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Synthesis and Antimicrobial Activity of some Trisubstituted Thioxoimidazolidinones

KEYWORDS: Thiophene, Thioxoimidazolidinone, hydrazinecarbothioamide, Heterocycles, Antimicrobial

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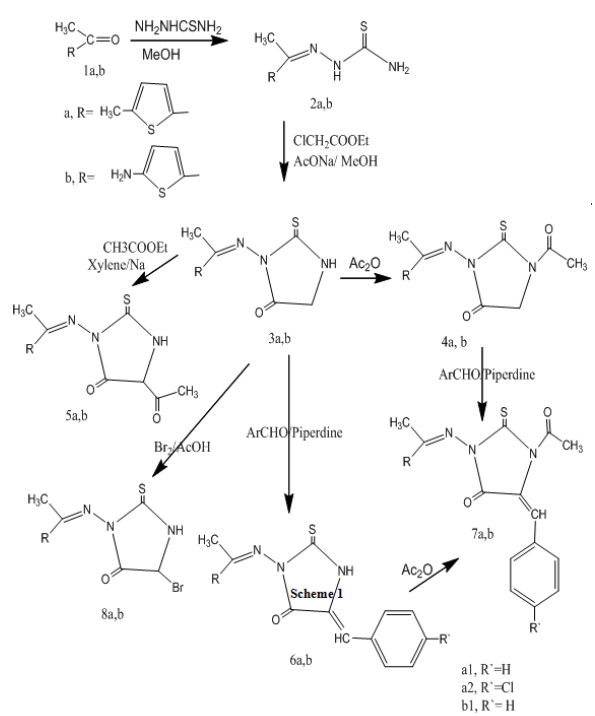
ABSTRACT *3-(Substituted) amino-2-thioxoimidazolidinones (3a, b) were prepared via condensation of 1-substitued thiosemicarbazones (2a, b) with ethyl chloroacetate in presence of fused sodium acetate. Reaction of (3a,b) with acetic anhydride, ethyl acetate in presence of sodium metal in Xylene and aromatic aldehydes in presence of piperidine yielded the corresponding 1-acetyl-3-(substituted)amino-2-thioxoimidazolidinones(4a,b),5-acetyl-3-(substituted)amino-2-thioxoimidazolidinones (5a,b) and 5-arylidene-3-(substituted) amino-2-thioxoimidazolidinones (6a,b). Reaction of (4a,b) with aromatic aldehydes in presence of piperidine and/or acetylation of (6a,b) by acetic anhydride yielded 1-acetyl-5-arylidene-3-(substituted) amino-2-thioxoimidazolidinones (7a,b). Bromination of (3a,b) with bromine gave the corresponding 5-bromo-3-(substituted)amino-2-thioxoimidazolidin-2-one (8a,b). Some of the synthesized compounds also exhibited antimicrobial activities.*

1-Introduction

Because of their interesting Antimicrobial activities, low molecular weights Heterocycles have attracted enormous attention in medicinal chemistry. The hydantion moiety represents an important pharmacophore, which is present in various biologically active compounds[1-3]. As such, there is an imminent need to develop new anticancer drugs. In the late 1990s, anew anticancer agent based on the pyridyl cyanoguandine system was discovered[4, 5]. Subsequently, we made a drastic change of the parent thiophene cyanoguandine core. We propose to install abridge connecting the two amino nitrogens and thus, forming a cyclic structure containing 3-[(thiophene-2-yl)ethylidene] amino-2-thioxoimidazolidin-2-one moiety. This paper now reports the synthesis of trisubstituted thioxoimidazolidinones from 2-acetyl-5-methylthiophene and 2-acetyl-5-aminothiophene as key starting materials. The chemical analysis of trisubstituted thioxoimidazolidinones was described and their biological activity was evaluated.

2- Results and Discussion.

The synthetic pathways leading to the new trisubstituted thioxoimidazolidinones are illustrated in Scheme 1. Treatment[6] of 2-acetyl-5-methylthiophene (1a) and 2-acetyl-5-aminothiophene (1b) with thiosemicarbazide in methanol under reflux yielded the corresponding 2-[1-(5-methylthiophen-2-yl) ethylidene] hydrazinecarbothioamide (2a) and 2-[1-(5-aminothiophen-2-yl)ethylidene]hydrazinecarbothioamide (2b), respectively. The reaction of (2a, b) with ethyl chloroacetate in presence of fused sodium acetate in methanol under reflux, gave the corresponding 3-[1-(5-methylthiophen-2-yl) ethylidene]amino-2-thioxoimidazolidin-4-one (3a) and 3-[1-(5-aminothiophen-2-yl)ethylidene]amino-2-thioxoimidazolidin-4-one (3b). Acetylation of compounds 3a and 3b with acetic anhydride under reflux led to the formation of 1-acetyl-3-(substituted)amino-2-thioxoimidazolidinones (4a, b). Acetylation[7] of compounds 3a and 3b with ethyl acetate in presence of sodium metal in xylene under reflux resulted in the formation of 5-acetyl-3-(substituted)amino-2-thioxoimidazolidinones (5a, b). Condensation [8] of compounds 3a and 3b with aromatic aldehydes (such as benzaldehyde and 4-chloro benzaldehyde) in presence of piperidine under fusion led to the formation of 5-arylidene-3-(substituted)amino-2-thioxoimidazolidinones (6a,b). Acetylation of compounds 6a and 6b with acetic anhydride under reflux yielded the corresponding 1-acetyl-5-arylidene-3-(substituted) amino-2-thioxoimidazolidinones (7a, b). The compound (7a, b) was obtained via another way by condensation of compound (4a, b) with aromatic aldehydes under reflux in acetic acid with fused sodium acetate. Bromination [9] of compound (3a, b) with one mole from the bromine in glacial acetic acid at room temperature gave the corresponding 5-bromo-3-(substituted) amino-2-thioxoimidazolidin-2-one (8).



Scheme-1

3-Antimicrobial Activity.

Applying the agar plate diffusion technique all of the newly synthesized compounds were screened in Vitro for antibacterial activity against Bacillus subtilis, Streptococcus Penumonia, Staphylococcus Aureas, E.Coli and Pseudomonas Solanarium. Also these compounds were tested in Vitro against some fungi such as Aspergillus Niger and Penicillium to know their antifungal activity. The compounds were tested at 100µg/ml concentration and the activity was determined by

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measuring the zone of inhibition. The screening results given in table 1 indicated that all the compounds exhibited antimicrobial activities against one or the other type of bacteria and fungi. The structure related 5-aminothiophene-thioxoimidazolidinones were found to have strong activity than the structure related 5-methylthiophene-thioxoimidazolidinones against bacteria and fungi.

Table 1.Antimicrobial activity of some synthesized compounds.

Comp.	Gram Positive Bacteria			Gram Negative Bacteria		Antifungal Activity	
	Bacillus Subtilis	Streptococcus Penumonia	Staphylococcus Aureas	E.Coli	Pseudomonas Sp.	Aspergillus Niger	Penicillium Sp.
2a	+	-	-	+	-	+	-
2b	+	-	+	+	+	+	-
3a	+	-	+	+	+	+	-
3b	++	+	++	+	+	+	-
4a	++	+	+	++	++	+	+
4b	+++	++	++	++	+++	+	+
5a	++	++	+	+	+++	+++	+++
5b	++	+++	+	++	+++	++	++
6a1	++	++	++	+	+	+++	++
6a2	+++	+++	+++	+	+++	+++	++
6b1	+++	++	+++	++	+	++	+++
6b2	+++	+++	+++	++	+++	+++	+++
7a1	++	++	+++	+	+	+++	+
7a2	+++	+	++	+++	+++	+	++
7b1	++	++	+++	++	+	++	+
7b2	+++	+++	++	+++	+++	+++	+++
8a	+++	+++	+++	+++	++	++	+++
8b	+++	+++	+++	+++	+++	+++	+++

Note: (**-**)No antimicrobial activity, (**+**) Mild activity, (**++**) Moderate activity, (**+++**) Marked activity.

4- Experimental.
NMR spectra were recorded on General Electric QE300 instrument. Chemical shifts were given with respect to TMS .IR spectra were recorded on a Perkin-Elmer 1420 Spectrometer and a Biorad FTS7 (KBr). Mass Spectra were obtained on Joel JMS D-300 spectrometer operating at 70ev. Microanalysis was conducted using an elemental analyzer, Heneaus CHN-OS Rapid. Melting points were determined on a MEL-TEM PII apparatus and uncorrected.

2-[1-(5-methylthiophen-2-yl)ethylidene]hydrazinecarbothioamide (2a)

2-[1-(5-aminothiophen-2-yl)ethylidene]hydrazinecarbothioamide (2b)

A mixture of 2-acetyl-5-methylthiophene and/or 2-acetyl-5-aminothiophene (0.01mol) and thiosemicarbazide (0.01mol) in methanol (50ml) was heated under reflux for 4hr and then cooled. The resulting solid was filtered off, washed with methanol, dried and recrystallized from methanol to give (2a,b.

Compound 2a as colourless, yield 85%, m.p. 225°C, IR (KBr): 3456, 3176(NH_2), 3290(NH), 1630(C=N), 1592(C=C), 1401(C=S), 885(C-S) cm^{-1}. ^{1}HNMR (DMSO-d_6): δ 1.23(S, 3H, CH_3-Ring), δ 1.93(S, 3H, CH_3-CH=N), δ 7.12 (d, 1H, thiophene-H), δ 7.82 (d, 1H, thiophene-H), δ 8.82(S, 1H, NH), δ 10.25(S, 2H, NH_2) ppm. MS(m/z,%): 213(M^+,17.10), 198(17.40), 197(21.40), 181(25.50), 153(31.80), 138(21.60), 124(5.40), 116(65.90), 97(100), 89(3.20), 75(5.30), 60(5.80). Anal. Calcd. For $C_8H_{11}N_3S_2$: C, 45.07; H, 5.16; N, 19.71; S, 30.04. Found: C, 44.86; H, 5.11; N, 19.24; S, 29.98.

Compound 2b as colourless, yield 65 %, m.p.: 190 °C, IR (KBr): 3411, 3182(NH_2), 3225(NH), 1629(C=N), 1585(C=C), 1413(C=S), 900(C-S) cm^{-1}. ^{1}HNMR (DMSO-d_6): δ 2.11(S, 3H, CH_3-CH=N), δ 6.89 (d, 1H, thiophene-H), δ 7.32 (d, 1H, thiophene-H), δ 7.92(S, 1H, NH), δ 8.25(S, 2H, NH_2-Ring), δ 10.51(S, 2H, NH_2-CS) ppm. MS(m/z,%): 214(M^+,24.33), 199(15.10), 198(11.86), 182(33.51), 154(42.60), 139(100), 125(12.71), 116(25.20), 98(89), 89(7.21), 75(61.03), 60(14.82). Anal. Calcd. For $C_7H_{10}N_4S_2$: C, 39.25; H, 4.67; N, 26.16; S, 29.90. Found: C, 38.88; H, 4.52; N, 25.91; S, 29.63.

3-(Substituted)amino-2-thioxoimidazolidin-4-one (3a, b)
A mixture of 2a, b (0.01mol), ethyl chloroacetate (0.01mol) and fused sodium acetate (0.03mol) in methanol (60ml) was heated under reflux for 6 hr. The reaction mixture was cooled and poured into water. The resulting solid was filtered off, washed with hot water, dried and recrystallized from methanol to give (3a,b).

Compound 3a as yellow crystals, yield 87%; m.p:250 °C; IR (KBr):3185 (NH), 1705 (C=O), 1625 (C=N), 1603 (C=C), 1411(C=S), 850(C-S) cm^{-1}. ^{1}H-NMR (DMSO-d_6): δ 1.53(S, 3H, CH_3-Ring), δ 1.99(S, 3H, CH_3-CH=N), δ 4.22 (S, 2H, CH_2), δ 6.99 (d, 1H, thiophene-H), δ 7.43 (d, 1H, thiophene-H), δ 9.23(S, 1H, NH) ppm. MS(m/z,%): 253(M^+,25.10), 238(33.52), 237(11.48), 221(28.11), 156(24.12), 138(68.71), 129(9.52), 124(63.12), 115(84.51), 97(100), 60(2.12). Anal. Calcd. For $C_{10}H_{11}N_3OS_2$: C, 47.43; H, 4.34; N, 16.60; S, 25.29. Found: C, 47.11; H, 4.18; N, 16.25; S, 24.97.

Compound 3b as colourless crystals, yield 75%, m.p.:281°C. IR (KBr): 3455, 3275(NH_2), 3188(NH), 1716(C=O), 1633(C=N), 1601, 1587(C=C), 1412(C=S), 925(C-S) cm^{-1}. ^{1}HNMR (DMSO-d_6): δ 2.19(S, 3H, CH_3-CH=N), δ 4.45 (S, 2H, CH_2), δ 7.15 (d, 1H, thiophene-H), δ 7.73 (d, 1H, thiophene-H), δ 8.23(S, 1H, NH), δ 9.42(S, 2H, NH_2), ppm. MS(m/z,%): 254(M^+,53.12), 239(39.81), 238(10.47), 222(89.12), 156(47.36), 139(100), 129(17.23), 125(22.23), 115(73.51), 98(88.27), 60(8.12). Anal. Calcd. For $C_7H_{10}N_4OS_2$: C, 42.52; H, 3.93; N, 22.04; S, 25.19. Found: C, 42.09; H, 3.59; N, 21.85; S, 24.78.

1-acetyl-3-(substituted)amino-2-thioxoimidazolidin-4-one (4a, b)
A solution of 3a, b (0.01mol) in acetic anhydride (30ml) was heated under reflux for 2hr, then cooled and poured into

Volume : 4 | Issue : 1 | Jan 2014 | ISSN - 2249-555X

6.58(s, 1H, CH=C),δ 6.84 (d, 1H, thiophene-H), δ 7.35 (d, 1H, thiophene-H), 7.01-7.72(m 5H, Ar-H), δ 9.44(S, 1H, NH) ppm. MS (m/z, %): 341(M^+, 5.80), 322(21.80), 321(23.80), 320(11.30), 308(2.20), 307(6.40), 306(7.80), 279(2.00), 278(2.10), 245(2.10), 244(6.70), 243(7.30), 218(1.70), 217(1.80),216(1.50), 190(2.00), 189(2.40), 188(1.40), 175(1.30), 174(1.40), 162(2.60), 161(8.70), 160(9.10), 159(4.80), 135(19.40), 134(100), 133(96.80), 132(8.10), 119(5.10), 118(5.40), 108), 7.70), 107(7.70), 105(12.00), 104(18.40), 103(15.10), 102(14.10), 101(20.10), 91(10.50), 90(19.10), 89(28.70), 88(22.30), 79(9.50), 78(34.10),77(36.90), 76(21.30), 75(14.60), 69(8.40), 68(10.20), 65(7.40), 63(19.20), 62(15.30), 52(24.00), 51(69.80),50(67.30). Anal. Calcd. For $C_{17}H_{15}N_3OS_2$: C, 59.82; H, 4.40; N, 12.32; S, 18.77. Found: C, 59.75; H, 4.21; N, 12.11; S, 18.27.

***5-(4-chlorobenzylidene)-3-[1-(5-methylthiophen-2-yl)ethylidene]amino-2-thioxoimidazolidin-4-one* ($6a_2$)** as yellow crystals, yield 83 %, m.p: 271°C.IR (KBr): 3330(NH), 1702(C=O), 1629(C=N), 1603, 1590(C=C), 1408(C=S) cm^{-1}. ^{1}H-NMR (DMSO-d_6): δ 1.22(S, 3H, CH_3-Ring), δ 1.85(S, 3H, CH_3-CH=N), 6.67(s, 1H, CH=C),δ 6.9 (d, 1H, thiophene-H), δ 7.48 (d, 1H, thiophene-H), 7.04(d, 2H, Ar-H), 7.88(d, 2H, Ar-H), δ 9.57(S, 1H, NH) ppm. MS(m/z, %): 377(M^{+1},6.50), 375(M^+,28.70), 340(1.30), 323(7.40), 322(9.40), 321(18.40), 320(9.20), 255(6.40), 254(8.00), 253(14.50),252(18.40), 251(6.50), 215(5.80), 214(8.70),213(15.70), 212(18.70), 196(2.00), 115(2.30), 179(2.60), 178(1.60), 167(1.70), 165(2.10), 154(9.10), 153(12.50), 152(12.80), 140(16.80), 139(19.40), 138(33.20), 137(37.70),126(10.90), 125(12.90), 124(29.20), 123(27.40), 119(6.30), 118(9.80), 117(7.00), 116(5.40), 112(11.30), 111(22.20), 110(25.40), 102(15.10), 101(19.80), 90(15.80), 89(88.30), 88(94.70), 86(13.60),84(10.60), 77(11.90), 76(49.90), 75(72.40), 74(62.80), 73(33.50), 72(18.70), 64(8.10), 63(46.00), 62(61.40), 61(28.80), 60(100), 59(97.90), 58(28.70), 51(32.70), 50(55.90). Anal Calcd. For $C_{17}H_{14}N_3ClOS_2$: C, 54.4; H, 3.73; N, 11.2; Cl, 9.33; S, 17.07. Found: C, 54.12; H, 3.23; N, 11.10; Cl, 9.21; S, 17.05.

***3-[1-(5-aminothiophen-2-yl)ethylidene]amino-5-benzylidene-2-thioxoimidazolidin-4-one* ($6b_1$)** as yellow crystals, yield 82%, m.p: 240°C.IR (KBr): 3400(NH_2),3225(NH), 1713(C=O), 1654(C=N), 1600,1592(C=C), 1414(C=S) cm^{-1}. ^{1}H-NMR (DMSO-d_6): δ 2.1(S, 3H, CH_3-CH=N), 6.51(s, 1H, CH=C),δ 6.67 (d, 1H, thiophene-H), δ 7.25 (d, 1H, thiophene-H), 7.32-7.98(m 5H, Ar-H), δ 9.32(S, 1H, NH), δ 10.2(S, 2H, NH_2) ppm. MS (m/z, %), 342(M^+,61.90), 326(3.50), 311(18.40), 286(3.50), 285(4.10), 230(11.20), 229(12.90), 219(2.70), 218(2.80), 184(3.60), 183(27.30), 182(21.50), 173(2.60), 172(2.20), 162(2.10), 161(3.20), 160(4.00), 158(4.70), 157(12.70), 156(12.00), 155(6.90), 154(8.40), 135(7.30), 134(35.00), 133(38.90), 132(3.40), 127(8.30), 126(9.20), 117(9.00), 116(14.90), 115(15.30), 106(14.30), 105(15.90), 104(29.80), 103(27.30), 102(18.40), 101(12.70), 100(10.50), 91(13.00), 90(70.00), 89(76.30), 88(55.40), 86(15.40), 78(11.60), 77(100), 76(100), 74(17.60), 72(18.50), 71(18.30), 69(13.50), 68(12.80), 64(14.50), 63(27.30), 62(28.80), 61(10.40), 59(17.50), 58(22.80), 51(92.90), 50(88.60). Anal. Calcd. For $C_{16}H_{14}N_4OS_2$: C, 56.14; H, 4.09; N, 16.37; S, 18.71. Found: C, 55.98; H, 4.01; N, 16.12; S, 18.54.

***3-[1-(5-aminothiophen-2-yl)ethylidene]amino-5-(4-chlorobenzylidene)-2-thioxoimidazolidin-4-one* ($6b_2$)** as yellow crystals, yield 55%, m.p: 232°C.IR (KBr): 3540(NH_2),3300(NH), 1725(C=O), 1620(C=N), 1619,1575(C=C), 1405(C=S) cm^{-1}. ^{1}H-NMR (DMSO-d_6): δ 1.98(S, 3H, CH_3-CH=N), 6.48(s, 1H, CH=C),δ 6.58 (d, 1H, thiophene-H), δ 7.64 (d, 1H, thiophene-H), 7.21(d, 2H, Ar-H), 7.78(d, 2H, Ar-H), δ 9.75(S, 1H, NH), δ 10.14(S, 2H, NH_2) ppm. Anal. Calcd. For $C_{16}H_{13}N_4ClOS_2$: C,51.06; H,3.46; N,14.89 ;Cl,9.30; S,17.02 . Found: C,50.88 ; H,3.33 ; N,14.59 ; Cl,9.21; S,16.98.

1-acetyl-5-arylidene-3-(substituted) amino-2-thioxoimidazolidin-4-one ($7a_{1,2}$, $b_{1,2}$).

ice-water. The resulting product was filtered off, washed with water, dried and recrystallized from benzene to give (4a, b).

Compound 4a as colourless crystals, yield 83 %, and m.p.:135°C. IR (KBr): 1710-1798(br. C=O), 1675(C=N), 1603, 1589(C=C), 1398(C=S), 933(C-S) cm^{-1}. ^{1}HNMR (DMSO-d_6): δ2.11(s, 3H, $COCH_3$), 2.42(s, 3H, CH_3), 2.83(s,3H, CH_3-C=N), 4.57(s, 2H, NCH_2CO), δ 7.01 (d, 1H, thiophene-H), δ 7.58 (d, 1H, thiophene-H) ppm. MS (m/z, %): 295(M^+,10.00), 280(6.50), 279(35.80), 263(40.70), 252(4.20), 198(5.10), 171(25.40), 157(29.40), 138(2.00), 124(2.10), 97(100), 43(4.50). Anal. Calcd. For $C_{12}H_{13}N_3O_2S_2$: C, 48.81; H, 4.40; N, 14.23; S, 21.69. Found: C, 48.52; H, 4.18; N 13.89; S, 21.29.

Compound 4b as colourless crystals, yield 73 %, m.p: 265°C. IR (KBr): 3420, 3153(NH_2), 1722-1689(broad C=O), 1654(C=N), 1612, 1556(C=C), 1422(C=S), 928(C-S) cm^{-1}. ^{1}HNMR (DMSO-d_6): δ1.91(s, 3H, $COCH_3$), 2.54(s,3H, CH_3-C=N), 4.32(s, 2H, NCH_2CO), δ 7.23 (d, 1H, thiophene-H), δ 7.71 (d, 1H, thiophene-H), δ9.24(s, 2H, NH_2) ppm. MS (m/z,%): 296(M^+,28.40), 281(47.20), 280(19.30), 264(44.60), 253(39.00), 198(11.30), 171(48.80), 157(89.00), 139(31.60), 125(50.90), 98(100), 43(18.70). Anal.Calcd. for $C_{11}H_{12}N_4O_2S_2$: C, 44.59; H, 4.05; N, 18.91; S, 21.62. Found: C, 44.12; H, 3.73; N, 18.55; S, 21.28.

5-acetyl-3-(substituted)amino-2-thioxoimidazolidin-4-one (5a, b).

A mixture of 3a, b (0.01 mol), ethyl acetate (0.03 mol) and sodium metal (0.03 mol) in Xylene (40ml) was heated under reflux for 4 hr., then cooled and poured into ice-dilute HCl. The organic layer was extracted with toluene and evaporated. The solid obtained was recrystallized from methanol to give (5a,b).

Compound 5a as pale yellow crystals, yield 73 %, m.p: 145 °C. IR (KBr): 3256(NH), 1701-1685(br. C=O), 1630(C=N), 1601, 1580(C=C), 1421(C=S), 850-1000(C-S) cm^{-1}. ^{1}H-NMR (DMSO-d_6): δ 1.21(s, 3H, CH_3C=N),1.98(s, 3H, CH_3CO),2.25(s, 3H, CH_3), 4.61(s, 1H, NHCH $(CO)_2$), δ 7.12 (d, 1H, thiophene-H), δ 7.67 (d, 1H, thiophene-H), δ 10.11(S, 1H, NH) ppm. MS(m/z,%): 295(M^+,30.85), 280(19.54), 279(41.58), 263(32.41), 252(80.21), 198(43.12), 171(11.24), 157(64.55), 138(100), 124(24.51), 97(92.53), 43(10.21). Anal. Calcd. For $C_{12}H_{13}N_3O_2S_2$: C, 48.81; H, 4.40; N, 14.23; S, 21.69. Found: C, 48.53; H, 4.02; N, 13.94; S, 21.38.

Compound 5b as pale yellow crystals, yield 65 %, m.p: 232 °C. IR (KBr): 3180(NH), 3443, 3260(NH_2), 1705-1695(br. C=O), 1625(C=N), 1605, 1592(C=C), 1413(C=S), 985(C-S) cm^{-1}. ^{1}HNMR (DMSO-d_6): δ 1.64(s, 3H, CH_3C=N),δ1.89 (s, 3H, CH_3CO), 4.45(s, 1H, NHCH $(CO)_2$), δ 7.32 (d, 1H, thiophene-H), δ 7.94 (d, 1H, thiophene-H), δ 9.35(S, 1H, NH), δ10.22(s, 2H, NH_2) ppm. MS(m/z,%): 296(M^+,49.12), 281(22.34), 280(9.15), 264(25.12), 253(98.21), 198(83.14), 171(18.65), 157(25.84), 139(100), 125(58.21), 98(19.47), 43(11.24). Anal. Calcd. For $C_{11}H_{12}N_4O_2S_2$: C, 44.59; H, 4.05; N, 18.91; S, 21.62. Found: C, 44.12; H, 3.87; N, 18.55; S, 21.38.

5-arylidene-3-(substituted) amino-2-thioxoimidazolidin-4-one ($6a_{1,2}$, $b_{1,2}$).

A mixture of 3a, b (0.01 mol) and aromatic aldehydes(such as benzaldehyde and 4-chlorobenzaldehyde)(0.01 mol) in presence of piperidine (1 ml) was fused on a hot plate at 120-125 °C for 1hr. the reaction mixture was cooled and acidified with dilute hydrochloric acid (2 %). The crude product was filtered off, washed with water, dried and purified by recrystallization from methanol to give 6.

***5-benzylidene-3-[1-(5-methylthiophen-2-yl)ethylidene]amino-2-thioxoimidazolidin-4-one* ($6a_1$)** as yellow crystals, yield 71%, m.p: 285 °C.IR (KBr): 3339(NH), 1704(C=O), 1620(C=N), 1605, 1580(C=C), 1432(C=S) cm^{-1}. ^{1}H-NMR (DMSO-d_6): δ 1.42(S, 3H, CH_3-Ring), δ 1.97(S, 3H, CH_3-CH=N),

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A solution of 6 (0.01 mol) in acetic anhydride (20ml) was heated under reflux for 2 hr, then cooled and poured into ice-water. The solid obtained was filtered off, washed with water, dried and recrystallization from benzene to give 7

1-acetyl-5-benzylidene-3-[1-(5-methylthiophen-2-yl)ethylidene]amino-2-thioxoimidazolidin-4-one (7a$_1$) as yellow crystals, yield 85%, m.p: 231 °C.IR (KBr): 1720(C=O), 1628(C=N), 1614, 1588(C=C), 1452(C=S) cm^{-1}. ^{1}H-NMR (DMSO-d$_6$): δ 1.36(S, 3H, CH_3-Ring), 1.68(s,3H,CH_3-CO) δ 2.12(S, 3H, CH_3-CH=N), 6.71(s, 1H, CH=C),δ 6.85 (d, 1H, thiophene-H), δ 7.55 (d, 1H, thiophene-H), 7.05-7.89(m 5H, Ar-H) ppm. Anal. Calcd. For $C_{19}H_{17}N_3O_2S_2$: C, 59.53; H, 4.44; N, 10.97; S, 16.71. Found: C, 59.48; H, 4.12; N, 10.85; S, 16.58.

1-acetyl-5-(4-chlorobenzylidene)-3-[1-(5-methylthiophen-2-yl)ethylidene]amino-2-thioxoimidazolidin-4-one (7a$_2$) as yellow crystals yield 81 %, m.p: 283 °C.IR (KBr): 1718(C=O), 1642(C=N), 1610, 1578(C=C), 1398(C=S) cm^{-1}. ^{1}H-NMR (DMSO-d$_6$): δ 1.18(S, 3H, CH_3-Ring),1.62(s,3H,CH_3-CO), δ 2.11(S, 3H, CH_3-CH=N), 6.58(s, 1H, CH=C),δ 6.88 (d, 1H, thiophene-H), δ 7.42 (d, 1H, thiophene-H), 7.21(d, 2H, Ar-H), 7.95(d, 2H, Ar-H)ppm. Anal. Calcd. For $C_{19}H_{16}N_3ClO_2S_2$: C, 54.67; H, 3.83; N, 10.07; Cl, 8.39; S, 15.34. Found: C, 54.52; H, 3.58; N, 10.01; Cl, 8.12; S, 15.11.

1-acetyl-3-[1-(5-aminothiophen-2-yl)ethylidene]amino-5-benzylidene-2-thioxoimidazolidin-4-one (7b$_1$) as yellow crystals, yield 85%, m.p: 265°C.IR (KBr): 3375(NH_2), 1728(C=O), 1661(C=N), 1599,1500(C=C), 1401(C=S) cm^{-1}. ^{1}H-NMR (DMSO-d$_6$): δ 1.94(S, 3H, CH_3-CH=N), δ 2.24(S, 3H, CH_3-CO), 6.42(s, 1H, CH=C),δ 6.51 (d, 1H, thiophene-H), δ 7.85 (d, 1H, thiophene-H), 7.24-7.77(m 5H, Ar-H), δ 9.87(S, 2H, NH_2) ppm. Anal. Calcd. For $C_{18}H_{16}N_4O_2S_2$: C, 56.25; H, 4.16; N, 14.58; S, 16.66. Found: C, 56.11; H, 4.08; N, 14.33; S, 16.42.

1-acetyl-3-[1-(5-aminothiophen-2-yl)ethylidene]amino-5-(4-chlorobenzylidene)-2-thioxoimidazolidin-4-one (7b$_2$) as yellow crystals, yield 55%, m.p: 294°C.IR (KBr): 3521(NH_2), 1718(C=O), 1617(C=N), 1610,1558(C=C), 1400(C=S) cm^{-1}. ^{1}H-NMR (DMSO-d$_6$): δ 1.87(S, 3H, CH_3-CH=N), 2.12(s,3H,CH_3-CO), 6.57(s, 1H, CH=C),δ 6.69 (d, 1H, thiophene-H), δ 7.71 (d, 1H, thiophene-H), 7.28(d, 2H, Ar-H), 7.95(d, 2H, Ar-H), δ 9.84(S, 2H, NH_2) ppm. Anal. Calcd. For $C_{18}H_{15}N_4ClO_2S_2$: C,51.67; H,3.58 ; N,13.39 ;Cl,8.37; S,15.31 . Found: C,51.55 ; H,3.27 ; N,13.11 ; Cl,8.24; S,15.27.

5-bromo-3-(substituted)amino-2-thioxoimidazolidin-4-one (8a,b).

A solution of 3a,b (0.01 mol) in glacial acetic acid (30ml) was added to a solution of bromine (0.01 mol) in glacial acetic acid (10 ml) with stirring at room temperature for 2hr. the solid formed was filtered off, washed with water, dried and recrystallized from toluene to give 8.

Compound 8a as pale orange crystals, yield 78%, m.p: 233 °C.IR (KBr): 3328 (NH), 1714 (C=O), 1621 (C=N), 1589 (C=C), 1401(C=S), 857(C-S) cm^{-1}. ^{1}H-NMR (DMSO-d$_6$): δ 1.68(S, 3H, CH_3-Ring), δ 2.12(S, 3H, CH_3-CH=N), δ 3.95 (S, 1H, CH-Br), δ 6.75 (d, 1H, thiophene-H), δ 7.25 (d, 1H, thiophene-H), δ 9.58(S, 1H, NH) ppm. Anal. Calcd. For $C_{10}H_{10}N_3BrOS_2$: C,36.25; H,3.02 ; N,12.68 ; Br,23.87 ; S,19.33 . Found: C,36.15 ; H,2.87 ; N,12.58 ; Br,23.74 ; S,19.21

Compound 8b as yellow crystals, yield 65%, m.p.:210°C. IR (KBr): 3405, 3217(NH_2), 3228(NH), 1719(C=O), 1657(C=N), 1587, 1489(C=C), 1399(C=S), 901(C-S) cm^{-1}. ^{1}HNMR (DMSO-d$_6$): δ 1.99(S, 3H, CH_3-CH=N), δ 4.22 (S, 1H, CH-Br), δ 7.24 (d, 1H, thiophene-H), δ 7.82 (d, 1H, thiophene-H), δ 9.57(S, 1H, NH), δ 10.22(S, 2H, NH_2), ppm. MS(m/z,%): 332(M^+,28.11), 253(48.18), 239(40.25), 238(18.57), 222(77.12), 156(33.58), 139(100), 129(23.23), 125(19.25), 115(68.25), 98(89.54), 60(9.25). Anal. Calcd. For $C_9H_9N_4BrOS_2$: C,32.53 ; H,2.71 ; N,16.86 ;Br,23.79; S,19.27 . Found: C, 32.41; H,2.55 ; N,16.57 ;Br,23.61; S,19.11

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