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ORIGINAL ARTICLE

2nd Heterocyclic Update

Synthesis, anti-inflammatory, analgesic and anticonvulsant activities of some new 4,6-dimethoxy-5-(heterocycles)benzofuran starting from naturally occurring visnagin

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Abstract Novel 3-(4,6-dimethoxybenzofuran-5-yl)-1-phenyl-1*H*-pyrazole-4-carboxaldehyde (3) and 3-chloro-3-(4,6-dimethoxybenzofuran-5-yl)propenal (**4**) were prepared *via* Vilsmeier–Haack reaction of 1-(4,6-dimethoxybenzofuran-5-yl)ethanone (**1**) and its hydrazone derivative **2**. Reaction of compound **4** with some hydrazine derivatives, namely hydrazine hydrate, phenylhydrazine and benzylhydrazine hydrochloride led to the formation of pyrazole derivatives **5**–**8**, respectively. On the other hand, reaction of compound **4** with thiourea, urea or guanidine gave the pyrimidine derivatives **9**–**11**, respectively. Reaction of amino compound **11** with acetic anhydride, benzoyl chloride and benzenesulphonyl chloride yielded *N*-substituted pyrimidine derivatives 12–14, respectively. Reaction of diazonium salt of compound **11** with sodium azide afforded azidopyrimidine derivative **15**, which upon reaction with ethyl acetoacetate gave 1,2,3-triazole derivative **16**. Acid catalyzed reaction of **11** with *p*-nitrobenzaldehyde gave Schiff base **17**, which cyclized upon reaction with thioglycolic acid or chloroacetyl chloride to give thiazolidin-4-one **18** and azetidin-2-one **19**, respectively. The newly synthesized compounds were tested for their anti-inflammatory, analgesic and anticonvulsant activities. Depending on the obtained results, the newly synthesized compounds possess significant anti-inflammatory, analgesic and anticonvulsant activities.

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1. Introduction

Vilsmeier–Haack reaction is a widely used method for the formylation of activated aromatic and heteroaromatic compounds (Vilsmeier and Haack, 1927). The reactions of aliphatic substrates, particularly carbonyl compounds (Thomas

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et al., 2004) and their hydrazones (Kira et al., 1969) with chloromethyleneiminium salts are highly versatile. They lead to multiple iminoalkylations in the presence of excess reagent and the resulting intermediates undergo cyclization to afford aromatic or heterocyclic compounds (El-Sawy et al., 2007; Quiroga et al., 2008; Damjanovic et al., 2009; Prakash et al., 2011). Furthermore, the reactions of methylene active compounds with chloromethyleneiminium salts lead mainly to the formation of β-haloencarboxaldehyde derivatives (Meesala and Nagarajan, 2006; Herbivo et al., 2009) which are useful precursors in the construction of different heterocyclic compounds (Meesala and Nagarajan, 2006; Herbivo et al., 2009; Paul et al., 2001; Park et al., 2005; Hegab and Abdulla, 2006; Hegab et al., 2008). On the other hand, benzofuran derivatives occupy a position of considerable significance for widespread occurrence in plants and their potential as important pharmaceuticals (Mandour et al., 1996; El-Shihi et al., 2005; Banskota et al., 2000; Choi et al., 2008; Liu et al., 2011). Literature revealed that pyrazole and pyrimidine are known for their pronounced pharmaceutical activities (Farag et al., 2008; Menozzi et al., 2003; El-Sawy et al., 2013). So, the goal of this work is the synthesis of some new benzofurans containing substituted pyrazole and pyrimidine moieties at their 5-position and evaluating their anti-inflammatory, analgesic and anticonvulsant activities.

2. Experimental

2.1. Chemistry

Melting points were determined in open capillary tubes on an Electrothermal 9100 digital melting point apparatus (Mount Holly, New Jersey, USA) and are uncorrected. Elemental analyses were performed on a Perkin–Elmer 2400 analyzer (Perkin-Elmer, USA) and were found within ±0.4 % of the theoretical values. IR spectra were recorded on a Perkin–Elmer 1600 FTIR (Perkin–Elmer, USA) in KBr discs. The ^{1}H and ^{13}C NMR spectra were recorded on Bruker spectrometer (500 and 125 MHz) (Bruker, Germany) in DMSO-d_6, and chemical shifts were recorded in δ ppm relative to the internal standard solvent TMS. Mass spectra (EI) were run at Gas Chromatograph Mass Spectrometer, single phase, 200 V, 50/60 Hz, 30 A (Jeol Ltd., Japan).

Visnagin was purchased from Chemical Industrial Developing Company (CID), Giza, Egypt. The starting 1-(4,6-dimethoxy benzofuran-5-yl) ethanone (1) was prepared *via* the alkaline hydrolysis of visnagin followed by methylation with dimethyl sulphate (Schonberg et al., 1953).

2.1.1. 1-(1-(4,6-Dimethoxybenzofuran-5-yl)ethylidene)-2-phenylhydrazine (2)

A mixture of 1-(4,6-dimethoxybenzofuran-5-yl)ethanone (**1**) (1 g, 0.0042 mol) and phenylhydrazine (0.45 g, 0.0042 mol) in glacial acetic acid (20 mL) was refluxed for 2 h. After cooling, the reaction mixture was poured onto water (50 mL) and the solid that formed was filtered off, washed with water, air dried and recrystallized from absolute ethanol. Yield 85 %, m.p. 104–6 °C. IR (KBr): *v* 3100 (NH), 1636 (C═N), 1568 (C═C), 1066, 1018, 1009 cm^{-1} (C–O–C). ^{1}H NMR (500 MHz, DMSO-d_6, 25 °C, TMS): δ = 2.01 (s, 3H, CH_3), 3.78 & 3.95 (2s, 6H, $2OCH_3$), 7.08 (s, 1H, H-7), 7.01–7.20 (m, 5H, Ar–H), 7.86 (d, 1H, H-3), 7.89 (d, 1H, H-2), 8.15 ppm (s, ^{1}H, NH). ^{13}C NMR (125 MHz, DMSO-d_6, 25 °C, TMS): δ = 18.2 (CH_3), 59.4 & 60.5 ($2OCH_3$), 89.9 (C-7), 104.9–157.2 ppm (Ar–C). Anal. For $C_{18}H_{18}N_2O_3$ (310.35) calcd: C 69.66, H 5.56, N 9.03. Found: C 69.45, H 5.32, N 8.99.

2.1.2. 3-(4,6-Dimethoxybenzofuran-5-yl)-1-phenyl-1H-pyrazole-4-carboxaldehyde (3)

To a solution of compounds **2** (0.93 g, 0.003 mol) in dimethylformamide (15 mL), phosphorus oxychloride (1.17 mL, 0.01 mol) was added dropwise at 0 °C while stirring. After complete addition of $POCl_3$, the reaction mixture was left to stir for 15 h, and then poured onto ice-water (20 mL). The solid that formed was filtered off, air dried and recrystallized from absolute ethanol. Yield 84 %, m.p. 59–61 °C. IR (KBr): *v* 1705 (C═O), 1640 (C═N), 1569 (C═C), 1102, 1084, 1055 cm^{-1} (C–O–C). ^{1}H NMR (500 MHz, DMSO-d_6, 25 °C, TMS): δ = 3.69 & 3.89 (2s, 6H, $2OCH_3$), 7.01 (m, 5H, Ar–H), 7.50 (s, 1H, H-7), 7.53 (d, 1H, H-3), 7.91 (d, 1H, H-2), 9.02 (s, 1H, H-5 pyrazole), 9.55 ppm (s, 1H, CHO). ^{13}C NMR (125 MHz, DMSO-d_6, 25 °C, TMS): δ = 56.1 & 60.5 ($2OCH_3$), 89.7 (C-7), 104.9–157.2 (Ar–C), 201.1 ppm (C═O). MS, *m*/*z* (%): 348 (M^+, 2), 77 (100). Anal. For $C_{20}H_{16}N_2O_4$ (348.35) calcd: C 68.96, H 4.63, N 8.03. Found: C 69.00, H 4.44, N 7.89.

2.1.3. 3-Chloro-3-(4,6-dimethoxybenzofuran-5-yl)propenal (4)

To a solution of compound (**1**) (1 g, 0.0042 mol) in dimethylformamide (15 mL), phosphorus oxychloride (1.17 mL, 0.012 mol) was added dropwise at 0 °C while stirring. After complete addition of $POCl_3$, the reaction mixture was warmed to room temperature and then heated at 60 °C for 3 h. After cooling, the reaction mixture was poured onto crushed ice and then neutralized with 10% aqueous sodium hydroxide solution. The precipitate that formed was filtered off, washed with water, air dried and recrystallized from methanol. Yield 30 %, m.p. 118–120 °C. IR (KBr): *v* 1722 (C═O), 1585 (C═C), 1085, 1054, 1005 (C–O–C), 739 cm^{-1} (Cl). ^{1}H NMR (500 MHz, DMSO-d_6, 25 °C, TMS): δ = 3.89 & 4.11 (2s, 6H, $2OCH_3$), 6.82 (d, 1H, CH═), 7.05 (s, 1H, H-7), 7.18 (d, 1H, H-3) 7.90 (d, 1H, H-2), 9.51 ppm (d, 1H, CHO). ^{13}C NMR (125 MHz, DMSO-d_6, 25 °C, TMS): δ = 56.2 & 59.9 ($2OCH_3$), 89.7 (C-7), 105.3–156.7 (Ar–C), 201.1 ppm (C═O). MS, *m*/*z* (%): 268 (M^+ + 2, 20), 266 (M^+, 7), 238 (100). Anal. For $C_{13}H_{11}ClO_4$ (266.68) calcd: C 58.55, H 4.16. Found: C 58.33, H 4.44.

2.1.4. 5-(4,6-Dimethoxybenzofuran-5-yl)-1H-pyrazole (5)

A mixture of compound **4** (0.53 g, 0.002 mol) and hydrazine hydrate 99% (0.1 g, 0.002 mol) in absolute ethanol (15 mL) containing few drops of glacial acetic acid was refluxed for 3 h. After cooling, the reaction mixture was poured onto water (20 mL) and the solid that formed was filtered off, air dried and recrystallized from methanol. Yield 77 %, m.p. 69–72 °C. IR (KBr): *v* 3100 (NH), 1637 (C═N), 1606 (C═C), 1062, 1020 cm^{-1} (C–O–C). ^{1}H NMR (500 MHz, DMSO-d_6, 25 °C, TMS): δ = 3.89 & 4.11 (2s, 6H, $2OCH_3$), 6.81 (d, 1H, CH), 7.01 (s, 1H, H-7), 7.06 (d, 1H, CH), 7.18 (d, 1H, H-3), 8.02 (d, 1H, H-2), 8.51 ppm (s, 1H, NH). ^{13}C NMR (125 MHz, DMSO-d_6, 25 °C, TMS): δ = 56.2 & 59.9 ($2OCH_3$), 89.7 (C-7), 104.1–156.3 ppm (Ar–C). Anal. For

$C_{13}H_{12}N_2O_3$ (244.25) calcd: C 63.93, H 4.95, N 11.47. Found: C 64.00, H 4.74, N 11.23.

*2.1.5. 1-(5-(4,6-Dimethoxybenzofuran-5-yl)-1H-pyrazol-1-yl)ethanone (**6**)*

To a solution of compound **4** (0.53 g, 0.002 mol) in a mixture of (10 mL) acetic anhydride and glacial acetic acid (2:1) was added hydrazine hydrate 99% (0.1 mL, 0.002 mol). The reaction mixture was refluxed for 4 h. After cooling, the reaction mixture was poured onto ice-water (50 mL), and the solid that formed was filtered off, air dried and recrystallized from aqueous ethanol. Yield 65 %, m.p. 128–130 °C. IR (KBr): ν 1699 (C═O), 1624 (C═N), 1567 (C═C), 1010, 1009, 1001 cm^{-1} (C–O–C). ^1H NMR (500 MHz, DMSO-d_6, 25 °C, TMS): δ = 2.39 (s, 3H, CH_3), 3.89 & 4.11 (2s, 6H, $2OCH_3$), 6.81 (d, 1H, CH), 7.03 (s, 1H, H-7), 7.10 (d, 1H, CH), 7.67 (d, 1H, H-3), 7.99 ppm (d, 1H, H-2). ^{13}C NMR (125 MHz, DMSO-d_6, 25 °C, TMS): δ = 21.0 (CH_3), 56.2 & 59.9 ($2OCH_3$), 89.7 (C-7), 104.1–156.7 (Ar–C), 201.1 ppm (C═O). Anal. For $C_{15}H_{14}N_2O_4$ (286.28) calcd: C 62.93, H 4.93, N 9.79. Found: C 62.77, H 4.74, N 9.55.

*2.1.6. 5-(4,6-Dimethoxybenzofuran-5-yl)-1-phenyl-1H-pyrazole (**7**)*

A mixture of compound **4** (0.53 g, 0.002 mol) and phenylhydrazine (0.22 g, 0.002 mol) in absolute ethanol (15 mL) containing few drops of glacial acetic acid was refluxed for 3 h. After cooling, the reaction mixture was poured onto water (20 mL) and the solid that formed was filtered off, air dried and recrystallized from methanol. Yield 45 %, m.p. 81–3 °C. IR (KBr): ν 1621 (C═N), 1599 (C═C), 1011, 1009, 1001 cm^{-1} (C–O–C). ^1H NMR (500 MHz, DMSO-d_6, 25 °C, TMS): δ = 2.89 & 3.99 (2s, 6H, $2OCH_3$), 6.81 (d, 1H, CH), 7.00 (s, 5H, Ph–H), 7.03 (s, 1H, H-7), 7.23 (d, 1H, CH), 7.44 (d, 1H, H-3), 7.98 ppm (d, 1H, H-2). ^{13}C NMR (125 MHz, DMSO-d_6, 25 °C, TMS): δ = 56.2 & 59.9 ($2OCH_3$), 89.7 (C-7), 111.1–155.3 ppm (Ar–C). Anal. For $C_{19}H_{16}N_2O_3$ (320.34) calcd: C 71.24, H 5.03, N 8.74. Found: C 71.44, H 4.94, N 8.55.

*2.1.7. 5-(4,6-Dimethoxybenzofuran-5-yl)-1-benzyl-1H-pyrazole (**8**)*

A mixture of compound **4** (0.53 g, 0.002 mol), benzylhydrazine dihydrochloride (0.39 g, 0.002 mol) and sodium acetate (0.3 g, 0.004 mol) in absolute ethanol (15 mL) was refluxed for 3 h. After cooling, the reaction mixture was poured onto water (20 mL) and the solid that formed was filtered off, air dried and recrystallized from absolute ethanol. Yield 80 %, m.p. 89–91 °C. IR (KBr): ν 1620 (C═N), 1555 (C═C), 1011, 1009, 1001 cm^{-1} (C–O–C). ^1H NMR (500 MHz, DMSO-d_6, 25 °C, TMS): δ = 3.80 & 4.04 (2s, 6H, $2OCH_3$), 4.56 (s, 2H, CH_2), 6.81 (d, 1H, CH), 7.05 (s, 1H, H-7), 7.18 (d, 1H, CH), 7.27 (d, 1H, H-3), 7.29 (s, 5H, Ph–H), 7.89 ppm (d, 1H, H-2). ^{13}C NMR (125 MHz, DMSO-d_6, 25 °C, TMS): δ = 32.4 (CH_2), 56.2 & 57.2 ($2OCH_3$), 89.7 (C-7), 105.3–161.4 ppm (Ar–C). Anal. For $C_{20}H_{18}N_2O_3$ (334.37) calcd: C 71.84, H 5.43, N 8.38. Found: C 71.71, H 5.25, N 8.51.

*2.1.8. 6-(4,6-Dimethoxybenzofuran-5-yl)pyrimidine-2(1H)-thione (**9**)*

A mixture of compound **4** (0.53 g, 0.002 mol) and thiourea (0.15 g, 0.002 mol) in absolute ethanol (15 mL) containing few drops of glacial acetic acid (0.5 mL) was refluxed for 2 h. After cooling, the reaction mixture was poured onto ice-water (50 mL) and the solid that formed was filtered off, air dried and recrystallized from absolute ethanol. Yield 92 %, m.p. 110–2 °C. IR (KBr): ν 3162 (NH), 1615 (C═N), 1573 (C═C), 1248 (C═S), 1169, 1097, 1028 cm^{-1} (C–O–C). ^1H NMR (500 MHz, DMSO-d_6, 25 °C, TMS): δ = 3.80 & 4.03 (2s, 6H, $2OCH_3$), 7.04 (s, 1H, H-7), 7.18 & 7.27 (2d, 2H, 2CH), 7.44 (d, 1H, H-3), 7.89 (d, 1H, H-2), 11.12 ppm (s, 1H, NH). ^{13}C NMR (125 MHz, DMSO-d_6, 25 °C, TMS): δ = 56.2 & 57.2 ($2OCH_3$), 89.7 (C-7), 105.3–161.4 ppm (Ar–C). Anal. For $C_{14}H_{12}N_2O_3S$ (288.32) calcd: C 58.32, H 4.20, N 9.72. Found: C 58.45, H 4.44, N 9.52.

*2.1.9. 6-(4,6-Dimethoxybenzofuran-5-yl)pyrimidin-2(1H)-one (**10**)*

A mixture of compound **4** (0.53 g, 0.002 mol) and urea (0.12 g, 0.002 mol) in absolute ethanol (15 mL) containing few drops of glacial acetic acid (0.5 mL) was refluxed for 2 h. After cooling, the reaction mixture was poured onto ice-water (50 mL) and the solid that formed was filtered off, air dried and recrystallized from absolute ethanol. Yield 85 %, m.p. 99–102 °C. IR (KBr): ν 3107 (NH), 1676 (C═O), 1641 (C═N), 1609 (C═C), 1153, 1075, 1007 cm^{-1} (C–O–C). ^1H NMR (500 MHz, DMSO-d_6, 25 °C, TMS): δ = 3.80 & 4.04 (2s, 6H, $2OCH_3$), 7.05 (s, 1H, H-7), 7.18 & 7.27 (2d, 2H, 2CH), 7.29 (d, 1H, H-3), 7.89 (d, 1H, H-2), 10.92 ppm (s, 1H, NH). ^{13}C NMR (125 MHz, DMSO-d_6, 25 °C, TMS): δ = 56.2 & 57.2 ($2OCH_3$), 89.7 (C-7), 105.3–157.4 (Ar–C), 201.1 ppm (C═O). Anal. For $C_{14}H_{12}N_2O_4$ (272.26) calcd: C 61.76, H 4.44, N 10.29. Found: C 61.55, H 4.22, N 10.01.

*2.1.10. 4-(4,6-Dimethoxybenzofuran-5-yl)pyrimidin-2-amine (**11**)*

A mixture of compound **4** (2.66 g, 0.01 mol), guanidine hydrochloride (0.96 g, 0.01 mol) and anhydrous sodium acetate (0.82 g, 0.01 mol) in absolute ethanol (15 mL) was refluxed for 2–3 h. The solid that formed while hot was filtered off, washed with water, air dried and recrystallized from absolute ethanol. Yield 40 %, m.p. 47–9 °C. IR (KBr): ν 3161 & 3122 (NH_2), 1616 (C═N), 1578 (C═C), 1103, 1022 cm^{-1} (C–O–C). ^1H NMR (500 MHz, DMSO-d_6, 25 °C, TMS): δ = 3.80 & 4.04 (2s, 6H, $2OCH_3$), 5.56 (s, 2H, NH_2), 7.05 (s, 1H, H-7), 7.27 & 7.54 (2d, 2H, 2CH), 7.84 (d, 1H, H-3), 8.09 ppm (d, 1H, H-2). ^{13}C NMR (125 MHz, DMSO-d_6, 25 °C, TMS): δ = 56.2 & 58.7 ($2OCH_3$), 89.7 (C-7), 104.3–157.4 ppm (Ar–C). Anal. For $C_{14}H_{13}N_3O_3$ (271.27) calcd: C 61.99, H 4.83, N 15.49. Found: C 62.11, H 5.00, N 15.32.

*2.1.11. N-(4-(4,6-Dimethoxybenzofuran-5-yl)pyrimidin-2-yl) acetamide (**12**)*

A solution of compound **11** (0.54 g, 0.002 mol) in a mixture of (10 mL) acetic anhydride and glacial acetic acid (2:1) was heated under reflux for 10 h. After cooling, the reaction mixture was poured onto ice-water (50 mL), and the solid that formed was filtered off, air dried and recrystallized from aqueous ethanol. Yield 78 %, m.p. 161–3 °C. IR (KBr): ν 3100 (NH), 1698 (C═O), 1622 (C═N), 1601 (C═C), 1011, 1009, 1001 cm^{-1} (C–O–C). ^1H NMR (500 MHz, DMSO-d_6, 25 °C, TMS): δ = 2.10 (s, 1H, NH), 3.2 (s, 3H, CH_3), 3.80 & 4.04 (2s, 6H, $2OCH_3$), 7.05 (s, 1H, H-7), 7.27 & 7.54 (2d, 2H,

2CH), 7.84 (d, 1H, H-3), 8.09 ppm (d, 1H, H-2). ^{13}C NMR (125 MHz, DMSO-d_6, 25 °C, TMS): δ = 23.1 (CH_3), 56.2 & 58.7 ($2OCH_3$), 89.7 (C-7), 104.3–157.4 (Ar–C), 175.1 ppm (C═O). Anal. For $C_{16}H_{15}N_3O_4$ (313.31) calcd: C 61.34, H 4.83, N 13.41. Found: C 61.50, H 4.61, N 13.55.

*2.1.12. N-(4-(4,6-Dimethoxybenzofuran-5-yl)pyrimidin-2-yl)-2-benzamide (**13**)*

A mixture of compound **11** (0.54 g, 0.002 mol) and benzoyl chloride (0.002 mol) in dry dioxane containing triethylamine (1 mL) was refluxed for 3 h. After cooling, the reaction mixture was poured onto water (30 mL) and the solid that formed was filtered off, air dried and recrystallized from absolute ethanol. Yield 60 %, m.p. 72–4 °C. IR (KBr): *v* 3150 (NH), 1678 (C═OO), 1622 (C═ON), 1599 (C═OC), 1011, 1009, 1001 cm^{-1} (C–O–C). ^{1}H NMR (500 MHz, DMSO-d_6, 25 °C, TMS): δ = 2.32 (s, 1H, NH), 3.80 & 4.04 (2s, 6H, $2OCH_3$), 7.01 (s, 5H, Ph–H), 7.05 (s, 1H, H-7), 7.27 & 7.54 (2d, 2H, 2CH), 7.77 (d, 1H, H-3), 8.09 ppm (d, 1H, H-2). Anal. For $C_{21}H_{17}N_3O_4$ (375.38) calcd: C 67.19, H 4.56, N 11.19. Found: C 67.44, H 4.60, N 11.27.

*2.1.13. N-(4-(4,6-Dimethoxybenzofuran-5-yl)pyrimidin-2-yl)-2-benzenesulphonamide (**14**)*

A mixture of compound **11** (0.54 g, 0.002 mol) and benzenesulphonyl chloride (0.002 mol) in dry dioxane (15 mL) containing triethylamine (1 mL) was refluxed for 3 h. After cooling, the reaction mixture was poured onto water (30 mL) and the solid that formed was filtered off, air dried and recrystallized from absolute ethanol. Yield 62 %, m.p. 85–7 °C. IR (KBr): *v* 3180 (NH), 1622 (C═ON), 1565 (C═OC), 1375 & 1150 (SO_2), 1011, 1009, 1001 cm^{-1} (C–O–C). ^{1}H NMR (500 MHz, DMSO-d_6, 25 °C, TMS): δ = 2.31 (s, 1H, NH), 3.80 & 4.04 (2s, 6H, $2OCH_3$), 7.01 (s, 5H, Ph–H), 7.08 (s, 1H, H-7), 7.27 & 7.54 (2d, 2H, 2CH), 7.77 (d, 1H, H-3), 7.98 ppm (d, 1H, H-2). Anal. For $C_{20}H_{17}N_3O_5S$ (411.43) calcd: C 58.38, H 4.16, N 10.21. Found: C 58.50, H 4.25, N 10.44.

*2.1.14. 4-(4,6-Dimethoxybenzofuran-5-yl)-2-azidopyrimidine (**15**)*

To a cooled solution of compound **11** (5.42 g, 0.02 mol) in concentrated sulphuric acid (5 mL) and ice (15 g), cooled solution of sodium nitrite (1.73 g, 0.025 mol) in ice-water (10 mL) was added dropwise while stirring at 0–5 °C and keeping at this temperature for 10 min. To the solution of diazonium salt, sodium azide (1.3 g, 0.02 mol) in ice-water (5 mL) was added dropwise while stirring. The solution was left at room temperature for 15 min then the azide was extracted by diethyl ether. Ether was evaporated in vacuo and azide was used without subsequent cleaning. 2-Azidopyrimidine derivative (**15**) was identified by chromatography mass spectrometry since it decomposed slowly during the preparation of the analyzed sample. Also, it is used in the reaction immediately after its formation because of its instability. Yield 71 %, m.p. 120–2 °C. MS, *m*/*z* (%): 297 for $C_{14}H_{11}N_5O_3$ (M^+, 2), 225 (100).

*2.1.15. 5-Methyl-1-(4-(4,6-dimethoxybenzofuran-5-yl)pyrimidin-2-yl)-1H-1,2,3-triazole-4-carboxylic acid (**16**)*

To a solution of sodium (0.23 g, 0.01 mol) in absolute methanol (20 mL) were added ethyl acetoacetate (1.34 g, 0.01 mol) and 2-azidopyrimidine **15** (2.71 g, 0.01 mol) dropwise while stirring and cooling in an ice-bath. The reaction mixture was kept in an ice water bath for 30 min and then gradually heated under reflux for 1 h. After cooling, the reaction mixture was neutralized by diluted hydrochloric acid (1:1). The solid that formed was filtered off, washed with water, air dried and recrystallized from methanol. Yield 63 %, m.p. 178–180 °C. IR (KBr): *v* 4300 (OH), 1645 (C═O), 1622 (C═N), 1578 (C═C), 1009, 1001 cm^{-1} (C–O–C). ^{1}H NMR (500 MHz, DMSO-d_6, 25 °C, TMS): δ = 2.31 (s, 3H, CH_3), 3.80 & 4.04 (2s, 6H, $2OCH_3$), 7.08 (s, 1H, H-7), 7.27 & 7.54 (2d, 2H, 2CH), 7.77 (d, 1H, H-3), 7.98 (d, 1H, H-2), 12.10 ppm (s, 1H, OH). Anal. For $C_{18}H_{15}N_5O_5$ (381.34) calcd: C 56.69, H 3.96, N 18.37. Found: C 56.44, H 4.01, N 18.50.

*2.1.16. N-(p-Nitrobenzylidene)-4-(4,6-dimethoxybenzofuran-5-yl) pyrimidine-2-amine (**17**)*

A mixture of compound **11** (0.81 g, 0.003 mol) and *p*-nitrobenzaldehyde (0.45 g, 0.003 mol) in absolute ethanol (20 mL) containing glacial acetic acid (1 mL) was refluxed for 3 h. After cooling, the reaction mixture was poured onto water (30 mL) and the solid that formed was filtered off, air dried and recrystallized from absolute ethanol. Yield 93 %, m.p. 79–81 °C. IR (KBr): *v* 1645 (C═N), 1589 (C═C), 1012, 1009, 1001 (C–O–C) cm^{-1}. ^{1}H NMR (500 MHz, DMSO-d_6, 25 °C, TMS): δ = 3.80 & 4.04 (2s, 6H, $2OCH_3$), 7.08 (s, 1H, H-7), 7.27 (d, 1H, CH), 7.29–7.56 (m, 4H, Ph–H), 7.62 (d, 1H, CH), 7.77 (d, 1H, H-3), 7.98 (d, 1H, H-2), 8.57 (s, 1H, CH═N) ppm. Anal. For $C_{21}H_{16}N_4O_5$ (404.38) calcd: C 62.37, H 3.99, N 13.86. Found: C 62.55, H 4.02, N 14.00.

*2.1.17. 3-(4-(4,6-Dimethoxybenzofuran-5-yl)pyrimidin-2-yl)-2-(p-nitrophenyl)thiazolidin-4-one (**18**)*

To a stirred solution of compound **17** (0.81 g, 0.002 mol) in dry dioxane (25 mL) was added thioglycolic acid (0.024 g, 0.003 mol). After stirring for 4 h, anhydrous sodium sulphate (5 g) was added and then refluxed for 6 h. The reaction mixture was filtered while hot. After cooling, the solid that obtained was filtered off, washed with water, air dried and recrystallized from dioxane. Yield 79 %, m.p. 94–6 °C. IR (KBr): *v* 1670 (C═O), 1622 (C═N), 1576 (C═C), 1012, 1009, 1001 cm^{-1} (C–O–C). ^{1}H NMR (500 MHz, DMSO-d_6, 25 °C, TMS): δ = 3.31 (s, 2H, CH_2), 3.80 & 4.04 (2s, 6H, $2OCH_3$), 5.61 (s, 1H, CH), 7.08 (s, 1H, H-7), 7.27 (d, 1H, CH), 7.29–7.56 (m, 4H, Ph–H), 7.62 (d, 1H, CH), 7.77 (d, 1H, H-3), 7.98 ppm (d, 1H, H-2). Anal. For $C_{23}H_{18}N_4O_6S$ (478.48) calcd: C 57.73, H 3.79, N 11.71. Found: C 57.62, H 4.00, N 11.55.

*2.1.18. 3-Chloro-1-(4-(4,6-dimethoxybenzofuran-5-yl)pyrimidin-2-yl)-4-(p-nitrophenyl)azetidin-2-one (**19**)*

A solution of compound **17** (0.81 g, 0.002 mol) and triethylamine (0.5 mL) in dry benzene (50 mL) was cooled and stirred. To this well-stirred cooled solution chloroacetyl chloride (0.004 mol) was added dropwise within a period of 20 min, and then the reaction mixture was stirred for an additional 3 h and left at room temperature for 48 h. The reaction mixture was poured onto water (30 mL) and the solid that formed was filtered off, air dried and recrystallized from *n*-hexane. Yield 71%, m.p. 226–8 °C. IR (KBr): *v* 1665 (C═O), 1621 (C═N), 1578 (C═C), 1010, 1009, 1001 cm^{-1} (C–O–C), 745 (Cl). ^{1}H NMR (500 MHz, DMSO-d_6, 25 °C, TMS): δ = 3.80

& 4.04 (2s, 6H, $2OCH_3$), 4.99 (s, 1H, CH), 5.61 (d, 1H, CH), 7.08 (s, 1H, H-7), 7.27 (d, 1H, CH), 7.29–7.56 (m, 4H, Ph–H), 7.62 (d, 1H, CH), 7.77 (d, 1H, H-3), 7.98 ppm (d, 1H, H-2). Anal. For $C_{23}H_{17}ClN_4O_6$ (480.86) calcd: C 57.45, H 3.56, N 11.65. Found: C 57.22, H 3.66, N 11.82.

2.2. Biological assays

2.2.1. Animals

Adult male albino rats (Harlan Sprague–Dawley, USA), weighing 150–180 g were used for the evaluation of the anti-inflammatory activity. Animals were fasted for 12 h before the assay. Adult Swiss Webster mice of both sexes (Harlan Sprague–Dawley, USA), weighing 20–25 g were fasted for 12–24 h and used for the assessment of the analgesic and anticonvulsant activities. All animals were obtained from the animal house colony of the National Research Centre, Cairo, Egypt. Animals were allowed free access to water and fed with standard diet. The research was conducted in accordance with the ethical rules on animal experimentation, approved by the Ethics Committee of the National Research Centre, Cairo, Egypt.

2.2.2. Anti-inflammatory activity

Evaluation of the anti-inflammatory activity was performed using carrageenean-induced rat paw oedema model according to the method of (Obukowicz et al., 1998). The animals were divided into groups (control, reference and test groups, each of 8 animals. Acute inflammation was produced by subplantar injection of 0.05 mL of 1 % suspension of carrageenean in saline into the plantar tissue of one (right) hind paw of the rat, one hour after oral administration of the test compound at dose levels of 20 and 5 mg kg^{-1}. The control group received equal volume of saline into the other (left) hind paw. The reference group was orally administered with flufenamic acid (20 mg kg^{-1}) and indomethacin (5 mg kg^{-1}) suspended in saline as reference drugs. The average mass of oedema was estimated for control, reference and the test groups four hours after drug administration. The inhibitory activity (percentage of inhibition of oedema) was evaluated (Winter et al., 1963).

The results were analyzed for statistical significance (expressed as mean ± SEM) between the vehicle control and the treated groups using one-way ANOVA followed by multiple comparisons by Duncan's multiple range tests.

2.2.3. Analgesic activity

It was studied using *p*-benzoquinone-induced writhing model in mice according to the method described by Okun et al. (1963). The test compounds and the reference drugs flufenamic acid and indomethacine were prepared as a suspension in 2 % Tween 80. A sensitivity test was carried out one day before drug administration when the animals were injected (*i.p.*) with 0.2–0.25 mL of 0.02 % freshly prepared solution of *p*-benzoquinone in distilled water. Animals showing writhing to *p*-benzoquinone within 30 min were chosen for studying the analgesic activity. On the following day, mice were divided into 13 groups each of 6 animals, and the drugs were administered according to the following protocol: the first group received 2% Tween 80 (solvent/negative control), the second group received flufenamic acid as a reference (20 mg kg^{-1}), the third group received indomethacine as a reference (5 mg kg^{-1}), while the other groups received two doses of the test compounds (20 and 5 mg kg^{-1}). One hour later, 0.02% solution of *p*-benzoquinone was administered (*i.p.*). The animals were observed for 30 min after injection of the irritant during which the animals showing writhing were counted (writhing is defined as stretch, torsion to one side, drawing up of hind leg, retraction of the abdomen, so that the belly of mouse touches the floor). All writhing is considered as a positive response. The analgesic activity was expressed as the percent protection.

2.2.4. Anticonvulsant activity

The electric shock seizure test (Vogel and Vogel, 1997) was taken as criteria for the evaluation of the anticonvulsant activity. Mice were injected intraperitoneally with 2% Tween 80 (solvent/negative control) and 5 mg kg^{-1} diazepam (reference drug). The other groups received two doses (25 and 12.5 mg kg^{-1}) of each test compound. One hour after the drug administration, animals were stimulated through ear electrode of 50 mA as a signal stimulator for 0.2 s. The characteristics of electric shock seizure are a tonic limb flexion of 1–2 s, followed by a tonic limb extension of roughly 10–12 s, and finally generalized clonic movement for 12 s. Only abolishment of the hind limb tonic extensor spasm is recorded as the measure of anticonvulsant potency. The tonic component is considered abolished if the hind leg extension does not exceed a 90° angle with the plane of the body. Animals showing protection against convulsion were counted in each group. The anticonvulsant activity was expressed as the percent protection.

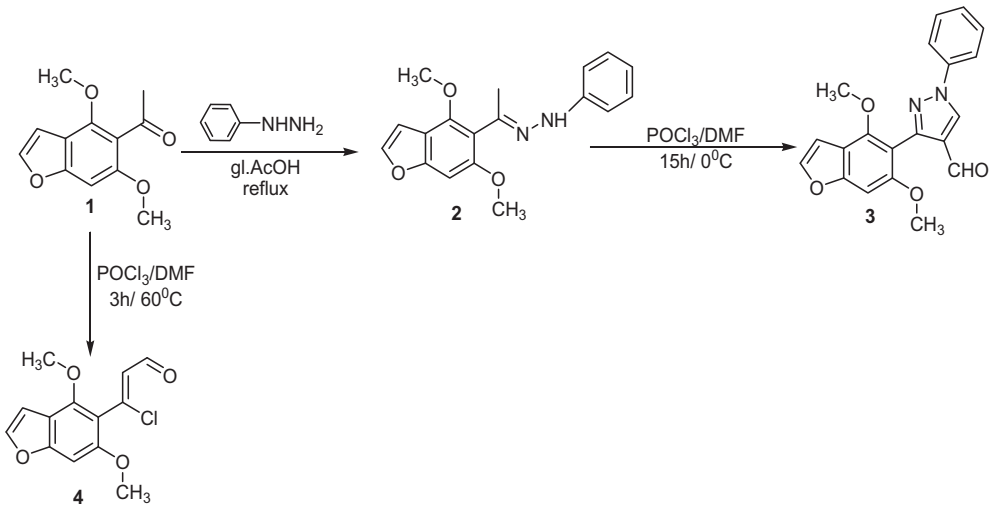
3. Results and discussion

3.1. Chemistry

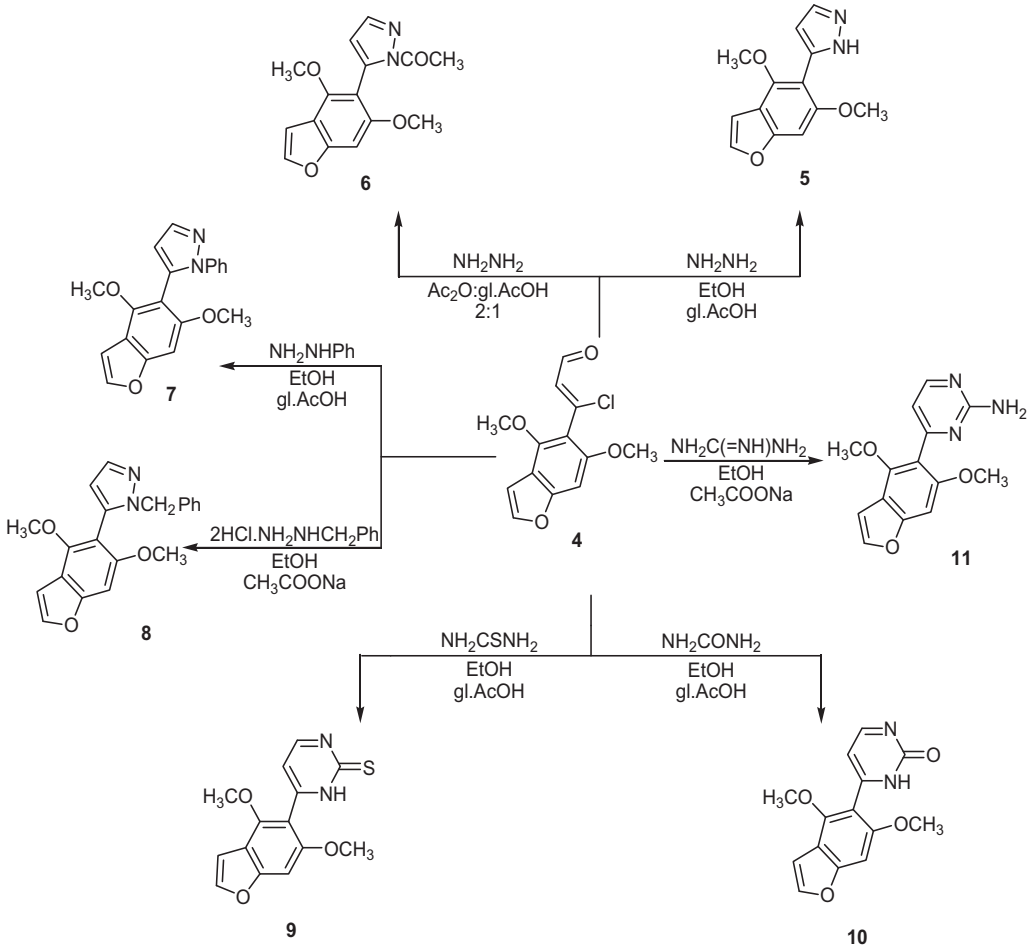
The synthetic route for the preparation of the target compounds is illustrated in Scheme 1–3. Condensation reaction of 1-(4,6-dimethoxybenzofuran-5-yl)ethanone (**1**) (Schonberg et al., 1953) with phenylhydrazine in glacial acetic acid led to the formation of the corresponding 1-(1-(4,6-dimethoxybenzofuran-5-yl)ethylidene)-2-phenylhydrazine (**2**) (Scheme 1). Vilsmeier–Haack reaction of the latter hydrazone 2 using 2.5 equivalent moles of Vilsmeier reagent (DMF/$POCl_3$) preformed double addition of reagent on the methyl group to afford ultimately after hydrolysis, the cyclize pyrazole-4-carboxaldehyde derivative **3** with good yield 84% (Scheme 1). The IR spectrum of compound **3** showed strong absorption bands at 1705 cm^{-1} characteristic for C=O of the aldehyde group. Its ^1H NMR spectrum lacks the presence of CH_3 protons of hydrazone 2 and revealed new singlet signal at 9.55 ppm for CHO proton besides H-5 of pyrazole at 9.02 ppm. In addition, ^{13}C NMR spectrum revealed signal at 201.1 ppm for (C=O). Its mass spectrum showed molecular ion peaks at m/z (%) = 348 (2) (c.f. Section 2).

On the other hand, reaction of compound **1** with 2.5 equivalent moles of Vilsmeier reagent (DMF/$POCl_3$) under heating at 60 °C for 3 h (Vilsmeier Haack Arnold reaction) led to the formation of 3-chloro-3-(4,6-dimethoxybenzofuran-5-yl)propenal (**4**) in 30% yield (Scheme 1).

Although there is very low yield of compound 4 it seems to have some interest due to the presence of α,β-bifunctional chloro and aldehyde groups. Reaction of compound 4 with

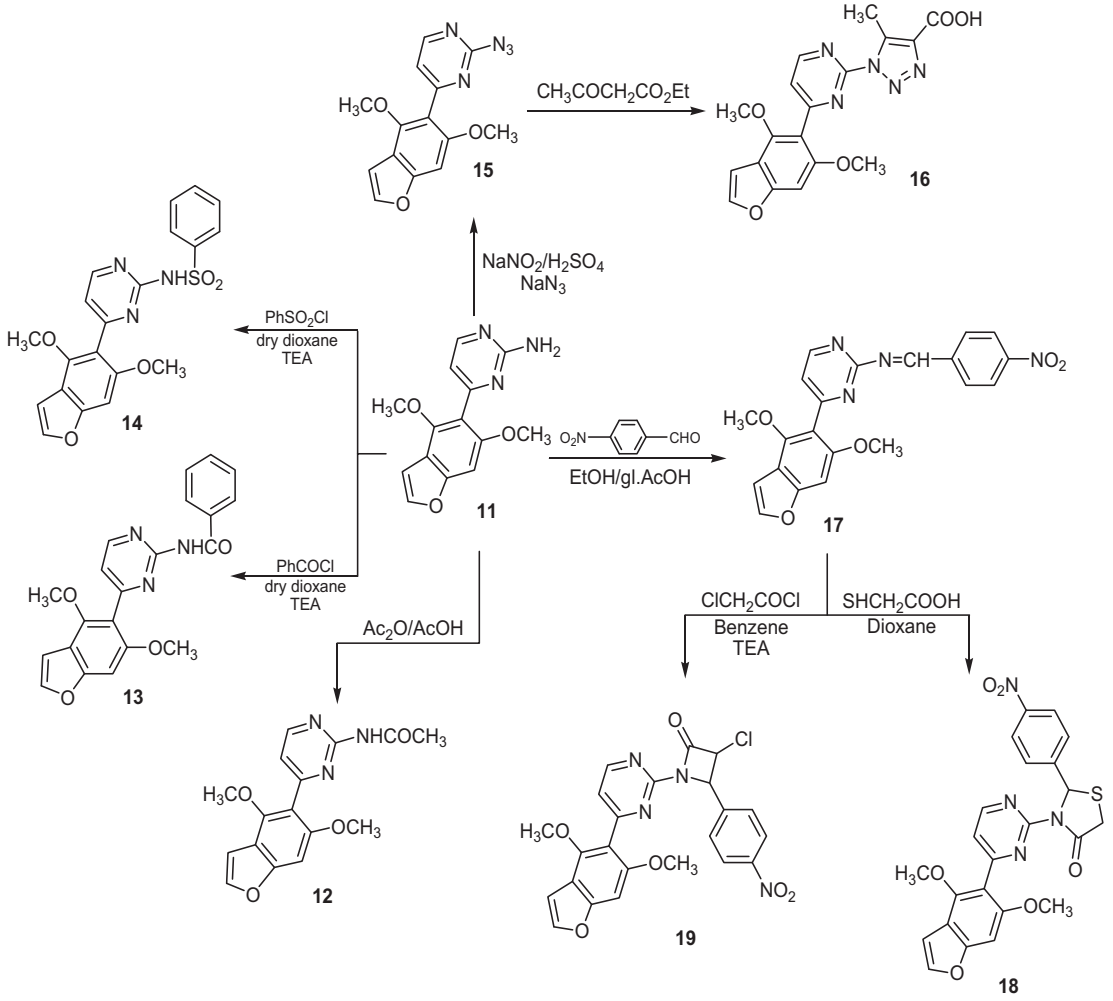


Scheme 1



Scheme 2

hydrazine hydrate in absolute ethanol and in the presence of few drops of glacial acetic acid afforded 5-(4,6-dimethoxybenzofuran-5-yl)-1*H*-pyrazole (**5**). Whereas, reaction of compound **4** with hydrazine hydrate under reflux in a mixture of acetic anhydride and glacial acetic acid (2:1) afforded, the corresponding *N*-acetylpyrazole derivative (**6**) (Scheme 2). Additionally, reaction of compound **4** with phenylhydrazine gave *N*-phenylpyrazole derivative **7**. While, reac-



Scheme 3

tion of compound **4** with benzylhydrazine dihydrochloride in the presence of anhydrous sodium acetate gave *N*-benzylpyrazole derivative **8** (Scheme 2).

Furthermore, reaction of compound **4** with thiourea and/or urea in absolute ethanol in the presence of glacial acetic acid as a catalyst gave 6-(4,6-dimethoxybenzofuran-5-yl) pyrimidin-2(1*H*)-thione (**9**) and 6-(4,6-dimethoxybenzofuran-5-yl)pyrimidin-2(1*H*)-one (10), respectively. Moreover, reaction of compound **4** with guanidine hydrochloride in absolute ethanol in the presence of anhydrous sodium acetate yielded 6-(4,6-dimethoxybenzofuran-5-yl)pyrimidin-2-amine (**11**) (Scheme 2).

Upon heating of 2-aminopyrimidine derivative (**11**) in a mixture of acetic anhydride and glacial acetic acid (2:1) led to the formation of N-(4-(4,6-dimethoxybenzofuran-5-yl)pyrimidin-2-yl)acetamide (**12**) (Scheme 3). On the other hand, reaction of compound (**11**) with benzoyl chloride and/or benzenesulphonyl chloride in dry dioxane and in the presence of triethylamine as a base afforded *N*-benzamide derivatives **13** and *N*-sulphonamide derivatives **14**, respectively (Scheme 3).

Diazotization of 2-aminopyrimidine derivative (**11**) with concentrated sulphuric acid and sodium nitrite at 0–5 °C yielded the corresponding diazonium salt which, upon reaction with sodium azide yielded 2-azidopyrimidine derivative (**15**) (Scheme 3).

It was previously reported that, organic azide undergoes base catalyzed condensation reaction with activated methylenic compound giving rise to the 1,2,3-triazole moiety (Pokhodylo et al., 2009). In the present work and under the above mentioned conditions, the new azidopyrimidine derivative (**15**) was allowed to react with ethyl acetoacetate in the presence of sodium methoxide and give the corresponding 5-methyl-1-(4-(4,6-dimethoxybenzofuran-5-yl)pyrimidin-2-yl)-1*H*-1,2,3-triazole-4-carboxylic acid (**16**) in 63% good yield (Scheme 3).

Acid catalyzed reaction of compound (**11**) with *p*-nitrobenzaldehyde in absolute ethanol yielded the corresponding Schiff base 17 (Scheme 3). Cyclocondensation of Schiff base 17 with thioglycollic acid in the presence of anhydrous sodium sulphate yielded 3-(4-(4,6-dimethoxybenzofuran-5-yl)pyrimidin-2-yl)-2-(*p*-nitrophenyl)thiazolidin-4-one (**18**). On the other hand, reaction of Schiff base 17 with chloroacetyl chloride in the presence of triethylamine afforded 3-chloro-1-(4-(4,6-dimethoxybenzofuran-5-yl)pyrimidin-2-yl)-4-(*p*-nitrophenyl) azetidin-2-one (**19**) (Scheme 3).

The structures of the newly synthesized compounds were confirmed on the basis of elemental analyses as well as IR, NMR, and MS spectral data (c.f. Section 2).

3.2. Biological activity

The newly synthesized compounds were evaluated for their anti-inflammatory activity against carrageenan-induced rat paw oedema by administration of 20 and 5 mg kg^{-1} (*p.o.*) using flufenamic acid (20 mg kg^{-1}) and indomethacin (5 mg kg^{-1}) as reference drugs. The data obtained (Table 1) revealed that, paw oedema was inhibited by the oral administration of the most of the test compounds at a dose level of 20 mg kg^{-1}. The most active test compounds were in the descending order of 5 > 6, 11 > 8 > 7 > 12 > 17 with inhibition effect ranging from 50% to 39% compared to flufenamic acid (53%) at a dose of 20 mg kg^{-1} and indomethacin (51%) at a dose of 5 mg kg^{-1}. The existence of pyrazole moiety at position-5 of benzofuran as in compounds **5** and **6** or pyrimidine moiety as in compound **11** showed inhibitions of 50%, 45% and 45% nearly to the reference flufenamic acid (53%). Only, compounds **5**, **6**, **7**, **8** and **17** exhibit inhibition effects of 39%, 33%, and 32% at a dose of 5 mg kg^{-1} compared to indomethacin (51%) at a dose of 5 mg kg^{-1}.

The analgesic activity of the investigated synthesized compounds was studied using *p*-benzoquinone induced writhing response in mice. The obtained data (Table 2) indicated that, compound **5** showed equipotent writhing inhibition of 83% as compared to the reference drug flufenamic acid (83%) at a dose of 20 mg kg^{-1}. Compounds **6**, **7** and **8** at a dose of

Table 1 Effect of the newly synthesized compounds on carrageenan induced rat paw oedema.

Compd. no.	Dose (mg kg^{-1})	Inhibition (%)	Compd. no.	Dose (mg kg^{-1})	Inhibition (%)
5	5	39	**13**	5	27
	20	50		20	33
6	5	33	**14**	5	20
	20	45		20	32
7	5	33	**16**	5	26
	20	42		20	33
8	5	32	**17**	5	32
	20	44		20	39
9	5	19	**18**	5	20
	20	33		20	32
10	5	22	**19**	5	16
	20	37		20	33
11	5	19	Negative control[a]	0	0
	20	45			
12	5	19	Indomethacin	5	51
	20	39	Flufenamic acid	20	53

[a] Saline is a respective control and solvent for test compounds and reference drugs (flufenamic acid and indomethacin).

Table 2 Effect of the newly synthesized compounds on *p*-benzoquinone induced writhing response in mice.

Compd. no.	Dose (mg kg^{-1})	Inhibition (%)	Compd. no.	Dose (mg kg^{-1})	Inhibition (%)
5	20	83	**13**	20	30
	5	50		5	5
6	20	66	**14**	20	42
	5	33		5	16
7	20	66	**16**	20	42
	5	33		5	33
8	20	66	**17**	20	42
	5	33		5	16
9	20	50	**18**	20	33
	5	33		5	16
10	20	50	**19**	20	33
	5	33		5	16
11	20	50	Negative control[a]	0	0
	5	33			
12	20	40	Flufenamic acid	20	83
	5	16	Indomethacin	5	66

[a] 2% Tween 80 is a respective control and solvent for tested compounds and reference drugs (flufenamic acid and indomethacin).

Table 3 Anticonvulsant activity of the newly synthesized compounds.

Compd. no.	Dose (mg kg^{-1})	Protection (%)	Compd. no.	Dose (mg kg^{-1})	Protection (%)
5	25	83	**13**	25	42
	12.5	45		12.5	16
6	25	50	**14**	25	40
	12.5	33		12.5	22
7	25	66	**16**	25	33
	12.5	33		12.5	16
8	25	50	**17**	25	66
	12.5	33		12.5	33
9	25	50	**18**	25	33
	12.5	27		12.5	16
10	25	42	**19**	25	33
	12.5	22		12.5	16
11	25	50	Negative control[a]	0	0
	12.5	16			
12	25	50	Diazepam	5	50
	12.5	33			

[a] 2% Tween 80 is a respective control and solvent for tested compounds and diazepam.

5 mg kg^{-1} showed equipotent writhing inhibition of 66% as compared to the reference drug indomethacin at a dose of 5 mg kg^{-1}. On the other hand, the most active test compounds were in the descending order of **5** > **6**, **7** and **8** > **9**, **10** and **11** with writhing inhibition of 66%, 50% and 42% compared to flufenamic acid (83%) at a dose of 20 mg kg^{-1}. Also, the most active test compounds were in the descending order of **5** > **6**, **7**, **8**, **9**, **10**, **11** and **16** with writhing inhibitions of 50% and 33% compared to indomethacin at a dose of 5 mg kg^{-1}. From the data obtained, the writhing inhibitions of the newly synthesized compounds seem to relate with the presence of pyrazole and pyrimidine moieties at these compounds.

The anticonvulsant properties of the tested compounds were studied using diazepam as reference which showed % protection of 50 in a dose of 5 mg kg^{-1} (Table 3). Data obtained revealed that, compounds **6**, **8**, **9**, **11** and **12** at a dose level of 25 mg kg^{-1} showed anticonvulsant protection (50%) as did the reference drug diazepam at 5 mg kg^{-1}, while compounds **5**, **7** and **17** at a dose level of 25 mg kg^{-1} exhibited higher protection (66–83%) compared to diazepam at 5 mg kg^{-1}. Compound **5** at a dose level of 25 and 12.5 mg kg^{-1}, respectively, was found to be the most potent compound as it induced 83% and 45% protection compared to diazepam (5 mg kg^{-1}) which caused 50% protection.

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