Selective anticancer activity of β-lactams derived from polyaromatic compound

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Abstract. Currently available anticancer drugs are cytotoxic to normal as well as to neoplastic cells, therefore the synthesis of β-lactams as new and novel anticancer agents is extremely significant. We previously developed synthetic methods for the preparation of β-lactams and anticancer agents resulting from polyaromatic amines. There have also been reports on the synthesis and biological evaluation of novel racemic β-lactams as anticancer agents. In cell cycle analysis, these compounds demonstrated a G2 blockage against sensitive tumor cell lines. In the present study, useful and selective biological activities of chrysene β-lactams are described.

Introduction

The synthesis of β-lactams as new and novel anticancer agents is extremely significant and timely since currently available anticancer drugs are cytotoxic to normal as well as to neoplastic cells (1). We have engaged in the development of synthetic methods for the preparation of β-lactams (2-4) and anticancer agents derived from polyaromatic amines (5). The synthesis and biological evaluation of novel racemic β-lactams as anticancer agents has also been reported (6). These compounds have demonstrated a G2 blockade in cell cycle analysis against sensitive tumor cell lines (7,8). In the present study, useful and selective biological activities of chrysene β-lactams are described.

Materials and methods

β-lactams and the MTT assay.

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Results

Three racemic β-lactams, 1, 2a and 2b, were prepared following the Staudinger reaction with the corresponding imines (Fig. 1).

It is known that the reaction of acyloxy, alkoxy and nitrogen-containing acid chloride with diaryl imines produces cis-β-lactams (9). However, in the present study we identified trans-β-lactams with chrysene as their only products (1, 2a and 2b).

In vitro cytotoxicity of β-lactams. The racemic β-lactams 1, 2a and 2b were tested using several human cancer cell lines, with cisplatin as the control (Table I).

Discussion

The cell growth inhibition data (IC_{50}) suggests that the racemic β-lactam 1 demonstrates reasonable anticancer activity against many human tumor lines, while the activity of the other compounds, 2a and 2b, is not promising. The results are of great interest, as all three β-lactams have N-chrysene system and trans stereochemistry at the ring junction. However, structurally they are different. For example, 1 has a single β-lactam ring, while 2a and 2b have two β-lactam rings. In contrast to the activities of 1, it is notable that 2a has two acetoxy groups, but remains inactive. Phenoxy compound 2b is also inactive. These results indicate that the presence of an acetoxy group in chrysene trans β-lactam is important and obligatory. Nevertheless, the presence of two such groups can destroy the activity completely. The presence of two phenoxy groups has no positive effects on the anticancer activity of any of the cancer cell lines describe above. The results described herein are unique and warrant further research on anticancer β-lactams with chrysene and other polyaromatic compounds.

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Table I. *In vitro* cytotoxicity of β-lactams on human cancer cell lines (μM).

Compounds	MDA-231	BRO	PC-3	SKOV-3	HL-60	K-562	HT-29
Cisplatin	12.33	7.66	4.66	5.99	1.66	2.33	16.99
(±)-1	11.98	15.70	16.32	3.90	3.64	4.33	5.66
(±)-2a	<20	<20	<20	<20	<20	<20	<20
(±)-2b	<20	<20	<20	<20	<20	<20	<20

In vitro cytotoxicity assays were performed at the Pharmacology and Analytic Core Laboratory of the University of Texas M.D. Anderson Cancer Center, Houston. An MTT assay was carried out using the seven human cancer cell lines.

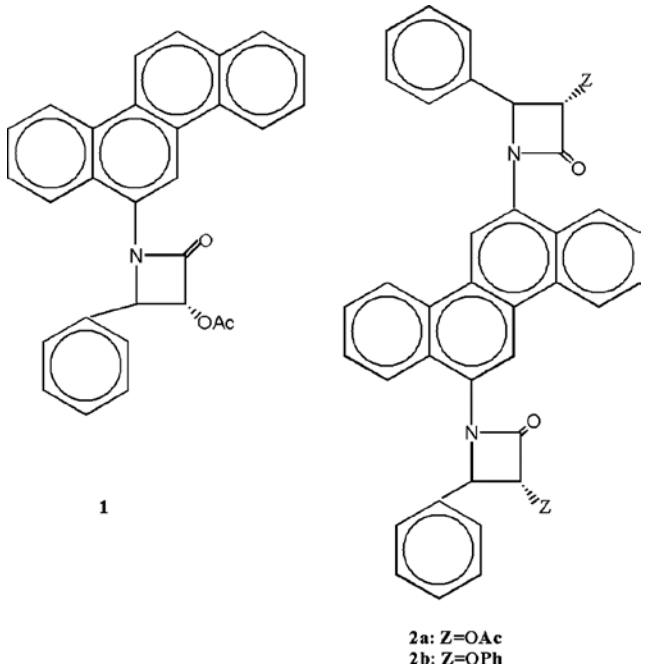

Figure 1. β-lactams derived from chrysene.

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