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New *N*-pyridinyl(methyl)-indolalkanamides acting as topical inflammation inhibitors

Alexandra Dassonville,[a] Anne Bretéché,[a] Johan Evano,[a] Muriel Duflos,[a,*] Guillaume le Baut,[a] Nicole Grimaud[b] and Jean-Yves Petit[b]

[a]*Laboratoires de Chimie Organique et de Chimie Thérapeutique, UPRES EA 1155, Faculté de Pharmacie, 1, Rue Gaston Veil, F-44035 Nantes, France*
[b]*Laboratoires de Pharmacologie et de Pharmacocinétique, UPRES EA 1155, Faculté de Pharmacie, 1, Rue Gaston Veil, F-44035 Nantes, France*

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Abstract—The authors have described the synthetic way to new *N*-pyridinyl(methyl)indolylpropanamides acting as non acidic NSAIDs. Pharmacomodulation was carried out at N-1 and C-5 of the indole ring and at the level of the propanamide chain. *N*-(pyridin-3-ylmethyl)-3-[5-chloro-1-(4-chlorobenzyl)-indol-3-yl]propanamide **32** represents one of the most potent compounds evaluated in the TPA-induced mouse ear swelling assay, with a level of activity higher than that of ibuprofen and comparable to that of dexamethasone.

The safe treatment of chronic inflammatory diseases, including rheumatoid arthritis, ulcerative colitis, multiple sclerosis and psoriasis, remains problematic considering today's therapeutical arsenal. We have previously studied *N*-(4,6-dimethyl-pyridin-2-yl)arylcarboxamides acting as nonacidic NSAIDs;[1] it has been determined that these compounds could act upstream from the phospholipasic level through an inhibitory process involving PLA2 activation by protein kinase C via MAP kinase; simultaneous down-regulation of TNF-α production by monocytes apparently originates from the same mechanism. Such compounds could be useful in the treatment of psoriatic lesions since it is clearly established that increased level of prostaglandins and leukotrienes are often found in psoriatic tissues. Moreover, during our investigations in that field, we have also examined *N*-(pyridin-4-yl or picol-3-yl)phthalimides[2] exerting potent inhibition of TNF-α, a pleiotropic pro-inflammatory cytokine that has received a considerable amount of attention as a molecular target notably for the treatment of various inflammatory disorders[3–5] including psoriasis.[6] The discovery that an aminoalkylindole class of compounds,[7] such as WIN-55212 **3** and **4**, act as agonists towards CB2 cannabinoid receptors,[8,9] resulting in a significant reduction of lipopolysaccharide-induced pro-inflammatory cytokine production (TNF-α and IL-1) in mice, prompted us to synthetize *N*-pyridinyl(methyl)indol-2 or 3-ylcarboxamides and indol-3-ylalkylcarboxamides.[10,11] It was demonstrated that incorporation of a propyl chain spacer at C-3 led to more efficient inhibitors; propanamide **1** exerted significant anti-oedema effect in the mouse ear swelling test: ID_{50} (PO) = 41 μmol/kg; but its therapeutic index was quite low (<8). Nevertheless, introduction of a fluorine atom at carbon 5 (leading to **2**) allowed a decrease of the toxic effects. Herein we report the preliminary results on the synthesis and evaluation of the incidence of (i) homocycle and/or N-1 substitution of *N*-pyridinyl(methyl)-3-indolylpropanamides, (ii) creation of an unsaturated amide chain (propenamide) and (iii) modification of the fixation site of the propanamide chain (from C-3 to N-1), such a pharmacomodulation allowing maintenance of activity in the series of indolic NSAIDs: indomethacin and clometacin[12] (Fig. 1).

The synthetic routes used to obtain the target (indol-3-yl)propanamides **1**, **2** and **22**–**33**, (*E*)-3-(indol-3-yl)propenamide **34** and 3-(indol-1-yl)propanamide **38** are

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* Corresponding author. Tel.: +33 2 40 41 11 00; fax: +33 2 40 41 28 76; e-mail: mduflos@sante.univ-nantes.fr

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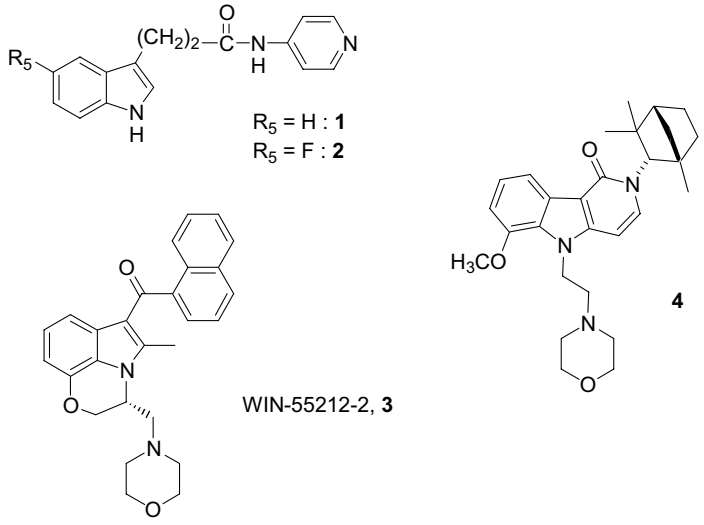
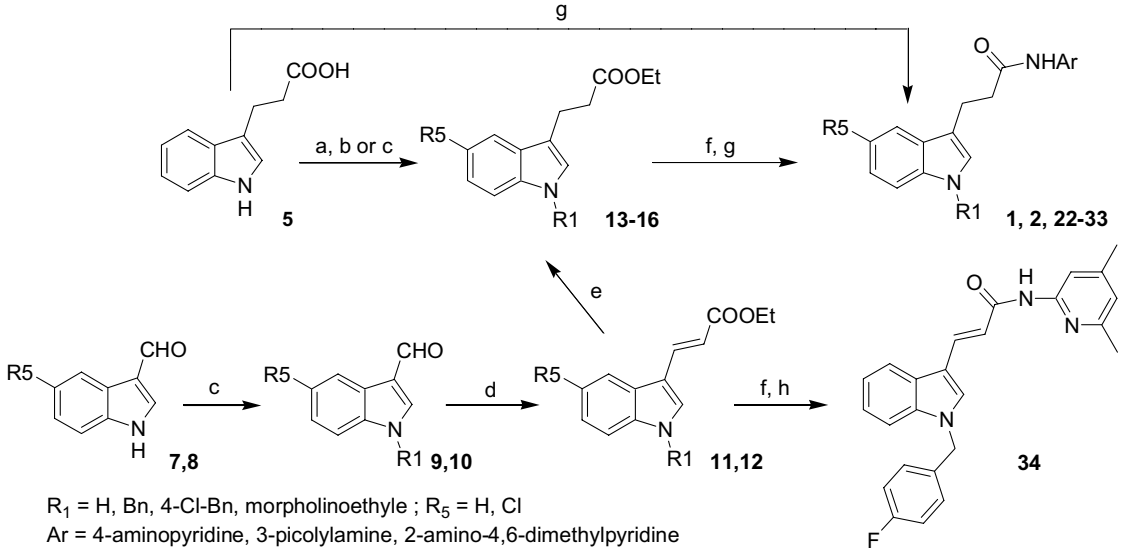
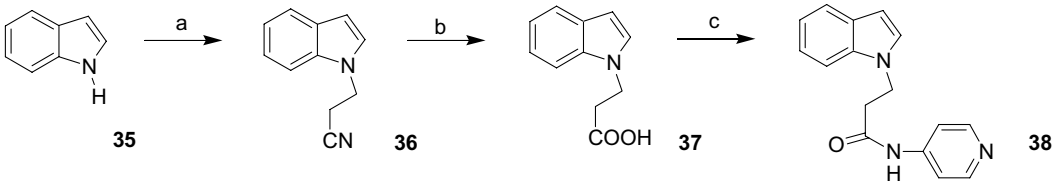


Figure 1. Potential nonacidic NSAIDs.



Scheme 1. Reaction conditions and yields: (a) EtOH, 0.6 M HCl, reflux, 92%; (b) (1) NaH, DMF, (2) R_1Cl, rt, 34–59%; (c) (1) Cs_2CO_3, CH_3CN, reflux, (2) R_1Cl, 72–96%; (d) $(EtO)_2POCH_2CO_2Et$, NaH, THF, rt, 67–85%; (e) H_2, Raney Ni, THF, rt, 99%; (f) (1) 2 M NaOH, EtOH, reflux, (2) 2 M HCl, 32–95%; (g) 2-chloro-1-methylpyridinium iodide, $ArNH_2$, Et_3N, CH_2Cl_2, reflux, 25–78%; (h) (1) $BrCCl_3$, PPh_3, THF, reflux, (2) 2-amino-4,6-dimethylpyridine, 33%.



Scheme 2. Reaction conditions and yields: (a) acrylonitrile, Triton B (40% in MeOH), dioxane, rt, 88%; (b) (1) 10 M KOH, reflux, (2) 10 M HCl, 49%; (c) 2-chloro-1-methylpyridinium iodide, 4-aminopyridine, Et_3N, CH_2Cl_2, reflux, 43%.

outlined in Schemes 1 and 2. (Indol-3-yl)propanoic acid esters are usually obtained by Michael reaction using ethyl acrylate and acetic anhydride[13] or bismuth triflate[14] or via Japp–Klingemann reaction.[15]

The key ethyl 3-(indol-3-yl)propanoates **13**–**16** were prepared according to two methods: (i) esterification of (indol-3-yl)propanoic acid **5** (method a) followed by N-1 substitution of ester **6**, in the presence of the couple

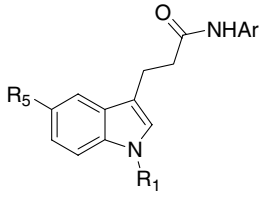
Cs_2CO_3/CH_3CN or NaH/DMF (methods b or c), leading to **13**–**15**, (ii) the same reaction (method c), carried out starting from the (indol-3-yl)carboxaldehydes **7**, **8** afforded the corresponding *N*-benzyl derivatives **9**, **10**, which were transformed into ethyl (*E*)-propenoates **11**, **12**, by Wittig–Horner reaction (method d); their (*E*) configuration was propped by the value of the coupling constant ($^3J = 16.2$ Hz). Catalytic reduction (method e) of ethyl (*E*) 3-[5-chloro-1-(4-chlorobenzyl)-indol-3-yl]propenoate **12** gave the corresponding propanoate **16** in quantitative yield. Amidification of 3-(indol-3-yl)propanoic acid **5** and its substituted congeners **17**–**20**, issued from the alkaline hydrolysis (method f) of **13**–**16**, was performed after activation by an acyloxypyridinium salt (method g), leading to **1**, **2** and **22**–**33**. Likewise, hydrolysis of **11** and activation of the corresponding acid **21**, by the couple $BrCCl_3/PPh_3$ (method h) afforded (*E*)-propenamide **34**.

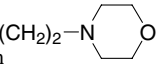
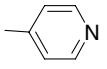
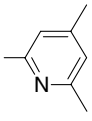
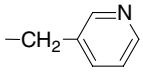
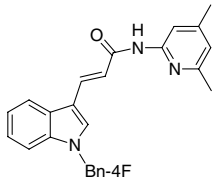
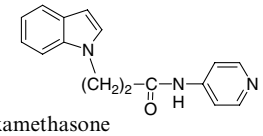
Lastly, alkaline hydrolysis of 3-(indol-1-yl)propionitrile **36**,[16] synthetized by Michael reaction in 88% yield (methods a and b, Scheme 2), gives the corresponding acid **37**,[17] which was transformed into *N*-(pyridin-4-yl)-3-(indol-1-yl)propanamide **38**, in the presence of 2-chloro-1-methylpyridinium iodide (method c, Scheme 2) in a 43% yield.

As psoriatic skin shares many of the pathologic features as phorbol ester-treated mouse skin,[18] the anti-oedematous effect of the target indolylpropanamides **1**, **2**, **22**–**33**, **38** and propenamide **34** was evaluated in a model of topical inflammation, the acute TPA-induced mouse ear swelling test.[19]

After oral administration of 0.1 mmol/kg, all compounds exerted an inhibition percentage >60% (Table 1). No favourable effect was obtained by introduction of a morpholinoethyl chain, present at N-5 of the indolopyridone core of **4**: **22** was less potent than **1**. Among the nine 1-benzyl or 1-(4-chlorobenzyl) derivatives only four (**23**, **29**, **32** and **33**) were more potent than their NH congeners (**1**, **26** and **30**); nevertheless, comparison between the *N*-4-chlorobenzyl derivatives and their previously described *N*-4-fluorobenzyl counterparts[11]

Table 1. Inhibition of the acute TPA-induced mouse ear swelling after oral administration of 3-indolylpropanamides **1**, **22**–**34** and **38**



Compound	R_1	R_5	Ar	Oral administration inhibition % at 0.1 mmol/kg
1	H	H		77 ± 3
22[a]		H		63 ± 1
23	Bn	H		84 ± 3
24	4Cl-Bn	H		72 ± 1
25	4Cl-Bn	Cl		64 ± 2
26	H	H		72 ± 2
27	Bn	H		61 ± 3
28	4Cl-Bn	H		64 ± 2.5
29	4Cl-Bn	Cl		83 ± 2
30	H	H		NA[b]
31	Bn	H		70 ± 1
32	4Cl-Bn	H		92 ± 1
33	4Cl-Bn	Cl		84 ± 1
34				80 ± 2
38				77 ± 0.3
Dexamethasone				82 ± 1.5
Ibuprofen				35 ± 7.5

[a] Tested as dimaleate salt.
[b] Nonactive.

Table 2. Inhibition of the acute TPA-induced mouse ear swelling after topical application of 3-indolylpropanamides

Compound	Topical application inhibition % at $2 \times 100\,\mu g$
1	38 ± 3
23	90 ± 1
26	66 ± 3
29	89 ± 1
32	71 ± 1
33	94 ± 3
34	66 ± 2
Dexamethasone	96 ± 2
Ibuprofen	59 ± 2.5

brought to the fore that the former were regularly more efficacious. *N*-(Pyridin-3-ylmethyl)-3-[5-chloro-1-(4-chlorobenzyl)-indol-3-yl]propanamide **32** constitutes the most potent nonacidic NSAI compound ever discovered in that series; its ID_{50} (24 ± 13 μmol/kg) is comparable with that of oxicam derivatives.[20]

Comparison of the inhibitory activity of (*E*)-propenamide **34** with that of the corresponding propanamide[11] was in favour of the former: 80% at 0.1 mmol/kg and 84% at 0.2 mmol/kg. The level of activity of the *N*-(pyridin-4-yl)propanamide **1** was maintained in **38**, resulting from the migration of the amidic chain from C-3 to N-1: 77% oedema inhibition; moreover, contrary to **1**, no toxic effect was observed at 0.1 mmol/kg. These encouraging results warrant ongoing pharmacomodulation in those two subseries.

The effect of the most active compounds, in the mouse ear thickness reduction assay, was evaluated after topical application of $2 \times 100\,\mu g$/ear (Table 2). Although propanamide **32** exhibited a significant inhibition percentage (71%), it was less efficacious in that test than **23**, **29** and **33**, which exerted an inhibition percentage in the range of 90%.

These preliminary results tend to confirm the favourable incidence of a 4-chlorobenzyl grouping fixed at the indolic nitrogen of the three subseries of 3-(indol-3-yl)propanamides. Their level of activity, comparable with that of dexamethasone, prompts us to investigate their inhibitory effect in the multiple TPA-induced model of chronic inflammation.[21]

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References and notes

1. Vernhet, L.; Petit, J. Y.; Lang, F. *J. Pharmacol. Exp. Ther.* **1997**, *283*, 358–365.
2. Collin, X.; Robert, J. M.; Wielgosz, G.; Le Baut, G.; Bobin-Dubigeon, C.; Grimaud, N.; Petit, J. Y. *Eur. J. Med. Chem.* **2001**, *36*, 639–649.
3. Trembly, B.; Slikker, J. N. Y. *Acad. Sci.* **1995**, *765*, 71–72.
4. Niwayama, S.; Turk, B. E.; Liu, J. O. *J. Med. Chem.* **1996**, *39*, 3044–3045.
5. Schreiber, S.; Nikolaus, S.; Hampe, J.; Homling, J.; Koop, I.; Grossner, B.; Lochs, H.; Raedler, A. *Lancet* **1999**, *353*, 459–461.
6. Schwartz, T.; Lugert, E. In *Pharmacology of the Skin*; Makart, H., Ed.; CRC: Boca Raton, FL, 1992; pp 283–313.
7. D'Ambra, T. E.; Estep, K. G.; Bell, M. R.; Eissenstat, M. A.; Josef, K. A.; Ward, S. J.; Haycock, D. A.; Baizman, E. R.; Casiano, F. M.; Beglin, N. C.; Chippart, S. M.; Grego, J. D.; Kulinig, R. K.; Daley, G. T. *J. Med. Chem.* **1992**, *35*, 124–135.
8. Hynes, J., Jr.; Leftheris, K.; Wu, H.; Pandit, C.; Chen, P.; Norris, D. J.; Chen, B. C.; Zhao, R.; Kiener, P. A.; Chen, X.; Turk, L. A.; Patil-Koota, V.; Gillooly, K. M.; Shuster, D. J.; McIntyre, K. W. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 2399–2402.
9. Wrobleski, S. T.; Hynes, J., Jr.; Lin, S.; Norris, D. J.; Pandit, C.; Spergel, S.; Wu, H.; Tokarski, J. S.; Chen, X.; Kiener, P. A.; Chen, X.; Gillooly, K. M.; Kiener, P. A.; McIntyre, K. W.; Patil-Koota, V.; Shuster, D. J.; Turk, L. A. *J. Med. Chem.* **2003**, *46*, 2110–2116.
10. Breteche, A.; Duflos, M.; Dassonville, A.; Nourrisson, M. R.; Brelet, J.; Le Baut, G.; Grimaud, N.; Petit, J. Y. *J. Enz. Inhib. Med. Chem.* **2002**, *17*, 415–424.
11. Gallard, A.; Duflos, M.; Nourrisson, M. R.; Le Baut, G.; Grimaud, N.; Petit, J. Y. *J. Enz. Inhib. Med. Chem.* **2003**, *18*, 201–208.
12. Allais, A.; Nomine, G. Ger. Patent 1,901,167, 1969; *Chem. Abstr.* **1970**, *72*, 43440x.
13. Cooper, L. C.; Chicchi, C. G.; Dinnell, K.; Elliott, J. M.; Hollingworth, G. J.; Kurtz, M. M.; Locker, K. L.; Morrison, D.; Shaw, D. E.; Tsao, K. L.; Watt, A. P.; Williams, A. R.; Swain, C. *J. Bioorg. Med. Chem. Lett.* **2001**, *11*, 1233–1236.
14. Alam, M. M.; Varala, R.; Adapa, R. *Tetrahedron Lett.* **2003**, *44*, 5115–5119.
15. Phillips, R. R. In *Organic Reactions*; Adams, R., Ed.; John Wiley and sons: New York, 1959; Vol. 10, pp 143–178.
16. Schoepfer, J.; Fretz, H.; Gay, B.; Furet, P.; García-Echeverría, C.; End, N.; Caravatti, G. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 221–226.
17. Hegedus, L. S.; Winton, P. M.; Varaprath, S. *J. Org. Chem.* **1981**, *46*, 2215–2221.
18. Carlson, R. P.; O'Neill-Davis, L.; Chang, J.; Lewis, A. J. *Agents Actions* **1985**, *7*, 197–204.
19. Chang, J.; Blazek, E.; Skowronek, M.; Miranari, L.; Carlson, R. P. *Eur. J. Pharmacol.* **1987**, *142*, 197–205.
20. Zinnes, H.; Sirca, J. C.; Lindo, N.; Schwarz, M.; Fabian, A. C.; Shavel, J.; Kasulanis, C. F.; Genzer, J. D.; Lumanski, C.; Dipasquale, G. *J. Med. Chem.* **1982**, *25*, 12–18.
21. Alfort, J. G.; Stanzey, P. L.; Todderud, G.; Tramposch, K. M. *Agents Actions* **1992**, *37*, 260–267.