

WITHAFERIN A ANALOG AND METHOD FOR TREATMENT USING THE SAME

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims priority and benefit of U.S. Provisional Patent Application No. 63/587,721 filed on October 03, 2023. The contents of this application are incorporated herein by reference in their entirety for all purposes.

TECHNICAL FIELD

[0002] The present disclosure relates generally to compounds, compositions, and methods for treating a variety of diseases and conditions, and more specifically, for treating inflammatory-related diseases.

BACKGROUND

[0003] Inflammation plays a crucial role in the immune response to injury and infection, but excessive or chronic inflammation can be detrimental, leading to a variety of diseases. Inflammatory bowel diseases (IBDs), such as ulcerative colitis and Crohn's disease, are characterized by chronic inflammation in the gastrointestinal tract and can lead to debilitating symptoms and complications, including severe pain, weight loss, and malnutrition. In addition, alcoholic hepatitis is a significant inflammatory condition resulting from prolonged excessive alcohol intake. Its symptoms can range from mild, including jaundice and malaise, to severe, leading to liver failure and potential death. The current treatment regimens for alcoholic hepatitis and other liver diseases are limited and often not wholly effective, necessitating the exploration for more targeted and potent therapeutic agents.

[0004] TNF- α , a pro-inflammatory cytokine, has been extensively identified as a crucial player in the pathogenesis of IBD. Overproduction of TNF- α results in enhanced inflammatory responses, tissue damage, and promotes the chronicity of intestinal inflammation observed in IBD patients. Consequently, therapies aimed at neutralizing TNF- α , such as monoclonal antibodies, have demonstrated efficacy in the treatment of IBD. However, despite their therapeutic benefits, anti-TNF- α therapies can also lead to potential adverse effects, such as infections, malignancies, and the development of anti-drug antibodies. Furthermore, a significant subset of IBD patients are non-responsive or lose their responsiveness to anti-TNF-

α treatments over time. Therefore, there exists a dire need for alternative or complementary strategies to target the TNF- α pathway.

[0005] The NLR Family Pyrin Domain Containing 3 (NLRP3) inflammasome, a multiprotein complex, has been identified as a key player in the initiation and progression of inflammation. It is involved in the activation of inflammatory responses, including the release of pro-inflammatory cytokines like IL-1 β and IL-18, which further aggravate liver damage. It has been shown that dysregulated NLRP3 inflammasome activation is associated with the pathogenesis of both IBD and alcoholic hepatitis, thus presenting an appealing target for therapeutic intervention. Current IBD treatments primarily focus on reducing inflammation and maintaining remission but do not directly target the pathophysiological processes underlying the disease.

[0006] HSP90, a heat shock protein, is a molecular chaperone involved in the folding and function of various proteins. HSP90 operates as a homodimer, and each monomer consists of three distinct domains: an N-terminal domain (N-domain), a middle domain, and a C-terminal domain. Each of these domains has specific functions and characteristics. The N-domain is known for its ATP/ADP-binding pocket, and is the main site for most of the HSP90 inhibitors known today. Examples of HSP90 inhibitors that target the N-domain of HSP90 include Geldanamycin and its derivative 17-AAG (Tanespimycin), Ganetespib (STA-9090), and PU-H71.

[0007] Interestingly, HSP90 has been found to regulate the stability of both TNF- α and the NLRP3 inflammasome. Specifically, the C-terminal domain of HSP90 binds to TNF- α and NLRP3, aiding in its stability and proper function. However, uncontrolled activation of TNF- α or NLRP3, often due to constant interaction with HSP90, can lead to persistent inflammation seen in diseases like IBD and alcoholic hepatitis.

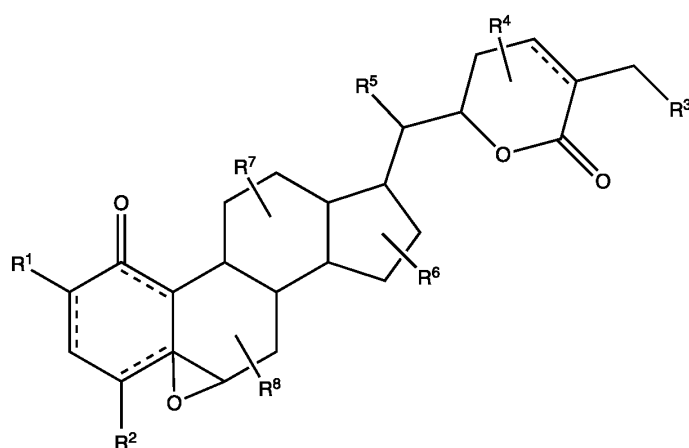
[0008] Accordingly, there is an ongoing need in the art for compounds, compositions and methods for treating inflammatory-related diseases, such as IBD and alcoholic hepatitis, along with a variety of other diseases and conditions.

BRIEF SUMMARY

[0009] Embodiments described herein relate to compounds, compositions, and methods for treating, reducing, or ameliorating a variety of diseases, disorders, or conditions in a subject in

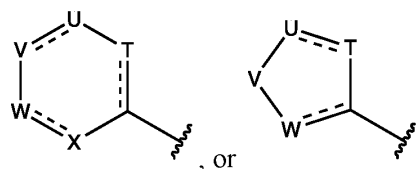
need thereof. Even though inflammation is a host's protective reaction to infections, it can be harmful and destructive in excess. In various circumstances, inflammation is regarded as a disease-modifying mechanism, prompting substantial efforts to address detrimental inflammatory reactions observed in conditions such as inflammatory bowel disease (IBD), Crohn's disease, colorectal cancer, alcoholic hepatitis, and other diseases.

[0010] A compound of Formula (I) is provided herein. The compound of Formula (I) is as follows:



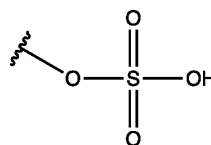
(I), or a pharmaceutically

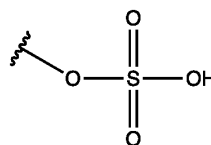
acceptable salt thereof, wherein:



R^1 is hydrogen, $-NR^9R^{10}$, $-COOR^9$, $-CN$,

R^2 is hydrogen, halogen, $-OR^9$, $-SR^9$, $-NR^9R^{10}$, $-COOR^9$, $-COHR^9R^{10}$, $-CR^9R^{10}R^{11}$, $-CN$, $-N_3$, C_1 - C_6 alkyl, C_1 - C_6 haloalkyl, C_2 - C_6 alkenyl, C_2 - C_6 alkynyl, C_1 - C_6 alkoxy, aryl,



aralkyl, heteroaryl, cycloaliphatic ring, heterocyclyl, or , wherein the C_1 - C_6 alkyl, the aryl, the heteroaryl, cycloaliphatic ring, or heterocyclyl are unsubstituted or substituted with one or more R^{12} ;

R^3 is hydrogen, halogen, $-OR^9$, $-SR^9$, $-NR^9R^{10}$, $-COOR^9$, $-COHR^9R^{10}$, $-CR^9R^{10}R^{11}$, $-CN$, $-N_3$, C_1 - C_6 alkyl, C_1 - C_6 haloalkyl, C_2 - C_6 alkenyl, C_2 - C_6 alkynyl, C_1 - C_6 alkoxy, aryl, aralkyl, heteroaryl, cycloaliphatic ring, heterocyclyl, $-(NR^9R^{10}R^{11})^+$, or $-OC(=O)NH-(C_2-C_6$

alkynyl), wherein the C₁-C₆ alkyl, the aryl, the heteroaryl, cycloaliphatic ring, or heterocyclyl are unsubstituted or substituted with one or more R¹²;

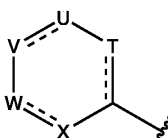
T, U, V, W, and X are each, independently, CH, CR¹², sulfur, nitrogen, NH, NR¹², or N⁺-O⁻;

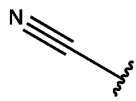
R⁴, R⁵, R⁶, R⁷, R⁸, R⁹, R¹⁰, and R¹¹ are each, independently, hydrogen, deuterium, halogen, or a C₁-C₆ unsubstituted or substituted alkyl; and

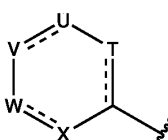
each R¹² is, independently, deuterium, halogen, =O, -OR⁹, -SR⁹, -NR⁹R¹⁰, -COOR⁹, -COHR⁹R¹⁰, -CR⁹R¹⁰R¹¹, -CN, -N₃, C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₁-C₆ alkoxy, aryl, aralkyl, heteroaryl, cycloaliphatic ring, heterocyclyl, or -O-(heterocyclyl);

with the proviso:

(1) when R¹ is hydrogen, then R² is a halogen;

(2) when R¹ is  and each of T, U, V, W, and X is CH or CR¹²,

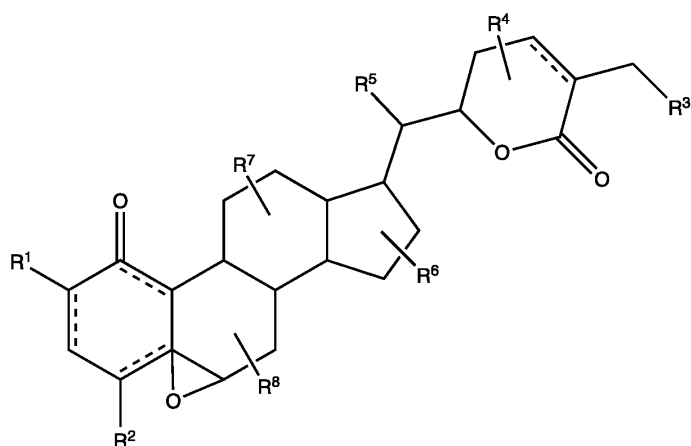
then only one of T, U, V, W, and X is CR¹², wherein R¹² is  or -OCH₃, and the remaining T, U, V, W, and X are CH; and

(3) when R¹ is , T and X are CH, one of W or U is nitrogen, and the other of W or U is CH, then V is not C(-OCH₃).

[0011] These compounds and pharmaceutically acceptable compositions are useful for treating or lessening the severity of a variety of diseases, disorders, or conditions, including, but not limited to, inflammatory diseases, such as Inflammatory Bowel Disease (IBD), Crohn's Disease (CD), and alcoholic hepatitis; and cancer, such as colorectal cancer. In various embodiments, the compounds of Formula (I) and pharmaceutically acceptable compositions are inhibitors, or modulators of one or more of the following therapeutic targets: heat shock protein 90 (HSP90), NLR family pyrin domain containing 3 (NLRP3) inflammasome, tumor necrosis factor alpha (TNF- α), and transforming growth factor beta (TGF- β), and thus are

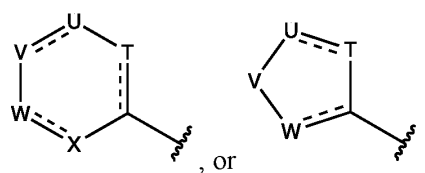
useful for treating or lessening the severity of the variety of diseases, disorders, or conditions described herein.

[0012] Also provided herein is a method of treating, ameliorating, or preventing an NLR Family Pyrin Domain Containing 3 (NLRP3) inflammasome-mediated condition or disease, or for comprising administering a compound of Formula (I):



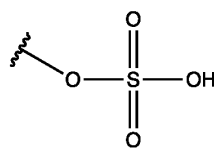
(I), or a pharmaceutically

acceptable salt thereof, wherein:



R^1 is hydrogen, $-NR^9R^{10}$, $-COOR^9$, $-CN$,

R^2 is hydrogen, halogen, $-OR^9$, $-SR^9$, $-NR^9R^{10}$, $-COOR^9$, $-COHR^9R^{10}$, $-CR^9R^{10}R^{11}$, $-CN$, $-N_3$, C_1 - C_6 alkyl, C_1 - C_6 haloalkyl, C_2 - C_6 alkenyl, C_2 - C_6 alkynyl, C_1 - C_6 alkoxy, aryl,



aralkyl, heteroaryl, cycloaliphatic ring, heterocyclyl, or C_6 alkyl, the aryl, the heteroaryl, cycloaliphatic ring, or heterocyclyl are unsubstituted or substituted with one or more R^{12} ;

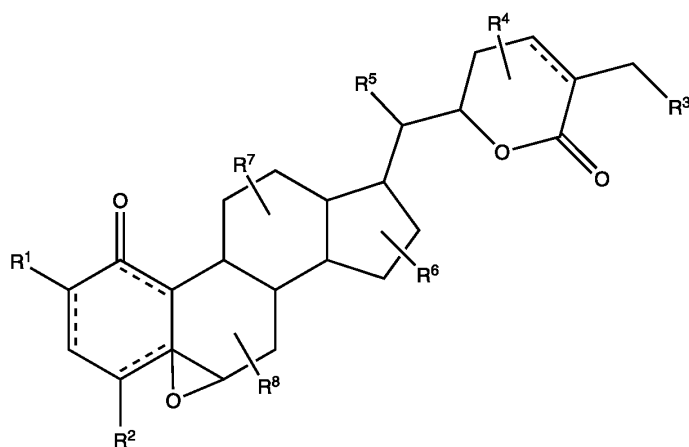
R^3 is hydrogen, halogen, $-OR^9$, $-SR^9$, $-NR^9R^{10}$, $-COOR^9$, $-COHR^9R^{10}$, $-CR^9R^{10}R^{11}$, $-CN$, $-N_3$, C_1 - C_6 alkyl, C_1 - C_6 haloalkyl, C_2 - C_6 alkenyl, C_2 - C_6 alkynyl, C_1 - C_6 alkoxy, aryl, aralkyl, heteroaryl, cycloaliphatic ring, heterocyclyl, $-(NR^9R^{10}R^{11})^+$, or $-OC(=O)NH-(C_2-C_6$ alkynyl), wherein the C_1 - C_6 alkyl, the aryl, the heteroaryl, cycloaliphatic ring, or heterocyclyl are unsubstituted or substituted with one or more R^{12} ;

T, U, V, W, and X are each, independently, CH, CR¹², sulfur, nitrogen, NH, NR¹², or N⁺-O⁻;

R⁴, R⁵, R⁶, R⁷, R⁸, R⁹, R¹⁰, and R¹¹ are each, independently, hydrogen, deuterium, halogen, or a C₁-C₆ unsubstituted or substituted alkyl; and

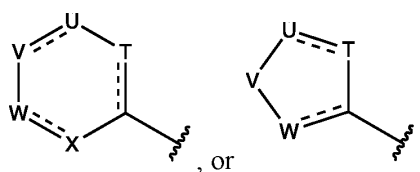
each R¹² is, independently, deuterium, halogen, =O, -OR⁹, -SR⁹, -NR⁹R¹⁰, -COOR⁹, -COHR⁹R¹⁰, -CR⁹R¹⁰R¹¹, -CN, -N₃, C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₁-C₆ alkoxy, aryl, aralkyl, heteroaryl, cycloaliphatic ring, heterocyclyl, or -O- (heterocyclyl). In some embodiments, the compound of Formula (I) is administered in a therapeutically effective amount.

[0013] In another aspect, provided herein is a method of treating, ameliorating, or preventing a tumor necrosis factor alpha (TNF- α)-mediated condition or disease, comprising administering a compound of Formula (I):



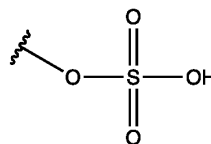
(I), or a pharmaceutically

acceptable salt thereof, wherein:



R¹ is hydrogen, -NR⁹R¹⁰, -COOR⁹, -CN,

R² is hydrogen, halogen, -OR⁹, -SR⁹, -NR⁹R¹⁰, -COOR⁹, -COHR⁹R¹⁰, -CR⁹R¹⁰R¹¹, -CN, -N₃, C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₁-C₆ alkoxy, aryl,



aralkyl, heteroaryl, cycloaliphatic ring, heterocyclyl, or , wherein the C₁-

C₆ alkyl, the aryl, the heteroaryl, cycloaliphatic ring, or heterocyclyl are unsubstituted or substituted with one or more R¹²;

R³ is hydrogen, halogen, -OR⁹, -SR⁹, -NR⁹R¹⁰, -COOR⁹, -COHR⁹R¹⁰, -CR⁹R¹⁰R¹¹, -CN, -N₃, C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₁-C₆ alkoxy, aryl, aralkyl, heteroaryl, cycloaliphatic ring, heterocyclyl, -(NR⁹R¹⁰R¹¹)⁺, or -OC(=O)NH-(C₂-C₆ alkynyl), wherein the C₁-C₆ alkyl, the aryl, the heteroaryl, cycloaliphatic ring, or heterocyclyl are unsubstituted or substituted with one or more R¹²;

T, U, V, W, and X are each, independently, CH, CR¹², sulfur, nitrogen, NH, NR¹², or N⁺-O⁻;

R⁴, R⁵, R⁶, R⁷, R⁸, R⁹, R¹⁰, and R¹¹ are each, independently, hydrogen, deuterium, halogen, or a C₁-C₆ unsubstituted or substituted alkyl; and each R¹² is, independently, deuterium, halogen, =O, -OR⁹, -SR⁹, -NR⁹R¹⁰, -COOR⁹, -COHR⁹R¹⁰, -CR⁹R¹⁰R¹¹, -CN, -N₃, C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₁-C₆ alkoxy, aryl, aralkyl, heteroaryl, cycloaliphatic ring, heterocyclyl, or -O- (heterocyclyl). In some embodiments, the compound of Formula (I) is administered in a therapeutically effective amount.

BRIEF DESCRIPTION OF THE DRAWINGS

[0014] The present application can be understood by reference to the following description taken in conjunction with the accompanying figures.

[0015] **FIGS. 1A** and **1B** are charts and graphs illustrating experimental results of non-limiting embodiments of a compound of Formula I inhibiting the NLRP3 pathway in human primary cells.

[0016] **FIGS. 2A** and **2B** represent pictorial and graphical representation of NLRP3 stability regulation by a compound of Formula I in accordance with one or more exemplary embodiments of the present disclosure.

[0017] **FIGS. 3A** and **3B** represent dose dependent NLRP3 protein degradation by a compound of Formula I in accordance with one or more exemplary embodiments of the present disclosure. While **FIG. 3C** represents proteasome rescue of NLRP3 protein by a compound of Formula I in accordance with one or more exemplary embodiments of the present disclosure.

[0018] **FIG. 4** illustrates dose dependent in-vitro target engagement of a compound of Formula I in accordance with one or more exemplary embodiments of the present disclosure.

[0019] **FIGS. 5A-5D** illustrate dose-dependent reduction in Disease Activity Index and combined histopathology score in dextran sodium sulfate (DSS) induced Colitis Murine model of a compound of Formula I in accordance with one or more exemplary embodiments of the present disclosure.

[0020] **FIGS. 6A-6F** depict reduction of disease Activity Index in Chronic dextran sodium sulfate (DSS) induced IBD Murine model by a compound of Formula I in accordance with one or more exemplary embodiments of the present disclosure.

[0021] **FIGS. 7A and 7B** depict dose responsive efficacy of a compound of Formula I in a dextran sodium sulfate (DSS) induced Colitis Murine model (Prophylactic mode) in accordance with one or more exemplary embodiments of the present disclosure.

[0022] **FIGS. 8A-8D** illustrates reduced DSS-induced DAI score on day 8 in dextran sodium sulfate (DSS) induced Colitis Murine model by a compound of Formula I in accordance with one or more exemplary embodiments of the present disclosure.

[0023] **FIGS. 9A and 9B** illustrate reduced DSS-induced colon shortening in dextran sodium sulfate (DSS) induced Colitis Murine model by a compound of Formula I in accordance with one or more exemplary embodiments of the present disclosure.

[0024] **FIGS. 10A-10D** demonstrate the prevention of DSS-induced intestinal permeability in dextran sodium sulfate (DSS) induced Colitis Murine model by a compound of Formula I in accordance with one or more exemplary embodiments of the present disclosure.

[0025] **FIGS. 11A-11C** depict reduction of DSS-induced clinically relevant markers in dextran sodium sulfate (DSS) induced Murine model by a compound of Formula I in accordance with one or more exemplary embodiments of the present disclosure.

[0026] **FIGS. 12A-12C** depict the effect of a compound of Formula I in DSS-induced proinflammatory markers in colon in accordance with one or more exemplary embodiments of the present disclosure.

[0027] **FIGS. 13A-13C** depict the effect of a compound of Formula I on DSS-induced systemic inflammation in accordance with one or more exemplary embodiments of the present disclosure.

[0028] **FIGS. 14A and 14B** depict the effect of a compound of Formula I on DSS-induced proinflammatory markers in serum in accordance with one or more exemplary embodiments of the present disclosure.

[0029] **FIG. 15** depicts the effect of a compound of Formula I in DSS-induced systemic inflammation in accordance with one or more exemplary embodiments of the present disclosure.

[0030] **FIG. 16** depicts the effect of a compound of Formula I in inhibiting IL-1 β release from differentiated THP1 cells in accordance with one or more exemplary embodiments of the present disclosure.

[0031] **FIG. 17** depicts the effect of a compound of Formula I on pyroptosis in differentiated THP1 cells in accordance with one or more exemplary embodiments of the present disclosure.

[0032] **FIGS. 18A-18D** depict the effect of a compound of Formula I in alcohol-induced liver injury mouse model in accordance with one or more exemplary embodiments of the present disclosure.

DETAILED DESCRIPTION

[0033] Provided herein are compounds, compositions, and methods for treating, reducing, or ameliorating a variety of diseases, disorders, or conditions in a subject in need thereof. Even though inflammation is a host's protective reaction to infections, it can be harmful and destructive in excess. In various circumstances, inflammation is regarded as a disease-modifying mechanism, prompting substantial efforts to address detrimental inflammatory reactions observed in conditions such as inflammatory bowel disease (IBD), Crohn's disease, colorectal cancer, alcoholic hepatitis and other diseases.

[0034] As used herein, the term “subject” refers to primates (e.g., humans, male or female), dogs, rabbits, guinea pigs, pigs, rats and mice. In certain embodiments, the subject is a primate. In yet another embodiment, the subject is a human.

[0035] As used herein, a subject is “in need of” or “in need thereof” a treatment if such subject would benefit biologically, medically or in quality of life from such treatment.

[0036] As an essential part of the innate immune system, NLRP3 (NACHT, LRR and PYD domain-containing protein 3) functions as a pattern recognition receptor (PRR) in cells like macrophages. The NLRP3 protein, a multimolecular complex, plays a central role in the pathogenesis of various diseases characterized by harmful inflammatory responses. The NLRP3 protein detects cellular stress caused by pathogens or damage, and it forms a complex with an adaptor protein called ASC (apoptosis-associated speck-like protein containing a CARD). This complex, known as the inflammasome, is responsible for activating the protease caspase-1. Caspase-1 then cleaves precursor forms of the pro-inflammatory cytokines interleukin (IL)-1 β and IL-18, converting them into their active forms, which are subsequently released. Caspase-1 is responsible for the proteolytic cleavage of gasdermin D, resulting in the formation of pores in the cellular membrane and subsequent pyroptotic cell death. This process enables the release of inflammasome complexes into the extracellular space, thereby amplifying the inflammatory response. In the context of Alzheimer's disease models, extracellular ASC specks have been observed to initiate the seeding of amyloid deposition and aggregation.

[0037] As used herein, the term “NLRP3” is meant to include, without limitation, nucleic acids, polynucleotides, oligonucleotides, sense and anti-sense polynucleotide strands, complementary sequences, peptides, polypeptides, proteins, homologous and/or orthologous NLRP molecules, isoforms, precursors, mutants, variants, derivatives, splice variants, alleles, different species, and active fragments thereof.

[0038] Consequently, there exists a significant level of interest in the development of inhibitors targeting the NLRP3 inflammasome. Heat-shock protein 90 (HSP90) is a highly abundant protein that plays a crucial role in numerous cellular signaling pathways, including inflammation. This is achieved through its ability to interact with and modulate the activity of various client proteins within the cellular environment. It has been proposed that HSP90 has the ability to interact with NLRP3, thereby exerting control over the activation of inflammasomes and the secretion of IL-1 β . To this end, the compounds and compositions as contemplated herein are HSP90 inhibitors that inhibit NLRP3-dependent inflammation.

[0039] In certain embodiments, the present disclosure relates to compounds and compositions that modulate NLRP3 stability by inhibiting the interaction of NLRP3 by the C-terminal domain of HSP90 to modulate the NLRP3 inflammasome's activity. By preventing HSP90's stabilizing action, the compounds and composition described herein may reduce overactivation of the inflammasome, thereby mitigating the inflammatory response.

[0040] TNF- α , or tumor necrosis factor-alpha, is a pro-inflammatory cytokine produced by various cell types, primarily macrophages and T-cells, in response to infection, injury, or other stimuli. It plays a pivotal role in the body's immune response by promoting inflammation, mediating apoptosis (cell death), regulating cell proliferation, and coordinating a wide range of cellular activities that are essential for host defense against pathogens. However, overproduction or chronic presence of TNF- α can lead to pathological inflammation and is implicated in various diseases, including alcoholic liver disease, inflammatory bowel disease, and psoriasis.

[0041] As used herein, the term "TNF- α " is meant to include, without limitation, nucleic acids, polynucleotides, oligonucleotides, sense and anti-sense polynucleotide strands, complementary sequences, peptides, polypeptides, proteins, homologous and/or orthologous TNF- α , isoforms, precursors, mutants, variants, derivatives, splice variants, alleles, different species, and active fragments thereof.

[0042] Consequently, there exists a significant level of interest in the development of inhibitors targeting TNF- α . It has been proposed that HSP90 has the ability to interact with TNF- α . To this end, the compounds and compositions as contemplated herein are HSP90 inhibitors that inhibit TNF- α -dependent inflammation.

[0043] In certain embodiments, the present disclosure relates to compounds and compositions that modulate TNF- α stability by inhibiting the interaction of TNF- α by the C-terminal domain of HSP90 to modulate TNF- α activity. By preventing HSP90's stabilizing action, the compounds and composition described herein may reduce overactivation of TNF- α , thereby mitigating the inflammatory response.

[0044] In other embodiments, HSP90 as a molecular chaperone, plays a vital role in stabilizing and assisting the conformational maturation of various proteins are involved in signaling pathways that can, directly or indirectly, influence the production, stability, or

activity of cytokines. Non-limiting examples of cytokines or cytokine pathways that are influenced by proteins regulated by HSP90, include:

(1) NF- κ B pathway: HSP90 regulates the stability of I κ B kinase (IKK). IKK plays a role in the degradation of I κ B, leading to the activation of NF- κ B. Activated NF- κ B then translocates to the nucleus and can induce the expression of various cytokines including TNF- α , IL-1 β , IL-6, and IL-8.

(2) STAT proteins wherein HSP90 is involved in stabilizing Signal Transducer and Activator of Transcription (STAT) proteins. STATs, once activated, can induce the expression of various cytokines and growth factors.

(3) HIF-1 α : Under hypoxic conditions, the stabilization of Hypoxia-Inducible Factor 1-alpha (HIF-1 α) by HSP90 can lead to the expression of VEGF and other cytokines.

(4) Toll-like receptors (TLRs): HSP90 is involved in the maturation and stability of some TLRs, which play a significant role in innate immunity and can induce the production of various cytokines upon activation.

(5) Receptor tyrosine kinases: HSP90 stabilizes various receptor tyrosine kinases. These receptors, upon activation, can activate downstream pathways leading to the production of various growth factors and cytokines.

(6) IL-1 receptor-associated kinase (IRAK): HSP90 stabilizes IRAK, which is involved in IL-1 signaling and can influence the production of cytokines downstream.

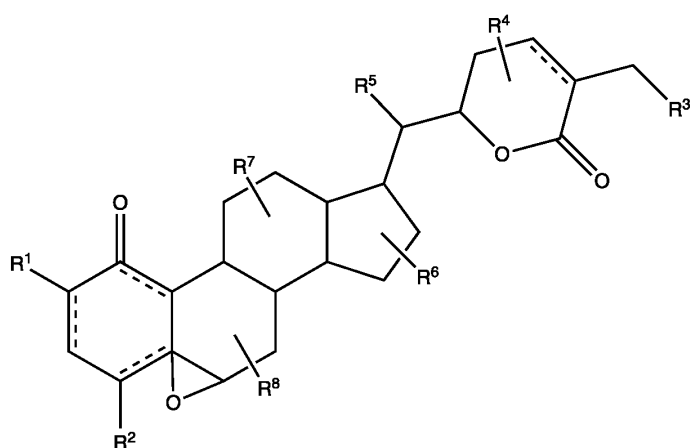
[0045] It should be noted that HSP90 may not directly regulate cytokines but rather stabilizes and assists in the function of many client proteins that, in turn, influence cytokine production, stability, or activity.

[0046] The compounds and compositions described herein are used to treat, prevent, or ameliorate (reduce the severity of) one or more symptoms associated with diseases and conditions characterized by aberrant NLRP3 inflammasome activity, aberrant TNF- α activity, or both. Such diseases and conditions include inflammatory bowel diseases, systemic inflammatory diseases, inflammatory skin diseases, gastrointestinal diseases, kidney diseases, cardiovascular diseases, liver diseases, autoimmune diseases, and respiratory diseases. The pharmaceutical compositions include a compound described herein and a pharmaceutically

acceptable carrier. The present disclosure further includes kits containing the pharmaceutical composition. The present disclosure further includes methods of treating a pathological state in a mammal through the administration of any compounds or composition described herein.

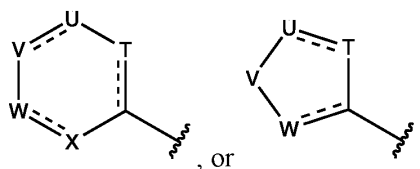
Compounds

[0047] A compound of Formula (I) is provided herein. The compound of Formula (I) is as follows:



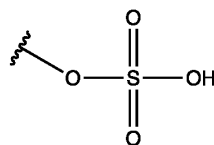
(I), or a pharmaceutically

acceptable salt thereof, wherein:



R¹ is hydrogen, -NR⁹R¹⁰, -COOR⁹, -CN,

R² is hydrogen, halogen, -OR⁹, -SR⁹, -NR⁹R¹⁰, -COOR⁹, -COHR⁹R¹⁰, -CR⁹R¹⁰R¹¹, -CN, -N₃, C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₁-C₆ alkoxy, aryl,



aralkyl, heteroaryl, cycloaliphatic ring, heterocyclyl, or C₆ alkyl, the aryl, the heteroaryl, cycloaliphatic ring, or heterocyclyl are unsubstituted or substituted with one or more R¹²;

R³ is hydrogen, halogen, -OR⁹, -SR⁹, -NR⁹R¹⁰, -COOR⁹, -COHR⁹R¹⁰, -CR⁹R¹⁰R¹¹, -CN, -N₃, C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₁-C₆ alkoxy, aryl, aralkyl, heteroaryl, cycloaliphatic ring, heterocyclyl, -(NR⁹R¹⁰R¹¹)⁺, or -OC(=O)NH-(C₂-C₆

alkynyl), wherein the C₁-C₆ alkyl, the aryl, the heteroaryl, cycloaliphatic ring, or heterocyclyl are unsubstituted or substituted with one or more R¹²;

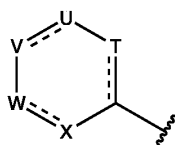
T, U, V, W, and X are each, independently, CH, CR¹², sulfur, nitrogen, NH, NR¹², or N⁺-O⁻;

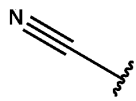
R⁴, R⁵, R⁶, R⁷, R⁸, R⁹, R¹⁰, and R¹¹ are each, independently, hydrogen, deuterium, halogen, or a C₁-C₆ unsubstituted or substituted alkyl; and

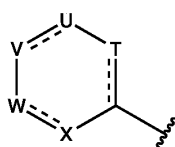
each R¹² is, independently, deuterium, halogen, =O, -OR⁹, -SR⁹, -NR⁹R¹⁰, -COOR⁹, -COHR⁹R¹⁰, -CR⁹R¹⁰R¹¹, -CN, -N₃, C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₁-C₆ alkoxy, aryl, aralkyl, heteroaryl, cycloaliphatic ring, heterocyclyl, or -O-(heterocyclyl);

with the proviso:

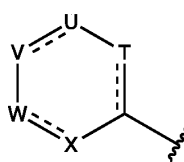
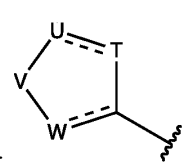
(1) when R¹ is hydrogen, then R² is a halogen;

(2) when R¹ is  and each of T, U, V, W, and X is CH or CR¹²,

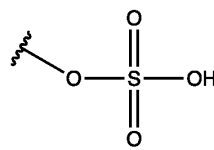
then only one of T, U, V, W, and X is CR¹², wherein R¹² is  or -OCH₃, and the remaining T, U, V, W, and X are CH; and

(3) when R¹ is , T and X are CH, one of W or U is nitrogen, and the other of W or U is CH, then V is not C(-OCH₃).

[0048] In some variations of the foregoing,

R¹ is hydrogen, -NR⁹R¹⁰, -COOR⁹, -CN, , or ;

R² is hydrogen, halogen, -OR⁹, -SR⁹, -NR⁹R¹⁰, -COOR⁹, -COHR⁹R¹⁰, -CR⁹R¹⁰R¹¹, -CN, -N₃, C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₁-C₆ alkoxy, aryl,



aralkyl, heteroaryl, cycloalkyl ring, heterocycloalkyl, or $\text{C}_1\text{-C}_6$ alkyl, the aryl, the heteroaryl, cycloalkyl ring, or heterocycloalkyl are unsubstituted or substituted with one or more R^{12} ;

R^3 is hydrogen, halogen, $-\text{OR}^9$, $-\text{SR}^9$, $-\text{NR}^9\text{R}^{10}$, $-\text{COOR}^9$, $-\text{COHR}^9\text{R}^{10}$, $-\text{CR}^9\text{R}^{10}\text{R}^{11}$, $-\text{CN}$, $-\text{N}_3$, $\text{C}_1\text{-C}_6$ alkyl, $\text{C}_1\text{-C}_6$ haloalkyl, $\text{C}_2\text{-C}_6$ alkenyl, $\text{C}_2\text{-C}_6$ alkynyl, $\text{C}_1\text{-C}_6$ alkoxy, aryl, aralkyl, heteroaryl, cycloalkyl ring, heterocycloalkyl, $-(\text{NR}^9\text{R}^{10}\text{R}^{11})^+$, or $-\text{OC}(=\text{O})\text{NH}-(\text{C}_2\text{-C}_6\text{ alkynyl})$, wherein the $\text{C}_1\text{-C}_6$ alkyl, the aryl, the heteroaryl, cycloalkyl ring, or heterocycloalkyl are unsubstituted or substituted with one or more R^{12} ;

T, U, V, W, and X are each, independently, CH, CR^{12} , sulfur, nitrogen, NH, NR^{12} , or N^+-O^- ;

R^4 , R^5 , R^6 , R^7 , R^8 , R^9 , R^{10} , and R^{11} are each, independently, hydrogen, deuterium, halogen, or a $\text{C}_1\text{-C}_6$ unsubstituted or substituted alkyl; and

each R^{12} is, independently, deuterium, halogen, $=\text{O}$, $-\text{OR}^9$, $-\text{SR}^9$, $-\text{NR}^9\text{R}^{10}$, $-\text{COOR}^9$, $-\text{COHR}^9\text{R}^{10}$, $-\text{CR}^9\text{R}^{10}\text{R}^{11}$, $-\text{CN}$, $-\text{N}_3$, $\text{C}_1\text{-C}_6$ alkyl, $\text{C}_1\text{-C}_6$ haloalkyl, $\text{C}_2\text{-C}_6$ alkenyl, $\text{C}_2\text{-C}_6$ alkynyl, $\text{C}_1\text{-C}_6$ alkoxy, aryl, aralkyl, heteroaryl, cycloalkyl ring, heterocycloalkyl, or $-\text{O}-(\text{heterocycloalkyl})$.

[0049] For purposes of this disclosure, the chemical elements are identified in accordance with the Periodic Table of the Elements, CAS version, Handbook of Chemistry and Physics, 75th Ed. Additionally, general principles of organic chemistry are described in “Organic Chemistry,” Thomas Sorrell, University Science Books, Sausalito: 1999, and “March's Advanced Organic Chemistry,” 5th Ed., Ed.: Smith, M. B. and March, J., John Wiley & Sons, New York: 2001.

[0050] As described herein, compounds of the disclosure can optionally be substituted with one or more substituents, such as are illustrated generally herein, or as exemplified by particular classes, subclasses, and species of the disclosure. As one of ordinary skill in the art will recognize, combinations of substituents envisioned by this disclosure are those combinations that result in the formation of stable or chemically feasible compounds.

[0051] The phrase “optionally substituted” may be used interchangeably with the phrase “substituted or unsubstituted.” In general, the term “substituted,” whether preceded by the term

“optionally” or not, refers to the replacement of hydrogen radicals in a given structure with the radical of a specified substituent. Specific substituents are described above in the definitions and below in the description of compounds and examples thereof. Unless otherwise indicated, an optionally substituted group can have a substituent at each substitutable position of the group, and when more than one position in any given structure can be substituted with more than one substituent selected from a specified group, the substituent can be either the same or different at every position. A ring substituent, such as a heterocyclyl, can be bound to another ring, such as a cycloaliphatic ring, to form a spiro-bicyclic ring system, *e.g.*, both rings share one common atom. As one of ordinary skill in the art will recognize, combinations of substituents envisioned by this disclosure are those combinations that result in the formation of stable or chemically feasible compounds.

[0052] The term “alkyl” or “alkyl group” as used herein, means a straight-chain (*i.e.* unbranched) or branched, substituted or unsubstituted hydrocarbon chain that is completely saturated. Unless otherwise specified, alkyl groups contain 1-20 carbon atoms. In some embodiments, alkyl groups contain 1-10 carbon atoms. In other embodiments, groups contain 1-8 carbon atoms. In still other embodiments, groups contain 1-6 carbon atoms, and in yet other embodiments groups contain 1-4 carbon atoms. Suitable alkyl groups include, but are not limited to, linear or branched, substituted or unsubstituted alkyl groups.

[0053] The term “alkenyl” or “alkenyl group” as used herein, means an unsaturated linear straight-chain (*i.e.* unbranched) or branched, substituted or unsubstituted hydrocarbon chain that contains at least one moiety of the formula (C=C). Unless otherwise specified, alkenyl groups contain 2-20 carbon atoms. In some embodiments, alkenyl groups contain 2-10 carbon atoms. In other embodiments, alkenyl groups contain 2-8 carbon atoms. In still other embodiments, alkenyl groups contain 2-6 carbon atoms, and in yet other embodiments alkenyl groups contain 2-4 carbon atoms. Suitable alkenyl groups include, but are not limited to, linear or branched, substituted or unsubstituted alkenyl groups.

[0054] The term “alkynyl” or “alkynyl group” as used herein, means an unsaturated linear straight-chain (*i.e.* unbranched) or branched, substituted or unsubstituted hydrocarbon chain that contains at least carbon-carbon triple bond. Unless otherwise specified, alkynyl groups contain 2-20 carbon atoms. In some embodiments, alkynyl groups contain 2-10 carbon atoms. In other embodiments, alkynyl groups contain 2-8 carbon atoms. In still other embodiments, alkynyl groups contain 2-6 carbon atoms, and in yet other embodiments alkynyl groups contain

2-4 carbon atoms. Suitable alkynyl groups include, but are not limited to, linear or branched, substituted or unsubstituted alkynyl groups.

[0055] The term “cycloaliphatic ring” mean a monocyclic hydrocarbon ring, or a polycyclic hydrocarbon ring system containing no heteroatoms, that is completely saturated or that contains one or more units of unsaturation, but which is not aromatic and that has a single point of attachment to the rest of the molecule. The term “polycyclic ring system,” as used herein, includes bicyclic and tricyclic 4- to 12-membered structures that form at least two rings, wherein the two rings have at least one atom in common (*e.g.*, 2 atoms in common) including fused, bridged, or spirocyclic ring systems. Particular cycloaliphatic ring groups include those having 3 to 12 carbon atoms (C_3 - C_{12} cycloaliphatic ring), those having 3 to 6 carbon atoms (C_3 - C_6 cycloaliphatic ring), and those having 5 to 6 carbon atoms (C_5 - C_6 cycloaliphatic ring). Additional exemplary cycloaliphatic ring groups include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, cyclononyl, and cyclodecyl.

[0056] The term “halogen” or “halo” as used herein, means F, Cl, Br or I.

[0057] Unless otherwise specified, the term “heterocyclyl” as used herein means non-aromatic, monocyclic, bicyclic, or tricyclic ring systems in which one or more ring atoms in one or more ring members is an independently selected heteroatom. Heterocyclic ring can be saturated or can contain one or more unsaturated bonds. In some embodiments, the “heterocyclyl” group has three to fourteen ring members in which one or more ring members is a heteroatom independently selected from oxygen, sulfur, nitrogen, or phosphorus, and each ring in the ring system contains 3 to 7 ring members. Particular heterocyclyl groups include 3- to 12-membered heterocyclyl; 4- to 6-membered heterocyclyl; 5- to 6-membered heterocyclyl; 5- to 6-membered heterocyclyl containing one or more heteroatoms selected from N, O, or S; and 5- to 6-membered heterocyclyl, containing 1-2 heteroatoms selected from N or O.

[0058] The term “heteroatom” means oxygen, sulfur, nitrogen, phosphorus, or silicon (including, any oxidized form of nitrogen, sulfur, phosphorus, or silicon; the quaternized form of any basic nitrogen or; a substitutable nitrogen of a heterocyclic ring, for example N (as in 3,4-dihydro-2H-pyrrolyl), NH (as in pyrrolidinyl) or NR^+ (as in N-substituted pyrrolidinyl)). In some embodiments, a heteroatom may be oxygen, sulfur, or nitrogen.

[0059] The term “unsaturated,” as used herein, means that a moiety has one or more units of unsaturation but is not aromatic.

[0060] The term “alkoxy,” or “thioalkyl,” as used herein, refers to an alkyl group, as previously defined, attached to the principal carbon chain through an oxygen (“alkoxy”) or sulfur (“thioalkyl”) atom.

[0061] The term “aryl” used alone or as part of a larger moiety as in “aralkyl,” “aralkoxy,” or “aryloxyalkyl,” refers to monocyclic, bicyclic, and tricyclic ring systems having a total of five to fourteen ring carbon atoms and containing no heteroatoms, wherein at least one ring in the system is aromatic and wherein each ring in the system contains 3 to 7 ring carbon atoms. The term “aryl” may be used interchangeably with the term “aryl ring.” Particular aryl groups include those having 6 to 12 carbon atoms (C₆-C₁₂ aryl) or those having 6 to 10 carbon atoms (C₆-C₁₀ aryl). Additional exemplary aryl groups include phenyl and naphthyl.

[0062] The term “heteroaryl,” used alone or as part of a larger moiety as in “heteroaralkyl” or “heteroarylalkoxy,” refers to monocyclic, bicyclic, and tricyclic ring systems having a total of five to fourteen ring members, wherein at least one ring in the system is aromatic, at least one ring in the system contains one or more heteroatoms, and wherein each ring in the system contains 3 to 7 ring members. In some embodiments, the one or more heteroatoms are selected from oxygen, sulfur, and nitrogen. The term “heteroaryl” may be used interchangeably with the term “heteroaryl ring” or the term “heteroaromatic.” Particular heteroaryl groups include 5- to 12-membered heteroaryl, 5- to 10-membered heteroaryl, and 5- to 6-membered heteroaryl.

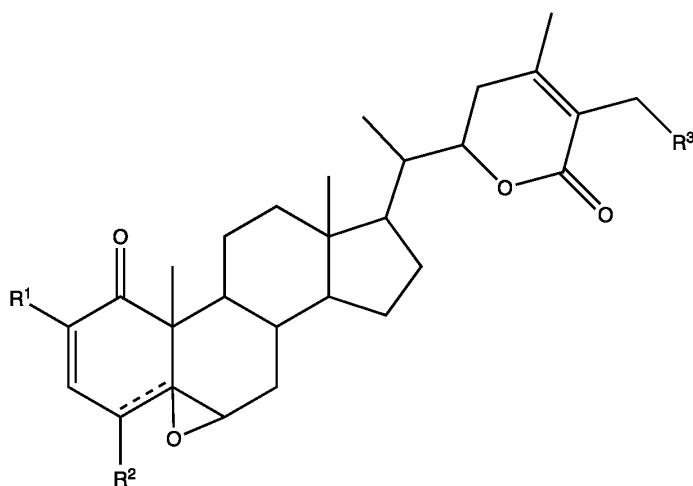
[0063] “D” and “d” both refer to deuterium.

[0064] Unless otherwise stated, structures depicted herein are also meant to include all isomeric (*e.g.*, enantiomeric, diastereomeric, and geometric (or conformational)) forms of the structure; for example, the R and S configurations for each asymmetric center, (Z) and (E) double bond isomers, and (Z) and (E) conformational isomers. Therefore, single stereochemical isomers as well as enantiomeric, diastereomeric, and geometric (or conformational) mixtures of the present compounds are within the scope of the disclosure. Unless otherwise stated, all tautomeric forms of the compounds of Formula (I) of the disclosure are within the scope of the disclosure. Thus, included within the scope of the disclosure are tautomers of compounds of Formula (I). The structures also include zwitterionic forms of the compounds or salts of Formula (I) where appropriate.

[0065] Additionally, unless otherwise stated, structures depicted herein are also meant to include compounds that differ only in the presence of one or more isotopically enriched or

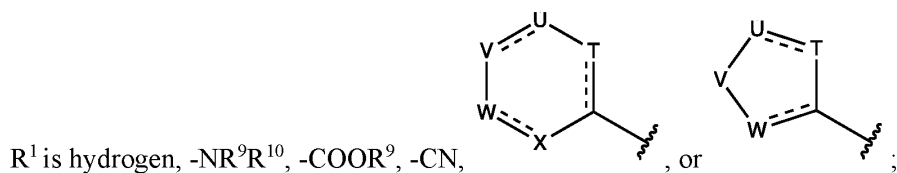
isotopically-labeled atoms. The isotopically-labeled compounds may have one or more atoms replaced by an atom having an atomic mass or mass number usually found in nature. Examples of isotopes present in compounds of Formula (I) include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorus, fluorine and chlorine, such as, but not limited to, ^2H , ^3H , ^{13}C , ^{14}C , ^{15}N , ^{18}O , ^{17}O , ^{35}S and ^{18}F . Certain isotopically-labeled compounds of Formula (I), in addition to being useful as therapeutic agents, are also useful in drug and/or substrate tissue distribution assays, as analytical tools or as probes in other biological assays. In one aspect of the present disclosure, tritiated (*e.g.*, ^3H) and carbon-14 (*e.g.*, ^{14}C) isotopes are useful given their ease of detectability. In another aspect of the present disclosure, replacement of one or more hydrogen atoms with heavier isotopes such as deuterium, (*e.g.*, ^2H) can afford certain therapeutic advantages.

[0066] In some embodiments, the compound of Formula (I) is Formula (Ia):

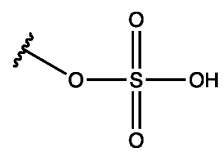


(Ia), or a

pharmaceutically acceptable salt thereof, and wherein:



R^2 is hydrogen, halogen, $-\text{OR}^9$, $-\text{SR}^9$, $-\text{NR}^9\text{R}^{10}$, $-\text{COOR}^9$, $-\text{COHR}^9\text{R}^{10}$, $-\text{CR}^9\text{R}^{10}\text{R}^{11}$, $-\text{CN}$, $-\text{N}_3$, $\text{C}_1\text{-C}_6$ alkyl, $\text{C}_1\text{-C}_6$ haloalkyl, $\text{C}_2\text{-C}_6$ alkenyl, $\text{C}_2\text{-C}_6$ alkynyl, $\text{C}_1\text{-C}_6$ alkoxy, aryl,

aralkyl, heteroaryl, cycloaliphatic ring, heterocyclyl, or , wherein the $\text{C}_1\text{-}$

C₆ alkyl, the aryl, the heteroaryl, cycloaliphatic ring, or heterocyclyl are unsubstituted or substituted with one or more R¹²;

R³ is hydrogen, halogen, -OR⁹, -SR⁹, -NR⁹R¹⁰, -COOR⁹, -COHR⁹R¹⁰, -CR⁹R¹⁰R¹¹, -CN, -N₃, C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₁-C₆ alkoxy, aryl, aralkyl, heteroaryl, cycloaliphatic ring, heterocyclyl, -(NR⁹R¹⁰R¹¹)⁺, or -OC(=O)NH-(C₂-C₆ alkynyl), wherein the C₁-C₆ alkyl, the aryl, the heteroaryl, cycloaliphatic ring, or heterocyclyl are unsubstituted or substituted with one or more R¹²;

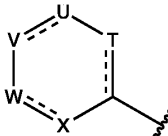
T, U, V, W, and X are each, independently, CH, CR¹², sulfur, nitrogen, NH, NR¹², or N⁺-O⁻;

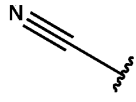
R⁴, R⁵, R⁶, R⁷, R⁸, R⁹, R¹⁰, and R¹¹ are each, independently, hydrogen, deuterium, halogen, or a C₁-C₆ unsubstituted or substituted alkyl; and

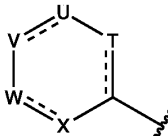
each R¹² is, independently, deuterium, halogen, =O, -OR⁹, -SR⁹, -NR⁹R¹⁰, -COOR⁹, -COHR⁹R¹⁰, -CR⁹R¹⁰R¹¹, -CN, -N₃, C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₁-C₆ alkoxy, aryl, aralkyl, heteroaryl, cycloaliphatic ring, heterocyclyl, or -O-(heterocyclyl);

with the proviso:

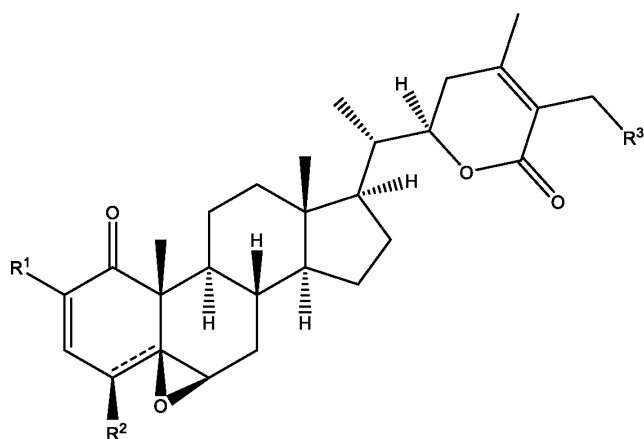
(1) when R¹ is hydrogen, then R² is a halogen;

(2) when R¹ is  and each of T, U, V, W, and X is CH or CR¹²,

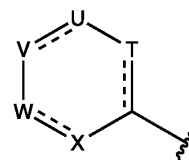
then only one of T, U, V, W, and X is CR¹², wherein R¹² is  or -OCH₃, and the remaining T, U, V, W, and X are CH; and

(3) when R¹ is , T and X are CH, one of W or U is nitrogen, and the other of W or U is CH, then V is not C(-OCH₃).

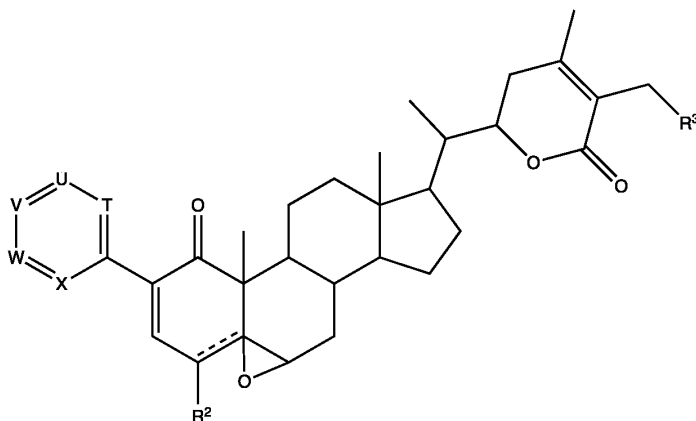
[0067] In some embodiments, the compound of Formula (Ia) is a compound of formula (Ia-1):



(Ia-1), or a pharmaceutically acceptable salt thereof.

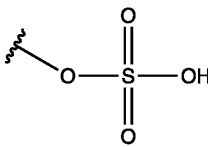


[0068] In certain embodiments, R¹ of Formula (I) or (Ia) is . In these and other embodiments, the compound of Formula (Ia) may be Formula (Iaa):



(Iaa), or a pharmaceutically acceptable salt thereof, and wherein:

R² is hydrogen, halogen, -OR⁹, -SR⁹, -NR⁹R¹⁰, -COOR⁹, -COHR⁹R¹⁰, -CR⁹R¹⁰R¹¹, -CN, -N₃, C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₁-C₆ alkoxy, aryl,

aralkyl, heteroaryl, cycloaliphatic ring, heterocyclyl, or , wherein the C₁-

C₆ alkyl, the aryl, the heteroaryl, cycloaliphatic ring, or heterocyclyl are unsubstituted or substituted with one or more R¹²;

R³ is hydrogen, halogen, -OR⁹, -SR⁹, -NR⁹R¹⁰, -COOR⁹, -COHR⁹R¹⁰, -CR⁹R¹⁰R¹¹, -CN, -N₃, C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₁-C₆ alkoxy, aryl, aralkyl, heteroaryl, cycloaliphatic ring, heterocyclyl, -(NR⁹R¹⁰R¹¹)⁺, or -OC(=O)NH-(C₂-C₆ alkynyl), wherein the C₁-C₆ alkyl, the aryl, the heteroaryl, cycloaliphatic ring, or heterocyclyl are unsubstituted or substituted with one or more R¹²;

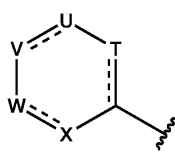
T, U, V, W, and X are each, independently, CH, CR¹², sulfur, nitrogen, NH, NR¹², or N⁺-O⁻;

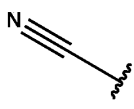
R⁹, R¹⁰, and R¹¹ are each, independently, hydrogen, deuterium, halogen, or a C₁-C₆ unsubstituted or substituted alkyl; and

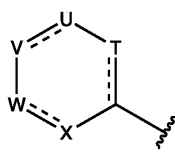
each R¹² is, independently, deuterium, halogen, =O, -OR⁹, -SR⁹, -NR⁹R¹⁰, -COOR⁹, -COHR⁹R¹⁰, -CR⁹R¹⁰R¹¹, -CN, -N₃, C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₁-C₆ alkoxy, aryl, aralkyl, heteroaryl, cycloaliphatic ring, heterocyclyl, or -O-(heterocyclyl);

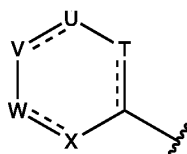
with the proviso:

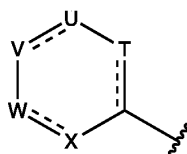
(1) when R¹ is hydrogen, then R² is a halogen;

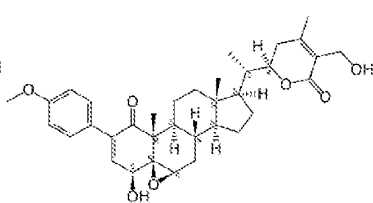
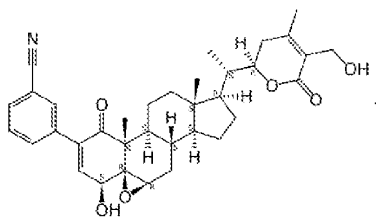
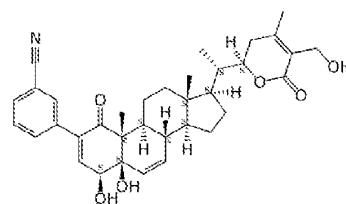
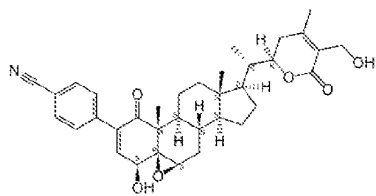
(2) when R¹ is  and each of T, U, V, W, and X is CH or CR¹²,

then only one of T, U, V, W, and X is CR¹², wherein R¹² is  or -OCH₃, and the remaining T, U, V, W, and X are CH; and

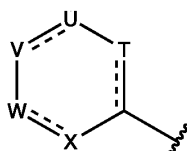
(3) when R¹ is , T and X are CH, one of W or U is nitrogen, and the other of W or U is CH, then V is not C(-OCH₃).

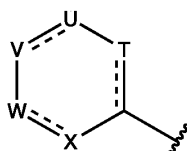


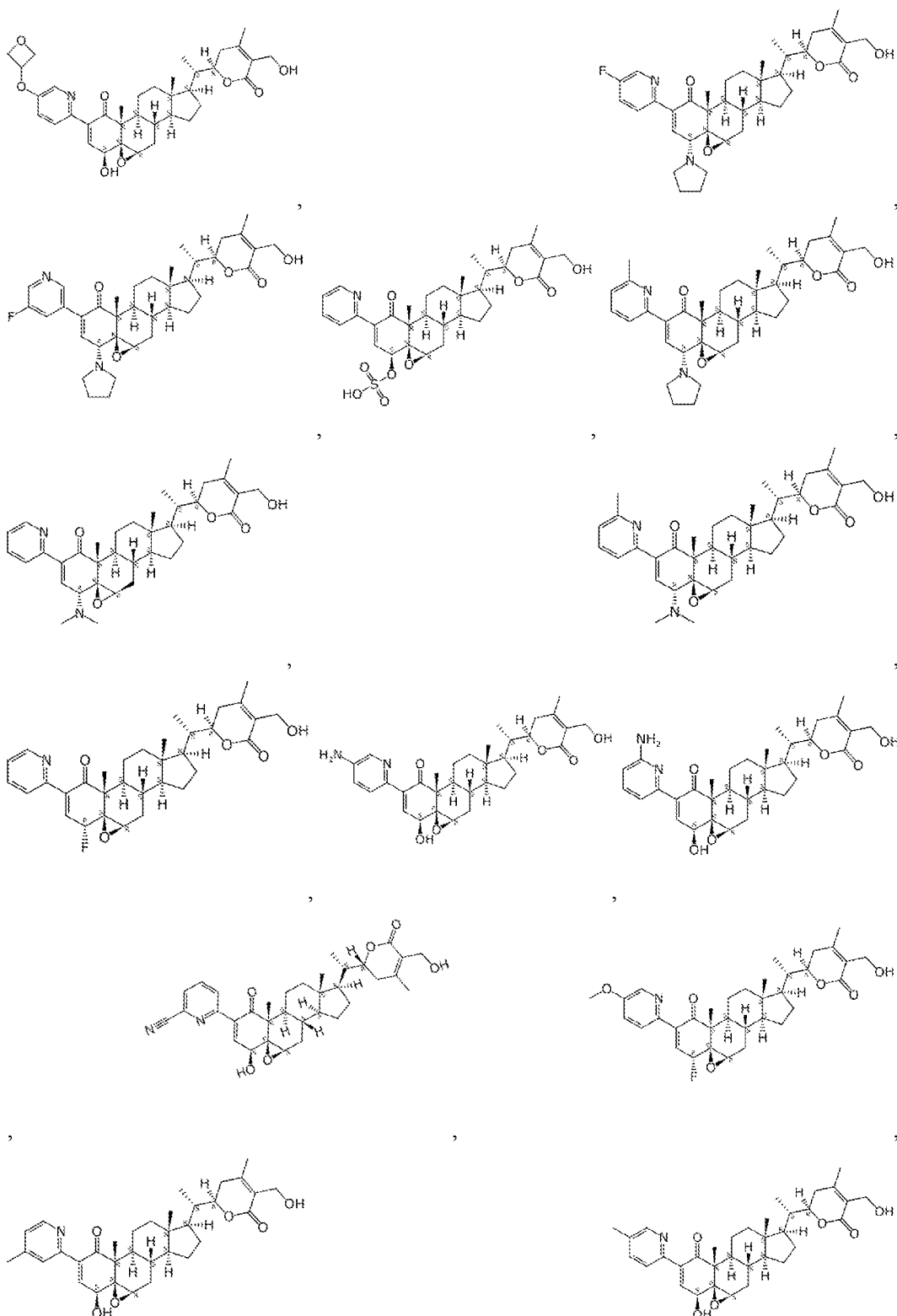
[0069] In some embodiments, R^1 is  and each of T, U, V, W, and X are CH or CR¹². In these and other embodiments, the compound of Formula (Iaa) is selected from the group of:

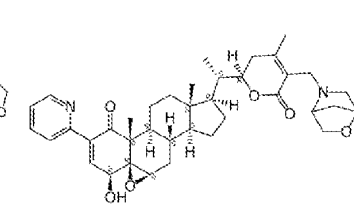
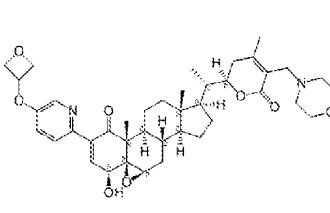
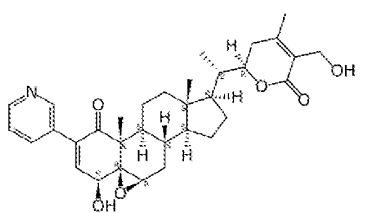
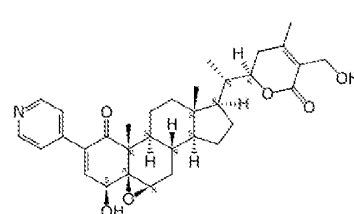
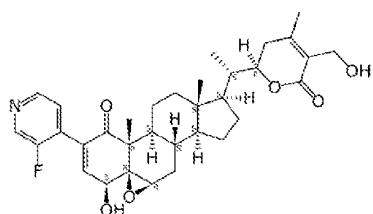
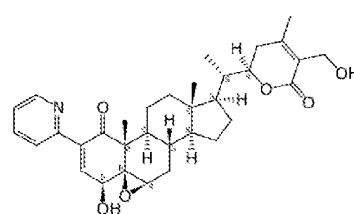
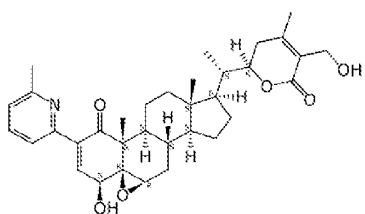
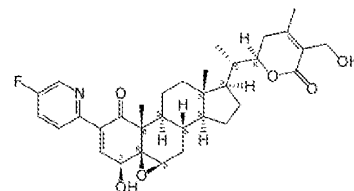
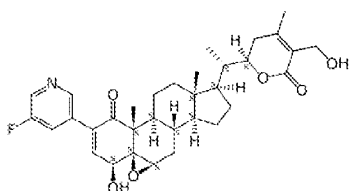
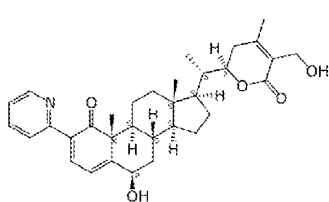
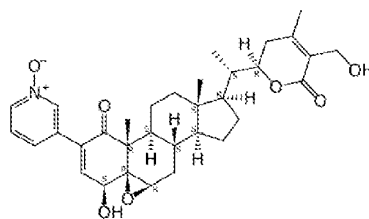
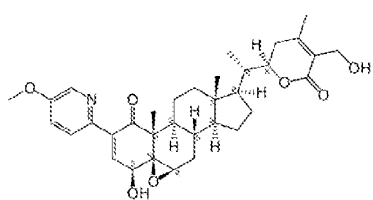


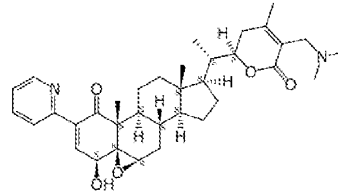
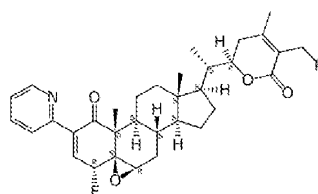
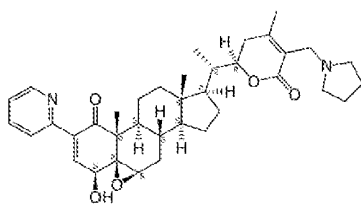
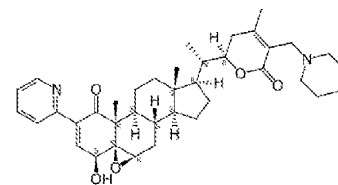
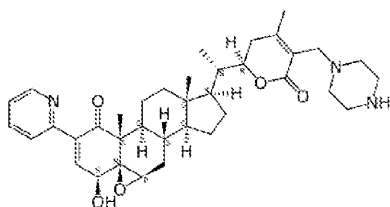
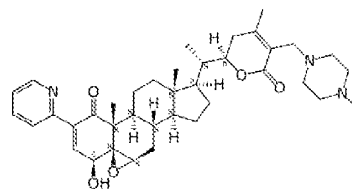
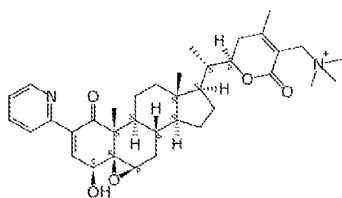
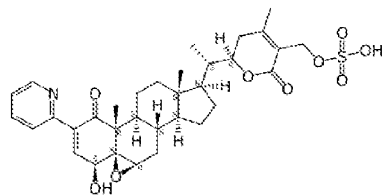
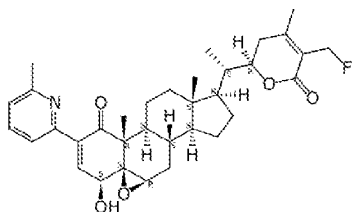
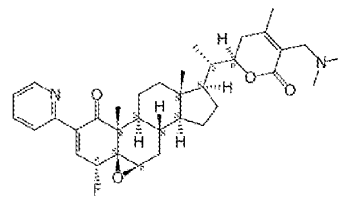
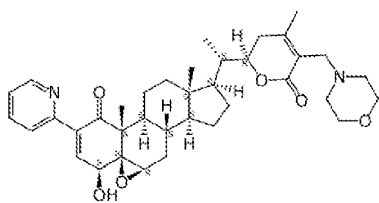
, or a pharmaceutically acceptable salt or stereoisomer thereof.

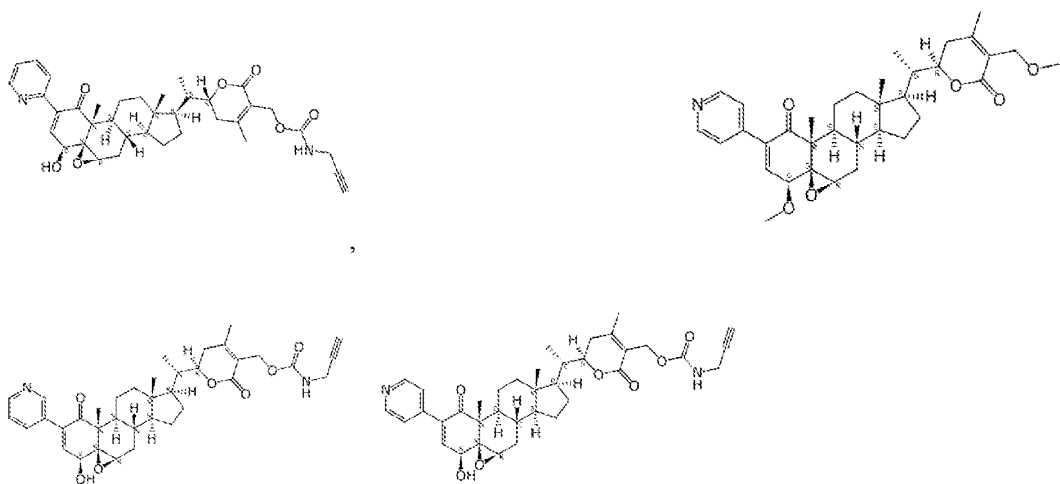


[0070] In some embodiments, R^1 is , only one of T, U, V, W, and X is sulfur, nitrogen, NH, NR¹², or N⁺-O⁻, and the remainder of T, U, V, W, and X are CH or CR¹². In these and other embodiments, the compound of Formula (Iaa) is selected from the group of:

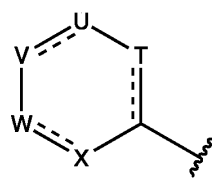




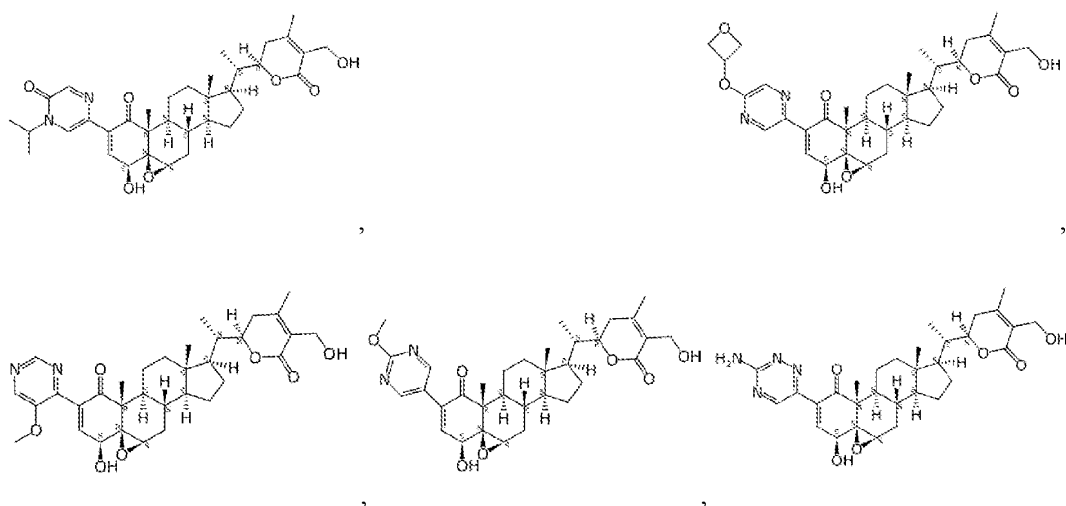


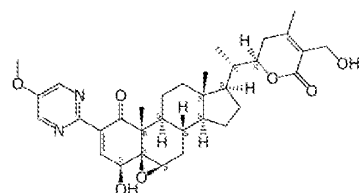
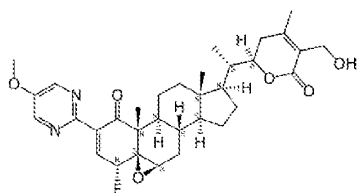
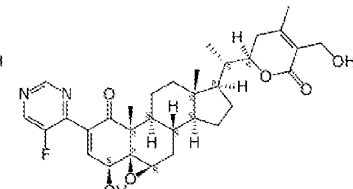
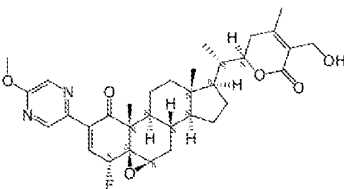
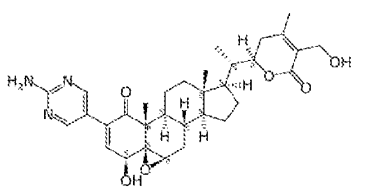
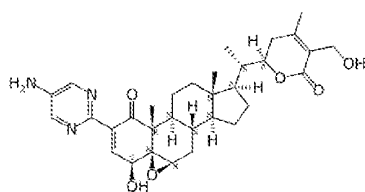
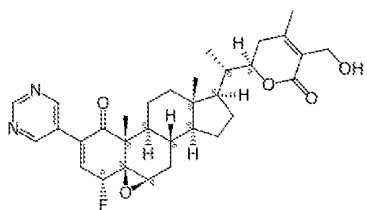
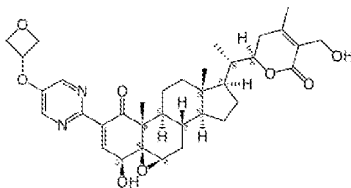
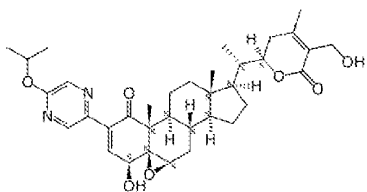
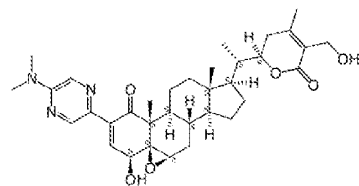
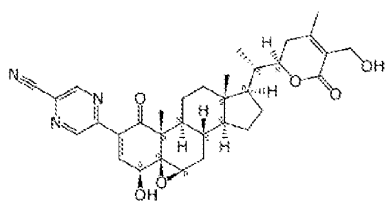


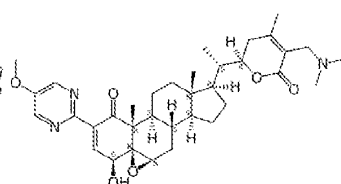
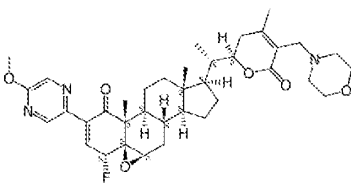
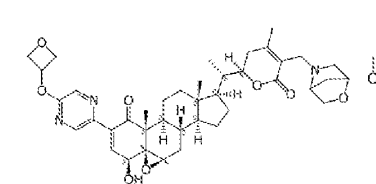
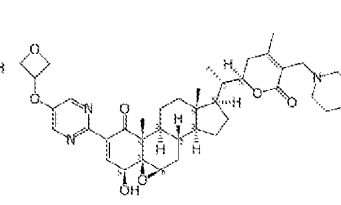
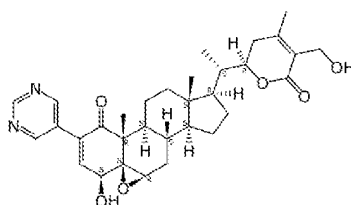
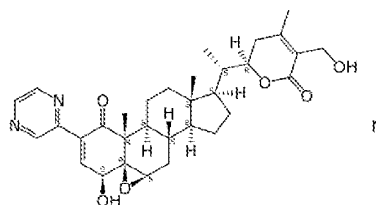
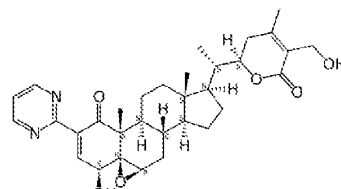
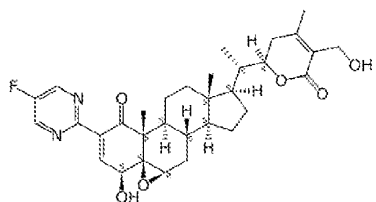
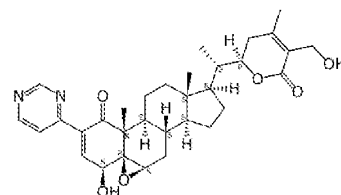
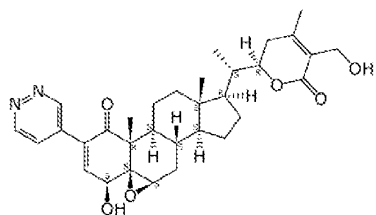
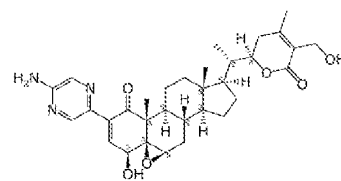
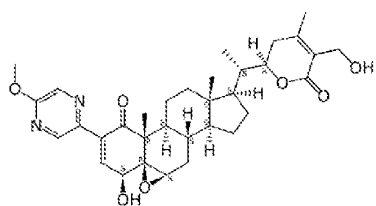
, or a pharmaceutically acceptable salt or stereoisomer thereof.

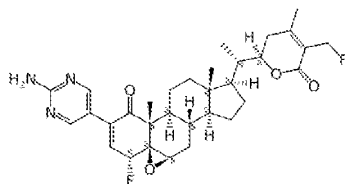
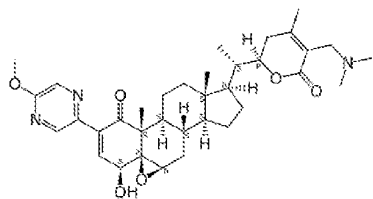
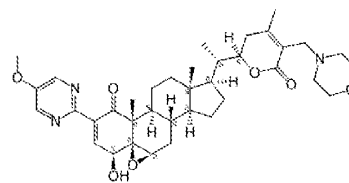
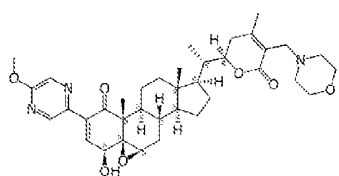


[0071] In some embodiments, R^1 is , at least two of T, U, V, W, and X are sulfur, nitrogen, NH, NR^{12} , or N^+-O^- , and the remaining of T, U, V, W, and X are CH or CR^{12} . In these and other embodiments, the compound of Formula (Iaa) is selected from the group of:

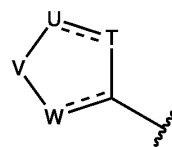


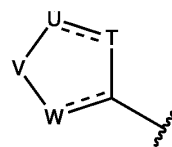


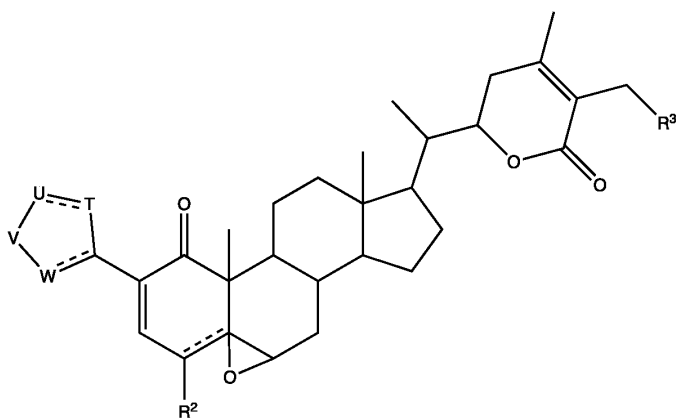




, or a pharmaceutically acceptable salt or stereoisomer thereof.



[0072] In certain embodiments, R^1 of Formula (I) or (Ia) is . In these and other embodiments, the compound of Formula (Ia) may be Formula (Iab):

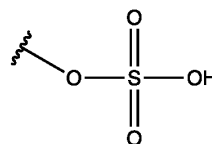


(Iab), or a

pharmaceutically acceptable salt thereof, and wherein:

R^2 is hydrogen, halogen, $-OR^9$, $-SR^9$, $-NR^9R^{10}$, $-COOR^9$, $-COHR^9R^{10}$, $-CR^9R^{10}R^{11}$, $-CN$, $-N_3$, C_1 - C_6 alkyl, C_1 - C_6 haloalkyl, C_2 - C_6 alkenyl, C_2 - C_6 alkynyl, C_1 - C_6 alkoxy, aryl,

aralkyl, heteroaryl, cycloaliphatic ring, heterocyclyl, or



, wherein the C_1 -

C₆ alkyl, the aryl, the heteroaryl, cycloaliphatic ring, or heterocyclyl are unsubstituted or substituted with one or more R¹²;

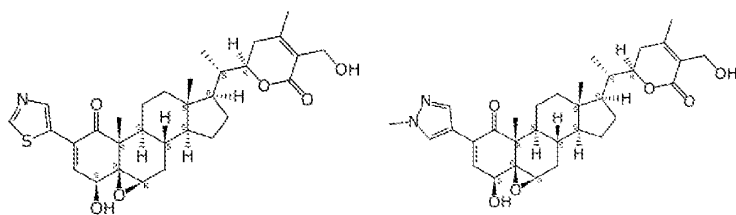
R³ is hydrogen, halogen, -OR⁹, -SR⁹, -NR⁹R¹⁰, -COOR⁹, -COHR⁹R¹⁰, -CR⁹R¹⁰R¹¹, -CN, -N₃, C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₁-C₆ alkoxy, aryl, aralkyl, heteroaryl, cycloaliphatic ring, heterocyclyl, -(NR⁹R¹⁰R¹¹)⁺, or -OC(=O)NH-(C₂-C₆ alkynyl), wherein the C₁-C₆ alkyl, the aryl, the heteroaryl, cycloaliphatic ring, or heterocyclyl are unsubstituted or substituted with one or more R¹²;

T, U, V, and W are each, independently, CH, CR¹², sulfur, nitrogen, NH, NR¹², or N⁺-O⁻;

R⁹, R¹⁰, and R¹¹ are each, independently, hydrogen, deuterium, halogen, or a C₁-C₆ unsubstituted or substituted alkyl; and

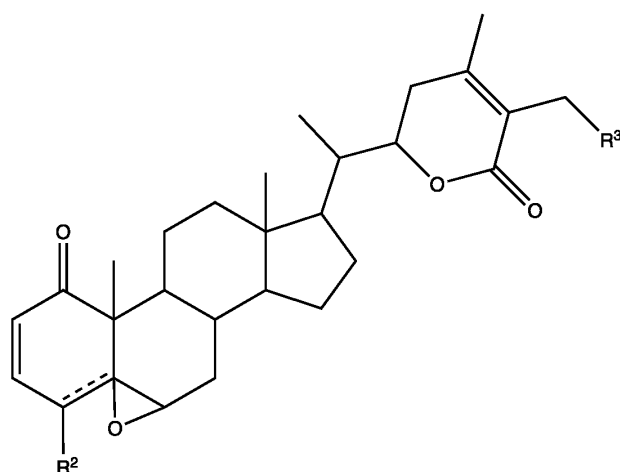
each R¹² is, independently, deuterium, halogen, =O, -OR⁹, -SR⁹, -NR⁹R¹⁰, -COOR⁹, -COHR⁹R¹⁰, -CR⁹R¹⁰R¹¹, -CN, -N₃, C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₁-C₆ alkoxy, aryl, aralkyl, heteroaryl, cycloaliphatic ring, heterocyclyl, or -O-(heterocyclyl).

[0073] In exemplary embodiments, the compound of Formula (Iab) is selected from the group of:



, or a pharmaceutically acceptable salt or stereoisomer thereof.

[0074] In some embodiments, R¹ of Formula (I) or (Ia) is hydrogen. In these embodiments when R¹ is hydrogen, the compound of Formula (Ia) may be Formula (Iac):



(Iac), or a pharmaceutically

acceptable salt thereof, wherein:

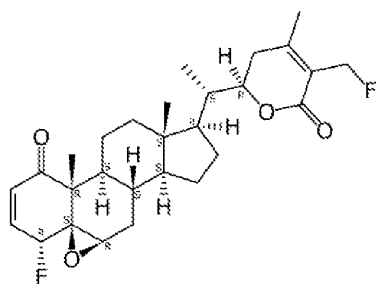
R^2 is halogen;

R^3 is hydrogen, halogen, $-OR^9$, $-SR^9$, $-NR^9R^{10}$, $-COOR^9$, $-COHR^9R^{10}$, $-CR^9R^{10}R^{11}$, $-CN$, $-N_3$, C_1 - C_6 alkyl, C_1 - C_6 haloalkyl, C_2 - C_6 alkenyl, C_2 - C_6 alkynyl, C_1 - C_6 alkoxy, aryl, aralkyl, heteroaryl, cycloaliphatic ring, heterocyclyl, $-(NR^9R^{10}R^{11})^+$, or $-OC(=O)NH-(C_2-C_6$ alkynyl), wherein the C_1 - C_6 alkyl, the aryl, the heteroaryl, cycloaliphatic ring, or heterocyclyl are unsubstituted or substituted with one or more R^{12} ;

R^9 , R^{10} , and R^{11} are each, independently, hydrogen, deuterium, halogen, or a C_1 - C_6 unsubstituted or substituted alkyl; and

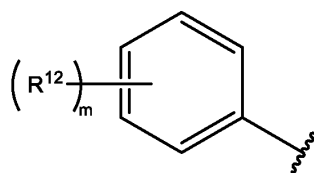
each R^{12} is, independently, deuterium, halogen, $=O$, $-OR^9$, $-SR^9$, $-NR^9R^{10}$, $-COOR^9$, $-COHR^9R^{10}$, $-CR^9R^{10}R^{11}$, $-CN$, $-N_3$, C_1 - C_6 alkyl, C_1 - C_6 haloalkyl, C_2 - C_6 alkenyl, C_2 - C_6 alkynyl, C_1 - C_6 alkoxy, aryl, aralkyl, heteroaryl, cycloaliphatic ring, heterocyclyl, or $-O$ -(heterocyclyl).

[0075] In exemplary embodiments, the compound of Formula (Iac) is:

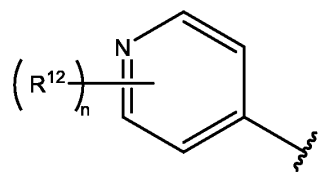


, or a pharmaceutically acceptable salt or

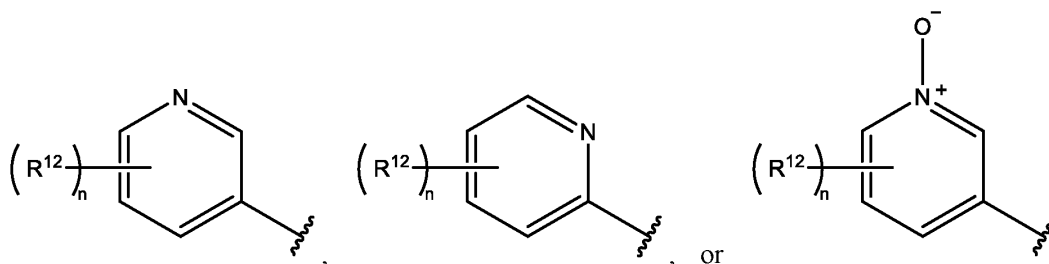
stereoisomer thereof.



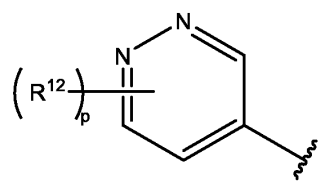
[0076] In some embodiments, R^1 is , wherein m is 0, 1, 2, 3, 4, 5, or 6.



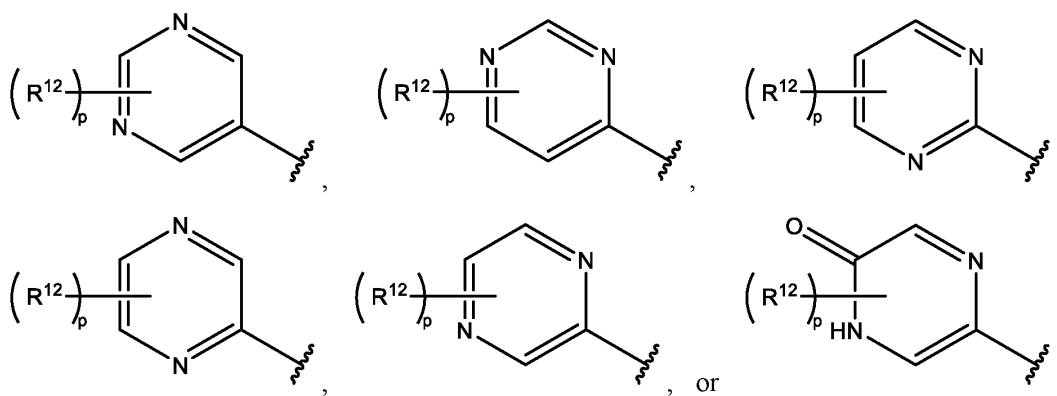
[0077] In some embodiments, R^1 is



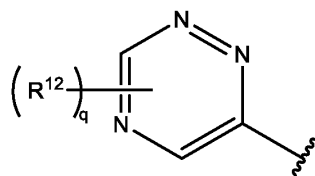
wherein n is 0, 1, 2, 3, or 4.



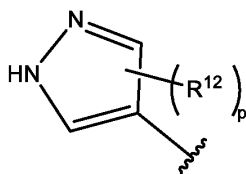
[0078] In some embodiments, R^1 is



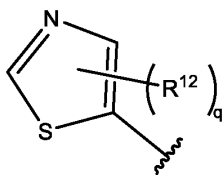
wherein p is 0, 1, 2, or 3.



[0079] In some embodiments, R^1 is , wherein q is 0, 1, or 2. In

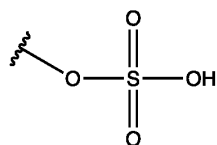


some embodiments, R^1 is , wherein p is 0, 1, 2, or 3. In some

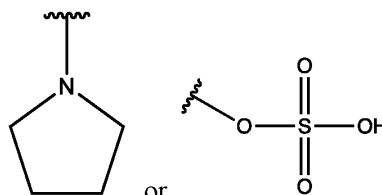


embodiments, R^1 is , wherein q is 0, 1, or 2.

[0080] In some embodiments, R^2 is halogen, $-OR^9$, $-NR^9R^{10}$, 5-membered heterocyclyl, or

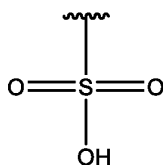


, wherein R^9 and R^{10} are each independently hydrogen or C_1 - C_6 alkyl. In

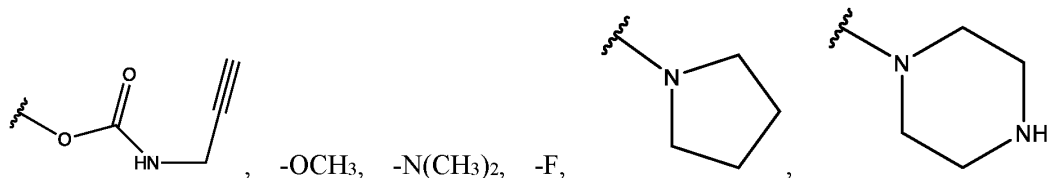


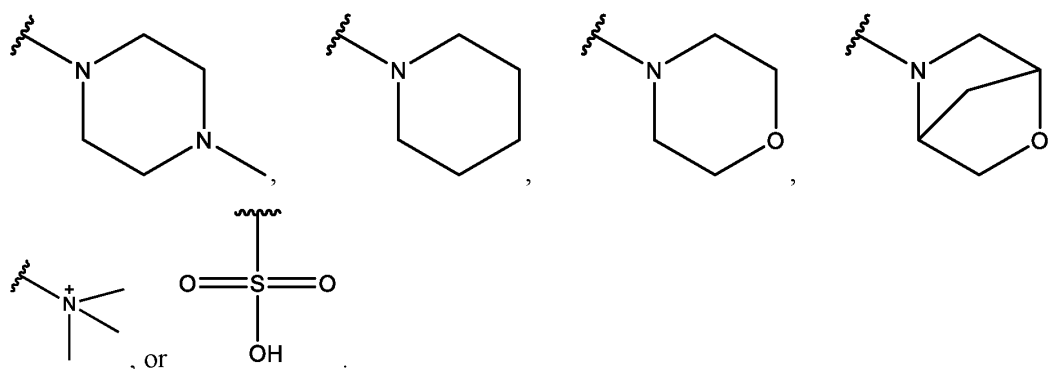
some embodiments, R^2 is $-OH$, $-F$, $-N(CH_3)_2$, , or .

[0081] In some embodiments, R^3 is hydrogen, halogen, $-OR^9$, $-NR^9R^{10}$, C_1 - C_6 alkoxy, 5- to 6-membered heterocyclyl optionally substituted by one or more C_1 - C_6 alkyl, $-(NR^9R^{10}R^{11})^+$,



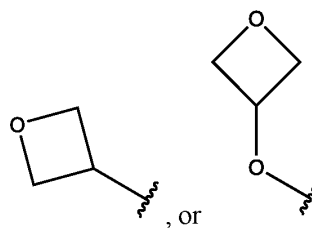
$-OC(=O)NH-(C_2-C_6 \text{ alkynyl})$, or , wherein R^9 , R^{10} , and R^{11} are each independently hydrogen or C_1 - C_6 alkyl. In some embodiments, R^3 is hydrogen, $-OH$,





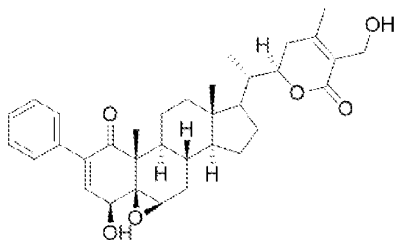
[0082] In some embodiments, R¹² is deuterium, halogen, =O, -NR⁹R¹⁰, -CN, C₁-C₆ alkyl, C₁-C₆ alkoxy, 4-membered heterocyclyl, or -O-(heterocyclyl), wherein R⁹ and R¹⁰ are each independently hydrogen or C₁-C₆ alkyl. In some embodiments, R¹² is deuterium, -F, -CN, =O,

-CH₃, -CH(CH₃)₂, -OCH₃, -OCD₃, -OCH(CH₃)₂, -NH₂, -N(CH₃)₂,

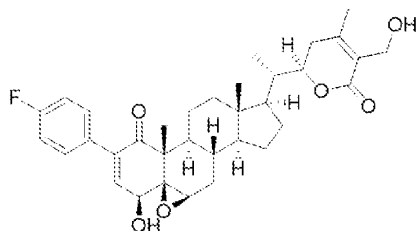


[0083] Non-limiting examples of suitable compounds include any of the following compounds, or pharmaceutically acceptable salts thereof.

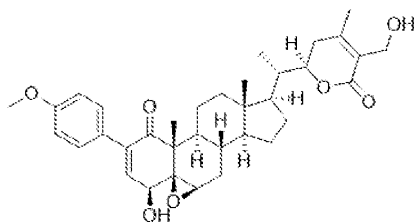
Compound 1



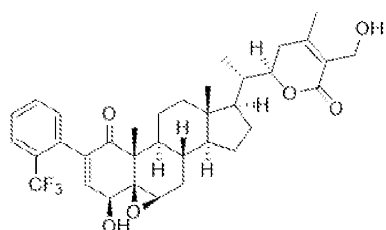
Compound 2



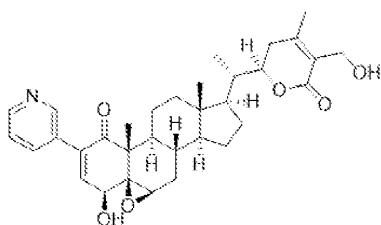
Compound 3



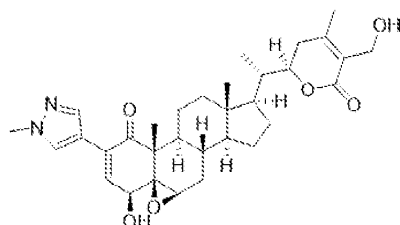
Compound 4



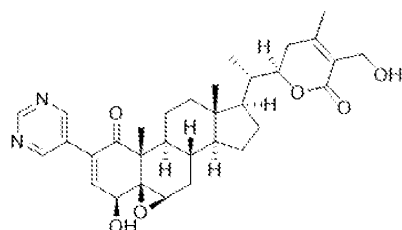
Compound 5



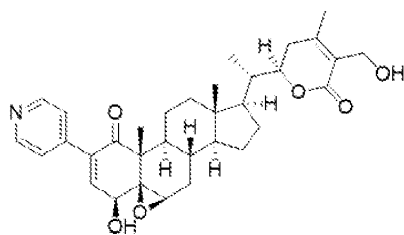
Compound 6



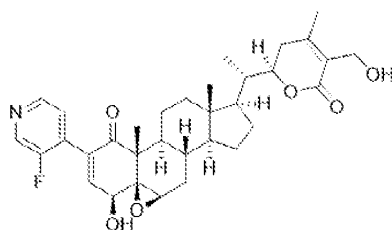
Compound 7



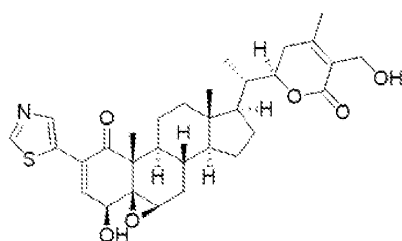
Compound 8



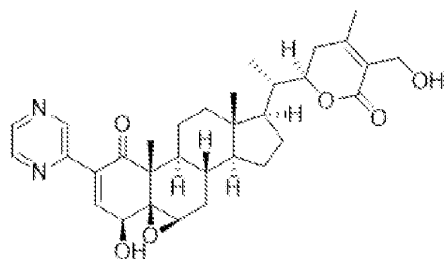
Compound 9



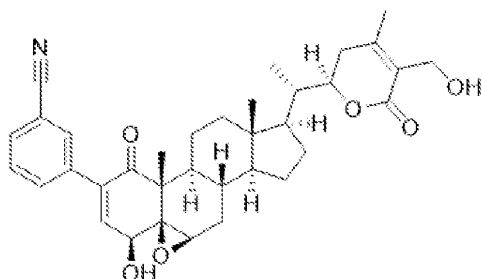
Compound 10



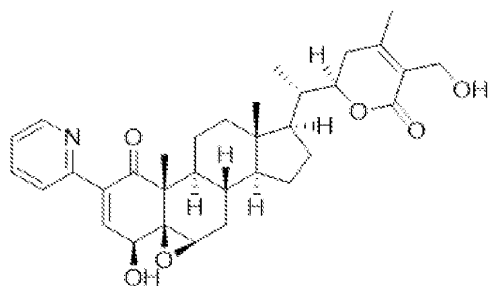
Compound 11



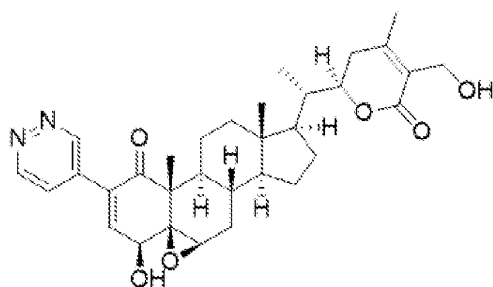
Compound 12



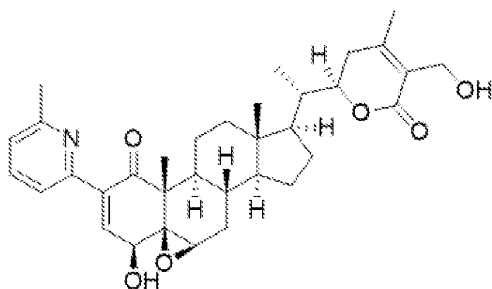
Compound 13



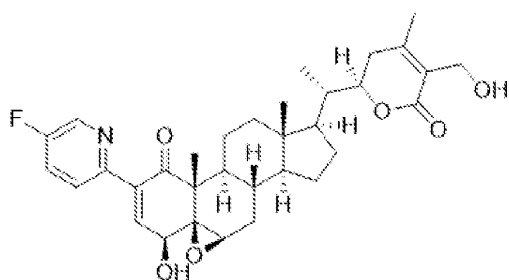
Compound 14



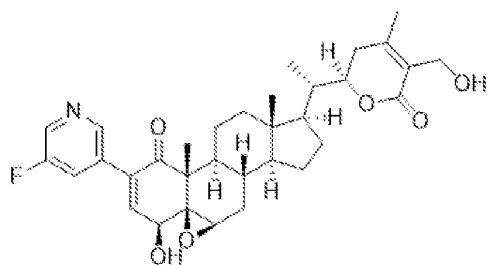
Compound 15



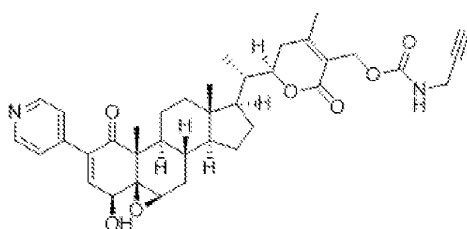
Compound 16



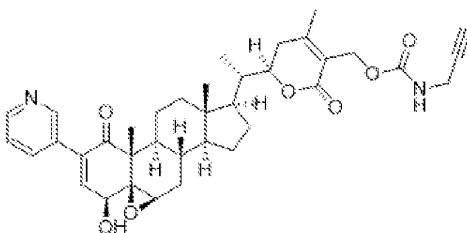
Compound 17



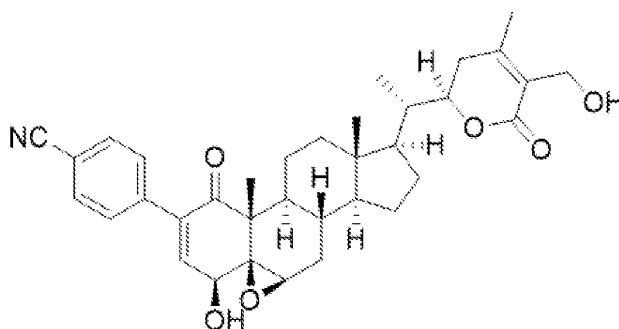
Compound 18



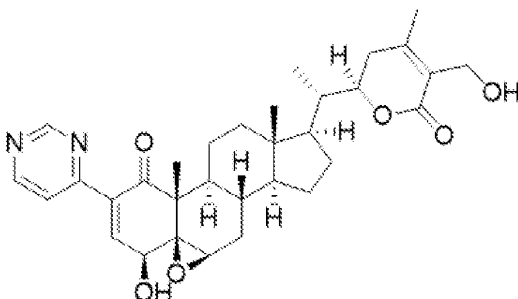
Compound 19



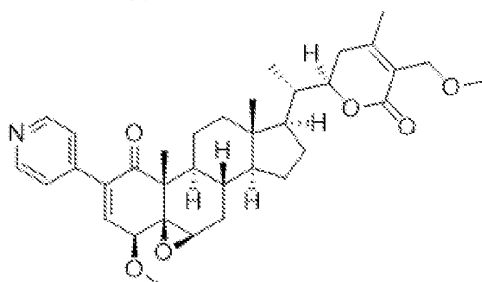
Compound 20



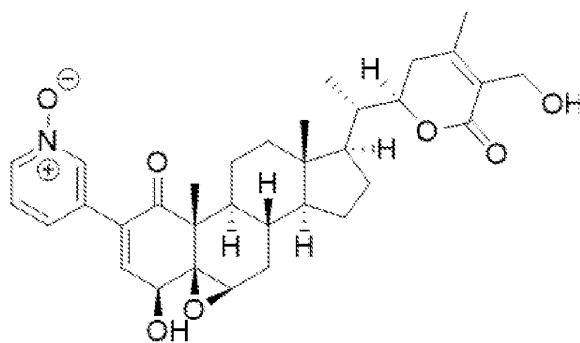
Compound 21



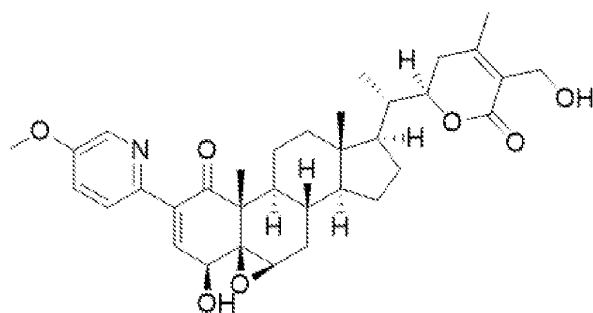
Compound 22



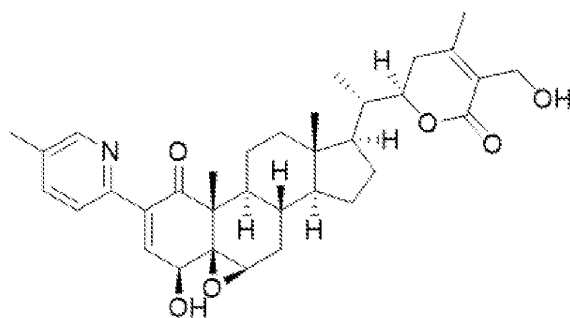
Compound 23



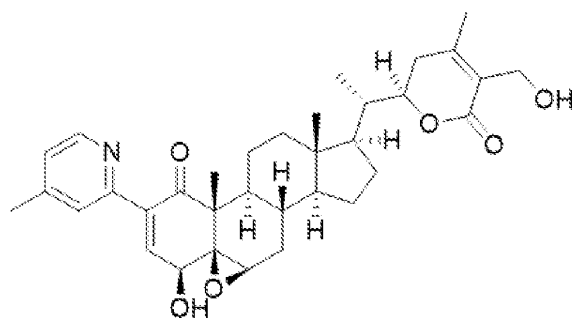
Compound 24



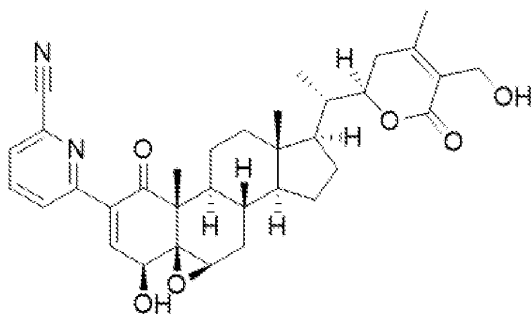
Compound 25



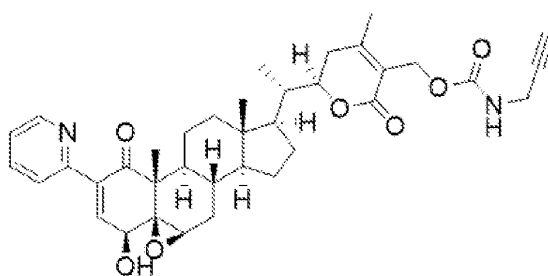
Compound 26



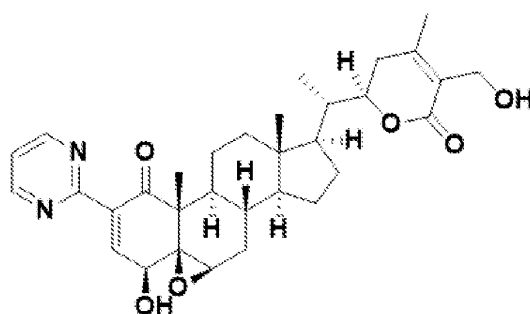
Compound 27



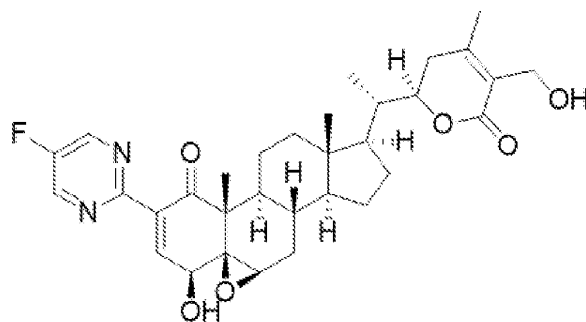
Compound 28



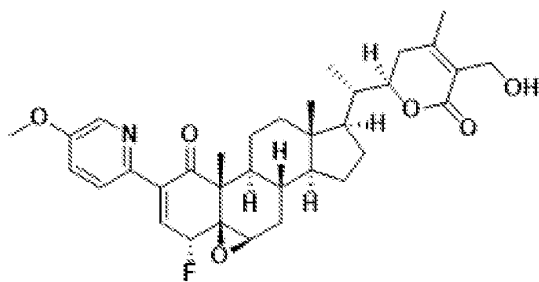
Compound 29



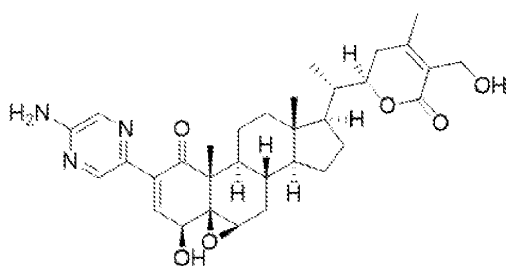
Compound 30



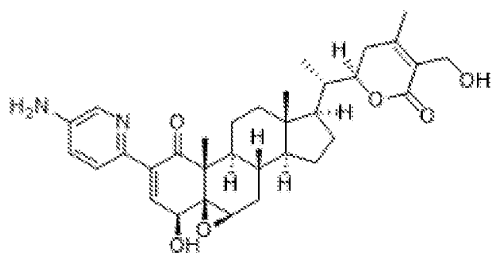
Compound 31



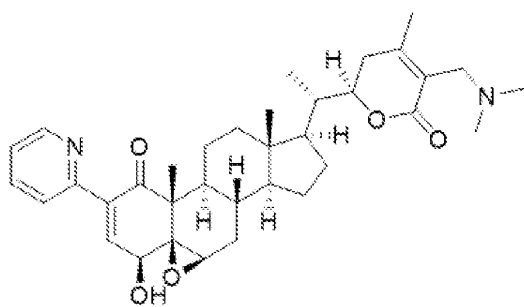
Compound 32



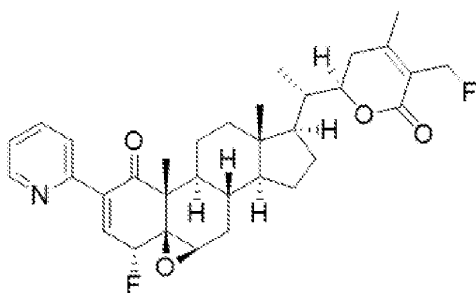
Compound 33



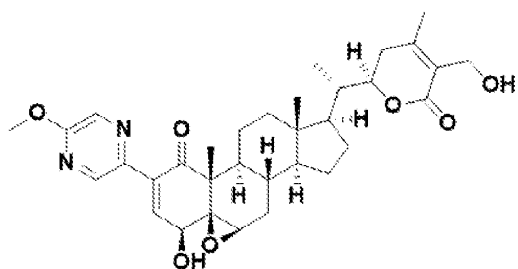
Compound 34



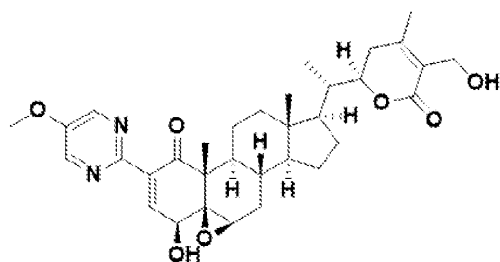
Compound 35



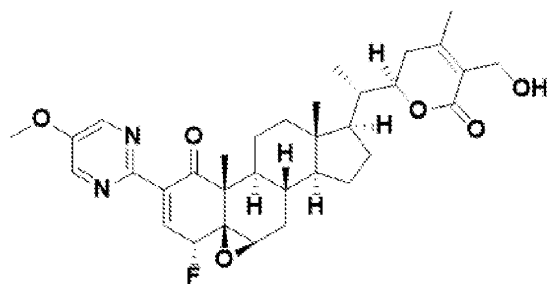
Compound 36



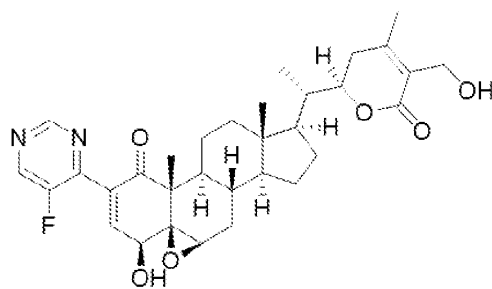
Compound 37



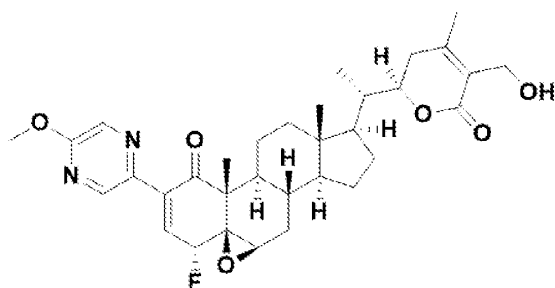
Compound 38



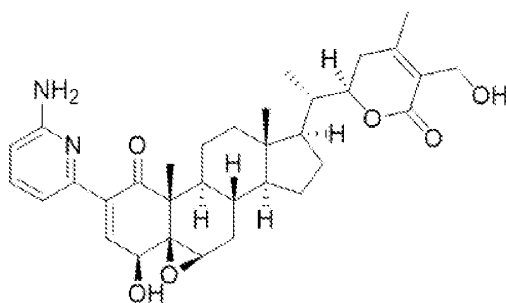
Compound 39



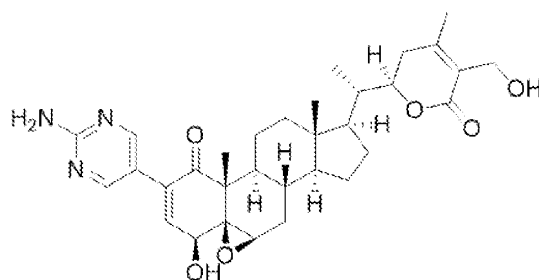
Compound 40



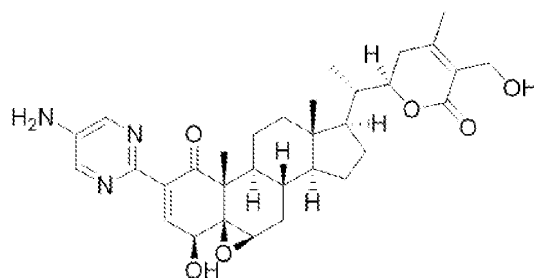
Compound 41



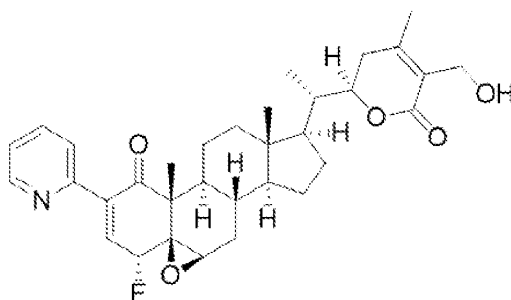
Compound 42



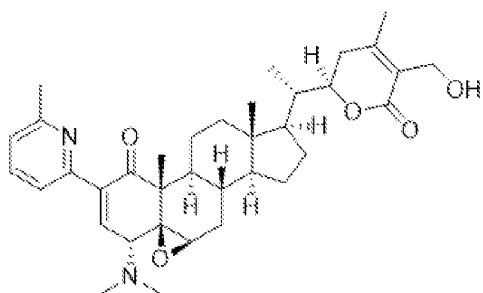
Compound 43



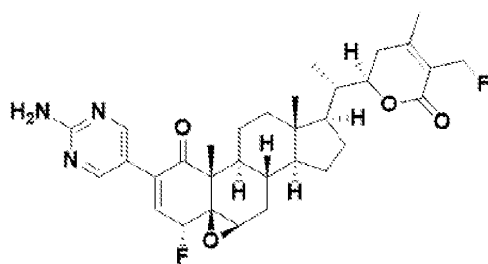
Compound 44



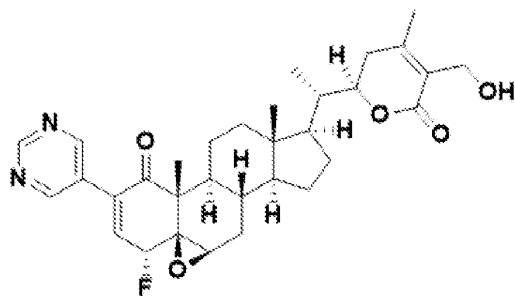
Compound 45



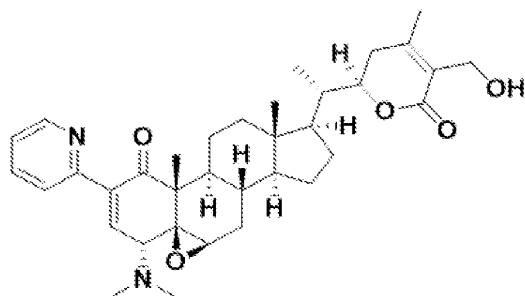
Compound 46



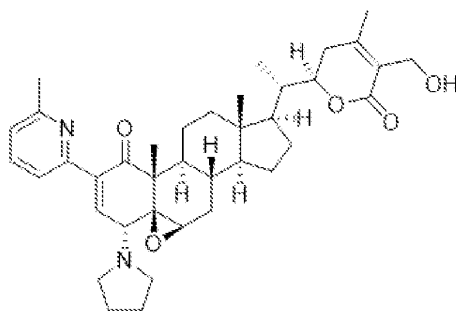
Compound 47



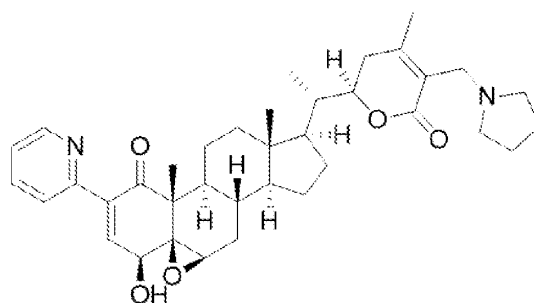
Compound 48



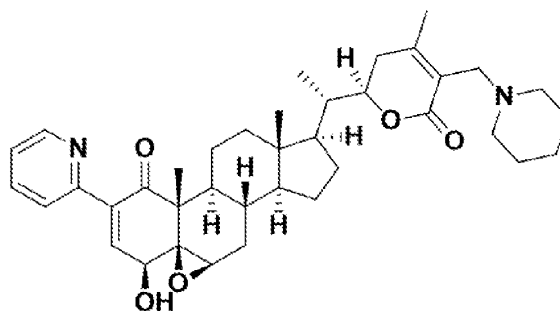
Compound 49



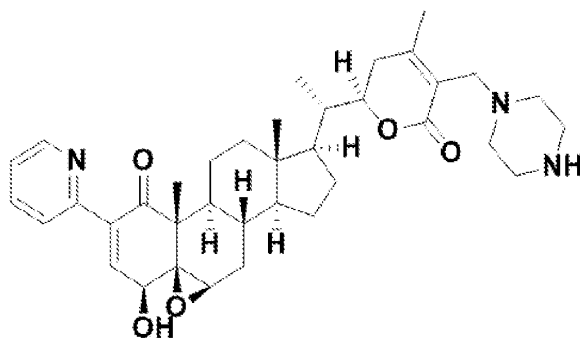
Compound 50



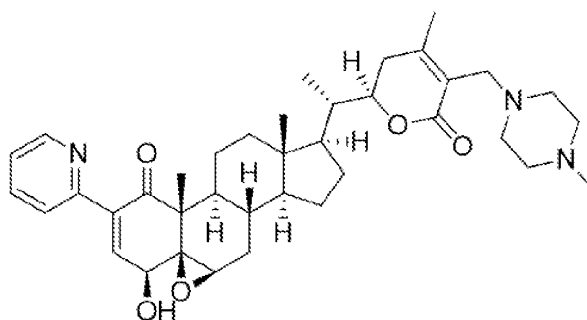
Compound 51



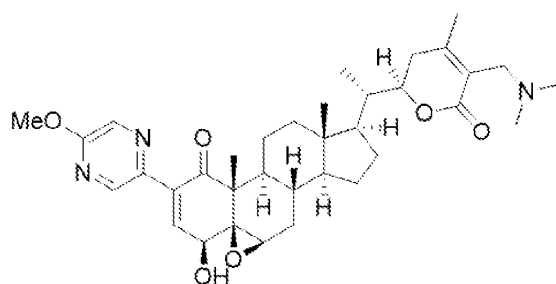
Compound 52



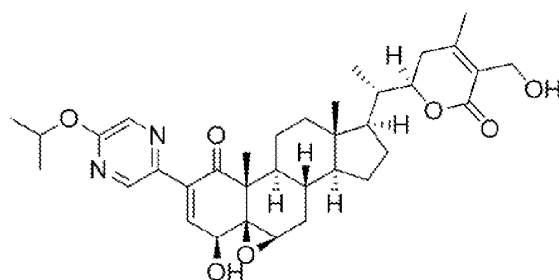
Compound 53



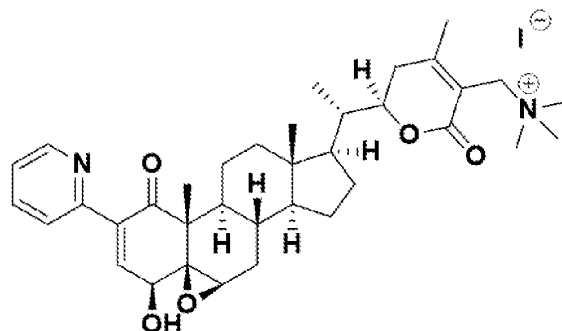
Compound 54



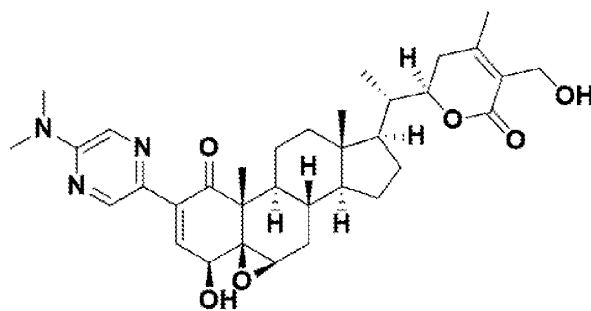
Compound 55



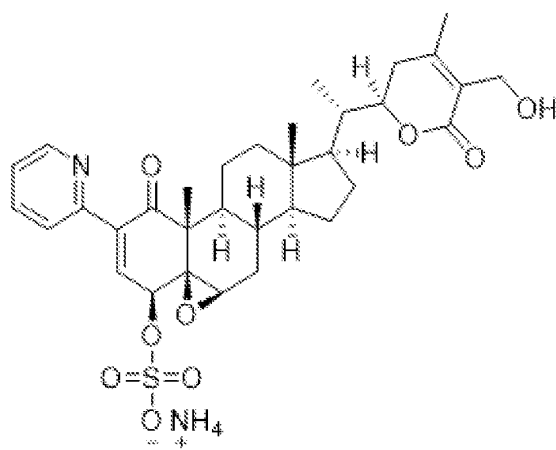
Compound 56



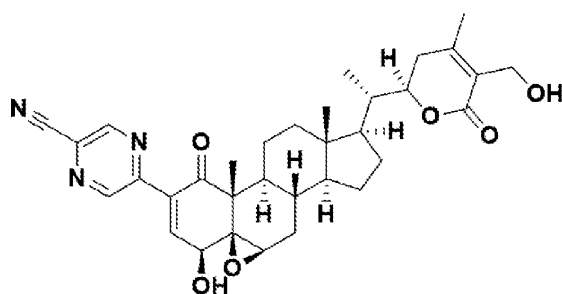
Compound 57



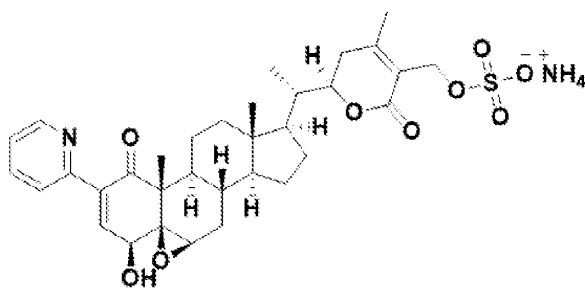
Compound 58



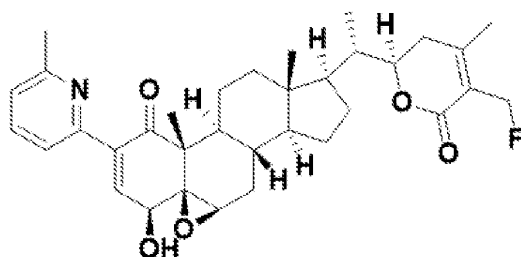
Compound 59



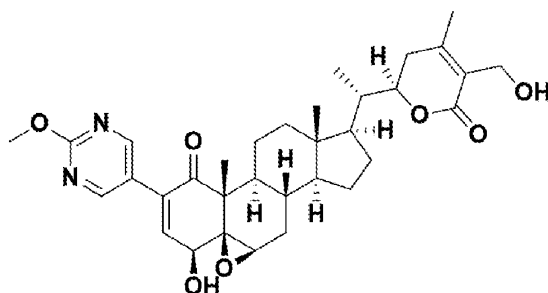
Compound 60



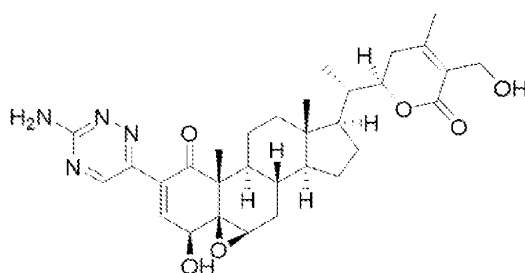
Compound 61



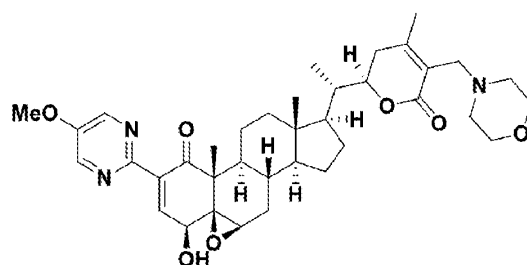
Compound 62



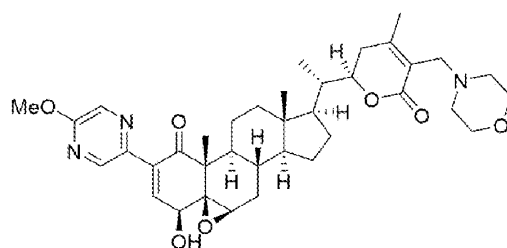
Compound 63



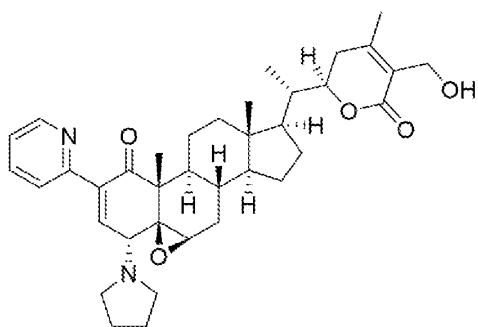
Compound 64



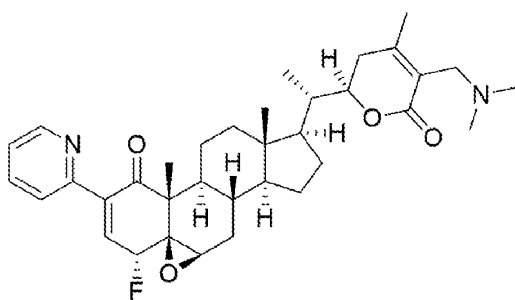
Compound 65



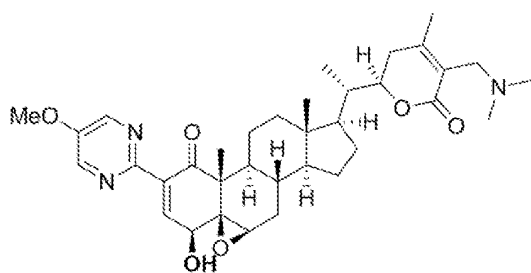
Compound 66



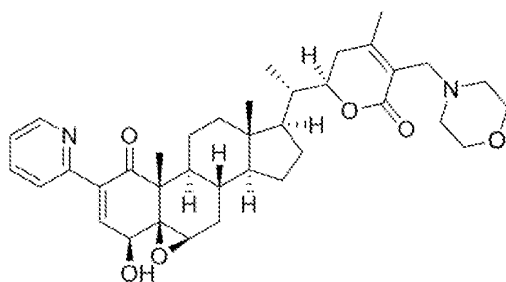
Compound 67



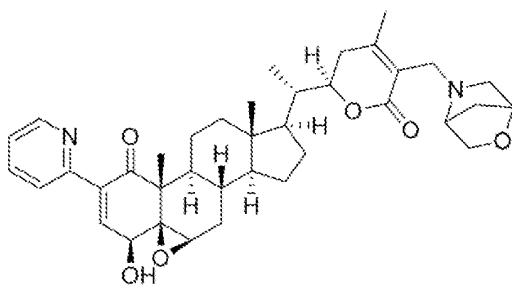
Compound 68



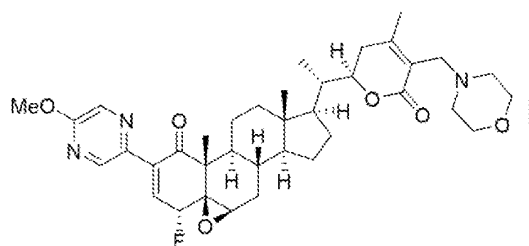
Compound 69



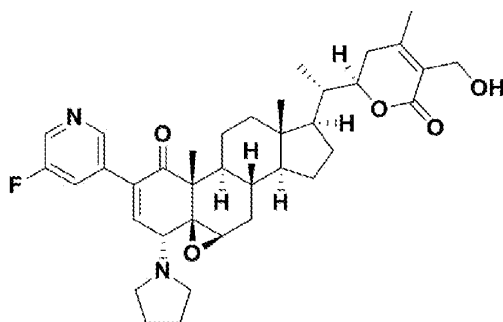
Compound 70



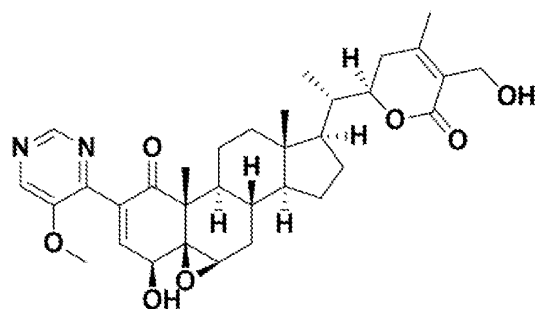
Compound 71



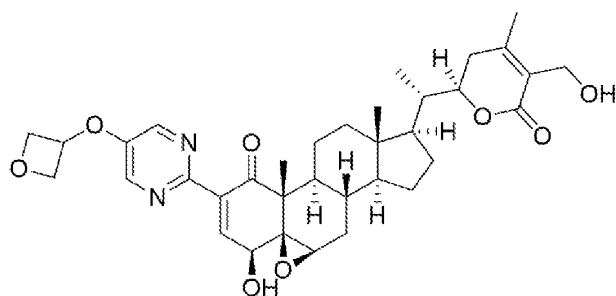
Compound 72



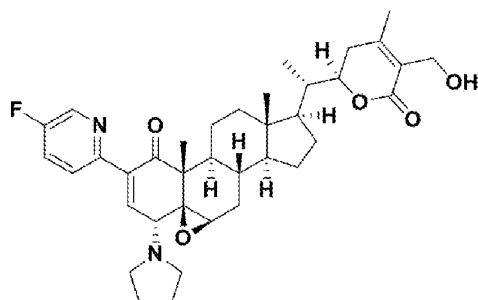
Compound 73



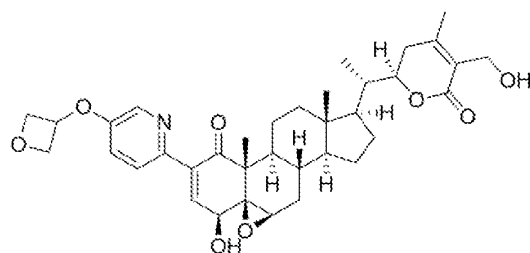
Compound 74



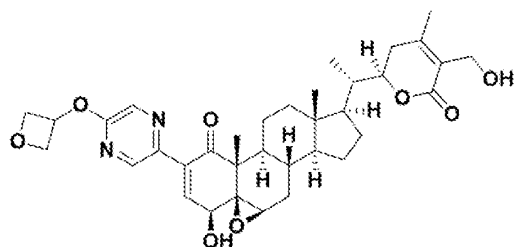
Compound 75



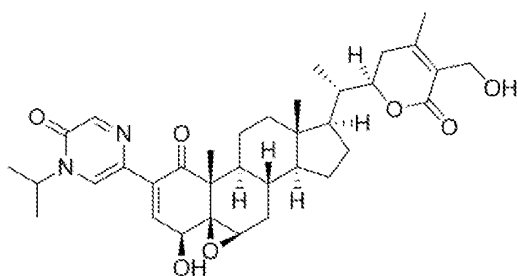
Compound 76



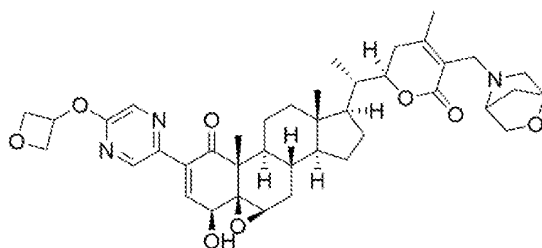
Compound 77



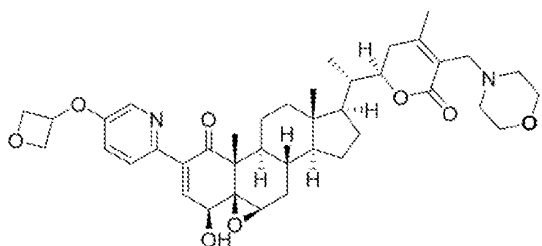
Compound 78



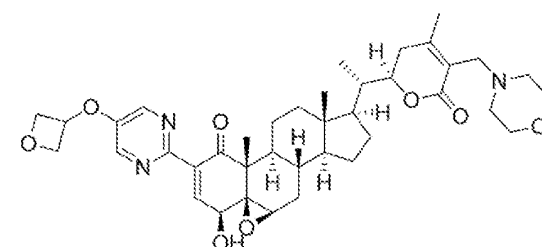
Compound 79



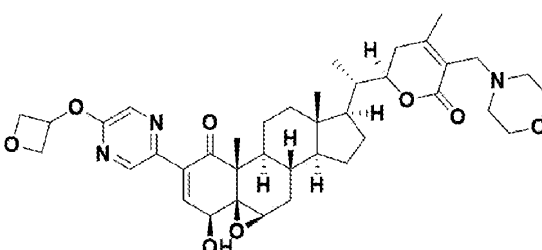
Compound 80



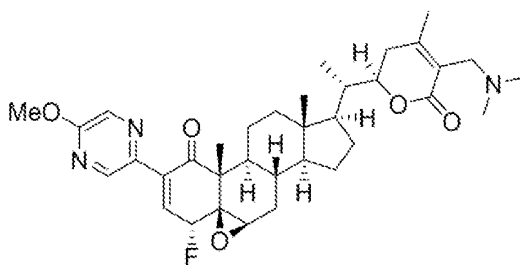
Compound 81



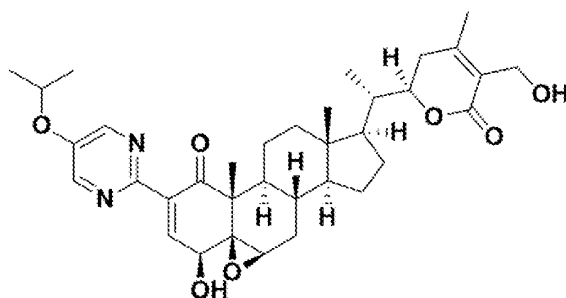
Compound 82



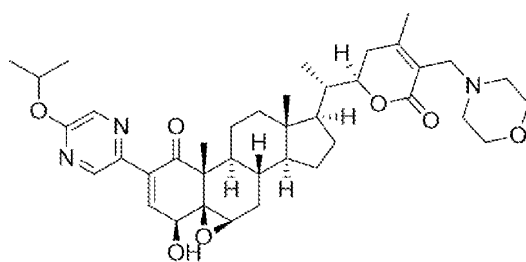
Compound 83



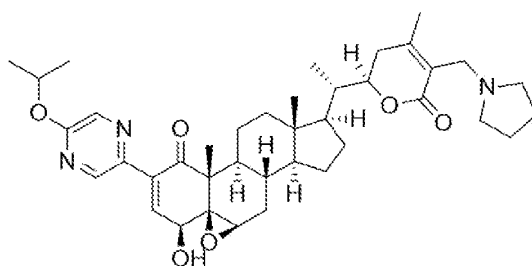
Compound 84



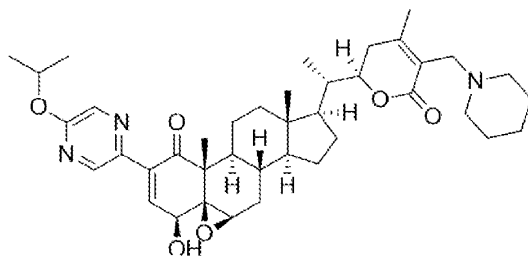
Compound 85



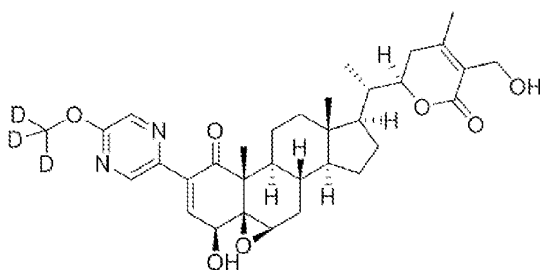
Compound 86



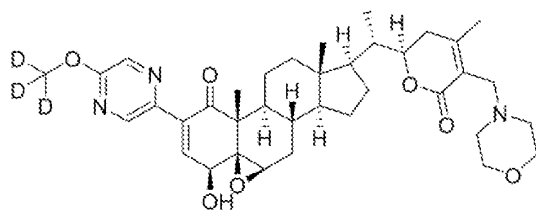
Compound 87



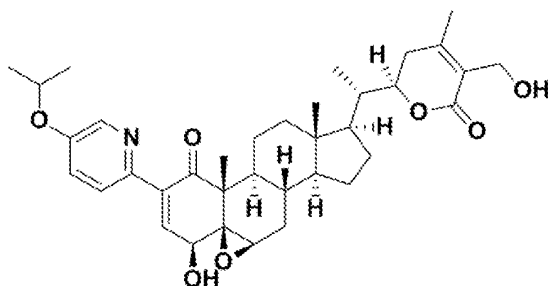
Compound 88



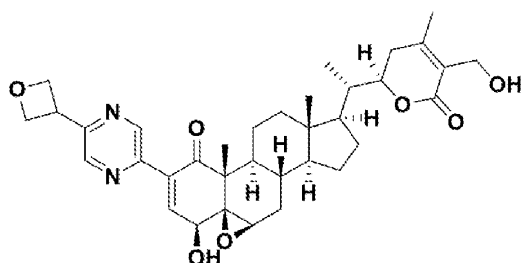
Compound 89



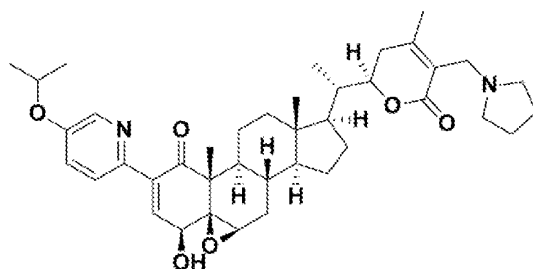
Compound 90



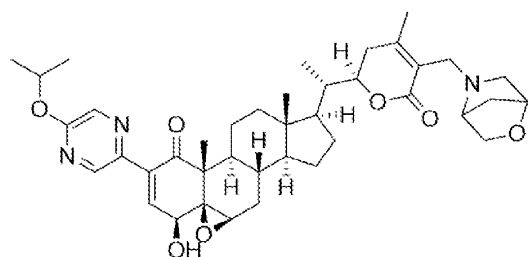
Compound 91



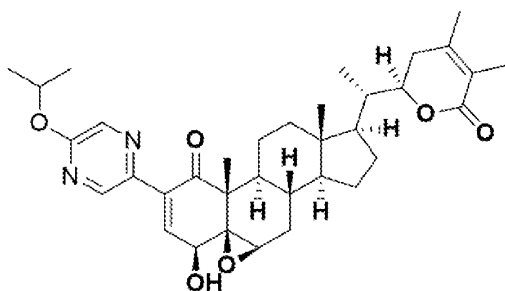
Compound 92



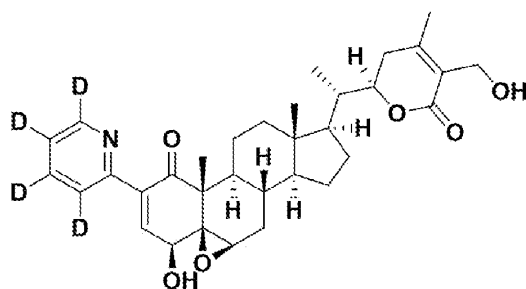
Compound 93



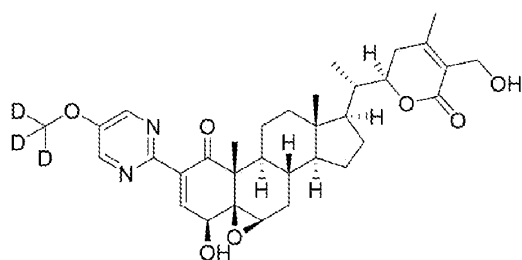
Compound 94



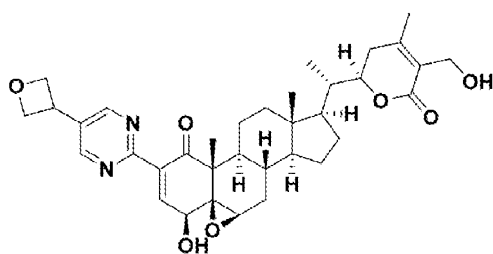
Compound 95



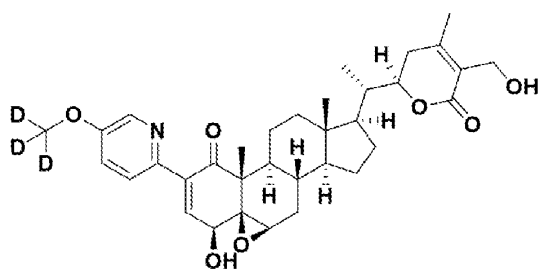
Compound 96



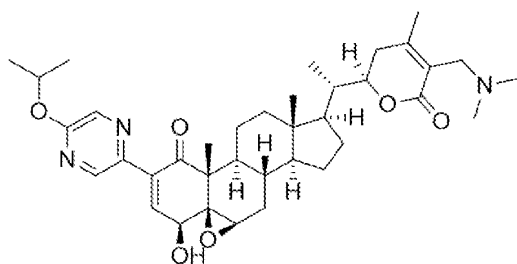
Compound 97



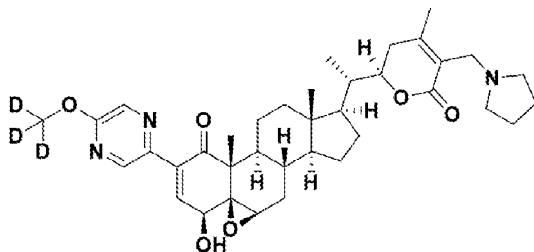
Compound 98



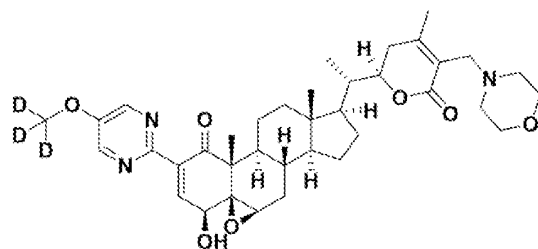
Compound 99



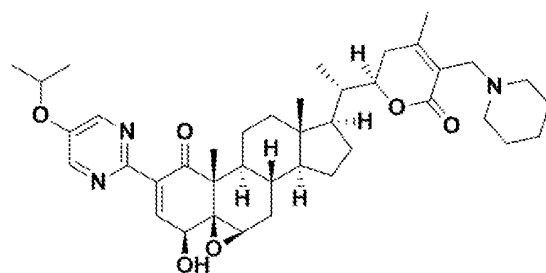
Compound 100



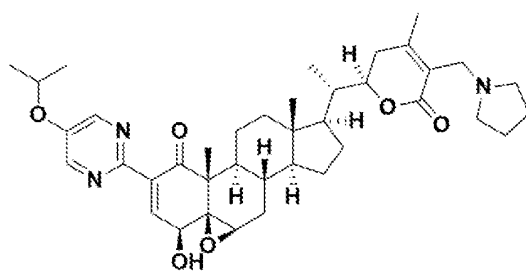
Compound 101



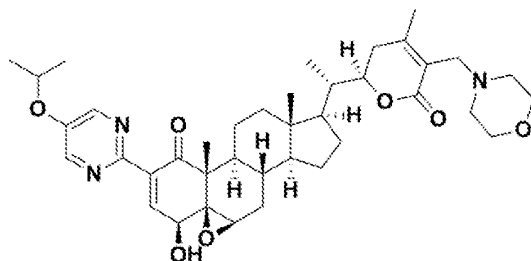
Compound 102



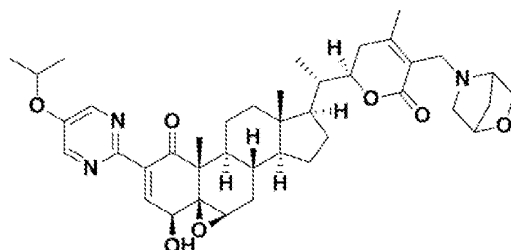
Compound 103



Compound 104



Compound 105



Pharmaceutically Acceptable Salts, Prodrugs, and Compositions

[0084] As described herein, the compounds of Formula (I) are provided as inhibitors or modulators of one or more of the following therapeutic targets: HSP90, NLRP3 inflammasome and TGF- β . In relation to, or independent of, this inhibitory or modulatory activity, the present compounds are useful for the treatment of diseases, disorders, and conditions including, but not limited to inflammatory bowel diseases, systemic inflammatory diseases, inflammatory skin diseases, gastrointestinal diseases, kidney diseases, cardiovascular diseases, liver diseases, autoimmune diseases, and respiratory diseases. Accordingly, in another aspect of the disclosure, pharmaceutically acceptable compositions are provided, wherein these compositions comprise any of the compounds of Formula (I) as described herein, and optionally comprise a pharmaceutically acceptable carrier, adjuvant or vehicle. In certain embodiments, these compositions optionally further comprise one or more additional therapeutic agents.

[0085] It will also be appreciated that certain compounds of this disclosure can exist in free form for treatment, or where appropriate, as a pharmaceutically acceptable derivative thereof. According to the disclosure, a pharmaceutically acceptable derivative includes, but is not limited to, pharmaceutically acceptable salts, esters, salts of such esters, or any other adduct or derivative which upon administration to a subject in need is capable of providing, directly or indirectly, a compound as otherwise described herein, or a metabolite or residue thereof.

Furthermore, a pharmaceutically acceptable derivative includes, but is not limited to, pharmaceutically acceptable prodrugs which upon administration to a subject in need is capable of providing, directly or indirectly, a compound as otherwise described herein, or a metabolite or residue thereof.

[0086] As used herein, the term “pharmaceutically acceptable salt” refers to those salts which are, within the scope of sound medical judgement, suitable for use in contact with the tissues of humans and lower animals without undue toxicity, irritation, allergic response and the like, and are commensurate with a reasonable benefit/risk ratio. A “pharmaceutically acceptable salt” means any non-toxic salt or salt of an ester of a compound of this disclosure that, upon administration to a recipient, is capable of providing, either directly or indirectly, a compound of this disclosure or an inhibitory active metabolite or residue thereof. As used herein, the term “inhibitory active metabolite or residue thereof” means that a metabolite or residue thereof is also an inhibitor or modulator of one or more of the therapeutic targets.

[0087] Pharmaceutically acceptable salts are well known in the art. For example, S. M. Berge, et al. describe pharmaceutically acceptable salts in detail in J. Pharmaceutical Sciences, 1977, 66, 1-19, incorporated herein by reference in its entirety. Pharmaceutically acceptable salts of the compounds of Formula (I) of this disclosure include those derived from suitable inorganic and organic acids and bases. Examples of pharmaceutically acceptable, nontoxic acid addition salts are salts of an amino group formed with inorganic acids such as hydrochloric acid, hydrobromic acid, phosphoric acid, sulfuric acid and perchloric acid or with organic acids such as acetic acid, oxalic acid, maleic acid, tartaric acid, citric acid, succinic acid or malonic acid or by using other methods used in the art such as ion exchange. Other pharmaceutically acceptable salts include adipate, alginate, ascorbate, aspartate, benzenesulfonate, benzoate, bisulfate, borate, butyrate, camphorate, camphorsulfonate, citrate, cyclopentanepropionate, digluconate, dodecylsulfate, ethanesulfonate, formate, fumarate, glucoheptonate, glycerophosphate, gluconate, hemisulfate, heptanoate, hexanoate, hydroiodide, 2-hydroxy-ethanesulfonate, lactobionate, lactate, laurate, lauryl sulfate, malate, maleate, malonate, methanesulfonate, 2-naphthalenesulfonate, nicotinate, nitrate, oleate, oxalate, palmitate, pamoate, pectinate, persulfate, 3-phenylpropionate, phosphate, picrate, pivalate, propionate, stearate, succinate, sulfate, tartrate, thiocyanate, p-toluenesulfonate, undecanoate, valerate salts, and the like. Salts derived from appropriate bases include alkali metal, alkaline earth metal, ammonium and $N^+(C_{1-4} \text{ alkyl})_4$ salts. This disclosure also envisions the quaternization

of any basic nitrogen-containing groups of the compounds of Formula (I) disclosed herein. Water or oil-soluble or dispersible products may be obtained by such quaternization. Representative alkali or alkaline earth metal salts include sodium, lithium, potassium, calcium, magnesium, and the like. Further pharmaceutically acceptable salts include, when appropriate, nontoxic ammonium, quaternary ammonium, and amine cations formed using counterions such as halide, hydroxide, carboxylate, sulfate, phosphate, nitrate, lower alkyl sulfonate and aryl sulfonate.

[0088] The term “pharmaceutically acceptable prodrugs” as used herein refers to those prodrugs of the compounds of the present disclosure which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of humans and lower animals without undue toxicity, irritation, allergic response, and the like, commensurate with a reasonable benefit/risk ratio, and effective for their intended use, as well as the zwitterionic forms, where possible, of the compounds of the disclosure. The term “prodrug” refers to compounds that are rapidly transformed in vivo to yield the parent compound of the above formula, for example by hydrolysis in blood, such an ester. A thorough discussion is provided in Higuchi, T., and V. Stella, “Pro-drugs as Novel Delivery Systems,” A.C.S. Symposium Series 14, and in “Bioreversible Carriers in Drug Design,” in Edward B. Roche (ed.), American Pharmaceutical Association, Pergamon Press, 1987, both of which are incorporated herein by reference.

[0089] As described herein, the pharmaceutically acceptable compositions of the disclosure additionally comprise a pharmaceutically acceptable carrier, adjuvant, or vehicle, which, as used herein, includes any and all solvents, diluents, or other liquid vehicle, dispersion or suspension aids, surface active agents, isotonic agents, thickening or emulsifying agents, preservatives, solid binders, lubricants and the like, as suited to the particular dosage form desired. Remington's Pharmaceutical Sciences, Sixteenth Edition, E. W. Martin (Mack Publishing Co., Easton, Pa., 1980) discloses various carriers used in formulating pharmaceutically acceptable compositions and known techniques for the preparation thereof. Except insofar as any conventional carrier medium is incompatible with the compounds of Formula (I) of the disclosure, such as by producing any undesirable biological effect or otherwise interacting in a deleterious manner with any other component(s) of the pharmaceutically acceptable composition, its use is contemplated to be within the scope of this disclosure. Some examples of materials which can serve as pharmaceutically acceptable

carriers include, but are not limited to, ion exchangers, alumina, aluminum stearate, lecithin, serum proteins, such as human serum albumin, buffer substances such as phosphates, glycine, sorbic acid, or 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, polyacrylates, waxes, polyethylene-polyoxypropylene-block polymers, wool fat, sugars such as lactose, glucose and sucrose; starches such as corn starch and potato starch; cellulose and its derivatives such as sodium carboxymethyl cellulose, ethyl cellulose and cellulose acetate; powdered tragacanth; malt; gelatin; talc; excipients such as cocoa butter and suppository waxes; oils such as peanut oil, cottonseed oil; safflower oil; sesame oil; olive oil; corn oil and soybean oil; glycols; such a propylene glycol or polyethylene glycol; esters such as ethyl oleate and ethyl laurate; agar; buffering agents such as magnesium hydroxide and aluminum hydroxide; alginic acid; pyrogen-free water; isotonic saline; Ringer's solution; ethyl alcohol, and phosphate buffer solutions, as well as other non-toxic compatible lubricants such as sodium lauryl sulfate and magnesium stearate, as well as coloring agents, releasing agents, coating agents, sweetening, flavoring and perfuming agents, preservatives and antioxidants can also be present in the composition, according to the judgment of the formulator.

[0090] In another aspect, the disclosure features a pharmaceutical composition comprising the compound of Formula (I) of the disclosure and a pharmaceutically acceptable carrier.

[0091] In another aspect, the disclosure features a pharmaceutical composition comprising a therapeutically effective amount of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, and one or more pharmaceutically acceptable carriers or vehicles.

[0092] The compound of Formula (I), or a pharmaceutically acceptable salt thereof used in the compositions administered may be obtained from any commercially available sources, or any methods or techniques known in the art. For example, in some variations, the compound of Formula (I) may be isolated from a natural source. In other variations, the compound of Formula (I) may be synthesized according to any methods known in the art.

[0093] Compositions for enteral or parenteral administration are, for example, those in unit dosage forms, such as sugar-coated tablets, tablets, capsules or suppositories, or ampoules. If not indicated otherwise, these are prepared in a manner known in the art, for example by conventional mixing, granulating, sugar-coating, dissolving or lyophilizing processes. It will

be appreciated that the unit content of the compound of Formula (I) contained in an individual dose of each dosage form need not in itself constitute a therapeutically effective amount since the necessary effective amount may be reached by administration of a plurality of dosage units.

[0094] In various embodiments, the composition includes the compound of Formula (I), or a pharmaceutically acceptable salt thereof, and optionally consists essentially of the compound of Formula (I), or a pharmaceutically acceptable salt thereof. As used herein, the phrase “consisting essentially of” generally encompasses the specifically recited elements/components for a particular embodiment. Further, the phrase “consisting essentially of” generally encompasses and allows for the presence of additional or optional elements/components that do not materially impact the basic and/or novel characteristics of that particular embodiment. In certain embodiments, “consisting essentially of” allows for the presence of ≤ 10 , ≤ 5 , or ≤ 1 , weight percent (wt. %) of additional or optional components based on the total weight of the composition.

[0095] In various embodiments, the composition includes one or more pharmaceutically acceptable additives that are inactive ingredients. Examples of inactive ingredients include, but are not limited to, excipients, such as diluents and binders, granulating agents, glidants (or flow aids), fillers, lubricants, preservatives, stabilizers, coatings, disintegrants, fragrances, pigments, preservatives, solvents (*e.g.*, alcohols), and combinations thereof. If utilized to form the composition, the inactive ingredient(s) can be used in various amounts and combined with the compound, or a pharmaceutically acceptable salt thereof, of Formula (I) to form a composition that is suitable for oral administration to humans or animals. It is to be further appreciated that the amounts of actives described herein can be normalized with respect to 100 parts by weight of the composition to account for the presence of inactive ingredients (if utilized).

[0096] Optionally, the composition may include one or more additional components such as additives. Suitable additives include those understood in the art, including but not limited to, moisturizers, emollients, emulsifiers, surfactants, oils, extracts, skin protectants, disinfectants, antiseptics, drugs and drug substances, analgesic compounds, anti-neuralgic compound, anti-oxidants, blood circulation promoters, antidepressant compounds, anti-anxiety compounds, anti-stress compounds, sunscreens, insect repellants, preservatives, exfoliants, fragrances, colors, fillers, solvents, vehicles, carriers, other types of additives known to those of skill in the art, and combinations thereof. Such additives may be utilized alone or in

combination. In general, the optional additives may be of any type used in pharmaceuticals, nutraceuticals, personal care products and cosmetic products.

[0097] Examples of such carrier components are oils, fats, waxes, surfactants, humectants, thickening agents, antioxidants, viscosity stabilizers, chelating agents, buffers, preservatives, perfumes, dyestuffs, lower alkanols, and the like. If desired, further ingredients may be incorporated in the compositions, *e.g.*, anti-inflammatory agents, antibacterials, antifungals, disinfectants, vitamins, sunscreens, antibiotics, skin bleaching agents, healing enhancers/fibroblast proliferation compounds, neuromuscular blocking agents, sunscreens, or other anti-acne agents.

[0098] Examples of oils as a carrier agent comprises fats and oils such as olive oil and hydrogenated oils; waxes such as beeswax and lanolin; hydrocarbons such as liquid paraffin, ceresin, and squalene; fatty acids such as stearic acid and oleic acid; alcohols such as cetyl alcohol, stearyl alcohol, lanolin alcohol, and hexadecanol; and esters such as isopropyl myristate, isopropyl palmitate and butyl stearate. As examples of surfactants as carrier agents, there may be cited anionic surfactants such as sodium stearate, sodium cetylsulfate, polyoxyethylene laurylether phosphate, sodium N-acyl glutamate; cationic surfactants such as stearyl dimethylbenzylammonium chloride and stearyl trimethylammonium chloride; ampholytic surfactants such as alkylaminoethylglycine hydrochloride solutions and lecithin; and nonionic surfactants such as glycerin monostearate, sorbitan monostearate, sucrose fatty acid esters, propylene glycol monostearate, polyoxyethylene oleylether, polyethylene glycol monostearate, polyoxyethylene sorbitan monopalmitate, polyoxyethylene coconut fatty acid monoethanolamide, polyoxypropylene glycol (such as the materials sold under the trademark "Pluronic"), polyoxyethylene castor oil, and polyoxyethylene lanolin. Examples of humectants as carrier agents include glycerin, 1,3-butylene glycol, and propylene glycol; examples of lower alcohols include ethanol and isopropanol; examples of thickening agents include xanthan gum, hydroxypropyl cellulose, hydroxypropyl methyl cellulose, polyethylene glycol and, sodium carboxymethyl cellulose. Examples of antioxidants comprise butylated hydroxytoluene, butylated hydroxyanisole, propyl gallate, citric acid, ethoxyquin, alpha lipoic acid, vitamin C, vitamin E, co-enzyme Q-10, and idebenone; botanical anti-oxidants include carotenoids such as lycopene; flavonoids such as silymarin (milk thistle), silybin, silydianin, silychristine; soybeans (isoflavins), grape seed extract; polyphenols such as green tea extract, rosmarinic acid (rosemary), hypericin (Saint John's wort), oleuropein (olive leaf), curcumin (tumeric root),

tetrahydrocurcumin, and pycogenol (marine bark pine). Examples of anti-inflammatory agents include anti-inflammatory botanicals such as allantoin, aloe vera, ginkgo biloba, green tea (also considered an antioxidant). Examples of skin bleaching agents are hydroquinone or kojic acid. Examples of healing enhancers/fibroblast proliferation compounds include copper peptides or palmitoyl-pentapeptide (pal-KTTKS). Examples of neuromuscular blocking agents such as acetyl hexapeptide 3 (argircline) or dimethylaminoethanol. Examples of chelating agents include disodium edetate and ethanediol diphosphate. Examples of buffers as carrier agents comprise citric acid, sodium citrate, boric acid, borax, and disodium hydrogen phosphate; and examples of preservatives are methyl parahydroxybenzoate, ethyl parahydroxybenzoate, dehydroacetic acid, salicylic acid and benzoic acid.

[0099] It is to be appreciated that certain components or additives may be classified under different terms of art and just because a component or additive is classified under such a term does not mean that they are limited to that function. If utilized, the additive or additives may be present in the composition in various amounts. Additional ingredients for optional use in the composition are described in U.S. Pat. No. 5,747,006 to Dornoff et al., U.S. Pat. Nos. 5,980,904, 6,994,874, 7,060,304, 7,247,321, and 7,364,759 to Leverett et al., and U.S. Publication No. 2017/0252293 to Brumbaugh et al., the disclosures of which are hereby incorporated by reference in their entirety.

[0100] The composition can be prepared using various methods. For example, actives of the composition, and optionally one or more inactives, can be mixed or blended and compressed or compounded utilizing various techniques understood in the art. The composition of this disclosure is not limited to a particular order of manufacturing steps or method of manufacture.

[0101] The composition may comprise at least about 0.375% w/w, at least about 0.75% w/w, at least about 1% w/w, at least about 1.5% w/w, at least about 3% w/w, at least 4% w/w, at least 5% w/w, at least 6% w/w, at least 7% w/w, at least 8% w/w, at least 9% w/w, at least 10% w/w, at least 11% w/w, at least 12% w/w, at least 13% w/w, at least 14% w/w, at least 15% w/w, at least 16% w/w, at least 17% w/w, at least 18% w/w, at least 19% w/w, at least 20% w/w, or even more of the compound, or a pharmaceutically acceptable salt thereof, of Formula (I). In certain variations, the composition comprises about 0.375%, about 0.75%, about 1%, about 1.5%, about 3% w/w, about 4% w/w, about 5% w/w, about 6% w/w, about 7% w/w, about 8% w/w, about 9% w/w, about 10% w/w, about 11% w/w, about 12% w/w,

about 13% w/w, about 14% w/w, about 15% w/w, about 16% w/w, about 17% w/w, about 18% w/w, about 19% w/w, about 20% w/w, or even more of the compound of Formula (I), or a pharmaceutically acceptable salt thereof.

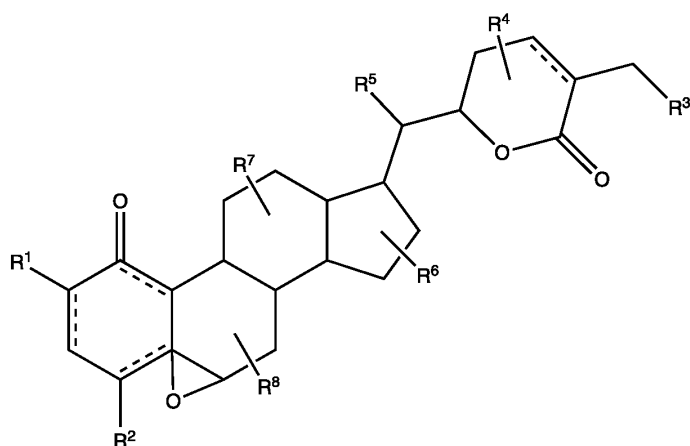
[0102] In certain variations, the composition comprises between about 0.1% and about 20% w/w, between about 0.1% and about 15% w/w, between about 0.1% and about 5% w/w, between about 0.1% and about 3% w/w, between about 0.1% and about 1.5% w/w, between about 0.1% and about 1% w/w, between about 0.1% and about 0.75% w/w, between about 0.1% and about 0.375% w/w, between about 0.375% and about 5% w/w, between about 0.375% and about 3% w/w, between about 0.375% and about 1.5% w/w, between about 0.375% and about 1% w/w, between about 0.375% and about 0.75% w/w, between about 0.75% and about 5% w/w, between about 0.75% and about 3% w/w, between about 0.75% and about 1.5% w/w, between about 0.75% and about 1% w/w, between about 1% and about 5% w/w, between about 1% and about 3% w/w, between about 1% and about 1.5% w/w, between about 1.5% and about 5% w/w, between about 1.5% and about 3% w/w, between about 3% and about 5% w/w, between about 1% and about 15% w/w, between about 2% and about 10% w/w, between about 4% and about 8% w/w, between about 5% and about 15% w/w, or between about 8% and about 12% w/w of the compound of Formula (I), or a pharmaceutically acceptable salt thereof.

[0103] In other embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is present in the composition has a purity of at least about 50% w/w, at least about 60% w/w, at least about 70% w/w, at least about 75% w/w, at least about 80% w/w, at least about 90% w/w, at least about 95% w/w, at least about 96% w/w, at least about 97% w/w, at least about 98% w/w, at least about 99% w/w, at least about 99.9% w/w, at least about 99.99% w/w, or at least about 99.999% w/w; or a purity of about 100% w/w.

[0104] In other variations of the foregoing, the composition further comprises one or more additional components, including for example, fragrances, colorants, and/or excipients.

Uses of Compounds and Pharmaceutically Acceptable Salts and Compositions

[0105] In one aspect, provided herein is a method of treating, ameliorating, or preventing a condition or disease in a subject in need thereof, comprising administering a compound of formula (I):

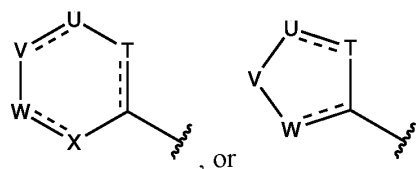


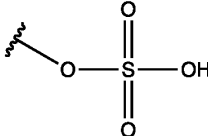
(I), or a pharmaceutically

acceptable salt thereof, wherein:

R¹ is hydrogen, -NR⁹R¹⁰, -COOR⁹, -CN,

R² is hydrogen, halogen, -OR⁹, -SR⁹, -NR⁹R¹⁰, -COOR⁹, -COHR⁹R¹⁰, -CR⁹R¹⁰R¹¹, -CN, -N₃, C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₁-C₆ alkoxy, aryl,



aralkyl, heteroaryl, cycloaliphatic ring, heterocyclyl, or , wherein the C₁-C₆ alkyl, the aryl, the heteroaryl, cycloaliphatic ring, or heterocyclyl are unsubstituted or substituted with one or more R¹²;

R³ is hydrogen, halogen, -OR⁹, -SR⁹, -NR⁹R¹⁰, -COOR⁹, -COHR⁹R¹⁰, -CR⁹R¹⁰R¹¹, -CN, -N₃, C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₁-C₆ alkoxy, aryl, aralkyl, heteroaryl, cycloaliphatic ring, heterocyclyl, -(NR⁹R¹⁰R¹¹)⁺, or -OC(=O)NH-(C₂-C₆ alkynyl), wherein the C₁-C₆ alkyl, the aryl, the heteroaryl, cycloaliphatic ring, or heterocyclyl are unsubstituted or substituted with one or more R¹²;

T, U, V, W, and X are each, independently, CH, CR¹², sulfur, nitrogen, NH, NR¹², or N⁺-O⁻;

R⁴, R⁵, R⁶, R⁷, R⁸, R⁹, R¹⁰, and R¹¹ are each, independently, hydrogen, deuterium, halogen, or a C₁-C₆ unsubstituted or substituted alkyl; and

each R¹² is, independently, deuterium, halogen, =O, -OR⁹, -SR⁹, -NR⁹R¹⁰, -COOR⁹, -COHR⁹R¹⁰, -CR⁹R¹⁰R¹¹, -CN, -N₃, C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl,

C₁-C₆ alkoxy, aryl, aralkyl, heteroaryl, cycloaliphatic ring, heterocyclyl, or -O-(heterocyclyl). In some embodiments, the compound of Formula (I) is administered in a therapeutically effective amount. In some embodiments, the condition or disease is mediated by the NLR Family Pyrin Domain Containing 3 (NLRP3) inflammasome. In some embodiments, the condition or disease is mediated by tumor necrosis factor alpha (TNF- α).

[0106] In another aspect, provided herein is a compound of Formula (I) as described herein, or a pharmaceutically acceptable salt thereof, for use in treating, ameliorating, or preventing a condition or disease. In some embodiments, the condition or disease is mediated by the NLR Family Pyrin Domain Containing 3 (NLRP3) inflammasome. In some embodiments, the condition or disease is mediated by tumor necrosis factor alpha (TNF- α).

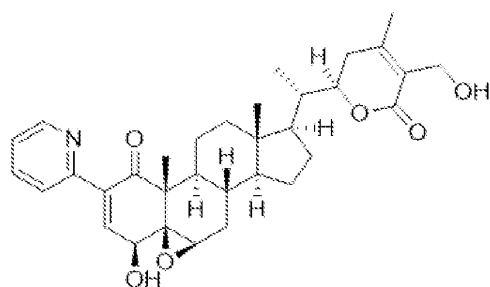
[0107] In another aspect, provided herein is a use of a compound of Formula (I) as described herein, or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for treating, ameliorating, or preventing a condition or disease. In some embodiments, the condition or disease is mediated by the NLR Family Pyrin Domain Containing 3 (NLRP3) inflammasome. In some embodiments, the condition or disease is mediated by tumor necrosis factor alpha (TNF- α).

[0108] In some embodiments, the condition or disease is selected from the group consisting of inflammatory bowel diseases such as ulcerative colitis (UC), and Crohn's disease; systemic inflammatory diseases such as autoinflammatory disorders, Cryopyrin-associated periodic syndromes, familial cold autoinflammatory syndrome (FCAS), Muckle-Wells syndrome (MWS), chronic infantile neurologic cutaneous articular (CINCA) syndrome, and neonatal onset multi-system inflammatory disease (NOMID); inflammatory skin diseases such as acne vulgaris, hidradenitis suppurativa, and psoriasis; gastrointestinal diseases such as colorectal cancer; kidney diseases such as acute kidney injury, chronic kidney disease, and diabetic kidney disease; cardiovascular diseases such as coronary atherosclerotic heart disease, cardiomyopathy, myocardial infarction, cardiac hypertrophy, and ischaemia-reperfusion injury; liver diseases such as nonalcoholic fatty liver disease, nonalcoholic steatohepatitis, alcoholic steatohepatitis, chronic hepatitis C virus infection, paracetamol-induced liver injury, and alcoholic liver injury; autoimmune diseases such as gout, pseudo gout, rheumatoid arthritis (RA), multiple sclerosis (MS), Addison's disease, celiac disease, systemic lupus erythematosus (SLE), and vitiligo; and respiratory diseases such as chronic pulmonary diseases, idiopathic pulmonary fibrosis (IPF), chronic obstructive pulmonary disease (COPD), and asthma. In

various embodiments, the compounds of Formula (I) and pharmaceutically acceptable compositions are inhibitors or modulators of one or more of the following therapeutic targets: HSP90, NLRP3 inflammasome and TGF- β , and thus are useful for treating or lessening the severity of the variety of diseases, disorders, or conditions described herein.

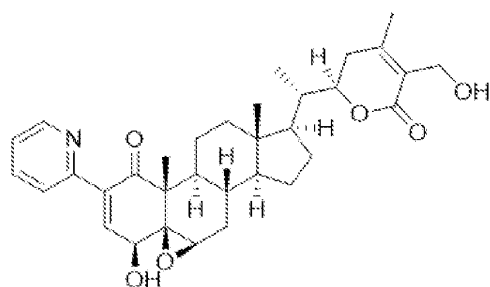
[0109] In some embodiments, the condition or disease is a tumor necrosis factor alpha (TNF- α)-mediated condition or disease. In some embodiments, the condition or disease is an NLR Family Pyrin Domain Containing 3 (NLRP3) inflammasome-mediated condition or disease. In some embodiments, the condition or disease is selected from the group of inflammatory bowel disease (IBD), Crohn's disease, colorectal cancer, alcoholic hepatitis, or a combination thereof. In some embodiments, the condition or disease is selected from the group of inflammatory bowel disease (IBD), Crohn's disease, or a combination thereof. In some embodiments, the condition or disease is selected from the group of colorectal cancer, alcoholic hepatitis, or a combination thereof.

[0110] In some embodiments, the compound of Formula (I) is



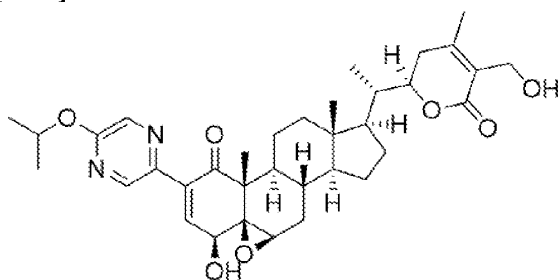
, or a pharmaceutically acceptable salt thereof.

[0111] In some embodiments, provided herein is a method of treating, ameliorating, or preventing inflammatory bowel disease (IBD) in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of



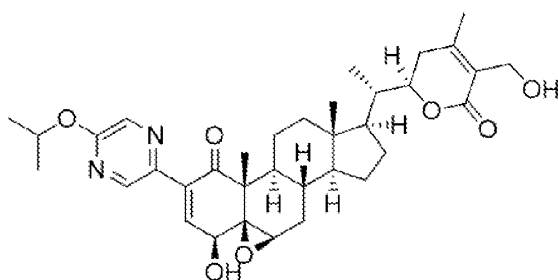
, or a pharmaceutically acceptable salt thereof.

[0112] In some embodiments, the compound of Formula (I) is



, or a pharmaceutically acceptable salt thereof.

[0113] In some embodiments, provided herein is a method of treating, ameliorating, or preventing alcoholic hepatitis in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of



, or a pharmaceutically acceptable salt thereof.

[0114] In various embodiments, the terms “inhibits” and “modulates” are used interchangeably to refer to the reduction or suppression of a given condition, symptom, or disorder, or disease, or a significant decrease in the baseline activity of a biological activity or process. Specifically, in some embodiment, inhibiting NLRP3 or inhibiting NLRP3 inflammasome pathway comprises reducing the ability of NLRP3 or NLRP3 inflammasome pathway to induce the production of IL-1 beta and/or IL-18. This can be achieved by mechanisms, including, but not limited to, inactivating, destabilizing, and/or altering distribution of NLRP3. This can be achieved by mechanisms, including, but not limited to, inactivating, destabilizing, and/or altering distribution of NLRP3. In other embodiments, inhibiting HSP90 or inhibiting HSP90 pathway comprises reducing the ability of HSP90 to stabilize NLRP3 and therefore reduce the ability of NLRP3 to induce the production of IL-1 beta and/or IL-18. This can be achieved by mechanisms, including, but not limited to, inactivating, destabilizing, and/or altering distribution of HSP90.

[0115] In certain embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, inhibits or modulated one or more of the therapeutic targets with an IC_{50} less than 50 micromolar (μM), optionally less than 40 μM , optionally less than 30 μM , optionally less than 20 μM , optionally less than 10 μM , or optionally less than 1 μM . Alternatively, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, inhibits or modulated one or more of the therapeutic targets with an IC_{50} from about 0.01 μM to about 100 μM , optionally from about 0.1 μM to about 75 μM , optionally from about 1 μM to about 50 μM , optionally from about 1 μM to about 25 μM , or optionally from about 1 μM to about 10 μM .

[0116] In some embodiments, “treating” or “treatment” refers to both prophylactic or preventative treatment as well as curative or disease modifying treatment, including treatment of patient at risk of contracting the disease or suspected to have contracted the disease as well as patients who are ill or have been diagnosed as suffering from a disease or medical condition, and includes suppression of clinical relapse. In these and other embodiments, “treating” or “treatment” refers to obtaining beneficial or desired results, for example clinical results, in a subject, including: (1) alleviating one or more symptoms caused by or associated with a disease, disorder, or condition; (2) reducing the extent of the disease, disorder, or condition; (3) slowing or stopping the development or progression of one or more symptoms caused by or associated with the disease, disorder, or condition (for example, stabilizing the disease, disorder, or condition); and (4) relieving the disease, for example, by causing the regression of one or more clinical symptoms (*e.g.*, ameliorating the disease state, enhancing the effect of another medication, delaying or stopping the progression of the disease, and/or increasing the quality of life).

[0117] In some aspects, the disclosure features a method of treating or lessening the severity in a subject of variety of diseases, disorders, or conditions comprising administering a therapeutically effective amount of a compound of Formula (I), a pharmaceutically acceptable salt thereof or a pharmaceutical composition of the compound, or a pharmaceutically acceptable salt thereof.

[0118] The term “a therapeutically effective amount” of a compound of the present disclosure refers to an amount of the compound of the present disclosure that will elicit the biological or medical response of a subject, for example, reduction or inhibition of an enzyme or a protein activity, or ameliorate symptoms, alleviate conditions, slow or delay disease

progression, or prevent a disease, etc. In one non-limiting embodiment, the term “a therapeutically effective amount” refers to the amount of the compound of the present disclosure that, when administered to a subject, is effective to (1) at least partially alleviate, inhibit, prevent and/or ameliorate a condition, or a disorder or a disease (i) mediated by NLRP3, or (ii) associated with NLRP3 activity, or (iii) characterized by activity (normal or abnormal) of NLRP3; (2) reduce or inhibit the activity of NLRP3 (*e.g.*, by binding to the C-terminal of HSP90 for preventing stabilization of NLRP3 by HSP90); or (3) reduce or inhibit the expression of NLRP3. In another non-limiting embodiment, the term “a therapeutically effective amount” of a compound of the present disclosure refers to the amount that when administered to a cell, or a tissue, or a non-cellular biological material, or a medium, is effective to at least partially reduce or inhibit the activity of NLRP3; or at least partially reduce or inhibit the expression of NLRP3. The therapeutically effective amount may be ascertained experimentally.

[0119] In some embodiments, the method comprises administering to the subject the compound of Formula (I), or a pharmaceutically acceptable salt thereof, in an excipient to form a composition. The composition may comprise between 10-500 mg, or between 10-800 mg, or between 20-1,000 mg, or between 30-1,200 mg, or between 50-1,500 mg, or between 100-2,000 mg or even more of the compound of Formula (I), or a pharmaceutically acceptable salt thereof in a single dosage unit. Viewed from a different perspective, at least 20 wt%, or at least 30 wt%, or at least 40 wt%, or at least 50 wt%, or at least 60 wt%, or at least 70 wt%, or at least 80 wt%, or at least 90 wt% of the composition will be the compound of Formula (I), or a pharmaceutically acceptable salt thereof. Consequently, preferred oral single dosage units (or recommended daily uptake) will be between 20-200 mg, or between 40-400 mg, or between 60-600 mg, or between 80-800 mg, or between 100-1,000 mg, or between 200-2,000 mg, and in some cases even higher.

[0120] As used herein, the term “administering” a pharmaceutical composition or drug refers to both direct and indirect administration of the pharmaceutical composition or drug, wherein direct administration of the pharmaceutical composition or drug is typically performed by a health care professional (*e.g.*, physician, nurse, etc.), and wherein indirect administration includes a step of providing or making available the pharmaceutical composition or drug to the health care professional for direct administration (*e.g.*, via injection, infusion, oral delivery, topical delivery, etc.).

[0121] In some variations, the method comprises administering to the subject a compound of Formula (I), or a pharmaceutically acceptable salt thereof, in a petroleum-based vehicle, such as petroleum jelly to form a composition. The composition comprises at least about 0.375% w/w, at least about 0.75% w/w, at least about 1% w/w, at least about 1.5% w/w, at least about 3% w/w, at least 4% w/w, at least 5% w/w, at least 6% w/w, at least 7% w/w, at least 8% w/w, at least 9% w/w, at least 10% w/w, at least 11% w/w, at least 12% w/w, at least 13% w/w, at least 14% w/w, at least 15% w/w, at least 16% w/w, at least 17% w/w, at least 18% w/w, at least 19% w/w, at least 20% w/w, or even more of Formula (I) or a pharmaceutically acceptable salt thereof. In certain variations, the composition comprises about 0.375%, about 0.75%, about 1%, about 1.5%, about 3% w/w, about 4% w/w, about 5% w/w, about 6% w/w, about 7% w/w, about 8% w/w, about 9% w/w, about 10% w/w, about 11% w/w, about 12% w/w, about 13% w/w, about 14% w/w, about 15% w/w, about 16% w/w, about 17% w/w, about 18% w/w, about 19% w/w, about 20% w/w, or even more of a compound of Formula (I) or a pharmaceutically acceptable salt thereof.

[0122] In various embodiments, the amount of composition administered to the subject is based on the amount of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, in milligrams (mg) per area of skin in centimeters-squared (cm²). The composition may be administered to the subject in an amount of at least 0.01 mg/cm² (mg of the compound per cm² of skin), at least 0.02 mg/cm², at least 0.03 mg/cm², at least 0.04 mg/cm², at least 0.05 mg/cm², at least 0.06 mg/cm², at least 0.07 mg/cm², at least 0.08 mg/cm², at least 0.09 mg/cm², at least 0.1 mg/cm², at least 0.12 mg/cm², at least 0.14 mg/cm², at least 0.16 mg/cm², at least 0.18 mg/cm², at least 0.2 mg/cm², at least 0.22 mg/cm², at least 0.24 mg/cm², at least 0.26 mg/cm², at least 0.28 mg/cm², at least 0.3 mg/cm², at least 0.32 mg/cm², at least 0.34 mg/cm², at least 0.36 mg/cm², at least 0.38 mg/cm², at least 0.4 mg/cm², or even more. The composition may be administered to the subject in an amount of between about 0.01 mg/cm² and about 0.4 mg/cm², between about 0.05 mg/cm² and about 0.3 mg/cm², between about 0.1 mg/cm² and about 0.3 mg/cm², or between about 0.15 mg/cm² and about 0.25 mg/cm².

[0123] The composition may be applied as needed, daily, several times per day or in any suitable regimen such that the desired outcome is achieved. In the method of this disclosure, the frequency of administration (*e.g.*, oral application) can depend on several factors, including the severity of the condition or symptoms of the same or the desired level of relief from the symptoms. Generally, a regimen includes application of the composition once or twice daily to

include an administration in the morning and/or an administration in the evening. The amount and/or frequency of application of the composition may depend on several factors, including the level of desired results and the specific composition. In some embodiments, the composition is administered once per day. In other embodiments, the composition is administered twice per day. In still other embodiments, the composition is administered three times per day. In yet other embodiments, the composition is administered four times per day. However, it is to be appreciated that the composition may be administered more than four times per day.

[0124] In some variations, the composition is administered for at least about 1 week, at least about 2 weeks, at least about 3 weeks, at least about 4 weeks, at least about 8 weeks, at least about 12 weeks, at least about 16 weeks, at least about 24 weeks, at least about 32 weeks, at least about 40 weeks, at least about 48 weeks, or at least about 1 year. In certain variations, the composition is administered for about 1 week, about 2 weeks, about 3 weeks, about 4 weeks, about 8 weeks, about 12 weeks, about 16 weeks, about 24 weeks, about 32 weeks, about 40 weeks, about 48 weeks, or about 1 year. In one variation, the composition is administered for between about 1 week and about 1 year, between about 4 weeks and about 8 weeks, between about 4 weeks and about 12 weeks, between about 4 weeks and about 16 weeks, between about 4 weeks and about 24 weeks, between about 4 weeks and about 32 weeks, between about 4 weeks and about 40 weeks, between about 4 weeks and about 48 weeks, or between about 4 weeks and about 1 year.

[0125] The compound of Formula (I) or a pharmaceutically acceptable salt thereof or a pharmaceutical composition thereof, may be administered as described herein. In some embodiments, the composition is topically administered to the subject. In other embodiments, the composition is orally administered.

[0126] In another aspect, the disclosure features a method of inhibiting a therapeutic target, such as at least one of HSP90, NLRP3 inflammasome and TGF- β , in a subject comprising administering to the subject a compound of Formula (I) or a pharmaceutically acceptable salt thereof or a pharmaceutical composition thereof.

[0127] In some exemplary embodiments, the disclosure features a method of treating or lessening the severity in a subject of inflammatory bowel diseases, such as ulcerative colitis and Crohn's disease comprising administering a therapeutically effective amount of a

compound of Formula (I), a pharmaceutically acceptable salt thereof or a pharmaceutical composition of the compound, or a pharmaceutically acceptable salt thereof.

[0128] In other exemplary embodiments, the disclosure features a method of treating or lessening the severity in a subject of gastrointestinal diseases, such as colorectal cancer comprising administering a therapeutically effective amount of a compound of Formula (I), a pharmaceutically acceptable salt thereof or a pharmaceutical composition of the compound, or a pharmaceutically acceptable salt thereof.

[0129] In some variations of the foregoing, the subject is formally diagnosed or clinically diagnosed with an inflammatory bowel disease, such as ulcerative colitis and Crohn's disease, or a gastrointestinal disease, such as colorectal cancer.

Manufacture of Medicaments

[0130] All methods described herein can be performed in any suitable order unless otherwise indicated herein or otherwise clearly contradicted by context. The use of any and all examples, or exemplary language (e.g., “such as”) provided herein is intended merely to better illuminate the disclosure and does not impose a limitation on the scope of the disclosure otherwise claimed.

[0131] Any asymmetric atom (e.g., carbon or the like) of the compound(s) of the present disclosure can be present in racemic or enantiomerically enriched, for example the (R)-, (S)- or (R,S)-configuration. In certain embodiments, each asymmetric atom has at least 50% enantiomeric excess, at least 60% enantiomeric excess, at least 70% enantiomeric excess, at least 80% enantiomeric excess, at least 90% enantiomeric excess, at least 95% enantiomeric excess, or at least 99% enantiomeric excess in the (R)- or (S)-configuration.

[0132] Accordingly, as used herein a compound of the present disclosure can be in the form of one of the possible stereoisomers, rotamers, atropisomers, tautomers or mixtures thereof, for example, as substantially pure geometric (cis or trans) stereoisomers, diastereomers, optical isomers (antipodes), racemates, or mixtures thereof.

[0133] Any resulting mixtures of stereoisomers can be separated on the basis of the physicochemical differences of the constituents, into the pure or substantially pure geometric

or optical isomers, diastereomers, racemates, for example, by chromatography and/or fractional crystallization.

[0134] Any resulting racemates of compounds of the present disclosure or of intermediates can be resolved into the optical antipodes by known methods, e.g., by separation of the diastereomeric salts thereof, obtained with an optically active acid or base, and liberating the optically active acidic or basic compound. In particular, a basic moiety may thus be employed to resolve the compounds of the present disclosure into their optical antipodes, e.g., by fractional crystallization of a salt formed with an optically active acid, e.g., tartaric acid, dibenzoyl tartaric acid, diacetyl tartaric acid, di-O,O'-p-toluoyl tartaric acid, mandelic acid, malic acid or camphor-10-sulfonic acid. Racemic products can also be resolved by chiral chromatography, e.g., high performance liquid chromatography (HPLC) using a chiral adsorbent.

[0135] A method of making a compound (e.g., a compound of Formula (I)) is provided. In various embodiments, the compound is of Formula (Iaa). The method comprises the step of providing a pyrazine as a first intermediate. The method further comprises the step of combining a 2-pyranone and the first intermediate to form a second intermediate. The method may further comprise purification of the second intermediate in ammonium bicarbonate to form the compound of Formula (Iaa).

[0136] In certain embodiments, the method may further comprise the step of providing a solvent, salt, a ligand, a catalyst, or combinations thereof. Other components may be provided, including, but not limited to, bases, acids, oxidizing agents, reducing agents, halogenating agents, coupling agents, protecting groups, and the like.

[0137] In these and other embodiment, the step of providing a pyrazine as a first intermediate is further defined as combining (i) the solvent, the salt, the ligand, the catalyst, or combinations thereof, and (ii) the pyrazine to form the first intermediate. In some aspects, the pyrazine is 2-chloro-5-isopropoxypyrazine.

[0138] In these and other embodiment, the step of combining a 2-pyranone and the first intermediate to form a second intermediate is further defined as combining (i) the solvent, the salt, the ligand, the catalyst, or combinations thereof, and (ii) the 2-pyranone and the first intermediate to form the second intermediate. In some aspects, the 2-pyranone is 2-pyranone is (4S,4aR,5aR,6aS,6bS,9R,9aS,11aS,11bR)-4-hydroxy-9-((S)-1-((R)-5-(hydroxymethyl)-4-

methyl-6-oxo-3,6-dihydro-2H-pyran-2-yl)ethyl)-2-iodo-9a,11b-dimethyl-5a,6,6a,6b,7,8,9,9a,10,11,11a,11b-dodecahydrocyclopenta[1,2]phenanthro[8a,9-b]oxiren-1(4H)-one.

[0139] The solvent may be selected from the group of 1,4-dioxane, tetrahydrofuran, ethyl acetate, heptane, water, or combinations thereof. The salt may be selected from the group of lithium chloride, sodium sulphate, ammonium bicarbonate, or combinations thereof.

[0140] The ligand may be selected from the group of hexabutyl distannane, tributyl(5-isopropoxy-2-pyrazinyl) stannane, tricyclohexyl phosphine, triphenylarsane and combinations thereof. The catalyst may be selected from the group of palladium—(1E,4E)-1,5-diphenyl-1,4-pentadien-3-one (2/3), Tris((1E,4E)-1,5-diphenylpenta-1,4-dien-3-one) dipalladium [Pd2(dba)3], Copper Iodide [CuI], Triphenylarsane [AsPh3], Tetrakis(triphenylphosphine)palladium(0) [Pd(PPh3)4], Bis(triphenylphosphine)palladium(II) dichloride [PdCl2(PPh3)2], and combinations thereof.

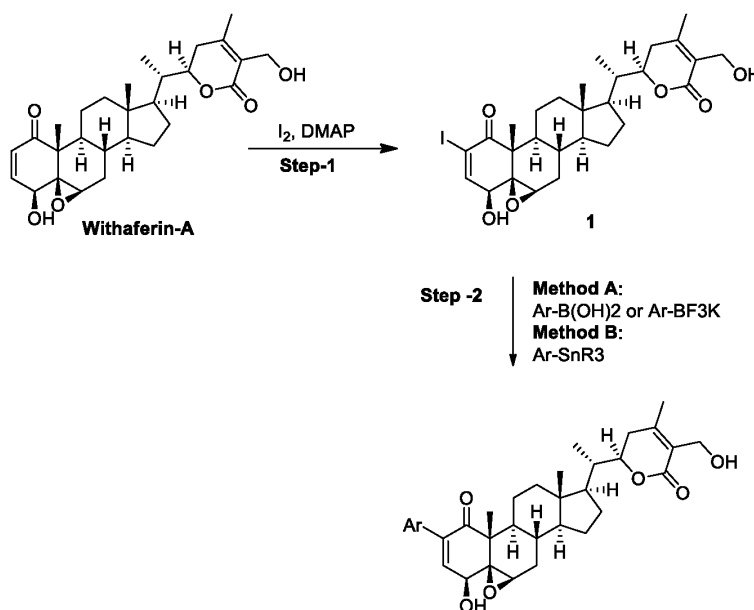
[0141] The base may be selected from the group of sodium hydride, potassium carbonate, triethylamine, sodium hydroxide, lithium diisopropylamide, and combinations thereof. The acid may be selected from the group of hydrochloric acid, sulfuric acid, acetic acid, trifluoroacetic acid, and combinations thereof.

[0142] The oxidizing agent may be selected from the group of hydrogen peroxide, meta-chloroperoxybenzoic acid, potassium permanganate, pyridinium chlorochromate, and combinations thereof. The reducing agent may be selected from the group of sodium borohydride, lithium aluminum hydride, hydrogen gas with palladium catalyst, diisobutylaluminum hydride, and combinations thereof.

[0143] The halogenating agent may be selected from the group of thionyl chloride, phosphorus tribromide, iodine monochloride, and combinations thereof. The coupling agent may be selected from the group of 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDC), dicyclohexylcarbodiimide (DCC), benzotriazol-1-yl-oxytripyrrolidinophosphonium hexafluorophosphate (PyBOP), and combinations thereof. The protecting group may be selected from the group of tert-butyldimethylsilyl chloride (TBSCl), di-tert-butyl dicarbonate (Boc anhydride), benzyl bromide, and combinations thereof.

[0144] The compounds of the present disclosure may be prepared in accordance with the compound of Formula (I), or a pharmaceutically acceptable salt thereof, by the routes described in the following Schemes or the Examples. All methods described herein can be performed in any suitable order unless otherwise indicated herein or otherwise clearly contradicted by context. The use of any and all examples, or exemplary language (e.g., “such as”) provided herein is intended merely to better illuminate the invention and does not pose a limitation on the scope of the disclosure otherwise claimed. In the following general methods, R¹, R², R³, R⁴, R⁵, R⁶, R⁷, R⁸, R⁹, R¹⁰, R¹¹, R¹², T, U, V, W, and X are as previously defined in the above embodiments, or limited to designations in the Schemes. Unless otherwise stated, starting materials are either commercially available or are prepared by known methods.

[0145] In some embodiments, compounds of the present disclosure, as described herein, may be prepared by a reaction sequence shown in Scheme 1 below and described below to provide a compound of Formula (I), or a pharmaceutically acceptable salt thereof.



[0146] **Step-1: Synthesis of (4S,4aR,5aR,6aS,6bS,9R,9aS,11aS,11bR)-4-hydroxy-9-((S)-1-((R)-5-(hydroxymethyl)-4-methyl-6-oxo-3,6-dihydro-2H-pyran-2-yl)ethyl)-2-iodo-9a,11b-dimethyl-5a,6,6a,6b,7,8,9,9a,10,11,11a,11b-dodecahydrocyclopenta[1,2]phenanthro[8a,9-b]oxiren-1(4H)-one:**

[0147] To the stirred solution of withaferin-A (3 g, 1 eq; 6.37 mmol) in dichloromethane (30 mL) was added N,N-dimethyl pyridin-4-amine (1.17 g, 1.5 eq., 9.56 mmol) at inert atmosphere. After 10 minutes, iodine (1.94 g, 1.2 eq., 7.65 mmol) was added to the reaction mixture and the resultant reaction mixture was allowed to stir at room temperature for 3 hours. The reaction mixture was quenched by saturated aqueous sodium thiosulfate solution (50 mL). The aqueous layer was extracted with dichloromethane (3 x 45 mL). Collected organics, dried over sodium sulphate and concentrated under reduced pressure to obtain crude. The crude was purified by combi-flash chromatography (using 5% methanol in dichloromethane) afforded (4S,4aR,5aR,6aS,6bS,9R,9aS,11aS,11bR)-4-hydroxy-9-((S)-1-((R)-5-(hydroxymethyl)-4-methyl-6-oxo-3,6-dihydro-2H-pyran-2-yl)ethyl)-2-iodo-9a,11b-dimethyl-5a,6,6a,6b,7,8,9,9a,10,11,11a,11b-dodecahydrocyclopenta[1,2]phenanthro[8a,9-b]oxiren-1(4H)-one (2.1 g, 55%) as a white solid.

Analytical data:

LCMS: 90.55% (m/z: 595.18, $[M-H]^+$, observed 595.18, $[M+H]^+$, 2.29 min (4 min run).

1H -NMR (400 MHz, DMSO- d_6): δ 7.78 (d, J = 6.4 Hz, 1H), 5.87 (d, J = 3.6 Hz, 1H), 5.87 (d, J = 3.6 Hz, 1H), 4.58 (t, J = 5.2 Hz, 1H), 4.30-4.27 (m, 1H), 4.18-4.08 (m, 2H), 3.51-3.48 (m, 1H), 3.19 (s, 1H), 2.35-2.43 (m, 1H), 2.00-2.12 (m, 5H), 1.86-1.89 (m, 1H), 1.73-1.80 (m, 2H), 1.55-1.58 (m, 1H), 1.24-1.38 (m, 9H), 0.95-1.10 (m, 4H), 0.91 (d, J = 6.4 Hz, 3H), 0.64-0.71 (m, 4H)

Step-2:

[0148] **Method A:** To a stirring solution of (4S,4aR,5aR,6aS,6bS,9R,9aS,11aS,11bR)-4-hydroxy-9-((S)-1-((R)-5-(hydroxymethyl)-4-methyl-6-oxo-3,6-dihydro-2H-pyran-2-yl)ethyl)-2-iodo-9a,11b-dimethyl-5a,6,6a,6b,7,8,9,9a,10,11,11a,11b-dodecahydrocyclopenta[1,2]phenanthro[8a,9-b]oxiren-1(4H)-one (1 eq; 1.02 mmol) in 1,4 dioxane and water were added dipotassium carbonate (2 eq., 2.04 mmol) and potassium- λ^6 -borane (1.5 eq., 1.53 mmol). The resulting reaction mixture was degassed by purging with nitrogen for 30 minutes. After that, [1,1'-Bis(diphenylphosphino)ferrocene]dichloropalladium(II) (0.2 eq., 204 μ mol) was added to the above mixture and resultant mixture was heated at 85°C for 5 hours. Reaction was monitored by TLC (5% methanol in dichloromethane). After completion of the reaction, reaction mass was quenched by citric acid solution followed by extraction with dichloromethane (2 x 40 mL).

Collected organics, dried over sodium sulphate and concentrated under reduced pressure to obtain crude. The crude was purified by combi-flash chromatography (5-10% methanol in dichloromethane) to furnish the corresponding compound

[0149] Method B: To a stirred solution of (1S,2R,6S,7R,9R,11S,12S,15R,16S)-6-hydroxy-15-[(1S)-1-[(2R)-5-(hydroxymethyl)-4-methyl-6-oxo-3,6-dihydro-2H-pyran-2-yl]ethyl]-4-iodo-2,16-dimethyl-8-oxapentacyclo[9.7.0.0^{2,7}.0^{7,9}.0^{12,16}]octadec-4-en-3-one (1 eq; 2.35 mmol) in tetrahydrofuran (14 mL) were added λ^1 -copper(1+) iodide (0.1 eq., 235 μ mol), triphenylarsane (71.9 mg, 0.1 eq., 235 μ mol), and (tributylstannyl)reagent (2 eq., 4.69 mmol). Reaction mixture was purged with continuous flow of nitrogen for 30 minutes. After that, tris((1E,4E)-1,5-diphenylpenta-1,4-dien-3-one) dipalladium (0.01 eq., 23.5 μ mol) was added and reaction mixture was degassed using nitrogen for 5 minutes. Resultant reaction mixture was stirred at 80°C for 16 hours. After completion of the reaction (monitored by TLC: 5% methanol in dichloromethane), reaction mixture was filtered through celite bed and filtrate was diluted by water (30 mL) followed by extraction with dichloromethane (2 x 50 mL). Collected organics, dried over sodium sulphate and then concentrated under reduced pressure to get crude, which was purified by prep HPLC to afford the compound.

[0150] The processes can be extended to prepare any of the compounds of Formula (I), any of its sub-formulas, or a pharmaceutically acceptable salt thereof, as described herein. Depending on the starting materials and the selected route, as mentioned in Scheme 1 above, a skilled person in the art would know how to prepare compound of Formula (I), or a pharmaceutically acceptable salt thereof. Certain variants or alternative processes are described herein below in the experimental section.

[0151] The disclosure further includes any variant of the present processes, in which an intermediate product obtainable at any stage thereof is used as starting material and the remaining steps are carried out, or in which the starting materials are formed *in situ* under the reaction conditions, or in which the reaction components are used in the form of their salts or optically pure material. Compounds of the disclosure and intermediates can also be converted into each other according to methods generally known to those skilled in the art.

[0152] In one aspect, the disclosure provides the use of a compound of Formula (I) or pharmaceutical composition described herein for the manufacture of a medicament for use in

inhibiting a therapeutic target, such as at least one of HSP90, NLRP3 inflammasome and TGF- β .

Administration of Pharmaceutically Acceptable Salts and Compositions

[0153] The compounds of Formula (I) and compositions, according to the method of the disclosure, may be administered using any amount and any route of administration effective for treating or lessening the severity of one or more of the pain or non-pain diseases recited herein. 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 infection, the particular agent, its mode of administration, and the like. The compounds of Formula (I) of the disclosure may be formulated in dosage unit form for ease of administration and uniformity of dosage. The expression “dosage unit form” as used herein refers to a physically discrete unit of agent appropriate for the subject to be treated. It will be understood, however, that the total daily usage of the compounds of Formula (I) and compositions of the disclosure will be decided by the attending physician within the scope of sound medical judgment. The specific effective dose level for any particular subject or organism will depend upon a variety of factors including the disorder being treated and the severity of the disorder; the activity of the specific compound employed; the specific composition employed; the age, body weight, general health, sex and diet of the subject; the time of administration, route of administration, and rate of excretion of the specific compound employed; the duration of the treatment; drugs used in combination or coincidental with the specific compound employed, and like factors well known in the medical arts. The term “subject” or “patient,” as used herein, means an animal, preferably a mammal, and most preferably a human.

[0154] The pharmaceutically acceptable compositions of this disclosure can be administered to humans and other animals orally, rectally, parenterally, intracisternally, intravaginally, intraperitoneally, topically (as by powders, ointments, or drops), buccally, as an oral or nasal spray, or the like, depending on the severity of the infection being treated. The phrases “parenteral administration” and “administered parenterally” as used herein means modes of administration other than enteral and topical administration, usually by injection, and includes, without limitation, intravenous, intramuscular, intraarterial, intrathecal, intracapsular, intraorbital, intracardiac, intradermal, intraperitoneal, transtracheal, subcutaneous, subcuticular, intraarticular, subcapsular, subarachnoid, intraspinal and intrasternal injection and infusion. In certain embodiments, the compounds of Formula (I) of the disclosure may be

administered orally or parenterally at dosage levels of about 0.01 mg/kg to about 100 mg/kg, about 0.01 mg/kg to about 50 mg/kg and optionally from about 1 mg/kg to about 25 mg/kg, of subject body weight per day, one or more times a day, to obtain the desired therapeutic effect.

[0155] Liquid dosage forms for oral administration include, but are not limited to, pharmaceutically acceptable emulsions, microemulsions, solutions, suspensions, syrups and elixirs. In addition to the active compounds, the liquid dosage forms may contain inert diluents commonly used in the art such as, for example, water or other solvents, solubilizing agents and emulsifiers such as ethyl alcohol, isopropyl alcohol, ethyl carbonate, ethyl acetate, benzyl alcohol, benzyl benzoate, propylene glycol, 1,3-butylene glycol, dimethylformamide, oils (in particular, cottonseed, groundnut, corn, germ, olive, castor, and sesame oils), glycerol, tetrahydrofurfuryl alcohol, polyethylene glycols and fatty acid esters of sorbitan, and mixtures thereof. Besides inert diluents, the oral compositions can also include adjuvants such as wetting agents, emulsifying and suspending agents, sweetening, flavoring, and perfuming agents.

[0156] Suspensions, in addition to the active compounds, may contain suspending agents as, for example, ethoxylated isostearyl alcohols, polyoxyethylene sorbitol and sorbitan esters, microcrystalline cellulose, aluminum metahydroxide, bentonite, agar-agar and tragacanth, and mixtures thereof.

[0157] It is known that sterols, such as cholesterol, will form complexes with cyclodextrins. Thus, in certain embodiments, where the inhibitor is a steroidal alkaloid, it may be formulated with cyclodextrins, such as α -, β - and γ -cyclodextrin, dimethyl- β cyclodextrin and 2-hydroxypropyl- β -cyclodextrin.

[0158] Injectable preparations, for example, sterile injectable aqueous or oleaginous suspensions may be formulated according to the known art using suitable dispersing or wetting agents and suspending agents. The sterile injectable preparation may also be a sterile injectable solution, suspension or emulsion in a nontoxic 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 water, Ringer's solution, U.S.P. 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 can be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid are used in the preparation of injectables.

[0159] The injectable formulations can be sterilized, for example, by filtration through a bacterial-retaining filter, by autoclave sterilization, or by incorporating sterilizing agents in the form of sterile solid compositions which can be dissolved or dispersed in sterile water or other sterile injectable medium prior to use. In various embodiments, a first portion of the formulation may be sterilized by filtration (*e.g.*, the compound) and the second portion may be sterilized by autoclave sterilization (*e.g.*, the excipient).

[0160] In order to prolong the effect of a compound of the disclosure, it is often desirable to slow the absorption of the compound from subcutaneous or intramuscular injection. This may be accomplished by the use of a liquid suspension of crystalline or amorphous material with poor water solubility. The rate of absorption of the compound then depends upon its rate of dissolution that, in turn, may depend upon crystal size and crystalline form. Alternatively, delayed absorption of a parenterally administered compound form is accomplished by dissolving or suspending the compound in an oil vehicle. Injectable depot forms are made by forming microcapsule matrices of the compound in biodegradable polymers such as polylactide-polyglycolide. Depending upon the ratio of compound to polymer and the nature of the particular polymer employed, the rate of compound release can be controlled. Examples of other biodegradable polymers include poly(orthoesters) and poly(anhydrides). Depot injectable formulations are also prepared by entrapping the compound in liposomes or microemulsions that are compatible with body tissues.

[0161] Solid dosage forms for oral administration include capsules, tablets, pills, powders, and granules. In such solid dosage forms, the active compound is mixed with at least one inert, pharmaceutically acceptable excipient or carrier such as sodium citrate or dicalcium phosphate and/or a) fillers or extenders such as starches, lactose, sucrose, glucose, mannitol, and silicic acid, b) binders such as, for example, carboxymethylcellulose, alginates, gelatin, polyvinylpyrrolidinone, sucrose, and acacia, c) humectants such as glycerol, d) disintegrating agents such as agar-agar, calcium carbonate, potato or tapioca starch, alginic acid, certain silicates, and sodium carbonate, e) solution retarding agents such as paraffin, f) absorption accelerators such as quaternary ammonium compounds, g) wetting agents such as, for example, cetyl alcohol and glycerol monostearate, h) absorbents such as kaolin and bentonite clay, and i) lubricants such as talc, calcium stearate, magnesium stearate, solid polyethylene glycols, sodium lauryl sulfate, and mixtures thereof. In the case of capsules, tablets and pills, the dosage form may also comprise buffering agents.

[0162] Solid compositions of a similar type may also be employed as fillers in soft and hard-filled gelatin capsules using such excipients as lactose or milk sugar as well as high molecular weight polyethylene glycols and the like. The solid dosage forms of tablets, dragees, capsules, pills, and granules can be prepared with coatings and shells such as enteric coatings and other coatings well known in the pharmaceutical formulating art. They may optionally contain opacifying agents and can also be of a composition that they release the active ingredient(s) only, or preferentially, in a certain part of the intestinal tract, optionally, in a delayed manner. Examples of embedding compositions that can be used include polymeric substances and waxes. Solid compositions of a similar type may also be employed as fillers in soft and hard-filled gelatin capsules using such excipients as lactose or milk sugar as well as high molecular weight polyethylene glycols and the like.

[0163] A tablet may be made by compression or molding, optionally with one or more accessory ingredients. Compressed tablets may be prepared using binder (for example, gelatin or hydroxypropylmethyl cellulose), lubricant, inert diluent, preservative, disintegrant (for example, sodium starch glycolate or cross-linked sodium carboxymethyl cellulose), surface-active or dispersing agent. Molded tablets may be made by molding in a suitable machine a mixture of the powdered compound moistened with an inert liquid diluent.

[0164] The tablets, and other solid dosage forms of the pharmaceutical compositions of the present disclosure, such as dragees, capsules, pills and granules, may optionally be scored or prepared with coatings and shells, such as enteric coatings and other coatings well known in the pharmaceutical-formulating art. They may also be formulated so as to provide slow or controlled release of the active ingredient therein using, for example, hydroxypropylmethyl cellulose in varying proportions to provide the desired release profile, other polymer matrices, liposomes and/or microspheres. They may be sterilized by, for example, filtration through a bacteria-retaining filter, or by incorporating sterilizing agents in the form of sterile solid compositions that can be dissolved in sterile water, or some other sterile injectable medium immediately before use. These compositions may also optionally contain opacifying agents and may be of a composition that they release the active ingredient(s) only, or preferentially, in a certain portion of the gastrointestinal tract, optionally, in a delayed manner. Examples of embedding compositions that can be used include polymeric substances and waxes. The active ingredient can also be in micro-encapsulated form, if appropriate, with one or more of the above-described excipients.

[0165] Formulations of the pharmaceutical compositions of the disclosure for rectal, vaginal, or urethral administration may be presented as a suppository, which may be prepared by mixing one or more compounds with one or more suitable nonirritating excipients or carriers comprising, for example, cocoa butter, polyethylene glycol, a suppository wax or a salicylate, and which is solid at room temperature, but liquid at body temperature and, therefore, will melt in the rectum or vaginal cavity and release the active compound.

[0166] Alternatively or additionally, compositions can be formulated for delivery via a catheter, stent, wire, or other intraluminal device. Delivery via such devices may be especially useful for delivery to the bladder, urethra, ureter, rectum, or intestine.

[0167] Formulations which are suitable for vaginal administration also include pessaries, tampons, creams, gels, pastes, foams or spray formulations containing such carriers as are known in the art to be appropriate.

[0168] The active compounds can also be in microencapsulated form with one or more excipients as noted above. The solid dosage forms of tablets, dragees, capsules, pills, and granules can be prepared with coatings and shells such as enteric coatings, release controlling coatings and other coatings well known in the pharmaceutical formulating art. In such solid dosage forms the active compound may be admixed with at least one inert diluent such as sucrose, lactose or starch. Such dosage forms may also comprise, as is normal practice, additional substances other than inert diluents, e.g., tableting lubricants and other tableting aids such as magnesium stearate and microcrystalline cellulose. In the case of capsules, tablets and pills, the dosage forms may also comprise buffering agents. They may optionally contain opacifying agents and can also be of a composition that they release the active ingredient(s) only, or preferentially, in a certain part of the intestinal tract, optionally, in a delayed manner. Examples of embedding compositions that can be used include polymeric substances and waxes.

[0169] Dosage forms for topical or transdermal administration of a compound of this disclosure include ointments, pastes, creams, lotions, gels, powders, solutions, sprays, inhalants or patches. The active component is admixed under sterile conditions with a pharmaceutically acceptable carrier and with any preservatives, buffers, or propellants that may be required.

[0170] Dosage forms for the topical or transdermal administration of a compound include powders, sprays, ointments, pastes, creams, lotions, gels, solutions, patches and inhalants. The

active compound may be mixed under sterile conditions with a pharmaceutically acceptable carrier, and with any preservatives, buffers, or propellants that may be required.

[0171] The ointments, pastes, creams and gels may contain, in addition to an active compound of this disclosure, excipients, such as animal and vegetable fats, oils, waxes, paraffins, starch, tragacanth, cellulose derivatives, polyethylene glycols, silicones, bentonites, silicic acid, talc and zinc oxide, or mixtures thereof.

[0172] Powders and sprays can contain, in addition to a compound of this disclosure, excipients such as lactose, talc, silicic acid, aluminum hydroxide, calcium silicates and polyamide powder, or mixtures of these substances. Sprays can additionally contain customary propellants, such as chlorofluorohydrocarbons and volatile unsubstituted hydrocarbons, such as butane and propane.

[0173] Transdermal patches have the added advantage of providing controlled delivery of a compound to the body. Such dosage forms can be made by dissolving or dispersing the compound in the proper medium. Absorption enhancers can also be used to increase the flux of the compound across the skin. The rate of such flux can be controlled by either providing a rate controlling membrane or dispersing the compound in a polymer matrix or gel.

[0174] Ophthalmic formulation, eye ointments, eye drops, and eardrops are also contemplated as being within the scope of this disclosure. Pharmaceutical compositions suitable for parenteral administration comprise one or more compounds in combination with one or more pharmaceutically acceptable sterile isotonic aqueous or nonaqueous solutions, dispersions, suspensions or emulsions, or sterile powders which may be reconstituted into sterile injectable solutions or dispersions just prior to use, which may contain antioxidants, buffers, bacteriostats, solutes which render the formulation isotonic with the blood of the intended recipient or suspending or thickening agents.

[0175] Examples of suitable aqueous and nonaqueous carriers that may be employed in the pharmaceutical compositions include water, ethanol, polyols (such as glycerol, propylene glycol, polyethylene glycol, and the like), and suitable mixtures thereof, vegetable oils, such as olive oil, and injectable organic esters, such as ethyl oleate. Proper fluidity can be maintained, for example, by the use of coating materials, such as lecithin, by the maintenance of the required particle size in the case of dispersions, and by the use of surfactants.

[0176] These compositions may also contain adjuvants such as preservatives, wetting agents, emulsifying agents and dispersing agents. Prevention of the action of microorganisms may be ensured by the inclusion of various antibacterial and antifungal agents, for example, paraben, chlorobutanol, phenol sorbic acid, and the like. It may also be desirable to include isotonic agents, such as sugars, sodium chloride, and the like into the compositions. In addition, prolonged absorption of the injectable pharmaceutical form may be brought about by the inclusion of agents that delay absorption such as aluminum monostearate and gelatin.

[0177] In some cases, in order to prolong the effect of a drug, it is desirable to slow the absorption of the drug from subcutaneous or intramuscular injection. This may be accomplished by the use of a liquid suspension of crystalline or amorphous material having poor water solubility. The rate of absorption of the drug then depends upon its rate of dissolution, which, in turn, may depend upon crystal size and crystalline form. Alternatively, delayed absorption of a parenterally administered drug form is accomplished by dissolving or suspending the drug in an oil vehicle.

[0178] When the compounds of Formula (I) are administered as pharmaceuticals, to humans and animals, they can be given per se or as a pharmaceutical composition containing, for example, 0.1 to 99.5% (more preferably, 0.5 to 90%) of active ingredient in combination with a pharmaceutically acceptable carrier.

[0179] The addition of the active compound to animal feed is preferably accomplished by preparing an appropriate feed premix containing the active compound in a therapeutically effective amount and incorporating the premix into the complete ration.

[0180] Alternatively, an intermediate concentrate or feed supplement containing the active ingredient can be blended into the feed. The way in which such feed premixes and complete rations can be prepared and administered are described in reference books (such as "Applied Animal Nutrition", W.H. Freedman and CO., San Francisco, U.S.A., 1969 or "Livestock Feeds and Feeding" O and B books, Corvallis, Ore., U.S.A., 1977).

[0181] Methods of introduction may also be provided by rechargeable or biodegradable devices. Various slow-release polymeric devices have been developed and tested in vivo in recent years for the controlled delivery of drugs, including proteinaceous biopharmaceuticals. A variety of biocompatible polymers (including hydrogels), including both biodegradable and

non-degradable polymers, can be used to form an implant for the sustained release of a compound at a particular target site.

[0182] Actual dosage levels of the active ingredients in the pharmaceutical compositions 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.

[0183] The selected dosage level will depend upon a variety of factors including the activity of the particular compound 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.

[0184] 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 Formula (I) 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.

[0185] In general, a suitable daily dose of a compound 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 Formula (I) for a patient will range from about 0.0001 to about 100 mg per kilogram of body weight per day.

[0186] 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.

[0187] The patient receiving this treatment is any animal in need, including primates, in particular humans, and other mammals such as equines, cattle, swine and sheep, and poultry and pets in general.

[0188] The compound can be administered as such or in admixtures with pharmaceutically acceptable and/or sterile carriers and can also be administered in conjunction with other antimicrobial agents such as penicillins, cephalosporins, aminoglycosides and glycopeptides. Conjunctive therapy thus includes sequential, simultaneous and separate administration of the active compound in a way that the therapeutic effects of the first administered one are still detectable when the subsequent therapy is administered.

[0189] The present disclosure contemplates formulation of the subject compounds in any of the aforementioned pharmaceutical compositions and preparations. Furthermore, the present disclosure contemplates administration via any of the foregoing routes of administration. One of skill in the art can select the appropriate formulation and route of administration based on the condition being treated and the overall health, age, and size of the patient being treated.

[0190] The activity of a compound utilized in this disclosure as an inhibitor of the therapeutic targets may be assayed according to methods described generally in the Examples herein, or according to methods available to one of ordinary skill in the art.

Combination Product and Combination Therapy

[0191] It will also be appreciated that the compounds of Formula (I) and pharmaceutically acceptable compositions of the disclosure can be employed in combination therapies, that is, the compounds of Formula (I) and pharmaceutically acceptable compositions can be administered concurrently with, prior to, or subsequent to, one or more other desired therapeutics or medical procedures. The particular combination of therapies (therapeutics or procedures) to employ in a combination regimen will take into account compatibility of the desired therapeutics and/or procedures and the desired therapeutic effect to be achieved. It will also be appreciated that the therapies employed may achieve a desired effect for the same disorder (for example, the compound of Formula (I) may be administered concurrently with an additional therapeutic agent used to treat the same disorder), or they may achieve different effects (*e.g.*, control of any adverse effects). As used herein, additional therapeutic agents that are normally administered to treat or prevent a particular disease, or condition, are known as “appropriate for the disease, or condition, being treated.”

[0192] “Combination” refers to either a fixed combination in one dosage unit form, or a combined administration where a compound of the present disclosure and a combination partner (*e.g.* another drug as explained below, also referred to as “therapeutic agent” or “co-

agent”) may be administered independently at the same time or separately within time intervals, especially where these time intervals allow that the combination partners show a cooperative, *e.g.* synergistic effect. The single components may be packaged in a kit or separately. One or both of the components (*e.g.* powders or liquids) may be reconstituted or diluted to a desired dose prior to administration. The terms “co-administration” or “combined administration” or the like as utilized herein are meant to encompass administration of the selected combination partner to a single subject in need thereof (*e.g.* a patient), and are intended to include treatment regimens in which the agents are not necessarily administered by the same route of administration or at the same time. The term “pharmaceutical combination” as used herein means a product that results from the mixing or combining of more than one therapeutic agent and includes both fixed and non-fixed combinations of the therapeutic agents. The term “pharmaceutical combination” as used herein refers to either a fixed combination in one dosage unit form, or non-fixed combination or a kit of parts for the combined administration where two or more therapeutic agents may be administered independently at the same time or separately within time intervals, especially where these time intervals allow that the combination partners show a cooperative, *e.g.* synergistic effect. The term “fixed combination” means that the therapeutic agents, *e.g.* a compound of the present disclosure and a combination partner, are both administered to a patient simultaneously in the form of a single entity or dosage. The term “non-fixed combination” means that the therapeutic agents, *e.g.* a compound of the present disclosure and a combination partner, are both administered to a patient as separate entities either simultaneously, concurrently or sequentially with no specific time limits, wherein such administration provides therapeutically effective levels of the two compounds in the body of the patient. The latter also applies to cocktail therapy, *e.g.* the administration of three or more therapeutic agents.

[0193] The term “combination therapy” refers to the administration of two or more therapeutic agents to treat a therapeutic condition or disorder described in the present disclosure. Such administration encompasses co-administration of these therapeutic agents in a substantially simultaneous manner, such as in a single capsule having a fixed ratio of active ingredients. Alternatively, such administration encompasses co-administration in multiple, or in separate containers (*e.g.*, tablets, capsules, powders, and liquids) for each active ingredient. Powders and/or liquids may be reconstituted or diluted to a desired dose prior to administration. In addition, such administration also encompasses use of each type of therapeutic agent in a sequential manner, either at approximately the same time or at different times. In either case,

the treatment regimen will provide beneficial effects of the drug combination in treating the conditions or disorders described herein.

[0194] The compound of the present disclosure may be administered either simultaneously with, or before or after, one or more additional therapeutic agents. The compound of the present disclosure may be administered separately, by the same or different route of administration, or together in the same pharmaceutical composition as the other agents. A therapeutic agent is, for example, a chemical compound, peptide, antibody, antibody fragment or nucleic acid, which is therapeutically active or enhances the therapeutic activity when administered to a patient in combination with a compound of the disclosure.

[0195] In one embodiment, a product is provided herein comprising a compound of Formula (I), or a pharmaceutical acceptable salt thereof, and at least one additional therapeutic agent as a combined preparation for simultaneous, separate or sequential use in therapy. In one embodiment, the therapy is the treatment of a disease or condition mediated by NLRP3. Products provided as a combined preparation include a composition comprising the compound of Formula (I), or a pharmaceutically acceptable salt thereof, and the additional therapeutic agent(s) together in the same pharmaceutical composition, or the compound of any one of Formula (I), or a pharmaceutically acceptable salt thereof, and the additional therapeutic agent(s) in separate form, *e.g.* in the form of a kit.

[0196] In one embodiment, the disclosure provides a pharmaceutical combination comprising a compound of Formula (I), or a pharmaceutically acceptable salt thereof, and additional therapeutic agent(s). Optionally, the pharmaceutical combination may comprise a pharmaceutically acceptable carrier, as described above.

[0197] In one embodiment, a kit is provided herein comprising two or more separate pharmaceutical compositions, at least one of which contains a compound of Formula (I), or a pharmaceutically acceptable salt thereof. In one embodiment, the kit is configured to separately retain the compositions, such as a container, divided bottle, or divided foil packet. An example of such a kit is a blister pack, as typically used for the packaging of tablets, capsules and the like.

[0198] The compound of the present disclosure may be administered either simultaneously with, or before or after, one or more additional therapeutic agents. The compound of the present disclosure may be administered separately, by the same or different route of administration, or

together in the same pharmaceutical composition as the additional therapeutic agent(s). A therapeutic agent is, for example, a chemical compound, peptide, antibody, antibody fragment or nucleic acid, which is therapeutically active or enhances the therapeutic activity when administered to a patient in combination with a compound of the present disclosure.

[0199] In one embodiment, the present disclosure provides a product comprising a compound of Formula (I), or a pharmaceutical acceptable salt thereof, and at least one additional therapeutic agent as a combined preparation for simultaneous, separate or sequential use in therapy. In one embodiment, the therapy is the treatment of a disease or condition mediated by NLRP3. Products provided as a combined preparation include a composition comprising the compound of Formula (I), or a pharmaceutically acceptable salt thereof, and the additional therapeutic agent(s) together in the same pharmaceutical composition, or the compound of Formula (I), or a pharmaceutically acceptable salt thereof, and the additional therapeutic agent(s) in separate form, *e.g.*, in the form of a kit.

[0200] In some embodiments, the present disclosure provides a pharmaceutical combination comprising a compound of Formula (I), or a pharmaceutically acceptable salt thereof, and additional therapeutic agent(s). Optionally, the pharmaceutical combination may comprise a pharmaceutically acceptable carrier, as described above.

[0201] In various embodiments, the present disclosure provides a kit comprising two or more separate pharmaceutical compositions, at least one of which contains a compound of Formula (I), or a pharmaceutically acceptable salt thereof. In one embodiment, the kit is configured for separately retaining the compositions, such as a container, divided bottle, or divided foil packet. An example of such a kit is a blister pack, typically used for the packaging of tablets, capsules and the like.

[0202] The kit of the disclosure may be used for administering different dosage forms, for example, oral and parenteral, for administering the separate compositions at different dosage intervals, or for titrating the separate compositions against one another. To assist compliance, the kit of the disclosure typically comprises directions for administration.

[0203] In some embodiments, the present disclosure relates to a kit that includes the pharmaceutical composition and specific instructions that explain how to use the pharmaceutical composition for treating, ameliorating, or preventing one or more conditions and diseases (*e.g.*, a disease or condition mediated by NLRP3) in a subject in need thereof.

[0204] In the combination therapies of the present disclosure, the compound of Formula (I) and the additional therapeutic agent may be manufactured and/or formulated by the same or different manufacturers. Moreover, the compound of Formula (I) and the additional therapeutic agent may be brought together into a combination therapy: (i) prior to release of the combination product to physicians (*e.g.*, in the case of a kit comprising the compound of Formula (I) and the additional therapeutic agent); (ii) by the physician themselves (or under the guidance of the physician) shortly before administration; (iii) in the patient themselves, *e.g.*, during sequential administration of the compound of the Formula (I) and the additional therapeutic agent.

[0205] Accordingly, the present disclosure provides the use of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, for treating a disease or condition mediated by NLRP3, wherein the medicament is prepared for administration with additional therapeutic agent. The present disclosure also provides the use of additional therapeutic agents for treating a disease or condition mediated by NLRP3 wherein the medicament is administered with a compound of Formula (I), or a pharmaceutically acceptable salt thereof.

[0206] The present disclosure also provides a compound of Formula (I), or a pharmaceutically acceptable salt thereof, for use in a method of treating a disease or condition mediated by NLRP3, wherein the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is prepared for administration with additional therapeutic agent. The present disclosure also provides additional therapeutic agent for use in a method of treating a disease or condition mediated by NLRP3, wherein the additional therapeutic agent is prepared for administration with a compound of Formula (I), or a pharmaceutically acceptable salt thereof. The present disclosure also provides a compound of Formula (I), or a pharmaceutically acceptable salt thereof, for use in a method of treating a disease or condition mediated by NLRP3, wherein the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered with additional therapeutic agent. The present disclosure also provides additional therapeutic agents for use in a method of treating a disease or condition mediated by NLRP3, wherein the additional therapeutic agent is administered with a compound of Formula (I), or a pharmaceutically acceptable salt thereof.

[0207] The present disclosure also provides the use of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, for treating a disease or condition mediated by NLRP3, wherein the patient has previously (*e.g.*, within 24 hours) been treated with the additional therapeutic agent. The present disclosure also provides the use of the additional

therapeutic agent for treating a disease or condition mediated by NLRP3 inflammasome pathway, wherein the patient has previously (*e.g.*, within 24 hours) been treated with a compound of Formula (I), or a pharmaceutically acceptable salt thereof.

[0208] In some embodiments, the additional therapeutic agent is a therapeutic agent useful in the treatment of inflammasome-related diseases/disorders, immune diseases, inflammatory diseases, auto-immune diseases, auto-inflammatory diseases, or cancer, as disclosed herein.

[0209] In various embodiment, the additional therapeutic agent useful in the combination therapy is selected from farnesoid X receptor (FXR) agonists; anti-steatotics; anti-fibrotics; JAK inhibitors; checkpoint inhibitors; chemotherapy, radiation therapy and surgical procedures; urate-lowering therapies; anabolics and cartilage regenerative therapy; blockade of IL-17; complement inhibitors; Bruton's tyrosine Kinase inhibitors (BTK inhibitors); Toll Like receptor inhibitors (TLR7/8 inhibitors); CAR-T therapy; anti-hypertensive agents; cholesterol lowering agents; leukotriene A4 hydrolase (LTAH4) inhibitors; SGLT2 inhibitors; β 2-agonists; anti-inflammatory agents; nonsteroidal anti-inflammatory drugs ("NSAIDs"); acetylsalicylic acid drugs (ASA) including aspirin; paracetamol; regenerative therapy treatments; cystic fibrosis treatments; and atherosclerotic treatment.

[0210] The amount of additional therapeutic agent present in the compositions of this disclosure will be no more than the amount that would normally be administered in a composition comprising that therapeutic agent as the only active agent. The amount of additional therapeutic agent in the presently disclosed compositions will range from about 10% to 100% of the amount normally present in a composition comprising that agent as the only therapeutically active agent.

[0211] The compounds of Formula (I) of this disclosure or pharmaceutically acceptable compositions thereof may also be incorporated into compositions for coating an implantable medical device, such as prostheses, artificial valves, vascular grafts, stents and catheters. Accordingly, the disclosure, in another aspect, includes a composition for coating an implantable device comprising a compound of the disclosure as described generally above, and in classes and subclasses herein, and a carrier suitable for coating said implantable device. In still another aspect, the disclosure includes an implantable device coated with a composition comprising a compound of the disclosure as described generally above, and in classes and subclasses herein, and a carrier suitable for coating said implantable device. Suitable coatings

and the general preparation of coated implantable devices are described in U.S. Pat. Nos. 6,099,562; 5,886,026; and 5,304,121. The coatings are typically biocompatible polymeric materials such as a hydrogel polymer, polymethyldisiloxane, polycaprolactone, polyethylene glycol, polylactic acid, ethylene vinyl acetate, and mixtures thereof. The coatings may optionally be further covered by a suitable topcoat of fluorosilicone, polysaccharides, polyethylene glycol, phospholipids or combinations thereof to impart controlled release characteristics in the composition.

[0212] Another aspect of the disclosure relates to inhibiting a therapeutic target activity in a biological sample or a subject, which method comprises administering to the subject, or contacting the biological sample with a compound of Formula (I) or a composition comprising the compound. The term “biological sample,” as used herein, includes, without limitation, cell cultures or extracts thereof, biopsied material obtained from a mammal or extracts thereof, and blood, saliva, urine, feces, semen, tears, or other body fluids or extracts thereof.

[0213] Inhibition of a therapeutic target activity in a biological sample is useful for a variety of purposes that are known to one of skill in the art. Examples of such purposes include, but are not limited to, the study of therapeutic targets in biological and pathological phenomena; and the comparative evaluation of new therapeutic target inhibitors.

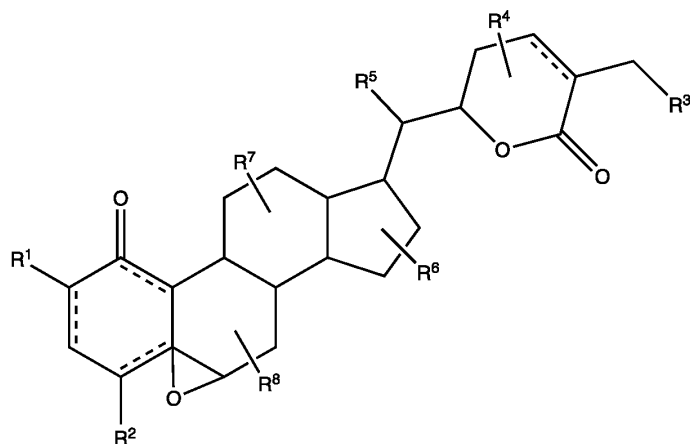
[0214] Reference to “about” a value or parameter herein includes (and describes) embodiments that are directed to that value or parameter per se. For example, description referring to “about X” includes description of “X”. In some embodiments, the term “about” when used in association with a measurement, or used to modify a value, a unit, a constant, or a range of values, refers to variations of +/- 10%, 5%, 2%, or 1%.

[0215] Reference to “between” two values or parameters herein includes (and describes) embodiments that include those two values or parameters per se. For example, description referring to “between x and y” includes description of “x” and “y” per se.

ENUMERATED EMBODIMENTS

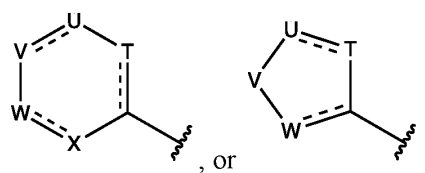
[0216] The following enumerated embodiments are representative of some aspects of the invention.

Embodiment 1. A compound of Formula (I):



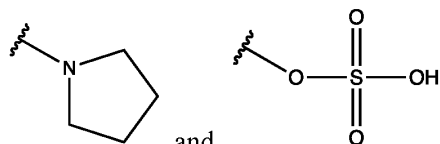
(I), or a

pharmaceutically acceptable salt thereof, wherein:



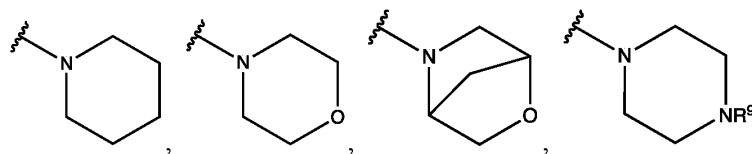
R^1 is hydrogen, $-NR^9R^{10}$, $-COOR^9$, $-CN$,

R^2 is hydrogen, halogen, $-OR^9$, $-SR^9$, $-NR^9R^{10}$, $-COOR^9$, $-COHR^9R^{10}$, $-CR^9R^{10}R^{11}$, $-CN$, $-N_3$, C_1 - C_6 alkyl, C_1 - C_6 haloalkyl, C_2 - C_6 alkenyl, C_2 - C_6 alkynyl, C_1 - C_6 alkoxy, aryl, aralkyl, heteroaryl, cycloalkane, heterocycloalkane, or a hetero(aryl)alkyl group selected from

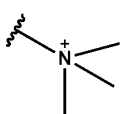
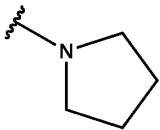
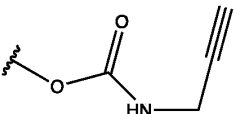


the group of and , wherein the C_1 - C_6 alkyl, the aryl, the heteroaryl, cycloalkane, or heterocycloalkane are unsubstituted or substituted with one or more R^{12} ,

R^3 is, independently, halogen, $-OR^9$, $-SR^9$, $-NR^9R^{10}$, $-COOR^9$, $-COHR^9R^{10}$, $-CR^9R^{10}R^{11}$, $-CN$, $-N_3$, C_1 - C_6 alkyl, C_1 - C_6 haloalkyl, C_2 - C_6 alkenyl, C_2 - C_6 alkynyl, C_1 - C_6 alkoxy, aryl, aralkyl, heteroaryl, cycloalkane, heterocycloalkane, or a hetero(aryl)alkyl group



selected from the group of , , , ,

, , , and , wherein the C₁-C₆ alkyl, the aryl, the heteroaryl, cycloalkane, or heterocycloalkane are unsubstituted or substituted with one or more R¹²;

T, U, V, W, and X are each, independently, CH, CR¹², sulfur, nitrogen, NR¹², or N⁺R¹²;

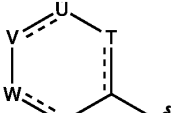
R⁴ to R¹¹ are each, independently, hydrogen, halogen, or a C₁-C₆ unsubstituted or substituted alkyl; and

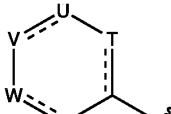
each R¹² is, independently, halogen, =O, -OR⁹, -SR⁹, -NR⁹R¹⁰, -COOR⁹, -COHR⁹R¹⁰, -CR⁹R¹⁰R¹¹, -CN, -N₃, C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₁-C₆ alkoxy, aryl, aralkyl, heteroaryl, isopropyl, cycloalkane, heterocycloalkane, or a

hetero(aryl)alkyl group selected from the group of
with the proviso:

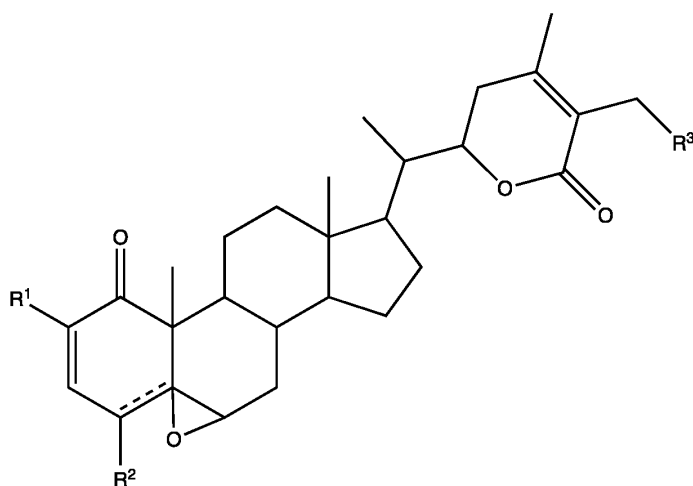
R² is a halogen when R¹ is hydrogen;

R¹² of CR¹² of only one of T, U, V, W, and X is

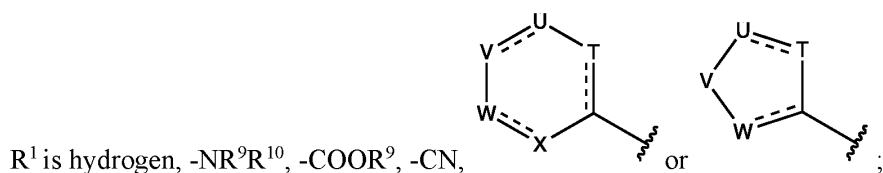
 is and none of T, U, V, W, and X are sulfur, nitrogen, NR¹², or N⁺R¹²;
and

 V of is not -OCH₂ when W is nitrogen.

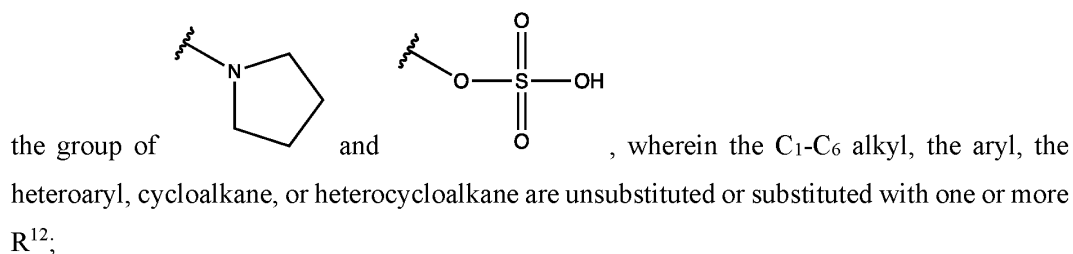
Embodiment 2. The compound of embodiment 1, wherein the compound of Formula (I) is Formula (Ia):



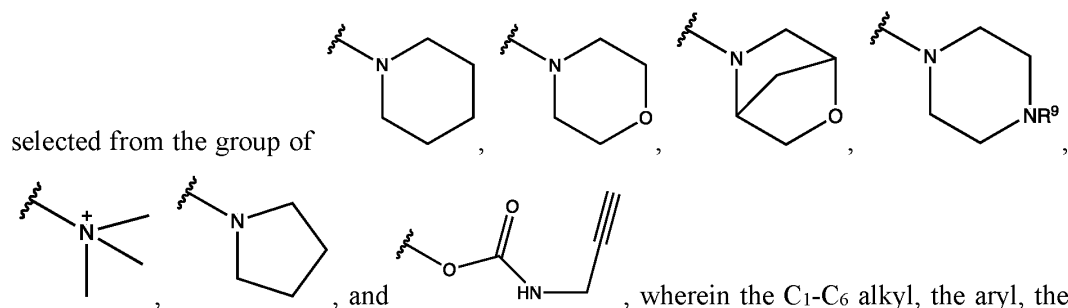
pharmaceutically acceptable salt thereof, and wherein:



R^2 is hydrogen, halogen, $-OR^9$, $-SR^9$, $-NR^9R^{10}$, $-COOR^9$, $-COHR^9R^{10}$, $-CR^9R^{10}R^{11}$, $-CN$, $-N_3$, C_1 - C_6 alkyl, C_1 - C_6 haloalkyl, C_2 - C_6 alkenyl, C_2 - C_6 alkynyl, C_1 - C_6 alkoxy, aryl, aralkyl, heteroaryl, cycloalkane, heterocycloalkane, or a hetero(aryl)alkyl group selected from



R^3 is, independently, halogen, $-OR^9$, $-SR^9$, $-NR^9R^{10}$, $-COOR^9$, $-COHR^9R^{10}$, $-CR^9R^{10}R^{11}$, $-CN$, $-N_3$, C_1 - C_6 alkyl, C_1 - C_6 haloalkyl, C_2 - C_6 alkenyl, C_2 - C_6 alkynyl, C_1 - C_6 alkoxy, aryl, aralkyl, heteroaryl, cycloalkane, heterocycloalkane, or a hetero(aryl)alkyl group



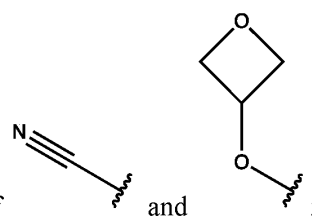
heteroaryl, cycloalkane, or heterocycloalkane are unsubstituted or substituted with one or more R^{12} ;

T, U, V, W, and X are each, independently, CH, CR^{12} , sulfur, nitrogen, NR^{12} , or N^+R^{12} ;

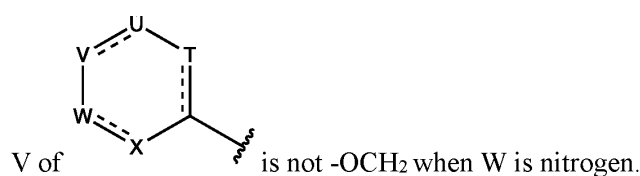
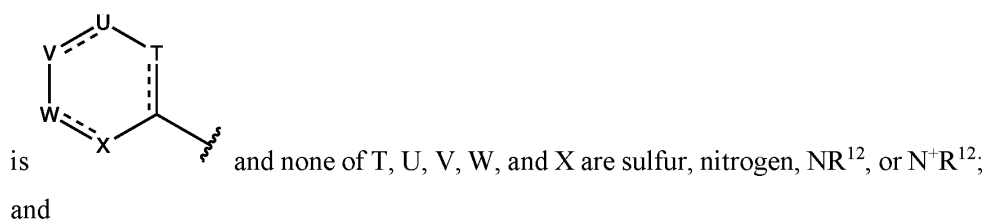
R^9 to R^{11} are each, independently, hydrogen, halogen, or a C_1 - C_6 unsubstituted or substituted alkyl; and

each R^{12} is, independently, halogen, =O, $-OR^9$, $-SR^9$, $-NR^9R^{10}$, $-COOR^9$, $-COHR^9R^{10}$, $-CR^9R^{10}R^{11}$, $-CN$, $-N_3$, C_1 - C_6 alkyl, C_1 - C_6 haloalkyl, C_2 - C_6 alkenyl, C_2 - C_6 alkynyl, C_1 - C_6 alkoxy, aryl, aralkyl, heteroaryl, isopropyl, cycloalkane, heterocycloalkane, or a

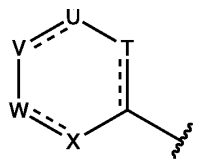
hetero(aryl)alkyl group selected from the group of
with the proviso that:



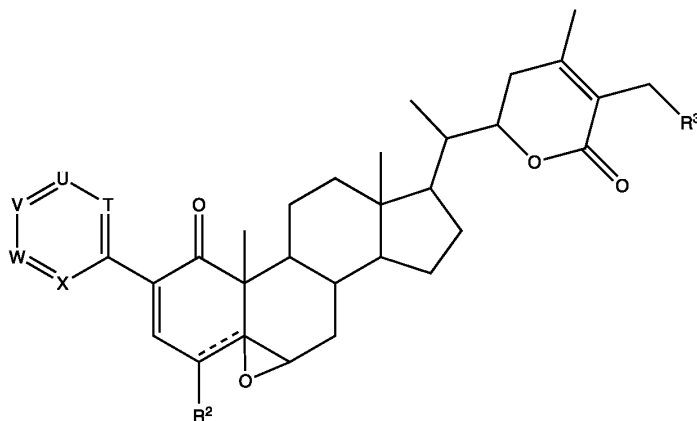
R^{12} of CR^{12} of only one of T, U, V, W, and X is



Embodiment 3. The compound of embodiment 2, wherein R^1 is:



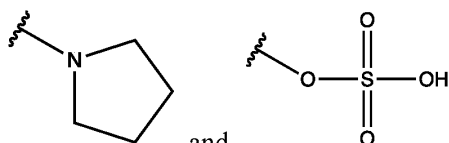
Embodiment 4. The compound of embodiment 3, wherein the compound of Formula (Ia) is Formula (Iaa):



(Iaa), or a

pharmaceutically acceptable salt thereof, and wherein:

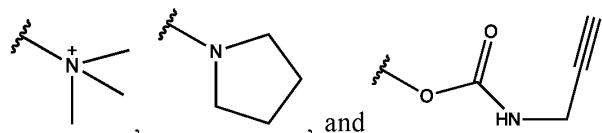
R^2 is hydrogen, halogen, $-OR^9$, $-SR^9$, $-NR^9R^{10}$, $-COOR^9$, $-COHR^9R^{10}$, $-CR^9R^{10}R^{11}$, $-CN$, $-N_3$, C_1 - C_6 alkyl, C_1 - C_6 haloalkyl, C_2 - C_6 alkenyl, C_2 - C_6 alkynyl, C_1 - C_6 alkoxy, aryl, aralkyl, heteroaryl, cycloalkane, heterocycloalkane, or a hetero(aryl)alkyl group selected from



the group of and , wherein the C_1 - C_6 alkyl, the aryl, the heteroaryl, cycloalkane, or heterocycloalkane are unsubstituted or substituted with one or more R^{12} ;

R^3 is, independently, halogen, $-OR^9$, $-SR^9$, $-NR^9R^{10}$, $-COOR^9$, $-COHR^9R^{10}$, $-CR^9R^{10}R^{11}$, $-CN$, $-N_3$, C_1 - C_6 alkyl, C_1 - C_6 haloalkyl, C_2 - C_6 alkenyl, C_2 - C_6 alkynyl, C_1 - C_6 alkoxy, aryl, aralkyl, heteroaryl, cycloalkane, heterocycloalkane, or a hetero(aryl)alkyl group

selected from the group of , , , , ,



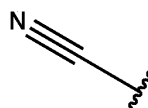
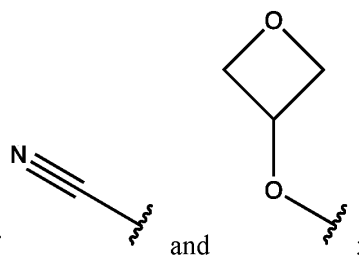
, and , wherein the C_1 - C_6 alkyl, the aryl, the heteroaryl, cycloalkane, or heterocycloalkane are unsubstituted or substituted with one or more R^{12} ;

T, U, V, W, and X are each, independently, CH, CR^{12} , sulfur, nitrogen, NR^{12} , or N^+R^{12} ;

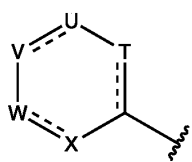
R^9 to R^{11} are each, independently, hydrogen, halogen, or a C_1 - C_6 unsubstituted or substituted alkyl; and

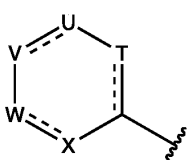
each R^{12} is, independently, halogen, $=O$, $-OR^9$, $-SR^9$, $-NR^9R^{10}$, $-COOR^9$, $-COHR^9R^{10}$, $-CR^9R^{10}R^{11}$, $-CN$, $-N_3$, C_1 - C_6 alkyl, C_1 - C_6 haloalkyl, C_2 - C_6 alkenyl, C_2 - C_6 alkynyl, C_1 - C_6 alkoxy, aryl, aralkyl, heteroaryl, isopropyl, cycloalkane, heterocycloalkane, or a

hetero(aryl)alkyl group selected from the group of
with the proviso:



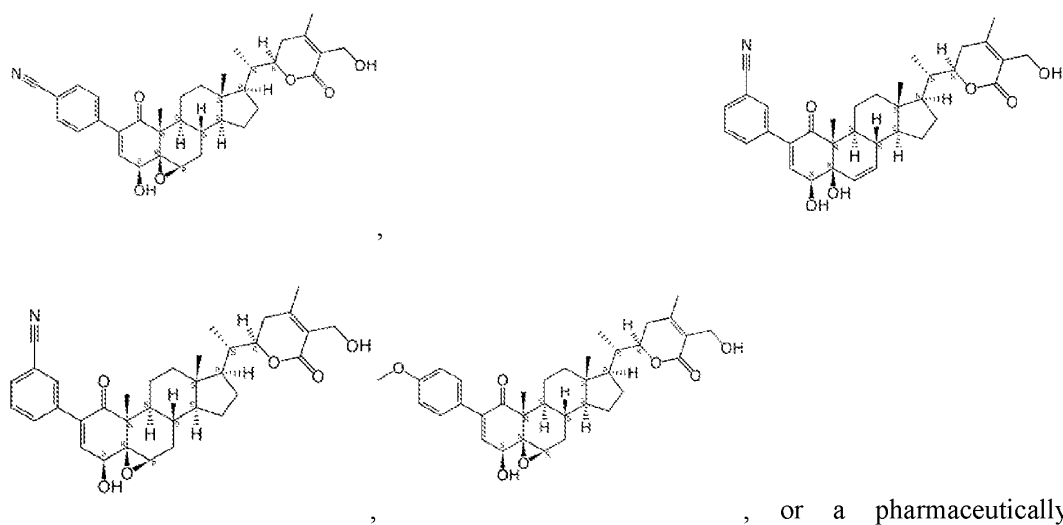
R^{12} of CR^{12} of only one of T, U, V, W, and X is or $-OCH_2$ when

R^1 is  and none of T, U, V, W, and X are sulfur, nitrogen, NR^{12} , or N^+R^{12} , and

 V of is not $-OCH_2$ when W is nitrogen.

Embodiment 5. The compound of embodiment 4, wherein T, U, V, W, and X are CR^{12} .

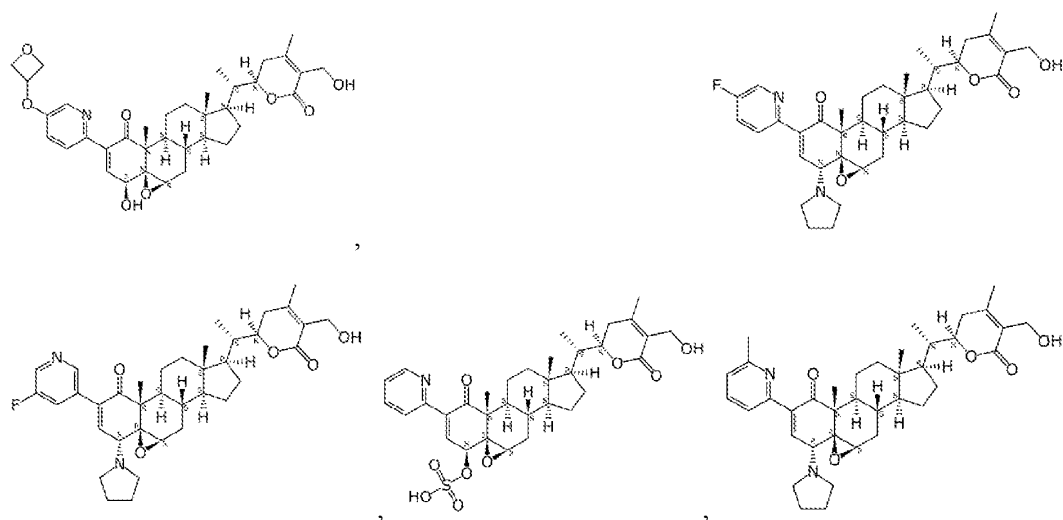
Embodiment 6. The compound of embodiment 5, wherein the compound of Formula (Iaa) is selected from the group of:

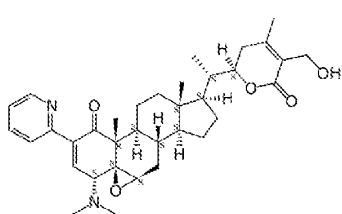


acceptable salt or stereoisomer thereof.

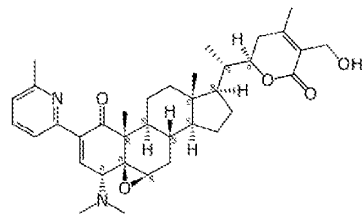
Embodiment 7. The compound of embodiment 4, wherein one of T or X is sulfur, nitrogen, NR^{12} , or N^+R^{12} , the other of T or X is CR^{12} , and U, V, W, and X are CR^{12} .

Embodiment 8. The compound of embodiment 7, wherein the compound of Formula (Iaa) is selected from the group of:

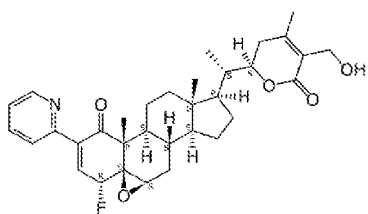




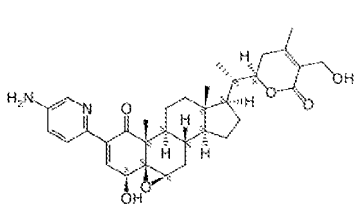
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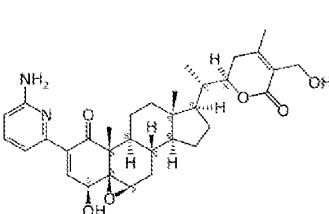
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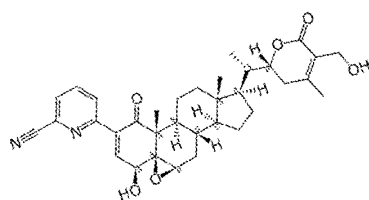
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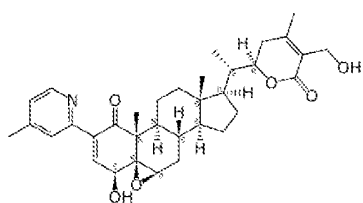
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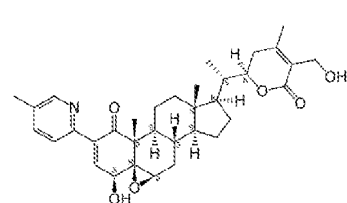
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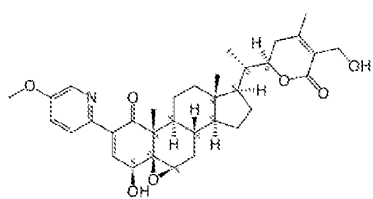
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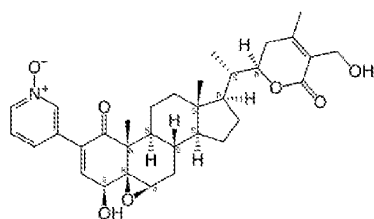
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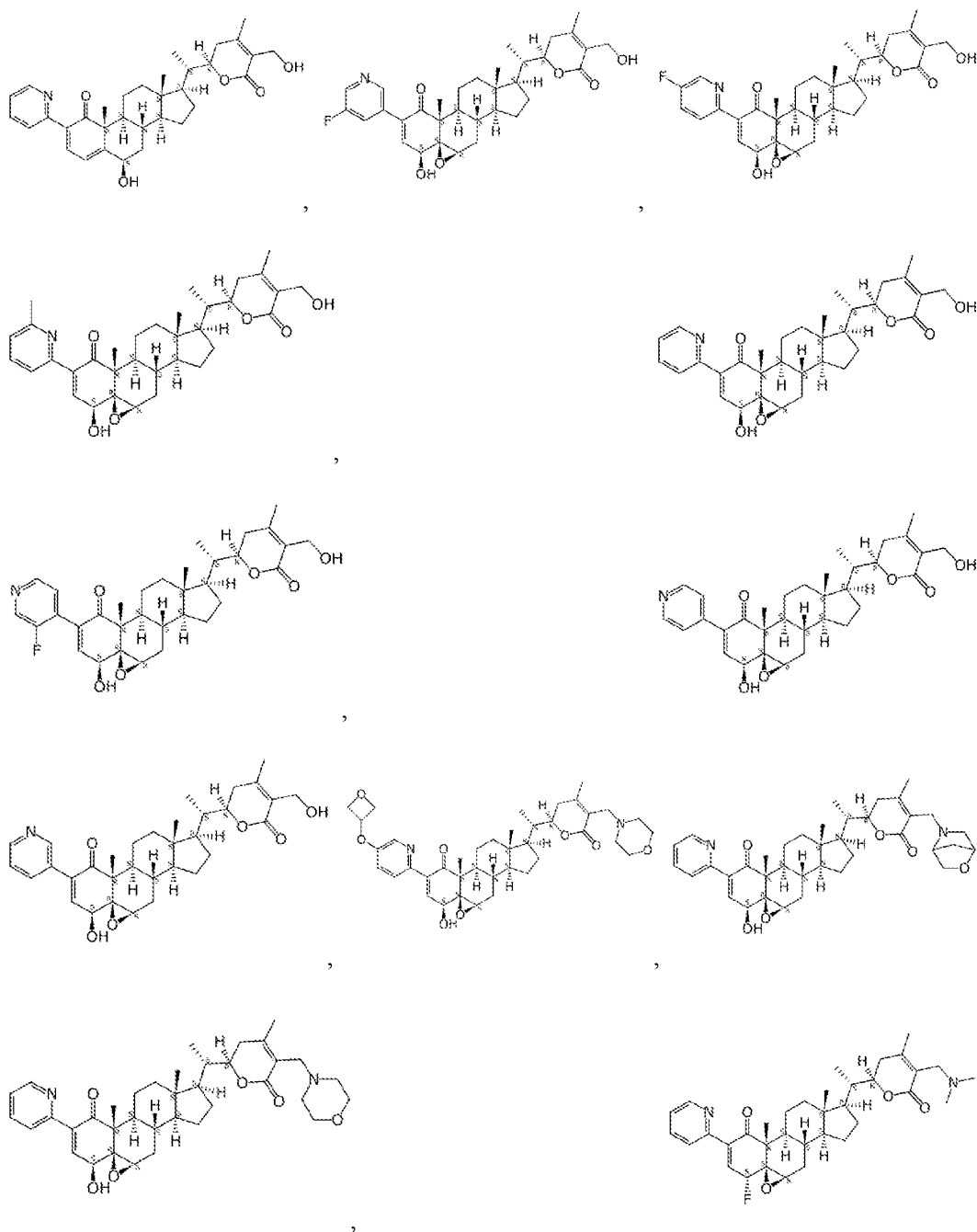
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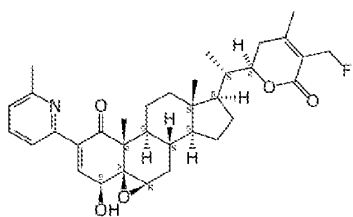


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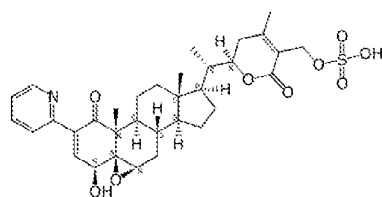


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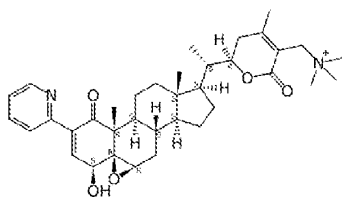




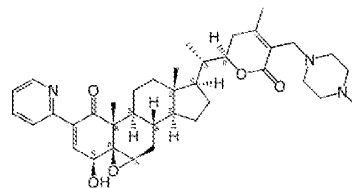
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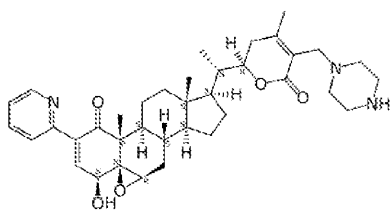
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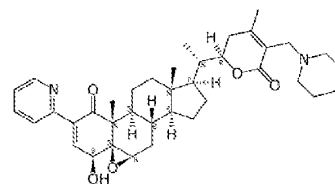
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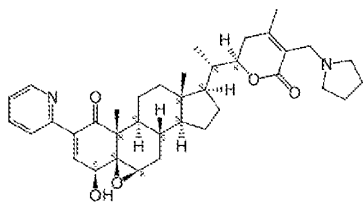
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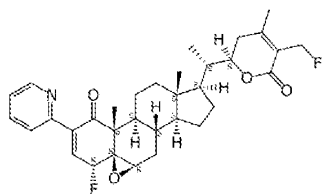
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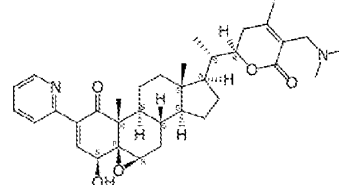
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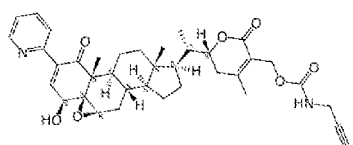
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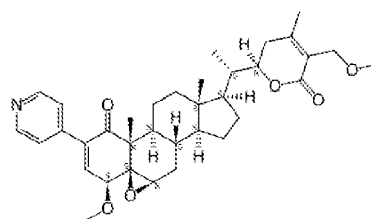
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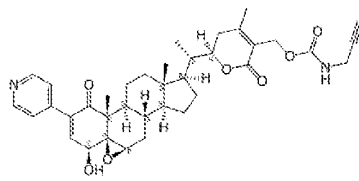
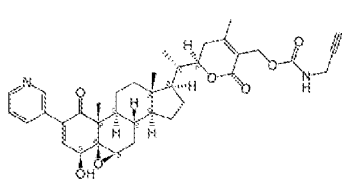
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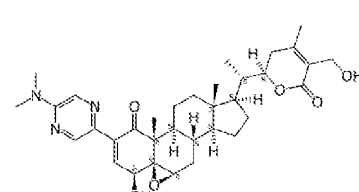
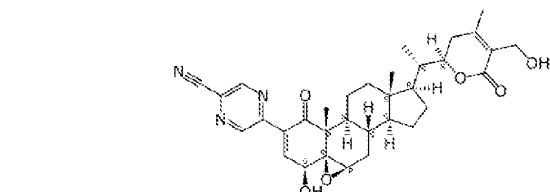
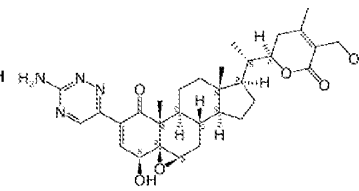
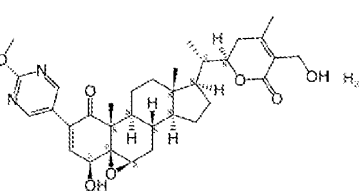
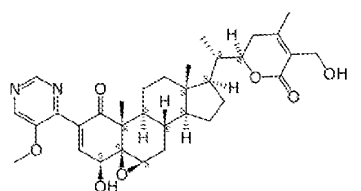
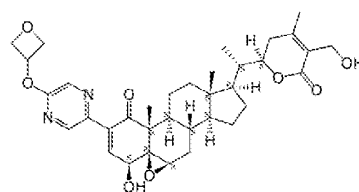
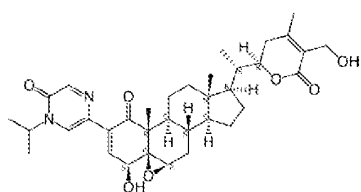
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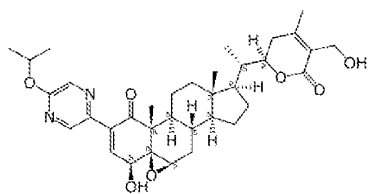


, or a pharmaceutically acceptable salt or stereoisomer thereof.

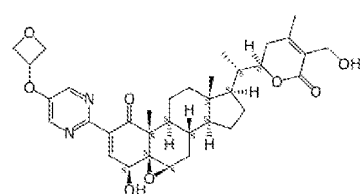
Embodiment 9. The compound of embodiment 4, wherein at least two of T, U, V, W, and X are sulfur, nitrogen, NR^{12} , or N^+R^{12} , the remaining of T, U, V, W, and X are CR^{12} .

Embodiment 10. The compound of embodiment 9, wherein the compound of Formula (Iaa) is selected from the group of:

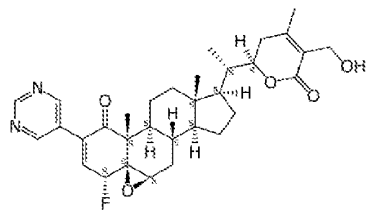




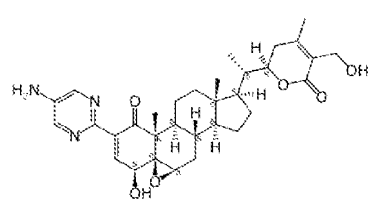
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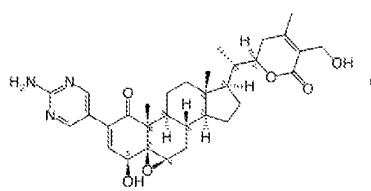
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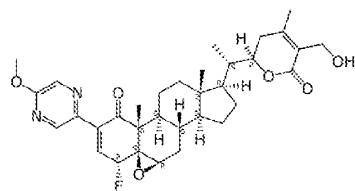
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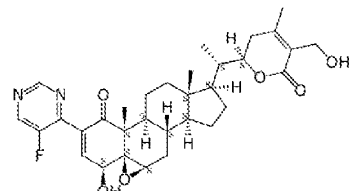
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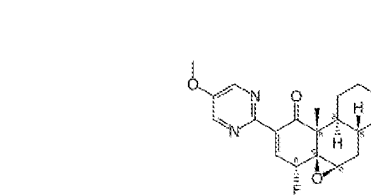
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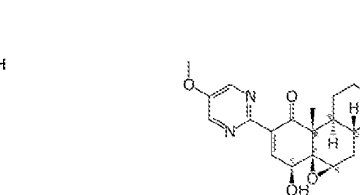
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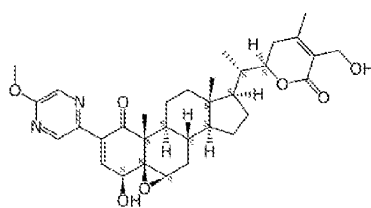
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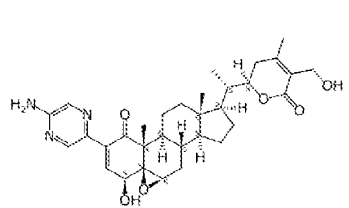
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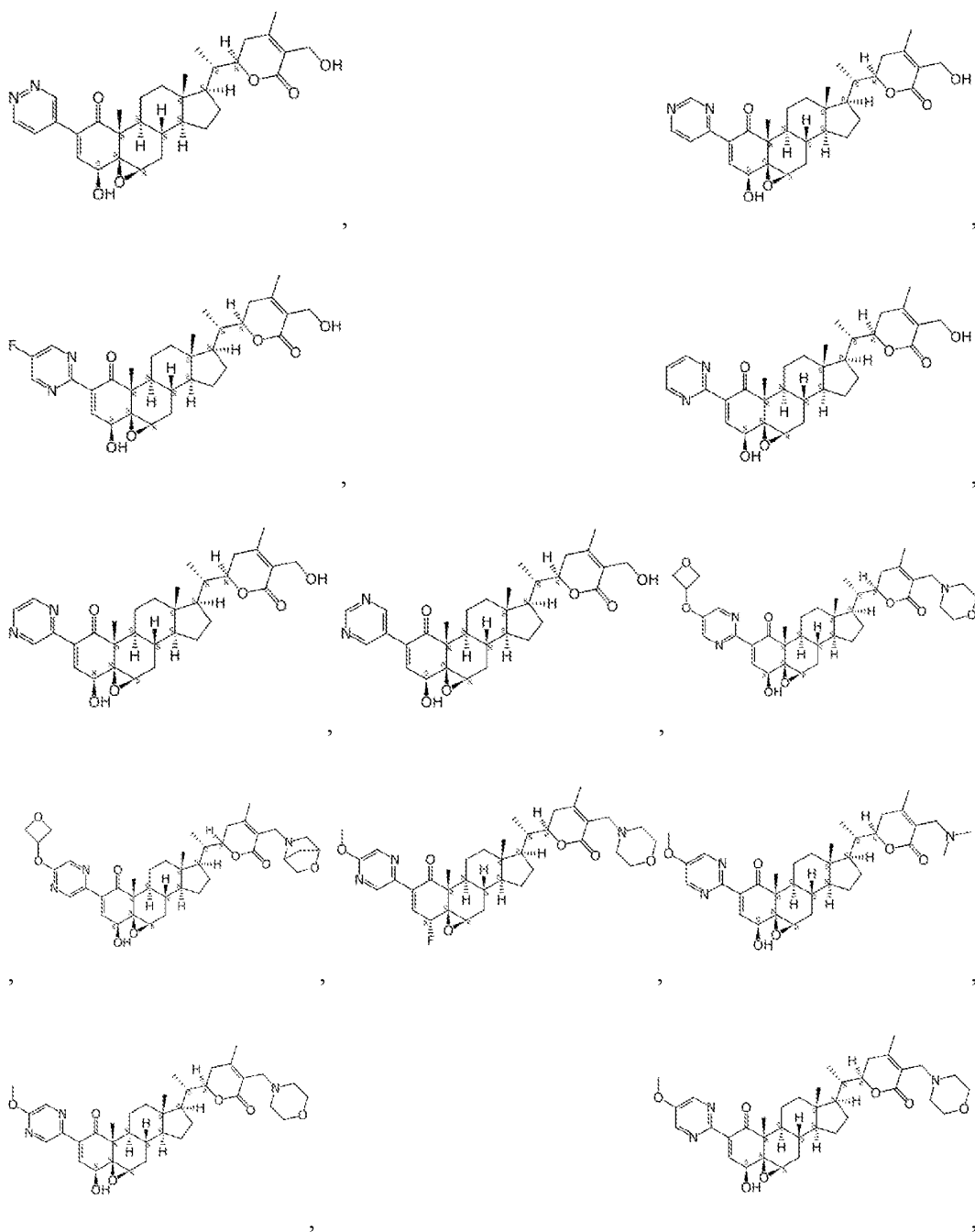
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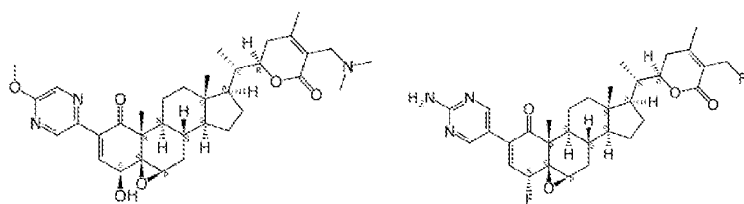


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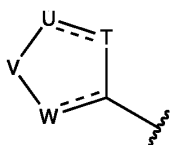
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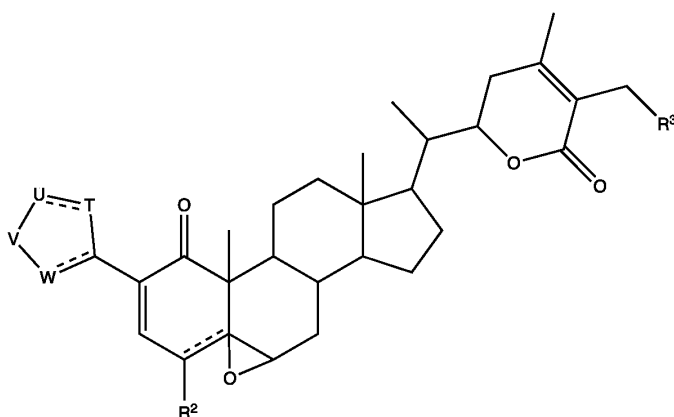


, or a pharmaceutically acceptable salt or stereoisomer thereof.

Embodiment 11. The compound of embodiment 2, wherein R¹ is:



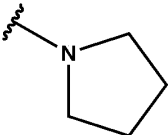
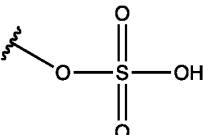
Embodiment 12. The compound of embodiment 11, wherein the compound of Formula (Ia) is Formula (Iab):



(Iab), or a

pharmaceutically acceptable salt thereof, and wherein:

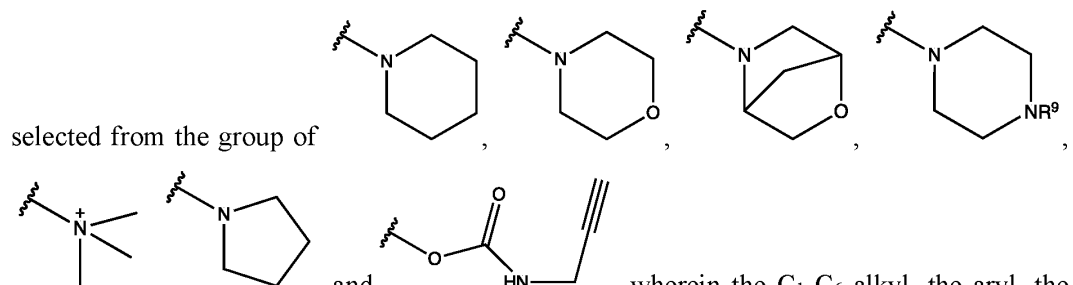
R² is hydrogen, halogen, -OR⁹, -SR⁹, -NR⁹R¹⁰, -COOR⁹, -COHR⁹R¹⁰, -CR⁹R¹⁰R¹¹, -CN, -N₃, C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₁-C₆ alkoxy, aryl, aralkyl, heteroaryl, cycloalkane, heterocycloalkane, or a hetero(aryl)alkyl group selected from

the group of  and , wherein the C₁-C₆ alkyl, the aryl, the

heteroaryl, cycloalkane, or heterocycloalkane are unsubstituted or substituted with one or more R^{12} ,

R^3 is, independently, halogen, $-OR^9$, $-SR^9$, $-NR^9R^{10}$, $-COOR^9$, $-COHR^9R^{10}$, $-CR^9R^{10}R^{11}$, $-CN$, $-N_3$, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, aryl, aralkyl, heteroaryl, cycloalkane, heterocycloalkane, or a hetero(aryl)alkyl group

selected from the group of



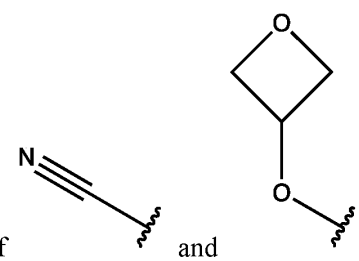
, wherein the C_1-C_6 alkyl, the aryl, the heteroaryl, cycloalkane, or heterocycloalkane are unsubstituted or substituted with one or more R^{12} ,

T, U, V, and W are each, independently, CH, CR^{12} , sulfur, nitrogen, NR^{12} , or N^+R^{12} ,

R^9 to R^{11} are each, independently, hydrogen, halogen, or a C_1-C_6 unsubstituted or substituted alkyl; and

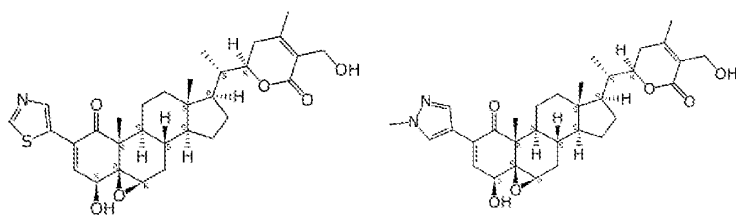
each R^{12} is, independently, halogen, $=O$, $-OR^9$, $-SR^9$, $-NR^9R^{10}$, $-COOR^9$, $-COHR^9R^{10}$, $-CR^9R^{10}R^{11}$, $-CN$, $-N_3$, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, aryl, aralkyl, heteroaryl, isopropyl, cycloalkane, heterocycloalkane, or a

hetero(aryl)alkyl group selected from the group of



and

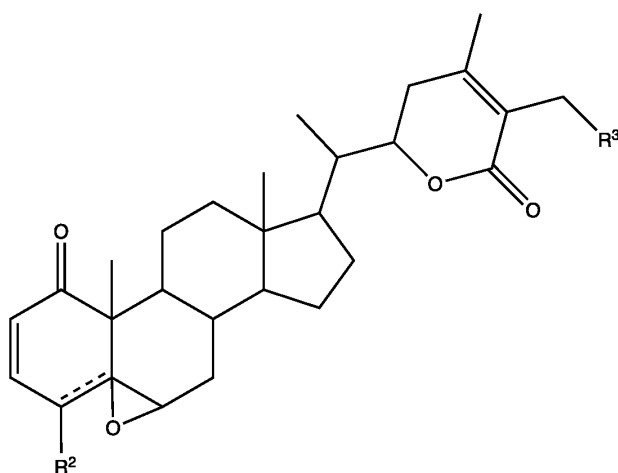
Embodiment 13. The compound of embodiment 11, wherein the compound of Formula (Ia) is selected from the group of:



, or a pharmaceutically acceptable salt or stereoisomer thereof.

Embodiment 14. The compound of embodiment 2, wherein R^1 is hydrogen.

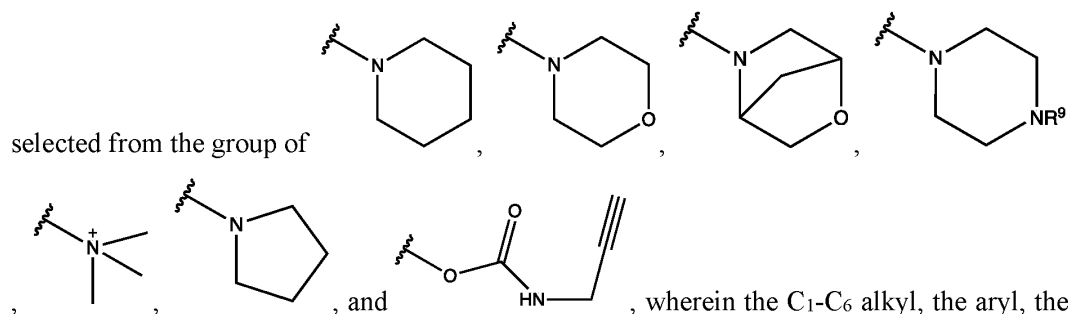
Embodiment 15. The compound of embodiment 14, wherein the compound of Formula (Ia) is Formula (Iac):



(Iac), or a pharmaceutically acceptable salt thereof, wherein:

R^2 is halogen;

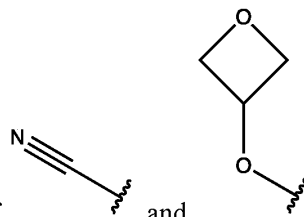
R^3 is, independently, halogen, $-OR^9$, $-SR^9$, $-NR^9R^{10}$, $-COOR^9$, $-COHR^9R^{10}$, $-CR^9R^{10}R^{11}$, $-CN$, $-N_3$, C_1 - C_6 alkyl, C_1 - C_6 haloalkyl, C_2 - C_6 alkenyl, C_2 - C_6 alkynyl, C_1 - C_6 alkoxy, aryl, aralkyl, heteroaryl, cycloalkane, heterocycloalkane, or a hetero(aryl)alkyl group



heteroaryl, cycloalkane, or heterocycloalkane are unsubstituted or substituted with one or more R^{12} ,

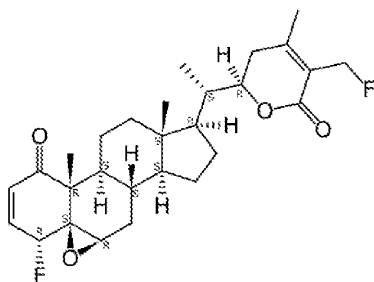
R^9 to R^{11} are each, independently, hydrogen, halogen, or a C_1 - C_6 unsubstituted or substituted alkyl; and

each R^{12} is, independently, halogen, $=O$, $-OR^9$, $-SR^9$, $-NR^9R^{10}$, $-COOR^9$, $-COHR^9R^{10}$, $-CR^9R^{10}R^{11}$, $-CN$, $-N_3$, C_1 - C_6 alkyl, C_1 - C_6 haloalkyl, C_2 - C_6 alkenyl, C_2 - C_6 alkynyl, C_1 - C_6 alkoxy, aryl, aralkyl, heteroaryl, isopropyl, cycloalkane, heterocycloalkane, or a



hetero(aryl)alkyl group selected from the group of and .

Embodiment 16. The compound of embodiment 15, wherein the compound of Formula (Iac) is:



, or a pharmaceutically acceptable salt or stereoisomer thereof.

Embodiment 17. A pharmaceutical composition comprising the compound of any one of embodiments 1 to 16, or a pharmaceutically acceptable salt or stereoisomer thereof, and at least one pharmaceutically acceptable carrier.

Embodiment 18. A method of treating, ameliorating, or preventing an NLR Family Pyrin Domain Containing 3 (NLRP3) inflammasome-mediated condition or disease, comprising administering a therapeutically effective amount of a compound according to any one of embodiments 1 to 16.

Embodiment 19. The method of embodiment 18, wherein the condition or disease is selected from the group of inflammatory bowel disease (IBD), Crohn's disease, colorectal cancer, alcoholic hepatitis, or a combination thereof.

Embodiment 20. A method of treating, ameliorating, or preventing a tumor necrosis factor alpha (TNF- α)-mediated condition or disease, comprising administering a therapeutically effective amount of a compound according to any one of embodiments 1 to 16.

Embodiment 21. The method of embodiment 20, wherein the condition or disease is selected from the group of inflammatory bowel disease (IBD), Crohn's disease, colorectal cancer, alcoholic hepatitis, or a combination thereof.

Embodiment 22. A method of treating, ameliorating, or preventing an NLR Family Pyrin Domain Containing 3 (NLRP3) inflammasome-mediated condition or disease, comprising administering a therapeutically effective amount of a pharmaceutical composition according to any one of embodiment 17.

Embodiment 23. The method of embodiment 22, wherein the condition or disease is selected from the group of cardiovascular condition or disease, an endocrine condition or disease, a neurological condition or disease, a gastrointestinal condition or disease, or a combination thereof.

Embodiment 24. A method of treating, ameliorating, or preventing tumor necrosis factor alpha (TNF- α)-mediated condition or disease, comprising administering a therapeutically effective amount of a pharmaceutical composition according to any one of embodiment 17.

Embodiment 25. The method of embodiment 24, wherein the condition or disease is selected from the group of cardiovascular condition or disease, an endocrine condition or disease, a neurological condition or disease, a gastrointestinal condition or disease, or a combination thereof.

Embodiment 26. A pharmaceutical composition comprising a compound of any one of embodiments 1 to 16, or a pharmaceutically acceptable salt or stereoisomer thereof, for use in a method of treating, ameliorating, or preventing an NLR Family Pyrin Domain Containing 3 (NLRP3) inflammasome-mediated condition or disease.

Embodiment 27. The pharmaceutical composition of embodiment 26, wherein the condition or disease is selected from the group of inflammatory bowel disease (IBD), Crohn's disease, colorectal cancer, alcoholic hepatitis, or a combination thereof.

Embodiment 28. A pharmaceutical composition comprising a compound of any one of embodiments 1 to 16, or a pharmaceutically acceptable salt or stereoisomer thereof, for use in a method of treating, ameliorating, or preventing a tumor necrosis factor alpha (TNF- α)-mediated condition or disease.

Embodiment 29. The pharmaceutical composition of embodiment 28, wherein the condition or disease is selected from the group of inflammatory bowel disease (IBD), Crohn's disease, colorectal cancer, alcoholic hepatitis, or a combination thereof.

Embodiment 30. Use of a compound of any one of embodiments 1 to 16, or a pharmaceutically acceptable salt or stereoisomer thereof, in the preparation of a medicament for use in treating, ameliorating, or preventing an NLR Family Pyrin Domain Containing 3 (NLRP3) inflammasome-mediated condition or disease.

Embodiment 31. The use of embodiment 30, wherein the condition or disease is selected from the group of inflammatory bowel disease (IBD), Crohn's disease, colorectal cancer, alcoholic hepatitis, or a combination thereof.

Embodiment 32. Use of a compound of any one of embodiments 1 to 16, or a pharmaceutically acceptable salt or stereoisomer thereof, in the preparation of a medicament for use in treating, ameliorating, or preventing a tumor necrosis factor alpha (TNF- α)-mediated condition or disease.

Embodiment 33. The use of embodiment 32, wherein the condition or disease is selected from the group of inflammatory bowel disease (IBD), Crohn's disease, colorectal cancer, alcoholic hepatitis, or a combination thereof.

Embodiment 34. A method of treating, ameliorating, or preventing an NLR Family Pyrin Domain Containing 3 (NLRP3) inflammasome-mediated condition or disease, comprising administering an inhibitor of the C-terminal domain of heat shock protein 90 (hsp90).

Embodiment 35. The method of embodiment 34, wherein the condition or disease is selected from the group of inflammatory bowel disease (IBD), Crohn's disease, colorectal cancer, alcoholic hepatitis, or a combination thereof.

Embodiment 36. A method of treating, ameliorating, or preventing a tumor necrosis factor alpha (TNF- α)-mediated condition or disease, comprising administering an inhibitor of the C-terminal domain of heat shock protein 90 (hsp90).

Embodiment 37. The method of embodiment 36, wherein the condition or disease is selected from the group of inflammatory bowel disease (IBD), Crohn's disease, colorectal cancer, alcoholic hepatitis, or a combination thereof.

EXAMPLES

[0217] The presently disclosed subject matter will be better understood by reference to the following examples, which are provided as exemplary embodiments of the disclosure, and not by way of limitation.

[0218] Compounds of the present disclosure may be prepared by methods known in the art of organic synthesis. In all of the methods it is understood that protecting groups for sensitive or reactive groups may be employed where necessary in accordance with general principles of chemistry. Protecting groups are manipulated according to standard methods of organic synthesis (T. W. Green and P. G. M. Wuts (2014) *Protective Groups in Organic Synthesis*, 5th edition, John Wiley & Sons). These groups are removed at a convenient stage of the compound synthesis using methods that are readily apparent to those skilled in the art.

[0219] Unless otherwise noted, reagents and solvents were used as received from commercial suppliers.

[0220] The chemical names were generated using ChemBioDraw Ultra v14 from CambridgeSoft.

[0221] Temperatures are given in degrees Celsius. If not mentioned otherwise, all evaporations are performed under reduced pressure, typically between about 15 mm Hg and 100 mm Hg (=20-133 mbar). The structure of final products, intermediates and starting materials is confirmed by standard analytical methods, e.g., microanalysis and spectroscopic characteristics, e.g., MS, IR, NMR. Abbreviations used are those conventional in the art.

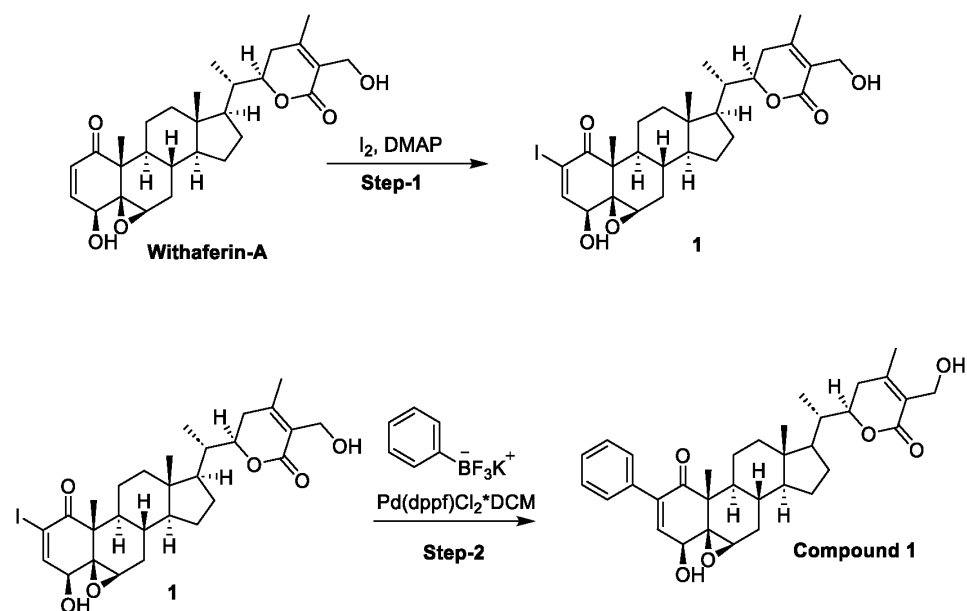
[0222] LC-MS: System: Waters Acquity UPLC with Waters SQ detector. Column: Acquity HSS T3 1.8 μ m 2.1 $\times$ 50 mm, column temperature: 60° C. Gradient: from 5 to 98% B in 1.4 min, A=water+0.05% formic acid+3.75 mM ammonium acetate, B=acetonitrile+0.04% formic acid, flow: 1.0 mL/min. Mass spectrometry results are reported as the ratio of mass over charge.

[0223] HPLC: System: Shimadzu LH-40 Auto sampler with PDA detector Column: X-Bridge PREP C18 (19 $\times$ 250)mm, 10 μ m Mobile phase: Acetonitrile: 5mM Ammonium Bicarbonate in H₂O

[0224] NMR: Measurements were performed on a Bruker Ultrashield™ 400 (400 MHz) or Bruker Ascend™ (400 MHz) or Bruker cryo system (600 MHz) spectrometer using or not tetramethylsilane (TMS) as an internal standard. Chemical shifts (δ) are reported in ppm downfield from TMS, spectra splitting pattern are designated as singlet (s), doublet (d), triplet (t), quartet (q), quintet (quint), septet (sept), multiplet, unresolved or overlapping signals (m), broad signal (bf). Deuterated solvents are given in parentheses and have chemical shifts of dimethyl sulfoxide (δ 2.50 ppm), methanol (δ 3.31 ppm), chloroform (δ 7.26 ppm), or other solvents as indicated in NMR spectral data.

Synthesis of Exemplary Embodiments of the Compound of Formula (I)

[0225] Synthesis of Compound 1



[0226] **Step-1: Synthesis of (4S,4aR,5aR,6aS,6bS,9R,9aS,11aS,11bR)-4-hydroxy-9-((S)-1-((R)-5-(hydroxymethyl)-4-methyl-6-oxo-3,6-dihydro-2H-pyran-2-yl)ethyl)-2-iodo-9a,11b-dimethyl-5a,6,6a,6b,7,8,9,9a,10,11,11a,11b-dodecahydrocyclopenta[1,2]phenanthro[8a,9-b]oxiren-1(4H)-one:**

To the stirred solution of withaferin-A (3 g, 1 eq; 6.37 mmol) in dichloromethane (30 mL) was added *N,N*-dimethyl pyridin-4-amine (1.17 g, 1.5 eq., 9.56 mmol) at inert atmosphere. After 10 minutes, iodine (1.94 g, 1.2 eq., 7.65 mmol) was added to the reaction mixture and the resultant reaction mixture was allowed to stir at room temperature for 3 hours. The reaction

mixture was quenched by saturated aqueous sodium thiosulfate solution (50 mL). The aqueous layer was extracted with dichloromethane (3 x 45 mL). Collected organics, dried over sodium sulphate and concentrated under reduced pressure to obtain crude. The crude was purified by combi-flash chromatography (using 5% methanol in dichloromethane) afforded (4*S*, 4*aR*, 5*aR*, 6*aS*, 6*bS*, 9*R*, 9*aS*, 11*aS*, 11*bR*)-4-hydroxy-9-((*S*)-1-((*R*)-5-(hydroxymethyl)-4-methyl-6-oxo-3,6-dihydro-2H-pyran-2-yl)ethyl)-2-iodo-9*a*,11*b*-dimethyl-5*a*, 6, 6*a*, 6*b*, 7, 8, 9, 9*a*, 10, 11, 11*a*, 11*b*-dodecahydrocyclopenta [1,2] phenanthrol [8*a*, 9-*b*]oxiren-1(4H)-one (2.1 g, 55%) as a white solid.

Analytical data:

LCMS: 90.55% (m/z: 595.18, [M-H]⁺, observed 595.18, [M+H]⁺, 2.29 min (4 min run).

¹H-NMR (400 MHz, DMSO-*d*₆): δ 7.78 (d, *J* = 6.4 Hz, 1H), 5.87 (d, *J* = 3.6 Hz, 1H), 5.87 (d, *J* = 3.6 Hz, 1H), 4.58 (t, *J* = 5.2 Hz, 1H), 4.30-4.27 (m, 1H), 4.18-4.08 (m, 2H), 3.51-3.48 (m, 1H), 3.19 (s, 1H), 2.35-2.43 (m, 1H), 2.00-2.12 (m, 5H), 1.86-1.89 (m, 1H), 1.73-1.80 (m, 2H), 1.55-1.58 (m, 1H), 1.24-1.38 (m, 9H), 0.95-1.10 (m, 4H), 0.91 (d, *J* = 6.4 Hz, 3H), 0.64-0.71 (m, 4H)

[0227] Step-2: Synthesis of (4*S*,4*aR*,5*aR*,6*aS*,6*bS*,9*aS*,11*aS*,11*bR*)-4-hydroxy-9-((*S*)-1-((*R*)-5-(hydroxymethyl)-4-methyl-6-oxo-3,6-dihydro-2H-pyran-2-yl)ethyl)-9*a*,11*b*-dimethyl-2-phenyl-5*a*,6,6*a*,6*b*,7,8,9,9*a*,10,11,11*a*,11*b*-dodecahydrocyclopenta[1,2]phenanthro[8*a*,9-*b*]oxiren-1(4H)-one:

To a stirring solution of (4*S*,4*aR*,5*aR*,6*aS*,6*bS*,9*R*,9*aS*,11*aS*,11*bR*)-4-hydroxy-9-((*S*)-1-((*R*)-5-(hydroxymethyl)-4-methyl-6-oxo-3,6-dihydro-2H-pyran-2-yl)ethyl)-2-iodo-9*a*,11*b*-dimethyl-5*a*,6,6*a*,6*b*,7,8,9,9*a*,10,11,11*a*,11*b*-dodecahydrocyclopenta[1,2]phenanthro[8*a*,9-*b*]oxiren-1(4H)-one (609 mg, 1 eq; 1.02 mmol) in 1,4 dioxane (9.74 mL) and water (2.44 mL) were added dipotassium carbonate (282 mg, 2 eq., 2.04 mmol) and trifluoro(phenyl) potassio-λ⁶-borane (282 mg, 1.5 eq., 1.53 mmol). The resulting reaction mixture was degassed by purging with nitrogen for 30 minutes. After that, [1,1'-Bis (diphenylphosphino) ferrocene] dichloropalladium (II) (149 mg, 0.2 eq., 204 μmol) was added to the above mixture and resultant mixture was heated at 85°C for 5 hours. Reaction was monitored by TLC (5% methanol in dichloromethane). After completion of the reaction, reaction mass was quenched by citric acid solution followed by extraction with dichloromethane (2 x 40 mL). Collected organics, dried over sodium sulphate and concentrated under reduced pressure to obtain crude.

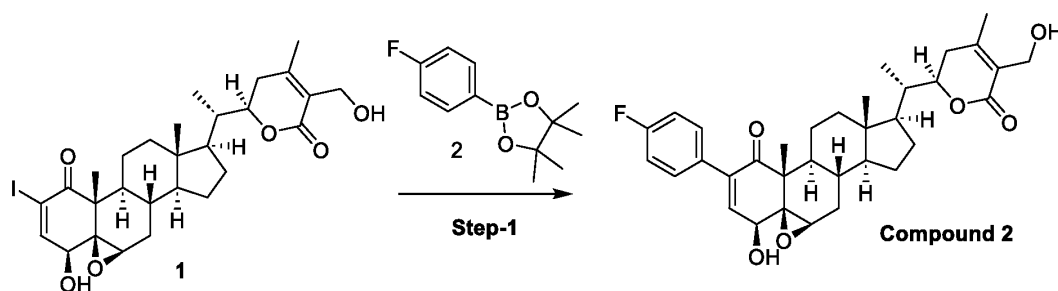
The crude was purified by combi-flash chromatography (5-10% methanol in dichloromethane) to furnish (4*S*, 4*aR*, 5*aR*, 6*aS*, 6*bS*, 9*aS*, 11*aS*, 11*bR*)-4-hydroxy-9-((*S*)-1-((*R*)-5-(hydroxymethyl)-4-methyl-6-oxo-3,6-dihydro-2H-pyran-2-yl)ethyl)-9*a*,11*b*-dimethyl-2-phenyl-5*a*, 6, 6*a*, 6*b*, 7, 8, 9, 9*a*, 10, 11, 11*a*, 11*b*-dodecahydrocyclopenta[1,2] phenanthrol [8*a*,9-*b*]oxiren-1(4*H*)-one (20 mg, 6%) as a white solid.

[0228] Analytical data:

LCMS: 99.10% (*m/z*: 547.45, [*M*+1]⁺, 569.45 [*M*+23]⁺, 6.12 min (10 min run).

¹H-NMR (400 MHz, DMSO-*d*₆): δ 7.40-7.35 (m, 5H), 7.03 (d, *J* = 6.40 Hz, 1H), 4.45-4.33 (m, 3H), 3.92 (d, *J* = 6.40 Hz, 1H), 3.20 (s, 1H), 2.54-2.45 (m, 1H), 2.21 (dd, *J* = 2.40, 14.80 Hz, 1H), 2.03-1.94 (m, 6H), 1.67-1.45 (m, 7H), 1.43-1.26 (m, 3H), 1.22-1.05 (m, 4H), 1.02-0.92 (m, 4H), 0.72 (s, 3H).

[0229] Synthesis of Compound 2



[0230] Step-1: Synthesis of ((4*S*, 4*aR*, 5*aR*, 6*aS*, 6*bS*, 9*R*, 9*aS*, 11*aS*, 11*bR*)-2-(4-fluorophenyl)-4-hydroxy-9-((*S*)-1-((*R*)-5-(hydroxymethyl)-4-methyl-6-oxo-3, 6-dihydro-2H-pyran-2-yl)ethyl)-9*a*, 11*b*-dimethyl-5*a*, 6, 6*a*, 6*b*, 7, 8, 9, 9*a*, 10, 11, 11*a*, 11*b*-dodecahydrocyclopenta [1, 2] phenanthrol [8*a*, 9-*b*]oxiren-1(4*H*)-one:

To a stirred solution of (4*S*,4*aR*,5*aR*,6*aS*,6*bS*,9*R*,9*aS*,11*aS*,11*bR*)-4-hydroxy-9-((*S*)-1-((*R*)-5-(hydroxymethyl)-4-methyl-6-oxo-3,6-dihydro-2H-pyran-2-yl)ethyl)-2-iodo-9*a*,11*b*-dimethyl-5*a*,6*a*,6*b*,7,8,9,9*a*,10,11,11*a*,11*b*-dodecahydrocyclopenta[1,2]phenanthro[8*a*,9-*b*]oxiren-1(4*H*)-one (450 mg, 1 eq; 754 μmol) in DME/Water (1/1) (90 mL) were added 2-(4-fluorophenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (335 mg, 2 eq., 1.51 mmol) and disodium carbonate (160 mg, 2 eq., 1.51 mmol). The resultant mixture was degassed using nitrogen for 15 minutes. After that, 10% palladium on carbon (0.1 g, 0.12 eq., 94 μmol) was added to the above mixture and continued stirring for 16 hours at room temperature. After

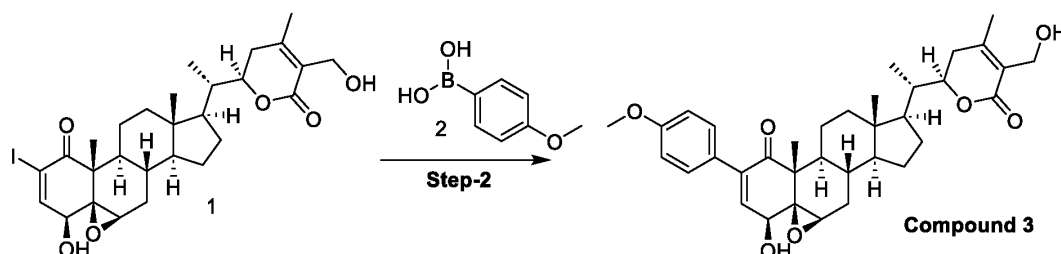
completion of the reaction (monitored by TLC: 5% methanol in dichloromethane), reaction mixture was passed through hy-flow celite and obtained filtrate was extracted with dichloromethane (3 x 25 mL). Collected organics, dried over sodium sulfate and concentrated under reduced pressure to obtain crude. Crude was further purified using preparative HPLC (using AA Method) to furnish ((4*S*, 4*aR*, 5*aR*, 6*aS*, 6*bS*, 9*R*, 9*aS*, 11*aS*, 11*bR*)-2-(4-fluorophenyl)-4-hydroxy-9-((*S*)-1-((*R*)-5-(hydroxymethyl)-4-methyl-6-oxo-3, 6-dihydro-2H-pyran-2-yl)ethyl)-9*a*,11*b*-dimethyl-5*a*, 6, 6*a*, 6*b*, 7, 8, 9, 9*a*, 10, 11, 11*a*, 11*b*-dodecahydrocyclopenta[1,2] phenanthrol [8*a*, 9-*b*]oxiren-1(4*H*)-one (239 mg, 56%) as a white solid.

[0231] Analytical data:

LCMS: 99.44% (*m/z*: 565.40, [*M*+1]⁺, 587.40 [*M*+23]⁺, 6.16 min (10 min run).

¹H-NMR (400 MHz, DMSO-*d*₆): δ 7.36-7.33 (m, 2H), 7.28-7.22 (m, 3H), 5.69 (d, *J* = 3.60 Hz, 1H), 4.57 (t, *J* = 5.60 Hz, 1H), 4.30-4.26 (m, 1H), 4.18-4.08 (m, 2H), 3.70 (dd, *J* = 3.60, 6.60 Hz, 1H), 3.16 (s, 1H), 2.43-2.35 (m, 1H), 2.09 (dd, *J* = 2.40, 18.40 Hz, 1H), 2.00-2.03 (m, 4H), 1.90-1.93 (m, 1H), 1.84-1.56 (m, 3H), 1.38-1.24 (m, 8H), 1.17-1.05 (m, 3H), 1.00-0.84 (m, 5H), 0.67 (s, 3H).

[0232] Synthesis of Compound 3



[0233] Step-1: Synthesis of (4*S*, 4*aR*, 5*aR*, 6*aS*, 6*bS*, 9*R*, 9*aS*, 11*aS*, 11*bR*)-4-hydroxy-9-((*S*)-1-((*R*)-5-(hydroxymethyl)-4-methyl-6-oxo-3, 6-dihydro-2H-pyran-2-yl)ethyl)-2-(4-methoxyphenyl)-9*a*, 11*b*-dimethyl-5*a*, 6, 6*a*, 6*b*, 7, 8, 9, 9*a*, 10, 11, 11*a*, 11*b*-dodecahydrocyclopenta [1, 2] phenanthrol [8*a*, 9-*b*] oxiren-1(4*H*)-one:

To a stirred solution of (1*S*, 2*R*, 6*S*, 7*R*, 9*R*, 11*S*, 12*S*, 15*R*, 16*S*)-6-hydroxy-15-[(1*S*)-1-[(2*R*)-5-(hydroxymethyl)-4-methyl-6-oxo-3, 6-dihydro-2H-pyran-2-yl] ethyl]-4-iodo-2, 16-dimethyl-8-oxapentacyclo [9.7.0.0^{2,7}.0^{7,9}.0^{12,16}] octadec-4-en-3-one (250 mg, 1 eq; 419 μmol)

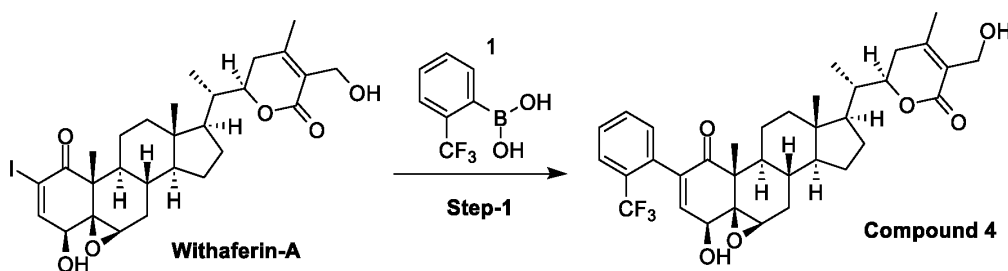
in dimethoxyethane and water (1:1 ratio; 5 mL) were added (4-methoxyphenyl) boronic acid (127 mg, 2 eq., 838 μmol), and disodium carbonate (88.8 mg, 2 eq., 838 μmol) and then the reaction mixture was purged with N_2 gas for 15 minutes. After that, 10% palladium on carbon (70 mg) was added to the above mixture and reaction is again purged with N_2 gas for 5 minutes. The reaction mixture was further stirred overnight at room temperature. The reaction mixture further passed through the celite bed and then the filtrate was washed with dichloromethane (30 mL). The collected organics was dried over sodium sulphate and concentrated under reduced pressure to obtain the crude. The crude was purified by preparative-HPLC (AA method) to afford (1*S*, 2*R*, 6*S*, 7*R*, 9*R*, 11*S*, 12*S*, 15*R*, 16*S*)-6-hydroxy-15-[(1*S*)-1-[(2*R*)-5-(hydroxymethyl)-4-methyl-6-oxo-3, 6-dihydro-2H-pyran-2-yl] ethyl] -4-(4-methoxyphenyl)-2, 16-dimethyl-8-oxapentacyclo [9.7.0.0^{2,7}.0^{7,9}.0^{12,16}] octadec-4-en-3-one (62 mg, 26%) as a white solid.

[0234] Analytical details:

LCMS: 99.55% (m/z : 577.40, $[\text{M}+1]^+$, 6.07 min (10 min run).

¹H-NMR (400 MHz, DMSO-*d*₆): δ 7.25 (d, J = 8.80 Hz, 2H), 7.16 (d, J = 6.80 Hz, 1H), 6.96 (d, J = 8.80 Hz, 2H), 5.62 (d, J = 3.60 Hz, 1H), 4.57 (t, J = 5.20 Hz, 1H), 4.30-4.27 (m, 1H), 4.18-4.08 (m, 2H), 3.77 (s, 3H), 3.68 (dd, J = 3.60, 6.60 Hz, 1H), 3.15 (s, 1H), 2.43-2.35 (m, 1H), 2.12-2.03 (m, 2H), 2.00 (s, 3H), 1.91-1.94 (m, 1H), 1.83-1.56 (m, 3H), 1.40-1.20 (m, 8H), 1.22-1.00 (m, 3H), 0.93-0.96 (m, 4H), 0.84 (m, 1H), 0.67 (s, 3H).

[0235] Synthesis of Compound 4



[0236] Step-1: Synthesis of (4*S*, 4*aR*, 5*aR*, 6*aS*, 6*bS*, 9*R*, 9*aS*, 11*aS*, 11*bR*)-4-hydroxy-9-((*S*)-1-((*R*)-5-(hydroxymethyl)-4-methyl-6-oxo-3, 6-dihydro-2H-pyran-2-yl) ethyl)-9a,

11b-dimethyl-2-(2-(trifluoromethyl) phenyl)-5a, 6, 6a, 6b, 7, 8, 9, 9a, 10, 11, 11a, 11b-dodecahydrocyclopenta [1, 2] phenanthrol [8a, 9-b] oxiren-1(4H)-one:

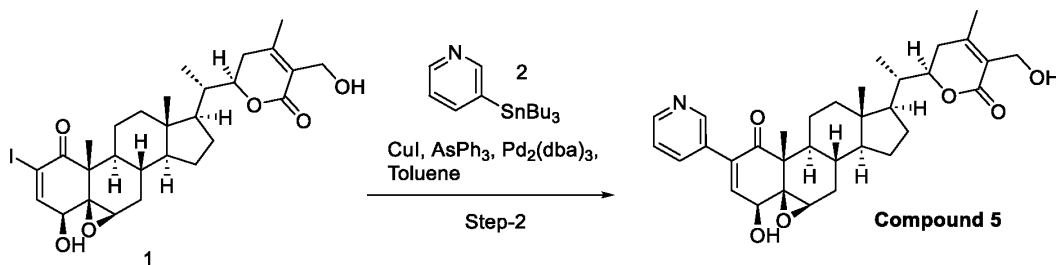
To a stirred solution of 2-iodo withaferin-A (450 mg, 754 μ mol) in DME-Water (7.89 mL) were added [2-(trifluoromethyl) phenyl] boronic acid (287 mg, 2 eq., 1.51 mmol), disodium carbonate (160 mg, 2 eq., 1.51 mmol). Resultant reaction mixture was degassed for 15 minutes. After that, 10% palladium on carbon (0.1 g, 940 μ mol) was heated at 50°C for 16 hours. Progress of reaction was monitored by TLC (5% methanol in dichloromethane) which showed formation of new spot. After completion of the reaction, the reaction mixture was passed through hy-flow celite and then the filtrate was extracted with dichloromethane (3 x 25 mL). The collected organics was dried over sodium sulphate and then concentrated under reduced pressure to obtain crude. The crude was purified by preparative HPLC (AA method) to furnish (4S, 4aR, 5aR, 6aS, 6bS, 9R, 9aS, 11aS, 11bR)-4-hydroxy-9-((S)-1-((R)-5-(hydroxymethyl)-4-methyl-6-oxo-3, 6-dihydro-2H-pyran-2-yl) ethyl)-9a, 11b-dimethyl-2-(2-(trifluoromethyl) phenyl)-5a, 6, 6a, 6b, 7, 8, 9, 9a, 10, 11, 11a, 11b-dodecahydrocyclopenta[1, 2] phenanthrol [8a, 9-b]oxiren-1(4H)-one (15 mg, 3%) as a white solid.

[0237] Analytical data:

LCMS: 98.45% (m/z: 615.45, $[M+1]^+$, 637.40 $[M+23]^+$, 6.37 min (10 min run).

$^1\text{H-NMR}$ (400 MHz, $\text{DMSO-}d_6$): δ 7.76 (d, J = 7.60 Hz, 1H), 7.70 (t, J = 7.60 Hz, 1H), 7.59 (t, J = 7.60 Hz, 1H), 7.28 (d, J = 7.20 Hz, 1H), 7.00 (d, J = 6.40 Hz, 1H), 5.79 (d, J = 4.00 Hz, 1H), 4.58 (t, J = 5.60 Hz, 1H), 4.27-4.30 (m, 1H), 4.18-4.08 (m, 2H), 3.69 (dd, J = 4.40, 6.40 Hz, 1H), 3.26 (s, 1H), 2.39-2.42 (m, 1H), 2.16-2.08 (m, 2H), 2.00 (s, 3H), 1.85-1.60 (m, 4H), 1.44-1.05 (m, 10H), 0.98-0.88 (m, 6H), 0.66 (s, 3H).

[0238] Synthesis of Compound 5



[0239] Step-1: Synthesis of (4*S*, 4*aR*, 5*aR*, 6*aS*, 6*bS*, 9*R*, 9*aS*, 11*aS*, 11*bR*)-4-hydroxy-9-((*S*)-1-((*R*)-5-(hydroxymethyl)-4-methyl-6-oxo-3, 6-dihydro-2H-pyran-2-yl) ethyl)-9*a*, 11*b*-dimethyl-2-(pyridin-3-yl)-5*a*, 6, 6*a*, 6*b*, 7, 8, 9, 9*a*, 10, 11, 11*a*, 11*b*-dodecahydrocyclopenta[1, 2] phenanthro[8*a*, 9-*b*]oxiren-1(4*H*)-one:

To a stirred solution of (1*S*, 2*R*, 6*S*, 7*R*, 9*R*, 11*S*, 12*S*, 15*R*, 16*S*)-6-hydroxy-15-[(1*S*)-1-[(2*R*)-5-(hydroxymethyl)-4-methyl-6-oxo-3,6-dihydro-2H-pyran-2-yl]ethyl]-4-iodo-2,16-dimethyl-8-oxapentacyclo [9.7.0.0^{2,7}.0^{7,9}.0^{12,16}] octadec-4-en-3-one (1.4 g, 1 eq; 2.35 mmol) in tetrahydrofuran (14 mL) were added λ^1 -copper(1+) iodide (44.7 mg, 0.1 eq., 235 μ mol), triphenylarsane (71.9 mg, 0.1 eq., 235 μ mol), and 3-(tributylstannyl) pyridine (1.73 g, 2 eq., 4.69 mmol). Reaction mixture was purged with continuous flow of nitrogen for 30 minutes. After that, tris((1*E*,4*E*)-1,5-diphenylpenta-1,4-dien-3-one) dipalladium (21.5 mg, 0.01 eq., 23.5 μ mol) was added and gain reaction mixture was degassed using nitrogen for 5 minutes. Resultant reaction mixture was stirred at 80°C for 16 hours. After completion of the reaction (monitored by TLC: 5% methanol in dichloromethane), reaction mixture was filtered through celite bed and filtrate was diluted by water (30 mL) followed by extraction with dichloromethane (2 x 50 mL). Collected organics, dried over sodium sulphate and then concentrated under reduced pressure to get crude.

Note: The crude from different batches was mixed together and enriched by combi-flash chromatography (4-10% of methanol in dichloromethane) to obtain crude with 47 g with 93% by LCMS. This was further purified by SFC (0.1 % of NH₄OH) to furnish 20.7 g of 99% pure (4*S*, 4*aR*, 5*aR*, 6*aS*, 6*bS*, 9*R*, 9*aS*, 11*aS*, 11*bR*)-4-hydroxy-9-((*S*)-1-((*R*)-5-(hydroxymethyl)-4-methyl-6-oxo-3, 6-dihydro-2H-pyran-2-yl)ethyl)-9*a*,11*b*-dimethyl-2-(pyridin-3-yl) 5*a*, 6, 6*a*, 6*b*, 7, 8, 9, 9*a*, 10, 11, 11*a*, 11*b*-dodecahydrocyclopenta [1, 2] phenanthrol [8*a*, 9-*b*] oxiren-1(4*H*)-one (20.7 g) as a white solid.

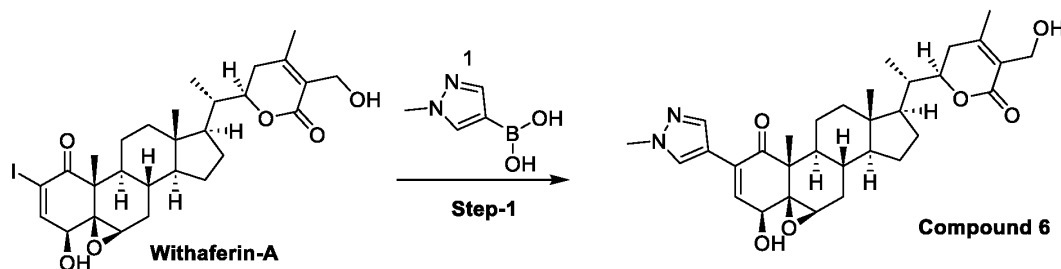
[0240] Analytical data:

LCMS: 99.47% (m/z: 548.45, [M+1]⁺, 5.14 min (10 min run).

¹H-NMR (400 MHz, DMSO-*d*₆): δ 8.55 (d, *J* = 3.60 Hz, 1H), 8.50 (s, 1H), 7.73-7.70 (m, 1H), 7.46-7.43 (m, 2H), 5.78 (d, *J* = 3.60 Hz, 1H), 4.59 (t, *J* = 5.20 Hz, 1H), 4.31-4.26 (m, 1H), 4.18-4.08 (m, 1H), 3.72 (dd, *J* = 3.60, 6.40 Hz, 1H), 3.19 (s, 1H), 2.50-2.35 (m, 1H), 2.11-2.07 (m, 2H), 1.99 (s, 3H), 1.93-1.56 (m, 4H), 1.41-1.28 (m, 8H), 1.16-1.00 (m, 5H), 0.88-0.90 (m, 4H), 0.67 (s, 3H).

¹³C-NMR (400 MHz, DMSO-*d*₆): 200.81, 165.32, 154.66, 149.22, 148.05, 139.54, 138.96, 134.82, 131.30, 125.44, 123.61, 77.51, 68.53, 63.31, 57.74, 55.26, 54.52, 51.05, 47.71, 42.29, 42.00, 38.40, 30.68, 29.33, 29.03, 26.51, 23.96, 20.48, 19.90, 15.43, 13.03, 11.26.

[0241] Synthesis of Compound 6



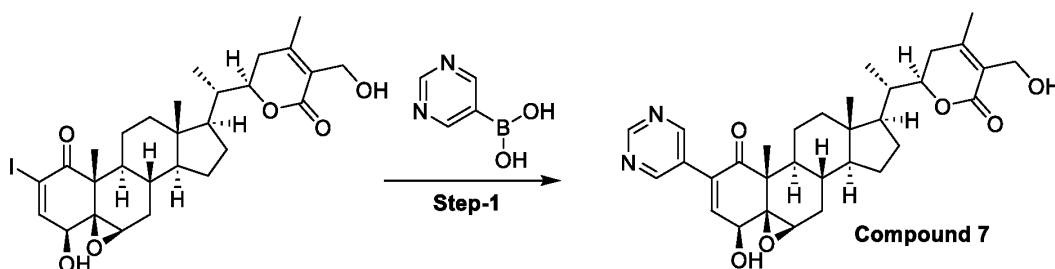
[0242] **Step-1: Synthesis of (4*S*, 4*aR*, 5*aR*, 6*aS*, 6*bS*, 9*R*, 9*aS*, 11*aS*, 11*bR*)-4-hydroxy-9-((*S*)-1-((*R*)-5-(hydroxymethyl)-4-methyl-6-oxo-3, 6-dihydro-2H-pyran-2-yl)ethyl)-9*a*, 11*b*-dimethyl-2-(1-methyl-1H-pyrazol-4-yl)-5*a*, 6, 6*a*, 6*b*, 7, 8, 9, 9*a*, 10, 11, 11*a*, 11*b*-dodecahydrocyclopenta [1, 2] phenanthrol [8*a*, 9-*b*]oxiren-1(4*H*)-one:**

To a stirred solution of (1*S*, 2*R*, 6*S*, 7*R*, 9*R*, 11*S*, 12*S*, 15*R*, 16*S*)-6-hydroxy-15-[(1*S*)-1-[(2*R*)-5-(hydroxymethyl)-4-methyl-6-oxo-3, 6-dihydro-2H-pyran-2-yl]ethyl]-4-iodo-2, 16-dimethyl-8-oxapentacyclo [9.7.0.0^{2,7}.0^{7,9}.0^{12,16}] octadec-4-en-3-one (0.4 g, 1 eq; 671 μmol) in DME/Water (1/1, 10 mL), were added (1-methyl-1H-pyrazol-4-yl)boronic acid (169 mg, 2 eq., 1.34 mmol) and disodium carbonate (142 mg, 2 eq., 1.34 mmol). Reaction mixture was degassed for 15 minutes using nitrogen and then 10% palladium on carbon (101 mg) was added. Resultant reaction mixture was stirred at 50°C for 16 hours. After completion of the reaction (5% methanol in dichloromethane), reaction mixture was passed through hy-flow celite and filtrate was quenched with saturated NaHCO₃ (40 mL) followed by extraction from dichloromethane (3 x 50 mL). The collected organics were dried over sodium sulfate and then concentrated under reduced pressure to obtain crude. The crude was purified by prep-HPLC (using AA method) afforded (4*S*, 4*aR*, 5*aR*, 6*aS*, 6*bS*, 9*R*, 9*aS*, 11*aS*, 11*bR*)-4-hydroxy-9-((*S*)-1-((*R*)-5-(hydroxymethyl)-4-methyl-6-oxo-3,6-dihydro-2H-pyran-2-yl)ethyl)-9*a*,11*b*-dimethyl-2-(1-methyl-1H-pyrazol-4-yl)-5*a*, 6, 6*a*, 6*b*, 7, 8, 9, 9*a*, 10, 11, 11*a*, 11*b*-dodecahydrocyclopenta [1, 2] phenanthrol [8*a*, 9-*b*] oxiren-1(4*H*)-one (106 mg, 29%) as a white solid.

[0243] Analytical data:

LCMS: 98.31% (m/z: 551.45, $[M+1]^+$, 573.40 $[M+23]^+$, 5.42 min (10 min run).

$^1\text{H-NMR}$ (400 MHz, $\text{DMSO-}d_6$): δ 7.88 (s, 1H), 7.69 (s, 1H), 7.11 (d, $J = 6.80$ Hz, 1H), 5.56 (d, $J = 3.60$ Hz, 1H), 4.57 (t, $J = 5.60$ Hz, 1H), 4.26-4.28 (m, 1H), 4.18-4.07 (m, 2H), 3.82 (s, 3H), 3.63 (dd, $J = 3.60, 6.80$ Hz, 1H), 3.15 (s, 1H), 2.41-2.33 (m, 1H), 2.10-1.99 (m, 5H), 1.91-1.54 (m, 5H), 1.38-0.99 (m, 10H), 0.94-0.90 (m, 4H), 0.72-0.69 (m, 1H), 0.65 (s, 3H).

[0244] Synthesis of Compound 7

[0245] Step-1: Synthesis of (4*S*, 4*aR*, 5*aR*, 6*aS*, 6*bS*, 9*R*, 9*aS*, 11*aS*, 11*bR*)-4-hydroxy-9-((*S*)-1-((*R*)-5-(hydroxymethyl)-4-methyl-6-oxo-3, 6-dihydro-2H-pyran-2-yl)ethyl)-9*a*, 11*b*-dimethyl-2-(pyrimidin-5-yl)-5*a*, 6, 6*a*, 6*b*, 7, 8, 9, 9*a*, 10, 11, 11*a*, 11*b*-dodecahydrocyclopenta [1, 2] phenanthrol [8*a*, 9-*b*]oxiren-1(4*H*)-one:

To a stirred solution of (1*S*, 2*R*, 6*S*, 7*R*, 9*R*, 11*S*, 12*S*, 16*S*)-6-hydroxy-15-[(1*S*)-1-[(2*R*)-5-(hydroxymethyl)-4-methyl-6-oxo-3, 6-dihydro-2H-pyran-2-yl]ethyl]-4-iodo-2, 16-dimethyl-8-oxapentacyclo [9.7.0.0^{2,7}.0^{7,9}.0^{12,16}] octadec-4-en-3-one (1 g, 1 eq; 1.68 mmol) in 1,4-dioxane: water (12 mL, 5:1) were added (pyrimidin-5-yl)boronic acid (312 mg, 1.5 eq., 2.51 mmol) and caesium carbonate (1.64 g, 3 eq., 5.03 mmol). The reaction mixture was degassed by N_2 for 30 minutes and after that palladium (2+) bis(triphenylphosphane) dichloride (118 mg, 0.1 eq., 168 μmol) was added. The reaction mixture was allowed to stir for 16 hours at 90°C. After completion of the reaction (monitored by TLC), the reaction mixture was quenched with ice cold water (20 mL) and then extracted with dichloromethane (3 x 50 mL). Collected organics, dried with Na_2SO_4 and concentrated under reduced pressure to obtain crude. The crude residue was purified by combi-flash chromatography (using 10% methanol in dichloromethane) to furnish crude. Crude was purified by preparative HPLC (Method: AA) afforded (4*S*, 4*aR*, 5*aR*, 6*aS*, 6*bS*, 9*R*, 9*aS*, 11*aS*, 11*bR*)-4-hydroxy-9-((*S*)-1-((*R*)-5-(hydroxymethyl)-4-methyl-6-oxo-3, 6-dihydro-2H-pyran-2-yl) ethyl)-9*a*, 11*b*-dimethyl-2-

(pyrimidin-5-yl)-5a, 6, 6a, 6b, 7, 8, 9, 9a, 10, 11, 11a, 11b-dodecahydrocyclopenta [1, 2] phenanthrol [8a,9-b] oxiren-1(4H)-one (119 mg; 13%) as a white solid.

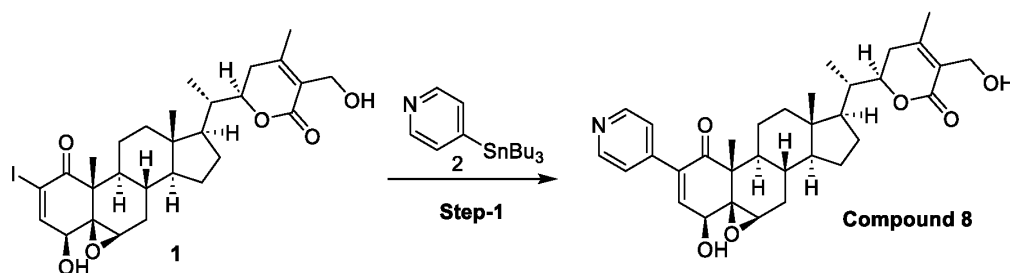
[0246] Analytical data:

LCMS: 95.51% (m/z: 549.40, $[M+1]^+$, 5.61 min (10 min run).

$^1\text{H-NMR}$ (400 MHz, $\text{DMSO-}d_6$): δ 9.18 (s, 1H), 8.77 (s, 2H), 7.61 (d, $J = 6.80$ Hz, 1H), 4.31-4.26 (m, 1H), 4.17-4.04 (m, 2H), 3.74 (d, $J = 6.80$ Hz, 1H), 3.21 (s, 1H), 2.39-2.42 (m, 1H), 2.10-2.06 (m, 2H), 2.00 (s, 3H), 1.88-1.91 (m, 1H), 1.83-1.56 (m, 3H), 1.42-1.22 (m, 9H), 1.20-1.06 (m, 3H), 1.05-0.95 (m, 2H), 0.91-0.93 (m, 4H), 0.66 (s, 3H).

$^{13}\text{C-NMR}$ (400 MHz, $\text{DMSO-}d_6$): δ 200.45, 165.31, 157.80, 155.37, 154.65, 154.65, 135.85, 129.26, 125.44, 77.51, 68.37, 63.10, 57.94, 55.12, 54.51, 51.11, 47.71, 42.23, 41.98, 38.33, 30.60, 29.36, 29.03, 26.49, 23.96, 20.50, 19.89, 15.60, 13.05, 11.26.

[0247] Synthesis of Compound 8



[0248] Step-1: Synthesis of (4*S*, 4a*R*, 5a*R*, 6a*S*, 6b*S*, 9*R*, 9a*S*, 11a*S*, 11b*R*)-4-hydroxy-9-((*S*)-1-((*R*)-5-(hydroxymethyl)-4-methyl-6-oxo-3, 6-dihydro-2H-pyran-2-yl)ethyl)-9a, 11b-dimethyl-2-(pyridin-4-yl)-5a, 6, 6a, 6b, 7, 8, 9, 9a, 10, 11, 11a, 11b-dodecahydrocyclopenta [1, 2] phenanthrol [8a, 9-b]oxiren-1(4H)-one:

To a stirred solution of (1*S*, 2*R*, 6*S*, 7*R*, 9*R*, 11*S*, 12*S*, 15*R*, 16*S*)-6-hydroxy-15-[(1*S*)-1-[(2*R*)-5-(hydroxymethyl)-4-methyl-6-oxo-3, 6-dihydro-2H-pyran-2-yl]ethyl]-4-iodo-2, 16-dimethyl-8-oxapentacyclo [9.7.0.0^{2,7}.0^{7,9}.0^{12,16}] octadec-4-en-3-one (1.2 g, 1 eq; 2.01 mmol) in tetrahydrofuran (24 mL) were added λ^1 -copper(1+) iodide (38.3 mg, 0.1 eq., 201 μmol), triphenylarsane (61.6 mg, 0.1 eq., 201 μmol), and 4-(tributylstannyl) pyridine (1.48 g, 2 eq., 4.02 mmol). Resultant reaction mixture is degassed using nitrogen gas for 30 minutes. After that, tris((1*E*,4*E*)-1,5-diphenylpenta-1,4-dien-3-one) dipalladium (92.1 mg, 0.05 eq., 101 μmol) was added to the above reaction mixture and allowed to stir at 80°C for 16 hours. After

completion of the reaction (reaction was monitored by TLC), mixture was filtered by using celite bed and filtrate was extracted by dichloromethane (3 x 30 mL). Collected organics, dried over anhydrous sodium sulphate and concentrated under reduced pressure to get crude. Crude was purified by using preparative-HPLC (ABC method) afforded. (4*S*, 4*aR*, 5*aR*, 6*aS*, 6*bS*, 9*R*, 9*aS*, 11*aS*, 11*bR*)-4-hydroxy-9-((*S*)-1-((*R*)-5-(hydroxymethyl)-4-methyl-6-oxo-3, 6-dihydro-2*H*-pyran-2-yl)ethyl)-9*a*, 11*b*-dimethyl-2-(pyridin-4-yl)-5*a*, 6, 6*a*, 6*b*, 7, 8, 9, 9*a*, 10, 11, 11*a*, 11*b*-dodecahydrocyclopenta [1, 2] phenanthrol [8*a*, 9-*b*] oxiren-1(4*H*)-one (112 mg, 10%) as a white solid.

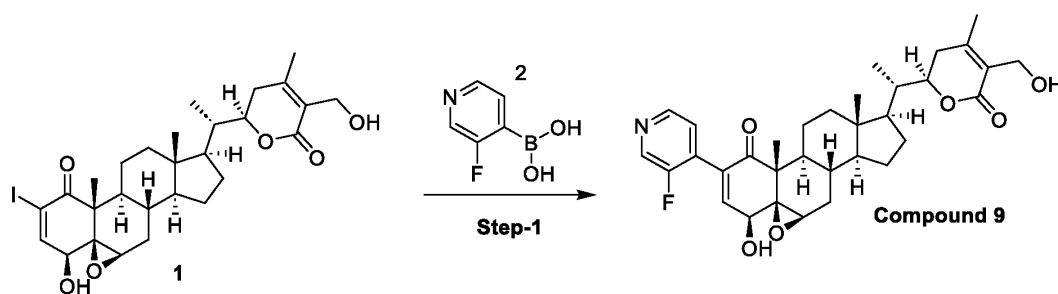
Analytical data:

LCMS: 93.94% (*m/z*: 548.35, [*M*+1]⁺, 5.10 min (10 min run).

¹H-NMR (400 MHz, DMSO-*d*₆): δ 8.61 (s, 1H), 7.55 (d, *J* = 6.80 Hz, 1H), 7.33 (d, *J* = 4.40 Hz, 2H), 5.83 (d, *J* = 3.60 Hz, 1H), 4.59 (t, *J* = 5.60 Hz, 1H), 4.29-4.27 (m, 1H), 4.17-4.08 (m, 2H), 3.74 (dd, *J* = 3.60, 6.80 Hz, 1H), 3.18 (s, 1H), 2.43-2.32 (m, 1H), 2.09 (dd, *J* = 2.40, 18.20 Hz, 1H), 1.99-2.03 (m, 4H), 1.90-1.93 (m, 1H), 1.81-1.56 (m, 3H), 1.45-1.23 (m, 8H), 1.16-0.97 (m, 5H), 0.92 (d, *J* = 6.40 Hz, 3H), 0.84-0.86 (m, 1H), 0.67 (s, 3H).

¹³C-NMR (400 MHz, DMSO-*d*₆): 200.34, 165.29, 154.64, 150.05, 150.05, 140.74, 139.38, 125.43, 77.49, 68.42, 63.25, 57.60, 55.26, 54.50, 51.02, 47.74, 42.20, 41.98, 30.63, 29.26, 29.01, 26.50, 23.93, 20.45, 19.88, 15.30, 13.01, 11.24

[0249] Synthesis of Compound 9



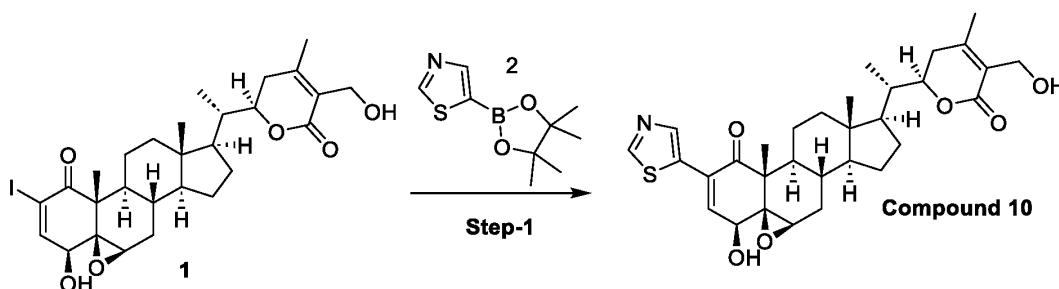
[0250] **Step-1: Synthesis of (4*S*, 4*aR*, 5*aR*, 6*aS*, 6*bS*, 9*R*, 9*aS*, 11*aS*, 11*bR*)-2-(3-fluoropyridin-4-yl)-4-hydroxy-9-((*S*)-1-((*R*)-5-(hydroxymethyl)-4-methyl-6-oxo-3, 6-dihydro-2*H*-pyran-2-yl)ethyl)-9*a*, 11*b*-dimethyl-5*a*, 6, 6*a*, 6*b*, 7, 8, 9, 9*a*, 10, 11, 11*a*, 11*b*-dodecahydrocyclopenta [1, 2] phenanthro [8*a*, 9-*b*] oxiren-1(4*H*)-one:**

To a stirred solution of (1S, 2R, 6S, 7R, 9R, 11S, 12S, 15R, 16S)-6-hydroxy-15-[(1S)-1-[(2R)-5-(hydroxymethyl)-4-methyl-6-oxo-3, 6-dihydro-2H-pyran-2-yl]ethyl]-4-iodo-2, 16-dimethyl-8-oxapentacyclo [9.7.0.0^{2,7}.0^{7,9}.0^{12,16}] octadec-4-en-3-one (0.5 g, 1 eq; 838 μ mol) in water (0.5 mL) and 1,4-dioxane (5 mL) were added (3-fluoropyridin-4-yl)boronic acid (177 mg, 1.5 eq., 1.26 mmol) and dicaesium(1+)carbonate (819 mg, 3 eq., 2.51 mmol) at room temperature. The reaction mixture was purged with nitrogen gas for 35 minutes and then palladium(2+)bis (triphenylphosphane) dichloride (58.8 mg, 0.1 eq., 83.8 μ mol) was added to the reaction mixture. The reaction mixture was again purged with nitrogen gas for 5 minutes. The reaction vessel was sealed and stirred at 85°C for 16 hours. After completion of the reaction (monitored by TLC: 5% methanol in dichloromethane), the reaction mixture was quenched with water (10 mL) and then extracted with dichloromethane (2 x 100 mL). The combined organic layers were dried over anhydrous sodium sulphate and then concentrated under reduced pressure to get crude. The crude residue was purified by combi-flash chromatography (using 5% methanol in dichloromethane) followed by preparative-HPLC (TFA method) purification (4S, 4aR, 5aR, 6aS, 6bS, 9R, 9aS, 11aS, 11bR)-2-(3-fluoropyridin-4-yl)-4-hydroxy-9-((S)-1-((R)-5-(hydroxymethyl)-4-methyl-6-oxo-3, 6-dihydro-2H-pyran-2-yl)ethyl)-9a, 11b-dimethyl-5a, 6, 6a, 6b, 7, 8, 9, 9a, 10, 11, 11a, 11b-dodecahydrocyclopenta [1, 2] phenanthro [8a, 9-b]oxiren-1(4H)-one (16 mg, 3%) as a white solid.

[0251] Analytical data:

LCMS: 98.88% (m/z: 566.35, [M+1]⁺, 5.78 min (10 min run).

¹H-NMR (400 MHz, DMSO-*d*₆): δ 8.59 (d, *J* = 2.00 Hz, 1H), 8.49 (d, *J* = 4.80 Hz, 1H), 7.48 (d, *J* = 6.80 Hz, 1H), 7.43-7.40 (m, 1H), 5.88 (d, *J* = 3.60 Hz, 1H), 4.57 (t, *J* = 5.60 Hz, 1H), 4.31-4.28 (m, 1H), 4.19-4.08 (m, 2H), 3.74 (dd, *J* = 4.00, 6.60 Hz, 1H), 3.21 (s, 1H), 2.50-2.37 (m, 1H), 2.15-2.06 (m, 2H), 2.00 (s, 3H), 1.90-1.94 (m, 1H), 1.84-1.58 (m, 3H), 1.43-1.46 (m, 1H), 1.38-1.18 (m, 7H), 1.16-0.90 (m, 8H), 0.60 (s, 3H).

[0252] Synthesis of Compound 10

[0253] Step-1: Synthesis of (4*S*, 4*aR*, 5*aR*, 6*aS*, 6*bS*, 9*R*, 9*aS*, 11*aS*, 11*bR*)-4-hydroxy-9-((*S*)-1-((*R*)-5-(hydroxymethyl)-4-methyl-6-oxo-3, 6-dihydro-2*H*-pyran-2-yl)ethyl)-9*a*, 11*b*-dimethyl-2-(thiazol-5-yl)-5*a*, 6, 6*a*, 6*b*, 7, 8, 9, 9*a*, 10, 11, 11*a*, 11*b*-dodecahydrocyclopenta [1, 2] phenanthro [8*a*, 9-*b*] oxiren-1(4*H*)-one:

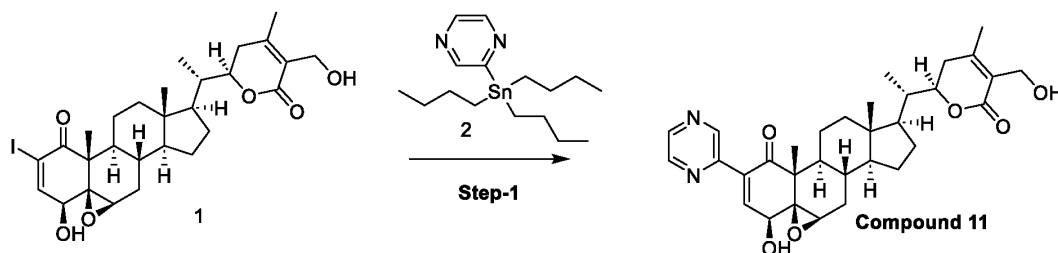
To a stirred solution of (1*S*, 2*R*, 6*S*, 7*R*, 9*R*, 11*S*, 12*S*, 15*R*, 16*S*)-6-hydroxy-15-[(1*S*)-1-[(2*R*)-5-(hydroxymethyl)-4-methyl-6-oxo-3, 6-dihydro-2*H*-pyran-2-yl] ethyl]-4-iodo-2, 16-dimethyl-8-oxapentacyclo [9.7.0.0^{2,7}.0^{7,9}.0^{12,16}] octadec-4-en-3-one (0.5 g, 1 eq; 838 μ mol) in 1, 4-dioxane (5 mL) and water (1 mL) were added 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3-thiazole (265 mg, 1.5 eq., 1.26 mmol) and dipotassium carbonate (348 mg, 3 eq., 2.51 mmol) at room temperature. The reaction mixture was purged with nitrogen gas for 35 minutes and then [1,1'-Bis(diphenylphosphino)ferrocene]dichloropalladium(II) (68.6 mg, 0.1 eq., 83.8 μ mol) was added to it. The reaction mixture was again purged with nitrogen gas for 5 minutes. The reaction vessel was sealed, and the reaction was stirred at 100°C for 16 hours. After completion of the reaction (monitoring by LCMS), reaction mixture was passed through celite, and filtrate was concentrated to get crude. The crude was enriched by combi-flash chromatography (5% methanol in dichloromethane) followed by purification by preparative HPLC (ABC method) 4*S*,4*aR*,5*aR*,6*aS*,6*bS*,9*R*,9*aS*,11*aS*,11*bR*)-4-hydroxy-9-((*S*)-1-((*R*)-5-(hydroxymethyl)-4-methyl-6-oxo-3,6-dihydro-2*H*-pyran-2-yl)ethyl)-9*a*,11*b*-dimethyl-2-(thiazol-5-yl)-5*a*,6,6*a*,6*b*,7,8,9,9*a*,10,11,11*a*,11*b*-dodecahydrocyclopenta[1,2]phenanthro[8*a*,9-*b*]oxiren-1(4*H*)-on (18 mg, 4%) as a white solid.

[0254] Analytical data:

LCMS: 95.19% (m/z: 554.30, [M+1]⁺, 5.82 min (10 min run).

¹H-NMR (400 MHz, DMSO-*d*₆): δ 9.08 (s, 1H), 8.20 (s, 1H), 7.48 (d, *J* = 6.40 Hz, 1H), 5.80 (s, 1H), 4.29-4.25 (m, 1H), 4.17-4.08 (m, 2H), 3.72 (d, *J* = 6.8 Hz, 1H), 3.20 (s, 1H), 2.40-2.33 (m, 1H), 2.09-2.02 (m, 2H), 1.99 (s, 3H), 1.89-1.54 (m, 4H), 1.35-1.21 (m, 8H), 1.11-0.89 (m, 8H), 0.76-0.72 (m, 1H), 0.65 (s, 3H).

[0255] Synthesis of Compound 11



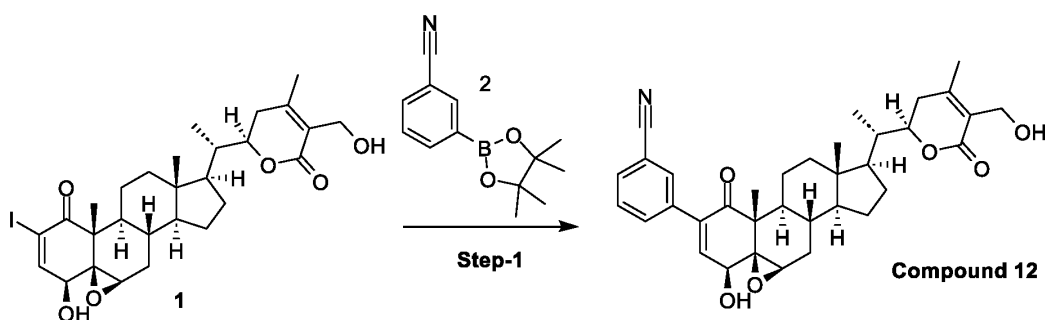
[0256] Step-1: Synthesis of (4*S*, 4*aR*, 5*aR*, 6*aS*, 6*bS*, 9*R*, 9*aS*, 11*aS*, 11*bR*)-4-hydroxy-9-((*S*)-1-((*R*)-5-(hydroxymethyl)-4-methyl-6-oxo-3, 6-dihydro-2H-pyran-2-yl)ethyl)-9*a*, 11*b*-dimethyl-2-(pyrazin-2-yl)-5*a*, 6, 6*a*, 6*b*, 7, 8, 9, 9*a*, 10, 11, 11*a*, 11*b*-dodecahydrocyclopenta [1, 2] phenanthro [8*a*, 9-*b*] oxiren-1(4*H*)-one:

To the stirred solution of (1*S*, 2*R*, 6*S*, 7*R*, 9*R*, 11*S*, 12*S*, 16*S*)-6-hydroxy-15-[(1*S*)-1-[(2*R*)-5-(hydroxymethyl)-4-methyl-6-oxo-3, 6-dihydro-2H-pyran-2-yl] ethyl]-4-iodo-2, 16-dimethyl-8-oxapentacyclo [9.7.0.0.2^{7,10}, 9.0^{12,16}] octadec-4-en-3-one (0.4 g, 1 eq; 671 μ mol) in N, N-dimethyl formamide (4 mL) were added to diiodocopper (31.9 mg, 0.15 eq., 101 μ mol) and 2-(tributylstannyl) pyrazine (248 mg, 671 μ mol). The reaction mixture was degassed by N₂ for 30 minutes and then after, 1,1'-Bis (diphenylphosphino) ferrocene] palladium (II) dichloride dichloromethane (27.4 mg, 0.05 eq., 33.5 μ mol) was added. The reaction mixture was allowed to stir for 4 hours at 60°C. After completion of the reaction (monitored by TLC), the reaction mixture was quenched with ice cold water (15 mL) and then extracted with dichloromethane (3 x 55 mL). Collected organics, dried over Na₂SO₄ and concentrated under reduced pressure to obtain crude. The crude residue was purified by combi-flash chromatography (eluted at 10% methanol in dichloromethane) to obtain crude. Crude was further purified by preparative HPLC (Method: AA) afforded 4*S*, 4*aR*, 5*aR*, 6*aS*, 6*bS*, 9*R*, 9*aS*, 11*aS*, 11*bR*)-4-hydroxy-9-((*S*)-1-((*R*)-5-(hydroxymethyl)-4-methyl-6-oxo-3, 6-dihydro-2H-pyran-2-yl)ethyl)-9*a*, 11*b*-dimethyl-2-(pyrazin-2-yl)-5*a*, 6, 6*a*, 6*b*, 7, 8, 9, 9*a*, 10, 11, 11*a*, 11*b*-dodecahydrocyclopenta [1, 2] phenanthro [8*a*, 9-*b*] oxiren-1(4*H*)-one (111 mg; 30%) as a white solid.

[0257] Analytical data:

LCMS: 99.41% (m/z: 549.40, $[M+1]^+$, 5.80 min (10 min run).

$^1\text{H-NMR}$ (400 MHz, $\text{DMSO-}d_6$): δ 8.70-8.69 (m, 1H), 8.65 (d, $J = 1.20$ Hz, 1H), 8.63 (d, $J = 2.40$ Hz, 1H), 7.77 (d, $J = 6.80$ Hz, 1H), 5.85 (d, $J = 3.60$ Hz, 1H), 4.58 (t, $J = 5.20$ Hz, 1H), 4.31-4.26 (m, 1H), 4.18-4.08 (m, 2H), 3.79 (dd, $J = 3.60, 6.80$ Hz, 1H), 3.18 (s, 1H), 2.42-2.33 (m, 1H), 2.09 (dd, $J = 3.20, 18.20$ Hz, 1H), 2.02-2.03 (m, 1H), 1.99 (s, 3H), 1.92 (s, 1H), 1.83-1.70 (m, 2H), 1.60-1.39 (m, 2H), 1.37-1.23 (m, 7H), 1.17-1.03 (m, 3H), 0.99-0.92 (m, 5H), 0.67 (s, 3H).

[0258] Synthesis of Compound 12

[0259] Step-1: Synthesis of 3-((4*S*, 4*aR*, 5*aR*, 6*aS*, 6*bS*, 9*R*, 9*aS*, 11*aS*, 11*bR*)-4-hydroxy-9-((*S*)-1-((*R*)-5-(hydroxymethyl)-4-methyl-6-oxo-3, 6-dihydro-2H-pyran-2-yl)ethyl)-9*a*, 11*b*-dimethyl-1-oxo-1, 4, 5*a*, 6, 6*a*, 6*b*, 7, 8, 9, 9*a*, 10, 11, 11*a*, 11*b*-tetradecahydrocyclopenta [1, 2] phenanthro [8*a*, 9-*b*] oxiren-2-yl) benzonitrile

To a stirred solution of (1*S*, 2*R*, 6*S*, 7*R*, 9*R*, 11*S*, 12*S*, 15*R*, 16*S*)-6-hydroxy-15-[(1*S*)-1-[(2*R*)-5-(hydroxymethyl)-4-methyl-6-oxo-3, 6-dihydro-2H-pyran-2-yl]ethyl]-4-iodo-2, 16-dimethyl-8-oxapentacyclo [9.7.0.0.^{2,7}.0.^{7,9}.0.^{12,16}] octadec-4-en-3-one (0.5 g, 1 eq; 838 μmol) in 1,4-dioxane (1 mL, 11.7 mmol) were added 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzonitrile (192 mg, 838 μmol) and sodium hydrogen carbonate (42.2 mg, 3 eq., 503 μmol). The resultant solution was purged with nitrogen for 40 minutes. After that, [1,1'-Bis (diphenylphosphino) ferrocene] dichloropalladium (II) dichloromethane (27.4 mg, 0.2 eq., 33.5 μmol) was added and again it was purged with nitrogen for 5 minutes. The reaction mixture was warmed to 60°C and was allowed to stir for 16 hours. After completion of the reaction, the

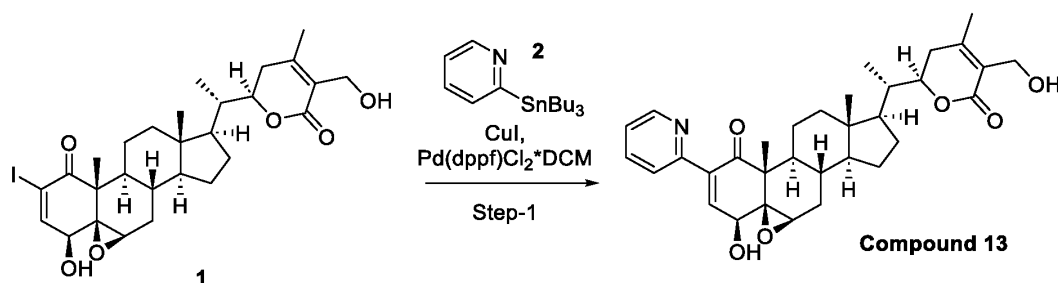
reaction mixture was filtered through celite, and filtrate was extracted with dichloromethane (3 x 40 mL). Collected organics, dried over sodium sulphate and then concentrated under reduced pressure to obtain crude. The crude residue was enriched by Combi-flash (eluting at 60% of ethyl acetate in n-heptane) and then purified preparative HPLC (ABC method) afforded and was afforded 3-((4*S*, 4*aR*, 5*aR*, 6*aS*, 6*bS*, 9*R*, 9*aS*, 11*aS*, 11*bR*)-4-hydroxy-9-((*S*)-1-((*R*)-5-(hydroxymethyl)-4-methyl-6-oxo-3, 6-dihydro-2H-pyran-2-yl)ethyl)-9*a*, 11*b*-dimethyl-1-oxo-1, 4, 5*a*, 6, 6*a*, 6*b*, 7, 8, 9, 9*a*, 10, 11, 11*a*, 11*b*-tetradecahydrocyclopenta [1, 2] phenanthro [8*a*, 9-*b*] oxiren-2-yl) benzonitrile (18 mg, 4%) as a white solid.

[0260] Analytical data:

LCMS: 95.30% (*m/z*: 572.45, $[M+1]^+$, 594.35, $[M+23]$, 6.33 min (10 min run).

¹H-NMR (400 MHz, DMSO-*d*₆): δ 7.84 (d, *J* = 6.00 Hz, 1H), 7.79 (s, 1H), 7.61-7.63 (m, 2H), 7.46 (d, *J* = 6.40 Hz, 1H), 5.72-5.79 (m, 1H), 4.59-4.56 (m, 1H), 4.27-4.30 (m, 1H), 4.17-4.08 (m, 2H), 3.72 (d, *J* = 5.60 Hz, 1H), 3.18 (s, 1H), 2.43-2.33 (m, 1H), 2.06-2.10 (m, 2H), 1.99 (s, 3H), 1.90-1.93 (m, 1H), 1.90-1.85 (m, 3H), 1.65-1.47 (m, 1H), 1.38-1.20 (m, 7H), 1.18-0.87 (m, 8H), 0.66 (s, 3H).

[0261] Synthesis of Compound 13



[0262] Step-1: Synthesis of (4*S*, 4*aR*, 5*aR*, 6*aS*, 6*bS*, 9*R*, 9*aS*, 11*aS*, 11*bR*)-4-hydroxy-9-((*S*)-1-((*R*)-5-(hydroxymethyl)-4-methyl-6-oxo-3, 6-dihydro-2H-pyran-2-yl)ethyl)-9*a*, 11*b*-dimethyl-2-(pyridin-2-yl)-5*a*, 6, 6*a*, 6*b*, 7, 8, 9, 9*a*, 10, 11, 11*a*, 11*b*-dodecahydrocyclopenta [1, 2] phenanthro [8*a*, 9-*b*] oxiren-1(4H)-one:

To a solution of (1*S*, 2*R*, 6*S*, 7*R*, 9*R*, 11*S*, 12*S*, 16*S*)-6-hydroxy-15-[(1*S*)-1-[(2*R*)-5-(hydroxymethyl)-4-methyl-6-oxo-3, 6-dihydro-2H-pyran-2-yl]ethyl]-4-iodo-2, 16-dimethyl-8-oxapentacyclo [9.7.0.0^{2,7}.0^{7,9}.0^{12,16}] octadec-4-en-3-one (5 g, 8.38 mmol) in dimethylformamide (50 mL, 646 mmol) were added diiodocopper (399 mg, 0.15 eq., 1.26

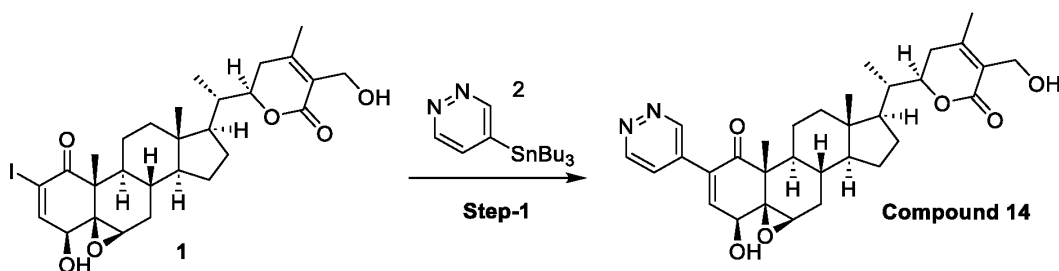
mmol), 2-(tributylstannyl) pyridine (6.17 g, 2 eq., 16.8 mmol) under inert atmosphere at room temperature. The above reaction mixture was purged with nitrogen for 40 minutes and then, 1,1'-Bis (diphenylphosphino) ferrocene]palladium (II) Dichloride Dichloromethane adduct (342 mg, 0.05 eq., 419 μ mol) was added to the reaction mixture. After that, reaction mixture was purged for another 5 minutes with nitrogen. The reaction mixture was heated at 65°C for 4 hours. After completion of the reaction, (monitored by TLC: 5% methanol in dichloromethane), reaction mixture was quenched with ice-cold (60 mL) water and extracted with dichloromethane (3 X 15 mL). The combined organics was dried over sodium sulphate and evaporated under reduced pressure to obtain crude. Crude was enriched by combi-flash chromatography (eluted at: 4-10% methanol in dichloromethane) followed by purification using preparative HPLC afforded 4S, 4aR, 5aR, 6aS, 6bS, 9R, 9aS, 11aS, 11bR)-4-hydroxy-9-((S)-1-((R)-5-(hydroxymethyl)-4-methyl-6-oxo-3, 6-dihydro-2H-pyran-2-yl) ethyl)-9a, 11b-dimethyl-2-(pyridin-2-yl)-5a, 6, 6a, 6b, 7, 8, 9, 9a, 10, 11, 11a, 11b-dodecahydrocyclopenta [1, 2] phenanthro [8a, 9-b] oxiren-1(4H)-one (1.1 g, 24%) as a white solid.

[0263] Analytical data:

LCMS: 96.60% (m/z: 548.60, $[M+1]^+$, 546.7 $[M-1]^+$, 5.36 min (10 min run).

$^1\text{H-NMR}$ (400 MHz, DMSO- d_6): δ 8.60 (d, J = 4.00 Hz, 1H), 7.83 (t, J = 7.60 Hz, 1H), 7.68 (d, J = 6.80 Hz, 1H), 7.39-7.34 (m, 2H), 5.75 (d, J = 3.20 Hz, 1H), 4.59 (t, J = 5.20 Hz, 1H), 4.42-4.32 (m, 1H), 4.30-4.07 (m, 2H), 3.77-3.74 (m, 1H), 3.16 (s, 1H), 2.42-2.33 (m, 1H), 2.11-2.02 (m, 2H), 1.99 (s, 3H), 1.90-1.93 (m, 1H), 1.80-1.90 (m, 1H), 1.70-1.72 (m, 1H), 1.55-1.57 (m, 1H), 1.38-1.41 (m, 2H), 1.28-1.35 (m, 4H), 1.22-1.25 (m, 2H), 1.05-1.15 (m, 3H), 0.86-0.98 (m, 5H), 0.66 (s, 3H).

$^{13}\text{C-NMR}$ (400 MHz, DMSO- d_6): 200.56, 165.29, 154.62, 152.47, 149.57, 141.12, 139.79, 136.90, 125.43, 123.38, 122.14, 77.50, 68.50, 63.50, 57.54, 55.30, 54.51, 51.01, 47.89, 42.08, 30.75, 29.22, 29.01, 26.49, 23.94, 20.47, 19.86, 15.10, 13.00, 11.23.

[0264] Synthesis of Compound 14

[0265] Step-1: Synthesis of (4*S*, 4*aR*, 5*aR*, 6*aS*, 6*bS*, 9*R*, 9*aS*, 11*aS*, 11*bR*)-4-hydroxy-9-((*S*)-1-((*R*)-5-(hydroxymethyl)-4-methyl-6-oxo-3, 6-dihydro-2H-pyran-2-yl)ethyl)-9*a*, 11*b*-dimethyl-2-(pyridazin-4-yl)-5*a*, 6, 6*a*, 6*b*, 7, 8, 9, 9*a*, 10, 11, 11*a*, 11*b*-dodecahydrocyclopenta [1, 2] phenanthro [8*a*, 9-*b*] oxiren-1(4*H*)-one:

To a stirred solution of (1*S*, 2*R*, 6*S*, 7*R*, 9*R*, 11*S*, 12*S*, 16*S*)-6-hydroxy-15-[(1*S*)-1-[(2*R*)-5-(hydroxymethyl)-4-methyl-6-oxo-3, 6-dihydro-2H-pyran-2-yl]ethyl]-4-iodo-2, 16-dimethyl-8-oxapentacyclo [9.7.0.0^{2,7}.0^{7,9}.0^{12,16}] octadec-4-en-3-one (1 g, 1 eq; 1.68 mmol) in *N, N'*-dimethylformamide (10 mL, 129 mmol) were added 4-(tributylstannyl) pyridazine (743 mg, 1.2 eq., 2.01 mmol) and diiodocopper (79.8 mg, 0.15 eq., 251 μ mol). The reaction mixture was purged with nitrogen gas for 35 minutes and then 1,1'-Bis (diphenylphosphino) ferrocene] palladium (II) Dichloride dichloromethane adduct (68.4 mg, 0.05 eq., 83.8 μ mol) was added to it . The reaction mixture was again purged with nitrogen gas for 5 minutes. The reaction vessel was sealed and stirred at 60°C for 16 hours. After completion of reaction (monitored by LCMS), it was quenched by adding sodium chloride solution (30 mL) followed by extraction with ethyl acetate (3 x 20 mL). Collected organics, dried over sodium sulfate and concentrated under reduced pressure to obtain crude. Crude was purified by preparative HPLC (ABC method) to get (1*S*, 2*R*, 6*S*, 7*R*, 9*R*, 11*S*, 12*S*, 16*S*)-6-hydroxy-15-[(1*S*)-1-[(2*R*)-5-(hydroxymethyl)-4-methyl-6-oxo-3, 6-dihydro-2H-pyran-2-yl]ethyl]-2, 16-dimethyl-4-(pyridazin-4-yl)-8-oxapentacyclo [9.7.0.0^{2,7}.0^{7,9}.0^{12,16}] octadec-4-en-3-one (75 mg, 2%) as a white solid.

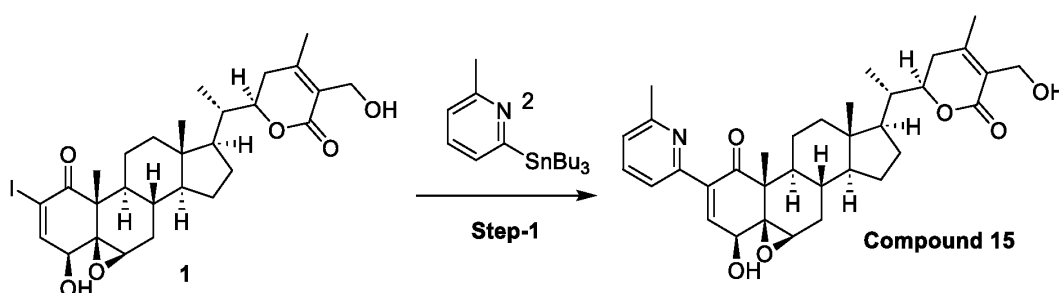
[0266] Analytical data:

LCMS: 95.11% (*m/z*: 549.40, [*M*+1]⁺, 571.40, [*M*+23]⁺, 5.45 min (10 min run).

¹H-NMR (400 MHz, DMSO-*d*₆): δ 9.26 (dd, *J* = 1.20, 5.60 Hz, 1H), 9.23 (dd, *J* = 1.20, 2.40 Hz, 1H), 7.78 (d, *J* = 6.80 Hz, 1H), 7.65 (dd, *J* = 2.40, 5.60 Hz, 1H), 5.93 (d, *J* = 4.00 Hz, 1H),

4.59 (t, $J = 5.60$ Hz, 1H), 4.31-4.26 (m, 1H), 4.18-4.07 (m, 2H), 3.76 (dd, $J = 3.60, 6.60$ Hz, 1H), 3.20 (s, 1H), 2.42-2.32 (m, 1H), 2.11-2.02 (m, 2H), 1.99 (s, 3H), 1.89-1.92 (m, 1H), 1.83-1.71 (m, 2H), 1.57-1.53 (m, 1H), 1.39-1.25 (m, 8H), 1.16-0.96 (m, 4H), 0.87-0.89 (m, 4H), 0.66 (s, 3H).

[0267] Synthesis of Compound 15



[0268] Step-1: Synthesis of (4*S*, 4*aR*, 5*aR*, 6*aS*, 6*bS*, 9*R*, 9*aS*, 11*aS*, 11*bR*)-4-hydroxy-9-((*S*)-1-((*R*)-5-(hydroxymethyl)-4-methyl-6-oxo-3, 6-dihydro-2H-pyran-2-yl)ethyl)-9*a*, 11*b*-dimethyl-2-(6-methylpyridin-2-yl)-5*a*, 6, 6*a*, 6*b*, 7, 8, 9, 9*a*, 10, 11, 11*a*, 11*b*-dodecahydrocyclopenta [1, 2] phenanthro [8*a*, 9-*b*] oxiren-1(4*H*)-one:

To a stirred solution of (1*S*, 2*R*, 6*S*, 7*R*, 9*R*, 11*S*, 12*S*, 16*S*)-6-hydroxy-15-[(1*S*)-1-[(2*R*)-5-(hydroxymethyl)-4-methyl-6-oxo-3, 6-dihydro-2H-pyran-2-yl]ethyl]-4-iodo-2, 16-dimethyl-8-oxapentacyclo [9.7.0.0^{2,7}.0^{7,9}.0^{12,16}] octadec-4-en-3-one (0.5 g, 1 eq; 838 μ mol) *N,N'*-dimethylformamide (2.62 mL) was added 2-methyl-6-(tributylstannyl) pyridine (961 mg, 3 eq., 2.51 mmol) and diiodocopper (39.9 mg, 0.15 eq., 126 μ mol). The reaction mixture was purged with nitrogen for 35 minutes and then 1,1'-Bis (diphenylphosphino) ferrocene]palladium(II) Dichloride dichloromethane Adduct (34.2 mg, 0.05 eq., 41.9 μ mol) was added to it. The reaction mixture was again purged with nitrogen for 5 minutes. The reaction vessel was sealed and stirred at 60°C for 16 hours. After completion of the reaction (monitored by LCMS), it was quenched with sodium chloride solution (30 mL). Further it was extracted using ethyl acetate (2 x 40 mL). Collected organics, dried over by sodium sulfate and then concentrated under reduced pressure to obtain crude. Crude was purified by preparative HPLC (ABC method) to obtain (4*S*, 4*aR*, 5*aR*, 6*aS*, 6*bS*, 9*R*, 9*aS*, 11*aS*, 11*bR*)-4-hydroxy-9-

((S)-1-((R)-5-(hydroxymethyl)-4-methyl-6-oxo-3, 6-dihydro-2H-pyran-2-yl)ethyl)-9a, 11b-dimethyl-2-(6-methylpyridin-2-yl)-5a, 6, 6a, 6b, 7, 8, 9, 9a, 10, 11, 11a, 11b-dodecahydrocyclopenta [1, 2] phenanthro [8a, 9-b] oxiren-1(4H)-one (89 mg, 19%) as a white solid.

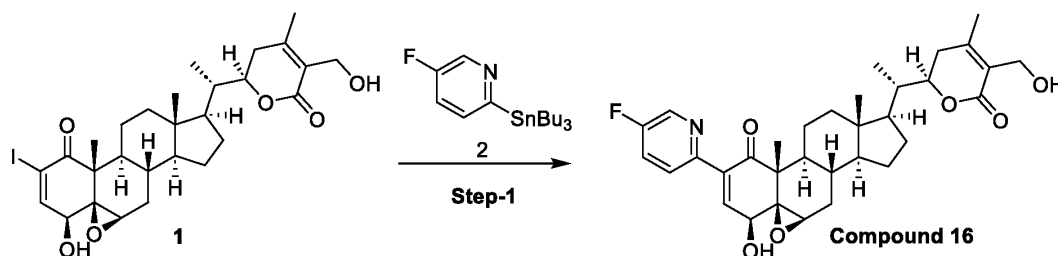
[0269] Analytical data:

LCMS: 98.56% (m/z: 562.6, [M+1]⁺, 560.6, [M-1]⁺, 5.21 min (10 min run).

¹H-NMR (400 MHz, DMSO-*d*₆): δ 7.71 (t, *J* = 8.00 Hz, 1H), 7.64 (d, *J* = 6.80 Hz, 1H), 7.21 (t, *J* = 8.40 Hz, 2H), 5.71 (d, *J* = 3.60 Hz, 1H), 4.59 (t, *J* = 5.20 Hz, 1H), 4.31-4.26 (m, 1H), 3.75 (dd, *J* = 3.60, 6.80 Hz, 1H), 3.15 (s, 1H), 2.47 (s, 3H), 2.44-2.31 (m, 1H), 2.11-2.02 (m, 2H), 1.99 (s, 3H), 1.90-1.93 (m, 1H), 1.83-1.67 (m, 2H), 1.57-1.33 (m, 4H), 1.30-1.21 (m, 6H), 1.15-1.04 (m, 4H), 0.97-0.84 (m, 5H), 0.66 (s, 3H).

¹³C-NMR (400 MHz, DMSO-*d*₆): 200.72, 165.30, 157.75, 154.65, 151.66, 141.23, 139.19, 137.11, 125.43, 122.73, 119.07, 77.51, 68.52, 63.59, 57.45, 55.34, 54.51, 51.02, 47.91, 42.06, 38.38, 30.80, 29.20, 29.01, 26.50, 24.21, 23.96, 20.49, 19.86, 14.98, 13.03, 11.23.

[0270] Synthesis of Compound 16



[0271] Step-1: Synthesis of (4*S*, 4a*R*, 5a*R*, 6a*S*, 6b*S*, 9*R*, 9a*S*, 11a*S*, 11b*R*)-2-(5-fluoropyridin-2-yl)-4-hydroxy-9-((*S*)-1-((*R*)-5-(hydroxymethyl)-4-methyl-6-oxo-3, 6-dihydro-2H-pyran-2-yl)ethyl)-9a, 11b-dimethyl-5a, 6, 6a, 6b, 7, 8, 9, 9a, 10, 11, 11a, 11b-dodecahydrocyclopenta [1, 2] phenanthro [8a, 9-b] oxiren-1(4H)-one:

To a stirred solution of (1*S*, 2*R*, 6*S*, 7*S*, 9*R*, 11*S*, 12*S*, 16*S*)-15-[(1*S*)-1-[(2*R*)-5-[(tert-butyl)dimethylsilyl]oxy]methyl]-4-methyl-6-oxo-3, 6-dihydro-2H-pyran-2-yl] ethyl]-4-iodo-2, 16-dimethyl-3-oxo-8-oxapentacyclo [9.7.0.0.2^{7,7},9.0^{12,16}] octadec-4-en-6-yl acetate (0.5 g, 1 eq; 664 μ mol) in tetrahydrofuran (6 mL, 73.7 mmol) were added 5-fluoro-2-(tributylstannyl)pyridine (282 mg, 1.1 eq., 731 μ mol), triphenylarsane (20.3 mg, 0.1 eq., 66.4 μ mol) and

diiodocopper (21.1 mg, 0.1 eq., 66.4 μmol). The reaction mixture was purged with nitrogen gas for 35 minutes and then added tris (1,5-diphenylpenta-1,4-dien-3-one) dipalladium (30.4 mg, 0.05 eq., 33.2 μmol). The reaction mixture was again purged with nitrogen gas for 10 minutes. The reaction vessel was sealed and stirred at 85°C for 3 hours. After completion of the reaction (monitored by LCMS), the reaction mixture was quenched with 10% citric acid solution (20 mL). Reaction mass was extracted with ethyl acetate (3 x 45 mL). The collected organics was dried over Na_2SO_4 and concentrated under reduced pressure to obtain crude. The crude was purified by preparative HPLC (ABC method) afforded (4S, 4aR, 5aR, 6aS, 6bS, 9R, 9aS, 11aS, 11bR)-2-(5-fluoropyridin-2-yl)-4-hydroxy-9-((S)-1-((R)-5-(hydroxymethyl)-4-methyl-6-oxo-3,6-dihydro-2H-pyran-2-yl)ethyl)-9a,11b-dimethyl-5a,6,6a,6b,7,8,9,9a,10,11,11a,11b-dodecahydrocyclopenta[1,2]phenanthro[8a,9-b]oxiren-1(4H)-one (100 mg, 27%) as a white solid.

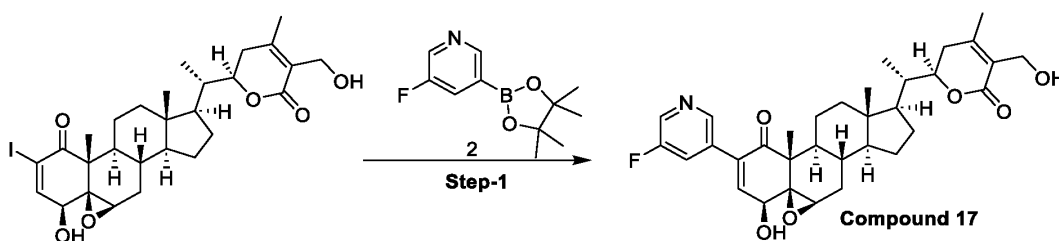
[0272] Analytical data:

LCMS: 99.20% (m/z: 566.6, $[\text{M}+1]^+$, 5.63 min (10 min run).

$^1\text{H-NMR}$ (400 MHz, $\text{DMSO}-d_6$): δ 8.61 (d, $J = 2.80$ Hz, 1H), 7.77 (dt, $J = 2.80, 12.67$ Hz, 1H), 7.64 (d, $J = 6.40$ Hz, 1H), 7.47 (dd, $J = 4.80, 8.80$ Hz, 1H), 5.76 (d, $J = 3.60$ Hz, 1H), 4.59 (t, $J = 5.60$ Hz, 1H), 4.27-4.30 (m, 1H), 4.18-4.08 (m, 2H), 3.75 (dd, $J = 3.60, 6.60$ Hz, 1H), 3.16 (s, 1H), 2.50-2.33 (m, 1H), 2.11-2.02 (m, 2H), 1.99 (s, 3H), 1.93-1.52 (m, 5H), 1.45-1.22 (m, 7H), 1.15-1.04 (m, 3H), 0.98-0.82 (m, 5H), 0.66 (s, 3H).

$^{13}\text{C-NMR}$ (400 MHz, $\text{DMSO}-d_6$): 200.47, 165.29, 165.29, 157.33, 154.63, 149.05, 140.04, 137.94, 137.70, 125.43, 123.55, 77.50, 68.43, 63.43, 57.57, 55.28, 54.51, 51.03, 47.89, 42.11, 41.98, 30.72, 29.24, 29.01, 26.49, 23.94, 20.46, 19.87, 15.14, 13.59, 13.01, 11.23.

[0273] Synthesis of Compound 17



[0274] Step-1: (R)-6-[(S)-1-{(1S, 2R, 6S, 7R, 9R, 11S, 12S, 15R, 16S)-4-(5-fluoro-3-pyridyl)-6-hydroxy-2, 16-dimethyl-3-oxo-8-oxapentacyclo [9.7.0.0^{2,7},⁹.0^{12,16}] octadec-4-en-15-yl}ethyl]-3-(hydroxymethyl)-4-methyl-5,6-dihydro-2H-pyran-2-one

To a stirred solution of (R)-6-[(S)-1-{(1S, 2R, 6S, 7R, 9R, 11S, 12S, 15R, 16S)-6-hydroxy-4-iodo-2, 16-dimethyl-3-oxo-8-oxapentacyclo [9.7.0.0^{2,7},⁹.0^{12,16}] octadec-4-en-15-yl}ethyl]-3-(hydroxymethyl)-4-methyl-5, 6-dihydro-2H-pyran-2-one (4 g, 6.71 mmol) in 1,4-dioxane (40 mL) were added 2-(5-fluoro-3-pyridyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (2.24 g, 1.5 eq., 10.1 mmol) and dicaesium(1+) carbonate (6.55 g, 3 eq., 20.1 mmol) dissolved in water (8 mL) at room temperature. The reaction mixture was purged with N₂ for 30 min then added palladium (2+) bis (triphenylphosphane) dichloride (471 mg, 0.1 eq., 671 μ mol) followed by further purging with N₂ for 5 min. The reaction vessel was sealed and stirred at 90°C for 4 hours. After completion of the reaction (monitored by LCMS), mixture was filtered through celite bed and washed with DCM (50 mL). Diluted the filtrate by water (50 mL) and extracted with DCM (2 x 70 mL). Collected organics, dried over Na₂SO₄, filtered and concentrated under reduced pressure to afford crude. The crude was purified by Prep-HPLC (ABC method) (R)-6-[(S)-1-{(1S, 2R, 6S, 7R, 9R, 11S, 12S, 15R, 16S)-4-(5-fluoro-3-pyridyl)-6-hydroxy-2, 16-dimethyl-3-oxo-8-oxapentacyclo [9.7.0.0^{2,7},⁹.0^{12,16}] octadec-4-en-15-yl}ethyl]-3-(hydroxymethyl)-4-methyl-5, 6-dihydro-2H-pyran-2-one (1 g, 25.8%) as a white solid.

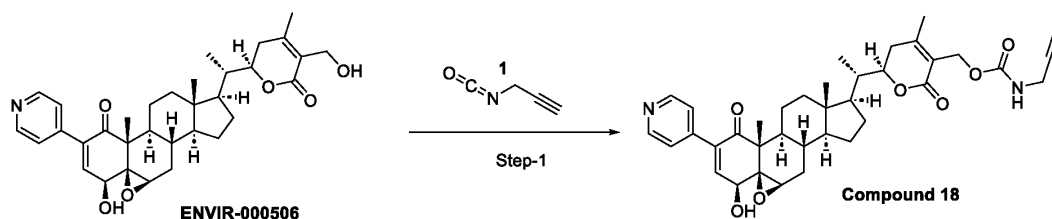
[0275] Analytical data:

LCMS: 98.01% (m/z: 566.4, [M+1]⁺, 5.44 min (10 min run).

¹H-NMR (400 MHz, DMSO-*d*₆): δ 8.59 (d, J = 2.40 Hz, 1H), 8.38 (s, 1H), 7.70-7.74 (m, 1H), 7.55 (d, J = 6.80 Hz, 1H), 5.84 (d, J = 3.60 Hz, 1H), 4.59 (t, J = 5.60 Hz, 1H), 4.26-4.30 (m, 1H), 4.07-4.18 (m, 2H), 3.72-3.75 (m, 1H), 3.20 (s, 1H), 2.34-2.42 (m, 1H), 2.03-2.07 (m, 2H), 1.99 (s, 3H), 1.56-1.92 (m, 4H), 1.25-1.38 (m, 8H), 0.87-1.15 (m, 8H), 0.66 (s, 3H).

¹⁹F-NMR (400 MHz, DMSO-*d*₆): δ -127.08

¹³C-NMR (400 MHz, DMSO-*d*₆): δ 200.47, 165.32, 160.11, 157.58, 154.66, 144.43, 144.40, 141.21, 137.45, 137.22, 132.86, 132.82, 125.44, 121.61, 121.42, 77.51, 68.41, 63.19, 57.80, 55.15, 54.51, 51.06, 47.76, 42.20, 41.99, 30.62, 29.33, 29.03, 26.51, 23.96, 20.50, 19.90, 15.49, 13.04, 11.25.

[0276] Synthesis of Compound 18

[0277] Step-1: Synthesis of ((R)-6-((S)-1-((4S, 4aR, 5aR, 6aS, 6bS, 9R, 9aS, 11aS, 11bR)-4-hydroxy-9a, 11b-dimethyl-1-oxo-2-(pyridin-4-yl)-1, 4, 5a, 6, 6a, 6b, 7, 8, 9, 9a, 10, 11, 11a, 11b-tetradecahydrocyclopenta [1, 2] phenanthro [8a, 9-b] oxiren-9-yl) ethyl)-4-methyl-2-oxo-5, 6-dihydro-2H-pyran-3-yl) methyl prop-2-yn-1-ylcarbamate:

To a stirred solution of (1S, 2R, 6S, 7R, 9R, 11S, 12S, 15R, 16S)-6-hydroxy-15-[(1S)-1-[(2R)-5-(hydroxymethyl)-4-methyl-6-oxo-3, 6-dihydro-2H-pyran-2-yl]ethyl]-2, 16-dimethyl-4-(pyridin-4-yl)-8-oxapentacyclo [9.7.0.0^{2,7}.0^{7,9}.0^{12,16}] octadec-4-en-3-one (0.2 g, 1 eq; 365 μ mol) in dichloromethane (2 mL) were added 3-isocyanatoprop-1-yne (35 mg, 1.2 eq., 438 μ mol) and triethylamine (102 μ L, 2 eq., 730 μ mol) drop wisely at 0°C. Resultant reaction mixture was allowed to stir at room temperature for 45 minutes. After completion of the reaction (monitored by TLC: 5% methanol in dichloromethane), the reaction mass was diluted with water (30 mL) and then extracted with dichloromethane (2 x 40 mL). Collected organics, dried over sodium sulphate and concentrated reduced pressure to get crude. Crude was purified by preparative HPLC (ABC method) afforded ((R)-6-((S)-1-((4S, 4aR, 5aR, 6aS, 6bS, 9R, 9aS, 11aS, 11bR)-4-hydroxy-9a, 11b-dimethyl-1-oxo-2-(pyridin-4-yl)-1, 4, 5a, 6, 6a, 6b, 7, 8, 9, 9a, 10, 11, 11a, 11b-tetradecahydrocyclopenta [1,2] phenanthro [8a, 9-b] oxiren-9-yl)ethyl)-4-methyl-2-oxo-5, 6-dihydro-2H-pyran-3-yl)methyl prop-2-yn-1-ylcarbamate (3 mg, 1.3%) as a white solid.

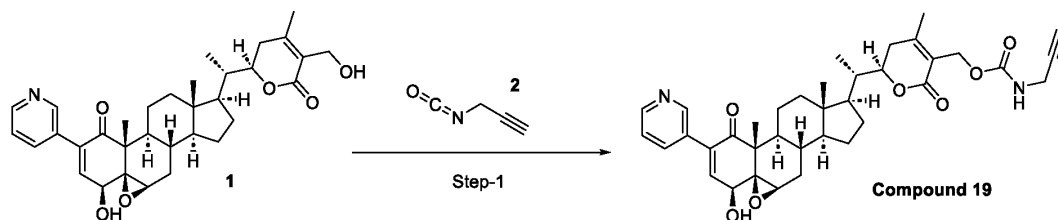
[0278] Analytical data:

LCMS: 97.07% (m/z: 629.15, [M+1]⁺, 2.35 min (6 min run).

¹H-NMR (400 MHz, DMSO-*d*₆): δ 8.60 (d, *J* = 5.60 Hz, 2H), 7.53-7.55 (m, 2H), 7.32 (d, *J* = 6.00 Hz, 2H), 5.80 (d, *J* = 3.60 Hz, 1H), 4.72-4.71 (m, 2H), 4.29-4.32 (m, 1H), 3.75-3.73 (m,

3H), 3.18 (s, 1H), 3.07 (s, 1H), 2.33-2.41 (m, 1H), 2.16-2.20 (m, 1H), 2.03-2.06 (m, 4H), 1.74 (s, 4H), 1.45-1.20 (m, 7H), 1.19-1.00 (m, 4H), 0.99-0.80 (m, 5H), 0.67 (s, 3H).

[0279] Synthesis of Compound 19



[0280] Step-1: Synthesis of ((R)-6-((S)-1-((4S, 4aR, 5aR, 6aS, 6bS, 9R, 9aS, 11aS, 11bR)-4-hydroxy-9a, 11b-dimethyl-1-oxo-2-(pyridin-3-yl)-1, 4, 5a, 6, 6a, 6b, 7, 8, 9, 9a, 10, 11, 11a, 11b-tetradecahydrocyclopenta [1, 2] phenanthro [8a, 9-b] oxiren-9-yl)ethyl)-4-methyl-2-oxo-5, 6-dihydro-2H-pyran-3-yl)methyl prop-2-yn-1-ylcarbamate:

To a stirred solution of (1S, 2R, 6S, 7R, 9R, 11S, 12S, 15R, 16S)-6-hydroxy-15-[(1S)-1-[(2R)-5-(hydroxymethyl)-4-methyl-6-oxo-3, 6-dihydro-2H-pyran-2-yl]ethyl]-2, 16-dimethyl-4-(pyridin-3-yl)-8-oxapentacyclo [9.7.0.0^{2,7}.0^{7,9}.0^{12,16}] octadec-4-en-3-one (56.6 mg, 1 eq; 103 μmol) in dichloromethane (10 mL) were added triethylamine (41.8 mg, 4 eq., 413 μmol) and 4-nitrophenyl N-(prop-2-yn-1-yl)carbamate (45.5 mg, 2 eq., 207 μmol) at 0°C under nitrogen atmosphere. The resulting mixture was stirred at room temperature for 2 hours. After completion of the reaction (monitored by TLC: 60% ethyl acetate in n-hexane), reaction mixture was diluted with water (30 mL) and then extracted with ethyl acetate (2 x 30 mL). Collected organics, dried over sodium sulphate and concentrated under reduced pressure to obtain crude. The crude was purified by preparative-HPLC (ABC method) afforded ((R)-6-((S)-1-((4S, 4aR, 5aR, 6aS, 6bS, 9R, 9aS, 11aS, 11bR)-4-hydroxy-9a, 11b-dimethyl-1-oxo-2-(pyridin-3-yl)-1, 4, 5a, 6, 6a, 6b, 7, 8, 9, 9a, 10, 11, 11a, 11b-tetradecahydrocyclopenta [1, 2] phenanthro [8a, 9-b] oxiren-9-yl)ethyl)-4-methyl-2-oxo-5, 6-dihydro-2H-pyran-3-yl)methyl prop-2-yn-1-ylcarbamate (21 mg, 32%) as a white solid.

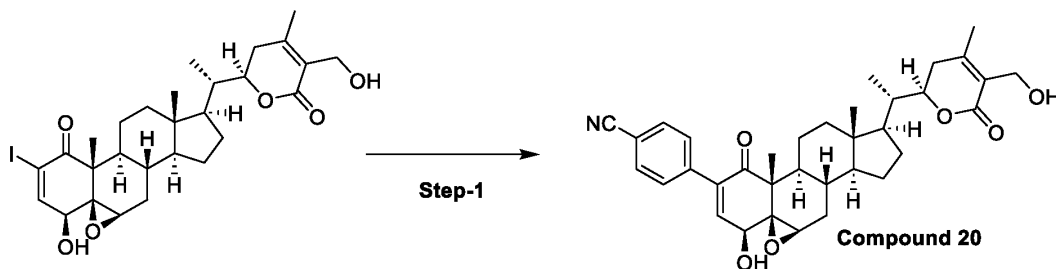
[0281] Analytical data:

LCMS: 99.44% (m/z: 629.30, [M+1]⁺, 2.35 min (6 min run).

¹H-NMR (400 MHz, DMSO-*d*₆): δ 8.56-8.54 (m, 1H), 8.50 (d, *J* = 1.60 Hz, 1H), 7.71 (d, *J* = 8.00 Hz, 1H), 7.60-7.56 (m, 1H), 7.46-7.43 (m, 2H), 5.77 (d, *J* = 3.60 Hz, 1H), 4.74-4.68 (m,

2H), 4.29-4.32 (m, 1H), 3.75-3.71 (m, 2H), 3.19 (s, 1H), 3.08 (s, 1H), 2.33-2.50 (m, 2H), 2.16-2.20 (m, 1H), 2.03-2.07 (m, 4H), 1.93-1.56 (m, 4H), 1.39-1.25 (m, 8H), 1.15-0.80 (m, 8H), 0.65 (s, 3H).

[0282] Synthesis of Compound 20



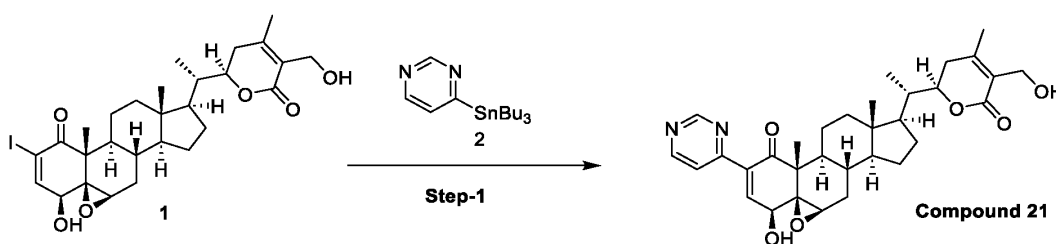
[0283] Step-1: Synthesis of 4-((4*S*, 4*aR*, 5*aR*, 6*aS*, 6*bS*, 9*R*, 9*aS*, 11*aS*, 11*bR*)-4-hydroxy-9-((*S*)-1-((*R*)-5-(hydroxymethyl)-4-methyl-6-oxo-3, 6-dihydro-2H-pyran-2-yl)ethyl)-9*a*, 11*b*-dimethyl-1-oxo-1, 4, 5*a*, 6, 6*a*, 6*b*, 7, 8, 9, 9*a*, 10, 11, 11*a*, 11*b*-tetradecahydrocyclopenta [1, 2] phenanthro [8*a*, 9-*b*] oxiren-2-yl)benzonitrile:

To a stirred solution of (4*S*, 4*aR*, 5*aR*, 6*aS*, 6*bS*, 9*R*, 9*aS*, 11*aS*, 11*bR*)-4-hydroxy-9-((*S*)-1-((*R*)-5-(hydroxymethyl)-4-methyl-6-oxo-3, 6-dihydro-2H-pyran-2-yl)ethyl)-2-iodo-9*a*, 11*b*-dimethyl-5*a*, 6, 6*a*, 6*b*, 7, 8, 9, 9*a*, 10, 11, 11*a*, 11*b*-dodecahydrocyclopenta [1, 2] phenanthro [8*a*, 9-*b*] oxiren-1(4H)-one (0.6 g, 1 eq; 1.01 mmol) in 1,4-dioxane (10 mL) were added 4-(4, 4, 5, 5-tetramethyl-1, 3, 2-dioxaborolan-2-yl) benzonitrile (346 mg, 1.5 eq., 1.51 mmol) and dicaesium (1+) carbonate (983 mg, 3 eq., 3.02 mmol). The reaction mixture was purged with N₂ gas for 35 minutes and then palladium (II) bis (triphenylphosphane) dichloride (70.6 mg, 0.1 eq., 101 μmol) was added to it. The reaction mixture was again purged with N₂ gas for 5 minutes. The reaction vessel was sealed and stirred at 80°C for 16 hours. After completion of the reaction (monitored by LCMS), reaction mixture was passed through celite. Collected filtrate, diluted by addition of water (30 mL) and then extracted with ethyl acetate (3 x 55 mL). Collected organics, dried over sodium sulphate and then concentrated under reduced pressure to obtain crude. The crude residue was purified by preparative HPLC (method: Ammonium Acetate) to afford 4-((4*S*, 4*aR*, 5*aR*, 6*aS*, 6*bS*, 9*R*, 9*aS*, 11*aS*, 11*bR*)-4-hydroxy-9-((*S*)-1-((*R*)-5-(hydroxymethyl)-4-methyl-6-oxo-3, 6-dihydro-2H-pyran-2-yl)ethyl)-9*a*, 11*b*-dimethyl-1-oxo-1, 4, 5*a*, 6, 6*a*, 6*b*, 7, 8, 9, 9*a*, 10, 11, 11*a*, 11*b*-tetradecahydrocyclopenta [1, 2] phenanthro [8*a*, 9-*b*] oxiren-2-yl)benzonitrile (29 mg, 5%) as a white solid.

[0284] Analytical data:

LCMS: 99.58% (m/z: 572.50, $[M+1]^+$, 5.63 min (10 min run).

¹H-NMR (400 MHz, DMSO-*d*₆, D₂O): δ 7.88 (d, J = 8.40 Hz, 2H), 7.49 (dd, J = 6.80, 10.00 Hz, 3H), 5.80 (d, J = 3.60 Hz, 1H), 4.58 (t, J = 5.20 Hz, 1H), 4.30-4.26 (m, 1H), 4.18-4.08 (m, 2H), 3.73 (dd, J = 3.60, 6.80 Hz, 1H), 3.18 (s, 1H), 2.39-2.43 (m, 1H), 2.12-2.06 (m, 2H), 2.00 (s, 3H), 1.95-1.50 (m, 4H), 1.45-1.20 (m, 8H), 1.14-1.00 (m, 3H), 0.99-0.80 (m, 5H), 0.67 (s, 3H).

[0285] Synthesis of Compound 21

[0286] Step-1: Synthesis of (4*S*, 4*aR*, 5*aR*, 6*aS*, 6*bS*, 9*R*, 9*aS*, 11*aS*, 11*bR*)-4-hydroxy-9-((*S*)-1-((*R*)-5-(hydroxymethyl)-4-methyl-6-oxo-3, 6-dihydro-2H-pyran-2-yl)ethyl)-9*a*, 11*b*-dimethyl-2-(pyrimidin-4-yl)-5*a*, 6*a*, 6*b*, 7, 8, 9, 9*a*, 10, 11, 11*a*, 11*b*-dodecahydrocyclopenta [1, 2] phenanthro [8*a*, 9-*b*] oxiren-1(4*H*)-one:

To a stirred solution of (1*S*, 2*R*, 6*S*, 7*R*, 9*R*, 11*S*, 12*S*, 16*S*)-6-hydroxy-15-[(1*S*)-1-[(2*R*)-5-(hydroxymethyl)-4-methyl-6-oxo-3, 6-dihydro-2H-pyran-2-yl]ethyl]-4-iodo-2, 16-dimethyl-8-oxapentacyclo [9.7.0.0^{2,7}.0^{7,9}.0^{12,16}] octadec-4-en-3-one (0.5 g, 1 eq; 838 μ mol) in tetrahydrofuran (5 mL, 61.4 mmol) were added 4-(tributylstannyl) pyrimidine (340 mg, 1.1 eq., 922 μ mol) and λ^1 -copper (1+) iodide (47.9 mg, 0.3 eq., 251 μ mol). The reaction mixture was degassed using nitrogen gas for 30 minutes. After that, tris ((1*E*,4*E*)-1,5-diphenylpenta-1,4-dien-3-one) dipalladium (38.4 mg, 0.05 eq., 41.9 μ mol) was added. The reaction mixture was degassed using nitrogen for 5 minutes and reaction was refluxed at 90°C for 16 hours. After the reaction was completed (monitored by TLC and LCMS), the reaction mixture was filtered through celite bed, filtrate was evaporated under vacuum to obtain crude. Crude was purified by Prep. HPLC (ABC method) afforded (1*S*, 2*R*, 6*S*, 7*R*, 9*R*, 11*S*, 12*S*, 15*R*, 16*S*)-6-hydroxy-15-[(1*S*)-1-[(2*R*)-5-(hydroxymethyl)-4-methyl-6-oxo-3, 6-dihydro-2H-pyran-2-

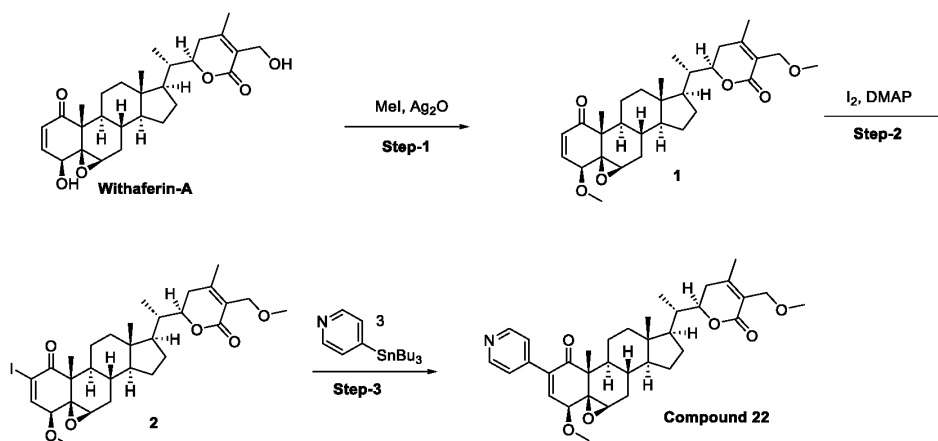
yl]ethyl]-2, 16-dimethyl-4-(pyrimidin-4-yl)-8-oxapentacyclo [9.7.0.0^{2,7}.0^{7,9}.0^{12,16}]octadec-4-en-3-one (68 mg, 26%) as a white solid.

[0287] Analytical data:

LCMS: 89.13% (m/z: 549.60, [M+1]⁺, 4.98 min (10 min run).

¹H-NMR (400 MHz, DMSO-*d*₆): δ 9.21 (s, 1H), 8.85 (d, *J* = 5.20 Hz, 1H), 7.95 (d, *J* = 6.80 Hz, 1H), 7.52 (dd, *J* = 1.20, 5.40 Hz, 1H), 5.90 (d, *J* = 3.60 Hz, 1H), 4.59 (t, *J* = 5.20 Hz, 1H), 4.31-4.22 (m, 1H), 4.18-4.07 (m, 2H), 3.80 (dd, *J* = 3.60, 6.80 Hz, 1H), 3.18 (s, 1H), 2.42-2.33 (m, 1H), 2.11-1.92 (m, 6H), 1.95-1.70 (m, 3H), 1.62-1.50 (m, 1H), 1.43-1.22 (m, 9H), 1.20-1.00 (m, 6H), 0.66 (s, 3H).

[0288] Synthesis of Compound 22



[0289] Step-1: Synthesis of (4*S*, 4*aS*, 5*aR*, 6*aS*, 6*bS*, 9*R*, 9*aS*, 11*aS*, 11*bR*)-2-iodo-4-methoxy-9-((*S*)-1-((*R*)-5-(methoxymethyl)-4-methyl-6-oxo-3, 6-dihydro-2H-pyran-2-yl)ethyl)-9*a*, 11*b*-dimethyl-5*a*, 6, 6*a*, 6*b*, 7, 8, 9, 9*a*, 10, 11, 11*a*, 11*b*-dodecahydrocyclopenta [1, 2] phenanthro [8*a*, 9-*b*]oxiren-1(4*H*)-one:

To a stirred solution of (1*S*, 2*R*, 6*S*, 7*R*, 9*R*, 11*S*, 12*S*, 16*S*)-6-hydroxy-15-[(1*S*)-1-[(2*R*)-5-(hydroxymethyl)-4-methyl-6-oxo-3, 6-dihydro-2H-pyran-2-yl]ethyl]-2, 16-dimethyl-8-oxapentacyclo [9.7.0.0^{2,7}.0^{7,9}.0^{12,16}] octadec-4-en-3-one (2 g, 4.25 mmol) in dichloromethane (20 mL, 312 mmol) was added silver oxide (3.97 g, 4 eq., 17 mmol) under inert atmosphere. Then iodomethane (9.05 g, 15 eq., 63.7 mmol) was added to it and reaction continued stirring at room temperature for 4 days. After completion of the reaction (monitored by LCMS), the reaction mixture was filtered through celite bed and filtrate was extracted with dichloromethane

(3 x 30 mL). Collected organics, dried over sodium sulphate and concentrated under reduced pressure to obtain crude. Crude was purified by combi-flash chromatography using (70% ethyl acetate in n-hexane) afforded (1S, 2R, 6S, 7S, 9R, 11S, 12S, 16S)-6-methoxy-15-[(1S)-1-[(2R)-5-(methoxymethyl)-4-methyl-6-oxo-3, 6-dihydro-2H-pyran-2-yl]ethyl]-2, 16-dimethyl-8-oxapentacyclo [9.7.0.0^{2,7}.0^{7,9}.0^{12,16}] octadec-4-en-3-one (1.2 g, 57%) as a white solid.

[0290] Analytical data:

LCMS: 95.60% (m/z: 499.19, [M+1]⁺, 2.55 min (4 min run).

[0291] Step-2: Synthesis of (4S, 4aS, 5aR, 6aS, 6bS, 9R, 9aS, 11aS, 11bR)-4-methoxy-9-((S)-1-((R)-5-(methoxymethyl)-4-methyl-6-oxo-3, 6-dihydro-2H-pyran-2-yl)ethyl)-9a, 11b-dimethyl-2-(pyridin-4-yl)-5a, 6, 6a, 6b, 7, 8, 9, 9a, 10, 11, 11a, 11b-dodecahydrocyclopenta [1, 2] phenanthro [8a, 9-b] oxiren-1(4H)-one:

To a stirred solution of (1S, 2R, 6S, 7S, 9R, 11S, 12S, 16S)-6-methoxy-15-[(1S)-1-[(2R)-5-(methoxymethyl)-4-methyl-6-oxo-3, 6-dihydro-2H-pyran-2-yl]ethyl]-2, 16-dimethyl-8-oxapentacyclo [9.7.0.0^{2,7}.0^{7,9}.0^{12,16}] octadec-4-en-3-one (0.4 g, 802 µmol) in dichloromethane (5 mL) were added N, N-dimethylpyridin-4-amine (294 mg, 3 eq., 2.41 mmol), iodine (285 mg, 2.8 eq., 2.25 mmol) and reaction stirred at room temperature for 2 hours. After completion of reaction (monitored by TLC and by LCMS), quenched by adding sodium thiosulfate solution (20 mL) and then extracted using dichloromethane (2 x 35 mL). Collected organics, dried over sodium sulphate and then concentrated under reduced pressure to obtain crude. Crude was purified by combi-flash chromatography (5% methanol and dichloromethane) to yield (1S, 2R, 6S, 7S, 9R, 11S, 12S, 16S)-4-iodo-6-methoxy-15-[(1S)-1-[(2R)-5-(methoxymethyl)-4-methyl-6-oxo-3, 6-dihydro-2H-pyran-2-yl]ethyl]-2, 16-dimethyl-8-oxapentacyclo [9.7.0.0^{2,7}.0^{7,9}.0^{12,16}] octadec-4-en-3-one. (340 mg, 68%) as a white solid.

[0292] Analytical data:

LCMS: 72.21% (m/z: 625.09, [M+1]⁺, 2.71 min (4 min run).

[0293] Step-3: Synthesis of (4S, 4aS, 5aR, 6aS, 6bS, 9R, 9aS, 11aS, 11bR)-2-iodo-4-methoxy-9-((S)-1-((R)-5-(methoxymethyl)-4-methyl-6-oxo-3,6-dihydro-2H-pyran-2-yl)ethyl)-9a, 11b-dimethyl-5a, 6, 6a, 6b, 7, 8, 9, 9a, 10, 11, 11a, 11b-dodecahydrocyclopenta [1, 2] phenanthro [8a, 9-b]oxiren-1(4H)-one:

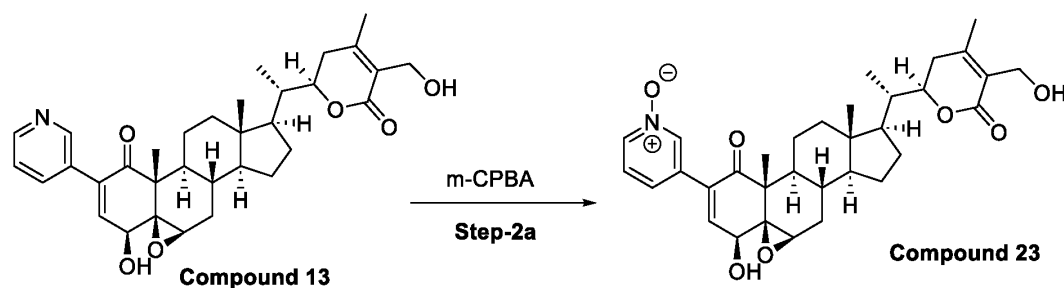
To a stirred solution of (1S, 2R, 6S, 7S, 9R, 11S, 12S, 16S)-4-iodo-6-methoxy-15-[(1S)-1-[(2R)-5-(methoxymethyl)-4-methyl-6-oxo-3, 6-dihydro-2H-pyran-2-yl]ethyl]-2, 16-dimethyl-8-oxapentacyclo [9.7.0.0^{2,7}.0^{7,9}.0^{12,16}] octadec-4-en-3-one (337 mg, 1 eq; 540 μ mol) in N,N-dimethylformamide (3.37 mL) were added 4-(tributylstannyl)pyridine (397 mg, 2 eq., 1.08 mmol) and diiodocopper (25.7 mg, 0.15 eq., 80.9 μ mol). The resultant reaction mixture was purged with nitrogen gas for 35 minutes and then 1,1'-Bis (diphenylphosphino) ferrocene] palladium(II) dichloride dichloromethane adduct (22 mg, 0.05 eq., 27 μ mol) was added to it. The reaction mixture was again purged with nitrogen gas for 5 minutes. The reaction vessel was sealed and stirred at 60°C for 16 hours. After completion of the reaction (monitored by TLC and LCMS), it was quenched by adding ice cold water (30 mL) and brine solution (30 mL). It was then extracted using ethyl acetate (3 x 35 mL). Collected organics, dried over sodium sulphate and concentrated under reduced pressure to obtain crude. Crude product was purified by preparative HPLC (ABC method) afforded (1S, 2R, 6S, 7S, 9R, 11S, 12S, 16S)-6-methoxy-15-[(1S)-1-[(2R)-5-(methoxymethyl)-4-methyl-6-oxo-3, 6-dihydro-2H-pyran-2-yl]ethyl]-2, 16-dimethyl-4-(pyridin-4-yl)-8-oxapentacyclo [9.7.0.0^{2,7}.0^{7,9}.0^{12,16}] octadec-4-en-3-one (22 mg, 7%) as a white solid.

[0294] Analytical data:

LCMS: 95.01% (m/z: 576.60, [M+1]⁺, 6.28 min (10 min run).

¹H-NMR (400 MHz, DMSO-*d*₆): δ 8.62 (d, *J* = 4.00 Hz, 2H), 7.62 (d, *J* = 6.40 Hz, 2H), 7.34 (d, *J* = 6.00 Hz, 2H), 4.32-4.29 (m, 1H), 4.12-4.02 (m, 2H), 3.55 (d, *J* = 6.40 Hz, 1H), 3.34 (s, 3H), 3.20 (s, 3H), 3.18 (s, 1H), 2.43-2.39 (m, 1H), 2.13 (dd, *J* = 3.20, 18.40 Hz, 1H), 2.04-2.07 (m, 1H), 2.00 (s, 3H), 1.90-1.93 (m, 1H), 1.89-1.50 (m, 3H), 1.45-1.20 (m, 8H), 1.15-1.04 (m, 3H), 0.97-1.00 (m, 1H), 0.92 (d, *J* = 6.80 Hz, 3H), 0.87-0.83 (m, 1H), 0.66 (s, 3H).

[0295] Synthesis of Compound 23



[0296] **Step-1: Synthesis of 3-((4*S*, 4*aR*, 5*aR*, 6*aS*, 6*bS*, 9*R*, 9*aS*, 11*aS*, 11*bR*)-4-hydroxy-9-((*S*)-1-((*R*)-5-(hydroxymethyl)-4-methyl-6-oxo-3, 6-dihydro-2H-pyran-2-yl)ethyl)-9*a*, 11*b*-dimethyl-1-oxo-1, 4, 5*a*, 6, 6*a*, 6*b*, 7, 8, 9, 9*a*, 10, 11, 11*a*, 11*b*-tetradecahydrocyclopenta [1, 2] phenanthro [8*a*, 9-*b*] oxiren-2-yl) pyridine 1-oxide:**

To a stirred solution of (1*S*, 2*R*, 6*S*, 7*R*, 9*R*, 11*S*, 12*S*, 15*R*, 16*S*)-6-hydroxy-15-[(1*S*)-1-[(2*R*)-5-(hydroxymethyl)-4-methyl-6-oxo-3, 6-dihydro-2H-pyran-2-yl]ethyl]-2, 16-dimethyl-4-(pyridin-3-yl)-8-oxapentacyclo [9.7.0.0^{2,7}.0^{7,9}.0^{12,16}] octadec-4-en-3-one (0.5 g, 1 eq; 913 μ mol) in dichloromethane (10 mL) was added 3-chlorobenzene-1-carboperoxoic acid (236 mg, 1.5 eq., 1.37 mmol) at -20°C and resultant reaction mixture was stirred for 16 hours at -20°C. After completion of the reaction (reaction was monitored by TLC), excess of solvent was evaporated under reduced pressure to get crude. Obtained crude was purified by prep HPLC (AA method) afforded 3-((4*S*, 4*aR*, 5*aR*, 6*aS*, 6*bS*, 9*R*, 9*aS*, 11*aS*, 11*bR*)-4-hydroxy-9-((*S*)-1-((*R*)-5-(hydroxymethyl)-4-methyl-6-oxo-3, 6-dihydro-2H-pyran-2-yl)ethyl)-9*a*, 11*b*-dimethyl-1-oxo-1, 4, 5*a*, 6, 6*a*, 6*b*, 7, 8, 9, 9*a*, 10, 11, 11*a*, 11*b*-tetradecahydrocyclopenta [1, 2] phenanthro [8*a*, 9-*b*] oxiren-2-yl) pyridine 1-oxide (82 mg, 16%) as an off white solid.

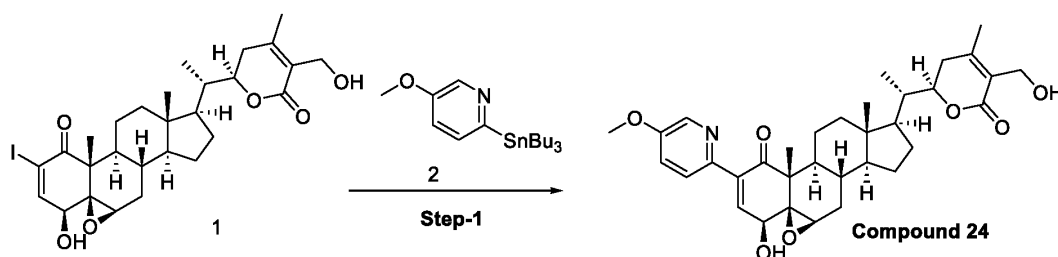
[0297] **Analytical data:**

LCMS: 99.02% (*m/z*: 564.50, [*M*+1]⁺, 4.42 min (10 min run).

¹H-NMR (400 MHz, DMSO-*d*₆): δ 8.22 (d, *J* = 6.40 Hz, 1H), 8.16 (d, *J* = 1.20 Hz, 1H), 7.54 (d, *J* = 6.40 Hz, 1H), 7.46 (t, *J* = 6.80 Hz, 1H), 7.30 (d, *J* = 8.00 Hz, 1H), 5.83 (d, *J* = 3.60 Hz, 1H), 4.59 (t, *J* = 5.20 Hz, 1H), 4.31-4.26 (m, 1H), 4.18-4.08 (m, 2H), 3.71 (dd, *J* = 3.60, 6.60 Hz, 1H), 3.19 (s, 1H), 2.42-2.32 (m, 1H), 2.11-2.02 (m, 2H), 1.99 (s, 3H), 1.91-1.71 (m, 3H), 1.56-1.58 (m, 1H), 1.40-1.20 (m, 8H), 1.15-0.97 (m, 4H), 0.92-0.84 (m, 4H), 0.66 (s, 3H).

¹³C-NMR (400 MHz, DMSO-*d*₆): 200.16, 165.31, 154.66, 141.60, 138.22, 136.99, 136.67, 134.42, 126.44, 125.44, 124.06, 77.51, 68.347, 63.08, 57.75, 55.16, 54.52, 51.083, 47.77, 42.17, 41.99, 38.37, 30.56, 29.33, 29.03, 26.50, 23.95, 20.48, 19.89, 15.43, 13.036, 11.24.

[0298] **Synthesis of Compound 24**



[0299] Step-1: Synthesis of (4*S*, 4*aR*, 5*aR*, 6*aS*, 6*bS*, 9*R*, 9*aS*, 11*aS*, 11*bR*)-4-hydroxy-9-((*S*)-1-((*R*)-5-(hydroxymethyl)-4-methyl-6-oxo-3, 6-dihydro-2*H*-pyran-2-yl)ethyl)-2-(5-methoxypyridin-2-yl)-9*a*, 11*b*-dimethyl-5*a*, 6, 6*a*, 6*b*, 7, 8, 9, 9*a*, 10, 11, 11*a*, 11*b*-dodecahydrocyclopenta [1, 2] phenanthro [8*a*, 9-*b*]oxiren-1(4*H*)-one:

To a stirred solution of (2*R*, 6*S*, 7*R*, 9*R*, 15*R*, 16*S*)-6-hydroxy-15-[(1*S*)-1-[(2*R*)-5-(hydroxymethyl)-4-methyl-6-oxo-3, 6-dihydro-2*H*-pyran-2-yl]ethyl]-4-iodo-2, 16-dimethyl-8-oxapentacyclo [9.7.0.0^{2,7}.0^{7,9}.0^{12,16}] octadec-4-en-3-one (0.8 g, 1 eq; 1.34 mmol) in tetrahydrofuran (15 mL, 184 mmol) was added 5-methoxy-2-(tributylstannyl) pyridine (534 mg, 1.34 mmol), triphenylarsane (41.1 mg, 0.1 eq., 134 μ mol) and diiodocopper (42.6 mg, 0.1 eq., 134 μ mol). The resultant reaction mixture was purged with nitrogen gas for 35 minutes and then added tris(1,5-diphenylpenta-1,4-dien-3-one) dipalladium (12.3 mg, 0.01 eq., 13.4 μ mol). The reaction mixture was again purged with nitrogen gas for 10 minutes. The reaction vessel was sealed and stirred at 85°C for 16 hours. After completion of reaction (monitored by LCMS), it was diluted with water (90 mL) and then it was extracted with dichloromethane (3 x 45 mL). Collected organics, dried over sodium sulphate and concentrated under reduced pressure to afford the crude. Crude was purified by preparative HPLC (ABC method) to afford (4*S*, 4*aR*, 5*aR*, 6*aS*, 6*bS*, 9*R*, 9*aS*, 11*aS*, 11*bR*)-4-hydroxy-9-((*S*)-1-((*R*)-5-(hydroxymethyl)-4-methyl-6-oxo-3, 6-dihydro-2*H*-pyran-2-yl) ethyl)-2-(5-methoxypyridin-2-yl)-9*a*, 11*b*-dimethyl-5*a*, 6, 6*a*, 6*b*, 7, 8, 9, 9*a*, 10, 11, 11*a*, 11*b*-dodecahydrocyclopenta [1, 2] phenanthro [8*a*, 9-*b*] oxiren-1(4*H*)-one (113 mg, 15%) as a white solid.

[0300] Analytical data:

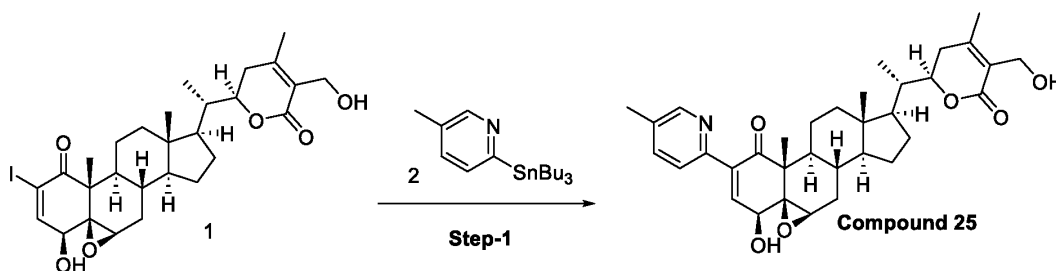
LCMS: 97.28% (m/z: 578.60, [M+1]⁺, 5.32 min (10 min run).

¹H-NMR (400 MHz, DMSO-*d*₆): δ 8.32 (d, *J* = 2.80 Hz, 1H), 7.55 (d, *J* = 6.80 Hz, 1H), 7.42 (dd, *J* = 2.80, 8.80 Hz, 1H), 7.35 (d, *J* = 8.80 Hz, 1H), 5.68 (d, *J* = 3.60 Hz, 1H), 4.58 (t, *J* = 5.60 Hz, 1H), 4.31-4.26 (m, 1H), 4.18-4.07 (m, 2H), 3.84 (s, 3H), 3.73 (dd, *J* = 3.60, 6.80 Hz, 1H), 3.15 (s, 1H), 2.42-2.49 (m, 1H), 2.11-2.06 (m, 2H), 1.99 (s, 3H), 1.93-1.55 (m, 4H), 1.34-

1.40 (m, 3H), 1.31 (s, 3H), 1.21-1.24 (m, 2H), 1.15-1.02 (m, 3H), 0.96-0.81 (m, 5H), 0.66 (s, 3H).

¹³C-NMR (400 MHz, DMSO-*d*₆): 200.77, 165.30, 155.10, 154.64, 144.72, 140.63, 137.63, 125.43, 122.62, 120.53, 77.50, 68.54, 63.57, 57.53, 55.66, 55.32, 54.50, 51.03, 47.90, 42.13, 38.89, 30.78, 29.24, 29.01, 26.49, 23.95, 20.52, 19.87, 15.09, 13.02, 11.24.

[0301] Synthesis of Compound 25



[0302] Step-1: Synthesis of (4*S*, 4*aR*, 5*aR*, 6*aS*, 6*bS*, 9*R*, 9*aS*, 11*aS*, 11*bR*)-4-hydroxy-9-((*S*)-1-((*R*)-5-(hydroxymethyl)-4-methyl-6-oxo-3, 6-dihydro-2H-pyran-2-yl)ethyl)-9*a*, 11*b*-dimethyl-2-(5-methylpyridin-2-yl)-5*a*, 6, 6*a*, 6*b*, 7, 8, 9, 9*a*, 10, 11, 11*a*, 11*b*-dodecahydrocyclopenta [1, 2] phenanthro [8*a*, 9-*b*] oxiren-1(4*H*)-one:

To a stirred solution of (1*S*, 2*R*, 6*S*, 7*R*, 9*R*, 11*S*, 12*S*, 15*R*, 16*S*)-6-hydroxy-15-[(1*S*)-1-[(2*R*)-5-(hydroxymethyl)-4-methyl-6-oxo-3, 6-dihydro-2H-pyran-2-yl]ethyl]-4-iodo-2, 16-dimethyl-8-oxapentacyclo [9.7.0.0.0^{2,7}.0^{7,9}.0^{12,16}] octadec-4-en-3-one (0.2 g, 1 eq; 335 μmol) in tetrahydrofuran (2 mL) were added λ¹-copper(1+) iodide (6.39 mg, 0.1 eq., 33.5 μmol), triphenylarsane (10.3 mg, 0.1 eq., 33.5 μmol) and 5-methyl-2-(tributylstannyl) pyridine (256 mg, 2 eq., 671 μmol). After that, the reaction mixture was degassed using nitrogen gas for 30 minutes. To this stirring solution, tris((1*E*,4*E*)-1,5-diphenylpenta-1,4-dien-3-one) dipalladium (3.07 mg, 0.01 eq., 3.35 μmol) was added followed by further degassing by nitrogen for 5 minutes. Finally, the reaction mixture was heated at 80°C for 16 hours. After completion of the reaction (monitored by TLC: 5% methanol in dichloromethane) mixture was filtered through celite bed and filtrate was diluted by water (20 mL) and then extracted using dichloromethane (3 x 45 mL). Collected organics, dried over anhydrous sodium sulphate and concentrated under reduced pressure to get crude. Crude was purified using prep-HPLC (ABC method) (4*S*, 4*aR*, 5*aR*, 6*aS*, 6*bS*, 9*R*, 9*aS*, 11*aS*, 11*bR*)-4-hydroxy-9-((*S*)-1-((*R*)-5-(hydroxymethyl)-4-methyl-6-oxo-3, 6-dihydro-2H-pyran-2-yl)ethyl)-9*a*, 11*b*-dimethyl-2-(5-methylpyridin-2-yl)-5*a*, 6, 6*a*,

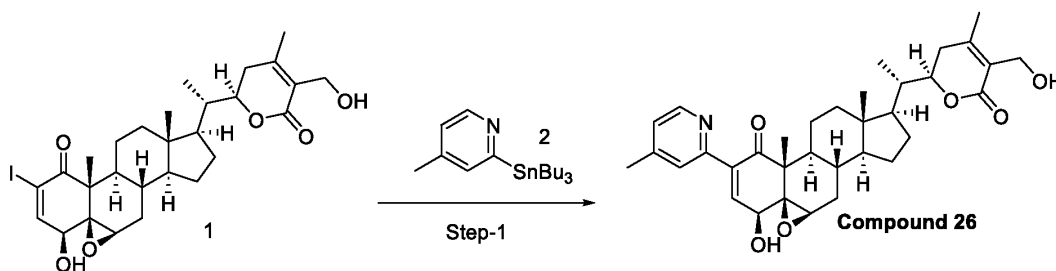
6b, 7, 8, 9, 9a, 10, 11, 11a, 11b-dodecahydrocyclopenta [1, 2] phenanthro [8a, 9-b] oxiren-1(4H)-one (160 mg, 85%) as a white solid.

[0303] Analytical data:

LCMS: 98.96% (m/z: 562.60, [M+1]⁺, 5.44 min (10 min run).

¹H-NMR (400 MHz, DMSO-*d*₆): δ 8.44 (s, 1H), 7.63 (d, *J* = 6.80 Hz, 2H), 7.29 (d, *J* = 8.00 Hz, 1H), 5.71 (d, *J* = 3.20 Hz, 1H), 4.59 (t, *J* = 5.20 Hz, 1H), 4.26-4.30 (m, 1H), 4.16-4.09 (m, 2H), 3.74 (dd, *J* = 3.20, 6.40 Hz, 1H), 3.15 (s, 1H), 2.31 (s, 3H), 2.11-2.02 (m, 5H), 1.93-1.99 (m, 1H), 1.90-1.55 (m, 3H), 1.41-1.23 (m, 8H), 1.12-1.06 (m, 3H), 0.96-0.84 (m, 5H), 0.66 (s, 3H).

[0304] Synthesis of Compound 26



[0305] Step-1: Synthesis of (4*S*, 4a*R*, 5a*R*, 6a*S*, 6b*S*, 9*R*, 9a*S*, 11a*S*, 11b*R*)-4-hydroxy-9-((*S*)-1-((*R*)-5-(hydroxymethyl)-4-methyl-6-oxo-3, 6-dihydro-2H-pyran-2-yl)ethyl)-9a, 11b-dimethyl-2-(4-methylpyridin-2-yl)-5a, 6, 6a, 6b, 7, 8, 9, 9a, 10, 11, 11a, 11b-dodecahydrocyclopenta [1, 2] phenanthro [8a, 9-b] oxiren-1(4H)-one:

To a stirred solution of (1*S*, 2*R*, 6*S*, 7*R*, 9*R*, 11*S*, 12*S*, 15*R*, 16*S*)-6-hydroxy-15-[(1*S*)-1-[(2*R*)-5-(hydroxymethyl)-4-methyl-6-oxo-3, 6-dihydro-2H-pyran-2-yl]ethyl]-4-iodo-2, 16-dimethyl-8-oxapentacyclo [9.7.0.0^{2,7}.0^{7,9}.0^{12,16}] octadec-4-en-3-one (0.2 g, 1 eq. 335 μ mol) in tetrahydrofuran (2 mL) were added λ^1 -copper(1+) iodide (6.39 mg, 0.1 eq., 33.5 μ mol), 4-methyl-2-(tributylstannyl) pyridine (247 mg, 2 eq; 671 μ mol) and then reaction was degassed using nitrogen gas for 30 minutes. After that, tris((1*E*,4*E*)-1,5-diphenylpenta-1,4-dien-3-one) dipalladium (3.07 mg, 0.01 eq., 3.35 μ mol) was added and again it was degassed by nitrogen for 5 minutes. Finally, the reaction mixture was heated 80°C for 16 hours. After completion of the reaction (monitored by TLC: 5% methanol in dichloromethane), reaction mixture was filtered through celite bed and filtrate was diluted by water (20 mL) and then extracted using

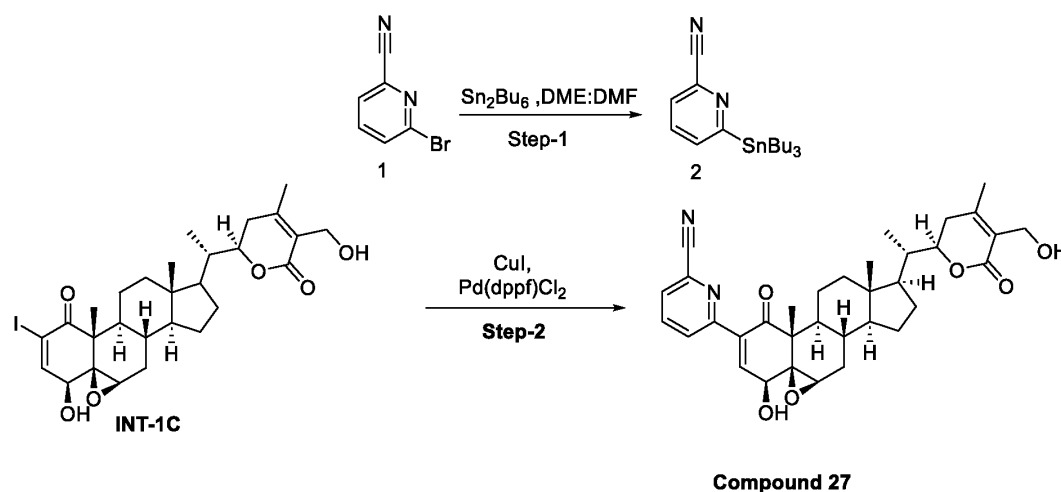
dichloromethane (3 x 45 mL). Collected organics, dried over anhydrous sodium sulphate and then concentrated under reduced pressure to get crude. Crude was purified by using preparative-HPLC (ABC method) afforded (4S, 4aR, 5aR, 6aS, 6bS, 9R, 9aS, 11aS, 11bR)-4-hydroxy-9-((S)-1-((R)-5-(hydroxymethyl)-4-methyl-6-oxo-3, 6-dihydro-2H-pyran-2-yl)ethyl)-9a, 11b-dimethyl-2-(4-methylpyridin-2-yl)-5a, 6, 6a, 6b, 7, 8, 9, 9a, 10, 11, 11a, 11b-dodecahydrocyclopenta [1,2] phenanthro [8a, 9-b] oxiren-1(4H)-one (115 mg, 61%) as a white solid.

[0306] Analytical data:

LCMS: 97.47% (m/z: 562.60, $[M+1]^+$, 5.40 min (10 min run).

$^1\text{H-NMR}$ (400 MHz, $\text{DMSO-}d_6$): δ 8.45 (d, $J = 5.20$ Hz, 1H), 7.63 (d, $J = 6.40$ Hz, 1H), 7.21-7.18 (m, 2H), 5.73 (s, 1H), 4.59 (t, $J = 5.20$ Hz, 1H), 4.30-4.27 (m, 1H), 4.15-4.10 (m, 2H), 3.74 (d, $J = 6.80$ Hz, 1H), 3.16 (s, 1H), 2.12-1.91 (m, 6H), 1.88-1.62 (m, 2H), 1.60-1.19 (m, 9H), 1.13-1.05 (m, 3H), 0.93-0.86 (m, 5H), 0.66 (s, 3H).

[0307] Synthesis of Compound 27



[0308] Step-1: Synthesis of 6-(tributylstannyl) picolinonitrile:

To a stirred solution 6-bromopyridine-2-carbonitrile (1 g, 5.46 mmol) in N, N-dimethylformamide (1 mL) and 1,2-dimethoxyethane (8 mL) was added bis(tributylstannane) (4.77 g, 1.5 eq., 8.2 mmol). Purged with nitrogen gas for 30 min. Added tetrakis(triphenylphosphine)

palladium (0) (0.505g, 0.08 eq, 0.436 mmol) and purged with nitrogen for 5 min. The reaction mixture was stirred at 100°C for 16h. The reaction mixture was quenched with chilled water (30 mL) and extracted with ethyl acetate (2 x 30 mL). The combined organic layer was washed with saturated brine solution (50 mL), dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure. The crude material was purified through combi flash using 25-30% ethyl acetate in hexane to get desired product 6-(tributylstannyl) picolinonitrile (0.26 g, 12.1%) as colour less liquid.

[0309] Analytical data:

¹H-NMR (400 MHz, DMSO-*d*₆): δ 7.87-7.82 (m, 2H), 7.80-7.78 (m, 1H), 1.61-1.44 (m, 6H), 1.32-1.23 (m, 6H), 1.20 -1.13 (m, 6H), 0.87-0.89 (m, 9H).

[0310] Step-2: Synthesis of 6-((4S, 4aR, 5aR, 6aS, 6bS, 9R, 9aS, 11aS, 11bR)-4-hydroxy-9-((S)-1-((R)-5-(hydroxymethyl)-4-methyl-6-oxo-3, 6-dihydro-2H-pyran-2-yl)ethyl)-9a, 11b-dimethyl-1-oxo-1, 4, 5a, 6, 6a, 6b, 7, 8, 9, 9a, 10, 11, 11a, 11b-tetradecahydrocyclopenta [1, 2] phenanthro [8a, 9-b] oxiren-2-yl) picolinonitrile:

To a stirred solution of (1S, 2R, 6S, 7R, 9R, 11S, 12S, 16S)-6-hydroxy-15-[(1S)-1-[(2R)-5-(hydroxymethyl)-4-methyl-6-oxo-3, 6-dihydro-2H-pyran-2-yl]ethyl]-4-iodo-2, 16-dimethyl-8-oxapentacyclo [9.7.0.0^{2,7}.0^{7,9}.0^{12,16}] octadec-4-en-3-one (0.2 g, 335 μ mol) in N,N-dimethylformamide (2.6 mL) added diiodocopper (16 mg, 0.15 eq., 50.3 μ mol) and 6-(tributylstannyl) pyridine-2-carbonitrile (132 mg, 335 μ mol). The reaction mixture was purged with nitrogen gas for 35 min. Added 1,1'-Bis (diphenylphosphino) ferrocene] palladium(II) dichloride dichloromethane adduct (13.7 mg, 0.05 eq., 16.8 μ mol) and purged with nitrogen gas for 5 min. Stirred the reaction mixture at 60 °C for 2h. Quenched the reaction mass with water (50 ml) and extracted with ethyl acetate (2 X 50 ml). The combined organic layer was washed with saturated brine solution, dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure. The crude was purified through preparative-HPLC (ABC method) to obtain 6-((4S, 4aR, 5aR, 6aS, 6bS, 9R, 9aS, 11aS, 11bR)-4-hydroxy-9-((S)-1-((R)-5-(hydroxymethyl)-4-methyl-6-oxo-3, 6-dihydro-2H-pyran-2-yl)ethyl)-9a, 11b-dimethyl-1-oxo-1, 4, 5a, 6, 6a, 6b, 7, 8, 9, 9a, 10, 11, 11a, 11b-tetradecahydrocyclopenta [1, 2] phenanthro [8a, 9-b] oxiren-2-yl) picolinonitrile (42 mg, 21.8%) as a white solid.

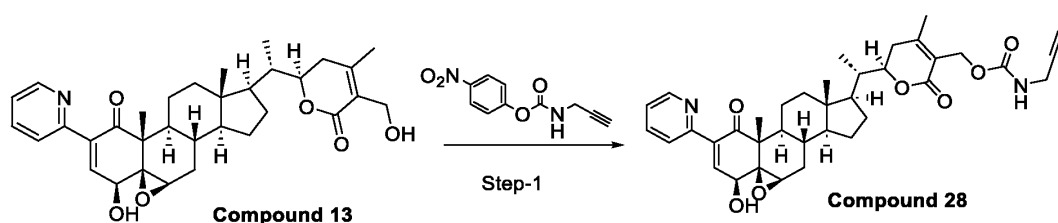
[0311] Analytical data:

LCMS: 99.92% (m/z: 573.35, [M+1]⁺, 6.24 min (10 min run).

¹H-NMR (400 MHz, DMSO-*d*₆): δ 8.12 (t, J = 7.60 Hz, 1H), 8.02 (d, J = 7.60 Hz, 1H), 7.76–7.71 (m, 2H), 5.85 (d, J = 3.60 Hz, 1H), 4.58 (t, J = 5.60 Hz, 1H), 4.30–4.25 (m, 1H), 4.17–4.07 (m, 2H), 3.79 (dd, J = 3.20, 6.40 Hz, 1H), 3.17 (s, 1H), 2.42–2.33 (m, 1H), 2.11–2.03 (m, 2H), 1.99 (s, 3H), 1.92 (d, J = 12.4 Hz, 1H), 1.83–1.76 (m, 1H), 1.76–1.68 (m, 1H), 1.60–1.52 (m, 1H), 1.46–1.34 (m, 3H), 1.32 (s, 3H), 1.29–1.23 (m, 2H), 1.14–1.01 (m, 3H), 0.92 (m, 5H), 0.66 (s, 3H).

¹³C-NMR (400 MHz, DMSO-*d*₆): δ 200.09, 165.29, 154.65, 154.23, 142.35, 139.47, 139.03, 132.60, 128.29, 126.18, 125.43, 117.29, 77.50, 68.33, 63.03, 57.56, 55.25, 54.51, 51.06, 47.92, 42.05, 41.98, 30.68, 29.23, 29.01, 26.49, 23.96, 20.44, 19.86, 15.09, 13.04, 11.24.

[0312] Synthesis of Compound 28



[0313] Step-1: ((R)-6-((S)-1-((4S, 4aR, 5aR, 6aS, 6bS, 9R, 9aS, 11aS, 11bR)-4-hydroxy-9a,11b-dimethyl-1-oxo-2-(pyridin-2-yl)-1, 4, 5a, 6, 6a, 6b, 7, 8, 9, 9a, 10, 11, 11a, 11b-tetradecahydrocyclopenta [1, 2] phenanthro [8a, 9-b] oxiren-9-yl)ethyl)-4-methyl-2-oxo-5, 6-dihydro-2H-pyran-3-yl) methyl prop-2-yn-1-ylcarbamate :

To a stirred solution of (1S, 2R, 6S, 7R, 9R, 11S, 12S, 15R, 16S)-6-hydroxy-15-[(1S)-1-[(2R)-5-(hydroxymethyl)-4-methyl-6-oxo-3, 6-dihydro-2H-pyran-2-yl]ethyl]-2, 16-dimethyl-4-(pyridin-2-yl)-8-oxapentacyclo [9.7.0.0^{2,7}.0^{7,9}.0^{12,16}] octadec-4-en-3-one (0.5 g, 913 μmol) in tetrahydrofuran (5 mL, 12.3 mmol) added lithium(1+) bis(trimethylsilyl)azanide (7.33 mg, 1.2 eq., 43.8 μmol) and 4-nitrophenyl N-(prop-2-yn-1-yl)carbamate (9.65 mg, 1.2 eq., 43.8 μmol) at -78 °C. Reaction was stirred for 4h at room temperature. After completion of the reaction (monitored by TLC: 70 % ethyl acetate in heptane), the reaction mixture was quenched with saturated NH₄Cl (30 ml) and extracted with DCM (2 X 30 ml). Collected organics, dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure to obtain crude. The crude residue was purified by combi flash (12g welch column) to afford 93% of desired

compound. The compound was further purified by preparative HPLC (ABC method) to get (3S, 4S, 4aR, 5aR, 6aS, 6bS, 9R, 9aS, 11aS, 11bR)-3-(3,3-difluoropiperidin-1-yl)-4-hydroxy-9-((S)-1-((R)-5-(hydroxymethyl)-4-methyl-6-oxo-3, 6-dihydro-2H-pyran-2-yl)ethyl)-9a, 11b-dimethyltetradecahydrocyclopenta [1,2] phenanthro [8a, 9-b] oxiren-1(2H)-one (72 mg, 12%) as a white solid.

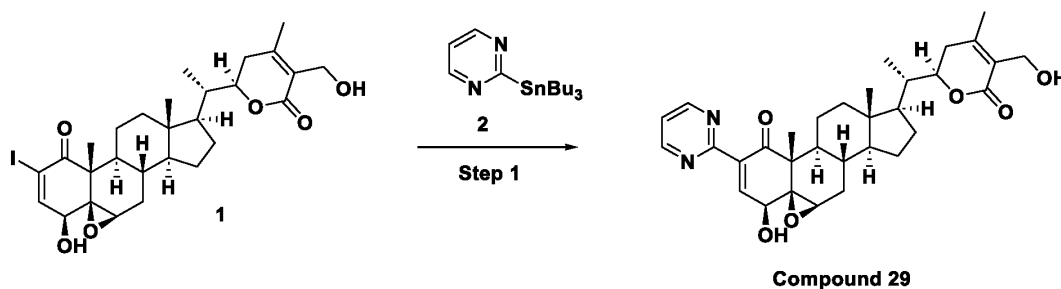
[0314] Analytical data:

LCMS: 99.10% (m/z: 629.6, [M+1]⁺, 5.97 min (10 min run).

¹H-NMR (400 MHz, DMSO-d₆- D₂O): δ 8.60 (d, J = 4.40 Hz, 1H), 7.83 (t, J = 7.60 Hz, 1H), 7.68 (d, J = 6.80 Hz, 1H), 7.58 (t, J = 5.60 Hz, 1H), 7.34-7.37 (m, 2H), 5.75 (s, 1H), 4.71 (t, J = 13.60 Hz, 2H), 4.29-4.32 (m, 1H), 3.75-3.76 (m, 3H), 3.16 (s, 1H), 3.09 (t, J = 2.40 Hz, 1H), 2.02-2.45 (m, 6H), 1.22-1.93 (m, 12H), 0.86-1.16 (m, 8H), 0.66 (s, 3H).

¹³C-NMR (400 MHz, DMSO-d₆): 200.57, 164.65, 158.45, 155.84, 152.48, 149.58, 141.12, 139.80, 136.92, 123.39, 122.16, 120.79, 81.36, 77.60, 72.99, 68.50, 63.52, 57.82, 57.55, 55.32, 50.96, 47.89, 42.08, 42.01, 30.75, 29.77, 29.23, 29.16, 26.44, 23.96, 20.48, 20.11, 15.12, 12.96, 11.23.

[0315] Synthesis of Compound 29



[0316] Step-1: Synthesis of (4S, 4aR, 5aR, 6aS, 6bS, 9R, 9aS, 11aS, 11bR)-4-hydroxy-9-((S)-1-((R)-5-(hydroxymethyl)-4-methyl-6-oxo-3, 6-dihydro-2H-pyran-2-yl)ethyl)-9a, 11b-dimethyl-2-(pyrimidin-2-yl)-5a, 6, 6a, 6b, 7, 8, 9, 9a, 10, 11, 11a, 11b-dodecahydrocyclopenta [1, 2] phenanthro [8a, 9-b] oxiren-1(4H)-one

A stirred solution of (1S, 2R, 6S, 7R, 9R, 11S, 12S, 15R, 16S)-6-hydroxy-15-[(1S)-1-[(2R)-5-(hydroxymethyl)-4-methyl-6-oxo-3, 6-dihydro-2H-pyran-2-yl]ethyl]-4-iodo-2, 16-dimethyl-

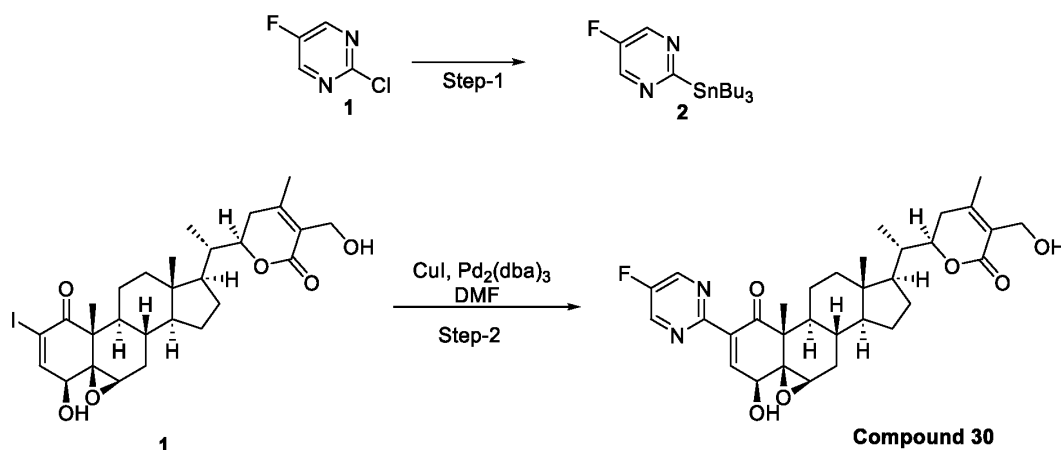
8-oxapentacyclo [9.7.0.0^{2,7},7.0^{7,9},1^{12,16}] octadec-4-en-3-one (0.5 g, 838 μ mol), 2-(tributylstannyl) pyrimidine (340 mg, 1.1 eq., 922 μ mol), diiodocopper (39.9 mg, 0.15 eq., 126 μ mol) and triphenylarsane (25.7 mg, 0.1 eq., 83.8 μ mol) in tetrahydrofuran (7 mL, 86 mmol) was purged with nitrogen for 30 min and tris (1,5-diphenylpenta-1,4-dien-3-one) dipalladium (38.4 mg, 0.05 eq., 41.9 μ mol) was added to it. The reaction mixture was again purged with nitrogen for 5 min. Stirred the reaction mass at 80 °C for 5h. After the completion of reaction (monitoring by tlc), the reaction mixture was quenched with water (30 mL) and extracted with (2 x 30 mL) ethyl acetate. The organic layer was dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure to afford 300 mg of crude. The compound was purified by Prep- HPLC purification in ABC method, to afford desired product (4S, 4aR, 5aR, 6aS, 6bS, 9R, 9aS, 11aS, 11bR)-4-hydroxy-9-((S)-1-((R)-5-(hydroxymethyl)-4-methyl-6-oxo-3, 6-dihydro-2H-pyran-2-yl)ethyl)-9a, 11b-dimethyl-2-(pyrimidin-2-yl)-5a, 6, 6a, 6b, 7, 8, 9, 9a, 10, 11, 11a, 11b-dodecahydrocyclopenta [1, 2] phenanthro[8a, 9-b]oxiren-1(4H)-one (43 mg, 9.35%) as off white solid.

[0317] Analytical data: 97.96% (m/z: 549.5, [M+1]⁺, 5.03 min (10 min run).

¹H-NMR (400 MHz, DMSO-*d*₆): δ 8.83 (d, J = 5.20 Hz, 2H), 7.66 (d, J = 6.40 Hz, 1H), 7.44 (t, J = 4.80 Hz, 1H), 5.80 (d, J = 3.20 Hz, 1H), 4.59 (t, J = 5.20 Hz, 1H), 4.26-4.30 (m, 1H), 4.08-4.18 (m, 2H), 3.74-3.76 (m, 1H), 3.15 (s, 1H), 2.33-2.43 (m, 1H), 1.93-2.13 (m, 6H), 1.49-1.90 (m, 5H), 1.24-1.36 (m, 7H), 0.92-1.15 (m, 9H), 0.66 (s, 3H).

¹³C-NMR (400 MHz, DMSO-*d*₆): δ 198.91, 165.31, 162.62, 157.53, 154.67, 141.93, 141.82, 125.43, 120.26, 77.53, 68.53, 63.76, 57.45, 55.44, 54.51, 51.01, 47.84, 42.02, 41.75, 30.85, 29.04, 26.52, 23.97, 20.18, 19.88, 14.83, 13.03, 11.22.

[0318] Synthesis of Compound 30



[0319] Step-1: Synthesis of 5-fluoro-2-(tributylstannyl)pyrimidine:

To a solution of 2-chloro-5-fluoropyrimidine (2 g, 15.1 mmol) in 1,4-dioxane (20 mL, 234 mmol) was added hexabutylditin (650 mg, 1.68 mmol) and purged nitrogen for 30 minutes. Add tetrakis(triphenylphosphine) palladium(0) (1.74 g, 0.1 eq., 1.51 mmol) and again purged with nitrogen gas for 5 minutes. The reaction mixture was stirred at 90°C for 16h. Reaction was monitored by TLC. After completion of reaction, it was filtered through celite bed and washed with ethyl acetate. The organic layer was washed with brine, dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure to get the crude material. The crude material was purified by Combi Flash by using 25-30% ethyl acetate in hexane to get 5-fluoro-2-(tributylstannyl) pyrimidine (650 mg, 11.13%).

[0320] Analytical data:

LCMS: 82.76% 3.68 min (m/z: 389.10, [M+1]⁺, (4 min run).

¹H-NMR (400 MHz, DMSO-*d*₆): δ 8.86 (d, *J* = 1.60 Hz, 2H), 1.61-1.47 (m, 6H), 1.33-1.23 (m, 6H), 1.19-1.02 (m, 6H), 0.95-0.75 (m, 9H).

[0321] Step-2: Synthesis of (4S, 4aR, 5aR, 6aS, 6bS, 9R, 9aS, 11aS, 11bR)-2-(5-fluoropyrimidin-2-yl)-4-hydroxy-9-((S)-1-((R)-5-(hydroxymethyl)-4-methyl-6-oxo-3, 6-dihydro-2H-pyran-2-yl)ethyl)-9a, 11b-dimethyl-5a, 6, 6a, 6b, 7, 8, 9, 9a, 10, 11, 11a, 11b-dodecahydrocyclopenta [1, 2] phenanthro [8a, 9-b] oxiren-1(4H)-one:

To a stirred solution of (1S, 2R, 6S, 7R, 9R, 11S, 12S, 15R, 16S)-6-hydroxy-15-[(1S)-1-[(2R)-5-(hydroxymethyl)-4-methyl-6-oxo-3, 6-dihydro-2H-pyran-2-yl]ethyl]-4-iodo-2, 16-

dimethyl-8-oxapentacyclo [9.7.0.0^{2,7}.0^{7,9}.0^{12,16}] octadec-4-en-3-one (0.3 g, 503 μ mol) in tetrahydrofuran (6 mL, 73.7 mmol) were added diiodocopper (23.9 mg, 0.15 eq., 75.4 μ mol), triphenylarsane (15.4 mg, 0.1 eq., 50.3 μ mol) and 5-fluoro-2-(tributylstannyl) pyrimidine (292 mg, 1.5 eq., 754 μ mol). Purged the reaction mixture with nitrogen gas for 35 min. Added tris(1,5-diphenylpenta-1,4-dien-3-one) dipalladium (23 mg, 0.05 eq., 25.1 μ mol) and again purged with nitrogen gas for 5 min. Stirred the reaction mass at 85 °C for 16h. After completion of reaction, it was filtered through celite bed and washed with ethyl acetate. The organic layer was washed with saturated brine solution, dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure to get the crude. The crude was purified through preparative HPLC (ABC method) to afford (4S, 4aR, 5aR, 6aS, 6bS, 9R, 9aS, 11aS, 11bR)-2-(5-fluoropyrimidin-2-yl)-4-hydroxy-9-((S)-1-((R)-5-(hydroxymethyl)-4-methyl-6-oxo-3, 6-dihydro-2H-pyran-2-yl)ethyl)-9a, 11b-dimethyl-5a, 6, 6a, 6b, 7, 8, 9, 9a, 10, 11, 11a, 11b-dodecahydrocyclopenta [1, 2] phenanthro [8a, 9-b] oxiren-1(4H)-one (28 mg, 9.82%) as a white solid.

[0322] Analytical data:

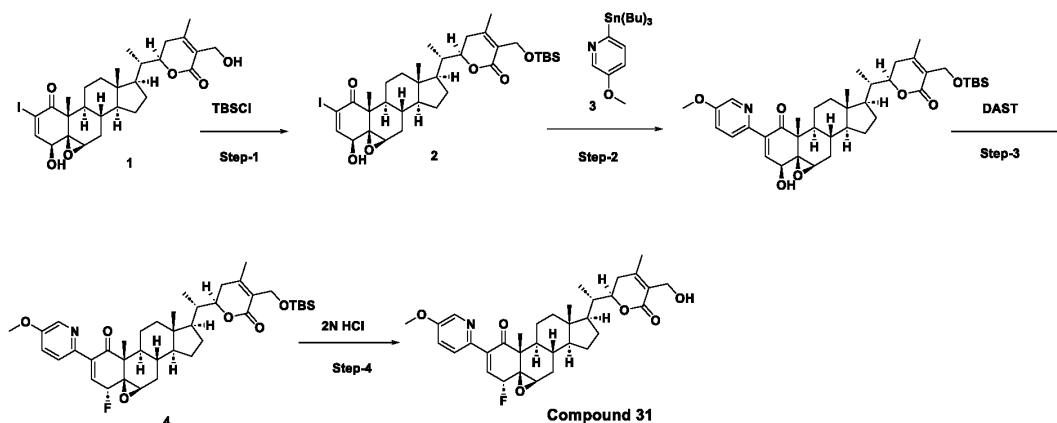
LCMS: 97.71% (m/z: 567.50, [M+1]⁺, 6.56 min (15 min run).

¹H-NMR (400 MHz, DMSO-*d*₆): δ 8.93 (s, 2H), 7.65 (d, *J* = 6.80 Hz, 1H), 5.83 (d, *J* = 3.20 Hz, 1H), 4.59 (t, *J* = 5.20 Hz, 1H), 4.31-4.26 (m, 1H), 4.18-4.07 (m, 2H), 3.76 – 3.74 (m, 1H), 3.14 (s, 1H), 2.41 0-2.31 (m, 1H), 2.12-2.07 (m, 2H), 1.99 (s, 3H), 1.93-1.89 (m, 1H), 1.81-1.78 (m, 1H), 1.77-1.72 (m, 1H), 1.57-1.47 (m, 2H), 1.36-1.23 (m, 7H), 1.21-1.11 (m, 3H), 1.08-0.91 (m, 5H), 0.65 (s, 3H).

¹³C-NMR (400 MHz, DMSO-*d*₆): δ 198.75, 165.33, 158.94, 158.88, 157.85, 155.23, 154.71, 145.68, 145.47, 142.22, 140.73, 125.44, 77.54, 68.47, 63.69, 57.47, 55.44, 54.52, 51.03, 47.86, 42.03, 41.81, 30.84, 29.06, 26.52, 23.98, 20.19, 19.90, 14.87, 13.05, 11.24.

¹⁹F-NMR (400 MHz, DMSO-*d*₆): δ 138.25.

[0323] Synthesis of Compound 31



[0324] Step-1: Synthesis of (4S, 4aR, 5aR, 6aS, 6bS, 9R, 9aS, 11aS, 11bR)-9-((S)-1-((R)-5-(((tert-butyldimethylsilyl) oxy) methyl)-4-methyl-6-oxo-3, 6-dihydro-2H-pyran-2-yl)ethyl)-4-hydroxy-2-iodo-9a, 11b-dimethyl-5a, 6, 6a, 6b, 7, 8, 9, 9a, 10, 11, 11a, 11b-dodecahydrocyclopenta [1, 2] phenanthro [8a, 9-b]oxiren-1(4H)-one:

To a stirred solution of (4S, 4aR, 5aR, 6aS, 6bS, 9R, 9aS, 11aS, 11bR)-4-hydroxy-9-((S)-1-((R)-5-(hydroxymethyl)-4-methyl-6-oxo-3, 6-dihydro-2H-pyran-2-yl)ethyl)-2-iodo-9a, 11b-dimethyl-5a, 6, 6a, 6b, 7, 8, 9, 9a, 10, 11, 11a, 11b-dodecahydrocyclopenta[1,2] phenanthro [8a, 9-b]oxiren-1(4H)-one (5 g, 8.38 mmol) in dimethylformamide (0.1 L, 1.29 mol) was added 4-(pyrrolidin-1-yl) pyridin-1-ium (6.25 g, 5 eq., 41.9 mmol). After 10 minutes tert-butyl(chloro)dimethylsilane (12.6 g, 10 eq., 83.8 mmol) was added and heated the reaction up to 85°C for 3hrs. After completion of reaction (monitored by TLC) the mixture was diluted with ice cold water (50 mL) and extracted with ethyl acetate (3 x 50 mL). The combined organic layer was washed with saturated brine solution (50 mL), dried the organic layer over anhydrous sodium sulphate, filtered and concentrated under reduced pressure to obtain the crude material, which was purified by column chromatography in 0 - 100% ethyl acetate in Heptane to obtain the compound (4S, 4aR, 5aR, 6aS, 6bS, 9R, 9aS, 11aS, 11bR)-9-((S)-1-((R)-5-(((tert-butyldimethylsilyl)oxy)methyl)-4-methyl-6-oxo-3, 6-dihydro-2H-pyran-2-yl)ethyl)-4-hydroxy-2-iodo-9a, 11b-dimethyl-5a, 6, 6a, 6b, 7, 8, 9, 9a, 10, 11, 11a, 11b-dodecahydrocyclopenta [1, 2] phenanthro [8a, 9-b]oxiren-1(4H)-one (1.8 g, 2.41 mmol, 29%) as off white solid.

[0325] Analytical data:

LCMS: 95.79% (m/z: 711.10, [M+H]⁺, 4.10 min (6 min run).

¹H-NMR (400 MHz, DMSO-*d*₆): δ 5.89 (d, *J* = 4.00 Hz, 1H), 4.27-4.35 (m, 3H), 3.48-3.51 (m, 1H), 3.19 (s, 1H), 2.31-2.51 (m, 1H), 2.16 (d, *J* = 2.80 Hz, 1H), 2.02 (m, 4H), 1.51-1.90 (m, 4H), 1.21-1.38 (m, 8H), 0.91-1.20 (m, 8H), 0.85 (s, 9H), 0.64 (s, 3H).

[0326] Step-2: Synthesis of (1S, 2R, 6S, 7R, 9R, 11S, 12S, 15R, 16S)-15-[(1S)-1-[(2R)-5-[[tert-butyl(dimethylsilyl)oxy]methyl]-4-methyl-6-oxo-3, 6-dihydro-2H-pyran-2-yl]ethyl]-6-hydroxy-4-(5-methoxypyridin-2-yl)-2, 16-dimethyl-8-oxapentacyclo [9.7.0.0^{2,7},0^{9,12},1⁶] octadec-4-en-3-one

To a stirred solution of (1S, 2R, 6S, 7R, 9R, 11S, 12S, 15R, 16S)-15-[(1S)-1-[(2R)-5-[[tert-butyl(dimethylsilyl)oxy]methyl]-4-methyl-6-oxo-3, 6-dihydro-2H-pyran-2-yl]ethyl]-6-hydroxy-4-iodo-2, 16-dimethyl-8-oxapentacyclo [9.7.0.0^{2,7},0^{9,12},1⁶] octadec-4-en-3-one (450 mg, 0.633 mmol) and 5-methoxy-2-(tributylstannyl) pyridine (378 mg, 1.5 eq., 0.950 mmol) in THF (8 mL) were added triphenylarsane (19.4 mg, 0.1 eq., 0.063 mmol) and iodocopper (18.1 mg, 0.15 eq., 0.095 mmol). The resulting mixture was purged with argon for 30 min. Tris ((1E,4E)-1,5-diphenylpenta-1,4-dien-3-one) dipalladium (58 mg, 0.1 eq., 0.063 μ mol) was added to the reaction mixture and stirred for 3h at 85 °C. The reaction was monitored by TLC, quenched by adding water (50 mL) and extracted with ethyl acetate (3 x 50 mL). Combined organics were dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure to obtain crude. The crude product was purified by combi flash column chromatography using (70-90%) ethyl acetate in heptane as an eluent to afford (1S, 2R, 6S, 7R, 9R, 11S, 12S, 15R, 16S) -15-[(1S)-1-[(2R)-5-[[tert-butyl(dimethylsilyl)oxy]methyl]-4-methyl-6-oxo-3, 6-dihydro-2H-pyran-2-yl]ethyl]-6-hydroxy-4-(5-methoxypyridin-2-yl)-2, 16-dimethyl-8-oxapentacyclo [9.7.0.0^{2,7},0^{9,12},1⁶] octadec-4-en-3-one (180 mg, 0.26 mmol, 41%) as an off white solid.

[0327] Analytical data:

LCMS: 91.13% (*m/z*: 692.28, [M+1]⁺), 3.08 min (4 min run).

[0328] Step-3: Synthesis of (1S, 2R, 6R, 7S, 9R, 11S, 12S, 15R, 16S)-15-[(1S)-1-[(2R)-5-[[tert-butyl(dimethylsilyl)oxy]methyl]-4-methyl-6-oxo-3, 6-dihydro-2H-pyran-2-yl]ethyl]-6-fluoro-4-(5-methoxypyridin-2-yl)-2, 16-dimethyl-8-oxapentacyclo [9.7.0.0^{2,7},0^{9,12},1⁶] octadec-4-en-3-one

To a stirred solution of (1S, 2R, 6S, 7R, 9R, 11S, 12S, 15R, 16S)-15-[(1S)-1-[(2R)-5-[[tert-butyl(dimethylsilyl)oxy]methyl]-4-methyl-6-oxo-3, 6-dihydro-2H-pyran-2-yl]ethyl]-6-

hydroxy-4-(5-methoxypyridin-2-yl)-2, 16-dimethyl-8-oxapentacyclo [9.7.0.0²,⁷.0⁷,⁹.0¹²,¹⁶] octadec-4-en-3-one (180 mg, 0.26 mmol) in dichloromethane (6 mL) was added diethyl(trifluoro-λ⁴-sulfanyl) amine (0.041 mL, 1.2 eq., 0.312 mmol) (dissolved in DCM (1 mL)) drop wise at -78°C under inert atmosphere and stirred for 15 min. Monitored the reaction by TLC, quenched it by saturated sodium bicarbonate solution (20 mL) and extracted using dichloromethane (2 x 35 mL). Combined organics were dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure to obtain crude. The crude was purified by over combi-flash chromatography in silica column (10-20% ethyl acetate in hexane) to yield (1S, 2R, 6R, 7S, 9R, 11S, 12S, 15R, 16S)-15-[(1S)-1-[(2R)-5- {[(tert-butyldimethylsilyl) oxy] methyl}-4-methyl-6-oxo-3, 6-dihydro-2H-pyran-2-yl] ethyl] -6-fluoro-4-(5-methoxypyridin-2-yl)-2, 16-dimethyl-8-oxapentacyclo [9.7.0.0²,⁷.0⁷,⁹.0¹²,¹⁶] octadec-4-en-3-one (0.1 g, 0.144 mmol, 55%) as light yellow solid.

[0329] Analytical data:

LCMS: 97.14 % (m/z: 694.28, [M+1]⁺), 3.37 min (4 min run).

[0330] Step-4: Synthesis of (1S, 2R, 6R, 7S, 9R, 11S, 12S, 15R, 16S)-6-fluoro-15-[(1S)-1-[(2R)-5-(hydroxymethyl)-4-methyl-6-oxo-3, 6-dihydro-2H-pyran-2-yl]ethyl]-4-(5-methoxypyridin-2-yl)-2, 16-dimethyl-8-oxapentacyclo [9.7.0.0²,⁷.0⁷,⁹.0¹²,¹⁶] octadec-4-en-3-one

To a solution of (1S, 2R, 6R, 7S, 9R, 11S, 12S, 15R, 16S)-15-[(1S)-1-[(2R)-5-{[(tert-butyldimethylsilyl)oxy]methyl}-4-methyl-6-oxo-3, 6-dihydro-2H-pyran-2-yl]ethyl]-6-fluoro-4-(5-methoxypyridin-2-yl)-2, 16-dimethyl-8-oxapentacyclo [9.7.0.0²,⁷.0⁷,⁹.0¹²,¹⁶] octadec-4-en-3-one (0.1 g, 0.144 mmol) in THF (1 mL) and methanol (1 mL) was added 2N hydrogen chloride solution (1 mL, 14 eq, 2 mmol) drop wise at 0 °C and stirred for 30 min. Monitored the reaction by TLC, quenched it by adding saturated sodium bicarbonate solution (20 mL) and extracted using dichloromethane (2 x 30 mL). Combined organics were dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure to obtain crude which was purified by combi-flash chromatography over silica column (0 - 5% methanol in dichloromethane) to afford (1S, 2R, 6R, 7S, 9R, 11S, 12S, 15R, 16S)-6-fluoro-15-[(1S)-1-[(2R)-5-(hydroxymethyl)-4-methyl-6-oxo-3, 6-dihydro-2H-pyran-2-yl]ethyl]-4-(5-

methoxypyridin-2-yl)-2, 16-dimethyl-8-oxapentacyclo [9.7.0.0.2^{7,7},9.0^{12,16}] octadec-4-en-3-one (45 mg, 0.077 mmol, 53%) as off white solid.

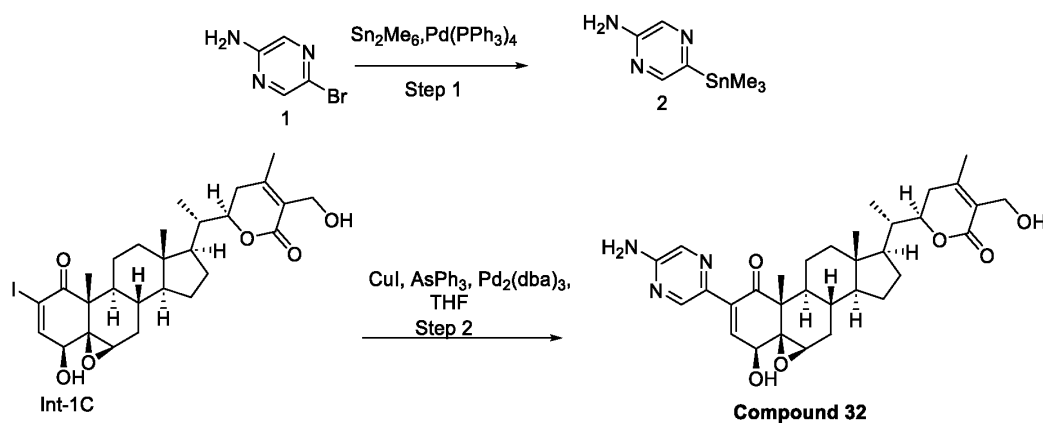
[0331] Analytical data:

LCMS: 93.34% (m/z: 580.5, [M+1]⁺, 6.22 min (10 min run).

¹H-NMR (400 MHz, DMSO-*d*₆): δ 8.33 (d, *J* = 1.6 Hz, 1H), 7.46-7.41 (m, 3H), 5.83 (d, *J* = 50.4 Hz, 1H), 4.59 (t, *J* = 5.2 Hz, 1H), 4.28 (d, *J* = 13.2 Hz, 1H), 4.18-4.07 (m, 2H), 3.85 (s, 3H), 3.51 (s, 1H), 3.40-3.35 (m, 1H), 2.42-2.32 (m, 1H), 2.12-2.02 (m, 2H), 1.99 (s, 3H), 1.90-1.93 (m, 1H), 1.89-1.58 (m, 2H), 1.58 – 1.50 (m, 2H), 1.44-1.28 (m, 4H), 1.21 (s, 3H), 1.16-0.95 (m, 5H), 0.92 (d, *J* = 6.40 Hz, 3H), 0.67 (s, 3H).

¹³C-NMR (400 MHz, DMSO-*d*₆): 197.91, 165.34, 155.34, 154.7, 143.3, 137.88, 137.75, 137.71, 137.62, 125.44, 123.22, 120.56, 85.20, 83.44, 77.52, 64.94, 63.03, 62.88, 55.73, 55.04, 54.51, 54.07, 53.95, 51.12, 47.32, 47.27, 43.16, 41.97, 40.14, 30.07, 29.07, 29.01, 26.49, 23.96, 20.98, 19.91, 15.19, 13.06, 12.81, 11.32.

[0332] Synthesis of Compound 32



[0333] Step-1: Synthesis of 5-(trimethylstannyl) pyrazin-2-amine:

To a stirred solution of 5-bromopyrazin-2-amine (0.5 g, 2.87 mmol) in toluene (10 mL) was added hexamethyldistannane (941 mg, 2.87 mmol). Purged with nitrogen for 30 min then added tetrakis(triphenylphosphine)palladium (99.6 mg, 0.03 eq., 86.2 μ mol) followed by further

purging with nitrogen for 5 min. The reaction mixture was stirred at 130°C for 3h. After completion of reaction, it was filtered through celite bed and washed with ethyl acetate. The filtrate was concentrated under reduced pressure to get crude. The crude material was purified by combi flash over silica gel using 0-30% ethyl acetate in hexane, to get 5-(trimethylstannyl)pyrazin-2-amine (710 mg, 95.2%) as white solid.

[0334] Analytical data:

LCMS: 99.82% (m/z: 259.93, [M+1]⁺, 1.82min (4 min run).

¹H-NMR (400 MHz, DMSO-*d*₆): δ 8.05 (s, 1H), 7.84 (s, 1H), 6.24 (br s, 2H), 0.23 (s, 9H).

[0335] Step-2: Synthesis of (4S, 4aR, 5aR, 6aS, 6bS, 9R, 9aS, 11aS, 11bR)-2-(5-aminopyrazin-2-yl)-4-hydroxy-9-((S)-1-((R)-5-(hydroxymethyl)-4-methyl-6-oxo-3, 6-dihydro-2H-pyran-2-yl)ethyl)-9a, 11b-dimethyl-5a, 6, 6a, 6b, 7, 8, 9, 9a, 10, 11, 11a, 11b-dodecahydrocyclopenta [1, 2] phenanthro [8a, 9-b] oxiren-1(4H)-one:

To a stirred solution of (1S, 2R, 6S, 7R, 9R, 11S, 12S, 15R, 16S)-6-hydroxy-15-[(1S)-1-[(2R)-5-(hydroxymethyl)-4-methyl-6-oxo-3, 6-dihydro-2H-pyran-2-yl]ethyl]-4-iodo-2, 16-dimethyl-8-oxapentacyclo [9.7.0.0^{2,7}.0^{7,9}.0^{12,16}] octadec-4-en-3-one (0.9 g, 1.51 mmol) in tetrahydrofuran (9 mL, 111 mmol) were added diiodocopper (71.8 mg, 0.15 eq., 226 μmol), triphenylarsane (46.2 mg, 0.1 eq., 151 μmol) and 5-(trimethylstannyl)pyrazin-2-amine (584 mg, 1.5 eq., 2.26 mmol). The reaction mixture was purged with nitrogen for 35 min and then tris(1,5-diphenylpenta-1,4-dien-3-one)dipalladium (69.1 mg, 0.05 eq., 75.4 μmol) was added to it. The reaction mixture was again purged with nitrogen for 5 min. The reaction was stirred at 80°C for 16h. The reaction mixture was quenched with cool water (50 mL) and was extracted with Ethyl acetate (2 x 50mL). The organic layer was dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure. The crude material was enriched by Combi Flash by using 40-50% ethyl acetate in hexane. Compound was further purified by preparative-HPLC (ABC method) to afford (4S, 4aR, 5aR, 6aS, 6bS, 9R, 9aS, 11aS, 11bR)-2-(5-aminopyrazin-2-yl)-4-hydroxy-9-((S)-1-((R)-5-(hydroxymethyl)-4-methyl-6-oxo-3, 6-dihydro-2H-pyran-2-yl)ethyl)-9a, 11b-dimethyl-5a, 6, 6a, 6b, 7, 8, 9, 9a, 10, 11, 11a, 11b-dodecahydrocyclopenta [1,2] phenanthro [8a, 9-b] oxiren-1(4H)-one (20 mg) as a white solid.

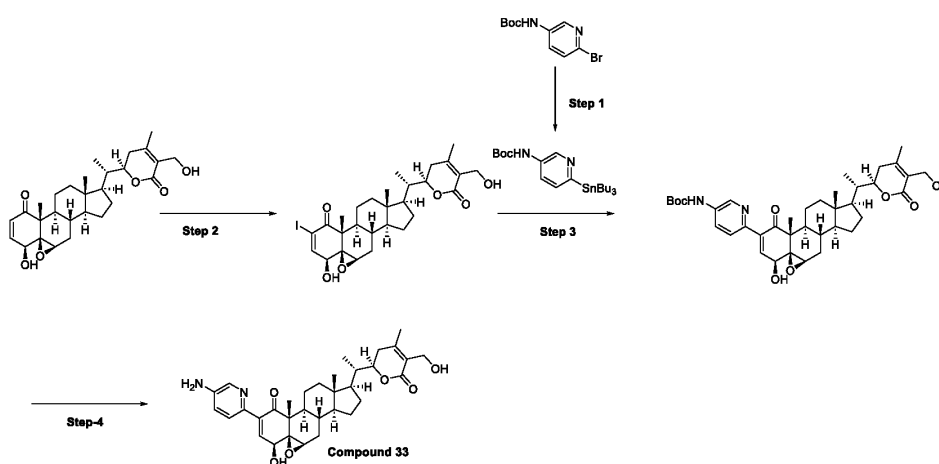
[0336] Analytical data:

LCMS: 96.59% (m/z: 564.40, [M+1]⁺, 5.34 min (10 min run).

¹H-NMR (400 MHz, DMSO-*d*₆): δ 7.93-7.89 (m, 2H), 7.42 (d, J = 6.80 Hz, 1H), 6.72 (s, 2H), 5.63 (d, J = 3.20 Hz, 1H), 4.59 (t, J = 5.20 Hz, 1H), 4.29-4.25 (m, 1H), 4.17-4.07 (m, 2H), 3.71 (dd, J = 3.20, 6.80 Hz, 1H), 3.13 (s, 1H), 2.41-2.33 (m, 1H), 2.10-2.05 (m, 2H), 1.98 (s, 3H), 1.92-1.89 (m, 1H), 1.82-1.77 (m, 1H), 1.73-1.70 (m, 1H), 1.60-1.54 (s, 1H), 1.36- 1.20 (m, 8H), 1.14-1.02 (m, 3H), 0.97-0.86 (m, 4H), 0.84-0.79 (m, 1H), 0.65 (s, 3H),

¹³C-NMR (400 MHz, DMSO-*d*₆): δ 200.69, 165.31, 155.19, 154.65, 140.42, 139.08, 135.28, 135.17, 132.11, 125.43, 77.52, 68.56, 63.57, 57.59, 55.25, 54.51, 51.03, 47.90, 42.16, 41.98, 30.79, 29.27, 29.02, 26.48, 23.96, 20.57, 19.87, 15.14, 13.02, 11.23.

[0337] Synthesis of Compound 33



[0338] Step-1: *tert*-butyl-*N*-[6-(tributylstannyl)pyridin-3-yl]carbamate:

To a stirred solution of *tert*-butyl-*N*-(6-bromopyridin-3-yl)carbamate (2 g, 1.0 eq, 7.32 mmol) in tetrahydrofuran (20 mL) was added lithium(1+) butan-1-ide (797 mg, 1.7 eq., 12.4 mmol) at -78 °C. The reaction mixture was allowed to stir for 1h at same temperature. Then, tributyltin chloride (3.71 mL, 1.7 eq., 12.4 mmol) was added dropwise to the resultant reaction mixture

and further the reaction was stirred for 3 hours at room temperature. After the completion of reaction (monitored by TLC), the reaction mixture was quenched with saturated ammonium chloride solution (30 mL) and then extracted by DCM (30 mL X 3). The combined organic layer was dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure to get crude product. The crude residue was purified by combi-flash column (eluted at 20% ethyl acetate in heptane) to afford *tert*-butyl-*N*-[6-(tributylstannyl)pyridin-3-yl]carbamate (1.3 g, 2.69 mmol) as yellow gum.

[0339] Analytical data:

LCMS: 95.10% (m/z: 485.22, [M+H]⁺, observed 485.25, [M+H]⁺, 3.37 min (4 min run).

[0340] Step-2: (1S, 2R, 6S, 7R, 9R, 11S, 12S, 15R, 16S)-6-hydroxy-15-[(1S)-1-[(2R)-5-(hydroxymethyl)-4-methyl-6-oxo-3, 6-dihydro-2H-pyran-2-yl]ethyl]-4-iodo-2, 16-dimethyl-8-oxapentacyclo [9.7.0.0^{2,7},⁹.0^{12,16}] octadec-4-en-3-one:

To a stirred solution of (1S, 2R, 6S, 7R, 9R, 11S, 12S, 15R, 16S)-6-hydroxy-15-[(1S)-1-[(2R)-5-(hydroxymethyl)-4-methyl-6-oxo-3, 6-dihydro-2H-pyran-2-yl]ethyl]-2, 16-dimethyl-8-oxapentacyclo [9.7.0.0^{2,7},⁹.0^{12,16}] octadec-4-en-3-one (20 g, 1.0 eq, 42.5 mmol) in dichloromethane (0.2 L) was added *N,N*-dimethylpyridin-4-amine (7.79 g, 1.5 eq., 63.7 mmol) followed by diiodine (12.9 g, 1.2 eq., 51 mmol) at 0 °C. The resultant reaction mixture was stirred for 2 h at room temperature. After the completion of reaction (monitored by TLC), the reaction mixture was quenched with 20% sodium thiosulfate solution (300 mL) and was extracted by dichloromethane (3 X 300 mL). The organic layer was dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure to get crude product. The crude was purified by combi-flash column (eluted at 5% methanol in DCM) to afford (1S, 2R, 6S, 7R, 9R, 11S, 12S, 15R, 16S)-6-hydroxy-15-[(1S)-1-[(2R)-5-(hydroxymethyl)-4-methyl-6-oxo-3, 6-dihydro-2H-pyran-2-yl]ethyl]-4-iodo-2, 16-dimethyl-8-oxapentacyclo [9.7.0.0^{2,7},⁹.0^{12,16}] octadec-4-en-3-one (14 g, 23.5 mmol) as a white solid.

[0341] Analytical data:

LCMS: 90.55% (m/z: 595.16, [M+H]⁺, observed 595.18, [M+H]⁺, 2.29 min (4 min run).

[0342] Step-3: *tert*-butyl-*N*-{6-[(1S, 2R, 6S, 7R, 9R, 11S, 12S, 15R, 16S)-6-hydroxy-15-[(1S)-1-[(2R)-5-(hydroxymethyl)-4-methyl-6-oxo-3, 6-dihydro-2H-pyran-2-yl]ethyl]-2, 16-dimethyl-3-oxo-8-oxapentacyclo [9.7.0.0^{2,7},⁹.0^{12,16}] octadec-4-en-4-yl]pyridin-3-yl} carbamate

To a stirred solution of (1S, 2R, 6S, 7R, 9R, 11S, 12S, 15R, 16S)-6-hydroxy-15-[(1S)-1-[(2R)-5-(hydroxymethyl)-4-methyl-6-oxo-3, 6-dihydro-2H-pyran-2-yl]ethyl]-4-iodo-2, 16-dimethyl-8-oxapentacyclo [9.7.0.0^{2,7},⁹.0^{12,16}] octadec-4-en-3-one (0.8 g, 1.34 mmol) in tetrahydrofuran (10 mL, 123 mmol) was added λ^1 -copper(1+) iodide (25.5 mg, 0.1 eq., 134 μ mol), triphenylarsane (41.1 mg, 0.1 eq., 134 μ mol), and tert-butyl N-[6-(tributylstannyl)pyridin-3-yl]carbamate (778 mg, 1.2 eq., 1.61 mmol). The reaction mixture was purged with argon for 30 min. Tris((1E,4E)-1,5-diphenylpenta-1,4-dien-3-one) dipalladium (12.3 mg, 0.01 eq., 13.4 μ mol) was added to the reaction mixture and again purged with argon for 5 min. The resultant reaction mixture was stirred for 2 hours at 80°C. After the completion of reaction (monitored by TLC), the reaction mixture was filtered through celite bed and was concentrated under reduced pressure to get crude product. The crude residue was purified by combi-flash column (eluted at 3% methanol in DCM) to afford *tert*-butyl-N-{6-[(1S, 2R, 6S, 7R, 9R, 11S, 12S, 15R, 16S)-6-hydroxy-15-[(1S)-1-[(2R)-5-(hydroxymethyl)-4-methyl-6-oxo-3, 6-dihydro-2H-pyran-2-yl]ethyl]-2, 16-dimethyl-3-oxo-8-oxapentacyclo [9.7.0.0^{2,7},⁹.0^{12,16}] octadec-4-en-4-yl]pyridin-3-yl}carbamate (0.6 g, 905 μ mol).

[0343] Analytical data:

LCMS: 93.68% (m/z: 663.3, [M+1]⁺, 2.07 min (4 min run).

¹H-NMR (400 MHz, DMSO-*d*₆): δ 9.68 (s, 1H), 8.63 (s, 1H), 7.88 (dd, *J* = 8.4 Hz, 6.0 Hz, 1H), 7.55 (d, *J* = 6.4 Hz, 1H), 7.33 (d, *J* = 8.8 Hz, 1H), 5.66 (d, *J* = 1.6 Hz, 1H), 4.57 (t, *J* = 0.8 Hz, 1H), 4.11-4.30 (m, 3H), 3.72-3.74 (m, 1H), 3.14 (s, 1H), 2.49-2.50 (m, 1H), 2.10-2.10 (m, 3H), 1.99 (s, 5H), 1.40-1.49 (m, 4H), 1.40 (s, 9H), 1.07-1.33 (m, 22H), 0.66 (s, 3H).

[0344] Step-4: (1S, 2R, 6S, 7R, 9R, 11S, 12S, 15R, 16S)-4-(5-aminopyridin-2-yl)-6-hydroxy-15-[(1S)-1-[(2R)-5-(hydroxymethyl)-4-methyl-6-oxo-3, 6-dihydro-2H-pyran-2-yl]ethyl]-2, 16-dimethyl-8-oxapentacyclo [9.7.0.0^{2,7},⁹.0^{12,16}] octadec-4-en-3-one

To a stirred solution of *tert*-butyl-N-{6-[(1S, 2R, 6S, 7R, 9R, 11S, 12S, 15R, 16S)-6-hydroxy-15-[(1S)-1-[(2R)-5-(hydroxymethyl)-4-methyl-6-oxo-3, 6-dihydro-2H-pyran-2-yl]ethyl]-2, 16-dimethyl-3-oxo-8-oxapentacyclo [9.7.0.0^{2,7},⁹.0^{12,16}] octadec-4-en-4-yl]pyridin-3-yl}carbamate (0.6 g, 905 μ mol) in dichloromethane (6 mL, 93.7 mmol) was added trifluoroacetic acid (1.5 mL) dropwise at 0°C. The reaction mass was stirred for 3 hours at 0°C. After the completion of reaction (monitored by TLC), the reaction mixture was quenched by saturated sodium bicarbonate solution (30 mL) and extracted with dichloromethane (3 x 30

mL). The combined organic layer was dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure to get crude product. The crude residue was purified by preparative HPLC (ABC method) to afford (1S, 2R, 6S, 7R, 9R, 11S, 12S, 15R, 16S)-4-(5-aminopyridin-2-yl)-6-hydroxy-15-[(1S)-1-[(2R)-5-(hydroxymethyl)-4-methyl-6-oxo-3, 6-dihydro-2H-pyran-2-yl]ethyl]-2, 16-dimethyl-8-oxapentacyclo [9.7.0.0^{2,7}.0^{7,9}.0^{12,16}] octadec-4-en-3-one (61 mg, 19.6%, 0.177 μ mol) as yellow solid.

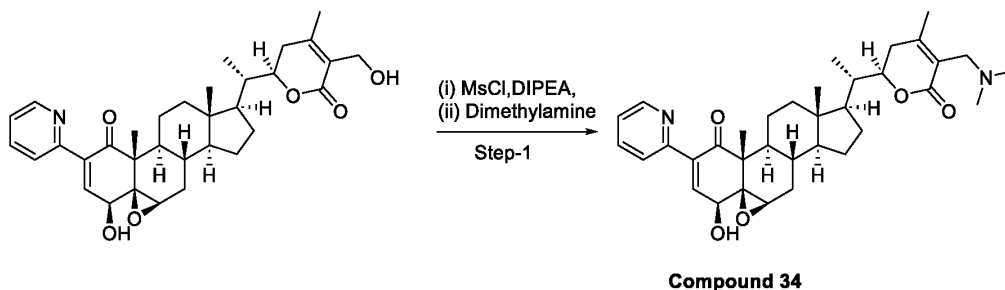
[0345] Analytical data:

LCMS: 93.72% (m/z: 563.5, [M+H]⁺, observed 563.50, [M+H]⁺, 6.11 min (15 min run).

¹H-NMR (400 MHz, DMSO-*d*₆) δ 7.94 (d, *J* = 2.8 Hz, 1H), 7.40 (d, *J* = 6.8 Hz, 1H), 7.07 (d, *J* = 8.8 Hz, 1H), 6.88-6.90 (m, 1H), 5.57 (bs, 3H), 4.59 (bs, 1H), 4.26-4.30 (m, 1H), 4.08-4.17 (q, *J* = 19.6 Hz, 2H), 3.68 (d, *J* = 6.4 Hz, 1H), 3.13 (s, 1H), 2.41-2.50 (m, 1H), 2.01-2.11 (m, 5H), 1.92-1.99 (m, 1H), 1.54-1.89 (m, 3H), 1.22-1.37 (m, 8H), 1.00-1.20 (m, 3H), 0.91-0.95 (m, 5H), 0.65 (s, 3H).

¹³C-NMR (400 MHz, DMSO-*d*₆) δ 201.02, 165.31, 154.66, 144.77, 141.07, 139.49, 136.04, 134.62, 125.43, 122.48, 119.40, 77.52, 68.67, 63.70, 57.56, 55.33, 54.51, 51.02, 47.88, 42.14, 42.0, 30.84, 29.26, 29.01, 26.49, 23.97, 20.55, 19.88, 15.13, 13.02, 11.24.

[0346] Synthesis of Compound 34



[0347] Step-1: Synthesis of (4S, 4aR, 5aR, 6aS, 6bS, 9R, 9aS, 11aS, 11bR)-9-((S)-1-((R)-5-((dimethylamino)methyl)-4-methyl-6-oxo-3, 6-dihydro-2H-pyran-2-yl)ethyl)-4-hydroxy-9a, 11b-dimethyl-2-(pyridin-2-yl)-5a, 6, 6a, 6b, 7, 8, 9, 9a, 10, 11, 11a, 11b-dodecahydrocyclopenta [1, 2] phenanthro [8a,9-b] oxiren-1(4H)-one:

To a stirred solution of (1S, 2R, 6S, 7R, 9R, 11S, 12S, 15R, 16S)-6-hydroxy-15-[(1S)-1-[(2R)-5-(hydroxymethyl)-4-methyl-6-oxo-3, 6-dihydro-2H-pyran-2-yl]ethyl]-2, 16-dimethyl-4-(pyridin-2-yl)-8-oxapentacyclo [9.7.0.0^{2,7}.0^{7,9}.0^{12,16}] octadec-4-en-3-one (250 mg, 456 μ mol)

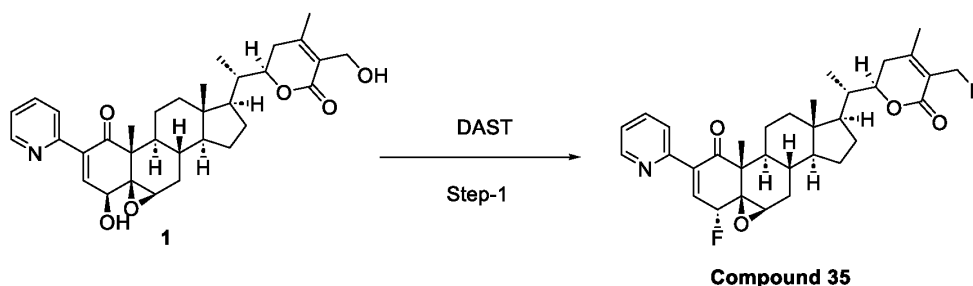
in dichloromethane (2.5 mL, 39 mmol) was added ethylbis (propan-2-yl)amine (147 mg, 2.5 eq., 1.14 mmol) then methanesulfonyl chloride (52.3 mg, 456 μ mol) at 0°C. The reaction mixture was stirred at 0°C for 30 minutes. After the completion of reaction, (monitored by TLC) quenched it with water (40 ml) and extracted with ethyl acetate (2 X 40 ml). The combined organic layer was washed with saturated brine solution, dried over sodium sulphate, filtered and concentrated under reduced pressure to get [(6R)-6-[(1S)-1-[(1S, 2R, 6S, 7R, 9R, 11S, 12S, 15R, 16S)-6-hydroxy-2,16-dimethyl-3-oxo-4-(pyridin-2-yl)-8-oxapentacyclo [9.7.0.0^{2,7}.0^{7,9}.0^{12,16}] octadec-4-en-15-yl]ethyl]-4-methyl-2-oxo-5, 6-dihydro-2H-pyran-3-yl]methyl methanesulfonate. It was forwarded as such to next reaction.

To a stirred solution of dipotassium carbonate (110 mg, 2 eq., 799 μ mol) in acetonitrile (3 mL, 57.4 mmol) was added dimethylamine (27 mg, 1.5 eq., 599 μ mol) followed by addition of [(6R)-6-[(1S)-1-[(1S, 2R, 6S, 7R, 9R, 11S, 12S, 15R, 16S)-6-hydroxy-2, 16-dimethyl-3-oxo-4-(pyridin-2-yl)-8-oxapentacyclo [9.7.0.0^{2,7}.0^{7,9}.0^{12,16}] octadec-4-en-15-yl]ethyl]-4-methyl-2-oxo-5, 6-dihydro-2H-pyran-3-yl] methyl methanesulfonate (250 mg, 0.4 mmol) at 0°C. The resultant reaction mixture was stirred at 60°C for 30 min. After the completion of reaction (monitored by TLC), quenched it with water (40 ml) and extracted with ethyl acetate (2 X 40 ml). The organic layer was washed with saturated brine solution, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to get crude. The crude was purified by using preparative-HPLC using ammonium acetate method to afford (4S, 4aR, 5aR, 6aS, 6bS, 9R, 9aS, 11aS, 11bR)-9-((S)-1-((R)-5-((dimethylamino)methyl)-4-methyl-6-oxo-3, 6-dihydro-2H-pyran-2-yl)ethyl)-4-hydroxy-9a, 11b-dimethyl-2-(pyridin-2-yl)-5a, 6, 6a, 6b, 7, 8, 9, 9a, 10, 11, 11a, 11b-dodecahydrocyclopenta [1, 2] phenanthro [8a, 9-b] oxiren-1(4H)-one (15 mg, 6.53%) as a white solid.

[0348] Analytical data:

LCMS: 88.53% (m/z: 575.50, [M+1]⁺, 4.81 min (10 min run).

¹H-NMR (400 MHz, DMSO-*d*₆): δ 8.60 (d, *J* = 4.40 Hz, 1H), 7.85-7.80 (m, 1H), 7.68 (d, *J* = 6.80 Hz, 1H), 7.39 (d, *J* = 8.40 Hz, 1H), 7.35-7.34 (m, 1H), 5.74 (d, *J* = 3.60 Hz, 1H), 4.29-4.26 (m, 1H), 3.76 (dd, *J* = 3.20, 6.80 Hz, 1H), 3.18 (d, *J* = 10.8 Hz, 2H), 2.98 (d, *J* = 12.4 Hz, 1H), 2.39 (d, *J* = 4.40 Hz, 1H), 2.12 (d, *J* = 2.80 Hz, 1H), 2.07 (s, 6H), 2.02-1.98 (m, 4H), 1.93-1.90 (m, 1H), 1.79-1.75 (m, 3H), 1.60-1.19 (m, 8H), 1.14-1.04 (m, 4H), 0.97-0.87 (m, 4H), 0.66 (s, 3H).

[0349] Synthesis of Compound 35

[0350] Step-1: Synthesis of (4R, 4aS, 5aR, 6aS, 6bS, 9R, 9aS, 11aS, 11bR)-4-fluoro-9-((S)-1-((R)-5-(fluoromethyl)-4-methyl-6-oxo-3, 6-dihydro-2H-pyran-2-yl)ethyl)-9a, 11b-dimethyl-2-(pyridin-2-yl)-5a, 6, 6a, 6b, 7, 8, 9, 9a, 10, 11, 11a, 11b-dodecahydrocyclopenta [1, 2] phenanthro [8a, 9-b] oxiren-1(4H)-one

To a stirred solution of (4S, 4aR, 5aR, 6aS, 6bS, 9R, 9aS, 11aS, 11bR)-4-hydroxy-9-((S)-1-((R)-5-(hydroxymethyl)-4-methyl-6-oxo-3, 6-dihydro-2H-pyran-2-yl)ethyl)-9a, 11b-dimethyl-2-(pyridin-2-yl)-5a, 6, 6a, 6b, 7, 8, 9, 9a, 10, 11, 11a, 11b-dodecahydrocyclopenta [1, 2] phenanthro [8a, 9-b] oxiren-1(4H)-one (0.5 g, 0.913 mmol) in dichloromethane (10 mL) was added diethyl(trifluoro- λ^4 -sulfany)amine (0.241 mL, 2 eq., 1.83 mmol) (dissolved in DCM (1 mL)) dropwise at -78 °C under inert atmosphere and stirred for 15 min. After completion of reaction (monitored by TLC and by LCMS), quenched it by saturated Sodium bicarbonate solution (20 mL) and extracted using dichloromethane (3 x 30 mL). Collected organics, dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure to obtain crude. The crude was purified by combi-flash chromatography over silica column (10-20% ethyl acetate in hexane) followed by prep HPLC purification in ammonium acetate method to yield (4R, 4aS, 5aR, 6aS, 6bS, 9R, 9aS, 11aS, 11bR)-4-fluoro-9-((S)-1-((R)-5-(fluoromethyl)-4-methyl-6-oxo-3, 6-dihydro-2H-pyran-2-yl)ethyl)-9a, 11b-dimethyl-2-(pyridin-2-yl)-5a, 6, 6a, 6b, 7, 8, 9, 9a, 10, 11, 11a, 11b-dodecahydrocyclopenta [1, 2] phenanthro [8a, 9-b] oxiren-1(4H)-one (7 mg, 0.0127 mmol, 2%) as white solid.

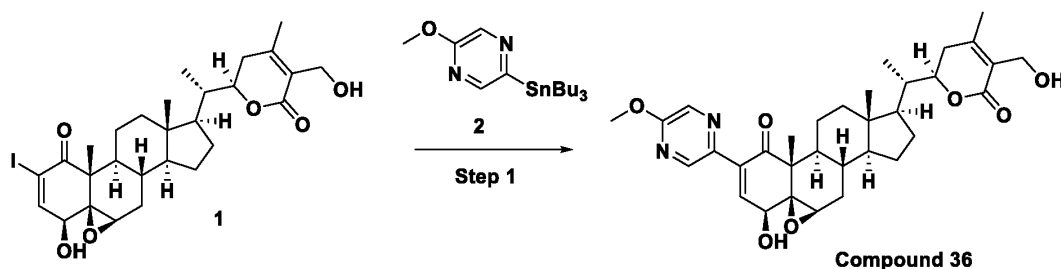
[0351] Analytical data:

LCMS: 97.63% (m/z: 552.50, $[M+1]^+$, 6.87 min (10 min run).

¹H-NMR (400 MHz, DMSO-*d*₆): δ 8.62 (d, *J* = 4.4 Hz, 1H), 7.85 (t, *J* = 7.6 Hz, 1H), 7.56 (d, *J* = 16.8 Hz, 1H), 7.47 (d, *J* = 7.6 Hz, 1H), 7.40-7.37 (m, 1H), 5.87 (d, *J* = 50.1 Hz, 1H), 5.19 – 5.14 (m, 1H), 5.07 – 5.02 (m, 1H), 4.36 (d, *J* = 12.8 Hz, 1H), 3.52 (s, 1H), 2.32-2.21 (m, 1H), 2.08-2.05 (m, 4H), 1.93-1.29 (m, 9H), 1.23 (s, 3H), 1.16-0.97 (m, 5H), 0.93 (d, *J* = 6.4 Hz, 3H), 0.68 (s, 3H).

¹⁹F-NMR (400 MHz, DMSO-*d*₆): δ 201.92, 206.73.

[0352] Synthesis of Compound 36



[0353] Step-1: Synthesis of (4S, 4aR, 5aR, 6aS, 6bS, 9R, 9aS, 11aS, 11bR)-4-hydroxy-9-((S)-1-((R)-5-(hydroxymethyl)-4-methyl-6-oxo-3, 6-dihydro-2H-pyran-2-yl)ethyl)-2-(5-methoxypyrazin-2-yl)-9a, 11b-dimethyl-5a, 6, 6a, 6b, 7, 8, 9, 9a, 10, 11, 11a, 11b-dodecahydrocyclopenta [1, 2] phenanthro [8a, 9-b] oxiren-1(4H)-one

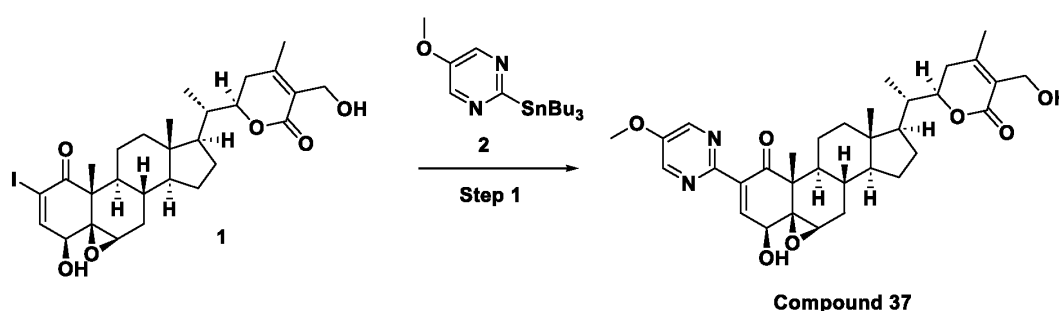
A stirred solution of (1S, 2R, 6S, 7R, 9R, 11S, 12S, 15R, 16S)-6-hydroxy-15-[(1S)-1-[(2R)-5-(hydroxymethyl)-4-methyl-6-oxo-3, 6-dihydro-2H-pyran-2-yl]ethyl]-4-iodo-2, 16-dimethyl-8-oxapentacyclo [9.7.0.0.2^{7,10},7.0^{9,12},16] octadec-4-en-3-one (0.2 g, 335 μ mol), 2-methoxy-5-(tributylstannyl) pyrazine (161 mg, 1.2 eq., 402 μ mol), triphenylarsine (10.3 mg, 0.1 eq., 33.5 μ mol) and diiodocopper (16 mg, 0.15 eq., 50.3 μ mol) in tetrahydrofuran (5 mL, 61.4 mmol) were purged with nitrogen for 35 min. Added palladium—(1E,4E)-1,5-diphenyl-1,4-pentadien-3-one (2/3) (15.4 mg, 0.05 eq., 16.8 μ mol) and again purged with nitrogen for 5 min. The reaction was stirred at 80°C for 8h. After completion of reaction (monitoring by TLC). The reaction mixture was cooled & quenched with water (50 mL) and was extracted with ethyl acetate (3 x 50 mL). The combined organic layer was dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure to afford the crude, which was purified in prep-HPLC by ABC method to get (4S, 4aR, 5aR, 6aS, 6bS, 9R, 9aS, 11aS, 11bR)-4-hydroxy-9-((S)-1-((R)-5-(hydroxymethyl)-4-methyl-6-oxo-3,6-dihydro-2H-pyran-2-yl)ethyl)-2-(5-

methoxypyrazin-2-yl)-9a,11b-dimethyl-5a, 6, 6a, 6b, 7, 8, 9, 9a, 10, 11, 11a, 11b-dodecahydrocyclopenta [1, 2] phenanthro [8a, 9-b] oxiren-1(4H)-one (39 mg, 20.1%) as white solid.

[0354] Analytical data: 98.57 % (m/z: 579.5, $[M+1]^+$, 5.62 min (10 min run).

¹H-NMR (400 MHz, DMSO-*d*₆): δ 8.36 (d, *J* = 1.60 Hz, 1H), 8.22 (d, *J* = 1.20 Hz, 1H), 7.60 (d, *J* = 6.80 Hz, 1H), 5.78 (d, *J* = 3.20 Hz, 1H), 4.60 (t, *J* = 5.60 Hz, 1H), 4.26-4.30 (m, 1H), 4.07-4.18 (m, 2H), 3.93 (s, 3H), 3.74-3.77 (m, 1H), 3.17 (s, 1H), 2.33-2.50 (m, 1H), 2.07-2.11 (m, 1H), 2.06 (s, 3H), 1.55-2.02 (m, 4H), 1.22-1.40 (m, 8H), 0.86-1.14 (m, 8H), 0.66 (s, 3H).

[0355] Synthesis of Compound 37



[0356] Step-1: Synthesis of (1S, 2R, 6S, 7R, 9R, 11S, 12S, 15R, 16S)-6-hydroxy-15-[(1S)-1-[(2R)-5-(hydroxymethyl)-4-methyl-6-oxo-3, 6-dihydro-2H-pyran-2-yl]ethyl]-4-(5-methoxypyrimidin-2-yl)-2, 16-dimethyl-8-oxapentacyclo [9.7.0.0^{2,7}.0^{7,9}.0^{12,16}] octadec-4-en-3-one

To a stirred solution of (1S, 2R, 6S, 7R, 9R, 11S, 12S, 15R, 16S)-6-hydroxy-15-[(1S)-1-[(2R)-5-(hydroxymethyl)-4-methyl-6-oxo-3, 6-dihydro-2H-pyran-2-yl]ethyl]-4-iodo-2, 16-dimethyl-8-oxapentacyclo [9.7.0.0^{2,7}.0^{7,9}.0^{12,16}] octadec-4-en-3-one (0.2 g, 0.335 mmol) and 5-methoxy-2-(tributylstannyl) pyrimidine (0.2g, 1.5 eq., 0.503 mmol) in N,N-dimethylformamide (4 mL) were added triphenylarsane (0.010 g, 0.1 eq., 0.033 mmol) and

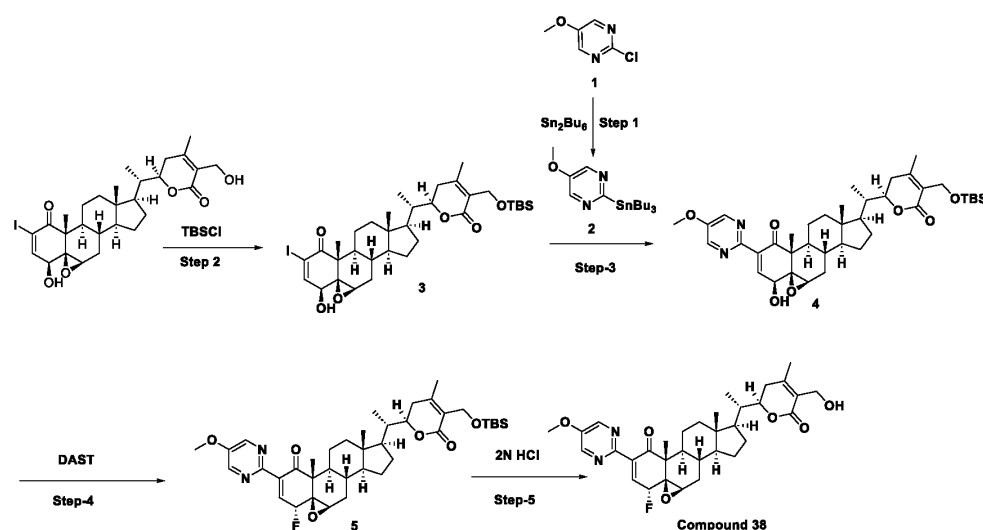
copper(1+) iodide (0.009 g, 0.15 eq., 0.05 mmol). The resulting reaction mixture was purged with argon for 30 min. Added tris((1E,4E)-1,5-diphenylpenta-1,4-dien-3-one) dipalladium (0.03 g, 0.1 eq., 0.033 mmol) and purged with argon for 5min. Stirred at 60°C for 3h. Cooled to room temperature. Quenched with water (50 mL) and extracted using ethyl acetate (3 x 50 mL). Collected organics, dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure to obtain crude. The crude product was purified by combi flash column chromatography using (70-90%) ethyl acetate in hexane as an eluent followed by Prep HPLC purification in ammonium acetate method to afford (1S, 2R, 6S, 7R, 9R, 11S, 12S, 15R, 16S)-6-hydroxy-15-[(1S)-1-[(2R)-5-(hydroxymethyl)-4-methyl-6-oxo-3, 6-dihydro-2H-pyran-2-yl]ethyl]-4-(5-methoxypyrimidin-2-yl)-2, 16-dimethyl-8-oxapentacyclo [9.7.0.0^{2,7}.0^{3,9}.0^{12,16}] octadec-4-en-3-one (0.027 g, 0.046 mmol, 14%) as white solid.

[0357] **Analytical data:** 99.25% (m/z: 579.5, [M+1]⁺, 5.24 min (10 min run).

¹H-NMR (400 MHz, DMSO-*d*₆): δ 8.57 (s, 2H), 7.53 (d, *J*=6.8, 1H), 5.76 (d, *J*= 3.6 Hz, 1H), 4.60 (t, *J*= 5.6 Hz, 1H), 4.30-4.26 (m, 1H), 4.18-4.07 (m, 2H), 3.92 (s, 3H), 3.74-3.71 (m, 1H), 3.13 (s, 1H), 2.40-2.32 (m, 1H), 2.13-2.07 (m, 2H), 1.99 (s, 3H), 1.92-1.90 (m, 2H), 1.80-1.71 (m, 2H), 1.57-1.48 (m, 2H), 1.39-1.23 (m, 7H), 1.16-1.04 (m, 3H), 0.93 (m, 5H), 0.65 (s, 3H).

¹³C-NMR (400 MHz, DMSO-*d*₆): δ 199.02, 165.33, 155.23, 154.70, 152.06, 143.61, 141.42, 139.96, 125.44, 77.54, 68.57, 63.83, 57.45, 56.19, 55.47, 54.51, 51.04, 42.03, 41.80, 30.89, 29.06, 29.02, 26.52, 23.98, 22.51, 21.21, 20.19, 19.90, 14.82, 13.05, 11.24.

[0358] Synthesis of Compound 38



[0359] Step-1: Synthesis of 5-methoxy-2-(tributylstannyl)pyrimidine

To a stirred solution of 2-chloro-5-methoxypyrimidine (1 g, 6.92 mmol) in toluene (10 mL) was added hexabutylstannane (5.62 g, 1.4 eq., 9.68 mmol). The reaction mixture was purged with argon gas for 30 min then Tetrakis (triphenylphosphine) palladium(0) (0.399 g, 0.05 eq., 0.346 mmol) was added to it. The reaction mixture was again purged with argon gas for 5 min. The reaction was stirred at 110°C for 16h. After completion of the reaction, the mixture was filtered through celite bed and washed with ethyl acetate. The filtrate was concentrated to get the crude which was then purified by column chromatography using 0-10% ethyl acetate in heptane as an eluent to afford 5-methoxy-2-(tributylstannyl) pyrimidine (1 g, 2.51 mmol, 36%) as colourless liquid.

[0360] Analytical data:

LCMS: 99.0% (m/z: 401.15, [M+1]⁺, 3.48 min (4 min run).

[0361] Step-2: Synthesis of (4S, 4aR, 5aR, 6aS, 6bS, 9R, 9aS, 11aS, 11bR)-9-((S)-1-((R)-5-(((tert-butyldimethylsilyl) oxy) methyl)-4-methyl-6-oxo-3, 6-dihydro-2H-pyran-2-yl)ethyl)-4-hydroxy-2-iodo-9a, 11b-dimethyl-5a, 6, 6a, 6b, 7, 8, 9, 9a, 10, 11, 11a, 11b-dodecahydrocyclopenta [1, 2] phenanthro [8a, 9-b] oxiren-1(4H)-one:

To a stirred solution of (4S, 4aR, 5aR, 6aS, 6bS, 9R, 9aS, 11aS, 11bR)-4-hydroxy-9-((S)-1-((R)-5-(hydroxymethyl)-4-methyl-6-oxo-3, 6-dihydro-2H-pyran-2-yl)ethyl)-2-iodo-9a, 11b-dimethyl-5a, 6, 6a, 6b, 7, 8, 9, 9a, 10, 11, 11a, 11b-dodecahydrocyclopenta [1, 2] phenanthro [8a, 9-b] oxiren-1(4H)-one (5 g, 8.38 mmol) in dimethylformamide (0.1 L, 1.29 mol) was added 4-(pyrrolidin-1-yl)pyridin-1-ium (6.25 g, 5 eq., 41.9 mmol). After 10 minutes tert-butyl (chloro) dimethylsilane (12.6 g, 10 eq., 83.8 mmol) was added and heated the reaction up to 85 °C for 3hrs. After completion of reaction (monitored by TLC) the mixture was diluted with ice cold water (50 mL) and extracted with ethyl acetate (3 x 50 mL). The combined organic layer was washed with saturated brine solution (50 mL), dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure to obtain the crude material, which was purified by column chromatography in 0 - 100% ethyl acetate in Heptane to obtain the compound (4S, 4aR, 5aR, 6aS, 6bS, 9R, 9aS, 11aS, 11bR)-9-((S)-1-((R)-5-(((tert-butyldimethylsilyl)oxy)methyl)-4-methyl-6-oxo-3, 6-dihydro-2H-pyran-2-yl)ethyl)-4-hydroxy-2-iodo-9a, 11b-dimethyl-5a, 6, 6a, 6b, 7, 8, 9, 9a, 10, 11, 11a, 11b-

dodecahydrocyclopenta [1, 2] phenanthro [8a, 9-b] oxiren-1(4H)-one (1.8 g, 2.41 mmol, 29%) as off white solid.

[0362] Analytical data:

LCMS: 95.79% (m/z: 711.10, [M+H]⁺, 4.10 min (6 min run).

¹H-NMR (400 MHz, DMSO-*d*₆): δ 5.89 (d, *J* = 4.00 Hz, 1H), 4.27-4.35 (m, 3H), 3.48-3.51 (m, 1H), 3.19 (s, 1H), 2.31-2.51 (m, 1H), 2.16 (d, *J* = 2.80 Hz, 1H), 2.02 (m, 4H), 1.51-1.90 (m, 4H), 1.21-1.38 (m, 8H), 0.91-1.20 (m, 8H), 0.85 (s, 9H), 0.64 (s, 3H), 0.41 (s, 6H).

[0363] Step-3: Synthesis of (1S, 2R, 6S, 7R, 9R, 11S, 12S, 15R, 16S)-15-[(1S)-1-[(2R)-5-[[tert-butyl(dimethylsilyl)oxy]methyl]-4-methyl-6-oxo-3, 6-dihydro-2H-pyran-2-yl]ethyl]-6-hydroxy-4-(5-methoxypyrimidin-2-yl)-2, 16-dimethyl-8-oxapentacyclo [9.7.0.0^{2,7}.0^{9,12},16] octadec-4-en-3-one

To a stirred solution of (1S, 2R, 6S, 7R, 9R, 11S, 12S, 15R, 16S)-15-[(1S)-1-[(2R)-5-[[tert-butyl(dimethylsilyl)oxy]methyl]-4-methyl-6-oxo-3, 6-dihydro-2H-pyran-2-yl]ethyl]-6-hydroxy-4-iodo-2, 16-dimethyl-8-oxapentacyclo [9.7.0.0^{2,7}.0^{9,12},16] octadec-4-en-3-one (0.8 g, 1.13 mmol) and 5-methoxy-2-(tributylstannyl) pyrimidine (0.674 g, 1.5 eq., 1.69 mmol) in THF (10 mL) were added triphenylarsane (0.035 g, 0.1 eq., 0.113 mmol) and λ^1 -copper(1+) iodide (0.032 g, 0.15 eq., 0.169 mmol) at room temperature. The resulting mixture was purged with argon for 30 min. After that tris ((1E,4E)-1,5-diphenylpenta-1,4-dien-3-one) dipalladium (0.103 g, 0.1 eq., 0.113 mmol) was added to the mixture and stirred for 3h at 85°C. After completion of the reaction (monitored by TLC and LCMS), it was quenched by adding water (50 mL) and extracted with ethyl acetate (3 x 50 mL). The combined organics were dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure to obtain crude, which was purified by combi flash column chromatography on silica column using (70-90%) ethyl acetate in heptane as an eluent to afford (1S, 2R, 6S, 7R, 9R, 11S, 12S, 15R, 16S)-15-[(1S)-1-[(2R)-5-[[tert-butyl(dimethylsilyl)oxy]methyl]-4-methyl-6-oxo-3, 6-dihydro-2H-pyran-2-yl]ethyl]-6-hydroxy-4-(5-methoxypyrimidin-2-yl)-2, 16-dimethyl-8-oxapentacyclo [9.7.0.0^{2,7}.0^{9,12},16] octadec-4-en-3-one (0.15 g, 19%) as an off white solid.

[0364] Analytical data: LCMS: 98.06% (m/z: 693.26, [M+1]⁺, 3.03 min (4 min run).

[0365] Step-4: Synthesis of (1S, 2R, 6R, 7S, 9R, 11S, 12S, 15R, 16S)-15-[(1S)-1-[(2R)-5-[[tert-butyl(dimethylsilyl)oxy]methyl]-4-methyl-6-oxo-3, 6-dihydro-2H-pyran-2-

yl]ethyl]-6-fluoro-4-(5-methoxypyrimidin-2-yl)-2, 16-dimethyl-8-oxapentacyclo [9.7.0.0^{2,7},⁹.0^{12,16}] octadec-4-en-3-one:

To a stirred solution of (1S, 2R, 6S, 7R, 9R, 11S, 12S, 15R, 16S)-15-[(1S)-1-[(2R)-5-[[tert-butyl(dimethylsilyl)oxy]methyl]-4-methyl-6-oxo-3, 6-dihydro-2H-pyran-2-yl]ethyl]-6-hydroxy-4-(5-methoxypyrimidin-2-yl)-2, 16-dimethyl-8-oxapentacyclo [9.7.0.0^{2,7},⁹.0^{12,16}] octadec-4-en-3-one (0.15 g, 0.216 mmol) in dichloromethane (5 mL) was added diethyl(trifluoro- λ^4 -sulfanyl) amine solution (0.034 mL, 1.2 eq., 0.26 mmol) (dissolved in DCM (1 mL)) drop wise at -78°C under inert atmosphere and stirred for 15 min. After completion of reaction (monitored by TLC and by LCMS), quenched by adding saturated Sodium bicarbonate solution (30 mL) and extracted using dichloromethane (2 x 30 mL). Collected organics, dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure to obtain crude, which was purified by combi-flash chromatography on silica column (10-20% ethyl acetate in heptane) to yield (1S, 2R, 6R, 7S, 9R, 11S, 12S, 15R, 16S)-15-[(1S)-1-[(2R)-5-[[tert-butyl(dimethylsilyl)oxy]methyl]-4-methyl-6-oxo-3, 6-dihydro-2H-pyran-2-yl]ethyl]-6-fluoro-4-(5-methoxypyrimidin-2-yl)-2, 16-dimethyl-8-oxapentacyclo [9.7.0.0^{2,7},⁹.0^{12,16}] octadec-4-en-3-one (0.055 mg, 0.079 mmol, 36%) as off white solid.

[0366] Analytical data: LCMS: 78.08% (m/z: 695.30, [M+1]⁺, 4.52 min (6 min run).

[0367] Step-5: Synthesis of (1S, 2R, 6R, 7S, 9R, 11S, 12S, 15R, 16S)-6-fluoro-15-[(1S)-1-[(2R)-5-(hydroxymethyl)-4-methyl-6-oxo-3, 6-dihydro-2H-pyran-2-yl]ethyl]-4-(5-methoxypyrimidin-2-yl)-2, 16-dimethyl-8-oxapentacyclo [9.7.0.0^{2,7},⁹.0^{12,16}] octadec-4-en-3-one:

To a solution of (1S, 2R, 6R, 7S, 9R, 11S, 12S, 15R, 16S)-15-[(1S)-1-[(2R)-5-[[tert-butyl(dimethylsilyl)oxy]methyl]-4-methyl-6-oxo-3, 6-dihydro-2H-pyran-2-yl]ethyl]-6-fluoro-4-(5-methoxypyrimidin-2-yl)-2, 16-dimethyl-8-oxapentacyclo [9.7.0.0^{2,7},⁹.0^{12,16}] octadec-4-en-3-one (50 mg, 0.309 mmol) in THF (0.5 mL) and methanol (0.5 mL) was added 2N HCl solution (0.5 mL) drop wise at 0°C and stirred for 30 min. After completion of the reaction (monitored by TLC and LCMS), it was quenched by adding sodium bicarbonate solution (20 mL). It was then extracted using dichloromethane (2 x 20 mL). Collected organics, dried over sodium sulphate and concentrated under reduced pressure to obtain crude which was then purified by combi-flash chromatography (5% methanol and dichloromethane) followed by prep HPLC purification in ammonium acetate method to afford (1S, 2R, 6R, 7S, 9R, 11S, 12S, 15R,

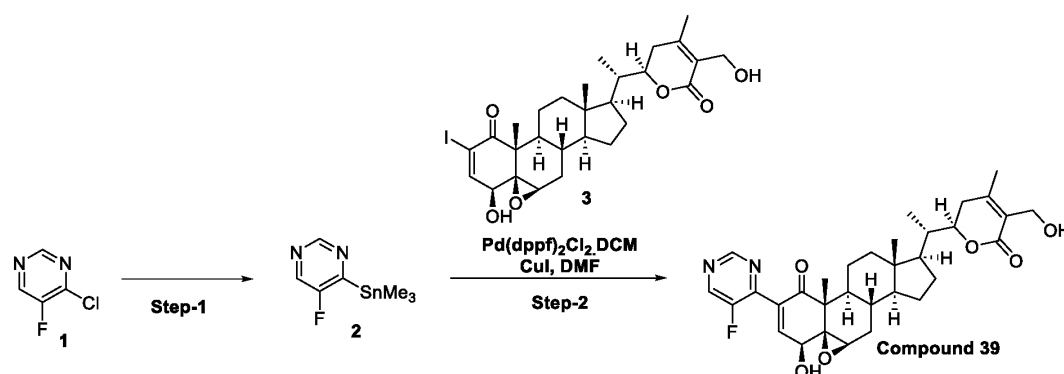
16S)-6-fluoro-15-[(1S)-1-[(2R)-5-(hydroxymethyl)-4-methyl-6-oxo-3, 6-dihydro-2H-pyran-2-yl]ethyl]-4-(5-methoxypyrimidin-2-yl)-2, 16-dimethyl-8 oxapentacyclo [9.7.0.0^{2,7}.0^{7,9}.0^{12,16}] octadec-4-en-3-one (10.8 mg, 60%) as white solid.

[0368] Analytical data: 92.82% (m/z: 581.5, [M+1]⁺, 7.65 min (14 min run).

¹H-NMR (400 MHz, DMSO-*d*₆): δ 8.60 (s, 2H), 7.41 (dd, $J = 1.6$ Hz, 16.8 Hz, 1H), 5.85 (d, $J = 50.0$ Hz, 1H), 4.60 (t, $J = 5.6$ Hz, 1H), 4.30-4.27 (m, 1H), 4.18-4.07 (m, 2H), 3.93 (s, 3H), 3.50 (s, 1H), 2.43-2.32 (m, 1H), 2.13-2.06 (m, 2H), 2.00 (s, 3H), 1.93-1.89 (m, 2H), 1.81-1.71 (m, 2H), 1.58 (br, 2H), 1.40-1.27 (m, 4H), 1.20 (s, 3H), 1.18-0.98 (m, 4H), 0.93 (d, $J = 6.4$ Hz, 3H), 0.67 (s, 3H).

¹⁹F-NMR (400 MHz, DMSO-*d*₆): δ 202.31

[0369] Synthesis of Compound 39



[0370] Step-1: Synthesis of 5-fluoro-4-(trimethylstannyl)pyrimidine:

To a stirred solution of 4-chloro-5-fluoropyrimidine (0.5 g, 3.77 mmol) in dry toluene (8 mL, 75.3 mmol) added hexamethyldistannane (1.85 g, 1.5 eq., 5.66 mmol). The reaction mixture was purged with argon gas for 30 min. Then tetrakis(triphenylphosphane) palladium (218 mg, 0.05 eq., 189 μmol) was added. Again, the reaction mixture was purged with argon gas for 5 min. The reaction mixture was heated at 110 °C for 3h. Monitored the reaction by TLC. Cooled the reaction mass to room temperature. The crude residue was poured into a KF solution (100

mL) and extracted with EtOAc (3 X 50 mL), dried over Na₂SO₄, filtered and evaporated under vacuum to get crude residue. The crude was directly forwarded to the next step without further purification. LCMS mass not supported. TLC showed prominent non-polar spot.

[0371] Step-2: Synthesis of (1S, 2R, 6S, 7R, 9R, 11S, 12S, 15R, 16S)-4-(5-fluoropyrimidin-4-yl)-6-hydroxy-15-[(1S)-1-[(2R)-5-(hydroxymethyl)-4-methyl-6-oxo-3,6-dihydro-2H-pyran-2-yl]ethyl]-2, 16-dimethyl-8-oxapentacyclo [9.7.0.0^{2,7},⁹.0^{12,16}] octadec-4-en-3-one:

A stirred solution of (1S, 2R, 6S, 7R, 9R, 11S, 12S, 15R, 16S)-6-hydroxy-15-[(1S)-1-[(2R)-5-(hydroxymethyl)-4-methyl-6-oxo-3, 6-dihydro-2H-pyran-2-yl]ethyl]-4-iodo-2, 16-dimethyl-8-oxapentacyclo [9.7.0.0^{2,7},⁹.0^{12,16}] octadec-4-en-3-one (0.5 g, 838 μmol), 5-fluoro-4-(trimethylstannyl) pyrimidine (437 mg, 2 eq., 1.68 mmol) and λ¹-copper(1+) iodide (23.9 mg, 0.15 eq., 126 μmol) in dimethylformamide (5 mL, 64.6 mmol) were purged with N₂ gas for 35 min, followed by addition of [1,1'-Bis (diphenylphosphino) ferrocene] dichloropalladium(II) (34.2 mg, 0.05 eq., 41.9 μmol). The reaction mixture was again purged with N₂ gas for 5 min. The reaction vessel was sealed and stirred at 60°C for 16h. The reaction was monitored by TLC (SM was consumed) and was quenched by adding ice-cold water (30 mL). The aqueous layer was extracted with ethyl acetate (3 x 20 mL). The organic layer was dried over anhydrous sodium sulphate and filtered. The filtrate was evaporated by high vacuum to get the crude residue, which was purified by prep. HPLC (ABC method) to afforded (1S, 2R, 6S, 7R, 9R, 11S, 12S, 15R, 16S)-4-(5-fluoropyrimidin-4-yl)-6-hydroxy-15-[(1S)-1-[(2R)-5-(hydroxymethyl)-4-methyl-6-oxo-3, 6-dihydro-2H-pyran-2-yl]ethyl]-2, 16-dimethyl-8-oxapentacyclo [9.7.0.0^{2,7},⁹.0^{12,16}] octadec-4-en-3-one (62 mg, 13.05%) desired compound.

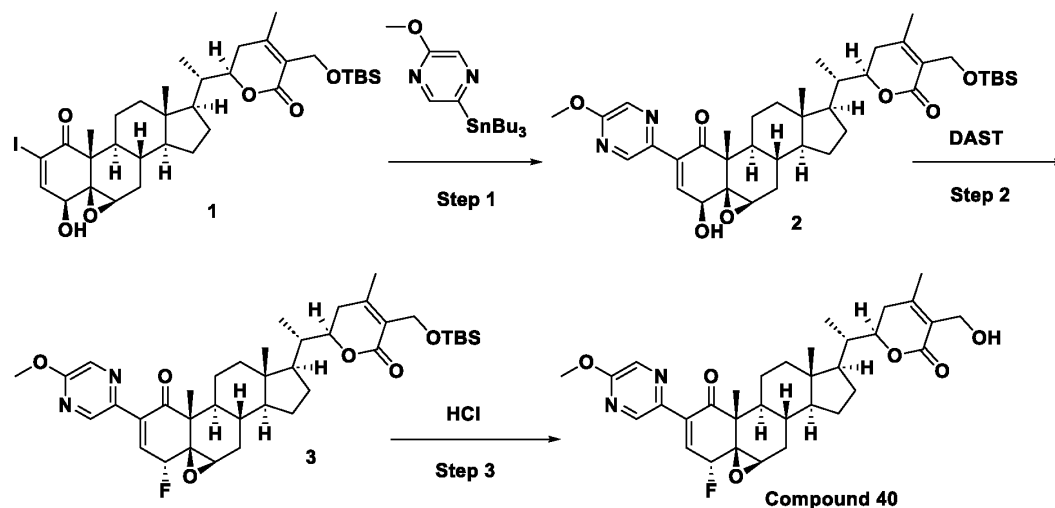
[0372] Analytical data:

LCMS: 98.77% (m/z: 567.70, [M+1]⁺, 5.33 min (10 min run).

¹H-NMR (400 MHz, DMSO-*d*₆): δ 8.93 (s, 2H), 7.64 (d, *J* = 6.8 Hz, 1H), 5.83 (d, *J* = 4.0 Hz, 1H), 4.60 (t, *J* = 5.2 Hz, 1H), 4.28 (m, 1H), 4.18 - 4.07 (m, 2H), 3.67 - 3.74 (m, 1H), 3.15 (s, 1H), 2.49-2.39 (m, 1H), 2.18 - 2.07 (m, 5H), 1.93-1.63 (m, 3H), 1.61 - 1.44 (m, 2H), 1.39-1.23 (m, 7H), 1.18-1.04 (m, 3H), 0.98 - 0.05 (m, 5H), 0.66 (s, 3H).

¹³C-NMR (400 MHz, DMSO-*d*₆): 198.75, 165.33, 158.94, 158.89, 157.85, 155.23, 154.70, 145.67, 145.47, 142.22, 140.73, 125.44, 77.54, 68.47, 63.69, 57.47, 55.44, 54.52, 51.03, 47.86, 30.84, 29.06, 26.53, 23.98, 21.29, 20.19, 19.9, 14.86, 13.05, 11.24.

[0373] Synthesis of Compound 40



[0374] **Step-1: Synthesis of (4S, 4aR, 5aR, 6aS, 6bS, 9R, 9aS, 11aS, 11bR)-9-((S)-1-((R)-5-(((tert-butyldimethylsilyl)oxy)methyl)-4-methyl-6-oxo-3, 6-dihydro-2H-pyran-2-yl)ethyl)-4-hydroxy-2-(5-methoxypyrazin-2-yl)-9a, 11b-dimethyl-5a, 6, 6a, 6b, 7, 8, 9, 9a, 10, 11, 11a, 11b-dodecahydrocyclopenta [1, 2] phenanthro [8a, 9-b] oxiren-1(4H)-one**

To a stirred solution of (1S, 2R, 6S, 7R, 9R, 11S, 12S, 15R, 16S)-15-[(1S)-1-[(2R)-5-[(tert-butyldimethylsilyl)oxy]methyl]-4-methyl-6-oxo-3, 6-dihydro-2H-pyran-2-yl]ethyl]-6-hydroxy-4-iodo-2, 16-dimethyl-8-oxapentacyclo [9.7.0.0²,7.0⁷,9.0¹²,16] octadec-4-en-3-one (1 g, 1.41 mmol), 2-methoxy-5-(tributylstannyl)pyrazine (618 mg, 1.1 eq., 1.55 mmol), triphenylarsine (43.1 mg, 0.1 eq., 141 μmol) and diiodocopper (67 mg, 0.15 eq., 211 μmol) in tetrahydrofuran (12 mL). The reaction mixture was purged with nitrogen for 35 min and palladium—(1E,4E)-1,5-diphenyl-1,4-pentadien-3-one (2/3) (64.4 mg, 0.05 eq., 70.3 μmol) was added to it. The reaction mixture was again purged with nitrogen for 5 min. The reaction was stirred at 60°C for 2h. After completion of reaction (monitoring by TLC), the reaction mixture was cooled & quenched water (50 mL) and extracted with ethyl acetate (2 x 50 mL). The organic layer was dried over sodium sulphate, filtered and concentrated under vacuum to afford the crude. The crude residue was purified through combi-flash purifier (12 g silica gel

welch column) and eluted with 40-50% EtOAc in heptane. The pure fractions were collected and evaporated under reduced pressure to get desired product (4S, 4aR, 5aR, 6aS, 6bS, 9R, 9aS, 11aS, 11bR)-9-((S)-1-((R)-5-(((tert-butyldimethylsilyl)oxy)methyl)-4-methyl-6-oxo-3, 6-dihydro-2H-pyran-2-yl)ethyl)-4-hydroxy-2-(5-methoxypyrazin-2-yl)-9a, 11b-dimethyl-5a, 6, 6a, 6b, 7, 8, 9, 9a, 10, 11, 11a, 11b-dodecahydrocyclopenta [1, 2] phenanthro [8a, 9-b] oxiren-1(4H)-one (350 mg, 35%) as yellowish solid.

[0375] Analytical data: 66.8 % (m/z: 693.20, [M+1]⁺, 2.67 min (4 min run).

[0376] Step-2: Synthesis of (4R, 4aS, 5aR, 6aS, 6bS, 9R, 9aS, 11aS, 11bR)-9-((S)-1-((R)-5-(((tert-butyldimethylsilyl)oxy)methyl)-4-methyl-6-oxo-3, 6-dihydro-2H-pyran-2-yl)ethyl)-4-fluoro-2-(5-methoxypyrazin-2-yl)-9a, 11b-dimethyl-5a, 6, 6a, 6b, 7, 8, 9, 9a, 10, 11, 11a, 11b-dodecahydrocyclopenta [1, 2] phenanthro [8a, 9-b] oxiren-1(4H)-one

To a stirred solution of (4S, 4aR, 5aR, 6aS, 6bS, 9R, 9aS, 11aS, 11bR)-9-((S)-1-((R)-5-(((tert-butyldimethylsilyl)oxy)methyl)-4-methyl-6-oxo-3, 6-dihydro-2H-pyran-2-yl)ethyl)-4-hydroxy-2-(5-methoxypyrazin-2-yl)-9a, 11b-dimethyl-5a, 6, 6a, 6b, 7, 8, 9, 9a, 10, 11, 11a, 11b-dodecahydrocyclopenta [1, 2] phenanthro [8a, 9-b] oxiren-1(4H)-one (230 mg, 332 μmol) in dichloromethane (3 mL) at -78°C, was added diethyl(trifluoro-λ⁴-sulfanyl) amine (52.6 μL, 1.2 eq., 398 μmol) dissolved in DCM (1 mL) drop wise under inert atmosphere and stirred for 15 min. After completion of reaction (monitored by TLC and by LCMS), quenched by adding saturated sodium bicarbonate solution (30 mL) and extracted using dichloromethane (2 x 30 mL). Collected organics, dried over sodium sulphate, filtered and concentrated under reduced pressure to obtain crude. The crude residue obtained was purified by combi-flash purifier (4g gel welch column) and eluted with 10-15% ethyl acetate in heptane. The pure fractions were collected and evaporated under reduced pressure to get desired product (4R, 4aS, 5aR, 6aS, 6bS, 9R, 9aS, 11aS, 11bR)-9-((S)-1-((R)-5-(((tert-butyldimethylsilyl)oxy)methyl)-4-methyl-6-oxo-3, 6-dihydro-2H-pyran-2-yl)ethyl)-4-fluoro-2-(5-methoxypyrazin-2-yl)-9a, 11b-dimethyl-5a, 6, 6a, 6b, 7, 8, 9, 9a, 10, 11, 11a, 11b-dodecahydrocyclopenta [1, 2] phenanthro [8a, 9-b] oxiren-1(4H)-one (0.1 g, 43%) as yellowish solid.

[0377] Analytical data: 49.91 % (m/z: 695.35, [M+1]⁺, 4.39 min (6 min run).

[0378] Step-3: Synthesis of (4R, 4aS, 5aR, 6aS, 6bS, 9R, 9aS, 11aS, 11bR)-4-fluoro-9-((S)-1-((R)-5-(hydroxymethyl)-4-methyl-6-oxo-3, 6-dihydro-2H-pyran-2-yl)ethyl)-2-(5-

methoxypyrazin-2-yl)-9a, 11b-dimethyl-5a, 6, 6a, 6b, 7, 8, 9, 9a, 10, 11, 11a, 11b-dodecahydrocyclopenta [1, 2] phenanthro [8a, 9-b] oxiren-1(4H)-one

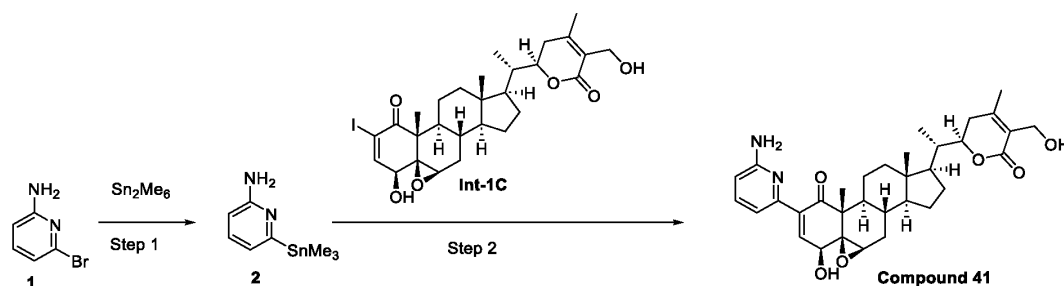
To a stirred solution of (R)-6-[(S)-1-{(1S, 2R, 6R, 7S, 9R, 11S, 12S, 15R, 16S)-6-fluoro-2, 16-dimethyl-3-oxo-4-(2-pyrimidinyl)-8-oxapentacyclo [9.7.0.0^{2,7}.0^{7,9}.0^{12,16}] octadec-4-en-15-yl}ethyl]-3-{[(tert-butyl)bis(methyl)siloxy]methyl}-4-methyl-5, 6-dihydro-2H-pyran-2-one (450 mg, 677 μ mol) in tetrahydrofuran (4 mL), and methanol (4 mL), 2N HCl (4 mL) was added at 0°C. Stirred the reaction mixture for 30 min at 0°C. After the completion of reaction (monitoring by TLC), the reaction mixture was quenched with saturated NaHCO₃ solution (40 mL) and extracted with ethyl acetate (2 x 40 mL). The organic layer was dried over anhydrous sodium sulphate, filtered and concentrated under vacuum to afford the crude. The compound was purified by prep-HPLC using ABC method to obtain desired product (4R, 4aS, 5aR, 6aS, 6bS, 9R, 9aS, 11aS, 11bR)-4-fluoro-9-((S)-1-((R)-5-(hydroxymethyl)-4-methyl-6-oxo-3, 6-dihydro-2H-pyran-2-yl)ethyl)-2-(5-methoxypyrazin-2-yl)-9a, 11b-dimethyl-5a, 6, 6a, 6b, 7, 8, 9, 9a, 10, 11, 11a, 11b-dodecahydrocyclopenta [1, 2] phenanthro [8a, 9-b] oxiren-1(4H)-one (12 mg, 14%) as white solid.

[0379] Analytical data: 97.79 % (m/z: 581.5, [M+1]⁺, 6.49 min (10 min run).

¹H-NMR (400 MHz, DMSO-*d*₆): δ 8.38 (d, J = 1.20 Hz, 1H), 8.33 (d, J = 0.80 Hz, 1H), 7.50 (dd, J = 1.60, 16.80 Hz, 1H), 5.88 (d, J = 49.60 Hz, 1H), 4.60 (t, J = 5.20 Hz, 1H), 4.27-4.30 (m, 1H), 4.08-4.18 (m, 2H), 3.94 (s, 3H), 3.53 (s, 1H), 2.33-2.43 (m, 1H), 2.08-2.13 (m, 2H), 2.00 (s, 3H), 1.28-1.93 (m, 9H), 1.23 (s, 3H), 0.97-1.16 (m, 4H), 0.92 (d, J = 6.80 Hz, 3H), 0.68 (s, 3H).

¹⁹F-NMR (400 MHz, DMSO-*d*₆): δ -201.82

[0380] Synthesis of Compound 41



[0381] Step-1: Synthesis of 6-(trimethylstannyl)pyridin-2-amine (0.4 g, 1.48 mmol)

To a stirred solution of 6-bromopyridin-2-amine (1 g, 5.78 mmol) in toluene (8 mL, 75.3 mmol) was added hexamethyldistannane (1.89 g, 5.78 mmol). The reaction mixture was purged by using nitrogen gas for 10 min. To the resulting reaction mixture, was added tetrakis (triphenylphosphane) palladium (0.2 g, 0.03 eq., 173 μ mol). The reaction mixture was stirred at 130 °C for 4h. After completion of the reaction (monitored by TLC), the reaction mixture was diluted with water (50 mL) and extracted with ethyl acetate (3 x 50 mL). The combined organic layer was dried over sodium sulphate, filtered and concentrated under reduced pressure to get crude compound. The crude compound was purified by combi flash over silica column (0 - 20% ethyl acetate in heptane) to obtain desired product 6-(trimethylstannyl)pyridin-2-amine (0.4 g, 25.5%) as brown gum.

[0382] Analytical data:

LCMS: 91% (m/z: 259.02, $[M+1]^+$, 1.49 min (4 min run).

[0383] Step-2: Synthesis of (1S, 2R, 6S, 7R, 9R, 11S, 12S, 16S)-4-(6-aminopyridin-2-yl)-6-hydroxy-15-[(1S)-1-[(2R)-5-(hydroxymethyl)-4-methyl-6-oxo-3, 6-dihydro-2H-pyran-2-yl]ethyl]-2, 16-dimethyl-8-oxapentacyclo [9.7.0.0^{2,7}.0^{7,9}.0^{12,16}] octadec-4-en-3-one (0.1 g, 172 μ mol)

To a stirred solution of (1S, 2R, 6S, 7R, 9R, 11S, 12S, 16S)-6-hydroxy-15-[(1S)-1-[(2R)-5-(hydroxymethyl)-4-methyl-6-oxo-3, 6-dihydro-2H-pyran-2-yl]ethyl]-4-iodo-2, 16-dimethyl-8-oxapentacyclo [9.7.0.0^{2,7}.0^{7,9}.0^{12,16}] octadec-4-en-3-one (1.5 g, 2.51 mmol) in tetrahydrofuran (10 mL) was added 6-(trimethylstannyl) pyridin-2-amine (775 mg, 1.2 eq., 3.02 mmol). The reaction mixture was purged with nitrogen gas for 10 min. To the resulting mixture, were added copper(I+) iodide (47.9 mg, 0.1 eq., 251 μ mol) and triphenylarsane (77 mg, 0.1 eq., 251 μ mol) followed by tris((1E,4E)-1,5-diphenylpenta-1,4-dien-3-one) dipalladium (115 mg, 0.05 eq., 126 μ mol). The reaction was stirred at 80°C for 2 hours. After the completion of the reaction (monitoring by TLC), reaction mixture was filtered through celite bed. The filtrate was diluted with water (70 mL) and extracted with ethyl acetate (2 x 50 ml). The combined organic layer was dried over sodium sulphate, filtered and concentrated under reduced pressure to get crude compound. The crude compound was purified by prep HPLC in ABC buffer to obtain the desired compound (1S, 2R, 6S, 7R, 9R, 11S, 12S, 16S)-4-(6-aminopyridin-2-yl)-6-hydroxy-15-[(1S)-1-[(2R)-5-(hydroxymethyl)-4-methyl-6-oxo-3, 6-

dihydro-2H-pyran-2-yl]ethyl]-2, 16-dimethyl-8-oxapentacyclo [9.7.0.0^{2,7}.0^{7,9}.0^{12,16}] octadec-4-en-3-one (0.1 g, 6.86%) as yellow solid.

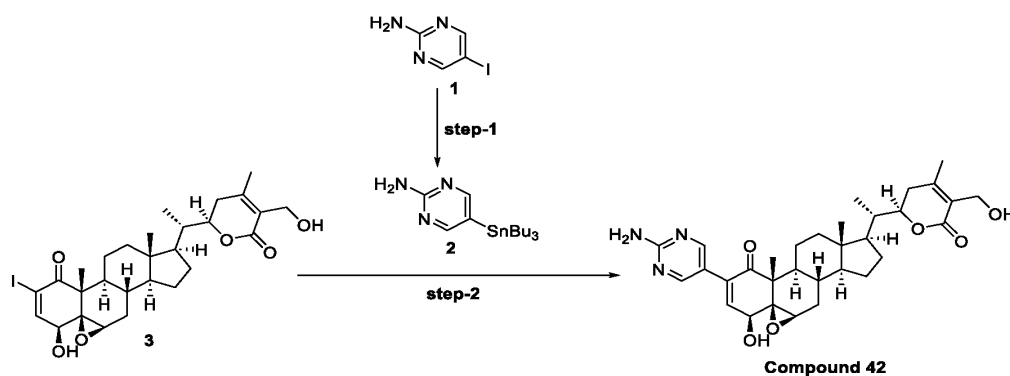
[0384] Analytical data:

LCMS: 97.76% (m/z: 563.5), [M+1]⁺, 5.16 min (10 min run).

¹H-NMR (400 MHz, DMSO-*d*₆): δ 7.53 (d, *J* = 6.8 Hz, 1H), 7.37 (t, *J* = 7.6 Hz, 1H), 6.53 (d, *J* = 7.6 Hz, 1H), 6.41 (d, *J* = 8.4 Hz, 1H), 5.95 (bs, 2H), 5.63 (d, *J* = 3.2 Hz, 1H), 4.59 (t, *J* = 5.2 Hz, 1H), 4.30 - 4.25 (m, 1H), 4.17 - 4.07 (m, 2H), 3.72 - 3.70 (m, 1H), 3.13 (s, 1H), 2.41 - 2.33 (m, 1H), 2.11 - 2.01 (m, 1H), 1.98 (s, 3H), 1.91 - 1.51 (m, 4H), 1.37 - 1.19 (m, 8H), 1.14 - 0.77 (m, 8H), 0.65 (s, 3H).

¹³C-NMR (400 MHz, DMSO-*d*₆): δ 200.75, 165.29, 159.22, 154.66, 149.88, 141.39, 137.85, 137.52, 125.40, 110.34, 108.40, 77.49, 68.52, 63.65, 57.40, 55.32, 54.49, 50.97, 47.91, 42.08, 41.98, 40.12, 30.79, 29.20, 28.98, 26.48, 23.94, 20.54, 19.86, 15.02, 12.99, 11.22.

[0385] Synthesis of Compound 42



[0386] Step-1: Synthesis of 5-(tributylstannyl) pyrimidin-2-amine

To a stirred solution of 5-iodopyrimidin-2-amine (1 g, 4.52 mmol) in N, N-dimethylformamide (10 mL) was added hexabutylstannane (3.15 g, 1.2 eq., 5.43 mmol). The reaction mixture was purged with argon gas for 30 min then tris(dibenzylideneacetone)dipalladium (0.41 g, 0.1 eq., 0.45 mmol) was added to it. The reaction mixture was again purged with argon gas for 5

min. The reaction mixture was stirred at 65°C for 3h. Cooled the reaction mass to room temperature, quenched with chilled water (50 mL) and extracted using ethyl acetate (2 x 50 mL). Collected organics, dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure to obtain crude. The crude product was purified by combi flash column chromatography using (20-30%) ethyl acetate in hexane as an eluent to afford 5-(tributylstannyl) pyrimidin-2-amine (1.4 g, 3.64 mmol, 80%) as an off white solid.

[0387] Analytical data:

LCMS: 99.89% (m/z: 386.21, [M+1]⁺, 3.12 min (4 min run).

[0388] Step-2: Synthesis of (1S, 2R, 6S, 7R, 9R, 11S, 12S, 15R, 16S)-4-(2-aminopyrimidin-5-yl)-6-hydroxy-15-[(1S)-1-[(2R)-5-(hydroxymethyl)-4-methyl-6-oxo-3, 6-dihydro-2H-pyran-2-yl]ethyl]-2, 16-dimethyl-8-oxapentacyclo [9.7.0.0^{2,7}.0^{12,16}] octadec-4-en-3-one

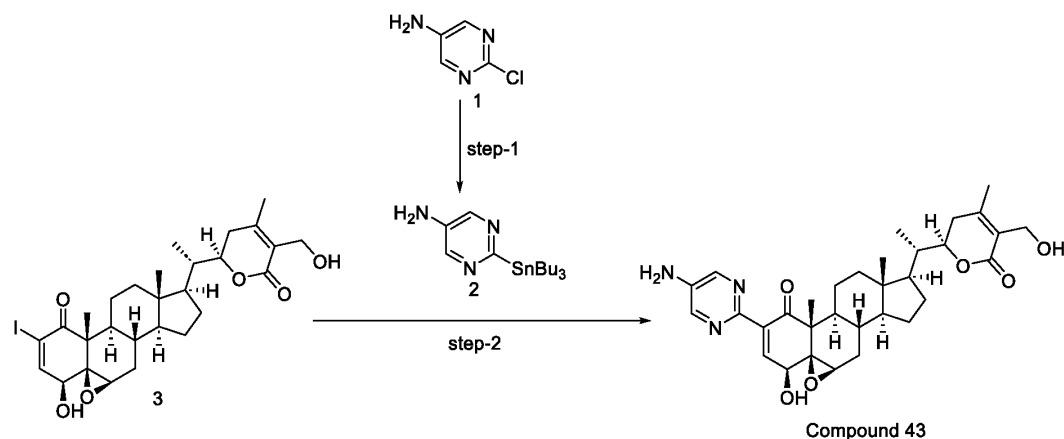
To a stirred solution of (1S, 2R, 6S, 7R, 9R, 11S, 12S, 15R, 16S)-6-hydroxy-15-[(1S)-1-[(2R)-5-(hydroxymethyl)-4-methyl-6-oxo-3, 6-dihydro-2H-pyran-2-yl]ethyl]-4-iodo-2, 16-dimethyl-8-oxapentacyclo [9.7.0.0^{2,7}.0^{12,16}] octadec-4-en-3-one (0.25 g, 0.41 mmol) and 5-(tributylstannyl) pyrimidin-2-amine (0.24 g, 1.5 eq., 0.63 mmol) in N, N-dimethylformamide (3 mL) were added triphenylarsane (0.013 g, 0.1 eq., 0.042 mmol) and λ¹-copper(1+) iodide (0.012 g, 0.15 eq., 0.063 mmol). The resulting mixture was purged with argon for 30 min. After that tris((1E, 4E)-1,5-diphenylpenta-1,4-dien-3-one) dipalladium (0.038 g, 0.1 eq., 0.042 mmol) was added and stirred for 3h at 60°C. Cooled to room temperature, quenched by adding water (50 mL) and extracted using ethyl acetate (2 x 50 mL). Collected organics, dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure to obtain crude. The crude product was purified by combi flash column chromatography using (5-10%) methanol in DCM as an eluent followed by Prep HPLC purification in ammonium acetate method to afford (1S, 2R, 6S, 7R, 9R, 11S, 12S, 15R, 16S)-4-(2-aminopyrimidin-5-yl)-6-hydroxy-15-[(1S)-1-[(2R)-5-(hydroxymethyl)-4-methyl-6-oxo-3, 6-dihydro-2H-pyran-2-yl]ethyl]-2, 16-dimethyl-8-oxapentacyclo [9.7.0.0^{2,7}.0^{12,16}] octadec-4-en-3-one (0.022 g, 0.039 mmol, 9%) as white solid.

[0389] Analytical data: 98.14% (m/z: 564.5, [M+1]⁺, 4.80 min (10 min run).

¹H-NMR (400 MHz, DMSO-*d*₆): δ 8.20 (s, 2H), 7.26 (d, *J*=6.8, 1H), 6.90 (s, 2H), 5.66 (d, *J*= 3.2 Hz, 1H), 4.59 (t, *J* = 5.2 Hz, 1H), 4.29-4.26 (m, 1H), 4.17-4.07 (m, 2H), 3.67-3.64 (m,

1H), 3.16 (s, 1H), 2.41-2.33 (m, 1H), 2.10-2.01 (m, 2H), 1.99 (s, 3H), 1.90-1.70 (m, 3H), 1.59-1.55 (m, 1H), 1.35-1.23 (m, 8H), 1.14-0.95 (m, 4H), 0.92 (d, $J = 6.8$ Hz, 3H), 0.86-0.80 (m, 1H), 0.65 (s, 3H).

[0390] Synthesis of Compound 43



[0391] Step-1: Synthesis of 2-(tributylstannyl) pyrimidin-5-amine

To a stirred solution of 2-chloropyrimidin-5-amine (4 g, 30.9 mmol) in toluene (40 mL) was added hexabutylstannane (21.5 g, 1.2 eq., 37.1 mmol) at room temperature. The reaction mixture was purged with N₂ for 30 minutes. After purging tetrakis (triphenylphosphane) palladium (3.57 g, 0.1 eq., 3.09 mmol) was added and again purged with N₂ for 5 minutes. Reaction mixture was heated at 130 °C for 16h. Filtered the reaction mixture through hyper flow celite bed and washed with ethyl acetate. The filtrate was concentrated under reduced pressure to obtain crude. Crude product was purified by combi flash column chromatography using 40-50% ethyl acetate in heptane as an eluent to afford 2-(tributylstannyl) pyrimidin-5-amine (362 mg) as an off white solid.

[0392] Analytical data:

LCMS: 90.82% (m/z: 385.21, [M+1]⁺, 2.59 min (4 min run).

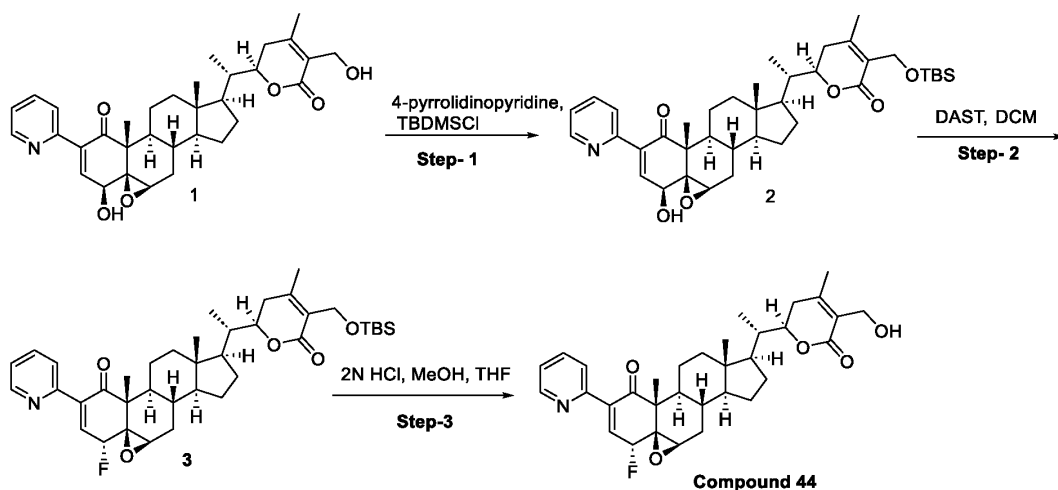
[0393] Step-2: Synthesis of (1S, 2R, 6S, 7R, 9R, 11S, 12S, 15R, 16S)-4-(5-aminopyrimidin-2-yl)-6-hydroxy-15-[(1S)-1-[(2R)-5-(hydroxymethyl)-4-methyl-6-oxo-3,6-dihydro-2H-pyran-2-yl]ethyl]-2, 16-dimethyl-8-oxapentacyclo [9.7.0.0^{2,7}.0^{9,12}.1⁶] octadec-4-en-3-one

To a stirred solution of (1S, 2R, 6S, 7R, 9R, 11S, 12S, 15R, 16S)-6-hydroxy-15-[(1S)-1-[(2R)-5-(hydroxymethyl)-4-methyl-6-oxo-3, 6-dihydro-2H-pyran-2-yl]ethyl]-4-iodo-2, 16-dimethyl-8-oxapentacyclo [9.7.0.0²,⁷.0⁷,⁹.0¹²,¹⁶] octadec-4-en-3-one (0.2 g, 335 μ mol) in dimethylformamide (3 mL), added 2-(tributylstannyl) pyrimidin-5-amine (155 mg, 1.2 eq., 402 μ mol), λ^1 -copper(I) diiodide (16 mg, 0.15 eq., 50.3 μ mol) and triphenylarsane (10.3 mg, 0.1 eq., 33.5 μ mol) at room temperature. The reaction mixture was purged with N₂ gas for 30 min and tris((1E,4E)-1,5-diphenylpenta-1,4-dien-3-one) dipalladium (3.07 mg, 0.01 eq., 3.35 μ mol) was added to it. The reaction mixture was again purged with N₂ gas for 5 min. The reaction was stirred at 60 °C for 4h. Subsequently, the reaction mass was quenched by adding water (50 mL) and extracted with ethyl acetate (3 x 30 mL). The collected organics, dried over sodium sulphate and concentrated under reduced pressure to obtain crude. The crude product was purified by combi flash column chromatography using (5-10%) methanol in DCM as an eluent followed by Prep HPLC purification in ammonium bicarbonate method to afford (1S, 2R, 6S, 7R, 9R, 11S, 12S, 15R, 16S)-4-(5-aminopyrimidin-2-yl)-6-hydroxy-15-[(1S)-1-[(2R)-5-(hydroxymethyl)-4-methyl-6-oxo-3, 6-dihydro-2H-pyran-2-yl]ethyl]-2, 16-dimethyl-8-oxapentacyclo [9.7.0.0²,⁷.0⁷,⁹.0¹²,¹⁶] octadec-4-en-3-one (9 mg, 4.3%) as white solid.

[0394] Analytical data: 92.29% (m/z: 564.5, [M+1]⁺, 4.72 min (10 min run).

¹H-NMR (400 MHz, DMSO-*d*₆): δ 8.08 (s, 2H), 7.35 (d, *J* = 6.8 Hz, 1H), 5.73 (s, 2H), 5.62 (d, *J* = 3.2 Hz, 1H), 4.60 (t, *J* = 5.2 Hz, 1H), 4.30-4.07 (m, 3H), 3.68-3.66 (m, 1H), 3.10 (s, 1H), 2.42-2.35 (m, 2H), 2.12-1.99 (m, 6H), 1.91-1.71 (m, 3H), 1.61-1.43 (m, 2H), 1.38-1.00 (m, 11H), 0.65 (s, 3H).

[0395] Synthesis of Compound 44



[0396] **Step-1: Synthesis of (4S, 4aR, 5aR, 6aS, 6bS, 9R, 9aS, 11aS, 11bR)-9-((S)-1-((R)-5-(((tert-butyldimethylsilyl)oxy)methyl)-4-methyl-6-oxo-3, 6-dihydro-2H-pyran-2-yl)ethyl)-4-hydroxy-9a, 11b-dimethyl-2-(pyridin-2-yl)-5a, 6, 6a, 6b, 7, 8, 9, 9a, 10, 11, 11a, 11b-dodecahydrocyclopenta [1, 2] phenanthro [8a, 9-b] oxiren-1(4H)-one:**

To a stirred solution of (1S, 2R, 6S, 7R, 9R, 11S, 12S, 15R, 16S)-6-hydroxy-15-[(1S)-1-[(2R)-5-(hydroxymethyl)-4-methyl-6-oxo-3, 6-dihydro-2H-pyran-2-yl]ethyl]-2, 16-dimethyl-4-(pyridin-2-yl)-8-oxapentacyclo [9.7.0.0^{2,7}.0^{7,9}.0^{12,16}] octadec-4-en-3-one (1 g, 1.83 mmol) in N, N-dimethylformamide (20 mL) were added 4-(1-pyrrolidinyl)pyridine (1.35 g, 5 eq., 9.13 mmol) and tert-butyl(chloro)dimethylsilane (2.75 g, 10 eq., 18.3 mmol) at room temperature. The resulting mixture was stirred at 85°C for 1h. Reaction was monitored by TLC. Quenched the reaction with water (40 mL) and extracted with ethyl acetate (2 X 50 mL). The organic layer was washed with chilled water followed by brine solution (50 mL). Dried the organics over sodium sulphate, filtered and concentrated under reduced pressure to get crude. The crude material was purified by Combi Flash by using 40-50% ethyl acetate in heptane as eluent, concentrated the desired fraction under reduced pressure to get (4S, 4aR, 5aR, 6aS, 6bS, 9R, 9aS, 11aS, 11bR)-9-((S)-1-((R)-5-(((tert-butyldimethylsilyl)oxy)methyl)-4-methyl-6-oxo-3, 6-dihydro-2H-pyran-2-yl)ethyl)-4-hydroxy-9a, 11b-dimethyl-2-(pyridin-2-yl)-5a, 6, 6a, 6b, 7, 8, 9, 9a, 10, 11, 11a, 11b-dodecahydrocyclopenta [1,2] phenanthro [8a, 9-b] oxiren-1(4H)-one (310 mg, 16.93%).

[0397] **Analytical data:**

LCMS: 66.10% 2.57 min (m/z: 662.30, [M+1]⁺, (4 min run).

[0398] **Step-2: Synthesis of (4R, 4aS, 5aR, 6aS, 6bS, 9R, 9aS, 11aS, 11bR)-9-((S)-1-((R)-5-(((tert-butyldimethylsilyl) oxy) methyl)-4-methyl-6-oxo-3, 6-dihydro-2H-pyran-2-yl)ethyl)-4-fluoro-9a, 11b-dimethyl-2-(pyridin-2-yl)-5a, 6, 6a, 6b, 7, 8, 9, 9a, 10, 11, 11a, 11b-dodecahydrocyclopenta [1, 2] phenanthro [8a, 9-b] oxiren-1(4H)-one:**

A mixture of (R)-6-[(S)-1-{(1S, 2R, 6S, 7R, 9R, 11S, 12S, 15R, 16S)-6-hydroxy-2, 16-dimethyl-3-oxo-4-(2-pyridyl)-8-oxapentacyclo [9.7.0.0^{2,7}.0^{7,9}.0^{12,16}] octadec-4-en-15-yl}ethyl]-3-{[(tert-butyl) bis(methyl) siloxy] methyl}-4-methyl-5, 6-dihydro-2H-pyran-2-one (0.3 g, 453 μ mol) in dichloromethane (3 mL) was added diethyl(trifluoro- λ^4 -sulfanyl)amine (71.9 μ L, 1.2 eq., 544 μ mol) at -78°C. The reaction mixture was stirred at the same temperature for 5 minutes. After the completion of reaction (as monitored by TLC), was quenched with sodium bicarbonate solution (20 mL) and extracted with DCM (2 X 20 mL). The organic layer was washed with brine solution, dried over sodium sulphate, filtered and concentrated under reduced pressure to get crude. The crude material was purified by Combi Flash using 25-30% ethyl acetate in heptane as a eluent, concentrated the desired fraction under reduced pressure to get (R)-6-[(S)-1-{(1S, 2R, 6R, 7S, 9R, 11S, 12S, 15R, 16S)-6-fluoro-2, 16-dimethyl-3-oxo-4-(2-pyridyl)-8-oxapentacyclo [9.7.0.0^{2,7}.0^{7,9}.0^{12,16}] octadec-4-en-15-yl} ethyl] -3- {[(tert-butyl) bis (methyl) siloxy] methyl}-4-methyl-5, 6-dihydro-2H-pyran-2-one (90 mg, 26.41%) as yellow solid.

[0399] **Analytical data:**

LCMS: 88.29% (m/z: 664.30, [M+1]⁺, 2.83 min (4 min run).

¹H-NMR (400 MHz, DMSO-*d*₆): δ 8.63 (d, *J* = 5.20 Hz, 1H), 7.95-7.84 (m, 1H), 7.59 (t, *J* = 16.50 Hz, 1H), 7.49 (d, *J* = 7.30 Hz, 1H), 7.40 (t, *J* = 6.20 Hz, 1H), 5.93-5.70 (m, 1H), 4.38-4.27 (m, 3H), 3.54 (s, 1H), 2.43 (t, *J* = 15.7 Hz, 1H), 2.17 (s, 1H), 2.11 (d, *J* = 12.6 Hz, 3H), 1.93 (d, *J* = 12.5 Hz, 1H), 1.83 (d, *J* = 6.9 Hz, 1H), 1.73 (s, 1H), 1.61 (t, *J* = 15.1 Hz, 2H), 1.43 (t, *J* = 10.9 Hz, 2H), 1.34 (d, *J* = 13.4 Hz, 2H), 1.24 (s, 4H), 1.14 (d, *J* = 9.8 Hz, 4H), 1.15-1.03 (m, 2H), 1.01 (t, *J* = 8.90 Hz, 3H), 0.94 (d, *J* = 6.30 Hz, 8H), 0.73 (s, 3H), 0.05 (d, *J* = 3.10 Hz, 6H).

[0400] **Step-3: Synthesis of (4R, 4aS, 5aR, 6aS, 6bS, 9R, 9aS, 11aS, 11bR)-4-fluoro-9-((S)-1-((R)-5-(hydroxymethyl)-4-methyl-6-oxo-3, 6-dihydro-2H-pyran-2-yl)ethyl)-9a, 11b-dimethyl-2-(pyridin-2-yl)-5a, 6, 6a, 6b, 7, 8, 9, 9a, 10, 11, 11a, 11b-dodecahydrocyclopenta [1, 2] phenanthro [8a, 9-b] oxiren-1(4H)-one:**

To a stirred solution of (R)-6-[(S)-1-{(1S, 2R, 6S, 7R, 9R, 11S, 12S, 15R, 16S)-6-hydroxy-2, 16-dimethyl-3-oxo-4-(2-pyridyl)-8-oxapentacyclo [9.7.0.0^{2,7}.0^{7,9}.0^{12,16}] octadec-4-en-15-yl}ethyl]-3-{[(tert-butyl)bis(methyl)siloxy]methyl}-4-methyl-5, 6-dihydro-2H-pyran-2-one (90 mg, 136 μ mol) in tetrahydrofuran (0.9 mL) was added methanol (0.9 mL) and 2N HCl (0.9 mL) at 0°C. The resultant reaction mixture was stirred for 1 hour at 0°C. After completion of reaction (as monitored by TLC), it was quenched with saturated sodium bicarbonate solution (20 mL) and extracted with DCM (2 x 30 mL). The combined organics were dried over sodium sulphate, filtered and concentrated under reduced pressure to get crude. The crude was purified by using preparative-HPLC (ABC method) to afford desired product (4R, 4aS, 5aR, 6aS, 6bS, 9R, 9aS, 11aS, 11bR)-4-fluoro-9-((S)-1-((R)-5-(hydroxymethyl)-4-methyl-6-oxo-3, 6-dihydro-2H-pyran-2-yl)ethyl)-9a, 11b-dimethyl-2-(pyridin-2-yl)-5a, 6, 6a, 6b, 7, 8, 9, 9a, 10, 11, 11a, 11b-dodecahydrocyclopenta [1, 2] phenanthro [8a, 9-b] oxiren-1(4H)-one (12 mg, 15.58%) as a white solid.

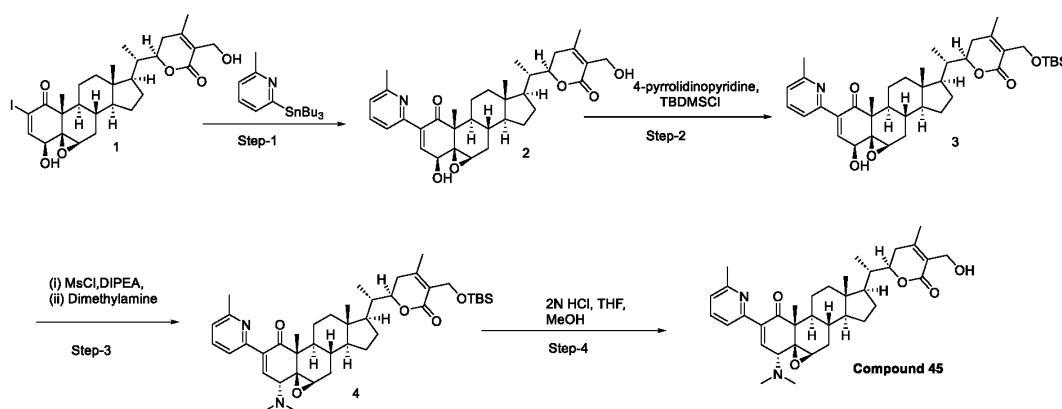
[0401] Analytical data:

LCMS: 97.03% (m/z: 550.50, [M+1]⁺, 6.40 min (10 min run).

¹H-NMR (400 MHz, DMSO-*d*₆): δ 8.62 (d, *J* = 4.40 Hz, 1H), 7.87-7.83 (m, 1H), 7.58-7.54 (m, 1H), 7.47 (d, *J* = 8.0 Hz, 1H), 7.40-7.37 (m, 1H), 5.88 (d, *J* = 50.4 Hz, 1H), 4.60 (t, *J* = 5.60 Hz, 1H), 4.30-4.27 (m, 1H), 4.17-4.07 (m, 2H), 3.52 (s, 1H), 2.42-2.34 (m, 1H), 2.12-2.08 (m, 2H), 2.04 (s, 3H), 1.99-1.81 (m, 1H), 1.80-1.73 (m, 1H), 1.73-1.71 (m, 1H), 1.63-1.55 (m, 2H), 1.53-1.44 (m, 2H), 1.42-1.31 (m, 2H), 1.22 (s, 3H), 1.65-1.08 (m, 3H), 1.07-0.97 (m, 2H), 0.92 (d, *J* = 6.80 Hz, 3H), 0.68 (s, 3H).

¹⁹F-NMR (400 MHz, DMSO-*d*₆): δ -202.099.

[0402] Synthesis of Compound 45



[0403] Step-1: Synthesis of (R)-6-[(S)-1-[(1S, 2R, 6S, 7R, 9R, 11S, 12S, 15R, 16S)-6-hydroxy-2, 16-dimethyl-4-(6-methyl-2-pyridyl)-3-oxo-8-oxapentacyclo [9.7.0.0^{2,7}.0^{7,9}.0^{12,16}] octadec-4-en-15-yl}ethyl]-3-(hydroxymethyl)-4-methyl-5, 6-dihydro-2H-pyran-2-one:

To a stirred solution of (R)-6-[(S)-1-[(1S, 2R, 6S, 7R, 9R, 11S, 12S, 15R, 16S)-6-hydroxy-2, 16-dimethyl-3-oxo-8-oxapentacyclo [9.7.0.0^{2,7}.0^{7,9}.0^{12,16}] octadec-4-en-15-yl}ethyl]-3-(hydroxymethyl)-4-methyl-5, 6-dihydro-2H-pyran-2-one (1 g, 1.68 mmol), in tetrahydrofuran (12 mL) added tributyl(6-methyl-2-pyridyl)stannane (769 mg, 1.2 eq., 2.01 mmol), triphenylarsine (51.3 mg, 0.1 eq., 168 μ mol) and diiodocopper (79.8 mg, 0.15 eq., 251 μ mol). The reaction mixture was purged with nitrogen gas for 30 min and palladium—(1E, 4E)-1,5-diphenyl-1,4-pentadien-3-one (2/3) (76.8 mg, 0.05 eq., 83.8 μ mol) was added to it. The reaction mixture was again purged with nitrogen gas for 5 min. The reaction was stirred at 80 °C for 2h. After the completion of reaction (as monitored by TLC 100% Ethyl acetate in hexane), the reaction mixture was diluted with water (50 mL) and extracted with ethyl acetate (2 x 50 mL). The organic layer was washed with saturated brine solution (50 mL), dried over sodium sulphate, filtered and concentrated under reduced pressure to obtain crude. The crude was purified by combi flash column chromatography using (60-70%) in ethyl acetate in hexane as an eluent to afford (R)-6-[(S)-1-[(1S, 2R, 6S, 7R, 9R, 11S, 12S, 15R, 16S)-6-hydroxy-2, 16-dimethyl-4-(6-methyl-2-pyridyl)-3-oxo-8-oxapentacyclo [9.7.0.0^{2,7}.0^{7,9}.0^{12,16}] octadec-4-en-15-yl}ethyl]-3-(hydroxymethyl)-4-methyl-5, 6-dihydro-2H-pyran-2-one (0.8 g, 68.8%b) as yellow solid.

[0404] Analytical data:

LCMS: 80.92% (m/z: 562.20, [M+1]⁺, 2.033 min (4 min run).

[0405] Step-2: Synthesis of (1S, 2R, 6S, 7R, 9R, 11S, 12S, 15R, 16S)-15-[(1S)-1-[(2R)-5-[[[(tert-butyl)dimethylsilyl]oxy]methyl]-4-methyl-6-oxo-3, 6-dihydro-2H-pyran-2-yl]ethyl]-6-hydroxy-2, 16-dimethyl-4-(6-methylpyridin-2-yl)-8-oxapentacyclo [9.7.0.0^{2,7},⁹.0^{12,16}] octadec-4-en-3-one:

To a stirred solution of (1S, 2R, 6S, 7R, 9R, 11S, 12S, 15R, 16S)-6-hydroxy-15-[(1S)-1-[(2R)-5-(hydroxymethyl)-4-methyl-6-oxo-3, 6-dihydro-2H-pyran-2-yl]ethyl]-2, 16-dimethyl-4-(6-methylpyridin-2-yl)-8-oxapentacyclo [9.7.0.0^{2,7},⁹.0^{12,16}] octadec-4-en-3-one (0.8 g, 1.42 mmol) in dimethylformamide (16 mL) was added 4-(pyrrolidin-1-yl)pyridin-1-ium (1.06 g, 5 eq., 7.12 mmol) and tert-butyl(chloro)dimethylsilane (2.15 g, 10 eq., 14.2 mmol) at room temperature. The reaction was stirred at 80°C for 1h. After the completion of reaction (as monitored by TLC 70% Ethyl acetate in hexane), the reaction mixture was diluted with ice cold water (30 mL) and extracted with ethyl acetate (2 x 50 mL). The organic layer was washed with saturated brine solution (50 mL), dried over sodium sulphate, filtered and concentrated under reduced pressure to obtain crude. The crude was purified by combi flash column chromatography using (40-50%) ethyl acetate in hexane as an eluent to afford (1S, 2R, 6S, 7R, 9R, 11S, 12S, 15R, 16S)-15-[(1S)-1-[(2R)-5-[[[(tert-butyl)dimethylsilyl]oxy]methyl]-4-methyl-6-oxo-3, 6-dihydro-2H-pyran-2-yl]ethyl]-6-hydroxy-2, 16-dimethyl-4-(6-methylpyridin-2-yl)-8-oxapentacyclo [9.7.0.0^{2,7},⁹.0^{12,16}] octadec-4-en-3-one (0.3 g, 29%) as white solid.

[0406] Analytical data:

LCMS: 94.23% (m/z: 676.65, [M+1]⁺, 2.66 min (4 min run).

[0407] Step-3: Synthesis of (1S, 2R, 6R, 7R, 9R, 11S, 12S, 15R, 16S)-15-[(1S)-1-[(2R)-5-[[[(tert-butyl)dimethylsilyl]oxy]methyl]-4-methyl-6-oxo-3,6-dihydro-2H-pyran-2-yl]ethyl]-6-(dimethylamino)-2,16-dimethyl-4-(6-methylpyridin-2-yl)-8-oxapentacyclo[9.7.0.0^{2,7},⁹.0^{12,16}]octadec-4-en-3-one:

To a stirred solution of (R)-6-[(S)-1-{(1S, 2R, 6S, 7R, 9R, 11S, 12S, 15R, 16S)-6-hydroxy-2, 16-dimethyl-4-(6-methyl-2-pyridyl)-3-oxo-8-oxapentacyclo [9.7.0.0^{2,7},⁹.0^{12,16}] octadec-4-en-15-yl}ethyl]-3-[[[(tert-butyl)bis(methyl)siloxy]methyl]-4-methyl-5,6-dihydro-2H-pyran-2-one (0.4 g, 592 µmol) in dichloromethane (4 mL) was added ethylbis (propan-2-yl)amine (382 mg, 5 eq., 2.96 mmol) then methane sulfonyl chloride (136 mg, 2 eq., 1.18 mmol) at 0°C. The reaction mixture was stirred at 0°C for 30 minutes. After the completion of reaction (monitored

by TLC 50% Ethyl acetate in hexane) mixture was diluted with water (20 mL) and extracted with DCM (2 x 30 mL). The organic layer was washed with brine solution, dried over sodium sulphate, filtered and concentrated under reduced pressure to get ((R)-6-((S)-1-((4R, 4aR, 5aR, 6aS, 6bS, 9R, 9aS, 11aS, 11bR)-4-(dimethyl amino)-9a, 11b-dimethyl-2-(6-methylpyridin-2-yl)-1-oxo-1, 4, 5a, 6, 6a, 6b, 7, 8, 9, 9a, 10, 11, 11a, 11b-tetradecahydrocyclopenta [1, 2] phenanthro [8a, 9-b] oxiren-9-yl) ethyl)-4-methyl-2-oxo-5, 6-dihydro-2H-pyran-3-yl) methyl methanesulfonate. It was forwarded as such to the next step. To a stirred solution of triethylamine (268 mg, 5 eq., 2.65 mmol) in acetonitrile (4 mL) was added dimethylamine (38.3 mg, 1.6 eq., 849 μ mol) followed by addition of ((R)-6-((S)-1-((4R, 4aR, 5aR, 6aS, 6bS, 9R, 9aS, 11aS, 11bR)-4-(dimethylamino)-9a, 11b-dimethyl-2-(6-methylpyridin-2-yl)-1-oxo-1, 4, 5a, 6, 6a, 6b, 7, 8, 9, 9a, 10, 11, 11a, 11b-tetradecahydrocyclopenta [1, 2] phenanthro [8a, 9-b] oxiren-9-yl)ethyl)-4-methyl-2-oxo-5, 6-dihydro-2H-pyran-3-yl)methyl methanesulfonate (0.4 g, 530 μ mol) at 0°C. The resultant reaction mixture was stirred at 60°C for 30 min. After the completion of reaction (monitored by TLC, 70% ethyl acetate in hexane), mixture was diluted with water (30 mL) and extracted with ethyl acetate (2 x 30 mL). The organic layer was washed with saturated brine solution, dried over sodium sulphate, filtered and concentrated under reduced pressure to get crude (410 mg crude). The crude material was as such used for next step without further purification.

[0408] Analytical data:

LCMS: 54.46% (m/z: 703.85, [M+1]⁺, 4.59 min (6 min run).

[0409] Step-4: Synthesis of (4R, 4aR, 5aR, 6aS, 6bS, 9R, 9aS, 11aS, 11bR)-4-(dimethylamino)-9-((S)-1-((R)-5-(hydroxymethyl)-4-methyl-6-oxo-3, 6-dihydro-2H-pyran-2-yl)ethyl)-9a, 11b-dimethyl-2-(6-methylpyridin-2-yl)-5a, 6, 6a, 6b, 7, 8, 9, 9a, 10, 11, 11a, 11b-dodecahydrocyclopenta [1, 2] phenanthro [8a, 9-b] oxiren-1(4H)-one:

[0410] To a stirred solution of (R)-6-[(S)-1-{(1S, 2R, 6R, 7R, 9R, 11S, 12S, 15R, 16S)-6-(dimethylamino)-2,16-dimethyl-4-(6-methyl-2-pyridyl)-3-oxo-8-oxapentacyclo [9.7.0.0^{2,7}.0^{7,9}.0^{12,16}] octadec-4-en-15-yl}ethyl]-3-[(tert-butyl) bis (methyl) siloxy] methyl}-4-methyl-5, 6-dihydro-2H-pyran-2-one (410 mg, 583 μ mol) in tetrahydrofuran (4 mL) was added methanol (4 mL) and 2N HCl solution (4 mL) at 0°C. The reaction mixture was stirred at 0°C for 30 min. After completion of reaction (monitoring by TLC 100% ethyl acetate in

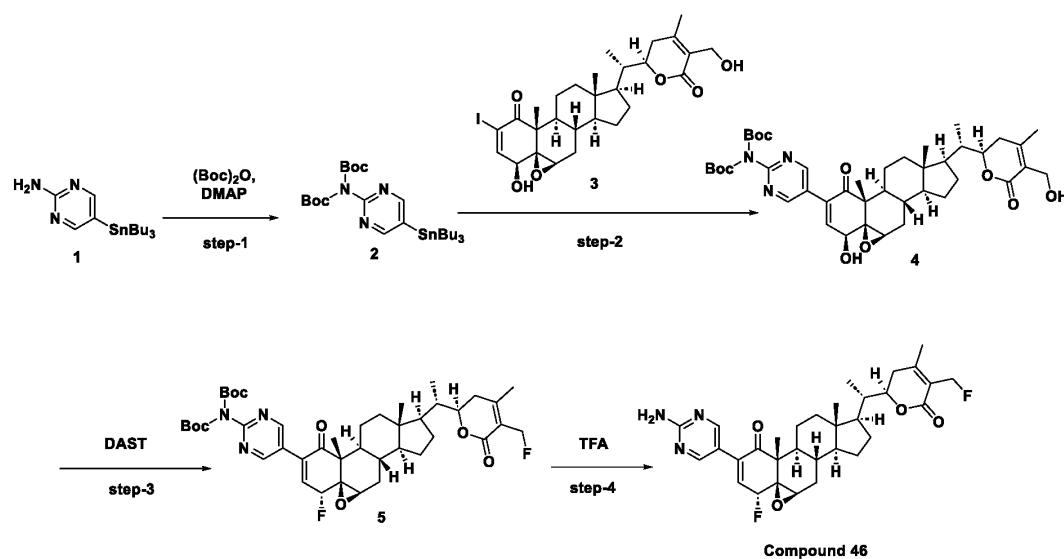
hexane), reaction mixture was quenched with saturated NaHCO₃ solution (30 mL) and extracted with ethyl acetate (2 x 30 mL). The organic layer was dried over sodium sulphate, filtered and concentrated under reduced pressure to afford crude. The crude was purified by using preparative-HPLC ammonium acetate method to afford (4R, 4aR, 5aR, 6aS, 6bS, 9R, 9aS, 11aS, 11bR)-4-(dimethylamino)-9-((S)-1-((R)-5-(hydroxymethyl)-4-methyl-6-oxo-3, 6-dihydro-2H-pyran-2-yl)ethyl)-9a, 11b-dimethyl-2-(6-methylpyridin-2-yl)-5a, 6, 6a, 6b, 7, 8, 9, 9a, 10, 11, 11a, 11b-dodecahydrocyclopenta [1, 2] phenanthro [8a, 9-b] oxiren-1(4H)-one (55 mg, 15%) as off white solid.

[0411] Analytical data:

LCMS: 95.56% (m/z: 589.50, [M+1]⁺, 6.86 min (10 min run).

¹H-NMR (400 MHz, DMSO-*d*₆): δ 7.69 (t, *J* = 7.6 Hz, 1H), 7.53 (d, *J* = 6.80 Hz, 1H), 7.29 (d, *J* = 8.00 Hz, 1H), 7.20 (d, *J* = 7.60 Hz, 1H), 4.59 (t, *J* = 5.6 Hz, 1H), 4.32-4.27 (m, 1H), 4.18-4.08 (m, 2H), 3.72 (d, *J* = 3.6 Hz, 1H), 3.57 (d, *J* = 2.00 Hz, 1H), 2.47 (s, 3H), 2.41-2.35 (m, 1H), 2.23 (s, 6H), 2.18 – 2.14 (m, 1H), 2.01- 1.98 (m, 4H), 1.95-1.57 (m, 5H), 1.42 – 1.32 (m, 2H), 1.35-1.01 (m, 10H), 0.93 (d, *J* = 6.8 Hz, 3H), 0.67 (s, 3H).

¹³C-NMR (400 MHz, DMSO-*d*₆): δ 201.42, 165.33, 157.61, 154.75, 151.67, 140.18, 138.97, 136.80, 130.04, 125.43, 122.53, 119.77, 118.59, 77.56, 64.16, 61.61, 58.24, 55.16, 54.52, 51.29, 49.49, 42.29, 42.14, 41.97, 30.53, 29.05, 28.77, 26.45, 24.30, 23.98, 22.67, 19.89, 16.62, 13.06, 11.51.

[0412] Synthesis of Compound 46**[0413] Step-1: Synthesis of tert-butyl N-[(tert-butoxy) carbonyl]-N-[5-(tributylstannyl) pyrimidin-2-yl] carbamate.**

To a stirred solution of 5-(tributylstannyl)pyrimidin-2-amine (2.3 g, 5.99 mmol) in THF (25 mL) were added N,N-dimethylpyridin-4-amine (0.073 g, 0.1 eq., 0.599 mmol) and di-tert-butyl dicarbonate (2.75 mL, 2 eq., 12.0 mmol) sequentially at 0 °C. The resulting mixture was stirred at 60 °C for 4h. After completion of the reaction (monitored by TLC), it was quenched by adding water (100 mL) and then extracted using ethyl acetate (2 x 100 mL). Combined organics were washed with saturated brine solution (50 mL), dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure to obtain crude. The crude product was purified through combi-flash using silica column chromatography in (20-30%) ethyl acetate in heptane as an eluent to afford tert-butyl N-[(tert-butoxy)carbonyl]-N-[5-(tributylstannyl)pyrimidin-2-yl]carbamate (2 g, 3.42 mmol, 57%).

[0414] Analytical data:

LCMS: 99.4% (m/z: 586.10, $[\text{M}+1]^+$), 2.75 min (4 min run).

[0415] Step-2: Synthesis of tert-butyl N-[(tert-butoxy)carbonyl]-N-{5-[(1S, 2R, 6S, 7R, 9R, 11S, 12S, 15R, 16S)-6-hydroxy-15-[(1S)-1-[(2R)-5-(hydroxymethyl)-4-methyl-6-oxo-3, 6-dihydro-2H-pyran-2-yl]ethyl]-2, 16-dimethyl -3- oxo -8-oxapentacyclo [9.7.0.0.2,7.0^{7,9}.0^{12,16}] octadec-4-en-4-yl] pyrimidin-2-yl} carbamate.

To a stirred solution of (1S, 2R, 6S, 7R, 9R, 11S, 12S, 15R, 16S)-6-hydroxy-15-[(1S)-1-[(2R)-5-(hydroxymethyl)-4-methyl-6-oxo-3, 6-dihydro-2H-pyran-2-yl]ethyl]-4-iodo-2, 16-dimethyl-8-oxapentacyclo [9.7.0.0^{2,7},^{9,12},¹⁶] octadec-4-en-3-one (1.0 g, 1.68 mmol) and tert-butyl N-[(tert-butoxy)carbonyl]-N-[5-(tributylstannyl) pyrimidin-2-yl]carbamate (1.18 g, 1.2 eq., 2.01 mmol) in were added λ^1 -copper(1+) iodide (0.048 g, 0.15 eq., 0.251 mmol) and triphenylarsane (0.051 g, 0.1 eq., 0.168 mmol) at RT. The resulting mixture was purged with argon for 30 min. After that tris (dibenzylideneacetone) dipalladium (0.076 g, 0.05 eq., 0.084 mmol) was added to the mixture and stirred for 1h at 60°C. After completion of the reaction (as monitored by TLC and LCMS), the reaction was quenched by adding ice water (200 mL) and brine solution (50 mL). It was then extracted using ethyl acetate (3 x 80 mL). Collected organics, dried over sodium sulphate and concentrated under reduced pressure to obtain crude. Crude product was purified by combi flash column chromatography using (70-90%) ethyl acetate in heptane as an eluent to afford tert-butyl N-[(tert-butoxy)carbonyl]-N-{5-[(1S, 2R, 6S, 7R, 9R, 11S, 12S, 15R, 16S)-6-hydroxy-15-[(1S)-1-[(2R)-5-(hydroxymethyl)-4-methyl-6-oxo-3, 6-dihydro-2H-pyran-2-yl]ethyl]-2, 16-dimethyl-3-oxo-8-oxapentacyclo [9.7.0.0^{2,7},^{9,12},¹⁶] octadec-4-en-4-yl]pyrimidin-2-yl}carbamate (0.9 g, 0.801 mmol, 45%) as yellow solid.

[0416] Analytical data:

LCMS: 68.18 % (m/z: 764.28, [M+1]⁺), 2.52 min (4 min run).

[0417] Step-3: Synthesis of tert-butyl N-[(tert-butoxy)carbonyl]-N-{5-[(1S, 2R, 6R, 7S, 9R, 11S, 12S, 15R, 16S) -6-fluoro- 15- [(1S)-1-[(2R)-5- (fluoromethyl) -4-methyl -6-oxo-3, 6-dihydro-2H-pyran-2-yl] ethyl] -2, 16-dimethyl -3-oxo-8-oxapentacyclo [9.7.0.0^{2,7},^{9,12},¹⁶] octadec-4-en-4-yl]pyrimidin-2-yl}carbamate

To a stirred solution of tert-butyl N-[(tert-butoxy)carbonyl]-N-{5-[(1S, 2R, 6S, 7R, 9R, 11S, 12S, 15R, 16S)-6-hydroxy-15-[(1S)-1-[(2R)-5-(hydroxymethyl)-4-methyl-6-oxo-3, 6-dihydro-2H-pyran-2-yl]ethyl]-2, 16-dimethyl-3-oxo-8-oxapentacyclo [9.7.0.0^{2,7},^{9,12},¹⁶] octadec-4-en-4-yl]pyrimidin-2-yl}carbamate (1.2 g, 1.1 mmol) in dichloromethane (15 mL) was added diethyl(trifluoro- λ^4 -sulfanyl) amine (0.29 mL, 2 eq., 2.2 mmol) dissolved in DCM (2 mL) drop wise at -78°C under inert atmosphere and stirred for 15 min. After completion of reaction (as monitored by TLC and by LCMS), it was quenched by adding sodium bicarbonate solution (30 mL) and then extracted using dichloromethane (3 x 50 mL). The collected organics was dried over anhydrous sodium sulphate, filtered and then concentrated under reduced

pressure to obtain crude. The crude was purified through combi-flash chromatography (10-20% ethyl acetate in heptane) to yield tert-butyl N-[(tert-butoxy)carbonyl]-N-{5-[(1S, 2R, 6R, 7S, 9R, 11S, 12S, 15R, 16S)-6-fluoro-15-[(1S)-1-[(2R)-5-(fluoromethyl)-4-methyl-6-oxo-3, 6-dihydro-2H-pyran-2-yl]ethyl]-2, 16-dimethyl-3-oxo-8-oxapentacyclo [9.7.0.0²,⁷.0⁷,⁹.0¹²,¹⁶] octadec-4-en-4-yl]pyrimidin-2-yl} carbamate (0.09 g, 0.117 mmol, 11%) as yellow solid.

[0418] Analytical data:

LCMS: 78.23% (m/z: 766.49, [M-1]⁻, 2.89 min (4 min run).

[0419] Step-4: Synthesis of (1S, 2R, 6R, 7S, 9R, 11S, 12S, 15R, 16S)-4-(2-aminopyrimidin-5-yl)-6-fluoro-15-[(1S)-1-[(2R)-5-(fluoromethyl)-4-methyl-6-oxo-3, 6-dihydro-2H-pyran-2-yl]ethyl]-2, 16-dimethyl-8-oxapentacyclo [9.7.0.0²,⁷.0⁷,⁹.0¹²,¹⁶] octadec-4-en-3-one

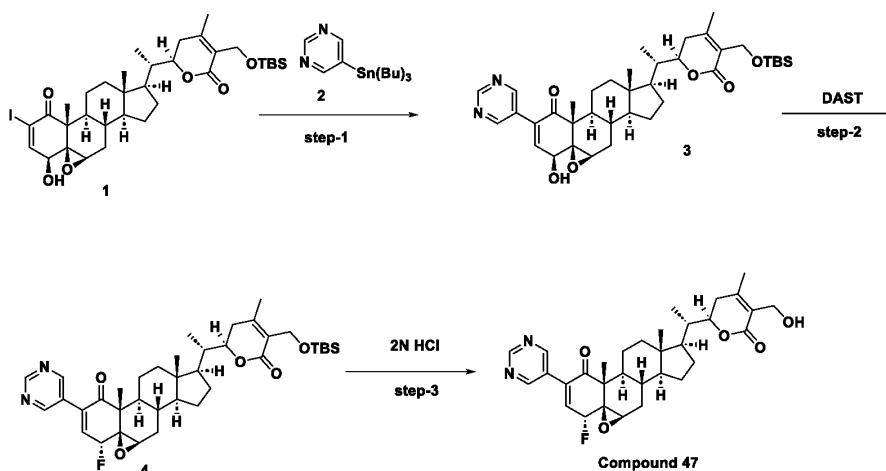
To a solution of tert-butyl N-[(tert-butoxy)carbonyl]-N-{5-[(1S, 2R, 6R, 7S, 9R, 11S, 12S, 15R, 16S)-6-fluoro-15-[(1S)-1-[(2R)-5-(fluoromethyl)-4-methyl-6-oxo-3, 6-dihydro-2H-pyran-2-yl]ethyl]-2, 16-dimethyl-3-oxo-8-oxapentacyclo [9.7.0.0²,⁷.0⁷,⁹.0¹²,¹⁶] octadec-4-en-4-yl]pyrimidin-2-yl} carbamate (0.08 g, 0.104 mmol) in dichloromethane (2 mL) was added trifluoroacetic acid (0.3 mL) at 0 °C and stirred for 5h. After completion of the reaction, the mixture was quenched with saturated NaHCO₃ solution (20 mL) and extracted with DCM (2x 20 mL). Combined organics were washed with brine solution, dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure to get the crude which was then purified by prep HPLC chromatography in ammonium bicarbonate method to afford (1S, 2R, 6R, 7S, 9R, 11S, 12S, 15R, 16S)-4-(2-aminopyrimidin-5-yl)-6-fluoro-15-[(1S)-1-[(2R)-5-(fluoromethyl)-4-methyl-6-oxo-3, 6-dihydro-2H-pyran-2-yl]ethyl]-2, 16-dimethyl-8-oxapentacyclo [9.7.0.0²,⁷.0⁷,⁹.0¹²,¹⁶] octadec-4-en-3-one (8 mg, 0.014 mmol) as white solid.

[0420] Analytical data:

LCMS: 98.58% (m/z: 568.55, [M+1]⁺, 6.47 min (10 min run).

¹H-NMR (400 MHz, DMSO-*d*₆): δ 8.25 (s, 2H), 7.26 (dd, *J* = 2 Hz, 16.8 Hz, 1H), 6.93 (s, 2H), 5.77 (d, *J* = 50.8 Hz, 1H), 5.10 (d, *J* = 45.6 Hz, 2H), 4.38-4.33 (m, 1H), 3.53 (s, 1H), 2.25-2.08 (m, 1H), 2.07-2.03 (m, 4H), 1.91-1.80 (m, 3H), 1.63-1.53 (m, 3H), 1.43-1.28 (m, 4H), 1.20 (s, 3H), 1.16-0.98 (m, 5H), 0.92 (d, *J* = 6.4 Hz, 3H), 0.67 (s, 3H).

¹⁹F-NMR (400 MHz, DMSO-*d*₆): δ -200.46, -206.88.

[0421] Synthesis of Compound 47

[0422] Step-1: Synthesis of (1S, 2R, 6S, 7R, 9R, 11S, 12S, 15R, 16S)-15-[(1S)-1-[(2R)-5-[[tert-butyldimethylsilyl] oxy] methyl]-4-methyl-6-oxo-3, 6-dihydro-2H-pyran-2-yl]ethyl]-6-hydroxy-2, 16-dimethyl-4-(pyrimidin-5-yl)-8-oxapentacyclo [9.7.0.0^{2,7}.0^{7,9}.0^{12,16}] octadec-4-en-3-one

To a stirred solution of (1S, 2R, 6S, 7R, 9R, 11S, 12S, 15R, 16S)-15-[(1S)-1-[(2R)-5-[[tert-butyldimethylsilyl] oxy] methyl]-4-methyl-6-oxo-3, 6-dihydro-2H-pyran-2-yl]ethyl]-6-hydroxy-4-iodo-2, 16-dimethyl-8-oxapentacyclo [9.7.0.0^{2,7}.0^{7,9}.0^{12,16}] octadec-4-en-3-one (0.5 g, 0.703 mmol) and 5-(tributylstannyl) pyrimidine (0.39 g, 1.5 eq., 1.06 mmol) in 1,4-dioxane (8 mL) was added λ^1 -copper(1+) iodide (0.02 g, 0.15 eq., 0.106 mmol) at RT. The resulting mixture was purged with argon for 30 min. Added tris(1,5-diphenylpenta-1,4-dien-3-one) dipalladium (0.032 g, 0.05 eq., 0.035 mmol) to the reaction mixture and stirred for at 80°C for 2h. After completion of the reaction (monitored by TLC and LCMS), it was quenched by adding water (30 mL) and brine solution (30 mL). It was then extracted using ethyl acetate (3 x 50 mL). Collected organics, dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure to obtain crude. The crude product was purified over combi flash silica column chromatography using (80-90%) EtOAc in heptane as an eluent to afford (1S, 2R, 6S, 7R, 9R, 11S, 12S, 15R, 16S)-15-[(1S)-1-[(2R)-5-[[tert-butyldimethylsilyl] oxy] methyl]-4-methyl-6-oxo-3, 6-dihydro-2H-pyran-2-yl] ethyl]-6-hydroxy-2, 16-dimethyl-4-(pyrimidin-5-yl)-8-oxapentacyclo [9.7.0.0^{2,7}.0^{7,9}.0^{12,16}] octadec-4-en-3-one (0.22 g, 0.33 mmol, 40%) as yellow solid.

[0423] Analytical data:

LCMS: 60.12% (m/z: 663.40, [M+1]⁺), 2.67 min (4 min run).

[0424] Step-2: Synthesis of (1S, 2R, 6R, 7S, 9R, 11S, 12S, 15R, 16S)-15-[(1S)-1-[(2R)-5-[[[(tert-butyldimethylsilyl) oxy] methyl]-4-methyl-6-oxo-3, 6-dihydro-2H-pyran-2-yl]ethyl]-6-fluoro-2, 16-dimethyl-4-(pyrimidin-5-yl)-8-oxapentacyclo [9.7.0.0^{2,7},9.0^{12,16}] octadec-4-en-3-one

To a stirred solution of (1S, 2R, 6S, 7R, 9R, 11S, 12S, 15R, 16S)-15-[(1S)-1-[(2R)-5-[[[(tert-butyldimethylsilyl) oxy] methyl]-4-methyl-6-oxo-3, 6-dihydro-2H-pyran-2-yl]ethyl]-6-hydroxy-2, 16-dimethyl-4-(pyrimidin-5-yl)-8-oxapentacyclo [9.7.0.0^{2,7},9.0^{12,16}] octadec-4-en-3-one (490 mg, 0.443 mmol) in dichloromethane (10 mL) was added diethyl (trifluoro-λ⁴-sulfanyl) amine (0.07 mL, 1.2 eq., 0.532 mmol) dissolved in DCM (1 mL) drop wise at -78 °C under inert atmosphere and stirred for 15 min. After completion of reaction (monitored by TLC and by LCMS), quenched by adding saturated sodium bicarbonate solution (30 mL) and then extracted using dichloromethane (2 x 30 mL). Collected organics, dried over anhydrous sodium sulphate, filtered and then concentrated under reduced pressure to obtain crude. The crude was purified over combi-flash chromatography (20-30% ethyl acetate in heptane) to yield (1S, 2R, 6R, 7S, 9R, 11S, 12S, 15R, 16S)-15-[(1S)-1-[(2R)-5-[[[(tert-butyldimethylsilyl) oxy] methyl]-4-methyl-6-oxo-3, 6-dihydro-2H-pyran-2-yl] ethyl]-6-fluoro-2, 16-dimethyl-4-(pyrimidin-5-yl)-8-oxapentacyclo [9.7.0.0^{2,7},9.0^{12,16}] octadec-4-en-3-one (0.2 g, 0.15 mmol, 33%) as yellow solid.

[0425] Analytical data:

LCMS: 84.83 % (m/z: 663.39, [M-1]⁻), 4.31 min (6 min run).

[0426] Step-3: Synthesis of (R)-6-[(S)-1-[(1S, 2R, 6R, 7S, 9R, 11S, 12S, 15R, 16S)-6-fluoro-2, 16-dimethyl-3-oxo-4-(5-pyrimidinyl)-8-oxapentacyclo [9.7.0.0^{2,7},9.0^{12,16}] octadec-4-en-15-yl]ethyl]-3-(hydroxymethyl)-4-methyl-5, 6-dihydro-2H-pyran-2-one

To a solution of (R)-6-[(S)-1-[(1S, 2R, 6R, 7S, 9R, 11S, 12S, 15R, 16S)-6-fluoro-2, 16-dimethyl-3-oxo-4-(5-pyrimidinyl)-8-oxapentacyclo [9.7.0.0^{2,7},9.0^{12,16}] octadec-4-en-15-yl]ethyl]-3-[[[(tert-butyl) bis (methyl) siloxy] methyl]-4-methyl-5, 6-dihydro-2H-pyran-2-one (0.19 g, 0.171 mmol) in THF (2 mL) and methanol (2 mL) was added 2N hydrogen chloride solution (2 mL) drop wise at 0 °C and stirred for 30 min. After completion of the reaction (monitored by TLC and LCMS), it was quenched by adding sodium bicarbonate solution (20

mL) and extracted using dichloromethane (2 x 30 mL). Collected organics, dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure to obtain crude which was then purified by prep HPLC purification in ammonium bicarbonate method to afford (R)-6-[(S)-1-[(1S, 2R, 6R, 7S, 9R, 11S, 12S, 15R, 16S)-6-fluoro-2, 16-dimethyl-3-oxo-4-(5-pyrimidinyl)-8-oxapentacyclo [9.7.0.0.0^{2,7},9.0^{12,16}] octadec-4-en-15-yl}ethyl]-3-(hydroxymethyl)-4-methyl-5, 6-dihydro-2H-pyran-2-one (0.032 g, 0.058 mmol, 34%) as white solid.

[0427] Analytical data:

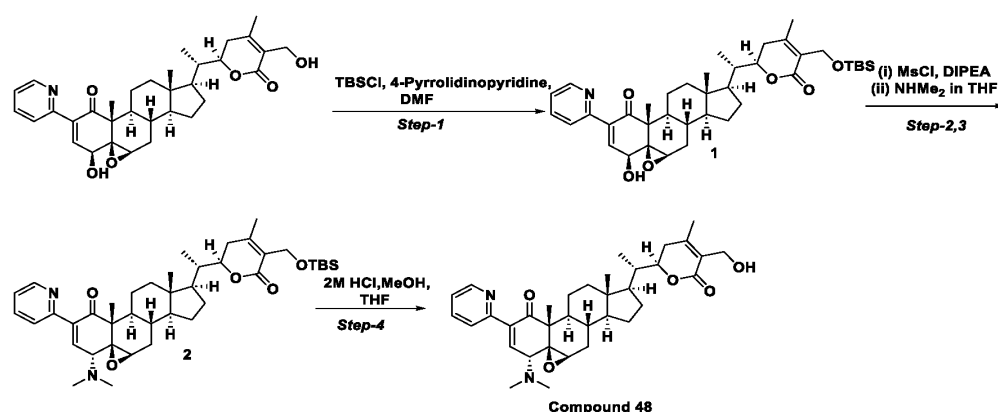
LCMS: 99.48% (m/z: 551.4, [M+1]⁺, 5.81 min (10 min run).

¹H-NMR (400 MHz, DMSO-*d*₆): δ 9.18 (s, 1H), 8.81 (s, 2H), 7.64 (d, *J* = 14.4 Hz, 1H), 5.90 (d, *J* = 50.0 Hz, 1H), 4.59 (t, *J* = 5.2 Hz, 1H), 4.31-4.26 (m, 1H), 4.18-4.07 (m, 2H), 3.57 (s, 1H), 2.43-2.32 (m, 1H), 2.12-2.03 (m, 2H), 2.00 (s, 3H), 1.91-1.88 (m, 1H), 1.84-1.69 (m, 3H), 1.56 (br, 1H), 1.44-1.31 (m, 4H), 1.24 (s, 3H), 1.19-0.97 (m, 5H), 0.92 (d, *J* = 6.4 Hz, 3H), 0.68 (s, 3H).

¹⁹F-NMR (400 MHz, DMSO-*d*₆): -202.09

¹³C-NMR (400 MHz, DMSO-*d*₆): δ 198.08, 165.33, 157.90, 156.25, 156.00, 154.71, 142.31, 142.02, 132.97, 132.87, 128.14, 125.44, 85.27, 83.50, 77.53, 62.99, 62.85, 54.89, 54.61, 54.51, 51.24, 47.03, 46.98, 43.42, 42.24, 41.97, 29.82, 29.23, 29.02, 26.48, 25.82, 23.97, 21.39, 19.91, 13.68, 13.07, 11.58.

[0428] Synthesis of Compound 48



[0429] Step-1: Synthesis of (4S, 4aR, 5aR, 6aS, 6bS, 9R, 9aS, 11aS, 11bR)-9-((S)-1-((R)-5-(((tert-butyldimethylsilyl) oxy) methyl)-4-methyl-6-oxo-3, 6-dihydro-2H-pyran-2-yl)ethyl)-4-hydroxy-9a, 11b-dimethyl-2-(pyridin-2-yl)-5a, 6, 6a, 6b, 7, 8, 9, 9a, 10, 11, 11a, 11b-dodecahydrocyclopenta [1, 2] phenanthro [8a, 9-b] oxiren-1(4H)-one:

To a stirred solution of (1S, 2R, 6S, 7R, 9R, 11S, 12S, 15R, 16S)-6-hydroxy-15-[(1S)-1-[(2R)-5-(hydroxymethyl)-4-methyl-6-oxo-3, 6-dihydro-2H-pyran-2-yl]ethyl]-2, 16-dimethyl-4-(pyridin-2-yl)-8-oxapentacyclo [9.7.0.0^{2,7}.0^{7,9}.0^{12,16}] octadec-4-en-3-one (0.6 g, 1.1 mmol) in N,N-dimethylformamide (12 mL) were added 4-(1-pyrrolidinyl) pyridine (812 mg, 5 eq., 5.48 mmol) and tert-butyl (chloro) dimethylsilane (1.65 g, 10 eq., 11 mmol) at RT. The resulting reaction mixture was stirred at 85 °C for 1h. Reaction was monitored by TLC. On completion, quenched it with cold water (40 mL) and extracted with ethyl acetate (2 X 50 mL). The organic layer was washed with chilled water followed by brine, dried the organics over anhydrous sodium sulphate, filtered and concentrated under reduced pressure. The crude material was purified by Combi Flash by using 40-50% ethyl acetate in heptane as a eluent, 5% MeOH in DCM was used to elute the pure product. Concentrated the desired fraction under reduced pressure to get (4S, 4aR, 5aR, 6aS, 6bS, 9R, 9aS, 11aS, 11bR)-9-((S)-1-((R)-5-(((tert-butyldimethylsilyl) oxy) methyl)-4-methyl-6-oxo-3, 6-dihydro-2H-pyran-2-yl)ethyl)-4-hydroxy-9a, 11b-dimethyl-2-(pyridin-2-yl)-5a, 6, 6a, 6b, 7, 8, 9, 9a, 10, 11, 11a, 11b-dodecahydrocyclopenta [1, 2] phenanthro [8a, 9-b] oxiren-1(4H)-one as yellowish solid (250 mg, 29.78%).

[0430] Analytical data:

LCMS: 86.38% 2.65 min (m/z: 662.45, [M+1]⁺, (4 min run).

[0431] Step-2: Synthesis of (4S, 4aS, 5aR, 6aS, 6bS, 9R, 9aS, 11aS, 11bR)-9-((S)-1-((R)-5-(((tert-butyldimethylsilyl) oxy) methyl)-4-methyl-6-oxo-3, 6-dihydro-2H-pyran-2-yl) ethyl)-9a, 11b-dimethyl-1-oxo-2-(pyridin-2-yl)-1, 4, 5a, 6, 6a, 6b, 7, 8, 9, 9a, 10, 11, 11a, 11b-tetradecahydrocyclopenta [1, 2] phenanthro [8a, 9-b] oxiren-4-yl methane sulfonate:

To a stirred solution of (R)-6-[(S)-1-{(1S, 2R, 6S, 7R, 9R, 11S, 12S, 15R, 16S)-6-hydroxy-2, 16-dimethyl-3-oxo-4-(2-pyridyl)-8-oxapentacyclo [9.7.0.0^{2,7}.0^{7,9}.0^{12,16}] octadec-4-en-15-yl}ethyl]-3-[[tert-butyl bis (methyl) siloxy] methyl}-4-methyl-5, 6-dihydro-2H-pyran-2-one (250 mg, 378 µmol) in dichloromethane (4 mL) was added ethylbis (propan-2-yl)amine (244 mg, 5 eq., 1.89 mmol) and methanesulfonyl chloride (86.5 mg, 2 eq., 755 µmol) at 0 °C. The

resultant reaction mixture was stirred at room temperature for 1h. After the completion of reaction (monitored by TLC), reaction mixture was diluted with water (40 mL) and extracted with DCM (2 X 30 mL). The organic layer was washed with brine solution, dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure to get (4S, 4aS, 5aR, 6aS, 6bS, 9R, 9aS, 11aS, 11bR)-9-((S)-1-((R)-5-(((tert-butyldimethylsilyl) oxy) methyl)-4-methyl-6-oxo-3,6-dihydro-2H-pyran-2-yl) ethyl)-9a, 11b-dimethyl-1-oxo-2-(pyridin-2-yl)-1, 4, 5a, 6, 6a, 6b, 7, 8, 9, 9a, 10, 11, 11a, 11b-tetradecahydrocyclopenta [1, 2] phenanthro [8a, 9-b] oxiren-4-yl methane sulfonate (250 mg, 89.45%) as yellow solid. The crude material was as such used for the next reaction.

[0432] Step-3: Synthesis of (4R, 4aR, 5aR, 6aS, 6bS, 9R, 9aS, 11aS, 11bR)-9-((S)-1-((R)-5-(((tert-butyldimethylsilyl) oxy) methyl)-4-methyl-6-oxo-3, 6-dihydro-2H-pyran-2-yl) ethyl)-4-(dimethylamino)-9a, 11b-dimethyl-2-(pyridin-2-yl)-5a, 6, 6a, 6b, 7, 8, 9, 9a, 10, 11, 11a, 11b-dodecahydrocyclopenta [1, 2] phenanthro [8a, 9-b] oxiren-1(4H)-one:

To a stirred solution of Dimethyl amine (24.4 mg, 1.6 eq., 541 μ mol) in THF, was added triethylamine (171 mg, 5 eq., 1.69 mmol) and (R)-6-[(S)-1-{(1S, 2R, 6S, 7S, 9R, 11S, 12S, 15R, 16S)-6-(mesyloxy)-2, 16-dimethyl-3-oxo-4-(2-pyridyl)-8-oxapentacyclo [9.7.0.0^{2,7}.0^{7,9}.0^{12,16}] octadec-4-en-15-yl}ethyl]-3-{[(tert-butyl)bis(methyl)siloxy]methyl}-4-methyl-5, 6-dihydro-2H-pyran-2-one (250 mg, 338 μ mol) in acetonitrile (2.5 mL) at 0 °C. Stirred the reaction mixture for 30 minutes at 60 °C. After the completion of reaction (monitored by TLC), reaction mixture was diluted with water (20 mL) and extracted with ethyl acetate (2 X 30 mL). The organic layer was washed with brine solution, dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure to get (4R, 4aR, 5aR, 6aS, 6bS, 9R, 9aS, 11aS, 11bR)-9-((S)-1-((R)-5-(((tert-butyldimethylsilyl) oxy) methyl)-4-methyl-6-oxo-3, 6-dihydro-2H-pyran-2-yl) ethyl)-4-(dimethylamino)-9a, 11b-dimethyl-2-(pyridin-2-yl)-5a, 6, 6a, 6b, 7, 8, 9, 9a, 10, 11, 11a, 11b-dodecahydrocyclopenta [1, 2] phenanthro [8a, 9-b]oxiren-1(4H)-one. It was used as such for next step without purification (due to stability issue of compound on silica/alumina column) (230 mg, 61.26%) as yellow solid.

[0433] Analytical data:

LCMS: 61.43% (m/z: 689.55, [M+1]⁺, 2.91 min (4 min run).

[0434] Step-4: Synthesis of (4R, 4aR, 5aR, 6aS, 6bS, 9R, 9aS, 11aS, 11bR)-4-(dimethylamino)-9-((S)-1-((R)-5-(hydroxymethyl)-4-methyl-6-oxo-3, 6-dihydro-2H-

pyran-2-yl) ethyl)-9a, 11b-dimethyl-2-(pyridin-2-yl)-5a, 6, 6a, 6b, 7, 8, 9, 9a, 10, 11, 11a, 11b-dodecahydrocyclopenta [1, 2] phenanthro [8a, 9-b] oxiren-1(4H)-one:

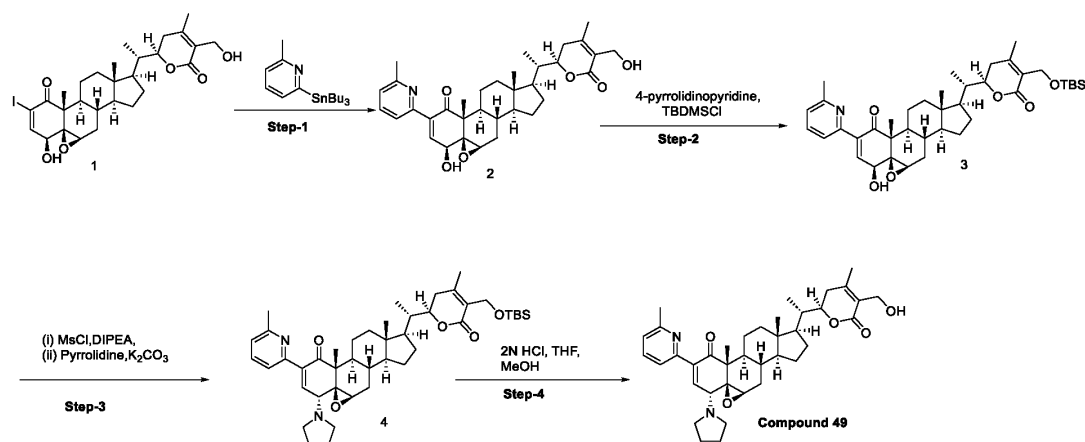
To a stirred solution of (R)-6-[(S)-1-{(1S, 2R, 6R, 7R, 9R, 11S, 12S, 15R, 16S)-6-(dimethylamino)-2, 16-dimethyl-3-oxo-4-(2-pyridyl)-8-oxapentacyclo [9.7.0.0.0^{2,7},9.0^{12,16}] octadec-4-en-15-yl}ethyl]-3-{[(tert-butyl) bis (methyl) siloxy] methyl}-4-methyl-5, 6-dihydro-2H-pyran-2-one (230 mg, 334 μ mol) in methanol (2.3 mL) was added tetrahydrofuran (2.3 mL) and 2N HCl (2.3 mL) at 0°C. Resultant reaction mixture was stirred for 1 hour at 0°C. After completion of reaction (monitored by TLC), it was quenched with saturated solution of sodium bicarbonate (20 mL) and extracted with ethyl acetate (40 mL). The organic layer was washed with brine, dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure. The crude was purified by using preparative-HPLC (ABC method) to afford (4R, 4aR, 5aR, 6aS, 6bS, 9R, 9aS, 11aS, 11bR)-4-(dimethylamino)-9-((S)-1-((R)-5-(hydroxymethyl)-4-methyl-6-oxo-3, 6-dihydro-2H-pyran-2-yl) ethyl)-9a, 11b-dimethyl-2-(pyridin-2-yl)-5a, 6, 6a, 6b, 7, 8, 9, 9a, 10, 11, 11a, 11b-dodecahydrocyclopenta [1, 2] phenanthro [8a, 9-b] oxiren-1(4H)-one (18.9 mg, 9.72%) as a white solid.

[0435] Analytical data:

LCMS: 98.69% (m/z: 575.50, [M+1]⁺, 6.46 min (10 min run).

¹H-NMR (400 MHz, DMSO-*d*₆): δ 8.60-8.59 (m, 1H), 7.82-7.78 (m, 1H), 7.56 (d, *J* = 3.60 Hz, 1H), 7.48 (d, *J* = 8.0 Hz, 1H), 7.36-7.33 (m, 1H), 4.59 (t, *J* = 5.20 Hz, 1H), 4.32-4.27 (m, 1H), 4.18-4.08 (m, 2H), 3.74 (d, *J* = 3.60 Hz, 1H), 3.58 (d, *J* = 2.40 Hz, 1H), 2.44-2.37 (m, 1H), 2.24 (s, 6H), 2.15 (d, *J* = 3.20 Hz, 1H), 2.12-2.07 (m, 1H), 2.01 (s, 4H), 1.92-1.86 (m, 1H), 1.84-1.78 (m, 1H), 1.75-1.71 (m, 1H), 1.69-1.66 (m, 1H), 1.59-1.57 (m, 1H), 1.43-1.41 (m, 2H), 1.33-1.30 (m, 2H), 1.26 (s, 3H), 1.22-1.21 (m, 2H), 1.18-0.99 (m, 2H), 0.93 (d, *J* = 6.80 Hz, 3H), 0.68 (s, 3H).

¹³C-NMR (400 MHz, DMSO-*d*₆): δ 201.32, 165.34, 154.75, 152.55, 149.38, 140.82, 138.87, 136.60, 125.43, 123.18, 122.81, 77.57, 64.12, 61.65, 58.41, 55.16, 54.52, 51.29, 49.48, 42.29, 42.15, 41.89, 30.52, 29.04, 28.77, 26.45, 23.98, 22.75, 19.89, 16.76, 13.07, 11.52.

[0436] Synthesis of Compound 49

[0437] Step-1: Synthesis of (R)-6-[(S)-1-[(1S, 2R, 6S, 7R, 9R, 11S, 12S, 15R, 16S)-6-hydroxy-2, 16-dimethyl-4-(6-methyl-2-pyridyl)-3-oxo-8-oxapentacyclo [9.7.0.0^{2,7}.0^{7,9}.0^{12,16}] octadec-4-en-15-yl]ethyl]-3-(hydroxymethyl)-4-methyl-5, 6-dihydro-2H-pyran-2-one :

To a stirred solution of (R)-6-[(S)-1-[(1S, 2R, 6S, 7R, 9R, 11S, 12S, 15R, 16S)-6-hydroxy-4-iodo-2, 16-dimethyl-3-oxo-8-oxapentacyclo [9.7.0.0^{2,7}.0^{7,9}.0^{12,16}] octadec-4-en-15-yl] ethyl]-3-(hydroxymethyl)-4-methyl-5, 6-dihydro-2H-pyran-2-one (1 g, 1.68 mmol) in tetrahydrofuran (12 mL) were added tributyl (6-methyl-2-pyridyl) stannane (769 mg, 1.2 eq., 2.01 mmol), triphenylarsine (51.3 mg, 0.1 eq., 168 μ mol) and diiodocopper (79.8 mg, 0.15 eq., 251 μ mol). The reaction mixture was purged with N₂ gas for 35 min and palladium—(1E,4E)-1,5-diphenyl-1,4-pentadien-3-one (2/3) (76.8 mg, 0.05 eq., 83.8 μ mol) was added to it. The reaction mixture was again purged with N₂ gas for 5 min. The reaction vial was sealed and stirred at 80 °C for 2h. After the completion of reaction (monitored by TLC 100% Ethyl acetate in heptane), it was diluted with water (50 mL) and extracted with ethyl acetate (2 X 100 mL). The organic layer was washed with chilled water followed by brine, dried the organics over anhydrous sodium sulphate, filtered and concentrated under reduced pressure to obtain crude. Crude was purified by combi flash column chromatography using, 60-70% ethyl acetate in heptane as an eluent to afford (R)-6-[(S)-1-[(1S, 2R, 6S, 7R, 9R, 11S, 12S, 15R, 16S)-6-hydroxy-2, 16-dimethyl-4-(6-methyl-2-pyridyl)-3-oxo-8-oxapentacyclo [9.7.0.0^{2,7}.0^{7,9}.0^{12,16}] octadec-4-en-15-yl]ethyl]-3-(hydroxymethyl)-4-methyl-5, 6-dihydro-2H-pyran-2-one (0.7 g, 773 μ mol) as yellowish solid.

[0438] Analytical data:

LCMS: 62.44% (m/z: 562.20, $[M+1]^+$, 2.27 min (4 min run).

[0439] Step-2: Synthesis of (1S, 2R, 6S, 7R, 9R, 11S, 12S, 15R, 16S)-15-[(1S)-1-[(2R)-5-[[tert-butyl(dimethylsilyl)oxy] methyl]-4-methyl-6-oxo-3, 6-dihydro-2H-pyran-2-yl] ethyl]-6-hydroxy-2, 16-dimethyl-4-(6-methylpyridin-2-yl)-8-oxapentacyclo [9.7.0.0^{2,7},⁹,0^{12,16}] octadec-4-en-3-one :

To a stirred solution of (R)-6-[(S)-1-[(1S, 2R, 6S, 7R, 9R, 11S, 12S, 15R, 16S)-6-hydroxy-2, 16-dimethyl-4-(6-methyl-2-pyridyl)-3-oxo-8-oxapentacyclo [9.7.0.0^{2,7},⁹,0^{12,16}] octadec-4-en-15-yl] ethyl]-3-(hydroxymethyl)-4-methyl-5, 6-dihydro-2H-pyran-2-one (0.7 g, 1.25 mmol) in dimethylformamide (14 mL) were added 4-(1-pyrrolidinyl)pyridine (923 mg, 5 eq., 6.23 mmol) and (tert-butyl)(chloro)bis(methyl)silane (1.88 g, 10 eq., 12.5 mmol) at RT. The reaction vial was sealed and stirred at 80 °C for 1h. After the completion of reaction (monitored by TLC 70% ethyl acetate in heptane), mixture was diluted with ice cold water (30 mL) and extracted with ethyl acetate (2 X 60 mL). The organic layer was washed with chilled water followed by chilled brine, dried the organics over anhydrous sodium sulphate, filtered and concentrated under reduced pressure to obtain crude. Crude was purified by combi flash column chromatography using, 40-50% ethyl acetate in heptane as an eluent to afford (1S, 2R, 6S, 7R, 9R, 11S, 12S, 15R, 16S)-15-[(1S)-1-[(2R)-5-[[tert-butyl(dimethylsilyl) oxy] methyl]-4-methyl-6-oxo-3, 6-dihydro-2H-pyran-2-yl]ethyl]-6-hydroxy-2, 16-dimethyl-4-(6-methylpyridin-2-yl)-8-oxapentacyclo[9.7.0.0^{2,7},⁹,0^{12,16}] octadec-4-en-3-one (0.3 g, 408 µmol) as yellowish solid.

[0440] Analytical data:

LCMS: 92.96% (m/z: 676.65, $[M+1]^+$, 2.68 min (4 min run).

[0441] Step-3: Synthesis of (R)-6-[(S)-1-[(1S, 2R, 6R, 7R, 9R, 11S, 12S, 15R, 16S)-2,16-dimethyl-4-(6-methyl-2-pyridyl)-3-oxo-6-(1-pyrrolidinyl)-8-oxapentacyclo [9.7.0.0^{2,7},⁹,0^{12,16}] octadec-4-en-15-yl] ethyl]-3-[[tert-butyl bis(methyl) siloxy] methyl]-4-methyl-5,6-dihydro-2H-pyran-2-one—ammonia(1/1):

To a stirred solution of (R)-6-[(S)-1-[(1S, 2R, 6S, 7R, 9R, 11S, 12S, 15R, 16S)-6-hydroxy-2,16-dimethyl-3-oxo-4-(2-pyridyl)-8-oxapentacyclo [9.7.0.0^{2,7},⁹,0^{12,16}] octadec-4-en-15-yl] ethyl]-3-[[tert-butyl]bis(methyl)siloxy]methyl]-4-methyl-5, 6-dihydro-2H-pyran-2-one (0.3

g, 453 μ mol) in dichloromethane (3 mL) was added ethylbis(propan-2-yl)amine (293 mg, 5 eq., 2.27 mmol) then methanesulfonyl chloride (104 mg, 2 eq., 906 μ mol) at 0 °C. The reaction mixture was stirred at 0 °C for 30 minutes. After the completion of reaction (monitored by TLC 50% ethyl acetate in heptane), it was diluted with water (20 mL) and extracted with DCM (2 X 30 mL). The organic layer was washed with brine, dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure to get (R)-6-[(S)-1-{(1S, 2R, 6S, 7S, 9R, 11S, 12S, 15R, 16S)-6-(mesyloxy)-2, 16-dimethyl-3-oxo-4-(2-pyridyl)-8-oxapentacyclo [9.7.0.0^{2,7},⁹,¹²,¹⁶] octadec-4-en-15-yl} ethyl]-3-[[tert-butyl) bis (methyl) siloxy] methyl}-4-methyl-5, 6-dihydro-2H-pyran-2-one. It was forwarded as such to the next step. To a stirred solution of dipotassium carbonate (137 mg, 2.5 eq., 995 μ mol) in acetonitrile (3.06 mL) was added pyrrolidine (70 mg, 2.5 eq, 995 μ mol) followed by addition of (R)-6-[(S)-1-{(1S, 2R, 6S, 7S, 9R, 11S, 12S, 15R, 16S)-6-(mesyloxy)-2, 16-dimethyl-4-(6-methyl-2-pyridyl)-3-oxo-8-oxapentacyclo [9.7.0.0^{2,7},⁹,¹²,¹⁶] octadec-4-en-15-yl}ethyl]-3-[[tert-butyl) bis (methyl) siloxy] methyl}-4-methyl-5, 6-dihydro-2H-pyran-2-one (0.3 g, 398 μ mol) at 0°C. The resultant reaction mixture was stirred at 60 °C for 30 min. After the completion of reaction (monitored by TLC 70% ethyl acetate in heptane), it was diluted with water (20 mL) and extracted with ethyl acetate (2 x 20 mL). The organic layer was washed with brine, dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure. The crude material was used as such for the next step without purification.

[0442] Analytical data:

LCMS: 70.62% (m/z:729.65, [M+1]⁺, 2.61 min (6 min run).

[0443] Step-4: Synthesis of (R)-6-[(S)-1-{(1S, 2R, 6R, 7R, 9R, 11S, 12S, 15R, 16S)-2, 16-dimethyl-4-(6-methyl-2-pyridyl)-3-oxo-6-(1-pyrrolidinyl)-8-oxapentacyclo [9.7.0.0^{2,7},⁹,¹²,¹⁶] octadec-4-en-15-yl}ethyl]-3-(hydroxymethyl)-4-methyl-5, 6-dihydro-2H-pyran-2-one:

To a stirred solution of (R)-6-[(S)-1-{(1S, 2R, 6R, 7R, 9R, 11S, 12S, 15R, 16S)-2, 16-dimethyl-4-(6-methyl-2-pyridyl)-3-oxo-6-(1-pyrrolidinyl)-8-oxapentacyclo [9.7.0.0^{2,7},⁹,¹²,¹⁶] octadec-4-en-15-yl}ethyl]-3-[[tert-butyl) bis (methyl) siloxy] methyl}-4-methyl-5, 6-dihydro-2H-pyran-2-one (0.3 g, 411 μ mol) in tetrahydrofuran (3 mL) were added methanol (3 mL) and 2N HCl (3 mL) at 0 °C. Reaction mixture was stirred at 0 °C for 30 min. After the completion of reaction (monitoring by TLC 100% ethyl acetate in heptane), it was quenched with saturated NaHCO₃ solution (20 mL) and extracted with ethyl acetate (2 x 20 mL). The

organic layer was dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to afford crude. Crude was purified by using preparative-HPLC using ABC method to afford (R)-6-[(S)-1-[(1S, 2R, 6R, 7R, 9R, 11S, 12S, 15R, 16S)-2,16-dimethyl-4-(6-methyl-2-pyridyl)-3-oxo-6-(1-pyrrolidinyl)-8-oxapentacyclo [9.7.0.0^{2,7}.0^{7,9}.0^{12,16}] octadec-4-en-15-yl}ethyl]-3-(hydroxymethyl)-4-methyl-5, 6-dihydro-2H-pyran-2-one (9 mg, 3.5%) as white solid.

[0444] Analytical data:

LCMS: 98.85% (m/z: 615.9, [M+1]⁺, 5.19 min (10 min run).

¹H-NMR (400 MHz, DMSO-*d*₆): δ 7.69 (t, *J* = 8.0 Hz, 1H), 7.57 (d, *J* = 2.8 Hz, 1H), 7.23-7.193 (m, 2H), 4.58 (t, *J* = 5.6 Hz, 1H), 4.30-4.25 (m, 1H), 4.17-4.07 (m, 2H), 3.55-3.53 (m, 2H), 2.69-2.65 (m, 4H), 2.49 (s, 3H), 2.46 – 2.39 (m, 1H), 2.12-1.89 (m, 7H), 1.82-1.54 (m, 8H), 1.39-0.95 (m, 11H), 0.92 (m, 4H), 0.67 (s, 3H).

[0445] Synthesis of Compound 50



[0446] Step-1: Synthesis of (R)-6-[(S)-1-[(1S, 2R, 6S, 7R, 9R, 11S, 12S, 15R, 16S)-6-hydroxy-2, 16-dimethyl-3-oxo-4-(2-pyridyl)-8-oxapentacyclo [9.7.0.0^{2,7}.0^{7,9}.0^{12,16}] octadec-4-en-15-yl}ethyl]-4-methyl-3-[(1-pyrrolidinyl)methyl]-5, 6-dihydro-2H-pyran-2-one

To a stirred solution of (R)-6-[(S)-1-[(1S, 2R, 6S, 7R, 9R, 11S, 12S, 15R, 16S)-6-hydroxy-2, 16-dimethyl-3-oxo-4-(2-pyridyl)-8-oxapentacyclo [9.7.0.0^{2,7}.0^{7,9}.0^{12,16}] octadec-4-en-15-yl}ethyl]-3-(hydroxymethyl)-4-methyl-5, 6-dihydro-2H-pyran-2-one—water (1/1) (0.5 g, 884 μmol, 1 eq) in dichloromethane (5 mL), added ethylbis (propan-2-yl)amine (232 μL, 1.5 eq., 1.33 mmol) followed by methane sulfonyl chloride (68.4 μL, 884 μmol, 1.0 eq) at 0 °C. The reaction mixture was stirred at 0 °C for 30 minutes. After the completion (monitored by TLC, 50% Ethyl acetate in hexane), reaction mixture was quenched with water (30 mL) and extracted with DCM (2 X 30 mL). The organic layer was washed with brine solution, dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure to get (R)-6-[(S)-

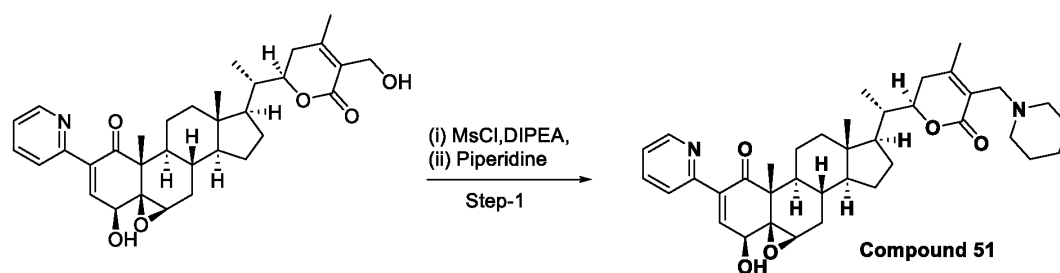
1-{(1S, 2R, 6S, 7R, 9R, 11S, 12S, 15R, 16S)-6-hydroxy-2, 16-dimethyl-3-oxo-4-(2-pyridyl)-8-oxapentacyclo [9.7.0.0^{2,7},⁹.0^{12,16}] octadec-4-en-15-yl} ethyl]-3-[(mesyloxy) methyl] -4-methyl-5, 6-dihydro-2H-pyran-2-one. It was forwarded as such to the next step.

To a stirred solution of dipotassium carbonate (225 mg, 2 eq., 1.63 mmol) in acetonitrile (5 mL) was added pyrrolidine (86.9 mg, 1.5 eq., 1.22 mmol) followed by addition of (R)-6-[(S)-1-{(1S, 2R, 6S, 7R, 9R, 11S, 12S, 15R, 16S)-6-hydroxy-2, 16-dimethyl-3-oxo-4-(2-pyridyl)-8-oxapentacyclo [9.7.0.0^{2,7},⁹.0^{12,16}] octadec-4-en-15-yl}ethyl]-3-[(mesyloxy)methyl]-4-methyl-5, 6-dihydro-2H-pyran-2-one (510 mg, 815 μ mol) dissolved in ACN at 0 °C. The resultant reaction mixture was stirred at 60 °C for 30 min. After the completion (monitored by TLC 70% Ethyl acetate in hexane), reaction mixture was diluted with water (30 mL) and extracted with ethyl acetate (2 X 30 mL). The organic layer was washed with brine solution, dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure. The crude product was purified by Prep HPLC in ABC method to afford (R)-6-[(S)-1-{(1S, 2R, 6S, 7R, 9R, 11S, 12S, 15R, 16S)-6-hydroxy-2, 16-dimethyl-3-oxo-4-(2-pyridyl)-8-oxapentacyclo [9.7.0.0^{2,7},⁹.0^{12,16}] octadec-4-en-15-yl}ethyl]-4-methyl-3-[(1-pyrrolidinyl)methyl]-5, 6-dihydro-2H-pyran-2-one (89 mg, 12%) as white solid.

[0447] Analytical data: 99.06 % (m/z: 601.5, [M+1]⁺, 5.02 min (10 min run).

¹H-NMR (400 MHz, DMSO-*d*₆): δ 8.60 (d, *J*=4.0 Hz, 1H), 7.85-7.80 (m, 1H), 7.67 (d, *J*=6.4 Hz, 1H), 7.38 - 7.34 (m, 2H), 5.74 (d, *J*= 3.6 Hz, 1H), 4.29- 4.25 (m, 1H), 3.77- 3.74 (m, 1H), 3.38-3.13 (m, 3H), 2.42-2.36 (m, 5H), 2.10-1.50 (m, 13H), 1.41-1.22 (m, 7H), 1.14-1.04 (m, 3H), 0.97 – 0.84 (m, 6H), 0.66 (s, 3H).

¹³C-NMR (400 MHz, DMSO-*d*₆): δ 200.59, 165.42, 154.46, 152.47, 149.60, 141.13, 139.81, 136.94, 123.41, 122.76, 122.17, 77.44, 68.51, 63.52, 57.55, 55.32, 53.23, 51.07, 49.30, 47.90, 42.09, 42.02, 30.76, 29.24, 29.13, 26.51, 23.93, 23.02, 20.49, 20.25, 15.13, 13.07, 11.25.

[0448] Synthesis of Compound 51**[0449] Step-1: Synthesis of (R)-6-[(S)-1-[(1S, 2R, 6S, 7R, 9R, 11S, 12S, 15R, 16S)-6-hydroxy-2, 16-dimethyl-3-oxo-4-(2-pyridyl)-8-oxapentacyclo [9.7.0.0^{2,7}.0^{7,9}.0^{12,16}] octadec-4-en-15-yl}ethyl]-3-(hydroxymethyl)-4-methyl-5, 6-dihydro-2H-pyran-2-one:**

To a stirred solution of (R)-6-[(S)-1-[(1S, 2R, 6S, 7R, 9R, 11S, 12S, 15R, 16S)-6-hydroxy-2, 16-dimethyl-3-oxo-4-(2-pyridyl)-8-oxapentacyclo [9.7.0.0^{2,7}.0^{7,9}.0^{12,16}] octadec-4-en-15-yl}ethyl]-3-(hydroxymethyl)-4-methyl-5, 6-dihydro-2H-pyran-2-one (1 g, 1.83 mmol) in dichloromethane (10 mL) was added ethylbis (propan-2-yl)amine (478 μ L, 1.5 eq., 2.74 mmol) then methanesulfonyl chloride (141 μ L, 1.83 mmol) at -20 °C. The reaction mixture was stirred at -20 °C for 10 minutes. After the completion (monitored by TLC), the reaction mixture was diluted with water (40 mL) and extracted with ethyl acetate (2 X 40 mL). The organic layer was washed with brine solution, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to get (R)-6-[(S)-1-[(1S, 2R, 6S, 7R, 9R, 11S, 12S, 15R, 16S)-6-hydroxy-2, 16-dimethyl-3-oxo-4-(2-pyridyl)-8-oxapentacyclo [9.7.0.0^{2,7}.0^{7,9}.0^{12,16}] octadec-4-en-15-yl}ethyl]-3-[(mesyloxy)methyl]-4-methyl-5, 6-dihydro-2H-pyran-2-one. It was forwarded as such to the next step.

To a stirred solution of dipotassium carbonate (442 mg, 2 eq., 3.2 mmol) in acetonitrile (10 mL) was added piperidine (237 μ L, 1.5 eq., 2.4 mmol) followed by addition of (R)-6-[(S)-1-[(1S, 2R, 6S, 7R, 9R, 11S, 12S, 15R, 16S)-6-hydroxy-2, 16-dimethyl-3-oxo-4-(2-pyridyl)-8-oxapentacyclo [9.7.0.0^{2,7}.0^{7,9}.0^{12,16}] octadec-4-en-15-yl}ethyl]-3-[(mesyloxy)methyl]-4-methyl-5, 6-dihydro-2H-pyran-2-one (1 g, 1.6 mmol) at 0°C. The resultant reaction mixture was stirred at 60 °C for 30 min. After the completion (monitored by TLC), the reaction mixture was diluted with water (40 mL) and extracted with ethyl acetate (2 X 40 mL). The organic layer was washed with brine solution, dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure. The crude was purified by using preparative-HPLC in

ABC method to afford (R)-6-[(S)-1-{(1S, 2R, 6S, 7R, 9R, 11S, 12S, 15R, 16S)-6-hydroxy-2, 16-dimethyl-3-oxo-4-(2-pyridyl)-8-oxapentacyclo [9.7.0.0^{2,7}.0^{7,9}.0^{12,16}] octadec-4-en-15-yl}ethyl]-4-methyl-3-(piperidinomethyl)-5, 6-dihydro-2H-pyran-2-one (85 mg, 8%) as a white solid.

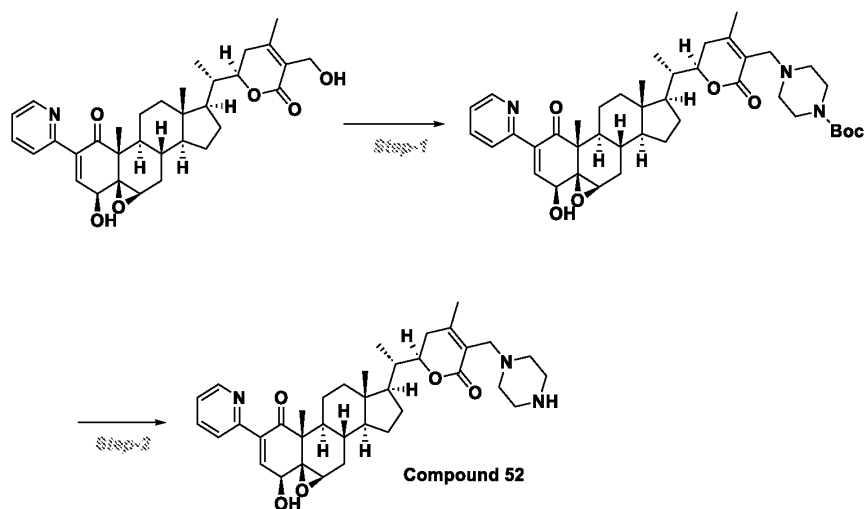
[0450] Analytical data:

LCMS: 95.41% (m/z: 615.50, [M+1]⁺, 5.38 min (10 min run).

¹H-NMR (400 MHz, DMSO-*d*₆): δ 8.60 (d, *J* = 4 Hz, 1H), 7.85-7.80 (m, 1H), 7.68 (d, *J* = 6.40 Hz, 1H), 7.38-7.34 (m, 2H), 5.75 (d, *J* = 3.60 Hz, 1H), 4.29-4.26 (m, 1H), 3.76-3.74 (m, 1H), 3.22-3.16 (m, 2H), 2.99 (d, *J* = 12.8 Hz, 1H), 2.49-2.39 (m, 1H), 2.31-2.2 (bs, 4H), 2.12 - 2.02 (m, 2H), 1.98 (s, 3H), 1.93-1.20 (m, 16H), 1.14-1.04 (m, 4H), 0.97-0.87 (m, 6H), 0.66 (s, 3H).

¹³C-NMR (400 MHz, DMSO-*d*₆): δ 200.59, 165.45, 155.25, 152.47, 149.60, 141.13, 139.80, 136.94, 123.41, 122.17, 122.04, 77.36, 68.51, 63.52, 57.55, 55.32, 53.79, 52.99, 51.07, 47.90, 42.09, 42.03, 30.77, 29.25, 26.52, 25.59, 24.00, 23.92, 20.49, 20.39, 15.14, 13.09, 11.25.

[0451] Synthesis of Compound 52



[0452] Step-1: Synthesis of tert-butyl 4-[(R)-6-[(S)-1-{(1S, 2R, 6S, 7R, 9R, 11S, 12S, 15R, 16S)-6-hydroxy-2, 16-dimethyl-3-oxo-4-(2-pyridyl)-8-oxapentacyclo [9.7.0.0^{2,7}.0^{7,9}.0^{12,16}] octadec-4-en-15-yl} ethyl]-4-methyl-2-oxo-5, 6-dihydro-2H-pyran-3-yl] methyl}-1-piperazinecarboxylate:

To a stirred solution of (R)-6-[(S)-1-{(1S, 2R, 6S, 7R, 9R, 11S, 12S, 15R, 16S)-6-hydroxy-2, 16-dimethyl-3-oxo-4-(2-pyridyl)-8-oxapentacyclo [9.7.0.0²,⁷.0⁷,⁹.0¹²,¹⁶] octadec-4-en-15-yl}ethyl]-3-(hydroxymethyl)-4-methyl-5,6-dihydro-2H-pyran-2-one (1 g, 1.83 mmol) in dichloromethane (10 mL) was added ethylbis (propan-2-yl)amine (478 μ L, 1.5 eq., 2.74 mmol) then methanesulfonyl chloride (141 μ L, 1.83 mmol) at -20 °C. The reaction mixture was stirred at -20 °C for 10 minutes. After the completion (monitored by TLC), the reaction mixture was diluted with water (40 mL) and extracted with ethyl acetate (2 X 40 mL). The organic layer was washed with brine solution, dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure to get (R)-6-[(S)-1-{(1S, 2R, 6S, 7R, 9R, 11S, 12S, 15R, 16S)-6-hydroxy-2, 16-dimethyl-3-oxo-4-(2-pyridyl)-8-oxapentacyclo [9.7.0.0²,⁷.0⁷,⁹.0¹²,¹⁶] octadec-4-en-15-yl}ethyl]-3-[(mesyloxy) methyl]-4-methyl-5, 6-dihydro-2H-pyran-2-one. It was forwarded to the next step as such.

To a stirred solution of tert-butyl 1-piperazinecarboxylate (446 mg, 1.5 eq., 2.4 mmol) in acetonitrile (10 mL) was added dipotassium carbonate (442 mg, 2 eq., 3.2 mmol) followed by addition of (R)-6-[(S)-1-{(1S, 2R, 6S, 7R, 9R, 11S, 12S, 15R, 16S)-6-hydroxy-2, 16-dimethyl-3-oxo-4-(2-pyridyl)-8-oxapentacyclo [9.7.0.0²,⁷.0⁷,⁹.0¹²,¹⁶] octadec-4-en-15-yl}ethyl]-3-[(mesyloxy) methyl]-4-methyl-5, 6-dihydro-2H-pyran-2-one (1 g, 1.6 mmol) at 0 °C. The resultant reaction mixture was stirred at 60 °C for 30 min. After the completion (monitored by TLC), the reaction mixture was diluted with water (40 mL) and extracted with ethyl acetate (2 X 40 mL). The organic layer was washed with brine solution, dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure to afford tert-butyl 4-{[(R)-6-[(S)-1-{(1S, 2R, 6S, 7R, 9R, 11S, 12S, 15R, 16S)-6-hydroxy-2, 16-dimethyl-3-oxo-4-(2-pyridyl)-8-oxapentacyclo [9.7.0.0²,⁷.0⁷,⁹.0¹²,¹⁶] octadec-4-en-15-yl} ethyl]-4-methyl-2-oxo-5, 6-dihydro-2H-pyran-3-yl] methyl}-1-piperazinecarboxylate (0.8 g, 1.12 mmol).

[0453] Analytical data:

LCMS: 58.31% (m/z: 716.15, [M+1]⁺, 2.29 min (4 min run).

[0454] Step-2: Synthesis of (R)-6-[(S)-1-{(1S, 2R, 6S, 7R, 9R, 11S, 12S, 15R, 16S)-6-hydroxy-2, 16-dimethyl-3-oxo-4-(2-pyridyl)-8-oxapentacyclo [9.7.0.0²,⁷.0⁷,⁹.0¹²,¹⁶] octadec-4-en-15-yl} ethyl]-4-methyl-3-[(1-piperazinyl)methyl]-5, 6-dihydro-2H-pyran-2-one :

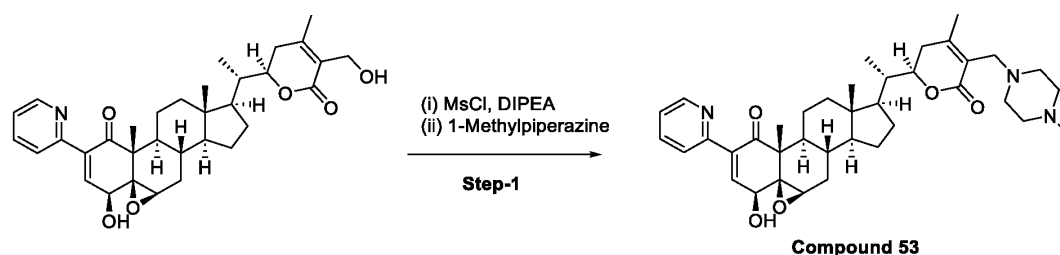
To a stirred solution of tert-butyl 4-{[(R)-6-[(S)-1-{(1S, 2R, 6S, 7R, 9R, 11S, 12S, 15R, 16S)-6-hydroxy-2, 16-dimethyl-3-oxo-4-(2-pyridyl)-8-oxapentacyclo [9.7.0.0²,⁷.0⁷,⁹.0¹²,¹⁶] octadec-

4-en-15-yl} ethyl]-4-methyl-2-oxo-5, 6-dihydro-2H-pyran-3-yl] methyl}-1-piperazinecarboxylate (0.8 g, 1.12 mmol) in dichloromethane (8 mL) was added trifluoroacetic acid (2.4 mL) dropwise at 0 °C. The resultant reaction mixture was stirred for 3h at room temperature. After the completion (monitored by TLC), reaction mixture was quenched by sat. sodium bicarbonate solution (40 mL) and extracted with DCM (2 X 40 mL). The organic layer was washed with brine solution, dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure. The crude was purified by using preparative-HPLC using ABC method to afford (R)-6-[(S)-1-{(1S, 2R, 6S, 7R, 9R, 11S, 12S, 15R, 16S)-6-hydroxy-2, 16-dimethyl-3-oxo-4-(2-pyridyl)-8-oxapentacyclo [9.7.0.0^{2,7},0^{7,9},0^{12,16}] octadec-4-en-15-yl}ethyl]-4-methyl-3-[(1-piperazinyl) methyl]-5, 6-dihydro-2H-pyran-2-one (66 mg, 8.6%) as white solid.

[0455] Analytical data:

LCMS: 90.41% (m/z: 616.5, [M+1]⁺, 4.82 min (10 min run).

[0456] Synthesis of Compound 53



[0457] Step-1: Synthesis of (R)-6-[(S)-1-{(1S, 2R, 6S, 7R, 9R, 11S, 12S, 15R, 16S)-6-hydroxy-2, 16-dimethyl-3-oxo-4-(2-pyridyl)-8-oxapentacyclo [9.7.0.0^{2,7},0^{7,9},0^{12,16}] octadec-4-en-15-yl}ethyl]-4-methyl-3-[(4-methyl-1-piperazinyl)methyl]-5, 6-dihydro-2H-pyran-2-one

To a stirred solution of (1S, 2R, 6S, 7R, 9R, 11S, 12S, 15R, 16S)-6-hydroxy-15-[(1S)-1-[(2R)-5-(hydroxymethyl)-4-methyl-6-oxo-3, 6-dihydro-2H-pyran-2-yl]ethyl]-2, 16-dimethyl-4-(pyridin-2-yl)-8-oxapentacyclo [9.7.0.0^{2,7},0^{7,9},0^{12,16}] octadec-4-en-3-one (0.57 g, 1.04 mmol) in dichloromethane (10 mL) was added ethylbis (propan-2-yl)amine (0.272 mL, 1.5 eq., 1.56 mmol) followed by methanesulfonyl chloride (0.072 mL, 0.9 eq., 0.937 mmol) at -30 °C. The reaction mixture was stirred at -30 °C for 10 minutes. After the completion of reaction

(monitored by TLC), mixture was diluted with water (50 mL) and extracted with DCM (3 X 50 mL). The organic layer was washed with brine solution, dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure to get crude [(6R)-6-[(1S)-1-[(1S, 2R, 6S, 7R, 9R, 11S, 12S, 15R, 16S)-6-hydroxy-2, 16-dimethyl-3-oxo-4-(pyridin-2-yl)-8-oxapentacyclo [9.7.0.0^{2,7}.0^{7,9}.0^{12,16}] octadec-4-en-15-yl] ethyl]-4-methyl-2-oxo-5, 6-dihydro-2H-pyran-3-yl] methyl methanesulfonate. It was forwarded to next step as such without further purification.

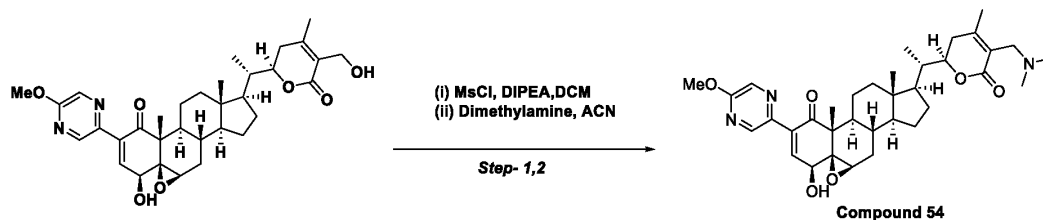
To a stirred solution of dipotassium carbonate (0.28 g, 2 eq., 2.08 mmol) in acetonitrile (10 mL) was added 1-methylpiperazine (0.15 g, 1.5 eq., 1.56 mmol) followed by addition of (R)-6-[(S)-1-[(1S, 2R, 6S, 7R, 9R, 11S, 12S, 15R, 16S)-6-hydroxy-2, 16-dimethyl-3-oxo-4-(2-pyridyl)-8-oxapentacyclo [9.7.0.0^{2,7}.0^{7,9}.0^{12,16}] octadec-4-en-15-yl}ethyl]-3-[(mesyloxy) methyl]-4-methyl-5, 6-dihydro-2H-pyran-2-one (0.65 g, 1.04 mmol) at 0 °C. The resultant reaction mixture was stirred at 60°C for 30 min. After the completion of reaction (monitored by TLC), mixture was diluted with water (50 mL) and extracted with ethyl acetate (2 X 50 mL). The collected organics were dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure to obtain crude which was then purified by using preparative-HPLC A-5 mM ammonium bicarbonate in Water, B- Acetonitrile to afford (R)-6-[(S)-1-[(1S, 2R, 6S, 7R, 9R, 11S, 12S, 15R, 16S)-6-hydroxy-2, 16-dimethyl-3-oxo-4-(2-pyridyl)-8-oxapentacyclo [9.7.0.0^{2,7}.0^{7,9}.0^{12,16}] octadec-4-en-15-yl}ethyl]-4-methyl-3-[(4-methyl-1-piperazinyl) methyl]-5, 6-dihydro-2H-pyran-2-one (0.112 g, 0.178 mmol, 17%) as white solid.

[0458] Analytical data:

LCMS: 97.10 % (m/z: 630.4, [M+1]⁺, 5.05 min (10 min run).

¹H-NMR (400 MHz, DMSO-*d*₆): δ 8.60 (d, *J* = 4.0 Hz, 1H), 7.85-7.80 (m, 1H), 7.68 (d, *J* = 6.80 Hz, 1H), 7.38-7.34 (m, 2H), 5.74 (d, *J* = 3.2 Hz, 1H), 4.29-4.26 (m, 1H), 3.75 (dd, *J* = 3.60, 6.80 Hz, 1H), 3.24 (d, *J* = 12.4 Hz, 1H), 3.16 (s, 1H), 3.04 (d, *J* = 12.4 Hz, 1H), 2.43-2.20 (m, 6H), 2.10 (s, 4H), 2.07-2.02 (m, 2H), 1.97 (s, 3H), 1.92-1.34 (m, 7H), 1.31 (s, 3H), 1.28-1.04 (m, 6H), 0.97-0.84 (m, 6H), 0.65 (s, 3H).

¹³C-NMR (400 MHz, DMSO-*d*₆): δ 200.58, 165.44, 155.61, 152.47, 149.59, 141.13, 139.81, 136.93, 123.41, 122.17, 121.70, 77.39, 68.51, 63.52, 57.55, 55.32, 54.76, 52.36, 52.17, 51.07, 47.90, 45.75, 42.10, 42.03, 30.77, 29.25, 26.53, 23.92, 20.49, 20.41, 15.14, 13.08, 11.25.

[0459] Synthesis of Compound 54

[0460] Step-1,2: Synthesis of (R)-6-[(S)-1-{(1S, 2R, 6S, 7R, 9R, 11S, 12S, 15R, 16S)-6-hydroxy-4-(5-methoxy-2-pyrazinyl)-2,16-dimethyl-3-oxo-8-oxapentacyclo [9.7.0.0^{2,7}.0^{7,9}.0^{12,16}] octadec-4-en-15-yl} ethyl]-3-[(dimethylamino) methyl]-4-methyl-5, 6-dihydro-2H-pyran-2-one:

To a stirred solution of (R)-6-[(S)-1-{(1S, 2R, 6S, 7R, 9R, 11S, 12S, 15R, 16S)-6-hydroxy-4-(5-methoxy-2-pyrazinyl)-2, 16-dimethyl-3-oxo-8-oxapentacyclo [9.7.0.0^{2,7}.0^{7,9}.0^{12,16}] octadec-4-en-15-yl} ethyl]-3-(hydroxymethyl)-4-methyl-5, 6-dihydro-2H-pyran-2-one (0.2 g, 346 μ mol) in dichloromethane (2 mL) was added ethylbis (propan-2-yl)amine (151 μ L, 2.5 eq., 864 μ mol) then methanesulfonyl chloride (26.7 μ L, 346 μ mol) at 0°C. The reaction mixture was stirred at 0°C for 30 minutes. After the completion of reaction (monitored by TLC, 70% Ethyl acetate in heptane), reaction mixture was diluted with water (25 mL) and extracted with DCM (2 X 25mL). The organic layer was washed with brine solution, dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure to get (R)-6-[(S)-1-{(1S, 2R, 6S, 7R, 9R, 11S, 12S, 15R, 16S)-6-hydroxy-4-(5-methoxy-2-pyrazinyl)-2,16-dimethyl-3-oxo-8-oxapentacyclo [9.7.0.0^{2,7}.0^{7,9}.0^{12,16}] octadec-4-en-15-yl} ethyl]-3-[(mesyloxy) methyl]-4-methyl-5, 6-dihydro-2H-pyran-2-one (210 mg crude). It was forwarded as such to the next step.

To a stirred solution of triethylamine (154 mg, 5 eq., 1.52 mmol) in acetonitrile (2 mL) was added dimethyl amine (2M in THF) (22 mg, 1.6 eq., 487 μ mol) followed by addition of (R)-6-[(S)-1-{(1S, 2R, 6S, 7R, 9R, 11S, 12S, 15R, 16S)-6-hydroxy-4-(5-methoxy-2-pyrazinyl)-2,16-dimethyl-3-oxo-8-oxapentacyclo [9.7.0.0^{2,7}.0^{7,9}.0^{12,16}] octadec-4-en-15-yl} ethyl]-3-[(mesyloxy)methyl]-4-methyl-5, 6-dihydro-2H-pyran-2-one (0.2 g, 305 μ mol) at 0°C. The resultant reaction mixture was stirred at 60°C for 30 min. After the completion of reaction (monitored by TLC 50% ethyl acetate in heptane), reaction mixture was diluted with water (25 mL) and extracted with ethyl acetate (2 X 25 mL). The organic layer was washed with brine

solution, dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure. Crude was purified by preparative-HPLC by ammonium bicarbonate method to afford (R)-6-[(S)-1-{(1S, 2R, 6S, 7R, 9R, 11S, 12S, 15R, 16S)-6-hydroxy-4-(5-methoxy-2-pyrazinyl)-2, 16-dimethyl-3-oxo-8-oxapentacyclo [9.7.0.0^{2,7}.0^{7,9}.0^{12,16}] octadec-4-en-15-yl} ethyl]-3-[(dimethylamino) methyl]-4-methyl-5, 6-dihydro-2H-pyran-2-one (31 mg, 16.4%) as white solid.

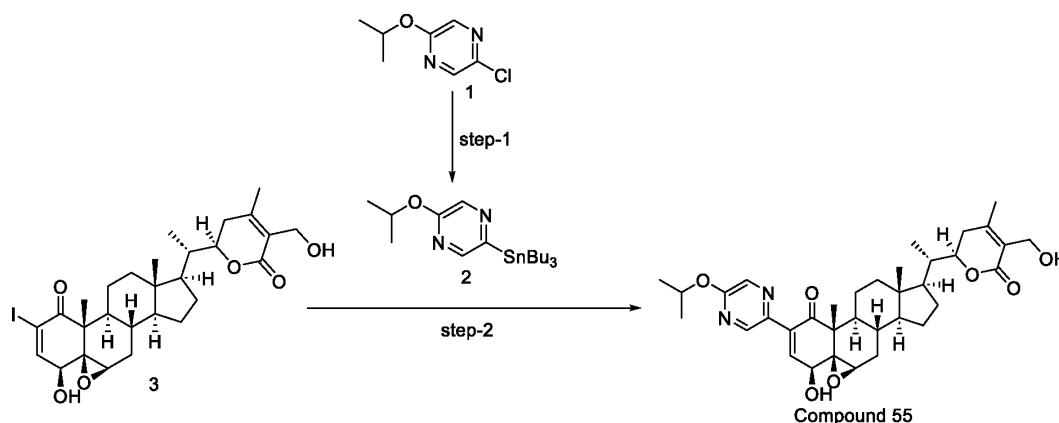
[0461] Analytical data:

LCMS: 97.71% (m/z: 606.60, [M+1]⁺, 5.49 min (21min run).

¹H-NMR (400 MHz, DMSO-d₆): δ 8.36 (s, 1H), 8.21 (s, 1H), 7.60 (d, J = 6.8 Hz, 1H), 5.76 (d, J = 3.6 Hz, 1H), 4.305-4.261 (m, 1H), 3.93 (s, 3H), 3.76-3.74 (m, 1H), 3.15-2.95 (m, 3H), 2.43-2.32 (m, 1H), 2.11-2.00 (m, 8H), 1.98 (s, 3H), 1.90 (d, J = 12.4 Hz, 1H), 1.81-1.55 (m, 3H), 1.40-1.21 (m, 8H), 1.14-0.86 (m, 8H), 0.65 (s, 3H).

¹³C-NMR (400 MHz, DMSO-d₆): δ 200.31, 165.41, 159.34, 155.37, 140.63, 139.144, 138.91, 138.29, 134.99, 122.36, 77.44, 68.41, 63.39, 57.57, 55.24, 53.78, 53.12, 51.07, 47.88, 44.87, 2.12, 41.98, 30.72, 29.25, 29.19, 26.47, 23.89, 20.48, 20.31, 15.13, 13.06, 11.22.

[0462] Synthesis of Compound 55



[0463] Step-1: Synthesis of tributyl(5-isopropoxy-2-pyrazinyl) stannane

To a stirred solution of 2-chloro-5-isopropoxypyrazine (0.5 g, 2.9 mmol) in 1,4-dioxane (7 mL) were added hexabutyl distannane (2.02 g, 1.2 eq., 3.48 mmol), tricyclohexyl phosphine (73.1 mg, 0.09 eq., 261 μmol) and lithium chloride (737 mg, 6 eq., 17.4 mmol) at RT. Reaction

mixture was purged with N₂ for 20 min. Then, palladium—(1E,4E)-1,5-diphenyl-1,4-pentadien-3-one (2/3) (133 mg, 0.05 eq., 145 μ mol) was added to it and again purged with N₂ for 5 min. Reaction was stirred at 100 °C for 3 h. After completion of the reaction (monitored by TLC), it was filtered through hyper flow celite by using sintered funnel and filtrate was directly concentrated under reduced pressure to obtain crude. Crude product was purified by combi flash column chromatography using (2-5%) ethyl acetate in heptane as an eluent to afford tributyl(5-isopropoxy-2-pyrazinyl) stannane (478 mg, 649 μ mol) as an light brown liquid. Other suitable catalysts that may be used herein include Tris((1E,4E)-1,5-diphenylpenta-1,4-dien-3-one) dipalladium [Pd₂(dba)₃], Copper Iodide [CuI], Triphenylarsane [AsPh₃], Tetrakis (triphenylphosphine)palladium(0) [Pd(PPh₃)₄] and Bis(triphenylphosphine)palladium(II) dichloride [PdCl₂(PPh₃)₂]

[0464] Analytical data:

LCMS: purity 58% (m/z: 427.00, [M+1]⁺, 2.52 min (4 min run).

[0465] Step-2: Synthesis of (R)-6-[(S)-1-{(1S, 2R, 6S, 7R, 9R, 11S, 12S, 15R, 16S)-6-hydroxy-4-(5-isopropoxy-2-pyrazinyl)-2, 16-dimethyl-3-oxo-8-oxapentacyclo [9.7.0.0^{2,7},0^{7,9},0^{12,16}] octadec-4-en-15-yl}ethyl]-3-(hydroxymethyl)-4-methyl-5, 6-dihydro-2H-pyran-2-one

To a stirred solution of (R)-6-[(S)-1-{(1S, 2R, 6S, 7R, 9R, 11S, 12S, 15R, 16S)-6-hydroxy-4-iodo-2, 16-dimethyl-3-oxo-8-oxapentacyclo [9.7.0.0^{2,7},0^{7,9},0^{12,16}] octadec-4-en-15-yl}ethyl]-3-(hydroxymethyl)-4-methyl-5, 6-dihydro-2H-pyran-2-one (0.2 g, 335 μ mol) in tetrahydrofuran (3 mL) were added tributyl(5-isopropoxy-2-pyrazinyl) stannane (286 mg, 2 eq., 671 μ mol) , copper iodide (6.39 mg, 0.1 eq., 33.5 μ mol) and triphenylarsane (10.3 mg, 0.1 eq., 33.5 μ mol) at RT. The reaction mixture was purged with N₂ gas for 20 min and tris ((1E, 4E)-1,5-diphenylpenta-1,4-dien-3-one) dipalladium (30.7 mg, 0.1 eq., 33.5 μ mol) was added to it . The reaction mixture was again purged with N₂ gas for 5 min. The reaction vial was sealed and stirred at 80 °C for 2h. After completion of the reaction (monitored by TLC and LCMS), it was quenched by adding water (10 mL) and extracted using ethyl acetate (3 x 15 mL). Collected organics were dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure to obtain crude. Crude product was purified by Prep HPLC in ammonium bicarbonate method to afford (R)-6-[(S)-1-{(1S, 2R, 6S, 7R, 9R, 11S, 12S, 15R, 16S)-6-hydroxy-4-(5-isopropoxy-2-pyrazinyl)-2, 16-dimethyl-3-oxo-8-oxapentacyclo [9.7.0.0^{2,7},0^{7,9},0^{12,16}] octadec-

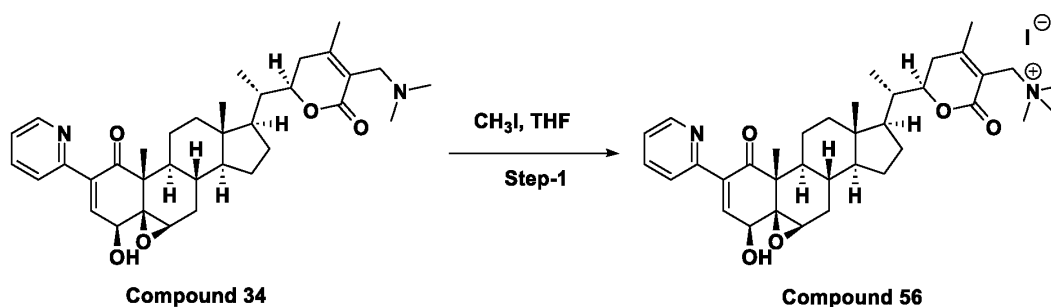
4-en-15-yl} ethyl]-3-(hydroxymethyl)-4-methyl-5, 6-dihydro-2H-pyran-2-one (23 mg, 11%)
as white solid.

[0466] Analytical data: 98.97 % (m/z: 607.45, [M+1]⁺, 6.68 min (10 min run).

¹H-NMR (400 MHz, DMSO-*d*₆): δ 8.27 (d, J = 1.2 Hz, 1H), 8.17 (d, J = 1.2 Hz, 1H), 7.59 (d, J = 6.4 Hz, 1H), 5.76 (d, J = 3.6 Hz, 1H), 5.27-5.21 (m, 1H), 4.59 (t, J = 5.2 Hz, 1H), 4.29-3.73 (m, 4H), 3.16 (s, 1H), 2.37-1.70 (m, 9H), 1.56-1.27 (m, 15H), 1.14-0.85 (m, 8H), 0.65 (s, 3H).

¹³C-NMR (400 MHz, DMSO-*d*₆): δ 200.33, 165.29, 158.60, 154.63, 140.18, 138.97, 138.31, 135.33, 125.41, 77.49, 69.16, 68.41, 63.39, 57.60, 55.22, 54.49, 51.04, 47.88, 42.10, 41.96, 30.73, 29.25, 29.00, 26.47, 23.95, 21.58, 20.48, 19.86, 15.17, 13.02, 11.22.

[0467] Synthesis of Compound 56



[0468] Step-1: Synthesis of 1-((R)-6-((S)-1-((4S, 4aR, 5aR, 6aS, 6bS, 9R, 9aS, 11aS, 11bR)-4-hydroxy-9a, 11b-dimethyl-1-oxo-2-(pyridin-2-yl)-1, 4, 5a, 6, 6a, 6b, 7, 8, 9, 9a, 10, 11, 11a, 11b-tetradecahydrocyclopenta [1, 2] phenanthro [8a, 9-b] oxiren-9-yl) ethyl)-4-methyl-2-oxo-5, 6-dihydro-2H-pyran-3-yl)-N, N, N-trimethylmethanaminium:

To a stirred solution of (R)-6-[(S)-1-{(1S,2R,6S,7R,9R,11S,12S,15R,16S)-6-hydroxy-2,16-dimethyl-3-oxo-4-(2-pyridyl)-8-oxapentacyclo[9.7.0.0.2^{7,0}7^{9,0}12¹⁶]octadec-4-en-15-yl}ethyl]-3-[(dimethylamino)methyl]-4-methyl-5,6-dihydro-2H-pyran-2-one (130 mg, 226 μmol) in tetrahydrofuran (2.5 mL) was added iodomethane (35.3 mg, 1.1 eq., 249 μmol) to 0°C, stirred the reaction mixture for 2 hours at room temperature. After completion of reaction (monitored by TLC), the reaction mixture was concentrated under reduced pressure, washed with diethyl

ether to get 1-((R)-6-((S)-1-((4S, 4aR, 5aR, 6aS, 6bS, 9R, 9aS, 11aS, 11bR)-4-hydroxy-9a, 11b-dimethyl-1-oxo-2-(pyridin-2-yl)-1, 4, 5a, 6, 6a, 6b, 7, 8, 9, 9a, 10, 11, 11a, 11b-tetradecahydrocyclopenta [1, 2] phenanthro [8a ,9-b] oxiren-9-yl)ethyl)-4-methyl-2-oxo-5, 6-dihydro-2H-pyran-3-yl)-N, N, N-trimethylmethanaminium (150 mg, 89%) as a white solid.

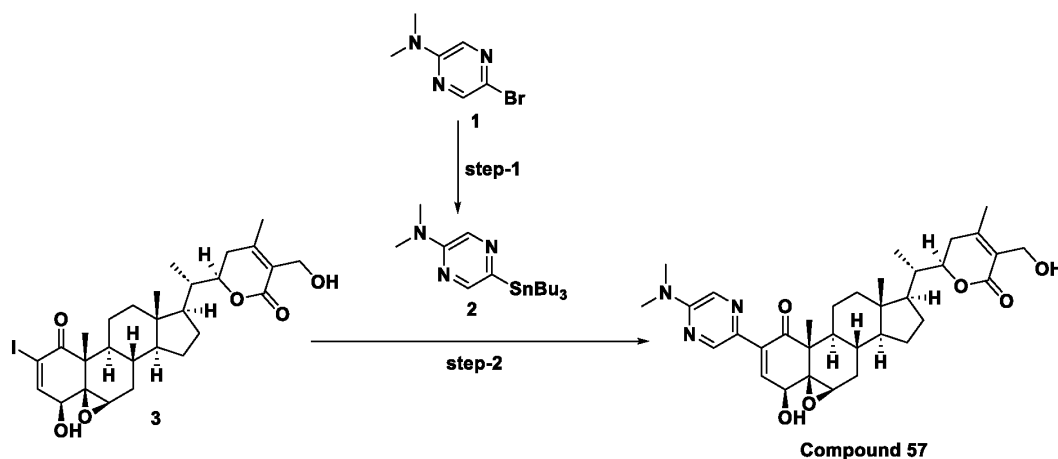
[0469] Analytical data:

LCMS: 70.92% + 26.3% (I⁻) (m/z: 589.50, [M+1]⁺, 4.88 min (10 min run).

¹H-NMR (400 MHz, DMSO-*d*₆): δ 8.60 (d, *J* = 4.0 Hz, 1H), 7.85-7.81 (m, 1H), 7.68 (d, *J* = 6.80 Hz, 1H), 7.40-7.34 (m, 2H), 5.75 (d, *J* = 3.20 Hz, 1H), 4.65-4.61 (m, 1H), 4.31 (d, *J* = 13.2 Hz, 1H), 4.20 (d, *J* = 13.2 Hz, 1H), 3.77-3.74 (m, 1H), 3.16 (s, 1H), 3.0 (s, 9H), 2.31-2.30 (m, 1H), 2.14 (s, 3H), 2.07-2.03 (m, 1H), 1.94-1.90 (m, 1H), 1.83-1.79 (m, 2H), 1.59-1.56 (m, 1H), 1.42-1.38 (m, 2H), 1.35-1.32 (m, 6H), 1.29-1.23 (m, 1H), 1.16-1.08 (m, 3H), 0.99-0.85 (m, 5H), 0.67 (s, 3H).

¹³C-NMR (400 MHz, DMSO-*d*₆): δ 200.56, 166.76, 165.07, 152.49, 149.58, 141.11, 139.84, 136.92, 123.40, 122.14, 115.09, 76.93, 68.49, 63.51, 59.14, 57.53, 55.34, 52.12, 51.03, 47.88, 42.10, 42.03, 30.74, 30.40, 30.33, 29.25, 26.76, 23.79, 21.89, 20.48, 15.12, 12.96, 11.23.

[0470] Synthesis of Compound 57



[0471] Step-1: Synthesis of N, N-dimethyl[5-(tributylstannyl)-2-pyrazinyl] amine

To a stirred solution of N,N-dimethyl(5-bromo-2-pyrazinyl)amine (0.5 g, 2.47 mmol) in 1,4-Dioxane (5 mL) were added hexabutylstannane (1.72 g, 1.2 eq., 0.297 mmol), tricyclohexylphosphane (0.069 g, 0.1 eq., 0.247 mmol), lithium(1+) chloride (0.629 g, 6 eq.,

14.8 mmol). The reaction mixture was purged with argon gas for 30 min then tris(dibenzylideneacetone)dipalladium (0.227 g, 0.1 eq., 0.24 mmol) was added to it. The reaction mixture was again purged with argon gas for 5 min. The reaction vessel was sealed and stirred at 100°C for 3 h. After completion of the reaction (monitored by TLC), it was quenched by adding water (50 mL) and then extracted using ethyl acetate (2 x 60 mL). Collected organics were dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure to obtain crude. Crude product was purified by combi flash column chromatography using (5-10%) ethyl acetate in heptane as an eluent to afford N,N-dimethyl[5-(tributylstannyl)-2-pyrazinyl]amine (0.6 g, 1.46 mmol, 58%) as a colourless liquid.

[0472] Analytical data:

¹H-NMR (400 MHz, DMSO-*d*₆): δ 8.34 (d, *J*=1.6 Hz, 1H), 7.95 (d, *J*=1.6 Hz, 1H), 3.03 (s, 6H), 1.58-1.43 (m, 6H), 1.34-1.23 (m, 6H), 1.11-0.96 (m, 6H), 0.89-0.86 (m, 9H).

[0473] Step-2: Synthesis of (R)-6-[(S)-1-{(1S, 2R, 6S, 7R, 9R, 11S, 12S, 15R, 16S)-4-[5-(dimethylamino)-2-pyrazinyl]-6-hydroxy-2, 16-dimethyl-3-oxo-8-oxapentacyclo [9.7.0.0^{2,7}.0^{12,16}] octadec-4-en-15-yl} ethyl]-3-(hydroxymethyl)-4-methyl-5, 6-dihydro-2H-pyran-2-one

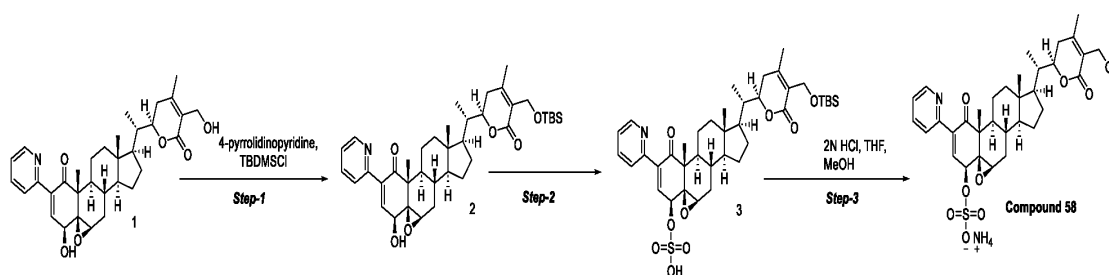
To a stirred solution of (R)-6-[(S)-1-{(1S, 2R, 6S, 7R, 9R, 11S, 12S, 15R, 16S)-6-hydroxy-4-iodo-2, 16-dimethyl-3-oxo-8-oxapentacyclo [9.7.0.0^{2,7}.0^{12,16}] octadec-4-en-15-yl} ethyl]-3-(hydroxymethyl)-4-methyl-5, 6-dihydro-2H-pyran-2-one (0.38 g, 0.647 mmol) and N,N-dimethyl[5-(tributylstannyl)-2-pyrazinyl]amine (0.40 g, 1.5 eq., 0.97 mmol) in 1,4-Dioxane (4 mL) was added copper (I+) iodide (0.018 g, 0.15 eq., 0.097 mmol) at RT. The resulting mixture was purged with argon for 30 min. Added tris (dibenzylideneacetone) dipalladium (0.029 g, 0.05 eq., 0.032 mmol) and stirred for 2h at 80°C. After completion of the reaction (monitored by TLC and LCMS), it was quenched by adding water (50 mL) and brine solution (50 mL), then extracted using ethyl acetate (3 x 50 mL). Collected organics were dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure to obtain crude. Crude product was purified by combi flash column chromatography using (5-10%) methanol in DCM as an eluent followed by Prep HPLC purification in ammonium bicarbonate method to afford (R)-6-[(S)-1-{(1S, 2R, 6S, 7R, 9R, 11S, 12S, 15R, 16S)-4-[5-(dimethylamino)-2-pyrazinyl]-6-hydroxy-2, 16-dimethyl-3-oxo-8-oxapentacyclo [9.7.0.0^{2,7}.0^{12,16}] octadec-4-en-15-yl}

ethyl]-3-(hydroxymethyl)-4-methyl-5, 6-dihydro-2H-pyran-2-one (12 mg, 0.020 mmol, 4%) as yellow solid.

[0474] **Analytical data:** 90.67% (m/z: 592.5, $[M+1]^+$, 5.66 min (10 min run).

$^1\text{H-NMR}$ (400 MHz, $\text{DMSO-}d_6$): δ 8.19 (d, $J = 1.2$ Hz, 1H), 8.05 (d, $J = 1.2$ Hz, 1H), 7.43 (d, $J = 6.8$ Hz, 1H), 5.64 (d, $J = 3.2$ Hz, 1H), 4.58 (t, $J = 5.2$ Hz, 1H), 4.29-4.26 (m, 1H), 4.16-4.08 (m, 2H), 3.72-3.70 (m, 1H), 3.14 (s, 1H), 3.10 (s, 6H), 2.41-2.33 (m, 1H), 2.10-2.05 (m, 2H), 1.98 (s, 3H), 1.92-1.70 (m, 3H), 1.56-1.54 (m, 1H), 1.37-1.20 (m, 8H), 1.14-1.04 (m, 3H), 0.92 (d, $J = 6.4$ Hz, 3H), 0.87-0.83 (m, 2H), 0.65 (s, 3H).

[0475] **Synthesis of Compound 58**



[0476] **Step-1: Synthesis of (R)-6-[(S)-1-[(1S, 2R, 6S, 7R, 9R, 11S, 12S, 15R, 16S)-6-hydroxy-2, 16-dimethyl-3-oxo-4-(2-pyridyl)-8-oxapentacyclo [9.7.0.0^{2,7}.0^{12,16}] octadec-4-en-15-yl]ethyl]-3-[(tert-butyl)bis(methyl)siloxy]methyl]-4-methyl-5, 6-dihydro-2H-pyran-2-one:**

To a stirred solution of (R)-6-[(S)-1-[(1S, 2R, 6S, 7R, 9R, 11S, 12S, 15R, 16S)-6-hydroxy-2, 16-dimethyl-3-oxo-4-(2-pyridyl)-8-oxapentacyclo [9.7.0.0^{2,7}.0^{12,16}] octadec-4-en-15-yl]ethyl]-3-(hydroxymethyl)-4-methyl-5, 6-dihydro-2H-pyran-2-one (1 g, 1.83 mmol) in dimethylformamide (10 mL) was added 4-(pyrrolidin-1-yl)pyridin-1-ium (817 mg, 3 eq., 5.48 mmol) and tert-butyl (chloro) dimethylsilane (826 mg, 3 eq., 5.48 mmol) at room temperature. The reaction was stirred at 80 °C for 1h. After the completion of reaction (monitored by TLC), mixture was diluted with ice cold water (30 mL) and extracted with ethyl acetate (2 x 50 mL). The organic layer was washed with saturated brine solution (50 mL), dried over sodium sulphate, filtered and concentrated under reduced pressure to obtain crude. The crude was purified by combi flash column chromatography using 40 - 50% ethyl acetate in heptane as an eluent to afford (R)-6-[(S)-1-[(1S, 2R, 6S, 7R, 9R, 11S, 12S, 15R, 16S)-6-hydroxy-2, 16-

dimethyl-3-oxo-4-(2-pyridyl)-8-oxapentacyclo [9.7.0.0²,7.0⁷,9.0¹²,1⁶] octadec-4-en-15-yl} ethyl]-3-{[(tert-butyl) bis(methyl) siloxy]methyl}-4-methyl-5, 6-dihydro-2H-pyran-2-one (1 g, 1.28 mmol, 70%) as pale yellow solid.

[0477] Analytical data:

LCMS: 84.77% (m/z: 662.40, [M+1]⁺, 2.66 min (4 min run).

[0478] Step-2: Synthesis of (1S, 2R, 6S, 7S, 9R, 11S, 12S, 15R, 16S)-15-[(S)-1-[(R)-3-(hydroxymethyl)-4-methyl-2-oxo-5, 6-dihydro-2H-pyran-6-yl]ethyl]-2, 16-dimethyl-3-oxo-4-(2-pyridyl)-8-oxapentacyclo [9.7.0.0²,7.0⁷,9.0¹²,1⁶] octadec-4-ene-6-sulfuric acid :

To a stirred solution of (R)-6-[(S)-1-[(1S, 2R, 6S, 7R, 9R, 11S, 12S, 15R, 16S)-6-hydroxy-2, 16-dimethyl-3-oxo-4-(2-pyridyl)-8-oxapentacyclo [9.7.0.0²,7.0⁷,9.0¹²,1⁶] octadec-4-en-15-yl}ethyl]-3-{[(tert-butyl) bis(methyl) siloxy]methyl}-4-methyl-5, 6-dihydro-2H-pyran-2-one (0.3 g, 453 μmol), in acetonitrile (5 mL), was added triethylamine—λ⁶-sulfanettrione (1/1) (164 mg, 2 eq., 906 μmol) at room temperature. The reaction was stirred at 100 °C for 1h. After the completion of reaction (monitored by TLC), reaction mixture was directly concentrated under reduced pressure to obtain crude compound, (1S, 2R, 6S, 7S, 9R, 11S, 12S, 15R, 16S)-15-[(S)-1-[(R)-3-{[(tert-butyl) bis (methyl) siloxy] methyl}-4-methyl-2-oxo-5, 6-dihydro-2H-pyran-6-yl] ethyl]-2, 16-dimethyl-3-oxo-4-(2-pyridyl)-8-oxapentacyclo [9.7.0.0²,7.0⁷,9.0¹²,1⁶] octadec-4-ene-6-sulfuric acid (0.3 g crude, 49%).

[0479] Analytical data:

LCMS: 55.75% (m/z: 742.15, [M+1]⁺, 2.26 min (4 min run).

[0480] Step-3: Synthesis of (1S, 2R, 6S, 7S, 9R, 11S, 12S, 15R, 16S)-15-[(S)-1-[(R)-3-(hydroxymethyl)-4-methyl-2-oxo-5, 6-dihydro-2H-pyran-6-yl] ethyl]-2, 16-dimethyl-3-oxo-4-(2-pyridyl)-8-oxapentacyclo [9.7.0.0²,7.0⁷,9.0¹²,1⁶] octadec-4-ene-6-sulfuric acid:

To a stirred solution of (1S, 2R, 6S, 7S, 9R, 11S, 12S, 15R, 16S)-15-[(S)-1-[(R)-3-{[(tert-butyl) bis (methyl) siloxy] methyl}-4-methyl-2-oxo-5, 6-dihydro-2H-pyran-6-yl] ethyl]-2, 16-dimethyl-3-oxo-4-(2-pyridyl)-8-oxapentacyclo [9.7.0.0²,7.0⁷,9.0¹²,1⁶] octadec-4-ene-6-sulfuric acid (0.3 g, 404 μmol) in tetrahydrofuran (5 mL) was added methanol (0.6 ml) and 2N HCl solution (3 ml) at 0°C. The reaction mixture was stirred at 0°C for 60 min. After completion of reaction (monitoring by TLC), reaction mixture was quenched with saturated NaHCO₃

solution (20 mL) and extracted with 10% methanol in dichloromethane (2 x 20 mL). The organic layer was dried over sodium sulphate and concentrated under reduced pressure to afford crude. The crude was purified by using preparative-HPLC in ammonium bicarbonate method to afford (1S, 2R, 6S, 7S, 9R, 11S, 12S, 15R, 16S)-15-[(S)-1-[(R)-3-(hydroxymethyl)-4-methyl-2-oxo-5, 6-dihydro-2H-pyran-6-yl]ethyl]-2, 16-dimethyl-3-oxo-4-(2-pyridyl)-8-oxapentacyclo [9.7.0.0²,⁷.0⁷,⁹.0¹²,¹⁶] octadec-4-ene-6-sulfuric acid as ammonium salt (22 mg, 13.8%) as off white solid.

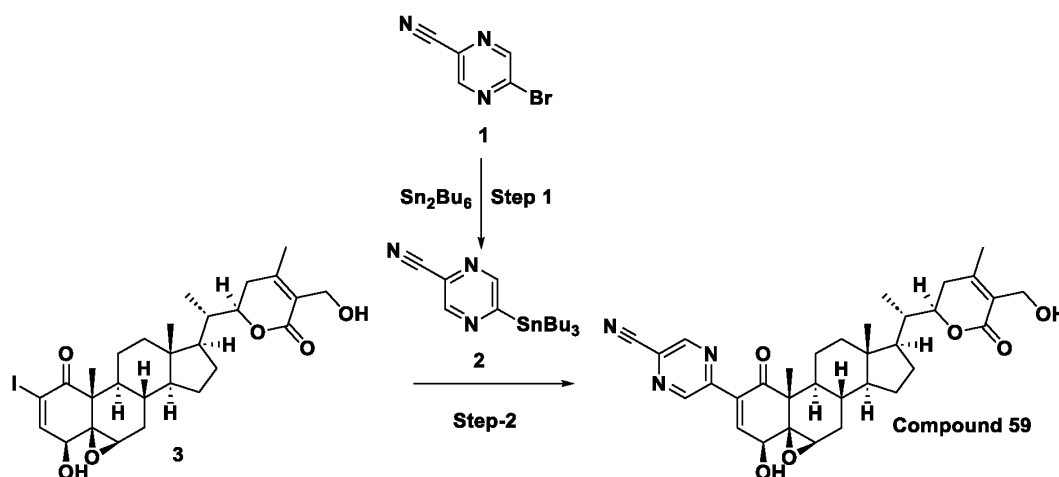
[0481] Analytical data:

LCMS: 92.42% (m/z: 628.4, [M+1]⁺, 4.74 min (10 min run).

¹H-NMR (400 MHz, DMSO-*d*₆): δ 8.60 (d, *J* = 4.8 Hz, 1H), 7.86-7.83 (m, 1H), 7.68 (d, *J* = 6.40 Hz, 1H), 7.42 (d, *J* = 7.6 Hz, 1H), 7.38-7.35 (m, 1H), 7.19 (s, 1H), 7.07 (s, 1H), 6.94 (s, 1H), 4.44-4.29 (m, 2H), 4.16 – 4.07 (m, 2H), 3.26 (s, 1H), 2.41-2.31 (m, 1H), 2.12 – 1.50 (m, 10H), 1.48-1.21 (m, 8H), 1.14-1.04 (m, 4H), 0.97-0.87 (m, 6H), 0.66 (s, 3H).

¹³C-NMR (400 MHz, DMSO-*d*₆): δ 199.71, 165.32, 154.69, 152.18, 149.13, 140.42, 140.12, 137.49, 125.42, 123.56, 122.41, 77.51, 73.18, 61.36, 57.73, 55.30, 54.52, 51.02, 47.94, 42.22, 41.97, 30.67, 29.00, 26.50, 23.91, 20.44, 19.88, 14.41, 13.00, 11.25.

[0482] Synthesis of Compound 59



[0483] Step-1: Synthesis of 5-(tributylstannyl)-2-pyrazinecarbonitrile.

To a stirred solution of 5-bromo-2-pyrazinecarbonitrile (1 g, 5.43 mmol) in dimethylformamide (10 mL, 129 mmol) was added hexabutylstannane (4.73 g, 1.5 eq., 8.15 mmol). The reaction mixture was purged with argon gas for 30 min then palladium—triphenylphosphine (1/4) (628 mg, 0.1 eq., 543 μ mol) was added to it. The reaction mixture was again purged with argon gas for 5 min. The reaction was stirred at 130°C for 4h. After completion of the reaction, the mixture was filtered through celite bed and washed with ethyl acetate. The filtrate was concentrated to get the crude which was then purified by column chromatography using 0-10% ethyl acetate in heptane as an eluent to afford 5-(tributylstannyl)-2-pyrazinecarbonitrile (350 mg, 888 μ mol) as colourless liquid.

[0484] Analytical data:

LCMS: 95.93% (m/z: 393.80, $[M+1]^+$, 3.18 min (4 min run).

[0485] Step-2: Synthesis of 5-[(1S, 2R, 6S, 7R, 9R, 11S, 12S, 15R, 16S)-15-[(S)-1-[(R)-3-(hydroxymethyl)-4-methyl-2-oxo-5, 6-dihydro-2H-pyran-6-yl]ethyl]-6-hydroxy-2, 16-dimethyl-3-oxo-8-oxapentacyclo [9.7.0.0^{2,7}.0^{7,9}.0^{12,16}] octadec-4-en-4-yl]-2-pyrazinecarbonitrile:

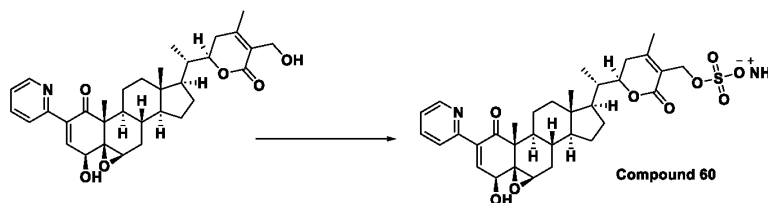
To a stirred solution of (R)-6-[(S)-1-[(1S, 2R, 6S, 7R, 9R, 11S, 12S, 15R, 16S)-6-hydroxy-4-iodo-2, 16-dimethyl-3-oxo-8-oxapentacyclo [9.7.0.0^{2,7}.0^{7,9}.0^{12,16}] octadec-4-en-15-yl]ethyl]-3-(hydroxymethyl)-4-methyl-5, 6-dihydro-2H-pyran-2-one (0.4 g, 671 μ mol) in 1,4-dioxane (5 mL, 58.6 mmol) was added, 5-(tributylstannyl)-2-pyrazinecarbonitrile (317 mg, 1.2 eq., 805 μ mol) and λ^1 -copper(I+) iodide (19.2 mg, 0.15 eq., 101 μ mol) The reaction mixture was purged with N₂ gas for 30 min, Then palladium—(1E,4E)-1,5-diphenyl-1,4-pentadien-3-one (2/3) (61.4 mg, 0.1 eq., 67.1 μ mol) was added to it. The reaction mixture was again purged with N₂ gas for 5 min. The resultant reaction mixture was stirred for 2h at 80°C. After the completion of reaction (Reaction was monitored by TLC) mixture was filtered by using through celite bed, filtrate was diluted with water then extracted in DCM. The organic layer was dried over anhydrous sodium sulfate then concentrated under reduced pressure. Crude was purified by using preparative-HPLC A- 5mM Ammonium Bicarbonate in Water. B- Acetonitrile. afforded 5-[(1S, 2R, 6S, 7R, 9R, 11S, 12S, 15R, 16S)-15-[(S)-1-[(R)-3-(hydroxymethyl)-4-methyl-2-oxo-5, 6-dihydro-2H-pyran-6-yl] ethyl]-6-hydroxy-2, 16-dimethyl-3-oxo-8-oxapentacyclo [9.7.0.0^{2,7}.0^{7,9}.0^{12,16}] octadec-4-en-4-yl]-2-pyrazinecarbonitrile (36 mg, 59.6 μ mol) as a white solid.

Analytical data:

LCMS: 95.30% (m/z: 574.4, $[M+H]^+$, 5.78 min (10 min run).

$^1\text{H-NMR}$ (400 MHz, $\text{DMSO-}d_6$): δ 9.24 (s, 1H), 8.86 (s, 1H), 7.96 (d, $J = 6.40$ Hz, 1H), 5.98 (d, $J = 3.2$ Hz, 1H), 4.59 (t, $J = 5.20$ Hz, 1H), 4.30-4.27 (m, 1H), 4.15-4.10 (m, 2H), 3.83-3.81 (m, 1H), 3.19 (s, 1H), 2.42-2.34 (m, 1H), 2.12-1.91 (m, 6H), 1.88-1.62 (m, 2H), 1.60-1.19 (m, 9H), 1.13-1.05 (m, 3H), 0.93-0.86 (m, 5H), 0.66 (s, 3H).

$^{13}\text{C-NMR}$ (400 MHz, $\text{DMSO-}d_6$): δ 199.61, 165.29, 154.63, 151.04, 148.25, 145.68, 143.79, 137.59, 128.41, 125.44, 116.14, 77.51, 68.24, 63.11, 57.65, 55.20, 54.51, 51.09, 47.95, 41.97, 41.9, 38.35, 30.63, 29.24, 29.02, 26.47, 23.95, 20.40, 19.87, 15.22, 13.04, 11.23.

[0486] Synthesis of Compound 60

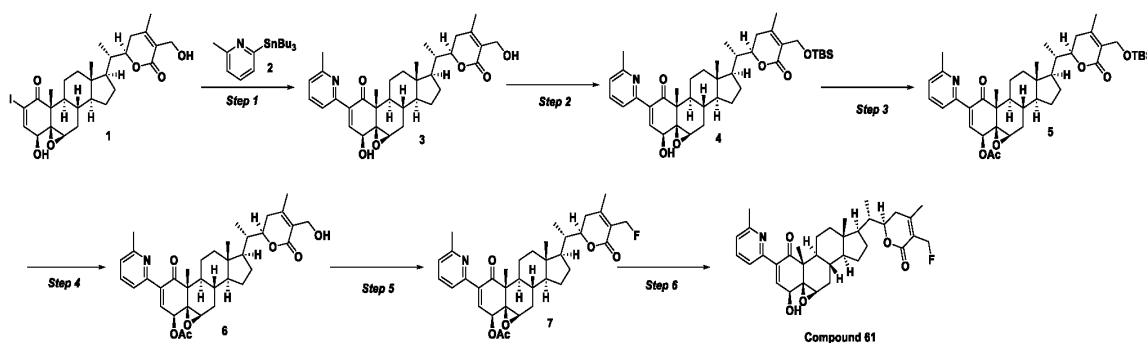
[0487] Step-1: Synthesis of ammonium [(R)-6-[(S)-1-[(1S, 2R, 6S, 7R, 9R, 11S, 12S, 15R, 16S)-6-hydroxy-2, 16-dimethyl-3-oxo-4-(2-pyridyl)-8-oxapentacyclo [9.7.0.0^{2,7},0^{12,16}] octadec-4-en-15-yl] ethyl]-4-methyl-2-oxo-5, 6-dihydro-2H-pyran-3-yl] methanesulfate:

To a stirred solution of (R)-6-[(S)-1-[(1S, 2R, 6S, 7R, 9R, 11S, 12S, 15R, 16S)-6-hydroxy-2, 16-dimethyl-3-oxo-4-(2-pyridyl)-8-oxapentacyclo [9.7.0.0^{2,7},0^{12,16}] octadec-4-en-15-yl] ethyl]-3-(hydroxymethyl)-4-methyl-5, 6-dihydro-2H-pyran-2-one (0.2 g, 365 μmol) in acetonitrile (5 mL), was added triethylamine— λ^6 -sulfanetrione (1/1) (72.8 mg, 1.1 eq., 402 μmol) at room temperature. The reaction was stirred at 100 °C for 1h. After the completion of reaction (monitored by TLC), reaction mixture was directly concentrated under reduced pressure to obtain crude. The crude was purified by using preparative-HPLC in ammonium bicarbonate method to afford ammonium [(R)-6-[(S)-1-[(1S, 2R, 6S, 7R, 9R, 11S, 12S, 15R, 16S)-6-hydroxy-2, 16-dimethyl-3-oxo-4-(2-pyridyl)-8-oxapentacyclo [9.7.0.0^{2,7},0^{12,16}] octadec-4-en-15-yl] ethyl]-4-methyl-2-oxo-5, 6-dihydro-2H-pyran-3-yl] methanesulfate (18 mg, 6%).

[0488] Analytical data:

LCMS: 81.63% + 12% (m/z: 628.3, $[M+1]^+$, 4.72 min, 4.76 min (10 min run).

$^1\text{H-NMR}$ (400 MHz, $\text{DMSO-}d_6$): δ 8.60 (d, $J = 4$ Hz, 1H), 7.86-7.81 (m, 1H), 7.68 (d, $J = 6.40$ Hz, 1H), 7.37-7.34 (m, 2H), 7.19 (s, 1H), 7.07 (s, 1H), 6.94 (s, 1H), 4.48 (d, $J = 10.8$ Hz, 1H), 4.41 – 4.38 (d, $J = 10.4$ Hz, 1H), 4.29-4.26 (m, 1H), 3.75 (d, $J = 6.80$ Hz, 1H), 3.16 (s, 1H), 2.45 – 2.37 (m, 1H), 2.16 – 1.68 (m, 9H), 1.61-1.20 (m, 11H), 1.18-1.04 (m, 6H), 0.66 (s, 3H).

[0489] Synthesis of Compound 61

[0490] Step 1: Synthesis of (R)-6-[(S)-1-[(1S, 2R, 6S, 7R, 9R, 11S, 12S, 15R, 16S)-6-hydroxy-2, 16-dimethyl-4-(6-methyl-2-pyridyl)-3-oxo-8-oxapentacyclo [9.7.0.0^{2,7}.0^{7,9}.0^{12,16}] octadec-4-en-15-yl}ethyl]-3-(hydroxymethyl)-4-methyl-5, 6-dihydro-2H-pyran-2-one.

To a stirred solution of (R)-6-[(S)-1-[(1S, 2R, 6S, 7R, 9R, 11S, 12S, 15R, 16S)-6-hydroxy-4-iodo-2, 16-dimethyl-3-oxo-8-oxapentacyclo [9.7.0.0^{2,7}.0^{7,9}.0^{12,16}] octadec-4-en-15-yl}ethyl]-3-(hydroxymethyl)-4-methyl-5, 6-dihydro-2H-pyran-2-one (3 g, 5.03 mmol) in tetrahydrofuran (30 mL) was added tributyl (6-methyl-2-pyridyl) stannane (2.31 g, 1.2 eq., 6.04 mmol), diiodocopper (239 mg, 0.15 eq., 754 μmol) and triphenylarsine (154 mg, 0.1 eq., 503 μmol) to it. The reaction mixture was purged with nitrogen gas for 30 min, then added palladium—(1E, 4E)-1, 5-diphenyl-1, 4-pentadien-3-one (2/3) (230 mg, 0.05 eq., 251 μmol). The reaction mixture was again purged with nitrogen gas for 5 min. The reaction vial was sealed and stirred at 80°C for 2h. The reaction was monitored by TLC and LCMS. After completion of reaction, it was quenched with water (30 mL) and extracted with ethyl acetate (40 mL x 3). The ethyl acetate layer was dried over anhydrous sodium sulphate, filtered and concentrated under vacuum to afford the crude. The crude compound was purified by column chromatography on

silica gel using eluent 0 - 85% ethyl acetate in heptane to get (R)-6-[(S)-1-[(1S, 2R, 6S, 7R, 9R, 11S, 12S, 15R, 16S)-6-hydroxy-2, 16-dimethyl-4-(6-methyl-2-pyridyl)-3-oxo-8-oxapentacyclo [9.7.0.0²,7.0⁷,9.0¹²,16] octadec-4-en-15-yl}ethyl]-3-(hydroxymethyl)-4-methyl-5, 6-dihydro-2H-pyran-2-one (1.8 g, 39%) as yellow solid.

[0491] Analytical Data:

LCMS: 70% (m/z: 562.41 [M+1]⁺), 2.22 min (4 min run).

[0492] Step 2: Synthesis of (1S, 2R, 6S, 7S, 9R, 11S, 12S, 15R, 16S)-15-[(S)-1-[(R)-3-[[tert-butyl] bis(methyl) siloxy] methyl]-4-methyl-2-oxo-5, 6-dihydro-2H-pyran-6-yl]ethyl]-2, 16-dimethyl-4-(6-methyl-2-pyridyl)-3-oxo-8-oxapentacyclo [9.7.0.0²,7.0⁷,9.0¹²,16] octadec-4-en-6-yl acetate.

To a stirred solution of (R)-6-[(S)-1-[(1S, 2R, 6S, 7R, 9R, 11S, 12S, 15R, 16S)-6-hydroxy-2, 16-dimethyl-4-(6-methyl-2-pyridyl)-3-oxo-8-oxapentacyclo [9.7.0.0²,7.0⁷,9.0¹²,16] octadec-4-en-15-yl}ethyl]-3-(hydroxymethyl)-4-methyl-5, 6-dihydro-2H-pyran-2-one (1.8 g, 3.2 mmol) and 4-(pyrrolidin-1-yl)pyridin-1-ium (956 mg, 2 eq., 6.41 mmol) in dimethylformamide (20 mL), added tert-butyl(chloro)dimethylsilane (724 mg, 1.5 eq., 4.81 mmol) RT and stirred for 2h at 80 °C. After completion of reaction, reaction mixture was poured into ice-cold water (50 mL) and extracted with ethyl acetate (50 mL x 2). The collective ethyl acetate layer was washed with brine (50 mL) and dried over anhydrous sodium sulfate, filtered and concentrated under vacuum to get crude compound. The crude compound was purified by column chromatography on silica gel using eluent 0 - 45% ethyl acetate in heptane to get (R)-6-[(S)-1-[(1S, 2R, 6S, 7R, 9R, 11S, 12S, 15R, 16S)-6-hydroxy-2, 16-dimethyl-4-(6-methyl-2-pyridyl)-3-oxo-8-oxapentacyclo [9.7.0.0²,7.0⁷,9.0¹²,16] octadec-4-en-15-yl}ethyl]-3-[[tert-butyl] bis(methyl) siloxy] methyl]-4-methyl-5, 6-dihydro-2H-pyran-2-one (1.14 g, 46%) as light yellow solid.

[0493] Analytical data:

LCMS: 87% (m/z: 676.40 [M+1]⁺), 2.67 min (4 min run).

[0494] Step 3: Synthesis of (1S, 2R, 6S, 7S, 9R, 11S, 12S, 15R, 16S)-15-[(S)-1-[(R)-3-[[tert-butyl] bis (methyl) siloxy] methyl]-4-methyl-2-oxo-5,6-dihydro-2H-pyran-6-yl]ethyl]-2, 16-dimethyl-4-(6-methyl-2-pyridyl)-3-oxo-8-oxapentacyclo [9.7.0.0²,7.0⁷,9.0¹²,16] octadec-4-en-6-yl acetate.

To a stirred solution of (R)-6-[(S)-1-[(1S, 2R, 6S, 7R, 9R, 11S, 12S, 15R, 16S)-6-hydroxy-2, 16-dimethyl-4-(6-methyl-2-pyridyl)-3-oxo-8-oxapentacyclo [9.7.0.0^{2,7}.0^{7,9}.0^{12,16}] octadec-4-en-15-yl]ethyl]-3-[(tert-butyl) bis (methyl) siloxy] methyl}-4-methyl-5, 6-dihydro-2H-pyran-2-one (1.14 g, 1.69 mmol) in pyridine (11.5 mL) were added 4-(dimethylamino)pyridine (41.5 mg, 0.2 eq., 337 μ mol) and acetyl acetate (2.1 mL, 1.42 mmol) at 0 °C. Reaction was stirred at RT for 16h. The reaction was monitored by TLC and LCMS. After the completion of reaction, it was quenched with 1N HCl (40 mL) and extracted with dichloromethane (2 x 50 mL). The dichloromethane layer was dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to get crude (1S, 2R, 6S, 7S, 9R, 11S, 12S, 15R, 16S)-15-[(S)-1-[(R)-3-[(tert-butyl) bis (methyl) siloxy] methyl}-4-methyl-2-oxo-5, 6-dihydro-2H-pyran-6-yl] ethyl]-2, 16-dimethyl-4-(6-methyl-2-pyridyl)-3-oxo-8-oxapentacyclo [9.7.0.0^{2,7}.0^{7,9}.0^{12,16}] octadec-4-en-6-yl acetate (1.18 g, 60%) as light yellow solid.

[0495] Analytical data:

LCMS: 62% (m/z: 718.70 [M+1]⁺), 2.32 min (4 min run).

[0496] Step 4: Synthesis of (1S, 2R, 6S, 7S, 9R, 11S, 12S, 15R, 16S)-15-[(S)-1-[(R)-3-(hydroxymethyl)-4-methyl-2-oxo-5, 6-dihydro-2H-pyran-6-yl] ethyl]-2, 16-dimethyl-4-(6-methyl-2-pyridyl)-3-oxo-8-oxapentacyclo [9.7.0.0^{2,7}.0^{7,9}.0^{12,16}] octadec-4-en-6-yl acetate.

To a stirred solution of (1S, 2R, 6S, 7S, 9R, 11S, 12S, 15R, 16S)-15-[(S)-1-[(R)-3-[(tert-butyl) bis (methyl) siloxy] methyl}-4-methyl-2-oxo-5, 6-dihydro-2H-pyran-6-yl] ethyl]-2, 16-dimethyl-4-(6-methyl-2-pyridyl)-3-oxo-8-oxapentacyclo [9.7.0.0^{2,7}.0^{7,9}.0^{12,16}] octadec-4-en-6-yl acetate (1.16 g, 1.62 mmol) in tetrahydrofuran (11.6 mL), added methanol (2.32 mL, 57.3 mmol) followed by 2N HCl solution (11.6 mL) and continued the reaction for 1h at RT. The reaction mixture was quenched carefully with saturated sodium bicarbonate solution (50 mL) and extracted by using dichloromethane (2 x 50 mL). Collective dichloromethane layer was washed with brine solution (50 mL), dried over anhydrous sodium sulfate, filtered and concentrated under vacuum to get (1S, 2R, 6S, 7S, 9R, 11S, 12S, 15R, 16S)-15-[(S)-1-[(R)-3-(hydroxymethyl)-4-methyl-2-oxo-5, 6-dihydro-2H-pyran-6-yl]ethyl]-2, 16-dimethyl-4-(6-methyl-2-pyridyl)-3-oxo-8-oxapentacyclo [9.7.0.0^{2,7}.0^{7,9}.0^{12,16}] octadec-4-en-6-yl acetate (1.05 g, 83%) as yellow solid.

[0497] Analytical data:

LCMS: 77% (m/z: 604.43 [M+1]⁺), 2.41 min (4 min run).

[0498] Step 5: Synthesis of (1S, 2R, 6S, 7S, 9R, 11S, 12S, 15R, 16S)-15-[(S)-1-[(R)-3-(fluoromethyl)-4-methyl-2-oxo-5, 6-dihydro-2H-pyran-6-yl]ethyl]-2, 16-dimethyl-4-(6-methyl-2-pyridyl)-3-oxo-8-oxapentacyclo [9.7.0.0^{2,7},^{9,0}^{12,16}] octadec-4-en-6-yl acetate.

To a stirred solution of (1S, 2R, 6S, 7S, 9R, 11S, 12S, 15R, 16S)-15-[(S)-1-[(R)-3-(hydroxymethyl)-4-methyl-2-oxo-5, 6-dihydro-2H-pyran-6-yl]ethyl]-2, 16-dimethyl-4-(6-methyl-2-pyridyl)-3-oxo-8-oxapentacyclo [9.7.0.0^{2,7},^{9,0}^{12,16}] octadec-4-en-6-yl acetate (0.5 g, 828 μmol) in dichloromethane (5 mL) was added diethyl (trifluoro-λ⁴-sulfanyl)amine (131 μL, 1.2 eq., 994 μmol) dissolved in dichloromethane (0.5 mL) drop wise at -78°C under inert atmosphere and stirred for 5 min. The reaction was quenched by adding sodium bicarbonate solution (25 mL) and then extracted with dichloromethane (2 x 25 mL). The collected dichloromethane layer was washed with brine (25 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to obtain crude. Crude compound was purified by combi-flash chromatography on silica gel using eluent 0 - 70% ethyl acetate in heptane to yield (1S, 2R, 6S, 7S, 9R, 11S, 12S, 15R, 16S)-15-[(S)-1-[(R)-3-(fluoromethyl)-4-methyl-2-oxo-5, 6-dihydro-2H-pyran-6-yl]ethyl]-2, 16-dimethyl-4-(6-methyl-2-pyridyl)-3-oxo-8-oxapentacyclo [9.7.0.0^{2,7},^{9,0}^{12,16}] octadec-4-en-6-yl acetate (0.1 g, 8%) as yellow solid.

[0499] Analytical data:

LCMS: 40% (m/z: 606.20 [M+1]⁺), 2.33 min (4 min run).

[0500] Step-6: Synthesis of (R)-6-[(S)-1-[(1S, 2R, 6S, 7R, 9R, 11S, 12S, 15R, 16S)-6-hydroxy-2, 16-dimethyl-4-(6-methyl-2-pyridyl)-3-oxo-8-oxapentacyclo [9.7.0.0^{2,7},^{9,0}^{12,16}] octadec-4-en-15-yl]ethyl]-3-(fluoromethyl)-4-methyl-5, 6-dihydro-2H-pyran-2-one.

To (1S, 2R, 6S, 7S, 9R, 11S, 12S, 16S)-15-[(S)-1-[(R)-3-(fluoromethyl)-4-methyl-2-oxo-5, 6-dihydro-2H-pyran-6-yl] ethyl]-2, 16-dimethyl-4-(6-methyl-2-pyridyl)-3-oxo-8-oxapentacyclo [9.7.0.0^{2,7},^{9,0}^{12,16}] octadec-4-en-6-yl acetate (90 mg, 149 μmol) in acetonitrile (970 μL, 18.6 mmol) were added lithium hydroxide (10.7 mg, 3 eq., 446 μmol) dissolved in water (0.32 μL, 17.8 μmol) at 0°C. Reaction was continued stirred for 3h at RT. After completion of reaction (monitoring by TLC), reaction mixture was quenched with water (25 mL) and extracted with ethyl acetate (2 x 25 mL). The ethyl acetate layer was dried over anhydrous sodium sulphate,

filtered and concentrated under reduced pressure to get crude. The crude compound was purified by Prep HPLC to get (R)-6-[(S)-1-{(1S, 2R, 6S, 7R, 9R, 11S, 12S, 15R, 16S)-6-hydroxy-2, 16-dimethyl-4-(6-methyl-2-pyridyl)-3-oxo-8-oxapentacyclo [9.7.0.0.0^{2,7}.0^{7,9}.0^{12,16}] octadec-4-en-15-yl}ethyl]-3-(fluoromethyl)-4-methyl-5, 6-dihydro-2H-pyran-2-one (6 mg, 7%) as white solid

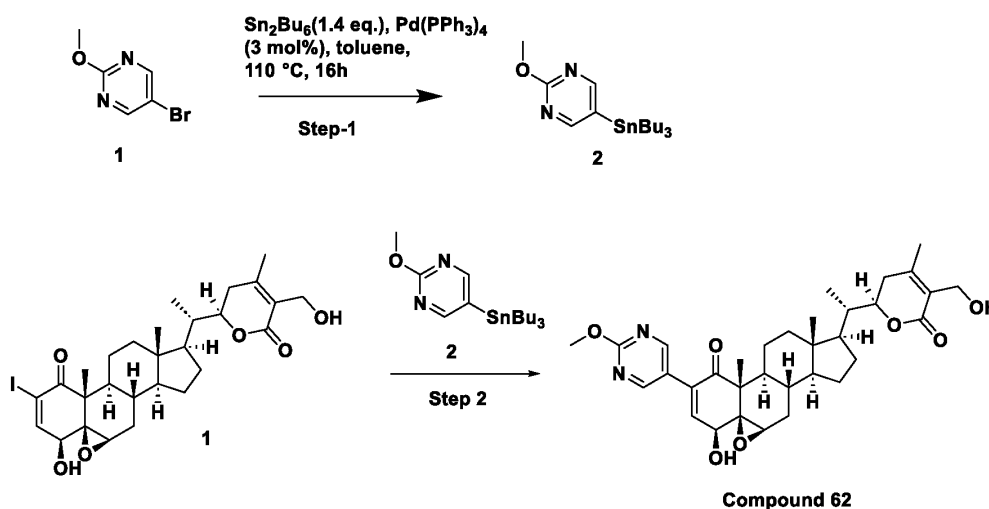
[0501] Analytical data:

LCMS: 90% (m/z: 564.4 [M+1]⁺), 6.51 min (10 min run).

¹H-NMR (400 MHz, DMSO-d₆): δ 7.70 (t, J = 8 Hz, 1H), 7.64 (d, J = 6.8 Hz, 1H), 5.71 (d, J = 3.2 Hz, 1H), 5.19-5.01 (m, 2H), 4.37-4.33 (m, 1H), 3.75-3.73 (m, 1H), 3.14 (s, 1H), 2.46 (s, 3H), 2.24-2.19 (m, 1H), 2.09-2.02 (m, 5H), 1.93-1.90 (m, 1H), 1.83-1.79 (m, 2H), 1.56-1.54 (m, 1H), 1.44-1.33 (m, 2H), 1.30 (s, 3H), 1.27-1.19 (m, 2H), 1.14-1.03 (m, 4H), 0.96-0.84 (m, 5H), 0.66 (s, 3H).

¹⁹F-NMR (400 MHz, DMSO-d₆): δ -206.91.

[0502] Synthesis of Compound 62



[0503] Step 1: Synthesis of tributyl(2-methoxy-5-pyrimidinyl) stannane

To a stirred solution of 5-Bromo-2-methoxypyrimidine (1 g, 5.29 mmol) in toluene (10 mL) was added hexabutyldistannane (4.31 g, 1.4 eq., 7.41 mmol). The reaction mixture was purged with argon gas for 30 min then Tetrakis (triphenylphosphine)palladium(0) (0.306 g, 0.05 eq., 0.265 mmol) was added to it. The reaction mixture was again purged with argon gas for 5 min.

The reaction was stirred at 110°C for 16h. After completion of the reaction, the mixture was filtered through celite bed and washed with ethyl acetate. The filtrate was concentrated to get the crude which was then purified by column chromatography using 0-10% ethyl acetate in hexane as an eluent to afford tributyl (2-methoxy-5-pyrimidinyl) stannane (0.8 g, 2 mmol, 37.88%) as colourless liquid.

[0504] Analytical data:

LCMS: 96.58% (m/z: 401.15, [M+1]⁺, 6.0 min (7.5 min run).

[0505] Step 2: Synthesis of (R)-6-[(S)-1-{(1S, 2R, 6S, 7R, 9R, 11S, 12S, 15R, 16S)-6-hydroxy-4-(2-methoxy-5-pyrimidinyl)-2, 16-dimethyl-3-oxo-8-oxapentacyclo [9.7.0.0²,7.0⁷,9.0¹²,16] octadec-4-en-15-yl}ethyl]-3-(hydroxymethyl)-4-methyl-5, 6-dihydro-2H-pyran-2-one

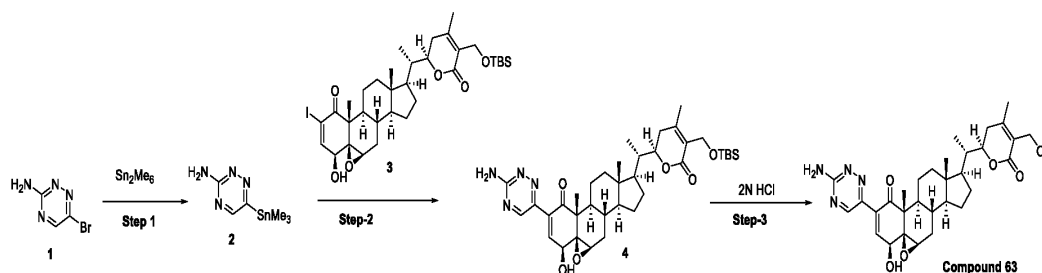
To a stirred solution of (R)-6-[(S)-1-{(1S, 2R, 6S, 7R, 9R, 11S, 12S, 15R, 16S)-6-hydroxy-4-iodo-2, 16-dimethyl-3-oxo-8-oxapentacyclo [9.7.0.0²,7.0⁷,9.0¹²,16] octadec-4-en-15-yl}ethyl]-3-(hydroxymethyl)-4-methyl-5, 6-dihydro-2H-pyran-2-one (0.2 g, 0.335 mmol) and tributyl(2-methoxy-5-pyrimidinyl) stannane (0.27g, 2.0 eq., 0.671 mmol) in 1,4-Dioxane (10 mL), The resulting reaction mixture was purged with argon for 20 min. to the reaction mixture added copper(1+) iodide (0.010 g, 0.15 eq., 0.05 mmol) followed by palladium—(1E,4E)-1,5-diphenyl-1,4-pentadien-3-one (2/3) (0.03 g, 0.1 eq., 0.033 mmol) and purged with argon for 5min. Stirred at 80°C for 6h. Cooled to room temperature. Filtered through celite bed, washed with ethyl acetate, quenched with water (50 mL) and extracted using ethyl acetate (3 x 50 mL). Collected organic layer dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure to obtain crude. The crude product was purified by combi flash column chromatography using (70-90%) ethyl acetate in hexane as an eluent followed by Prep HPLC purification in ammonium acetate method to afford (R)-6-[(S)-1-{(1S, 2R, 6S, 7R, 9R, 11S, 12S, 15R, 16S)-6-hydroxy-4-(2-methoxy-5-pyrimidinyl)-2, 16-dimethyl-3-oxo-8-oxapentacyclo [9.7.0.0²,7.0⁷,9.0¹²,16] octadec-4-en-15-yl}ethyl]-3-(hydroxymethyl)-4-methyl-5, 6-dihydro-2H-pyran-2-one (0.060 g, 0.104 mmol, 30%) as white solid.

[0506] Analytical data:

LCMS: 99.92% (m/z: 579.5, [M+1]⁺, 2.95 min (7.5 min run).

¹H-NMR (400 MHz, DMSO-*d*₆): δ 8.57 (s, 2H), 7.48 (d, *J*=6.8, 1H), 5.77 (d, *J*=3.6 Hz, 1H), 4.58 (t, *J*=5.6 Hz, 1H), 4.30-4.26 (m, 1H), 4.15-4.10 (m, 2H), 3.94 (s, 3H), 3.74-3.70 (m, 1H), 3.19 (s, 1H), 2.37-2.34 (m, 1H), 2.11-2.10 (m, 2H), 1.99 (s, 3H), 1.90-1.87 (m, 2H), 1.80-1.71 (m, 2H), 1.58-1.56 (m, 1H), 1.37-1.27 (m, 7H), 1.16-1.04 (m, 3H), 0.98-0.91 (m, 5H), 0.65 (s, 3H).

[0507] Synthesis of Compound 63



[0508] Step 1: Synthesis of 6-(trimethylstannyl)-1,2,4-triazin-3-amine:

To a stirred solution of (6-bromo-1,2,4-triazin-3-amine (4 g, 22.9 mmol) in 1,4-dioxane (40 mL) were added lithium(1+) chloride (1.45 g, 1.5 eq., 34.3 mmol), tricyclohexylphosphane (tricyclohexylphosphane (385 mg, 0.06 eq., 1.37 mmol) and hexamethyldistannane (8.99 g, 1.2 eq., 27.4 mmol) at room temperature. Resultant reaction mixture was purged with nitrogen for 20 min, then added tris((1E,4E)-1,5-diphenylpenta-1,4-dien-3-one) dipalladium (1.05 g, 0.05 eq., 22.9 mmol) at same temperature. Reaction mixture was stirred at 100°C for 4 h. Progress of reaction was monitored by TLC. On completion, the reaction mixture was passed through celite bed, washed with ethyl acetate and resulting filtrate was diluted with water (100 mL) and extracted using ethyl acetate (2 X 75 mL). The organic layer was dried over sodium sulphate, filtered and concentrated under reduced pressure to get crude compound. The crude was purified by combi-flash on neutral alumina using 5% methanol in DCM, which afforded (trimethylstannyl)-1,2,4-triazin-3-amine as off white solid (4.5 g, 54%).

[0509] Analytical data:

LCMS: purity 71.98% (m/z: 260.80, [M+1]⁺, 1.43 min (4 min run).

¹H-NMR (400 MHz, DMSO-*d*₆): δ 8.208 (s, 1H), 6.98 (s, 2H), 0.39-0.25 (s, 9H).

[0510] Step-2: Synthesis of (4S, 4aR, 5aR, 6aS, 6bS, 9R, 9aS, 11aS, 11bR)-2-(3-amino-1, 2, 4-triazin-6-yl)-9-((S)-1-((R)-5-(((tert-butyldimethylsilyl)oxy)methyl)-4-methyl-6-

oxo-3, 6-dihydro-2H-pyran-2-yl)ethyl)-4-hydroxy-9a, 11b-dimethyl-5a, 6, 6a, 6b, 7, 8, 9, 9a, 10, 11, 11a, 11b-dodecahydrocyclopenta [1, 2] phenanthro [8a, 9-b] oxiren-1(4H)-one:

A stirred solution of (R)-6-[(S)-1-{(1S, 2R, 6S, 7R, 9R, 11S, 12S, 15R, 16S)-6-hydroxy-4-iodo-2, 16-dimethyl-3-oxo-8-oxapentacyclo [9.7.0.0²,⁷.0⁷,⁹.0¹²,¹⁶] octadec-4-en-15-yl}ethyl]-3-{[(tert-butyl) bis (methyl) siloxy] methyl}-4-methyl-5, 6-dihydro-2H-pyran-2-one (1 g, 1.41 mmol), 6-(trimethylstannyl)-1,2,4-triazin-3-ylamine (1.06 g, 2 eq., 2.81 mmol), λ^1 -copper(I) iodide (40.2 mg, 0.15 eq., 211 μ mol) in 1,4-dioxane (20 mL) were purged with nitrogen for 20 min at room temperature, then added tris((1E, 4E)-1,5-diphenylpenta-1,4-dien-3-one) dipalladium (64.4 mg, 0.05 eq., 70.3 μ mol). The reaction mixture was stirred at 80°C for 4 h. Progress of reaction was monitored by TLC. On completion, the reaction mixture was passed through celite bed, and the resulting filtrate was diluted with cold water (50 mL) and extracted using ethyl acetate (2 X 40 mL). The organic layer was dried over sodium sulphate, filtered and concentrated under reduced pressure to get crude compound. The crude was purified by combi-flash over silica column using 0-5% methanol in dichloromethane, which afforded (R)-6-[(S)-1-{(1S, 2R, 6S, 7R, 9R, 11S, 12S, 15R, 16S)-4-(3-amino-1, 2, 4 -triazin-6-yl)-6-hydroxy-2,16-dimethyl-3-oxo-8-oxapentacyclo [9.7.0.0²,⁷.0⁷,⁹.0¹²,¹⁶] octadec-4-en-15-yl}ethyl]-3-{[(tert-butyl) bis (methyl) siloxy] methyl}-4-methyl-5, 6-dihydro-2H-pyran-2-one (210 mg, 10%) as white solid.

[0511] Analytical data:

LCMS: purity 46% (m/z: 679.30, [M+1]⁺, 2.50 min (4 min run).

[0512] Step 3: Synthesis of (4S, 4aR, 5aR, 6aS, 6bS, 9R, 9aS, 11aS, 11bR)-2-(3-amino-1,2,4-triazin-6-yl)-4-hydroxy-9-((S)-1-((R)-5-(hydroxymethyl)-4-methyl-6-oxo-3, 6-dihydro-2H-pyran-2-yl)ethyl)-9a, 11b-dimethyl-5a, 6, 6a, 6b, 7, 8, 9, 9a, 10, 11, 11a, 11b-dodecahydrocyclopenta [1, 2] phenanthro [8a, 9-b] oxiren-1(4H)-one.

A stirred solution of (R)-6-[(S)-1-{(1S, 2R, 6S, 7R, 9R, 11S, 12S, 15R, 16S)-4-(3-amino-1, 2, 4-triazin-6-yl)-6-hydroxy-2, 16-dimethyl-3-oxo-8-oxapentacyclo [9.7.0.0²,⁷.0⁷,⁹.0¹²,¹⁶] octadec-4-en-15-yl}ethyl]-3-{[(tert-butyl) bis (methyl) siloxy] methyl}-4-methyl-5, 6-dihydro-2H-pyran-2-one (0.2 g, 295 μ mol) in tetrahydrofuran (5 mL) and MeOH (5 mL) was cooled to 0°C. Then added 2N HCl (5 mL) at same temperature and stirring for 30 minute at 0°C. Progress of reaction was monitored by TLC. The reaction mixture was diluted with dichloromethane (30 mL), followed by saturated sodium bicarbonate solution (30 mL), and

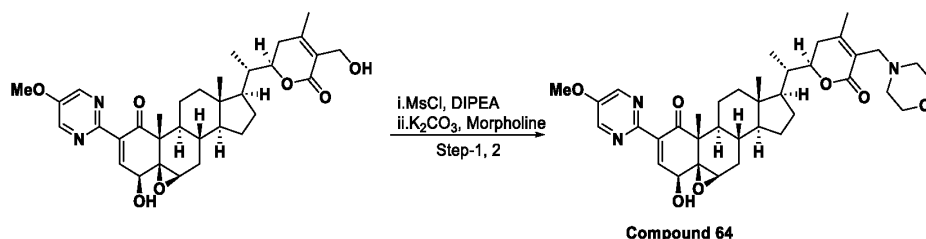
saturated brine solution (30 mL) washings. The organic layer was dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure to afford crude compound. The crude was purified by Prep-HPLC using ammonium acetate buffer to afford (R)-6-[(S)-1-[(1S, 2R, 6S, 7R, 9R, 11S, 12S, 15R, 16S)-4-(3-amino-1, 2, 4-triazin-6-yl)-6-hydroxy-2, 16-dimethyl-3-oxo-8-oxapentacyclo [9.7.0.0^{2,7}.0^{9,12}.1⁶] octadec-4-en-15-yl}ethyl]-3-(hydroxymethyl)-4-methyl-5, 6-dihydro-2H-pyran-2-one (22 mg, 39 μ mol, 13.2%) as off white solid.

[0513] Analytical data:

LCMS: purity 97.62% (m/z: 565.4, [M+1]⁺), 4.90 min (10 min run).

¹H-NMR (400 MHz, DMSO-*d*₆): δ 8.19 (s, 1H), 7.61 (d, *J* = 6.80 Hz, 1H), 7.45 (s, 2H), 5.76 (d, *J* = 3.6 Hz, 1H), 4.57 (t, *J* = 5.20 Hz, 1H), 4.31-4.07 (m, 3H), 3.75-3.73 (m, 1H), 3.18 (s, 1H), 2.41-2.31 (m, 1H), 2.11-1.99 (m, 2H), 1.90 (s, 3H), 1.87-1.68 (m, 3H), 1.62-1.11 (m, 12H), 0.99-0.88 (m, 5H), 0.65 (s, 3H).

[0514] Synthesis of Compound 64



[0515] Step 1: Synthesis of ((R)-6-((S)-1-((4S, 4aR, 5aR, 6aS, 6bS, 9R, 9aS, 11aS, 11bR)-4-hydroxy-2-(5-methoxypyrimidin-2-yl)-9a, 11b-dimethyl-1-oxo-1, 4, 5a, 6, 6a, 6b, 7, 8, 9, 9a, 10, 11, 11a, 11b-tetradecahydrocyclopenta [1, 2] phenanthro [8a, 9-b] oxiren-9-yl)ethyl)-4-methyl-2-oxo-5, 6-dihydro-2H-pyran-3-yl) methyl methanesulfonate:

To a stirred solution of (R)-6-[(S)-1-[(1S, 2R, 6S, 7R, 9R, 11S, 12S, 15R, 16S)-6-hydroxy-4-(5-methoxy-2-pyrimidinyl)-2, 16-dimethyl-3-oxo-8-oxapentacyclo [9.7.0.0^{2,7}.0^{9,12}.1⁶] octadec-4-en-15-yl}ethyl]-3-(hydroxymethyl)-4-methyl-5, 6-dihydro-2H-pyran-2-one (0.2 g, 346 μ mol) in dichloromethane (3 mL) was added ethylbis (propan-2-yl)amine (112 mg, 2.5 eq., 864 μ mol) followed by methanesulfonyl chloride (39.6 mg, 346 μ mol) at 0°C. The reaction mixture was stirred at 0°C for 30 minutes. After the completion of reaction (monitored by TLC), mixture was quenched with water (20 mL) and extracted with dichloromethane (2 X 20

mL). The organic layer was washed with brine, dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure to get (R)-6-((S)-1-((4S, 4aR, 5aR, 6aS, 6bS, 9R, 9aS, 11aS, 11bR)-4-hydroxy-2-(5-methoxypyrimidin-2-yl)-9a, 11b-dimethyl-1-oxo-1, 4, 5a, 6, 6a, 6b, 7, 8, 9, 9a, 10, 11, 11a, 11b-tetradecahydrocyclopenta [1, 2] phenanthro [8a, 9-b] oxiren-9-yl) ethyl)-4-methyl-2-oxo-5, 6-dihydro-2H-pyran-3-yl) methyl methanesulfonate (0.2 g crude) as crude. It was used as such for next step.

[0516] Step 2: Synthesis of (4S, 4aR, 5aR, 6aS, 6bS, 9R, 9aS, 11aS, 11bR)-4-hydroxy-2-(5-methoxypyrimidin-2-yl)-9a, 11b-dimethyl-9-((S)-1-((R)-4-methyl-5-(morpholinomethyl)-6-oxo-3, 6-dihydro-2H-pyran-2-yl)ethyl)-5a, 6, 6a, 6b, 7, 8, 9, 9a, 10, 11, 11a, 11b-dodecahydrocyclopenta [1, 2] phenanthro [8a, 9-b] oxiren-1(4H)-one :

To a stirred solution of dipotassium carbonate (84.2 mg, 2 eq., 609 μ mol) in acetonitrile (8 mL) was added morpholine (39.8 mg, 1.5 eq., 457 μ mol) followed by addition of (R)-6-[(S)-1-{(1S, 2R, 6S, 7R, 9R, 11S, 12S, 15R, 16S)-6-hydroxy-4-(5-methoxy-2-pyrimidinyl)-2, 16-dimethyl-3-oxo-8-oxapentacyclo [9.7.0.0^{2,7}.0^{7,9}.0^{12,16}] octadec-4-en-15-yl} ethyl]-3-[(mesyloxy) methyl]-4-methyl-5, 6-dihydro-2H-pyran-2-one (0.2 g, 305 μ mol) at 0°C. The resultant reaction mixture was stirred at room temperature for 30 minutes. After the completion of reaction (monitored by TLC), it was quenched with water (40 mL) and extracted with ethyl acetate (2 X 40 mL). The organic layer was washed with brine, dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure.

The crude compound was purified by using preparative-HPLC using ammonium bicarbonate method, to afford (R)-6-[(S)-1-{(1S, 2R, 6S, 7R, 9R, 11S, 12S, 15R, 16S)-6-hydroxy-4-(5-methoxy-2-pyrimidinyl)-2, 16-dimethyl-3-oxo-8-oxapentacyclo [9.7.0.0^{2,7}.0^{7,9}.0^{12,16}] octadec-4-en-15-yl} ethyl]-4-methyl-3-(morpholinomethyl)-5, 6-dihydro-2H-pyran-2-one (32.9 mg, 16.5%) as a white solid.

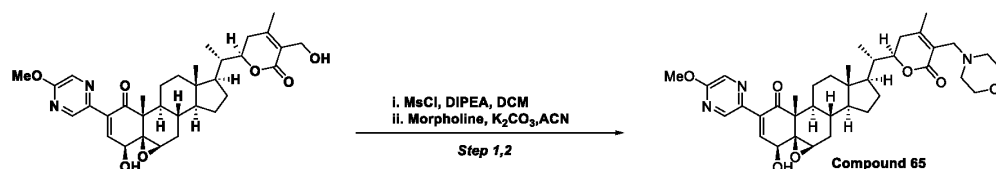
[0517] Analytical data:

LCMS: 98.96% (m/z: 648.5, [M+1]⁺, 5.74 min (10 min run).

¹H-NMR (400 MHz, DMSO-*d*₆): δ 8.57 (s, 2H), 7.53 (d, *J* = 6.8 Hz, 1H), 5.74 (d, *J* = 3.6 Hz, 1H), 4.32-4.28 (m, 1H), 3.92 (s, 3H), 3.74-3.71 (m, 1H), 3.50 (t, *J* = 4.4 Hz, 4H), 3.25 (d, *J* = 12 Hz, 1H), 3.13 (s, 1H), 3.06 (d, *J* = 12.4 Hz, 1H), 2.40-2.37 (m, 1H), 2.32-2.30 (m, 4H), 2.14-2.08 (m, 2H), 2.03 (s, 3H), 1.92-1.89 (m, 1H), 1.81-1.77 (m, 1H), 1.73-1.72 (m, 1H), 1.61-1.48 (m, 2H), 1.32-1.23 (m, 7H), 1.12-1.01 (m, 4H), 0.99-0.91 (m, 4H), 0.65 (s, 3H).

¹³C-NMR (400 MHz, DMSO-*d*₆): δ 199.00, 165.43, 155.91, 155.22, 152.04, 143.59, 141.42, 139.94, 121.34, 77.41, 68.57, 66.21, 63.82, 57.43, 56.18, 55.47, 52.99, 52.56, 51.04, 47.83, 42.05, 41.80, 30.89, 29.27, 29.06, 26.53, 23.91, 20.44, 20.19, 14.80, 13.08, 11.23.

[0518] Synthesis of Compound 65



Steps 1,2: Synthesis of (R)-6-[(S)-1-{(1S, 2R, 6S, 7R, 9R, 11S, 12S, 15R, 16S)-6-hydroxy-4-(5-methoxy-2-pyrazinyl)-2, 16-dimethyl-3-oxo-8-oxapentacyclo [9.7.0.0²,⁷.0⁷,⁹.0¹²,¹⁶] octadec-4-en-15-yl}ethyl]-4-methyl-3-(morpholinomethyl)-5, 6-dihydro-2H-pyran-2-one:

To a stirred solution of (R)-6-[(S)-1-{(1S, 2R, 6S, 7R, 9R, 11S, 12S, 15R, 16S)-6-hydroxy-4-(5-methoxy-2-pyrazinyl)-2,16-dimethyl-3-oxo-8-oxapentacyclo [9.7.0.0²,⁷.0⁷,⁹.0¹²,¹⁶] octadec-4-en-15-yl}ethyl]-3-(hydroxymethyl)-4-methyl-5, 6-dihydro-2H-pyran-2-one (0.3 g, 518 μ mol) in dichloromethane (3 mL) was added ethylbis (propan-2-yl)amine (220 μ L, 2.5 eq., 1.3 mmol) followed by methanesulfonyl chloride (40.1 μ L, 518 μ mol) at 0°C. The reaction mixture was stirred at 0°C for 30 minutes. After the completion of reaction (monitored by TLC), mixture was quenched with water (15 mL) and extracted with dichloromethane (2 x 20 mL). The organic layer was washed with brine solution, dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure to get crude (R)-6-[(S)-1-{(1S, 2R, 6S, 7R, 9R, 11S, 12S, 15R, 16S)-6-hydroxy-4-(5-methoxy-2-pyrazinyl)-2, 16-dimethyl-3-oxo-8-oxapentacyclo [9.7.0.0²,⁷.0⁷,⁹.0¹²,¹⁶] octadec-4-en-15-yl} ethyl]-3-[(mesyloxy)methyl]-4-methyl-5, 6-dihydro-2H-pyran-2-one. It was forwarded as such to the next step. To a stirred solution of dipotassium carbonate (126 mg, 2 eq., 914 μ mol) in acetonitrile (3 mL) was added morpholine (59.1 μ L, 1.5 eq., 685 μ mol) followed by addition of (R)-6-[(S)-1-{(1S, 2R, 6S, 7R, 9R, 11S, 12S, 15R, 16S)-6-hydroxy-4-(5-methoxy-2-pyrazinyl)-2, 16-dimethyl-3-oxo-8-oxapentacyclo [9.7.0.0²,⁷.0⁷,⁹.0¹²,¹⁶] octadec-4-en-15-yl}ethyl]-3-[(mesyloxy) methyl]-4-methyl-5, 6-dihydro-2H-pyran-2-one (0.3 g, 457 μ mol) at 0°C. The resultant reaction mixture was stirred at room temperature for 30 min. After the completion of reaction

(monitored by TLC), it was diluted with water (20 mL) and extracted with ethyl acetate (2 X 20 mL). The organic layer was washed with brine, dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure to get crude. The crude was purified by using preparative-HPLC (ABC method) to afford (R)-6-[(S)-1-{(1S, 2R, 6S, 7R, 9R, 11S, 12S, 15R, 16S)-6-hydroxy-4-(5-methoxy-2-pyrazinyl)-2, 16-dimethyl-3-oxo-8-oxapentacyclo [9.7.0.0^{2,7}, 9.0^{12,16}] octadec-4-en-15-yl}ethyl]-4-methyl-3-(morpholinomethyl)-5, 6-dihydro-2H-pyran-2-one (80 mg, 121 μ mol, 26%) as white solid.

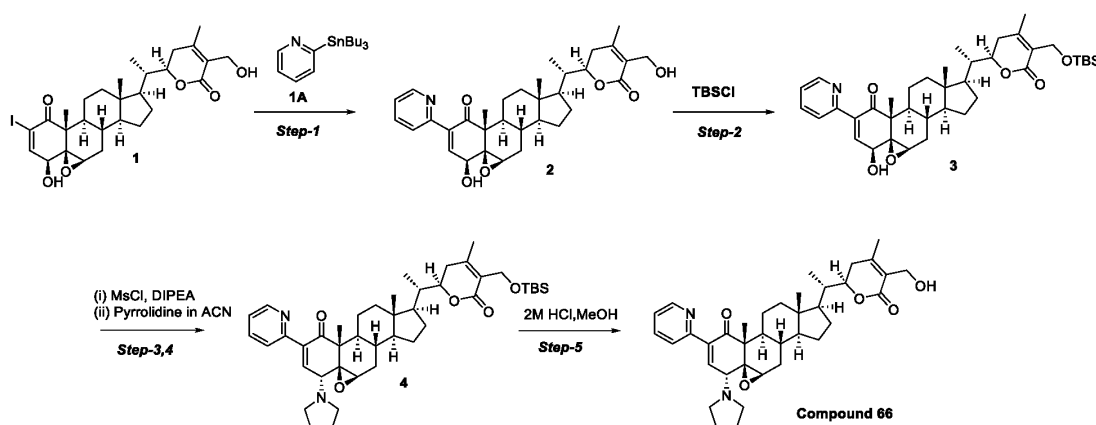
[0519] Analytical data:

LCMS: 98.44% (m/z: 648.5, [M+1]⁺, 6.24 min (18 min run).

¹H-NMR (400 MHz, DMSO-*d*₆): δ 8.36 (d, *J* = 1.6 Hz, 1H), 8.21 (d, *J* = 1.2 Hz, 1H), 7.60 (d, *J* = 6.4 Hz, 1H), 5.77 (d, *J* = 3.6 Hz, 1H), 4.30-4.26 (m, 1H), 3.93 (s, 3H), 3.76-3.74 (m, 1H), 3.51-3.49 (m, 4H), 3.27-3.29 (d, *J* = 12.4 Hz, 1H), 3.16 (s, 1H), 3.07-3.04 (d, *J* = 12.4 Hz, 3H), 2.50-1.54 (m, 14H), 1.39-0.86 (m, 16H), 0.65 (s, 3H).

¹³C-NMR (400 MHz, DMSO-*d*₆): δ 200.33, 165.42, 159.37, 155.88, 140.66, 139.16, 138.93, 138.31, 135.01, 121.34, 77.39, 68.43, 66.21, 63.41, 57.59, 55.26, 53.80, 52.98, 52.56, 51.10, 47.90, 42.14, 42.01, 38.42, 38.33, 30.75, 29.27, 26.51, 23.90, 20.51, 20.44, 15.15, 13.08, 11.24.

[0520] Synthesis of Compound 66



[0521] Step 1: Synthesis of (R)-6-[(S)-1-{(1S, 2R, 6S, 7R, 9R, 11S, 12S, 15R, 16S)-6-hydroxy-2, 16-dimethyl-3-oxo-4-(2-pyridyl)-8-oxapentacyclo [9.7.0.0^{2,7}, 9.0^{12,16}] octadec-4-en-15-yl}ethyl]-3-(hydroxymethyl)-4-methyl-5, 6-dihydro-2H-pyran-2-one.

To a stirred solution of (R)-6-[(S)-1-[(1S, 2R, 6S, 7R, 9R, 11S, 12S, 15R, 16S)-6-hydroxy-4-iodo-2, 16-dimethyl-3-oxo-8-oxapentacyclo [9.7.0.0²,⁷.0⁷,⁹.0¹²,¹⁶] octadec-4-en-15-yl} ethyl]-3-(hydroxymethyl)-4-methyl-5, 6-dihydro-2H-pyran-2-one (3 g, 5.03 mmol) in 1,4-dioxane (30 mL) were added copper iodide (144 mg, 0.15 eq., 754 μ mol) and tributyl(2-pyridyl) stannane (3.7 g, 2 eq., 10.1 mmol) at room temperature. The reaction mixture was purged with nitrogen gas for 30 min and palladium—(1E, 4E)-1,5-diphenyl-1,4-pentadien-3-one (2/3) (461 mg, 0.1 eq., 503 μ mol) was added to it. The reaction mixture was again purged with nitrogen gas for 5 min and stirred at 80 °C for 2 h. After completion of the reaction (monitored by TLC), it was filtered through celite bed and washed with ethyl acetate. The ethyl acetate layer was washed with chilled water followed by brine. Dried the organics over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to get crude. To the crude material n-pentane was added and the solids were filtered to get (R)-6-[(S)-1-[(1S, 2R, 6S, 7R, 9R, 11S, 12S, 15R, 16S)-6-hydroxy-2, 16-dimethyl-3-oxo-4-(2-pyridyl)-8-oxapentacyclo [9.7.0.0²,⁷.0⁷,⁹.0¹²,¹⁶] octadec-4-en-15-yl} ethyl]-3-(hydroxymethyl)-4-methyl-5, 6-dihydro-2H-pyran-2-one (2.7 g, 79%).

[0522] Analytical Data:

LCMS: 81% (m/z: 548.35 [M+1]⁺), 1.88 min (4 min run).

[0523] Step 2: Synthesis of (1S, 2R, 6S, 7R, 9R, 11S, 12S, 15R, 16S)-15-[(1S)-1-[(2R)-5-[(tert-butyldimethylsilyl)oxy]methyl]-4-methyl-6-oxo-3, 6-dihydro-2H-pyran-2-yl]ethyl]-6-hydroxy-2, 16-dimethyl-4-(pyridin-2-yl)-8-oxapentacyclo [9.7.0.0²,⁷.0⁷,⁹.0¹²,¹⁶] octadec-4-en-3-one.

To a stirred solution of (1S, 2R, 6S, 7R, 9R, 11S, 12S, 15R, 16S)-6-hydroxy-15-[(1S)-1-[(2R)-5-(hydroxymethyl)-4-methyl-6-oxo-3,6-dihydro-2H-pyran-2-yl]ethyl]-2, 16-dimethyl-4-(pyridin-2-yl)-8-oxapentacyclo [9.7.0.0²,⁷.0⁷,⁹.0¹²,¹⁶] octadec-4-en-3-one (2.7 g, 4.93 mmol) and 4-(pyrrolidin-1-yl)pyridin-1-ium (1.47 g, 2 eq., 9.86 mmol) in dimethylformamide (25.7 mL) for 10-15 min., then tert-butyl(chloro)dimethylsilane (1.11 g, 1.5 eq., 7.39 mmol) was added at room temperature and stirred for 30 min at 80 °C. After completion of reaction, the reaction mixture was poured into crushed ice-cold water (75 mL) and extracted with ethyl acetate (30 mL x 3). The combined ethyl acetate layer was washed with brine (50 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to get crude compound. The crude compound was purified by column chromatography on silica gel using 0-65% ethyl acetate in heptane to get (1S, 2R, 6S, 7R, 9R, 11S, 12S, 15R, 16S)-15-[(1S)-1-

[(2R)-5-{[(tert-butyldimethylsilyl) oxy] methyl}-4-methyl-6-oxo-3,6-dihydro-2H-pyran-2-yl]ethyl]-6-hydroxy-2,16-dimethyl-4-(pyridin-2-yl)-8-oxapentacyclo [9.7.0.0²,⁷.0⁷,⁹.0¹²,¹⁶] octadec-4-en-3-one (1.7 g, 49%).

[0524] Analytical data:

LCMS: purity 93% (m/z: 662.50 [M+1]⁺), 2.72 min (4 min run).

[0525] Step-3: Synthesis of (1S, 2R, 6S, 7S, 9R, 11S, 12S, 15R, 16S)-15-[(1S)-1-[(2R)-5-{[(tert-butyldimethylsilyl) oxy] methyl}-4-methyl-6-oxo-3, 6-dihydro-2H-pyran-2-yl]ethyl]-2, 16-dimethyl-3-oxo-4-(pyridin-2-yl)-8-oxapentacyclo [9.7.0.0²,⁷.0⁷,⁹.0¹²,¹⁶] octadec-4-en-6-yl methanesulfonate

To a stirred solution of (1S, 2R, 6S, 7R, 9R, 11S, 12S, 15R, 16S)-15-[(1S)-1-[(2R)-5-{[(tert-butyldimethylsilyl) oxy] methyl}-4-methyl-6-oxo-3, 6-dihydro-2H-pyran-2-yl]ethyl]-6-hydroxy-2, 16-dimethyl-4-(pyridin-2-yl)-8-oxapentacyclo [9.7.0.0²,⁷.0⁷,⁹.0¹²,¹⁶] octadec-4-en-3-one (0.2 g, 302 μmol) in dichloromethane (2 mL); N-ethylbis (isopropyl) amine (78.1 mg, 2 eq., 604 μmol) was added at 0 °C and stirred for 5 mins then (chlorosulfonyl) methane (51.9 mg, 1.5 eq., 453 μmol) was added and stirred for 1 min at room temperature. The reaction was monitored by TLC. After completion of reaction, the reaction mixture was quenched with saturated sodium bicarbonate solution (20 mL) and extracted with dichloromethane (25 mL x 2). Collective dichloromethane layer was washed with brine, dried over anhydrous sodium sulphate, filtered and concentrated under vacuum to get (1S, 2R, 6S, 7S, 9R, 11S, 12S, 15R, 16S)-15-[(1S)-1-[(2R)-5-{[(tert-butyldimethylsilyl) oxy] methyl}-4-methyl-6-oxo-3, 6-dihydro-2H-pyran-2-yl] ethyl]-2, 16-dimethyl-3-oxo-4-(pyridin-2-yl)-8-oxapentacyclo [9.7.0.0²,⁷.0⁷,⁹.0¹²,¹⁶] octadec-4-en-6-yl methanesulfonate (0.2 g, 89%), the crude was as such forwarded to next step.

[0526] Step-4: Synthesis of (R)-6-[(S)-1-[(1S, 2R, 6R, 7R, 9R, 11S, 12S, 15R, 16S)-2, 16-dimethyl-3-oxo-4-(2-pyridyl)-6-(1-pyrrolidinyl)-8-oxapentacyclo [9.7.0.0²,⁷.0⁷,⁹.0¹²,¹⁶] octadec-4-en-15-yl]ethyl]-3-{[(tert-butyl) bis(methyl) siloxy]methyl}-4-methyl-5, 6-dihydro-2H-pyran-2-one.

A stirred solution of pyrrolidine (8.65 mg, 1.5 eq., 122 μmol) and triethylamine (16.4 mg, 2 eq., 162 μmol) in acetonitrile (1 mL) was cooled to 0 °C and stirred for 5 minutes then (1S, 2R, 6S, 7S, 9R, 11S, 12S, 15R, 16S)-15-[(1S)-1-[(2R)-5-{[(tert-butyldimethylsilyl) oxy] methyl}-4-methyl-6-oxo-3, 6-dihydro-2H-pyran-2-yl]ethyl]-2, 16-dimethyl-3-oxo-4-(pyridin-2-yl)-8-

oxapentacyclo [9.7.0.0^{2,7},⁹.0^{12,16}] octadec-4-en-6-yl methanesulfonate (0.1 g, 1.7 eq., 135 μ mol) was added and stirred for 10 min. The reaction was monitored by TLC and LCMS. After completion of reaction, the reaction mixture was quenched with water (20 mL) and extracted with ethyl acetate (15 mL x 2). Collective ethyl acetate layer was washed with brine (25 mL), dried over anhydrous sodium sulfate, filtered and concentrated under vacuum to get crude compound (R)-6-[(S)-1-[(1S, 2R, 6R, 7R, 9R, 11S, 12S, 15R, 16S)-2, 16-dimethyl-3-oxo-4-(2-pyridyl)-6-(1-pyrrolidinyl)-8-oxapentacyclo [9.7.0.0^{2,7},⁹.0^{12,16}] octadec-4-en-15-yl]ethyl]-3-[[tert-butyl bis(methyl) siloxy] methyl]-4-methyl-5, 6-dihydro-2H-pyran-2-one (150 mg crude, 56%).

Analytical data:

LCMS: purity 54% (m/z: 715.85 [M+1]⁺), 3.06 min (4 min run).

[0527] Step-5: Synthesis of (R)-6-[(S)-1-[(1S, 2R, 6R, 7R, 9R, 11S, 12S, 15R, 16S)-2, 16-dimethyl-3-oxo-4-(2-pyridyl)-6-(1-pyrrolidinyl)-8-oxapentacyclo [9.7.0.0^{2,7},⁹.0^{12,16}] octadec-4-en-15-yl]ethyl]-3-(hydroxymethyl)-4-methyl-5, 6-dihydro-2H-pyran-2-one.

To a stirred solution of (R)-6-[(S)-1-[(1S, 2R, 6R, 7R, 9R, 11S, 12S, 15R, 16S)-2, 16-dimethyl-3-oxo-4-(2-pyridyl)-6-(1-pyrrolidinyl)-8-oxapentacyclo [9.7.0.0^{2,7},⁹.0^{12,16}] octadec-4-en-15-yl]ethyl]-3-[[tert-butyl bis(methyl) siloxy] methyl]-4-methyl-5, 6-dihydro-2H-pyran-2-one (0.3 g, 420 μ mol) in tetrahydrofuran (3 mL) was added methanol (0.5 mL) followed by 2N HCl (3 mL) and stirred the reaction for 20 min at room temperature. The reaction mixture was quenched with sodium bicarbonate solution (30 mL) and extracted by dichloromethane (2 x 30 mL). The combined dichloromethane layer was dried over anhydrous sodium sulphate, filtered and evaporated under vacuum to get crude compound. The crude compound was purified by Prep HPLC (ABC method) to get (R)-6-[(S)-1-[(1S, 2R, 6R, 7R, 9R, 11S, 12S, 15R, 16S)-2, 16-dimethyl-3-oxo-4-(2-pyridyl)-6-(1-pyrrolidinyl)-8-oxapentacyclo [9.7.0.0^{2,7},⁹.0^{12,16}] octadec-4-en-15-yl]ethyl]-3-(hydroxymethyl)-4-methyl-5, 6-dihydro-2H-pyran-2-one (22 mg, 9%).

[0528] Analytical data:

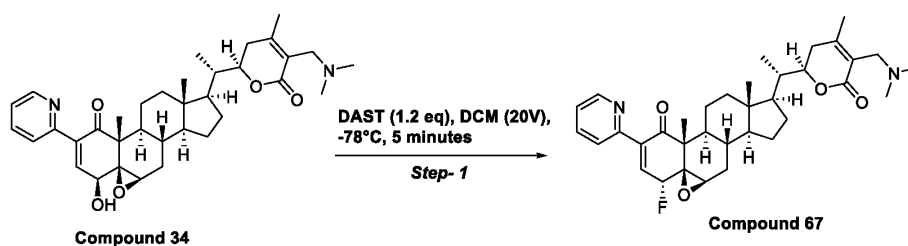
LCMS: purity 97.17% (m/z: 601.5 [M+1]⁺), 7.23 min (10 min run).

¹H-NMR (400 MHz, DMSO-d₆): δ 8.59 (d, J = 4.0 Hz, 1H), 7.83-7.79 (dt, J_1 = 7.6 Hz, J_2 = 2 Hz, 1H), 7.62 (d, J = 3.2 Hz, 1H), 7.41 (d, J = 7.6 Hz, 1H), 7.36-7.32 (m, 1H), 4.57 (t, J = 5.6 Hz, 1H), 4.31-4.27

(m, 1H), 4.18-4.07 (m, 2H), 3.63 (d, J = 2.8 Hz, 1H), 3.54 (s, 1H), 2.67-2.66 (m, 4H), 2.39-2.35 (m, 1H), 2.13-2.07 (m, 1H), 2.02-1.99 (m, 4H), 1.92-1.89 (m, 1H), 1.81-1.70 (m, 3H), 1.65 (s, 3H), 1.59-1.56 (m, 2H), 1.41-1.23 (m, 4H), 1.21 (s, 3H), 1.98-0.97 (m, 4H), 1.0-0.92 (m, 4H), 0.67(s, 3H).

¹³C-NMR (400 MHz, DMSO-d₆): δ 200.50, 165.32, 154.69, 152.01, 149.52, 141.30, 138.37, 136.85, 125.43, 123.21, 122.15, 77.53, 64.74, 59.60, 55.72, 55.16, 54.51, 51.45, 51.12, 49.59, 42.81, 42.08, 38.75, 38.41, 30.41, 29.20, 29.03, 26.48, 23.98, 23.15, 21.61, 19.88, 13.59, 13.03, 11.39.

[0529] Synthesis of Compound 67



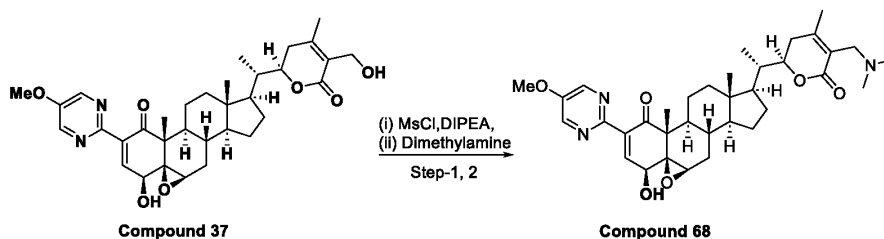
[0530] Step 1: Synthesis of (4R, 4aS, 5aR, 6aS, 6bS, 9R, 9aS, 11aS, 11bR)-9-((S)-1-((R)-5-((dimethylamino) methyl)-4-methyl-6-oxo-3, 6-dihydro-2H-pyran-2-yl)ethyl)-4-fluoro-9a, 11b-dimethyl-2-(pyridin-2-yl)-5a, 6, 6a, 6b, 7, 8, 9, 9a, 10, 11, 11a, 11b-dodecahydrocyclopenta [1, 2] phenanthro [8a, 9-b] oxiren-1(4H)-one:

To a stirred solution of (R)-6-[(S)-1-{(1S, 2R, 6S, 7R, 9R, 11S, 12S, 15R, 16S)-6-hydroxy-2, 16-dimethyl-3-oxo-4-(2-pyridyl)-8-oxapentacyclo [9.7.0.0^{2,7}.0^{7,9}.0^{12,16}] octadec-4-en-15-yl}ethyl]-3-[(dimethylamino) methyl]-4-methyl-5, 6-dihydro-2H-pyran-2-one (0.2 g, 348 μmol) in dichloromethane (5 mL) was added N,N-diethyl (trifluorothio) amine (67.3 mg, 1.2 eq., 418 μmol) at -78°C. The resultant reaction mixture was stirred at the same temperature for 5 minutes. After the completion of reaction (monitored by TLC), it was diluted with sodium bicarbonate solution (20 mL) and extracted with dichloromethane (2 X 20 mL). The organic layer was washed with brine, dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure to get crude. Crude compound was purified by preparative HPLC using ammonium acetate method to afford (4R, 4aS, 5aR, 6aS, 6bS, 9R, 9aS, 11aS, 11bR)-9-((S)-1-((R)-5-((dimethylamino) methyl)-4-methyl-6-oxo-3, 6-dihydro-2H-pyran-2-yl) ethyl)-4-fluoro-9a, 11b-dimethyl-2-(pyridin-2-yl)-5a, 6, 6a, 6b, 7, 8, 9, 9a, 10, 11, 11a, 11b-dodecahydrocyclopenta [1, 2] phenanthro [8a, 9-b] oxiren-1(4H)-one (27 mg, 12.8%) as a white solid.

LCMS: 95.04% (m/z: 577.50, [M+1]⁺, 5.95 min (10 min run).

¹H-NMR (400 MHz, DMSO-*d*₆): δ 8.62-8.61 (m, 1H), 7.87-7.83 (m, 1H), 7.56 (dd, J = 17.2, 1.60 Hz, 1H), 7.47 (d, J = 8.0 Hz, 1H), 7.40-7.37 (m, 1H), 5.87 (d, J = 50 Hz, 1H), 4.31- 4.26 (m, 1H), 3.52 (s, 1H), 3.20 (d, J = 12.4 Hz, 1H), 2.99 (d, J = 11.6 Hz, 1H), 2.50 - 2.36 (m, 1H), 2.14-2.01 (m, 8H), 1.99 (s, 3H), 1.93 -1.29 (m, 9H), 1.23 (s, 3H), 1.16 – 0.91 (m, 8H), 0.68 (s, 3H).

[0532] Synthesis of Compound 68



[0533] Step 1: Synthesis of ((R)-6-((S)-1-((4S, 4aR, 5aR, 6aS, 6bS, 9R, 9aS, 11aS, 11bR)-4-hydroxy-2-(5-methoxypyrimidin-2-yl)-9a, 11b-dimethyl-1-oxo-1, 4, 5a, 6, 6a, 6b, 7, 8, 9, 9a, 10, 11, 11a, 11b-tetradecahydrocyclopenta [1, 2] phenanthro [8a, 9-b] oxiren-9-yl) ethyl)-4-methyl-2-oxo-5, 6-dihydro-2H-pyran-3-yl)methyl methanesulfonate:

To a stirred solution of (R)-6-[(S)-1-[(1S, 2R, 6S, 7R, 9R, 11S, 12S, 15R, 16S)-6-hydroxy-4-(5-methoxy-2-pyrimidinyl)-2, 16-dimethyl-3-oxo-8-oxapentacyclo [9.7.0.0²,7⁰,9⁰,12¹,16¹octadec-4-en-15-yl] ethyl]-3-(hydroxymethyl)-4-methyl-5, 6-dihydro-2H-pyran-2-one (0.2 g, 346 μmol) in dichloromethane dichloromethane (2 mL) was added N-ethylbis(isopropyl)amine (112 mg, 2.5 eq., 864 μmol) then (chlorosulfonyl) methane (39.6 mg, 346 μmol) at 0°C. The reaction mixture was stirred at 0°C for 30 minutes. After the completion of reaction (monitored by TLC), mixture was diluted with water (30 mL) and extracted with dichloromethane (2 X 30 mL). The organic layer was washed with brine, dried the organics over anhydrous sodium sulphate, filtered and concentrated under reduced pressure to get ((R)-6-((S)-1-((4S, 4aR, 5aR, 6aS, 6bS, 9R, 9aS, 11aS, 11bR)-4-hydroxy-2-(5-methoxypyrimidin-2-yl)-9a, 11b-dimethyl-1-

oxo-1, 4, 5a, 6, 6a, 6b, 7, 8, 9, 9a, 10, 11, 11a, 11b-tetradecahydrocyclopenta [1, 2] phenanthro [8a, 9-b] oxiren-9-yl) ethyl)-4-methyl-2-oxo-5, 6-dihydro-2H-pyran-3-yl) methyl methanesulfonate as a crude compound. It was forwarded as such to the next step.

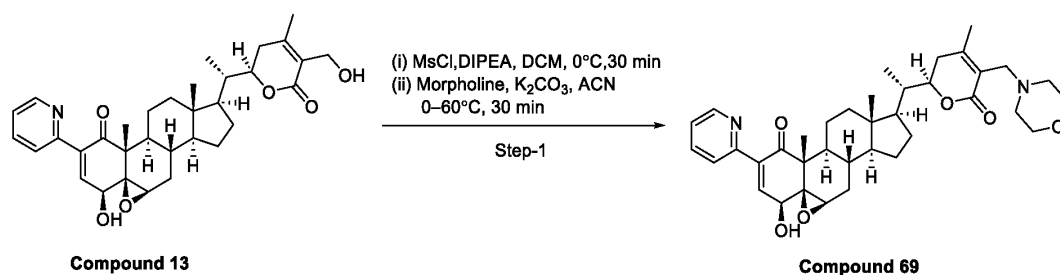
[0534] Step 2: Synthesis of (4S, 4aR, 5aR, 6aS, 6bS, 9R, 9aS, 11aS, 11bR)-9-((S)-1-((R)-5-((dimethylamino)methyl)-4-methyl-6-oxo-3, 6-dihydro-2H-pyran-2-yl)ethyl)-4-hydroxy-2-(5-methoxypyrimidin-2-yl)-9a, 11b-dimethyl-5a, 6, 6a, 6b, 7, 8, 9, 9a, 10, 11, 11a, 11b-dodecahydrocyclopenta [1, 2] phenanthro [8a, 9-b] oxiren-1(4H)-one:

To a stirred solution of dipotassium carbonate (88.4 mg, 2 eq., 639 μ mol) in acetonitrile (2.5 mL) was added dimethylamine, 2M in THF, (21.6 mg, 1.5 eq., 480 μ mol) followed by addition of (R)-6-[(S)-1-{(1S, 2R, 6S, 7R, 9R, 11S, 12S, 15R, 16S)-6-hydroxy-4-(5-methoxy-2-pyrimidinyl)-2, 16-dimethyl-3-oxo-8-oxapentacyclo [9.7.0.0^{2,7}.0^{7,9}.0^{12,16}] octadec-4-en-15-yl}ethyl]-3-[(mesyloxy) methyl]-4-methyl-5, 6-dihydro-2H-pyran-2-one (210 mg, 320 μ mol) at 0°C. The resultant reaction mixture was stirred at 60°C for 1 h. After the completion of reaction (monitored by TLC), mixture was diluted with water (20 mL) and extracted with ethyl acetate (2 X 20 mL). The organic layer was washed with brine, dried the organics over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. Crude was purified by using preparative-HPLC using ammonium bicarbonate method under freezing condition to afford (4S, 4aR, 5aR, 6aS, 6bS, 9R, 9aS, 11aS, 11bR)-9-((S)-1-((R)-5-((dimethylamino) methyl)-4-methyl-6-oxo-3, 6-dihydro-2H-pyran-2-yl) ethyl)-4-hydroxy-2-(5-methoxypyrimidin-2-yl)-9a, 11b-dimethyl-5a, 6, 6a, 6b, 7, 8, 9, 9a, 10, 11, 11a, 11b-dodecahydrocyclopenta [1, 2] phenanthro [8a, 9-b] oxiren-1(4H)-one (19 mg, 30.7 μ mol), 9.61%) as a white solid.

[0535] Analytical data:

LCMS: 98.03% (m/z: 606.50, [M+1]⁺, 4.77 min (10 min run).

¹H-NMR (400 MHz, DMSO-*d*₆): δ 8.57 (s, 2H), 7.52 (d, *J* = 6.40 Hz, 1H), 5.73 (d, *J* = 3.60 Hz, 1H), 4.30-4.27 (m, 1H), 3.92 (s, 3H), 3.74-3.71 (m, 1H), 3.19-3.13 (m, 2H), 2.96 (d, *J* = 12.4 Hz, 1H), 2.44-2.36 (m, 1H), 2.12 (d, *J* = 2.80 Hz, 1H), 2.07 (s, 6H), 2.03-1.72 (m, 7H), 1.57-1.02 (m, 12H), 1.08-0.92 (m, 5H), 0.65 (s, 3H).

[0536] Synthesis of Compound 69

[0537] Step-1: Synthesis of (4S, 4aR, 5aR, 6aS, 6bS, 9R, 9aS, 11aS, 11bR)-4-hydroxy-9a, 11b-dimethyl-9-((S)-1-((R)-4-methyl-5-(morpholinomethyl)-6-oxo-3, 6-dihydro-2H-pyran-2-yl) ethyl)-2-(pyridin-2-yl)-5a, 6, 6a, 6b, 7, 8, 9, 9a, 10, 11, 11a, 11b-dodecahydrocyclopenta [1, 2] phenanthro [8a, 9-b] oxiren-1(4H)-one:

To a stirred solution of (4S, 4aR, 5aR, 6aS, 6bS, 9R, 9aS, 11aS, 11bR)-4-hydroxy-9a, 11b-dimethyl-9-((S)-1-((R)-5-(hydroxymethyl)-4-methyl-6-oxo-3, 6-dihydro-2H-pyran-2-yl)ethyl)-9a, 11b-dimethyl-2-(pyridin-2-yl)-5a, 6, 6a, 6b, 7, 8, 9, 9a, 10, 11, 11a, 11b-dodecahydrocyclopenta [1, 2] phenanthro [8a, 9-b] oxiren-1(4H)-one (0.4 g, 0.730 mmol) in dichloromethane (8 mL) was added ethylbis (propan-2-yl)amine (0.296 mL, 1.46 mmol) followed by methanesulfonyl chloride (83.7 mg, 0.73 mmol) at 0 °C. The reaction mixture was stirred at 0 °C for 30 min. After the completion of reaction, (monitored by TLC, shown 50% conversion) quenched it with ice cold water (10 mL) and extracted with dichloromethane (2 X 10 mL). The combined organic layer was washed with saturated brine solution (20 mL), dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure to get ((R)-6-((S)-1-((4S, 4aR, 5aR, 6aS, 6bS, 9R, 9aS, 11aS, 11bR)-4-hydroxy-9a, 11b-dimethyl-1-oxo-2-(pyridin-2-yl)-1, 4, 5a, 6, 6a, 6b, 7, 8, 9, 9a, 10, 11, 11a, 11b-tetradecahydrocyclopenta [1, 2] phenanthro [8a, 9-b] oxiren-9-yl) ethyl)-4-methyl-2-oxo-5, 6-dihydro-2H-pyran-3-yl) methyl methanesulfonate. It was forwarded as such to the next reaction.

In a 10 mL RBF, added dipotassium carbonate (202 mg, 1.46 mmol) and morpholine (95.4 mg, 1.1 mmol) in acetonitrile (2 mL), followed by dropwise addition of ((R)-6-((S)-1-((4S, 4aR, 5aR, 6aS, 6bS, 9R, 9aS, 11aS, 11bR)-4-hydroxy-9a, 11b-dimethyl-1-oxo-2-(pyridin-2-yl)-1, 4, 5a, 6, 6a, 6b, 7, 8, 9, 9a, 10, 11, 11a, 11b-tetradecahydrocyclopenta [1, 2] phenanthro [8a, 9-b] oxiren-9-yl) ethyl)-4-methyl-2-oxo-5, 6-dihydro-2H-pyran-3-yl) methyl methanesulfonate dissolved in acetonitrile (2 mL) at 0°C. The resultant reaction mixture was stirred at 60 °C for 30 min. After the completion of reaction (monitored by TLC), the reaction mixture was filtered

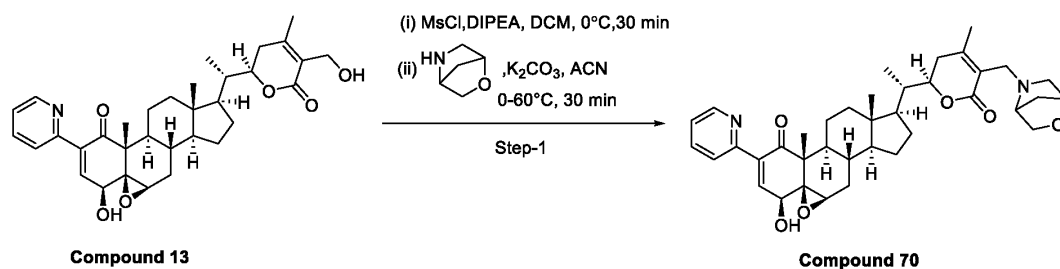
through celite, filtrate was concentrated and purified by preparative-HPLC using column YMC Actus Triart C18 ExRS (20*250mm) 5 μ m A ammonium acetate in water, B Acetonitrile method followed by lyophilization to afford (4S, 4aR, 5aR, 6aS, 6bS, 9R, 9aS, 11aS, 11bR)-4-hydroxy-9a, 11b-dimethyl-9-((S)-1-((R)-4-methyl-5-(morpholinomethyl)-6-oxo-3,6-dihydro-2H-pyran-2-yl)ethyl)-2-(pyridin-2-yl)-5a, 6, 6a, 6b, 7, 8, 9, 9a, 10, 11, 11a, 11b-dodecahydrocyclopenta [1, 2] phenanthro [8a, 9-b] oxiren-1(4H)-one (30 mg, 6.6%) as a off white solid.

[0538] Analytical data:

LCMS: 99.37% (m/z: 617.51, [M+1]⁺, 2.59 min (5.50 min run).

¹H-NMR (400 MHz, DMSO-*d*₆): δ 8.59 (d, *J* = 4.0 Hz, 1H), 7.85-7.80 (m, 1H), 7.68 (d, *J* = 6.80 Hz, 1H), 7.39-7.34 (m, 2H), 5.73 (d, *J* = 3.20 Hz, 1H), 4.31-4.27 (m, 1H), 3.76-3.74 (m, 1H), 3.51-3.49 (m, 4H), 3.27 (d, *J* = 9.6 Hz, 1H), 3.15 (s, 1H), 3.06 (d, 1H), 2.39-2.33 (m, 6H), 2.12-2.06 (m, 3H), 2.02 (s, 3H), 1.97-1.89 (m, 1H), 1.81-1.71 (m, 2H), 1.56-1.54 (m, 1H), 1.41-1.21 (m, 6H), 1.14-1.04 (m, 3H), 0.92-0.84 (m, 5H), 0.66 (s, 3H).

[0539] Synthesis of Compound 70



[0540] Step-1: Synthesis of (4S, 4aR, 5aR, 6aS, 6bS, 9R, 9aS, 11aS, 11bR)-9-((1S)-1-((2R)-5-(2-oxa-5-azabicyclo [2.2.1] heptan-5-ylmethyl) -4-methyl- 6-oxo-3, 6-dihydro -2H-pyran-2-yl) ethyl) -4-hydroxy-9a, 11b-dimethyl-2-(pyridin-2-yl)-5a, 6, 6a, 6b, 7, 8, 9, 9a, 10, 11, 11a, 11b-dodecahydrocyclopenta [1, 2] phenanthro [8a, 9-b] oxiren-1(4H)-one:

To a stirred solution of (4S, 4aR, 5aR, 6aS, 6bS, 9R, 9aS, 11aS, 11bR)-4-hydroxy-9-((S)-1-((R)-5-(hydroxymethyl)-4-methyl-6-oxo-3, 6-dihydro-2H-pyran-2-yl) ethyl)-9a, 11b-dimethyl-2-(pyridin-2-yl)-5a, 6, 6a, 6b, 7, 8, 9, 9a, 10, 11, 11a, 11b-dodecahydrocyclopenta [1, 2] phenanthro [8a, 9-b] oxiren-1(4H)-one (0.4 g, 0.730 mmol) in dichloromethane (8 mL) was

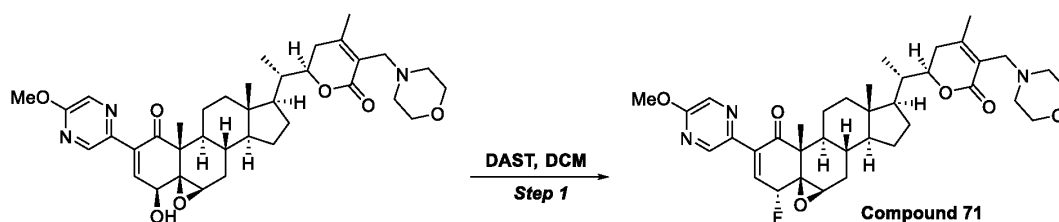
added ethylbis (propan-2-yl)amine (0.296 mL, 1.46 mmol) followed by methanesulfonyl chloride (83.7 mg, 0.73 mmol) at 0 °C. The reaction mixture was stirred at 0 °C for 30 min. After the completion of reaction, (monitored by TLC, shown 50% conversion) quenched it with ice cold water (10 mL) and extracted with dichloromethane (2 X 10 mL). The combined organic layer was washed with saturated brine solution (20 mL), dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure to get ((R)-6-((S)-1-((4S, 4aR, 5aR, 6aS, 6bS, 9R, 9aS, 11aS, 11bR)-4-hydroxy-9a, 11b-dimethyl-1-oxo-2-(pyridin-2-yl)-1, 4, 5a, 6, 6a, 6b, 7, 8, 9, 9a, 10, 11, 11a, 11b-tetradecahydrocyclopenta [1, 2] phenanthro [8a, 9-b] oxiren-9-yl) ethyl)-4-methyl-2-oxo-5, 6-dihydro-2H-pyran-3-yl) methyl methanesulfonate. It was forwarded as such to next reaction.

In a 10 mL RBF, added dipotassium carbonate (202 mg, 1.46 mmol) and 2-oxa-5-azabicyclo [2.2.1] heptane (109 mg, 1.1 mmol) in acetonitrile (2 mL), followed by dropwise addition of ((R)-6-((S)-1-((4S, 4aR, 5aR, 6aS, 6bS, 9R, 9aS, 11aS, 11bR)-4-hydroxy-9a, 11b-dimethyl-1-oxo-2-(pyridin-2-yl)-1, 4, 5a, 6, 6a, 6b, 7, 8, 9, 9a, 10, 11, 11a, 11b-tetradecahydrocyclopenta [1, 2] phenanthro [8a, 9-b] oxiren-9-yl)ethyl)-4-methyl-2-oxo-5, 6-dihydro-2H-pyran-3-yl) methyl methanesulfonate dissolved in acetonitrile (2 mL) at 0 °C. The resultant reaction mixture was stirred at 60 °C for 30 min. After the completion of reaction (monitored by TLC), the reaction mixture was filtered through celite, filtrate was concentrated and purified by preparative- using column YMC Actus Triart C18 ExRS (20*250mm) 5µm A ammonium acetate in water B Acetonitrile method followed by lyophilization to afford (4S, 4aR, 5aR, 6aS, 6bS, 9R, 9aS, 11aS, 11bR)-9-((1S)-1-((2R)-5-(2-oxa-5-azabicyclo [2.2.1] heptan-5-yl)methyl)-4-methyl-6-oxo-3, 6-dihydro-2H-pyran-2-yl) ethyl)-4-hydroxy-9a, 11b-dimethyl-2-(pyridin-2-yl)-5a, 6, 6a, 6b, 7, 8, 9, 9a, 10, 11, 11a, 11b-dodecahydrocyclopenta [1, 2] phenanthrol [8a, 9-b] oxiren-1(4H)-one (50 mg, 10.89%) as an off white solid.

[0541] Analytical data:

LCMS: 93.91% (m/z: 629.52, [M+1]⁺, 2.59 min (5.50 min run).

¹H-NMR (400 MHz, DMSO-*d*₆): δ 8.59 (d, *J* = 4.0 Hz, 1H), 7.85-7.80 (m, 1H), 7.68 (d, *J* = 6.80 Hz, 1H), 7.39-7.34 (m, 2H), 5.73 (d, *J* = 3.20 Hz, 1H), 4.29-4.26 (m, 1H), 3.88-3.74 (m, 2H), 3.51-3.42 (m, 4H), 3.15 (s, 1H), 2.76-2.67 (m, 1H), 2.45-2.35 (m, 2H), 2.10-2.02 (m, 5H), 1.93-1.89 (m, 1H), 1.83-1.77 (m, 3H), 1.61-1.51 (m, 2H), 1.41-1.23 (m, 8H), 1.12-1.04 (m, 4H), 0.91-0.87 (m, 5H), 0.66 (s, 3H).

[0542] Synthesis of Compound 71**[0543] Step-1: (R)-6-[(S)-1-[(1S, 2R, 6R, 7S, 9R, 11S, 12S, 15R, 16S)-6-fluoro-4-(5-methoxy-2-pyrazinyl)-2, 16-dimethyl-3-oxo-8-oxapentacyclo [9.7.0.0^{2,7}.0^{7,9}.0^{12,16}] octadec-4-en-15-yl}ethyl]-4-methyl-3-(morpholinomethyl)-5,6-dihydro-2H-pyran-2-one:**

To a stirred solution of (R)-6-[(S)-1-[(1S, 2R, 6S, 7R, 9R, 11S, 12S, 15R, 16S)-6-hydroxy-4-(5-methoxy-2-pyrazinyl)-2, 16-dimethyl-3-oxo-8-oxapentacyclo [9.7.0.0^{2,7}.0^{7,9}.0^{12,16}] octadec-4-en-15-yl} ethyl]-4-methyl-3-(morpholinomethyl)-5, 6-dihydro-2H-pyran-2-one (130 mg, 201 μ mol) in dichloromethane (2 mL) was added diethyl (trifluoro- λ^4 -sulfanyl) amine (31.8 μ L, 1.2 eq., 241 μ mol) dissolved in DCM (1 mL) drop wise at -78°C under inert atmosphere and stirred for 15 min. After completion of reaction (monitored by TLC), quenched it by adding sodium bicarbonate solution (25 mL) and extracted with dichloromethane (2 X 25 mL). Collected organics were dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure to obtain crude. The crude was purified by using preparative-HPLC (ABC method) to afford (R)-6-[(S)-1-[(1S, 2R, 6R, 7S, 9R, 11S, 12S, 15R, 16S)-6-fluoro-4-(5-methoxy-2-pyrazinyl)-2, 16-dimethyl-3-oxo-8-oxapentacyclo [9.7.0.0^{2,7}.0^{7,9}.0^{12,16}] octadec-4-en-15-yl}ethyl]-4-methyl-3-(morpholinomethyl)-5, 6-dihydro-2H-pyran-2-one (26 mg, 39.2 μ mol, 19.5%) as white solid.

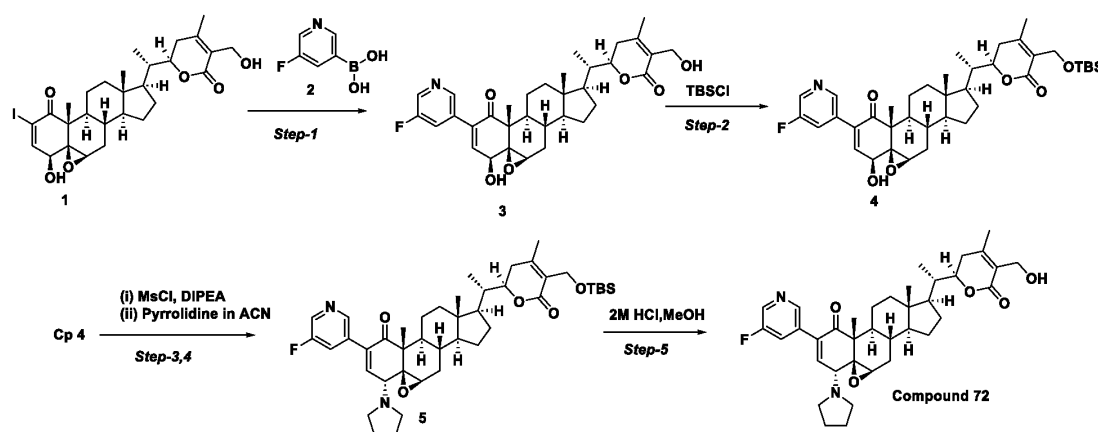
[0544] Analytical data:

LCMS: 98.87% (m/z: 650.5, [M+1]⁺, 7.22 min (20 min run).
¹H-NMR (400 MHz, DMSO-*d*₆): δ 8.37 (d, *J* = 1.2 Hz 1H), 8.33 (d, *J* = 1.2 Hz, 1H), 7.49 (dd, *J* = 1.6 Hz, 16.8 Hz, 1H), 5.93 (d, *J* = 50.4 Hz, 1H), 4.30 (d, *J* = 12.8 Hz 1H), 3.94 (s, 3H), 3.53 – 3.511 (m, 5H), 3.25 (d, *J* = 12.4 Hz, 1H), 3.06 (d, *J* = 12.4 Hz, 1H), 2.45-2.32 (m, 5H), 2.13-1.56 (m, 15H), 1.44-0.97 (m, 12H), 0.92 (d, *J* = 6.4 Hz 3H), 0.67 (s, 3H).
¹³C-NMR (400 MHz, DMSO-*d*₆): δ 165.40, 159.49, 155.89, 139.60, 139.43, 139.14, 135.44, 135.34, 135.00, 121.36, 85.17, 83.40, 77.41, 66.21, 62.95, 62.80, 54.99, 54.16, 54.05, 53.84,

52.97, 52.54, 51.17, 47.29, 47.24, 43.21, 41.97, 38.51, 38.31, 30.02, 29.29, 29.08, 26.50, 23.88, 21.01, 20.44, 13.08, 12.95, 11.30.

^{19}F -NMR (400 MHz, $\text{DMSO}-d_6$): δ -201.62.

[0545] Synthesis of Compound 72



[0546] **Step 1: Synthesis of (R)-6-[(S)-1-[(1S, 2R, 6S, 7R, 9R, 11S, 12S, 15R, 16S)-4-(5-fluoro-3-pyridyl)-6-hydroxy-2, 16-dimethyl-3-oxo-8-oxapentacyclo [9.7.0.0^{2,7}.0^{12,16}] octadec-4-en-15-yl] ethyl]-3-(hydroxymethyl)-4-methyl-5, 6-dihydro-2H-pyran-2-one.**

[0547] To a stirred solution of (R)-6-[(S)-1-[(1S, 2R, 6S, 7R, 9R, 11S, 12S, 15R, 16S)-4-(5-fluoro-3-pyridyl)-6-hydroxy-2, 16-dimethyl-3-oxo-8-oxapentacyclo [9.7.0.0^{2,7}.0^{12,16}] octadec-4-en-15-yl] ethyl]-3-(hydroxymethyl)-4-methyl-5, 6-dihydro-2H-pyran-2-one (3 g, 5.03 mmol) in 1,4-dioxane (30 mL) was added 3-fluoro-5-(4, 4, 5, 5-tetramethyl-1, 3, 2-dioxaborolan-2-yl) pyridine (561 mg, 1.5 eq., 2.51 mmol) and dicesium (1+) carbonate (4.92 g, 3 eq., 15.1 mmol) dissolved in water (2 mL) at room temperature. The reaction mixture was purged with nitrogen for 30 min then added palladium(2+) bis (triphenylphosphane) dichloride (353 mg, 0.1 eq., 503 μmol) followed by further purging with nitrogen for 5 min. The reaction mixture was stirred at 90 °C for 4h, monitored the reaction by TLC. After the completion of reaction, reaction mixture was filtered through celite bed and given ethyl acetate washings. The filtrate was quenched with water (80 mL) and extracted using ethyl acetate (50 mL X 3). The ethyl acetate layer was dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure to get crude. The crude residue was purified by column chromatography on silica gel using eluent 0-90% ethyl acetate in heptane to get desired product (R)-6-[(S)-1-[(1S, 2R, 6S, 7R, 9R, 11S, 12S, 15R, 16S)-4-(5-fluoro-3-pyridyl)-6-hydroxy-2, 16-dimethyl-3-oxo-8-oxapentacyclo

[9.7.0.0^{2,7,9,12,16}] octadec-4-en-15-yl}ethyl]-3-(hydroxymethyl)-4-methyl-5, 6-dihydro-2H-pyran-2-one (1.17 g, 37%) as white solid.

[0548] Analytical Data:

LCMS: 89% (m/z: 566.20 [M+1]⁺), 2.01 min (4 min run).

[0549] Step 2: Synthesis of (R)-6-[(S)-1-{(1S, 2R, 6S, 7R, 9R, 11S, 12S, 15R, 16S)-4-(5-fluoro-3-pyridyl)-6-hydroxy-2, 16-dimethyl-3-oxo-8-oxapentacyclo [9.7.0.0^{2,7,9,12,16}] octadec-4-en-15-yl} ethyl]-3-[(tert-butyl) bis(methyl) siloxy] methyl}-4-methyl-5, 6-dihydro-2H-pyran-2-one.

To a stirred solution of (R)-6-[(S)-1-{(1S, 2R, 6S, 7R, 9R, 11S, 12S, 15R, 16S)-4-(5-fluoro-3-pyridyl)-6-hydroxy-2, 16-dimethyl-3-oxo-8-oxapentacyclo [9.7.0.0^{2,7,9,12,16}] octadec-4-en-15-yl} ethyl]-3-(hydroxymethyl)-4-methyl-5, 6-dihydro-2H-pyran-2-one (650 mg, 1.02 mmol) in dimethylformamide (6 mL) was added 4-(pyrrolidin-1-yl)pyridin-1-ium (305 mg, 2 eq., 2.05 mmol) and stirred for 5-10 min then tert-butyl (chloro)dimethylsilane (231 mg, 1.5 eq., 1.53 mmol) was added at room temperature. Reaction was stirred at 80 °C for 1h, monitored the reaction by TLC and LCMS. After the completion of reaction, it was quenched with crushed ice and then extracted with ethyl acetate (3 X 30 mL). The collective ethyl acetate layer was washed with brine (50 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to get crude. The crude compound was washed with heptane (20 mL X 3) and filtered to get (R)-6-[(S)-1-{(1S, 2R, 6S, 7R, 9R, 11S, 12S, 15R, 16S)-4-(5-fluoro-3-pyridyl)-6-hydroxy-2, 16-dimethyl-3-oxo-8-oxapentacyclo [9.7.0.0^{2,7,9,12,16}] octadec-4-en-15-yl} ethyl]-3-[(tert-butyl) bis (methyl) siloxy] methyl}-4-methyl-5, 6-dihydro-2H-pyran-2-one (620 mg, 66%) as off white solid.

[0550] Analytical data:

LCMS: 74% (m/z: 680.48 [M+1]⁺), 3.02 min (4 min run).

[0551] Step 3: Synthesis of (R)-6-[(S)-1-{(1S, 2R, 6S, 7S, 9R, 11S, 12S, 15R, 16S)-4-(5-fluoro-3-pyridyl)-6-(mesyloxy)-2, 16-dimethyl-3-oxo-8-oxapentacyclo [9.7.0.0^{2,7,9,12,16}] octadec-4-en-15-yl}ethyl]-3-[(tert-butyl) bis (methyl) siloxy] methyl}-4-methyl-5, 6-dihydro-2H-pyran-2-one.

To a stirred solution of (R)-6-[(S)-1-{(1S, 2R, 6S, 7R, 9R, 11S, 12S, 15R, 16S)-4-(5-fluoro-3-pyridyl)-6-hydroxy-2, 16-dimethyl-3-oxo-8-oxapentacyclo [9.7.0.0^{2,7,9,12,16}] octadec-4-en-

15-yl}ethyl]-3-{[(tert-butyl) bis (methyl) siloxy] methyl}-4-methyl-5, 6-dihydro-2H-pyran-2-one (0.3 g, 441 μ mol) in dichloromethane (3 mL) were added ethylbis (propan-2-yl)amine (154 μ L, 2 eq., 882 μ mol) and methanesulfonyl chloride (51.2 μ L, 1.5 eq., 662 μ mol) and stirred for 1 min at room temperature. The reaction was monitored by TLC. After completion of reaction, the reaction mixture was quenched with saturated sodium bicarbonate solution (20 mL) and extracted with dichloromethane (30 mL x 2). The collective dichloromethane layer was washed with brine (20 mL), dried over anhydrous sodium sulfate, filtered and concentrated under vacuum to get (R)-6-[(S)-1-{(1S, 2R, 6S, 7S, 9R, 11S, 12S, 15R, 16S)-4-(5-fluoro-3-pyridyl)-6-(mesyloxy)-2, 16-dimethyl-3-oxo-8-oxapentacyclo [9.7.0.0^{2,7}.0^{7,9}.0^{12,16}] octadec-4-en-15-yl}ethyl]-3-{[(tert-butyl) bis (methyl) siloxy] methyl}-4-methyl-5,6-dihydro-2H-pyran-2-one (0.3 g, 13%) as brown gum.

[0552] Analytical data:

LCMS: 15% (m/z: 758.00 [M+1]⁺), 2.61 min (4 min run).

[0553] Step 4: Synthesis of (R)-6-[(S)-1-{(1S, 2R, 6R, 7R, 9R, 11S, 12S, 15R, 16S)-4-(5-fluoro-3-pyridyl)-2, 16-dimethyl-3-oxo-6-(1-pyrrolidinyl)-8-oxapentacyclo [9.7.0.0^{2,7}.0^{7,9}.0^{12,16}] octadec-4-en-15-yl}ethyl]-3-{[(tert-butyl) bis (methyl) siloxy] methyl}-4-methyl-5, 6-dihydro-2H-pyran-2-one.

To a stirred solution of triethylamine (0.1 g, 2.5 eq., 989 μ mol) in acetonitrile (3 mL) were added pyrrolidine (50 μ L, 2 eq., 792 μ mol) at 0 °C and (R)-6-[(S)-1-{(1S, 2R, 6S, 7S, 9R, 11S, 12S, 15R, 16S)-4-(5-fluoro-3-pyridyl)-6-(mesyloxy)-2, 16-dimethyl-3-oxo-8-oxapentacyclo [9.7.0.0^{2,7}.0^{7,9}.0^{12,16}] octadec-4-en-15-yl}ethyl]-3-{[(tert-butyl) bis (methyl) siloxy] methyl}-4-methyl-5, 6-dihydro-2H-pyran-2-one (0.3 g, 396 μ mol) was added and stirred for 10 min. The reaction was monitored by TLC and LCMS. After completion of reaction, the reaction mixture was quenched with water (30 mL) and extracted with ethyl acetate (30 mL x 2). Collective ethyl acetate layer was washed with brine (20 mL), dried over anhydrous sodium sulfate, filtered and concentrated under vacuum to get (R)-6-[(S)-1-{(1S, 2R, 6R, 7R, 9R, 11S, 12S, 15R, 16S)-4-(5-fluoro-3-pyridyl)-2, 16-dimethyl-3-oxo-6-(1-pyrrolidinyl)-8-oxapentacyclo [9.7.0.0^{2,7}.0^{7,9}.0^{12,16}] octadec-4-en-15-yl}ethyl]-3-{[(tert-butyl) bis (methyl) siloxy] methyl}-4-methyl-5, 6-dihydro-2H-pyran-2-one (390 mg, 43%) as brown solid.

[0554] Analytical data:

LCMS: 32% (m/z: 733.25 [M+1]⁺), 7.11 min (10 min run).

[0555] Step 5: Synthesis of (R)-6-[(S)-1-{(1S, 2R, 6R, 7R, 9R, 11S, 12S, 15R, 16S)-4-(5-fluoro-3-pyridyl)-2, 16-dimethyl-3-oxo-6-(1-pyrrolidinyl)-8-oxapentacyclo [9.7.0.0^{2,7},^{9,0}^{12,16}] octadec-4-en-15-yl} ethyl]-3-(hydroxymethyl)-4-methyl-5, 6-dihydro-2H-pyran-2-one.

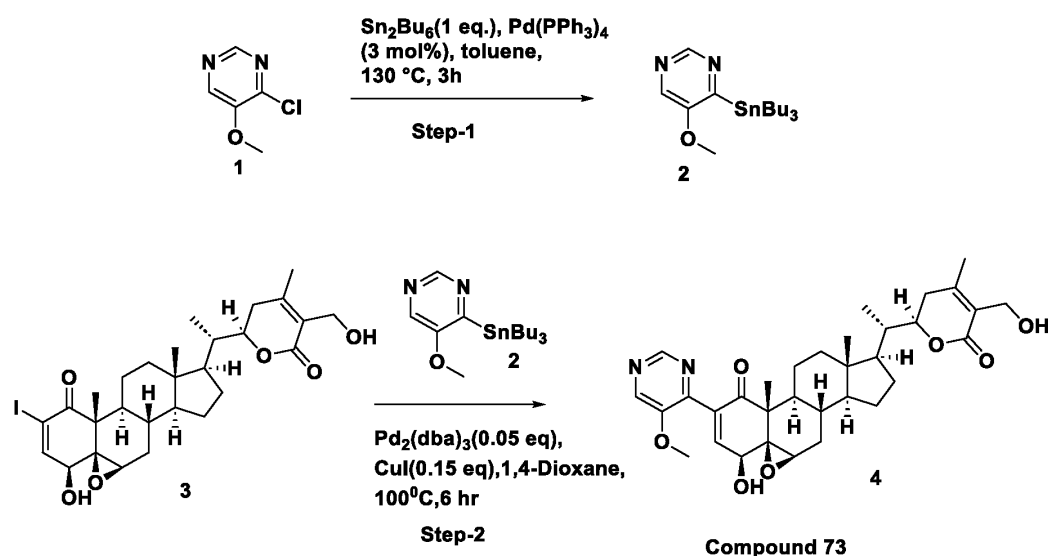
To a stirred solution of (R)-6-[(S)-1-{(1S, 2R, 6R, 7R, 9R, 11S, 12S, 15R, 16S)-4-(5-fluoro-3-pyridyl)-2, 16-dimethyl-3-oxo-6-(1-pyrrolidinyl)-8-oxapentacyclo [9.7.0.0^{2,7},^{9,0}^{12,16}] octadec-4-en-15-yl} ethyl]-3-[[tert-butyl bis (methyl) siloxy] methyl]-4-methyl-5,6-dihydro-2H-pyran-2-one (0.4 g, 546 μ mol) in tetrahydrofuran (1 mL), added methanol (0.5 mL) followed by addition of 2 N HCl (0.4 mL) and stirred the reaction for 1h at room temperature. Monitored the reaction by TLC. The reaction mixture was quenched carefully with sodium bicarbonate solution (30 mL) and extracted using dichloromethane (2 x 30 mL). The dichloromethane layer was dried over anhydrous sodium sulphate, filtered and evaporated under vacuum to get crude compound. The crude compound was purified by Prep HPLC using ABC method to get (R)-6-[(S)-1-{(1S, 2R, 6R, 7R, 9R, 11S, 12S, 15R, 16S)-4-(5-fluoro-3-pyridyl)-2, 16-dimethyl-3-oxo-6-(1-pyrrolidinyl)-8-oxapentacyclo [9.7.0.0^{2,7},^{9,0}^{12,16}] octadec-4-en-15-yl} ethyl]-3-(hydroxymethyl)-4-methyl-5, 6-dihydro-2H-pyran-2-one (12 mg, 3%) as off white solid.

[0556] Analytical data:

LCMS: 91.11% (m/z: 619.45 [M+1]⁺), 5.58 min (10 min run).

¹H-NMR (400 MHz, DMSO-d⁶): δ 8.55 (d, J = 2.8 Hz, 1H), 8.413 (t, J = 1.6 Hz, 1H), 7.79 – 7.76 (m, 1H), 7.41 (d, J = 2.8 Hz, 1H), 4.58 (t, J = 5.2 Hz, 1H), 4.30 - 4.27 (m, 1H), 4.18 - 4.07 (m, 2H), 3.74 (d, J = 2.8 Hz, 1H), 3.55 (d, J = 1.2 Hz, 1H), 2.70 – 2.65 (m, 4H), 2.43 – 2.35 (m, 1H), 2.13-2.07 (m, 1H), 2.00 – 1.97 (m, 4H), 1.91-1.87 (m, 1H), 1.81-1.79 (m, 1H), 1.71 – 1.55 (m, 7H), 1.40 - 1.27 (m, 4H), 1.24 (m, 3H), 1.20 - 1.13 (m, 3H), 1.02-0.97 (m, 2H), 0.93 – 0.91 (m, 3H), 0.67(s, 3H).

¹⁹F-NMR (400 MHz, DMSO-D⁶): δ -127.66

[0557] Synthesis of Compound 73**[0558] Step-1: Synthesis of 5-methoxy-4-(tributylstannyl)pyrimidine**

To a stirred solution of 4-chloro-5-methoxypyrimidine (0.7 g, 4.84 mmol) in Toluene (10 mL) was added bis (tributylstannane) (2.82 g, 4.84 mmol). Reaction was purged with nitrogen for 30 min then added palladium—triphenylphosphine (280 mg, 0.05 eq., 242 μ mol) followed by further purging with nitrogen for 5 min. The reaction mixture was stirred at 130°C for 3h. After completion of reaction, it was filtered through celite bed and washed with ethyl acetate. The filtrate was concentrated under reduced pressure to get crude. The crude material was purified by combi flash over silica gel using 0-30% ethyl acetate in hexane, to get tributyl(5-methoxy-4-pyrimidinyl) stannane (0.5 g, 1.25 mmol) as colourless liquid. Yield: 24.57%.

[0559] Analytical data:

LCMS: 95.73% (m/z: 399.2, [M+1], 6.14min (7 min run).

¹H-NMR (400 MHz, DMSO-*d*₆): δ 8.84 (s, 1H), 8.33 (s, 1H), 1.27 (m, 12H), 1.1 (m, 6H), 0.8 (m, 9H)

[0560] Step:2 Synthesis of (4S, 4aR, 5aR, 6aS, 6bS, 9R, 9aS, 11aS, 11bR)-4-hydroxy-9-((S)-1-((R)-5-(hydroxymethyl)-4-methyl-6-oxo-3, 6-dihydro-2H-pyran-2-yl) ethyl)-2-(5-methoxypyrimidin-4-yl)-9a, 11b-dimethyl-5a, 6, 6a, 6b, 7, 8, 9, 9a, 10, 11, 11a, 11b-dodecahydrocyclopenta [1, 2] phenanthro [8a, 9-b]oxiren-1(4H)-one

To a stirred solution of (1S, 2R, 6S, 7R, 9R, 11S, 12S, 15R, 16S)-6-hydroxy-15-[(1S)-1-[(2R)-5-(hydroxymethyl)-4-methyl-6-oxo-3, 6-dihydro-2H-pyran-2-yl] ethyl]-4-iodo-2, 16-dimethyl-8-oxapentacyclo [9.7.0.0^{2,7}.0^{7,9}.0^{12,16}] octadec-4-en-3-one (0.5 g, 0.83 mmol) in 1,4-Dioxane (10 mL) were added copper iodide (4.79 mg 0.2 eq) and tributyl (5-methoxy-4-pyrimidinyl) stannane (435 mg, 1.3 eq., 1.09 mmol). The reaction mixture was purged with nitrogen for 35 min and then palladium—(1E, 4E)-1,5-diphenyl-1,4-pentadien-3-one (2/3) (38.4 mg, 0.05 eq., 41.9 μ mol) was added to it. The reaction mixture was again purged with nitrogen for 5 min. The reaction was stirred at 100°C for 6h. The reaction mixture was quenched with cool water (50 mL) and was extracted with Ethyl acetate (2 x 100mL). The organic layer was dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure. The crude material was enriched by Combi Flash by using 10% Methanol in DCM. Compound was further purified by preparative-HPLC (Formic Acid method) to afford (4S, 4aR, 5aR, 6aS, 6bS, 9R, 9aS, 11aS, 11bR)-4-hydroxy-9-((S)-1-((R)-5-(hydroxymethyl)-4-methyl-6-oxo-3, 6-dihydro-2H-pyran-2-yl) ethyl)-2-(5-methoxypyrimidin-4-yl)-9a, 11b-dimethyl-5a, 6, 6a, 6b, 7, 8, 9, 9a, 10, 11, 11a, 11b-dodecahydrocyclopenta [1, 2] phenanthro [8a, 9-b] oxiren-1(4H)-one (10 mg) as a white solid. Yield: 2%.

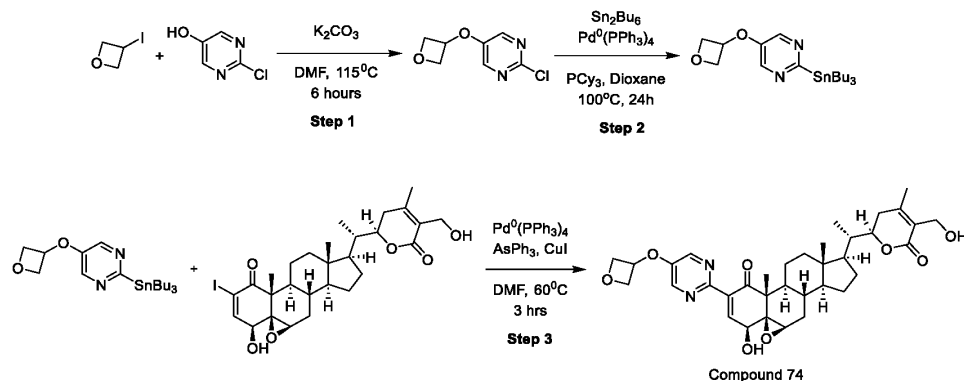
[0561] Analytical data:

HPLC: 94.78% at RT- 7.84 (25 min run)

LCMS: 94.84% (m/z: 578.9, [M+1], 2.86 min (7 min run).

¹H-NMR (400 MHz, DMSO-*d*₆): δ 8.82 (s, 1H), 8.63 (s, 1H), 7.48 (d, J = 6.80 Hz, 1H), 4.58 (t, J = 5.20 Hz, 1H), 4.30 (dd, J = 13.20, Hz, 1H), 4.16-4.12 (m, 2H), 3.84 (s, 2H), 3.74-3.71 (m, 1H), 3.19 (t, J = Hz, 1H), 2.40 (d, J = 17.60 Hz, 2H), 2.11-2.06 (m, 2H), 2.01-1.95 (m, 4H), 1.82-1.73 (m, 2H), 1.60 (d, J = 8.40 Hz, 1H), 1.46 (s, 1H), 1.34-1.27 (m, 2H), 1.23 (d, J = 4.40 Hz, 4H), 1.20-1.13 (m, 2H), 1.12-1.02 (m, 4H), 0.97 (dd, J = 6.80, 20.60 Hz, 4H), 0.67 (d, J = 13.60 Hz, 3H),

[0562] Synthesis of Compound 74



[0563] Step 1: Synthesis of 2-chloro-5-(oxetan-3-yloxy) pyrimidine:

1310 mg of 2-chloro-5-hydroxy pyrimidine (10 mmol, 1 eqv), 1100 μ L 3-Iodoioxetane (12.5 mmol, 1.25 eqv) and 3550 mg K_2CO_3 (25 mmol, 2.5 eqv) were dissolved in 15 ml of DMF at room temperature. The reaction mixture was heated to 115°C under N_2 -atm for 6 hours. In LC-MS a major peak was observed with m/z 186.9 along with a pattern of halogen. The reaction mixture was cooled at room temperature, 30 ml water was added and finally extracted thrice using EtOAc. Org layer was combined, dried over sodium sulfate and evaporated. The crude was purified by column chromatography using ethylacetate and hexane mixture (0 to 50%) with 40% of isolated yield.

[0564] Analytical:

LCMS: purity 96.65% (m/z: 186.97, [M+1]⁺, 2.22 min (7.5 min run).

¹H NMR (400 MHz, CDCl₃): δ 8.13 (s, 2H), 5.27 (m, 1H), 5.00 (m, 2H), 4.77 (m, 2H).

[0565] Step 2: Synthesis of 5-(oxetan-3-yloxy)-2-(tributylstannyl) pyrimidine:

To a stirred solution of 2-chloro-5-(oxetan-3-yloxy) pyrimidine (500 mg, 2.68 mmol, 1 eqv) in dioxane (15 ml) was added hexabutyldistannane (1.9 ml, 3.75 mmol, 1.4 eqv). The reaction mixture was purged with nitrogen gas for 15 min then $\text{Pd}^0(\text{PPh}_3)_4$ (155 mg, 0.134 mmol 0.05 eqv) and PCy_3 (38 mg, 0.134 mmol 0.05 eqv) were added to it. The reaction mixture was again purged with nitrogen gas for 5 min. The reaction mixture was stirred at 100°C for 24h. After 24h, the reaction mixture was cooled at rt and passed through celite. The reaction mixture was

evaporated, and the product was purified by silica column chromatography using EtOAc (0-20%) and hexane. The compound was isolated as yellow liquid with 56% of isolated yield.

[0566] Analytical:

LCMS: purity 80.82 % (m/z: 443.24, $[M+1]^+$, 4.66 min (6.5 min run).

^1H NMR (400 MHz, CDCl_3): δ 8.25 (s, 2H), 5.24 (q, $J = 5.6$ Hz, 1H), 4.98 (dd, $J = 7.4, 6.1$ Hz, 2H), 4.78 (dd, $J = 7.6, 5.1$ Hz, 2H), 1.33 (t, $J = 7.3$ Hz, 12H), 1.18 – 1.12 (m, 6H), 0.87 (t, $J = 7.3$ Hz, 18H).

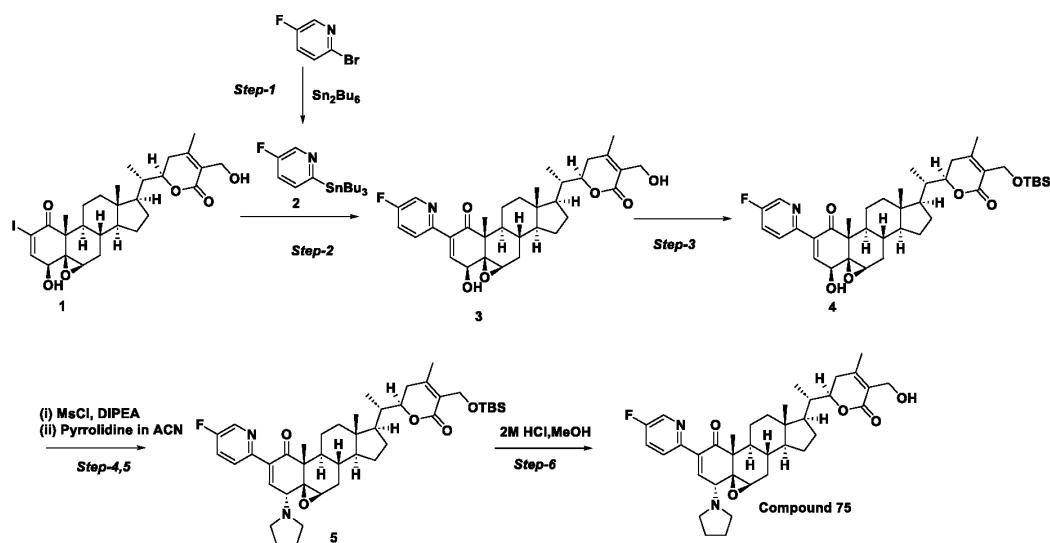
[0567] Step 3: Synthesis of (4S, 4aR, 5aR, 6aS, 6bS, 9R, 9aS, 11aS, 11bR)-4-hydroxy-9-((S)-1-((R)-5-(hydroxymethyl)-4-methyl-6-oxo-3, 6-dihydro-2H-pyran-2-yl)ethyl)-9a, 11b-dimethyl-2-(5-(oxetan-3-yloxy) pyrimidin-2-yl)-5a, 6, 6a, 6b, 7, 8, 9, 9a, 10, 11, 11a, 11b-dodecahydrocyclopenta [1, 2] phenanthro [8a, 9-b]oxiren-1(4H)-one

680 mg 2-iodowithaferin (1.14 mmol, 1 eqv) was dissolved in 10 ml of degassed DMF in a 50 ml sealed RB. Followed by, 629 mg Tributyl[5-(3-oxetanyloxy)-2-pyrimidinyl] stannane (1.42 mmol, 1.25 eqv), 66 mg $\text{Pd}^0(\text{PPh}_3)_4$ (0.057 mmol, 0.05 eqv), 53 mg AsPh_3 (0.171 mmol, 0.15 eqv) and 33 mg CuI (0.171 mmol, 0.15 eqv) were added and heated the reaction mixture at 60°C for 3 hours. The reaction mixture was cooled and quenched with 30 ml of water at rt and extracted twice with EtOAc. The organic layer was combined and washed with water. The organic layer was dried over Na_2SO_4 and purified in silica column chromatography using 0-100% ethylacetate in hexane. An off-white solid product was isolated with 58% yield.

[0568] Analytical:

LCMS: purity 93.39 % (m/z: 621.50, $[M]^+$, 2.92 min (7.5 min run).

^1H NMR (400 MHz, CDCl_3): δ 8.25 (s, 2H), 7.60 (d, $J = 6.2$ Hz, 1H), 5.31 – 5.27 (m, 1H), 5.00 (ddd, $J = 7.2, 6.0, 1.0$ Hz, 2H), 4.82 – 4.73 (m, 2H), 4.45 – 4.30 (m, 3H), 3.97 (dd, $J = 6.2, 2.8$ Hz, 1H), 3.17 (s, 1H), 2.89 – 2.82 (m, 1H), 2.53 – 2.42 (m, 2H), 2.24 – 2.15 (m, 1H), 2.03 – 1.93 (m, 6H), 1.65 (q, $J = 7.1$ Hz, 3H), 1.45 (s, 5H), 1.43 – 1.30 (m, 3H), 1.20 – 1.07 (m, 4H), 1.01 (d, $J = 6.7$ Hz, 3H), 0.71 (s, 3H).

[0569] Synthesis of Compound 75**[0570] Step 1: Synthesis of 5-fluoro-2-(tributylstannyl) pyridine.**

To a stirred solution of 2-bromo-5-fluoropyridine (3 g, 17 mmol) in 1,4-dioxane (30 mL) were added hexabutyl distannane (11.9 g, 1.2 eq., 20.5 mmol), tricyclohexyl phosphane (430 mg, 0.09 eq., 1.53 mmol) and lithium(1+) chloride (4.34 g, 6 eq., 102 mmol) at room temperature. Reaction mixture was purged with nitrogen for 30 min. Then tris((1E,4E)-1,5-diphenylpenta-1,4-dien-3-one) dipalladium (781 mg, 0.05 eq., 852 μmol) was added and again purged with nitrogen for 10 min. Reaction was stirred at 100 °C for 3h. After completion of reaction, the reaction mixture was cooled to room temperature, filtered through celite bed by using sintered funnel and given ethyl acetate washings. The filtrate was collected and evaporated under vacuum to get crude. The crude compound was purified by column chromatography on silica gel using eluent 5 % ethyl acetate in Heptane. The pure fractions were collected and evaporated under reduced pressure to get desired product 5-fluoro-2-(tributylstannyl) pyridine (6.4 g) as light yellow liquid.

[0571] Analytical Data:

LCMS: 83% (m/z : 387.65 [$m+1$]⁺), 2.27 min (6 min run).

[0572] Step 2: Synthesis of (1S, 2R, 6S, 7R, 9R, 11S, 12S, 15R, 16S)-4-(5-fluoropyridin-2-yl)-6-hydroxy-15-[(1S)-1-[(2R)-5-(hydroxymethyl)-4-methyl-6-oxo-3, 6-

dihydro-2H-pyran-2-yl]ethyl]-2, 16-dimethyl-8-oxapentacyclo [9.7.0.0²,⁷.0⁷,⁹.0¹²,¹⁶] octadec-4-en-3-one.

To a stirred solution of (1S, 2R, 6S, 7R, 9R, 11S, 12S, 15R, 16S)-6-hydroxy-15-[(1S)-1-[(2R)-5-(hydroxymethyl)-4-methyl-6-oxo-3, 6-dihydro-2H-pyran-2-yl] ethyl]-4-iodo-2, 16-dimethyl-8-oxapentacyclo [9.7.0.0²,⁷.0⁷,⁹.0¹²,¹⁶] octadec-4-en-3-one (2 g, 3.35 mmol) in tetrahydrofuran (20 mL) were added copper iodide (63.9 mg, 0.1 eq., 3.35 mmol), 5-fluoro-2-(tributylstannyl) pyridine (3.24 g, 2.5 eq., 8.38 mmol) and triphenylarsane (103 mg, 0.1 eq., 3.35 mmol) at room temperature. Reaction mixture was purged with nitrogen for 30 min. Then, tris((1E,4E)-1,5-diphenylpenta-1,4-dien-3-one) dipalladium (154 mg, 0.05 eq., 168 μ mol) was added to it and again purged with nitrogen for 5 min. Reaction mixture was stirred at 85 °C for 4h. Cooled the reaction to room temperature, filtered through celite bed by using sintered funnel and washed with ethyl acetate. The filtrate was then quenched with water (100 mL) and extracted with EtOAc (50 mL X 3). The combined ethyl acetate layer was dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure to get crude. The crude was purified by column chromatography on silica gel using eluent 0 - 90% ethyl acetate in heptane to get desired product (1S, 2R, 6S, 7R, 9R, 11S, 12S, 15R, 16S)-4-(5-fluoropyridin-2-yl)-6-hydroxy-15-[(1S)-1-[(2R)-5-(hydroxymethyl)-4-methyl-6-oxo-3, 6-dihydro-2H-pyran-2-yl] ethyl]-2, 16-dimethyl-8-oxapentacyclo [9.7.0.0²,⁷.0⁷,⁹.0¹²,¹⁶] octadec-4-en-3-one (1.8 g, 1.69 mmol, 50%) as off white solid.

[0573] Analytical Data:

LCMS: 53% (m/z: 566.25 [M+1]⁺), 2.06 min (4 min run).

[0574] Step 3: Synthesis of (R)-6-[(S)-1-{(1S, 2R, 6S, 7R, 9R, 11S, 12S, 15R, 16S)-4-(5-fluoro-2-pyridyl)-6-hydroxy-2, 16-dimethyl-3-oxo-8-oxapentacyclo [9.7.0.0²,⁷.0⁷,⁹.0¹²,¹⁶] octadec-4-en-15-yl} ethyl]-3-[(tert-butyl) bis (methyl) siloxy] methyl}-4-methyl-5, 6-dihydro-2H-pyran-2-one.

To stirred solution of (R)-6-[(S)-1-{(1S, 2R, 6S, 7R, 9R, 11S, 12S, 15R, 16S)-4-(5-fluoro-2-pyridyl)-6-hydroxy-2, 16-dimethyl-3-oxo-8-oxapentacyclo [9.7.0.0²,⁷.0⁷,⁹.0¹²,¹⁶] octadec-4-en-15-yl} ethyl]-3-(hydroxymethyl)-4-methyl-5, 6-dihydro-2H-pyran-2-one (1.8 g, 3.18 mmol) in dimethylformamide (18 mL) was added 4-(pyrrolidin-1-yl)pyridin-1-ium (950 mg, 2 eq., 6.36 mmol) and stirred for 5-10 min then tert-butyl(chloro) dimethylsilane (719 mg, 1.5 eq., 4.77 mmol) was added at room temperature. Reaction mixture was stirred at 80°C for 16h. Reaction

was monitored by TLC and LCMS. After completion of reaction, the reaction mass was quenched with crushed ice and then extracted with ethyl acetate (3 X 50 mL). The collective ethyl acetate layer was washed with brine (50 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to get crude. The crude compound was purified by column chromatography on silica gel using eluent 0-65% ethyl acetate in heptane to get (R)-6-[(S)-1-{(1S, 2R, 6S, 7R, 9R, 11S, 12S, 15R, 16S)-4-(5-fluoro-2-pyridyl)-6-hydroxy-2, 16-dimethyl-3-oxo-8-oxapentacyclo [9.7.0.0²,⁷.0⁷,⁹.0¹²,¹⁶] octadec-4-en-15-yl} ethyl]-3-{[(tert-butyl) bis (methyl) siloxy] methyl}-4-methyl-5, 6-dihydro-2H-pyran-2-one (0.5 g, 15%) as off white solid.

[0575] Analytical data:

LCMS: 66% (m/z: 680.55 [M+1]⁺), 4.08 min (6 min run).

[0576] Step 4: Synthesis of (R)-6-[(S)-1-{(1S, 2R, 6S, 7S, 9R, 11S, 12S, 15R, 16S)-4-(5-fluoro-2-pyridyl)-6-(mesyloxy)-2, 16-dimethyl-3-oxo-8-oxapentacyclo [9.7.0.0²,⁷.0⁷,⁹.0¹²,¹⁶] octadec-4-en-15-yl} ethyl]-3-{[(tert-butyl) bis (methyl) siloxy] methyl}-4-methyl-5, 6-dihydro-2H-pyran-2-one.

To a stirred solution of (R)-6-[(S)-1-{(1S, 2R, 6S, 7R, 9R, 11S, 12S, 15R, 16S)-4-(5-fluoro-2-pyridyl)-6-hydroxy-2, 16-dimethyl-3-oxo-8-oxapentacyclo [9.7.0.0²,⁷.0⁷,⁹.0¹²,¹⁶] octadec-4-en-15-yl} ethyl]-3-{[(tert-butyl) bis (methyl) siloxy] methyl}-4-methyl-5, 6-dihydro-2H-pyran-2-one (0.5 g, 735 μmol) in dichloromethane (5 mL) were added ethylbis (propan-2-yl)amine (257 μL, 2 eq., 1.47 mmol) and methanesulfonyl chloride (85.4 μL, 1.5 eq., 1.1 mmol) and stirred for 1 min at room temperature. The reaction was monitored by TLC. After completion of reaction, the reaction mixture was quenched with saturated sodium bicarbonate solution (30 mL) and extracted with dichloromethane (20 mL x 3). Collective dichloromethane layer was washed with brine (40 mL), dried over anhydrous sodium sulfate, filtered and concentrated under vacuum to get (R)-6-[(S)-1-{(1S, 2R, 6S, 7S, 9R, 11S, 12S, 15R, 16S)-4-(5-fluoro-2-pyridyl)-6-(mesyloxy)-2, 16-dimethyl-3-oxo-8-oxapentacyclo [9.7.0.0²,⁷.0⁷,⁹.0¹²,¹⁶] octadec-4-en-15-yl} ethyl]-3-{[(tert-butyl) bis (methyl) siloxy] methyl}-4-methyl-5, 6-dihydro-2H-pyran-2-one (0.5 g crude) as brown solid.

[0577] Analytical data:

LCMS: 41% (m/z: 758.0 [M+1]⁺), 2.64 min (4 min run).

[0578] Step 5: Synthesis of (R)-6-[(S)-1-{(1S, 2R, 6R, 7R, 9R, 11S, 12S, 15R, 16S)-4-(5-fluoro-2-pyridyl)-2,16-dimethyl-3-oxo-6-(1-pyrrolidinyl)-8-oxapentacyclo [9.7.0.0^{2,7},⁹.0^{12,16}] octadec-4-en-15-yl}ethyl]-3-{[(tert-butyl) bis (methyl) siloxy] methyl}-4-methyl-5, 6-dihydro-2H-pyran-2-one.

To a stirred solution of triethylamine (167 mg, 2.5 eq., 1.65 mmol) in acetonitrile (8 mL) were added pyrrolidine (94 mg, 2 eq., 1.32 mmol) and (R)-6-[(S)-1-{(1S, 2R, 6S, 7S, 9R, 11S, 12S, 15R, 16S)-4-(5-fluoro-2-pyridyl)-6-(mesyloxy)-2, 16-dimethyl-3-oxo-8-oxapentacyclo [9.7.0.0^{2,7},⁹.0^{12,16}] octadec-4-en-15-yl}ethyl]-3-{[(tert-butyl) bis (methyl) siloxy] methyl}-4-methyl-5, 6-dihydro-2H-pyran-2-one (0.5 g, 660 µmol) at 0 °C and stirred for 10 min. The reaction was monitored by TLC and LCMS. After completion of reaction, the reaction mixture was quenched with water (30 mL) and extracted with ethyl acetate (30 mL x 2). Collective ethyl acetate layer was washed with brine (20 mL), dried over anhydrous sodium sulfate, filtered and concentrated under vacuum to get crude compound, (R)-6-[(S)-1-{(1S, 2R, 6R, 7R, 9R, 11S, 12S, 15R, 16S)-4-(5-fluoro-2-pyridyl)-2, 16-dimethyl-3-oxo-6-(1-pyrrolidinyl)-8-oxapentacyclo [9.7.0.0^{2,7},⁹.0^{12,16}] octadec-4-en-15-yl} ethyl]-3-{[(tert-butyl) bis (methyl) siloxy] methyl}-4-methyl-5, 6-dihydro-2H-pyran-2-one (0.6 g crude, 43%) as brown solid.

[0579] Analytical data:

LCMS: purity 35% (m/z: 733.40 [M+1]⁺), 2.40 min (6 min run).

[0580] Step 6: Synthesis of (R)-6-[(S)-1-{(1S, 2R, 6R, 7R, 9R, 11S, 12S, 15R, 16S)-4-(5-fluoro-2-pyridyl)-2,16-dimethyl-3-oxo-6-(1-pyrrolidinyl)-8-oxapentacyclo [9.7.0.0^{2,7},⁹.0^{12,16}] octadec-4-en-15-yl} ethyl]-3-(hydroxymethyl)-4-methyl-5, 6-dihydro-2H-pyran-2-one.

To a stirred solution of (R)-6-[(S)-1-{(1S, 2R, 6R, 7R, 9R, 11S, 12S, 15R, 16S)-4-(5-fluoro-2-pyridyl)-2, 16-dimethyl-3-oxo-6-(1-pyrrolidinyl)-8-oxapentacyclo [9.7.0.0^{2,7},⁹.0^{12,16}] octadec-4-en-15-yl} ethyl]-3-{[(tert-butyl) bis (methyl) siloxy] methyl}-4-methyl-5, 6-dihydro-2H-pyran-2-one (550 mg, 750 µmol) in tetrahydrofuran (1 mL), added methanol (0.5 mL) followed by addition of 2N HCl (1 mL) and stirred for 1h at room temperature. The reaction mixture was quenched with saturated sodium bicarbonate solution (50 mL) and extracted using dichloromethane (2 x 30 mL). The dichloromethane layer was dried over anhydrous sodium sulphate, filtered and concentrated under vacuum to yield crude compound. The crude compound was purified by Prep HPLC using ABC method to get (R)-6-[(S)-1-{(1S,

2R, 6R, 7R, 9R, 11S, 12S, 15R, 16S)-4-(5-fluoro-2-pyridyl)-2, 16-dimethyl-3-oxo-6-(1-pyrrolidinyl)-8-oxapentacyclo [9.7.0.0^{2,7}.0^{7,9}.0^{12,16}] octadec-4-en-15-yl} ethyl]-3-(hydroxymethyl)-4-methyl-5, 6-dihydro-2H-pyran-2-one. (30 mg, 6%) as light yellow solid.

[0581] Analytical data:

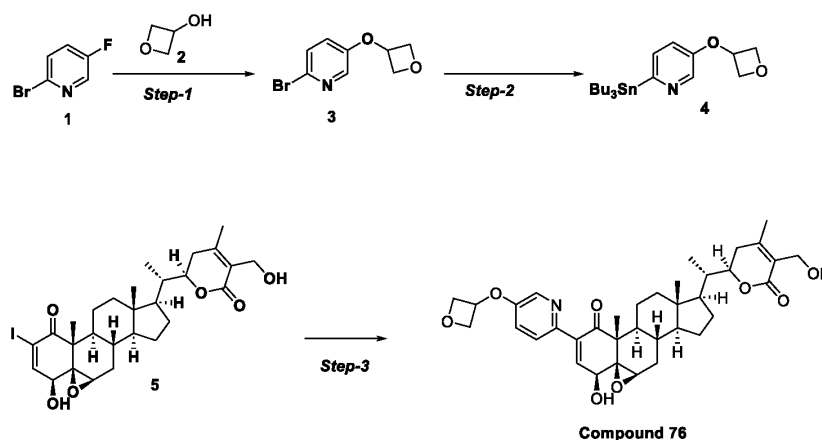
LCMS: purity 95.44% (m/z: 619.5 [M+1]⁺), 5.09 min (10 min run).

¹H-NMR (400 MHz, DMSO-d⁶): δ 8.59 (d, J = 2.8 Hz, 1H), 7.77-7.72 (m, 1H), 7.57 (d, J = 2.8 Hz, 1H), 7.53-7.50 (m, 1H), 4.58 (t, J = 5.2 Hz, 1H), 4.30-4.27 (m, 1H), 4.18-4.07 (m, 2H), 3.66 (d, J = 2.8 Hz, 1H), 3.54 (s, 1H), 2.66 (s, 4H), 2.43-2.32 (m, 1H), 2.13-2.08 (m, 1H), 2.00 (s, 4H), 1.90 (d, J = 12.4 Hz, 1H), 1.81-1.79 (m, 1H), 1.71 (m, 1H), 1.68 (s, 3H), 1.60-1.57 (m, 2H), 1.41-1.23 (m, 4H), 1.21 (s, 3H), 1.17-1.05 (m, 4H), 0.98-0.91 (m, 4H), 0.67 (s, 3H).

¹³C-NMR (400 MHz, DMSO-d⁶): δ 200.41, 159.80, 157.27, 154.66, 148.71, 148.67, 141.73, 137.78, 137.54, 137.31, 125.43, 123.70, 123.65, 123.60, 123.523, 77.53, 64.64, 59.39, 55.94, 55.15, 54.51, 51.28, 51.14, 49.53, 42.84, 42.07, 38.40, 30.38, 29.18, 29.03, 26.48, 23.96, 23.18, 21.70, 19.87, 13.82, 13.03, 11.39.

¹⁹F-NMR (400 MHz, DMSO-d⁶): δ -127.854.

[0582] Synthesis of Compound 76



[0583] Step-1: Synthesis of 2-bromo-5-(oxetan-3-yloxy) pyridine:

A stirred solution of 3-oxetanol (2 g, 27 mmol) in tetrahydrofuran (20 mL) was cooled to 0°C under N₂ atmosphere. Then added potassium 2-methyl-2-propanolate (4.54 g, 1.5 eq., 40.5 mmol) and 2-bromo-5-fluoropyridine (4.75 g, 27 mmol) at room temperature. The resultant reaction mixture was stirred at 60°C for 5 h. Progress of the reaction was monitored by TLC.

Reaction mixture was diluted with cold water (50 mL) and extracted with ethyl acetate (3 x 50 mL). The combined organic layer was dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure to get crude compound. The crude was purified by combi-flash on silica column using 0-30% ethyl acetate in heptane, which afforded 3-(6-bromo-3-pyridyloxy) oxetane (4.5 g, 71%) as white solid.

[0584] Analytical data:

LCMS: 99.6% (m/z: 229.85, $[M+1]^+$, 1.45 min (4 min run).

[0585] Step-2: Synthesis of 5-(oxetan-3-yloxy)-2-(tributylstannyl)pyridine:

A stirred solution of 3-(6-bromo-3-pyridyloxy)oxetane (2 g, 8.69 mmol), bis (tributylstannane) (6.05 g, 1.2 eq., 10.4 mmol), lithium chloride (2.2 g, 6 eq, 52.40 mmol), tricyclohexylphosphine (244 mg, 0.1 eq., 869 μ mol), in 1,4-dioxane (30 mL) was purged with nitrogen for 30 min, then added palladium—(1E,4E)-1,5-diphenyl-1,4-pentadien-3-one (1/3) (704 mg, 0.1 eq., 869 μ mol) at room temperature. The reaction mixture was stirred at 100°C for 4h. Progress of reaction was monitored by TLC. On completion, the reaction mixture was passed through celite bed. The filtrate was quenched with cold water (50 mL) and extracted using ethyl acetate (2 x 50 mL). The organic layer was dried over sodium sulphate, filtered and concentrated under reduced pressure to get crude compound. The crude was purified by combi-flash on silica column using 0 – 10% ethyl acetate in heptane as eluent, which afforded 5-(oxetan-3-yloxy)-2-(tributylstannyl) pyridine (2 g, 51%) as yellow oil.

[0586] Analytical data:

LCMS: 70.86% (m/z: 442.25, $[M+1]^+$, 2.53 min (6 min run).

[0587] Step-3: Synthesis of (4S, 4aR, 5aR, 6aS, 6bS, 9R, 9aS, 11aS, 11bR)-4-hydroxy-9-((S)-1-((R)-5-(hydroxymethyl)-4-methyl-6-oxo-3, 6-dihydro-2H-pyran-2-yl) ethyl)-9a, 11b-dimethyl-2-(5-(oxetan-3-yloxy) pyridin-2-yl)-5a, 6, 6a, 6b, 7, 8, 9, 9a, 10, 11, 11a, 11b-dodecahydrocyclopenta [1, 2] phenanthro [8a, 9-b]oxiren-1(4H)-one:

A stirred solution of (R)-6-[(S)-1-{(1S, 2R, 6S, 7R, 9R, 11S, 12S, 15R, 16S)-6-hydroxy-4-iodo-2, 16-dimethyl-3-oxo-8-oxapentacyclo [9.7.0.0^{2,7}.0^{7,9}.0^{12,16}] octadec-4-en-15-yl} ethyl]-3-(hydroxymethyl)-4-methyl-5, 6-dihydro-2H-pyran-2-one (1.0 g, 1.68 mmol), tributyl[5-(3-oxetanyloxy)-2-pyridyl] stannane (1.58 mg, 1.5 eq., 2.51 mmol), λ^1 -copper(1+) iodide (31.9 mg, 0.1 eq., 168 μ mol) in 1,4-dioxane (30 mL) was purged with nitrogen at room temperature

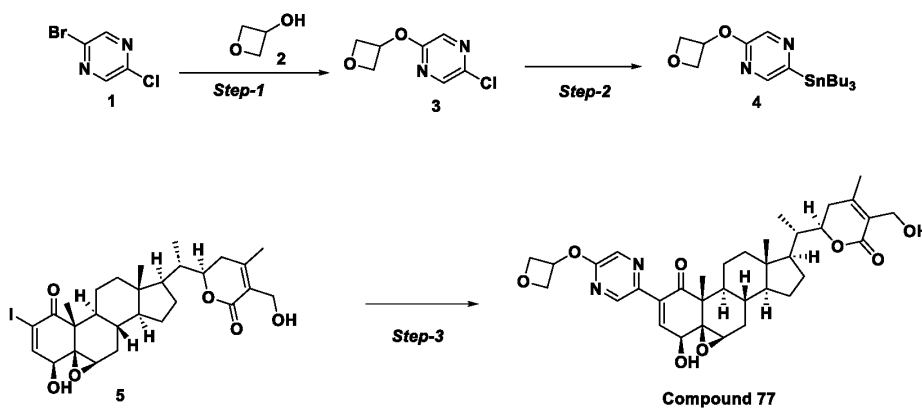
for 20 min, then added tris((1E,4E)-1,5-diphenylpenta-1,4-dien-3-one) dipalladium (154 mg, 0.1 eq., 168 μmol). The reaction mixture was stirred at 80°C for 5 h. The progress of reaction was monitored by TLC. On completion, the reaction mixture was passed through celite bed. The resulting filtrate was diluted with cold water (50 mL) and extracted using ethyl acetate (3 x 50 mL). The organic layer was dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure to get crude compound. The crude was purified by Prep HPLC in ammonium acetate buffer using ACN: water solvent system, which afforded (R)-6-[(S)-1-[(1S, 2R, 6S, 7R, 9R, 11S, 12S, 15R, 16S)-6-hydroxy-2, 16-dimethyl-4-[5-(3-oxetanyloxy)-2-pyridyl]-3-oxo-8-oxapentacyclo [9.7.0.0^{2,7}.0^{7,9}.0^{12,16}] octadec-4-en-15-yl} ethyl]-3-(hydroxymethyl)-4-methyl-5, 6-dihydro-2H-pyran-2-one (0.2 g, 19%) as white solid.

[0588] Analytical data:

LCMS: 97.31% (m/z: 620.40, $[\text{M}+1]^+$, 5.32 min (10 min run).

¹H-NMR (400 MHz, DMSO-*d*₆): δ 8.23 (d, J = 2.8 Hz, 1H), 7.56 (d, J = 8.0 Hz, 1H), 7.33 - 7.09 (m, 2H), 5.67 (d, 3.2 Hz, 1H), 5.46-5.34 m, 1H), 4.96-4.87 (m, 2H), 4.59-4.54 (m, 3H), 4.30-4.28 (m, 1H), 4.18 - 4.07 (m, 2H), 3.74-3.71 (m, 1H), 3.14 (s, 1H), 2.49-2.34 (m, 1H), 2.11 - 1.54 (m, 9H), 1.42 - 0.80 (m, 16H), 0.65 (s, 3H).

[0589] Synthesis of Compound 77



[0590] Step 1: Synthesis of 5-chloro-2-(3-oxetanyloxy) pyrazine

To stirred solution of oxetane-3-ol (1.12 g, 1.5 eq., 15.5 mmol) in dimethylformamide (30 mL) was added sodium hydride (60%) (496 mg, 2 eq., 20.7 mmol) at 0°C and stirred for 30 min. Then, 2-bromo-5-chloropyrazine (2 g, 10.3 mmol) dissolved in dimethylformamide (30 mL)

was added dropwise to the reaction mixture at 0°C. Reaction was stirred for 30 min at same temperature. After completion of the reaction (monitored by TLC and LCMS), it was quenched by adding chilled water (100 mL) and extracted using ethyl acetate (3 x 40 mL). Collected organics, dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure to obtain crude. The crude product was purified by combi flash on silica column using (25-30%) ethyl acetate in heptane as an eluent to get desired product 5-chloro-2-(3-oxetanyloxy)pyrazine (1.5 g, 62%) as white solid.

[0591] Analytical data:

LCMS: 80% (m/z: 187, [M+1]⁺, 1.90 min (4 min run).

[0592] Step-2: Synthesis of tributyl [5-(3-oxetanyloxy)-2-pyrazinyl] stannane

To stirred solution of 5-chloro-2-(3-oxetanyloxy)pyrazine (1.3 g, 6.97 mmol) in 1,4-dioxane (14 mL) were added bis (tributylstannane) (4.87 g, 1.2 eq., 8.36 mmol), tricyclohexylphosphine (176 mg, 0.09 eq., 627 μmol) and lithium chloride (1.77 g, 6 eq., 41.8 mmol) at room temperature. Reaction mixture was purged with N₂ for 30 min. Then, palladium—(1E,4E)-1,5-diphenyl-1,4-pentadien-3-one (2/3) (319 mg, 0.05 eq., 348 μmol) was added to it and again purged with N₂ for 10 min. Reaction was stirred at 100°C for 5h. After completion of the reaction (monitored by TLC), it was filtered through hyper flow celite by using cintered funnel and filtrate was concentrated under reduced pressure to obtain crude. Crude product was purified by combi flash column chromatography over silica gel using 0 - 50% ethyl acetate in heptane as an eluent to afford tributyl [5-(3-oxetanyloxy)-2-pyrazinyl] stannane (1.63 g, 49%) as light brown gum.

[0593] Analytical data:

LCMS: 92% (m/z: 442.0, [M+1]⁺, 2.97 min (4 min run).

[0594] Step-3: Synthesis of (R)-6-[(S)-1-{(1S, 2R, 6S, 7R, 9R, 11S, 12S, 15R, 16S)-6-hydroxy-2,16-dimethyl-4-[5-(3-oxetanyloxy)-2-pyrazinyl]-3-oxo-8-oxapentacyclo [9.7.0.0^{2,7},0^{7,9},0^{12,16}] octadec-4-en-15-yl} ethyl]-3-(hydroxymethyl)-4-methyl-5, 6-dihydro-2H-pyran-2-one

To a stirred solution of (R)-6-[(S)-1-{(1S, 2R, 6S, 7R, 9R, 11S, 12S, 15R, 16S)-6-hydroxy-4-iodo-2, 16-dimethyl-3-oxo-8-oxapentacyclo [9.7.0.0^{2,7},0^{7,9},0^{12,16}] octadec-4-en-15-yl} ethyl]-3-(hydroxymethyl)-4-methyl-5, 6-dihydro-2H-pyran-2-one (1.1 g, 1.84 mmol) in

tetrahydrofuran (12 mL) were added tributyl[5-(3-oxetanyloxy)-2-pyrazinyl]stannane (1.63 g, 2 eq., 3.69 mmol), copper iodide (35.1 mg, 0.1 eq., 184 μ mol) and triphenylarsane (56.5 mg, 0.1 eq., 184 μ mol) at room temperature. The reaction mixture was purged with N₂ gas for 25 min and palladium—(1E,4E)-1,5-diphenyl-1,4-pentadien-3-one (2/3) (169 mg, 0.1 eq., 184 μ mol) was added to it. The reaction mixture was again purged with N₂ gas for 5 min. The reaction vial was sealed and stirred at 80°C for 2h. After completion of the reaction (monitored by TLC and LCMS), it was quenched by adding water (50 mL) and extracted using ethyl acetate (3 x 40 mL). Collected organics, dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure to obtain crude. Crude product was purified by Prep HPLC in ammonium bicarbonate method to afford (R)-6-[(S)-1-[(1S, 2R, 6S, 7R, 9R, 11S, 12S, 15R, 16S)-6-hydroxy-2, 16-dimethyl-4-[5-(3-oxetanyloxy)-2-pyrazinyl]-3-oxo-8-oxapentacyclo [9.7.0.0²,7.0⁷,9.0¹²,16] octadec-4-en-15-yl} ethyl]-3-(hydroxymethyl)-4-methyl-5, 6-dihydro-2H-pyran-2-one (52 mg, 4.4%) as white solid.

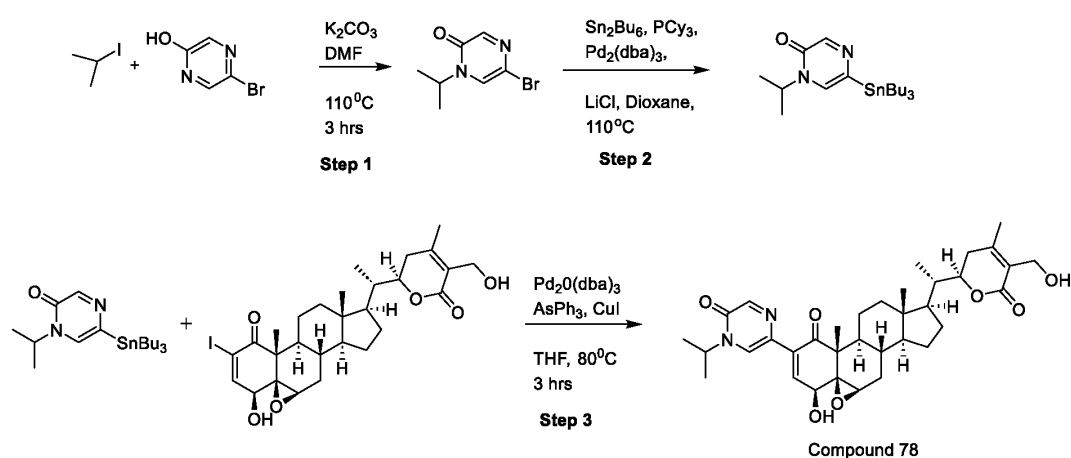
[0595] Analytical data:

LCMS: 97.12 % (m/z: 621.4, [M+1]⁺, 5.49 min (10 min run).

¹H-NMR (400 MHz, DMSO-*d*₆): δ 8.44 (d, *J*=0.8 Hz, 1H), 8.14 (d, *J*=0.8 Hz, 1H), 7.62 (d, *J*=6.4 Hz, 1H), 5.77 (d, *J*=3.6 Hz, 1H), 5.63-5.57 (m, 1H), 4.91 (t, *J*=6.8 Hz, 2H), 4.63-4.58 (m, 3H), 4.30-4.26 (m, 1H), 4.18-4.07 (m, 2H), 3.76-3.74 (m, 1H), 3.16 (s, 1H), 2.42-2.34 (m, 1H), 2.10 - 2.05 (m, 2H), 1.99 (s, 3H), 1.91 – 1.88 (m, 1H), 1.83-1.77 (m, 1H), 1.72-1.67 (m, 1H), 1.60-1.52 (m, 1H), 1.40-1.21 (m, 8H), 1.14-1.01 (m, 3H), 0.94-0.84 (m, 5H), 0.65 (s, 3H).

¹³C-NMR (400 MHz, DMSO-*d*₆): δ 200.26, 165.30, 157.65, 154.64, 141.35, 139.69, 138.90, 138.15, 135.09, 125.44, 77.51, 76.54, 76.53, 69.83, 68.40, 63.37, 57.62, 55.21, 54.51, 51.04, 47.89, 42.09, 41.98, 30.73, 29.27, 29.02, 26.49, 23.96, 20.46, 19.89, 15.20, 13.03, 11.23.

[0596] Synthesis of Compound 78



[0597] Step 1: Synthesis of 5-bromo-1-isopropylpyrazin-2(1H)-one:

1.5 gm 5-bromopyrazin-2-ol (8.57 mmol, 1 eqv) and 2.96 gm K_2CO_3 (21.4 mmol, 2.5 eqv) were dissolved in 15 ml of DMF at ambient temperature. Followed by, 1.07 mL 2-iodopropane (10.7 mmol, 1.25 eqv) was added to the reaction mixture and heated at 110°C for 3 hours. The reaction mixture was cooled at room temp and concentrated. Finally, the mixture was extracted twice with EtOAc and brine mixture. The organic layer was combined and washed once more with brine solution. The organic layer was dried over Na_2SO_4 and evaporated. The crude was purified by silica column chromatography using 0-50% EtOAc in hexane. The desired product was obtained as brown powder with 12 % isolated yield.

[0598] Analytical data:

LCMS: Purity 98.09 %, m/z: 218.03, [M+1]⁺, 2.25 min (5.5 min run).

¹H NMR (400 MHz, CDCl₃): δ 7.94 (d, J = 1.1 Hz, 1H), 7.31 (d, J = 1.1 Hz, 1H), 5.06 (m, 1H), 1.38 (d, J = 6.8 Hz, 6H).

[0599] Step 2: Synthesis of 1-isopropyl-5-(tributylstannyl) pyrazin-2(1H)-one:

200 mg 5-bromo-1-isopropyl-1,2-dihydro-2-pyrazinone (0.921 mmol, 1 eqv) was dissolved in 3 ml of 1,4-Dioxane at rt in a sealed tube. Followed by, 561 μ L bis (tributylstannane) (1.11 mmol, 1.2 eqv), 26 mg PCy₃ (0.092 mmol, 0.1 eqv), 59 mg LiCl (1.38 mmol, 1.5 eqv) and 42 mg Pd₂dba₃ (0.0461 mmol, 0.05 eqv) were added one by one at rt. The reaction mixture was purged with N₂ for 2-3 min and heated to 100°C for 3 hours. The reaction mixture was cooled

at room temp and TLC was taken. Further, the product was purified using silica column chromatography (0-20% EtOAc in hexane). The desired product was obtained as yellow oil with 36% of isolated yield.

[0600] Analytical data:

¹H NMR (400 MHz, CDCl₃): δ 8.29 (d, J = 1.2 Hz, 1H), 6.95 (d, J = 1.2 Hz, 1H), 5.11 (m, 1H), 1.38 – 1.32 (m, 12H), 1.11 – 1.05 (m, 6H), 0.89 (t, J = 7.3 Hz, 9H).

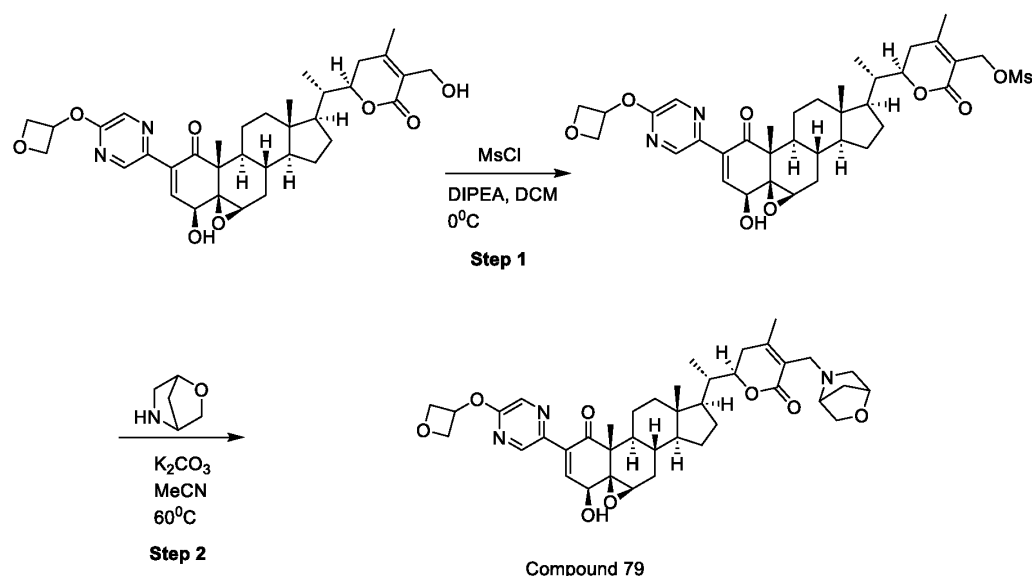
[0601] Step 3: Synthesis of 5-((4S, 4aR, 5aR, 6aS, 6bS, 9R, 9aS, 11aS, 11bR)-4-hydroxy-9-((S)-1-((R)-5-(hydroxymethyl)-4-methyl-6-oxo-3, 6-dihydro-2H-pyran-2-yl)ethyl)-9a, 11b-dimethyl-1-oxo-1, 4, 5a, 6, 6a, 6b, 7, 8, 9, 9a, 10, 11, 11a, 11b-tetradecahydrocyclopenta [1, 2] phenanthro [8a, 9-b] oxiren-2-yl)-1-isopropylpyrazin-2(1H)-one:

150 mg 2-Iodowithaferin (0.251 mmol, 1 eqv), 129 mg Sn-complex (step 2, 0.302 mmol, 1.2 eqv), 7.7 mg AsPh₃ 0.025 mmol, 0.1 eqv) and 4.8 mg CuI 0.025 mmol, 0.1 eqv) were taken in a 10 ml sealed tube and dissolved them in 5 ml of THF. Followed by 23 mg Pd₂(dba)₃ (0.025 mmol, 0.1 eqv) was added and purged with N₂ for 2-3 min. Finally, the reaction mixture was heated to 80°C for 4 hours. The reaction mixture was cooled at room temp. Further, the desired product was purified by silica column chromatography using 0-4% methanol in DCM. An off-white solid product was isolated with 51 % yield.

[0602] Analytical data:

LCMS: Purity 97.00 %, m/z: 607.58, [M+1]⁺, 3.01 min (5.5 min run).

¹H NMR (400 MHz, DMSO-d₆): δ 8.06 (d, J = 1.0 Hz, 1H), 7.71 (d, J = 1.1 Hz, 1H), 7.46 (d, J = 6.7 Hz, 1H), 5.68 (d, J = 3.5 Hz, 1H), 4.89 (p, J = 6.7 Hz, 1H), 4.57 (t, J = 5.4 Hz, 1H), 4.28 (dt, J = 13.2, 3.5 Hz, 1H), 4.13 (qd, J = 11.5, 5.4 Hz, 2H), 3.73 (dd, J = 6.8, 3.5 Hz, 1H), 3.16 (s, 1H), 2.47 – 2.29 (m, 1H), 2.14 – 1.96 (m, 5H), 1.95 – 1.86 (m, 1H), 1.83 – 1.65 (m, 2H), 1.62 – 1.51 (m, 2H), 1.34 – 1.23 (m, 13H), 1.08 (ddd, J = 18.7, 10.4, 4.8 Hz, 3H), 0.89 (dd, J = 18.3, 7.2 Hz, 5H), 0.65 (s, 3H).

[0603] Synthesis of Compound 79

[0604] Step 1: Synthesis of ((R)-6-((S)-1-((4S, 4aR, 5aR, 6aS, 6bS, 9R, 9aS, 11aS, 11bR)-4-hydroxy-9a, 11b-dimethyl-2-(5-(oxetan-3-yloxy) pyrazin-2-yl)-1-oxo-1, 4, 5a, 6, 6a, 6b, 7, 8, 9, 9a, 10, 11, 11a, 11b-tetradecahydrocyclopenta [1, 2] phenanthro [8a, 9-b] oxiren-9-yl) ethyl)-4-methyl-2-oxo-5, 6-dihydro-2H-pyran-3-yl) methyl methanesulfonate:

About 130 mg (0.21 mmol, 1 eqv) of (4S, 4aR, 5aR, 6aS, 6bS, 9R, 9aS, 11aS, 11bR)-4-hydroxy-9-((S)-1-((R)-5-(hydroxymethyl)-4-methyl-6-oxo-3, 6-dihydro-2H-pyran-2-yl) ethyl)-9a, 11b-dimethyl-2-(5-(oxetan-3-yloxy) pyrazin-2-yl)-5a, 6, 6a, 6b, 7, 8, 9, 9a, 10, 11, 11a, 11b-dodecahydrocyclopenta [1, 2] phenanthro [8a, 9-b] oxiren-1(4H)-one was dissolved in 2 ml of DCM under N₂-atm. The reaction mixture was placed on an ice bath and stirred for 20 min at -10°C. Followed by 92 µL (0.524 mmol, 2.5 eqv) of DIPEA and 21 µL (0.21 mmol, 1 eqv) of MsCl were added one by one at -10°C under N₂-atm. After 1 hour, the reaction mixture was quenched using ice water. Further, the reaction mixture was extracted with DCM twice and dried over Na₂SO₄. The organic layer was evaporated and dried. The crude was used for the next step without any further purification.

[0605] Step 2: Synthesis of (4S, 4aR, 5aR, 6aS, 6bS, 9R, 9aS, 11aS, 11bR)-9-((1S)-1-((2R)-5-(2-oxa-5-azabicyclo[2. 2. 1] heptan-5-ylmethyl)-4-methyl-6-oxo-3, 6-dihydro-2H-pyran-2-yl) ethyl)-4-hydroxy-9a, 11b-dimethyl-2-(5-(oxetan-3-yloxy) pyrazin-2-yl)-5a, 6,

6a, 6b, 7, 8, 9, 9a, 10, 11, 11a, 11b-dodecahydrocyclopenta[1, 2] phenanthro [8a, 9-b] oxiren-1(4H)-one

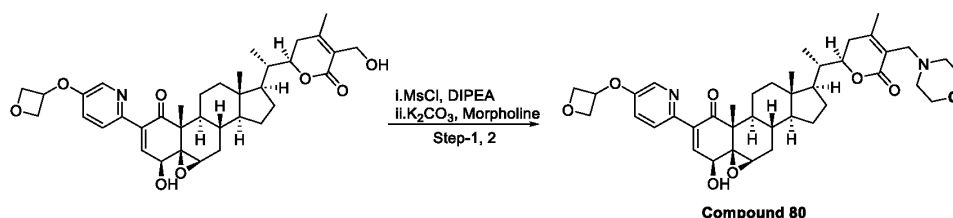
Mixture A: 145 mg of crude reaction mixture of step 1 (around ~70-80% conversion) was dissolved in 3 ml of acetonitrile at 0°C under N₂ atm.

Mixture B: 72 mg of K₂CO₃ (0.52 mmol, 2.5 eqv) and 32 mg of bridged morpholine (0.31 mmol, 1 eqv) were dissolved in 4 ml of acetonitrile under N₂-atm. Further the reaction mixture was placed on an ice bath for 15 min. Finally, the acetonitrile solution of crude (mixture A) was added to the reaction mixture at 0°C under N₂ atm. After 5 min, the reaction mixture was removed from the ice bath and heated to 70°C for 2.5 hours under N₂-atm. The reaction mixture was cooled at ambient temperature and TLC was taken. A new polar spot was identified in comparison to Compound 77. The reaction mixture was filtered and concentrated. The concentrated mass was dissolved in DCM and washed with water. The organic layer was dried over Na₂SO₄. The crude was obtained after evaporation of DCM. Finally, the desired product was purified by silica column chromatography using 0-2% MeOH in DCM. The desired product was isolated with 32 % yield.

[0606] Analytical data:

LCMS: purity 96.19 % (m/z: 703.08, [M+H]⁺, 2.49 min (5.5 min run).

¹H NMR (400 MHz, DMSO-d₆): δ 8.45 (d, J = 1.4 Hz, 1H), 8.14 (d, J = 1.4 Hz, 1H), 7.62 (d, J = 6.8 Hz, 1H), 5.77 (d, J = 3.6 Hz, 1H), 5.65 – 5.57 (m, 1H), 4.96 – 4.87 (m, 2H), 4.61 (td, J = 7.1, 4.9 Hz, 2H), 4.28 (d, J = 12.4 Hz, 2H), 3.85 (dd, J = 24.9, 7.5 Hz, 1H), 3.75 (dd, J = 6.7, 3.6 Hz, 1H), 3.52 – 3.34 (m, 4H), 3.16 (s, 1H), 2.78 – 2.66 (m, 1H), 2.47 – 2.30 (m, 3H), 2.11 – 1.99 (m, 6H), 1.88 (s, 1H), 1.80 (dt, J = 10.9, 6.3 Hz, 1H), 1.68 (d, J = 9.9 Hz, 2H), 1.52 (d, J = 9.9 Hz, 3H), 1.43 – 1.36 (m, 2H), 1.30 – 1.25 (m, 2H), 1.15 – 1.02 (m, 4H), 0.92 (d, J = 6.6 Hz, 5H), 0.65 (s, 3H).

[0607] Synthesis of Compound 80

[0608] Step 1: Synthesis of ((R)-6-((S)-1-((4S, 4aR, 5aR, 6aS, 6bS, 9R, 9aS, 11aS, 11bR)-4-hydroxy-9a, 11b-dimethyl-2-(5-(oxetan-3-yloxy) pyridin-2-yl)-1-oxo-1, 4, 5a, 6, 6a, 6b, 7, 8, 9, 9a, 10, 11, 11a, 11b-tetradecahydrocyclopenta [1, 2] phenanthro [8a, 9-b] oxiren-9-yl) ethyl)-4-methyl-2-oxo-5, 6-dihydro-2H-pyran-3-yl) methyl methane sulfonate :

To a stirred solution of (R)-6-[(S)-1-{(1S, 2R, 6S, 7R, 9R, 11S, 12S, 15R, 16S)-6-hydroxy-2, 16-dimethyl-4-[5-(3-oxetanyloxy)-2-pyridyl]-3-oxo-8-oxapentacyclo [9.7.0.0^{2,7}.0^{7,9}.0^{12,16}] octadec-4-en-15-yl} ethyl]-3-(hydroxymethyl)-4-methyl-5, 6-dihydro-2H-pyran-2-one (0.1 g, 161 μ mol) in dichloromethane (4 mL) was added ethylbis (propan-2-yl)amine (52.1 mg, 2.5 eq., 403 μ mol) followed by methanesulfonyl chloride (18.5 mg, 1.0 eq., 161 μ mol) at 0°C. The reaction mixture was stirred at 0°C for 30 minutes. Reaction was monitored by TLC, the reaction mixture was diluted with water (20 mL) and extracted with DCM (2 X 20 mL). The organic layer was washed with brine, dried the organics over sodium sulphate, filtered and concentrated under reduced pressure to get ((R)-6-((S)-1-((4S, 4aR, 5aR, 6aS, 6bS, 9R, 9aS, 11aS, 11bR)-4-hydroxy-9a, 11b-dimethyl-2-(5-(oxetan-3-yloxy) pyridin-2-yl)-1-oxo-1, 4, 5a, 6, 6a, 6b, 7, 8, 9, 9a, 10, 11, 11a, 11b-tetradecahydrocyclopenta [1, 2] phenanthro [8a, 9-b] oxiren-9-yl) ethyl)-4-methyl-2-oxo-5, 6-dihydro-2H-pyran-3-yl) methyl methane sulfonate (105 mg, 93%) as crude. It was used as such for the next step.

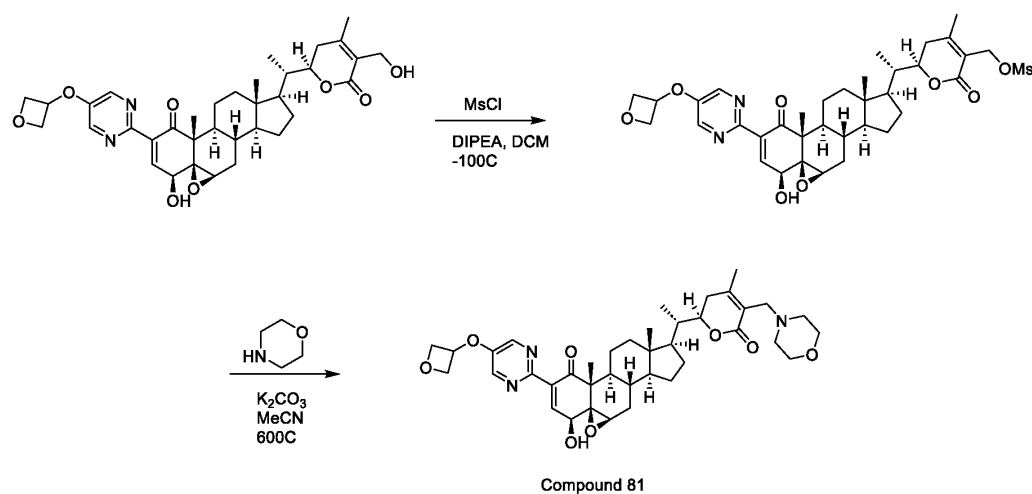
[0609] Step 2: Synthesis of (4S, 4aR, 5aR, 6aS, 6bS, 9R, 9aS, 11aS, 11bR)-4-hydroxy-9a, 11b-dimethyl-9-((S)-1-((R)-4-methyl-5-(morpholinomethyl)-6-oxo-3, 6-dihydro-2H-pyran-2-yl) ethyl)-2-(5-(oxetan-3-yloxy) pyridin-2-yl)-5a, 6, 6a, 6b, 7, 8, 9, 9a, 10, 11, 11a, 11b-dodecahydrocyclopenta [1, 2] phenanthro [8a, 9-b] oxiren-1(4H)-one :

To a stirred solution of dipotassium carbonate (41.6 mg, 2 eq., 301 μ mol) in acetonitrile (2 mL) was added morpholine (19.7 mg, 1.5 eq., 226 μ mol) followed by addition of (R)-6-[(S)-1-{(1S, 2R, 6S, 7R, 9R, 11S, 12S, 15R, 16S)-6-hydroxy-2, 16-dimethyl-4-[5-(3-oxetanyloxy)-2-pyridyl]-3-oxo-8-oxapentacyclo [9.7.0.0^{2,7}.0^{7,9}.0^{12,16}] octadec-4-en-15-yl} ethyl]-3-[(mesyloxy) methyl]-4-methyl-5, 6-dihydro-2H-pyran-2-one (105 mg, 150 μ mol) at 0°C. The resultant reaction mixture was stirred at room temperature for 30 minutes. After the completion of reaction (monitored by TLC), it was diluted with water (20 mL) and extracted with ethyl acetate (2 X 20 mL). The organic layer was washed with brine, dried the organics over sodium sulphate, filtered and concentrated under reduced pressure to get crude. Crude compound was purified by using preparative -HPLC A- 5 mM Ammonium bicarbonate in Water, B- Acetonitrile to afford (4S, 4aR, 5aR, 6aS, 6bS, 9R, 9aS, 11aS, 11bR)-4-hydroxy-9a, 11b-dimethyl-9-((S)-1-((R)-4-methyl-5-(morpholinomethyl)-6-oxo-3, 6-dihydro-2H-pyran-2-yl) ethyl)-2-(5-(oxetan-3-yloxy) pyridin-2-yl)-5a, 6, 6a, 6b, 7, 8, 9, 9a, 10, 11, 11a, 11b-dodecahydrocyclopenta [1, 2] phenanthro [8a, 9-b] oxiren-1(4H)-one (11.5 mg, 10.98%) as a white solid.

[0610] Analytical data:

LCMS: 99.45% (m/z: 689.4, [M+1]⁺, 5.71 min (10 min run).

¹H-NMR (400 MHz, DMSO-*d*₆): δ 8.22 (d, *J* = 2.8 Hz, 1H), 7.56 (d, *J* = 6.8 Hz, 1H), 7.31 (d, *J* = 8.8 Hz, 1H), 7.24 (dd, *J* = 2.8, 8.8 Hz, 1H), 5.70 (d, *J* = 3.2 Hz, 1H), 5.40-5.34 (m, 1H), 4.94 (t, *J* = 6.4 Hz, 2H), 4.58-4.54 (m, 2H), 4.29 (d, *J* = 13.2 Hz, 1H), 3.74-3.71 (m, 1H), 3.50 (t, *J* = 3.6 Hz, 4H), 3.24 (d, *J* = 12.4 Hz, 1H), 3.14 (s, 1H), 3.05 (d, *J* = 12.4 Hz, 1H), 2.50-2.38 (m, 1H), 2.36-2.30 (m, 4H), 2.15-2.01 (m, 5H), 1.99-1.88 (m, 1H), 1.79-1.71 (m, 2H), 1.56-1.54 (m, 1H), 1.37-1.20 (m, 8H), 1.13-1.03 (m, 3 H), 0.99-0.80 (m, 5H), 0.65 (s, 3H).

[0611] Synthesis of Compound 81

[0612] Step 1: Synthesis of ((R)-6-((S)-1-((4S, 4aR, 5aR, 6aS, 6bS, 9R, 9aS, 11aS, 11bR)-4-hydroxy-9a, 11b-dimethyl-2-(5-(oxetan-3-yloxy) pyrimidin-2-yl)-1-oxo-1, 4, 5a, 6, 6a, 6b, 7, 8, 9, 9a, 10, 11, 11a, 11b-tetradecahydrocyclopenta [1, 2] phenanthro [8a, 9-b] oxiren-9-yl) ethyl)-4-methyl-2-oxo-5,6-dihydro-2H-pyran-3-yl)methyl methanesulfonate

145 mg (0.234 mmol, 1 eqv) of (4S, 4aR, 5aR, 6aS, 6bS, 9R, 9aS, 11aS, 11bR)-4-hydroxy-9-((S)-1-((R)-5-(hydroxymethyl)-4-methyl-6-oxo-3, 6-dihydro-2H-pyran-2-yl) ethyl)-9a, 11b-dimethyl-2-(5-(oxetan-3-yloxy) pyrimidin-2-yl)-5a, 6, 6a, 6b, 7, 8, 9, 9a, 10, 11, 11a, 11b-dodecahydrocyclopenta [1, 2] phenanthro [8a, 9-b] oxiren-1(4H)-one was dissolved in 2 ml of DCM under N₂-atmosphere. The reaction mixture was placed on an ice bath and stirred for 20 min at -10°C. Followed by 102 µL (0.584 mmol, 2.5 eqv) of DIPEA and 24 uL (0.234 mmol, 1 eqv) of MsCl were added one by one at -10°C under N₂-atm. After 1.5 hours, the reaction mixture was quenched using ice water. Further, the reaction mixture was extracted with DCM twice and dried over Na₂SO₄. The organic layer was evaporated and dried. The crude was used for the next step without any purification.

[0613] Step 2: Synthesis of (4S, 4aR, 5aR, 6aS, 6bS, 9R, 9aS, 11aS, 11bR)-4-hydroxy-9a, 11b-dimethyl-9-((S)-1-((R)-4-methyl-5-(morpholinomethyl)-6-oxo-3, 6-dihydro-2H-pyran-2-yl) ethyl)-2-(5-(oxetan-3-yloxy) pyrimidin-2-yl)-5a, 6, 6a, 6b, 7, 8, 9, 9a, 10, 11, 11a, 11b-dodecahydrocyclopenta [1, 2] phenanthro [8a, 9-b] oxiren-1(4H)-one

Mixture A: 163 mg of step 1 crude (around 50% conversion) was dissolved in 3 ml of acetonitrile at 0°C under N₂ atmosphere.

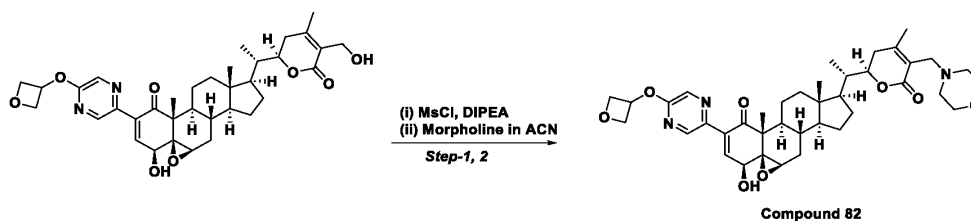
Mixture B: 82 mg of K₂CO₃ (0.584 mmol, 2.5 eqv) and 21 uL of morpholine (0.234 mmol, 1 eqv) were dissolved in 4 ml of acetonitrile under N₂-atm. Further the reaction mixture was placed on an ice bath for 15 min. Finally, the acetonitrile solution of crude (Mixture A) was added to the reaction mixture B at 0°C under N₂ atm. After 5 min, the reaction mixture was removed from the ice bath and heated to 70°C for 2.5 hours under N₂-atm. The reaction mixture was cooled, and TLC was taken. In TLC, the mono-OMs spot was majorly consumed although no new spot was identified. Conversely, the intensity of the spot for Compound 74 was increased. Possibly, the R_f of the product and Compound 74 are same. In LC-MS of the reaction mixture contained 50% of product and 31% Compound 74. The reaction mixture concentrated by evaporation and extracted using DCM and water. The organic layer was combined and dried over Na₂SO₄. The solid crude was purified using HPLC. A white solid product was isolated with 22 % yield.

[0614] Analytical data:

LCMS: Purity 99.52 %, m/z: 690.67, [M+1]⁺, 2.53 min (5.5 min run).

¹H NMR (400 MHz, DMSO-d₆): δ 8.46 (s, 2H), 7.55 (d, J = 6.7 Hz, 1H), 5.75 (d, J = 3.4 Hz, 1H), 5.51 – 5.44 (m, 1H), 4.97 (dq, J = 8.4, 3.2 Hz, 2H), 4.63 – 4.56 (m, 2H), 4.30 (dt, J = 13.0, 3.5 Hz, 1H), 3.77 – 3.71 (m, 1H), 3.51 (t, J = 4.7 Hz, 3H), 3.24 (s, 1H), 3.13 (s, 1H), 3.07 (d, J = 12.4 Hz, 1H), 2.43 – 2.38 (m, 1H), 2.35 – 2.28 (m, 4H), 2.14 (d, J = 3.3 Hz, 1H), 2.11 – 2.06 (m, 1H), 2.00 (s, 3H), 1.89 (s, 3H), 1.74 (d, J = 7.7 Hz, 2H), 1.53 (dd, J = 28.4, 11.7 Hz, 2H), 1.26 (d, J = 19.1 Hz, 6H), 1.09 (dd, J = 24.9, 11.9 Hz, 3H), 0.93 (t, J = 7.2 Hz, 5H), 0.65 (s, 3H).

[0615] Synthesis of Compound 82



[0616] Step 1: Synthesis of ((R)-6-((S)-1-((4S, 4aR, 5aR, 6aS, 6bS, 9R, 9aS, 11aS, 11bR)-4-hydroxy-9a, 11b-dimethyl-2-(5-(oxetan-3-yloxy) pyrazin-2-yl)-1-oxo-1, 4, 5a, 6,

6a, 6b, 7, 8, 9, 9a, 10, 11, 11a, 11b-tetradecahydrocyclopenta [1, 2] phenanthro [8a, 9-b] oxiren-9-yl) ethyl)-4-methyl-2-oxo-5, 6-dihydro-2H-pyran-3-yl) methyl methanesulfonate

To a stirred solution of (R)-6-[(S)-1-{(1S, 2R, 6S, 7R, 9R, 11S, 12S, 15R, 16S)-6-hydroxy-2, 16-dimethyl-4-[5-(3-oxetanyloxy)-2-pyrazinyl]-3-oxo-8-oxapentacyclo [9.7.0.0²,⁷.0⁷,⁹.0¹²,¹⁶] octadec-4-en-15-yl} ethyl]-3-(hydroxymethyl)-4-methyl-5, 6-dihydro-2H-pyran-2-one (410 mg, 660 μ mol) in dichloromethane (4 mL) were added ethylbis (propan-2-yl)amine (288 μ L, 2.5 eq., 1.65 mmol) and methanesulfonyl chloride (51.1 μ L, 660 μ mol) at 0°C. The reaction mixture was stirred at 0°C for 30 minutes. After the completion of reaction (monitored by TLC), it was quenched with water (20 mL) and extracted with DCM (2 x 30 mL). The organic layer was washed with saturated brine solution, dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure to get ((R)-6-((S)-1-((4S, 4aR, 5aR, 6aS, 6bS, 9R, 9aS, 11aS, 11bR)-4-hydroxy-9a, 11b-dimethyl-2-(5-(oxetan-3-yloxy) pyrazin-2-yl)-1-oxo-1, 4, 5a, 6, 6a, 6b, 7, 8, 9, 9a, 10, 11, 11a, 11b-tetradecahydrocyclopenta [1, 2] phenanthro [8a, 9-b] oxiren-9-yl) ethyl)-4-methyl-2-oxo-5, 6-dihydro-2H-pyran-3-yl) methyl methanesulfonate (420 mg crude). It was forwarded as such to the next step.

[0617] Step-2: Synthesis of (4S, 4aR, 5aR, 6aS, 6bS, 9R, 9aS, 11aS, 11bR)-4-hydroxy-9a, 11b-dimethyl-9-((S)-1-((R)-4-methyl-5-(morpholinomethyl)-6-oxo-3, 6-dihydro-2H-pyran-2-yl) ethyl)-2-(5-(oxetan-3-yloxy) pyrazin-2-yl)-5a, 6, 6a, 6b, 7, 8, 9, 9a, 10, 11, 11a, 11b-dodecahydrocyclopenta [1, 2] phenanthro [8a, 9-b] oxiren-1(4H)-one.

To a stirred solution of dipotassium carbonate (162 mg, 2 eq., 1.17 mmol) in acetonitrile (2 mL) were added morpholine (75.9 μ L, 1.5 eq., 880 μ mol) followed by addition of (R)-6-[(S)-1-{(1S, 2R, 6S, 7R, 9R, 11S, 12S, 15R, 16S)-6-hydroxy-2, 16-dimethyl-4-[5-(3-oxetanyloxy)-2-pyrazinyl]-3-oxo-8-oxapentacyclo [9.7.0.0²,⁷.0⁷,⁹.0¹²,¹⁶] octadec-4-en-15-yl} ethyl]-3-[(mesyloxy) methyl]-4-methyl-5, 6-dihydro-2H-pyran-2-one (420 mg, 587 μ mol) dissolved in acetonitrile (3 mL) at room temperature. The resultant reaction mixture was stirred for 30 min at room temperature. After the completion of reaction (monitored by TLC), mixture was quenched with water (20 mL) and extracted with ethyl acetate (2 x 30 mL). The organic layer was washed with saturated brine solution, dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure. The crude product was purified by Prep HPLC. Purification in ammonium bicarbonate method to afford (4S, 4aR, 5aR, 6aS, 6bS, 9R, 9aS, 11aS, 11bR)-4-hydroxy-9a, 11b-dimethyl-9-((S)-1-((R)-4-methyl-5-(morpholinomethyl)-6-oxo-3, 6-dihydro-2H-pyran-2-yl) ethyl)-2-(5-(oxetan-3-yloxy) pyrazin-2-yl)-5a, 6, 6a, 6b, 7, 8,

9, 9a, 10, 11, 11a, 11b-dodecahydrocyclopenta [1, 2] phenanthro [8a, 9-b] oxiren-1(4H)-one (64 mg, 14.6%) as white solid.

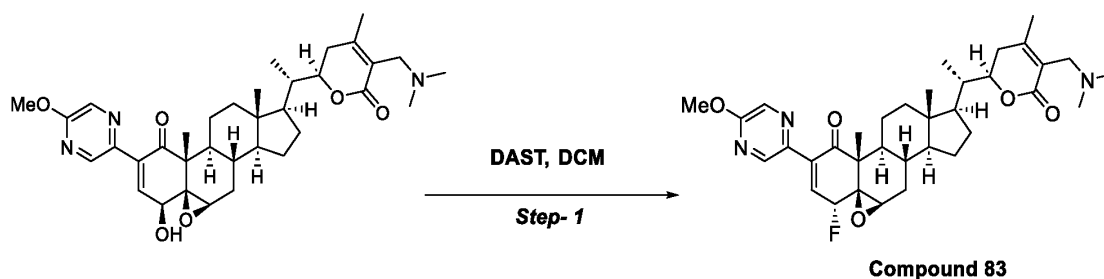
[0618] Analytical data:

LCMS: Purity 95.10 % (m/z: 690.5, [M+1]⁺, 6.02 min (10 min run).

¹H-NMR (400 MHz, DMSO-*d*₆): δ 8.45 (d, *J* = 0.8 Hz, 1H), 8.14 (d, *J* = 0.8 Hz, 1H), 7.62 (d, *J* = 6.8 Hz, 1H), 5.78 (d, *J* = 3.6 Hz, 1H), 5.63-5.57 (m, 1H), 4.91 (t, *J* = 7.2 Hz, 2H), 4.63-4.58 (m, 2H), 4.32-4.27 (m, 1H), 3.76-3.74 (m, 1H), 3.51 (t, *J* = 4.4 Hz, 4H), 3.27-3.04 (m, 3H), 2.44 - 2.30 (m, 5H), 2.13-2.02 (m, 5H), 1.88-1.71 (m, 3H), 1.60-1.47 (m, 1H), 1.42-1.21 (m, 8H), 1.13-1.05 (m, 3H), 0.98-0.81 (m, 5H), 0.65 (s, 3H).

¹³C-NMR (400 MHz, DMSO-*d*₆): δ 200.28, 165.45, 157.66, 155.94, 141.36, 139.70, 138.92, 138.17, 135.11, 121.32, 77.41, 76.55, 69.84, 68.41, 66.20, 66.38, 57.63, 55.22, 52.99, 52.57, 51.10, 47.90, 42.10, 42.03, 40.14, 38.89, 38.43, 38.35, 30.75, 29.28, 26.53, 23.92, 20.48, 15.22, 13.10, 11.25.

[0619] Synthesis of Compound 83



[0620] Step-1: Synthesis of (4R, 4aS, 5aR, 6aS, 6bS, 9R, 9aS, 11aS, 11bR)-9-((S)-1-((R)-5-((dimethylamino) methyl)-4-methyl-6-oxo-3, 6-dihydro-2H-pyran-2-yl) ethyl)-4-fluoro-2-(5-methoxypyrazin-2-yl)-9a, 11b-dimethyl-5a, 6, 6a, 6b, 7, 8, 9, 9a, 10, 11, 11a, 11b-dodecahydrocyclopenta [1, 2] phenanthro [8a, 9-b] oxiren-1(4H)-one :

To a stirred solution of (R)-6-[(S)-1-{(1S, 2R, 6S, 7R, 9R, 11S, 12S, 15R, 16S)-6-hydroxy-4-(5-methoxy-2-pyrazinyl)-2, 16-dimethyl-3-oxo-8-oxapentacyclo [9.7.0.0^{2,7}.0^{7,9}.0^{12,16}] octadec-4-en-15-yl} ethyl]-3-[(dimethylamino) methyl]-4-methyl-5, 6-dihydro-2H-pyran-2-one (160 mg, 264 μmol) in dichloromethane (4 mL) was added diethyl (trifluoro-λ⁴-sulfanyl) amine

(41.9 μ L, 1.2 eq., 317 μ mol) at -78°C . The resultant reaction mixture was stirred at the same temperature for 5 minutes. After the completion of reaction (monitored by TLC), mixture was diluted with saturated sodium bicarbonate solution (20 mL) and extracted with dichloromethane (2 x 20 mL). The organic layer was washed with saturated brine solution, dried the organics over anhydrous sodium sulphate, filtered and concentrated under reduced pressure to get crude. The crude was purified by preparative-HPLC purification using ammonium bicarbonate method to afford (4R, 4aS, 5aR, 6aS, 6bS, 9R, 9aS, 11aS, 11bR)-9-((S)-1-((R)-5-((dimethylamino) methyl)-4-methyl-6-oxo-3, 6-dihydro-2H-pyran-2-yl) ethyl)-4-fluoro-2-(5-methoxypyrazin-2-yl)-9a, 11b-dimethyl-5a, 6, 6a, 6b, 7, 8, 9, 9a, 10, 11, 11a, 11b-dodecahydrocyclopenta [1, 2] phenanthro [8a, 9-b] oxiren-1(4H)-one (26 mg, 16.2%) as a white solid.

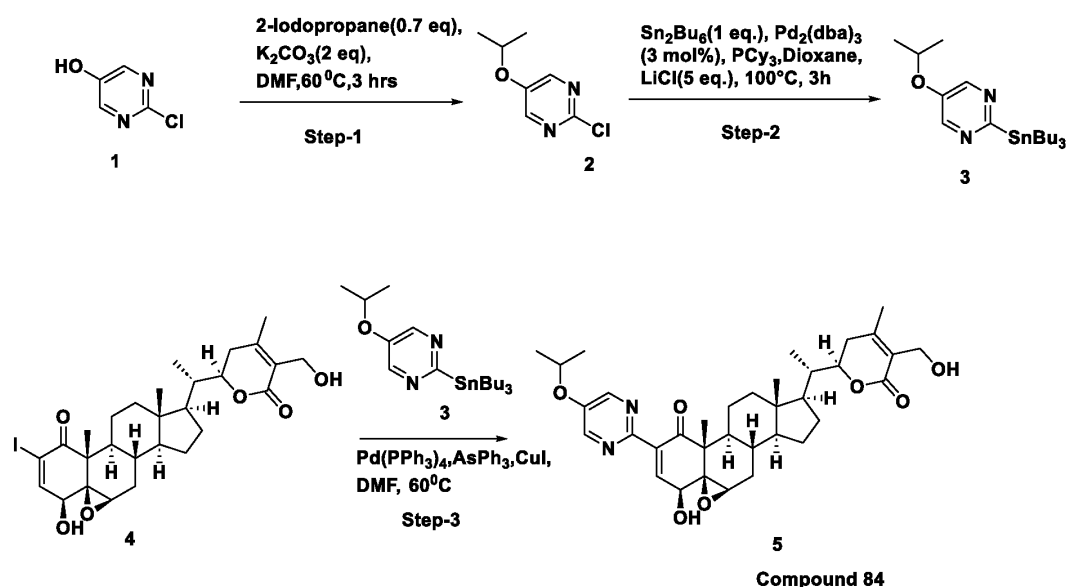
[0621] Analytical data:

LCMS: 90.57% (m/z: 608.50, $[\text{M}+1]^+$, 6.33 min (10 min run).

^1H -NMR (400 MHz, $\text{DMSO}-d_6$): δ 8.37 (d, $J = 1.2$ Hz, 1H), 8.33 (d, $J = 1.2$ Hz, 1H), 7.49 (dd, $J = 1.6, 16.8$ Hz, 1H), 5.88 (d, $J = 50$ Hz, 1H), 4.31-4.26 (m, 1H), 3.94 (s, 3H), 3.53 (s, 1H), 3.18 (d, $J = 12.4$ Hz, 1H), 2.97 (d, $J = 12.4$ Hz, 1H), 2.44-2.36 (m, 1H), 2.14-2.04 (m, 8H), 1.98 (s, 3H), 1.92-1.73 (m, 3H), 1.64-1.51 (m, 2H), 1.44-1.28 (m, 4H), 1.23 (s, 3H), 1.18-0.96 (m, 5H), 0.92 (d, $J = 6.8$ Hz, 3H), 0.67 (s, 3H).

^{13}C -NMR (400 MHz, $\text{DMSO}-d_6$): 201.41, 197.55, 165.47, 159.51, 159.34, 155.83, 140.41, 139.63, 139.45, 139.17, 135.45, 135.36, 135.04, 134.90, 122.08, 85.18, 83.42, 77.50, 62.97, 62.82, 61.24, 55.01, 54.90, 54.17, 54.06, 53.87, 53.09, 51.19, 48.91, 47.31, 47.25, 44.79, 43.22, 42.31, 41.99, 30.03, 29.24, 29.10, 26.50, 24.17, 23.93, 21.60, 21.02, 20.39, 18.96, 13.11, 12.97, 11.76, 11.32.

^{19}F -NMR (400 MHz, $\text{DMSO}-d_6$): -201.78

[0622] Synthesis of Compound 84**[0623] Step-1: Synthesis of 2-chloro-5-isopropoxypyrimidine**

To a stirred solution of 2-chloro-5-pyrimidinol (1 g, 7.66 mmol) in dimethylformamide (4 mL, 51.7 mmol) was added dipotassium carbonate (2.12 g, 2 eq., 15.3 mmol) and 2-iodopropane (781 mg, 0.6 eq., 4.6 mmol) at RT. Reaction was allowed to stir at 60°C for 3 hrs. After completion, the reaction was quenched by water and extracted with ethyl acetate. The filtrate was concentrated under reduced pressure to get crude. The crude material was purified by combi flash over silica gel using 0-50% ethyl acetate in hexane, to get 2-chloro-5-isopropoxypyrimidine (0.8 g, 4.63 mmol) as white solid. Yield: 60.5%

[0624] Analytical data:

LCMS: 100% (m/z: 173.01, [M+1], 3.01min (5min run).

1H -NMR (400 MHz, DMSO- d_6): δ 8.52 (s, 2H), 4.77-4.83 (m, 1H), 1.30 (d, J = -8.00 Hz, 6H)

[0625] Step 2: Synthesis of 5-isopropoxy-2-(tributylstannyl) pyrimidine

To a stirred solution of 2-chloro-5-isopropoxypyrimidine (0.8 g, 4.63 mmol) in 1,4-dioxane was added bis (tributylstannane) (3.24 g, 1.2 eq., 5.56 mmol) and degassed with nitrogen for 5 min followed by addition of lithium chloride (1.18 g, 6 eq., 27.8 mmol) and again degassed for 10 min. To the reaction mixture were added tricyclohexylphosphine (130 mg, 0.1 eq., 463

μmol) and palladium—(1E,4E)-1,5-diphenyl-1,4-pentadien-3-one (2/3) (424 mg, 0.1 eq., 463 μmol) and purged with nitrogen for 10 min. The resulting mixture was stirred at 100°C for 3 hrs in Seal tube. The reaction mixture was quenched with cool water (100 mL) and was extracted with Ethyl acetate (2 x 200mL). The organic layer was dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure. The crude material was purified by Combi Flash by using 10% Ethyl acetate in Hexane to afford tributyl(5-isopropoxy-2-pyrimidinyl) stannane (450 mg, 969 μmol) as a colourless solid. Yield: 20.91%

[0626] Analytical data:

LCMS: 92.46% (m/z: 429.35, [M+2], 6.24min (7min run).

¹H-NMR (400 MHz, DMSO-*d*₆): δ 8.52 (s, 2H), 4.77-4.83 (m, 1H), 1.56-1.50 (m, 12H), 1.33-1.29 (m, 12H), 1.28-1.11 (m, 9H)

[0627] Step:3 Synthesis of (R)-6-[(S)-1-{(1S, 2R, 6S, 7R, 9R, 11S, 12S, 15R, 16S)-6-hydroxy-4-(5-isopropoxy-2-pyrimidinyl)-2,16-dimethyl-3-oxo-8-oxapentacyclo [9.7.0.0^{2,7}.0^{7,9}.0^{12,16}] octadec-4-en-15-yl} ethyl]-3-(hydroxymethyl)-4-methyl-5, 6-dihydro-2H-pyran-2-one

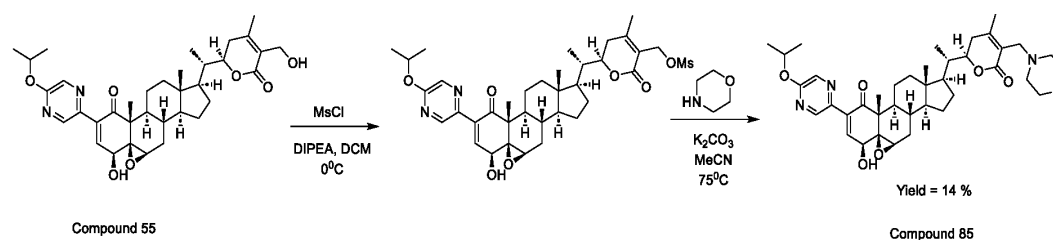
To a stirred solution of (R)-6-[(S)-1-{(1S, 2R, 6S, 7R, 9R, 11S, 12S, 15R, 16S)-6-hydroxy-4-iodo-2, 16-dimethyl-3-oxo-8-oxapentacyclo [9.7.0.0^{2,7}.0^{7,9}.0^{12,16}] octadec-4-en-15-yl} ethyl] - 3-(hydroxymethyl)-4-methyl-5, 6-dihydro-2H-pyran-2-one (0.5 g, 838 μmol) in dimethylformamide (5 mL, 64.6 mmol) were added tributyl (5-isopropoxy-2-pyrimidinyl) stannane (358 mg, 838 μmol) and copper diiodide (39.9 mg, 0.15 eq., 126 μmol). The reaction mixture was purged with nitrogen for 15 min and then palladium—triphenylphosphine (1/4) (48.4 mg, 0.05 eq., 41.9 μmol) and triphenylarsine (38.5 mg, 0.15 eq., 126 μmol) were added to it. The reaction mixture was again purged with nitrogen for 5 min. The reaction was stirred at 60°C for 6h. The reaction mixture was quenched with cool water (50 mL) and was extracted with Ethyl acetate (2 x 100mL). The organic layer was dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure. The crude material was enriched by Combi Flash by using 10% Methanol in DCM. Compound was further purified by preparative-HPLC (Formic Acid method) to afford (R)-6-[(S)-1-{(1S, 2R, 6S, 7R, 9R, 11S, 12S, 15R, 16S)-6-hydroxy-4-(5-isopropoxy-2-pyrimidinyl)-2, 16-dimethyl-3-oxo-8-oxapentacyclo [9.7.0.0^{2,7}.0^{7,9}.0^{12,16}] octadec-4-en-15-yl} ethyl]-3-(hydroxymethyl)-4-methyl-5, 6-dihydro-2H-pyran-2-one (46 mg, 68.2 μmol) as an off white solid. Yield: 8.14%

[0628] Analytical data:

HPLC: 90% at RT- 17.19 (30 min run)

LCMS: 93.59% (m/z: 607.5, [M+1], 3.26 min (5 min run).

¹H-NMR (400 MHz, DMSO-*d*₆): δ 8.54 (s, 2H), 7.53 (d, J = 6.80 Hz, 1H), 5.73 (d, J = 3.60 Hz, 1H), 4.84 (m, 1H), 4.58 (t, J = Hz, 1H), 4.12 (m, 2H), 3.73 (m, 1H), 3.13 (t, J = Hz, 1H), 2.50-2.49 (m, 2H), 2.13-2.07 (m, 2H), 2.02 (m, 1H), 2.00 (s, 3H), 1.93-1.89 (m, 1H), 1.82-1.80 (m, 1H), 1.73-1.71 (m, 1H), 1.58-1.49 (m, 2H), 1.33-1.27 (m, 9H), 1.12-1.05 (m, 5H), 0.93 (d, J = 6.40 Hz, 5H), 0.66 (s, 3H),

[0629] Synthesis of Compound 85

[0630] Step 1: Synthesis of ((R)-6-((S)-1-((4S, 4aR, 5aR, 6aS, 6bS, 9R, 9aS, 11aS, 11bR)-4-hydroxy-2-(5-isopropoxypyrazin-2-yl)-9a, 11b-dimethyl-1-oxo-1, 4, 5a, 6, 6a, 6b, 7, 8, 9, 9a, 10, 11, 11a, 11b-tetradecahydrocyclopenta [1, 2] phenanthro [8a, 9-b] oxiren-9-yl) ethyl)-4-methyl-2-oxo-5, 6-dihydro-2H-pyran-3-yl) methyl methanesulfonate.

About 120 mg (0.2 mmol, 1 eqv) of Compound 55 was dissolved in 2 ml of DCM under N₂-atm. The reaction mixture was placed on an ice bath and stirred for 15 min at -10°C. Followed by 86 μL (0.5 mmol, 2.5 eqv) of DIPEA and 20 μL (0.2 mmol, 1 eqv) of MsCl were added one by one at -10°C under N₂-atm. After 1 hour, the reaction mixture was quenched using ice water. Further, the reaction mixture was extracted with DCM twice and dried over Na₂SO₄. The organic layer was evaporated and dried. The crude was used for the next step without any further purification.

[0631] Step 2: Synthesis of (4S, 4aR, 5aR, 6aS, 6bS, 9R, 9aS, 11aS, 11bR)-4-hydroxy-2-(5-isopropoxypyrazin-2-yl)-9a, 11b-dimethyl-9-((S)-1-((R)-4-methyl-5-

(morpholinomethyl)-6-oxo-3, 6-dihydro-2H-pyran-2-yl) ethyl)-5a, 6, 6a, 6b, 7, 8, 9, 9a, 10, 11, 11a, 11b-dodecahydrocyclopenta [1, 2] phenanthro [8a, 9-b] oxiren-1(4H)-one

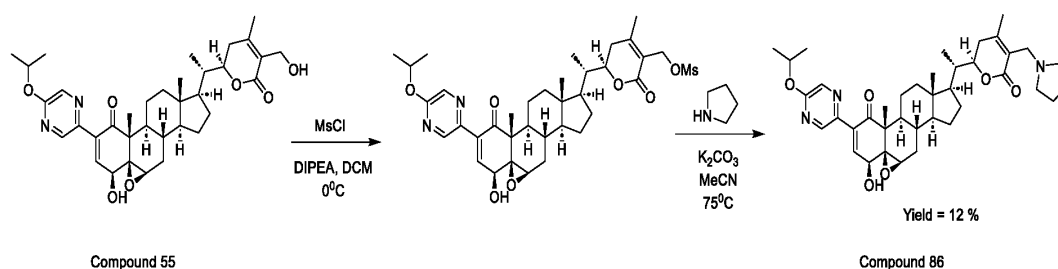
About 55 mg of K₂CO₃ (0.4 mmol, 2 eqv) and 26 μ L of Morpholine (0.3 mmol, 1.5 eqv) were dissolved in 4 ml of acetonitrile under N₂-atm. Further the reaction mixture was placed on an ice bath for 15 min. Finally, the acetonitrile solution of crude (of step 1 crude) was added to the reaction mixture at 0°C under N₂ atm. After 5 min, the reaction mixture was removed from the ice bath and heated to 75°C for 2.5 hours under N₂-atm. The reaction mixture was cooled at ambient temperature and TLC was taken. A new polar spot was identified in comparison to Compound 55. The reaction mixture was filtered and concentrated. The concentrated mass was dissolved in DCM and washed with water. The organic layer was dried over Na₂SO₄. The crude was obtained after evaporation of DCM. Finally, the desired product was purified by HPLC. The desired product was isolated with 14 % yield.

[0632] Analytical data:

LCMS: purity 98.72 % (m/z: 676.61, [M+H]⁺, 2.98 min (5.5 min run).

¹H NMR (400 MHz, DMSO-d₆): δ 8.27 (s, 1H), 8.18 (s, 1H), 7.59 (d, J = 6.7 Hz, 1H), 5.75 (d, J = 3.6 Hz, 1H), 5.25 (m, 1H), 4.29 (m, 1H), 3.75 (m, 1H), 3.51 (s, 4H), 3.27 (d, J = 16.4 Hz, 2H), 3.16 (s, 1H), 3.07 (d, J = 12.4 Hz, 1H), 2.36 (m, 5H), 2.12 – 1.98 (m, 5H), 1.90 (m, 1H), 1.80 (m, 2H), 1.56 (m, 2H), 1.40 – 1.28 (m, 12H), 1.10 (m, 3H), 0.92 (m, 5H), 0.66 (s, 3H).

[0633] Synthesis of Compound 86



[0634] Step 1: Synthesis of ((R)-6-((S)-1-((4S, 4aR, 5aR, 6aS, 6bS, 9R, 9aS, 11aS, 11bR)-4-hydroxy-2-(5-isopropoxypyrazin-2-yl)-9a, 11b-dimethyl-1-oxo-1, 4, 5a, 6, 6a, 6b,

7, 8, 9, 9a, 10, 11, 11a, 11b-tetradecahydrocyclopenta [1, 2] phenanthro [8a, 9-b] oxiren-9-yl) ethyl)-4-methyl-2-oxo-5, 6-dihydro-2H-pyran-3-yl) methyl methanesulfonate.

120 mg (0.2 mmol, 1 eqv) of Compound 55 was dissolved in 2 ml of DCM under N₂-atm. The reaction mixture was placed on an ice bath and stirred for 15 min at -10°C. Followed by 86 µL (0.5 mmol, 2.5 eqv) of DIPEA and 20 µL (0.2 mmol, 1 eqv) of MsCl were added one by one at -10°C under N₂-atm. After 1 hour, the reaction mixture was quenched using ice water. Further, the reaction mixture was extracted with DCM twice and dried over Na₂SO₄. The organic layer was evaporated and dried. The crude was used for the next step without any further purification.

[0635] Step 2: Synthesis of (4S, 4aR, 5aR, 6aS, 6bS, 9R, 9aS, 11aS, 11bR)-4-hydroxy-2-(5-isopropoxy-pyrazin-2-yl)-9a, 11b-dimethyl-9-((S)-1-((R)-4-methyl-6-oxo-5-(pyrrolidin-1-ylmethyl)-3, 6-dihydro-2H-pyran-2-yl)ethyl)-5a, 6, 6a, 6b, 7, 8, 9, 9a, 10, 11, 11a, 11b-dodecahydrocyclopenta [1, 2] phenanthro [8a, 9-b] oxiren-1(4H)-one:

Mixture A: 135 mg of crude reaction mixture of step 1 was dissolved in 3 ml of acetonitrile at 0°C under N₂ atm.

Mixture B: 69 mg of K₂CO₃ (0.5 mmol, 2.5 eqv) and 26 µL of Pyrrolidine (0.3 mmol, 1.5 eqv) were dissolved in 4 ml of acetonitrile under N₂-atm. Further the reaction mixture was placed on an ice bath for 15 min. Finally, the acetonitrile solution of crude (mixture A) was added to the reaction mixture at 0°C under N₂ atm. After 5 min, the reaction mixture was removed from the ice bath and heated to 75°C for 2.5 hours under N₂-atm. The reaction mixture was cooled at ambient temperature and TLC was taken. A new polar spot was identified in comparison to Compound 55. The reaction mixture was filtered and concentrated. The concentrated mass was dissolved in DCM and washed with water. The organic layer was dried over Na₂SO₄. The crude was obtained after evaporation of DCM. Finally, the desired product was purified by HPLC. The desired product was isolated with 12 % yield.

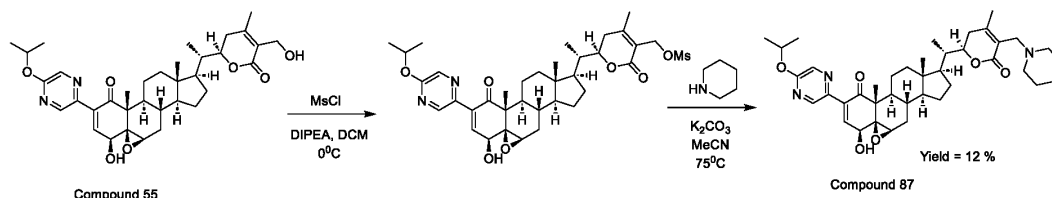
[0636] Analytical data:

LCMS: purity 97.69 % (m/z: 660.60, [M+H]⁺, 3.05 min (5.5 min run).

¹H NMR (400 MHz, MeOD): δ 8.28 (s, 1H), 8.13 (s, 1H), 7.62 (d, J = 6.8 Hz, 1H), 5.32 (m, 1H), 4.53 (m, 1H), 4.17 (d, J = 13.5 Hz, 1H), 4.07 (d, J = 13.5 Hz, 1H), 3.85 (d, J = 6.8 Hz,

1H), 3.17 (s, 1H), 2.64 (m, 1H), 2.30 (dd, J = 18.4, 3.3 Hz, 1H), 2.22 – 2.09 (m, 8H), 2.02 (m, 3H), 1.86 – 1.66 (m, 2H), 1.57 – 1.48 (m, 2H), 1.45 (m, 4H), 1.38 (dd, J = 6.2, 2.7 Hz, 7H), 1.31 (m, 2H), 1.20 (m, 4H), 1.10 – 0.89 (m, 6H), 0.77 (s, 3H).

[0637] Synthesis of Compound 87



[0638] Step 1: Synthesis of ((R)-6-((S)-1-((4S, 4aR, 5aR, 6aS, 6bS, 9R, 9aS, 11aS, 11bR)-4-hydroxy-2-(5-isopropoxypyrazin-2-yl)-9a, 11b-dimethyl-1-oxo-1, 4, 5a, 6, 6a, 6b, 7, 8, 9, 9a, 10, 11, 11a, 11b-tetradecahydrocyclopenta [1, 2] phenanthro [8a, 9-b] oxiren-9-yl) ethyl)-4-methyl-2-oxo-5, 6-dihydro-2H-pyran-3-yl) methyl methanesulfonate:

160 mg (0.264 mmol, 1 eqv) of Compound 55 was dissolved in 2 ml of DCM under N₂-atm. The reaction mixture was placed on an ice bath and stirred for 15 min at -10°C. Followed by 115 µL (0.659 mmol, 2.5 eqv) of DIPEA and 27 µL (0.264 mmol, 1 eqv) of MsCl were added one by one at -10°C under N₂-atm. After 1 hour, the reaction mixture was quenched using ice water. Further, the reaction mixture was extracted with DCM twice and dried over Na₂SO₄. The organic layer was evaporated and dried. The crude was used for the next step without any further purification.

[0639] Step 2: Synthesis of (4S, 4aR, 5aR, 6aS, 6bS, 9R, 9aS, 11aS, 11bR)-4-hydroxy-2-(5-isopropoxypyrazin-2-yl)-9a, 11b-dimethyl-9-((S)-1-((R)-4-methyl-6-oxo-5-(piperidin-1-ylmethyl)-3, 6-dihydro-2H-pyran-2-yl)ethyl)-5a, 6, 6a, 6b, 7, 8, 9, 9a, 10, 11, 11a, 11b-dodecahydrocyclopenta [1, 2] phenanthro [8a, 9-b] oxiren-1(4H)-one:

Mixture A: 217 mg of crude reaction mixture of step 1 was dissolved in 2 ml of acetonitrile at 0°C under N₂ atm.

Mixture B: 73 mg of K₂CO₃ (0.527 mmol, 2.5 eqv) and 39 µL of Piperidine (0.396 mmol, 1.5 eqv) were dissolved in 3 ml of acetonitrile under N₂-atm. Further the reaction mixture was placed on an ice bath for 15 min. Finally, the acetonitrile solution of crude (mixture A) was added to the reaction mixture at 0°C under N₂ atm. After 5 min, the reaction mixture was

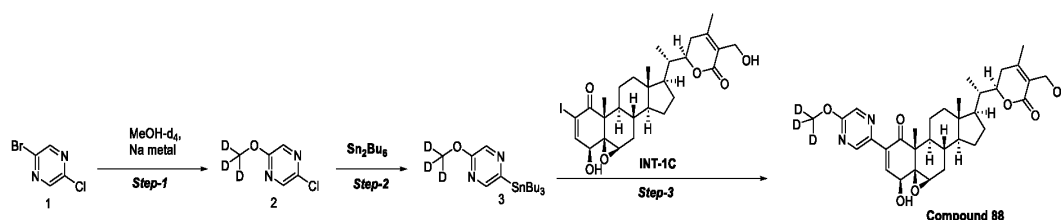
removed from the ice bath and heated to 75°C for 1 hour under N₂-atm. The reaction mixture was cooled at ambient temperature and TLC was taken. A new polar spot was identified in comparison to Compound 55. The reaction mixture was filtered and concentrated. The concentrated mass was dissolved in DCM and washed with water. The organic layer was dried over Na₂SO₄. The crude was obtained after evaporation of DCM. Finally, the desired product was purified by HPLC. The desired product was isolated with 12 % yield.

[0640] Analytical data:

LCMS: purity 99.38 % (m/z: 674.66, [M+H]⁺, 3.25 min (5.5 min run).

¹H NMR (400 MHz, MeOD): δ 8.28 (d, J = 1.4 Hz, 1H), 8.13 (d, J = 1.4 Hz, 1H), 7.62 (d, J = 6.8 Hz, 1H), 5.32 (m, J = 6.2 Hz, 1H), 4.53 (dt, J = 13.3, 3.5 Hz, 1H), 4.08 (d, J = 13.6 Hz, 1H), 3.91 (d, J = 13.6 Hz, 1H), 3.85 (d, J = 6.8 Hz, 1H), 3.15 (m, 2H), 2.69 – 2.58 (m, 1H), 2.30 (m, 1H), 2.16 (m, 4H), 2.02 (m, 2H), 1.83 (m, 5H), 1.66 (m, 3H), 1.58 – 1.47 (m, 3H), 1.45 (s, 3H), 1.38 (m, 7H), 1.31 (m, 2H), 1.20 (m, 4H), 1.08 – 0.90 (m, 6H), 0.77 (s, 3H).

[0641] Synthesis of Compound 88



[0642] Step -1: Synthesis of 2-chloro-5-(methoxy-d3) pyrazine:

In a two neck R.B.F fitted with condenser (²H₃) methan (²H)ol (6 mL) was taken and sodium metal (1.5 g) was added lot wise to it at room temperature. It was stirred at room temperature till a clear solution formed. In another R.B.F solution of 2-bromo-5-chloropyrazine (2 g, 10.3 mmol) in acetonitrile (10 mL) was added to former solution (25% Na in MeOH-d₄) at room temperature dropwise. Reaction mixture was heated at 65°C for 1 hour. After completion of the reaction (monitored by TLC), mixture was concentrated, diluted with water (50 mL) and extracted using ethyl acetate (2 X 50 mL). The organic layer was washed with water and saturated brine solution. Collected organics, dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure to obtain 2-chloro-5-(methoxy-d₃) pyrazine (1.2 g, 78%) as brown solid. It was used as such for the next step.

[0643] Analytical data:

No ionization was observed in LCMS; it was confirmed in the next step.

[0644] Step-2: Synthesis of 2-(methoxy-d3)-5-(tributylstannyl) pyrazine:

To a stirred solution of 2-chloro-5-(²H₃) methoxypyrazine (1.2 g, 8.13 mmol) in 1,4-dioxane (12 mL) were added hexabutylstannane (5.66 g, 1.2 eq., 9.76 mmol), tricyclohexylphosphine (228 mg, 0.1 eq., 813 μmol) and lithium chloride (2.07 g, 6 eq., 48.8 mmol) at room temperature. Reaction mixture was purged with N₂ for 30 min. Then, palladium—(1E, 4E)-1,5-diphenyl-1,4-pentadien-3-one (2/3) (745 mg, 0.1 eq., 813 μmol) was added to it and again purged with N₂ for 10 min. Reaction was stirred at 100°C for 3 hours. After completion of the reaction (monitored by TLC), it was filtered through hyper flow celite by using sintered funnel and the filtrate was concentrated under reduced pressure to obtain crude. Crude product was purified by combi flash column chromatography over silica gel using 0 - 10% ethyl acetate in heptane as an eluent to afford 2-(methoxy-d3)-5-(tributylstannyl) pyrazine (1.6 g, 39%) as light yellow gum.

[0645] Analytical data:

LCMS: 86.70 % (m/z: 404.2, [M+1]⁺, 2.95 min (4 min run).

[0646] Step-3: Synthesis of (4S, 4aR, 5aR, 6aS, 6bS, 9R, 9aS, 11aS, 11bR)-4-hydroxy-9-((S)-1-((R)-5-(hydroxymethyl)-4-methyl-6-oxo-3, 6-dihydro-2H-pyran-2-yl) ethyl)-2-(5-(methoxy-d3) pyrazin-2-yl)-9a, 11b-dimethyl-5a, 6, 6a, 6b, 7, 8, 9, 9a, 10, 11, 11a, 11b-dodecahydrocyclopenta [1, 2] phenanthro [8a, 9-b] oxiren-1(4H)-one:

To a stirred solution of (R)-6-[(S)-1-{(1S, 2R, 6S, 7R, 9R, 11S, 12S, 15R, 16S)-6-hydroxy-4-iodo-2, 16-dimethyl-3-oxo-8-oxapentacyclo [9.7.0.0², 7.0⁷, 9.0¹², 16] octadec-4-en-15-yl} ethyl]-3-(hydroxymethyl)-4-methyl-5, 6-dihydro-2H-pyran-2-one (0.6 g, 1.01 mmol) in tetrahydrofuran (12 mL) were added tributyl [5-(²H₃)methoxy-2-pyrazinyl] stannane (485 mg, 1.2 eq., 1.21 mmol), copper iodide (19.2 mg, 0.1 eq., 101 μmol) and triphenylarsine (30.8 mg, 0.1 eq., 101 μmol) at room temperature. The reaction mixture was purged with N₂ gas for 25 min and then palladium—(1E,4E)-1,5-diphenyl-1,4-pentadien-3-one (2/3) (92.1 mg, 0.1 eq., 101 μmol) was added to it . The reaction mixture was again purged with N₂ gas for 5 min. The reaction vial was sealed and stirred at 80°C for 3 hours. After completion of the reaction

(monitored by TLC), it was quenched by adding water (40 mL) and extracted using ethyl acetate (3 x 40 mL). The combined organics were dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure to obtain crude. Crude product was purified by Prep HPLC using ammonium bicarbonate method to afford (R)-6-[(S)-1-[(1S, 2R, 6S, 7R, 9R, 11S, 12S, 15R, 16S)-6-hydroxy-4-[5-(²H₃) methoxy-2-pyrazinyl]-2, 16-dimethyl-3-oxo-8-oxapentacyclo [9.7.0.0^{2,7},^{7,0},^{9,0}^{12,16}] octadec-4-en-15-yl} ethyl]-3-(hydroxymethyl)-4-methyl-5, 6-dihydro-2H-pyran-2-one (63 mg, 104 μmol) as white solid.

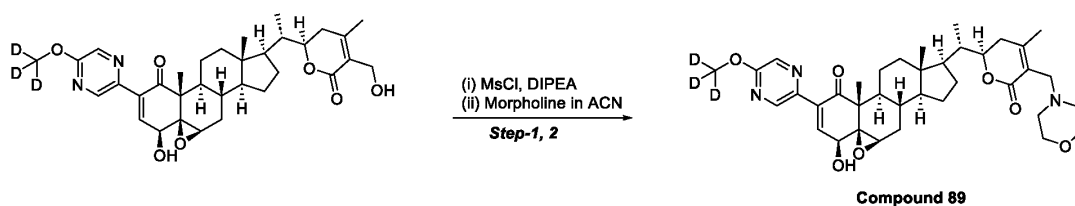
[0647] Analytical data:

LCMS: 96.48 % (m/z: 582.4, [M+1]⁺, 6.19 min (10 min run).

¹H-NMR (400 MHz, DMSO-*d*₆): δ 8.35 (d, *J* = 0.8 Hz, 1H), 8.21 (s, 1H), 7.60 (d, *J* = 6.8 Hz, 1H), 5.75 (d, *J* = 3.2 Hz, 1H), 4.57 (t, *J* = 5.2 Hz, 1H), 4.35-4.26 (m, 1H), 4.18-4.07 (m, 2H), 3.76-3.74 (m, 1H), 3.16 (s, 1H), 2.42-2.34 (m, 1H), 2.11 - 2.05 (m, 2H), 1.99 (s, 3H), 1.92 – 1.83 (m, 1H), 1.81-1.77 (m, 1H), 1.71-1.70 (m, 1H), 1.57-1.55 (m, 1H), 1.40-1.24 (m, 8H), 1.15-1.04 (m, 3H), 0.97-0.86 (m, 5H), 0.66 (s, 3H).

¹³C-NMR (400 MHz, DMSO-*d*₆): δ 200.33, 165.29, 159.37, 154.63, 140.64, 139.15, 138.93, 138.31, 134.99, 125.43, 77.51, 68.43, 63.41, 57.59, 55.25, 54.51, 51.05, 47.90, 42.13, 41.98, 30.74, 29.26, 29.02, 26.49, 23.95, 20.50, 19.87, 15.14, 13.03, 11.23.

[0648] Synthesis of Compound 89



[0649] Step 1: Synthesis of (R)-6-[(S)-1-[(1S, 2R, 6S, 7R, 9R, 11S, 12S, 15R, 16S)-6-hydroxy-4-[5-(²H₃)methoxy-2-pyrazinyl]-2, 16-dimethyl-3-oxo-8-oxapentacyclo [9.7.0.0^{2,7},^{7,0},^{9,0}^{12,16}] octadec-4-en-15-yl} ethyl]-4-methyl-3-(morpholinomethyl)-5, 6-dihydro-2H-pyran-2-one

To a stirred solution of (R)-6-[(S)-1-[(1S, 2R, 6S, 7R, 9R, 11S, 12S, 15R, 16S)-6-hydroxy-4-[5-(²H₃) methoxy-2-pyrazinyl]-2, 16-dimethyl-3-oxo-8-oxapentacyclo [9.7.0.0^{2,7},^{7,0},^{9,0}^{12,16}]

octadec-4-en-15-yl} ethyl]-3-(hydroxymethyl)-4-methyl-5, 6-dihydro-2H-pyran-2-one (0.3 g, 516 μ mol) in dichloromethane (6 mL) was added ethylbis (propan-2-yl)amine (167 mg, 2.5 eq., 1.29 mmol) followed by methanesulfonyl chloride (59.1 mg, 516 μ mol) at 0°C. The reaction mixture was stirred at 0°C for 1h. After the completion of reaction (monitored by TLC), mixture was diluted with water (30 mL) and extracted with DCM (2 X 30 mL). The organic layer was washed with brine, dried the organics over anhydrous sodium sulphate, filtered and concentrated under reduced pressure to get (R)-6-[(S)-1-{(1S, 2R, 6S, 7R, 9R, 11S, 12S, 15R, 16S)-6-hydroxy-4-[5-(²H₃) methoxy-2-pyrazinyl]-2, 16-dimethyl-3-oxo-8-oxapentacyclo [9.7.0.0^{2,7}.0^{7,9}.0^{12,16}] octadec-4-en-15-yl} ethyl]-3-[(mesyloxy) methyl]-4-methyl-5, 6-dihydro-2H-pyran-2-one (285 mg crude). It was forwarded as such to the next step. To a stirred solution of dipotassium carbonate (117 mg, 2 eq., 849 μ mol) in acetonitrile (5 mL) was added morpholine (55.5 mg, 1.5 eq., 637 μ mol) followed by addition of (R)-6-[(S)-1-{(1S, 2R, 6S, 7R, 9R, 11S, 12S, 15R, 16S)-6-hydroxy-4-[5-(²H₃) methoxy-2-pyrazinyl]-2, 16-dimethyl-3-oxo-8-oxapentacyclo [9.7.0.0^{2,7}.0^{7,9}.0^{12,16}] octadec-4-en-15-yl} ethyl]-3-[(mesyloxy) methyl]-4-methyl-5, 6-dihydro-2H-pyran-2-one (280 mg, 424 μ mol) at 0°C. The resultant reaction mixture was stirred at room temperature for 1h. After the completion of reaction (monitored by TLC), mixture was diluted with water (30 mL) and extracted with ethyl acetate (2 X 30 mL). The organic layer was washed with brine, dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure. The crude compound was purified by Prep HPLC using ammonium bicarbonate method to afford (R)-6-[(S)-1-{(1S, 2R, 6S, 7R, 9R, 11S, 12S, 15R, 16S)-6-hydroxy-4-[5-(²H₃)methoxy-2-pyrazinyl]-2, 16-dimethyl-3-oxo-8-oxapentacyclo [9.7.0.0^{2,7}.0^{7,9}.0^{12,16}] octadec-4-en-15-yl} ethyl]-4-methyl-3-(morpholinomethyl)-5, 6-dihydro-2H-pyran-2-one (56 mg, 84.8 μ mol) as white solid.

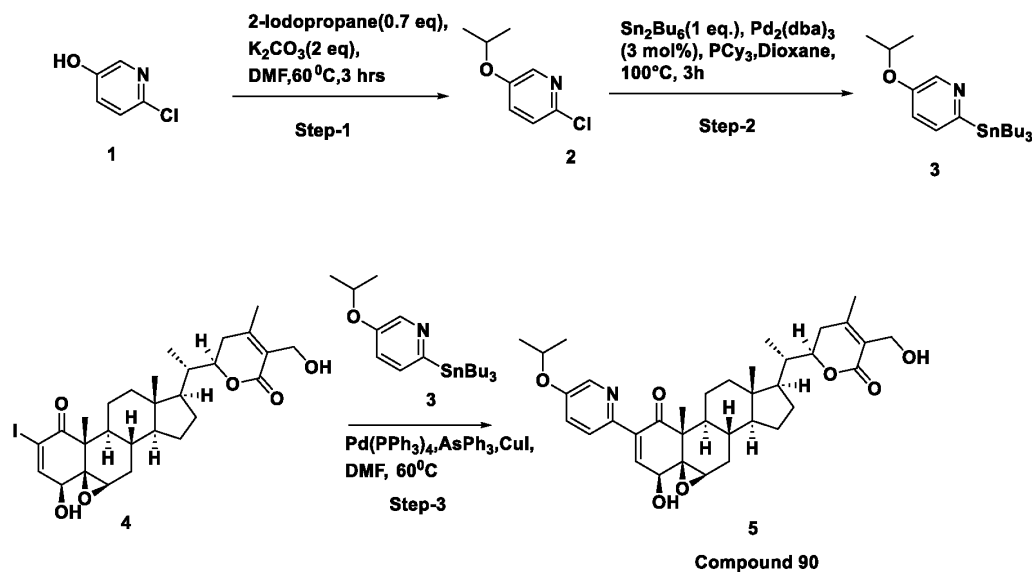
[0650] Analytical data:

LCMS: 98.66 % (m/z: 651.5, [M+1]⁺, 6.12 min (10 min run).

¹H-NMR (400 MHz, DMSO-*d*₆): δ 8.35 (d, *J*=1.2 Hz, 1H), 8.21 (d, *J*=1.2 Hz, 1H), 7.60 (d, *J*=6.8 Hz, 1H), 5.76 (d, *J*=3.2 Hz, 1H), 4.31-4.27 (m, 1H), 3.76-3.74 (m, 1H), 3.50 (t, *J*=4.4 Hz, 4H), 3.25 (d, *J*=12.4 Hz, 1H), 3.16 (s, 1H), 3.06 (d, *J*=12.4 Hz, 1H), 2.43-2.28 (m, 5H), 2.12-2.06 (m, 2H), 1.99 (s, 3H), 1.92-1.89 (m, 1H), 1.81-1.72 (m, 2H), 1.56-1.54 (m, 1H), 1.40-1.24 (m, 8H), 1.11-1.03 (m, 3H), 0.91 (m, 5H), 0.65 (s, 3H).

¹³C-NMR (400 MHz, DMSO-*d*₆): 200.32, 165.41, 159.36, 155.85, 140.63, 139.14, 138.92, 138.30, 134.98, 121.33, 77.38, 68.42, 66.20, 63.40, 57.58, 55.26, 52.97, 52.55, 51.09, 47.90, 42.14, 42.00, 30.74, 29.26, 26.50, 23.89, 20.50, 20.43, 15.14, 13.07, 11.23.

[0651] Synthesis of Compound 90



[0652] Step 1: Synthesis of 2-chloro-5-isopropoxy-pyridine

To a stirred solution of 6-chloro-3-pyridinol (1 g, 7.72 mmol) in N, N-dimethylformamide (10 mL) was added dipotassium carbonate (2.13 g, 2 eq., 15.4 mmol) and 2-iodopropane (919 mg, 0.7 eq., 5.4 mmol) at RT. Reaction was allowed to stir at 60°C for 3 hrs. After completion, the reaction was quenched by water and extracted with ethyl acetate. The filtrate was concentrated under reduced pressure to get crude. The crude material was purified by combi flash over silica gel using 0-50% ethyl acetate in hexane, to get 2-chloro-5-isopropoxy-pyridine (1.1 g, 6.4 mmol) as white solid. Yield: 82.87%.

[0653] Analytical data:

LCMS: 99.81% (m/z: 172, [M+1], 3.33min (5min run).

¹H-NMR (400 MHz, DMSO-*d*₆): δ 8.02 (d, J = 2.40 Hz, 1H), 7.20 (d, J = 0.40 Hz, 1H), 7.16 (d, J = 3.20 Hz, 1H), 4.55-4.52 (m, 1H), 1.34 (d, J = 6.00 Hz, 6H).

[0654] Step 2: Synthesis of 5-isopropoxy-2-(tributylstannyl) pyrimidine

To a stirred solution of 2-chloro-5-isopropoxypyridine (1.1 g, 6.41 mmol) in dimethylformamide (10 mL, 129 mmol) was added bis (tributylstannane) (4.48 g, 1.2 eq., 7.69 mmol) and degassed for 10 min. To the reaction mixture were added tricyclohexylphosphine (180 mg, 0.1 eq., 641 μ mol) and palladium—(1E, 4E)-1,5-diphenyl-1,4-pentadien-3-one (2/3) (587 mg, 0.1 eq., 641 μ mol) and purged with nitogene for 10 min. The resulting mixture was stirred at 1000C for 3 hrs in Seal tube. The reaction mixture was quenched with cool water (100 mL) and was extracted with Ethyl acetate (2 x 200mL). The organic layer was dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure. The crude material was purified by Combi Flash by using 10% Ethyl acetate in Hexane to afford tributyl(5-isopropoxy-2-pyridyl) stannane (470 mg, 1.1 mmol) as a colourless liquid. Yield: 20.91%.

[0655] Analytical data:

¹H-NMR (400 MHz, DMSO-*d*₆): δ 8.02 (d, J = 2.40 Hz, 1H), 7.20 (d, J = 0.40 Hz, 1H), 7.16 (d, J = 3.20 Hz, 1H), 4.55-4.52 (m, 1H), 1.34 (d, J = 6.00 Hz, 6H) 1.56-1.50 (m, 12H), 1.33-1.29 (m, 12H), 1.28-1.11 (m, 9H)

[0656] Step 3: Synthesis of (R)-6-[(S)-1-{(1S, 2R, 6S, 7R, 9R, 11S, 12S, 15R, 16S)-6-hydroxy-4-(5-isopropoxy-2-pyridyl)-2, 16-dimethyl-3-oxo-8-oxapentacyclo [9.7.0.0^{2,7}.0^{7,9}.0^{12,16}] octadec-4-en-15-yl} ethyl]-3-(hydroxymethyl)-4-methyl-5, 6-dihydro-2H-pyran-2-one

To a stirred solution of (R)-6-[(S)-1-{(1S, 2R, 6S, 7R, 9R, 11S, 12S, 15R, 16S)-6-hydroxy-4-iodo-2, 16-dimethyl-3-oxo-8-oxapentacyclo [9.7.0.0^{2,7}.0^{7,9}.0^{12,16}] octadec-4-en-15-yl} ethyl]-3-(hydroxymethyl)-4-methyl-5, 6-dihydro-2H-pyran-2-one (0.5 g, 838 μ mol) in dimethylformamide (5 mL, 64.6 mmol) were added tributyl (5-isopropoxy-2-pyridyl) stannane (357 mg, 838 μ mol) and copper diiodide (39.9 mg, 0.15 eq., 126 μ mol). The reaction mixture was purged with nitrogen for 15 min and then palladium—triphenylphosphine (1/4) (48.4 mg, 0.05 eq., 41.9 μ mol) and triphenyl arsine (38.5 mg, 0.15 eq., 126 μ mol) were added to it .The reaction mixture was again purged with nitrogen for 5 min. The reaction was stirred at 60°C for 6h. The reaction mixture was quenched with cool water (50 mL) and was extracted with Ethyl acetate (2 x 100mL). The organic layer was dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure. The crude material was enriched by Combi

Flash by using 10% Methanol in DCM. Compound was further purified by preparative-HPLC (Formic Acid method) to afford (R)-6-[(S)-1-[(1S, 2R, 6S, 7R, 9R, 11S, 12S, 15R, 16S)-6-hydroxy-4-(5-isopropoxy-2-pyridyl)-2, 16-dimethyl-3-oxo-8-oxapentacyclo [9.7.0.0^{2,7}.0^{7,9}.0^{12,16}] octadec-4-en-15-yl] ethyl]-3-(hydroxymethyl)-4-methyl-5, 6-dihydro-2H-pyran-2-one (140 mg, 229 μ mol) as an off white solid. Yield: 27.3%.

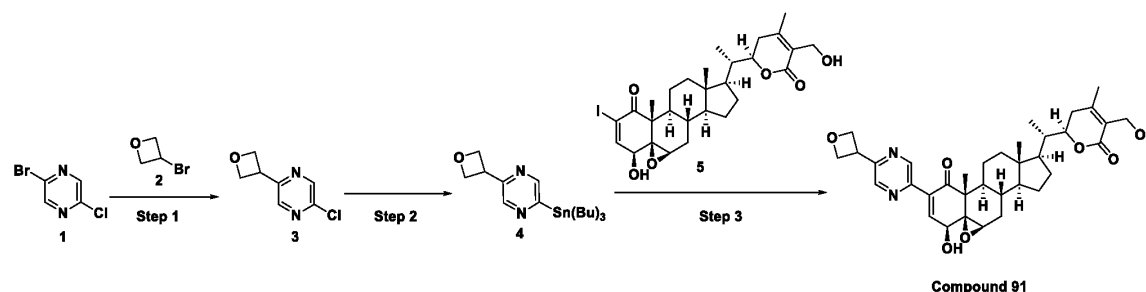
[0657] Analytical data:

HPLC: 96.20% at RT- 14.46 (30 min run)

LCMS: 98.36% (m/z: 606.54, [M+1], 3.37 min (5 min run).

¹H-NMR (400 MHz, DMSO-*d*₆): δ 8.26 (d, J = 2.80 Hz, 1H), 7.56 (d, J = 6.80 Hz, 1H), 7.42-7.39 (m, 1H), 7.32 (d, J = 8.80 Hz, 1H), 5.67 (d, J = 3.20 Hz, 1H), 4.84 (m, 1H), 4.58 (t, J = Hz, 1H), 4.12 (m, 2H), 3.73 (m, 1H), 3.13 (t, J = Hz, 1H), 2.50-2.49 (m, 2H), 2.13-2.07 (m, 2H), 2.02 (m, 1H), 2.00 (s, 3H), 1.93-1.89 (m, 1H), 1.82-1.80 (m, 1H), 1.73-1.71 (m, 1H), 1.58-1.49 (m, 2H), 1.33-1.27 (m, 9H), 1.12-1.05 (m, 5H), 0.93 (d, J = 6.40 Hz, 5H), 0.66 (s, 3H)

[0658] Synthesis of Compound 91



[0659] Step-1: Synthesis of 5-chloro-2-(3-oxetanyl) pyrazine

N, N-dimethylacetamide (15 mL) was added to a reaction vial and purged with nitrogen for 10 min. then 2, 6-pyridinedicarboximidine (0.084 g, 0.05 eq., 0.517 mmol), nickel diiodide (0.162 g, 0.05 eq., 0.517 mmol), sodium iodide (0.387 g, 0.25 eq., 2.58 mmol), 2-bromo-5-chloropyrazine (2.0 g, 10.3 mmol), 3-bromooxetane (1.7 g, 1.2 eq., 12.4 mmol), zinc dust (1.35 g, 2 eq., 20.7 mmol) and trifluoroacetic acid (0.08 mL, 0.1 eq., 1.03 mmol) were added to the reaction vial in this following order. The vial was capped under inert atmosphere and the reaction mixture was heated to 60°C with stirring for 16h. After completion of reaction

(monitored by TLC and by LCMS), quenched it by adding saturated sodium bicarbonate solution (20 mL) and then filtered through celite bed and washed with ethyl acetate. The filtrate was extracted using ethyl acetate (2 x 30 mL). Collected organics were dried over anhydrous sodium sulphate, filtered then concentrated under reduced pressure to obtain crude. Crude was purified by combi-flash chromatography (20-30% ethyl acetate in heptane) to afford 5-chloro-2-(3-oxetanyl)pyrazine (0.1 g, 0.604 mmol, 6%) as off white solid.

[0660] Analytical data:

¹H-NMR (400 MHz, DMSO-*d*₆): δ 8.84 (s, 1H), 8.46 (s, 1H), 4.91-4.87 (m, 2H), 4.75-4.72 (m, 2H), 4.53-4.49 (m, 1H).

[0661] Step 2: Synthesis of tributyl [5-(3-oxetanyl)-2-pyrazinyl] stannane

To a stirred solution of 5-chloro-2-(3-oxetanyl) pyrazine (0.630 g, 3.69 mmol) in 1,4-dioxane (8.0 mL) were added hexabutylstannane (2.57 g, 1.2 eq., 4.43 mmol), lithium chloride (0.94 g, 6 eq., 22.2 mmol) and tricyclohexylphosphine (0.10 g, 0.1 eq., 0.369 mmol) at room temperature. Reaction mixture was purged with argon for 20 min, then tris (dibenzylideneacetone)dipalladium (0.169 g, 0.05 eq., 0.185 mmol) was added to it and again purged with argon for 5 min. Reaction was stirred at 100°C for 16 h. After the completion of reaction (monitored by TLC) it was filtered through celite bed and washed it with ethyl acetate, the filtrate was concentrated under reduced pressure to get crude. Crude was purified by combi-flash chromatography (20-30% ethyl acetate in heptane) to afford tributyl[5-(3-oxetanyl)-2-pyrazinyl] stannane (0.75g, 1.76 mmol, 47%) as light yellow liquid.

[0662] Analytical data:

LCMS: 85.69% (m/z: 426.65, [M+1]⁺, 3.02 min (4 min run).

[0663] Step 3: Synthesis of (R)-6-[(S)-1-[(1S, 2R, 6S, 7R, 9R, 11S, 12S, 15R, 16S)-6-hydroxy-2, 16-dimethyl-4-[5-(3-oxetanyl)-2-pyrazinyl]-3-oxo-8-oxapentacyclo [9.7.0.0^{2,7},9.0^{12,16}] octadec-4-en-15-yl} ethyl]-3-(hydroxymethyl)-4-methyl-5, 6-dihydro-2H-pyran-2-one.

To a stirred solution of (R)-6-[(S)-1-[(1S, 2R, 6S, 7R, 9R, 11S, 12S, 15R, 16S)-6-hydroxy-4-iodo-2, 16-dimethyl-3-oxo-8-oxapentacyclo [9.7.0.0^{2,7},9.0^{12,16}] octadec-4-en-15-yl} ethyl]-3-(hydroxymethyl)-4-methyl-5, 6-dihydro-2H-pyran-2-one (0.3 g, 0.503 mmol) and tributyl

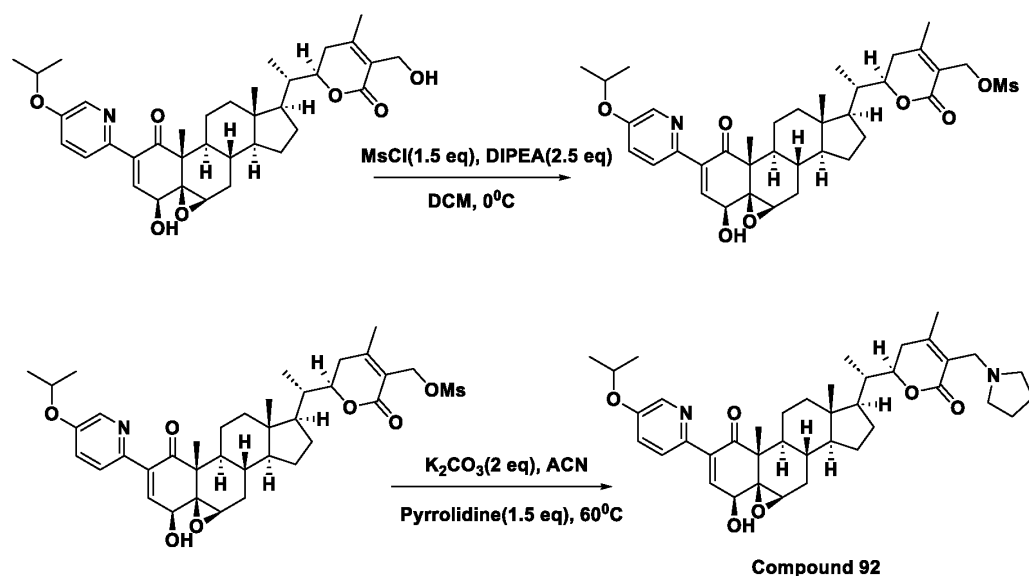
[5-(3-oxetanyl)-2-pyrazinyl] stannane (0.214 g, 0.503 mmol) in tetrahydrofuran (8 mL) was added λ^1 -copper(1+) iodide (0.014 g, 0.15 eq., 0.075 mmol) and triphenylarsine (0.015 g, 0.1 eq., 0.050 mmol) at room temperature. The resulting mixture was purged with argon for 30 min. Tris (dibenzylideneacetone) dipalladium (0.046 g, 0.1 eq., 0.050 mmol) was added to the mixture, again purged with argon for 10 min and stirred for 2 h at 80°C. After completion of the reaction, (monitored by TLC & LCMS), it was quenched by adding water (50 mL) and then extracted using ethyl acetate (2 x 50 mL). The collected organics, dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure to obtain crude. Crude product was purified by combi flash column chromatography using, 90-100% ethyl acetate in heptane as an eluent followed by Prep HPLC purification in ammonium bicarbonate method to afford (R)-6-[(S)-1-[(1S, 2R, 6S, 7R, 9R, 11S, 12S, 15R, 16S)-6-hydroxy-2, 16-dimethyl-4-[5-(3-oxetanyl)-2-pyrazinyl]-3-oxo-8-oxapentacyclo [9.7.0.0^{2,7}.0^{7,9}.0^{12,16}] octadec-4-en-15-yl} ethyl]-3-(hydroxymethyl)-4-methyl-5, 6-dihydro-2H-pyran-2-one (0.06 g, 0.099 mmol, 20%) as off white solid.

[0664] Analytical data:

LCMS: 91.95% (m/z: 605.5, $[M+1]^+$, 5.10 min (10 min run).

¹H-NMR (400 MHz, DMSO-*d*₆): δ 8.67 (s, 1H), 8.62 (s, 1H), 7.75 (d, J = 6.8 Hz, 1H), 5.85 (d, J = 3.6 Hz, 1H), 4.92-4.89 (m, 2H), 4.80-4.75 (m, 2H), 4.59-4.50 (m, 2H), 4.30-4.26 (m, 1H), 4.18-4.07 (m, 2H), 3.79-3.76 (m, 1H), 3.18 (s, 1H), 2.42-2.32 (m, 1H), 2.10-2.01 (m, 2H), 1.99 (s, 3H), 1.93-1.90 (m, 1H), 1.83-1.76 (m, 1H), 1.75 – 1.66 (m, 1H), 1.61-1.51 (m, 1H), 1.48-1.21 (m, 8H), 1.19-1.01 (m, 4H), 0.98 -0.88 (m, 4H), 0.66 (s, 3H).

¹³C-NMR (400 MHz, DMSO-*d*₆): δ 200.21, 165.31, 154.89, 151.64, 146.73, 143.45, 142.39, 141.66, 138.64, 125.44, 77.52, 75.16, 68.40, 63.36, 57.62, 55.26, 54.51, 51.07, 47.91, 42.09, 42.00, 30.72, 29.26, 29.02, 26.49, 26.96, 20.48, 19.88, 15.16, 13.05, 11.25

[0665] Synthesis of Compound 92

[0666] Step 1: Synthesis of ((R)-6-((S)-1-((4S, 4aR, 5aR, 6aS, 6bS, 9R, 9aS, 11aS, 11bR)-4-hydroxy-2-(5-isopropoxy-2-pyridyl)-9a, 11b-dimethyl-1-oxo-1, 4, 5a, 6, 6a, 6b, 7, 8, 9, 9a, 10, 11, 11a, 11b-tetradecahydrocyclopenta [1, 2] phenanthro [8a, 9-b] oxiren-9-yl) ethyl)-4-methyl-2-oxo-5, 6-dihydro-2H-pyran-3-yl) methyl methane sulfonate

To a stirred solution of (R)-6-[(S)-1-{(1S, 2R, 6S, 7R, 9R, 11S, 12S, 15R, 16S)-6-hydroxy-4-(5-isopropoxy-2-pyridyl)-2, 16-dimethyl-3-oxo-8-oxapentacyclo [9.7.0.0^{2,7}.0^{9,12}.1⁶] octadec-4-en-15-yl} ethyl]-3-(hydroxymethyl)-4-methyl-5, 6-dihydro-2H-pyran-2-one (0.1 g, 0.165 μ mol) in DCM (2 mL) was added N-ethylbis (isopropyl) amine (71.9 μ L, 2.5 eq., 413 μ mol) and (chlorosulfonyl) methane (19.2 μ L, 1.5 eq., 248 μ mol) at 0°C. The reaction was allowed to stir at 0°C for 5 min. After completion, the reaction was quenched by water and extracted with DCM. The filtrate was concentrated under reduced pressure to get crude. The crude material ((R)-6-((S)-1-((4S, 4aR, 5aR, 6aS, 6bS, 9R, 9aS, 11aS, 11bR)-4-hydroxy-2-(5-isopropoxy-2-pyridyl)-9a, 11b-dimethyl-1-oxo-1, 4, 5a, 6, 6a, 6b, 7, 8, 9, 9a, 10, 11, 11a, 11b-tetradecahydrocyclopenta [1, 2] phenanthro [8a, 9-b] oxiren-9-yl) ethyl)-4-methyl-2-oxo-5, 6-dihydro-2H-pyran-3-yl) methyl methane sulfonate (150 mg) as such used for the next step.

[0667] Analytical data:

LCMS: 15.37% (m/z: 684.49, [M+1], 3.64 min (5 min run).

[0668] **Step 2: Synthesis of (4S, 4aR, 5aR, 6aS, 6bS, 9R, 9aS, 11aS, 11bR)-4-hydroxy-2-(5-isopropoxy-2-pyridin-2-yl)-9a, 11b-dimethyl-9-((S)-1-((R)-4-methyl-6-oxo-5-(pyrrolidin-1-ylmethyl)-3,6-dihydro-2H-pyran-2-yl) ethyl)-5a, 6, 6a, 6b, 7, 8, 9, 9a, 10, 11, 11a, 11b-dodecahydrocyclopenta [1, 2] phenanthro [8a, 9-b] oxiren-1(4H)-one**

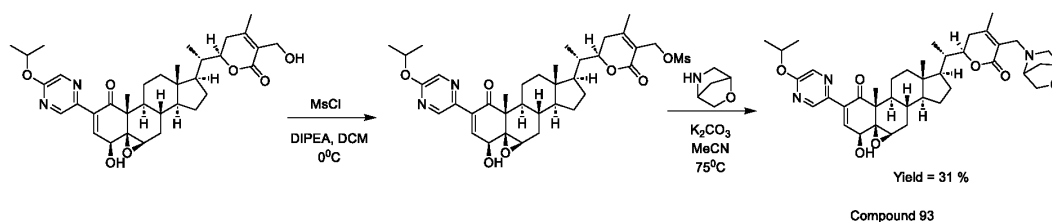
To a stirred solution of material ((R)-6-((S)-1-((4S, 4aR, 5aR, 6aS, 6bS, 9R, 9aS, 11aS, 11bR)-4-hydroxy-2-(5-isopropoxy-2-pyridin-2-yl)-9a, 11b-dimethyl-1-oxo-1, 4, 5a, 6, 6a, 6b, 7, 8, 9, 9a, 10, 11, 11a, 11b-tetradecahydrocyclopenta [1, 2] phenanthro [8a, 9-b] oxiren-9-yl) ethyl)-4-methyl-2-oxo-5, 6-dihydro-2H-pyran-3-yl) methyl methane sulfonate (150 mg) in acetonitrile (2 mL, 95.7 mmol) was added dipotassium carbonate (45.6 mg, 2 eq., 330 μ mol) at 0°C. After 5 min was added pyrrolidine (17.6 mg, 1.5 eq., 248 μ mol) drop wise. The resulting mixture was stirred at 60°C for 15 min. Reaction was monitor by TLC. After completion, the reaction mixture was quenched with cool water (100 mL) and was extracted with Ethyl acetate (2 x 200mL). The organic layer was dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure. The crude material was purified by Combi Flash by using 10% Ethyl acetate in Hexane to afford (R)-6-[(S)-1-{(1S, 2R, 6S, 7R, 9R, 11S, 12S, 15R, 16S)-6-hydroxy-4-(5-isopropoxy-2-pyridyl)-2, 16-dimethyl-3-oxo-8-oxapentacyclo [9.7.0.0^{2,7}, 0^{7,9}, 0^{12,16}] octadec-4-en-15-yl} ethyl]-4-methyl-3-[(1-pyrrolidinyl) methyl]-5, 6-dihydro-2H-pyran-2-one (10 mg, 14.7 μ mol) as off white solid. Yield: 8.92%.

[0669] **Analytical data:**

LCMS: 97.78% (m/z: 659.65, [M+1], 1.95 min (5 min run).

HPLC: 97.66% at rt 14.91 (30 min run)

¹H-NMR (400 MHz, DMSO-*d*₆): ¹H-NMR (400 MHz, DMSO-*d*₆): δ 8.27 (d, J = 2.40 Hz, 1H), 7.56 (d, J = 6.80 Hz, 1H), 7.41 (dd, J = 3.20, 9.00 Hz, 1H), 7.32 (d, J = 8.40 Hz, 1H), 6.52 (s, 2H), 6.28 (s, 1H), 5.67 (d, J = 3.60 Hz, 1H), 4.70 (q, J = 6.00 Hz, 1H), 4.33 (d, J = 11.60 Hz, 1H), 3.73 (dd, J = 3.60, 6.80 Hz, 1H), 3.15 (s, 1H), 2.41 (d, J = 14.40 Hz, 2H), 2.13 (d, J = 17.60 Hz, 2H), 2.03 (s, 4H), 1.93-1.90 (m, 1H), 1.82-1.72 (m, 5H), 1.57-1.55 (m, 2H), 1.40 (d, J = 2.80 Hz, 2H), 1.31-1.28 (m, 11H), 1.22 (d, J = 9.20 Hz, 1H), 1.10-1.07 (m, 4H), 0.92 (d, J = 6.80 Hz, 4H), 0.88-0.81 (m, 1H), 0.66 (s, 3H),

[0670] Synthesis of Compound 93

[0671] Step 1: Synthesis of ((R)-6-((S)-1-((4S, 4aR, 5aR, 6aS, 6bS, 9R, 9aS, 11aS, 11bR)-4-hydroxy-2-(5-isopropoxy-pyrazin-2-yl)-9a, 11b-dimethyl-1-oxo-1, 4, 5a, 6, 6a, 6b, 7, 8, 9, 9a, 10, 11, 11a, 11b-tetradecahydrocyclopenta [1, 2] phenanthro [8a, 9-b] oxiren-9-yl) ethyl)-4-methyl-2-oxo-5, 6-dihydro-2H-pyran-3-yl) methyl methanesulfonate:

(R)-6-[(S)-1-{(1S, 2R, 6S, 7R, 9R, 11S, 12S, 15R, 16S)-6-hydroxy-4-(5-isopropoxy-2-pyrazinyl)-2, 16-dimethyl-3-oxo-8-oxapentacyclo [9.7.0.0^{2,7}.0^{7,9}.0^{12,16}] octadec-4-en-15-yl} ethyl]-3-(hydroxymethyl)-4-methyl-5, 6-dihydro-2H-pyran-2-one (0.5 g, 412 μ mol) was dissolved in 4 ml of DCM under N₂-atmosphere. The reaction mixture was placed on an ice bath and stirred for 15 min at -100C. Followed by 165 μ L (0.95 mmol, 2.5 eqv) of DIPEA and 38 μ L (0.38 mmol, 1 eqv) of MsCl were added one by one at -100C under N₂-atm. After 1 hour, the reaction mixture was quenched using ice water. Further, the reaction mixture was extracted with DCM twice and dried over Na₂SO₄. The organic layer was evaporated and dried. The crude was used for the next step without any further purification.

[0672] Step 2: Synthesis of (4S, 4aR, 5aR, 6aS, 6bS, 9R, 9aS, 11aS, 11bR)-9-((1S)-1-((2R)-5-(2-oxa-5-azabicyclo [2. 2. 1] heptan-5-ylmethyl)-4-methyl-6-oxo-3, 6-dihydro-2H-pyran-2-yl) ethyl)-4-hydroxy-2-(5-isopropoxy-pyrazin-2-yl)-9a, 11b-dimethyl-5a, 6, 6a, 6b, 7, 8, 9, 9a, 10, 11, 11a, 11b-dodecahydrocyclopenta [1, 2] phenanthrol [8a,9-b] oxiren-1(4H)-one

Mixture A: The crude reaction mixture of step 1 was dissolved in 3 ml of acetonitrile at 0°C under N₂ atm.

Mixture B: Dipotassium carbonate (114 mg, 2 eq., 824 μ mol) and 2-oxa-5-azabicyclo [2.2.1] heptane (61.3 mg, 1.5 eq., 618 μ mol) were dissolved in 3 ml of acetonitrile under N₂-atm. Further the reaction mixture was placed on an ice bath for 15 min. Finally, the acetonitrile solution of crude (mixture A) was added to the reaction mixture at 0°C under N₂ atm. After 5

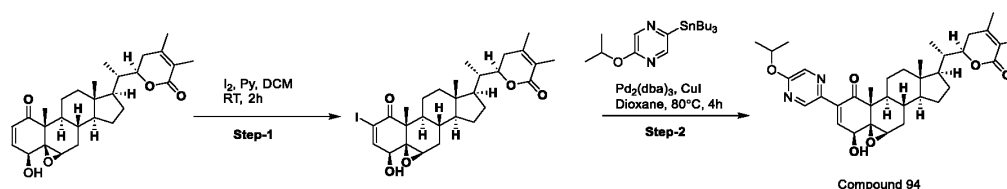
min, the reaction mixture was removed from the ice bath and heated to 75°C for 1 hour under N₂-atm. The reaction mixture was cooled at ambient temperature and TLC was taken. A new polar spot was identified in comparison to Compound 55. The reaction mixture was filtered and concentrated. The concentrated mass was dissolved in DCM and washed with water. The organic layer was dried over Na₂SO₄. The crude was obtained after evaporation of DCM. Finally, the desired product was purified by HPLC. The desired product was isolated with 31% yield.

[0673] Analytical data:

LCMS: purity 99.11 % (m/z: 688.68, [M+H]⁺, 3.01 min (5.5 min run).

¹H NMR (400 MHz, MeOD): δ 8.28 (d, J = 1.4 Hz, 1H), 8.13 (d, J = 1.4 Hz, 1H), 7.62 (d, J = 6.8 Hz, 1H), 5.32 (p, J = 6.2 Hz, 1H), 4.46 – 4.37 (m, 2H), 4.07 (m, 1H), 3.85 (d, J = 6.8 Hz, 1H), 3.67 – 3.58 (m, 2H), 3.58 – 3.42 (m, 3H), 3.17 (s, 1H), 2.87 (m, 1H), 2.71 – 2.63 (m, 1H), 2.58 – 2.45 (m, 1H), 2.19 – 2.11 (m, 2H), 2.09 (d, J = 6.0 Hz, 3H), 2.04 – 1.87 (m, 3H), 1.78 (m, 1H), 1.70 (t, J = 10.4 Hz, 2H), 1.57 – 1.45 (m, 3H), 1.44 (s, 3H), 1.40 (s, 1H), 1.37 (m, 6H), 1.34 – 1.28 (m, 1H), 1.24 – 1.12 (m, 3H), 1.06 – 0.94 (m, 5H), 0.76 (s, 3H).

[0674] Synthesis of Compound 94



[0675] Step 1: Synthesis of (R)-6-[(S)-1-[(1S, 2R, 6S, 7R, 9R, 11S, 12S, 15R, 16S)-6-hydroxy-2, 16-dimethyl-3-oxo-8-oxapentacyclo [9.7.0.0^{2,7}.0^{7,9}.0^{12,16}] octadec-4-en-15-yl] ethyl]-3, 4-dimethyl-5, 6-dihydro-2H-pyran-2-one.

To a stirred solution of (R)-6-[(S)-1-[(1S, 2R, 6S, 7R, 9R, 11S, 12S, 15R, 16S)-6-hydroxy-2, 16-dimethyl-3-oxo-8-oxapentacyclo [9.7.0.0^{2,7}.0^{7,9}.0^{12,16}] octadec-4-en-15-yl] ethyl]-3, 4-dimethyl-5, 6-dihydro-2H-pyran-2-one (80 mg, 176 μmol) and pyridine (64 μL) (8 volume) in DCM (3 mL) was added diiodine (62.5 mg, 1.4 eq., 246 μmol) at 0°C. The resulting mixture was stirred at RT for 2h. The progress of reaction was monitored by LCMS. The reaction mixture was quenched with 30% sodium thiosulphate solution (2 mL), diluted with DCM (10

mL), washed with 20% citric acid solution (2×5 mL), the organic layer was dried over Na_2SO_4 , concentrated and purified by combiflash chromatography elution 0-50% EtOAc in Hexane to afford the desired compound (R)-6-[(S)-1-{(1S, 2R, 6S, 7R, 9R, 11S, 12S, 15R, 16S)-6-hydroxy-4-iodo-2, 16-dimethyl-3-oxo-8-oxapentacyclo [9.7.0.0^{2,7},⁹.0^{12,16}] octadec-4-en-15-yl} ethyl]-3, 4-dimethyl-5, 6-dihydro-2H-pyran-2-one (85 mg, 83.21%) as white solid.

[0676] Analytical data:

LCMS: (ESI) m/z : -581.36 ($M+1$)⁺

[0677] Step 2: Synthesis of (R)-6-[(S)-1-{(1S, 2R, 6S, 7R, 9R, 11S, 12S, 15R, 16S)-6-hydroxy-4-(5-isopropoxy-2-pyrazinyl)-2, 16-dimethyl-3-oxo-8-oxapentacyclo [9.7.0.0^{2,7},⁹.0^{12,16}] octadec-4-en-15-yl} ethyl]-3, 4-dimethyl-5, 6-dihydro-2H-pyran-2-one.

To a stirred solution of (R)-6-[(S)-1-{(1S, 2R, 6S, 7R, 9R, 11S, 12S, 15R, 16S)-6-hydroxy-4-iodo-2, 16-dimethyl-3-oxo-8-oxapentacyclo [9.7.0.0^{2,7},⁹.0^{12,16}] octadec-4-en-15-yl} ethyl]-3, 4-dimethyl-5, 6-dihydro-2H-pyran-2-one (80 mg, 138 μmol) and tributyl (5-isopropoxy-2-pyrazinyl) stannane (118 mg, 2 eq., 276 μmol) in 1, 4-dioxane (2 mL, 23.4 mmol) was added copper iodide (3.94 mg, 0.15 eq., 20.7 μmol) and palladium—(1E, 4E)-1, 5-diphenyl-1, 4-pentadien-3-one (2/3) (6.31 mg, 0.05 eq., 6.89 μmol) under N_2 degas. The resulting mixture was heated for 3h at 80°C. The progress of reaction was monitored by LCMS and TLC. The reaction mixture was filtered through celite, residue was rinsed with EtOAc (5 mL), concentrated and purified by pre-HPLC to afford the desired compound (R)-6-[(S)-1-{(1S, 2R, 6S, 7R, 9R, 11S, 12S, 15R, 16S)-6-hydroxy-4-(5-isopropoxy-2-pyrazinyl)-2, 16-dimethyl-3-oxo-8-oxapentacyclo [9.7.0.0^{2,7},⁹.0^{12,16}] octadec-4-en-15-yl} ethyl]-3, 4-dimethyl-5, 6-dihydro-2H-pyran-2-one (7 mg, 8.6%) as white solid.

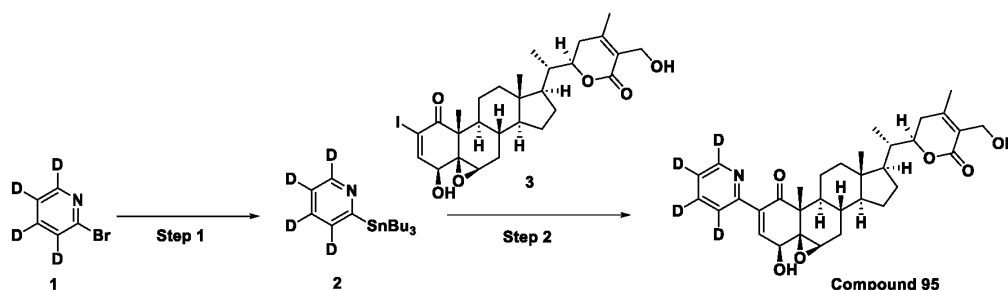
[0678] Analytical data:

LCMS: 97.72% (m/z): 591.61, [$M+1$]⁺, 2.74 min (5.50 min run).

¹H NMR (400 MHz, DMSO): δ 8.26 (s, 1H), 8.18 (s, 1H), 7.59 (d, 1H), 5.75 (brs, 1H), 5.26-5.21 (m, 1H), 4.29 (dt, $J = 13.2, 3.6$ Hz, 1H), 4.22 (t, 1H), 3.74 (dd, $J = 6.3, 4.2$ Hz, 1H), 3.16 (s, 1H), 2.40 – 2.31 (m, 1H), 2.05 – 2.00 (m, 2H), 1.94 – 1.89 (m, 3H), 1.81 (m, 1H), 1.75 (m,

1H), 1.62 – 1.50 (m, 1H), 1.45 – 1.37 (m, 2H), 1.35-1.28 (m, 11H), 1.24-1.21 (m, 3H), 1.18 – 1.01 (m, 3H), 0.97-0.85 (m, 6H), 0.64 (s, 3H).

[0679] Synthesis of Compound 95



[0680] Step 1: Synthesis of tributyl [(3,4,5,6-²H₄)-2-pyridyl] stannane

To a stirred solution of 2-bromo(3,4,5,6-²H₄) pyridine (0.5 g, 3.09 mmol) in 1,4-dioxane (8 mL) were added hexabutyldistannane (2.51 g, 1.4 eq., 4.32 mmol), lithium chloride (0.785 g, 6 eq., 18.5 mmol) and tricyclohexylphosphine (0.086 g, 0.1 eq., 0.309 mmol) at room temperature. Reaction mixture was purged with argon for 20 minutes, then Tris (dibenzylideneacetone) dipalladium (0.141 g, 0.05 eq., 0.154 mmol) was added to it and again purged with argon for 5 min. Reaction was continuously stirred at 100°C for 3 h. After completion of the reaction (monitored by TLC and LCMS), it was quenched by adding water (30 mL) and extracted using diethyl ether (2 x 30 mL). The collected organics, dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure to obtain crude. Crude product was purified by combi flash column chromatography on neutral alumina using (5-10%) ethyl acetate in heptane as an eluent to afford tributyl [(3, 4, 5, 6-²H₄)-2-pyridyl] stannane (2.3 g crude) as yellow liquid.

[0681] Analytical data:

LCMS: 93.03% (m/z: 374.00, [M+1]⁺), 3.12 min (4 min run).

[0682] Step 2: Synthesis of (R)-6-[(S)-1-[(1S, 2R, 6S, 7R, 9R, 11S, 12S, 15R, 16S)-6-hydroxy-2,16-dimethyl-3-oxo-4-[(3,4,5,6-²H₄)-2-pyridyl]-8-oxapentacyclo

[9.7.0.0²,7.0⁷,9.0¹²,16] octadec-4-en-15-yl] ethyl]-3-(hydroxymethyl)-4-methyl-5, 6-dihydro-2H-pyran-2-one

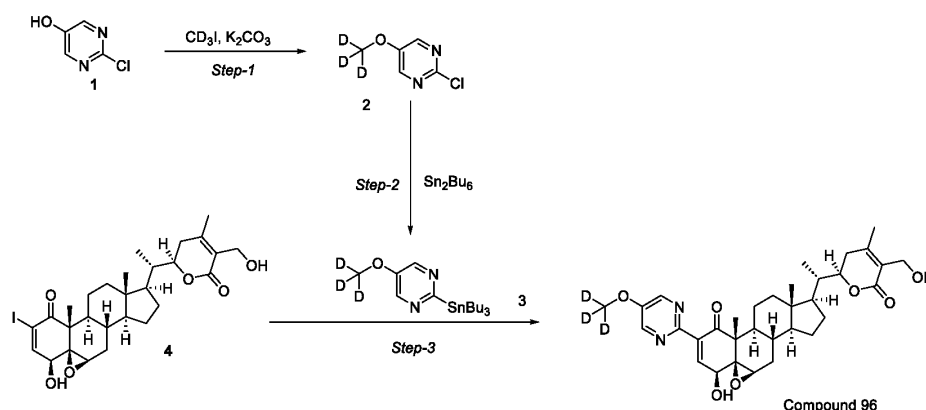
To a stirred solution of (R)-6-[(S)-1-{(1S, 2R, 6S, 7R, 9R, 11S, 12S, 15R, 16S)-6-hydroxy-4-iodo-2, 16-dimethyl-3-oxo-8-oxapentacyclo [9.7.0.0^{2,7}.0^{7,9}.0^{12,16}] octadec-4-en-15-yl} ethyl]-3-(hydroxymethyl)-4-methyl-5, 6-dihydro-2H-pyran-2-one (0.6 g, 1.01 mmol) and tributyl [(3,4,5,6-²H₄)-2-pyridyl] stannane (1.31 g, 3.5 eq., 3.52 mmol) in 1,4-dioxane (8 mL) was added λ^1 -copper(1+) iodide (0.029 g, 0.15 eq., 0.151 mmol) at room temperature. The resulting mixture was purged with argon for 30 min. After that Tris (dibenzylideneacetone) dipalladium (0.092 g, 0.1 eq., 0.101 mmol) was added to it and again purged with argon for 5 minutes. The reaction mixture was stirred for 2 hours at 80°C. After completion of the reaction (monitored by TLC & LCMS), it was quenched by adding water (60 mL) and extracted using ethyl acetate (3 x 50 mL). Collected organics, dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure to obtain crude. Crude product was purified by combi flash column chromatography using (80-90 %) ethyl acetate in heptane as an eluent followed by Prep HPLC purification in ammonium bicarbonate method to afford (R)-6-[(S)-1-{(1S, 2R, 6S, 7R, 9R, 11S, 12S, 15R, 16S)-6-hydroxy-2, 16-dimethyl-3-oxo-4-[(3,4,5,6-²H₄)-2-pyridyl]-8-oxapentacyclo [9.7.0.0^{2,7}.0^{7,9}.0^{12,16}] octadec-4-en-15-yl} ethyl]-3-(hydroxymethyl)-4-methyl-5, 6-dihydro-2H-pyran-2-one (0.175 g, 31%) as off white solid.

[0683] Analytical data:

LCMS: 96.29% (m/z: 552.5, [M+1]⁺), 5.35 min (10 min run).

¹H-NMR (400 MHz, DMSO-*d*₆): δ 7.68 (d, *J* = 6.8 Hz, 1H), 5.74 (d, *J* = 3.2 Hz, 1H), 4.57 (t, *J* = 5.6 Hz, 1H), 4.29-4.26 (m, 1H), 4.18-4.07 (m, 2H), 3.76-3.74 (m, 1H), 3.16 (s, 1H), 2.42 – 2.32 (m, 1H), 2.11-2.02 (m, 2H), 1.98 (s, 3H), 1.93-1.90 (m, 1H), 1.82-1.77 (m, 1H), 1.73-1.70 (m, 1H), 1.57-1.54 (m, 1H), 1.41-1.21 (m, 7H), 1.14-1.04 (m, 3H), 0.93-0.84 (m, 5H), 0.66 (s, 3H).

¹³C-NMR (400 MHz, DMSO-*d*₆): δ 200.59, 165.31, 154.65, 152.39, 141.10, 139.78, 125.44, 77.51, 68.51, 63.52, 57.55, 55.31, 54.51, 51.02, 47.90, 42.10, 42.00, 38.47, 38.39, 30.76, 29.24, 29.01, 26.50, 23.96, 20.49, 19.88, 15.13, 13.02, 11.24

[0684] Synthesis of Compound 96**[0685] Step 1: Synthesis of 2-chloro-5-($^2\text{H}_3$)methoxypyrimidine**

To a stirred solution of 2-chloro-5-pyrimidinol (2 g, 15.3 mmol) in acetone (20 mL) were added dipotassium carbonate (4.24 g, 2 eq., 30.6 mmol) and iodo($^2\text{H}_3$)methane (2.67 g, 1.2 eq., 18.4 mmol) at room temperature. Reaction was stirred at room temperature for 2 h. After the completion of the reaction (monitored by TLC), mixture was concentrated under vacuum, diluted with water (50 mL) and extracted using ethyl acetate (50 mL x 2). The organic layer was washed with water (50 mL) and saturated brine solution. Collected organics, dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure to obtain crude. Crude product was purified by combi flash column chromatography using, 20-25% ethyl acetate in hexane as an eluent to afford 2-chloro-5-($^2\text{H}_3$)methoxypyrimidine (1.8 g, 11.1 mmol) as white solid.

[0686] Analytical data:

LCMS: 91% (m/z: 148, $[\text{M}+1]^+$, 1.14 min (4 min run).

[0687] Step-2: Synthesis of tributyl[5-($^2\text{H}_3$) methoxy-2-pyrimidinyl] stannane

To a stirred solution of 2-chloro-5-($^2\text{H}_3$) methoxypyrimidine (1.2 g, 8.13 mmol) in 1,4-dioxane (14 mL) were added bis (tributylstannane) (5.68 g, 1.2 eq., 9.76 mmol), tricyclohexylphosphine (228 mg, 0.1 eq., 813 μmol) and lithium chloride (2.07 g, 6 eq., 48.8 mmol) at room temperature. Reaction mixture was purged with N_2 for 20 min. Then, palladium—(1E,4E)-1,5-diphenyl-1,4-pentadien-3-one (2/3) (372 mg, 0.05 eq., 407 μmol) was added to it and again purged with N_2 for 5 min. The reaction vial was sealed and stirred at 120°C for 2h. After

completion of the reaction (monitored by TLC and LCMS), it was quenched by adding water (50 mL) and extracted using ethyl acetate (50 mL x 2). Collected organics, dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure to obtain crude. Crude product was purified by combi flash column chromatography using, 5-10% ethyl acetate in heptane as an eluent to afford tributyl[5-(²H₃)methoxy-2-pyrimidinyl] stannane (3.1 g, 7.71 mmol) as light yellow liquid.

[0688] Analytical data:

LCMS: 92.42 % (m/z: 405 [M+1]⁺, 3.06 min (4 min run).

[0689] Step 3 : Synthesis of (R)-6-[(S)-1-{(1S, 2R, 6S, 7R, 9R, 11S, 12S, 15R, 16S)-6-hydroxy-4-[5-(²H₃) methoxy-2-pyrimidinyl]-2, 16-dimethyl-3-oxo-8-oxapentacyclo [9.7.0.0^{2,7}.0^{7,9}.0^{12,16}] octadec-4-en-15-yl} ethyl]-3-(hydroxymethyl)-4-methyl-5, 6-dihydro-2H-pyran-2-one

To stirred solution of (R)-6-[(S)-1-{(1S, 2R, 6S, 7R, 9R, 11S, 12S, 15R, 16S)-6-hydroxy-4-iodo-2, 16-dimethyl-3-oxo-8-oxapentacyclo [9.7.0.0^{2,7}.0^{7,9}.0^{12,16}] octadec-4-en-15-yl} ethyl]-3-(hydroxymethyl)-4-methyl-5, 6-dihydro-2H-pyran-2-one (0.5 g, 838 μmol) in tetrahydrofuran (5 mL) were added tributyl[5-(²H₃)methoxy-2-pyrimidinyl] stannane (405 mg, 1.2 eq., 1.01 mmol), copper iodide (16 mg, 0.1 eq., 83.8 μmol) and triphenylarsane (25.7 mg, 0.1 eq., 83.8 μmol) at room temperature. Reaction mixture was purged with Nitrogen gas for 30 minutes, then palladium—(1E, 4E)-1, 5-diphenyl-1, 4-pentadien-3-one (2/3) (76.8 mg, 0.1 eq., 83.8 μmol) was added to it and again purged with Nitrogen for 5 minutes. The reaction vial was sealed and stirred at 80°C for 3h. After completion of the reaction (monitored by TLC), it was quenched by adding water (30 mL) and extracted using ethyl acetate (30 mL x 2). The collected organics was dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure to obtain crude. The crude product was purified by Prep HPLC using ammonium bicarbonate method to afford (R)-6-[(S)-1-{(1S, 2R, 6S, 7R, 9R, 11S, 12S, 15R, 16S)-6-hydroxy-4-[5-(²H₃) methoxy-2-pyrimidinyl]-2, 16-dimethyl-3-oxo-8-oxapentacyclo [9.7.0.0^{2,7}.0^{7,9}.0^{12,16}] octadec-4-en-15-yl} ethyl]-3-(hydroxymethyl)-4-methyl-5, 6-dihydro-2H-pyran-2-one (25 mg, 5%) as white solid.

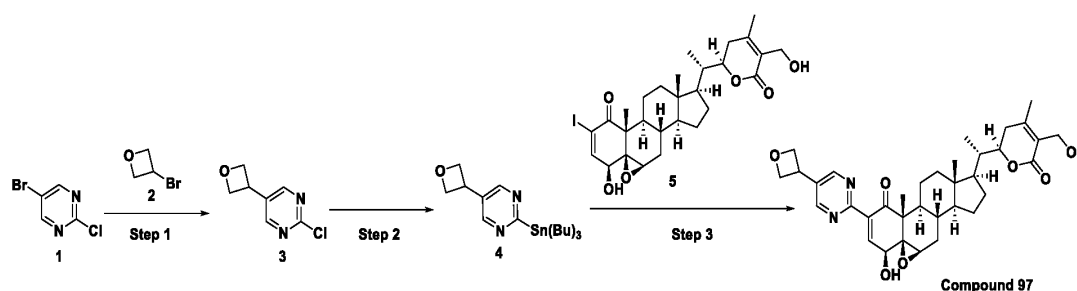
[0690] Analytical data:

LCMS: 96.79 % (m/z: 582.5, [M+1]⁺, 5.24 min (10 min run).

¹H-NMR (400 MHz, DMSO-*d*₆): δ 8.57 (s, 2H), 7.53 (d, *J* = 6.40 Hz, 1H), 5.74 (d, *J* = 3.20 Hz, 1H), 4.58 (t, *J* = 5.20 Hz, 1H), 4.26-4.30 (m, 1H), 4.08-4.18 (m, 2H), 3.72-3.74 (m, 1H), 3.13 (s, 1H), 2.32-2.44 (m, 1H), 2.03-2.13 (m, 2H), 2.00 (s, 3H), 1.49-1.93 (m, 5H), 1.21-1.35 (m, 7H), 0.88-1.21 (m, 8H), 0.66 (s, 3H).

¹³C-NMR (400 MHz, DMSO-*d*₆): δ 199.015, 165.31, 155.20, 154.67, 152.04, 143.59, 141.42, 141.42, 139.93, 125.43, 77.53, 68.57, 63.82, 57.44, 55.47, 54.51, 51.04, 47.83, 42.02, 41.79, 30.88, 29.05, 26.51, 23.97, 20.18, 19.88, 14.80, 13.04, 11.23.

[0691] Synthesis of Compound 97



[0692] Step 1: Synthesis of 2-chloro-5-(3-oxetanyl) pyrimidine.

N, N-dimethylacetamide (50 mL) was added to a reaction vial and purged with nitrogen for 10 min. then 2,6-pyridinedicarboximidine (0.253 g, 0.05 eq., 1.55 mmol), nickel diiodide (0.485 g, 0.05 eq., 1.55 mmol), sodium iodide (1.16 g, 0.25 eq., 7.75 mmol), 5-bromo-2-chloropyrimidine (6 g, 31 mmol), 3-bromooxetane (5.1 g, 1.2 eq., 37.2 mmol), zinc dust (4.06 g, 2 eq., 62 mmol) and trifluoroacetic acid (0.237 mL, 0.1 eq., 3.1 mmol) were added in the following order. The vial was sealed under an inert atmosphere and the reaction mixture was stirred at 60°C for 16h. After completion of reaction (monitored by TLC and by LCMS), it was quenched by using saturated sodium bicarbonate solution (30 mL) and then filtered through celite bed and washed with ethyl acetate (50 mL). The layers were separated, and the aqueous layer was extracted using ethyl acetate (2 x 30 mL). Collected organics were dried over anhydrous sodium sulphate, filtered and then concentrated under reduced pressure to obtain crude. Crude was purified by combi-flash chromatography using 20-30% ethyl acetate in heptane as eluent to afford 2-chloro-5-(3-oxetanyl)pyrimidine (0.335 g, 1.96 mmol, 7%) as off white solid.

[0693] Analytical data:

¹H-NMR (400 MHz, DMSO-*d*₆): δ 8.85 (s, 2H), 4.92-4.86 (m, 2H), 4.76-4.63 (m, 2H), 4.36-4.28 (m, 1H).

Step 2: Synthesis of tributyl [5-(3-oxetanyl)-2-pyrimidinyl] stannane

To a stirred solution of 2-chloro-5-(3-oxetanyl)pyrimidine (0.5 g, 2.93 mmol) in 1,4-dioxane (7 mL) were added hexabutyldistannane (2.04 g, 1.2 eq., 3.52 mmol), lithium chloride (0.746 g, 6 eq., 17.6 mmol) and tricyclohexylphosphine (0.082 g, 0.1 eq., 0.293 mmol) at room temperature. Reaction mixture was purged with argon for 15 minutes, then tris(dibenzylideneacetone)dipalladium (0.134 g, 0.05 eq., 0.147 mmol) was added to it and again purged with argon for 5 min. Reaction was stirred at 130°C for 3 h. After the completion of reaction (monitored by TLC), it was filtered through celite bed and washed it with ethyl acetate (30 mL). The filtrate was concentrated under reduced pressure to get crude. Crude was then purified by combi-flash chromatography using 20-30% ethyl acetate in heptane as eluent to afford tributyl[5-(3-oxetanyl)-2-pyrimidinyl] stannane (0.550 g, 1.29 mmol, 44%).

[0694] Analytical data:

LCMS: 94.84% (m/z: 426.65, [M+1]⁺, 2.92 min (4 min run).

[0695] Step 3: Synthesis of (R)-6-[(S)-1-{(1S, 2R, 6S, 7R, 9R, 11S, 12S, 15R, 16S)-6-hydroxy-2,16-dimethyl-4-[5-(3-oxetanyl)-2-pyrimidinyl]-3-oxo-8-oxapentacyclo [9.7.0.0.2⁷,7.0⁷,9.0¹²,16] octadec-4-en-15-yl} ethyl]-3-(hydroxymethyl)-4-methyl-5, 6-dihydro-2H-pyran-2-one

To a stirred solution of (R)-6-[(S)-1-{(1S, 2R, 6S, 7R, 9R, 11S, 12S, 15R, 16S)-6-hydroxy-4-iodo-2, 16-dimethyl-3-oxo-8-oxapentacyclo [9.7.0.0.2⁷,7.0⁷,9.0¹²,16] octadec-4-en-15-yl} ethyl]-3-(hydroxymethyl)-4-methyl-5, 6-dihydro-2H-pyran-2-one (0.250 g, 0.419 mmol) and tributyl [5-(3-oxetanyl)-2-pyrimidinyl] stannane (0.214 g, 1.2 eq., 0.503 mmol) in tetrahydrofuran (5 mL) were added λ^1 -copper(1+) iodide (0.012 g, 0.15 eq., 0.629 mmol) and triphenylarsine (0.013 g, 0.1 eq., 0.042 mmol) at room temperature. It was purged with argon for 30 min. Then tris (dibenzylideneacetone)dipalladium (0.038 g, 0.1 eq., 0.042 mmol) was added to the mixture, again purged with argon for 10 min and stirred for 2 h at 80°C. After completion of the reaction (monitored by TLC & LCMS), it was quenched by adding water (50 mL) and then

extracted using ethyl acetate (2 x 40 mL). Collected organics, dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure to obtain crude. Crude product was purified by combi flash column chromatography using 90-100% ethyl acetate in heptane as an eluent followed by Prep HPLC purification in ammonium bicarbonate method to afford (R)-6-[(S)-1-[(1S, 2R, 6S, 7R, 9R, 11S, 12S, 15R, 16S)-6-hydroxy-2, 16-dimethyl-4-[5-(3-oxetanyl)-2-pyrimidinyl]-3-oxo-8-oxapentacyclo [9.7.0.0²,⁷.0⁷,⁹.0¹²,¹⁶] octadec-4-en-15-yl} ethyl]-3-(hydroxymethyl)-4-methyl-5, 6-dihydro-2H-pyran-2-one (0.035 g, 0.058 mmol, 13%) as off white solid.

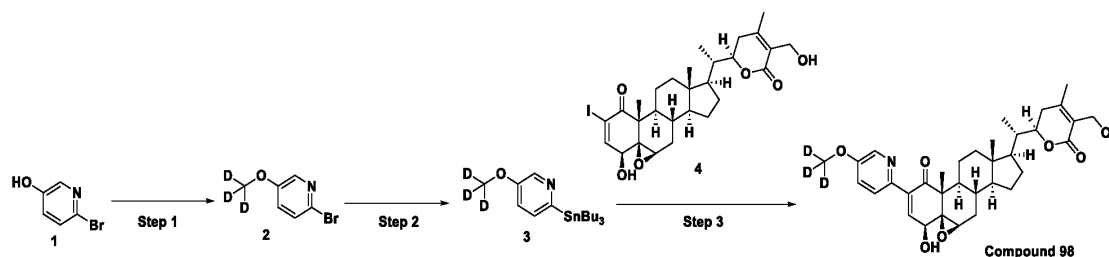
[0696] Analytical data:

LCMS: 91.7% (m/z: 605.5, [M+1]⁺, 4.94 min (10 min run).

¹H-NMR (400 MHz, DMSO-*d*₆): δ 8.89 (s, 2H), 7.64 (d, *J* = 6.8 Hz, 1H), 5.79 (s, 1H), 5.01-4.92 (m, 2H), 4.73-4.68 (m, 2H), 4.58 (t, *J* = 5.2 Hz, 1H), 4.35-4.27 (m, 2H), 4.18-4.08 (m, 2H), 3.75 (d, *J* = 6.0 Hz, 1H), 3.14 (s, 1H), 2.43 – 2.32 (m, 1H), 2.15-2.11 (m, 2H), 1.99 (s, 3H), 1.93-1.89 (m, 1H), 1.88 – 1.50 (m, 4H), 1.33-1.23 (m, 7H), 1.15-0.97 (m, 4H), 0.94 – 0.92 (m, 4H), 0.66 (s, 3H).

¹³C-NMR (400 MHz, DMSO-*d*₆): δ 198.96, 165.31, 161.20, 156.11, 154.66, 141.68, 141.54, 133.16, 125.43, 77.53, 76.40, 76.34, 68.54, 63.79, 57.41, 55.48, 54.51, 51.04, 47.85, 42.03, 41.78, 38.53, 38.40, 34.87, 30.87, 29.03, 26.51, 23.97, 20.19, 19.88, 14.79, 13.04, 11.23.

[0697] Synthesis of Compound 98



[0698] Step 1: Synthesis of 2-bromo-5-(²H₃) methoxypyridine

To a stirred solution of 6-bromo-3-pyridinol (1 g, 5.75 mmol) in N, N-dimethylformamide (10 mL) was added diccesium carbonate (2.81 g, 1.5 eq., 8.62 mmol) followed by addition of iodo (²H₃) methane (0.590 mL, 1.1 eq., 6.21 mmol) at room temperature. The resultant reaction

mixture was stirred at 40°C for 1h. After the completion of reaction (monitored by TLC) mixture was diluted with water (40 mL) and extracted with ethyl acetate (2 x 50 mL). The organic layer was washed with brine, organics were dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure to get 2-bromo-5-(²H₃) methoxypyridine (0.96 g, 5.03 mmol, 87%) as crude which was directly used for next step without any further purification.

[0699] Analytical data:

LCMS: 99.89 % (m/z: 190.99, [M+1]⁺, 1.55 min (4 min run).

[0700] Step 2: Synthesis of tributyl[5-(²H₃) methoxy-2-pyridyl] stannane

To a stirred solution of 2-bromo-5-(²H₃) methoxypyridine (0.9 g, 4.71 mmol) in 1,4-dioxane (9 mL) were added hexabutyldistannane (3.28 g, 1.2 eq., 5.65 mmol), lithium chloride (1.2 g, 6 eq., 28.3 mmol) and tricyclohexylphosphine (0.132 g, 0.1 eq., 0.471 mmol) at room temperature. Reaction mixture was purged with argon for 30 minutes, then Tris (dibenzylideneacetone)dipalladium (0.216 g, 0.05 eq., 0.236 mmol) was added to it and again purged with argon for 5 min. Reaction was stirred at 100°C for 3 h. After completion of reaction (monitored by TLC), it was filtered through celite bed and washed it with ethyl acetate (30 mL). The filtrate was concentrated under reduced pressure to get crude. The crude material was purified by combi flash column chromatography using 0-10% ethyl acetate in heptane as an eluent to afford tributyl[5-(²H₃)methoxy-2-pyridyl] stannane (0.8 g, 1.67 mmol, 35%) as yellow liquid.

[0701] Analytical data:

LCMS: 84.10% (m/z: 402.75, [M+1]⁺, 3.15 min (4 min run).

[0702] Step 3: Synthesis of (R)-6-[(S)-1-{(1S, 2R, 6S, 7R, 9R, 11S, 12S, 15R, 16S)-6-hydroxy-4-[5-(²H₃) methoxy-2-pyridyl]-2, 16-dimethyl-3-oxo-8-oxapentacyclo [9.7.0.0^{2,7},^{9,0}^{12,16}] octadec-4-en-15-yl} ethyl] -3-(hydroxymethyl)-4-methyl-5, 6-dihydro-2H-pyran-2-one

To the stirred solution of (R)-6-[(S)-1-{(1S, 2R, 6S, 7R, 9R, 11S, 12S, 15R, 16S)-6-hydroxy-4-iodo-2, 16-dimethyl-3-oxo-8-oxapentacyclo [9.7.0.0^{2,7},^{9,0}^{12,16}] octadec-4-en-15-yl} ethyl]-3-(hydroxymethyl)-4-methyl-5, 6-dihydro-2H-pyran-2-one (0.6 g, 1.01 mmol) in

tetrahydrofuran (8 mL) were added tributyl[5-(²H₃)methoxy-2-pyridyl] stannane (0.404 g, 1.01 mmol), copper iodide (0.19 g, 0.1 eq., 0.101 mmol) and triphenylarsine (0.031 g, 0.1 eq., 0.101 mmol) at room temperature. Reaction mixture was purged with argon gas for 30 minutes, then Tris (dibenzylideneacetone)dipalladium (0.092g, 0.1 eq., 0.101 mmol) was added to it and again purged with argon for 5 minutes. The reaction mixture was stirred for 2 hours at 80°C. After completion of the reaction (monitored by TLC & LCMS), it was quenched by adding water (50 mL) and extracted using ethyl acetate (2 x 50 mL). Collected organics, dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure to obtain crude. Crude product was purified by combi flash column chromatography using (90-100%) ethyl acetate in heptane as an eluent followed by Prep HPLC purification in ammonium bicarbonate method to afford (R)-6-[(S)-1-{(1S, 2R, 6S, 7R, 9R, 11S, 12S, 15R, 16S)-6-hydroxy-4-[5-(²H₃)methoxy-2-pyridyl]-2, 16-dimethyl-3-oxo-8-oxapentacyclo [9.7.0.0^{2,7}.0^{7,9}.0^{12,16}] octadec-4-en-15-yl} ethyl] -3-(hydroxymethyl)-4-methyl-5, 6-dihydro-2H-pyran-2-one (0.120 g, 0.207 mmol, 20%) as white solid.

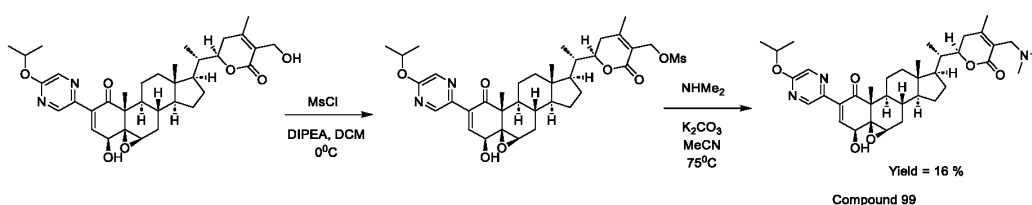
[0703] Analytical data:

LCMS: 97.09% (m/z: 581.5, [M+1]⁺), 5.50 min (10 min run).

¹H-NMR (400 MHz, DMSO-*d*₆): δ 8.31 (d, *J* = 2.8 Hz, 1H), 7.55 (d, *J* = 6.8 Hz, 1H), 7.43 – 7.34 (m, 2H), 5.68 (d, *J* = 3.2 Hz, 1H), 4.57 (t, *J* = 5.6 Hz, 1H), 4.29-4.26 (m, 1H), 4.18-4.07 (m, 2H), 3.74-3.71 (m, 1H), 3.14 (s, 1H), 2.41-2.32 (m, 1H), 2.11-2.01 (m, 2H), 1.99 (s, 3H), 1.93-1.89 (m, 1H), 1.83-1.77 (m, 1H), 1.76-1.70 (m, 1H), 1.59-1.54 (m, 1H), 1.40-1.21 (m, 8H), 1.14-1.03 (m, 3H), 0.96 – 0.81 (m, 5H), 0.66 (s, 3H).

¹³C-NMR (400 MHz, DMSO-*d*₆): δ 200.76, 165.29, 155.09, 154.63, 144.69, 140.62, 137.61, 125.43, 122.61, 120.51, 77.50, 68.54, 63.57, 57.53, 55.32, 54.50, 51.02, 47.89, 42.13, 41.99, 38.47, 38.36, 30.78, 29.24, 29.01, 26.49, 23.94, 20.52, 19.87, 15.09, 13.01, 11.23.

[0704] Synthesis of Compound 99



[0705] **Step 1: Synthesis of ((R)-6-((S)-1-((4S, 4aR, 5aR, 6aS, 6bS, 9R, 9aS, 11aS, 11bR)-4-hydroxy-2-(5-isopropoxy-pyrazin-2-yl)-9a, 11b-dimethyl-1-oxo-1, 4, 5a, 6, 6a, 6b, 7, 8, 9, 9a, 10, 11, 11a, 11b-tetradecahydrocyclopenta [1, 2] phenanthro [8a, 9-b] oxiren-9-yl) ethyl)-4-methyl-2-oxo-5, 6-dihydro-2H-pyran-3-yl) methyl methanesulfonate:**

(R)-6-[(S)-1-{(1S, 2R, 6S, 7R, 9R, 11S, 12S, 15R, 16S)-6-hydroxy-4-(5-isopropoxy-2-pyrazinyl)-2, 16-dimethyl-3-oxo-8-oxapentacyclo [9.7.0.0^{2,7}.0^{7,9}.0^{12,16}] octadec-4-en-15-yl} ethyl]-3-(hydroxymethyl)-4-methyl-5, 6-dihydro-2H-pyran-2-one (0.3 g, 494 μ mol) was dissolved in 3 ml of DCM under N₂-atmosphere. The reaction mixture was placed on an ice bath and stirred for 15 min at -10°C. Followed by N-ethylbis (isopropyl) amine (215 μ L, 2.5 eq., 1.24 mmol) and (chlorosulfonyl) methane (49.3 μ L, 494 μ mol) were added one by one at -10°C under N₂-atmosphere. After 1 hour, the reaction mixture was quenched using ice water. Further, the reaction mixture was extracted with DCM twice and dried over Na₂SO₄. The organic layer was evaporated and dried. The crude was used for the next step without any further purification.

[0706] **Step 2: Synthesis of (4S, 4aR, 5aR, 6aS, 6bS, 9R, 9aS, 11aS, 11bR)-9-((S)-1-((R)-5-((dimethylamino) methyl)-4-methyl-6-oxo-3, 6-dihydro-2H-pyran-2-yl) ethyl)-4-hydroxy-2-(5-isopropoxy-pyrazin-2-yl)-9a, 11b-dimethyl-5a, 6, 6a, 6b, 7, 8, 9, 9a, 10, 11, 11a, 11b-dodecahydrocyclopenta [1, 2] phenanthro [8a, 9-b] oxiren-1(4H)-one**

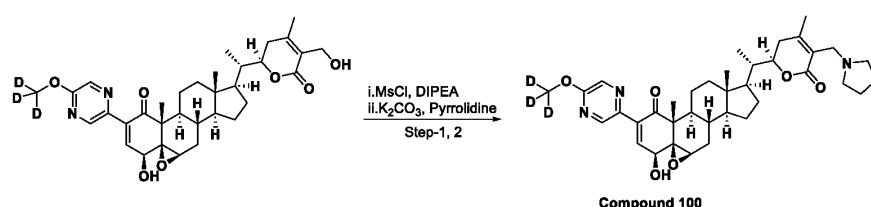
Mixture A: The crude reaction mixture of step 1 was dissolved in 3 ml of acetonitrile at 0°C under N₂ atmosphere.

Mixture B: Dipotassium carbonate (137 mg, 2 eq., 989 μ mol) and dimethylamine (33.4 mg, 1.5 eq., 742 μ mol) were dissolved in 3 ml of acetonitrile under N₂-atm. Further the reaction mixture was placed on an ice bath for 15 min. Finally, the acetonitrile solution of crude (mixture A) was added to the reaction mixture at 0°C under N₂ atm. After 5 min, the reaction mixture was removed from the ice bath and heated to 75°C for 1 hour under N₂-atm. The reaction mixture was cooled at ambient temperature and TLC was taken. A new polar spot was identified in comparison to Compound 55. The reaction mixture was filtered and concentrated. The concentrated mass was dissolved in DCM and washed with water. The organic layer was dried over Na₂SO₄. The crude was obtained after evaporation of DCM. Finally, the desired product was purified by HPLC. The desired product was isolated with 16% of yield.

[0707] Analytical data:

LCMS: purity 94.06 % (m/z: 634.61, [M+H]⁺, 2.97 min (5.5 min run).

¹H NMR (400 MHz, MeOD): δ 8.28 (d, J = 1.5 Hz, 1H), 8.13 (d, J = 1.5 Hz, 1H), 7.62 (d, J = 6.9 Hz, 1H), 5.32 (p, J = 6.1 Hz, 1H), 4.44 (dt, J = 13.1, 3.4 Hz, 1H), 3.85 (d, J = 6.8 Hz, 1H), 3.56 – 3.47 (m, 1H), 3.23 (d, J = 12.8 Hz, 1H), 3.17 (s, 1H), 2.54 (m, 1H), 2.31 (s, 6H), 2.22 – 2.13 (m, 2H), 2.07 (s, 3H), 2.03 – 1.93 (m, 2H), 1.84 – 1.67 (m, 2H), 1.51 (m, 2H), 1.44 (s, 4H), 1.37 (m, 7H), 1.31 (d, J = 13.3 Hz, 1H), 1.25 – 1.11 (m, 4H), 1.06 – 0.95 (m, 5H), 0.76 (s, 3H).

[0708] Synthesis of Compound 100

[0709] Step 1: Synthesis of ((R)-6-((S)-1-((4S, 4aR, 5aR, 6aS, 6bS, 9R, 9aS, 11aS, 11bR)-4-hydroxy-2-(5-(methoxy-d3) pyrazin-2-yl)-9a, 11b-dimethyl-1-oxo-1, 4, 5a, 6, 6a, 6b, 7, 8, 9, 9a, 10, 11, 11a, 11b-tetradecahydrocyclopenta [1, 2] phenanthro [8a, 9-b] oxiren-9-yl) ethyl)-4-methyl-2-oxo-5, 6-dihydro-2H-pyran-3-yl) methyl methane sulfonate :

To a stirred solution of (R)-6-[(S)-1-{(1S, 2R, 6S, 7R, 9R, 11S, 12S, 15R, 16S)-6-hydroxy-4-[5-(²H₃) methoxy-2-pyrazinyl]-2, 16-dimethyl-3-oxo-8-oxapentacyclo [9.7.0.0^{2,7}.0^{7,9}.0^{12,16}] octadec-4-en-15-yl} ethyl]-3-(hydroxymethyl)-4-methyl-5, 6-dihydro-2H-pyran-2-one (0.2 g, 344 μmol) in dichloromethane (4 mL) was added ethylbis (propan-2-yl) amine (111 mg, 2.5 eq., 860 μmol) followed by methanesulfonyl chloride (39.4 mg, 344 μmol) at -10°C. The reaction mixture was stirred at -10°C for 1 hour. Reaction was monitored by TLC, the reaction mixture was quenched with water (20 mL) and extracted with DCM (2 X 20 mL). The organic layer was washed with saturated brine, dried the organics over anhydrous sodium sulphate, filtered and concentrated under reduced pressure to get ((R)-6-((S)-1-((4S, 4aR, 5aR, 6aS, 6bS, 9R, 9aS, 11aS, 11bR)-4-hydroxy-2-(5-(methoxy-d3) pyrazin-2-yl)-9a, 11b-dimethyl-1-oxo-1,

4, 5a, 6, 6a, 6b, 7, 8, 9, 9a, 10, 11, 11a, 11b-tetradecahydrocyclopenta [1, 2] phenanthro [8a, 9-b] oxiren-9-yl) ethyl)-4-methyl-2-oxo-5, 6-dihydro-2H-pyran-3-yl) methyl methanesulfonate (220 mg crude) as crude. It was used as such for the next step.

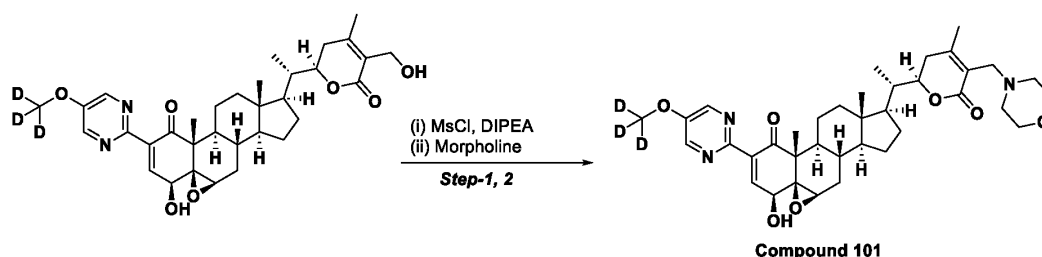
[0710] Step 2: Synthesis of (4S, 4aR, 5aR, 6aS, 6bS, 9R, 9aS, 11aS, 11bR)-4-hydroxy-2-(5-(methoxy-d3) pyrazin-2-yl)-9a, 11b-dimethyl-9-((S)-1-((R)-4-methyl-6-oxo-5-(pyrrolidin-1-ylmethyl)-3, 6-dihydro-2H-pyran-2-yl)ethyl)-5a, 6, 6a, 6b, 7, 8, 9, 9a, 10, 11, 11a, 11b-dodecahydrocyclopenta [1, 2] phenanthro [8a, 9-b] oxiren-1(4H)-one :

To a stirred solution of dipotassium carbonate (115 mg, 2.5 eq., 834 μ mol) in acetonitrile (4.4 mL) was added pyrrolidine (59.3 mg, 2.5 eq., 834 μ mol) followed by addition of (R)-6-[(S)-1-((1S, 2R, 6S, 7R, 9R, 11S, 12S, 15R, 16S)-6-hydroxy-4-[5-(²H₃) methoxy-2-pyrazinyl]-2, 16-dimethyl-3-oxo-8-oxapentacyclo [9.7.0.0.2^{7,7}, 9.0^{12,16}] octadec-4-en-15-yl} ethyl]-3-[(mesyloxy) methyl]-4-methyl-5, 6-dihydro-2H-pyran-2-one (220 mg, 333 μ mol) at 0°C. The resultant reaction mixture was stirred at room temperature for 30 minutes. After the completion of reaction (monitored by TLC), it was quenched with water (30 mL) and extracted with ethyl acetate (2 X 30 mL). The organic layer was washed with saturated brine. The collected organics, dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure to obtain crude. Crude was purified by using preparative -HPLC, using 5 mM ammonium bicarbonate in Water, acetonitrile method to afford (4S, 4aR, 5aR, 6aS, 6bS, 9R, 9aS, 11aS, 11bR)-4-hydroxy-2-(5-(methoxy-d3) pyrazin-2-yl)-9a, 11b-dimethyl-9-((S)-1-((R)-4-methyl-6-oxo-5-(pyrrolidin-1-ylmethyl)-3, 6-dihydro-2H-pyran-2-yl)ethyl)-5a, 6, 6a, 6b, 7, 8, 9, 9a, 10, 11, 11a, 11b-dodecahydrocyclopenta [1, 2] phenanthro [8a, 9-b] oxiren-1(4H)-one (16 mg, 6.88%) as a white solid.

[0711] Analytical data:

LCMS: 94.13% (m/z: 635.5, [M+1]⁺, 5.36 min (10 min run).

¹H-NMR (400 MHz, DMSO-*d*₆): δ 8.36 (d, *J* = 1.6 Hz, 1H), 8.21 (d, *J* = 1.6 Hz, 1H), 7.60 (d, *J* = 6.8 Hz, 1H), 5.75 (d, *J* = 3.2 Hz, 1H), 4.28-4.25 (m, 1H), 3.76-3.74 (m, 1H), 3.38 (s, 1H), 3.16-3.14 (m, 2H), 2.37 - 2.33 (m, 5H), 2.10 - 2.09 (m, 2H), 2.05 - 2.01 (m, 1H), 1.98 (s, 3H), 1.91 - 1.89 (m, 1H), 1.80-1.71 (m, 2H), 1.61-1.57 (m, 4H), 1.54-1.50 (m, 1H), 1.39-1.38 (m, 2H), 1.34-1.31 (m, 4H), 1.28-1.23 (m, 2H), 1.11-1.03 (m, 3H), 0.92-0.85 (m, 5H), 0.65 (s, 3H).

[0712] Synthesis of Compound 101

[0713] Synthesis of (R)-6-[(S)-1-{(1S, 2R, 6S, 7R, 9R, 11S, 12S, 15R, 16S)-6-hydroxy-4-[5-(²H₃) methoxy-2-pyrimidinyl]-2, 16-dimethyl-3-oxo-8-oxapentacyclo [9.7.0.0^{2,7}.0^{7,9}.0^{12,16}] octadec-4-en-15-yl} ethyl]-4-methyl-3-(morpholinomethyl)-5, 6-dihydro-2H-pyran-2-one

Step 1: To a stirred solution of (R)-6-[(S)-1-{(1S, 2R, 6S, 7R, 9R, 11S, 12S, 15R, 16S)-6-hydroxy-4-[5-(²H₃) methoxy-2-pyrimidinyl]-2, 16-dimethyl-3-oxo-8-oxapentacyclo [9.7.0.0^{2,7}.0^{7,9}.0^{12,16}] octadec-4-en-15-yl} ethyl]-3-(hydroxymethyl)-4-methyl-5, 6-dihydro-2H-pyran-2-one (130 mg, 223 μ mol) in dichloromethane (3 mL) was added ethylbis (propan-2-yl)amine (72.2 mg, 2.5 eq., 559 μ mol) then methanesulfonyl chloride (25.6 mg, 223 μ mol) at -20°C. The reaction mixture was stirred at -20°C for 1h. After completion of reaction (monitored by TLC, 5% MeOH in DCM), mixture was quenched with water (20 mL) and extracted with DCM (2 X 30 mL). The organic layer was washed with saturated brine solution, dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure to get (R)-6-[(S)-1-{(1S, 2R, 6S, 7R, 9R, 11S, 12S, 15R, 16S)-6-hydroxy-4-[5-(²H₃) methoxy-2-pyrimidinyl]-2, 16-dimethyl-3-oxo-8-oxapentacyclo [9.7.0.0^{2,7}.0^{7,9}.0^{12,16}] octadec-4-en-15-yl} ethyl]-3-[(mesyloxy) methyl]-4-methyl-5, 6-dihydro-2H-pyran-2-one (133 mg crude). It was forwarded as such to the next step.

Step 2: To a stirred solution of dipotassium carbonate (55.7 mg, 2 eq., 403 μ mol) in acetonitrile (3 mL) was added morpholine (26.3 mg, 1.5 eq., 302 μ mol) followed by addition of (R)-6-[(S)-1-{(1S, 2R, 6S, 7R, 9R, 11S, 12S, 15R, 16S)-6-hydroxy-4-[5-(²H₃) methoxy-2-pyrimidinyl]-2, 16-dimethyl-3-oxo-8-oxapentacyclo [9.7.0.0^{2,7}.0^{7,9}.0^{12,16}] octadec-4-en-15-yl} ethyl]-3-[(mesyloxy) methyl]-4-methyl-5, 6-dihydro-2H-pyran-2-one (133 mg, 202 μ mol) at 0°C. The resultant reaction mixture was stirred at room temperature for 15 min. After the completion of reaction (monitored by TLC, 5% MeOH in DCM), mixture was quenched with water (20 mL) and extracted with ethyl acetate (2 X 30 mL). The organic layer was washed with saturated

brine solution, dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure. The crude product was purified by Prep HPLC. Purification in ammonium bicarbonate method to afford (R)-6-[(S)-1-[(1S, 2R, 6S, 7R, 9R, 11S, 12S, 15R, 16S)-6-hydroxy-4-[5-(²H₃) methoxy-2-pyrimidinyl]-2, 16-dimethyl-3-oxo-8-oxapentacyclo [9.7.0.0.2⁷,7.0⁷,9.0¹²,16] octadec-4-en-15-yl] ethyl]-4-methyl-3-(morpholinomethyl)-5, 6-dihydro-2H-pyran-2-one (30 mg, 22.6%) as white solid.

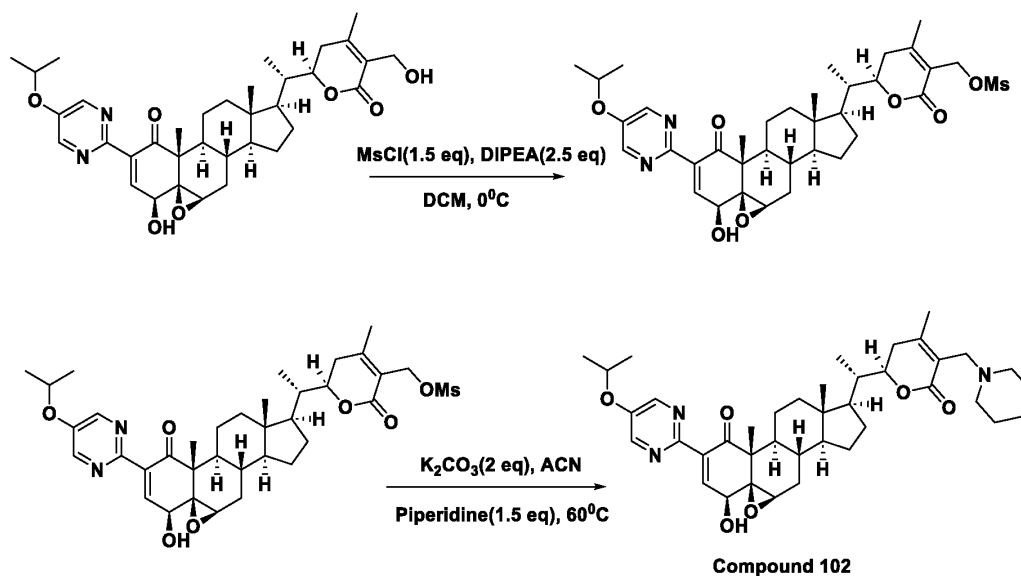
[0714] Analytical data:

LCMS: 99.84 % (m/z: 651.6, [M+1]⁺, 5.69 min (10 min run).

¹H-NMR (400 MHz, DMSO-*d*₆): δ 8.57 (s, 2H), 7.52 (d, *J* = 6.4 Hz, 1H), 5.74 (s, 1H), 4.31-4.27 (m, 1H), 3.72 (d, *J* = 6.8 Hz, 1H), 3.52-3.49 (m, 4H), 3.25 (d, *J* = 12.8 Hz, 1H), 3.13 (s, 1H), 3.06 (d, *J* = 12.4 Hz, 1H), 2.41-2.37 (m, 1H), 2.31-2.30 (m, 4H), 2.14-2.13 (m, 1H), 2.09-2.00 (m, 4H), 1.92-1.89 (m, 1H), 1.81-1.77 (m, 2H), 1.57-1.48 (m, 2H), 1.32-1.23 (m, 7H), 1.13-0.95 (m, 3H), 1.00 - 0.91 (m, 5H), 0.65 (s, 3H).

¹³C-NMR (100 MHz, DMSO-*d*₆): δ 199.02, 165.45, 155.94, 155.21, 152.05, 143.60, 141.43, 139.94, 121.34, 77.42, 68.57, 66.22, 63.83, 57.45, 55.48, 53.00, 52.57, 51.09, 47.83, 42.06, 41.80, 30.90, 29.27, 29.06, 26.54, 23.93, 20.46, 20.20, 14.82, 13.10, 11.24.

[0715] Synthesis of Compound 102



[0716] Step-1: Synthesis of ((R)-6-((S)-1-((4S, 4aR, 5aR, 6aS, 6bS, 9R, 9aS, 11aS, 11bR)-4-hydroxy-2-(5-isopropoxy-2-pyrimidin-2-yl)-9a, 11b-dimethyl-1-oxo-1, 4, 5a, 6, 6a, 6b, 7, 8, 9, 9a, 10, 11, 11a, 11b-tetradecahydrocyclopenta [1, 2] phenanthro [8a, 9-b] oxiren-9-yl) ethyl)-4-methyl-2-oxo-5, 6-dihydro-2H-pyran-3-yl) methyl methane sulfonate

To a stirred solution of (R)-6-[(S)-1-{(1S, 2R, 6S, 7R, 9R, 11S, 12S, 15R, 16S)-6-hydroxy-4-(5-isopropoxy-2-pyrimidin-2-yl)-2, 16-dimethyl-3-oxo-8-oxapentacyclo [9.7.0.0.0^{2,7}, 9.0^{12,16}] octadec-4-en-15-yl} ethyl]-3-(hydroxymethyl)-4-methyl-5, 6-dihydro-2H-pyran-2-one (0.5 g, 824 µmol) in DCM (10 mL) was added N-ethylbis (isopropyl)amine (359 µL, 2.5 eq., 2.06 mmol) and (chlorosulfonyl) methane (95.7 µL, 1.5 eq., 1.24 mmol) at 0°C. Reaction was allowed to stir at 0°C for 5 min. After 50% conversion of starting material completion, reaction was quenched by water and extracted with DCM. The organic layer was concentrated under reduced pressure to get crude. Crude ((R)-6-((S)-1-((4S, 4aR, 5aR, 6aS, 6bS, 9R, 9aS, 11aS, 11bR)-4-hydroxy-2-(5-isopropoxy-2-pyrimidin-2-yl)-9a, 11b-dimethyl-1-oxo-1, 4, 5a, 6, 6a, 6b, 7, 8, 9, 9a, 10, 11, 11a, 11b-tetradecahydrocyclopenta [1, 2] phenanthro [8a, 9-b] oxiren-9-yl) ethyl)-4-methyl-2-oxo-5, 6-dihydro-2H-pyran-3-yl) methyl methane sulfonate (600 mg) as such used for next step.

[0717] Analytical data:

LCMS: 64.75% (m/z: 685.55, [M+1], 2.25 min (5 min run).

[0718] Step 2: Synthesis of (4S, 4aR, 5aR, 6aS, 6bS, 9R, 9aS, 11aS, 11bR)-4-hydroxy-2-(5-isopropoxy-2-pyrimidin-2-yl)-9a, 11b-dimethyl-9-((S)-1-((R)-4-methyl-6-oxo-5-(piperidin-1-ylmethyl)-3, 6-dihydro-2H-pyran-2-yl) ethyl)-5a, 6, 6a, 6b, 7, 8, 9, 9a, 10, 11, 11a, 11b-dodecahydrocyclopenta [1, 2] phenanthro [8a, 9-b] oxiren-1(4H)-one

To a stirred solution of piperidine (105 mg, 1.5 eq., 1.24 mmol) in acetonitrile (2 mL, 95.7 mmol) was added dipotassium carbonate (228 mg, 2 eq., 1.65 mmol) at 00C. After 5 min was added ((R)-6-((S)-1-((4S, 4aR, 5aR, 6aS, 6bS, 9R, 9aS, 11aS, 11bR)-4-hydroxy-2-(5-isopropoxy-2-pyrimidin-2-yl)-9a, 11b-dimethyl-1-oxo-1, 4, 5a, 6, 6a, 6b, 7, 8, 9, 9a, 10, 11, 11a, 11b-tetradecahydrocyclopenta [1, 2] phenanthro [8a, 9-b] oxiren-9-yl) ethyl)-4-methyl-2-oxo-5, 6-dihydro-2H-pyran-3-yl) methyl methane sulfonate (600 mg) by dissolving into acetonitrile (7 mL, 95.7 mmol) drop wise. The resulting mixture was stirred at 600C for 15 min. Reaction was monitored by TLC. After completion, the reaction mixture was quenched with cool water

(100 mL) and was extracted with Ethyl acetate (2 x 200mL). The organic layer was dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure. The crude material was enriched and purified by Combi Flash by using 5% of MeOH in DCM and then purified by Prep-HPLC in (Ammonium Bicarbonate method) to afford (R)-6-[(S)-1-{(1S, 2R, 6S, 7R, 9R, 11S, 12S, 15R, 16S)-6-hydroxy-4-(5-isopropoxy-2-pyrimidinyl)-2, 16-dimethyl-3-oxo-8-oxapentacyclo [9.7.0.0^{2,7}.0^{7,9}.0^{12,16}] octadec-4-en-15-yl} ethyl]-4-methyl-3-(piperidinomethyl)-5, 6-dihydro-2H-pyran-2-one (27 mg, 39.2 μ mol) as off white solid. Yield: 4.12%.

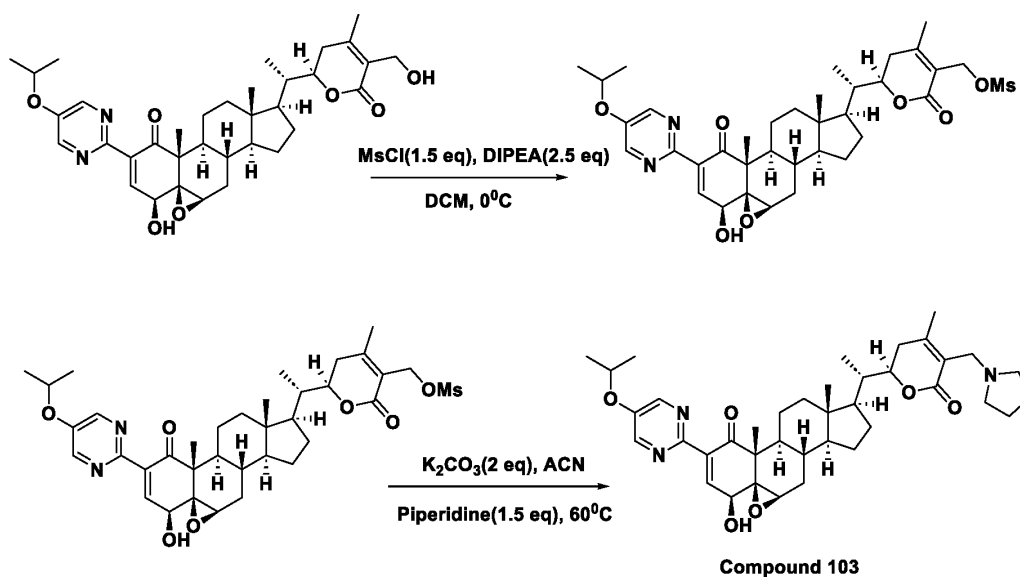
[0719] Analytical data:

LCMS: 95.49% (m/z: 674.58, [M+1], 2.46 min (5 min run).

HPLC: 88.23% at rt 7.05 (20 min run).

¹H-NMR (400 MHz, DMSO-*d*₆): ¹H-NMR (400 MHz, DMSO-*d*₆): δ 8.54 (s, 2H), 7.53 (d, J = 6.80 Hz, 1H), 5.73 (d, J = 2.80 Hz, 1H), 4.29-4.26 (m, 1H), 3.72 (dd, J = 2.80, 6.60 Hz, 1H), 3.22-3.13 (m, 3H), 3.00 (dd, J = 12.40, Hz, 1H), 2.51-2.49 (m, 2H), 2.28-2.27 (m, 4H), 2.13 (d, J = 3.20 Hz, 1H), 2.09 (d, J = 2.00 Hz, 2H), 2.01 (d, J = 18.00 Hz, 3H), 1.91 (d, J = 12.40 Hz, 1H), 1.81 (m, 3H), 1.49 (m, 3H), 1.43-1.42 (m, 5H), 1.34 (s, 3H), 1.23 (s, 3H), 1.15-1.07 (m, 6H), 0.93 (dd, J = 6.80, Hz, 5H), 0.66 (s, 3H),

[0720] Synthesis of Compound 103



[0721] Step 1: Synthesis of ((R)-6-((S)-1-((4S, 4aR, 5aR, 6aS, 6bS, 9R, 9aS, 11aS, 11bR)-4-hydroxy-2-(5-isopropoxy-2-pyrimidin-2-yl)-9a, 11b-dimethyl-1-oxo-1, 4, 5a, 6, 6a, 6b, 7, 8, 9, 9a, 10, 11, 11a, 11b-tetradecahydrocyclopenta [1, 2] phenanthro [8a, 9-b] oxiren-9-yl) ethyl)-4-methyl-2-oxo-5, 6-dihydro-2H-pyran-3-yl) methyl methane sulfonate

To a stirred solution of (R)-6-[(S)-1-{(1S, 2R, 6S, 7R, 9R, 11S, 12S, 15R, 16S)-6-hydroxy-4-(5-isopropoxy-2-pyrimidin-2-yl)-2, 16-dimethyl-3-oxo-8-oxapentacyclo [9.7.0.0^{2,7},9.0^{12,16}] octadec-4-en-15-yl} ethyl]-3-(hydroxymethyl)-4-methyl-5, 6-dihydro-2H-pyran-2-one (0.5 g, 824 µmol) in DCM (10 mL) was added N-ethylbis (isopropyl) amine (359 µL, 2.5 eq., 2.06 mmol) and (chlorosulfonyl) methane (95.7 µL, 1.5 eq., 1.24 mmol) at 0°C. Reaction was allowed to stir at 0°C for 5 min. After 50% conversion of starting material completion, reaction was quenched by water and extracted with DCM. The organic layer was concentrated under reduced pressure to get crude. The crude ((R)-6-((S)-1-((4S, 4aR, 5aR, 6aS, 6bS, 9R, 9aS, 11aS, 11bR)-4-hydroxy-2-(5-isopropoxy-2-pyrimidin-2-yl)-9a, 11b-dimethyl-1-oxo-1, 4, 5a, 6, 6a, 6b, 7, 8, 9, 9a, 10, 11, 11a, 11b-tetradecahydrocyclopenta [1, 2] phenanthro [8a, 9-b] oxiren-9-yl) ethyl)-4-methyl-2-oxo-5, 6-dihydro-2H-pyran-3-yl) methyl methane sulfonate (540 mg) as such used for next step.

[0722] Analytical data:

LCMS: 51% (m/z: 685.55, [M+1], 2.30 min (5 min run).

[0723] Step 2: Synthesis of (R)-6-[(S)-1-{(1S, 2R, 6S, 7R, 9R, 11S, 12S, 15R, 16S)-6-hydroxy-4-(5-isopropoxy-2-pyrimidin-2-yl)-2, 16-dimethyl-3-oxo-8-oxapentacyclo [9.7.0.0^{2,7},9.0^{12,16}] octadec-4-en-15-yl} ethyl]-4-methyl-3-[(1-pyrrolidinyl) methyl]-5, 6-dihydro-2H-pyran-2-one

To a stirred solution of pyrrolidine (87.9 mg, 1.5 eq., 1.24 mmol) in acetonitrile (2 mL, 95.7 mmol) was added dipotassium carbonate (228 mg, 2 eq., 1.65 mmol) at 0°C. After 5 min was added ((R)-6-((S)-1-((4S, 4aR, 5aR, 6aS, 6bS, 9R, 9aS, 11aS, 11bR)-4-hydroxy-2-(5-isopropoxy-2-pyrimidin-2-yl)-9a, 11b-dimethyl-1-oxo-1, 4, 5a, 6, 6a, 6b, 7, 8, 9, 9a, 10, 11, 11a, 11b-tetradecahydrocyclopenta [1, 2] phenanthro [8a, 9-b] oxiren-9-yl) ethyl)-4-methyl-2-oxo-5, 6-dihydro-2H-pyran-3-yl) methyl methane sulfonate (540 mg) by dissolving into acetonitrile (7 mL, 95.7 mmol) drop wise. The resulting mixture was stirred at 60°C for 15 min. Reaction was monitored by TLC. After completion, the reaction mixture was quenched with cool water

(100 mL) and was extracted with Ethyl acetate (2 x 200mL). The organic layer was dried over anhydrous sodium sulphate, filtered, and concentrated under reduced pressure. The crude material was enriched and purified by Combi Flash by using 5% of MeOH in DCM and then purified by Prep-HPLC in (Ammonium Bicarbonate method) to afford (R)-6-[(S)-1-[(1S, 2R, 6S, 7R, 9R, 11S, 12S, 15R, 16S)-6-hydroxy-4-(5-isopropoxy-2-pyrimidinyl)-2, 16-dimethyl-3-oxo-8-oxapentacyclo [9.7.0.0^{2,7}.0^{7,9}.0^{12,16}] octadec-4-en-15-yl} ethyl]-4-methyl-3-[(1-pyrrolidinyl) methyl]-5, 6-dihydro-2H-pyran-2-one (3 mg, 4.46 μ mol) as off white solid.

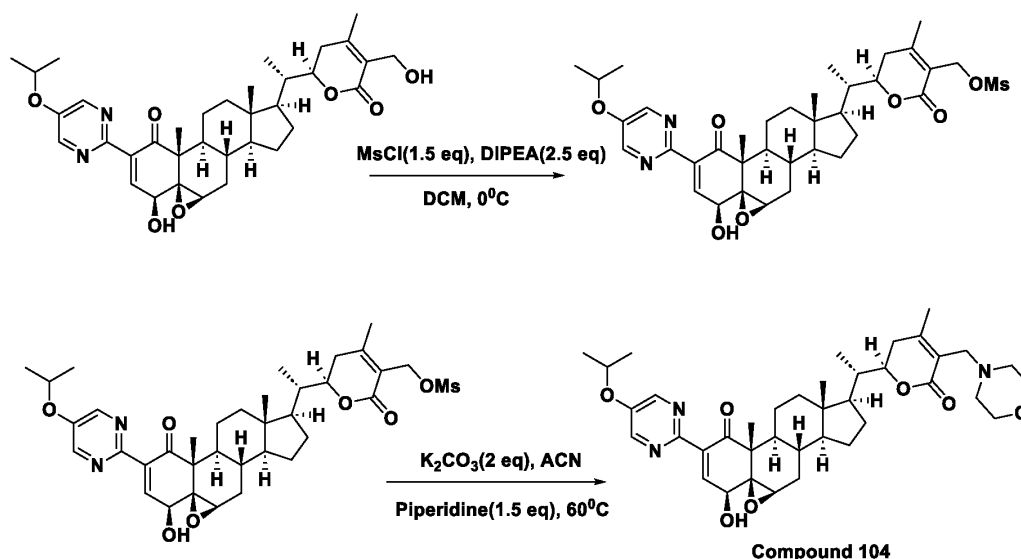
[0724] Analytical data:

LCMS: 98.04% (m/z:658.67 [M+1], 3.54min (5 min run).

HPLC: 96.12 % at 7.804 rt (20 min run).

¹H-NMR (400 MHz, DMSO-*d*₆): ¹H-NMR (400 MHz, DMSO-*d*₆): δ 8.68 (s, 2H), 7.20 (s, 1H), 6.52 (s, 2H), 6.28 (s, 1H), 4.92-4.89 (m, 1H), 4.34 (d, J = 10.80 Hz, 1H), 3.50 (d, J = 6.80 Hz, 2H), 2.04 (s, 5H), 1.88 (d, J = -34.80 Hz, 2H), 1.69-1.64 (m, 9H), 1.43-1.41 (m, 3H), 1.34 (dd, J = 6.00, Hz, 8H), 1.23 (s, 6H), 1.06 (m, 3H), 1.06 (d, J = Hz, 3H), 0.69 (s, 4H),

[0725] Synthesis of Compound 104



[0726] Step 1: Synthesis of ((R)-6-((S)-1-((4S, 4aR, 5aR, 6aS, 6bS, 9R, 9aS, 11aS, 11bR)-4-hydroxy-2-(5-isopropoxypyrimidin-2-yl)-9a, 11b-dimethyl-1-oxo-1, 4, 5a, 6, 6a, 6b, 7, 8, 9, 9a, 10, 11, 11a, 11b-tetradecahydrocyclopenta [1, 2] phenanthro [8a, 9-b]

oxiren-9-yl) ethyl)-4-methyl-2-oxo-5, 6-dihydro-2H-pyran-3-yl) methyl methane sulfonate

To a stirred solution of (R)-6-[(S)-1-{(1S, 2R, 6S, 7R, 9R, 11S, 12S, 15R, 16S)-6-hydroxy-4-(5-isopropoxy-2-pyrimidinyl)-2, 16-dimethyl-3-oxo-8-oxapentacyclo [9.7.0.0^{2,7},^{9,0}^{12,16}] octadec-4-en-15-yl} ethyl]-3-(hydroxymethyl)-4-methyl-5, 6-dihydro-2H-pyran-2-one (340 g, 560 μmol) in DCM (10 mL) was added N-ethylbis(isopropyl)amine (181 mg, 2.5 eq., 2.06 mmol) and (chlorosulfonyl) methane (77 mg, 1.2 eq., 672 μmol) at 0°C. Reaction was allowed to stir at 0°C for 5 min. After starting material completion, reaction was quenched by water and extracted with DCM. The organic layer was concentrated under reduced pressure to get crude. Crude ((R)-6-((S)-1-((4S, 4aR, 5aR, 6aS, 6bS, 9R, 9aS, 11aS, 11bR)-4-hydroxy-2-(5-isopropoxypyrimidin-2-yl)-9a, 11b-dimethyl-1-oxo-1, 4, 5a, 6, 6a, 6b, 7, 8, 9, 9a, 10, 11, 11a, 11b-tetradecahydrocyclopenta [1, 2] phenanthro [8a, 9-b] oxiren-9-yl) ethyl)-4-methyl-2-oxo-5, 6-dihydro-2H-pyran-3-yl) methyl methane sulfonate (400 mg) as such used for next step.

[0727] Analytical data:

LCMS: 44.84% (m/z: 685.55, [M+1], 2.25min (5 min run).

[0728] Step 2: Synthesis of (R)-6-[(S)-1-{(1S, 2R, 6S, 7R, 9R, 11S, 12S, 15R, 16S)-6-hydroxy-4-(5-isopropoxy-2-pyrimidinyl)-2, 16-dimethyl-3-oxo-8-oxapentacyclo [9.7.0.0^{2,7},^{9,0}^{12,16}] octadec-4-en-15-yl} ethyl]-4-methyl-3-(morpholinomethyl)-5, 6-dihydro-2H-pyran-2-one

To a stirred solution of morpholine (73.2 mg, 1.5 eq., 841 μmol) in acetonitrile (2 mL, 95.7 mmol) was added dipotassium carbonate (155 mg, 2 eq., 1.12 mmol) at 0°C. After 5 min was added ((R)-6-((S)-1-((4S, 4aR, 5aR, 6aS, 6bS, 9R, 9aS, 11aS, 11bR)-4-hydroxy-2-(5-isopropoxypyrimidin-2-yl)-9a, 11b-dimethyl-1-oxo-1, 4, 5a, 6, 6a, 6b, 7, 8, 9, 9a, 10, 11, 11a, 11b-tetradecahydrocyclopenta [1, 2] phenanthro [8a, 9-b] oxiren-9-yl) ethyl)-4-methyl-2-oxo-5, 6-dihydro-2H-pyran-3-yl) methyl methane sulfonate (400 mg) by dissolving into acetonitrile (7 mL, 95.7 mmol) drop wise. The resulting mixture was stirred at 60°C for 15 min. Reaction was monitored by TLC. After completion, the reaction mixture was quenched with cool water (100 mL) and was extracted with Ethyl acetate (2 x 200mL). The organic layer was dried over anhydrous sodium sulphate, filtered, and concentrated under reduced pressure. The crude material was enriched and purified by Combi Flash by using 5% of MeOH in DCM and then purified by Prep-HPLC in (Ammonium Bicarbonate method) to afford (R)-6-[(S)-1-{(1S,

2R, 6S, 7R, 9R, 11S, 12S, 15R, 16S)-6-hydroxy-4-(5-isopropoxy-2-pyrimidinyl)-2, 16-dimethyl-3-oxo-8-oxapentacyclo [9.7.0.0^{2,7},^{9,10},¹⁶] octadec-4-en-15-yl} ethyl]-4-methyl-3-(morpholinomethyl)-5, 6-dihydro-2H-pyran-2-one (20 mg, 29 μ mol) as off white solid.

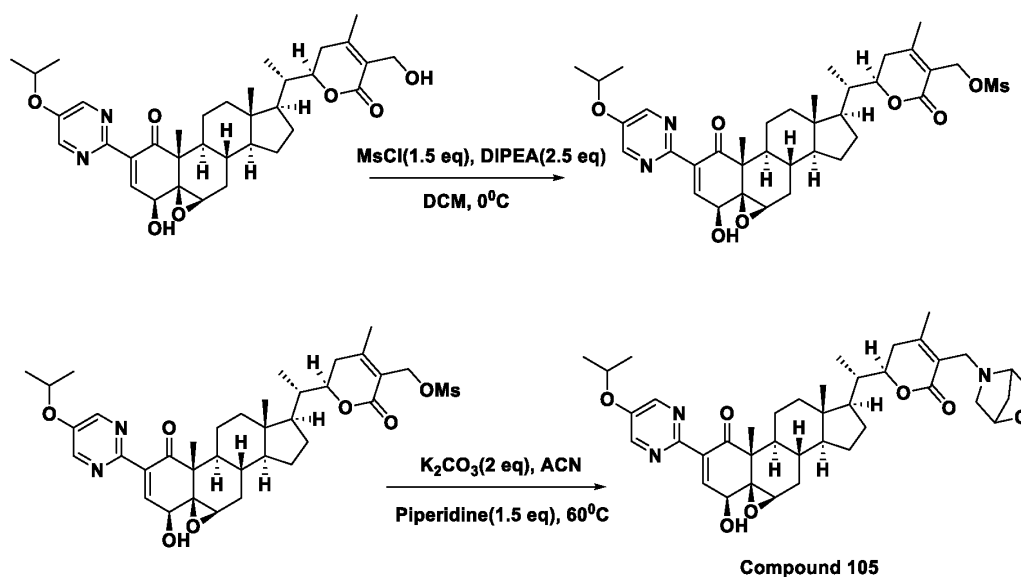
[0729] Analytical data:

LCMS: 98.14% (m/z: 676.64, [M+1], 2.39 min (5 min run).

HPLC: 92.33% at rt 6.093 (20 min run).

¹H-NMR (400 MHz, DMSO-*d*₆): ¹H-NMR (400 MHz, DMSO-*d*₆): δ 8.54 (s, 2H), 7.53 (d, J = 6.80 Hz, 1H), 6.52 (s, 1H), 4.85-4.82 (m, 1H), 4.30 (dd, J = 13.20, Hz, 1H), 3.74-3.71 (m, 1H), 3.51 (s, 3H), 3.30-3.24 (m, 2H), 3.13-3.05 (m, 2H), 2.41 (d, J = Hz, 1H), 2.32 (d, J = 5.20 Hz, 4H), 2.08 (s, 3H), 2.01 (s, 2H), 1.91 (d, J = 6.00 Hz, 1H), 1.81-1.75 (m, 3H), 1.55-1.49 (m, 3H), 1.33-1.28 (m, 8H), 1.23 (s, 3H), 1.08-1.04 (m, 4H), 0.94 (dd, J = 6.40, Hz, 4H), 0.65 (s, 3H).

[0730] Synthesis of Compound 105



[0731] Step 1: Synthesis of ((R)-6-((S)-1-((4S, 4aR, 5aR, 6aS, 6bS, 9R, 9aS, 11aS, 11bR)-4-hydroxy-2-(5-isopropoxypyrimidin-2-yl)-9a, 11b-dimethyl-1-oxo-1, 4, 5a, 6, 6a, 6b, 7, 8, 9, 9a, 10, 11, 11a, 11b-tetradecahydrocyclopenta [1, 2] phenanthro [8a, 9-b]

oxiren-9-yl) ethyl)-4-methyl-2-oxo-5, 6-dihydro-2H-pyran-3-yl) methyl methane sulfonate

To a stirred solution of (R)-6-[(S)-1-{(1S, 2R, 6S, 7R, 9R, 11S, 12S, 15R, 16S)-6-hydroxy-4-(5-isopropoxy-2-pyrimidinyl)-2, 16-dimethyl-3-oxo-8-oxapentacyclo [9.7.0.0^{2,7}, 0^{7,9}.0^{12,16}] octadec-4-en-15-yl} ethyl]-3-(hydroxymethyl)-4-methyl-5, 6-dihydro-2H-pyran-2-one (0.4 g, 659 μ mol) in DCM (10 mL) was added N-ethylbis (isopropyl)amine (213 mg, 2.5 eq., 1.65 mmol) and (chlorosulfonyl) methane (106 mg, 1.4 eq., 923 μ mol) at 0°C. The reaction was allowed to stir at 0°C for 5 min. After starting material completion, the reaction was quenched by water and extracted with DCM. The organic layer was concentrated under reduced pressure to get crude. Crude ((R)-6-((S)-1-((4S, 4aR, 5aR, 6aS, 6bS, 9R, 9aS, 11aS, 11bR)-4-hydroxy-2-(5-isopropoxypyrimidin-2-yl)-9a, 11b-dimethyl-1-oxo-1, 4, 5a, 6, 6a, 6b, 7, 8, 9, 9a, 10, 11, 11a, 11b-tetradecahydrocyclopenta [1, 2] phenanthro [8a, 9-b] oxiren-9-yl) ethyl)-4-methyl-2-oxo-5, 6-dihydro-2H-pyran-3-yl) methyl methane sulfonate (450 mg) as such used for next step.

[0732] Analytical data:

LCMS: 45% (m/z: 685.55, [M+1], 3.43 min (5 min run).

[0733] Step 2: Synthesis of (R)-6-[(S)-1-{(1S, 2R, 6S, 7R, 9R, 11S, 12S, 15R, 16S)-6-hydroxy-4-(5-isopropoxy-2-pyrimidinyl)-2, 16-dimethyl-3-oxo-8-oxapentacyclo [9.7.0.0^{2,7}, 0^{7,9}.0^{12,16}] octadec-4-en-15-yl} ethyl]-4-methyl-3-{(2-oxa-5-azabicyclo [2. 2. 1] hept-5-yl) methyl}-5, 6-dihydro-2H-pyran-2-one

To a stirred solution of 2-oxa-5-azabicyclo [2.2.1] heptane (133 mg, 1.5 eq., 989 μ mol) in acetonitrile (2 mL, 95.7 mmol) was added dipotassium carbonate (273 mg, 2 eq., 923 μ mol) at 0°C. After 5 min was added ((R)-6-((S)-1-((4S, 4aR, 5aR, 6aS, 6bS, 9R, 9aS, 11aS, 11bR)-4-hydroxy-2-(5-isopropoxypyrimidin-2-yl)-9a, 11b-dimethyl-1-oxo-1, 4, 5a, 6, 6a, 6b, 7, 8, 9, 9a, 10, 11, 11a, 11b-tetradecahydrocyclopenta [1, 2] phenanthro [8a, 9-b] oxiren-9-yl) ethyl)-4-methyl-2-oxo-5, 6-dihydro-2H-pyran-3-yl) methyl methane sulfonate (450 mg) by dissolving into acetonitrile (7 mL, 95.7 mmol) drop wise. The resulting mixture was stirred at 60°C for 15 min. Reaction was monitor by TLC. After completion, the reaction mixture was quenched with cool water (100 mL) and was extracted with Ethyl acetate (2 x 200mL). The organic layer was dried over anhydrous sodium sulphate, filtered, and concentrated under reduced pressure. The crude material was enriched and purified by Combi Flash by using 5% of MeOH in DCM and then purified by Prep-HPLC in (Ammonium Bicarbonate method) to

afford (R)-6-[(S)-1-[(1S, 2R, 6S, 7R, 9R, 11S, 12S, 15R, 16S)-6-hydroxy-4-(5-isopropoxy-2-pyrimidinyl)-2, 16-dimethyl-3-oxo-8-oxapentacyclo [9.7.0.0^{2,7}.0^{12,16}] octadec-4-en-15-yl] ethyl]-4-methyl-3-[(2-oxa-5-azabicyclo [2.2.1] hept-5-yl) methyl]-5, 6-dihydro-2H-pyran-2-one (30 mg, 43.2 μmol) as off white solid.

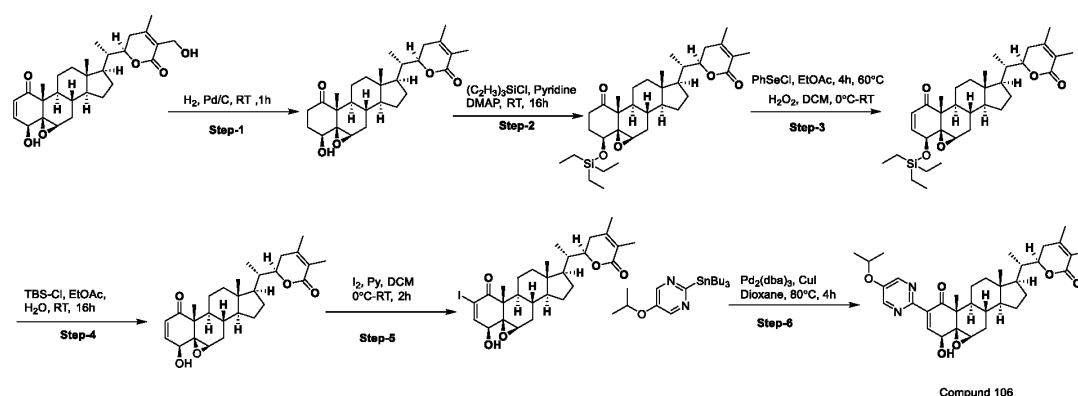
[0734] Analytical data:

LCMS: 99.06% (m/z: 688.65 [M+1], 2.38 min (5 min run).

HPLC: 97.77% at 7.724 rt (20 min run).

¹H-NMR (400 MHz, DMSO-*d*₆): ¹H-NMR (400 MHz, DMSO-*d*₆): δ 8.55 (s, 2H), 7.53 (d, J = 6.80 Hz, 1H), 5.73 (d, J = 3.20 Hz, 1H), 4.87-4.81 (m, 1H), 4.28 (dd, J = 3.20, Hz, 2H), 4.28 (dd, J = 3.20, Hz, 2H), 3.74 (m, 1H), 3.35 (m, 2H), 3.32 (s, 4H), 3.13 (s, 1H), 2.75 (dd, J = 9.20, Hz, 1H), 2.40-2.37 (m, 3H), 2.09 (d, J = 18.80 Hz, 1H), 2.01 (dd, J = 6.00, Hz, 4H), 1.92-1.89 (m, 1H), 1.80 (d, J = 3.60 Hz, 2H), 1.48 (d, J = 2.80 Hz, 2H), 1.31 (dd, J = 6.00, Hz, 8H), 1.28 (s, 3H), 0.91 (d, J = 403.60 Hz, 4H), 0.92 (dd, J = 6.40, Hz, 4H), 0.65 (s, 3H).

[0735] Synthesis of Compound 106



[0736] Step-1: Synthesis of (4S, 4aR, 5aR, 6aS, 6bS, 9R, 9aS, 11aS, 11bR)-9-((S)-1-((R)-4, 5-dimethyl-6-oxo-3, 6-dihydro-2H-pyran-2-yl) ethyl)-4-hydroxy-9a, 11b-dimethyltetradecahydrocyclopenta [1, 2] phenanthrol [8a, 9-b] oxiren-1(2H)-one:

To the solution (4S, 4aR, 5aR, 6aS, 6bS, 9R, 9aS, 11aS, 11bR)-4-hydroxy-9-((S)-1-((R)-5-(hydroxymethyl)-4-methyl-6-oxo-3, 6-dihydro-2H-pyran-2-yl) ethyl)-9a, 11b-dimethyl-5a, 6, 6a, 6b, 7, 8, 9, 9a, 10, 11, 11a, 11b-dodecahydrocyclopenta [1, 2] phenanthro [8a, 9-b] oxiren-1(4H)-one (5 g, 10.6 mmol) in methanol (100 mL) was added 10% palladium on carbon (1.0

g) at RT. The resulting mixture was purged with H₂ for 1h, the progress of reaction was monitored by LCMS and TLC. The reaction mixture was filtered and concentrated to afford the desired compound (4S, 4aR, 5aR, 6aS, 6bS, 9R, 9aS, 11aS, 11bR)-9-((S)-1-((R)-4, 5-dimethyl-6-oxo-3, 6-dihydro-2H-pyran-2-yl) ethyl)-4-hydroxy-9a, 11b-dimethyltetradecahydro cyclopenta [1, 2] phenanthro [8a, 9-b] oxiren-1(2H)-one (3.5 g, 36.07%) as white solid.

Analytical Data:

LCMS: (ESI): m/z:- 457.48 (M+1)⁺

[0737] Step-2: Synthesis of (R)-6-[(S)-1-{(1S, 2R, 6S, 7S, 9R, 11S, 12S, 15R, 16S)-2, 16-dimethyl-3-oxo-6-(triethylsiloxy)-8-oxapentacyclo [9.7.0.0^{2,7},⁹,⁰^{12,16}] octadec-15-yl} ethyl]-3, 4-dimethyl-5, 6-dihydro-2H-pyran-2-one

To the solution of (R)-6-[(S)-1-{(1S, 2R, 6S, 7R, 9R, 11S, 12S, 15R, 16S)-6-hydroxy-2, 16-dimethyl-3-oxo-8-oxapentacyclo [9.7.0.0^{2,7},⁹,⁰^{12,16}] octadec-15-yl} ethyl]-3, 4-dimethyl-5, 6-dihydro-2H-pyran-2-one (4 g, 8.76 mmol) in Pyridine (22.7 mL) was added N, N-dimethyl-4-pyridylamine (107 mg, 0.1 eq., 876 μmol) followed by dropwise addition of chloride—triethylsilane (1/1) (1.99 g, 1.5 eq., 13.1 mmol) at 0°C. The reaction mixture was allowed to stirred at room temp for 16 hrs. The progress of reaction was monitored by LCMS and TLC. The reaction mixture was diluted with EtOAc (50 mL), washed with 20% citric acid solution (2 × 10 mL), the organic layer was dried on Na₂SO₄, filtered and concentrated and purified by combiflash chromatography elution 0-30% EtOAc in Hexane to afford the desired compound (R)-6-[(S)-1-{(1S, 2R, 6S, 7S, 9R, 11S, 12S, 15R, 16S)-2, 16-dimethyl-3-oxo-6-(triethylsiloxy)-8-oxapentacyclo [9.7.0.0^{2,7},⁹,⁰^{12,16}] octadec-15-yl} ethyl]-3, 4-dimethyl-5, 6-dihydro-2H-pyran-2-one (2.5 g, 49.99%) as white solid

Analytical Data:

LCMS: (ESI): m/z:- 571.61 (M+1)⁺

[0738] Step-3: Synthesis of (R)-6-[(S)-1-{(1S, 2R, 6S, 7S, 9R, 11S, 12S, 15R, 16S)-2, 16-dimethyl-3-oxo-6-(triethylsiloxy)-8-oxapentacyclo [9.7.0.0^{2,7},⁹,⁰^{12,16}] octadec-4-en-15-yl} ethyl]-3, 4-dimethyl-5, 6-dihydro-2H-pyran-2-one

To the solution of (R)-6-[(S)-1-{(1S, 2R, 6S, 7S, 9R, 11S, 12S, 15R, 16S)-2, 16-dimethyl-3-oxo-6-(triethylsiloxy)-8-oxapentacyclo [9.7.0.0^{2,7},⁹,⁰^{12,16}] octadec-15-yl} ethyl]-3, 4-

dimethyl-5, 6-dihydro-2H-pyran-2-one (1 g, 1.75 mmol) in ethyl acetate (50 mL, 507 mmol) was added (chloroseleno) benzene (403 mg, 1.2 eq., 2.1 mmol) the resulting mixture was stirred at 60°C for 4h. The progress of reaction was monitored by LCMS and TLC. The reaction mixture was concentrated and purified by combiflash chromatography elution 0-30% EtOAc in Hexane to afford the (R)-6-[(S)-1-{(1S, 2R, 6S, 7S, 9R, 11S, 12S, 15R, 16S)-2, 16-dimethyl-3-oxo-4-(phenylseleno)-6-(triethylsiloxy)-8-oxapentacyclo [9.7.0.0^{2,7}.0^{7,9}.0^{12,16}] octadec-15-yl}ethyl]-3, 4-dimethyl-5, 6-dihydro-2H-pyran-2-one (75 mg) which was dissolved in DCM (20 mL), followed by addition of hydrogen peroxide (2 mL) at 0°C, the resulting mixture was stirred at RT for 30 min the progress of reaction was monitored by LCMS and TLC. The reaction mixture was quenched with saturated solution of sodium thiosulphate solution (20 mL), extracted with DCM (2 × 50 mL), combined layer was washed with NaHCO₃ solution (50 mL), with brine (50 mL), dried over Na₂SO₄, concentrated to afford the desired compound (R)-6-[(S)-1-{(1S, 2R, 6S, 7S, 9R, 11S, 12S, 15R, 16S)-2, 16-dimethyl-3-oxo-6-(triethylsiloxy)-8-oxapentacyclo [9.7.0.0^{2,7}.0^{7,9}.0^{12,16}] octadec-4-en-15-yl} ethyl]-3, 4-dimethyl-5, 6-dihydro-2H-pyran-2-one (0.4 g, 50.18% , over two step) as colorless gummy solid.

Analytical Data:

LCMS:- (ESI): m/z:- 569.66 (M+1)⁺

[0739] Step-4: Synthesis of (R)-6-[(S)-1-{(1S, 2R, 6S, 7R, 9R, 11S, 12S, 15R, 16S)-6-hydroxy-2, 16-dimethyl-3-oxo-8-oxapentacyclo [9.7.0.0^{2,7}.0^{7,9}.0^{12,16}] octadec-4-en-15-yl} ethyl]-3, 4-dimethyl-5, 6-dihydro-2H-pyran-2-one

To a stirred solution of (R)-6-[(S)-1-{(1S, 2R, 6S, 7S, 9R, 11S, 12S, 15R, 16S)-2, 16-dimethyl-3-oxo-6-(triethylsiloxy)-8-oxapentacyclo [9.7.0.0^{2,7}.0^{7,9}.0^{12,16}] octadec-4-en-15-yl} ethyl]-3,4-dimethyl-5, 6-dihydro-2H-pyran-2-one (300 mg, 0.527 mmol) in water (0.903 mL) and Ethyl Acetate (5.59 mL) was added (tert-butyl) (chloro) bis (methyl) silane (119 mg, 1.5 eq., 0.791 mmol) at RT. The resulting mixture was stirred at RT for 16h. The progress of reaction was monitored by LCMS. Reaction mixture quenched by water (20 mL) and extracted twice with ethyl acetate (50 mL), combined organic layer was dried over sodium sulphate, concentrated on Rota evaporated, crude was obtained as (R)-6-[(S)-1-{(1S, 2R, 6S, 7R, 9R, 11S, 12S, 15R, 16S)-6-hydroxy-2, 16-dimethyl-3-oxo-8-oxapentacyclo [9.7.0.0^{2,7}.0^{7,9}.0^{12,16}] octadec-4-en-15-yl} ethyl]-3, 4-dimethyl-5, 6-dihydro-2H-pyran-2-one (240 mg, 81.97%) yellowish solid.

Analytical Data:

LCMS:- (ESI): m/z:- 455.39, (M+1)⁺.

[0740] Step-5: Synthesis of (R)-6-[(S)-1-{(1S, 2R, 6S, 7R, 9R, 11S, 12S, 15R, 16S)-6-hydroxy-4-iodo-2, 16-dimethyl-3-oxo-8-oxapentacyclo [9.7.0.0^{2,7},⁹.0^{12,16}] octadec-4-en-15-yl} ethyl]-3, 4-dimethyl-5, 6-dihydro-2H-pyran-2-one.

To a stirred solution of (R)-6-[(S)-1-{(1S, 2R, 6S, 7R, 9R, 11S, 12S, 15R, 16S)-6-hydroxy-2, 16-dimethyl-3-oxo-8-oxapentacyclo [9.7.0.0^{2,7},⁹.0^{12,16}] octadec-4-en-15-yl} ethyl]-3, 4-dimethyl-5, 6-dihydro-2H-pyran-2-one (320 mg, 704 μ mol) and pyridine (0.26 mL) (0.8 volume) in DCM (12 mL) was added diiodine (357 mg, 2.0 eq., 1.41 mmol) at 0°C. The resulting mixture was stirred at RT for 2h. The progress of reaction was monitored by LCMS. The reaction mixture was quenched with 30% sodium thiosulphate solution (5 mL), diluted with DCM (10 mL), washed with 20% citric acid solution (2 $\times$ 5 mL), the organic layer was dried over Na₂SO₄, concentrated and purified by combi flash chromatography elution 0-50% EtOAc in Hexane to afford the desired compound (R)-6-[(S)-1-{(1S, 2R, 6S, 7R, 9R, 11S, 12S, 15R, 16S)-6-hydroxy-4-iodo-2, 16-dimethyl-3-oxo-8-oxapentacyclo [9.7.0.0^{2,7},⁹.0^{12,16}] octadec-4-en-15-yl} ethyl]-3, 4-dimethyl-5, 6-dihydro-2H-pyran-2-one (320 mg, 72.05%) as white solid.

Analytical Data:

LCMS: - (ESI) m/z:- 581.36 (M+1)⁺

[0741] Step-6: Synthesis of (R)-6-[(S)-1-{(1S, 2R, 6S, 7R, 9R, 11S, 12S, 15R, 16S)-6-hydroxy-4-(5-isopropoxy-2-pyrimidinyl)-2, 16-dimethyl-3-oxo-8-oxapentacyclo [9.7.0.0^{2,7},⁹.0^{12,16}] octadec-4-en-15-yl} ethyl]-3, 4-dimethyl-5, 6-dihydro-2H-pyran-2-one.

To a stirred solution of (R)-6-[(S)-1-{(1S, 2R, 6S, 7R, 9R, 11S, 12S, 15R, 16S)-6-hydroxy-4-iodo-2, 16-dimethyl-3-oxo-8-oxapentacyclo [9.7.0.0^{2,7},⁹.0^{12,16}] octadec-4-en-15-yl} ethyl]-3, 4-dimethyl-5, 6-dihydro-2H-pyran-2-one (150 mg, 258 μ mol) and tributyl (5-isopropoxy-2-pyrimidinyl) stannane (166 mg, 1.5 eq., 388 μ mol) in 1,4-dioxane (5 mL, 13.1 mmol) was added copper iodide (12.3 mg, 0.15 eq., 38.8 μ mol) and palladium—(1E, 4E)-1,5-diphenyl-1,4-pentadien-3-one (2/3) (11.8 mg, 0.05 eq., 12.9 μ mol) under N₂ degas. The resulting mixture was heated for 4h at 80°C. The progress of reaction was monitored by LCMS and TLC. The reaction mixture was filtered through celite, residue was rinsed with EtOAc (5 mL),

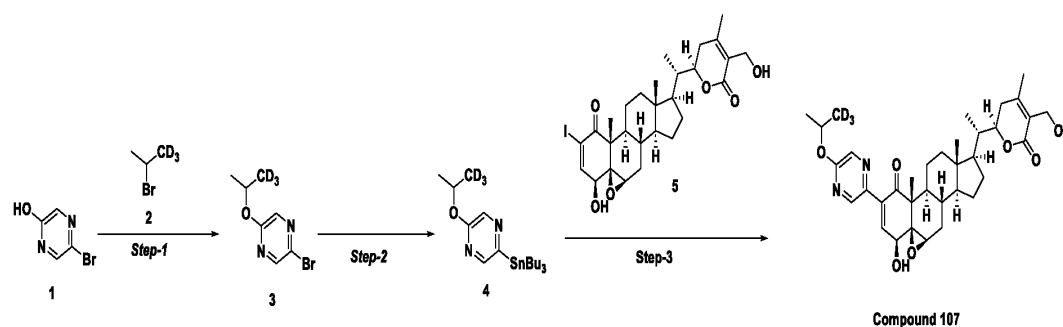
concentrated and purified by pre-HPLC to afford the desired compound (R)-6-[(S)-1-{(1S, 2R, 6S, 7R, 9R, 11S, 12S, 15R, 16S)-6-hydroxy-4-(5-isopropoxy-2-pyrimidinyl)-2, 16-dimethyl-3-oxo-8-oxapentacyclo [9.7.0.0.0²,7.0⁷,9.0¹²,16] octadec-4-en-15-yl} ethyl]-3, 4-dimethyl-5, 6-dihydro-2H-pyran-2-one (3.0 mg, 91.35%) as white solid.

Analytical data:

LCMS: 84.0% (m/z): 591.61, [M+1]⁺, 2.54 min (5.50 min run).

¹H NMR (400 MHz, DMSO) δ: 8.37 (s, 2H), 7.59 (d, 1H), 5.75 (brs, 1H), 5.26-5.21 (m, 1H), 4.29 (dt, J = 13.2, 3.6 Hz, 1H), 4.22 (t, 1H), 3.74 (dd, J = 6.3, 4.2 Hz, 1H), 3.16 (s, 1H), 2.40 – 2.31 (m, 1H), 2.05 – 2.00 (m, 2H), 1.94 – 1.89 (m, 3H), 1.81 (m, 1H), 1.75 (m, 1H), 1.62 – 1.50 (m, 1H), 1.45 – 1.37 (m, 2H), 1.35-1.28 (m, 11H), 1.24-1.21 (m, 3H), 1.18 – 1.01 (m, 3H), 0.97-0.85 (m, 6H), 0.64 (s, 3H).

[0742] Synthesis of Compound 107



[0743] Step-1: Synthesis of 2-bromo-5-((propan-2-yl-1,1,1-d₃) oxy) pyrazine:

To a stirred solution of 5-bromopyrazin-2-ol (0.5 g, 2.86 mmol) in hexane (5 mL) were added disilver carbonate (945 mg, 1.2 eq., 3.43 mmol) and 2-bromopropane-1,1,1-d₃ (720 mg, 2 eq., 5.71 mmol) at room temperature. The reaction was stirred at 110 °C for 16h. After completion (monitored by TLC) of reaction, reaction mass was filtered and the filtrate was concentrated under reduced pressure to get the crude material, which was purified by over silica gel column by combi flash using 0-5% ethyl acetate in heptane's as an eluent. Desired fractions were concentrated under reduced pressure to afford 2-bromo-5-((propan-2-yl-1,1,1-d₃) oxy) pyrazine (460 mg, 2.09 mmol) as light-yellow liquid.

[0744] Analytical data:

¹H-NMR (400 MHz, DMSO-d₆): δ 8.41 (d, J = 1.12 Hz, 1H), 8.12 (d, J = 1.12 Hz, 1H), 5.16 (d, J = 6.00 Hz, 1H), 1.32 (d, J = 6.16 Hz, 3H).

[0745] Step-2: Synthesis of 2-((propan-2-yl-1,1,1-d₃) oxy)-5-(tributylstannyl) pyrazine:

To a stirred solution of 2-bromo-5-((propan-2-yl-1,1,1-d₃) oxy) pyrazine (460 mg, 2.09 mmol) in 1,4-dioxane (5 mL, 58.6 mmol) were added lithium chloride (532 mg, 6 eq., 12.5 mmol), tricyclohexylphosphine (58.6 mg, 0.1 eq., 209 μ mol) and bis(tributyl- λ^3 -stannane) (1.46 g, 1.2 eq., 2.51 mmol) at RT. The reaction mixture was purged with N₂ gas for 10-15 min. Then, (1E,4E)-1,5-diphenyl-1,4-pentadien-3-one—1,5-diphenyl-1,4-pentadien-3-one—palladium (1/2/2) (95.7 mg, 0.05 eq., 105 μ mol) was added to the reaction mixture and again purged with N₂ gas for 3-5 min. The reaction was stirred at 100 °C for 2h. After completion of reaction (monitor by TLC), reaction mass was concentrated under reduced pressure to get the crude material, which was purified by combi flash column chromatography using 1-5% ethyl acetate in heptane's as an eluent to afford 2-((propan-2-yl-1,1,1-d₃)oxy)-5-(tributylstannyl)pyrazine (520 mg, 1.21 mmol) as light brown liquid.

Analytical data:

LCMS: purity 84 % (m/z: 431.50 [M+1]⁺, 3.35 min (4 min run).

[0746] Step-3: Synthesis of (4S, 4aR, 5aR, 6aS, 6bS, 9R, 9aS, 11aS, 11bR)-4-hydroxy-9-((S)-1-((R)-5-(hydroxymethyl)-4-methyl-6-oxo-3, 6-dihydro-2H-pyran-2-yl) ethyl)-9a, 11b-dimethyl-2-(5-((propan-2-yl-1,1,1-d₃)oxy)pyrazin-2-yl)-5a, 6, 6a, 6b, 7, 8, 9, 9a, 10, 11, 11a, 11b-dodecahydrocyclopenta [1, 2] phenanthro [8a, 9-b]oxiren-1(4H)-one:

To a stirred solution of (4S, 4aR, 5aR, 6aS, 6bS, 9R, 9aS, 11aS, 11bR)-4-hydroxy-9-((S)-1-((R)-5-(hydroxymethyl)-4-methyl-6-oxo-3, 6-dihydro-2H-pyran-2-yl) ethyl)-2-iodo-9a, 11b-dimethyl-5a, 6, 6a, 6b, 7, 8, 9, 9a, 10, 11, 11a, 11b-dodecahydrocyclopenta [1, 2] phenanthro [8a, 9-b] oxiren-1(4H)-one (0.4 g, 671 μ mol) in tetrahydrofuran (4 mL, 49.1 mmol) were added 2-((propan-2-yl-1,1,1-d₃) oxy)-5-(tributylstannyl)pyrazine (1.01 g, 2 eq., 1.34 mmol), copper iodide (12.8 mg, 0.1 eq., 67.1 μ mol) and triphenylarsine (20.5 mg, 0.1 eq., 67.1 μ mol) at RT. The reaction mixture was purged with nitrogen for 8-10 min and then added (1E, 4E)-1,5-diphenyl-1,4-pentadien-3-one—1,5-diphenyl-1,4-pentadien-3-one—palladium (1/2/2)

(61.4 mg, 0.1 eq., 67.1 μ mol). The reaction mixture was again purged with nitrogen for 3-4 min. The reaction was stirred at 80°C for 4h. After completion of reaction (monitor by TLC), reaction mass was concentrated under reduced pressure to get crude, which was purified by combi flash over silica gel column using 50-60% ethyl acetate in heptane's as an in eluent to afford crude desired compound which was further purified by prep HPLC purification using ABC method to afford (4S, 4aR, 5aR, 6aS, 6bS, 9R, 9aS, 11aS, 11bR)-4-hydroxy-9-((S)-1-((R)-5-(hydroxymethyl)-4-methyl-6-oxo-3, 6-dihydro-2H-pyran-2-yl)ethyl)-9a, 11b-dimethyl-2-(5-((propan-2-yl-1,1,1-d3)oxy)pyrazin-2-yl)-5a, 6, 6a, 6b, 7, 8, 9, 9a, 10, 11, 11a, 11b-dodecahydrocyclopenta [1, 2] phenanthro [8a, 9-b] oxiren-1(4H)-one, (51 mg, 83.6 μ mol, yield 12%) as white solid.

Analytical data:

LCMS: purity 99.13 % (m/z: 610.35 [M+1]⁺, 6.71 min (10 min run).

¹H-NMR (400 MHz, DMSO-d₆): δ 8.27 (d, J = 1.32 Hz, 1H), 8.18 (d, J = 1.32 Hz, 1H), 7.59 (d, J = 6.72 Hz, 1H), 5.75 (d, J = 3.48 Hz, 1H), 5.24 (q, J = 6.20 Hz, 1H), 4.57 (t, J = 5.36 Hz, 1H), 4.31-4.26 (m, 1H), 4.18-4.08 (m, 2H), 3.76-3.74 (m, 1H), 3.17 (s, 1H), 2.43-2.34 (m, 1H), 2.11-2.06 (m, 2H), 1.99 (s, 3H), 1.92-1.89 (m, 1H), 1.82-1.80 (m, 1H), 1.79-1.72 (m, 1H), 1.57-1.55 (m, 1H), 1.41-1.34 (m, 2H), 1.33-1.32 (m, 7H), 1.30-1.25 (m, 2H), 1.15-1.06 (m, 3H), 0.98-0.88 (m, 5H), 0.66 (s, 3H).

¹³C-NMR (100 MHz, DMSO-d₆): δ 200.35, 158.64, 165.31, 154.65, 140.19, 138.99, 138.33, 135.35, 125.43, 77.51, 69.06, 68.43, 63.41, 57.62, 55.23, 54.51, 51.05, 47.89, 42.11, 41.99, 38.36, 30.75, 29.27, 29.01, 26.49, 23.96, 21.52, 20.49, 19.88, 15.19, 13.03, 11.24.

Melting point: 166-167 °C.

Example 1**THP-1 Inflammasome Assay**

[0747] THP-1 inflammasome assay (PI uptake): THP1 cells (TIB-202) were cultured in RPMI media with 10% FBS, 100 U/ ml of penicillin, 100 μ g / ml of streptomycin, and 0.05 mM 2-mercaptoethanol. Cells were seeded at the density of 7.5 x 10⁴/ well in black clear bottom 96 well plate in complete RPMI media with 15 ng/ ml PMA. After overnight differentiation, media was replaced with complete RPMI (without phenol red) containing 0.5

µg/ ml LPS for 3 h for priming. Replace the existing media with respective drugs (starting from 100uM to 0.01uM) and nigericin (10uM) in assay buffer (10% FBS, 1 ug/ ml PI in HBSS) and incubated in CO2 incubator for 2h for inflammasome activation. Fluorescence measurement was taken at excitation of 535 nm and the emission of 615 nm in plate reader. The percentage of PI uptake in each treatment was calculated and percentage of inflammasome inhibition was plotted using GraphPad.

[0748] Table 1. Inflammasome IC₅₀ (THP-1)

Compound ID	THP-1 Inflammasome IC ₅₀ (µM)
1	+
2	+
3	+
4	+
5	++
6	++
7	++
8	+++
9	+++
10	++
11	+++
12	++
13	+++
14	++
15	+++
16	+++
17	++
18	+++
19	++
20	++
21	+++
22	++

23	++
24	+++
25	+++
26	+++
27	+++
28	+++
29	++
30	+++
31	+++
32	++
33	++
34	+++
35	+++
36	+++
37	+++
38	+++
39	+++
40	+++
41	++
42	++
43	++
44	+++
45	++
46	++
47	++
48	++
49	++
50	+++
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76	+++
77	+++
78	++
79	+++
80	++
81	++
82	++
83	++
84	+++
85	++
86	+++

87	+++
88	+++
89	++
90	+++
91	+++
92	+++
93	+++
94	++
95	+++
96	+++
97	++
98	+++
99	+++
100	+++
101	-
102	-
103	-
104	-
105	-
106	++
107	++

+ = IC₅₀ > 50 μ M; ++ = IC₅₀ 1-50 μ M; +++ = IC₅₀ < 1 μ M

Example 2

Compound 13 and its analogs potently inhibit NLRP3 pathway activation in human primary cells

[0749] **Inflammasome inhibition assay in THP-1:** 75000 THP1-wild type cells/well in 200ul complete RPMI media with 15ng/ml PMA were seeded in black clear bottom plate. After overnight incubation at 37°C in CO₂ incubator, the media was replaced with complete RPMI (w/o phenol red; 200ul) containing 0.5ug/ml LPS for 3hrs. The media was replaced with 160ul of assay buffer (HBSS with Propidium Iodide), followed by addition of 20ul 10X drug and

20ul of 10X Nigericin. After 2hrs incubation with Compound 13 and its analogs, Nigericin fluorescence reading was taken at Ex/Em 535/615nm using plate reader.

[0750] Assay in NOMID/CAPs model: The iPSCs with NLRP3 Y570C somatic mutation were generated from a patient with neonatal onset multisystem inflammatory disease (NOMID) as a model of a constitutively activated NLRP3 inflammasome (mut). The NLRP3-nonmutated (wild-type - WT) clone derived from the same donor was used as an isogenic control iPSC line. iPSC-derived immortalized myeloid cell line (iPS-ML) was differentiated for 7days into macrophages (ML-MP) to establish the “Disease-in-a-Dish”. iPSC-ML derived ML-MPs were seeded in 384-well plate and treated with test compounds for 4h at 37°C. Cells were then treated with LPS for 18h to secrete IL-1 β . After 18h of LPS treatment supernatant was collected to perform HTRF assay.

[0751] Compound 13 was equally efficacious both in THP-1 and NOMID (‘disease-in-a-dish’) systems to prevent inflammasome activation. IC₅₀ for Compound 13 in THP-1 inflammasome assay was determined to be ~130nM (As shown in **FIG.1A**). Similarly, Compound 13 showed dose-dependent inhibition of IL-1 β release in NOMID systems (As depicted in **FIG.1B**).

Example 3

Compound 13 and its analogs regulate NLRP3 stability and suppresses inflammasome assembly in human primary cells

[0752] Cells were resuspended in complete media at concentration of 1 million cells/ml and treated with PMA 35ng/ml for 3hrs in a flask. After 3hrs cells were scraped out and washed twice with media. Then cells were seeded in 96 well plate and allowed to differentiate for 3 days at 37°C with 5% CO₂. After 3 days the media was removed, and fresh media (with selection antibiotics) was added. Plates were incubated for 24hrs. Next day media was changed with LPS-containing media (200ul) and incubated for 3hrs at 37° C with 5% CO₂. After 3hrs, media containing LPS was removed, and cells were washed with PBS. Then 150ul media containing Compound 13 and its analogs were added to the respective wells and 50ul 4X nigericin was top-upped. Plates were incubated for 2hrs at 37°C with 5% CO₂. After 2hrs 20ul of Hoechst and PI solution (11X) was added and incubated for 10 min. After 10 mins PI fluorescence was measured by plate reader and high throughput imaging was done using ImageXpress Micro Confocal High-Content Imaging System.

[0753] While adequate activation of the inflammasome is critical to protect the host from pathogens infection and heal tissue wounds, excessive inflammasome activation causes severe autoinflammatory and autoimmune diseases. Hence, there is a need to determine the anti-inflammasome activity of Compound 13 and its analogs. The effect of Withaferin A (Compound NP) and Compound 13 on speck formation (NLRP3-NEK7-ASC Protein complex i.e., NLRP3 inflammasome complex) was determined using THP-1 cells transfected with ASC-GFP. Speck formation is observed in cells following inflammasome activation (LPS + Nig); NP, Compound 13 and MCC950 inhibit the speck formation, whereas Neg-Con did not inhibit the speck formation (As shown in **FIG.2A**) Further, the % PI uptake in the same groups was also determined as shown in **FIG.2B**).

Example 4

Compound 13 and its analogs causes degradation of NLRP3 protein

[0754] **Dose dependent NLRP3 degradation:** 2×10^6 THP-1 cells were seeded in 2 ml of RPMI complete media in each well of clear bottom 6-well plate. Cells (respective wells) were treated with Compound NP (10 μ M), Compound 13 (1 μ M), MCC950 (10 μ M) and Neg Con (10 μ M) for 2 h (top up). After 2h of compound treatment cells were primed with 0.5 μ g/ml LPS (top up). After 1h 45 min of LPS treatment cells were activated with 5 μ g/ml of Nigericin for 15 mins (top up). Then the cells were collected along with media and centrifuged at 200g for 5 minutes at RT. The supernatant was discarded and the lysis reagent along with protease inhibitor was added to the pellet, left it for 45 min on ice, centrifuged it at 15000 RPM for 20 Minutes at 4°C. Supernatant was collected for further use. Then the protein estimation was done, and Western Blotting analysis was performed.

[0755] **Proteasome rescue of NLRP3:** 2×10^6 THP-1 cells were seeded in 2 ml of RPMI complete media in each well of clear bottom 6-well plate. Cells (respective wells) were treated with MG132 (5 μ M) and Bafilomycin (50nM) for 1 hr (top up). After 1 h, Compound 13 was added at proper concentrations to respective wells for 2 hrs (top up). Then the cells were collected along with media and centrifuged at 200g for 5 minutes at RT. The supernatant was discarded and the lysis reagent along with protease inhibitor cocktail was added to the pellet, left it for 45 min on ice, centrifuged it at 15000 RPM for 20 Minutes at 4°C. Supernatant was collected for further use. Then the protein estimation was done, and Western Blotting analysis was performed.

[0756] The speck formation assay results suggested that both Compound NP and Compound 13 can inhibit NLRP3 inflammasome activation. However, further experiments need to be performed to determine whether these compounds are direct binder of NLRP3 protein, or they are inhibiting some upstream factors of NLRP3 inflammasome. Now, to determine whether Compound NP and Compound 13 are direct binders of NLRP3 protein, we performed Western Blot analysis in primed (with LPS) and activated (with Nigericin) THP-1 cells. A decrease in NLRP3 protein expression was observed post treatment of Compound NP and Compound 13. MCC950 was used as a known direct binder of NLRP3 protein and because of that NLRP3 protein expression was not decreased upon MCC950 treatment. Dose dependent decrease in NLRP3 protein expression post treatment with Compound 13 was observed. Now, to know the effect of Compound NP and Compound 13 on caspase-1-mediated downstream signalling of NLRP3 inflammasome, Western Blot analysis was performed. Cleaved Caspase-1 and cleaved-gasdermin-D protein contents are elevated in activated THP-1 cells (post LPS+Nig treatment) and treatment with Compound NP, Compound 13 and MCC950 (but not Neg Con) reverses this effect, Compound 13 reverses this effect in dose dependent manner. The results of the above experiments are depicted in **FIG.3A** and **FIG.3B** respectively.

[0757] In conjunction with the ubiquitin ligase-associated protein suppressor of the G2 allele of SKP1 (SGT1), Hsp90 forms a complex with NLRP3 and retains the receptor protein in an inactive but competent form for activation after reception of the priming signal. If this complex is not formed, then the NLRP3 protein will be degraded by proteasomes or via the lysosomal (autophagy) pathway. In the present study, the effects of Compound 13 on the fate of NLRP3 were explored post HSP90 inhibition in THP-1 cells. Cells were exposed to MG132 (cell-permeable proteasome inhibitor) and Bafilomycin A (autophagy inhibitor) to reactivate NLRP3 via the inhibition of proteasomes and autophagy, respectively. Herein, we found that MG132 and Bafilomycin A rescued the protein degradation of NLRP3 after Compound 13 mediated HSP90 inhibition. However, because HSP90 is essential for the correct NLRP3 protein folding, it is very likely that NLRP3 goes through misfolding before degradation by the proteasome in the presence of HSP90 inhibitors. In such a situation, even though MG132 rescues the protein amount of NLRP3, the misfolded protein may not be efficient to assemble inflammasome and mediate pyroptosis. Collectively, it can be stated that protein degradation of NLRP3 post Compound 13 binding with HSP90 causes NLRP3 inflammasome inhibition. (As shown in **FIG.3C**)

Example 5

Compound 13 shows dose-dependent in-vitro target engagement

[0758] Dose dependent in-vitro target engagement: The assay was performed by TR-FRET technology using a recombinant HSP90 α C-terminal Domain and PPID Ligand. The TR-FRET signal from the assay is correlated with the amount of PPID Ligand binding to the HSP90 α C-terminal domain. The compounds were diluted in 10 % DMSO and 2 μ l of the dilution was added to a 20 μ l reaction so that the final concentration of DMSO is 1 % in all of reactions. All the binding reactions were conducted at room temperature. The 20 μ l reaction mixture in C-terminal Assay Buffer contains HSP90 C-terminal domain enzyme, the test compound, PPID, and the reaction dyes. The reaction mixture incubated for 120 min prior to reading the TR-FRET signal. For the negative control, buffer was added instead of PPID.

[0759] Once activated, the intracellular receptor NLRP3 assembles an inflammasome protein complex that facilitates the caspase-1-mediated maturation of IL-1 β as discussed above. Inactive NLRP3 is guarded by a protein complex containing Hsp90. In response to stress stimuli, Hsp90 is released, and NLRP3 can be activated to promote inflammation. NLRP3 has also emerged as one of the Hsp90 clients. It has been reported that Withaferin A (WA) exhibited Hsp90 inhibition characteristics by decreasing the levels of Hsp90 client proteins. Thus, we intend to investigate the efficacy of NP analogs and Hsp90 inhibition mechanisms in our study. Hsp90 has three distinct domains. The N-terminal domain has the ATP binding site, the middle domain may interact with clients, and the C-terminal domain is responsible for dimerization of Hsp90. Several Hsp90 inhibitors, which block the ATP binding sites of Hsp90, have been developed and tested in preclinical and clinical models, e.g., Geldanamycin blocks the N-terminal ATP binding pocket, whereas novobiocin (and its derivatives) block the C-terminal ATP binding pocket. Upon ATP binding to Hsp90, client proteins and Hsp90 form a mature complex. This mature super-chaperone complex catalyzes the conformational maturation of client proteins. To investigate the efficacy and mechanism of Compound 13 and its analogs for Hsp90 inhibition we have performed substrate binding assay with recombinant HSP90 α (C-terminal) domain. Binding of Compound NP and Compound 13 with HSP90 α (C-terminal binding) was observed and Compound 13 showed dose dependent binding with HSP90 α (C-terminal binding) (As shown in **FIG.4**).

Example 6

Compound 13 shows dose-dependent reduction in Disease Activity Index and Combined histopathology score in dextran sodium sulfate (DSS) induced Colitis Murine model

[0760] Preclinical animal model of ulcerative colitis was developed by DSS. In the current study, the test item Compound 13 was screened to evaluate its efficacy in DSS-induced Ulcerative colitis model. Male C57BL/6 mice (100) of age 8-10 weeks were procured from CPCSEA approved vendor. All the animals were allowed to acclimatize for four days prior to experiment initiation. During this period, the mice were observed daily for clinical signs. On Day-3, Animals were randomized based on their body weight into 7 different groups and treatment was administered as per experimental design from day -3 to 8. G2 was administered with vehicle. G3, G4 & G5 were administered with Compound 13 (3mg/kg, p.o., BID), Compound 13 (10mg/kg, p.o., BID) and Compound 13 (30mg/kg, p.o., BID) respectively. G6 and G7 were administered with Fingolimod (1mg/kg, p.o., BID) and Mesalamine (50 mg/kg, p.o., QD) respectively. G1 was untreated.

[0761] The disease was induced by 2% DSS in drinking water daily for 7 days, except naïve group. During the study period body weight of animals were recorded daily and clinical scoring for Stool Consistency Index, Rectal Bleeding index were recorded daily. A significant increase in in-life phase disease activity index (DAI) (stool consistency, rectal bleeding) was observed in the disease control group from day 4 onwards (See FIG.5A). Treatment with Compound 13, Fingolimod and Mesalamine reduced DSS induced DAI from day 4-5 onwards. A significant increase in histopathology was observed in the disease control group on day 8. Treatment with Compound 13, Fingolimod and Mesalamine reduced DSS induced histopathology scoring on day 8 (See FIG.5B, FIG.5C and FIG.5D)

Example 7

Compound 13 reduces Disease Activity Index in Chronic dextran sodium sulfate (DSS) induced IBD Murine model

[0762] Preclinical animal model of intestinal fibrosis was developed by DSS. In the current study, the test Compound 13 was screened to evaluate its efficacy in DSS-induced intestinal fibrosis model. Male C57BL/6 mice of age 8-10 weeks were procured from CPCSEA approved vendor. All the animals were allowed to acclimatize for four days prior to experiment

initiation. During this period, the mice were observed daily for clinical signs. On Day 1, animals were randomized based on their body weight into 2 groups (No DSS, 10 animals and DSS 75 animals). On day 16, DSS group animals were randomized based on DAI score and divided into 5 groups. Treatment with test compound started on day 16 after randomization based on DAI score.

[0763] On the day of DSS administration (day 1), experimental mice were weighed and, average group weight was equilibrated to eliminate any significant weight difference between groups (randomization). 100 ml of DSS water was provided (ad-libitum) in each cage and fresh DSS was supplied every 3 days. Control mice received the same amount of water without DSS. Mice received DSS water for 5 days. On day 6, DSS water was removed and replaced with regular autoclaved water. After 10 days of regular water, steps 3 and 4 were repeated 3 more times. There was a total of 4 DSS cycles and 4 regular water cycles. All the animals were humanely sacrificed by carbon dioxide asphyxiation on day 62-63. Blood was collected in heparin coated plasma tubes and centrifuged at 4°C, 5000 RPM for 10 minutes, plasma was separated and stored at -80°C for further analysis. The distal part of colon was used for histopathology analysis, middle colon was used for RNA extraction and proinflammatory markers, and Proximal colon was used for fibrosis markers. For intestinal permeability analysis FITC-dex (60 mg/100 g) was administered orally and after 4 h animals were sacrificed as per protocol.

[0764] For TIMP-1 qRT-PCR analysis, small piece of middle colon (20 mg) was stored in RNAlater at -80°C until RNA extraction. On the day of RNA extraction, colons were removed from RNAlater and RNA was extracted by using Qiagen RNeasy Protect Mini Kit 250 as per manufacturer protocol and then q-PCR was performed. The expression analysis of TIMP1 was evaluated. The hydroxyproline level in colon tissue was measured using Hydroxyproline assay kit (MAK008; Sigma Aldrich; USA) following the instruction manual provided with kit. The amount of hydroxyproline generated was calculated by plotting the value against the standard curve of hydroxyproline, generated in similar manner. For IHC analysis (Collagen type-1 and alpha SMA), distal colon was collected and stored in phosphate buffered formalin (HT501320; Sigma Aldrich) for 24 hrs at 4°C for fixation. After fixation, samples were switched to 70% alcohol and processed further. Samples were then analyzed in a blind manner by histopathologist.

[0765] A significant decrease in colon length, increase in colon weight and increase in colon thickness was observed in the disease control group. A significant increase in intestinal permeability was also observed in the disease control group. Treatment with Compound 13 and mesalamine (ASA) protected from DSS-induced colon damage in terms of length, weight, thickening and high permeability. A significant increase in type-I collagen and alpha SMA staining was observed in different regions of disease control (DSS + vehicle) colon tissue vs naïve animals. Treatment with Compound 13 and ASA reduced DSS-induced type-I collagen, alpha SMA and TIMP expression in colon (As depicted in **FIGS.6A-6F**).

Example 8

Dose responsive efficacy of Compound 13 in dextran sodium sulfate (DSS) induced Colitis Murine model (Prophylactic mode)

[0766] Preclinical animal model of ulcerative colitis was developed by DSS. In the current study, the test item Compound 13 was screened to evaluate its efficacy in DSS-induced Ulcerative colitis model. Male C57BL/6 mice of age 8-10 weeks were procured from CPCSEA approved vendor. All the animals were allowed to acclimatize for seven days prior to experiment initiation. During this period, the mice were observed daily for clinical signs. On Day-3, Animals were randomized based on their body weight into 7 different groups and treatment was administered as per experimental design from day -3 to 8. G2 was administered with vehicle. G3, G4, G5 & G6 were administered with Compound 13 (1 mg/kg, 3mg/kg, 10mg/kg, and 30mg/kg, p.o., BID) respectively. G7 was administered Mesalamine (50 mg/kg, p.o., QD) respectively. G1 was untreated. The disease was induced by 2.5% DSS in drinking water daily for 7 days, except naïve group. During the study period body weight of animals were recorded daily and clinical scoring for Stool Consistency Index, Rectal Bleeding index were recorded daily. The disease activity index was calculated as a sum of the stool consistency index, rectal bleeding index and body weight loss index.

[0767] A significant increase in in-life phase disease activity index (DAI) was observed in the disease control group. Treatment with Compound 13 and Mesalamine reduced DSS induced DAI (See **FIG.7A** and **FIG.7B**).

Example 9

Compound 13 reduced DSS-induced DAI score on day 8 in dextran sodium sulfate (DSS) induced Colitis Murine model

[0768] Preclinical animal model of ulcerative colitis was developed by DSS. In the current study, the test Compound 13 was screened to evaluate its efficacy in DSS-induced Ulcerative colitis model. Male C57BL/6 mice of age 8-10 weeks were procured from CPCSEA approved vendor. All the animals were allowed to acclimatize for seven days prior to experiment initiation. During this period, the mice were observed daily for clinical signs. On Day-3, Animals were randomized based on their body weight into 7 different groups and treatment was administered as per experimental design from day 3 to day 8. G2 was administered with vehicle. G3, G4, G5 & G6 were administered with Compound 13 (1 mg/kg, 3mg/kg, 10mg/kg, and 30mg/kg, p.o., BID) respectively. G7 was administered Mesalamine (50 mg/kg, p.o., QD) respectively. G1 was untreated.

[0769] The disease was induced by 2.5% DSS in drinking water daily for 7 days, except naïve group. During the study period body weight of animals were recorded daily and clinical scoring for Stool Consistency Index, Rectal Bleeding index were recorded daily. The disease activity index was calculated as a sum of the stool consistency index, rectal bleeding index and body weight loss index.

[0770] A significant increase in the disease activity index (DAI) on day 8 was observed in the disease control group. Treatment with Compound 13 and Mesalamine significantly reduced DSS induced DAI (See **FIGS.8A-8D**).

Example 10

Compound 13 reduced DSS-induced colon shortening in dextran sodium sulfate (DSS) induced Colitis Murine model

[0771] DSS induced Colitis mice model was developed as described above. On the day of termination (day 8), 1 h prior to dissection animals were gavaged with different doses of Compound 13. Animals were euthanized with CO₂ asphyxiation in accordance with approved institutional animal ethical protocols.

[0772] Animals were sprayed with 70% ethanol and carefully opened by ventral midline incision. Colon was collected by lifting the colon with forceps carefully by separating them from the small intestine at the ileocecal junction and from the anus at the distal end of rectum. Representative colon pictures were captured. Colon length was measured by straightening the colon without stretching.

[0773] A significant decrease in colon length on day 8 was observed in the disease control group. Treatment with Compound 13 and Mesalamine significantly prevented DSS induced colon shortening (See FIG.9A and FIG.9B).

Example 11

Compound 13 prevents DSS-induced intestinal permeability in dextran sodium sulfate (DSS) induced Colitis Murine model

[0774] DSS induced Colitis mice model was developed as described above. On the day of termination (day 8), all animals received FITC-dextran (60 mg/100g body weight) via PO route in PBS and bled after 4h to collect hemolysis-free serum/plasma. 1 h prior to dissection animals were gavage with Compound 13 doses. For qRT-PCR analysis, small pieces of middle colon (20 mg) were stored in RNAlater at -80°C until RNA extraction. On the day of RNA extraction, colons were removed from RNAlater and RNA was extracted by using Qiagen RNeasy Protect Mini Kit 250 as per manufacturer protocol and then q-PCR was performed. The expression analysis of Claudin-1, Occludin and zona occludin-1 was evaluated.

[0775] A significant increase in FITC-dextran permeability was observed on day 8 in the disease control group. Treatment groups with Compound 13 and Mesalamine significantly prevented DSS induced FITC-dextran permeability. Treatment with Compound 13 and Mesalamine significantly prevented DSS induced decrease in tight junction proteins (See FIG.10A-FIG.10D).

Example 12

Compound 13 reduced DSS-induced clinically relevant markers in dextran sodium sulfate (DSS) induced Murine model

[0776] DSS induced Colitis mice model was developed as described above. Fecal samples were collected and stored in -80°C until analysis. Fecal samples were homogenized in PBS

(100 mg/ml or max 500 μ L) and vortexed for 30 min at 4 °C in Thermo shaker. Samples were centrifuged at 12,000 rpm for 15 min at 4 °C. Supernatant were collected, and fecal level of calprotectin and lipocalin-2 were evaluated using Mouse calprotectin ELISA assay kit (EM1620, FineTest) and mouse lipocalin-2 (NGAL) kit (DY1857; R&D system), respectively as per protocol mentioned with kit after proper dilution. The level of fecal calprotectin and Lipocalin-2 were normalized with fecal weight. Serum CRP was measured by ELISA.

[0777] The presence of calprotectin in faeces is a consequence of neutrophil migration into the gastrointestinal tissue due to an inflammatory process. Compound 13 dose dependently reduced levels of clinically relevant biomarkers in the DSS model namely fecal calprotectin, Lipocalin-2 and serum CRP. (See **FIG.11A-FIG.11C**).

Example 13

Effect of Compound 13 on DSS-induced proinflammatory markers in colon

[0778] DSS induced Colitis mice model was developed as described above. For expression analysis of cytokines (IL-6, TNF- α , IL-1 β , and NLRP3) q-PCR was performed on RNA isolated from middle colon region. A small piece of middle colon (20 mg) was stored in RNAlater at -80°C until RNA extraction. On the day of RNA extraction, colons were removed from RNAlater and RNA was extracted by using Qiagen RNeasy Protect Mini Kit 250 as per manufacturer protocol and then q-PCR was performed. The expression analysis of IL-6, TNF- α , IL-1 β , and NLRP3 was evaluated.

[0779] A Significant increase in tissue inflammatory markers was observed in disease control group colon. Treatment with Compound 13 and Mesalamine significantly prevented DSS induced inflammatory markers in colon. (See **FIG.12A-FIG.12C**).

Example 14

Effect of Compound 13 on DSS-induced systemic inflammation

[0780] DSS induced Colitis mice model was developed as described above. Animals were sprayed with 70% ethanol and carefully opened by ventral midline incision. Spleen was collected, weighed and picture was captured. Increased spleen weights generally correlate with the extent of inflammation and anaemia. Spleen weight was normalized with body weight (spleen index).

[0781] A Significant increase in spleen index (splenomegaly) was observed in the disease control group. Treatment with Compound 13 and Mesalamine showed a trend towards decrease in DSS induced spleen index (See FIG.13A-FIG.13C).

Example 15

Effect of Compound 13 on DSS-induced proinflammatory markers in serum

[0782] DSS induced Colitis mice model was developed as described above. ELISA of IL-6 and TNF- α from serum was performed using Mouse IL-1B Elisa Kit (R&D systems, DY401) and Mouse IL-6 Elisa Kit (R&D systems, DY406) as per manufacturer's protocol. A significant increase in serum proinflammatory markers (IL-6 and TNF- α) was observed on day 8 in the disease control group. Treatment with Compound 13 and Mesalamine reduced DSS induced proinflammatory markers (IL-6 and TNF- α) (See FIG.14A and FIG.14B).

Example 16

Effect of Compound 13 on DSS-induced systemic inflammation

[0783] DSS induced Colitis mice model was developed as described above. For histopathology, distal colons (~1 cm) were collected and stored in 10% formalin solution. Sample processing and staining were performed as per standard procedure. A significant increase in histopathological score was observed on day-8 in the disease control group. Treatment with Compound 13 and Mesalamine reduced DSS induced histopathology scoring. (See FIG.15).

Example 17

Jurkat TL1A HTS Reporter Assay

[0784] TL1A, also known as TNFSF15, is part of the tumor necrosis family, and competitively binds to death receptor 3 to stimulate multiple signaling pathways. Research has implicated TL1A in autoimmune diseases, including rheumatoid arthritis, inflammatory bowel disease, psoriasis, primary biliary cirrhosis, systemic lupus erythematosus and ankylosing spondylitis. A high throughput screen for receptor antagonist or pathway inhibitors using TNF-like ligand 1A (TL1A)-Responsive Luciferase Reporter Jurkat Cell Line (BPS Bioscience) was developed. The cells produce firefly luciferase, controlled via the NF- κ B signaling and

stimulation with human TL1A cytokine. The Jurkat reporter cells are amenable to high throughput screening in 1536 well as the assay can be miniaturized to the small volumes HTS requires. The reporter cells are suspension cells that are directly thawed in the testing media/assay media.

[0785] Table 2: Composition of the assay or testing media:

Component	Vendor	Catalog Number	Volume	Final Concentration
RPMI 1640 (L-glutamine, No Phenol Red)	R&D Systems Inc.	M30350	500mL	1X
FBS (Heat Inactivated)	Gibco (Thermo)	A56698-01	50mL	10%
Penicillin-Streptomycin (10,000 U/mL)	Gibco (Thermo)	15140122	5.5mL	1%
Sodium Pyruvate	Fischer Scientific	11-360-070	5.55 mL	1%
HEPES	Gibco	15630080	5.55 mL	1%
D-(+)-Glucose solution	Sigma-Aldrich	G8644-100ML	14 mL	

[0786] A brief experimental protocol for the TL1a HTS assay is given below:

[0787] Day 1: 24 hours Prior to Running the Assay: The TL1A test media was equilibrated in the incubator for 15 to 30 minutes and then used to thaw the cells. The cells were thawed in a 37°C water bath by adding cells in a dropwise manner into prewarmed test media. Up to 7 x 3 mL vials of cells into a 50mL conical with corresponding amounts of media. The cells were spun down at 275g for 5 mins. Media was aspirated off of the cells leaving around 3-5 mL remaining as to not disturb the cell pellet. An appropriate amount of test media was added to resuspend the cells as to not go below 1.5M c/mL. A small aliquot of cells was diluted in 1:1 ratio in Trypan blue and cell count/viability was measured. The cells were diluted to 1.5M/mL in test media for ~24 hr incubation at 37°C prior to use in the assay.

[0788] Day 2: Prior to Beginning the Following Steps were performed to reduce cell time out of the incubator: rhTL1a cytokine dilution was prepared for 1 uL addition into each well. The treatment was done at 85 ng/mL, the dilution must be at 5X in the tube (425 ng/mL). 1 uL

of test media was added to column 1 of each plate. For cell plating, the cells that have been incubating for 24h at 37°C were collected into an appropriate size container. The cells were vigorously pipetted up and down with a serological pipette of ~10 mL to break up any clumps and obtain a more homogenous suspension (at least 5 times). Cell viability by trypan blue method was repeated for atleast three counts and appropriate dilutions per cell tube corresponding to 5,500 cells/well in 4 µl or 1,374,000 cells/mL was done. Additional testing media was added as required and 4 µl of cells to each well was added. Cytokine addition was dispensed i.e., 1 uL of test media into column 1 of each plate for the positive control. Then 1 uL of the 5X cytokine solution to the remaining columns 2-48 was added and the plate was incubated at 37°C for 4 hours. Around 30 minutes before the 4-hour incubation is done the reagent was added. When the 4-hour incubation was completed, the assay plates were removed from the incubator and allowed to cool at RT for 30 min

With their lids removed and single monolayer on the benchtop. After 30 minutes of cooling, the plates were ready to have SteadyLite added. Using the SteadyLite specific cassette 2 uL of 1X reagent was added to each well. The plates were placed into a plate hotel with NO lid and let sit for 60 min. The plates into a room above 70°C. After 60 min, readout the plates on the Nexus or Envision 2105 using programs for ultrasensitive luminescence with 50 ms and High Aperture. The data was normalized to DMSO and column 1. The reference compound was Amlexanox, TBK1 and IKKε inhibitor with a top concentration of 100 uM in well and other test compounds i.e., Compound 13 and its analogs whose IC₅₀ was to be determined were taken. Dose response cuves of the reference compound and the test compounds was taken and the IC₅₀ was determined (As shown in Table 3)

[0789] Table 3. HTS TL1a: IC₅₀ (uM)

Compound ID	HTS TL1a: IC ₅₀ (µM)
1	-
2	++
3	++
4	++
5	+++
6	++
7	+++
8	-
9	+++
10	++

11	+++
12	-
13	+++
14	++
15	+++
16	-
17	+++
18	-
19	-
20	+++
21	+++
22	++
23	-
24	+++
25	+++
26	+++
27	+++
28	+++
29	++
30	+++
31	+++
32	++
33	++
34	-
35	-
36	-
37	-
38	-
39	-
40	++
41	++
42	++
43	-
44	++
45	++
46	-
47	++
48	++
49	-
50	-
51	+++
52	++
53	+++
54	+++
55	+++
56	++
57	-
58	++

59	+++
60	++
61	-
62	+++
63	++
64	+++
65	+++
66	++
67	+++
68	+++
69	-
70	+++
71	+++
72	++
73	-
74	+++
75	++
76	+++
77	+++
78	+++
79	+++
80	+++
81	+++
82	+++
83	-
84	+++
85	-
86	+++
87	-
88	+++
89	+++
90	+++
91	+++
92	-
93	+++
94	-
95	+++
96	+++
97	++
98	+++
99	+++
100	+++
101	+++
102	+++
103	-
104	-
105	+++
106	-

107	-
-----	---

+ = IC₅₀ > 50 μ M; ++ = IC₅₀ 1-50 μ M; +++ = IC₅₀ < 1 μ M

Example 18

Compound 55 inhibited IL-1 β release from differentiated THP1 cells

[0790] Intracellular receptor NLRP3 assembles an inflammasome protein complex that facilitates the caspase-1-mediated maturation and release of IL-1 β from cell. This experiment was performed to determine the potency of Compound 55 in inhibition of IL-1 β release. For the experiment cells were seeded in flat bottom plate (75000 cells /well) in 200 μ l. During seeding PMA (15ng/ml) was added for differentiation of cells. Then plates were incubated for overnight (16-18 hr). Next day, the old media was changed with fresh RPMI media (180 μ l) and 20 μ l of 10X LPS (Final conc. 0.5 μ g/ml) was added. Then cells were incubated for 2h @ 37°C with 5% CO₂. After incubation LPS media was removed and washed with PBS (One Time) and 160 μ l fresh media was added. Then cells were treated with Compounds (10x drug_20 μ l) and Nigericin (10X_20 μ l). Then Plates were incubated for overnight (16-18h). After incubation, supernatant was collected for ELISA (Kept in -80 degree C for further use). CTG was done from pellet. Next day IL-1 β ELISA was performed.

[0791] The anti-inflammasome activity of synthesized analogs such as Compound 55 on IL-1 β release post LPS and nigericin treatment of differentiated THP1 cells was determined. It was observed that Compound 55 inhibited IL-1 β release dose dependent manner. Calculated IC₅₀ of Compound 55 is ~460 nM (See **FIG.16**).

Example 19

Effect of Compound 55 on pyroptosis in differentiated THP1 cells

[0792] Intracellular receptor NLRP3 assembles an inflammasome protein complex that facilitates the caspase-1-mediated maturation of IL-1 β in cell and activates Gasdermin D to create pore in the cell membrane which is known as pyroptosis. The mature IL-1 β comes out to extracellular space through these pores. This experiment was designed and performed to determine the efficacy of Compound 55 in inhibition of pyroptosis. For the experiment, THP1 cells were seeded in black transparent flat bottom plate (75000 cells /well) in 200 μ l with PMA

(15ng/ml) for differentiation of cells. Then plates were incubated for overnight (16-18h). Next day, the old media was changed with fresh RPMI media (200 μ l) containing 0.5 μ g/ml LPS. Then cells were incubated for 3h @ 37° C with 5% CO₂. After incubation LPS media was removed and washed with PBS (One Time) and 160 μ l fresh propidium iodide containing HBSS was added. Then cells were treated with Compounds (10x drug_20 μ l) and Nigericin (10X_20 μ l). Then Plates were incubated for 2h. After incubation, fluorescence read was taken at Ex/Em 535/615nm in plate reader.

[0793] We have clearly observed that Compound 55 inhibits release of IL-1 β post LPS and nigericin treatment. However, we validated the data with different assay/PI uptake inflammasome assay. Pyroptosis is the upstream step of IL-1 β release, here we have used propidium iodide, which is a dye, that stains nuclei but is unable to enter to live cells until there is pore in the cell membrane. Compound 55 treated cells led to a dose dependent inhibition of PI uptake/ pyroptosis post LPS and nigericin stimulation of differentiated THP1 cells. The calculated IC₅₀ is ~370 nM. (See **FIG.17**).

Example 20

Effect of Compound 55 in Alcohol-induced liver injury mouse model

[0794] Animals were acclimatized to control liquid diet from day 1 to 5. On day 6 of the study, animals with preference to liquid diet were included in study and randomized based on body weight into seven groups. Liver injury was induced by 5% EtOH liquid diet daily for 11 days (from day 6 to day 16) in animals from Group 2- Group 7 (G2-G7). The 5% EtOH liquid diet was offered at 3h post respective treatment on day 6. Group G1 was given control liquid diet for 11 days. G2 group was administered orally with vehicle. Groups G3 to G6 received Compound 55 at 0.1, 1, 3 and 10 mg/kg p.o., QD for 11 days respectively. G7 group was administered with internal reference compound, Compound NP, 5 mg/kg, i.p. for 11 days. On day 16, mice in G1 group were administered with maltose dextrin (9 g/kg, p.o.). G2 to G7 groups animals were administered with ethyl alcohol (31.5 %, single binge, 5g/kg, p.o.) post 3h of respective treatments.

[0795] At end of study on day 16th (treatment day 11), blood was collected at 9h post ethyl alcohol binge by retro-orbital plexus under isoflurane anesthesia and the serum was separated by allowing the blood to clot for 15-20 min and centrifuged at 4°C, 8000 RPM for 10 minutes, and then stored at -80°C. Serum was used for AST, ALT estimation by Selectra Pro M Lite -

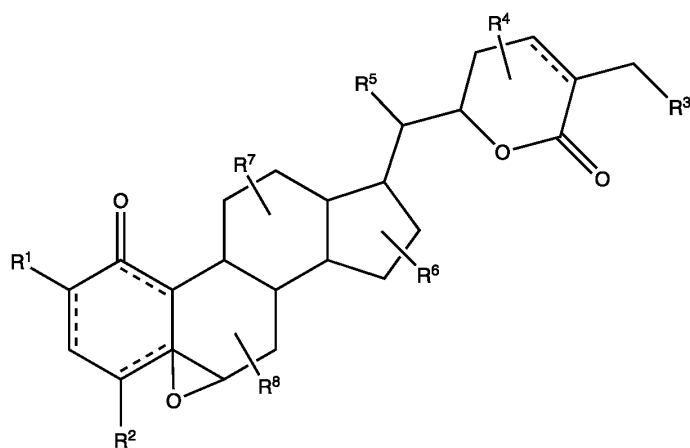
Fully Automated Biochemistry Analyzer. Liver was collected and part of each lobe of liver was snap frozen in liquid nitrogen followed by storage at -80°C. Liver samples were further processed for the hepatic total cholesterol and triglyceride levels estimation by Selectra Pro M Lite - Fully Automated Biochemistry Analyzer.

[0796] Serum ALT and AST levels were significantly increased in the disease control group compared to normal control and Compound 55 at 10 mg/Kg treated group (G6) showed significant reduction compared to disease group. Similarly, liver triglyceride and cholesterol levels were elevated significantly in disease control groups. In Compound 55 at 10 mg/Kg group (G6), liver triglyceride levels were significantly lowered than disease control. In case of liver cholesterol levels, all the Compound 55 treated groups showed significant reduction compared to disease control group. Internal in-house control group treated with Compound NP at 5mg/Kg dose showed efficacy in all the parameters. These results clearly suggest that Compound 55 protects against alcohol-induced liver injury model in C57BL/6 female mice (See **FIG.18A-18D**).

CLAIMS

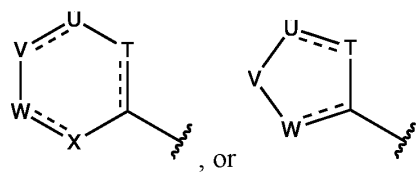
What is claimed is:

1. A compound of Formula (I):



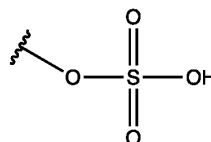
(I), or a

pharmaceutically acceptable salt thereof, wherein:



R^1 is hydrogen, $-NR^9R^{10}$, $-COOR^9$, $-CN$,

R^2 is hydrogen, halogen, $-OR^9$, $-SR^9$, $-NR^9R^{10}$, $-COOR^9$, $-COHR^9R^{10}$, $-CR^9R^{10}R^{11}$, $-CN$, $-N_3$, C_1 - C_6 alkyl, C_1 - C_6 haloalkyl, C_2 - C_6 alkenyl, C_2 - C_6 alkynyl, C_1 - C_6 alkoxy, aryl,



aralkyl, heteroaryl, cycloaliphatic ring, heterocyclyl, or $-SO_3H$, wherein the C_1 - C_6 alkyl, the aryl, the heteroaryl, cycloaliphatic ring, or heterocyclyl are unsubstituted or substituted with one or more R^{12} ;

R^3 is hydrogen, halogen, $-OR^9$, $-SR^9$, $-NR^9R^{10}$, $-COOR^9$, $-COHR^9R^{10}$, $-CR^9R^{10}R^{11}$, $-CN$, $-N_3$, C_1 - C_6 alkyl, C_1 - C_6 haloalkyl, C_2 - C_6 alkenyl, C_2 - C_6 alkynyl, C_1 - C_6 alkoxy, aryl, aralkyl, heteroaryl, cycloaliphatic ring, heterocyclyl, $-(NR^9R^{10}R^{11})^+$, or $-OC(=O)NH-(C_2-C_6 \text{ alkynyl})$, wherein the C_1 - C_6 alkyl, the aryl, the heteroaryl, cycloaliphatic ring, or heterocyclyl are unsubstituted or substituted with one or more R^{12} ;

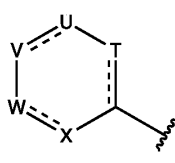
T, U, V, W, and X are each, independently, CH, CR^{12} , sulfur, nitrogen, NH, NR^{12} , or N^+-O^- ;

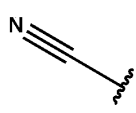
R^4 , R^5 , R^6 , R^7 , R^8 , R^9 , R^{10} , and R^{11} are each, independently, hydrogen, deuterium, halogen, or a C₁-C₆ unsubstituted or substituted alkyl; and

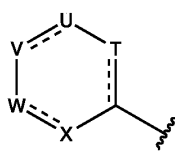
each R^{12} is, independently, deuterium, halogen, =O, -OR⁹, -SR⁹, -NR⁹R¹⁰, -COOR⁹, -COHR⁹R¹⁰, -CR⁹R¹⁰R¹¹, -CN, -N₃, C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₁-C₆ alkoxy, aryl, aralkyl, heteroaryl, cycloaliphatic ring, heterocyclyl, or -O-(heterocyclyl);

with the proviso:

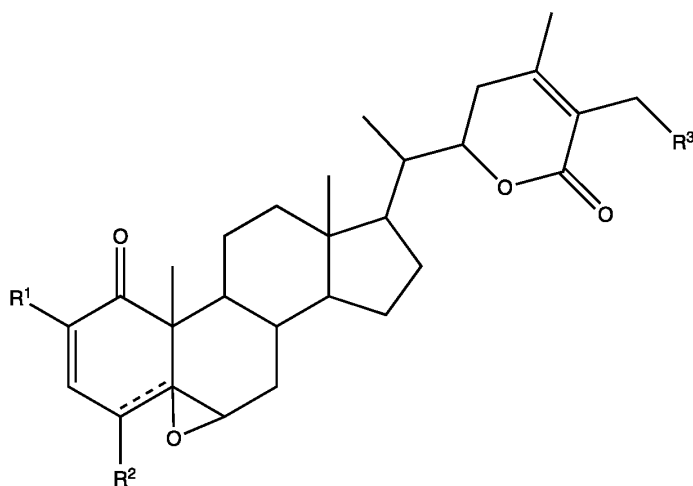
(1) when R^1 is hydrogen, then R^2 is a halogen;

(2) when R^1 is  and each of T, U, V, W, and X is CH or CR¹²,

then only one of T, U, V, W, and X is CR¹², wherein R^{12} is  or -OCH₃, and the remaining T, U, V, W, and X are CH; and

(3) when R^1 is , T and X are CH, one of W or U is nitrogen, and the other of W or U is CH, then V is not C(-OCH₃).

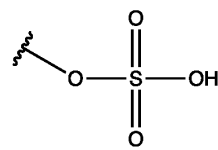
2. The compound of claim 1, wherein the compound of Formula (I) is a compound of Formula (Ia):



(Ia), or a

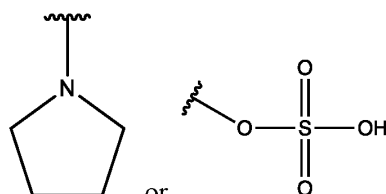
pharmaceutically acceptable salt thereof.

3. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein R^2 is



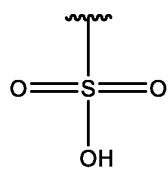
halogen, $-OR^9$, $-NR^9R^{10}$, 5-membered heterocyclyl, or R^9 and R^{10} are each independently hydrogen or C₁-C₆ alkyl.

4. The compound of claim 3, or a pharmaceutically acceptable salt thereof, wherein R^2 is



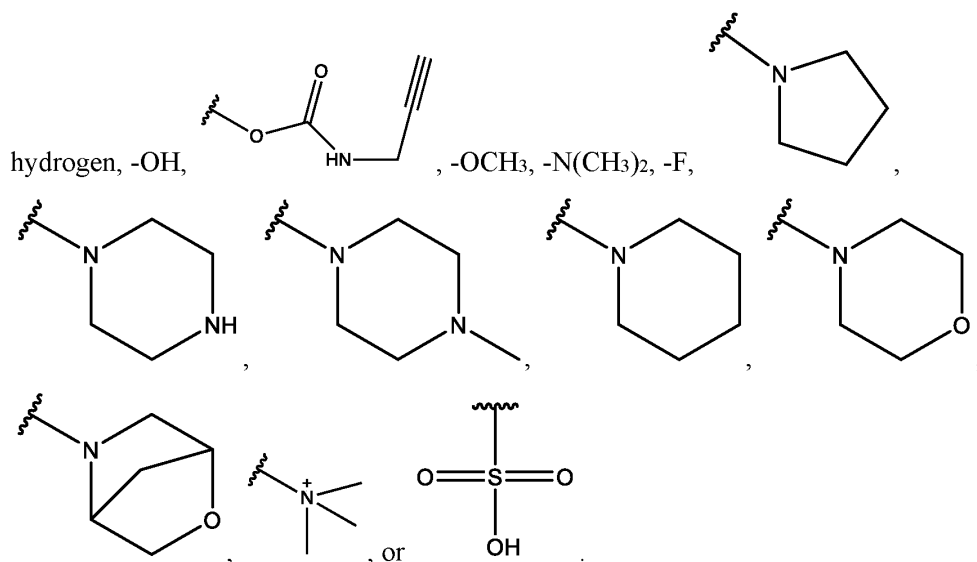
$-OH$, $-F$, $-N(CH_3)_2$, or

5. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein R^3 is hydrogen, halogen, $-OR^9$, $-NR^9R^{10}$, C₁-C₆ alkoxy, 5- to 6-membered heterocyclyl optionally substituted by one or more C₁-C₆ alkyl, $-(NR^9R^{10}R^{11})^+$, $-OC(=O)NH-(C_2-$

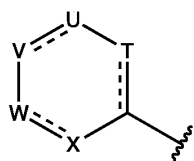


C₆ alkynyl), or R^9 , R^{10} , and R^{11} are each independently hydrogen or C₁-C₆ alkyl.

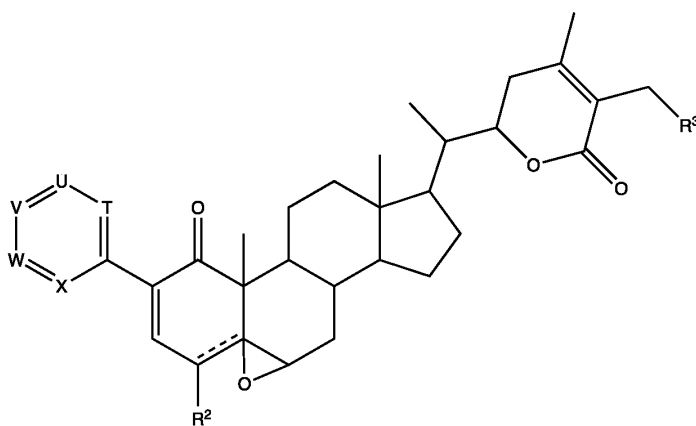
6. The compound of claim 5, or a pharmaceutically acceptable salt thereof, wherein R^3 is



7. The compound of claim 2, or a pharmaceutically acceptable salt thereof, wherein R¹ is:



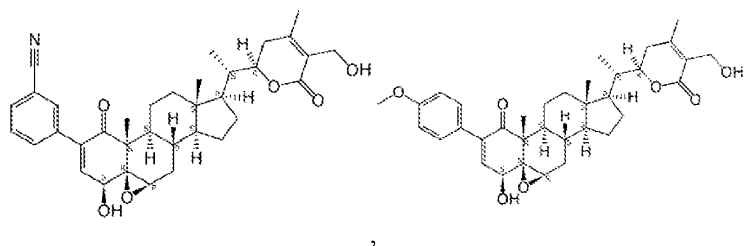
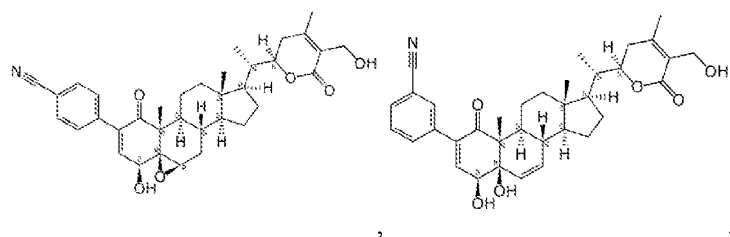
8. The compound of claim 7, wherein the compound of Formula (Ia) is a compound of Formula (Iaa):



(Iaa), or a

pharmaceutically acceptable salt thereof.

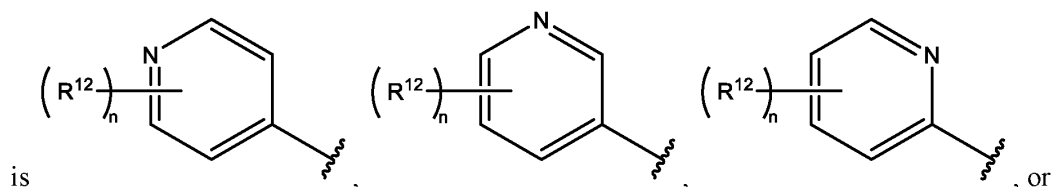
9. The compound of claim 8, or a pharmaceutically acceptable salt thereof, wherein T, U, V, W, and X are each CH or CR¹².
10. The compound of claim 9, wherein the compound of Formula (Iaa) is selected from the group consisting of:



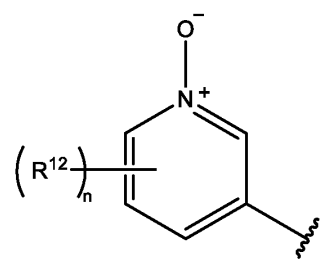
, or a pharmaceutically acceptable salt or stereoisomer thereof.

11. The compound of claim 8, or a pharmaceutically acceptable salt thereof, wherein only one of T, U, V, W, and X is sulfur, nitrogen, NH, NR¹², or N⁺-O⁻, and the remainder of T, U, V, W, and X are each CH or CR¹².

12. The compound of claim 11, or a pharmaceutically acceptable salt thereof, wherein R¹

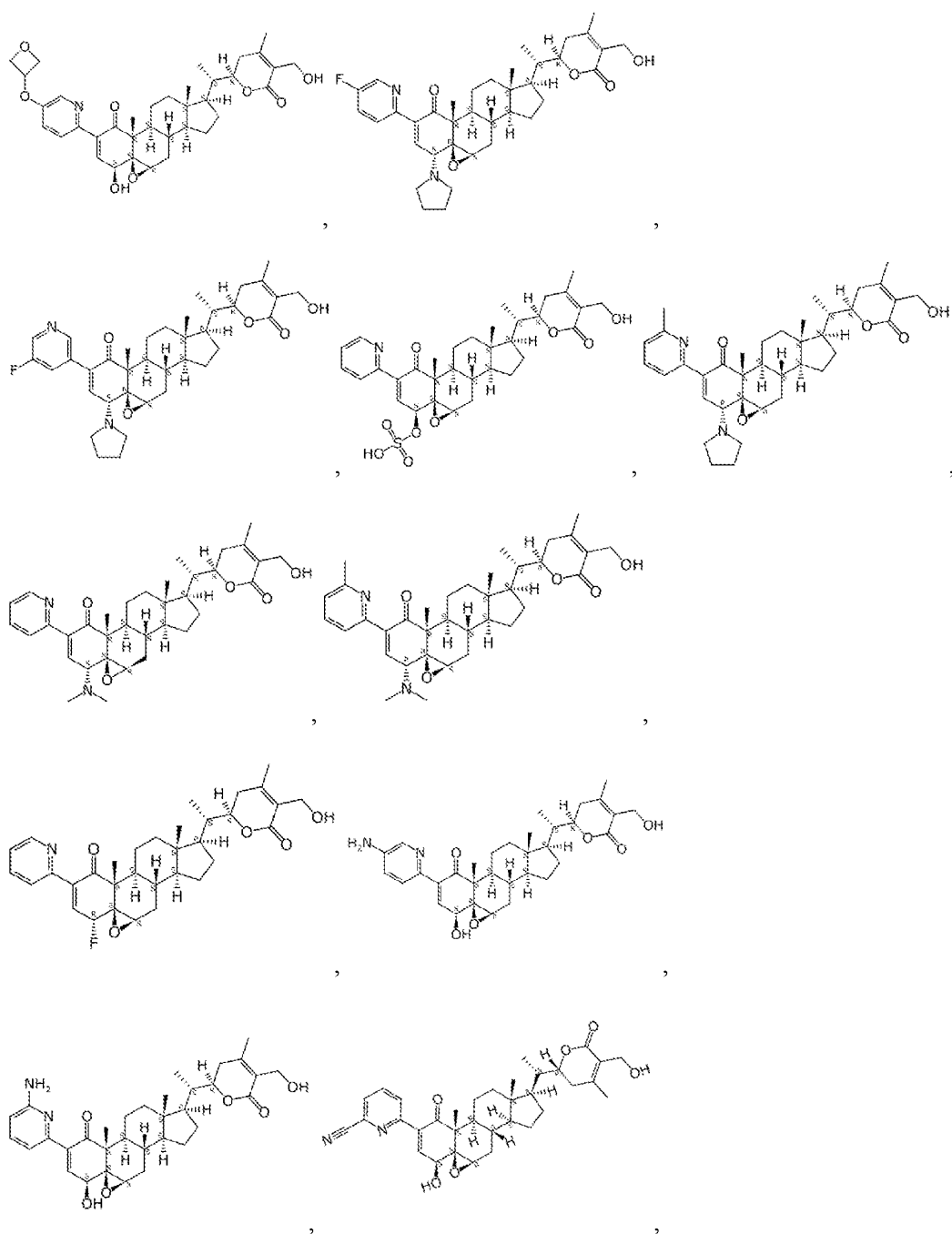


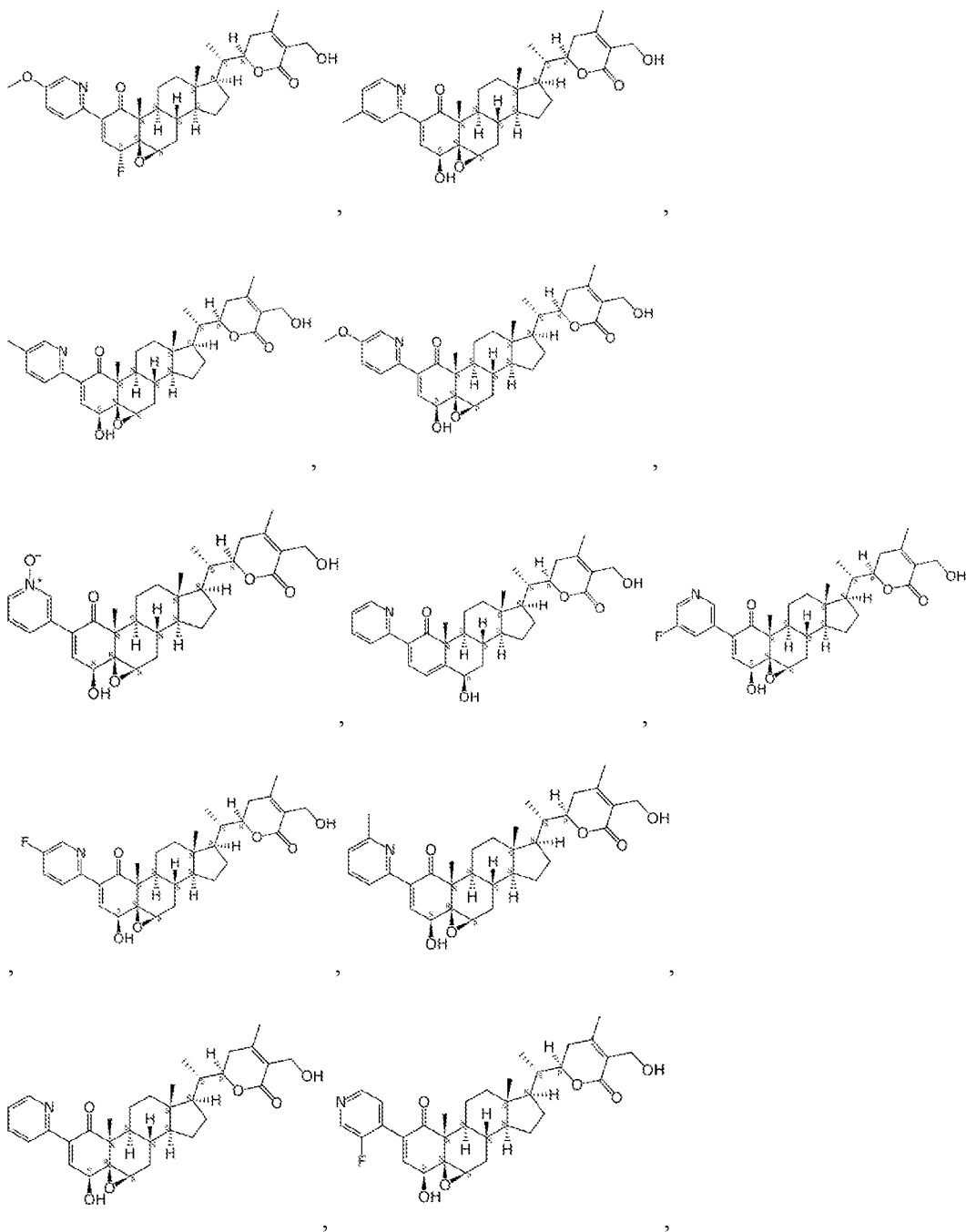
is

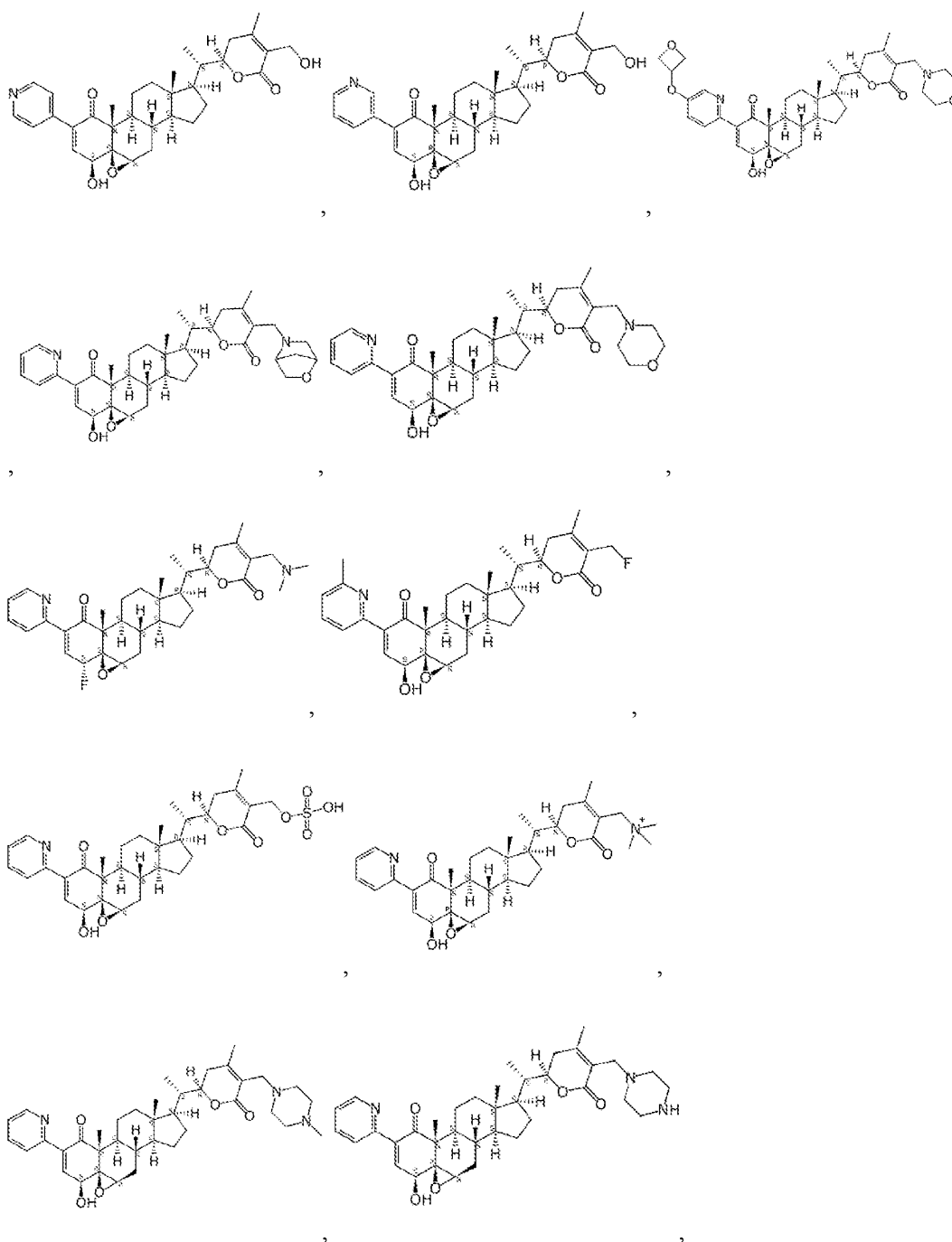


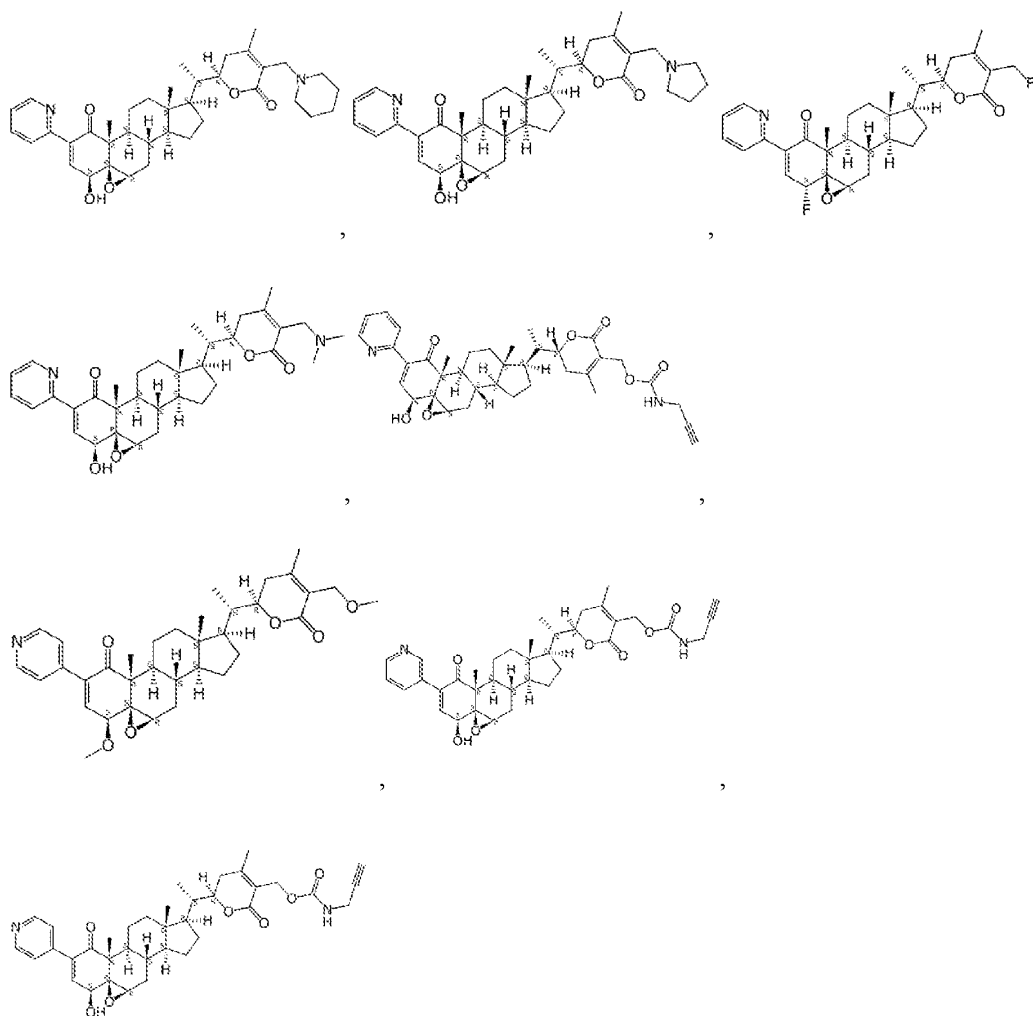
wherein n is 0, 1, 2, 3, or 4.

13. The compound of claim 11, wherein the compound of Formula (Iaa) is selected from the group consisting of:







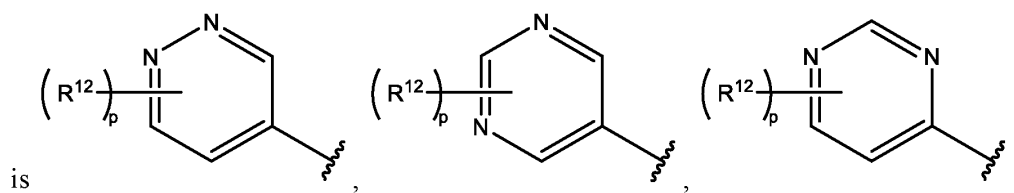


, or a pharmaceutically acceptable salt or stereoisomer

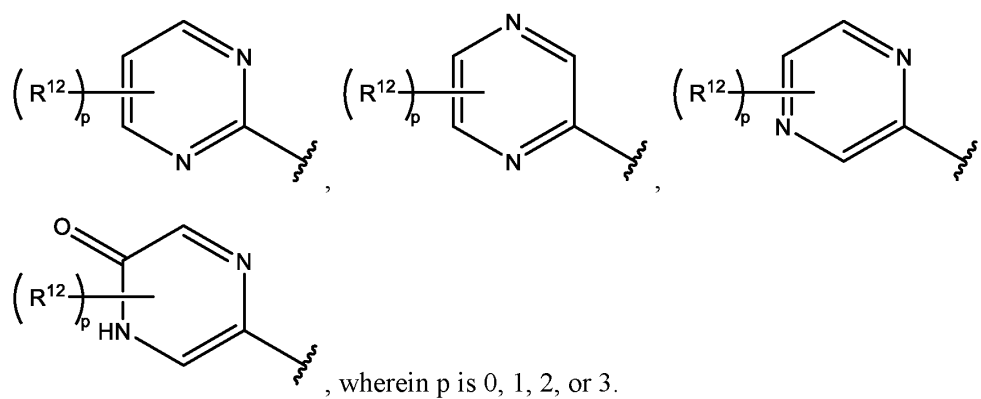
thereof.

14. The compound of claim 8, or a pharmaceutically acceptable salt thereof, wherein at least two of T, U, V, W, and X are sulfur, nitrogen, NR^{12} , or N^+R^{12} , and the remaining T, U, V, W, and X are CH or CR^{12} .

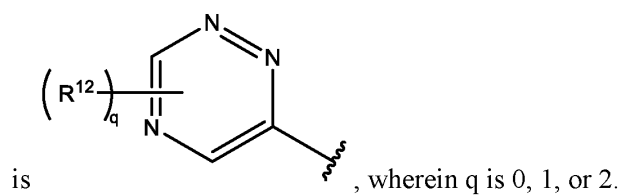
15. The compound of claim 14, or a pharmaceutically acceptable salt thereof, wherein R^1



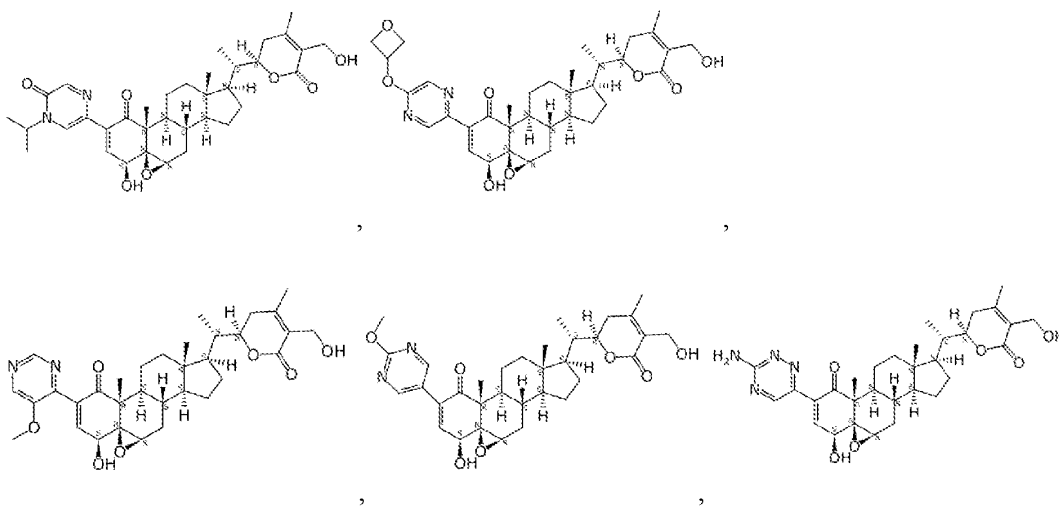
is

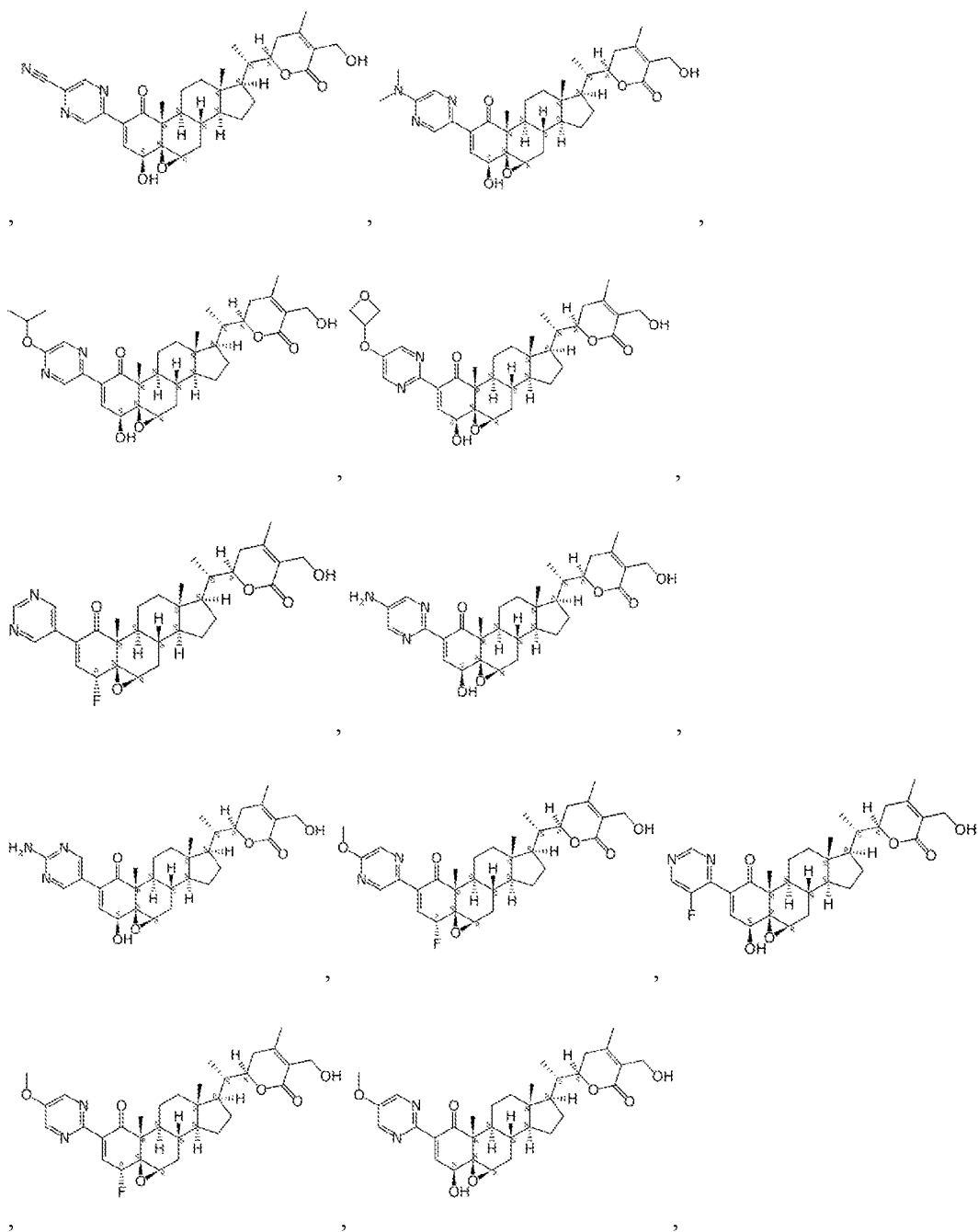


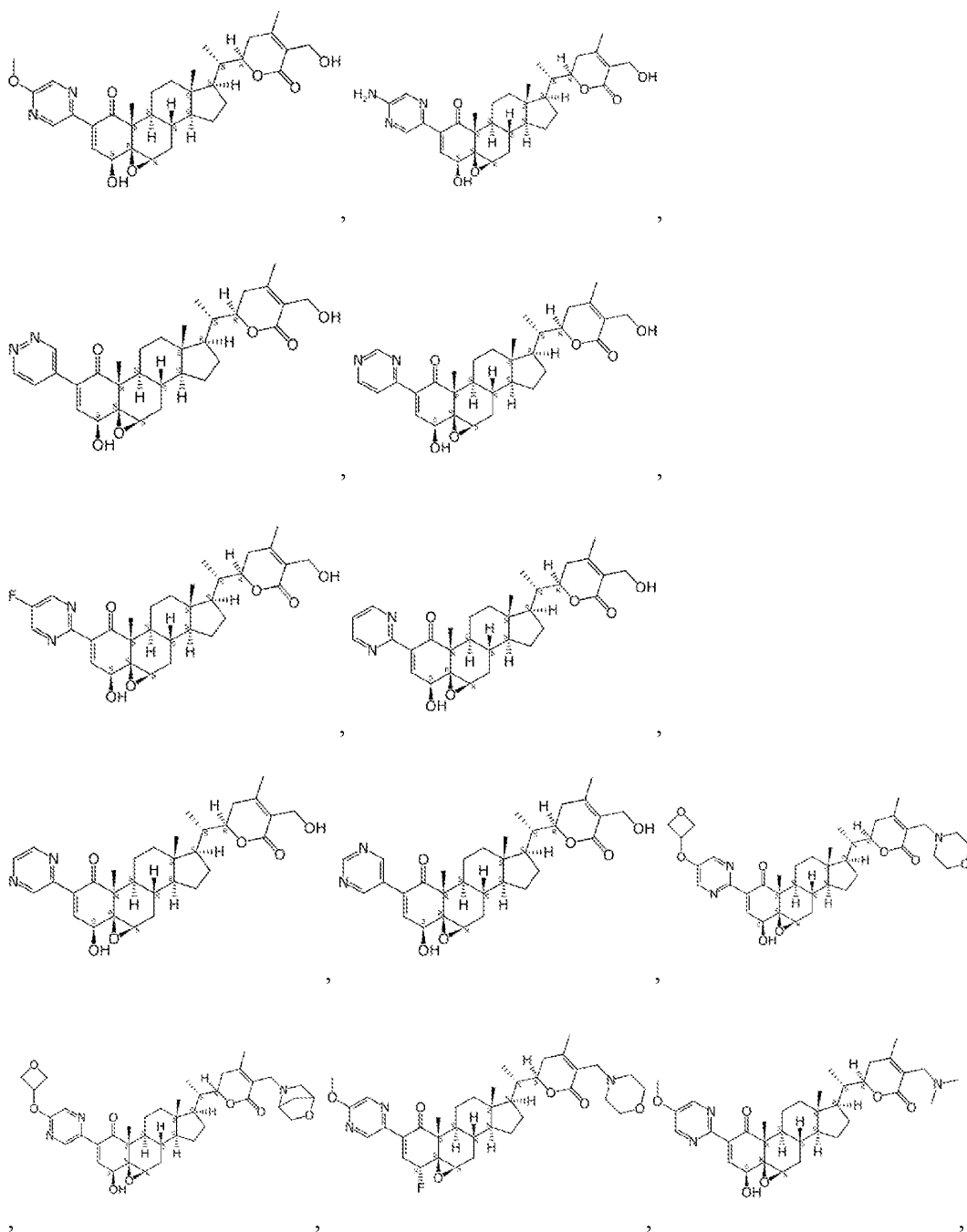
16. The compound of claim 14, or a pharmaceutically acceptable salt thereof, wherein R^1

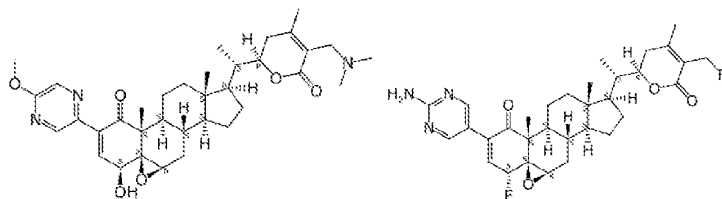
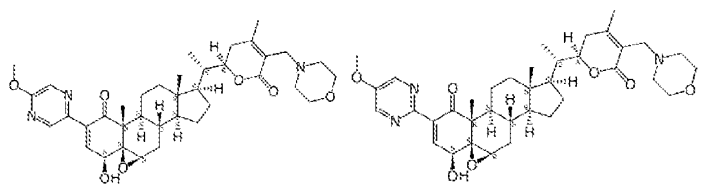


17. The compound of claim 14, wherein the compound of Formula (Iaa) is selected from the group consisting of:



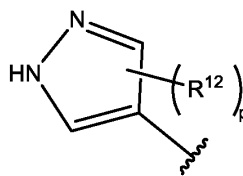
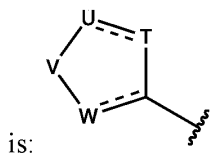




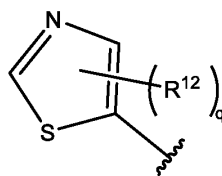


, or a pharmaceutically acceptable salt or stereoisomer thereof.

18. The compound of claim 2, or a pharmaceutically acceptable salt thereof, wherein R^1

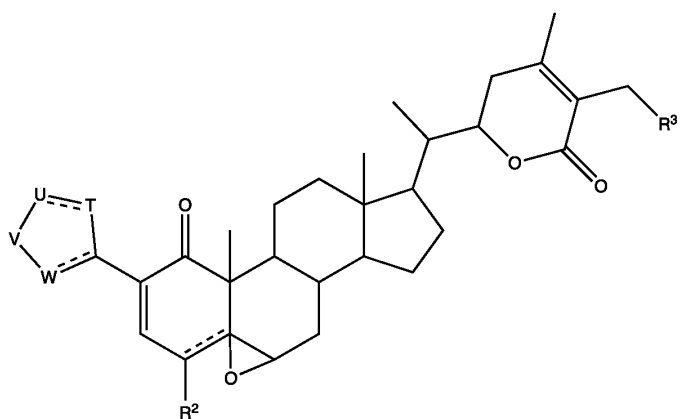


19. The compound of claim 18, wherein R^1 is or 3. , wherein p is 0, 1, 2,



20. The compound of claim 18, wherein R^1 is , wherein q is 0, 1, or 2.

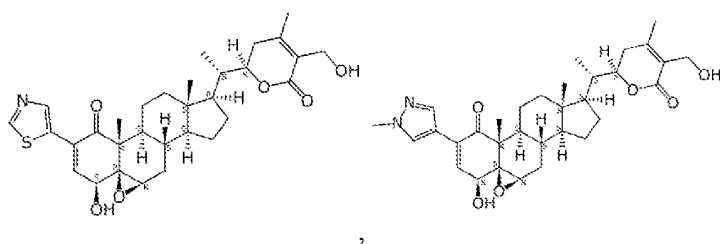
21. The compound of claim 18, wherein the compound of Formula (Ia) is a compound of Formula (Iab):



(Iab), or a

pharmaceutically acceptable salt thereof.

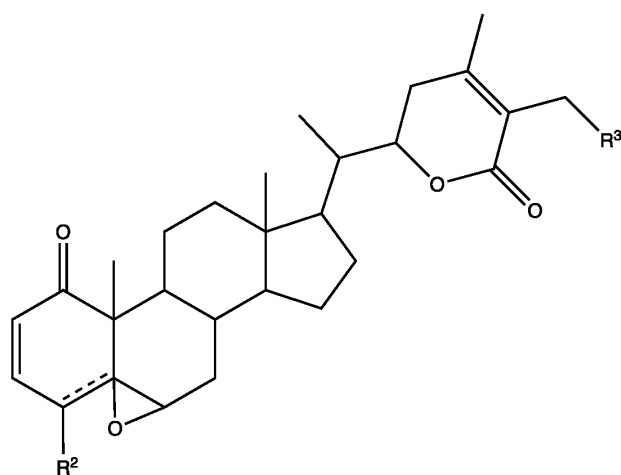
22. The compound of claim 18, wherein the compound of Formula (Iab) is selected from the group consisting of:



, or a pharmaceutically acceptable salt or stereoisomer thereof.

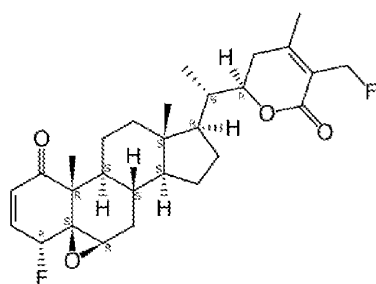
23. The compound of claim 2, or a pharmaceutically acceptable salt thereof, wherein R^1 is hydrogen.

24. The compound of claim 23, wherein the compound of Formula (Ia) is a compound of Formula (Iac):



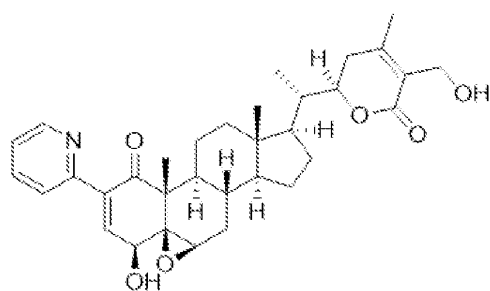
(Iac), or a pharmaceutically acceptable salt thereof, and wherein R^2 is halogen.

25. The compound of claim 24, wherein the compound of Formula (Iac) is:



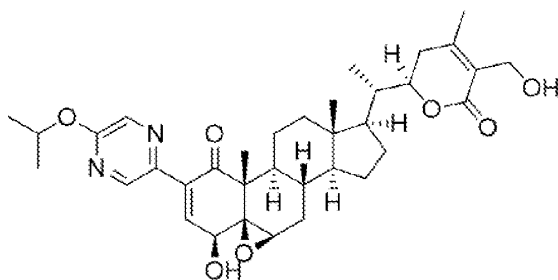
, or a pharmaceutically acceptable salt or stereoisomer thereof.

26. The compound of claim 1, wherein the compound is



, or a pharmaceutically acceptable salt thereof.

27. The compound of claim 1, wherein the compound is



, or a pharmaceutically acceptable salt thereof.

28. A pharmaceutical composition comprising the compound of any one of claims 1 to 27, or a pharmaceutically acceptable salt or stereoisomer thereof, and at least one pharmaceutically acceptable carrier.

29. A method of treating, ameliorating, or preventing a condition or disease in a subject in need thereof, wherein the disease is mediated by the NLR Family Pyrin Domain Containing 3 (NLRP3) inflammasome or by tumor necrosis factor alpha (TNF- α), and wherein the method comprises administering to the subject a therapeutically effective amount of a compound according to any one of claims 1 to 27, or a pharmaceutically acceptable salt thereof.

30. The method of claim 29, wherein the condition or disease is mediated by the NLR Family Pyrin Domain Containing 3 (NLRP3) inflammasome.

31. The method of claim 29, wherein the condition or disease is mediated by tumor necrosis factor alpha (TNF- α).

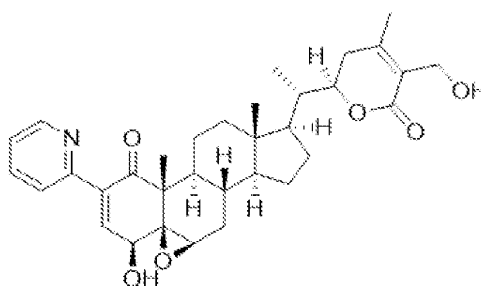
32. The method of claim 29, wherein the condition or disease is a cardiovascular condition or disease, an endocrine condition or disease, a neurological condition or disease, a gastrointestinal condition or disease, or a combination thereof.

33. The method of claim 29, wherein the condition or disease is inflammatory bowel disease (IBD), Crohn's disease, colorectal cancer, alcoholic hepatitis, or a combination thereof.

34. The method of claim 32, wherein the condition or disease is inflammatory bowel disease (IBD), Crohn's disease, or a combination thereof.

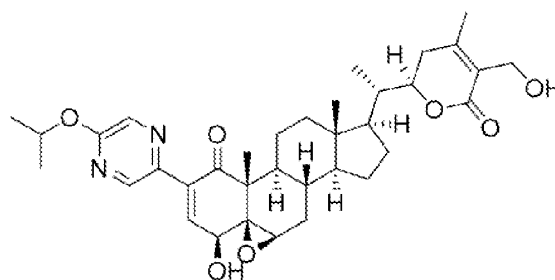
35. The method of claim 32, wherein the condition or disease is colorectal cancer, alcoholic hepatitis, or a combination thereof.

36. The method of claim 29, wherein the condition or disease is inflammatory bowel



disease (IBD), and wherein the compound is
or a pharmaceutically acceptable salt thereof.

37. The method of claim 29, wherein the condition or disease is alcoholic hepatitis, and



wherein the compound is
pharmaceutically acceptable salt thereof.

38. The method of claim 29, wherein the compound, or a pharmaceutically acceptable salt thereof, is administered orally.

39. A method of treating, ameliorating, or preventing a condition or disease in a subject in need thereof, wherein the disease is mediated by the NLR Family Pyrin Domain Containing 3 (NLRP3) inflammasome or by tumor necrosis factor alpha (TNF- α), and wherein the method comprises administering to the subject a therapeutically effective amount of a pharmaceutical composition according to claim 28.

40. The method of claim 39, wherein the condition or disease is mediated by the NLR Family Pyrin Domain Containing 3 (NLRP3) inflammasome.

41. The method of claim 39, wherein the condition or disease is mediated by tumor necrosis factor alpha (TNF- α).

42. The method of claim 39, wherein the condition or disease is a cardiovascular condition or disease, an endocrine condition or disease, a neurological condition or disease, a gastrointestinal condition or disease, or a combination thereof.

43. The method of claim 39, wherein the pharmaceutical composition is administered orally.

44. A pharmaceutical composition comprising a compound of any one of claims 1 to 27, or a pharmaceutically acceptable salt or stereoisomer thereof, for use in a method of treating, ameliorating, or preventing a condition or disease mediated by the NLR Family Pyrin Domain Containing 3 (NLRP3) inflammasome or by tumor necrosis factor alpha (TNF- α).

45. The pharmaceutical composition for use of claim 44, wherein the condition or disease is mediated by the NLR Family Pyrin Domain Containing 3 (NLRP3) inflammasome.

46. The pharmaceutical composition for use of claim 44, wherein the condition or disease is mediated by tumor necrosis factor alpha (TNF- α).
47. The pharmaceutical composition for use of claim 44, wherein the condition or disease is a cardiovascular condition or disease, an endocrine condition or disease, a neurological condition or disease, a gastrointestinal condition or disease, or a combination thereof.
48. The pharmaceutical composition for use of claim 44, wherein the condition or disease is inflammatory bowel disease (IBD), Crohn's disease, colorectal cancer, alcoholic hepatitis, or a combination thereof.
49. The pharmaceutical composition for use of claim 44, wherein the condition or disease is inflammatory bowel disease (IBD), Crohn's disease, or a combination thereof.
50. The pharmaceutical composition for use of claim 44, wherein the condition or disease is colorectal cancer, alcoholic hepatitis, or a combination thereof.
51. Use of a compound of any one of claims 1 to 27, or a pharmaceutically acceptable salt or stereoisomer thereof, in the preparation of a medicament for use in treating, ameliorating, or preventing a condition or disease mediated by the NLR Family Pyrin Domain Containing 3 (NLRP3) inflammasome or by tumor necrosis factor alpha (TNF- α).
52. The use of claim 51, wherein the condition or disease is mediated by the NLR Family Pyrin Domain Containing 3 (NLRP3) inflammasome.
53. The use of claim 51, wherein the condition or disease is mediated by tumor necrosis factor alpha (TNF- α).
54. The use of claim 51, wherein the condition or disease is a cardiovascular condition or disease, an endocrine condition or disease, a neurological condition or disease, a gastrointestinal condition or disease, or a combination thereof.

55. The use of claim 51, wherein the condition or disease is inflammatory bowel disease (IBD), Crohn's disease, colorectal cancer, alcoholic hepatitis, or a combination thereof.
56. The use of claim 51, wherein the condition or disease is inflammatory bowel disease (IBD), Crohn's disease, or a combination thereof.
57. The use of claim 51, wherein the condition or disease is colorectal cancer, alcoholic hepatitis, or a combination thereof.
58. A method of treating, ameliorating, or preventing a condition or disease in a subject in need thereof, wherein the disease is mediated by the NLR Family Pyrin Domain Containing 3 (NLRP3) inflammasome or by tumor necrosis factor alpha (TNF- α), and wherein the method comprises administering to the subject a therapeutically effective amount of an inhibitor of the C-terminal domain of heat shock protein 90 (hsp90).
59. The method of claim 58, wherein the condition or disease is mediated by the NLR Family Pyrin Domain Containing 3 (NLRP3) inflammasome.
60. The use of method of claim 58, wherein the condition or disease is mediated by tumor necrosis factor alpha (TNF- α).
61. The method of claim 58, wherein the condition or disease is inflammatory bowel disease (IBD), Crohn's disease, colorectal cancer, alcoholic hepatitis, or a combination thereof.
62. The method of claim 58, wherein the condition or disease is inflammatory bowel disease (IBD), Crohn's disease, or a combination thereof.
63. The method of claim 58, wherein the condition or disease is colorectal cancer, alcoholic hepatitis, or a combination thereof.

64. A method of making a compound of claim 17, wherein the compound is of Formula (Iaa), the method comprising:
- providing a pyrazine as a first intermediate; and
 - combining a 2-pyranone and the first intermediate to form a second intermediate.
65. The method of claim 64 further comprising providing a solvent, salt, a ligand, a catalyst, or combinations thereof.
66. The method of claim 65, wherein:
- the step of providing a pyrazine as a first intermediate is further defined as combining:
 - (i) the solvent, the salt, the ligand, the catalyst, or combinations thereof, and
 - (ii) the pyrazine to form the first intermediate; and
 - the step of combining a 2-pyranone and the first intermediate to form a second intermediate is further defined as combining:
 - (i) the solvent, the salt, the ligand, the catalyst, or combinations thereof, and
 - (ii) the 2-pyranone and the first intermediate to form the second intermediate.
67. The method of claim 64, wherein the pyrazine is 2-chloro-5-isopropoxypyrazine.
68. The method of claim 64, wherein the 2-pyranone is (R)-6-[(S)-1-{(1S, 2R, 6S, 7R, 9R, 11S, 12S, 15R, 16S)-6-hydroxy-4-iodo-2, 16-dimethyl-3-oxo-8-oxapentacyclo [9.7.0.0^{2,7}.0^{7,9}.0^{12,16}] octadec-4-en-15-yl}ethyl]-3-(hydroxymethyl)-4-methyl-5, 6-dihydro-2H-pyran-2-one.
69. The method of claim 65, wherein the solvent is selected from the group of 1,4-dioxane, tetrahydrofuran, ethyl acetate, heptane, water, and combination thereof.
70. The method of claim 65, wherein the salt is selected from the group of lithium chloride, sodium sulphate, ammonium bicarbonate, and combinations thereof.
71. The method of claim 65, wherein the ligand is selected from the group of hexabutyl distannane, tributyl(5-isopropoxy-2-pyrazinyl) stannane, tricyclohexyl phosphine, triphenylarsane, and combinations thereof.

72. The method of claim 65, wherein the catalyst is selected from the group of palladium—(1E,4E)-1,5-diphenyl-1,4-pentadien-3-one (2/3), Tris((1E,4E)-1,5-diphenylpenta-1,4-dien-3-one) dipalladium [Pd₂(dba)₃], Copper Iodide [CuI], Triphenylarsane [AsPh₃], Tetrakis (triphenylphosphine)palladium(0) [Pd(PPh₃)₄], Bis(triphenylphosphine)palladium(II) dichloride [PdCl₂(PPh₃)₂], and combinations thereof.