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PATENT HIGHLIGHT

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New Synthetic Enediynes and Their Conjugates May Provide Effective Treatment for Cancer

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Title:	Enediyne Compounds, Conjugates Thereof, and Uses and Methods Therefor		
Patent Application Number:	WO 2013/122823 A1	**Publication date:**	22 August 2013
Priority Application:	US 61/598,143	**Priority date:**	13 February 2012
	US 61/653,785		31 May 2012
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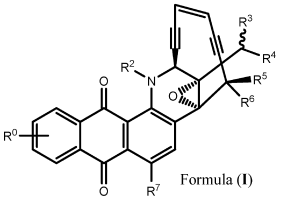
Assignee Company:	Bristol-Myers Squibb Company; Route 206 and Province Line Road, Princeton, New Jersey 08543−4000, USA		
Disease Area:	cancer	**Biological Target:**	DNA of cancerous tumor cells

Summary: The invention in this patent application relates to synthetic enediyne compounds based on the natural enediyne uncialamycin scaffold, which are represented generally by formula (I). These compounds, used as such or in conjugates, are potent cytotoxins that may be useful as chemotherapeutic drugs for the treatment of cancer.

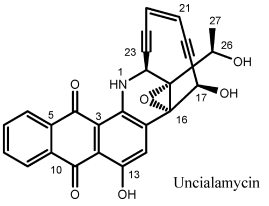
Enediynes are a class of antibiotic natural products characterized by either 9- or 10-membered rings containing two C−C triple bonds separated by a Z−C−C double bond. Enediynes are capable of undergoing Bergman cyclization to form 1,4-benzenoid diradicals, which abstract hydrogen atoms from other molecules. When the diradical is generated near DNA, it abstracts hydrogen atoms from the sugar backbone of the DNA molecule, which results in single and double strand lesions. This high reactivity against DNA makes enediynes very toxic. However, their potent activity may be beneficial if used to target the DNA of cancerous tumors specifically. Most endiynes have shown potent activity against the proliferation of various cancer cells including those with resistance to other chemotherapeutic drugs, and several of the naturally occurring ones have entered clinical trials against cancer. Uncialamycin (structure below) is a natural enediyne in which both epimers at C26 are active against several ovarian tumor cell lines with IC_{50} values ranging from 9×10^{-12} to 1×10^{-10}, depending on the epimer and cell line or subline. The synthetic endiynes described in this patent application are derivatives of uncialamycin.

The use of such highly toxic molecules demanded very specific delivery systems. Conjugates are innovative drug-delivery systems designed to precisely target tumor cells and minimize the risk of systemic toxicity. Typically, drugs are covalently linked to conjugates that act as targeting moieties, which specifically or preferentially bind to a chemical entity characteristic of the cancer cell. The covalent linker is designed to only be cleaved by a factor prevalent inside a cancer cell but not in plasma so that the drug remains in an inactive form until released from the conjugate. Typical targeting moiety may be a polymer or an antibody. Polymer-conjugated and antibody-linked enediyne drugs (such as SMANCS and Mylotarg) have been used successfully to deliver enediyne drugs to cancer cells.

Important Compound Classes:



Formula (**I**)

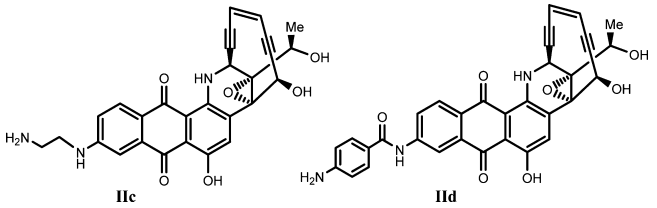


Uncialamycin

Conjugates: Compounds of formula (I) may be conjugated to a targeting moiety through a chemical bond to the group R^0.

Received: September 14, 2013
Published: September 20, 2013

Key Structures: Structures **IIc** and **IId** are examples of the reported compounds of formula (I)



Biological Assay: Antiproliferative activity against cancer cell lines

Biological Data: The biological activities of several compounds were tested, some representative EC_{50} data for compounds **IIc** and **IId** are shown in the table:

Antiproliferative Activity Against 786-O Cells			Antiproliferative Activity Against H226 Cells		
Compound	IIc	IId	Compound	IIc	IId
EC_{50} (nM)	1.275	0.05803	EC_{50} (nM)	0.9859	0.8729

Several assays were also conducted on a number of conjugates derived from other compounds of formula (I).

Claims: Claims 1−4: Composition of matter; variations of formula (I)

Claims 5−9: Composition of matter; compounds with conjugates

Claims 10−13: Method of treating cancer

Claims 14−15: Pharmaceutical compositions

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1. Shao, R.-G. *Curr. Mol. Pharmacol.* **2008**, *1*, 50−60.

2. Hamann, P. R. *Expert Opin. Ther. Pat.* **2005**, *15* (9), 1087−1103.

3. Jones, G. B.; Fouad, F. S. *Curr. Pharm. Des.* **2002**, *8* (27), 2415−2440.

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Notes

The authors declare no competing financial interest.