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Abstract

This paper describes the synthesis of *N*-pyridinyl(alkyl)phthalimides related to *N*-phenyl-4,5,6,7-tetrafluorophthalimides known to be inhibitors of tumour necrosis factor- α (TNF α) production. Pharmacomodulation at the phthalimidic nitrogen led to the selection of two pharmacophoric fragments (2,4-lutidinyl and β -picolyl), allowing significant inhibition of TNF α production (compounds **12** and **17**). Variation of the substituents linked to the homocycle of their phthalimide scaffold indicated that high (TNF α production) inhibitory potency could be achieved, notably by 5-fluoro, 4- or 5-nitro, 5-amino and especially tetrafluoro substitution. The most active compound, *N*-(pyridin-3-ylmethyl)-4,5,6,7-tetrafluorophthalimide (**32**) (84% inhibition at 10 μ M), also produced an anti-oedematous effect in the PMA-induced mouse-ear swelling test.

Although less active than dexamethasone, it exerted a marked reduction in ear thickness after oral administration (63% vs. 85% for dexamethasone at 0.2 mg kg^{-1}) and remained efficient after topical application (46% vs. 96% for the dexamethasone). It also induced potent inhibition in the rat carrageenan foot oedema test with an ID_{50} (0.14 mg kg^{-1}) comparable with that of *N*-(2,6-diisopropylphenyl)phthalimide (**4**) (0.15 mg kg^{-1}).



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Keywords

N-pyridinylphthalimides; non-acidic NSAIDs; TNF \pm inhibitors; PMA oedema; carrageenan-induced oedema

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