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SYNTHESIS OF NEW PYRIMIDINE DERIVATIVES WITH EVALUATION OF THEIR ANTI-INFLAMMATORY AND ANALGESIC ACTIVITIES

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Abstract: 5-Formyl-6-aminopyrimidine-2,4-(1H, 3H)-dione (**2**) has been previously prepared from compound **1**. Cyclocondensation reaction of compound **2** with cyanoacetamide gave substituted pyridopyrimidine **3**. Also, compound **2** was condensed with p-amino acetophenone and hydrazine derivatives to give 5-{[(4-acetylphenyl)imino]methyl}-6-aminopyrimidine (**4**) and 5-substituted carboaldehyde-6-amino pyrimidine derivatives (**5a-d**), respectively. Moreover, cyclocondensation reaction of compound **2** with thiosemcarbazide and semicarbazide hydrochloride gave 5-(5-thioxo or oxo-triazol-3-yl)-6-amino pyrimidine (**6**) and (**7**), respectively. Cyclocondensation reaction of compound **2** with thiourea and ethyl acetoacetate led to the formation of substituted ethyl bipyrimidine-5-carboxylate **8**. Also, compound **2** was reacted with acetoacetic acid hydrazide and 2-cyanoacetohydrazide to give 5-(acetylpyrazol-6-aminopyrimidine **9** and 3-(6-aminopyrimidine-5-yl) pyrazole-4-carboxamide **10**, respectively. Furthermore, compound **1** was diazotized to afford the diazonium salt **11**. Its coupling with ethyl acetoacetate, ethyl cyanoacetate, acetylacetone, malononitrile, cyanoacetamide, diethylmalonate, in sodium acetate buffered solution afforded substituted hydrazonopyrimidines: ethylhydrazono-3-oxobutanoate **12**, ethylhydrazono-3-oxopropanoate **13**, pentane-2,3,4-trione hydrazone **14**, cyanohydrazonoacetamide **15**, diazenyl malonamide **16** and diethylhydrazonomalonate **17**, respectively. Moreover, substituted pyrazolediazenylpyrimidine derivatives **18a**,**b**, **19a**,**b**, **20**, **21a-c**, **22** were synthesized by the cyclization of substituted hydrazonopyrimidines **12**, **17**, **15**, **14** and **13**, respectively. The analgesic and anti-inflammatory activities of some of the synthesized compounds were evaluated. Compounds **C18a**, **C20**, **C21b** and **C22** showed the most significant analgesic effects among synthesized moieties. All tested compounds, nonetheless, **C18b** showed significant anti-inflammatory effect in carrageenan induced paw edema model.

Keywords: pyrimidine derivatives, cyclization, diazo-coupling reaction, condensation reaction, anti-inflammatory, analgesic activities

Selective cyclooxygenase-2 (COX-2) inhibitors are a new kind of non-steroidal anti-inflammatory drugs (NSAIDs). Due to their excellent therapeutic effect on the treatment or alleviation of inflammation such as osteoarthritis (OA) and rheumatoid arthritis (RA) with little side effects to gastrointestinal tract, there is an increasing interest in the research and development of selective COX-2 inhibitors (1). In recent years, as some NSAIDs including selective COX-2 inhibitors have been shown to be associated with cardiovascular events, it has become a great challenge to explore novel NSAIDs with reduced gastrointestinal tract and cardiovascular side effects (2). Some imidazo[1,2-a]pyrimidine compounds have been reported to have significant anti-inflammatory and analgesic action in experimental animal models (3–5). Pyrazole and pyrimidine derivatives attracted organic chemists very much due to their biological and chemotherapeutic importance (6). Pyrimidines represent a broad class of compounds, which have received considerable attention due to their wide range of biological activities (7). Several patents have been reported on the preparation of these heterocycles, derivatives of which are useful as bronchodilators, vasodilators, antiallergic, antihypertensive (8), anti-inflammatory, and anticancer agents (9). In fact, there are many pyrimidine derivatives with pharmacological activities (10).The pyrazole ring has attracted great attention as it has become fairly accessible and it shows diverse properties (11). Pyrazole based derivatives have shown several biological activities as seen in COX-2 inhibitors (12). We perceived that when two moieties, such as pyrazole and pyrimidine are joined

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the new molecules might exhibit superior anti-inflammatory activity. With this idea in mind the present work was undertaken.

EXPERIMENTAL

All melting points are uncorrected and were determined in capillary tubes in Gallenkamp apparatus. IR spectra were recorded on a Beckman infrared spectrophotometer PU9712 using KBr discs. The ^{1}H-NMR spectra were obtained on Joel EX270, 500 MHz spectrometer using TMS as an internal standard. Mass spectra were recorded on Finnigan SSQ7000 mass spectrometer at 70 eV. All reactions were followed and checked by TLC using chloroform / methanol (9:3) as a mobile phase and spots were examined by UV lamp. The compounds throughout this work were named according to the IUPAC system using Chem Draw Ultra computer program version 8.

7-Amino-2,4-dioxo-1,2,3,4-tetrahydropyrido[2,3-d]pyrimidine-6-carboxamide (3)

A mixture of compound **2** (0.155 g, 0.001 mol) and cyanoacetamide (0.001 mol) in glacial acetic acid (5 mL) was refluxed for two days. The solid formed was filtered off, and recrystallized from pyridine to give compound **3**.

Yield 64%, m.p. 330^{o}C. IR (KBr, cm^{-1}): 3440.11, 3342.56, 3145.55 (NH, NH_2), 1710.43 (2 CO), 1642.83 (CO amide), 1558.95 (C=N, C=C). ^{1}H-NMR (DMSO-d_6, δ, ppm): 6.00 (br.s, 2H, NH_2, exchangeable with D_2O), 7.85 (s, 1H, CH of pyridine ring), 9.20 (s, 2H, NH_2CO, exchangeable with D_2O), 10.70, 11.25 (2s, 2H, 2NH, exchangeable with D_2O). MS: m/z (%): 220 (M^+ – 1; 19.85), 127 (100). Analysis: calcd. for $C_8H_7N_5O_3$ (221.17): C, 43.44; H, 3.19; N, 31.66%; found: C, 43.27; H, 3.20; N, 31.57%.

5-{[(4-Acetylphenyl)imino]methyl}-6-aminopyrimidine-2,4(1H,3H)-dione (4)

To a solution of compound **2** (0.155 g, 0.001 mol) in glacial acetic acid (5 mL), p-aminoacetophenone (0.135 g, 0.001 mol) was added. The reaction mixture was refluxed for 20 h, the excess solvent was removed under reduced pressure and the solid was collected by filtration and after recrystallization from DMF/ H_2O (1:1) yielded compound **4**.

Yield 83%, m.p. >330^{o}C. IR (KBr, cm^{-1}): 3148.93 (NH, NH_2), 1750, 1674, 1649.75 (3 CO), 1595.72 (C=N). ^{1}H-NMR (DMSO-d_6, δ, ppm): 1.80 (s, 3H, CH_3), 6.50, 7.65 (dd, 4H, Ar-H), 9.15 (s, 1H, CH=N), 7.35 (d, 2H, NH_2, exchangeable with D_2O), 9.15, 10.80 (2s, 2H, 2NH, exchangeable with D_2O). MS. m/z (%): 273 (M^+ + 1, 9.42), 272.1 (M^+, 30.25), 271 (M^+ – 1, 12.48), 135 (59.91), 120 (100). Analysis: calcd. for $C_{13}H_{12}N_4O_3$ (272.260): C, 57.35; H, 4.44; N, 20.58%; found: C, 57.22; H , 4.33; N, 20.46%.

General procedure for preparation of 6-amino-2,4-dioxo-1,2,3,4-tetrahydropyrimidine-5-substituted carbaldehyde derivatives (5a-d)

Mixture of compound **2** (0.155 g, 0.001 mol) and hydrazine derivatives (0.001 mol) in absolute ethanol (5 mL) was refluxed for three days. The reactions mixtures were concentrated, cooled and the solids formed were filtered, washed with ethanol and diethyl ether and then recrystallized from DMF to give **5a-d**.

6-Amino-2,4-dioxo-1,2,3,4-tetrahydropyrimidine-5-carbaldehyde hydrazone (5a)

Yield 95%, m.p. >300^{o}C. IR (KBr, cm^{-1}): 3300, 3212.53 (NH, NH_2), 1734.83 (2 CO), 1633.61 (C=N), 1540.54 (C=C). ^{1}H-NMR (DMSO-d_6, δ, ppm): 7.50 (br.s, 2H, NH_2, exchangeable with D_2O), 9.15 (s, 2H, NH_2, exchangeable with D_2O), 9.60 (s, 1H, CH=N), 10.70 (br.s. 2H, 2NH, exchangeable with D_2O). Analysis: calcd. for $C_5H_7N_5O_2$ (169.142): C, 35.50; H, 4.17; N, 41.41%; found: C, 35.59; H, 4.21; N, 41.21%.

6-Amino-2,4-dioxo-1,2,3,4-tetrahydropyrimidine-5-carbaldehyde phenyl hydrazone (5b)

Yield 75%, m.p. >300^{o}C. IR (KBr, cm^{-1}): 3286.36 (NH_2, NH), 3000 (CH-aromatic), 1704.80 (2 CO), 1619.95 (C=N, C=C). ^{1}H-NMR (DMSO-d_6, δ, ppm): 6.60–7.10 (m, 5H, Ar-H), 8.10 (s, 1H, CH=N), 8.45 (br.s, 1H, NH, exchangeable with D_2O), 9.75 (s, 2H, NH_2), 10.60 (s, 2H, 2NH, exchangeable with D_2O). MS: m/z (%): 247 (M^+ + 2, 100). Analysis: calcd. for $C_{11}H_{11}N_5O_2$ (245.238): C, 53.87; H, 4.52; N, 28.56%; found: C, 53.66; H, 4.34; N, 28.29%.

6-Amino-2,4-dioxo-1,2,3,4-tetrahydropyrimidine-5-carbaldehyde (3-chlorophenyl) hydrazone (5c)

Yield 81%, m.p. >300^{o}C. IR (KBr, cm^{-1}): 3410.17, 3350 (NH_2, NH), 3000 (CH-aromatic), 1708.40 (2 CO), 1646.79 (C=N), 1536.39 (C=C), 846.82, 764.68 (C-Cl). ^{1}H-NMR (DMSO-d_6, δ, ppm): 6.65–7.20 (m, 4H, Ar-H), 7.40 (s, 1H, NH, exchangeable with D_2O), 8.15 (s, 1H, CH=N), 9.20 (s, 2H, NH_2, exchangeable with D_2O), 10.60, 10.90 (2s, 2H, 2NH, exchangeable with D_2O). MS. m/z (%): 279 (M^+, 1.08), 142 (100). Analysis: calcd. for

$C_{11}H_{10}ClN_5O_2$ (279.68): C, 47.24; H, 3.60; N, 25.04%; found: C, 47.51; H, 3.59; N, 25.35%.

N_1-[(6-amino-2,4-dioxo-1,2,3,4-tetrahydropyrimidin-5-yl)methylene]-N_2-(4-methylbenzo)hydrazide (5d)

Yield 60%, m.p. >330°C. IR (KBr, cm^{-1}): 3350, 3250, 3219.41 (NH_2, NH), 1741.91 (3 CO), 1628.37 (C=N, C=C). ^{1}H-NMR (DMSO-d_6, δ ppm): 2.35 (s, 3H, CH_3), 7.20–7.80 (dd, 4H, Ar-H), 8.60(s, 1H, CH=N), 9.20 (d, 2H, NH_2, exchangeable with D_2O), 10.70, 10.85 (2s, 2H, 2NH, exchangeable with D_2O), 11.50 (s, 1H, NHCOAr, exchangeable with D_2O). Analysis: calcd. for $C_{13}H_{13}N_5O_3$ (287.274): C, 54.35; H, 4.56; N, 24.38%; found: C, 54.49; H, 4.62; N, 24.47%.

6-Amino-5-(5-thioxo-4,5-dihydro-1H-1,2,4-triazol-3-yl)pyrimidine-2,4-(1H,3H)-dione (6)

A mixture of compound **2** (0.155 g, 0.001 mol) and thiosemicarbazide (0.001 mol) in absolute ethanol (5 mL) and a few drops of glacial acetic acid was refluxed for 10 h. The reaction mixture was concentrated, cooled and the solid formed was filtered, washed with ethanol and diethyl ether, then recrystallized from DMF/H_2O (1:1) to give compound **6**.

Yield 91%, m.p. >330°C. IR (KBr, cm^{-1}): 3370.96, 3300.57, 3272.61, 3192.58 (NH_2, NH), 1715.37, 1648.84 (2 CO), 1596.77 (C=N, C=C), 1278.56 (C=S).^{1}H-NMR (DMSO-d_6, δ, ppm): 7.62, 7.90 (2s, 2H, NH_2, exchangeable with D_2O), 8.30 (1s, 1H, NH exchangeable with D_2O), 10.23 (1s, 1H, NH, exchangeable with D_2O), 10.70, 10.92 (2s, 2H, 2NH, exchangeable with D_2O). MS: m/z (%): 225 (M^+ – 1, 5), 191 (90), 159 (100), 128 (35), 63 (94). Analysis: calcd. for $C_6H_6N_6O_2S$ (226.217): C, 31.86; H, 2.67; N, 37.15%; found: C, 31.93; H, 2.40; N, 37.28%.

6-Amino-5-(5-oxo-4,5-dihydro-1H-1,2,4-triazol-3-yl)pyrimidine-2,4-(1H,3H)-dione (7)

A mixture of compound **2** (0.155 g, 0.001 mol) and semicarbazide hydrochloride (0.001 mol) and crystalline sodium acetate (0.001 mol) in ethanol (5 mL) was stirred at room temperature for 1 h, then refluxed for 10 h, cooled and the solid formed was filtered and recrystallized from DMF/ H_2O (1:1) to give compound **7**.

Yield 87%, m.p. >330°C. IR (KBr, cm^{-1}): 3462.25, 3214.65 (NH, NH_2), 1724.46, 1627.91 (3 CO).^{1}H-NMR (DMSO-d_6, δ, ppm): 8.50, (s, 2H, NH_2), 9.00 (s, 2H, 2NH exchangeable with D_2O), 11.50, 11.90 (2s, 2H, 2NH, exchangeable with D_2O). MS: m/z (%): 211 (M^+ + 1, 3), 195 (25), 180 (25), 178 (10), 127 (100), 84 (20). Analysis: calcd. for $C_6H_6N_6O_3$ (210.15): C, 34.29; H, 2.88; N, 39.99%; found: C, 34.33; H, 3.09; N, 40.13%.

Ethyl-6'-amino-6-methyl-2',4'-dioxo-2-thioxo-1,1',2,2',3,3',4,4'-octahydro-4,5'-bipyrimidine-5-carboxylate (8)

To a solution of compound **2** (0.155 g, 0.001 mol) in absolute ethanol (10 mL), thiourea (0.001 mol) and ethyl acetoacetate (0.001 mol) were added. The reaction mixture was refluxed for 8 h, the excess solvent was removed under reduced pressure, the solid was collected by filtration and recrystallized from DMF/ H_2O (1:1) to give compound **8**.

Yield 70%, m.p. >300°C. IR (KBr, cm^{-1}): 3154.97, 3040.23 (NH, NH_2), 2803.99 (CH aliph.), 1700.91, 1653.66 (3 CO), 1577.49 (C=N, C=C), 1257.36 (C=S). ^{1}H-NMR (DMSO-d_6, δ, ppm): 1.10 (t, 3H, CH_2-$\underline{CH_3}$), 2.50 (s, 3H, CH_3), 4.20 (q, 2H, $\underline{CH_2}$-CH_3), 6.20 (s, 1H, CH of thiopyrimidine ring), 6.80 (s, 1H, NH), 7.00 (s, 2H, NH_2, exchangeable with D_2O), 7.20 (s, H, NH exchangeable with D_2O), 10.00, 11.00 (2s, 2H, 2NH, exchangeable with D_2O). MS: m/z (%): 326.8 (M^+ + 1, 3.94), 324.2 (M^+ – 1, 14.53), 252 (20), 199.83 (10), 174 (100). Analysis: calcd. for $C_{12}H_{15}N_5O_4S$ (325.345): C, 44.30; H, 4.65; N, 21.53%; found: C, 44.49; H, 4.79; N, 21.62%.

5-(4-Acetyl-5-oxo-4,5-dihydro-1H-pyrazol-3-yl)-6-aminopyrimidine-2,4-(1H,3H)-dione (9)

A mixture of compound **2** (0.155 g, 0.001 mol), acetoacetic acid hydrazide (0.001 mol) in absolute ethanol (10 mL) containing few drops of acetic acid was refluxed for 10 h. The excess solvent was removed under reduced pressure, the reaction mixture was cooled and the solid formed was filtered, and recrystallized from DMF/H_2O (1:1) to give compound **9**.

Yield 75%, m.p. >330°C. IR (KBr, cm^{-1}): 3172.33, 3051.80 (NH, NH_2), 2853.17 (CH aliph.), 1696.06, 1618.95 (4 CO), 1570.74 (C=N, C=C). ^{1}H-NMR (DMSO-d_6, δ, ppm): 3.00 (s, 3H, CO-CH_3), 4.40 (s, 1H, CH of pyrazolone), 6.50 (s, H, NH of pyrazlone ring, exchangeable with D_2O), 7.30 (br.s, 2H, NH_2, exchangeable with D_2O), 11.20, 11.50 (2s, 2H, 2NH, exchangeable with D_2O). MS. m/z (%): 250 (M^+ – 1, 2.30), 238 (100), 236 (1.14), 124 (27.75). Analysis: calcd. for $C_9H_9N_5O_4$ (251.199): C, 43.03; H, 3.61; N, 27.88%; found: C, 43.16; H, 3.43; N, 28.07%.

3-(6-Amino-2,4-dioxo-1,2,3,4-tetrahydropyrimidin-5-yl)-5-oxo-4,5-dihydro-1H-pyrazole-4-carboxamide (10)

A mixture of compound **2** (0.155 g, 0.001 mol), 2-cyanoacetohydrazide (0.001 mole) in

absolute ethanol (10 mL) containing few drops of acetic acid was refluxed for 23 h. The excess solvent was removed under reduced pressure, the mixture was cooled and the solid formed was filtered and recrystallized from DMF/ H_2O (1:1) to give compound **10**.

Yield 81%, m.p. >330°C. IR (KBr, cm^{-1}): 3175.80, 3040.87 (NH, NH_2), 1732.15 (3 CO), 1645.80 ($CONH_2$). ^{1}H-NMR (DMSO-d_6, δ, ppm): 4.44 (s, 1H, CH of pyrazolone), 6.40 (s, 4H, $2NH_2$), 10.15, 11.50 (2s, 3H, 3NH). MS: m/z (%): 252 (M^+, 4.28), 250 ($M^+ - 2$, 13.05), 208 (5), 177 (28), 174 (100). Analysis: calcd. for $C_8H_8N_6O_4$ (252.187): C, 38.10; H, 3.20; N, 33.32%; found: C, 38.21; H, 3.16; N, 33.25%.

Ethyl (2Z)-2-[(2,6-dioxo-1,2,3,6-tetrahydropyrimidin-4-yl)hydrazono]-3-oxobutanoate (12)

Compound **1** (0.127 g, 0.001 mol) was dissolved in concentrated hydrochloric acid (5 mL) and the solution was then cooled to 0–5°C. Sodium nitrite (0.001 mol) in water (3 mL) was then added to this solution dropwise with vigorous stirring during about 1 h, while cooling at 0–5°C. The clear diazonium salt solution **11** was then added dropwise to a well-cooled (0–5°C) and stirred solution of ethyl acetoacetate (0.001 mol) in sodium acetate (1 g, dissolved in 5 mL of 25% aqueous ethanol). The pH of the coupling mixture, in each case, was maintained at 5–6 through the coupling process by adding sodium acetate. Stirring was continued for 4 h at 0–5°C and the precipitated product separated upon dilution with cold water (25 mL) was filtered, washed with water several times, dried, and recrystallized from ethanol/H_2O (1:1) to give compound **12**.

Yield 60%, m.p. >330°C. IR (KBr, cm^{-1}): 3295.75, 3187.76 (NH) 2792.42 (CH aliph.), 1751.05, 1679.69 (4 CO), 1579.41(C=N, C=C). ^{1}H-NMR (DMSO-d_6, δ, ppm): 1.19 (t, 3H, CH_2-$\underline{CH_3}$) 2.00 (s, 3H, $COCH_3$), 4.10 (q, 2H, $\underline{CH_2}CH_3$), 8.50 (s, H, CH pyrimidine ring), 8.90, 9.00, 9.30 (3s, 3H, 3NH, exchangeable with D_2O). MS. m/z (%): 267 ($M^+ - 1$, 0.27), 157 (5.63), 156 (54.46), 139 (5.81), 112 (28.60), 53 (39.13), 53 (100). Analysis: calcd. for $C_{10}H_{12}N_4O_5$ (268.226): C, 44.78; H, 4.51; N, 20.89%; found: C, 44.67; H, 4.66; N, 21.01%.

General procedure for preparation of 2,6-dioxo-1,2,3,6-tetrahydropyrimidine compounds (13-17)

The clear diazonium salt solution **11** was added dropwise to a well-cooled (0–5°C) and stirred solution of ethyl cyanoacetate, acetylacetone, malononitrile, cyanoacetamide, and diethylmalonate (0.001 mole) in sodium acetate (1 g, dissolved in 5 mL of 25% aqueous ethanol). The pH of the coupling mixture, in each case, was maintained at 5–6 through the coupling process by adding sodium acetate. Stirring was continued for 4 h at 0–5°C and the precipitated products separated upon dilution with cold water (25 mL) were filtered, washed with water several times, dried, and recrystallized from ethanol/H_2O (1:1) to give compounds **13**, **14**, **15**, **16** and **17**, respectively.

Ethyl (2)-3-amino-2-[(2,6-dioxo-1,2,3,6-tetrahydropyrimidin-4-yl)hydrazono]-3-oxopropanoate (13)

Yield 55%, m.p. >330°C. IR (KBr, cm^{-1}): 3459.77, 3294.73, 3185.29, (NH, NH_2), 2808.39 (CH aliph.), 1790.54, 1752.67, 1707.03 (4 CO), 1581.77 (C=C).^{1}H-NMR (DMSO-d_6, δ, ppm): 1.20 (t, 3H, CH_2-$\underline{CH_3}$), 4.10 (q, 2H, $\underline{CH_2}CH_3$), 4.60 (s, H, N-CH), 5.00 (s, H, CH of pyrimidine ring), 8.50 (s, 2H, NH_2), 8.80, 9.00, (2s, 2H, 2NH, exchangeable with D_2O). MS: m/z (%): 269 (M^+, 10), 254 (9), 256 (38), 157 (13), 159 (10), 111 (37), 71 (100). Analysis: calcd. for $C_9H_{11}N_5O_5$ (269.214): C, 40.15; H, 4.12; N, 26.01%; found: C, 40.28; H, 4.21; N, 26.31%.

Pentane-2,3,4-trione-3-[(2,6-dioxo-1,2,3,6-tetrahydropyrimidin-4-yl)hydrazone] (14)

Yield 62%, m.p. >330°C. IR (KBr, cm^{-1}): 3294.79, 3188.72 (NH), 2783.74 (CH aliph.), 1755.87, 1678.73 (4 CO). ^{1}H-NMR (DMSO-d_6, δ, ppm): 2.50 (s, 6H, 2 CH_3), 4.40 (s, H, CH-N), 6.35 (s, H, CH of pyrimidine ring), 11.20, 11.50 (2s, 2H, 2 NH). MS: m/z (%): 238 (M^+, 0.03), 239 ($M^+ + 1$, 0.27), 182 (0.38), 156 (100), 154 (1.57), 139 (3.40). Analysis: calcd. for $C_9H_{10}N_4O_4$ (238.200): C, 45.38; H, 4.23; N, 23.52%; found: C, 45.45; H, 4.22; N, 23.43%.

2-Cyano-2-[(2,6-dioxo-1,2,3,6-tetrahydropyrimidin-4-yl)hydrazono]acetamide (15)

Yield 80%, m.p. >330°C. IR (KBr, cm^{-1}): 3477.99, 3293.82, 3187.76 (NH, NH_2), 2163.74 (C=N), 1750.08, 1679.69 (3 CO). ^{1}H-NMR (DMSO-d_6, δ, ppm): 6.30 (s, H, CH of pyrimidine ring), 9.90 (s, 2H, NH_2, exchangeable with D_2O), 10.00, 11.65, 11.80 (3s, 3H, 3NH, exchangeable with D_2O). MS: m/z (%): 224.39 ($M^+ + 2$, 3.33), 222 (M^+, 30), $M^+ - 1$ 221 (8.36), 209.09 (100), 168 (77.73). Analysis: calcd. for $C_7H_6N_6O_3$ (222.16): C, 37.84; H, 2.72; N, 37.83%; found: C, 37.94; H, 2.78; N, 37.80%.

2-[(2,6-Dioxo-1,2,3,6-tetrahydropyrimidin-4-yl)diazenyl] malonamide (16)

Yield 83%, m.p. >330°C. IR (KBr, cm^{-1}): 3293.14, 3187.97 (NH, NH2), 1735.92, 1681.45 (4

CO), 1508.16 (C=N). ^{1}H-NMR (DMSO-d_6, δ, ppm): 8.00, (s, 4H, $2CONH_2$), 8.30 (s, H, CH of pyrimidine ring), 11.20, 11.60 (2s, 3H, 3NH). MS: m/z (%): 239 (M^+ – 1, 15), 222 (10), 101 (12), 50 (100). Analysis: calcd. for $C_7H_8N_6O_4$ (240.176): C, 35.01; H, 3.36; N, 34.99%; found: C, 35.11; H, 3.28; N, 34.88%.

Diethyl[(2,6-dioxo-1,2,3,6-tetrahydropyrimidin-4-yl)hydrazono] malonate (17)

Yield 94%, m.p. >330°C. IR (KBr, cm^{-1}): 3294.79, 3186.79, (NH), 2783.74 (CH aliph.) 1756.83, 1680.66, 1646.91(4 CO).^{1}H-NMR (DMSO-d_6, δ ppm): 1.20 (t, 6H, $2CH_3$), 4.30 (q, 4H, $2CH_2$), 5.50 (s, H, N-CH), 6.10 (s, H. CH of pyrimidine ring), 8.30, 8.50 (2s, 2H, 2NH). MS: m/z (%): 298.2 (M^+, 10), 297 (M^+ – 1, 40), 296 (20), 188 (12), 173 (100). Analysis: calcd. for $C_{11}H_{14}N_4O_6$ (298.252): C, 44.30; H, 4.73; N, 18.79%; found: C, 44.15; H 4.74; N, 18.58%.

General procedure for preparation of 6-[(3-methyl-5-oxo-1-phenyl or 3-chlorophenyl-4,5-dihydro-1H-pyrazol-4-yl)diazenyl]pyrimidine-2,4-(1H,3H)-dione derivatives (18a,b)

Substituted hydrazines namely, phenylhydrazine or 3-chlorophenylhydrazine (0.01 mol) were added to a solution of compound **12** (0.01 mole) and pyridine 0.5 mL in 30 mL of ethanol. The reaction mixture was heated under reflux for 3–4 h, then cooled to room temperature and the precipitated products that separated upon dilution with water were filtered, washed with water several times, dried and recrystallized from ethanol/H_2O (1:1) to give compounds **18a,b**, respectively.

6-[(3-Methyl-5-oxo-1-phenyl-4,5-dihydro-1H-pyrazol-4-yl)diazenyl]pyrimidine-2,4-(1H,3H)-dione derivatives (18a)

Yield 71%, m.p. >330°C. IR (KBr, cm^{-1}): 3346.85, 3223.43, 3103.87 (NH), 2793.38 (CH aliph.), 1734.66, 1671.02, 1635.34 (3 CO) .^{1}H-NMR (DMSO-d_6, δ, ppm): 2.50 (s, 3H, CH_3), 4.45 (s, H, pyrazolone ring) 6.60–7.50 (m, 6H, Ar-H, CH of pyrimidine ring), 9.70, 11.20 (2s, 2H, 2NH). MS: m/z (%): 312 (M^+, 5.4), 217 (13.5), 174 (100), 139 (13). Analysis: calcd. for $C_{14}H_{12}N_6O_3$ (312.284): C, 53.85; H, 3.87; N, 26.91%; found: C, 53.92; H, 3.86; N, 26.99%.

6-[(1-(3-Chlorophenyl)-3-methyl-5-oxo-4,5-dihydro-1H-pyrazol-4-yl)diazenyl]pyrimidine-2,4-(1H,3H)-dione (18b)

Yield 62%, m.p. >330°C. IR (KBr, cm^{-1}): 3413.39, 3324.68 (NH), 3050.83 (CH arom.) 2851.24 (CH aliph.), 1725.01, 1680.66 (3 CO), 1598.70 (C=N, C=C), 766.56 (C-Cl). ^{1}H-NMR (DMSO-d_6, δ, ppm): 2.50 (s, 3H, CH_3), 4.40 (s, H, pyrazolone ring), 6.20 (s, H, CH of pyrimidine ring), 6.85–7.60 (m, 4H, Ar-H), 9.80, 11.25 (2s, 2H, 2NH). MS: m/z (%): 349 (M^+ + 2, 2.5), 347 (M^+, 7.5), 139 (20), 127 (100), 126 (25), 113 (21), 111 (62). Analysis: calcd. for $C_{14}H_{11}ClN_6O_3$ (346.728): C, 48.50; H, 3.20; N, 24.24%; found: C, 48.66; H, 3.24; N, 24.28%.

General procedure for preparation of 6-{[1H- or 1-(3-chlorophenyl)-3,5-dioxopyrazolidin-4-yl]diazenyl}pyrimidine-2,4-(1H,3H)-dione derivatives (19a,b)

Hydrazine hydrate or 3-chlorophenylhydrazine (0.01 mol) was added to a solution of compound **17** (0.01 mol) and pyridine 0.5 mL in 30 mL of ethanol. The reaction mixture was heated under reflux for 3–4 h, then cooled to room temperature and the precipitated products that separated upon dilution with water were filtered, washed with water several times, dried and recrystallized from ethanol/H_2O to give compounds **19a,b**, respectively.

6-{[1H-3,5-dioxopyrazolidin-4-yl]diazenyl}pyrimidine-2,4-(1H,3H)-dione (19a)

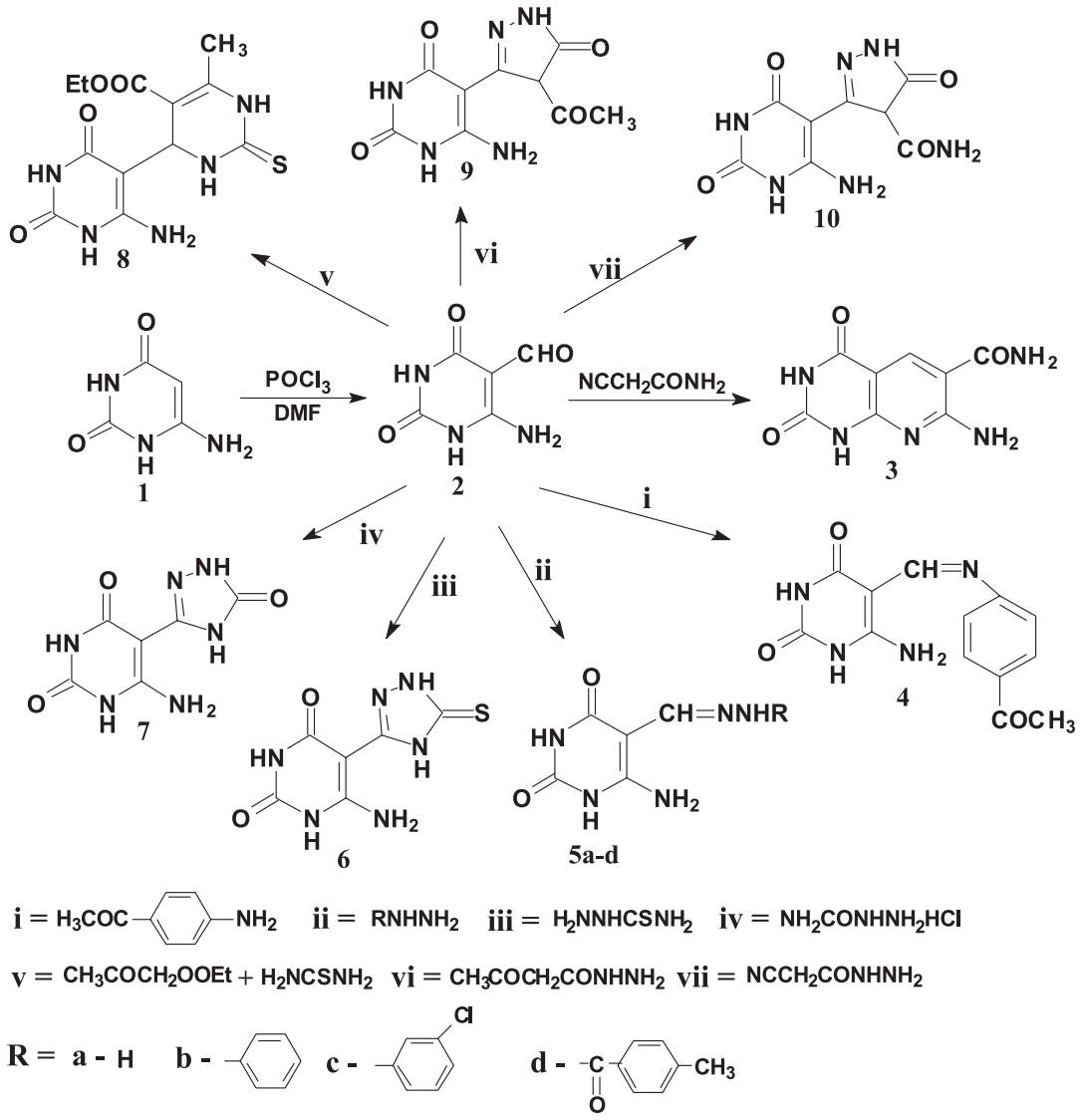
Yield 60%, m.p. >330°C. IR (KBr, cm^{-1}): 3295.75, 3188.72 (NH), 1752.98, 1732.73, 1679.69 (4 CO), 1578.45 (C=C, C=N). ^{1}H-NMR (DMSO-d_6, δ, ppm): 4.40 (s, H, CH of pyrazolidinedione ring), 6.29 (s, H, CH of pyrimidine ring), 8.40, 10.10 ((br.s, s, 2H, 2NH of pyrazolidinedione ring) 11.10, 11.50 (2s, 2H, 2NH). MS: m/z (%): 238 (M^+ 0.06), 154 (84.07), 156 (100), 140 (3.70), 100 (4.75), 82 (5.83), 99 (4.4). Analysis: calcd. for $C_7H_6N_6O_4$ (238.161): C, 35.30; H, 2.54; N, 35.29%; found: C, 35.43; H, 2.52; N, 35.23%.

6-{[1-(3-Chlorophenyl)-3,5-dioxopyrazolidin-4-yl]diazenyl}pyrimidine-2,4-(1H,3H)-dione (19b)

Yield 73%, m.p. >330°C. IR (KBr, cm^{-1}): 3437.49 ((NH), 1630.52 (4 CO), 1593.88 (C=C, C=N). ^{1}H-NMR (DMSO-d_6, δ, ppm): 4.40 (s, H, pyrazolidinedione ring), 6.90–7.70 (m, 5H, Ar-H, CH of pyrimidine ring), 11.20, 11.70 (2s, 3H, 3NH). MS: m/z (%): 351 (M^+ + 2, 0.40), 350 (M^+ + 1, 1.31), 349 (M^+, 0.01), 252 (9.43), 250 (26.24), 175 (15.23), 174 (100), 139 (3.66), 140 (2.19). Analysis: calcd. for $C_{13}H_9ClN_6O_4$ (348.701): C, 44.78; H, 2.60; N, 24.10%, Found: C, 44.67; H, 2.62; N, 24.18%.

6-[(3,5-Diamino-1H-pyrazol-4-yl)diazenyl]pyrimidine-2,4-(1H,3H)-dione (20)

Hydrazine hydrate (0.01 mol) was added to a solution of compound **15** (0.01 mol) and pyridine



Scheme 1.

0.5 mL in 30 mL of ethanol. The reaction mixture was heated under reflux for 3–4 h, then cooled to room temperature and the precipitated product that separated upon dilution with water was filtered, washed with water several times, dried and recrystallized from ethanol/H_2O to give compound **20**.

Yield 65%, m.p. > 330°C. IR (KBr, cm^{-1}): 3321.78, 3289.00, 3139.54 (NH, NH_2), 1683.55, 1636.30 (2 CO). ^{1}H-NMR (DMSO-d_6, δ, ppm): 6.40 (br.s, H, CH of pyrimidine ring), 8.30 (br.s. 4H, $2NH_2$), 10.30, 10.40, 10.60 (3s, 3H, 3NH). MS: m/z (%): 236 (M^+, 10.21), 220.19 (46.10), 171.13 (100). Analysis: calcd. for $C_7H_8N_8O_2$ (236.191): C, 35.60; H, 3.41; N, 47.44%; found: C, 35.88; H, 3.46; N, 47.65%.

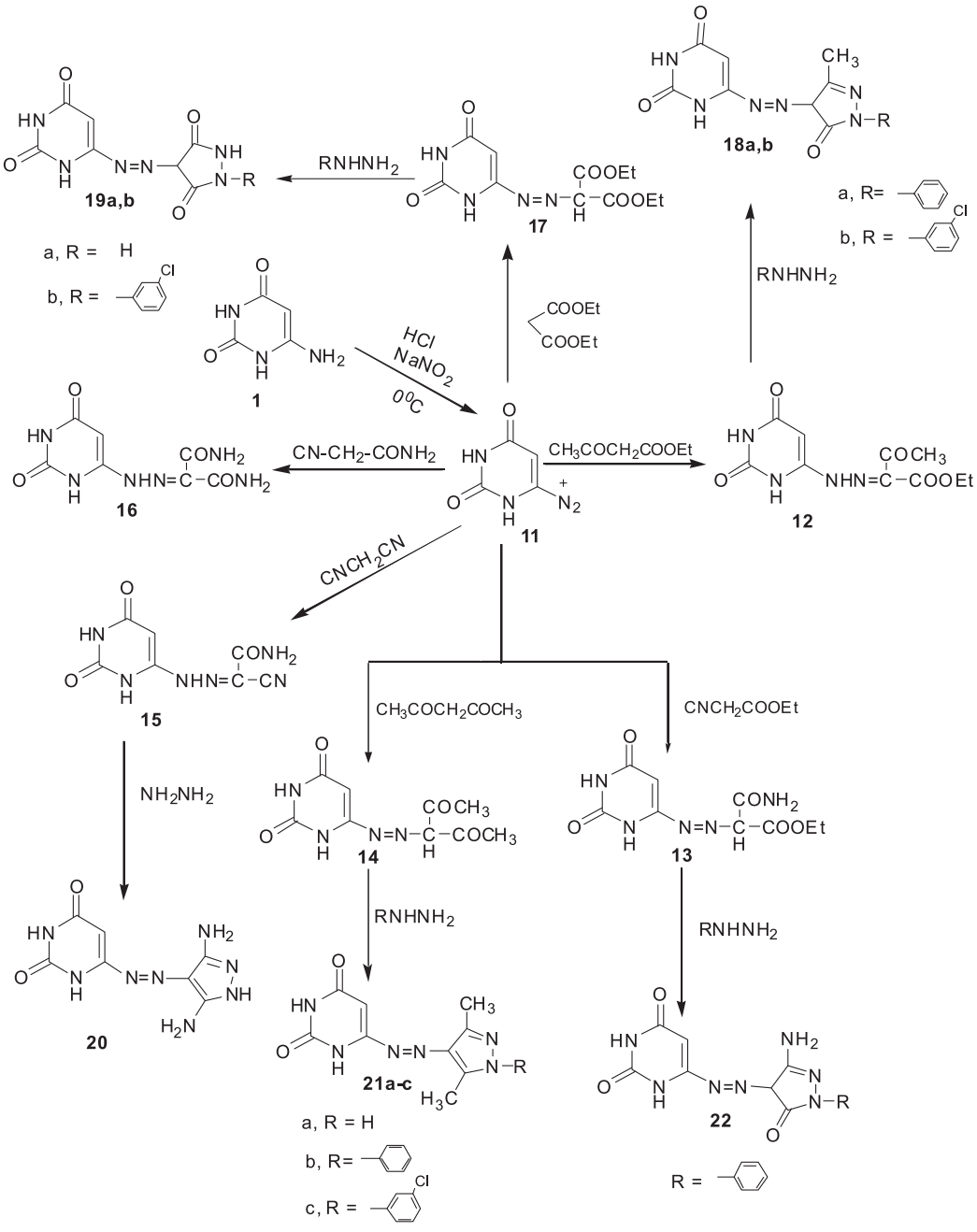
General procedure for preparation of 6-[(3,5-dimethyl-1H or phenyl or substituted phenyl -pyrazol-4-yl)diazenyl]pyrimidine-2,4-(1H,3H)-dione derivatives (21a-c)

Hydrazine hydrate or phenylhydrazine or 3-chlorophenylhydrazine (0.01 mol) were added to a solution of compound **14** (0.01 mol) and pyridine 0.5 mL in 30 mL of ethanol. The reaction mixture was heated under reflux for 3–4 h, then cooled to room temperature and the precipitated products that

separated upon dilution with water were filtered, washed with water several times, dried and recrystallized from ethanol/H_2O to give compounds **21a-c**, respectively**.**

6-[(3,5-Dimethyl-1H-pyrazol-4-yl)diazenyl]pyrimidine-2,4-(1H,3H)-dione (21a)

Yield 61%, m.p. >330°C. IR (cm^{-1}): 3492.45, 3334.32, 3152.08 (NH), 1678.73, 1643.05 (2 CO), 1573.63 (C=N, C=C). ^{1}H-NMR (DMSO-d_6, δ, ppm): 2.50 (s, 6H, $2CH_3$), 6.25(s, H, CH of pyrimidine ring), 10.00 (s, H, NH of pyrazole ring exchangeable with D_2O), 11.67, 11.73 (2s, 2H, 2NH, exchangeable with D_2O). MS: m/z (%): 232.29 (M^+ – 2, 0.03), 206.09 (2.68), 180 (83), 178.03 (10.34), 165.04 (100), 136.03 (6.29). Analysis: calcd. for $C_9H_{10}N_6O_2$ (234.22): C, 46.15; H, 4.30; N, 35.88%; found: C, 46.05; H, 4.22; N, 35.77%.



Scheme 2.

6-[(3,5-Dimethyl-1-phenylpyrazol-4-yl)diazenyl]pyrimidine-2,4-(1H,3H)-dione (21b)

Yield 76%, m.p. >330°C. IR (KBr, cm^{-1}): 3357.22, 3170.88 (NH), 2968.40 (CH aliph.), 1664.05 (2 CO), 1596.64 (C=N, C=C). ^{1}H-NMR (DMSO-d_6, δ, ppm): 2.58 (s, 6H, $2CH_3$), 5.70 (s, 1H, CH of pyrimidine ring) 6.80–7.60 (m, 5H, Ar-H), 10.30, 10.90 (2br.s, 2H, 2NH exchangeable with D_2O). MS: m/z (%): 312 (M^+ + 2, 1.75), 310.3 (M^+, 1.05), 233 (4.22), 217 (4.73), 139 (1.93), 218 (8.98), 95 (29.71), 123 (14.76), 55 (100). Analysis: calcd. for $C_{15}H_{14}N_6O_2$ (310.311): C, 58.06; H, 4.55; N, 27.08%; found: C, 58.04; H, 4.45; N, 27.05%.

6-[(1-(3-chlorophenyl)-3,5-dimethylpyrazol-4-yl)diazenyl]pyrimidine-2,4-(1H,3H)-dione (21c)

Yield 79%, m.p. >330°C. IR (KBr, cm^{-1}): 3291.89, 3184.86 (NH), 3055.66 (CH arom.), 2851.24 (CH aliph.), 1727.91, 1712.48 (2CO), 1575.56 (C=N, C=C), 771.38 (C-Cl). ^{1}H-NMR (DMSO-d_6, δ, ppm): 2.50 (s, 6H, $2CH_3$), 6.90–8.15 (m, 5H, Ar-H, CH of pyrimidine ring), 11.20, 11.70 (2s, 2H, 2NH exchangeable with D_2O). MS: m/z (%): 347 (M^+ + 2, 1.5), 345 (M^+, 5), 266 (45), 220 (13), 156 (100), 112 (10), 111 (62), 96 (49), 139 (22), 110 (70). Analysis: calcd. for $C_{15}H_{13}ClN_6O_2$ (344.76): C, 52.26; H, 3.80; N, 24.38%; found: C, 52.45; H, 3.84; N, 24.43%.

6-[(3-Amino-5-oxo-1-phenyl-4,5-dihydro-1H-pyrazol-4-yl)diazenyl]pyrimidine-2,4-(1H,3H)-dione (22)

Phenyl hydrazine hydrate (0.01 mol) was added to a solution of compound **13** (0.01 mol) and pyridine 0.5 mL in 30 mL of ethanol. The reaction mixture was heated under reflux for 3–4 h, then cooled to room temperature and the precipitated product that separated upon dilution with water, was filtered, washed several times with water, dried and recrystallized from ethanol/H_2O to give compound **22**.

Yield 59%, m.p. >330°C. IR (KBr, cm^{-1}): 3732.55, 3623.59, 3565.74 (NH, NH_2), 1744.30, 1698.98, 1648.84 (3 CO). ^{1}H-NMR (DMSO-d_6, δ, ppm): 6.30 (s, 2H, NH_2, exchangeable with D_2O), 6.50–8.10 (m, 7H, Ar-H, CH of pyrimidine ring, CH of pyrazolone ring), 10.10, 11.30 (s, br.s, 2H, 2NH, exchangeable with D_2O). MS. m/z (%):314.35 (M^+ + 1, 4.41), 255.74 (16.74), 96.03 (22.83), 64.12 (100). Analysis: calcd. for $C_{13}H_{11}N_7O_3$ (313.272): C 49.84, H 3.45, N 31.30%; found: C 50.01, H 3.43, N 31.40%.

PHARMACOLOGICAL SCREENING

Carragenan was purchased from Sigma-Aldrich (St. Louis, MO, USA) Tramadol hydrochloride was gifted from October Pharmaceutical Company, (6th of October City, Egypt). Selected compounds (**9**, **10**, **18a**, **18b**, **19a**, **19b**, **20**, **21a**, **21b** and **22**) of expected promising efficacy were evaluated as analgesic using hot plate assay and as anti-inflammatory using carragenan induced paw edema model.

Animals

Male Swiss albino mice (25–30 g) and male Sprague Dawley rats (120–130 g) were purchased from the animal house facility the National Research Center (Dokki, Giza, Egypt). Animals were acclimatized in the animal house unite of the pharmacology Dept., National Research Center of Egypt for at least one week prior to experimentation. Animals were kept at 22 ± 3°C and 55 ± 5% relative humidity during the whole experiment. Standard food pellets and water were supplied *ad libitum*. All tested compounds were dispensed in 10% Tween-80 solution in distilled water. Animals' treatment protocol was approved by the National Research Center Animal Rights committee.

Assessment of central analgesia

Central analgesia was assessed using hot plate assay; briefly, mice were divided into 12 groups (n = 6). Mice were introduced to electronically controlled hot-plate surface adjusted to 52 ± 0.1°C (7280 Hot-plate module, Ugo Basile, Comerio, Italy) at 0, 1 and 2 h after oral administration of tested compounds (50 mg/kg). Time required for mice to lick paw/jump was recorded using built-in digital timer and designated as withdrawal latency (WDL). Tramadol hydrochloride (20 mg/kg) was used as a standard reference analgesic (17, 18).

Assessment of anti-inflammatory activity

Anti-inflammatory activity of tested compounds was assessed using carrageenan-induced paw edema; briefly, rats were divided into 12 groups (n = 6). One hour after oral administration of test compound (50 mg/kg), 0.1 mL of 1% carrageenan solution was injected sub-plantar to the left hind paw of each animal. Paw volumes were measured using standard fluid displacement procedures (7140 plesthysmometer Ugo Basile, Comerio, Italy) by dipping the hind left paw in 0.45% saline solution at 1, 2, 3, and 4 h after carragenan injection. The percent change in paw volume relative to base line measurement was taken as the criteria of comparison. Indomethacin (10 mg/kg) was used as an internal standard anti-inflammatory agent (19).

Statistical analysis

Data are presented as the mean ± SEM. Analysis of variance (ANOVA) with Dunnet's *post*

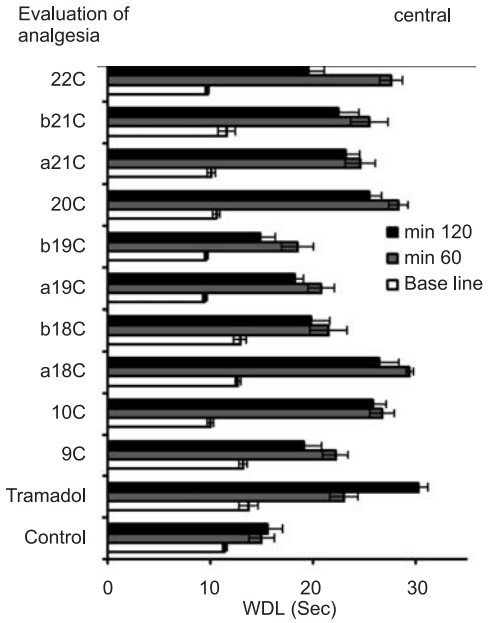


Figure 1. Mice were treated with test compounds (50 mg/kg) and their response to thermal noxious stimulation was compared to untreated group (n = 6). Tramadol (20 mg/kg) was used as reference central analgesic agent. Latent time in seconds (WDL) required for mice to lick paw or jump from hot surface (52 ± 0.1°C) was measured and compared between different treatment groups at 0, 60, and 120 min post drug administration. Data are presented as the mean ± SE

hoc test was used for testing the significance of data using SPSS® for Windows, version 17.0. $p < 0.05$ was taken as a cut off value for significance.

RESULTS AND DISCUSSION

It was reported that, 5-formyl-6-aminopyrimidine-2,4-dione **(2)** has been previously prepared by Cherdantseva et al. (13), which was very useful starting material for many successful reactions. Cyclocondansation reaction of compound **2** with cyanoacetamide (13) gave 2,4-dioxopyrido[2,3-d]pyrimidine derivative **3**. Also, compound **2** was condensed with p-aminoacetophenone in glacial acetic acid to give 5-{[(4-acetylphenyl)imino]methyl}-6-amino pyrimidine-2,4-(1H,3H)-dione (**4**). On the other hand, compound **2** was allowed to react with different hydrazine derivatives to give 6-amino-2,4-dioxo-1,2,3,4-tetrahydropyrimidine-5-substituted carbaldehyde derivatives (**5a-d**), whereas reaction with thiosemicarbazide (14) in absolute ethanol and a few drops of glacial acetic acid gave 6-amino-5-triazolopyrimidine-2,4-(1H,3H)-dione (**6**). Moreover, condensation reaction of compound **2** with semicarbazide hydrochloride (14) in the presence of crystalline sodium acetate gave the corresponding compound **7**. Cyclocondensation reaction of compound **2** with thiourea and ethyl acetoacetate (14) in ethanol led to the formation of ethyl bipyrimidine-5-carboxylate **8**. Aminopyrimidine-5-carboxaldehyde **2** was reacted with some hydrazide derivatives (14), namely acetoacetic acid and cyanoacetic acid hydrazides in refluxing ethanol containing a few drops of acetic acid to form the pyrazolinone derivatives **9, 10**, respectively (Scheme 1).

6-Aminopyrimidine-2,4(1H,3H)-dione (**1**) (15) can serve as the key compound for several condensation with different reagents. Compound **1** was diazotized to afford the diazonium salt **11**, which coupled with ethyl acetoacetate, ethyl cyanoacetate, acetyl acetone, malononitrile, cyano acetamide, diethylmalonate, in sodium acetate buffered solution (16) afforded substituted hydrazonopyrimidines **12**, **13**, **14**, **15**, **16** and **17**, respectively in good yields. It is worthy to note that the IR spectra of compounds **13** and **16** showed the absence of C=N group at 2220, due to the hydrolysis of C=N to CO-NH_2.

Cyclocondensation reaction of substituted hydrazonopyrimidines **12**, **13**, **14**, **15** and **17** with hydrazine derivatives (16) in ethanol and pyridine under reflux for 4–6 h afforded substituted [(pyrazolone, pyrazole or pyrazolidindione-4-yl)diazenyl]pyrimidine-2,4-(1H,3H)-dione derivatives **(18a,b**, **22**, **21a-c**, **20**, **19a,b)**, respectively (Scheme 2).

Assessment of central analgesic effect of tested compounds

Central analgesic effect of the synthesized compounds was examined using hot-plat technique. All compounds showed significant analgesic effect after 60 min of drug administration (50 mg/kg) compared to base line reading. Interestingly, compounds **18a**, **20**, **21b** and **22** showed longer withdrawal latency compared to tramadol (20 mg/kg) 60 min after drug administration. On the other hand, analgesic effect slightly decreased in all tested compounds after 120 min compared to their effect after 60 min, which might be attributed to drug elimination. However, all tested compounds, except **19b**, remain their analgesic potency up to 120 min after drug administration (Fig. 1).

Evaluating the potential anti-inflammatory effect of tested compounds

The potential anti-inflammatory effect of the synthesized compounds was examined using carrageenan-induced paw edema model. Hind paw volumes were measured using standard liquid displacement technique at 1, 2, 3 and 4 hours post carrageenan injection and percent change (increase) in paw

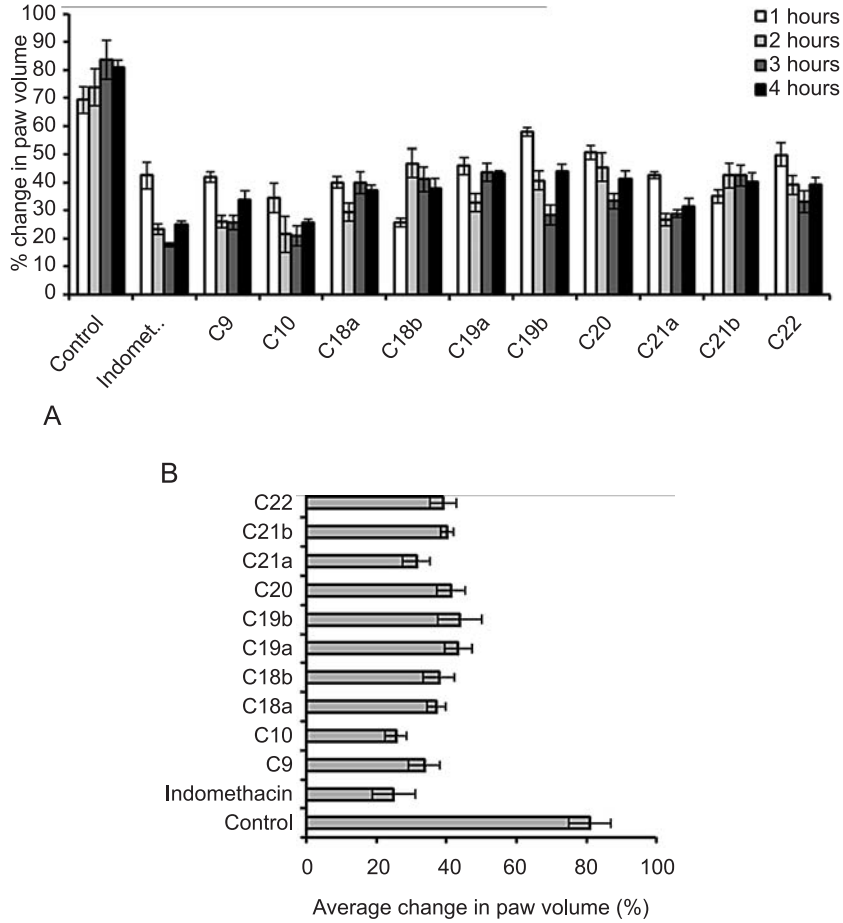


Figure 2. Rats were treated with test compounds (50 mg/kg) and their inflammatory response to sub-planter injection of carrageenan was compared to untreated group (n = 6). Indomethacin (10 mg/kg) was used as reference anti-inflammatory drug. Volumes of hind paws were measured using standard liquid displacement technique. Percent change in paw volumes at 0, 1, 2, 3 and 4 hours post drug administration were calculated and compared between different treatments (**A**). The cumulative anti-inflammatory effect over the whole 4 hours was represented by the average change in paw volumes (**B**). Data are presented as the mean ± SEM

volume was calculated and used for comparison. The untreated animals showed excessive edematous inflammation manifested as change in paw volume ranging from 69 to 97%. In contrary, indomethacin (10 mg/kg) and all tested compounds showed significantly less change in paw volume from the first hour after carragenan injection and sustained up to 4 h. Nonetheless, **18b** showed the most prompt and strongest anti-inflammatory effect after 1 h of induction showing about 63% inhibition in edema formation (25.6% increased paw volume) which was slightly decreased later on (Fig. 2A). On the other hand, **10** showed the most sustainable anti-inflammatory effect over the whole experimental duration with average change in paw volume of about 25% (67% inhibition in edema formation) which was comparable to indomethacin (10 mg/kg) (Fig. 2).

Evaluation of central analgesia

Mice were treated with test compounds (50 mg/kg) and their response to thermal noxious stimulation was compared to untreated group (n = 6). Tramadol (20 mg/kg) was used as reference central analgesic agent. Latent time in seconds (WDL) required for mice to lick paw or jump from hot surface (52 ± 0.1°C) was measured and compared between different treatment groups at 0, 60, and 120 min post drug administration. Data are presented as the mean ± SE.

Evaluation of anti-inflammatory activity

Rats were treated with test compounds (50 mg/kg) and their inflammatory response to subplantar injection of carragenan was compared to untreated group (n = 6). Indomethacin (10 mg/kg)

was used as reference anti-inflammatory drug. Volumes of hind paws were measured using standard liquid displacement technique. Percent change in paw volumes at 0, 1, 2, 3 and 4 h after drug administration were calculated and compared between different treatments (A). The cumulative anti-inflammatory effect over the whole 4 h was represented by the average change in paw volumes (B). Data are presented as the mean ± SEM.

SAR discussion

Some general features can be drawn from the pharmacological data:

1. All the tested compounds showed significant analgesic effect due to the presence of heterocyclic pentaatomic nucleus (pyrazole, pyrazolone, pyrazolidindione) at postion 5 of the pyrimidine moiety.

2. Compounds **18a**, **21b** and **22** showed longer withdrawal latency compared to tramadol due to the presence of phenyl group at position 1 of pyrazolone or pyrazole nucleus.

3. Compound **18b** showed the most prompt and strongest anti-inflammatory effect due to the presence of 3-chlorophenyl group at postion 1 of pyrazolone. On the other hand, compound **10** showed the most sustainable anti-inflammatory effect which was comparable to indomethacin due to the presence of carboxamide group at position 4 of pyrazolone.

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