Nogawa et al. from the same source, which were tested against human carcinoma of the nasopharyx (KB), human leukaemia (HL-60), murine leukaemia (MH60), pancreas adenocarcinoma (BXPC3), breast adenocarcinoma (MCF7), CNS glioblastoma (SF268), lung NSC (NCIH460), colon carcinoma (KM20L2), and prostate cancer (DU145) cell lines (J. Nat. Prod. 2001, 64, 1148-1152).

Ye et al. prepared novel bufadienolide compounds from bufalin by microbial hydroxylation. The compounds were tested against human hepatoma Bel-7402, human gastric cancer BGC-823, human cervical carcinoma HeLa, and human leukaemia HL-60 cell lines, showing some of them potent cytotoxicities comparable to that of bufalin (J. Steroid. Biochem. Mol. Biol. 2004, 91, 87-98; J. Nat. Prod. 2005, 68, 626-628).

Since cancer is a leading cause of death in animals and humans, several efforts have been and are still being undertaken in order to obtain an anticancer therapy active and safe to be administered to patients suffering from a cancer. The problem to be solved by the present invention is to provide compounds that are useful in the treatment of cancer.

SUMMARY

Disclosed are compounds of general formula **I** or pharmaceutically acceptable salts, prodrugs or stereoisomers thereof

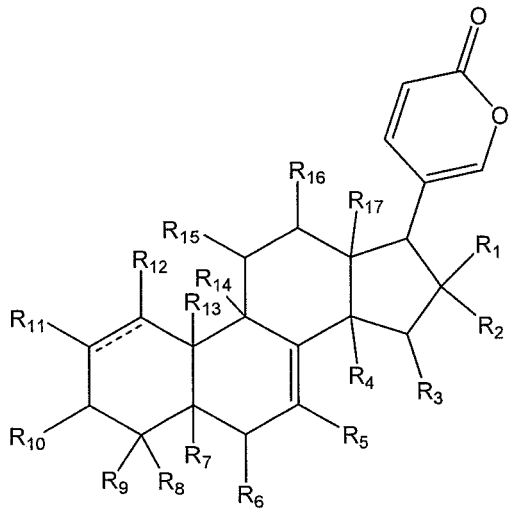
R_{13} is selected from hydrogen, COR_a, substituted or unsubstituted C_1-C_{12} alkyl, substituted or unsubstituted C_2-C_{12} alkenyl, and substituted or unsubstituted C_2-C_{12} alkynyl;

each R_a is independently selected from hydrogen, substituted or unsubstituted C_1-C_{12} alkyl, substituted or unsubstituted C_2-C_{12} alkenyl, substituted or unsubstituted C_2-C_{12} alkynyl, substituted or unsubstituted aryl, and substituted or unsubstituted heterocyclic group;

each R_b is independently selected from hydrogen, substituted or unsubstituted C_1-C_{12} alkyl, substituted or unsubstituted C_2-C_{12} alkenyl, substituted or unsubstituted C_2-C_{12} alkynyl, substituted or unsubstituted aryl, substituted or unsubstituted heterocyclic group, and substituted or unsubstituted sugar; and

the ------- line represents an additional bond, an epoxy group, or is absent.

In one aspect, there is provided a compound of general formula **I**



(I)

wherein

R_1 is selected from hydrogen and halogen;

R_2 is halogen;

each R_3, R_{15}, and R_{16} is independently selected from hydrogen, OR_a, $OCOR_a$, $OCOOR_a$, and =O, with the proviso that when a =O group exists the hydrogen of the C atom to which the =O is attached is absent;

each R_4, R_5, R_6, R_7, R_{11}, R_{12}, and R_{14} is independently selected from hydrogen, OR_a, $OCOR_a$, and $OCOOR_a$;

each R_8, R_9, and R_{17} is independently selected from hydrogen, OR_a, $OCOR_a$, $OCOOR_a$, substituted or unsubstituted C_1-C_{12} alkyl, substituted or unsubstituted C_2-C_{12} alkenyl, and substituted or unsubstituted C_2-C_{12} alkynyl;

R_{10} is selected from hydrogen, OR_b, $OCOR_a$, $OCOOR_a$, and =O, with the proviso that when a =O group exists the hydrogen of the C atom to which the =O is attached is absent;

R_{13} is selected from hydrogen, COR_a, substituted or unsubstituted C_1-C_{12} alkyl, substituted or unsubstituted C_2-C_{12} alkenyl, and substituted or unsubstituted C_2-C_{12} alkynyl;

each R_a is independently selected from hydrogen, substituted or unsubstituted C_1-C_{12} alkyl, substituted or unsubstituted C_2-C_{12} alkenyl, substituted or unsubstituted C_2-C_{12} alkynyl, substituted or unsubstituted aryl, and substituted or unsubstituted heterocyclic group;

each R_b is independently selected from hydrogen, substituted or unsubstituted C_1-C_{12} alkyl, substituted or unsubstituted C_2-C_{12} alkenyl, substituted or unsubstituted C_2-C_{12} alkynyl, substituted or unsubstituted aryl, substituted or unsubstituted heterocyclic group, and substituted or unsubstituted sugar; and

the ------- line represents an additional bond, an epoxy group, or is absent;

or a pharmaceutically acceptable salt or stereoisomer thereof.

Disclosed is a compound of formula **I**, or a pharmaceutically acceptable salt, prodrug or stereoisomer thereof, for use as a medicament, in particular as a medicament for treating cancer.

In another aspect, there is provided a compound as described herein, or a pharmaceutically acceptable salt or stereoisomer thereof, for use as a medicament.

Disclosed is the use of a compound of formula **I**, or a pharmaceutically acceptable salt, prodrug or stereoisomer thereof, in the treatment of cancer, or in the preparation of a medicament, preferably for the treatment of cancer. Other embodiments of the disclosure are methods of treatment, and compounds for use in these methods. Therefore, the present disclosure

further provides a method of treating any mammal, notably a human, affected by cancer which comprises administering to the affected individual a therapeutically effective amount of a compound as defined above.

Disclosed is a compound of formula **I**, or a pharmaceutically acceptable salt, prodrug or stereoisomer thereof, for use as an anticancer agent.

In another aspect, there is provided use of a compound as described herein, or a pharmaceutically acceptable salt or stereoisomer thereof, in the preparation of a medicament for the treatment of cancer.

Disclosed are pharmaceutical compositions comprising a compound of formula **I**, or a pharmaceutically acceptable salt, prodrug or stereoisomer thereof, together with a pharmaceutically acceptable carrier or diluent.

In another aspect, there is provided a pharmaceutical composition comprising a compound as described herein, or a pharmaceutically acceptable salt or stereoisomer thereof, and a pharmaceutically acceptable carrier or diluent.

DETAILED DESCRIPTION OF THE INVENTION

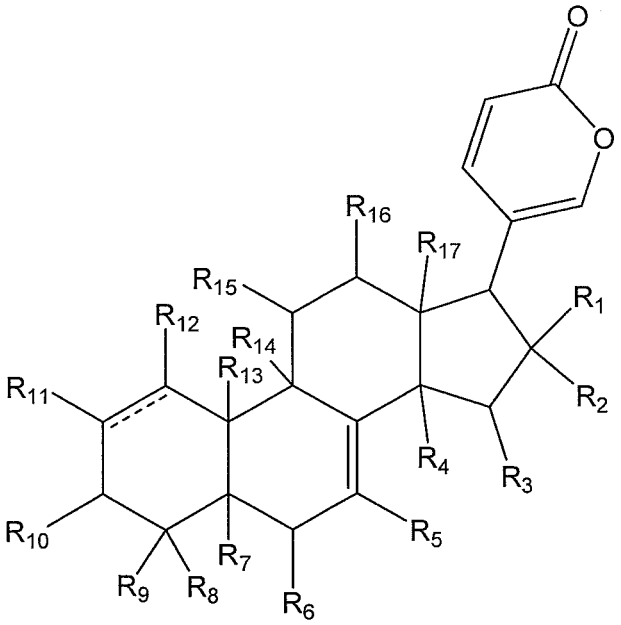
The present invention relates to compounds of general formula **I** as defined above.

In these compounds the groups can be selected in accordance with the following guidance:

Alkyl groups may be branched or unbranched, and preferably have from 1 to about 12 carbon atoms. One more preferred class of alkyl groups has from 1 to about 6 carbon atoms. Even more preferred are alkyl groups having 1, 2, 3 or 4 carbon atoms. Methyl, ethyl, n-propyl, isopropyl and butyl, including n-butyl, *tert*-butyl, *sec*-butyl and isobutyl are particularly preferred alkyl groups in the compounds of the present invention. As used herein, the term alkyl, unless otherwise stated, refers to both cyclic and noncyclic groups, although cyclic groups will comprise at least three carbon ring members.

CLAIMS

1. A compound of general formula **I**



(I)

wherein

R_1 is selected from hydrogen and halogen;

R_2 is halogen;

each R_3, R_{15}, and R_{16} is independently selected from hydrogen, OR_a, $OCOR_a$, $OCOOR_a$, and =O, with the proviso that when a =O group exists the hydrogen of the C atom to which the =O is attached is absent;

each R_4, R_5, R_6, R_7, R_{11}, R_{12}, and R_{14} is independently selected from hydrogen, OR_a, $OCOR_a$, and $OCOOR_a$;

each R_8, R_9, and R_{17} is independently selected from hydrogen, OR_a, $OCOR_a$, $OCOOR_a$, substituted or unsubstituted C_1-C_{12} alkyl, substituted or unsubstituted C_2-C_{12} alkenyl, and substituted or unsubstituted C_2-C_{12} alkynyl;

R_{10} is selected from hydrogen, OR_b, $OCOR_a$, $OCOOR_a$, and =O, with the proviso that when a =O group exists the hydrogen of the C atom to which the =O is attached is absent;

R_{13} is selected from hydrogen, COR_a, substituted or unsubstituted C_1-C_{12} alkyl, substituted or unsubstituted C_2-C_{12} alkenyl, and substituted or unsubstituted C_2-C_{12} alkynyl;

each R_a is independently selected from hydrogen, substituted or unsubstituted C_1-C_{12} alkyl, substituted or unsubstituted C_2-C_{12} alkenyl, substituted or unsubstituted C_2-C_{12} alkynyl, substituted or unsubstituted aryl, and substituted or unsubstituted heterocyclic group;

each R_b is independently selected from hydrogen, substituted or unsubstituted C_1-C_{12} alkyl, substituted or unsubstituted C_2-C_{12} alkenyl, substituted or unsubstituted C_2-C_{12} alkynyl, substituted or unsubstituted aryl, substituted or unsubstituted heterocyclic group, and substituted or unsubstituted sugar; and

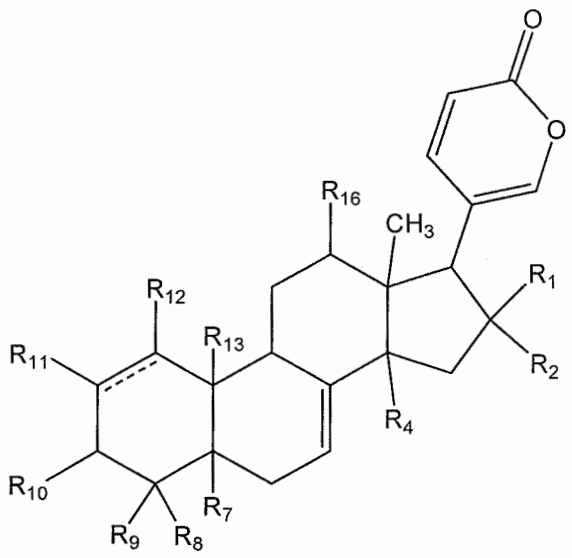
the ------- line represents an additional bond, an epoxy group, or is absent;

or a pharmaceutically acceptable salt or stereoisomer thereof.

2. A compound according to claim 1, wherein R_3, R_5, R_6, R_{14}, and R_{15} are each independently selected from hydrogen, OR_a, and $OCOR_a$, and wherein R_a is selected from hydrogen and substituted or unsubstituted C_1-C_6 alkyl.

3. A compound according to any preceding claim, wherein R_{17} is a substituted or unsubstituted C_1-C_6 alkyl.

4. A compound according to claim 1, having the following formula **II**



(II)

wherein R_1, R_2, R_4, R_7, R_8-R_{13}, R_{16}, and the ------- line are as defined in claim 1, or a pharmaceutically acceptable salt or stereoisomer thereof.

5. A compound according to any preceding claim, wherein R_1 is selected from hydrogen and Cl; and wherein R_2 is Cl.

6. A compound according to any preceding claim, wherein R_4 is selected from hydrogen and OR_a, and wherein R_a is selected from hydrogen and substituted or unsubstituted C_1-C_6 alkyl.

7. A compound according to any preceding claim, wherein R_7 is selected from hydrogen, OR_a, and $OCOR_a$, and wherein R_a is selected from hydrogen and substituted or unsubstituted C_1-C_6 alkyl.

8. A compound according to any preceding claim, wherein R_8 and R_9 are each independently selected from hydrogen, substituted or unsubstituted C_1-C_{12} alkyl, OR_a, and $OCOR_a$, and wherein R_a is selected from hydrogen and substituted or unsubstituted C_1-C_6 alkyl.

9. A compound according to any preceding claim, wherein R_{10} is selected from OR_b, $OCOR_a$, and =O, and wherein R_a is selected from hydrogen and substituted or unsubstituted C_1-C_6 alkyl and R_b is selected from hydrogen, substituted or unsubstituted C_1-C_6 alkyl, monosaccharide, disaccharide, and trisaccharide, with the proviso that when R_{10} is =O the hydrogen of the C atom to which R_{10} is attached is absent.

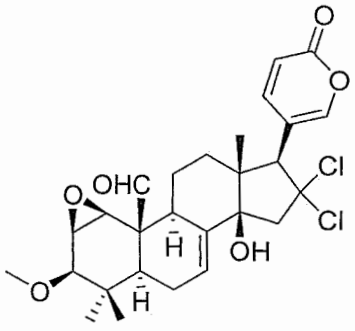
10. A compound according to any preceding claim, wherein R_{13} is selected from hydrogen, substituted or unsubstituted C_1-C_{12} alkyl, and COR_a, and wherein R_a is selected from hydrogen and substituted or unsubstituted C_1-C_6 alkyl.

11. A compound according to any preceding claim, wherein R_{16} is selected from hydrogen, OR_a, and $OCOR_a$, and wherein R_a is selected from hydrogen and substituted or unsubstituted C_1-C_6 alkyl.

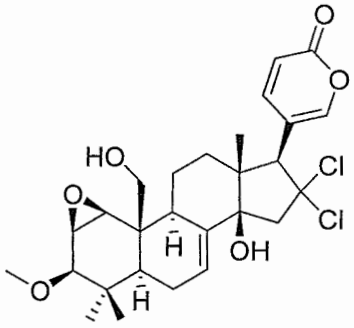
12. A compound according to any preceding claim, wherein the ------- line is absent, R_{11} and R_{12} are each independently selected from hydrogen, OR_a, and $OCOR_a$, and R_a is selected from hydrogen and substituted or unsubstituted C_1-C_6 alkyl.

13. A compound according to any of claims 1 to 11, wherein the ------- line represents an additional bond or an epoxy group, and R_{11} and R_{12} are hydrogen.

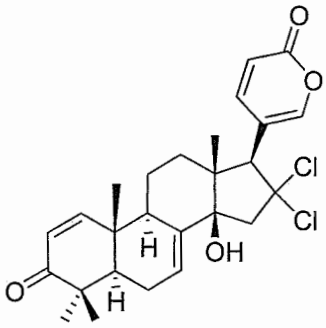
14. A compound according to claim 1, having the following structure:



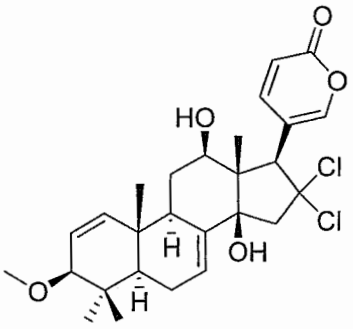
Aegomycin A,



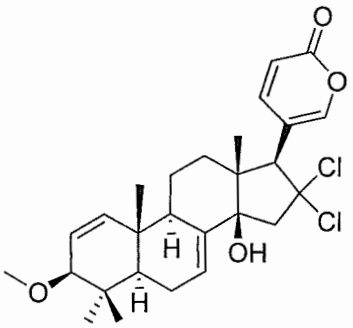
Aegomycin B,



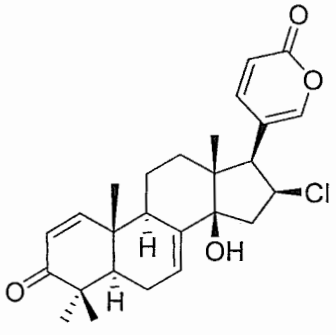
Aegomycin C,



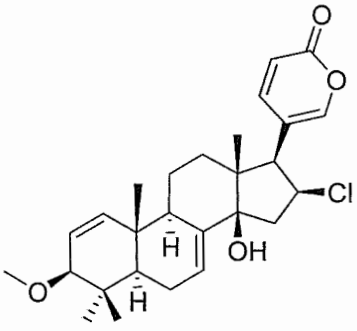
Aegomycin D,



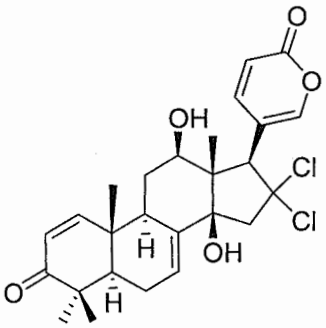
Aegomycin E,



Aegomycin F,



Aegomycin G, or



Aegomycin H;

or a pharmaceutically acceptable salt thereof.

15. A pharmaceutical composition comprising a compound according to any preceding claim, or a pharmaceutically acceptable salt or stereoisomer thereof, and a pharmaceutically acceptable carrier or diluent.

16. A compound according to any of claims 1 to 14, or a pharmaceutically acceptable salt or stereoisomer thereof, for use as a medicament.

17. Use of a compound according to any of claims 1 to 14, or a pharmaceutically acceptable salt or stereoisomer thereof, in the preparation of a medicament for the treatment of cancer.