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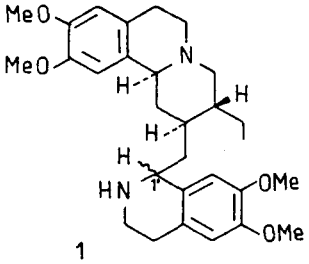
ANTIAMOEBIC ACTIVITY OF INDOLE ANALOGUES OF EMETINE WITH IN-VITRO POTENCY GREATER THAN THAT OF EMETINE

C.W. Wright[1], M.J. O'Neill[2], J.D. Phillipson[1], D.C. Warhurst[3], L. Angenot[4] and J. Quetin-Leclercq[4]. [1]Dept. of Pharmacognosy, The School of Pharmacy, London [2]Glaxo Group Research, Greenford UB6 OHE; [3]Dept. of Medical Parasitology, London School of Hygiene and Tropical Medicine, London WC1E 7HT; [4]Service de pharmacognosie, Institut de Pharmacie, Universite de Liege, Belgium

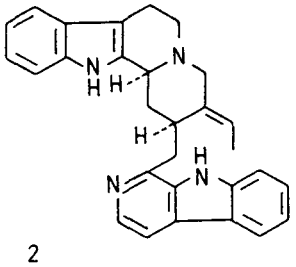
Nitroimidazole drugs such as metronidazole are highly effective in the treatment of acute amoebiasis. However, there is a need for new antiamoebic drugs because tolerance to nitroimidazoles may be poor due to adverse effects and there is the possibility that amoebae may develop resistance. Many attempts have been made to synthesise analogues of emetine (1: C-1'Hβ) with greater activity against Entamoeba histolytica but potency tends to be reduced with increasing divergence of structure (Openshaw et al, 1969).

Using a microplate assay (Wright et al, 1988) we have tested three indole alkaloids isolated from the East African tree Strychnos usambarensis for their activity against E. histolytica in vitro. The IC50 values for usambarensine (2), usambarine (3) and 18,19-dihydrousambarine were determined as 0.49, 0.46 and 0.65 μg mL^{-1} respectively, compared to 1.7 μg mL^{-1} for emetine. In a previous study with 18 emetine-related alkaloids tested in vitro using flat-sided tissue culture tubes, we had concluded that indole analogues of emetine were less amoebicidal than emetine itself (Keene et al 1986). Emetine (1,C-1'Hβ) is able to adopt a planar conformation of the two aromatic rings thus resembling the highly cytotoxic alkaloid cryptopleurine (4) whereas the less active isoemetine (1, C-1'Hα) cannot adopt this conformation. Indole analogues of emetine (2,3) are also not able to adopt planar conformations of their aromatic rings and hence the present results with the three Strychnos alkaloids usambarensine, usambarine and 18,19-dihydrousambarine are unexpected. These findings challenge the previous structure-activity requirements for emetine-related alkaloids as amoebicides (Keene et al 1986). It seems possible that indole analogues of emetine may have a different mode of action to that of emetine itself which is a potent inhibitor of protein synthesis. Further studies of the mode of action of indole analogues of emetine would be worthwhile.



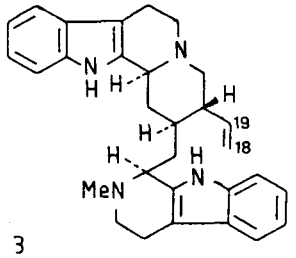
1

emetine, C-1' Hα
isoemetine, C-1' Hβ



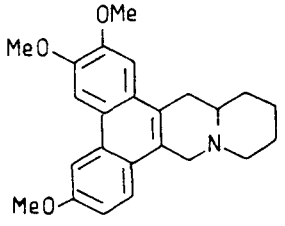
2

usambarensine



3

usambarine



4

crytpopleurine

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Keene et al (1986) Planta Medica: 201-206
Openshaw et al (1969) J. Chem. Soc. C: 101-105
Wright et al (1988) Antimicrob. Ag. Chemother. 32(11): 1725-1729