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N-Pyridinyl(methyl)-indole-1- or 3-propanamides and propenamides acting as topical and systemic inflammation inhibitors

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Abstract

In this study, the synthetic way to new *N*-pyridinyl(methyl)indolylpropanamides acting as non acidic NSAIDs has been described. Pharmacomodulation was carried out at N^1 and C^5 of the indole ring and at the level of the propanamide chain. N^3-pyridinylmethyl-[1(4-chlorobenzyl-5-chloroindol-3-yl)propanamide represents one of the most potent compounds in the TPA-induced mouse ear swelling assay, with a level of activity higher than that of ibuprofen and comparable to that of dexamethasone.

Keywords: N-*pyridinyl and* N-*pyridinylmethyl-indole-1-or-3-propanamides and propenamides, topical and systemic inflammation inhibitors*

Introduction

Since the discovery of the anti-inflammatory activity of indomethacin, the indole ring constitutes a frequently used template in the field of inflammation inhibitors acting as inhibitors of enzymes or key proteins such as cytokines, involved in the inflammation process [1]. Recently an indole-1-sulfonyl-3-acetic acid derivative, **A** [2], was described as a potent and selective $CRTH_2$ receptor antagonist, inhibiting PGD_2-induced lymphocyte activation and liable to treat allergic diseases such as atopic dermatitis; reversed amides of indomethacin, such as **B**, were evaluated as selective COX-2 inhibitors [3] and many of the selective peripheral CB2 receptor agonists [4–7], currently under study, are cannabimimetic indoles such as WIN-55212-2 [8], possessing potential in alleviating inflammation and pain. Moreover this heterocycle is present in (i) CCR2b antagonists such as the indole-2-carboxylic acid **C** [9] inhibiting binding of MCP-1, a pro-inflammatory cytokine, to the chemokine receptor CCR2b, (ii) inhibitors of human non pancreatic secretory or cytosolic phospholipases A_2 like the 4-[(indol-3-yl)ethoxy]benzoic acid **D** [10] and (iii) P38α MAP kinase inhibitors [11]. These last classes of compounds and the CB2 cannabinoid receptor agonists induce a significant reduction of TNF-α and Il-β production, cytokines that play a pivotal pathophysiological role in the initiation and progression of various inflammatory disorders: rheumatoid arthritis, psoriasis, inflammatory bowel disease and other autoimmune diseases.

During our previous investigations, we have studied anti-inflammatory *N*-pyridinyl(methyl)-indole carbox mides or alcanamides [12–15] and *N*-pyridinyl-(methyl)-phthalimides [16] that induce down-regulation of TNF-α production. In continuation of our

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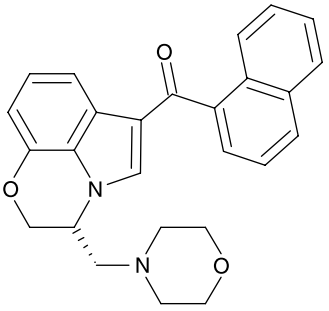

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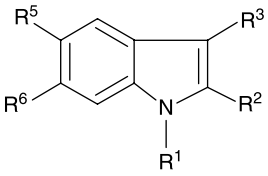

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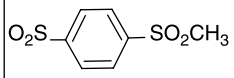
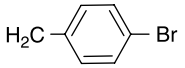
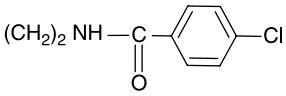
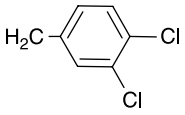
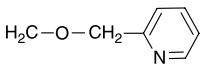
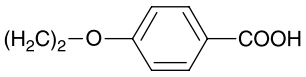
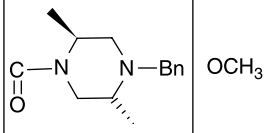
A		H	CH_2 COOH	F	H
B		CH_3		H	H
C		COOH	H	H	H
D	$CH(C_6H_5)_2$			Cl	H
E	H	H	H		OCH_3

Figure 1. Structure of some indole-based anti-inflammatory compounds.

works in that field, we describe here indolpropanamide-based topical inflammation inhibitors exerting anti-oedema effect in the mouse ear swelling test.

Materials and methods

Chemistry

Instrumentation. Melting points (m.p. (dec.)), determined on a Tottoli-Büchi apparatus, were uncorrected. The structure of the products described were confirmed by IR and ^{1}H-NMR. IR spectra were run with KBr pellets or a film on NaCl plates using a Perkin-Elmer Paragon PC 1000 spectrophotometer. ^{1}H-NMR spectra were recorded on a Bruker AC 250 spectrometer (250 MHz) using Me_2SO-d_6 as solvent. Chemical shifts (δ) were reported in parts per million (ppm) downfield from tetramethylsilane (Me_4Si, 0.00 ppm) as the internal standard, and coupling constants in Hertz. Analytical thin-layer chromatography was performed on pre-coated silica-gel aluminium plates (0.2 mm, GF254, E. Merck). Spots were located by UV illumination. Evaporations were performed *in vacuo* (rotary evaporator). Sodium sulphate was used as the drying agent. Crude products were passed through short

silica gel columns (silica gel 60, 70-230 mesh, E. Merck). Commercially available solvents and chemicals were used for syntheses. Ethyl 3-(indol-3-yl)propanoate (**2**) was prepared by refluxing the corresponding acid **1** according to a previously described method (*method a*) [14]. Ethyl 3-(1-methylindol-3-yl)propanoate (**3**) was obtained by *method b* as described previously [14]. The carbaldehyde **14**, the propenoate **17**, the propanoate **19**, the acid **21** [17] and the propanamides **29** [12], **31**, **32**, **36**, **37**, **40**, **41**, **42**, **45**, **46**, **47** [17], **34** [18], **38** [14] have been previously prepared.

*Method c: Ethyl 3-(1-benzylindol-3-yl)propanoate (**4**)*. To a solution of ethyl 3-(indol-3-yl)propanoate **2** (1.9 g, 8.74 mmol) in dry CH_3CN (25 mL) was added Cs_2CO_3 (5.7 g, 17.48 mmol). The suspension was stirred for 2 h under reflux and cooled at room temperature. Benzyl chloride (1.1 mL, 9.61 mmol) was then added and the reaction mixture was stirred at room temperature for 30 min. The precipitate was filtered and washed with CH_3CN. The filtrate was evaporated under reduced pressure. The residue was dissolved in CH_2Cl_2 and the organic layer was washed with water, dried (Na_2SO_4) and concentrated. The crude was purified by column chromatography using a mixture of dichloromethane/cyclohexane 90/10 to afford a pale yellow oil (1.94 g). Yield: 72%; IR (KBr) ν_{max}: 1730 (C=O) cm^{-1}; ^{1}H-NMR (DMSO-d_6, ppm): δ 1.17 (t, 3H, J = 7.0 Hz, CH_3), 2.70 (t, 2H, J = 7.3 Hz, CH_2—CO), 3.01 (t, 2H, CH_2), 4.06 (q, 2H, O—CH_2), 5.38 (s, 2H, N—CH_2), 7.04 (dd, 1H, J = 7.6, 7.0 Hz, H^5), 7.12 (dd, 1H, J = 8.2, 7.0 Hz, H^6), 7.30 (m, 5H, Bn), 7.30 (s, 1H, H^2), 7.43 (d, 1H, H^7), 7.58 (d, 1H, H^4).

*Ethyl 3-[1-(4-chlorobenzyl)indol-3-yl]propanoate (**5**)*. Pale yellow oil, Yield: 96%; IR (KBr) ν_{max}: 1731 (C=O) cm^{-1}; ^{1}H-NMR (DMSO-d_6, ppm): δ 1.65 (t, 3H, J = 7.0 Hz, CH_3), 2.70 (t, 2H, J = 7.3 Hz, CH_2—CO), 3.70 (t, 2H, CH_2), 4.06 (q, 2H, O—CH_2), 5.39 (s, 2H, N—CH_2), 7.04 (dd, 1H, J = 7.6, 7.0 Hz, H^5), 7.13 (dd, 1H, J = 7.9, 7.0 Hz, H^6), 7.21 (d, 2H, J = 8.5 Hz, Bn-H^2, H^6), 7.30 (s, 1H, H^2), 7.39 (d, 2H, Bn-H^3, H^5), 7.42 (d, 1H, H^7), 7.58 (d, 1H, H^4).

*Ethyl 3-[1-(4-morpholinoethyl)indol-3-yl]propanoate (**6**)*. Pale yellow oil, yield: 83%; IR (KBr) ν_{max}: 1728 (C=O) cm^{-1}; ^{1}H-NMR (DMSO-d_6, ppm): δ 1.19 (t, 3H, J = 7.0 Hz, CH_3), 2,45 (m, 4H, morph.-H^3, H^5), 2.66 (m, 4H, CH_2—CO, CH_2-Nmorph.), 2.98 (t, 2H, J = 7,0 Hz, CH_2), 3.58 (m, 4H, morph.-H^2, H^6), 4.10 (q, 2H, O—CH_2), 4,25 (t, 2H, J = 6.7 Hz, N—CH_2), 7.03 (dd, 1H, J = 7.9, 7.3 Hz, H^5), 7.15 (dd, 1H, J = 8.2, 7.3 Hz, H^6), 7.21 (s, 1H, H^2), 7.45 (d, 1H, H^7), 7.55 (d, 1H, H^4).

*(5-Chloro-1-(4-chlorobenzyl)indol-3-yl)carboxaldehyde (**15**)*. White powder, yield: 95%; m. p. (dec.): 146–147°C; IR (KBr) ν_{max}: 1657 (C=O) cm^{-1}; ^{1}H-NMR (DMSO-d_6, ppm): δ 5.60 (s, 2H, CH_2), 7,35 (dd, 1H, J = 8.5, 1.8 Hz, H^6), 7,37 (d, 2H, J = 8,5 Hz, Bn-H^2, H^6), 7,45 (d, 2H, Bn, H^3, H^5), 7.67 (d, 1H, H^7), 8.13 (d, 1H, H^4), 8.59 (s, 1H, H^2), 9.98 (s, 1H, CHO).

*Method d: 1-(4-fluorobenzyl)indol-3-ylcarboxaldehyde (**13**)*. To a solution of indol-3-ylcarboxaldehyde (1.5 g, 10.3 mmol) in dry DMSO (20 mL) was added K_2CO_3 (2.1 g, 15.2 mmol) and 4-fluorobenzyl chloride (1.64 g, 13.0 mmol). After stirring for 2 h at room temperature, the reaction mixture was poured on water (100 mL) and extracted with CH_2Cl_2. The organic layer was washed, dried (Na_2SO_4) and concentrated under reduced pressure. Purification on silica gel chromatography, eluting with CH_2Cl_2 afforded an oil which crystallized in diisopropylic ether as white crystals. Yield: 88%; m. p. (dec.): 116–118°C; IR (KBr) ν_{max}: 1650 (C=O) cm^{-1}; ^{1}H-NMR (DMSO-d_6, ppm): δ 5.57 (s, 2H, CH_2), 7.18-7.45 (m, 6H, H^5, H^6, Bn), 7.64 (d, 1H, J = 6.7 Hz, H^7), 8.16 (m, 1H, H^4), 8.51 (s, 1H, H^2), 9.98 (s, 1H, CHO).

*Method e: Methyl 3-[1-(4-fluorobenzyl)indol-3-yl]prop-2-enoate (**16**)*. A solution of aldehyde **13** (7.60 g, 30 mmol) and methyl triphenylphosphoranylidenyl-acetate (20 g, 60 mmol) in anhydrous dioxane (200 mL) was heated under reflux for 48 h. After evaporation of the solvent, the crude ester was purified by silica gel chromatography, eluting with a mixture of dichloromethane/petroleum ether 60/40 affording an oil which crystallized in diisopropylic ether as white crystals. Yield: 85%; m. p. (dec.): 104-106°C; IR (KBr) ν_{max}: 1710 (C=O), 1625 (C=C) cm^{-1}; ^{1}H-NMR (DMSO-d_6, ppm): δ 3.74 (s, 3H, O-CH_3), 5.48 (s, 2H, CH_2), 6.43 (d, 1H, J = 16.0 Hz, CH—CO), 7.15–7.38 (m, 6H, H^5, H^6, Bn), 7.60 (d, 1H, J = 7.5 Hz, H^7), 7.87-7.95 (m, 2H, H^4, CH), 8.17 (s, 1H, H^2).

*Method f: Ethyl 3-[5-chloro-1-(4-chlorobenzyl)indol-3-yl]prop-2-enoate (**18**)*. To a suspension of NaH (0.79 g, 19.72 mmol) in dry THF (40 mL) was progressively added ethyl diethylphosphonoacetate (4.42 g, 19.72 mmol). The reaction mixture was stirred until cessation of gas evolution and a solution of (5-chloro-1-(4-chlorobenzyl)indol-3-yl)carboxaldehyde **14** (4 g, 13.15 mmol) in anhydrous THF (40 mL) was then added. The solution was stirred overnight at room temperature. The solvent was removed under reduced pressure and the residue obtained was treated with CH_2Cl_2 (200 mL) and washed with water (2 × 100 mL), dried (Na_2SO_4) and evaporated.

Purification by column chromatography on silica gel, eluting with dichloromethane, afforded **18** as a white powder. Yield: 67%; m. p. (dec.): 155–156°C; IR (KBr) ν_{max}: 1697 (C=O), 1627 (C=C) cm^{-1}; ^{1}H-NMR (DMSO-d_6, ppm): δ 1.30 (t, 3H, J = 7.0 Hz, CH_3), 4.21 (q, 2H, OCH_2), 5.51 (s, 2H, CH_2), 6.43 (d, 1H, J = 16.2 Hz, CH—CO), 7.28 (dd, 1H, J = 8.5, 1.8 Hz, H^6), 7.30 (d, 2H, J = 8,5 Hz, Bn-H^2, H^6), 7.42 (d, 2H, Bn-H^3, H^5), 7.62 (d, 1H, H^7), 7.86 (d, 1H, CH), 7.99 (d, 1H, H^4), 8.25 (s, 1H, H^2).

*Method g: Ethyl 3-[5-chloro-1-(4-chlorobenzyl)indol-3-yl]propanoate (**20**)*. Ethyl 3-(5-chloro-1-(4-chlorobenzyl)indol-3-yl)prop-2-enoate **18** (2 g, 5.34 mmol) was dissolved in dry THF (200 mL) and a suspension of Raney nickel (2 g) was quickly added. The reaction mixture was purged three times with hydrogen and was stirred at room temperature overnight. The inorganic layer was filtered, washed with THF and the filtrate was removed under reduced pressure to obtain **20** as a yellow oil. Yield: quantitative; IR (KBr) ν_{max}: 1735 (C=O) cm^{-1}; ^{1}H-NMR (DMSO-d_6, ppm): δ 1.16 (t, 3H, J = 7.0 Hz, CH_3), 2.67 (t, 2H, J = 7.3 Hz, CH_2—CO), 2.98 (t, 2H, CH_2), 4.23 (q, 2H, O-CH_2), 5.40 (s, 2H, N—CH_2), 7.09 (dd, 1H, J = 8.5, 1.8 Hz, H^6), 7.20 (d, 2H, J = 8.2 Hz, Bn- H^2, H^6), 7.39 (s, 1H, H^2), 7.40 (d, 2H, Bn-H^3, H^5), 7.46 (d, 1H, H^7), 7.64 (d, 1H, H^4).

Method h: 3-(1-Methylindol-3-yl)propanoic acid (7). A mixture of ethyl 3-(1-methylindol-3-yl)propanoate **3** (1.47 g, 6.48 mmol), ethanol (20 mL) and 2M aqueous NaOH (20 mL) was refluxed with stirring for 2 h, cooled to room temperature and acidified with 2M aqueous HCl. The precipitate was then filtered, washed with cold water and dried (P_2O_5). By recrystallization from diisopropylic ether, a pure product was obtained. White powder; yield: 96%; m. p. (dec.): 123–125°C; IR (KBr) ν_{max}: 3100-2600 (OH), 1711 (C=O) cm^{-1}; ^{1}H-NMR (DMSO-d_6, ppm): δ 2.61 (t, 2H, J = 7.5 Hz, CH_2—CO), 2.96 (t, 2H, CH_2), 3.76 (s, 3H, NCH_3), 7.04 (dd, 1H, = 7.8, 7.2 Hz, H^5), 7.13 (s, 1H, H^2), 7,17 (dd, 1H, J = 8.0, 7.2 Hz, H^6), 7.41 (d, 1H, H^7), 7.57 (d, 1H, H^4), 12.13 (s, 1H, COOH).

*3-(1-Benzylindol-3-yl)propanoic acid (**8**)*. White powder, yield: 82%; m. p. (dec.): 115-116°C; IR (KBr) ν_{max}: 3100-2600 (O-H), 1710 (C=O) cm^{-1}; ^{1}H-NMR (DMSO-d_6, ppm): δ 2.62 (t, 2H, J = 7.0 Hz, CH_2—CO), 2.98 (t, 2H, CH_2), 5.38 (s, 2H, N—CH_2), 7.04 (dd, 1H, J = 8.0, 7.6 Hz, H^5), 7.12 (dd, 1H, J = 8.0, 7.6 Hz, H^6), 7.27 (m, 6H, H^2, Bn), 7.42 (d, 1H, H^7), 7.58 (d, 1H, H^4), 10;21 (s, 1H, OH).

*3-[1-(4-Chlorobenzyl)indol-3-yl]propanoic acid (**9**)*. White powder, yield: 90%; m. p. (dec.): 136–137°C; IR (KBr) ν_{max}: 3100-2600 (OH), 1710 (C=O) cm^{-1}; ^{1}H-NMR (DMSO-d_6, ppm): δ 2.62 (t, 2H, J = 7.3 Hz, CH_2—CO), 2.97 (t, 2H, CH_2), 5.39 (s, 2H, N—CH_2), 7.04 (dd, 1H, J = 7.9, 7.3 Hz, H^5), 7.12 (dd, 1H, J = 7.9, 6.7 Hz, H^6), 7.21 (d, 2H, J = 8.5 Hz, Bn-H^2, H^6), 7.31 (s, 1H, H^2), 7.40 (m, 3H, H^7, Bn-H^3, H^5), 7.58 (d, 1H, H^4).

*3-[1-(2-Morpholin-4-ylethyl)indol-3-yl]propanoic acid (**10**)*. White powder, yield: 32%; m. p. (dec.): 120–121°C; IR (KBr) ν_{max}: 3100-2600 (OH), 1710 (C=O) cm^{-1}; ^{1}H-NMR (DMSO-d_6, ppm): δ 2.44 (m, 4H, morph-H^3, H^5), 2.61 (t, 2H, J = 7.6 Hz, CH_2—CO), 2.65 (t, 2H, J = 6.8 Hz, NCH_2), 2.95 (t, 2H, CH_2), 3.58 (m, 4H, morph-H^2, H^6), 4.25 (t, 2H, N—CH_2), 7.03 (dd, 1H, J = 7.6, 7.2 Hz, H^5), 7.15 (dd, 1H, J = 8.0, 7.6 Hz, H^6), 7.21 (s, 1H, H^2), 7.45 (d, 1H, H^7), 7.55 (d, 1H, H^4), 12.13 (s, 1H, OH).

*3-[5-Chloro-1-(4-chlorobenzyl)indol-3-yl]propanoic acid (**22**)*. White powder, yield: 74%; m. p. (dec.): 135–137°C. IR (KBr) ν_{max}: 3000-2700 (OH), 1701 (C=O) cm^{-1}; ^{1}H-NMR (DMSO-d_6, ppm): δ 2.61 (t, 2H, J = 7.6 Hz, CH_2—CO), 2.95 (t, 2H, CH_2), 5.41 (s, 2H, N—CH_2), 7.13 (dd, 1H, J = 8.8, 2.1 Hz, H^6), 7.21 (d, 2H, J = 8.5 Hz, Bn-H^2, H^6), 7.39 (d, 2H, Bn-H^3, H^5), 7.40 (s, 1H, H^2), 7.46 (d, 1H, H^7), 7.64 (d, 1H, H^4), 12.13 (s, 1H, COOH).

*3-[1-(4-fluorobenzyl)indol-3-yl]prop-2-enoic acid (**23**)*. White crystals, yield: 95%; m. p.: 166–168°C. IR (KBr) ν_{max}: 3200-2800 (OH), 1670 (C=O), 1627 (C=C) cm^{-1}. ^{1}H-NMR (DMSO-d_6, ppm): δ 5.48 (s, 2H, CH_2), 6.35 (d, 1H, J = 16.0 Hz, CH—CO), 7.15-7.39 (m, 6H, H^5, H^6, Bn), 7.60 (dd, 1H, J = 8.2, 2.0 Hz, H^7), 7.82 (d, 1H, CH), 7.91 (dd, 1H, J = 7.5, 2.0 Hz, H^4), 8.13 (s, 1H, H^2), 11.97 (s, 1H, OH).

*3-[5-Chloro-1-(4-chlorobenzyl)indol-3-yl]prop-2-enoic acid (**24**)*. White powder, yield: 97%; m. p. (dec.): 220–222°C; IR (KBr) ν_{max}: 2900-2700 (OH), 1674 (C=O), 1615 (C=C) cm^{-1}; ^{1}H-NMR (DMSO-d_6, ppm): δ 5.50 (s, 2H, CH_2), 6.37 (d, 1H, J = 16.2 Hz, CH—CO), 7.27 (dd, 1H, J = 8.8, 1.8 Hz, H^6), 7.29 (d, 2H, J = 8.4 Hz, Bn-H^2, H^6), 7.43 (d, 2H, Bn-H^3, H^5), 7.61 (d, 1H, H^7), 7.80 (d, 1H, CH), 7.94 (d, 1H, H^4), 8.21 (s, 1H, H^2), 11.95 (s, 1H, OH).

*Method i: 3-(Indol-1-yl)propionitrile (**25**)*. Indole (5 g, 42.68 mmol) was dissolved in dioxane (60 mL) then a 40% triton B solution in methanol (2.13 mL) was added. The mixture was stirred vigourously and acrylonitrile (5.62 mL, 85.36 mmol) was added. The solution was heated at 80-90°C for 2 h. Then, stirring was continued for 72 h at room temperature. The reaction mixture was extracted with CH_2Cl_2 (2 × 50 mL). The organic layers were washed with water, dried (Na_2SO_4) and evaporated under reduced pressure. The residue was purified by column chromatography eluting with CH_2Cl_2 to afford a

green oil [19] (6.44 g). Yield: 88%; IR (NaCl) ν_{max}: ν(C ≡ N) 2245 cm^{-1}; ^{1}H-NMR (DMSO-d_6, ppm): δ 3.06 (t, 2H, J = 6.4 Hz, CH_2), 4.53 (t, 2H, N—CH_2), 6.52 (d, 1H, J = 3.35 Hz, H^3), 7.09 (dd, 1H, J = 7.9, 7.3 Hz, H^5), 7.20 (dd, 1H, J = 7.9, 7.3 Hz, H^6), 7.47 (d, 1H, H^2), 7.61 (d, 2H, H^4, H^7).

*(5-chloro-3-(indol-1-yl))propionitrile (**26**)*. Oil, yield: 84%; IR (NaCl) ν_{max}: 2248 (C═N) cm^{-1}; ^{1}H-NMR (DMSO-d_6, ppm): δ 3.07 (t, 2H, J = 6.7 Hz, CH_2), 4.54 (t, 2H, N—CH_2), 6.52 (d, 1H, J = 3.0 Hz, H^3), 7.20 (dd, 1H, J = 8.8, 1.8 Hz, H^6), 7.55 (d, 1H, H^2), 7.65 (m, 2H, H^4, H^7).

*Method j: 3-(Indol-1-yl)propanoic acid (**27**)*. A mixture of 3-(indol-1-yl)propionitrile **25** (1.7 g, 6.40 mmol) in 10% aqueous KOH (100 mL) was refluxed with stirring for 3 h, cooled to room temperature and acidified with 10M aqueous HCl. The precipitate was then filtered, washed with cold water and dried (P_2O_5). By recrystallization from diisopropylic ether, a pure white product was obtained. Yield: 49%; m. p. (dec.): 87–88°C [20]; IR (KBr) ν_{max}: 3000-2700 (OH), 1721 (C═O) cm^{-1}; ^{1}H-NMR (DMSO-d_6, ppm): δ 2.78 (t, 2H, J = 7.3 Hz, CH_2—CO), 4.43 (t, 2H, N—CH_2), 6.45 (d, 1H, J = 3.35 Hz, H^3), 7.05 (dd, 1H, J = 7.9, 7.0 Hz, H^5), 7.17 (dd, 1H, J = 7.9, 7.0 Hz, H^6), 7.38 (d, 1H, H^2), 7.52 (d, 1H, H^7), 7.57 (d, 1H, H^4).

*3-(5-Chloroindol-1-yl)propanoic acid (**28**)*. Oil, yield: 91%; IR (NaCl) ν_{max}: 3100-2800 (OH), 1712 (C═O) cm^{-1}; ^{1}H-NMR (DMSO-d_6, ppm): δ 2.69 (t, 2H, J = 6.8 Hz, CH_2—CO), 4.40 (t, 2H, N—CH_2), 6.42 (d, 1H, J = 3.0 Hz, H^3), 7.14 (dd, 1H, J = 8.8, 1.8 Hz, H^6), 7.46 (d, 1H, H^2), 7.55 (d, 1H, H^7), 7.60 (d, 1H, H^4).

*Method k: N-(Pyridin-4-yl)-3-[1-(4-ethylmorpholinyl)-indol-3-yl]propanamide (**33**)*. To a solution of 3-(1-morpholinylethylindol-3-yl)propanoic acid **10** (0.76 g, 2.51 mmol) in dry CH_2Cl_2 (50 mL), were added 2-chloro-1-methylpyridinium iodide (0.64 g, 2.51 mmol), triethylamine (0.88 mL, 6.27 mmol) and 4-aminopyridine (0.26 g, 2.76 mmol). The mixture was refluxed for 12 h and after cooling, washed with water, dried over Na_2SO_4 and concentrated. The crude was purified by chromatography on silica gel using dichloromethane:ethanol 95:5 as the eluent. The residue was dissolved in ethyl acetate in presence of maleic acid to afford **33** as a bis maleate. White powder. Yield: 32%; m. p. (dec.): 161–162°C; IR (KBr) ν_{max}:, 3303 (NH), 1696 (C═O) cm^{-1}; ^{1}H-NMR (DMSO-d_6, ppm): δ 2.82 (t, 2H, J = 7.2 Hz, CH_2—CO), 3.00 (m, 4H, morph-H^3, H^5), 3.08 (t, 2H, CH_2), 3.21 (m, 2H, NCH_2), 3.74 (m, 4H, morph-H^2, H^6), 4.45 (t, 2H, N—CH_2), 6.17 (s, 4H, CH═CH maleate), 7.09 (dd, 1H, J = 7.6, 7.2 Hz, H^5), 7.21 (dd, 1H, J = 7.9, 7.6 Hz, H^6), 7.25 (s, 1H, H^2), 7.52 (d, 1H, H^7), 7.64 (d, 1H, H^4), 7.80 (d, 1H, J = 5.6 Hz, pyr-H^3, H^5), 8.57 (d, 1H, pyr-H^2, H^6), 10.77 (s, 1H, NH).

*N-(4,6-Dimethylpyridin-2-yl)-3-(1-methylindol-3-yl)propanamide (**35**)*. Orange oil, yield: 73%; IR (NaCl) ν_{max}: 3274 (NH), 1694 (C═O) cm^{-1}. ^{1}H-NMR (DMSO-d_6, ppm): δ 2.29 (s, 3H, γ-CH_3), 2.37 (s, 3H, α-CH_3), 2.76 (t, 2H, J = 7.5 Hz, CH_2—CO), 3.03 (t, 2H, CH_2), 3.75 (s, 3H, NCH_3), 6.81 (s, 1H, pyr. H^5), 7.05 (dd, 1H, J = 7.5, 7.0 Hz, H^5), 7.13 (s, 1H, H^2), 7.17 (dd, 1H, J = 8.1, 7.0 Hz, H^6), 7.40 (d, 1H, H^7), 7.63 (d, 1H, H^4), 7.84 (s, 1H, pyr. H^3), 10.42 (s, 1H, NH).

*N-(Pyridin-3-ylmethyl)-3-(indol-3-yl)propanamide (**38**)*. Yellow oil, yield: 60%; IR (NaCl) ν_{max}: 3270 (NH), 1651 (C═O) cm^{-1}; ^{1}H-NMR (DMSO-d_6, ppm): δ 2.56 (t, 2H, J = 7.6 Hz, CH_2—CO), 3.00 (t, 2H, CH_2), 4.32 (d, 2H, J = 5.9 Hz, NH-CH_2), 7.00 (dd, 1H, J = 7.9, 6.9 Hz, H^5), 7.07 (dd, 1H, J = 8.0, 6.9 Hz, H^6), 7.12 (d, 1H, J = 2.6 Hz, H^2), 7.30 (m, 1H, pyr-H^5), 7.37 (d, 1H, H^7), 7.54 (m, 1H, pyr-H^4), 7.57 (d, 1H, H^4), 8.45 (m, 3H, pyr-H^2, H^6, NH), 10.86 (bs, 1H, H^1).

*N-(Pyridin-3-ylmethyl)-3-(1-methylindol-3-yl)propanamide (**39**)*. Orange oil, yield: 78%; IR (NaCl) ν_{max}: 3285 (NH), 1651 (C═O) cm^{-1}; ^{1}H-NMR (DMSO-d_6, ppm): δ 2.55 (t, 2H, J = 7.4 Hz, CH_2CO), 3.01 (t, 2H, CH_2), 3.74 (s, 3H, NCH_3), 4.33 (d, 2H, J = 5.7 Hz, NH-CH_2), 7.05 (m, 2H, H^2, H^5), 7.18 (m, 1H, H^6), 7.36 (m, 2H, H^7, pyr. H^5), 7.57 (m, 2H, H^4, pyr. H^4), 8.47 (m, 3H, pyr-H^2, H^6, NH).

*N-(Pyridin-4-yl)-3-[5-chloro-1-(4-chlorobenzyl)indol-3-yl]propanamide (**43**)*. Beige powder, yield: 46%; m. p. (dec.): 128-129°C; IR (NaCl) ν_{max}: 3285 (NH), 1652 (C═O) cm^{-1}; ^{1}H-NMR (DMSO-d_6, ppm): δ 2.74 (t, 2H, J = 7.2 Hz, CH_2CO), 3.05 (t, 2H, CH_2), 5.39 (s, 2H, NCH_2), 7.12 (d, 1H, J = 8.8 Hz, H^6), 7.16 (d, 2H, J = 8.0 Hz, Bn-H^2, H^6), 7.29 (d, 2H, Bn-H^3, H^5), 7.41 (s, 1H, H^2), 7.45 (d, 1H, H^7), 7.60 (m, 2H, pyr-H^3, H^5), 7.70 (se, 1H, H^4), 8.45 (m, 2H, pyr-H^2, H^6), 10.33 (s, 1H, NH).

*N-(4,6-Dimethylpyridin-2-yl)-3-(5-chloro-1-methylindol-3-yl)propanamide (**44**)*. Yellow oil, yield: 44%, IR (KBr) ν_{max}: 3271 (NH), 1675 (C═O) cm^{-1}; ^{1}H-NMR (DMSO-d_6, ppm): δ 2.29 (s, 3H, γ-CH_3), 2.37 (s, 3H, α-CH_3), 2.72 (t, 2H, J = 7.6 Hz, CH_2—CO), 2.99 (t, 2H, CH_2), 3.75 (s, 3H, N-CH_3), 6.82 (s, 1H, pyr. H^5), 7.15 (dd, 1H, J = 8.8, 2.0 Hz, H^6), 7.23 (s, 1H, H^2), 7.43 (d, 1H, H^7), 7.69 (d, 1H, H^4), 7.81 (s, 1H, pyr. H^3), 10.41 (s, 1H, NH).

*N-(Pyridin-4-yl)-3-[5-chloro-1-(4-chlorobenzyl)indol-3-yl]prop-2-enamide (**49**)*. Yellow powder, yield: 25%; m. p. (dec.): 244–245°C; IR (KBr) ν_{max}: 3260 (NH), 1670 (C═O), 1620 (C═C) cm^{-1}; ^{1}H-NMR (DMSO-d_6, ppm): δ 5.50 (s, 2H, N—CH_2), 6.80 (d, 1H, J = 15.6 Hz, CH—CO), 7.27 (d, 2H, J = 8.4 Hz,

Bn-H^2, H^6), 7.30 (dd, 1H, J = 8.8, 2.0 Hz, H^6), 7.40 (d, 2H, Bn-H^3, H^5), 7.62 (d, 1H, H^7), 7.65 (d, 2H, J = 6.4 Hz, pyr-H^3, H^5), 7.79 (d, 1H, CH), 7.98 (d, 1H, H^4), 8.15 (s, 1H, H^2), 8.48 (d, 2H, pyr-H^2, H^6), 10.41 (s, 1H, NH).

*N-(4,6-Dimethylpyridin-2-yl)-3-[5-chloro-1-(4-chlorobenzyl)indol-3-yl]prop-2-enamide (**50**)*. White powder, yield: 20%; m.p (dec.): 146-147°C; IR (KBr) ν_{max}: 3270 (NH), 1670 (C═O), 1616 (C═C) cm^{-1}; ^{1}H-NMR (DMSO-d_6, ppm): δ 2.32 (s, 3H, γ-CH_3), 2.41 (s, 3H, α-CH_3), 5.51 (s, 2H, NCH_2), 7.09 (d, 1H, J = 16.0 Hz, CH—CO), 7.29 (d, 2H, J = 8.5 Hz, Bn-H^2, H^6), 7.31 (dd, 2H, J = 8.5, 2.1 Hz, H^6), 7.43 (d, 2H, J = 8.50 Hz, Bn-H^3, H^5), 7.62 (d, 1H, H^7), 7.75 (d, 1H, CH), 7.98 (s, 1H, pyr-H^3), 8.13 (s, 1H, H^2), 8.17 (d, 1H, H^4), 10.44 (s, 1H, NH).

*N- (Pyridin-3-ylmethyl)-3-[5-chloro-1-(4-chlorobenzyl)indol-3-yl]prop-2-enamide (**51**)*. White powder; yield: 38.5%; m. p. (dec.): 204-205°C; IR (KBr) ν_{max}: 3256 (NH), 1656 (C═O), 1615 (C═C) cm^{-1}; ^{1}H-NMR (DMSO-d_6, ppm): δ 4.45 (d, 2H, J = 5.9 Hz, NH-CH_2), 5.47 (s, 2H, N—CH_2), 6.72 (d, 1H, J = 16.0 Hz, CH—CO), 7.25 (m, 3H, pyr-H^5, Bn-H^2, H^6), 7.41 (m, 3H,H^6, Bn-H^3, H^5), 7.59 (d, 1H, J = 8.80 Hz, H^7), 7.62 (d, 1H, CH), 7.75 (d, 1H, J = 7.80 Hz, pyr-H^4), 7.95 (d, 1H, J = 1.6 Hz, H^4), 8.05 (s, 1H, H^2), 8.54 (m, 3H, pyr-H^2, H^6, NH).

*N-(Pyridin-4-yl)-3-(indol-1-yl)propanamide (**52**)*. White powder, yield: 53%; m. p. (dec.): 178–179°C; IR (KBr) ν_{max}: 3215 (NH), 1690 (C═O) cm^{-1}; ^{1}H-NMR (DMSO-d_6, ppm): δ 2.92 (t, 2H, J = 6.7 Hz, CH_2), 4.54 (t, 2H, N—CH_2), 6.44 (d, 1H, J = 3.05 Hz, H^3), 7.05 (dd, 1H, J = 7.9, 7.0 Hz, H^5), 7.18 (dd, 1H, J = 7.9, 7.3 Hz, H^6), 7.37 (d, 1H, H^2), 7.62 (m, 4H, H^4, H^7, pyr. H^3, H^5), 8.45 (d, 2H, J = 5.1 Hz, pyr-H^2, H^6), 10.37 (s, 1H, NH).

*N-(4,6-Dimethylpyridin-2-yl)-3-(indol-1-yl)propanamide (**53**)*. Brown oil, yield: 43%; IR (NaCl) ν_{max}: 3225 (NH), 1689 (C═O) cm^{-1}; ^{1}H-NMR (DMSO-d_6, ppm): δ 2.29 (s, 3H, γ-CH_3), 2.35 (s, 3H, α-CH_3), 2.93 (t, 2H, J = 6.7 Hz, CH_2—CO), 4.51 (t, 2H, N—CH_2), 6.43 (d, 1H, J = 3.05 Hz, H^3), 6.82 (s, 1H, pyr. H^5), 7.05 (dd, 1H, J = 7.9, 7.9 Hz, H^5), 7.18 (dd, 1H, J = 7.9, 7.6 Hz, H^6), 7.55 (m, 3H, H^2, H^4, H^7), 7.78 (s, 1H, pyr. H^3), 10.46 (s, 1H, NH).

*N-[(Pyridin-3-yl)methyl]-3-(indol-1-yl)propanamide (**54**)*. Brown oil, yield: 43%; IR (NaCl) ν_{max}: 3277 (NH), 1656 (C═O) cm^{-1}; ^{1}H-NMR (DMSO-d_6, ppm): δ 2.72 (t, 2H, J = 6.7 Hz, CH_2), 4.30 (d, 2H, J = 5.8 Hz, CH_2-NH), 4.50 (t, 2H, CH_2N), 6.44 (d, 1H, J = 3.0 Hz, H^3), 7.05 (dd, 1H, J = 7.9, 7.9 Hz, H^5), 7.17 (dd, 1H, J = 7.9, 7.6 Hz, H^6), 7.29 (m, 2H, pyr.H^5, H^6), 7.45 (d, 1H, H^7), 7.55 (m, 2H, H^4, H^2), 8.45 (m, 3H, pyr.H^2, H^4, NH).

*N-(Pyridin-4-yl)-3-(5-chloroindol-1-yl)propanamide (**55**)*. Beige powder, yield: 54%; m.p.: 149–150°C; IR (KBr) ν_{max}: 3153 (NH), 1688 (C═O) cm^{-1}; ^{1}H-NMR (DMSO-d_6, ppm): δ 2.92 (t, 2H, J = 6.7 Hz, CH_2—CO), 4.54 (t, 2H, NCH_2), 6.45 (d, 1H, J = 3.1 Hz, H^3), 7.17 (dd, 1H, J = 8.8, 1.8 Hz, H^6), 7.45 (d, 1H, H^2), 7.54 (m, 2H, H^4, H^7), 7.61 (m, 2H, pyr-H^3, H^5), 8.43 (m, 2H, pyr-H^2, H^6), 10.37 (s, 1H, NH).

*N-(4,6-Dimethylpyridin-2-yl)-3-(5-chloroindol-1-yl)propanamide (**56**)*. Beige powder, yield: 56%; m.p.: 151-152°C; IR (KBr) ν_{max}: 3246 (NH), 1647 (C═O): cm^{-1}; ^{1}H-NMR (DMSO-d_6, ppm): δ 2.28 (s, 3H, γ-CH_3), 2.34 (s, 3H, α-CH_3), 2.92 (t, 2H, J = 6.7 Hz, CH_2—CO), 4.51 (t, 2H, NCH_2), 6.44 (d, 1H, J = 2.8 Hz, H^3), 6.81 (s, 1H, pyr-H^5), 7.17 (dd, 1H, J = 8.8, 2.0 Hz, H^6), 7.45 (d, 1H, H^2), 7.60 (m, 2H, H^4, H^7), 7.77 (s, 1H, pyr-H^3), 10.46 (s, 1H, NH).

*N-[(Pyridin-3-yl)methyl]-3-(5-chloroindol-1-yl)propanamide (**57**)*. Beige powder, yield: 40%; m.p.: 99–100°C; IR (KBr) ν_{max}: 3299 (NH), 1643 (C═O): cm^{-1}; ^{1}H-NMR (DMSO-d_6, ppm): δ 2.69 (t, 2H, J = 6.8 Hz, CH_2—CO), 4.27 (d, 2H, J = 5.6 Hz, CH_2NH), 4.48 (t, 2H, NCH_2), 6.44 (d, 1H, J = 2.8 Hz, H^3), 7.15 (dd, 1H, J = 8.8, 2.0 Hz, H^6), 7.28 (dd, 1H, J = 8.0, 4.8 Hz, pyr-H^5), 7.40 (m, 2H, H^2, pyr-H^4), 7.56 (d, 1H, H^7), 7.62 (d, 1H, H^4), 8.46 (m, 3H, pyr-H^2, H^6, NH).

*Method l: N-(4,6-Dimethylpyridin-2-yl)-3-[1-(4-fluorobenzyl)indol-3-yl]propenamide (**48**)*. To a solution of triphenylphosphine (0.7 g, 2.65 mmol) and bromotrichloromethane (1.05 g, 5.3 mmol) in anhydrous THF (30 mL) were added **23** (7.83 g, 2.65 mmol) and 2-amino-4,6-dimethylpyridine (0.65 g, 5.3 mmol). The solution was heated under reflux for 3 h. The precipitate of 2-amino-4,6-dimethylpyridinium halohydrate was filtered and the crude amide **48** was purified by silica gel chromatography eluting with a mixture of dichloromethane/ethanol 98/2. Recrystallization from diisopropylic ether afforded ***48*** as a pure white powder. Yield: 33%; m. p.: 175–176°C. IR (KBr, ν_{max}): 3420 (NH), 1685 (C═O), 1620 (C═C) cm^{-1}. ^{1}H-NMR (DMSO-d_6, ppm): δ 2.30 (s, 3H, γ-CH_3), 2.39 (s, 3H, α-CH_3), 5.50 (s, 2H, CH_2), 6.79 (s, 1H, pyr-H^5), 6.86 (d, 1H, J = 15.5 Hz, CH—CO), 7.16-7.40 (m, 6H, H^5, H^6, 4H Bn), 7.61–7.65 (m, 1H, H^7), 7.78 (s, 1H, pyr-H^3), 7.85 (d, 1H, CH), 8.11 (s, 1H, H^2), 10.41 (s, 1H, NH).

Pharmacology

PMA-induced mouse-ear oedema (orally administrated drugs). Induction of mouse-ear oedema was based on the method of Carlson et al. [21] with some

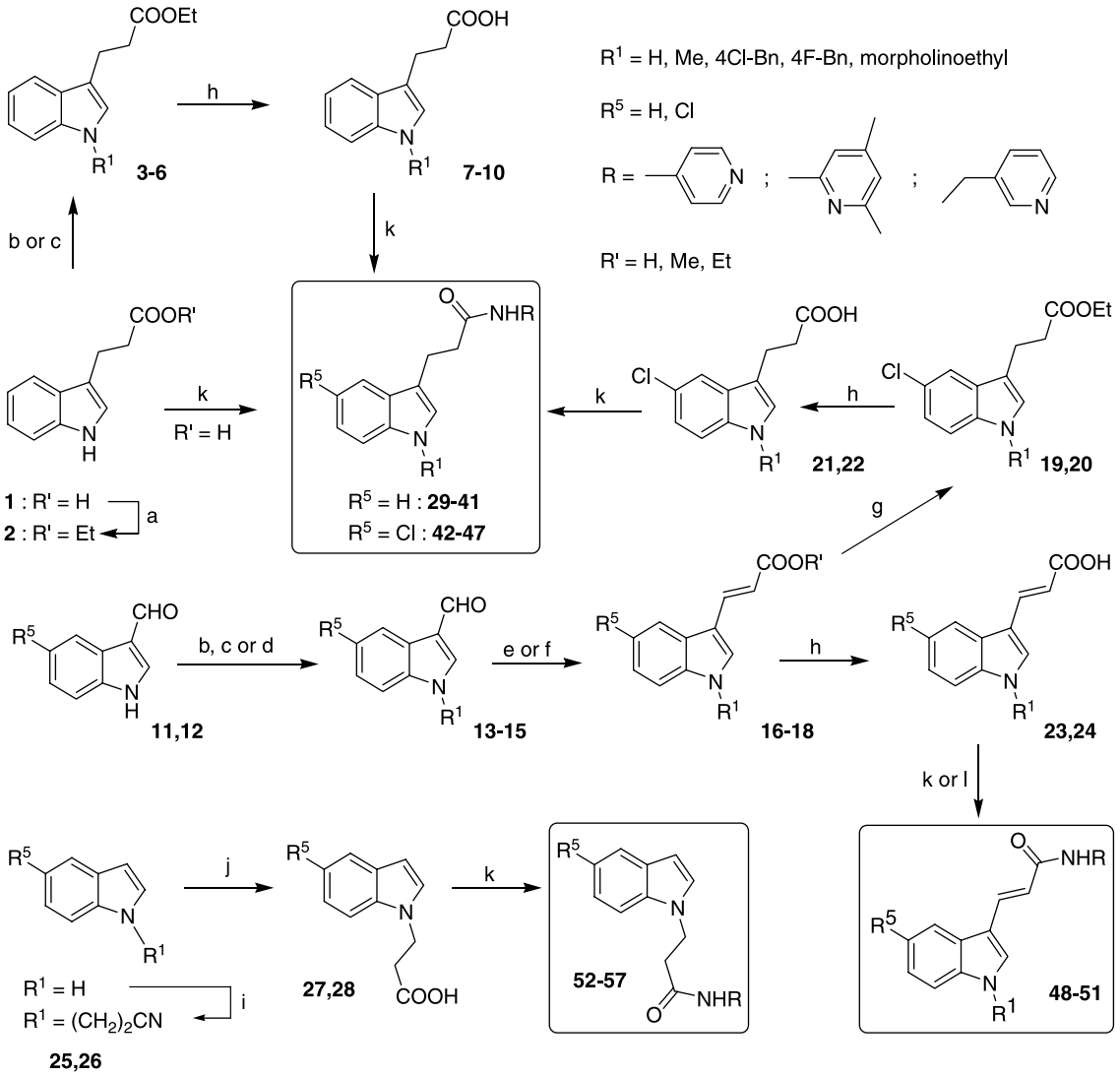
modifications. Groups of five Swiss mice, weighing 20–23 g, were used. The experiments were carried out according to the previously described procedure [13]. Ear oedema, calculated by substracting the thickness of the right ear (PMA), was expressed as an increase in ear thickness. The percentage of inhibition of the inflammatory reaction was determined for each animal by comparison of ear oedema in treated and non-treated animals.

PMA-induced mouse-ear oedema (topically applied drugs). Groups of five male Swiss mice (19–21 g) were used. PMA was dissolved in 80% aqueous ethanol at a concentration of 250 µl/mL; 10 µL was applied topically to the anterior and posterior surfaces of the right ear of each mouse. The left ear (control) received the vehicle (10µL of 80% aqueous ethanol). Ear oedema reduction was measured according to the previously described protocol [13]. Ear oedema, calculated by substracting the thickness of the right ear (PMA), was expressed as an increase in ear thickness. The percentage of inhibition of the inflammatory reaction was determined for each animal by comparison of each oedema in treated and non-treated animals.

Results and discussion

Chemistry

The target (indol-3-yl) propanamides **29-47** and propenamides **48-51** were prepared from the corresponding acids **1,7-10** and **21-24** (Scheme 1). N^1- substitution of (indol-3-yl)propanoic acid **1** was

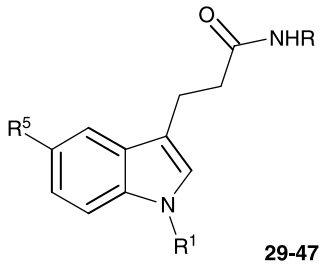


Scheme 1. Reagents: (a) EtOH, 0.6M HCl, reflux, 92%; (b) NaH, DMF, MeI, rt, 68%; (c) (1) Cs_2CO_3, MeCN, (2) R^1Cl reflux, 72-96%; (d) K_2CO_3, DMSO, R^1Cl, rt, 88%; (e) Ph_3PCH_2COOMe, dioxane, reflux, 85%; (f) $(EtO)_2POCH_2CO_2Et$, NaH, THF, rt, 58-67%; (g) H_2, Raney Ni, THF, rt, quantitative; (h) 2M NaOH, EtOH, reflux, 32-97%; (i) acrylonitrile, triton B (40% in MeOH), dioxane, rt, 84-88%; (j) 10% KOH, reflux, 49-91%; (k) 2-chloro-1-methylpyridinium iodide, RNH_2, Et_3N, CH_2Cl_2, reflux, 30-82%; (l) (1) $BrCCl_3$, PPh_3, THF, (2) 2-amino-4,6-dimethylpyridine, reflux, 33-58%.

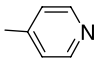
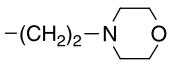
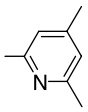
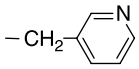
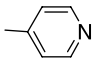
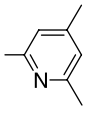
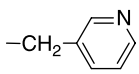
carried out after conversion (method a) into the corresponding ester **2**, in presence of the couples NaH/DMF or Cs_2CO_3/CH_3CN, using methyl iodide, benzyl chlorides or morpholinoethyl chloride (methods b, c). N^1-substitution, could also be performed at the level of (indol-3-yl)carboxaldehyde **11** and its 5-chloro derivative **12**, using the same methods b, c or method d (K_2CO_3/DMSO); they afforded compounds **13–15** in excellent yields (90%).

The non commercially-available 5-chloro-3-(1-methylindol-3-yl)propanoic acid **23** could be prepared by the six-step sequence starting from 4-chloroaniline diazotation, condensation with ethyl 2-oxocyclopentane-carboxylate under Japp-Klingemann reaction conditions: hydrolysis of the diester, monoesterification and C^2-decarboxylation by the couple Cu/*N*-methyl-pyrrolidinone followed by N^1- methylation; but the overall yield remained quite low: 8%. A more straightforward sequence consisted in creating an acrylic ester and reducing it into the waited propanoic ester. A first assay carried out starting with [1-(4-fluorobenzyl)indol-3-yl]carboxaldehyde **13** using Wittig reaction (method e), afforded the corresponding *(E)*-propenoate **16**, in a 85% yield. A temptative assay via the corresponding acrylonitrile under Horner conditions (NaH, benzene), was not successful: a 9/1 mixture of *E*/*Z* isomers was formed and yield in that step, as well as in the final hydrolysis of the nitrile, remained quite moderate: about 40% and 20%,

Table I. Chemical data and TPA-induced mouse ear swelling inhibition of 3-(indol-3-yl)propanamides **29–47**



29-47

Compound	R	R^1	R^5	Method Yield (%)	Anti-oedema effect after mouse oral administration	
					at 0.1 mM/kg	ID_{50}(μM/kg)
29		H	H	1:76	77 ± 3	41 ± 13
30		CH_3	H	k:58	94 ± 0.1[a]	32 ± 12
31		Bn	H	k:69	84 ± 3	
32		4Cl-Bn	H	k:64	72 ± 1	
33[b]			H	k:32	63 ± 1	
34		H	H	k:58	67 ± 5	29 ± 17
35		CH_3	H	k:73	64 ± 5[c]	
36		Bn	H	k:52	61 ± 3	
37		4Cl-Bn	H	k:58	64 ± 2.5	
38		H	H	k:60	77 ± 5[c]	
39		CH_3	H	k:78	69 ± 1.5	45 ± 37
40		Bn	H	k:78	70 ± 1	
41		4Cl-Bn	H	k:78	92 ± 1	24 ± 13
42		CH_3	Cl	k:61	84 ± 2	
43		4Cl-Bn	Cl	k:46	64 ± 2	
44		CH_3	Cl	k:44	79 ± 1	
45		4Cl-Bn	Cl	k:27	83 ± 2	
46		CH_3	Cl	k:82	66 ± 0.5	
47		4Cl-Bn	Cl	k:75	84 ± 1	
		Dexamethasone			82 ± 1.5	12 ± 1
		Ibuprofen			35 ± 7.5	180 ± 5

[a] toxic; [b] tested as a dimaleate; [c] tested at 0.2 mM/kg.

respectively. The (*E*) N-methyl and N-(4-chlorobenzyl)-3-[5-chlorindol-3-yl]propenoates **17** and **18** could be obtained, by Horner reaction, (method f) in satisfactory yields: 58 and 67%. Catalytic reduction of these esters (method g) led to the desired propanoates **19** and **20**; these esters and propenoates **16**, **18** were finally easily saponified (method h) affording acids **21-24** in fair overall yields: 40 to 60%.

Activation of the acids by formation of an acyloxypyridinium salt with 2-chloro-1-methylpyridinium iodide (CMPI), or an acid chloride using the couple $CBrCl_3/Ph_3P$ (method k or l) and condensation with 4-aminopyridine, 2-amino-4,6-dimethylpyridine or 3-amino-methylpyridine afforded the target propanamides **29-47** and propenamides **48-51**.

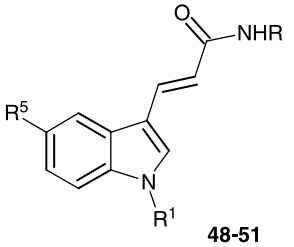
Lastly, construction of the 3-(indol-1-yl) propanamide congeners **52-57** was carried out by *N*-cyanoethylation of indole or 5-chloroindole by Michael reaction (method i) followed by alkaline hydrolysis (method j), leading to the corresponding acids **27** and **28**, which were condensed with the previously described amines, after acid activation by CMPI (method k).

Physisochemical data of all these amides are described in Tables I, II and III and in the experimental part.

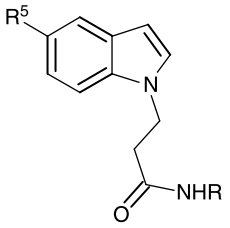
Pharmacology

The psoriatic skin shares many of the pathologic features (increase of arachidonic acid metabolism,

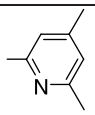
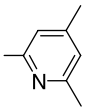
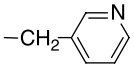
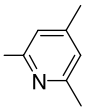
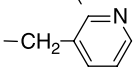
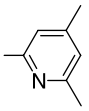
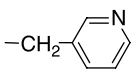
Table II. Chemical data and TPA-induced mouse ear swelling inhibition of 3-(indol-3-yl)propenamides **48-51** and 3-(indol-1-yl)propanamides **52-57**.



48-51



52-57

Compound	R	R^1	R^5	Method Yield (%)	Anti-oedema effect after mouse oral administration at 0.1 mM/Kg
48		4F-Bn	H	1: 33	80 ± 2
49		4Cl-Bn	Cl	k: 25	80 ± 1
50		4Cl-Bn	Cl	k: 20	86 ± 1
51		4Cl-Bn	Cl	k: 38.5	ND[a]
52		–	H	k: 53	77 ± 0.5
53		–	H	k: 43	74 ± 2
54		–	H	k: 43	88 ± 0.2
55		–	Cl	k: 54	80 ± 4
56		–	Cl	k: 56	62 ± 1.5
57		–	Cl	k: 40	64 ± 1.5
		Dexamethasone			82 ± 1.5
		Ibuprofen			35 ± 7.5

[a] ND: not determinated (unstable compound).

Table III. TPA-induced mouse ear swelling inhibition after topical application.

Compound	Anti-oedema effect after mouse topical application of	
	2 × 100 μg/ear	2 × 50 μg/ear
29	38 ± 3	ND
30	72 ± 2	50 ± 1
31	90 ± 1	70 ± 1
34	66 ± 3	53 ± 2
39	83 ± 1	72 ± 1
41	71 ± 1	53 ± 1
42	96 ± 1	75 ± 1
44	89 ± 1	74 ± 1
47	94 ± 3	74 ± 1
48	66 ± 2	52 ± 2
54	85.5 ± 1.5	ND
Dexamethasone	96 ± 2	
Ibuprofen	59 ± 2.5	

inflammatory cells and cell proliferation) of mouse skin treated by tetradecanoyl phorbol acetate (TPA).

Obtained compounds (**29-47** and **48-57**) were tested *in vivo*; the investigation included determination of anti-oedematous effects against the acute TPA-induced mouse ear swelling after oral administration and topical application.

Results of oedema inhibition after oral administration of 0.1 mM/kg of test compounds are gathered in Tables I and II. They confirm that a propanamide linker between the indole core and the pyridinyl(methyl) moieties allows emergence of a high activity, as the inhibition percentage was always >60%. Among the amides of the three subseries of N-pyridinyl(methyl)-3-indolyl propanamides **29-41**, those of the N-(4-pyridinyl) subseries **29-33** exert, generally speaking, the highest inhibitory effect. This subseries includes one of the most potent compounds, the N^1-methyl derivative **30** (94% inhibition); unfortunately this amide displayed severe toxic effects at 0.4 mM/kg. Although the N^1-4-chlorobenzyl derivatives **32** was less active (72% inhibition), it was found to exhibit a significant selective immunosuppressive effect; it inhibited mouse foot pad swelling in the *in vivo* delayed type hypersensitivity reaction [17], a response that is mainly linked to the proliferation of the Th1 lymphocytes. Lastly pharmacomodulation aimed at incorporating on indolic nitrogen a morpholinoethyl chain, present notably in CB2 cannabinoid receptor agonists such as WIN-55212-2 [8,9], failed in increasing the activity level of **33** (63% inhibition).

In the third subseries, corresponding to *N*-(3-picolyl)propanamides **38-41**, the highest anti-oedematous effect was obtained by introduction of a 4-chlorobenzyl group at N^1; this amide **41** induced, at 0.1 mM/kg^{-1}, 92% inhibition and its ID_{50} although higher than that of dexamethasone compares favourably with that of ibuprofen and even propanamide **30**: 24 ± 13, 12 ± 1, 80 ± 5 and 32 ± 12 μM/kg, respectively. The favourable effect of a chloro group introduction at indolic C^5 was obvious only in the subseries of N-2,4-lutidinyl propanamides: **44** and **45**. Study of the incidence of the replacement of the propanamide chain by a propenamide one was experimented in the subseries of N^1-halogenobenzyl compounds. Although the instability of the 3-picolyl derivative **51** did not allow a reliable test, comparison with the activity of the saturated congeners (compounds **27** in [3], **43** and **45** in Table I) underlines maintenance (**50**) and even increase of the topical anti-oedema effect (**48** and **49**).

Displacement of the propanamide moiety from carbon 3 to indolic nitrogen allowed also maintenance of a significant activity; although this pharmacomodulation induced irregular effects, three compounds out of six (**52**, **53** and **55**) were more active than their 3-substituted congeners (**32**, **37** and **43**) and the 3-picolyl derivative **54** was practically as efficient as its counterpart **41** (88% and 92% inhibition). This promising result obtained with **54** was confirmed in the mouse ear swelling assay after topical application. Introduction of a chloro group at indolic C^5 (compounds **55-57**) exerted no favourable effect.

Some of the most active compounds, in the mouse ear thickness reduction assay, were selected for evaluation after topical application of 2 × 100 μg/ear and 2 × 50 μg/ear (Table III). Among the eleven tested amides, six exerted an inhibitory effect in the range of 80-95% at the former dosage, and oedema reduction remained quite high at the latter one: 70–75%. Although discrepancies between the results obtained in the two types of *in vivo* assays were observed, globally the most efficient compounds, **31**, **42**, **44**, and **47**, exhibited also a regular potent effect in the precedent assay: about 84% inhibition at 0.1 mM/kg. Unexpectedly, propanamide **41** was less efficacious in that assay: 71% at 2 × 100 μg/ear; determination of its ID_{50} afforded nevertheless a fair value: 2 × 35 ± 16 μg/ear.

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Declaration of interest: The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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