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CHEMICAL SYNTHESIS, DNA CLEAVAGE AND ANTITUMOR ACTIVITY OF MOLECULES WITH (Z)-7-SULFONYL-3-HEXENE-1,5-DIYNE FUNCTIONALITIES

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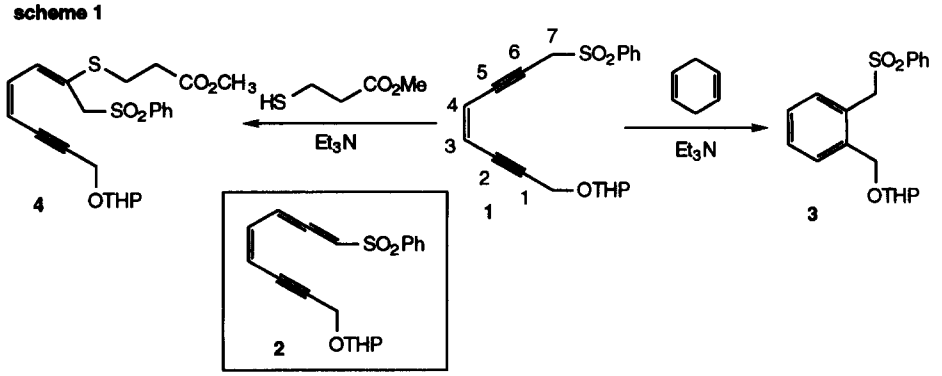
Abstract: Compounds **20a-d, 21a, 21d** and **22** were synthesized from the corresponding (Z)-1,2-dichloroethylene, 1,2-diiodobenzene and 2,3-naphthylene bistriflate respectively and exhibited DNA cleaving properties at 37 °C in pH 8.0 as well as potent cytotoxicity against human carcinoma cells with no additive.

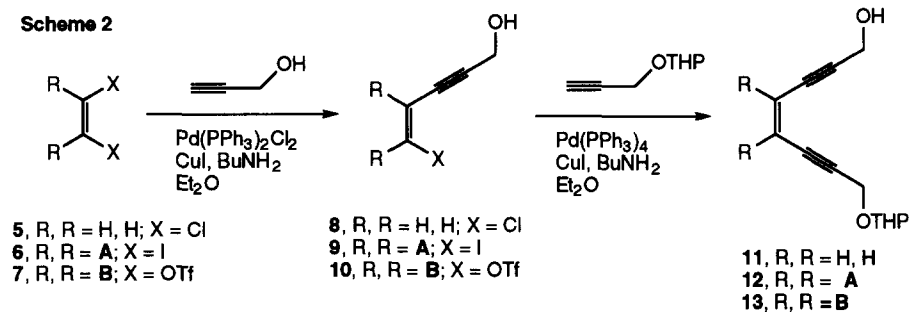
The DNA cleaving properties and antitumor activities of enediyne antitumor antibiotics[1] have attracted much interests to design and synthesis of new DNA-cleaving enediynes. Among these studies, Myers reported that molecules with (Z)-allene-ene-yne undergo mild thermal reaction to form the α,3-didehydrotoluene biradical.[2] Based on the Myers cyclization, various allen-ene-yne containing molecules have been synthesized and tested to exist DNA cleaving properties.[3] However, some of designed molecules are not stable and cyclized spontaneously to aromatic systems.[3b-d] In order to search for a new stable enediyne which would have the value to molecular biology and medicine, we developed a new class of enediyne containing (Z)-7-sulfonyl-3-hexen-1,5-diyne functionalities such as compound **1**.[4] Compound **1** proceeded base-catalyzed conversion to (Z)-eneyne-allene-sulfone **2** and subsequent Myers cyclization to form aromatic products **3** or 1,4-addition reaction with a nucleophile to **4** (scheme 1). Herein, we report the synthesis, DNA cleavage and antitumor activities of these new series compounds.

scheme 1



Compounds **20a-d, 21a, 21d** and **22** were synthesized according to the reported synthetic procedures[4] starting from (Z)-1,2-dichloroethylene, 1,2-diiodobenzene and 2,3-naphthylene bistriflate respectively[5] as shown in scheme 2. The key operations involved (a) palladium catalyzed couplings with propargyl alcohol and subsequent with tetrahydropyrane protected propargyl alcohol; (b) conversion of the alcohols to aryl sulfides; (c) oxidation of sulfides to sulfones with meta-chloroperbenzoic acid (mCPBA); and (d) finally, removal of tetrahydropyrane protection. Compounds **20a-d, 21a, 21d** and **22** were stable for isolation and storage in freezer for three months without significant decomposition.

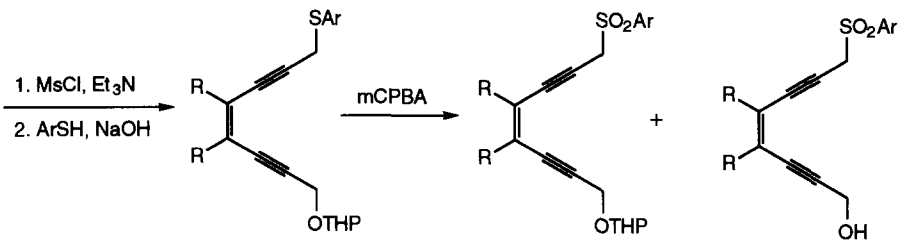
Scheme 2



5, R, R = H, H; X = Cl
6, R, R = **A**; X = I
7, R, R = **B**; X = OTf

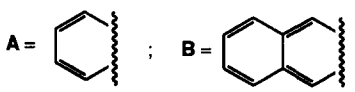
8, R, R = H, H; X = Cl
9, R, R = **A**; X = I
10, R, R = **B**; X = OTf

11, R, R = H, H
12, R, R = **A**
13, R, R = **B**



14a-d, 15a, 15d,16 **17a-d, 18a, 18d,19** **20a-d, 21a, 21d, 22**

14a, **17a**, **20a**. R, R = H, H; Ar = phenyl
14b, **17b**, **20b**. R, R = H, H; Ar = p-$CH_3OC_6H_4$
14c, **17c**, **20c**. R, R = H, H; Ar = o-$CH_3O_2CC_6H_4$
14d, **17d**, **20d**. R, R = H, H; Ar = 2-naphtyl
15a, **18a**, **21a**. R, R = **A**; Ar = phenyl
15d, **18d**, **21d**. R, R = **A**; Ar = 2-naphthyl
16, **19**, **22**. R, R = **B**; Ar = phenyl



Compounds **20a-d, 21a, 21d** and **22** cleaved double-stranded DNA in alkaline solution. Thus incubation of compounds **20a-d, 21a, 21d** and **22** with supercoiled ΦX 174 DNA (form I) aerobically at pH 8.0 and 37 °C for 14 h produced DNA rupture, leading to form II as shown in Figure 1. The potencies were increased by the introduction of an aromatic ring at C(3) and C(4) (compounds **21a**, **21b** and **22**).

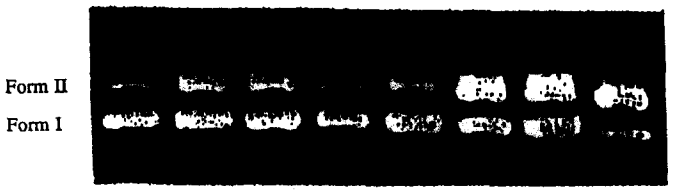


Figure 1. DNA cleavage patterns on 1% agarose (ethidium bromide stain) of ΦX 174 (RF1) DNA (100 μM per base pair) incubated at 37 °C, 14 h at pH 8.0, 50 mM Tris-HCl, and the following additions. Lane 1. DNA plasmid as received; Lane 2. 50 μM **20a**; Lane 3. 50 μM **20b**; Lane 4. 50 μM **20c**; Lane 5. 50 μM **20d**; Land 6. 50 μM **21a**; Lane 7. 50 μM **21b**; Lane 8. 50 μM **22**.

Compounds **20a-d, 21a, 21d** and **22** were evaluated *in vitro* against four human tumor cell lines (colo 205, Hep G2, SK-BR-3, KB and Molt-4). For each compound, dose-response curves for each cell line were measured with five different drug concentration and the concentration causing 50% cell growth inhibition (IC_{50}) compared with the control was calculated.[6] The results were summarized in Table 1. Most of them demonstrated marginal activity against the growth of leukemia (Molt-4), colon (colo 205), epidermoid (Hep G2, KB) and melanoma (SK-BR-3) cancer cell lines. Particularly, compounds **21a, 21b** and **22** bearing with aromatic ring at C(3) and C(4) proved to be active against these cancer cell lines. Their sulfide analogs **14a-d, 15a, 15d** and **16** proved to be inactive against these cancer cell lines.

Table 1. Inhibition of *in vitro* Human Tumor Cell[a] Growth by **20a-d, 21a, 21d** and **22** (IC_{50}, μg/ml)[b]

compound	Hep G2	Colo 205	SK-BR-3	KB	Molt-4
20a	---	+	+	+	
20b	---	+	+	+	
20c	---	+	+	+	
20d	---	+	+	+	
21a	+	++	++	++	++
21d	++[c]				
22	+	+	+		++

[a]Cell type: Hep G2, larynx epidermoid cell line; Colo 205, colon cell line; SK-BR-3, melanoma cell line; KB, oral epidermoid cell line; Molt-4, leukemia cell line. [b]Relative potency of growth inhibition of cancer cell line was graded by concentration required for 50% inhibition: ++ (IC_{50}: <4 μg/ml), + (IC_{50}: 4-10 μg/ml), --- (IC_{50}: >10 μg/ml). [c]Data from Graduate Institute of Medicine, Kaohsiung Medical College.

The DNA cleaving properties and potent cytotoxicity against human carcinoma cell of compounds **20a-d**, **21a**, **21d** and **22** suggest the possibility for the development of new anticancer therapeutical agents. The synthesis of more potent anticancer drugs based on this new class of enediyne system is currently under investigation.

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