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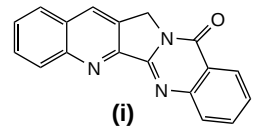
monitor

ANTITUMOR MOLECULES

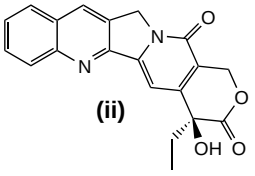
Luotonin A derivatives as novel cytotoxic agents

Luotonin A (**i**), an alkaloid isolated from *Peganum nigellastrum*, is receiving increasing attention as a result of its structural similarity to the cytotoxic alkaloid camptothecin (**ii**; CPT). Although luotonin A is much less active than CPT, it induces the same sequence-selective DNA cleavage by topoisomerase I [1]. As an ongoing element of studies on luotonin A, Dallavalle and collaborators [2] recently reported on the synthesis and biological profile of a series of analogues that were substituted either at ring E (**iiia–iiif**) or ring A (**iva** and **ivb**).

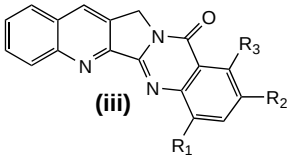
Compounds **iiia–iiif** were prepared by condensation of 3-oxo-1*H*-pyrrolo[3,4-*b*]quinoline with the appropriate anthranilic acid derivative or by microwave reaction with the required isatoic anhydride. All the compounds synthesized were tested for their cytotoxicity against the human non-small lung carcinoma cell line H460, which is particularly sensitive to topoisomerase I inhibition: SN38 was used as the reference compound [3]. It should be noted that compound **iiia** was also recently described by another group [4], but no data on tumor cell lines were given. All the tested compounds were shown to be cytotoxic, with IC_{50} values in the range from 21–172 μM one hour after exposure, which significantly decreased, after a prolonged period of exposure (72 h), to 3.8–45.0 μM [2]. In the same assay, SN38 had an IC_{50} value of 0.21 μM (after one h).



(i)

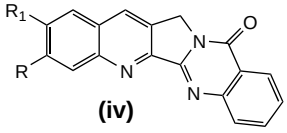


(ii)



(iii)

(a) $R_1 = OCH_3$; $R_2 = R_3 = H$
(b) $R_1 = R_3 = H$; $R_2 = NO_2$
(c) $R_1 = CH_3$; $R_2 = R_3 = H$
(d) $R_1 = R_2 = H$; $R_3 = Cl$
(e) $R_1 = R_3 = H$; $R_2 = Cl$
(f) $R_1 = R_3 = H$; $R_2 = OH$



(iv)

(a) $R = R_1 = OCH_3$
(b) $R = R_1 = -OCH_2O-$

According to Dallavalle and co-workers [2], the low cytotoxic potency of luotonin A derivatives could be the result of a reduced affinity for topoisomerase I or increased reversibility of the complex, although unfavorable pharmacokinetics could also be a factor. In addition, stimulation of the topoisomerase I-mediated cleavage of DNA was studied for several compounds. The results demonstrated that the luotonin A derivatives induce cleavage at the same sites as CPT, but to a lesser extent. Thus, from these data, it can be concluded that the functionalities in ring E of CPT remain, up to now, an unparalleled feature for antitumor activity.

1 Ma, Z.Z. *et al.* (2000) Alkaloids and phenylpropanoids from *Peganum nigellastrum*. *Phytochemistry* 53, 1075–1078
2 Dallavalle, S. *et al.* (2004) Synthesis and cytotoxic activity of substituted Luotonin A derivatives. *Bioorg. Med. Chem. Lett.* 14, 5757–5761
3 Giaccone, G. *et al.* (1992) Multidrug sensitivity phenotype of human lung cancer cells associated with topoisomerase II expression. *Cancer Res.* 52, 1666–1674
4 Cagir, A. *et al.* (2004) Synthesis and biochemical properties of E-ring modified luotonin A derivatives. *Bioorg. Med. Chem. Lett.* 14, 2051–2054

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