BJPS

Brazilian Journal of Pharmaceutical Sciences

http://dx.doi.org/10.1590/s2175-97902018000400153

Article

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

Karam Ahmed El-Sharkawy,[1,2]* Mohammed Mofreh AlBratty,[1] Hassan Ahmad Alhazmi[1]

[1]Department of Pharmaceutical Chemistry, College of pharmacy, Jazan University, Jazan 45142, Saudi Arabia, [2]Department of Chemistry, Faculty of Biotechnology, October University for Modern Sciences and Arts(MSA), Egypt

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

***Correspondence:** K. A. El-Sharkawy. Department of Pharmaceutical Chemistry, College of Pharmacy, Jazan University. P.O. Box 114, Jazan 45142, Saudi Arabia. Phone: 00201010698361, 0966559686517 / Fax: 00238371543. E-mail: karamsyn@yahoo.com

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

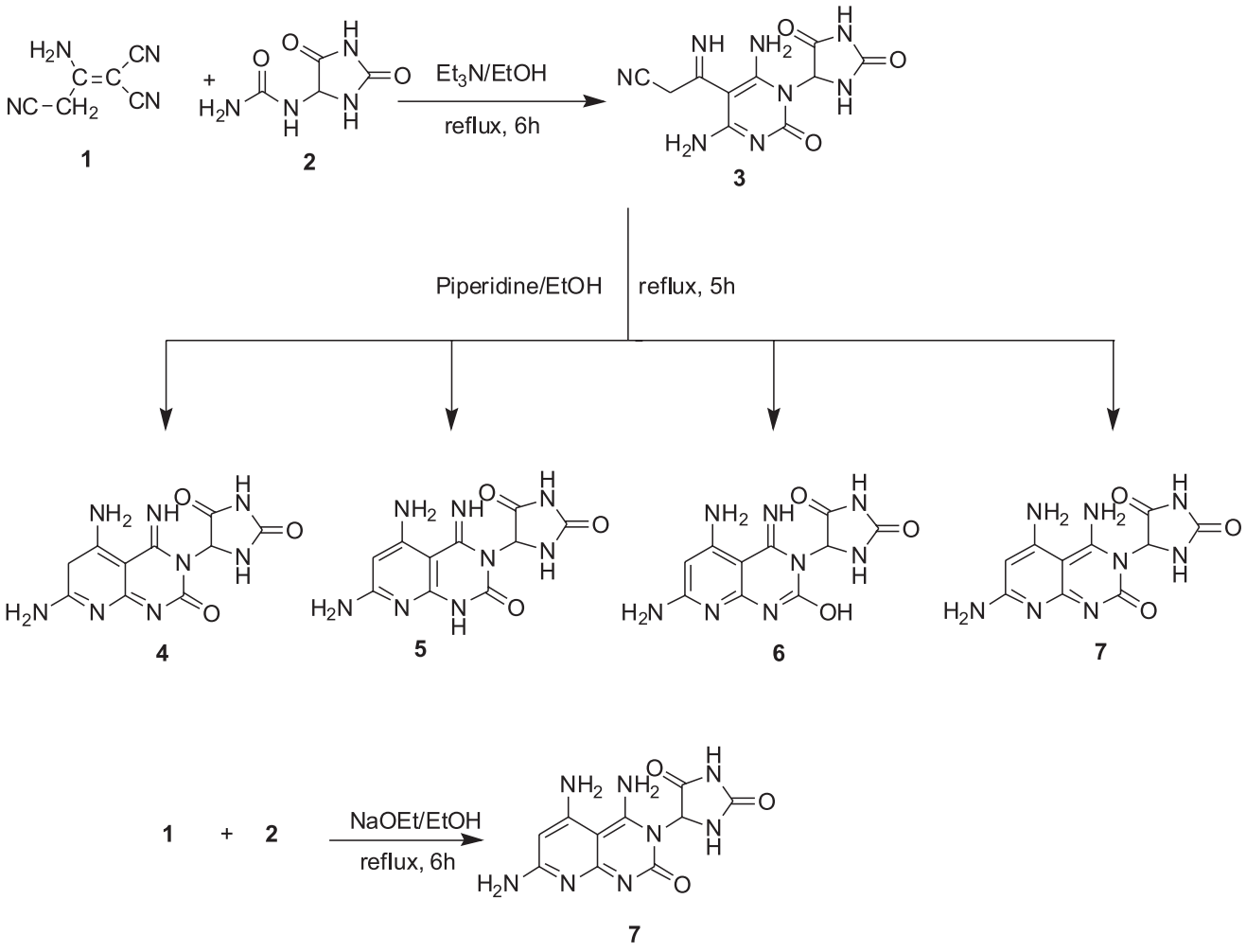

FIGURE 1 - Synthesis rout for compounds **3** and **7**.

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

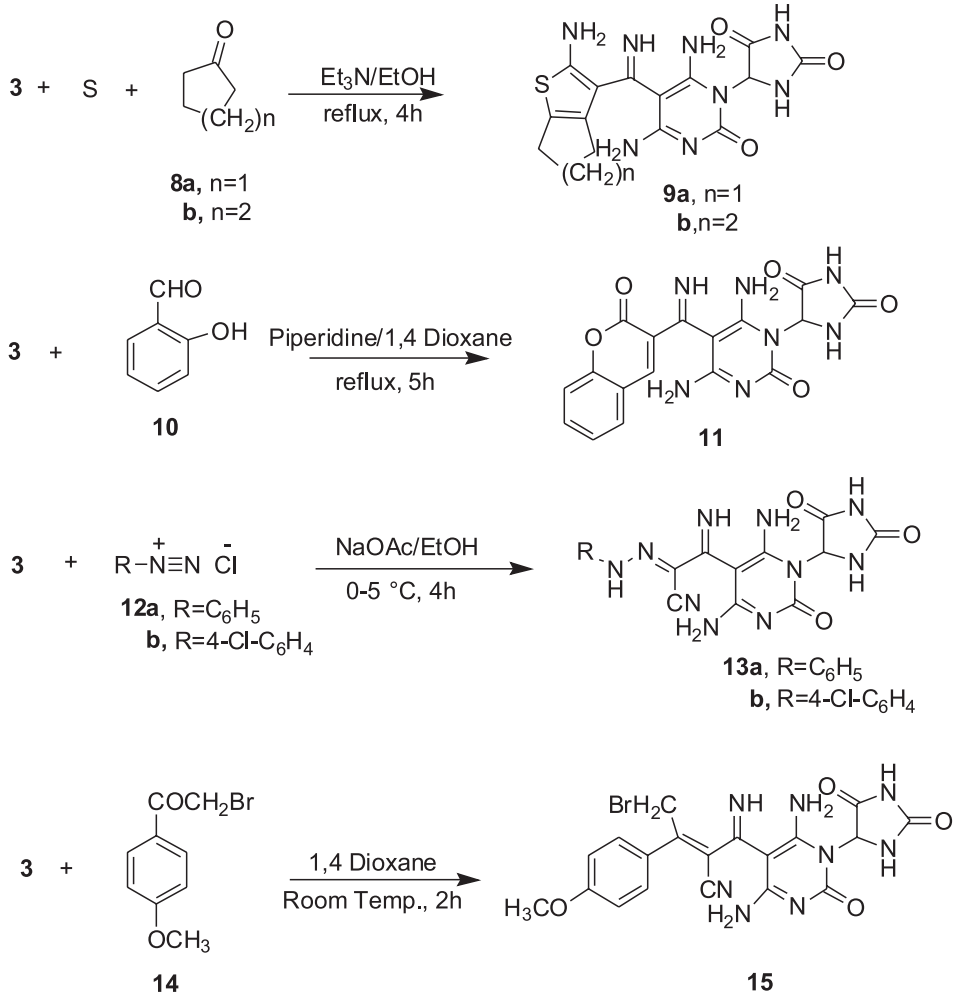

FIGURE 2 - Synthesis rout for compounds **9a**,**b**, **11**, **13a**,**b** and **15**.

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**

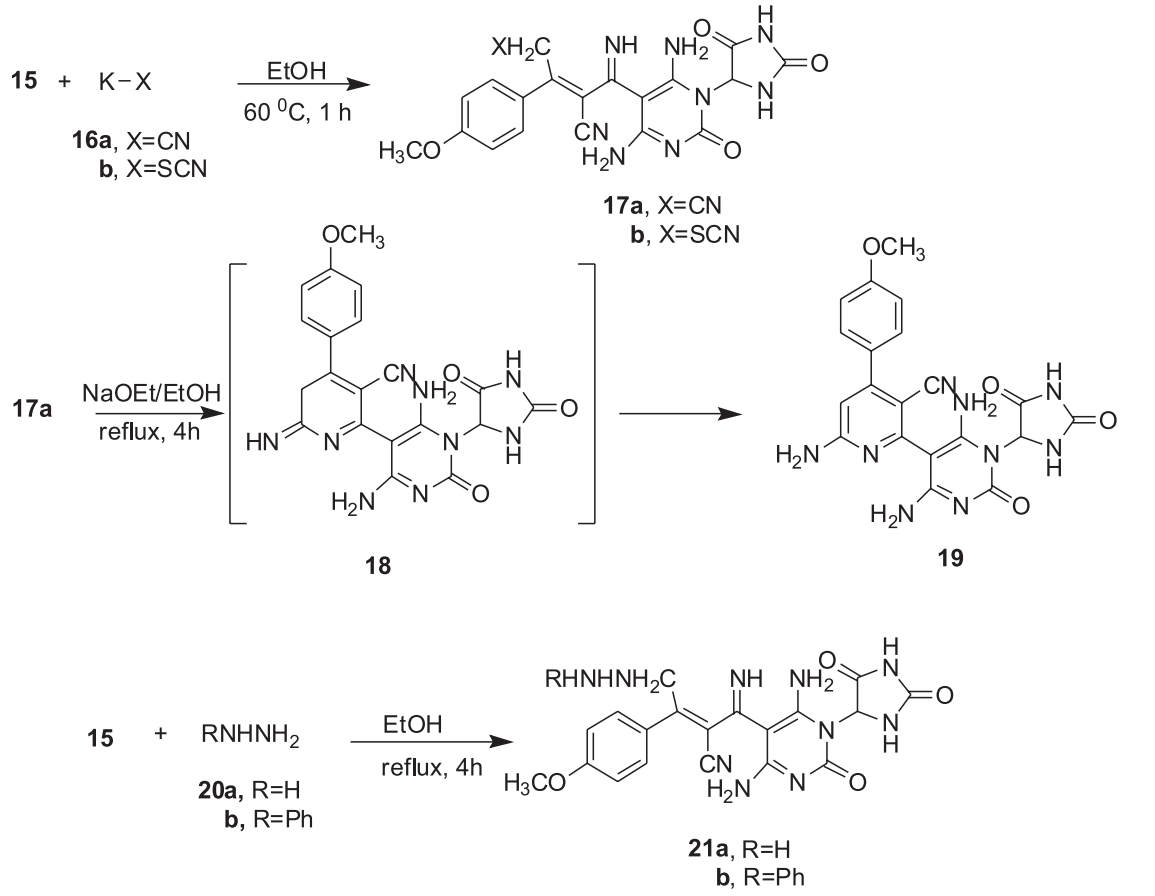

FIGURE 3 - Synthesis rout for compounds **17a**,**b**, **19** and **21a**,**b**.

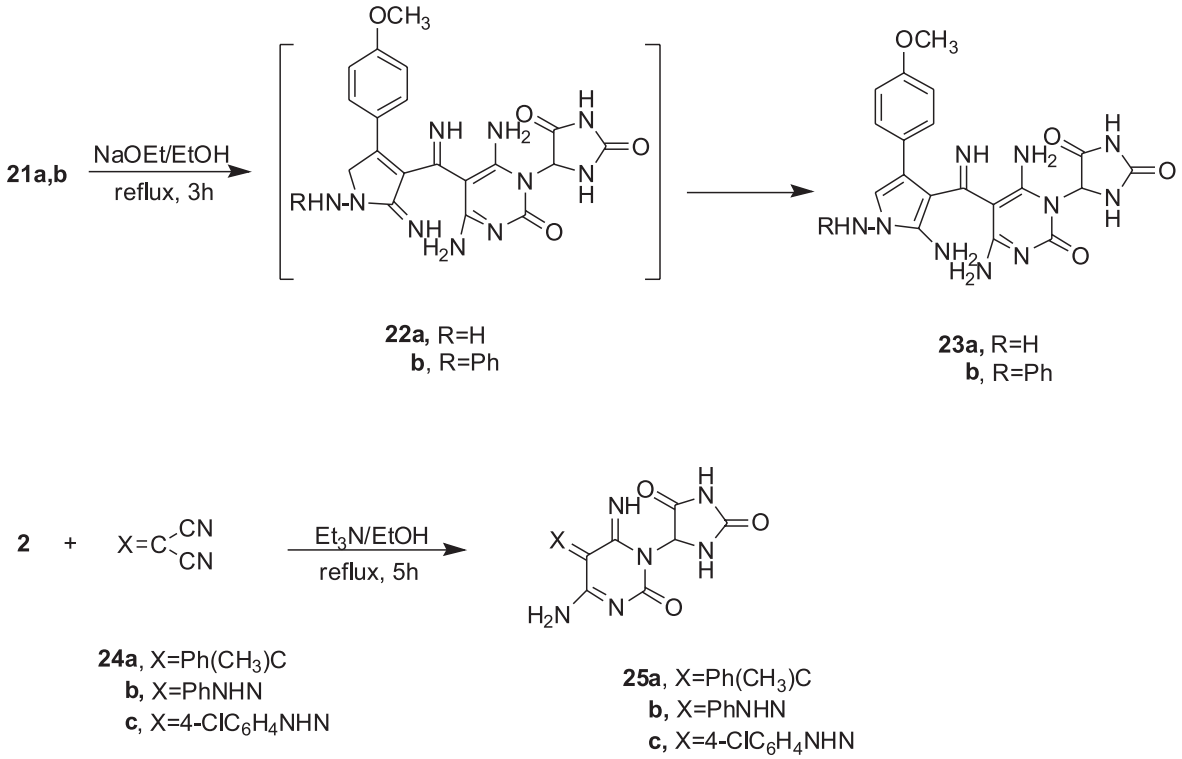

FIGURE 4 - Synthesis rout for compounds **23a**,**b** and **25a**,**b**,**c**.

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.

ACKNOWLEDGEMENTS

The authors would like to thank the research group working in the Pharamacology Depatment, Faculty of Pharmacy, October University for Modern Sciences and Arts. We would also like to thank the Poison Control and Medical Forensic Chemistry Center team from Jazan Health, Jazan City, Kingdom of Saudi Arabia for recording the analytical and spectral data for the newly synthesized compounds.

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.

REFERNCES

Agarwal A, Ashutosh R, Goyal N, Chawhan PMS, Gupta S. Dihydropyrido [2,3-*d*]pyrimidines as a new class of antileishmanial agents. Bioorg Med Chem. 2005;13(24):6678-6684.

Dallemagne P, Khanh LP, Alsaidi A, Varlet I, Collot V, Paillet M, Bureau R, Rault S. Synthesis and biological evaluation of five-Membered heterocycles fused to cyclopenta*[c]*thiophene as new antitumor agents. Bioorg Med Chem. 2003;11(7):1161-1167.

El-Sharkawy KA, Nasser NE, Zaki MY. Uses of 2-Amino-5, 6-dihydro-4*H*-cyclopenta [*b*] thiophene-3-carbonitrile in the synthesis of novel heterocyclic compounds with anticonvulsant, behavioral and CNS antidepressant activities. Int Res J Pure App Chem. 2012;2(1):91-104.

Fadeyi OO, Obafemi CA, Adewunmi CO, Iwalewa EO. Antipyretic, analgesic, anti-inflammatory and cytotoxic effects of four derivatives of salicylic acid and anthranilic acid in mice and rats. Afr J Biotech. 2004;3(8):426-431.

Gus'Kov EP, Prokofev VN, Kletskii ME, Kornienko IV, Ogapurenko A, Olekhnovich LP, Chistyakov VA, Shestopalov AV, Sazykina MA. Allantoin as a vitamin. Dokl Biochem Biophys. 2004;398:320-324.

Horvati K, Bacasa B, Szabo N, Fodor K, Balaka G, Rusavai M, Kiss É, Mezo G, Grolmusz V, Vertessy B, Hudecz F, Bosze S. Antimycobacterial activity of peptide conjugate of pyridopyrimidine derivative against Mycobacterium tuberculosis in a series of *in vitro* and *in vivo* models. Tuberculosis. 2015;95(Suppl 1):S207-S211.

Iqbal Z, Hameed S, Ali S, Tehseen Y, Shahid M, Iqbal J. Synthesis, characterization, hypoglycemic and aldose reductase inhibition activity of arylsulfonylspiro[fluorene-9,5′-imidazolidine]-2′,4′-diones. Eur J Med Chem. 2015;98:127-138.

Keri RS, Hosamani KM, Shingalapure RV, Hugar MH. Analgesic, anti-pyretic and DNA cleavage studies of novel pyrimidine derivatives of coumarin moiety. Eur J Med Chem. 2010;45(6):2597-2605.

Kulkarni SK. Handbook of Experimental Pharmacology. 3 ed. Delhi: Vallabh Prakashan; 2003. P. 123-125; 128-131; 172-186.

Mohareb R, El-Sharkawy KA, Sherif SM. The reaction of β-amino-α,γ-dicyano -crotononitrile with acetophenone: Synthesis of pyridine, pyridazine and thiophene derivatives with antimicrobial activities. Acta Pharm. 2008;58:429-444.

Padmavathi V, Prema Kumari C, Venkatesh BC, Padmaja A. Synthesis and antimicrobial activity of amido linked pyrrolyl and pyrazolyl-oxazoles, thiazoles and imidazoles. Eur J Med Chem. 2011;46(11):5317-5326.

Rajesh SM, Kumar RS, Libertsen LA, Perumal S, Yogeeswari P, Sriram D. A green expedient synthesis of pyridopyrimidine-2-thiones and their antitubercular activity. Bioorg Med Chem Lett. 2011;21(10):3012-3016.

Reddy YT, Reddy PN, Kodru S, Damodran C, Crooks PA. Aplysinopsin analogs: Synthesis and anti-proliferative activity of substituted (Z)-5-(N-benzylindol-3-ylmethylene) imidazolidine-2,4-diones. Bioorg Med Chem. 2010;18(10):3570-3574.

Sztanke M, Rzymowska J, Sztanke K. Synthesis, structure elucidation and *in vitro* anticancer activities of novel derivatives of diethyl (2*E*)-2-[(2*E*)-(1-aryl- imidazolidin-2-ylidene) hydrazono]succinate and ethyl (4-oxo-8-aryl-4,6,7,8-tetra-hydroimidazo[2,1-*c*][1,2,4]triazin-3-yl)acetate. Bioorg Med Chem. 2013;21(23):7465-7480.

Vogel HG. Drug discovery and evaluation. Pharmacological assay. 2 ed. Berlin, Heidelberg: Springer-Verlag; 2002. p. 695-696; 759-762; 772-773.

Wang G, Wang Y, Wang L, Han L, Hou X, Fu H, Fang H. Design, synthesis and preliminary bioactivity studies of imidazolidine-2,4-dione derivatives as Bcl-2 inhibitors. Bioorg Med Chem. 2015;23(23):7359-7365.

Received for publication on 16th October 2016
Accepted for publication on 09th January 2018