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# Synthesis and biological activities of 3-substituted-2-thioxoimidazolidin-4-one and 2-thioxotetrahydropyrimidin-4(1H)-one derivatives

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**ABSTRACT**

Cyclization of 2-(furan-2-ylmethylene)hydrazinecarbothioamide (**1**) with ethyl 2-chloroacetate and ethyl 3-chloropropanoate in fused sodium acetate yielded 3-(furan-2-yl-methyleneamino)-2-thioxoimidazolidin-4-one (**2**) and 3-(furan-2-ylmethyleneamino)-2-thioxotetrahydropyrimidin-4(1H)-one **(6)**. Treatment of **2**, **6** with acetic anhydride, benzyl chloride and aromatic aldehydes furnished 1-substituted-3-(furan-2-yl-methyleneamino)-2-thioxoimidazolidin-4-one (**3**, **4),** 1-substituted- 3-(furan-2-ylmethyleneamino)-2-thioxotetrahydropyrimidin-4(1H)-one **(7, 8),** 5-arylidene-3-(furan-2-yl-methyleneamino)-2-thioxoimidazolidin-4-one**(5a-c**) and 5-arylidene-3-(furan-2-ylmethyleneamino)-2-thioxotetrahydropyrimidin-4(1H)-one **(9a-c)** respectively. The antimicrobial and CNS depressant activities of some of the synthesized compounds were studied.

**Keywords:** Furan-2-carbaldehyde, hydrazinecarbothioamide, ethyl 2-chloroacetate, ethyl 3-chloropropanoate sodium acetate, Antimicrobial and CNS depressant activities.

## INTRODUCTION

Thiohydantoins, a class of cyclic imides, have diverse biological effects as anticonvulsant[1,2], fungicidal[3], herbicidal[4], antitumer[5], anti-inflammatory[5], anti-HIV[6], antibacterial[7] and antihypertensive activities[8]. So, it was decided to synthesize 1-substituted-3-(furan-2-yl-methyleneamino)-2-thioxoimidazolidin-4-one, 1-substituted- 3-(furan-2-ylmethyleneamino)-2-thioxotetrahydropyrimidin-4(1H)-one, 5-arylidene-3-(furan-2-yl-methyleneamino)-2-thioxoimidazolidin-4-one and 5-arylidene-3-(furan-2-ylmethyleneamino)-2-thioxotetrahydropyrimidin-4(1H)-one then tested them for antimicrobial and CNS depressant activities.

## EXPERIMENTAL

Melting points were uncorrected and measured in open capillary tubes using Griffin apparatus. Microanalyses were carried out at the Microanalytical Center; Cairo University. Infra-red spectra were recorded using KBr discs on a Shimadzu 435 Spectrophotometer. Proton magnetic resonance measurements were performed using TMS as internal standard on: Varian EM-390 NMR 90 MHz Spectrometer. Mass Spectra were recorded on: Hewlett-Packard 5988 Spectrometer at Microanalytical Center, Cairo University.

### 2-(Furan-2-ylmethylene)hydrazine carbothioamide (1)

A mixture of furan-2-carbaldehyde (0.01 mol), hydrazinecarbothioamide (0.01 mol) and ethanol (30 ml) was refluxed for 4 hrs, and then cooled. The solid formed was filtered, dried and recrystallized from ethanol. M.p.145 °C, (Yield 86%), IR ($cm^{-1}$): 3407(NH), 3220-3136($NH_2$), 3016(CH Aromatic), 2977(CH Aliphatic), 1608(C=N), 1341(C=S). Mass spectrum: M/z: 169($M^+$, 31.80%), 152(9.27%), 109(6.48%), 94(5.43%), 81(12.18%), 60(100%, base peak).

**3-(Furan-2-yl-methyleneamino)-2-thioxoimidazolidin-4-one (2) and 3-(furan-2-ylmethyleneamino)-2-thioxotetrahydropyrimidin-4(1H)-one (6)[9]**

A mixture of 1 (0.01 mol), ethyl 2-chloroacetate (0.01 mol) or ethyl 3-chloropropanoate and fused sodium acetate (0.03 mol) was refluxed in ethanol (50 ml) for 4 hrs, then cooled and poured into water. The resulting solid was filtered, washed with water, dried and recrystallized from ethanol. Found that compound (2) M.p. 224°C, (Yield 70%), IR ($cm^{-1}$): 3405(NH), 3114.5-3026(CH Aromatic), 2948(CH Aliphatic), 1707(C=O), 1647(C=N), 1358(C=S). Mass spectrum: M/z: 209($M^+$, 78.10%), 192(4.52%), 136(3.37%), 112(7.8%), 95(34.22%), 80(45.39%), 52(100%, base peak). And also compound (6) M.p. 135°C, (Yield 75%), IR (cm-1): 3405(NH), 3150(CH Aromatic), 2980(CH Aliphatic), 1707(C=O amide), 1616(C=N), 1355(C=S). Mass spectrum: M/z: 223($M^+$, 55.10%), 176(50%), 152(20%), 95(60%), 52(100%, base peak). $^1$H-NMR (DMSO, 200 MHz): 1.49(s,1H,NH), 3.19(t,2H,$CH_2$), 3.89(t,2H,$CH_2$), 6.61-7.26(m,3H, furan-H), 8.61(s, 1H, CH=N).

**1-Acetyl-3-(furan-2-yl-methyleneamino)-2-thioxoimidazolidin-4-one (3) and 1-acetyl- 3-(furan-2-ylmethyleneamino)-2-thioxotetrahydropyrimidin-4(1H)-one (7)[10]**

A solution of 2, 6 (0.01 mol) in acetic anhydride (25 ml) was heated under reflux for 4 hrs, cooled then poured into ice-water. The resulting product was filtered off, washed with water, dried and recrystallized from ethanol. Compound (3) M.p.160 °C, (Yield 75%), IR ($cm^{-1}$): 3137(CH Aromatic), 2977(CH Aliphatic), 1720(C=O),

**Table 1: Shows that compounds 3,4 and 5a have significant anticonvulsant activity than control and less significant than phenobarbital while their activity is significant higher than diazepam.on the other hand compound 6 has insignificant anticonvulsant activity**

| Groups | Death time | Significant than strychnine and vehicle | Significant than phenobarbital | Significant than diazepam |
|---|---|---|---|---|
| Vehicle | 4.08 ± 0.1062 | - | - | - |
| Phenobarbital | 9.49 ± 0.1636 | ↑ ($p < 0.05$) | - | - |
| Diazepam | 7.37 ± 0.1578 | ↑ ($p < 0.05$) | - | - |
| 3 | 8.29 ± 0.1312 | ↑ ($p < 0.05$) | ↓($p < 0.05$) | ↑ ($p < 0.05$) |
| 4 | 8.45 ± 0.1478 | ↑ ($p < 0.05$) | ↓($p < 0.05$) | ↑ ($p < 0.05$) |
| 5a | 8.36 ± 0.1056 | ↑ ($p < 0.05$) | ↓($p < 0.05$) | ↑ ($p < 0.05$) |
| 6 | 4.00 ± 0.06992 | Non significant | - | - |

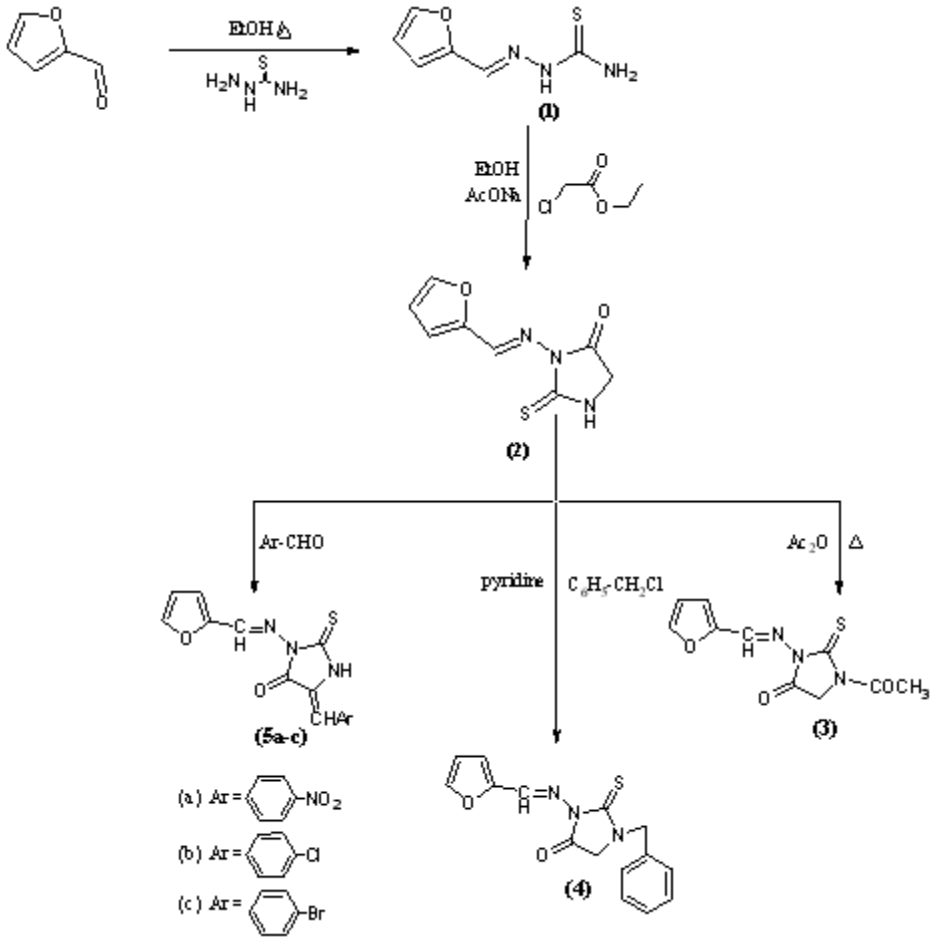
**Table 2: As shown in all tested compounds have motor incoordination behaviour**

| Groups | Time intervals per minutes | | | |
|---|---|---|---|---|
| | 30 | 60 | 90 | 120 |
| chloropromazine | 100% | 100% | 100% | 100% |
| 3 | 100% | 100% | 100% | 100% |
| 4 | 100% | 100% | 100% | 100% |
| 5a | 100% | 100% | 100% | 100% |
| 6 | 100% | 100% | 100% | 100% |

1711(C=O amide), 1609(C=N), 1341(C=S). Mass spectrum: M/z: 251($M^+$, 16.06%), 209(44.74%), 138(100%, base peak), 106(33.06%), 83(41.02%), 51(64.31%). $^1$H-NMR (DMSO, 200 MHz): 2.11(s,3H,$COCH_3$), 4.46(s,2H,$CH_2$), 6.47-6.86(m,3H, furan-H), 7.69(s, 1H, CH=N). Anal.Calcd. for $C_{10}H_9N_3O_3S$: C, 47.80; H, 3.61; N, 16.72. Found: C, 47.33; H, 3.50; N, 16.61. And compound (7) M.p.195-197 °C, (Yield 70%), IR ($cm^{-1}$): 3156(CH Aromatic), 2955(CH Aliphatic), 1725(C=O), 1715(C=O amide), 1620(C=N), 1333(C=S). Mass spectrum: M/z: 265 ($M^+$, 76.06%), 223(55.74%), 108(100%, base peak), 96(23.06%), 60(74.02%). $^1$H-NMR (DMSO, 200 MHz): 2.13(s,3H,$COCH_3$), 3.13(t,2H,$CH_2$), 4.22(t,2H,$CH_2$), 7.25-8.21(m,3H, furan-H), 8.42(s, 1H, CH=N). Anal.Calcd. for $C_{11}H_{11}N_3O_3S$: C, 49.80; H, 4.18; N, 15.84. Found: C, 49.60; H, 4.00; N, 15.70.

**1-Benzyl-3-(furan-2-yl-methyleneamino)-2-thioxoimidazolidin-4-one (4) and 1-benzyl- 3-(furan-2-ylmethyleneamino)-2-thioxotetrahydropyrimidin-4(1H)-one (8).**

A mixture of compounds 2 or 6 (0.01 mol), benzyl alcohol (0.01 mol) and pyridine (1 ml) was heated under reflux for 2 hrs, cooled then acidified with dilute hydrochloric acid. The resulting solid was filtered, washed with water, dried and recrystallized from ethanol. Compound (4) M.p. 215 °C, (Yield 65%), IR ($cm^{-1}$): 3026(CH Aromatic), 2919(CH Aliphatic), 1711(C=O), 1646(C=N), 1359(C=S). Mass spectrum: M/z: 299 ($M^+$, 4.68%), 209(63.16%), 192(7.60%), 173(6.14%), 94(33.04%), 52(100%, base peak). $^1$H-NMR (DMSO, 200 MHz): 3.94(s, 2H, $CH_2$), 5.15(s, 2H, $CH_2$ benzyl), 6.67-8.24(m, 8H, Ar-H, furan-H), 8.66(s, 1H, CH=N). Anal.Calcd. for $C_{15}H_{13}N_3O_2S$:

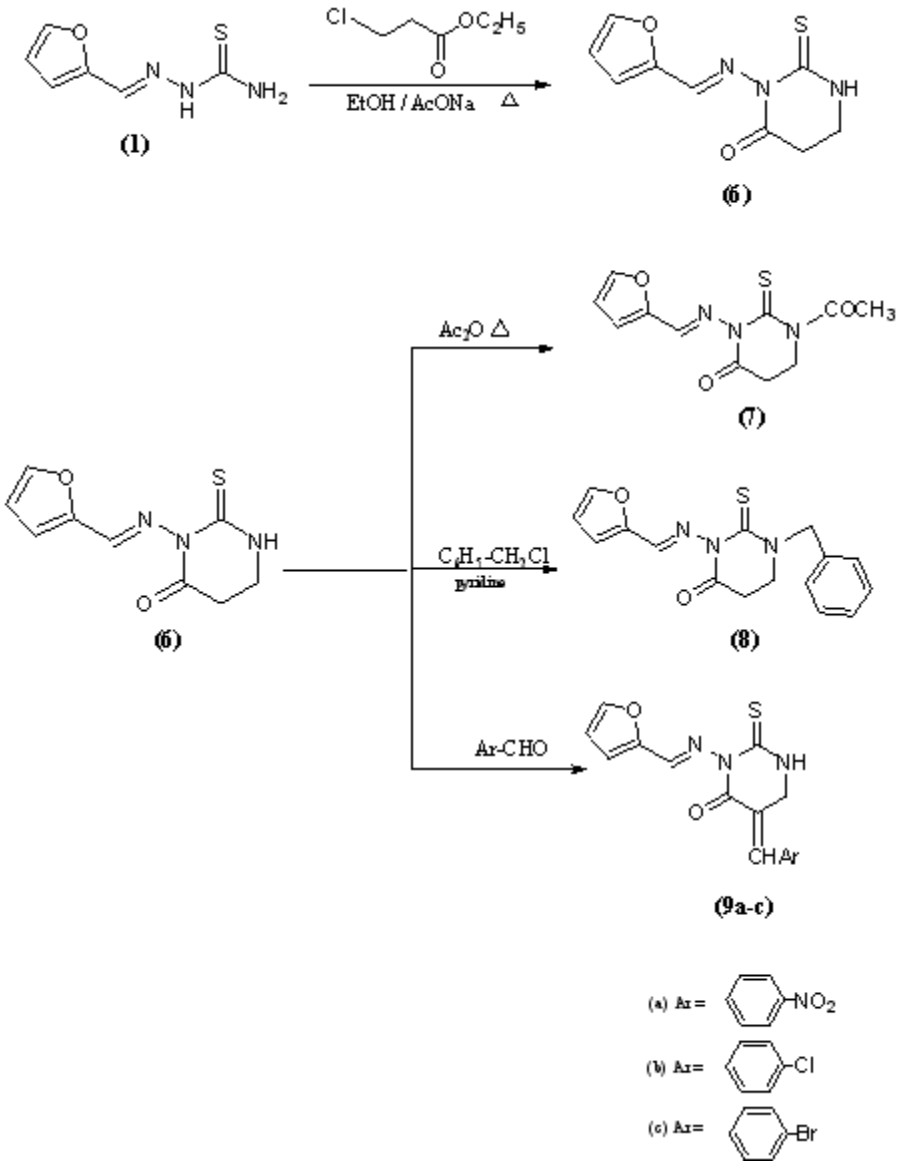



**Scheme 1**

C, 60.18; H, 4.38; N, 14.04.Found: C, 60.00; H, 4.00; N, 13.89. And compound (8) M.p. 125 °C, (Yield 60%), IR ($cm^{-1}$): 3015(CH Aromatic), 2980(CH Aliphatic), 1722(C=O), 1650(C=N), 1339(C=S). Mass spectrum: M/z: 313 ($M^+$, 68%), 223(43.16%), 152(100%, base peak), 108(86.14%), 75(23.04%). $^1$H-NMR (DMSO, 200 MHz): 3.48(t, 2H, $CH_2$), 4.17(t, 2H, $CH_2$), 5.61(s, 2H, $CH_2$ benzyl), 7.19-8.38(m, 8H, Ar-H, furan-H), 9.19(s, 1H, CH=N). Anal.Calcd. for $C_{16}H_{15}N_3O_2S$: C, 61.32; H, 4.82; N, 13.41.Found: C, 61.11; H, 4.77; N, 13.25.

**5-Arylidene-3-(furan-2-yl-methyleneamino)-2-thioxoimidazolidin-4-one (5a-c) and 5-arylidene-3-(furan-2-ylmethyleneamino)-2-thioxotetrahydropyrimidin-4(1H)-one (9a-c)**

A mixture of compounds 2 or 6 (0.01 mol), aromatic aldehydes (0.011 mol) and piperidine (1 ml) was fused on a hot plate for 2 hrs. The reaction mixture was cooled then acidified with dilute hydrochloric acid. The crude product was filtered, washed with water, dried and recrystallized from ethanol.




**Scheme 2**

**3-(Furan-2-yl-methyleneamino)-5-(4-nitrobenzylidene)-2-thioxoimidazolidin-4-one (5a)**

Mp 252 °C, (Yield 60%), IR ($cm^{-1}$): 3423(NH), 3112(CH Aromatic), 2953(CH Aliphatic), 1712(C=O), 1647(C=N), 1349(C=S). Mass spectrum: M/z: 342($M^+$, 29.38%), 287(47.65%), 264(79.83%), 209(17.41%), 124(100%,base peak) 89(56.24%), 69(40.35%). $^1$H-NMR(DMSO, 200 MHz): 6.41-8.38(m,7H,Ar-H, furan-H), 7.10 (s,1H,CH benzylidene), 8.89(s, 1H, CH=N), 11.97(s,1H,NH). Anal.Calcd. for $C_{15}H_{10}N_4O_4S$: C, 52.63; H, 2.94; N, 16.37.Found: C, 52.50; H, 2.89; N, 16.13.

**5-(4-Chlorobenzylidene)-3-(Furan-2-yl-methyleneamino)-2-thioxoimidazolidin-4-one (5b)**

Mp 258 °C, (yield 70%), IR ($cm^{-1}$): 3420(NH), 3111(CH Aromatic), 2950(CH Aliphatic), 1713(C=O), 1643(C=N), 1357(C=S), 795(C-Cl). Mass spectrum: M/z: 331/333($M^+$/M+2, 78.29%, 31.13%), 253(53.55%), 220(24.47%), 160(12.93%), 124(100%, base peak), 89(44.50%). Anal.Calcd. for $C_{15}H_{10}ClN_3O_2S$: C, 54.30; H, 3.04; N, 12.67.Found: C, 54.15; H, 2.98; N,12.60

**5-(4-Bromobenzylidene)-3-(Furan-2-yl-methyleneamino)-2-thioxoimidazolidin-4-one (5c)**

Mp 270°C, (yield 66 %), IR ($cm^{-1}$): 3408(NH), 3219(CH Aromatic), 2977(CH Aliphatic), 1711(C=O), 1608(C=N), 1342(C=S).Mass spectrum: M/z: 375/377 ($M^+$/M+2, 37%, 30%), 287(21.57%), 220(35.37%), 182(12.12%), 124(100%, base peak), 89(48%). Anal.Calcd. for $C_{15}H_{10}BrN_3O_2S$: C, 47.89; H, 2.68; N, 11.17.Found: C, 47.70; H, 2.51; N, 11.07.

**3-(furan-2-ylmethyleneamino)-5-(4-nitrobenzylidene)-2-thioxotetrahydropyrimidin-4(1H)-one (9a)**

Mp 180-182 °C, (Yield 70%), IR ($cm^{-1}$): 3323(NH), 3122(CH Aromatic), 2983(CH Aliphatic), 1725(C=O), 1650(C=N), 1350(C=S). Mass spectrum: M/z: 356($M^+$, 19%), 298(100%, base peak), 223(49.83%), 176(27.41%), 95(50.24%), 60(75.35%). Anal.Calcd. for $C_{16}H_{12}N_4O_4S$: C, 53.93; H, 3.39; N, 15.72.Found: C, 53.81; H, 3.13; N, 15.66.

**5-(4-chlorobenzylidene)-3-(furan-2-ylmethyleneamino)-2-thioxotetrahydropyrimidin-4(1H)-one (9b)**

Mp 175°C, (yield 80%), IR ($cm^{-1}$): 3330(NH), 3166(CH Aromatic), 2985(CH Aliphatic), 1733(C=O), 1645(C=N), 1377(C=S), 789(C-Cl). Mass spectrum: M/z: 345/347($M^+$/M+2, 78%, 33%), 310(49%), 244(24.47%), 223(25%), 176(55%), 107(100%, base peak), 75(76.50%). $^1$H-NMR(DMSO, 200 MHz): 2.28(s,1H,NH), 3.89(s,2H,$CH_2$), 6.61-8.23(m,7H,Ar-H, furan-H), 6.96(s,1H,CH benzylidene), 9.30(s, 1H, CH=N). Anal.Calcd. for $C_{16}H_{12}ClN_3O_2S$: C, 55.57; H, 3.50; N, 12.15.Found: C, 55.46; H, 3.40; N,11.95.

**5-(4-bromobenzylidene)-3-(furan-2-ylmethyleneamino)-2-thioxotetrahydropyrimidin-4(1H)-one (9c)**

Mp 195°C, (yield 68 %), IR ($cm^{-1}$): 3308(NH), 3222(CH Aromatic), 2988(CH Aliphatic), 1730(C=O), 1618(C=N), 1344(C=S).Mass spectrum: M/z: 389/391 ($M^+$/M+2, 25%, 20%), 281(60%), 239(100%, base peak), 223(22.12%), 122(27%), 76(48%). Anal.Calcd. for $C_{16}H_{12}BrN_3O_2S$: C, 49.24; H, 3.10; N, 10.77.Found: C, 49.13; H, 2.95; N, 10.55.

N.B. compounds 2 and 5a-c were reported to be prepared by different method [7]

**Biological studies**

Compounds 3, 4, 5a and 6 were evaluated for their anticonvulsant as well as tranquilizing activities:

**Anticonvulsant activity**

The anticonvulsant activity was determined according to the method of Kerley, et. al.[11] using 42male mice. The mice were divided into 7 groups, of 6 mice each. The first group served as control and injected with the vehicle. The second was given Phenobarbital sodium (PB) (200 mg/kg b.wt; ip). The third one was injected by diazepam (DZP) (1 mg / kg b.wt; ip). The other groups were injected with the tested compounds 3, 4, 5a and 6 (100 mg/kg b.wt; ip). After 60 min., each mouse was injected with strychnine sulfate (2 mg/kg b.wt; ip; $LD_{99}$ for mice). The end point was the measure of the ability of these four compounds to prolong life beyond the time of death observed after strychnine injection.

Compounds which provided significant anticonvulsant activity were additionally compared to the classical standard anticonvulsant drugs, PB and DZP.

**Tranquilizing activity**

The tranquillizing activity of the tested compounds 3, 4, 5a and 6 was studied by observing their effect on the behavior of mice while monitoring their activity on catalepsy test [(12)]. chlorpromazine (CPZ) (4 mg/kg b.wt; ip) was used as refrence standard.the number of animals that failed to remain on the rotating rod for 180 seconds at intervals of 30,60,90,120 minutes after administration of the tested compounds were recorded and calculated as percentage .failure of the mouse to remain on the rod for 3 minutes indicate motor incoordination (table 2).

## RESULTS AND DISCUSSION

In the present investigation, the condensation of furan-2-carbaldehyde with hydrazinecarbothioamide gave 2-(furan-2-ylmethylene)hydrazinecarbothioamide (1) which was cyclized with ethyl 2-chloroacetate and ethyl 3-chloropropanoate[9] in presence of fused sodium acetate to yield 3-(furan-2-yl-methyleneamino)-2-thioxoimidazolidin-4-one (2) and 3-(furan-2-ylmethyleneamino)-2-thioxotetrahydropyrimidin-4(1H)-one (6). Acylation[10] of 2, 6 with acetic anhydride led to the formation of 1-acetyl-3-(furan-2-yl-methyleneamino)-2-thioxoimidazolidin-4-one (3) and 1-acetyl- 3-(furan-2-ylmethyleneamino)-2-thioxotetrahydropyrimidin-4(1H)-one (7). Alkylation of compounds 2 and 6 with benzyl chloride in pyridine gave 1-benzyl-3-(furan-2-yl-methyleneamino)-2-thioxoimidazolidin-4-one (4) and 1-benzyl- 3-(furan-2-ylmethyleneamino)-2-thioxotetrahydropyrimidin-4(1H)-one (8).

Condensation of compounds 2 and 6 with aromatic aldehydes in the presence of piperidine under fusion gave 5-arylidene-3-(furan-2-yl-methyleneamino)-2-thioxoimidazolidin-4-one (5a-c) and 5-arylidene-3-(furan-2-ylmethyleneamino)-2-thioxotetrahydropyrimidin-4(1H)-one (9a-c) respectively. In this report, the target compounds were prepared as outlined in Scheme I, II.

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