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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
24 January 2013 (24.01.2013)

WIPO | PCT

(10) International Publication Number
WO 2013/013240 A2

(51) International Patent Classification:
C07D 313/00 (2006.01) *A61K 31/335* (2006.01)
C07D 225/02 (2006.01) *A61K 31/357* (2006.01)
C07D 321/00 (2006.01) *A61P 35/00* (2006.01)

(21) International Application Number:
PCT/US2012/047863

(22) International Filing Date:
23 July 2012 (23.07.2012)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
61/510,177 21 July 2011 (21.07.2011) US

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

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *without international search report and to be republished upon receipt of that report (Rule 48.2(g))*

(54) **Title**: MACROCYCLIC COMPOUNDS AND RELATED COMPOSITONS AND METHODS OF USE

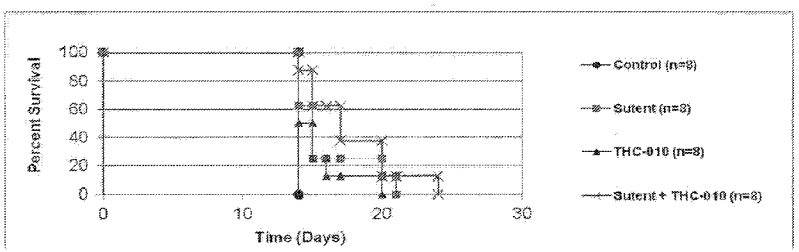

Figure 1

(57) **Abstract**: Compounds and compositions, which can be use for example, for treating cancer, are described herein.

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Macrocyclic Compounds and Related Compositions and Methods of Use

Claim of Priority

This application claims priority from U.S.S.N. 61/510,177, filed July 21, 2011 which is incorporated herein by reference in its entirety.

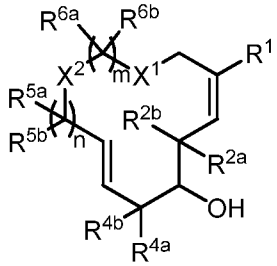
Background

Migrastatin is a 14-membered ring macrolide natural product that was first isolated from a cultured broth of Steptomyces sp. MK929-43F1. Migrastatin and related compounds have been shown to inhibit migration and anchorage-independent growth of human tumor cells. Specifically, migration of tumor cells is part of the process of metastasis, which is a leading cause of death in cancer patients. Therefore, Migrastatin, derivatives thereof, and related compounds could be useful as therapeutic agents in the treatment of cancer.

Summary of the invention

Described herein are macrocyclic compounds of formula (I), compositions comprising a compound of formula (I), and methods of using these compounds and compositions. In some embodiments, the compounds can inhibit cell migration, and be useful, for example, in the treatment of cancer.

In one aspect, the invention features a compound having formula (I), shown below.



formula (I),

wherein

n and m are each independently 0, 1, 2, 3 or 4;

X^1 is –O-, -NR^7-, -$CR^{9a}R^{9b}$-, -C(O)-NR^7-, -NR^7-C(O)-, -NR^8-$S(O)_2$- or -$S(O)_2$-NR^8-;

X^2 is –NR^8-,-$CR^{9a}R^{9b}$-, -S-, -O-, -S(O)-, -$S(O)_2$-, -C(O)-NR^8-, -NR^8-C(O)-, -NR^8-$S(O)_2$- or -$S(O)_2$-NR^8-;

R^1 is halo, C_{1-6} alkyl or C_{1-6} alkoxy;

R^{2a} and R^{2b} are each independently hydrogen or C_{1-6} alkyl;

each R^{4a} and R^{4b} are independently hydrogen, hydroxyl, C_{1-6} alkyl or C_{1-6} alkoxy;

each R^{5a} and R^{5b} are independently hydrogen, halo, amino, amido, C_{1-6} alkyl or C_{1-6} alkoxy;

each R^{6a} and R^{6b} are independently hydrogen, halo, amino, amido, C_{1-6} alkyl or C_{1-6} alkoxy;

R^7 is hydrogen, C_{1-6} alkyl, acyl, aryl or aralkyl;

R^8 is hydrogen, C_{1-6} alkyl, acyl, aryl or aralkyl; and

R^{9a} and R^{9b} are each independently hydrogen, C_{1-6} alkyl, C_{1-6} alkoxy, halo, amino, amido, aryl or heteroaryl,

wherein when X^1 is –O-, X^2 is not $–CR^{9a}R^{9b}$-.

In one aspect, the invention features a composition comprising a compound of formula (I).

In one aspect, the invention features a method of treating a subject, e.g., a method of treating cancer, comprising administering to the subject a compound of formula (I) or a composition comprising a compound of formula (I).

In one aspect, the invention features a kit comprising a compound of formula (I) or a composition comprising a compound of formula (I).

Brief Description of the Figures

Figure 1 represents the efficacy of THC-010 and Sutent in an intracranial glioma rat model.

Detailed Description of the Invention

Definitions:

The term "halo" or "halogen" refers to any radical of fluorine, chlorine, bromine or iodine.

The term "alkyl" refers to a hydrocarbon chain that may be a straight chain or branched chain, containing the indicated number of carbon atoms. For example, C_1-C_{12} alkyl indicates that the group may have from 1 to 12 (inclusive) carbon atoms in it. The term "haloalkyl" refers to an alkyl in which one or more hydrogen atoms are replaced by halo, and includes alkyl moieties in

which all hydrogens have been replaced by halo (e.g., perfluoroalkyl). The terms "arylalkyl" or "aralkyl" refer to an alkyl moiety in which an alkyl hydrogen atom is replaced by an aryl group. Aralkyl includes groups in which more than one hydrogen atom has been replaced by an aryl group. Examples of "arylalkyl" or "aralkyl" include benzyl, 2-phenylethyl, and 3-phenylpropyl.

The terms "heteroarylalkyl" or "heteroaralkyl" refer to an alkyl moiety in which an alkyl hydrogen atom is replaced by a heteroaryl group. Heteroaralkyl includes groups in which more than one hydrogen atom is replaced by a heteroaryl group. Examples or "heteroarylalkyl" or "heteroaralkyl" include methyl-3-pyridyl and methyl-2-pyridyl.

The term "alkylene" refers to a divalent alkyl, e.g., $-CH_2-$, $-CH_2CH_2-$, and $-CH_2CH_2CH_2-$.

The term "alkenyl" refers to a straight or branched hydrocarbon chain containing 2-12 carbon atoms and having one or more double bonds. Examples of alkenyl groups include, but are not limited to, allyl, propenyl, 2-butenyl, 3-hexenyl and 3-octenyl groups. One of the double bond carbons may optionally be the point of attachment of the alkenyl substituent. The term "alkynyl" refers to a straight or branched hydrocarbon chain containing 2-12 carbon atoms and characterized in having one or more triple bonds. Examples of alkynyl groups include, but are not limited to, ethynyl, propargyl, and 3-hexynyl. One of the triple bond carbons may optionally be the point of attachment of the alkynyl substituent.

The terms "alkylamino" and "dialkylamino" refer to $-NH(alkyl)$ and $-NH(alkyl)_2$ radicals respectively. The term "aralkylamino" refers to a -NH(aralkyl) radical. The term alkylaminoalkyl refers to a (alkyl)NH-alkyl- radical; the term dialkylaminoalkyl refers to a $(alkyl)_2N$-alkyl- radical The term "alkoxy" refers to an -O-alkyl radical. The term "mercapto" refers to an SH radical. The term "thioalkoxy" refers to an -S-alkyl radical. The term thioaryloxy refers to an -S-aryl radical.

The term "aryl" refers to an aromatic monocyclic, bicyclic, or tricyclic hydrocarbon ring system, wherein any ring atom capable of substitution can be substituted (e.g., by one or more substituents). Examples of aryl moieties include, but are not limited to, phenyl, naphthyl, and anthracenyl.

The term "cycloalkyl" as employed herein includes saturated cyclic, bicyclic, tricyclic,or polycyclic hydrocarbon groups having 3 to 12 carbons. Any substitutable ring atom can be substituted (e.g., by one or more substituents). The cycloalkyl groups can contain fused rings. Fused rings are rings that share a common carbon atom. Examples of cycloalkyl moieties

include, but are not limited to, cyclopropyl, cyclohexyl, methylcyclohexyl, adamantyl, and norbornyl. The term "cycloalkylenyl" refers to a divalent cycloalkyl.

The terms "heterocyclyl" or "heterocyclic group" refer to 3- to 14-membered non-aromatic ring structures (e.g., 3- to 10-membered rings, more preferably 3- to 7-membered rings), whose ring structures include one to four heteroatoms independently selected from O, N and S. The heterocyclyl or heterocyclic groups can contain fused or spiro rings. Heterocycles can also be polycycles, with each group having, e.g., 5-7 ring members. The term "heterocyclyl" or "heterocyclic group" includes saturated and partially saturated heterocyclyl structures.

The term "heteroaryl" refers to a 5-14 membered (i.e., a 5-8 membered monocyclic, 8-12 membered bicyclic, or 11-14 membered tricyclic) aromatic ring system having 1-3 ring heteroatoms if monocyclic, 1-6 ring heteroatoms if bicyclic, or 1-9 ring heteroatoms if tricyclic, said ring heteroatoms independently selected from O, N, and S (e.g., 1-3, 1-6, or 1-9 ring heteroatoms of N, O, or S if monocyclic, bicyclic, or tricyclic, respectively). Any substitutable ring atom can be substituted (e.g., by one or more substituents). Heterocyclyl and heteroaryl groups include, for example, thiophene, thianthrene, furan, pyran, isobenzofuran, chromene, xanthene, phenoxathiin, pyrrole, imidazole, pyrazole, isothiazole, isoxazole, pyridine, pyrazine, pyrimidine, pyridazine, indolizine, isoindole, indole, indazole, purine, quinolizine, isoquinoline, quinoline, phthalazine, naphthyridine, quinoxaline, quinazoline, cinnoline, pteridine, carbazole, carboline, phenanthridine, acridine, pyrimidine, phenanthroline, phenazine, phenarsazine, phenothiazine, furazan, phenoxazine, pyrrolidine, oxolane, thiolane, oxazole, piperidine, piperazine, morpholine, lactones, lactams such as azetidinones and pyrrolidinones, sultams, sultones, and the like. The heterocyclic or heteroaryl ring can be substituted at one or more positions with such substituents as described herein, as for example, halogen, alkyl, aralkyl, alkenyl, alkynyl, cycloalkyl, hydroxyl, amino, nitro, sulfhydryl, imino, amido, phosphate, phosphonate, phosphinate, carbonyl, carboxyl, silyl, ether, alkylthio, sulfonyl, ketone, aldehyde, ester, a heterocyclyl, an aromatic or heteroaromatic moiety, -CF3, -CN, or the like.

The term "cycloalkenyl" refers to partially unsaturated, nonaromatic, cyclic, bicyclic, tricyclic, or polycyclic hydrocarbon groups having 5 to 12 carbons, preferably 5 to 8 carbons. The unsaturated carbon may optionally be the point of attachment of the cycloalkenyl substituent. Any substitutable ring atom can be substituted (e.g., by one or more substituents). The cycloalkenyl groups can contain fused or spiro rings. Fused rings are rings that share a

common carbon atom. Examples of cycloalkenyl moieties include, but are not limited to, cyclohexenyl, cyclohexadienyl, or norbornenyl.

The term "heterocycloalkenyl" refers to a partially saturated, nonaromatic 5-10 membered monocyclic, 8-12 membered bicyclic, or 11-14 membered tricyclic ring system having 1-3 heteroatoms if monocyclic, 1-6 heteroatoms if bicyclic, or 1-9 heteroatoms if tricyclic, said heteroatoms independently selected from O, N, or S (e.g., 1-3, 1-6, or 1-9 ring heteroatoms of N, O, or S if monocyclic, bicyclic, or tricyclic, respectively). The unsaturated carbon or the heteroatom may optionally be the point of attachment of the heterocycloalkenyl substituent. Any substitutable ring atom can be substituted (e.g., by one or more substituents). The heterocycloalkenyl groups can contain fused rings. Fused rings are rings that share a common carbon atom. Examples of heterocycloalkenyl include but are not limited to tetrahydropyridyl and dihydropyranyl.

The terms "hetaralkyl" and "heteroaralkyl", as used herein, refers to an alkyl group substituted with a heteroaryl group. The ring heteroatoms of the compounds provided herein may be in the form of N-O, S(O), or $S(O)_2$.

The term "oxo" refers to an oxygen atom, which forms a carbonyl when attached to carbon, an N-oxide when attached to nitrogen, and a sulfoxide or sulfone when attached to sulfur.

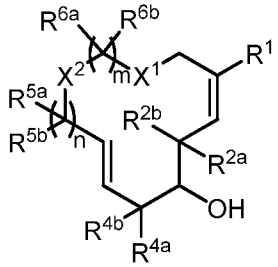
The term "acyl" refers to an alkylcarbonyl, alkoxycarbonyl, cycloalkylcarbonyl, arylcarbonyl, heterocyclylcarbonyl, or heteroarylcarbonyl substituent, any of which may be further substituted (e.g., by one or more substituents).

The term "substituents" refers to a group "substituted" on an alkyl, cycloalkyl, alkenyl, alkynyl, heterocyclyl, heterocycloalkenyl, cycloalkenyl, aryl, or heteroaryl group at any substitutable atom of that group. Any substitutable atom can be substituted. Unless otherwise specified, such substituents include, without limitation, alkyl (e.g., Cl, C2, C3, C4, C5, C6, C7, C8, C9, C10, C11, C12 straight or branched chain alkyl), cycloalkyl, haloalkyl (e.g., perfluoroalkyl such as CF_3), aryl, heteroaryl, aralkyl, heteroaralkyl, heterocyclyl, alkenyl, alkynyl, cycloalkenyl, heterocycloalkenyl, alkoxy, haloalkoxy (e.g., perfluoroalkoxy such as OCF_3), halo, hydroxy, carboxy, carboxylate, cyano, nitro, amino, alkyl amino, SO_3H, sulfate, phosphate, methylenedioxy (-O-CH_2-O- wherein oxygens are attached to vicinal atoms), ethylenedioxy, oxo, thioxo (e.g., C=S), imino (alkyl, aryl, aralkyl), $S(O)_n$alkyl (where n is 0-2), $S(O)_n$ aryl (where n is 0-2), $S(O)_n$ heteroaryl (where n is 0-2), $S(O)_n$ heterocyclyl (where n is 0-

2), amine (mono-, di-, alkyl, cycloalkyl, aralkyl, heteroaralkyl, aryl, heteroaryl, and combinations thereof), ester (alkyl, aralkyl, heteroaralkyl, aryl, heteroaryl), amide (mono-, di-, alkyl, aralkyl, heteroaralkyl, aryl, heteroaryl, and combinations thereof), sulfonamide (mono-, di-, alkyl, aralkyl, heteroaralkyl, and combinations thereof). In one aspect, the substituents on a group are independently any one single, or any subset of the aforementioned substituents. In another aspect, a substituent may itself be substituted with any one of the above substituents.

Compounds:

Described herein are compounds of formula (I)



Formula (I),

wherein

n and m are each independently 0, 1, 2, 3 or 4;

X^1 is –O-, -NR^7-, -$CR^{9a}R^{9b}$-, -C(O)-NR^7-, -NR^7-C(O)-, -NR^8-$S(O)_2$- or -$S(O)_2$-NR^8-;

X^2 is –NR^8-,-$CR^{9a}R^{9b}$-, -S-, -O-, -S(O)-, -$S(O)_2$-, -C(O)-NR^8-, -NR^8-C(O)-, -NR^8-$S(O)_2$- or -$S(O)_2$-NR^8-;

R^1 is halo, C_{1-6} alkyl or C_{1-6} alkoxy;

R^{2a} and R^{2b} are each independently hydrogen or C_{1-6} alkyl;

each R^{4a} and R^{4b} are independently hydrogen, hydroxyl, C_{1-6} alkyl or C_{1-6} alkoxy;

each R^{5a} and R^{5b} are independently hydrogen, halo, amino, amido, C_{1-6} alkyl or C_{1-6} alkoxy;

each R^{6a} and R^{6b} are independently hydrogen, halo, amino, amido, C_{1-6} alkyl or C_{1-6} alkoxy;

R^7 is hydrogen, C_{1-6} alkyl, acyl, aryl or aralkyl;

R^8 is hydrogen, C_{1-6} alkyl, acyl, aryl or aralkyl; and

R^{9a} and R^{9b} are each independently hydrogen, C_{1-6} alkyl, C_{1-6} alkoxy, halo, amino, amido, aryl or heteroaryl,

wherein when X^1 is –O-, X^2 is not –$CR^{9a}R^{9b}$-.

In certain embodiments, R^1 is C_{1-6} alkyl (e.g., methyl).

In certain embodiments, one of R^{2a} and R^{2b} is hydrogen and the other is C_{1-6} alkyl (e.g., methyl). In some embodiments, both R^{2a} and R^{2b} are C_{1-6} alkyl (e.g., methyl).

In certain embodiments, one or R^{4a} and R^{4b} is hydrogen and the other is C_{1-6} alkoxy (e.g., methoxy).

In certain embodiments, X^1 is –O-. In some embodiments, X^1 is $–NR^7$-. In some embodiments, X^1 is $–C(O)-NR^7$-. In some embodiments, X^1 is $–NR^7-C(O)$-. In some embodiments, X^1 is $–S(O)_2-NR^7$-. In some embodiments, R^7 is hydrogen. In some embodiments, R^7 is C_{1-6} alkyl (e.g., methyl). In some embodiments, R^7 is acyl.

In certain embodiments, X^1 is $–CR^{9a}R^{9b}$-. In some embodiments, R^{9a} and R^{9b} are both hydrogen. In some embodiments, one of R^{9a} and R^{9b} is hydrogen and the other is amido (e.g., -C(O)-NHMe).

In certain embodiments, n is 0. In some embodiments, n is 1. In some embodiments, n is 2. In some embodiments, n is 3. In some embodiments, n is 4.

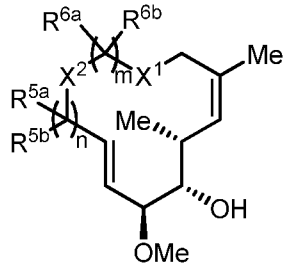
In certain embodiments, m is 0. In some embodiments m is 1. In some embodiments, m is 2. In some embodiments, m is 3.

In certain embodiments, n is 1 and m is 3. In some embodiments, n is 2 and m is 2. In some embodiments, n is 3 and m is 1. In some embodiments, n is 4 and m is 0.

In certain embodiments, X^2 is $–CR^{9a}R^{9b}$-. In some embodiments, R^{9a} and R^{9b} are both halo (e.g., fluoro). In some embodiments, R^{9a} and R^{9b} are both hydrogen. In some embodiments, one of R^{9a} and R^{9b} is amino and the other is hydrogen.

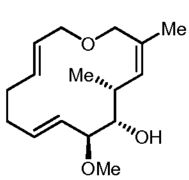
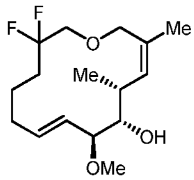
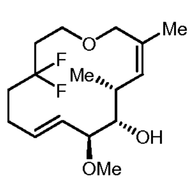
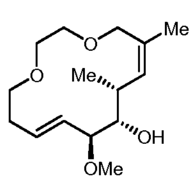
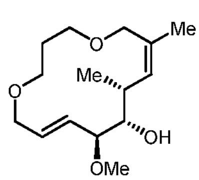
In some embodiments, X^2 is –O-. In some embodiments, X^2 is –S-. In some embodiments, X^2 is –S(O)-. In some embodiments, X^2 is $–S(O)_2$-. In some embodiments, X^2 is $–NR^8-C(O)$-. In some embodiments, X^2 is $–NR^8-S(O)_2$-. In some embodiments, X^2 is $–S(O)_2-NR^8$-. In some embodiments, X^2 is $–NR^8$-. In some embodiments, R^8 is hydrogen. In some embodiments, R^8 is C_{1-6} alkyl (e.g., methyl). In some embodiments, R^8 is acyl.

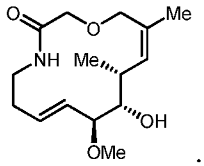
In certain embodiments, the compound of formula (I) is a compound of formula (Ia):



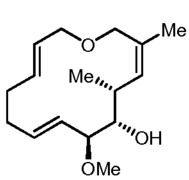
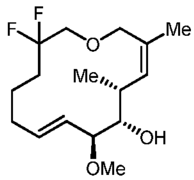
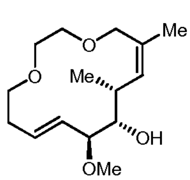
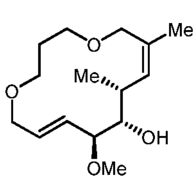
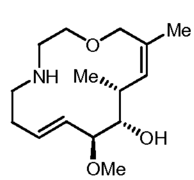
formula (Ia).

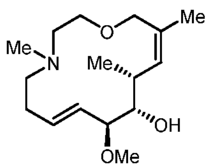
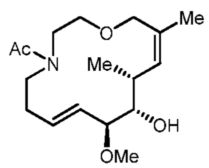
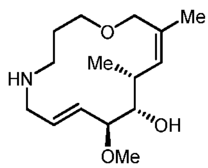
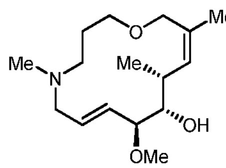
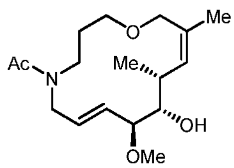
In certain embodiments, the compound of formula (I) is selected from the following:

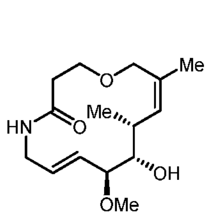
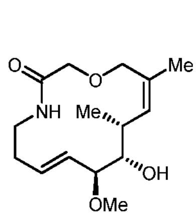
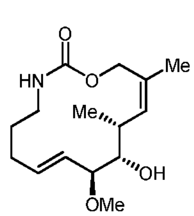
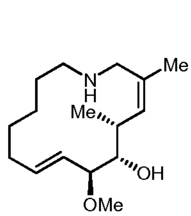
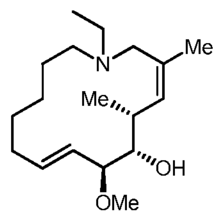
 ,  ,  ,  ,  and

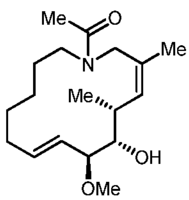
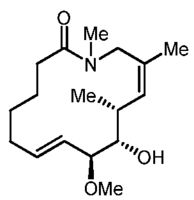
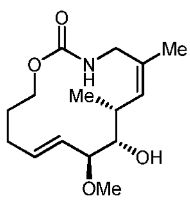
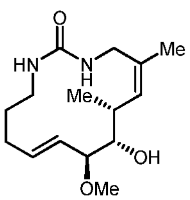
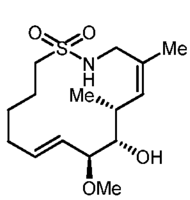
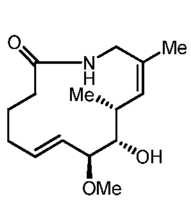
 .

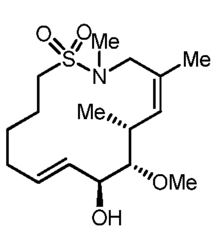
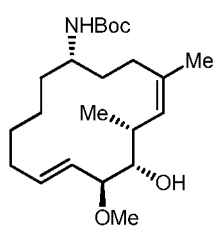
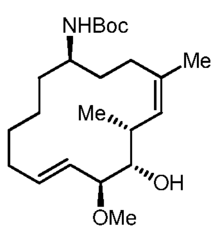
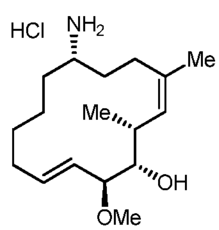
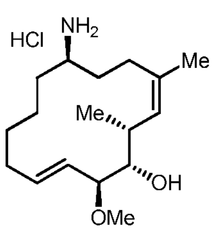
In certain embodiments, the compound of formula (I) is selected from the following:

 ,  ,  ,  ,  ,

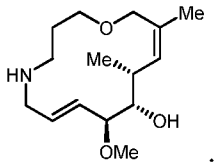
 ,  ,  ,  ,  ,

 ,  ,  ,  ,  ,

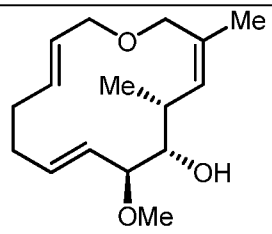
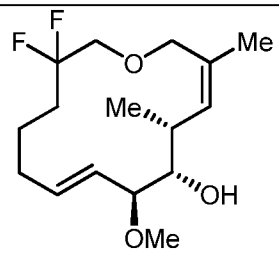
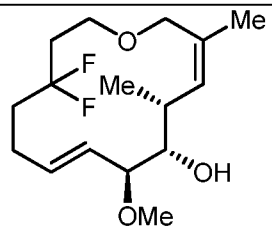
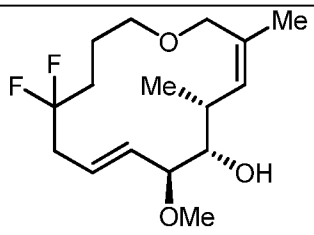
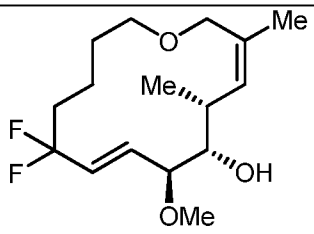
 ,  ,  ,  ,  ,  ,

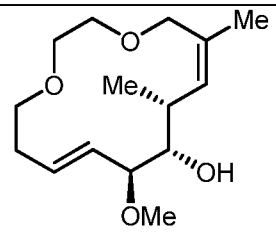
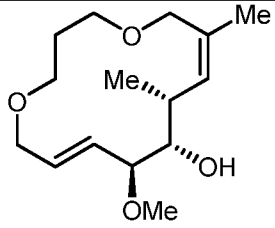
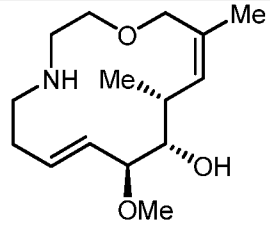
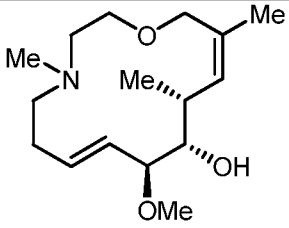
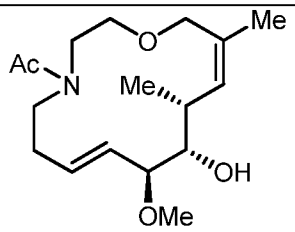
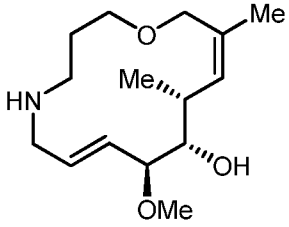
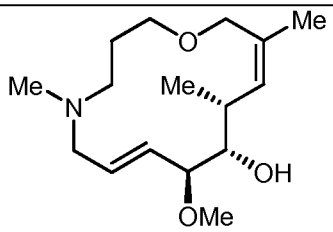
 ,  ,  ,  and  .

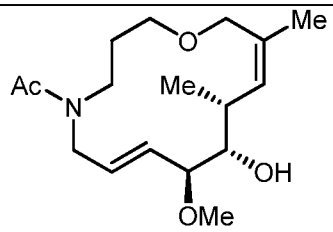
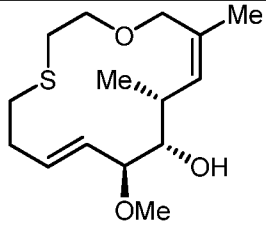
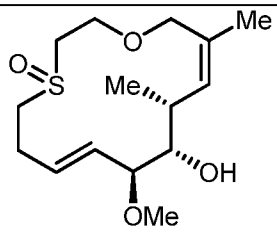
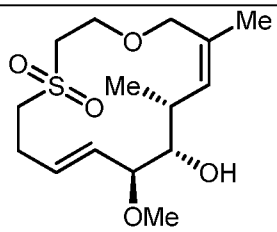
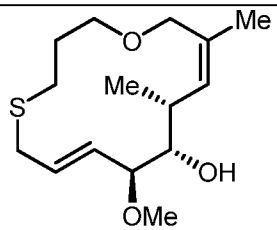
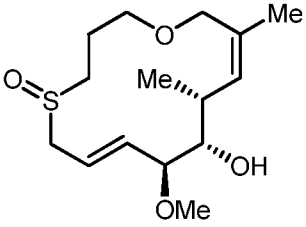
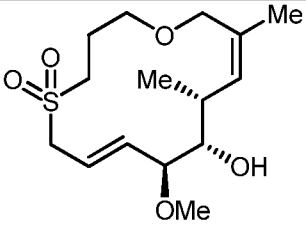
In certain embodiments, the compound of formula (I) is:

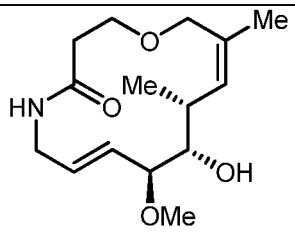
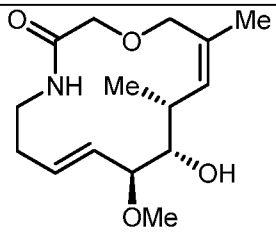
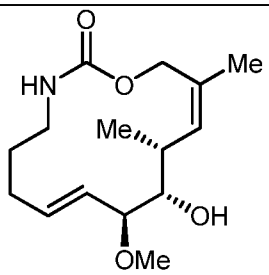
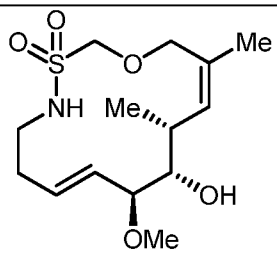
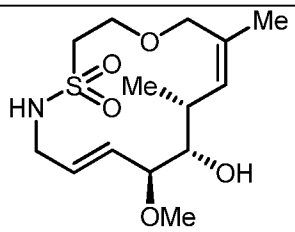
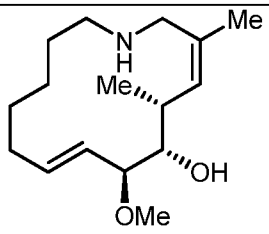


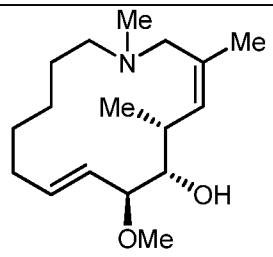
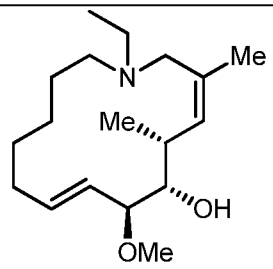
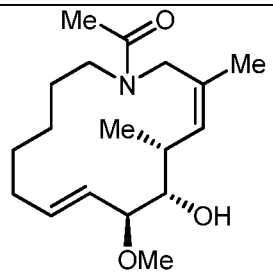
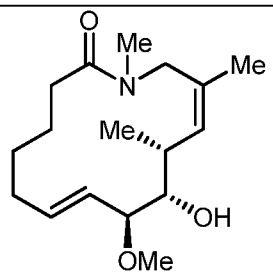
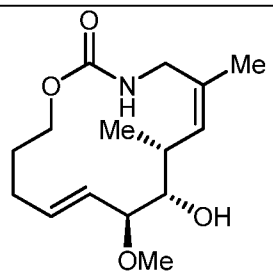
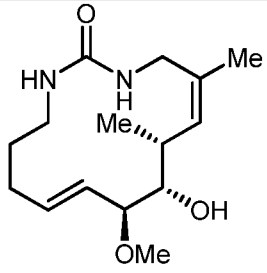
Exemplary compounds are described below in Table 1:

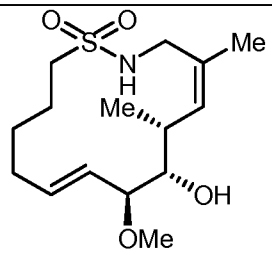
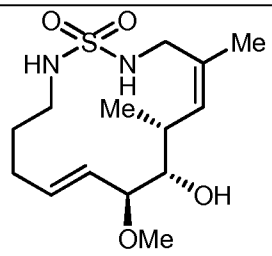
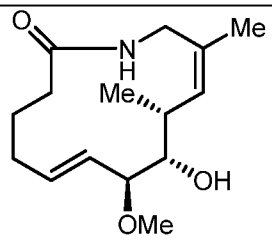
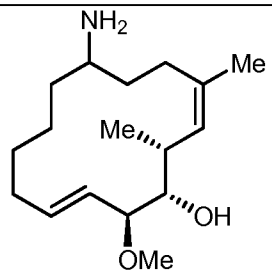
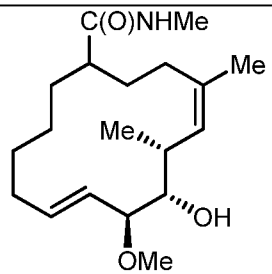
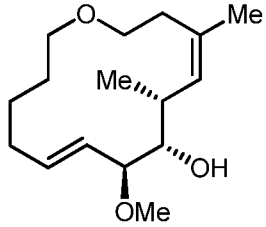
Compound	Cancer Cell Migration Inhibitory Activity
	+
	+
	++
	ND
	ND

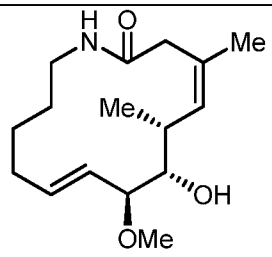
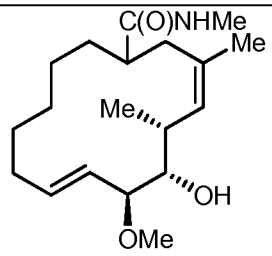
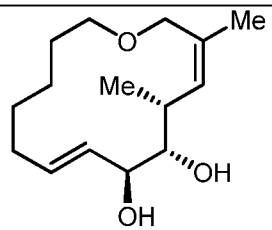
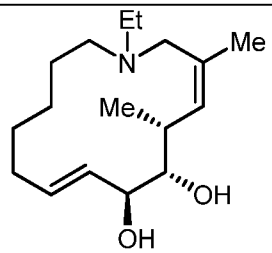
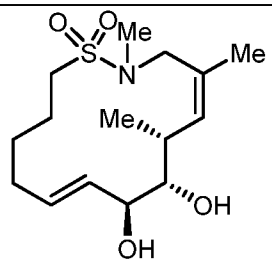
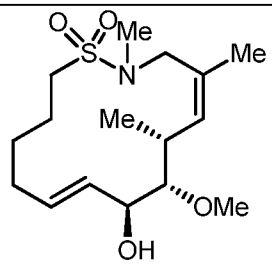
	++
	++
	ND
	ND
	ND
	ND
	ND

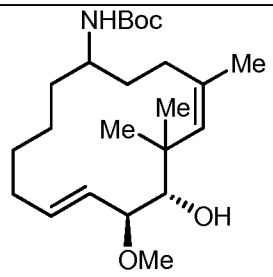
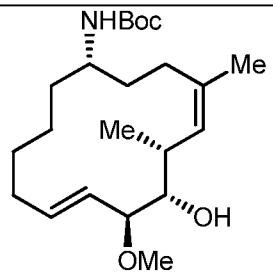
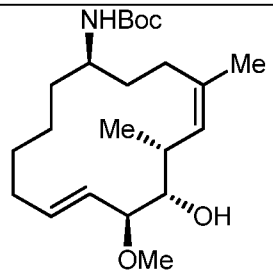
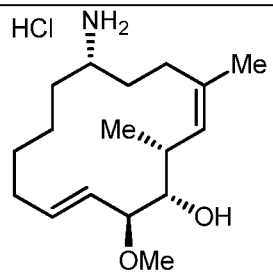
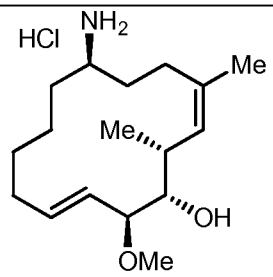
	ND
	ND
	ND
	ND
	ND
	ND
	ND

	ND
	-/+
	ND
	ND
	ND
	ND

	ND
	ND
	ND
	ND
	ND
	ND

	ND
	ND
	ND
	ND
	ND
	ND

	ND
	ND
	ND
	ND
	ND
	ND

	ND
	ND
	ND
	ND
	ND

*Activity is as measured in a cell migration assay. Numeric representation is depicted in nanomolar. + indicates the compound was active, but not quantified; ++ indicates the compound was very active, but not quantified, -/+ indicates the compound was marginally active, but not quantified; and – indicates the compound was not active. ND means the activity was not determined.

Combinations of substituents and variables envisioned by this invention are only those that result in the formation of stable compounds. The term "stable", as used herein, refers to

compounds which possess stability sufficient to allow manufacture and which maintains the integrity of the compound for a sufficient period of time to be useful for the purposes detailed herein (e.g., therapeutic or prophylactic administration to a subject).

Certain compounds disclosed herein may exist in particular geometric or stereoisomeric forms. The present invention contemplates all such compounds, including cis- and trans-isomers, *R*- and *S*-enantiomers, diastereomers, (d)-isomers, (l)-isomers, the racemic mixtures thereof, and other mixtures thereof, as falling within the scope of the invention. For example, if one chiral center is present in a molecule, the invention includes racemic mixtures, enantiomerically enriched mixtures, and substantially enantiomerically pure compounds. The composition can contain, e.g., more than 50%, more than 60%, more than 70%, more than 80%, more than 90%, more than 95%, or more than 99% of a single enantiomer.

The "enantiomeric excess" or "% enantiomeric excess" of a composition can be calculated using the equation shown below. In the example shown below a composition contains 90% of one enantiomer, e.g., the S enantiomer, and 10% of the other enantiomer, i.e., the R enantiomer.

$$ee = (90\text{-}10)/100 = 80\%.$$

Thus, a composition containing 90% of one enantiomer and 10% of the other enantiomer is said to have an enantiomeric excess of 80%.

Methods of preparing substantially isomerically pure compounds are known in the art. If, for instance, a particular enantiomer of a compound disclosed herein is desired, it may be prepared by asymmetric synthesis, or by derivation with a chiral auxiliary, where the resulting diastereomeric mixture is separated and the auxiliary group cleaved to provide the pure desired enantiomers. Alternatively, where the molecule contains a basic functional group, such as amino, or an acidic functional group, such as carboxyl, diastereomeric salts may be formed with an appropriate optically active acid or base, followed by resolution of the diastereomers thus formed by fractional crystallization or chromatographic means well known in the art, and subsequent recovery of the pure enantiomers. Alternatively, enantiomerically enriched mixtures and pure enantiomeric compounds can be prepared by using synthetic intermediates that are enantiomerically pure in combination with reactions that either leave the stereochemistry at a chiral center unchanged or result in its complete inversion. Techniques for inverting or leaving unchanged a particular stereocenter, and those for resolving mixtures of stereoisomers are well known in the art, and it is well within the ability of one of skill in the art to choose an appropriate

method for a particular situation. See, generally, Furniss *et al.* (eds.), *Vogel's Encyclopedia of Practical Organic Chemistry 5th Ed.*, Longman Scientific and Technical Ltd., Essex, 1991, pp. 809-816; and Heller, *Acc. Chem. Res.* 23: 128 (1990).

The compounds described herein may also contain unnatural proportions of atomic isotopes at one or more of the atoms that constitute such compounds. For example, the compounds may be radiolabeled with radioactive isotopes, such as for example tritium (^{3}H), iodine-125 (^{125}I) or carbon-14 (^{14}C). All isotopic variations of the compounds disclosed herein, whether radioactive or not, are intended to be encompassed within the scope of the present invention. For example, deuterated compounds and compounds incorporating ^{13}C are intended to be encompassed within the scope of the invention.

Certain compounds disclosed herein can exist in unsolvated forms as well as solvated forms, including hydrated forms. In general, the solvated forms are equivalent to unsolvated forms and are encompassed within the scope of the present invention. Certain compounds disclosed herein may exist in multiple crystalline or amorphous forms. In general, all physical forms are equivalent for the uses contemplated by the present invention and are intended to be within the scope of the present invention.

As set out above, certain embodiments of the present compounds may contain a basic functional group, such as amino or alkylamino, and are, thus, capable of forming pharmaceutically acceptable salts with pharmaceutically acceptable acids. The term "pharmaceutically acceptable salts" in this respect, refers to the relatively non-toxic, inorganic and organic acid addition salts of compounds disclosed herein. These salts can be prepared *in situ* during the final isolation and purification of the compounds of the invention, or by separately reacting a purified compound of the invention in its free base form with a suitable organic or inorganic acid, and isolating the salt thus formed. Representative salts include the hydrobromide, hydrochloride, sulfate, bisulfate, phosphate, nitrate, acetate, valerate, oleate, palmitate, stearate, laurate, benzoate, lactate, phosphate, tosylate, citrate, maleate, fumarate, succinate, tartrate, napthylate, mesylate, glucoheptonate, lactobionate, and laurylsulphonate salts and the like. (See, for example, Berge et al. (1977) "Pharmaceutical Salts", *J. Pharm. Sci.* 66:1-19.)

In other cases, the compounds disclosed herein may contain one or more acidic functional groups and, thus, are capable of forming pharmaceutically acceptable salts with pharmaceutically acceptable bases. The term "pharmaceutically acceptable salts" in these instances refers to the

relatively non-toxic, inorganic and organic base addition salts of compounds disclosed herein. These salts can likewise be prepared *in situ* during the final isolation and purification of the compounds, or by separately reacting the purified compound in its free acid form with a suitable base, such as the hydroxide, carbonate or bicarbonate of a pharmaceutically acceptable metal cation, with ammonia, or with a pharmaceutically acceptable organic primary, secondary or tertiary amine. Representative alkali or alkaline earth salts include the lithium, sodium, potassium, calcium, magnesium, and aluminum salts and the like. Representative organic amines useful for the formation of base addition salts include ethylamine, diethylamine, ethylenediamine, ethanolamine, diethanolamine, piperazine and the like. (See, for example, Berge et al., *supra*)

Methods of Making

The compounds described herein can be synthesized by conventional methods. As can be appreciated by the skilled artisan, methods of synthesizing the compounds of the formulae herein will be evident to those skilled in the art. Synthetic chemistry transformations and protecting group methodologies (protection and deprotection) useful in synthesizing the compounds described herein may be known in the art and include, for example, those described in R. Larock, *Comprehensive Organic Transformations*, VCH Publishers (1989); T.W. Greene and P.G.M. Wuts, *Protective Groups in Organic Synthesis*, 2d. Ed., John Wiley and Sons (1991); L. Fieser and M. Fieser, *Fieser and Fieser's Reagents for Organic Synthesis,* John Wiley and Sons (1994); and L. Paquette, ed., *Encyclopedia of Reagents for Organic Synthesis*, John Wiley and Sons (1995), and subsequent editions thereof.

The compounds described herein can be separated from a reaction mixture and further purified by methods such as column chromatography, high-pressure liquid chromatography, or recrystallization. Techniques useful for the separation of isomers, e.g., stereoisomers are within skill of the art and are described in Eliel E.L.; Wilen, S.H.; Mander, L.N. *Stereochemistry of Organic Compounds*, Wiley Interscience, NY, 1994.

Methods of use:

Described herein are methods of treating a subject having disorder associated with metastasis and/or increased angiogenic activity, such as cancer. For example, included herein

are methods of inhibiting metastasis and/or the growth of tumor cells by administering to a subject a compound or composition described herein.

As used herein, the term "subject" is intended to include human and non-human animals. Exemplary human subjects include a human patient having a disorder, e.g., a disorder described herein or a normal subject. The term "non-human animals" of the invention includes all vertebrates, e.g., non-mammals (such as chickens, amphibians, reptiles) and mammals, such as non-human primates, domesticated and/or agriculturally useful animals, e.g., sheep, dog, cat, cow, pig, etc.

Methods of treating cancer include administering a therapeutically effective amount of a compound of formula (I), as described herein, to a subject in need thereof. For example, a method for the treatment of cancer is can include administering a therapeutically effective amount of a compound described herein, or a pharmaceutical composition comprising an compound described herein to a subject in need thereof, in such amounts and for such time as is necessary to achieve the desired result. Exemplary cancers include glioblastoma, retinoblastoma, breast cancer, cervical cancer, colon and rectal cancer, leukemia, lymphoma, lung cancer (including, but not limited to small cell lung cancer), melanoma and/or skin cancer, multiple myeloma, non-Hodgkin's lymphoma, ovarian cancer, pancreatic cancer, prostate cancer and gastric cancer, bladder cancer, uterine cancer, kidney cancer, testicular cancer, stomach cancer, brain cancer, liver cancer, or esophageal cancer). In an embodiment, a compound described herein can be used to treat ovarian cancer, for example, metastatic ovarian cancer.

As discussed above, the compounds of the present invention inhibit metastasis of tumor cells and/or inhibiting the growth of tumor cells. In general, the compounds are useful in the treatment of cancers and other proliferative disorders, including, but not limited to breast cancer, cervical cancer, colon and rectal cancer, leukemia, lung cancer, melanoma, multiple myeloma, non-Hodgkin's lymphoma, ovarian cancer, pancreatic cancer, prostate cancer, and gastric cancer, to name a few. In certain embodiments, the compounds are active against leukemia cells and melanoma cells, and thus are useful for the treatment of leukemias (e.g., myeloid, lymphocytic, myelocytic and lymphoblastic leukemias) and malignant melanomas. In still other embodiments, the compounds are active against solid tumors. In certain exemplary embodiments, the compounds as useful for the treatment of ovarian cancer. In certain exemplary embodiments, the compounds as useful for the treatment of metastatic ovarian cancer. In another aspect, the present invention provides a method for the treatment for solid tumors.

In certain embodiments, the present invention provides a method for treating and/or preventing metastasis and/or proliferation of tumor cells in a subject comprising administering to a subject (including, but not limited to, a human or animal) in need thereof a therapeutically effective amount of a compound of the invention and a pharmaceutically acceptable carrier, adjuvant or vehicle. In certain exemplary embodiments, the method is used to treat and/or prevent metastasis and/or proliferation of prostate, breast, colon, bladder, cervical, skin, testicular, kidney, ovarian, stomach, brain, liver, pancreatic or esophageal cancer or lymphoma, leukemia, or multiple myeloma, to name a few. In preferred embodiments, the method is for treating and/or preventing ovarian and/or colon cancer. In preferred embodiments, the method is for treating and/or preventing metastatic ovarian and/or colon cancer.

In another aspect, the present invention provides methods for decreasing migration of tumor cells. In a further aspect, the present invention provides methods for decreasing anchorage-independent growth of tumor cells.

In yet a further aspect, the present invention provides methods for inhibiting angiogenesis. In yet another aspect, the present invention provides methods for preventing unwanted angiogenesis in a subject (including, but not limited to, a human or animal). As used herein, the term "angiogenesis" means the generation of new blood vessels into a tissue or organ. Angiogenesis is prominent in solid tumor formation and metastasis. Angiogenic factors have been found associated with several solid tumors such as rhabdomyosarcomas, retinoblastoma, Ewing sarcoma, neuroblastoma, and osteosarcoma. A tumor cannot expand without a blood supply to provide nutrients and remove cellular wastes. Tumors in which angiogenesis is important include solid tumors, and benign tumors such as acoustic neuroma, neurofibroma, trachoma and pyogenic granulomas. Prevention of angiogenesis could halt the growth of these tumors and the resultant damage to the animal due to the presence of the tumor.

Angiogenesis has been associated with blood-born tumors such as leukemias, any of various acute or chronic neoplastic diseases of the bone marrow in which unrestrained proliferation of white blood cells occurs, usually accompanied by anemia, impaired blood clotting, and enlargement of the lymph nodes, liver, and spleen. It is believed that angiogenesis plays a role in the abnormalities in the bone marrow that give rise to leukemia-like tumors.

Angiogenesis can be important in two stages of tumor metastasis. The first stage where angiogenesis stimulation is important is in the vascularization of the tumor which allows tumor cells to enter the blood stream and to circulate throughout the body. After the tumor cells have

left the primary site, and have settled into the secondary, metastasis site, angiogenesis must occur before the new tumor can grow and expand. Therefore, prevention of angiogenesis could lead to the prevention of metastasis of tumors and possibly contain the neoplastic growth at the primary site.

Thus, in certain embodiments, the invention provides a method for preventing unwanted angiogenesis in a subject (including, but not limited to, a human or animal) comprising administering to a subject in need thereof a therapeutically effective amount of the compound of the invention in an amount effective to inhibit angiogenesis.

It will be appreciated that the compounds and compositions, according to the method of the present invention, may be administered using any amount and any route of administration effective for the treatment of cancer and/or disorders associated with metastasis and/or angiogenesis. Thus, the expression "effective amount" as used herein, refers to a sufficient amount of agent to inhibit the growth of tumor cells, or refers to a sufficient amount to reduce the effects of cancer. The exact amount required will vary from subject to subject, depending on the species, age, and general condition of the subject, the severity of the diseases, the particular anticancer agent, its mode of administration, and the like.

Administration of compounds and formulations thereof

The compounds of the formulae described herein can, for example, be administered to a subject by injection, intravenously, intraarterially, subdermally, intraperitoneally, intramuscularly, or subcutaneously; or orally, buccally, nasally, transmucosally, topically, in an ophthalmic preparation, or by inhalation, with a dosage ranging from about 0.001 to about 100 mg/kg of body weight, e.g., between 0.001-1mg/kg, 1-100mg/kg, or 0.01-5mg/kg, every 4 to 120 hours, e.g., about every 6, 8, 12, 24, 48, or 72 hours, or according to the requirements of the particular compound. The methods herein contemplate administration of an effective amount of compound or compound composition to achieve the desired or stated effect (e.g., reduction of feeding in a subject). Typically, the pharmaceutical compositions of this invention will be administered from about 1 to about 6 times per day, for example, the compounds can be administered about 1 to about 4 (e.g., 1, 2, 3, or 4) hours prior to meal time. Alternatively, the compounds can be administered as a continuous infusion. Such administration can be used as a chronic or acute therapy. The amount of active ingredient that may be combined with the carrier materials to produce a single dosage form will vary depending upon the host treated and the particular mode

of administration. A typical preparation will contain from about 5% to about 95% active compound (w/w). Alternatively, such preparations contain from about 20% to about 80% active compound.

Lower or higher doses than those recited above may be required. Specific dosage and treatment regimens for any particular patient will depend upon a variety of factors, including the activity of the specific compound employed, the age, body weight, general health status, sex, diet, time of administration, rate of excretion, drug combination, the severity and course of the disease, condition or symptoms, the patient's disposition to the disease, condition or symptoms, and the judgment of the treating physician.

Upon improvement of a patient's condition, a maintenance dose of a compound, composition or combination of this invention may be administered, if necessary. Subsequently, the dosage or frequency of administration, or both, may be reduced, as a function of the symptoms, to a level at which the improved condition is retained. Patients may, however, require intermittent treatment on a long-term basis upon any recurrence of disease symptoms.

Pharmaceutical compositions of this invention comprise a compound of the formulae described herein or a pharmaceutically acceptable salt thereof; an additional compound including for example, a steroid or an analgesic; and any pharmaceutically acceptable carrier, adjuvant or vehicle. Alternate compositions of this invention comprise a compound of the formulae described herein or a pharmaceutically acceptable salt thereof; and a pharmaceutically acceptable carrier, adjuvant or vehicle. The compositions delineated herein include the compounds of the formulae delineated herein, as well as additional therapeutic compounds if present, in amounts effective for achieving a modulation of disease or disease symptoms, including kinase mediated disorders or symptoms thereof. The compositions are made by methods including the steps of combining one or more compounds delineated herein with one or more carriers and, optionally, one or more additional therapeutic compounds delineated herein.

The term "pharmaceutically acceptable carrier or adjuvant" refers to a carrier or adjuvant that may be administered to a patient, together with a compound of this invention, and which does not destroy the pharmacological activity thereof and is nontoxic when administered in doses sufficient to deliver a therapeutic amount of the compound.

The pharmaceutical compositions of this invention may be orally administered in any orally acceptable dosage form including, but not limited to, capsules, tablets, emulsions and aqueous suspensions, dispersions and solutions. In the case of tablets for oral use, carriers which

are commonly used include lactose and corn starch. Lubricating agents, such as magnesium stearate, are also typically added. For oral administration in a capsule form, useful diluents include lactose and dried corn starch. When aqueous suspensions and/or emulsions are administered orally, the active ingredient may be suspended or dissolved in an oily phase which can be combined with emulsifying and/or suspending agents. If desired, certain sweetening and/or flavoring and/or coloring agents may be added.

The pharmaceutical compositions may be in the form of a sterile injectable preparation, for example, as a sterile injectable aqueous or oleaginous suspension. This suspension may be formulated according to techniques known in the art using suitable dispersing or wetting agents (such as, for example, Tween 80) and suspending agents. The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally acceptable diluent or solvent, for example, as a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that may be employed are mannitol, water, Ringer's solution and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose, any bland fixed oil may be employed including synthetic mono- or diglycerides. Fatty acids, such as oleic acid and its glyceride derivatives are useful in the preparation of injectables, as are natural pharmaceutically-acceptable oils, such as olive oil or castor oil, especially in their polyoxyethylated versions. These oil solutions or suspensions may also contain a long-chain alcohol diluent or dispersant, or carboxymethyl cellulose or similar dispersing agents which are commonly used in the formulation of pharmaceutically acceptable dosage forms such as emulsions and or suspensions. Other commonly used surfactants such as Tweens or Spans and/or other similar emulsifying agents or bioavailability enhancers which are commonly used in the manufacture of pharmaceutically acceptable solid, liquid, or other dosage forms may also be used for the purposes of formulation.

The pharmaceutical compositions of this invention may also be administered in the form of suppositories for rectal administration. These compositions can be prepared by mixing a compound of this invention with a suitable non-irritating excipient which is solid at room temperature but liquid at the rectal temperature and therefore will melt in the rectum to release the active components. Such materials include, but are not limited to, cocoa butter, beeswax and polyethylene glycols.

Pharmaceutically acceptable carriers, adjuvants and vehicles that may be used in the pharmaceutical compositions of this invention include, but are not limited to, ion exchangers,

alumina, aluminum stearate, lecithin, self-emulsifying drug delivery systems (SEDDS) such as d-α-tocopherol polyethyleneglycol 1000 succinate, surfactants used in pharmaceutical dosage forms such as Tweens or other similar polymeric delivery matrices, serum proteins, such as human serum albumin, buffer substances such as phosphates, glycine, sorbic acid, potassium sorbate, partial glyceride mixtures of saturated vegetable fatty acids, water, salts or electrolytes, such as protamine sulfate, disodium hydrogen phosphate, potassium hydrogen phosphate, sodium chloride, zinc salts, colloidal silica, magnesium trisilicate, polyvinyl pyrrolidone, cellulose-based substances, polyethylene glycol, sodium carboxymethylcellulose, polyacrylates, waxes, polyethylene-polyoxypropylene-block polymers, polyethylene glycol and wool fat. Cyclodextrins such as α -, β-, and γ-cyclodextrin, may also be advantageously used to enhance delivery of compounds of the formulae described herein.

In some cases, the pH of the formulation may be adjusted with pharmaceutically acceptable acids, bases or buffers to enhance the stability of the formulated compound or its delivery form.

The term parenteral as used herein includes subcutaneous, intracutaneous, intravenous, intramuscular, intraarticular, intraarterial, intrasynovial, intrasternal, intrathecal, intralesional and intracranial injection or infusion techniques.

The pharmaceutical compositions of this invention may be administered by nasal aerosol or inhalation. Such compositions are prepared according to techniques well-known in the art of pharmaceutical formulation and may be prepared as solutions in saline, employing benzyl alcohol or other suitable preservatives, absorption promoters to enhance bioavailability, fluorocarbons, and/or other solubilizing or dispersing agents known in the art.

When the compositions of this invention comprise a combination of a compound of the formulae described herein and one or more additional therapeutic or prophylactic agents, both the compound and the additional compound should be present at dosage levels of between about 1 to 100%, and more preferably between about 5 to 95% of the dosage normally administered in a monotherapy regimen. Additionally, combinations of a plurality of compounds described herein are also envisioned. The additional compounds may be administered separately, as part of a multiple dose regimen, from the compounds of this invention. Alternatively, those compounds may be part of a single dosage form, mixed together with the compounds of this invention in a single composition.

Dosages:

Actual dosage levels of the active ingredients in the pharmaceutical compositions of this invention may be varied so as to obtain an amount of the active ingredient that is effective to achieve the desired therapeutic response for a particular patient, composition, and mode of administration, without being toxic to the patient.

The selected dosage level will depend upon a variety of factors including the activity of the particular compound disclosed herein employed, or the ester, salt or amide thereof, the route of administration, the time of administration, the rate of excretion of the particular compound being employed, the duration of the treatment, other drugs, compounds and/or materials used in combination with the particular compound employed, the age, sex, weight, condition, general health and prior medical history of the patient being treated, and like factors well known in the medical arts.

A physician or veterinarian having ordinary skill in the art can readily determine and prescribe the effective amount of the pharmaceutical composition required. For example, the physician or veterinarian could start doses of the compounds of the invention employed in the pharmaceutical composition at levels lower than that required in order to achieve the desired therapeutic effect and gradually increase the dosage until the desired effect is achieved.

In general, a suitable daily dose of a compound of the invention will be that amount of the compound that is the lowest dose effective to produce a therapeutic effect. Such an effective dose will generally depend upon the factors described above. Generally, intravenous, intracerebroventricular and subcutaneous doses of the compounds of this invention for a patient will range from about 0.0001 to about 100 mg per kilogram of body weight per day. If desired, the effective daily dose of the active compound may be administered as two, three, four, five, six or more sub-doses administered separately at appropriate intervals throughout the day, optionally, in unit dosage forms. In some embodiments, the dose will be 1-20, or 5-10 mg per kilogram of body weight, administed twice daily.

Kits:

A compound described herein can be provided in a kit. The kit includes (a) a composition that includes a compound described herein, and, optionally (b) informational material. The informational material can be descriptive, instructional, marketing or other

material that relates to the methods described herein and/or the use of the compound described herein for the methods described herein.

The informational material of the kits is not limited in its form. In one embodiment, the informational material can include information about production of the compound, molecular weight of the compound, concentration, date of expiration, batch or production site information, and so forth. In one embodiment, the informational material relates to use of the compound described herein to treat a disorder described herein.

In one embodiment, the informational material can include instructions to administer the compound described herein in a suitable manner to perform the methods described herein, e.g., in a suitable dose, dosage form, or mode of administration (e.g., a dose, dosage form, or mode of administration described herein). Preferred doses, dosage forms, or modes of administration are parenteral, e.g., intravenous, intramuscular, subcutaneous, intraparenteral, bucosal, sublingual, intraoccular, and topical. In another embodiment, the informational material can include instructions to administer the compound described herein to a suitable subject, e.g., a human, e.g., a human having or at risk for a disorder described herein. For example, the material can include instructions to administer the compound described herein to such a subject.

The informational material of the kits is not limited in its form. In many cases, the informational material, e.g., instructions, is provided in printed matter, e.g., a printed text, drawing, and/or photograph, e.g., a label or printed sheet. However, the informational material can also be provided in other formats, such as computer readable material, video recording, or audio recording. In another embodiment, the informational material of the kit is contact information, e.g., a physical address, email address, website, or telephone number, where a user of the kit can obtain substantive information about an compound described herein and/or its use in the methods described herein. Of course, the informational material can also be provided in any combination of formats.

In addition to a compound described herein, the composition of the kit can include other ingredients, such as a solvent or buffer, a stabilizer, a preservative, and/or a second compound for treating a condition or disorder described herein. Alternatively, the other ingredients can be included in the kit, but in different compositions or containers than the compound described herein. In such embodiments, the kit can include instructions for admixing the compound described herein and the other ingredients, or for using a compound described herein together with the other ingredients.

The compound described herein can be provided in any form, e.g., liquid, dried or lyophilized form. It is preferred that the compound described herein be substantially pure and/or sterile. When the compound described herein is provided in a liquid solution, the liquid solution preferably is an aqueous solution, with a sterile aqueous solution being preferred. When the compound described herein is provided as a dried form, reconstitution generally is by the addition of a suitable solvent. The solvent, e.g., sterile water or buffer, can optionally be provided in the kit.

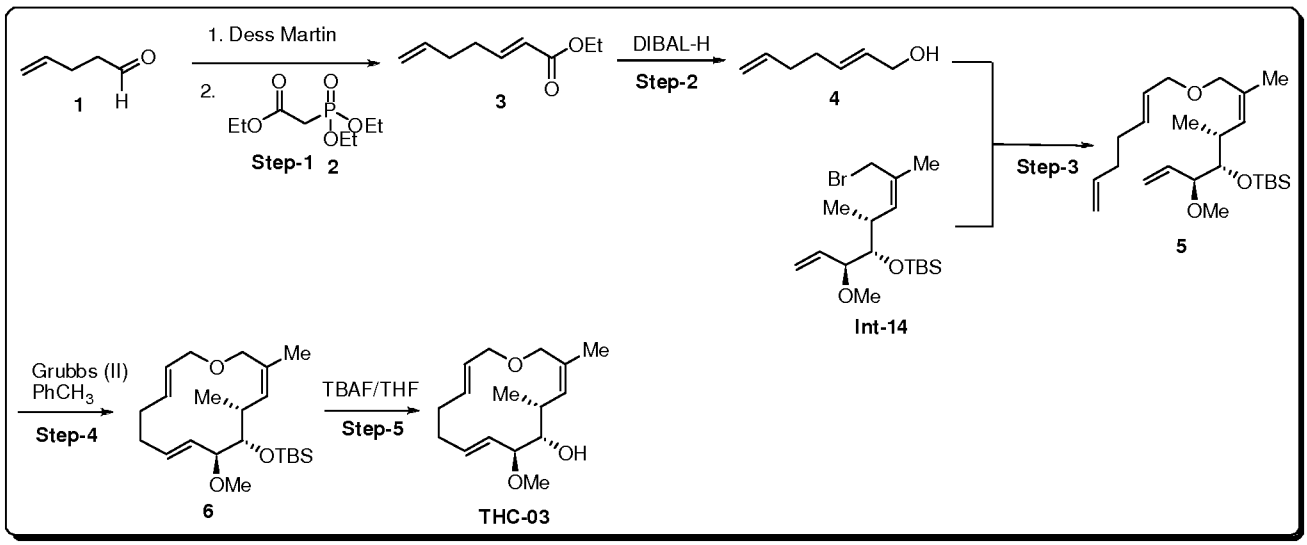
The kit can include one or more containers for the composition containing the compound described herein. In some embodiments, the kit contains separate containers, dividers or compartments for the composition and informational material. For example, the composition can be contained in a bottle, vial, or syringe, and the informational material can be contained in a plastic sleeve or packet. In other embodiments, the separate elements of the kit are contained within a single, undivided container. For example, the composition is contained in a bottle, vial or syringe that has attached thereto the informational material in the form of a label. In some embodiments, the kit includes a plurality (e.g., a pack) of individual containers, each containing one or more unit dosage forms (e.g., a dosage form described herein) of a compound described herein. For example, the kit includes a plurality of syringes, ampules, foil packets, or blister packs, each containing a single unit dose of a compound described herein. The containers of the kits can be air tight, waterproof (e.g., impermeable to changes in moisture or evaporation), and/or light-tight.

The kit optionally includes a device suitable for administration of the composition, e.g., a syringe, inhalant, pipette, forceps, measured spoon, dropper (e.g., eye dropper), swab (e.g., a cotton swab or wooden swab), or any such delivery device. In a preferred embodiment, the device is an implantable delivery device.

Examples

Example 1. Synthesis of cyclic compounds.

Scheme 1:



(E)-Ethyl hepta-2,6-dienoate (**3**):

A mixture of lithium chloride (1.376 g, 32.5 mmol), triethyl phosphonoacetate (5.36 mL, 27.04 mmol) in MeCN (35 mL), DBU (4.04 mL, 27.04 mmol) was stirred at RT for 1 h. A solution of pent-4-enal (**1**) (1.52 g, 18.03 mmol) in CH_3CN (20 mL) was added to the reaction mixture at 0°C and gradually warmed to room temperature (25-27°C) and stirred for another 16 h. The volatiles from the reaction were removed under reduced pressure and the residue was extracted with Et_2O (3 x 15 mL). The combined organic extracts were concentrated under reduced pressure to give the crude material, which was purified by silica gel column chromatography (Et_2O/Hexane 3:97) to afford compound **3** (0.402 g, 14.4%) as yellow syrup.

TLC: 15% EtOAc/Hexane (R_f: 0.2)

^{1}H NMR (500MHz, $CDCl_3$): δ 6.96 (m, 1H), 5.85-5.77 (m, 2H), 5.03 (dd, *J* = 24.0, 17.0 Hz, 2H), 4.19 (m, 2H), 2.31 (m, 2H), 2.22 (m, 2H), 1.28 (t, *J* = 7.0 Hz, 3H).

Mass (ESI): 156 (M^++1).

(E)-Hepta-2,6-dien-1-ol (**4**):

To a stirred solution of compound **3** (0.40 g, 2.59 mmol) in CH_2Cl_2 (25 mL), cooled to -78°C, DIBAL-H (5.2 mL, 5.19 mmol) was added and stirred for 2 h. The reaction mixture was slowly warmed to 0°C and continued for further 30 min. and quenched with concentrated sodium potassium tartrate solution, filtered and the filtrate was extracted with CH_2Cl_2 (3 x 15 mL). The combined organic extracts were dried over anhydrous Na_2SO_4, filtered and concentrated under

reduced pressure to give the crude material which was purified by silica gel column chromatography (EtOAc/Hexane 1:9) to furnish compound **4** (0.162 g, 55.8%) as a syrup.

TLC: 10% EtOAc/Hexane (R_f: 0.1)

^{1}H NMR (500MHz, $CDCl_3$): δ 5.84-5.78 (m, 1H), 5.72-5.63 (m, 2H), 5.00 (dd, *J* = 29.5, 18.0 Hz, 2H), 4.09 (t, *J* = 5.5 Hz, 2H), 2.15 (s, 4H), 1.25 (t, *J* = 6.0 Hz, 1H).

tert-Butyl (((3S, 4S, 5R, Z)-8-((E)-hepta-2,6-dien-1-yloxy)-3-methoxy-5,7-dimethylocta-1, 6-dien-4-yl) oxy) dimethylsilane (**5**):

To a stirred solution of compound **4** (0.082 g, 0.73 mmol) in DMF (1 mL) at 0°C, NaH (0.035 g, 0.79 mmol, 55% dispersion in mineral oil) was added and stirred for 20 min. The reaction mixture was warmed to RT and stirred for further 30 min. The reaction was cooled to 0°C, a solution of **Int-14** (0.25 g, 0.66 mmol) in DMF (1 mL) was added to reaction mixture and stirred for 4h at room temperature. After consumption of the starting material (by TLC), the reaction was diluted with Ether (10 ml) and quenched with saturated NH_4Cl solution. The aqueous layer was extracted with Et_2O (2 x 10 mL); the combined organic extracts were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to provide the crude material which was purified by silica gel column chromatography (EtOAc/Hexane 1:99) to afford compound **5** (0.15 g, 55%) as liquid.

TLC: 5% EtOAc/Hexane (R_f: 0.7)

^{1}H NMR (500MHz, $CDCl_3$): δ 5.85-5.79 (m, 1H), 5.71-5.55 (m, 3H), 5.39-5.37 (d, *J* = 10.0 Hz, 1H), 5.27 (t, *J* = 10.0 Hz, 2H), 5.01 (m, 2H), 3.97 (d, *J* = 11.5 Hz, 1H), 3.87-3.80 (m, 3H), 3.44 (m, 1H), 3.37 (m, 1H), 3.20 (s, 3H), 2.62-2.59 (m, 1H), 2.16 (t, *J* = 2.5 Hz, 4H), 1.75 (s, 3H), 0.91 (s, 12H), 0.02 (t, *J* = 16.5 Hz, 6H).

Mass (ESI): 409.8 (M^++1).

tert-Butyl (((3Z,5R,6S,7S,8E,12E)-7-methoxy-3, 5-dimethyloxacyclotetradeca-3,8,12-trien-6-yl) oxy) dimethylsilane (**6**):

To a stirred solution of compound **5** (0.15 g, 0.363 mmol) in refluxing PhMe (600 mL), Grubbs-II catalyst (0.063 g, 0.073 mmol) (dissolved in toluene (115 mL)) was slowly added and continued for 15 min. The reaction was slowly brought to RT and filtered through a pad of silica gel, the filtrate was concentrated under reduced pressure to give the crude residue which was

purified by silica gel column chromatography (EtOAc/Hexane 1:49) to obtain compound **6** (0.081 g, 56.8%) as a pale yellow liquid.

TLC: 5% EtOAc/Hexane(R_f: 0.42)

^{1}H NMR (500MHz, $CDCl_3$): δ 5.62-5.52 (m, 2H), 5.45-5.39 (m, 2H), 5.20 (dd, *J* = 15.5, 7.5 Hz, 1H), 3.98 (d, *J* = 10.5 Hz, 1H), 3.92-3.81 (m, 2H), 3.61 (d, *J* = 10.5 Hz, 1H), 3.33 (m, 2H), 3.19 (s, 3H), 2.72 (t, *J* = 6.5 Hz, 1H), 2.37-2.31 (m, 2H), 2.21-2.16 (m, 2H), 1.75 (s, 3H), 0.89 (s, 12H), 0.03 (s, 6H).

Mass (ESI): 412 (M^++18).

(3Z, 5R, 6S, 7S, 8E, 12E)-7-methoxy-3,5-dimethyloxacyclotetradeca-3,8,12-trien-6-ol (**THC-003**):

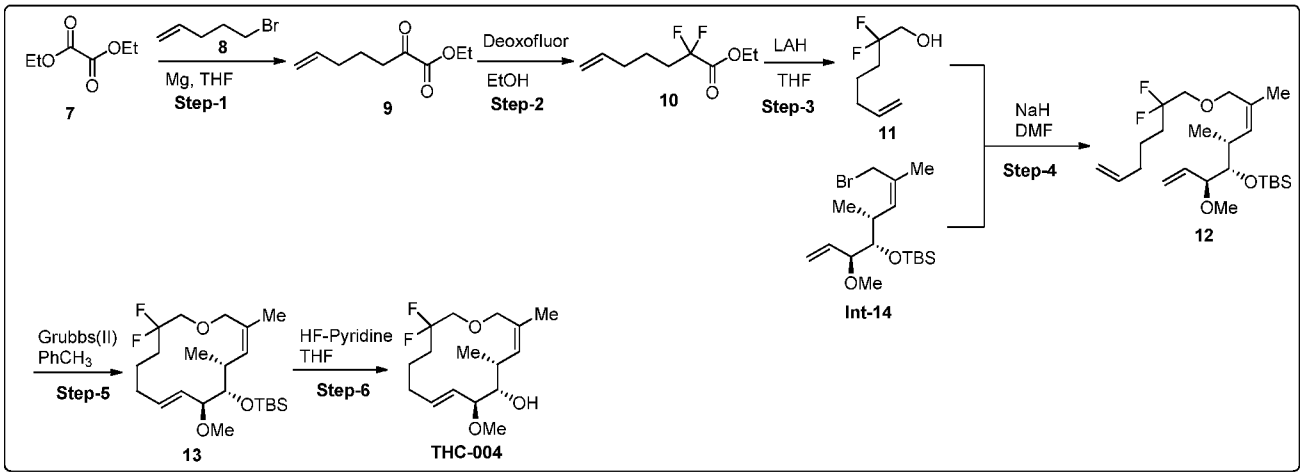
To a stirred solution of compound **6** (0.081 g, 0.21 mmol) in THF (2 mL), TBAF (1.0M in THF, 0.25 mL, 0.247 mmol) was added and stirred at RT for 6 h. The reaction was heated to 60°C for another 16 h and diluted with Et_2O (10 ml). The organic layer was separated, washed with saturated sodium bicarbonate solution, brine, dried over anhydrous sodium sulphate and concentrated under reduced pressure to give the crude material which was purified by silica gel column chromatography (EtOAc/Hexane 1:9) to furnish **THC-003** (0.034 g, 62.4%) as a liquid.

TLC: 20% EtOAc/Hexane (R_f: 0.25)

^{1}H NMR (500MHz, $CDCl_3$): δ 5.65-5.42 (m, 4H), 5.18 (dd, *J* = 15.5, 8.5 Hz, 1H), 3.94 (d, *J* = 9.5 Hz, 2H), 3.82-3.78 (m, 1H), 3.63 (d, *J* = 10.5 Hz, 1H), 3.40 (t, *J* = 9.5 Hz, 1H), 3.30 (s, 4H), 2.72 (s, 1H), 2.68 (t, *J* = 8.5 Hz, 1H), 2.40-2.34 (m, 2H), 2.21-2.14 (m, 2H), 1.78 (s, 3H), 0.93 (d, *J* = 6.5 Hz, 3H).

Mass (ESI): 289.17 (M^++Na).

Scheme 2:



Ethyl 2-oxohept-6-enoate (**9**):

Magnesium turnings (0.74 g, 0.03 mol) were taken in dry THF (10 mL), a pinch of iodine was added followed by 5-bromopent-1-ene **8** (2 g, 0.013 mol) and stirred for 30 min. A solution of diethyl oxalate (1.57 g, 0.01 mol) in THF: ether (20 mL, 1:1) was cooled to -78 °C. The Grignard solution was added to the reaction mixture maintaining the temperature at -78°C and stirred for another 2 h. After consumption of the starting material (by TLC), the reaction was quenched with saturated ammonium chloride solution and extracted with EtOAc (3 x 15 mL). The combined organic extracts were dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure to afford compound **9** (1.5 g, 65%) as a crude material which was carried for the next step without further purification.

TLC: 10% EtOAc/Hexane (R_f: 0.5)

Mass (ESI): 171.5 (M^++1).

Ethyl 2,2-difluorohept-6-enoate (**10**):

To a stirred solution of compound **9** (1.5 g, 8.82 mol) in DCM (5 mL), cooled to 0°C, EtOH (0.102 ml, 1.76 mmol) was added followed by Deoxo-fluor (3.3 g, 14.9 mmol) under N_2 atmosphere. The reaction mixture was slowly warmed to RT and stirred for 16 h. After completion of reaction (by TLC), the reaction was quenched with saturated sodium bicarbonate solution and extracted with DCM (3 x 20 mL). The combined organic extracts were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give the crude material

which was purified by column chromatography using silica gel (EtOAc/Hexane 1:19) to afford compound **10** (0.91 g, 53%) as a liquid.

TLC: 10% EtOAc/Hexane (R_f: 0.6)

^{1}H NMR (500MHz, $CDCl_3$): δ 5.80-5.72 (m, 1H), 5.05-4.99 (m, 2H), 4.33 (q, *J* = 6.5 Hz, 2H), 2.14-2.01 (m, 4H), 1.61-1.54 (m, 2H), 1.35 (d, *J* = 7.0 Hz, 3H).

2, 2-Difluorohept-6-en-1-ol (**11**):

To a stirred solution of compound **10** (0.91 g, 4.74 mmol) in THF (20 mL) at 0°C, $LiAlH_4$ (0.09 g, 2.34 mmol) was slowly added under N_2 atmosphere. The reaction mixture was warmed to RT and stirred for 3 h. After consumption of the starting material (by TLC), the reaction was quenched with 10% NaOH solution (5 ml) and precipitated solid was filtered through a pad of celite. The filtrate was dried over anhydrous sodium sulphate and concentrated under reduced pressure to give the crude residue which was purified by silica gel column chromatography (EtOAc/Hexane 1:4) to afford compound **11** (260 mg, 37%) as a syrup.

TLC: 10% EtOAc/Hexane (R_f: 0.5)

^{1}H NMR (500MHz, $CDCl_3$): δ 5.83-5.74 (m, 1H), 5.06-4.99 (m, 2H), 3.77-3.70 (m, 2H), 2.12 (q, *J* = 7.0 Hz, 2H), 1.97-1.87 (m, 2H), 1.80 (t, *J* = 7.0 Hz, 1H), 1.64-1.56 (m, 2H).

tert-Butyl (((3S, 4S, 5R, Z)-8-((2, 2-difluorohept-6-en-1-yl) oxy)-3-methoxy-5, 7-dimethylocta-1, 6-dien-4-yl) oxy) dimethylsilane (**12**):

To a stirred solution of compound **11** (97 mg, 0.65 mmol) in DMF (4 mL), cooled to -5 °C, NaH (21.1 mg, 0.88 mmol) was added under N_2 atmosphere. After 10 min Int-14 (220 mg, 0.59 mmol), dissolved in anhydrous DMF (1.5 ml), was slowly added to the reaction mixture maintaining the temperature at 0°C. The reaction mass was slowly warmed to RT and stirred for 30 min. After consumption of the starting material (by TLC), the reaction was quenched with ice cold water and extracted with EtOAc (3 x 15 mL). The combined organic extracts were dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure to give the crude material which was purified by silica gel column chromatography (EtOAc/Hexane 1:19) to afford compound **12** (150.6 mg, 63%) as a liquid.

TLC: 5% EtOAc/Hexane(R_f: 0.5)

^{1}H NMR (500MHz, $CDCl_3$): δ 5.81-5.74 (m, 1H), 5.66-5.59 (m, 1H), 5.43 (d, *J* = 10.0 Hz, 1H), 5.27 (t, *J* = 12.5 Hz, 2H), 5.04-4.97 (m, 2H), 4.05 (m, 2H), 3.51-3.36 (m, 4H), 3.20 (s, 3H), 2.58

(t, J = 7.0 Hz, 1H), 2.11 (m, 2H), 1.96-1.86 (m, 2H), 1.72 (s, 3H), 1.62-1.50 (m, 2H), 0.91 (s, 12H), 0.04 (d, J = 17.5 Hz, 6H).

tert-Butyl (((3Z, 5R, 6S, 7S, 8E)-13, 13-difluoro-7-methoxy-3, 5-dimethyloxacyclotetradeca-3, 8-dien-6-yl) oxy) dimethylsilane (**13**):

To a stirred solution of compound **12** (150.6 mg, 0.37 mmol) in PhMe (600 mL), heated at 110°C, Grubbs -II catalyst (31.9 mg, 0.037 mmol) dissolved in toluene (97 mL) was added and refluxed for 15 min under argon atmosphere. After consumption of the starting material (by TLC), the reaction was slowly brought to rt and the volatiles from the reaction mixture were removed under reduced pressure. The crude residue was purified by silica gel column chromatography eluting with (EtOAc/Hexane 1: 19) to afford compound **13** (93.6 mg, 60%) as a pale yellow liquid.

TLC: 5% EtOAc/Hexane (R_f: 0.5)

^{1}H NMR (500MHz, $CDCl_3$): δ 5.68-5.63 (m, 1H), 5.57 (d, J = 10.0 Hz, 1H), 5.31-5.27 (m, 1H), 3.98 (d, J = 10.0 Hz, 1H), 3.83 (d, J = 10.0 Hz, 1H), 3.67-3.53 (m, 2H), 3.45-3.38 (m, 2H), 3.20 (s, 3H), 2.78-2.76 (m, 1H), 2.19 (d, J = 12.5 Hz, 2H), 2.02-1.91 (m, 2H), 1.74 (s, 4H), 1.64 (m, 1H), 0.91 (s, 12H), 0.05 (d, J = 18.5 Hz, 6H).

(3Z, 5R, 6S, 7S, 8E)-13, 13-difluoro-7-methoxy-3, 5-dimethyloxacyclotetradeca-3, 8-dien-6-ol (**THC-004**):

To a stirred solution of compound **13** (93.6 mg, 0.22 mmol) in dry THF (3 mL), cooled to 0°C, HF-pyridine (1.7 mL) was added dropwise. The reaction mixture was slowly warmed to RT and stirred for 16 h. After consumption of the starting material (by TLC), the reaction was quenched with saturated sodium bicarbonate solution and the aqueous layer was extracted with EtOAc (2 x 15 mL). The combined organic extracts were dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure to give the crude material which was purified by silica gel column chromatography (EtOAc/Hexane 1:19) to afford **THC-004** (45.2 mg, 66.5%) as a liquid.

TLC: 20% EtOAc/Hexane (R_f: 0.2)

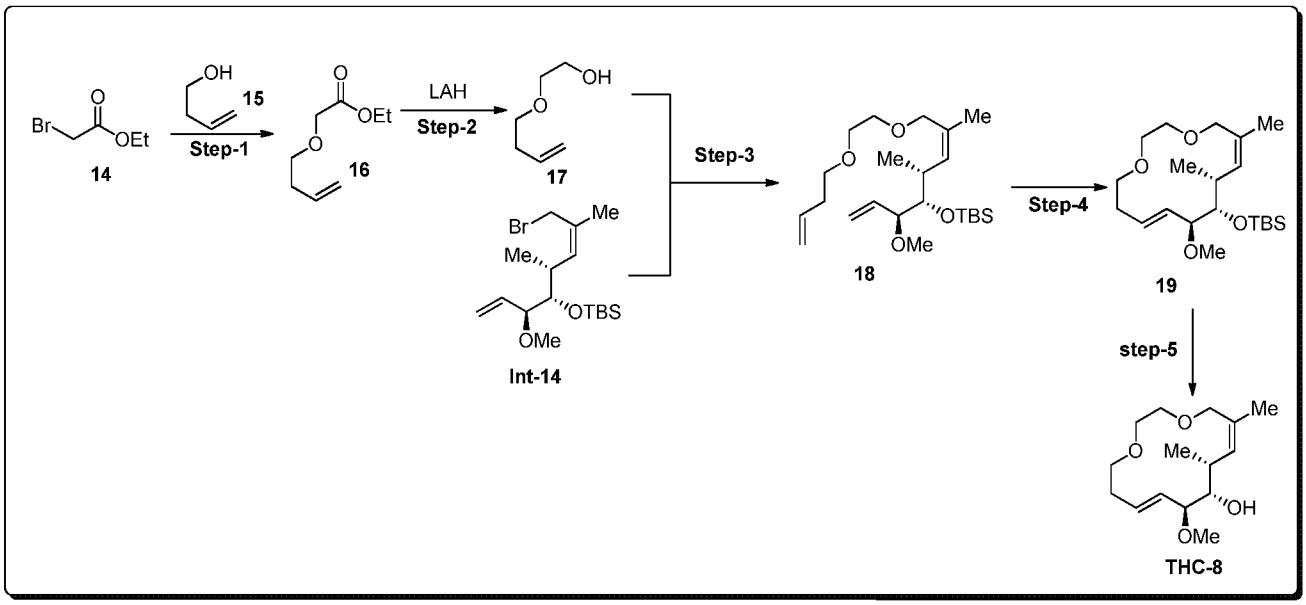
^{1}H NMR (500MHz, $CDCl_3$): δ 5.72-5.66 (m, 2H), 5.27-5.22 (m, 1H), 4.10 (d, J = 10.0 Hz, 1H), 3.71 (d, J = 9.5 Hz, 1H), 3.68-3.52 (m, 2H), 3.48-3.39 (m, 2H), 3.31 (s, 3H), 2.77 (t, J = 7.0 Hz,

2H), 2.31-2.29 (m, 1H), 2.12-2.01 (m, 2H), 1.86-1.82 (m, 1H), 1.75 (s, 3H), 1.57 (m, 1H), 0.94 (d, J = 7.0 Hz, 3H).

Mass (ESI): 303.4 (M^+-1).

LC-MS: m/z = 301.3[M^+-2)] at RT 4.72 (89.09% purity).

Scheme 3:



Ethyl 2-(but-3-en-1-yloxy) acetate (**16**):

To a stirred solution of but-3-en-1-ol (**15**) (2 g, 0.03 mol) in DMF (20 mL), cooled to 0°C, NaH (0.8 g, 0.03 mol, 60% dispersion in mineral oil) was added slowly, stirred for 30 min and Ethyl 2-bromoacetate (**14**) (5 g, 0.03 mol) was added to the reaction mixture maintaining the temperature at 0°C. The reaction was stirred for further 30 min, slowly brought to RT and the stirred for another 2 h. The reaction was quenched with cold water and extracted with *n*-hexane (3 x 20 mL). The combined organic extracts were dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure to give the crude material which was purified by silica gel column chromatography (EtOAc/Hexane 1:9) to afford ester **16** (0.6 g, 15%) as a liquid.

TLC: 20% EtOAc/Hexane (R_f: 0.25)

^{1}H NMR (500MHz, $CDCl_3$): δ 5.84-5.80 (m, 1H), 5.14-5.07 (m, 2H), 4.10 (s, 2H), 3.75 (s, 3H), 3.60 (t, J = 7.0 Hz, 2H), 2.42-2.37 (m, 2H).

Mass (ESI): 162 (M^++18).

2-(But-3-en-1-yloxy) ethanol (**17**):

To a stirred solution of ester **16** (0.6 g, 4.16 mmol) in dry THF (10 mL), cooled to 0°C, $LiAlH_4$ (0.19 g, 5.0 mmol) was added portionwise and stirred for 30 min. The reaction mixture was slowly brought to RT and stirred for further 16 h. After consumption of the starting material (by TLC), reaction was quenched with 4N NaOH solution (3 ml) and extracted with EtOAc (3 x 20 mL). The combined organic extracts were washed with brine, dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure to provide alcohol **17** (0.3 g, 64%) as syrup.

TLC: 20% EtOAc/Hexane (R_f: 0.15)

^{1}H NMR (500MHz, $CDCl_3$): δ 5.85-5.78 (m, 1H), 5.12-5.04 (m, 2H), 3.73-3.70 (m, 2H), 3.56-3.53 (m, 4H), 2.37 (q, *J* = 7.0 Hz, 2H), 2.00 (t, *J* = 6.0 Hz, 1H) .

(5S, 6R, Z)-5-((S)-1-methoxyallyl)-2, 2, 3, 3, 6, 8-hexamethyl-4, 10, 13-trioxa-3-silaheptadeca-7, 16-diene (**18**):

To a stirred suspension of NaH (60 mg, 2.5 mmol, 60% dispersion in mineral oil) in DMF (1 ml), cooled to 0°C, a solution of alcohol 4 (0.3 g, 2.5 mmol) dissolved in DMF (1 mL) was added and stirred for 15 min. **Int-14** (0.5 g, 1.34 mmol) taken in DMF (1 mL) was added to the reaction mixture maintaining the temperature at 0°C and stirred for 30 min. The reaction was slowly warmed to RT and the stirred for another 1 h and quenched with cold water and extracted with hexane (2 x 15 mL). The combined organic extracts were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to provide the crude material which was purified by silica gel column chromatography eluting with (EtOAc/Hexane 3:97) to afford **18** (234 mg, 42.5%) as a syrup.

TLC: 5% EtOAc/Hexane (R_f: 0.25)

^{1}H NMR (500MHz, $CDCl_3$): δ 5.85-5.79 (m, 1H), 5.66-5.59 (m, 1H), 5.39 (d, *J* = 10.0 Hz, 1H), 5.27 (t, *J* = 10.5 Hz, 2H), 5.10-5.01 (m, 2H), 4.02 (d, *J* = 12.0 Hz, 1H), 3.93 (d, *J* = 11.0 Hz, 1H), 3.59-3.35 (m, 8H), 3.19 (s, 3H), 2.62-2.59 (m, 1H), 2.36 (q, *J* = 7.0 Hz, 2H), 1.73 (s, 3H), 0.90 (s, 12H), 0.06 (d, *J* = 10.0 Hz, 6H).

Mass (ESI): 430 (M^++18).

tert-Butyl(((6Z,8R,9S,10S,11E)-10-methoxy-6,8-dimethyl-1,4-dioxacyclotetradeca-6,11-dien-9-yl)oxy)dimethylsilane (**19**):

To a solution of **18** (239.3 mg, 0.58 mmol) in PhMe (600 mL) under reflux, Grubbs-II catalyst (101 mg, 0.01 mmol) taken in toluene (330 mL) was added and the reflux was continued for 15 min. The reaction was concentrated under reduced pressure to give the crude material which was purified by silica gel column chromatography (EtOAc/Hexane 1:19) to afford **19** (145.3 mg, 65.4%) as a light yellow liquid.

TLC: 10% EtOAc/Hexane (R_f: 0.25)

^{1}H NMR (500MHz, $CDCl_3$): δ 5.65-5.60 (m, 1H), 5.47 (d, *J* = 9.5 Hz, 1H), 5.33-5.29 (m, 1H), 4.18 (d, *J* = 10.5 Hz, 1H), 3.85 (d, *J* = 10.5 Hz, 1H), 3.61-3.45 (m, 6H), 3.37 (s, 2H), 3.20 (s, 3H), 3.00-2.97 (m, 1H), 2.36-2.27 (m, 2H), 1.72 (s, 3H), 0.88 (d, *J* = 7.0 Hz, 12H), 0.04 (s, 3H), 0.01 (s, 3H).

Mass (ESI): 385 (M^++1).

(6Z, 8R, 9S, 10S, 11E)-10-methoxy-6, 8-dimethyl-1, 4-dioxacyclotetradeca-6, 11-dien-9-ol (**THC-008**):

To a stirred solution of **19** (97.3 mg, 0.25 mmol) in dry THF (1 mL), cooled to 0°C, HF-pyridine (2 mL) was added slowly. The reaction mixture was warmed to RT and stirred for 24 h and neutralized with saturated $NaHCO_3$ solution. The aqueous layer was separated and extracted with CH_2Cl_2 (2 x 20 mL). The combined organic extracts were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give the crude material which was purified by silica gel column chromatography (EtOAc/Hexane 3:7) to afford **THC-008** (47.3 mg, 73%) as a liquid.

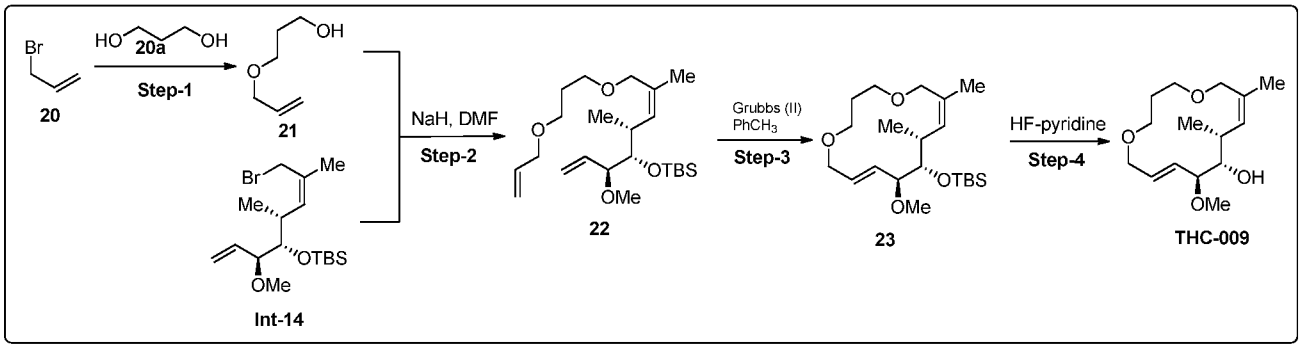
TLC: 20% EtOAc/Hexane (R_f: 0.2)

^{1}H NMR (500MHz, $CDCl_3$): δ 5.71-5.66 (m, 1H), 5.57 (d, *J* = 9.5 Hz, 1H), 5.32-5.28 (m, 1H), 4.16 (d, *J* = 10.5 Hz, 1H), 3.88 (d, *J* = 10.0 Hz, 1H), 3.59-3.50 (m, 5H), 3.48-3.43 (m, 2H), 3.35-3.31 (m, 4H), 2.98 (t, *J* = 8.5 Hz, 1H), 2.69 (s, 1H), 2.41-2.30 (m, 2H), 1.75 (s, 3H), 0.94 (d, *J* = 7.0 Hz, 3H).

Mass (ESI): 271 (M^++1).

LC-MS: *m/z* = 271.3[M^++1)] at RT 3.82 (94.62% purity).

Scheme 4:



3-(Allyloxy) propan-1-ol (**21**):

To a stirred suspension of NaH (5.2 g, 0.22 mmol, 60% dispersion in mineral oil) in anhydrous THF (600 mL), alcohol **20a** (15 g, 0.2 mmol) was added at rt and stirred for 45 min. Allyl bromide (26.26 g, 0.22 mmol) was added to reaction and stirred at RT for another 1 h. After consumption of the starting material (by TLC), the reaction was diluted with ether (300 mL). The organic layer was washed with 10% K_2CO_3 solution (500 mL), dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure to give the crude material which was purified by silica gel column chromatography (EtOAc/Hexane 3:7) to afford compound **21** (1 g, 4.3%) as a liquid.

TLC: 50% EtOAc/Hexane (R_f: 0.5)

^{1}H NMR (500MHz, $CDCl_3$): δ 5.94-5.86 (m, 1H), 5.28-5.17 (m, 2H), 3.99 (d, *J* = 5.5 Hz, 2H), 3.80 (q, *J* = 5.0 Hz, 2H), 3.64 (t, *J* = 6.0 Hz, 2H), 2.28 (br s, 1H), 1.88-1.83 (m, 2H).

(5S, 6R, Z)-5-((S)-1-methoxyallyl)-2, 2, 3, 3, 6, 8-hexamethyl-4, 10, 14-trioxa-3-silaheptadeca-7, 16-diene (**22**):

To a stirred suspension of NaH (47 mg, 1.98 mmol, 60% dispersion in mineral oil) in anhydrous DMF (2.5 mL), cooled to 0°C, alcohol 2 (0.17 g, 1.46 mmol) was added, stirred for 30 min and **Int-14** (0.5 g, 1.32 mmol) was added maintaining the temperature at 0°C. The reaction was stirred for another 30 min, quenched with ice cold water (20 mL) and extracted with EtOAc (2 x 15 mL). The combined organic extracts were dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure to provide the crude material which was purified by silica gel column chromatography (EtOAc/Hexane 1: 19) to afford compound **22** (0.18 g, 33.3%) as a liquid.

TLC: 10% EtOAc/Hexane (R_f: 0.5)

^{1}H NMR (500MHz, $CDCl_3$): δ 5.95-5.87 (m, 1H), 5.67-5.59 (m, 1H), 5.37 (d, *J* = 10.0 Hz, 2H), 5.29-5.23 (m, 1H), 5.17 (d, *J* = 10.5 Hz, 2H), 3.96 (t, *J* = 12.0 Hz, 3H), 3.87 (d, *J* = 11.0 Hz, 1H), 3.52 (t, *J* = 6.5 Hz, 2H), 3.46-3.36 (m, 4H), 3.20 (s, 3H), 2.62-2.60 (m, 1H), 1.88-1.83 (m, 2H), 1.73 (d, *J* = 7.0 Hz, 3H), 0.90 (d, *J* = 7.0 Hz, 12H), 0.04 (d, *J* = 16.0 Hz, 6H).

Mass (ESI): 430.5 [(M^++H_2O)].

tert-Butyl (((7Z, 9R, 10S, 11S, 12E)-11-methoxy-7, 9-dimethyl-1,5-dioxacyclotetradeca-7,12-dien-10-yl) oxy) dimethyl silane (**23**):

To a stirred solution of compound **22** (0.18 g, 0.43 mmol) in dry PhMe (947 mL), heated at 100°C Grubbs -II catalyst (8.1 mg, 0.009 mmol) was added and refluxed for further 1h under argon atmosphere. The reaction mixture was brought to RT and concentrated under vacuum, to give the crude material which was purified by silica gel column chromatography (EtOAc/Hexane 1:9) to furnish compound **23** (122 mg, 76%) as a liquid.

TLC: 10% EtOAc/Hexane (R_f: 0.5)

^{1}H NMR (500MHz, $CDCl_3$): δ 5.78-5.73 (m, 1H), 5.66-5.62 (m, 1H), 5.48 (d, *J* = 9.0 Hz, 1H), 4.08-3.96 (m, 2H), 3.83 (q, *J* = 10.0 Hz, 2H), 3.61-3.44 (m, 7H), 3.21 (s, 3H), 2.91 (t, *J* = 6.5 Hz, 1H), 1.83 (br s, 2H), 1.75 (s, 3H), 0.91 (d, *J* = 5.5 Hz, 11H), 0.05 (d, *J* = 16.0 Hz, 6H).

(7Z, 9R, 10S, 11S, 12E)-11-methoxy-7, 9-dimethyl-1, 5-dioxacyclotetradeca-7, 12-dien-10-ol (**THC-009**):

To a stirred solution of compound **23** (0.12 g, 0.31 mmol) in dry THF (2 mL), cooled to 0°C, HF-pyridine (1.5 mL) was slowly added. The reaction mixture was warmed to RT and stirred for 24 h. After complete consumption of starting material (by TLC), the reaction was neutralized with saturated $NaHCO_3$ solution (25 mL) and aqueous layer was extracted with CH_2Cl_2 (2 x 10 mL). The combined organic extracts were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give the crude material which was purified by silica gel column chromatography (EtOAc/Hexane 3:17) to afford **THC-009** (35 mg, 42%) as a liquid.

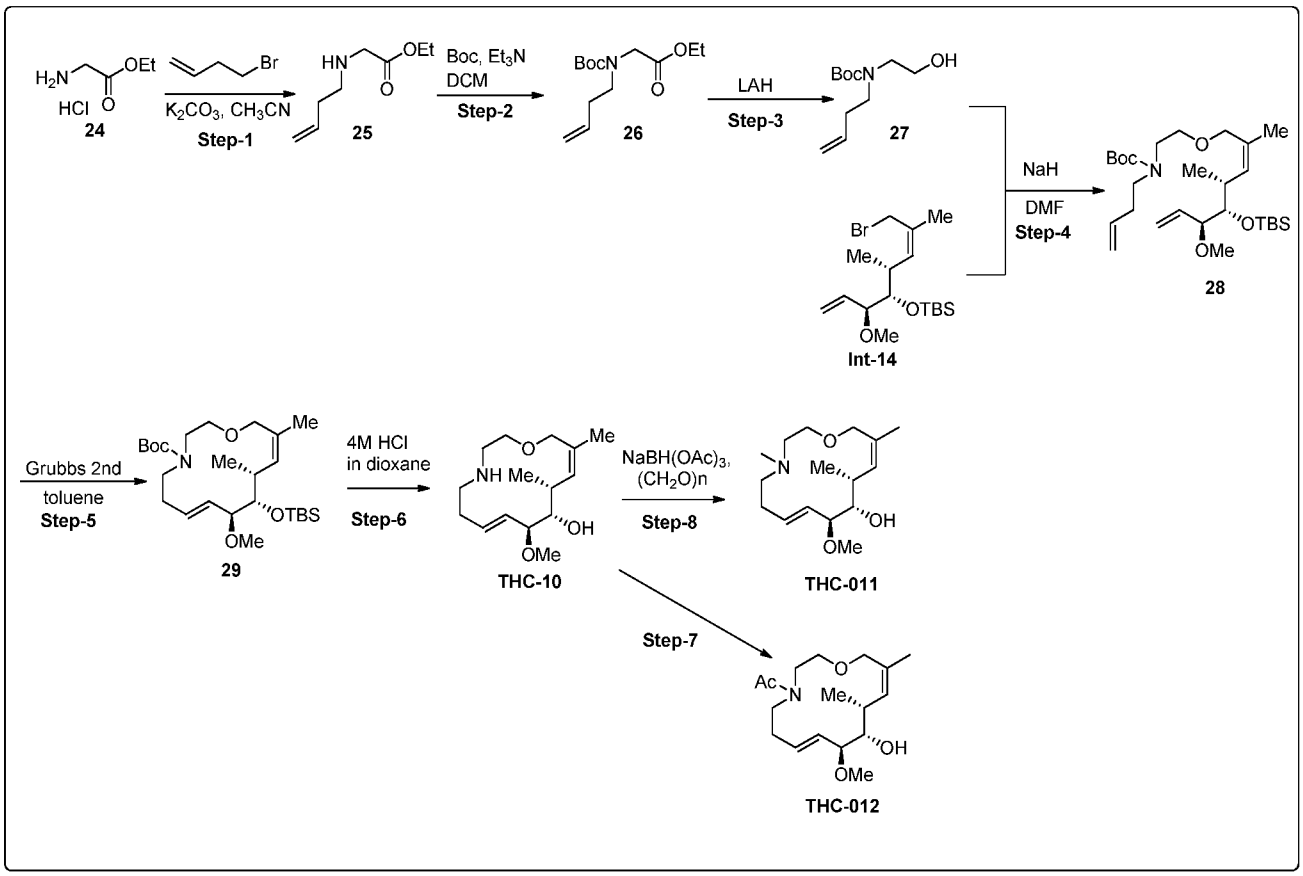
TLC: 20% EtOAc/Hexane(R_f: 0.3)

^{1}H NMR (500MHz, $CDCl_3$): δ 5.84-5.79 (m, 1H), 5.64 (d, *J* = 9.5 Hz, 1H), 5.58-5.53 (m, 1H), 4.12 (d, *J* = 8.5 Hz, 1H), 3.93 (d, *J* = 10.0 Hz, 1H), 3.87 (q, *J* = 8.0 Hz, 1H), 3.66-3.56 (m, 2H),

3.55-3.44 (m, 4H), 3.41-3.37 (m, 1H), 3.32 (d, J = 6.5 Hz, 3H), 2.87 (q, J = 8.5 Hz, 1H), 2.72 (s, 1H), 1.83-1.80 (m, 2H), 1.77 (s, 3H), 0.94 (d, J = 9.5 Hz, 3H).

Mass (ESI): 271 (M^++1).

Scheme 5:



Ethyl 2-(but-3-en-1-ylamino)acetate (**25**):

To a stirred solution of compound **24** (30 g, 214.8 mmol) in MeCN (300 mL), cooled to 0°C, Et_3N (60 mL, 450 mmol) was added followed by 4-bromobut-1-ene (24.0 mL, 236.4 mmol). The reaction was slowly brought to RT, stirred for further 48 h and filtered through a pad of celite. The filtrate was concentrated under reduced pressure to give the crude material which was purified by alumina column chromatography (EtOAc/Hexane 1:9) to afford compound **25** (5 g, 14.8%) as a light brown liquid.

TLC: 50% EtOAc/Hexane (R_f: 0.5)

^{1}H NMR (500MHz, $CDCl_3$): δ 5.82-5.77 (m, 1H), 5.12-4.97 (m, 2H), 4.21-4.12 (m, 2H), 3.45-3.41 (s, 2H), 2.73-2.67 (m, 2H), 2.27-2.2.18 (m, 2H), 1.32-1.30 (m, 3H).
Mass (ESI): 158.6 (M^++1).

Ethyl 2-(but-3-en-1-yl(tert-butoxycarbonyl)amino)acetate (**26**):

To a stirred solution of compound **25** (2 g, 12.7 mmol) in dry THF (20 mL), cooled to 0°C, Et_3N (8.74 mL, 63.3 mmol), cat. DMAP (0.2 g) and $(Boc)_2O$ (4.1 mL, 19.1 mmol) were added. The reaction was stirred at RT for 12 h, the volatiles were removed under reduced pressure and the residue was dissolved in EtOAc (30 mL). The organic extract was washed with water (2 x 20 mL), dried over anhydrous sodium sulphate and concentrated under reduced pressure to give the crude material which was purified by silica gel column chromatography (EtOAc/Hexane 3: 17) to afford compound **26** (3 g, 93%) as a pale yellow liquid.
TLC: 30% EtOAc/Hexane (R_f: 0.8)
^{1}H NMR (500MHz, $CDCl_3$): δ 5.78-5.75 (m, 1H), 5.09-5.01 (m, 2H), 4.21-4.16 (m, 2H), 3.95 (s, 1H), 3.85 (s, 1H), 3.36 (t, *J* = 7.0 Hz, 1H), 3.31 (t, *J* = 7.5 Hz, 1H), 2.29 (t, *J* = 7.0 Hz, 2H), 1.47 (s, 9H), 1.29-1.25 (m, 3H).

tert-Butyl but-3-en-1-yl(2-hydroxyethyl)carbamate (**27**):

To a stirred solution of compound **26** (5 g, 19.4 mmol) in dry THF (50 mL), cooled to 0°C, $LiAlH_4$ (0.73 g, 19.4 mmol) was added portion-wise maintaining the temperature at 0°C. The reaction mixture was warmed to RT and stirred for 1h. After consumption of the starting material (by TLC), the reaction, maintained at 0°C, was quenched with saturated Na_2SO_4 solution (1 mL) during which white solid precipitated out which was filtered. The filtrate was concentrated under reduced pressure to furnish compound **27** (3 g, 72%) as a light brown thick syrup which was carried forward without any purification.
TLC: 20% EtOAc/Hexane (R_f: 0.2)
^{1}H NMR (500MHz, $CDCl_3$): δ 5.77-5.76 (m, 1H), 5.09-5.02 (m, 2H), 3.74-3.70 (m, 2H), 3.38-3.29 (m, 4H), 2.29 (d, *J* = 6.5 Hz, 2H), 1.47 (s, 9H).
Mass (ESI): 214 (M^+)

tert-Butyl but-3-en-1-yl(2-(((4R, 5S, 6S, Z)-5-((tert-butyldimethylsilyl) oxy)-6-methoxy-2, 4-dimethylocta-2,7-dien-1-yl) oxy) ethyl) carbamate (**28**):

To a stirred solution of compound **27** (0.11 g, 0.52 mmol) in DMF (1 mL), cooled to -10°C, NaH (22.40 mg, 0.57 mmol, 60% dispersion in mineral oil) was added and stirred for 30 min. **Int-14** (0.1 g, 0.26 mmol) was dissolved in DMF (0. 5mL) and added to the reaction mixture maintaining the temperature at -10°C. The reaction was slowly warmed to 0°C, quenched with ice and extracted with Et_2O (2 x 10 mL). The combined organic extracts were dried over anhydrous sodium sulphate and concentrated under reduced pressure to give the crude material which was purified by silica gel column chromatography (EtOAc/Hexane 1: 19) to furnish compound **28** (70 mg, 51.85%) as a pale yellow liquid.

TLC: 20% EtOAc/Hexane(R_f: 0.5)

^{1}H NMR (500MHz, $CDCl_3$): δ 5.75-5.71 (m, 1H), 5.66-5.59 (m, 1H), 5.37-5.35 (m, 1H), 5.29-5.23 (m, 2H), 5.06-4.99 (m, 2H), 3.97-3.85 (m, 2H), 3.45-3.31 (m, 8H), 3.20 (s, 3H), 2.60-2.57 (m, 1H), 2.27-2.25 (m, 2H), 1.70 (s, 3H), 1.45 (s, 9H), 0.90 (s, 12H), 0.06 (s, 6H).

Mass (ESI): 412 [M^+- (Boc)].

(7E,9S,10S,11R,12Z)-tert-butyl 10-((tert-butyldimethylsilyl)oxy)-9-methoxy-11,13-dimethyl-1-oxa-4-azacyclotetradeca-7,12-diene-4-carboxylate (**29**):

To a stirred solution of compound **28** (0.42 g, 0.82 mmol) in PhMe (2.22 L) heated to 100°C, Grubbs -II catalyst (0.143 g, 0.16 mmol) was added. The reaction was continued for 30 min. After consumption of the starting material (by TLC), the volatiles were removed under reduced pressure and the crude residue was purified by silica gel column chromatography (EtOAc/Hexane 3:17) to provide compound **29** (250 mg, 64%) as a pale yellow liquid.

TLC: 15% EtOAc/Hexane (R_f: 0.4)

^{1}H NMR (500MHz, $CDCl_3$): δ 5.72-5.67 (m, 1H), 5.43-5.28 (m, 2H), 4.12-3.98 (m, 2H), 3.51-3.30 (m, 8H), 3.21 (s, 3H), 2.71-2.68 (m, 1H), 2.54-2.31 (m, 2H), 1.73-1.69 (m, 3H), 1.45 (s, 9H), 0.95 (s, 12H), 0.06 (d, J = 15 Hz, 6H).

Mass (ESI): 384 [M^+ (Boc)].

(7E,9S,10S,11R,12Z)-9-methoxy-11,13-dimethyl-1-oxa-4-azacyclotetradeca-7,12-dien-10-ol (**THC-010**):

To a stirred solution of compound **29** (0.2 g, 0.41 mmol) in CH_2Cl_2 (2 mL), HCl in 1,4-dioxane (4.0M, 2 mL) was added at rt and stirred for 4 h. After the completion of reaction (by TLC), the reaction was basified with 10% sodium carbonate solution (10 mL). The organic layer

was separated, dried over anhydrous sodium sulphate and concentrated under reduced pressure to provide the crude material which was purified by alumina column chromatography ($MeOH/CH_2Cl_2$ 1:24) to afford **THC-010** (65 mg, 58%) as a white solid.

TLC: 10% $MeOH/CH_2Cl_2$ (R_f: 0.3)

^{1}H NMR (500MHz, $CDCl_3$): δ 5.71-5.62 (m, 2H), 5.44-5.39 (m, 1H), 4.04 (d, *J* = 10.5 Hz, 1H), 3.72-3.70 (m, 1H), 3.67-3.65 (m, 1H), 3.58-3.55 (m, 1H), 3.50-3.47 (m, 2H), 3.41-3.39 (m, 1H), 3.31 (s, 3H), 2.91-2.66 (m, 5H), 2.39-2.36 (m, 2H), 1.72 (s, 3H), 0.93 (d, *J* = 7.0 Hz, 3H).

Mass (ESI): 270 [M^++1].

LC-MS: *m/z* = 270.3 (M^++1) at 2.67 RT (96.33% purity).

(7E, 9S, 10S, 11R, 12Z)-9-methoxy-4, 11, 13-trimethyl-1-oxa-4-azacyclotetradeca-7, 12-dien-10-ol (**THC-011**):

THC-10 (110 mg, 408mmol), HCHO (12mg, 0.408mmol), $NaBH(OAc)_3$ (173mg, 0.817mmol), DCM (2mL), were stirred at room temperature for 16h. The volatiles from the reaction were removed under reduced pressure to obtain the crude residue which was purified by silica gel column chromatography ($MeOH/CHCl_3$ 1:19) to afford **THC-011** (34.2 mg, 76.5%) as a pale yellow liquid.

TLC: 1% $MeOH/CHCl_3$ (R_f: 0.3)

^{1}H NMR (500MHz, $CDCl_3$): δ 5.73-5.67 (m, 1H), 5.56 (d, *J* = 9.5 Hz, 1H), 5.31 (dd, *J* = 16.0, 8.0 Hz, 1H), 4.01 (d, *J* = 10.5 Hz, 1H), 3.92 (d, *J* = 10.0 Hz, 1H), 3.54 (t, *J* = 5.0 Hz, 2H), 3.48-3.36 (m, 2H), 3.30 (s, 3H), 3.01 (t, *J* = 8.5 Hz, 1H), 2.69 (br s, 1H), 2.56-2.39 (m, 4H), 2.29-2.21 (m, 2H), 2.17 (s, 3H), 1.74 (s, 3H), 0.91 (d, *J* = 6.5 Hz, 3H).

Mass (ESI): 284.3 (M^++1).

1-((7E,9S,10S,11R,12Z)-10-hydroxy-9-methoxy-11,13-dimethyl-1-oxa-4-azacyclotetradeca-7,12-dien-4-yl)ethanone (**THC-012**):

To a stirred solution of **THC-010** (0.13 g, 0.48 mmol) in CH_2Cl_2 (2 mL), cooled to 0°C, Et_3N (0.33 mL, 2.41 mmol) followed by acetyl chloride (0.14 mL, 1.92 mmol) was added. The reaction mixture was stirred at RT for 1 h. After the consumption of starting material (by TLC), the reaction was quenched with 5% citric acid (10 mL) solution. The organic layer was separated, dried over anhydrous sodium sulphate and concentrated under reduced pressure to

give the crude material which was purified by silica gel column chromatography (MeOH/CH_2Cl_2 1: 99) to furnish **THC-012** (49.5 mg, 33%) as a white solid.

TLC mobile phase: 10% MeOH/CH_2Cl_2 (R_f: 0.3)

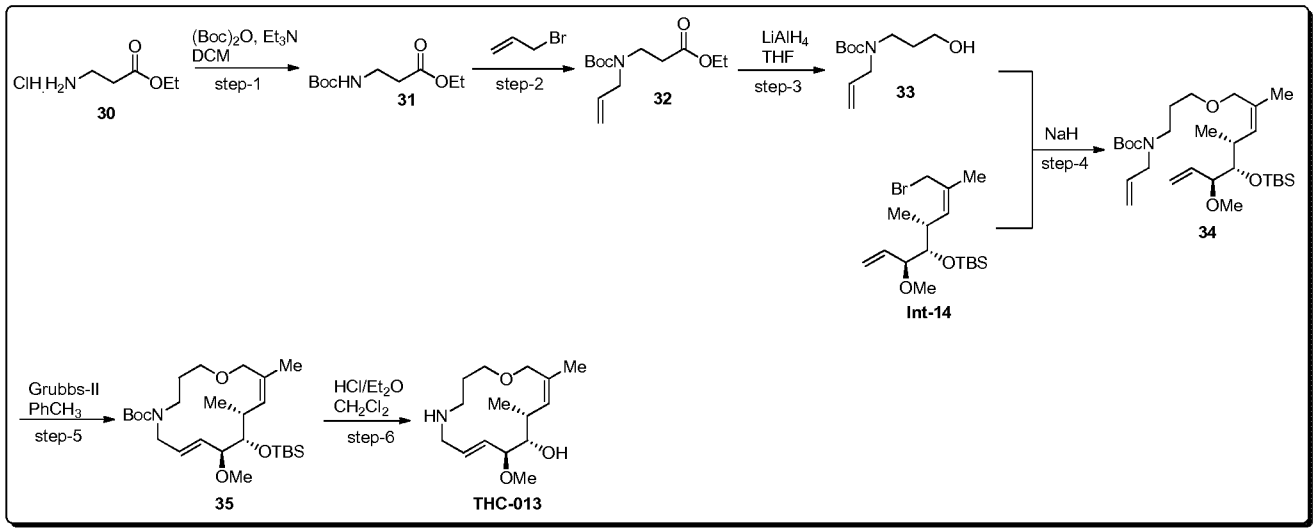
^{1}H NMR (500MHz, DMSO-d_6): δ 5.70-5.64 (m, 1H), 5.36 (d, *J* = 9.5 Hz, 2H), 3.97-3.94 (m, 1H), 3.87-3.85 (m, 1H), 3.72-3.65 (m, 1H), 3.59-3.55 (m, 1H), 3.49-3.48 (m, 2H), 3.37-3.35 (m, 1H), 3.29-3.26 (m, 2H), 3.22-3.19 (m, 4H), 2.73-2.70 (m, 1H), 2.35-2.34 (m, 2H), 1.98 (s, 3H), 1.65 (s, 3H), 0.82 (d, *J* = 7.0 Hz, 3H).

Mass (ESI): 312.5 (M^++1).

LC-MS: *m/z* = 312.4 (M^++1) at 3.64 RT (90.77% purity).

IR (Cm^{-1}): 3434.6, 3000.7, 2929.3, 2878.2, 1635.3, 1422.2, 1217.8, 1106.9, 1086.7, 984.5, 756.9, 666.3.

Scheme 6:



Ethyl 3-((tert-butoxycarbonyl) amino) propanoate (**31**):

To a solution of compound **30** (20 g, 0.13 mol) in CH_2Cl_2 (20 mL), cooled to 0°C, Et_3N (53 mL, 0.39 mol) was added dropwise and stirred for 30 min. Boc-anhydride (34 mL, 78.1 mmol) was added to the reaction mixture at 0°C and the stirred at RT for 16 h. The reaction was quenched with saturated NH_4Cl solution and the aqueous layer was extracted with CH_2Cl_2 (3 x 150 mL). The combined organic extracts were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to afford compound **31** (26 g, 92%) as a liquid.

TLC: 30% EtOAc/Hexane (R_f: 0.7)

^{1}H NMR (500MHz, $CDCl_3$): δ 5.01 (br s, 1H), 4.16 (q, *J* = 7.5 Hz, 2H), 3.39 (d, *J* = 6.0 Hz, 2H), 2.51 (t, *J* = 5.5 Hz, 2H), 1.43 (s, 9H), 1.26 (t, *J* = 7.5 Hz, 3H).

Ethyl 3-(allyl (tert-butoxycarbonyl) amino) propanoate (**32**):

To a solution of compound **31** (2.0 g, 9.21 mmol) in DMF (15 mL), cooled to 0°C, NaH (405 mg, 10.1 mmol, 60% dispersion in mineral oil) was added portion wise and stirred for 30 min. Allyl bromide (0.86 mL, 10.1 mmol) was added drop wise to the reaction mixture maintaining the temperature at 0°C and stirred at RT for 24 h. The reaction was quenched with ice cold water (20 mL) and extracted with EtOAc (3 x 25 mL). The combined organic extracts were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give the crude material which was purified by silica gel column chromatography (EtOAc/Hexane 2:23) to afford compound **32** (0.6 g, 25%) as a pale yellow liquid.

TLC: 10% EtOAc/Hexane (R_f: 0.3)

^{1}H NMR (500MHz, $CDCl_3$): δ 5.77-5.74 (m, 1H), 5.12 (d, *J* = 9.5 Hz, 2H), 4.14 (q, *J* = 7.0 Hz, 2H), 3.84 (br s, 2H), 3.46 (br s, 2H), 2.55 (br s, 2H), 1.45 (s, 9H), 1.25 (t, *J* = 7.0 Hz, 3H).

tert-Butyl allyl (3-hydroxypropyl) carbamate (**33**):

To a stirred solution of compound **32** (1.24 g, 4.85 mmol) in dry THF (20 mL), cooled to 0°C, $LiAlH_4$ (0.22 g, 5.8 mmol) was added portion-wise maintaining the temperature at 0°C. The reaction mixture was slowly warmed to RT and stirred for 1 h. After consumption of the starting material (by TLC), the reaction was quenched with 5M NaOH solution (5 ml) during which white solid precipitated out which was filtered off and the filtrate was concentrated under reduced pressure. The crude material was purified by silica gel column chromatography (EtOAc/Hexane 1:3) to afford compound **33** (786.2 mg, 78.7%) as a pale yellow liquid.

TLC: 40% EtOAc/Hexane (R_f: 0.3)

^{1}H NMR (500MHz, $CDCl_3$): δ 5.79 (s, 1H), 5.18 (d, 2H), 3.75 (br s, 3H), 3.56 (s, 2H), 3.38 (s, 2H), 1.66 (s, 2H), 1.46 (s, 9H).

Mass (ESI): 214.3 (M^+-1).

tert-Butyl allyl (3-(((4R, 5S, 6S, Z)-5-((tert-butyldimethylsilyl) oxy)-6-methoxy-2, 4-dimethylocta-2,7-dien-1-yl) oxy) propyl) carbamate (**34**):

To a stirred solution of compound **33** (432.1 mg, 2.0 mmol) in DMF (3 mL), cooled to 0°C, NaH (48.2 mg, 2.0 mmol, 60% dispersion in mineral oil) was added portion-wise and stirred for 10 min. A solution of **Int-14** (503.8 mg, 1.33 mmol) in DMF (3 mL) was added drop-wise to the reaction mixture maintaining the temperature at 0°C. The reaction was slowly brought to RT and stirred for 1 h. After consumption of the starting material (by TLC), the reaction was quenched with ice-water and extracted with Et_2O (2 x 10 mL). The combined organic extracts were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give the crude material which was purified by silica gel column chromatography (EtOAc/Hexane 1:19) to provide compound **34** (378 mg, 56%) as a pale yellow liquid.

TLC: 5% EtOAc/Hexane(R_f: 0.3)

^{1}H NMR (500MHz, $CDCl_3$): δ 5.76-5.73 (m, 1H), 5.66-5.58 (m, 1H), 5.37-5.35 (m, 1H), 5.29-5.23 (m, 2H), 5.11-5.09 (m, 2H), 3.95-3.92 (m, 1H), 3.85-3.83 (m, 3H), 3.43-3.41 (m, 1H), 3.38-3.30 (m, 3H), 3.24 (br s, 2H), 3.24 (s, 3H), 2.61-2.57 (m, 1H), 1.78-1.75 (m, 2H), 1.71 (s, 3H), 1.45 (s, 9H), 0.90 (s, 12H), 0.05 (s, 6H).

Mass (ESI): 512.8 (M^++1).

(7E, 9S, 10S, 11R, 12Z)-Tert-butyl 10-((tert-butyldimethylsilyl) oxy)-9-methoxy-11, 13-dimethyl-1-oxa-5-azacyclotetradeca-7, 12-diene-5-carboxylate (**35**):

To a stirred solution of compound **34** (426.3 mg, 0.83 mmol) in PhMe (2 L) heated at 100°C, Grubbs -II catalyst (144.7 mg, 0.16 mmol) taken in PhMe (100 mL) was added drop-wise and refluxed for further 30 min. After consumption of the starting material (by TLC), the volatiles were evaporated under reduced pressure to provide the crude material which was purified by silica gel column chromatography (EtOAc/Hexane 1:19) to afford compound **35** (262 mg, 65%) as a pale yellow liquid.

TLC: 10% EtOAc/Hexane (R_f: 0.3)

^{1}H NMR (500MHz, $CDCl_3$): δ 5.64-5.61 (m, 1H), 5.49-5.44 (m, 2H), 3.86-3.77 (m, 2H), 3.49-3.40 (m, 5H), 3.21 (s, 4H), 3.01-2.98 (m, 2H), 1.82-1.79 (m, 2H), 1.68 (s, 4H), 1.46 (s, 9H), 0.91-0.88 (m, 12H), 0.06-0.33 (m, 6H).

Mass (ESI): 384.9 [M^+-(Boc)].

(7E, 9S, 10S, 11R, 12Z)-9-methoxy-11, 13-dimethyl-1-oxa-5-azacyclotetradeca-7, 12-dien-10-ol (**THC-013**):

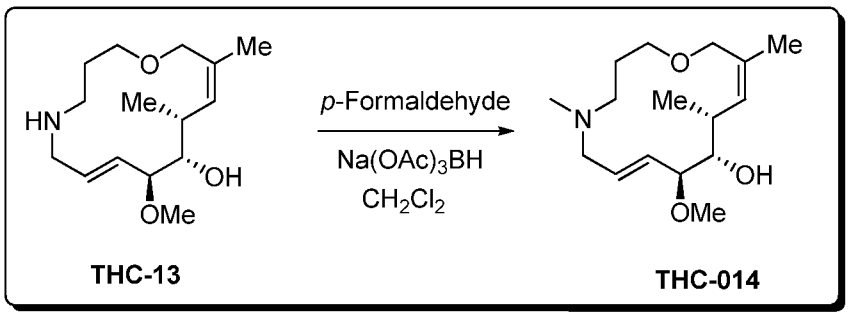
To a stirred solution of compound **35** (264.3 mg, 0.54 mmol) in CH_2Cl_2 (5 mL), cooled to 0°C, Et_2O-HCl (5 mL) was added drop wise. The reaction was slowly warmed to RT and stirred for 16 h. After consumption of the starting material (by TLC), volatiles were removed under reduced pressure to give the residue. The residue was diluted with water (2 mL), basified using saturated sodium bicarbonate solution (3 mL) and the aqueous layer was extracted with 10% $MeOH/CH_2Cl_2$ (2 x 20 mL). The combined organic extracts were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to provide the crude material which was purified by neutral alumina column chromatography ($MeOH/CH_2Cl_2$ 1:19) to afford **THC-013** (95 mg, 64.6%) as an off-white solid.

TLC: 20% $MeOH/CH_2Cl_2$ (R_f: 0.2)

^{1}H NMR (500MHz, $CDCl_3$): δ 5.76-5.70 (m, 1H), 5.63 (d, *J* = 9.5 Hz, 1H), 5.42-5.38 (m, 1H), 3.92 (d, *J* = 10.0 Hz, 1H), 3.65 (d, *J* = 9.5 Hz, 1H), 3.60-3.58 (m, 1H), 3.52-3.39 (m, 5H), 3.31 (s, 3H), 3.23-3.18 (m, 1H), 2.93-2.87 (m, 1H), 2.79-2.73 (m, 2H), 2.67-2.61 (m, 1H), 1.76 (s, 4H), 1.68-1.62 (m, 1H), 0.94 (d, *J* = 7.0 Hz, 3H).

Mass (ESI): 270.3 (M^++1).

Scheme 7:



(7E, 9S, 10S, 11R, 12Z)-9-methoxy-5, 11, 13-trimethyl-1-oxa-5-azacyclotetradeca-7, 12-dien-10-ol (**THC-14**):

To a stirred solution of **THC-13** (50.3 mg, 0.187 mmol) in CH_2Cl_2 (5 mL) *p*-formaldehyde (6.73 mg, 0.224 mmol) was added at RT, stirred for 30 min and sodium tri acetoxy borohydride (79.2 mg, 0.372 mmol) was added slowly. The reaction was continued for another 16 h and after consumption of the starting material (by TLC), the volatiles were evaporated

under vacuo to give the crude material which was purified by neutral alumina column chromatography (MeOH/CH_2Cl_2 2: 48) to afford **THC-014** (23.54 mg, 44.2%).

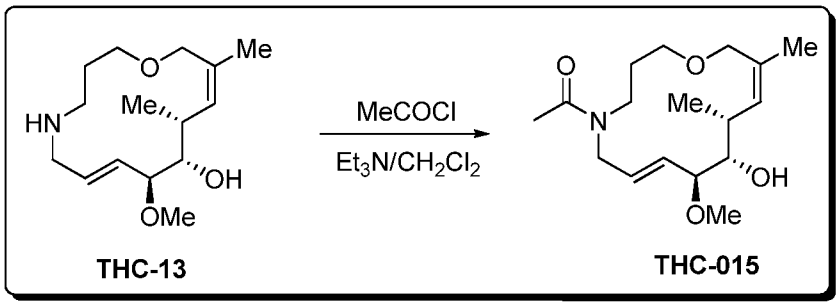
TLC: 10% MeOH/CH2Cl2 (R_f: 0.45)

^{1}H NMR (500MHz, $CDCl_3$): δ 5.82-5.76 (m, 1H), 5.63 (d, *J* = 10.5 Hz, 1H), 5.41 (q, *J* = 7.5 Hz, 1H), 3.96 (d, *J* = 10.0 Hz, 1H), 3.59-3.44 (m, 5H), 3.31 (s, 3H), 3.15(dd, *J* = 17, 4.0 Hz, 1H), 2.93-2.84 (m, 2H), 2.74-2.70 (m, 2H), 2.34 (s, 3H), 2.19-2.14 (m, 1H), 1.75-1.71 (m, 5H), 0.93 (d, *J* = 7.0 Hz, 3H).

Mass (ESI): 284 (M^++1).

LC-MS: *m/z* = 284.5[(M^++1)] at RT 3.80 (97.86% purity).

Scheme 8:



THC-13 THC-015

1-((7E, 9S, 10S, 11R, 12Z)-10-hydroxy-9-methoxy-11, 13-dimethyl-1-oxa-5-azacyclotetradeca-7, 12-dien-5-yl) ethanone (**THC-015**):

To a stirred solution of **THC-13** (50.01 mg, 0.185 mmol) in CH_2Cl_2 (3 mL) cooled to -40°C, Et_3N (37.5 mg, 0.37 mmol) was added and stirred for 5 min. A solution of acetyl chloride (15.94 mg, 0.204 mmol) dissolved in CH_2Cl_2 (2 mL) was added to the reaction drop-wise over a period of 15 min maintaining the temperature at -40°C. The reaction was quenched with saturated $NaHCO_3$ solution and extracted with CH_2Cl_2 (2 x 7 mL). The combined organic extracts were washed with brine, dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure to give the crude material which was purified by silica gel column chromatography (MeOH/CH_2Cl_2 3:97) to afford **THC-015** (22.4 mg, 38.7%).

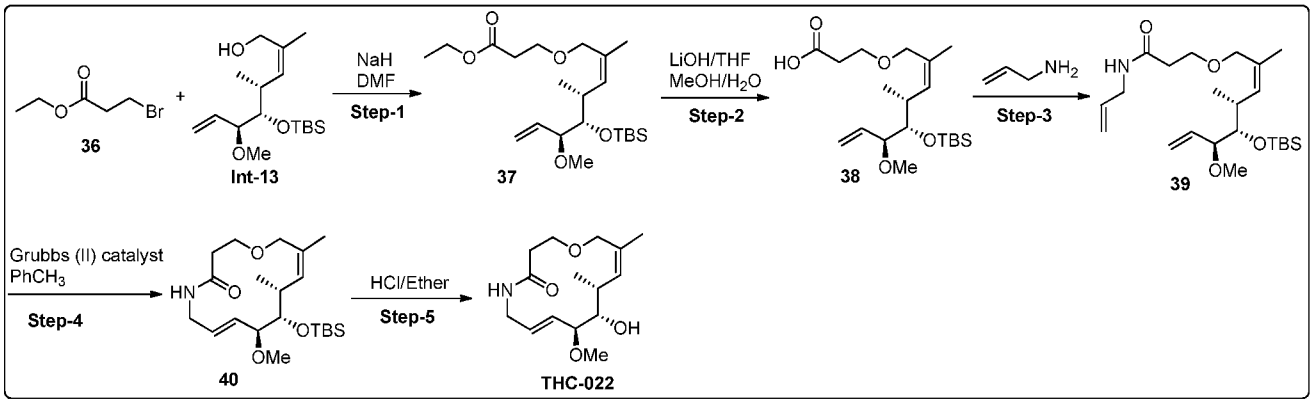
TLC: 10% MeOH/CH_2Cl_2 (R_f: 0.45)

^{1}H NMR (500MHz, DMSO-d_6): δ 5.65-5.51 (m, 3H), 5.41 (d, *J* = 9.0 Hz, 1H), 4.59 (s, 1H), 4.39-4.36 (m, 1H), 4.08-4.06 (m, 1H), 3.81-3.74 (m, 3H), 3.45-3.42 (m, 3H), 3.19 (d, *J* = 8.0 Hz, 5H), 2.92-2.90 (m, 2H), 2.02 (s, 3H), 1.62 (s, 3H), 0.81 (d, *J* = 6.5 Hz, 3H).

Mass (ESI): 312.4 (M^++1).

LC-MS: *m/z* = 312 [(M^++1)] at RT 3.07 (98.76% purity).

Scheme 9:



Ethyl 3-(((4R, 5S, 6S, Z)-5-((tert-butyldimethylsilyl) oxy)-6-methoxy-2, 4-dimethylocta-2,7-dien-1-yl) oxy) propanoate (**37**):

To a stirred solution of **Int-13** (0.5 g, 1.59 mmol) in DMF (5 mL), cooled to 0°C, NaH (0.30 g, 7.95 mmol, 60% dispersion in mineral oil) was added and stirred for 10 min. Ethyl 3-bromopropanoate (**36**) (0.41 mL, 3.18 mmol) was added drop wise over a period of 10 min and stirred for 30 min. The reaction was quenched with ice and extracted with EtOAc (2 x 10 mL). The combined organic extracts were dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure to afford crude compound **37** (0.7 g) which was used for the next step without further purification.

TLC: 20% EtOAc/Hexane (R_f: 0.8)

3-(((4R, 5S, 6S, Z)-5-((tert-butyldimethylsilyl) oxy)-6-methoxy-2, 4-dimethylocta-2, 7-dien-1-yl) oxy) propanoic acid (**38**):

To a stirred solution of compound **37** (0.7 g, 1.68 mmol) in THF (5 mL), MeOH: H_2O (10 mL, 1:1) followed by LiOH (0.14 g, 3.37 mmol) was added and stirred at RT for 3 h. The volatiles from the reaction were removed under vacuo and the aqueous layer was washed with ether (2 x 15 mL), acidified with $KHSO_4$ till pH 4 and extracted with EtOAc (3 x 30 mL). The combined organic extracts were dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure to afford crude compound **38** (0.6 g) which was carried for the next step without further purification.

TLC: 30% EtOAc/Hexane (R_f: 0.2)

N-allyl-3-(((4R, 5S, 6S, Z)-5-((*tert*-butyldimethylsilyl) oxy)-6-methoxy-2, 4-dimethylocta-2, 7-dien-1-yl) oxy) propanamide (**39**):

To a stirred solution of compound **38** (0.6 g, 1.55 mmol) in DMF (6 mL), cooled to 0°C, allyl amine (0.22 mL, 3.10 mmol), Et_3N (0.53 ml, 3.87 mmol), HOBt (0.41 g, 3.10 mmol) followed by EDCI.HCl (0.59 g, 3.10 mmol) was added. The reaction was slowly warmed to RT and stirred for further 6 h, diluted with EtOAc: water (100mL, 1:1) and further stirred for 15 min. The organic layer was separated, dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure to give the crude material which was purified by silica gel column chromatography (EtOAc/Hexane 1:4) to furnish compound **39** (0.3 g, 45%).

TLC: 50% EtOAc/Hexane (R_f: 0.4)

^{1}H NMR (500MHz, $CDCl_3$): δ 6.37 (br s, 1H), 5.86-5.81 (m, 1H), 5.66-5.59 (m, 1H), 5.40 (d, *J* = 10.0 Hz, 1H), 5.30-5.10 (m, 4H), 4.00 (d, *J* = 11.5 Hz, 1H), 3.92-3.88 (m, 3H), 3.64-3.57 (m, 2H), 3.43-3.36 (m, 2H), 3.20 (s, 3H), 2.59 (t, *J* = 6.5 Hz, 1H), 2.48 (d, *J* = 5.5 Hz, 2H), 1.71 (s, 3H), 0.89 (s, 12H), 0.03 (d, *J* = 9.0 Hz, 6H).

Mass (ESI): 426 (M^++1).

(7E, 9S, 10S, 11R, 12Z)-10-((tert-butyldimethylsilyl) oxy)-9-methoxy-11, 13-dimethyl-1-oxa-5-azacyclotetradeca-7, 12-dien-4-one (**40**):

To a stirred solution of compound **39** (0.3 g, 0.7 mmol) in PhMe (1.5 L), heated to 100°C, Grubbs-II catalyst (0.12 g, 0.14 mmol) was added under argon atmosphere and stirred for 30 min. The volatiles were removed under reduced pressure to give the crude material which was purified by silica gel column chromatography (EtOAc/Hexane 1:1) to provide compound **40** (0.14 g, 50%).

TLC: 70% EtOAc/Hexane (R_f: 0.3)

^{1}H NMR (500MHz, $CDCl_3$): δ 6.26 (br s, 1H), 5.77-5.66 (m, 2H), 5.41 (d, *J* = 10.5 Hz, 1H), 4.16-4.11 (m, 2H), 3.90 (d, *J* = 12.0 Hz, 1H), 3.79 (d, *J* = 10.0 Hz, 1H), 3.69-3.66 (m, 2H), 3.56-3.45 (m, 2H), 3.19 (s, 3H), 2.53-2.46 (m, 3H), 1.76 (s, 3H), 0.90 (s, 12H), 0.07 (m, 6H).

Mass (ESI): 398 (M^++1).

(7E, 9S, 10S, 11R, 12Z)-10-hydroxy-9-methoxy-11, 13-dimethyl-1-oxa-5-azacyclotetradeca-7, 12-dien-4-one (**THC-022**):

To a stirred solution of compound **40** (0.14 g, 0.35 mmol) in CH_2Cl_2 (1 mL) MeOH (0.1 mL) followed by HCl in ether (1 mL) was added and stirred at RT for 1 h. The volatiles were removed under reduced pressure to provide the crude material which was purified by silica gel column chromatography (MeOH/CH_2Cl_2 1:24) to afford **THC-022** (30 mg, 30%).

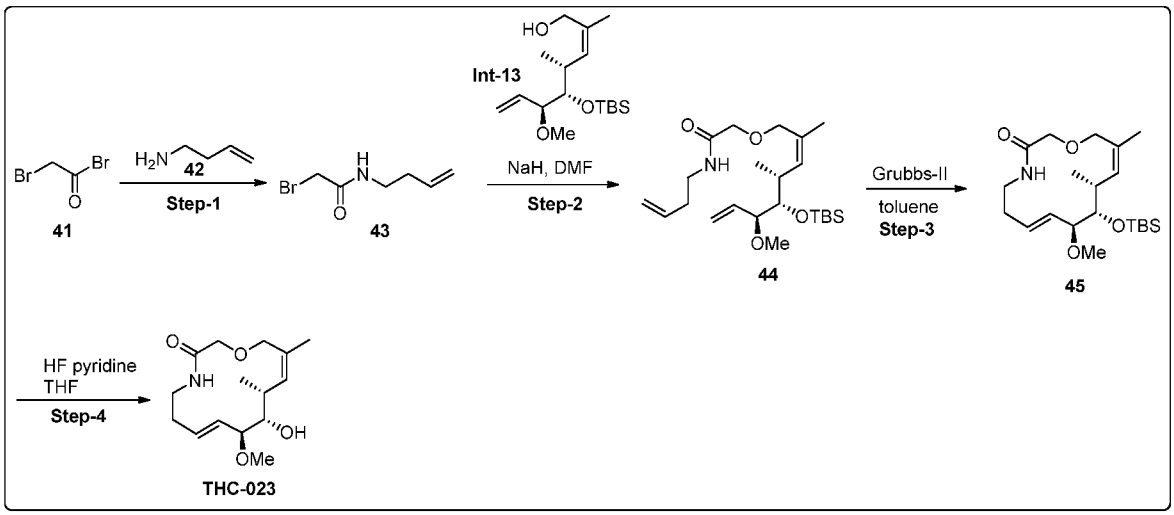
TLC: 5% MeOH/CH_2Cl_2 (R_f: 0.3)

^{1}H NMR (500MHz, $CDCl_3$): δ 6.15 (br s, 1H), 5.91-5.85 (m, 1H), 5.63-5.54 (m, 2H), 4.19-4.12 (m, 2H), 3.80-3.76 (m, 1H), 3.71 (t, *J* = 8.0 Hz, 1H), 3.57-3.49 (m, 3H), 3.36 (d, *J* = 7.5 Hz, 1H), 3.29 (s, 3H), 2.57-2.36 (m, 4H), 1.76 (s, 3H), 0.94 (d, *J* = 7.0 Hz, 3H).

Mass (ESI): 284 (M^++1).

LC-MS: *m/z* = 284 [(M^++1)] at RT 2.16 (91.57% purity).

Scheme 10:



2-Bromo-N-(but-3-en-1-yl) acetamide (**43**):

To a stirred solution of but-3-en-1-amine (**42**) (0.45 mL, 4.95 mmol) in CH_2Cl_2 (5 mL), cooled to -78°C, Et_3N (0.75 mL, 5.45 mmol) followed by 2-bromoacetyl bromide (**41**) (0.43 mL, 4.95 mmol) were added. The reaction was slowly brought to RT and stirred for 2 h. After consumption of the starting material (by TLC), the organic layer was washed with water (2 x 10 mL), 5% citric acid solution (10 mL), dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure to afford compound **34** (0.75 g, 78%) which was carried forward for the next step without further purification.

TLC: 30% EtOAc/Hexane (R_f: 0.3)

^{1}H NMR (500MHz, $CDCl_3$): δ 6.55 (br s, 1H), 5.81-5.73 (m, 1H), 5.16-5.12 (m, 2H), 3.87 (s, 2H), 3.36 (m, 2H), 2.31 (m, 2H).

N-(but-3-en-1-yl)-2-(((4R, 5S, 6S, Z)-5-((tert-butyldimethylsilyl) oxy)-6-methoxy-2, 4-dimethylocta-2,7-dien-1-yl) oxy) acetamide (**44**):

To a stirred solution of NaH (47.0 mg, 1.22 mmol, 60% in mineral oil) in dry DMF (3.5 mL), cooled to 0°C, **Int-13** (0.35 g, 1.11 mmol) dissolved in anhydrous DMF (0.5 mL) was added and stirred for 15 min. Compound **3** (0.42 g, 2.23 mmol) was added to the reaction mixture maintaining the temperature at 0°C, slowly brought to RT and stirred for further 30 min. The reaction was quenched with ice and extracted with ether (2 x 20 mL) and the combined organic extracts were dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure to give the crude material which was purified by silica gel column chromatography (EtOAc/Hexane 3:17) to afford compound **44** (0.25 g, 53%).

TLC: 30% EtOAc/Hexane (R_f: 0.4)

^{1}H NMR (500MHz, $CDCl_3$): δ 6.60 (br s, 1H), 5.80-5.73 (m, 1H), 5.65-5.58 (m, 1H), 5.43 (d, *J* = 10.0 Hz, 1H), 5.27 (t, *J* = 11.5 Hz, 2H), 5.09 (t, *J* = 15.0 Hz, 2H), 3.96 (q, *J* = 11.0 Hz, 2H), 3.85 (m, 2H), 3.42-3.35 (m, 4H), 3.19 (s, 3H), 2.57-2.54 (m, 1H), 2.29 (q, *J* = 7.0 Hz, 2H), 1.72 (s, 3H), 0.90 (s, 12H), 0.03 (d, *J* = 17.0 Hz, 6H).

Mass (ESI): 426.4 [M^++1].

(7E, 9S, 10S, 11R, 12Z)-10-((tert-butyldimethylsilyl) oxy)-9-methoxy-11, 13-dimethyl-1-oxa-4-azacyclotetradeca-7, 12-dien-3-one (**45**):

To a stirred solution of compound **44** (0.27 g, 0.63 mmol) in PhMe (1.35 L), heated at 100°C, Grubbs- II catalyst (0.11 g, 0.12 mmol) was slowly added and stirred for 30 min. The reaction was slowly brought to RT and the volatiles were removed under vacuo to give the crude material which was purified by silica gel column chromatography (EtOAc/Hexane 2:3) to furnish compound **45** (0.12 g, 48%).

TLC: 40% EtOAc/Hexane (R_f: 0.2)

^{1}H NMR (500MHz, $CDCl_3$): δ 6.51 (br s, 1H), 5.65-5.55 (m, 2H), 5.37 (dd, *J* = 15.5, 6.0 Hz, 1H), 4.00-3.86 (m, 4H), 3.53-3.48 (m, 1H), 3.41 (q, *J* = 8.5 Hz, 2H), 3.34-3.32 (m, 1H), 3.22 (s, 3H), 2.81-2.76 (m, 1H), 2.37-2.28 (m, 2H), 1.73 (s, 3H), 0.92 (s, 12H), 0.05 (d, *J* = 13.0 Hz, 6H).

Mass (ESI): 398.3 [(M^++1)].

(7E, 9S, 10S, 11R, 12Z)-10-hydroxy-9-methoxy-11, 13-dimethyl-1-oxa-4-azacyclotetradeca-7, 12-dien-3-one (**THC-23**):

To a stirred solution of compound **45** (0.12 g, 0.3 mmol) in THF (2 mL), HF-pyridine (0.5 mL) was added and stirred at RT for 12 h. The reaction mixture was neutralized with saturated 20% $NaHCO_3$ solution (15 mL) and extracted with CH_2Cl_2 (2 x 10 mL). The combined organic extracts were dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure to afford the crude residue which was purified by silica gel column chromatography (EtOAc/Hexane 4:1) to furnish **THC-023** (50.2 mg, 59%).

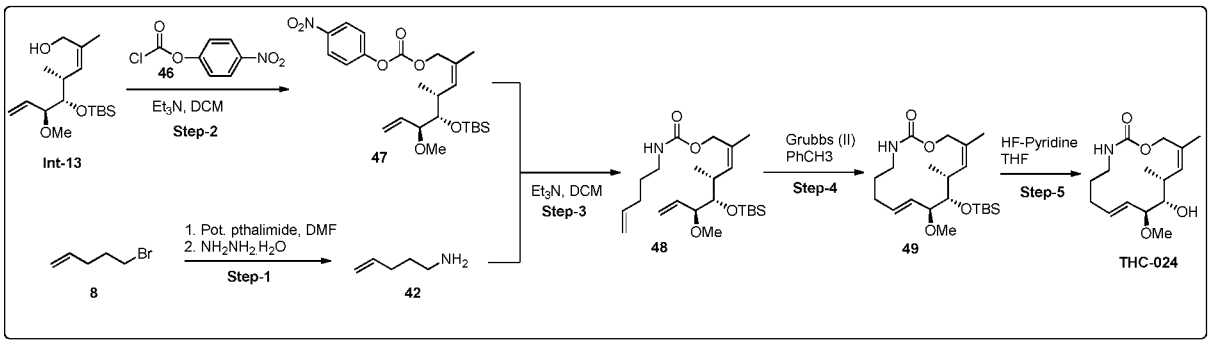
TLC: 50% EtOAc/Hexane (R_f: 0.4)

^{1}H NMR (500MHz, $CDCl_3$): δ 6.48 (br s, 1H), 5.73-5.66 (m, 2H), 5.37 (dd, *J* = 15.5, 7.5 Hz, 1H), 4.05-4.03 (m, 2H), 3.86 (q, *J* = 11.0 Hz, 2H), 3.52-3.45 (m, 2H), 3.39-3.35 (m, 2H), 3.32 (s, 3H), 2.76 (s, 2H), 2.42 (m, 1H), 2.34-2.29 (m, 1H), 1.75 (s, 3H), 0.96 (d, *J* = 6.5 Hz, 3H).

Mass (ESI): 284.2 [(M^++1)].

LC-MS: *m/z* = 284.2[(M^++1)] at RT 2.93 (94.22% purity).

Scheme 11:



Pent-4-en-1-amine (**42**):

A mixture of 5-bromopent-1-ene (**8**) (2 g, 13.4 mmol) and Potassium Phthalimide (2.73 g, 14.73 mmol) in DMF (25 mL) was heated at 60°C for 4 h. The reaction was slowly brought to RT and filtered. To the filtrate aqueous NaCl (30 ml) was added and extracted with ether (4 x 25 mL). The combined organic extracts were washed with saturated NaCl solution (2 x 20 mL), dried over anhydrous K_2CO_3, filtered and concentrated under reduced pressure to give 2-(pent-4-en-1-yl)isoindoline-1,3-dione which was taken in EtOH (20 mL), $NH_2NH_2.H_2O$ (20 mL) was

added and heated at 60°C for 4 h. The reaction mixture was brought to RT, cooled to 0°C, concentrated HCl (drop wise addition) was added dropwise till pH 3-4 and extracted with EtOAc (3 x 20 mL). To the aqueous phase KOH pellets were added (pH 10) and extracted in CH_2Cl_2 (3 x 20 ml), the combined organic extracts was washed with brine, dried over anhydrous sodium sulphate and concentrated under vacuo to afford compound **42** (0.5 g, 45%) as yellow syrup.

TLC: 10% MeOH/CH_2Cl_2 (R_f: 0.1)

^{1}H NMR (500MHz, $CDCl_3$): δ 5.85-5.79 (m, 1H), 5.04-4.95 (m, 2H), 2.72 (t, *J* = 7.0 Hz, 2H), 2.11 (m, 2H), 1.57-1.51 (m, 2H).

(4R, 5S, 6S, Z)-5-((tert-butyldimethylsilyl) oxy)-6-methoxy-2, 4-dimethylocta-2, 7-dien-1-yl (4-nitrophenyl) carbonate (**47**):

To a stirred solution of **Int-13** (500.2 mg, 1.58 mmol) in dry CH_2Cl_2 (10 mL) at 0°C, Et_3N (0.35 mL, 3.16 mmol) was added followed by 4-nitrophenyl chloroformate (**46**) (480 mg, 2.38 mmol) and stirred for 2h. The reaction was diluted with water (20 mL) and extracted with CH_2Cl_2 (3 x 15 mL). The combined organic extracts were dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure to provide the crude material which was purified by silica gel column chromatography (EtOAc/Hexane 1:24) to furnish compound **47** (400 mg, 52%) as a colorless syrup.

TLC: 10% EtOAc/Hexane (R_f: 0.6)

^{1}H NMR (500MHz, $CDCl_3$): δ 8.28 (d, *J* = 9.5 Hz, 2H), 7.38 (d, *J* = 9.0 Hz, 2H), 5.67-5.61 (m, 1H), 5.54 (d, *J* = 10.0 Hz, 1H), 5.28 (t, *J* = 10.5 Hz, 2H), 4.76 (m, 2H), 3.49-3.47 (m, 1H), 3.39 (t, *J* = 8.0 Hz, 1H), 3.21 (s, 3H), 2.66-2.63 (m, 1H), 1.81 (s, 3H), 0.93 (s, 12H), 0.04 (d, *J* = 17.5 Hz, 6H).

Mass (ESI): 478.9 [M^+].

(4R, 5S, 6S, Z)-5-((tert-butyldimethylsilyl) oxy)-6-methoxy-2, 4-dimethylocta-2, 7-dien-1-yl pent-4-en-1-ylcarbamate (**48**):

To a stirred solution of compound **47** (400 mg, 0.834 mmol) in CH_2Cl_2 (5 mL), cooled to 0°C, Et_3N (0.1 mL, 1.668 mmol) was added followed by compound **42** (141 mg, 1.66 mmol), dissolved in CH_2Cl_2 (0.5 mL), and stirred for 24 h. The reaction was diluted with water (20 mL) and extracted with CH_2Cl_2 (3 x 15 mL). The combined organic extracts were washed with water, dried over anhydrous sodium sulphate, filtered and concentrated under vacuo to provide the

crude material which was purified by silica gel column chromatography (EtOAc/Hexane 1:9) to afford compound **48** (250 mg, 70%).

TLC: 20% EtOAc/Hexane (R_f: 0.2)

^{1}H NMR (500MHz, $CDCl_3$): δ 5.82-5.77 (m, 1H), 5.67-5.59 (m, 1H), 5.41 (d, *J* = 9.5 Hz, 1H), 5.29-5.22 (m, 2H), 5.01 (dd, *J* = 30, 15.0 Hz, 2H), 4.65 (br s, 1H), 4.54 (q, *J* = 11.5 Hz, 2H), 3.45 (d, *J* = 5.0 Hz, 1H), 3.36 (t, *J* = 7.5 Hz, 1H), 3.20 (s, 5H), 2.60 (t, *J* = 6.0 Hz, 1H), 2.11-2.07 (m, 2H), 1.72 (s, 3H), 1.60 (d, *J* = 5.5 Hz, 2H), 0.90 (s, 13H), 0.04 (d, *J* = 18.0 Hz, 5H).

Mass (ESI): 426.6 [M^++1].

(7E, 9S, 10S, 11R, 12Z)-10-((tert-butyldimethylsilyl) oxy)-9-methoxy-11, 13-dimethyl-1-oxa-3-azacyclotetradeca-7, 12-dien-2-one (**49**):

To a stirred solution of compound **48** (250 mg, 0.59 mmol) in PhMe (2 L), heated at 100°C, Grubbs-II catalyst (110 mg, 0.12 mmol) was added slowly under argon atmosphere and stirred for 15 min. The reaction was slowly brought to RT and the volatiles were removed under vacuo to provide the crude material which was purified by silica gel column chromatography (EtOAc/Hexane 1:9) to furnish compound **49** (130 mg, 51.5%) as a light yellow colored syrup.

TLC: 20% EtOAc/Hexane (R_f: 0.4)

^{1}H NMR (500MHz, DMSO-d_6): δ 6.67 (br s, 1H), 5.69-5.63 (m, 1H), 5.41-5.28 (m, 1H), 5.17 (d, *J* = 16.0 Hz, 1H), 4.56-4.46 (m, 1H), 4.09-4.06 (m, 1H), 3.16 (s, 4H), 3.11 (s, 2H), 3.00 (br s, 1H), 2.78-2.75 (m, 1H), 2.25-2.23 (m, 2H), 1.59-1.61 (m, 2H), 1.23 (s, 3H), 0.89 (s, 12H), 0.03 (d, *J* = 6.5 Hz, 6H).

Mass (ESI): 399.1 [(M^++2)].

(7E, 9S, 10S, 11R, 12Z)-10-hydroxy-9-methoxy-11, 13-dimethyl-1-oxa-3-azacyclotetradeca-7, 12-dien-2-one (**THC-024**):

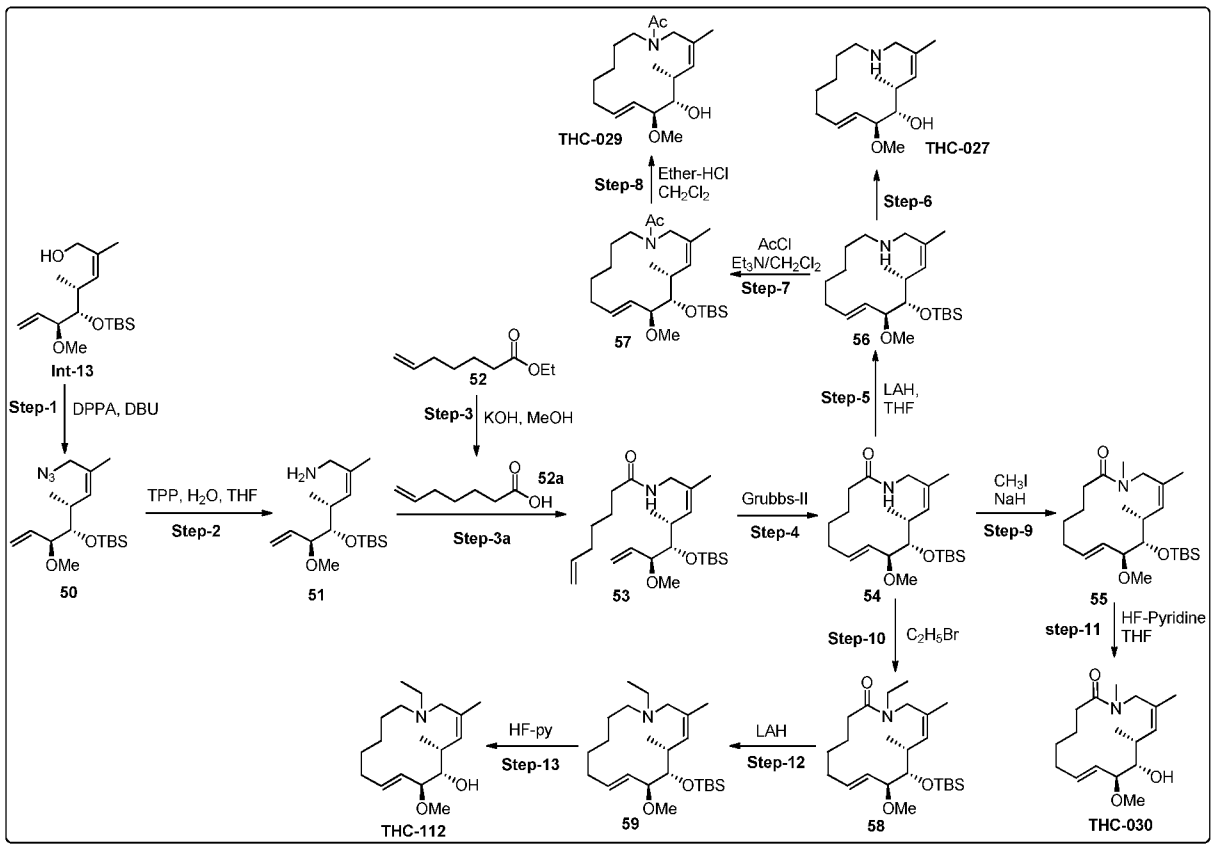
To a stirred solution of compound **49** (120 mg, 0.302 mmol) in THF (5 mL), HF-pyridine (1.2 mL) was added and stirred at RT for 16 h. The reaction mixture was neutralized with saturated $NaHCO_3$ solution and extracted with EtOAc (2 x 15 mL), the combined organic extracts were dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure. The crude residue was purified by silica gel column chromatography (EtOAc/Hexane 3:7) to afford **THC-024** (35 mg, 41%) as viscous oil.

TLC: 40% EtOAc/Hexane (R_f: 0.2)

^{1}H NMR (500MHz, DMSO-d_6): δ 6.65 (br s, 1H), 5.59-5.47 (m, 2H), 5.20-5.17 (m, 1H), 4.63-4.56 (m, 1H), 4.42-4.34 (m, 1H), 4.11-4.06 (m, 1H), 3.38 (m, 1H), 3.17 (s, 3H), 3.02-2.87 (m, 3H), 2.63 (s, 1H), 2.19-2.08 (m, 2H), 1.63 (s, 3H), 1.57 (br s, 2H), 0.82 (s, 3H).

LC-MS: *m/z* = 306.8[(M^++Na)] at RT 3.47 (100% purity).

Scheme 12:



(((3S, 4S, 5R, Z)-8-azido-3-methoxy-5, 7-dimethylocta-1, 6-dien-4-yl) oxy)(tert-butyl) dimethylsilane (**50**):

To a stirred solution of **Int-13** (1.5 g, 4.78 mmol) in PhMe (20 mL), DBU (1.089 g, 7.16 mmol) was added followed by DPPA (1.97 g, 7.165 mmol) at RT and stirred for 4 h. After consumption of the starting material (by TLC), the reaction was quenched with saturated NH_4Cl solution and extracted with Et_2O (3 x 20 ml). The combined organic extracts were dried over anhydrous sodium sulphate, filtered and concentrated under vacuo to give the crude material which was purified by silica gel column chromatography (EtOAc/Hexane 1:19) to afford compound **50** (1.38 g, 84.1%) as colorless liquid.

TLC: 10% EtOAc/Hexane (R_f: 0.6)

^{1}H NMR (500MHz, $CDCl_3$): δ 5.67-5.60 (m, 1H), 5.51 (d, *J* = 10.5 Hz, 1H), 5.29 (dd, *J* = 17, 10.5 Hz, 2H), 3.81 (d, *J* = 13.0 Hz, 1H), 3.67-3.64 (m, 1H), 3.45-3.37 (m, 2H), 3.20 (s, 3H), 2.55 (t, *J* = 7.0 Hz, 1H), 1.77 (s, 2H), 1.66 (d, *J* = 5.0 Hz, 1H), 0.88 (s, 12H), 0.04 (d, *J* = 13.5 Hz, 6H).

Hept-6-enoic acid (**52a**):

To a stirred solution of Ethyl hept-6-enoate (**52**) (3 g, 19.2 mmol) in EtOH (100 mL), 1N NaOH (7.6 g, 192.3 mmol) was added and refluxed for 4 h. The volatiles from the reaction were removed under reduced pressure, the residue was acidified (pH 5) with 1N HCl and extracted with CH_2Cl_2 (3 x 25 mL). The combined organic extracts were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to afford compound **52a** (2.26 g, 91.8%) as colorless liquid.

TLC: 20% EtOAc/Hexane (R_f: 0.1)

^{1}H NMR (500MHz, $CDCl_3$): δ 5.83-5.75 (m, 1H), 5.06 (dd, *J* = 17, 1.5 Hz, 2H), 2.39 (t, *J* = 7.5 Hz, 2H), 2.09-2.04 (m, 2H), 1.66-1.60 (m, 2H), 1.47-1.43 (m, 2H).

Mass (ESI): 127 (M^+-1).

N-((4R, 5S, 6S, Z)-5-((tert-butyldimethylsilyl) oxy)-6-methoxy-2, 4-dimethylocta-2, 7-dien-1-yl) hept-6-enamide (**53**):

To a stirred solution of compound **50** (1.38 g, 4.13 mmol) in THF (30 mL), PPh_3 (1.84 g, 7.02 mmol) was added followed by water (0.37 mL, 20.65 mmol) and refluxed for 4 h. The organic layer was dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure, to give the crude residue which was dissolved in anhydrous CH_2Cl_2 (30 mL). EDC.HCl (1.57 g, 8.26 mmol), DIPEA (2.85 mL, 16.52 mmol) and hept-6-enoic acid (**52**) (1.06 g, 8.26 mmol) were added at RT and stirred for 1 h. The reaction mixture was concentrated under vacuo to get the crude material which was purified by silica gel column chromatography (EtOAc/Hexane 1:9) to afford compound **53** (1.38 g, 81%).

TLC: 20% EtOAc/Hexane (R_f: 0.3)

^{1}H NMR (500MHz, $CDCl_3$): δ 5.82-5.76 (m, 1H), 5.70-5.63 (m, 1H), 5.37-5.23 (m, 4H), 4.98 (dd, *J* = 30.5, 17.5 Hz, 2H), 3.88-3.77 (m, 2H), 3.45-3.39 (m, 2H), 3.22 (s, 3H), 2.59 (t, *J* = 6.5 Hz, 1H), 2.19-2.15 (m, 2H), 2.09-1.62 (m, 2H), 1.69-1.62 (m, 4H), 1.45-1.39 (m, 2H), 0.90 (s, 12H), 0.03 (d, *J* = 16.5 Hz, 6H).

Mass (ESI): 424 (M^++1).

(7E, 9S, 10S, 11R, 12Z)-10-((tert-butyldimethylsilyl) oxy)-9-methoxy-11, 13-dimethylazacyclo-tetradeca-7,12-dien-2-one (**54**):

To a stirred solution of compound **53** (73.5 mg, 0.173 mmol) in PhMe (3.5 L) heated at 100°C, Grubbs-II catalyst (302.3 mg, 0.347 mmol) was added under argon atmosphere and stirred for 15 min. The solvent from the reaction was concentrated under reduced pressure to give the crude material which was purified by silica gel column chromatography (EtOAc/Hexane 3:2) to afford compound **54** (320.3 mg, 46.6%) as brown solid.

TLC: 50% EtOAc/Hexane (R_f: 0.2)

^{1}H NMR (500MHz, $CDCl_3$): δ 5.80-5.77 (m, 1H), 5.47 (d, *J* = 9.5 Hz, 1H), 5.37-5.29 (m, 2H), 3.77 (dd, *J* = 10.5, 2.5 Hz, 1H), 3.67 (dd, *J* = 8.5, 1.5 Hz,1H), 3.47 (s, 2H), 3.21 (s, 3H), 2.59 (t, *J* = 6.5 Hz, 1H), 2.27-2.14 (m, 3H), 2.09-2.04 (m, 2H), 1.74 (s, 3H), 1.64-1.59 (m, 3H), 0.95 (s, 12H), 0.05 (d, *J* = 8.0 Hz, 6H).

Mass (ESI): 396 (M^++1).

(3Z, 5R, 6S, 7S, 8E)-6-((tert-butyldimethylsilyl) oxy)-7-methoxy-3, 5-dimethylazacyclotetradeca-3,8-diene (**56**):

To a stirred solution of compound **54** (320.3 mg, 0.81 mmol) in THF (20 mL), cooled to 0°C, LAH (46.2 mg, 1.29 mmol) was added portion wise. The reaction was brought to RT, stirred for 6 h and quenched with 4N NaOH solution during which solid precipitated out which was filtered through celite pad. The filtrate was concentrated under vacuo to get the crude residue which was purified by silica gel column chromatography (MeOH/CH_2Cl_2 3: 47) to afford compound **56** (218.3 mg, 71%) as brown liquid.

TLC: 10% MeOH/CH_2Cl_2 (R_f: 0.2)

^{1}H NMR (500MHz, $CDCl_3$): δ 5.60-5.54 (m, 1H), 5.36 (d, *J* = 9.5 Hz, 1H), 5.26 (dd, *J* = 15.5, 7.5 Hz, 1H), 3.39-3.34 (m, 2H), 3.20 (s, 3H), 2.78-2.60 (m, 4H), 2.23-2.14 (m, 2H), 1.76 (s, 3H), 1.70-1.67 (m, 1H), 1.55-1.48 (m, 4H), 1.32-1.91 (m, 3H), 0.90 (s, 12H), 0.04 (d, *J* = 17.5 Hz, 6H).

Mass (ESI): 382 (M^++1).

(3Z, 5R, 6S, 7S, 8E)-7-methoxy-3, 5-dimethylazacyclotetradeca-3, 8-dien-6-ol (**THC-027**):

To a stirred solution of compound **56** (130 mg, 0.341 mmol) in THF (2 mL) at 0°C, TBAF (1.0M in THF, 133 mg, 0.51 mmol) was added slowly and stirred at RT for 16 h. The reaction mixture was concentrated under vacuum and the crude material was purified by silica gel column chromatography (MeOH/CH_2Cl_2 3:47) to afford **THC-027** (23 mg, 25.5%).

TLC: 10% MeOH/CH_2Cl_2 (R_f: 0.1)

^{1}H NMR (500MHz, $CDCl_3$): δ 5.66-5.61 (m, 1H), 5.47 (d, *J* = 9.5 Hz, 1H), 5.25 (dd, *J* = 15.5, 8.0 Hz, 1H), 3.45 (t, *J* = 9.0 Hz, 1H), 3.37 (d, *J* = 9.5 Hz, 1H), 3.31 (s, 3H), 3.07 (d, *J* = 11.0 Hz, 1H), 2.92 (d, *J* = 11.0 Hz, 1H), 2.75-2.63 (m, 4H), 2.28-2.26 (m, 1H), 2.14-2.10 (m, 1H), 1.79 (s, 3H), 1.64-1.47 (m, 3H), 1.31-1.25 (m, 4H), 0.95 (d, *J* = 6.5 Hz, 3H).

LC-MS: *m/z* = 268.3[(M^++1)] at RT 2.94 (99.71% purity).

(7E, 9S, 10S, 11R, 12Z)-10-((tert-butyldimethylsilyl) oxy)-9-methoxy-1, 11, 13-trimethylazacyclo-tetradeca-7,12-dien-2-one (**55**):

To a stirred solution of compound **54** (115 mg, 0.291 mmol) in DMF (2 mL), cooled to at 0°C, NaH (8.376 mg, 0.35 mmol, 60% dispersion in mineral oil) was added followed by MeI (49.5 mg, 0.35 mmol) and stirred for 15 min. The reaction was quenched with ice and extracted with Et_2O (2 x 10 mL). The combined organic extracts were dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure to give the crude material which was purified by silica gel column chromatography (EtOAc/Hexane 1:4) to afford compound **55** (78.5 mg, 67%).

TLC: 50% EtOAc/Hexane (R_f: 0.6)

^{1}H NMR (500MHz, $CDCl_3$): δ 5.66-5.53 (m, 2H), 5.26-5.20 (m, 1H), 3.87 (q, *J* = 15.0 Hz, 2H), 3.38 (s, 2H), 3.20 (s, 3H), 2.93 (s, 2H), 2.85 (s, 1H), 2.50-2.41 (m, 2H), 2.22-2.18 (m, 3H), 1.75 (s, 3H), 1.70-1.64 (m, 4H), 0.94 (s, 12H), 0.04 (d, *J* = 11.0 Hz, 6H).

Mass (ESI): 410 (M^++1).

(7E, 9S, 10S, 11R, 12Z)-10-hydroxy-9-methoxy-1, 11, 13-trimethylazacyclotetradeca-7, 12-dien-2-one (**THC-030**):

To a stirred solution of compound **55** (78.5 mg, 0.195 mmol) in THF (1 mL) at 0°C, HF-pyridine (1 mL) was added slowly and stirred at RT for 16 h. The reaction was quenched with saturated $NaHCO_3$ solution and extracted with EtOAc (3 x 10 mL). The organic extracts were dried over anhydrous sodium sulphate, filtered and concentrated under vacuum to give the crude

residue which was purified by silica gel column chromatography (EtOAc/Hexane 1: 4) to afford **THC-030** (36.23 mg, 64%).

TLC: 50% EtOAc/Hexane (R_f: 0.2)

^{1}H NMR (400MHz, $CDCl_3$): δ 5.78-5.68 (m, 1H), 5.58 (d, *J* = 10.0 Hz, 1H), 5.24 (dd, *J* = 14.8, 6.4 Hz, 1H), 4.11-3.96 (m, 1H), 3.75 (d, *J* = 15.2 Hz, 1H), 3.41-3.29 (m, 2H), 3.25 (s, 3H), 2.95 (s, 2H), 2.84 (d, *J* = 11.6 Hz, 1H), 2.51-2.35 (m, 3H), 2.24-2.12 (m, 2H), 1.78 (s, 3H), 1.76-1.65 (m, 3H), 1.03 (d, *J* = 6.8 Hz, 1H), 0.90 (d, *J* = 6.8 Hz, 3H).

Mass (ESI): 296.5 (M^++1).

LC-MS: *m/z* = 296.8[(M^++1)] at RT 3.30 (83.69% purity).

1-((3Z, 5R, 6S, 7S, 8E)-6-((tert-butyldimethylsilyl) oxy)-7-methoxy-3, 5-dimethylazacyclo-tetradeca-3, 8-dien-1-yl) ethanone (**57**):

To a stirred solution of compound **56** (162.3 mg, 0.425 mmol) in anhydrous CH_2Cl_2 (5 mL), cooled to 0°C, Et_3N (0.12 mL, 0.85 mmol) followed by AcCl (0.04 mL, 0.637 mmol) was added drop wise and stirred for 15 min. The reaction was quenched with saturated $NaHCO_3$ and extracted with CH_2Cl_2 (2 x 10 mL). The combined organic extracts were dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure to provide the crude material which was purified by silica gel column chromatography (EtOAc/Hexane 3:7) to afford compound **57** (93.4 mg, 52%).

TLC: 50% EtOAc/Hexane (R_f: 0.5)

^{1}H NMR (500MHz, DMSO-d_6): δ 5.59-5.54 (m, 1H), 5.49-5.37 (m, 2H), 3.84-3.71 (m, 1H), 3.44-3.40 (m, 1H), 3.30 (s, 1H), 3.14 (s, 3H), 3.12-3.06 (m, 1H), 2.79-2.78 (m, 1H), 2.58 (t, *J* = 7.5 Hz, 1H), 2.23-2.19 (m, 2H), 2.01 (s, 3H), 1.53 (br s, 5H), 1.40 (br s, 2H), 1.22 (d, *J* = 8.0 Hz, 2H), 1.10 (br s, 1H), 0.89 (s, 12H), 0.03 (d, *J* = 11.0 Hz, 6H).

Mass (ESI): 424 (M^++1).

1-((3Z, 5R, 6S, 7S, 8E)-6-hydroxy-7-methoxy-3, 5-dimethylazacyclotetradeca-3, 8-dien-1-yl) ethanone (**THC-029**):

To a stirred solution of compound **57** (126 mg, 0.297 mmol) in CH_2Cl_2 (2 mL) at 0°C, Et_2O-HCl (2 mL) and stirred at RT for 48 h. The volatiles from the reaction were evaporated under vacuo and the residue was basified with saturated $NaHCO_3$ solution and extracted with EtOAc (3 x 10 mL). The combined organic extracts were dried over anhydrous sodium sulphate,

filtered and concentrated under vacuum. The crude residue was purified by silica gel column chromatography (EtOAc/Hexane 3:2) to furnish **THC-029** (56.4 mg, 64%).

TLC: 50% EtOAc/Hexane (R_f: 0.1)

^{1}H NMR (500MHz, DMSO-d_6 at 80°C): δ 5.55-5.45 (m, 3H), 4.20 (br s, 1H), 3.96 (m, 2H), 3.79 (d, *J* = 13.5 Hz, 1H), 3.41 (t, *J* = 7.5 Hz, 1H), 3.20 (s, 3H), 3.16-3.14 (m, 1H), 2.80-2.78 (m, 2H), 2.57 (m, 1H), 2.02 (m, 2H), 2.20 (s, 3H), 1.49-1.36 (m, 5H), 1.15-1.06 (m, 2H), 0.85 (d, *J* = 6.0 Hz, 3H).

Mass (ESI): 310.5 (M^++1).

LC-MS: *m/z* = 310.7[(M^++1)] at RT 3.68 (95.99% purity).

(7E, 9S, 10S, 11R, 12Z)-10-((tert-butyldimethylsilyl) oxy)-1-ethyl-9-methoxy-11, 13-dimethylazacyclotetradeca-7,12-dien-2-one (**58**):

To a stirred solution of compound **54** (103.4 mg, 0.26 mmol) in DMF (2 mL) at 0°C, NaH (7.48 mg, 0.313 mmol, 60% dispersion in mineral oil) was added followed by EtBr (0.021 mL, 0.313 mmol) and stirred for 1 h maintaining the temperature at 0°C. The reaction was quenched with ice cold water and extracted with Et_2O (2 x 10 mL). The combined organic extracts were dried over anhydrous sodium sulphate, filtered and concentrated under vacuum to give the crude material which was purified by silica gel column chromatography (EtOAc/Hexane 3:17) to provide compound **58** (70.7 mg, 64.2%).

TLC: 50% EtOAc/Hexane (R_f: 0.6)

^{1}H NMR (500MHz, $CDCl_3$): δ 5.66-5.60 (m, 1H), 5.46 (d, *J* = 9.5 Hz, 1H), 5.25-5.20 (m, 1H), 3.90 (d, *J* = 16.0 Hz, 1H), 3.74 (d, *J* = 15.5 Hz, 1H), 3.62-3.61 (m, 1H), 3.38 (t, *J* = 6.5 Hz, 2H), 3.20 (s, 5H), 2.37-2.35 (m, 2H), 2.18 (br s, 3H), 2.04-2.00 (m, 1H), 1.73 (s, 4H), 1.10-1.07 (m, 4H), 0.91 (s, 12H), 0.06 (d, *J* = 10.0 Hz, 6H).

Mass (ESI): 424 (M^++1).

(3Z, 5R, 6S, 7S, 8E)-6-((tert-butyldimethylsilyl) oxy)-1-ethyl-7-methoxy-3, 5-dimethylazacyclo-tetradeca-3,8-diene (**59**):

To a stirred solution of compound **58** (70.7 mg, 0.165 mmol) in THF (2 mL), cooled to 0°C, LAH (7.5 mg, 0.2 mmol) was added. The reaction was slowly brought to RT and stirred for 2 h and quenched with 4N NaOH solution during which white solid precipitated out which was filtered through a pad of celite. The filtrated was dried over anhydrous sodium sulphate, filtered

and concentrated under vacuum, to give the crude material which was purified by silica gel column chromatography (EtOAc/Hexane 1:4) to provide compound **59** (47.9 mg, 70%).

TLC: 50% EtOAc/Hexane (R_f: 0.5)

^{1}H NMR (400MHz, $CDCl_3$): δ 5.56-5.43 (m, 2H), 5.23 (dd, *J* = 19.5, 8.0 Hz, 1H), 3.39-3.23 (m, 2H), 3.19 (s, 4H), 2.73-2.67 (m, 1H), 2.52-2.39 (m, 2H), 2.34-2.14 (m, 6H), 1.70 (s, 4H), 1.54 (s, 4H), 0.98 (t, *J* = 7.2 Hz, 3H), 0.91 (s, 9H), 0.84 (d, *J* = 6.8 Hz, 3H), 0.04 (d, *J* = 11.2 Hz, 6H).

Mass (ESI): 410 (M^++1).

(3Z, 5R, 6S, 7S, 8E)-1-ethyl-7-methoxy-3,5-dimethylazacyclotetradeca-3,8-dien-6-ol (**THC-112**):

To a stirred solution of compound **59** (47.9 mg, 0.12 mmol) in THF (1 mL) at 0°C, HF-pyridine (1 mL) was added. The reaction was slowly brought to RT and stirred for further 16 h. The reaction was quenched with saturated $NaHCO_3$ solution and extracted with 5% MeOH/CH_2Cl_2 (3 x 10 mL). The combined organic extracts were dried over anhydrous sodium sulphate, filtered and concentrated under vacuo. The crude residue was purified by silica gel column chromatography (MeOH/CH_2Cl_2 1:19) to furnish **THC-112** (23 mg, 67%).

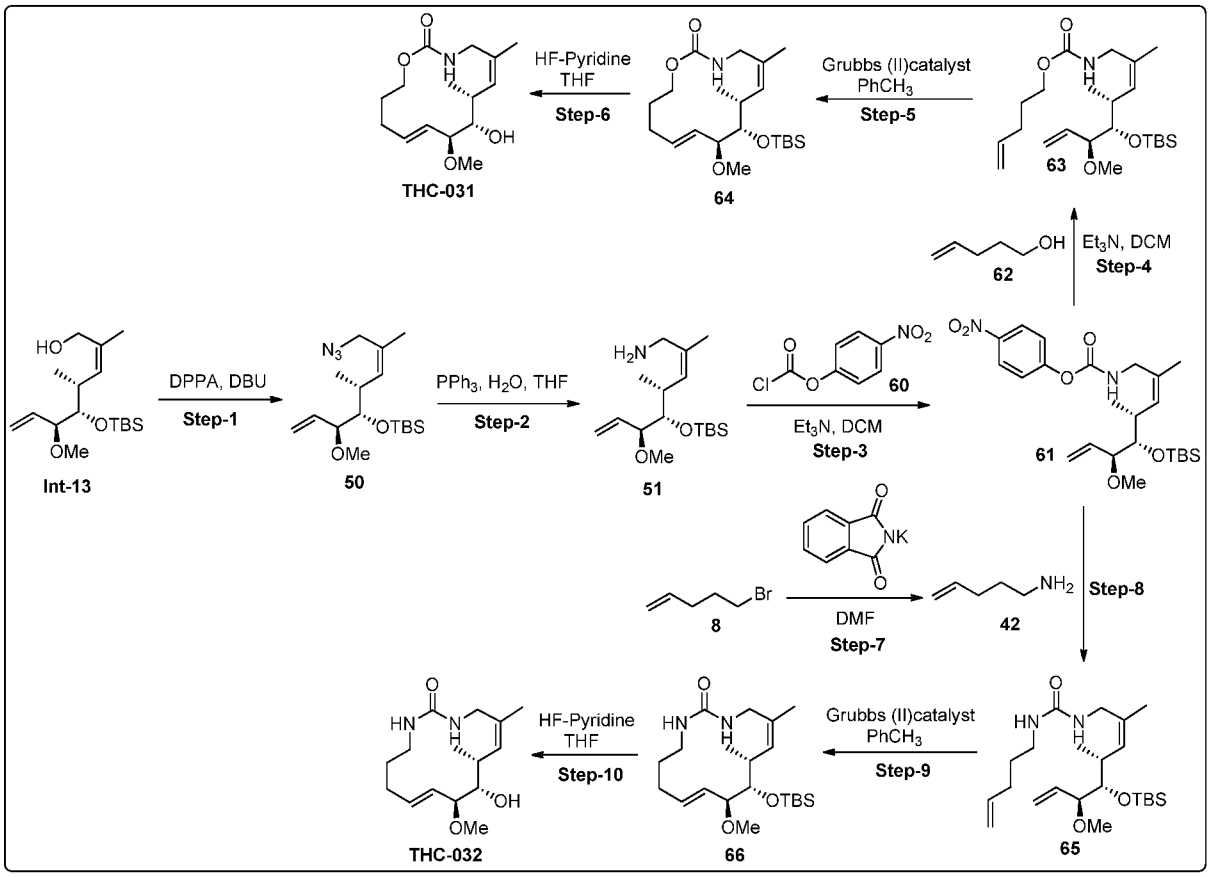
TLC: 100% EtOAc (R_f: 0.1)

^{1}H NMR (400MHz, $CDCl_3$): δ 5.66-5.65 (m, 2H), 5.25 (dd, *J* = 15.2, 8.4 Hz, 1H), 3.47 (t, *J* = 8.8 Hz, 1H), 3.37 (d, *J* = 9.2 Hz, 1H), 3.30 (s, 3H), 3.18 (br s, 1H), 2.85-2.80 (m, 1H), 2.65 (br s, 1H), 2.49 (d, *J* = 5.2 Hz, 2H), 2.36-2.17 (m, 4H), 1.75 (br s, 3H), 1.25-1.21 (m, 3H), 1.09 (s, 1H), 1.03 (s, 2H), 0.98 (m, 3H), 0.91 (d, *J* = 6.5 Hz, 3H).

Mass (ESI): 296 (M^++1).

LC-MS: *m/z* = 296.6[(M^++1)] at RT 2.98 (94.597% purity).

Scheme 13:



(((3S, 4S, 5R, Z)-8-azido-3-methoxy-5, 7-dimethylocta-1, 6-dien-4-yl) oxy)(tert-butyl) dimethylsilane (**50**):

To a stirred solution of **Int-13** (570 mg, 1.815 mmol) in PhMe (6 mL), DBU (0.4 mL, 2.72 mmol) followed by DPPA (0.6 mL, 2.72 mmol) were added at RT and stirred for 3 h. After consumption of the starting material (by TLC), the reaction was quenched with NH_4Cl solution and diluted with Et_2O (10 mL). The aqueous layer was extracted with Et_2O (3 x 15 mL) and the combined organic extracts were dried over anhydrous sodium sulphate, filtered and concentrated under vacuo. The crude material was purified by silica gel column chromatography (EtOAc/Hexane 1:19) to furnish compound **50** (470 mg, 76%) as a colorless liquid.

TLC: 20% EtOAc/Hexane (R_f: 0.9)

^{1}H NMR (500MHz, $CDCl_3$): δ 5.67-5.60 (m, 1H), 5.51 (d, *J* = 10.0 Hz, 1H), 5.31-5.24 (m, 2H), 3.81 (d, *J* = 13.0 Hz, 1H), 3.65 (d, *J* = 13.0 Hz, 1H), 3.46-3.37 (m, 2H), 3.20 (s, 3H), 2.56-2.53 (m, 1H), 1.77 (s, 3H), 0.91 (s, 12H), 0.04 (d, *J* = 14.0 Hz, 6H).

(4R, 5S, 6S, Z)-5-((tert-butyldimethylsilyl) oxy)-6-methoxy-2, 4-dimethylocta-2, 7-dien-1-amine (**51**):

To a stirred solution of compound **50** (470 mg, 1.407 mmol) in THF (10 mL), water (0.126 mL, 7.035 mmol) followed by PPh_3 (626.7 mg, 2.39 mmol) were added at RT. The reaction was heated at 70 °C for 3h and volatiles were removed under reduced pressure to afford compound **51** (1.1 g) which was carried forward without further purification.

TLC: 30% EtOAc/Hexane (R_f: 0.8)

4-Nitrophenyl ((4R, 5S, 6S, Z)-5-((tert-butyldimethylsilyl) oxy)-6-methoxy-2, 4-dimethylocta-2, 7-dien-1-yl) carbamate (**61**):

To a stirred solution of compound **51** (400 mg, 1.29 mmol) in CH_2Cl_2 (5 mL), cooled to 0°C, Et_3N (0.36 mL, 2.58 mmol) followed by 4-nitrophenyl chloroformate (**60**) (392.5 mg, 1.94 mmol) were and stirred for 2h. The reaction was diluted with water; organic layer was separated, dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure. The crude material was purified by silica gel column chromatography (EtOAc/Hexane 1:9) to provide compound **61** (300 mg, 45%) as colorless liquid.

TLC: 30% EtOAc/Hexane (R_f: 0.7)

^{1}H NMR (500MHz, $CDCl_3$): δ 8.26 (d, *J* = 9.0 Hz, 2H), 7.32 (d, *J* = 9.5 Hz, 2H), 5.75-5.63 (m, 1H), 5.43-5.24 (m, 4H), 3.85-3.79 (m, 2H), 3.51-3.40 (m, 2H), 3.26 (d, *J* = 14.0 Hz, 3H), 2.65-2.56 (m, 1H), 1.78 (s, 2H), 1.65 (s, 1H), 0.91 (s, 12H), 0.08 (d, *J* = 9.0 Hz, 6H).

Mass (ESI): 447 (M^+-OMe).

Pent-4-en-1-yl ((4R, 5S, 6S, Z)-5-((tert-butyldimethylsilyl) oxy)-6-methoxy-2, 4-dimethylocta-2, 7-dien-1-yl) carbamate (**63**):

To a stirred solution of compound **61** (300 mg, 0.627 mmol) in CH_2Cl_2 (10 mL), Et_3N (0.17 mL, 1.255 mmol) was added followed by pent-4-en-1-ol (**62**) (81 mg, 0.94 mmol) and stirred at RT for 16 h. The reaction was heated at 40°C for 3h and diluted with water; the organic layer was separated and dried over anhydrous sodium sulphate, filtered and concentrated under

vacuum. The crude material was purified by silica gel column chromatography (EtOAc/Hexane 7:93) to provide compound **63** (120 mg, 45%) as colorless oil.

TLC: 30% EtOAc/Hexane (R_f: 0.8)

^{1}H NMR (500MHz, $CDCl_3$): δ 5.85-5.77 (m, 1H), 5.68-5.61 (m, 1H), 5.33-5.23 (m, 3H), 5.01 (dd, *J* = 30.0, 16.5 Hz, 2H), 4.64 (br s, 1H), 4.07 (s, 2H), 3.79-3.69 (m, 2H), 3.45-3.39 (m, 2H), 3.21 (s, 3H), 2.59 (m, 1H), 2.12 (d, *J* = 7.5 Hz, 2H), 1.70 (s, 5H), 0.90 (s, 12H), 0.04 (d, *J* = 17.0 Hz, 6H).

(5Z, 7R, 8S, 9S, 10E)-8-((tert-butyldimethylsilyl) oxy)-9-methoxy-5,7-dimethyl-1-oxa-3-azacyclotetradeca-5,10-dien-2-one (**64**):

To a stirred solution of compound **63** (120 mg, 0.282 mmol) in PhMe (558 mL), heated at 120°C, Grubbs-II catalyst (49.12 mg, 0.056 mmol) was added under argon atmosphere and stirred for 30 min. The reaction mixture was concentrated under reduced pressure to give the crude material which was purified by silica gel column chromatography (EtOAc/Hexane 7:93) to furnish compound **64** (35 mg, 31%) as colorless liquid.

TLC: 30% EtOAc/Hexane (R_f: 0.4)

^{1}H NMR (500MHz, DMSO-d_6): δ 6.69 (br s, 1H), 5.72-5.66 (m, 1H), 5.33-5.26 (m, 2H), 4.10-4.04 (m, 2H), 3.65 (d, *J* = 12.0 Hz, 1H), 3.45 (d, *J* = 12.0 Hz, 1H), 3.40 (d, *J* = 8.0 Hz, 1H), 3.32 (t, *J* = 8.0 Hz, 1H), 3.14 (s, 3H), 2.83-2.77 (m, 1H), 2.28-2.26 (m, 2H), 1.82-1.81 (m, 1H), 1.71-1.68 (m, 1H), 1.63 (s, 3H), 0.91 (s, 9H), 0.83 (d, *J* = 7.0 Hz, 3H), 0.04 (d, *J* = 13.0 Hz, 6H).

Mass (ESI): 366 (M^+-OCH_3).

(5Z, 7R, 8S, 9S, 10E)-8-hydroxy-9-methoxy-5,7-dimethyl-1-oxa-3-azacyclotetradeca-5,10-dien-2-one (**THC-031**):

To a stirred solution of compound **64** (45 mg, 0.113 mmol) in THF (2 mL), HF-pyridine (1.5 mL) was added and stirred at RT for 5 h. The reaction mixture was neutralized with saturated $NaHCO_3$ solution and extracted with EtOAc (3 x 10). The combined organic extracts was dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure to provide the crude material which was purified by silica gel column chromatography (EtOAc/Hexane 2:3) to afford **THC-031** (23 mg, 71%) as liquid.

TLC: 40% EtOAc/Hexane (R_f: 0.2)

^{1}H NMR (500MHz, DMSO-d_6): δ 6.64 (br s, 1H), 5.70-5.65 (m, 1H), 5.36-5.27 (m, 2H), 4.10 (d, *J* = 8.5 Hz, 1H), 4.01 (br s, 1H), 3.88 (s, 1H), 3.76-3.73 (m, 1H), 3.38 (t, *J* = 8.5 Hz, 2H), 3.25 (d, *J* = 9.5 Hz, 1H), 3.21 (s, 3H), 2.71 (t, *J* = 9.5 Hz, 1H), 2.26 (br s, 2H), 1.80-1.65 (m, 2H), 1.65 (s, 3H), 0.81 (d, *J* = 7.0 Hz, 3H).

LC-MS: *m/z* = 253.6[(M^+-OCH_3)] at RT 3.37 (93.81% purity).

Pent-4-en-1-amine (**42**):

To a stirred solution of 5-bromo-1-pentene (**8**) (2.1 g, 13.4 mmol) in DMF (20 mL), potassium Phthalimide (2.78 g, 14.7 mmol) was added and heated at 60°C for 4 h. The reaction mixture was slowly brought to RT, filtered, diluted with water and extracted with Et_2O (3 x 15 mL). The organic layer was washed with saturated brine solution, dried over anhydrous sodium sulphate, filtered and concentrated under vacuo to give the crude material was dissolved in EtOH (20 mL) and hydrazine hydrate (80% solution, 0.24 g, 13.4 mmol) was added. The resulting reaction mixture was heated at 60°C for 8 h and filtered, diluted with water and basified (pH 9) with KOH pellets. The aqueous layer was extracted with CH_2Cl_2 (3 x 15 mL), dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure to afford compound **42** (530 mg, 45%).

TLC: 10% MeOH/CH_2Cl_2 (R_f: 0.1)

^{1}H NMR (500MHz, $CDCl_3$): δ 5.85-5.77 (m, 1H), 5.02 (dd, *J* = 17, 1.5 Hz, 2H), 2.72 (t, *J* = 7.0 Hz, 2H), 2.11 (q, *J* = 7.0 Hz, 2H), 1.59-1.51 (m, 2H).

1-((4R, 5S, 6S, Z)-5-((tert-butyldimethylsilyl) oxy)-6-methoxy-2,4-dimethylocta-2,7-dien-1-yl)-3-(pent-4-en-1-yl) urea (**65**):

To a stirred solution of compound **61** (206.3 mg, 0.428 mmol) in CH_2Cl_2 (5 mL), cooled to 0°C, pent-4-en-1-amine (**42**) (54.6 mg, 0.643 mmol) was added followed by Et_3N (0.12 mL, 0.86 mmol). The reaction was slowly brought to RT and stirred for 2h. The reaction was diluted with CH_2Cl_2 (10 mL), organic layer was separated, washed with 10% citric acid solution, saturated sodium bicarbonate solution followed by brine. The organic phase was dried over anhydrous sodium sulphate, filtered and concentrated under vacuum. The crude material was purified by silica gel column chromatography (EtOAc/Hexane 3:7) to afford compound **65** (75.8 mg, 41%).

TLC: 50% EtOAc/Hexane (R_f: 0.2)

^{1}H NMR (500MHz, $CDCl_3$): δ 5.84-5.76 (m, 1H), 5.69-5.62 (m, 1H), 5.34-5.23 (m, 3H), 5.01 (dd, *J* = 30.5, 17.0 Hz, 2H), 4.23-4.19 (m, 2H), 3.79-3.67 (m, 2H), 3.45-3.39 (m, 2H), 3.21-3.16 (m, 5H), 2.61-2.57 (m, 1H), 2.11 (m, 2H), 1.71 (s, 3H), 1.62-1.56 (m, 2H), 0.90 (s, 12H), 0.05 (d, *J* = 17.5 Hz, 6H).

Mass (ESI): 425 (M^++1).

(5Z, 7R, 8S, 9S, 10E)-8-((tert-butyldimethylsilyl) oxy)-9-methoxy-5,7-dimethyl-1,3-diazacyclotetradeca-5,10-dien-2-one (**66**):

To a stirred solution of compound **65** (75.8 mg, 0.178 mmol) in PhMe (375 mL), heated at 100°C, Grubbs-II catalyst (31.1 mg, 0.035 mmol) was added under argon atmosphere and stirred for 15 min. The reaction mixture was concentrated under reduced pressure to provide the crude material which was purified by silica gel column chromatography (EtOAc/Hexane 3:2) to afford compound **66** (33.5 mg, 49%).

TLC: 100% EtOAc (R_f: 0.3)

^{1}H NMR (500MHz, $CDCl_3$): δ 5.64-5.60 (m, 1H), 5.50-5.41 (m, 2H), 4.36 (br s, 1H), 4.20 (br s, 1H), 3.84 (dd, *J* = 14.5, 4.5 Hz, 1H), 3.55-3.42 (m, 3H), 3.24 (s, 3H), 3.11-3.08 (m, 1H), 2.64-2.60 (m, 1H), 2.28 (m, 2H), 1.72 (s, 3H), 1.67 (m, 3H), 0.93 (s, 12H), 0.07 (d, *J* = 6.0 Hz, 6H).

Mass (ESI): 397 (M^++1).

(5Z, 7R, 8S, 9S, 10E)-8-hydroxy-9-methoxy-5,7-dimethyl-1,3-diazacyclotetradeca-5,10-dien-2-one (**THC-032**):

To a stirred solution of compound **66** (35.5 mg, 0.089 mmol) in THF (2 mL), cooled to 0°C, HF-pyridine (1 mL) was added and stirred at RT for 5h. The reaction mixture was neutralized with saturated $NaHCO_3$ solution and extracted with CH_2Cl_2 (2 x 10 mL). The combined organic extracts were dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure to give the crude material which was purified by silica gel column chromatography (EtOAc/Hexane 1:19) to afford **THC-032** (15.8 mg, 62.6%) as yellow liquid.

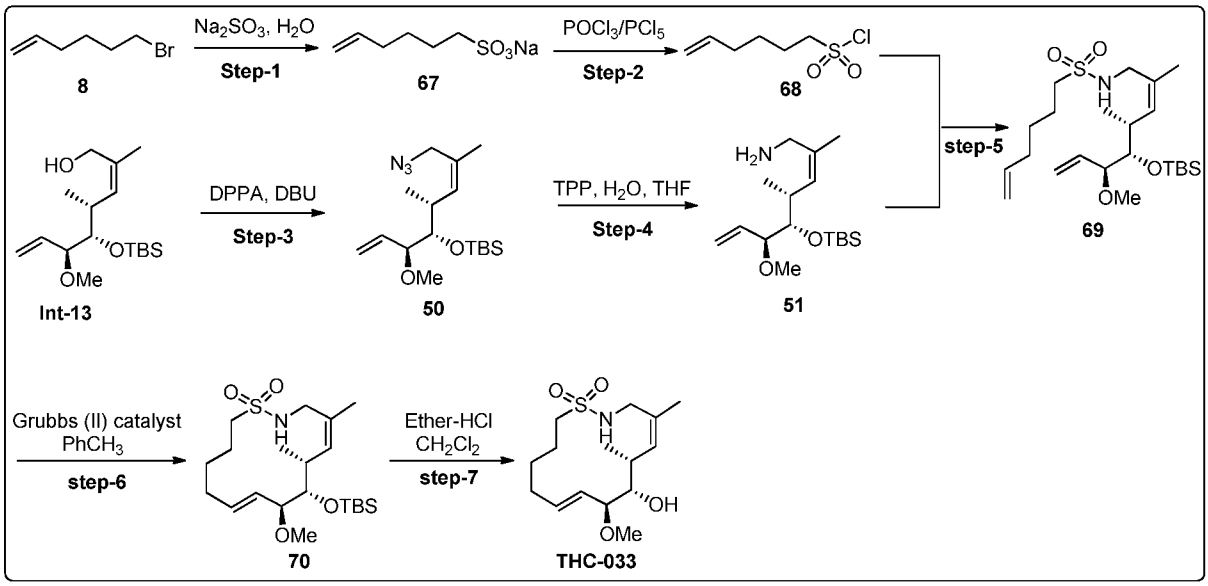
TLC: 10% MeOH/CH_2Cl_2 (R_f: 0.3)

^{1}H NMR (500MHz, $CDCl_3$): δ 5.70-5.66 (m, 1H), 5.55 (d, *J* = 10.5 Hz, 1H), 5.43 (dd, *J* = 15.0, 6.0 Hz, 1H), 4.17 (br s, 2H), 3.96 (dd, *J* = 14.5, 5.5 Hz, 1H), 3.44-3.37 (m, 3H), 3.32 (s, 4H), 3.02-2.99 (m, 1H), 2.87 (s, 1H), 2.64-2.60 (m, 1H), 2.35-2.26 (m, 2H), 1.74 (s, 3H), 1.66-1.62 (m, 2H), 0.96 (d, *J* = 7.0 Hz, 3H).

Mass (ESI): 283.97 (M^++1).

LC-MS: *m/z* = 283.6[(M^++1)] at RT 2.67 (93.41% purity).

Scheme 14:



Sodium hex-5-ene-1-sulfonate (**67**):

To a stirred solution of 6-bromohex-1-ene (**8**) (0.82 mL, 6.1 mmol) in water (4.6 mL), Na_2SO_3 (0.92 g, 7.36 mmol) was added and refluxed for 5 h. The volatiles from the reaction mixture was removed under vacuo to afford compound **67** (1 g) as crude salt which was carried forward.

^{1}H NMR (500MHz, DMSO-d_6): δ 5.83-5.75 (m, 1H), 5.00 (dd, *J* = 31.5, 15.5 Hz, 2H), 3.53 (t, *J* = 7.0 Hz, 2H), 2.05 (q, *J* = 7.0 Hz, 2H), 1.82-1.77 (m, 2H), 1.50-1.44 (m, 2H).

Hex-5-ene-1-sulfonyl chloride (**68**):

To a stirred solution of crude salt **67** (2 g, 10.75 mmol) in $POCl_3$ (2.99 mL, 32.2 mmol), PCl_5 (2.23 g, 10.75 mmol) was added and refluxed for 8h. The reaction mixture was poured into crushed ice and stirred for 10 min. The aqueous layer was extracted with benzene (2 x 20 mL) and the combined organic extracts were dried over anhydrous sodium sulphate, filtered and concentrated to afford compound **68** (1.5 g) which was directly used in the next step without further purification.

TLC: 30% EtOAc/Hexane (R_f: 0.8)

(((3S, 4S, 5R, Z)-8-azido-3-methoxy-5,7-dimethylocta-1,6-dien-4-yl) oxy)(tert-butyl) dimethyl silane (**50**):

To a stirred solution of **Int-13** (570 mg, 1.815 mmol) in PhMe (6 mL), DBU (0.4 mL, 2.72 mmol) followed by DPPA (0.6 mL, 2.72 mmol) was added and stirred at RT for 3 h. After consumption of the starting material (by TLC), the reaction was quenched with NH_4Cl solution and diluted with Et_2O (20 mL). The aqueous layer was extracted with Et_2O (2 x 15 mL) and the combined organic extracts were dried over anhydrous sodium sulphate, filtered and concentrated under vacuum. The crude residue was purified by silica gel column chromatography (EtOAc/Hexane 1:19) to afford compound **50** (470 mg, 76%) as a colorless liquid.

TLC: 20% EtOAc/Hexane (R_f: 0.9)

^{1}H NMR (500MHz, $CDCl_3$): δ 5.67-5.60 (m, 1H), 5.51 (d, *J* = 9.5 Hz, 1H), 5.31-5.24 (m, 2H), 3.81 (d, *J* = 13.0 Hz, 1H), 3.65 (d, *J* = 13.0 Hz, 1H), 3.46-3.37 (m, 2H), 3.20 (s, 3H), 2.56-2.53 (m, 1H), 1.77 (s, 3H), 0.91 (s, 12H), 0.04 (d, *J* = 14.0 Hz, 6H).

(4R, 5S, 6S, Z)-5-((tert-butyldimethylsilyl) oxy)-6-methoxy-2,4-dimethylocta-2,7-dien-1-amine (**51**):

To a stirred solution of compound **50** (470 mg, 1.407 mmol) in THF (10 mL), water (0.1 mL, 7.035 mmol) followed by PPh_3 (626.7 mg, 2.39 mmol) was added. The reaction was heated at 70°C for 3h. The volatiles were removed under reduced pressure to furnish compound **51** (1.1 g) as crude residue which was directly used for the next step without further purification.

TLC: 20% EtOAc/Hexane (R_f: 0.8)

N-((4R, 5S, 6S, Z)-5-((tert-butyldimethylsilyl) oxy)-6-methoxy-2, 4-dimethylocta-2, 7-dien-1-yl) hex-5-ene-1-sulfonamide (**69**):

To a stirred solution of compound **51** (80 mg, 0.25 mmol) in CH_2Cl_2 (1 mL), cooled to 0°C, Et_3N (0.1 mL, 0.75 mmol) was added followed by compound **68** (70 mg, 0.38 mmol) maintaining the temperature at 0°C. The reaction was slowly brought to RT and stirred for another 30 min. The reaction was quenched with ice-water; organic layer was separated and washed with water (2 x 2mL), dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure. The crude material was purified by silica gel column chromatography (EtOAc/Hexane 2:23) to afford compound **69** (20 mg, 17%).

TLC: 30% EtOAc/Hexane (R_f: 0.7)

^{1}H NMR (500MHz, $CDCl_3$): δ 5.78-5.70 (m, 2H), 5.37-5.25 (m, 3H), 5.01 (dd, *J* = 23.5, 17.5 Hz, 2H), 4.34 (br s, 1H), 3.68-3.59 (m, 3H), 3.46 (s, 3H), 3.23 (s, 3H), 2.99 (t, *J* = 7.5 Hz, 2H), 2.60 (m, 1H), 2.10 (d, *J* = 7.0 Hz, 2H), 1.82 (t, *J* = 7.0 Hz, 2H), 1.77 (s, 3H), 0.90 (s, 12H), 0.06 (d, *J* = 15.5 Hz, 6H).

Mass (ESI): 460 (M^++1).

(4Z, 6R, 7S, 8S, 9E)-7-((tert-butyldimethylsilyl) oxy)-8-methoxy-4,6-dimethyl-1-thia-2-azacyclotetradeca-4,9-diene 1,1-dioxide (**70**):

To a solution of compound **69** (0.3 g, 0.65 mmol) in PhMe (1.5 L), heated to 100°C, Grubbs-II catalyst (0.11 g, 0.13 mmol) was added under argon atmosphere and stirred for 30 min. The solvent from the reaction was removed under reduced pressure to give the crude material which was purified by silica gel column chromatography (EtOAc/Hexane 1:9) to provide compound **70** (0.1 g, 35.7%).

TLC: 20% EtOAc/Hexane (R_f: 0.3)

^{1}H NMR (500MHz, $CDCl_3$): δ 5.61-5.54 (m, 2H), 5.24 (d, *J* = 16.0 Hz, 1H), 3.67 (m, 1H), 3.54-3.45 (m, 2H), 3.37 (s, 2H), 3.20 (s, 3H), 3.16-3.13 (m, 1H), 2.87 (t, *J* = 9.0 Hz, 1H), 2.55-2.51 (m, 1H), 2.31 (d, *J* = 10.0 Hz, 1H), 2.09-2.07 (m, 1H), 1.88 (d, *J* = 11.0 Hz, 1H), 1.79 (s, 3H), 1.62 (m, 3H), 0.92 (s, 12H), 0.09 (d, *J* = 22.0 Hz, 6H).

Mass (ESI): 430 (M^+-1).

(4Z, 6R, 7S, 8S, 9E)-7-hydroxy-8-methoxy-4,6-dimethyl-1-thia-2-azacyclotetradeca-4,9-diene 1, 1-dioxide (**THC-033**):

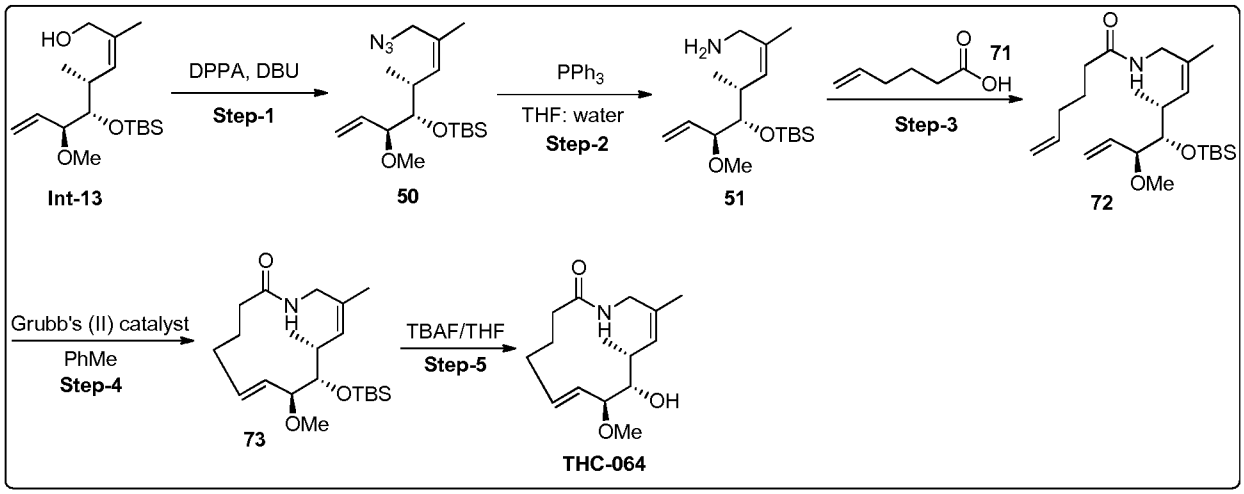
To a stirred solution of compound **70** (0.1 g, 0.23 mmol) in CH_2Cl_2 (1 mL), ether-HCl (1 mL) was added and stirred at RT for 30 min. The volatile from the reaction was removed under vacuo to obtain the crude residue which was purified by silica gel column chromatography (EtOAc/Hexane 1:4) to afford **THC033** (45 mg, 61.6%).

TLC: 40% EtOAc/Hexane (R_f: 0.5)

^{1}H NMR (500MHz, $CDCl_3$): δ 5.67-5.61 (m, 2H), 5.25 (dd, *J* = 15.5, 8.5 Hz, 1H), 3.77 (s, 1H), 3.53-3.43 (m, 3H), 3.35-3.28 (m, 4H), 3.17-3.10 (m, 1H), 2.93-2.88 (m, 1H), 2.79 (s, 1H), 2.52 (t, *J* = 8.5 Hz, 1H), 2.36 (d, *J* = 13.5 Hz, 1H), 2.08 (q, *J* = 10.5 Hz, 1H), 1.87-1.81 (m, 4H), 1.67-1.60 (m, 2H), 0.97 (d, *J* = 7.0 Hz, 3H).

LC-MS: *m/z* = 316.2[(M^+-1)] at RT 3.52 (97.76% purity).

Scheme 15:



(((3S,4S,5R,Z)-8-azido-3-methoxy-5,7-dimethylocta-1,6-dien-4-yl) oxy)(tert-butyl) dimethylsilane (**50**):

To a stirred solution of **Int-13** (500 mg, 1.59 mmol) in PhMe (5 mL), DBU (0.35 mL, 2.38 mmol) was added followed by DPPA (0.52 mL, 2.38 mmol) and stirred at RT for 3 h. After consumption of the starting material (by TLC), the reaction was quenched with saturated NH_4Cl solution and extracted with Et_2O (2 x 15 mL). The combined organic extracts were dried over anhydrous sodium sulphate, filtered and concentrated under vacuum to give the crude material which was purified by silica gel column chromatography (EtOAc/Hexane 3:97) to furnish compound **50** (435.4 mg, 81%) as colorless liquid.

TLC: 10% EtOAc/Hexane (R_f: 0.6)

^{1}H NMR (500MHz, $CDCl_3$): δ 5.67-5.60 (m, 1H), 5.51 (d, *J* = 10.5 Hz, 1H), 5.29 (dd, *J* = 16, 10.5 Hz, 2H), 3.81 (d, *J* = 13.0 Hz, 1H), 3.65 (d, *J* = 13.0 Hz, 1H), 3.46-3.37 (m, 2H), 3.20 (s, 3H), 2.56-2.53 (m, 1H), 1.77 (s, 3H), 0.91 (s, 12H), 0.04 (d, *J* = 7.5 Hz, 6H).

N-((4R, 5S, 6S, Z)-5-((tert-butyldimethylsilyl) oxy)-6-methoxy-2,4-dimethylocta-2,7-dien-1-yl) hex-5-enamide (**72**):

To a stirred solution of compound **50** (435.4 mg, 1.28 mmol) in THF (15 mL), water (0.1 mL, 6.43 mmol) was added followed by PPh_3 (590 mg, 2.25 mmol). The reaction was heated at

70°C for 4 h and concentrated under reduced pressure to provide the crude compound **51** which was dissolved in CH_2Cl_2 (7 mL) and DIPEA (0.89 mL, 5.15 mmol), EDC.HCl (493.2 mg, 2.57 mmol) followed by hex-5-enoic acid (0.32 mL, 2.57 mmol) were added and stirred at RT for 2h. The volatiles were evaporated under reduced pressure to give the crude material which was purified by silica gel column chromatography (EtOAc/Hexane 1:9) to provide compound **72** (380.5 mg, 72.5%) as a colorless liquid.

TLC: 20% EtOAc/Hexane (R_f: 0.5)

^{1}H NMR (500MHz, $CDCl_3$): δ 5.79-5.65 (m, 2H), 5.38-5.24 (m, 4H), 4.99 (dd, *J* = 23, 17.5 Hz, 2H), 3.84 (q, *J* = 5.5 Hz, 2H), 3.47-3.41 (m, 2H), 3.22 (s, 3H), 2.59 (br t, 1H), 2.17 (t, *J* = 7.5 Hz, 2H), 2.10 (q, *J* = 6.5 Hz, 2H), 1.75 (t, *J* = 7.5 Hz, 2H), 1.69 (s, 3H), 1.00 (s, 12H), 0.05 (d, *J* = 16.0 Hz, 6H).

Mass (ESI): 410.5 (M^++1).

(6E, 8S, 9S, 10R, 11Z)-9-((tert-butyldimethylsilyl) oxy)-8-methoxy-10,12-dimethylazacyclotrideca-6,11-dien-2-one (**73**):

To a stirred solution of compound **72** (380.5 mg, 0.94 mmol) in PhMe (2 L) heated at 100°C, Grubbs-II catalyst (163.7 mg, 0.19 mmol) was added under argon atmosphere and stirred for 30 min. The reaction mixture was concentrated under reduced pressure and the crude material obtained was purified by silica gel column chromatography (EtOAc/Hexane 3:17) to afford compound **73** (245 mg, 68.4%) as brown colored solid.

TLC: 20% EtOAc/Hexane (R_f: 0.2)

^{1}H NMR (500MHz, $CDCl_3$): δ 5.60-5.56 (m, 1H), 5.46 (d, *J* = 10.5 Hz, 1H), 5.34 (dd, *J* = 15.5, 5.5 Hz, 1H), 5.22 (br s, 1H), 4.16 (dd, *J* = 14, 6.0 Hz, 1H), 3.40 (t, *J* = 6.5 Hz, 1H), 3.28-3.25 (m, 2H), 3.22 (s, 3H), 2.47 (t, *J* = 6.5 Hz, 1H), 2.35-2.16 (m, 4H), 2.03 (d, *J* = 11.5 Hz, 2H), 1.76 (s, 3H), 0.91 (s, 12H), 0.06 (d, *J* = 8.5 Hz, 6H).

Mass (ESI): 382.4 (M^++1).

(6E,8S,9S,10R,11Z)-9-hydroxy-8-methoxy-10,12-dimethylazacyclotrideca-6,11-dien-2-one (**THC-064**):

To a stirred solution of compound **73** (240 mg, 0.63 mmol) in THF (2 mL), cooled to 0°C, TBAF (1.0M in THF, 0.26 mL, 0.94 mmol) was added drop-wise. The reaction mixture was slowly brought to RT and stirred for 16h. The volatiles were removed under reduced pressure to

give the crude material which was purified by silica gel column chromatography (EtOAc/Hexane 4:1) to furnish **THC-064** (83 mg, 49.4%) as an off-white solid.

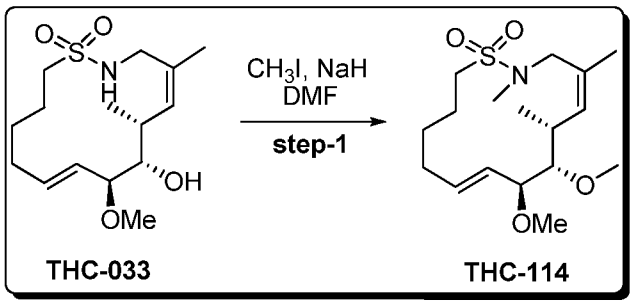
TLC: 50% EtOAc/Hexane (R_f: 0.2)

^{1}H NMR (500MHz, $CDCl_3$): δ 5.65-5.58 (m, 2H), 5.23 (dd, *J* = 15.5, 6.0 Hz, 1H), 5.13 (d, *J* = 7.0 Hz, 1H), 4.47 (q, *J* = 8.5 Hz, 1H), 3.36 (t, *J* = 9.0 Hz, 1H), 3.30 (s, 3H), 3.22 (d, *J* = 9.5 Hz, 1H), 3.04 (d, *J* = 14.0 Hz, 1H), 2.84 (s, 1H), 2.42-2.33 (m, 3H), 2.16-2.03 (m, 2H), 1.90-1.84 (m, 1H), 1.78 (s, 3H), 1.65 (t, *J* = 7.0 Hz, 1H), 0.94 (d, *J* = 7.5 Hz, 3H).

Mass (ESI): 268.8 (M^++1).

LC-MS: *m/z* = 268.5[(M^++1)] at RT 2.79 (99.79% purity).

Scheme 16:



(4Z, 6R, 7S, 8S, 9E)-7, 8-dimethoxy-2,4,6-trimethyl-1-thia-2-azacyclotetradeca-4,9-diene 1,1-dioxide (**THC-114**):

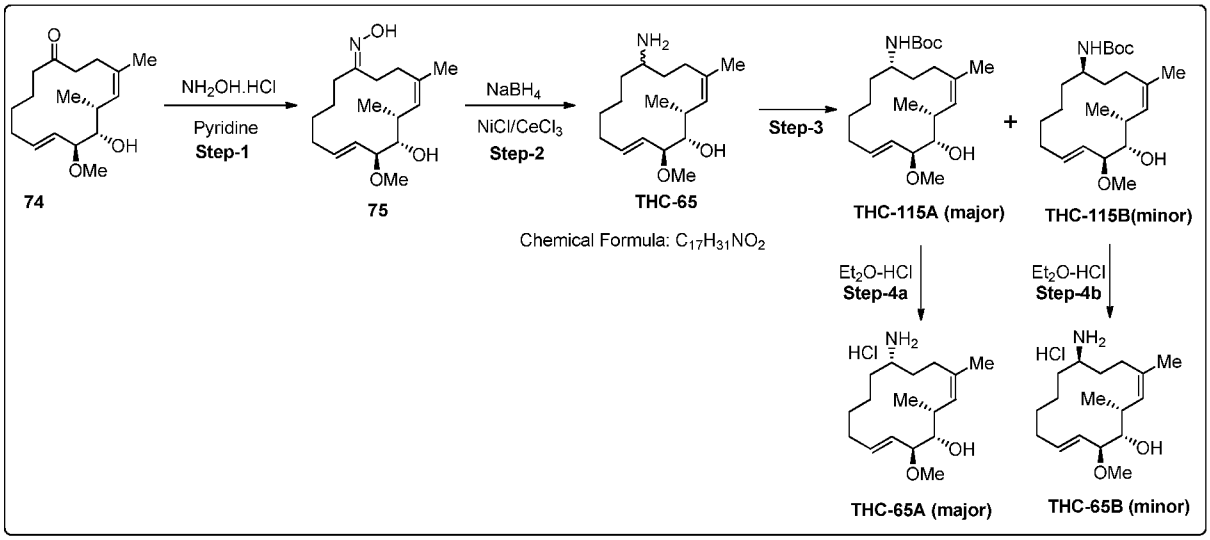
To a stirred solution of **THC-033** (12 mg, 0.037 mmol) in DMF (0.5 mL) at 0°C, NaH (4.3 mg, 0.113 mmol, 60% dispersion in mineral oil) was added, stirred for 15 min and MeI (0.007 mL, 0.113 mmol) was added slowly. The reaction was warmed to RT and continued for another 30 min and quenched with ice-water and extracted with EtOAc (2 x 10 mL). The combined organic extracts were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give the crude material which was purified twice by silica gel column chromatography (EtOAc/Hexane 1:9) to provide **THC-114** (10.12 mg, 77.54%).

TLC: 30% EtOAc/Hexane (R_f: 0.6)

^{1}H NMR (500MHz, $CDCl_3$): δ 5.65-5.58 (m, 2H), 5.28 (dd, *J* = 15.5, 8.0 Hz, 1H), 3.77 (d, *J* = 11.5 Hz, 1H), 3.64-3.57 (m, 2H), 3.53 (s, 3H), 3.29 (s, 3H), 3.23-3.17 (m, 1H), 2.94 (m, 2H), 2.71 (s, 3H), 2.59 (t, *J* = 7.5 Hz, 1H), 2.35-2.27 (m, 2H), 2.12-2.08 (m, 1H), 1.86 (br s, 1H), 1.78 (s, 3H), 1.65-1.54 (m, 2H), 0.93 (d, *J* = 7.0 Hz, 3H).

Mass (ESI): 346 (M^++1).

Scheme 17:



(1Z,4Z,6R,7S,8S,9E)-7-hydroxy-8-methoxy-4,6-dimethylcyclotetradeca-4,9-dienone oxime (**75**):

To a stirred solution of **74** (50.1 mg, 0.18 mmol) in pyridine (3.0 mL), $NH_2OH.HCl$ (0.120 g, 1.78 mmol) was added and the reaction mixture was heated to 45°C for 5 h. The reaction was concentrated under reduced pressure and the crude material was purified by silica gel column chromatography (EtOAc/Hexane 3:17) to afford compound **75** (21.1 mg, 40%) as pale yellow syrup.

TLC: 20% EtOAc/Hexane (R_f: 0.35)

^{1}H NMR (500 MHz, $CDCl_3$): δ 5.70-5.64 (m, 1H), 5.36 (d, *J* = 9.5 Hz, 1H), 5.28 (dd, *J* = 8.0, 13.0 Hz, 1H), 3.48 (t, *J* = 8.5 Hz, 1H), 3.38-3.35 (m, 1H), 3.32 (s, 3H), 2.83 (br s, 1H), 2.60 (m, 1H), 2.42-2.37 (m, 2H), 2.28-2.05 (m, 4H), 1.76 (s, 2H), 1.73 (s, 2H), 1.60 (br s, 2H), 1.53 (s, 3H), 0.96 (d, *J* = 6.5 Hz, 3H).

Mass (ESI): 296 [M^++1]

(1S,2R 3Z,12E,14S)-7-amino-14-methoxy-2,4-dimethylcyclotetradeca-3,12-dienol (**THC-65**):

A solution of compound **75** (53.2 mg, 0.180 mmol) in MeOH (1.8 mL), cooled to -78°C, $NiCl_2.6H_2O$ (85.7 mg, 0.36 mmol) was added followed by $NaBH_4$ (61.6 mg, 1.62 mmol). The resulting reaction mixture was allowed to warm to -30 °C and stirred for further 6 h. The reaction

was quenched with few drops of water. The reaction mixture was concentrated under reduced pressure to give the crude **THC-65** (37.1 mg, 74%) as a mixture of diastereomers which was carried forward without any further purification.

TLC: 20% EtOAc/Hexane (R_f: 0.01); 10% $MHCl_3$ (R_f: 0.1)

LC-MS: *m/z* = 282 [(M^++1)] at RT 6.71 (72.02% purity) and 282 [(M^++1)] at RT 6.531 (25.24% purity)

tert-Butyl ((1S, 4Z, 6R, 7S, 8S, 9E)-7-hydroxy-8-methoxy-4,6-dimethylcyclotetradeca-4,9-dien-1-yl) carbamate (**THC-115**):

To a stirred solution of the diastereomeric mixture of **THC-65** (66.1 g, 0.24 mmol) in CH_2Cl_2 (2.0 mL), cooled to 0 °C, Et_3N (65 µL, 0.47 mmol) followed by $(Boc)_2O$ (77µL, 0.35 mmol) were added. The reaction mixture warmed to RT and stirred for 16 h. The reaction was diluted with CH_2Cl_2 (20 mL), the organic phase was washed with 10% citric acid (1 x 5 mL), water, brine and dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to provide the crude material which was purified by silica gel column chromatography (EtOAc/Hexane 1:9) to afford **THC-115A & THC-115B** (73.1 g, 82%) as a mixture of diastereomers. The mixture of diastereomers was separated by chiral prep HPLC.

TLC: 20% EtOAc/Hexane (R_f: 0.3)

^{1}H NMR (500 MHz, $CDCl_3$): δ 5.62 (m, 1H), 5.30 (br s, 1H), 5.25 (s, 1H), 5.20 (m, 1H), 4.25 (m, 1H),

3.61 (m, 1H), 3.41 (m, 1H), 3.39 (m, 1H), 3.30 s, 3H), 2.74 (m, 1H), 2.56 (m, 1H), 2.35 (m, 1H), 2.15 (m, 1H), 1.91 (m, 1H), 1.87 (m, 1H), 1.71 (s, 3H), 1.45 (m, 3H), 1.42 (s, 9H), 1.40-1.21 (m, 3H), 0.9 (d, *J* = 6.5 Hz, 3H).

LC-MS: *m/z* = 382 [(M^++1)] at RT 4.86 (93.82% purity).

HPLC (ELSD): 43% & 39% (mixture of diastereomers)

Chiral preparative HPLC method:

The diastereomers of **THC-115** (73.1 g) were separated by normal-phase preparative high performance liquid chromatography (Chiralpak IA, 250 x 20 mm, 5µ; using (A) n-hexane – (B) ethanol (A:B : 98:2) as a mobile phase; Flow rate: 15 mL/min) to obtain **THC-115A** (28 mg) and **THC-115B** (19 mg).

Analytical data for THC-115A:

^{1}H NMR (500 MHz, $CDCl_3$): δ 5.65-5.59 (m, 1H), 5.33 (d, *J* = 10.0 Hz, 1H), 5.24-5.19 (m, 1H), 4.49 (m, 1H), 3.65 (m, 1H), 3.44 (t, *J* = 9.0 Hz, 1H), 3.37 (t, *J* = 7.0 Hz, 1H), 3.29 (s, 3H), 2.74 (s, 1H), 2.54-2.51 (m, 1H), 2.26 (m, 1H), 2.10 (m, 1H), 1.92-1.86 (m, 1H), 1.80-1.74 (m, 1H), 1.69 (s, 3H), 1.58 (m, 1H), 1.38 (m, 1H), 1.40 (s, 12H), 1.36-1.31 (m, 2H), 1.20-1.18 (m, 1H), 0.9 (d, *J* = 6.5 Hz, 3H).

Mass (ESI): 404 [M^++Na]

LC-MS: *m/z* = 404 [M^++Na]; 250 [(M^+-Boc-OMe)] at RT 4.23 (99.12% purity).

Analytical data for THC-115B:

^{1}H NMR (500MHz, $CDCl_3$): δ 5.65-5.60 (m, 1H), 5.32 (m, 2H), 5.23-5.18 (m, 1H), 4.47 (br s, 1H), 3.60 (br s 1H), 3.34 (m, 1H), 3.37 (m, 1H), 3.30 (s, 3H), 2.74 (s, 1H), 2.50 (m, 1H), 2.27 (m, 1H), 2.04 (m, 1H), 1.97 (m, 1H), 1.74 (m, 1H), 1.69 (s, 3H), 1.51 (m, 2H), 1.44 (br s, 12H), 1.35 (m, 1H), 1.18 (m, 1H), 0.9 (d, *J* =6.9 Hz, 3H).

Mass (ESI): 404 [M^++Na]

LC-MS: *m/z* = 382 [(M^++1)] at RT 4.18 (98.04% purity).

(1S,2R,3Z,7S,12E,14S)-7-amino-14-methoxy-2,4-dimethylcyclotetradeca-3,12-dienol (**THC-65A**):

To a stirred solution of **THC-115A** (17 mg, 0.04 mmol) in CH_2Cl_2 (1 mL), cooled to 0 °C, Et_2O-HCl (0.5 mL) was added. The reaction mixture slowly warmed to RT and stirred for 16 h and concentrated under reduced pressure to afford **THC-65A** (11.6 mg, 83%) as low melting white solid.

TLC: 20% EtOAc/Hexane (R_f: 0.00)

^{1}H NMR (500MHz, CD_3OD): δ 5.71-5.65 (m, 1H), 5.36 (d, *J* = 9.5 Hz, 1H), 5.29-5.24 (m, 1H), 3.50-3.46 (m, 1H), 3.30-3.21 (m, 4H), 2.58-2.55 (m, 1H), 2.30-3.27 (m, 1H), 2.17-2.13 (m, 1H), 2.09-2.02 (m, 1H), 1.87-1.81 (m, 2H), 1.70 (s, 3H), 1.67 (m, 1H), 1.59-1.27 (m, 5H), 1.30-1.27 (m, 2H), 0.91 (d, *J* = 6.5 Hz, 3H).

LC-MS: *m/z* = 282.4 [(M^++1)] at RT 0.073 (90.15% purity).

(1S,2R,3Z,7R,12E,14S)-7-amino-14-methoxy-2,4-dimethylcyclotetradeca-3,12-dienol (**THC-65B**):

To a stirred solution of **THC-115B** (14 mg, 0.036 mmol) in CH_2Cl_2 (1 mL), cooled to 0°C, Et_2O-HCl (1 mL) was added. The reaction mixture warmed to RT and stirred for 16 h, while TLC examination revealed complete consumption of the starting material. The reaction mixture was concentrated under reduced pressure to afford **THC-65B** (9.1 mg, 80%) as amorphous white solid.

TLC: 20% EtOAc/Hexane (R_f: 0.00)

^{1}H NMR (500MHz, CD_3OD): δ 5.69-5.66 (m, 1H), 5.35 (d, *J* = 9.5 Hz, 1H), 5.29-5.25 (m, 1H), 3.54-3.46 (m, 1H), 3.30-3.27 (m, 4H), 2.30-2.09 (m, 4H), 1.85 (m, 3H), 1.78-1.71 (m, 3H), 1.64 (m, 3H), 1.63 (m, 2H), 1.46-1.42 (m, 2H), 0.91 (d, *J* = 6.5 Hz, 3H).

LC-MS: *m/z* = 282.6 [(M^++1)] at RT 3.053 (89.75% purity).

Example 2. Use of fascin inhibitor THC-010 for treatment of glioma in an orthotopic glioma model.

Fascin is highly expressed in glioma cells where it plays a major role in migration and invasion of this cancer type. Glioma can be modeled in orthotopic tumor models in mice or rats, with rats being the preferred host due to the greater ease of injection of cancer cells into the brain. In this case, either rat glioma cells such as 9L cells are introduced into immune-competent rats or human glioma cells such as U-87 MG, U251, SNB19 or LN-229, are inoculated into immune-deficient rats such as nude rats. In addition, nerve models have utilized glioma tumor-initiating cells or glioma stem cells taken from human glioma patients. The glioma cancer cells are injected into the brain by stereotactic injection. In one commonly used model, rat 9L glioma cells are injected into the brains of normal Fisher 344 rats by stereotactic intracranial injection. Alternatively, the 9L tumors can be grown subcutaneously in the flanks of mice and hen tumor chunks can be implanted into the brain in a surgical procedure. The glioma cells grow as a tumor mass in the brain parenchyma and invade into distant sites within the brain. Drugs and controls can be administered at the time of cancer cell injection or various numbers of days thereafter. Drugs can be administered by intracranial injection, perhaps in polymer formulation or, preferentially by oral administration of drugs that cross the blood-brain barrier. In the case of the fascin inhibitor THC-10, both high oral bioavailability (Table 2; %F = 97.1) and excellent distribution to the brain tissue was observed in PK studies in rats (Table 3).

Table 2. Rat single-dose PK study of the fascin inhibitor THC-10

	iv (2mg/kg dose)				oral (20mg/kg dose)			
Compound Number	**T1/2 (h)**	**Cl (ml/min/kg)**	**Vss (L/kg)**	**AUC(last) (h-ng/ml)**	**Cmax (ng/ml)**	**Tmax (h)**	**AUC(last) (h-ng/ml)**	**%F**
THC-10	2.54	18.6	3.12	1808	5358	0.5	17547	97.1

In this rat PK study:

- THC-10 exhibited low to moderate systemic clearance. The value of 18.6 mL/min/kg for CL in the rat is 33.8 % of hepatic blood flow (55 mL/min/kg in rat).
- The volume of distribution at steady state for THC-10 was 4.5-fold higher than the total body water in rat (0.7 L/kg), indicating extensive extravascular distribution.
- Following intravenous administration, the plasma concentrations of THC-10 declined bi-exponentially with terminal elimination plasma half-life of 2.54 hr.
- Following oral administration, THC-10 exhibited rapid absorption as maximum plasma concentrations were observed from the first time point (0.25 hr) to the 3rd time point (1 h) with a mean Tmax at 0.5 hr.
- The absolute bioavailability of THC-10 was 97.1%.

Table 3. Rat brain tissue concentration of THC-10

	iv (2mg/kg)			oral (20mg/kg)		
Compound number	**Brain Tissue (ng/g)**	**Plasma (1h) (ng/mL)**	**B/P ratio**	**Brain Tissue (ng/g)**	**Plasma (1h) (ng/mL)**	**B/P ratio**
THC-010	414	481	0.86	5637	4935	1.14

The levels of THC-10 in the brain tissue were roughly equivalent to the plasma levels.

In glioma models, tumor size can be monitored by imaging or measured at sacrifice and dissection of the brain to determine the effect of drug treatment on tumor size and invasion within the brain. Animal behavior, body weight and survival also would be evaluated. Published studies indicate that treatment with angiogenesis inhibitors such as antibody inhibitors of VEGF or small molecule inhibitors of VEGFR can induce increased tumor invasion and metastasis (Paez-Ribes *et al. Cancer Cell* 15:220, 2009; Ebos *et al. Cancer Cell* 15:232, 2009). One promising therapeutic use of a fascin inhibitor is in combination with an angiogenesis inhibitor or treatment soon after treatment with an angiogenesis inhibitor to block invasion and metastasis. This may be particularly beneficial in the treatment of glioma, a setting in which the angiogenesis inhibitor bevacizumab is widely used. Clinical findings suggest that glioma patients treated with the bevacizumab display greater cancer invasion to distant parts of the brain. Combination treatment with a fascin inhibitor could increase the duration of clinical benefit of treatment with angiogenesis inhibitors. This drug combination could be modeled in the orthotopic glioma model. A small molecule angiogenesis inhibitor such as sunitinib (Sutent) could be used. A study design is shown in Table 4. In this model, rat 9L glioma cells were implanted intracranially into the brains of immune-competent rats in a surgical procedure. After recovery from anesthesia, rat received their corresponding drugs by mouth. They then received the same treatments daily by mouth until the last animal died on day 24. In this case, the compounds were formulated in 0.5% methylcellulose (MC). The control group received 0.5% MC without any compounds. Dosing was done orally once per day starting at the time at which the tumor chunks were surgically implanted.

Table 4. Rat glioma model study design

Group #	Treatment	Dose	Dose regimen	Rats/group
1	Control (0.5% MC)	-	1X/day from day 0	8
2	THC-010	30 mg/kg, p.o.	1X/day from day 0	8
3	Sutent	25 mg/kg), p.o.	1X/day from day 0	8
4	THC-010 + Sutent	30 mg/kg + 25 mg/kg	1X/day from day 0	8

The implantation of 9L glioma tumor chunks into the brain is a highly aggressive glioma model. Despite the highly aggressive nature of this model, both THC-010 and Sutent showed evidence of single-agent activity, with an increase in survival time being seen (**Figure 1**). The combination appeared to be superior to either single-agent alone. All rats in the control group succumbed to the tumor rapidly at day 14. Rats in the Sutent plus THC-010 combination group appeared most healthy throughout the experiment and lived the longest, with the last one dying at day 24 ($p = 0.0006$; Figure 1). None of the drug treatments showed any clinical signs of toxicity such as body weight loss or behavioral changes. All of the data, in comparison to the control group, were statistically significant ($p < 0.05$).

Incorporation by Reference

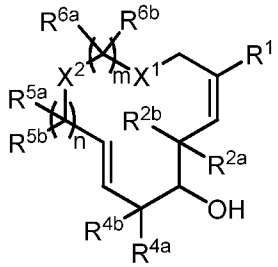
All publications and patents mentioned herein are hereby incorporated by reference in their entirety as if each individual publication or patent was specifically and individually indicated to be incorporated by reference.

Equivalents

Those skilled in the art will recognize, or be able to ascertain using no more than routine experimentation, many equivalents to the specific embodiments of the invention described herein. Such equivalents are intended to be encompassed by the following claims.

We claim:

1. A compound of Formula (I):



Formula (I),

wherein

n and m are each independently 0, 1, 2, 3 or 4;

X^1 is –O-, -NR^7-, -$CR^{9a}R^{9b}$-, -C(O)-NR^7-, -NR^7-C(O)-, -NR^8-$S(O)_2$- or -$S(O)_2$-NR^8-;

X^2 is –NR^8-,-$CR^{9a}R^{9b}$-, -S-, -O-, -S(O)-, -$S(O)_2$-, -C(O)-NR^8-, -NR^8-C(O)-, -NR^8-$S(O)_2$- or -$S(O)_2$-NR^8-;

R^1 is halo, C_{1-6} alkyl or C_{1-6} alkoxy;

R^{2a} and R^{2b} are each independently hydrogen or C_{1-6} alkyl;

each R^{4a} and R^{4b} are independently hydrogen, hydroxyl, C_{1-6} alkyl or C_{1-6} alkoxy;

each R^{5a} and R^{5b} are independently hydrogen, halo, amino, amido, C_{1-6} alkyl or C_{1-6} alkoxy;

each R^{6a} and R^{6b} are independently hydrogen, halo, amino, amido, C_{1-6} alkyl or C_{1-6} alkoxy;

R^7 is hydrogen, C_{1-6} alkyl, acyl, aryl or aralkyl;

R^8 is hydrogen, C_{1-6} alkyl, acyl, aryl or aralkyl; and

R^{9a} and R^{9b} are each independently hydrogen, C_{1-6} alkyl, C_{1-6} alkoxy, halo, amino, amido, aryl or heteroaryl,

wherein when X^1 is –O-, X^2 is not –$CR^{9a}R^{9b}$-.

2. The compound of claim 1, wherein R^1 is C_{1-6} alkyl.

3. The compound of claim 1, wherein one of R^{2a} and R^{2b} is hydrogen and the other is C_{1-6} alkyl.

4. The compound of claim 1, wherein one of R^{4a} and R^{4b} is hydrogen and the other is C_{1-6} alkyl.

5. The compound of claim 1, wherein X^1 is –O-, -NR^7-, -C(O)-NR^7-, -NR^7-C(O)- or -$S(O)_2$-NR^7-.

6. The compound of claim 5, wherein R^7 is hydrogen, C_{1-6} alkyl or acyl.

7. The compound of claim 1, wherein X^1 is –$CR^{9a}R^{9b}$-.

8. The compound of claim 7, wherein both R^{9a} and R^{9b} are hydrogen.

9. The compound of claim 7, wherein one of R^{9a} and R^{9b} is hydrogen and the other is amido.

10. The compound of claim 1, wherein X^2 is –O-, -S-, -S(O)-, -$S(O)_2$-, -NR^8-C(O)-, -NR^8-$S(O)_2$-, -$S(O)_2$-NR^8- or –NR^8-.

11. The compound of claim 10, wherein R^8 is hydrogen, C_{1-6} alkyl or acyl.

12. The compound of claim 1, wherein X^2 is –$CR^{9a}R^{9b}$-.

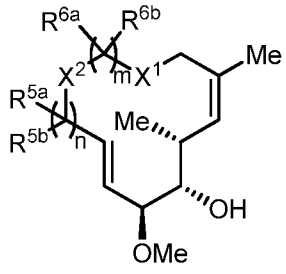
13. The compound of claim 12, wherein R^{9a} and R^{9b} are both hydrogen or halo.

14. The compound of claim 12, wherein one or R^{9a} and R^{9b} is amino and the other is hydrogen.

15. The compound of claim 1, wherein R^{5a} and R^{5b} are each independently selected from hydrogen or halo.

16. The compound of claim 1, wherein R^{6a} and R^{6b} are each independently selected from hydrogen or halo.

17. The compound of claim 1, wherein the compound is a compound of formula (Ia):



(Ia).

18. The compound of claim 1, wherein the compound is a compound of Table 1.

19. A pharmaceutical composition comprising a compound of claim 1 or 2.

20. A method of treating cancer in a subject, the method comprising administering a compound of claim 1 or 2 or a composition of claim 3.

21. Use of a compound of claim 1 or 2 or a composition of claim 3 in the manufacture of a medicament for the treatment of cancer.

22. Use of a compound of claim 1 or 2 or a composition of claim 3 for the treatment of cancer.

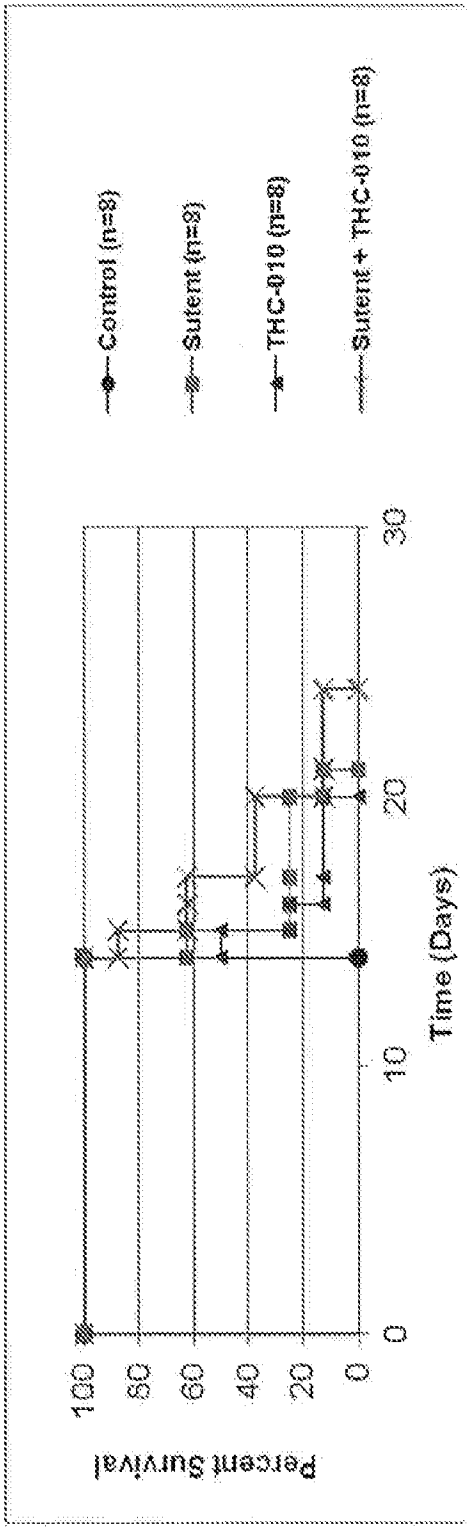

Control (n=8)
Sutent (n=8)
THC-010 (n=8)
Sutent + THC-010 (n=8)
Percent Survival
100
80
60
40
20
0
0
10
20
30
Time (Days)

Figure 1