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Synthesis and biological activity of new arenediyne-linked isoxazolidines

Roberto Romeo [a,*], Michele Navarra [a], Salvatore V. Giofrè [a,*], Caterina Carnovale [a], Santa Cirmi [a], Giuseppe Lanza [b], Maria A. Chiacchio [b]

[a] Dipartimento di Scienze del farmaco e dei prodotti per la salute, University of Messina, Via SS Annunziata, 98168 Messina, Italy
[b] Dipartimento di Scienze del Farmaco, University of Catania, Viale Andrea Doria 6, 95125 Catania, Italy

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ABSTRACT

Arenediyne–isoxazolidine conjugates have been synthesized as a new scaffold for the development of bioactive mimics. Some of the synthesized compounds are endowed with antiproliferative activity against three human cancer cell lines. Their thermal reactivity suggests that the biological activity probably could not be linked to the Bergman cyclization.

1. Introduction

Since the initial reports of the enediyne anticancer antibiotics in the late 1980s,[1] an ever increasing attention has been addressed to the chemistry, biology and potential medicinal applications of this class of compounds.[2] The antitumor activity of these substrates is linked to the presence of a highly unsaturated hex-1-ene-1,5-diyne system, which undergoes Bergman cyclization (BC)[3] and generates a benzene-1,4-diradical, able to abstract H-atoms from the DNA backbone, thus causing cell death. BC is a thermal rearrangement of (*Z*)-hex-3-ene-1,5-diynes to benzene-1,5-diyls which, after quenching by H-atom donors, afford new benzene rings.[4]

Due to their highly interesting biological properties, the design of new low molecular weight enediynes, with good and multiple DNA-binding features, within a structurally well defined architecture, constitutes a research area of present interest. Thus, enediynes containing either DNA intercalating groups or DNA minor groove binding functions have been synthesized: all these derivatives are potent DNA-damaging agents due to their ability to generate benzenoid diradicals.

Apart their role in anticancer drug development, enediynes exhibit a wide spectrum of biological features, such as antibacterial,[5] protein degradation,[6] topoisomerase inhibiting activities.[7]

Recently, several new acyclic enediynes have been reported that do not undergo the Bergman or Myers cyclization under physiological conditions, but which still display interesting cancer cell cytotoxicity.[8] Some possible mechanisms have been proposed: the most probable pathway to induce the death of cancer cells is the inhibition of physiological enzymes, especially the topological enzymes, although other targets such as MAPK pathway or the arrest or G2/M cell cycle have also been proposed.[9]

The isoxazolidine framework has successfully been applied as surrogate for a riboside ring in the synthesis of nucleoside analogs with anticancer or antiviral activity.[10] In this context, we reasoned that arenediyne–isoxazolidine conjugates might provide a new scaffold for the development of bioactive mimics. Thus, the main focus of this paper is to design a new group of arenediynes and to verify whether this new hybrid agents induce antiproliferative effect, leading to cell growth perturbation.

The obtained results showed that some of the synthesized compounds are endowed with antiproliferative activity against three human cancer cell lines: the neuroblastoma SH-SY5Y, the HT-29 colon rectal adenocarcinoma and the HepG2 hepatocelluar carcinoma cells. Thermal reactivity shows that their biological activity probably could not be linked to the Bergman cyclization, that is, the formation of active biradical intermediates.

* Corresponding authors. Tel.: +39 090 356230; fax: +39 090 6766474 (R.R.); tel.: +39 090 6766566; fax: +39 090 6766474 (S.V.G.).
E-mail addresses: robromeo@unime.it (R. Romeo), sgiofre@unime.it (S.V. Giofrè).

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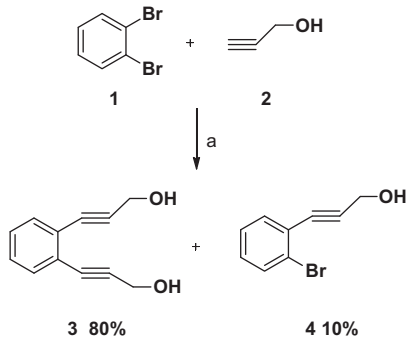


Scheme 1. Synthetic route to compounds **3** and **4**. Reagents and conditions: (a) $Pd(PPh_3)_4$, *n*-$BuNH_2$, reflux, 20 h.

2. Results and discussion

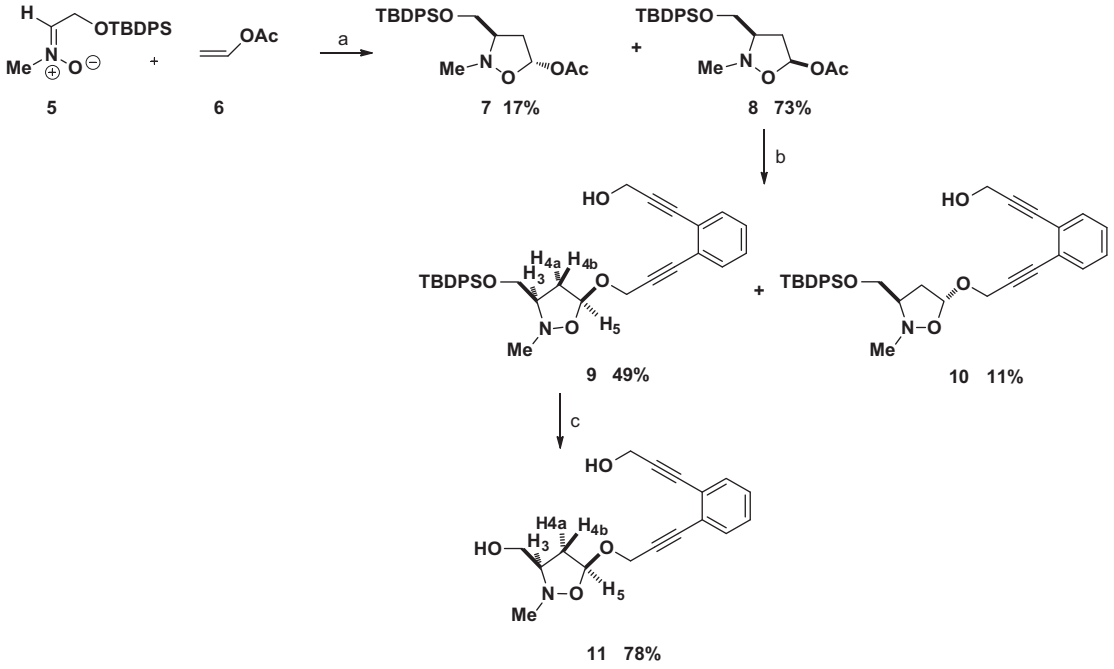
2.1. Chemistry

The synthetic approach towards acyclic arenediyne-linked isoxazolidines **9**–**11** involves the coupling of the arenediyne unit, the 1,2-bis(1-hydroxyprop-2-ynyl)benzene **3**,[11] with the isoxazolidine systems **7** and **8**.

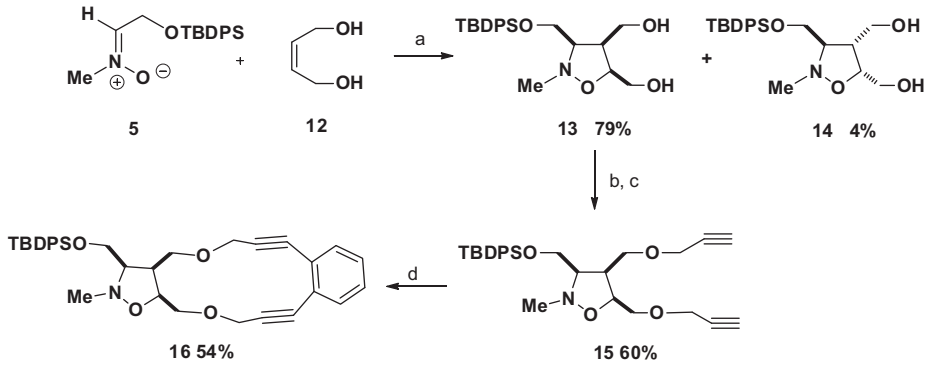
The arenediyne partner for the coupling reaction, the compound **3**, was prepared by a Pd(0)-catalyzed Sonogashira coupling[12] of 1,2-dibromobenzene **1** and propargyl alcohol **2** (1:3 ratio).

The coupling reaction, carried out in the absence of CuI to reduce the oxidative dimerization of the acetylenic alcohol, led to the formation of a 8:1 mixture of products **3** and **4**, respectively (global yield 90%) (Scheme 1).[13]

The isoxazolidines **7** and **8** were obtained via the 1,3-dipolar cycloaddition of C-[(*tert*-butyldiphenylsilyl)oxy]-N-methyl-nitrone **5**[14] and vinyl acetate **6** in anhydrous ether at room temperature. The reaction proceeded with a good stereoselectivity, affording a



Scheme 2. Synthetic route to compounds **9**–**11**. Reagents and conditions: (a) Nitrone **5** (10 mmol),vinyl acetate (20 mL), ether (20 mL), 48 h, rt; (b) **3**, $BF_3(OEt)_2$, CH_2Cl_2, rt, 14 h; (c) TBAF, THF, rt, 16 h.



Scheme 3. Synthetic route to compound **16**. Reagents and conditions: (a) THF, 72 h, reflux; (b) NaH, THF, 0 °C, 20 m, 2 h, rt; (c) propargyl bromide, THF, 16 h; (d) 1,2-dibromobenzene, $Pd(PPh_3)_4$, DMF, NEt_3, 60 °C, 4 h.

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