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# New *N*-Pyridinyl(methyl)-N$^1$-substituted-3-indolepropanamides Acting as Topical and Systemic Anti-inflammatory Agents

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**N-Pyridinyl(methyl)-N$^1$-substituted-3-indolepropanamides (17–32) were prepared starting from the corresponding acids and screened for their anti-inflammatory activity. Pharmacomodulation was carried out on the indole and amidic nitrogens by incorporation of substituents associated with higher potency in previously synthesized related 3-indolepropanamides series. In the inhibition of topical inflammation determined by reduction of ear thickness in the acute PMA mouse ear swelling test, high levels of activity ($ID_{50} \sim 0.030\,mMol\,kg^{-1}$) were noticed for the five propanamides 17, 21, 22, 27 and 31. A comparative study showed the positive influence of a methyl group at the indole nitrogen in the 4-pyridinyl sub-series (1 → 21) and of a 4-fluorobenzyl group in the 3-pyridinylmethyl sub-series (19 → 31), at least after oral administration. After topical application, although compounds 17, 21, 22, 27 and 31 exerted significant (50%) ear œdema inhibition at 2 × 50 μg/ear, they remained less potent than 24, 29 and 30 (almost 70% inhibition). Among these eight amides, only 17, 21, 22 and 27 showed a significant activity in the carrageenan rat paw œdema model at $0.2\,mMol\,kg^{-1}$. Finally, although less active than the N-(4-pyridinyl) amide 21, the N-4,6-dimethyl-2-pyridinyl derivatives 17 and 27 were devoid of the toxic effects observed with 21 and to a lesser extent with 22.**

*Keywords*: *N*-pyridinyl and *N*-pyridinylmethyl-3-indolepropanamides; Topical and systemic inflammation inhibitors

## INTRODUCTION

In a preceeding work,[1] we synthetized and evaluated a series of *N*-azaaryl-3-indol-yl(alkyl)carboxamides as inhibitors of the inflammation process. It was established that incorporation of a propanamide chain afforded the most efficient compound **1**. Moreover, pharmacomodulation at the level of the homocycle of indole showed that incorporation of a fluorine at carbon 5 (leading to **2**) allowed a clear-cut decrease in the toxic effects of **1**. The $ID_{50}$ value of **1** in the carrageenan rat paw œdema test ($9.1\,mg\,kg^{-1}$) was comparable to that of the oxicams.[2] Moreover, this non-acidic NSAI compound exerted a high level of inhibitory activity ($78 \pm 2\%$) after topical application of $2 \times 100\,\mu g$/ear in the acute PMA-induced mouse ear swelling assay. Besides, it has been established that different compounds incorporating an indole core such as **3** (WIN-55212-2) and **4**, identified as CB2 selective agonists,[3] could be useful for the treatment of inflammatory disorders such as rheumatoid arthritis, asthma and chronic obstructive pulmonary disease.

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*__Abbreviations__: NSAI, non steroidal anti-inflammatory; ID, inhibitory dose; PMA, phorbol-12-myristate-13-acetate.

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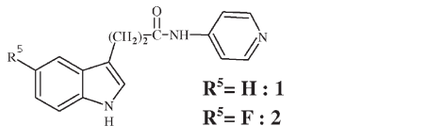
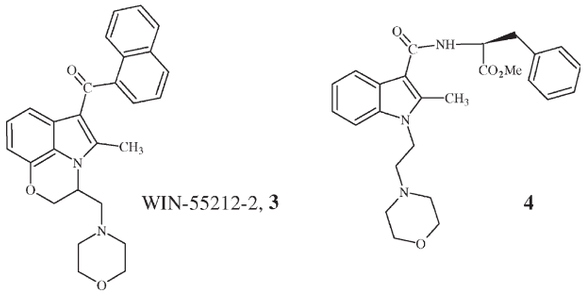



These promising results prompted us to envisage pharmacomodulation especially on the indolic and amidic nitrogens in *N*-pyridinyl(methyl)-3-indolepropanamides.

## MATERIALS AND METHODS

### Chemistry

Melting points were determined in open glass capillaries and uncorrected. $^1$H NMR spectra were recorded on a Bruker AC 250 spectrometer (250 MHz) (Bruker, Wissembourg, France), using DMSO-$d_6$ as solvent; chemical shifts are reported in parts per million (ppm) relative to tetramethylsilane as an internal standard. Coupling constants *J* (H-H) and *J′* (H-F) are in Hertz. Protons $H^a$ and $H^b$ correspond to protons $H^2$, $H^6$ and $H^3$, $H^5$ in the 4F-benzyl-*N* [1]-derivatives. IR spectra were recorded on a Perkin-Elmer Paragon PC 1000 spectrometer as KBr pellets or a film on NaCl plates (Perkin-Elmer, Courtaboeuf Cedex, France). Chemicals and solvents used were commercially available. *N*-(4,6-Dimethylpyridin-2-yl)-3-(indol-3-yl)propanamide (**17**)[1] was prepared after activation of the corresponding acid by phenyl dichlorophosphate in a 23% yield according to a previously described method.

#### *Method a: Ethyl 3-(Indol-3-yl)propanoate (6)*

A solution of (indol-3-yl)propanoic acid **5** (3 g, 15.8 mmol) in 0.8 M ethanolic HCl (50 mL) was refluxed for 17 h. After evaporation, the mixture was cooled and made alkaline with 1 M NaOH and extracted with ethyl acetate. The organic layer was dried ($Na_2SO_4$), filtered and concentrated to provide **6** as yellow crystals. 83% yield; mp = 40°C (ethyl acetate); IR (KBr) $\nu$ cm$^{-1}$: 3324 ($\nu$ NH), 1719 ($\nu$ C=O); $^1$H NMR (DMSO-$d_6$), δ ppm, *J* Hz: 1.19 (t, 3H, $J = 7.1$, $CH_3$-$CH_2$), 2.69 (t, 2H, $J = 7.5$, $CH_2$-$CH_2$CO), 3.00 (t, 2H, $J = 7.5$, $CH_2$-$CH_2$CO), 4.02 (q, 2H, $J = 7.1$, $CH_3$-$CH_2$), 7.01 (dd, 1H, $J = 7.8$, $J = 6.8$, $H^5$), 7.08 (dd, 1H, $J = 7.9$, $J = 6.8$, $H^6$), 7.15 (d, 1H, $J = 2.1$, $H^2$), 7.39 (d, 1H, $J = 7.9$, $H^7$), 7.55 (d, 1H, $J = 7.8$, $H^4$), 10.84 (s, 1H, $H^1$).

#### *Method b: Ethyl 3-(5-Fluoroindol-3-yl)propanoate (7)*

Step 1: Ethyl 3-(2-ethoxycarbonyl-5-fluoroindol-3-yl)propanoate

4-Fluoroaniline (1.71 mL, 18 mmol) was dissolved in 12 M HCl (8 mL) and cooled to 0°C. $NaNO_2$ (1.37 g, 19.9 mmol) in $H_2O$ (9 mL) was added dropwise so that the temperature remained below 5°C. Separately, a mixture of ethyl 2-oxocyclopentanecarboxylate (2.7 mL, 18 mmol) was prepared in absolute ethanol (18 mL), ice (20 g), and 8 M KOH (7 mL). The solution of diazonium salt was added to this mixture with stirring. After 3 h, the mixture was concentrated, dichloromethane added and the organic solution washed several times with $H_2O$. The organic layer was dried ($Na_2SO_4$), filtered and concentrated to leave a dark oil which was added to a solution of sulfuric acid (3 mL) in absolute ethanol (30 mL). After refluxing for 18 h dichloromethane was added to the mixture. The organic layer was washed several times with $H_2O$, dried ($Na_2SO_4$) and filtered. The organic layer was concentrated and purified by chromatography on silica gel, eluting with dichloromethane/ethyl acetate (98/2) to give the diester as yellow crystals. 45% yield; mp = 107°C ($CH_2Cl_2$/ethyl acetate (98/2).

Step 2: 3-(2-Carboxy-5-fluoroindol-3-yl)propanoic Acid

The diester (16.62 g, 54.1 mmol) was dissolved in absolute ethanol (100 mL). 2 M NaOH was added (75 mL), and the mixture was refluxed for 2 h. After evaporation, the mixture was cooled and acidified with 6 M HCl. The precipitate was then filtered, washed with cold water and dried *in vacuo* to afford the diacid as white crystals. 94% yield; mp = 208°C (water).

Step 3: Ethyl 3-(2-carboxy-5-fluoroindol-3-yl)-propanoate

A solution of the diacid (4.51 g, 17.95 mmol) in 0.01 M ethanolic HCl (50 mL) was refluxed for 1.5 h. After evaporation, the mixture was cooled and filtered. The crystals were washed with cold absolute ethanol to give the required monoester as white crystals. 73% yield; mp = 205°C (EtOH).

Step 4: Ethyl 3-(5-fluoroindol-3-yl)propanoate (**7**)

To a solution of the monoester (3.64 g, 13 mmol), in quinoline (25 mL), copper chromite (811 mg, 2.61 mmol) was added and the mixture was refluxed

under $N_2$ for 2 h. After cooling, dichloromethane was added and the mixture was filtered. The filtrate was washed with 2 M HCl and dried ($Na_2SO_4$), filtered, concentrated, and purified by chromatography on silica gel, eluting with dichloromethane/ethyl acetate (99/1) to give **7** as red crystals. 59% yield; mp = 51°C (petroleum ether) (lit.[4] 54°C); IR (KBr) $\nu$ $cm^{-1}$: 3346 ($\nu$ NH), 1717 ($\nu$ C═O); $^1$H NMR (DMSO-$d_6$), δ ppm, *J*, *J′* Hz: 1.19 (t, 3H, *J* = 7.1, $CH_3$), 2.68 (t, 2H, *J* = 7.6, $CH_2$-*$CH_2$*CO), 2.96 (t, 2H, *J* = 7.6, *$CH_2$*-$CH_2$CO), 4.08 (q, 2H, *J* = 7.1, $CH_2$), 6.94 (ddd, 1H, *J* = 9.2, *J* = 2.5, *J′* = 9.2, $H^6$), 7.24 (d, 1H, *J* = 2.3, $H^2$), 7.29 (dd, 1H, *J′* = 12.6, *J* = 2.5, $H^4$), 7.35 (dd, 1H, *J* = 9.2, *J′* = 4.6, $H^7$), 10.95 (bs, 1H, $H^1$).

### *Method c: Ethyl 3-(1-methylindol-3-yl)propanoate (9)*

To a solution of ester **6** (0.73 g, 3.4 mmol) in dry DMF (15 mL), under $N_2$, was added NaH (60%) (0.27 g, 6.8 mmol) and the mixture was stirred for 1 h. Iodomethane (0.42 mL, 6.8 mmol) was then added and the mixture was stirred for 24 h and then $H_2O$ was added and the mixture extracted with dichloromethane. The organic layer was washed several times with $H_2O$, dried ($Na_2SO_4$), filtered, concentrated, and purified by chromatography on silica gel, eluting with dichloromethane/ethyl acetate to give **9** as a yellow oil. 68% yield; IR (NaCl) $\nu$ $cm^{-1}$: 1734 ($\nu$ C═O); $^1$H NMR (DMSO-$d_6$), δ ppm, *J* Hz: 1.20 (t, 3H, *J* = 7.1, *$CH_3$*-$CH_2$), 2.68 (t, 2H, *J* = 7.6, $CH_2$-*$CH_2$*CO), 3.00 (t, 2H, *J* = 7.6, *$CH_2$*-$CH_2$CO), 3.74 (s, 3H, N*$CH_3$*), 4,10 (q, 2H, *J* = 7.1, $CH_3$-*$CH_2$*), 7.06 (dd, 1H, *J* = 7.8, *J* = 7.0, $H^5$), 7.08 (dd, 1H, *J* = 8.0, *J* = 7.0, $H^6$), 7.12 (s, 1H, $H^2$), 7.40 (d, 1H, *J* = 8.0, $H^7$), 7.57 (d, 1H, *J* = 7.8, $H^4$).

#### Ethyl 3-(5-fluoro-1-methylindol-3-yl)propanoate (**10**)

Yellow oil; 85% yield; IR (NaCl) $\nu$ $cm^{-1}$: 1733 ($\nu$ C═O); $^1$H NMR (DMSO-$d_6$), δ ppm, *J*, *J′* Hz: 1.19 (t, 3H, *J* = 7.1, $CH_3$), 2.67 (t, 2H, *J* = 7.4, $CH_2$-*$CH_2$*CO), 2.97 (t, 2H, *J* = 7.4, *$CH_2$*-$CH_2$CO), 3.74 (s, 3H, N*$CH_3$*), 4.08 (q, 2H, *J* = 7.1, $CH_2$), 7.01 (ddd, 1H, *J* = 9.0, *J* = 2.3, *J′* = 9.0, $H^6$), 7.17 (s, 1H, $H^2$), 7.35 (dd, 1H, *J′* = 10.2, *J* = 2.3, $H^4$), 7.38 (dd, 1H, *J* = 9.0, *J′* = 4.6, $H^7$).

### *Method d: Ethyl 3-[1-(4-fluorobenzyl)indol-3-yl] propanoate (11)*

To a solution of ester **6** (1 g, 4.6 mmol) in dry acetonitrile was added anhydrous $Cs_2CO_3$ (1.1 g, 4.6 mmol). The mixture was refluxed for 25 h with stirring. 4-Fluorobenzylchloride (0.17 mL, 6.9 mmol) was then added and, after 20 h stirring at reflux, the mixture was filtered and concentrated. The residue was extracted with dichloromethane and washed with $H_2O$. The organic layer was dried ($Na_2SO_4$), filtered, concentrated, and purified by chromatography on silica gel, eluting with dichloromethane to give **11** as a yellow oil. 70% yield; IR (NaCl) $\nu$ $cm^{-1}$: 1730 ($\nu$ C═O); $^1$H NMR (DMSO-$d_6$), δ ppm, *J*, *J′* Hz: 1.17 (t, 3H, *J* = 7.1, *$CH_3$*-$CH_2$), 2.69 (t, 2H, *J* = 7.5, $CH_2$-*$CH_2$*CO), 2.99 (t, 2H, *J* = 7.5, *$CH_2$*-$CH_2$CO), 4.05 (q, 2H, *J* = 7.1, $CH_3$-*$CH_2$*), 5.37 (s, 2H, pF-$C_6H_4$*$CH_2$*-N), 7.04 (dd, 1H, *J* = 7.6, *J* = 6.9, $H^5$), 7.13 (dd, 1H, *J* = 8.0, *J* = 6.9, $H^6$), 7.15 (dd, 2H, *J* = *J′* = 8.8, $H^b$), 7.25 (dd, 2H, *J* = 8.8, *J′* = 5.6, $H^a$), 7.30 (s, 1H, $H^2$), 7.45 (d, 1H, *J* = 8.0, $H^7$), 7.57 (d, 1H, *J* = 7.6, $H^4$).

#### Ethyl 3-[5-fluoro-1-(4-fluorobenzyl)indol-3-yl]-propanoate (**12**)

Yellow oil; 83% yield; IR (NaCl) $\nu$ $cm^{-1}$: 1732 ($\nu$ C═O); $^1$H NMR (DMSO-$d_6$), δ ppm, *J*, *J′* Hz: 1.16 (t, 3H, *J* = 7.1, $CH_3$), 2.68 (t, 2H, *J* = 7.4, $CH_2$-*$CH_2$*CO), 2.97 (t, 2H, *J* = 7.4, *$CH_2$*-$CH_2$CO), 4.05 (q, 2H, *J* = 7.1, $CH_2$), 5.37 (s, 2H, pF-$C_6H_4$*$CH_2$*N), 6.98 (ddd, 1H, *J* = 9.1, *J* = 2.5, *J′* = 9.1, $H^6$), 7.15 (dd, 2H, *J* = *J′* = 8.7, $H^b$), 7,26 (dd, 2H, *J* = 8.7, *J′* = 5.6, $H^a$), 7.36 (dd, 1H, *J′* = 10.1, *J* = 2.5, $H^4$), 7.39 (s, 1H, $H^2$), 7.45 (dd, 1H, *J* = 9.1, *J′* = 4.5, $H^7$).

### *Method e: 3-(5-Fluoroindol-3-yl)propanoic Acid (8)*

The ester **7** (1 g, 42.5 mmol) was dissolved in absolute ethanol (15 mL), 1 M NaOH was added (10 mL) and the mixture was refluxed for 2 h. After evaporation, the mixture was cooled and acidified with 6 M HCl. The precipitate was then filtered, washed with cold water and dried *in vacuo* to afford the acid **8** as beige crystals. 80% yield; mp = 119°C (petroleum ether); IR (KBr) $\nu$ $cm^{-1}$: 3050–2800 ($\nu$ OH), 1696 ($\nu$ C═O); $^1$H NMR (DMSO-$d_6$), δ ppm, *J*, *J′* Hz: 2.60 (t, 2H, *J* = 7.5, $CH_2$-*$CH_2$*CO), 2.93 (t, 2H, *J* = 7.5, *$CH_2$*-$CH_2$CO), 6.93 (ddd, 1H, *J* = 9.0, *J* = 2.4, *J′* = 9.0, $H^6$), 7.24 (d, 1H, *J* = 2.7, $H^2$), 7.31 (dd, 1H, *J′* = 12.7, *J* = 2.4, $H^4$), 7.35 (dd, 1H, *J* = 9.0, *J′* = 4.5, $H^7$), 10.93 (bs, 1H, $H^1$), 12.13 (s, 1H, $CH_2CO_2$*H*).

#### 3-(1-Methylindol-3-yl)propanoic Acid (**13**)

White crystals; 95% yield; mp = 123–125°C (water); IR (KBr) $\nu$ $cm^{-1}$: 3100–2600 ($\nu$ OH), 3049, 3033, 2915, 2858 ($\nu$ CH), 1711 ($\nu$ C═O); $^1$H NMR (DMSO-$d_6$), δ ppm, *J* Hz: 2.61 (t, 2H, *J* = 7.5, $CH_2$-*$CH_2$*CO), 2.96 (t, 2H, *J* = 7.5, *$CH_2$*-$CH_2$CO), 3.76 (s, 3H, N*$CH_3$*), 7.04 (dd, 1H, *J* = 7.8, *J* = 7.2, $H^5$), 7.13 (s, 1H, $H^2$), 7.17 (dd, 1H, *J* = 8.0, *J* = 7.2, $H^6$), 7.41 (d, 1H, *J* = 8.0, $H^7$), 7.57 (d, 1H, *J* = 7.8, $H^4$), 12.13 (s, 1H, $CH_2CO_2$*H*).

#### 3-(5-Fluoro-1-methylindol-3-yl)propanoic Acid (**14**)

White crystals; 95% yield; mp = 105.5–107.5°C (water); IR (KBr) $\nu$$cm^{-1}$: 3105–2800 ($\nu$ OH), 2925, ($\nu$CH), 1711 ($\nu$C═O); $^1$H NMR (DMSO-$d_6$), δ ppm, *J*,

$J'$ Hz: 2.59 (t, 2H, $J = 7.5$, $CH_2$-$CH_2CO$), 2.92 (t, 2H, $J = 7.5$, $CH_2$-$CH_2CO$), 3.76 (s, 3H, $NCH_3$), 7.00 (ddd, 1H, $J = 9.0$, $J = 2.5$, $J' = 9.0$, $H^6$), 7.21 (s, 1H, $H^2$), 7.34 (dd, 1H, $J' = 10.1$, $J = 2.5$, $H^4$), 7.41 (dd, 1H, $J = 9.0$, $J' = 4.5$, $H^7$), 12.12 (s, 1H, $CH_2CO_2H$).

3-[1-(4-Fluorobenzyl)indol-3-yl]propanoic Acid (**15**)

White crystals; 94% yield; mp = 105–107°C (water); IR (KBr) $\nu$ cm$^{-1}$: 3100–2600 ($\nu$ OH); 3073, 2914, 2858 ($\nu$ CH), 1698 ($\nu$ C═O); $^1$H NMR (DMSO-$d_6$), δ ppm, $J$, $J'$ Hz: 2.62 (t, 2H, $J = 7.5$, $CH_2$-$CH_2CO$), 2.97 (t, 2H, $J = 7.5$, $CH_2$-$CH_2CO$), 5.37 (s, 2H, pF-$C_6H_4CH_2N$), 7.04 (dd, 1H, $J = 7.4$, $J = 6.9$, $H^5$), 7,12 (dd, 1H, $J = 7.9$, $J = 6.9$, $H^6$), 7.15 (dd, 2H, $J = J' = 8.8$, $H^b$), 7.26 (dd, 2H, $J = 8.8$, $J' = 5.6$, $H^a$), 7.32 (s, 1H, $H^2$), 7.43 (d, 1H, $J = 7.9$, $H^7$), 7.57 (d, 1H, $J = 7.4$, $H^4$), 12.10 (s, 1H, $CH_2CO_2H$).

3-[1-(4-Fluorobenzyl)-5-fluoroindol-3-yl]propanoic Acid (**16**)

White crystals; 88% yield; mp = 76–77°C (petroleum ether); IR (KBr) $\nu$ cm$^{-1}$: 3060–2840 ($\nu$ OH), 3044, 2926, 2858 ($\nu$ CH), 1701 ($\nu$ C═O); $^1$H NMR (DMSO-$d_6$), δ ppm, $J$, $J'$ Hz: 2.62 (t, 2H, $J = 7.5$, $CH_2$-$CH_2CO$), 2.94 (t, 2H, $J = 7.4$, $CH_2$-$CH_2CO$), 5.38 (s, 2H, pF-$C_6H_4CH_2N$), 6.97 (ddd, 1H, $J = 9.0$, $J = 2.5$, $J' = 9.0$, $H^6$), 7.16 (dd, 2H, $J = J' = 8.7$, $H^b$), 7.26 (dd, 2H, $J = 8.7$, $J' = 5.6$, $H^a$), 7.36 (dd, 1H, $J' = 10.1$, $J = 2.5$, $H^4$), 7,41 (s 1H, $H^2$), 7.45 (dd, 1H, $J = 9.0$, $J' = 4.5$, $H^7$), 12.15 (s, 1H, $CH_2CO_2H$).

### *Method f: N-(4,6-dimethylpyridin-2-yl) -3-(5-fluoroindol-3-yl)propanamide (18)*

To a solution of 3-(5-fluoroindol-3-yl)propanoic acid ***(8)*** (0.33 g, 1.74 mmol) in dry dichloromethane (25 mL), were added 2-chloro-*N*-methylpyridinium iodide (0.407 g, 1.59 mmol), triethylamine (0.56 mL, 3.98 mmol) and 2-amino-4,6-dimethylpyridine (0.195 g, 1.59 mmol). The mixture was refluxed for 15 h and after cooling, washed with $H_2O$, dried ($Na_2SO_4$), concentrated and purified by chromatography on silica gel, eluting with dichloromethane/ethanol (93/7) to give **18** as orange crystals. 58% yield; mp = 102°C (petroleum ether); IR (KBr) $\nu$ cm$^{-1}$: 3267 ($\nu$ NH), 1681 ($\nu$ C═O); $^1$H NMR (DMSO-$d_6$), δ ppm, $J$, $J'$ Hz: 2.29 (s, 3H, $CH_3^{4'}$), 2.37 (s, 3H, $CH_3^{6'}$), 2.76 (t, 2H, $J = 7.5$, $CH_2$-$CH_2CO$), 3.01 (t, 2H, $J = 7.5$, $CH_2$-$CH_2CO$), 6.80 (s, 1H, $H^{5'}$), 7.04 (ddd, 1H, $J = 9.1$, $J = 2.4$, $J' = 9.1$, $H^6$), 7.26 (d, 1H, $J = 2.1$, $H^2$), 7.36 (dd, 1H, $J = 9.1$, $J' = 4.7$, $H^7$), 7.41 (dd, 1H, $J' = 10.4$, $J = 2.4$, $H^4$), 7.84 (s, 1H, $H^{3'}$), 10.43 (bs, 1H, CO*NH*), 10.92 (s, 1H, $H^1$).

*N*-(Pyridin-3-ylmethyl)-3-(indol-3-yl)propanamide (**19**)

Yellow oil; 60% yield; IR (NaCl) $\nu$ cm$^{-1}$: 3270 ($\nu$ NH), 1651 ($\nu$ C═O); $^1$H NMR (DMSO-$d_6$), δ ppm, $J$ Hz: 2.56 (t, 2H, $J = 7.6$, $CH_2$-$CH_2CO$), 3.00 (t, 2H, $J = 7.6$, $CH_2$-$CH_2CO$), 4.32 (d, 2H, $J = 5.9$, $CH_2NH$), 7.00 (dd, 1H, $J = 7.9$, $J = 6.9$, $H^5$), 7.07 (dd, 1H, $J = 8.0$, $J = 6.9$, $H^6$), 7.12 (d, 1H, $J = 2.6$, $H^2$), 7.29–7.33 (m, 1H, $H^{5'}$), 7.37 (d, 1H, $J = 8.0$, $H^7$), 7.52–7.55 (m, 1H, $H^{4'}$), 7.57 (d, 1H, $J = 7.9$, $H^4$), 8.42–8.46 (m, 3H, CO*NH* and $H^{2'}$, $H^{6'}$), 10.86 (bs, 1H, $H^1$).

*N*-(Pyridin-3-ylmethyl)-3-(5-fluoroindol-3-yl)-propanamide (**20**)

Brown oil; 26% yield; IR (NaCl) $\nu$ cm$^{-1}$: 3271 ($\nu$ NH), 1651 ($\nu$ C═O); $^1$H NMR (DMSO-$d_6$), δ ppm, $J$, $J'$ Hz: 2.53 (t, 2H, $J = 7.5$, $CH_2$-$CH_2CO$), 2.96 (t, 2H, $J = 7.5$, $CH_2$-$CH_2CO$), 4.33 (d, 2H, $J = 5.8$, $CH_2NH$), 6.92 (ddd, 1H, $J = 9.1$, $J = 2.5$, $J' = 9.1$, $H^6$), 7.20 (d, 1H, $J = 2.1$, $H^2$), 7.30–7.39 (m, 1H, $H^{5'}$), 7.33 (dd, 1H, $J' = 12.6$, $J = 2.5$, $H^4$), 7.36 (dd, 1H, $J = 9.1$, $J' = 4.5$, $H^7$), 7.57–7.61 (m, 1H, $H^{4'}$), 8.42–8.46 (m, 3H, CO*NH* and $H^{2'}$, $H^{6'}$), 10.93 (bs, 1H, $H^1$).

*N*-(Pyridin-4-yl)-3-(1-methylindol-3-yl)propanamide (**21**)

White crystals; 58% yield; mp = 142°C (petroleum ether); IR (KBr) $\nu$ cm$^{-1}$: 3238 ($\nu$ NH), 1705 ($\nu$ C═O); $^1$H NMR (DMSO-$d_6$), δ ppm, $J$ Hz: 2.77 (t, 2H, $J = 7.5$, $CH_2$-$CH_2CO$), 3.07 (t, 2H, $J = 7.5$, $CH_2$-$CH_2CO$), 3.75 (s, 3H, $NCH_3$), 7.02–7.08 (m, 1H, $H^5$), 7.14–7.20 (m, 2H, $H^2$, $H^6$), 7.38–7.42 (m, 1H, $H^7$), 7.58–7.65 (m, 3H, $H^4$ and $H^{3'}$, $H^{5'}$), 8.44–8.46 (m, 2H, $H^{2'}$, $H^{6'}$), 10.36 (s, 1H, CO*NH*).

*N*-(Pyridin-4-yl)-3-(5-fluoro-1-methylindol-3-yl)propanamide (**22**)

White crystals; 84% yield; mp = 131°C (petroleum ether); IR (KBr) $\nu$ cm$^{-1}$: 3232 ($\nu$ NH), 1703 ($\nu$ C═O); $^1$H NMR (DMSO-$d_6$), δ ppm, $J$, $J'$ Hz: 2.77–3.02 (m, 2H, $CH_2$-$CH_2CO$ and $CH_2$-$CH_2CO$), 3.75 (s, 3H, $NCH_3$), 6.97–7.04 (m, 1H, $H^6$), 7.23 (s, 1H, $H^2$), 7.41–7.72 (m, 4H, $H^4$, $H^7$ and $H^{3'}$, $H^{5'}$), 8.49–8.53 (m, 2H, $H^{2'}$, $H^{6'}$), 10.64 (s, 1H, CO*NH*).

*N*-(Pyridin-4-yl)-3-[1-(4-fluorobenzyl)indol-3-yl]propanamide (**23**)

Orange oil; 56% yield; IR (NaCl) $\nu$ cm$^{-1}$: 3247 ($\nu$ NH), 1695 ($\nu$ C═O); $^1$H NMR (DMSO-$d_6$), δ ppm, $J$, $J'$ Hz: 2.76 (t, 2H, $J = 7.4$, $CH_2$-$CH_2CO$), 3.08 (t, 2H, $J = 7.4$, $CH_2$-$CH_2CO$), 5.37 (s, 2H, pF-$C_6H_4CH_2N$), 7.05 (m, 2H, $H^5$, $H^6$), 7.07 (dd, 2H, $J = J' = 8.7$, $H^b$), 7.22 (dd, 2H, $J = 8.7$, $J' = 5.6$, $H^a$), 7.32 (s, 1H, $H^2$), 7.43–7.46 (m, 1H, $H^7$), 7.58–7.65 (m, 3H, $H^4$ and $H^{3'}$, $H^{5'}$), 8.43–8.46 (m, 2H, $H^{2'}$, $H^{6'}$), 10.33 (s, 1H, CO*NH*).

*N*-(Pyridin-4-yl)-3-[5-fluoro-1-(4-fluorobenzyl)-indol-3-yl]propanamide (**24**)

White crystals; 63% yield; mp = 128°C (Lit.[5] 131°C); IR (KBr) $\nu$ cm$^{-1}$: 3232 ($\nu$ NH), 1702 ($\nu$ C═O); $^1$H NMR (DMSO-$d_6$), δ ppm, $J$, $J'$ Hz: 2.75 (t, 2H, $J = 7.3$, $CH_2$-$CH_2CO$), 3.04 (t, 2H, $J = 7.3$, $CH_2$-$CH_2CO$), 5.37 (s, 2H, pF-$C_6H_4CH_2N$), 6.97 (ddd, 1H, $J = 8.9$, $J = 2.5$, $J' = 8.9$, $H^6$), 7.07

(dd, 2H, $J = J' = 8.7$, $H^b$), 7.22 (dd, 2H, $J = 8.7$, $J' = 5.6$, $H^a$), 7.40 (s, 1H, $H^2$), 7.41 (dd, 1H, $J' = 9.9$, $J = 2.5$, $H^4$), 7.44 (dd, 1H, $J = 8.9$, $J' = 4.5$, $H^7$), 7.61–7.64 (m, 2H, $H^{3'}$, $H^{5'}$), 8.45–8.48 (m, 2H, $H^{2'}$, $H^{6'}$), 10.41 (s, 1H, CO*NH*).

***N*-(4,6-Dimethylpyridin-2-yl)-3-(1-methylindol-3-yl)propanamide (25)**

Orange oil; 73% yield; IR (NaCl) $\nu$ $cm^{-1}$: 3274 ($\nu$ NH), 1694 ($\nu$ C═O); $^1H$ NMR (DMSO-$d_6$), δ ppm, *J* Hz: 2.29 (s, 3H, $CH_3^{4'}$), 2.37 (s, 3H, $CH_3^{6'}$), 2.76 (t, 2H, $J = 7.5$, $CH_2$-$CH_2$CO), 3.03 (t, 2H, $J = 7.5$, $CH_2$-$CH_2$CO), 3.75 (s, 3H, N$CH_3$), 6.81 (s, 1H, $H^{5'}$), 7.05 (dd, 1H, $J = 7.5$, $J = 7.0$, $H^5$), 7.13 (s, 1H, $H^2$), 7.17 (dd, 1H, $J = 8.1$, $J = 7.0$, $H^6$), 7.40 (d, 1H, $J = 8.1$, $H^7$), 7.63 (d, 1H, $J = 7.5$, $H^4$), 7.84 (s, 1H, $H^{3'}$), 10.42 (s, 1H, CO*NH*).

***N*-(4,6-Dimethylpyridin-2-yl)-3-(5-fluoro-1-methylindol-3-yl)propanamide (26)**

White crystals; 59% yield; mp = 136°C (petroleum ether); IR (KBr) $\nu$ $cm^{-1}$: 3244($\nu$ NH), 1655 ($\nu$ C═O); $^1H$ NMR (DMSO-$d_6$), δ ppm, *J*, *J'* Hz: 2.30 (s, 3H, $CH_3^{4'}$), 2.38 (s, 3H, $CH_3^{6'}$), 2.74 (t, 2H, $J = 7.5$, $CH_2$-$CH_2$CO), 2.98 (t, 2H, $J = 7.5$, $CH_2$-$CH_2$CO), 3.75 (s, 3H, N$CH_3$), 6.83 (s, 1H, $H^{5'}$), 6.97–7.04 (m, 1H, $H^6$), 7.23 (s, 1H, $H^2$), 7.37–7.44 (m, 2H, $H^4$, $H^7$), 7.81 (s, 1H, $H^{3'}$), 10.48 (s, 1H, CO*NH*).

***N*-(4,6-Dimethylpyridin-2-yl)-3-[1-(4-fluorobenzyl)indol-3-yl]propanamide (27)**

Orange oil; 72% yield; IR (NaCl) $\nu$ $cm^{-1}$: 3269 ($\nu$ NH), 1694 ($\nu$ C═O); $^1H$ NMR (DMSO-$d_6$), δ ppm, *J*, *J'* Hz: 2.29 (s, 3H, $CH_3^{4'}$), 2.37 (s, 3H, $CH_3^{6'}$), 2.77 (t, 2H, $J = 7.4$, $CH_2$-$CH_2$CO), 3.04 (t, 2H, $J = 7.4$, $CH_2$-$CH_2$CO), 5.36 (s, 2H, pF-$C_6H_4CH_2$N), 6.83 (s, 1H, $H^{5'}$), 7.03 (dd, 2H, $J = J' = 8.7$, $H^b$), 7.04 (dd, 1H, $J = 7.5$, $J = 6.9$, $H^5$), 7.13 (dd, 1H, $J = 7.9$, $J = 6.9$, $H^6$), 7.21 (dd, 2H, $J = 8.7$, $J' = 5.6$, $H^a$), 7.32 (s, 1H, $H^2$), 7.43 (d, 1H, $J = 7.9$, $H^7$), 7.64 (d, 1H, $J = 7.5$, $H^4$), 7.82 (s, 1H, $H^{3'}$), 10.40 (s, 1H, CO*NH*).

***N*-(4,6-Dimethylpyridin-2-yl)-3-[5-fluoro-1-(4-fluorobenzyl)indol-3-yl]propanamide (28)**

White crystals; 60% yield; mp = 110°C (petroleum ether); IR (KBr) $\nu$ $cm^{-1}$: 3287 ($\nu$ NH), 1671 ($\nu$ C═O); $^1H$ NMR (DMSO-$d_6$), δ ppm, *J*, *J'* Hz: 2.29 (s, 3H, $CH_3^{4'}$), 2.37 (s, 3H, $CH_3^{6'}$), 2.74 (t, 2H, $J = 7.3$, $CH_2$-$CH_2$CO), 3.01 (t, 2H, $J = 7.3$, $CH_2$-$CH_2$CO), 5.37 (s, 2H, pF-$C_6H_4CH_2$N), 6.83 (s, 1H, $H^{5'}$), 6.97 (ddd, 1H, $J = 8.9$, $J = 2.4$, $J' = 8.9$, $H^6$), 7.03 (dd, 2H, $J = J' = 8.7$, $H^b$), 7.21 (dd, 2H, $J = 8.7$, $J' = 5.6$, $H^a$), 7.41 (s, 1H, $H^2$), 7.42 (dd, 1H, $J' = 10.2$, $J = 2.4$, $H^4$), 7.44 (dd, 1H, $J = 8.9$, $J' = 4.8$, $H^7$), 7.82 (s, 1H, $H^{3'}$), 10.40 (s, 1H, CO*NH*).

***N*-(Pyridin-3-ylmethyl)-3-(1-methylindol-3-y)-propanamide (29)**

Orange oil; 78% yield; IR (NaCl) $\nu$ $cm^{-1}$: 3285 ($\nu$ NH), 1651 ($\nu$ C═O); $^1H$ NMR (DMSO-$d_6$), δ ppm, *J* Hz: 2.55 (t, 2H, $J = 7.4$, $CH_2$-$CH_2$CO), 3.01 (t, 2H, $J = 7.4$, $CH_2$-$CH_2$CO), 3.74 (s, 3H, N$CH_3$), 4.33 (d, 2H, $J = 5.7$, $CH_2$NH), 7.02–7.08 (m, 2H, $H^2$, $H^5$), 7.14–7.21 (m, 1H, $H^6$), 7.30–7.43 (m, 2H, $H^{5'}$, $H^7$), 7.54–7.62 (m, 2H, $H^4$, $H^{4'}$), 8.45–8.50 (m, 3H, CO*NH* and $H^{2'}$, $H^{6'}$).

***N*-(Pyridin-3-ylmethyl)-3-(5-fluoro-1-methylindol-3-yl)propanamide (30)**

Brown oil; 62% yield; IR (NaCl) $\nu$ $cm^{-1}$: 3274 ($\nu$ NH), 1651 ($\nu$ C═O); $^1H$ NMR (DMSO-$d_6$), δ ppm, *J*, *J'* Hz: 2.54 (t, 2H, $J = 7.2$, $CH_2$-$CH_2$CO), 2.96 (t, 2H, $J = 7.2$, $CH_2$-$CH_2$CO), 3.74 (s, 3H, N$CH_3$), 4.33 (d, 2H, $J = 5.5$, $CH_2$NH), 7.00 (dd, 1H, $J = 8.9$, $J = 2.3$, $J' = 8.9$, $H^6$), 7.16 (s, 1H, $H^2$), 7.23–7.32 (m, 1H, $H^{5'}$), 7.34–7.45 (m, 1H, $H^{4'}$), 7.36 (dd, 1H, $J = 10.2$, $J = 2.3$, $H^4$), 7.41 (dd, 1H, $J = 8.9$, $J' = 4.5$, $H^7$), 8.46–8.55 (m, 3H, CO*NH* and $H^{2'}$, $H^{6'}$).

***N*-(Pyridin-3-ylmethyl)-3-[1-(4-fluorobenzyl)-indol-3-yl]propanamide (31)**

White crystals; 69% yield; mp = 147°C ($CH_2Cl_2$/EtOH:95/5); IR (KBr) $\nu$ $cm^{-1}$: 3303 ($\nu$ NH), 1647 ($\nu$ C═O); $^1H$ NMR (DMSO-$d_6$), δ ppm, *J*, *J'* Hz: 2.55 (t, 2H, $J = 7.5$, $CH_2$-$CH_2$CO), 3.00 (t, 2H, $J = 7.5$, $CH_2$-$CH_2$CO), 4.30 (d, 2H, $J = 5.8$, $CH_2$NH), 5.36 (s, 2H, pF-$C_6H_4CH_2$N), 7.04 (dd, 1H, $J = 8.1$, $J = 6.9$, $H^5$), 7.11 (dd, 1H, $J = 8.0$, $J = 6.9$, $H^6$), 7,15 (dd, 2H, $J = J' = 8.9$, $H^b$), 7.24 (dd, 2H, $J = 8.9$, $J' = 5.6$, $H^a$), 7.25 (s, 1H, $H^2$), 7.28–7.33 (m, 1H, $H^{5'}$), 7.44 (d, 1H, $J = 8.0$, $H^7$), 7.54–7.58 (m, 1H, $H^{4'}$), 7.59 (d, 1H, $J = 8.1$, $H^4$), 8.42–8.49 (m, 3H, CO*NH* and $H^{2'}$, $H^{6'}$).

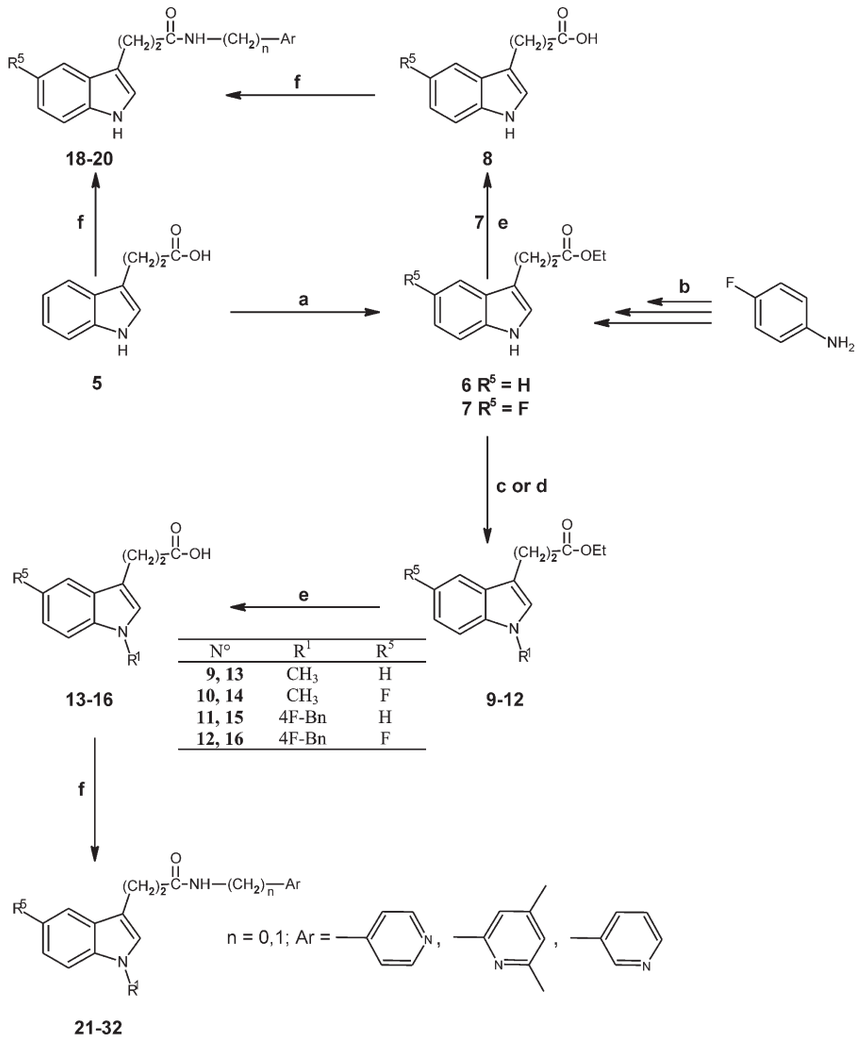
***N*-(Pyridin-3-ylmethyl)-3-[5-fluoro-1-(4-fluorobenzyl)indol-3-yl]propanamide (32)**

White crystals, 55% yield; mp = 118°C (petroleum ether); IR (KBr) $\nu$ $cm^{-1}$: 3294 ($\nu$ NH), 1646 ($\nu$ C═O); $^1H$ NMR (DMSO-$d_6$), δ ppm, *J*, *J'* Hz: 2.53 (t, 2H, $J = 7.5$, $CH_2$-$CH_2$CO), 2.96 (t, 2H, $J = 7.5$, $CH_2$-$CH_2$CO), 4.31 (d, 2H, $J = 5.5$, $CH_2$NH), 5.37 (s, 2H, pF-$C_6H_4CH_2$N), 6.97 (dd, 1H, $J = J' = 8.9$, $H^6$), 7.15 (dd, 2H, $J = J' = 8.6$, $H^b$), 7.25 (dd, 2H, $J = 8.6$, $J' = 5.6$, $H^a$), 7.23–7.32 (m, 1H, $H^{5'}$), 7.32–7.44 (m, 2H, $H^2$, $H^4$), 7.45 (dd, 1H, $J = 8.9$, $J' = 4.6$, $H^7$), 7.52–7.56 (m, 1H, $H^{4'}$), 8.42–8.46 (m, 3H, CO*NH* and $H^{2'}$, $H^{6'}$), 10.93 (bs, 1H, $H^1$).

## Biological Experiments

### *PMA-induced Mouse-ear Œdema (Orally Administered Drugs)*

Induction of mouse-ear œdema was based on the method of Carlson *et al.*[6] with some modifications. Groups of five male Swiss mice, weighing 20–23 g, were used. The experiments were carried out according to the previously described procedure.[1] Ear œdema, calculated by substracting the thickness of the right ear (PMA), was expressed as an increase in ear thickness. The percentage of inhibition of




| N° | $R^1$ | $R^5$ |
|---|---|---|
| **9, 13** | $CH_3$ | H |
| **10, 14** | $CH_3$ | F |
| **11, 15** | 4F-Bn | H |
| **12, 16** | 4F-Bn | F |

SCHEME 1 Chemical synthesis of amides **18–32**. **(a)** EtOH, HCl, reflux; **(b)** (i) $NaNO_2$, HCl, 0°C; (ii) ethyl 2-oxocyclopentanecarboxylate, KOH, EtOH, r.t.; (iii) EtOH, $H_2SO_4$, reflux; (iv) NaOH, EtOH, reflux; (v) EtOH, HCl, reflux; (vi) $Cu_2Cr_2O_5$, quinoline, reflux; **(c)** NaH, $CH_3I$, DMF, r.t.; **(d)** $Cs_2CO_3$, 4F-BnCl, $CH_3CN$, reflux; **(e)** NaOH, EtOH, reflux; **(f)** $Ar(CH_2)_nNH_2$, 2-chloro-*N*-methylpyridinium iodide, $Et_3N$, $CH_2Cl_2$, reflux.

the inflammatory reaction was determined for each animal by comparison of ear œdema in treated and non-treated animals.

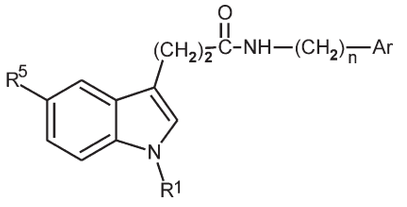
### *PMA-induced Mouse-ear Œdema (Topically Applied Drugs)*

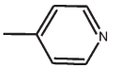
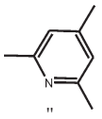
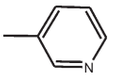
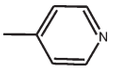
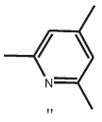
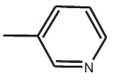
Groups of five male Swiss mice (19–21 g) were used. PMA was dissolved in 80% aqueous ethanol at a concentration of 250 μg/mL; 10 μl was applied topically to the anterior and posterior surfaces of the right ear of each mouse. The left ear (control) received the vehicle (10 μl of 80% aqueous ethanol). Ear œdema reduction was measured according to the previously described protocol.[1] Ear œdema, calculated by subtracting 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 the comparison of ear œdema in treated and non-treated animals.

### *Carrageenan-induced Rat-paw Œdema*

Anti-inflammatory activity against rat-paw œdema was assayed in adult male Wistar CF rats (145–170 g) using the method of Winter *et al.*[7] with slight modifications as previously described.[1] The inhibition percentage of the inflammatory reaction was determined for each animal by comparison with controls, and calculated by the formula $I(\%) = 100 \times (1 - \mathrm{dt/dc})$, where *dt* is the difference in paw volume in the drug-treated group and *dc* the difference in the control group.

TABLE I I Anti-œdema effect of (indol-3-yl)propanamides **1**, **2** and **17**–**32**




| | | | | | Mouse ear swelling test | | | | Rat paw œdema |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | Oral administration | | Topical application | | Oral administration |
| N° | $R^1$ | $R^5$ | n | Ar | % inhibition at 0.2 mM kg$^{-1}$ | $ID_{50}$ mM kg$^{-1}$ | % inhibition at 2 × 100 µg | % inhibition at 2 × 50 µg | % inhibition at 0.2 mM kg$^{-1}$ |
| **1** | H | H | 0 |  | 77 ± 2[a] | 0.041 ± 0.013 | 38 ± 3 | | 95 ± 3[b] |
| **2** | H | F | 0 | " | 59 ± 4 | 0.042 ± 0.016 | 78 ± 2 | | 86 ± 8[b] |
| **17** | H | H | 0 |  | 84 ± 2 | 0.029 ± 0.017 | 66 ± 3 | 53 ± 2 | 58 ± 4 |
| **18** | H | F | 0 | " | 48 ± 2 | | | | |
| **19** | H | H | 1 |  | 68 ± 5 | | | | |
| **20** | H | F | 1 | " | 55 ± 2 | | | | |
| **21** | $CH_3$ | H | 0 |  | toxic | 0.032 ± 0.012 | 72 ± 1 | 50 ± 1 | 72 ± 7[c] |
| **22** | $CH_3$ | F | 0 | " | 90 ± 3 | 0.029 ± 0.015 | 75 ± 3 | 39 ± 3 | 47 ± 4 |
| **23** | 4F-Bn | H | 0 | " | 68 ± 3 | | | | |
| **24** | 4F-Bn | F | 0 | " | 73 ± 1.5 | 0.059 ± 0.035 | 78 ± 1 | 68 ± 1 | |
| **25** | $CH_3$ | H | 0 |  | 64 ± 5 | | | | |
| **26** | $CH_3$ | F | 0 | " | 67 ± 3 | | | | |
| **27** | 4F-Bn | H | 0 | " | 84 ± 2 | 0.035 ± 0.020 | 66 ± 2 | 52 ± 2 | 51 ± 6 |
| **28** | 4F-Bn | F | 0 | " | 69 ± 2 | | | | |
| **29** | $CH_3$ | H | 1 |  | 72 ± 2 | 0.045 ± 0.037 | 83 ± 1 | 72 ± 1 | 38 ± 6 |
| **30** | $CH_3$ | F | 1 | " | 72 ± 2 | 0.064 ± 0.041 | 83 ± 1 | 70 ± 1 | |
| **31** | 4F-Bn | H | 1 | " | 79 ± 2 | 0.035 ± 0.014 | 74 ± 2 | 37 ± 2 | 22 ± 4 |
| **32** | 4F-Bn | F | 1 | " | 62 ± 2 | | | | |
| | | **Dexamethasone** | | | 85 ± 1 | 0.012 ± 0.01 | 96 ± 2 | | 96 ± 1.5 |
| | | **Ibuprofen** | | | 56 ± 4 | 0.18 ± 0.05 | 59 ± 2.5 | | 50 ± 1 |

[a] Toxic at 0.4 mM kg$^{-1}$; [b] At 0.1 mM kg$^{-1}$; [c] 45 ± 7 at 0.1 mM kg$^{-1}$.

## RESULTS AND DISCUSSION

### Chemical Synthesis

The synthetic routes used to obtain the target *N*-pyridinyl and *N*-(pyridin-3-ylmethyl)-3-(indol-3-yl)propanamides **18**–**32** are described in Scheme 1. The starting acids **5** and **8** were activated via acyloxypyridinium salt formation (method f). $N^1$-substitution was carried out using the corresponding esters **6** and **7** in presence of the couple NaH/DMF or $Cs_2CO_3/CH_3CN$ (leading to **9**–**12**) in excellent yields (methods c or d). These esters were readily hydrolyzed (method e) into the corresponding acids **13**–**16**. The non-commercially available ethyl 3-(5-fluoroindol-3-yl)propanoic acid **(7)**[4] was prepared in an overall yield of 18% by a four-step sequence under Japp-Klingemann reaction[8] conditions (method b). The synthetic procedures and the physicochemical data of the amides **18**–**32** and their precursors are described in the Materials and Methods section.

### Pharmacology

#### *Effect in the Acute PMA-induced Mouse Ear Swelling Test*

The anti-œdematous effect of the target 3-indolylpropanamides **17**–**32** was evaluated in a model of topical inflammation, the acute PMA-induced mouse ear swelling assay.[6] After oral administration of $0.2\,mM\,kg^{-1}$, all the compounds exerted an inhibition percentage $> 50\%$ (Table I). The $ID_{50}$ of the most potent amides (**17, 21, 22, 24, 27, 29, 30**, and **31**) was determined. Taken together these results showed that, in the sub-series of *N*-lutidinyl-3-indolylpropanamides, by reference to **17**, neither $N^1$-substitution ($CH_3$, 4F-Bn) nor fluorination at carbon 5, leading to **18**, **25**–**28**, was able to increase activity. In the N-4-pyridinyl sub-series, the toxic effects exerted by amide **1**, especially at $0.4\,mM\,kg^{-1}$, could be attenuated by the simultaneous presence of a methyl group at $N^1$ and a fluorine at C-5, with maintenance of a high level of activity, especially for **22** which was as active as **17**: $ID_{50} = 0.029\,mMol\,kg^{-1}$. In the N-β-picolyl sub-series, the most prominent phenomenon was the clear-cut increase in activity of **19** after $N^1$-4F-benzylation, leading to **31**, whose inhibition percentages at $0.2\,mMol\,kg^{-1}$ were $68 \pm 5$ and $79 \pm 2$, respectively, with $ID_{50} = 0.035 \pm 0.014\,mMol\,kg^{-1}$ for the latter.

The previously studied eight amides also proved to be highly efficient in mouse-ear thickness reduction after topical application of $2 \times 500\,\mu g$/ear (data not shown). Although less potent than dexamethasone at $2 \times 100\,\mu g$/ear, they remained significantly active at $2 \times 50\,\mu g$/ear, the most potent amides, **24**, **29** and **30**, exerting 70% œdema inhibition.

#### *Effect in the Carrageenan Rat Paw œdema Test*

As previous pharmacomodulation showed that the propanamide **2** constitutes the most efficient systemic anti-inflammatory compound ever discovered in the series of *N*-pyridinyl heteroarylalkanamides, the six indolepropanamides exhibiting high anti-œdema effect in the mouse ear swelling test ($ID_{50} \leq 0.045\,mM\,kg^{-1}$ after oral administration) were tested on carrageeenan-induced rat paw œdema. Experimentation was carried out by the oral route, using $0.2\,mMol\,kg^{-1}$. Amides **17** and **27** exhibited inhibition percentages in the range of 50%. They were devoid of toxic effects, contrarily to **21, 22** and the previously studied N-4-pyridinyl propanamides **1, 2**.

As the multiple PMA-induced model of chronic inflammation is considered to be a relevant model of human psoriasis, we are now evaluating the most potent 3-indolylpropanamides **24**, **29** and **30** in the subchronic mouse ear swelling test.[9] Moreover, their *in vitro* TNF-α production inhibitory effect will be determined, taking into account that previously studied *N*-pyridinylmethylphthalimides[2] are potent inhibitors of this cytokine which has received a considerable amount of attention as a molecular target for the treatment of a variety of pathological conditions including rheumatoid arthritis, ulcerative colitis, Crohn's disease and multiple sclerosis.[10]

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