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Short communication

N-Pyridinyl-indole-3-(alkyl)carboxamides and derivatives as potential systemic and topical inflammation inhibitors

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Abstract – *N*-substituted-(indol-3-yl)carboxamides **10**–**15** and alkanamides **16**–**18** were prepared starting from the corresponding acids and submitted to screening for evaluation of their anti-inflammatory activity. None of the considered carboxamides exhibited significant inhibitory effect in the carrageenin-induced rat paw oedema after oral administration of 0.1 mM kg^{-1}; nevertheless introduction of an alkyl chain, leading to alkanamides **16**–**18**, induced moderate to high activity: 46–95% inhibition. The efficacy of these compounds in the inhibition of topical inflammation was confirmed by measuring reduction of ear thickness in the acute tetradecanoyl phorbol acetate (TPA)-induced mouse ear swelling assay. Preliminary pharmacomodulation brought to the fore that toxic effects induced, at 0.4 mM kg^{-1}, by *N*-(pyridin-4-yl)(indol-3-yl)propanamide (**17**) could be attenuated or suppressed by 5-fluorination or introduction of a methoxycarbonylborane moiety, leading to **18** and **21**. © 2001 Éditions scientifiques et médicales Elsevier SAS

amino(methyl)pyridines (derivatives of) / 3-indol(alkyl)carboxamides / systemic and topical inflammation inhibitors

1. Introduction

In a previous work we reported on the synthesis and biological evaluation of *N*-(4,6-dimethylpyridin-2-yl)heteroarylcarboxamides and acetamides as a novel type of non-acidic anti-inflammatory agents [1]. It was also established that incorporation of amino acid residues, especially glycine and alanine into 2-amino-4,6-dimethylpyridine led to potent systemic and topical inflammation inhibitors [2]. The fact that some indolylcarboxamides act as anti-allergic [3] and that indole constitutes the central core of numerous efficient LTD_4 antagonists [4, 5] or inhibitors of FLAP [6] prompted us to envision pharmacomodulation in the series of related *N*-pyridinyl-indolyl-(alkyl)carboxamides I (*figure 1*). As replacement of

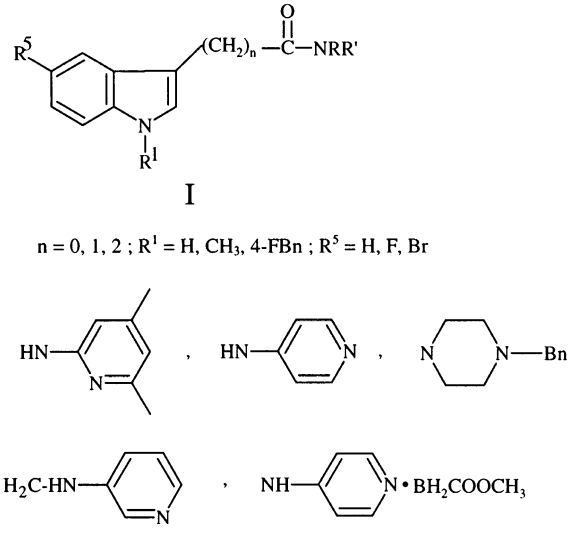

Figure 1. General structure of indole-3-(alkyl)carboxamides **10**–**18** and **21**.

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the methylene carbon in α-amino-acids or dipeptides by a boron atom leads to compounds exhibiting significant anti-arthritic [7] and anti-inflammatory activities [8, 9], in rodents, we also studied the incidence of incorporation of a methoxycarbonylborane residue in the pyridine moiety of one active amide.

Their synthesis and preliminary structure–activity relationships, based on two in vivo assays — the carrageenin-induced rat paw oedema and the tetradecanoyl phorbol acetate (TPA)-induced mouse ear oedema tests — will be presented in this paper.

2. Chemistry

The synthetic routes to targeting (indol-3-yl)carboxamides and alkanamides I are outlined in *figures 2* and *3*. The starting acids **5**–**9** were activated via phosphoric anhydride, acyloxypyridinium salt,

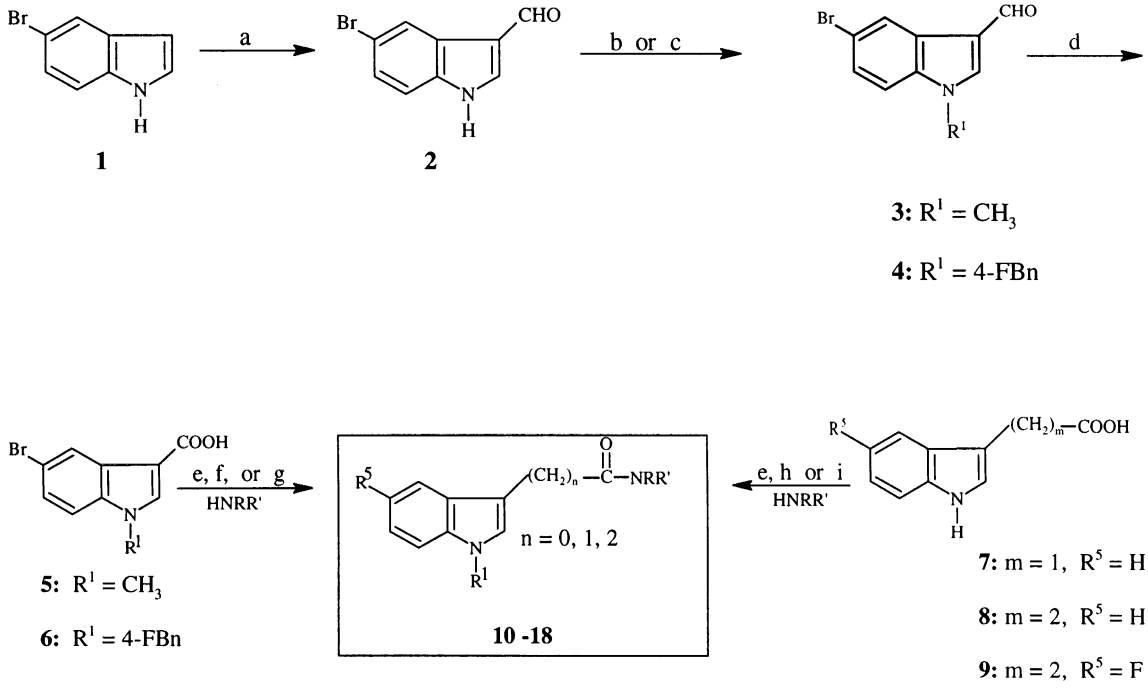


Figure 2. Reagents: (a) $POCl_3$, DMF, 10 °C, 2 h; (b) NaH, DMF, CH_3I, room temperature, 2 h; (c) Cs_2CO_3, 4F-BnCl, CH_3CN, reflux, 3 h; (d) $NaClO_2$, NaH_2PO_4, 2-methyl-2-butene, *t*-BuOH, THF, room temperature, 15 h; (e) phenyl dichlorophosphate, CH_2Cl_2, room temperature, 12–20 h; (f) 2-chloro-1-methylpyridinium iodide, THF, reflux 20 min; (g) CDI, THF, room temperature, 14 h; (h) DCC, THF, reflux, 48 h; (i) Ph_3P, $CBrCl_3$, THF, reflux, 3 h.

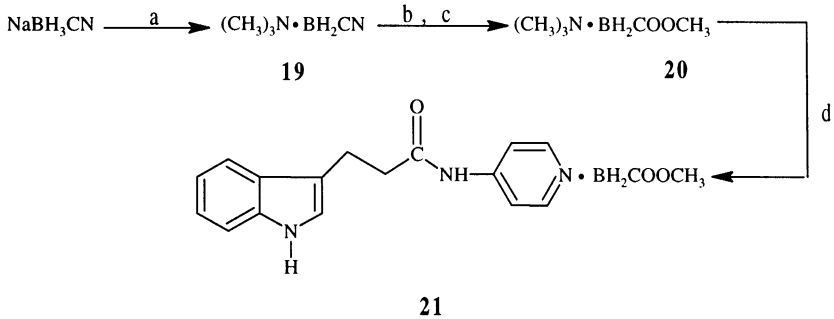
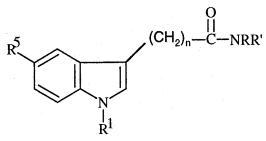


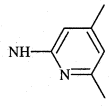
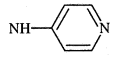
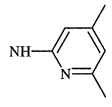
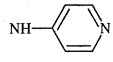
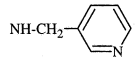
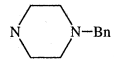
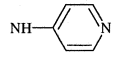
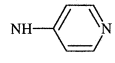
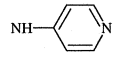
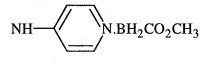
Figure 3. Reagents: (a) $(CH_3)_3N$–HCl, THF, reflux, 48 h; (b) (1) Et_3OBF_4, $CHCl_3$, reflux, 24 h; (2) H_2O, room temperature, 72 h; (c) DCC, CH_3OH, room temperature, 7 days; (d) **17**, CH_3CN, reflux, 48 h.

imidazolide, isourea ester or acyloxyphosphonium salt formation (methods e–i), leading to amides **10**–**18** in moderate to excellent yields. Their physicochemical data are summarised in *table I*.

N-substituted-(indol-3-yl)carboxylic acids **5** and **6** were obtained in excellent yields (83 and 94%, respectively) by oxidation of the corresponding carbaldehydes **3** and **4** by the couple $NaClO_2/NaH_2PO_4$ in the

Table I. Physicochemical data and anti-oedema effect of (indol-3-yl)carboxamides **10**–**15** and alkanamides **16**–**18** and **21**.



N°	R^1	R^5	n	NRR'	Formula M_r	Method Yield (%)	Mp (°C) Solvent	Rat paw edema inhibition %, at 0.1 mM kg^{-1}
10	CH_3	Br	0		$C_{17}H_{16}BrN_3O$ 358.24	e: 27	201 *a*	NA
11	CH_3	Br	0		$C_{15}H_{12}BrN_3O$ 330.18	e: 55	308 *a*	33 ± 6
12	4-FBn	Br	0		$C_{23}H_{19}BrFN_3O$ 452.33	e: 56	144 *a*	29 ± 5
13	4-FBn	Br	0		$C_{21}H_{15}BrFN_3O$ 424,27	e: 42	240 *a*	27 ± 3
14	4-FBn	Br	0		$C_{22}H_{17}BrFN_3O$ 438.30	e: 70	187 *a*	NA
15	4-FBn	Br	0		$C_{27}H_{25}BrFN_3O$ 506.42	f: 62 g: 55	115 *b*	26 ± 6
16	H	H	1		$C_{15}H_{13}N_3O$ 251.29	h: 58 i: 35	230 *c*	41 ± 11
17	H	H	2		$C_{16}H_{15}N_3O$ 265.32	e: 76 h: 66	100 *d*	95 ± 3
18	H	F	2		$C_{16}H_{14}FN_3O$ 283.31	h: 58	150-155 *e*	86 ± 8
21	H	H	2		$C_{18}H_{20}BN_3O_3$ 337.18	11[f]	135 *a*	84 ± 9

Crystallization solvents : [a]dicloromethane ; [b]diethyl ether; [c]ethanol , [d]petroleum ether; [e] ethyl acetate ; [f] see figure 3 ; NA : inhibition % < 20 %.

Table II. Inhibition percentage of the acute TPA-induced mouse ear swelling after oral administration of 0.1 mM kg^{-1} of the indolyl(alkyl)carboxamides **16–18** and **21**.

16	54 ± 2
17	77 ± 4
18	78 ± 2
21	58 ± 3

presence of 2-methyl-2-butene, according to Ref. [10]. The non-commercially available 3-(5-fluoroindol-3-yl)propionic acid **9** [11] was prepared in an overall yield of 25% by the four-step sequence starting from 4-fluoroaniline:diazotation, condensation with ethyl 2-oxocyclopentane carboxylate under Japp–Klingemann reaction conditions, hydrolysis of the diester and C-2-decarboxylation by the couple Cu/*N*-methylpyrrolidinone. The boron derivative **21** was obtained, via an amine exchange reaction [12], from *N*-(pyridin-4-yl)-3-(indol-3-yl)propanamide (**17**) and trimethylaminomethoxycarbonylborane (**20**), in refluxing acetonitrile (*figure 3*); due to delicate purification, the yield remained poor (11%); attempts to improve it by operating in DMF, at different temperatures, failed. Compound **20** [12, 13] was synthesised by the reaction of trimethylamine hydrochloride with sodium cyanoborohydride leading to trimethylaminocyanoborane (**19**); hydrolysis of the intermediate nitrilium tetrafluoroborate afforded the acid which was converted into the corresponding ester **20** after DCC activation.

3. Pharmacology

3.1. Effect in the carrageenin paw oedema test

The nine indole(alkyl)carboxamides **10–18** were tested on carrageenin-induced rat paw oedema, by the oral route, using 0.1 mM kg^{-1}. Our earlier work in the field of non-acidic anti-inflammatory aryl(alkyl)carboxamides, incorporating different amino groupings, brought to the fore that 2-amino-4,6-dimethylpyridine [14], 4-aminopyridine [15], 3-aminomethylpyridine [16] and *N*-benzylpiperazine (J. Brelet, personal communication) represent the most potent pharmacophoric moieties in inflammation process inhibition. Although it was previously stated that nuclear bromination of *N*-pyridinyl(hetero)arylcarboxamides was liable to increase their anti-oedematous effect [17], none of the six used (5-bromoindol-3-yl) carboxamides **10–15** elicits significant inhibitory effect (see *table I*). Nevertheless, introduction of a methylene and especially an ethylene chain at C-3, leading to acetamide **16** and propanamide **17** induced a marked increase of activity: 41 ± 11 and 95 ± 3% inhibition, respectively. Unfortunately, this potent amide **17** elicited toxic effects at 0.4 mM kg^{-1}. Toxicity could be attenuated or suppressed by the introduction of a fluorine at C-5 or incorporation of a methoxycarbonylborane moiety in the pyridinyl nucleus, leading to **18** and **21**, respectively, with maintenance of a high level of inhibitory activity (86 ± 8 and 84 ± 9%) at 0.1 mM kg^{-1}. Determination of their ID_{50} afforded the following values: 35 ± 13, 26 ± 5 and 49 ± 14 μM kg^{-1}. Thus, *N*-(pyridin-4-yl)-5-fluoro-indol-3-yl)propanamide (**18**) appears as the most potent non-acidic NSAID ever discovered in our series of *N*-pyridinyl-heteroaryl(alkyl)carboxamides. The level of activity is comparable with that of oxicam derivatives [18].

3.2. Effect in the acute TPA-induced mouse ear swelling test

It is well established that prostaglandin [19] and leucotriene (LTB_4, 12-HETE) [20] concentrations are elevated in psoriatic skin. Moreover, evidence was found in psoriatic tissue of increased expression of human non-pancreatic phospholipase A_2 [21] and of the up-regulation of various cytokines (IL-1, TNFα) stimulating endothelial cell adhesiveness for lymphocytes [22]. As psoriatic skin shares many of the pathologic features of phorbol ester-treated mouse skin [23], the effect of the most active compounds was evaluated in a model of topical inflammation, the acute TPA-induced mouse ear swelling test [24]. After oral administration of 0.1 mM kg^{-1}, the four selected amides **16–18** and **21** exerted a significant reduction in ear thickness (see *table II*). The 5-fluorinated propanamide **18,** less toxic than **17,** exhibited a level of activity comparable to that of the latter: 78 ± 2 and 77 ± 4%, respectively.

4. Conclusions

The present preliminary results suggest that **18** may prove to be a valuable candidate as the lead structure for further pharmacomodulation in the series of amides issued from 3-(indol-3-yl)propionic acids. This new lead compound and derivatives are now being evaluated in the multiple TPA-induced model of

chronic inflammation [25] considered to be a relevant model of human psoriasis. Moreover, a first approach of the mechanism of action of **18** will be carried out by in vitro determination of the inhibition of TNFα production, taking into account that structurally related compounds inhibit TNFα production from LPS-activated macrophages [26].

5. Experimental protocols

5.1. Chemistry

Melting points (m.p.) were determined on a Tottoli–Büchi apparatus and were uncorrected. Structures were supported by IR and ^{1}H-NMR. IR spectra were recorded on a Perkin–Elmer Paragon PC 1000 spectrometer as potassium bromide discs or as a film on NaCl plates. ^{1}H-NMR spectra were recorded on a Bruker AC 250 spectrometer (250 MHz) using $CDCl_3$ or $(CH_3)_2SO$-d_6 as solvent. Chemical shifts δ (ppm) refer to tetramethylsilane, which was used as the internal reference; coupling constants are in Hz. Analytical TLC was performed on precoated silica-gel aluminium (0.2 mm, GF254, E. Merck). Spots were located by UV illumination. Sodium sulfate or phosphorus pentoxide was used as the drying agent. Column chromatography was conducted on silica-gel (Kieselgel 60, 70–230 mesh, E. Merck) and for delicate separations, a preparative centrifugally accelerated TLC (Chromatotron 7924 T, Harrisson Research, Palo Alto, CA) was used. Microanalyses for C, H, and N, were performed using a Perkin–Elmer C, H, N 240 apparatus; the analytical results were within ±0.4% of the theoretical values.

(Indol-3-yl)acetic and propionic acids **7** and **8** were purchased from Aldrich Chimie (Saint-Quentin-Fallavier, France); (5-fluoroindol-3-yl)propionic acid (**9**) was prepared according to Ref. [11]. Other starting materials and reagents were obtained commercially from Aldrich Chimie, Acros (Noisy-le Grand, France) or Interchim (Montluçon, France).

5.1.1. (5-Bromoindol-3-yl)carboxaldehyde (2) [27]

This aldehyde was prepared from 5-bromoindole (**1**), by the Vilsmeyer–Hack method ($POCl_3$, DMF). The precipitate formed by heating in alkaline solution was separated by filtration, washed with water (4×100 mL) affording 5.7 g of pure aldehyde **2** as a pale yellow powder, yield: 99.5%; m.p. 201 °C (H_2O), lit. [27] 205 °C (H_2O). IR (KBr, cm^{-1}): ν(C=O) 1644. ^{1}H-NMR (DMSO-d_6, ppm): δ 7.43 (dd, 1H, H^6, J = 8.6, 2.0 Hz), 7.54 (d, 1H, H^7), 8.26 (d, 1H, H^4), 8.39 (s, 1H, H^2), 9.97 (s, 1H, CHO), 12.35 (s, 1H, NH).

5.1.2. (5-Bromo-1-methylindol-3-yl)carboxaldehyde (3) [28]

Methylation of (5-bromoindol-3-yl) carboxaldehyde (**2**) was carried out with methyl iodide after deprotonation by NaH in DMF. The crude N-derivative **3** was purified by chromatography on silica-gel eluting with dichloromethane, yield: 98.5%; m.p. 133 °C (CH_2Cl_2), lit. [28] 130–133 °C (CH_2Cl_2–petroleum ether). IR (KBr, cm^{-1}): ν(C=O) 1653. ^{1}H-NMR (DMSO-d_6, ppm): δ 3.93 (s, 3H, H, CH_3), 7.50 (dd, 1H, H^6, J = 8.7, 2.0 Hz), 7.62 (d, 1H, H^7), 8.26 (d, 1H, H^4), 8.37 (s, 1H, H^2), 9.93 (s, 1H, CHO).

5.1.3. [5-Bromo-1-(4-fluorobenzyl)indol-3-yl]-carboxaldehyde (4)

To a solution of (5-bromoindol-3-yl)carboxaldehyde (**2**) (2.5 g, 11.15 mmol) in dry CH_3CN (50 mL) was added Cs_2CO_3 (7.26 g, 22.3 mmol). The suspension was stirred for 2 h under reflux and 4-fluorobenzylchloride (1.5 mL, 12.5 mmol) was progressively added. The reaction mixture was stirred under reflux for 1 h. After filtration and addition of water (50 mL), the aqueous phase was extracted with dichloromethane (3×50 mL); the organic layers were washed with saturated NaCl solution, dried (Na_2SO_4), filtered and concentrated. Purification by chromatography on silica-gel, eluting with dichloromethane, afforded **4** (3.7 g) as a pale pink powder, yield: 99%; m.p. 130 °C (CH_2Cl_2). IR (KBr, cm^{-1}): ν(C=O) 1653. ^{1}H-NMR (DMSO-d_6, ppm): δ 5.58 (s, 2H, CH_2), 7.22 (m, 2H, benz. H^2, H^6), 7.43 (m, 2H, benz. H^3, H^5), 7.46 (dd, 1H, H^6, J = 8.8, 2.0 Hz), 7.64 (d, 1H, H^7), 8.28 (d, 1H, H^4), 8.57 (s, 1H, H^2), 9.97 (s, 1H, CHO).

5.1.4. (5-Bromo-1-methylindol-3-yl)carboxylic acid (5)

Aldehyde **3** (3 g, 12.6 mmol) was dissolved in a mixture of THF (225 ml) and t-butanol (63 mL). A 2 M 2-methyl-2-butene solution in THF (72 mL, 14.4 mmol) was first added, followed by a solution of $NaClO_2$ (3.43 g, 37.9 mmol) and NaH_2PO_4 (6.86 g, 57.2 mmol) in water (55 mL). The mixture was stirred overnight at room temperature (r.t.). A solution of $NaClO_2$ (2.25 g, 25 mmol) and NaH_2PO_4 (4.5 g, 37.5 mmol) in 90 mL of water was then added and the reaction medium was stirred for 2 h. The organic solvents were removed, and the aqueous phase was filtered. The precipitate contain-

ing the expected acid was purified by chromatography on silica-gel; elution with diethyl ether afforded **5** (2.55 g) as a white powder, yield: 80%; m.p. 270 °C (Et_2O). IR (KBr, cm^{-1}): ν(OH) 2924, 2582, ν(C=O) 1650, δ(OH) 907. ^{1}H-NMR (DMSO-d_6, ppm): δ 3.87 (s, 3H, CH_3), 7.40 (dd, 1H, H^6, $J = 8.7$, 2.0 Hz), 7.55 (d, 1H, H^7), 8.11 (s, 1H, H^2), 8.18 (d, 1H, H^4), 12.28 (s, 1H, COOH).

5.1.5. [5-Bromo-1(4-fluorobenzyl)indol-3-yl]carboxylic acid (6)

Carboxylic acid **6** was prepared according to the same procedure 'd' and was isolated as a white powder, yield: 94%; m.p. 218 °C (Et_2O). IR (KBr, cm^{-1}): ν(OH) 2885, 2750, ν(C=O) 1651, δ(OH) 939. ^{1}H-NMR (DMSO-d_6, ppm): δ 5.53 (s, 2H, CH_2), 7.19 (m, 2H, benz. H^2, H^6), 7.36 (m, 2H, benz. H^3, H^5), 7.36 (dd, 1H, H^6, $J = 8.8$, 2.0 Hz), 7.58 (d, 1H, H^7), 8.19 (d, 1H, H^4), 8.34 (s, 1H, H^2), 12.34 (s, 1H, COOH).

5.1.6. N-(4,6-Dimethylpyridin-2-yl)-(5-bromo-1-methylindol-3-yl)carboxamide (10)

A suspension of **5** (0.9 g, 3.5 mmol), triethylamine (1.4 mL, 10.5 mmol) and 2-amino-4,6-dimethylpyridine (0.44 g, 3.5 mmol) in dry CH_2Cl_2 (20 mL) was cooled to 0 °C. Phenyl dichlorophosphate (0.53 mL, 3.5 mmol) was then added dropwise. The mixture was stirred at r.t. for 20 h. After washing with water (2×20 mL) and with 5% aqueous $NaHCO_3$ (30 mL), the organic layer was dried (Na_2SO_4) and evaporated under reduced pressure. The residue was purified by column chromatography (CH_2Cl_2–ethanol, 95:5) to afford 0.37 g of **10** which was recrystallised from CH_2Cl_2 to provide a white solid, yield: 27%; m.p. 201 °C (CH_2Cl_2). IR (KBr, cm^{-1}): ν(NH) 3415, ν(C=O)1657. ^{1}H-NMR (DMSO-d_6, ppm): δ 2.33 (s, 3H, γ-CH_3), 2.42 (s, 3H, α-CH_3), 3.88 (s, 3H, N–CH_3), 6.83 (s, 1H, pyr. H^5), 7.42 (dd, 1H, H^6, $J =$ 8.75, 1.8 Hz), 7.56 (d, 1H, H^7), 7.96 (s, 1H, pyr. H^3), 8.43 (d, 1H, H^4), 8.62 (s, 1H, H^2), 10.23 (s, 1H, NH). Anal. $C_{17}H_{16}BrN_3O$ (C, H, N).

5.1.7. N-(4-Pyridinyl)-(5-bromo-1-methylindol-3-yl)-carboxamide (11)

Amide **11** was prepared according to the same procedure 'e' and isolated as a white solid; yield:55%; m.p. 308 °C (CH_2Cl_2). IR (KBr, cm^{-1}): ν(NH) 3409, ν(C=O) 1676. ^{1}H-NMR (DMSO-d_6, ppm): δ 3.93 (s, 1H, CH_3), 7.47 (dd, 1H, H^6, $J = 8.70$, 1.9 Hz), 7.61 (d, 1H, H^7), 8.32 (m, 2H, pyr. H^3, H^5), 8.36 (d, 1H, H^4), 8.65 (m, 2H, pyr. H^2, H^6), 8.88 (s, H, H^2), 11.34 (s, 1H, NH). Anal. $C_{15}H_{12}BrN_3O$ (C, H, N).

5.1.8. N-(4,6-Dimethylpyridin-2-yl)-[5-bromo-1-(4-fluorobenzyl)indol-3-yl]carboxamide (12)

Amide **12** was prepared according to procedure 'e' and isolated as a white powder; yield: 56%; m.p. 144 °C (CH_2Cl_2). IR (KBr, cm^{-1}): ν(NH) 3417, ν(C=O) 1664. ^{1}H-NMR (DMSO-d_6, ppm): δ 2.34 (s, 3H, γ-CH_3), 2.42 (s, 3H, α-CH_3), 5.50 (s, 2H, CH_2), 6.84 (s, 1H, pyr. H^5), 7.23 (m, 2H, benz. H^2, H^6), 7.39 (dd, 1H, H^6, $J = 8.7$, 2.0 Hz), 7.45 (m, 2H, benz. H^3, H^5), 7.65 (d, 1H, H^7), 7.96 (s, 1H, pyr. H^3), 8.42 (d, 1H, H^4) 8.75 (s, 1H, H^2), 10.34 (s, 1H, NH). Anal. $C_{23}H_{19}BrFN_3O$ (C, H, N).

5.1.9. N-(Pyridin-4-yl)-[5-bromo-1-(4-fluorobenzyl)-indol-3-yl]carboxamide (13)

Amide **13** was synthesised according to procedure 'e' and isolated as white crystals; yield: 42%; m.p. 240 °C (CH_2Cl_2). IR (KBr, cm^{-1}): ν(NH) 3415, ν(C=O) 1646. ^{1}H-NMR (DMSO-d_6, ppm): δ 5.58 (s, 2H, CH_2), 7.23 (m, 2H, benz. H^2, H^6), 7.37 (m, 2H, benz. H^3, H^5), 7.43 (dd, 1H, H^6, $J = 8.8$, 2.1 Hz), 7.64 (d, 1H, H^7), 7.77 (m, 2H, pyr. H^3, H^5), 8.40 (d, 1H, H^4), 8.48 (m, 2H, pyr. H^2, H^6), 8.53 (s, 1H, H^2), 10.24 (s, 1H, NH). Anal. $C_{21}H_{15}BrFN_3O$ (C, H, N).

5.1.10. N-[(Pyridin-3-yl)methyl]-(5-bromo-1-(4-fluorobenzyl)indol-3-yl)carboxamide (14)

Amide **14** was prepared according to procedure 'e' and isolated as a white solid; yield: 70%; m.p. 187 °C (CH_2Cl_2). IR (KBr, cm^{-1}): ν(NH) 3417, ν(C=O) 1630. ^{1}H-NMR (DMSO-d_6, ppm): δ 4.52 (d, 2H, CH_2–NH, $J = 5.7$ Hz), 5.50 (s, 2H, CH_2), 7.21 (m, 2H, benz. H^2, H^6), 7.37 (m, 3H, pyr. H^5, benz. H^3, H^5), 7.40 (dd, 1H, H^6, $J = 8.8$ Hz, 2.0 Hz), 7.60 (d, 1H, H^7), 7.78 (d, 1H, pyr. H^6, $J = 7.8$ Hz), 8.24 (s, 1H, pyr. H^2), 8.37 (d, 1H, H^4), 8.50 (d, 1H, pyr. H^4, $J = 3.5$ Hz), 8.61 (s, 1H, H^2), 8.69 (t, 1H, NH, $J = 5.7$ Hz). Anal. $C_{22}H_{17}BrFN_3O$ (C, H, N).

5.1.11. 1-{[5-Bromo-1-(4-fluorobenzyl)indol-3-yl]-carbonyl}-4-benzylpiperazine (15)

5.1.11.1. Method f

A solution of **6** (0.5 g, 1.4 mmol), 1-benzylpiperazine (0.3 mL, 1.4 mmol) triethylamine (0.5 mL, 3.57 mmol) and 2-chloro-1-methylpyridinium iodide (0.4 g, 1.4 mmol) in dry CH_2Cl_2 was refluxed for 20 min. The solvent was evaporated and the residue was purified by column chromatography (diethyl ether) to give 0.45 g of **15** as a white powder, yield: 62%; m.p. 115 °C (Et_2O). IR (KBr, cm^{-1}): ν(NH) 3445, ν(C=O) 1600. ^{1}H-NMR

(DMSO-d_6, ppm): δ 2.45 (m, 4H, pip. H), 3.55 (s, 2H, benz. CH_2), 3.69 (m, 4H, pip. H), 5.48 (s, 2H, benz. CH_2), 7.14–7.37 (m, 8H, H^6+7 benz. H), 7.18 (m, 2H, benz. H^3, H^5), 7.53 (d, 1H, H^7, $J = 8.7$ Hz), 7.92 (d, 1H, H^4, $J = 1.7$ Hz), 8.05 (s, 1H, H^2). Anal. $C_{27}H_{25}BrFN_3O$ (C, H, N).

5.1.11.2. Method g

N-*N*′-Carbonyldiimidazole (0.23 g,1.4 mmol) was added gradually to a solution of **6** (0.5 g, 1.4 mmol) in dry THF (20 mL). The mixture was stirred at r.t. for 1 h. *N*-Benzylpiperazine (0.25 g, 1.4 mmol) was added and stirring was continued for one night. The solvent was evaporated and the crude amide **15** was purified by chromatography on silica-gel eluting with diethyl ether to give 0.39 g of **15** as white powder, yield: 55%; m.p. 115 °C (Et_2O).

*5.1.12. N-(Pyridin-4-yl)-indol-3-yl)acetamide (**16**)*

5.1.12.1. Method h

N-*N*′-Dicyclohexylcarbodiimide (2.1 g, 10.2 mmol) and 4-aminopyridine (0.99 g, 10 mmol) were added to a solution of indole-3-acetic acid **7** (1.75 g, 10 mmol) in anhydrous THF (50 mL). After 48 h reflux under stirring, the white precipitate of dicyclohexylurea was filtered and washed with AcOEt. The filtrate was evaporated under reduced pressure. The residue was purified by silica-gel chromatrography (CH_2Cl_2–EtOH, 95:5) to afford 1.46 g of pure **16** as pale yellow crystals, yield: 58%; m.p. 230 °C (EtOH). IR (KBr, cm^{-1}): ν(NH) 3295, ν(C=O) 1700, δ(NH) 1515, (comb. NH/CN) 1290. ^{1}H-NMR (DMSO-d_6, ppm): δ 3.78 (s, 1H, CH_2), 6.98 (m, 1H, H^5), 7.08 (m, 1H, H^6), 7.27 (d, 1H, H^2, $J = 1.5$ Hz), 7.36 (dd, 1H, H^7, $J = 7.75$, 1.0 Hz), 7.55–7.60 (m, 3H, H^4, pyr. H^3, H^5), 8.41 (dd, 2H, pyr. H^2, H^6, $J = 4.5$, 1.25 Hz), 10.49 (s, 1H, amid. NH), 10.95 (s, 1H, NH). Anal. $C_{15}H_{13}N_3O$ (C, H, N).

5.1.12.2. Method i

Triphenylphosphine (4.49 g, 17.1 mmol), bromotrichloromethane (6.8 g, 34.2 mmol) and indole-3-acetic acid (**7**) (3 g, 17.1 mmol) were dissolved in dry THF (100 mL). After 10 min stirring, 4-aminopyridine (3.22 g, 34.2 mmol) was added and the reaction mixture was heated under reflux for 3 h. After filtration, the organic phase was concentrated under vacuum to give a yellow residue. Purification by column chromatography afforded pure **16** in 35% yield.

*5.1.13. N-(Pyridin-4-yl)-(indol-3-yl)propanamide (**17**)*

Amide **17** was prepared according to procedure 'h' and was obtained as a white powder, yield: 66%, m.p. 100 °C (petroleum ether). IR (KBr, cm^{-1}): ν(NH) 3300, ν(C=O) 1700, δ(NH) 1520, (comb. NH/CN) 1305. ^{1}H-NMR (DMSO-d_6, ppm): δ 2.80 (t, 2H, CH_2CO, $J = 7$ Hz), 3.07 (t, 2H, CH_2), 7.00 (ddd, 1H, H^6, $J = 7.95$, 6.9, 1.2 Hz), 7.09 (ddd, 1H, H^5, $J = 7.6$, 6.9, 1.1 Hz), 7.19 (d, 1H, H^2, $J = 2.3$ Hz), 7.36 (d, 1H, H^7), 7.60 (d, 1H, H^4), 7.81 (d, 2H, pyr. H^3, H^5, $J = 4.5$ Hz), 8.60 (d, 2H, pyr. H^2, H^6), 10.92 (s, 1H, amid. NH), 11.60 (s, 1H, NH). Anal. $C_{16}H_{15}N_3O$ (C, H, N).

This amide was obtained in a higher yield (76%) by method 'e'.

*5.1.14. N-(Pyridin-4-yl)-(5-fluoroindol-3-yl)propanamide (**18**)*

Amide **18** was obtained according to procedure 'h' and was isolated as a white solid, yield: 58%; m.p. 150–155 °C (AcOEt). IR (KBr, cm^{-1}): ν(NH) 3400, 3305, 3260, ν(C=O) 1675, δ(NH) 1525, (comb. NH/CN) 1285. ^{1}H-NMR (DMSO-d_6, ppm): δ 2.74 (t, 2H, CH_2–CO, $J = 7.0$ Hz), 3.03 (t, 2H, CH_2), 6.94 (ddd, 1H, H^6, $J = 8.5$, 1.5 Hz), 7.25 (s, 1H, H^2), 7.33–7.39 (m, 2H, H^4, H^7), 7.60 (dd, 2H, pyr. H^3, H^5, $J = 4.5$, 1.2 Hz), 8.45 (d, 2H, pyr. H^2, H^6), 10.33 (s, 1H, amid. NH), 10.92 (s, 1H, NH). Anal. $C_{16}H_{14}FN_3O$ (C, H, N).

*5.1.15. N,N,N-Trimethylaminomethoxycarbonylborane (**20**) [12]*

N,*N*,*N*-Trimethylaminocyanoborane (**19**), obtained according to Ref. [29] in 74% yield, was refluxed for 24 h in a freshly prepared [30] solution of 1 M triethyloxonium tetrafluoroborate in CH_2Cl_2. Hydrolysis (H_2O) afforded *N*,*N*,*N*-trimethylaminocarboxyborane as white crystals; yield: 54%. The waited ester was prepared by reaction of the previously activated acid **19** with DCC, in methanol for 7 days at r.t. Recrystallisation from hexane–CH_2Cl_2 (9:1) afforded **20** as a white powder in a quantitative yield; m.p. 98–100 °C, lit. [13] 90–92 °C. IR (KBr, cm^{-1}): ν(BH) 2387, ν(C=O) 1670. ^{1}H-NMR ($CDCl_3$, ppm): δ 2.68 (s, 9H, $3CH_3$), 3.39 (s, 3H, CH_3).

*5.1.16. 4-{[3-Indol-3-yl)-1-oxopropyl]amino}-pyridine-methoxycarbonylborane (**21**)*

A solution of amide **17** (1.32 g, 5 mmol) and trimethylaminomethoxycarbonylborane (**20**) (0.65 g, 5 mmol) in freshly distilled CH_3CN was maintained under reflux for 48 h. After evaporation of the solvent under reduced pressure, the organic residue was purified by column

chromatography; elution with CH_2Cl_2–ethanol (98:2 up to 96:4) afforded 0.185 g of pure **21** as a pale yellow powder, yield: 11%; m.p. 135 °C (CH_2Cl_2). IR (KBr, cm^{-1}): ν(BH) 2399, ν(C=O) 1628. ^{1}H-NMR (DMSO-d_6, ppm): δ 3.2 (t, 2H, CH_2–CO, $J = 7.0$ Hz), 3.5 (t, 2H, CH_2), 3.8 (s, 3H, CH_3), 7.38 (s, 1H, H^2), 7.42 (dd, 1H, H^5, $J = 7.6$, 6.7 Hz), 7.52 (dd, 1H, H^6, $J = 7.9$, 6.7 Hz), 7.6 (d, 1H, H^7), 7.91 (d, 1H, H^4), 7.97 (d, 2H, pyr. H^3, H^5, $J = 6.7$ Hz), 8.40 (d, 2H, pyr. H^2, H^6), 10.83 (s, 1H, amid. NH), 11.0 (s, 1H, NH). Anal. $C_{18}H_{20}BN_3O_3$ (C, H, N).

5.2. Pharmacology

5.2.1. Carrageenin-induced rat paw oedema test

Anti-inflammatory activity against carrageenin-induced rat paw oedema was assayed in adult male Wistar CF rats weighing 180–220 g according to the method of Winter et al. [31] with slight modifications. The test compounds were orally administered 1 h before injection of 0.05 mL of a 1% suspension of carrageenin saline into the subcutaneous tissue of one hind paw. The other hind paw was injected in the same way with 0.05 mL of a saline solution. Rats were fasted 24 h before the experiment and water (1.5 mL per 100 g body weight) was orally administered twice (20 and 4 h) before injections. The volume of both hind paws of control and treated animals was measured with a plethysmograph, 3 h after injection. Rats were kept in the same experimental conditions. The inhibition percentage of the inflammatory reaction was determined for each animal by comparison with controls, and calculated by the formula $I\ (\%) = 100 \times (1 - dt/dc)$, where d$t$ is the difference in paw volume in the drug-treated group and dc the difference in paw volume in the control group.

5.2.2. Acute phorbol ester-induced mouse ear swelling test

Evaluation of mouse ear oedema inhibition was based on the method of Carlson et al. [23] with some modifications. Groups of five male Swiss mice weighing 20–25 g were used. All animals were fasted 24 h before the experiments and maintained in suitable environmental conditions throughout the experiments. Tetradecanoyl phorbol acetate (TPA) was dissolved in aqueous ethanol 80% at a concentration of 250 $\mu g\,mL^{-1}$; 10 μL were applied topically to the anterior and posterior surfaces on the right ear of each mouse. Left ear (control) received the vehicle (10 μL of aqueous ethanol 80%). The studied molecules were orally administered 1 h before TPA application. Ear thickness was measured with a model micrometer gauge (Oditest Kroeplin) 3.5 h after treatment. Ear oedema was calculated by subtracting the thickness of the left ear (vehicle) from the thickness of the right ear (treatment) and was expressed as an increase in ear thickness. The percentage of inhibition of the inflammatory reaction was determined for each animal by comparison with controls.

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