

SMALL MOLECULE INHIBITORS OF ISOPRENYLCYSTEINE CARBOXYL METHYLTRANSFERASE WITH POTENTIAL ANTICANCER ACTIVITY

CROSS-REFERENCE TO RELATED APPLICATIONS

5 [0001] This application claims the benefit of priority of Singapore application number 200905128-5, filed 30 July 2009, and Singapore application number 200907728-0, filed on 20 November 2009, the content of both applications being hereby incorporated by reference in its entirety for all purposes.

FIELD OF THE INVENTION

10 [0002] The present invention relates to compounds having anti-cancer activity, in particularly to inhibitors of isoprenylcysteine carboxyl methyltransferase (Icmt), and methods of its use. The invention also provides a method of killing a cell using the compounds, to methods of diseases treatment and to pharmaceutical compositions of the compounds.

BACKGROUND OF THE INVENTION

15 [0003] Proteins with a CaaX motif regulate a number of pathways important in oncogenesis. These proteins undergo a series of post-translational modifications that are important for their localization, stability and function. The modifications are initiated by the addition of an isoprenoid moiety (farnesyl or geranylgeranyl) to the cysteine of the CaaX motif
20 by protein farnesyltransferase (FTase) or protein geranylgeranyltransferase-1 (GGTase-1) respectively. This is followed by the endoproteolytic release of the terminal tripeptide (AAX) by RAS converting enzyme (RCE1) and carboxymethylation of the C-terminal prenylcysteine by isoprenylcysteine carboxyl methyltransferase (Icmt).

25 [0004] The most widely studied example of CaaX proteins is the RAS family of regulatory proteins. RAS is a very important molecular switch for a variety of signaling pathways that control diverse processes like cytoskeletal integrity, proliferation, cell adhesion, apoptosis and cell migration. Activating mutations in RAS genes are implicated in the pathogenesis of a large number of solid tumors and hematologic malignancies. Many cancers contain alterations upstream of RAS in signaling cascades and the resultant hyperactivation of
30 RAS is thought to contribute to tumorigenesis.

[0005] The possibility of blocking RAS-induced oncogenic transformation by inhibiting the enzymes involved in the post-translational processing of the CaaX motif has been explored

for its therapeutic potential. The protein prenyltransferases in particular FTase have been targets of major drug discovery programs. FTase inhibitors showed significant activity in mouse models but clinical trials in cancer patients had been disappointing, possibly due to the geranylgeranylation of substrates by GGTase1 when FTase is inhibited. Hence, attention has been shifted to the post-prenylation enzymes RCE1 and Icmt as potential therapeutic targets. In particular, there is keen interest in developing Icmt inhibitors in view of studies that showed that genetic and pharmacological intervention with Icmt activity led to significant impairment of oncogenesis in several tumor cell models.

[0006] To date, three classes of Icmt inhibitors have been investigated. The first class comprises of S-adenosylhomocysteine (AdoHcy) and compounds that increase intracellular AdoHcy. AdoHcy is formed when a methyltransferase catalyzes the transfer of the methyl group from S-adenosylmethionine (AdoMet) to the substrate. AdoHcy binds to and competitively inhibits methyltransferase activity. However, AdoHcy is not a selective inhibitor of Icmt and affects the activity of other cellular methyltransferases. The second class of Icmt inhibitors is structural analogues of the substrate prenylcysteine. Examples are N-acetyl-S-farnesyl-L-cysteine (AFC) and N-acetyl-S-geranylgeranyl-L-cysteine (AGGC). These compounds are competitive inhibitors of Icmt but as structural mimics of the carboxy-terminal prenylcysteine of processed CaaX proteins, they would impact a large number of processes controlled by CaaX proteins.

[0007] Cysmethynil (2-[5-(3-methylphenyl)-1-octyl-1H-indolo-3-yl]acetamide) is a competitive inhibitor of the isoprenylated cysteine substrate and a non-competitive inhibitor of the methyl donor AdoMet. Cysmethynil caused the mislocation of RAS and impaired epidermal growth factor signaling in cancer cells. It blocked anchorage-independent growth in a colon cancer cell line which was reversed by overexpression of Icmt. A recent report showed that induction of autophagy by cysmethynil is a major contributor to the cell death that accompanies pharmacological inhibition of Icmt.

[0008] Some natural products from marine sponges (spermatinamine, aplysamine 6) and plants (prenylated β hydroxychalcones, a flavanone S-glabrol) have been identified as Icmt inhibitors but they were either weakly potent inhibitors or lack drug-like features. Cysmethynil remains the most promising compound to date. However, cysmethynil has no dissociable functionalities and its high lipophilicity and poor aqueous solubility may potentially restrict its clinical application. Although modifications made at the N-substituent of the indole ring and the

phenyl substituents of cysmethynil have been studied, the clinical relevance of these analogs is unknown.

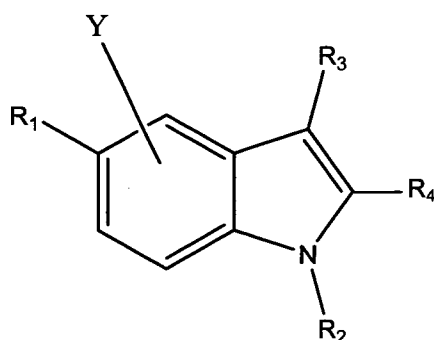
[0009] Therefore, there remains a need to identify effective inhibitors of Icmt that can have potential therapeutic effects for treating cancer and diseases or disorders associated with Icmt activity.

[0010] It is a further object of the invention to provide a compound that can be a potent inhibitor of Icmt.

[0011] Another object of the invention is to provide a pharmaceutical composition that can have an anti-proliferative effect on cancer cells.

SUMMARY OF THE INVENTION

[0012] In one aspect, the invention provides a compound of formula I or a pharmaceutically acceptable salt thereof



(I)

wherein

R₁ and Y are independently selected from the group consisting of hydrogen, hydroxyl, C₁₋₂₀alkyl, C₂₋₂₀alkenyl, C₂₋₂₀alkynyl, C₁₋₂₀acyl, C₃₋₈cycloalkyl, C₃₋₈cycloalkenyl, aryl, heteroaryl, heteroalicycyl, halogen, carbonyl, thiocarbonyl, O-carbamyl, O-thiocarbonyl, O-carboxy, isocyanato, thiocyanato, silyl, sulfonamide, thio, -CN, -COOH, -SH, -N=N, -N=O and NX₁X₂, wherein one or more of the hydrogen atoms of the indole ring can be replaced by Y;

R₂ is selected from the group consisting of hydrogen, C₁₋₂₀alkyl, C₂₋₂₀alkenyl, C₂₋₂₀alkynyl, C₁₋₂₀acyl, C₃₋₈cycloalkyl, C₃₋₈cycloalkenyl, aryl, heteroaryl and heteroalicycyl;

R₃ is (CH₂)_nNX₁X₂, n being an integer from 1 to 4;

R₄ is hydrogen or C₁-C₄ alkyl;

X₁ and X₂ are independently selected from the group consisting of hydrogen, C₁₋₂₀alkyl, C₂₋₂₀alkenyl, C₂₋₂₀alkynyl, C₁₋₂₀acyl, C₃₋₈cycloalkyl, C₃₋₈cycloalkenyl, aryl, heteroaryl, and heteroalicycyl; or

X₁ or X₂ may, together with the nitrogen atom bearing them, form a 3-8 membered ring, wherein the 3-8 membered ring is preferably a saturated ring, and wherein the 3-8 membered ring can be fused to at least one 3-8 membered ring, wherein the ring can optionally comprise 0, 1, 2, 3 or 4 further heteroatoms selected from the group consisting of oxygen, nitrogen, sulphur and phosphorus; and wherein the ring can be substituted by at least one substituent selected from the group consisting of hydrogen, hydroxyl, C₁₋₂₀alkyl, C₂₋₂₀alkenyl, C₂₋₂₀alkynyl, C₁₋₂₀acyl, C₃₋₈cycloalkyl, C₃₋₈cycloalkenyl, aryl, heteroaryl, heteroalicycyl, halogen, carbonyl, thiocarbonyl, O-carbamyl, O-thiocarbonyl, O-carboxy, isocyanato, thiocyanato, silyl, sulfonamide, thio, -CN, -COOH, -SH, -N=N, -N=O and NX₁X₂;

with the proviso that the following compounds are excluded:

3-(1-piperidinylmethyl)-1H-Indole-1-hexanamine;

1-(4-methyl-3-penten-1-yl)-N-(phenylmethyl)-1H-Indole-3-methanamine;

1-(3-buten-1-yl)-N-(phenylmethyl)-1H-Indole-3-methanamine;

5-ethenyl-N,N-dimethyl-1-h(phenylmethyl)-1H-Indole-3-methanamine, homopolymer (9CI);

N,1-dimethyl-N-(3-phenyl-2-propen-1-yl)-1H-Indole-3-methanamine;

N,1-dimethyl-N-(3-phenyl-2-propenyl)-1H-Indole-3-methanamine, (E)- (9CI);

3-[[4-(2,6-dimethylphenyl)-1-piperidinyl]methyl]-1-(phenylmethyl)-1H-Indole;

5-phenyl-3-(1-piperidinylmethyl)-1H-Indole;

1-methyl-3-(1-piperidinylmethyl)-5-[3-(1-piperidinyl)-1-propyn-1-yl]-1H-Indole;

1-(phenylmethyl)-3-(1-piperidinylmethyl)-1H-Indole, hydrochloride (1:1);

1-(phenylmethyl)-3-(1-piperidinylmethyl)-1H-Indole;

N,N-dimethyl-N-nonyl-1-(phenylmethyl)-1H-Indole-3-methanaminium;

N,N-dimethyl-N-octyl-1-(phenylmethyl)-1H-Indole-3-methanaminium;

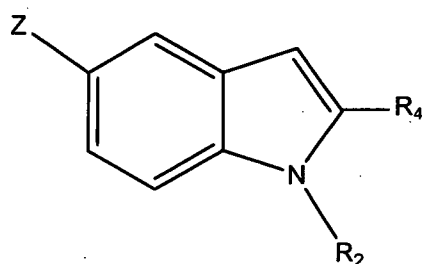
N,N-dimethyl-N-[[1-(phenylmethyl)-1H-indol-3-yl]methyl]-1-heptanaminium;

N-(phenylmethyl)-1-(2-propen-1-yl)-N-(4-pyridinylmethyl)-1H-Indole-3-methanamine;

5-methyl-3-(1-piperidinylmethyl)-1-(2-propen-1-yl)-1H-Indole; and

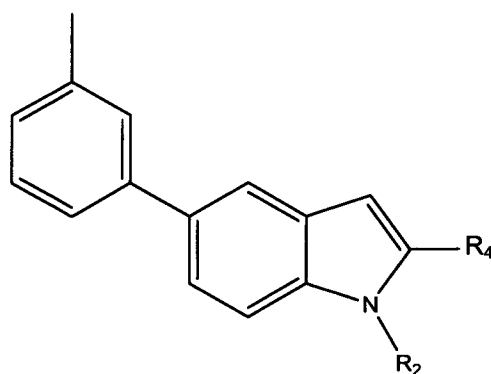
N-ethyl-N-((5-fluoro-1-(3-methylbut-2-enyl)-1H-indol-3-yl) methyl) ethanamine.

[0013] In a second aspect, the invention provides a method of preparing a compound of formula I. The method includes adding a phosphine compound to a solution containing the compound of formula II



(II);

wherein Z is a leaving group, under conditions to form a compound of formula III



(III)

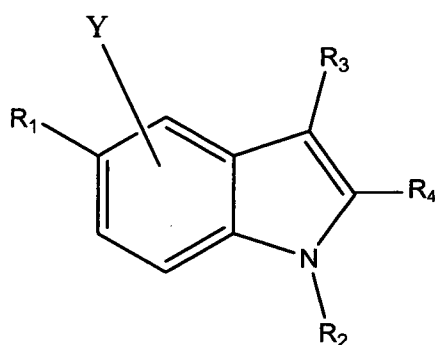
The method further includes adding an amine and an aldehyde to the solution obtained in the first step to form a compound of formula I.

[0014] In a third aspect, the invention provides a method of killing the cell. The method includes administering to the cell a compound of formula I as described above.

[0015] In a fourth aspect, the invention provides a pharmaceutical composition. The pharmaceutical composition includes the compound of formula I as described above.

[0016] In a fifth aspect, the invention provides a method of treating a mammal with a disease or disorder associated with Icmt activity. The method includes administering a compound of formula I or a pharmaceutical composition as described above.

[0017] In a sixth aspect, the invention provides a compound of Formula VII



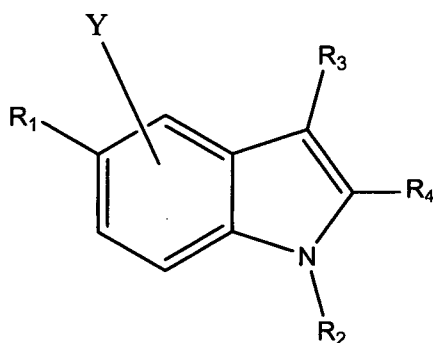
(VII)

or a pharmaceutically acceptable salt thereof,

wherein

- 5 R_1 and Y are independently selected from the group consisting of hydrogen, hydroxyl, C_{1-20} alkyl, C_{2-20} alkenyl, C_{2-20} alkynyl, C_{1-20} acyl, C_{3-8} cycloalkyl, C_{3-8} cycloalkenyl, aryl, heteroaryl, heteroalicycyl, halogen, carbonyl, thiocarbonyl, O-carbamyl, O-thiocarbonyl, O-carboxy, isocyanato, thiocyanato, silyl, sulfonamide, thio, -CN, -COOH, -SH, -N=N, -N=O and NX_1X_2 , wherein one or more of the hydrogen atoms of the indole ring can be replaced by Y;
- 10 R_2 is a terpenoid;
 R_3 is $(CH_2)_nCONX_1X_2$, n being an integer from 1 to 4; R_4 is hydrogen or C_1-C_4 alkyl;
 X_1 and X_2 are independently selected from the group consisting of hydrogen, C_{1-20} alkyl, C_{2-20} alkenyl, C_{2-20} alkynyl, C_{1-20} acyl, C_{3-8} cycloalkyl, C_{3-8} cycloalkenyl, aryl, heteroaryl, and heteroalicycyl; or
- 15 X_1 or X_2 may, together with the nitrogen atom bearing them, form a 3-8 membered ring, wherein the 3-8 membered ring can be fused to at least one 3-8 membered ring, wherein the ring can optionally comprise 0, 1, 2, 3 or 4 further heteroatoms selected from the group consisting of oxygen, nitrogen, sulphur and phosphorus; and wherein the ring can be substituted by at least one substituent selected from the group consisting of hydrogen, hydroxyl, C_{1-20} alkyl,
- 20 C_{2-20} alkenyl, C_{2-20} alkynyl, C_{1-20} acyl, C_{3-8} cycloalkyl, C_{3-8} cycloalkenyl, aryl, heteroaryl, heteroalicycyl, halogen, carbonyl, thiocarbonyl, O-carbamyl, O-thiocarbonyl, O-carboxy, isocyanato, thiocyanato, silyl, perhaloalkyl, sulfonyl, sulfonamide, thio, -CN, -COOH, -SH, -N=N, -N=O and NX_1X_2 .

[0018] In a seventh aspect, the invention provides a compound of Formula VIII



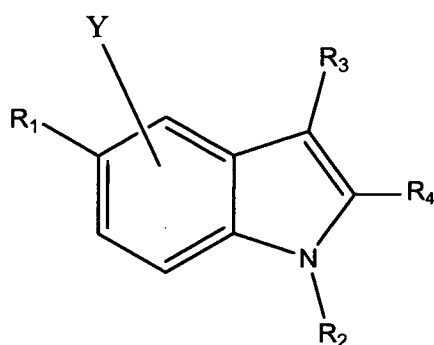
(VIII)

or a pharmaceutically acceptable salt thereof,

wherein

- 5 R_1 and Y are independently selected from the group consisting of hydrogen, hydroxyl, C_{1-20} alkyl, C_{2-20} alkenyl, C_{2-20} alkynyl, C_{1-20} acyl, C_{3-8} cycloalkyl, C_{3-8} cycloalkenyl, aryl, heteroaryl, heteroalicycyl, halogen, carbonyl, thiocarbonyl, O-carbamyl, O-thiocarbonyl, O-carboxy, isocyanato, thiocyanato, silyl, sulfonamide, thio, -CN, -COOH, -SH, -N=N, -N=O and NX_1X_2 , wherein one or more of the hydrogen atoms of the indole ring can be replaced by Y;
- 10 R_2 is selected from the group consisting of hydrogen, C_{1-20} alkyl, C_{2-20} alkenyl, C_{2-20} alkynyl, C_{1-20} acyl, C_{3-8} cycloalkyl, C_{3-8} cycloalkenyl, aryl, heteroaryl and heteroalicycyl;
- R_3 is $(CH_2)_nCONX_1X_2$, n being an integer from 1 to 4; R_4 is hydrogen or C_1-C_4 alkyl;
- wherein
- X_1 and X_2 together with the nitrogen atom bearing them, form a 3-8 membered ring, wherein
- 15 the 3-8 membered ring can be fused to at least one 3-8 membered ring, wherein the ring can optionally comprise 0, 1, 2, 3 or 4 further heteroatoms selected from the group consisting of oxygen, nitrogen, sulphur and phosphorus; and wherein the ring can be substituted by at least one substituent selected from the group consisting of hydrogen, hydroxyl, C_{1-20} alkyl, C_{2-20} alkenyl, C_{2-20} alkynyl, C_{1-20} acyl, C_{3-8} cycloalkyl, C_{3-8} cycloalkenyl, aryl, heteroaryl, heteroalicycyl, halogen, carbonyl, thiocarbonyl, O-carbamyl, O-thiocarbonyl, O-carboxy,
- 20 $N=N$, $N=O$ and NX_1X_2 .

[0019] In an eighth aspect, the invention provides a compound of Formula IX



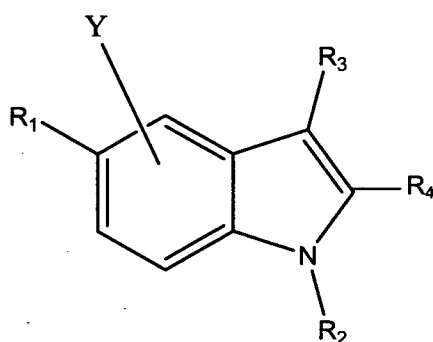
(IX)

or a pharmaceutically acceptable salt thereof,

wherein

- 5 R_1 and Y are independently selected from the group consisting of hydrogen, hydroxyl, C_{1-20} alkyl, C_{2-20} alkenyl, C_{2-20} alkynyl, C_{1-20} acyl, C_{3-8} cycloalkyl, C_{3-8} cycloalkenyl, aryl, heteroaryl, heteroalicycyl, halogen, carbonyl, thiocarbonyl, O-carbamyl, O-thiocarbonyl, O-carboxy, isocyanato, thiocyanato, silyl, sulfonamide, thio, -CN, -COOH, -SH, -N=N, -N=O and NX_1X_2 , wherein one or more of the hydrogen atoms of the indole ring can be replaced by Y;
- 10 R_2 is selected from the group consisting of hydrogen, C_{1-20} alkyl, C_{2-20} alkenyl, C_{2-20} alkynyl, C_{1-20} acyl, C_{3-8} cycloalkyl, C_{3-8} cycloalkenyl, aryl, heteroaryl and heteroalicycyl; and R_3 is $-(CH_2)_2CONH_2$ or $CH_2NH_2SO_2CH_3$; R_4 is hydrogen or C_1-C_4 alkyl.

[0020] In a ninth aspect, the invention provides a compound of Formula X



(X)

or a pharmaceutically acceptable salt thereof,

wherein

- 20 R_1 and Y are independently selected from the group consisting of hydrogen, hydroxyl, C_{1-20} alkyl, C_{2-20} alkenyl, C_{2-20} alkynyl, C_{1-20} acyl, C_{3-8} cycloalkyl, C_{3-8} cycloalkenyl, aryl, heteroaryl, heteroalicycyl, halogen, carbonyl, thiocarbonyl, O-carbamyl, O-thiocarbonyl, O-carboxy,

isocyanato, thiocyanato, silyl, sulfonamide, thio, -CN, -COOH, -SH, -N=N, -N=O and NX_1X_2 , wherein one or more of the hydrogen atoms of the indole ring can be replaced by Y;

R_2 is selected from the group consisting of hydrogen, C_{1-20} alkyl, C_{2-20} alkenyl, C_{2-20} alkynyl, C_{1-20} acyl, C_{3-8} cycloalkyl, C_{3-8} cycloalkenyl, aryl, heteroaryl and heteroalicycyl; and

- 5 R_3 is $(CH_2)_nCONX_1X_2$, n being an integer from 1 to 4; R_4 is hydrogen or C_1-C_4 alkyl; wherein X_1 is hydrogen and X_2 is one selected from the group consisting of C_{1-20} alkyl, C_{2-20} alkenyl, C_{2-20} alkynyl, C_{1-20} acyl, C_{3-8} cycloalkyl, C_{3-8} cycloalkenyl, aryl, heteroaryl, and heteroalicycyl.

BRIEF DESCRIPTION OF THE DRAWINGS

10 [0021] The invention will be better understood with reference to the detailed description when considered in conjunction with the non-limiting examples and the accompanying drawings.

[0022] Figure 1 shows Table 1 listing the compounds of Series 1 and their IC_{50} values for Icmt inhibition and cell viability, in which the R_1 substituent is modified.

15 [0023] Figure 2 shows Table 2 listing the compounds of Series 2 and their IC_{50} values for Icmt inhibition and cell viability, in which the R_2 substituent is modified.

[0024] Figure 3 shows Table 3 listing the compounds of Series 3 and their IC_{50} values for Icmt inhibition and cell viability, in which the R_3 substituent is replaced by a tertiary amide side chain.

20 [0025] Figure 4 shows Table 4 listing the compounds of Series 4 and their IC_{50} values for Icmt inhibition and cell viability, in which the R_3 substituent is replaced by a substituent other than tertiary amides.

[0026] Figure 5 shows Table 5 listing the compounds of Series 5 and their IC_{50} values for Icmt inhibition and cell viability, in which the R_1 substituent is replaced by an amine side chain.

25 [0027] Figure 6 shows Table 6 listing the compounds of Series 6 and their IC_{50} values for Icmt inhibition and cell viability, in which the R_3 substituent is replaced with an amine side chain along with a modification of the R_2 substituent.

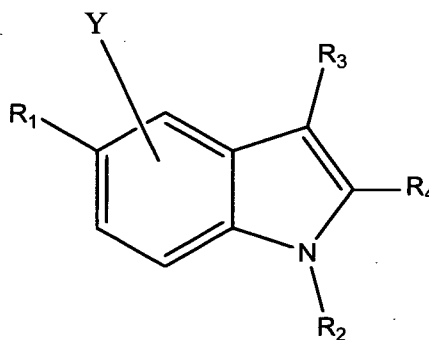
[0028] Figure 7 depicts the Icmt inhibition activity of cysmethynil (cys), compound J17G (taken from Table 5); compound J38G (taken from Table 6); and compound J3 (taken from Table 4).

30 [0029] Figure 8 depicts the anti-proliferative activity of cysmethynil (cys), compound J17G (taken from Table 5); compound J38G (taken from Table 6); and compound J3 (taken from Table 4).

[0030] Figure 9 shows the binding capacities (%) of cysmethynil ($\diamond$), compounds (J17G) 4-3 (Δ) and (J38G) 6-4 ($\square$) to fetal bovine serum (FBS) using 4 different concentrations (1, 4, 10 and 25 μ M) of each respective compound.

DETAILED DESCRIPTION OF THE INVENTION

[0031] The present invention is based on the finding that the compounds of the present invention described herein can retain or improve on biological profiles as compared to cysmethynil, while maintaining a more favourable drug-like profile, in terms of lower lipophilicities for example. In general, the compounds described herein have enhanced IC_{50} inhibition activity and more potent anti-proliferative activities in cancer cells for example. Such anti-proliferative effect can be seen in breast cancer cells for example, as shown in Example 7, Figures 1 and 2. Accordingly, the present invention provides a compound of Formula I or a pharmaceutically acceptable salt thereof:



(I)

[0032] In the compound of Formula I, R_1 and Y are independently selected from the group consisting of hydrogen, hydroxyl, C_{1-20} alkyl, C_{2-20} alkenyl, C_{2-20} alkynyl, C_{1-20} acyl, C_{3-8} cycloalkyl, C_{3-8} cycloalkenyl, aryl, heteroaryl, heteroalicyclic, halogen, carbonyl, thiocarbonyl, O-carbamyl, O-thiocarbonyl, O-carboxy, isocyanato, thiocyanato, silyl, sulfonamide, thio, -CN, -COOH, -SH, -N=N-, -N=O and NX_1X_2 , wherein X_1 and X_2 are defined in the R_3 substituent described herein. In this formula, one or more of the hydrogen atoms of the indole ring can be replaced by Y. In some embodiments, R_1 can be halogen which may be one of fluorine, chlorine, iodine or bromine. In other embodiments, R_1 can be $(CH_3)_m$ -aryl and m is an integer of 0, 1, 2, 3 or 4. In this context, the term "aryl" refers to an aromatic ring wherein each of the atoms forming the ring is a carbon atom. Aryl rings may be formed by five, six, seven, eight, nine, or more than nine carbon atoms. In some embodiments, aryl groups may be optionally substituted. Examples of aryl groups include, but are not limited to phenyl and naphthyl. The

methyl (CH_3) substituent may be attached to any one of the main chain atoms of the aryl ring. As an illustrative example, when R_1 is a $-\text{CH}_3-\text{C}_6\text{H}_5$, the $-\text{CH}_3$ substituent can be attached to any of the carbon atoms of the phenyl ring. In some embodiments, R_1 may be 2'- $\text{CH}_3-\text{C}_6\text{H}_5$, 3'- $\text{CH}_3-\text{C}_6\text{H}_5$ or 4'- $\text{CH}_3-\text{C}_6\text{H}_5$.

5 **[0033]** In the compound of the present invention, R_2 can typically be an aliphatic chain having a main chain length of about 1 to about 10, to about 8, to about 5 or to about 3 carbon atoms. In this context, the term "aliphatic", alone or in combination, refers to a straight chain or branched chain hydrocarbon comprising at least one carbon atom, which may be saturated or mono- or poly-unsaturated and include heteroatoms. An unsaturated aliphatic group contains
10 one or more double and/or triple bonds (alkenyl or alkynyl moieties). The branches of the hydrocarbon chain may include linear chains as well as non-aromatic cyclic elements. The hydrocarbon chain, which may, unless otherwise stated, be of any length, and contain any number of branches. Typically, the hydrocarbon (main) chain includes 1 to about 5, to about 8, to about 10 or to about 15 carbon atoms.

15 **[0034]** In some embodiments, R_2 can include, but are not limited to hydrogen, C_{1-20} alkyl, C_{1-15} alkyl, C_{1-10} alkyl, C_{1-8} alkyl, C_{1-6} alkyl, C_{2-20} alkenyl, C_{2-10} alkenyl, C_{2-8} alkenyl, C_{2-20} alkynyl, C_{2-10} alkynyl, C_{2-8} alkynyl, C_{1-20} acyl, C_{1-10} acyl, C_{1-8} acyl, C_{1-6} acyl, C_{3-8} cycloalkyl, C_{3-8} cycloalkenyl, aryl, heteroaryl or heteroalicycyl. In other embodiments, R_2 can be C_{1-8} alkyl or C_{2-8} alkenyl. As an illustrative example, R_2 can include, but are not limited to methyl, ethyl, n-
20 propyl, propyl, isopropyl, butyl, n-butyl, isobutyl, sec-butyl, tert-butyl, tert-amyl, pentyl, hexyl, heptyl, octyl, vinyl, 1-propenyl, allyl, 1-butenyl, 3-butenyl, isoprenyl, 1-pentenyl, 3-pentenyl, 4-pentenyl, dimethylallyl, 1-hexenyl, 3-hexenyl, 5-hexenyl, 1-heptenyl, 3-heptenyl, 6-heptenyl and 7-octenyl. In certain embodiments, R_2 can be octyl or isoprenyl.

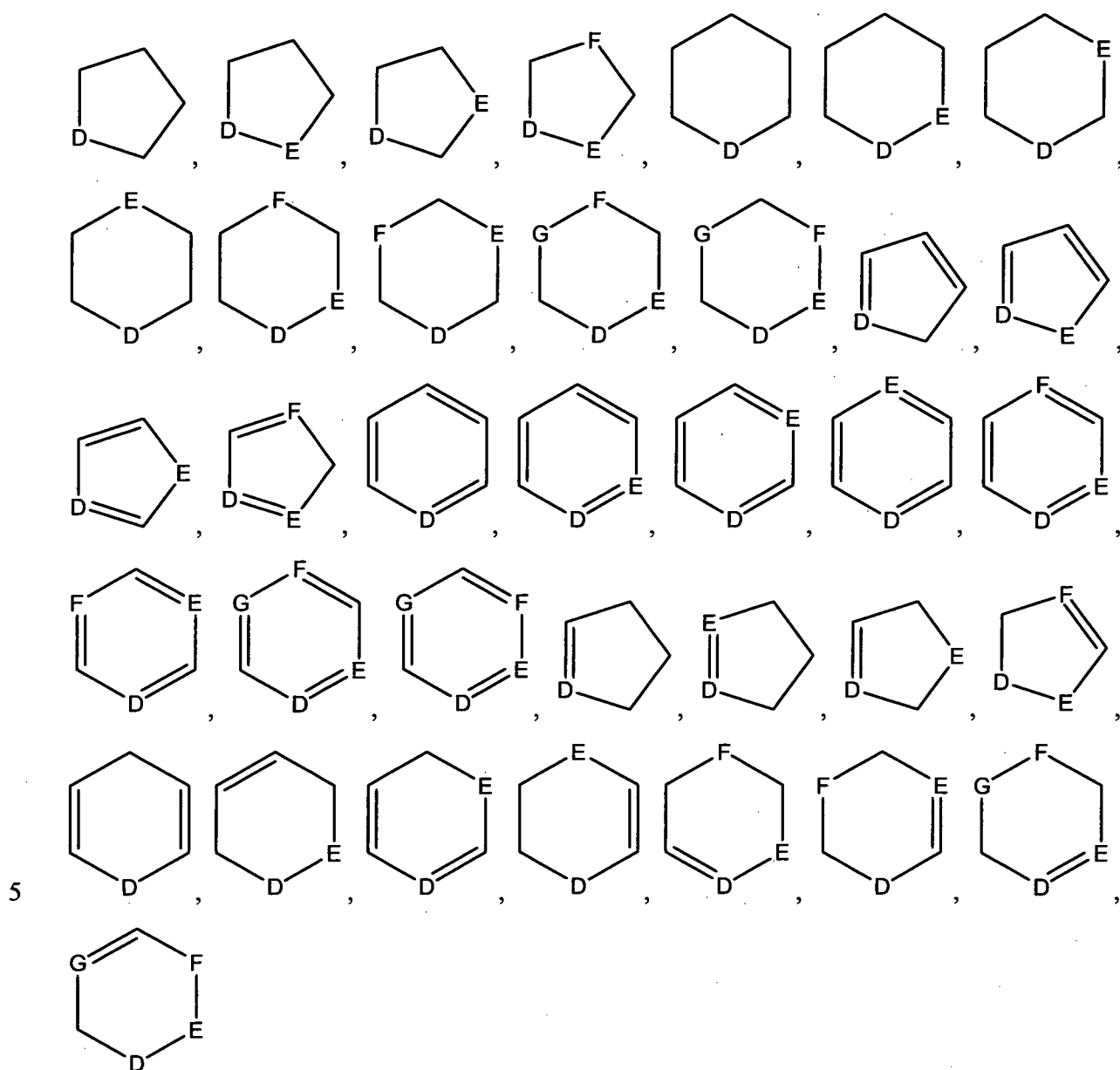
25 **[0035]** In some embodiments, R_3 has the formula of $(\text{CH}_2)_n\text{NX}_1\text{X}_2$ n being an integer of 1, 2, 3 or 4. In this formula of $(\text{CH}_2)_n\text{NX}_1\text{X}_2$, X_1 and X_2 can be the same substituent or can be different substituents. In certain embodiments, X_1 and X_2 can be independently selected from the group consisting of hydrogen, C_{1-20} alkyl, C_{1-15} alkyl, C_{1-10} alkyl, C_{1-8} alkyl, C_{1-6} alkyl, C_{2-20} alkenyl, C_{2-10} alkenyl, C_{2-8} alkenyl, C_{2-20} alkynyl, C_{2-10} alkynyl, C_{2-8} alkynyl, C_{1-20} acyl, C_{1-10} acyl, C_{1-8} acyl, C_{1-6} acyl, C_{3-8} cycloalkyl, C_{3-8} cycloalkenyl, aryl, heteroaryl, and heteroalicycyl.
30 In other embodiments, X_1 or X_2 may, together with the nitrogen atom bearing them, form a 3-8 membered ring or a 5-6 membered ring. The 3-8 or 5-6 membered ring can be a saturated ring. The 3-8 or 5-6 membered ring can be fused to at least one other respective 3-8 or 5-6 membered

ring. The ring can also comprise 0, 1, 2, 3 or 4 further heteroatoms selected from the group consisting of oxygen, nitrogen, sulphur and phosphorus. The ring can be substituted by at least one substituent selected from the group consisting of hydrogen, hydroxyl, C₁₋₂₀alkyl, C₂₋₂₀alkenyl, C₂₋₂₀alkynyl, C₁₋₂₀acyl, C₃₋₈cycloalkyl, C₃₋₈cycloalkenyl, aryl, heteroaryl, heteroalicycyl, halogen, carbonyl, thiocarbonyl, O-carbamyl, O-thiocarbonyl, O-carboxy, isocyanato, thiocyanato, silyl, sulfonamide, thio, -CN, -COOH, -SH, -N=N, -N=O and NX₁X₂. The X₁ and X₂ substituents are defined in the compound of formula I.

[0036] In some embodiments, R₄ can be a hydrogen or C₁-C₄ alkyl, for example methyl, ethyl, propyl, isopropyl, butyl, not to mention a few.

[0037] The term "ring" as described herein refers to any covalently closed structure. Rings may include, for example, heterocycles (e.g. heteroaryls and non-aromatic heterocycles), aromatics (e.g. aryls and heteroaryls), and non-aromatics (e.g. non-aromatic heterocycles). Rings may be optionally substituted or rings may be fused to at least one ring to form part of a ring system. The term "ring system" refers to two or more rings, wherein two or more of the rings are fused. The term "fused" refers to structures which two or more rings share one or more bonds.

[0038] The term "heterocycle" refers to a group comprising a covalently closed ring wherein at least one atom forming the ring is a carbon atom and at least one atom forming the ring is a heteroatom. Heterocyclic rings may be formed by three, four, five, six, seven, eight, nine, or more than nine atoms. Any number of those atoms may be heteroatoms (i.e., a heterocyclic ring may comprise one, two, three, four, five, six, seven, eight, nine, or more than nine heteroatoms). As an illustrative example, whenever the number of carbon atoms in a heterocycle is indicated (e.g., C₁-C₆ heterocycle), at least one other atom (the heteroatom) must be present in the ring. Designations such as "C₁-C₆ heterocycle" refer only to the number of carbon atoms in the ring and do not refer to the total number of atoms in the ring. It is understood that the heterocyclic ring will have additional heteroatoms in the ring. In heterocycles comprising two or more heteroatoms, those two or more heteroatoms may be the same or different from one another. Heterocycles may be optionally substituted. Binding to a heterocycle can be at a heteroatom or via a carbon atom. Examples of heterocycles include, but are not limited to the following:



wherein D, E, F, and G independently represents a heteroatom. Each of D, E, F, and G may be the same or different from one another.

- 10 [0039] The term "heteroatom" refers to an atom other than carbon or hydrogen. Heteroatoms are typically independently selected from oxygen, sulfur, nitrogen, and phosphorus, but are not limited to those atoms. In embodiments in which two or more heteroatoms are present, the two or more heteroatoms may all be the same as one another, or some or all of the two or more heteroatoms may each be different from the others.

[0040] The term "aromatic" refers to a group comprising a covalently closed planar ring having a delocalized [pi]-electron system comprising $4n+2$ [pi] electrons, where n is an integer. Aromatic rings may be formed by five, six, seven, eight, nine, or more than nine atoms. Aromatics may be optionally substituted. Examples of aromatic groups include, but are not limited to phenyl, naphthalenyl, phenanthrenyl, anthracenyl, tetralinyl, fluorenyl, indenyl, and indanyl. The term aromatic includes, for example, benzenoid groups, connected via one of the ring-forming carbon, atoms, and optionally carrying one or more substituents selected from an aryl, a heteroaryl, a cycloalkyl, a non-aromatic heterocycle, a halo, a hydroxy, an amino, a cyano, a nitro, an alkylamido, an acyl, a C_1 - C_6 alkoxy, a C_1 - C_6 alkyl, a C_1 - C_6 aminoalkyl, alkylamino, an alkylsulfenyl, an alkylsulfinyl, an alkylsulfonyl, a sulfamoyl, or a trifluoromethyl. In certain embodiments, an aromatic group is substituted at one or more of the para, meta, and/or ortho positions. Examples of aromatic groups comprising substitutions include, but are not limited to, phenyl, 3-halophenyl, 4-halophenyl, 3-hydroxyphenyl, 4-hydroxyphenyl, 3-aminophenyl, 4-aminophenyl, 3-methylphenyl, 4-methylphenyl, 3-methoxyphenyl, 4-methoxyphenyl, 4-trifluoromethoxyphenyl, 3-cyanophenyl, 4-cyanophenyl, dimethylphenyl, naphthyl, hydroxynaphthyl, hydroxymethylphenyl, (trifluoromethyl)phenyl, alkoxyphenyl, 4-morpholin-4-ylphenyl, 4-pyrrolidin-1-ylphenyl, 4-pyrazolylphenyl, 4-triazolylphenyl, and 4-(2-oxopyrrolidin-1-yl)phenyl.

[0041] The term "heteroaryl" refers to an aromatic heterocycle. Heteroaryl rings may be formed by three, four, five, six, seven, eight, nine, or more than nine atoms. Heteroaryls may be optionally substituted. Examples of heteroaryl groups include, but are not limited to, aromatic C_{3-8} heterocyclic groups comprising one oxygen or sulfur atom or up to four nitrogen atoms, or a combination of one oxygen or sulfur atom and up to two nitrogen atoms, and their substituted as well as benzo- and pyrido-fused derivatives, for example, connected via one of the ring-forming carbon atoms. In certain embodiments, heteroaryl groups are optionally substituted with one or more substituents, independently selected from halo, hydroxy, amino, cyano, nitro, alkylamido, acyl, C_1 - C_6 alkoxy, C_1 - C_6 alkyl, C_1 - C_6 hydroxyalkyl, C_1 - C_6 aminoalkyl, alkylamino, alkylsulfenyl, alkylsulfinyl, alkylsulfonyl, sulfamoyl, or trifluoromethyl. Examples of heteroaryl groups include, but are not limited to, unsubstituted and mono- or di-substituted derivatives of furan, benzofuran, thiophene, benzothiophene, pyrrole, pyridine, indole, oxazole, benzoxazole, isoxazole, benzisoxazole, thiazole, benzothiazole, isothiazole, imidazole, benzimidazole, pyrazole, indazole, tetrazole, quinoline, isoquinoline, pyridazine, pyrimidine,

purine and pyrazine, furazan, 1,2,3-oxadiazole, 1,2,3-thiadiazole, 1,2,4-thiadiazole, triazole, benzotriazole, phenoxazole, oxadiazole, benzopyrazole, quinolizine, cinnoline, phthalazine, quinazoline, and quinoxaline. In some embodiments, the substituents are halo, hydroxy, cyano, O- C₁₋₆ -alkyl, C₁₋₆-alkyl, hydroxy- C₁₋₆ -alkyl, and amino- C₁₋₆ -alkyl.

5 **[0042]** The term "non-aromatic ring" refers to a group comprising a covalently closed ring that is not aromatic.

10 **[0043]** The term "alkyl", alone or in combination, refers to a fully saturated aliphatic hydrocarbon. In certain embodiments, alkyls are optionally substituted. When substituted, the substituent group(s) is(are) one or more group(s) independently selected from cycloalkyl, aryl, heteroaryl, heteroalicycyl, hydroxyl, protected hydroxyl, alkoxy, aryloxy, mercapto, alkylthio, arylthio, cyano, halogen, carbonyl, thiocarbonyl, O-carbamyl, O-thiocarbonyl, O-carboxy, isocyanato, thiocyanato, silyl, trihalomethanesulfonyl, and amino. In certain embodiments, an alkyl comprises 1 to 30 carbon atoms, for example 1 to 20 carbon atoms, 1 to 15 carbon atoms, 1 to 10 carbon atoms, or 1 to 5 carbon atoms, wherein a numerical range, such as "1 to 20" or
15 "C₁-C₂₀", refers to each integer in the given range, e.g. "C₁-C₂₀ alkyl" means that an alkyl group comprising only 1 carbon atom, 2 carbon atoms, 3 carbon atoms, etc., up to and including 20 carbon atoms. Examples of alkyl groups include, but are not limited to, methyl, ethyl, n-propyl, propyl, isopropyl, butyl, n-butyl, isobutyl, sec-butyl, tert-butyl, tert-amyl, pentyl, hexyl, heptyl, octyl and the like.

20 **[0044]** The term "alkoxy", alone or in combination, refers to an aliphatic hydrocarbon having an alkyl-O- moiety. In certain embodiments, alkoxy groups are optionally substituted. When substituted, the substituent(s) may be selected from the same group disclosed above with regard to alkyl group substitution. Examples of alkoxy groups include, but are not limited to, methoxy, ethoxy, propoxy, butoxy and the like.

25 **[0045]** The term "alkenyl" or "alkene" as used herein refers to an alkyl group that contains in the straight or branched hydrocarbon chain one or more double bonds. In certain embodiments, an alkenyl comprises 2 to 30 carbon atoms, for example 2 to 20 carbon atoms, 2 to 15 carbon atoms, 2 to 10 carbon atoms, or 2 to 5 carbon atoms, wherein a numerical range, such as "2 to 20" or "C₂-C₂₀", refers to each integer in the given range, e.g. "C₂-C₂₀ alkenyl"
30 means that an alkenyl group comprising 2 carbon atoms, 3 carbon atoms, etc., up to and including 20 carbon atoms. An alkenyl or alkene group of this invention may be substituted or unsubstituted. When substituted, the substituent(s) may be selected from the same group

disclosed above with regard to alkyl group substitution. Examples of such groups include, but are not limited to, ethenyl, propenyl, butenyl, 1,4-butadienyl, pentenyl, hexenyl, 4-methylhex-1-enyl, 4-ethyl-2-methylhex-1-enyl and the like.

[0046] The term “alkynyl” or “alkyne” as used herein refers to an alkyl group that contains in the straight or branched hydrocarbon chain one or more triple bonds. In certain embodiments, an alkynyl comprises 2 to 30 carbon atoms, for example 2 to 20 carbon atoms, 2 to 15 carbon atoms, 2 to 10 carbon atoms, or 2 to 5 carbon atoms, wherein a numerical range, such as “2 to 20” or “C₂-C₂₀”, refers to each integer in the given range, e.g. “C₂-C₂₀ alkynyl” means that an alkynyl group comprising 2 carbon atoms, 3 carbon atoms, etc., up to and including 20 carbon atoms. An alkynyl group of this invention may be substituted or unsubstituted. When substituted, the substituent(s) may be selected from the same group disclosed above with regard to alkyl group substitution. Examples of alkyne groups include, but are not limited to, ethynyl, propynyl, butynyl, and the like.

[0047] The term “acyl” as used herein is a group -RC(=O), an acyl group of this invention may be substituted or unsubstituted. In certain embodiments, an acyl comprises 1 to 30 carbon atoms, for example 1 to 20 carbon atoms, 1 to 15 carbon atoms, 1 to 10 carbon atoms, or 1 to 5 carbon atoms, wherein a numerical range, such as “1 to 20” or “C₁-C₂₀”, refers to each integer in the given range, e.g. “C₁-C₂₀ acyl” means that an acyl group comprising 2 carbon atoms, 3 carbon atoms, etc., up to and including 20 carbon atoms. When substituted, the substituent(s) may be selected from the same group disclosed above with regard to alkyl group substitution. Examples of acyl groups include, but are not limited to formyl, acetyl, propanoyl, 2-methylpropanoyl, butanoyl and the like.

[0048] As used herein, “cycloalkyl” refers to a completely saturated hydrocarbon ring. Cycloalkyl groups of this invention may range from C₃ to C₈. A cycloalkyl group of this invention may be substituted or unsubstituted. When substituted, the substituent(s) may be selected from the same group disclosed above with regard to alkyl group substitution. Examples of cycloalkyl groups include, but are not limited to cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and the like.

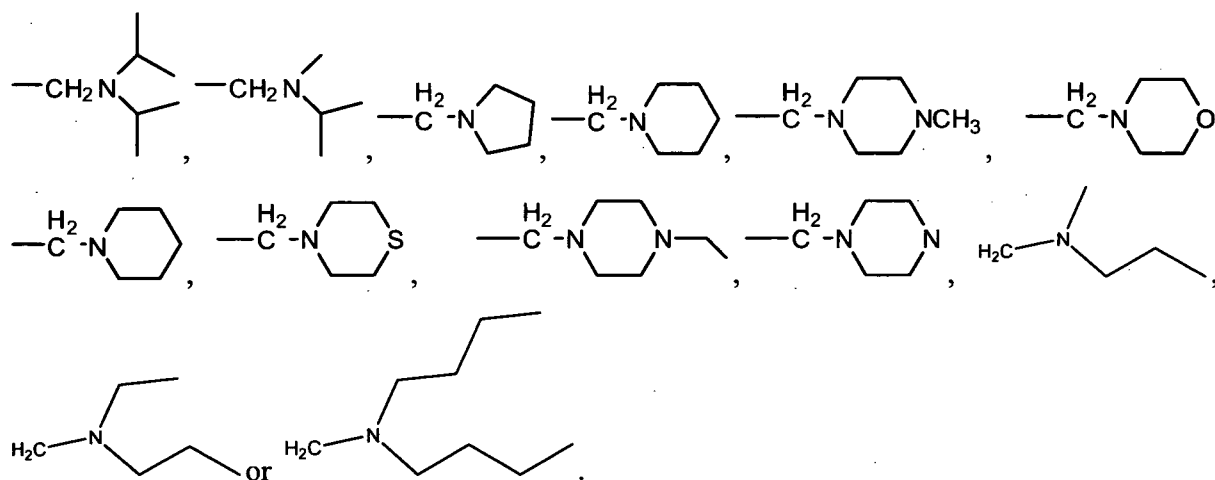
[0049] The term “cycloalkenyl” as used herein refers to a cycloalkyl group that contains one or more double bonds in the ring although, if there is more than one, they cannot form a fully delocalized pi-electron system in the ring (otherwise the group would be “aryl” as defined herein). Cycloalkyl groups of this invention may range from C₃ to C₈. A cycloalkenyl group of

this invention may be substituted or unsubstituted. When substituted, the substituent(s) may be selected from the same group disclosed above with regard to alkyl group substitution. Examples of cycloalkenyl groups include, but are not limited to cyclohexenyl, cyclohepta-1,3-dienyl, cyclopropenyl, cyclobutenyl, cyclopentenyl, cyclohexenyl, cycloheptenyl and the like.

5 **[0050]** As used herein, the term “heteroalicycyl” refers to a ring or one or more fused rings having in the ring system one or more heteroatoms. The rings may also contain one or more double bonds provided that they do not form a fully delocalized pi-electron system in the rings. Heteroalicycyl groups of this invention may be unsubstituted or substituted. When substituted, the substituent(s) may be one or more groups independently selected from the group consisting of halogen, hydroxyl, protected hydroxyl, cyano, nitro, alkyl, alkoxy, acyl, 10 acyloxy, carboxy, amino and carboxamide.

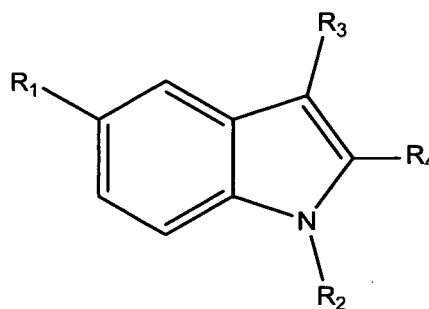
[0051] The term "optionally substituted" refers to a group in which none, one, or more than one of the hydrogen atoms has been replaced with one or more group(s) are independently selected from: alkyl, heteroalkyl, haloalkyl, heterohaloalkyl, cycloalkyl, aryl, arylalkyl, heteroaryl, non-aromatic heterocycle, hydroxy, alkoxy, aryloxy, mercapto, alkylthio, arylthio, cyano, halo, carbonyl, thiocarbonyl, O-carbamyl, N-carbamyl, O-thiocarbamyl, N-thiocarbamyl, C-amido, N-amido, S-sulfonamido, N-sulfonamido, C-carboxy, O-carboxy, isocyanato, thiocyanato, isothiocyanato, nitro, silyl, trihalomethanesulfonyl, and amino, including mono- and di-substituted amino groups.

20 **[0052]** In some embodiments, R₃ can be CH₂NH₂, CH₂N(CH₃)₂, CH₂N(C₂H₅)₂,
CH₂N(C₃H₇)₂,



[0053] The inventors have shown that modifications at the R_3 substituent or concurrently at both the R_3 and R_2 substituents as depicted in Formula I for example, resulted in a surprising effect on the biological activities of the compounds described herein. As an illustrative example (see for example Figures 5 to 8), a conversion from an amide side chain to a basic amine side chain at the R_3 position of Formula I can results in compounds that are up to about three times as potent as cysmethynil as Icmt inhibitors and/or at least about eight times more potent as anti-proliferative agents. In another illustrative example, when the R_3 substituent is replaced with an amine side chain followed by a concurrent replacement of the R_2 substituent with a shorter and less lipophilic side chain such as isoprenyl for example, up to a 10-fold increase in anti-proliferative activity is seen although the Icmt inhibitory activity is retained (Series 6, Table 6).

[0054] In certain embodiments, the compound of the invention can be a compound of formula Ia



(Ia)

or a pharmaceutically acceptable salt thereof. In this compound, R_1 is a halogen or $(CH_3)_m$ -aryl, m being an integer between 0 to 4. R_2 is C_{1-10} alkyl or C_{2-10} alkenyl; R_3 is $(CH_2)_nNX_1X_2$, n being an integer from 1 to 4; R_4 is a hydrogen or C_1-C_4 alkyl; X_1 and X_2 are independently C_1-C_{10} alkyl; or X_1 or X_2 may, together with the nitrogen bearing them, form a 5-6 membered ring, wherein the 5-6 membered ring can be fused to at least one 5-6 membered ring, wherein the ring can optionally comprise 0, 1, 3 or 4 further heteroatoms selected from the group consisting of oxygen, nitrogen, sulphur, and phosphorus; and wherein the ring can be substituted by at least one substituent selected from the group consisting of halogen, hydroxyl, oxo, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 acyl, C_{3-8} cycloalkyl, and C_{3-8} cycloalkenyl.

[0055] In some embodiments, compounds of the present invention may include any of the following:

1-octyl-5-m-tolyl-1H-indol-3-yl) methanamine (J18);

N,N-dimethyl(1-octyl-5-m-tolyl-1H-indol-3-yl) methanamine (J25G);

- N-ethyl-N-((1-octyl-5-*m*-tolyl-1*H*-indol-3-yl) methyl) ethanamine (J17G);
 N-((1-octyl-5-*m*-tolyl-1*H*-indol-3-yl) methyl)-N-propylpropan-1-amine (J27G);
 N-isopropyl-N-((1-octyl-5-*m*-tolyl-1*H*-indol-3-yl) methyl) propan-2-amine (J26G);
 N-methyl-N-((1-octyl-5-*m*-tolyl-1*H*-indol-3-yl) methyl) propan-2-amine (J29G);
 5 1-octyl-3-(pyrrolidin-1-ylmethyl)-5-*m*-tolyl-1*H*-indole (J31G);
 1-octyl-3-(piperidin-1-ylmethyl)-5-*m*-tolyl-1*H*-indole (J32G);
 3-((4-methylpiperazin-1-yl) methyl)-1-octyl-5-*m*-tolyl-1*H*-indole (J30G);
 3-(morpholinomethyl)-1-octyl-5-*m*-tolyl-1*H*-indole (J34G);
 N-ethyl-N-((1-octyl-5-*o*-tolyl-1*H*-indol-3-yl) methyl) ethanamine (J36G);
 10 N-ethyl-N-((1-octyl-5-*p*-tolyl-1*H*-indol-3-yl) methyl) ethanamine (J37G);
 N-ethyl-N-((5-fluoro-1-octyl-1*H*-indol-3-yl) methyl) ethanamine (J40G);
 N-ethyl-N-((1-(3-methylbut-2-enyl)-5-*m*-tolyl-1*H*-indol-3-yl) methyl) ethanamine (J38G);
 1-(3-methylbut-2-enyl)-3-(piperidin-1-ylmethyl)-5-*m*-tolyl-1*H*-indole (J39G);
 N-ethyl-N-((1-(3-methylbut-2-enyl)-1*H*-indol-3-yl) methyl) ethanamine (J35G);
 15 1-(5-fluoro-1-octyl-1*H*-indol-3-yl)-*N,N*-dimethylmethanamine;
 5-fluoro-1-octyl-3-(piperidin-1-ylmethyl)-1*H*-indole;
 4-((5-fluoro-1-octyl-1*H*-indol-3-yl)methyl)thiomorpholine;
 4-((5-fluoro-1-octyl-1*H*-indol-3-yl)methyl)morpholine;
 5-fluoro-1-octyl-3-(pyrrolidin-1-ylmethyl)-1*H*-indole;
 20 5-fluoro-3-((4-methylpiperazin-1-yl)methyl)-1-octyl-1*H*-indole; and
 4-((1-(3-methylbut-2-enyl)-5-*m*-tolyl-1*H*-indol-3-yl)methyl)morpholine.

[0056] In other embodiments, the compounds of the present invention can also include

- 2-(5-Fluoro-1-octyl-1*H*-indol-3-yl)acetamide (1-8);
 2-(5-Fluoro-1-(3-methylbut-2-enyl)-1*H*-indol-3-yl)acetamide (6-8);
 25 1-(4-Methylpiperazin-1-yl)-2-(1-octyl-5-*m*-tolyl-1*H*-indol-3-yl)ethanone (3-6);
N-Methyl-2-(1-octyl-5-*m*-tolyl-1*H*-indol-3-yl)acetamide (3-7);
 1-Octyl-5-*m*-tolyl-1*H*-indole-3-carboxamide (5-1);
 3-(1-Octyl-5-*m*-tolyl-1*H*-indol-3-yl)propanamide (5-2);
 1-(3-Methylbut-2-enyl)-5-*m*-tolyl-1*H*-indole (6-3);
 30 4-((1-(3-methylbut-2-enyl)-5-*m*-tolyl-1*H*-indol-3-yl)methyl)morpholine (6-6)
N-((5-fluoro-1-octyl-1*H*-indol-3-yl)methyl)-*N*-methylpropan-1-amine (6-9(7));
N-ethyl-*N*-((5-fluoro-1-octyl-1*H*-indol-3-yl)methyl)propan-1-amine (6-9 (8));

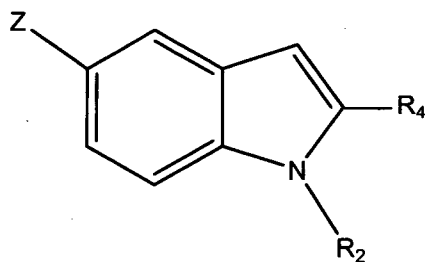
- N*-butyl-*N*-((5-fluoro-1-octyl-1*H*-indol-3-yl)methyl)butan-1-amine (6-9-(9));
- (*E*)-1-(1-(3,7-dimethylocta-2,6-dienyl)-5-fluoro-1*H*-indol-3-yl)-*N,N*-dimethylmethanamine (6-13a);
- (*E*)-*N*-((1-(3,7-dimethylocta-2,6-dienyl)-5-fluoro-1*H*-indol-3-yl)methyl)-*N*-ethylethanamine (6-13b);
- (*E*)-1-(3,7-dimethylocta-2,6-dienyl)-5-fluoro-3-(piperidin-1-ylmethyl)-1*H*-indole (6-13c);
- (*E*)-4-((1-(3,7-dimethylocta-2,6-dienyl)-5-fluoro-1*H*-indol-3-yl)methyl) thiomorpholine (6-13d);
- (*E*)-4-((1-(3,7-dimethylocta-2,6-dienyl)-5-fluoro-1*H*-indol-3-yl)methyl)morpholine (6-13e);
- (*E*)-1-(3,7-dimethylocta-2,6-dienyl)-5-fluoro-3-(pyrrolidin-1-ylmethyl)-1*H*-indole (6-13f);
- (*E*)-1-(3,7-dimethylocta-2,6-dienyl)-5-fluoro-3-((4-methylpiperazin-1-yl)methyl)-1*H*-indole (6-13g);
- (*E*)-*N*-((1-(3,7-dimethylocta-2,6-dienyl)-5-fluoro-1*H*-indol-3-yl)methyl)-*N*-methylpropan-1-amine (6-13h);
- N*-ethyl-*N*-((5-fluoro-1-octyl-1*H*-indol-3-yl)methyl)propan-1-amine (6-13i);
- (*E*)-*N*-butyl-*N*-((1-(3,7-dimethylocta-2,6-dienyl)-5-fluoro-1*H*-indol-3-yl)methyl)butan-1-amine (6-13j);
- (*E*)-1-(3,7-dimethylocta-2,6-dienyl)-3-((4-ethylpiperazin-1-yl)methyl)-5-fluoro-1*H*-indole (6-13k);
- N,N*-dimethyl-1-(1-(3-methylbut-2-enyl)-5-*m*-tolyl-1*H*-indol-3-yl)methanamine (6-14);
- 4-((1-(3-methylbut-2-enyl)-5-*m*-tolyl-1*H*-indol-3-yl)methyl)thiomorpholine (6-15);
- 1-(3-methylbut-2-enyl)-3-(pyrrolidin-1-ylmethyl)-5-*m*-tolyl-1*H*-indole (6-16);
- 1-(3-methylbut-2-enyl)-3-((4-methylpiperazin-1-yl)methyl)-5-*m*-tolyl-1*H*-indole (6-17);
- N*-methyl-*N*-((1-(3-methylbut-2-enyl)-5-*m*-tolyl-1*H*-indol-3-yl)methyl)propan-1-amine (6-18);
- N*-ethyl-*N*-((1-(3-methylbut-2-enyl)-5-*m*-tolyl-1*H*-indol-3-yl)methyl)propan-1-amine (6-19);
- N*-butyl-*N*-((1-(3-methylbut-2-enyl)-5-*m*-tolyl-1*H*-indol-3-yl)methyl)butan-1-amine (6-20); and
- N*-((1-(3-methylbut-2-enyl)-5-*m*-tolyl-1*H*-indol-3-yl)methyl)-*N*-propylpropan-1-amine (6-21).

[0057] The present invention also encompass the corresponding physiologically or toxicologically acceptable salts, in particular the pharmaceutically acceptable salts. Thus, compounds of the present invention which may contain one or more basic, that is protonatable, groups may be in the form of their acid addition salts with physiologically acceptable inorganic or organic salts and used according to the invention, for examples salts with hydrochloric acid,

hydrobromic acid, phosphoric acid, sulfuric acid, nitric acid, methanesulfonic acid, p-toluenesulfonic acid, naphthalenedisulfonic acid, oxalic acid, acetic acid, tartaric acid, lactic acid, salicylic acid, benzoic acid, formic acid, propionic acid, pivalic acid, diethylacetic acid, malonic acid, succinic acid, pimelic acid, fumaric acid, maleic acid, malic acid, sulfamic acid, phenylpropionic acid, gluconic acid, ascorbic acid, isonicotinic acid, citric acid, adipic acid etc.

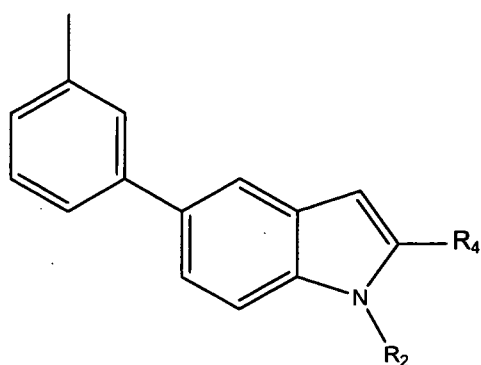
[0058] Salts can be obtained from the compounds of the present invention by conventional processes known to the person skilled in the art, for example, by combining with an organic or inorganic acid or base in a solvent or dispersant, or else by anion exchange or cation exchange from other salts. The present invention further encompasses all solvates of the compounds of the present invention, for example hydrates or adducts with alcohols, and derivatives of the compounds disclosed herein such as, for example, esters and prodrugs and active metabolites.

[0059] The compounds of the present invention or pharmaceutically acceptable salts thereof, can be synthesized using techniques commonly known in the art and readily available starting materials. The synthesis procedure can for example be carried out as described in Na, Y, M et al, *Eur. J. Med Chem.* 2003, 38, 75-87. The synthesis route for the compounds described herein is described further in the Examples described herein. Compounds according to the invention for example, the compound of the general formula I can be obtained as shown in the synthesis scheme in Example 5, Scheme 6. In an illustrative embodiment, the compound(s) of formula I can be prepared by adding a phosphine compound to a solution containing the compound of formula II



(II);

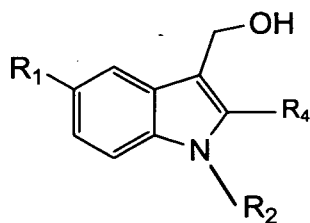
under conditions to form a compound of formula III



(III);

and adding an amine and a carbonyl compound to the solution in step i) to form a compound of formula I. The R_2 and R_4 substituents in formulae II and III is defined in the compound of formula I described herein. In certain embodiments, the phosphine compound can be $\text{Pd}(\text{PH}_3)_4$. The leaving group Y can be a halogen atom for example, one of chlorine, iodine or bromine. In this context, when adding the phosphine compound to obtain the compound of formula III, a boronic acid such as a meta-substituted phenylboronic acid for example, can be added to the solution containing the compound of formula II, to obtain the compound of formula III.

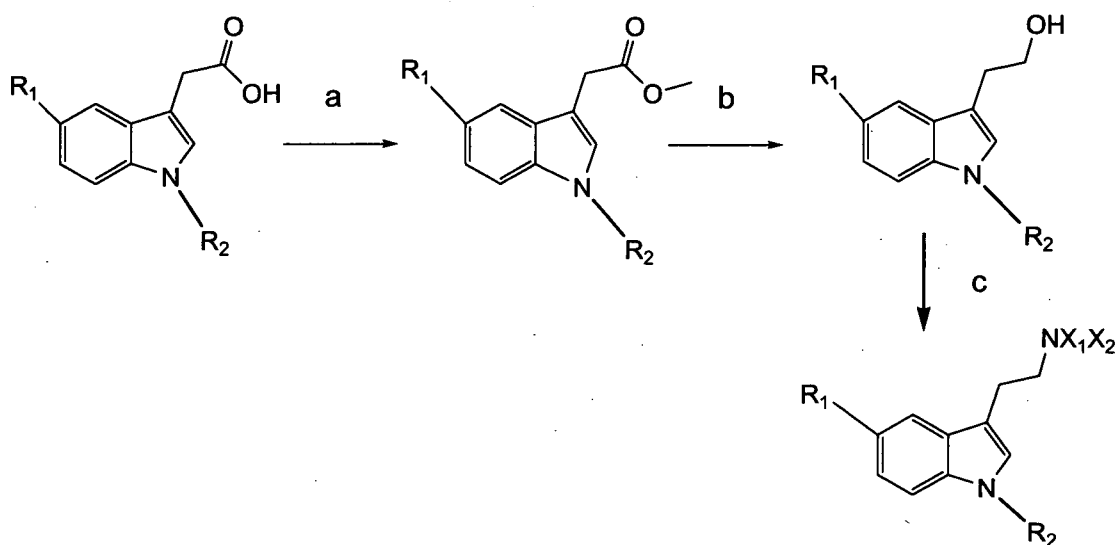
[0060] In other embodiments, to obtain a compound of formula I for example, a sulphonyl compound can be added to a solution containing the compound of formula IV



(IV);

under conditions to form a sulphonate ester compound. An amine is then added to the solution containing the sulphonate ester compound, under conditions to form a compound of formula I. In this context, the R_1 , R_2 and R_4 substituents in formula IV are defined in the compound of formula I described herein.

[0061] As an illustrative example, the compound of formula I as described in the present invention can be obtained using the following scheme:



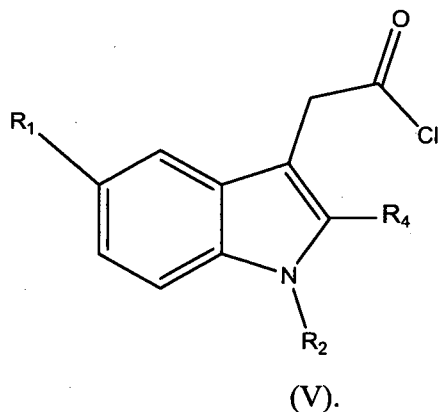
a) MeOH, H₂SO₄, reflux: To form ester

b) LiAlH₄, THF: Reduction of ester to alcohol

c) (i) TEA, Methanesulphonylchloride

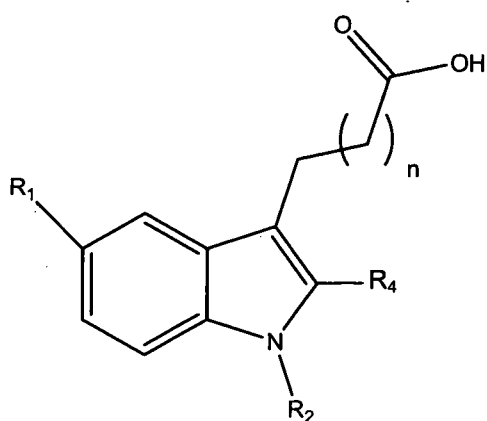
5 (ii) Amine, reflux if necessary (replacement of methane sulphonyl ester with amine)

[0062] In some embodiments, to obtain a compound of formula I, in which R₃ is (CH₂)_nNX₁X₂, n being an integer from 2 to 4, a methylating agent such as diazomethane for example, is added into a solution containing the compound of formula V



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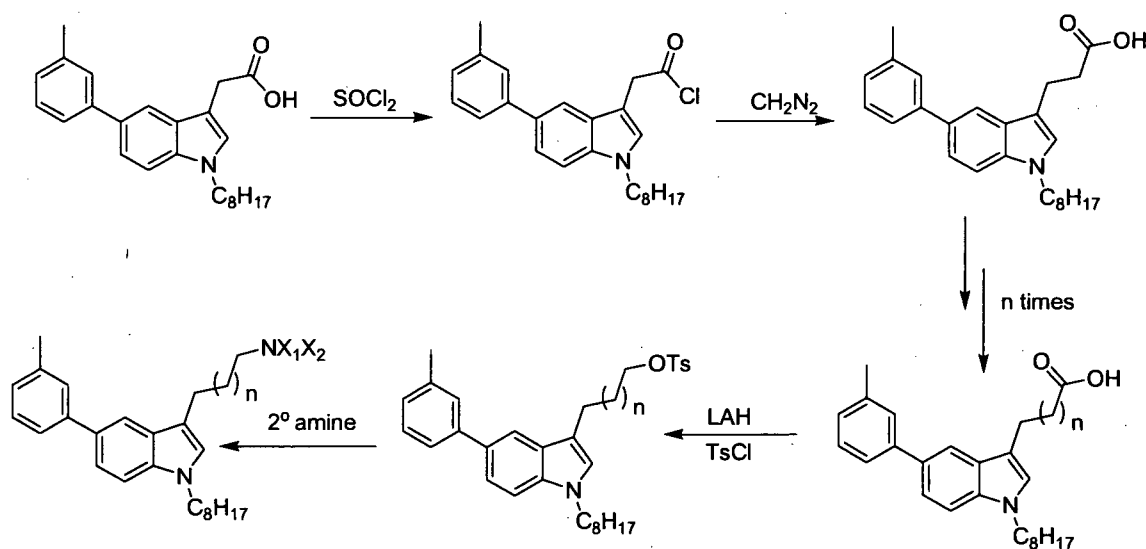
The methylating agent is added into the solution containing the compound of formula V, in order to add a carbon atom to the acid chloride side chain, to form a compound of formula VI



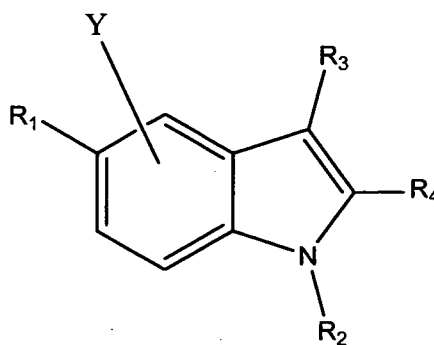
(VI).

In this context, the step of adding the methylating agent can be repeated 1, 2, 3 or 4 times, in order to add a respective 1, 2, 3, or 4 extra carbon atom(s) to the acid chloride side chain. Once the acid compound of formula VI is obtained, the acid compound of formula VI can be converted to an ester which is followed by a reduction to an alcohol compound by adding lithium aluminium hydride. A sulphonyl compound can be added to the solution containing the alcohol compound of formula VI to form a sulphonyl ester compound. To form the compound of formula I, the sulphonyl ester group can be substituted by an amine, by adding an amine to the solution containing the sulphonyl ester compound.

[0063] As an illustrative example, the compound of formula I can be obtained using the following scheme:



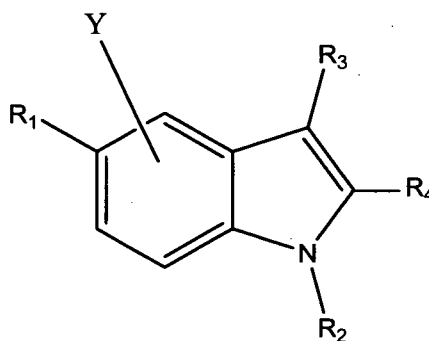
[0064] The present invention also provides a compound of formula VII,



(VII)

in which R_1 and Y are respectively defined above. In this compound of formula VII, R_2 can be a terpenoid. The term "terpenoid" is understood to cover terpenes and oxygen containing derivatives thereof having at least one C_5H_8 hydrocarbyl unit which may have one or more points of unsaturation and/or be part of a cyclic unit within the compound. Terpenoids can include, but are not limited to hemiterpenoids, monoterpenoids, sesquiterpenoids, diterpenoids, sesterterpenoids, triterpenoids, tetraterpenoids, and polyterpenoids. As an illustrative example, the substituent R_2 in the compound of general formula VII can be geranyl. In this context, when R_2 is a terpenoid, R_3 is $(CH_2)_nCONX_1X_2$, in which n can be an integer from 1 to 4, and X_1 and X_2 are respectively defined above.

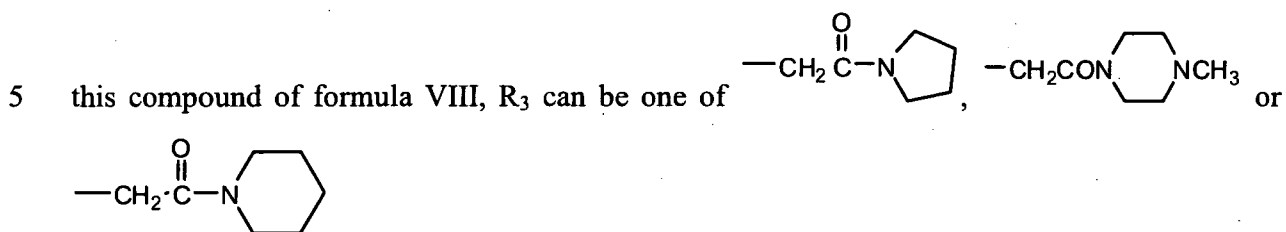
[0065] The present invention also provides a compound of formula VIII,



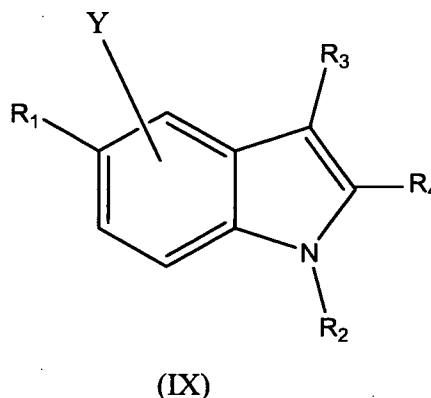
(VIII)

in which R_1 , Y and R_2 are respectively defined above. In this compound of formula VIII, R_3 can be $(CH_2)_nCONX_1X_2$, n being an integer from 1 to 4. X_1 and X_2 together with the nitrogen atom bearing them, form a 3-8 membered ring, wherein the 3-8 membered ring can be fused to at least one 3-8 membered ring, wherein the ring can optionally comprise 0, 1, 2, 3 or 4 further heteroatoms selected from the group consisting of oxygen, nitrogen, sulphur and phosphorus; and wherein the ring can be substituted by at least one substituent selected from the group

consisting of hydrogen, hydroxyl, C₁₋₂₀alkyl, C₂₋₂₀alkenyl, C₂₋₂₀alkynyl, C₁₋₂₀acyl, C₃₋₈cycloalkyl, C₃₋₈cycloalkenyl, aryl, heteroaryl, heteroalicyclic, halogen, carbonyl, thiocarbonyl, O-carbamyl, O-thiocarbonyl, O-carboxy, isocyanato, thiocyanato, silyl, perhaloalkyl, sulfonyl, sulfonamide, thio, -CN, -COOH, -SH, -N=N-, -N=O and NX₁X₂. As an illustrative example for

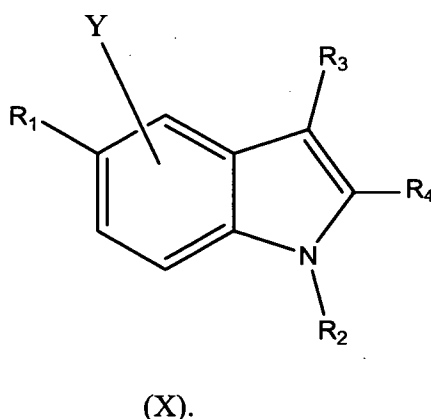


[0066] The present invention also provides a compound of formula IX,



10 in which R₁, Y and R₂ are respectively defined above. In this compound of formula IX, the R₃ substituent can be -(CH₂)₂CONH₂ or CH₂NH₂SO₂CH₃.

[0067] The present invention also provides a compound of formula X



15 [0068] In this compound, R₁ and Y are independently selected from the group consisting of hydrogen, hydroxyl, C₁₋₂₀alkyl, C₂₋₂₀alkenyl, C₂₋₂₀alkynyl, C₁₋₂₀acyl, C₃₋₈cycloalkyl, C₃₋₈cycloalkenyl, aryl, heteroaryl, heteroalicyclic, halogen, carbonyl, thiocarbonyl, O-carbamyl, O-thiocarbonyl, O-carboxy, isocyanato, thiocyanato, silyl, sulfonamide, thio, -CN, -COOH, -

SH, -N=N, -N=O and NX_1X_2 , wherein one or more of the hydrogen atoms of the indole ring can be replaced by Y; R_2 is selected from the group consisting of hydrogen, C_{1-20} alkyl, C_{2-20} alkenyl, C_{2-20} alkynyl, C_{1-20} acyl, C_{3-8} cycloalkyl, C_{3-8} cycloalkenyl, aryl, heteroaryl and heteroalicyclic; and R_3 is $(CH_2)_nCONX_1X_2$, n being an integer from 1 to 4; wherein X_1 is hydrogen and X_2 is one selected from the group consisting of C_{1-20} alkyl, C_{2-20} alkenyl, C_{2-20} alkynyl, C_{1-20} acyl, C_{3-8} cycloalkyl, C_{3-8} cycloalkenyl, aryl, heteroaryl, and heteroalicyclic.

[0069] The present invention also relates to a method of killing a cell such as a tumor cell, e.g. a cancerous cell or a precancerous cell. The method includes administering a compound of the present invention as described herein. Any cell may be used in the present method of the invention. In some embodiments, the cell used according to the invention may be comprised in a mammal. In other embodiments, the cell as used in the invention may be cultured. The cultured cell may also be obtained from a mammal. Examples of mammals include, but are not limited to, a rat, a cow, a goat, a sheep, a pig, a dog, a mouflon, a guinea pig, a hamster, a chimpanzee, a rhesus monkey and a human. In some embodiments, the cell used in the invention may be a tumor cell. In other embodiments, the tumor may derive from a cancer. Any tumor or cancer may be used in the invention including for example, a benign tumor and a metastatic malignant tumor. Examples of tumors include, but are not limited to, haematological malignancies and solid tumours. Solid tumours include for instance a sarcoma, arising from connective or supporting tissues, a carcinoma, arising from the body's glandular cells and epithelial cells or a lymphoma, a cancer of lymphatic tissue, such as the lymph nodes, spleen, and thymus. Examples of a solid tumour include, but are not limited to, breast cancer, lung cancer, a brain tumour, a neuroblastoma, colon cancer, rectal cancer, bladder cancer, a liver tumour, a pancreatic tumour, ovarian cancer, prostate cancer, melanoma, cancer of the head or neck and leukaemia.

[0070] The compounds of the present invention can be formulated into compositions, for example pharmaceutical compositions, suitable for administration. Where applicable, a compound of the present invention may be used in its ionic transition state or any pharmaceutically acceptable salt thereof. A compound as defined above, or a pharmaceutically acceptable salt thereof, can be used per se, or in a pharmaceutical composition where it may be mixed with other active ingredients, as in combination therapy, and/or a suitable carrier or diluent.

[0071] Examples of other active ingredients that may be included in a pharmaceutical composition include, but are not limited to, a nucleic acid alkylator, a nucleoside analogue, an

anthracycline, an antibiotic, an aromatase inhibitor, a folate antagonist, an estrogen receptor modulator, an inorganic arsenate, a microtubule inhibitor, a nitrosourea, an osteoclast inhibitor, a platinum containing compound, a retinoid, a topoisomerase 1 inhibitor, a topoisomerase 2 inhibitor, a thymidylate synthase inhibitor, an aromatase inhibitor, a cyclo-oxygenase inhibitor, an isoflavone, a tyrosine kinase inhibitor, a growth factor, a bisphosphonate, and a monoclonal antibody.

[0072] Alkylators that may be included in the pharmaceutical composition of the present invention include but are not limited to busulfan (Myleran®, Busilvex®), chlorambucil (Leukeran®), ifosfamide (Mitoxana®, with or without MESNA), cyclophosphamide (Cytosan®, Neosar®), glufosfamide, melphalan/ L-PAM (Alkeran®), dacarbazine (DTIC-Dome®), and temozolamide (Temodar®). As an illustrative example, the compound 2-bis[(2-chloroethyl)amino]tetra-hydro-2H-1,3,2-oxazaphosphorine, 2-oxide, also commonly known as cyclophosphamide, is an alkylator used in the treatment of stages III and IV malignant lymphomas, multiple myeloma, leukemia, mycosis fungoides, neuroblastoma, ovarian adenocarcinoma, retinoblastoma, and carcinoma of the breast.

[0073] Nucleoside analogues that may be included in the pharmaceutical composition of the present invention include, but are not limited to, cytarabine (Cytosar®) and gemcitabine (Gemzar®), two fluorinated deoxycytidine analogues, fludarabine (Fludara®), a purine analog, 6-mercaptopurine (Puri-Nethol®) and its prodrug azathioprine (Imuran®).

[0074] Anthracyclines that may be included in the pharmaceutical composition of the present invention include, but are not limited to, doxorubicin (Adriamycin®, Doxil®, Rubex®), mitoxantrone (Novantrone®), idarubicin (Idamycin®), valrubicin (Valstar®), and epirubicin (Ellence®). As one example, the compound (8S,10S)-10-(4-amino-5-hydroxy-6-methyl-tetrahydro-2H-pyran-2-yloxy)-6,8,11-trihydroxy-8-(2-hydroxyacetyl)-1-methoxy-7,8,9,10-tetrahydrotetracene-5,12-dione, more commonly known as doxorubicin, is a cytotoxic anthracycline antibiotic isolated from cultures of *Streptomyces peucetius* var. *caesius*. Doxorubicin has been used successfully to produce regression in disseminated neoplastic conditions such as acute lymphoblastic leukemia, acute myeloblastic leukemia, Wilm's tumour, neuroblastoma, soft tissue and bone sarcomas, breast carcinoma, ovarian carcinoma, transitional cell bladder carcinoma, thyroid carcinoma, lymphomas of both Hodgkin and non-Hodgkin types, bronchogenic carcinoma, and gastric carcinoma.

[0075] Antibiotics that may be included in the pharmaceutical composition of the present invention include but are not limited to dactinomycin, actinomycin D (Cosmegen®), daunorubicin/daunomycin (Cerubidine®, DanuoXome®), bleomycin (Blenoxane®), epirubicin (Pharmorubicin®) and mitoxantrone (Novantrone®). Aromatase inhibitors useful in the practice of the present invention include but are not limited to anastrozole (Arimidex®) and letrozole (Femara®). Bisphosphonate inhibitors that may be included in the pharmaceutical composition of the present invention include but are not limited to zoledronate (Zometa®).

[0076] Cyclooxygenase inhibitors that may be included in the pharmaceutical composition of the present invention include but are not limited to acetylsalicylic acid (Aspirin®), celecoxib (Celebrex®) and rofecoxib (Vioxx®, Ceoxx®, Ceeoxx®). Estrogen receptor modulators that may be included in the composition of the present invention include but are not limited to tamoxifen (Nolvadex®) and fulvestrant (Faslodex®). Folate antagonists that may be included in the composition of the present invention include but are not limited to methotrexate (Trexall®, Rheumatrex®) and trimetrexate (Neutrexin®). As an illustrative example, the compound (S)-2-(4-(((2,4-diaminopteridin-6-yl)methyl)methylamino)benzamido)pentanedioic acid, commonly known as methotrexate, is an antifolate drug that has been used in the treatment of gestational choriocarcinoma and in the treatment of patients with chorioadenoma destruens and hydatiform mole. It is also useful in the treatment of advanced stages of malignant lymphoma and in the treatment of advanced cases of mycosis fungoides.

[0077] Inorganic arsenates that may be included in the pharmaceutical composition of the present invention include but are not limited to arsenic trioxide (Trisenox®). Microtubule inhibitors (as used herein, a "microtubule inhibitor" is any agent that interferes with the assembly or disassembly of microtubules) that may be included in the composition of the present invention include but are not limited to vincristine (Oncovin®), vinblastine (Velban®), paclitaxel (Taxol®, Paxene®), vinorelbine (Navelbine®), docetaxel (Taxotere®), epothilone B or D or a derivative of either, and discodermolide or its derivatives.

[0078] Nitrosoureas that may be included in the pharmaceutical composition of the present invention include but are not limited to procarbazine (Matulane®), lomustine (CeeNU®), carmustine (BCNU®, BiCNU®, Gliadel Wafer®), and estramustine (Emcyt®). Nucleoside analogs that may be included in the pharmaceutical composition of the present invention include

but are not limited to 6-mercaptopurine (Purinethol®), 5-fluorouracil (Adrucil®), 6-thioguanine (Thioguanine®), hydroxyurea (Hydrea®), cytarabine (Cytosar-U®, DepoCyt®), floxuridine (FUDR®), fludarabine (Fludara®), pentostatin (Nipent®), cladribine (Leustatin®, 2-CdA®), gemcitabine (Gemzar®), and capecitabine (Xeloda®). As an illustrative example, the compound
5 5-fluoro-2,4(1H,3H)-pyrimidinedione, also commonly known as 5-fluorouracil, is an antimetabolite nucleoside analogue effective in the palliative management of carcinoma of the colon, rectum, breast, stomach, and pancreas in patients who are considered incurable by surgical or other means. Another example of a nucleoside analogue is Gemcitabine. Gemcitabine is 2'-deoxy-2',2'-difluoro-cytidine. It is commercially available as the monohydrochloride salt, and as
10 the beta-isomer. It is also known chemically as 1-(4-amino-2-oxo-1-H-pyrimidin-1-yl)-2-desoxy-2,2-difluororibose.

[0079] An illustrative example of an osteoclast inhibitor that may be included in the pharmaceutical composition of the present invention is pamidronate (Aredia®). Platinum compounds that may be included in the pharmaceutical composition of the present invention
15 include, but are not limited to, cisplatin (Platinol®) and carboplatin (Paraplatin®). Retinoids that may be included in the pharmaceutical composition of the present invention include but are not limited to tretinoin, ATRA (Vesanoid®), alitretinoin (Panretin®), and bexarotene (Targretin®). Topoisomerase 1 inhibitors that may be included in the pharmaceutical composition of the present invention include, but are not limited to, topotecan (Hycamtin®) and irinotecan (Camptostar®,
20 Camptothecin-11®). Topoisomerase 2 inhibitors that may be included in the pharmaceutical composition of the present invention include, but are not limited to, etoposide (Etopophos®, Vepesid®) and teniposide (Vumon®).

[0080] Examples of a tyrosine kinase inhibitors that may be included in the pharmaceutical composition of the present invention include, but are not limited to, dasatinib (Sprycel®),
25 erlotinib (Tarceva®), gefitinib (Iressa®), imatinib (Gleevec®), lapatinib (Tykerb®), sorafenib (Nexavar®) and vandetanib (Zactima®). Examples of a (recombinant) growth factor that may be included in the pharmaceutical composition of the present invention include, but are not limited to, interleukin-11, interferon- α -2b and interleukin-2. An illustrative example of a thymidylate synthase inhibitor that may be included in the pharmaceutical composition of the
30 present invention is Raltitrexed®. Examples of a monoclonal antibody that may be included in

the pharmaceutical composition of the present invention include, but are not limited to, rituximab (MabThera®) or cetuximab (Erbix®).

[0081] The invention also provides a pharmaceutical composition comprising a compound of the present invention, for example, a compound of formula I. The pharmaceutical composition may be administered by, for example, the oral, topical, dermal, ocular, intravenous, intraarticular, rectal, vaginal, inhalation, intranasal, sublingual or buccal route. Exemplary routes of administration of a respective compound or pharmaceutical composition include oral, transdermal, and parenteral delivery. Suitable routes of administration may, for example, include depot, oral, rectal, transmucosal, or intestinal administration; parenteral delivery, including intramuscular, subcutaneous, intravenous, intramedullary injections, as well as intrathecal, direct intraventricular, intraperitoneal, intranasal, or intraocular injections. One may also administer the compound or pharmaceutical composition in a local rather than systemic manner, for example, via injection of the compound directly into a solid tumour, such as in a depot or sustained release formulation. Furthermore, a respective compound or pharmaceutical composition may be used in a targeted drug delivery system, for example, in a liposome coated with a tumour-specific antibody. Such liposomes may for example be targeted to and taken up selectively by a tumour.

[0082] The present invention also relates to a method of treating a mammal having a disease or disorder associated with Icmt activity. The method includes administering to the mammal a compound of the present invention, for example, formula I or a pharmaceutical composition as defined above. In certain embodiments, the compound or the pharmaceutical composition described herein can be used for treating cancer or a disease or disorder associated with Icmt activity. A respective use may for example be the manufacture of a medicament for this purpose. Accordingly, the method of the invention includes the use of a compound as defined above, including the use in the manufacture of a medicament.

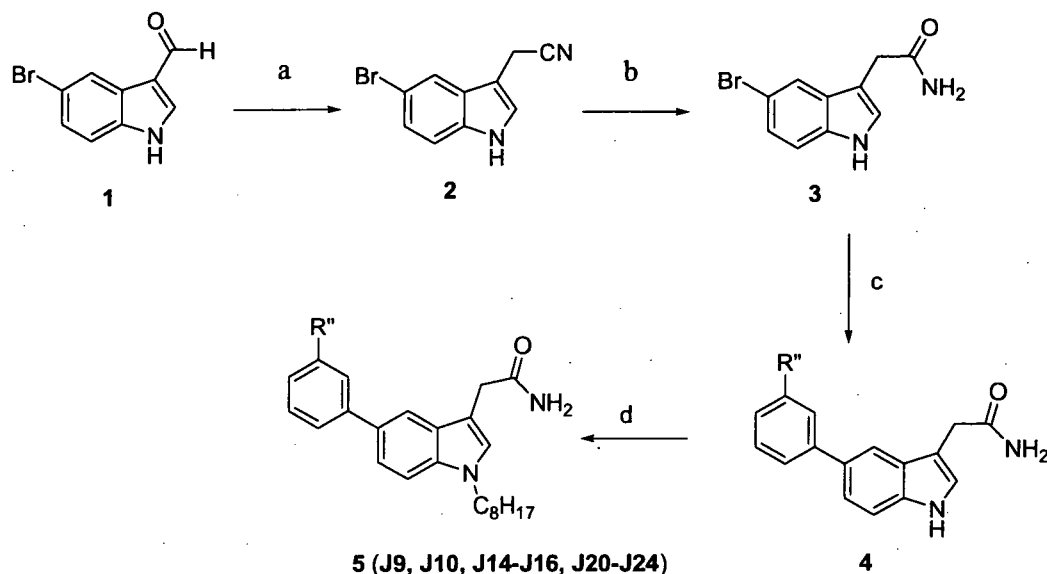
[0083] In order that the invention may be readily understood and put into practical effect, particular embodiments will now be described by way of the following non-limiting examples.

EXAMPLES

[0084] The following experimental examples are provided to further illustrate the present invention and are not intended to be limiting to the scope of the invention.

Example 1: Synthesis of Compounds of Series 1, Table 1

Scheme 1: Preparation of Primary amides (Cysmethynil, J9, J10, J14-J16, J20-J24)



R=n-Octyl, Isoprenyl, Geranyl

(a) (i) NaBH_4 , $\text{NH}_2\text{CHO}\cdot\text{MeOH}$, rt (0.5 h) (ii) KCN, 100°C (3 h) (b) KOH, *t*-BuOH, reflux (3 h) (c) meta-substituted phenylboronic acid, $\text{Pd}(\text{PPh}_3)_4$, NaHCO_3 , EtOH/toluene, reflux (1-6 h) (d) R-X (X=halogen), NaH, DMF, rt (1.5h) $53\text{--}58^\circ\text{C}$ (3-6 h)

[0085] Preparation of 2-(5-bromo-1H-indol-3-yl) acetonitrile (2). To a solution of 5-bromo-1H-indole-3-carbaldehyde (**1**) (1 g, 4.5 mmol) in $\text{NH}_2\text{CHO}\cdot\text{MeOH}$ (1:1, v/v, 200 ml) was added NaBH_4 (0.5 g, 13.5 mmol) and the mixture was stirred for 0.5 h. To the reaction mixture was added KCN (3 g, 45 mmol) and the whole was refluxed on oil bath at 100°C for 2.5 h with stirring. After cooling to room temperature, brine was added and the whole was extracted with CHCl_3 . The extract was washed with brine dried over Na_2SO_4 , and evaporated under reduced pressure to give the nitrile **2**. Recrystallization from EtOH/water gave needle-like white crystals (0.861 g, 81 %).

[0086] Preparation of 2-(5-bromo-1H-indol-3-yl) acetamide (3). Nitrile **2** (0.826 g, 3.5 mmol), was refluxed in *t*-BuOH (10 ml) containing finely powdered 85% KOH (1.85 g, 28 mmol) for 3 h. The reaction mixture was cooled to room temperature, diluted with water, and acidified with 1 N HCl. The resulting suspension was filtered at the vacuum and filter cake was washed with water then dried *in vacuo*. The product was isolated as an off-white/light brown solid (0.789 g, 89 %).

[0087] General procedure for preparation of 5-phenyl-1H-indoles (4). To a suspension of bromoindole (**3**) (2 mmol) in anhydrous toluene (40 ml) in an ice bath was added

Pd(PPh₃)₄ (0.12 g, 5.7 mol%). The suspension was stirred for 0.5 h. To the resulting bright yellow suspension was added in one portion a solution of meta-substituted phenylboronic acid (3 mmol, 1.5 equiv) in absolute EtOH (10 ml) followed immediately by a saturated aqueous solution of NaHCO₃ (25 ml). After refluxing for 1-6 h, the biphasic mixture was cooled to room temperature and then poured into a solution of saturated aqueous NaCl. The organic phase was separated and the aqueous phase was extracted with EtOAc. Organic extracts were combined and dried (Na₂SO₄). The drying agent was removed by filtration and the filtrate was concentrated under reduced pressure to give the crude product 4.

[0088] General procedure for preparation of 1-octyl-5-phenyl-1H-indoles (5).

To a stirred suspension of NaH (60% dispersion in mineral oil, 0.12g, 3 mmol) in anhydrous dimethylformamide (DMF; 5 ml) in ice bath was added a solution of crude phenyl indole 4 (2 mmol) in anhydrous DMF (10 ml) drop wise over a period of 10 min. After stirring at room temperature for 1.5 h, following which 1-bromooctane (1.0 ml, 6 mmol) was added drop wise over 5 min. After being heated on an oil bath at 53-58°C for 3-6 h, the reaction mixture was cooled to room temperature and poured into ice water. The suspension was stirred 10 min and extracted with Et₂O. The organic extracts were combined, washed with brine, and dried (Na₂SO₄). The drying agent was removed by filtration and the filtrate was concentrated under reduced pressure to give the crude product 5.

[0089] Cysmethynil (2-(1-octyl-5-m-tolyl-1H-indol-3-yl) acetamide) MS-APCI:

[M+1]⁺ 377.5 (377.3); δ_H (CD₃OD, 300 MHz): 0.92 (t, 3 H, *J* 15 Hz, CH₃), 1.29-1.35 (m, 10 H, CH₂), 1.88 (t, 2 H, *J* 15 Hz, CH₂), 2.42 (s, 3 H, CH₃), 3.70 (s, 2 H, CH₂), 4.20 (t, 2 H, *J* 15 Hz, CH₂), 7.12 (d, 1 H, *J* 9 Hz, ArH), 7.21-7.32 (m, 2 H, ArH), 7.37-7.48 (m, 4 H, ArH), 7.80 (s, 1 H, ArH) δ_C (CD₃OD, 75 MHz): 13.6, 20.8, 22.8, 27.2, 29.5, 29.6, 30.6, 32.1, 32.6, 46.3, 108.6, 110.0, 117.3, 121.5, 124.5, 127.1, 127.6, 128.2, 128.7, 131.1, 133.1, 136.6, 138.4, 143.0, 177.0

[0090] J8 2-(5-(3-ethoxyphenyl)-1-octyl-1H-indol-3-yl) acetamide MS-APCI:

[M+1]⁺ 407.4 (407.5) δ_H (DMSO-d₆, 300 MHz): 0.90 (t, 3 H, *J* 12 Hz, CH₃), 1.05-1.15 (m, 6 H, CH₃), 1.27-1.31 (m, 10 H, CH₂), 1.84 (t, 2 H, *J* 9 Hz, CH₂), 3.40-3.48 (m, 4 H, CH₂), 3.87 (s, 3 H, CH₃), 3.88 (s, 2 H, CH₂), 4.19 (t, 2 H, *J* 15 Hz, CH₂), 6.87 (d, 1 H, *J* 6 Hz, ArH), 7.14-7.44 (m, 6 H, ArH), 7.83 (s, 1 H, ArH) δ_C (DMSO-d₆, 75 MHz): 15.0, 15.8, 23.1, 27.4, 29.7, 29.8, 31.0, 32.2, 33.3, 46.5, 64.0, 110.1, 111.0, 113.0, 114.0, 118.4, 120.0, 121.4, 128.9, 129.2, 130.8, 131.8, 136.6, 144.4, 160.0, 173.8

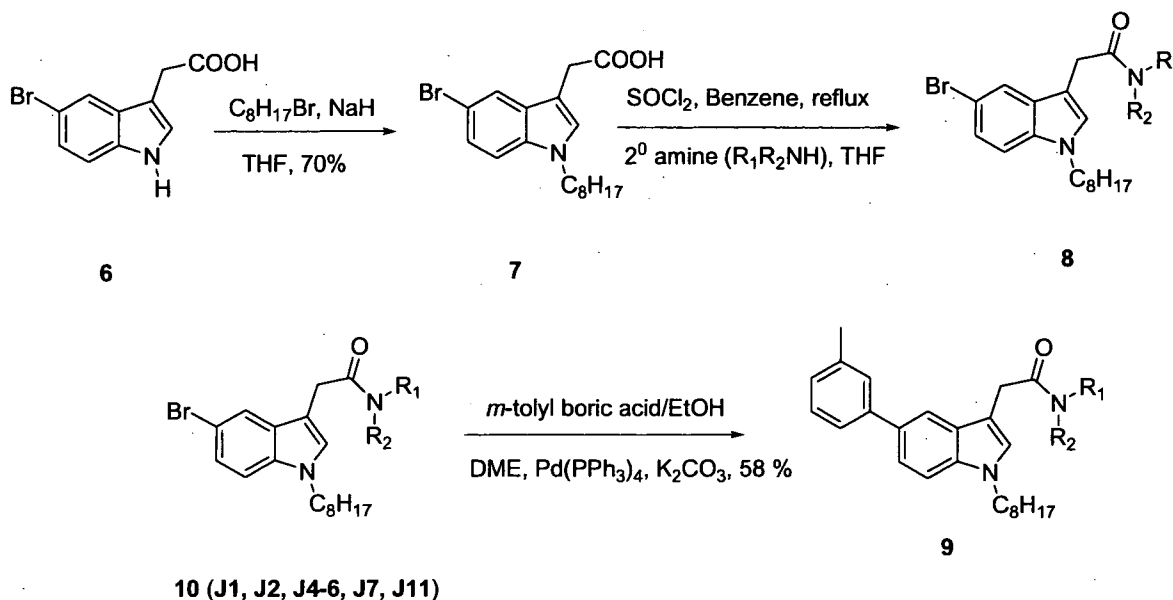
[0091] J9 (2-(5-(3-methoxyphenyl)-1-octyl-1H-indol-3-yl) acetamide) MS-APCI: $[M+1]^+$ 393.5 (393.4); δ_H (CD3OD, 300 MHz): 0.91 (t, 3 H, J 12 Hz, CH₃), 1.29-1.34 (m, 10 H, CH₂), 1.88 (t, 2 H, J 12 Hz, CH₂), 3.71 (s, 2 H, CH₂), 3.87 (s, 3 H, CH₃), 4.20 (t, 2 H, J 12 Hz, CH₂), 6.87 (d, 1 H, J 6 Hz, ArH), 7.17-7.44 (m, 6 H, ArH), 7.82 (s, 1 H, ArH) δ_C (DMSO-
5 d_6 ; 75 MHz): 14.9, 15.7, 23.0, 27.3, 29.6, 29.7, 30.9, 32.2, 33.3, 46.5, 56.1, 109.9, 111.0, 112.6, 113.4, 118.3, 120.1, 121.4, 129.0, 129.1, 130.9, 131.8, 136.6, 144.4, 160.7, 174.2

[0092] J14 2-(1-octyl-5-phenyl-1H-indol-3-yl)acetamide MS-APCI: $[M+1]^+$ 363.6 (363.2); δ_H (CDCl₃, 300 MHz): 0.85 (t, 3 H, J 15 Hz, CH₃), 1.26-1.31 (m, 10 H, CH₂), 1.84 (t, 2 H, J 12 Hz, CH₂), 3.77 (s, 2 H, CH₂), 4.10 (t, 2 H, J 15 Hz, CH₂), 7.07 (d, 1 H, J 6 Hz, ArH),
10 7.30 (t, 1 H, J 12 Hz, ArH), 7.40-7.52 (m, 3 H, ArH), 7.63 (d, 1 H, J 6 Hz, ArH), 7.77 (s, 1 H, ArH). δ_C (CDCl₃, 75 MHz): 14.1, 22.6, 27.0, 29.1, 29.1, 30.3, 31.7, 32.9, 46.5, 108.0, 110.0, 117.3, 121.9, 124.9, 126.5, 127.3, 127.3, 128.7, 128.7, 133.2, 136.0, 142.1, 174.3

[0093] J15 2-(1-octyl-1H-indol-3-yl)acetamide MS-APCI: $[M+1]^+$ 287.5 (287.4); δ_H (CDCl₃, 300 MHz): 0.85 (t, 3 H, J 12 Hz, CH₃), 1.25-1.31 (m, 10 H, CH₂), 1.81 (t, 2 H, J
15 15 Hz, CH₂), 3.73 (s, 2 H, CH₂), 4.07 (t, 2 H, J 15 Hz, CH₂), 7.06 (s, 1 H, ArH), 7.12 (t, 1 H, J 15 Hz, ArH), 7.22 (t, 1 H, J 12 Hz, ArH), 7.34 (d, 1 H, J 9 Hz, ArH), 7.57 (d, 1 H, J 6 Hz, ArH) δ_C (CDCl₃, 75 MHz): 14.0, 22.6, 27.0, 29.1, 29.1, 30.2, 31.7, 32.9, 46.4, 107.6, 109.7, 118.9, 119.5, 122.0, 127.2, 127.4, 136.5, 174.3

[0094] J23 (2-(1-octyl-5-o-tolyl-1H-indol-3-yl) acetamide) MS-APCI: $[M+1]^+$ 377.3 (377.3); δ_H (CDCl₃, 300 MHz): 0.85(t, 3 H, J 15 Hz, CH₃), 1.27-1.34 (m, 10 H, CH₂),
20 1.85 (t, 2 H, J 15 Hz, CH₂), 2.30 (s, 3 H, CH₃), 3.72 (s, 2 H, CH₂), 4.09 (t, 2 H, J 15 Hz, CH₂), 7.12 (d, 1 H, J 9 Hz, ArH), 7.21-7.32 (m, 5 H, ArH), 7.37-7.48 (m, 3 H, ArH), 7.80 (s, 1 H, ArH) δ_C (CDCl₃, 75 MHz): 14.1, 20.6, 22.6, 27.0, 29.1, 29.1, 30.3, 31.7, 32.9, 46.5, 107.7, 109.1, 119.2, 123.8, 125.7, 126.8, 127.3, 127.6, 130.3, 130.3, 133.5, 135.5, 135.6, 142.6, 174.3

[0095] J24 (2-(1-octyl-5-p-tolyl-1H-indol-3-yl) acetamide) MS-APCI: $[M+1]^+$ 377.3 (377.3); δ_H (CDCl₃, 300 MHz): 0.85 (t, 3 H, J 15 Hz, CH₃), 1.26-1.33 (m, 10 H, CH₂),
25 1.83 (t, 2 H, J 12 Hz, CH₂), 2.40 (s, 3 H, CH₃), 3.76 (s, 2 H, CH₂), 4.09 (t, 2 H, J 12 Hz, CH₂), 7.07, (s, 1 H, ArH) , 7.24 (d, 2 H, J 6 Hz, ArH), 7.38 (d, 1 H, J 6 Hz, ArH), 7.48-7.55 (m, 3 H, ArH), 7.75 (s, 1 H, ArH) δ_C (CDCl₃, 75 MHz): 14.0, 21.0, 22.6, 27.0, 29.1, 29.1, 30.2, 31.7, 32.9, 46.5, 107.9, 109.9, 117.0, 121.8, 127.2, 127.2, 127.8, 129.4, 129.4, 133.2, 135.9, 136.2,
30 139.2, 174.3

Example 2: Synthesis of Compounds of Series 2, Table 2**Scheme 2: Preparation of 3⁰ amides (J1, J2, J4-6, J7, J11)**

5 **J10, J16, J21 and J22** were prepared following the experimental procedure Example 1, Scheme 1

[0096] **2-(5-bromo-1-octyl-1H-indol-3-yl)acetic acid (7):** To a stirred suspension of NaH (5.54 g, 138 mmol, 60% dispersion in mineral oil) in THF (100 mL THF) at 0 °C was added a solution of indole-3-acetic acid (6.65 g, 27.7 mmol) in THF (50 mL). After stirring the mixture for 30 min at 0 °C, a solution of 1-Bromo Octane (14.3 mL, 83.1 mmol) in THF (50 mL) was added drop wise. The mixture was allowed to slowly reach room temp and continued to stir for 4 h. The reaction mixture was then cooled to 0 °C and excess hydride was carefully destroyed by slow addition of MeOH with vigorous stirring followed by cold water until a clear yellow solution resulted. Ether (100 mL) was added. The aqueous phase was separated, acidified with 6 N HCl, and extracted with sufficient dichloromethane 3 times. The combined dichloromethane extracts were dried (Na₂SO₄) and concentrated, purified by crystallisation in chloroform subsequently column chromatography using ethylacetate.

[0097] **General procedure for the preparation of 3⁰ amides (8):** A mixture of 2-(5-bromo-1-octyl-1H-indol-3-yl)acetic acid (6) (1mmol) and SOCl₂ (2 ml) in dry Benzene (5 ml) was refluxed for 4 hours then distilled out the excess of thionyl chloride and Benzene and dried in vacuum evaporated to dryness to give the corresponding acid chloride, which was

dissolved in dry THF (4 ml). The THF solution was added dropwise to appropriate 2⁰ amine in dry THF solution at 0-5 °C. The reaction mixture was stirred at the same temperature for 1 hr; THF was removed under vacuum extracted with dichloromethane dried over Na₂SO₄ and evaporated to give the corresponding amide in nearly 80% in all cases.

- 5 **[0098]** **General procedure for the preparation of compound (9):** To a solution of compound (7) (1 mmol, 1 eq.) in 4 ml DME was added Pd(PPh₃)₄ (0.05 eq) and the mixture was stirred under argon for 15 min. A solution of *m*-tolyl boric acid (1 mmol, 1 eq) in 1.5ml EtOH (in case of **J7** *m*-methoxy boric acid and) was added, the mixture was stirred for another 15 min, and then 2 M aqueous Na₂CO₃ (4mL) was added. The resulting mixture was refluxed
10 for 5 h under argon and cooled, and the organic solvent was removed under reduced pressure. The resulting suspension was extracted with CH₂Cl₂ and dried over Na₂SO₄, and the solvent was evaporated. The residue was chromatographed on silica gel eluted with Ethylacetate and n-hexane to yield the required compound nearly 60%.

[0099] **J10** (2-(5-*m*-tolyl-1-(3-(trifluoromethyl) benzyl)-1H-indol-3-yl) acetamide)
15 MS-APCI: [M+1]⁺ 423.4 (423.3) δ_H (CDCl₃, 300 MHz): 2.43 (s, 3 H, CH₃), 3.79 (s, 2 H, CH₂), 5.38 (s, 2 H, CH₂), 7.13 (d, 2 H, *J* 9 Hz, ArH), 7.30 (t, 2 H, *J* 18 Hz, ArH), 7.41-7.50 (m, 5 H, ArH), 7.54 (d, 2 H, *J* 6 Hz, ArH) 7.79 (s, 1 H, ArH). δ_C (CDCl₃, 75 MHz): 28.7, 37.8, 51.5, 100.3, 106.3, 110.5, 111.2, 112.0, 112.2, 114.4, 114.8, 115.0, 114.5, 116.1, 116.5, 119.7, 121, 5, 123.0

20 **[00100]** **J11** (N, N-diethyl-2-(5-*m*-tolyl-1-(3-(trifluoromethyl) benzyl) -1H-indol-3-yl) acetamide) MS-APCI: [M+1]⁺ 479.5 (479.5) δ_H (CDCl₃, 300 MHz): 1.10 (t, 6 H, *J* 15 Hz, CH₃), 2.43, (s, 3 H, CH₃), 3.34-3.45 (m, 4 H, CH₂), 3.85 (s, 2 H, CH₂), 5.34 (s, 2 H, CH₂), 7.11-7.14 (m, 2 H, ArH), 7.25-7.27 (m, 2 H, ArH), 7.30 (t, 1 H, *J* 15 Hz, ArH), 7.40-7.45 (m, 5 H, ArH), 7.51 (d, 1 H, *J* 9 Hz, ArH), 7.80 (s, 1 H, ArH) δ_C (CDCl₃, 75 MHz): 12.9, 14.4, 21.6,
25 30.8, 40.2, 42.5, 49.6, 109.7, 110.0, 117.4, 122.1, 123.4, 124.5, 126.9, 127.1, 128.2, 128.2, 128.5, 128.5, 129.4, 130.1, 133.4, 135.9, 138.2, 138.5, 142.3, 170.5

[00101] **J16** (2-(5-*m*-tolyl-1H-indol-3-yl) acetamide) MS-APCI: [M+1]⁺ 264.3 (265.2) δ_H (CDCl₃, 300 MHz): 2.44 (s, 3 H, CH₃), 3.79 (s, 2 H, CH₂), 7.14 (d, 1 H, *J* 6 Hz, ArH), 7.20 (s, 1 H, ArH), 7.31 (t, 1 H, *J* 15 Hz, ArH), 7.43-7.52 (m, 4 H, ArH), 7.78 (s, 1 H, ArH), 8.25 (s, 1 H, ArNH) δ_C (CDCl₃, 75 MHz): 21.5, 32.9, 109.7, 111.6, 117.1, 122.6, 124.2,
30 124.5, 127.3, 127.4, 128.1, 128.6, 134.0, 135.8, 138.3, 142.0, 174.1

[00102] J21 (2-(1-(3-methylbut-2-enyl)-5-m-tolyl-1H-indol-3-yl) acetamide) MS-APCI: $[M+1]^+$ 333.4 (333.3) δ_H (CDCl₃, 300 MHz): 1.79 (s, 3 H, CH₃), 1.84 (s, 3 H, CH₃), 2.43 (s, 3 H, CH₃), 3.75 (s, 2 H, CH₂), 4.68 (d, 2 H, *J* 6 Hz, CH₂), 5.37 (t, 1 H, *J* 15 Hz, CH), 7.05-7.15 (m, 2 H, ArH), 7.30-7.51 (m, 5 H, ArH), 7.75 (s, 1 H, ArH) δ_C (CDCl₃, 75 MHz): 18.0, 21.6, 25.7, 33.0, 44.2, 108.0, 110.0, 117.3, 119.5, 121.9, 124.5, 127.2, 127.4, 128.0, 128.1, 128.6, 133.4, 136.0, 136.9, 138.3, 142.1, 174.4

[00103] J22 ((E)-2-(1-(3,7-dimethylocta-2,6-dienyl)-5-m-tolyl-1H-indol-3-yl)acetamide) MS-APCI: $[M+1]^+$ 401.5 (401.5) δ_H (CDCl₃, 300 MHz): 1.59 (s, 3 H, CH₃), 1.66 (s, 3 H, CH₃), 1.80 (s, 3 H, CH₃), 2.10 (t, 4 H, *J* 21 Hz, CH₂), 2.43 (s, 3 H, CH₃), 3.65 (s, 2 H, CH₂), 4.70 (d, 2 H, *J* 6 Hz, CH₂), 5.04 (t, 1 H, *J* 9 Hz, CH), 5.39 (t, 1 H, *J* 6 Hz, CH), 7.05-7.15 (m, 2 H, ArH), 7.30-7.51 (m, 5 H, ArH), 7.75 (s, 1 H, ArH) δ_C (CDCl₃, 75 MHz): 16.4, 17.7, 21.5, 25.7, 26.2, 32.9, 39.4, 44.1, 107.9, 110.1, 117.2, 119.3, 121.9, 123.6, 124.4, 127.2, 127.4, 128.1, 128.6, 131.9, 133.4, 136.0, 138.3, 140.4, 140.7, 142.8, 174.5

Example 3: Synthesis of Compounds of Series 3, Table 3

[00104] J1, J2 and J4-7 were prepared following the experimental procedure mentioned in Example 2, Scheme 2.

[00105] J1 (N,N-diethyl-2-(1-octyl-5-m-tolyl-1H-indol-3-yl) acetamide) MS-APCI: $[M+1]^+$ 433.3 (433.6) δ_H (CDCl₃, 300 MHz): 0.89 (t, 3 H, *J* 12 Hz, CH₃), 1.13-1.15 (m, 6 H, CH₃), 1.26-1.30 (m, 10 H, CH₂), 1.85 (t, 2 H, *J* 12 Hz, CH₂), 2.44 (s, 3 H, CH₃), 3.33-3.44 (m, 4 H, CH₂), 3.84 (s, 2 H, CH₂), 4.11 (t, 2 H, *J* 15 Hz, CH₂), 7.08-7.14 (m, 2 H, ArH), 7.26-7.48 (m, 4 H, ArH), 7.78 (s, 1 H, ArH) δ_C (CDCl₃, 75 MHz): 14.1, 14.3, 20.8, 21.6, 22.6, 27.0, 29.3, 29.4, 30.8, 31.8, 32.8, 40.1, 42.7, 46.4, 108.4, 109.6, 117.2, 121.4, 124.5, 126.7, 127.0, 128.1, 128.2, 128.5, 132.7, 135.7, 138.1, 142.6, 170.9

[00106] J2 (2-(1-octyl-5-m-tolyl-1H-indol-3-yl)-1-(piperidin-1-yl) ethanone) MS-APCI: $[M+1]^+$ 445.7 (445.6) δ_H (CD₃OD, 300 MHz): 0.90 (t, 3 H, *J* 12 Hz, CH₃), 1.26-1.29 (m, 10 H, CH₂), 1.47-1.57 (m, 6 H, CH₂), 1.84 (t, 2 H, *J* 12 Hz, CH₂), 2.42 (s, 3 H, CH₃), 3.51-3.58 (m, 4 H, CH₂), 3.90 (s, 2 H, CH₂), 4.18 (t, 2 H, *J* 15 Hz, CH₂), 7.09-7.12 (m, 2 H, ArH), 7.32 (t, 1 H, *J* 15 Hz, ArH), 7.40-7.48 (m, 4 H, ArH), 7.85 (s, 1 H, ArH) δ_C (CD₃OD, 75 MHz): 13.6, 20.8, 22.8, 24.5, 25.9, 26.4, 27.1, 29.5, 29.6, 30.7, 31.6, 32.1, 43.3, 43.4, 46.2, 108.4, 110.0, 117.4, 121.5, 124.5, 127.1, 127.4, 128.0, 128.6, 128.7, 133.1, 136.6, 138.4, 143.0, 171.6

[00107] J4 (2-(1-octyl-5-m-tolyl-1H-indol-3-yl)-1-(pyrrolidin-1-yl) ethanone) MS-APCI: $[M+1]^+$ 431.4 (431.6): δ_H (CD3OD, 300 MHz): 0.91 (t, 3 H, J 15 Hz, CH₃), 1.27-1.31 (m, 10 H, CH₂), 1.84-1.96 (m, 6 H, CH₂), 2.42 (s, 3 H, CH₃), 3.49 (t, 2 H, J 15 Hz, CH₂), 3.60 (t, 2 H, J 15 Hz, CH₂), 3.84 (s, 2 H, CH₂), 4.19 (t, 2 H, J 12 Hz, CH₂), 7.09-7.15 (m, 2 H, ArH), 7.32 (t, 1 H, J 12 Hz, ArH), 7.40-7.48 (m, 4 H, ArH), 7.83 (s, 1 H, ArH) δ_C (CD3OD, 75 MHz): 13.6, 20.8, 22.8, 24.5, 26.2, 27.1, 29.5, 30.6, 32.1, 32.5, 46.4, 50.2, 52.0, 107.8, 110.0, 117.5, 121.5, 124.5, 127.1, 127.7, 128.0, 128.7, 128.9, 133.1, 136.6, 138.4, 143.1, 172.0

[00108] J5 (N,N-dimethyl-2-(1-octyl-5-m-tolyl-1H-indol-3-yl) acetamide) MS-APCI: $[M+1]^+$ 405.4 (405.5): δ_H (CD3OD, 300 MHz): 0.91 (t, 3 H, J 12 Hz, CH₃), 1.27-1.31 (m, 10 H, CH₂), 1.86 (t, 2 H, J 9 Hz, CH₂), 2.42 (s, 3 H, CH₃), 3.10 (s, 6 H, CH₃), 3.90 (s, 2 H, CH₂), 4.18 (t, 2 H, J 15 Hz, CH₂), 7.09-7.13 (m, 2 H, ArH), 7.29 (t, 1 H, ArH), 7.40-7.48 (m, 4 H, ArH), 7.83 (s, 1 H, ArH) δ_C (CD3OD, 75 MHz): 13.6, 20.8, 22.8, 27.1, 29.5, 29.6, 30.6, 32.1, 32.5, 35.2, 37.6, 46.3, 107.8, 110.0, 117.5, 121.5, 124.5, 127.1, 127.7, 128.0, 128.7, 128.9, 133.0, 136.6, 138.4, 143.1, 172.0

[00109] J6 (2-(5-(3-ethoxyphenyl)-1-octyl-1H-indol-3-yl)-N,N-diethylacetamide) MS-APCI: $[M+1]^+$ 463.4 (463.6): δ_H (CD3OD, 300 MHz): 0.91 (t, 3 H, J 15 Hz, CH₃), 1.05-1.15 (m, 6 H, CH₃), 1.27-1.31 (m, 10 H, CH₂), 1.46 (t, 3 H, J 15 Hz, CH₃), 1.85 (t, 2 H, J 9 Hz, CH₂), 3.38-3.49 (m, 4 H, CH₂), 3.89 (s, 2 H, CH₂), 4.09-4.19 (m, 4 H, CH₂), 6.86 (d, 1 H, J 9 Hz, ArH), 7.14-7.43 (m, 6 H, ArH), 7.83 (s, 1 H, ArH) δ_C (CD3OD, 75 MHz): 12.5, 13.5, 13.6, 14.4, 22.8, 27.1, 29.5, 29.6, 30.6, 31.4, 32.1, 40.8, 43.2, 46.3, 63.7, 108.6, 110.0, 112.4, 113.7, 117.5, 119.8, 121.5, 127.6, 128.7, 129.8, 132.8, 136.7, 144.6, 169.9, 172.8

[00110] J7 (N,N-diethyl-2-(5-(3-methoxyphenyl)-1-octyl-1H-indol-3-yl)acetamide) MS-APCI: $[M+1]^+$ 449.5 (449.6) δ_H (CD3OD, 300 MHz): 0.90 (t, 3 H, J 12 Hz, CH₃), 1.05-1.15 (m, 6 H, CH₃), 1.27-1.31 (m, 10 H, CH₂), 1.84 (t, 2 H, J 9 Hz, CH₂), 3.40-3.48 (m, 4 H, CH₂), 3.87 (s, 3 H, CH₃), 3.88 (s, 2 H, CH₂), 4.19 (t, 2 H, J 15 Hz, CH₂), 6.87 (d, 1 H, J 6 Hz, ArH), 7.14-7.44 (m, 6 H, ArH), 7.83 (s, 1 H, ArH) δ_C (CD3OD, 75 MHz): 12.4, 13.5, 13.6, 15.7, 22.8, 27.1, 29.5, 29.6, 30.6, 31.4, 32.1, 40.8, 43.2, 46.3, 54.9, 108.6, 110.0, 111.8, 113.0, 117.5, 119.9, 121.5, 127.5, 128.7, 129.8, 132.8, 136.7, 144.6, 160.7, 172.7

[00111] J11 (N, N-diethyl-2-(5-m-tolyl-1-(3-(trifluoromethyl) benzyl) -1H-indol-3-yl) acetamide) (mentioned earlier in Series 2) MS-APCI: $[M+1]^+$ 479.5 (479.5) δ_H (CDCl₃, 300 MHz): 1.10 (t, 6 H, J 15 Hz, CH₃), 2.43, (s, 3 H, CH₃), 3.34-3.45 (m, 4 H, CH₂), 3.85 (s, 2 H,

CH₂), 5.34 (s, 2 H, CH₂), 7.11-7.14 (m, 2 H, ArH), 7.25-7.27 (m, 2 H, ArH), 7.30 (t, 1 H, *J* 15 Hz, ArH), 7.40-7.45 (m, 5 H, ArH), 7.51 (d, 1 H, *J* 9 Hz, ArH), 7.80 (s, 1 H, ArH) δ_c (CDCl₃, 75 MHz): 12.9, 14.4, 21.6, 30.8, 40.2, 42.5, 49.6, 109.7, 110.0, 117.4, 122.1, 123.4, 124.5, 126.9, 127.1, 128.2, 128.2, 128.5, 128.5, 129.4, 130.1, 133.4, 135.9, 138.2, 138.5, 142.3, 170.5

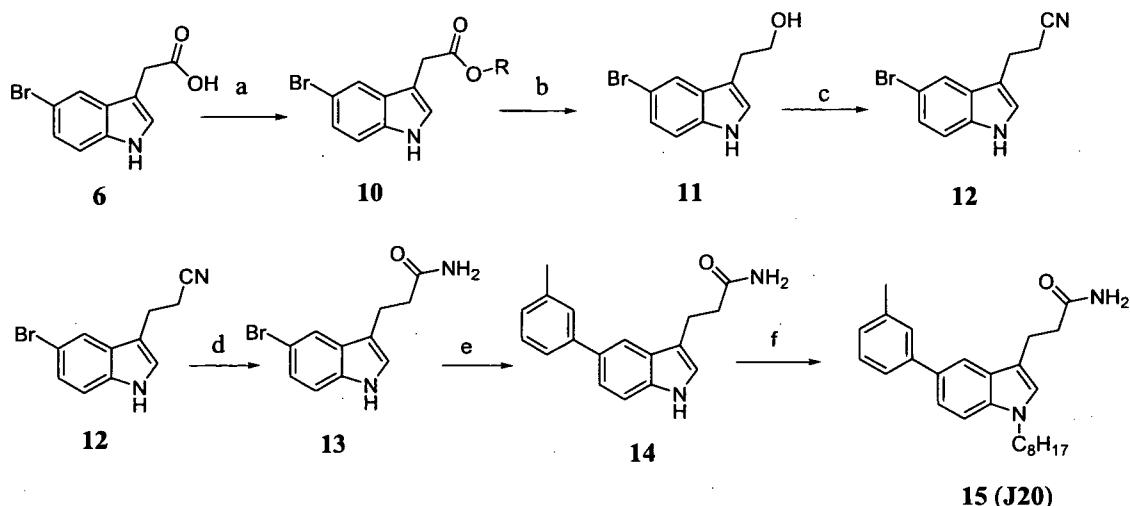
5

Example 4: Synthesis of Compounds of Series 4, Table 4

[00112]

J3 1-octyl-5-m-tolyl-1H-indole. J3 was prepared by the method described for compound **26** in Example 5, Scheme 6. MS-APCI: [M+1]⁺ 320.3 (320.4) δ_H (CD₃OD, 300 MHz): 0.91 (t, 3 H, *J* 18 Hz, CH₃), 1.20-1.30 (m, 12 H, CH₂), 1.85 (t, 2 H, *J* 15 Hz, CH₂), 2.41 (s, 3 H, CH₃), 4.17 (t, 2 H, *J* 12 Hz, CH₂), 6.48 (d, 1 H, *J* 3 Hz, ArH), 7.10 (d, 1 H, *J* 6 Hz, ArH), 7.20 (d, 1 H, *J* 3 Hz, ArH), 7.31 (t, 1 H, *J* 15 Hz, ArH), 7.40-7.45 (m, 4 H, ArH), 7.76 (s, 1 H, ArH) δ_c (CD₃OD, 300 MHz): 13.6, 20.8, 22.8, 27.1, 29.4, 29.5, 30.6, 32.1, 46.4, 101.3, 109.8, 119.2, 121.1, 124.4, 127.0, 128.0, 128.7, 128.9, 129.8, 133.0, 136.2, 138.4, 143.2

Scheme 3: Preparation of homologated Cysmethynil (J20)



(a) MeOH, H₂SO₄, reflux (1 h), (b) LiAlH₄, THF, rt (30 min), (c) TEA, MsCl, CH₂Cl₂, 0°C (30 min), (d) KOH, t-BuOH, reflux (3 h) (e) meta-substituted phenylboronic acid, Pd(PPh₃)₄, NaHCO₃, EtOH/toluene, reflux (1-6 h) (f) bromooctane, NaH, DMF, rt (1.5h) 53-58°C (3-6 h),

15

[00113] Preparation of ethyl or methyl 2-(5-bromo-1H-indol-3-yl) acetate (10).

To a solution of **6** (4 mmol) in 20 ml of alcohol were added 10 drops of concentrated sulphuric acid. The mixture was heated under reflux with continuous stirring for a period of 1-1.5 h. Following reflux, the reaction mixture was cooled to room temperature and evaporated in vacuo. The residue was added with a saturated solution of NaHCO₃ (50 mL) to neutralize acid, and the resulting alkaline aqueous mixture was extracted with EtOAc (3 x 50 mL) and dried

over Na₂SO₄. Evaporation of the solvent gave a residue which was purified by flash silica gel column chromatography. Elution with CHCl₂ yielded the corresponding ester **10** (86-89%) as off-white solid.

[00114] Preparation of methyl 2-(5-bromo-1H-indol-3-yl)ethanol (11). To a solution of **10** (4 mmol) in anhydrous THF (50 mL), LiAlH₄ (16 mmol) was added in portions and the reaction mixture was stirred at rt for 30 min. The excess of LiAlH₄ was destroyed with sat. aq. solution of Na₂SO₄ at 0°C, filtered, and washed with THF (5x20 mL). The combined filtrates were concentrated under reduced pressure, the residue was acidified to pH=6 with 10% HCl and extracted with CHCl₃ (5x20 mL). The combined organic layers were dried (Na₂SO₄), filtered, evaporated to dryness, and purified by flash silica gel column chromatography to obtain alcohol **11** (yield 83 %)

[00115] Preparation of 3 methyl 2-(5-bromo-1H-indol-3-yl) propanenitrile (12). To a solution of alcohol **11** (0.76g, 3.2 mmol), triethylamine (0.9ml) in anhydrous CH₂Cl₂ (20 mL), mesyl chloride (0.55mL) was added, and the reaction mixture was stirred at 0°C for 30 min. under N₂. After dilution with glacial 5 % NaOH solution (40 mL) the mixture was extracted with CH₂Cl₂ (3x40 mL). The combined organic layers were washed with water (10 mL), dried (Na₂SO₄), evaporated to dryness under reduced pressure, gives residue, The residue was dissolved in anhydrous DMSO (20 mL), KCN (0.21 g, 3.25 mmol) was added, and the reaction mixture was heated at 100 °C for 1 h. After dilution with ice-water (20 mL), the mixture was extracted with chloroform (4x30 mL), the combined organic layers were washed with water (2x10 mL), dried (Na₂SO₄), and evaporated to dryness under reduced pressure. And purified by flash silica gel column chromatography (100% CHCl₃) to obtain nitrile **12** (75 %)

[00116] Preparation of methyl 2-(5-bromo-1H-indol-3-yl) propanamide (13). This compound prepared similar to **3**. Yield: 82%

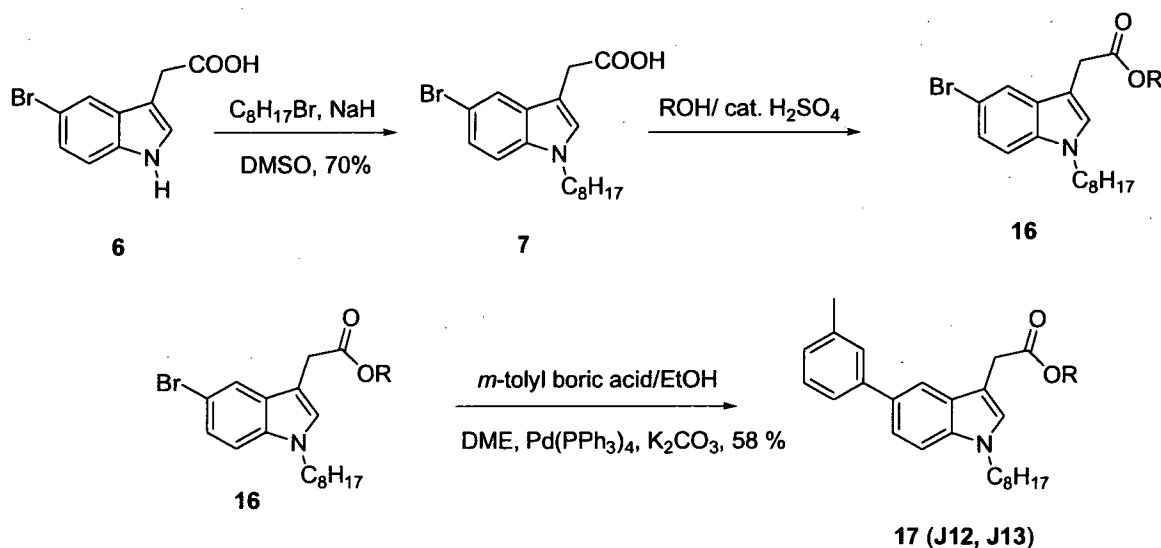
[00117] Preparation of 3-(5-m-tolyl-1H-indol-3-yl) propanamide (14): this compound was prepared by a similar method as **4**.

[00118] Preparation of 3-(1-octyl-5-m-tolyl-1H-indol-3-yl) propanamide (15): this compound was prepared by a similar method as **5**.

[00119] J20 (3-(1-octyl-5-m-tolyl-1H-indol-3-yl) propanamide) MS-APCI: [M+1]⁺ 391.5 (391.3) δ_H (DMSO-d₆, 300 MHz): 0.82 (t, 3 H, *J* 12 Hz, CH₃), 1.22-1.30 (m, 10 H, CH₂), 1.71 (t, 2 H, *J* 12 Hz, CH₂), 2.39 (s, 3 H, CH₃), 2.41 (t, 2 H, *J* 15 Hz, CH₂), 2.92 (t, 2 H, *J* 15 Hz, CH₂), 4.08, (t, 2 H, *J* 15 Hz, CH₂), δ_C (CDCl₃, 75 MHz): 14.1, 21.0, 21.6, 22.6, 27.0,

29.2, 29.2, 30.3, 31.8, 36.7, 46.3, 109.7, 113.6, 117.3, 121.4, 124.5, 126.1, 127.1, 128.0, 128.2, 128.6, 132.4, 135.9, 138.2, 142.6, 175.4

Scheme 4: Preparation of esters (J12 and J13)



[00120] Preparation of ethyl or methyl 2-(5-bromo-1H-indol-3-yl) acetate (16):

Synthetic procedure was similar to compound 10.

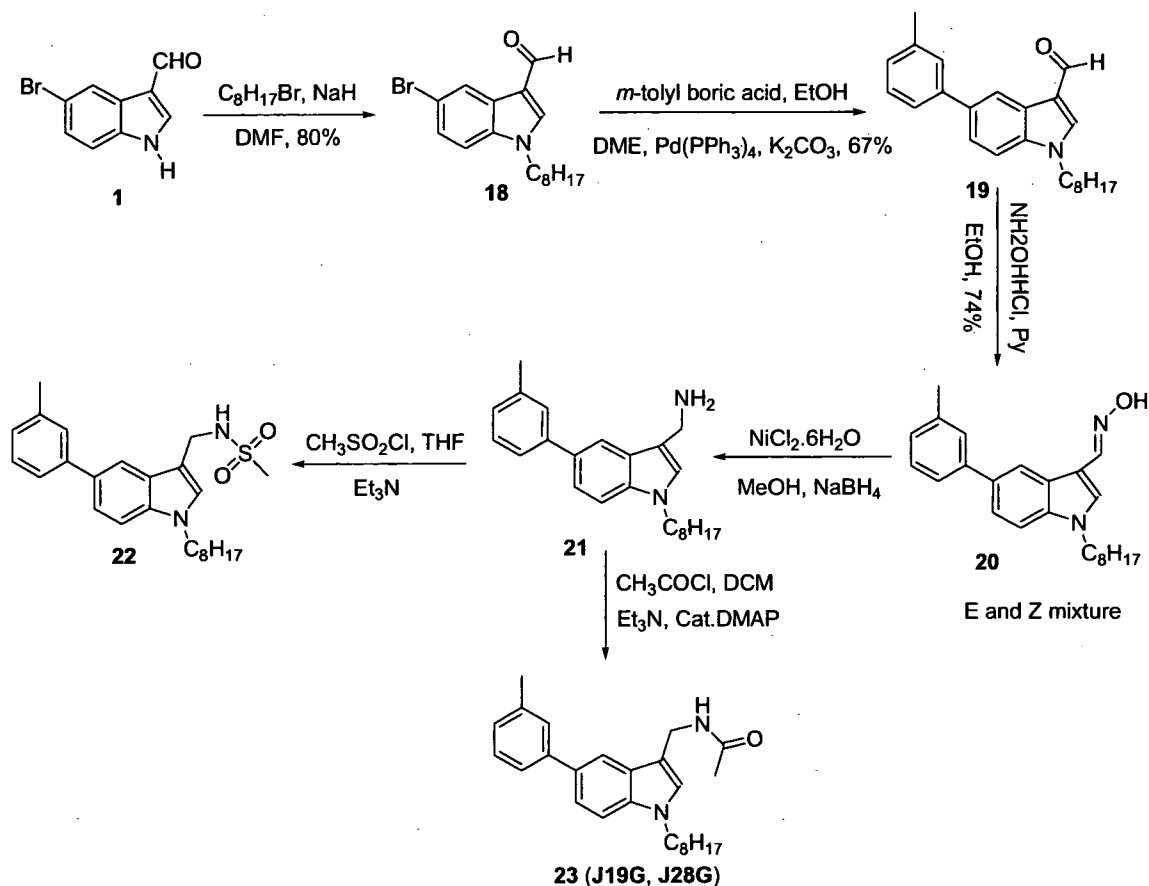
[00121] Preparation of compound (17): Compound 17 was prepared by a similar method as described for 26.

[00122] J12 (methyl 2-(1-octyl-5-m-tolyl-1H-indol-3-yl) acetate) MS-APCI: $[M+1]^+$ 392.5 (392.5) δ_H (CDCl₃, 300 MHz): 0.85 (t, 3 H, *J* 12 Hz, CH₃), 1.26-1.32 (m, 10 H, CH₂), 1.82 (t, 2 H, *J* 6 Hz, CH₂), 2.44 (s, 3 H, CH₃), 3.70 (s, 2 H, CH₂), 3.81 (s, 3 H, CH₃), 4.06 (t, 2 H, *J* 15 Hz, CH₂), 7.11 (d, 2 H, *J* 3 Hz, ArH), 7.32-7.37 (m, 2 H, ArH), 7.44 (d, 3 H, *J* 6 Hz, ArH), 7.78 (s, 1 H, ArH) δ_C (CDCl₃, 75 MHz): 14.1, 21.6, 22.6, 27.0, 29.1, 29.2, 30.3, 31.1, 31.8, 46.5, 52.0, 107.0, 109.6, 117.5, 121.5, 124.5, 127.0, 127.3, 128.1, 128.2, 128.5, 132.8, 135.7, 138.1, 142.6, 172.6

[00123] J13 (ethyl 2-(1-octyl-5-m-tolyl-1H-indol-3-yl) acetate) MS-APCI: $[M+1]^+$ 406.5 (406.5) δ_H (CDCl₃, 300 MHz): 0.85 (t, 3 H, *J* 12 Hz, CH₃), 1.19-1.31 (m, 12 H, CH₂), 1.82 (t, 2 H, *J* 6 Hz, CH₂), 2.43 (s, 3 H, CH₃), 3.79 (s, 2 H, CH₂), 4.06 (t, 2 H, *J* 9 Hz, CH₂), 4.13 (q, 2 H, *J* 21 Hz, CH₂), 7.12 (d, 2 H, *J* 3 Hz, ArH), 7.32-7.36 (m, 2 H, ArH), 7.44 (d, 3 H, *J* 6 Hz, ArH), 7.79 (s, 1 H, ArH). δ_C (CDCl₃, 75 MHz): 14.0, 14.2, 21.6, 22.6, 27.0, 29.1, 29.1,

30.3, 31.3, 31.7, 46.5, 60.7, 107.2, 109.6, 117.6, 121.4, 124.5, 127.0, 127.3, 128.2, 128.5, 128.7, 132.7, 135.7, 138.1, 142.6, 172.1

Scheme 5: Preparation of sulphonamides and reverse amides (J19G and J28G)



5

[00124] 5-bromo-1-octyl-1H-indole-3-carbaldehyde (18): experimental procedure is similar to that of compound 25. Yields are quantitative.

[00125] 1-octyl-5-*m*-tolyl-1H-indole-3-carbaldehyde (19): This compound was made by following the general procedure for Suzuki reaction. Similar to compound 26.

10 [00126] (E & Z)-1-octyl-5-*m*-tolyl-1H-indole-3-carbaldehyde oxime (20): 1-octyl-5-*m*-tolyl-1H-indole-3-carbaldehyde (1eq., 1.03 mmol) was refluxed together with hydroxylamine hydrochloride (2.5 eq., 2.57 mmol) and pyridine (2.6 eq. 2.67 mmol) in ethanol (20 mL) until the formyl derivative disappeared from the reaction mixture (TLC), Reaction completed in 2 h. After being cooled to room temperature and diluting with water, the mixture
15 was acidified with 10% HCl and extracted with diethyl ether. The combined organic extracts

were washed successively with 10% HCl and water. After drying (Na_2SO_4), the organic extract was evaporated to a small volume under reduced pressure, triturated with petroleum ether and filtered to obtain the solid product (74 %).

[00127] (1-octyl-5-m-tolyl-1H-indol-3-yl) methanamine (21 / J18): To a solution of $\text{NiCl}_{2.6}\text{H}_2\text{O}$ (182 mg, 0.76 mmol) in methanol (12 ml) was added corresponding oxime **20** (280 mg 0.76 mmol) and NaBH_4 (174 mg, 4.16 mmol) was added in one portion with stirring. After 5 min the black precipitate was filtered off, filtrate concentrated in vacuum to approx. 1/3 of its original volume and poured into 20 ml of water containing 3 ml of ammonia solution. After extraction with ethyl acetate (three time), drying the extract with anhydrous. Na_2SO_4 and evaporation of the solvent, the crude amines **21** obtained as viscous, black oil. This crude product was used as it is further step without any purification.

[00128] N-((1-octyl-5-m-tolyl-1H-indol-3-yl)methyl) methanesulfonamide (22): Methanesulfonyl chloride ($33\mu\text{l}$, 0.434 mmol) was added to a solution of (1-octyl-5-m-tolyl-1H-indol-3-yl)methanamine (152mg, 0.434 mmol) and triethylamine ($91\mu\text{l}$, 0.651 mmol) in THF (4 mL) at 0°C . The reaction mixture was allowed to stir at room temp for 60 min, the precipitate formed was filtered off, the filtrate was concentrated, and the residue was subjected to column chromatography (silica gel, CH_2Cl_2) to give sulphonamide **22** in 61% yield.

[00129] N-((1-octyl-5-m-tolyl-1H-indol-3-yl)methyl)acetamide (23): Acetyl chloride ($44\mu\text{l}$, 0.434 mmol) was added to a solution of (1-octyl-5-m-tolyl-1H-indol-3-yl)methanamine (220mg, 0.628 mmol) and triethylamine ($131\mu\text{l}$, 0.651 mmol) in THF (4 mL) at 0°C . The reaction mixture was allowed to stir at room temp for 60 min, the precipitate formed was filtered off, the filtrate was concentrated, and the residue was subjected to column chromatography (silica gel, CH_2Cl_2) to give sulphonamide **23** in 65% yield.

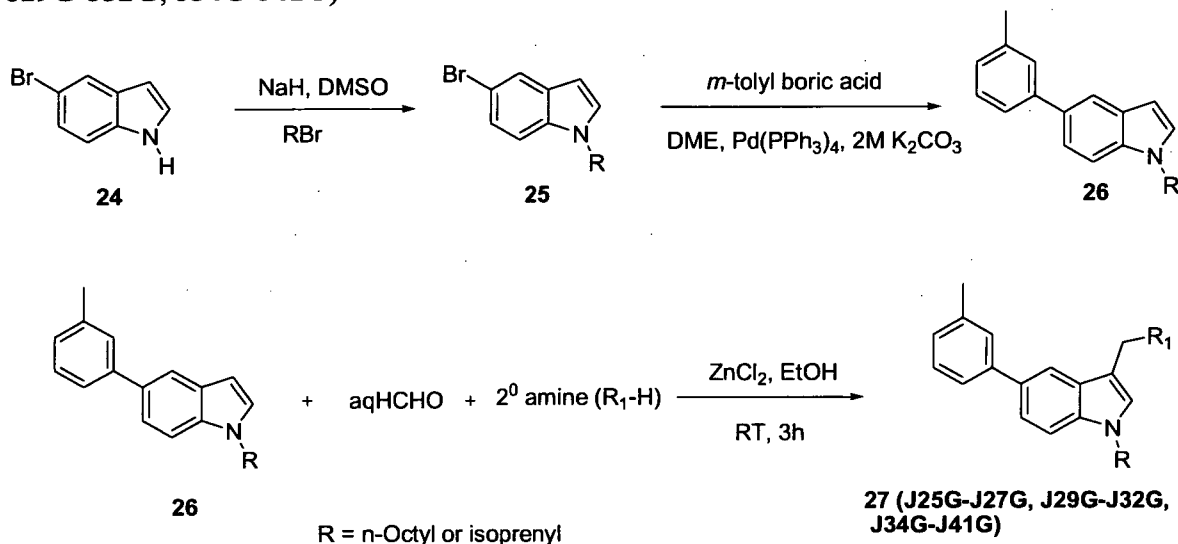
[00130] J19G (N-((1-octyl-5-m-tolyl-1H-indol-3-yl) methyl) acetamide) MS-APCI: $[\text{M}+1]^+$ 391.1 (391.5); 7.71 (1H, s), 7.49-7.05 (6H, m), 7.01 (1H, s), 5.73 (1H, bs), 4.49 (2H, d, J 4.8Hz), 4.04 (2H, t, J 6.9Hz), 2.43 (3H, s), 1.80 (2H, t, J 6.3Hz), 1.95 (3H, s), 1.28-1.24 (10H, m), 0.86 (3H, t, J 7.2Hz). δ_{C} (CDCl_3 , 75 MHz) 169.9, 142.2, 138.2, 135.9, 133.0, 128.6, 128.1, 127.5, 127.1, 124.6, 124.4, 121.7, 117.3, 111.3, 109.8, 46.4, 35.1, 31.7, 30.3, 29.2, 29.1, 27.0, 23.1, 22.6, 21.5, 14.0.

[00131] J28G (N-((1-octyl-5-m-tolyl-1H-indol-3-yl) methyl)methanesulfonamide) MS-APCI: $[\text{M}+1]^+$ 427.3 (427.6); 7.19 (1H, s), 7.50-7.31 (7H, m), 7.15 (1H, s), 4.54(2H, d, J 4.8Hz), 4.10 (2H, t, J 7.2Hz), 2.85 (3H, s), 2.44 (3H, s), 1.84 (2H, t, J 6.3Hz), 1.31-1.25 (10H,

m), 0.87 (3H, t, J 7.2Hz). δ_c (CDCl₃, 75 MHz) 142.1, 138.2, 135.9, 133.3, 128.6, 128.1, 127.8, 127.26, 127.22, 124.4, 121.9, 117.1, 110.1, 109.9, 60.4, 46.5, 40.8, 38.8, 31.7, 30.2, 29.1, 26.9, 22.6, 21.5, 14.0.

Example 5: Synthesis of Compounds of Series 5, Table 5

5 Scheme 6: General experimental procedure for 3^o amine (for compounds J25G-J27G, J29G-J32G, J34G-J41G)



[00132] 5-Bromo-1-alkyl-1H-indole (25): Sodium hydride (60% in dispersion, 1.2eq.) was added to a solution of 5-bromoindole (1eq) in anhydrous DMSO at room temperature (r.t.) with stirring. After 1 h stirring at the same temperature, 1-bromooctane (or Isoprenyl chloride) was added to the solution. The mixture was stirred at the same temperature for 3 h. After addition of water, the mixture was extracted with dichloromethane. The organic layer was washed with brine, dried over anhydrous Na₂SO₄ and evaporated under reduced pressure. The residue was chromatographed on a silica gel column using Ethyl acetate: n-hexane to give **25** in quantitative yield.

[00133] 1-Alkyl-5-*m*-tolyl-1H-indole (26): To a solution of 5-bromo-1-alkyl-1H-indole (4 mmol, 1 eq.) in 15 ml DME was added Pd(PPh₃)₄ (0.2 mmol, 0.05 eq.) and the mixture was stirred under argon for 15 min. A solution of *m*-tolyl boric acid (4 mmol, 1 eq.) in 4mmL EtOH (in case of **J36G** and **J37G** *o*-tolyl boric acid and *p*-tolyl boric acid were added subsequently) was added, the mixture was stirred for another 15 min, and then 2M aqueous Na₂CO₃ (15mL) was added. The resulting mixture was refluxed for 5 h under argon and cooled, and the organic solvent was removed under reduced pressure. The resulting suspension was extracted with CH₂Cl₂ and dried over Na₂SO₄, and the solvent was evaporated. The residue was

chromatographed on silica gel eluted with Ethyl acetate and n-hexane to yield the 1-octyl-5-*m*-tolyl-1H-indole (~80%).

[00134] J18 (1-octyl-5-*m*-tolyl-1H-indol-3-yl) methanamine

The synthesis of **J18** (also known as compound 21) was described in Scheme 5, under Series 4.

5 MS-APCI: $[M+1]^+$ 348.3 (348.5) δ_H (DMSO- d_6 , 300 MHz): 0.82 (t, 3 H, $J = 9$ Hz, CH₃), 1.22-1.30 (m, 10 H, CH₂), 1.72 (t, 2 H, $J = 9$ Hz, CH₂), 2.39 (s, 3 H, CH₃), 3.93 (s, 2 H, CH₂), 4.12, (t, 2 H, $J = 12$ Hz, CH₂), 7.10-7.49 (m, 7H, ArH), 7.87 (s, 1H, ArH) δ_H (DMSO- d_6 , 75 MHz): 14.0, 21.5, 22.6, 27.0, 29.1, 29.2, 30.3, 31.7, 46.4, 109.7, 117.2, 121.5, 124.4, 126.6, 127.1, 127.3, 128.1.

10 **[00135] Preparation of indole 3⁰ amines (27):** In a round flask was charged with secondary amine (1 mmol, 1eq), EtOH (3 mL), zinc chloride (1.5 mmol), formaldehyde (1 eq., 1 mmol, 36% aq.), and 1-octyl-5-*m*-tolyl-1H-indole (3). The mixture was stirred for a period of 10h (over night). After dilution with water, the mixture was basified with aq. 4M NaOH and extracted three times with ethyl acetate. Ethyl acetate was evaporated under reduced pressure.

15 The residue was chromatographed quickly using Dichloromethane/Methanol or Ethyl acetate and n-hexane.

[00136] J17G (N-ethyl-N-((1-octyl-5-*m*-tolyl-1H-indol-3-yl) methyl) ethanamine)

Yield 68% MS-APCI: $[M]^+$ 404.9 (404.6); δ_H (CDCl₃, 300 MHz) 7.88 (1H, s, ArH), 7.44-7.39 (3H, m, ArH), 7.30 (1H, s, ArH), 7.23 (1H, s, ArH), 7.09 (1H, d, J 6.9Hz, ArH), 7.04 (1H, s), 20 4.06 (2H, t, J 7.2Hz), 3.81 (2H, s), 2.56 (4H, q, J 6.9Hz), 2.41 (3H, s), 1.81 (2H, t, J 6.9Hz), 1.28-1.23 (10H, m), 1.08 (6H, t, J 7.2Hz), 0.84 (3H, t, J 4.8Hz). δ_C (CDCl₃, 75 MHz) 142.8, 138.0, 135.7, 132.4, 129.1, 128.5, 128.2, 127.7, 126.9, 124.5, 121.1, 118.1, 112.3, 109.4, 47.8, 46.6, 46.3, 31.7, 30.2, 29.2, 29.2, 27.0, 22.6, 21.6, 14.0, 12.1. Found (calcd. for C₂₈H₄₈N₂) C 83.12 (83.11), H 9.59 (9.96).

25 **[00137] J25G** (N,N-dimethyl(1-octyl-5-*m*-tolyl-1H-indol-3-yl) methanamine) Yield

61 % MS-APCI: $[M+1]^+$ 377.3 (377.5); δ_H (CDCl₃, 300 MHz) 7.84 (1H, s), 7.46-7.42 (3H, m), 7.36 (1H, s), 7.32 (1H, d, J 4.5Hz), 7.11 (1H, d, J 7.5Hz), 7.07 (1H, s), 4.09 (2H, t, J 7.2Hz), 3.66 (2H, s), 2.43 (3H, s), 2.29 (6H, s), 1.84 (2H, t, J 6.6Hz), 1.31-1.25 (10H, m), 0.86 (3H, t, J 5.7Hz). δ_C (CDCl₃, 75 MHz) 142.7, 138.0, 135.7, 132.6, 128.8, 128.4, 128.2, 127.9, 30 126.9, 125.5, 121.2, 117.8, 111.8, 109.4, 54.2, 46.3, 45.2, 31.7, 30.2, 29.1, 29.1, 26.9, 22.5, 21.5, 14.0

[00138] J26G (N-isopropyl-N-((1-octyl-5-m-tolyl-1H-indol-3-yl) methyl) propan-2-amine) Yield 62 % MS-APCI: $[M+1]^+$ 433.0 (433.6) δ_H (CDCl₃, 300 MHz) 8.08 (1H, s), 7.46-7.30 (4H, m), 7.1 (2H, d, *J* 5.4Hz), 7.01 (1H, s), 4.05 (2H, t, *J* 7.2Hz), 3.85 (2H, s), 3.13 (2H, p, *J* 6.6Hz), 2.41 (3H, s), 1.80 (2H, t, *J* 5.7Hz), 1.28-1.24 (10H, m), 1.07 (12H, d, *J* 6.3Hz), 0.86 (3H, t, *J* 6.9Hz). δ_C (CDCl₃, 75 MHz) 142.9, 138.0, 136.1, 131.8, 128.5, 128.3, 128.1, 127.3, 126.7, 124.4, 120.9, 118.5, 115.7, 109.3, 47.3, 46.3, 40.4, 31.7, 30.3, 29.2, 29.2, 27.0, 22.6, 21.6, 20.6, 14.0.

[00139] J27G (N-((1-octyl-5-m-tolyl-1H-indol-3-yl) methyl)-N-propylpropan-1-amine) Yield 65 % MS-APCI: $[M]^+$ 433.6 (433.6); δ_H (CDCl₃, 300 MHz) 7.90 (1H, s), 7.46-7.41 (3H, m), 7.33 (2H, d, *J* 8.4Hz), 7.11 (1H, d, *J* 7.5Hz), 7.02 (1H, s), 4.07 (2H, t, *J* 7.2Hz), 3.79 (2H, s), 2.42 (3H, s), 2.42 (2H, t, *J* 4.2Hz), 1.82 (2H, t, *J* 5.7Hz), 1.54 (4H, q, *J* 7.5Hz), 1.28-1.24 (10H, m), 0.87 (9H, t, *J* 7.2H). δ_C (CDCl₃, 75 MHz) 142.7, 138.0, 135.8, 132.2, 128.9, 128.4, 128.1, 127.6, 126.8, 124.4, 121.0, 118.2, 112.6, 109.3, 55.8, 49.2, 46.3, 31.7, 30.2, 29.1, 29.1, 27.0, 22.6, 21.5, 20.3, 14.0, 12.0.

[00140] J29G (N-methyl-N-((1-octyl-5-m-tolyl-1H-indol-3-yl) methyl) propan-2-amine) Yield 52 % MS-APCI: $[M+1]^+$ 405.5 (405.6); δ_H (CDCl₃, 300 MHz) 7.87 (1H, s), 7.46-7.41 (3H, m), 7.32 (2H, d, *J* 8.4Hz), 7.10 (1H, d, *J* 7.5Hz), 7.07 (1H, s), 4.06 (2H, t, *J* 6.9Hz), 3.76 (2H, s), 2.98 (1H, p, *J* 6.6Hz), 2.42 (3H, s), 2.23 (3H, s), 1.81 (2H, t, *J* 6.3Hz), 1.30-1.24 (10H, m), 1.11 (6H, d, *J* 6.6Hz), 0.86 (3H, t, *J* 6.9Hz). δ_C (CDCl₃, 75 MHz) 142.8, 138.0, 135.8, 132.5, 128.8, 128.5, 128.2, 127.8, 126.9, 124.5, 121.2, 117.9, 112.6, 109.5, 52.7, 48.3, 46.3, 36.8, 31.7, 30.3, 29.2, 29.2, 27.0, 22.6, 21.6, 18.0, 14.1.

[00141] J30G (3-((4-methylpiperazin-1-yl) methyl)-1-octyl-5-m-tolyl-1H-indole) Yield 87 % MS-APCI: $[M]^+$ 432.6 (432.6); δ_H (CDCl₃, 300 MHz) 7.89 (1H, s), 7.46-7.41 (3H, m), 7.33-7.29 (2H, m), 7.05 (1H, s), 7.01 (1H, d, *J* 7.2Hz), 4.04 (2H, t, *J* 6.9Hz), 3.73 (2H, s), 2.54-2.47 (8H, m), 2.42 (3H, s), 2.25 (3H, s), 1.80 (2H, t, *J* 5.7Hz), 1.28-1.24 (10H, m), 0.86 (3H, t, *J* 5.4Hz). δ_C (CDCl₃, 75 MHz) 142.7, 138.1, 135.8, 132.6, 129.0, 128.5, 128.2, 128.0, 126.9, 124.5, 121.3, 118.1, 111.2, 109.5, 55.2, 53.3, 53.0, 46.3, 46.0, 31.7, 30.2, 29.2, 27.0, 22.6, 21.6, 14.1.

[00142] J31G (1-octyl-3-(pyrrolidin-1-ylmethyl)-5-m-tolyl-1H-indole) Yield 71 % MS-APCI: $[M+1]^+$ 403.5 (403.6); δ_H (CDCl₃, 300 MHz) 7.85 (1H, s), 7.46-7.41 (3H, m), 7.32 (2H, d, *J* 8.1Hz), 7.10 (1H, s), 7.01 (1H, d, *J* 7.2Hz), 4.04 (2H, t, *J* 7.2Hz), 3.87 (2H, s), 2.61

(4H, bs), 2.42 (3H, s), 1.78 (6H, bs), 1.29-1.24 (10H, m), 0.86 (3H, t, J 6.3Hz). δ_c (CDCl₃, 75 MHz) 142.7, 138.1, 135.6, 132.6, 128.7, 128.5, 128.2, 127.9, 127.0, 124.6, 121.2, 117.7, 112.0, 109.5, 54.0, 50.1, 46.4, 31.8, 30.3, 29.26, 29.22, 27.0, 23.5, 22.6, 21.6, 14.1.

[00143] **J32G** (1-octyl-3-(piperidin-1-ylmethyl)-5-*m*-tolyl-1H-indole) Yield 78 %

5 MS-APCI: $[M+H]^+$ 417.5 (417.6); δ_H (CDCl₃, 300 MHz) 7.87 (1H, s), 7.46-7.41 (3H, m), 7.34-7.32 (2H, m), 7.11 (1H, d, J 7.2Hz), 7.07 (1H, s), 4.06 (2H, t, J 6.9 Hz), 3.72 (2H, s), 2.45 (3H, s), 2.46-2.43 (4H, m), 1.84 (2H, t, J 6.3Hz), 1.58-1.55 (4H, m), 1.41-1.22 (12H, m), 0.86 (3H, t, J 6.9 Hz). δ_c (CDCl₃, 75 MHz) 142.8, 138.1, 135.6, 132.5, 129.2, 128.5, 128.28, 128.21, 126.9, 124.5, 121.8, 118.0, 111.2, 109.4, 60.3, 54.3, 53.8, 46.3, 31.7, 30.2, 29.1, 27.0, 26.0, 24.4, 22.6, 21.6, 14.1.

[00144] **J34G** (3-(morpholinomethyl)-1-octyl-5-*m*-tolyl-1H-indole) MS-APCI: $[M]^+$

419.3 (419.6); δ_H (CDCl₃, 300 MHz) 7.90 (1H, s), 7.46 (3H, m), 7.33-7.28 (2H, m), 7.09 (1H, d, J 7.5Hz), 7.01 (1H, s), 4.01 (2H, t, J 6.9Hz), 3.69 (2H, s), 3.68 (4H, t, J 4.8Hz), 2.48 (4H, t, J 4.8Hz), 2.41 (3H, s), 1.78 (2H, t, J 6Hz), 1.27-1.21(10H,m), 0.86(3H,t, J 6.9Hz). δ_c (CDCl₃, 75 MHz) 142.8, 138.1, 135.9, 132.7, 129.0, 128.6, 128.3, 128.1, 127.1, 124.6, 121.4, 118.2, 110.9, 109.6, 67.2, 54.0, 53.7, 46.4, 31.8, 30.3, 29.2, 29.2, 27.0, 22.7, 21.7, 14.2.

Example 6: Synthesis of Compounds of Series 6, Table 6

[00145] **J17G** and **J35-J41G** were prepared similar to the experimental procedure mentioned in Example 5, Scheme 6.

20 [00146] **J17G** (N-ethyl-N-((1-octyl-5-*m*-tolyl-1H-indol-3-yl) methyl) ethanamine) Yield 68% MS-APCI: $[M]^+$ 404.9 (404.6); δ_H (CDCl₃, 300 MHz) 7.88 (1H, s, ArH), 7.44-7.39 (3H, m, ArH), 7.30 (1H, s, ArH), 7.23 (1H, s, ArH), 7.09 (1H, d, J 6.9Hz, ArH), 7.04 (1H, s), 4.06 (2H, t, J 7.2Hz), 3.81 (2H, s), 2.56 (4H, q, J 6.9Hz), 2.41 (3H, s), 1.81 (2H, t, J 6.9Hz), 1.28-1.23 (10H, m), 1.08 (6H, t, J 7.2Hz), 0.84 (3H, t, J 4.8Hz). δ_c (CDCl₃, 75 MHz) 142.8, 138.0, 135.7, 132.4, 129.1, 128.5, 128.2, 127.7, 126.9, 124.5, 121.1, 118.1, 112.3, 109.4, 47.8, 46.6, 46.3, 31.7, 30.2, 29.2, 29.2, 27.0, 22.6, 21.6, 14.0, 12.1. Found (calcd. for C₂₈H₄₈N₂) C 83.12 (83.11), H 9.59 (9.96).

30 [00147] **J35G** (N-ethyl-N-((1-(3-methylbut-2-enyl)-1H-indol-3-yl) methyl) ethanamine) MS-APCI: $[M+1]^+$ 271.5 (271.4); δ_H (CDCl₃, 300 MHz) 7.69 (1H, d, J 7.5Hz), 7.28 (1H, d, J 8.1Hz), 7.18 (1H, t, J 6.9Hz), 7.10 (1H, d, J 7.2Hz), 7.04 (1H, s), 5.36 (1H, t, J 6.6Hz), 4.64 (2H, d, J 6.6Hz), 3.77 (2H, s), 2.56 (4H, q, J 6Hz), 1.80 (3H, s), 1.74 (3H, s), 1.08

(6H, t, J 7.2Hz). δ_c (CDCl₃, 75 MHz) 136.1, 135.9, 128.8, 126.8, 121.2, 120.1, 119.4, 118.8, 111.6, 109.3, 47.8, 46.5, 44.0, 40.9, 25.6, 18.0, 11.8.

[00148] J36G (N-ethyl-N-((1-octyl-5-*o*-tolyl-1H-indol-3-yl) methyl) ethanamine)

Yield 72% MS-APCI: $[M+H]^+$ 405.7 (405.6); δ_H (CDCl₃, 300 MHz) 7.63 (1H, s, ArH), 7.33-7.22 (9H, m, ArH), 7.16 (1H, d, J 8.4Hz, ArH), 7.08 (1H, s), 4.09 (2H, t, J 7.2Hz), 7.39 (2H, s), 2.56 (4H, q, J 7.2Hz), 2.32 (3H, s), 1.85 (2H, t, J 6.9Hz), 1.32-1.26 (10H, m), 1.08 (6H, t, J 7.2Hz), 0.87 (3H, t, J 4.8Hz). δ_c (CDCl₃, 75 MHz) 143.2, 135.7, 135.2, 132.6, 130.3, 130.1, 128.4, 127.7, 126.5, 125.5, 122.9, 119.9, 111.5, 108.7, 47.7, 46.5, 46.3, 31.7, 30.2, 29.1, 29.1, 27.0, 22.6, 20.7, 14.0, 11.9. Found (calcd. for C₂₈H₄₈N₂) C 83.01 (83.11), H 9.21 (9.96).

[00149] J37G (N-ethyl-N-((1-octyl-5-*p*-tolyl-1H-indol-3-yl) methyl) ethanamine)

Yield 65% MS-APCI: $[M+H]^+$ 405.3 (405.6); δ_H (CDCl₃, 300 MHz) 7.87 (1H, s), 7.55 (2H, d, J 7.8Hz), 7.42 (2H, d, J 8.1Hz), 7.33 (1H, d, J 8.4Hz), 7.24 (2H, d, J 7.8Hz), 7.06 (1H, s), 4.08 (2H, t, J 6.9Hz), 3.81 (2H, s), 2.54 (4H, q, J 6.9Hz), 2.39 (2H, s), 1.83 (2H, t, J 6.6Hz), 1.31-1.29 (10H, m), 1.10 (6H, t, J 7.2Hz), 0.86 (3H, t, J 6.9Hz). δ_c (CDCl₃, 75 MHz) 139.9, 135.7, 135.5, 132.2, 129.3, 129.0, 127.8, 127.2, 121.0, 117.7, 111.8, 109.4, 47.7, 46.8, 46.3, 31.7, 30.2, 29.1, 29.1, 26.9, 22.5, 21.0, 14.0, 11.9.

[00150] J38G (N-ethyl-N-((1-(3-methylbut-2-enyl)-5-*m*-tolyl-1H-indol-3-yl) methyl) ethanamine)

MS-APCI: $[M+1]^+$ 361.1 (361.5); δ_H (CDCl₃, 300 MHz) 7.88 (1H, s), 7.46-7.41 (3H, m), 7.34-7.29 (2H, m), 7.11 (1H, d, J 7.2Hz), 7.06 (1H, s), 5.38 (1H, t, J 6.9Hz), 4.67 (2H, d, J 6.6Hz), 3.80 (2H, s), 2.57 (4H, q, J 6.9Hz), 2.43 (3H, s), 1.82 (3H, s), 1.76 (3H, s), 1.09 (6H, t, J 7.2Hz). δ_c (CDCl₃, 75 MHz) 142.7, 138.1, 136.1, 135.6, 132.6, 129.2, 128.5, 128.2, 127.7, 126.9, 124.5, 121.2, 119.9, 117.8, 111.6, 109.6, 47.7, 46.5, 44.1, 25.6, 21.6, 18.0, 11.7. C82.92% (83.28) H8.85 (8.95)

[00151] J39G (1-(3-methylbut-2-enyl)-3-(piperidin-1-ylmethyl)-5-*m*-tolyl-1H-indole)

Yield 71 % MS-APCI: $[M+1]^+$ 373.3 (373.5); δ_H (CDCl₃, 300 MHz) 7.86 (1H, s), 7.46-7.42 (3H, m), 7.34 (2H, d, J 7.2Hz), 7.12 (1H, d, J 10.2Hz), 7.03 (1H, s), 5.39 (1H, t, J 5.1Hz), 4.68 (2H, d, J 6.6Hz), 3.73 (2H, s), 2.49 (4H, bs), 2.44 (3H, s), 1.83 (3H, s), 1.77 (3H, s), 1.42 (2H, m), 0.86 (4H, m). δ_c (CDCl₃, 75 MHz) 142.8, 138.1, 136.1, 135.6, 132.6, 129.4, 128.5, 128.2, 127.8, 126.9, 124.5, 121.1, 120.0, 118.0, 111.4, 109.5, 54.3, 53.8, 44.1, 26.0, 25.6, 24.4, 21.6, 18.0.

[00152] J40G (N-ethyl-N-((5-fluoro-1-octyl-1H-indol-3-yl) methyl) ethanamine) MS-APCI: $[M+1]^+$ 330.0 (333.4); δ_H (CDCl₃, 300 MHz) 7.35 (1H, dd, J_1 10.5Hz, J_2 =0.9Hz), 7.18 (1H, dd, J_1 9Hz, J_2 =4.2Hz), 7.05 (1H,s), 6.91 (1H, dt, J_1 9Hz, J_2 2.4Hz), 4.03 (2H, t, J 6.9Hz), 3.70 (2H, s), 2.53 (4H, q, J 6.9Hz), 1.79 (2H, t, J 6.9Hz), 1.28-1.24 (10H, m), 1.07 (6H, t, J 7.2Hz), 0.86 (3H, t, J 6.3Hz). δ_C (CDCl₃, 75 MHz) 159.0, 155.9, 132.8, 128.6, 111.9, 109.7, 109.3, 104.6, 47.9, 46.5, 46.4, 31.7, 30.1, 29.1, 29.1, 26.9, 22.5, 14.0, 11.8. C 75.68% (75.86) H 9.85% (10.00)

[00153] J41G (N-ethyl-N-((5-fluoro-1-(3-methylbut-2-enyl)-1H-indol-3-yl) methyl) ethanamine) MS-APCI: $[M]^+$ 289.0 (289.4); δ_H (CDCl₃, 300 MHz) 7.34 (1H,dd, J_1 9.6Hz, J_2 2.1Hz), 7.17 (1H, d, J 3.6Hz), 7.09 (1H, s), 6.91 (1H,dd, J_1 8.7Hz, J_2 4.2Hz), 5.34 (1H, t, J 6.6Hz), 4.64 (2H, d, J 6.9Hz), 3.84 (2H, s), 2.66 (4H,q, J 7.2Hz), 1.81 (3H,s), 1.76 (3H,s), 1.16 (6H, t, J 6.9Hz). δ_C (CDCl₃, 75 MHz) 159.1, 156.0, 136.3, 132.8, 128.4, 119.7, 111.6, 111.5, 110.0, 109.8, 109.7, 109.4, 104.5, 104.2, 47.9, 46.4, 44.3, 25.6, 17.9, 11.7.

Example 7: Biological Evaluation

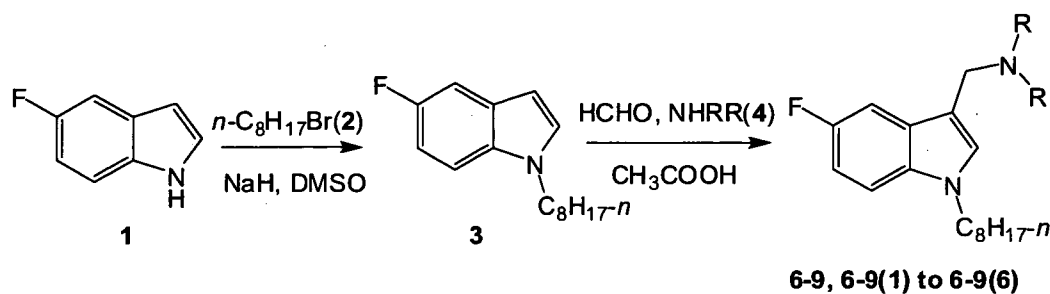
[00154] Measurement of ICMT activity. Icmt activity was determined by following incorporation of ³H from [³H]AdoMet (Amersham Biosciences) into the small molecule substrate biotin-S-farnesyl L-cysteine (BFC). Inhibitors were first incubated at 37 °C for 20 min, with the Sf9 membranes containing ICMT. An assay mixture containing 4μM BFC and 5μM [³H]AdoMet in 100 mM Hepes, pH 7.4 and 5 mM MgCl₂ was added to initiate the reaction. Reactions were carried out at 37 °C for 20 min, and terminated by addition of 10 % Tween 20 and streptavidin beads (GE Healthcare, 10uL of packed beads suspended in 500μL of 20 mM NaH₂PO₄, pH 7.4, containing 150 mM NaCl). The mixtures were mixed by gentle agitation overnight at 4°C. The beads were harvested by centrifugation in a tabletop microcentrifuge at 10,000 rpm for 5 min and washed three times with 500μL of 20 mM NaH₂PO₄, pH 7.4, containing 150 mM NaCl. The beads were then suspended in the same buffer, transferred to scintillation vials, and radioactivity determined.

[00155] Cell Culture and Proliferation Assays. The MDA-MB-231 human breast cells were maintained at 37 °C with 5% CO₂ in DMEM (Sigma) supplemented with 10% fetal bovine serum (FBS, Hyclone), 50 U/ml penicillin (Gibco), and 50 μg/ml streptomycin (Gibco). For proliferation assays, cells were seeded at 20% confluency in DMEM containing 5% FBS in 96-well plates for 24 h prior to treatment with specific agents (e.g. cysmethynil) or vehicle at various concentrations for 72 h. The relative number of the live cells was determined using the

CellTiter® 96 AQueous One Solution Cell Proliferation Assay (Promega). Each condition was performed in triplicate, and data presented represent that obtained from at least two separate experiments.

Example 8: Synthesis of amine analogs of 1-(5-fluoro-1-octyl-1H-indol-3-yl) -N,N-diethylmethanamine (6-9)

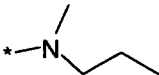
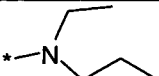
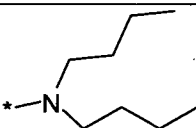
[00156] Six analogs of 1-(5-fluoro-1-octyl-1H-indol-3-yl)-N,N-diethylmethanamine were synthesized by the reactions shown in Scheme 7. The structure of 1-(5-fluoro-1-octyl-1H-indol-3-yl) -N,N-diethylmethanamine (6-9) and its analogues are illustrated in Table 7 below.



10 Scheme 7

Table 7: Structures of 6-9 and its analogs 6-9(1) to 6-9(6)

Entry	*-NRR
6-9(1)	
6-9	
6-9(2)	
6-9(3)	
6-9(4)	
6-9(5)	
6-9(6)	

6-9(7)	
6-9(8)	
6-9 (9)	

Experimental Section

[00157] Reagents were purchased from Sigma-Aldrich Chemical Company Inc or Alfa Aesar and used without further purification. ¹H NMR (300 MHz) and ¹³C NMR (75 MHz) spectra were measured on a Bruker Spectrospin 300 Ultrashield magnetic resonance spectrometer using CDCl₃ as the solvent. Chemical shifts (δ) were reported in ppm and referenced to residual deuterated solvents. Coupling constants (*J*) were reported in Hz. Reactions were monitored by thin layer chromatography (TLC, Silica Gel 60 F254, Merck) with ultraviolet light as visualizing agent. Column chromatography was carried out with Silica Gel 60 (0.04–0.06 mm). Mass spectra were recorded in positive ion mode using electro spray ionization (ESI) or high-resolution LC-MS (IT TOF). Elemental analysis had carbon and hydrogen values that were within ± 5% of theoretical values.

General procedure for the synthesis of 5-fluoro-1-octyl-1*H*-indole (3)

[00158] The procedure for the synthesis of compound 3 mentioned in Scheme 7 can be carried out as described in Na, Y. M.; Le Borgne, M.; Pagniez, F.; Le Baut, G.; Le Pape, P., *Eur. J. Med. Chem.* 2003, 38, 75-87. Semi-automatic high-throughput determination of plasma protein binding using a 96-well plate filtrate assembly and fast liquid chromatography–tandem mass spectrometry.

[00159] To the solution of 5-fluore-1*H*-indole (1, 5 mmol, 1 equiv.) in anhydrous dimethylsulfoxide (DMSO) was added NaH (60% in mineral oil dispersion, 6 mmol, 1.2 equiv.) at room temperature. The mixture was stirred for about 1 h at the same temperature, then 1-bromooctane (2, 6 mmol, 1.2 equiv.) was added and the mixture was stirred for 4 h. Water was added to stop the reaction. The mixture was extracted by dichloromethane and the organic layer was washed with brine, dried (Na₂SO₄), filtered, and evaporated. The residue was purified by column chromatography of silica gel to get yellow oil. Yield: 85.0 %. ¹H NMR (300 MHz,

CDCl₃): δ 0.85 (t, J = 6.9 Hz, 3 H), 1.23-1.27 (m, 10 H), 1.79 (t, J = 6.9 Hz, 2 H), 4.06 (t, J = 6.9 Hz, 2 H), 6.41 (d, J = 2.7 Hz, 1 H), 6.88-6.95 (m, 1H), 7.10 (d, J = 2.7 Hz, 1 H), 7.09-7.25 (m, 2H). ¹³C NMR (75 MHz, CDCl₃) δ 14.0, 22.5, 26.9, 29.1 (2C), 30.2, 31.7, 46.6, 100.7, 105.4, 109.4, 109.8, 128.6, 129.2, 132.5, 157.6. IT TOF-HRMS calculated for (C₁₆H₂₂FN + H⁺) 248.1814, found 248.1720.

General procedure for the synthesis of *N*-substituted (1-octyl-1*H*-indol-3-yl) methyl amine (6-9, 6-9(1) to 6-9(9))

[00160] The procedure for the synthesis of *N*-substituted (1-octyl-1*H*-indol-3-yl) methyl amine can be carried out as described in Brehm, W. J.; Lindwall, H. G. The preparation of Mannich bases related to gramine. *J. Org. Chem.* 1950, 15, 685-687.

[00161] To the mixture of appropriate secondary amine (4, 0.97 mmol, 1.2 equiv.), 36% aqueous formaldehyde (0.97 mmol, 1.2 equiv.) in acetic acid (5 mL) was added 5-fluoro-1-octyl-1*H*-indole (3, 200mg, 1 equiv.) 0 °C. The reaction mixture was stirred at room temperature overnight. After the reaction was completed, the reaction mixture was basified by 50% NaOH aqueous solution to pH=9 and extracted by dichloromethane (10 mL×3). The combined extracts were washed with brine (20 mL) and dried over Na₂SO₄. The organic layer was concentrated under reduced pressure. The crude product was purified by column chromatography of silica gel using or ethyl acetate/hexane or dichloromethane/methanol as eluent solvent.

[00162] **1-(5-fluoro-1-octyl-1*H*-indol-3-yl)-*N*, *N*-dimethylmethanamine 6-9(1).** Yellow oil. Yield: 71.1 %. ¹H NMR (300 MHz, CDCl₃): δ 0.86 (br, 3 H), 1.25-1.28 (m, 10 H), 1.81 (br, 2 H), 2.28 (s, 6 H), 3.58 (s, 2 H), 4.05 (t, J = 6.9 Hz, 2 H), 6.90-6.96 (m, 1 H), 7.10 (s, 1H), 7.16-7.22 (m, 1 H), 7.30 (d, J = 9.3 Hz, 1H). ¹³C NMR (75 MHz, CDCl₃) δ 14.0, 22.5, 29.1 (2C), 30.1, 31.5, 31.7, 45.0 (2C), 46.5, 54.2, 103.9, 109.8, 111.0, 128.5, 129.0, 132.8, 141.9, 161.0. IT TOF-HRMS calculated for (C₁₉H₃₀FN₂ + H⁺) 305.2393, found 305.2282. Elemental analysis: calc./found (C, H): 74.96, 9.60 74.73, 9.31.

[00163] ***N*-ethyl-*N*-((5-fluoro-1-octyl-1*H*-indol-3-yl)methyl)ethanamine 6-9.** Yellow oil. Yield: 46.1 %. ¹H NMR (300 MHz, CDCl₃): δ 0.86 (t, J = 6.6 Hz, 3 H), 1.10 (t, J = 6.9 Hz, 6 H), 1.28 (br, 10 H), 1.80 (br, 2 H), 2.57 (q, J = 6.9 Hz, 4 H), 3.74 (s, 2 H), 4.04 (t, J = 6.9 Hz, 2 H), 6.93 (t, J = 9.0 Hz, 1 H), 7.11 (s, 1H), 7.17-7.22 (m, 1H), 7.34 (d, J = 9.6 Hz, 1 H). ¹³C NMR (75 MHz, CDCl₃) δ 11.7(2C), 14.0, 22.5, 26.9, 29.1 (2C), 30.1, 31.7, 46.4 (2C), 47.8, 104.4, 109.4, 109.9, 111.2, 128.9, 132.8, 155.9, 159.0. IT TOF-HRMS calculated for

($C_{21}H_{34}FN_2 + H^+$) 333.2706, found 333.2616. Elemental analysis: calc./found (C, H): 75.86, 10.00 75.99, 9.83.

[00164] 5-fluoro-1-octyl-3-(piperidin-1-ylmethyl)-1H-indole 6-9(2). Yellow oil.

Yield: 75.8 %. 1H NMR (300 MHz, $CDCl_3$): δ 0.86 (t, $J = 6.9$ Hz, 3 H), 1.24-1.28 (m, 10 H), 1.42 (d, $J = 4.5$ Hz, 2 H), 1.59 (t, $J = 5.4$ Hz, 4 H), 1.80 (br, 2 H), 2.45 (br, 4 H), 3.65 (s, 2 H), 4.04 (t, $J = 7.2$ Hz, 2 H), 6.93 (t, $J = 8.1$ Hz, 1 H), 7.11 (s, 1H), 7.17-7.22 (m, 1H), 7.35 (d, $J = 1.5$ Hz, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 11.7(2C), 14.0, 22.5, 24.2, 25.8 (2C), 26.9, 29.1 (2C), 30.1, 31.7, 46.5, 53.8, 54.1 (2C), 104.4, 109.7, 109.9, 110.5, 129.0, 132.7, 155.9, 159.1. IT TOF-HRMS calculated for ($C_{22}H_{34}FN_2 + H^+$) 345.2706, found 345.2620. Elemental analysis: calc./found (C, H): 76.70, 9.65 76.43, 9.42.

[00165] 4-((5-fluoro-1-octyl-1H-indol-3-yl)methyl)thiomorpholine 6-9(3). Yellow oil.

Yield: 91.4 %. 1H NMR (300 MHz, $CDCl_3$): δ 0.87 (t, $J = 6.6$ Hz, 3 H), 1.25-1.29 (m, 10 H), 1.80 (br, 2 H), 2.69 (br, 4 H), 2.73 (br, 4 H), 3.66 (s, 2 H), 4.04 (t, $J = 6.9$ Hz, 2 H), 6.94 (t, $J = 8.1$ Hz, 1 H), 7.05 (s, 1 H), 7.18-7.26 (m, 1H), 7.35 (d, $J = 8.1$ Hz, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.0, 22.5, 26.9, 28.0 (2C), 29.1 (2C), 30.1, 31.7, 46.5, 54.3, 54.7 (2C), 104.5, 109.8, 110.4, 128.5, 128.9, 132.7, 155.9, 159.0. ESI-LCMS calculated for ($C_{21}H_{32}FN_2S + Na^+$) 385.20, found 384.90. Elemental analysis: calc./found (C, H): 69.57, 8.62 69.44, H 8.75.

[00166] 4-((5-fluoro-1-octyl-1H-indol-3-yl)methyl)morpholine 6-9(4). Yellow oil.

Yield: 88.5 %. 1H NMR (300 MHz, $CDCl_3$): δ 0.87 (t, $J = 6.9$ Hz, 3 H), 1.24-1.28 (m, 10 H), 1.80 (t, $J = 6.3$ Hz, 2 H), 2.48 (br, 4 H), 3.64 (s, 2 H), 3.69-3.72 (m, 4 H), 4.04 (t, $J = 7.2$ Hz, 2 H), 6.94 (t, $J = 8.7$ Hz, 1 H), 7.07 (s, 1 H), 7.18-7.22 (m, 1H), 7.37 (d, $J = 9.9$ Hz, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.0, 22.5, 26.9, 29.1 (2C), 30.1, 31.7, 46.5, 53.4, 53.9 (2C), 67.0, 104.5, 109.8, 110.2, 128.5, 128.9, 132.9, 156.0, 159.1. ESI-LCMS calculated for ($C_{21}H_{32}FN_2O + H^+$) 347.25, found 347.10. Elemental analysis: calc./found (C, H): 72.80, 9.02 73.05, 8.73.

[00167] 5-fluoro-1-octyl-3-(pyrrolidin-1-ylmethyl)-1H-indole 6-9(5). Yellow oil.

Yield: 67.0 %. 1H NMR (300 MHz, $CDCl_3$): δ 0.86 (t, $J = 6.6$ Hz, 3 H), 1.24-1.28 (m, 10 H), 1.80 (br, 6 H), 2.62 (br, 4 H), 3.81 (s, 2 H), 4.04 (t, $J = 6.9$ Hz, 2 H), 6.93 (t, $J = 8.7$ Hz, 1 H), 7.17-7.22 (m, 2H), 7.30 (d, $J = 9.6$ Hz, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.0, 22.5, 23.4 (2C), 26.9, 29.1 (2C), 30.1, 31.7, 46.5, 50.1, 53.8 (2C), 104.1, 109.8, 111.1, 128.3, 128.9, 132.7, 156.0, 159.1. ESI-LCMS calculated for ($C_{21}H_{32}FN_2 + H^+$) 331.25, found 331.15. Elemental analysis: calc./found (C, H): 76.32, 9.45 76.28, 9.23.

[00168] 5-fluoro-3-((4-methylpiperazin-1-yl)methyl)-1-octyl-1H-indole 6-9(6).

Yellow oil. Yield: 56.4 %. ¹H NMR (300 MHz, CDCl₃): δ 0.86 (t, *J* = 6.6 Hz, 3 H), 1.24-1.28 (m, 10 H), 1.79 (br, 2 H), 2.27 (br, 4 H), 2.45 (br, 7 H), 3.64 (s, 2 H), 4.03 (t, *J* = 6.9 Hz, 2 H), 6.92 (t, *J* = 8.1 Hz, 1 H), 7.06 (s, 1 H), 7.16-7.20 (m, 1H), 7.36 (d, *J* = 8.4 Hz, 1 H). ¹³C NMR (75 MHz, CDCl₃) δ 14.0, 22.5, 26.9, 29.1 (2C), 30.1, 31.6, 45.9, 46.4, 52.8 (2C), 53.3, 55.0 (2C), 104.5, 109.8, 110.7, 128.6, 128.8, 132.8, 155.9, 159.0. ESI-LCMS calculated for (C₂₂H₃₅FN₃ + H⁺) 360.28, found 360.20. Elemental analysis: calc./found (C, H): 73.50, 9.53 73.66, H 9.42.

[00169] N-((5-fluoro-1-octyl-1H-indol-3-yl)methyl)-N-methylpropan-1-amine (6-9(7)).

Yellow oil. Yield: 78.9 %. ¹H NMR (300 MHz, CDCl₃): δ 0.85-0.94 (m, 6 H), 1.25-1.29 (m, 10 H), 1.51-1.64 (m, 2 H), 1.81 (t, *J* = 6.6 Hz, 2 H), 2.21 (s, 3 H), 2.37 (t, *J* = 7.5 Hz, 2 H), 3.62 (s, 2 H), 4.05 (t, *J* = 7.2 Hz, 2 H), 6.90-6.97 (m, 1 H), 7.06 (s, 1H), 7.18-7.22 (m, 1H), 7.33, 7.36 (dd, *J* = 3.2 Hz, 1 H). ¹³C NMR (75 MHz, CDCl₃) δ 11.9, 14.0, 20.7, 22.5, 26.9, 29.1, 30.2, 31.7, 42.1, 46.5, 52.6, 59.5, 104.2, 104.5, 109.4, 109.7, 111.7, 128.7, 132.9, 155.9, 159.1. Elemental analysis: calc./found (C, H): 75.86, 10.00 76.14, 9.52.

[00170] N-ethyl-N-((5-fluoro-1-octyl-1H-indol-3-yl)methyl)propan-1-amine (6-9(8)).

Yellow oil. Yield: 70.7 %. ¹H NMR (300 MHz, CDCl₃): δ 0.85-0.91 (m, 6 H), 1.07 (t, *J* = 7.2 Hz, 3 H), 1.25-1.29 (m, 10 H), 1.48-1.61 (m, 2 H), 1.81 (t, *J* = 6.9 Hz, 2 H), 2.42 (t, *J* = 7.2 Hz, 2 H), 2.53 (q, *J* = 7.2 Hz, 2 H), 3.71 (s, 2 H), 4.05 (t, *J* = 7.2 Hz, 2 H), 6.98-6.96 (m, 1 H), 7.05 (s, 1H), 7.17-7.22 (m, 1H), 7.34, 7.37 (dd, *J* = 2.4 Hz, 1 H). ¹³C NMR (75 MHz, CDCl₃) δ 11.8, 12.0, 14.0, 20.3, 22.6, 26.9, 29.1, 30.2, 31.7, 46.4, 47.1, 48.6, 55.2, 104.4, 104.7, 109.4, 109.7, 112.1, 128.7, 132.9, 155.9, 158.9. Elemental analysis: calc./found (C, H): 76.25, 10.18 76.55, 10.08.

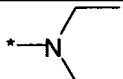
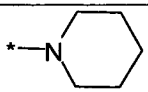
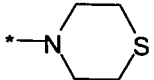
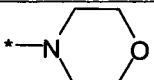
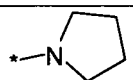
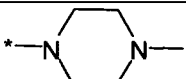
[00171] N-butyl-N-((5-fluoro-1-octyl-1H-indol-3-yl)methyl)butan-1-amine [6-9(9)].

Yellow oil. Yield: 74.8 %. ¹H NMR (300 MHz, CDCl₃): δ 0.86-0.91 (m, 9 H), 1.26-1.36 (m, 14 H), 1.41-1.61 (m, 4 H), 1.80 (t, *J* = 6.9 Hz, 2 H), 2.43 (t, *J* = 7.2 Hz, 4 H), 3.69 (s, 2 H), 4.05 (t, *J* = 7.2 Hz, 2 H), 6.89-6.96 (m, 1 H), 7.04 (s, 1H), 7.17-7.21 (m, 1H), 7.34, 7.37 (dd, *J* = 2.4 Hz, 1 H). ¹³C NMR (75 MHz, CDCl₃) δ 14.03, 14.06, 20.7, 22.6, 26.9, 29.1, 29.2, 29.3, 30.2, 31.7, 46.4, 49.3, 53.4, 104.4, 104.7, 109.3, 109.7, 112.3, 128.6, 132.9, 155.9, 158.9. Elemental analysis: calc./found (C, H): 77.27, 10.63 78.09, 10.40.

Example 9: Evaluation of antiproliferative activity of 6-9, 6-9(1) to 6-9(6) in MDA-MB-231 cells by the MTS colorimetric assay

[00172] Cell Culture and Proliferation Assays. The MDA-MB-231 human breast cells were maintained at 37 °C with 5% CO₂ in DMEM (Sigma) supplemented with 10% fetal bovine serum (FBS, Hyclone), 50 U/ml penicillin (Gibco), and 50 µg/ml streptomycin (Gibco). For proliferation assays, cells were seeded at 20% confluency in DMEM containing 5% FBS in 96-well plates for 24 h prior to treatment with specific agents (e.g. cysmethynil) or vehicle at various concentrations for 72 h. The relative number of the live cells was determined using the CellTiter® 96 AQueous One Solution Cell Proliferation Assay (Promega). Each condition was performed in triplicate, and data presented to date were obtained from one determination. IC₅₀ values were obtained using GraphPad Prism 4.0 and are given in Table 8. The results showed that 6-9(2), 6-9 (5) were comparable in terms of IC₅₀ to 6-9.

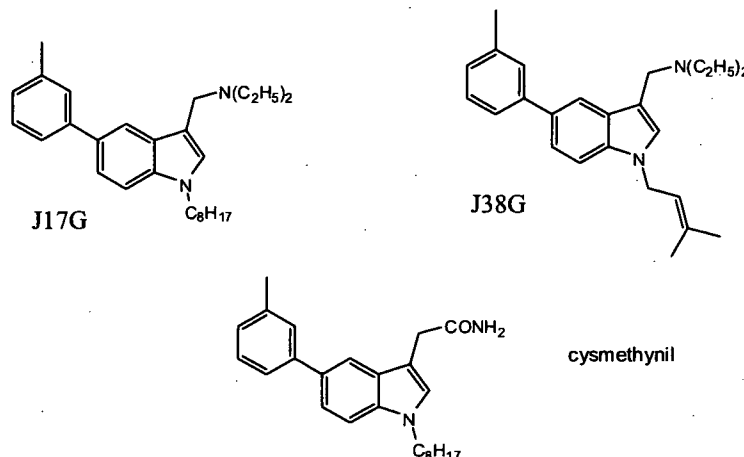
Table 8: IC₅₀ values of 6-9 and its analogs 6-9(1) to 6-9(6)

Entry	*-NRR	IC ₅₀ (µM)
6-9(1)		4.9
6-9		2.0 ^a
6-9(2)		2.3
6-9(3)		ND ^b
6-9(4)		3.2
6-9(5)		2.2
6-9(6)		ND ^b

^a Obtained with re-synthesized 6-9. A determination of an earlier sample of 6-9 gave IC₅₀ of 2.7 µM. IC₅₀ values of cysmethynil were concurrently determined and found to be 13.1 µM and 31.5 µM (2 separate determinations).

^b Not determined because initial screen at a fixed concentration of 10 µM showed approximately 45% inhibition which was low compared to the levels observed with the other compounds.

Example 10: Plasma protein binding of cysmethynil, N-ethyl-N-((1-octyl-5-*m*-tolyl-1H-indol-3-yl) methyl) ethanamine (J17G) and N-ethyl-N-((1-(3-methylbut-2-enyl)-5-*m*-tolyl-1H-indol-3-yl) methyl) ethanamine (J38G)



5 **[00173]** The binding capacities of cysmethynil, N-ethyl-N-((1-octyl-5-*m*-tolyl-1H-indol-3-yl) methyl) ethanamine and N-ethyl-N-((1-(3-methylbut-2-enyl)-5-*m*-tolyl-1H-indol-3-yl) methyl) ethanamine to fetal bovine serum were determined by an ultracentrifugation method (see Fung EN, Chen YH, Lau YY. Semi-automatic high-throughput determination of plasma protein binding using a 96-well plate filtrate assembly and fast liquid chromatography–tandem mass spectrometry. *J Chromatogr B* 795 (2003) 187-194) using 4 different concentrations (1, 4, 10 and 25 μ M) of each compound. Stock solutions were prepared in DMSO at 100 x higher concentrations. A 5% w/v solution of fetal bovine serum in phosphate buffered saline was prepared. An aliquot (10 μ L) of the stock solution was added to 990 μ L of the PBS solution containing 5% fetal bovine serum in a glass tube which was then incubated in a shaking water bath at 37°C for 30 min. 500 μ L of the solution was then transferred to a centrifugal filter device (Amicon Ultra 0.5 ml # UFC503096) and centrifuged at 14 000 g, 15 min. After this time, the filter units were removed and placed (upside down) in a collecting tube containing 477 μ L of PBS. The latter was centrifuged at 2000g, 2 min to obtain the retentate. An aliquot of the retentate was added to an equal volume of acetonitrile containing the internal standard (3-1, 1-octyl-5-*m*-tolyl-1H-indole) and analyzed by HPLC (Wang, M.; Khoo, Y.M.; Zhou, J.; Casey, P.J.; Lee, H.S. A HPLC method for the quantification of cysmethynil, an inhibitor of isoprenylcysteine carboxyl methyltransferase, in mouse plasma. *J. Chromatography B*. 2009, 877, 553-557). The percentage of bound cysmethynil, compounds 4-3 and 6-4 to fetal bovine serum (FBS) are illustrated in Figure 9.

[00174] The results are also given in Table 9 below. It can be seen that compounds J17G and J38G have lower binding capacities than cysmethynil.

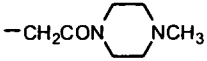
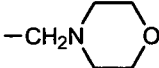
Table 9

	Conc (uM)	% Bound			Average	SD
		Run 1	Run 2	Run 3		
CYS	1	89.27	93.89	87.99	90.38	3.10
	4	94.43	87.59	86.86	89.63	4.18
	10	86.45	90.57	94.62	90.55	4.08
	25	78.11	93.64	91.56	87.77	8.43
				all conc	89.58	
J38G	1	25.31	15.55	26.34	22.40	5.95
	4	38.39	32.39	37.88	36.22	3.33
	10	30.27	21.66	18.52	23.48	6.08
	25	27.47	20.77	30.66	26.30	5.05
				all conc	27.10	
J17G	1	82.96	77.61	84.85	81.81	3.75
	4	72.64	69.93	75.73	72.77	2.90
	10	68.32	64.74	77.38	70.15	6.52
	25	71.39	64.78	72.52	69.56	4.18
				all conc	73.57	

5

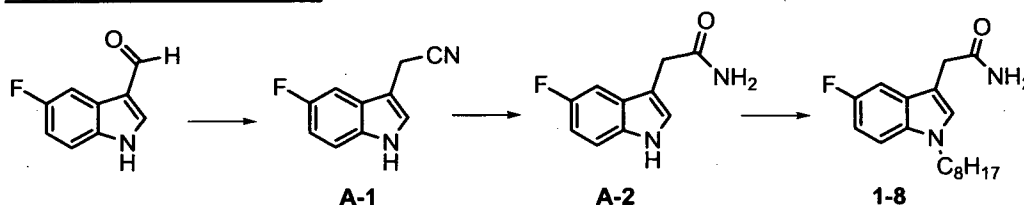
Example 10: Chemical synthesis of target compounds

Table 10

	R ₂	R ₃	R ₁	IC ₅₀ (μM)	
				lcmt inhibition ¹	Antiproliferative activity ¹
1-1 ²	n-octyl	-CH ₂ CONH ₂	m-tolyl	1.5 ± 0.2	21.8 ± 0.8
1-8	n-octyl	-CH ₂ CONH ₂	5-F	7.0 ± 3.4	70 ± 20
3-6	n-octyl		m-tolyl	1.7 ± 0.4	19.7 ± 0.9
3-7	n-octyl	-CH ₂ CONHCH ₃	m-tolyl	2.1 ± 0.4	4.7 ± 0.3
5-1	n-octyl	-CONH ₂	m-tolyl	30 ± 29	>100
5-2 or J20	n-octyl	-CH ₂ CH ₂ CONH ₂	m-tolyl	1.2 ± 0.3	20.7 ± 0.8
6-3	isoprenyl	H	m-tolyl	>100	>100
6-6	isoprenyl		m-tolyl	2.0 ± 0.8	34 ± 3
6-8	isoprenyl	-CH ₂ CONH ₂	5-F	69 ± 56	>100

¹ Mean of two separate determinations. Standard deviations (± SD) are provided for compounds that had more than two separate determinations. ² cysmethynil

Synthesis of 1-8 and 6-8



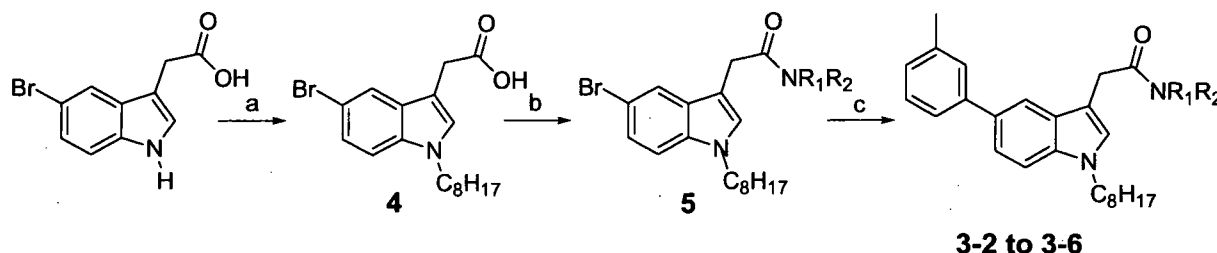
[00175] **2-(5-Fluoro-1H-indol-3-yl)acetonitrile (A-1).** To a solution of 5-fluoro-1H-indole-3-carbaldehyde (4.5 mmol, 1 equiv.) in formamide-methanol (NH₂CHO-MeOH; 1:1, v/v; 200 mL) was added sodium borohydride (NaBH₄; 13.5 mmol, 3 equiv.) and the mixture was stirred for 0.5 h. To the reaction mixture was added potassium cyanide (KCN; 45 mmol, 10 equiv.) and the whole was refluxed on oil bath at 100 °C for 2.5 h with stirring. After cooling to room temperature, brine was added and the mixture was extracted with chloroform (CHCl₃), washed with brine dried over anhydrous sodium sulphate (Na₂SO₄), and evaporated under reduced pressure to give the nitrile 1. Recrystallization from ethanol (EtOH)/water gave needle-

like white crystals. Yield: 52 %; ^1H NMR (300 MHz, CDCl_3): δ 3.66 (s, 2H), 6.90 (dt, $J_1 = 9$ Hz, $J_2 = 2.1$ Hz, 1 H), 7.08 (s, 1 H), 7.13-7.22 (m, 2 H), 8.4 (1H, NH); ^{13}C NMR (75 MHz, CDCl_3) δ 14.2, 102.8, 104.2, 111.0, 112.4, 118.3, 124.8, 126.2, 132.8, 156.3.

[00176] **2-(5-Fluoro-1H-indol-3-yl)acetamide (A-2).** Nitrile A-1 (3.5 mmol, 1 equiv.), was refluxed in tertiary butanol (*t*-BuOH; 10 mL) containing finely powdered 85% potassium hydroxide (KOH; 28 mmol, 8 equiv.) for 3 h. The reaction mixture was cooled to room temperature, diluted with water, and acidified with 1 M hydrochloric acid (HCl). The resulting suspension was filtered under reduced pressure. The filter cake was washed with water then dried *in vacuo*. The product was isolated as an off-white/light brown solid. Yield: 61 %; ^1H NMR (300 MHz, CDCl_3): δ 3.69 (s, 2 H), 5.29 (s, 2 H), 6.98 (dt, $J_1 = 9$ Hz, $J_2 = 2.4$ Hz, 1 H), 7.21 (s, 1 H), 7.25-7.33 (m, 2 H), 8.34 (s, 1 H).

[00177] **2-(5-Fluoro-1-(3-methylbut-2-enyl)-1H-indol-3-yl)acetamide (6-8).** NaH (60% in mineral oil dispersion, 6 mmol, 1.2 equiv.) was added to a stirred solution of 2-(5-Fluoro-1H-indol-3-yl)acetamide (5 mmol, 1 equiv.) in anhydrous dimethylsulfoxide (DMSO) at room temperature. After 1 h of stirring at the same temperature, 1-chloro-3-methylbut-2-ene was added and the mixture stirred for another 3 h. Distilled water was added to the reaction mixture which was then extracted with CH_2Cl_2 . The organic layer was washed with brine, dried (anhydrous Na_2SO_4) and evaporated under reduced pressure. The residue was purified by column chromatography with EtOAc/hexane as eluting solvents. Yield: 67 %; ^1H NMR (300 MHz, CDCl_3): δ 7.26-7.23 (m, 2 H), 7.19 (s, 1 H), 6.98 (t, $J = 9$ Hz, 1 H), 5.72 (br s, 2 H), 5.36 (t, $J = 6$ Hz, 1 H), 4.65 (d, $J = 6.6$ Hz, 2 H), 3.65 (s, 2 H), 1.82 (s, 3 H), (1.79 s, 3 H); ^{13}C NMR (75 MHz, CDCl_3) δ 174.16, 137.04, 133.04, 128.29, 119.27, 110.62, 110.45, 110.27, 107.54, 103.86, 103.55, 44.30, 32.85, 25.63, 18.00. MS (APCI): m/z 261.3 $[\text{M} + \text{H}]^+$.

[00178] **2-(5-Fluoro-1-octyl-1H-indol-3-yl)acetamide (1-8).** The reaction between Amide A-2 and bromooctane can be carried out as described by Na, Y. M.; Le Borgne, M.; Pagniez, F.; Le Baut, G.; Le Pape, P. Synthesis and antifungal activity of new 1-halogenobenzyl-3-imidazolylmethylindole derivatives. Eur J Med Chem 2003, 38, 75-87. Yield: 70 %; ^1H NMR (300 MHz, CDCl_3): δ 7.26 – 7.18 (m, 2 H), 7.09 (s, 1 H), 6.97 (dt, $J_1 = 9$ Hz, $J_2 = 2.4$ Hz, 1 H), 5.73 (br. s, 2 H), 4.06 (t, $J = 7.2$ Hz, 2 H), 3.65 (s, 2 H), 1.83 (t, $J = 6.3$ Hz, 2 H), 1.29-1.25 (m, 10 H), 0.86 (t, $J = 6.3$ Hz, 3H); ^{13}C NMR (75 MHz, CDCl_3) δ 174.10, 159.39, 156.27, 139.66, 133.03, 128.67, 127.68, 127.55, 110.66, 117.23, 103.88, 46.63, 32.81, 31.70, 30.17, 29.09 (2C), 26.94, 22.55, 14.02; MS (APCI): m/z 305.5 $[\text{M} + \text{H}]^+$

[00179] Synthesis of 3-6 and 3-7

Reagents and conditions: (a) $\text{C}_8\text{H}_{17}\text{Br}$, NaH, DMF, rt $\rightarrow$ 53-58°C (b) (i) SOCl_2 , benzene, reflux, (ii) 2° amine/heterocyclic amine, THF; (c) m-tolyl boronic acid $\text{Pd}(\text{PPh}_3)_4$, NaHCO_3 , EtOH/toluene, reflux.

[00180] 2-(5-Bromo-1-octyl-1H-indol-3-yl)acetic acid (4). The method of Roy, S.; Eastman, A.; Gribble, G. W. Synthesis of *N*-alkyl substituted bioactive indolocarbazoles related to Gö6976 *Tetrahedron* **2006**, 62, 7838-45, was followed. To a stirred suspension of NaH (60% dispersion in mineral oil, 138 mmol, 5 equiv.) in tetrahydrofuran (THF; 100 mL) at 0 °C was added a solution of 2-(5-bromo-1H-indol-3-yl)acetic acid (27.7 mmol, 1 equiv.) in THF (50 mL). The mixture was stirred for 30 min at 0 °C after which a solution of 1-bromooctane (83.1 mmol, 3 equiv.) in THF (50 mL) was added dropwise. The mixture was allowed to slowly reach room temperature after which it was stirred for another 4 h. The reaction mixture was cooled to 0 °C and excess NaH was carefully destroyed by the slow addition of MeOH with vigorous stirring, followed by cold water until a clear yellow solution was obtained. Et_2O (100 mL) was added, the aqueous phase was separated, acidified with 6 M HCl, and extracted with sufficient CH_2Cl_2 . The combined organic extracts were dried (anhydrous Na_2SO_4) and concentrated in vacuo. The crude product was purified by column chromatography with hexane/EtOAc. Yield: 64 %; ^1H NMR (300 MHz, CDCl_3): δ 7.71 (s, 1 H), 7.26 (d, J = 2.1 Hz, 1 H), 7.16 (d, J = 8.7 Hz, 1H), 7.07 (s, 1 H), 4.03 (t, J = 7.2 Hz, 2 H), 3.73 (s, 2 H), 1.79 (t, J = 9.9 Hz), 1.28-1.24 (m, 10 H), 0.86 (t, J = 6.3 Hz). ^{13}C NMR (75 MHz, CDCl_3): δ 177.3, 134.8, 129.2, 128.0, 124.5, 121.5, 112.5, 110.9, 105.6, 46.5, 31.7, 30.7, 30.1, 29.1, 29.0, 26.9, 22.5, 14.0.

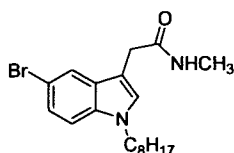
[00181] General procedure for the synthesis of 2-(5-bromo-1-octyl-1H-indol-3-yl)-*N*-substituted acetamides (5). A mixture of 4 (1 mmol, 1 equiv.) and thionyl chloride (SOCl_2 ; 2 mL, 27 equiv.) were refluxed for 4 h in dry benzene (5 mL), after which excess SOCl_2 and benzene were removed by distillation in vacuo to give the corresponding acid chloride. The acid chloride was dissolved in dry THF (4 mL) and added dropwise to a stirred solution of the amine (methylamine or *N*-methylpiperazine) in dry THF at 0-5 °C. The reaction mixture was stirred at the same temperature for 1 h after which THF was removed in vacuo and

the residue extracted with CH_2Cl_2 and dried (anhydrous Na_2SO_4). Removal of the solvent under reduced pressure gave the desired amide which was purified by column chromatography with EtOAc/hexane as eluting solvents. Yields and spectroscopic data of the amides are given below:

5 **[00182] 2-(5-Bromo-1-octyl-1*H*-indol-3-yl)-1-(4-methylpiperazin-1-yl)ethanone.**

Yield: 58 %; ^1H NMR (300 MHz, CDCl_3): δ 0.85 (t, $J = 6.9$ Hz, 3 H), 1.23–1.25 (m, 10 H), 1.76 (t, $J = 6.9$ Hz, 2 H), 2.20 (t, $J = 6.3$ Hz, 2 H), 2.23 (s, 3 H), 2.35 (t, $J = 4.8$ Hz, 2 H), 3.46 (t, $J = 4.8$ Hz, 2 H), 3.66 (t, $J = 4.5$ Hz, 2 H), 3.74 (s, 2 H), 4.01 (t, $J = 7.2$ Hz, 2 H), 7.0 (s, 1 H), 7.15 (d, $J = 8.7$ Hz, 1 H), 7.25 (d, $J = 8.7$ Hz, 1 H), 7.70 (s, 1 H); ^{13}C NMR (75 MHz, CDCl_3): δ 14.0, 22.5, 26.8, 29.10, 29.12, 30.7, 31.7, 41.6, 45.9, 46.4, 54.5, 54.9, 107.2, 110.9, 112.3, 121.3, 124.4, 127.2, 129.1, 134.8, 169.6.

[00183] 2-(5-Bromo-1-octyl-1*H*-indol-3-yl)-*N* methylacetamide



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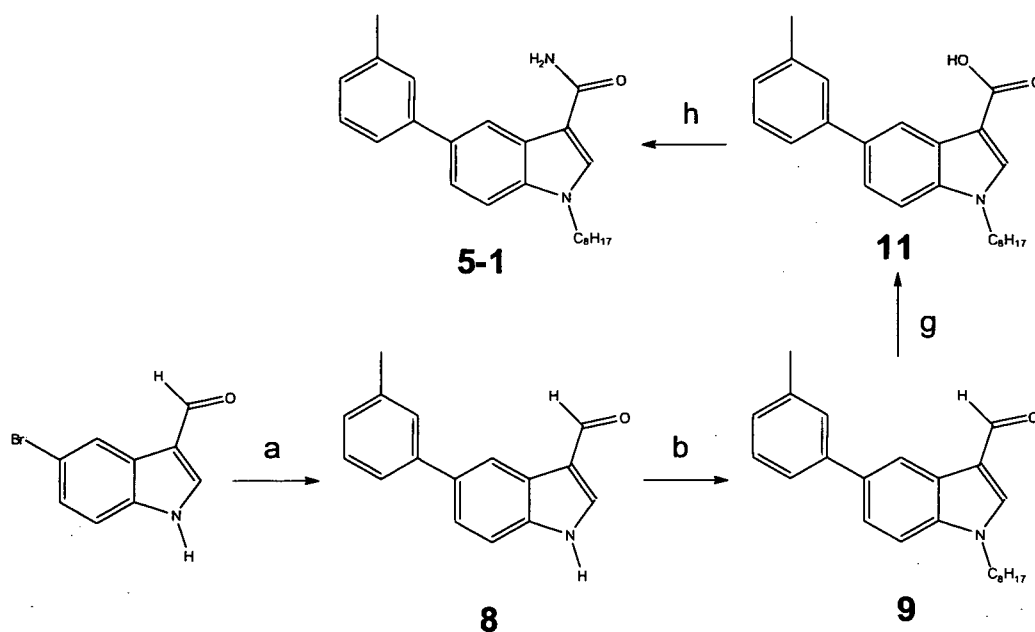
Yield: 73 %; ^1H NMR (300 MHz, CDCl_3): δ 0.87 (t, $J = 6.9$ Hz, 3 H), 1.26–1.29 (m, 10 H), 1.82 (t, $J = 6.9$ Hz, 2 H), 2.74 (d, $J = 4.8$ Hz, 3 H), 3.66 (s, 2 H), 4.07 (t, $J = 7.2$ Hz, 2 H), 7.04 (s, 1 H), 7.20–7.34 ((m, 2 H), 7.67 (s, 1 H); ^{13}C NMR (75 MHz, CDCl_3) δ 14.0, 22.5, 26.4, 26.9, 29.1, 29.1, 30.1, 31.6, 32.9, 46.5, 107.0, 111.1, 112.8, 121.4, 124.8, 128.4, 129.2, 135.0, 171.7.

[00184] 1-(4-Methylpiperazin-1-yl)-2-(1-octyl-5-*m*-tolyl-1*H*-indol-3-yl)ethanone (3-6). To a solution of the acetamide (1 mmol, 1 equiv.) in 4 ml dimethoxyethane (DME) was added $\text{Pd}(\text{PPh}_3)_4$ (0.05 mmol, 0.05 equiv.) followed by stirring under argon for 15 min. A solution of *m*-tolylboronic acid (1 mmol, 1 equiv.) in 1.5 ml EtOH was added and stirring was continued for another 15 min. A solution of 2 M aqueous sodium carbonate (Na_2CO_3 ; 4 mL) was added and the mixture was refluxed for another 5 h under argon. On cooling, the organic solvent was removed under reduced pressure, the resulting suspension was extracted with CH_2Cl_2 and dried (anhydrous Na_2SO_4). The residue obtained on removal of the solvent was purified by column chromatography on silica gel with EtOAc/hexane as eluting solvents. Yield: 45 %; ^1H NMR (300 MHz, CDCl_3): δ 7.75 (s, 1 H), 7.46–7.29 (m, 5 H), 7.12 (d, $J = 6.9$ Hz, 1

H), 7.02 (s, 1 H), 4.07 (t, $J = 6.9$ Hz, 2 H), 3.85 (s, 2 H) 3.68 (t, $J = 6.9$ Hz, 2 H), 3.48 (t, $J = 6.9$ Hz, 2 H), 2.43 (s, 3 H), 2.36 (t, $J = 6.9$ Hz, 2 H), 2.23 (s, 3 H), 2.20 (t, $J = 6.9$ Hz, 2 H), 1.81 (t, $J = 6.9$ Hz, 2 H), 1.29-1.25 (m, 10 H), 0.87 (t, $J = 6.9$ Hz, 3 H); ^{13}C NMR (75 MHz, CDCl_3) δ 172.54, 142.54, 138.15, 135.60, 133.07, 132.13, 131.69, 128.41, 127.33, 127.06, 126.24, 124.52, 121.39, 114.06, 109.74, 57.2, 53.3, 53.0, 46.3, 46.0, 31.7, 30.2, 29.2 (2C), 27.0, 22.6, 21.6, 14.1; MS (APCI): m/z 460.5 $[\text{M} + \text{H}]^+$.

[00185] N-Methyl-2-(1-octyl-5-*m*-tolyl-1*H*-indol-3-yl)acetamide (3-7). Reaction was carried out as described above. Yield: 68 %; ^1H NMR (300 MHz, CDCl_3): δ 7.72 (s, 1 H), 7.49-7.30 (m, 5 H), 7.12 (d, $J = 6.6$ Hz, 1 H), 7.01 (s, 1 H), 5.89 (bs, 1 H), 4.06 (t, $J = 6.6$ Hz, 2 H), 2.68 (d, $J = 4.5$ Hz, 3 H), 2.41 (s, 3 H), 1.82 (t, $J = 6.8$ Hz, 2 H), 1.39-1.25 (m, 10 H), 0.86 (t, $J = 6.3$ Hz, 3 H); ^{13}C NMR (75 MHz, CDCl_3) δ 174.10, 159.39, 156.27, 139.66, 133.03, 128.67, 127.68, 127.55, 110.66, 110.47, 110.31, 107.52, 107.46, 103.88, 103.57; MS (APCI): m/z 391.8 $[\text{M} + \text{H}]^+$; Found (calcd. for $\text{C}_{26}\text{H}_{34}\text{N}_2\text{O}$) C 79.86 % (79.96); H 8.96 % (8.77).

[00186] Synthesis of 5-1



Reagents and conditions: (a) *m*-tolylboronic acid, EtOH/DME, $\text{Pd}(\text{PPh}_3)_4$, K_2CO_3 ; (b) $\text{C}_8\text{H}_{17}\text{Br}$, NaH, DMF; (c) $\text{NH}_2\text{OH} \cdot \text{HCl}$, Py, EtOH; (g) KMnO_4 , acetone; (h) (i) SOCl_2 , benzene, reflux, (ii) NH_3 (g), THF.

[00187] 5-*m*-Tolyl-1*H*-indole-3-carbaldehyde (8). 5-Bromo-1*H*-indole-3-carbaldehyde was reacted with *m*-tolylboronic acid as described for 3-6 and 3-7. Yield: 85 %; ^1H NMR (300 MHz, CDCl_3): δ 9.91 (s, 1 H), 8.43 (s, 1 H), 7.66 (s, 1 H), 7.36 (d, $J = 7.5$ Hz, 1 H),

7.20 (d, $J = 8.7$, 1 H), 4.11 (t, $J = 7.2$ Hz, 2 H), 1.85 (t, $J = 6.3$ Hz, 2 H), 1.30-1.24 (m, 10 H), 0.86 (t, $J = 6$ Hz, 3 H); ^{13}C NMR (75 MHz, CDCl_3): δ 184.1, 138.7, 135.8, 126.8, 126.8, 124.7, 117.3, 116.4, 111.4, 47.4, 32.7, 31.6, 29.6, 29.0, 26.7, 22.5, 14.0.

[00188] 1-Octyl-5-*m*-tolyl-1*H*-indole-3-carbaldehyde (9). NaH (60% in mineral oil

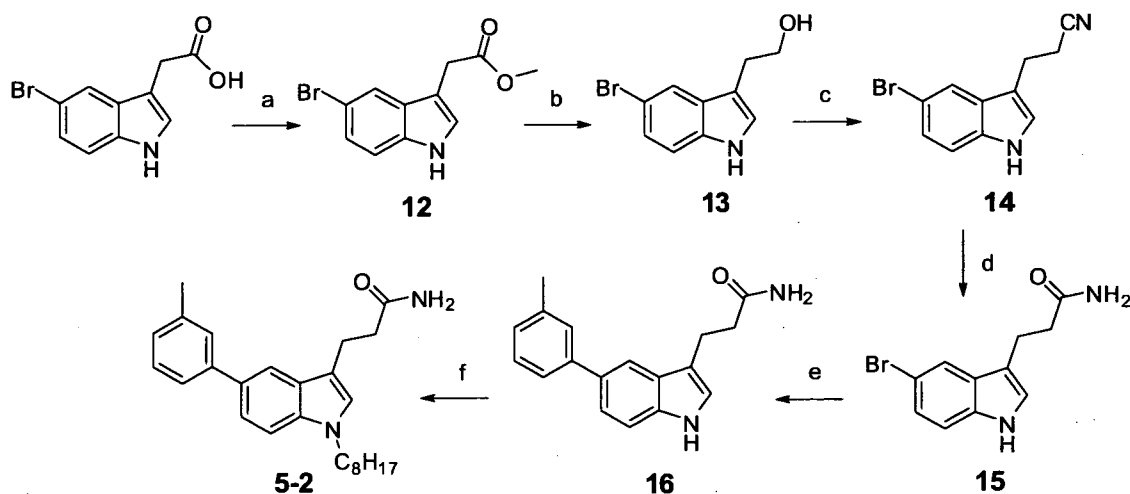
5 dispersion, 6 mmol, 1.2 equiv.) was added to a stirred solution of aldehyde 8 (5 mmol, 1 equiv.) in anhydrous dimethylsulfoxide (DMSO) at room temperature. After 1 h of stirring at the same temperature, 1-bromooctane was added and the mixture stirred for another 3 h. Distilled water was added to the reaction mixture which was then extracted with CH_2Cl_2 . The organic layer was washed with brine, dried (anhydrous Na_2SO_4) and evaporated under reduced pressure. The
10 residue was purified by column chromatography with EtOAc/hexane as eluting solvents as described in Section 5.4.1. Yield: 62 %; ^1H NMR (300 MHz, CDCl_3): δ 9.98 (s, 1 H), 8.53 (s, 1 H), 7.66 (s, 1 H), 7.57-7.46 (m, 3 H), 7.39-7.29 (m, 2 H), 7.13 (d, $J = 7.2$ Hz, 1 H), 4.1 (t, $J = 8.7$ Hz, 2 H), 2.42 (s, 3 H), 1.86 (t, $J = 3$ Hz), 1.29-1.24 (m, 10 H), 0.86 (t, $J = 6.6$ Hz, 3 H); ^{13}C NMR (75 MHz, CDCl_3): δ 184.8, 143.7, 141.6, 138.9, 135.4, 135.1, 129.1, 128.9, 127.1, 119.3,
15 119.2, 118.5, 116.8, 111.6, 47.4, 32.7, 31.6, 29.6, 29.0, 26.7, 22.5, 14.0.

[00189] 1-Octyl-5-*m*-tolyl-1*H*-indole-3-carboxylic acid (11). The method of

Andreani, A.; Granaola, M.; Leoni, A.; Locatelli, A.; Morigi, R.; Rambaldi, M.; Roda, A.; Guardigli, M.; Traniello, S.; Spisani, S. N-Benzyl-2-chloroindole-3-carboxylic acids as potential anti-inflammatory agents. Synthesis and screening for effects on human neutrophil
20 functions and on COX1/COX2 activity. *Eur J Med Chem.* **2004**, *39*, 785-91, was followed. Compound 9 (0.573 mmol, 1 equiv) was dissolved in 10 mL of acetone and treated with a solution of potassium permanganate (KMnO_4 , 1.5 mmol) in water (5 mL). The reaction mixture was stirred at room temperature for 5h, treated with 10 % H_2O_2 until the pink color of KMnO_4 was not observed and then filtered. The solvent was removed under reduced pressure
25 and the resulting residue was filtered again (if necessary), acidified with 2M HCl and extracted with Et_2O . The organic solvent was removed in vacuo and the residue was purified by column chromatography with hexane/EtOAc as eluting solvents. Yield: 62 %; ^1H NMR (300 MHz, CDCl_3): δ 8.84 (s, 1 H), 7.92 (s, 1 H), 7.54-7.48 (m, 2 H), 7.41-7.29 (m, 3 H), 7.14 (d, $J = 6.6$ Hz, 1 H), 4.12 (t, $J = 6.6$ Hz, 2 H), 2.44 (s, 3 H), 1.87 (t, $J = 6.6$ Hz, 3 H), 1.37-1.25 (m, 10 H),
30 0.86 (t, $J = 6.6$ Hz, 3 H); ^{13}C NMR (75 MHz, CDCl_3): δ 170.3, 142.3, 141.9, 138.4, 138.2, 136.1, 136.0, 135.8, 128.5, 128.3, 127.4, 124.6, 120.3, 110.3, 106.3, 47.2, 31.7, 31.1, 29.8, 29.1, 22.6, 21.5, 21.5, 14.0.

[00190] 1-Octyl-5-*m*-tolyl-1*H*-indole-3-carboxamide (5-1). A mixture of 11 (0.4 mmol, 1 equiv.) and SOCl₂ (1 mL, 13 equiv.) in dry benzene (5 mL) were refluxed for 4 h. Excess SOCl₂ and benzene were removed by distillation under reduced pressure and the residue containing the acid chloride was dried in vacuo. It was dissolved in dry THF (4 mL) and ammonia gas was bubbled into the stirred solution for 30 min. THF was removed under vacuum, the residue was extracted with CH₂Cl₂, dried (anhydrous Na₂SO₄) and the solvent removed under reduced pressure to give carboxamide 5-1. Yield: 74 %; ¹H NMR (300 MHz, CDCl₃): δ 8.16 (s, 1 H), 7.74 (s, 1 H), 7.49-7.13 (m, 6 H), 5.99 (bs, 2 H), 4.09 (t, *J* = 7.2 Hz), 2.42 (s, 3 H); 1.82 (t, *J* = 6.8 Hz, 2 H), 1.28-1.24 (m, 10 H) 0.86 (t, *J* = 6.3 Hz, 3 H); ¹³C NMR (75 MHz, CDCl₃) δ 167.32, 141.92, 138.25, 136.07, 135.31, 132.61, 128.58, 128.29, 127.47, 126.18, 124.60, 122.37, 118.94, 110.43, 110.00, 47.02, 31.71, 29.92, 29.11, 29.08, 26.86, 22.57, 21.53, 14.0; MS (APCI): *m/z* 363.5 [M + H]⁺.

[00191] Synthesis of 5-2 (J20)



Reagents and conditions: (a) MeOH, H₂SO₄, reflux (1 h), (b) LiAlH₄, THF, rt (30 min), (c) (i) TEA, MsCl, CH₂Cl₂, 0 °C (30 min), (ii) KCN, DMSO, 100 °C (d) KOH, *t*-BuOH, reflux (3 h) (e) *m*-tolylboronic acid, Pd(PPh₃)₄, NaHCO₃, EtOH/toluene, reflux (1-6 h) (f) bromooctane, NaH, DMF, rt (1.5 h) 53-58 °C (3-6 h)

[00192] Methyl-2-(5-bromo-1*H*-indol-3-yl)acetate (12). To a solution of 2-(5-bromo-1*H*-indol-3-yl)acetic acid (4 mmol) in 20 mL of MeOH was added 10 drops of concentrated sulphuric acid. The mixture was heated under reflux with continuous stirring for a period of 1-1.5 h. Following reflux, the reaction mixture was cooled to room temperature and evaporated in vacuo. The residue was added with a saturated solution of NaHCO₃ (50 mL) to

neutralize acid, and the resulting alkaline aqueous mixture was extracted with EtOAc and dried over Na₂SO₄. Evaporation of the solvent gave a residue which was purified by flash silica gel column chromatography. Elution with CH₂Cl₂ yielded the corresponding ester **11** as an off-white solid. Yield: 89 %; ¹H NMR (300 MHz, CDCl₃): δ 3.66 (s, 3 H), 3.68 (s, 2 H), 7.18-7.21 (m, 4 H); MS (APCI), *m/z* 269.2 [M + H]⁺.

[00193] 2-(5-Bromo-1*H*-indol-3-yl)ethanol (13). The method of Bascop, S. I.; Laronze, J. Y.; Sapi, J. Synthesis of 2-aminopropyle-3-indole-acetic(propionic) acid derivatives. *ARKIVOC* 2003, 46-61, was followed. To a solution of ester **12** (4 mmol, 1 equiv) in anhydrous THF (50 mL) was added lithium aluminium hydride (LiAlH₄; 16 mmol, 4 equiv) in portions with the temperature maintained at 0 °C. The reaction mixture was brought to room temperature and stirred for 30 min. Excess LiAlH₄ was destroyed by careful addition of a saturated aqueous solution of Na₂SO₄ with the temperature maintained at about 0 °C. The mixture was filtered and the filtrate washed with THF. The combined filtrates were concentrated under reduced pressure, the residue was acidified to pH 6 with 10 % HCl and extracted with CHCl₃. The combined organic layer was dried (anhydrous Na₂SO₄), filtered, evaporated to dryness and purified using flash column chromatography by elution with EtOAc/hexane to give the alcohol **13**. Yield: 83 %; ¹H NMR (300 MHz, CDCl₃): δ 2.97 (t, *J* = 18 Hz, 2 H), 3.86-3.93 (m, 2 H), 4.09 (t, *J* = 21 Hz, 1 H), 7.09 (d, *J* = 3 Hz, 1 H), 7.22 (d, *J* = 9 Hz, 1 H), 7.75 (s, 1 H), 8.10 (s, 1 H); MS (APCI): *m/z* 241.2 [M + H]⁺.

[00194] 2-(5-Bromo-1*H*-indol-3-yl)propanenitrile (14). The method of Bascop, S. I.; Laronze, J. Y.; Sapi, J. Synthesis of 2-aminopropyle-3-indole-acetic(propionic) acid derivatives. *ARKIVOC* 2003, 46-61, was followed. Methane sulphonyl chloride (MsCl, 0.55 mL, 2 equiv) was added to a stirred solution of **13** (3.2 mmol, 1 equiv), triethylamine (0.9 mL, 2 equiv) and anhydrous CH₂Cl₂ (20 mL) maintained at 0 °C. The reaction mixture was then stirred for 30 min at 0 °C under N₂, after which it was treated with 2M NaOH and extracted with CH₂Cl₂. The combined organic layer was washed with water, dried (anhydrous Na₂SO₄) and evaporated to dryness under reduced pressure. The residue was dissolved in anhydrous DMSO (20 mL), KCN (3.25 mmol, 3 equiv) was added and the reaction mixture was heated at 100 °C in an oil bath for 1 h. It was diluted with a water-ice mixture, extracted with chloroform, the combined organic layer was washed with water, dried (anhydrous Na₂SO₄), and evaporated to dryness under reduced pressure. The residue was purified by column chromatography with CHCl₃ as eluting solvent and **14** was obtained. Yield: 75 %; ¹H NMR (300 MHz, DMSO-*d*₆): δ

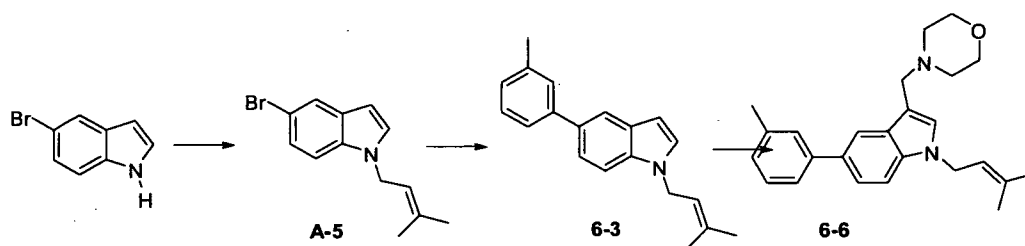
2.78 (t, $J = 15$ Hz, 2 H), 3.58 (t, $J = 12$ Hz, 2 H), 7.14-7.17 (m, 2 H), 7.20 (d, $J = 27$ Hz, 1 H), 7.68 (s, 1 H), 11.01 (s, 1 H); MS (APCI): m/z 261.3 $[M + H]^+$.

[00195] **2-(5-Bromo-1*H*-indol-3-yl)propanamide (15).** Amide 15 was prepared from the nitrile 14 by the method described for A-2. Yield: 82 %; ^1H NMR (300 MHz, CDCl_3): δ 2.44 (t, $J = 15$ Hz, 2 H), 2.96 (t, $J = 15$ Hz, 2 H), 7.09-7.58 (m, 4 H); MS (APCI): m/z 268.1 $[M + H]^+$.

[00196] **3-(5-*m*-Tolyl-1*H*-indol-3-yl)propanamide (16).** Amide 16 was prepared from the 15 by the method described for 3-6 and 3-7. Yield: 50 %; ^1H NMR (300 MHz, CDCl_3): δ 2.38 (s, 3 H), 2.49 (t, $J = 18$ Hz, 2 H), 3.02 (t, $J = 15$ Hz, 2 H), 7.12-7.61 (m, 8 H); MS (APCI), m/z 279.4 $[M + H]^+$.

[00197] **3-(1-Octyl-5-*m*-tolyl-1*H*-indol-3-yl)propanamide (5-2).** Amide 5-2 was prepared from 16 by the method described for 1-8. Yield: 77 %; ^1H NMR (300 MHz, CDCl_3): δ 0.78 (t, $J = 12$ Hz, 3 H), 1.18-1.21 (m, 10 H), 1.69 (t, $J = 9$ Hz, 2 H), 2.35 (s, 3 H), 2.49 (t, $J = 15$ Hz, 2 H), 3.01 (t, $J = 15$ Hz, 2 H), 3.92 (t, $J = 15$ Hz, 2 H), 6.84 (s, 1 H), 7.02 (d, $J = 9$ Hz, 1 H), 7.22 (d, $J = 12$ Hz, 2 H), 7.35-7.38 (m, 3 H), 7.68 (s, 1 H); ^{13}C NMR (75 MHz, CDCl_3): δ 14.1, 21.0, 21.6, 22.6, 27.0, 29.2, 29.2, 30.3, 31.8, 36.7, 46.3, 109.7, 113.6, 117.3, 121.4, 124.5, 126.1, 127.1, 128.0, 128.2, 128.6, 132.4, 135.9, 138.2, 142.6, 175.4; MS (APCI), $m/z = 391.5$ $[M + H]^+$.

[00198] **Synthesis of 6-3 and 6-6**



[00199] **5-Bromo-1-(3-methylbut-2-enyl)-1*H*-indole (A-5).** 5-Bromo-1*H*-indole was reacted with 1-chloro-3-methylbut-ene by the method described for 6-8. Yield: 96 %; ^1H NMR (300 MHz, CDCl_3): δ 7.32 (d, $J = 1.5$ Hz, 1H), 7.23 (d, $J = 1.5$ Hz), 7.23 (d, $J = 1.5$ Hz, 1 H), 7.16 (s, 1 H), 7.06 (d, $J = 3$ Hz, 1H), 6.39 (d, $J = \text{Hz}$, 1H), 5.32 (t, $J = 6.9$ Hz, 1 H), 4.61 (d, $J = 6.9$ Hz, 2 H), 1.78 (s, 3H), 1.74 (s, 3H); ^{13}C NMR (75 MHz, CDCl_3) δ 136.7, 134.6, 130.4, 128.5, 124.1, 123.3, 119.5, 112.5, 110.9, 100.5, 44.3, 25.6, 18.0.

[00200] 1-(3-Methylbut-2-enyl)-5-*m*-tolyl-1*H*-indole (6-3). A-5 was reacted with *m*-tolylboronic acid as described for 3-6 and 3-7.. 6-3 was obtained in 75 %; ¹H NMR (300 MHz, CDCl₃): δ 7.87 (d, *J* = 0.9 Hz, 1 H), 7.45-7.28 (m, 5 H), 7.11-7.09 (m, 2 H), 6.57 (dd, *J*₁ = 3.0 Hz, *J*₂ = 0.6 Hz, 1 H), 5.46-5.43 (m, 1 H), 4.76 (d, *J* = 6.9 Hz, 2 H), 2.47 (s, 3 H), 1.89 (s, 3 H), 1.82 (s, 3 H); ¹³C NMR (75 MHz, CDCl₃) δ 142.70, 138.14, 136.34, 135.55, 132.98, 129.25, 128.57, 128.26, 128.06, 127.01, 124.54, 121.31, 119.99, 119.47, 109.71, 101.39, 44.30, 25.70, 21.66, 18.08. LC-MS (APCI), *m/z* = 276.5 [*M* + *H*]⁺.

[00201] 4-((1-(3-methylbut-2-enyl)-5-*m*-tolyl-1*H*-indol-3-yl)methyl)morpholine (6-6). Morpholine (1 mmol, 1equiv.), zinc chloride (ZnCl₂; 1.5 mmol, 1.5 equiv.), formaldehyde (HCHO; 1 mmol, 36% aq., 1 equiv.), indole 6-3 (1 mmol, 1equiv.) and EtOH (3 mL) were stirred together in a round bottom flask for 10 h at room temperature. Distilled water was added to the mixture which was made alkaline by the addition of 4 M sodium hydroxide (NaOH). The mixture was extracted with EtOAc, the solvent was removed under reduced pressure and the residue purified by column chromatography with CH₂Cl₂/MeOH or EtOAc/hexane as eluting solvents. Yield: 68 %; ¹H NMR (300 MHz, CDCl₃): δ 7.76 (s, 1 H), 7.44-7.40 (m, 3 H), 7.34-7.30 (m, 3 H), 7.10 (d, *J* = 7.5 Hz, 1 H), 5.35 (t, *J* = 6.6 Hz, 1 H), 4.67 (*J* = 6.6 Hz, 2 H), 3.93 (s, 2 H), 2.68 (br. s, 2 H), 2.41 (s, 3 H), 1.80 (s, 3 H), 1.74 (s, 3 H), 1.71 (t, *J* = 8.7 Hz, 4 H); ¹³C NMR (75 MHz, CDCl₃) δ 142.45, 138.22, 136.60, 135.54, 133.33, 129.73, 129.26, 128.58, 128.22, 127.17, 124.53, 121.56, 119.62, 117.27, 110.27, 110.02, 100.61, 53.32, 44.41, 25.66, 24.69, 23.40, 21.59, 18.09. LC-MS (APCI) *m/z* 375.4 [*M* + *H*]⁺; Found (calcd. for C₂₅H₃₀N₂O): C 79.92% (80.17); H 8.10 (8.07).

[00202] Purity determination

Compound	Mobile Phase A			Mobile Phase B		
	Composition ^a	RT (min) ^c	Area (%) ^d	Composition ^b	RT (min) ^c	Area (%) ^d
1-8	A2	2.0	93.5	B2	2.1	93.3
3-7	Combustion Analysis ^e			Combustion Analysis ^e		
3-6	A2	3.5	92.1	B2	4.0	92.8
5-1	A5	3.6	99.0	B6	3.4	99
5-2	A1	6.0	97.5	B1	4.1	96.9
6-3	A4	3.7	96	B5	5.8	95.3
6-6	Combustion Analysis ^e			Combustion Analysis ^e		
6-8	A2	1.8	93.2	B2	2.0	93.0

^a Composition of Mobile Phase A: Methanol and Water

A1: 90% methanol

A2: 95% methanol + 0.1% triethylamine (TEA)

A4: 92% methanol + 0.1% TEA

A5: 100 % methanol

5 ^b Composition of Mobile Phase B: Acetonitrile and Water

B1: 90% acetonitrile

B2: 95% acetonitrile + 0.1% triethylamine (TEA)

B5: 92% acetonitrile + 0.1% TEA

B6: 100% acetonitrile

10

^c Retention time of Major Peak in chromatogram. Chromatogram was run for at least 15 min for the detection of the major peak

^d Area (%) of Major Peak = [Area of Major Peak / Total Area of All Peaks] x 100

15 ^e Combustion analysis for carbon were within 0.4% of calculated values and are stated in the respective compound monographs.

Biological Evaluation

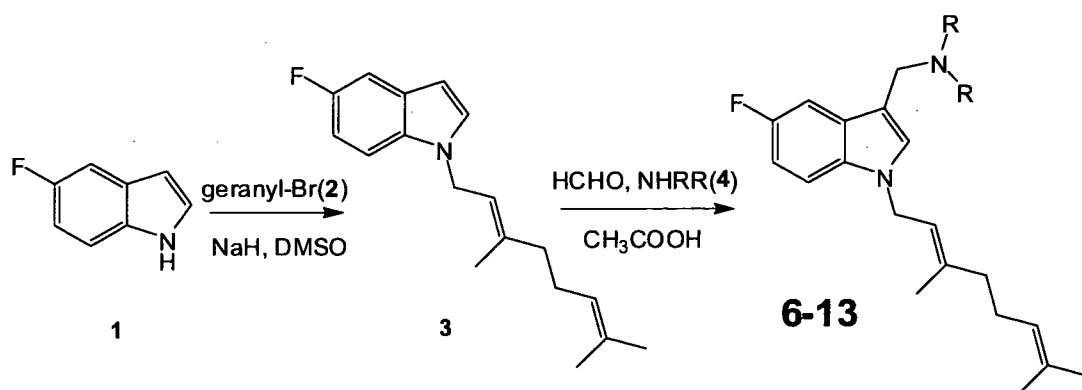
[00203] **Measurement of ICMT activity.** Icmt activity was determined by following
20 incorporation of ³H from [³H]AdoMet (Amersham Biosciences) into the small molecule substrate biotin-S-farnesyl L-cysteine (BFC). Inhibitors were first incubated at 37 °C for 20 min, with the Sf9 membranes containing ICMT. An assay mixture containing 4 μM BFC and 5 μM [³H]AdoMet in 100 mM Hepes, pH 7.4 and 5 mM MgCl₂ was added to initiate the reaction. Reactions were carried out at 37 °C for 20 min, and terminated by addition of 10 %
25 Tween 20 and streptavidin beads (GE Healthcare, 10 μL of packed beads suspended in 500 μL of 20 mM NaH₂PO₄, pH 7.4, containing 150 mM NaCl). The mixtures were mixed by gentle agitation overnight at 4 °C. The beads were harvested by centrifugation in a tabletop microcentrifuge at 10,000 rpm for 5 min and washed three times with 500 μL of 20 mM NaH₂PO₄, pH 7.4, containing 150 mM NaCl. The beads were then suspended in the same
30 buffer, transferred to scintillation vials, and radioactivity determined.

[00204] **Cell Culture and Proliferation Assays.** The MDA-MB-231 human breast cells were maintained at 37 °C with 5% CO₂ in DMEM (Sigma) supplemented with 10% fetal

bovine serum (FBS, Hyclone), 50 U/ml penicillin (Gibco), and 50 μ g/ml streptomycin (Gibco). For proliferation assays, cells were seeded at 20% confluency in DMEM containing 5% FBS in 96-well plates for 24 h prior to treatment with specific agents (e.g. cysmethynil) or vehicle at various concentrations for 72 h. The relative number of the live cells was determined using the

5 CellTiter® 96 Aqueous One Solution Cell Proliferation Assay (Promega). Each condition was performed in triplicate, and data presented represent that obtained from at least two separate experiments.

Example 11: Synthetic Scheme for 5-Fluoro-1-geranyl-1H-indole analogs (6-13)



10 Structures of 5-fluoro-1-geranyl -1H-Indole analogs

Entry	*-NRR
6-13a	
6-13b	
6-13c	
6-13d	
6-13e	

6-13f	
6-13g	
6-13h	
6-13i	
6-13j	
6-13k	

Experimental Section

[00205] Reagents were purchased from Sigma-Aldrich Chemical Company Inc or Alfa Aesar and used without further purification. ¹H NMR (300 MHz) and ¹³C NMR (75 MHz) spectra were measured on a Bruker Spectrospin 300 Ultrashield magnetic resonance spectrometer using CDCl₃ as the solvent. Chemical shifts (δ) were reported in ppm and referenced to residual deuterated solvents. Coupling constants (*J*) were reported in Hz. Reactions were monitored by thin layer chromatography (TLC, Silica Gel 60 F254, Merck) with ultraviolet light as visualizing agent. Column chromatography was carried out with Silica Gel 60 (0.04–0.06 mm).

General procedure for the synthesis of (E)-1-(3,7-dimethylocta-2,6-dienyl)-5-fluoro-1H-indole (3)

[00206] The general procedure for the synthesis of (E)-1-(3,7-dimethylocta-2,6-dienyl)-5-fluoro-1H-indole (3) can be carried out as described in Na, Y. M et al., *Eur. J. Med. Chem.* 2003, 38, 75-87. To the solution of 5-fluore-1H-indole (1, 5 mmol, 1 equiv.) in anhydrous dimethylsulfoxide (DMSO) was added NaH (60% in mineral oil dispersion, 6 mmol, 1.2 equiv.) at room temperature. The mixture was stirred for about 1 h at the same temperature, then geranyl bromide (2, 6 mmol, 1.2 equiv.) was added and the mixture was stirred for 4 h.

Water was added to stop the reaction. The mixture was extracted by dichloromethane and the organic layer was washed with brine, dried (Na₂SO₄), filtered, and evaporated. The residue was purified by column chromatography of silica gel to get off-yellow oil. Yield: 85.0 %. ¹H NMR (300 MHz, CDCl₃): δ 1.62 (s, 3 H), 1.70 (s, 3 H), 1.83 (s, 3 H), 2.05-2.14 (m, 4 H), 4.70 (d, *J* = 6.6 Hz, 2 H), 5.09 (t, *J* = 6.0 Hz, 1 H), 5.40 (t, *J* = 6.6 Hz, 1 H), 6.45 (d, *J* = 2.7 Hz, 1 H), 6.91-7.00 (m, 1H), 7.16 (d, *J* = 3.0 Hz, 1 H), 7.23-7.31 (m, 1H). ¹³C NMR (75 MHz, CDCl₃) δ 27.9, 28.9, 35.4, 35.9, 46.6, 50.6, 96.2, 99.9, 100.1, 103.4, 103.7, 111.4, 114.8, 118.9, 121.4, 122.0, 128.1, 141.1, 143.6.

General procedure for the synthesis of *N*-substituted 5-fluoro-1-geranyl-1*H*-indole methylamine (6-13a to 6-13k)

[00207] This procedure can be carried out as described in Brehm, W. J.; Lindwall, H. G. The preparation of Mannich bases related to gramine. *J. Org. Chem.* 1950, 15, 685-687. To the mixture of appropriate secondary amine (4, 1.2 equiv.), 36% aqueous formaldehyde (1.2 equiv.) in acetic acid (5 mL) was added (*E*)-1-(3,7-dimethylocta-2,6-dienyl)-5-fluoro-1*H*-indole (3, 200mg, 1 equiv.) 0°C. The reaction mixture was stirred at room temperature overnight. After the reaction was completed, the reaction mixture was basified by 50% NaOH aqueous solution to pH 9 and extracted with dichloromethane (10 mL×3). The combined extracts were washed with brine (20 mL) and dried over Na₂SO₄. The organic layer was concentrated under reduced pressure. The crude product was purified by column chromatography of silica gel using or ethyl acetate/hexane or dichloromethane/methanol as eluting solvents.

[00208] (*E*)-1-(1-(3,7-dimethylocta-2,6-dienyl)-5-fluoro-1*H*-indol-3-yl)-*N,N*-dimethylmethanamine (6-13a). Yellow oil. Yield: 37.2 %. ¹H NMR (300 MHz, CDCl₃): δ 1.59 (s, 3 H), 1.67 (s, 3 H), 1.80 (s, 3 H), 2.09 (br, 4 H), 2.27 (s, 6 H), 3.56 (s, 2 H), 4.65 (d, *J* = 6.3 Hz, 2 H), 5.07 (br, 1 H), 5.36 (t, *J* = 6.3 Hz, 1 H), 6.90-6.96 (m, 1 H), 7.09 (s, 1H), 7.17-7.22 (m, 1 H), 7.31-7.34 (m, 1H). ¹³C NMR (75 MHz, CDCl₃) δ 16.3, 17.7, 25.6, 26.2, 39.4, 44.2, 45.2, 54.4, 104.0, 104.3, 109.5, 109.8, 109.9, 110.1, 111.6, 119.5, 123.6, 128.5, 128.8, 131.8, 132.9, 139.9, 156.1, 159.2.

[00209] (*E*)-*N*-((1-(3,7-dimethylocta-2,6-dienyl)-5-fluoro-1*H*-indol-3-yl)methyl)-*N*-ethylethanamine (6-13b). Yellow oil. Yield: 43.4 %. ¹H NMR (300 MHz, CDCl₃): δ 1.09 (t, *J* = 6.9 Hz, 6 H), 1.59 (s, 3 H), 1.67 (s, 3 H), 1.80 (s, 3 H), 2.09 (br, 4 H), 2.55 (q, *J* = 6.9 Hz, 4 H), 3.72 (s, 2 H), 4.65 (d, *J* = 6.6 Hz, 2 H), 5.07 (br, 1 H), 5.36 (t, *J* = 6.0 Hz, 1 H), 6.90-6.96 (m, 1 H), 7.08 (s, 1H), 7.17-7.21 (m, 1 H), 7.35-7.38 (m, 1H). ¹³C NMR (75 MHz, CDCl₃) δ

11.8, 16.4, 17.7, 25.6, 26.2, 39.4, 44.3, 46.5, 48.0, 104.3, 104.6, 109.4, 109.7, 109.9, 110.0, 111.8, 119.7, 123.6, 128.4, 128.9, 131.8, 132.9, 139.8, 156.0, 159.1.

[00210] (E)-1-(3,7-dimethylocta-2,6-dienyl)-5-fluoro-3-(piperidin-1-ylmethyl)-1H-indole (6-13c). Yellow oil. Yield: 14.7 %. ¹H NMR (300 MHz, CDCl₃): δ 1.42 (br, 2 H), 1.59 (br, 7 H), 1.66 (s, 3 H), 1.80 (s, 3 H), 2.08 (br, 4 H), 2.45 (br, 4 H), 3.64 (s, 2 H), 4.65 (d, *J* = 6.3 Hz, 2 H), 5.06 (br, 1 H), 5.36 (t, *J* = 6.3 Hz, 1 H), 6.90-6.96 (m, 1 H), 7.11 (s, 1H), 7.17-7.21 (m, 1 H), 7.33-7.36 (m, 1H). ¹³C NMR (75 MHz, CDCl₃) δ 16.4, 17.7, 24.3, 25.7, 25.9, 26.2, 39.4, 44.3, 53.9, 54.2, 104.2, 104.5, 109.4, 109.8, 109.9, 110.1, 110.7, 119.6, 123.6, 128.9, 129.1, 129.3, 131.9, 132.8, 156.1, 159.2.

[00211] (E)-4-((1-(3,7-dimethylocta-2,6-dienyl)-5-fluoro-1H-indol-3-yl)methyl)thiomorpholine (6-13d). Yellow oil. Yield: 43.2 %. ¹H NMR (300 MHz, CDCl₃): δ 1.59 (s, 3 H), 1.67 (s, 3 H), 1.80 (s, 3 H), 2.09 (br, 4 H), 2.68-2.69 (m, 4 H), 2.73-2.75 (m, 4 H), 3.66 (s, 2 H), 4.65 (d, *J* = 6.6 Hz, 2 H), 5.06 (br, 1 H), 5.36 (t, *J* = 6.6 Hz, 1 H), 6.90-6.97 (m, 1 H), 7.17 (s, 1H), 7.19-7.22 (m, 1 H), 7.34-7.38 (m, 1H). ¹³C NMR (75 MHz, CDCl₃) δ 16.4, 17.7, 25.7, 26.2, 28.0, 39.4, 44.3, 54.4, 54.7, 104.4, 104.7, 109.6, 109.7, 109.9, 110.0, 110.4, 119.5, 123.6, 128.6, 128.9, 131.9, 133.0, 139.9, 156.1, 159.2.

[00212] (E)-4-((1-(3,7-dimethylocta-2,6-dienyl)-5-fluoro-1H-indol-3-yl)methyl)morpholine (6-13e). Yellow oil. Yield: 58.6 %. ¹H NMR (300 MHz, CDCl₃): δ 1.59 (s, 3 H), 1.67 (s, 3 H), 1.80 (s, 3 H), 2.05-2.13 (m, 4 H), 2.49 (br, 4 H), 3.64 (s, 2 H), 3.70-3.73 (m, 4 H), 4.65 (d, *J* = 6.6 Hz, 2 H), 5.06 (d, *J* = 6.0 Hz, 1 H), 5.36 (t, *J* = 6.0 Hz, 1 H), 6.90-6.97 (m, 1 H), 7.08 (s, 1H), 7.19-7.22 (m, 1 H), 7.36-7.40 (m, 1H). ¹³C NMR (75 MHz, CDCl₃) δ 16.4, 17.7, 25.7, 26.2, 39.4, 44.3, 53.5, 54.0, 67.0, 104.3, 104.6, 109.6, 109.9, 110.0, 110.2, 110.4, 119.5, 123.6, 128.6, 128.9, 131.9, 133.0, 140.0, 156.1, 159.2.

[00213] (E)-1-(3,7-dimethylocta-2,6-dienyl)-5-fluoro-3-(pyrrolidin-1-ylmethyl)-1H-indole (6-13f) Yellow oil. Yield: 45.9 %. ¹H NMR (300 MHz, CDCl₃): δ 1.58 (s, 3 H), 1.66 (s, 3 H), 1.79 (br, 7 H), 2.04-2.12 (m, 4 H), 2.59 (br, 4 H), 3.78 (s, 2 H), 4.65 (d, *J* = 6.6 Hz, 2 H), 5.06 (t, *J* = 6.3 Hz, 1 H), 5.36 (t, *J* = 6.6 Hz, 1 H), 6.89-6.96 (m, 1 H), 7.14 (s, 1H), 7.17-7.21 (m, 1 H), 7.31-7.35 (m, 1H). ¹³C NMR (75 MHz, CDCl₃) δ 11.9, 16.4, 17.7, 25.6, 26.3, 39.4, 44.3, 46.5, 48.0, 104.3, 104.6, 109.4, 109.7, 109.9, 110.0, 111.8, 119.7, 123.6, 128.4, 128.9, 131.9, 132.9, 139.8, 156.0, 159.2.

[00214] (E)-1-(3,7-dimethylocta-2,6-dienyl)-5-fluoro-3-((4-methylpiperazin-1-yl)methyl)-1H-indole (6-13g). Yellow oil. Yield: 17.7 %. ¹H NMR (300 MHz, CDCl₃): δ 1.58

(s, 3 H), 1.66 (s, 3 H), 1.79 (s, 3 H), 2.08-2.10 (m, 4 H), 2.28 (s, 3 H), 2.45 (br, 8 H), 3.64 (s, 2 H), 4.63 (d, $J = 6.3$ Hz, 2 H), 5.06 (d, $J = 6.3$ Hz, 1 H), 5.35 (t, $J = 6.3$ Hz, 1 H), 6.89-6.96 (m, 1 H), 7.07 (s, 1H), 7.16-7.20 (m, 1 H), 7.34-7.38 (m, 1H). ^{13}C NMR (75 MHz, CDCl_3) δ 16.4, 17.7, 25.7, 26.2, 39.4, 44.3, 45.9, 52.9, 53.4, 55.1, 104.3, 104.7, 109.5, 109.8, 109.9, 110.1, 110.7, 110.8, 119.6, 123.6, 128.6, 128.9, 131.9, 132.9, 139.9, 156.1, 159.2.

[00215] (E)-N-((1-(3,7-dimethylocta-2,6-dienyl)-5-fluoro-1H-indol-3-yl)methyl)-N-methylpropan-1-amine (6-13h). Yellow oil. Yield: 66.6 %. ^1H NMR (300 MHz, CDCl_3): δ 0.92 (t, $J = 7.5$ Hz, 3 H), 1.51-1.70 (m, 5 H), 1.72 (s, 3 H), 1.80 (s, 3 H), 2.05-2.14 (m, 4 H), 2.21 (s, 3 H), 2.37 (t, $J = 7.5$ Hz, 2 H), 3.62 (s, 2 H), 4.65 (d, $J = 6.6$ Hz, 2 H), 5.05 (br, 1 H), 5.36 (t, $J = 6.6$ Hz, 1 H), 6.90-7.00 (m, 1 H), 7.11 (s, 1H), 7.17-7.21 (m, 1 H), 7.32-7.36 (m, 1H). ^{13}C NMR (75 MHz, CDCl_3) δ 11.9, 16.4, 17.7, 20.7, 25.7, 26.2, 39.4, 42.1, 44.2, 52.7, 59.5, 104.2, 104.5, 109.4, 109.7, 109.9, 110.0, 111.8, 119.6, 123.6, 128.4, 128.9, 131.9, 132.9, 139.8, 156.0, 159.2.

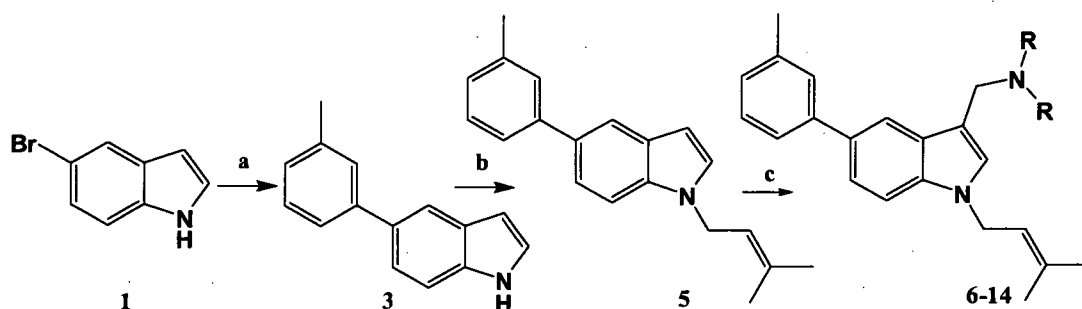
[00216] N-ethyl-N-((5-fluoro-1-octyl-1H-indol-3-yl)methyl)propan-1-amine (6-13i). Yellow oil. Yield: 61.5 %. ^1H NMR (300 MHz, CDCl_3): δ 0.88 (t, $J = 7.5$ Hz, 3 H), 1.07 (t, $J = 7.2$ Hz, 3 H), 1.48-1.80 (m, 11 H), 2.05-2.11 (m, 4 H), 2.42 (t, $J = 7.2$ Hz, 2 H), 2.53 (q, $J = 7.2$ Hz, 2 H), 3.71 (s, 2 H), 4.65 (d, $J = 6.6$ Hz, 2 H), 5.06 (br, 1 H), 5.36 (t, $J = 6.6$ Hz, 1 H), 6.89-6.96 (m, 1 H), 7.06 (s, 1H), 7.16-7.21 (m, 1 H), 7.35-7.39 (m, 1H). ^{13}C NMR (75 MHz, CDCl_3) δ 11.8, 12.0, 16.4, 17.7, 20.2, 25.7, 26.2, 39.4, 44.2, 47.1, 48.7, 55.1, 104.4, 104.7, 109.4, 109.7, 109.8, 110.0, 112.1, 119.7, 123.7, 128.2, 128.9, 131.9, 132.9, 139.7, 156.0, 159.1. Elemental analysis: calc./found (C, H): 77.79, 9.52 78.26, 9.66.

[00217] (E)-N-butyl-N-((1-(3,7-dimethylocta-2,6-dienyl)-5-fluoro-1H-indol-3-yl)methyl)butan-1-amine (6-13j). Yellow oil. Yield: 41.8 %. ^1H NMR (300 MHz, CDCl_3): δ 0.88 (t, $J = 7.2$ Hz, 6 H), 1.23-1.35 (m, 4 H), 1.44-1.54 (m, 4 H), 1.67 (s, 3 H), 1.72 (s, 3 H), 1.80 (s, 3 H), 2.05-2.12 (m, 4 H), 2.43 (t, $J = 7.5$ Hz, 4 H), 3.69 (s, 2 H), 4.65 (d, $J = 6.6$ Hz, 2 H), 5.07 (br, 1 H), 5.36 (t, $J = 6.6$ Hz, 1 H), 6.89-6.95 (m, 1 H), 7.04 (s, 1H), 7.16-7.20 (m, 1 H), 7.34-7.38 (m, 1H). ^{13}C NMR (75 MHz, CDCl_3) δ 14.1, 16.4, 17.7, 20.7, 25.7, 26.2, 29.2, 39.4, 44.2, 49.4, 53.4, 104.4, 104.7, 109.3, 109.7, 109.8, 110.0, 112.4, 119.7, 123.7, 128.2, 128.9, 131.9, 133.0, 139.8, 156.0, 159.0.

[00218] (E)-1-(3,7-dimethylocta-2,6-dienyl)-3-((4-ethylpiperazin-1-yl)methyl)-5-fluoro-1H-indole (6-13k). Yellow oil. Yield: 51.9 %. ^1H NMR (300 MHz, CDCl_3): δ 1.07 (t, $J = 6.9$ Hz, 3 H), 1.58 (s, 3 H), 1.66 (s, 3 H), 1.79 (s, 3 H), 2.01-2.12 (m, 4 H), 2.37-2.53 (m, 10

H), 3.65 (s, 2 H), 4.63 (t, $J = 6.63$ Hz, 2 H), 5.06 (t, $J = 6.0$ Hz, 1 H), 5.35 (t, $J = 6.6$ Hz, 1 H), 6.88-6.95 (m, 1 H), 7.06 (s, 1H), 7.15-7.20 (m, 1 H), 7.34-7.38 (m, 1H). ^{13}C NMR (75 MHz, CDCl_3) δ 11.9, 16.3, 17.7, 25.7, 26.1, 39.4, 44.2, 52.2, 52.8, 52.9, 53.4, 104.3, 104.6, 109.5, 109.8, 109.9, 110.0, 110.7, 110.8, 119.6, 123.6, 128.5, 128.9, 131.8, 132.9, 139.9, 156.0, 159.1.

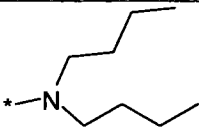
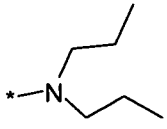
5 **Synthetic scheme for 5-Tolyl-1-isoprenyl-indole analogs related to J 38 G**



Scheme 1. Reagents and conditions: (a) 3-tolylboronic acid (2), $\text{Pd}(\text{dppf})\text{Cl}_2$, K_2CO_3 (aqueous), 1,4-dioxane, microwave, 130°C , 25min, twice; (b) 1-chloro-3-methylbut-2-ene (4), NaH (60%), DMF, rt, 4 h; (c) formaldehyde, secondary amine (RRNH), acetic acid, rt, overnight.

10 **Structures of 5-tolyl-1-isoprenyl--1H-Indole analogs**

Entry	*-NRR
6-14	
6-15	
6-16	
6-17	
6-18	
6-19	

6-20	
6-21	

Experimental Section

[00219] Reagents were purchased from Sigma-Aldrich Chemical Company Inc or Alfa Aesar and used without further purification. ¹H NMR (300 MHz) and ¹³C NMR (75 MHz) spectra were measured on a Bruker Spectrospin 300 Ultrashield magnetic resonance spectrometer using CDCl₃ as the solvent. Chemical shifts (δ) were reported in ppm and referenced to residual deuterated solvents. Coupling constants (*J*) were reported in Hz. Reactions were monitored by thin layer chromatography (TLC, Silica Gel 60 F254, Merck) with ultraviolet light as visualizing agent. Column chromatography was carried out with Silica Gel 60 (0.04–0.06 mm). Mass spectra were recorded in positive ion mode using electro spray ionization (ESI) or high-resolution LC-MS (IT TOF). Nominal mass spectra were captured on an LCQ Finnigan MAT equipped with an atmospheric pressure chemical ionization (APCI) probe and *m/z* values for the molecular ion were reported. Purity of final compounds was verified by reverse phase HPLC on two different solvent systems (isocratic mode) and found to be ≥ 95%. Elemental analysis had carbon and hydrogen values that were within ± 5% of theoretical values.

General procedure for the synthesis of 5-*m*-tolyl-1*H*-indole (3)

[00220] To the mixture of 5-bromo-1*H*-indole (1, 5 mmol, 1 equiv.), 3-tolylboronic acid (2, 5.5 mmol, 1.1 equiv.) and Pd(dppf)Cl₂ (0.25 mmol, 0.05 equiv.) in 12 mL 1,4-dioxane was added 4 mL aqueous solution of K₂CO₃ (15 mmol, 3 equiv.). The mixture was stirred under argon for about 15 min then stirred under microwave in 130 °C for about 25min twice. On cooling, the solvent was evaporated and the resulting residue was extracted with CH₂Cl₂ (20 mL×3), the dichloromethane layer was washed with brine, dried (Na₂SO₄) and filtered. The residue obtained on removal of the solvent was purified by column chromatography on silica gel with EtOAc/hexane as eluting solvents to give the target compound 5-*m*-tolyl-1*H*-indole (3). Yield: 55.0 %. ¹H NMR (300 MHz, CDCl₃): δ 2.31 (s, 3 H), 6.47 (s, 1 H), 6.92-7.12 (m, 2 H),

7.18-7.23 (m, 1 H), 7.29-7.35 (m, 4H), 7.74 (s, 1 H), 7.99 (br, 1H). ¹³C NMR (75 MHz, CDCl₃) δ 21.5, 102.9, 111.1, 119.2, 121.9, 124.4, 124.8, 127.0, 128.2, 128.3, 128.5, 133.4, 135.2, 138.1, 142.5.

General procedure for the synthesis of 1-(3-methylbut-2-enyl)-5-*m*-tolyl-1*H*-indole (5)

5 [00221] To the solution of 5-*m*-tolyl-1*H*-indole (3, 4 mmol, 1 equiv.) in anhydrous dimethylsulfoxide(DMSO) was added NaH (60% in mineral oil dispersion, 4.8 mmol, 1.2 equiv.) at room temperature. The mixture was stirred for about 1 h at the same temperature, then 1-chloro-3-methylbut-2-ene (4, 4.8 mmol, 1.2 equiv.) was added and the mixture was stirred for 4 h. Water was added to stop the reaction. The mixture was extracted by
10 dichloromethane and the organic layer was washed with brine, dried (Na₂SO₄), filtered, and evaporated. The residue was purified by column chromatography of silica gel to get off-yellow oil. Yield: 87.1 %. ¹H NMR (300 MHz, CDCl₃): δ 1.82 (s, 3 H), 1.88 (s, 3 H), 2.48 (s, 3 H), 4.74 (d, *J* = 6.6 Hz, 2 H), 5.45 (t, *J* = 6.9 Hz, 1 H), 6.57 (d, *J* = 2.4 Hz, 1 H), 7.17 (t, *J* = 3.3 Hz, 2 H), 7.34-7.43 (m, 2H), 7.49-7.52 (m, 3H), 7.89 (s, 1H). ¹³C NMR (75 MHz, CDCl₃) δ 18.0,
15 21.6, 25.6, 44.2, 101.3, 109.6, 119.4, 119.9, 121.2, 124.4, 126.9, 128.0, 128.2, 128.5, 129.2, 132.9, 135.5, 136.3, 138.1, 142.6.

General procedure for the synthesis of *N*-substituted 1-isoprenyl-5-*m*-tolyl-1*H*-indole methylamines (6-14 to 6-21)

20 [00222] To the mixture of appropriate secondary amine (1.2 equiv.), 36% aqueous formaldehyde (1.2 equiv.) in acetic acid (5 mL) was added 1-(3-methylbut-2-enyl)-5-*m*-tolyl-1*H*-indole (5, 200mg, 1 equiv.) 0 °C. The reaction mixture was stirred at room temperature overnight. After the reaction was completed, the reaction mixture was basified by 50% NaOH aqueous solution to pH=9 and extracted by dichloromethane (10 mL×3). The combined extracts were washed with brine (20 mL) and dried over Na₂SO₄. The organic layer was concentrated
25 under reduced pressure. The crude product was purified by column chromatography of silica gel using ethyl acetate/hexane or dichloromethane/methanol as eluting solvents.

30 [00223] *N,N*-dimethyl-1-(1-(3-methylbut-2-enyl)-5-*m*-tolyl-1*H*-indol-3-yl)methanamine (6-14). Yellow oil. Yield: 33.1 %. ¹H NMR (300 MHz, CDCl₃): δ 1.79 (s, 3 H), 1.85 (s, 3 H), 2.33 (s, 6 H), 2.45 (s, 3 H), 3.69 (s, 2 H), 4.70 (d, *J* = 6.6 Hz, 2 H), 5.41 (t, *J* = 6.6 Hz, 1 H), 7.11-7.15 (m, 2 H), 7.32-7.38 (m, 2 H), 7.45-7.49 (m, 3H), 7.86 (s, 1H). ¹³C NMR (75 MHz, CDCl₃) δ 18.0, 21.6, 25.6, 44.1, 45.2, 54.2, 109.6, 111.8, 117.7, 119.9, 121.3, 124.6, 126.9, 127.7, 128.2, 128.5, 129.0, 132.8, 135.7, 136.3, 138.1, 142.7.

[00224] 4-((1-(3-methylbut-2-enyl)-5-*m*-tolyl-1*H*-indol-3-

yl)methyl)thiomorpholine (6-15). Yellow oil. Yield: 52.9 %. ¹H NMR (300 MHz, CDCl₃): δ 1.79 (s, 3 H), 1.85 (s, 3 H), 2.46 (s, 3 H), 2.68-2.71 (m, 4H), 2.80-2.81 (m, 4H), 3.77 (s, 2 H), 4.69 (d, *J* = 6.9 Hz, 2 H), 5.40 (t, *J* = 6.9 Hz, 1 H), 7.08 (s, 1 H), 7.15 (d, *J* = 7.2 Hz, 1 H), 7.32-7.37 (m, 2 H), 7.45-7.47 (m, 3H), 7.89 (s, 1H). ¹³C NMR (75 MHz, CDCl₃) δ 18.0, 21.6, 25.7, 28.0, 44.2, 54.3, 54.8, 109.7, 110.7, 118.1, 119.9, 121.4, 124.5, 127.0, 127.8, 128.2, 128.5, 129.1, 132.8, 135.8, 136.3, 138.1, 142.7. Elemental analysis: calc./found (C, H): 76.88, 7.74 75.95, 7.57.

[00225] 1-(3-methylbut-2-enyl)-3-(pyrrolidin-1-ylmethyl)-5-*m*-tolyl-1*H*-indole (6-

16). Yellow oil. Yield: 31.1 %. ¹H NMR (300 MHz, CDCl₃): δ 1.78-1.81 (m, 7 H), 1.84 (s, 3 H), 2.454 (s, 3 H), 2.63 (br, 4H), 3.88 (s, 2 H), 4.687 (d, *J* = 6.9 Hz, 2 H), 5.40 (t, *J* = 6.9 Hz, 1 H), 7.12-7.17 (m, 2 H), 7.26-7.36 (m, 2 H), 7.44-7.48 (m, 3H), 7.86 (s, 1H). ¹³C NMR (75 MHz, CDCl₃) δ 18.0, 21.6, 23.5, 25.7, 44.1, 50.2, 54.1, 109.6, 112.3, 117.7, 119.9, 121.2, 124.5, 126.9, 127.4, 128.2, 128.5, 128.9, 132.7, 135.6, 136.2, 138.1, 142.8.

[00226] 1-(3-methylbut-2-enyl)-3-((4-methylpiperazin-1-yl)methyl)-5-*m*-tolyl-1*H*-

indole (6-17). Yellow oil. Yield: 38.4 %. ¹H NMR (300 MHz, CDCl₃): δ 1.78 (s, 3 H), 1.84 (s, 3 H), 2.29 (s, 3 H), 2.45-2.60 (m, 11H), 3.77 (s, 2 H), 4.67 (d, *J* = 6.6 Hz, 2 H), 5.39 (br, 1 H), 7.11-7.15 (m, 2 H), 7.33-7.36 (m, 2H), 7.44-7.47 (m, 3H), 7.89 (s, 1H). ¹³C NMR (75 MHz, CDCl₃) δ 18.0, 21.6, 25.6, 44.1, 45.9, 52.8, 53.2, 55.0, 109.6, 110.9, 118.0, 119.9, 121.3, 124.5, 127.0, 127.9, 128.2, 128.5, 129.1, 132.7, 135.7, 136.3, 138.1, 142.7.

[00227] *N*-methyl-*N*-((1-(3-methylbut-2-enyl)-5-*m*-tolyl-1*H*-indol-3-

yl)methyl)propan-1-amine (6-18). Yellow oil. Yield: 59.2 %. ¹H NMR (300 MHz, CDCl₃): δ 0.94 (t, *J* = 7.2 Hz, 3 H), 1.56-1.65 (m, 2 H), 1.78 (s, 3 H), 1.84 (s, 3 H), 2.42 (s, 3 H), 2.45-2.47 (m, 5 H), 3.76 (s, 2 H), 4.69 (d, *J* = 6.6 Hz, 2 H), 5.41 (t, *J* = 5.7 Hz, 1 H), 7.08-7.15 (m, 2 H), 7.32-7.37 (m, 2H), 7.44-7.48 (m, 3H), 7.88 (s, 1H). ¹³C NMR (75 MHz, CDCl₃) δ 11.9, 18.0, 20.6, 21.6, 25.7, 42.0, 44.1, 52.5, 59.3, 109.6, 111.6, 118.0, 119.9, 121.3, 124.5, 127.0, 127.7, 128.2, 128.5, 129.1, 132.7, 135.7, 136.2, 138.0, 142.7.

[00228] *N*-ethyl-*N*-((1-(3-methylbut-2-enyl)-5-*m*-tolyl-1*H*-indol-3-

yl)methyl)propan-1-amine (6-19). Yellow oil. Yield: 36.8 %. ¹H NMR (300 MHz, CDCl₃): δ 0.93 (t, *J* = 7.2 Hz, 3 H), 1.11 (t, *J* = 7.2 Hz, 3 H), 1.54-1.66 (m, 2 H), 1.79 (s, 3 H), 1.85 (s, 3 H), 2.42 (s, 3 H), 2.46-2.51 (m, 5 H), 2.59 (q, *J* = 7.2 Hz, 2 H), 3.83 (s, 2 H), 4.69 (d, *J* = 6.6 Hz, 2 H), 5.42 (t, *J* = 6.3 Hz, 1 H), 7.08 (s, 1 H), 7.14 (d, *J* =

7.5 Hz, 1 H), 7.32-7.37 (m, 2H), 7.45-7.49 (m, 3H), 7.93 (s, 1H). ¹³C NMR (75 MHz, CDCl₃) δ 11.9, 12.0, 18.0, 20.3, 21.6, 25.6, 44.1, 47.1, 48.6, 55.2, 109.5, 112.6, 118.2, 120.1, 121.1, 124.5, 126.9, 127.3, 128.2, 128.5, 129.2, 132.5, 135.8, 136.1, 138.1, 142.8.

[00229] *N*-butyl-*N*-((1-(3-methylbut-2-enyl)-5-*m*-tolyl-1*H*-indol-3-

5 *yl*)methyl)butan-1-amine (6-20). Yellow oil. Yield: 42.1 %. ¹H NMR (300 MHz, CDCl₃): δ ¹H NMR (300 MHz, CDCl₃): δ 0.91 (t, *J* = 7.2 Hz, 6 H), 1.28-1.40 (m, 4 H), 1.49-1.59 (m, 4 H), 1.79 (s, 3 H), 1.85 (s, 3 H), 2.45-2.52 (m, 7 H), 3.81 (s, 2 H), 4.69 (d, *J* = 6.6 Hz, 2 H), 5.41 (t, *J* = 6.3 Hz, 1 H), 7.06 (s, 1 H), 7.14 (d, *J* = 7.5 Hz, 1 H), 7.32-7.36 (m, 2H), 7.44-7.49 (m, 3H), 7.93 (s, 1H). ¹³C NMR (75 MHz, CDCl₃) δ 14.1, 18.0, 20.8, 21.6, 25.6, 29.3, 44.1, 49.2, 53.5, 109.4, 112.8, 118.3, 120.1, 121.1, 124.4, 126.8, 127.3, 128.2, 128.5, 129.2, 132.4, 135.8, 136.1, 138.0, 142.8. Elemental analysis: calc./found (C, H): 83.60, 9.68 83.54, 9.82.

[00230] *N*-((1-(3-methylbut-2-enyl)-5-*m*-tolyl-1*H*-indol-3-yl)methyl)-*N*-

propylpropan-1-amine (6-21). Yellow oil. Yield: 57.4 %. ¹H NMR (300 MHz, CDCl₃): δ ¹H NMR (300 MHz, CDCl₃): δ 0.91 (t, *J* = 7.2 Hz, 6 H), 1.52-1.64 (m, 4 H), 1.79 (s, 3 H), 1.85 (s, 15 3 H), 2.44-2.49 (m, 7 H), 3.82 (s, 2 H), 4.69 (d, *J* = 6.6 Hz, 2 H), 5.42 (t, *J* = 6.6 Hz, 1 H), 7.07 (s, 1 H), 7.14 (d, *J* = 7.5 Hz, 1 H), 7.32-7.37 (m, 2H), 7.45-7.49 (m, 3H), 7.94 (s, 1H). ¹³C NMR (75 MHz, CDCl₃) δ 12.0, 18.0, 20.3, 21.6, 25.6, 44.1, 49.3, 55.8, 109.5, 112.8, 118.3, 120.1, 121.1, 124.4, 126.8, 127.3, 128.2, 128.5, 129.1, 132.4, 135.8, 136.1, 138.1, 142.8.

[00231] The listing or discussion of a previously published document in this 20 specification should not necessarily be taken as an acknowledgement that the document is part of the state of the art or is common general knowledge. All documents listed are hereby incorporated herein by reference in their entirety.

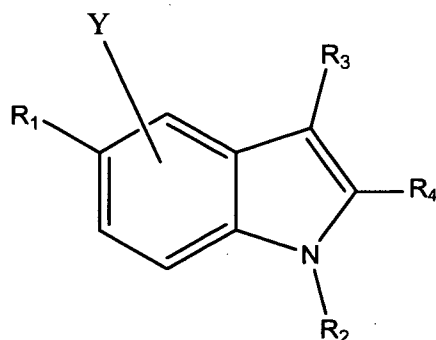
[00232] The invention has been described broadly and generically herein. Each of the narrower species and subgeneric groupings falling within the generic disclosure also form part 25 of the invention. This includes the generic description of the invention with a proviso or negative limitation removing any subject matter from the genus, regardless of whether or not the excised material is specifically recited herein.

[00233] Other embodiments are within the following claims. In addition, where features or aspects of the invention are described in terms of Markush groups, those skilled in 30 the art will recognise that the invention is also thereby described in terms of any individual member or subgroup of members of the Markush group.

CLAIMS

What is claimed is:

1. A compound of Formula I



(I)

or a pharmaceutically acceptable salt thereof,

wherein

R₁ and Y are independently selected from the group consisting of hydrogen, hydroxyl, C₁-
20alkyl, C₂-20alkenyl, C₂-20alkynyl, C₁-20acyl, C₃-8cycloalkyl, C₃-8cycloalkenyl, aryl, heteroaryl,
heteroalicycyl, halogen, carbonyl, thiocarbonyl, O-carbamyl, O-thiocarbonyl, O-carboxy,
isocyanato, thiocyanato, silyl, sulfonamide, thio, -CN, -COOH, -SH, -N=N, -N=O and NX₁X₂,
wherein one or more of the hydrogen atoms of the indole ring can be replaced by Y;

R₂ is selected from the group consisting of hydrogen, C₁-20alkyl, C₂-20alkenyl, C₂-20alkynyl, C₁-
20acyl, C₃-8cycloalkyl, C₃-8cycloalkenyl, aryl, heteroaryl and heteroalicycyl;

R₃ is (CH₂)_nNX₁X₂, n being an integer from 1 to 4;

R₄ is hydrogen or C₁-C₄ alkyl;

X₁ and X₂ are independently selected from the group consisting of hydrogen, C₁-20alkyl, C₂-
20alkenyl, C₂-20alkynyl, C₁-20acyl, C₃-8cycloalkyl, C₃-8cycloalkenyl, aryl, heteroaryl, and
heteroalicycyl; or

X₁ or X₂ may, together with the nitrogen atom bearing them, form a 3-8 membered ring,

wherein the 3-8 membered ring can be fused to at least one 3-8 membered ring, wherein the 3-8 membered ring is preferably a saturated ring, and wherein ring can optionally comprise 0, 1, 2, 3 or 4 further heteroatoms selected from the group consisting of oxygen, nitrogen, sulphur and phosphorus; and wherein the ring can be substituted by at least one substituent selected from the group consisting of hydrogen, hydroxyl, C₁₋₂₀alkyl, C₂₋₂₀alkenyl, C₂₋₂₀alkynyl, C₁₋₂₀acyl, C₃₋₈cycloalkyl, C₃₋₈cycloalkenyl, aryl, heteroaryl, heteroalicyclic, halogen, carbonyl, thiocarbonyl, O-carbamyl, O-thiocarbonyl, O-carboxy, isocyanato, thiocyanato, silyl, perhaloalkyl, sulfonyl, sulfonamide, thio, -CN, -COOH, -SH, -N=N, -N=O and NX₁X₂;

with the proviso that the following compounds are excluded:

- 10 3-(1-piperidinylmethyl)-1H-Indole-1-hexanamine;
1-(4-methyl-3-penten-1-yl)-N-(phenylmethyl)-1H-Indole-3-methanamine;
1-(3-buten-1-yl)-N-(phenylmethyl)-1H-Indole-3-methanamine;
5-ethenyl-N,N-dimethyl-1-h(phenylmethyl)-1H-Indole-3-methanamine, homopolymer (9CI);
N,1-dimethyl-N-(3-phenyl-2-propen-1-yl)-1H-Indole-3-methanamine;
- 15 N,1-dimethyl-N-(3-phenyl-2-propenyl)-1H-Indole-3-methanamine, (E)- (9CI);
3-[[4-(2,6-dimethylphenyl)-1-piperidinyl]methyl]-1-(phenylmethyl)-1H-Indole;
5-phenyl-3-(1-piperidinylmethyl)-1H-Indole;
1-methyl-3-(1-piperidinylmethyl)-5-[3-(1-piperidinyl)-1-propyn-1-yl]-1H-Indole;
1-(phenylmethyl)-3-(1-piperidinylmethyl)-1H-Indole, hydrochloride (1:1);
- 20 1-(phenylmethyl)-3-(1-piperidinylmethyl)-1H-Indole;
N,N-dimethyl-N-nonyl-1-(phenylmethyl)-1H-Indole-3-methanaminium;
N,N-dimethyl-N-octyl-1-(phenylmethyl)-1H-Indole-3-methanaminium;
N,N-dimethyl-N-[[1-(phenylmethyl)-1H-indol-3-yl]methyl]-1-heptanaminium;
N-(phenylmethyl)-1-(2-propen-1-yl)-N-(4-pyridinylmethyl)-1H-Indole-3-methanamine;
- 25 5-methyl-3-(1-piperidinylmethyl)-1-(2-propen-1-yl)-1H-Indole; and
N-ethyl-N-((5-fluoro-1-(3-methylbut-2-enyl)-1H-indol-3-yl) methyl) ethanamine.

2. The compound according to claim 1, wherein Y is hydrogen.

- 30 3. The compound according to claim 1 or 2, wherein R₃ is (CH₂)_nNX₁X₂, n being an integer of 1 or 2.

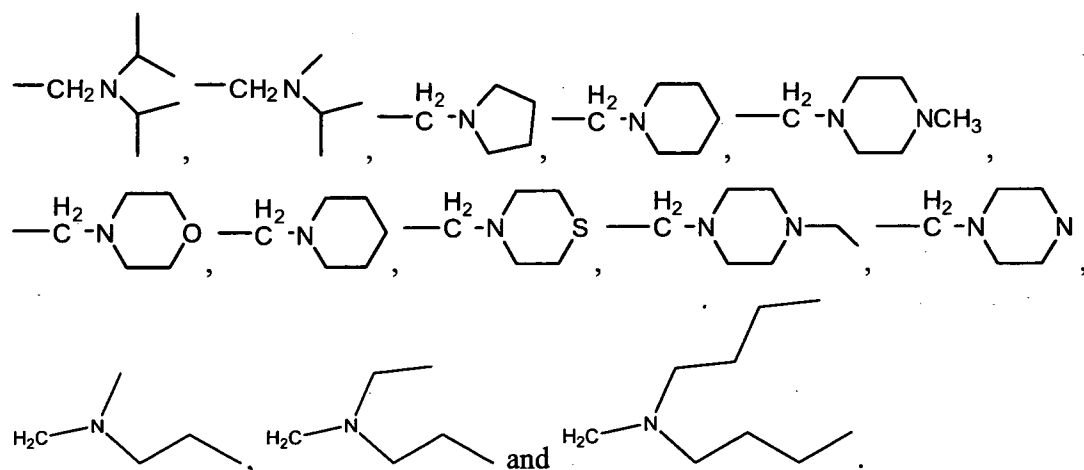
4. The compound according to any one of claims 1 to 3, wherein X_1 and X_2 are independently selected from the group consisting of hydrogen, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, C_{1-10} acyl, C_{3-8} cycloalkyl, C_{3-8} cycloalkenyl, aryl, heteroaryl and heteroalcyclyl; or

5 X_1 or X_2 may, together with the nitrogen atom bearing them, form a 3-8 membered ring, wherein the 3-8 membered ring can be fused to at least one 3-8 membered ring, wherein the ring can optionally comprise 0, 1, 2, 3 or 4 further heteroatoms selected from the group consisting of oxygen, nitrogen, sulphur and phosphorus; and wherein the ring can be substituted by at least one substituent selected from the group consisting of hydrogen, hydroxyl, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, C_{1-10} acyl, C_{3-8} cycloalkyl, C_{3-8} cycloalkenyl, aryl, heteroaryl, heteroalcyclyl, halogen, carbonyl, thiocarbonyl, O-carbamyl, O-thiocarbonyl, O-carboxy, isocyanato, thiocyanato, silyl, perhaloalkyl, sulfonyl, sulfonamide, thio, -CN, -COOH, -SH, -N=N, -N=O and NX_1X_2 .

5. The compound according to any one of claims 1 to 4, wherein X_1 and X_2 are independently selected from hydrogen or C_{1-10} alkyl; or

X_1 or X_2 may, together with the nitrogen atom bearing them, form a 5 or 6-membered ring.

6. The compound according to any one of claims 1 to 5, wherein R_3 is selected from the group consisting of CH_2NH_2 , $CH_2N(CH_3)_2$, $CH_2N(C_2H_5)_2$, $CH_2N(C_3H_7)_2$,



7. The compound according to any of claims 1 to 6, wherein R_2 is selected from the group consisting of hydrogen, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, C_{1-10} acyl, C_{3-8} cycloalkyl, C_{3-8} cycloalkenyl, aryl, heteroaryl and heteroalcyclyl; or

cycloalkenyl, aryl, heteroaryl and heteroalicycyl.

8. The compound according to any one of claims 1 to 7, wherein R₂ is C₁₋₈alkyl or C₂₋₈alkenyl.

5 9. The compound according to claim 8, wherein R₂ is selected from the group consisting of methyl, ethyl, n-propyl, propyl, isopropyl, butyl, n-butyl, isobutyl, sec-butyl, tert-butyl, tert-amyl, pentyl, hexyl, heptyl, octyl, vinyl, 1-propenyl, allyl, 1-butenyl, 3-butenyl, isoprenyl, 1-pentenyl, 3-pentenyl, 4-pentenyl, dimethylallyl, 1-hexenyl, 3-hexenyl, 5-hexenyl, 1-heptenyl, 3-heptenyl, 6-heptenyl, 7-octenyl and geranyl.

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10. The compound according to any one of claims 1 to 9, wherein R₂ is octyl or isoprenyl.

11. The compound according to any one of claims 1 to 10, wherein R₁ is selected from the group consisting of hydrogen, hydroxyl, C₁₋₁₀alkyl, C₂₋₁₀alkenyl, C₂₋₁₀alkynyl, C₁₋₁₀acyl, C₃₋₈cycloalkyl, C₃₋₈cycloalkenyl, aryl, heteroaryl, heteroalicycyl, halogen, carbonyl, thiocarbonyl, O-carbamyl, O-thiocarbonyl, O-carboxy, isocyanato, thiocyanato, silyl, perhaloalkyl, sulfonyl, sulfonamide, thio, -CN, -COOH, -SH, -N=N, -N=O and NX₁X₂.

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12. The compound according to any one of claims 1 to 11, wherein the halogen is selected from the group consisting of fluorine, chlorine, iodine and bromine.

20

13. The compound according to any one of claims 1 to 12, wherein R₁ is aryl or (CH₃)_m-aryl, wherein m being an integer between 0 to 4.

25 14. The compound according to claim 13, wherein m is 1.

15. The compound according to claim 13 or 14, wherein one of more of the hydrogen atoms of the aryl ring is replaced by a substituent selected from the group consisting of alkyl, heteroalkyl, haloalkyl, heterohaloalkyl, cycloalkyl, aryl, arylalkyl, heteroaryl, non-aromatic heterocycle, hydroxy, alkoxy, aryloxy, mercapto, alkylthio, arylthio, cyano, fluoro, chloro, bromo, carbonyl, thiocarbonyl, O-carbamyl, N-carbamyl, O-thiocarbamyl, N-thiocarbamyl, C-amido, N-amido, S-sulfonamido, N-sulfonamido, C-carboxy, O-carboxy, isocyanato,

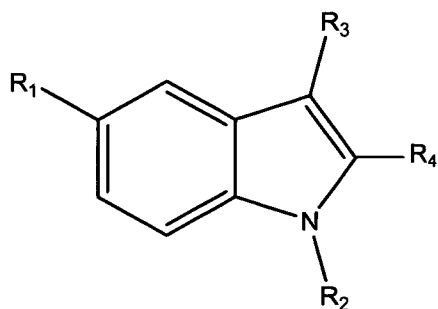
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thiocyanato, isothiocyanato, nitro, silyl, trihalomethanesulfonyl, amino group, and mono- and di-substituted amino groups.

16. The compound according to any one of claims 13 to 15, wherein the aryl is phenyl or naphthyl.

17. The compound according to any one of claims 1 to 16, wherein R_1 is selected from the group consisting of 2'-CH₃-C₆H₅, 3'-CH₃-C₆H₅ and 4'-CH₃-C₆H₅.

18. The compound according to any one of claims 1 to 17, wherein the compound is a compound of formula Ia



(Ia)

or a pharmaceutically acceptable salt thereof,

wherein

R_1 is a halogen or (CH₃)_m-aryl, m being an integer between 0 to 4;

R_2 is C₁₋₁₀ alkyl or C₂₋₁₀ alkenyl;

R_3 is (CH₂)_nNX₁X₂, n being an integer from 1 to 4;

R_4 is hydrogen or C₁₋₄ alkyl;

X_1 and X_2 are independently C₁₋₁₀ alkyl; or

X_1 or X_2 may, together with the nitrogen bearing them, form a 5-6 membered ring, wherein the 5-6 membered ring can be fused to at least one 5-6 membered ring, wherein the ring can optionally comprise 0, 1, 3 or 4 further heteroatoms selected from the group consisting of oxygen, nitrogen, sulphur, and phosphorus; and wherein the ring can be substituted by at least one substituent selected from the group consisting of halogen, hydroxyl, oxo, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ acyl, C₃₋₈ cycloalkyl, and C₃₋₈ cycloalkenyl.

19. The compound according to any one of claims 1 to 18, wherein the compound is selected from the group consisting of:

- 1-octyl-5-*m*-tolyl-1H-indol-3-yl) methanamine (J18);
 N,N-dimethyl(1-octyl-5-*m*-tolyl-1H-indol-3-yl) methanamine (J25G);
 5 N-ethyl-N-((1-octyl-5-*m*-tolyl-1H-indol-3-yl) methyl) ethanamine (J17G);
 N-((1-octyl-5-*m*-tolyl-1H-indol-3-yl) methyl)-N-propylpropan-1-amine (J27G);
 N-isopropyl-N-((1-octyl-5-*m*-tolyl-1H-indol-3-yl) methyl) propan-2-amine (J26G);
 N-methyl-N-((1-octyl-5-*m*-tolyl-1H-indol-3-yl) methyl) propan-2-amine (J29G);
 1-octyl-3-(pyrrolidin-1-ylmethyl)-5-*m*-tolyl-1H-indole (J31G);
 10 1-octyl-3-(piperidin-1-ylmethyl)-5-*m*-tolyl-1H-indole (J32G);
 3-((4-methylpiperazin-1-yl) methyl)-1-octyl-5-*m*-tolyl-1H-indole (J30G);
 3-(morpholinomethyl)-1-octyl-5-*m*-tolyl-1H-indole (J34G);
 N-ethyl-N-((1-octyl-5-*o*-tolyl-1H-indol-3-yl) methyl) ethanamine (J36G);
 N-ethyl-N-((1-octyl-5-*p*-tolyl-1H-indol-3-yl) methyl) ethanamine (J37G);
 15 N-ethyl-N-((5-fluoro-1-octyl-1H-indol-3-yl) methyl) ethanamine (J40G);
 N-ethyl-N-((1-(3-methylbut-2-enyl)-5-*m*-tolyl-1H-indol-3-yl) methyl) ethanamine (J38G);
 1-(3-methylbut-2-enyl)-3-(piperidin-1-ylmethyl)-5-*m*-tolyl-1H-indole (J39G);
 N-ethyl-N-((1-(3-methylbut-2-enyl)-1H-indol-3-yl) methyl) ethanamine (J35G);
 1-(5-fluoro-1-octyl-1H-indol-3-yl)-N,N-dimethylmethanamine;
 20 5-fluoro-1-octyl-3-(piperidin-1-ylmethyl)-1H-indole;
 4-((5-fluoro-1-octyl-1H-indol-3-yl)methyl)thiomorpholine;
 4-((5-fluoro-1-octyl-1H-indol-3-yl)methyl)morpholine;
 5-fluoro-1-octyl-3-(pyrrolidin-1-ylmethyl)-1H-indole;
 5-fluoro-3-((4-methylpiperazin-1-yl)methyl)-1-octyl-1H-indole;
 25 4-((1-(3-methylbut-2-enyl)-5-*m*-tolyl-1H-indol-3-yl)methyl)morpholine;
 N-((5-fluoro-1-octyl-1H-indol-3-yl)methyl)-N-methylpropan-1-amine;
 N-ethyl-N-((5-fluoro-1-octyl-1H-indol-3-yl)methyl)propan-1-amine;
 N-butyl-N-((5-fluoro-1-octyl-1H-indol-3-yl)methyl)butan-1-amine;
 (E)-1-(1-(3,7-dimethylocta-2,6-dienyl)-5-fluoro-1H-indol-3-yl)-N,N-dimethylmethanamine;
 30 (E)-N-((1-(3,7-dimethylocta-2,6-dienyl)-5-fluoro-1H-indol-3-yl)methyl)-N-ethylethanamine;
 (E)-1-(3,7-dimethylocta-2,6-dienyl)-5-fluoro-3-(piperidin-1-ylmethyl)-1H-indole;
 (E)-4-((1-(3,7-dimethylocta-2,6-dienyl)-5-fluoro-1H-indol-3-yl)methyl) thiomorpholine;

(*E*)-4-((1-(3,7-dimethylocta-2,6-dienyl)-5-fluoro-1*H*-indol-3-yl)methyl)morpholine;
 (*E*)-1-(3,7-dimethylocta-2,6-dienyl)-5-fluoro-3-(pyrrolidin-1-ylmethyl)-1*H*-indole;
 (*E*)-1-(3,7-dimethylocta-2,6-dienyl)-5-fluoro-3-((4-methylpiperazin-1-yl)methyl)-1*H*-indole;
 (*E*)-*N*-((1-(3,7-dimethylocta-2,6-dienyl)-5-fluoro-1*H*-indol-3-yl)methyl)-*N*-methylpropan-1-amine;

N-ethyl-*N*-((5-fluoro-1-octyl-1*H*-indol-3-yl)methyl)propan-1-amine;

(*E*)-*N*-butyl-*N*-((1-(3,7-dimethylocta-2,6-dienyl)-5-fluoro-1*H*-indol-3-yl)methyl)butan-1-amine;

(*E*)-1-(3,7-dimethylocta-2,6-dienyl)-3-((4-ethylpiperazin-1-yl)methyl)-5-fluoro-1*H*-indole;

N,N-dimethyl-1-(1-(3-methylbut-2-enyl)-5-*m*-tolyl-1*H*-indol-3-yl)methanamine;

4-((1-(3-methylbut-2-enyl)-5-*m*-tolyl-1*H*-indol-3-yl)methyl)thiomorpholine;

1-(3-methylbut-2-enyl)-3-(pyrrolidin-1-ylmethyl)-5-*m*-tolyl-1*H*-indole;

1-(3-methylbut-2-enyl)-3-((4-methylpiperazin-1-yl)methyl)-5-*m*-tolyl-1*H*-indole;

N-methyl-*N*-((1-(3-methylbut-2-enyl)-5-*m*-tolyl-1*H*-indol-3-yl)methyl)propan-1-amine;

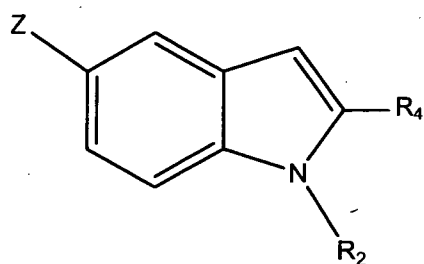
N-ethyl-*N*-((1-(3-methylbut-2-enyl)-5-*m*-tolyl-1*H*-indol-3-yl)methyl)propan-1-amine;

N-butyl-*N*-((1-(3-methylbut-2-enyl)-5-*m*-tolyl-1*H*-indol-3-yl)methyl)butan-1-amine; and

N-((1-(3-methylbut-2-enyl)-5-*m*-tolyl-1*H*-indol-3-yl)methyl)-*N*-propylpropan-1-amine.

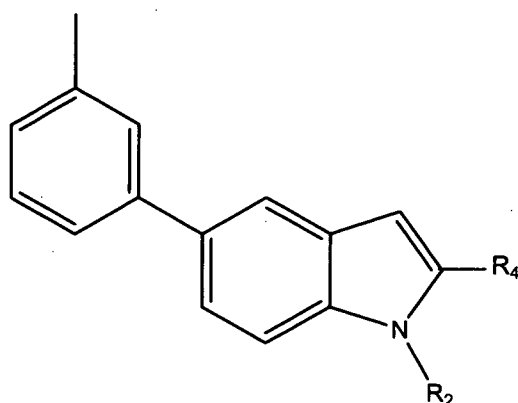
20. A method of preparing a compound of formula I, the method comprising:

i) adding a phosphine compound to a solution containing the compound of formula II



(II);

wherein Z is a leaving group, under conditions to form a compound of formula III



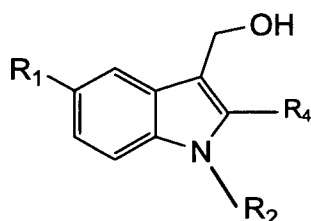
(III);

and

ii) adding an amine and an aldehyde to the solution obtained in step i) to form a compound of
5 formula I.

21. A method of preparing a compound of formula I, the method comprising:

i) adding a sulphonyl compound to a solution containing the compound of formula IV



(IV);

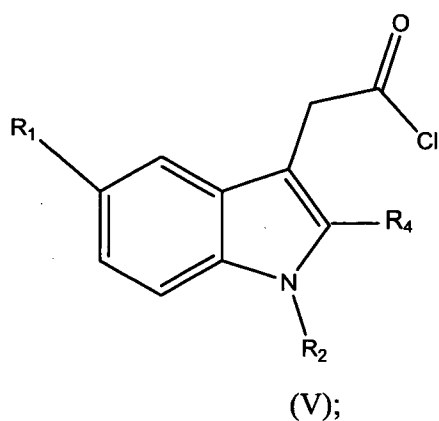
under conditions to form a sulphonate ester compound; and

ii) adding an amine to the solution containing the sulphonate ester compound under conditions
to form a compound of formula I.

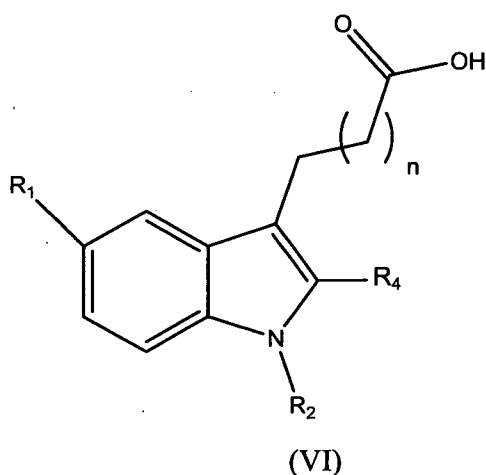
22. The method according to claim 21, wherein the sulphonyl compound is methanesulphonyl
chloride or *p*-toluenesulphonyl chloride.

23. A method of preparing a compound of formula I, wherein R_3 is $(CH_2)_nNX_1X_2$, n being
an integer from 2 to 4, the method comprising:

i) adding a methylating agent into a solution containing the compound of formula V



under conditions to form a compound of formula VI



wherein n corresponds to the number of times step i) is repeated;

ii) adding a sulphonyl compound to the solution containing the compound of formula VI, under conditions to form a sulphonyl ester compound; and

iii) adding an amine to the solution containing the sulphonyl ester compound to form a compound of formula I.

24. The method according to claim 23, wherein the methylating agent is diazomethane.

25. The method according to claims 23 or 24, wherein the sulphonyl compound is methanesulphonyl chloride or *p*-toluenesulphonyl chloride.

26. A method of killing a cell comprising administering to the cell a compound of any of claims 1 to 19.

27. The method according to claim 26, wherein the cell is comprised in a mammal.

28. The method according to claim 26, wherein the cell is cultured.

5 29. The method according to claim 28, wherein the cell is obtained from a mammal.

30. The method according to claim 29, wherein the mammal is selected from the group consisting of a rat, a cow, a goat, a sheep, a pig, a dog, a mouflon, a guinea pig, a hamster, a chimpanzee, a rhesus monkey and a human.

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31. The method according to claim 30, wherein the mammal is a human.

32. The method according to any one of claims 26 to 31, wherein the cell is a tumor cell.

15 33. The method according to claim 32, wherein the tumor cell is derived from a cancer selected from a group consisting of breast cancer, lung cancer, brain cancer, neuroblastoma, colon cancer, rectal cancer, bladder cancer, liver tumor, a pancreatic tumor, ovarian cancer, prostate cancer, melanoma, cancer of the head or neck and leukaemia.

20 34. A method of treating a mammal with a disease or disorder associated with Icmt activity comprising administering to the animal a compound of any of claims 1 to 19.

35. The method according to claim 34, wherein the disease or disorder is cancer.

25 36. The method according to claim 35, wherein the cancer is selected from a group consisting of breast cancer, lung cancer, brain cancer, neuroblastoma, colon cancer, rectal cancer, bladder cancer, liver tumor, a pancreatic tumor, ovarian cancer, prostate cancer, melanoma, cancer of the head or neck and leukaemia.

30 37. The method according to claim 34, wherein the mammal is selected from the group consisting of a rat, a cow, a goat, a sheep, a pig, a dog, a mouflon, a guinea pig, a hamster, a chimpanzee, a rhesus monkey and a human.

38. The method according to claim 37, wherein the mammal is a human.

39. A pharmaceutical composition comprising a compound according to any one of claims 1 to 19.

40. The pharmaceutical composition according to claim 39, further comprising a carrier or diluent.

41. The pharmaceutical composition according to claim 39 or 40, wherein the compound is selected from the group consisting of:

1-octyl-5-*m*-tolyl-1H-indol-3-yl) methanamine (J18);

N,N-dimethyl(1-octyl-5-*m*-tolyl-1H-indol-3-yl) methanamine (J25G);

N-ethyl-*N*-((1-octyl-5-*m*-tolyl-1H-indol-3-yl) methyl) ethanamine (J17G);

N-((1-octyl-5-*m*-tolyl-1H-indol-3-yl) methyl)-*N*-propylpropan-1-amine (J27G);

N-isopropyl-*N*-((1-octyl-5-*m*-tolyl-1H-indol-3-yl) methyl) propan-2-amine (J26G);

N-methyl-*N*-((1-octyl-5-*m*-tolyl-1H-indol-3-yl) methyl) propan-2-amine (J29G);

1-octyl-3-(pyrrolidin-1-ylmethyl)-5-*m*-tolyl-1H-indole (J31G);

1-octyl-3-(piperidin-1-ylmethyl)-5-*m*-tolyl-1H-indole (J32G);

3-((4-methylpiperazin-1-yl) methyl)-1-octyl-5-*m*-tolyl-1H-indole (J30G);

3-(morpholinomethyl)-1-octyl-5-*m*-tolyl-1H-indole (J34G);

N-ethyl-*N*-((1-octyl-5-*o*-tolyl-1H-indol-3-yl) methyl) ethanamine (J36G);

N-ethyl-*N*-((1-octyl-5-*p*-tolyl-1H-indol-3-yl) methyl) ethanamine (J37G);

N-ethyl-*N*-((5-fluoro-1-octyl-1H-indol-3-yl) methyl) ethanamine (J40G);

N-ethyl-*N*-((1-(3-methylbut-2-enyl)-5-*m*-tolyl-1H-indol-3-yl) methyl) ethanamine (J38G);

1-(3-methylbut-2-enyl)-3-(piperidin-1-ylmethyl)-5-*m*-tolyl-1H-indole (J39G);

N-ethyl-*N*-((1-(3-methylbut-2-enyl)-1H-indol-3-yl) methyl) ethanamine (J35G);

1-(5-fluoro-1-octyl-1H-indol-3-yl)-*N,N*-dimethylmethanamine;

5-fluoro-1-octyl-3-(piperidin-1-ylmethyl)-1H-indole;

4-((5-fluoro-1-octyl-1H-indol-3-yl)methyl)thiomorpholine;

4-((5-fluoro-1-octyl-1H-indol-3-yl)methyl)morpholine;

5-fluoro-1-octyl-3-(pyrrolidin-1-ylmethyl)-1H-indole;

- 5-fluoro-3-((4-methylpiperazin-1-yl)methyl)-1-octyl-1*H*-indole;
 4-((1-(3-methylbut-2-enyl)-5-*m*-tolyl-1*H*-indol-3-yl)methyl)morpholine;
N-((5-fluoro-1-octyl-1*H*-indol-3-yl)methyl)-*N*-methylpropan-1-amine;
N-ethyl-*N*-((5-fluoro-1-octyl-1*H*-indol-3-yl)methyl)propan-1-amine;
 5 *N*-butyl-*N*-((5-fluoro-1-octyl-1*H*-indol-3-yl)methyl)butan-1-amine;
 (*E*)-1-(1-(3,7-dimethylocta-2,6-dienyl)-5-fluoro-1*H*-indol-3-yl)-*N,N*-dimethylmethanamine;
 (*E*)-*N*-((1-(3,7-dimethylocta-2,6-dienyl)-5-fluoro-1*H*-indol-3-yl)methyl)-*N*-ethylethanamine;
 (*E*)-1-(3,7-dimethylocta-2,6-dienyl)-5-fluoro-3-(piperidin-1-ylmethyl)-1*H*-indole;
 (*E*)-4-((1-(3,7-dimethylocta-2,6-dienyl)-5-fluoro-1*H*-indol-3-yl)methyl)thiomorpholine;
 10 (*E*)-4-((1-(3,7-dimethylocta-2,6-dienyl)-5-fluoro-1*H*-indol-3-yl)methyl)morpholine;
 (*E*)-1-(3,7-dimethylocta-2,6-dienyl)-5-fluoro-3-(pyrrolidin-1-ylmethyl)-1*H*-indole;
 (*E*)-1-(3,7-dimethylocta-2,6-dienyl)-5-fluoro-3-((4-methylpiperazin-1-yl)methyl)-1*H*-indole;
 (*E*)-*N*-((1-(3,7-dimethylocta-2,6-dienyl)-5-fluoro-1*H*-indol-3-yl)methyl)-*N*-methylpropan-1-amine;
 15 *N*-ethyl-*N*-((5-fluoro-1-octyl-1*H*-indol-3-yl)methyl)propan-1-amine;
 (*E*)-*N*-butyl-*N*-((1-(3,7-dimethylocta-2,6-dienyl)-5-fluoro-1*H*-indol-3-yl)methyl)butan-1-amine;
 (*E*)-1-(3,7-dimethylocta-2,6-dienyl)-3-((4-ethylpiperazin-1-yl)methyl)-5-fluoro-1*H*-indole;
N,N-dimethyl-1-(1-(3-methylbut-2-enyl)-5-*m*-tolyl-1*H*-indol-3-yl)methanamine;
 4-((1-(3-methylbut-2-enyl)-5-*m*-tolyl-1*H*-indol-3-yl)methyl)thiomorpholine;
 20 1-(3-methylbut-2-enyl)-3-(pyrrolidin-1-ylmethyl)-5-*m*-tolyl-1*H*-indole;
 1-(3-methylbut-2-enyl)-3-((4-methylpiperazin-1-yl)methyl)-5-*m*-tolyl-1*H*-indole;
N-methyl-*N*-((1-(3-methylbut-2-enyl)-5-*m*-tolyl-1*H*-indol-3-yl)methyl)propan-1-amine;
N-ethyl-*N*-((1-(3-methylbut-2-enyl)-5-*m*-tolyl-1*H*-indol-3-yl)methyl)propan-1-amine;
N-butyl-*N*-((1-(3-methylbut-2-enyl)-5-*m*-tolyl-1*H*-indol-3-yl)methyl)butan-1-amine; and
 25 *N*-((1-(3-methylbut-2-enyl)-5-*m*-tolyl-1*H*-indol-3-yl)methyl)-*N*-propylpropan-1-amine.

42. The pharmaceutical composition according to any one of claims 39 to 41, further comprising at least one of a nucleic acid alkylator, a nucleoside analogue, an anthracycline, an antibiotic, an aromatase inhibitor, a folate antagonist, an estrogen receptor modulator, an
 30 inorganic arsenate, a microtubule inhibitor, a nitrosourea, an osteoclast inhibitor, a platinum containing compound, a retinoid, a topoisomerase 1 inhibitor, a topoisomerase 2 inhibitor, a thymidylate synthase inhibitor, an aromatase inhibitor, a cyclo-oxygenase inhibitor, an

isoflavone, a tyrosine kinase inhibitor, a growth factor, a bisphosphonate, and a monoclonal antibody.

43. A method of treating a mammal with a disease or disorder associated with Icmt activity comprising administering to the animal a pharmaceutical composition of any one of claims 39 to 42.

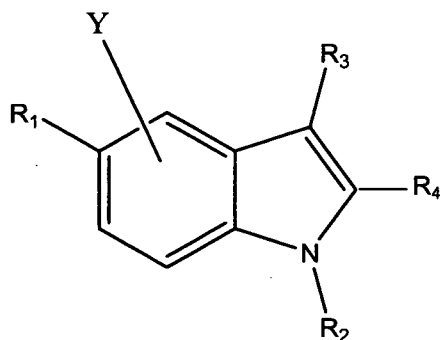
44. The method according to claim 43, wherein the disease or disorder is cancer.

45. The method according to claim 44, wherein the cancer is selected from a group consisting of breast cancer, lung cancer, brain cancer, neuroblastoma, colon cancer, rectal cancer, bladder cancer, liver tumor, a pancreatic tumor, ovarian cancer, prostate cancer, melanoma, cancer of the head or neck and leukaemia.

46. The method according to claim 43, wherein the mammal is selected from the group consisting of a rat, a cow, a goat, a sheep, a pig, a dog, a mouflon, a guinea pig, a hamster, a chimpanzee, a rhesus monkey and a human.

47. The method according to claim 46, wherein the mammal is a human.

48. A compound of Formula VII



(VII)

or a pharmaceutically acceptable salt thereof, wherein

R₁ and Y are independently selected from the group consisting of hydrogen, hydroxyl, C₁₋₂₀alkyl, C₂₋₂₀alkenyl, C₂₋₂₀alkynyl, C₁₋₂₀acyl, C₃₋₈cycloalkyl, C₃₋₈cycloalkenyl, aryl, heteroaryl, heteroalicycyl, halogen, carbonyl, thiocarbonyl, O-carbamyl, O-thiocarbonyl, O-carboxy, isocyanato, thiocyanato, silyl, sulfonamide, thio, -CN, -COOH, -SH, -N=N, -N=O and NX₁X₂,
5 wherein one or more of the hydrogen atoms of the indole ring can be replaced by Y;

R₂ is a terpenoid;

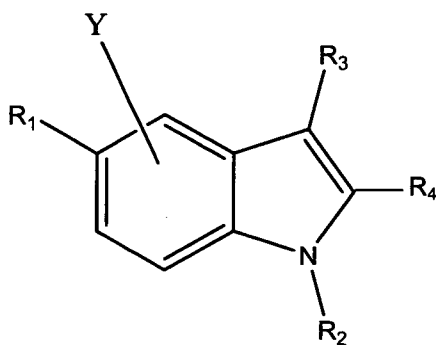
10 R₃ is (CH₂)_nCONX₁X₂, n being an integer from 1 to 4,

R₄ is hydrogen or C₁-C₄ alkyl;

X₁ and X₂ are independently selected from the group consisting of hydrogen, C₁₋₂₀alkyl, C₂₋₂₀alkenyl, C₂₋₂₀alkynyl, C₁₋₂₀acyl, C₃₋₈cycloalkyl, C₃₋₈cycloalkenyl, aryl, heteroaryl, and heteroalicycyl; or
15

X₁ or X₂ may, together with the nitrogen atom bearing them, form a 3-8 membered ring, wherein the 3-8 membered ring can be fused to at least one 3-8 membered ring, wherein the
20 ring can optionally comprise 0, 1, 2, 3 or 4 further heteroatoms selected from the group consisting of oxygen, nitrogen, sulphur and phosphorus; and wherein the ring can be substituted by at least one substituent selected from the group consisting of hydrogen, hydroxyl, C₁₋₂₀alkyl, C₂₋₂₀alkenyl, C₂₋₂₀alkynyl, C₁₋₂₀acyl, C₃₋₈cycloalkyl, C₃₋₈cycloalkenyl, aryl, heteroaryl, heteroalicycyl, halogen, carbonyl, thiocarbonyl, O-carbamyl, O-thiocarbonyl, O-carboxy,
25 isocyanato, thiocyanato, silyl, perhaloalkyl, sulfonyl, sulfonamide, thio, -CN, -COOH, -SH, -N=N, -N=O and NX₁X₂.

49. A compound of Formula VIII



(VIII)

or a pharmaceutically acceptable salt thereof,

wherein

- 5 R_1 and Y are independently selected from the group consisting of hydrogen, hydroxyl, C_{1-20} alkyl, C_{2-20} alkenyl, C_{2-20} alkynyl, C_{1-20} acyl, C_{3-8} cycloalkyl, C_{3-8} cycloalkenyl, aryl, heteroaryl, heteroalicycyl, halogen, carbonyl, thiocarbonyl, O-carbamyl, O-thiocarbonyl, O-carboxy, isocyanato, thiocyanato, silyl, sulfonamide, thio, -CN, -COOH, -SH, -N=N, -N=O and NX_1X_2 , wherein one or more of the hydrogen atoms of the indole ring can be replaced by Y;

10

R_2 is selected from the group consisting of hydrogen, C_{1-20} alkyl, C_{2-20} alkenyl, C_{2-20} alkynyl, C_{1-20} acyl, C_{3-8} cycloalkyl, C_{3-8} cycloalkenyl, aryl, heteroaryl and heteroalicycyl;

R_3 is $(CH_2)_nCONX_1X_2$, n being an integer from 1 to 4;

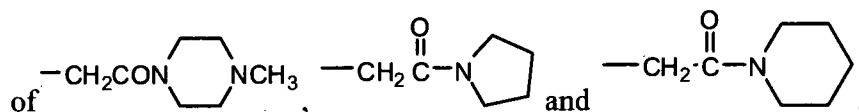
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R_4 is hydrogen or C_1 - C_4 alkyl;

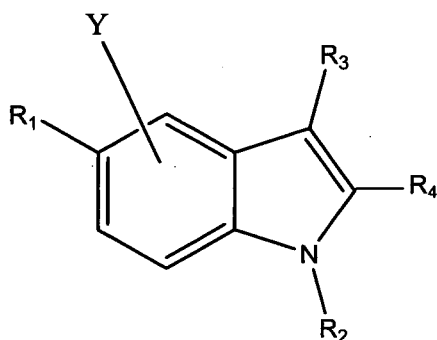
X_1 and X_2 together with the nitrogen atom bearing them, form a 3-8 membered ring, wherein the 3-8 membered ring can be fused to at least one 3-8 membered ring, wherein the ring can optionally comprise 0, 1, 2, 3 or 4 further heteroatoms selected from the group consisting of oxygen, nitrogen, sulphur and phosphorus; and wherein the ring can be substituted by at least one substituent selected from the group consisting of hydrogen, hydroxyl, C_{1-20} alkyl, C_{2-20} alkenyl, C_{2-20} alkynyl, C_{1-20} acyl, C_{3-8} cycloalkyl, C_{3-8} cycloalkenyl, aryl, heteroaryl, heteroalicycyl, halogen, carbonyl, thiocarbonyl, O-carbamyl, O-thiocarbonyl, O-carboxy, isocyanato, thiocyanato, silyl, perhaloalkyl, sulfonyl, sulfonamide, thio, -CN, -COOH, -SH, -N=N, -N=O and NX_1X_2 .

25

50. The compound of claim 49, wherein R_3 is one selected from the group consisting



5 51. A compound of Formula IX



(IX)

or a pharmaceutically acceptable salt thereof,

10 wherein

R_1 and Y are independently selected from the group consisting of hydrogen, hydroxyl, C_{1-20} alkyl, C_{2-20} alkenyl, C_{2-20} alkynyl, C_{1-20} acyl, C_{3-8} cycloalkyl, C_{3-8} cycloalkenyl, aryl, heteroaryl, heteroalicycyl, halogen, carbonyl, thiocarbonyl, O-carbamyl, O-thiocarbonyl, O-carboxy, isocyanato, thiocyanato, silyl, sulfonamide, thio, $-\text{CN}$, $-\text{COOH}$, $-\text{SH}$, $-\text{N}=\text{N}$, $-\text{N}=\text{O}$ and NX_1X_2 ,
 15 wherein one or more of the hydrogen atoms of the indole ring can be replaced by Y ;

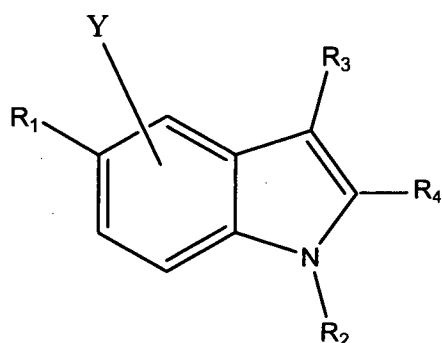
R_2 is selected from the group consisting of hydrogen, C_{1-20} alkyl, C_{2-20} alkenyl, C_{2-20} alkynyl, C_{1-20} acyl, C_{3-8} cycloalkyl, C_{3-8} cycloalkenyl, aryl, heteroaryl and heteroalicycyl; and

20

R_3 is $-(\text{CH}_2)_2\text{CONH}_2$ or $\text{CH}_2\text{NH}_2\text{SO}_2\text{CH}_3$; and

R_4 is hydrogen or $\text{C}_1\text{-C}_4$ alkyl.

25 52. A compound of Formula X



(X)

- 5 or a pharmaceutically acceptable salt thereof,
wherein

R₁ and Y are independently selected from the group consisting of hydrogen, hydroxyl, C₁-
20alkyl, C₂₋₂₀alkenyl, C₂₋₂₀alkynyl, C₁₋₂₀acyl, C₃₋₈cycloalkyl, C₃₋₈cycloalkenyl, aryl, heteroaryl,
10 heteroalicycyl, halogen, carbonyl, thiocarbonyl, O-carbamyl, O-thiocarbonyl, O-carboxy,
isocyanato, thiocyanato, silyl, sulfonamide, thio, -CN, -COOH, -SH, -N=N, -N=O and NX₁X₂,
wherein one or more of the hydrogen atoms of the indole ring can be replaced by Y;

R₂ is selected from the group consisting of hydrogen, C₁₋₂₀alkyl, C₂₋₂₀alkenyl, C₂₋₂₀alkynyl, C₁-
15 20acyl, C₃₋₈cycloalkyl, C₃₋₈cycloalkenyl, aryl, heteroaryl and heteroalicycyl; and

R₃ is (CH₂)_nCONX₁X₂, n being an integer from 1 to 4;

R₄ is hydrogen or C₁-C₄ alkyl;

20

wherein

X₁ is hydrogen and X₂ is one selected from the group consisting of C₁₋₂₀alkyl, C₂₋₂₀alkenyl, C₂-
20alkynyl, C₁₋₂₀acyl, C₃₋₈cycloalkyl, C₃₋₈cycloalkenyl, aryl, heteroaryl, and heteroalicycyl.

- 25 53. The compound of claim 52, wherein R₁ is (CH₃)_m-aryl, m being an integer between 0 to 4
and Y is hydrogen.

54. The compound of claim 53, wherein R₁ is selected from the group consisting of 2'-CH₃-

C₆H₅, 3'-CH₃-C₆H₅ and 4'-CH₃-C₆H₅.

55. The compound of any one of claims 52 or 54, wherein R₂ is C₁₋₈alkyl or C₂₋₈alkenyl.

5 56. The compound of claim 55, wherein R₂ is octyl or isoprenyl.

57. The compound of any one of claims 52 to 56, wherein n is 1.

10 58. The compound of any one of claims 52 to 57 wherein X₂ is one selected from the group consisting of C₁₋₁₀alkyl, C₂₋₁₀alkenyl, C₂₋₁₀alkynyl, C₁₋₁₀acyl, C₃₋₈cycloalkyl, C₃₋₈cycloalkenyl, aryl, heteroaryl and heteroalicycyl.

59. A pharmaceutical composition comprising a compound of any one of claims 52 to 58.

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