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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
12 April 2012 (12.04.2012)

PCT

(10) International Publication Number
WO 2012/047762 A2

(51) **International Patent Classification**:
A01N 43/647 (2006.01) *A01N 25/00* (2006.01)
A01N 43/48 (2006.01) *A01P 1/00* (2006.01)

(21) **International Application Number**:
PCT/US2011/054371

(22) **International Filing Date**:
30 September 2011 (30.09.2011)

(25) **Filing Language**: English

(26) **Publication Language**: English

(30) **Priority Data**:
61/391,555 8 October 2010 (08.10.2010) US

(71) **Applicant** *(for all designated States except US)*: **AMPLYX PHARMACEUTICALS, INC.** [US/US]; 6370 Nancy Ridge Drive, Suite 112, San Diego, California 92121 (US).

(72) **Inventors; and**

(75) **Inventors/Applicants** *(for US only)*: **TÓTH, Flórián** [HU/HU]; Rákóczi Street 14/c, H-7394 Magyarhertelend (HU). **AUNGST, JR., Ronald Alan** [US/US]; 30 Summerlin Drive, Clifton Park, New York 12065 (US). **BULUSU, Atchyuta Rama Chandra Murty** [AT/AT]; Hochbergstrasse 38, A-2380 Perchtoldsdorf (AT). **WEBB, Robert** [US/US]; 7625 Salix Place, San Diego, California 92129 (US). **MUTZ, Mitchell** [US/US]; 6623 Avenida Manana, La Jolla, California 92037 (US).

(74) **Agent**: **RUTENBERG, Isaac M.**; Bozicevic, Field & Francis LLP, 1900 University Avenue, Suite 200, East Palo Alto, California 94303 (US).

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

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

Published:

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

WO 2012/047762 A2

(54) **Title**: ANTIFUNGAL AGENTS

(57) **Abstract**: Compounds and compositions useful as antifungals are provided, as are methods of use and preparation of such compounds and compositions containing such compounds. In some embodiments, the compounds are bifunctional, comprising two active moieties connected by a linking moiety. The compounds of the invention are useful for treating infections by microorganisms.

ANTIFUNGAL AGENTS

Cross Reference to Related Applications

[0001] This application claims priority under 35 U.S.C. 119(e) to Provisional U.S. Patent Application Serial No. 61/391,555, filed October 8, 2010, the entire contents of which is incorporated herein by reference.

Introduction

[0002] Nosocomial infections (i.e., infections resulting from treatment in a hospital or other medical care facililty) are a growing problem worldwide. Particularly, nosocomial fungal infections of *Candida albicans* or *Aspergillus fumigatus* have become significant health concerns, as the scope and efficacy of antifungal agents to treat such infections is sub-optimal.

[0003] Microbial infections were ranked as the fourth leading cause of death worldwide in 2008 according to the World Health Organization. Fungal infections represent a significant challenge due to the limited armamentarium available to treat diseases caused by fungi and low success rates of treatment. *Candida albicans* is the fourth-ranked cause of nosocomial infections with a 50% mortality rate among patients who suffer from systemic infections. The estimated cost of treating invasive fungal infections is over $2.6 billion annually in the United States alone. Sales of antifungal drugs represent an increasingly large market with 2008 sales of over $1.1 billion combined for the leading triazole antifungals, voriconazole and fluconazole. One reason for the increase in market size is the rise in numbers of immunocompromised patients, who are more subject to fungal infections than healthy individuals. Moreover, treatment of immunocompromised patients is often complicated by toxicities associated with antifungals.

[0004] In addition to the problematic development of microorganisms resistant to known antifungals, some antifungal agents are difficult to prepare, are expensive to obtain, have a poor pharmacokinetic profile (which may be reflected in a shorter than desirable half-life), have a poor intracellular distribution for infections (where such a distribution would be desirable), and/or have significant adverse side effects; all of these drawbacks may result in lower patient compliance and/or less effective treatment. Accordingly, there continues to be a need for the development of new antifungal agents.

Summary of the Disclosure

[0005] The present disclosure provides compounds that address one or more of the abovementioned drawbacks. In particular, the present disclosure provides compounds useful as antifungal agents.

[0006] In one aspect of the invention, there is provided a compound comprising a first active moiety having antifungal activity and selected from triazole moieties, imidazole moieties, and echinocandin moieties, a second active moiety, and a linking moiety. The first and second active moieties are covalently bonded to the linker moiety. The invention also provides pharmaceutically acceptable salts, prodrugs, and metabolites of such compounds.

[0007] In another aspect of the invention, there is provided a compound comprising first and second active moieties and a linker moiety, wherein the first active moiety is capable of binding to a first enzyme, and wherein the second active moiety is capable of binding to a second enzyme, and wherein the two active moieties are each covalently attached to the linker moiety.

[0008] In another aspect of the invention, there is provided a compound comprising first and second active moieties and a linker moiety, wherein the first active moiety is capable of binding to a protein, and wherein the second active moiety is capable of binding to an enzyme, and wherein the two active moieties are each covalently attached to the linker moiety.

[0009] In yet another aspect of the invention, there is provided a compound having the structure of formula (I)

(I) A-L-U

wherein A is a first active moiety, L is a linking moiety, and U is a second active moiety. In some embodiments, the first and second active moieties are not linked covalently, and such embodiments can, for example, be represented by formula (I) wherein L is absent entirely. In such embodiments, A and U are administered together, such as in a liposome.

[00010] In still another aspect, the invention provides a pharmaceutical formulation comprising a compound selected from those described herein and a pharmaceutically acceptable carrier.

[00011] In still another aspect, the disclosure provides a method for treating a patient with an antifungal compound comprising administering an effective amount of a compound selected from those described herein.

[00012] In yet another aspect of the invention there is provided a method for treating a fungal infection comprising administering a composition described herein.

[00013] These and other aspects of the invention will be apparent from the disclosure provided herein, including the examples and claims.

Detailed Description

[00014] Unless otherwise indicated, the disclosure is not limited to specific procedures, starting materials, or the like, as such may vary. It is also to be understood that the terminology used herein is for the purpose of describing particular embodiments only and is not intended to be limiting.

[00015] As used in the specification and the appended claims, the singular forms "a," "an," and "the" include plural referents unless the context clearly dictates otherwise. Thus, for example, reference to "a reactant" includes not only a single reactant but also a combination or mixture of two or more different reactant, reference to "a substituent" includes a single substituent as well as two or more substituents, and the like.

[00016] In describing and claiming the present invention, certain terminology will be used in accordance with the definitions set out below. It will be appreciated that the definitions provided herein are not intended to be mutually exclusive. Accordingly, some chemical moieties may fall within the definition of more than one term.

[00017] As used herein, the phrases “for example,” “for instance,” “such as,” or “including” are meant to introduce examples that further clarify more general subject matter. These examples are provided only as an aid for understanding the disclosure, and are not meant to be limiting in any fashion.

[00018] As used herein, the phrase "having the formula" or "having the structure" is not intended to be limiting and is used in the same way that the term "comprising" is commonly used. The term "independently selected from" is used herein to indicate that the recited elements, e.g., R groups or the like, can be identical or different.

[00019] As used herein, the terms “may,” "optional," "optionally," or “may optionally” mean that the subsequently described circumstance may or may not occur, so that the description includes instances where the circumstance occurs and instances where it does not. For example, the phrase "optionally substituted" means that a non-hydrogen substituent may or may not be present on a given atom, and, thus, the description includes structures wherein a non-hydrogen substituent is present and structures wherein a non-hydrogen substituent is not present.

[00020] The term "alkyl" as used herein refers to a branched or unbranched saturated hydrocarbon group (i.e., a mono-radical) typically although not necessarily containing 1 to about 24 carbon atoms, such as methyl, ethyl, *n*-propyl, isopropyl, *n*-butyl, isobutyl, *t*-butyl, octyl, decyl, and the like, as well as cycloalkyl groups such as cyclopentyl, cyclohexyl and the like. Generally, although not necessarily, alkyl groups herein may contain 1 to about 18 carbon atoms, and such groups may contain 1 to about 12 carbon atoms. The term "lower alkyl" intends an alkyl group of 1 to 6 carbon atoms. "Substituted alkyl" refers to alkyl substituted with one or more substituent groups, and this includes instances wherein two hydrogen atoms from the same carbon atom in an alkyl substituent are replaced, such as in a carbonyl group (i.e., a substituted alkyl group may include a -C(=O)- moiety). The terms "heteroatom-containing alkyl" and "heteroalkyl" refer to an alkyl substituent in which at least one carbon atom is replaced with a heteroatom, as described in further detail infra. If not otherwise indicated, the terms "alkyl" and "lower alkyl" include linear, branched, cyclic, unsubstituted, substituted, and/or heteroatom-containing alkyl or lower alkyl, respectively.

[00021] The term "alkenyl" as used herein refers to a linear, branched or cyclic hydrocarbon group of 2 to about 24 carbon atoms containing at least one double bond, such as ethenyl, *n*-propenyl, isopropenyl, *n*-butenyl, isobutenyl, octenyl, decenyl, tetradecenyl, hexadecenyl, eicosenyl, tetracosenyl, and the like. Generally, although again not necessarily, alkenyl groups herein may contain 2 to about 18 carbon atoms, and for example may contain 2 to 12 carbon atoms. The term "lower alkenyl" intends an alkenyl group of 2 to 6 carbon atoms. The term "substituted alkenyl" refers to alkenyl substituted with one or more substituent groups, and the terms "heteroatom-containing alkenyl" and "heteroalkenyl" refer to alkenyl in which at least one carbon atom is replaced with a heteroatom. If not otherwise indicated, the terms "alkenyl" and "lower alkenyl" include linear, branched, cyclic, unsubstituted, substituted, and/or heteroatom-containing alkenyl and lower alkenyl, respectively.

[00022] The term "alkynyl" as used herein refers to a linear or branched hydrocarbon group of 2 to 24 carbon atoms containing at least one triple bond, such as ethynyl, *n*-propynyl, and the like. Generally, although again not necessarily, alkynyl groups herein may contain 2 to about 18 carbon atoms, and such groups may further contain 2 to 12 carbon atoms. The term "lower alkynyl" intends an alkynyl group of 2 to 6 carbon atoms. The term "substituted alkynyl" refers to alkynyl substituted with one or more substituent groups, and the terms "heteroatom-containing alkynyl" and "heteroalkynyl" refer to alkynyl in which at least one carbon atom is replaced with a heteroatom. If not otherwise indicated, the terms

"alkynyl" and "lower alkynyl" include linear, branched, unsubstituted, substituted, and/or heteroatom-containing alkynyl and lower alkynyl, respectively.

[00023] The term "alkoxy" as used herein intends an alkyl group bound through a single, terminal ether linkage; that is, an "alkoxy" group may be represented as -O-alkyl where alkyl is as defined above. A "lower alkoxy" group intends an alkoxy group containing 1 to 6 carbon atoms, and includes, for example, methoxy, ethoxy, *n*-propoxy, isopropoxy, *t*-butyloxy, etc. Substituents identified as "C_1-C_6 alkoxy" or "lower alkoxy" herein may, for example, may contain 1 to 3 carbon atoms, and as a further example, such substituents may contain 1 or 2 carbon atoms (i.e., methoxy and ethoxy).

[00024] The term "aryl" as used herein, and unless otherwise specified, refers to an aromatic substituent generally, although not necessarily, containing 5 to 30 carbon atoms and containing a single aromatic ring or multiple aromatic rings that are fused together, directly linked, or indirectly linked (such that the different aromatic rings are bound to a common group such as a methylene or ethylene moiety). Aryl groups may, for example, contain 5 to 20 carbon atoms, and as a further example, aryl groups may contain 5 to 12 carbon atoms. For example, aryl groups may contain one aromatic ring or two or more fused or linked aromatic rings (i.e., biaryl, aryl-substituted aryl, etc.). Examples include phenyl, naphthyl, biphenyl, diphenylether, diphenylamine, benzophenone, and the like. "Substituted aryl" refers to an aryl moiety substituted with one or more substituent groups, and the terms "heteroatom-containing aryl" and "heteroaryl" refer to aryl substituent, in which at least one carbon atom is replaced with a heteroatom, as will be described in further detail infra. If not otherwise indicated, the term "aryl" includes unsubstituted, substituted, and/or heteroatom-containing aromatic substituents.

[00025] The term "aralkyl" refers to an alkyl group with an aryl substituent, and the term "alkaryl" refers to an aryl group with an alkyl substituent, wherein "alkyl" and "aryl" are as defined above. In general, aralkyl and alkaryl groups herein contain 6 to 30 carbon atoms. Aralkyl and alkaryl groups may, for example, contain 6 to 20 carbon atoms, and as a further example, such groups may contain 6 to 12 carbon atoms.

[00026] The term "alkylene" as used herein refers to a di-radical alkyl group. Unless otherwise indicated, such groups include saturated hydrocarbon chains containing from 1 to 24 carbon atoms, which may be substituted or unsubstituted, may contain one or more alicyclic groups, and may be heteroatom-containing. "Lower alkylene" refers to alkylene linkages containing from 1 to 6 carbon atoms. Examples include, methylene (--CH_2--),

ethylene (--CH_2CH_2--), propylene (--$CH_2CH_2CH_2$--), 2-methylpropylene (--CH_2--$CH(CH_3)$--CH_2--), hexylene (--$(CH_2)_6$--) and the like.

[00027] Similarly, the terms "alkenylene," "alkynylene," "arylene," "aralkylene," and "alkarylene" as used herein refer to di-radical alkenyl, alkynyl, aryl, aralkyl, and alkaryl groups, respectively.

[00028] The term "amino" is used herein to refer to the group $-NZ^1Z^2$ wherein Z^1 and Z^2 are hydrogen or nonhydrogen substituents, with nonhydrogen substituents including, for example, alkyl, aryl, alkenyl, aralkyl, and substituted and/or heteroatom-containing variants thereof.

[00029] The terms "halo" and "halogen" are used in the conventional sense to refer to a chloro, bromo, fluoro or iodo substituent.

[00030] The term "heteroatom-containing" as in a "heteroatom-containing alkyl group" (also termed a "heteroalkyl" group) or a "heteroatom-containing aryl group" (also termed a "heteroaryl" group) refers to a molecule, linkage or substituent in which one or more carbon atoms are replaced with an atom other than carbon, e.g., nitrogen, oxygen, sulfur, phosphorus or silicon, typically nitrogen, oxygen or sulfur. Similarly, the term "heteroalkyl" refers to an alkyl substituent that is heteroatom-containing, the term "heterocyclic" refers to a cyclic substituent that is heteroatom-containing, the terms "heteroaryl" and "heteroaromatic" respectively refer to "aryl" and "aromatic" substituents that are heteroatom-containing, and the like. Examples of heteroalkyl groups include alkoxyaryl, alkylsulfanyl-substituted alkyl, N-alkylated amino alkyl, and the like. Examples of heteroaryl substituents include pyrrolyl, pyrrolidinyl, pyridinyl, quinolinyl, indolyl, furyl, pyrimidinyl, imidazolyl, 1,2,4-triazolyl, tetrazolyl, etc., and examples of heteroatom-containing alicyclic groups are pyrrolidino, morpholino, piperazino, piperidino, tetrahydrofuranyl, etc.

[00031] "Hydrocarbyl" refers to univalent hydrocarbyl radicals containing 1 to about 30 carbon atoms, including 1 to about 24 carbon atoms, further including 1 to about 18 carbon atoms, and further including about 1 to 12 carbon atoms, including linear, branched, cyclic, saturated and unsaturated species, such as alkyl groups, alkenyl groups, aryl groups, and the like. "Substituted hydrocarbyl" refers to hydrocarbyl substituted with one or more substituent groups, and the term "heteroatom-containing hydrocarbyl" refers to hydrocarbyl in which at least one carbon atom is replaced with a heteroatom. Unless otherwise indicated, the term "hydrocarbyl" is to be interpreted as including substituted and/or heteroatom-containing hydrocarbyl moieties.

[00032] By "substituted" as in "substituted hydrocarbyl," "substituted alkyl," "substituted aryl," and the like, as alluded to in some of the aforementioned definitions, is meant that in the hydrocarbyl, alkyl, aryl, or other moiety, at least one hydrogen atom bound to a carbon (or other) atom is replaced with one or more non-hydrogen substituents. Examples of such substituents include, without limitation: functional groups such as halo, hydroxyl, sulfhydryl, C_1-C_{24} alkoxy, C_2-C_{24} alkenyloxy, C_2-C_{24} alkynyloxy, C_5-C_{20} aryloxy, acyl (including C_2-C_{24} alkylcarbonyl (-CO-alkyl) and C_6-C_{20} arylcarbonyl (-CO-aryl)), acyloxy (-O-acyl), C_2-C_{24} alkoxycarbonyl (-(CO)-O-alkyl), C_6-C_{20} aryloxycarbonyl (-(CO)-O-aryl), halocarbonyl (-CO)-X where X is halo), C_2-C_{24} alkylcarbonato (-O-(CO)-O-alkyl), C_6-C_{20} arylcarbonato (-O-(CO)-O-aryl), carboxy (-COOH), carboxylato (-COO^-), carbamoyl (-(CO)-NH_2), mono-substituted C_1-C_{24} alkylcarbamoyl (-(CO)-NH(C_1-C_{24} alkyl)), di-substituted alkylcarbamoyl (-(CO)-N(C_1-C_{24} alkyl)$_2$), mono-substituted arylcarbamoyl (-(CO)-NH-aryl), thiocarbamoyl (-(CS)-NH_2), carbamido (-NH-(CO)-NH_2), cyano (-C≡N), isocyano (-N^+≡C^-), cyanato (-O-C≡N), isocyanato (-O-N^+≡C^-), isothiocyanato (-S-C≡N), azido (-N=N^+=N^-), formyl (-(CO)-H), thioformyl (-(CS)-H), amino (-NH_2), mono- and di-(C_1-C_{24} alkyl)-substituted amino, mono- and di-(C_5-C_{20} aryl)-substituted amino, C_2-C_{24} alkylamido (-NH-(CO)-alkyl), C_5-C_{20} arylamido (-NH-(CO)-aryl), imino (-CR=NH where R = hydrogen, C_1-C_{24} alkyl, C_5-C_{20} aryl, C_6-C_{20} alkaryl, C_6-C_{20} aralkyl, etc.), alkylimino (-CR=N(alkyl), where R = hydrogen, alkyl, aryl, alkaryl, etc.), arylimino (-CR=N(aryl), where R = hydrogen, alkyl, aryl, alkaryl, etc.), nitro (-NO_2), nitroso (-NO), sulfo (-SO_2-OH), sulfonato (-SO_2-O^-), C_1-C_{24} alkylsulfanyl (-S-alkyl; also termed "alkylthio"), arylsulfanyl (-S-aryl; also termed "arylthio"), C_1-C_{24} alkylsulfinyl (-(SO)-alkyl), C_5-C_{20} arylsulfinyl (-(SO)-aryl), C_1-C_{24} alkylsulfonyl (-SO_2-alkyl), C_5-C_{20} arylsulfonyl (-SO_2-aryl), phosphono (-P(O)($OH)_2$), phosphonato (-P(O)($O^-)_2$), phosphinato (-P(O)(O^-)), phospho (-PO_2), and phosphino (-PH_2), mono- and di-(C_1-C_{24} alkyl)-substituted phosphino, mono- and di-(C_5-C_{20} aryl)-substituted phosphino; and the hydrocarbyl moieties C_1-C_{24} alkyl (including C_1-C_{18} alkyl, further including C_1-C_{12} alkyl, and further including C_1-C_6 alkyl), C_2-C_{24} alkenyl (including C_2-C_{18} alkenyl, further including C_2-C_{12} alkenyl, and further including C_2-C_6 alkenyl), C_2-C_{24} alkynyl (including C_2-C_{18} alkynyl, further including C_2-C_{12} alkynyl, and further including C_2-C_6 alkynyl), C_5-C_{30} aryl (including C_5-C_{20} aryl, and further including C_5-C_{12} aryl), and C_6-C_{30} aralkyl (including C_6-C_{20} aralkyl, and further including C_6-C_{12} aralkyl). In addition, the aforementioned functional groups may, if a particular group permits, be further substituted with one or more additional functional groups or with one or more hydrocarbyl moieties such as those specifically enumerated above. Analogously, the above-

mentioned hydrocarbyl moieties may be further substituted with one or more functional groups or additional hydrocarbyl moieties such as those specifically enumerated.

[00033] By "linking" or "linker" as in "linking group," "linker moiety," etc., is meant a bivalent radical moiety. Examples of such linking groups include alkylene, alkenylene, alkynylene, arylene, alkarylene, aralkylene, and linking moieties containing functional groups including, without limitation: amido (-NH-CO-), urethane (i.e., carbamate, -O-CO-NH-), -NH-CO-NH-, imido (-CO-NH-CO-) , epoxy (-O-), epithio (-S-), epidioxy (-O-O-), carbonyldioxy (-O-CO-O-), alkyldioxy (-O-$(CH_2)_n$-O-), epoxyimino (-O-NH-), epimino (-NH-), carbonyl (-CO-), etc., as well as substituted versions thereof (e.g., -NR-CO-, -O-CO-NR-, etc. wherein R is non-hydrogen such as alkyl, aryl, etc.). Further examples of linking groups are provided below.

[00034] When the term "substituted" appears prior to a list of possible substituted groups, it is intended that the term apply to every member of that group. For example, the phrase "substituted alkyl and aryl" is to be interpreted as "substituted alkyl and substituted aryl."

[00035] Unless otherwise specified, reference to an atom is meant to include isotopes of that atom. For example, reference to H is meant to include ^{1}H, ^{2}H (i.e., D) and ^{3}H (i.e., T), and reference to C is meant to include ^{12}C and all isotopes of carbon (such as ^{13}C).

[00036] Unless otherwise indicated, the terms "treating" and "treatment" as used herein refer to reduction in severity and/or frequency of symptoms, elimination of symptoms and/or underlying cause, prevention of the occurrence of symptoms and/or their underlying cause, and improvement or remediation of damage. Thus, the terms include prophylactic use of active agents. "Preventing" a disorder or unwanted physiological event in a patient refers specifically to the prevention of the occurrence of symptoms and/or their underlying cause, wherein the patient may or may not exhibit heightened susceptibility to the disorder or event.

[00037] By the term "effective amount" of a therapeutic agent is meant a nontoxic but sufficient amount of a beneficial agent to provide a desirable effect.

[00038] As used herein, and unless specifically stated otherwise, an “effective amount” of a beneficial refers to an amount covering both therapeutically effective amounts and prophylactically effective amounts.

[00039] As used herein, a "therapeutically effective amount" of an active agent refers to an amount that is effective to achieve a desirable therapeutic result, and a "prophylactically effective amount" of an active agent refers to an amount that is effective to prevent or lessen the severity of an unwanted physiological condition.

[00040] By a "pharmaceutically acceptable" component is meant a component that is not biologically or otherwise undesirable, i.e., the component may be incorporated into a pharmaceutical formulation of the disclosure and administered to a patient as described herein without causing any significant undesirable biological effects or interacting in a deleterious manner with any of the other components of the formulation in which it is contained. When the term "pharmaceutically acceptable" is used to refer to an excipient, it is generally implied that the component has met the required standards of toxicological and manufacturing testing or that it is included on the Inactive Ingredient Guide prepared by the U.S. Food and Drug Administration.

[00041] The term "pharmacologically active" (or simply "active"), as in a "pharmacologically active" derivative or analog, refers to a derivative or analog (e.g., a salt, ester, amide, conjugate, metabolite, isomer, fragment, etc.) having the same type of pharmacological activity as the parent compound and approximately equivalent in degree.

[00042] The term "controlled release" refers to a formulation, dosage form, or region thereof from which release of a beneficial agent is not immediate, i.e., with a "controlled release" dosage form, administration does not result in immediate release of the beneficial agent in an absorption pool. The term is used interchangeably with "nonimmediate release" as defined in *Remington: The Science and Practice of Pharmacy*, Nineteenth Ed. (Easton, PA: Mack Publishing Company, 1995). In general, the term "controlled release" as used herein includes sustained release and delayed release formulations.

[00043] The term "sustained release" (synonymous with "extended release") is used in its conventional sense to refer to a formulation, dosage form, or region thereof that provides for gradual release of a beneficial agent over an extended period of time, and that preferably, although not necessarily, results in substantially constant blood levels of the agent over an extended time period.

[00044] The term "naturally occurring" refers to a compound or composition that occurs in nature, regardless of whether the compound or composition has been isolated from a natural source or chemically synthesized.

[00045] The term “non-immunosuppressive” as used herein refers to moieties, compounds, and/or formulations that, when administered to a patient according to the disclosure provided herein (i.e., using the compounds, dosages, methods of administration, etc. disclosed herein), do not substantially inhibit one or more aspects of the patient’s immune system. For example, using a lymphocyte assay, a non-immunosuppressive

compound would be one with an IC_{50} towards lymphocyte growth of greater than about 500 fold the IC_{50} of FK-506.

[00046] In some embodiments, the disclosure provides compounds capable of dual binding - i.e., specifically binding both fungal calcineurin and an additional antifungal target to yield a more efficacious, fungicidal drug. In some preferred embodiments, the dual binding is accomplished using non-immunosuppressive ligands that inhibit fungal calcineurin but not human calcineurin. Examples of the additional antifungal target include thimidylate synthase (targeted, for example, by flucytosine), DNA (targeted, for example, by flucytosine), β glucan synthase (targeted, for example, by echinocandins), squalene monooxygenase (targeted, for example, by terfinabine), ergosterol (targeted, for example, by amphotericin B), lanosterol 14 α-demethylase (targeted, for example, by triazoles), microtubules (targeted, for example, by griseofulvin). Additionally, the additional antifungal target may include blocking of the G1/S phase initiation of the cell cycle and HSP90 which mediates fungal resistance to triazoles, such as by the hydroxypyridone class of antifungal agents.

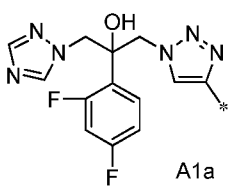
[00047] In some embodiments, the disclosure provides compounds having three components: a first active moiety, a second active moiety, and a linker moiety that links the first active moiety with the second active moiety. The three components are typically linked via covalent bonds.

[00048] In some embodiments the first active moiety is selected from triazoles such as ketoconazole, posaconazole, fluconazole, voriconazole, and derivatives and analogs thereof. In other embodiments, the first active moiety is selected from echinocardins (naturally-occurring, synthetic, or semi-synthetic) such as micafungin, anidulafungin, and caspofungin. Any of the aforementioned moieties may be used as the first active moiety, although it will be appreciated that one or more of the atoms (typically, although not necessarily, hydrogen atoms) in each of these moieties will be replaced to accommodate one or more covalent linkages of the first active moiety to the linking moiety. For example, when the first active moiety is said herein to be "ketoconazole," it will be appreciated that the moiety is in fact a ketoconazole moiety having an atom replaced with a covalent bond to the linking moiety. Furthermore, analogs of the above mentioned example triazole compounds are within the scope of the invention. For example, fluconazole contains a 1*H*-1,2,4-triazole ring, but analogs having a 1*H*-1,2,3-triazole ring are also embodiments of the invention.

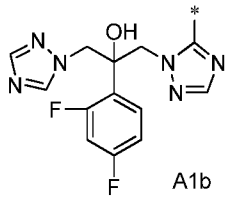
[00049] In further embodiments, the first active moiety is selected from imidazoles or triazoles such as clotrimazole, miconazole, econazole, butoconazole, omoconazole, oxiconazole, terconazole, itraconazole, ravuconazole, flutrimazole, and derivatives and

analogs thereof. In further embodiments, the first active moiety is selected from aminocandin, echinocandin B (ECB), echinocandin C, aculeacin Aγ, mulundocandin, sporiofungin A, pneumocandin A_0, WF11899A, pneumocandin B_0, analogues of echinocandin B, such as cilofungin, analogues of WF11899A, and analogues of pneumocandin B_0.

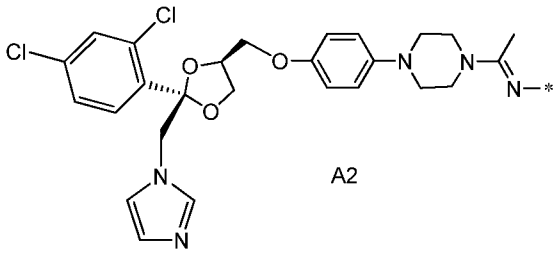
[00050] In some embodiments, the first active moiety has the structure of any one of A1a, A1b, A2, A3, A4, A5, A6, or A7:



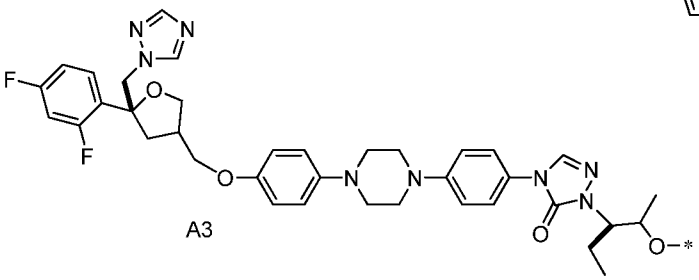
A1a



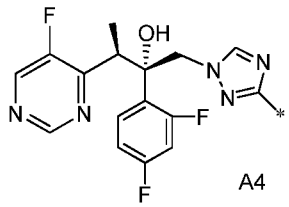
A1b



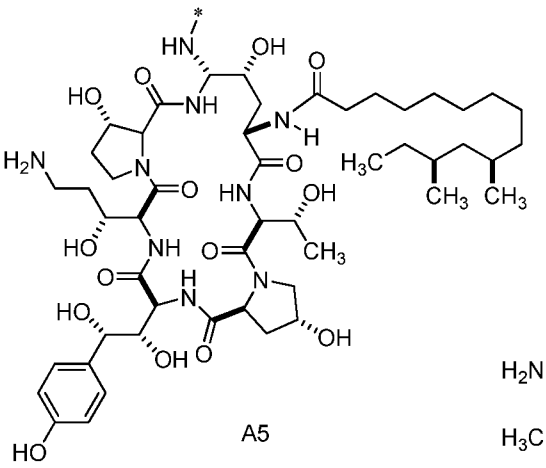
A2



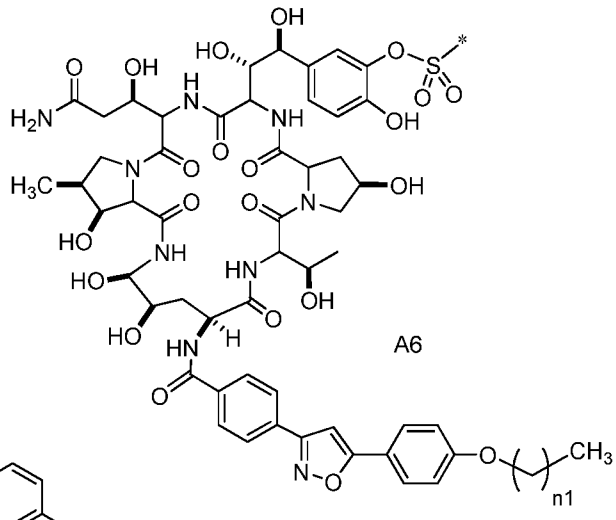
A3



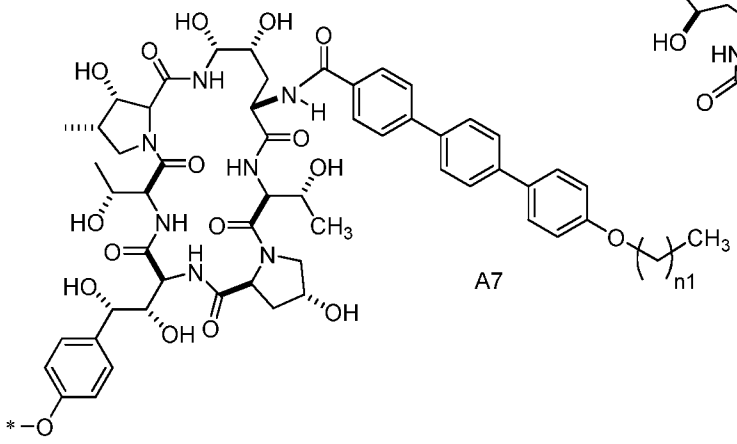
A4



A5



A6

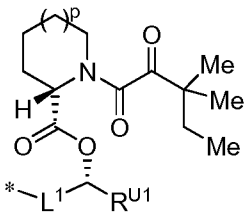


A7

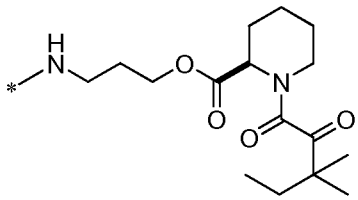
wherein n1 is an integer from 0 to 6, and the star represents the point of attachment to the linking moiety. It will be appreciated that alternative sites for attachment of the linking moiety are within the scope of the invention in addition to those shown above in A1-A7.

[00051] For example, in some embodiments, n1 is 1, 2, 3, 4, or 5. In preferred embodiments, n is 4.

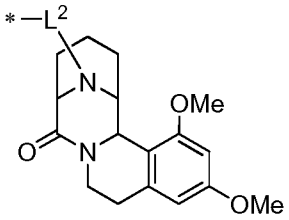
[00052] In some embodiments, the second active moiety has the structure of any one of U1 – U6:



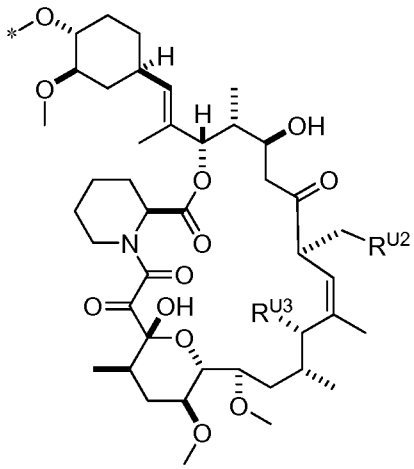
U1



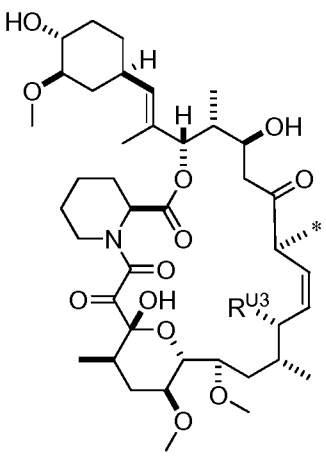
U2



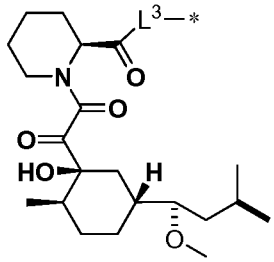
U3



U4



U5



U6

[00053] wherein:

[00054] p represents in integer in the range of 0-2;

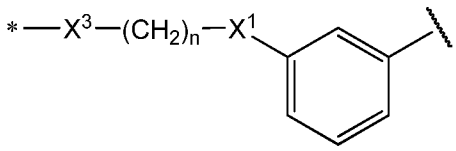
[00055] L^1, L^2, and L^3 are selected from a bond, a heteroatom, C_1-C_{24} alkylene, C_1-C_{24} heteroalkylene, C_5-C_{24} arylene, C_5-C_{24} heteroarylene, and combinations thereof, any of which may be substituted or unsubstituted;

[00056] R^{U1} and R^{U2} are selected from C_1-C_{24} hydrocarbyl, substituted C_1-C_{24} hydrocarbyl, heteroatom-containing C_1-C_{24} hydrocarbyl, and substituted heteroatom-containing C_1-C_{24} hydrocarbyl;

[00057] R^{U3} is selected from H and OH; and

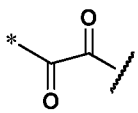
[00058] the stars represents the point of attachment to the linking moiety.

[00059] In some embodiments, L^1 is a bond, –O–, or is selected from C_1-C_{12} alkylene, C_5-C_{12} arylene, and C_1-C_{24} alkylarylene, any of which may comprise from 0 to 3 heteroatoms and from 0 to 3 substituents. For example, L^1 is methylene, ethylene, or propylene. Also for example, L^1 is 1,2-phenylene, 1,3-phenylene, 1,4-phenylene, or

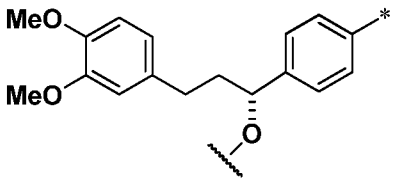


where X^1 and X^3 are independently selected from –O– and –NH–, and n is an integer from 1 to 3. For example, X^1 is –O–, X^3 is –NH–, and n is 2.

[00060] In some embodiments, L^2 is selected from a bond and C_1-C_{12} alkylene, and comprises from 0 to 3 heteroatoms and from 0 to 3 substituents. For example, in some embodiments, L^2 is

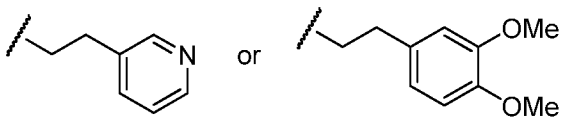


[00061] In some embodiments, L^3 is –O– or is selected from C_1-C_{12} alkylene, C_5-C_{12} arylene, and C_1-C_{24} alkylarylene and comprises from 0 to 3 heteroatoms and from 0 to 3 substituents. For example, L^3 is



[00062] In the above examples of L^1, L^2, and L^3, the stars represent the attachment points to the linking moiety of the compounds of the invention (i.e., the stars are the same as those shown in U1-U6), and the wavy lines represent the attachment points to the remaining portions of the second active moiety. However, it will be appreciated that the stars and wavy lines may be reversed, such that the groups identified above for L^1, L^2, and L^3 may be incorporated in either direction into the compounds of the invention.

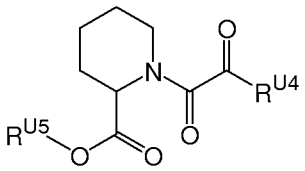
[00063] In some embodiments, R^{U1} is selected from C_1-C_{12} alkyl, C_5-C_{12} aryl, C_5-C_{12} alkaryl, and C_5-C_{12} aralkyl, and comprises from 0 to 3 heteroatoms and from 0 to 3 substituents. For example, R^{U1} is $–(CH_2)_n–Ar^1$, wherein n is an integer from 1 to 3 and Ar^1 is an aryl group that may be substituted or unsubstituted and may have one or more heteroatoms. For example, n is 2 and Ar^1 is pyridinyl or substituted phenyl. For example, Ar^1 is



[00064] In some embodiments, R^{U2} is selected from C_1-C_{12} alkyl, C_2-C_{12} alkenyl, C_5-C_{12} aryl, C_5-C_{12} alkaryl, and C_5-C_{12} aralkyl, and comprises from 0 to 3 heteroatoms and from 0 to 3 substituents. For example, R^{U2} is methyl, ethyl, propyl, $–CH_2–CH=CH_2$, $–CH=CH–(CH_2)_3–CN$, etc.

[00065] In some embodiments, the second active moiety may be selected from derivatives and analogs of any one of U1-U6. For example, derivatives include those having protected functional groups. For example, one or more of the hydroxyl groups may be protected by a hydroxyl protecting group. For example, R^{U3} may be –OP, wherein P is a protecting group such as alkyl, silyl ester, etc. Other derivatives and analogs include U4 wherein R^{U2} is hexenenitrile, pentenenitrile, etc.

[00066] In some embodiments, the second active moiety comprises a pipecolyl ester moiety. For example, the second active moiety may be



wherein R^{U4} and R^{U5} are hydrocarbyl groups (e.g., alkyl, alkenyl, aryl, etc.) that may contain one or more substituents and one or more heteroatoms, provided that one of R^{U4} and R^{U5} contains a linkage to the linking groups (and therefore the first active moieties) described herein. In some embodiments, R^{U4} and R^{U5} are linked to form a cycle.

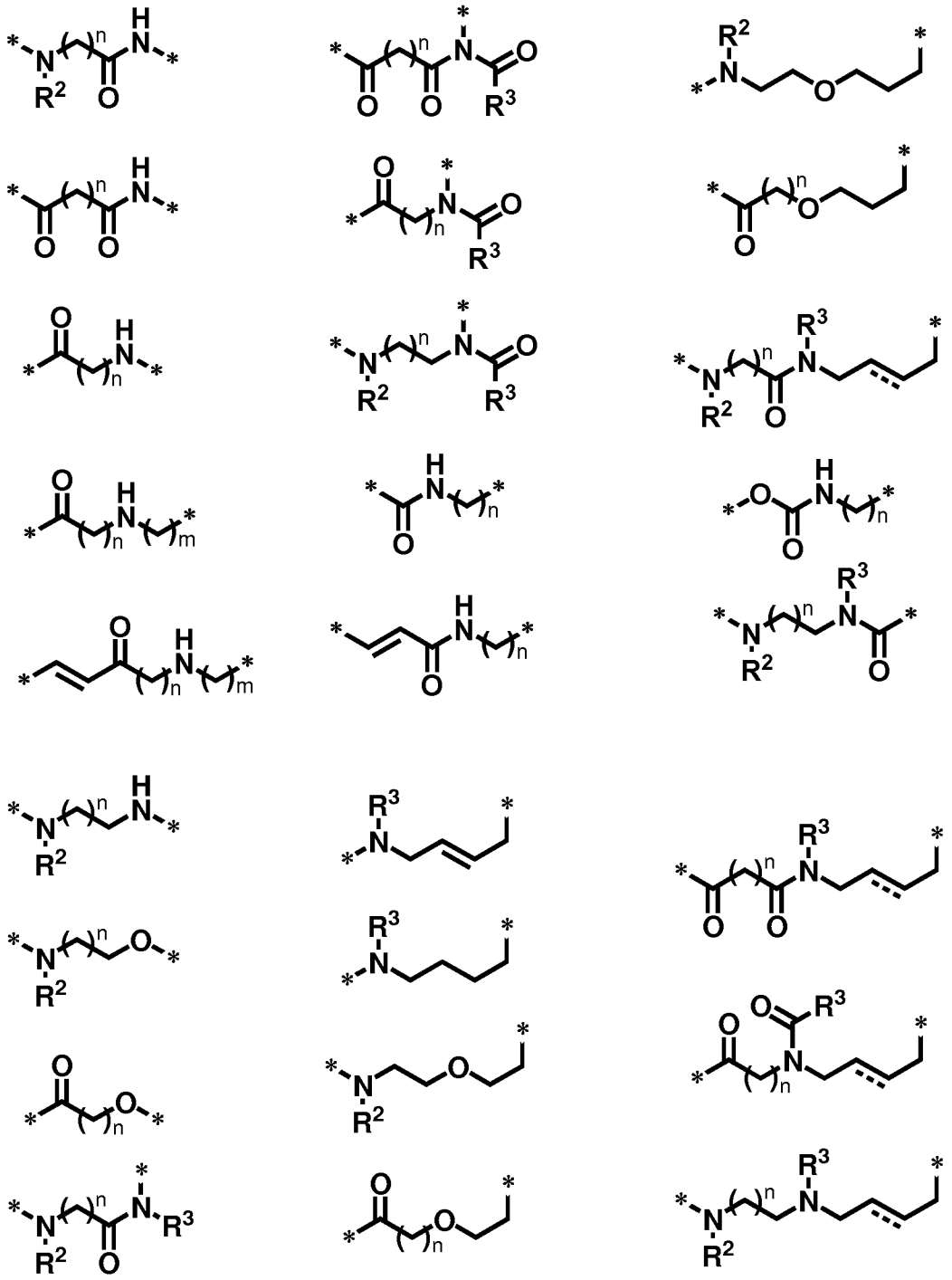
[00067] In some embodiments, the second active moiety is FK506 or a derivative thereof.

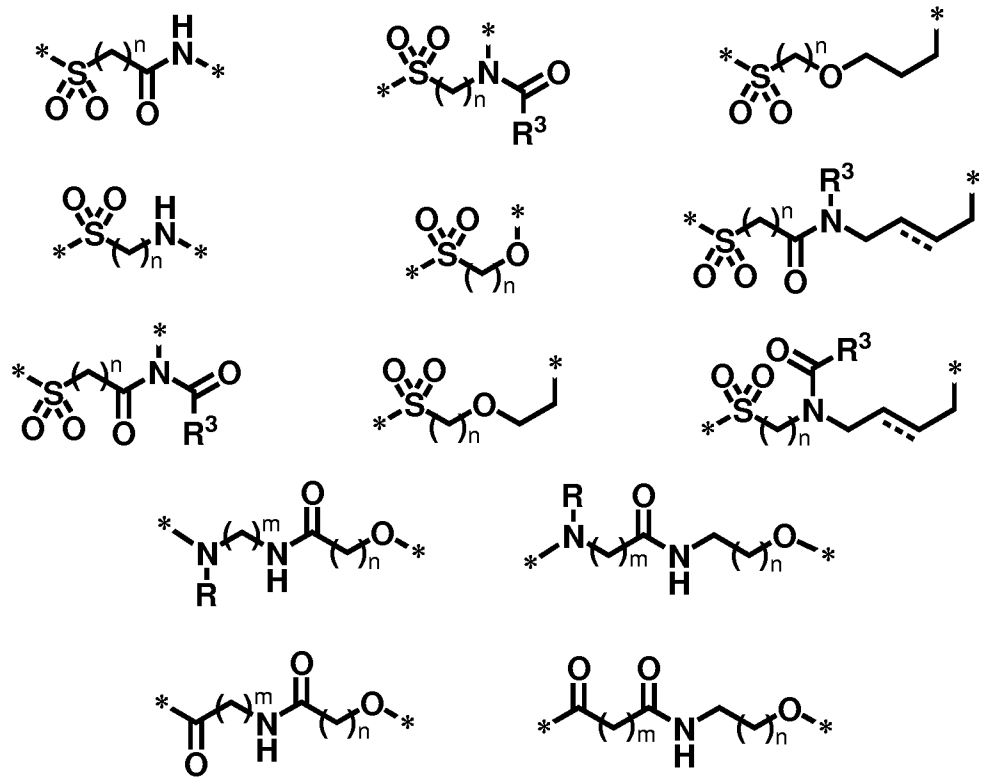
[00068] In some embodiments, the second active moiety is non-immunosuppressive as a stand-alone moiety (e.g., a compound having the structure of any one of U1-U6, wherein the star is replaced with a chemical moiety such as a hydrogen atom) and/or as a moiety conjugated according to the invention. For example, using a lymphocyte assay, a non-immunosuppressive compound containing a second active moiety as described herein would be one with an IC_{50} towards lymphocyte growth of greater than 0.5 μM, or greater than 1.0 μM, or greater than 5 μM.

[00069] The linking moiety is any moiety that is capable of covalently linking the first and second active moieties, and does not interfere with the pharmacological activity of the first active moiety, the second active moiety, or the compound as a whole. The linking moiety

may be a bond, although, typically, the linking moiety is a bi-radical moiety that may be substituted or unsubstituted and/or may have one or more heteroatoms. Examples of linking moieties are mentioned *supra*. For example, the linking moiety may be selected from a bond, C_1-C_{24} hydrocarbylene, substituted C_1-C_{24} hydrocarbylene, heteroatom-containing C_1-C_{24} hydrocarbylene, and substituted heteroatom-containing C_1-C_{24} hydrocarbylene. For example, the linking moiety may be selected from C_1-C_{24} alkylene, C_2-C_{24} alkenylene, C_2-C_{24} alkynylene, C_5-C_{24} arylene, and combinations thereof (such as, for example, C_6-C_{24} arylalkylene, etc.), any of which may contain one or more (e.g., 2, 3, or 4) heteroatoms and/or may be unsubstituted or substituted with one or more (e.g., 2, 3, or 4) substituents. In some embodiments, the linking moiety is a C_8-C_{24} arylene that comprises two or more fused aryl rings. In some embodiments, the linking moiety is a C_7-C_{24} alkylene that comprises two or more fused cycloalkyl rings. In some embodiments, the linking moiety comprises a combination of aryl and alkyl rings, either fused or separated by another moiety.

[00070] In some embodiments, linking moieties include alkylene linkers, arylenes, amides, amines, carbonyls, ureas, carbamates, sulfoxides, sulfonamides, ethers, and combinations such as amide/urea combinations, amide/amide combinations, sulfoxide/ether combinations, amide/ether combinations, amine/ether combinations, amide/amine combinations, carbonyl/amide combinations, and other combinations as appropriate. Such linkers may include unsaturated or saturated segments. Examples of linking moieties include the structures shown below.





wherein R, R^2, and R^3 are selected from H, hydrocarbyl, and functional groups, and the stars represent attachment points to the first and second active moieties. In the linker compounds disclosed herein, "m" and "n" represent integers that are independently selected. These integers may, for example, have the value 0, 1, 2, etc.

[00071] In some embodiments, the compounds of the invention can be represented by the formula (I)

(I) A-L-U,

wherein A is the first active moiety, L is a linking moiety, and U is the second active moiety. A number of example compounds according to formula (I) are shown in the Examples provided below. Furthermore, as described in more detail below, in some embodiments the first and second active moieties are not covalently linked to one another. Such embodiments may, for example, be represented by formula (I) wherein L is absent entirely. In such embodiments, A and U are administered together and may be physically associated (i.e., close in space) to one another such as when encapsulated within a liposome.

[00072] In some embodiments, the compounds of the invention are bifunctional molecules - i.e., compounds having two moieties that are biologically active. For example, one active moiety may capable of binding to calcineurin. In preferred such embodiments, the active moiety is capable of binding fungal calcineurin but not human calcineurin. In another example, one active moiety is capable of binding to fungal HSP90. In these examples, the

second active moiety may be an antifungal biomoiety. Some preferred examples are compounds that target lanosterol 14α-demethylase, calcineurin, and the enzyme β(1,3)-D-Glucan synthase.

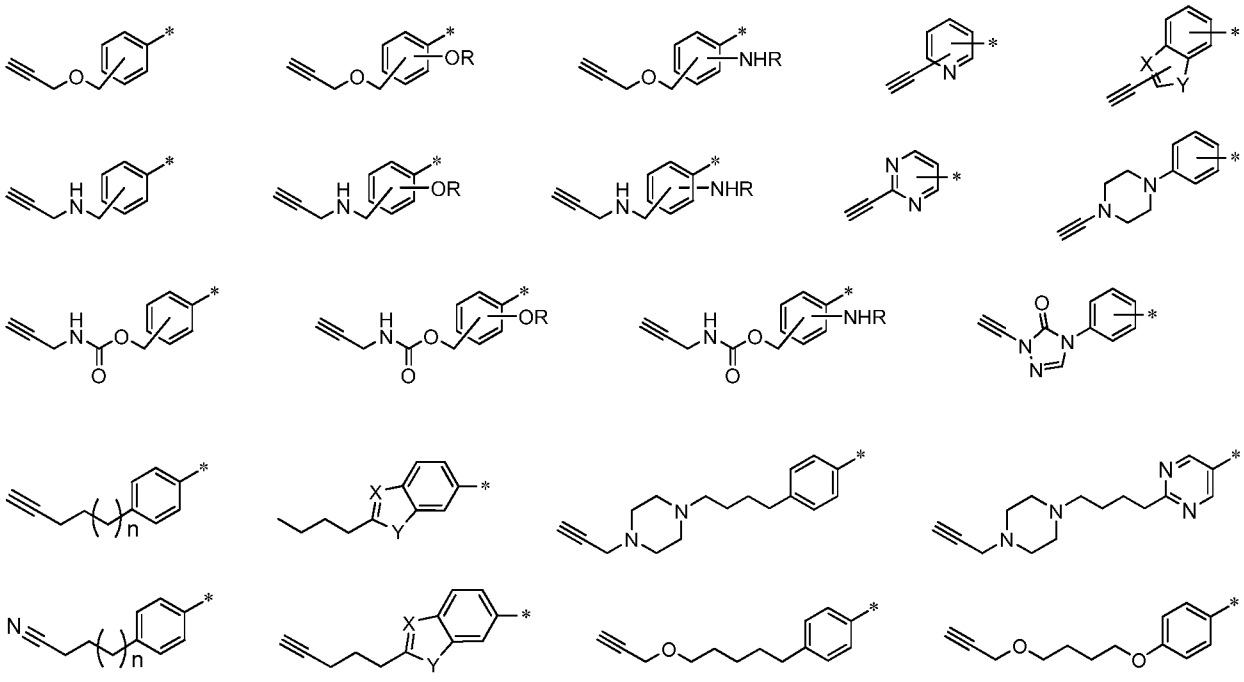
[00073] The compounds of the invention may be prepared according to the Examples provided herein *infra*, wherein such procedures may be supplemented with synthetic techniques known in the art. In some embodiments, for example, the compounds are prepared using a bismuth coupling reagent. Scheme 1 provides a generalized linking reaction for the compounds of the invention.

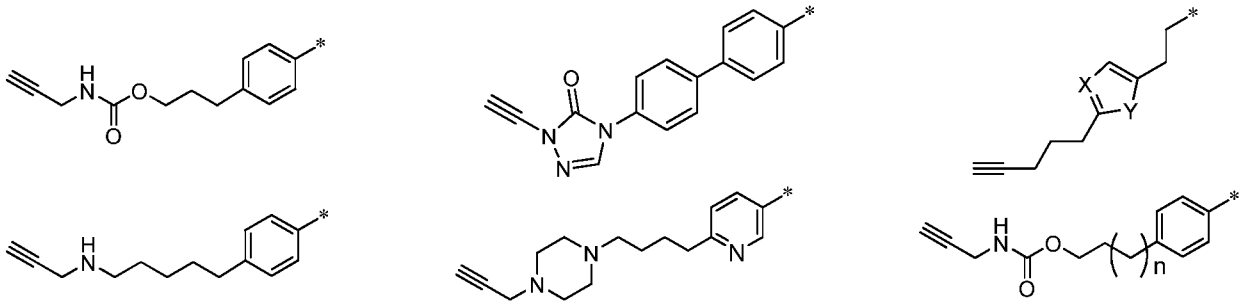
Scheme 1

$$A'\text{–}OH + (R')_3Bi \rightarrow A'\text{–}OR'$$

$$A'\text{–}OR' + N_3\text{–}B' \rightarrow A\text{–}L\text{–}B$$

wherein R' is generally a group having an aromatic ring and an alkynyl group, A represents the first active moiety (and A'–OH represents the precursor reactant that provides the first active moiety), B represents the second active moiety (and B'–OH represents the precursor reactant that provides the first active moiety), N_3 is an azide group, and L represents the linker moiety that results from the coupling reaction. Examples of suitable R' groups include





wherein the star represents the attachment point to Bi or O. In the above examples of R', n is an integer in the range of 0 to 6, R is hydrocarbyl (including substituted, unsubstituted, heteroatom containing, and substituted heteroatom-containing hydrocarbyl) or hydrogen, X is selected from -CH-, and -N-, and Y is selected from -CH_2-, -O-, -NH-, and -S-.

[00074] As mentioned previously, in some embodiments, the first and second active moieties are non-covalently associated with each other. Optionally in such embodiments, there may be non-covalent bonding interactions between the two active moieties, such as hydrogen bonding, Van der Waals bonding, and/or ionic bonding. In some embodiments, minimal or no such non-covalently bonding interactions are present, or such interactions are disrupted by the presence of salts, solvents, etc. Futhermore, in some embodiments, the first and second active moieties are not covalently attached to one another, but are together encapsulated within a liposome or a similar structure. In such embodiments, the first and second active moieties are co-administered via the liposome. It will be appreciated that, in embodiments where the first and second active moieties are not covalently linked, the structures shown herein for such moieties will be adjusted accordingly. For example, in the structures for U1-U6 and A1-A7, the stars will represent a chemical moiety (rather than a connection to the linker moiety). The chemical moiety will typically be selected from H, hydrocarbyl, substituted hydrocarbyl, heteroatom-containing substituted hydrocarbyl, functional groups, and protecting groups. For example, in some embodiments, the star represents H. As further examples, in some embodiments of U2 and U4, the star represents an amine protecting group or a hydroxyl protecting group, respectively. In some embodiments of U5, the star represents any of the groups defined herein for R^{U2}.

[00075] In embodiments wherein the first and second active moieties are not covalently attached, they may be co-administered in any ratio that is appropriate for optimal dosing. Such ratios will typically be between 1:1 (i.e., equal molar parts of each active moiety) and $1:10^4$, or between 1:1 and 1:1000, or between 1:1 and 1:100, or between 1:1 and 1:10, or between 1:1 and 1:5, or between 1:1 and 1:2. In some embodiments, preferred ratios

are between 1:1 and 1:100, or between 1:1 and 1:10. When the active moieties are co-administered via encapsulation within a liposome or other means, the moieties will generally be randomly distributed within the liposomes according to the aforementioned ratios.

[00076] A compound of the disclosure may be administered in the form of a salt, ester, amide, prodrug, active metabolite, analog, or the like, provided that the salt, ester, amide, prodrug, active metabolite or analog is pharmaceutically acceptable and pharmacologically active in the present context. Salts, esters, amides, prodrugs, active metabolites, analogs, and other derivatives of the active agents may be prepared using standard procedures known to those skilled in the art of synthetic organic chemistry and described, for example, by J. March, *Advanced Organic Chemistry: Reactions, Mechanisms and Structure*, 5th Ed. (New York: Wiley-Interscience, 2001). Furthermore, where appropriate, functional groups on the compounds of the disclosure may be protected from undesired reactions during preparation or administration using protecting group chemistry. Suitable protecting groups are described, for example, in Green, *Protective Groups in Organic Synthesis*, 3rd Ed. (New York: Wiley-Interscience, 1999).

[00077] For example, where appropriate, any of the compounds described herein may be in the form of a pharmaceutically acceptable salt. A pharmaceutically acceptable salt may be prepared from any pharmaceutically acceptable organic acid or base, any pharmaceutically acceptable inorganic acid or base, or combinations thereof. The acid or base used to prepare the salt may be naturally occurring.

[00078] Suitable organic acids for preparing acid addition salts include, e.g., C_1-C_6 alkyl and C_6-C_{12} aryl carboxylic acids, di-carboxylic acids, and tri-carboxylic acids such as acetic acid, propionic acid, succinic acid, maleic acid, fumaric acid, tartaric acid, glycolic acid, citric acid, pyruvic acid, oxalic acid, malic acid, malonic acid, benzoic acid, cinnamic acid, mandelic acid, salicylic acid, phthalic acid, and terephthalic acid, and aryl and alkyl sulfonic acids such as methanesulfonic acid, ethanesulfonic acid, and p-toluenesulfonic acid, and the like. Suitable inorganic acids for preparing acid addition salts include, e.g., hydrochloric acid, hydrobromic acid, hydroiodic acid, sulfuric acid, nitric acid, and phosphoric acid, and the like. An acid addition salt may be reconverted to the free base by treatment with a suitable base.

[00079] Suitable organic bases for preparing basic addition salts include, e.g., primary, secondary and tertiary amines, such as trimethylamine, triethylamine, tripropylamine, N,N-dibenzylethylenediamine, 2-dimethylaminoethanol, ethanolamine, ethylenediamine, glucamine, glucosamine, histidine, and polyamine resins, cyclic amines such as caffeine, N-

ethylmorpholine, N-ethylpiperidine, and purine, and salts of amines such as betaine, choline, and procaine, and the like. Suitable inorganic bases for preparing basic addition salts include, e.g., salts derived from sodium, potassium, ammonium, calcium, ferric, ferrous, aluminum, lithium, magnesium, or zinc such as sodium hydroxide, potassium hydroxide, calcium carbonate, sodium carbonate, and potassium carbonate, and the like. A basic addition salt may be reconverted to the free acid by treatment with a suitable acid.

[00080] Preparation of esters involves transformation of a carboxylic acid group via a conventional esterification reaction involving nucleophilic attack of an RO^- moiety at the carbonyl carbon. Esterification may also be carried out by reaction of a hydroxyl group with an esterification reagent such as an acid chloride. Esters can be reconverted to the free acids, if desired, by using conventional hydrogenolysis or hydrolysis procedures. Amides may be prepared from esters, using suitable amine reactants, or they may be prepared from an anhydride or an acid chloride by reaction with ammonia or a lower alkyl amine. Prodrugs and active metabolites may also be prepared using techniques known to those skilled in the art or described in the pertinent literature. Prodrugs are typically prepared by covalent attachment of a moiety that results in a compound that is therapeutically inactive until modified by an individual's metabolic system.

[00081] Other derivatives and analogs of the active agents may be prepared using standard techniques known to those skilled in the art of synthetic organic chemistry, or may be deduced by reference to the pertinent literature. In addition, chiral active agents may be in isomerically pure form, or they may be administered as a racemic mixture of isomers.

[00082] Any of the compounds of the disclosure may be the active agent in a formulation as described herein. Formulations containing the compounds of the disclosure may include 1, 2, 3 or more of the compounds described herein, and may also include one or more additional active agents such as analgesics and other antibiotics.

[00083] The amount of active agent in the formulation typically ranges from about 0.05 wt% to about 95 wt% based on the total weight of the formulation. For example, the amount of active agent may range from about 0.05 wt% to about 50 wt%, or from about 0.1 wt% to about 25 wt%. Alternatively, the amount of active agent in the formulation may be measured so as to achieve a desired dose.

[00084] Formulations containing the compounds of the disclosure may be presented in unit dose form or in multi-dose containers with an optional preservative to increase shelf life.

[00085] The compositions of the disclosure may be administered to the patient by any appropriate method. In general, both systemic and localized methods of administration are

acceptable. It will be obvious to those skilled in the art that the selection of a method of administration will be influenced by a number of factors, such as the condition being treated, frequency of administration, dosage level, and the wants and needs of the patient. For example, certain methods may be better suited for rapid delivery of high doses of active agent, while other methods may be better suited for slow, steady delivery of active agent. Examples of methods of administration that are suitable for delivery of the compounds of the disclosure include parental and transmembrane absorption (including delivery via the digestive and respiratory tracts). Formulations suitable for delivery via these methods are well known in the art.

[00086] For example, formulations containing the compounds of the disclosure may be administered parenterally, such as via intravenous, subcutaneous, intraperitoneal, or intramuscular injection, using bolus injection and/or continuous infusion. Generally, parenteral administration employs liquid formulations.

[00087] The compositions may also be administered via the digestive tract, including orally and rectally. Examples of formulations that are appropriate for administration via the digestive tract include tablets, capsules, pastilles, chewing gum, aqueous solutions, and suppositories.

[00088] The formulations may also be administered via transmucosal administration. Transmucosal delivery includes delivery via the oral (including buccal and sublingual), nasal, vaginal, and rectal mucosal membranes. Formulations suitable for transmucosal deliver are well known in the art and include tablets, chewing gums, mouthwashes, lozenges, suppositories, gels, creams, liquids, and pastes.

[00089] The formulations may also be administered transdermally. Transdermal delivery may be accomplished using, for example, topically applied creams, liquids, pastes, gels and the like as well as what is often referred to as transdermal "patches."

[00090] The formulations may also be administered via the respiratory tract. Pulmonary delivery may be accomplished via oral or nasal inhalation, using aerosols, dry powders, liquid formulations, or the like. Aerosol inhalers and imitation cigarettes are examples of pulmonary dosage forms.

[00091] Liquid formulations include solutions, suspensions, and emulsions. For example, solutions may be aqueous solutions of the active agent and may include one or more of propylene glycol, polyethylene glycol, and the like. Aqueous suspensions can be made by dispersing the finely divided active agent in water with viscous material, such as natural or synthetic gums, resins, methylcellulose, sodium carboxymethylcellulose, or other well known

suspending agents. Also included are formulations of solid form which are intended to be converted, shortly before use, to liquid form.

[00092] Tablets and lozenges may comprise, for example, a flavored base such as compressed lactose, sucrose and acacia or tragacanth and an effective amount of an active agent. Pastilles generally comprise the active agent in an inert base such as gelatin and glycerine or sucrose and acacia. Mouthwashes generally comprise the active agent in a suitable liquid carrier.

[00093] For topical administration to the epidermis the chemical compound according to the disclosure may be formulated as ointments, creams or lotions, or as a transdermal patch. Ointments and creams may, for example, be formulated with an aqueous or oily base with the addition of suitable thickening and/or gelling agents. Lotions may be formulated with an aqueous or oily base and will in general also contain one or more emulsifying agents, stabilizing agents, dispersing agents, suspending agents, thickening agents, or coloring agents.

[00094] Transdermal patches typically comprise: (1) a impermeable backing layer which may be made up of any of a wide variety of plastics or resins, e.g. aluminized polyester or polyester alone or other impermeable films; and (2) a reservoir layer comprising, for example, a compound of the disclosure in combination with mineral oil, polyisobutylene, and alcohols gelled with USP hydroxymethylcellulose. As another example, the reservoir layer may comprise acrylic-based polymer adhesives with resinous crosslinking agents which provide for diffusion of the active agent from the reservoir layer to the surface of the skin. The transdermal patch may also have a delivery rate-controlling membrane such as a microporous polypropylene disposed between the reservoir and the skin. Ethylene-vinyl acetate copolymers and other microporous membranes may also be used. Typically, an adhesive layer is provided which may comprise an adhesive formulation such as mineral oil and polyisobutylene combined with the active agent.

[00095] Other typical transdermal patches may comprise three layers: (1) an outer layer comprising a laminated polyester film; (2) a middle layer containing a rate-controlling adhesive, a structural non-woven material and the active agent; and (3) a disposable liner that must be removed prior to use. Transdermal delivery systems may also involve incorporation of highly lipid soluble carrier compounds such as dimethyl sulfoxide (DMSO), to facilitate penetration of the skin. Other carrier compounds include lanolin and glycerin.

[00096] Rectal or vaginal suppositories comprise, for example, an active agent in combination with glycerin, glycerol monopalmitate, glycerol, monostearate, hydrogenated

palm kernel oil and fatty acids. Another example of a suppository formulation includes ascorbyl palmitate, silicon dioxide, white wax, and cocoa butter in combination with an effective amount of an active agent.

[00097] Nasal spray formulations may comprise a solution of active agent in physiologic saline or other pharmaceutically suitable carder liquids. Nasal spray compression pumps are also well known in the art and can be calibrated to deliver a predetermined dose of the solution.

[00098] Aerosol formulations suitable for pulmonary administration include, for example, formulations wherein the active agent is provided in a pressurized pack with a suitable propellant. Suitable propellants include chlorofluorocarbons (CFCs) such as dichlorodifluoromethane, trichlorofluoromethane, or dichlorotetrafluoroethane, carbon dioxide, or other suitable gases. The aerosol may also contain a surfactant such as lecithin. The dose of drug may be controlled by provision of a metered valve.

[00099] Dry powder suitable for pulmonary administration include, for example, a powder mix of the compound in a suitable powder base such as lactose, starch, starch derivatives such as hydroxypropylmethyl cellulose and polyvinylpyrrolidone (PVP). Conveniently the powder carrier will form a gel in the nasal cavity. Unit doses for dry powder formulations may be, for example, in the form of capsules or cartridges of, e.g., gelatin, or blister packs from which the powder may be administered by means of an inhaler.

[000100] In addition to the foregoing components, it may be necessary or desirable in some cases (depending, for instance, on the particular composition or method of administration) to incorporate any of a variety of additives, e.g., components that improve drug delivery, shelf-life, patient acceptance, etc. Suitable additives include acids, antioxidants, antimicrobials, buffers, colorants, crystal growth inhibitors, defoaming agents, diluents, emollients, fillers, flavorings, gelling agents, fragrances, lubricants, propellants, thickeners, salts, solvents, surfactants, other chemical stabilizers, or mixtures thereof. Examples of these additives can be found, for example, in M. Ash and I. Ash, *Handbook of Pharmaceutical Additives* (Hampshire, England: Gower Publishing, 1995), the contents of which are herein incorporated by reference.

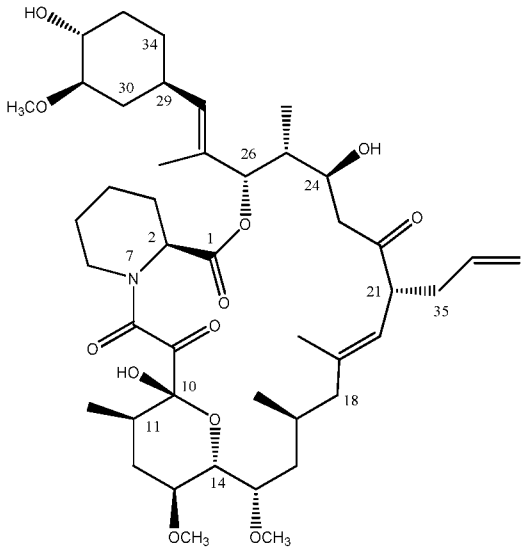
[000101] Appropriate dose and regimen schedules will be apparent based on the present disclosure and on information generally available to the skilled artisan. When the compounds of the disclosure are used in the treatment of infections, achievement of the desired effects may require weeks, months, or years of controlled, low-level administration of the

formulations described herein. Other dosage regimens, including less frequent administration of high-intensity dosages, are also within the scope of the disclosure.

[000102] The amount of active agent in formulations that contain the compounds of the disclosure may be calculated to achieve a specific dose (i.e., unit weight of active agent per unit weight of patient) of active agent. Furthermore, the treatment regimen may be designed to sustain a predetermined systemic level of active agent. For example, formulations and treatment regimen may be designed to provide an amount of active agent that ranges from about 0.001 mg/kg/day to about 100 mg/kg/day for an adult. As a further example, the amount of active agent may range from about 0.1 mg/kg/day to about 50 mg/kg/day, about 0.1mg/kg/day to about 25 mg/kg/day, or about 1mg/kg/day to about 10 mg/kg/day. One of skill in the art will appreciate that dosages may vary depending on a variety of factors, including method and frequency of administration, and physical characteristics of the patient.

[000103] In some embodiments, the compounds of the disclosure may be prepared using standard procedures that are known to those skilled in the art of synthetic organic chemistry and used for the preparation of analogous compounds. Appropriate synthetic procedures may be found, for example, in J. March, *Advanced Organic Chemistry: Reactions, Mechanisms and Structure*, 5th Edition (New York: Wiley-Interscience, 2001). Syntheses of representative compounds are detailed in the Examples.

[000104] In some embodiments, the invention further includes an improved method for preparation of the compounds of the invention. For example, in some embodiments, the inventive methods include forming a carbamate or carbonate on either the first active moiety or the second active moiety with a carbamate- or carbonate-forming reagent. The carbamate or carbonate thus formed is able to react with a nucleophile present on the other moiety (i.e., the first moiety if the carbamate or carbonate is formed on the second moiety, or the second moiety if the carbamate or carbonate is formed on the first moiety). In preferred such embodiments, the carbamate or carbonate is formed on a first hydroxyl group of the first or second active moiety, wherein the moiety may have one or more additional hydroxyl groups that are unreactive (relative to the first hydroxyl group) with the carbamate- or carbonate-forming reagent. For example, the carbamate or carbonate is formed at the C-32 position of FK-506 or a derivative thereof (FK-506 numbering shown below) without the need to protect the other hydroxyl groups (i.e., at C-24, C-10, and, when present, C-18). For example, it is not necessary, using this method, to silyl-protect (or otherwise protect) such hydroxyl groups on FK-506 or a derivative thereof when forming a conjugate with FK-506. In some embodiments, long reaction times at room temperature allow this selective reaction to occur.



FK-506 numbering

[000105] Accordingly, the compounds find utility in treating infections by microorganisms. Accordingly, the disclosure provides a method for treating an infected patient, the method comprising administering to the patient an effective amount of any of the compounds disclosed herein. The disclosure also provides a method for preventing infection, the method comprising administering an effective amount of any of the compounds disclosed herein. The disclosure also provides a method for treating a patient suffering from an infection, the method comprising administering an effective amount of any of the compounds disclosed herein to a patient in need thereof. The disclosure also provides a method for inhibiting the spread of an infection, the method comprising contacting a cell infected with a microorganism with an effective amount of any of the compounds disclosed herein. The disclosure also provides a method for inhibiting the spread of an infection, the method comprising contacting a tissue infected with a microorganism (wherein the infection is either within the cells of the tissue, in the intercellular matrix of the tissue, or both) with an effective amount of any of the compounds disclosed herein. As described in more detail herein, in any of the aforementioned methods, the compound may be administered in a composition comprising one or more active agents and one or more additives.

[000106] In some embodiments, the compounds and compositions of the invention are suitable for treating fungal infections. In some embodiments, the compounds inhibit fungal calcineurin.

[000107] In some embodiments, the compounds of the invention are useful in treating fungal infections. In some preferred embodiments, the compounds are useful in treating

fungal infections wherein the fungal infection is of a fungus from the genus Candida, Aspergillus, or Cryptococcus. For example, the compounds are useful in treating infections of *C. albicans, A. fumigatus, C. neoformans, C. glabrata, C. krusei*, or *C. gattii.*

[000108] All patents, patent applications, and publications mentioned herein are hereby incorporated by reference in their entireties. However, where a patent, patent application, or publication containing express definitions is incorporated by reference, those express definitions should be understood to apply to the incorporated patent, patent application, or publication in which they are found, and not to the remainder of the text of this application, in particular the claims of this application.

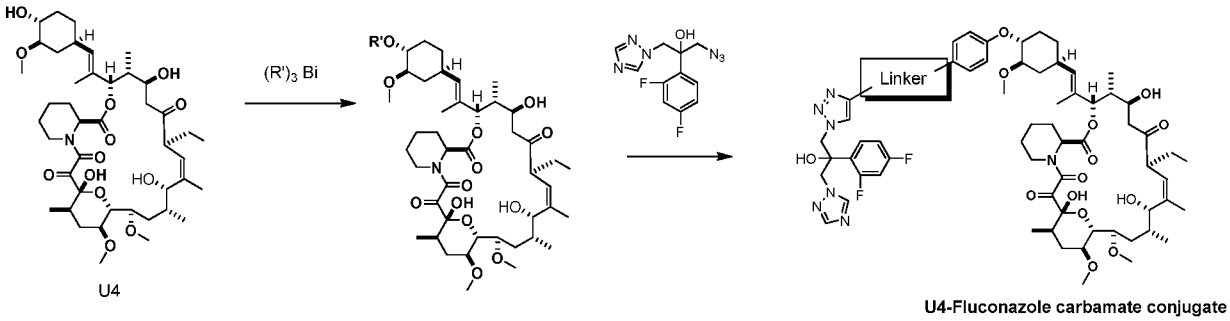
[000109] It is to be understood that while the invention has been described in conjunction with the preferred specific embodiments thereof, that the foregoing description and the examples that follow are intended to illustrate and not limit the scope of the invention. It will be understood by those skilled in the art that various changes may be made and equivalents may be substituted without departing from the scope of the invention, and further that other aspects, advantages and modifications will be apparent to those skilled in the art to which the invention pertains.

Examples

Example 1

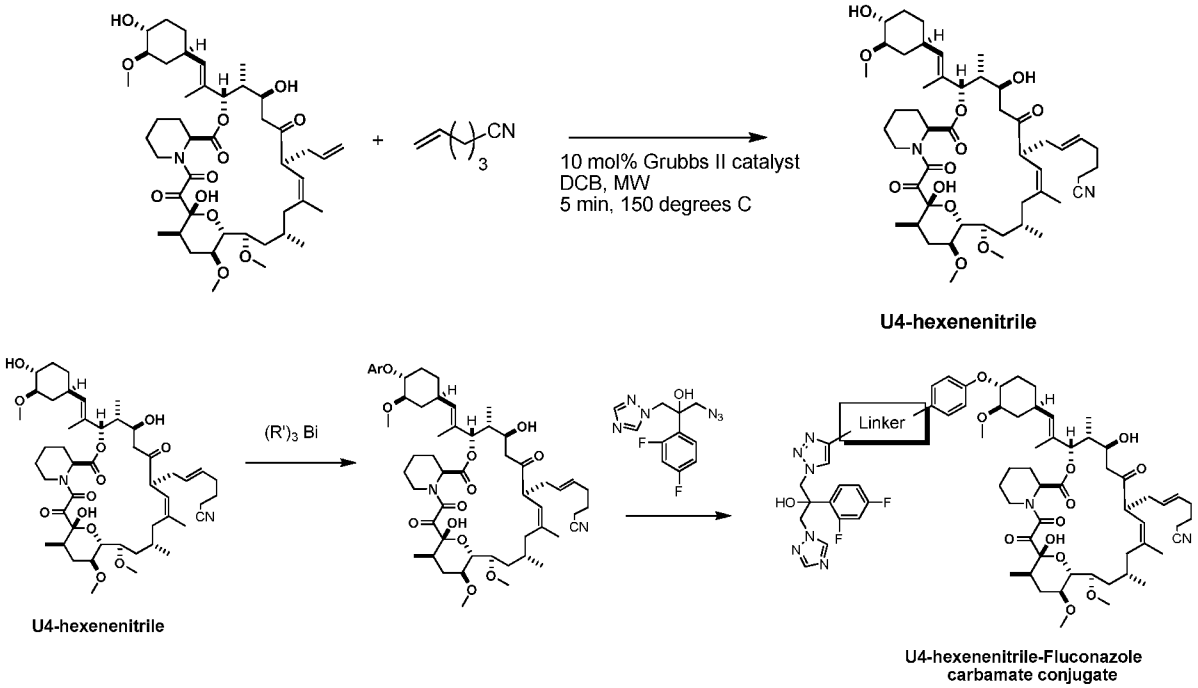
[000110] A generalized synthesis of exemplary compounds according to the invention is shown in Scheme 2.

Scheme 2



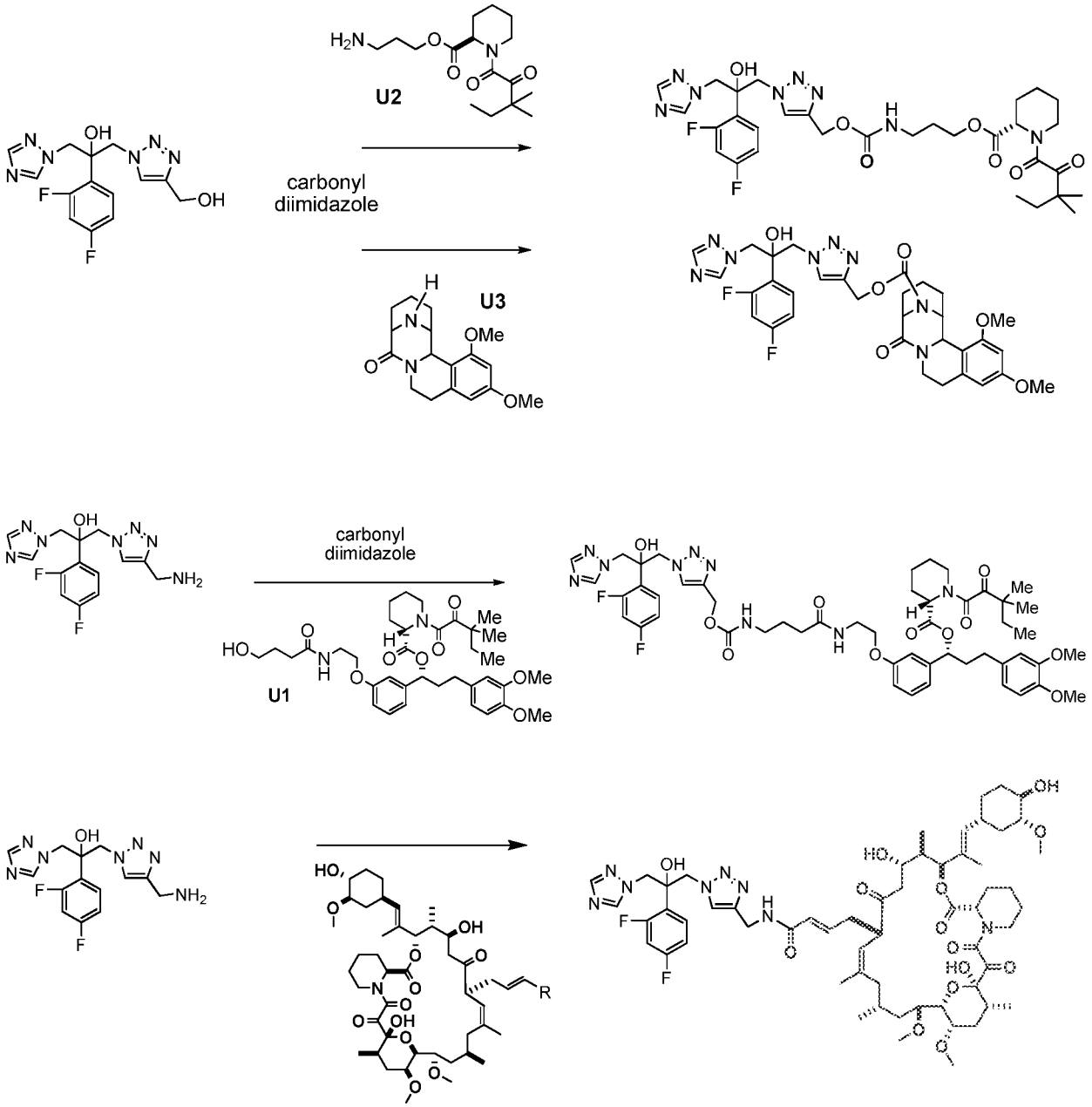
[000111] wherein $(R')_3Bi$ is as described herein *supra*. Another example is provided in Scheme 3.

Scheme 3



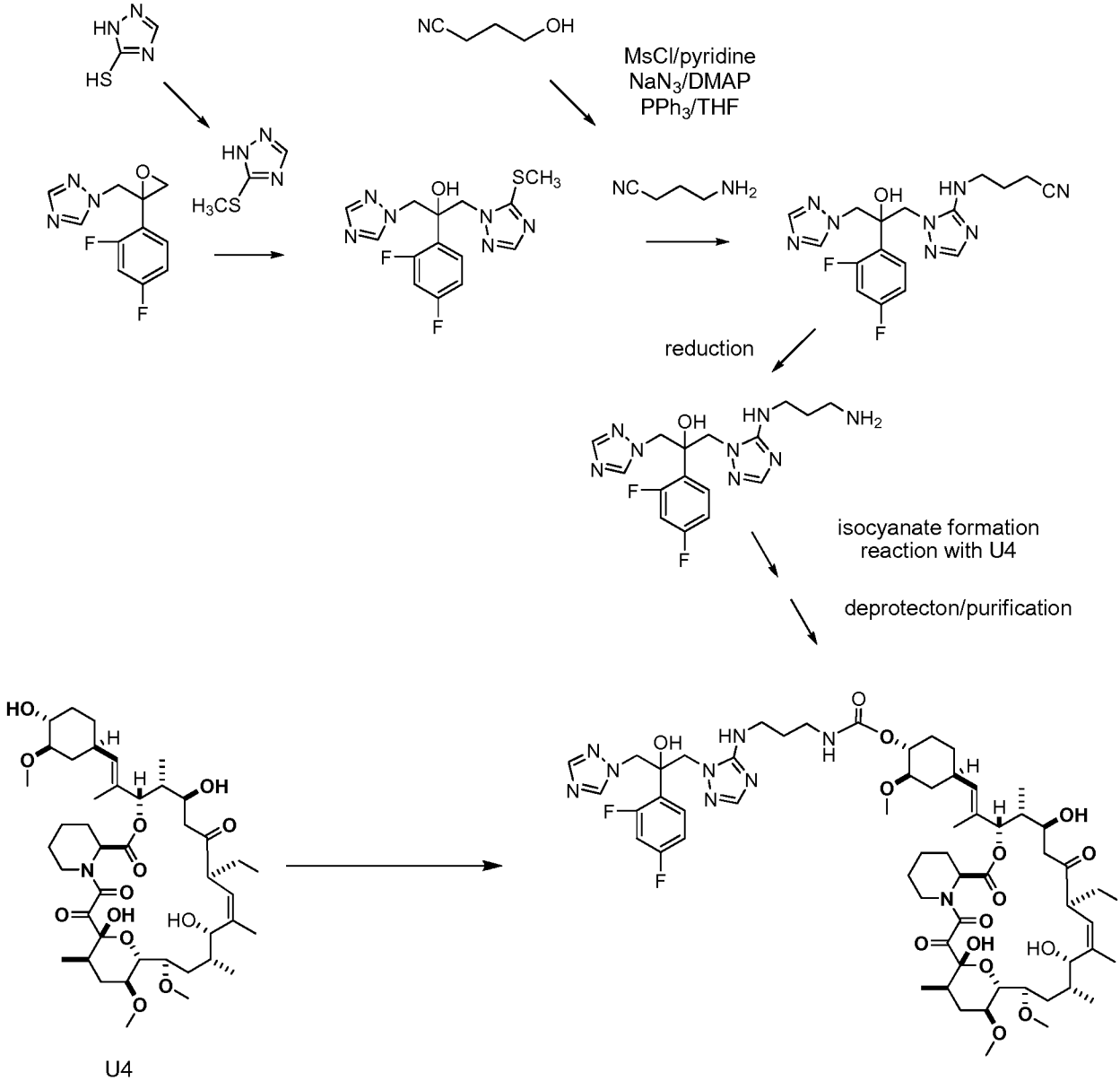
[000112] Further conjugates of Fluconazole are prepared according to the reactions shown in the following schemes.

Scheme 4a



R = CO_2H : acrylic acid

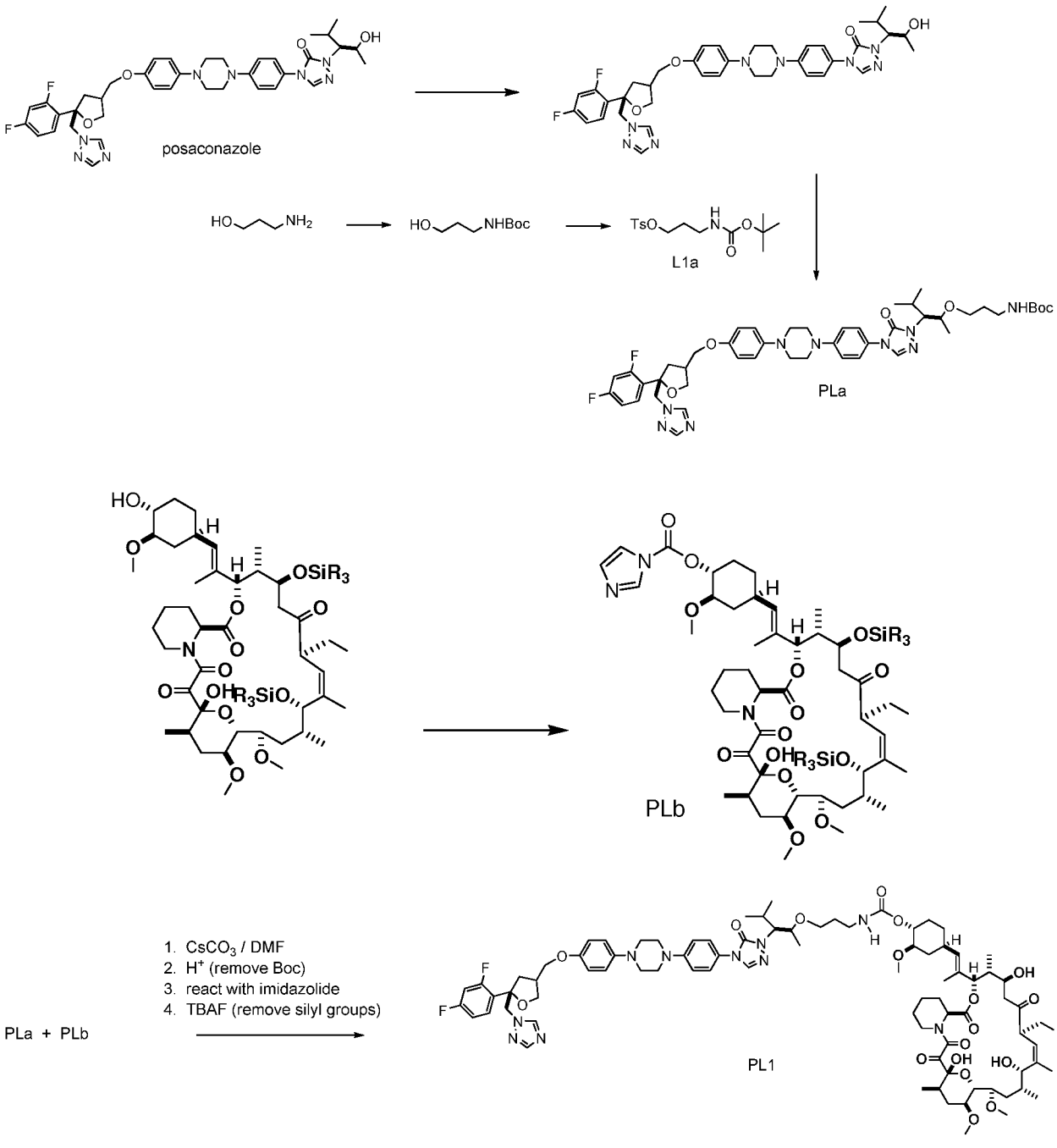
Scheme 4b


MsCl/pyridine
NaN3/DMAP
PPh3/THF
reduction
isocyanate formation
reaction with U4
deprotecton/purification
U4

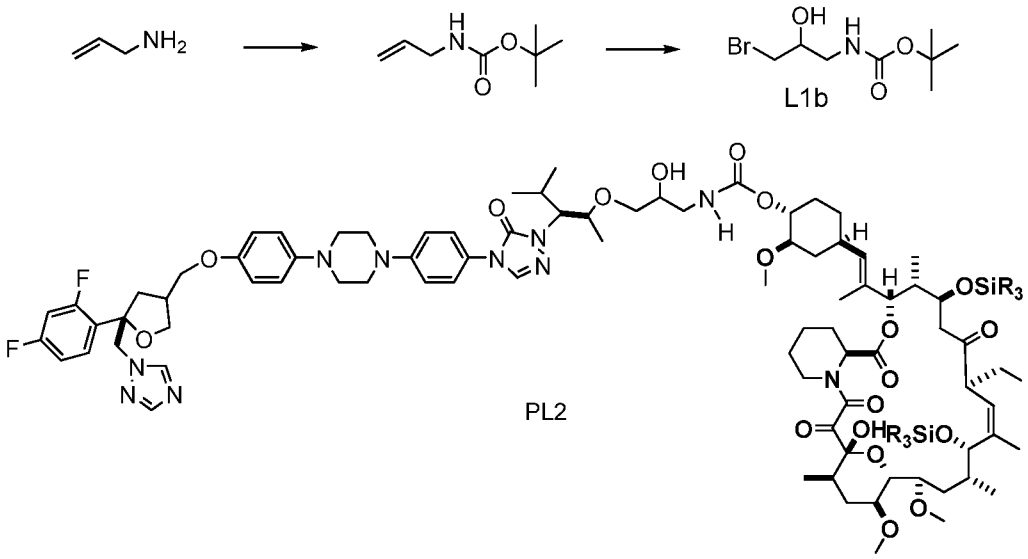
Example 2

[000113] The synthesis of a further exemplary compound, PL1, which incorporates a posaconazole moiety, is shown in the following scheme.

Scheme 5

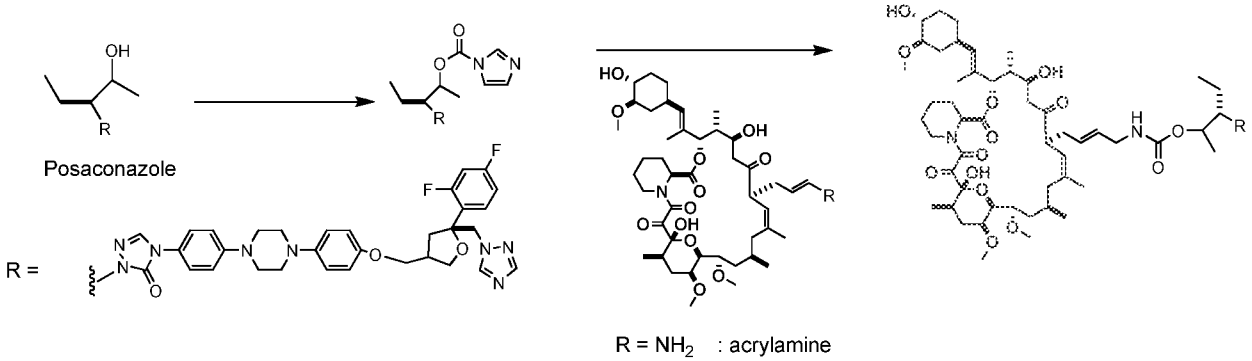


[000114] In Scheme 5, the linker L1a can be replaced with the following linker L1b, with a corresponding change in the final product (i.e., PL2, shown below prior to removal of the silyl group):



[000115] A further synthesis involving posaconazole is shown in the following scheme.

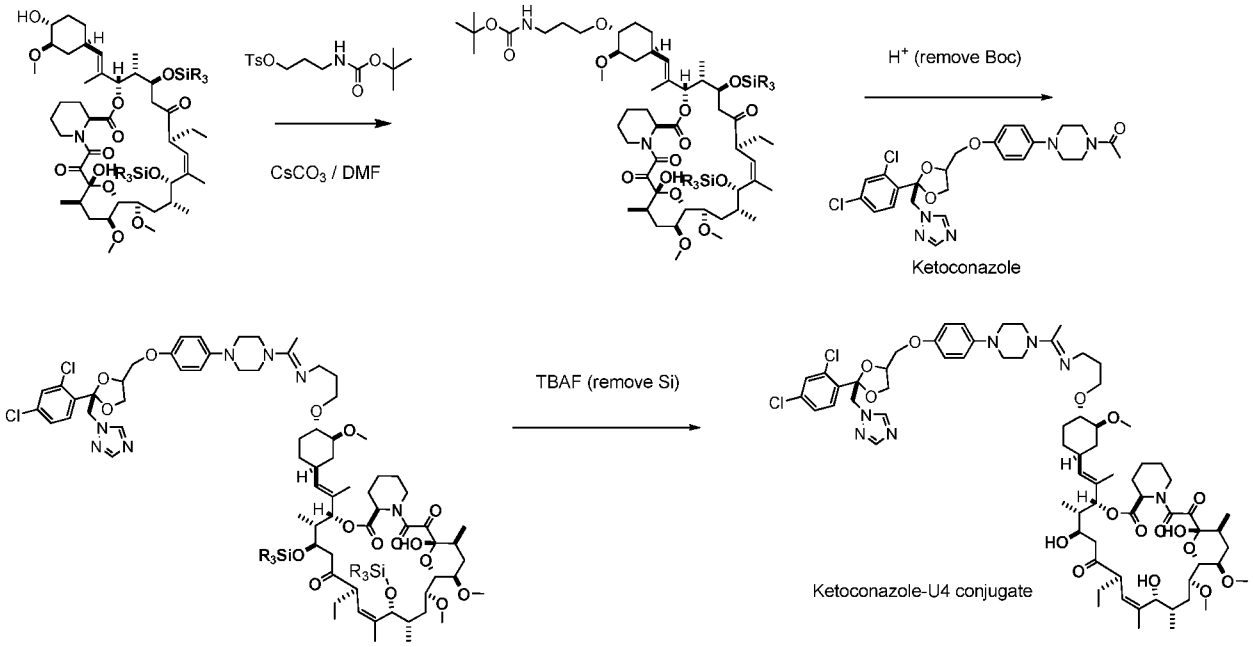
Scheme 6



Example 3

[000116] The synthesis of a further exemplary compound, which incorporates a ketoconazole moiety, is shown in the following scheme.

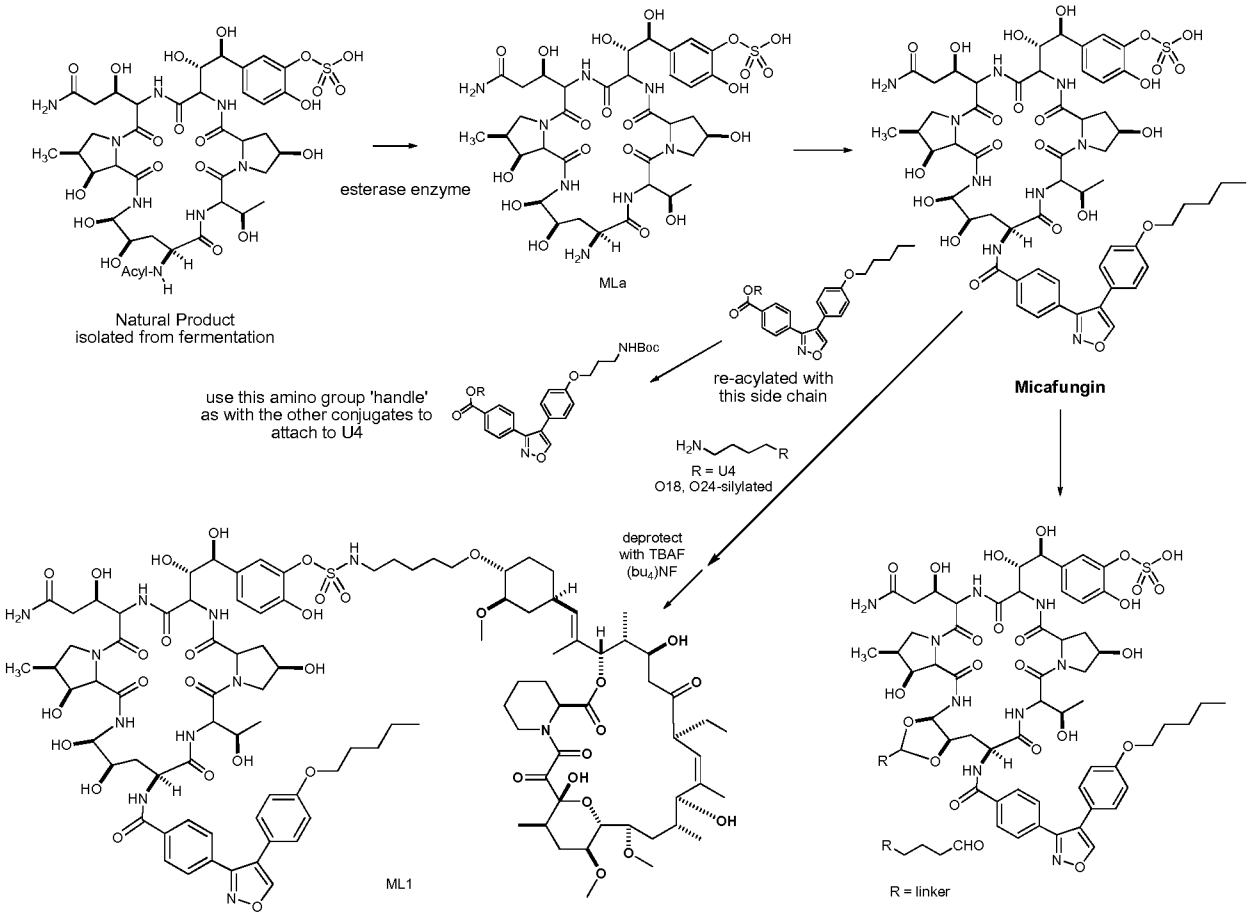
Scheme 7



Example 4

[000117] The synthesis of a further exemplary compound, ML1, which incorporates a micafungin moiety and the unit U4, is shown in the following scheme.

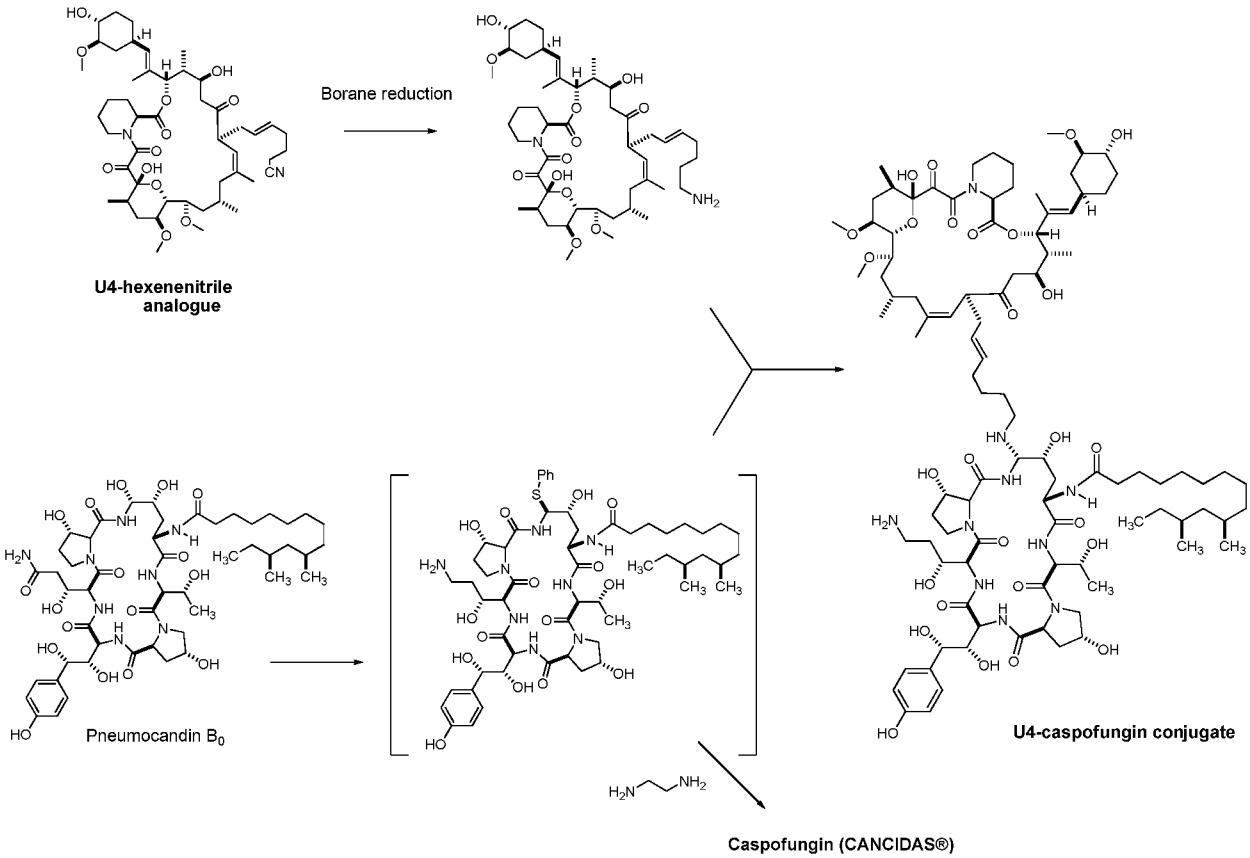
Scheme 8



Example 5

[000118] The synthesis of a further exemplary compound which incorporates a caspofungin moiety and the unit U4 is shown in the following scheme.

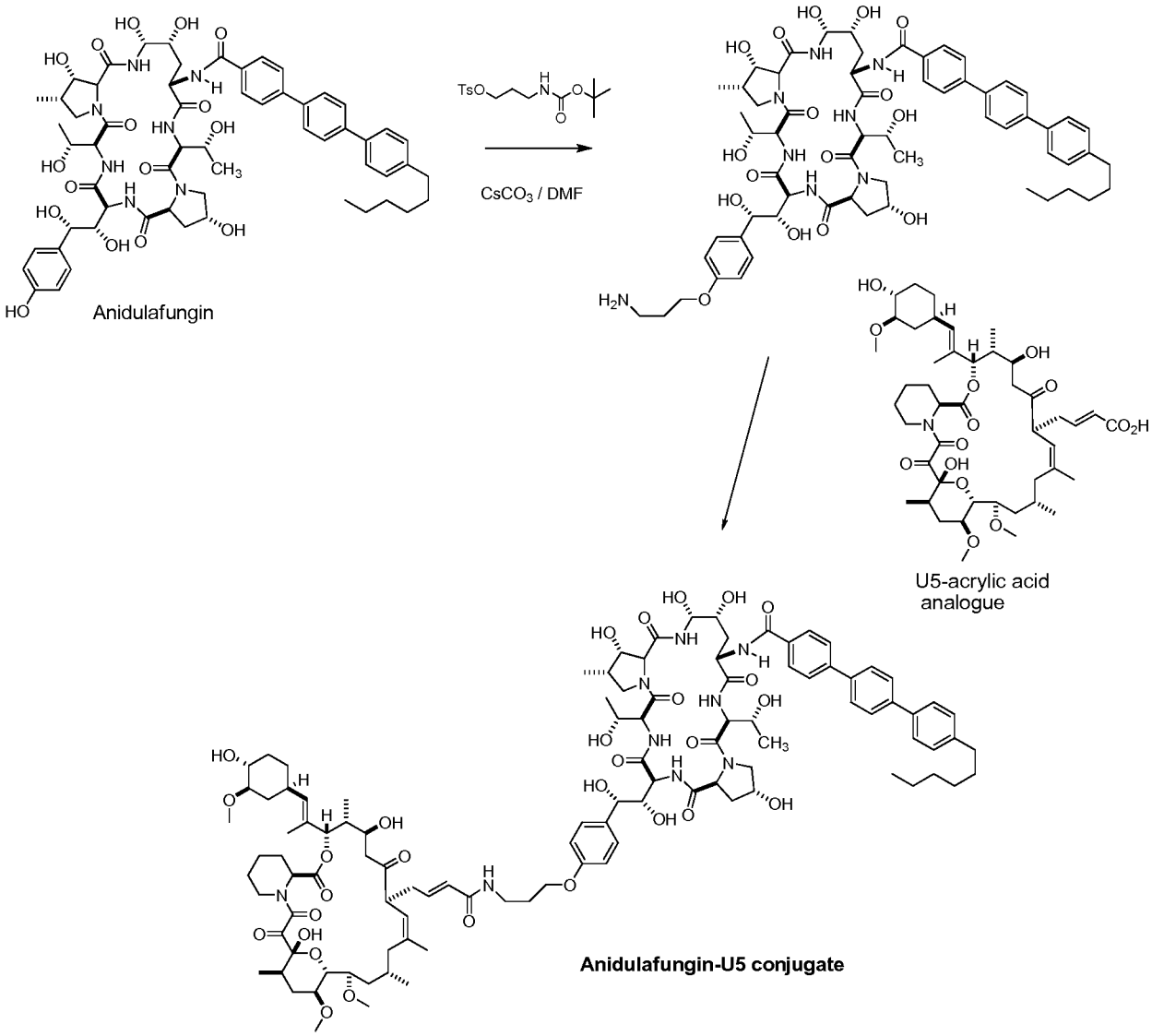
Scheme 9



Example 6

[000119] The synthesis of a further exemplary compound which incorporates a anidulafungin moiety and the unit U5 is shown in the following scheme.

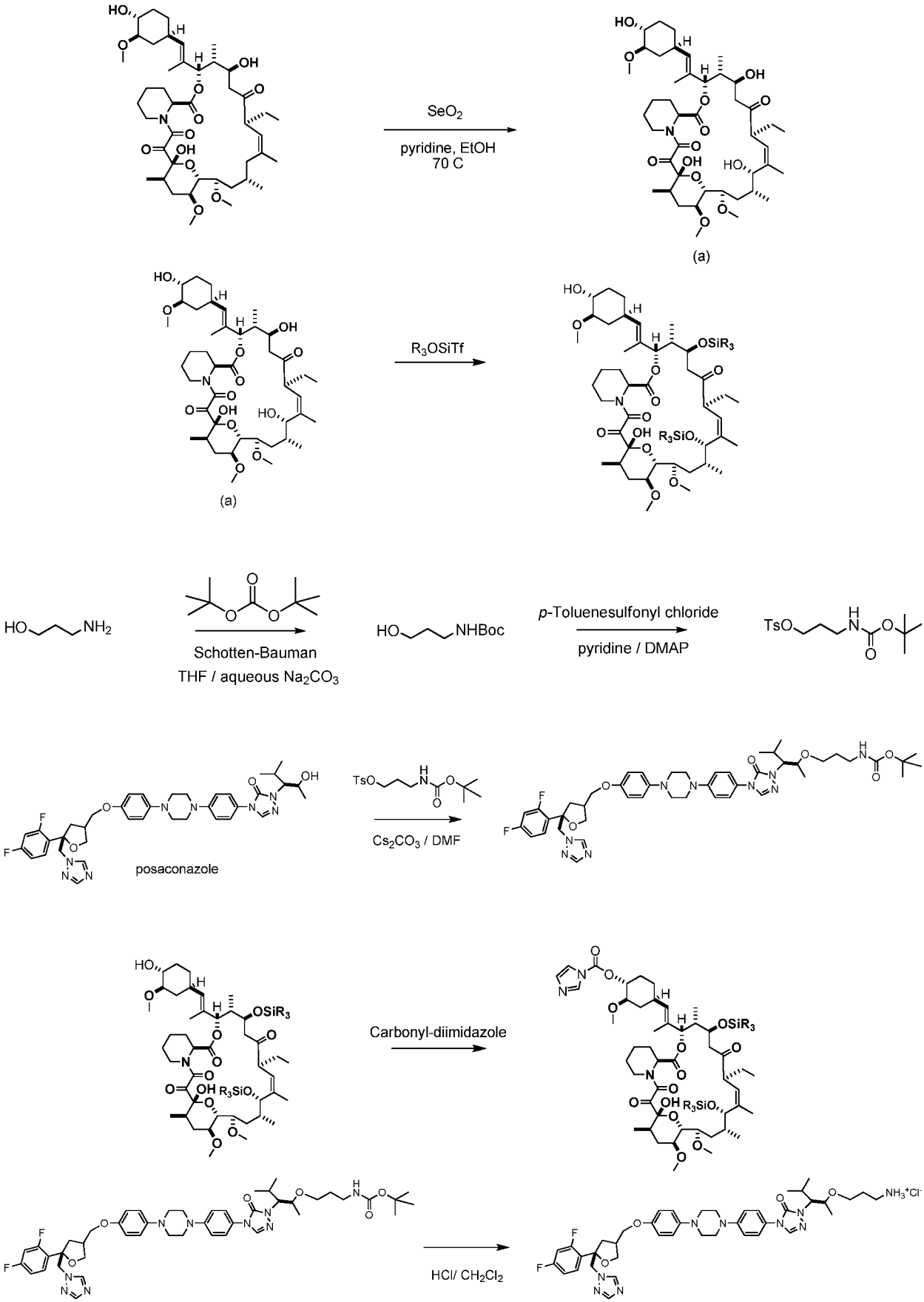
Scheme 10

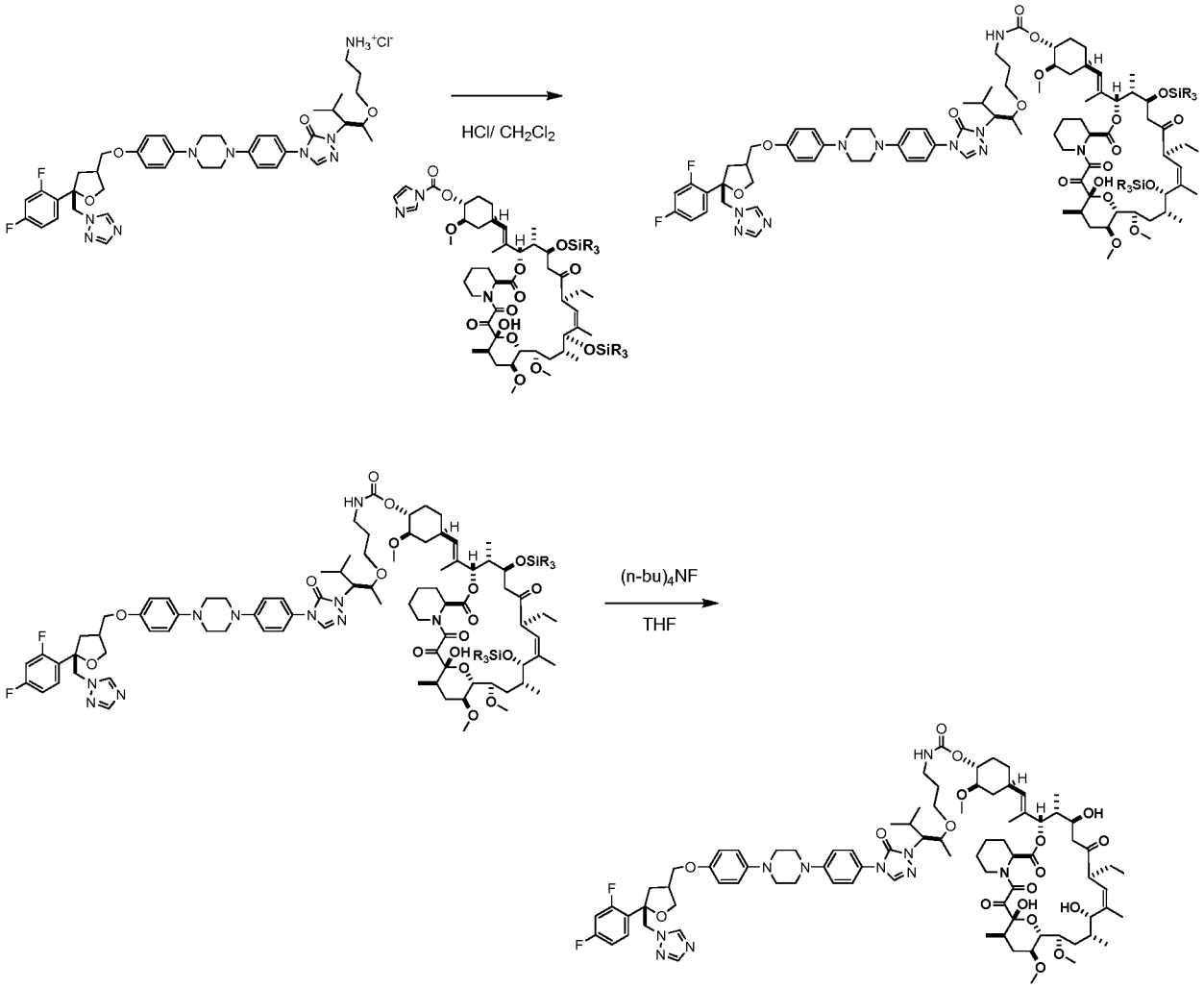


Example 7

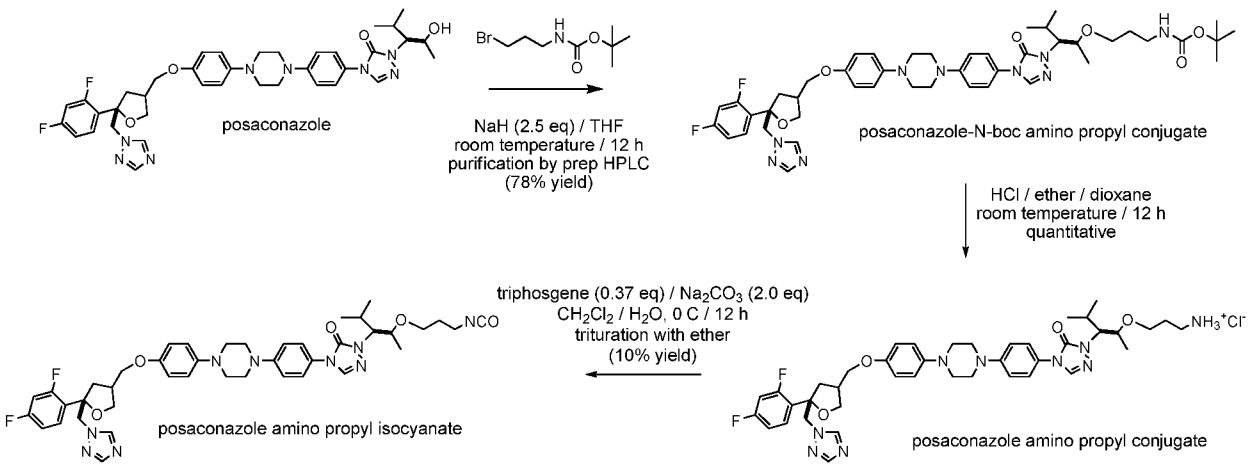
[000120] Alternative syntheses of a further exemplary compound incorporating a posaconazole moiety and the unit U4 are shown in the following schemes.

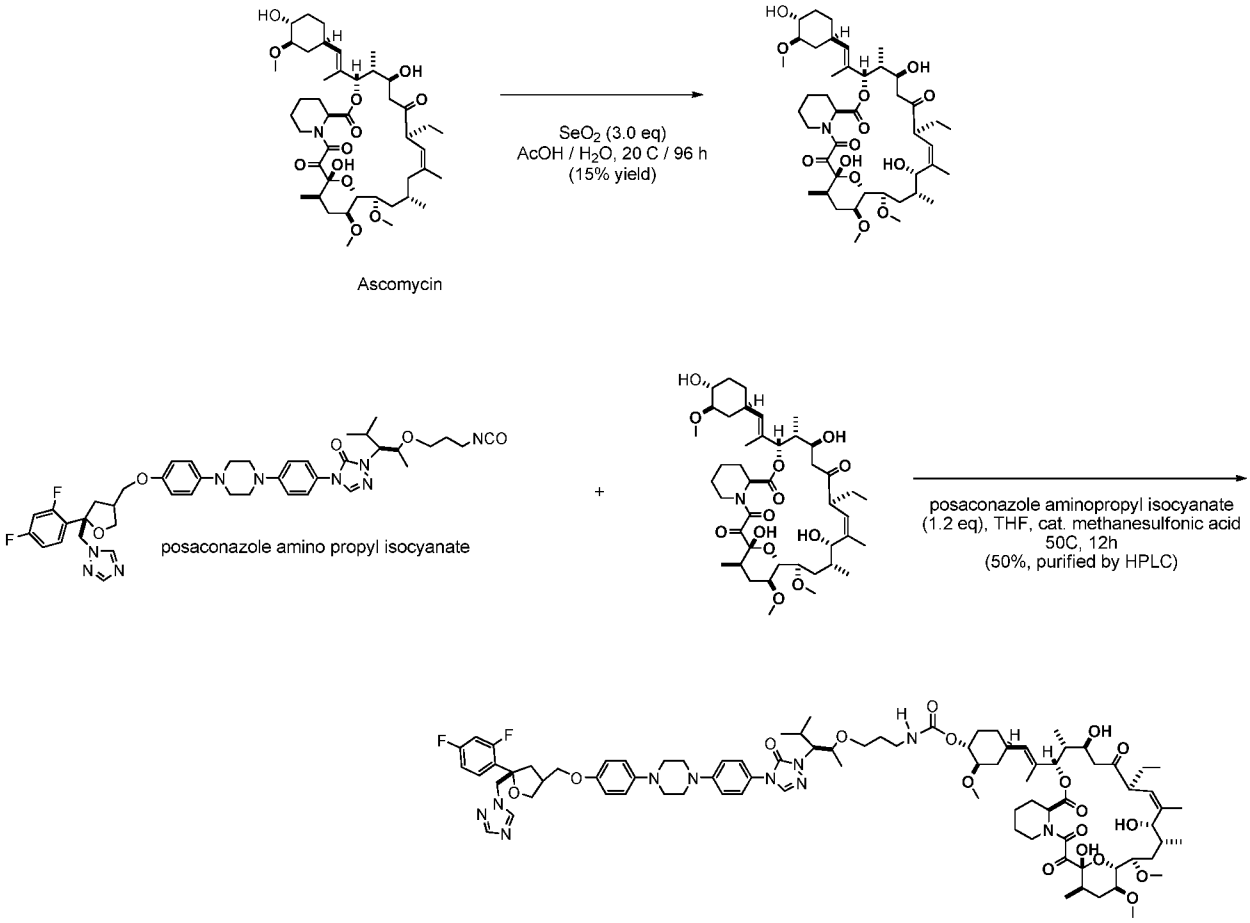
Scheme 11a


SeO2
pyridine, EtOH
70 C
(a)
R3OSiTf
(a)
HO NH2
Schotten-Bauman
THF / aqueous Na2CO3
HO NHBoc
p-Toluenesulfonyl chloride
pyridine / DMAP
TsO
posaconazole
Cs2CO3 / DMF
Carbonyl-diimidazole
HCl/ CH2Cl2

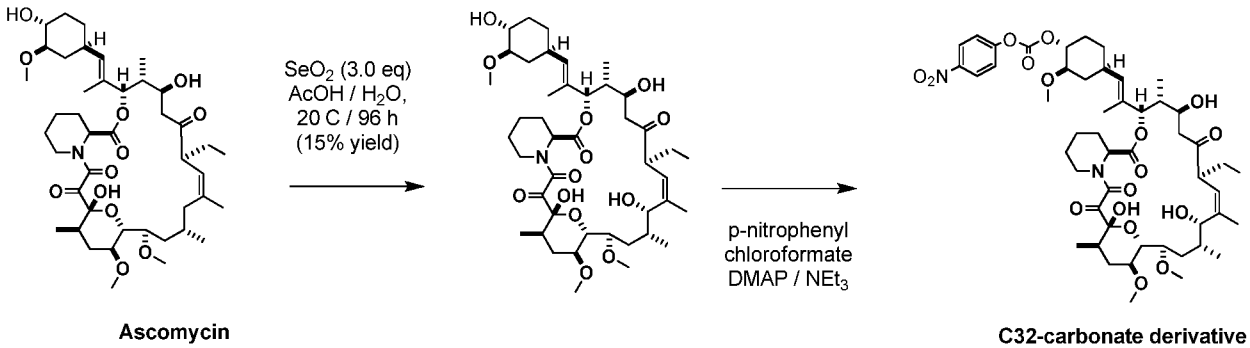

HCl/ CH2Cl2
(n-bu)4NF
THF

Scheme 11b

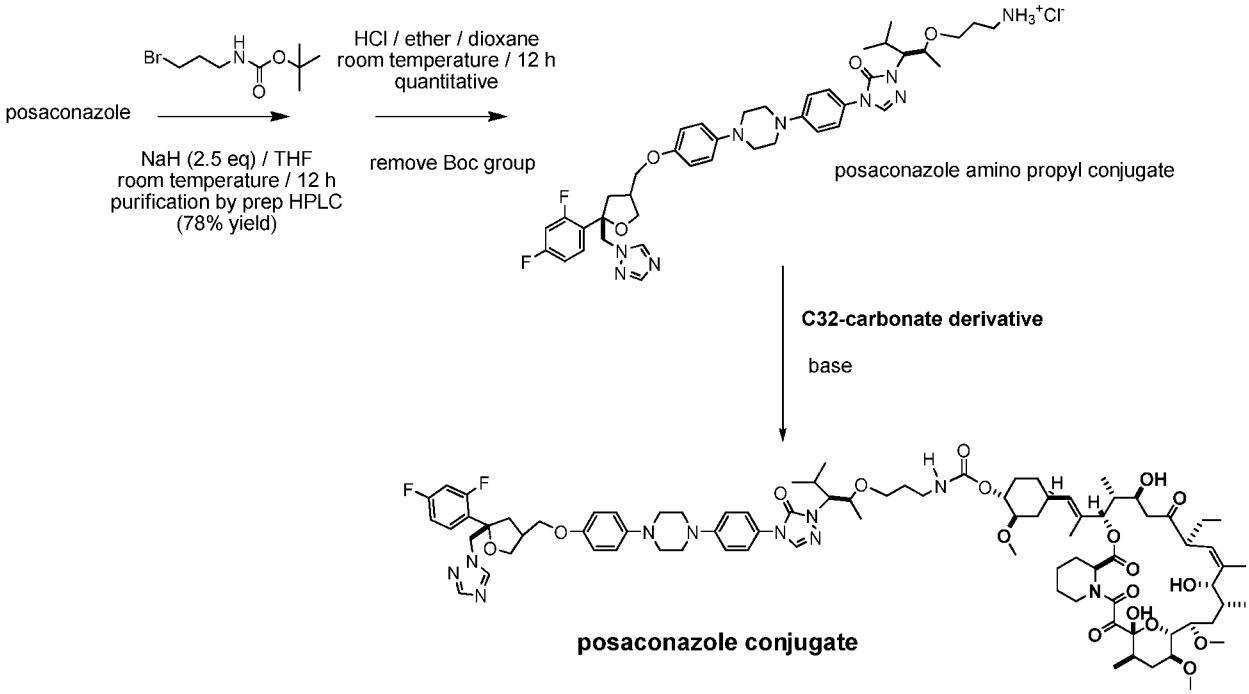

posaconazole
NaH (2.5 eq) / THF
room temperature / 12 h
purification by prep HPLC
(78% yield)
posaconazole-N-boc amino propyl conjugate
HCl / ether / dioxane
room temperature / 12 h
quantitative
triphosgene (0.37 eq) / Na2CO3 (2.0 eq)
CH2Cl2 / H2O, 0 C / 12 h
trituration with ether
(10% yield)
posaconazole amino propyl isocyanate
posaconazole amino propyl conjugate



Scheme 11c



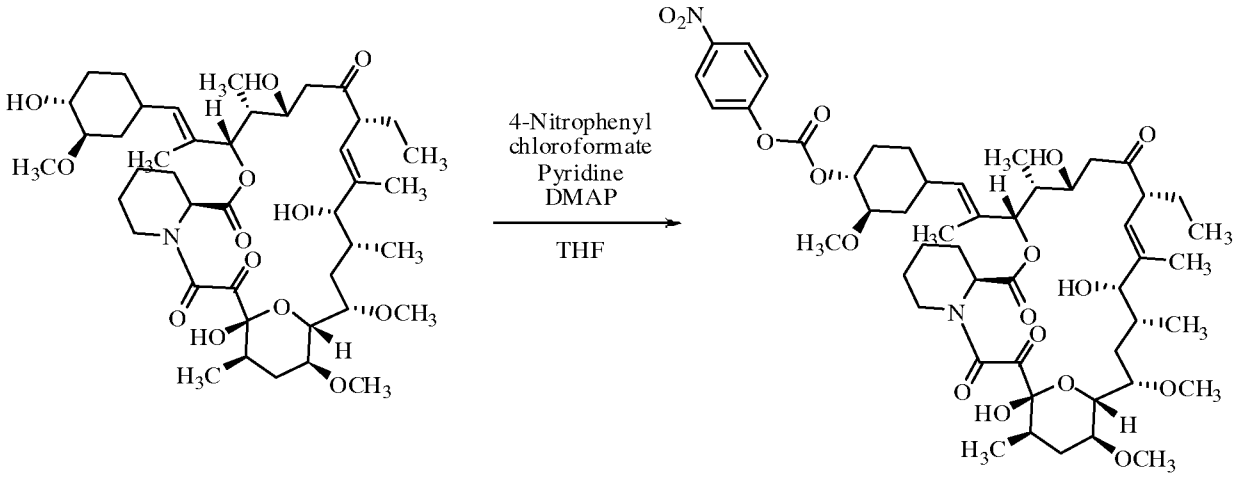
Ascomycin **C32-carbonate derivative**


HCl / ether / dioxane
room temperature / 12 h
quantitative
posaconazole
NaH (2.5 eq) / THF
room temperature / 12 h
purification by prep HPLC
(78% yield)
remove Boc group
posaconazole amino propyl conjugate
C32-carbonate derivative
base
posaconazole conjugate

Example 8

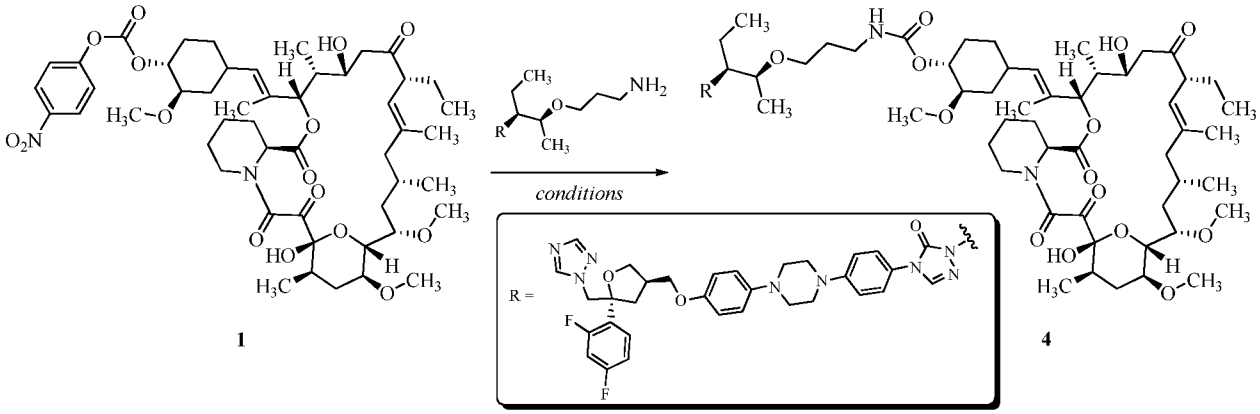
[000121] Additional syntheses of further exemplary compounds incorporating a posaconazole moiety and an additional unit are shown in the following schemes.

Scheme 12

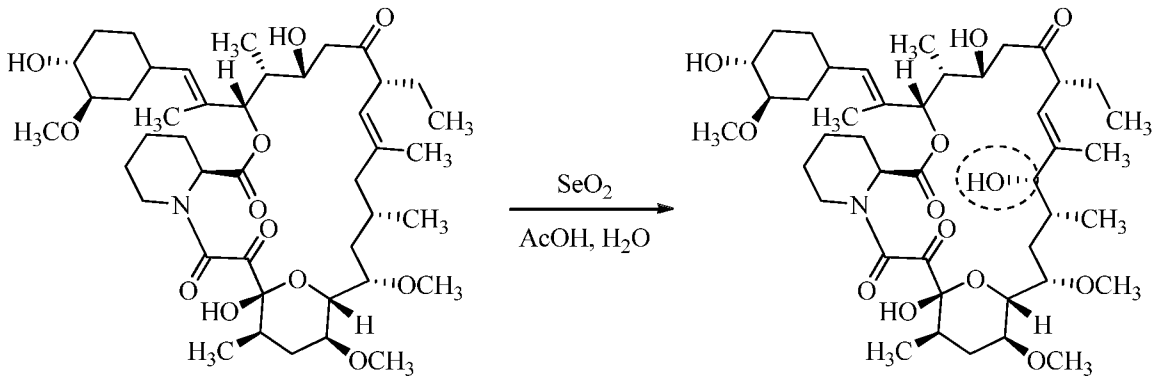


1a **1**

To a solution of 1a (100 mg, 0.12 mmol), 4-nitrophenyl chloroformate (30 mg, 0.15 mmol, 1.2 equiv) and 4-(dimethylamino)pyridine (0.8 mg, 5 mol%) in THF (300 µL) were added pyridine (12 mg, 12 µL, 0.15 mmol) dropwise at 0 °C in 3 equal portions in time intervals of 3 min under exclusion of moisture. After completion of the addition, the reaction mixture was stirred overnight. Further amounts of 4-nitrophenyl chloroformate (5 mg, 0.025 mmol) and pyridine (2 mg, 2 µL, 0.025 mmol) were added to the reaction mixture at rt and stirring continued for a further 24 h. TLC (40% ethyl acetate in *n*-heptane) and UPLC indicated the presence of the product (ca. 55%) and unreacted starting material (ca. 15%). The mixture was diluted with $CHCl_3$ (8 mL) and washed with 0.5% aqueous solution of HCl (2×2 mL), 0.5% aqueous solution of Na_2CO_3 (2×2 mL) and brine (2 mL). The organic layer was dried over $MgSO_4$ and stripped of the solvent and the crude product was purified by column chromatography on silica gel (40% ethyl acetate in *n*-heptane) to afford **1** (31 mg, 26%) as a white foam. ES+ MS *m/z* 991 $[M + 18]^+$; HPLC-MS 93.9% (AUC).



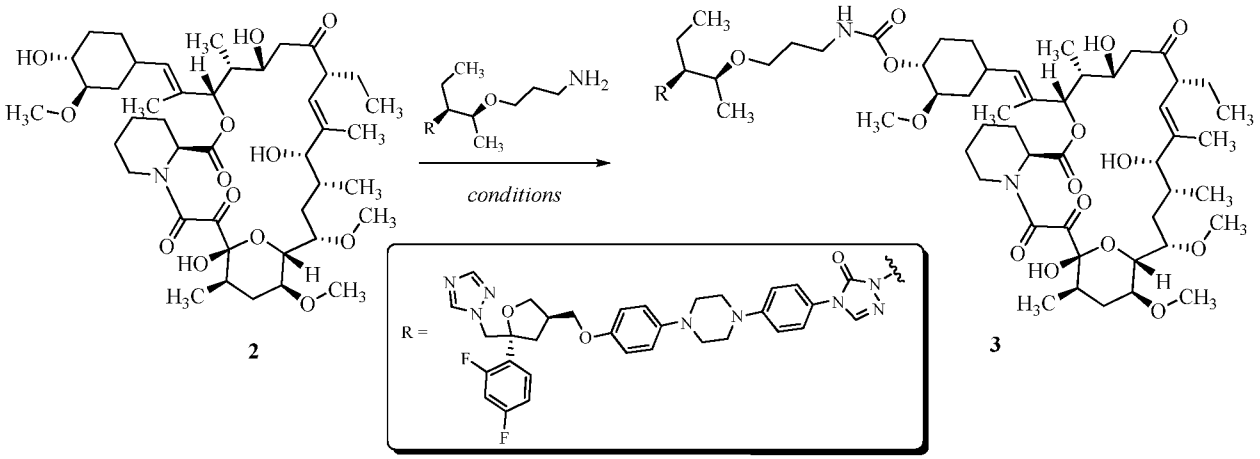
Reaction	Scale	Yield (%)	Comments/conditions
1 to **4**	20 mg	9 mg (27%)	Posaconazole-amine (1.0 equiv.), pyridine (1.0 equiv.), THF (60 µL); Stirred at rt and monitored by TLC and LCMS at regular intervals. • 1 day: product formation could be detected (LC-MS, ca. 30%); • 2 days: product formation could be detected (LC-MS, ca. 40%); extractive work-up and UPLC confirmation of the carbamate formation; purified by prep-HPLC.



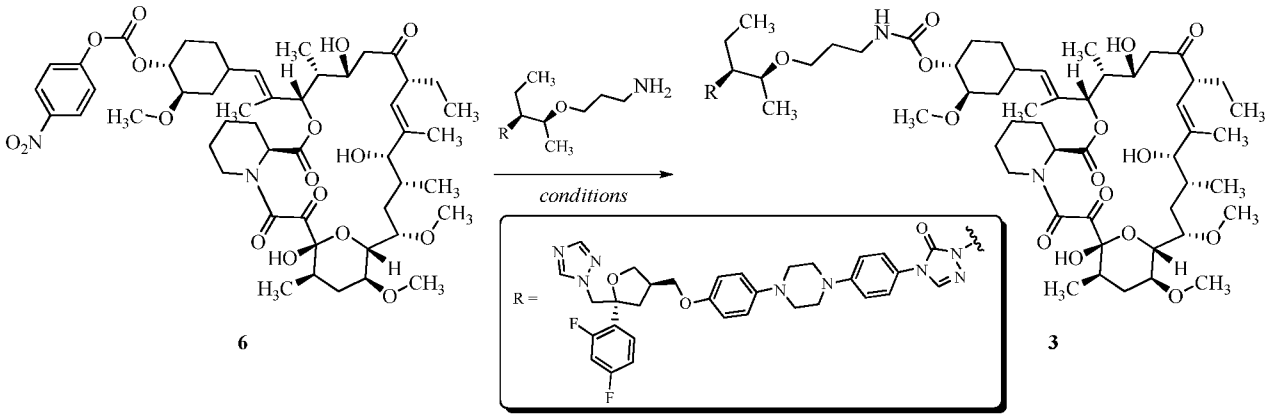
5
Ascomycin

2

Reaction	Scale	Yield (%)	Comments/conditions
5 to **2**	600 mg	205 mg (33%)	SeO_2 (2×1.5 equiv.), AcOH, water, 20 °C, 24 h; purified by prep-HPLC (ca. 85% (UPLC)).



Reaction	Scale	Yield (%)	Comments/conditions
2 to **3**	20 mg	1.5 mg (4%)	Triphosgene (0.37 equiv.), DMAP (5.0 equiv.), –70 °C, 1 h then posaconazole amine (1.5 equiv.), rt, 2 d; product formation detected by UPLC; extractive work-up; purified by prep-HPLC.



[000122] Sample Procedure: To a solution of 32-*O*-PNP-carbonate (**6**, 30 mg, 0.03 mmol) in THF (60 µL) were added posaconazole-linker amine (23.4 mg, 0.03 mmol) and pyridine (2.7 mg, 3 µL, 0.034 mmol) and the mixture was stirred at rt for 48 h. After completion of the reaction the mixture was diluted with $CHCl_3$ (5 mL) and washed with 0.5% aqueous solution of Na_2CO_3 (2×1 mL) and brine (1 mL). The organic layer was dried over $MgSO_4$ and evaporated. The crude product was purified by preparative HPLC to afford **7** (10 mg, 20%) as a white foam.

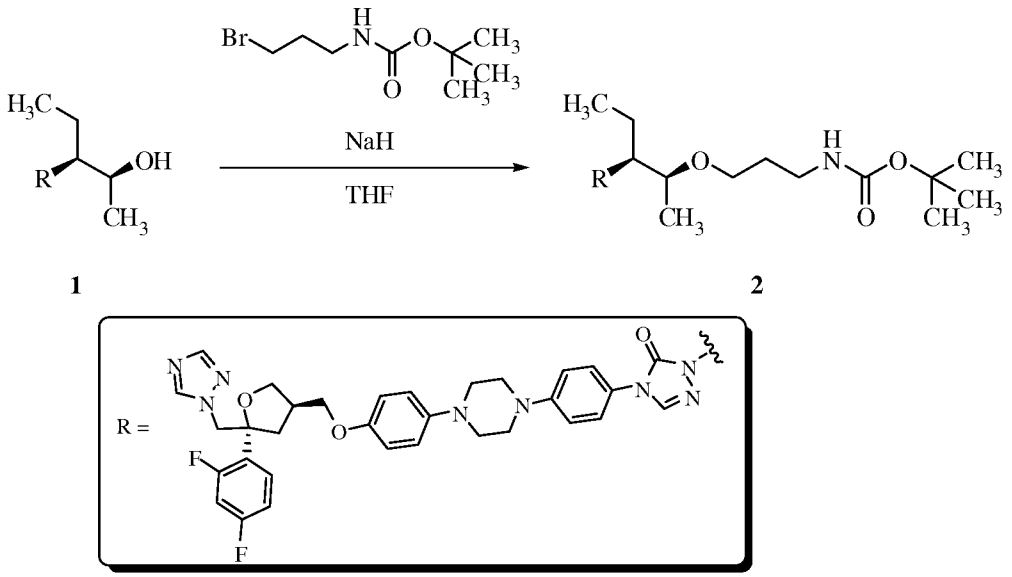
Reaction	Scale	Yield (%)	Comments/conditions
6 to **3**	30 mg	35 mg (crude)	Posaconazole-amine (1.0 equiv.), pyridine (1.3 equiv.), THF (60 µL); Stirred at rt and monitored by TLC and LCMS at regular intervals. • 1 day: product formation could be detected (LC-MS, ca. 30%); • 4 days: product formation could be detected (LC-MS, ca. 50%); extractive work-up and UPLC confirmation of the carbamate formation; submitting to prep-HPLC.

Example 9

[000123] Additional syntheses of further exemplary compounds incorporating a posaconazole moiety and an additional unit are shown in the following schemes.

Scheme 13

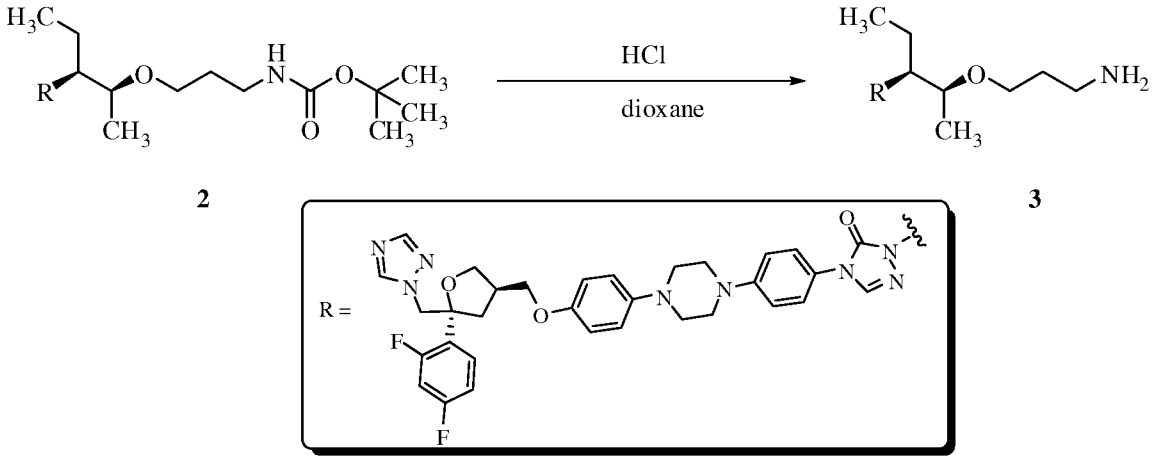
Preparation of the Boc-protected Posaconazole-linker Amine 2:



[000124] To a solution of posaconazole (**1,** 200 mg, 0.29 mmol) in THF (10 mL) was added under stirring NaH (19 mg, 0.80 mmol) in 4-5 portions at rt. After completion of the addition, the reaction mixture was stirred at the same temperature for 30 min and 1-boc-3-bromopropylamine (82 mg, 0.34 mmol) was added to it in one portion and stirring continued

overnight. After completion of the reaction (TLC: 30% methanol in chloroform) it was diluted with water (5 mL) and extracted with $CHCl_3$ (3×10 mL). The combined organic layers were washed with water (10 mL) and brine (10 mL), dried over $MgSO_4$ and evaporated. The crude product was purified by preparative TLC (5% methanol in chloroform) to yield **2** (193 mg, 78 %) as a colorless oil. ES+ MS *m/z* 858 $[M + H]^+$; HPLC-MS >99.0% (AUC).

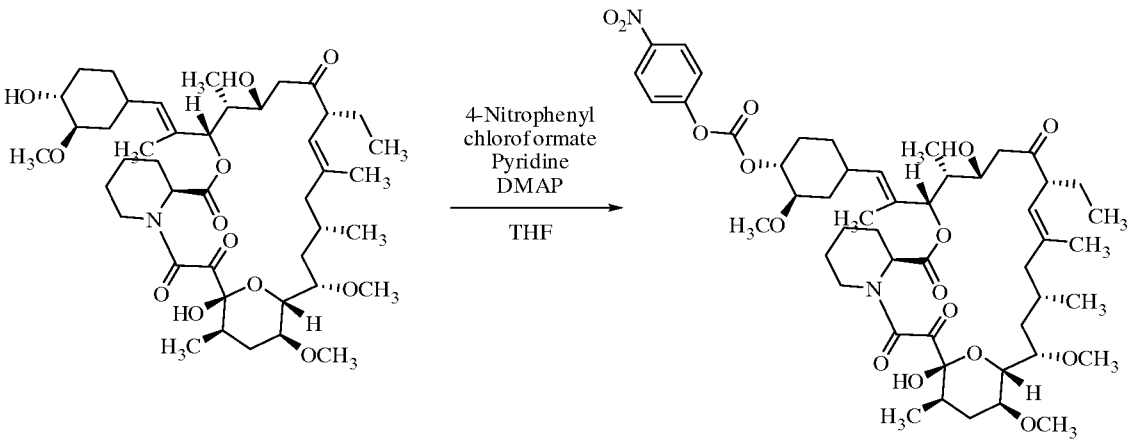
Preparation of the Posaconazole-linker Amine 3:



2 **3**

[000125] The protected posaconazole-linker amine **2** (193 mg, 0.22 mmol) was dissolved in dioxane (5 mL) and 200 µL HCl in dioxane was added to it at rt. The mixture was stirred overnight. After completion of the reaction, the solvent was removed in vacuo and the residue was diluted with $CHCl_3$ (10 mL) and washed with 10% aqueous solution of Na_2CO_3 (3×5 mL), water (5 mL) and brine (5 mL), dried over $MgSO_4$ and evaporated. The crude product was purified by preparative TLC (20% methanol in chloroform) to provide **3** (116 mg, 68 %) as a colorless oil. ES+ MS *m/z* 759 $[M + H]^+$; HPLC-MS 91.2% (AUC).

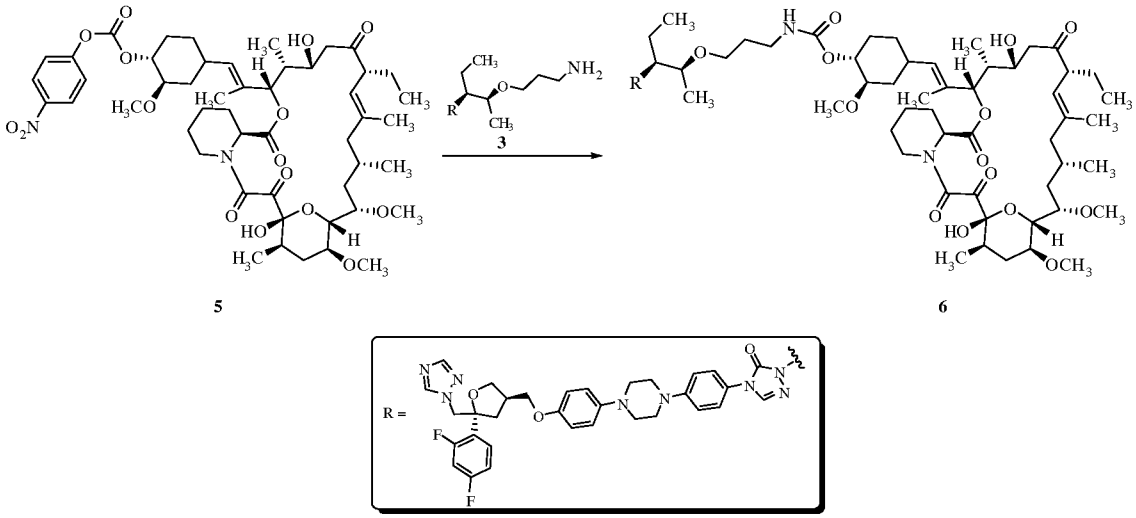
Preparation of 32-*O*-PNP-Carbonate of Ascomycin (5):



4 5

[000126] To a mixture of ascomycin (**4**, 180 mg, 0.23 mmol), 4-nitrophenyl chloroformate (55 mg, 0.27 mmol, 1.2 equiv) and 4-(dimethylamino)pyridine (1.4 mg, 5 mol%) in THF (540 µL) was added pyridine (22 mg, 22 µL, 0.27 mmol) dropwise at 0 °C in 5 equal portions in time intervals of 5 min under exclusion of moisture. After completion of the addition, the reaction mixture was stirred overnight at rt. Additional amounts of 4-nitrophenyl-chloroformate (9.2 mg, 0.045 mmol, 0.2 equiv) and pyridine (3.6 mg, 4 µL, 0.045 mmol, 0.2 equiv) were added to the reaction mixture at rt and stirring continued for further 24 h. TLC (40% ethyl acetate in *n*-heptane) and UPLC indicated the presence of the product (ca. 50%) and unreacted starting material (ca. 20%). The mixture was diluted with $CHCl_3$ (10 mL) and washed with 0.5% aqueous solution of Na_2CO_3 (2×2 mL) and brine (2 mL). The organic layer was dried over $MgSO_4$ and evaporated. The crude product was purified by column chromatography (40% ethyl acetate in *n*-heptane) to afford **5** (63 mg, 29%) as a white foam. ES+ MS *m/z* 958 $[M + H]^+$; HPLC-MS >99.0% (AUC).

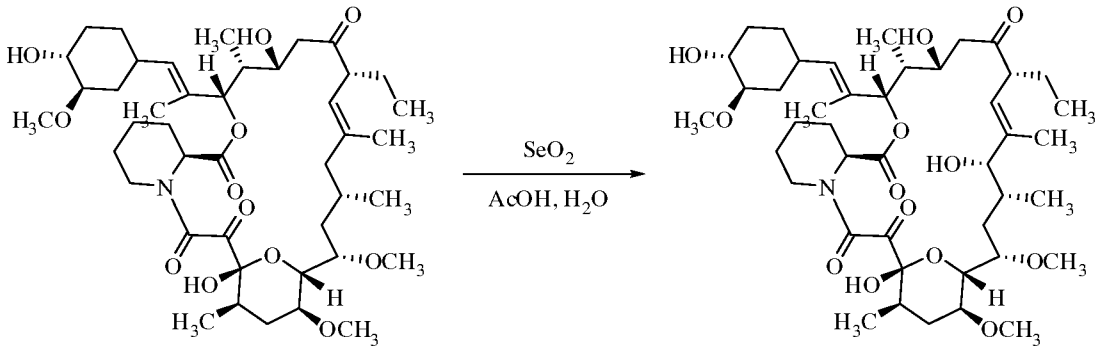
Preparation of the Conjugate 6 by Reaction of the Posaconazole-linker Amine 3 with 32-*O*-PNP-Carbonate of Ascomycin (5):



5 6

[000127] To a solution of 32-*O*-PNP-carbonate of ascomycin (**5**, 20 mg, 0.02 mmol) in THF (60 µL) were added the posaconazole-linker amine **3** (15.8 mg, 0.02 mmol) and pyridine (1.7 mg, 2 µL, 0.021 mmol). The mixture was stirred at rt for 48 h. After completion of the reaction (TLC: 40% ethyl acetate in *n*-heptane), it was diluted with $CHCl_3$ (5 mL) and washed with 0.5% aqueous solution of Na_2CO_3 (2×1 mL) and brine (1 mL). The organic layer was dried over $MgSO_4$ and stripped of the solvent. The crude product was purified by preparative HPLC to afford **6** (9 mg, 27%) as a colorless oil. ES+ MS *m/z* 1593 $[M + 18]^+$; HPLC-MS 84.3% (AUC).

Preparation of (7):

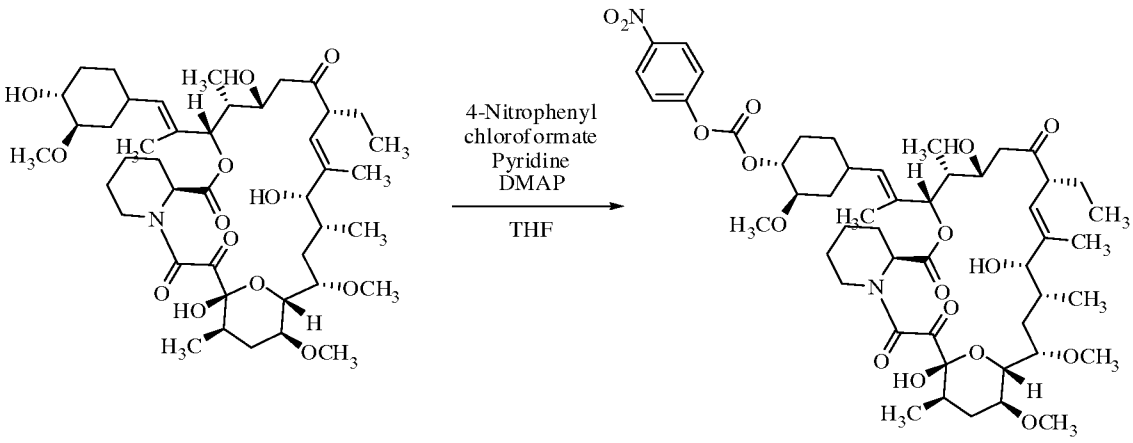


4 7

[000128] Ascomycin (**4**, 2.0 g, 2.53 mmol) was dissolved in a mixture of AcOH (32 mL) and water (32 mL) and SeO_2 (420 mg, 3.79 mmol) was added to it. The reaction mixture was stirred at rt for 24 h. An additional amount of SeO_2 (420 mg, 3.79 mmol) was added to the reaction mixture and stirring continued for 24 h. After completion of the reaction (TLC: 3% methanol in chlorofom), the reaction mixture was diluted with EtOAc (100 mL) and the pH was adjusted to 7 by saturated Na_2CO_3. The phases were separated and the aqueous phase

was extracted with EtOAc (3×50 mL). The combined organic layers were washed with water (75 mL) and brine (75 mL), dried over $MgSO_4$ and evaporated. The crude product was purified first by preparative HPLC and then by column chromatography over silica gel (3% methanol in chloroform) to yield **7** (685 mg, 33%) as a white foam. ES+ MS *m/z* 826 $[M + 18]^+$; HPLC-MS 93.3% (AUC).

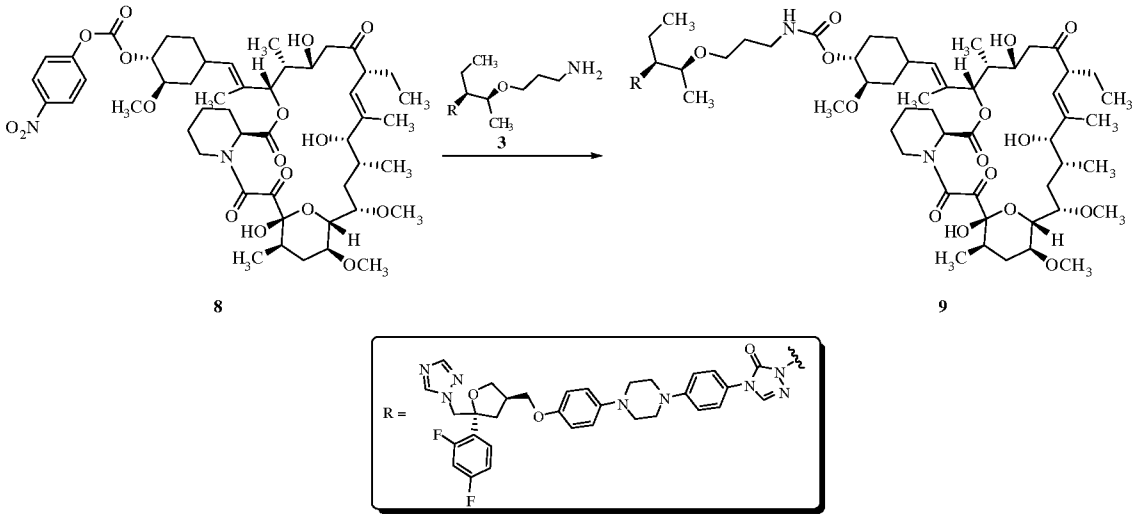
Preparation of 32-*O*-PNP-Carbonate of (7) - i.e., (8):



7 8

[000129] To a solution of (**7**) (100 mg, 0.12 mmol), 4-nitrophenyl chloroformate (30 mg, 0.15 mmol, 1.2 equiv) and 4-(dimethylamino)pyridine (0.8 mg, 5 mol%) in THF (300 µL) were added pyridine (12 mg, 12 µL, 0.15 mmol) dropwise at 0 °C in 3 equal portions in time intervals of 3 min under exclusion of moisture. After completion of the addition, the reaction mixture was stirred overnight. Further amounts of 4-nitrophenyl chloroformate (5 mg, 0.025 mmol) and pyridine (2 mg, 2 µL, 0.025 mmol) were added to the reaction mixture at rt and stirring continued for a further 24 h. TLC (40% ethyl acetate in *n*-heptane) and UPLC indicated the presence of the product (ca. 55%) and unreacted starting material (ca. 15%). The mixture was diluted with $CHCl_3$ (8 mL) and washed with 0.5% aqueous solution of HCl (2×2 mL), 0.5% aqueous solution of Na_2CO_3 (2×2 mL) and brine (2 mL). The organic layer was dried over $MgSO_4$ and stripped of the solvent and the crude product was purified by column chromatography on silica gel (40% ethyl acetate in *n*-heptane) to afford **8** (31 mg, 26%) as a white foam. ES+ MS *m/z* 991 $[M + 18]^+$; HPLC-MS 93.9% (AUC).

Preparation of Conjugate 9 by Reaction of the Posaconazole-linker Amine 3 with 32-*O*-PNP-Carbonate (8):



[000130] To a solution of (**8**) (30 mg, 0.03 mmol) in THF (60 μL) were added posaconazole-linker amine (**3**, 23.4 mg, 0.03 mmol) and pyridine (2.7 mg, 3 μL, 0.034 mmol) and the mixture was stirred at rt for 48 h. After completion of the reaction the mixture was diluted with $CHCl_3$ (5 mL) and washed with 0.5% aqueous solution of Na_2CO_3 (2×1 mL) and brine (1 mL). The organic layer was dried over $MgSO_4$ and evaporated. The crude product was purified by preparative HPLC to afford **7** (10 mg, 20%) as a white foam.

Claims

What is claimed is

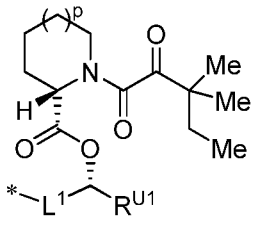
1. A compound comprising: a first active moiety having antifungal activity and selected from triazole moieties, imidazole moieties, and echinocandin moieties; a second active moiety; and a linking moiety, wherein the first and second active moieties are covalently bonded to the linker moiety, or a pharmaceutically acceptable salt, prodrug, or metabolite, thereof.

2. The compound of claim 1, wherein the second active moiety is a non-immunosuppressive derivative of FK-506.

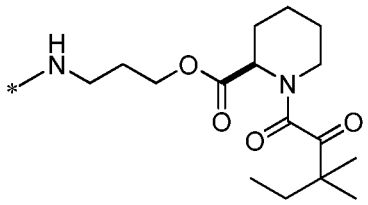
3. The compound of claim 1, wherein the second active moiety is antifungal.

4. The compound of claim 1, wherein the linking moiety is selected from a bond, C_1-C_{24} hydrocarbylene, substituted C_1-C_{24} hydrocarbylene, heteroatom-containing C_1-C_{24} hydrocarbylene, and substituted heteroatom-containing C_1-C_{24} hydrocarbylene.

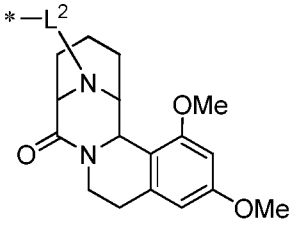
5. The compound of claim 1, wherein the second active moiety has the structure of any one of U1 – U6



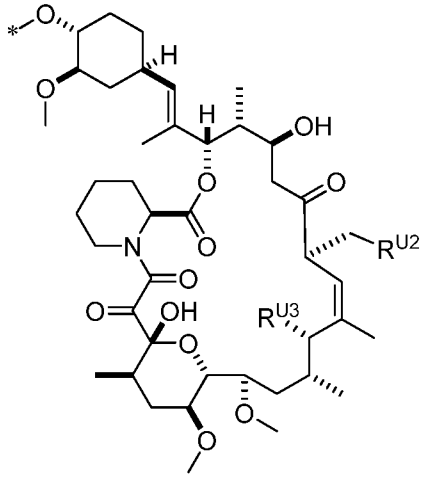
U1



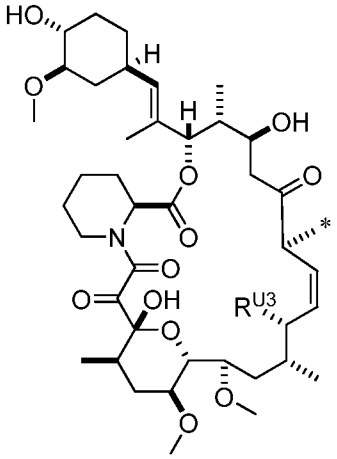
U2



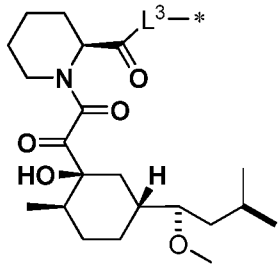
U3



U4



U5



U6

wherein:

p represents in integer in the range of 0-2;

L^1, L^2, and L^3 are selected from a bond, a heteroatom, C_1-C_{24} alkylene, C_1-C_{24} heteroalkylene, C_5-C_{24} arylene, C_5-C_{24} heteroarylene, and combinations thereof, any of which may be substituted or unsubstituted;

R^{U1} and R^{U2} are selected from C_1-C_{24} hydrocarbyl, substituted C_1-C_{24} hydrocarbyl, heteroatom-containing C_1-C_{24} hydrocarbyl, and substituted heteroatom-containing C_1-C_{24} hydrocarbyl;

R^{U3} is selected from H and OH; and

the stars represents the point of attachment to the linking moiety.

6. The compound of claim 5, wherein

L^1 is selected from a bond, C_1-C_{12} alkylene, C_5-C_{12} arylene, and C_1-C_{24} alkylarylene and comprises from 0 to 3 heteroatoms and from 0 to 3 substituents;

L^2 is selected from a bond and C_1-C_{12} alkylene, and comprises from 0 to 3 heteroatoms and from 0 to 3 substituents;

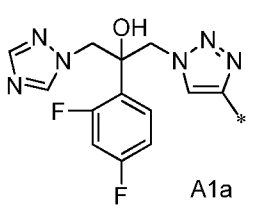
L^3 is selected from a C_1-C_{12} alkylene, C_5-C_{12} arylene, and C_1-C_{24} alkylarylene and comprises from 0 to 3 heteroatoms and from 0 to 3 substituents;

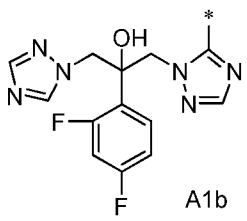
R^{U1} is selected from C_1-C_{12} alkyl, C_5-C_{12} aryl, C_5-C_{12} alkaryl, and C_5-C_{12} aralkyl, and comprises from 0 to 3 heteroatoms and from 0 to 3 substituents;

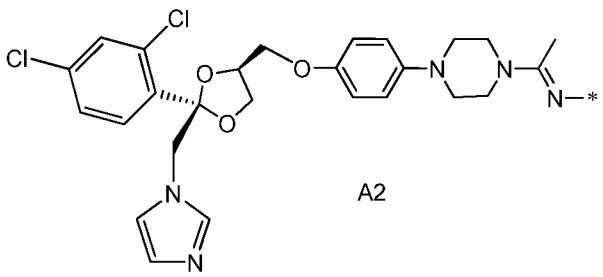
R^{U2} are selected from C_1-C_{12} alkyl, C_2-C_{12} alkenyl, C_5-C_{12} aryl, C_5-C_{12} alkaryl, and C_5-C_{12} aralkyl, and comprises from 0 to 3 heteroatoms and from 0 to 3 substituents.

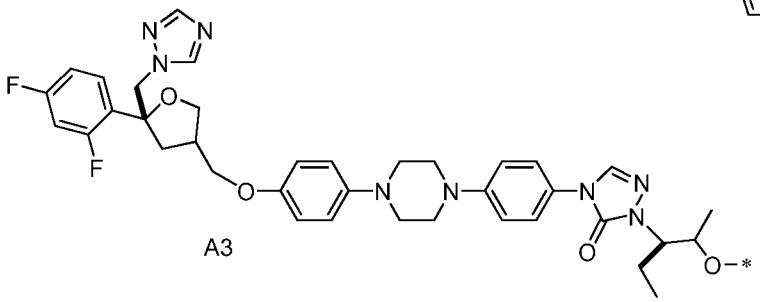
7. The compound of claim 1, wherein the first active moiety is selected from fluconazole, voriconazole, ketoconazole, posaconazole, micafungin, caspofungin, anidulafungin, derivatives thereof, and analogs thereof.

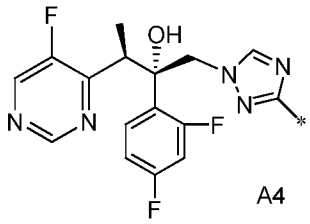
8. The compound of claim 7, wherein the first active moiety has the structure of any one of A1a, A1b, A2, A3, A4, A5, A6, or A7:

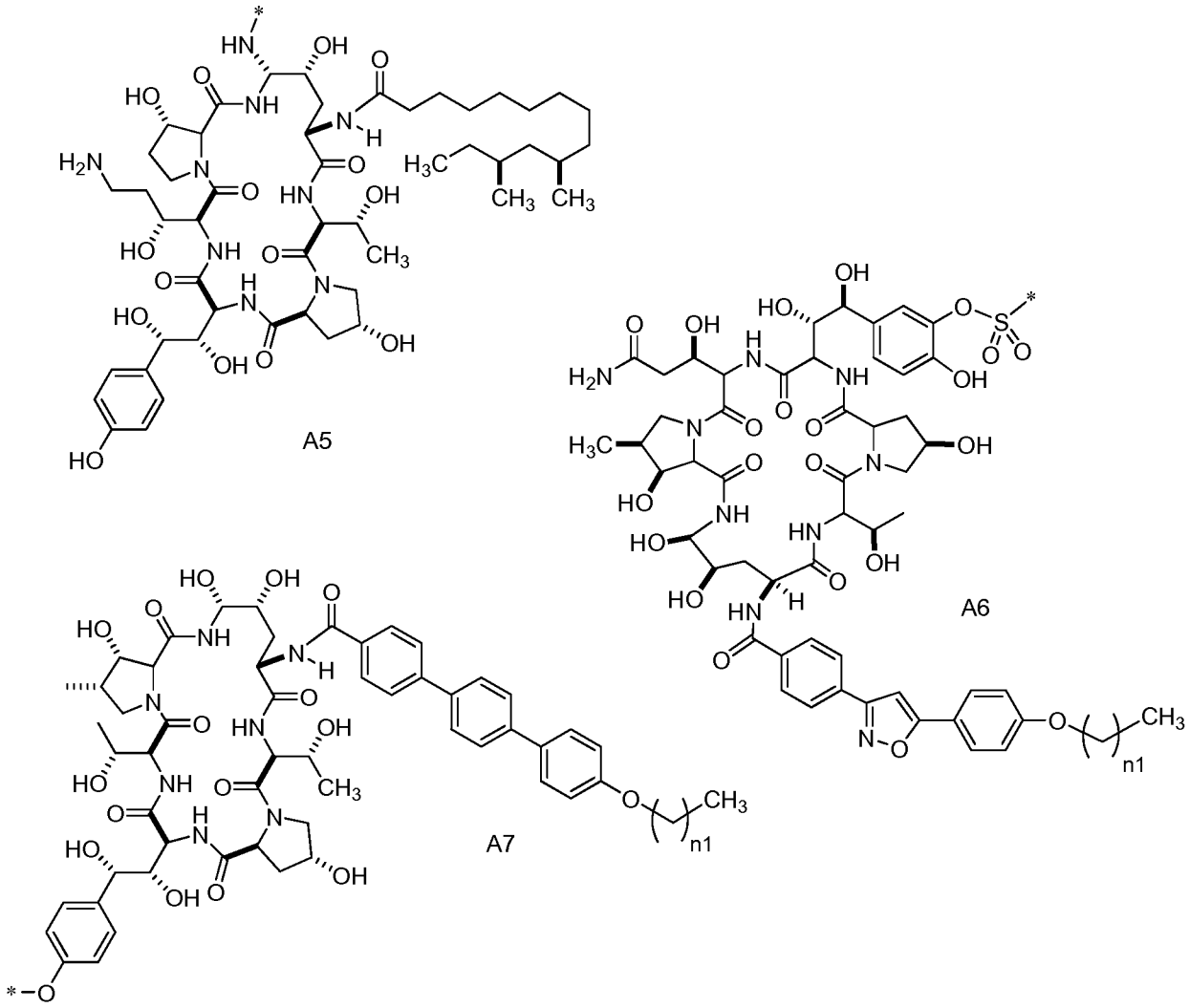

A1a


A1b


A2


A3


A4



wherein n is an integer from 0 to 6 and the stars represent the point of attachment to the linking moiety.

9. A compound comprising first and second active moieties and a linker moiety, wherein the first active moiety is capable of binding to a first enzyme, and wherein the second active moiety is capable of binding to a second enzyme, and wherein the two active moieties are each covalently attached to the linker moiety.

10. The compound of claim 9, wherein the first enzyme is calcineurin, and the second enzyme is selected from lanosterol 14α-demethylase and β(1,3)-D-Glucan synthase.

11. A compound comprising first and second active moieties and a linker moiety, wherein the first active moiety is capable of binding to a protein, and wherein the second active moiety is capable of binding to an enzyme, and wherein the two active moieties are each covalently attached to the linker moiety.

12. The compound of claim 11, wherein the protein is HSP90, and the enzyme is selected from lanosterol 14α-demethylase and β(1,3)-D-Glucan synthase.

13. A compound having the structure of formula (I)

(I) A-L-U

wherein

A is a first active moiety;

L is a linking moiety; and

U is a second active moiety.

14. A compound comprising a first active moiety having antifungal activity and selected from triazole moieties, imidazole moieties, and echinocandin moieties, and a second active moiety capable of binding to an enzyme, or a pharmaceutically acceptable salts, prodrugs, or metabolites thereof.

15. A composition comprising the compound of any one of the preceding claims and a pharmaceutically acceptable carrier.

16. A method for treating a fungal infection comprising administering the composition of claim 15.

17. The method of claim 16, wherein the fungal infection is of a fungus from the genus Candida, Aspergillus, or Cryptococcus.

18. A composition for treating a fungal infection comprising a first active moiety having antifungal activity and selected from triazole moieties, imidazole moieties, echinocandin moieties and pharmaceutically acceptable salts, prodrugs, or metabolites

thereof, and a second active moiety capable of binding to an enzyme, wherein the first and second active moieties are not linked via covalent bonds.

19. The composition of claim 18, wherein the first and second active moieties are contained within a liposome.

20. A method for preparing a compound having antifungal properties comprising covalently linking a first active moiety with a second active moiety via a linking moiety, wherein the first active moiety has antifungal activity and is selected from triazole moieties, imidazole moieties, and echinocandin moieties, and wherein the second active moiety is non-immunosuppressive, antifungal, or both non-immunosuppressive and antifungal.

21. The method of claim 20, wherein the linking moiety is selected from a bond, C_1-C_{24} hydrocarbylene, substituted C_1-C_{24} hydrocarbylene, heteroatom-containing C_1-C_{24} hydrocarbylene, and substituted heteroatom-containing C_1-C_{24} hydrocarbylene.

22. A composition according to claim 15, wherein the composition is suitable for treating a fungal infection on an indwelling medical device in situ.

23. A method for forming a conjugate molecule having a first active moiety covalently attached to a second active moiety via a linking moiety, wherein the method comprises:

(a) forming a carbamate or carbonate by contacting either the first active moiety or the second active moiety with a carbamate- or carbonate-forming reagent;

(b) reacting the carbamate or carbonate from (a) with a nucleophilic group present on: (i) the first active moiety if the carbamate or carbonate from (a) is formed on the second active moiety; or (ii) the second active moiety if the carbamate or carbonate from (a) is formed on the first active moiety.

24. The method of claim 23, wherein the first active moiety has antifungal activity and is selected from triazole moieties, imidazole moieties, and echinocandin moieties, and wherein the second active moiety is immunosuppressive, antifungal, or both immunosuppressive and antifungal.

25. The method of claim 23, wherein the linking moiety is selected from a bond, C_1-C_{24} hydrocarbylene, substituted C_1-C_{24} hydrocarbylene, heteroatom-containing C_1-C_{24} hydrocarbylene, and substituted heteroatom-containing C_1-C_{24} hydrocarbylene.

26. The method of claim 23, wherein the carbamate or carbonate is formed by reacting one hydroxyl group on the first or second active moiety with the carbamate- or carbonate-forming reagent.

27. The method of claim 26, wherein the first or second active moiety has one or more additional hydroxyl groups that do not substantially react with the carbamate- or carbonate-forming reagent.

28. The method of claim 23, wherein the method is applied to the synthesis of any of the conjugate compounds disclosed herein.