

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

Hanan M. Refaat, Omneya M. Khalil* and Suzan M. Abuel-Maaty

Organic Chemistry Department, Faculty of Pharmacy, Cairo University, Cairo 11562, Egypt

In this study, a novel series of 6-oxopyridazinyl benzazoles and 3, 6-dioxypyridazinyl 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 ^1H 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-dioxypyridazinyl 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 investigation²⁵ 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-acetylaspatic 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-trifluoroacetylaspatic 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.

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. ^1H 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-trifluoroacetylaspatic 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.

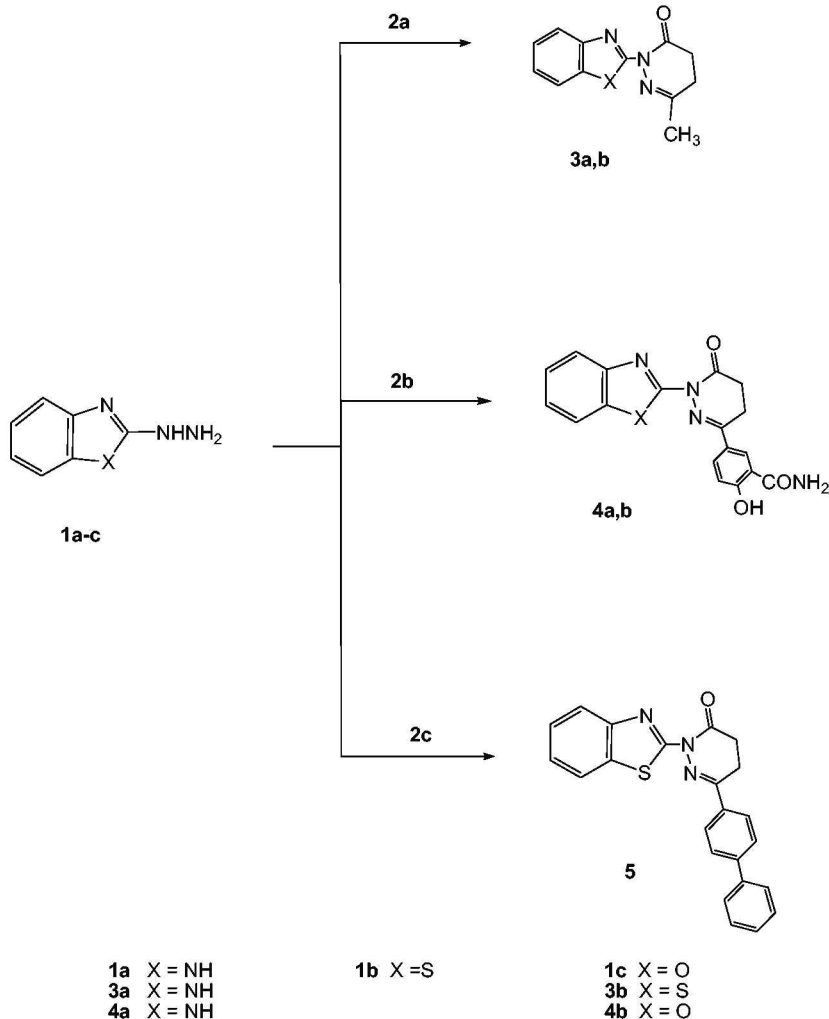
2-(3-Methyl-6-oxo-1, 4, 5, 6-tetrahydropyridazin-1-yl)benzimidazole (3a): Yield: 51.0%; m.p. 196–199°C; IR: 3200(NH), 2900(CH aliph.), 1710 (C=O); ^1H NMR (CDCl₃-d₁): 1.25 (s, 3H, CH₃), 2.66 (t, 2H, J = 8 Hz, C-CH₂), 3.36 (t, 2H, J = 8 Hz, CO-CH₂), 7.20–7.29 (m, 3H, benzimidazole-C_{5, 6, 7}-H), 8.18 (d, 1H, J = 7.8 Hz, benzimidazole-C₄-H), 10.54 (brs, 1H, NH, D₂O exchangeable); MS: *m/z* 228 (M⁺, 8.0%). Anal. Calcd for C₁₂H₁₁N₄O: 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); ^1H NMR (DMSO-d₆): 1.96 (s, 3H, CH₃), 2.48 (t, 2H, J = 7.6 Hz, C-CH₂), 3.41 (t, 2H, J = 7.6 Hz, CO-CH₂), 7.06 (t, 1H, J = 7.8 Hz, benzothiazole-C₆-H), 7.25 (t, 1H, J = 7.8 Hz, benzothiazole-C₅-H), 7.34 (d, 1H, J = 7.8 Hz, benzothiazole-C₇-H), 7.68 (d, 1H, J = 7.8 Hz, benzothiazole-C₄-H); MS: *m/z* 245 (M⁺, 42.74%). Anal. Calcd for C₁₂H₁₁N₃OS: 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 (4a): Yield: 48.0%; m.p. < 300°C; IR: 3200–3100 (NH, OH), 2900(CH aliph.), 1700, 1665 (2C=O); ^1H NMR (DMSO-d₆): 2.55–2.59 (m, 2H, C-CH₂), 3.23–3.25 (m, 2H, CO-CH₂), 7.01–7.06 (d, 2H, J = 7.9 Hz, benzimidazole-C_{5, 6}-H), 7.18 (d, 1H, J = 7.8 Hz, benzimidazole-C₇-H), 7.28 (d, 1H, J = 7.8 Hz, benzimidazole-C₄-H), 7.68 (d, 1H, J = 8.0 Hz, salicylamido-C₄-H), 7.94 (d, 1H, J = 8.0 Hz, salicylamido-C₃-H), 8.20 (s, 1H, salicylamido-C₆-H), 12.05 (s, 1H, NH, D₂O exchangeable), 13.37 (s, 1H, OH, D₂O exchangeable); MS: *m/z* 349 (M⁺, 6.15%). Anal. Calcd for C₁₈H₁₅N₅O₅: 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 (4b): Yield: 41.0%; m.p. 178–180°C; IR: 3300–3100 (NH, OH), 2950(CH aliph.), 1700, 1670 (2C=O); ^1H NMR (DMSO-d₆): 2.43 (t, 1H, J = 8 Hz, C-CH₂), 2.53 (t, 1H, J = 8 Hz, C-CH₂), 2.94 (t, 1H, J = 8 Hz, CO-CH₂), 3.24 (t, 1H, J = 8 Hz, CO-CH₂), 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,

* Correspondent. E-mail: omneyafawzy@yahoo.com



Scheme 1

salicylamido-C₄-H), 8.02 (d, 1H, *J* = 8.2 Hz, salicylamido-C₃-H), 8.15 (s, 1H, salicylamido-C₆-H), 8.68 (brs, 2H, NH₂, D₂O exchangeable), 12.16 (s, 1H, NH, D₂O exchangeable), 13.36 (s, 1H, OH, D₂O exchangeable). Anal. Calcd for C₁₃H₁₄N₄O₄: 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 C₂₃H₁₇N₃O₃: 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); ¹H NMR (DMSO-*d*₆): 2.41–2.44(m, 2H, NH-CO-CH₂), 2.80–2.83 (m, 2H, N-CO-CH₂), 7.36(t, 1H, *J* = 7.8 Hz, benzimidazole-C₆-H), 7.46(t, 1H, *J* = 7.8 Hz, benzimidazole-C₅-H), 7.79(d, 1H, *J* = 7.8 Hz, benzimidazole-C₇-H), 7.95(d, 1H, *J* = 7.8 Hz, benzimidazole-C₄-H), 11.02, 11.22(2 s, each 1H, 2NH, D₂O exchangeable). Anal. Calcd for C₁₁H₁₀N₄O₂: C, 57.39; H, 4.34; N, 24.34. Found: C, 57.41; H, 4.33; N, 24.35%.

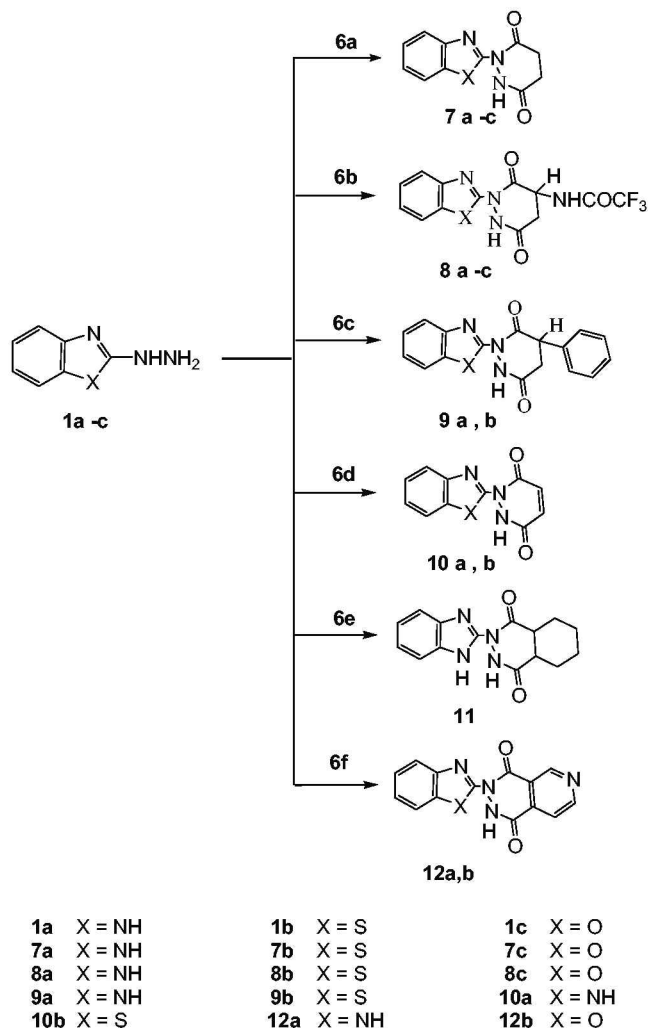
2-(3,6-Dioxo-perhydropyridazin-1-yl) benzothiazole (**7b**): Yield: 65.0%; m.p. 201–203°C; IR: 3250 (NH), 2900 (CH aliph.) 1700, 1670 (2C=O); ¹H NMR (DMSO-*d*₆): 2.44–2.49(m, 2H, NH-CO-CH₂), 2.66–2.71 (m, 2H, N-CO-CH₂), 7.12–7.33(m, 2H, benzothiazole-C_{5,6}-H), 8.09–8.12(m, 2H, benzothiazole-C_{4,7}-H), 12.47(s, 1H, NH,

D₂O exchangeable). Anal. Calcd for C₁₁H₉N₃O₂S: 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); ¹H NMR (DMSO-*d*₆): 2.79–2.80(m, 2H, NH-CO-CH₂), 2.89–2.90 (m, 2H, N-CO-CH₂), 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 C₁₁H₉N₃O₃: 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); ¹H NMR (DMSO-*d*₆): 2.84 (m, 2H, CH₂), 3.46 (m, 1H, CH), 3.79 (brs, 1H, NH, D₂O exchangeable), 7.13–7.46(m, 4H, benzimidazole-H), 12.53, 12.86 (2 s, each 1H, 2NH, D₂O exchangeable). Anal. Calcd for C₁₃H₁₀F₃N₅O₃: 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); ¹H NMR (DMSO-*d*₆): 1.96 (m, 2H, CH₂), 3.36 (m, 1H, CH), 4.07 (brs, 1H, NH, D₂O exchangeable), 7.12(t, 1H, *J* = 7.6 Hz, benzothiazole-C₆-H), 7.32 (t, 1H, *J* = 7.6 Hz, benzothiazole-C₅-H), 7.47 (d, 1H, *J* = 7.6 Hz, benzothiazole-C₇-H), 7.76 (d, 1H, *J* = 7.6 Hz, benzothiazole-C₄-H), 10.29 (s, 1H, NH, D₂O exchangeable); MS: *m/z* 358 (M⁺, 6.79%). Anal. Calcd for



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

Scheme 2

$C_{13}H_9F_3N_4O_3$: 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 (C=O); 1H NMR (DMSO- d_6): 2.49–2.51 (m, 2H, CH₂), 3.34 (m, 1H, CH), 7.22–7.29(m, 2H, benzoxazole -C₅-H), 7.32 (d, 1H, J = 7.8 Hz, benzoxazole -C₄-H), 7.52 (d, 1H, J = 7.8 Hz, benzoxazole -C₇-H), 13.82(s, 1H, NH, D₂O 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); 1H NMR (DMSO- d_6): 2.49 (dd, 1H, J = 17.1, 5.1 CHH₂), 2.92 (dd, 1H, J = 17.1, 10.2 CHH₂), 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-C₆-H), 7.48(t, 1H, J = 7.5 Hz, benzimidazole-C₅-H), 7.83 (d, 1H, J = 7.5 Hz, benzimidazole-C₇-H), 8.03(d, 1H, J = 7.5 Hz, benzimidazole-C₄-H), 12.31(s, 1H, NH, D₂O 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); 1H NMR (DMSO- d_6): 2.18, 2.32 (2 m, each 1H, CH₂), 3.94(m, 1H, CH), 7.20–7.36(m, 5H, ArH), 7.37 (t, 1H, J = 7.5 Hz, benzothiazole-C₆-H), 7.49(t, 1H, J = 7.5 Hz, benzothiazole-C₅-H), 7.84(d, 1H, J = 7.5 Hz, benzothiazole-C₇-H), 8.06(d, 1H, J = 7.5 Hz, benzothiazole-C₄-H), 11.30(s, 1H, NH, D₂O 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); 1H 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-C₆-H), 7.51 (t, 1H, J = 7.8 Hz, benzothiazole-C₅-H), 7.76 (d, 1H, J = 7.8 Hz, benzothiazole-C₇-H), 7.92 (d, 1H, J = 7.8 Hz, benzothiazole-C₄-H), 10.80 (s, 1H, NH, D₂O 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-tetrahydroperhydropyridazin-1-yl) benzimidazole (11): Yield: 38.0%; m.p. 225–227°C; IR: 3200, 3100 (NH), 2900 (CH aliph.), 1700, 1680 (2C = O); 1H 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 $_2$ O 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); 1H NMR (DMSO- d_6): 7.08–8.57(m, 7H, ArH), 12.48(s, 2H, 2NH, D $_2$ O exchangeable); MS: m/z 279 (M^+ , 0.14%). Anal. Calcd for $C_{14}H_{10}N_5O_2$: 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); 1H 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(2brs, 1H, NH, D $_2$ O exchangeable). Anal. Calcd for $C_{14}H_{10}N_4O_3$: 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.

The authors wish to thank Assoc. Prof. Dr. Dalal Mostafa, Department of Pharmacology, Faculty of Pharmacy, Cairo University for help in performing the anti-inflammatory screening.

Received 2 March 2009; accepted 25 May 2009

Paper 09/0470 doi: 10.3184/030823409X466050

Published online: 15 July 2009

References

- W. Xie, J.G. Chipman, D.L. Robertson, R.L. Erikson and D.L. Simmons, *Proc. Natl. Acad. Sci. USA*, 1991, **88**, 2692.
- D.A. Kujubu, B.S. Fletcher, B.C. Varnum, R.W. Lim and H.R. Herschman, *J. Biol. Chem.*, 1991, **266**, 12866.
- T. Hla and K. Neilson, *Proc. Natl. Acad. Sci. USA*, 1992, **89**, 7384.
- P. Brooks, P. Emery, J.F. Evans, H. Fenner, C.J. Hawkey, C. Patrono, J. Smolen, F. Breedveld, R. Day, M. Dougados, E.W. Ehrlich, J. Gijon – Bannos, T.K. Kvien, M.H. Van Rijswijk, T. Warner and H. Zeidler, *Rheumatology*, 1999, **38**, 779.
- E.A. Meade, W.L. Smith and D.L. Dewitt, *J. Biol. Chem.*, 1993, **268**, 6610.
- C.J. Hawkey, *The Lancet*, 1999, **353**, 307.
- J. Meyer-Kirchhath and K. Schrör, *Curr. Med. Chem.*, 2000, **7**, 1121.
- T.D. Penning, J.J. Talley, S.R. Bertenshaw, J.S. Carter, P.W. Collins, S. Docter, M.J. Graneto, L.F. Lee, J.W. Malecha, J.M. Miyashiro, R.S. Rogers, D.J. Rogier, S.S. Yu, G.D. Anderson, E.G. Burton, J.N. Cogburn, S.A. Gregory, C.M. Koboldt, W.E. Perkins, K. Seibert, A.W. Veenhuizen, Y.Y. Zhang and P.C. Isakson, *J. Med. Chem.*, 1997, **40**, 1347.
- P. Prasit, Z. Wang, C. Brideau, C.C. Chan, S. Charleson, W. Cromlish, D. Ethier, J.F. Evans, A.W. Ford-Hutchinson, J.Y. Gauthier, R. Gordon, J. Guay, M. Gresser, S. Kargman, B. Kennedy, Y. Leblanc, S. Léger, J. Mancini, G.P. O' Neill, M. Ouellet, M.D. Percival, H. Perrier, D. Riendeau, I. Rodger, P. Tagari, M. Thérien, P. Vieckers, E. Wong, L.J. Xu, R.N. Young and R. Zamboni, *Bioorg. Med. Chem. Lett.*, 1999, **9**, 1773.
- G. Dannhardt and S. Laufer, *Curr. Med. Chem.*, 2000, **7**, 1101.
- C.H. Park, X. Siomboing, S. Youn, B. Gressier, M. Luyckx and P. Chavatte, *Eur. J. Med. Chem.*, 2002, **37**, 461.
- S. Unlu, S.N. Baytas, E. Kupeli and E. Yesilada, *Arch. Pharm.*, 2003, **336**, 310.
- T. Onkol, M.F. Sahin, E. Yildirim, K. Erol and S. Ito, *Arch. Pharm. Res.*, 2004, **27**, 1086.
- D. Sridhar, M. Arjun, M. Jyothi, T. Raviprasad and M. Sarangapani, *Ind. J. Heterocycl. Chem.*, 2006, **16**, 99.
- D.S. Dogruer, S. Unlu, M.F. Sahin and E. Yesilada, *Farmaco*, 1998, **53**, 80.
- S. Unlu, T. Onkol, Y. Dundar, B. Okcelik, E. Kupeli, E. Yesilada, N. Noyanalan and M.F. Sahin, *Arch. Pharm.*, 2003, **336**, 353.
- R. Paramashivappa, P. Kumar, P.V. Subba Rao and A. Srinivasa Rao, *Bioorg. Med. Chem. Lett.*, 2003, **13**, 657.
- L.K. Labanasuskas, A.B. Brukstus, P.G. Gaidelis, V.A. Buchinskaitė, E.B. Udrenaitė and V.K. Daukas, *Pharm. Chem. J.*, 2000, **34**, 353.
- P. Vicini, M. Incerti, L. Amoretti, V. Ballabeni, M. Tognolini and E. Barocelli, *Farmaco*, 2002, **57**, 363.
- S.M. Sondhi, N. Singh, A. Kumar, O. Lozach and L. Meijer, *Bioorg. Med. Chem.*, 2006, **14**, 3758.
- E.P. Jesudason, S.K. Sridhar, E.J. Padma Malar, P. Shanmugapandian, M. Inayathullah, V. Arul, D. Selvaraj and R. Jayakumar, *Eur. J. Med. Chem. In Press*, 2008, doi: 10.1016/j.ejmech.2008.03.043.
- F. Rohet, C. Rubat, P. Couderet, E. Albuissou and J. Couquelet, *Chem. Pharm. Bull.*, 1996, **44**, 980.
- C.S. Li, C. Brideau, C.C. Chan, C. Savoie, D. Claveau, S. Charleson, R. Gordon, G. Greig, J.Y. Gauthier, C.K. Lau, D. Riendeau, M. Thérien, E. Wong and P. Prasit, *Bioorg. Med. Chem. Lett.*, 2003, **13**, 597.
- E. Banoglu, C. Akoglu, S. Unlu, E. Kupeli, E. Yesilada and M.F. Sahin, *Arch. Pharm. Pharm. Med. Chem.*, 2004, **337**, 7.
- H.M. Refaat, O.M. Khalil and H.H. Kadry, *Arch. Pharm. Res.*, 2007, **30**, 803.
- M.Z.A. Badr, A.M. Mahmoud, S.A. Mahgoub and Z.A. Hozién, *Bull. Chem. Soc. Jpn.*, 1988, **61**, 1339.
- G.P. Moretti and P. Foresta, *PCT Int Appl Wo 98 33 762 (Cl C 07C 217/74) 6 Aug 1998 Chem. Abst.*, 1998, **129**, 161424 p.
- C.A. Winter, E.A. Risley and G.W. Nuss, *Proc. Soc. Exp. Biol. Med.*, 1962, **111**, 544.

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

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

^aSignificantly different from control group at $P < 0.05$ (One way ANOVA followed by Tukey-Kramer multiple comparison test).