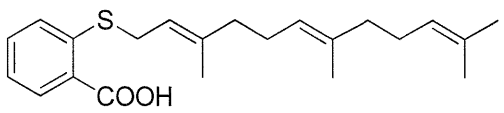
[00011] S-Farnesyl-thiosalicylic acid to inhibits both Icmt and H-ras driven cell growth. However it was considered that inhibition of ras dependent cell growth was not related to the inhibition of ras methylation by Icmt.



farnesylthiosalicyclic acid

[00012] The last category of compounds comprises a miscellaneous group of natural products that have been found to possess Icmt inhibitory activity. They range from chemical entitites isolated from marine sponges (spermatinamine, aplysamine 6) to plants (prenylated β hydroxychalcones, a flavanone S-glabrol). Most of these compounds are modest inhibitors (IC_{50} > 10 μM) and lack drug-like features.

Summary ~~of Invention~~

[00013] In a first aspect, ~~of the invention~~ there is provided a 1,3,5-substituted indole wherein:

- the substituent at position 1 is C6 to C12 alkyl group;
- the substituent at position 3 is $CH_2NR^1R^2$ wherein R^1 is H or C1 to C3 alkyl, R^1 being optionally substituted with -OH, -SH, $-NH_2$ or NHalkyl, wherein alkyl is a C1 to C4 alkyl group, and R^2 is C1 to C3 alkyl or $(CH_2)_n$ bonded to position 2 of the indole, wherein n is 1, 2 or 3; and
- the substituent at position 5 is either an optionally substituted nitrogen containing heteroaromatic ring or an aminosulfonylphenyl group or an alkylsulfonylphenyl group.

[00014] The following options may be used in conjunction with the ~~first aspect~~indole as defined above, either individually or in any suitable combination.

[00015] The substituent at position 1 may be a straight chain alkyl group. It may be octyl, e.g. n-octyl.

[00016] R^1 and R^2 may both be ethyl. Alternatively R^1 may be H or Me and R^2 $(CH_2)_2$ bonded to position 2 of the indole. In the latter case the indole is a tetrahydrocarboline.

[00017] The substituent at position 5 may be a 6-membered heteroaromatic ring. It may contain no heteroatoms other than N. It may contain 1 or 2 ring nitrogen atoms. It may be for example 2-aminopyrimidine-5-yl

[00018] The indole may have lipophilicity (logD at pH 7.4) of less than about 5. It may have an aqueous solubility of greater than about 10^{-4}M at pH 7.4. It may have an $IC_{50MDA\text{-}MB\text{-}231}$ of less than about 6. It may have an $IC_{50\ PC3}$ of less than about 6.

[00019] In an embodiment, there is provided a 1,3,5-substituted indole wherein the substituent at position 1 is octyl; the substituent at position 3 is NEt_2; and the substituent at position 5 is either an optionally substituted nitrogen containing heteroaromatic ring having one or two ring nitrogen atoms or an aminosulfonylphenyl group or an alkylsulfonylphenyl group. The substituent at position 5 may be 2-aminopyrimidine-5-yl.

[00020] In a further embodiment there is provided a 1,3,5-substituted indole wherein the substituent at position 1 is octyl; the substituent at position 3 is NEt_2; and the substituent at position 5 is either an optionally substituted pyridine or pyrimidine ring or a methylaminosulfonylphenyl group or a methylsulfonylphenyl group.

[00021] In another embodiment, there is provided a 1,3,5-substituted indole wherein the substituent at position 1 is octyl; the substituent at position 3 is CH_2NMeR^2 wherein R^2 is $(CH_2)_2$ bonded to position 2 of the indole; and the substituent at position 5 is either an optionally substituted nitrogen containing heteroaromatic ring or an aminosulfonylphenyl group or an alkylsulfonylphenyl group.

[00022] In a further embodiment there is provided a 1,3,5-substituted indole wherein the substituent at position 1 is octyl; the substituent at position 3 is CH_2NMeR^2 wherein R^2 is $(CH_2)_2$ bonded to position 2 of the indole; and the substituent at position 5 is either a 2-aminopyrimidine-5-yl group or a 4-methylsulfonylphenyl group. The substituent at position 5 may be 2-aminopyrimidine-5-yl.

[00023] In the disclosure, ~~a second aspect of the invention~~ there is provided use of an indole ~~according to the first aspect~~as defined herein for any one or more, optionally all, of: inhibiting Icmt activity, treating cancer and inhibiting oncogenesis.

[00024] In the disclosure, ~~a third aspect of the invention~~ there is provided a method of treating a cancer comprising administering to a patient in need thereof a therapeutically effective quantity of a compound as defined herein ~~according to the first aspect~~.

[00025] In another ~~a fourth~~ aspect, ~~of the invention~~ there is provided use of a compound ~~according to the first aspect~~as defined herein for the manufacture of a medicament for the treatment of cancer.

[00026] In another ~~a fifth~~ aspect, ~~of the invention~~ there is provided a composition for treatment of cancer comprising a compound ~~according to the first aspect~~ as defined herein and one or more pharmaceutically acceptable carriers, diluents or adjuvants.

[00027] In the disclosure,~~a sixth aspect of the invention~~ there is provided a compound according to the first aspect when used for one or more, optionally all, of inhibiting Icmt activity, inhibiting oncogenesis and treating cancer.

[00028] In another~~a seventh~~ aspect, ~~of the invention~~ there is provided a compound ~~according to the first aspect~~as defined herein for use in therapy.

Brief Description of Drawings

[00029] Figure 1: Post-translational processing of proteins with CAAX motif [

[00030] Figure 2: Structures of active ICMT inhibitors that are structural mimics of the minimal substrate AFC

[00031] Figure 3: Syntheses of indoleamines

[00032] Figure 4: Synthesis of tetrahydrocarbolines 199 and 205

[00033] Figure 5: Synthesis of tetrahydrocarbolines 235, 240, 260 and 300

[00034] Figure 6: Synthesis of tetrahydrocarboline 305 and 306

[00035] Figure 7: Synthesis of tetrahydrocarbolines 309, 314 and 315

[00036] Figure 8: Representative viability vs concentration plots for cysmethynil and **8-12**

12. The indole of any one of claims 1 to 9 having an $IC_{50\ PC3}$ of less than about 6 μM.

~~13. Use of an indole according to any one of claims 1 to 11 for inhibiting Icmt activity.~~

~~14. Use of an indole according to any one of claims 1 to 11 for treating cancer.~~

~~15. Use of an indole according to any one of claims 1 to 11 for inhibiting oncogenesis.~~

~~16. A method of treating a cancer comprising administering to a patient in need thereof a therapeutically effective quantity of a compound according to any one of claims 1 to 11.~~

~~17.~~13. Use of a compound according to any one of claims 1 to 11 for the manufacture of a medicament for the treatment of cancer.

~~18.~~14. A composition for treatment of cancer comprising a compound according to any one of claims 1 to 11 and one or more pharmaceutically acceptable carriers, diluents or adjuvants.

~~19. A compound according to any one of claims 1 to 11 when used for one or more of inhibiting Icmt activity, inhibiting oncogenesis and treating cancer.~~

~~20.~~15. A compound according to any one of claims 1 to 11 for use in therapy.