DOI 10.1515/hc-2014-0022 — Heterocycl. Commun. 2014; 20(2): 111–115

Stanislava Vladimirova* and Atanas Bijev

An access to new *N*-pyrrolylcarboxylic acids as potential COX-2 inhibitors via Paal-Knorr cyclization

Abstract: Twenty new *N*-pyrrolylcarboxylic acids were designed to assume the architecture of contemporary selective COX-2 inhibitors as potential anti-inflammatory agents. The targeted products were synthesized in 70–82% yields by Paal-Knorr cyclization of a set of eight amino acids, acting as primary amines, and four 1,4-dicarbonyl compounds. The latter substrates were prepared by *C*-alkylation of three commercially available β-dicarbonyl compounds with two ω-bromoacetophenones and used *in situ*. These compounds inhibit carrageenin-induced rat paw edema and show analgesic activity.

Keywords: COX-2 inhibitors; Paal-Knorr cyclization; pyrroles; synthesis.

***Corresponding author: Stanislava Vladimirova,** Department of Organic Synthesis and Fuels, University of Chemical Technology and Metallurgy, 1756 Sofia, Bulgaria, e-mail: vladimirova.s@mail.bg
Atanas Bijev: Department of Organic Synthesis and Fuels, University of Chemical Technology and Metallurgy, 1756 Sofia, Bulgaria

Introduction

Both the well-known negative gastrointestinal effects of the widely used nonsteroidal anti-inflammatory drugs (NSAIDs) and the concern related to the cardiovascular risk recently associated with some selective cyclooxygenase-2 (COX-2) inhibitors [1, 2] have challenged the global research for new and more reliable agents. These activities focus on a wide range of heterocyclic compounds, including derivatives of pyrrole [3–5].

The carboxylic acids of pyrrole have been recognized as the pharmacophore system of a number of conventional NSAIDs [such as tolmetin (CAS 64490-92-2), zomepirac (CAS 64092-48-4), clopirac (CAS 42779-28-8), and ketorolac (CAS 74103-06-3)]. Certain pyrrole derivatives synthesized in our laboratory in the past years have also been found to exhibit up to 100% inhibition of edema [6, 7]. The current study aims to complete the available platform of potential NSAIDs by 20 new derivatives of pyrrole, designed as potential COX-2 inhibitors and reliable candidates for pharmacological evaluations.

Results and discussion

Design of the targeted structures

To achieve a structural alternative to the known template of the conventional anti-inflammatory pyrroles mentioned above, a ligand-based design, focused on the general architecture of contemporary selective COX-2 inhibitors (celecoxib – CAS 169590-42-5 selected as a prototype), was applied to assure the desired compatibility with the binding sites of the COX-2 enzyme.

Figure 1 visualizes the analogy between the steric properties of substituents, occupying the same positions at the central heterocycle of targeted compounds and their prototype, as a prerequisite for binding to the same target. The introduced structural features provided a capability for the 4′-X-phenyl group and for the group R_1 to occupy the same cavities in the enzyme active site as the 4′-methyl- and 3-trifluoromethyl groups of the prototype, respectively. At the same time, the acyl chain should fit the specific 'pocket' in the COX enzymes (otherwise occupied by the phenylsulfonamide moiety of celecoxib), known to be more accessible in COX-2 than in COX-1, due to the substitution of isoleucine (COX-1) with valine (COX-2) at position 523 [8]. The meanings of the substituents R, R_1, and X are disclosed in Scheme 1. The nature of the substituent R_1 divides the set of compounds into three subseries: 1 (R_1 = COOEt), 2 [R_1 = CON(Et)$_2$], and 3 (R_1 = COMe). The structural specificity of the products in Scheme 1 is denoted in the relevant compound IDs: the digit corresponds to one of the three subseries defined by R_1 and the letter – to the residue R in the acyl chain. The structural diversity aimed at changes in hydrophobicity, molar volume, and polarity of the molecules, and was achieved by variations in the substituents R and R_1. The introduction of 4′-Cl-substituent X in the aromatic ring was motivated by the high anti-inflammatory activity found in similarly substituted compounds [6].

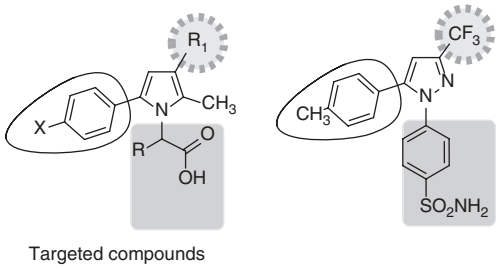


Figure 1 Specific moieties in the targeted compounds, compatible with the selected ligand and its target.

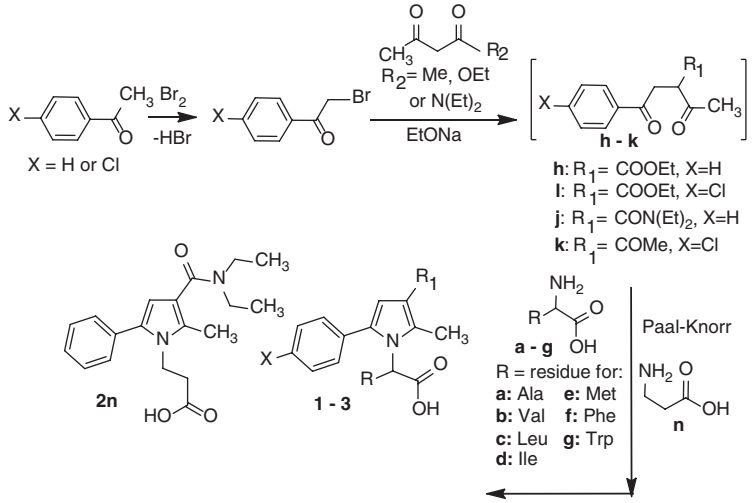
Synthesis

Paal-Knorr pyrrole synthesis, well known as a powerful reaction in a retrosynthetic context, was chosen as a reliable access to the targeted structures. The reaction was performed according to Scheme 1 as a cyclization between 1,4-dicarbonyl compounds and relevant primary amines. The selection of amino acids **a–n**, acting as amino-partners, defined the nature of the variable residue R, whereas the substituents X and R_1 were introduced by an appropriate substitution in 1,4-dicarbonyl compounds **h–k**.

The intermediate 1,4-dicarbonyl compounds **h–k** were synthesized by condensation of X-substituted ω-bromoacetophenones with R_2-substituted commercially available β-dicarbonyl compounds. Conditions for *C*-alkylation were chosen to suppress the concurrent *O*-targeted reaction intrinsic to this class of ambident compounds [9, 10]. The ω-bromoacetophenones, well known as strong lachrymators, were prepared in our laboratory [11].

The syntheses within subseries **1** and **2** were conducted in boiling acetic acid and were completed within 2 h (TLC control). The short reaction time was found to be favorable for competing with the concurrent *N*-acetylation of participating amines by the solvent. By contrast, the reaction temperature at subseries **3** was reduced to 60°C (in the same solvent) to prevent a secondary condensation of the peculiar carbonyl group in position 3 with amines; the reaction time in this case was prolonged to up to 4 h (TLC control).

The total yields were in the range of 70–82% calculated in regard to the starting ω-bromoacetophenones. The identity of all newly synthesized compounds was shown by ^{1}H NMR and IR spectra. Their purity and homogeneity was confirmed both by elemental analyses and by thin layer chromatography (TLC).



1b: X = Cl, R = CH_3CHCH_3, R_1 = COOEt;
1d: X = Cl, R = $CH_3CH_2CHCH_3$, R_1 = COOEt;
1e: X = Cl, R = $CH_3SCH_2CH_2$, R_1 = COOEt;
1f: X = Cl, R = $PhCH_2$, R_1 = COOEt;
1g: X = Cl, R = (1H-Indolyl)-3-CH_2, R_1 = COOEt;
2a: X = H, R = Me, R_1 = $CON(Et)_2$;
2b: X = H, R = CH_3CHCH_3, R_1 = $CON(Et)_2$;
2c: X = H, R = $(CH_3)_2CHCH_2$, R_1 = $CON(Et)_2$;
2d: X = H, R = $CH_3CH_2CHCH_3$, R_1 = $CON(Et)_2$;
2e: X = H, R = $CH_3SCH_2CH_2$, R_1 = $CON(Et)_2$;
2f: X = H, R = $PhCH_2$, R_1 = $CON(Et)_2$;
2g: X = H, R = (1H-Indolyl)-3-CH_2, R_1 = $CON(Et)_2$;
3a: X = Cl, R = Me, R_1 = COMe;
3b: X = Cl, R = CH_3CHCH_3, R_1 = COMe;
3c: X = Cl, R = $(CH_3)_2CHCH_2$, R_1 = COMe;
3d: X =Cl, R = $CH_3CH_2CHCH_3$, R_1 = COMe;
3e: X =Cl, R = $CH_3SCH_2CH_2$, R_1 = COMe;
3f: X = Cl, R = $PhCH_2$, R_1 = COMe;
3g: X = Cl, R = (1H-Indolyl)-3-CH_2, R_1 = COMe;

Scheme 1 A synthetic access to the targeted products via Paal-Knorr cyclization.

Preliminary biological activity

The evaluation of both anti-inflammatory and analgesic activities of the new compounds in 'Wistar' rats (180–220 g) at doses of 10, 20, and 40 mg/kg i.p. is in progress. Preliminary tests have revealed compound **1b** as the most active anti-inflammatory compound with 83% (at 40 mg/kg) inhibition of carrageenin-induced rat paw edema, against 60% (at 10 mg/kg) for indomethacin (CAS 53-86-1), used as a reference. The least active structure **1g** exhibits 45% inhibition at 40 mg/kg.

The highest analgesic activity (measured as a time for escape from a 'hot plate', 57°C ± 0.5°C) was registered for compound **2c** (64.7 s at 40 mg/kg), compared with 50.0 s for metamizole (CAS 0050567-35-6), used as a reference. The least active structure was again **1g** (33.5 s at 40 mg/kg). The reduced activity of **1g** in both tests could be related to the presence of 1-indolyl residue as a bulky substituent R, hindering the binding to the target. Details about the pharmacological evaluations of the total set of new compounds and some structure-activity trends will be published in a specialized journal.

Conclusions

In the search for new anti-inflammatory agents, Paal-Knorr cyclization was adopted as a convenient access to active pyrrole derivatives, complying with the architecture of tricyclic selective COX-2 inhibitors.

Experimental

All commercial starting materials and reagents were purchased from Merck (Darmstadt, Germany). Melting points were determined with a capillary digital melting point apparatus IA 9200 Electrothermal AZ9003MK4, Southend-on-Sea, UK. The IR spectra were registered in KBr pellets on Specord IR-71, Carl Zeiss, Jena, Germany. The ^{1}H NMR spectra (250 MHz, 20°C) were registered on a Bruker Spectrospin WM250 spectrometer (Faenlanden, Switzerland), using TMS as internal standard. All OH protons are D_2O exchangeable. The elemental analysis was performed with Elementar Analysensysteme GmbH, VarioEL V5.18.0 18., S. No.11062020. TLC characteristics of the products were measured on aluminum sheets of silica gel 60 F_{254}, Merck 1.05554 at ambient temperature using a mobile phase chloroform-ethanol. The R_f value for the new compounds at the relevant $CHCl_3$-EtOH ratio is given below.

General procedure for the synthesis of 1,4-dicarbonyl compounds h–k

Sodium (0.10 mol) was allowed to react with anhydrous ethanol (50 mL) and the resulting solution was cooled to 20–25°C and treated with a 1,3-dicarbonyl compound (0.10 mol), ensuring that the temperature did not exceed 30°C. The mixture was stirred for 15–20 min. After cooling, the corresponding α-brominated acetophenone (0.10 mol) was added in portions at a temperature not exceeding 30°C. The mixture was stirred for 30–40 min, treated with benzene (100 mL), and the resulting solution was washed successively with 5% HCl and water. The organic layer was dried with anhydrous sodium sulfate. The solvent was removed by rotary evaporation at a temperature below 45°C. The oily residue of the 1,4-dicarbonyl compound was used directly in the next step.

General procedure for the synthesis of *N*-pyrrolylcarboxylic acids 1–3

A 1,4-dicarbonyl compound (0.10 mol) and an amino acid (0.12 mol) were dissolved in glacial acetic acid (50 mL). For the preparation of compounds of subseries **1** and **2**, the reaction was performed at the boiling point of the mixture and at 60°C for compounds of subseries **3**. The reaction progress was monitored by TLC. After completion of the reaction, the mixture was poured into water. The resultant precipitate was filtered off, washed with water, dried, and crystallized from warm ethanol. If necessary, further wash with ether or hexane was conducted. The reaction time was varied from 1 h to 4 h depending on the reacting compounds (TLC control). All compounds **1–3** are soluble in warm ethanol, chloroform, and dimethyl sulfoxide, but insoluble in water and hexane.

Ethyl 1-(1-carboxy-2-methylpropyl)-5-(4-chlorophenyl)-2-methyl-1*H*-pyrrole-3-carboxylate (1b) White solid; yield 82%; mp 167–168°C; R_f 0.47 (10:0.2); IR: ν 3600–2400 (COOH), 3300 (O-H), 1720, 1695 (C=O), 820 cm^{-1} (*p*-C_6H_4); ^{1}H NMR ($CDCl_3$): δ 7.31–7.41 (m, 4H, C_6H_4), 6.55 (s, 1H, H-4), 5.40 (br, s, 1H, COOH), 4.32 (d, 1H, J = 10.7 Hz, C<u>H</u>COOH), 4.26 (q, 2H, J = 7.1 Hz, $CH_3C\underline{H}_2$), 2.53–2.62 [m, 4H, $C\underline{H}_3$-2 + C<u>H</u> (isopropyl)], 1.34 (t, 3H, J = 7.1 Hz, $C\underline{H}_3CH_2$), 0.97 [d, 3H, J = 6.3 Hz, $C\underline{H}_3$ (isopropyl)], 0.49 [d, 3H, J = 6.8 Hz, $C\underline{H}_3$ (isopropyl)]. Anal. Calcd for $C_{19}H_{22}ClNO_4$: C, 62.72; H, 6.09; N, 3.85. Found: C, 62.49; H, 6.02; N, 4.13.

Ethyl 1-(1-carboxy-2-methylbutyl)-5-(4-chlorophenyl)-2-methyl-1*H*-pyrrole-3-carboxylate (1d) White solid; yield 79%; mp 173–174°C; R_f 0.63 (10:0.3); IR: ν 3500–2200 (COOH), 3400 (O-H), 1710, 1590 (C=O), 830 cm^{-1} (*p*-C_6H_4); ^{1}H NMR ($CDCl_3$): δ 9.50 (br, s, 1H, COOH), 7.25–7.40 (m, 4H, C_6H_4), 6.40 (s, 1H, H-4), 4.10–4.40 (m, 3H, $CH_3C\underline{H}_2$ + C<u>H</u>COOH), 2.55–2.60 (m, 1H, C<u>H</u>CH_3), 2.45 (s, 3H, CH_3-2), 1.20 (t, 3H, J = 7.1 Hz, $C\underline{H}_3CH_2$), 0.85 (d, 3H, J = 6.3 Hz, $CHC\underline{H}_3$), 0.60 (m, 5H, $C\underline{H}_2C\underline{H}_3$). Anal. Calcd for $C_{20}H_{24}ClNO_4$: C, 63.57; H, 6.40; N, 3.71. Found: C, 63.46; H, 6.72; N, 3.86.

Ethyl 1-[1-carboxy-3-(methylthio)propyl]-5-(4-chlorophenyl)-2-methyl-1*H*-pyrrole-3-carboxylate (1e) White solid; yield 70%; mp 103–104°C; R_f 0.45 (10:0.3); IR: ν 3600–2300 (COOH), 3400 (O-H), 1730, 1640 (C=O), 840 cm^{-1} (*p*-C_6H_4); ^{1}H NMR ($CDCl_3$): δ 7.20–7.35 (m, 4H, C_6H_4), 6.95 (br, s, 1H, COOH), 6.40 (s, 1H, H-4), 4.90–5.00 (m, 1H, C<u>H</u>COOH), 4.10 (q, 2H, J = 7.1 Hz, $CH_3C\underline{H}_2$), 2.45 (s, 3H, CH_3-2), 1.90–2.20 (m, 4H, $C\underline{H}_2C\underline{H}_2S$), 1.80 (s, 3H, S-$CH_3$), 1.25 (t, 3H, J = 7.1 Hz, $C\underline{H}_3CH_2$). Anal. Calcd for $C_{19}H_{22}ClNO_4S$: C, 57.64; H, 5.60; N, 3.54. Found: C, 57.24; H, 5.53; N, 3.69.

Ethyl 1-(1-carboxy-2-phenylethyl)-5-(4-chlorophenyl)-2-methyl-1*H*-pyrrole-3-carboxylate (1f) White solid; yield 82%; mp 144–145°C; R_f 0.56 (10:0.2); IR: ν 3600–2400 (COOH), 3400 (O-H), 1760, 1640 (C=O), 840 cm^{-1} (*p*-C_6H_4); ^{1}H NMR ($CDCl_3$): δ 9.90 (s, 1H, COOH), 6.80–7.15 (m, 4H, C_6H_4), 6.35–6.60 (m, 5H, C_6H_5), 6.20 (s, 1H, H-4), 4.75–4.85 (m, 1H, CH_2-C<u>H</u>), 4.18 (q, 2H, *J* = 7.1 Hz, $CH_3C\underline{H}_2$), 3.20–3.35 (m, 2H, C<u>H</u>$_2$-CH), 2.58 (s, 3H, CH_3-2), 1.30 (t, 3H, *J* = 7.1, C<u>H</u>$_3$CH$_2$). Anal. Calcd for $C_{23}H_{22}ClNO_4$: C, 67.07; H, 5.38; N, 3.40. Found: C, 66.82; H, 5.55; N, 3.69.

Ethyl 1-[1-carboxy-2-(1*H*-indol-3-yl)-ethyl]-5-(4-chlorophenyl)-2-methyl-1*H*-pyrrole-3-carboxylate (1g) White solid; yield 72%; mp 183–184°C; R_f 0.47 (10:0.3); IR: ν 3600–2300 (COOH), 3350 (O-H), 1700, 1580 (C=O), 840 cm^{-1} (*p*-C_6H_4); ^{1}H NMR ($CDCl_3$): δ 9.20 (br, s, 2H, COOH + NH), 6.35–7.30 [m, 9H, 4H (C_6H_4) + 5H (indolyl-H)], 6.10 (s, 1H, H-4), 4.85–4.95 (m, 1H, C<u>H</u>COOH), 4.10 (q, 2H, *J* = 7.1 Hz, $CH_3C\underline{H}_2$), 3.20–3.40 (m, 2H, C<u>H</u>$_2$-CH), 2.55 (s, 3H, CH_3-2), 1.20 (t, 3H, *J* = 7.1 Hz, C<u>H</u>$_3$CH$_2$). Anal. Calcd for $C_{25}H_{23}ClN_2O_4$: C, 66.59; H, 5.14; N, 6.21. Found: C, 66.24; H, 5.50; N, 6.44.

2-(3-Diethylcarbamoyl-2-methyl-5-phenylpyrrol-1-yl)propionic acid (2a) Creamy solid; yield 75%; mp 178–179°C; R_f 0.38 (10:0.2); IR: ν 3600–2200 (COOH), 3300 (O-H), 1720, 1580 (C=O), 770, 700 cm^{-1} (C_6H_5); ^{1}H NMR (DMSO-d_6): δ 7.40–7.80 (m, 6H, C_6H_5 + COOH), 6.20 (s, 1H, H-4), 5.05–5.15 (m, 1H, C<u>H</u>COOH), 3.60 (q, 4H, *J* = 7.1 Hz, 2 × NC<u>H</u>$_2$CH$_3$), 2.40 (s, 3H, CH_3-2), 1.65 (d, 3H, *J* = 7.1 Hz, CHC<u>H</u>$_3$), 1.35 (t, 6H, *J* = 7.1 Hz, 2 × $NCH_2C\underline{H}_3$). Anal. Calcd for $C_{19}H_{24}N_2O_3$: C, 69.49; H, 7.37; N, 8.53. Found: C, 69.09; H, 7.21; N, 8.68.

2-(3-Diethylcarbamoyl-2-methyl-5-phenylpyrrol-1-yl)-3-methylbutyric acid (2b) White solid; yield 76%; mp 211–212°C; R_f 0.65 (10:0.5); IR: ν 3600–2200 (COOH), 3400 (O-H), 1710, 1590 (C=O), 780, 730 cm^{-1} (C_6H_5); ^{1}H NMR (DMSO-d_6): δ 7.40–7.50 (m, 6H, C_6H_5 + COOH), 6.10 (s, 1H, H-4), 4.50 (d, 1H, *J* = 10.7 Hz, C<u>H</u>COOH), 3.50 (q, 4H, *J* = 7.1 Hz, 2 × NC<u>H</u>$_2$CH$_3$), 2.30–2.40 [m, 4H, CH_3-2 + CH (*i*-pr)], 1.20 (t, 6H, *J* = 7.1, 2 × $NCH_2C\underline{H}_3$), 0.95 [d, 3H, *J* = 6.3 Hz, CH_3 (isopropyl)], 0.45 [d, 3H, *J* = 6.8, CH_3 (isopropyl)]. Anal. Calcd for $C_{21}H_{28}N_2O_3$: C, 70.76; H, 7.92; N, 7.86. Found: C, 70.45; H, 7.88; N, 7.70.

2-(3-Diethylcarbamoyl-2-methyl-5-phenylpyrrol-1-yl)-4-methylpentanoic acid (2c) White solid; yield 72%; mp 158–159°C; R_f 0.38 (10:0.3); IR: ν 3600–2300 (COOH), 3300 (O-H), 1740, 1590 (C=O), 780, 710 cm^{-1} (C_6H_5); ^{1}H NMR ($CDCl_3$): δ 6.95–7.20 (m, 6H, C_6H_5 + COOH), 5.90 (s, 1H, H-4), 4.65–4.70 (m, 1H, C<u>H</u>COOH), 3.40 (q, 4H, *J* = 7.1 Hz, 2 × NC<u>H</u>$_2$CH$_3$), 2.10 (s, 3H, CH_3-2), 1.50–1.55 (m, 2H, CH-C<u>H</u>$_2$-CH), 1.10–1.20 [m, 7H, CH (*i*-Pr) + 2 × $NCH_2C\underline{H}_3$)], 0.40–0.50 [m, 6H, 2 × CH_3 (isopropyl)]. Anal. Calcd for $C_{22}H_{30}N_2O_3$: C, 71.32; H, 8.16; N, 7.56. Found: C, 71.09; H, 8.02; N, 7.40.

2-(3-Diethylcarbamoyl-2-methyl-5-phenylpyrrol-1-yl)-3-methylpentanoic acid (2d) White solid; yield 74%; mp 237–238°C; R_f 0.51 (10:0.4); IR: ν 3500–2200 (COOH), 3400 (O-H), 1720, 1580 (C=O), 770, 710 cm^{-1} (C_6H_5); ^{1}H NMR ($CDCl_3$): δ 10.00 (s, 1H, COOH), 7.10–7.30 (m, 5H, C_6H_5), 5.95 (s, 1H, H-4), 4.35–4.40 (m, 1H, C<u>H</u>COOH), 3.35–3.55 (m, 4H, 2 × NC<u>H</u>$_2$CH$_3$), 2.20–2.30 (m, 4H, CH_3-2 + C<u>H</u>CH$_3$), 1.20 (t, 6H, *J* = 7.1 Hz, 2 × $NCH_2C\underline{H}_3$), 0.90 (d, 3H, *J* = 6.3 Hz, CHC<u>H</u>$_3$), 0.50–0.60 (m, 5H, C<u>H</u>$_2$C<u>H</u>$_3$). Anal. Calcd for $C_{22}H_{30}N_2O_3$: C, 71.32; H, 8.16; N, 7.56. Found: C, 71.11; H, 8.10; N, 7.43.

2-(3-Diethylcarbamoyl-2-methyl-5-phenylpyrrol-1-yl)-4-(methylthio)butyric acid (2e) White solid: yield 75%; mp 185–186°C; R_f 0.56 (10:0.6); IR: ν 3300–2400 (COOH), 3250 (O-H), 1770, 1610 (C=O), 780, 750 cm^{-1} (C_6H_5); ^{1}H NMR ($CDCl_3$): δ 10.20 (s, 1H, COOH), 7.10–7.40 (m, 5H, C_6H_5), 6.00 (s, 1H, H-4), 4.85–4.95 (m, 1H, C<u>H</u>COOH), 3.40–3.60 (m, 4H, 2 × NC<u>H</u>$_2$CH$_3$), 2.25 (s, 3H, CH_3-2), 1.90–2.15 (m, 4H, C<u>H</u>$_2$C<u>H</u>$_2$S), 1.80 (s, 3H, S-CH_3), 1.20 (t, 6H, *J* = 7.1, 2 × $NCH_2C\underline{H}_3$). Anal. Calcd for $C_{21}H_{28}N_2O_3S$: C, 64.92; H, 7.26; N, 7.21. Found: C, 64.57; H, 6.98; N, 7.01.

2-(3-Diethylcarbamoyl-2-methyl-5-phenylpyrrol-1-yl)-3-phenylpropionic acid (2f) White solid; yield 79%; mp 132–133°C; R_f 0.33 (10:0.6); IR: ν 3600–2200 (COOH), 3300 (O-H), 1720, 1570 (C=O), 750, 700 cm^{-1} (C_6H_5); ^{1}H NMR (DMSO-d_6): δ 6.50–7.25 (m, 10H, 2 × C_6H_5), 5.95 (s, 1H, COOH), 5.80 (s, 1H, H-4), 4.85–4.95 (m, 1H, CH_2-C<u>H</u>), 2.90–3.40 (m, 6H, 2 × NC<u>H</u>$_2$CH$_3$ + C<u>H</u>$_2$CH), 2.25 (s, 3H, CH_3-2), 1.00 (t, 6H, *J* = 7.1 Hz, 2 × $NCH_2C\underline{H}_3$). Anal. Calcd for $C_{25}H_{28}N_2O_3$: C, 74.23; H, 6.98; N, 6.93. Found: C, 73.94; H, 6.77; N, 6.75.

2-(3-Diethylcarbamoyl-2-methyl-5-phenyl-pyrrol-1-yl)-3-(1*H*-indol-3-yl)propionic acid (2g) White solid; yield 78%; mp 198–199°C; R_f 0.62 (10:0.7); IR: ν 3600–2200 (COOH), 3350 (O-H), 1710, 1580 (C=O), 760, 700 cm^{-1} (C_6H_5); ^{1}H NMR (DMSO-d_6): δ 7.20–7.45 (m, 7H, C_6H_5 + COOH + NH), 6.00 (s, 1H, H-4), 5.05–5.10 (m, 1H, C<u>H</u>COOH), 3.20–3.40 (m, 6H, C<u>H</u>$_2$-Ind + 2 × NC<u>H</u>$_2$CH$_3$), 2.25 (s, 3H, CH_3-2), 1.10 (t, 6H, *J* = 7.1 Hz, 2 × $NCH_2C\underline{H}_3$). Anal. Calcd for $C_{27}H_{29}N_3O_3$: C, 73.11; H, 6.59; N, 9.47. Found: C, 72.73; H, 6.71; N, 9.87.

3-(3-Diethylcarbamoyl-2-methyl-5-phenylpyrrol-1-yl)propionic acid (2n) White solid; yield 81%; mp 82–83°C; R_f 0.54 (10:0.3); IR: ν 3600–2200 (COOH), 3400 (O-H), 1700, 1590 (C=O), 770, 720 cm^{-1} (C_6H_5); ^{1}H NMR ($CDCl_3$): δ 7.20–7.40 (m, 5H, C_6H_5), 6.20 (s, 1H, H-4), 5.20 (br, s, 1H, COOH), 4.15–4.25 (m, 2H, C<u>H</u>$_2$N), 3.45–3.55 (m, 4H, 2 × NC<u>H</u>$_2$CH$_3$), 2.20–2.40 (m, 5H, CH_3-2 + C<u>H</u>$_2$COOH), 1.20 (t, 6H, *J* = 7.1 Hz, 2 × $NCH_2C\underline{H}_3$). Anal. Calcd for $C_{19}H_{24}N_2O_3$: C, 69.49; H, 7.37; N, 8.53. Found: C, 69.10; H, 7.51; N, 8.13.

2-[3-Acetyl-5-(4-chlorophenyl)-2-methylpyrrol-1-yl]propionic acid (3a) White solid; yield 78%; mp 225–226°C; R_f 0.42 (10:0.5); IR: ν 3600–2300 (COOH), 3300 (O-H), 1730, 1610 (C=O), 830 cm^{-1} (*p*-C_6H_4); ^{1}H NMR ($CDCl_3$): δ 7.30 (s, 1H, COOH), 7.15–7.25 (m, 4H, C_6H_4), 6.30 (s, 1H, H-4), 4.60–4.80 (m, 1H, C<u>H</u>COOH), 2.50 (s, 3H, CH_3-2), 2.30 (s, 3H, $COCH_3$), 1.50 (d, 3H, *J* = 7.1 Hz, CHC<u>H</u>$_3$). Anal. Calcd for $C_{16}H_{16}ClNO_3$: C, 62.85; H, 5.27; N, 4.58. Found: C, 62.63; H, 5.04; N, 4.28.

2-[3-Acetyl-5-(4-chlorophenyl)-2-methylpyrrol-1-yl]-3-methylbutyric acid (3b) Creamy solid; yield 82%; mp 202–203°C; R_f 0.55 (10:0.4); IR: ν 3600–2400 (COOH), 3350 (O-H), 1720, 1610 (C=O), 820 cm^{-1} (*p*-C_6H_4); ^{1}H NMR (DMSO-d_6): δ 7.35–7.50 (m, 4H, C_6H_4), 6.60 (s, 1H, H-4), 5.70 (s, 1H, COOH), 4.30–4.35 (m, 1H, C<u>H</u>COOH), 2.60 [br, s, 4H, CH_3-2 + CH (isopropyl)], 2.40 (s, 3H, $COCH_3$), 1.00 [d, 3H, *J* = 6.3 Hz, CH_3 (isopropyl)], 0.45 [d, 3H, *J* = 6.3 Hz, CH_3 (isopropyl)]; Anal. Calcd for $C_{18}H_{20}ClNO_3$: C, 64.77; H, 6.04; N, 4.20. Found: C, 64.62; H, 5.82; N, 4.07.

2-[3-Acetyl-5-(4-chlorophenyl)-2-methylpyrrol-1-yl]-4-methylpentanoic acid (3c) Creamy solid; yield 75%; mp 178–179°C; R_f 0.53 (10:0.3). IR: ν 3600–2200 (COOH), 3400 (O-H), 1710, 1610 (C=O), 830 cm^{-1} (*p*-C_6H_4); ^{1}H NMR ($CDCl_3$): δ 9.20 (s, 1H, COOH), 7.15–7.30 (m, 4H, C_6H_4), 6.35 (s, 1H, H-4), 4.75–4.80 (m, 1H, C<u>H</u>COOH), 2.50 (s, 3H, CH_3-2), 2.35 (s, 3H, $COCH_3$), 1.80–1.90 (m, 2H, CH-C<u>H</u>$_2$-CH), 1.10–1.15 [m, 1H, CH (isopropyl)], 0.65 [d, 3H, *J* = 6.3 Hz, CH_3 (isopropyl)], 0.50

[d, 3H, J = 6.3 Hz, CH_3 (isopropyl)]. Anal. Calcd for $C_{19}H_{22}ClNO_3$: C, 65.61; H, 6.38; N, 4.03. Found: C, 65.43; H, 6.03; N, 3.74.

2-[3-Acetyl-5-(4-chlorophenyl)-2-methylpyrrol-1-yl]-3-methylpentanoic acid (3d) White solid; yield 80%; mp 207–208°C; R_f 0.55 (10:0.3); IR: ν 3400–2100 (COOH), 3300 (O-H), 1710, 1600 (C=O), 820 cm^{-1} (p-C_6H_4); ^1H NMR ($CDCl_3$): δ 7.35–7.45 (m, 4H, C_6H_4), 6.71 (s, 1H, COOH), 6.48 (s, 1H, H-4), 4.43 (d, 1H, J = 10.8 Hz, CHCOOH), 2.62 (s, 3H, CH_3-2), 2.43 (s, 3H, $COCH_3$), 2.35–2.38 (m, 1H, $CHCH_3$), 0.95 (d, 3H, J = 6.3 Hz, $CHCH_3$), 0.52–0.62 (m, 5H, CH_2CH_3). Anal. Calcd for $C_{19}H_{22}ClNO_3$: C, 65.61; H, 6.38; N, 4.03. Found: C, 65.40; H, 6.12; N, 3.85.

2-[3-Acetyl-5-(4-chlorophenyl)-2-methylpyrrol-1-yl]-4-(methylthio)butyric acid (3e) White solid; yield 78%; mp 99–100°C; R_f 0.40 (10:0.3); IR: ν 3600–2200 (COOH), 3400 (O-H), 1740, 1610 (C=O), 840 cm^{-1} (p-C_6H_4); ^1H NMR ($CDCl_3$): δ 7.26–7.37 (m, 4H, C_6H_4), 6.50 (s, 1H, H-4), 5.94 (s, 1H, COOH), 5.10–5.20 (m, 1H, CHCOOH), 2.59 (s, 3H, CH_3-2), 2.45 (s, 3H, $COCH_3$), 2.02–2.32 (m, 4H, CH_2CH_2S), 1.91 (s, 3H, S-CH_3). Anal. Calcd for $C_{18}H_{20}ClNO_3S$: C, 59.09; H, 5.51; N, 3.83. Found: C, 58.77; H, 5.15; N, 3.44.

2-[3-Acetyl-5-(4-chlorophenyl)-2-methylpyrrol-1-yl]-3-phenylpropionic acid (3f) White solid; yield 80%; mp 163–164°C; R_f 0.59 (10:0.4); IR: ν 3400–2100 (COOH), 3300 (O-H), 1710, 1600 (C=O), 820 cm^{-1} (p-C_6H_4); ^1H NMR ($CDCl_3$): δ 7.09–7.26 (m, 5H, C_6H_4 + COOH), 6.63–6.68 (m, 5H, C_6H_5), 6.29 (s, 1H, H-4), 4.85–4.95 (m, 1H, CH_2-CH), 3.16–3.26 (m, 2H, CH_2-CH), 2.72 (s, 3H, CH_3-2), 2.44 (s, 3H, $COCH_3$). Anal. Calcd for $C_{22}H_{20}ClNO_3$: C, 69.20; H, 5.28; N, 3.67. Found: C, 68.88; H, 5.12; N, 3.34.

2-[3-Acetyl-5-(4-chlorophenyl)-2-methylpyrrol-1-yl]-3-(1*H*-indol-3-yl)propionic acid (3g) White solid; yield 72%; mp 196–197°C; R_f 0.48 (10:0.2); IR: ν 3600–2400 (COOH), 3350 (O-H), 1720, 1610 (C=O), 820 cm^{-1} (p-C_6H_4); ^1H NMR ($CDCl_3$): δ 8.90 (br, s, 2H, COOH + NH), 6.35–7.30 [m, 9H, 4H (C_6H_4) + 5H (indolyl-H)], 6.10 (s, 1H, H-4), 4.90–5.00 (m, 1H, CHCOOH), 3.20–3.40 (m, 2H, CH_2-CH), 2.55 (s, 3H, CH_3-2), 2.40 (s, 3H, $COCH_3$). Anal. Calcd for $C_{24}H_{21}ClN_2O_3$: C, 68.49; H, 5.03; N, 6.66. Found: C, 68.27; H, 4.76; N, 6.32.

Received January 6, 2014; accepted March 1, 2014

References

[1] Marx, V. Merck pulls the plug on painkiller Vioxx. *Chem. Eng. News* **2004**, *82*, 8.

[2] Solomon, D. H. *UpToDate*® **2013**, accessed June 17, 2013.

[3] Lindner, M.; Sippl, W.; Radwan, A. Pharmacophore elucidation and molecular docking studies on 5-phenyl-1-(3-pyridyl)-1*H*-1,2,4-triazole-3-carboxylic acid derivatives as COX-2 inhibitors. *Sci. Pharm.* **2010**, *78*, 195–214.

[4] Zarghi, A.; Arfaei, S. Selective COX-2 inhibitors: a review of their structure-activity relationships. *Iran. J. Pharm. Res.* **2011**, *10*, 655–683.

[5] Kumar, R.; Subramanian, A.; Masand, N.; Patil, V. M. Design and synthesis of substituted pyrrole derivatives as COX-2 inhibitors. *Dig. J. Nanomater. Biostruct.* **2010**, *5*, 667–674.

[6] Lessigiarska, I.; Nankov, A.; Bocheva, A.; Pajeva, I.; Bijev, A. 3D-QSAR and preliminary evaluation of anti-inflammatory activity of series of *N*-pyrrolylcarboxylic acids. *Il Farmaco* **2005**, *60*, 209–218.

[7] Bijev, A.; Yaneva, D.; Bocheva, A.; Stoev, G. Ligand-based design, synthesis and primary *in vivo* screening of pyrrole derivatives as potential tricyclic anti-inflammatory agents. *Drug Res.* **2006**, *56*, 753–762.

[8] Dannhardt, G.; Kiefer, W.; Kramer, G.; Maehrlein, S.; Nowe, U.; Fiebich, B. The pyrrole moiety as a template for COX-1/COX-2 inhibitors. *Eur. J. Med. Chem.* **2000**, *35*, 499–510.

[9] Paal, C. Ueber die Einwirkung von Bromacetophenon auf Natriumacetessigäther. *Berich. Deutsch. Chem. Gesellsch.* **1883**, *16*, 2865–2869.

[10] Kornblum, N.; Smiley, R. A.; Blackwood, R. K.; Iffland, D. C. The reduction of optically active 2-nitrooctane and α-phenylnitroethane. *J. Am. Chem. Soc.* **1955**, *77*, 6269.

[11] Kröhnke, F. Zur Theorie und Praxis der Halogenierung aktiver Methyl-und Methylengruppen. *Berich. Deutsch. Chem. Gesellsch.* **1936**, *69*, 921–935.