophene)-2-phenyl-4-(4'-chloroben-zylidine)-5-imidazolone 3d. m.p. 95ºC, yield 76%; IR (KBr): 3066 (=CH str.), 1630 (C=C str.), 826 (-CH bending, 1,4 disubstitution), 1760 (-C=O, imidazolone moiety), 1609 (C=N str.), 1265 (C-O-C str., asym), 1038 (C-O-C str., sym.), 619 (C-S-C, thiophene ring), 784 cm^{-1} (C-Cl); ^{1}H NMR ($CDCl_3$): δ 2.90 (t, 2H, -CH_2-CH_2), 3.34 (t, 2H, -CH_2-CH_2), 6.72-7.84 (m, 12H, Ar-H+ Ar-CH= + CH of thiophene). Anal. Calcd for

$C_{22}H_{17}N_2OSCl$: C, 67.26; H, 4.36; N, 7.13. Found: C, 67.22; B, 4.40; N, 7.17%.

1-(2'-Ethylthiophene)-2-phenyl-4-(2'-methoxybenzylidine)-5-imidazolone 3e. m.p. 88ºC, yield 73%; IR (KBr): 3064 (=CH str.), 1633 (C=C str.), 745 (-CH bending, 1,2 disubstitution), 1761 (-C=O, imidazolone moiety), 1606 (C=N str.), 1257 (C-O-C str., asym), 1030 (C-O-C str., sym), 630 cm^{-1} (C-S-C, thiophene ring); ^1H NMR ($CDCl_3$): δ 2.88 (t, 2H, $-CH_2-CH_2$), 3.14 (t, 2H, $-CH_2-CH_2$), 3.70 (S, 3H, *o*-OCH_3), 6.78-7.88 (m, 12H, Ar-*H*+ Ar-CH= + CH of thiophene). Anal. Calcd for $C_{23}H_{20}N_2O_2S$: C, 71.11; H, 5.18; N, 7.21. Found: C, 71.18; H, 5.10; N, 7.26%.

1-(2'-Ethylthiophene)-2-phenyl-4-(4'-methoxy-benzylidine)-5-imidazolone 3f. m.p. 179ºC, yield 76%; IR (KBr): 3062 (=CH str.), 1634 (C=C str.), 827 (-CH bending, 1,4 disubstitution), 1760 (-C=O, imidazolone moiety), 1606 (C=N str.), 1257 (C-O-C str., asym), 1033 (C-O-C str., sym.), 650 cm^{-1} (C-S-C, thiophene ring); ^1H NMR ($CDCl_3$): δ 2.95 (t, 2H, $-CH_2-CH_2$), 3.2 (t, 2H, - CH_2-CH_2), 3.71 (s, 3H, *p*-OCH_3), 6.78-7.88 (m, 12H, Ar-H+ Ar-CH= + CH of thiophene). Anal. Calcd for $C_{23}H_{20}N_2O_2S$: C, 71.11; H, 5.18; N, 7.21. Found: C, 71.06; H, 5.17; N, 7.17%.

1-(2'-Ethylthiophene)-2-phenyl-4-(2'-nitrobenzylidine)-5-imidazolone 3g. m.p. 170ºC, yield 74%; IR (KBr): 3033 (=CH str.), 1636 (C=C str.), 760 (-CH bending, 1,2 disubstitution), 1778 (-C=O, imidazolone moiety), 1608 (C=N str.), 1255 (C-O-C str., asym), 1040 (C-O-C str., sym.) 638 (C-S-C, thiophene ring), 1460, 1310 cm^{-1} (N=O); ^1H NMR ($CDCl_3$): δ 2.99 (t, 2H, $-CH_2-CH_2$), 3.48 (t, 2H, $-CH_2-CH_2$), 6.72-7.84 (m, 12H, Ar-*H*+ Ar-*CH*= + CH of thiophene). Anal. Calcd for $C_{22}H_{17}N_3O_3S$: C, 65.50; H, 4.24; N, 10.42. Found: C, 65.48; H, 4.20; N, 10.39%.

1-(2'-Ethylthiophene)-2-phenyl-4-(4'-nitrobenzylidine)-5-imidazolone 3h. m.p. 174ºC, yield 71%; IR (KBr): 30396 (=CH str.), 1638 (C=C str.), 828 (-CH bending, 1,4 disubstitution), 1766 (-C=O, imidazolone moiety), 1610 (C=N str.), 1253 (C-O-C str., asym), 1015 (C-O-C str., sym.), 640 (C-S-C, thiophene ring), 1465, 1320 cm^{-1} (N=O); ^1H NMR ($CDCl_3$): δ 2.81 (t, 2H, $-CH_2-CH_2$), 3.16 (t, 2H, $-CH_2-CH_2$), 6.72-7.82 (m, 12H, Ar-*H*+ Ar-*CH*= + -CH of thiophene). Anal. Calc for $C_{22}H_{17}N_3O_3S$: C, 65.50; H, 4.24; N, 10.42. Found: C, 65.54; H, 4.18 N, 10.48%.

1-(2'-Ethylthiophene)-2-Phenyl-4-(3'-bromobenzylidine)-5-imidazolone 3i. m.p. 129ºC, yield 70%; IR (KBr): 3040(=CH str.), 1633 (C=C str.), 800 (-CH bending, 1,3 disubstitution), 1760 (-C=O, imidazolone moiety), 1606 (C=N str.), 1254 (C-O-C str., asym), 1023 (C-O-C str., sym.) m 645 (C-S-C, thiophene ring), 785 cm^{-1} (C-Br); ^1H NMR ($CDCl_3$); δ 2.95 (t, 2H, $-CH_2-CH_2$), 3.22 (t, 2H, $-CH_2-CH_2$), 6.80-7.86 (m, 12H, Ar-H+ Ar-CH= + CH of thiophene). Anal. Calcd for $C_{22}H_{17}N_2OSBr$: C, 60.42; H, 3.91; N, 6.41. Found: C, 60.46; H, 3.79; N, 6.49%.

1-(2'-Ethylthiophene)-2-phenyl-4-(4'-bromoben-zylidine)-5-imidazolone 3j. m.p. 133ºC, yield 73%; IR (KBr): 3048 (=CH str.), 1632 (C=C str.), 828 (-CH bending, 1,4 disubstitution), 1760 (-C=O, imidazolone moiety), 1610 (C=N str.), 1260 (C-O-C str., asym), 1026 (C-O-C str., sym.), 645 (C-S-C, thiophene ring), 781 cm^{-1} (C-Br); ^1H NMR ($CDCl_3$): δ 2.96 (t, 2H, $-CH_2-CH_2$), 3.40 (t, 2H $-CH_2-CH_2$), 6.84-7.88 (m, 12H, Ar-H+ Ar-CH= + -CH of thiophene). Anal. Calcd for $C_{22}H_{17}N_2OSBr$: C, 60.42; H, 3.91; N, 641. Found: C, 60.38; H, 3.87; N, 6.48%.

V. CONCLUSION

From the biological activity data reported in table I, it is apparent that all the target compounds are antibacterially active against two strains of bacteria viz. ***B subtilis*** **(MTCC 441) [Gram-postive bacterial] and *E. coli* (MTCC 443) [Gram-negative bacteria]** while seven such compounds have displayed quite promising antibacterial activity against one strain of bacteria i.e. ***S. aureus*** **(MTCC 96).** These results suggest that imidazolone compounds might confer better therapeutic results if other pharmacophoric groups are introduced in the imidazolone nucleus.

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