Pergamon

Bioorganic & Medicinal Chemistry Letters, Vol. 7, No. 23, pp. 2955-2958, 1997

0960-894X/97 $17.00 + 0.00

PII: S0960-894X(97)10122-6

NEW 7-ARYL ANALOGUES OF ANTHRACYCLINES: SYNTHESIS AND CYTOTOXIC ACTIVITY OF (±)-7-(3,4,5-TRIMETHOXYPHENYL)-7-DEOXYIDARUBICINONE

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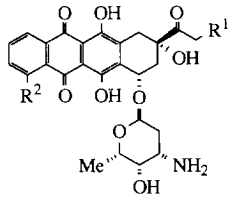
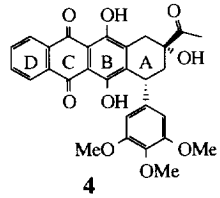
Abstract.- The synthetic methodology for the preparation of 7-aryl-7-deoxyanthracyclinones, a new class of anthracycline analogues, is described. Readily available materials are easily transformed into the key intermediate ketone, that is converted into bent and planar tetracyclic compounds. Cytotoxic studies of the final and intermediate products reveal a moderate activity of bent products and a lack of activity of planar products, thus supporting a non-intercalating mechanism for their cytotoxic activity. © 1997 Elsevier Science Ltd.

The anthracyclines daunorubicin (**1**) and doxorubicin (**2**) are two of the more successful anticancer drugs used worldwide.[1] However their cardiotoxic side effect has prompted the scientific community to develop different analogues to overcome this problem. In fact, a huge number of antitumor anthracycline analogues has been obtained, either isolated from different *Streptomyces* cultures or by synthetic and semisynthetic ways.[2] Among them, idarubicin **3** is a totally synthetic anthracycline used in clinical medicine, which in some aspects shows a better therapeutic index than daunorubicin.

Anthracycline antibiotics act as antineoplastic agents mainly by DNA intercalation and inhibiting topoisomerase. It has been pointed out that the modulation of both mechanisms[3] of action could be used to obtain an improvement of their therapeutic profile. For instance, 3'-morpholino[4] and N-acyl[5] analogues of doxorubicin are respectively topoisomerase I and topoisomerase II targeted-drugs.

1 Daunorubicin: R^1=H, R^2=OMe
2 Doxorubicin: R^1=OH, R^2=OMe
3 Idarubicin: R^1=R^2=H





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Taking the aforesaid facts into account, we have started out a wide research project aimed at the synthesis of the new unnatural 7-aryl-7-deoxyanthracyclinones, that up to our knowledge have not been prepared or isolated so far.

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Initially, we defined the idarubicin analogue **4** as the first target in this new family. The structure **4** shows three interesting features:

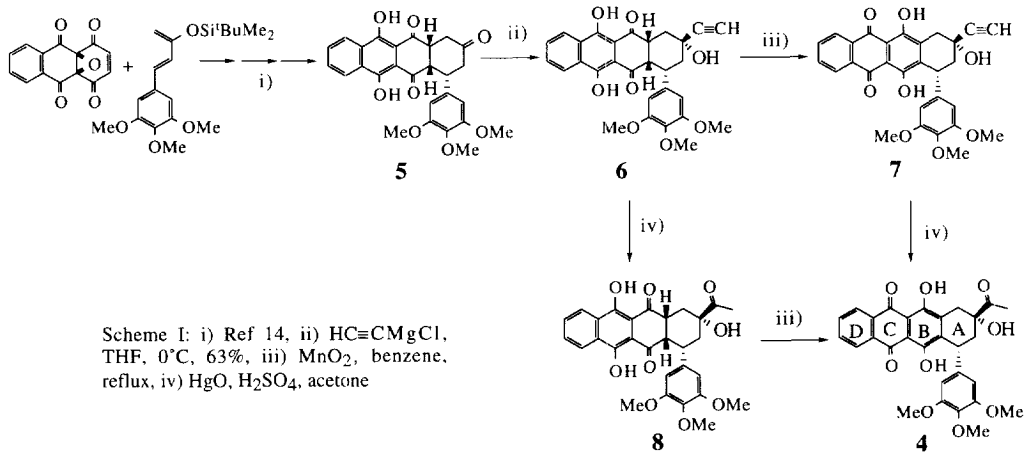
a) A planar BCD ring system, which can act as the DNA intercalating moiety.

b) The acetyl and hydroxy anchoring groups on C-9, which according to X-ray[6] and modelling studies are crucial for the stabilization of the complex with DNA, through H-bonding to base sites in the minor groove.

c) A trimethoxyphenyl unit that is present in a wide variety of cytotoxic drugs, such as the tubuline polymerization inhibitor agents colchicine,[7] podophyllotoxin[8] and synthetic 1069C,[9] the synthetic antifolates trimetrexate[10] and trimethoprim[11] and some alkylating antibiotics such as duocarmycins.[12]

The combination of these structural features offers the possibility of obtaining derivatives that could act as intercalating agents and topoisomerase inhibitors, producing the blockade of the cleavable DNA-topoisomerase complex[13] that is observed for other drugs such as etoposide. In this preliminary paper, we present our first results in this field, including a straightforward synthesis from readily available dienes and the cytotoxic results.

The synthesis has been performed using ketone **5** as starting material, previously synthesized in our laboratory[14] in three steps from 4a,9a-epoxy-4a,9a-dihydroanthracene-1,4,9,10-tetrone and 1-(3,4,5-trimethoxyphenyl)-3-trimethylsiloxy-1,3-butadiene. Ethynylation afforded ethynylalcohol **6**,[15] that by oxidation to **7** and hydration produced final product **4**. The overall yield from starting ketone **5** is 32%. In order to have other intermediates carrying the hydroxy and acetyl units at C-9, although without the planar structure of ring B, the synthesis was also achieved through hydroxyketone **8** that is also transformed into the final product **4** by oxidation. (Scheme I)



Scheme I: i) Ref 14, ii) HC≡CMgCl, THF, 0°C, 63%, iii) MnO_2, benzene, reflux, iv) HgO, H_2SO_4, acetone

Cytotoxic activity

In this preliminary study, the cytotoxic activities of final product 7-(3,4,5-trimethoxyphenyl)-7-deoxyidarubicinone **4** and those of the synthetic intermediates (**5**, **6**, **7** and **8**) were tested against several cell lines, representative of solid tumors and leukemias (Table I).

	P-388	A-549	HT-29	MEL-28
4	>10	>10	>10	>10
5	5	5	5	5
6	0.5	0.5	0.5	0.5
7	>10	>10	>10	>10
8	5	5	5	5

Table 1: Cytotoxic activities for compounds **4**, **5**, **6**, **7** and **8**.(IC_{50} μM inhibition of cell growth[16]). Described values for **2**[17] are IC_{50}= 0.02μM.

As Table I shows, the ethynyl derivative **6** displays a noticeable activity against the assayed tumoral cell lines, while ketone **5** or methyl ketone **8** only displayed a 10% of the activity of compound **6**. Compounds **5**, **6** and **8** are bent structures due to the lack of aromaticity at ring B. On the other hand, compounds **4** and **7**, analogues with planar B-C-D system, showed a complete lack of cytotoxic activity at the assayed concentrations. Molecular modelling[18] of compounds **6** and **4** showing the most stable conformations are represented in figure 1.

Figure 1: Low energy conformation of anthracycline analogues **6** and **4**.

From these results, a non-intercalative mode of action can be suggested, although molecular modelling of anthracycline analogue **4** with a six base pair DNA,[19] showed that the molecule can intercalate into DNA with a small modification of the anthracycline-DNA complex geometry, to accommodate the trimethoxyphenyl moiety in the minor groove. Either the inhibition of topoisomerases or a redox mechanism could be the explanation by which these structures act as cytotoxic agents.

The decrease of activity from the ethynyl derivative **6** to the acetyl derivative **8** is another significant feature, as the latter moiety is present in daunorubicin and idarubicin playing a stabilizing role at the complex. This fact also supports a non intercalating mode of action for these compounds.

The study of new compounds with planar and bent B-C-D ring systems by modification of the 7-aryl or 9-hydroxy-9-acetyl moieties will give more information about their influence in the activity. In this way, we are currently preparing new derivatives with other aryl residues in position 7, in order to improve their cytotoxicity and selectivity.

Acknowledgements: Financial support came from Junta de Castilla y León (SA 18/95) and DGICYT (SAF 95-1566). H.S. thanks the University of Salamanca a predoctoral fellowship position. We wish to thank to Ministerio de Educación y Ciencia and British Council for funding the Cooperative Projects Spain/UK (HB 93-078, HB 94-034). Molecular modelling by R. Peláez-Lamamié de Clairac and J. L. López is gratefully acknowledged.

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(*Received in Belgium* 22 *August* 1997; *accepted* 17 *October* 1997)