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Synthesis of new antitumor anthracyclines: Derivatives bearing a fluorine substitution at position 8 or 10

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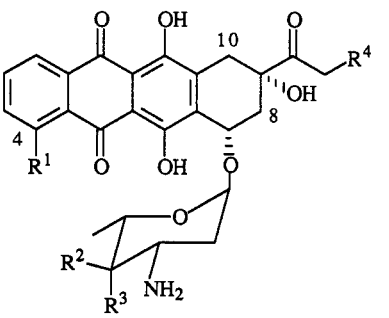
Abstract - Concentration of drug bound to nuclear DNA of cancer cells is clearly associated with the main pharmacological effects of the anthracycline aminoglycosides, the molecular mechanism of antitumor activity being identified with an interference with the topoisomerase II-DNA complex. Both x-ray diffraction analysis and theoretical computations indicate the presence of a stabilizing hydrogen bond between the 9-OH of the anthracyclines and the amino group and N-3 of a guanine residue in the DNA-drug complex. We have therefore synthesized analogs containing a fluorine atom at position 8 or 10 with the aim at obtaining derivatives with higher affinity for the typical anthracycline intercalation sites 5'-(A,T)CG-3' or 5'-(A,T)GC-3' in double stranded DNA.

The anthracyclines showing clinically useful antitumor activity constitute a restricted set of molecules (those of major clinical interest are reported in fig. 1) within a larger class of natural compounds of microbial origin whose study was pioneered in the fifties by H. Brockmann at the University of Göttingen

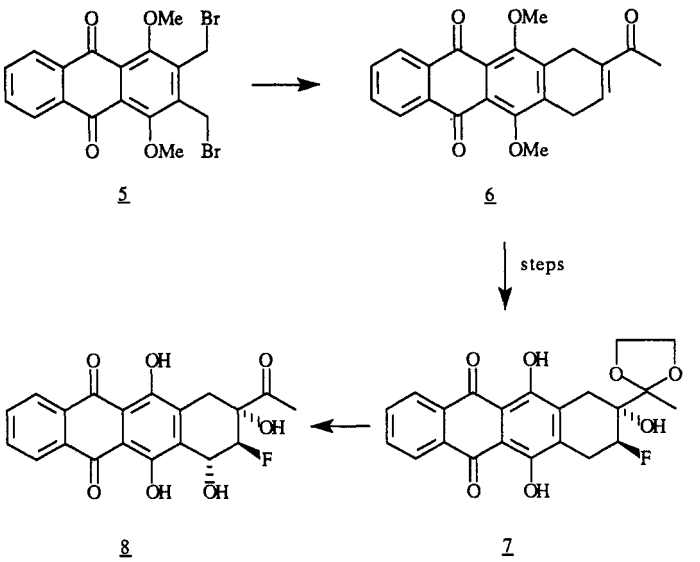


1: R^1 = OMe, R^2 = H, R^3 = R^4 = OH
2: R^1 = OMe, R^2 = R^4 = H, R^3 = OH
3: R^1 = OMe, R^2 = R^4 = OH, R^3 = H
4: R^1 = R^2 = R^4 = H, R^3 = OH

Fig. 1 Anthracylines of major pharmaceutical interest. 1: doxorubicin. 2: daunorubicin. 3: epirubicin. 4: idarubicin

and doxorubicin 1 is the most important member in that selected group. This compound, the discovery and the structure elucidation of which were described in 1969 (ref. 1-2), is still today recognized as the antineoplastic drug showing the broadest spectrum of antitumor activity. However, since its utilization is hampered by serious side effects, by the appearence of resistance phenomena and by the lack of efficacy in important tumor types, including colon and renal cancers, melanoma and chronic leukemia, intense efforts

have been paid over the last 25 years to develop new derivatives endowed with reduced toxicity, and/or improved curative properties (ref. 3-4).



5 6 7 8

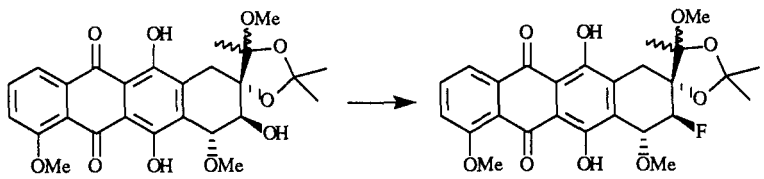
scheme 1

As for the synthetic chemistry approach, more than 2000 doxorubicin analogs are estimated to have been synthesized (ref. 5), but modifications at the ring A of doxorubicin skeleton have never been systematically explored, even though theoretical computation (ref. 6) and x-ray analysis (ref. 7) show that this part of the molecule is an important structural determinant in the interactions of these drugs with DNA , the latter being the accepted anthracycline biological receptor (ref. 8). Particularly, the acyloinic alcohol at position 9 could be strictly involved in the ultimate biological event, probably identified as an interference with topoisomerase II reaction (ref. 9), responsible for the appearence of cytotoxicity and analogs lacking DNA binding functions at that position are not bioactive (ref. 3).

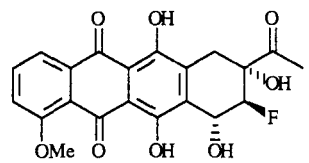
With this considerations in mind, we started a few years ago a program directed to the extensive modification of the ring A in antitumor anthracyclines, and as a part of this program, we decided to synthesize analogs bearing a fluorine substitution at position 8 or 10; in fact it was thought that such a substitution could alter the hydrogen bond forming capability of the C-9 alcoholic function through the modulation of its electronic environement, with minimal changes at the steric bulk of ring A.

The racemic aglycone of 4-demethoxy-8-(S)-fluorodaunorubicin was synthetized (ref. 10), as outlined in scheme 1, following an adaptation of Cava's route to anthracyclinones (ref. 11). α,β-Unsaturated ketone 6 was obtained in 80% yield by trapping the orthoquinodimethane generated *in situ* from 1,4-dimethoxy-2,3-bis(bromomethyl)anthraquinone 5, with an excess of 3-butyn-2-one. The crucial reaction in the multistep conversion of 6 into compound 7 was the regio and stereoselective oxirane ring opening of an intermediate epoxyketone by means of Olah' s reagent (ref. 12). The hydroxylation at position 7 was finally carried out applying the classical radical bromination-solvolysis procedure (ref. 13),

although unexpected problems concerning the reactivity and the regioselectivity of the bromination step resulted in relatively lower yields .



9 10

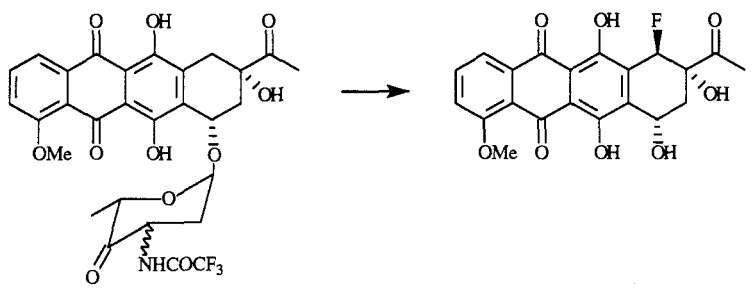


11

scheme 2

The synthesis of 8-(S)-fluorodaunorubicinone 11 was achieved (ref. 14) starting from compound 9 (scheme 2) that, as a mixture of epimers at C-13 (ref. 15), was fluorodehydroxylated (35% yield) with retention of configuration when it was allowed to react with DAST (ref. 16) and the desired optically active aglycone was eventually obtained after trifluoroacetic treatment and subsequent mild basic hydrolysis of the intermediate 7-O-trifluoroacetic ester.

With these two fluorinated aglycones in hand, the glycosidation step was accomplished following Terashima' s procedure (ref. 17) and, in the case of the 4-demethoxy racemic aglycone, the desired N-trifluoroacetylated glycoside was identified on the basis of the CD curve. Additionally, 8-(S) fluorodaunorubicin was converted into 8-(S)-fluorodoxorubicin applying the conditions developed for the synthesis of the parent compound (ref. 18).



12 13

scheme 3

As for 10-(R)-fluoro-4'-epidaunorubicin (scheme 3), compound 13 was obtained as the sole fluorinated product after treatment of compound 12 , epimeric mixture at C-3' (ref. 19), with Olah's reagent at room temperature and was coupled with acosamine.

The new deprotected fluoroaminoglycosides exhibit cytotoxic properties in vitro and antitumor activity in animal models comparable to those shown by compounds 1-4 (ref. 20). Further studies at the preclinical stage are in progress.

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