Synthesis of novel pyridazinyl benzimidazole, benzothiazole and benzoxazole of expected anti-inflammatory activity

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In this study, a novel series of 6-oxopyridazinyl benzazoles and 3, 6-dioxopyridazinyl benzazoles were prepared from the starting compounds, 2-hydrazinobenzimidazole, 2-hydrazinobenzothiazole and 2-hydrazinobenzoxazole by reaction with butyric acid derivatives and cyclic anhydrides respectively. The structures of the new compounds were confirmed by elemental analysis as well as ^{1}H NMR, IR and MS data. Some of the newly prepared compounds were subjected to evaluation for their anti-inflammatory activity using carrageenan induced paw edema at dose 100 mg kg^{-1} using indomethacin as a reference standard and were found to be bioactive.

Keywords: 6-oxopyridazinyl benzazoles, 3, 6-dioxopyridazinyl benzazoles, anti-inflammatory activity

Commercially available nonsteroidal anti-inflammatory drugs (NSAIDs) are widely used for reducing inflammatory pain. NSAIDs act through the inhibition of a cyclooxygenase (COX) enzyme. This enzyme exists in two isoforms, one constitutive (COX-1) which is produced in many tissues such as the kidney and the gastrointestinal tract, and an inducible form (COX-2), which is expressed during inflammation at a site of injury.[1-4] Prostaglandins made by COX-1 enzyme are important for gastric cytoprotection, whereas prostaglandins made by COX-2 cause inflammation.[5-7] Therefore, the development of new compounds which selectively inhibit COX-2 has emerged as a growing research area for generation of new anti-inflammatory drugs lacking the gastrointestinal and renal side effects of currently used NSAIDs.[8-11]

In this respect, many benzoxazole[12-14] and benzothiazole[15-17] derivatives have been synthesised and claimed to have significant analgesic and anti-inflammatory activity. In addition, benzimidazole derivatives have also been reported as potent analgesic and anti-inflammatory agents.[18-21] Meantime, many pyridazinone derivatives have been reported to function as novel potent analgesic and anti-inflammatory agents and some have been shown to selectively inhibit COX-2 function.[22-25]

The above mentioned findings prompted us to continue our investigation[25] of pyridazinone derivatives in an attempt to generate new lead compounds for future development as anti-inflammatory agents. The aim of the present work is to incorporate both molecules, pyridazinone and benzazole into the same molecule, with an anticipation of enhanced drug activity.

The starting materials, 2-hydrazinobenzimidazole (**1a**), 2-hydrazinobenzothiazole (**1b**) and 2-hydrazinobenzoxazole (**1c**) were prepared using literature methods.[26] Also, N-trifluoro-acetylaspartic anhydride (**6b**) was prepared as reported by reacting aspartic acid with trifluoroacetic anhydride in trifluoroacetic acid.[27] The synthesis of compounds **3–5** and **7–12** were accomplished by refluxing the requisite 2-hydrazinobenzazole (**1a–c**) with either butyric acid derivatives (**2a–c**) or cyclic anhydrides (**6a–f**) in acetic acid containing acetic anhydride. The reaction took place with the least sterically hindered carbonyl group upon the reaction of N-trifluoroacetylaspartic anhydride (**6b**) and 2-phenyl succinic anhydride. On the other hand, upon reaction of the hydrazino derivatives with 3, 4-pyridinedicarboxylic anhydride, the more electrophilic carbonyl group *para* to the pyridine –N was thought to be attacked by the hydrazino group and therefore the regioisomers (**12a** and **12b**) were the sole products.

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Experimental

Melting points were obtained on a Griffin apparatus and are uncorrected. Microanalyses for C, H and N were carried out at the Microanalytical Centre, Cairo University. IR spectra were recorded on a Shimadzu 435 spectrometer, using KBr discs. ^{1}H NMR spectra were performed on a Joel NMR FXQ-200 MHz spectrometer, using TMS as the internal standard.

Mass spectra were recorded on a GCMP-QP1000 EX Mass spectrometer. Progress of the reactions were monitored by TLC using precoated aluminum sheet silica gel MERCK 60F 254 and were visualised by a UV lamp.

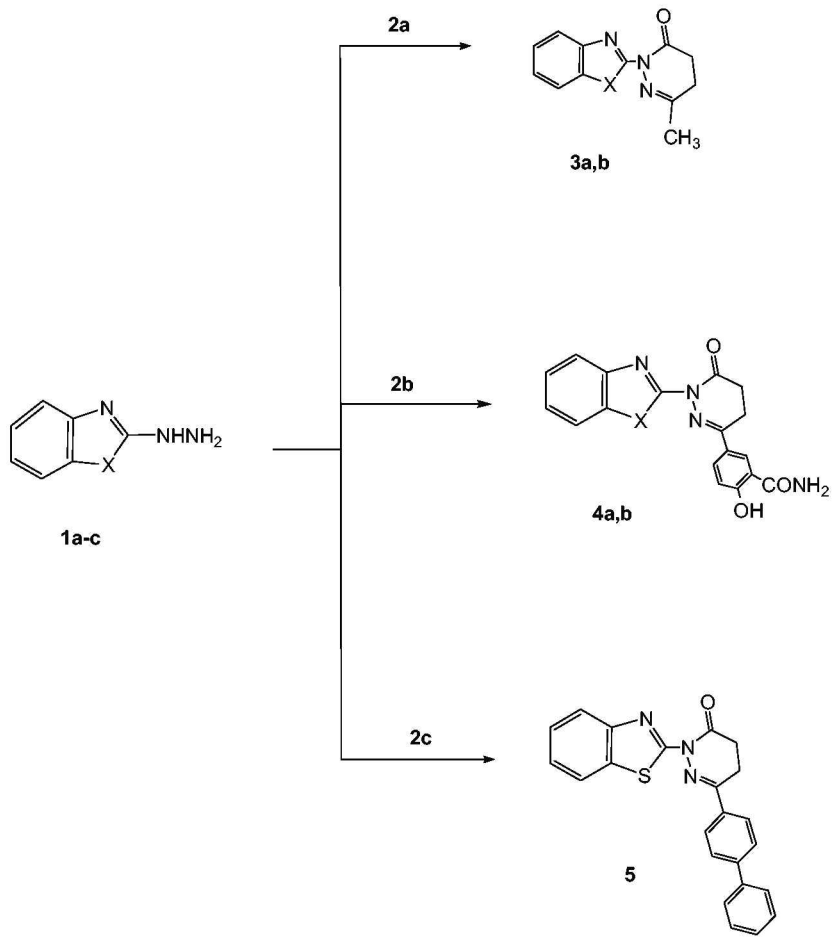
General procedure for the synthesis of compounds **3–5** *and* **7–12**: To a stirred solution of (**1a**, **1b** or **1c**) (0.01 mol) in glacial acetic acid (20 mL) and acetic anhydride (1 mL), the respective acid (0.01 mol) (levulinic acid (**2a**), 4-(5-salicylamido)-4-oxobutyric acid (**2b**) and 4-biphenyl-4-oxobutyric acid (**2c**) or the respective acid anhydride (0.01 mol) (succinic anhydride (**6a**), N-trifluoroacetylaspartic anhydride (**6b**), 2-phenylsuccinic anhydride (**6c**), maleic anhydride (**6d**), 1, 2-cyclohexane dicarboxylic anhydride (**6e**) and 3, 4-pyridine dicarboxylic anhydride (**6f**) were added and the mixture was refluxed for 8 h. The solvent was evaporated under reduced pressure to half its volume, cooled and poured onto water. The precipitate thus formed was filtered, dried and recrystallised from ethanol.

2-(3-Methyl-6-oxo-1, 4, 5, 6-tetrahydropyridazin-1-yl)benzimidazole (**3a**): Yield: 51.0%; m.p.196–199 °C; IR: 3200(NH), 2900(CH aliph.), 1710 (C = O); ^{1}H NMR ($CDCl_3$-d_1): 1.25 (s, 3H, CH_3), 2.66 (t, 2H, J = 8 Hz, C–CH_2), 3.36 (t, 2H, J = 8 Hz, CO–CH_2), 7.20–7.29 (m, 3H, benzimidazole–$C_{5,6,7}$–H), 8.18 (d, 1H, J = 7.8 Hz, benzimidazole–C_4–H), 10.54 (brs, 1H, NH, D_2O exchangeable); MS: *m/z* 228 (M+, 8.0%). Anal. Calcd for $C_{12}H_{12}N_4O$: C, 63.15; H, 5.26; N, 24.56. Found: C, 63.39; H, 5.25; N, 24.57%.

2-(3-Methyl-6-oxo-1,4,5,6-tetrahydropyridazin-1-yl)benzothiazole (**3b**): Yield: 40.0%; m.p. < 300 °C; IR: 2900(CH aliph.), 1690 (C = O); ^{1}H NMR (DMSO-d_6): 1.96 (s, 3H, CH_3), 2.48 (t, 2H, J = 7.6 Hz, C–CH_2), 3.41 (t, 2H, J = 7.6 Hz, CO–CH_2), 7.06 (t, 1H, J = 7.8 Hz, benzothiazole–C_6–H), 7.25 (t, 1H, J = 7.8 Hz, benzothiazole–C_5–H), 7.34(d, 1H, J = 7.8 Hz, benzothiazole–C_7–H), 7.68 (d, 1H, J = 7.8 Hz, benzothiazole–C_4–H), MS: *m/z* 245 (M^+, 42.74%). Anal. Calcd for $C_{12}H_{11}N_3OS$: C, 58.77; H, 4.48; N, 17.14. Found: C, 58.71; H, 4.48; N, 17.10%.

2-(3-(5-Salicylamido)-6- oxo – 1, 4, 5, 6- tetrahydropyridazin-1-yl) benzimidazole (**4 a**): Yield: 48.0%; m.p. < 300 °C; IR: 3200–3100 (NH, OH), 2900(CH aliph.), 1710, 1665 (2C = O); ^{1}H NMR (DMSO-d_6): 2.55–2.59 (m, 2H, C– CH_2), 3.23–3.25 (m, 2H, CO– CH_2), 7.01–7.06 (d, 2H, J = 7.9 Hz, benzimidazole–$C_{5,6}$–H), 7.18 (d, 1H, J = 7.8 Hz, benzimidazole–C_7–H), 7.28 (d, 1H, J = 7.8 Hz, benzimidazole–C_4–H), 7.68 (d, 1H, J = 8.0 Hz, salicylamido-C_4–H), 7.94 (d, 1H, J = 8.0 Hz, salicylamido-C_3–H), 8.20(s, 1H, salicylamido-C_6–H), 12.05 (s, 1H, NH, D_2O exchangeable), 13.37(s, 1H, OH, D_2O exchangeable); MS: *m/z* 349 (M^+, 6.15%). Anal. Calcd for $C_{18}H_{15}N_5O_3$: C, 61.89; H, 4.29; N, 20.05. Found: C, 61.71; H, 4.31; N, 20.03%.

2-(3-(5-Salicylamido)-6- oxo – 1, 4, 5, 6- tetrahydropyridazin-1-yl) benzoxazole (**4 b**): Yield: 41.0%; m.p. 178–180 °C; IR: 3300–3100 (NH, OH), 2950(CH aliph.), 1700, 1670 (2C = O); ^{1}H NMR (DMSO-d_6): 2.43 (t, 1H, J = 8 Hz, C-$CH H_e$), 2.53 (t, 1H, J = 8 Hz, C-$CH H_a$), 2.94 (t, 1H, J = 8 Hz, CO – $CH H_e$), 3.24(t, 1H, J = 8 Hz, CO – $CH H_a$), 6.97 (t, 2H, J = 8.8 Hz, benzoxazole –$C_{5,6}$–H), 7.28–7.58 (m, 2H, benzoxazole –$C_{4,7}$–H), 7.88 (d, 1H, J = 8.2 Hz,



Scheme 1

salicylamido-C_4–H), 8.02 (d, 1H, J = 8.2 Hz, salicylamido-C_3–H), 8.15 (s, 1H, salicylamido-C_6–H), 8.68 (brs, 2H, NH_2, D_2O exchangeable), 12.16 (s, 1H, NH, D_2O exchangeable), 13.36 (s, 1H, OH, D_2O exchangeable). Anal. Calcd for $C_{18}H_{14}N_4O_4$: C, 61.71; H, 4.00; N, 16.00. Found: C, 61.69; H, 4.02; N, 16.17%.

2-(3-(4-Biphenyl)-6-oxo–1,4,5,6-tetrahydropyridazin-1-yl)benzothiazole **(5)**: Yield: 40.0%; m.p. 220–222 °C; IR: 2900 (CH aliph.), 1680 (C = O); MS: *m/z* 283 (M^+, 1.26). Anal. Calcd for $C_{23}H_{17}N_3OS$: C, 72.06; H, 4.43; N, 10.96. Found: C, 72.15; H, 4.42; N, 10.91%.

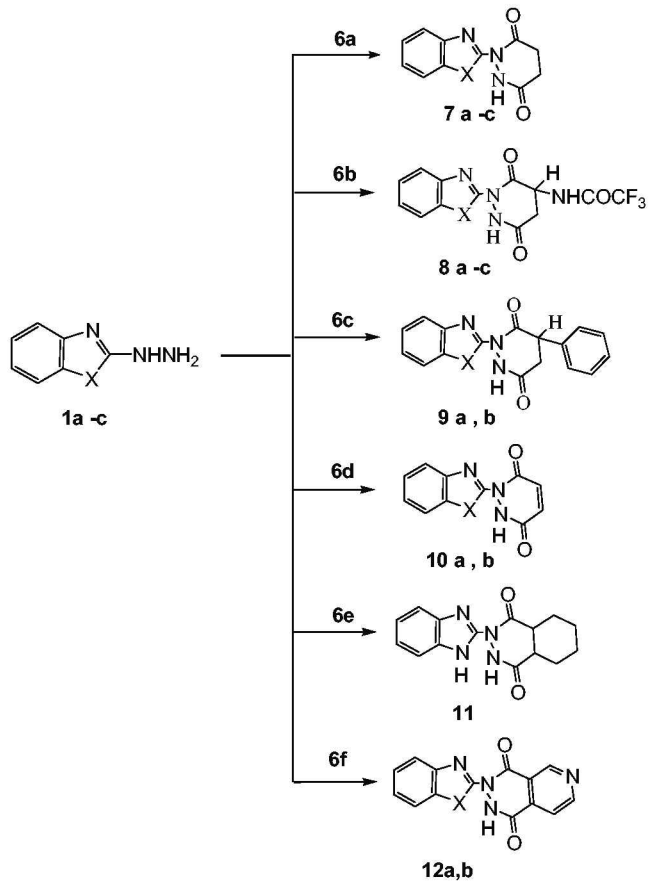
2-(3,6-Dioxo-perhydropyridazin-1-yl) benzimidazole **(7a)**: Yield: 73.0%; m.p. 194–195 °C; IR: 3300 (NH), 2950 (CH aliph.) 1700, 1680 (2C = O); ^{1}H NMR (DMSO-d_6): 2.41–2.44(m, 2H, NH-CO-CH_2), 2.80–2.83 (m, 2H, N–CO–CH_2), 7.36(t, 1H, J = 7.8 Hz, benzimidazole–C_6-H), 7.46(t, 1H, J = 7.8 Hz, benzimidazole–C_5–H), 7.79(d, 1H, J = 7.8 Hz, benzimidazole–C_7–H), 7.95(d, 1H, J = 7.8 Hz, benzimidazole–C_4–H), 11.02, 11.22(2 s, each 1H, 2NH, D_2O exchangeable). Anal. Calcd for $C_{11}H_{10}N_4O_2$: C, 57.39; H, 4.34; N, 24.34. Found: C, 57.41; H, 4.33; N, 24.35%.

2-(3, 6-Dioxo- perhydropyridazin-1-yl) benzothiazole **(7b)**: Yield: 65.0%; m.p. 201–203 °C; IR: 3250 (NH), 2900 (CH aliph.) 1700, 1670 (2C = O); ^{1}H NMR (DMSO-d_6): 2.44–2.49(m, 2H, NH–CO– CH_2), 2.66–2.71 (m, 2H, N–CO–CH_2), 7.12–7.33(m, 2H, benzothiazole–$C_{5,6}$–H), 8.09–8.12(m, 2H, benzothiazole–$C_{4,7}$–H), 12.47(s, 1H, NH, D_2O exchangeable). Anal. Calcd for $C_{11}H_9N_3O_2S$: C, 53.44; H, 3.64; N, 17.00. Found: C, 53.43; H, 3.65; N, 17.01%.

2-(3, 6-Dioxo-perhydropyridazin-1-yl) benzoxazole **(7c)**: Yield: 25.0%; m.p. 178–180 °C; IR: 3200 (NH), 2900 (CH aliph.), 1700, 1680 (2C = O); ^{1}H NMR (DMSO-d_6): 2.79–2.80(m, 2H, NH–CO CH_2), 2.89–2.90 (m, 2H, N–CO–CH_2), 7.12–7.15(m, 2H, benzoxazole –$C_{5,6}$–H), 7.16–7.26(m, 2H, benzoxazole –$C_{4,7}$–H). Anal. Calcd for $C_{11}H_9N_3O_3$: C, 57.14; H, 3.89; N, 18.18. Found: C, 57.21; H, 3.90; N, 18.22%.

2-(3, 6-Dioxo-5-trifluoroacetylamino perhydropyridazin-1-yl) benzimidazole **(8a)**: Yield: 70.0%; m.p. 192–194 °C; IR: 3300–3200 (NH), 1700, 1680, 1620 (3C = O); ^{1}H NMR (DMSO-d_6): 2.84 (m, 2H, CH_2), 3.46 (m, 1H, CH), 3.79 (brs, 1H, NH, D_2O exchangeable), 7.13–7.46(m, 4H, benzimidazole–H), 12.53, 12.86 (2 s, each 1H, 2NH, D_2O exchangeable). Anal. Calcd for $C_{13}H_{10}F_3N_5O_3$: C, 45.74; H, 2.93; N, 20.52. Found: C, 45.75; H, 2.94; N, 20.51%.

2-(3, 6-Dioxo-5-trifluoroacetylamino perhydropyridazin-1-yl) benzothiazole **(8b)**: Yield: 45.0%; m.p. 204–206 °C; IR: 3300–3200 (NH), 1700, 1680, 1620 (3C = O); ^{1}H NMR (DMSO-d_6): 1.96 (m, 2H, CH_2), 3.36 (m, 1H, CH), 4.07 (brs, 1H, NH, D_2O exchangeable), 7.12(t, 1H, J = 7.6 Hz, benzothiazole–C_6–H), 7.32 (t, 1H, J = 7.6 Hz, benzothiazole–C_5–H), 7.47 (d, 1H, J = 7.6 Hz, benzothiazole–C_7-H), 7.76 (d, 1H, J = 7.6 Hz, benzothiazole–C_4–H), 10.29 (s, 1H, NH, D_2O exchangeable); MS: *m/z* 358 (M^+, 6.79%). Anal. Calcd for



1a	X = NH	**1b**	X = S	**1c**	X = O
7a	X = NH	**7b**	X = S	**7c**	X = O
8a	X = NH	**8b**	X = S	**8c**	X = O
9a	X = NH	**9b**	X = S	**10a**	X = NH
10b	X = S	**12a**	X = NH	**12b**	X = O

6a = Succinic anhydride
6b = Trifluoroacetylaspartic anhydride
6c = 2-Phenyl succinic anhydride
6d = Maleic anhydride
6e = 1, 2-Cyclohexane dicarboxylic anhydride
6f = 3, 4-Pyridine dicarboxylic anhydride

Scheme 2

$C_{13}H_9F_3N_4O_3S$: C, 43.57; H, 2.51; N, 15.64. Found: C, 43.58; H, 2.50; N, 15.66.

2-(3, 6-Dioxo-5-trifluoroacetylamino perhydropyridazin-1-yl) benzoxazole (**8c**): Yield: 55.0%; m.p. 185–187 °C; IR: 3300–3200 (NH), 1720, 1660, 1620 (3C = O); ^{1}H NMR (DMSO-d_6): 2.49–2.51 (m, 2H, CH_2), 3.34 (m, 1H, CH), 7.22–7.29(m, 2H, benzoxazole –C_5, $_6$–H), 7.32 (d, 1H, J = 7.8 Hz, benzoxazole –C_4–H), 7.52 (d, 1H, J = 7.8 Hz, benzoxazole–C_7–H), 13.82(s, 1H, NH, D_2O exchangeable). Anal. Calcd for $C_{13}H_9F_3N_4O_4$: C, 45.61; H, 2.63; N, 16.37. Found: C, 45.60; H, 2.64; N, 16.36%.

2-(3, 6-Dioxo-5-phenylperhydropyridazin-1-yl) benzimidazole (**9a**): Yield: 43.0%; m.p. 170–172 °C; IR: 3250–3100 (NH), 2900(CH aliph.), 1720, 1700 (2C = O); ^{1}H NMR (DMSO-d_6): 2.49 (dd, 1H, J = 17.1, 5.1 CHH_e), 2.92 (dd, 1H, J = 17.1, 10.2 CHH_a), 3.91(dd, 1H, J = 10.2, 5.1, CH), 7.23–7.35(m, 5H, ArH), 7.39(t, 1H, J = 7.5 Hz, benzimidazole–C_6–H), 7.48(t, 1H, J = 7.5 Hz, benzimidazole–C_5–H), 7.83 (d, 1H, J = 7.5 Hz, benzimidazole–C_7–H), 8.03(d, 1H, J = 7.5 Hz, benzimidazole–C_4–H), 12.31(s, 1H, NH, D_2O exchangeable). Anal. Calcd for $C_{17}H_{14}N_4O_2$: C, 66.66; H, 4.57; N, 18.30. Found: C, 66.59; H, 4.56; N, 18.32%.

2-(3, 6-Dioxo-5-phenylperhydropyridazin-1-yl) benzothiazole (**9b**): Yield: 58.0%; m.p.196–198 °C; IR: 3200–3100 (NH), 2970 (CH aliph.), 1710, 1690(2C = O); ^{1}H NMR (DMSO-d_6): 2.18, 2.32 (2 m, each 1H, CH_2), 3.94(m, 1H, CH), 7.20–7.36(m, 5H, ArH), 7.37 (t, 1H, J = 7.5 Hz, benzothiazole–C_6–H), 7.49(t, 1H, J = 7.5 Hz, benzothiazole–C_5–H), 7.84(d, 1H, J = 7.5 Hz, benzothiazole–C_7–H), 8.06(d, 1H, J = 7.5 Hz, benzothiazole–C_4–H), 11.30(s, 1H, NH, D_2O exchangeable). Anal. Calcd for $C_{17}H_{13}N_3O_2S$: C, 63.15; H, 4.02; N, 13.00. Found: C, 63.19; H, 4.04; N, 13.02%.

2-(3, 6-Dioxo-1, 2, 3, 6- tetrahydropyridazin-1-yl) benzimidazole (**10a**): Yield: 48.0%; m.p. 270–272 °C; IR: 3200 (NH), 1720, 1700 (2C = O); MS: *m/z* 228 (M^+, 12.42%). Anal. Calcd for $C_{11}H_8N_4O_2$: C, 57.89; H, 3.50; N, 24.56. Found: C, 57.91; H, 3.51; N, 24.54%.

2-(3, 6-Dioxo-1, 2, 3, 6- tetrahydropyridazin-1-yl) benzothiazole (**10b**): Yield: 56.0%; m.p. 160–163 °C; IR: 3200 (NH), 1720, 1690 (2C = O); ^{1}H NMR (DMSO-d_6): 7.25(d, 1H, J = 9.6 Hz, pyridazinone H), 7.33 (d, 1H, J = 9.6 Hz, pyridazinone H), 7.44 (t, 1H, J = 7.8 Hz, benzothiazole–C_6–H), 7.51 (t, 1H, J = 7.8 Hz, benzothiazole–C_5–H), 7.76 (d, 1H, J = 7.8 Hz, benzothiazole–C_7–H), 7.92 (d, 1H, J = 7.8 Hz, benzothiazole–C_4–H), 10.80 (s, 1H, NH, D_2O exchangeable); MS:

m/z 245 (M^+, 20.01%). Anal. Calcd for $C_{11}H_7N_3O_2S$: C, 53.87; H, 2.85; N, 17.14. Found: C, 53.85; H, 2.84; N, 17.11%.

2-(3, 6-Dioxo-4, 5-tetramethylene perhydropyridazin-1-yl) benzimidazole (**11**): Yield: 38.0%; m.p. 225–227°C; IR: 3200, 3100 (NH), 2900(CH aliph.), 1700, 1680 (2C = O); ^{1}H NMR (DMSO-d_6): 1.38–1.64(m, 4H, CH_2–(CH_2)$_2$– CH_2, 1.65–1.92(m, 4H, CH_2–(CH_2)$_2$– CH_2), 2.66–2.68 (m, 1H, pyridazinyl–C_4–H), 3.07–3.09(m, 1H, pyridazinyl–C_5–H), 6.95–7.28(m, 4H, benzimidazole–H), 11.20, 12.50 (2 s, each 1H, 2NH, D_2O exchangeable); MS: *m/z* 284 (M^+, 21.51%). Anal. Calcd for $C_{15}H_{16}N_4O_2$: C, 63.38; H, 5.63; N, 19.71. Found: C, 63.31; H, 5.63; N, 19.73%.

2-(1, 4-Dioxo-1, 2, 3, 4-tetrahydropyrido [3, 4-d] pyridazin-1-yl) benzimidazole (**12a**): Yield: 35.7%; m.p. 278–280°C; IR: 3200 (NH), 1700, 1680 (2C = O); ^{1}H NMR (DMSO-d_6): 7.08–8.57(m, 7H, ArH), 12.48(s, 2H, 2NH, D_2O exchangeable); MS: *m/z* 279 (M^+, 0.14%). Anal. Calcd for $C_{14}H_9N_5O_2$: C, 60.21; H, 3.22; N, 25.08. Found: C, 60.29; H, 3.23; N, 25.12%.

2-(1, 4-Dioxo-1, 2, 3, 4-tetrahydropyrido [3, 4-d] pyridazin-1-yl) benzoxazole (**12b**): Yield: 30.0%; m.p. <300°C; IR: 3200–3100 (NH), 1700, 1680 (2C = O); ^{1}H NMR (DMSO-d_6): 7.27–7.29(m, 2H, benzoxazole –$C_{5,6}$–H), 7.85–7.93(m, 2H, benzoxazole –$C_{4,7}$–H), 8.50–8.54(2 overlapped d, 2H, pyrido-$C_{5,6}$–H), 9.10–9.14(m, 1H, pyrido-C_2–H), 11.55–11.68(brs, 1H, NH, D_2O exchangeable). Anal. Calcd for $C_{14}H_8N_4O_3$: C, 60.00; H, 2.85; N, 20.00. Found: C, 60.09; H, 2.83; N, 20.08%.

Evaluation of anti-inflammatory activity

The preliminary screening was performed applying the procedure of Winter *et al.*[28] using groups of albino rats weighing 100–120 g each, six rats per group. The first group was injected with 0.05 mL of 1% carrageenan in the subplantar tissue of the right hind paw and served as untreated control.

The positive control group was given 10 mg kg^{-1} indomethacin one hour before carrageenan injection.

The test compounds were suspended in 0.5% carboxymethylcellulose (CMC) and given to the rats orally at a dose of 10 mg kg^{-1} one hour prior to carrageenan injection. In all groups, both hind limbs were dissected 4 h after carrageenan injection and weighed and the difference in weight was calculated. The effect of the test compounds were compared to control and standard by ordinary one-way ANOVA (Table 1).

Results of anti-inflammatory activity assessment

It is interesting that most of the compounds of the present series exhibit good activity relative to the standard, ranging from 37.1 to 58.2% oedema reduction (Table 1).

Compound **11**, in which benzimidazole is linked to pyridazinone, showed superior anti-inflammatory activity to that of indomethacin.

It is apparent that compound **4a**, with a benzimidazole ring, displayed a higher inhibition of paw oedema (44.7%) than its derivative **4b**, with a benzoxazole moiety (41.0%), whereas, compounds **3b**, **10b** and **12a** were found to be nearly equipotent. Thus, one could say that benzimidazole and pyridazinone groups exert a significant contribution to the activities when they are present together in the same molecule.

Table 1 Anti-inflammatory activity of the tested compounds assessed in comparison to indomethacin as reference

Group	Increase in paw weight (Mean ± SEM)	% inhibition of oedema
Control	0.65±0.05	–
3b	0.41±0.06[a]	37.1
4b	0.39±0.07[a]	41.0
10b	0.39±0.03[a]	39.8
11	0.27±0.03[a]	58.2
12a	0.40±0.03[a]	39.4
4a	0.36±0.03[a]	44.7
Indomethacin	0.32±0.03[a]	50.5

[a]Significantly different from control group at $P<0.05$ (One way ANOVA followed by Tukey-Kramer multiple comparison test).

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