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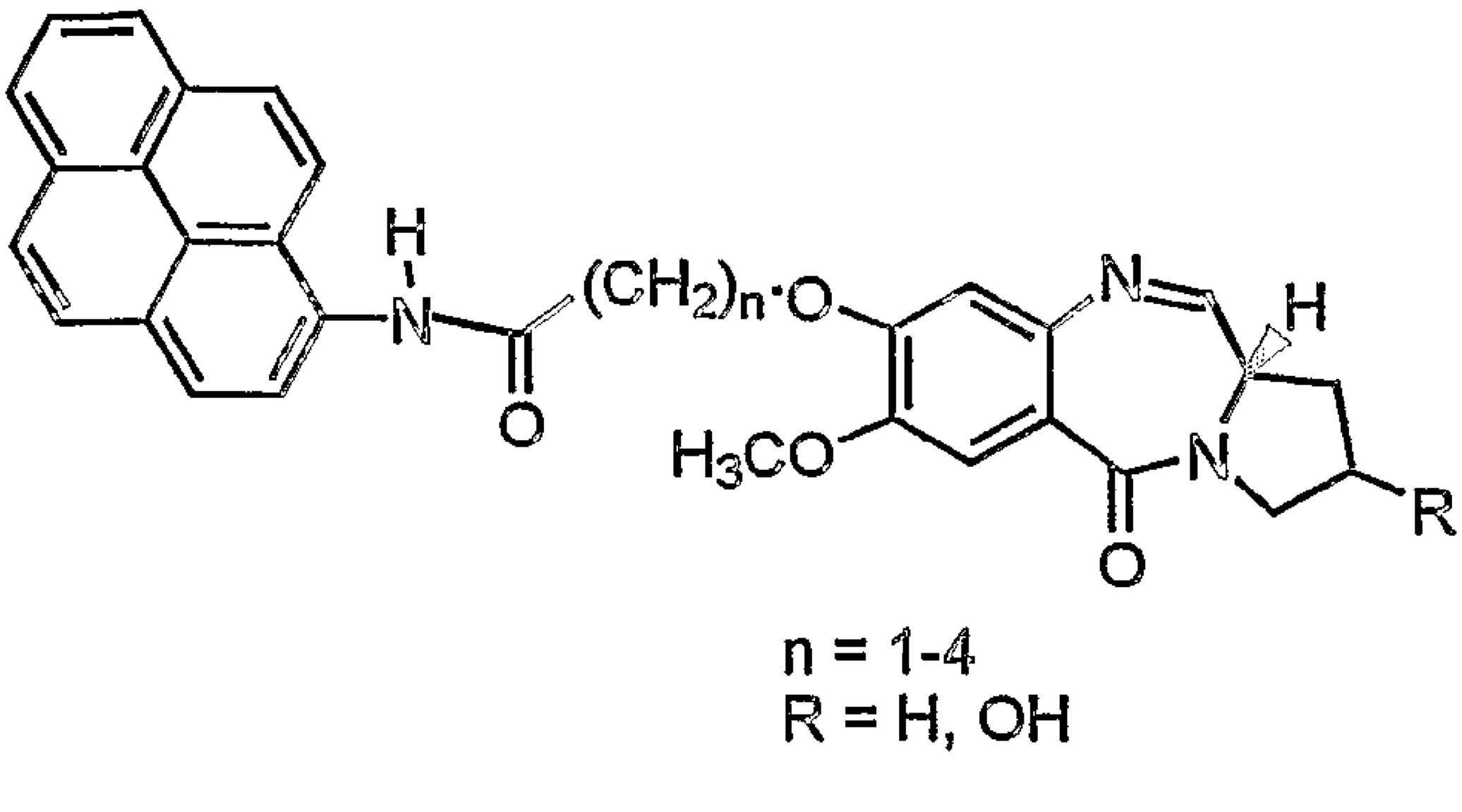
(54) Titre : DERIVES DE PYRROLO (2,1-C) (1,4) BENZODIAZEPINE LIES AU PYRENE UTILES EN TANT QU'AGENTS ANTICANCEREUX

(54) Title: PYRENE-LINKED PYRROLO (2,1-C) (1,4) BENZODIAZEPINE DERIVATIVES USEFUL AS ANTICANCER AGENTS



n = 1-4
R = H, OH

FORMULA V

(57) Abrégé/Abstract:
The present invention relates to pyrrolo [2,1-c][1,4]benzodiazepine hybrids useful as potential antitumour agents. This invention also relates to a process for the preparation of new pyrrolo[2,1-c][1,4]benzodiazepine hybrids as potential antitumour agents. More particularly, it provides 7-methoxy-8-[N-(1''-pyrenyl)-alkane-3'-carboxamide]-oxy-(11aS)-1,2,3,11a-tetraydro 5H-pyrrolo[2,1-c][1,4]benzodiazepin-5-one, with aliphatic chain length variation of these compounds and it also describes the DNA binding, anticancer (antitumour) activity. The structural formula of this novel pyrrolo[2,1-c][1,4]benzodiazepine is given below, formula (I):

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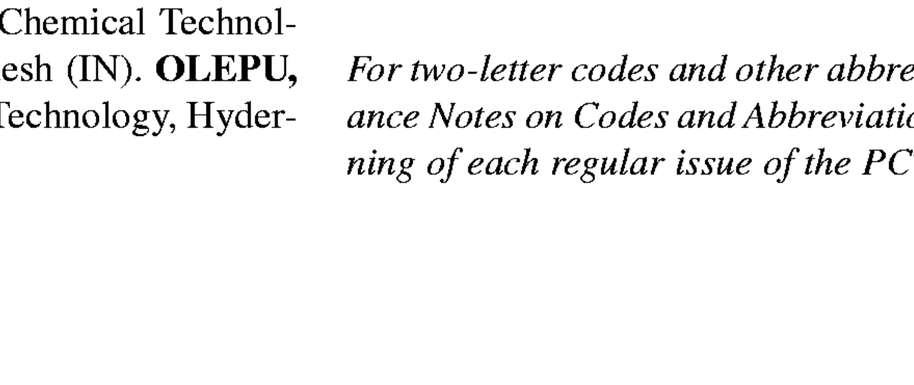
(54) Title: PYRENE-LINKED PYRROLO (2,1-C) (1,4) BENZODIAZEPINE DERIVATIVES USEFUL AS ANTICANCER AGENTS



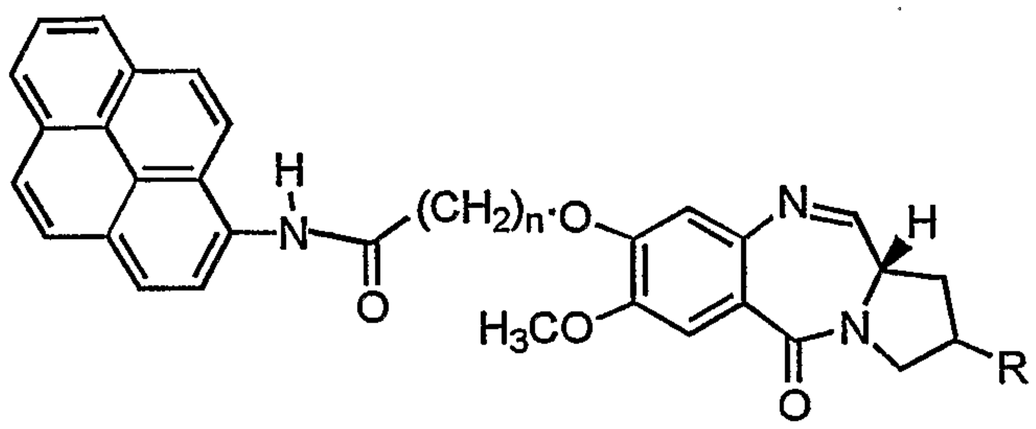
(I)

(57) Abstract: The present invention relates to pyrrolo [2,1-*c*][1,4]benzodiazepine hybrids useful as potential antitumour agents. This invention also relates to a process for the preparation of new pyrrolo[2,1-*c*][1,4]benzodiazepine hybrids as potential antitumour agents. More particularly, it provides 7-methoxy-8-[N-(1″-pyrenyl)-alkane-3′-carboxamide]-oxy-(11aS)-1,2,3,11a-tetraydro 5H-pyrrolo[2,1-*c*][1,4]benzodiazepin-5-one, with aliphatic chain length variation of these compounds and it also describes the DNA binding, anticancer (antitumour) activity. The structural formula of this novel pyrrolo[2,1-*c*][1,4]benzodiazepine is given below, formula (I):

PYRENE-LINKED PYRROLO(2,1-C)(1,4) BENZODIAZEPINE DERIVATIVES USEFUL AS ANTICANCER AGENTS

Field of the invention

The present invention relates to a process for the preparation of novel pyrrolo [2,1-*c*][1,4]benzodiazepine hybrids useful as potential antitumour agents. This invention also relates to a process for the preparation of new pyrrolo[2,1-*c*][1,4]benzodiazepine hybrids as potential antitumour agents. More particularly, it provides a process for the preparation of 7-methoxy-8-[N-(1″-pyrenyl)-alkane-3′-carboxamide]-oxy-(11a*S*)-1,2,3,11a-tetraydro 5*H*-pyrrolo[2,1-*c*][1,4]benzodiazepin-5-one, with aliphatic chain length variation of these compounds and it also describes the DNA binding, anticancer (antitumour) activity. The structural formula of this novel pyrrolo[2,1-*c*] [1,4]benzodiazepine is given below:



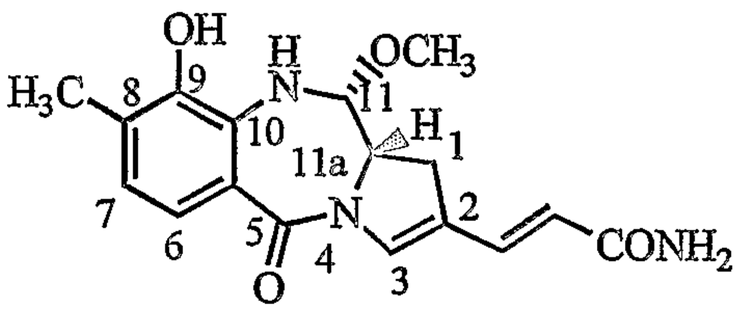
n = 1-4
R = H, OH

Background of the invention

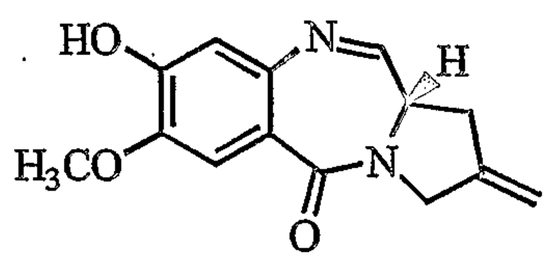
Pyrrolo[2,1-*c*][1,4]benzodiazepine antitumour antibiotics are commonly known as anthramycin class of compounds. In the last few years, a growing interest has been shown in the development of new pyrrolo[2,1-*c*][1,4]benzodiazepines (PBDs). These antibiotics react covalently with DNA to form an N2-guanine adduct that lies within the minor groove of duplex DNA *via* an acid-labile aminal bond to the electrophilic imine at the N10-C11 position (Kunimoto, S.; Masuda, T.; Kanbayashi, N.; Hamada, M.; Naganawa, H.; Miyamoto, M.; Takeuchi, T.; and Unezawa, H. *J. Antibiot.*, **1980**, *33*, 665.; Kohn, K. W. and Speous, C. L. *J. Mol. Biol.*, **1970**, *51*, 551.; Hurley, L. H.; Gairpla, C. and Zmijewski, M. *Biochem. Biophys. Acta.*, **1977**, *475*, 521.; Kaplan, D. J. and Hurley, L. H. *Biochmestry*, **1981,** *20*, 7572). The molecules have a right-handed twist, which allows them to follow the curvature of the minor groove of B-form double-stranded DNA spanning three base pairs. Recently, PBD dimers have been developed that comprises two C2-exo-methylene substituted DC-81 subunits tethered through their C-8 position via an inert propanedioxy linker (Gregson, S. J.; Howard, P. W.; Hartely, J. A.; Brooks, N. A.; Adams, L. J.; Jenkins, T. C.; Kelland, L. R. and Thurston, D. E. *J. Med. Chem.* **2001**, *44*, 737). A recent development has been the linking of two PBD units through their C-8 positions to give bisfunctional

alkylating agents capable of cross-linking DNA (Thurston, D. E.; Bose, D. S.; Thomson, A. S.; Howard, P. W.; Leoni, A.; Croker, S. J.; Jenkins, T. C.; Neidle, S. and Hurley, L. H. *J. Org. Chem.*, **1996**, *61*, 8141).

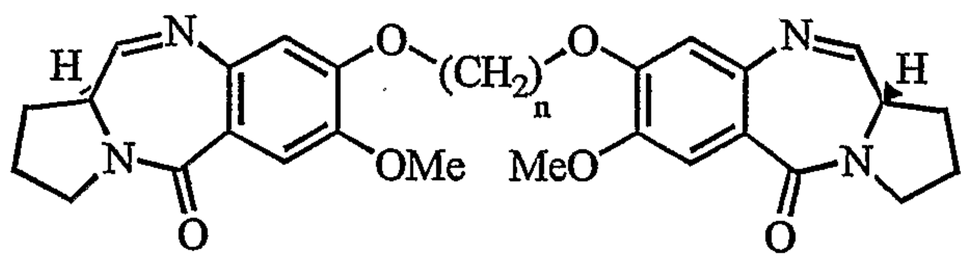
Recently, a noncross-linking mixed imine-amide PBD dimers have been synthesized that have significant DNA binding ability and potent anti tumour activitiy. (Kamal, A.; Ramesh, G.; Laxman, N.; Ramulu, P.; Srinivas, O.; Neelima, K.; Kondapi, A. K.; Srinu, V. B.; Nagarajaram, H. M. *J. Med. Chem.* **2002**, *45*, 4679).



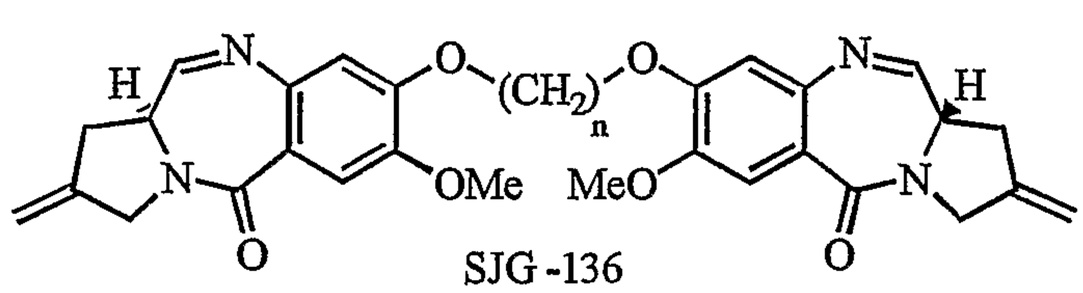
anthramycin



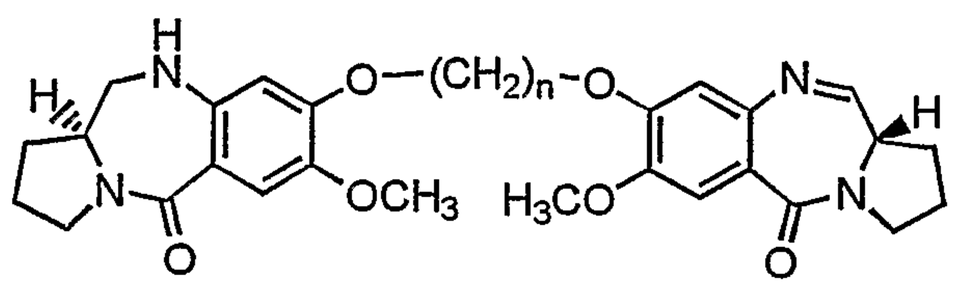
C2-exo-methylene-substituted DC-81



DC-81 dimers (n = 3-5); DSB-120 (n = 3)



SJG-136



imine-amide PBD dimers; n = 3 - 5

Naturally occurring pyrrolo[2,1-*c*][1,4]benzodiazepines belong to a group of antitumour antibiotics derived from *Streptomyces* species. Recently, there is much impetus for the PBD systems as they can recognize and bind to specific sequence of DNA. Examples of naturally occurring PBD's include anthramycin, DC-81, tomaymycin, sibiromycin and neothramycin. However, the clinical efficacy for these antibiotics is hindered by several limitations, such as poor water solubility, cardiotoxicity, development of drug resistance and metabolic inactivation.

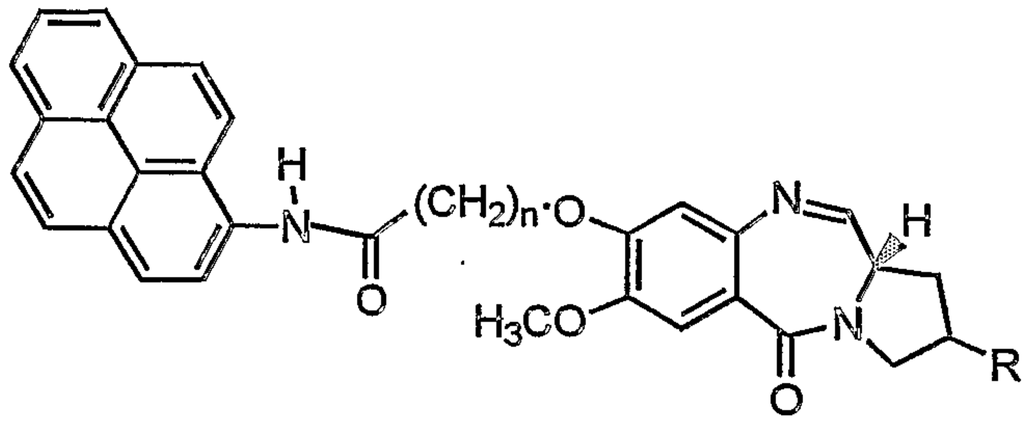
Objects if the invention

The main object of the present invention is to provide new pyrrolo[2,1-*c*][1,4]-benzodiazepine hybrids useful as antitumour agents.

Another objective of the present invention is to provide a process for the preparation of novel pyrrolo[2,1-*c*][1,4]-benzodiazepine hybrids useful as antitumour agents.

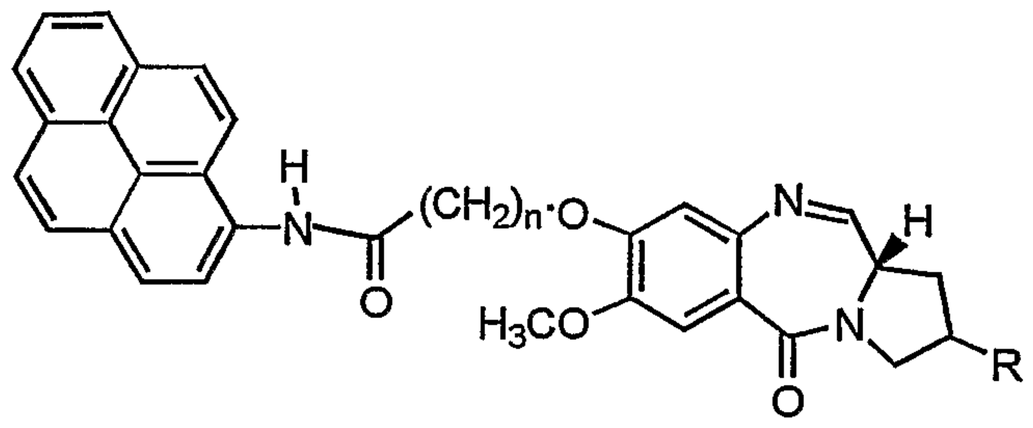
Summary of the invention

Accordingly the present invention provides a process for the preparation of a novel pyrrolo[2,1-*c*][1,4]benzodiazepine hybrids of formula V wherein R = H, OH and n is 1-4



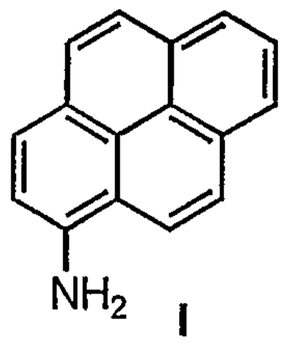
FORMULA V

Accordingly the present process provides a process for preparation of pyrrolo[2,1-*c*][1,4]benzodiazepine hybrids of formula V



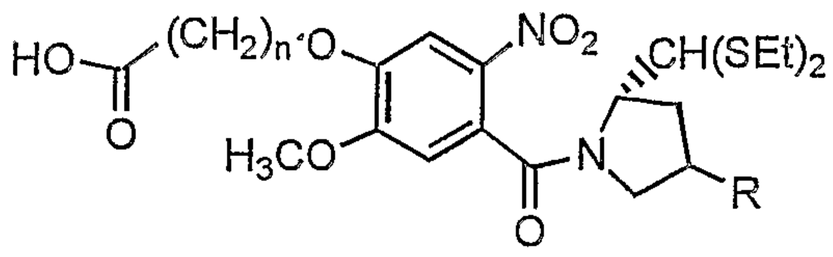
FORMULA V

which comprises reacting pyrene amine of formula I



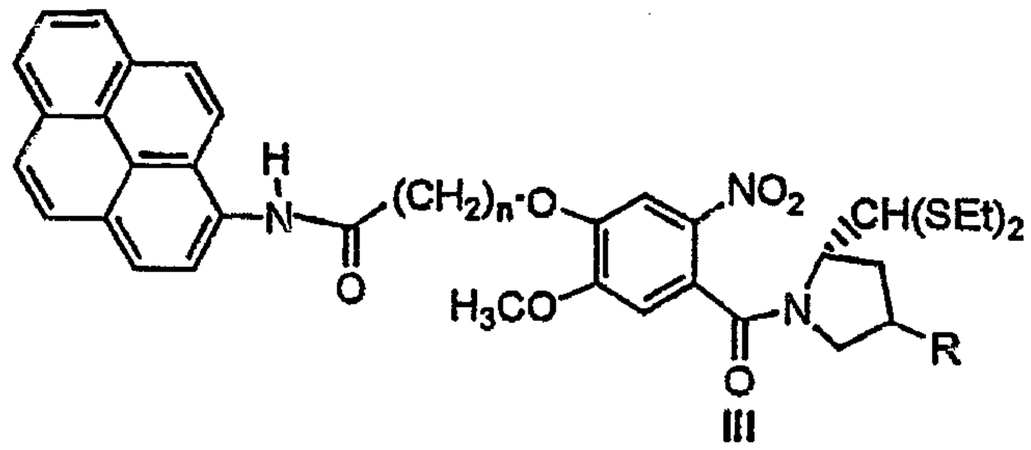
I

with (2*S*)-N-{4-[(3′-carboxy alkyl)oxy]-5-methoxy-2-nitrobenzoyl}pyrrolidine-2-carboxaldehyde diethyl thioacetal of formula II where R is as stated above



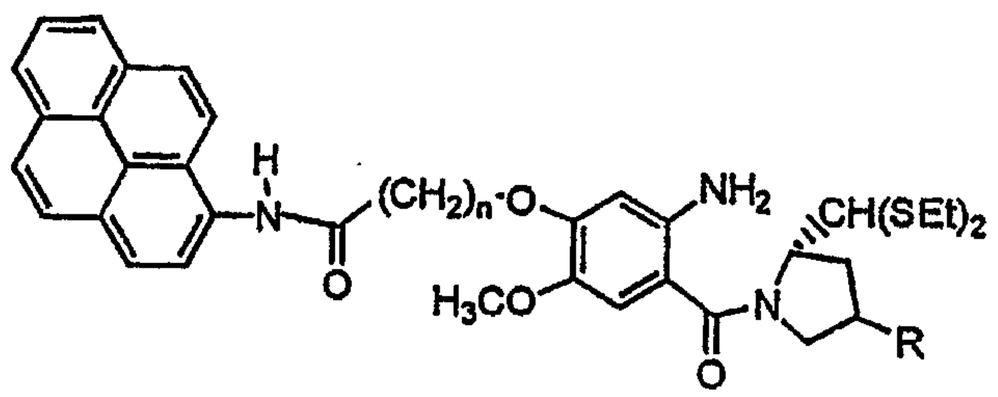
II

in the presence of isobutyl chloroformate, bases like triethyl amine, DBU in presence of organic solvents up to refluxing for a period of 24 h isolating (2S)-N-{4-[N-(l"-pyrenyl)-alkane-3'-carboxamide]-oxy--5-methoxy-2-nitrobenzoyl}pyrrolidine-2-carboxaldehyde diethyl thioacetal III where n is 1-4 and R is as stated above by conventional methods,



III

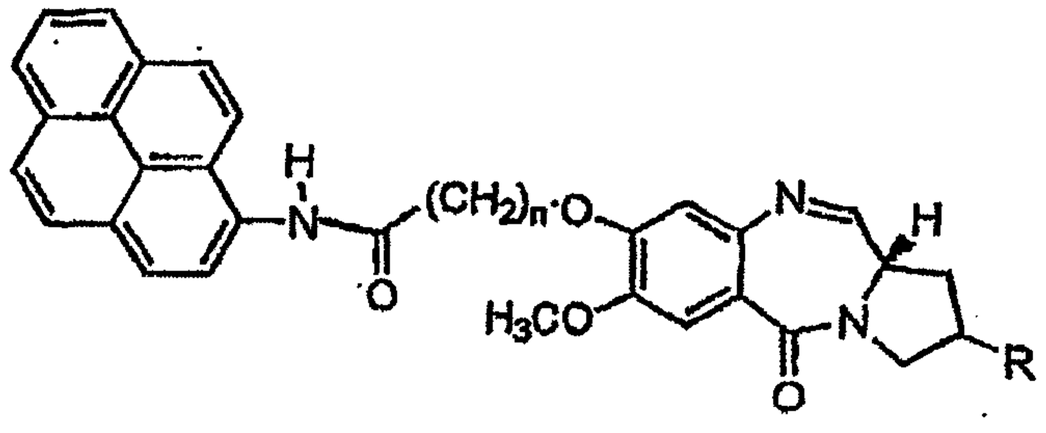
reducing the above nitro compounds of formula III with $SnCl_2.2H_2O$ in presence of organic solvent up to a reflux temperature, isolating the (2*S*)-N-{4-[N-(l"-pyrenyl)-alkane-3'-carboxamide]-oxy--5-methoxy-2-aminobenzoyl}pyrrolidine-2-carboxaldehyde diethyl thioacetal of formula IV where n is 1-4 and R is as stated above by known methods,



IV

reacting the above said amino compound of formula IV with known deprotecting agents in a conventional manner to give novel pyrrolo[2,1-*c*][1,4]benzodiazepine hybrids of formula V wherein n and R are as stated above.

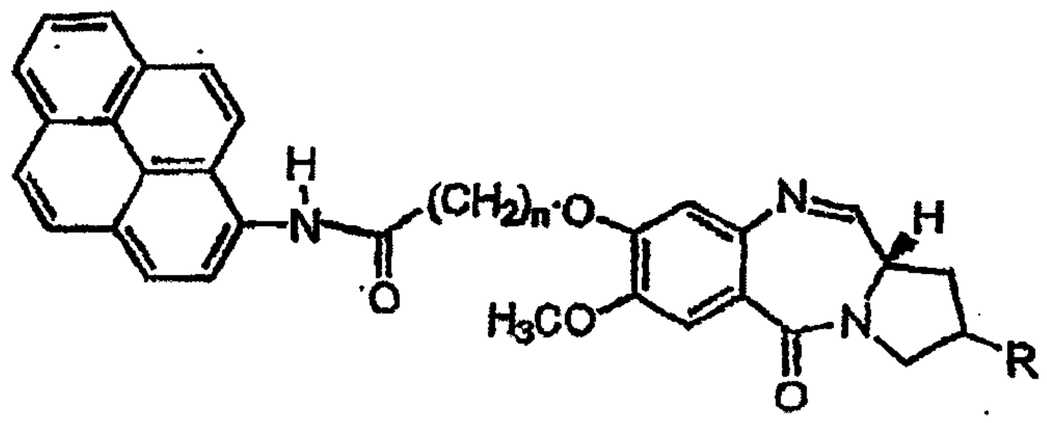
In accordance with an aspect of the present invention, there is provided pyrrolo[2,1-c][1,4]benzodiazepine hybrid of formula V wherein R is H, OH and n is 1-4.



n = 1-4
R = H, OH

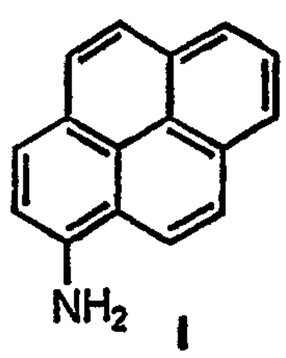
FORMULA V

In accordance with another aspect of the present invention, there is provided a process for preparing a pyrrolo[2,1-*c*][1,4]benzodiazepine hybrid of formula V



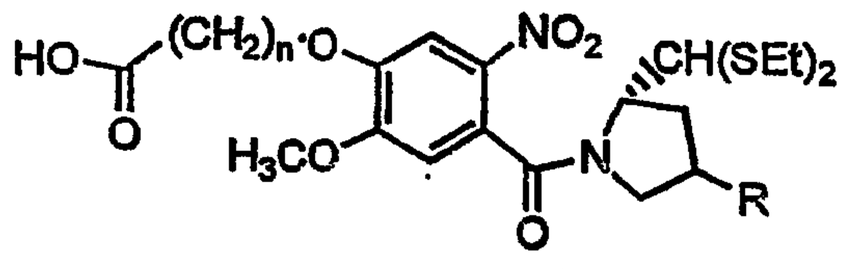
FORMULA V

which comprises reacting pyrene amine of formula I



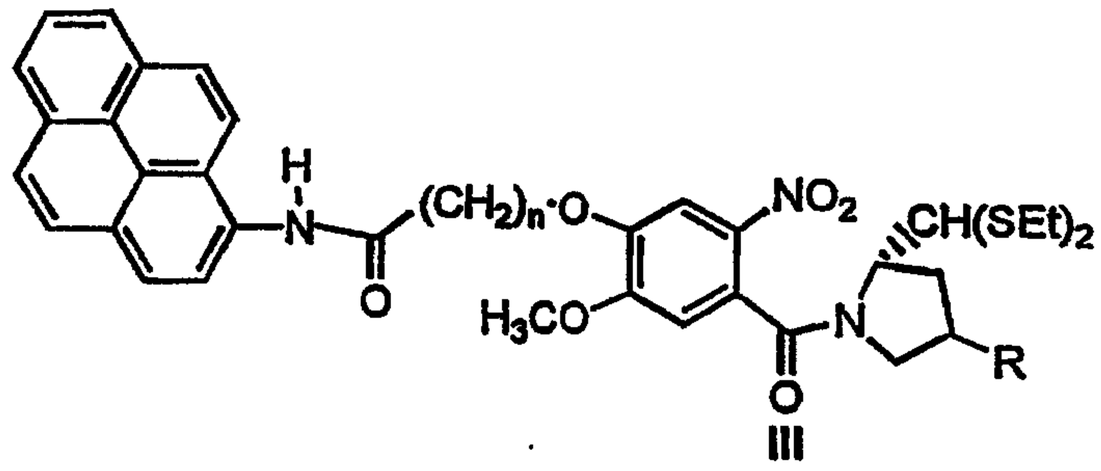
I

with (2*S*)-N-{4-[(3′-carboxy alky1)oxy]-5-methoxy-2-nitrobenzoyl)pyrrolidine-2-carboxaldehyde diethyl thioacetal of formula II where R is as stated above



II

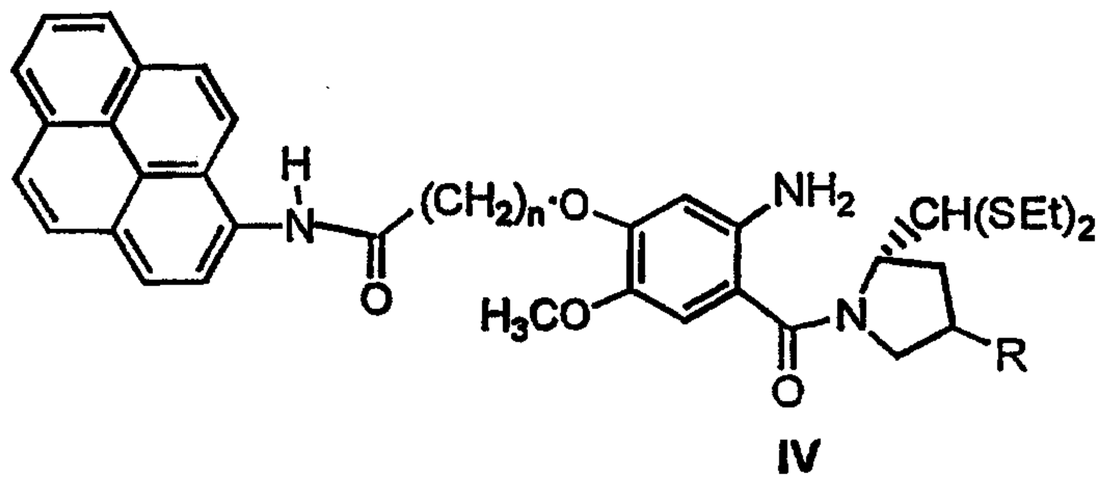
up to refluxing for a period of 24 h isolating (2*S*)-N-{4-N-(1"-pyreny1)-alkane-3′-carboxamide]-oxy--5-methoxy-2-nitrobenzoyl}pyrrolidine-2-carboxaldehyde diethyl thioacetal III where n is 1-4 and R is as stated above,



III

reducing the nitro compounds of formula III with $SnCl_2.2H_2O$ in presence of an organic

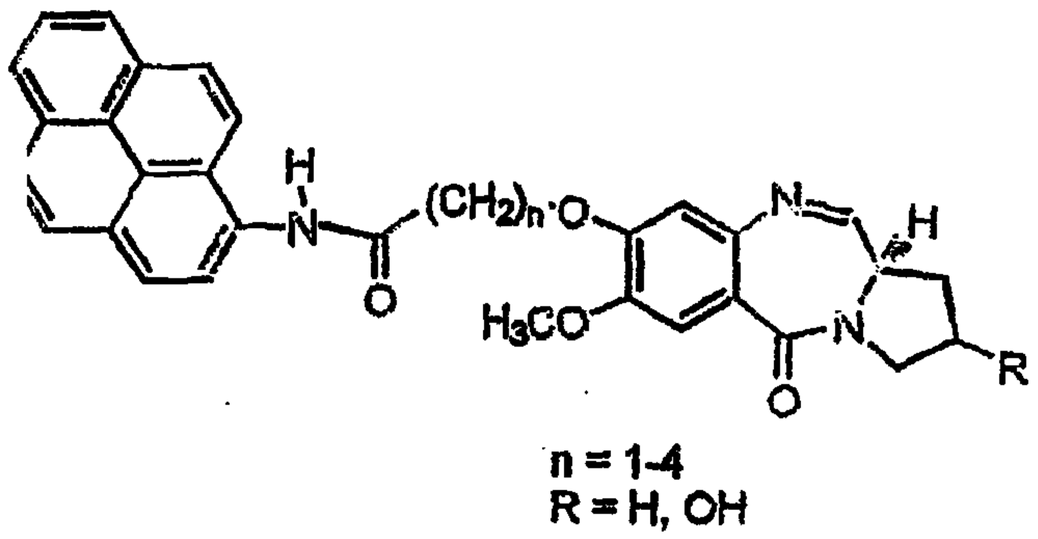
solvent up to a reflux temperature, isolating the (2*S*)-N-{4-[N-(1"-pyrenyl)-alkane-3'-carboxarnide]-oxy--5-methoxy-2-aminobenzoyl}pyrrolidine-2-carboxaldehyde diethyl thioacetal of formula IV where n is 1-4 and R is as stated above,



IV

reacting the amino compound of formula IV with a deprotecting agent to give pyrrole [2,1-*c*][1,4]benzodiazepine hybrids of formula V wherein n and R are as stated above.

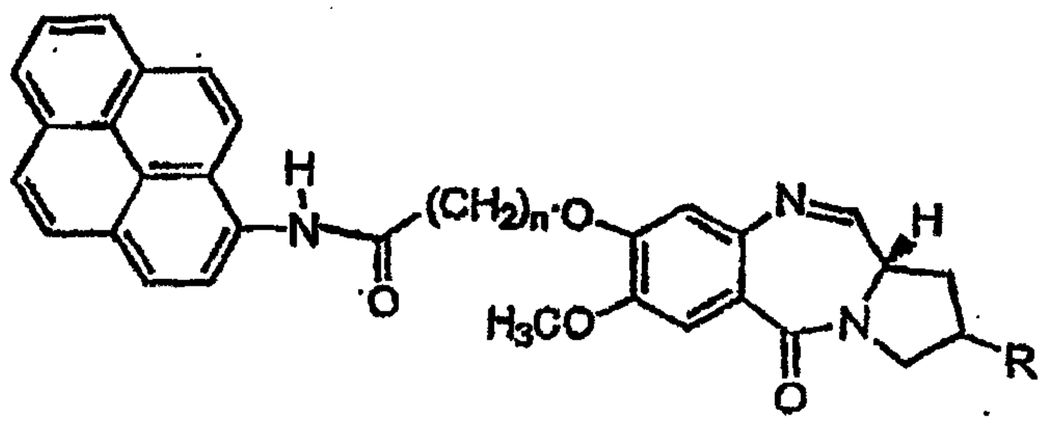
In accordance with still another aspect of the present invention, there is provided a use of pyrrolo[2,1-*c*][1,4]benzodiazepine hybrid of formula, V wherein R is H, OH and n is 1-4.



FORMULA V

for the treatment of cancer in a subject suffering therefrom.

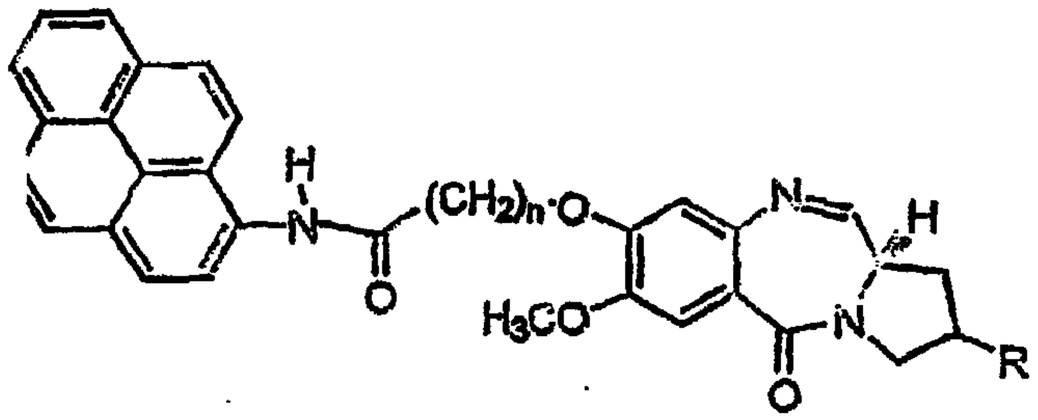
In accordance with a further aspect of the present invention, there is provided a method for the treatment of cancer comprising administering to a subject suffering therefrom, a therapeutically effective amount of a pyrrolo [2,1-*c*][1,4]benzodiazepine hybrid of formula V wherein R is H, OH and n is 1-4.



n = 1-4
R = H, OH

FORMULA V

In accordance with an even further aspect of the present invention, there is provided a use of pyrrole[2,1-*c*][1,4]benzodiazepine hybrid of formula, V wherein R is H, OH and n is 1-4.



n = 1-4
R = H, OH

FORMULA V

for preparation of a medicament, for the treatment of cancer in a subject suffering therefrom.

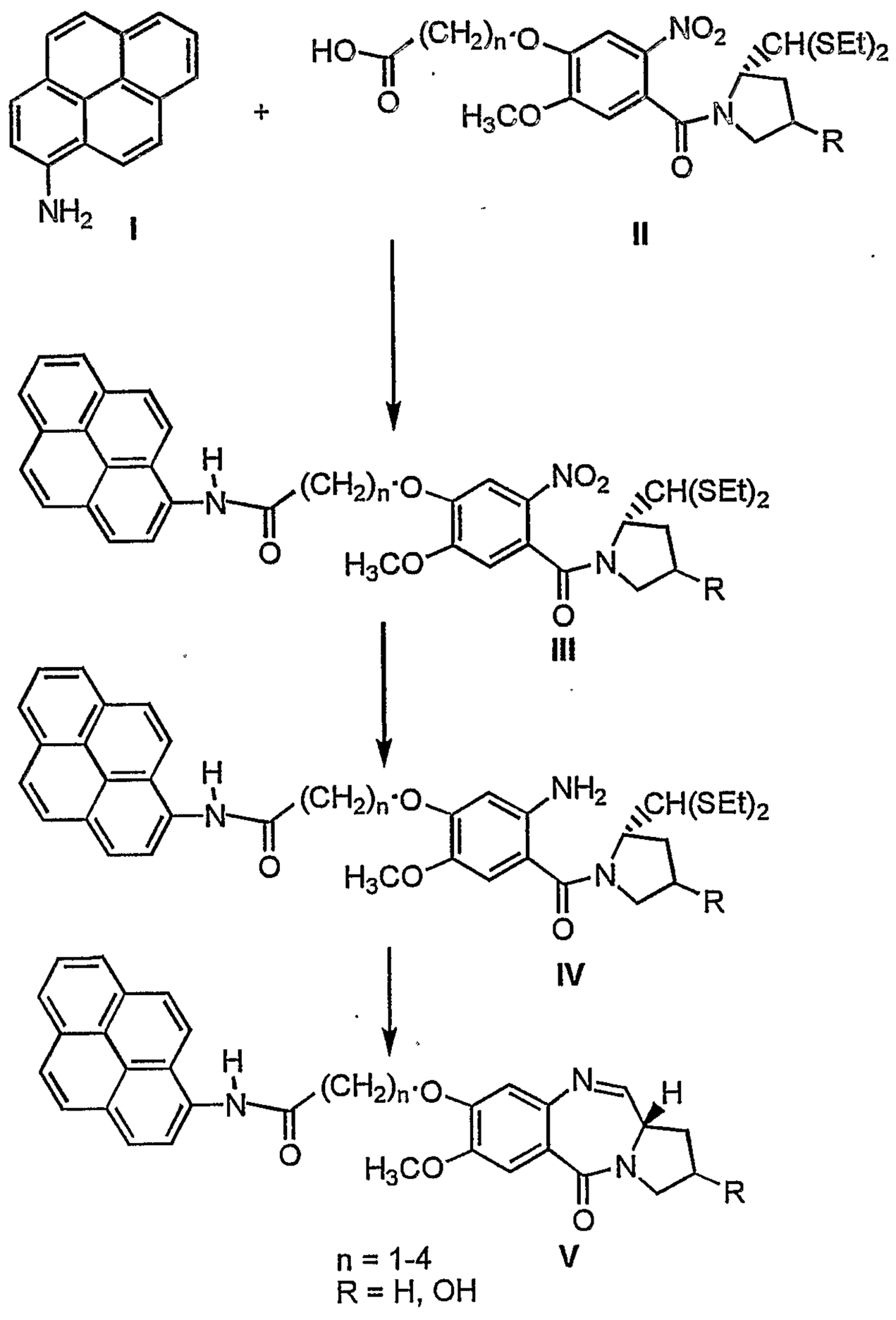
Detailed description of the invention

The precursors, pyrene amine of formula I (Banik, B. K.; Becker, F. F. *Bioorg Med. Chem.* **2001**, 9, 593) and (2*S*)-N-{4-[(3'-carboxy alkyl)oxy]-5-methoxy-2-nitrobenzoyl}pyrrolidine-2-carboxaldehyde diethyl thioacetal of formula II (Baraldi, P. G.; Balboni, G.; Cacciari, B.; Guiotto, A.; Manfredini, S.; Romagnoli, R.; Spalluto, G.; Thurston, D. E.; Howard, P. W.; Bianchi, N.; Rutigiiano, C.; Mischiati, C. and Gambari, R. *J. Med Chem.* **1999**, *42,* 5131. ; Reddy, B. S. P.; Damayanthi, Y.; Reddy, B. S. N.; Lown, W. J. *Anti-Cancer Drug Design* **2000,** *15*, 225) have been prepared by literature methods.

These new analogues of pyrrolo[2,1-*c*][1,4]benzodiazepine hybrids linked at C-8 position have shown promising DNA binding activity and efficient anticancer activity in various cell lines. The molecules synthesized are of immense biological significance with

potential sequence selective DNA-binding property. This resulted in design and synthesis of new congeners as illustrated in Scheme-1, which comprise:

1. The ether linkage at C-8 position of DC-81 intermediates with pyrene ring moiety.
2. Refluxing the reaction mixture for 24-48 h.
3. Synthesis of C-8 linked PBD antitumour antibiotic hybrid imines.
4. Purification by column chromatography using different solvents like ethyl acetate, hexane, dichloromethane and methanol.



SCHEME I

Some representative compounds of formula V present invention are given below

1. 7-Methoxy-8-[N-(1″-pyrenyl)-methane-1′-carboxamide]-oxy-(11a*S*)1,2,3,11a tetrahydro-5*H*-pyrrolo[2,1-*c*][1,4]benzodiazepin-5-one
2. 7-Methoxy-8-[N-(1″-pyrenyl)-methane-1′-carboxamide]-oxy-(4*R*)-hydroxy (11a*S*) 1,2,3,11a tetrahydro-5*H*-pyrrolo[2,1-*c*][1,4]benzodiazepin-5-one

3. 7-Methoxy-8-[N-(1″-pyrenyl)-ethane-2′-carboxamide]-oxy-(11a*S*)1,2,3,11a tetrahydro-5*H*-pyrrolo[2,1-*c*][1,4]benzodiazepin-5-one

4. 7-Methoxy-8-[N-(1″-pyrenyl)-ethane-2′-carboxamide]-oxy-(4*R*)-hydroxy (11a*S*) 1,2,3,11a tetrahydro-5*H*-pyrrolo[2,1-*c*][1,4]benzodiazepin-5-one

5. 7-Methoxy-8-[N-(1″-pyrenyl)-propane-3′-carboxamide]-oxy-(11a*S*)-1,2,3,11a tetra-hydro-5*H*-pyrrolo[2,1-*c*][1,4]benzodiazepin-5-one

6. 7-Methoxy-8-[N-(1″-pyrenyl)-propane-3′-carboxamide]-oxy-(4*R*)-hydroxy (11a*S*)-1,2,3,11a-tetra-hydro-5*H*-pyrrolo[2,1-*c*][1,4]benzodiazepin-5-one

7. 7-Methoxy-8-[N-(1″-pyrenyl)-butane-4′-carboxamide]-oxy-(11a*S*)-1,2,3,11a-tetra-hydro-5*H*-pyrrolo[2,1-*c*][1,4]benzodiazepin-5-one

8. 7-Methoxy-8-[N-(1″-pyrenyl)-butane-4′-carboxamide]-oxy-(4*R*)-hydroxy (11a*S*)-1,2,3,11a-tetra-hydro-5*H*-pyrrolo[2,1-*c*][1,4]benzodiazepin-5-one

The process for the preparation of new pyrrolo[2,1-*c*][1,4]benzodiazepine hydrids is disclosed and claimed in our copending copatent application no._____

The following examples are given by way of illustration and therefore should not be construed to the present limit of the scope of invention.

Example 1

Compound (2*S*)-N-[4-[(1′-carboxy methyl)oxy]-5-methoxy-2-nitrobenzoyl] pyrrolidine-2-carboxaldehyde diethyl thioacetal of formula II (2.29 g, 5 mmol) was taken in dry CH_2Cl_2 (20 mL), TEA (707 mg, 7 mmol) was added and the mixture was cooled at 0-5 °C. Isobutyl chloroformate (819 mg, 6 mmol) in dry CH_2Cl_2 (10 mL) was added dropwise and the mixture was kept at 0-5 °C for 15 min. A solution of 1-amino pyrene of formula I (251 mg, 5 mmol) in CH_2Cl_2 was added to it at the same temperature and the solution was stirred at room temperature for overnight. The mixture was washed with saturated $NaHCO_3$ (50 mL), brine, dried and solvent was evaporated. The crude material was chromatographed over silica gel using ethyl acetate/hexane (8:2) solvent to give compound (2*S*)-N-{4-[N-(1″-pyrenyl)-methane-3′-carboxamide]-oxy--5-methoxy-2-nitro-benzoyl}pyrrolidine-2-carboxaldehyde diethyl thioacetal of formula III as a yellow liquid.

The (2*S*)-N-{4-[N-(1″-pyrenyl)-methane-1′-carboxamide]-oxy--5-methoxy-2-nitro benzoyl}pyrrolidine-2-carboxaldehyde diethyl thioacetal of formula III (0.657 g, 1 mmol) was dissolved in ethyl acetate (15 mL) and added $SnCl_2.2H_2O$ (1.12 g, 5 mmol) was refluxed for 3 h or until the TLC indicated that reaction was completed. The reaction mixture was then adjusted to pH 8 carefully with saturated $NaHCO_3$ solution, diluted with ethyl acetate, filtered through celite and extracted. The combined organic phase was dried over Na_2SO_4, and

evaporated under vacuum to afford the crude (2*S*)-N-{4-[N-(1″-pyrenyl)-methane-1′-carboxamide]-oxy--5-methoxy-2-aminobenzoyl}pyrrolidine-2-carboxaldehyde diethyl thioacetal of formula IV.

A solution of (2*S*)-N-{4-[N-(1″-pyrenyl)-methane-1′-carboxamide]-oxy--5-methoxy-2-aminobenzoyl}pyrrolidine-2-carboxaldehyde diethyl thioacetal of formula IV (627 mg, 1 mmol), $HgCl_2$ (613 mg, 2.26 mmol) and $CaCO_3$ (246 mg, 2.46 mmol) in MeCN-water (4:1) was stirred slowly at room temperature until TLC indicates complete loss of starting material. The reaction mixture was diluted with EtOAc (30 mL) and filtered through a celite bed. The clear yellow organic supernatant was extracted with saturated 5% $NaHCO_3$ (20 mL), brine (20 mL) and the combined organic phase is dried (Na_2SO_4). The organic layer was evaporated in vacuum and purified by column chromatography (90% CH_2Cl_2-MeOH) to give compound 7-Methoxy-8-[N-(1″-pyrenyl)-propane-3′-carboxamide]-oxy-(11a*S*)-1,2,3,11a tetra-hydro-5*H*-pyrrolo[2,1-*c*][1,4]benzo-diazepin-5-one as pale yellow oil.

Example 2

Compound (4*R*)-hydroxy-(2*S*)-N-[4-[(1′-carboxy methyl)oxy]-5-methoxy-2-nitro-benzoyl]pyrrolidine-2-carboxaldehyde diethyl thioacetal of formula II (2.37 g, 5 mmol) was taken in dry CH_2Cl_2 (20 mL), TEA (707 mg, 7 mmol) was added and the mixture was cooled at 0-5 °C. Isobutyl chloroformate (819 mg, 6 mmol) in dry CH_2Cl_2 (10 mL) was added dropwise and the mixture was kept at 0-5 °C for 15 min. A solution of 1-amino pyrene formula I (251 mg, 5 mmol) in CH_2Cl_2 was added to it at the same temperature and the solution was stirred at room temperature for overnight. The mixture was washed with saturated $NaHCO_3$ (50 mL), brine, dried and solvent was evaporated. The crude material was chromatographed over silica gel using ethyl acetate/hexane (8:2) solvent to give compound (2*S*)-N-{4-[N-(1″-pyrenyl)-methane-1′-carboxamide]-oxy--5-methoxy-2-nitrobenzoyl} pyrrolidine-2-carboxaldehyde diethyl thioacetal of formula III as a yellow liquid.

The (4*R*)-hydroxy-(2*S*)-N-{4-[N-(1″-pyrenyl)-methane-1′-carboxamide]-oxy--5-methoxy-2-nitrobenzoyl}pyrrolidine-2-carboxaldehyde diethyl thioacetal of formula III (0.673 g, 1 mmol) was dissolved in ethyl acetate (15 mL) and added $SnCl_2.2H_2O$ (1.12 g, 5 mmol) was refluxed for 3 h or until the TLC indicated that reaction was completed. The reaction mixture was then adjusted to pH 8 carefully with saturated $NaHCO_3$ solution, diluted with ethyl acetate, filtered through celite and extracted. The combined organic phase was dried over Na_2SO_4, and evaporated under vacuum to afford the crude (4*R*)-hydroxy-(2*S*)-N-{4-[N-(1″-pyrenyl)-methane-1′-carboxamide]-oxy--5-methoxy-2-amino-benzoyl}pyrrolidine-2-carboxaldehyde diethyl thioacetal of formula IV.

A solution of (4*R*)-hydroxy-(2*S*)-N-{4-[N-(1″-pyrenyl)-methane-1′-carboxamide]-oxy--5-methoxy-2-aminobenzoyl}pyrrolidine-2-carboxaldehyde diethyl thioacetal of formula IV (643 mg, 1 mmol), $HgCl_2$ (613 mg, 2.26 mmol) and $CaCO_3$ (246 mg, 2.46 mmol) in MeCN-water (4:1) was stirred slowly at room temperature until TLC indicates complete loss of starting material. The reaction mixture was diluted with EtOAc (30 mL) and filtered through a celite bed. The clear yellow organic supernatant was extracted with saturated 5% $NaHCO_3$ (20 mL), brine (20 mL) and the combined organic phase is dried (Na_2SO_4). The organic layer was evaporated in vacuum and purified by column chromatography (90% CH_2Cl_2-MeOH) to give compound 7-methoxy-8-[N-(1″-pyrenyl)-methane-1′-carboxamide]-oxy-(4*R*)-hydroxy-(11a*S*)-1,2,3,11atetra-hydro-5*H*-pyrrolo[2,1-*c*][1,4]benzodiazepin-5-one as pale yellow oil.

Example 3

Compound (2*S*)-N-[4-[(2′-carboxy ethyl)oxy]-5-methoxy-2-nitrobenzoyl] pyrrolidine-2-carboxaldehyde diethyl thioacetal of formula II (2.36 g, 5 mmol) was taken in dry CH_2Cl_2 (20 mL), TEA (707 mg, 7 mmol) was added and the mixture was cooled at 0-5 °C. Isobutyl chloroformate (819 mg, 6 mmol) in dry CH_2Cl_2 (10 mL) was added dropwise and the mixture was kept at 0-5 °C for 15 min. A solution of 1-amino pyrene of formula I (251 mg, 5 mmol) in CH_2Cl_2 was added to it at the same temperature and the solution was stirred at room temperature for overnight. The mixture was washed with saturated $NaHCO_3$ (50 mL), brine, dried and solvent was evaporated. The crude material was chromatographed over silica gel using ethyl acetate/hexane (8:2) solvent to give compound (2*S*)-N-{4-[N-(1″-pyrenyl)-ethane-2′-carboxamide]-oxy--5-methoxy-2-nitro-benzoyl}pyrrolidine-2-carboxaldehyde diethyl thioacetal of formula III as a yellow liquid.

The (2*S*)-N-{4-[N-(1″-pyrenyl)-ethane-2′-carboxamide]-oxy--5-methoxy-2-nitro benzoyl}pyrrolidine-2-carboxaldehyde diethyl thioacetal of formula III (0.671 g, 1 mmol) was dissolved in ethyl acetate (15 mL) and added $SnCl_2.2H_2O$ (1.12 g, 5 mmol) was refluxed for 3 h or until the TLC indicated that reaction was completed. The reaction mixture was then adjusted to pH 8 carefully with saturated $NaHCO_3$ solution, diluted with ethyl acetate, filtered through celite and extracted. The combined organic phase was dried over Na_2SO_4, and evaporated under vacuum to afford the crude (2*S*)-N-{4-[N-(1″-pyrenyl)-ethane-2′-carboxamide]-oxy--5-methoxy-2-aminobenzoyl}pyrrolidine-2-carboxaldehyde diethyl thioacetal of formula IV.

A solution of (2*S*)-N-{4-[N-(1″-pyrenyl)-ethane-2′-carboxamide]-oxy--5-methoxy-2-aminobenzoyl}pyrrolidine-2-carboxaldehyde diethyl thioacetal of formula IV (641 mg, 1 mmol), $HgCl_2$ (613 mg, 2.26 mmol) and $CaCO_3$ (246 mg, 2.46 mmol) in MeCN-water (4:1)

was stirred slowly at room temperature until TLC indicates complete loss of starting material. The reaction mixture was diluted with EtOAc (30 mL) and filtered through a celite bed. The clear yellow organic supernatant was extracted with saturated 5% $NaHCO_3$ (20 mL), brine (20 mL) and the combined organic phase is dried (Na_2SO_4). The organic layer was evaporated in vacuum and purified by column chromatography (90% CH_2Cl_2-MeOH) to give compound 7-Methoxy-8-[N-(1″-pyrenyl)-ethane-2′-carboxamide]-oxy-(11a*S*)-1,2,3,11atetra-hydro-5*H*-pyrrolo[2,1-*c*][1,4]benzodiazepin-5-one as pale yellow oil.

Example 4

Compound (4*R*)-hydroxy-(2*S*)-N-[4-[(2′-carboxy ethyl)oxy]-5-methoxy-2-nitrobenzoyl] pyrrolidine-2-carboxaldehyde diethyl thioacetal of formula II (2.44 g, 5 mmol) was taken in dry CH_2Cl_2 (20 mL), TEA (707 mg, 7 mmol) was added and the mixture was cooled at 0-5 °C. Isobutyl chloroformate (819 mg, 6 mmol) in dry CH_2Cl_2 (10 mL) was added dropwise and the mixture was kept at 0-5 °C for 15 min. A solution of 1-amino pyrene of formula I (251 mg, 5 mmol) in CH_2Cl_2 was added to it at the same temperature and the solution was stirred at room temperature for overnight. The mixture was washed with saturated $NaHCO_3$ (50 mL), brine, dried and solvent was evaporated. The crude material was chromatographed over silica gel using ethyl acetate/hexane (8:2) solvent to give compound (4*R*)-hydroxy-(2*S*)-N-{4-[N-(1″-pyrenyl)-ethane-2′-carboxamide]-oxy--5-methoxy-2-nitrobenzoyl}pyrrolidine-2-carboxaldehyde diethyl thioacetal of formula III as a yellow liquid.

The(4*R*)-hydroxy-(2*S*)-N-{4-[N-(1″-pyrenyl)-ethane-2′-carboxamide]-oxy-5-methoxy -2-nitrobenzoyl}pyrrolidine-2-carboxaldehyde diethyl thioacetal of formula III (0.687 g, 1 mmol) was dissolved in ethyl acetate (15 mL) and added $SnCl_2.2H_2O$ (1.12 g, 5 mmol) was refluxed for 3 h or until the TLC indicated that reaction was completed. The reaction mixture was then adjusted to pH 8 carefully with saturated $NaHCO_3$ solution, diluted with ethyl acetate, filtered through celite and extracted. The combined organic phase was dried over Na_2SO_4, and evaporated under vacuum to afford the crude (4*R*)-hydroxy-(2*S*)-N-{4-[N-(1″-pyrenyl)-ethane-2′-carboxamide]-oxy--5-methoxy-2-amino-benzoyl}pyrrolidine-2-carboxaldehyde diethyl thioacetal of formula IV.

A solution of (4*R*)-hydroxy-(2*S*)-N-{4-[N-(1″-pyrenyl)-ethane-2′-carboxamide]-oxy--5-methoxy-2-aminobenzoyl}pyrrolidine-2-carboxaldehyde diethyl thioacetal of formula IV (657 mg, 1 mmol), $HgCl_2$ (613 mg, 2.26 mmol) and $CaCO_3$ (246 mg, 2.46 mmol) in MeCN-water (4:1) was stirred slowly at room temperature until TLC indicates complete loss of starting material. The reaction mixture was diluted with EtOAc (30 mL) and filtered through

a celite bed. The clear yellow organic supernatant was extracted with saturated 5% $NaHCO_3$ (20 mL), brine (20 mL) and the combined organic phase is dried (Na_2SO_4). The organic layer was evaporated in vacuum and purified by column chromatography (90% CH_2Cl_2-MeOH) to give compound 7-Methoxy-8-[N-(1″-pyrenyl)-ethane-2′-carboxamide]-oxy-(4*R*)-hydroxy-(11a*S*)-1,2,3,11atetra-hydro-5*H*-pyrrolo[2,1-*c*][1,4]benzodiazepin-5-one as pale yellow oil.

Example 5

Compound (2*S*)-N-[4-[(3′-carboxy propyl)oxy]-5-methoxy-2-nitrobenzoyl] pyrrolidine-2-carboxaldehyde diethyl thioacetal of formula II (2.43 g, 5 mmol) was taken in dry CH_2Cl_2 (20 mL), TEA (707 mg, 7 mmol) was added and the mixture was cooled at 0-5°C. Isobutyl chloroformate (819 mg, 6 mmol) in dry CH_2Cl_2 (10 mL) was added dropwise and the mixture was kept at 0-5 °C for 15 min. A solution of 1-amino pyrene formula I (251 mg, 5 mmol) in CH_2Cl_2 was added to it at the same temperature and the solution was stirred at room temperature for overnight. The mixture was washed with saturated $NaHCO_3$ (50 mL), brine, dried and solvent was evaporated. The crude material was chromatographed over silica gel using ethyl acetate/hexane (8:2) solvent to give compound (2*S*)-N-{4-[N-(1″-pyrenyl)-propane-3′-carboxamide]-oxy--5-methoxy-2-nitrobenzoyl}pyrrolidine-2-carboxaldehyde diethyl thioacetal of formula III as a yellow liquid (1.92 g, 56%).

^1H NMR ($CDCl_3$) δ 1.10-1.40 (m, 6H), 1.40-2.40 (m, 6H), 2.50-2.90 (m, 4H), 3.10-3.25 (m, 2H), 3.60 (s, 3H), 4.0-4.20(m, 2H), 4.55-4.85 (m, 2H), 6.70 (s, 1H), 7.62 (s, 1H), 7.70-8.40 (m, 9H), 8.60-8.90 (m, 1H); MS (FAB) 686 $[M + H]^{+\cdot}$.

The (2*S*)-N-{4-[N-(1″-pyrenyl)-propane-3′-carboxamide]-oxy--5-methoxy-2-nitro benzoyl}pyrrolidine-2-carboxaldehyde diethyl thioacetal of formula III (0.685 g, 1 mmol) was dissolved in ethyl acetate (15 mL) and added $SnCl_2.2H_2O$ (1.12 g, 5 mmol) was refluxed for 3 h or until the TLC indicated that reaction was completed. The reaction mixture was then adjusted to pH 8 carefully with saturated $NaHCO_3$ solution, diluted with ethyl acetate, filtered through celite and extracted. The combined organic phase was dried over Na_2SO_4, and evaporated under vacuum to afford the crude (2*S*)-N-{4-[N-(1″-pyrenyl)-propane-3′-carboxamide]-oxy-5-methoxy-2-aminobenzoyl}pyrrolidine-2-carboxaldehyde diethyl thioacetal of formula IV (458 mg, 70%).

^1H NMR ($CDCl_3$) δ 1.10-1.40 (m, 6H), 1.50-2.30 (m, 8H), 2.40-2.80 (m, 4H), 3.40 (s, 3H), 3.45-3.60 (m, 2H), 4.05-4.15 (m, 2H), 4.50-4.70 (m, 2H), 6.25 (s, 1H), 6.70 (s, 1H), 7.65-8.30 (m, 9H), 9.10-9.25 (m, 1H).

A solution of (2*S*)-N-{4-[N-(1″-pyrenyl)-propane-3′-carboxamide]-oxy--5-methoxy-2-aminobenzoyl}pyrrolidine-2-carboxaldehyde diethyl thioacetal of formula IV (655 mg, 1

mmol), $HgCl_2$ (613 mg, 2.26 mmol) and $CaCO_3$ (246 mg, 2.46 mmol) in MeCN-water (4:1) was stirred slowly at room temperature until TLC indicates complete loss of starting material. The reaction mixture was diluted with EtOAc (30 mL) and filtered through a celite bed. The clear yellow organic supernatant was extracted with saturated 5% $NaHCO_3$ (20 mL), brine (20 mL) and the combined organic phase is dried (Na_2SO_4). The organic layer was evaporated in vacuum and purified by column chromatography (90% CH_2Cl_2-MeOH) to give compound 7-Methoxy-8-[N-(1″-pyrenyl)-propane-3′-carboxamide]-oxy-(11a*S*)-1,2,3,11atetra-hydro-5*H*-pyrrolo[2,1-*c*][1,4]benzodiazepin-5-one as pale yellow oil of formula V (285 mg, 54%).

^1H NMR ($CDCl_3$) δ 1.40-2.40 (m, 10H), 2.60-2.90 (m, 2H), 3.40-4.05 (m, 4H), 4.10-4.40 (m, 2H), 6.85 (s, 1H), 7.40 (s, 1H), 7.65 (d, 1H), 7.75-8.20 (m, 8H), 8.20-8.40 (m, 1H), 9.0-9.10 (m, 1H); MS (FAB) 530 $[M + H]^{+\cdot}$.

Example 6

Compound (4*R*)-hydroxy-(2*S*)-N-[4-[(3′-carboxy propyl)oxy]-5-methoxy-2-nitrobenzoyl] pyrrolidine-2-carboxaldehyde diethyl thioacetal of formula II (2.51 g, 5 mmol) was taken in dry CH_2Cl_2 (20 mL), TEA (707 mg, 7 mmol) was added and the mixture was cooled at 0-5 °C. Isobutyl chloroformate (819 mg, 6 mmol) in dry CH_2Cl_2 (10 mL) was added dropwise and the mixture was kept at 0-5 °C for 15 min. A solution of 1-amino pyrene of formula I (251 mg, 5 mmol) in CH_2Cl_2 was added to it at the same temperature and the solution was stirred at room temperature for overnight. The mixture was washed with saturated $NaHCO_3$ (50 mL), brine, dried and solvent was evaporated. The crude material was chromatographed over silica gel using ethyl acetate/hexane (8:2) solvent to give compound (4*R*)-hydroxy-(2*S*)-N-{4-[N-(1″-pyrenyl)-propane-3′-carboxamide]-oxy--5-methoxy-2-nitrobenzoyl}pyrrolidine-2-carboxaldehyde diethyl thioacetal of formula III as a yellow liquid.

The (4*R*)-hydroxy-(2*S*)-N-{4-[N-(1″-pyrenyl)-propane-3′-carboxamide]-oxy--5-methoxy-2-nitrobenzoyl}pyrrolidine-2-carboxaldehyde diethyl thioacetal of formula III (0.701 g, 1 mmol) was dissolved in ethyl acetate (15 mL) and added $SnCl_2.2H_2O$ (1.12 g, 5 mmol) was refluxed for 3 h or until the TLC indicated that reaction was completed. The reaction mixture was then adjusted to pH 8 carefully with saturated $NaHCO_3$ solution, diluted with ethyl acetate, filtered through celite and extracted. The combined organic phase was dried over Na_2SO_4, and evaporated under vacuum to afford the crude (4*R*)-hydroxy-(2*S*)-N-{4-[N-(1″-pyrenyl)-propane-3′-carboxamide]-oxy--5-methoxy-2-aminobenzoyl}pyrrolidine-2-carboxaldehyde diethyl thioacetal of formula IV.

A solution of (4*R*)-hydroxy-(2*S*)-N-{4-[N-(1″-pyrenyl)-propane-3′-carboxamide]-oxy--5-methoxy-2-aminobenzoyl}pyrrolidine-2-carboxaldehyde diethyl thioacetal of formula IV (671 mg, 1 mmol), $HgCl_2$ (613 mg, 2.26 mmol) and $CaCO_3$ (246 mg, 2.46 mmol) in MeCN-water (4:1) was stirred slowly at room temperature until TLC indicates complete loss of starting material. The reaction mixture was diluted with EtOAc (30 mL) and filtered through a celite bed. The clear yellow organic supernatant was extracted with saturated 5% $NaHCO_3$ (20 mL), brine (20 mL) and the combined organic phase is dried (Na_2SO_4). The organic layer was evaporated in vacuum and purified by column chromatography (90% CH_2Cl_2-MeOH) to give compound 7-Methoxy-8-[N-(1″-pyrenyl)-propane-3′-carboxamide]-oxy-(4*R*) hydroxy-(11a*S*)-1,2,3,11atetra-hydro-5*H*-pyrrolo[2,1-*c*][1,4]benzodiazepin-5-one as pale yellow oil of formula V.

Example 7

Compound (2*S*)-N-{4-[(3′-carboxy butyl)oxy]-5-methoxy-2-nitrobenzoyl}pyrrolidine -2-car-boxaldehyde diethyl thioacetal of formula II (2.50 g, 5 mmol) was taken in dry CH_2Cl_2 (20 mL), TEA (707 mg, 7 mmol) was added and the mixture was cooled at 0-5 °C. Isobutyl chloroformate (819 mg, 6 mmol) in dry CH_2Cl_2 (10 mL) was added dropwise and the mixture was kept at 0-5 °C for 15 min. A solution of 1-amino pyrene of formula I (251 mg, 5 mmol) in CH_2Cl_2 was added to it at the same temperature and the solution was stirred at room temperature for overnight. The mixture was washed with saturated $NaHCO_3$ (50 mL), brine, dried and solvent was evaporated. The crude material was chromatographed over silica gel using ethyl acetate/hexane (8:2) solvent to give compound (2*S*)-N-{4-[N-(1″-pyrenyl)-butane-3′-carboxamide]-oxy-5-methoxy-2-nitrobe-nzoyl}pyrrolidine-2-carboxaldehyde diethyl thioacetal of formula III as a yellow liquid (1.92 g, 55%).

^1H NMR ($CDCl_3$) δ 1.10-1.40 (m, 6H), 1.40-2.40 (m, 8H), 2.50-2.90 (m, 4H), 3.10-3.25 (m, 2H), 3.60 (s, 3H), 4.0-4.20 (m, 2H), 4.55-4.85 (m, 2H), 6.70 (s, 1H), 7.62 (s, 1H), 7.70-8.40 (m, 9H), 8.60-8.90 (m, 1H); MS (FAB) 700 $[M + H]^{+\cdot}$.

The nitro diethyl thioacetal (2*S*)-N-{4-[N-(1″-pyrenyl)-butane-3′-carboxamide]-oxy-5-methoxy-2-nitrobenzo-yl}pyrrolidine-2-carboxaldehyde diethyl thioacetal of formula III (0.699 g, 1 mmol) was dissolved in ethyl acetate (15 mL) and added $SnCl_2.2H_2O$ (1.12 g, 5 mmol) was refluxed for 3 h or until the TLC indicated that reaction was completed. The reaction mixture was then adjusted to pH 8 carefully with saturated $NaHCO_3$ solution, diluted with ethyl acetate, filtered through celite and extracted. The combined organic phase was dried over Na_2SO_4, and evaporated under vacuum to afford the crude amino diethyl thioacetal

(2*S*)-N-{4-[N-(1″-pyrenyl)-butane-3′-carboxamide]-oxy-5-methoxy-2-aminobenzoyl} pyrrolidine-2-carboxaldehyde diethyl thioacetal of formula IV (482 mg, 72%).
^{1}H NMR ($CDCl_3$) δ 1.10-1.40 (m, 6H), 1.50-2.30 (m, 10H), 2.40-2.80 (m, 6H), 3.40 (s; 3H), 3.45-3.60 (m, 2H), 4.05-4.15 (m, 2H), 4.50-4.70 (m, 2H), 6.25 (s, 1H), 6.70 (s, 1H), 7.65-8.30 (m, 9H), 9.10-9.25 (m, 1H).

A solution of (2*S*)-N-{4-[N-(1″-pyrenyl)-butane-3′-carboxamide]-oxy-5-methoxy-2-aminobenzoyl}pyrrolidine-2-carboxaldehyde diethyl thioacetal of formula IV (669 mg, 1 mmol), $HgCl_2$ (613 mg, 2.26 mmol) and $CaCO_3$ (246 mg, 2.46 mmol) in MeCN-water (4:1) was stirred slowly at room temperature until TLC indicates complete loss of starting material. Reaction mixture was diluted with EtOAc (30 mL) and filtered through a celite bed. The clear yellow organic supernatant was extracted with saturated 5% $NaHCO_3$ (20 mL), brine (20 mL) and combined organic phase is dried (Na_2SO_4). The organic layer was evaporated in vacuum and purified by column chromatography (90% CH_2Cl_2-MeOH) to give compound 7-Methoxy-8-[N-(1″-pyrenyl)-butne-4′-carboxamide]-oxy-(11a*S*)-1,2,3,11a-tetra-hydro-5*H*-pyrrolo[2,1-*c*][1,4]benzodiazepin-5-one of formula V as pale yellow oil (266 mg, 49%).
^{1}H NMR ($CDCl_3$) δ 1.40-2.40 (m, 12H), 2.60-2.90 (m, 2H), 3.40-4.05 (m, 4H), 4.10-4.40 (m, 2H), 6.85 (s, 1H), 7.40 (s, 1H), 7.65 (d, 1H), 7.75-8.20 (m, 8H), 8.20-8.40 (m, 1H), 9.0-9.10 (m, 1H); MS (FAB) 544 $[M + H]^{+\cdot}$.

Example 8

Compound (4*R*)-hydroxy-(2*S*)-N-{4-[(3′-carboxy butyl)oxy]-5-methoxy-2-nitrobenzoyl}pyrrolidine-2-car-boxaldehyde diethyl thioacetal of formula II (2.58 g, 5 mmol) was taken in dry CH_2Cl_2 (20 mL), TEA (707 mg, 7 mmol) was added and the mixture was cooled at 0-5 °C. Isobutyl chloroformate (819 mg, 6 mmol) in dry CH_2Cl_2 (10 mL) was added dropwise and the mixture was kept at 0-5 °C for 15 min. A solution of 1-amino pyrene of formula I (251 mg, 5 mmol) in CH_2Cl_2 was added to it at the same temperature and the solution was stirred at room temperature for overnight. The mixture was washed with saturated $NaHCO_3$ (50 mL), brine, dried and solvent was evaporated. The crude material was chromatographed over silica gel using ethyl acetate/hexane (8:2) solvent to give compound (4*R*)-hydroxy-(2*S*)-N-{4-[N-(1″-pyrenyl)-butane-3′-carboxamide]-oxy-5-methoxy-2-nitrobenzoyl}pyrrolidine-2-carboxaldehyde diethyl thioacetal of formula III as a yellow liquid.

The nitro diethyl thioacetal (4*R*)-hydroxy-(2*S*)-N-{4-[N-(1″-pyrenyl)-butane-3′-carboxamide]-oxy-5-methoxy-2-nitrobenzo-yl}pyrrolidine-2-carboxaldehyde diethyl thioacetal of formula III (0.715 g, 1 mmol) was dissolved in ethyl acetate (15 mL) and added $SnCl_2.2H_2O$ (1.12 g, 5 mmol) was refluxed for 3 h or until the TLC indicated that reaction

was completed. The reaction mixture was then adjusted to pH 8 carefully with saturated $NaHCO_3$ solution, diluted with ethyl acetate, filtered through celite and extracted. The combined organic phase was dried over Na_2SO_4, and evaporated under vacuum to afford the crude amino diethyl thioacetal ((4*R*)-hydroxy-(2*S*)-N-{4-[N-(1″-pyrenyl)-butane-3′-carboxamide]-oxy-5-methoxy-2-aminobenzoyl}pyrrolidine-2-carboxaldehyde diethyl thioacetal of formula IV.

A solution of (4*R*)-hydroxy-(2*S*)-N-{4-[N-(1″-pyrenyl)-butane-3′-carboxamide]-oxy-5-methoxy-2-aminobenzoyl}pyrrolidine-2-carboxaldehyde diethyl thioacetal of formula IV (685 mg, 1 mmol), $HgCl_2$ (613 mg, 2.26 mmol) and $CaCO_3$ (246 mg, 2.46 mmol) in MeCN-water (4:1) was stirred slowly at room temperature until TLC indicates complete loss of starting material. The reaction mixture was diluted with EtOAc (30 mL) and filtered through a celite bed. The clear yellow organic supernatant was extracted with saturated 5% $NaHCO_3$ (20 mL), brine (20 mL) and the combined organic phase is dried (Na_2SO_4). The organic layer was evaporated in vacuum and purified by column chromatography (90% CH_2Cl_2-MeOH) to give compound 7-Methoxy-8-[N-(1″-pyrenyl)-butne-4′-carboxamide]-oxy-(4*R*)-hydroxy-(11a*S*)-1,2,3,11a-tetra-hydro-5*H*-pyrrolo[2,1-*c*][1,4]benzodiazepin-5-one of formula V as pale yellow oil.

Biological Activity:

In vitro biological activity studies were carried out at National Cancer Institute (USA).

Cytotoxicity:

Compounds Ve and Vg were evaluated the primary anti-cancer activity (**Table 1**) and further Ve have been evaluated in vitro against sixty human tumour cells derived from nine cancer types (leukemia, non-small-cell lung, colon, CNS, melanoma, ovarian, prostate, and breast cancer). For each compound, dose response curves for each cell line were measured at a minimum of five concentrations at 10 fold dilutions. A protocol of 48 h continuous drug exposure was used and a sulforhodamine B (SRB) protein assay was used to estimate cell viability or growth. The concentration causing 50% cell growth inhibition (GI50), total cell growth inhibition (TGI 0% growth) and 50% cell death (LC50, -50% growth) compared with the control was calculated. The mean graph midpoint values of log_{10}TGI and log_{10}LC50 as well as log_{10} GI50 for Ve are listed in **Table 2**. As demonstrated by mean graph pattern, compound Ve exhibits an interesting profile of activity and selectivity for various cell lines. The mean graph mid point of log_{10} TGI and log_{10} LC50 showed similar pattern to the log_{10} GI50 mean graph mid points.

Table 1. *In vitro* one dose primary anticancer assay[a] pyrene linked PBD hybrid of formula **Ve** and **Vg**

PBD hybrids	Growth percentages		
	(Lung) NCI-H460	(Breast) MCF7	(CNS) SF-268
Ve	11	31	70
Vg	106	72	131

[a]One dose of Ve and Vg at 10^{-4} molar concentration

The novel pyrrolobenzodiazepine hybrid formula VIIa has shown to possess 10 nano molar potency (at the LC_{50} level) against one non-small cell lung cancer (NCI-H226) and one colon cancer (HCC-2998). and 0.1 micro molar potency against leukemia cancer (SR), melanoma cancer (M14), renal cancer (A498) and CNS cancer (SF-539) and also have 10 micro molar potency against two CNS cancer cell lines (SF539, SNB75) and one prostate cancer (DU-145). The LC50 values of nine cancers (average of six to nine cancer cell lines) of compound VIIa listed in **Table 3**

Table 2. $\log_{10}$ GI50 $\log_{10}$ TGI and $\log_{10}$ LC50 mean graphs midpoints(MG_MID) of in vitro cytotoxicity data for the compound **Ve** against human tumour cell lines.

Compound	**$\log_{10}$ GI50**	**$\log_{10}$ TGI**	**$\log_{10}$ LC50**
Ve	-7.75	-6.89	-4.74

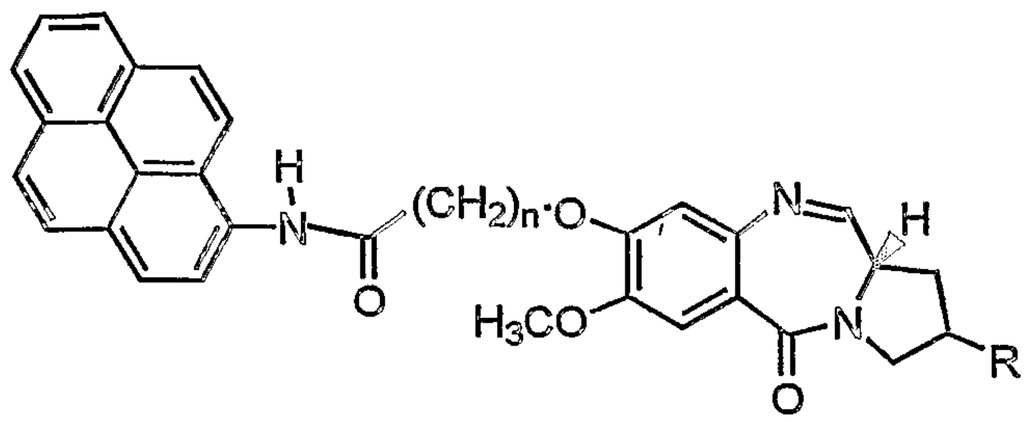
Table 3. Log LC50 (concentration in mol/L causing 50% lethality) Values for Compounds **Ve**

Cancer	**Compound Ve**
Leukemia	-4.65
Non-small-cell lung	-4.67
Colon	-5.00
CNS	-5.23
Melanoma	-5.62
Ovarian	> -4.00
Renal	-5.05
Prostate	-5.30
Breast	> -4.00

Each cancer type represents the average of six to nine different cancer cell lines.

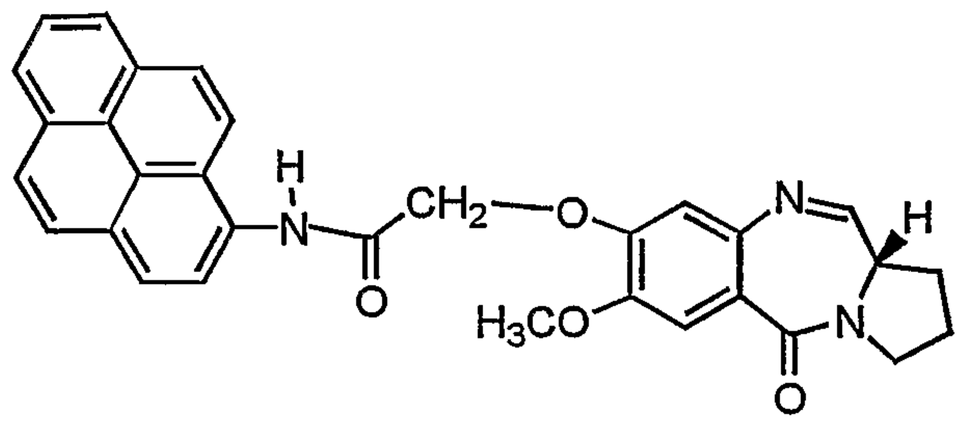
We Claim:

1 Pyrrolo[2,1-*c*][1,4]benzodiazepine hybrid of formula V wherein R is H, OH and n is 1-4.

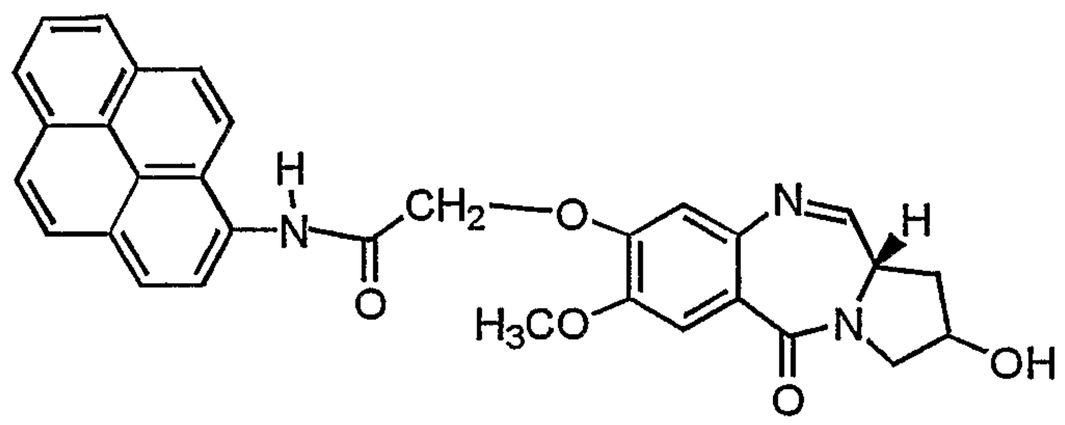


FORMULA V

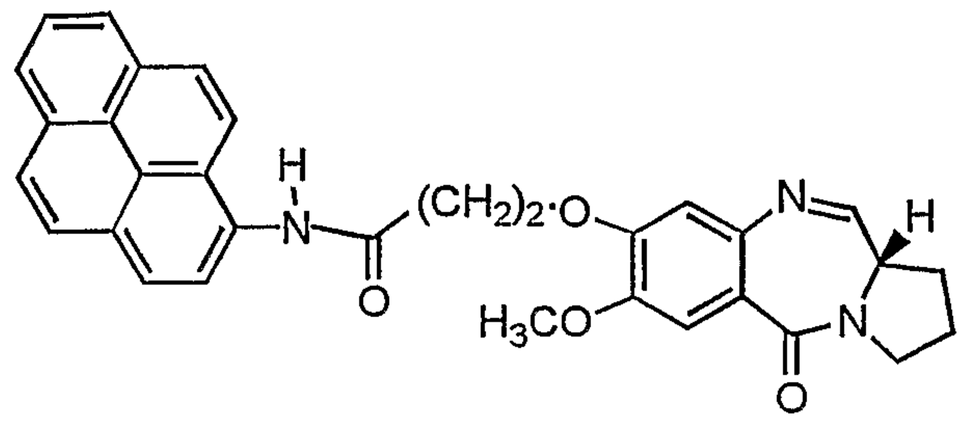
2 A pyrrolobenzodiazepine hybrid as claimed in claim 1 of the structural formula



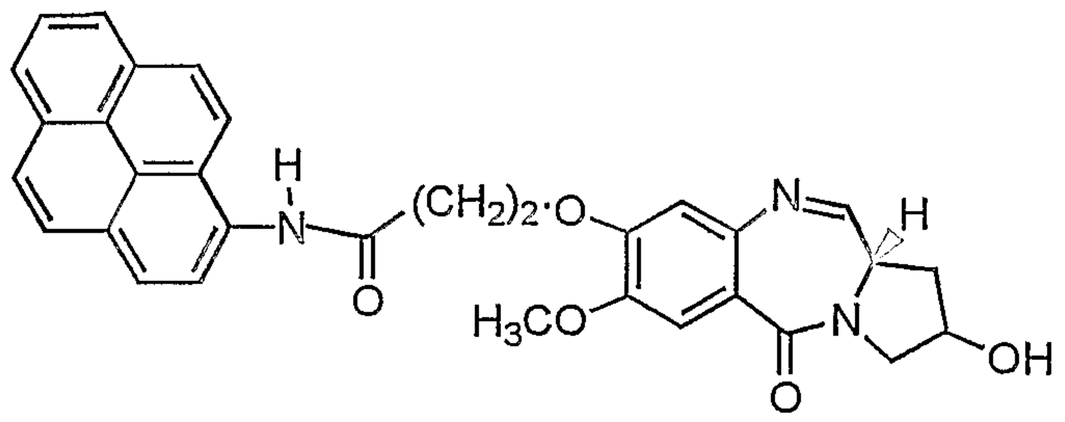
3 A pyrrolobenzodiazepine hybrid as claimed in claim 1 of the structural formula



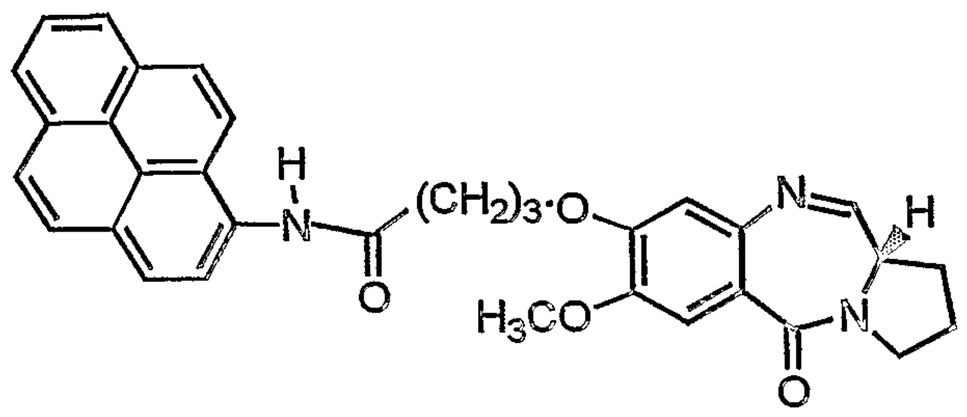
4 A pyrrolobenzodiazepine as claimed in claim 1 of the structural formula



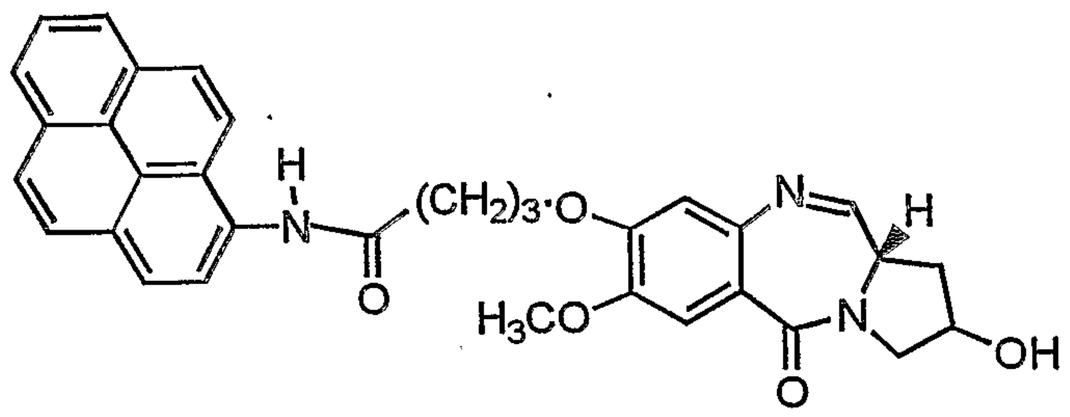
5 A pyrrolobenzodiazepine as claimed in claim 1 of the structural formula



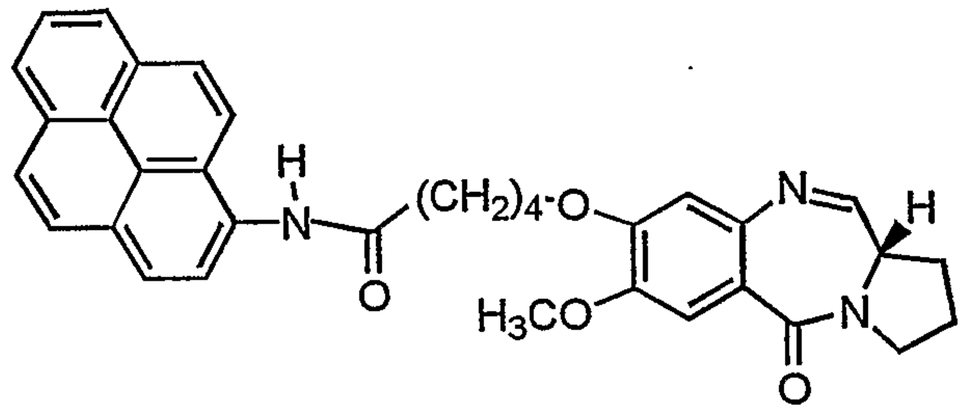
6 A pyrrolobenzodiazepine as claimed in claim 1 of the structural formula



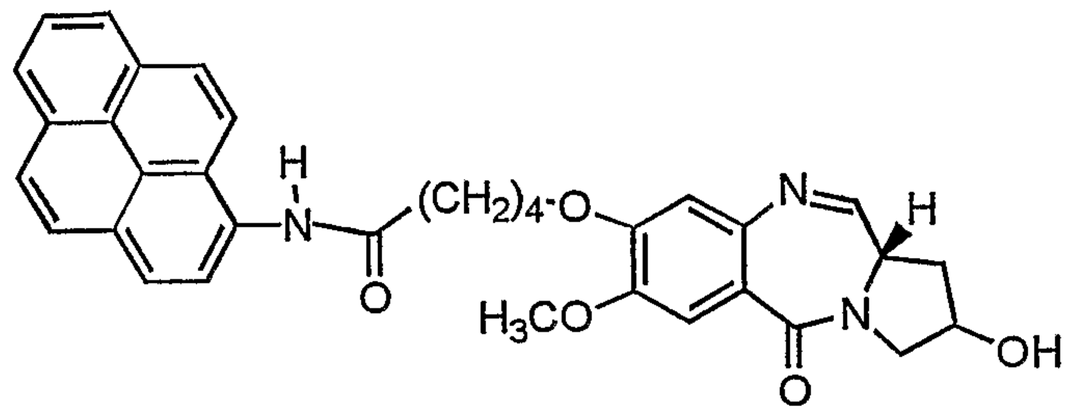
7 A pyrrolobenzodiazepine as claimed in claim 1 of the structural formula



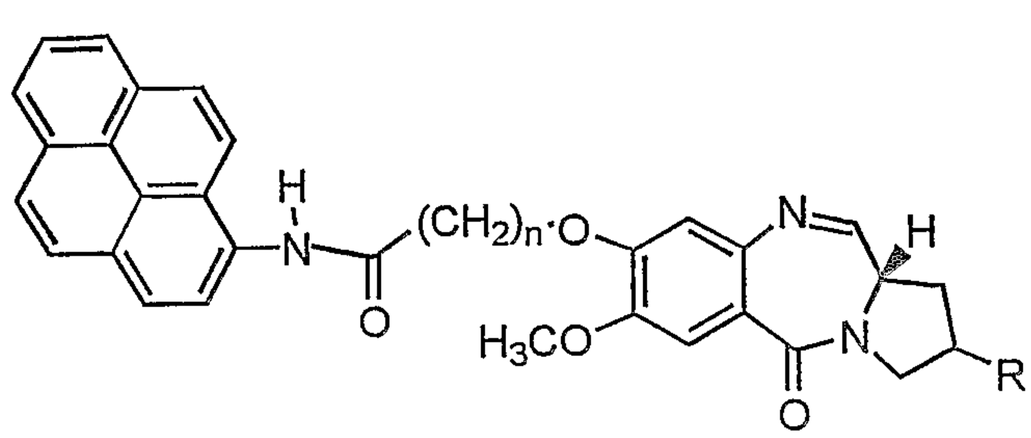
5 8 A pyrrolobenzodiazepine as claimed in claim 1 of the structural formula



9 A pyrrolobenzodiazepine as claimed in claim 1 of the structural formula



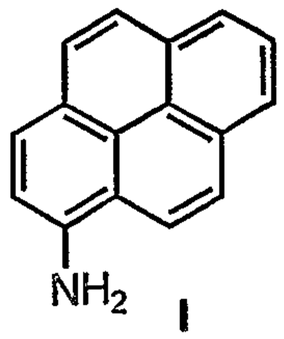
10. A process for preparing a pyrrolo[2,1-*c*][1,4]benzodiazepine hybrid of formula V



10

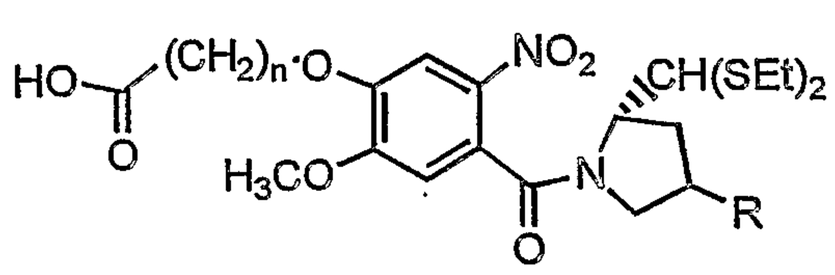
FORMULA V

which comprises reacting pyrene amine of formula I



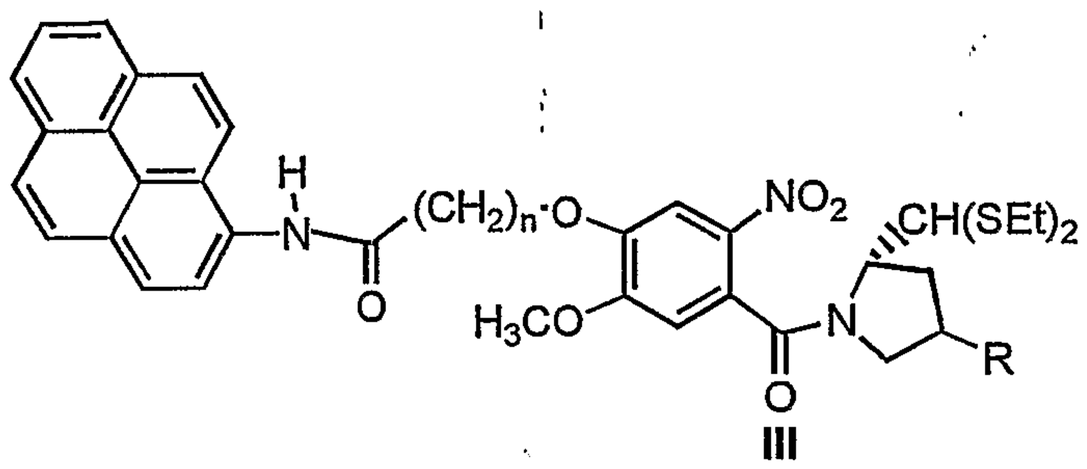
I

with (2*S*)-N-{4-[(3′-carboxy alkyl)oxy]-5-methoxy-2-nitrobenzoyl}pyrrolidine-2-carboxaldehyde diethyl thioacetal of formula II where R is as stated above



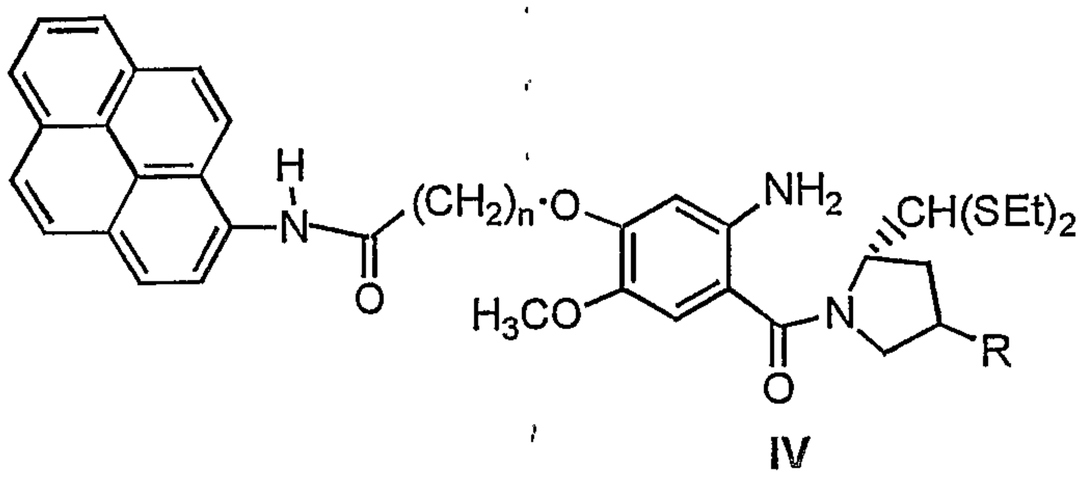
II

up to refluxing for a period of 24 h isolating (2*S*)-N-{4-[N-(1″-pyrenyl)-alkane-3′-carboxamide]-oxy--5-methoxy-2-nitrobenzoyl}pyrrolidine-2-carboxaldehyde diethyl thioacetal III where n is 1-4 and R is as stated above,



III

reducing the nitro compounds of formula III with $SnCl_2.2H_2O$ in presence of an organic solvent up to a reflux temperature, isolating the (2*S*)-N-{4-[N-(1″-pyrenyl)-alkane-3′-carboxamide]-oxy--5-methoxy-2-aminobenzoyl}pyrrolidine-2-carboxaldehyde diethyl thioacetal of formula IV where n is 1-4 and R is as stated above,



IV

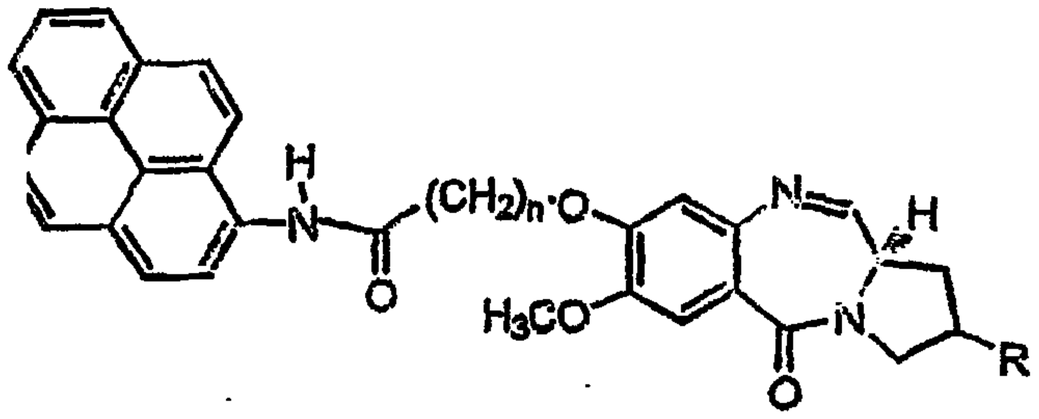
reacting the amino compound of formula IV with a deprotecting agent to give pyrrolo [2,1-*c*][1,4]benzodiazepine hybrids of formula V wherein n and R are as stated above.

11. A process as claimed in claim 10 wherein the reaction between the compound of formula I and the compound of formula II carried out in in the presence of isobutyl chloroformate and in the presence of a base selected from the group consisting of triethyl amine and

DBU; and in the presence of an organic solvent selected from the group consisting of ethyl acetate, hexane and dichloromethane.

12. A process as claimed in claim 10 wherein the organic solvent used for the reduction of the nitro compound of formula III comprises ethyl acetate.

13. Use of pyrrolo[2,1-*c*][1,4]benzodiazepine hybrid of formula V wherein R is H, OH and n is 1-4

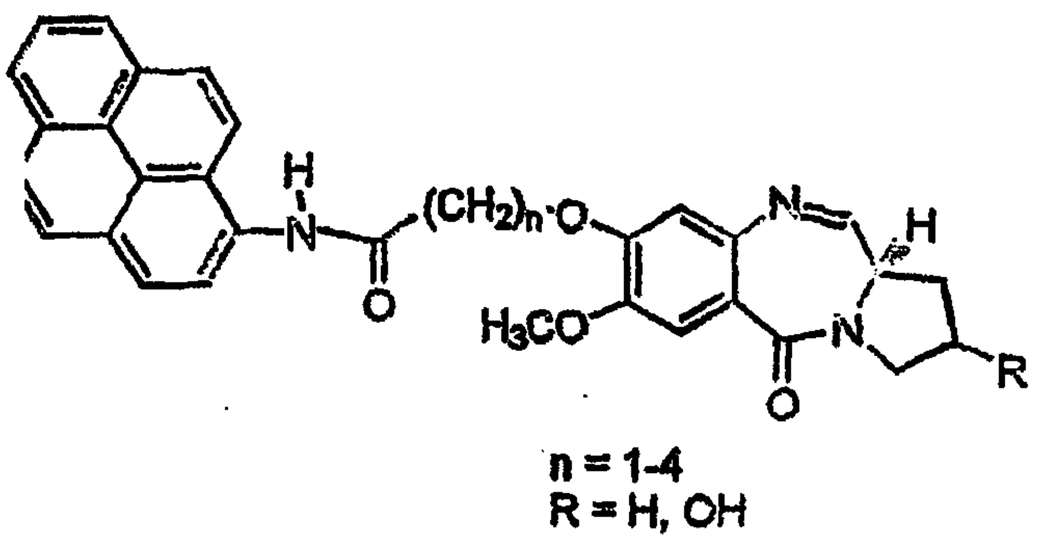


FORMULA V

for the treatment of cancer in a subject suffering therefrom.

14. Use as claimed in claim 13 wherein the cancer is selected from the group consisting of leukemia, non-small-cell lung, colon, CNS, melanoma, ovarian, prostate, and breast cancer.

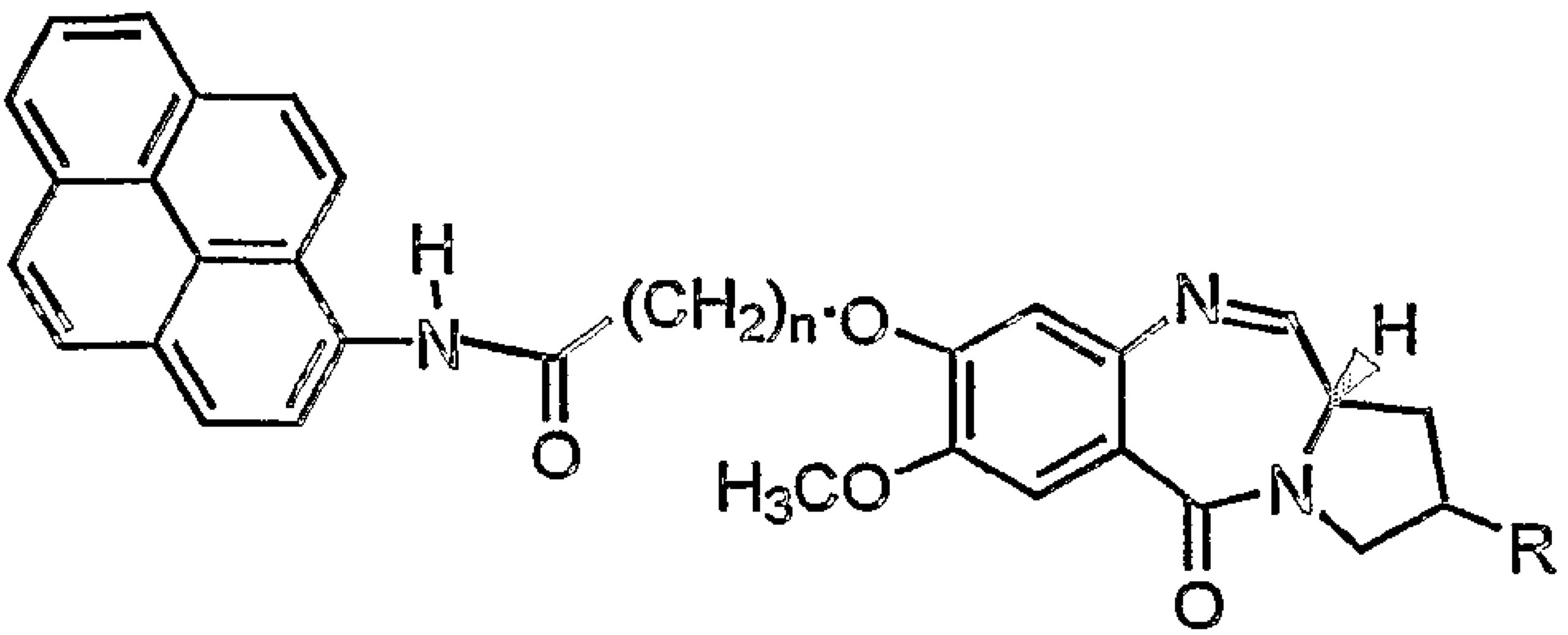
15. Use of pyrrolo[2,1-*c*][1,4]benzodiazepine hybrid of formula V wherein R is H, OH and n is 1-4



FORMULA V

for preparation of a medicament for the treatment of cancer in a subject suffering therefrom.

16. Use as claimed in claim 15 wherein the cancer is selected from the group consisting of leukemia, non-small-cell-lung, colon, CNS, melanoma, ovarian, prostate, and breast cancer.



n = 1-4
R = H, OH

FORMULA V