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Article

# Synthesis of some novel pyrimidine, thiophene, coumarin, pyridine and pyrrole derivatives and their biological evaluation as analgesic, antipyretic and anti-inflammatory agents

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Pyrimidine derivative **3** was afforded through the reaction of compound (**1**) with 5-ureidohydantion (**2**). Product **3** underwent a cyclization to produce fused pyrimidine derivative **7**, although the latter product **7** was synthesized through one step via the reaction of compound (**1**) with 5-ureidohydantion (**2**) using another catalyst. Compound **3** was oriented to react with cyclic ketones **8a**,**b** in the presence of elemental sulfur, salicylaldehyde (**10**), aryldiazonium chlorides **12a**,**b** and ω-bromo-4-methoxy- acetophenone (**14**), which afforded, fused thiophene derivatives **9a**,**b**, coumarin derivative **11**, arylhdrazono derivatives **13a**,**b** and 4-methoxyphenyl butenyl derivative **15,** respectively. The latter product **15** was reacted with either potassium cyanide (**16a**) or potassium thiocyanide (**16b**) to form cyano and thiocyano derivatives **17a**,**b**, respectively. Compound **17a** underwent further cyclization to afford pyridopyrimidine derivative **19.** Compound **15** was reacted with either hydrazine (**20a**) or phenylhydrazine (**20b**) to produce hydrazo derivatives **21a**,**b** and these products were cyclize to produce pyrrole derivatives **23a**,**b**. Finally, 5-ureidohydantion (**2**) was reacted with compounds **24a**,**b**,**c** to afford pyrimidine derivatives **25a**,**b**,**c**. The structures of the synthesized compounds were confirmed using IR, $^{1}$H NMR, $^{13}$C NMR and mass spectrometry techniques. Compounds **11** and **19** have promising as analgesic and antipyretic activities.

**Keywords:** Pyrimidine derivative. Thiophene. Coumarin. Pyridine. Pyrrole. Analgesic. Antipyretic and anti-inflammatory agents.

## INTRODUCTION

A series of studies was introduced to discover that hydantoin derivatives, important heterocyclic compounds, act as antioxidant agents (Gus'kov *et al*., 2004). Moreover, Imidazolidine-2,4 dione derivatives are specific biologically active compounds and act as anti-proliferative agents (Reddy *et al*., 2010), hypoglycemic, aldose reductase inhibitor agents (Iqbal *et al*., 2015) and Bcl-2 inhibitors (Wang *et al*., 2015).

Pyridopyrimidine derivatives have a wide variety of biological properties, including antileishmanial (Agarwal *et al*., 2005) and antitubercular activities (Horvati *et al*., 2015; Rajesh *et al*., 2011). Additionally fused thiophene derivatives have antitumor activity (Dallemagne *et al*., 2003) and pyrimidine derivatives containing the coumarin moiety have analgesic and anti-pyretic effects (Keri *et al*., 2010). Hydrazono derivatives have shown anticancer activity (Sztanke, Rzymowska, Sztanke, 2013) and pyrrole derivatives have antibacterial activity (Padmavathi *et al*., 2011). In this article we aimed to improve and discover the analgesic, antipyretic and anti-inflammatory activities of synthesized compounds.

## MATERIAL AND METHODS

### General procedures

The melting points of the synthesized compounds were determined in open capillaries and are uncorrected. Elemental analyses were performed on a Yanaco CHNS Corder elemental analyzer (Japan). IR spectra were measured using KBr discs on a Pye Unicam SP-1000 spectrophotometer. $^{1}$H NMR and $^{13}$C NMR spectra were measured on a Varian EM 390-200 M*Hz* instrument

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with $CD_3SOCD_3$ as the solvent using TMS as an internal standard material, the chemical shifts were expressed as δ ppm. Mass spectra were recorded on Kratos (75 eV) MS equipment (Germany).

*General procedures for the synthesis of compound: 3-(4,6-diamino-1-(2,5-dioxoimidazolidin-4-yl)-2-oxo-1,2-dihydropyrimidin-5-yl)-3-iminopropanenitrile (**3**)*

β-amino-α,γ-dicyanocrotononitrile (**1**) (3.96 g, 0.03 mol) was added to a 5-ureidohydantoin solution (**2**) (4.743 g, 0.03 mol) in 100 mL of ethanol containing dimethylformamide (5mL) and triethylamine (1.0 mL) as a catalyst. The reaction mixture was heated under reflux for 6 h, cooled and poured onto ice containing a few drops of HCl. Then, the formed solid product was filtered out.

Compound **3**: Faint yellow crystals from ethanol, yield 54%, 4.701 g, m.p. 168-170 ºC. IR (KBr): υ/$cm^{-1}$ = 3438-3355 ($2NH_2$, 3NH), 2883 ($CH_2$), 2765 (CH), 2223 (CN), 1673, 1668, 1661 (3CO), 1648 (C=C). $^1$H NMR (DMSO-$d_6$) δ = 3.05-3.13 (s, 2H, $CH_2$), 4.87, 5.12 (2s, 4H, $D_2O$-exchangeable, $2NH_2$), 5.74 (s, 1H, imidazolidindione ring), 8.35, 9.22, 9.79 (3s, 3H, $D_2O$-exchangeable, 3NH). $^{13}$C NMR: δ = 40.9 ($CH_2$), 62.1 (CH), 106.4 (C=NH), 116.9 (CN), 120.1, 148.6, 152.7 (pyrimidine C), 164.4, 168.3, 171.7 (3C=O). MS (relative intensity) m/z: 290 ($M^+$, 32.2%). Calcd for $C_{10}H_{10}N_8O_3$ (290.24): C, 41.38; H, 3.47; N, 38.61%. Found: C, 41.65; H, 3.24; N, 38.90%.

*General procedure for the synthesis of compound: 5-(4,5,7-triamino-2-oxopyrido-[2,3-d]pyrimidin-3(2H)-yl) imidazolidine-2,4-dione (**7**)*

Method (A): A solution of compound **3** (0.58 g, 0.002 mol) in ethanol (50 mL) containing a catalytic amount of piperidine (0.5 mL) was heated under reflux for 5 h, poured onto an ice/water mixture containing a few drops of hydrochloric acid. The formed solid product was collected by filtration.

Method (B): β-Amino-α, γ-dicyanocrotononitrile (**1**) (0.396 g, 0.003 mol) was added to a solution of compound **2** (0.474 g, 0.003 mol) in sodium ethoxide (0.003 mol) [prepared by dissolving sodium metal (0.069 g, 0.003 mol) in absolute ethanol (50 mL)]. The reaction mixture was heated under reflux for 6 h and then evaporated under vacuum. The product was triturated with ethanol and the formed solid product was collected by filtration.

Compound **7**: Brown crystals from ethanol, yield 66%, 0.575 g, m.p. 115-117 ºC. IR (KBr): υ/$cm^{-1}$ = 3488-3327 ($3NH_2$, 2NH), 2783 (CH), 1695, 1684, 1662 (3CO), 1651 (C=N). $^1$H NMR (DMSO-$d_6$) δ = 4.78, 4.93, 5.27 (3s, 6H, $D_2O$-exchangeable, $3NH_2$), 5.67 (s, 1H, imidazolidindione ring), 6.87 (s, 1H, pyridine ring), 8.73, 9.95 (2s, 2H, $D_2O$-exchangeable, 2NH). $^{13}$C NMR: δ = 55.7 (CH), 124.3, 133.4, 138.5, 144.7, 150.3, 152.4 (pyridine C, pyrimidine C), 166.1, 169.7, 173.2 (3C=O). Calcd for $C_{10}H_{10}N_8O_3$ (290.24): C, 41.38; H, 3.47; N, 38.61%. Found: C, 41.11; H, 3.73; N, 38.99%.

*General procedure for the synthesis of compounds: 5-(4,6-diamino-5-((2-amino-5,6-dihydro-4H-cyclopenta[b]thiophen-3-yl)(imino)methyl)-2-oxo-pyrimidin-1(2H)-yl) imidazolidine-2,4-dione (**9a**) and 5-(4,6-diamino-5-((2-amino-4,5,6,7-tetrahydrobenzo [b]thiophen-3-yl(imino) methyl)-2-oxopyrimidin-1(2H) yl) imidazolidine-2,4-dione (**9b**)*

To a solution of compound **3** (0.58 g, 0.002 mol) in ethanol (50 mL) containing trimethylamine (0.5 mL), either cyclopentanone **(8a)** (0.168 g, 0.002 mol) or cyclohexanone **(8b)** (0.196 g, 0.002 mol) together with elemental sulfur (0.064 g, 0.002 mol) were added. The reaction mixture was heated under reflux for 4 h, cooled and poured onto an ice/water mixture containing a few drops of HCl. The formed precipitate was collected by filtration.

Compound **9a**: Brown crystals from 1,4-dioxane, yield 63%, 0.489 g, m.p. 202-204 ºC. IR (KBr): υ/$cm^{-1}$ = 3458-3336 ($3NH_2$, 3NH), 2880 ($CH_2$), 2796 (CH), 1683, 1674, 1663 (3CO), 1653 (C=N), 1646 (C=C), 684 (C-S). $^1$H NMR (DMSO-$d_6$) δ = 2.07-2.18 (m, 6H, $3CH_2$), 4.54, 4.65, 5.81 (3s, 6H, $D_2O$-exchangeable, $3NH_2$), 5.98 (s, 1H, imidazolidindione ring), 8.52, 8.77, 9.12 (3s, 3H, $D_2O$-exchangeable, 3NH). $^{13}$C NMR: δ = 22.4, 27.3, 29.9 (3 $CH_2$), 51.3 (CH), 93.8 (C=NH), 126.2, 131.5, 136.3, 140.5, 142.7, 149.1, 151.6 (thiophene C, pyrimidine C), 165.4, 168.8, 172.1 (3C=O). Calcd for $C_{15}H_{16}N_8O_3S$ (388.40): C, 46.38; H, 4.15; N, 28.85; S, 8.26%. Found: C, 46.17; H, 3.89; N, 28.66; S, 8.01%.

Compound **9b**: Brown crystals from 1,4-dioxane, yield 58%, 0.477 g, m.p. 212-214 ºC. IR (KBr): υ/$cm^{-1}$ = 3460-3349 ($3NH_2$, 3NH), 2882 ($CH_2$), 2768 (CH), 1677, 1671, 1664 (3CO), 1655 (C=N), 1649 (C=C), 676 (C-S). $^1$H NMR (DMSO-$d_6$) δ = 2.18-2.39 (m, 8H, $4CH_2$), 4.48, 4.69, 5.45 (3s, 6H, $D_2O$-exchangeable, $3NH_2$), 5.86 (s, 1H, imidazolidindione ring), 8.61, 8.86, 9.08 (3s, 3H, $D_2O$-exchangeable, 3NH). $^{13}$C NMR: δ = 22.8, 25.4, 27.3, 29.6 (4 $CH_2$), 54.7 (CH), 97.1 (C=NH), 128.1, 134.7, 138.6, 141.5, 146.6, 150.8, 153.3 (thiophene C, pyrimidine C), 162.2, 166.7, 170.6 (3C=O). Calcd for $C_{16}H_{18}N_8O_3S$ (402.43): C, 47.75; H, 4.51; N, 27.84; S, 7.97%. Found: C, 47.56; H, 4.78; N, 28.09; S, 7.68%.

*General procedure for the synthesis of compound:-5-(4,6-diamino-5-(imino(2-oxo-2H-chromen-3-yl) methyl)-2-oxopyrimidin-1(2H)-yl)imidazolidine-2,4-dione (**11**)*

Salicylaldehyde (**10**) (0.244 g, 0.002 mol) was added to a solution of compound **3** (0.58 g, 0.002 mol) in 1,4-dioxane (50 mL) containing piperidine (0.5 mL). The reaction mixture was heated under reflux for 5 h and then evaporated under vacuum. The solid product was triturated with ethanol and the formed solid product was collected by filtration.

Compound **11**: Yellowish brown crystals from 1,4-dioxane, yield 70%, 0.553 g, m.p. 185-187 ºC. IR (KBr): υ/cm$^{-1}$ = 3443-3311 ($2NH_2$, 3NH), 3052 (CH-aromatic.), 2762 (CH), 1835, 1681, 1666, 1660 (4C=O), 1652 (C=N), 1112 (CO), 1649 (C=C). $^1$H NMR (DMSO-$d_6$) δ = 4.76, 5.25 (2s, 4H, $D_2O$-exchangeable, $2NH_2$), 5.53 (s, 1H, imidazolidindione ring), 6.73 (s, 1H, coumarin H-4), 7.51- 7.66 (m, 4H, $C_6H_4$), 8.88, 9.28, 9.55 (3s, 3H, $D_2O$-exchangeable, 3NH). $^{13}$C NMR: δ = 59.5 (CH), 95.3 (C=NH), 125.5, 131.9, 136.8, 140.7, 144.5, 147.2, 149.1, 151.3, 153.5 (pyrimidine C, coumarin C), 161.5, 165.8, 170.3, 181.5 (4C=O). Calcd for $C_{17}H_{13}N_7O_5$ (395.33): C, 51.65; H, 3.31; N, 24.80%. Found: C, 51.93; H, 3.59; N, 24.55%.

*General procedure for the synthesis of compounds:-2-(4,6-diamino-1-(2,5-dioxo- imidazolidin-4-yl)-2-oxo 1,2-dihydropyrimidin-5-yl)-2-imino-N′-phenyl-acetohydrazonoyl cyanide (**13a**) and N′-(4-chlorophenyl)-2-(4,6-diamino-1-(2,5-dioxo- imidazolidin-4-yl-2-oxo-1,2-dihydropyrimidin-5-yl)-2-iminoaceto-hydrazonoyl cyanide (**13b**)*

To a cold solution (0-5 °C) of pyrimidine derivative **3** (0.58 g, 0.002 mol) in ethanol (50 mL) containing sodium acetate (0.164 g, 0.002 mol) either benzenediazonium chloride (**12a**) or 4-chlorobenzenediazonium chloride (**12b**) (0.002 mol) [prepared by adding an aqueous sodium nitrite solution (0.138 g, 0.002 mol) to a cold solution of either aniline or 4-chloroaniline (0.002 mol) in the appropriate amount of glacial acetic acid at (0-5 °C) with continuous stirring] was added with continuous stirring. The reaction mixture was stirred at room temperature for an additional 4 h and the solid product was collected by filtration.

Compound **13a**: Pale brown crystals from ethanol, yield 67%, 0.528 g, m.p. 137- 139 ºC. IR (KBr): υ/cm$^{-1}$ = 3476-3354 ($2NH_2$, 4NH), 3053 (CH aromatic), 2761 (CH), 2223 (CN), 1678, 1667, 1663 (3CO), 1657 (C=N), 1646 (C=C). $^1$H NMR (DMSO-$d_6$) δ = 4.54, 5.17 (2s, 4H, $D_2O$-exchangeable, $2NH_2$), 5.61 (s, 1H, imidazolidindione ring), 7.31- 7.62 (m, 5H, $C_6H_5$), 8.76, 9.13, 9.38, 9.59 (4s, 4H, $D_2O$-exchangeable, 4NH). $^{13}$C NMR: δ = 67.3 (CH), 92.4, 109.2 (2C=N), 120.4 (CN), 123.3, 125.9, 127.9, 130.4, 132.8, 134.6, 138.4, 142.5 (pyrimidine C, $C_6H_5$), 163.9, 166.8, 169.3 (3C=O). MS (relative intensity) m/z: 394 ($M^+$, 17.9%). Calcd for $C_{16}H_{14}N_{10}O_3$ (394.35): C, 48.73; H, 3.58; N, 35.52%. Found: C, 48.48; H, 3.29; N, 35.80%.

Compound **13b**: Dark brown crystals from ethanol, yield 61%, 0.523 g, m.p. 193-195 ºC. IR (KBr): υ/cm$^{-1}$ = 3451-3290 ($2NH_2$, 4NH), 3050 (CH aromatic), 2770 (CH), 2224 (CN), 1673, 1663, 1659 (3CO), 1652 (C=N), 1647 (C=C). $^1$H NMR (DMSO-$d_6$) δ = 4.63, 5.08 (2s, 4H, $D_2O$-exchangeable, $2NH_2$), 5.89 (s, 1H, imidazolidindione ring), 7.44- 7.58 (d.d, 4H, $C_6H_4$), 8.58, 9.24, 9.55, 9.67 (4s, 4H, $D_2O$-exchangeable, 4NH). $^{13}$C NMR: δ = 62.5 (CH), 98.4, 106.4 (2C=N), 121.7 (CN), 122.5, 124.8, 125.8, 128.3, 131.6, 135.3, 137.7, 141.5 (pyrimidine C, $C_6H_5$), 162.8, 165.7, 168.8 (3C=O). MS (relative intensity) m/z: 428 ($M^+$, 23.4%). Calcd for $C_{16}H_{13}ClN_{10}O_3$ (428.79): C, 44.82; H, 3.06; N, 32.67%. Found: C, 44.56; H, 3.33; N, 32.40%.

*General procedure for synthesis of compound: 4-bromo-2-((4,6-diamino-1-(2,5-dioxo- imidazolidin-4-yl)-2-oxo-1,2-dihydropyrimidin-5-yl) (imino) methyl)-3-(4-methoxy-phenyl) but-2-enenitrile (**15**)*

ω-Bromo-4-methoxyacetophenone (**14**) (0.524 g, 0.002 mol) was added to a solution of compound **3** (0.58 g, 0.002 mol) in 1,4-dioxane (40 mL). The reaction mixture was stirred at room temperature for 2 h and then poured on to a beaker containing ice/water mixture. The formed solid product was collected by filtration.

Compound **15**: Brown crystals from ethanol, yield 72%, 0.712 g, m.p. 121-123 ºC. IR (KBr): υ/cm$^{-1}$ = 3422-3286 ($2NH_2$, 3NH), 3055 (CH aromatic), 2986 ($CH_3$), 2867 ($CH_2$), 2766 (CH), 2225 (CN), 1680, 1669, 1662 (3CO), 1658 (C=N), 1648 (C=C). $^1$H NMR (DMSO-$d_6$) δ = 3.32 (s, 3H, $OCH_3$), 3.77 (s, 2H, $CH_2$), 4.81, 5.29 (2s, 4H, $D_2O$-exchangeable, $2NH_2$), 5.55 (s, 1H, imidazolidindione ring), 7.48-7.71 (d.d, 4H, $C_6H_4$), 8.66, 9.22, 9.45 (3s, 3H, $D_2O$-exchangeable, 3NH). $^{13}$C NMR: δ = 41,2 ($CH_3$), 49.5 ($CH_2$), 65.3 (CH), 81.3, 88.6 (C=C), 103.7 (C=N), 118.3 (CN), 124.6, 126.7, 129.3, 131.5, 133.9, 135.4, 137.8 (pyrimidine C, $C_6H_4$), 160.7, 165.7, 169.8 (3C=O). MS (relative intensity) m/z: 500 ($M^+$, 13.8%), 502 ($M^+$, 13.4%), Calcd for $C_{19}H_{17}BrN_8O_4$ (501.29): C, 45.52; H, 3.42; N, 22.35%. Found: C, 45.81; H, 3.19; N, 22.63%.

*General procedure for the synthesis of compounds: 2-((4,6-diamino-1-(2,5-dioxo- imidazolidin-4-yl)-2-oxo-1,2-dihydropyrimidin-5-yl) (imino) methyl)-3-(4- methoxy-phenyl-pent-2-enedinitrile (**17a**) and 2-((4,6-diamino-1-(2,5-dioxo-imidazolidin-4-yl)-2-oxo-1,2-dihydropyrimidin-5-yl)(imino)methyl)-3-(4-methoxyphenyl)-4-thio-cyanatobut-2-enenitrile (**17b**)*

Either potassium cyanide (**16a**) (0.122 g, 0.002 mol) or potassium thiocyanate (**16b**) (0.189 g, 0.002 mol) was added to a solution of compound **15** (1.002 g, 0.002 mol) in ethanol (50 mL) in water bath at 60 ºC, with continuous stirring. The reaction mixture was maintained in the water bath for 1 h at 60 ºC and then poured into a beaker containing an ice/water mixture and a few drops of HCl. The formed solid product was collected by filtration.

Compound **17a**: Dark brown crystals from ethanol, yield 69%, 0.617 g, m.p. 157-159 ºC. IR (KBr): υ/$cm^{-1}$ = 3445-3266 ($2NH_2$, 3NH), 3051 (CH aromatic), 2978 ($CH_3$), 2881 ($CH_2$), 2754 (CH), 2225, 2223 (2CN), 1682, 1673, 1661 (3CO), 1657 (C=N), 1649 (C=C). $^1$H NMR (DMSO-$d_6$) δ = 3.41 (s, 3H, $OCH_3$), 3.76 (s, 2H, $CH_2$), 4.55, 4.87 (2s, 4H, $D_2O$-exchangeable, $2NH_2$), 5.63 (s, 1H, imidazolidindione ring), 7.33-7.54 (d.d, 4H, $C_6H_4$), 8.45, 8.76, 9.33 (3s, 3H, $D_2O$-exchangeable, 3NH). $^{13}$C NMR: δ = 38.1 ($CH_3$), 48.9 ($CH_2$), 62.7 (CH), 77.7, 83.5 (C=C), 97.6 (C=N), 116.5, 119.2 (2CN), 122.8, 125.4, 128.6, 130.6, 134.4, 136.7, 138.9 (pyrimidine C, $C_6H_4$), 161.4, 164.5, 168.1 (3C=O). MS (relative intensity) m/z: 447 ($M^+$, 28.4%). Calcd for $C_{20}H_{17}N_9O_4$ (447.41): C, 53.69; H, 3.83; N, 28.18%. Found: C, 53.96; H, 3.59; N, 28.43%.

Compound **17b**: Brown crystals from ethanol, yield 64%, 0.613 g, m.p. 181-183 ºC. IR (KBr): υ/$cm^{-1}$ = 3423-3233 ($2NH_2$, 3NH), 3053 (CH aromatic), 2960 ($CH_3$), 2884 ($CH_2$), 2760 (CH), 2224, 2221 (2CN), 1680, 1672, 1662 (3CO), 1659 (C=N), 1651 (C=C). $^1$H NMR (DMSO-$d_6$) δ = 3.25 (s, 3H, $OCH_3$), 3.44 (s, 2H, $CH_2$), 4.51, 4.73 (2s, 4H, $D_2O$-exchangeable, $2NH_2$), 5.55 (s, 1H, imidazolidindione ring), 7.39- 7.61 (d.d, 4H, $C_6H_4$), 8.56, 8.74, 9.22 (3s, 3H, $D_2O$-exchangeable, 3NH). $^{13}$C NMR: δ = 41.2 ($CH_3$), 49.7 ($CH_2$), 63.9 (CH), 76.7, 86.8 (C=C), 97.9 (C=N), 117.2, 119.8 (2CN), 123.9, 126.7, 129.9, 132.5, 136.2, 138.9, 140.7 (pyrimidine C, $C_6H_4$), 162.2, 164.8, 167.8 (3C=O). MS (relative intensity) m/z: 479 ($M^+$, 23.3%). Calcd for $C_{20}H_{17}N_9O_4S$ (479.47): C, 50.10; H, 3.57; N, 26.29; S, 6.69%. Found: C, 50.34; H, 3.28; N, 26.57; S, 6.41%.

*General procedure for the synthesis of compound: 6-amino-2-(4,6-diamino-1-(2,5-dioxoimidazolidin-4-yl)-2-oxo-1,2-dihydropyrimidin-5-yl)-4-(4-methoxyphenyl)-nicotinonitrile (**19**)*

The solution of compound **17a** (0.447 g, 0.001 mol) in sodium ethoxide (0.001 mol) [prepared by dissolving sodium metal (0.023 g, 0.001 mol) in absolute ethanol (50 mL)]. The reaction was heated under reflux for 4 h and then evaporated under vacuum. The product was triturated with ethanol and the formed product was collected by filtration.

Compound **19**: Yellow crystals from ethanol, yield 57%, 0.255 g, m.p. 207-209 ºC. IR (KBr): υ/$cm^{-1}$ = 3462-3220 ($3NH_2$, 2NH), 3054 (CH aromatic), 2985 ($CH_3$), 2766 (CH), 2221 (CN), 1688, 1672, 1664 (3CO), 1655 (C=N), 1647 (C=C). $^1$H NMR (DMSO-$d_6$) δ = 3.68 (s, 3H, $OCH_3$), 4.38, 4.93, 5.33 (3s, 6H, $D_2O$-exchangeable, $3NH_2$), 5.77 (s, 1H, imidazolidindione ring), 7.14 (s, 1H, pyridine), 7.28-7.49 (d.d, 4H, $C_6H_4$), 8.41, 8.82 (2s, 2H, $D_2O$-exchangeable, 2NH). $^{13}$C NMR: δ = 40.4 ($CH_3$), 63.3 (CH), 117.8 (CN), 120.6, 123.9, 125.2, 127.6, 131.1, 133.5, 136.2, 138.4, 140.7, 142.6, 144.5, 145.8 (Pyridine C, pyrimidine C, $C_6H_4$), 160.8, 163.3, 166.7 (3C=O). MS (relative intensity) m/z: 447 ($M^+$, 30.5%). Calcd for $C_{20}H_{17}N_9O_4$ (447.41): C, 53.69; H, 3.83; N, 28.18%. Found: C, 53.44; H, 4.09; N, 28.37%.

*General procedure for the synthesis of compounds: 2-((4,6-diamino -1-(2,5-dioxo- imidazolidin-4-yl) -2-oxo -1,2-dihydropyrimidin -5-yl) (imino) methyl) -4-hydrazinyl-3-(4-methoxyphenyl)but-2-enenitrile (**21a**) and 2-((4,6-diamino-1-(2,5-dioxo –imidazol- idin-4-yl)-2-oxo-1,2-dihydropyrimidin-5-yl) (imino) methyl)-3-(4-methoxy -phenyl)-4-(2-phenyl- hydrazinyl)but-2-enenitrile (**21b**)*

Either hydrazine hydrate (**20a**) (0.1 g, 0.002 mol) or phenylhydrazine (**20b**) (0.22 g, 0.002) was added to a solution of compound **15** (1.002 g, 0.002 mol) in ethanol (50 mL). The reaction mixture was heated under reflux for 4 h and then poured onto an ice/water mixture containing a few drops of hydrochloric acid. The formed solid product was collected by filtration.

Compound **21a**: Pale yellow crystals from ethanol, yield 74%, 0.67 g, m.p. 221-223 ºC. IR (KBr): υ/$cm^{-1}$ = 3389-3212 ($3NH_2$, 4NH), 3050 (CH aromatic), 2974 ($CH_3$), 2881 ($CH_2$), 2760 (CH), 2227 (CN), 1683, 1667, 1660 (3CO), 1655 (C=N), 1649 (C=C). $^1$H NMR (DMSO-$d_6$) δ = 3.19 (s, 3H, $OCH_3$), 3.28 (s, 2H, $CH_2$), 4.58, 5.12, 5.28 (3s, 6H, $D_2O$-exchangeable, $3NH_2$), 5.71 (s, 1H, imidazolidindione ring), 6.83-7.17 (d.d, 4H, $C_6H_4$),

8.43, 8.68, 8.77, 9.53 (4s, 4H, $D_2O$-exchangeable, 4NH). $^{13}C$ NMR: δ = 37.5 ($CH_3$), 53.3 ($CH_2$), 66.7 (CH), 79.4, 86.4 (C=C), 107.6 (C=N), 115.7 (CN), 120.5, 125.9, 128.2, 132.3, 134.7, 136.7, 138.9 (pyrimidine C, $C_6H_4$), 164.4, 166.9, 170.2 (3C=O). MS (relative intensity) m/z: 452 ($M^+$, 27.4%). Calcd for $C_{19}H_{20}N_{10}O_4$ (452,43): C, 50.44; H, 4.46; N, 30.96%. Found: C, 50.71; H, 4.73; N, 30.68%.

Compound **21b**: Pale yellow crystals from ethanol, yield 65%, 0.688 g, m.p. 240-242 ºC. IR (KBr): υ/$cm^{-1}$= 3368-3188 ($2NH_2$, 5NH), 3056 (CH aromatic), 2988 ($CH_3$), 2879 ($CH_2$), 2758 (CH), 2225 (CN), 1688, 1666, 1661 (3CO), 1657 (C=N), 1650 (C=C). $^1H$ NMR (DMSO-$d_6$) δ = 3.12 (s, 3H, $OCH_3$), 3.22 (s, 2H, $CH_2$), 5.17, 5.44 (2s, 4H, $D_2O$-exchangeable, $2NH_2$), 5.55 (s, 1H, imidazolidindione ring), 6.91-7.12 (d.d, 4H, $C_6H_4$), 7.38-7.53 (m, 5H, $C_6H_5$), 8.22, 8.51, 8.79, 9.11, 9.58 (5s, 5H, $D_2O$-exchangeable, 5NH). $^{13}C$ NMR: δ = 39.4 ($CH_3$), 51.7 ($CH_2$), 69.5 (CH), 78.8, 83.2 (C=C), 110.4 (C=N), 117.6 (CN), 120.3, 122.5, 124.7, 127.1, 130.8, 132.6, 134.8, 136.5, 139.6, 141.2, 143.4, 146.4 (pyrimidine C, $C_6H_4$, $C_6H_5$), 163.3, 165.8, 167.8 (3C=O). MS (relative intensity) m/z: 528 ($M^+$, 23.6%). Calcd for $C_{25}H_{24}N_{10}O_4$ (528.52): C, 56.81; H, 4.58; N, 26.50%. Found: C, 56.55; H, 4.33; N, 26.21%.

*General procedure for the synthesis of compounds: 5-(4,6-diamino-5-((1,2-diamino-4-(4-methoxyphenyl)-1H-pyrrol-3-yl)(imino)methyl)-2-oxopyrimidin-1(2H)-yl) imidazolidine-2,4-dione (**23a**) and 5-(4,6-diamino-5-((2-amino-4-(4-methoxyphenyl)-1-(phenylamino)-1H-pyrrol-3-yl)(imino)methyl)-2-oxopyrimidin-1(2H)-yl) imidazolidine-2,4-dione (**23b**)*

The reactions began either with solutions of compound **21a** (0.452 g, 0.001 mol) or compound **21b** (0.528 g, 0.001 mol) in sodium ethoxide (0.001 mol) in absolute ethanol (50 mL). The reaction was heated under reflux for 3 h and then evaporated under vacuum. The product was triturated with ethanol and the formed product was collected by filtration.

Compound **23a**: Creamy white crystals from ethanol, yield 57%, 0.258 g, m.p. 178-180 ºC. IR (KBr): υ/$cm^{-1}$ = 3411-3264 ($4NH_2$, 3NH), 3055 (CH aromatic), 2981 ($CH_3$), 2768 (CH), 1689, 1668, 1663 (3CO), 1651 (C=N), 1645 (C=C). $^1H$ NMR (DMSO-$d_6$) δ = 3.27 (s, 3H, $OCH_3$), 4.38, 4.59, 4.95, 5.23 (4s, 8H, $D_2O$-exchangeable, $4NH_2$), 5.63 (s, 1H, imidazolidindione ring), 6.95-7.28 (m, 4H, $C_6H_4$, 1H, pyrrole), 8.51, 8.77, 9.38 (3s, 3H, $D_2O$-exchangeable, 3NH). $^{13}C$ NMR: δ = 39.2 ($CH_3$), 64.4 (CH), 103.8 (C=N), 121.7, 123.6, 126.7, 128.9, 131.4, 133.6, 136.5, 138.5, 140.2, 143.4, 145.1 (pyrrole C, pyrimidine C, $C_6H_4$), 167.1, 169.8, 173.4 (3C=O). MS (relative intensity) m/z: 452 ($M^+$, 21.5%). Calcd for $C_{19}H_{20}N_{10}O_4$ (452,43): C, 50.44; H, 4.46; N, 30.96%. Found: C, 50.18; H, 4.69; N, 30.72%.

Compound **23b**: Pale yellow crystals from ethanol, yield 55%, 0.29 g, m.p. 150-152 ºC. IR (KBr): υ/$cm^{-1}$= 3386-3187 ($3NH_2$, 4NH), 3053 (CH aromatic), 2975 ($CH_3$), 2782 (CH), 1685, 1671, 1665 (3CO), 1656 (C=N), 1650 (C=C). $^1H$ NMR (DMSO-$d_6$) δ = 3.41 (s, 3H, $OCH_3$), 4.44, 4.67, 5.21 (3s, 6H, $D_2O$-exchangeable, $3NH_2$), 5.54 (s, 1H, imidazolidindione ring), 6.86-7.37 (m, 4H, $C_6H_4$, 5H, $C_6H_5$, 1H, pyrrole), 8.43, 8.68, 9.17, 9.56 (4s, 4H, $D_2O$-exchangeable, 4NH). $^{13}C$ NMR: δ = 35.7 ($CH_3$), 57.4 (CH), 101.4 (C=N), 120.2, 121.9, 123.3, 125.8, 127.5, 130.1, 132.7, 134.6, 136.7, 139.1, 141.5, 144.1, 146.3, 147.5 (pyrrole C, pyrimidine C, $C_6H_4$, $C_6H_5$), 163.3, 169.4, 171.8 (3C=O). MS (relative intensity) m/z: 528 ($M^+$, 28.3%). Calcd for $C_{25}H_{24}N_{10}O_4$ (528.52): C, 56.81; H, 4.58; N, 26.50%. Found: C, 56.55; H, 4.86; N, 26.33%.

*General procedure for the synthesis of compounds: 5-(4-amino-6-imino-2-oxo-5-(1-phenylethylidene)-5,6-dihydropyrimidin-1(2H)-yl)imidazolidine-2,4-diones (**25a**), 5-(4-amino-6-imino-2-oxo-5-(2-phenylhydrazono-5,6-dihydropyrimidin-1(2H)-yl) imidazol- idine-2,4-dione (**25b**) and 5-(4-amino-5-(2-(4-chlorophenyl) hydrazono)-6-imino-2-oxo-5,6-dihydro- pyrimidin-1(2H)-yl)imidazolidine-2,4-dione (**25c**)*

Either compound **24a** (0.505 g, 0.003 mol), **24b** (0.614 g, 0.003 mol) or **24c** (0.474 g, 0.003 mol) was added to a solution of 5-ureidohydantion (**2**) (0.474 g, 0.003 mol) in 50 mL of ethanol containing dimethylformamide (5.0 mL) and triethylamine (1.0 mL) as a catalyst. The reaction mixture was heated under reflux for 5 h, cooled and poured onto ice containing a few drops of HCl. The formed solid product was filtered out.

Compound **25a**: Pale brown crystals from ethanol, yield 61%, 0.597 g, m.p. 251-253 ºC. IR (KBr): υ/$cm^{-1}$= 3407-3326 ($NH_2$, 3NH), 3051 (CH aromatic), 2978 ($CH_3$), 2734 (CH), 1688, 1671, 1662 (3CO), 1657 (C=N), 1647 (C=C). $^1$HNMR (DMSO) δ = 1.87 (s, 3H, $CH_3$), 4.63 (s, 2H, $D_2O$-exchangeable, $NH_2$), 5.65 (s, 1H, imidazolidindione ring), 7.27-7.44 (m, 5H, $C_6H_5$), 8.22, 8.46, 9.37 (3s, 3H, $D_2O$-exchangeable, 3NH). $^{13}C$ NMR: δ = 23.3 ($CH_3$), 61.4 (CH), 86.4 (C=C), 118.7, 123.5, 126.7, 128.9, 130.2, 133.6, 137.4, 139.3 (pyrimidine C, $C_6H_5$), 160.2, 162.7, 165.6 (3C=O). MS (relative intensity) m/z: 326 ($M^+$, 19.8%). Calcd for $C_{15}H_{14}N_6O_3$ (326.31): C,

55.21; H, 4.32; N, 25.75%. Found: C, 55.48; H, 4.05; N, 25.49%.

Compound **25b**: Brown crystals from ethanol, yield 53%, 0.522 g, m.p. 197-199 ºC. IR (KBr): υ/cm$^{-1}$ = 3428-3335 ($NH_2$, 4NH), 3053 (CH aromatic), 2766 (CH), 1684, 1672, 1664 (3CO), 1656 (C=N), 1649 (C=C). $^1$HNMR (DMSO) δ = 4.55 (s, 2H, $D_2O$-exchangeable, $NH_2$), 5.43 (s, 1H, imidazolidindione ring), 7.18-7.37 (m, 5H, $C_6H_5$), 8.33, 8.49, 8.74, 9.37 (4s, 4H, $D_2O$-exchangeable, 4NH). $^{13}$C NMR: δ = 65.5 (CH), 120.4, 122.7, 125.9, 127.4, 130.4, 132.8, 135.8, 138.7 (pyrimidine C, $C_6H_5$), 161.7, 163.9, 165.5 (3C=O). MS (relative intensity) m/z: 328 ($M^+$, 15.7%). Calcd for $C_{13}H_{12}N_8O_3$ (328.29): C, 47.56; H, 3.68; N, 34.13%. Found: C, 47.31; H, 3.94; N, 34.37%.

Compound **25c**: Brown crystals from ethanol, yield 57%, 0.62 g, m.p. 218-220 ºC. IR (KBr): υ/cm$^{-1}$= 3444-3352 ($NH_2$, 4NH), 3057 (CH aromatic), 2761 (CH), 1682, 1670, 1663 (3CO), 1653 (C=N), 1647 (C=C). $^1$HNMR (DMSO) δ = 4.72 (s, 2H, $D_2O$-exchangeable, $NH_2$), 5.66 (s, 1H, imidazolidindione ring), 7.39-7.54 (d.d, 4H, $C_6H_4$), 8.38, 8.62, 8.88, 9.28 (4s, 4H, $D_2O$-exchangeable, 4NH). $^{13}$C NMR: δ = 54.8 (CH), 121.4, 123.6, 125.7, 128.5, 131.5, 133.9, 135.7, 139.5 (pyrimidine C, $C_6H_4$), 162.8, 164.7, 167.3 (3C=O). MS (relative intensity) m/z: 362 ($M^+$, 15.7%). Calcd for $C_{13}H_{11}ClN_8O_3$ (362.73): C, 43.05; H, 3.06; N, 30.89%. Found: C, 43.33; H, 3.34; N, 30.62%.

## Pharmacology

### *Analgesic activity*

Analgesic activity was introduced by the tail flick method (Fadeyi *et al*., 2004; Vogel, 2002). Healthy albino mice weighing 20.0 g to 30.0 g were divided into different groups with six animals in each group. The control group received a 0.5% w/v carboxymethylcellulose (CMC) solution and the treated groups were given a 132 µmol/kg orally dose of compounds **3**, **7**, **9a** ,**b**, **11**, **13a** ,**b**, **15**, **17a**, **b**, **19**, **21a**, **b**, **23a**, **b** and **25a**, **b**, **c**. The reaction times were noted at 2 h and 4 h intervals after drug administration. The percentage analgesic activity was calculated by the following formula:-

$$\text{Percentage analgesic activity} = T_2\text{-}T_1/T_1\times 100$$

where:- $T_1$ is the normal reaction time; $T_2$ is the reaction time after treatment.

### *Antipyretic activity*

Healthy Wistar rats were given s.c. 10mL/kg of a 20% aqueous suspension of sterilized brewer's yeast powder (Fadeyi *et al*., 2004; Vogel, 2002) weighting between 150 g and 200 g. Eighteen hours later, the animals showing an increase in rectal temperature greater than 0.5 ºC were selected. The control group received a 0.5% w/v carboxymethylcellulose solution and the treated groups received a of 132 µmol/kg dose of compounds **3**, **7**, **9a**, **b**, **11**, **13a**, **b**, **15**, **17a**, **b**, **19**, **21a**, **b**, **23a**, **b** and **25a**, **b**, **c**. Rectal temperatures were noted using digital thermometer 30 minute before (pretreated) and at 1 h, 2 h and 4 h after administration of the dose.

### Anti-inflammatory activity

The anti-inflammatory activity was examined using a hind paw edema method on albino rats of either six (Fadeyi *et al*., 2004; Vogel, 2002). A freshly prepared of carrageenan solution (0.1mL, 1%w/v) was injected into the sub-plantar surface of the right hind limb of each animal. The control group received a 0.5% w/v CMC solution and the treated groups were orally given a 132 µmol/kg dose of compounds **3**, **7**, **9a** ,**b**, **11**, **13a** ,**b**, **15**, **17a**, **b**, **19**, **21a**, **b**, **23a**, **b** and **25a**, **b**, **c** 30 minute before carrageenan. The volume of each paw was measured with a plethysmometer at 2 h and 4 h intervals after carrageenan injection. The percentage inhibition of edema was calculated by the following formula:

$$\text{Percentage inhibition of edema: } V_C\text{-}V_T/V_C\times 100$$

where: $V_C$ is the paw volume of control animal; $V_T$ is the paw volume of treated animals (standard /test compound).

## RESULTS AND DISCUSSION

This study was a continuation of our efforts aimed at the synthesis of new heterocyclic compounds with significant biological potential (El-Sharkawy *et al*., 2012; Mohareb, El-Sharkawy, Sherif, 2008). The goals of this work were to study the possibility of using compounds **2** and **3** in heterocyclic synthesis to produce the pyridopyrimidine derivative **7**; thiophene derivatives **9a**,**b**; coumarin derivative **11**; pyrimidine derivatives **13**,**15**,**17a**,**b**,**21a**,**b**; pyridine derivative **19**; pyrazole derivatives **23a**,**b** and iminopyrimidine derivatives **25a**,**b**,**c**, as well as biologically evaluate these compounds for analgesic, antipyretic and anti-inflammatory activities**.** The reaction of β-amino-α, γ-dicyanocrotono- nitrile (**1**) with 5-ureidohydantion (**2**) using triethylamine as catalyst produced compound **3**. The latter product underwent cyclization in the presence of piperidine. Four isomeric

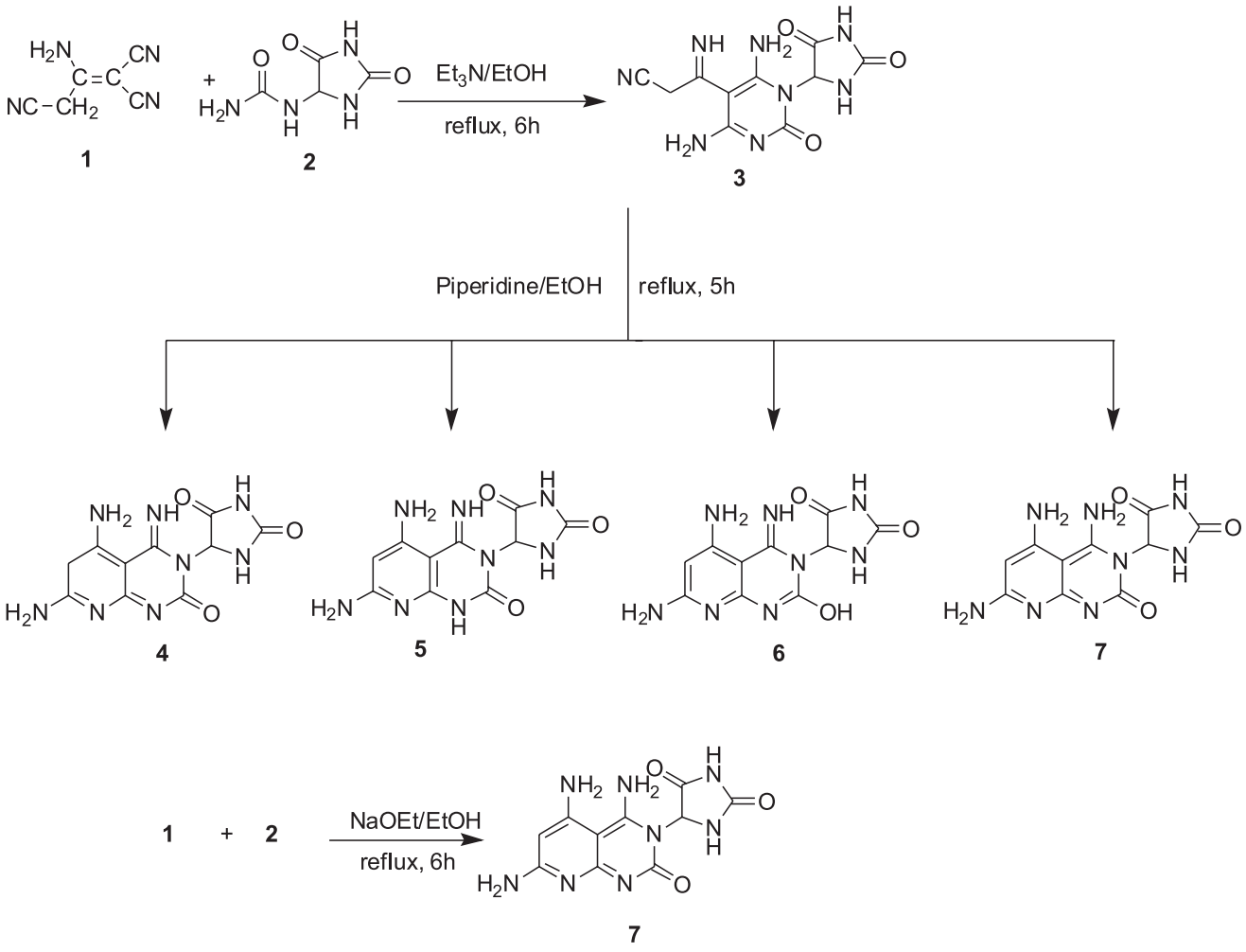


**FIGURE 1 -** Synthesis rout for compounds **3** and **7**.

structures were considered, including **4**,**5**,**6** and **7.** The $^{1}$HNMR spectral data showed that the final product contained three singlets at δ = 4.78, 4.93, 5.27 ppm and two singlets at δ = 8.73, 9.95 ppm which represented the presence of $3NH_2$ and 2NH groups, respectively; thus, the structures of compounds **4**,**5** and **6** were ruled out, as those latter structures only containing $2NH_2$ groups. Additionally, structure **6** contained an OH group which it was absent in the analytical and spectral data. In contrast, compound **7** was produced by another pathway, through the reaction of β-amino-α, γ-dicyanocrotononitrile (**1**) with 5-ureidohydantion (**2**) in the presence of sodium ethoxide directly. Compound **3** reacted with either cyclopentanone (**8a**) or cyclohexanone (**8b**) in the presence of elemental sulfur and trimethylamine afforded compounds **9a**,**b** respectively. The structures of compounds **9a**,**b** were verified by elemental analysis and spectral data. In compound **9a**, the $^{1}$HNMR spectrum indicated the presence of a multiplet at δ = 2.07-2.18 ppm which could be assigned to the $3CH_2$ groups; three singlets at δ = 4.54, 4.65, 5.81 ppm, which indicate the presence of $3NH_2$ groups; a singlet at δ = 5.98 ppm, which indicate the presence of 1H of an imidazolidindione ring and three singlets at δ = 8.52, 8.77, 9.12 ppm corresponding to 3NH groups. Coumarin derivative **11** was formed via the reaction of compound **3** with salicylaldehyde (**10**) and the structure of the compound was confirmed. The $^{1}$HNMR spectrum indicated the presence of two singlets at δ = 4.76, 5.25 ppm, which indicate the presence of $2NH_2$ groups; a singlet at δ = 5.53 ppm, which indicates the presence of an 1H of imidazolidindione ring; a singlet at δ = 6.73 ppm, which indicate the presence of a coumarin 1H; a multiplet at δ = 7.51-7.66 ppm corresponding to 4H of benzene ring; and three singlets at δ = 8.88, 9.28, 9.55 ppm, which indicate the presence of 3NH groups. Compound **3** was also reacted with aryldiazonium salts **12a**,**b** to afford arylhydrazono derivatives **13a**,**b** respectively. The elucidation of the structure for these compounds was then

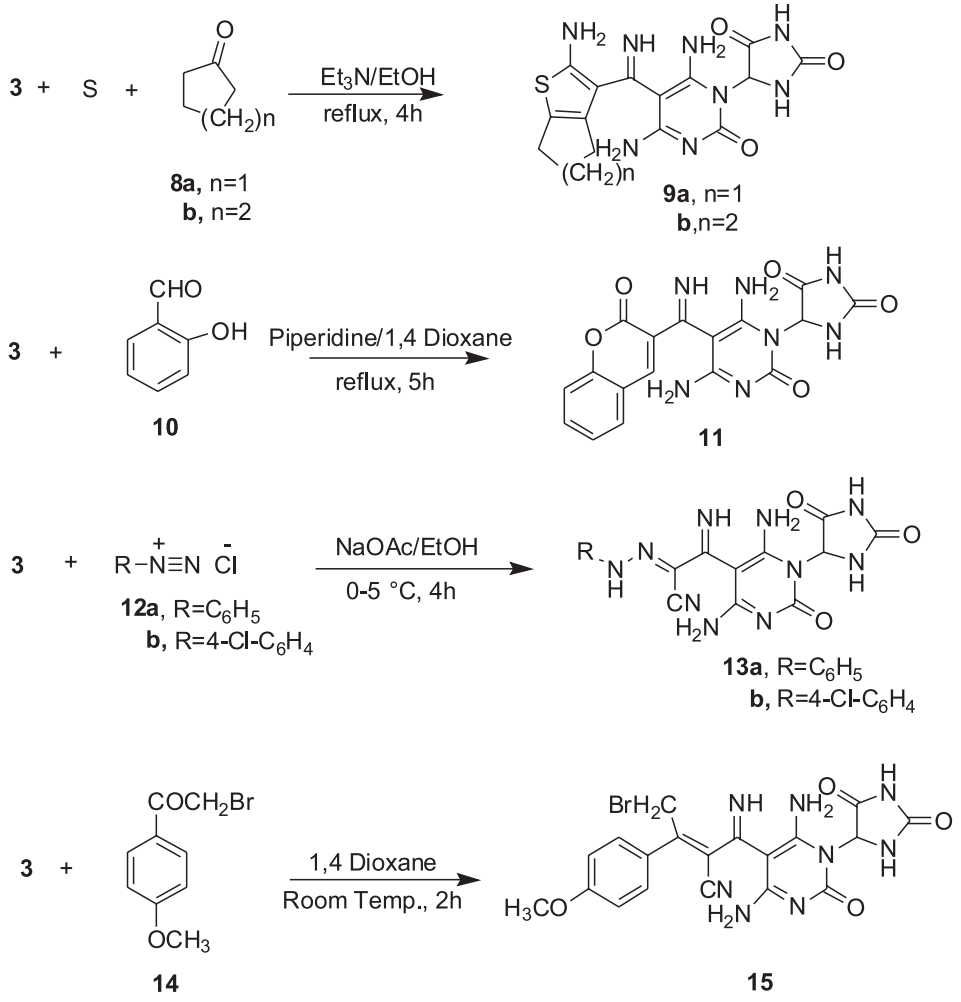


**FIGURE 2 -** Synthesis rout for compounds **9a**,**b**, **11**, **13a**,**b** and **15**.

confirmed. The $^1$HNMR spectrum for compound **13a** showed the presence of two singlets at δ = 4.54, 5.17 ppm, which indicate the presence of $2NH_2$ groups; a singlet at δ = 5.61 ppm, which indicates the presence of 1H of an imidazolidindione ring; a multiplet at δ = 7.31-7.62 ppm corresponding to 5H of benzene ring; and four singlets at δ = 8.76, 9.13, 9.38, 959 ppm which indicate the presence of 4NH groups.

The last reaction of compound **3**, was performed with ω-bromo-4-methoxyacetophenone (**14**), and the 4-methoxyphenylbutenyl derivative **15** was afforded. The elucidation of this structure was based on analytical and spectral data. Compound **15** was reacted with either potassium cyanide (**16a**) or potassium thiocyanate (**16b**) to form either the 4-methoxyphenylbutenyl cyanide derivative **17a** or 4-methoxyphenylbutenyl thiocyanide derivative **17b**, respectively. The structures of compounds **17a**,**b** were verified by analytical and spectral data. Compound **17a** underwent a cyclization in presence of sodium ethoxide to afford pyridine derivative **19** via formation of intermediate **18**. The structure of compound **19** was then confirmed. The $^1$HNMR spectrum of compound **19** detected the presence of singlet at δ = 3.68 ppm, which indicates the presence of 3H of $CH_3$ group; three singlets at δ = 4.38, 4.93 5.33 ppm, which indicate the presence of $3NH_2$ groups; a singlet at δ = 5.77 ppm, which indicates the presence of 1H of imidazolidindione ring; a singlet at δ = 7.14 ppm which indicates the presence of 1H of pyridine ring; a doublet of doublets at δ = 7.28-7.49 ppm corresponding to 4H of benzene ring and two singlets at δ = 8.41, 8.82 ppm, which indicate the presence of 2NH groups. Compound **15** was reacted with either hydrazine hydrate (**20a**) or phenyl hydrazine (**20b**) to produce hydrazono derivatives **21a,b**, respectively. The structures of these compounds were confirmed by analytical and spectral data. The latter products underwent a cyclization to form pyrrole derivatives **23a**,**b** through the intermediate formation of **22a**,**b**, respectively. The structures of compounds **23a**,**b** were confirmed using analytical and spectral data. The $^1$HNMR spectrum of compound **23a**

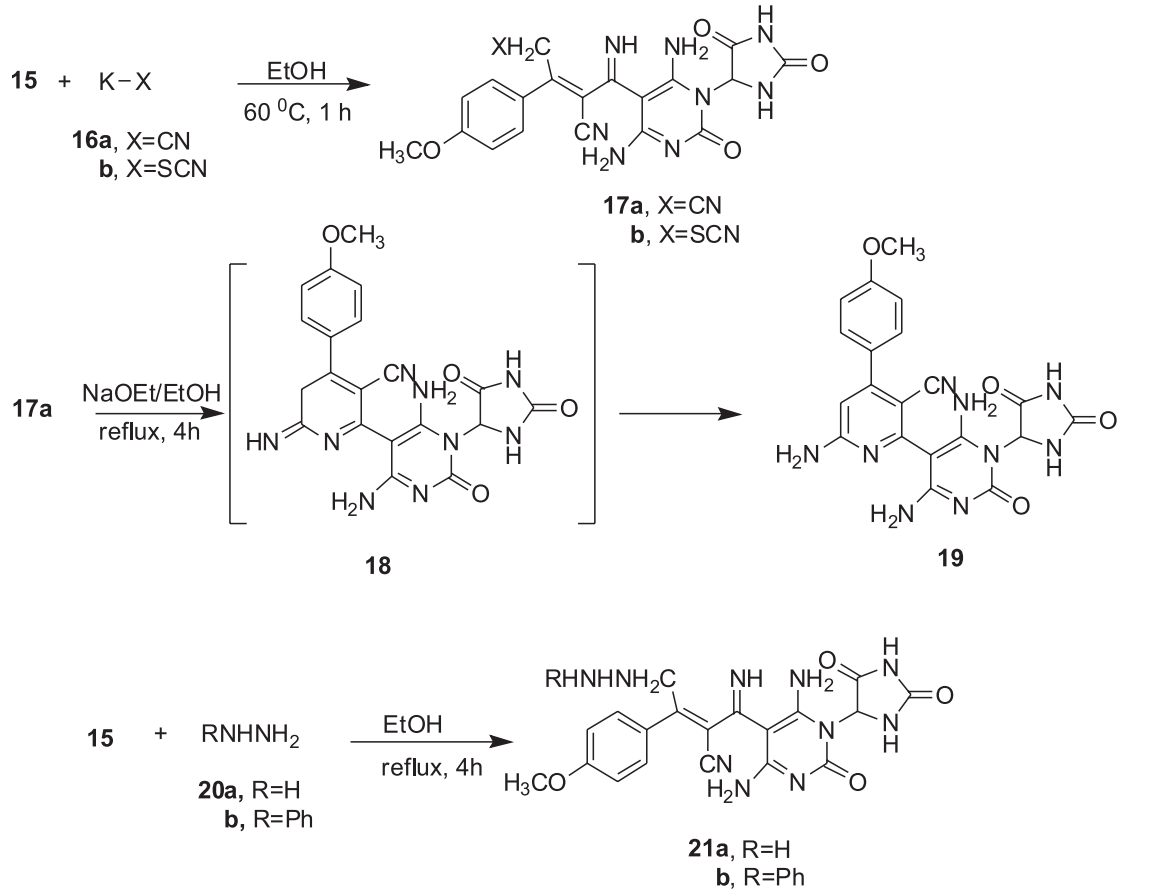


**FIGURE 3 -** Synthesis rout for compounds **17a**,**b**, **19** and **21a**,**b**.

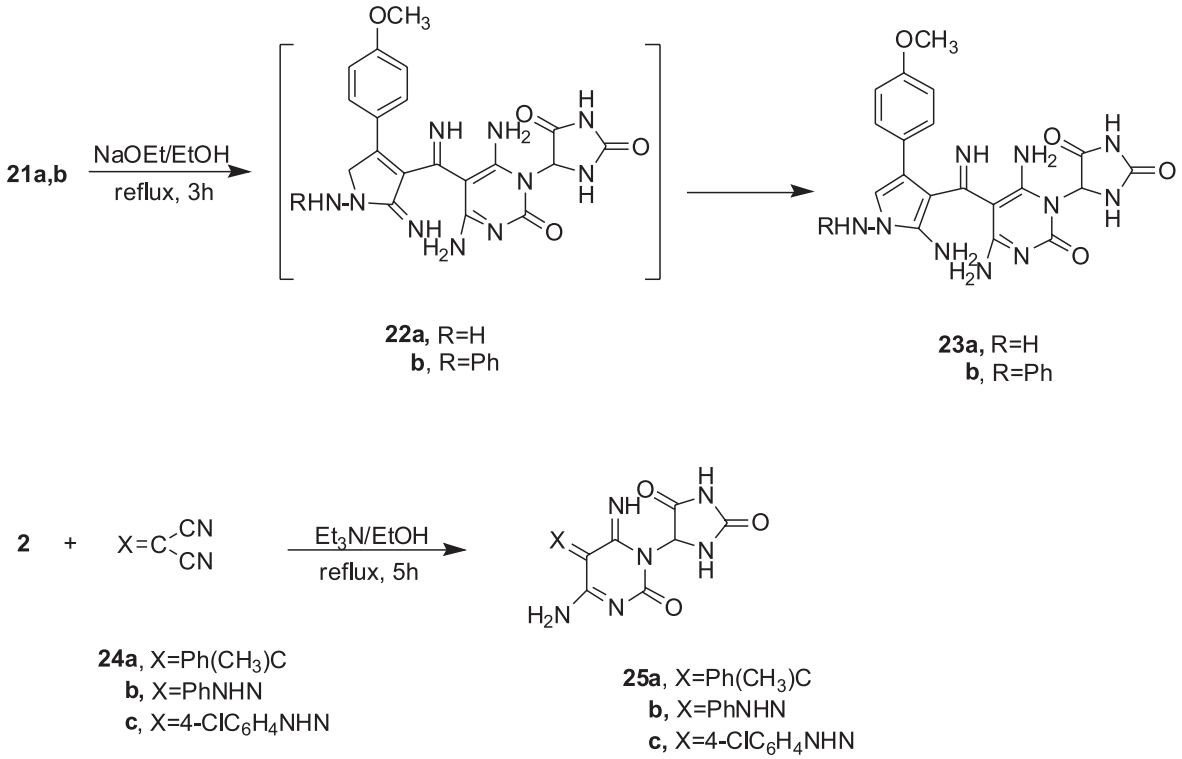


**FIGURE 4 -** Synthesis rout for compounds **23a**,**b** and **25a**,**b**,**c**.

detected the presence of a singlet at δ = 3.27 ppm, which indicates the presence of 3H from a $CH_3$ group; four singlets at δ = 4.38, 4.59, 4.95, 5.23 ppm, which indicate the presence of $4NH_2$ groups; a singlet at δ = 5.63 ppm, which indicates the presence of 1H of imidazolidindione ring; a multiplet at δ = 6.95-7.28 ppm corresponding to 4H of benzene ring and 1H of pyrrole ring and three singlets at δ = 8.51, 8.77, 9.38 ppm, which indicate the presence of 3NH groups. Finally 5-ureidohydantion (**2**) was reacted with compounds **24a**,**b**,**c** to produce iminopyrimidine derivatives **25a**,**b**,**c**, respectively and the structure of these compounds were confirmed by analytical and spectral data.

All the synthesized compounds were evaluated for their *in vitro* analgesic, antipyretic and anti-inflammatory activities. Acetaminophen was used as a reference standard drug. Based on the results from (Tables I and II), it is clear that compounds **11** and **19** showed promising actions as analgesic and antipyretic agents. This may be due their containing a coumarin moiety and 4-methoxyphenylpyridine moiety, respectively. In contrast, compounds **7**, **9a**, **b**, **13a**, **b** showed moderate analgesic and antipyretic effects. The remaining compounds **3**, **15**, **17a**, **b**, **21a**, **b**, **23a**, **b**, **25a**, **b**, **c** exhibited poor analgesic and antipyretic effects. Compound **11** exhibited high significance as an anti-inflammatory agent, which may be due to the presence of the coumarin moiety. Compounds **7**, **9b**, **13b**, **19** were considered as moderate anti-inflammatory effects. The remaining compounds **3**, **9a**, **13a**, **15**, **17a**, **b**, **21a**, **b**, **23a**, **b**, **25a**, **b**, **c** exhibited poor biological significance as anti-inflammatory agents (Table III).

**TABLE I** - Analgesic activities of the synthesized compounds

| Comp. No | Normal reaction time (sec) | Change in reaction time (sec) ± SEM | | % Analgesic activity ± SD | |
|---|---|---|---|---|---|
| | | 2 h | 4 h | 2 h | 4 h |
| **Control** | 2.80±0.15 | 0.20±0.014 | 0.25±0.018 | 7.09±1.45 | 9.05±0.87 |
| **3** | 2.20±0.09 | 3.21±0.15 | 2.25±0.08 | 113.1±1.57 | 89.76±2.23 |
| **7** | 2.35±0.08 | 3.24±0.10 | 2.35±0.07 | 115.4±1.38 | 94.53±0.44** |
| **9a** | 2.60±0.07 | 3.20±0.08 | 2.33±0.06 | 129.1±1.65 | 95.24±1.53** |
| **9b** | 2.57±0.07 | 3.17±0.09 | 2.36±0.05 | 131.3±1.58 | 92.56±1.38** |
| **11** | **2.38±0.08** | **3.18±0.08** | **2.43±0.03** | **125.1±1.68** | **97.56±0.55*****|
| **13a** | 2.56±0.06 | 3.22±0.11 | 2.38±0.04 | 133.6±1.76 | 95.84±2.05** |
| **13b** | 2.48±0.06 | 3.21±0.08 | 2.29±0.07 | 136.4±1.48 | 94.11±0.43** |
| **15** | 2.53±0.08 | 3.32±0.15 | 2.42±0.08 | 140.5±1.54 | 84.82±1.23 |
| **17a** | 2.16±0.07 | 3.33±0.19 | 1.96±0.05 | 145.6±1.64 | 86.52±1.18 |
| **17b** | 2.36±0.12 | 3.48±0.12 | 2.21±0.03 | 138.8±1.98 | 89.33±2.66 |
| **19** | **2.20±0.11** | **3.15±0.07** | **2.40±0.06** | **119.5±1.45** | **96.5±0.25***** |
| **21a** | 2.25±0.09 | 3.44±0.13 | 2.25±0.08 | 147.1±1.77 | 90.5±1.46 |
| **21b** | 3.15±0.06 | 3.38±0.14 | 2.05±0.07 | 144.3±1.48 | 103.55±1.53 |
| **23a** | 2.60±0.12 | 3.47±0.18 | 1.98±0.07 | 141.1±1.88 | 92.4±2.36* |
| **23b** | 2.50±0.12 | 3.31±0.13 | 1.96±0.06 | 112.3±1.93 | 90.9±0.95* |
| **25a** | 2.75±0.09 | 3.34±0.16 | 2.15±0.08 | 117.3±1.73 | 89.5±1.65 |
| **25b** | 2.80±0.08 | 3.38±0.17 | 2.22±0.05 | 113.1±2.00 | 104.2±2.44 |
| **25c** | 2.65±0.06 | 3.39±0.15 | 2.18±0.06 | 108.3±1.43 | 88.7±2.98 |
| Ref. Standard (Acetaminophen) | 2.50±0.10 | 3.10±0.05 | 2.5±0.03 | 128.6±1.75 | 103.6±1.58*** |

Note: The reaction time value is the mean ± SEM (n=6). Statistical analysis was performed with the student's unpaired t-test (Kulkarni, 2003). *p < 0.05, **p < 0.01 and ***p < 0.001, 132 μmol/kg dose.

**TABLE II** - Antipyretic activities of the synthesized compounds

| Comp. No | Before drug (°C) | | After drug (°C) | | |
|---|---|---|---|---|---|
| | -18 h | 0.0 h | 1 h | 2 h | 4 h |
| **Control** | 37.47±5.68 | 38.22±0.05 | 38.08±0.08 | 38.04±0.05 | 37.83±0.5 |
| **3** | 37.35±0.05 | 38.17±0.75 | 37.88±0.07 | 37.58±0.08 | 37.33±0.05 |
| **7** | 37.41±0.05 | 38.38±0.05 | 38.12±0.05 | 37.55±0.06 | 37.28±0.05** |
| **9a** | 37.36±0.04 | 38.33±0.06 | 37.95±0.08 | 37.65±0.07 | 37.32±0.05** |
| **9b** | 37.32±0.05 | 38.35±0.06 | 38.14±0.07 | 37.54±0.08 | 37.26±0.05** |
| **11** | **37.23±0.09** | **38.40±0.08** | **37.93±0.06** | **37.63±0.05** | **37.44±0.06*****|
| **13a** | 37.40±0.05 | 38.37±0.05 | 38.25±0.08 | 37.55±0.06 | 37.31±0.05** |
| **13b** | 37.44±0.06 | 38.39±0.05 | 37.98±0.06 | 37.38±0.08 | 37.27±0.05** |
| **15** | 37.36±0.06 | 38.34±0.05 | 38.08±0.07 | 37.88±0.06 | 37.45±0.05 |
| **17a** | 37.34±0.06 | 38.37±0.08 | 38.05±0.08 | 37.68±0.07 | 37.39±0.03 |
| **17b** | 37.44±0.05 | 38.39±0.08 | 38.18±0.06 | 37.91±0.05 | 37.58±0.07 |
| **19** | **37.28±0.04** | **38.31±0.07** | **38.05±0.07** | **37.60±0.05** | **37.37±0.04***** |
| **21a** | 37.30±0.06 | 38.27±0.35 | 37.95±0.08 | 37.58±0.07 | 37.31±0.05 |
| **21b** | 37.43±0.08 | 38.41±0.45 | 38.12±0.07 | 37.74±0.08 | 37.47±0.02 |
| **23a** | 37.39±0.08 | 38.44±0.53 | 38.19±0.08 | 37.87±0.05 | 37.55±0.04* |
| **23b** | 37.31±0.07 | 38.39±0.06 | 38.10±0.07 | 37.64±0.05 | 37.42±0.07* |
| **25a** | 37.29±0.06 | 38.32±0.07 | 38.04±0.07 | 37.34±0.09 | 37.18±0.09 |
| **25b** | 37.35±0.05 | 38.38±0.07 | 37.85±0.08 | 37.85±0.06 | 37.46±0.09 |
| **25c** | 37.44±0.08 | 38.44±0.35 | 37.92±0.07 | 37.92±0.05 | 37.42±0.08 |
| Ref. Standard (Acetaminophen) | 37.18±0.07 | 37.88±0.05 | 37.72±0.04 | 37.41±0.04 | 37.20±0.05*** |

Note: The reaction time value is the mean ± SEM (n=6). Statistical analysis was performed with student's unpaired t-test (Kulkarni, 2003). *p < 0.05, **p < 0.01 and *** p < 0.001, 132 µmol/kg dose.

## CONCLUSIONS

In this article, the synthesized pyrimidines **3**, **7**, **13a**,**b**, **15**, **17a**,**b**, **21a**,**b**, **25a**, **b**, **c**; thiophenes **9a**, **b**; coumarin **11**, pyridine **19** and pyrroles **23a**, **b** were evaluated as analgesic, antipyretic and anti-inflammatory agents compared to the reference standard drug acetaminophen. Among the newly synthesized compounds, compounds **11** and **19** showed promising significant analgesic and antipyretic activities compared to the other compounds. Additionally compounds **7**, **9a**,**b** and **13a**,**b** had moderately significant analgesic and antipyretic activities. Moreover, compound **11** had clear anti-inflammatory properties compared to the remaining compounds.

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**TABLE III** - Anti-inflammatory activities of the synthesized compounds

| Comp. No | Change in reaction time (sec)±SEM | | % Anti-inflammatory activity±SD | |
|---|---|---|---|---|
| | 2 h | 4 h | 2 h | 4 h |
| **Control** | 1.29±0.01 | 1.32±0.007 | | |
| **3** | 0.83±0.01 | 0.80±0.01 | 34.56±3.38 | 35.78±3.52 |
| **7** | 0.82±0.02 | 0.83±0.01 | 31.34±2.87 | 33.59±2.26** |
| **9a** | 0.82±0.01 | 0.85±0.01 | 32.44±2.55 | 34.23±2.68 |
| **9b** | 0.81±0.03 | 0.82±0.01 | 31.12±3.51 | 34.19±3.07** |
| **11** | **0.82±0.02** | **0.84±0.01** | **29.34±2.97** | **32.08±2.05***** |
| **13a** | 0.81±0.01 | 0.85±0.01 | 32.56±3.08 | 33.38±3.17 |
| **13b** | 0.83±0.03 | 0.84±0.01 | 32.34±2.26 | 35.27±2.02** |
| **15** | 0.84±0.02 | 0.81±0.01 | 27.88±2.66 | 32.17±1.87 |
| **17a** | 0.83±0.02 | 0.86±0.01 | 34.23±3.44 | 37.18±3.25 |
| **17b** | 0.86±0.01 | 0.87±0.01 | 35.56±3.14 | 36.34±1.48 |
| **19** | 0.81±0.01 | 0.83±0.01 | 30.34±3.24 | 34.03±2.53** |
| **21a** | 0.83±0.03 | 0.85±0.01 | 26.23±2.57 | 29.28±1.38 |
| **21b** | 0.85±0.01 | 0.81±0.01 | 35.39±3.28 | 37.31±1.93 |
| **23a** | 0.84±0.02 | 0.88±0.01 | 34.18±2.73 | 35.98±3.02 |
| **23b** | 0.78±0.02 | 0.82±0.01 | 33.85±3.27 | 35.58±2.17 |
| **25a** | 0.83±0.02 | 0.80±0.01 | 33.37±3.26 | 36.18±1.59 |
| **25b** | 0.79±0.01 | 0.83±0.01 | 32.94±2.62 | 35.42±3.46 |
| **25c** | 0.83±0.03 | 0.87±0.01 | 34.23±3.17 | 36.14±1.83 |
| Ref. Standard (Acetaminophen) | 0.83±0.01 | 0.84±0.01 | 28.83±3.05 | 32.82±1.33*** |

Note: The reaction time value is the mean ± SEM (n=6). Statistical analysis was performed with student's unpaired t-test (Kulkarni, 2003). *p < 0.05, **p < 0.01 and *** p < 0.001, 132 μmol/kg dose.

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