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DESIGN AND SYNTHESIS OF 3,5-DIALKYLAMINO SUBSTITUTED 8*H*,10*H*-3(*R*),5(*R*),15b(*S*)-2,3,6,7-TETRAHYDRO-1,5,3-DIOXAZEPINO[3,2-*c*]INDOLO[3,2-*g*]PTERIDINE-7-ONES

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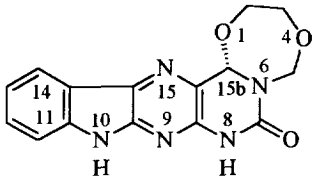
Abstract: 3,5-Dialkylamino substituted 8*H*,10*H*,15b(*S*)-2,3,6,7-tetrahydro-1,5,3-dioxazepino[3,2-*c*]indolo[3,2-*g*]pteridine-7-one derivatives **6a-6e** were synthesized as potential anticancer agents. Preliminary results showed that they were active as inhibitors of the growth of murine leukemia L1210 cells in vitro with IC_{50} -values of 4 to 24 μM.

Introduction

DNA intercalating agents are an important class of anticancer drugs used widely in the clinic. Representative members of this class are the antibiotic doxorubicin, the alkaloid ellipticine, and the synthetic drug mitoxantrone. Recently, we synthesized a series of compounds that contain a new heterocyclic system, 8*H*,10*H*,15b(*S*)-2,3,6,7-tetrahydro-1,5,3-dioxazepino[3,2-*c*]indolo[3,2-*g*]pteridine-7-one (TDIP, **1**) as a novel class of potential DNA intercalators. Preliminary evaluation of the 16,17-dihydroxy-3,5-ethano derivatives (**2**) as inhibitors of the growth of murine leukemia L1210 cells in vitro suggested that the integrity of the pentacyclic skeleton of **1** is essential for cytotoxicity,[1] and that modifications in the indole moiety at position 13 has a minor effect on the activity.



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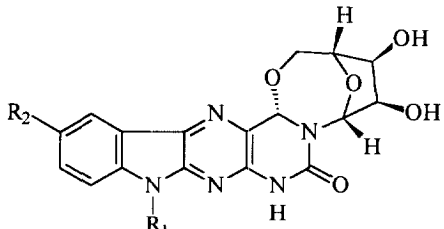


2

We now report the synthesis and evaluation of TDIP derivatives **6a-6e**, which contain alkylamino side chains on the dioxazepine ring (Scheme 1). The apparent structural similarity of the indolopteridine moiety of TDIP to the tetracyclic ellipticine prompted us to explore modifications of TDIP based in part on reported structure-activity studies of ellipticines.[2]

As DNA intercalators, ellipticine and its derivatives exhibit their cytotoxic activities by a multimodal mechanism.[3] For structure-activity relationship studies, many ellipticine derivatives and analogues including modification at positions 1, 2, 9, and modification of the pyridocarbazole skeleton have been synthesized.[4] In addition to the remarkable success of the 9-hydroxy substitution,[5] the most significant modification of the ellipticines was the introduction of a basic chain. This led to the development of datelliptium acetate[6] (**3**) with favorable solubility characteristics. However, alkylation of *N*2 generated a quaternary ammonium ion, which generally decreases biological activity. Therefore, latter designs moved the basic side chain to position 1 resulting in increased antitumor activity.[7] The most active compounds of this class[7] are pazelliptine (**4**) and reteliptine (**5**).

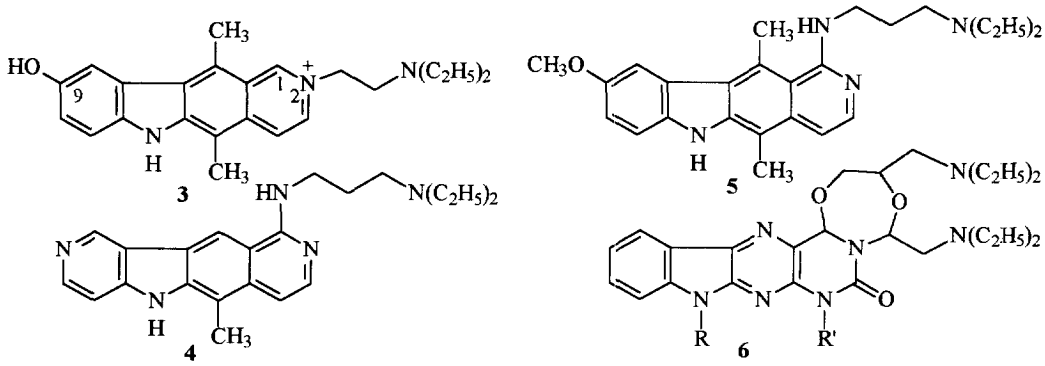


Figure 1. Structural Similarities between Target Compounds **6** and the Ellipticine Derivatives **3**, **4**, and **5**.

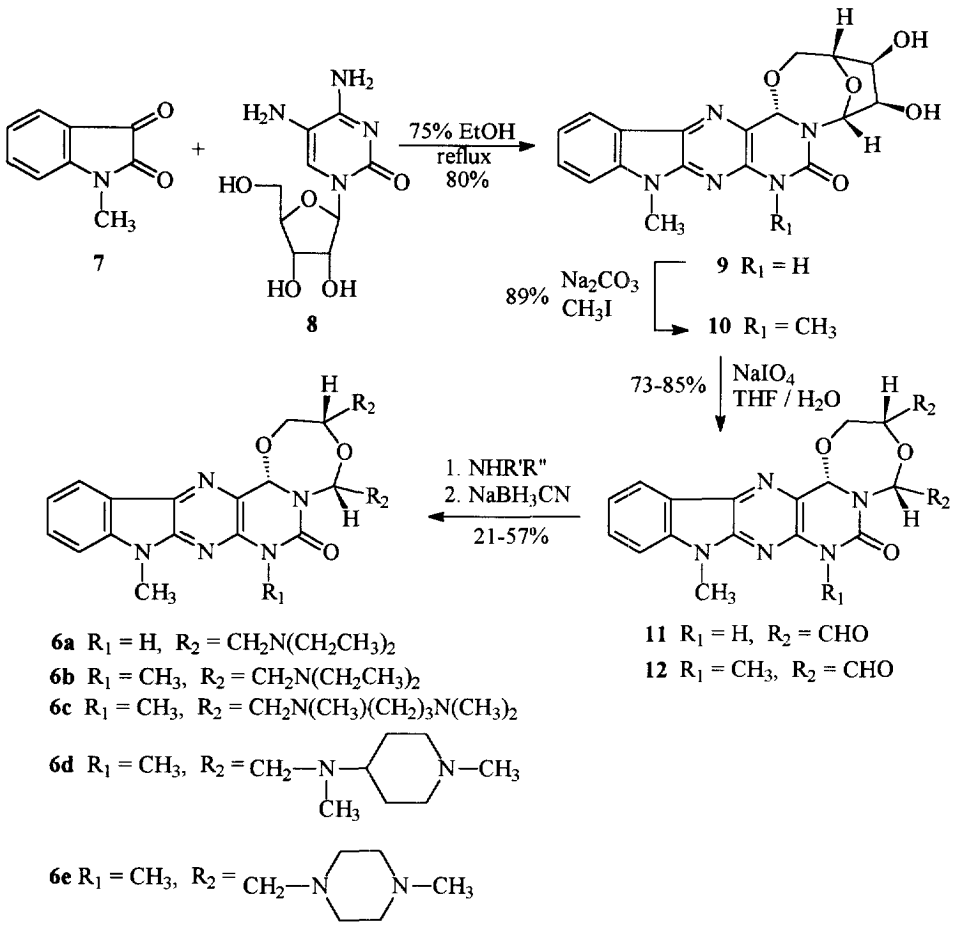
Integration of some of the structural features of **3**, **4**, and **5** into the TDIP heterocycle resulted in the synthesis of target compounds **6** (Figure 1). The basic side chains correspond to those at position 1 and 2 in the ellipticines. A two- or three-carbon unit[8] was placed between two heteroatoms (**6a-6e**, Scheme **1**) to promote electrostatic interactions with the negatively charged phosphate groups of DNA and to stabilize the intercalation complex. Such complexes may interfere with the activity of DNA topoisomerase II resulting in DNA cleavage.[9]

Results and Discussion

The TDIP heterocycle **9** was constructed by the condensation of *N*-methyl isatin (**7**) with 5-aminocytidine (**8**)[10] with the indicated stereochemistry[1] at 15b. Oxidative cleavage of **9** by using $NaIO_4$ gave dialdehyde **11**, followed by reductive amination to give **6a** (Scheme 1). Dialdehyde **12** was similarly obtained by methylation of **9**, followed by oxidative cleavage of **10**. Reductive amination of **12** yielded target compounds **6b-6e**.

Preliminary evaluation of TDIP derivatives **6a-6e** as inhibitors of the growth of murine leukemia L1210 cells

Scheme 1.



6a R_1 = H, R_2 = $CH_2N(CH_2CH_3)_2$
6b R_1 = CH_3, R_2 = $CH_2N(CH_2CH_3)_2$
6c R_1 = CH_3, R_2 = $CH_2N(CH_3)(CH_2)_3N(CH_3)_2$

6d R_1 = CH_3, R_2 =

6e R_1 = CH_3, R_2 =

in vitro showed that they were moderately active with IC_{50} values from 4 to 24 μM (Table 1). The activity varied

Table 1. Growth inhibition of murine leukemia L1210 cells by **6a-6e** in vitro.[11]

Compound	IC_{50} (μM)
6a	17
6b	6
6c	24
6d	4
6e	20
ellipticine	0.5

depending on the type of side chain. A longer, dibasic side chain did not enhance the activity in agreement with the results obtained with ellipticines.[4] Methylation of N-8 resulted in a three-fold increase in activity, which may be due to the effect of the exchange of H to CH_3 on cellular uptake or binding to the target, or is related to the fact that substitution of position 8 precludes the opening of the seven-membered ring at 15b by 1-4 elimination.

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