(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
11 May 2017 (11.05.2017)

WIPO | PCT

(10) International Publication Number
WO 2017/077307 A1

(51) International Patent Classification:
C07D 403/12 (2006.01) *A61K 31/404* (2006.01)
C07F 5/02 (2006.01) *A61P 35/00* (2006.01)
C07F 7/08 (2006.01)

(21) International Application Number:
PCT/GB2016/053418

(22) International Filing Date:
3 November 2016 (03.11.2016)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
1519644.7 6 November 2015 (06.11.2015) GB

(71) Applicant: **UNIVERSITY OF SOUTHAMPTON** [GB/GB]; Building 37, 4107, Highfield Southampton SO17 1BJ (GB).

(72) Inventors: **GALE, Philip Alan**; c/o Research and Innovation Services, Building 37, 4107, University of Southampton, Highfield Southampton SO17 1BJ (GB). **HOWE, Ethan Nam Wei**; c/o Research and Innovation Services, Building 37, 4107, University of Southampton, Highfield Southampton SO17 1BJ (GB). **ROSSOM, Wim Van**; c/o Research and Innovation Services, Building 37, 4107, University of Southampton, Highfield Southampton SO17 1BJ (GB).

(74) Agent: **BARKER BRETTELL LLP**; 100 Hagley Road, Edgbaston, Birmingham West Midlands B16 8QQ (GB).

(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DJ, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JP, KE, KG, KN, KP, KR, KW, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE,

[Continued on next page]

(54) Title: THERAPY AND PHARMACEUTICAL COMPOSITION

(57) Abstract: A novel class of compounds called perenosins, and their use in the treatment and/or prevention of cancer or a neoplastic condition.

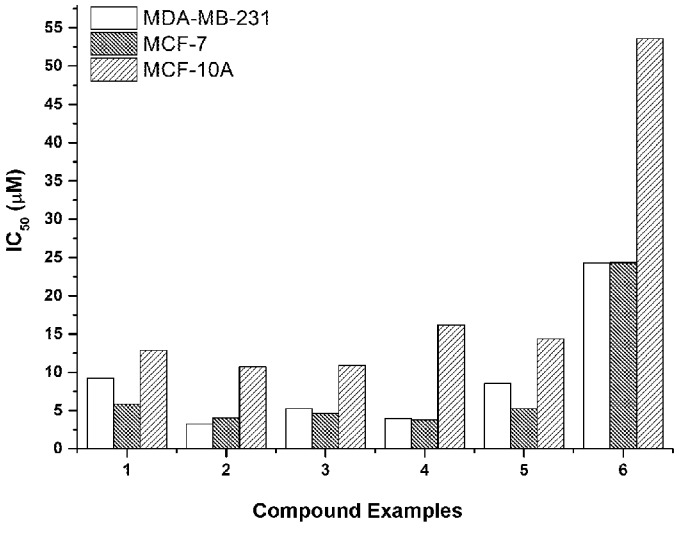


Figure 1.

WO 2017/077307 A1

DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

Published:

— *with international search report (Art. 21(3))*

THERAPY AND PHARMACEUTICAL COMPOSITION

The present invention relates to novel compounds and compositions and their use in therapy, in particular for the treatment or prevention of cancer or, a neoplastic disorder, or for inhibiting the growth of a cancer cell or neoplastic cell.

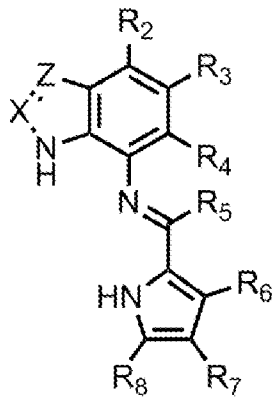
Cancer ranks first as a cause of death in the Western world, with breast cancer (28% of all cancers in woman) and lung cancer being responsible for 25% of the 14.1 million incidents each year (Ferlay *et al.,* 2013 Eur. J. Cancer. 29, 1374-1403). Although improved diagnostic methods have greatly improved the survival rate, the treatment of cancer still relies heavily on antineoplastic agents (chemotherapy) as it provides the most systemic approach, targeting cancerous cells that may remain after surgery and radiation therapy. Currently available anti-cancer drugs mainly target cancer cells *via* the inhibition of specific proteins such as aromatase inhibitors (L.Xu *et al*., 2014 Med. Oncol. 31:128).

Prodigiosenes (PGs) are a family of naturally occurring tripyrollic compounds, produced by a group of microorganisms including some Serratiai and Streptomyces strains, which were first isolated in pure form in 1929 (F.Wrede & O.Hettche 1929 Ber. Dtsch. Chem Ges. B. 62B, 2678-2685). Since the observation by Fullan *et al*., in 1977 that prodigiosenes have anti-tumour activity, many different natural and synthetic prodigiosenes have been tested for their anti-cancer properties. Prodigiosenes have been shown to passively transport chloride over vesicle and cell membranes and it has been proposed that their anti-cancer properties may be linked to this process. Many prodigiosenes have also shown potent antimicrobial, antimalarial, immunosuppressive properties. Unfortunately, their high toxicity prevents their use as clinical antibiotics. Closely related compounds including the tambjamines and obatoclax, having similar structures, have also been shown to exhibit similar biological properties. However, such compounds also exhibit a toxic profile.

Therefore, there is a significant need for novel compounds, compositions and methods that are useful for treating cancer or neoplastic disease wherein the compounds and compositions have a decreased toxicity profile.

The present invention provides a novel class of compounds (herein named perenosins). Preferably the compounds exhibit anticancer properties and have a non-toxic, or reduced toxicity, profile enabling them to be used for the treatment or prevention of cancer or neoplastic disease.

According to a first aspect the invention provides a compound of Formula I:



Formula I

wherein:

X is selected from –CH, –N or –CR_1 wherein R_1 is an (C1-C20) alkyl or an (C1-C20) alkoxy;

Z is selected from –CH, –N or –CR_1 wherein R_1 is an (C1-C20) alkyl or an (C1-C20) alkoxy;

R_2 is selected from –H, an (C1-C20) alkyl or an (C1-C20) alkoxy;

R_3 is selected from –H, –F,–Cl, –Br, –CN,–CF_3, an (C1-C20) alkyl, an (C1-C20) alkoxy; or wherein R_2 and R_3 can together form an (C5-C20) alicyclic ring;

R_4 is selected from –H, an (C1-C20) alkyl or an (C1-C20) alkoxy;

R_5 is –H;

R_6 is selected from –H, an (C1-C20) alkyl or an (C1-C20) alkoxy;

R_7 is selected from –H, an (C1-C20) alkyl or an (C1-C20) alkoxy;

R_8 is selected from –H, an (C1-C20) alkyl or an (C1-C20) alkoxy; or wherein R_7 and R_8 can together form a substituted phenyl ring, with one to four substituents selected from the group consisting of R_9, R_{10}, R_{11} and R_{12}; wherein

R_9 is selected from –H, an (C1-C20) alkyl or an (C1-C20) alkoxy;

R_{10} is selected from –H, –F, –Cl, –Br, –CN, –NO_2, –CF_3, an (C1- C20) alkyl or an (C1-C20) alkoxy;

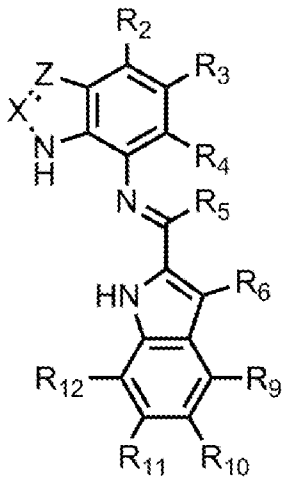
R_{11} is selected from –H, an (C1-C20) alkyl or an (C1-C20) alkoxy; and

R_{12} is selected from –H, an (C1-C20) alkyl or an (C1-C20) alkoxy;

or a pharmaceutically acceptable salt or solvate thereof.

In a preferred embodiment of the invention, R_6 and R_7 or R_7 and R_8 or R_6 and R_8 can together form an (C5-C20) alicyclic ring.

The compound of the present invention may be represented preferably by the following formula (Ia):



Formula Ia

wherein:

X is selected from –CH, –N or $–CR_1$ wherein R_1 is an (C1-C20) alkyl or an (C1-C20) alkoxy;

Z is selected from –CH, –N or $–CR_1$ wherein R_1 is an (C1-C20) alkyl or an (C1-C20) alkoxy;

R_2 is selected from –H, an (C1-C20) alkyl or an (C1-C20) alkoxy;

R_3 is selected from –H, –F,–Cl, –Br, –CN,$–CF_3$, an (C1-C20) alkyl or an (C1-C20) alkoxy; or wherein R_2 and R_3 can together form an (C5-C20) alicyclic ring;

R_4 is selected from –H, an (C1-C20) alkyl or an (C1-C20) alkoxy;

R_5 is –H;

R_6 is selected from –H, an (C1-C20) alkyl or an (C1-C20) alkoxy ;

R_9 is selected from –H, an (C1-C20) alkyl or an (C1-C20) alkoxy;

R_{10} is selected from –H, –F, –Cl, –Br, –CN, $–NO_2$, $–CF_3$, an (C1- C20) alkyl or an (C1-C20 alkoxy);

R_{11} is selected from –H or an (C1-C20) alkyl or an (C1-C20 alkoxy); and
R_{12} is selected from –H or an (C1-C20) alkyl or an (C1-C20 alkoxy);
or a pharmaceutically acceptable salt or solvate thereof.

In a preferred embodiment of the invention, (C1-C20) alkoxy is (C5-19) alkoxy, or (C5-16) alkoxy, or (C5-12) alkoxy, or (C5-C10) alkoxy, (C5-C8) alkoxy or (C1-C6 alkoxy).

In a preferred embodiment of the invention, R_9, R_{10} or R_{11} is (C1-C6 alkoxy).

In one embodiment, the invention provides a compound of Formula I or a pharmaceutically acceptable salt or solvate thereof, wherein the groups X, Z, R_1, R_2, R_3, R_4, R_5, R_6, R_7, R_8 have the following meanings:

X is selected from –CH, N or CR_1 wherein R_1 is an (C1-C6) alkyl;
Z is selected from –CH or N or CR_1 wherein R_1 is an (C1-C6) alkyl;
R_2 is selected from –H or an (C1-C6) alkyl;
R_3 is selected from –H, $–CH_3$,$–CF_3$, $–OCH_3$, or an (C1-C6) alkyl;
R_4 is selected from –H or an (C1-C6) alkyl;
R_5 is –H;
R_6 is –H or $–CH_3$;
R_7 is selected from –H or an (C1-C6) alkyl;
R_8 is –H or $–CH_3$.

Preferably, R_1 is C5-C6 alkyl. More preferably, R_1 is pentyl, isopentyl, hexyl or isohexyl. More preferably, R_1 is pentyl or isopentyl.

Preferably, R_2 is C5-C6 alkyl. More preferably, R_2 is pentyl, isopentyl, hexyl or isohexyl. More preferably, R_2 is pentyl or isopentyl.

Preferably, R_3 is C5-C6 alkyl. More preferably, R_3 is pentyl, isopentyl, hexyl or isohexyl. More preferably, R_3 is pentyl or isopentyl.

Preferably, R_4 is C5-C6 alkyl. More preferably, R_4 is pentyl, isopentyl, hexyl or isohexyl. More preferably, R_4 is pentyl or isopentyl.

Preferably, R_7 is C5-C6 alkyl. More preferably, R_7 is pentyl, isopentyl, hexyl or isohexyl. More preferably, R_7 is pentyl or isopentyl.

In another embodiment, the invention provides a compound of Formula I or a pharmaceutically acceptable salt or solvate thereof, wherein the groups X, Z, R_1, R_2, R_3, R_4, R_5, R_6, R_7, R_8 have the following meanings:

X is selected from –CH, N or CR_1 wherein R_1 is an (C1-C6) alkyl;
Z is selected from –CH or N or CR_1 wherein R_1 is an (C1-C6) alkyl;
R_2 is–H;
R_3 is selected from –H, $–CH_3$,$–CF_3$, $–OCH_3$ or C_5H_{11};
R_4 is–H;
R_5 is –H;
R_6 is –H or $–CH_3$;
R_7 is –H;
R_8 is –H or $–CH_3$.

In another embodiment, the invention provides a compound of Formula I or a pharmaceutically acceptable salt or solvate thereof, wherein the groups X, Z, R_1, R_2, R_3, R_4, R_5, R_6, R_7 and R_8 have the following meanings:

X is –CH;
Z is–CH;
R_2 is–H;
R_3 is selected from –H, $–CH_3$,$–CF_3$, $–OCH_3$ or C_5H_{11};
R_4 is–H;
R_5 is –H;
R_6 is$–CH_3$;
R_7 is –H;
R_8 is $–CH_3$.

In one embodiment, the invention provides a compound of Formula Ia or a pharmaceutically acceptable salt or solvate thereof, wherein the groups X, Z, R_1, R_2, R_3, R_4, R_5, R_6, R_7, R_8, R_9, R_{10}, R_{11} and R_{12} have the following meanings:

X is selected from –CH, N or CR_1 wherein R_1 is an (C1-C6) alkyl;

Z is selected from –CH or N or CR_1 wherein R_1 is an (C1-C6) alkyl;

R_2 is selected from –H or an (C1-C6) alkyl;

R_3 is selected from –H, $–CH_3$,$–CF_3$, $–OCH_3$, or an (C1-C6) alkyl;

R_4 is selected from –H or an (C1-C6) alkyl;

R_5 is –H;

R_6 is –H or $–CH_3$;

R_7 is selected from –H or an (C1-C6) alkyl;

R_8 is –H or $–CH_3$; or

wherein R_7 and R_8 can together form a substituted phenyl ring, with one to four substituents selected from the group consisting of R_9, R_{10}, R_{11} and R_{12};

wherein

R_9 is selected from –H or an (C1-C6) alkyl;

R_{10} is selected from –H, –F, –Cl, –Br, –CN, $–NO_2$, $–CF_3$, $–OCH_3$ or an (C1-C6) alkyl;

R_{11} is selected from –H or an (C1-C6) alkyl; and

R_{12} is selected from –H or an (C1-C6) alkyl;

or wherein R_7 and R_8 or R_7 and R_9 or R_8 and R_9 can together form an (C5-C20) alicyclic ring.

Preferably, R_1 is C5-C6 alkyl. More preferably, R_1 is pentyl, isopentyl, hexyl or isohexyl. More preferably, R_1 is pentyl or isopentyl.

Preferably, R_2 is C5-C6 alkyl. More preferably, R_2 is pentyl, isopentyl, hexyl or isohexyl. More preferably, R_2 is pentyl or isopentyl.

Preferably, R_3 is C5-C6 alkyl. More preferably, R_3 is pentyl, isopentyl, hexyl or isohexyl. More preferably, R_3 is pentyl or isopentyl.

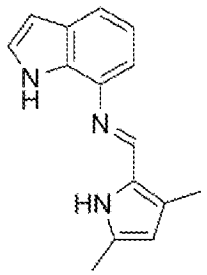
Preferably, R_4 is C5-C6 alkyl. More preferably, R_4 is pentyl, isopentyl, hexyl or isohexyl. More preferably, R_4 is pentyl or isopentyl.

Preferably, R_7 is C5-C6 alkyl. More preferably, R_7 is pentyl, isopentyl, hexyl or isohexyl. More preferably, R_7 is pentyl or isopentyl.

In another embodiment, the invention provides a compound of Formula Ia or a pharmaceutically acceptable salt or solvate thereof, wherein the groups X, Z, R_1, R_2, R_3, R_4, R_5, R_6, R_7, R_8, R_9, R_{10}, R_{11} and R_{12} have the following meanings:

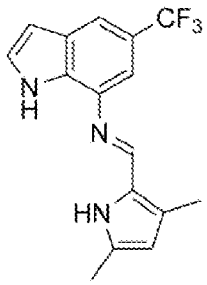
X is selected from –CH, N or CR_1 wherein R_1 is an (C1-C6) alkyl;
Z is selected from –CH or N or CR_1 wherein R_1 is an (C1-C6) alkyl;
R_2 is–H;
R_3 is selected from –H, $–CH_3$,$–CF_3$, $–OCH_3$ or C_5H_{11};
R_4 is–H;
R_5 is –H;
R_6 is –H or $–CH_3$;
R_7 is –H;
R_8 is –H or $–CH_3$; or
wherein R_7 and R_8 can together form a substituted phenyl ring, with one to four substituents selected from the group consisting of R_9, R_{10}, R_{11} and R_{12};
wherein
R_9 is selected from –H or an (C1-C6) alkyl;
R_{10} is selected from –H, –F, –Cl, –Br, –CN, $–NO_2$, $–CF_3$, $–OCH_3$ or an (C1-C6) alkyl;
R_{11} is selected from –H or an (C1-C6) alkyl; and
R_{12} is selected from –H or an (C1-C6) alkyl;
or wherein R_7 and R_8 or R_7 and R_9 or R_8 and R_9 can together form an (C5-C20) alicyclic ring.

In one embodiment, X is –CH; Z is –CH, R_2 is –H, R_3 is –H, R_4 is –H, R_5 is –H; R_6 is $–CH_3$, R_7 is –H and R_8 is $–CH_3$.



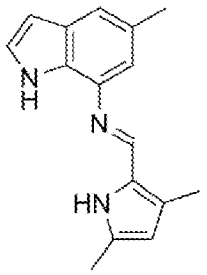
Compound Example 1 ($C_{15}H_{15}N_3$) Formula II

In one embodiment, X is –CH; Z is –CH, R_2 is –H, R_3 is $–CF_3$, R_4 is –H, R_5 is –H; R_6 is $–CH_3$, R_7 is –H and R_8 is $–CH_3$.



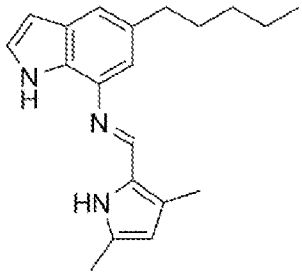
Compound Example 2 ($C_{16}H_{14}F_3N_3$) Formula III

In one embodiment, X is –CH; Z is –CH, R_2 is –H, R_3 is $–CH_3$, R_4 is –H, R_5 is –H; R_6 is $–CH_3$, R_7 is –H and R_8 is $–CH_3$.



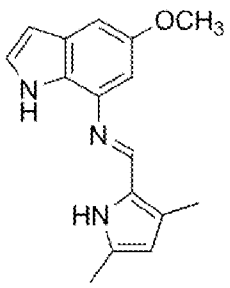
Compound Example 3 ($C_{16}H_{17}N_3$) Formula IV

In one embodiment, X is –CH; Z is –CH, R_2 is –H, R_3 is $–C_5H_{11}$, R_4 is –H, R_5 is –H; R_6 is $–CH_3$, R_7 is –H and R_8 is $–CH_3$.



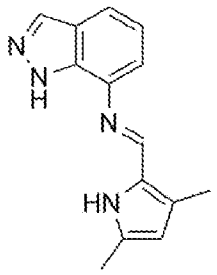
Compound Example 4 ($C_{20}H_{25}N_3$) Formula V

In one embodiment, X is –CH; Z is –CH, R_2 is –H, R_3 is $–OCH_3$, R_4 is –H, R_5 is –H; R_6 is $–CH_3$, R_7 is –H and R_8 is $–CH_3$.



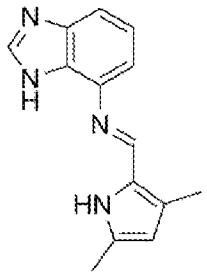
Compound Example 5 ($C_{16}H_{17}N_3O$) Formula VI

In one embodiment, X is –N; Z is –CH, R_2 is –H, R_3 is –H, R_4 is –H, R_5 is –H; R_6 is –CH_3, R_7 is –H and R_8 is –CH_3.



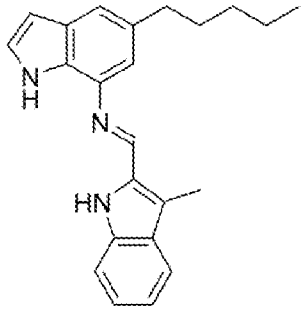
Compound Example 6 ($C_{14}H_{14}N_4$) Formula VII

In one embodiment, X is –CH; Z is –N, R_2 is –H, R_3 is –H, R_4 is –H, R_5 is –H; R_6 is –CH_3, R_7 is –H and R_8 is –CH_3.



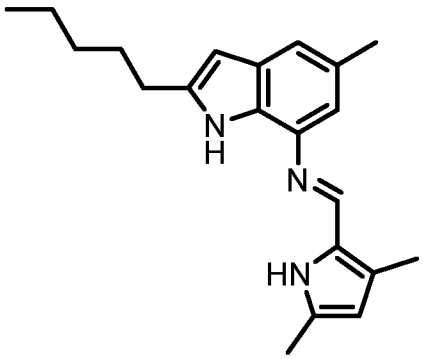
Compound Example 7 ($C_{14}H_{14}N_4$) Formula VIII

In one embodiment, X is –CH; Z is –CH, R_2 is –H, R_3 is –C_5H_{11}, R_4 is –H, R_5 is –H; R_6 is –CH_3, R_9 is –H, R_{10} is –H, R_{11} is –H and R_{12} is –H.



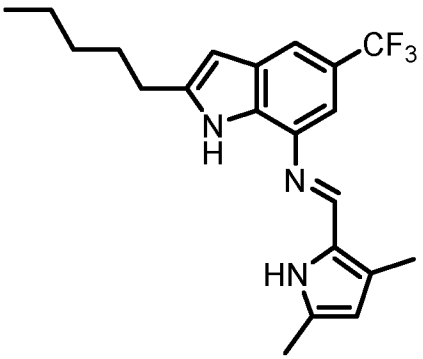
Compound Example 8 ($C_{23}H_{25}N_3$) Formula IX

In one embodiment, X is $-CR_1$ wherein R_1 is $-C_5H_{11}$; Z is –CH, R_2 is –H, R_3 is $-CH_3$, R_4 is –H, R_6 is $-CH_3$, R_7 is –H and R_8 is $-CH_3$.



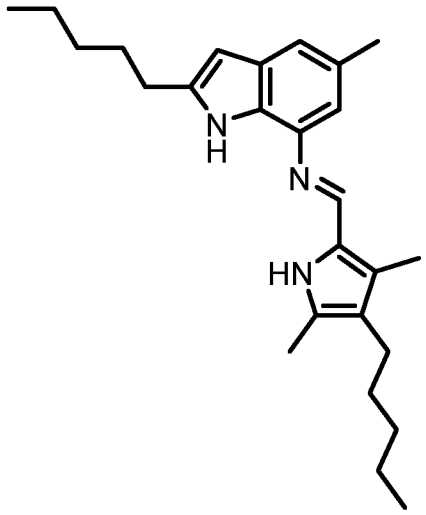
Compound Example 9 ($C_{21}H_{27}N_3$) Formula X

In one embodiment, X is - X is $-CR_1$ wherein R_1 is $-C_5H_{11}$; Z is –CH, R_2 is –H, R_3 is $-CF_3$, R_4 is –H, R_5 is –H, R_6 is $-CH_3$, R_7 is –H and R_8 is $-CH_3$.



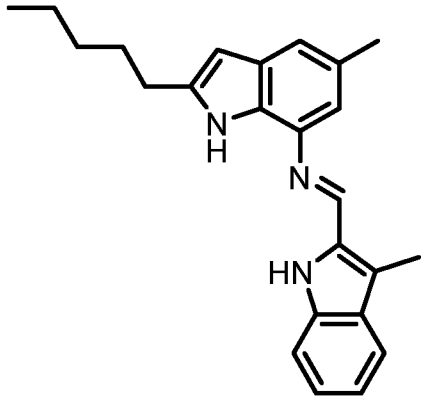
Compound Example 10 ($C_{21}H_{24}F_3N_3$) Formula XI

In one embodiment, X is - X is $-CR_1$ wherein R_1 is $-C_5H_{11}$; Z is –CH, R_2 is –H, R_3 is $-CH_3$, R_4 is –H, R_5 is –H, R_6 is $-CH_3$, R_7 is $-C_5H_{11}$ and R_8 is $-CH_3$.



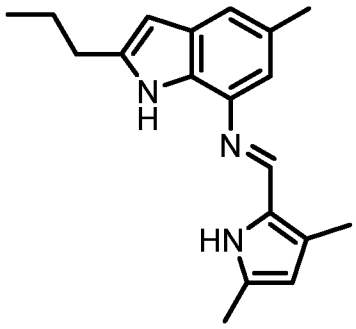
Compound Example 11 ($C_{26}H_{37}N_3$) Formula XII

In one embodiment, X is - X is $-CR_1$ wherein R_1 is $-C_5H_{11}$; Z is –CH, R_2 is –H, R_3 is $-CH_3$, R_4 is –H, R_5 is –H, R_6 is $-CH_3$, R_9 is –H, R_{10} is –H, R_{11} is –H and R_{12} is –H.



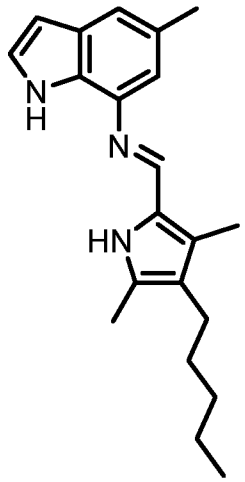
Compound Example 12 ($C_{24}H_{27}N_3$) Formula XIII

In one embodiment, X is $-CR_1$ wherein R_1 is $-C_3H_7$; Z is –CH, R_2 is –H, R_3 is $-CH_3$, R_4 is –H, R_5 is –H, R_6 is $-CH_3$, R_7 is –H and R_8 is $-CH_3$.



Compound Example 13 ($C_{19}H_{23}N_3$) Formula XIV

In one embodiment, X is –CH; Z is –CH, R_2 is –H, R_3 is $-CH_3$, R_4 is –H, R_5 is –H, R_6 is $-CH_3$, R_7 is $-C_5H_{11}$ and R_8 is $-CH_3$.



Compound Example 14 ($C_{21}H_{27}N_3$) Formula XV

As used herein, the term 'alkyl' refers to a saturated straight-chain or branched-chain alkyl group containing from 1 to 20 carbon atoms. An (C1-C20) alkyl has from 1 to 20 carbon atoms. Examples of alkyl groups include, but are not limited to, methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, pentyl, isopentyl, neo-pentyl, iso-amyl, hexyl, isohexyl, heptyl, octyl, nonyl, decyl or undecyl.

As used herein, the term 'alkoxy' refers to an alkyl group bonded to an oxygen atom. An (C1-C20) alkoxy group has from 1 to 20 carbon atoms.

As used herein, the term 'alicylic ring' refers to an organo carbocyclic group with heteroatoms. An (C5-C20) alicyclic ring has from 5 to 20 carbon atoms and contains one or more rings which may be either saturated or unsaturated.

Some compounds among those represented by Formula I and Formula Ia contain a chiral centre or geometrical isomer centre (E and Z isomers). Also included within the scope of the invention are all isomers, including all stereoisomers, and mixtures thereof, of a compound of Formula I or Formula Ia, as well as all salts and solvates thereof. Also included within the scope of the invention are all physical forms (including polymorphic forms and amorphous forms) of any such compounds.

According to a second aspect the invention provides a pharmaceutical composition comprising a compound of Formula I or Ia as herein described, or a pharmaceutically acceptable salt thereof, together with a pharmaceutically acceptable carrier, diluent or excipient.

In one aspect, the invention provides a stereoisomer or a mixture thereof, of a compound of Formula I, Formula Ia, Formula II, Formula III, Formula IV, Formula V, Formula VI, Formula VII, Formula VIII, Formula IX, Formula X, Formula XI, Formula XII, Formula XIII, Formula XIV or Formula XV.

In another aspect, the invention relates to a derivative or analogue of a compound of Formula I, Formula Ia, Formula II, Formula III, Formula IV, Formula V, Formula VI, Formula VII, Formula VIII Formula, Formula IX, Formula X, Formula XI, Formula XII, Formula XIII, Formula XIV or Formula XV.

In yet another aspect, the invention relates to a solvate or polymorph of a compound of Formula I, Formula Ia, Formula II, Formula III, Formula IV, Formula V, Formula VI, Formula VII, Formula VIII, Formula IX, Formula X, Formula XI, Formula XII, Formula XIII, Formula XIV or Formula XV.

In another aspect, the invention relates to a salt of the compound of Formula I, Formula Ia, Formula II, Formula III, Formula IV, Formula V, Formula VI, Formula VII, Formula VIII, Formula IX, Formula X, Formula XI, Formula XII, Formula XIII, Formula XIV or Formula XV.

In yet another aspect, the invention relates to a prodrug of a compound of Formula I, Formula Ia, Formula II, Formula III, Formula IV, Formula V, Formula VI, Formula VII, Formula VIII, Formula IX, Formula X, Formula XI, Formula XII, Formula XIII, Formula XIV or Formula XV.

In yet another aspect, the invention relates to a metabolite of a compound of Formula I, Formula Ia, Formula II, Formula III, Formula IV, Formula V, Formula VI, Formula VII, Formula VIII, Formula IX, Formula X, Formula XI, Formula XII, Formula XIII, Formula XIV or Formula XV.

In another aspect, the invention provides a compound of Formula I or Formula 1a, a pharmaceutical composition comprising a compound of Formula I or Formula 1a, or a pharmaceutically acceptable salt thereof, for use in the treatment and/or prevention of cancer or a neoplastic disease. According to another aspect, the invention provides the use of a compound of Formula I or Formula Ia, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment and or prevention of cancer or a neoplastic disease.

The cancer may be selected from carcinoma, lymphoma, blastoma, sarcoma, and leukemia. More particularly, examples of such cancers include squamous cell cancer, small-cell lung cancer, non-small cell lung cancer, adenocarcinoma of the lung, squamous carcinoma of the lung, cancer of the peritoneum, hepatocellular cancer, gastrointestinal cancer, pancreatic cancer, glioblastoma, cervical cancer, ovarian cancer, liver cancer, bladder cancer, hepatoma, breast cancer, colon cancer, colorectal cancer, endometrial or uterine carcinoma, salivary gland carcinoma, kidney cancer, liver cancer, prostate cancer, renal cancer, vulval cancer, thyroid cancer, hepatic carcinoma, gastric cancer, melanoma, and various types of head and neck cancer. The cancer may be selected from breast, lung or ovarian cancer.

The compound of Formula I or Formula Ia, or a pharmaceutically acceptable salt thereof, may be intended to be administered in combination with an anti-cancer agent, such as a chemotherapeutic agent and it may have an additive therapeutic effect or a synergistic effect when administered.

A chemotherapeutic agent is a chemical compound useful in the treatment of cancer. Examples of chemotherapeutic agents include chemical compounds useful in the treatment of cancer. Examples of chemotherapeutic agents include alkylating agents such as thiotepa and CYTOXAN® cyclosphosphamide; alkyl sulfonates such as busulfan, improsulfan and piposulfan; aziridines such as benzodopa, carboquone, meturedopa, and uredopa; ethylenimines and methylamelamines including altretamine, triethylenemelamine, trietylenephosphoramide, triethiylenethiophosphoramide and trimethylolomelamine; acetogenins (especially bullatacin and bullatacinone); a camptothecin (including the synthetic analogue topotecan); bryostatin; callystatin; CC- 1065 (including its adozelesin, carzelesin and bizelesin synthetic analogues); cryptophycins (particularly cryptophycin 1 and cryptophycin 8); dolastatin; duocarmycin (including the synthetic analogues, KW-2189 and CBl-TMl); eleutherobin; pancratistatin; a sarcodictyin; spongistatin; nitrogen mustards such as chlorambucil, chlornaphazine, cholophosphamide, estramustine, ifosfamide, mechlorethamine, mechlorethamine oxide hydrochloride, melphalan, novembichin, phenesterine, prednimustine, trofosfamide, uracil mustard; nitrosureas such as carmustine, chlorozotocin, fotemustine, lomustine, nimustine, and ranimnustine; antibiotics such as the enediyne antibiotics (e. g., calicheamicin, especially calicheamicin gammall and calicheamicin omegall (see, e.g., Agnew, Chem Intl. Ed. Engl, 33: 183-186 (1994)); dynemicin, including dynemicin A; bisphosphonates, such as clodronate; an esperamicin; as well as neocarzinostatin chromophore and related chromoprotein enediyne antiobiotic chromophores), aclacinomysins, actinomycin, authramycin, azaserine, bleomycins, cactinomycin, carabicin, carminomycin, carzinophilin, chromomycinis, dactinomycin, daunorubicin, detorubicin, 6-diazo-5-oxo-L-norleucine, ADRIAM YCIN® doxorubicin (including morpholino-doxorubicin, cyanomorpholino-doxorubicin, 2-pyrrolino-doxorubicin and deoxydoxorubicin), epirubicin, esorubicin, idarubicin, marcellomycin, mitomycins such as mitomycin C, mycophenolic acid, nogalamycin, olivomycins, peplomycin, potfiromycin, puromycin, quelamycin, rodorubicin, streptonigrin, streptozocin, tubercidin, ubenimex, zinostatin, zorubicin; anti-metabolites such as methotrexate and 5-fluorouracil (5-FU); folic acid analogues such as denopterin, methotrexate, pteropterin, trimetrexate; purine analogs such as fludarabine, 6-mercaptopurine, thiamiprine, thioguanine; pyrimidine analogs such as ancitabine, azacitidine, 6-azauridine, carmofur, cytarabine, dideoxyuridine, doxifluridine, enocitabine, floxuridine; androgens such as calusterone, dromostanolone propionate, epitiostanol, mepitiostane, testolactone; anti-adrenals

such as aminoglutethimide, mitotane, trilostane; folic acid replenisher such as frolinic acid; aceglatone; aldophosphamide glycoside; aminolevulinic acid; eniluracil; amsacrine; bestrabucil; bisantrene; edatraxate; defofamine; demecolcine; diaziquone; elfornithine; elliptinium acetate; an epothilone; etoglucid; gallium nitrate; hydroxyurea; lentinan; lonidainine; maytansinoids such as maytansine and ansamitocins; mitoguazone; mitoxantrone; mopidanmol; nitraerine; pentostatin; phenamet; pirarubicin; losoxantrone; podophyllinic acid; 2- ethylhydrazide; procarbazine; PSK® polysaccharide complex (JHS Natural Products, Eugene, OR); razoxane; rhizoxin; sizofïran; spirogermanium; tenuazonic acid; triaziquone; 2,2',2"-trichlorotriethylamine; trichothecenes (especially T-2 toxin, verracurin A, roridin A and anguidine); urethan; vindesine; dacarbazine; mannomustine; mitobronitol; mitolactol; pipobroman; gacytosine; arabinoside ("Ara-C"); cyclophosphamide; thiotepa; taxoids, e.g., TAXOL® paclitaxel (Bristol- Myers Squibb Oncology, Princeton, N.J.), ABRAXANE® Cremophor-free, albumin-engineered nanoparticle formulation of paclitaxel (American Pharmaceutical Partners, Schaumberg, Illinois), and TAXOTERE® doxetaxel (Rhone- Poulenc Rorer, Antony, France); chloranbucil; GEMZAR® gemcitabine; 6-thioguanine; mercaptopurine; methotrexate; platinum analogs such as cisplatin, oxaliplatin and carboplatin; vinblastine; platinum; etoposide (VP- 16); ifosfamide; mitoxantrone; vincristine; NAVELBINE® vinorelbine; novantrone; teniposide; edatrexate; daunomycin; aminopterin; xeloda; ibandronate; irinotecan (Camptosar, CPT-11) (including the treatment regimen of irinotecan with 5 -FU and leucovorin); topoisomerase inhibitor RFS 2000; difluorometlhylornithine (DMFO); retinoids such as retinoic acid; capecitabine; combretastatin; leucovorin (LV); oxaliplatin, including the oxaliplatin treatment regimen (FOLFOX); inhibitors of PKC-alpha, Raf, H-Ras, EGFR (e.g., erlotinib (Tarceva®)) and VEGF-A that reduce cell proliferation and pharmaceutically acceptable salts, acids or derivatives of any of the above. Also included in this definition are anti-hormonal agents that act to regulate or inhibit hormone action on tumors such as anti-estrogens and selective estrogen receptor modulators (SERMs), including, for example, tamoxifen (including NOLVADEX® tamoxifen), raloxifene, droloxifene, 4-hydroxytamoxifen, trioxifene, keoxifene, LYl 17018, onapristone, and FARESTON- toremifene; aromatase inhibitors that inhibit the enzyme aromatase, which regulates estrogen production in the adrenal glands, such as, for example, 4(5)-imidazoles, aminoglutethimide, MEGASE® megestrol acetate, AROMASIN® exemestane, formestanie, fadrozole, RIVISOR® vorozole, FEMARA® letrozole, and ARIMIDEX® anastrozole; and anti-androgens

such as flutamide, nilutamide, bicalutamide, leuprolide, and goserelin; as well as troxacitabine (a 1,3-dioxolane nucleoside cytosine analog); antisense oligonucleotides, particularly those which inhibit expression of genes in signaling pathways implicated in abherant cell proliferation, such as, for example, PKC- alpha, RaIf and H-Ras; ribozymes such as a VEGF expression inhibitor (e.g., ANGIOZYME® ribozyme) and a HER2 expression inhibitor; vaccines such as gene therapy vaccines, for example, ALLOVECTIN® vaccine, LEUVECTIN® vaccine, and VAXID® vaccine; PROLEUKIN® rIL-2; LURTOTECAN® topoisomerase 1 inhibitor; ABARELIX® rmRH; and pharmaceutically acceptable salts, acids or derivatives of any of the above.

Depending on the type and severity of the disease or condition to be treated the therapeutic dose of a compound of Formula I or Formula 1a, or a pharmaceutically acceptable salt thereof, may vary.

For example, for the treatment of cancer, wherein the compound of Formula I or Formula Ia, or a pharmaceutically acceptable salt thereof, is being used as a chemotherapeutic agent the dose used may be between about 30mg and about 1200mg per day. The compound of Formula I or Formula Ia, or a pharmaceutically acceptable salt thereof, may be administered in a single dose, or in multiple doses. The multiple doses may be administered over the course of one day or over several days, for example over 2 or 3 days, or over 4 or 5 days or more. The dose per day may be between about 60 and 300 mg per 70 kg of subject weight per day.

According to another aspect the invention provides a method of treating and or preventing cancer or a neoplastic disease in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a compound of Formula I or Formula Ia or a pharmaceutically acceptable salt thereof.

The compound of Formula I or Formula Ia, or a pharmaceutically acceptable salt thereof, may be administered alone or in combination with another active agent. For example, to treat cancer, the compound of Formula I or Formula Ia, or a pharmaceutically acceptable salt thereof, may be administered in combination with a chemotherapeutic agent. Administration of the compound of Formula I or Formula Ia may mean that the chemotherapeutic agent is more effective or is effective at a lower dose.

The compound or composition according to the invention may act as an antiproliferative agent slowing the proliferation of cells, in particular cancer cells.

The invention may further provide a product containing at least a compound of Formula I or Formula Ia, or a pharmaceutically acceptable salt thereof, and a chemotherapeutic agent as a combined preparation for simultaneous, separate or sequential use in an anticancer therapy. The compound of Formula I or Formula Ia and the chemotherapeutic agent may be provided in the same or different preparations.

In another aspect the invention provides a kit comprising as a first therapeutic agent a compound of Formula I or Formula Ia, , or a pharmaceutically acceptable salt thereof, and as a second therapeutic agent an anti-cancer agent, wherein the anti-cancer agent is provided in a form suitable for, and/or with instructions for, administration in a daily dosage which is significantly reduced compared to the dosage of the anti-cancer agent if administered alone. The first and second therapeutic agents may be intended to be administered simultaneously, sequentially or separately. The anti-cancer agent may be a chemotherapeutic agent.

In another aspect the invention provides a method for producing a compound of Formula I or Formula Ia according to Scheme 1.

Preferably compounds of Formula I or Formula Ia, or a pharmaceutically acceptable salt thereof, do not have any significant side effects when administered to a subject. Preferably at the doses required for efficacy the compounds are not toxic to a subject.

The compound of the invention may be formulated as a prodrug or a protected formula. The compound may be a prodrug or a protected form of the compound which releases the compound after administration to a subject. For example, the compound may carry a protective group which is split off by hydrolysis in body fluids, *e.g.*, in the bloodstream, thus releasing the active compound or is oxidized or reduced in body fluids to release the compound. Reference to a "prodrug" is intended to indicate a compound that may be converted under physiological conditions or by solvolysis to a biologically active compound of the invention. Thus, the term "prodrug" refers to a metabolic precursor of a compound of the invention that is pharmaceutically

acceptable. A prodrug may be inactive when administered to a subject in need thereof, but is converted *in vivo* to an active compound of the invention. Prodrugs are typically rapidly transformed *in vivo* to yield the parent compound of the invention, for example, by hydrolysis in blood. The prodrug compound often offers advantages of solubility, tissue compatibility or delayed release in a subject.

The term "prodrug" may include any covalently bonded carriers which release the active compound of the invention *in vivo* when such prodrug is administered to a subject. Prodrugs of a compound of the invention may be prepared by modifying functional groups present in the compound of the invention in such a way that the modifications are cleaved, either in routine manipulation or *in vivo*, to the parent compound of the invention. Prodrugs include compounds of the invention wherein a hydroxy, amino or mercapto group is bonded to any group that, when the prodrug of the compound of the invention is administered to a mammalian subject, cleaves to form a free hydroxy, free amino or free mercapto group, respectively. Examples of prodrugs include, but are not limited to, acetate, formate and benzoate derivatives of alcohol and acetamide, formamide, and benzamide derivatives of amine functional groups in the compounds of the invention and the like.

A discussion of prodrugs may be found in "Smith and Williams' Introduction to the Principles of Drug Design," H.J. Smith, Wright, Second Edition, London (1988); which is incorporated in full by reference herein.

Compositions or compounds according to the invention, or for use according to the invention, can be provided alone or in combination with other compounds, for example they may be provided in the presence of a liposome, an adjuvant, or any pharmaceutically acceptable carrier, diluent or excipient, in a form suitable for administration to a subject such as a mammal, for example, humans, cattle, sheep, etc. If desired, treatment with a compound according to the invention may be combined with more traditional and existing therapies for the therapeutic indications described herein. For example, in the treatment of cancer compositions according to the invention may be administered in combination with one or more additional anti-cancer therapies. Examples of anti-cancer therapies include, without limitation, surgery, radiation therapy (radiotherapy), biotherapy, immunotherapy, chemotherapy, or a combination of these therapies. Chemotherapy may include the administration of one

or more chemotherapeutic agents. The composition according to the invention and the one or more additional anti-cancer therapies, such as one or more chemotherapeutic agents, may be administered separately, sequentially or simultaneously.

The combined administration of a compound of Formula I or Formula Ia, or a pharmaceutically acceptable salt thereof, and an additional anti-cancer therapy includes co-administration or concurrent administration, using separate formulations or a single pharmaceutical formulation, and consecutive administration in either order, wherein optionally there is a time period while both (or all) active agents simultaneously exert their biological activities.

"Pharmaceutically acceptable carrier, diluent or excipient" includes without limitation any adjuvant, carrier, excipient, glidant, sweetening agent, diluent, preservative, dye/colorant, flavour enhancer, surfactant, wetting agent, dispersing agent, suspending agent, stabilizer, isotonic agent, solvent, or emulsifier that has been approved, for example, by the United States Food and Drug Administration or other governmental agency as being acceptable for use in humans or domestic animals.

The compounds of the present invention may be administered in the form of pharmaceutically acceptable salts. In such cases, pharmaceutical compositions in accordance with this invention may comprise a salt of such a compound, preferably a physiologically acceptable salt, which are known in the art. In some embodiments, the term "pharmaceutically acceptable salt" as used herein means an active ingredient comprising compounds of Formula 1 used in the form of a salt thereof, particularly where the salt form confers on the active ingredient improved pharmacokinetic properties as compared to the free form of the active ingredient or other previously disclosed salt form.

The term "pharmaceutically acceptable salt" encompasses all acceptable salts including but not limited to acetate, lactobionate, benzenesulfonate, laurate, benzoate, malate, bicarbonate, maleate, bisulfate, mandelate, bitartarate, mesylate, borate, methylbromide, bromide, methylnitrite, calcium edetate, methylsulfate, camsylate, mucate, carbonate, napsylate, chloride, nitrate, clavulanate, N-methylglucamine, citrate, ammonium salt, dihydrochloride, oleate, edetate, oxalate, edisylate, pamoate (embonate), estolate, palmitate, esylate, pantothenate, fumarate,

phosphate/diphosphate, gluceptate, polygalacturonate, gluconate, salicylate, glutame, stearate, glycollylarsanilate, sulfate, hexylresorcinate, subacetate, hydradamine, succinate, hydrobromide, tannate, hydrochloride, tartrate, hydroxynaphthoate, teoclate, iodide, tosylate, isothionate, triethiodide, lactate, panoate, valerate, and the like.

Pharmaceutically acceptable salts of the compounds of the present invention may be used to modify solubility or hydrolysis characteristics, or to produce a sustained release formulations. Also, pharmaceutically acceptable salts of the compounds of this invention may include those formed from cations such as sodium, potassium, aluminum, calcium, lithium, magnesium, zinc, and from bases such as ammonia, ethylenediamine, N-methyl-glutamine, lysine, arginine, ornithine, choline, N,N'-dibenzylethylene-diamine, chloroprocaine, diethanolamine, procaine, N-benzylphenethyl-amine, diethylamine, piperazine, tris(hydroxymethyl)aminomethane, and tetramethylammonium hydroxide.

Pharmaceutical formulations will typically include one or more carriers acceptable for the mode of administration of the preparation, be it by injection, inhalation, topical administration, lavage, enteral or other modes suitable for the selected treatment. Suitable carriers are those known in the art for use in such modes of administration.

Suitable pharmaceutical compositions may be formulated by means known in the art and their mode of administration and dose determined by the skilled practitioner. For parenteral administration, a compound may be dissolved in sterile water or saline or a pharmaceutically acceptable vehicle used for administration of non-water soluble compounds such as those used for vitamin K. For enteral administration, the compound may be administered in a tablet, capsule or dissolved in liquid form. The table or capsule may be enteric coated, or in a formulation for sustained release. Many suitable formulations are known, including, polymeric or protein microparticles encapsulating a compound to be released, ointments, gels, hydrogels, or solutions which can be used topically or locally to administer a compound. A sustained release patch or implant may be employed to provide release over a prolonged period of time. Many techniques known to skilled practitioners are described in Remington: the Science & Practice of Pharmacy by Alfonso Gennaro, 20th ed., Williams & Wilkins, (2000). Formulations for parenteral administration may, for example, contain

excipients, polyalkylene glycols such as polyethylene glycol, oils of vegetable origin, or hydrogenated naphthalenes. Biocompatible, biodegradable lactide polymer, lactide/glycolide copolymer, or polyoxyethylene-polyoxypropylene copolymers may be used to control the release of the compounds. Other potentially useful parenteral delivery systems for modulatory compounds include ethylene-vinyl acetate copolymer particles, osmotic pumps, implantable infusion systems, and liposomes. Formulations for inhalation may contain excipients, for example, lactose, or may be aqueous solutions containing, for example, polyoxyethylene-9-lauryl ether, glycocholate and deoxycholate, or may be oily solutions for administration in the form of nasal drops, or as a gel.

The compounds or pharmaceutical compositions according to the present invention may be administered by oral or non-oral, e.g., intramuscular, intraperitoneal, intravenous, intracisternal injection or infusion, subcutaneous injection, transdermal or transmucosal routes. Preferably, the compounds or pharmaceutical compositions according to the present invention are administered by intravenous injection or infusion. In some embodiments, compounds or pharmaceutical compositions in accordance with this invention or for use in this invention may be administered by means of a medical device or appliance such as an implant, graft, prosthesis, stent, etc. Implants may be devised which are intended to contain and release such compounds or compositions. An example would be an implant made of a polymeric material adapted to release the compound over a period of time. The compounds may be administered alone or as a mixture with a pharmaceutically acceptable carrier e.g., as solid formulations such as tablets, capsules, granules, powders, etc; liquid formulations such as syrups, injections, etc.; injections, drops, suppositories, pessaries. In some embodiments, compounds or pharmaceutical compositions in accordance with this invention or for use in this invention may be administered by inhalation spray, nasal, vaginal, rectal, sublingual, or topical routes and may be formulated, alone or together, in suitable dosage unit formulations containing conventional non-toxic pharmaceutically acceptable carriers, adjuvants and vehicles appropriate for each route of administration.

The compounds of the invention may be used to treat animals, including mice, rats, horses, cattle, sheep, dogs, cats, and monkeys. The compounds of the invention may also be effective for use in humans. The term “subject” is intended to refer to an

animal, preferably a mammal, most preferably a human, who has been the object of treatment, observation or experiment. However, the compounds, methods and pharmaceutical compositions of the present invention may be used in the treatment of animals. Accordingly, as used herein, a "subject" may be a human, non-human primate, rat, mouse, cow, horse, pig, sheep, goat, dog, cat, etc.

An "effective amount" of a compound according to the invention includes a therapeutically effective amount or a prophylactically effective amount. A "therapeutically effective amount" refers to an amount effective, at dosages and for periods of time necessary, to achieve the desired therapeutic result. A therapeutically effective amount of a compound may vary according to factors such as the disease state, age, sex, and weight of the individual, and the ability of the compound to elicit a desired response in the individual. Dosage regimens may be adjusted to provide the optimum therapeutic response. A therapeutically effective amount is also one in which any toxic or detrimental effects of the compound are outweighed by the therapeutically beneficial effects. A "prophylactically effective amount" refers to an amount effective, at dosages and for periods of time necessary, to achieve the desired prophylactic result. Typically, a prophylactic dose is used in subjects prior to or at an earlier stage of disease, so that a prophylactically effective amount may be less than a therapeutically effective amount. A suitable range for therapeutically or prophylactically effective amounts of a compound may be any integer from 0.1 nM-0.1M, 0.1 nM-0.05M, 0.05 nM-15μM or 0.01 nM-10μM.

The term 'antiproliferative agents' is intended to mean a pharmacological agent that blocks cellular, parasitic or viral growth.

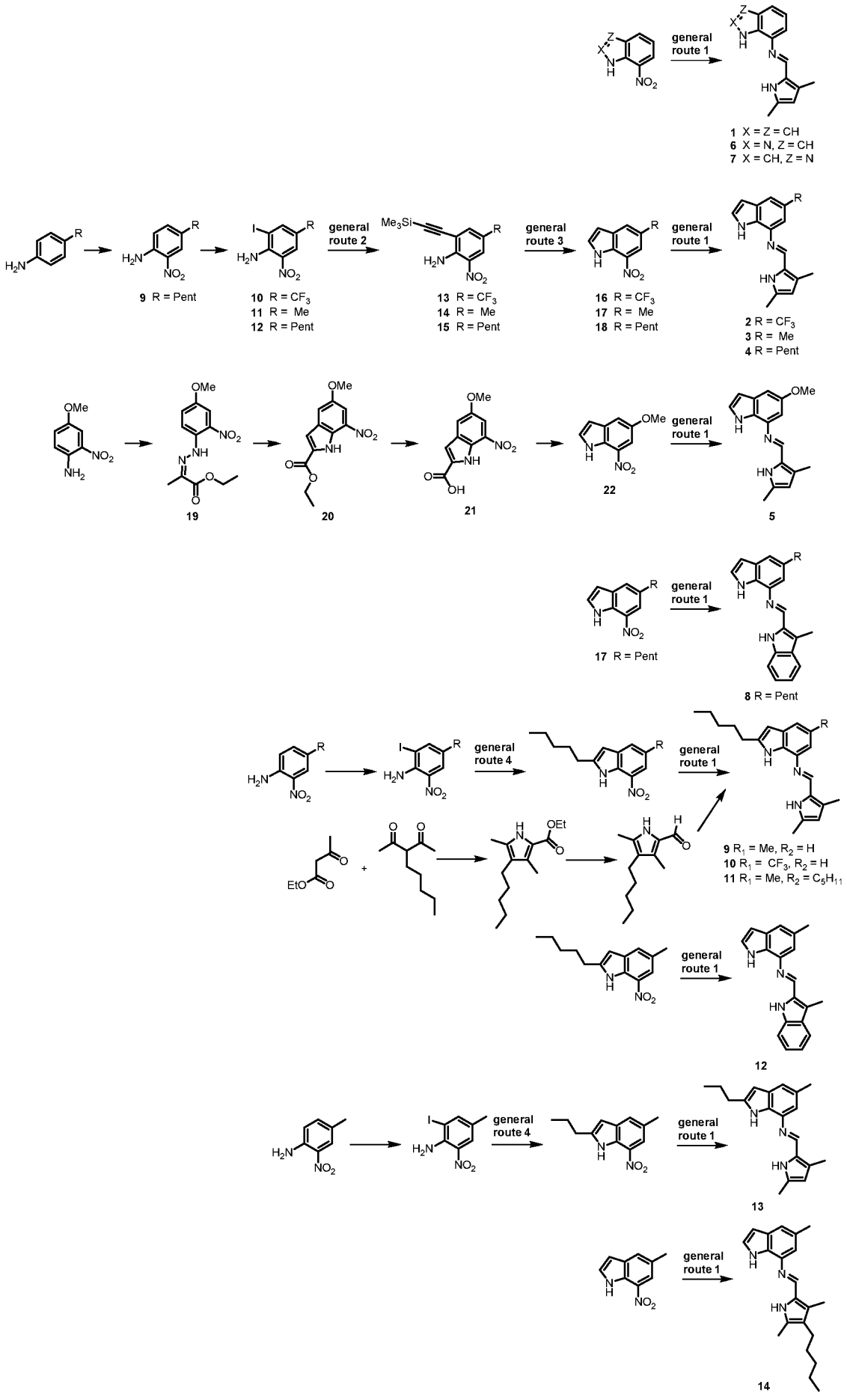
The term 'adjuvant' is intended to mean a pharmacological agent that would be added to, or administered with or alongside, a drug or therapeutic agent to enhance or aid the effect of the drug or therapeutic agent.

The skilled person will appreciate that all preferred or optional features of the invention may be applied to all aspects of the invention.

General Synthetic Routes Description

The compounds of Formula I or Formula Ia can be obtained by following the procedures described below. As it will be obvious to one skilled in the art, the exact method used to prepare a given compound may vary depending on its chemical structure. Unless otherwise stated, in the methods described below the meanings of the different substituents are the meanings described above with regard to a compound of Formula I or Formula Ia.

The compounds of Formula I or Formula Ia can be synthesised, for example, by the general routes and procedures described in the following overall Scheme 1 below:


general route 1
1 X = Z = CH
6 X = N, Z = CH
7 X = CH, Z = N
general route 2
general route 3
general route 1
9 R = Pent
10 R = CF3
11 R = Me
12 R = Pent
13 R = CF3
14 R = Me
15 R = Pent
16 R = CF3
17 R = Me
18 R = Pent
2 R = CF3
3 R = Me
4 R = Pent
19
20
21
22
5
17 R = Pent
8 R = Pent
general route 4
9 R1 = Me, R2 = H
10 R1 = CF3, R2 = H
11 R1 = Me, R2 = C5H11
12
13
14

Compounds of Formula I and Ia can be prepared according to the above general route 1. The 7-nitro-1*H*-indole, 7-nitro-1*H*-benzimidazole and 7-nitro-1*H*-indazole precursors are subjected to a standard reduction reaction of the nitro group to an amino group, under a hydrogen atmosphere in the presence of palladium on carbon (10 wt. % loading) catalyst in ethanol at room temperature and protected from light for 5 hours. The reduced 7-amino-1*H*-indole intermediate was added with magnesium sulphate as a drying agent, before the pyrrole-2-carbaldehyde reactant was added for the formation of imine via the condensation of amine and aldehyde. The crude mixture were purified by cation exchange column chromatography, followed by silica column chromatography to give the corresponding compounds of the present invention as defined above. Examples 1-8 were prepared according to general route 1.

The 7-nitro-1*H*-indole precursors (examples 22-24) can be prepared according to general route 2 and 3. In general route 2, the 2-nitroaniline compounds was first subjected to an iodination procedure with iodine added in the presence of silver sulphate in ethanol, and stirred for 36 hours and protected from light, and gave the 2-iodo-6-nitroaniline compounds (examples 16-18). The non-commercially available 2-nitro-4-pentylaniline (example 15) was obtained from the 4-pentylaniline precursor. Firstly, 4-pentylaniline was *N*-protected with acetic anhydride, and subjected to nitration with HNO_3 added dropwise at –10 °C, followed by deprotection in the presence of potassium hydroxide, and gave 2-nitro-4-pentylaniline. The 2-iodo-6-nitroaniline compounds are subjected to a Sonogashira cross-coupling reaction with ethynyltrimethylsilane in a suitable solvent such as toluene, in the presence of bis(triphenylphosphine)palladium(II) dichloride (10 mol%) and copper(I) iodide (20 mol%) catalysts, with piperidine added dropwise at 0 °C, under an atmosphere of argon. The reaction mixture was allowed to stir at room temperature for 4 hours, before a solution of saturated aqueous ammonium chloride was added to quench the reaction, followed by purification with silica column chromatography, and gave the 2-nitro-6-((trimethylsilyl)ethynyl)aniline compounds (examples 19-21). In general route 3, the 2-nitro-6-((trimethylsilyl)ethynyl)aniline compounds are subjected to the deprotection of trimethylsilane in the presence of potassium *tert*-butoxide in *N*-methyl-2-pyrrolidone solvent, followed by in situ base mediated cyclisation of deprotected 2-nitro-6-ethynylaniline intermediates, stirred at room temperature for 4 hours. A solution of saturated aqueous ammonium chloride was added to neutralise the

resulting reaction mixture, followed by extraction with ethyl actate and purification with silica column chromatography, and gave the 7-nitro-1*H*-indole compounds.

The 7-nitro-2-pentyl-1*H*-indole (7-nitro-2-propyl-1*H*-indole for example 13) precursors can be prepared according to general route 4. In general route 4 commercially available 2-nitroaniline compounds were subjected to an iodination procedure, where iodine was added in the presence of sliver sulphate in ethanol, protected from light and stirred for 36 hours to give the 2-iodo-6-nitroaniline compounds. The 2-iodo-6-nitroaniline compounds were subjected to a Sonogashira cross-coupling reaction with heptyne (pentyne for example 13) in DMF in the presence of bis(triphenylphosphine)palladium(II) dichloride (10 mol%) and copper(I) iodide (20 mol%) catalysts, with diethylamine added dropwise at 0 °C, under an atmosphere of nitrogen. The reaction mixture was allowed to stir at room temperature for 1 hour before addition of sodium hydroxide pellets and heating to 140 °C, followed by stirring at this temperature for 4 hours. After cooling, water was added followed by extraction with dichloromethane and purification with silica column chromatography to give the 7-nitro-2-pentyl-1*H*-indole compounds.

Examples 16-18 were prepared according to the iodination procedure.

Examples 19-21 were prepared according to general route 2, by the Sonogashira cross-coupling reaction.

Examples 22-24 were prepared according to general route 3, by the base mediated cyclisation.

5-Methoxy-7-nitro-1H-indole (example 28) was synthesised by an alternative Fisher indole synthesis – decarboxylation route, from the 4-methoxy-2-nitroaniline precursor in 4 reaction steps.

In one embodiment, the invention provides a compound of Formula I or Ia or a pharmaceutically acceptable salt or solvate thereof, wherein the compound is chosen from:

(*E*)-1-(3,5-dimethyl-1*H*-pyrrol-2-yl)-*N*-(1*H*-indol-7-yl)methanimine

(*E*)-1-(3,5-dimethyl-1*H*-pyrrol-2-yl)-*N*-(5-(trifluoromethyl)-1*H*-indol-7-yl)methanimine

(*E*)-1-(3,5-dimethyl-1*H*-pyrrol-2-yl)-*N*-(5-methyl-1*H*-indol-7-yl)methanimine

(*E*)-1-(3,5-dimethyl-1*H*-pyrrol-2-yl)-*N*-(5-pentyl-1*H*-indol-7-yl)methanimine

(*E*)-1-(3,5-dimethyl-1*H*-pyrrol-2-yl)-*N*-(5-methoxy-1*H*-indol-7-yl)methanimine

(*E*)-1-(3,5-dimethyl-1*H*-pyrrol-2-yl)-*N*-(1*H*-benzimidazole-7-yl)methanimine

(*E*)-1-(3,5-dimethyl-1*H*-pyrrol-2-yl)-*N*-(1*H*-indazol-7-yl)methanimine

(*E*)-1-(3-methyl-1*H*-indol-2-yl)-*N*-(5-pentyl-1*H*-indol-7-yl)methanimine

2-Nitro-4-pentylaniline

2-Iodo-6-nitro-4-(trifluoromethyl)aniline

2-Iodo-4-methyl-6-nitroaniline

2-Iodo-6-nitro-4-pentylaniline

2-Nitro-4-(trifluoromethyl)-6-((trimethylsilyl)ethynyl)aniline

4-Methyl-2-nitro-6-((trimethylsilyl)ethynyl)aniline

2-Nitro-4-pentyl-6-((trimethylsilyl)ethynyl)aniline

7-Nitro-5-(trifluoromethyl)-1*H*-indole

5-Methyl-7-nitro-1*H*-indole

7-Nitro-5-pentyl-1*H*-indole

Ethyl 2-(2-(4-methoxy-2-nitrophenyl)hydrazono)propanoate

Ethyl 5-methoxy-7-nitro-1*H*-indole-2-carboxylate

5-Methoxy-7-nitro-1*H*-indole-2-carboxylic acid

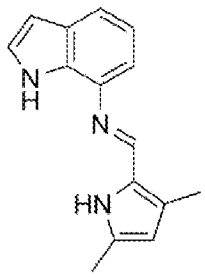
5-Methoxy-7-nitro-1*H*-indole

7-(4,6-Dimethyl-1,1-diphenyl-1*H*-1λ^4,2λ^4-pyrrolo[1,2-*c*][1,3,2]diazaborol-2-yl)-1*H*-indole

7-(4,6-Dimethyl-1,1-diphenyl-1*H*-1λ^4,2λ^4-pyrrolo[1,2-*c*][1,3,2]diazaborol-2-yl)-5-pentyl-1*H*-indole

EXAMPLES

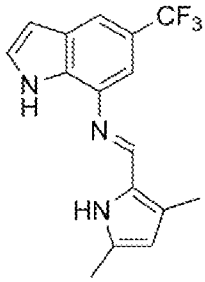
Example 1: (*E*)-1-(3,5-dimethyl-1*H*-pyrrol-2-yl)-*N*-(1*H*-indol-7-yl)methanimine



Synthesis according to general route 1: A 100 mL round-bottom flask was charged with 7-nitro-1*H*-indole (500 mg, 3.0 mmol), Pd/C 10% (200 mg) and EtOH (10 mL). The flask was evacuated, the mixture placed under a hydrogen atmosphere and stirred vigorously at rt during 5 h in the dark. The mixture was filtered over a glass fibre filter to remove the catalyst. To the filtrate were added $MgSO_4$ (250 mg, 2.1 mmol) and 3,5-dimethylpyrrole-2-carbaldehyde (380 mg, 3.0 mmol) and the mixture was stirred overnight at rt shielded from light. The reaction mixture was filtered and run through a SCX-2 column (eluent: MeOH; wash out NH_3 1.0 M in MeOH) and the solvent was evaporated. Purification by column chromatography (silica, eluent hexane–ethyl acetate–Et_3N, 80–20–3) and recrystallization from hexane gave (*E*)-1-(3,5-dimethyl-1*H*-pyrrol-2-yl)-*N*-(1*H*-indol-7-yl)methanimine as a yellow solid (95 mg, 13%). **mp** 97-98 °C;

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.81 (s, 1H; NH), 8.51 (s, 1H; CH), 7.47 (d, J = 8.0 Hz, 1H; Ar-H), 7.19 (s, 1H; NH), 7.12 (t, J = 8.0 Hz, 1H; Ar-H), 6.98 (d, J = 7.2 Hz, 1H; Ar-H), 6.56 (s, 1H; Ar-H), 5.84 (s, 1H; Ar-H), 2.27 (s, 3H; CH_3), 2.25 (s, 3H; CH_3); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 146.8, 137.2, 133.8, 131.7, 128.6, 128.3, 126.7, 123.9, 120.3, 117.6, 110.9, 108.6, 102.6, 13.1, 10.7; **HRMS** (ESI+) calcd. for $C_{15}H_{16}N_3$ $[M+H]^+$: 238.1339, found *m/z* 238.1218.

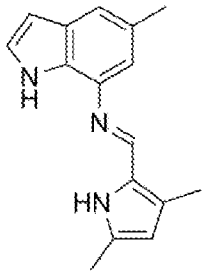
Example 2: (*E*)-1-(3,5-dimethyl-1*H*-pyrrol-2-yl)-*N*-(5-(trifluoromethyl)-1*H*-indol-7-yl)methanimine



Synthesis according to general route 1: 7-nitro-5-(trifluoromethyl)-1*H*-indole (300 mg, 1.3 mmol), Pd/C 10% (200 mg), EtOH (8 mL); $MgSO_4$ (250 mg, 2.1 mmol), 3,5-dimethylpyrrole-2-carbaldehyde (161 mg, 1.3 mmol). Eluent: hexane–ethyl acetate–Et_3N, 80–20–3. The compound (*E*)-1-(3,5-dimethyl-1*H*-pyrrol-2-yl)-*N*-(5-(trifluoromethyl)-1*H*-indol-7-yl)methanimine was obtained as a yellow solid (123 mg, 31%). **mp** 143-144 °C;

^{1}H NMR (400 MHz, DMSO-d_6): δ 11.35 (s, 1H; NH), 11.06 (s, 1H; NH), 8.57 (s, 1H; CH), 7.69 (s, 1H; Ar-H), 7.50 (t, J = 2.8 Hz, 1H; Ar-H), 7.20 (d, J = Hz, 1H; Ar-H), 6.60 (t, J = Hz, 1H; Ar-H), 5.81 (s, 1H; Ar-H), 2.27 (s, 3H; CH_3), 2.24 (s, 3H; CH_3); **^{13}C NMR** (100 MHz, DMSO-d_6): δ 148.1, 137.8, 134.1, 133.0, 127.4 (q), 120.7, 120.4, 113.6 (q), 110.6, 104.3, 102.5, 12.9, 10.8; **HRMS** (ESI+) calcd. for $C_{16}H_{14}N_3F_3$ $[M+H]^+$: 306.1213, found *m/z* 306.1218.

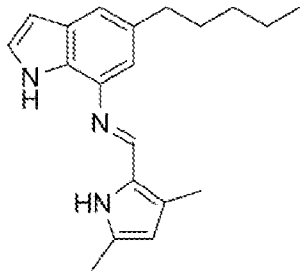
Example 3: (*E*)-1-(3,5-dimethyl-1*H*-pyrrol-2-yl)-*N*-(5-methyl-1*H*-indol-7-yl)methanimine



Synthesis according to general route 1: 5-methyl-7-nitro-1*H*-indole (300 mg, 1.7 mmol), Pd/C 10% (100 mg), EtOH (10 mL); $MgSO_4$ (250 mg, 2.1 mmol), 3,5-dimethylpyrrole-2-carbaldehyde (210 mg, 1.7 mmol). Eluent: hexane–ethyl acetate–Et_3N, 60–40–3. The compound (*E*)-1-(3,5-dimethyl-1*H*-pyrrol-2-yl)-*N*-(5-methyl-1*H*-indol-7-yl)methanimine was obtained as a yellow solid (168 mg, 39%). **mp** 171-172 °C;

^{1}H NMR (400 MHz, DMSO-d_6): δ 10.97 (s, 1H; NH), 10.74 (s, 1H; NH), 8.46 (s, 1H; CH), 7.25 (t, J = 2.4 Hz, 1H; Ar-H), 7.09 (s, 1H; Ar-H), 6.74 (s, 1H; Ar-H), 6.32 (t, J = 2.4 Hz, 1H; Ar-H), 5.78 (s, 1H; Ar-H), 2.38 (s, 3H; CH_3), 2.25 (s, 3H; CH_3), 2.22 (s, 3H; CH_3); **^{13}C NMR** (100 MHz, DMSO-d_6): δ 146.3, 136.9, 133.1, 129.9, 128.6, 127.9, 126.8, 126.1, 124.8, 116.1, 110.2, 109.6, 100.6, 21.3, 12.8, 10.7; **HRMS** (ESI+) calcd. for $C_{16}H_{18}N_3$ $[M+H]^+$: 252.1495, found *m/z* 252.1497.

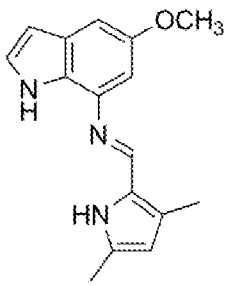
Example 4: (*E*)-1-(3,5-dimethyl-1*H*-pyrrol-2-yl)-*N*-(5-pentyl-1*H*-indol-7-yl)methanimine



Synthesis according to general route 1: 7-nitro-5-pentyl-1*H*-indole (360 mg, 1.5 mmol), Pd/C 10% (140 mg), EtOH (10 mL); $MgSO_4$ (250 mg, 2.1 mmol), 3,5-dimethylpyrrole-2-carbaldehyde (190 mg, 1.5 mmol). Eluent: hexane–ethyl acetate–Et_3N, 75–25–3. The compound (*E*)-1-(3,5-dimethyl-1*H*-pyrrol-2-yl)-*N*-(5-pentyl-1*H*-indol-7-yl)methanimine was obtained as a yellow solid (296 mg, 62%). **mp** 119-120 °C;

^{1}H NMR (400 MHz, DMSO-d_6): δ 10.96 (s, 1H; NH), 10.75 (s, 1H; NH), 8.48 (s, 1H; CH), 7.26 (t, J = 2.8 Hz, 1H; Ar-H), 7.09 (s, 1H; Ar-H), 6.76 (d, J = 0.8 Hz, 1H; Ar-H), 6.33 (dd, J = 2.8 Hz, J = 2.4 Hz, 1H; Ar-H), 5.78 (s, 1H; Ar-H), 2.63 (t, J = 7.2 Hz, 2H; CH_2), 2.26 (s, 3H; CH_3), 2.22 (s, 3H; CH_3), 1.67–1.59 (m, 2H; CH_2), 1.38–1.26 (m, 4H; CH_2), 0.87 (t, J = 6.8 Hz, 3H; CH_3); **^{13}C NMR** (100 MHz, DMSO-d_6): δ 146.2, 136.8, 133.3, 133.1, 130.1, 128.5, 126.8, 126.1, 124.8, 115.6, 110.2, 109.0, 100.8, 22.0, 13.9, 12.8, 10.8; **HRMS** (ESI+) calcd. for $C_{20}H_{26}N_3$ $[M+H]^+$: 308.2121, found *m/z* 308.2123.

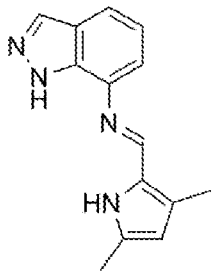
Example 5: (*E*)-1-(3,5-dimethyl-1*H*-pyrrol-2-yl)-*N*-(5-methoxy-1*H*-indol-7-yl)methanimine



Synthesis according to general route 1: 5-methoxy-7-nitro-1*H*-indole (305 mg, 1.6 mmol), Pd/C 10% (105 mg), EtOH (10 mL); $MgSO_4$ (200 mg, 1.7 mmol), 3,5-dimethylpyrrole-2-carbaldehyde (192 mg, 1.6 mmol). Eluent: hexane–ethyl acetate–Et_3N, 50–50–3. The compound (*E*)-1-(3,5-dimethyl-1*H*-pyrrol-2-yl)-*N*-(5-methoxy-1*H*-indol-7-yl)methanimine was obtained as a yellow solid (180 mg, 42%). **mp** 165-166 °C;

^{1}H NMR (400 MHz, DMSO-d_6): δ 11.00 (s, 1H; NH), 10.73 (s, 1H; NH), 8.46 (s, 1H; CH), 7.26 (t, J = 2.8 Hz, 1H; Ar-H), 6.82 (s, 1H; Ar-H), 6.58 (s, 1H; Ar-H), 6.34 (q, J = 2.8 Hz, J = 2.4 Hz, 1H; Ar-H), 5.79 (s, 1H; Ar-H), 3.76 (s, 3H; CH_3), 2.25 (s, 3H; CH_3), 2.22 (s, 3H; CH_3); **^{13}C NMR** (100 MHz, DMSO-d_6): δ 154.0, 147.0, 137.6, 133.5, 128.3, 126.9, 126.7, 125.3, 110.3, 101.0, 98.5, 98.3, 55.3, 12.8, 10.8; **HRMS** (ESI+) calcd. for $C_{16}H_{18}N_3O$ $[M+H]^+$: 268.1444, found *m/z* 268.1446.

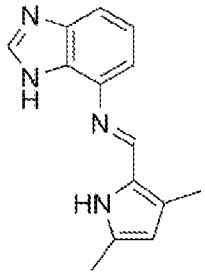
Example 6: (*E*)-1-(3,5-dimethyl-1*H*-pyrrol-2-yl)-*N*-(1*H*-benzimidazole-7-yl)methanimine



Synthesis according to general route 1: 7-nitro-1*H*-benzimidazole (300 mg, 1.8 mmol), Pd/C 10% (90 mg), EtOH (10 mL); $MgSO_4$ (250 mg, 2.1 mmol), 3,5-dimethylpyrrole-2-carbaldehyde (226 mg, 1.8 mmol). The reaction mixture was filtered and run through a SCX-2 column (eluent: MeOH; wash out NH_3 1.0 M in MeOH) and the solvent was evaporated. The residue was dissolved in a minimal amount of isopropanol to which were added a few drops of HCl 6.0 M isopropanol solution and Et_2O. The precipitate was collected, dissolved in H_2O and neutralized with saturated $NaHCO_3$ solution. Extraction with ethyl acetate (3x), evaporation of the solvent, and recrystallization from ethyl acetate–hexane gave (*E*)-1-(3,5-dimethyl-1*H*-pyrrol-2-yl)-*N*-(1*H*-benzimidazole-7-yl)methanimine as a yellow solid (184 mg, 42%). **mp** 115-116 °C;

^{1}H NMR (400 MHz, DMSO-d_6): δ 12.47 (s, 0.6H; NH), 12.41 (s, 0.4H; NH), 11.16 (s, 0.6H; NH), 11.06 (s, 0.4H; NH), 9.22 (s, 0.6H; Ar-H), 8.42 (s, 0.4H; Ar-H), 8.18 (s, 0.6H; CH), 8.14 (s, 0.4H; CH), 7.40 (d, 0.4H; Ar-H), 7.25 (d, J = Hz, 0.6H; Ar-H), 7.19–7.11 (m, 1H; Ar-H), 6.94 (m, 1H; Ar-H), 5.79 (s, 0.4H; Ar-H), 5.77 (s, 0.6H; Ar-H), 2.25-2.19 (m, 6H; CH_3); **^{13}C NMR** (100 MHz, DMSO-d_6): δ 150.9, 148.0, 144.0, 142.9, 144.6, 141.1, 138.5, 135.8, 134.7, 133.8, 133.7, 127.1, 126.7, 126.4, 122.7, 121.7, 115.9, 115.0, 110.6, 110.4, 110.1, 107.5, 12.7, 10.8; **HRMS** (ESI+) calcd. for $C_{14}H_{15}N_4$ $[M+H]^+$: 239.1291, found *m/z* 239.1290.

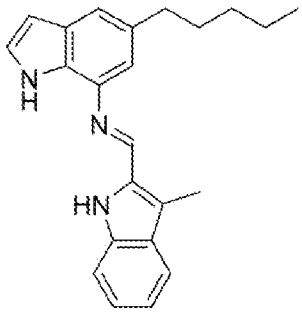
Example 7: (*E*)-1-(3,5-dimethyl-1*H*-pyrrol-2-yl)-*N*-(1*H*-indazol-7-yl)methanimine



Synthesis according to general route 1: 7-nitro-1*H*-indazole (400 mg, 2.5 mmol), Pd/C 10% (150 mg), EtOH (10 mL); $MgSO_4$ (250 mg, 2.1 mmol), 3,5-dimethylpyrrole-2-carbaldehyde (302 mg, 2.5 mmol). Eluent gradient: hexane–ethyl acetate–Et_3N, 70–30–3 to 50–50–3. The compound (*E*)-1-(3,5-dimethyl-1*H*-pyrrol-2-yl)-*N*-(1*H*-indazol-7-yl)methanimine was obtained as a yellow solid (28 mg, 5%). **mp** 107-108 °C;

^{1}H NMR (400 MHz, DMSO-d_6): δ 13.04 (s, 1H; NH), 11.03 (s, 1H; NH), 8.49 (s, 1H; CH), 8.05 (s, 1H; Ar-H), 7.51–7.46 (m, 1H; Ar-H), 7.10–7.06 (m, 2H; Ar-H), 5.08 (s, 1H; Ar-H), 2.25 (s, 3H; CH_3), 2.23 (s, 3H; CH_3); **^{13}C NMR** (100 MHz, DMSO-d_6): δ 147.8, 137.0, 136.1, 134.0, 133.5, 127.3, 126.6, 123.9, 121.1, 112.1, 116.1, 112.6, 110.5, 12.8, 10.8; **HRMS** (ESI+) calcd. for $C_{14}H_{15}N_4$ $[M+H]^+$: 239.1291, found *m/z* 239.1287.

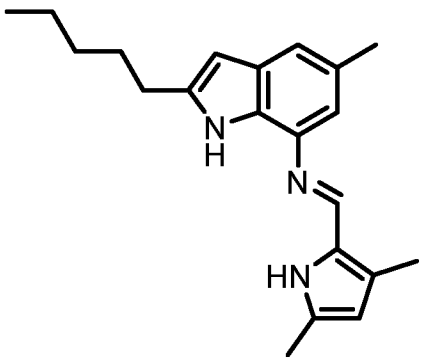
Example 8: (*E*)-1-(3-methyl-1*H*-indol-2-yl)-*N*-(5-pentyl-1*H*-indol-7-yl)methanimine



Synthesis according to general route 1: 7-nitro-5-pentyl-1*H*-indole (140 mg, 0.6 mmol), Pd/C 10% (70 mg), EtOH (10 mL); $MgSO_4$ (150 mg, 1.2 mmol), 3-methyl-1*H*-indole-2-carboxaldehyde (96 mg, 0.6 mmol). Eluent: hexane–ethyl acetate–Et_3N, 80–20–3. The compound (*E*)-1-(3-methyl-1*H*-indol-2-yl)-*N*-(5-pentyl-1*H*-indol-7-yl)methanimine was obtained as a yellow solid (15 mg, 7%);

^{1}H NMR (400 MHz, CD_3CN): δ 9.82 (s, 1H; NH), 9.48 (s, 1H; NH), 8.94 (s, 1H; CH), 7.66 (d, J = 8.0 Hz, 1H; Ar-H), 7.46 (d, J = 8.2 Hz, 1H; Ar-H), 7.34-7.25 (m, 3H; Ar-H), 7.15-7.08 (m, 1H; Ar-H), 7.04 (s, 1H; Ar-H), 6.45 (dd, J = 2.8 Hz, J = 2.4 Hz, 1H; Ar-H), 2.72 (t, J = 7.5 Hz, 2H; CH_2), 2.57 (s, 3H; CH_3), 1.76–1.65 (m, 2H; CH_2), 1.40–1.33 (m, 4H; CH_2), 0.90 (t, J = 6.9 Hz, 3H; CH_3); **^{13}C NMR** (100 MHz, CD_3CN): δ 148.13, 138.27, 136.62, 135.73, 133.66, 131.77, 130.20, 130.02, 125.98, 125.87, 120.90, 120.42, 119.06, 118.71, 112.37, 110.35, 102.53, 36.82, 32.83, 32.35, 23.33, 14.41, 8.64.; **HRMS** (ESI+) calcd. for $C_{23}H_{26}N_3$ $[M+H]^+$: 344.2127, found *m/z* 344.2130.

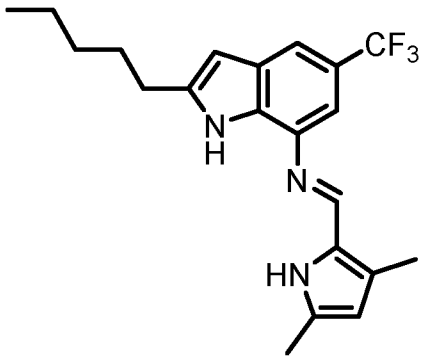
Example 9: (*E*)-1-(3,5-dimethyl-1*H*-pyrrole-2-yl)-*N*-(2-pentyl-5-methyl-1*H*-indole-7-yl)methanimine



Synthesis according to general route 1: 7-nitro-2-pentyl-5-methyl-1*H*-indole (367 mg, 1.49 mmol), Pd/C 10% (150 mg), EtOH (30 mL); $MgSO_4$ (250 mg, 2.1 mmol), 3,5-dimethylpyrrole-2-carbaldehyde (185 mg, 1.50 mmol). Eluent: hexane–ethyl acetate–Et_3N, 80–20–3. The compound (*E*)-1-(3,5-dimethyl-1*H*-pyrrol-2-yl)-*N*-2-pentyl-5-methyl-1*H*-indol-7-yl)methanimine was obtained as a yellow solid (308 mg, 64%);

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 10.90 (br s, 1 H) 10.42 (s, 1 H) 8.42 (s, 1 H) 6.96 (s, 1 H) 6.63 (s, 1 H) 6.03 (d, *J*=1.83 Hz, 1 H) 5.78 (s, 1 H) 2.71 (t, *J*=7.52 Hz, 2 H) 2.35 (s, 3 H) 2.26 (s, 3 H) 2.21 (s, 3 H) 1.68 (quin, *J*=7.21 Hz, 2 H) 1.28 - 1.36 (m, 4 H) 0.88 (t, *J*=6.80 Hz, 3 H); **^{13}C NMR** (101 MHz, DMSO-d_6) δ ppm 146.29, 140.28, 136.45, 133.09, 129.62, 129.40, 127.64, 126.76, 126.07, 115.43, 110.20, 109.00, 98.02, 30.99, 28.76, 27.62, 21.93, 21.38, 13.95. 12.92. 10.79; **HRMS** (ESI^+) calcd for $C_{21}H_{27}N_3$ $[M+H]^+$: 322.2278, found *m/z* 322.285 **MS** (ESI^+) m/z 332.3 $[M + H]^+$.

Example 10: (*E*)-1-(3,5-dimethyl-1*H*-pyrrole-2-yl)-*N*-(2-pentyl-5-(trifluoromethyl)-1*H*-indole-7-yl)methanimine

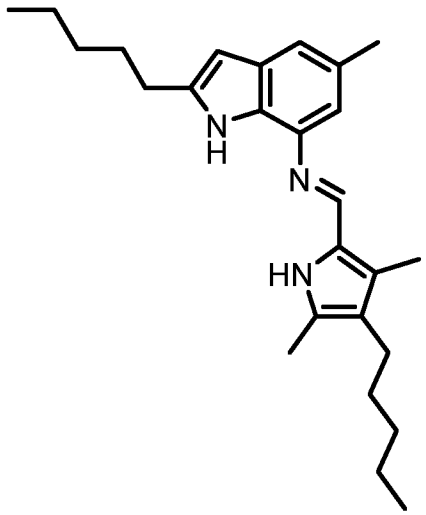


Synthesis according to general route 1: 7-nitro-2-pentyl-5-trifluoromethyl-1*H*-indole (80 mg, 0.27 mmol), Pd/C 10% (48 mg), EtOH (30 mL); $MgSO_4$ (250 mg, 2.1 mmol), 3,5-dimethylpyrrole-2-carbaldehyde (119 mg, 0.97 mmol). Eluent: hexane–ethyl acetate–Et_3N, 80–20–3. The compound (*E*)-1-(3,5-dimethyl-1*H*-pyrrol-2-yl)-*N*-2-pentyl-5-(trifluoromethyl)-1*H*-indol-7-yl)methanimine was obtained as an orange solid (57 mg, 57%);

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 11.06 (br s, 1 H) 11.01 (br s, 1 H) 8.51 (s, 1 H) 7.55 (s, 1 H) 7.07 (s, 1 H) 6.31 (s, 1 H) 5.82 (s, 1 H) 2.77 (t, *J*=7.58 Hz, 2 H) 2.28 (s, 3 H) 2.25 (s, 3 H) 1.65 - 1.77 (m, 2 H) 1.31 - 1.36 (m, 4 H) 0.86 - 0.91 (m, 3 H); **^{13}C**

NMR (101 MHz, DMSO-d_6) δ ppm 148.06, 142.47, 137.15, 133.90, 132.52, 128.34, 127.41, 126.48, 122.44, 110.40, 110.34, 103.76, 103.72, 99.50, 30.75, 28.42, 27.32, 21.72, 13.75, 12.76, 10.65; **HRMS** (ESI^+) calcd for $C_{21}H_{25}F_3N_3$ $[M+H]^+$: 376.1995, found *m/z* 376.2001; **MS** (ESI^+) m/z 376.4 $[M + H]^+$.

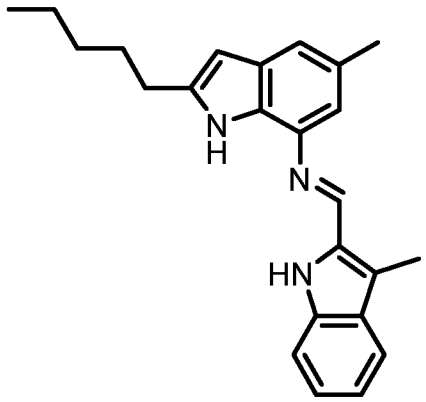
Example 11: (*E*)-1-(3,5-dimethyl-4-pentyl-1*H*-pyrrole-2-yl)-*N*-(2-pentyl-5-methyl-1*H*-indole-7-yl)methanimine



Synthesis according to general route 1: 7-nitro-2-pentyl-5-methyl-1*H*-indole (503 mg, 2.03 mmol), Pd/C 10% (36 mg), EtOH (35 mL); $MgSO_4$ (250 mg, 2.1 mmol), 3,5-dimethyl-4-pentyl-pyrrole-2-carbaldehyde (550 mg, 2.85 mmol). Eluent: hexane–ethyl acetate–Et_3N, 80–20–3. The compound (*E*)-1-(3,5-dimethyl-4-pentyl-1*H*-pyrrol-2-yl)-*N*-2-pentyl-5-methyl-1*H*-indol-7-yl)methanimine was obtained as a brown/yellow solid (204 mg, 26%);

^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 10.75 (br s, 1 H) 10.40 (br s, 1 H) 8.41 (s, 1 H) 6.95 (s, 1 H) 6.62 (s, 1 H) 6.02 (s, 1 H) 2.70 (t, *J*=7.56 Hz, 2 H) 2.31 - 2.37 (m, 5 H) 2.22 (s, 3 H) 2.17 (s, 3 H) 1.64 - 1.72 (m, 2 H) 1.37 - 1.45 (m, 2 H) 1.22 - 1.32 (m, 8 H) 0.87 (t, *J*=7.05 Hz, 6 H); **^{13}C NMR** (101 MHz, DMSO-d_6) δ ppm 140.24, 136.66, 131.99, 130.18, 129.38, 128.34, 127.65, 125.72, 124.57, 120.84, 115.28, 108.99, 98.05, 30.99, 30.15, 28.75, 27.61, 23.40, 22.03, 21.92, 21.37, 13.99, 13.94, 11.88, 9.03; **HRMS** (ESI^+) calcd for $C_{26}H_{38}N_3$ $[M+H]^+$: 392.3060, found *m/z* 392.3057; **MS** (ESI^+) m/z 392.5 $[M + H]^+$.

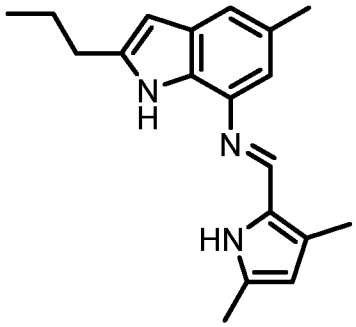
Example 12: (*E*)-1-(3-methyl-1*H*-indol-2-yl)-*N*-(2-pentyl-5-methyl-1*H*-indol-7-yl)methanimine



Synthesis according to general route 1: 7-nitro-2-pentyl-5-methyl-1*H*-indole (785 mg, 3.19 mmol), Pd/C 10% (70 mg), EtOH (30 mL); $MgSO_4$ (150 mg, 1.2 mmol), 3-methyl-1*H*-indole-2-carboxaldehyde (296 mg, 1.71 mmol). Eluent: hexane–ethyl acetate–Et_3N, 80–20–3. The compound (*E*)-1-(3-methyl-1*H*-indol-2-yl)-*N*-(2-pentyl-5-methyl-1*H*-indol-7-yl)methanimine was obtained as a yellow solid (321 mg, 53%);

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 11.11 (s, 1 H) 10.63 (s, 1 H) 8.91 (s, 1 H) 7.63 (d, *J*=7.83 Hz, 1 H) 7.46 (d, *J*=8.19 Hz, 1 H) 7.24 (ddd, *J*=8.19, 7.03, 1.16 Hz, 1 H) 7.07 (s, 1 H) 7.05 (ddd, *J*=8.20, 7.00, 1.00 Hz, 1 H) 6.89 (d, *J*=0.86 Hz, 1 H) 6.08 (d, *J*=2.08 Hz, 1 H) 2.74 (t, *J*=7.60 Hz, 2 H) 2.54 (s, 3 H) 2.39 (s, 3 H) 1.71 (quin, *J*=7.40 Hz, 2 H) 1.30 - 1.40 (m, 4 H) 0.86 - 0.89 (m, 3 H); **^{13}C NMR** (101 MHz, DMSO-d_6) δ ppm 147.39, 140.87, 137.25, 135.05, 133.04, 130.37, 129.91, 128.76, 127.95, 124.68, 119.96, 119.15, 117.20, 117.12, 111.79, 109.29, 98.37, 31.23, 28.94, 27.90, 22.15, 21.55, 14.17, 8.55; **HRMS** (ESI^+) calcd for $C_{24}H_{28}N_3$ $[M+H]^+$: 358.2278, found *m/z* 358.2275; **MS** (ESI^+) m/z 358.4 $[M + H]^+$.

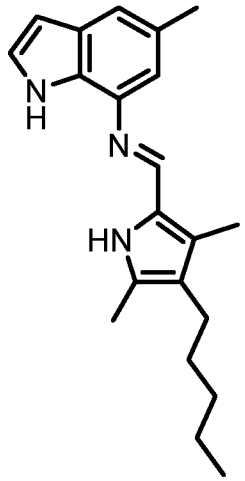
Example 13: (*E*)-1-(3,5-dimethyl-1*H*-pyrrole-2-yl)-*N*-(2-propyl-5-methyl-1*H*-indole-7-yl)methanimine



Synthesis according to general route 1: 7-nitro-2-propyl-5-methyl-1*H*-indole (813 mg, 3.72 mmol), Pd/C 10% (50 mg), EtOH (60 mL); $MgSO_4$ (250 mg, 2.1 mmol), 3,5-dimethylpyrrole-2-carbaldehyde (504 mg, 4.09 mmol). Eluent: hexane–ethyl acetate–Et_3N, 80–20–3. The compound (*E*)-1-(3,5-dimethyl-1*H*-pyrrol-2-yl)-*N*-2-propyl-5-methyl-1*H*-indol-7-yl)methanimine was obtained as a yellow solid (356 mg, 33%);

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 10.89 (br s, 1 H) 10.41 (br s, 1 H) 8.42 (s, 1 H) 6.96 (s, 1 H) 6.64 (s, 1 H) 6.03 (s, 1 H) 5.78 (s, 1 H) 2.68 (t, J=7.52 Hz, 2 H) 2.35 (s, 3 H) 2.25 (s, 3 H) 2.21 (s, 2 H) 1.64 - 1.74 (m, 2 H) 0.93 (t, *J*=7.34 Hz, 3 H); **^{13}C NMR** (101 MHz, DMSO-d_6) δ ppm 146.26, 140.07, 136.44, 133.11, 129.67, 129.40, 127.65, 126.78, 126.08, 115.45, 110.21, 108.98, 98.13, 29.73, 22.34, 21.38, 13.76, 12.93, 10.78; **HRMS** (ESI^+) calcd for $C_{19}H_{24}N_3$ $[M+H]^+$: 294.1965, found *m/z* 294.1971; **MS** (ESI^+) m/z 294.3 $[M + H]^+$.

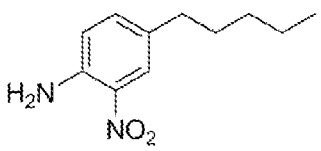
Example 14: (*E*)-1-(3,5-dimethyl-4-pentyl-1*H*-pyrrol-2-yl)-*N*-(5-methyl-1*H*-indol-7-yl)methanimine



Synthesis according to general route 1: 5-methyl-7-nitro-1*H*-indole (334 mg, 1.9 mmol), Pd/C 10% (53 mg), EtOH (20 mL); $MgSO_4$ (250 mg, 2.1 mmol), 3,5-dimethyl-4-pentyl-pyrrole-2-carbaldehyde (104 mg, 0.54 mmol). Eluent: hexane–ethyl acetate–Et_3N, 60–40–3. The compound (*E*)-1-(3,5-dimethyl-4-pentyl-1*H*-pyrrol-2-yl)-*N*-(5-methyl-1*H*-indol-7-yl)methanimine was obtained as a yellow solid (115 mg, 66%);

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 10.82 (br s, 1 H) 10.73 (br s, 1 H) 8.45 (s, 1 H) 7.25 (t, *J*=2.69 Hz, 1 H) 7.08 (s, 1 H) 6.73 (d, *J*=1.20 Hz, 1 H) 6.32 (dd, *J*=3.00, 2.02 Hz, 1 H) 2.37 (s, 3 H) 2.33 (t, *J*=7.40 Hz, 2 H) 2.21 (s, 3 H) 2.17 (s, 3 H) 1.41 (quin, *J*=7.24 Hz, 2 H) 1.23 - 1.34 (m, 4 H) 0.85 - 0.90 (m, 3 H); **^{13}C NMR** (101 MHz, DMSO-d_6) δ ppm 146.36, 137.13, 130.33, 129.92, 128.65, 127.98, 125.80, 124.83, 124.68, 120.91, 116.02, 109.60, 100.60, 31.00, 30.15, 23.40, 22.02, 21.38, 13.98, 11.14, 9.03; **HRMS** (ESI^+) calcd for $C_{21}H_{28}N_3$ $[M+H]^+$: 322.2278, found *m/z* 322.2282; **MS** (ESI^+) m/z 322.4 $[M + H]^+$.

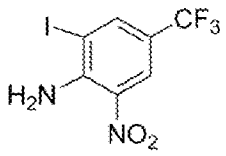
Example 15: 2-Nitro-4-pentylaniline



A mixture of 4-pentylaniline (2.2 mL, 12 mmol) and acetic anhydride 3.51 (7.0 mL, 72 mmol) was stirred at rt for 1h. The precipitate was filtered, dissolved in acetic acid (10 mL), the solution was cooled to −10°C and HNO_3 (70%; 2.2mL, 36 mmol) was added dropwise. The mixture was stirred at rt during 3h, poured in ice-water and the precipitate was collected. To a solution of EtOH (20 mL) and KOH (40% aqueous solution; 5 mL) was added the precipitate and the mixture was refluxed during 1h. The reaction mixture was left to cool to rt, poured into water, neutralized with NH_4Cl and extracted with ethyl acetate (3x). The organic fases were combined, dried (Na_2SO_4) and the solvent evaporated under vacuo. The crude product was purified by column chromatography (silica, eluent hexane–ethyl acetate, 4–1) to give 2-nitro-4-pentylaniline as a red oil (overall 72%).

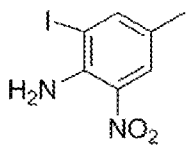
^{1}H NMR (400 MHz, DMSO-d_6): δ 7.73 (d, J = 2.0 Hz, 1H; Ar-H), 7.28 (s, 2H; NH_2), 7.25 (q, J = 8.4 Hz, J = 1.6 Hz, 1H; Ar-H), 6.94 (d, J = 8.8 Hz, 1H; Ar-H), 2.45 (t, J = 7.2, 2H; CH_2), 1.54–1.46 (m, 2H; CH_2), 1.31–1.18 (m, 4H; CH_2), 0.84 (t, J = 6.8 Hz, 3H; CH_3); **^{13}C NMR** (100 MHz, DMSO-d_6): δ 144.5, 136.5, 129.8, 129.4, 123.4, 119.2, 33.5, 30.6, 30.2, 21.8, 13.8; **HRMS** (ESI+) calcd. for $C_{11}H_{17}N_2O_2$ $[M+H]^+$: 209.1285, found *m/z* 209.1283.

Example 16: 2-Iodo-6-nitro-4-(trifluoromethyl)aniline



This compound has been prepared according to the procedure reported by Koradin *et al.*-2003 *Tetrahedron*, 59, 1571–1587. Material identity was confirmed by MS, ^{1}H and ^{13}C NMR.

Example 17: 2-Iodo-4-methyl-6-nitroaniline

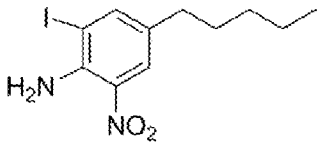


To a solution of 4-methyl-2-nitroaniline (3.00 g, 20 mmol), $Ag_2(I)SO_4$ (8.50 g, 28 mmol) in ethanol (150 mL) was added iodine (7 g, 28 mmol). The reaction mixture, shielded from light, was stirred at rt during 36h, filtered and the solvent evaporated. The residue was diluted with

CH_2Cl_2, washed with aqueous $Na_2S_2O_3$ solution and dried (Na_2SO_4). After evaporation of the solvent, 2-iodo-4-methyl-6-nitroaniline was obtained as an orange solid (5.48 g, quant.). **mp** 79-80 °C;

^{1}H NMR (400 MHz, DMSO-d_6): δ 7.93 (s, 1H; Ar-H), 7.87 (s, 1H; Ar-H), 6.87 (s, 2H; NH_2), 2.19 (s, 3H; CH_3); **^{13}C NMR** (100 MHz, DMSO-d_6): δ 147.1, 142.5, 130.5, 126.8, 125.6, 88.0, 18.8; **HRMS** (ESI+) calcd. for $C_7H_8N_2O_2I$ $[M+H]^+$: 278.9625, found *m/z* 278.9625.

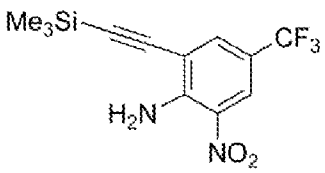
Example 18: 2-Iodo-6-nitro-4-pentylaniline



To a solution of 2-nitro-4-pentylaniline (1.79 g, 8.7 mmol), $Ag_2(I)SO_4$ (3.79 g, 12 mmol), ethanol (75 mL) was added iodine (3.07 g, 12 mmol). The reaction mixture, shielded from light, was stirred at rt during 36h, filtered and the solvent evaporated. The residue was diluted with CH_2Cl_2, washed with aqueous $Na_2S_2O_3$ solution and dried (Na_2SO_4). Purification by column chromatography (silica, eluent hexane–ethyl acetate, 9–1) gave 2-iodo-6-nitro-4-pentylaniline as a dark red solid (2.76 g, 95%). **mp** 45-46 °C;

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.96 (d, J = 2.0 Hz;, 1H; Ar-H), 7.78 (d, J = 1.6 Hz;, 1H; Ar-H), 6.51 (s, 2H; NH_2), 2.50 (t, J = 7.6 Hz;, 2H; CH_2), 1.57 (m, 2H; CH_2), 1.34–1.29 (m, 4H; CH_2), 0.90 (t, J = 6.8 Hz, 3H; CH_3); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 146.2, 142.1, 132.8, 131.6, 125.9, 87.3, 34.1, 31.1, 30.7, 22.4, 13.9; **HRMS** (ESI+) calcd. for $C_{11}H_{16}N_2O_2I$ $[M+H]^+$: 335.0251, found *m/z* 335.0243.

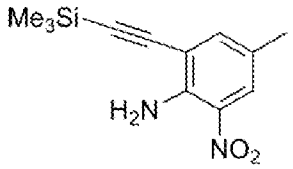
Example 19: 2-Nitro-4-(trifluoromethyl)-6-((trimethylsilyl)ethynyl)aniline



Synthesis according to general route 2: To a stirred mixture of 2-iodo-6-nitro-4-(trifluoromethyl)aniline (2.038 g, 6.25 mmol), $Pd(PPh_3)_2Cl_2$ (430 mg, 10 mol%), CuI (233 mg, 20 mol%) and ethynyl trimethylsilane (1.31 mL, 9.18 mmol) in toluene (5 mL) at 0 °C under Ar was added dropwise piperidine (1.81 mL, 19 mmol). The reaction mixture was stirred at rt during 4h, saturated NH_4Cl solution was added, extracted by CH_2Cl_2 (3x) and dried (Na_2SO_4). Purification by column chromatography (silica, eluent CH_2Cl_2–hexane, 7–3) gave 2-nitro-4-(trifluoromethyl)-6-((trimethylsilyl)ethynyl)aniline as a yellow solid (1.34g, 74%). **mp** 139-140 °C;

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.41 (d, J = 1.2 Hz, 1H; Ar-H), 7.41 (d, J = 1.6 Hz, 1H; Ar-H), 1.55 (s, 2H; NH_2), 0.31 (s, 9H; CH_3); **^{13}C NMR** (100 MHz, DMSO-d_6): δ 146.8, 134.5 (q), 131.1, 124.3 (q), 117.9, 113.1, 105.3, 97.4, -0.23; **HRMS** (ESI+) calcd. for $C_{12}H_{14}N_2O_2F_3Si$ $[M+H]^+$: 303.0771, found *m/z* 303.0765.

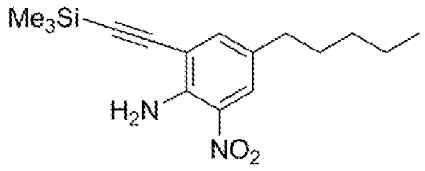
Example 20: 4-Methyl-2-nitro-6-((trimethylsilyl)ethynyl)aniline



Synthesis according to general route 2: 2-iodo-4-methyl-6-nitroaniline (2.00 g, 7.19 mmol), $Pd(PPh_3)_2Cl_2$ (505 mg, 10 mol%), CuI (274 mg, 20 mol%), ethynyl trimethylsilane (1.53 mL, 9.18 mmol), toluene (5 mL), piperidine (2.13 mL, 22 mmol). Purification by column chromatography (silica, eluent CH_2Cl_2–hexane, 4–2) gave 4-methyl-2-nitro-6-((trimethylsilyl)ethynyl)aniline as a yellow solid (1.23 g, 69%). **mp** 71-72 °C;

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.93 (s, 1H; Ar-H), 7.41 (s, 1H; Ar-H), 6.59 (s, 2H; NH_2), 2.25 (s, 3H; CH_3), 0.29 (s, 9H; CH_3); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 143.6, 139.8, 131.8, 126.4, 125.2, 111.9, 102.8, 99.1, 19.9, -0.09; **HRMS** (ESI+) calcd. for $C_{12}H_{17}N_2O_2Si$ $[M+H]^+$: 249.1054, found *m/z* 249.1050; calcd. for $C_{12}H_{17}N_2O_2SiNa$ $[M+Na]^+$: 271.0873, found *m/z* 271.0869.

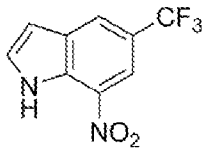
Example 21: 2-Nitro-4-pentyl-6-((trimethylsilyl)ethynyl)aniline



Synthesis according to general route 2: 2-iodo-6-nitro-4-pentylaniline (2.60 g, 11 mmol), $Pd(PPh_3)_2Cl_2$ (546 mg, 10 mol%), CuI (296 mg, 20 mol%), ethynyl trimethylsilane (1.66 mL, 16 mmol), toluene (10 mL), piperidine (2.30 mL, 33 mmol). Purification by column chromatography (silica, eluent CH_2Cl_2–hexane, 1–1) gave 2-nitro-4-pentyl-6-((trimethylsilyl)ethynyl)aniline as a yellow solid (1.94 g, 81%). **mp** 45-46 °C;

^{1}H NMR (400 MHz, DMSO-d_6): δ 7.85 (d, J = 1.2 Hz, 1H; Ar-H), 7.50 (d, J = 1.2 Hz, 1H; Ar-H), 6.90 (s, 2H; NH_2), 2.46 (t, J = 7.6 Hz, 2H; CH_2), 1.54–1.46 (m, 2H; CH_2), 1.30–1.20 (m, 4H; CH_2), 0.84 (t, J = 6.8 Hz, 3H; CH_3), 0.26 (s, 9H; CH_3); **^{13}C NMR** (100 MHz, DMSO-d_6): δ 143.7, 139.4, 130.9, 129.6, 125.5, 111.1, 102.1, 99.3, 33.1, 30.5, 30.1, 21.8, 13.8, -0.23; **HRMS** (ESI+) calcd. for $C_{16}H_{24}N_2O_2SiNa$ $[M+Na]^+$: 327.1499, found *m/z* 327.1506.

Example 22: 7-Nitro-5-(trifluoromethyl)-1*H*-indole

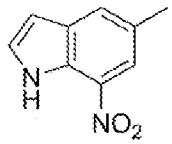


Synthesis according to general route 3: A mixture of 2-nitro-4-(trifluoromethyl)-6-((trimethylsilyl)ethynyl)aniline (1.327 g, 4.3 mmol), *t*-BuOK (1.489 g, 12.9 mmol) and NMP (50 mL) was stirred at rt during 4h. The reaction mixture as neutralized with saturated NH_4Cl solution, extracted with ethyl actate (3x), and dried over Na_2SO_4. Purification by column chromatography (silica, eluent hexane–ethyl acetate, 4–1) gave 7-nitro-5-(trifluoromethyl)-1*H*-indole as a yellow solid (645 mg, 64%). **mp** 151-152 °C;

^{1}H NMR (400 MHz, $CDCl_3$): δ 10.10 (s, 1H; NH), 8.44 (s, 1H; Ar-H), 8.26 (s, 1H; Ar-H), 7.54 (t, J = 2.8 Hz, 1H; Ar-H), 6.85 (t, J = 2.4 Hz, 1H; Ar-H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 131.7,

130.2, 128.4, 125.4 (q), 125.2, 122.4, 122.1, 116.2 (q), 105.1; **HRMS** (ESI–) calcd. for $C_9H_4N_2O_2F_3$ $[M–H]^-$: 229.0230, found *m/z* 229.0233.

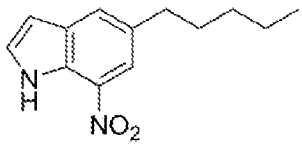
Example 23: 5-Methyl-7-nitro-1*H*-indole



Synthesis according to general procedure 3: 4-methyl-2-nitro-6-((trimethylsilyl)ethynyl)aniline (1.20 g, 4.8 mmol), *t*-BuOK (1.63 g, 14.4 mmol), NMP (50 mL). Purification by column chromatography (silica, eluent hexane–ethyl acetate, 5–1) gave 5-methyl-7-nitro-1*H*-indole as a yellow solid (668 mg, 81%). **mp** 111-112 °C;

^{1}H NMR (400 MHz, $CDCl_3$): δ 9.80 (s, 1H; NH), 8.01 (s, 1H; Ar-H), 7.79 (s, 1H; Ar-H), 7.37 (t, J = 2.0 Hz, 1H; Ar-H), 6.63 (t, J = 2.0 Hz, 1H; Ar-H), 2.53 (s, 3H; CH_3); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 132.5, 131.8, 129.1, 127.8, 126.6, 123.0, 120.0, 103.4, 21.0; **HRMS** (ESI+) calcd. for $C_9H_8N_2O_2$ $[M]^+$: 176.0586, found *m/z* 176.0579.

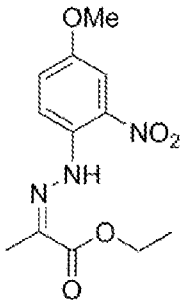
Example 24: 7-Nitro-5-pentyl-1*H*-indole



Synthesis according to general route 3: 2-nitro-4-pentyl-6-((trimethylsilyl)ethynyl)aniline (1.80 g, 5.9 mmol), *t*-BuOK (1.99 g, 17.7 mmol), NMP (60 mL). Purification by column chromatography (silica, eluent hexane–ethyl acetate, 6–1) gave 7-nitro-5-pentyl-1*H*-indole as an orange-brown solid (827 mg, 60%). **mp** 64-65 °C;

^{1}H NMR (400 MHz, $CDCl_3$): δ 9.83 (s, 1H; NH), 8.01 (s, 1H; Ar-H), 7.79 (s, 1H; Ar-H), 7.37 (t, J = 2.4 Hz, 1H; Ar-H), 6.64 (t, J = 2.4 Hz, 1H; Ar-H), 2.77 (t, J = 7.6, 2H; CH_2), 1.74–1.66 (m, 2H; CH_2), 1.38–1.33 (m, 4H; CH_2), 0.91 (t, J = 6.8 Hz, 3H; CH_3); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 134.4, 132.6, 131.7, 128.6, 127.9, 126.5, 119.5, 103.5, 35.4, 31.5, 31.3, 22.4, 14.0; **HRMS** (ESI+) calcd. for $C_{13}H_{17}N_2O_2$ $[M+H]^+$: 233.1285, found *m/z* 233.1286.

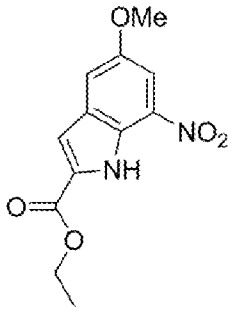
Example 25: Ethyl 2-(2-(4-methoxy-2-nitrophenyl)hydrazono)propanoate



To a solution of ethyl-2-methylacetoacetate (8.6 g, 59 mmol) in EtOH (72 mL) at 0 °C were added ice (84 g), a solution of KOH (18 g, 321 mmol) in H_2O (20 mL) and a cold solution of 4-methoxy-2-nitroaniline (10.0 g, 59 mmol), $NaNO_2$ (4.2 g, 59 mmol) and HCl 12M (30 mL) in H_2O (48 mL) was added slowly. The reaction mixture was stirred during 1 h and the precipitate was collected. Purification by recrystallization from wet MeOH gave ethyl 2-(2-(4-methoxy-2-nitrophenyl)hydrazono)propanoate as a red solid (16.3 g, 97%). **mp** 100-101 °C;

^{1}H NMR (400 MHz, DMSO-d_6): δ 10.49 (s, 1H; NH), 7.79 (d, J = 9.2 Hz, 1H; Ar-H), 7.57 (d, J = 2.8 Hz, 1H; Ar-H), 7.45 (dd, J = 9.6 Hz, J = 2.8 Hz, 1H; Ar-H), 4.27–4.21 (m, 2H; CH_2), 3.81 (s, 3H; CH_3), 2.13 (s, 3H; CH_3), 1.29 (t, J = 7.2 Hz, 3H; CH_3); **^{13}C NMR** (100 MHz, DMSO-d_6): δ 164.0, 152.7, 138.1, 134.7, 132.4, 125.9, 117.6, 106.9, 60.8, 55.7, 14.1, 11.3; **HRMS** (ESI+) calcd. for $C_{12}H_{15}N_3O_5Na$ $[M+Na]^+$: 304.0904, found *m/z* 304.0906.

Example 26: Ethyl 5-methoxy-7-nitro-1*H*-indole-2-carboxylate

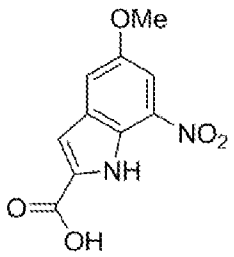


To a solution of ethyl 2-(2-(4-methoxy-2-nitrophenyl)hydrazono)propanoate (7.42 g, 26 mmol) in xylene (20 mL) was added polyphosphoric acid (12.5 g) and the mixture was stirred at 180 °C during 4 h. The reaction mixture was cooled to rt, H_2O was added (50 mL) and the

phosphoric acid layer was extracted with toluene (10x, decanted). The organic layers were combined, washed with H_2O, dried (Na_2SO_4) and the solvent evaporated under vacuo. Purification by recrystallization from EtOH gave ethyl 5-methoxy-7-nitro-1*H*-indole-2-carboxylate as a yellow solid (3.03 g, 43%). **mp** 91-92 °C;

^{1}H NMR (400 MHz, DMSO-d_6): δ 11.23 (s, 1H; NH), 7.84 (d, J = 2.4 Hz, 1H; Ar-H), 7.79 (d, J = 2.4 Hz, 1H; Ar-H), 7.34 (d, J = 1.6 Hz, 1H; Ar-H), 4.37 (m, 2H; CH_2), 3.88 (s, 3H; CH_3), 1.35 (t, J = 7.2, 3H; CH_3); **^{13}C NMR** (100 MHz, $CDCl_3$): δ160.2, 152.8, 133.1, 131.0, 130.9, 124.8, 113.5, 110.6, 108.8, 61.0, 56.2, 14.1; **HRMS** (ESI+) calcd. for $C_{12}H_{13}N_2O_5$ $[M+H]^+$: 265.0819, found *m/z* 265.0817; calcd. for $C_{12}H_{12}N_2O_5Na$ $[M+Na]^+$: 287.0638, found *m/z* 287.0636.

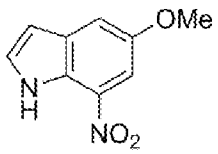
Example 27: 5-Methoxy-7-nitro-1*H*-indole-2-carboxylic acid



To a solution of ethyl 5-methoxy-7-nitro-1*H*-indole-2-carboxylate (2.45 g, 9.3 mmol) in THF (25 mL) was added NaOH 1.0 M (25 mL) and the mixture was stirred at 80 °C during 2h. The reaction mixture was cooled to rt, neutralized with HCl 1.0 M and the precipitate was filtered and dried under vacuo to give 5-methoxy-7-nitro-1*H*-indole-2-carboxylic acid as a dark yellow solid (1.55 g, 70%). **mp** decomposes;

^{1}H NMR (400 MHz, DMSO-d_6): δ 10.96 (s, 1H; NH), 7.81 (d, J = 2.4 Hz, 1H; Ar-H), 7.79 (d, J = 2.4 Hz, 1H; Ar-H), 7.28 (s, 1H; Ar-H), 3.87 (s, 3H; CH_3); **^{13}C NMR** (100 MHz, DMSO-d_6): δ161.7, 152.8, 132.9, 132.1, 131.2, 124.7, 113.5, 110.2, 108.4, 56.2; **HRMS** (ESI–) calcd. for $C_{10}H_7N_2O_5$ $[M]^-$: 235.0360, found *m/z* 235.0365.

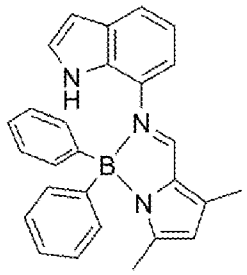
Example 28: 5-Methoxy-7-nitro-1*H*-indole



A solution of 5-methoxy-7-nitro-1*H*-indole-2-carboxylic acid (1.50 g, 6.3 mmol), $CuCO_3.Cu(H_2O)_2.H_2O$ (296 mg, mmol) in DMI (1,3-dimethyl-2-imidazolidinone; 10 mL) was stirred at 180 °C during 2h. The reaction mixture was cooled to rt, Et_2O added, filtered and the filtrate washed with HCl 2.0 M and brine. Purification by column chromatography (silica, eluent hexane–ethyl acetate, 9–1) gave 5-methoxy-7-nitro-1*H*-indole as an orange solid (800 mg, 63%). **mp** 109-110 °C;

^{1}H NMR (400 MHz, DMSO-d_6): δ 11072 (s, 1H; NH), 7.69 (d, J = 2.0 Hz, 1H; Ar-H), 7.65 (d, J = 2.4 Hz, 1H; Ar-H), 7.50 (t, J = 2.8 Hz, 1H; Ar-H), 6.63 (q, J = 2.8 Hz, J = 2.0 Hz, 1H; Ar-H), 3.86 (s, 3H; CH_3); **^{13}C NMR** (100 MHz, DMSO-d_6): δ 152.0, 132.5, 132.0, 129.6, 123.9, 113.2, 105.5, 102.5, 56.1; **HRMS** (ESI+) calcd. for $C_9H_9N_2O_3$ $[M+H]^+$: 193.0608, found *m/z* 193.0608; calcd. for $C_9H_8N_2O_3Na$ $[M+Na]^+$: 215.0427, found *m/z* 215.0427.

Example 29: 7-(4,6-Dimethyl-1,1-diphenyl-1*H*-1λ^4,2λ^4-pyrrolo[1,2-*c*][1,3,2]diazaborol-2-yl)-1*H*-indole

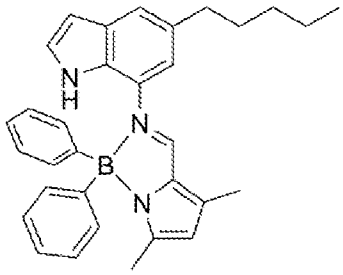


A mixture of (*E*)-1-(3,5-dimethyl-1*H*-pyrrol-2-yl)-*N*-(1*H*-indol-7-yl)methanimine **(Example 1)** (19 mg, 0.08 mmol), triphenylborane (20 mg, 0.08 mmol) and toluene (5 mL) was refluxed overnight under an nitrogen atmosphere. The solvent was removed under vacuo and the crude was redissolved in a minimal amount of dichloromethane. A small amount of hexane was added, the dichloromethane was evaporated under reduced pressure and the precipitate was filtered and washed with cold hexane to give 7-(4,6-dimethyl-1,1-diphenyl-1*H*-1λ^4,2λ^4-pyrrolo[1,2-*c*][1,3,2]diazaborol-2-yl)-1*H*-indole as a yellow-brownish solid (26 mg, 81%). **mp** 219-220 °C;

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.04 (s, 1H; CH), 7.50 (d, J = 8.0 Hz, 1H; Ar-H), 7.26–7.20 (m, 10H; Ar-H), 7.13 (s, 1H; NH), 6.93 (t, J = 7.6 Hz, 1H; Ar-H), 6.69 (t, J = 2.8 Hz, 1H; Ar-H),

6.66 (d, J = 7.6 Hz, 1H; Ar-H), 6.41 (dd, J = 2.8 Hz, J = 2.0 Hz, 1H; Ar-H), 6.17 (s, 1H; Ar-H), 2.40 (s, 3H; CH_3), 1.98 (s, 3H; CH_3); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 150.4, 145.1, 134.6, 133.3, 130.5, 129.4, 128.78, 128.73, 127.9, 127.6, 126.8, 124.6, 119.8, 119.6, 118.29, 117.4, 102.0, 14.0, 11.7; **HRMS** (ESI+) calcd. for $C_{27}H_{25}N_3B_1$ $[M+H]^+$: 402.2136, found *m/z* 402.2130; $\lambda_{abs,\ max}$ 387 nm, ε 18000 M^{-1} cm^{-1}, $\lambda_{em,\ max}$ = 545 nm (toluene).

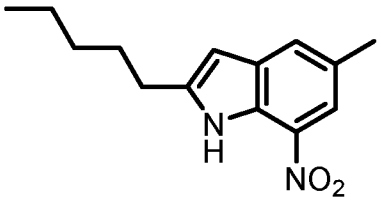
Example 30: 7-(4,6-Dimethyl-1,1-diphenyl-1*H*-1λ^4,2λ^4-pyrrolo[1,2-*c*][1,3,2]diazaborol-2-yl)-5-pentyl-1*H*-indole



A mixture of (*E*)-1-(3,5-dimethyl-1*H*-pyrrol-2-yl)-*N*-(5-pentyl-1*H*-indol-7-yl)methanimine **(Example 4)** (30 mg, 0.10 mmol), triphenylborane (25 mg, 0.10 mmol) and toluene (5 mL) was refluxed overnight under an nitrogen atmosphere. The solvent was removed under vacuo. Purification by column chromatography (silica, eluent hexane–ethyl acetate, 98–2) gave 7-(4,6-dimethyl-1,1-diphenyl-1*H*-1λ^4,2λ^4-pyrrolo[1,2-*c*][1,3,2]diazaborol-2-yl)-5-pentyl-1*H*-indole as a yellow solid (44 mg, 95%). **mp** 37-38 °C;

^{1}H NMR (400 MHz, DMSO-d_6): δ 11.10 (s, 1H; NH), 8.92 (s, 1H; CH), 7.25–7.22 (m, 4H; Ar-H), 7.15–7.12 (m, 7H; Ar-H), 6.51 (d, J = 0.8 Hz, 1H; NH), 6.36 (dd, J = 2.4 Hz, J = 1.2 Hz, 1H; Ar-H), 6.09 (t, J = 0.4 Hz, 1H; Ar-H), 2.36 (s, 3H; CH_3), 2.32 (t, J = 6.0 Hz, 2H; CH_2), 1.87 (s, 3H; CH_3), 1.34–1.27 (m, 2H; CH_2), 1.24–1.16 (m, 2H; CH_2), 1.11–1.04 (m, 2H; CH_2), 0.80 (t, J = 6.0 Hz, 3H; CH_3); **^{13}C NMR** (100 MHz, DMSO-d_6): δ 151.9, 142.0, 133.2, 132.1, 130.1, 127.4, 127.2, 127.1, 126.9, 126.1, 126.0, 117.8, 117.0, 116.5, 101.6, 34.7, 30.4, 30.3, 21.8, 13.8, 13.7, 11.5; **HRMS** (ESI+) calcd. for $C_{32}H_{35}N_3B_1$ $[M+H]^+$: 472.2919, found *m/z* 472.2917; $\lambda_{abs,\ max}$ 388 nm, ε 14000 M^{-1} cm^{-1}, $\lambda_{em,\ max}$ = 546 nm (toluene).

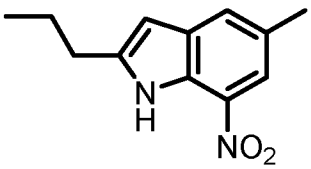
Example 31: 2-pentyl-5-methyl-7-nitro-1*H*-indole



Synthesis according to general route 4: A 100 mL round-bottom flask was charged with 6-iodo-4-methyl-2-nitroaniline (548 mg, 2 mmol), $Pd(PPh_3)_2Cl_2$ (140 mg, 10 mol%), copper iodide (90 mg, 20 mol%) and heptyne (0.4 mL, 3 mmol). The flask was evacuated and the mixture placed under a nitrogen atmosphere and anhydrous DMF (6 mL) was added. The mixture was cooled to 0 °C and diethylamine (0.3 mL, 3 mmol) was added dropwise. The mixture was stirred for 1 hour, after this time sodium hydroxide pellets (777 mg, 10 mmol) were added, the reaction was heated to 140 °C and allowed to stir for 4 hours. After cooling to RT, water was added and extracted with dichloromethane (3x). Organic phases were combined, washed with water (3x), dried ($MgSO_4$) and solvent evaporated under vacuo. The crude product was purified by column chromatography (silica, eluent hexane-ethyl acetate, 9-1) to give 2-pentyl-5-methyl-7-nitro-1*H*-indole as a yellow solid (overall 75%).

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 11.52 (br s, 1 H) 7.81 (s, 1 H) 7.72 (s, 1 H) 6.34 (s, 1 H) 2.79 (t, *J*=7.58 Hz, 2 H) 2.44 (s, 3 H) 1.69 (quin, *J*=7.43 Hz, 2 H) 1.23 - 1.37 (m, 4 H) 0.83 - 0.92 (m, 3 H); **^{13}C NMR** (101 MHz, DMSO-d_6) δ ppm 144.48, 132.74, 131.26, 127.60, 126.85, 117.48, 99.32, 30.78, 28.25, 26.99, 21.69, 20.22, 13.72; **MS** (ESI^+) m/z 247.2 $[M + H]^+$.

Example 32: 2-propyl-5-methyl-7-nitro-1*H*-indole

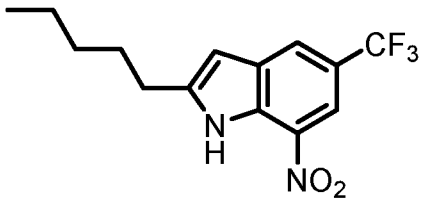


Synthesis according to general route 4: 6-iodo-4-methyl-2-nitroaniline (2.00 g, 7.19 mmol), $Pd(PPh_3)_2Cl_2$ (505 mg, 10 mol%), copper iodide (260 mg, 20 mol%), pentyne

(1.1 mL, 10.7 mmol), anhydrous DMF (20 mL) and diethylamine (1.1 mL, 10.7 mmol); NaOH (1.44 g, 35.9 mmol). Eluent hexane-ethyl acetate 9-1. The compound 2-propyl-5-methyl-7-nitro-1*H*-indole was obtained as a yellow solid (overall 52%).

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 11.52 (br s, 1 H) 7.82 (s, 1 H) 7.73 (s, 1 H) 6.34 (s, 1 H) 2.78 (t, *J*=7.52 Hz, 2 H) 2.44 (s, 3 H) 1.71 (sxt, *J*=7.38 Hz, 2 H) 0.94 (t, *J*=7.34 Hz, 3 H); **MS** (ESI^+) m/z 219.1 $[M + H]^+$.

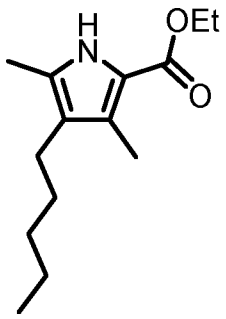
Example 33: 2-pentyl-5-trifluoromethyl-7-nitro-1*H*-indole



Synthesis according to general route 4: 6-iodo-4-trifluoromethyl-2-nitroaniline (365 mg, 1.10 mmol), $Pd(PPh_3)_2Cl_2$ (20 mg, 10 mol%), copper iodide (10 mg, 20 mol%), heptyne (0.2 mL, 1.5 mmol), anhydrous DMF (5 mL) and diethylamine (0.15 mL, 1.5 mmol); NaOH (787 mg, 10 mmol). Eluent hexane-ethyl acetate 9-1. The compound 2-propyl-5-methyl-7-nitro-1*H*-indole was obtained as a yellow solid (overall 46%).

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 12.12 (br s, 1 H) 8.33 (s, 1 H) 8.19 (d, *J*=0.98 Hz, 1 H) 6.62 (s, 1 H) 2.86 (t, *J*=7.64 Hz, 2 H) 1.67 - 1.76 (m, 2 H) 1.31 - 1.37 (m, 4 H) 0.87 - 0.91 (m, 3 H); δ ppm ; **MS** (ESI^-) 299.8 $[M - H]^-$.

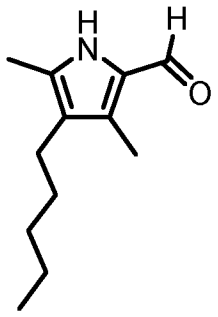
Example 34: 3,5-dimethyl-4-pentyl-pyrrole-2-carboxylic acid ethyl ester



A mixture of ethylacetoacetate (0.86 mL, 6.75 mmol) and acetic acid (2.5 mL) was cooled to -10 °C. Then a solution of $NaNO_2$ (451 mg, 6.75 mmol) in water (5 mL) was added dropwise and the mixture was warmed to RT and stirred for 12 hours. A mixture of 3-pentyl-2,4-pentanedione (1.17 g, 6.82 mmol) and acetic acid (5 mL) was heated to 90 °C when zinc powder (1.76 g, 27 mmol) and the previous solution were added simultaneously. The solution was heated to 95 °C and stirred for 1 hour, after which it was cooled to RT and water was added. The yellow precipitate was filtered and washed, dissolved in dichloromethane and filtered. The organic phase was washed with water, dried ($MgSO_4$) and solvent evaporated under vacuo. The crude product was purified by recrystallization from methanol to give 3,5-dimethyl-4-pentyl-pyrrole-2-carboxylic acid ethyl ester as a pearly white solid (overall 68%).

^{1}H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 8.51 (br s, 1 H) 4.30 (q, *J*=7.09 Hz, 2 H) 2.35 (t, *J*=7.60 Hz, 2 H) 2.27 (s, 3 H) 2.20 (s, 3 H) 1.39 - 1.46 (m, 2 H) 1.26 - 1.37 (m, 7 H) 0.90 (t, *J*=7.03 Hz, 3 H); **^{13}C NMR** (101 MHz, DMSO-d_6) δ ppm 161.66, 129.27, 122.45, 116.68, 77.20, 59.53, 31.63, 30.53, 23.96, 22.59, 14.60, 14.07, 11.53, 10.56; **MS** (ESI^+) m/z 238.3 $[M + H]^+$

Example 35: 3,5-dimethyl-4-pentyl-pyrrole-2-carboxaldehyde



A mixture of 3,5-dimethyl-4-pentyl-pyrrole-2- carboxylic acid ethyl ester (1.267 g, 5.34 mmol), EtOH (10 mL) and KOH (4.5 mL, 5M) was heated to reflux (82 °C) and stirred at this temperature for 2 hours. The reaction was cooled to RT and adjusted to pH 4 with acetic acid. The solvent was evaporated under vacuo to give a brown oil which was immediately dissolved in anhydrous dichloromethane and cooled to 0 °C. Trifluoroacetic acid (4 mL, 52 mmol) was added and the mixture stirred for 10 minutes at 0 °C, after this trimethylorthoformate (3 mL, 27 mmol) was added and the mixture warmed to RT and stirred for 10 minutes. Addition of $NaHCO_3$ quenched the

reaction followed by extraction with dichloromethane (3x). The organic phases were combined, washed (brine (3x)), dried ($MgSO_4$) and solvent evaporated under vacuo. The crude product was purified by column chromatography (silica, eluent hexane-ethyl acetate, 4-1) to give 3,5-dimethyl-4-pentyl-pyrrole-2-carboxaldehyde as white crystals (overall 61%);

^{1}H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 9.33 - 9.57 (m, 2 H) 2.35 (t, *J*=7.70 Hz, 2 H) 2.26 (s, 3 H) 2.24 (s, 3 H) 1.43 (quin, *J*=7.30 Hz, 2 H) 1.24 - 1.34 (m, 4 H) 0.85 - 0.93 (m, 3 H); **^{13}C NMR** (101 MHz, DMSO-d_6) δ ppm 175.66, 171.14, 135.36, 132.17, 127.83, 123.43, 60.38, 31.58, 30.26, 23.69 22.64, 22.56, 21.02, 14.17, 14.09, 11.68, 8.80; **MS** (ESI^+) m/z 194.3 $[M + H]^+$

Embodiments of the present invention will now be described, purely by way of example, with reference to the accompanying drawings, in which:

Figure 1 – illustrates the IC_{50} values for Example compounds 1-6 on MDA-MB-231, MCF-7 and MCF-10A cells.

Figure 2A – shows that treatment with a compound of Formula I, compound Example 1, inhibits the growth of the cancer cell line MCF-7, human breast adenocarcinoma. Cells were treated with a range of doses of active for 24h. Each data point is representative of at least 3 biological repetitions.

Figure 2B – shows that treatment with a compound of Formula I, compound Example 2, inhibits the growth of the cancer cell line MCF-7, human breast adenocarcinoma. Cells were treated with a range of doses of active for 24h. Each data point is representative of at least 3 biological repetitions.

Figure 2C – shows that treatment with a compound of Formula I, compound Example 3, inhibits the growth of the cancer cell line MCF-7, human breast adenocarcinoma. Cells were treated with a range of doses of active for 24h. Each data point is representative of at least 3 biological repetitions.

Figure 2D – shows that treatment with a compound of Formula I, compound Example 4, inhibits the growth of the cancer cell line MCF-7, human breast adenocarcinoma.

Cells were treated with a range of doses of active for 24h. Each data point is representative of at least 3 biological repetitions.

Figure 2E – shows that treatment with a compound of Formula I, compound Example 5, inhibits the growth of the cancer cell line MCF-7, human breast adenocarcinoma. Cells were treated with a range of doses of active for 24h. Each data point is representative of at least 3 biological repetitions.

Figure 2F – shows that treatment with a compound of Formula Ia, compound Example 6, inhibits the growth of the cancer cell line MCF-7, human breast adenocarcinoma. Cells were treated with a range of doses of active for 24h. Each data point is representative of at least 3 biological repetitions.

Figure 3A – shows that treatment with a compound of Formula I, compound Example 1, inhibits the growth of the cancer cell line MDA-MB-231, metastatic human breast adenocarcinoma. Cells were treated with a range of doses of active for 24h. Each data point is representative of at least 3 biological repetitions.

Figure 3B – shows that treatment with a compound of Formula I, compound Example 2, inhibits the growth of the cancer cell line MDA-MB-231, metastatic human breast adenocarcinoma. Cells were treated with a range of doses of active for 24h. Each data point is representative of at least 3 biological repetitions.

Figure 3C – shows that treatment with a compound of Formula I, compound Example 3, inhibits the growth of the cancer cell line MDA-MB-231, metastatic human breast adenocarcinoma. Cells were treated with a range of doses of active for 24h. Each data point is representative of at least 3 biological repetitions.

Figure 3D – shows that treatment with a compound of Formula I, compound Example 4, inhibits the growth of the cancer cell line MDA-MB-231, metastatic human breast adenocarcinoma. Cells were treated with a range of doses of active for 24h. Each data point is representative of at least 3 biological repetitions.

Figure 3E – shows that treatment with a compound of Formula I, compound Example 5, inhibits the growth of the cancer cell line MDA-MB-231, metastatic human breast

adenocarcinoma. Cells were treated with a range of doses of active for 24h. Each data point is representative of at least 3 biological repetitions.

Figure 3F – shows that treatment with a compound of Formula Ia, compound Example 6, inhibits the growth of the cancer cell line MDA-MB-231, metastatic human breast adenocarcinoma. Cells were treated with a range of doses of active for 24h. Each data point is representative of at least 3 biological repetitions.

Figure 4A – shows that treatment with a compound of Formula I, compound Example 1, inhibits the growth of the cell line MCF-10A, human mammary normal epithelial cells. Cells were treated with a range of doses of active for 24h. Each data point is representative of at least 3 biological repetitions.

Figure 4B – shows that treatment with a compound of Formula I, compound Example 2, inhibits the growth of the cell line MCF-10A, human mammary normal epithelial cells. Cells were treated with a range of doses of active for 24h. Each data point is representative of at least 3 biological repetitions.

Figure 4C – shows that treatment with a compound of Formula I, compound Example 3, inhibits the growth of the cell line MCF-10A, human mammary normal epithelial cells. Cells were treated with a range of doses of active for 24h. Each data point is representative of at least 3 biological repetitions.

Figure 4D – shows that treatment with a compound of Formula I, compound Example 4, inhibits the growth of the cell line MCF-10A, human mammary normal epithelial cells. Cells were treated with a range of doses of active for 24h. Each data point is representative of at least 3 biological repetitions.

Figure 4E – shows that treatment with a compound of Formula I, compound Example 5, inhibits the growth of the cell line MCF-10A, human mammary normal epithelial cells. Cells were treated with a range of doses of active for 24h. Each data point is representative of at least 3 biological repetitions.

Figure 4F – shows that treatment with a compound of Formula Ia, compound Example 6, inhibits the growth of the cell line MCF-10A, human mammary

normal epithelial cells. Cells were treated with a range of doses of active for 24h. Each data point is representative of at least 3 biological repetitions.

RESULTS

***In vitro* assays**

The potential activity of the novel perenosin compounds as cytotoxic agents in cancerous and non-cancerous cell lines was investigated through the evaluation of cell viability.

Cell viability assays

Compound Examples 1-6 were applied in a series of *in vitro* viability assays to investigate their effect on breast carcinoma cell lines using MDA-MB-231 (invasive) and MCF-7 (non-invasive), and mammary normal cells MCF-10A cells.

The above cell lines were treated with various doses of Compound Examples 1-6 for 24 h and the effect on the degree of cell viability was determined giving a dose-response curve affording the IC_{50} values (Inhibitory Concentration of 50% of cell population). The results are shown in Table 1.

Compound Example	MDA-MB-231 (μM)	MCF-7 (μM)	MCF-10A (μM)	Fold increase MCF-10A/MDA-MB-231	Fold increase MCF-10A/MCF7
1	9.24	5.84	12.90	1.4	2.2
2	3.26	4.07	10.77	3.3	2.6
3	5.27	4.64	10.92	2.1	2.4
4	3.98	3.84	16.21	**4.1**	**4.2**
5	8.57	5.28	14.36	1.7	2.7
6	24.27	24.32	53.57	2.2	2.2

Table 1. IC_{50} (μM) values for compound Examples 1-6 on MDA-MB-231, MCF-7 and MCF-10A cells.

As shown in **Figure 1**, Compound Examples 1-5 showed a significant cytotoxicity towards the malignant cell lines with IC_{50} as low as 3.84 μM, while a substantially weaker activity was found for benzimidazole derivative Compound Example 6 (IC_{50} 24.32 μM). The most active compounds, Examples 2 and 4 also are the most lipophilic in the series (logP 3.84 and 5.06, respectively). A significantly reduced cytotoxicity was observed towards non-cancerous MCF-10A cells with an outstanding 4.2 fold decrease (MCF-10A/MCF-7) for Example 4. This suggests a certain cytotoxic specificity of these transporters towards cancerous cells.

Materials and Methods

***In vitro* assays**

Cell culture, cell treatments, transfection and cell counting

All cell culture reagents were purchased from Life Technologies unless otherwise stated. Cell lines were sourced from the American Type Culture Collection (ATCC) and not grown continually for more than 3 months. All cells were cultured at 37°C in a humidified 5% CO_2 atmosphere.

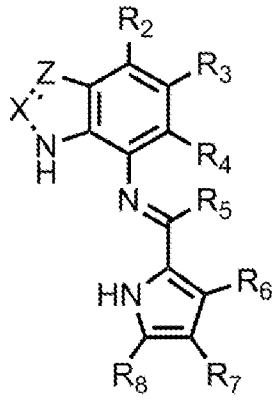
Cell viability assays

MCF-7 (human breast adenocarcinoma) cells, MDA-MB-231 (metastatic human breast adenocarcinoma) cells and MCF-10A (human mammary normal epithelial) cells were seeded in triplicate at 8000 cells per well, 10,000 cells per well and 10,000 cells per well, respectively, on 96-well plates 16 hours prior to dosing with the test compounds in 200 μl of fresh medium; final concentration of solvent DMSO in each well was 0.5% v/v. MTT-based cell proliferation assays were performed 24 hours post-dosing, as follows: MTT (Sigma) was prepared in sterile PBS and added to cells to a final concentration of 1 mM (10% v/v). Cells were then incubated for 4 hours at 37 ^{o}C until intracellular punctate purple precipitates were clearly visible under the microscope. An equal volume of DMSO was then added and the cells incubated for 10 minutes in the dark at room temperature with agitation to dissolve the insoluble formazan particles. Absorbance was measured at 570 nm on a microplate reader (Tecan Infinite M200 Pro). Each experiment was repeated three times. All values are expressed as the mean ± SEM.

Other embodiments are intentionally within the scope of the invention as defined by the appended claims.

CLAIMS

1. A compound of Formula I



Formula I

wherein:

X is selected from –CH, –N or –CR_1 wherein R_1 is an (C1-C20) alkyl or an (C1-C20) alkoxy;

Z is selected from –CH, –N or –CR_1 wherein R_1 is an (C1-C20) alkyl or an (C1-C20) alkoxy;

R_2 is selected from –H, an (C1-C20) alkyl or an (C1-C20) alkoxy;

R_3 is selected from –H, –F,–Cl, –Br, –CN,–CF_3, an (C1-C20) alkyl, an (C1-C20) alkoxy; or wherein R_2 and R_3 can together form an (C5-C20) alicyclic ring;

R_4 is selected from –H, an (C1-C20) alkyl or an (C1-C20) alkoxy;

R_5 is –H;

R_6 is selected from –H, an (C1-C20) alkyl or an (C1-C20) alkoxy;

R_7 is selected from –H, an (C1-C20) alkyl or an (C1-C20) alkoxy;

R_8 is selected from –H, an (C1-C20) alkyl or an (C1-C20) alkoxy; or wherein R_7 and R_8 can together form a substituted phenyl ring, with one to four substituents selected from the group consisting of R_9, R_{10}, R_{11} and R_{12}; wherein

R_9 is selected from –H, an (C1-C20) alkyl or an (C1-C20) alkoxy;

R_{10} is selected from –H, –F, –Cl, –Br, –CN, –NO_2, –CF_3, an (C1- C20) alkyl or an (C1-C20) alkoxy;

R_{11} is selected from –H, an (C1-C20) alkyl or an (C1-C20) alkoxy; and

R_{12} is selected from –H, an (C1-C20) alkyl or an (C1-C20) alkoxy;

or a pharmaceutically acceptable salt or solvate thereof.

2. The compound of claim 1, wherein R_1, R_2, R_3, R_4, or R_7 is (C1-C6) alkyl.

3. The compound of claim 2 wherein R_1, R_2, R_3, R_4, or R_7 is pentyl, isopentyl, hexyl or isohexyl.

4. The compound of claim 1, wherein X is –CH; Z is –CH, R_2 is –H, R_3 is –H, R_4 is –H, R_5 is –H; R_6 is $-CH_3$, R_7 is –H and R_8 is $-CH_3$.

5. The compound of claim 1, wherein X is CH; Z is –CH, R_2 is –H, R_3 is $-CF_3$, R_4 is –H, R_5 is –H; R_6 is $-CH_3$, R_7 is –H and R_8 is $-CH_3$.

6. The compound of claim 1, wherein X is –CH; Z is –CH, R_2 is –H, R_3 is $-CH_3$, R_4 is –H, R_5 is –H; R_6 is $-CH_3$, R_7 is –H and R_8 is $-CH_3$.

7. The compound of claim 1, wherein X is –CH; Z is –CH, R_2 is –H, R_3 is $-C_5H_{11}$, R_4 is –H, R_5 is –H; R_6 is $-CH_3$, R_7 is –H and R_8 is $-CH_3$.

8. The compound of claim 1, wherein X is –CH; Z is –CH, R_2 is –H, R_3 is $-OCH_3$, R_4 is –H, R_5 is –H; R_6 is $-CH_3$, R_7 is –H and R_8 is $-CH_3$.

9. The compound of claim 1, wherein X is –N; Z is –CH, R_2 is –H, R_3 is –H, R_4 is –H, R_5 is –H; R_6 is $-CH_3$, R_7 is –H and R_8 is $-CH_3$.

10. The compound of claim 1, wherein X is -CH; Z is –N, R_2 is –H, R_3 is –H, R_4 is –H, R_5 is –H; R_6 is $-CH_3$, R_7 is –H and R_8 is $-CH_3$.

11. The compound of claim 1, wherein X is -CH; Z is –CH, R_2 is –H, R_3 is $-C_5H_{11}$, R_4 is –H, R_5 is –H; R_6 is $-CH_3$, R_9 is –H, R_{10} is –H, R_{11} is –H and R_{12} is –H.

12. The compound of claim 1, wherein X is $-CR_1$ wherein R_1 is $-C_5H_{11}$; Z is –CH, R_2 is –H, R_3 is $-CH_3$, R_4 is –H, R_6 is $-CH_3$, R_7 is –H and R_8 is $-CH_3$.

13. The compound of claim 1, wherein X is - X is $-CR_1$ wherein R_1 is $-C_5H_{11}$; Z is –CH, R_2 is –H, R_3 is $-CF_3$, R_4 is –H, R_5 is –H, R_6 is $-CH_3$, R_7 is –H and R_8 is $-CH_3$.

14. The compound of claim 1, wherein X is - X is $-CR_1$ wherein R_1 is $-C_5H_{11}$; Z is –CH, R_2 is –H, R_3 is $-CH_3$, R_4 is –H, R_5 is –H, R_6 is $-CH_3$, R_7 is $-C_5H_{11}$ and R_8 is $-CH_3$.

15. The compound of claim 1, wherein X is - X is $-CR_1$ wherein R_1 is $-C_5H_{11}$; Z is –CH, R_2 is –H, R_3 is $-CH_3$, R_4 is –H, R_5 is –H, R_6 is $-CH_3$, R_9 is –H, R_{10} is –H, R_{11} is –H and R_{12} is –H.

16. The compound of claim 1, wherein X is $-CR_1$ wherein R_1 is $-C_3H_7$; Z is –CH, R_2 is –H, R_3 is $-CH_3$, R_4 is –H, R_5 is –H, R_6 is $-CH_3$, R_7 is –H and R_8 is $-CH_3$.

17. The compound of claim 1, wherein X is –CH; Z is –CH, R_2 is –H, R_3 is $-CH_3$, R_4 is –H, R_5 is –H, R_6 is $-CH_3$, R_7 is $-C_5H_{11}$ and R_8 is $-CH_3$.

18. The compound of claim 1, wherein said compound is chosen from:
(*E*)-1-(3,5-dimethyl-1*H*-pyrrol-2-yl)-*N*-(1*H*-indol-7-yl)methanimine
(*E*)-1-(3,5-dimethyl-1*H*-pyrrol-2-yl)-*N*-(5-(trifluoromethyl)-1*H*-indol-7-yl)methanimine
(*E*)-1-(3,5-dimethyl-1*H*-pyrrol-2-yl)-*N*-(5-methyl-1*H*-indol-7-yl)methanimine
(*E*)-1-(3,5-dimethyl-1*H*-pyrrol-2-yl)-*N*-(5-pentyl-1*H*-indol-7-yl)methanimine
(*E*)-1-(3,5-dimethyl-1*H*-pyrrol-2-yl)-*N*-(5-methoxy-1*H*-indol-7-yl)methanimine
(*E*)-1-(3,5-dimethyl-1*H*-pyrrol-2-yl)-*N*-(1*H*-benzimidazole-7-yl)methanimine
(*E*)-1-(3,5-dimethyl-1*H*-pyrrol-2-yl)-*N*-(1*H*-indazol-7-yl)methanimine
(*E*)-1-(3-methyl-1*H*-indol-2-yl)-*N*-(5-pentyl-1*H*-indol-7-yl)methanimine
2-Nitro-4-pentylanilineo
4-Methyl-2-nitro-6-((trimethylsilyl)ethynyl)aniline
2-Nitro-4-pentyl-6-((trimethylsilyl)ethynyl)aniline
7-Nitro-5-(trifluoromethyl)-1*H*-indole
5-Methyl-7-nitro-1*H*-indole
7-Nitro-5-pentyl-1*H*-indole
Ethyl 2-(2-(4-methoxy-2-nitrophenyl)hydrazono)propanoate
Ethyl 5-methoxy-7-nitro-1*H*-indole-2-carboxylate

5-Methoxy-7-nitro-1*H*-indole-2-carboxylic acid

5-Methoxy-7-nitro-1*H*-indole

7-(4,6-Dimethyl-1,1-diphenyl-1*H*-1λ^4,2λ^4-pyrrolo[1,2-*c*][1,3,2]diazaborol-2-yl)-1*H*-indole

7-(4,6-Dimethyl-1,1-diphenyl-1*H*-1λ^4,2λ^4-pyrrolo[1,2-*c*][1,3,2]diazaborol-2-yl)-5-pentyl-1*H*-indole.

19. A pharmaceutical composition comprising the compound of any one of claims 1 to 18 and a pharmaceutically acceptable carrier.

20. The compound of any one of claims 1 to 18 or the pharmaceutical composition of claim 19 for use as a medicament.

21. The compound of any one of claims 1 to 18 or the pharmaceutical composition of claim 19 for use in treating or preventing cancer.

22. A method of treating or preventing cancer, the method comprising administering, to a subject in need of such treatment or prevention, the compound of any one of claims 1 to 18 or the pharmaceutical composition of claim 19.

23. The compound of claims 1 to 18 or the pharmaceutical composition of claim 19 or the method of claim wherein said cancer is chosen from breast, lung or ovarian cancer.

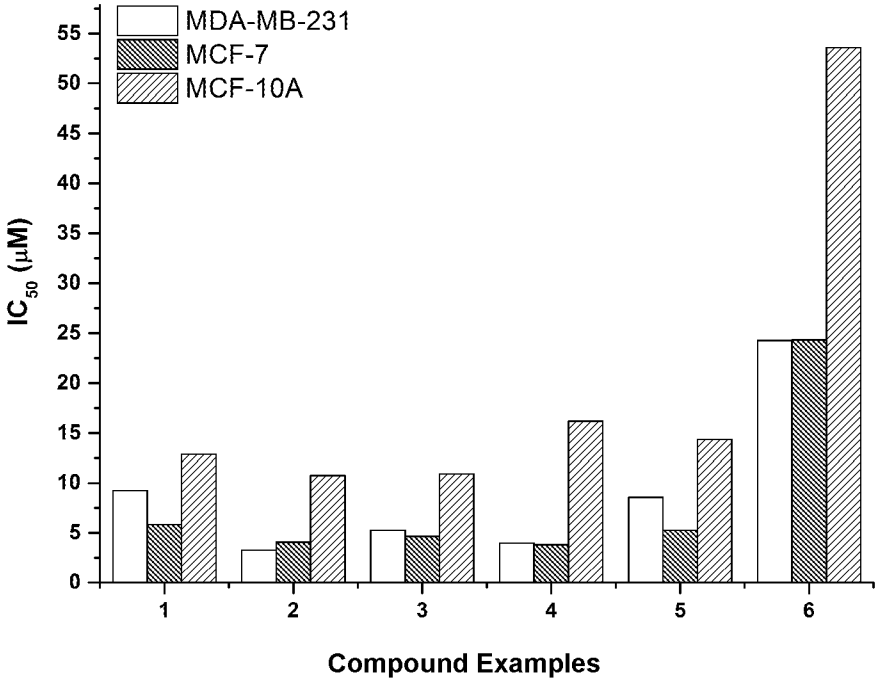

MDA-MB-231
MCF-7
MCF-10A
IC50 (μM)
0
5
10
15
20
25
30
35
40
45
50
55
1
2
3
4
5
6
Compound Examples

Figure 1.

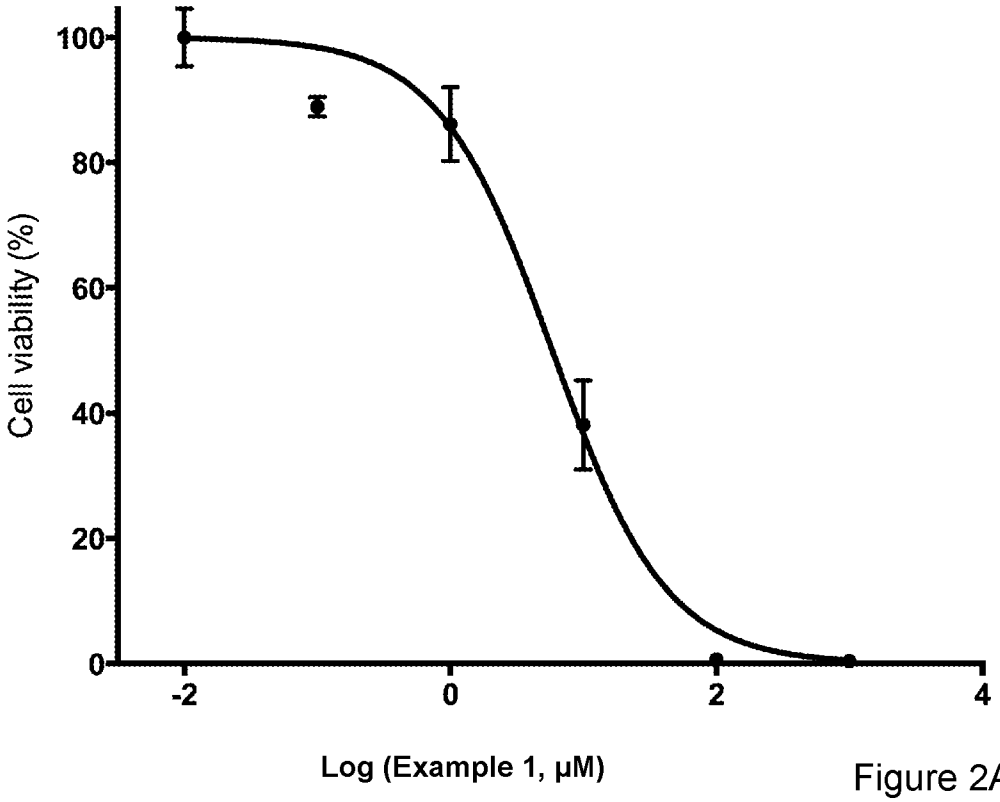


Figure 2A

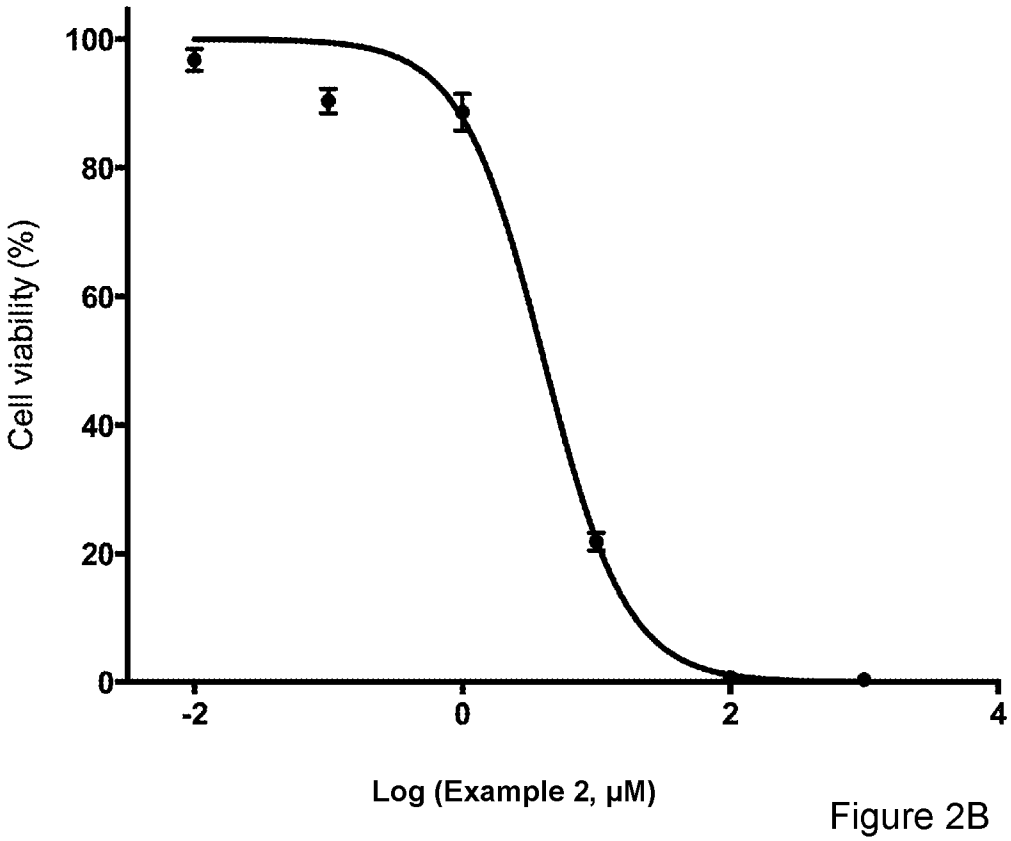


Figure 2B

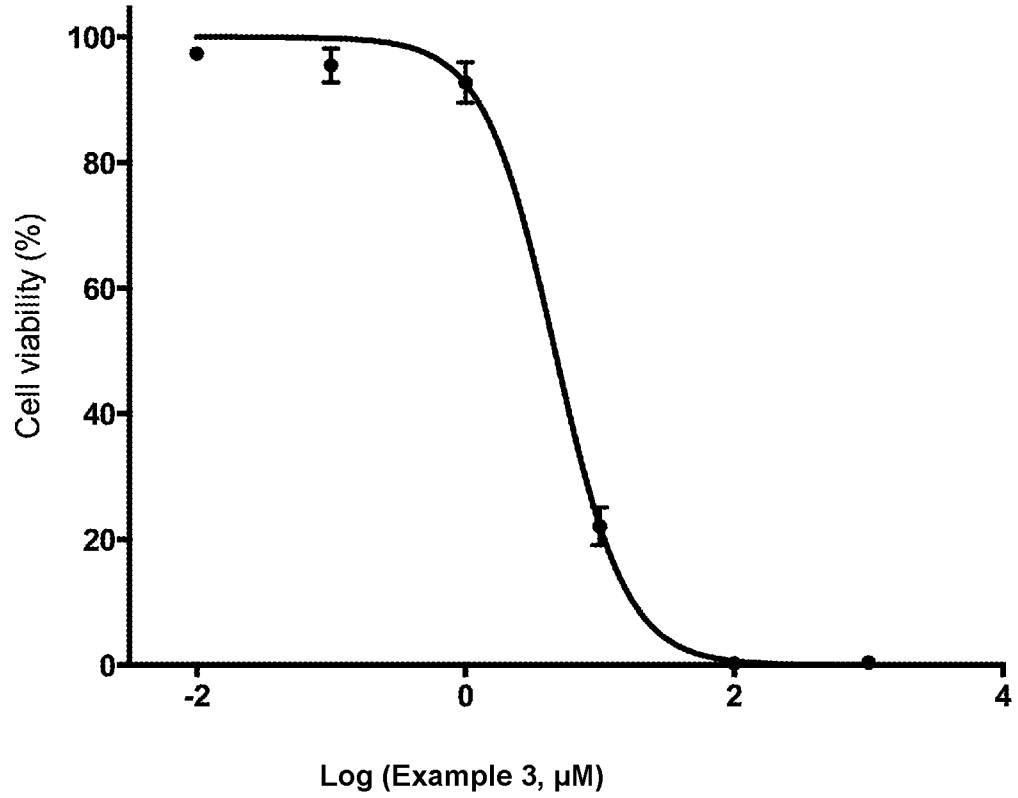


Figure 2C

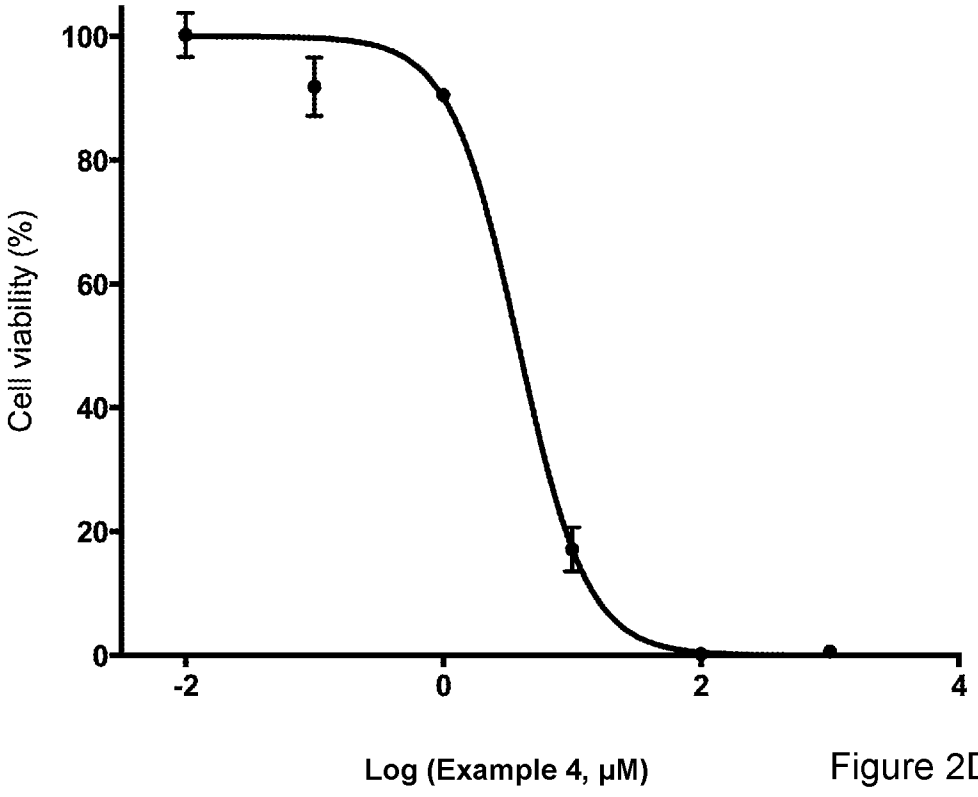


Figure 2D

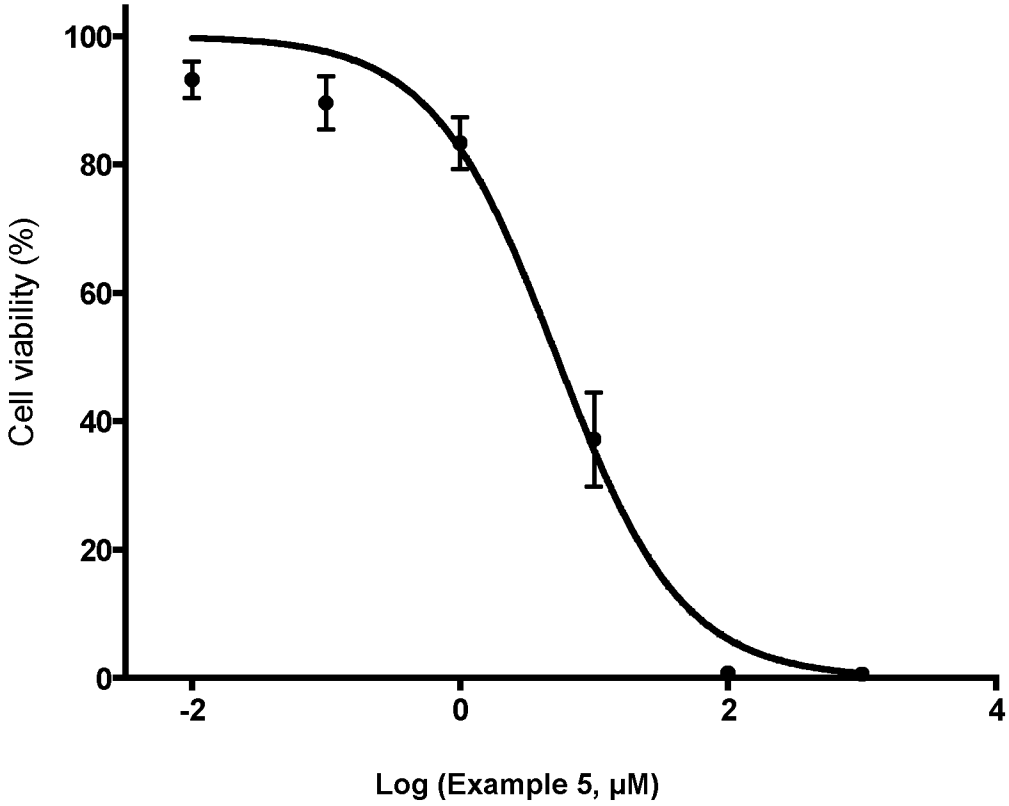


Figure 2E

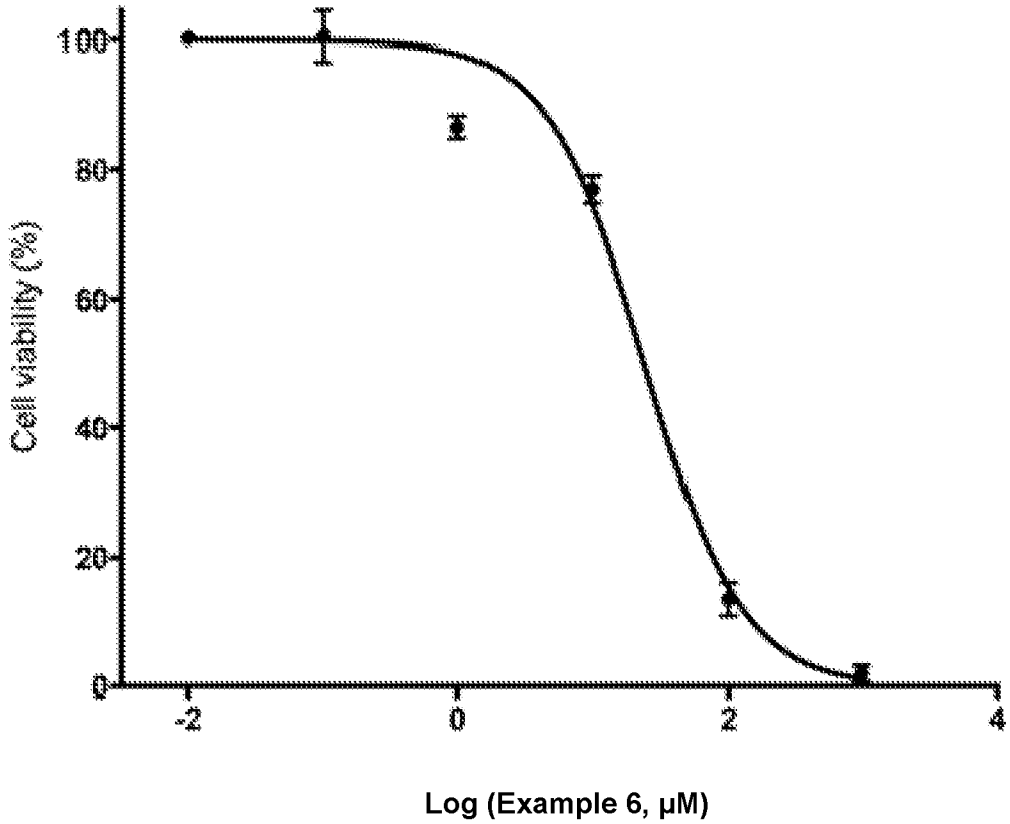


Figure 2F

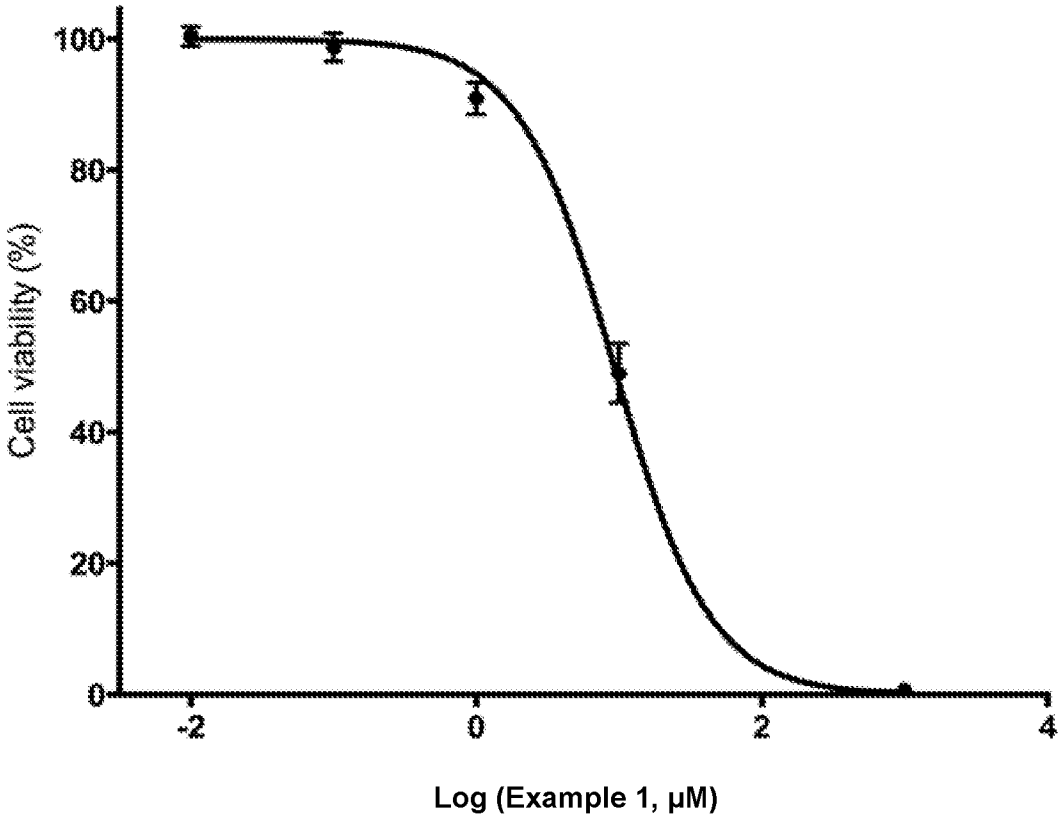


Figure 3A

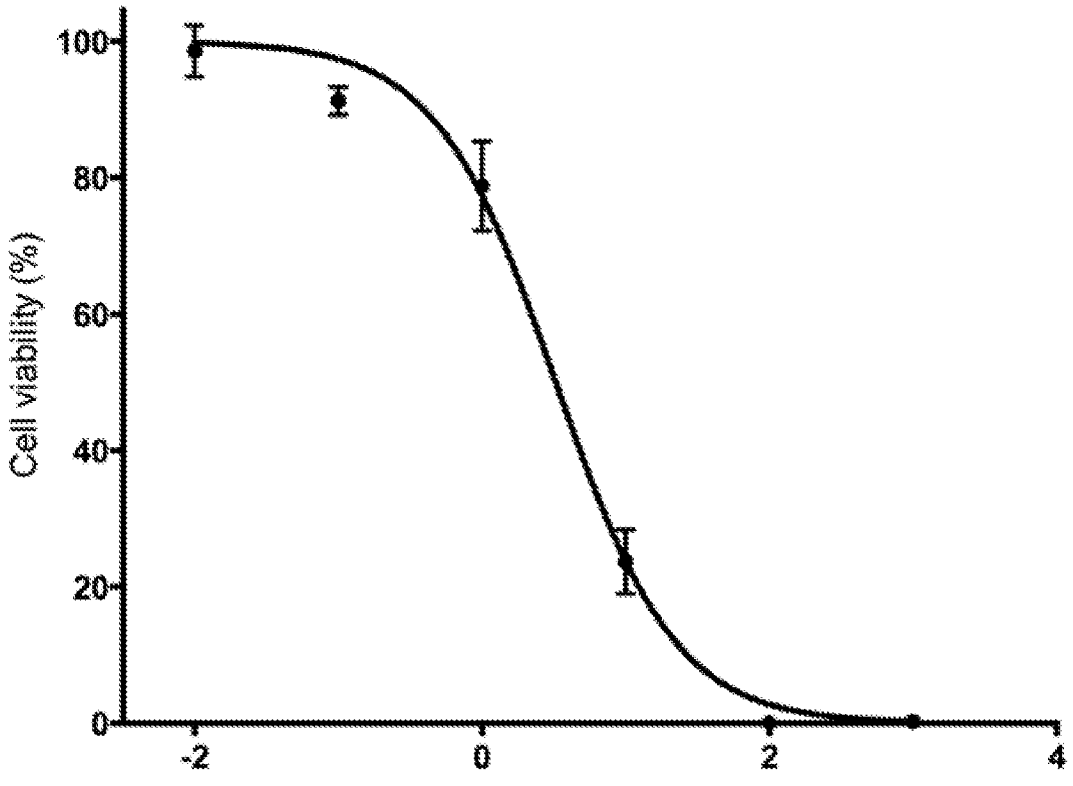


Figure 3B

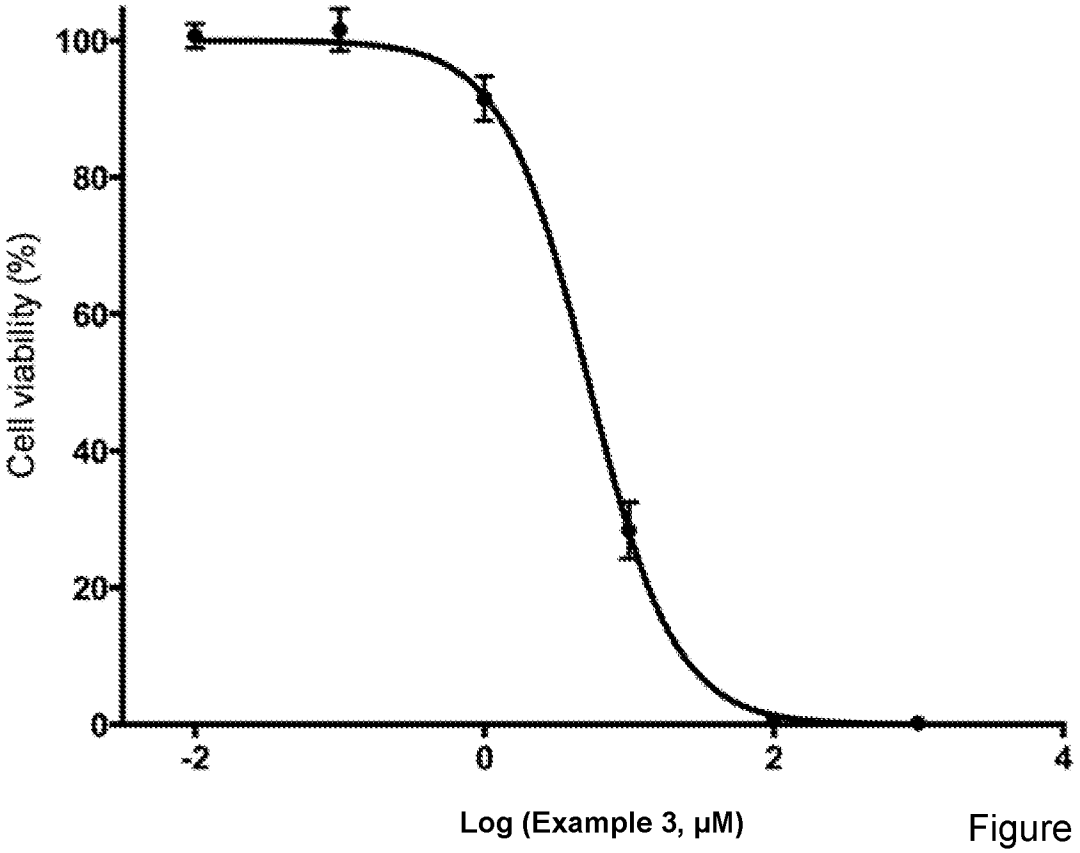


Figure 3C

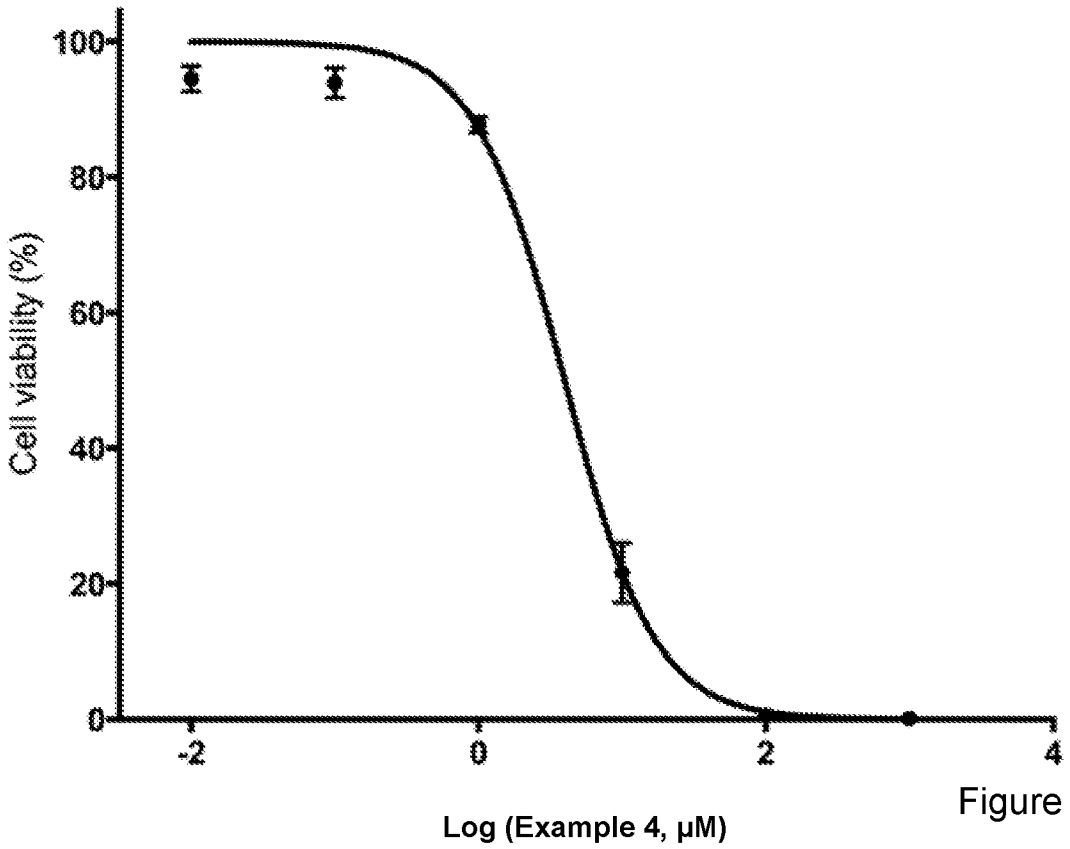


Figure 3D

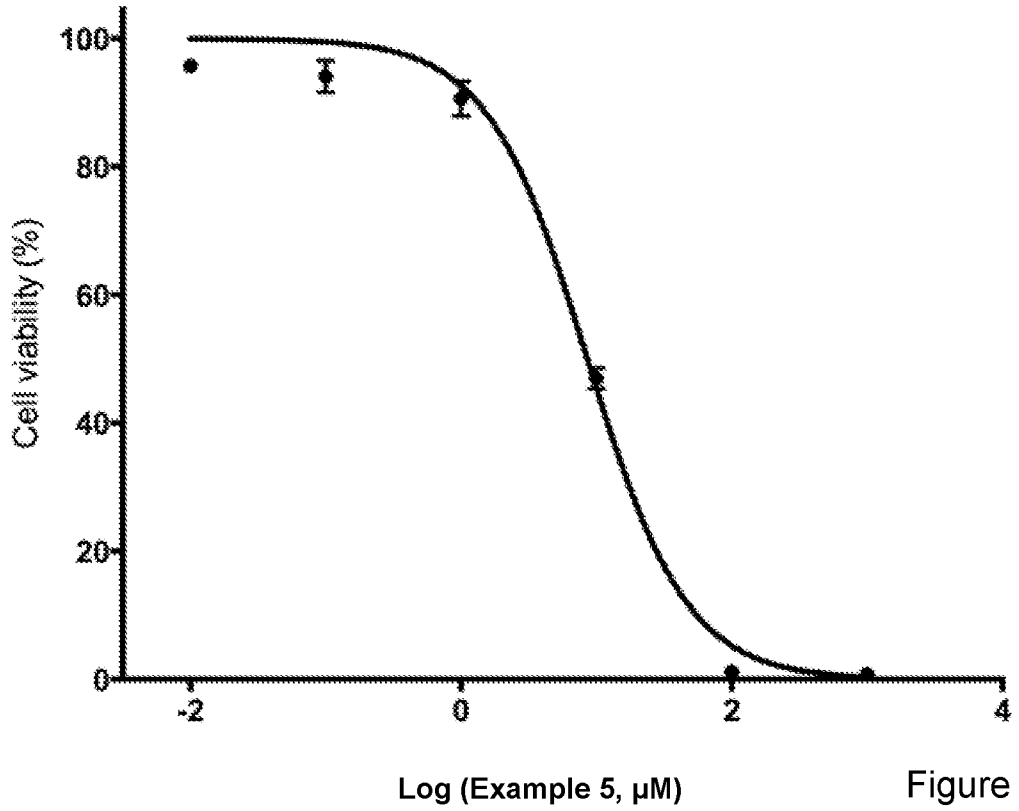


Figure 3E

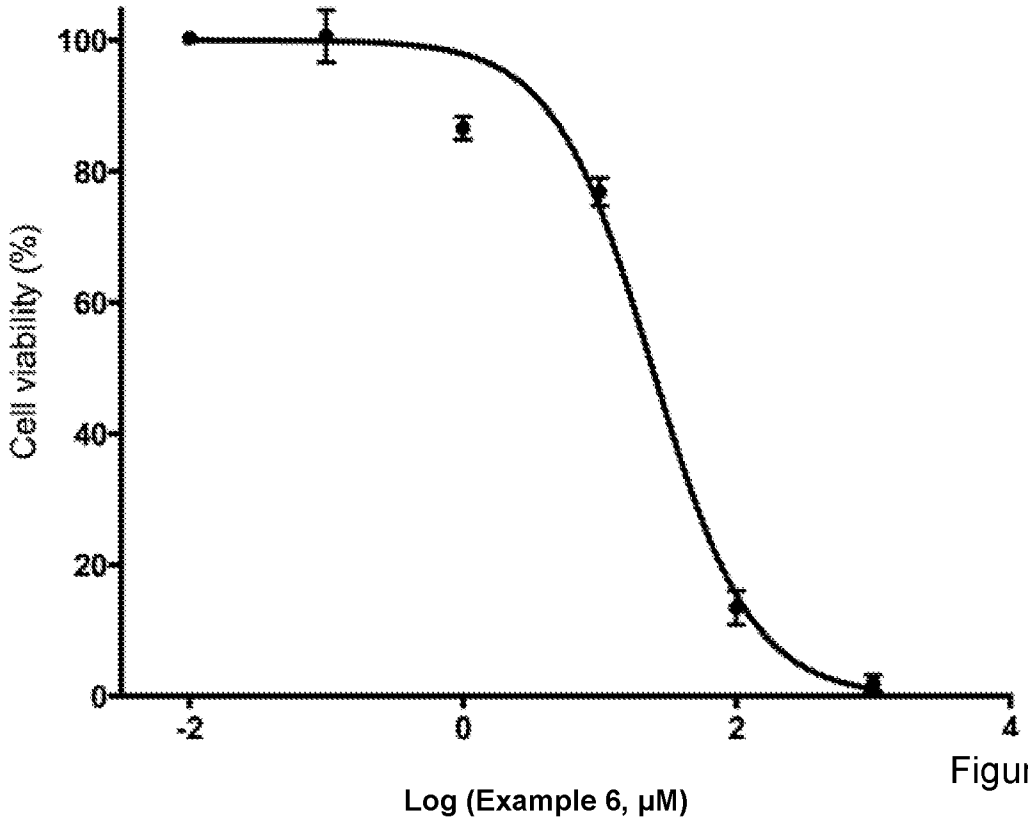


Figure 3F

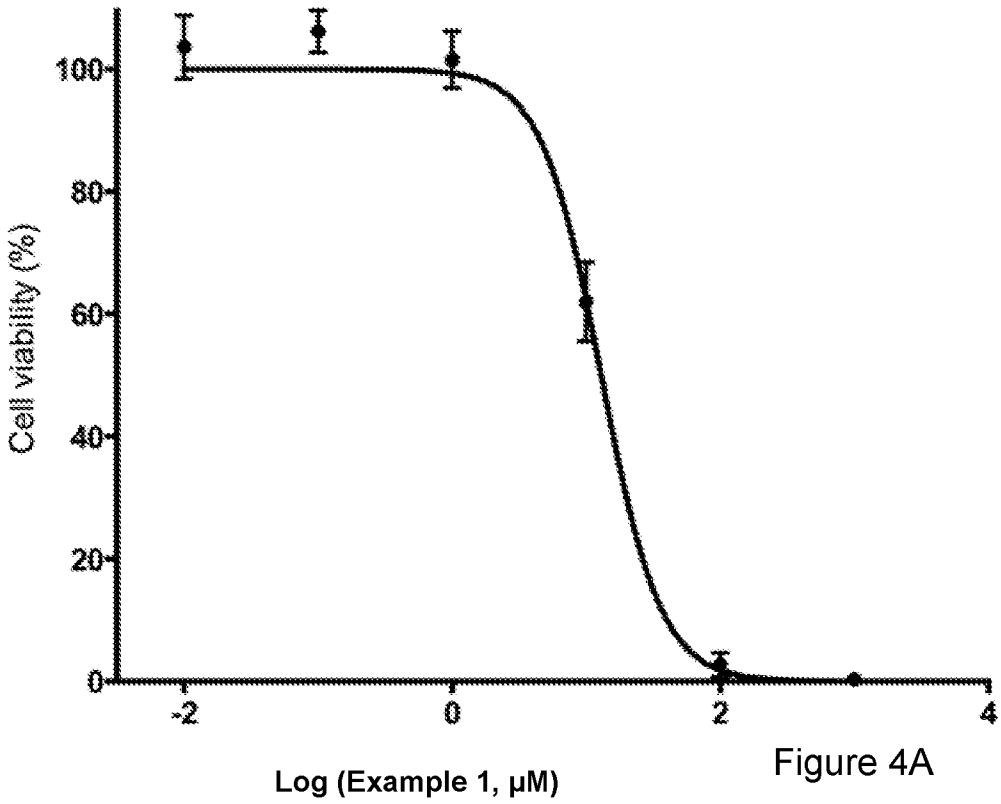


Figure 4A

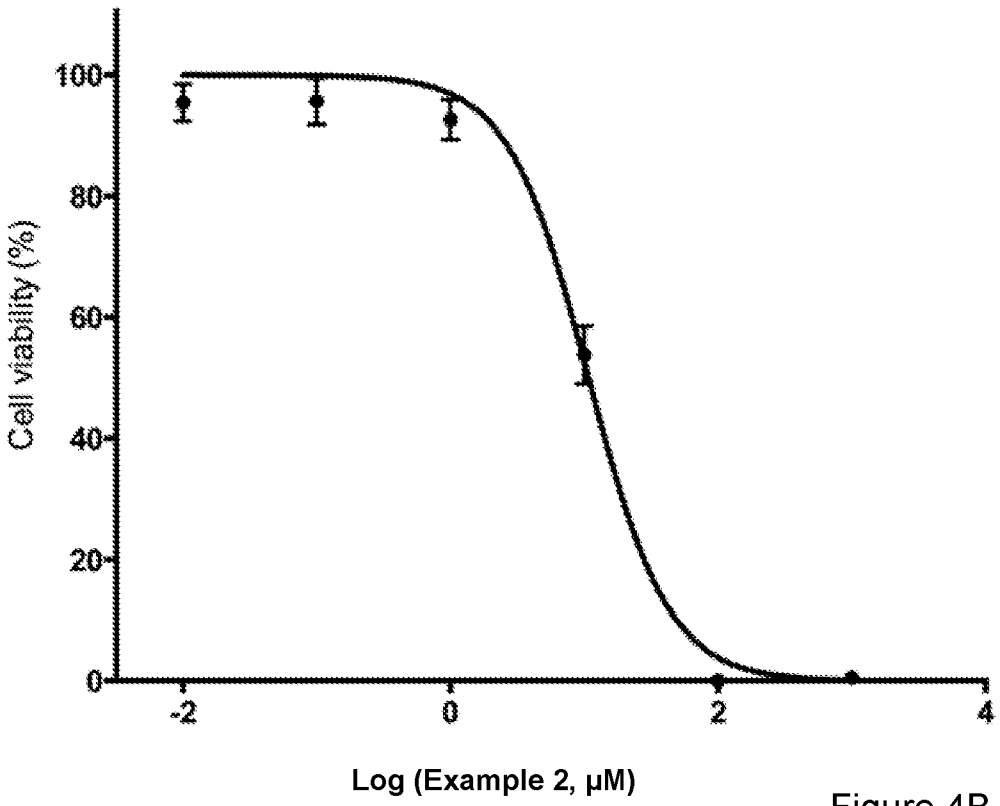


Figure 4B

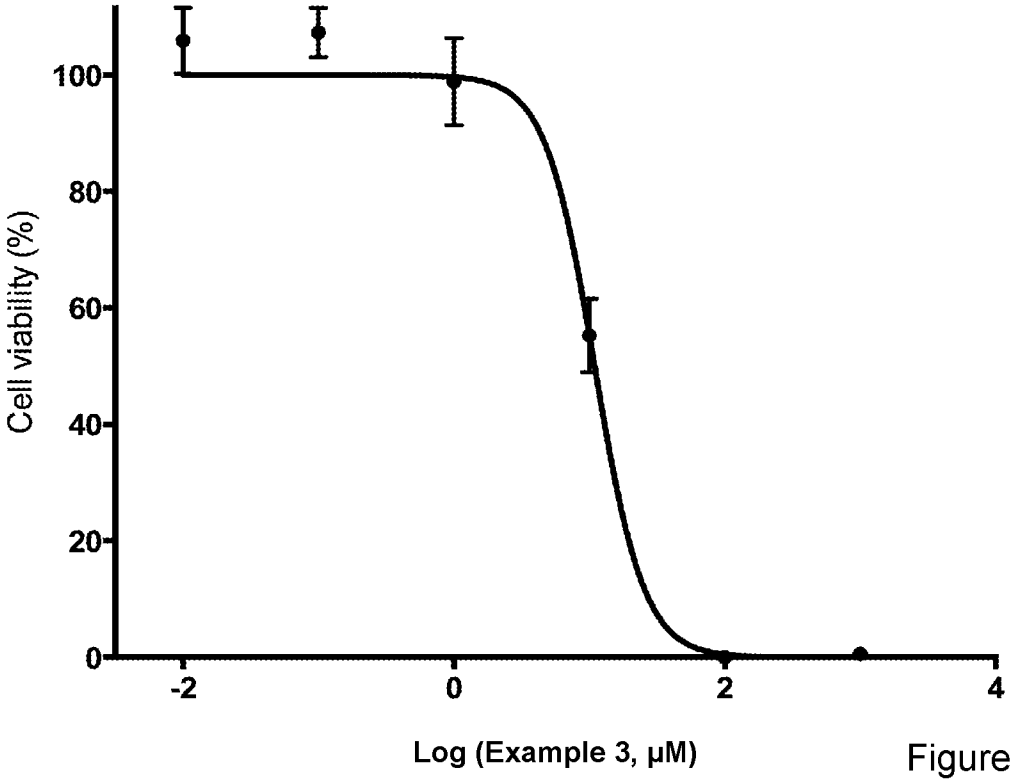


Figure 4C

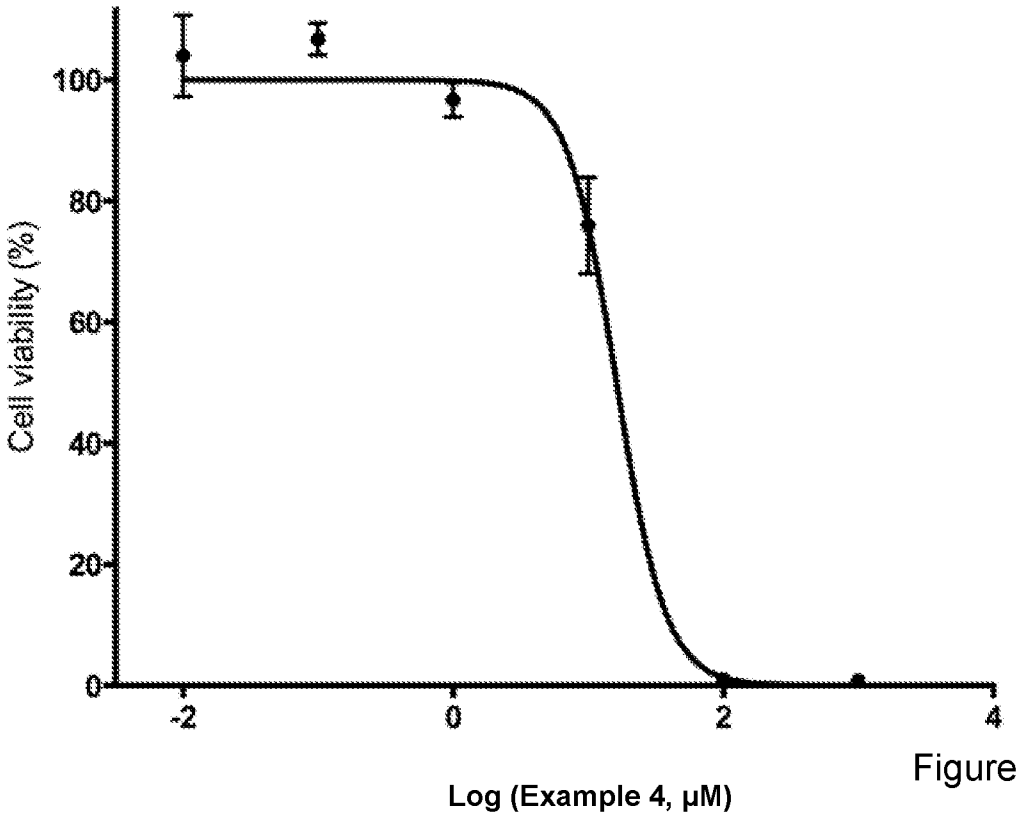


Figure 4D

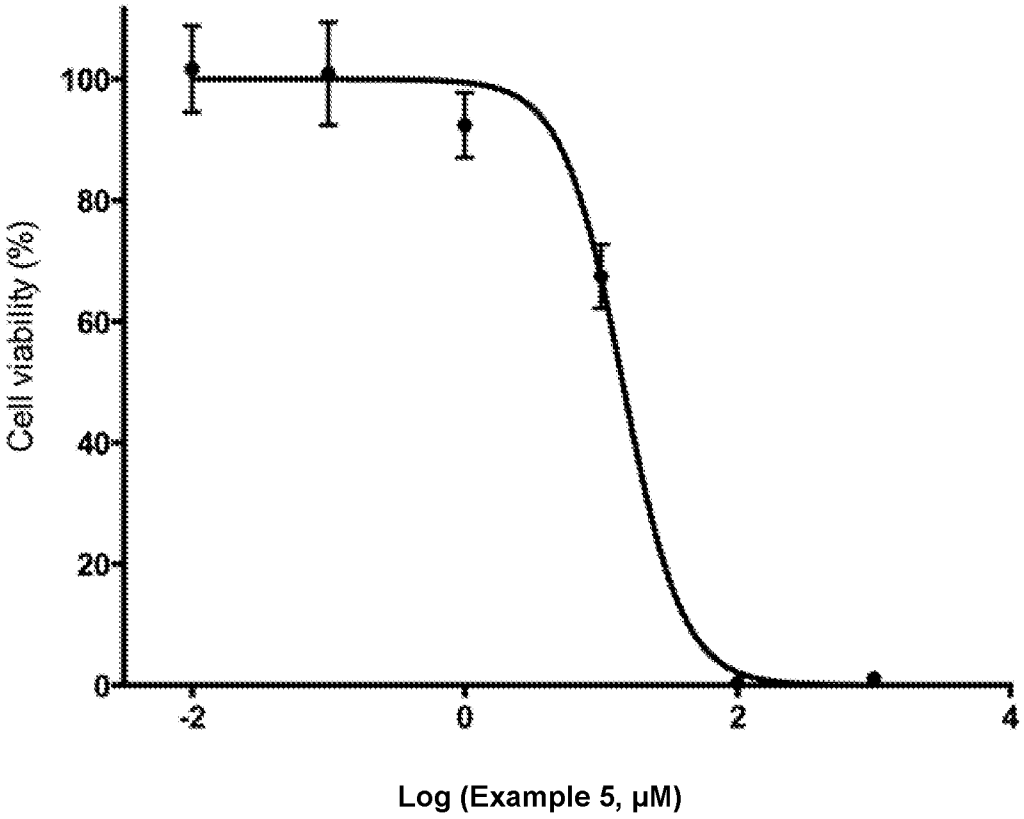


Figure 4E

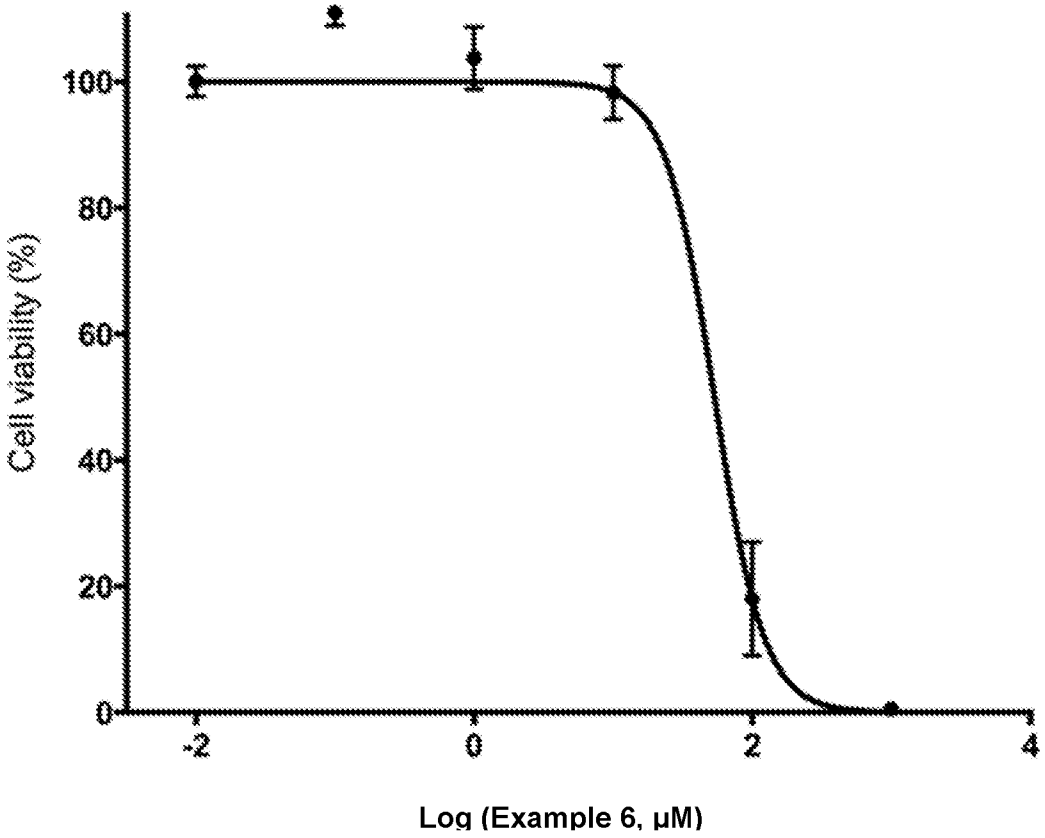


Figure 4F

INTERNATIONAL SEARCH REPORT

International application No
PCT/GB2016/053418

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D403/12 C07F5/02 C07F7/08 A61K31/404 A61P35/00
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D C07F

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal, CHEM ABS Data, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	HIREMATH S P ET AL: "STUDIES IN THE INDOLE FIELD. PART VI. SYNTHESIS OF SOME NITRO- AND AMINO-INDOLES", JOURNAL OF THE INDIAN CHEMICAL SOCIETY, THE INDIAN CHEMICAL SOCIETY, CALCUTTA; IN, vol. 41, no. 5, 1 May 1964 (1964-05-01), pages 357-361, XP002039341, ISSN: 0019-4522 compound IVd ----- -/--	18

[X] Further documents are listed in the continuation of Box C. [ ] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
1 December 2016	08/12/2016

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Gutke, Hans-Jürgen

3

Form PCT/ISA/210 (second sheet) (April 2005)

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	Wayland Noland ET AL: "Ultraviolet and Infrared Spectra of Some Nitroindoles and Nitroindole-3-carboxaldehydes", Journal of Chemical and Engineering Data, 1966 , vol. 11, p. 418, 1 July 1966 (1966-07-01), XP055324224, Retrieved from the Internet: URL:http://pubs.acs.org/doi/pdf/10.1021/je60030a040 [retrieved on 2016-11-29] compounds 3b, 3c	18
X	SZTANKE KRZYSZTOF ET AL: "An insight into synthetic Schiff bases revealing antiproliferative activities in vitro", BIOORGANIC & MEDICINAL CHEMISTRY, PERGAMON, GB, vol. 21, no. 13, 22 April 2013 (2013-04-22), pages 3648-3666, XP028558890, ISSN: 0968-0896, DOI: 10.1016/J.BMC.2013.04.037	1-3,10, 18-23
A	compounds 5, 17	4-9, 11-17
X,P	WIM VAN ROSSOM ET AL: "Perenosins: a new class of anion transporter with anti-cancer activity", ORGANIC & BIOMOLECULAR CHEMISTRY, vol. 14, no. 9, 1 January 2016 (2016-01-01), pages 2645-2650, XP055324624, GB ISSN: 1477-0520, DOI: 10.1039/C6OB00002A table 3 figure 2	1-23

3