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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
28 October 2004 (28.10.2004)

PCT

(10) International Publication Number
WO 2004/092123 A2

(51) International Patent Classification[7]: C07D

(21) International Application Number:
PCT/US2004/011187

(22) International Filing Date: 12 April 2004 (12.04.2004)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:

60/461,727	10 April 2003 (10.04.2003)	US
60/469,286	9 May 2003 (09.05.2003)	US
60/485,678	9 July 2003 (09.07.2003)	US

(71) Applicant *(for all designated States except US)*: **MICROBIA, INC.** [US/US]; 320 Bent Street, Cambridge, MA 02141 (US).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **TALLEY, John, Jeffrey** [US/US]; 96 North Street, Somerville, MA 02144 (US). **FRETZEN, Angelika** [DE/US]; 155R Summer Street, #1, Somerville, MA 02143 (US). **ZIMMERMAN, Craig** [US/US]; 31 North Street, Topsfield, MA 01983 (US). **BARDEN, Timothy.** [US/US]; 19 Intervale Road, Salem, MA 01970 (US). **YANG, Jing, Jing** [CN/US]; 248 South Brooksvale Road, Cheshire, CT 06410 (US). **MARTINEZ, Eduardo** [US/US]; 1156 Cambridge Street, Apt. 1, Cambridge, MA 02139 (US). **MILNE, G. Todd** [US/US]; 169 Mason Terrace, Brookline, MA 02146 (US). **ETCHELL, A. Cordero** [US/US]; Microbia, Inc., North Reading, MA 01864 (US). **CHRISTINE, M. Pierce** [US/US]; c/o Microbia, Inc., 320 Bent Street, Cambridge, MA 02141 (US). **HOUMAN, Fariba**; ********** (**). **BUSBY, Robert** [US/US]; 84 Vine Street, Weymouth, MA 02199 (US). **SUMMERS, Eric, F.** [US/US]; 204 Summit Avenue, Brookline,MA 02446 (US). **ANTONELLI, Stephen**; ********** (**). **LEE, Peter**; ********** (**). **FARWELL, Michael**; ********** (**). **MAYORGA, Maria** [GT/US]; 85 Elm Street, Belmont, MA 02478 (US). **O'LEARY, Jessica**; ********** (**).

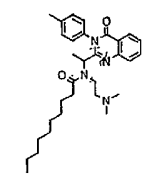
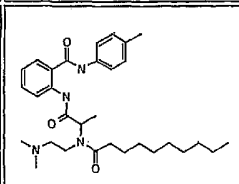
(74) Agent: **MEIKLEJOHN, Anita, L.**; Fish & Rickardson P.C., 225 Franklin Street, Boston, MA 02110-2804 (US).

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

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH,

[Continued on next page]

(54) Title: INHIBITORS OF FUNGAL INVASION

					Result	Result	Result	Result	Result
Counter	Structure	SampleID	Parent	Compound Class	C. albicans LOG IC50 (uM)	C. albicans STAT IC50 (uM)	C. albicans MIC (ug/ml)	C. albicans Overnight Growth Inhibtion (%)	C. albicans Phenotype Rating
1		3151	3151	A	0.571uM .826uM	3.68uM 6.574uM	>64ug/ml >64ug/ml	- 61.79% - 15.16% 66.16%	2__Phenotype 5__Phenotype 5__Phenotype 5__Phenotype
2		270270	3151	A	4.660uM	4.730uM	8ug/ml	- 9.87% - 3.71%	2*__Phenotype 2*__Phenotype

(57) Abstract: This invention relates to various anti-fungall agents including agents that are inhibitors of fungal invasion.

WO 2004/092123 A2

GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Declarations under Rule 4.17:

— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii)) for all designations*

— *as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii)) for all designations*

Published:

— *without international search report and to be republished upon receipt of that report*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

Inhibitors of Fungal Invasion

This invention relates to nitrogenous heterocycle-based inhibitors of fungal invasion.

BACKGROUND

Fungal infections are a serious health concern, particularly for patients whose immune systems have been compromised by disease, chemotherapy, or immunosuppressive drugs. The frequency of Candida infections has increased in recent years and has been accompanied by a significant rise in morbidity and mortality. Candidiasis, which is most often caused by the pathogenic yeast *Candida albicans*, is the most frequent fungal infection associated with AIDS and other immunocompromised states. Many of these infections take place in the hospital setting.

A wide variety of plant-pathogenic fungi (e.g., blights, rusts, molds, smuts, and mildews) cause huge food crop loss and damage to ornamental plants. Plant diseases are caused by a myriad of invasive fungal pathogens falling into many genera, for example, soft rot (e.g., Rhizopus), leaf curl (e.g., Taphrina), powdery mildew (e.g., Sphaerotheca), leaf spots (e.g., Fulvia), blight (e.g., Alternaria), blast (e.g., Magnaporthe), black rot (e.g., Guignardia), scab (e.g., Venturia), wilts (e.g., Fusarium), rusts (e.g., Puccinia), smuts (e.g., Ustilago), and cankers (e.g., Rhizoctonia).

Recently, there has been great interest in identifying genes that may be implicated as important virulence factors in these infections. The virulence of *Candida albicans* has been shown to be dependent upon invasion of host tissues; mutations in any of several genes required for invasive growth substantially reduce virulence in a mouse model of systemic infection.

The *SSK1* response regulator gene from *C. albicans* is essential for normal hyphal development and virulence. Cos1, a two-component histidine kinase, is required for normal hyphal growth of *C. albicans*, and may play a role in virulence properties of the organism. Deletion of the *C. albicans* gene encoding the mitogen-activated protein kinase Hog1 causes derepression of serum induced hyphal formation and a dramatic increase in the survival time of systemically infected mice. Disruption of the *C. albicans* mitogen activated protein kinase gene, *CEK1*, adversely affects the growth of serum induced mycelial colonies and attenuates virulence in a mouse model for systemic candidiasis. These and other studies have suggested that hyphal growth may be an important virulence factor in *C. albicans*. Nonfilamentous *C. albicans* mutants are avirulent.

The exact mechanism by which hyphal growth acts as a virulence factor is also not known with certainty, but it is believed that there is a correlation between germ tube length and organ invasion in *C.*

albicans clinical isolates. *C. albicans* may resist intracellular killing by macrophages through the formation of germ tubes.

A variety of antifungal compounds have been developed, some of which also affect hyphal growth. But there is a need for less toxic treatment regimens than those presently available. For example, over 5% of patients treated with fluconazole had adverse reactions, possibly related to the treatment, about half of which necessitated discontinuation of therapy. There is also a need for effective anti-Candida agents having fewer toxicological problems than amphotericin B, which by virtue of their lower toxicities can be administered to high risk patients either prophylactically or at the earliest signs of infection, without the need for a firm diagnosis.

SUMMARY

This invention relates to nitrogenous heterocycle-based inhibitors of fungal invasion (i.e. anti-invasion or anti-invasin agents), compositions comprising such compounds, and methods of treating fungal infections.

The invention features compounds useful in the therapeutic or prophylactic treatment of fungal infection. Examples of fungi which cause fungal infections in humans include, without limitation, *Absidia spp., Absidia corymbifera, Ajellomyces capsulatus, Ajellomyces dermatitidis, Allescheria boydii, Alternaria spp., Anthopsis deltoidea, Aphanomyces spp., Apophysomyces elequans, Armillaria spp., Arnium leoporinum, Arthroderma benhamiae, Arthroderma fulvum, Arthroderma gypseum, Arthroderma incurvatum, Arthroderma otae, Arthroderma vanbreuseghemii, Aspergillus spp., Aspergillus flavus, Aspergillus fumigatus, Aspergillus niger, Aureobasidium pullulans, Basisdiobolus ranarum, Bipolaris spp., Blastomyces dermatitidis, Botrytis spp., Candida spp., Candida albicans, Candida glabrata, Candida guilliermondii, Candida kefyr, Candida krusei, Candida parapsilosis, Candida pelliculosa, Candida tropicalis, Centrospora spp., Cephalosporium spp., Ceratocystis spp., Chaetoconidium spp., Chaetomium spp., Cladophialophora carrionii, Cladosporium spp., Coccidioides immitis, Colletotrichium spp., Conidiobolus spp., Cryptoporiopsis spp., Cylindrocladium spp., Cryptococcus spp., Cryptococcus neoformans, Cunninghamella spp., Cunninghamella bertholletiae, Curvularia spp., Dactylaria spp., Diplodia spp., Epidermophyton spp., Epidermophyton floccosum, Exserophilium spp., Exophiala spp., Exophiala dermatitidis, Filobasidiella neoformans, Fonsecaea spp., Fonsecaea pedrosoi, Fulvia spp., Fusarium spp., Fusarium solani, Geotrichum spp., Geotrichum candidum, Guignardia spp., Helminthosporium spp., Histoplasma spp., Histoplasma capsulatum, Hortaea werneckii, Issatschenkia orientalis, Lecythophora spp., Macrophomina spp., Madurella spp., Madurella grisae, Magnaporthe spp., Malassezia furfur, Malassezia globosa, Malassezia obtuse, Malassezia pachydermatis, Malassezia restricta, Malassezia slooffiae, Malassezia sympodialis, Microsporum spp., Microsporum canis, Microsporum fulvum, Microsporum gypseum, Monilinia spp., Mucor spp., Mucor circinelloides,*

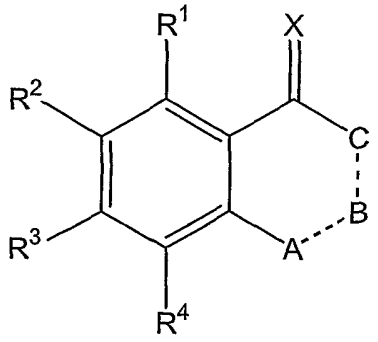
Mycocentrospora acerina, Nectria spp., Nectria haematococca, Nocardia spp., Oospora spp., Ophiobolus spp., Paecilomyces spp., Paecilomyces variotii, Paracoccidioides brasiliensis, Penicillium spp., Penicillium marneffei, Phaeosclera dematioides, Phaeoannellomyces spp., Phialemonium obovatum, Phialophora spp., Phlyctaena spp., Phoma spp., Phomopsis spp., Phymatotrichum spp., Phytophthora spp., Pichia anomala, Pichia guilliermondii, Pythium spp., Piedraia hortai, Pneumocystis carinii, Pseudallescheria boydii, Puccinia spp., Pythium insidiosum, Rhinocladiella aquaspersa, Rhizomucor pusillus, Rhizoctonia spp., Rhizopus spp., Rhizopus oryzae, Rhodotorula rubra, Saccharomyces spp., Saccharomyces cerevisiae, Saksénaea vasiformis, Sarcinomyces phaeomuriformis, Scedosporium apiospermum, Scerotium spp., Schizophyllum commune, Sclerotinia spp., Sphaerotheca spp., Sporothrix schenckii, Syncephalastrum racemosum, Taeniolella boppii, Taphrina spp., Thielaviopsis spp., Torulopsis spp., Trichophyton spp., Trichophyton mentagrophytes, Trichophyton rubrum, Trichophyton verrucosum, Trichophyton violaceum, Trichosporon spp., Trichosporon asahii, Trichosporon cutaneum, Trichosporon inkin, Trichosporon mucoides, Ulocladium chartarum, Ustilago spp., Venturia spp., Verticillium spp., Wangiella dermatitidis, Whetxelinia spp., and *Xylohypha spp.*

Examples of fungi that cause infections in animals include, without limitation, *Alternaria spp., Aspergillus spp. Candida spp., Cladosporium spp., Geotrichum spp., Microsporum canis, Microsporum eguinum, Microsporum gallinae, Microsporum nanum, Paecilomyces spp., Penicillium spp., Trichophyton mentagrophytes,* and *Trichophyton verucosum.*

Certain compounds described herein inhibit fungal invasion and/or reduce viability and/or the replication of fungal cells. The compounds may also be useful for treating, either therapeutically or prophylactically, fungal infections that are not invasive. Preferred compounds are substantially non-toxic to a mammal at dosages that are effective for inhibiting fungal invasion *in vivo*. Some inhibitors of fungal invasion are not by themselves fungicidal or fungistatic but when administered alone result in effective treatment of disease. Additionally, some compounds described herein, when administered in combination with a fungicidal or fungistatic agent, the combination is an effective therapy and is more effective than the fungicidal or fungistatic agent alone.

Compounds of Formula A

In one aspect this invention features compounds having a formula (A):



(A)

wherein,

each of R^1, R^2, R^3, and R^4 is, independently, hydrogen, or C_1-C_6 alkyl;

A is NR^5R^6;

B is CR^7R^8; or is absent;

C is NR^9R^{10};

the dashed lines between A and B and between B and C are bonds when B is present, or unshared electron pairs on A and C when B is absent;

R^5 is hydrogen; or R^5 and R^7 together are a bond when B is present;

R^6 is $R^aC(O)$-, or is absent;

R^7 and R^5 together are a bond when B is present;

R^8 is C_1-C_4 alkyl, optionally substituted with NR^bR^c or $R^aC(O)$-;

R^9 is C_6-C_{10} aryl, optionally substituted with hydrogen, halo, or C_1-C_4 alkyl;

R^{10} is hydrogen, or is absent;

R^a is C_1-C_4 alkyl, optionally substituted with halo, NR^bR^c or -C(O)NHNHC(O)R^d;

Each of R^b and R^c is, independently, C_1-C_6 alkyl, C_2-C_6 aminoalkyl, C_2-C_6 alkylaminoalkyl, C_2-C_6 dialkylaminoalkyl, C_7-C_{11} aralkyl, or $R^eC(O)$-; or R^b and R^c together are heterocyclyl, or heterocycloalkenyl, optionally substituted with 1-3 R^f;

R^d is C_6-C_{10} aryl or 3-10 membered heteroaryl, optionally substituted with 1-3 R^g;

R^e is C_1-C_6 alkyl, C_7-C_{11} aralkyl, C_6-C_{10} aryl, or C_6-C_{10} arylamino, each of which may be substituted with C_1 – C_4 alkyl, halo or C_1-C_4 alkoxy;

R^f is oxo or C_1-C_6 alkyl;

R^g is hydrogen, halo, hydroxy, alkoxy, nitro, amino, cyano, carboxy, C_1-C_6 alkyl, C_6-C_{10} aryl, or 5-8 membered heteroaryl; and X is O or S.

Embodiments can include one or more of the following:

B can be present or absent.

When B is present, e.g., when B is CHR^7R^8, R^5 and R^7 together can be a bond, and R^8 can be substituted with NR^bR^c, e.g., $CH(NR^bR^c)CH_3$ or $CH(NR^bR^c)CH_2CH_3$.

R^b can be $(CH_3)_2NCH_2CH_2$, benzyl, or C_1-C_6 alkyl and R^c can be $R^eC(O)$-, in which R^e can be C_5-C_{11} alkyl or substituted or unsubstituted C_6–C_{10} arylamino; preferred substituents include CH_3 or OCH_3.

R^c can be $R^eC(O)$-.

R^e can be C_5-C_{11} alkyl or substituted or unsubstituted C_6–C_{10} arylamino, wherein the substituents are selected from CH_3 or OCH_3.

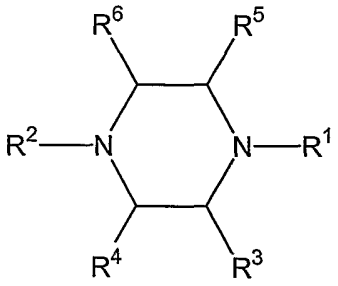
R^9 can be a substituted or unsubstituted phenyl, wherein the substituents are selected from halo or C_1-C_4 alkyl (e.g., CH_3 or chloro).

The invention also includes a method of treating a fungal infection in a subject, the method including administering to the subject an effective amount of a compound having a formula (**A**). Optionally, the method also includes administering to the subject an antifungal agent in combination with the compound. In various embodiments: the compound of formula (**A**) and the antifungal agent are administered simultaneously, the compound of formula (**A**) and the antifungal agent are administered sequentially, the method further includes identifying the subject as a subject in need of treatment for a fungal infection, and the subject is a human.

The invention also features a pharmaceutical composition comprising a compound having a formula (**A**) in an amount effective to treat a fungal infection and a pharmaceutically acceptable carrier. In certain embodiments, the composition includes an antifungal agent.

Compounds of Formula **O**

In another aspect, this invention relates to compounds having a formula (**O**):



(O)

wherein,

Each of R^1 and R^2 is, independently, C_4-C_9 alkyl; C_7-C_{10} aralkyl; C_3-C_9 alkenyl, optionally substituted with aryl; C_3-C_8 cycloalkyl, optionally substituted with C_1-C_4 alkyl; or $R^aC(O)$-;

Each of R^3, R^4, R^5, and R^6 is, independently, hydrogen or C_1-C_4 alkyl; and

R^a is 3-8 membered heterocyclyl, optionally substituted with acyl; C_7-C_{16} aralkyl optionally substituted with halo; or C_6-C_{10} arylamino, optionally substituted with 0-3 C_1-C_4 alkyl.

Embodiments can include one or more of the following:

One or both of R^1 and R^2 can be C_7-C_{10} aralkyl, e.g., benzyl, -$(CH_2)_2$Ph, or -$(CH_2)_3$Ph.

One of R^1 and R^2 can be C_3-C_9 alkenyl, e.g., 3-phenylallyl.

One of R^1 and R^2 can be C_4-C_9 alkyl.

One of R^1 and R^2 can be C_7-C_{10} aralkyl.

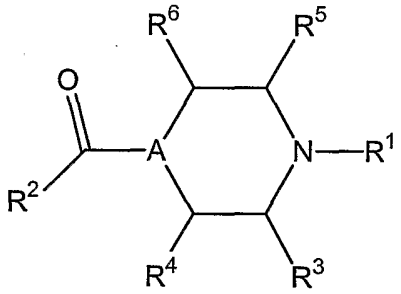
One of R^4 and R^5 can be C_7-C_{10} aralkyl and the other can be C_3-C_9 alkenyl.

The invention also includes a method of treating a fungal infection in a subject, the method including administering to the subject an effective amount of a compound having a formula (**O**). Optionally, the method also includes administering to the subject an antifungal agent in combination with the compound. In various embodiments: the compound of formula (**O**) and the antifungal agent are administered simultaneously, the compound of formula (**O**) and the antifungal agent are administered sequentially, the method further includes identifying the subject as a subject in need of treatment for a fungal infection, and the subject is a human.

The invention also features a pharmaceutical composition comprising a compound having a formula (**O**) in an amount effective to treat a fungal infection and a pharmaceutically acceptable carrier. In certain embodiments, the composition includes an antifungal agent.

Compounds of Formula **L**

In a further aspect, this invention relates to compounds having a formula (**L**):



(**L**)

wherein,

A is N or CH;

R^1 is C_1-C_{12} alkyl, C_2-C_{12} alkenyl, 5-12 membered heteroaryl, or $R^aC(O)$-;

R^2 is C_1-C_{12} alkyl, optionally substituted with $-NHC(O)R^b$; or C_1-C_4 alkoxy;

Each of R^3, R^4, R^5, and R^6 is, independently, hydrogen, or C_1-C_4 alkyl;

R^a is C_1-C_{12} alkyl; and

R^b is C_6-C_{10} aryl.

Embodiments can include one or more of the following.

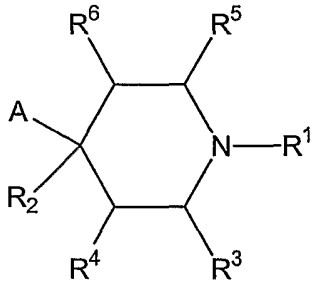
R^1 can be C_3-C_{10} alkenyl (e.g., $-(CH_2)_6CH=CH_2$).

R^2 can be $-OCH_2CH_3$.

The invention also includes a method of treating a fungal infection in a subject, the method including administering to the subject an effective amount of a compound having a formula (**L**). Optionally, the method also includes administering to the subject an antifungal agent in combination with the compound. In various embodiments: the compound of formula (**L**) and the antifungal agent are administered simultaneously, the compound of formula (**L**) and the antifungal agent are administered sequentially, the method further includes identifying the subject as a subject in need of treatment for a fungal infection, and the subject is a human.

The invention also features a pharmaceutical composition comprising a compound having a formula (**L**) in an amount effective to treat a fungal infection and a pharmaceutically acceptable carrier. In certain embodiments, the composition includes an antifungal agent.

Compounds of Formula **E**



(**E**)

In one aspect, this invention relates to compounds having a formula (**E**):

wherein,

R^1 is C_1-C_4 alkyl, optionally substituted with 1-3 R^a; C_7-C_{16} aralkyl, optionally substituted with 1-3 R^a; 6-16 membered heteroaralkyl, optionally substituted with 1-3 R^a; C_3-C_4 alkenyl, optionally substituted with 1-2 R^a;

A is C_6-C_{10} aryloxy, optionally substituted with thioaryloxy or thioalkoxy; 3-8 membered heterocyclyl, optionally substituted with C_7-C_{16} aralkyl; or CHR^7R^8;

R^2 is hydrogen or hydroxy; or R^2 and R^7 together are a bond;

Each of R^3, R^4, R^5, and R^6 is, independently, hydrogen, C_1-C_4 alkyl, or C_1-C_4 alkoxy;

R^7 is hydrogen; or R^7 and R^2 together are a bond;

R^8 is aryl, optionally substituted with C_1-C_4 alkoxy; and

Each R^a is, independently, hydroxy; C_1-C_6 alkyl; C_1-C_4 alkoxy; C_6-C_{10} aryloxy, optionally substituted with halo; 5-8 membered heteroaryl, optionally substituted with C_1-C_4 alkyl; C_6-C_{10} aryl, optionally substituted with C_2-C_6 dialkylamino or methylenedioxo; C_7-C_{16} aralkoxy; or allyloxy.

Embodiments can include one or more of the following:

R^1 can be C_1-C_4 alkyl, substituted or unsubstituted C_7 aralkyl, or substituted or unsubstituted 6-membered heteroaralkyl; preferred substituents include C_1-C_2 alkoxy, benzyloxy, allyloxy, F, Br, $(CH_3)_2N$, CH_3, methylenedioxo, or $(CH_3)_2CHNHC(O)$-.

A can be CHR^7R^8 or aryloxy.

R^8 can be C_7 aralkyl.

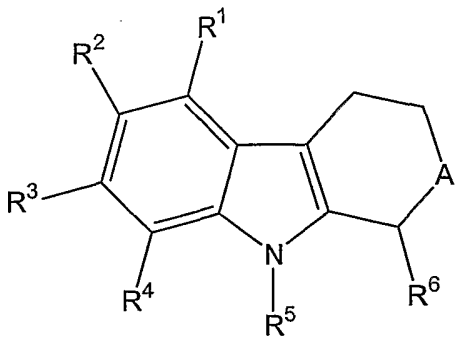
R^7 and R^2 together can be a bond.

The invention also includes a method of treating a fungal infection in a subject, the method including administering to the subject an effective amount of a compound having a formula (**E**). Optionally, the method also includes administering to the subject an antifungal agent in combination with the compound. In various embodiments: the compound of formula (**E**) and the antifungal agent are administered simultaneously, the compound of formula (**E**) and the antifungal agent are administered sequentially, the method further includes identifying the subject as a subject in need of treatment for a fungal infection, and the subject is a human.

The invention also features a pharmaceutical composition comprising a compound having a formula (**E**) in an amount effective to treat a fungal infection and a pharmaceutically acceptable carrier. In certain embodiments, the composition includes an antifungal agent.

Compounds of Formula C

In another aspect, this invention relates to compounds having a formula (C):



(C)

wherein,

Each of R^1, R^2, R^3, and R^4 is, independently, hydrogen, halo, or C_1-C_4 alkyl;

R^5 is hydrogen;

A is NR^7 or CH_2;

R^6 is hydrogen; C_1-C_6 alkylamino, optionally substituted with R^a; C_6-C_{10} aryl, optionally substituted with 1-3 R^a; or C_5-C_{10} heteroaryl, optionally substituted with 1-3 R^a; or R^6 and R^7 together are 3-8 membered heterocyclyl, optionally substituted with 1-3 R^b;

R^7 is hydrogen; C_7-C_{16} aralkyl, optionally substituted with 1-3 R^c; or $-C(O)R^d$; or R^7 and R^6 together are 3-8 membered heterocyclyl, optionally substituted with 1-3 R^b;

Each R^a is, independently, halo; methylenedioxo; C_6-C_{10} aryloxy, optionally substituted with halo; or C_1-C_4 alkoxy;

Each R^b is, independently, hydroxy, oxo, or C_1-C_6 alkyl;

Each R^c is, independently, C_1-C_4 alkyl or C_1-C_4 alkoxy; and

R^d is C_6-C_{10} aryl, optionally substituted with halo or C_1-C_4 alkyl; 5-8 membered heteroaryl; 3-8 membered heterocyclyl; or 5-10 membered heterocycloalkenyl.

Embodiments can include one or more of the following:

A can be CH_2 or NR^7, in which R^7 can be C_7 aralkyl or $-C(O)R^d$.

R^c can be C_1-C_4 alkylamino substituted with 4-halophenoxy, e.g., when A is CH_2.

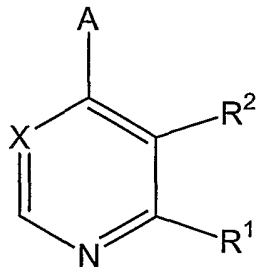
R^d can be phenyl or halo-substituted phenyl.

The invention also includes a method of treating a fungal infection in a subject, the method including administering to the subject an effective amount of a compound having a formula (**C**). Optionally, the method also includes administering to the subject an antifungal agent in combination with the compound. In various embodiments: the compound of formula (**C**) and the antifungal agent are administered simultaneously, the compound of formula (**C**) and the antifungal agent are administered sequentially, the method further includes identifying the subject as a subject in need of treatment for a fungal infection, and the subject is a human.

The invention also features a pharmaceutical composition comprising a compound having a formula (**C**) in an amount effective to treat a fungal infection and a pharmaceutically acceptable carrier. In certain embodiments, the composition includes an antifungal agent.

Compounds of Formula **AA**

In a further aspect, this invention relates to compounds having a formula (**AA**):



(AA)

wherein,

X is N or C

A is $-NHR^3$; $-OR^4$; SR^5; 3-8 membered heteroaryl, optionally substituted with C_6 arylsulfonyl that is substituted with 1-3R^a; 3-8 membered heterocyclyl, optionally substituted with C_6 arylsulfonyl that is substituted with 1-3R^a;

R^c and R^c together are fused C_6 aryl, optionally substituted with 1-3 R^a; or fused 5-membered heteroaryl, optionally substituted with 1-2 R^a;

R^3, R^4, and R^5 are each, independently, C_1-C_{12} alkyl, optionally substituted with 1-3 R^b; C_7-C_{10} aralkyl, optionally substituted with 1-3 R^b; 6-12 membered heteroaralkyl, optionally substituted with with 1-3 R^b; 5-10 membered heteroaryl, optionally substituted with with 1-3 R^b; (C_1-C_3) alkylene-O-(C_1-C_4) alkyl; or (C_1-C_3) alkylene-O-(C_6-C_{10}) aryl;

Each R^a is, independently, halo, C_1-C_6 alkyl, fused C_5-C_7 cycloalkyl, C_6-C_{10} aryl or 5-10 membered heteroaryl; and

Each R^b is, independently, halo, C_1-C_4 alkoxy, methylenedioxo, C_1-C_4 haloalkyl, NH_2, di(C_1-C_4 alkyl)amino, (C_1-C_4 alkyl)amino; or a salt thereof.

Embodiments can include one or more of the following:

X is N.

R^1 and R^2 together can be fused substituted or unsubstituted thienyl; preferred substituents include C_1-C_4 alkyl, fused cyclohexyl, or phenyl.

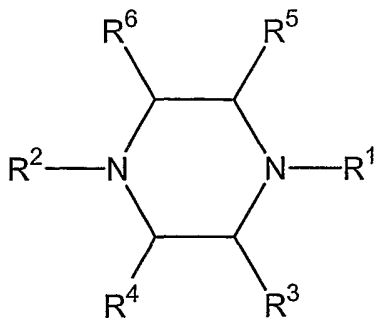
A can be -NHR^3, in which R^3 can be substituted or unsubstituted C_1-C_5 alkyl or substituted or unsubstituted C_7-C_8 aralkyl; preferred substituents include halo, OCH_3, methylenedioxo, or $(CH_3)_2N$.

The invention also includes a method of treating a fungal infection in a subject, the method including administering to the subject an effective amount of a compound having a formula (**AA**). Optionally, the method also includes administering to the subject an antifungal agent in combination with the compound. In various embodiments: the compound of formula (**AA**) and the antifungal agent are administered simultaneously, the compound of formula (**AA**) and the antifungal agent are administered sequentially, the method further includes identifying the subject as a subject in need of treatment for a fungal infection, and the subject is a human.

The invention also features a pharmaceutical composition comprising a compound having a formula (**AA**) in an amount effective to treat a fungal infection and a pharmaceutically acceptable carrier. In certain embodiments, the composition includes an antifungal agent.

Compounds of Formula AB

In one aspect, this invention relates to compounds having a formula (**AB**):



(**AB**)

wherein,

R^1 is C_5-C_{10} heteroaryl, optionally substituted with 1-3 R^a;

R^2 is C_6-C_{10} arylsulfonyl, optionally substituted with halo; C_1-C_6 alkyl; -C(O)R^b; or C_7-C_{16} aralkyl;

Each of R^3, R^4, R^5, and R^6 is hydrogen;

Each R^a is, independently, halo; C_6-C_{10} aryl, optionally substituted with halo, hydroxy, or C_1-C_4 alkoxy; or C_1-C_4 alkyl;

R^b is NHR^c; 5-10 membered heteroaryl; or C_6-C_{10} aryl, optionally substituted with1-2 C_1-C_2 alkoxy; and

R^c is C_6-C_{10} aryl, optionally substituted with 1-3 halo.

Embodiments can include one or more of the following:

R^1 can be substituted or unsubstituted quinazolinyl, quinolinyl, or pyrimidinyl.

R^2 can be C_1-C_4 alkyl (e.g., CH_2CH_3)or -C(O)R^b, in which R^b can be substituted or unsubstituted arylamino or heteroaryl.

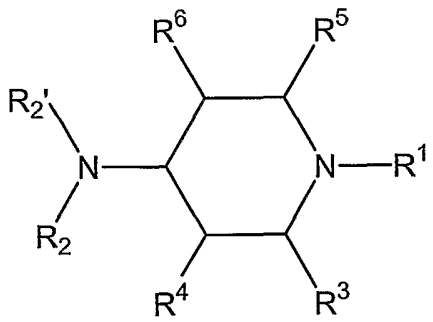
The invention also includes a method of treating a fungal infection in a subject, the method including administering to the subject an effective amount of a compound having a formula (**AB**). Optionally, the method also includes administering to the subject an antifungal agent in combination with the compound. In various embodiments: the compound of formula (**AB**) and the antifungal agent are administered simultaneously, the compound of formula (**AB**) and the antifungal agent are administered

sequentially, the method further includes identifying the subject as a subject in need of treatment for a fungal infection, and the subject is a human.

The invention also features a pharmaceutical composition comprising a compound having a formula (**AB**) in an amount effective to treat a fungal infection and a pharmaceutically acceptable carrier. In certain embodiments, the composition includes an antifungal agent.

Compounds of Formula **K**

In another aspect, this invention relates to compounds having a formula (**K**):



(K)

wherein,

R^1 is C_1-C_7 alkyl, C_7-C_9 aralkyl, or $-C(O)R^a$;

R^2 and $R^{2'}$ are each, independently, hydrogen; C_1-C_4 alkyl; C_3-C_5 cycloalkyl; $-C(O)R^b$; C_7-C_{16} aralkyl, optionally substituted with R^c; or 6-16 membered heteroaralkyl, optionally substituted with R^c; or R^2 and $R^{2'}$ together are 3-10 membered heterocyclyl, optionally substituted with 1-5 C_1-C_4 alkyl;

Each of R^3, R^4, R^5, and R^6 is hydrogen;

R^a is C_1-C_4 alkyl or C_1-C_4 alkoxy;

R^b is C_6-C_{10} aryl, optionally substituted with R^c and/or 1-3 R^d; or 5-10 membered heteroaryl, optionally substituted with R^c and/or 1-3 R^d;

R^c is C_6-C_{10} aryl, optionally substituted with 1-3 R^d; C_6-C_{10} aryloxy, optionally substituted with 1-3 R^d; C_3-C_8 cycloalkyl-C_1-C_4 alkoxy; C_6-C_{10} arylamino, optionally substituted with 1-3 R^d; C_6-C_{10} thioaryloxy, optionally substituted with 1-3 R^d; or C_7-C_{16} aralkoxy, optionally substituted with 1-3 R^d; and

Each R^d is, independently, halo, C_1-C_6 alkyl, C_1-C_4 alkoxy, or C_1-C_4 haloalkyl.

Embodiments can include one or more of the following:

R^1 can be C_1-C_5 alkyl or C_7-C_8 aralkyl.

One of R^2 and $R^{2'}$ can be substituted or unsubstituted C_7-C_{16} aralkyl (e.g., substituted or unsubstituted benzyl, -$(CH_2)_2$Ph, or-$(CH_2)_3$Ph); preferred substituents include aryloxy substituted with CH_3, CF_3, halo, or OCH_3.

One of R^2 and $R^{2'}$ can be CH_3.

One of R^2 and $R^{2'}$ can be hydrogen.

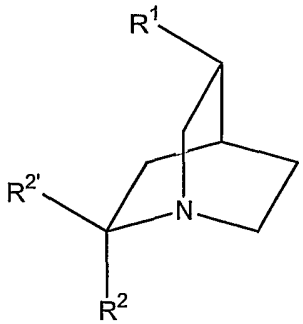
One of R^1 and R^2 can be substituted or unsubstituted C_7-C_{16} aralkyl and the other can be CH_3; preferred substituents include aryloxy substituted with CH_3, CF_3, halo, or OCH_3.

The invention also includes a method of treating a fungal infection in a subject, the method including administering to the subject an effective amount of a compound having a formula (**K**). Optionally, the method also includes administering to the subject an antifungal agent in combination with the compound. In various embodiments: the compound of formula (**K**) and the antifungal agent are administered simultaneously, the compound of formula (**K**) and the antifungal agent are administered sequentially, the method further includes identifying the subject as a subject in need of treatment for a fungal infection, and the subject is a human.

The invention also features a pharmaceutical composition comprising a compound having a formula (**K**) in an amount effective to treat a fungal infection and a pharmaceutically acceptable carrier. In certain embodiments, the composition includes an antifungal agent.

Compounds of Formula **R**

In a further aspect, this invention features compounds having a formula (**R**):



(**R**)

wherein,

R^1 is C_1-C_2 alkyl or C_2 alkenyl;

R^2 and $R^{2'}$ are each, independently, hydrogen or CHR^3R^4;

R^3 is C_5-C_{14} heteroaryl, optionally substituted with C_1-C_4 alkoxy;

R^4 is OR^5;

R^5 is C_6-C_{14} aryl, optionally substituted with 1-3 R^a; -C(O)R^b; 6-14 membered heteroaryl, optionally substituted with 1-3 R^a; C_7-C_{16} aralkyl, optionally substituted with 1-3 R^a;

Each R^a is, independently, halo, C_1-C_6 alkyl, or C_1-C_4 alkoxy; and

R^b is C_6-C_{10} aryl, optionally substituted with 1-3 R^a; or 5-10 membered heteroaryl, optionally substituted with 1-3 R^a.

Embodiments can include one or more of the following:

R^1 can be CH_2CH_3 or $CH{=}CH_2$.

R^3 can be unsubstituted or methoxy-substituted quinolinyl.

R^5 can be aryl or heteroaryl.

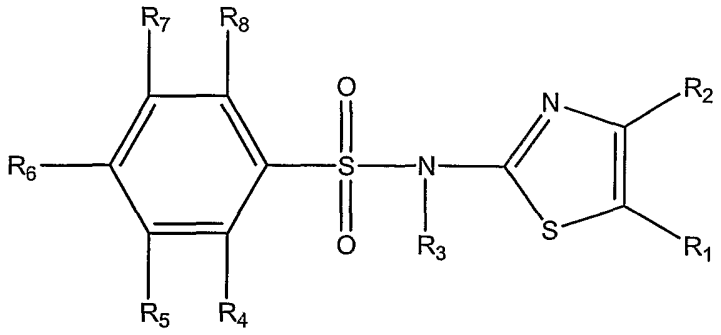
The carbon to which R^3 and R^4 is attached can have the S configuration or the R configuration.

The invention also includes a method of treating a fungal infection in a subject, the method including administering to the subject an effective amount of a compound having a formula (**R**). Optionally, the method also includes administering to the subject an antifungal agent in combination with the compound. In various embodiments: the compound of formula (**R**) and the antifungal agent are administered simultaneously, the compound of formula (**R**) and the antifungal agent are administered sequentially, the method further includes identifying the subject as a subject in need of treatment for a fungal infection, and the subject is a human.

The invention also features a pharmaceutical composition comprising a compound having a formula (**R**) in an amount effective to treat a fungal infection and a pharmaceutically acceptable carrier. In certain embodiments, the composition includes an antifungal agent.

Compound of Formula I

In one aspect, this invention features compounds having a formula (I):



(I)

or a pharmaceutically acceptable salt thereof, wherein, R_1 is substituted or unsubstituted C_1-C_{12} alkyl, or substituted or unsubstituted C_1-C_{12} alkoxy, wherein the substituents are selected from the group consisting of halo and hydroxy; R_2 is H or halo; R_3 is H, formyl, acetyl, or substituted or unsubstituted C_1-C_3 alkyl, wherein the substituents are selected from the group consisting of halo and hydroxy. Each of R_4-R_8 is, independently:

(i) H;

(ii) halo;

(iii) substituted or unsubstituted C_1-C_{12} alkyl, substituted or unsubstituted C_3-C_{10} cycloalkyl, substituted or unsubstituted C_2-C_{12} alkenyl, substituted or unsubstituted C_2-C_{12} alkynyl, or NH(C_1-C_6 alkyl), wherein the substituents are selected from hydroxy, halo, C_1-C_{12} alkyl, and C_3-C_8 cycloalkyl;

(iv) OR^9; or

(v) phenyl or heteroaryl optionally substituted with 1-5 R^{10}.

R^9 is C_3-C_{10} cycloalkyl, optionally substituted with halo or hydroxy; or C_1-C_{12} alkyl, optionally substituted with halo, hydroxy, or C_3-C_{10} cycloalkyl.

Each R^{10} is, independently, halo, hydroxy, OR_a, OR_b, acyloxy, nitro, amino, NHR_a, $N(R_a)_2$, NHR_b, $N(R_b)_2$, aralkylamino, mercapto, thioalkoxy, $S(O)R_a$, $S(O)R_b$, SO_2R_a, SO_2R_b, $NHSO_2R_a$, $NHSO_2R_b$, sulfate, phosphate, cyano, carboxyl, $C(O)R_a$, $C(O)R_b$, $C(O)OR_a$, $C(O)NH_2$, $C(O)NHR_a$, $C(O)N(R_a)_2$, alkyl, haloalkyl, C_3-C_{10} cycloalkyl containing 0-3 R_c, C_3-C_{10} heterocyclyl containing 0-3 R_c,

C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_5-C_{10} cycloalkenyl, C_5-C_{10} heterocycloalkenyl, C_6-C_{20} aryl containing 0-3 R_d, or C_6-C_{20} heteroaryl containing 0-3 R_d.

R_a is C_1-C_6 alkyl optionally substituted with halo, hydroxy, alkoxy, amino, alkylamino, dialkylamino, sulfate, or phosphate.

R_b is aryl optionally substituted with halo, haloalkyl, hydroxy, alkoxy, nitro, amino, alkylamino, dialkylamino, sulfate, or phosphate.

Each R_c is independently halo, haloalkyl, hydroxy, alkoxy, oxo, amino, alkylamino, dialkylamino, sulfate, or phosphate.

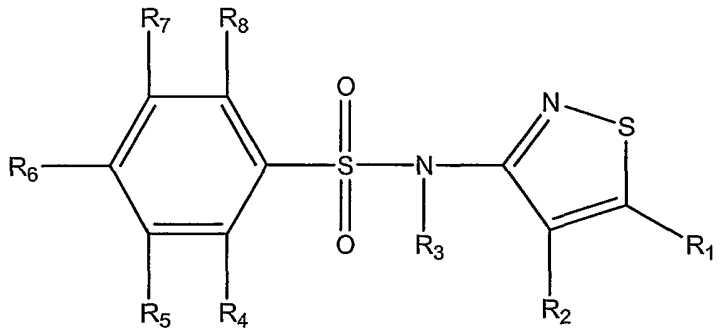
Each R_d is independently halo, haloalkyl, hydroxy, alkoxy, nitro, amino, alkylamino, dialkylamino, sulfate, or phosphate; provided that at least one of R_4-R_8 is not hydrogen; further provided that when R^1 is $(CH_3)_2CCH_2CH_3$ or $C(CH_3)_3$, R^6 is not CH_3; further provided that when R^1 is $CH(CH_3)_2$, R^6 is not OCH_3 or CH_3; and further provided that when R^1 is CH_3, R^4 and R^7 are not Cl.

In a further aspect, this invention features a pharmaceutical composition that contains an amount (e.g., an effective amount) of at least one of the compounds described above (e.g. a compound having the formula **I** and a pharmaceutically acceptable carrier. In certain embodiments, the composition can contain a second antimicrobial agent.

In one aspect, this invention features a method of treating a fungal infection in a subject (including a subject identified as in need of such treatment), the method includes administering an effective amount of a compound (e.g. a compound having the formula **I** or a pharmaceutical composition described above to the subject. In certain embodiments, the method can include administering a compound or a pharmaceutical composition described above to the subject in combination with a second antimicrobial agent.

Compounds of Formula **II**

In another aspect, this invention features compounds having a formula (**II**):



(**II**)

or a pharmaceutically acceptable salt thereof, wherein, each of R^1 and R^2 is, independently, H, substituted or unsubstituted C_1-C_{12} alkyl, or substituted or unsubstituted C_1-C_{12} alkoxy, wherein the substituents are selected from the group consisting of hydroxy and halo;

R^3 is H, formyl, acetyl, or substituted or unsubstituted C_1-C_3 alkyl, wherein the substituents are selected from the group consisting of hydroxy and halo.

Each of R^4-R^8 is, independently:

(i) H;

(ii) halo;

(iii) substituted or unsubstituted C_1-C_{12} alkyl, substituted or unsubstituted C_3-C_{10} cycloalkyl, substituted or unsubstituted C_2-C_{12} alkenyl, substituted or unsubstituted C_2-C_{12} alkynyl, or -NH-(C_1-C_6 alkyl), wherein the substituents are selected from the group consisting of hydroxy, halo, C_1-C_4 alkyl, and C_3-C_8 cycloalkyl;

(iv) OR^9; or

(v) phenyl or heteroaryl optionally substituted with 1-5 R^{10}.

R^9 is C_3-C_{10} cycloalkyl, optionally substituted with halo or hydroxy, or C_1-C_{12} alkyl, optionally substituted with halo, hydroxy, or C_3-C_{10} cycloalkyl.

Each of R^{10} is, independently, halo, hydroxy, OR_a, OR_b, acyloxy, nitro, amino, NHR_a, $N(R_a)_2$, NHR_b, $N(R_b)_2$, aralkylamino, mercapto, thioalkoxy, $S(O)R_a$, $S(O)R_b$, SO_2R_a, SO_2R_b, $NHSO_2R_a$,

$NHSO_2R_b$, sulfate, phosphate, cyano, carboxyl, $C(O)R_a$, $C(O)R_b$, $C(O)OR_a$, $C(O)NH_2$, $C(O)NHR_a$, $C(O)N(R_a)_2$, alkyl, haloalkyl, C_3-C_{10} cycloalkyl containing 0-3 R_c, C_3-C_{10} heterocyclyl containing 0-3 R_c, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_5-C_{10} cycloalkenyl, C_5-C_{10} heterocycloalkenyl, C_6-C_{20} aryl containing 0-3 R_d, or C_6-C_{20} heteroaryl containing 0-3 R_d.

R_a is C_1-C_6 alkyl optionally substituted with halo, hydroxy, alkoxy, amino, alkylamino, dialkylamino, sulfate, or phosphate.

R_b is aryl optionally substituted with halo, haloalkyl, hydroxy, alkoxy, nitro, amino, alkylamino, dialkylamino, sulfate, or phosphate.

Each R_c is independently halo, haloalkyl, hydroxy, alkoxy, oxo, amino, alkylamino, dialkylamino, sulfate, or phosphate; and

Each R_d is independently halo, haloalkyl, hydroxy, alkoxy, nitro, amino, alkylamino, dialkylamino, sulfate, or phosphate.

Embodiments include one or more of the following.

R^1 can be C_1-C_4 alkyl (e.g., CH_3).

R^4, R^5, R^7, and R^8 can be H.

R^3 can be H.

R^6 can be C_1-C_6 alkyl.

R^6 can be OR^9, and R^9 can be C_1-C_6 alkyl, C_5-C_8 cycloalkyl (e.g., cyclopentyl or 2-norbornyl), or C_1-C_4 alkyl substituted with C_3-C_5 cycloalkyl.

R^6 can be phenyl substituted with R^{10} (e.g., halo). In certain embodiments, R^4 or R^5 can be fluoro when R^6 is phenyl substituted with R^{10}.

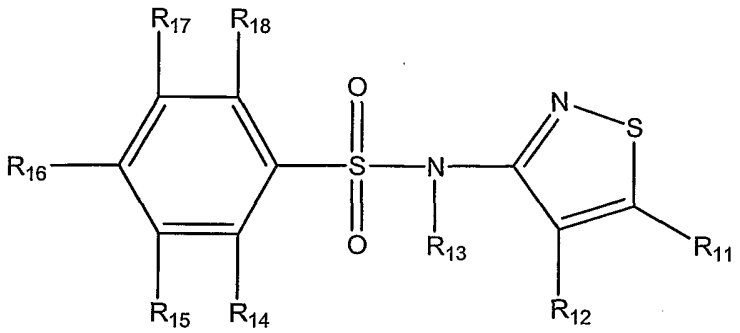
In a further aspect, this invention features a pharmaceutical composition that contains an amount (e.g., an effective amount) of at least one of the compounds described above (e.g., a compound having the formula **II** and a pharmaceutically acceptable carrier. In certain embodiments, the composition can contain a second antimicrobial agent.

In one aspect, this invention features a method of treating a fungal infection in a subject (including a subject identified as in need of such treatment), the method includes administering an effective amount of a compound (e.g. a compound having the formula **II** or a pharmaceutical composition described above to the subject. In certain embodiments, the method can include administering a

compound or a pharmaceutical composition described above to the subject in combination with a second antimicrobial agent.

Compounds of Formula **III**

In a further aspect, this invention features compounds having a formula (**III**):



(**III**)

or a pharmaceutically acceptable salt thereof, wherein, each of R^{11} and R^{12} is, independently, H, substituted or unsubstituted C_1-C_{12} alkyl, or substituted or unsubstituted C_{1-12} alkoxy, wherein the substituents are selected from the group consisting of hydroxy and halo.

R^{13} is H, formyl, acetyl, or substituted or unsubstituted C_1-C_3 alkyl, wherein the substituents are selected from the group consisting of hydroxy and halo.

Each of R^{14}-R^{18} is, independently, H, halo, substituted or unsubstituted C_1-C_{12} alkyl, substituted or unsubstituted C_3-C_{10} cycloalkyl, substituted or unsubstituted C_2-C_{12} alkenyl, substituted or unsubstituted C_2-C_{12} alkynyl, substituted or unsubstituted C_1-C_{12} alkoxy, substituted or unsubstituted C_2-C_{12} alkenyloxy, substituted or unsubstituted (C_2-C_{12} alkynyl)oxy, (C_1-C_6 alkyl)oxy(C_1-C_6 alkyl), substituted or unsubstituted C_6-C_{12} aryloxy, (C_3-C_6 heteroaryl)-(C_1-C_6 alkyl)oxy, (C_1-C_6 alkyl)thio, substituted or unsubstituted (C_1-C_4 alkyl)-thio-(C_1-C_4 alkyl), substituted or unsubstituted aryl, substituted or unsubstituted styryl, substituted or unsubstituted C_{3-12} heteroaryl, substituted or unsubstituted C_{4-8} heterocyclic, -NH-C(O)-NH-(substituted or unsubstituted heteroaryl), or $-NR^{19}R^{20}$, wherein each of R^{19} and R^{20} is, independently, H or C_1-C_{12} alkyl, wherein the substituents are selected from the group consisting of hydroxy, halo, C_1-C_4 alkyl, C_3-C_8 cycloalkyl, C_1-C_4 trihaloalkyl, C_1-C_6 alkoxy, C_1-C_4 trihaloalkoxy, bivalent oxyalkyloxy, acylamino, amino, and azido.

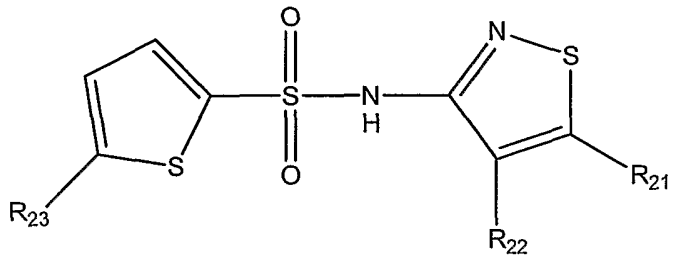
In a further aspect, this invention features a pharmaceutical composition that contains an amount (e.g., an effective amount) of at least one of the compounds described above (e.g. a compound having the

formula **III** and a pharmaceutically acceptable carrier. In certain embodiments, the composition can contain a second antimicrobial agent.

In one aspect, this invention features a method of treating a fungal infection in a subject (including a subject identified as in need of such treatment), the method includes administering an effective amount of a compound (e.g. a compound having the formula **III** or a pharmaceutical composition described above to the subject. In certain embodiments, the method can include administering a compound or a pharmaceutical composition described above to the subject in combination with a second antimicrobial agent.

Compounds of Formula **IV**

In one aspect, this invention features compounds having a Formula (**IV**):



(IV)

or a pharmaceutically acceptable salt thereof, wherein each of R^{21} and R^{22} is, independently, substituted or unsubstituted C_1-C_6 alkyl, or substituted or unsubstituted C_1-C_6 alkoxy, wherein the substituents are selected from the group consisting of hydroxy and halo.

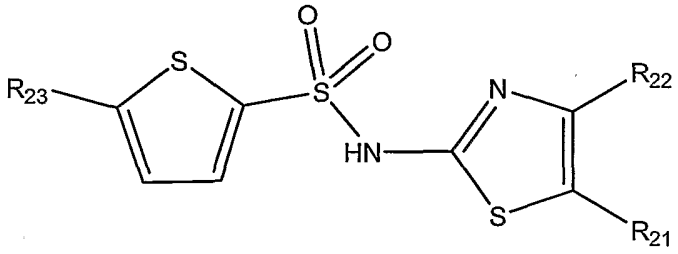
R^{23} is substituted or unsubstituted C_1-C_6 alkyl, substituted or unsubstituted C_3-C_{10} cycloalkyl, substituted or unsubstituted C_6-C_{12} aryl, substituted or unsubstituted C_3-C_{12} heteroaryl, wherein the substituents are selected from the group consisting of halo, C_1-C_6 alkyl, C_3-C_8 cycloalkyl, and C_1-C_6 trihaloalkyl.

In a further aspect, this invention features a pharmaceutical composition that contains an amount (e.g., an effective amount) of at least one of the compounds described above (e.g. a compound having the formula **IV** and a pharmaceutically acceptable carrier. In certain embodiments, the composition can contain a second antimicrobial agent.

In one aspect, this invention features a method of treating a fungal infection in a subject (including a subject identified as in need of such treatment), the method includes administering an effective amount of a compound (e.g. a compound having the formula **IV** or a pharmaceutical composition described above to the subject. In certain embodiments, the method can include administering a compound or a pharmaceutical composition described above to the subject in combination with a second antimicrobial agent.

Compounds of Formula **V**

In another aspect, this invention features compounds having a Formula (**V**):



(**V**)

or a pharmaceutically acceptable salt thereof, wherein each of R^{21} and R^{22} is, independently, substituted or unsubstituted C_1-C_6 alkyl, or substituted or unsubstituted C_1-C_6 alkoxy, wherein the substituents are selected from the group consisting of hydroxy and halo.

R^{23} is substituted or unsubstituted C_1-C_6 alkyl, substituted or unsubstituted C_3-C_{10} cycloalkyl, substituted or unsubstituted C_6-C_{12} aryl, substituted or unsubstituted C_3-C_{12} heteroaryl, wherein the substituents are selected from the group consisting of halo, C_1-C_6 alkyl, C_3-C_8 cycloalkyl, and C_1-C_6 trihaloalkyl.

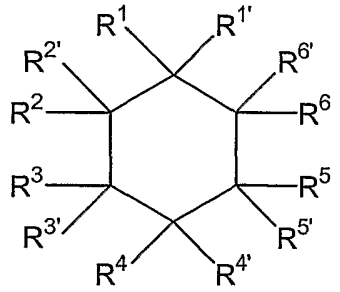
In certain embodiments, R^{21} is CH_3 and R^{23} is CH_3, *n*-hexyl, cyclopentyl, phenyl, 4'-fluorophenyl, or thienyl.

In a further aspect, this invention features a pharmaceutical composition that contains an amount (e.g., an effective amount) of at least one of the compounds described above (e.g. a compound having the formula **V** and a pharmaceutically acceptable carrier. In certain embodiments, the composition can contain a second antimicrobial agent.

In one aspect, this invention features a method of treating a fungal infection in a subject (including a subject identified as in need of such treatment), the method includes administering an effective amount of a compound (e.g. a compound having the formula **V** or a pharmaceutical composition described above to the subject. In certain embodiments, the method can include administering a compound or a pharmaceutical composition described above to the subject in combination with a second antimicrobial agent.

Compound of Formula **VI**

In one aspect, this invention relates to a method of treating a fungal infection in a subject, the method includes administering to the subject an effective amount of a compound having a formula (**VI**):



(VI)

wherein:

R^1 is $(CH_2)_nCO_2H$, wherein n is 0, 1, 2, 3, 4, or 5;

$R^{1'}$ and $R^{2'}$, independently, are hydrogen or C_1-C_6 alkyl, or $R^{1'}$ and $R^{2'}$ together are a bond, $R^{3'}$ and $R^{4'}$, independently, are hydrogen or C_1-C_6 alkyl, or $R^{3'}$ and $R^{4'}$ together are a bond, $R^{5'}$ and $R^{6'}$, independently, are hydrogen or C_1-C_6 alkyl, or $R^{5'}$ and $R^{6'}$ together are a bond, or $R^{2'}$, $R^{3'}$, $R^{5'}$, and $R^{6'}$, independently, are hydrogen or C_1-C_6 alkyl and $R^{1'}$ and $R^{4'}$ together are a C_1-C_3 alkylene group;

each R^2, R^3, R^5, and R^6, independently, is hydrogen or C_1-C_6 alkyl; and

R^4 is: C_1-C_{12} alkyl optionally substituted with C_3-C_8 cycloalkyl, halo, hydroxy, mercapto, C_1-C_{10} alkoxy, C_1-C_{10} thioalkoxy, amino, C_1-C_{10} alkylamino, C_1-C_{10} dialkylamino, or oxo; C_3-C_8 cycloalkyl optionally substituted with C_3-C_8 cycloalkyl, halo, hydroxy, mercapto, C_1-C_{10} alkoxy, C_1-C_{10} thioalkoxy, amino, C_1-C_{10} alkylamino, C_1-C_{10} dialkylamino, or oxo; aryl optionally substituted with C_3-C_8 cycloalkyl, halo, C_1-C_{10} haloalkyl, hydroxy, mercapto, C_1-C_{10} alkoxy, C_1-C_{10} hydroxyalkyl, C_1-C_{10} thioalkoxy, amino, C_1-C_{10} alkylamino, C_1-C_{10} dialkylamino, or acyl; C_2-C_{12} alkenyl optionally substituted with C_3-C_8 cycloalkyl, halo, hydroxy, mercapto, C_1-C_{10} alkoxy, C_1-C_{10} thioalkoxy, amino, C_1-C_{10} alkylamino, C_1-C_{10} dialkylamino, or oxo; or C_2-C_{12} alkynyl optionally substituted with C_3-C_8 cycloalkyl, halo, hydroxy, mercapto, C_1-C_{10} alkoxy, C_1-C_{10} thioalkoxy, amino, C_1-C_{10} alkylamino, C_1-C_{10} dialkylamino, or oxo.

"Embodiments can include one or more of the following.

$R^{1'}$ and $R^{2'}$ together can be a bond, $R^{3'}$ and $R^{4'}$ together can be a bond, and $R^{5'}$ and $R^{6'}$ together can be a bond. In certain embodiments, n can be 0 or 1 and R^4 can be C_3-C_6 alkyl (e.g., *n*-propyl, *iso*-propyl, *sec*-butyl, *n*-butyl, *n*-pentyl, or *n*-hexyl) or R^4 can be C_3-C_6 cycloalkyl (e.g., cyclohexyl).

R^2, R^3, R^5, and R^6 can be hydrogen.

$R^{1'}$, $R^{2'}$, $R^{3'}$, $R^{4'}$, $R^{5'}$, and $R^{6'}$ can be hydrogen, and R^1 and R^4 can be *trans* or R^1 and R^4 can be *cis*. In certain embodiments, n is 0 and R^1 and R^4 are *trans*, R^4 being C_3-C_6 alkyl (e.g., *n*-propyl, *n*-butyl, *n*-pentyl, or *n*-hexyl). In other embodiments, the method can further include administering a mixture of the *cis* isomer of the compound and the *trans* isomer of the compound. The mixture can include at least about 95 percent of the *trans* isomer, at least about 98 percent of the *trans* isomer, or at least about 99 percent of the *trans* isomer. Alternatively, the mixture can include at least about 95 percent of the *cis* isomer, at least about 98 percent of the *cis* isomer, or at least about 99 percent of the *cis* isomer.

$R^{2'}$, $R^{3'}$, $R^{5'}$, and $R^{6'}$ can be hydrogen, and $R^{1'}$ and $R^{4'}$ together can be a $-CH_2CH_2-$ group. In certain embodiments, n can be 0 or 1 and R^4 can be C_3-C_6 alkyl (e.g., *n*-propyl, *n*-butyl, *n*-pentyl, or *n*-hexyl).

n can be 0, 1, 2, or 3.

R^4 can be *n*-propyl, *n*-butyl, *n*-pentyl, or *n*-hexyl.

R^4 can be phenyl.

R^4 can be C_3-C_8 cycloalkyl.

R^4 can be C_2-C_{12} alkenyl.

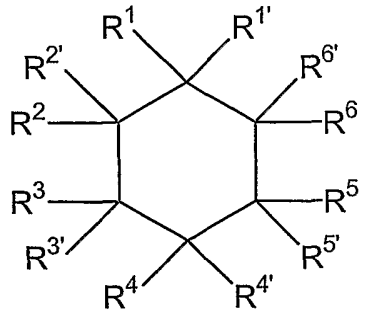
R^4 can be C_2-C_{12} alkynyl.

R^4 can beC_1-C_{12} alkyl substituted with halo, hydroxy, C_3-C_8 cycloalkyl, C_1-C_{10} alkoxy, C_1-C_{10} thioalkoxy, amino, C_1-C_{10} alkylamino, C_1-C_{10} dialkylamino, or oxo.

The method can further include administering to the subject an antimicrobial agent in combination with the compound. The compound of formula (I) and the antimicrobial agent can be administered simultaneously or sequentially.

The method can further include identifying the subject (e.g., a human subject) as a subject in need of treatment for a fungal infection.

In another aspect, this invention relates to a pharmaceutical composition comprising a compound having a formula (VI) in an amount effective to treat a fungal infection and a pharmaceutically acceptable carrier,



(VI)

wherein:

R^1 is $(CH_2)_nCO_2H$, wherein n is 0, 1, 2, 3, 4, or 5;

$R^{1'}$ and $R^{2'}$, independently, are hydrogen or C_1-C_6 alkyl, or $R^{1'}$ and $R^{2'}$ together are a bond, $R^{3'}$ and $R^{4'}$, independently, are hydrogen or C_1-C_6 alkyl, or $R^{3'}$ and $R^{4'}$ together are a bond, $R^{5'}$ and $R^{6'}$, independently, are hydrogen or C_1-C_6 alkyl, or $R^{5'}$ and $R^{6'}$ together are a bond, or $R^{2'}$, $R^{3'}$, $R^{5'}$, and $R^{6'}$, independently, are hydrogen or C_1-C_6 alkyl and $R^{1'}$ and $R^{4'}$ together are a C_1-C_3 alkylene group;

each R^2, R^3, R^5, and R^6, independently, is hydrogen or C_1-C_6 alkyl; and

R^4 is: C_1-C_{12} alkyl optionally substituted with C_3-C_8 cycloalkyl, halo, hydroxy, mercapto, C_1-C_{10} alkoxy, C_1-C_{10} thioalkoxy, amino, C_1-C_{10} alkylamino, C_1-C_{10} dialkylamino, or oxo; C_3-C_8 cycloalkyl optionally substituted with C_3-C_8 cycloalkyl, halo, hydroxy, mercapto, C_1-C_{10} alkoxy, C_1-C_{10} thioalkoxy, amino, C_1-C_{10} alkylamino, C_1-C_{10} dialkylamino, or oxo; aryl optionally substituted with C_3-C_8 cycloalkyl, halo, C_1-C_{10} haloalkyl, hydroxy, mercapto, C_1-C_{10} alkoxy, C_1-C_{10} hydroxyalkyl, C_1-C_{10} thioalkoxy, amino, C_1-C_{10} alkylamino, C_1-C_{10} dialkylamino, or acyl; C_2-C_{12} alkenyl optionally substituted with C_3-C_8 cycloalkyl, halo, hydroxy, mercapto, C_1-C_{10} alkoxy, C_1-C_{10} thioalkoxy, amino, C_1-C_{10} alkylamino, C_1-C_{10} dialkylamino, or oxo; or C_2-C_{12} alkynyl optionally substituted with C_3-C_8 cycloalkyl, halo, hydroxy, mercapto, C_1-C_{10} alkoxy, C_1-C_{10} thioalkoxy, amino, C_1-C_{10} alkylamino, C_1-C_{10} dialkylamino, or oxo.

Embodiments can include one or more of the following.

$R^{1'}$ and $R^{2'}$ together can be a bond, $R^{3'}$ and $R^{4'}$ together can be a bond, and $R^{5'}$ and $R^{6'}$ together can be a bond. In certain embodiments, n can be 0 or 1 and R^4 can be C_3-C_6 alkyl (e.g., *n*-propyl, *n*-butyl, *n*-pentyl, or *n*-hexyl) or R^4 can be C_3-C_6 cycloalkyl (e.g., cyclohexyl).

$R^{2'}$, $R^{3'}$, $R^{5'}$, and $R^{6'}$ can be hydrogen.

$R^{1'}$, $R^{2'}$, $R^{3'}$, $R^{4'}$, $R^{5'}$, and $R^{6'}$ can be hydrogen, and R^1 and R^4 can be *trans* or R^1 and R^4 can be *cis*. In certain embodiments, n can be 0 and R^1 and R^4 are *trans*, R^4 being C_3-C_6 alkyl (e.g., *n*-propyl, *n*-butyl, *n*-pentyl, or *n*-hexyl). In other embodiments, the composition can include a mixture of the *cis* isomer of the compound and the *trans* isomer of the compound. The mixture can include at least about 95 percent of the *trans* isomer, at least about 98 percent of the *trans* isomer, or at least about 99 percent of the *trans* isomer. Alternatively, the mixture can include at least about 95 percent of the *cis* isomer, at least about 98 percent of the *cis* isomer, or at least about 99 percent of the *cis* isomer.

$R^{2'}$, $R^{3'}$, $R^{5'}$, and $R^{6'}$ are hydrogen, and $R^{1'}$ and $R^{4'}$ together are a $-CH_2CH_2-$ group. In certain embodiments, n can be 0 or 1 and R^4 can be C_3-C_6 alkyl (e.g., *n*-propyl, *n*-butyl, *n*-pentyl, or *n*-hexyl).

n can be 0, 1, 2, or 3.

R^4 can be *n*-propyl, *n*-butyl, *n*-pentyl, or *n*-hexyl

R^4 can be phenyl.

R^4 can be C_3-C_8 cycloalkyl.

R^4 can be C_2-C_{12} alkenyl.

R^4 can be C_2-C_{12} alkynyl.

R^4 can C_1-C_{12} alkyl substituted with halo, hydroxy, C_3-C_8 cycloalkyl, C_1-C_{10} alkoxy, C_1-C_{10} thioalkoxy, amino, C_1-C_{10} alkylamino, C_1-C_{10} dialkylamino,or oxo.

The composition may further include an antimicrobial agent.

The composition may include a compound in which $R^{1'}$, $R^{2'}$, $R^{3'}$, $R^{4'}$, $R^{5'}$, and $R^{6'}$ can be hydrogen and R^1 and R^4 can be *trans*, and may further include an antimicrobial agent, which is also a compound of formula (**VI**) in which $R^{1'}$, $R^{2'}$, $R^{3'}$, $R^{4'}$, $R^{5'}$, and $R^{6'}$ are hydrogen and R^1 and R^4 are *cis*.

In a further aspect, this invention features a pharmaceutical composition that contains an amount (e.g., an effective amount) of at least one of the compounds described above (e.g. a compound having the formula (**VI**)) and a pharmaceutically acceptable carrier. In certain embodiments, the composition can contain a compound having the formula (**VI**), e.g., an antifungal compound, an antimicrobial agent, and a pharmaceutically acceptable carrier.

In one aspect, this invention features a method of treating a fungal infection in a subject (including a subject identified as in need of such treatment), the method includes administering an

effective amount of a compound (e.g., a compound having the formula (VI)) or a pharmaceutical composition described above to the subject. In certain embodiments, the method can further include administering a compound or a pharmaceutical composition described above to the subject in combination with an antimicrobial, e.g., antifungal, agent. The compound or pharmaceutical composition and the antimicrobial agent can be administered simultaneously or sequentially.

In one aspect, this invention relates to a pharmaceutical composition including a compound having any of the formulae herein in an amount effective to treat a fungal infection and a pharmaceutically acceptable carrier. In certain embodiments, the composition can include a compound having any of the formulae herein in an amount effective to treat a fungal infection, a second agent (e.g., an antimicrobial agent, a fungicidal agent, a fungistatic agent or an antifungal agent), and a pharmaceutically acceptable carrier.

In another aspect, this invention features a method of inhibiting fungal invasion in a subject (including a subject identified as in need of such treatment), the method includes administering an effective amount of an anti-invasin agent and an antimicrobial agent (e.g., an antifungal agent such as a fungicidal agent or a fungistatic agent) to the subject.

In another aspect, this invention features a method of treating a fungal infection in a subject (including a subject identified as in need of such treatment), the method includes administering an effective amount of a compound having any of the formulae herein in an amount effective to treat a fungal infection or a pharmaceutical composition described above to the subject. In certain embodiments, the method can further include administering a compound or a pharmaceutical composition described above to the subject in combination with an antimicrobial agent, e.g., an antifungal agent that is fungistatic or fungicidal. In some embodiments the compound having any of the formulae described above is an anti-invasin compound that is effective in therapeutic application only in combination with a fungicidal agent or a fungistatic agent. The compound or pharmaceutical composition and the antimicrobial agent can be administered simultaneously or sequentially.

In various embodiments of the methods for treating a fungal infection: the antifungal agent is selected from the group consisting of: a polyene, a candin, a sordarin, an azole, an allylamine, a morpholine, and a pradimicin; and the antifungal agent acts by blocking ergosterol synthesis, by interfering with the cell wall, by interfering with the cell membrane, or by interfering with protein translation.

In various embodiments of the compositions: antifungal agent is agent is selected from the group consisting of: a polyene, a candin, a sordarin, an azole, an allylamine, a morpholine, and a pradimicin and the antifungal agent acts by blocking ergosterol synthesis, by interfering with the cell wall, by interfering with the cell membrane, or by interfering with protein translation.

The invention also features: a method of treating a fungal infection in a subject, the method comprising administering an effective amount of an anti-invasin agent and an antifungal agent selected from the group consisting of a polyene, a candin, a sordarin, an azole, an allylamine, a morpholine, and a pradimicin; and a method of treating a fungal infection in a subject, the method comprising administering an effective amount of an anti-invasin agent and an antifungal agent, wherein the antifungal agent acts by blocking ergosterol synthesis, by interfering with the cell wall, by interfering with the cell membrane, or by interfering with protein translation.

In another aspect, the invention features: a pharmaceutical composition comprising an anti-invasin agent and an antifungal agent selected from the group consisting of: a polyene, a candin, a sordarin, an azole, an allylamine, a morpholine, and a pradimicin; and a pharmaceutical composition comprising an anti-invasin agent and an antifungal agent, wherein the antifungal agent acts by blocking ergosterol synthesis, by interfering with the cell wall, by interfering with the cell membrane, or by interfering with protein translation.

In various embodiments of the treatment methods of the invention the anti-invasin agent has greater anti-invasin activity than fungal growth inhibition activity.

In some embodiments of the methods, the anti-invasin agent is characterized as having: a) an IC_{50} as determined in the *HWP1-lacZ* reporter assay that is 100x lower than the MIC_{growth} as determined in liquid media; b) a $MIC_{invasion}$ as determined in the morphology assay that is 10x lower than the MIC_{growth} as determined in liquid media; c) a $MIC_{invasion}$ as determined in the plastic adherence assay that is 10x lower than the MIC_{growth} as determined in liquid media; d) a $MIC_{invasion}$ as determined in the agar invasion assay that is 10x lower than the MIC_{growth} as determined in the agar invasion assay; or e) a $MIC_{invasion}$ as determined in the migration across Caco-2 monolayer assay that is 10x lower than the MIC_{growth} as determined in liquid media.

In other embodiments of the methods, the anti-invasin agent is characterized as having: a) an IC_{50} as determined in the *HWP1-lacZ* reporter assay that is 1000x lower than the MIC_{growth} as determined in liquid media; b) a $MIC_{invasion}$ as determined in the morphology assay that is 100x lower than the MIC_{growth} as determined in liquid media; c) a $MIC_{invasion}$ as determined in the plastic adherence assay that is 100x lower than the MIC_{growth} as determined in liquid media; d) a $MIC_{invasion}$ as determined in the agar invasion assay that is 100x lower than the IC_{growth} as determined in the agar invasion assay; or e) a $MIC_{invasion}$ as determined in the migration across Caco-2 monolayer assay that is 100x lower than the MIC_{growth} as determined in liquid media.

In still other embodiments of the methods, the anti-invasin agent is characterized as having: a) an IC_{50} as determined in the *HWP1-lacZ* reporter assay that is 10000x lower than the MIC_{growth} as determined in liquid media; b) a $MIC_{invasion}$ as determined in the morphology assay that is 1000x lower than the

MIC_{growth} as determined in liquid media; c) a $MIC_{invasion}$ as determined in the plastic adherence assay that is 1000x lower than the MIC_{growth} as determined in liquid media; d) a $MIC_{invasion}$ as determined in the agar invasion assay that is 1000x lower than the MIC_{growth} as determined in the same assay; or e) a $MIC_{invasion}$ as determined in the migration across Caco-2 monolayer assay that is 1000x lower than the MIC_{growth} as determined in liquid media.

In additional embodiments, the invention features a pharmaceutical composition comprising any of the forgoing anti-invasin agents and a pharmaceutically acceptable carrier. In various embodiments, the pharmaceutical composition further includes: an antifungal agent selected from the group consisting of: a polyene, a candin, a sordarin, an azole, an allylamine, a morpholine, and a pradimicin; or an antifungal agent, wherein the antifungal agent acts by blocking ergosterol synthesis, by interfering with the cell wall, by interfering with the cell membrane, or by interfering with protein translation.

Anti-invasin agents are agents which have anti-invasin activity as measured by one or more of the assays described herein for measuring anti-invasin activity (e.g., the *HWP1-lacZ* reporter assay, the morphology assay, the plastic adherence assay, the invasion in agar substrate assay, and the migration across Caco-2 monolayer assay). Certain desirable anti-invasin agents have substantially greater anti-invasin activity than growth inhibition activity, e.g., the $MIC_{invasion}$ is 10X, 20X, 50X, 100X, 200X, 500X, 1000X, 2000X, 5000X or 10000X or more less than the MIC_{growth} when determined in same strain. Thus, certain desirable compounds have significant anti-invasin activity yet have a MIC_{growth} that is greater than 3 μg/ml, greater than 4 μg/ml, greater than 5 μg/ml, greater than 6 μg/ml, greater than 8 μg/ml, greater than 10 μg/ml, greater than 12 μg/ml, greater than 15 μg/ml, or even greater than 20 μg/ml.

The subject can be a mammal, preferably a human. In certain embodiments the method can further include identifying a subject having a fungal infection. Identifying a subject in need of such treatment can be in the judgment of a subject or a health care professional and can be subjective (e.g., opinion) or objective (e.g., measurable by a test or diagnostic method).

The term "treating" or "treated" refers to administering a compound described herein to a subject with the purpose to cure, heal, alleviate, relieve, alter, remedy, ameliorate, improve, or affect a disease, e.g., an infection, the symptoms of the disease or the predisposition toward the disease.

"An effective amount" refers to an amount of a compound that confers a therapeutic effect on the treated subject. The therapeutic effect may be objective (i.e., measurable by some test or marker) or subjective (i.e., subject gives an indication of or feels an effect). An effective amount of the compound described above may range from about 0.1 mg/Kg to about 500 mg/Kg, alternatively from about 1 to about 50 mg/Kg. Effective doses will also vary depending on route of administration, as well as the possibility of co-usage with other agents.

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

The term "alkyl" refers to a hydrocarbon chain that may be a straight chain or branched chain, containing the indicated number of carbon atoms. For example, C_1-C_{12} alkyl indicates that the group may have from 1 to 12 (inclusive) carbon atoms in it. The term "haloalkyl" refers to an alkyl in which one or more hydrogen atoms are replaced by halo, and includes alkyl moieties in which all hydrogens have been replaced by halo (e.g., perfluoroalkyl). The terms "arylalkyl" or "aralkyl" refer to an alkyl moiety in which an alkyl hydrogen atom is replaced by an aryl group. Aralkyl includes groups in which more than one hydrogen atom has been replaced by an aryl group. Examples of "arylalkyl" or "aralkyl" include benzyl, 2-phenylethyl, 3-phenylpropyl, 9-fluorenyl, benzhydryl, and trityl groups.

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

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

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

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

The term "cycloalkyl" as employed herein includes saturated cyclic, bicyclic, tricyclic,or polycyclic hydrocarbon groups having 3 to 12 carbons. Any ring atom can be substituted. The cycloalkyl groups can contain fused rings. Fused rings are rings that share a common carbon atom. Examples of cycloalkyl moieties include, but are not limited to, cyclopropyl, cyclohexyl, methylcyclohexyl, adamantyl, and norbornyl.

The term "heterocyclyl" refers to a nonaromatic 3-10 membered monocyclic, 8-12 membered bicyclic, or 11-14 membered tricyclic ring system having 1-3 heteroatoms if monocyclic, 1-6 heteroatoms if bicyclic, or 1-9 heteroatoms if tricyclic, said heteroatoms selected from O, N, or S (e.g., carbon atoms

and 1-3, 1-6, or 1-9 heteroatoms of N, O, or S if monocyclic, bicyclic, or tricyclic, respectively). The heteroatom may optionally be the point of attachment of the heterocyclyl substituent. Any ring atom can be substituted. The heterocyclyl groups can contain fused rings. Fused rings are rings that share a common carbon atom. Examples of heterocyclyl include, but are not limited to, tetrahydrofuranyl, tetrahydropyranyl, piperidinyl, morpholino, pyrrolinyl, pyrimidinyl, quinolinyl, and pyrrolidinyl.

The term "cycloalkenyl" refers to partially unsaturated, nonaromatic, cyclic, bicyclic, tricyclic, or polycyclic hydrocarbon groups having 5 to 12 carbons, preferably 5 to 8 carbons. The unsaturated carbon may optionally be the point of attachment of the cycloalkenyl substituent. Any ring atom can be substituted. The cycloalkenyl groups can contain fused rings. Fused rings are rings that share a common carbon atom. Examples of cycloalkenyl moieties include, but are not limited to, cyclohexenyl, cyclohexadienyl, or norbornenyl.

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

The term "heteroaryl" refers to an aromatic 5-8 membered monocyclic, 8-12 membered bicyclic, or 11-14 membered tricyclic ring system having 1-3 heteroatoms if monocyclic, 1-6 heteroatoms if bicyclic, or 1-9 heteroatoms if tricyclic, said heteroatoms selected from O, N, or S (e.g., carbon atoms and 1-3, 1-6, or 1-9 heteroatoms of N, O, or S if monocyclic, bicyclic, or tricyclic, respectively). Any ring atom can be substituted.

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

The term "acyl" refers to an alkylcarbonyl, cycloalkylcarbonyl, arylcarbonyl, heterocyclylcarbonyl, or heteroarylcarbonyl substituent, any of which may be further substituted by substituents.

The term "substituents" refers to a group "substituted" on an alkyl, cycloalkyl, alkenyl, alkynyl, heterocyclyl, heterocycloalkenyl, cycloalkenyl, aryl, or heteroaryl group at any atom of that group. Any atom can be substituted. Suitable substituents include, without limitation, alkyl (e.g., C1, C2, C3, C4, C5,

C6, C7, C8, C9, C10, C11, C12 straight or branched chain alkyl), cycloalkyl, haloalkyl (e.g., perfluoroalkyl such as CF_3), aryl, heteroaryl, aralkyl, heteroaralkyl, heterocyclyl, alkenyl, alkynyl, cycloalkenyl, heterocycloalkenyl, alkoxy, haloalkoxy (e.g., perfluoroalkoxy such as OCF_3), halo, hydroxy, carboxy, carboxylate, cyano, nitro, amino, alkyl amino, SO_3H, sulfate, phosphate, methylenedioxy (-O-CH_2-O- wherein oxygens are attached to vicinal atoms), ethylenedioxy, oxo, thioxo (e.g., C=S), imino (alkyl, aryl, aralkyl), $S(O)_n$alkyl (where n is 0-2), $S(O)_n$ aryl (where n is 0-2), $S(O)_n$ heteroaryl (where n is 0-2), $S(O)_n$ heterocyclyl (where n is 0-2), amine (mono-, di-, alkyl, cycloalkyl, aralkyl, heteroaralkyl, aryl, heteroaryl, and combinations thereof), ester (alkyl, aralkyl, heteroaralkyl, aryl, heteroaryl), amide (mono-, di-, alkyl, aralkyl, heteroaralkyl, aryl, heteroaryl, and combinations thereof), sulfonamide (mono-, di-, alkyl, aralkyl, heteroaralkyl, and combinations thereof). In one aspect, the substituents on a group are independently any one single, or any subset of the aforementioned substituents. In another aspect, a substituent may itself be substituted with any one of the above substituents.

The term "mammal" includes organisms, which include mice, rats, gerbils, cows, sheep, pigs, rabbits, goats, horses, monkeys, dogs, cats, and preferably humans.

The compounds and methods described herein can be used to treat various fungal mycoses. Mycoses that occur in humans include, without limitation, Actinomycosis, Aspergillosis, Blastomycosis, Candidiasis, Chromomycosis, Coccidioidomycosis, Cryptococcosis, Entomophthoramycosis, Geotrichosis, Histoplasmosis, Mucormycosis, Mycetoma, Nocardiosis, Paracoccidiomycosis, Phaeohyphomycosis, Pneumoscystic pneumonia, Pythiosis, Sporotrichosis, Torulopsosis, Zygomycosis, Chromoblastomycosis, eye infections (e.g., Mycotic keratitis, Endogenous oculomycosis, Extension oculomycosis), Lobomycosis, and Mycetoma. Other syndromes include nail, hair, and skin diseases such as Onychomycosis (Tinea unguium), Piedra, Pityriasis versicolor, Dermatophytosis (e.g., Tinea barbae, Tinea capitis, Tinea corporis, Tinea cruris, Tinea favosa, Tinea imbricata, Tinea manuum, Tinea nigra, Tinea pedis, and Tinea unguium), Dermatomycosis, Otomycosis, Phycomycosis, Phaeohyphomycosis, Rhinosporidiosis, and Trichomycosis. Mycoses affecting animals include, without limitation, Aspergillosis, Candidiasis, Chromomycosis, Cryptococcosis, Dermatophytosis, Entomophthoramycosis, Fungal Keratitis, Mucormycosis, Oomycosis, Pythiosis, and Torulopsosis.

Patients most at risk for fungal infections are those with impairment of neutrophil function due to decreased neutrophil production in the bone marrow, increased neutrophil destruction, or qualitative defects in neutrophil function.

Factors that can cause a decrease in neutrophil production include, but are not limited to (1) administration of cytotoxic drugs, including alkylating agents such as cyclophosphamide, busulfan, and chlorambucil, and antimetabolites such as methotrexate, 6-mercaptopurine and 5-flurocytosine; (2) administration of other drugs known to inhibit neutrophil production including, but not limited to, certain antibiotics, phenothiazines, diuretics, anti-inflammatory agents, and antithyroid drugs; (3) bacterial sepsis

infections, viral infections such as HIV, EBV or hepatitis; typhoid, malaria, brucellosis, and tularemia; (4) primary hematologic diseases resulting in bone marrow failure, as well as both hereditary syndromes and acquired defects; (5) bone marrow failure due to tumor invasion or myelofibrosis; and (6) nutritional deficiencies such as deficiency of either vitamin B12 or folate.

Factors that can cause an increase in destruction of neutrophils, thereby rendering an individual susceptible to fungal infections, include, without limitation, the presence of antineutrophil antibodies, autoimmune disease (such as Felty's syndrome, rheumatoid arthritis, or systemic lupus erythematosis), or idiosyncratic reactions to drugs that, in an idiosyncratic way, act as haptens at the surface of neutrophils, initiating immune destruction of neutrophils.

Qualitative defects in neutrophil function that can lead to increased susceptibility to fungal infections include many disease states, for example, leukocyte adhesion deficiency syndromes, neutrophil chemotactic defects, and neutrophil phagocytic and killing defects.

Neutrophil function is also compromised by administration of corticosteroids used in the treatment of a wide variety of diseases. Thus, patients treated with corticosteroids are at increased risk of fungal infections.

Additional factors increasing individual susceptibility to fungal infections include: (1) treatment with broad spectrum antibiotics, especially in the hospital setting and in Intensive Care settings in particular; (2) application of intravenous catheters, particularly central venous catheters;(3) surgical wounds, particularly those associated with intra-abdominal surgeries; (4) bone marrow or solid organ transplantation; (5) cancer chemotherapy; (6) Acquired Immune Deficiency Syndrome; (7) Intensive Care Unit stay; and (8) diabetes. In addition, neonates and aged patients are at increased risk.

The compounds described herein can be used alone or in combination with other antimicrobial compounds, including conventional antimicrobial agents such as known antifungal agents for therapeutic or prophylactic treatment of infection or potential infection. Useful antifungal compounds include fungicidal (e.g., Amphotericin) and fungistatic (e.g., Fluconazole) compounds. Whether a given agent is fungicidal or fungistatic can be dependent on the fungal species and other factors such as whether activity is measured *in vitro* or *in vivo*. Combination therapies are particularly useful for treatment of infections that respond poorly to single agent therapy and are also useful in the treatment of infections by organisms that exhibit resistance, e.g., acquired or intrinsic resistance, to one or more antifungal agents. Thus, combination therapies can be useful for treatment of infection by an organism that exhibits resistance due to either genetic changes or physiological conditions. Combination therapies are also useful in situations where an effective dose of one or more of the agents used in the combination therapy is associated with undesirable toxicity or side effects when not used in combination. This is because a combination therapy can be used to reduce the required dosage or duration of administration of the individual agents.

Moreover, the lower dosages often used in a combination therapy may reduce the incidence of acquired resistance to one or more of the agents used in the combination therapy. The individual agents used in combination can act by reducing the growth, replication, viability, invasiveness or virulence of a microbe. Moreover, one or more of the individual agents can act by simply reducing the resistance (or increasing the sensitivity) of the microbe to one or more other agents used in the combination.

Among the agents that can be used in combination therapy are polyenes (e.g., Amphotericin B, Mepartricin, Nystatin, Pimaricin, SPA-S-843), candins (e.g., Anidulafungin, Caspofungin, Micofungin, and Cilofungin, V-echinocandin), aminocandins, sordarins (e.g., Azasordarin, GM 222712, GM 237354), azoles (e.g., Azoline, Albaconazole, bal 8557, Bifonazole, Butoconazole, Clotrimazole, Croconazole, CS-758, Eberconazole, Econazole, Fenticonazole, Fluconazole, Flutrimazole, Fosfluconazole, Isoconazole, Itraconazole, Ketoconazole, Ianoconazole, Miconazole, Neticonazole, Oxiconazole, Posaconazole, PR-2699, Propenidazole, Ravuconazole, Sertaconazole, SSY-726, Sulconazole, Terconazole, Tioconazole, and Voriconazole), allylamines (e.g., Butenafine, Naftifine, Terbinafine), morpholines (e.g., amorolfine), pradimicins (e.g., BMS-181184), and other antifungals (e.g., Alpha interferon; Amantanium bromide; aminopyridine; amphotech; α-MSH (melanocyte stimulating hormone) peptide; BAY-10-8888/PLD-118; β-(1,6)-glucan synthesis inhibitors; Ciclopirox; Cyclopiroxalamine; DB-289; ECO-02301; ECO-14401; Exalamide; Flucytosine; Fumagiline; Griseofulvin; Haloprogin; Iseganan; Liranaftate; Natamycin; Nikkomycin; Siccanin; Tolciclate; Undecylenate; Zadaxin; beta-amino acids, e.g., PLD-118 or derivatives thereof).

The antifungal agent can act, for example, by blocking ergosterol synthesis (e.g., azoles or allylamines), by interfering with the cell wall (e.g., candins), by interfering with the cell membrane (polyenes) or by interfering with protein translation (e.g., sordarins).

Combination therapy can be achieved by administering two or more agents, each of which is formulated and administered separately, or by administering two or more agents in a single formulation. Other combinations are also encompassed by combination therapy. For example, two agents can be formulated together and administered in conjunction with a separate formulation containing a third agent. While the two or more agents in the combination therapy can be administered simultaneously, they need not be. For example, administration of a first agent (or combination of agents) can precede administration of a second agent (or combination of agents) by minutes, hours, days, or weeks. Thus, the two or more agents can be administered within minutes of each other or within 1, 2, 3, 6, 9, 12, 15, 18, or 24 hours of each other or within 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 12, 14 days of each other or within 2, 3, 4, 5, 6, 7, 8, 9, or 10 weeks of each other. In some cases even longer intervals are possible. While in many cases it is desirable that the two or more agents used in a combination therapy be present in within the patient's body at the same time, this need not be so.

Combination therapy can also include two or more administrations of one or more of the agents used in the combination. For example, if agent X and agent Y are used in a combination, one could administer them sequentially in any combination one or more times, e.g., in the order X-Y-X, X-X-Y, Y-X-Y, Y-Y-X, X-X-Y-Y, etc.

The antifungal agents, alone or in combination, can be combined with any pharmaceutically acceptable carrier or medium. Thus, they can be combined with materials that do not produce an adverse, allergic or otherwise unwanted reaction when administered to a patient. The carriers or mediums used can include solvents, dispersants, coatings, absorption promoting agents, controlled release agents, and one or more inert excipients (which include starches, polyols, granulating agents, microcrystalline cellulose, diluents, lubricants, binders, disintegrating agents, and the like), etc. If desired, tablet dosages of the disclosed compositions may be coated by standard aqueous or nonaqueous techniques.

Compositions of the present invention may also optionally include other therapeutic ingredients, anti-caking agents, preservatives, sweetening agents, colorants, flavors, desiccants, plasticizers, dyes, and the like. Any such optional ingredient must be compatible with the compound of the invention to insure the stability of the formulation.

The composition may contain other additives as needed, including for exanple lactose, glucose, fructose, galactose, trehalose, sucrose, maltose, raffinose, maltitol, melezitose, stachyose, lactitol, palatinite, starch, xylitol, mannitol, myoinositol, and the like, and hydrates thereof, and amino acids, for example alanine, glycine and betaine, and peptides and proteins, for example albumen.

Examples of excipients for use as the pharmaceutically acceptable carriers and the pharmaceutically acceptable inert carriers and the aforementioned additional ingredients include, but are not limited to binders, fillers, disintegrants, lubricants, anti-microbial agents, and coating agents such as:

BINDERS: corn starch, potato starch, other starches, gelatin, natural and synthetic gums such as acacia, sodium alginate, alginic acid, other alginates, powdered tragacanth, guar gum, cellulose and its derivatives (*e.g.*, ethyl cellulose, cellulose acetate, carboxymethyl cellulose calcium, sodium carboxymethyl cellulose), polyvinyl pyrrolidone, methyl cellulose, pre-gelatinized starch (*e.g.*, STARCH 1500® and STARCH 1500 LM®, sold by Colorcon, Ltd.), hydroxypropyl methyl cellulose, microcrystalline cellulose (*e.g.* AVICEL™, such as, AVICEL-PH-101™, -103™ and -105™, sold by FMC Corporation, Marcus Hook, PA, USA), or mixtures thereof,

FILLERS: talc, calcium carbonate (*e.g.*, granules or powder), dibasic calcium phosphate, tribasic calcium phosphate, calcium sulfate (*e.g.*, granules or powder), microcrystalline cellulose, powdered

cellulose, dextrates, kaolin, mannitol, silicic acid, sorbitol, starch, pre-gelatinized starch, or mixtures thereof,

DISINTEGRANTS: agar-agar, alginic acid, calcium carbonate, microcrystalline cellulose, croscarmellose sodium, crospovidone, polacrilin potassium, sodium starch glycolate, potato or tapioca starch, other starches, pre-gelatinized starch, clays, other algins, other celluloses, gums, or mixtures thereof,

LUBRICANTS: calcium stearate, magnesium stearate, mineral oil, light mineral oil, glycerin, sorbitol, mannitol, polyethylene glycol, other glycols, stearic acid, sodium lauryl sulfate, talc, hydrogenated vegetable oil (*e.g.*, peanut oil, cottonseed oil, sunflower oil, sesame oil, olive oil, corn oil and soybean oil), zinc stearate, ethyl oleate, ethyl laurate, agar, syloid silica gel (AEROSIL 200, W.R. Grace Co., Baltimore, MD USA), a coagulated aerosol of synthetic silica (Deaussa Co., Plano, TX USA), a pyrogenic silicon dioxide (CAB-O-SIL, Cabot Co., Boston, MA USA), or mixtures thereof,

ANTI-CAKING AGENTS: calcium silicate, magnesium silicate, silicon dioxide, colloidal silicon dioxide, talc, or mixtures thereof,

ANTIMICROBIAL AGENTS: benzalkonium chloride, benzethonium chloride, benzoic acid, benzyl alcohol, butyl paraben, cetylpyridinium chloride, cresol, chlorobutanol, dehydroacetic acid, ethylparaben, methylparaben, phenol, phenylethyl alcohol, phenoxyethanol, phenylmercuric acetate, phenylmercuric nitrate, potassium sorbate, propylparaben, sodium benzoate, sodium dehydroacetate, sodium propionate, sorbic acid, thimersol, thymo, or mixtures thereof, and COATING AGENTS: sodium carboxymethyl cellulose, cellulose acetate phthalate, ethylcellulose, gelatin, pharmaceutical glaze, hydroxypropyl cellulose, hydroxypropyl methylcellulose, hydroxypropyl methyl cellulose phthalate, methylcellulose, polyethylene glycol, polyvinyl acetate phthalate, shellac, sucrose, titanium dioxide, carnauba wax, microcrystalline wax, or mixtures thereof.

Antifungal agents can be administered, e.g., by intravenous injection, intramuscular injection, subcutaneous injection, or by other routes. They can be injected or otherwise introduced (e.g., via catheter or direct placement) at a site of infection or potential injection. The agents can be administered orally, e.g., as a tablet or cachet containing a predetermined amount of the active ingredient, pellet, gel, paste, syrup, bolus, electuary, slurry, capsule; powder; granules; as a solution or a suspension in an aqueous liquid or a non-aqueous liquid; as an oil-in-water liquid emulsion or a water-in-oil liquid emulsion, via a liposomal formulation (see, e.g., EP 736299) or in some other form.. Orally administered compositions can include binders, flavoring agents, and humectants. The agents can be included in dentifrices or oral washes. Thus, oral formulations can include abrasives and foaming agents. The agents can also be administered transdermally, parenterally, or in the form a suppository. They can also be administered in eyedrops.

Antifungal agents can be a free acid or base, or a pharmacologically acceptable salt thereof. Solids can be dissolved or dispersed immediately prior to administration or earlier. In some circumstances the preparations include a preservative to prevent the growth of microorganisms. The pharmaceutical forms suitable for injection can include sterile aqueous or organic solutions or dispersions which include, e.g., water, an alcohol, an organic solvent, an oil or other solvent or dispersant (e.g., glycerol, propylene glycol, polyethylene glycol, and vegetable oils). The formulations may contain antioxidants, buffers, bacteriostats, and solutes that render the formulation isotonic with the blood of the intended recipient, and aqueous and non-aqueous sterile suspensions that can include suspending agents, solubilizers, thickening agents, stabilizers, and preservatives. Pharmaceutical agents can be sterilized by filter sterilization or by other suitable means.

The agents either in their free form or as a salt can be combined with a polymer such as polylactic-glycoloic acid (PLGA), poly-(I)-lactic-glycolic-tartaric acid (P(I)LGT) (WO 01/12233), polyglycolic acid (U.S. 3,773,919), polylactic acid (U.S. 4,767,628), poly(ε-caprolactone) and poly(alkylene oxide) (U.S. 20030068384) to create a sustained release formulation. Such formulations can be used to implants that release a compound of the invention or another agent over a period of a few days, a few weeks or several months depending on the polymer, the particle size of the polymer, and the size of the implant (see, e.g., U.S. 6,620,422). Other sustained release formulations are described in EP 0 467 389 A2, WO 93/241150, U.S. 5,612,052, WO 97/40085, WO 03/075887, WO 01/01964A2, U.S. 5,922,356, WO 94/155587, WO 02/074247A2, WO 98/25642, U.S. 5,968,895, U.S. 6,180,608, U.S. 20030171296, U.S. 20020176841, U.S. 5,672,659, U.S. 5,893,985, U.S. 5,134,122, U.S. 5,192,741, U.S. 5,192,741, U.S. 4,668,506, U.S. 4,713,244, U.S. 5,445,832 U.S. 4,931,279, U.S. 5,980,945, WO 02/058672, WO 9726015, WO 97/04744, and. US20020019446. In such sustained release formulations microparticles of peptide are combined with microparticles of polymer. One or more sustained release implants can be used. U.S. 6,011,011 and WO 94/06452 describe a sustained release formulation providing either polyethylene glycols (where PEG 300 and PEG 400 are most preferred) or triacetin. WO 03/053401 describes a formulation which may both enhance bioavailability and provide controlled release of the agent within the GI tract. Additional controlled release formulations are described in WO 02/38129, EP 326 151, U.S. 5,236,704, WO 02/30398, WO 98/13029; U.S. 20030064105, U.S. 20030138488A1, U.S. 20030216307A1,U.S. 6,667,060, WO 01/49249, WO 01/49311, WO 01/49249, WO 01/49311, and U.S. 5,877,224.

The agents can be administered, e.g., by intravenous injection, intramuscular injection, subcutaneous injection, intraperitoneal injection, topical, sublingual, intraarticular (in the joints), intradermal, buccal, ophthalmic (including intraocular), intranasaly (including using a cannula), or by other routes. The agents can be administered orally, e.g., as a tablet or cachet containing a predetermined amount of the active ingredient, gel, pellet, paste, syrup, bolus, electuary, slurry, capsule, powder, granules, as a solution or a suspension in an aqueous liquid or a non-aqueous liquid, as an oil-in-water

liquid emulsion or a water-in-oil liquid emulsion, via a micellar formulation (see, e.g. WO 97/11682) via a liposomal formulation (see, e.g., EP 736299,WO 99/59550 and WO 97/13500), via formulations described in WO 03/094886 or in some other form. Orally administered compositions can include binders, lubricants, inert diluents, lubricating, surface active or dispersing agents, flavoring agents, and humectants. Orally administered formulations such as tablets may optionally be coated or scored and may be formulated so as to provide sustained, delayed or controlled release of the active ingredient therein. The agents can also be administered transdermally (i.e. via reservoir-type or matrix-type patches, microneedles, thermal poration, hypodermic needles, iontophoresis, electroporation, ultrasound or other forms of sonophoresis, jet injection, or a combination of any of the preceding methods (Prausnitz et al. 2004, Nature Reviews Drug Discovery 3:115-124)). The agents can be administered using high-velocity transdermal particle injection techniques using the hydrogel particle formulation described in U.S. 20020061336. Additional particle formulations are described in WO 00/45792, WO 00/53160, and WO 02/19989. An example of a transdermal formulation containing plaster and the absorption promoter dimethylisosorbide can be found in WO 89/04179. WO 96/11705 provides formulations suitable for transdermal adminisitration. The agents can be administered in the form a suppository or by other vaginal or rectal means. The agents can be administered in a transmembrane formulation as described in WO 90/07923. The agents can be administed non-invasively via the dehydrated particicles described in U.S. 6,485,706. The agent can be administered in an enteric-coated drug formulation as described in WO 02/49621. The agents can be administered intranassaly using the formulation described in U.S. 5,179,079. Formulations suitable for parenteral injection are described in WO 00/62759. The agents can be administered using the casein formulation described in U. S. 20030206939 and WO 00/06108. The agents can be administered using the particulate formulations described in U.S. 20020034536.

The agents, alone or in combination with other suitable components, can be administered by pulmonary route utilizing several techniques including but not limited to intratracheal instillation (delivery of solution into the lungs by syringe), intratracheal delivery of liposomes, insufflation (administration of powder formulation by syringe or any other similar device into the lungs) and aerosol inhalation. Aerosols (e.g., jet or ultrasonic nebulizers, metered-dose inhalers (MDIs), and dry-powder inhalers (DPIs)) can also be used in intranasal applications. Aerosol formulations are stable dispersions or suspensions of solid material and liquid droplets in a gaseous medium and can be placed into pressurized acceptable propellants, such as hydrofluroalkanes (HFAs, i.e. HFA-134a and HFA-227, or a mixture thereof), dichlorodifluoromethane (or other chlorofluocarbon propellants such as a mixture of Propellants 11, 12, and/or 114), propane, nitrogen, and the like. Pulmonary formulations may include permeation enhancers such as fatty acids, and saccharides, chelating agents, enzyme inhibitors (e.g., protease inhibitors), adjuvants (e.g., glycocholate, surfactin, span 85, and nafamostat), preservatives (e.g., benzalkonium chloride or chlorobutanol), and ethanol (normally up to 5% but possibly up to 20%, by weight). Ethanol is commonly included in aerosol compositions as it can improve the function of the metering valve and in some cases also improve the stability of the dispersion. Pulmonary formulations

may also include surfactants which include but are not limited to bile salts and those described in U.S. 6,524,557 and references therein. The surfactants described in U.S. 6,524,557, e.g., a C8-C16 fatty acid salt, a bile salt, a phospholipid, or alkyl saccaride are advantageous in that some of them also reportedly enhance absorption of the peptide in the formulation. Also suitable in the invention are dry powder formulations comprising a therapeutically effective amount of active compound blended with an appropriate carrier and adapted for use in connection with a dry-powder inhaler. Absorption enhancers which can be added to dry powder formulations of the present invention include those described in U.S. 6,632,456. WO 02/080884 describes new methods for the surface modification of powders. Aerosol formulations may include U.S. 5,230,884, U.S. 5,292,499, WO 017/8694, WO 01/78696, U.S. 2003019437, U. S. 20030165436, and WO 96/40089 (which includes vegetable oil). Sustained release formulations suitable for inhalation are described in U.S. 20010036481A1, 20030232019A1, and U.S. 20040018243A1 as well as in WO 01/13891, WO 02/067902, WO 03/072080, and WO 03/079885. Pulmonary formulations containing microparticles are described in WO 03/015750, U.S. 20030008013, and WO 00/00176. Pulmonary formulations containing stable glassy state powder are described in U.S. 20020141945 and U.S. 6,309,671. Other aerosol formulations are desribed in EP 1338272A1 WO 90/09781, U. S. 5,348,730, U.S. 6,436,367, WO 91/04011, and U.S. 6,294,153 and U.S. 6,290,987 describes a liposomal based formulation that can be administered via aerosol or other means. Powder formulations for inhalation are described in U.S. 20030053960 and WO 01/60341. The agents can be administered intranasally as described in U.S. 20010038824.

Solutions of medicament in buffered saline and similar vehicles are commonly employed to generate an aerosol in a nebulizer. Simple nebulizers operate on Bernoulli's principle and employ a stream of air or oxygen to generate the spray particles. More complex nebulizers employ ultrasound to create the spray particles. Both types are well known in the art and are described in standard textbooks of pharmacy such as Sprowls' American Pharmacy and Remington's The Science and Practice of Pharmacy. Other devices for generating aerosols employ compressed gases, usually hydrofluorocarbons and chlorofluorocarbons, which are mixed with the medicament and any necessary excipients in a pressurized container, these devices are likewise described in standard textbooks such as Sprowls and Remington.

The agent can be fused to immunoglobulins or albumin, or incorporated into a lipsome to improve half-life. The agent can also be conjugated to polyethylene glycol (PEG) chains. Methods for pegylation and additional formulations containing PEG-conjugates (i.e. PEG-based hydrogels, PEG modified liposomes) can be found in Harris and Chess, Nature Reviews Drug Discovery 2: 214-221 and the references therein. The agent can be administered via a nanocochleate or cochleate delivery vehicle (BioDelivery Sciences International). The agents can be delivered transmucosally (i.e. across a mucosal surface such as the vagina, eye or nose) using formulations such as that described in U.S. 5,204,108. The agents can be formulated in microcapsules as described in WO 88/01165. The agent can be administered intra-orally using the formulations described in U.S. 20020055496, WO 00/47203, and U.S. 6,495,120. The agent can be delivered using nanoemulsion formulations described in WO 01/91728A2.

Methods to increase chemical and/or physical stability of the agents the described herein are found in WO 00/04880, and WO 97/04796 and the references cited therein.

Methods to increase bioavailability of the agents described herein are found in U.S. 20030198619, WO 01/49268, WO 00/32172, and WO 02/064166. Glycyrrhizinate can also be used as an absorption enhancer (see, e.g., EP397447). WO 03/004062 discusses Ulex europaeus I (UEAl) and UEAI mimetics which may be used to target the agents of the invention to the GI tract.

Suitable pharmaceutical compositions in accordance with the invention will generally include an amount of the active compound(s) with an acceptable pharmaceutical diluent or excipient, such as a sterile aqueous solution, to give a range of final concentrations, depending on the intended use. The techniques of preparation are generally well known in the art, as exemplified by Remington's Pharmaceutical Sciences, 18th Ed., Mack Publishing Company, 1995.

A prophylactically effective amount of a compound is an amount that, in a given dosage regime, reduces the frequency or severity of infection by a fungal pathogen compared to treatment with a placebo. A therapeutically effective amount of a compound is an amount that, in a given dosage regime, results in improved therapeutic outcome (e.g., reduces manifestations or impact of infection). In the context of a combination therapy, a therapeutically effective amount is one which results in improved therapeutic outcome compared to one agent used alone. A therapeutically effective amount may also reduce the fungal bioburden within a patient and/or reduces the time to reduce the fungal bioburden to a lower level compared to treatment with a placebo and/or improves therapeutic outcome. By "fungal bioburden" is meant the number of fungal cells or spores per unit of sample (e.g., the number of cells or spores per gram of tissue). The number of cells can be determined by methods including, but not limited to, calculation of fungal biomass, PCR signal with fungal-specific primers, hybridization, histologic examination, detection of fungal metabolites or products, and plating for colony forming units. Specific methods can be more or

less applicable depending on the characteristics of the organism and the treatment. Improved therapeutic outcome can be assessed by a variety of measures including increased survival rate, reduced percentage of culture-positive body fluid samples (e.g., blood, urine, sputum), reduced rate of x-ray findings consistent with infection (e.g., chest x-ray, body CT scan), and reduced number of days with fever. Therapeutically effective doses can be determined using an animal model or via clinical studies. Experimental animals suffering from a microbial infection are often used to determine an initial therapeutic regime that can be further verified in human clinical trials according to standard testing methods. The activity of compounds *in vivo* and the likely useful dosage for human patients can be determined using various animal models including those that are described by Abruzzo et al. (Antimicrobial Agents and Chemotherapy 44:2310 (2000)); Bowan et al. (Antimicrobial Agents and Chemotherapy 45:3474 (2001)); Kirkpatrick et al. (Antimicrobial Agents and Chemotherapy 46:2564 (2002)); and Odds et al. (Antimicrobial Agents and Chemotherapy 44:3180 (2000)).

The agents described herein and combination therapy agents can be packaged as a kit that includes single or multiple doses of two or more agents, each packaged or formulated individually, or single or multiple doses of two or more agents packaged or formulated in combination. Thus, one or more agents can be present in first container, and the kit can optionally include one or more agents in a second container. The container or containers are placed within a package, and the package can optionally include administration or dosage instructions. A kit can include additional components such as syringes or other means for administering the agents as well as diluents or other means for formulation.

For agricultural uses, the compositions or agents identified using the methods disclosed herein may be used as chemicals applied as sprays or dusts on the foliage of plants, or in irrigation systems. Typically, such agents are to be administered on the surface of the plant in advance of the pathogen in order to prevent infection. Seeds, bulbs, roots, tubers, and corms are also treated to prevent pathogenic attack after planting by controlling pathogens carried on them or existing in the soil at the planting site. Soil to be planted with vegetables, ornamentals, shrubs, or trees can also be treated for control of a variety of microbial pathogens. Treatment is preferably done several days or weeks before planting. The chemicals can be applied by either a mechanized route, e.g., a tractor, or with hand applications. In addition, chemicals identified using the methods of the assay can be used as disinfectants.

In addition, the compounds described herein can be coated onto or integrated into materials used to make catheters, including but not limited to intravenous, urinary, intraperitoneal, ventricular, spinal and surgical drainage catheters, and other medical devices in order to prevent colonization and systemic seeding by potential pathogens. Similarly, the compounds described herein may be coated onto or integrated into materials that constitute various surgical prostheses and to dentures to prevent colonization by pathogens and thereby prevent more serious invasive infection or systemic seeding by pathogens.

It will be recognized that the compounds of this invention can exist in radiolabeled form, i.e., the compounds may contain one or more atoms containing an atomic mass or mass number different from the atomic mass or mass number usually found in nature. Radioisotopes of hydrogen, carbon, phosphorous, fluorine, iodine and chlorine include ^{3}H, ^{14}C, ^{35}S, ^{32}P, ^{18}F, ^{125}I and ^{36}Cl, respectively. Compounds that contain those radioisotopes and/or other radioisotopes of other atoms are within the scope of this invention. Tritiated, i.e. ^{3}H, and carbon-14, i.e., ^{14}C, radioisotopes are particularly preferred for their ease in preparation and detectability. Radiolabeled compounds of this invention and prodrugs thereof can generally be prepared by methods well known to those skilled in the art. Conveniently, such radiolabeled compounds can be prepared by carrying out the procedures disclosed in the Examples and Schemes by substituting a readily available radiolabeled reagent for a non-radiolabeled reagent.

The details of one or more embodiments of the invention are set forth in the accompanying drawings and the description below. Other features, objects, and advantages of the invention will be apparent from the description and drawings, and from the claims.

DESCRIPTION OF DRAWINGS

FIG. 1A is a table of representative compounds and anti-fungal activity data for compounds of formulas **(A)**, **(O)**, **(L)**, **(E)**, **(C)**, **(AA)**, **(AB)**, **(K)**, and **(R)**.

FIG. 1B is a table of representative compounds and anti-fungal activity data for compounds of formula **(AA)**.

FIG. 2 is a summary of representative compounds and anti-fungal activity data for compounds of formulas: **(I)**, **(II)**, **(III)**, **(IV)**, and **(V)**.

FIG. 3 is a listing of representative compounds of formula **(VI)**.

FIG. 4 is a schematic showing a synthesis of a precursor to compounds having formula **H"**.

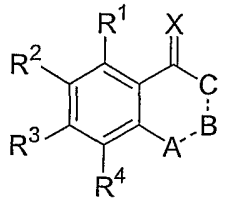
FIG. 5 is a schematic showing a synthesis of compounds having formula **H"**.

FIG. 6 is a table of representative compounds and anti-fungal activity data for compounds of formula **(VI)**.

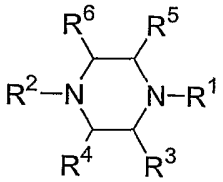
DETAILED DESCRIPTION

COMPOUNDS OF FORMULAS: (A), (O), (L), (E), (C), (AA), (AB), (K), AND (R)

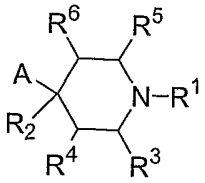
Among the compounds that can be used in practicing the invention are those that contain nitrogenous heterocyclic moieties and have one of the general formulae shown below.



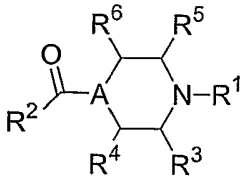
(A)



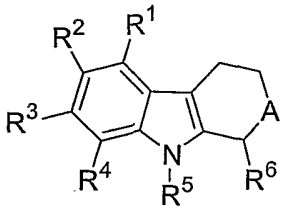
(O)



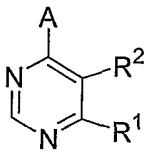
(E)



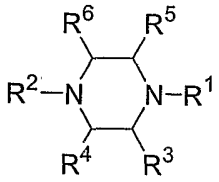
(L)



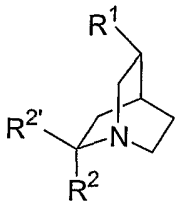
(C)



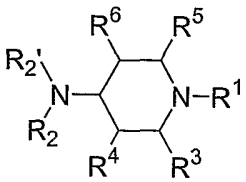
(AA)



(AB)

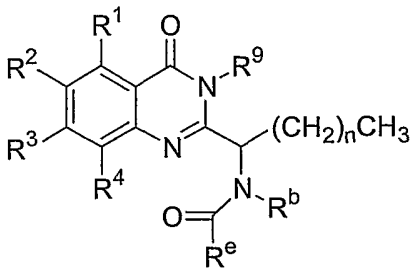


(R)



(K)

Compounds having formula (**A**) can include cyclic ("B" is present, dashed lines are bonds) or acyclic (B is absent, dashed lines are unshared electron pairs) compounds. A preferred subset of formula (**A**) compounds is represented by formula (**A-1**). One or more of R^1, R^2, R^3,



(A-1)

and R^4 may be halo, hydroxy, alkoxy, nitro, amino, cyano,carboxy, C_1-C_6 alkyl, C_6-C_{10} aryl, or 5-8 membered heteroaryl. R^e can be C_1-C_{12} alkyl, C_7-C_{16} aralkyl, C_6-C_{10} aryl, or C_6-C_{10} arylamino. Preferred R^e substituents include unbranched C_5-C_{11} alkyl, alkoxy-substituted anilino, halo-substituted benzyl, and alkyl-substituted phenyl. R^b can be $(CH_3)_2NCH_2CH_2$, benzyl, or branched or unbranched C_1-C_6 alkyl. R^9 can be phenyl, preferably substituted with halo and/or alkyl, and n can be 0-2.

Compounds having formula (**O**) may contain a substituted or unsubstituted piperazine core (e.g., with C_1-C_4 alkyl; C_1-C_4 alkoxy; or halo, preferably fluoro). R^1 and R^2 each can be C_1-C_{12} alkyl; C_7-C_{16} aralkyl; C_2-C_{12} alkenyl, optionally substituted with aryl; C_3-C_8 cycloalkyl, optionally substituted with C_1-C_4 alkyl; or $R^aC(O)$-, and all combinations of these substituents are expressly included in this invention. In certain embodiments, one of R^1 and R^2 can be aralkyl (e.g., benzyl, -$(CH_2)_2$Ph, or-$(CH_2)_3$Ph) or alkenyl (e.g., 3-phenylallyl). In other embodiments, both of R^1 and R^2 can be aralkyl, and the two aralky groups may be the same or different. In still other embodiments, one of R^1 and R^2 is aralkyl and the other is alkenyl.

Compounds having formula (**E**) may have substituted or unsubstituted C_7-C_{16} aralkyl (e.g., benzyl), substituted or unsubstituted C_6-C_{10} aryloxy, or an exocyclic double bond at C-4 of the piperidine ring. The remaining ring carbons may be substituted or unsubstituted (e.g., with C_1-C_4 alkyl; C_1-C_4 alkoxy; or halo, preferably fluoro). R^1 can be C_1-C_{12} alkyl, optionally substituted with 1-3 substituents; C_7-C_{16} aralkyl, optionally substituted with 1-3 substituents; 6-16 membered heteroaralkyl, optionally substituted with 1-3 substituents; C_2-C_{12} alkenyl, optionally substituted with 1-2 substituents; C_6-C_{10} arylsulfonyl, optionally substituted with 1-3 substituents; -$NHC(O)R^b$; or $C(O)R^c$. R^b can be C_6-C_{10} aryl or 5-8 membered heteroaryl; and R^c can be C_6-C_{10} aryl, optionally substituted with C_1-C_4 alkyl. Substituents may be the same or different and may be selected from halo; hydroxy, C_1-C_6 alkyl; C_1-C_4 alkoxy; C_6-C_{10} aryloxy, optionally substituted with halo; 5-8 membered heteroaryl, optionally substituted

with C_1-C_4 alkyl; C_6-C_{10} aryl, optionally substituted with C_2-C_6 dialkylamino or methylenedioxo; C_7-C_{16} aralkoxy; allyloxy; alkylaminocarbonyl; dialkylaminocarbonyl. Preferred R^1 substituents include C_1-C_4 alkyl, substituted or unsubstituted benzyl, or substituted or unsubstituted 6-membered heteroaralkyl, wherein the substituents are selected from C_1-C_2 alkoxy, benzyloxy, allyloxy, F, Br, $(CH_3)_2N$, CH_3, methylenedioxo, or $(CH_3)_2CHNHC(O)$-.

Compounds having formula (**L**) include 4-acyl, carboxy or alkoxycarbonyl [e.g., -C(O)OR] substituted piperidines (A = CH) or 4-acyl or alkoxycarbonyl substituted piperazines (A = N). The remaining ring carbons may be substituted or unsubstituted (e.g., with C_1-C_4 alkyl; C_1-C_4 alkoxy; or halo, preferably fluoro). R^1 can be C_1-C_{12} alkyl, C_2-C_{12} alkenyl, 5-10 membered heteroaryl, or $R^aC(O)$-, preferably R^1 is C_3-C_{10} alkenyl (e.g., $-(CH_2)_6CH=CH_2$).

Compounds having formula (**C**) may contain a cyclohexyl ring (A = CH_2) or a piperidine (A =NR^7) ring fused to the five-membered ring of the indole core. One or more of R^1, R^2, R^3, and R^4 may be halo, hydroxy, alkoxy, nitro, amino, cyano, carboxy, C_1-C_6 alkyl, C_6-C_{10} aryl, or 5-8 membered heteroaryl. R^5 can be hydrogen, optionally substituted aryl sulfonyl (e.g., *p*-tolyl), C_1-C_6 alkyl, or C_1-C_6 alkoxycarbonyl. R^6 can be hydrogen; C_1-C_6 alkylamino, optionally substituted with 1-3 substituents; C_6-C_{10} aryl, optionally substituted with 1-3 substituents; or C_5-C_{10} heteroaryl, optionally substituted with 1-3 substituents. Substituents may be the same or different and may include halo; methylenedioxo; C_6-C_{10} aryloxy, optionally substituted with halo; or C_1-C_4 alkoxy. R^7 can be hydrogen; C_7-C_{16} aralkyl, optionally substituted with 1-3 C_1-C_4 alkyl or C_1-C_4 alkoxy; or $-C(O)R^d$. R^d can be C_6-C_{10} aryl, optionally substituted with halo or C_1-C_4 alkyl; 5-8 membered heteroaryl; 3-8 membered heterocyclyl; or 5-10 membered heterocycloalkenyl. In certain embodiments, R^6 and R^7 together are 3-8 membered heterocyclyl, optionally substituted with 1-3 substituents, which may be the same or different and may include hydroxy, oxo, or C_1-C_6 alkyl.

Compounds having formula (**AA**) may contain a phenyl or thienyl ring fused to the pyrimidine ring. The fused phenyl or thienyl ring may be optionally substituted with 1-3 substituents, which may be the same or different and include halo, C_1-C_6 alkyl, fused C_5-C_7 cycloalkyl, or C_6-C_{10} aryl. A can be halo; $-NHR^3$; $-OR^4$; or C_3-C_8 heteroaryl, optionally substituted with substituted C_6 arylsulfonyl, preferably A is NR^3. R^3 and R^4 each can be C_1-C_{12} alkyl, optionally substituted with 1-3 substituents or C_7-C_{16} aralkyl, optionally substituted with 1-3 substituents. Substituents may be the same or different and may include halo, C_1-C_4 alkoxy (e.g., OCH_3), methylenedioxo, or dialkylamino (e.g., dimethylamino).

Compounds of formula (**AB**) may have one of the piperazine nitrogens attached to a 6-10 membered heteroaryl (pyridine, pyrimidine, quinoline, etc.). Any one of the ring atoms of the 6-10 membered heteroaryl may be the point of attachment. The heteroaryl group may be substituted with 1-3 substituents, which may be the same or different and include , halo; C_6-C_{10} aryl, optionally substituted with halo, hydroxy, or C_1-C_4 alkoxy; C_1-C_4 alkoxycarbonyl; or C_1-C_4 alkyl. The other piperazine nitrogen

may be unsubstituted or substituted with C_6-C_{10} arylsulfonyl, optionally substituted with halo; C_1-C_{12} alkyl; -C(O)R^b;or C_7-C_{16} aralkyl. R^b can be NHR^c; 5-10 membered heteroaryl; or C_6-C_{10} aryl, optionally substituted with 1-3 C_1-C_4 alkoxy. R^c can be C_6-C_{10} aryl and may contain 1-3 halo.

Compounds having formula (**K**) contain an amino substituent at C-4 of the piperidine ring. The remaining ring carbons may be substituted or unsubstituted (e.g., with C_1-C_4 alkyl; C_1-C_4 alkoxy; C_1-C_4 alkoxycarbonyl; or halo, prefereably fluoro). R^1 can be C_1-C_{12} alkyl, C_7-C_{16} aralkyl, or –C(O)R^a; R^a can be C_1-C_6 alkyl or C_1-C_4 alkoxy. Preferably R^1 is C_1-C_5 alkyl (e.g., methyl, ethyl, propyl, isopropyl or isobutyl) or C_7-C_8 aralkyl (e.g., benzyl or 2-phenylethyl). R^2 and $R^{2'}$ can each be hydrogen; C_1-C_6 alkyl; C_3-C_8 cycloalkyl; -C(O)R^b; substituted or unsubstituted C_7-C_{16} aralkyl; or substituted or unsubstituted 6-16 membered heteroaralkyl; R^bcan be substituted or unsubstituted aryl. All combinations of the above substituents forR^2 and $R^{2'}$ are expressly included in this invention. In certain embodiments, R^2 and $R^{2'}$ together are 3-10 membered heterocyclyl, optionally substituted with 1-5 C_1-C_4 alkyl. Substitutents may be the same or different and may include C_6-C_{10} aryl, optionally substituted with 1-3 R^d; C_6-C_{10} aryloxy, optionally substituted with 1-3 R^d; C_3-C_8 cycloalkyl-C_1-C_4 alkoxy; C_6-C_{10} arylamino, optionally substituted with 1-3 R^d; C_6-C_{10} thioaryloxy, optionally substituted with 1-3 R^d; or C_7-C_{16} aralkoxy, optionally substituted with 1-3 R^d; each R^d is, independently, halo, C_1-C_6 alkyl, C_1-C_4 alkoxy, or C_1-C_4 haloalkyl.

Compounds having formula (**R**) contain a disubstituted bicycloamino core in which a nitrogen occupies a bridgehead position. R^1 can be hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, or C_7-C_{16} aralkoxy; preferably R^1 is ethyl or vinyl. R^2 and $R^{2'}$ can each be hydrogen or CHR^3R^4. The carbon to which R^3 and R^4 is attached is a stereogenic carbon and may have either the R or the S configuration. R^3 can be C_5-C_{14} heteroaryl, optionally substituted with C_1-C_4 alkoxy; R^4 can be OR^5; and R^5 can be hydrogen, C_6-C_{14} aryl, optionally substituted with 1-3 substituents; -C(O)R^b; 6-14 membered heteroaryl, optionally substituted with 1-3 substituents; C_7-C_{16} aralkyl, optionally substituted with 1-3 substituents; R^b can be C_6-C_{10} aryl, optionally substituted with 1-3 substituents; or 5-10 membered heteroaryl, optionally substituted with 1-3 substituents. Substituents may be the same or different and may include halo, C_1-C_6 alkyl, or C_1-C_4 alkoxy.

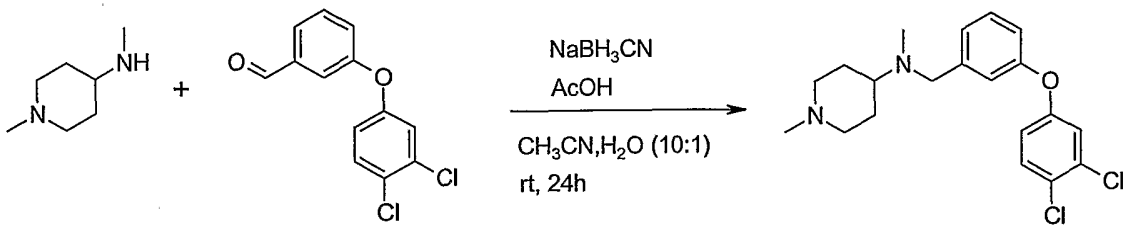
Representative compounds are provided in FIG. 1.

Combinations of substituents and variables envisioned by this invention are only those that result in the formation of stable compounds. The term "stable", as used herein, refers to compounds which possess stability sufficient to allow manufacture and which maintains the integrity of the compound for a sufficient period of time to be useful for the purposes detailed herein (e.g., therapeutic or prophylactic administration to a subject).

Compounds that can be useful in treating fungal infection can be identified through both *in vitro* (cell and non-cell based) and *in vivo* methods, for example, the method described below in Example 2

The compounds described herein can be obtained from commercial sources (e.g., Specs Biospecs, Chembridge, InterBioscreen, Maybridge, TimTec, Comgenex) or synthesized by conventional methods as shown below using commercially available starting materials and reagents. For example, compounds having formula (**K**) can be synthesized via reductive alkylation as shown in Scheme 1 below.

Scheme 1



The compounds described herein can be separated from a reaction mixture and further purified by a method such as column chromatography, high-pressure liquid chromatography, or recrystallization. As can be appreciated by the skilled artisan, further methods of synthesizing the compounds of the formulae herein will be evident to those of ordinary skill in the art. Additionally, the various synthetic steps may be performed in an alternate sequence or order to give the desired compounds. Synthetic chemistry transformations and protecting group methodologies (protection and deprotection) useful in synthesizing the compounds described herein are known in the art and include, for example, those such as described in R. Larock, *Comprehensive Organic Transformations*, VCH Publishers (1989); T.W. Greene and P.G.M. Wuts, *Protective Groups in Organic Synthesis*, 2d. Ed., John Wiley and Sons (1991); L. Fieser and M. Fieser, *Fieser and Fieser's Reagents for Organic Synthesis*, John Wiley and Sons (1994); and L. Paquette, ed., *Encyclopedia of Reagents for Organic Synthesis*, John Wiley and Sons (1995), and subsequent editions thereof.

The compounds of this invention may contain one or more asymmetric centers and thus occur as racemates and racemic mixtures, single enantiomers, individual diastereomers and diastereomeric mixtures. All such isomeric forms of these compounds are expressly included in the present invention. The compounds of this invention may also contain linkages (e.g., carbon-carbon bonds) wherein bond rotation is restricted about that particular linkage, e.g. restriction resulting from the presence of a ring or double bond. Accordingly, all *cis/trans* and *E/Z* isomers are expressly included in the present invention. The compounds of this invention may also be represented in multiple tautomeric forms, in such instances; the invention expressly includes all tautomeric forms of the compounds described herein, even though

only a single tautomeric form may be represented (e.g., alkylation of a ring system may result in alkylation at multiple sites, the invention expressly includes all such reaction products). All such isomeric forms of such compounds are expressly included in the present invention. All crystal forms of the compounds described herein are expressly included in the present invention.

The compounds of this invention include the compounds themselves, as well as their salts and their prodrugs, if applicable. A salt, for example, can be formed between an anion and a positively charged substituent (e.g., amino) on a compound described herein. Suitable anions include chloride, bromide, iodide, sulfate, nitrate, phosphate, citrate, methanesulfonate, trifluoroacetate, and acetate. Likewise, a salt can also be formed between a cation and a negatively charged substituent (e.g., carboxylate) on a compound described herein. Suitable cations include sodium ion, potassium ion, magnesium ion, calcium ion, and an ammonium cation such as tetramethylammonium ion. Examples of prodrugs include esters and other pharmaceutically acceptable derivatives, which, upon administration to a subject, are capable of providing active compounds.

The compounds of this invention may be modified by appending appropriate functionalities to enhance selected biological properties. Such modifications are known in the art and include those which increase biological penetration into a given biological compartment (e.g., blood, lymphatic system, central nervous system), increase oral availability, increase solubility to allow administration by injection, alter metabolism and alter rate of excretion.

The invention will be further described in the following examples. It should be understood that these examples are for illustrative purposes only and are not to be construed as limiting this invention in any manner.

EXAMPLE 1

Depicted in FIG. 1A are examples of several compounds having formula **A**, several compound having formula **O**, several compounds having formula **L**, several compounds having formula **C**, several compounds having formula **AA**, several compounds having formula **AB**, several compounds having formula **R**, and several compound having formula **K**. The various compounds are inhibitors of fungal invasion. The activity of the compounds in various assays of fungal invasion and mammalian cell toxicity was measured as described below in Example 2 and the results are presented in FIG. 1A. Thus, results are reported for the following tests: *C. albicans HWP1*-lacZ Reporter logarithmic phase growth invasion assay (column 2), *C. albicans HWP1-lacZ* Reporter stationary phase growth invasion assay (column 3), *C. albicans* MIC_{growth} assay (column 4), *C. albicans* morphology assay (no units) (column 5), and mammalian cell toxicity (column 6). FIG. 1B depicts additional compounds within formula (**AA**). The structure of each compound is shown in the first column and the activity of the compound in the *C. albicans HWP1-lacZ* Reporter logarithmic phase growth invasion assay is shown in the second column.

EXAMPLE 1-A

Representative Synthesis of Compounds Having Formula (K)

1-Methyl-4-(methylamino)piperidine (500 mg, 3.90mmol, 1.2 eq.) was dissolved in acetonitrile (5 mL). To the resulting solution was added glacial acetic acid (1.94 mL, 32.5 mmol, 10eq.) followed by 3-(3,4-dichloropheneoxy) benzaldehyde (868 mg, 3.25 mmol, 1.0 eq.) and sodium cyanoborohydride (612 mg, 9.75 mmol, 3.0 eq.). After initial dissolution of all reactants the reaction mixture was stirred until a fine colorless precipitate started to form. Water (0.5mL) was added to redissolve the colorless solid. The reaction mixture was then stirred at room temperature for 24h.

1N NaOH (20 mL) was added and the reaction mixture was stirred at room temperature for 15 min., before being extracted with dichloromethane (3x40 mL). The combined organic layers were washed with brine (20 mL) and dried over $MgSO_4$. Volatiles were removed *in vacuo* and the oily residue was purified by flash column chromatography (CH_2Cl_2: MeOH 20:1 to CH_2Cl_2: MeOH 10:1, 0.5% NH_4Cl). After concentration the product was obtained as a colorless oil (899 mg, 2.37 mmol, 73%). ^1H NMR ($CDCl_3$/300MHz): 7.35 (d, 1H, J = 9.0 Hz), 7.28 (t, 1H, J = 7.7 Hz), 7.11 (brd, 1H), 7.05 (d, 1H, J = 3.2 Hz), 7.03-6.99 (m, 1H), 6.89-6.84 (m, 1H), 6.84 (dd, 1H, J = 9.0, 3.2 Hz), 3.56 (s, 2H), 2.93 (brd, 2H, J = 11.7 Hz), 2.48-2.33 (m, 1H), 2.28 (s, 3H), 2.20 (s, 3H), 2.01-1.92 (m, 2H), 1.81-1.60 (m, 4H). LRMS m/z 380 (M+H).

EXAMPLE 2

Described below are various assays for measuring anti-invasin activity and the effect of compounds on cell growth. These assays are useful for assessing the compounds described herein and related compounds.

HWP-lacZ Reporter Assay (logarithmic phase growth)

The expression of the *HWP1* gene has been correlated with invasion in *C. albicans* and thus can be used as a marker for invasion. Fusion of the *HWP1* promoter with *lacZ* provides an easy assay to measure the potential anti-invasin effects of test compounds.

Briefly, stock cultures for use in this assay are prepared by streaking *C. albicans* (MC295: *ura3 Δ::imm434/ura3Δ::imm434 arg4::hisG/arg4::hisG his1::hisG/HIS1 HWP1::HWP1p-lacZ(URA3)/HWP1 gal1::ARG4/GAL1*) cells on a YPD plate. The cells are grown at 30°C for 14-18 hr and an isolated colony is picked and inoculated into a 250 ml Erlenmeyer flask containing Non-Inducing Media (NI) (per

liter: 1.5 g yeast nitrogen base w/o amino acids or ammonium sulfate, 5 g ammonium sulfate, 0.2mmol Inositol, 50 ml of 40% glucose, 120 ml of 0.5M succinate, pH adjusted to 4.5) that is sterilized by passing it through a 0.22 μm filter. The flask is placed on a rotary shaker at 30°C between 200-250 rpm, for 14-18 hr. The optical density at 600 nm (OD_{600}) is determined using NI media as a blank. The overnight culture is diluted with 15% glycerol to a final OD_{600} of 0.1 and aliquotted into 1 ml sterile cryonic tubes that are capped and stored at –80°C.

To prepare assay cultures, approximately 350 μl of thawed *Candida albicans* (MC295) stock is inoculated into a flask containing 50 ml of NI medium. In addition, 1/1 (vol/vol) serial dilutions are made into two additional flasks, each containing 25 ml of NI medium. The flasks are placed on a rotary shaker at 30 °C between 200-250 rpm, for 14-18 h. At the end of the growth period, the OD_{600} for each culture is determined using NI medium as a blank. The flask containing cells at an OD_{600} of 0.8-1.0 is transferred to a 50 ml Falcon tube and centrifuged 5 minutes at 2000 rpm. The supernatant is discarded and the pellet is resuspended in an equal volume of Inducing Media. The washed cells are immediately used as a 10X stock for the *HWP1-lacZ* reporter assay. To prepare an assay culture, 10 μl of 10X cell stock is added to 80 μl of Inducing Media (per liter: 1.5 g yeast nitrogen base w/o amino acids or ammonium sulfate, 5 g ammonium sulfate, 0.2 mmol Inositol, 50 ml of 40% glucose, 50 ml of 1M MOPS, pH adjusted to 7.5 with 1N NaOH) and 10 μl of 10X test compound stock or, as a control, DMSO, in a Corning, tissue culture treated, flat-bottom, microtiter plate. The plate is incubated at 37°C for 3 hr. Expression of the *HWP1-lacZ* reporter is assessed by measuring β-galactosidase activity with a fluorogenic substrate. Briefly, MUG stock (54 mg/ml 4-methylumbelliferyl beta-D-galactoside in DMSO) is diluted to 0.4 mg/ml in Z buffer (per liter: 16.1 g $Na_2HPO_4 \cdot 7H_2O$), 5.5 g $NaH_2PO_4 \cdot H_2O$, 0.75g KCl, 0.246 g $MgSO_4 \cdot H20$, 100mg of sodium deoxycholic acid, 200mg of CTAB, 1.62 ml beta-mercaptoethanol, pH 7.0) to create MUG/Z solution.

To initiate the reaction 100 μλ of MUG/Z solution is added to each test well (final MUG concentration of 0.2 mg/ml) and the plate is incubated at 22°C for 1 hr. The reaction is quenched with 60 μl of 1 M sodium bicarbonate and fluorescence is measured using a Spectromax Gemini Fluorometer (Excitation 360 nm, Emission 449 nm). Negative and positive controls are used in each experiment. DMSO treated cells define the maximal level of reporter induction ("no drug control") while cells treated with 15 μg/ml amphotericin B (AMB) mimic the effect of complete inhibition of reporter induction. Inhibition of reporter expression is calculated using the formula: % inhibition = $(1-(F[449]_{\text{test compound}} - F[449]_{\text{AMB control}})/(F[449]_{\text{DMSO control}} - F(449)_{\text{AMB control}})*100$. The IC_{50} is determined for each compound of interest.

HWP-lacZ Reporter Assay (stationary phase growth)

This assay is similar to the *HWP-lacZ* Reporter Assay (logarithmic phase growth) assays described above, except that the assay takes place when the cells are in the stationary phase.

Briefly, stock cultures for use in this assay are prepared by streaking *C. albicans* (MC-295: *ura3Δ::imm434/ura3Δ::imm434 his1::hisG/his1::hisG arg4::hisG/arg4::hisG his1::hisG/+ HWP1/HWP1p-lacZ(URA3) gal::ARG4/GAL*) cells for isolation on a YPD agar plate. The cells are grown at 30°C for 14-18 h, and an isolated colony is added to 5 mL of YPD broth and grown on a roller drum (60 rpm) for 14-18 h at 30°C. Stocks are prepared by aliquotting 600 µL of culture into 1 mL of 25% glycerol. The stocks are stored at –80°C.

Cultures for assays are prepared by streaking frozen culture stock on a YPD agar plate and growing the cells for 30 °C for 14-18 h. A single colony is inoculated into 5 mL of YPD in a test tube and grown on a roller drum (60 rpm) for 2 days at 30°C to late stationary phase (OD_{600} ~ 30). For the assay, the primary cell suspension stock is diluted to an OD_{600} of 1.0 (~$2x10^7$ cells/mL) to make a 10X stock.

To prepare an assay culture, 10 µL of 10X cell stock is added to 80 µL of Inducing Media (see below) and 10 µL of 10X test compound stock or, as a control, DMSO in a Corning, tissue-culture treated, flat-bottom, microtiter plate. The plate is incubated at 37°C for 3 h. To measure invasion activity, β-galactosidase activity is determined using MUG. Briefly, MUG stock is diluted to 0.4 mg/mL in Z buffer to create MUG/Z solution (see below). To initiate the reaction 100 µL of MUG/Z solution is added to each test well (final MUG concentration of 0.2 mg/mL) and the plate is incubated at 22 °C for 1 h. The reaction is quenched with 60 µL of 1 M sodium bicarbonate and fluorescence is measured using a Spectromax Gemini Fluorometer (Excitation 360 nm, Emission 449 nm). Inhibition of invasion is calculated using the formula: %inhibition = $(1-((\text{unknown})_{ave}-(\text{positive drug control})_{ave})/((\text{no drug control})_{ave}-(\text{positive drug control})_{ave}))*100$.

Growth Inhibition Assay (MIC_{growth} assay)

The minimum growth inhibitory concentration for an antifungal drug MIC_{growth} is assessed using a standardized protocol that is described by NCCLS (method M27-A). Briefly, MC305 (ATCC 90028) is streaked from a glycerol stock onto a YPD plate. Cells are incubated for 24 hr at 35°C. Five isolated colonies are picked and resuspended in 5 ml of 0.85 % saline. A hemocytometer is used to verify that this is a yeast stock suspension of 1-5 x 10^6 cells/ml. Cells are then diluted in RPMI 1640 to obtain 1-5 x 10^5 (20X) cells/ml stock (this is the adjusted 10x inoculum). The RPMI 1640 media (with glutamine, without bicarbonate and with a pH indicator) media is made by dissolving 10.4 g powdered medium in 900-ml dH_2O and 34.53 g MOPS are added (to a final concentration of 0.165 M). While stirring, the pH is

adjusted to 7.0 at 25° using 1 N NaOH and 45 ml of 40% dextrose is added to give a 2 % final concentration. Finally, the volume is adjusted to 1 liter and the media is filter sterilized and stored at 4°C.

Test compounds are diluted from 100 mM to 6.4 mg/ml (100X) stock in DMSO in triplicate. All subsequent series of 2x dilutions are performed in DMSO. Aliquots can be kept 6 months at –80 °C. The test compound should be in DMSO at room temperature for several hours before the test. The final DMSO is concentration is 1% for the test compound solution and the compound control.

A series of 2-fold test compound dilutions are tested (e.g., 64, 32, 16, 8, 4 , 2, 1, 0.5, 0.25, and 0.125 µg/ml) along with a "no test compound control" and a "no cells" control. The testing is performed in a 96 well plate. Each well contains: 2 µl of 100x-test compound stock; 163 µl of RPMI 1640, 25 µl of Alamar Blue (Biosource; Catalog Number DAL1100); 10 µl of the adjusted inoculum (yields about 500-2500 cells/well) (except for the "no cells" control). The plate is incubated in a moist chamber for 24 hr at 35°C. MIC_{growth} is defined as the lowest concentration of an antifungal that substantially inhibits growth of the organism as detected visually. Various known anti-fungal drugs can be used as additional controls as indicated below.

Antifungal Drug	Expected MIC_{growth} for ATCC 90028	Range of test concentrations
Amphotericin B	0.5-2.0 µg/ml	0.0313-16 µg/ml
Fluconazole	0.25-1.0 µg/ml	0.125-64 µg/ml
5FC	0.5-2.0 µg/ml	0.125-64 µg/ml
Ketoconazole		0.0313-16 µg/ml
Itraconazole		0.0313-16 µg/ml

Morphology Assay

Invasion can be associated with dramatic morphological transitions. In the case of *C. albicans*, this is the transition from yeast form cells in non-inducing media to filamentous forms in inducing media. This analysis can be performed using a variety of *C. albicans* strains but MC303 (*ura3 Δ::imm434/ura3Δ::imm434 arg4::hisG/arg4::hisG ade2::URA3:pTEF1-lacZ/ADE2 his1::hisG/HIS1 gal1::ARG4/GAL1*) or its closely related strains are preferred as they perform very reproducibly in this

assay. MC303 *C. albicans* is streaked from a frozen cell stock onto a YPD plate and incubated at 30°C for 14-18 h. A single colony is inoculated into 5 ml of YPD in a test tube and grown on a roller drum (60 rpm) for 2 days at 30°C to stationary phase (OD_{600} ~ 30). Cells are pelleted and washed with water and can be stored at 4°C for up to 2 weeks before use. For the assay, this stock is diluted to $2.5x10^5$ cells/ml to make a 10X stock. Next, 10 µl of this cell stock is added to 80 µl of Inducing Media and 10 µl of 10X compound stock or DMSO in a Corning, tissue culture treated, flat-bottom, microtiter plate. The plate is incubated at 37°C for 24 hr without agitation. Each well is observed microscopically and cells are scored on a scale of 1-5 with regard to cellular morphology. A score of 5 indicates that *C. albicans* cells have many long hyphae and is the wild type (WT) phenotype (no drug control). A score of 1 indicates cells are non-hyphal with only "yeast-like" cells and budding cells. Scores of 2, 3, and 4 indicate shorter length or reduced quantity of hyphae when compared with WT (a score of 2 being very near non-hyphal and a score of 4 being close to WT. Compounds that result in a phenotypic score of 1 or 2 at a given concentration are considered to have significant anti-invasin properties. The $MIC_{invasion}$ is defined in this assay as the minimum concentration of test compound that results in a phenotypic score of 1 or 2.

Mammalian cell toxicity assay

To investigate the toxicity of for mammalian cells, human hepatoma cell line HepG2 are exposed to a compound and the (LD_{50}) was determined. Briefly, HepG2 human hepatoma cells (American Type Culture Collection, Bethesda MD) are plated at 1 x 10^5 cells/well in tissue culture treated 96 well plates and incubated at 5% CO_2, 37 °C for 18 h prior to initiation of the assay. The compound stocks at 100 mM in DMSO are added to DM (defined media, media without serum with added insulin, selenium and transferrin) at an initial concentration of 1000 μM and serially diluted 1 to 3 in DM in a 96 well plate. For 20 μL of a test solution, 3.5 μL sample is added to 346.5 μL media for an initial concentration of 1000 μM. These dilutions are added to the cells at final sample concentrations between 0.5 and 1000 μM (≤ 1% DMSO). Controls included: media only (negative control) and 0.1% Triton-X (positive control). Control drugs (tamoxifen and 2-thiouracil) are also used to verify each assay. The samples are incubated at 37 °C in humidified 5% CO_2 atmosphere for 4 h. Next, sterile Alamar Blue solution (final 0.5% w/v) is added to each well and the cells were incubated at 37 °C in 5% CO2 for at least 3 h. The plate is read directly on the Tecan Spectrafluor Plus reader in the fluorescent mode at excitation 530 nm and emission 595 nm. The blank is subtracted from the total fluorescence to give the net fluorescence for that well. This total is compared to the control in the absence of the compound. An LD50 (concentration at 50% of lethal dose) is calculated as the concentration that leads to a response of 50% compared to the control cells. Thus, cytotoxicity is measured as percent of inhibition of cell viability as determined by the Alamar Blue assay. The expected LD50 ranges of the two control drugs are as follows: tamoxifen, LD50=30-80 μM and 2-thiouracil, LD50 >1000 μM.

Plastic Adherence Assay

Invasion is often associated with changes in cell adherence properties. A straightforward method to assess this behavior *in vitro* is to measure the ability of *C. albicans* to adhere to plastic surfaces in the presence and absence of a potential anti-invasin compound. Stocks of *C. albicans* (MC295) are prepared by growing strains 48 hrs in YPD at 30°C with shaking. Cells are pelleted by centrifugation and diluted in sterile water to an OD_{600} of 1.0. This stock is stored at 4°C until ready for use (up to one week). To perform the assay, the following reagents are mixed in individual wells of a 96 well plate: 85μl of RPMI media, 5 μl of test compound (diluted in 25mM HEPES buffer, pH 7.5), and 10 μl of stock *C. albicans* cells. Plates are incubated at 37°C overnight to allow time for adherence. Non-adherent cells are removed by washing with 150 μl of water using an M384 Atlas platewasher; program: Dispense Height: 150; Dispense Rate: 1; Dispense Orientation X/Y/Z: 0/0/0, Aspiration Height: 50, Aspiration Rate: 2; Aspiration Orientation X/Y/Z: 0/0/0; Method: 96 wells, 1x). Cell adherence is quantified by measuring OD_{600} of each well. Percent inhibition of adherence is calculated as: [1-(OD_{600} of well containing the test compound/OD_{600} of DMSO treated control well)]*100. Percent inhibition values of greater than 80% were scored as significantly inhibited. Due to the nature of this assay, compounds that inhibit growth at a

given concentration falsely score positive in the adherence assay. These false positives can be readily identified by a variety of secondary assays including the MIC_{growth} analysis described below. The $MIC_{invasion}$ is defined in this assay as the minimum concentration of test compound that results greater than 80% inhibition of adherence as defined above.

Invasion into Agar Substrate Assay

Invasion into agar substrates can be used as an *in vitro* surrogate to mimic the process of fungal invasion *in vivo*. This assay can be performed in high throughput with many *C. albicans* isolates or to test the response of specific strains to many different potential anti-invasin compounds. *C. albicans* strain MC12 (SC5314) is a well-studied clinical isolate that performs very robustly in this assay. MC12 is inoculated into each well of a 96-well plate containing 150 µl YPD/well and grown overnight (12-18 hrs) on an orbital shaker at 30°C. Cells are serially diluted (1:10) into fresh YPD and plated in 5 µl droplets (in a grid formation) on YPD plates with and without test compound. Plates are incubated at 37°C for 4 days and scored for the invasion response. To distinguish cells that have invaded into the agar from those growing on the surface, plates are washed under a stream of tap water and non-invaded cells are removed by rubbing gentle, manual rubbing. In the absence of an anti-invasin compound, masses of filaments are readily observable below both isolated colonies and dense patches of cells. Anti-invasin compounds block the ability of *C. albicans* to invade the agar and therefore only isolated cells, clumps of cells, or occasional filaments are observed on plates containing anti-invasin compounds. This assay can be influenced by position on the plate and, consequently, the most reproducible results are obtained when comparing colonies in similar relative plate positions and in regions of similar colony density. This assay can be used to score both MIC_{growth} and $MIC_{invasion}$ on solid media. MIC_{growth} is defined as the minimum concentration of a test compound necessary to dramatically inhibit growth on the plate. $MIC_{invasion}$ is defined as the minimum concentration of test compound necessary to significantly reduce the number of invaded cells.

Migration Across Caco-2 Monolayer Assay

A key aspect of fungal pathogenesis is the invasion of fungal cells across the epithelial and endothelial cell barriers. An *in vitro* system to mimic this has been described by Weide and Ernst (*Mycoses* (1999), 42, (SUPPL. 2), 61-67). Caco-2 monolayers are prepared by seeding cells in 6-well culture dishes containing removable porous inserts (3µm pore diameter). Caco-2 cells are grown in media consisting of Dulbeccos Modified Eagle Media (DMEM) (lacking glutamine and sodium pyruvate) supplemented with 4.5 g/l glucose, 20% fetal calf serum (heat inactivated), 292 mg/ml glutamine, 1% non-essential amino acids, and 1 mM sodium pyruvate. 2 ml of growth media is added to both the upper and lower compartments and replaced every 2-3 days. Plates of cells are maintained at 37°C, 5% CO_2, 95% humidity for 10-25 days to generate confluent monolayers of differentiated Caco-2 cells. Immediately prior to addition of *C. albicans*, Caco-2 media is removed, cells are washed once with PBS,

and fresh Caco-2 culture media (without fetal calf serum) is added. *C. albicans* cells of the strain MC12 are grown overnight in YPD, pelleted, and washed once in sterile water. C. *albicans* are added to each test well +/- compound at a final concentration of 2 x 10^6 *C. albicans* cells/ml. *C. albicans* and Caco-2 cells are co-cultured for up to 24 hrs (37°C, 5% CO_2, 95% humidity). Migration across the Caco-2 monolayer is assessed by detection of *C. albicans* in the lower compartment (collected by washing and centrifugation to concentrate). Cells that are able to invade can be readily detected in the lower compartment within 12-24 hrs while *C. albicans* that are inhibited by an effective dose of anti-invasin are trapped within the upper compartment only. The $MIC_{invasion}$ in this assay is defined in this assay as the minimum concentration of test compound that completely inhibits migration of *C. albicans* across the Caco-2 monolayer after incubation for 24 hrs.

Effectiveness of Inhibitors of Fungal Invasion *In Vivo*

A mouse model of fungal invasion is used to examine the *in vivo* efficacy of a test compound in reducing invasion by *C. albicans*. This can be done in several ways. Two specific variations are described below.

Method 1 (IP administration): Thirty min prior to infection (t = -30 min), 1 mg of a test compound in buffer (10 treatment mice) or buffer only (10 control mice) is administered IP. At t=0 all mice are inoculated with 2x10^6 *C. albicans*. At t=6 h and t=14 h the IP treatment with a test compound or buffer is repeated. In addition, at t=2, t=4h, t=10 h, and t=18 h 1 mg of a test compound or buffer only is administered orally. The mice are sacrificed at about t=19h and the kidneys of the mice are examined for histologic signs of fungal invasion by counting the number of lesions.

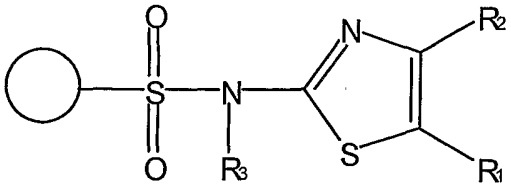
Method 2 (oral administration): Alternatively, one day prior to infection (t = -24 h) mice are switched to a powdered diet supplemented a test compound (treatment mice) or no supplement (control mice). This diet is continued until the mice are sacrificed at t=48 h. The kidneys of the mice are then examined for histologic signs of fungal invasion. In the scoring system used, a score of 5 indicates the presence of many, large fungus-dominated lesions, a score of 3 indicates the presence of many inflammatory lesion and fungus-dominated lesion of mixed size, and a score of 1 indicates few, mainly inflammatory lesions.

COMPOUNDS OF FORMULAS: (I), (II), (III), (IV), and (V)

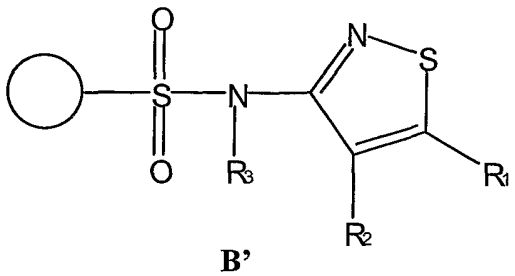
The compounds of formulas **(I)**, **(II)**, **(III)**, **(IV)**, and **(V)** are thiazolesulfonamide and isothiazolesulfonamide-based inhibitors of fungal invasion. They can be represented by the general formulas **A'** and **B'** respectively. Compounds of formula **A'** contain a substituted or unsubstituted phenyl or thienyl sulfonamide group at C-2 of the thiazole ring, while compounds of formula **B'** contain a

substituted or unsubstituted phenyl or thienyl sulfonamide group at the C-3 position of the isothiazole ring.

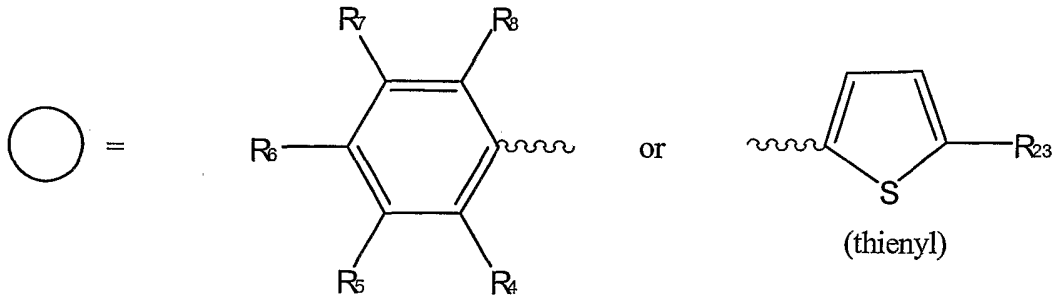
Representative compounds are provided in FIG. 2.



A'



B'



(phenyl) (thienyl)

Combinations of substituents and variables envisioned by this invention are only those that result in the formation of stable compounds. The term "stable", as used herein, refers to compounds which possess stability sufficient to allow manufacture and which maintains the integrity of the compound for a sufficient period of time to be useful for the purposes detailed herein (e.g., therapeutic or prophylactic administration to a subject).

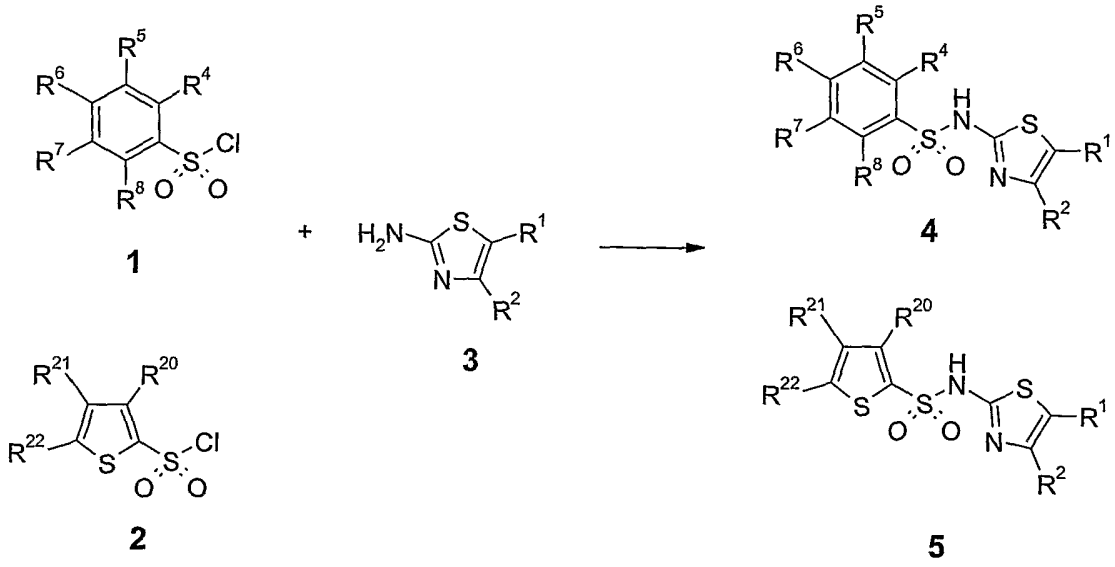
Fungus inhibiting compounds can be identified through both *in vitro* (cell and non-cell based) and *in vivo* methods. A description of these methods is described in the Examples.

Synthesis of Thiazole Compounds

Compounds of formula **A'** can be prepared as shown in Scheme 2 by the reaction between a 2-aminothiazole **3** with either a phenylsulfonyl chloride **1** or a thienylsulfonyl chloride **2**. The reaction is typically run in the presence of a base (e.g., aqueous sodium hydroxide or a tertiary amine) to scavenge

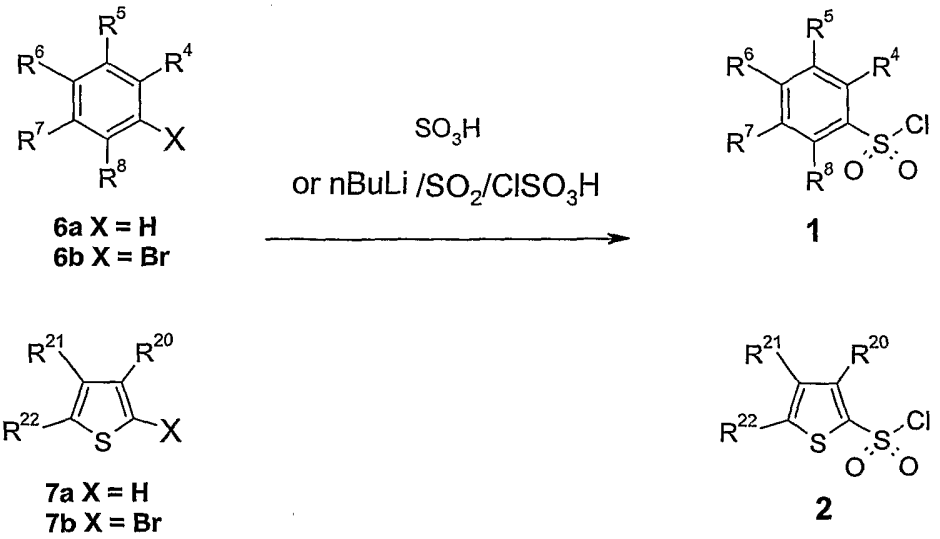
the HCl by-product. The resulting sulfonamides **4** and **5** can be obtained in moderate to good yields. The 2-aminothiazoles are commercially available (e.g., Aldrich Chemical, Milwaukee, WI) or may be synthesized by the method of Kulkarni et al.(See Kulkarni, K. D.; Shirsat, M. V., "Chemistry of the thiazoles-synthesis of 2-amino-5-alkylthiazoles," *J. Sci. and Ind. Research (India)* 1959, *18B*, 411-13). In general, all or some of the substituents (R^1, R^2, R^4, etc.) desired in the final sulfonamide product may also be present in the reactants **1**, **2**, and/or **3** when the amine-sulfonyl chloride coupling reaction takes place.

Scheme 2



The sulfonyl chlorides **1** and **2** in turn can be prepared by methods that are within skill of the art. For example, compound **1** can be obtained by the direct chlorosulfonation of an aromatic compound e.g., **6a** (X = H), with excess chlorosulfonic acid (Scheme 3). This method can also be used for the preparation of **2** when thiophene **7a** is employed as the starting material (X = H) (Scheme 3). Alternatively, sulfonyl chlorides **1** and **2** can be prepared from the corresponding bromo compounds **6a** and **6b** (X = Br). For example, metallation of bromides **6a** and **6b** with *n*-butyllithium, followed by the sequential addition of sulfur dioxide and sulfuryl chloride, can also afford aromatic and heteroaromatic sulfonylchlorides **1** and **2**.

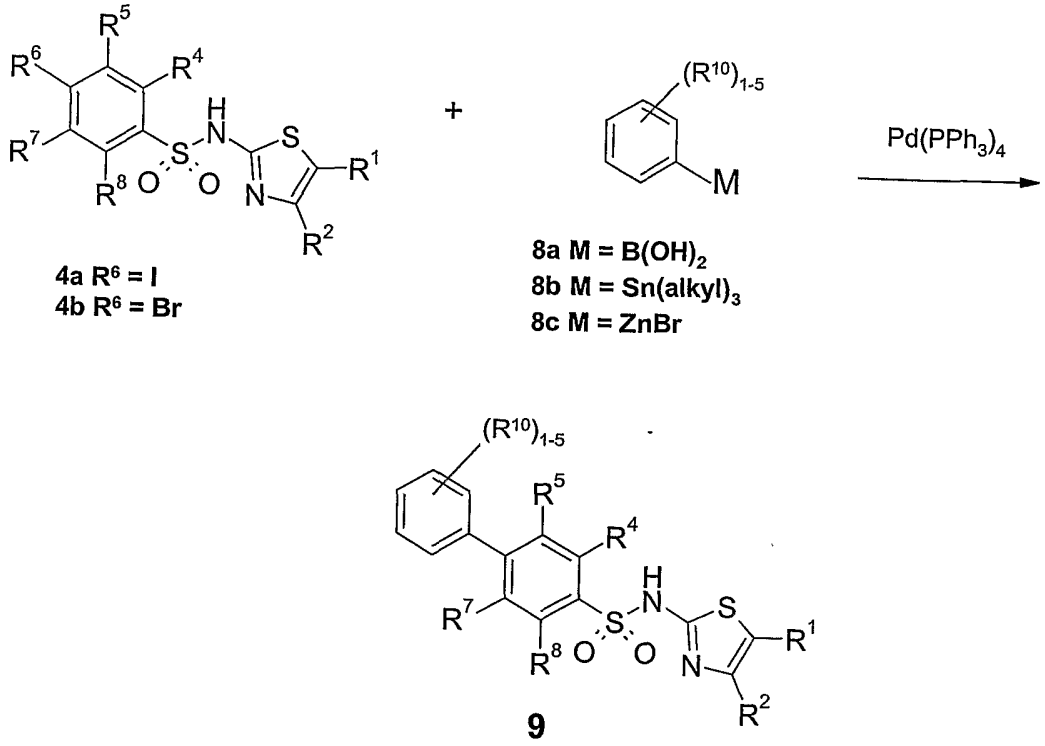
Scheme 3



In compound **4**, when R^6 is a leaving group (e.g., halo, triflate, mesylate, nosylate, etc.), it is possible to replace the leaving group with another substituent.

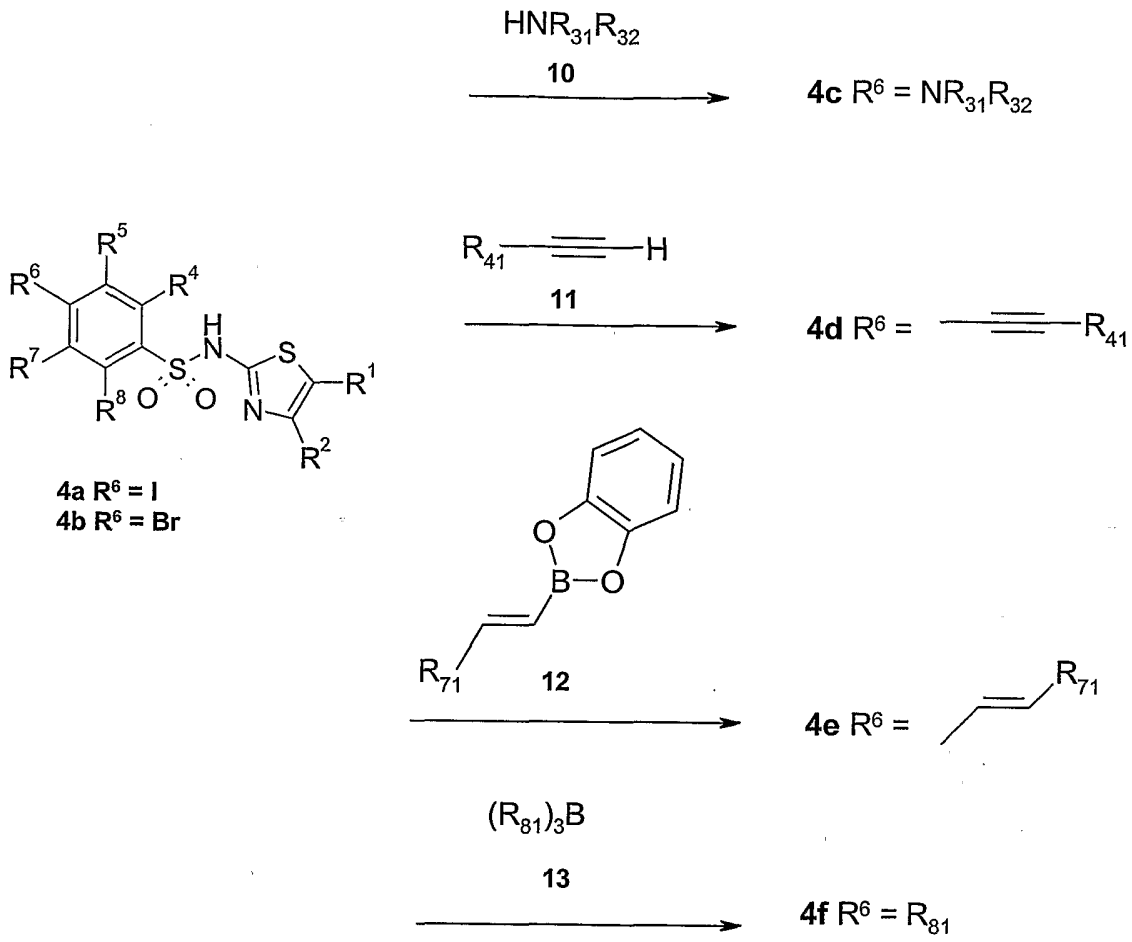
For example, exposure of **4a** or **4b** (R^6 = I or Br respectively) to an aryl boronic acid e.g., **8a**, an aryl stannane e.g., **8b**, or an aryl zinc halide e.g., **8c**, in the presence of a palladium catalyst [e.g., $Pd(PPh_3)_4$ or $PdCl_2(dppf)$] can result in the production of biphenyl derivatives e.g., **9** (Scheme 4). The reaction may be carried out in the presence of a base (e.g., K_2CO_3 or triethylamine). The transformation may also be conducted with heteroaromatic coupling partners (e.g., thiophene, pyridine, furan, etc.) bearing boronic acid, trialkyltin, and halozinc substituents. Metal catalyzed coupling reactions are described in: Herrmann, Wolfgang A. The Suzuki cross-coupling. *Applied Homogeneous Catalysis with Organometallic Compounds* (2nd Edition) (2002), 1 591-598 (boronic acid cross couplings); Hassan, Jwanro; Sevignon, Marc; Gozzi, Christel; Schulz, Emmanuelle; Lemaire, Marc. Aryl-Aryl Bond Formation One Century after the Discovery of the Ullmann Reaction. *Chemical Reviews* (2002), 102(5), 1359-1469 (trialkyltin cross couplings); and Negishi, Ei-Ichi; Liu, Fang. Palladium- or nickel-catalyzed cross-coupling with organometals containing zinc, magnesium, aluminum, and zirconium. *Metal-Catalyzed Cross-Coupling Reactions* (1998), 1-47 (organozinc cross couplings).

Scheme 4

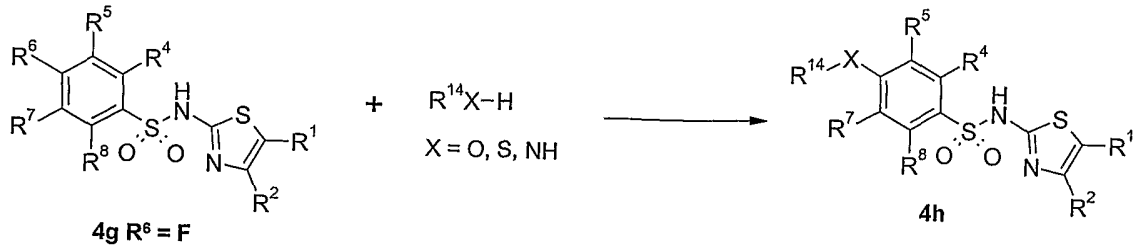


As shown in Scheme 5, palladium-catalyzed coupling of **4a** or **4b** with (i) an amine **10**, (ii) an alkyne **11**, (iii) an *E*-vinyl borinate ester **12**, or (iv) a trialkyl borane **13** can afford compounds **4c**, **4d**, **4e**, and **4f**, containing an amino group, an alkynyl group, an alkenyl group, and an alkyl group respectively at R^6. The coupling reactions shown in Scheme 5 are described in M. H. Ali, S.L. Buchwald, *J. Org. Chem.* 2001, *66*, 2560-2565, and J. P. Wolfe, H. Tomori, J. P. Sadighi, J. Yin, S. L. Buchwald *J. Org. Chem.* 2000, *65*, 1158-1174 (amines); W. G. B. van Henegouwen, R. M. Fieseler, F. P. J. T. Rutjes, H. Hiemstra, *Angew. Chem. Int. Ed. Engl.* 1999, *38*, 2214, and G. Esteban, M. A. Lopez-Sanchez. M. E. Martinez, J. Plumet *Tetrahedron* 1998, *54*, 197 (vinyl borinates); N. Miyaura et al. *Tetrahedron Lett.* 1986, *27*, 6369, and S. R. Chemler, D. Trauner, S. J. Danishefsky *Angew. Chem. Int. Ed. Engl.* 2001, *40*, 4544 (trialkylboranes); K. Songashira, Y. Tohda, N. Hagihira *Tetrahedron Lett.* 1975, 4467-70, and S. Thorand, N. Krause *J. Org. Chem.* 1998, 8551 (alkynes). The alkynylated compounds e.g., **4d** can subsequently be hydrogenated with a reduced activity catalyst, e.g., Lindlar's catalyst, to afford the corresponding *Z*-olefins. This two-step *Z*-olefin synthesis is complementary to the vinyl borinate coupling above, which yields *E*-olefins.

Scheme 5



Compounds containing alkoxy or thioalkoxy groups at R^6 e.g. **4h** can be formed by the reaction between **4g** (R^6 = F) and the corresponding alkoxides, phenoxides, mercaptides or thiophenoxides. The latter species can be generated *in situ* from the corresponding alcohols, phenols, thiols or thiophenol (e.g., $R^{14}XH$) with a base e.g., sodium hydride, potassium hydride, potassium hydroxide, or a tertiary amine (Scheme 6).



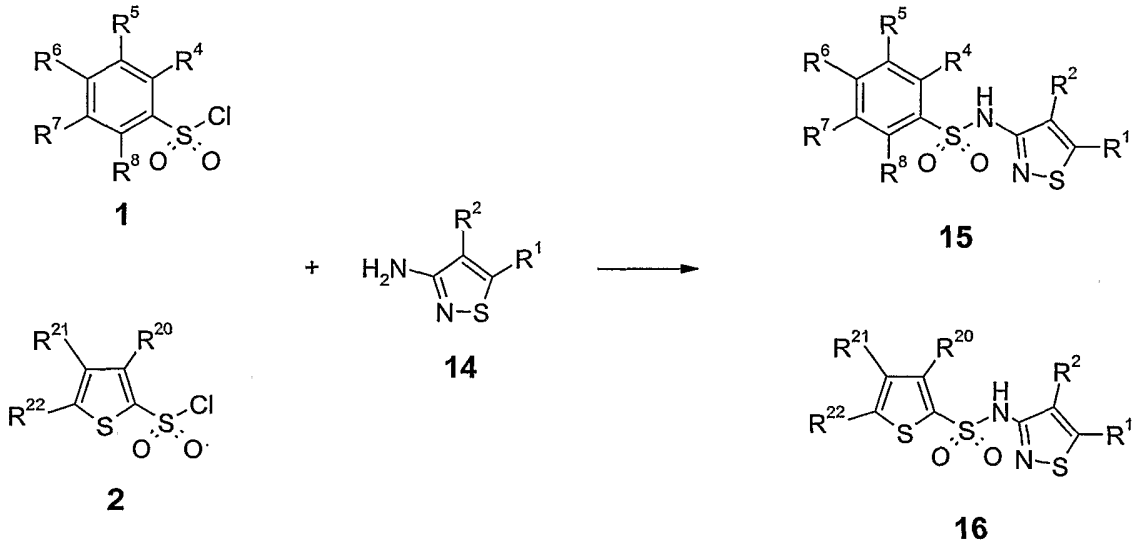
Scheme 6

Compounds containing an unsubstituted amino group (e.g., **4c** in which R^{31} and R^{32} are = H) at R^6 can be condensed with an aldehyde or ketone to form an aldimine or ketimine respectively. When the condensation is carried out in the presence of a reducing agent, e.g., triacetoxyborohydride, the C=N can be reduced *in situ* to form a monosubstituted amine. Alternatively, the imine may be isolated and may be optionally reduced with other reducing agents, e.g., chiral reducing agents to form monosubstituted amines.

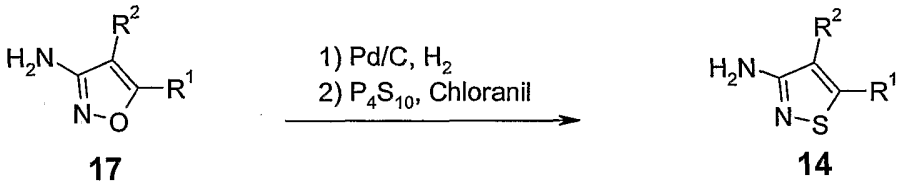
Synthesis of Isothiazoles

The compounds of formula **B'** e.g., **15** and **16** can also be prepared as described above by the reaction between the 3-aminothiazole **14** with either phenylsulfonyl chloride **1** or thienylsulfonyl chloride **2** (Scheme 7). The 3-aminoisothiazoles may be obtained in a stepwise manner (Scheme 8) from the corresponding 3-aminoisoxazole **17** *via* palladium catalyzed hydrogenation, followed by *in situ* treatment of the acyclic reduction product with phosphorus pentasulfide and chloranil (see e.g., D. N. McGregor, U. Corbin, J. E. Swigor, L. C. Cheney, *Tetrahedron* 1969, *25*, 389). In general, all or some of the substituents (R^1, R^2, R^4, etc.) desired in the final sulfonamide product may also be present in the reactants **1**, **2**, and/or **3** when the amine-sulfonyl chloride coupling reaction takes place.

Scheme 7

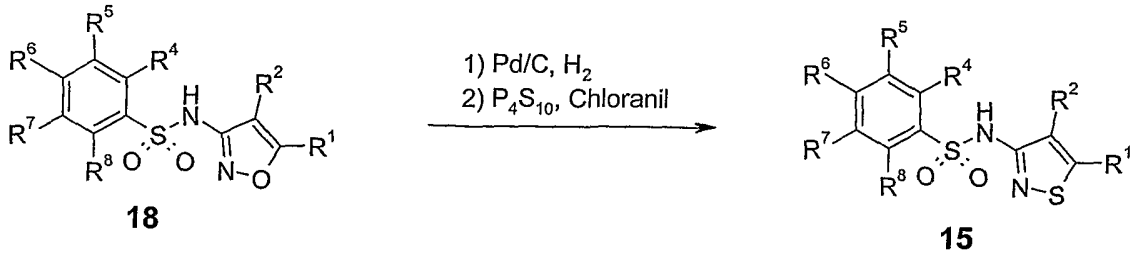


Scheme 8



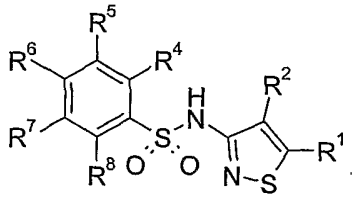
Alternatively, isothiazole compounds, e.g., **15** can be obtained from the corresponding isoxzaole compound **18** using essentially the same reaction conditions as those employed in Scheme 8 to covert compound **17** to compound **14** (see Scheme 9).

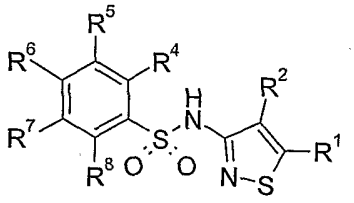
Scheme 9



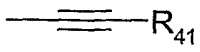
18 15

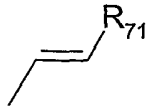
Isothiazole compounds **19**, **15c**, **15d**, **15e**, **15f**, and **15h** (shown below) are analogous to thiazole compounds **9**, **4c**, **4d**, **4e**, **4f**, and **4h**. The compounds can be prepared by the methods described above from the R^6-halo substituted compounds **15a**, **15b**, and **15g** and the reaction partners described in Schemes 4-8.

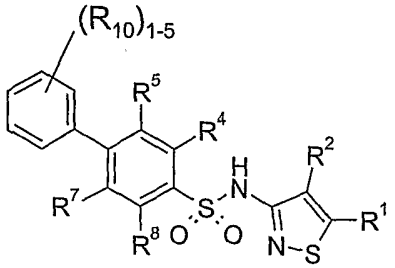




15a R^6 = I
15b R^6 = Br
15c R^6 = $NR_{31}R_{32}$
15f R^6 = R_{81}
15g R^6 = F
15h R^6 = X-R^{14}

15d R^6 = 

15e R^6 = 



19

The synthesized thiazole and isothiazole compounds can be separated from a reaction mixture and further purified by a method such as column chromatography, high pressure liquid chromatography, or recrystallization. As can be appreciated by the skilled artisan, further methods of synthesizing the compounds of the formulae herein will be evident. Additionally, the various synthetic steps may be performed in an alternate sequence or order to give the desired compounds. Synthetic chemistry transformations and protecting group methodologies (protection and deprotection) useful in synthesizing the compounds described herein are known in the art and include, for example, those such as described in R. Larock, *Comprehensive Organic Transformations*, VCH Publishers (1989); T.W. Greene and P.G.M. Wuts, *Protective Groups in Organic Synthesis*, 2d. Ed., John Wiley and Sons (1991); L. Fieser and M. Fieser, *Fieser and Fieser's Reagents for Organic Synthesis*, John Wiley and Sons (1994); and L. Paquette, ed., *Encyclopedia of Reagents for Organic Synthesis*, John Wiley and Sons (1995), and subsequent editions thereof.

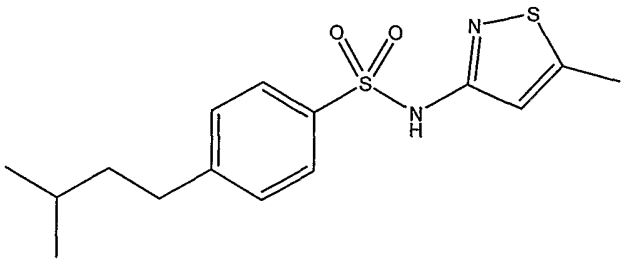
The thiazole and isothiazole compounds of this invention may contain one or more asymmetric centers and thus occur as racemates and racemic mixtures, single enantiomers, individual diastereomers and diastereomeric mixtures. All such isomeric forms of these compounds are expressly included in the present invention. The compounds of this invention may also be represented in multiple tautomeric forms, in such instances, the invention expressly includes all tautomeric forms of the compounds described herein (e.g., alkylation of a ring system may result in alkylation at multiple sites, the invention expressly includes all such reaction products). All such isomeric forms of such compounds are expressly included in the present invention. All crystal forms of the compounds described herein are expressly included in the present invention.

The thiazole and isothiazole compounds of this invention include the compounds themselves, as well as their salts and their prodrugs, if applicable. A salt, for example, can be formed between an anion and a positively charged substituent (e.g., amino) on a thiazole or isothiazole compound. Suitable anions include chloride, bromide, iodide, sulfate, nitrate, phosphate, citrate, methanesulfonate, trifluoroacetate, and acetate. Likewise, a salt can also be formed between a cation and a negatively charged substituent (e.g., carboxylate) on a thiazole or isothiazole compound. Suitable cations include sodium ion, potassium ion, magnesium ion, calcium ion, and an ammonium cation such as tetramethylammonium ion. Examples of prodrugs include esters and other pharmaceutically acceptable derivatives, which, upon administration to a subject, are capable of providing active thiazole or isothiazole compounds.

The compounds of this invention may be modified by appending appropriate functionalities to enhance selective biological properties. Such modifications are known in the art and include those which increase biological penetration into a given biological compartment (e.g., blood, lymphatic system, central nervous system), increase oral availability, increase solubility to allow administration by injection, alter metabolism and alter rate of excretion.

EXAMPLE 3

4-(3-Methylbutyl)-N-(5-methylisothiazol-3-yl)benzenesulfonamide



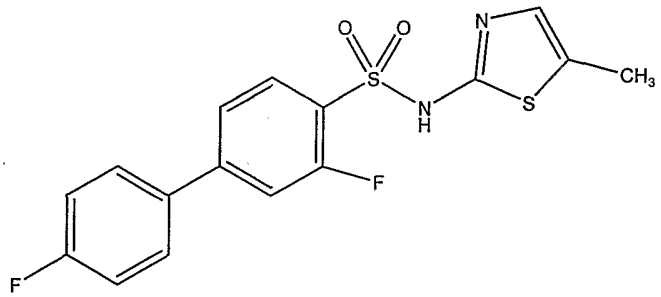
Step 1. Preparation of 4-bromo-N-(5-methylisothiazol-3-yl)benzenesulfonamide. A 50 mL round bottom flask was charged with 3-amino-5-methylisothiazole (125 mg, 1.1 mmol), pyridine (5 mL, 62 mmol) and 4-bromobenzenesulfonyl chloride (280 mg, 1.1 mmol). The reaction mixture was stirred at 23 °C for 20 h, and then diluted with ethyl acetate (50 mL), partitioned with water (20 mL), and adjusted to pH 1 with 3N HCl. The aqueous layer was extracted with 3 x 30 mL of ethyl acetate. The organic fractions were combined and washed with brine (10 mL), dried over Na_2SO_4, filtered and concentrated. The residue was purified by silica gel chromatography (5% ethyl acetate/hexanes to 60% ethyl acetate/hexanes) to give 4-bromo-N-(5-methylisothiazol-3-yl)benzenesulfonamide as a white crystalline solid, 230 mg, 63%, mp 184.3 °C. ^{1}H NMR ($CDCl_3$/300 MHz) 9.75 (s, 1H, N**H**), 7.67 (d, 2H, J = 8.4 Hz, Ar**H**), 7.58 (d, 2H, J = 8.5 Hz, Ar**H**), 7.00 (s, 1H, C**H**), 2.53 (s, 3H, C**H**$_3$).

Step 2. Preparation of 4-(3-methylbutyl)-N-(5-methylisothiazol-3-yl)benzenesulfonamide. 4-Bromo-N-(5-methylisothiazol-3-yl)benzenesulfonamide (500 mg, 0.1.50 mmol) and tetrakis(triphenylphosphine) palladium (93 mg, 0.08 mmol) were dissolved in 6.5 mL of dry DMF. 3-Methylbutylzinc bromide (0.5M in THF, 6.50 mL, 3.25 mmol) was added via syringe at room temperature. The brownish-green solution was stirred for 2h at 85 °C until analysis by LC-MS indicated complete consumption of the starting material. The reaction mixture was cooled to room temperature, quenched with 20 mL of sat. NH_4Cl and brought to pH = 2-4 with 1N HCl. The mixture was extracted with dichloromethane (3 x 50 mL) the combined organic layers were washed with of brine, dried over Na_2SO_4 and concentrated *in vacuo*. The crude product was purified by flash chromatography

(hexanes/ethyl acetate 2:1) followed by recrystallization from hexanes/diethyl ether 3:1 gave pure product (276 mg, 57%) as a white solid mp 160 °C, dec. ^{1}H NMR ($CDCl_3$/300 MHz) 8.09 (s, 1H), 7.79 (d, J = 8.2 Hz, 2H), 7.26 (d, J = 8.2 Hz, 2H), 6.78 (s, m or d, 1H, J = 1.4 Hz), 2.64 (t, J = 7.9 Hz, 2H), 2.24 (d, J = 1.2 Hz, 3H), 1.62-1.44 (m, 3H), 0.93 (d, J = 6.3 Hz, 6H).

EXAMPLE 4

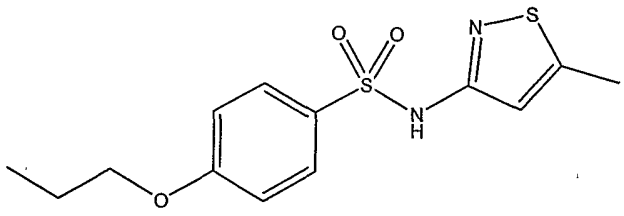
3,4'-Difluoro-N-(5-methyl-1,3-thiazol-2-yl)-1,1'-biphenyl-4-sulfonamide



Preparation of 3,4'-difluoro-N-(5-methyl-1,3-thiazol-2-yl)-1,1'-biphenyl-4-sulfonamide. To a round bottom flask under nitrogen atmosphere was added 4-bromo-2-fluoro-N-(5-methyl-1,3-thiazol-2-yl)benzenesulfonamide (260 mg, 0.74 mmol), 4-fluorobenzeneboronic acid (145 mg, 1.04 mmol) and tetrakistriphenylphoshine palladium (43 mg, 0.037 mmol). Dry toluene (6 mL) was added followed by dry ethanol (1 mL), dry isopropyl alcohol (2 mL) and 2N potassium carbonate (0.9 mL, 1.8 mmol). The reaction was heated to 80 °C and stirred for 16 h. The reaction was cooled, diluted with ethyl acetate (60 mL) quenched with 1N HCl (20 mL). The organic layer was separated and washed with water (20 mL), brine (20 mL), dried over sodium sulfate and concentrated to afford the crude residue. Flash chromatography ethyl acetate/hexane (3/1 as gradient afforded the product 38 mg. 0.103 mmol, 15%, as a white solid, mp 216 °C. ^{1}H NMR ($CDCl_3$/300 MHz) 8.05(1H, m), 7.54 (2H, m), 7.40 (1H, m), 7.27 (1H, m), 7.15 (2H, m), 6.91 (1H, s), 2.25 (3H, s). M-H$^+$ = 365.

EXAMPLE 5

N-(5-Methylisothiazol-3-yl)-4-propoxybenzenesulfonamide



Step 1. Preparation of 4-fluoro-N-(5-methylisothiazol-3-yl)benzenesulfonamide. Palladium, 10 wt. % (dry basis) on activated carbon (2.6 g, 1.2 mmol, 0.03 equiv) was added to a solution of 4-fluoro-N-(5-methylisoxazol-3-yl)benzenesulfonamide (9.0 g, 35 mmol) in 200 mL of ethyl acetate. The reaction mixture was flushed with hydrogen and stirred under 1 ATM of hydrogen at 23 °C for 20 h. The palladium on carbon was removed by flushing the crude reaction mixture through a plug of silica gel with ethyl acetate. The filtrate was then concentrated to afford a clear oil. The clear oil was dissolved in toluene, and then P_4S_{10} (23.4 g, 52.6 mmol, 1.5 equiv) was added followed by p-chloranil (8.6 g, 35.0 mmol). The reaction mixture was heated to 115 °C with vigorous stirring for 25 min. After cooling to 23 °C, the mixture was filtered and rinsed with water (50 mL) and dichloromethane (300 mL). All of the organic and aqueous layers were combined, diluted with water (150 mL), and adjusted to pH 1 with a solution of 1N HCl. The aqueous layer was then separated and washed with 3 x 150 mL of dichloromethane. The organic layers were combined, dried over Na_2SO_4, filtered and concentrated to afford a dark brown solid. This solid was purified by silica gel chromatography (15% ethyl acetate/hexanes to 40% ethyl acetate/hexanes) to give crude 4-fluoro-N-(5-methylisothiazol-3-yl)benzenesulfonamide, which was recrystallized in ethyl acetate/hexanes to furnish pure product as an off-white crystalline solid (1.93 g, 20% yield, mp 154.3 °C. ^{1}H NMR ($CDCl_3$/300 MHz) 9.75 (s, 1H, N**H**), 7.86-7.79 (m, 2H, Ar**H**), 7.15-7.07 (m, 2H, Ar**H**), 7.01 (d, 1H, J = 0.9 Hz, C**H**), 2.53 (d, 3H, J = 0.9 Hz, $C\mathbf{H}_3$).

Step 2. Preparation of Preparation of N-(5-methylisothiazol-3-yl)-4-propoxybenzenesulfonamide. Sodium hydride (95%, 35.3 mg, 1.4 mmol) was covered with dry dimethyl sulfoxide (0.5 mL) at room temperature. The mixture was rapidly stirred and heated to 60 – 70 °C for 1 h to generate the dimsyl anion. The pale gray-green solution was cooled to room temperature, neat 1-

propanol (0.12 mL, 1.6 mmol) was added by syringe and stirring was continued 20 min at room temperature. 4-Fluoro-N-(5-methylisothiazol-3-yl)benzenesulfonamide (100 mg, 0.36 mmol) was added to the stirred solution and the solution heated at 120 °C for 1 h or until TLC (SiO_2, 2:1 hexane/ethyl acetate) or LCMS indicated complete consumption of the starting material fluorobenzenesulfonamide. The reaction mixture was cooled to room temperature, poured into water (3 mL), and rapidly stirred as the pH was reduced to 5 by addition of 1 N HCl. This mixture was extracted with ethyl acetate. The organic phase was then washed with water, brine, dried over sodium sulfate, decolorized with charcoal, filtered and the solvent was removed by rotary evaporation to give the crude product as a white solid. Column chromatography (hexane/ethyl acetate) gave pure product (70 mg, 61 %) as a white solid, mp 163-165 °C. ^{1}H NMR: ($CDCl_3$/ 300 MHz) 8.75 (br s, 1H), 7.75 (d, 2H), 7.00 (s, 1H), 6.90 (d, 2H), 3.95, (t, 2H), 2.50 (s, 3H), 1.80 (m, 2H), 1.10 (t, 3H).

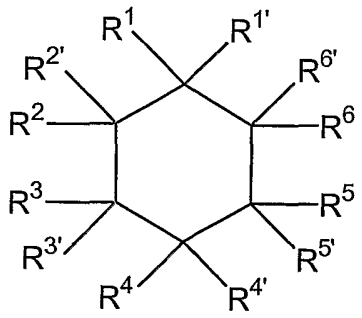
EXAMPLE 6

Generation and Testing of Additional Compounds of Formulas (I)-(V)

Based on compounds that received a score of less than 5 in the morphology assay described above in Example 2, a number of structurally related compounds having Formulas (I) – (V) were prepared and tested for the ability to inhibit fungal invasion using the methods described in Example 2. These compounds are depicted in the table of FIG. 2. In this Table the structure of the tested compound in depicted in the first column. Results are reported for the following tests: *C. albicans* logarithmic phase growth invasion assay (column 2), *C. albicans* stationary phase growth invasion assay (column 3), *C. albicans* minimum inhibitory concentration (column 4), *C. albicans* overnight growth inhibition (%) (column 5), *C albicans* phenotype rating (no units) (column 6), and mammalian cell toxicity (column 7). The mouse model of fungal invasion *in vivo*, described above in Example 2, can also be used to further characterize the compounds in FIG. 2 as well as related compounds and other compounds described herein.

COMPOUNDS OF FORMULA **VI**

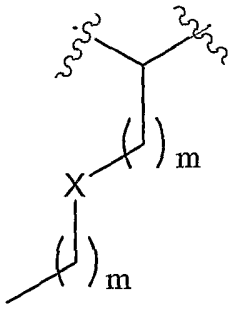
Certain compounds that can be used in practicing the invention have the general formula **VI**, in which R^1, $R^{1'}$, R^2, $R^{2'}$, R^3, $R^{3'}$, R^4, $R^{4'}$, R^5, $R^{5'}$, R^6, and $R^{6'}$ are attached to a 6-membered, carbocyclic core as shown below.



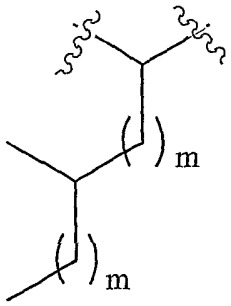
(VI)

R^1 includes a carboxylic acid group, which may be connected either directly to the core or indirectly through a $(CH_2)_n$ tether. Preferably, n is 0 or 1. R^4 can be any alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, cycloalkenyl, heterocycloalkenyl, aryl, or heteroaryl group. Each of these possible R^4 groups can be unsubstituted, or substituted with one or more substituents. Preferred R^4 groups include substituted or unsubstituted straight or branched C_1-C_{12} alkyl (e.g., C_1-C_{10}, C_1-C_8, C_1-C_6, C_1-C_4); substituted or unsubstituted straight or branched C_1-C_{12} alkyl (e.g., C_1-C_{10}, C_1-C_8, C_1-C_6, C_1-C_4) containing one or more heteroatoms (e.g., nitrogen, sulfur, or oxygen) inserted into one or more positions in the straight or branched alkyl chain; substituted or unsubstituted straight or branched C_2-C_{12} alkenyl (e.g., C_2-C_{10}, C_2-C_8, C_2-C_6, C_2-C_4); substituted or unsubstituted straight or branched C_2-C_{12} alkynyl (e.g., C_2-C_{10}, C_2-C_8, C_2-C_6, C_2-C_4); C_3-C_8 (e.g., C_3-C_7, C_3-C_6, C_3-C_5) cycloalkyl; and C_6-C_{10} aryl. Substituents for R^4 can include C_3-C_8 cycloalkyl, halo, hydroxy, mercapto, C_1-C_{10} alkoxy, C_1-C_{10} thioalkoxy, amino, C_1-C_{10} alkylamino, C_1-C_{10} dialkylamino, C_1-C_{10} haloalkyl, acyl and oxo. In certain embodiments, R^4 can have any one of formulas **A"**, **B"**, **C"**, **D"**, or **E"**. X may be N, O, or S, m may be 0-4 and n may be 1-4.

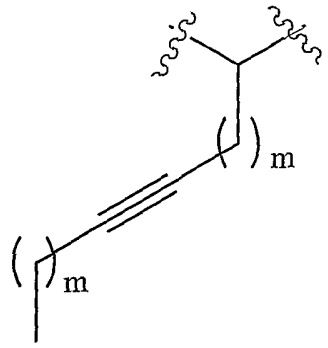
The core may be a saturated moiety, i.e., it does not contain any double bonds. The remaining positions



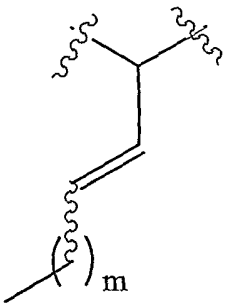
A"



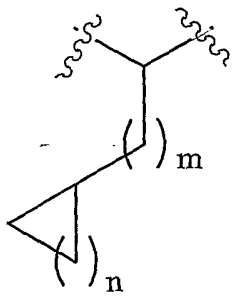
B"



C"

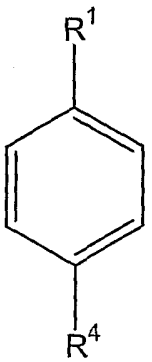


D"

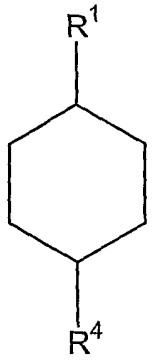


E"

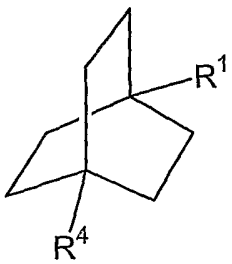
of a saturated core, $R^{1'}$, R^2, $R^{2'}$, R^3, $R^{3'}$, $R^{4'}$, R^5, $R^{5'}$, R^6, and $R^{6'}$, may be filled by any combination of hydrogen and C_1-C_6 alkyl. In certain embodiments, one of $R^{1'}$, $R^{2'}$, $R^{3'}$, $R^{4'}$, $R^{5'}$, or $R^{6'}$ and another of $R^{1'}$, $R^{2'}$, $R^{3'}$, $R^{4'}$, $R^{5'}$, or $R^{6'}$ together form a bridging C_1-C_3 alkylene group, e.g., $-CH_2CH_2-$, between two of the ring carbons of the core. Alternatively, the core may be unsaturated and contain 1-3 double bonds in the carbocyclic ring. Preferred core structures include formulas **F"**, **G"**, and **H"**



F"



G"



H"

Compounds having formula **G"** can exhibit *cis-trans* isomerism. In the *cis* isomer, R^1 and

R^1 occur on the same face or side of the cyclohexyl ring, while in the *trans* isomer, R^1 and R^4 occur on opposite faces or sides of the cyclohexyl ring. In some embodiments, the methods and compositions of the invention include the use of a mixture of both the *cis* isomer and the *trans* isomer of a compound having formula **G"**. In certain embodiments, the mixture contains at least about 50 percent (at least about 60 percent, at least about 70 percent, at least about 80 percent, at least about 90 percent, at least about 95 percent, at least about 98 percent, at least about 99 per cent) of the *cis* isomer. In other embodiments, the mixture contains at least about 50 percent (at least about 60 percent, at least about 70 percent, at least about 80 percent, at least about 90 percent, at least about 95 percent, at least about 98 percent, at least about 99 percent) of the *trans* isomer. In one aspect of the invention, both the *cis* and the *trans* isomer can be used in combination to treat a bacterial infection.

Representative compounds having Formula (**VI**) are provided in FIG. 3.

Combinations of substituents and variables envisioned by this invention are only those that result in the formation of stable compounds. The term "stable", as used herein, refers to compounds which possess stability sufficient to allow manufacture and which maintains the integrity of the compound for a sufficient period of time to be useful for the purposes detailed herein (e.g., therapeutic or prophylactic administration to a subject).

Compounds that can be useful in treating fungal infection can be identified through both *in vitro* (cell and non-cell based) and *in vivo* methods. A description of these methods is described in the Examples.

The compounds described herein can be obtained from commercial sources or synthesized by conventional methods as shown below.

Compounds having formula **H"**, e.g., 4-substituted bicyclo[2.2.2]octane-1-carboxylic acids and 4-substituted bicyclo[2.2.2]octane-1-acetic acids can be prepared as shown in FIG. 4 and FIG. 5. As shown in FIG. 4, the substituted acetone derivative (**1**) can be condensed with two equivalents of acrylonitrile in the presence of base to provide the bis-cyanoketones (**2**) following essentially the same procedure of Brunson and Reiner (Brunson, H. C.; Reiner, T. W. *J. Am. Chem. Soc.*, 1942, *64*, 2850; and

Brunson, H. C.; Reiner, T. W. *J. Am. Chem. Soc.*, 1942, *64*, 2857). The cyano moieties can then be hydrolyzed to the corresponding acids (**3**) by heating in aqueous sodium hydroxide followed by acidification. Intramolecular cyclization can be promoted under Perkin condensation conditions to provide 4-acetyl-4-R-cyclohexanone derivatives (**4**). The 4-substituted bicyclo[2.2.2]octane-1-ol derivatives (**5**) can then be prepared from **4** by intramolecular Aldol condensation. Reduction of the 3-oxo group of **5** can be achieved under Wolff-Kishner conditions to form **6**. Alternatively, the 3-oxo group

may first be converted to the bis-thioketal (not shown) using 1,2-ethanedithiol. The bis-thioketal can subsequently be reduced in the presence of Raney nickel to afford the des-keto derivative **6**.

As shown in FIG. 5, compound **6** may be used to prepare compounds having formula **H"**. Treatment of bicyclo[2.2.2]octan-1-ol **6** with a mixture of concentrated hydrobromic acid and zinc bromide can afford the corresponding tertiary bromide **7** in good yield. The bromo derivative can then be converted to the corresponding carboxylic acid **8** using sulfuric acid, silver sulfate and formic acid following essentially the same method as that described in Koch and Haaf (W. *Angew. Chem.*, 1958, *70*, 3113). The acetic acid derivative **10** can be prepared as follows. Acid **8** can be reduced to the alcohol **9** by reduction with lithium aluminum hydride. Tosylate formation, followed by cyanide displacement and hydrolysis can provide **10**. Other methods known in the art for the preparation of bicyclo[2.2.2]octane carboxylic acids (e.g., Holtz, H. D.; Stock, L. M. J. Am. Chem. Soc., 1964, 86, 5183-5188; Dewar, M. J. S.; Goldberg, R. S. J. Am. Chem. Soc., 1970, 92, 1582-1586; Kelly, S. M.; Schad, H. Helv. Chim. Acta., 1984, 67, 1580-1587; Osman, M. A.; Huynh-Ba, T. Helv. Chim. Acta., 1983, 66, 1786-1789; Gray, G. W.; Kelly, S. M. J. Chem. Soc., Chem. Commun., 1980, 465-466; Gray, G. W.; and Kelly, S. M. J. Chem. Soc., Chem. Commun., 1979, 974-975).

The compounds described herein can be separated from a reaction mixture and further purified by a method such as column chromatography, high-pressure liquid chromatography, or recrystallization. As can be appreciated by the skilled artisan, further methods of synthesizing the compounds of the formulae herein will be evident. Additionally, the various synthetic steps may be performed in an alternate sequence or order to give the desired compounds. Synthetic chemistry transformations and protecting group methodologies (protection and deprotection) useful in synthesizing the compounds described herein are known in the art and include, for example, those such as described in R. Larock, *Comprehensive Organic Transformations*, VCH Publishers (1989); T.W. Greene and P.G.M. Wuts, *Protective Groups in Organic Synthesis*, 2d. Ed., John Wiley and Sons (1991); L. Fieser and M. Fieser, *Fieser and Fieser's Reagents for Organic Synthesis*, John Wiley and Sons (1994); and L. Paquette, ed., *Encyclopedia of Reagents for Organic Synthesis*, John Wiley and Sons (1995), and subsequent editions thereof.

The compounds of this invention may contain one or more asymmetric centers and thus occur as racemates and racemic mixtures, single enantiomers, individual diastereomers and diastereomeric mixtures. All such isomeric forms of these compounds are expressly included in the present invention. The compounds of this invention may also contain linkages (e.g., carbon-carbon bonds) wherein bond rotation is restricted about that particular linkage, e.g. restriction resulting from the presence of a ring or double bond. Accordingly, all *cis/trans* and *E/Z* isomers are expressly included in the present invention. The compounds of this invention may also be represented in multiple tautomeric forms, in such instances, the invention expressly includes all tautomeric forms of the compounds described herein, even though only a single tautomeric form may be represented (e.g., alkylation of a ring system may result in

alkylation at multiple sites, the invention expressly includes all such reaction products). All such isomeric forms of such compounds are expressly included in the present invention. All crystal forms of the compounds described herein are expressly included in the present invention.

The compounds of this invention include the compounds themselves, as well as their salts and their prodrugs, if applicable. A salt, for example, can be formed between an anion and a positively charged substituent (e.g., amino) on a compound described herein. Suitable anions include chloride, bromide, iodide, sulfate, nitrate, phosphate, citrate, methanesulfonate, trifluoroacetate, and acetate. Likewise, a salt can also be formed between a cation and a negatively charged substituent (e.g., carboxylate) on a compound described herein. Suitable cations include sodium ion, potassium ion, magnesium ion, calcium ion, and an ammonium cation such as tetramethylammonium ion. Examples of prodrugs include esters and other pharmaceutically acceptable derivatives, which, upon administration to a subject, are capable of providing active compounds.

The compounds of this invention may be modified by appending appropriate functionalities to enhance selective biological properties. Such modifications are known in the art and include those which increase biological penetration into a given biological compartment (e.g., blood, lymphatic system, central nervous system), increase oral availability, increase solubility to allow administration by injection, alter metabolism and alter rate of excretion.

EXAMPLE 7

Compounds of formula **H"** may be obtained by the methods described herein or obtained from the Aldrich Chemical Company (see sigmaaldrich.com) or Specs and Biospecs (see spec.net). Compounds of formula **G"** may be obtained from TCI Americas (see tciamerica.com) or Avacado (see alfa.com). Compounds of formula **F"** may be obtained from Aldrich Chemical Company, TCI Americas, or Lancaster Synthesis (see lancastersynthesis.com).

EXAMPLE 8

Generation and Testing of Additional Compounds of Formula (VI)

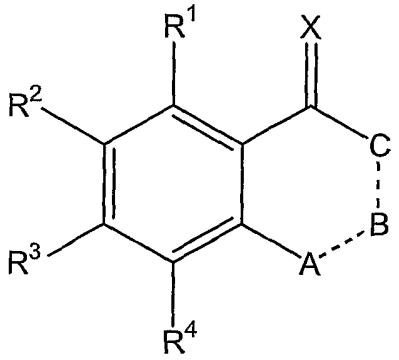
Based on compounds that received a score of less than 5 in the morphology assay described above, a number of structurally related compounds having Formula (**VI**) were prepared and tested for the ability to inhibit fungal invasion. These compounds are depicted in the table of FIG. 6. In this Table the structure of the tested compound is depicted in the first column. Results are reported for the following tests, all of which are described in Example 2: *C. albicans* logarithmic phase growth invasion assay (column 2), *C. albicans* stationary phase growth invasion assay (column 3), *C. albicans* minimum inhibitory concentration (column 4), *C albicans* phenotype rating (no units) (column 5), and mammalian cell toxicity (column 6).

All references cited herein, whether in print, electronic, computer readable storage media or other form, are expressly incorporated by reference in their entirety, including but not limited to, abstracts, articles, journals, publications, texts, treatises, internet web sites, databases, patents, and patent publications.

Other embodiments are in the claims.

CLAIMS

1. A compound having a formula (A):



(A)

wherein,

each of R^1, R^2, R^3, and R^4 is, independently, hydrogen, or C_1-C_6 alkyl;

A is NR^5R^6;

B is CR^7R^8; or is absent;

C is NR^9R^{10};

the dashed lines between A and B and between B and C are bonds when B is present, or unshared electron pairs on A and C when B is absent;

R^5 is hydrogen; or R^5 and R^7 together are a bond when B is present;

R^6 is $R^aC(O)$-, or is absent;

R^7 and R^5 together are a bond when B is present;

R^8 is C_1-C_4 alkyl, optionally substituted with NR^bR^c or $R^aC(O)$-;

R^9 is C_6-C_{10} aryl, optionally substituted with hydrogen, halo, or C_1-C_4 alkyl;

R^{10} is hydrogen, or is absent;

R^a is C_1-C_4 alkyl, optionally substituted with halo, NR^bR^c or -C(O)NHNHC(O)R^d;

Each of R^b and R^c is, independently, C_1-C_6 alkyl, C_2-C_6 aminoalkyl, C_2-C_6 alkylaminoalkyl, C_2-C_6 dialkylaminoalkyl, C_7-C_{11} aralkyl, or $R^eC(O)$-; or R^b and R^c together are heterocyclyl, or heterocycloalkenyl, optionally substituted with 1-3 R^f;

R^d is C_6-C_{10} aryl or 3-10 membered heteroaryl, optionally substituted with 1-3 R^g;

R^e is C_1-C_6 alkyl, C_7-C_{11} aralkyl, C_6-C_{10} aryl, or C_6-C_{10} arylamino, each of which may be substituted with C_1 – C_4 alkyl, halo or C_1-C_4 alkoxy;

R^f is oxo or C_1-C_6 alkyl;

R^g is hydrogen, halo, hydroxy, alkoxy, nitro, amino, cyano, carboxy, C_1-C_6 alkyl, C_6-C_{10} aryl, or 5-8 membered heteroaryl; and

X is O or S.

2. The compound of claim 1, wherein B is CHR^7R^8, R^5 and R^7 together are a bond, and R^8 is substituted with NR^bR^c.

3. The compound of claim 2, wherein R^8 is $CH(NR^bR^c)CH_3$ or $CH(NR^bR^c)CH_2CH_3$.

4. The compound of claim 2, wherein R^b is $(CH_3)_2NCH_2CH_2$, benzyl, or C_1-C_6 alkyl.

5. The compound of claim 2, wherein R^c is $R^eC(O)$-.

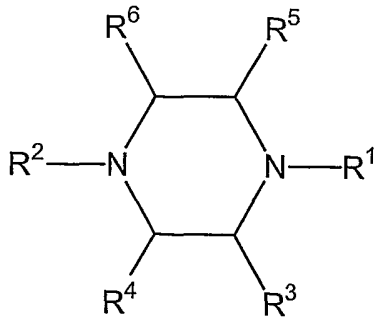
6. The compound of claim 5, wherein R^e is C_5-C_{11} alkyl or substituted or unsubstituted C_6–C_{10} arylamino, wherein the substituents are selected from CH_3 or OCH_3.

7. The compound of claim 1, wherein R^9 is substituted or unsubstituted phenyl, wherein the substituents are selected from halo or C_1-C_4 alkyl.

8. The compound of claim 7, wherein the substituents are CH_3 and chloro.

9. The compound of claim 1, wherein B is absent.

10. A compound having a formula (O):



(O)

wherein,

Each of R^1 and R^2 is, independently, C_4-C_9 alkyl; C_7-C_{10} aralkyl; C_3-C_9 alkenyl, optionally substituted with aryl; C_3-C_8 cycloalkyl, optionally substituted with C_1-C_4 alkyl; or $R^aC(O)$-;

Each of R^3, R^4, R^5, and R^6 is, independently, hydrogen or C_1-C_4 alkyl; and

R^a is 3-8 membered heterocyclyl, optionally substituted with acyl; C_7-C_{16} aralkyl optionally substituted with halo; or C_6-C_{10} arylamino, optionally substituted with 0-3 C_1-C_4 alkyl.

11. The compound of claim 10, wherein one of R^1 and R^2 is C_7-C_{10} aralkyl.

12. The compound of claim 11, wherein one of R^1 and R^2 is benzyl, -$(CH_2)_2$Ph, or -$(CH_2)_3$Ph.

13. The compound of claim 10, wherein one of R^1 and R^2 is C_3-C_9 alkenyl.

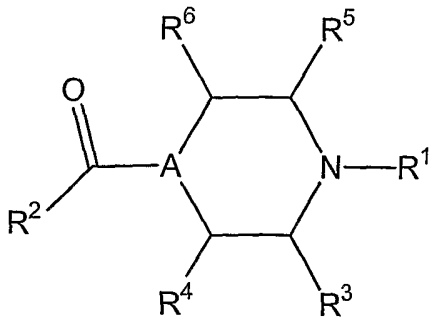
14. The compound of claim 10, wherein one of R^1 and R^2 is C_4-C_9 alkyl.

15. The compound of claim 13, wherein one of R^1 and R^2 is 3-phenylallyl.

16. The compound of claim 10, wherein R^1 and R^2 are C_7-C_{10} aralkyl.

17. The compound of claim 10, wherein one of R^1 and R^2 is C_7-C_{10} aralkyl and the other is C_3-C_9 alkenyl.

18. A compound having a formula (L):



wherein,

A is N or CH;

R^1 is C_1-C_{12} alkyl, C_2-C_{12} alkenyl, 5-12 membered heteroaryl, or $R^aC(O)$-;

R^2 is C_1-C_{12} alkyl, optionally substituted with $-NHC(O)R^b$; or C_1-C_4 alkoxy;

Each of R^3, R^4, R^5, and R^6 is, independently, hydrogen, or C_1-C_4 alkyl;

R^a is C_1-C_{12} alkyl; and

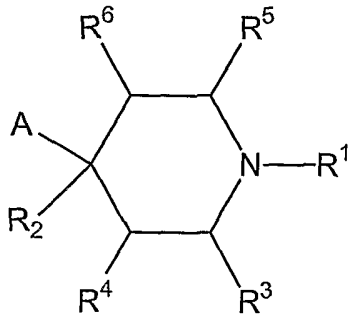
R^b is C_6-C_{10} aryl.

19. The compound of claim 18, wherein R^1 is C_3-C_{10} alkenyl.

20. The compound of claim 19, wherein R^1 is $-(CH_2)_6CH=CH_2$.

21. The compound of claim 18, wherein R^2 is $-OCH_2CH_3$.

22. A compound having a formula (E):



(E)

wherein,

R^1 is C_1-C_4 alkyl, optionally substituted with 1-3 R^a; C_7-C_{16} aralkyl, optionally substituted with 1-3 R^a; 6-16 membered heteroaralkyl, optionally substituted with 1-3 R^a; C_3-C_4 alkenyl, optionally substituted with 1-2 R^a;

A is C_6-C_{10} aryloxy, optionally substituted with thioaryloxy or thioalkoxy; 3-8 membered heterocyclyl, optionally substituted with C_7-C_{16} aralkyl; or CHR^7R^8;

R^2 is hydrogen or hydroxy; or R^2 and R^7 together are a bond;

Each of R^3, R^4, R^5, and R^6 is, independently, hydrogen, C_1-C_4 alkyl, or C_1-C_4 alkoxy;

R^7 is hydrogen; or R^7 and R^2 together are a bond;

R^8 is aryl, optionally substituted with C_1-C_4 alkoxy; and

Each R^a is, independently, hydroxy; C_1-C_6 alkyl; C_1-C_4 alkoxy; C_6-C_{10} aryloxy, optionally substituted with halo; 5-8 membered heteroaryl, optionally substituted with C_1-C_4 alkyl; C_6-C_{10} aryl, optionally substituted with C_2-C_6 dialkylamino or methylenedioxo; C_7-C_{16} aralkoxy; or allyloxy.

23. The compound of claim 22, wherein R^1 is C_1-C_4 alkyl, substituted or unsubstituted C_7 aralkyl, or substituted or unsubstituted 6-membered heteroaralkyl, wherein the substituents are selected from C_1-C_2 alkoxy, benzyloxy, allyloxy, F, Br, $(CH_3)_2N$, CH_3, methylenedioxo, or $(CH_3)_2CHNHC(O)$-.

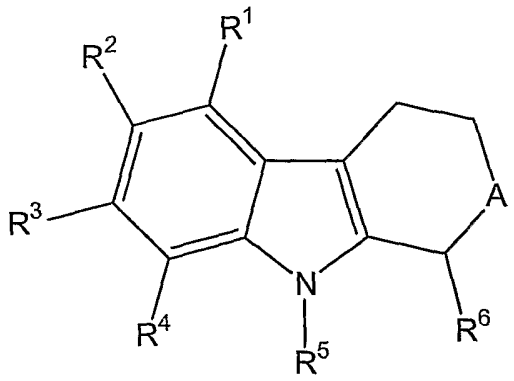
24. The compound of claim 22, wherein A is CHR^7R^8.

25. The compound of claim 24, wherein R^8 is C_7 aralkyl.

26. The compound of claim 24, wherein R^7 and R^2 together are a bond.

27. The compound of claim 22, wherein A is aryloxy.

28. A compound having a formula (C):



(C)

wherein,

Each of R^1, R^2, R^3, and R^4 is, independently, hydrogen, halo, or C_1-C_4 alkyl;

R^5 is hydrogen;

A is NR^7 or CH_2;

R^6 is hydrogen; C_1-C_6 alkylamino, optionally substituted with R^a; C_6-C_{10} aryl, optionally substituted with 1-3 R^a; or C_5-C_{10} heteroaryl, optionally substituted with 1-3 R^a; or R^6 and R^7 together are 3-8 membered heterocyclyl, optionally substituted with 1-3 R^b;

R^7 is hydrogen; C_7-C_{16} aralkyl, optionally substituted with 1-3 R^c; or $-C(O)R^d$; or R^7 and R^6 together are 3-8 membered heterocyclyl, optionally substituted with 1-3 R^b;

Each R^a is, independently, halo; methylenedioxo; C_6-C_{10} aryloxy, optionally substituted with halo; or C_1-C_4 alkoxy;

Each R^b is, independently, hydroxy, oxo, or C_1-C_6 alkyl;

Each R^c is, independently, C_1-C_4 alkyl or C_1-C_4 alkoxy; and

R^d is C_6-C_{10} aryl, optionally substituted with halo or C_1-C_4 alkyl; 5-8 membered heteroaryl; 3-8 membered heterocyclyl; or 5-10 membered heterocycloalkenyl.

29. The compound of claim 28, wherein A is CH_2.

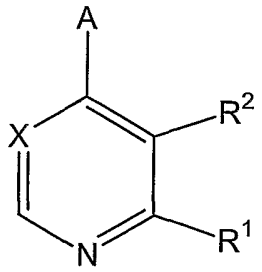
30. The compound of claim 29, wherein R^6 is C_1-C_4 alkylamino substituted with 4-halophenoxy.

31. The compound of claim 28, wherein A is NR^7.

32. The compound of claim 31, wherein R^7 is C_7 aralkyl or $-C(O)R^d$.

33. The compound of claim 32, wherein R^d is phenyl or halo-substituted phenyl.

34. A compound having a formula (AA):



(AA)

wherein,

X is N or C;

A is $-NHR^3$; $-OR^4$; SR^5; 3-8 membered heteroaryl, optionally substituted with C_6 arylsulfonyl that is substituted with 1-3R^a; 3-8 membered heterocyclyl, optionally substituted with C_6 arylsulfonyl that is substituted with 1-3R^a;

R^1 and R^2 together are fused C_6 aryl, optionally substituted with 1-3 R^a; or fused 5-membered heteroaryl, optionally substituted with 1-2 R^a;

R^3, R^4, and R^5 are each, independently, C_1-C_{12} alkyl, optionally substituted with 1-3 R^b; C_7-C_{10} aralkyl, optionally substituted with 1-3 R^b; 6-12 membered heteroaralkyl, optionally substituted with with 1-3 R^b; 5-10 membered heteroaryl, optionally substituted with with 1-3 R^b; (C_1-C_3) alkylene-O-(C_1-C_4) alkyl; or (C_1-C_3) alkylene-O-(C_6-C_{10}) aryl;

Each R^a is, independently, halo, C_1-C_6 alkyl, fused C_5-C_7 cycloalkyl, C_6-C_{10} aryl or 5-10 membered heteroaryl; and

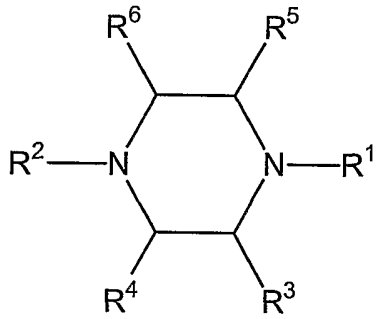
Each R^b is, independently, halo, C_1-C_4 alkoxy, methylenedioxo, C_1-C_4 haloalkyl, NH_2, di(C_1-C_4 alkyl)amino, (C_1-C_4 alkyl)amino; or a salt thereof.

35. The compound of claim 34 wherein X is N.

36. The compound of claim 34, wherein A is $-NHR^3$.

37. The compound of claim 34, wherein R^3 is substituted or unsubstituted C_1-C_5 alkyl or substituted or unsubstituted C_7-C_8 aralkyl, wherein the substituents are selected from halo, OCH_3, methylenedioxo, or $(CH_3)_2N$.

38.. A compound having a formula (AB):



(AB)

wherein,

R^1 is C_5-C_{10} heteroaryl, optionally substituted with 1-3 R^a;

R^2 is C_6-C_{10} arylsulfonyl, optionally substituted with halo; C_1-C_6 alkyl; $-C(O)R^b$; or C_7-C_{16} aralkyl;

Each of R^3, R^4, R^5, and R^6 is hydrogen;

Each R^a is, independently, halo; C_6-C_{10} aryl, optionally substituted with halo, hydroxy, or C_1-C_4 alkoxy; or C_1-C_4 alkyl;

R^b is NHR'; 5-10 membered heteroaryl; or C_6-C_{10} aryl, optionally substituted with1-2 C_1-C_2 alkoxy; and

R^c is C_6-C_{10} aryl, optionally substituted with 1-3 halo.

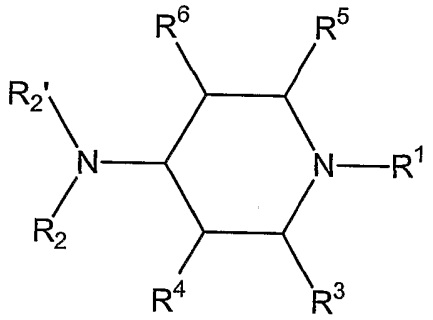
39. The compound of claim 38, wherein R^1 is substituted or unsubstituted quinazolinyl, quinolinyl, or pyrimidinyl.

40. The compound of claim 39, wherein R^2 is C_1-C_4 alkyl or -C(O)R^b.

41. The compound of claim 40, wherein R^2 is CH_2CH_3.

42. The compound of claim 40, wherein R^b is substituted or unsubstituted arylamino or heteroaryl.

43. (Class K) A compound having a formula (K):



(K)

wherein,

R^1 is C_1-C_7 alkyl, C_7-C_9 aralkyl, or –C(O)R^a;

R^2 and $R^{2'}$ are each, independently, hydrogen; C_1-C_4 alkyl; C_3-C_5 cycloalkyl; -C(O)R^b; C_7-C_{16} aralkyl, optionally substituted with R^c; or 6-16 membered heteroaralkyl, optionally substituted with R^c; or R^2 and $R^{2'}$ together are 3-10 membered heterocyclyl, optionally substituted with 1-5 C_1-C_4 alkyl;

Each of R^3, R^4, R^5, and R^6 is hydrogen;

R^a is C_1-C_4 alkyl or C_1-C_4 alkoxy;

R^b is C_6-C_{10} aryl, optionally substituted with R^c and/or 1-3 R^d; or 5-10 membered heteroaryl, optionally substituted with R^c and/or 1-3 R^d;

R^c is C_6-C_{10} aryl, optionally substituted with 1-3 R^d; C_6-C_{10} aryloxy, optionally substituted with 1-3 R^d; C_3-C_8 cycloalkyl-C_1-C_4 alkoxy; C_6-C_{10} arylamino, optionally substituted with 1-3 R^d; C_6-C_{10} thioaryloxy, optionally substituted with 1-3 R^d; or C_7-C_{16} aralkoxy, optionally substituted with 1-3 R^d; and

Each R^d is, independently, halo, C_1-C_6 alkyl, C_1-C_4 alkoxy, or C_1-C_4 haloalkyl.

44. The compound of claim 43, wherein R^1 is C_1-C_5 alkyl or C_7-C_8 aralkyl.

45. The compound of claim 43, wherein one of R^2 and $R^{2'}$ is substituted or unsubstituted C_7-C_{16} aralkyl, wherein substituents are selected from aryloxy substituted with CH_3, CF_3, halo, or OCH_3.

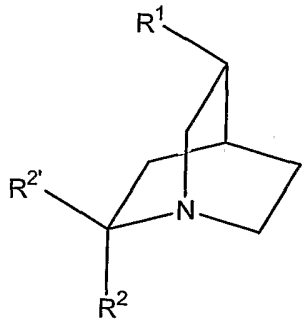
46. The compound of claim 45, wherein one of R^2 and $R^{2'}$ is substituted or unsubstituted benzyl, -$(CH_2)_2$Ph, or-$(CH_2)_3$Ph.

47. The compound of claim 43, wherein one of R^2 and $R^{2'}$ is CH_3.

48. The compound of claim 43, wherein one of R^2 and $R^{2'}$ is hydrogen.

49. The compound of claim 43, wherein one of R^1 and R^2 is substituted or unsubstituted C_7-C_{16} aralkyl and the other is CH_3, wherein substituents are selected from aryloxy substituted with CH_3, CF_3, halo, or OCH_3.

50. A compound having a formula (R):



(R)

wherein,

R^1 is C_1-C_2 alkyl or C_2 alkenyl;

R^2 and $R^{2'}$ are each, independently, hydrogen or CHR^3R^4;

R^3 is C_5-C_{14} heteroaryl, optionally substituted with C_1-C_4 alkoxy;

R^4 is OR^5;

R^5 is C_6-C_{14} aryl, optionally substituted with 1-3 R^a; -$C(O)R^b$; 6-14 membered heteroaryl, optionally substituted with 1-3 R^a; C_7-C_{16} aralkyl, optionally substituted with 1-3 R^a;

Each R^a is, independently, halo, C_1-C_6 alkyl, or C_1-C_4 alkoxy; and

R^b is C_6-C_{10} aryl, optionally substituted with 1-3 R^a; or 5-10 membered heteroaryl, optionally substituted with 1-3 R^a.

51. The compound of claim 50, wherein R^1 is CH_2CH_3 or $CH=CH_2$.

52. The compound of claim 50, wherein R^3 is unsubstituted or methoxy-substituted quinolinyl.

53. The compound of claim 50, wherein R^5 is aryl or heteroaryl.

54. The compound of claim 50, wherein the carbon to which R^3 and R^4 is attached has the S configuration.

55. The compound of claim 50, wherein the carbon to which R^3 and R^4 is attached has the R configuration.

56. A method of treating a fungal infection in a subject, the method comprising administering an effective amount of an anti-invasin agent and an antifungal agent.

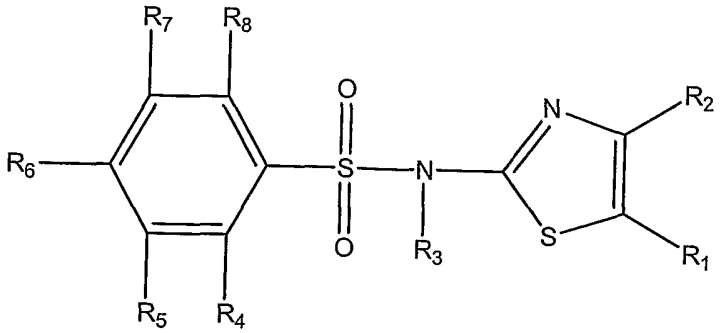
57. The method of claim 56 wherein the antifungal agent is a fungistatic agent.

58. The method of claim 56 wherein the antifungal agent is a fungicidal agent.

59. A pharmaceutical composition comprising an anti-invasin agent and a fungistatic agent.

60. A pharmaceutical composition comprising an anti-invasin agent and a fungicidal agent.

61. A compound having the formula (I):



(I)

or a pharmaceutically acceptable salt thereof, wherein,

R_1 is substituted or unsubstituted C_1-C_{12} alkyl, or substituted or unsubstituted C_1-C_{12} alkoxy, wherein the substituents are selected from the group consisting of halo and hydroxy;

R_2 is H or halo;

R_3 is H, formyl, acetyl, or substituted or unsubstituted C_1-C_3 alkyl, wherein the substituents are selected from the group consisting of halo and hydroxy;

Each of R_4-R_8 is, independently:

(i) H;

(ii) halo;

(iii) substituted or unsubstituted C_1-C_{12} alkyl, substituted or unsubstituted C_3-C_{10} cycloalkyl, substituted or unsubstituted C_2-C_{12} alkenyl, substituted or unsubstituted C_2-C_{12} alkynyl, or NH(C_1-C_6 alkyl), wherein the substituents are selected from hydroxy, halo, C_1-C_{12} alkyl and C_3-C_8-cycloalkyl;

(iv) OR; or

(v) phenyl or heteroaryl optionally substituted with 1-5 R^{10};

R^9 is C_3-C_{10} cycloalkyl, optionally substituted with halo or hydroxy; or C_1-C_{12} alkyl, optionally substituted with halo, hydroxy, or C_3-C_{10} cycloalkyl;

Each R^{10} is, independently, halo, hydroxy, OR_a, OR_b, acyloxy, nitro, amino, NHR_a, $N(R_a)_2$, NHR_b, $N(R_b)_2$, aralkylamino, mercapto, thioalkoxy, $S(O)R_a$, $S(O)R_b$, SO_2R_a, SO_2R_b, $NHSO_2R_a$, $NHSO_2R_b$, sulfate, phosphate, cyano, carboxyl, $C(O)R_a$, $C(O)R_b$, $C(O)OR_a$, $C(O)NH_2$, $C(O)NHR_a$, $C(O)N(R_a)_2$, alkyl, haloalkyl, C_3-C_{10} cycloalkyl containing 0-3 R_c, C_3-C_{10} heterocyclyl containing 0-3 R_c, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_5-C_{10} cycloalkenyl, C_5-C_{10} heterocycloalkenyl, C_6-C_{20} aryl containing 0-3 R_d, or C_6-C_{20} heteroaryl containing 0-3 R_d;

R_a is C_1-C_6 alkyl optionally substituted with halo, hydroxy, alkoxy, amino, alkylamino, dialkylamino, sulfate, or phosphate;

R_b is aryl optionally substituted with halo, haloalkyl, hydroxy, alkoxy, nitro, amino, alkylamino, dialkylamino, sulfate, or phosphate;

Each R_c is independently halo, haloalkyl, hydroxy, alkoxy, oxo, amino, alkylamino, dialkylamino, sulfate, or phosphate;

Each R_d is independently halo, haloalkyl, hydroxy, alkoxy, nitro, amino, alkylamino, dialkylamino, sulfate, or phosphate;

provided that at least one of R_4-R_8 is not hydrogen; further provided that when R^1 is $(CH_3)_2CCH_2CH_3$ or $C(CH_3)_3$, R^6 is not CH_3; further provided that when R^1 is $CH(CH_3)_2$, R^6 is not OCH_3 or CH_3; further provided that when R^1 is CH_3, R^4 and R^7 are not Cl; and further provided that when R1 is $C(CH_3)_3$, R6 is not CH_3.

62. The compound of claim 61, wherein R^1 is C_1-C_4 alkyl.

63. The compound of claim 61, wherein R^1 is CH_3.

64. The compound of claim 61, wherein R^4, R^5, R^7, and R^8 are H.

65. The compound of claim 61, wherein R^3 is H.

66. The compound of claim 61, wherein R^6 is C_1-C_6 alkyl.

67. The compound of claim 61, wherein R^6 is OR^9.

68. The compound of claim 67, wherein R^9 is C_1-C_6 alkyl.

69. The compound of claim 67, wherein R^9 is C_5-C_8 cycloalkyl.

70. The compound of claim 69, wherein R^9 is cyclopentyl.

71. The compound of claim 69, wherein R^9 is 2-norbornyl.

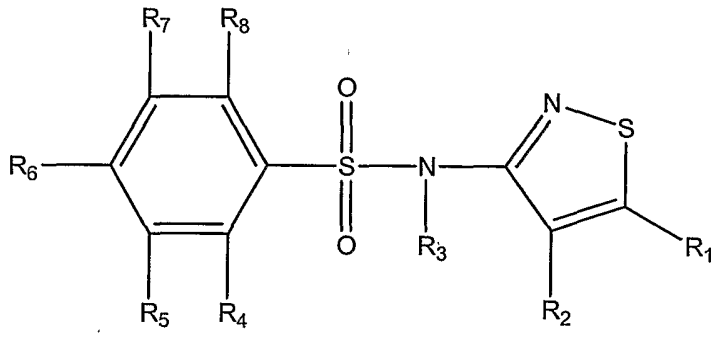
72. The compound of claim 67, wherein R^9 is C_1-C_4 alkyl substituted with C_3-C_5 cycloalkyl.

73. The compound of claim 61, wherein R^6 is phenyl substituted with R^{10}.

74. The compound of claim 73, wherein R^{10} is halo.

75. The compound of claim 73, wherein R^4 or R^5 is fluoro.

76. A compound having the Formula (**II**):



(**II**)

or a pharmaceutically acceptable salt thereof, wherein,

each of R^1 and R^2 is, independently, H, substituted or unsubstituted C_{1-12} alkyl, or substituted or unsubstituted C_{1-12} alkoxy, wherein the substituents are selected from the group consisting of hydroxy and halo;

R^3 is H, formyl, acetyl, or substituted or unsubstituted C_{1-3} alkyl, wherein the substituents are selected from the group consisting of hydroxy and halo;

each of R^1-R^6 is, independently:

(i) H;

(ii) halo;

(iii) substituted or unsubstituted C_{1-12} alkyl, substituted or unsubstituted C_3-C_{10} cycloalkyl, substituted or unsubstituted C_{2-12} alkenyl, substituted or unsubstituted C_{2-12} alkynyl, or -NH-(C_{1-6} alkyl), wherein the substituents are selected from the group consisting of hydroxy, halo, C_{1-4} alkyl, and C_3-C_8-cycloalkyl;

(iv) OR^9; or

(v) phenyl or heteroaryl optionally substituted with 1-5 R^{10};

R^9 is C_3-C_{10} cycloalkyl, optionally substituted with halo or hydroxy, or C_1-C_{12} alkyl, optionally substituted with halo, hydroxy, or C_3-C_{10} cycloalkyl;

Each of R^{10} is, independently, halo, hydroxy, OR_a, OR_b, acyloxy, nitro, amino, NHR_a, $N(R_a)_2$, NHR_b, $N(R_b)_2$, aralkylamino, mercapto, thioalkoxy, $S(O)R_a$, $S(O)R_b$, SO_2R_a, SO_2R_b, $NHSO_2R_a$, $NHSO_2R_b$, sulfate, phosphate, cyano, carboxyl, $C(O)R_a$, $C(O)R_b$, $C(O)OR_a$, $C(O)NH_2$, $C(O)NHR_a$, $C(O)N(R_a)_2$, alkyl, haloalkyl, C_3-C_{10} cycloalkyl containing 0-3 R_c, C_3-C_{10} heterocyclyl containing 0-3 R_c, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_5-C_{10} cycloalkenyl, C_5-C_{10} heterocycloalkenyl, C_6-C_{20} aryl containing 0-3 R_d, or C_6-C_{20} heteroaryl containing 0-3 R_d;

R_a is C_1-C_6 alkyl optionally substituted with halo, hydroxy, alkoxy, amino, alkylamino, dialkylamino, sulfate, or phosphate;

R_b is aryl optionally substituted with halo, haloalkyl, hydroxy, alkoxy, nitro, amino, alkylamino, dialkylamino, sulfate, or phosphate;

Each R_c is independently halo, haloalkyl, hydroxy, alkoxy, oxo, amino, alkylamino, dialkylamino, sulfate, or phosphate; and

Each R_d is independently halo, haloalkyl, hydroxy, alkoxy, nitro, amino, alkylamino, dialkylamino, sulfate, or phosphate;

77. The compound of claim 76, wherein R^4, R^5, R^7, and R^8 are H.

78. The compound of claim 76, wherein R^3 is H.

79. The compound of claim 76, wherein R^1 is C_1-C_4 alkyl.

80. The compound of claim 76, wherein R^1 is CH_3.

81. The compound of claim 76, wherein R^6 is C_1-C_6 alkyl.

82. The compound of claim 76, wherein R^6 is OR^9.

83. The compound of claim 82, wherein R^9 is C_1-C_6 alkyl.

84. The compound of claim 82, wherein R^9 is C_5-C_8 cycloalkyl.

85. The compound of claim 83, wherein R^9 is cyclopentyl.

86. The compound of claim 83, wherein R^9 is 2-norbornyl.

87. The compound of claim 82, wherein R^9 is C_1-C_4 alkyl substituted with C_3-C_5 cycloalkyl.

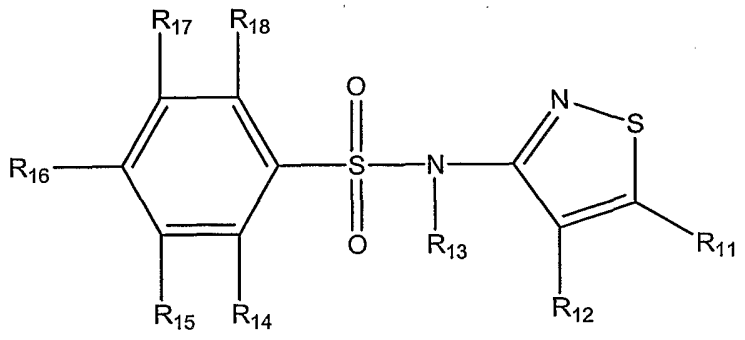
88. The compound of claim 76, wherein R^6 is phenyl substituted with R^{10}.

89. The compound of claim 88, wherein R^{10} is halo.

90. The compound of claim 88, wherein R^4 or R^5 is fluoro.

91. A pharmaceutical composition comprising a compound of Formula (II) and a pharmaceutically acceptable carrier.

92. A compound having a formula (**III**):



(**III**)

or a pharmaceutically acceptable salt thereof, wherein,

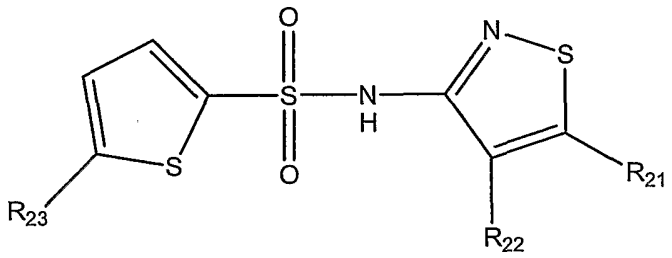
each of R^{11} and R^{12} is, independently, H, substituted or unsubstituted C_{1-12} alkyl, or substituted or unsubstituted C_{1-12} alkoxy, wherein the substituents are selected from the group consisting of hydroxy and halo;

R^{13} is H, formyl, acetyl, or substituted or unsubstituted C_{1-3} alkyl, wherein the substituents are selected from the group consisting of hydroxy and halo;

each of R^{14}-R^{18} is, independently, H, halo, substituted or unsubstituted C_{1-12} alkyl, substituted or unsubstituted C_3-C_{10} cycloalkyl, substituted or unsubstituted C_{2-12} alkenyl, substituted or unsubstituted C_{2-12} alkynyl, substituted or unsubstituted C_{1-12} alkoxy, substituted or unsubstituted C_{2-12} alkenyloxy, substituted or unsubstituted (C_{2-12} alkynyl)oxy, (C_{1-6} alkyl)oxy(C_{1-6} alkyl), substituted or unsubstituted C_{6-12} aryloxy, (C_{3-6} heteroaryl)-(C_{1-6} alkyl)oxy, (C_{1-6} alkyl)thio, substituted or unsubstituted (C_{1-4} alkyl)-thio-(C_{1-4} alkyl), substituted or unsubstituted aryl, substituted or unsubstituted styryl, substituted or unsubstituted C_{3-12} heteroaryl, substituted or unsubstituted C_{4-8} heterocyclic, -NH-C(O)-NH-(substituted or unsubstituted heteroaryl), or $-NR^{19}R^{20}$, wherein each of R^{19} and R^{20} is, independently, H or C_{1-12} alkyl, wherein the substituents are selected from the group

consisting of hydroxy, halo, C_{1-4} alkyl, C_3-C_8 cycloalkyl, C_{1-4} trihaloalkyl, C_{1-6} alkoxy, C_{1-4} trihaloalkoxy, bivalent oxyalkyloxy, acylamino, amino, and azido.

93. A compound having a Formula (**IV**):



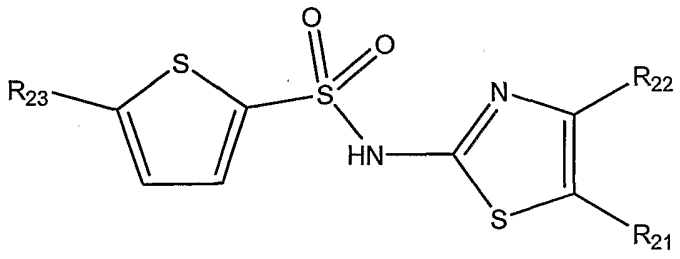
(IV)

or a pharmaceutically acceptable salt thereof, wherein

each of R^{21} and R^{22} is, independently, substituted or unsubstituted C_{1-6} alkyl, or substituted or unsubstituted C_{1-6} alkoxy, wherein the substituents are selected from the group consisting of hydroxy and halo;

R^{23} is substituted or unsubstituted C_{1-6} alkyl, substituted or unsubstituted C_{3-10} cycloalkyl, substituted or unsubstituted C_{6-12} aryl, substituted or unsubstituted C_{3-12} heteroaryl, wherein the substituents are selected from the group consisting of halo, C_{1-6} alkyl, C_3-C_8 cycloalkyl, and C_{1-6} trihaloalkyl.

94. A compound having a Formula (V):



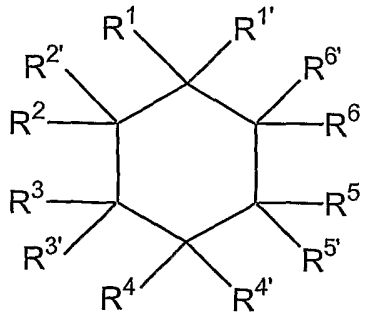
(V)

or a pharmaceutically acceptable salt thereof, wherein

each of R^{21} and R^{22} is, independently, substituted or unsubstituted C_{1-6} alkyl, or substituted or unsubstituted C_{1-6} alkoxy, wherein the substituents are selected from the group consisting of hydroxy and halo;

R^{23} is substituted or unsubstituted C_{1-6} alkyl, substituted or unsubstituted C_{3-10} cycloalkyl, substituted or unsubstituted C_{6-12} aryl, substituted or unsubstituted C_{3-12} heteroaryl, wherein the substituents are selected from the group consisting of halo, C_{1-6} alkyl, C_3-C_8 cycloalkyl, and C_{1-6} trihaloalkyl.

95. A pharmaceutical composition comprising a compound having a formula (VI) in an amount effective to treat a fungal infection and a pharmaceutically acceptable carrier,



(VI)

wherein:

R^1 is $(CH_2)_nCO_2H$, wherein n is 0, 1, 2, 3, 4, or 5;

$R^{1'}$ and $R^{2'}$, independently, are hydrogen or C_1-C_6 alkyl, or $R^{1'}$ and $R^{2'}$ together are a bond, $R^{3'}$ and $R^{4'}$, independently, are hydrogen or C_1-C_6 alkyl, or $R^{3'}$ and $R^{4'}$ together are a bond, $R^{5'}$ and $R^{6'}$, independently, are hydrogen or C_1-C_6 alkyl, or $R^{5'}$ and $R^{6'}$ together are a bond, or $R^{2'}$, $R^{3'}$, $R^{5'}$, and $R^{6'}$, independently, are hydrogen or C_1-C_6 alkyl and $R^{1'}$ and $R^{4'}$ together are a C_1-C_3 alkylene group;

each R^2, R^3, R^5, and R^6, independently, is hydrogen or C_1-C_6 alkyl; and

R^4 is: C_1-C_{12} alkyl optionally substituted with C_3-C_8 cycloalkyl, halo, hydroxy, mercapto, C_1-C_{10} alkoxy, C_1-C_{10} thioalkoxy, amino, C_1-C_{10} alkylamino, C_1-C_{10} dialkylamino, or oxo; C_3-C_8 cycloalkyl optionally substituted with C_3-C_8 cycloalkyl, halo, hydroxy, mercapto, C_1-C_{10} alkoxy, C_1-C_{10} thioalkoxy, amino, C_1-C_{10} alkylamino, C_1-C_{10} dialkylamino, or oxo; aryl optionally substituted with C_3-C_8 cycloalkyl, halo, C_1-C_{10} haloalkyl, hydroxy, mercapto, C_1-C_{10} alkoxy, C_1-C_{10} hydroxyalkyl, C_1-C_{10} thioalkoxy, amino, C_1-C_{10} alkylamino, C_1-C_{10} dialkylamino, or acyl; C_2-C_{12} alkenyl optionally substituted with C_3-C_8 cycloalkyl, halo, hydroxy, mercapto, C_1-C_{10} alkoxy, C_1-C_{10} thioalkoxy, amino, C_1-C_{10} alkylamino, C_1-C_{10} dialkylamino, or oxo; or C_2-C_{12} alkynyl optionally substituted with C_3-C_8 cycloalkyl, halo, hydroxy, mercapto, C_1-C_{10} alkoxy, C_1-C_{10} thioalkoxy, amino, C_1-C_{10} alkylamino, C_1-C_{10} dialkylamino, or oxo.

96. The composition of claim 95, wherein $R^{1'}$ and $R^{2'}$ together are a bond, $R^{3'}$ and $R^{4'}$ together are a bond, and $R^{5'}$ and $R^{6'}$ together are a bond.

97. The composition of claim 96, wherein n is 0 or 1.

98. The composition of claim 97, wherein R^4 is C_3-C_6 alkyl.

99. The composition of claim 97, wherein R^4 is C_3-C_6 cycloalkyl.

100. The composition of claim 95, wherein R^2, R^3, R^5, and R^6 are hydrogen.

101. The composition of claim 95, wherein $R^{1'}$, $R^{2'}$, $R^{3'}$, $R^{4'}$, $R^{5'}$, and $R^{6'}$ are hydrogen.

102. The composition of claim 101 wherein R^1 and R^4 are *trans*.

103. The composition of claim 101, wherein R^1 and R^4 are *cis*.

104. The composition of claim 101, wherein n is 0.

105. The composition of claim 104, wherein R^4 is C_3-C_6 alkyl.

106. The composition of claim 105, wherein R^1 and R^4 are *trans*.

107. The composition of claim 101, further comprising a mixture of a *cis* isomer of the compound and a *trans* isomer of the compound.

108. The composition of claim 95, wherein $R^{2'}$, $R^{3'}$, $R^{5'}$, and $R^{6'}$ are hydrogen, and $R^{1'}$ and $R^{4'}$ together are a $-CH_2CH_2-$ group.

109. The composition of claim 108, wherein n is 0 or 1.

110. The composition of claim 109, wherein R^4 is C_3-C_6 alkyl.

111. The composition of claim 95, wherein n is 0.

112. The composition of claim 95, wherein n is 1.

113. The composition of claim 95, wherein n is 2.

114. The composition of claim 95, wherein n is 3.

115. The composition of claim 95, wherein R^4 is n-propyl.

116. The composition of claim 95, wherein R^4 is n-butyl.

117. The composition of claim 95, wherein R^4 is n-pentyl.

118. The composition of claim 95, wherein R^4 is n-hexyl.

119. The composition of claim 95, wherein R^4 is phenyl.

120. The composition of claim 95, wherein R^4 is C_3-C_8 cycloalkyl.

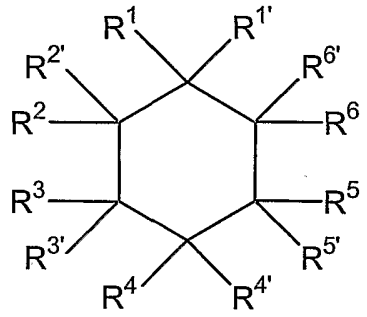
121. The composition of claim 95, wherein R^4 is C_2-C_{12} alkenyl.

122. The composition of claim 95, wherein R^4 is C_2-C_{12} alkynyl.

123. The composition of claim 95, wherein R^4 is C_1-C_{12} alkyl substituted with halo, hydroxy, C_3-C_8 cycloalkyl, C_1-C_{10} alkoxy, C_1-C_{10} thioalkoxy, amino, C_1-C_{10} alkylamino, C_1-C_{10} dialkylamino,or oxo.

124. The composition of claim 95, further comprising an antimicrobial agent.

125. The composition of claim 124, wherein $R^{1'}$, $R^{2'}$, $R^{3'}$, $R^{4'}$, $R^{5'}$, and $R^{6'}$ are hydrogen and R^1 and R^4 are *trans*, and the antimicrobial agent is a compound of formula (VI):



(VI)

wherein:

R^1 is $(CH_2)_nCO_2H$, wherein n is 0, 1, 2, 3, 4, or 5;

$R^{1'}$ and $R^{2'}$, independently, are hydrogen or C_1-C_6 alkyl, or $R^{1'}$ and $R^{2'}$ together are a bond, $R^{3'}$ and $R^{4'}$, independently, are hydrogen or C_1-C_6 alkyl, or $R^{3'}$ and $R^{4'}$ together are a bond, $R^{5'}$ and $R^{6'}$, independently, are hydrogen or C_1-C_6 alkyl, or $R^{5'}$ and $R^{6'}$ together are a bond, or $R^{2'}$, $R^{3'}$, $R^{5'}$, and $R^{6'}$, independently, are hydrogen or C_1-C_6 alkyl and $R^{1'}$ and $R^{4'}$ together are a C_1-C_3 alkylene group;

each R^2, R^3, R^5, and R^6, independently, is hydrogen or C_1-C_6 alkyl; and

R^4 is: C_1-C_{12} alkyl optionally substituted with C_3-C_8 cycloalkyl, halo, hydroxy, mercapto, C_1-C_{10} alkoxy, C_1-C_{10} thioalkoxy, amino, C_1-C_{10} alkylamino, C_1-C_{10} dialkylamino, or oxo; C_3-C_8 cycloalkyl optionally substituted with C_3-C_8 cycloalkyl, halo, hydroxy, mercapto, C_1-C_{10} alkoxy, C_1-C_{10} thioalkoxy, amino, C_1-C_{10} alkylamino, C_1-C_{10} dialkylamino, or oxo; aryl optionally substituted with C_3-C_8 cycloalkyl,

halo, C_1-C_{10} haloalkyl, hydroxy, mercapto, C_1-C_{10} alkoxy, C_1-C_{10} hydroxyalkyl, C_1-C_{10} thioalkoxy, amino, C_1-C_{10} alkylamino, C_1-C_{10} dialkylamino, or acyl; C_2-C_{12} alkenyl optionally substituted with C_3-C_8 cycloalkyl, halo, hydroxy, mercapto, C_1-C_{10} alkoxy, C_1-C_{10} thioalkoxy, amino, C_1-C_{10} alkylamino, C_1-C_{10} dialkylamino, or oxo; or C_2-C_{12} alkynyl optionally substituted with C_3-C_8 cycloalkyl, halo, hydroxy, mercapto, C_1-C_{10} alkoxy, C_1-C_{10} thioalkoxy, amino, C_1-C_{10} alkylamino, C_1-C_{10} dialkylamino, or oxo.

wherein $R^{1'}$, $R^{2'}$, $R^{3'}$, $R^{4'}$, $R^{5'}$, and $R^{6'}$ are hydrogen and R^1 and R^4 are *cis*.

126. A method of treating a fungal infection in a subject, the method comprising administering to the subject an effective amount of a compound having a formula selected from (A), (O), (L), (E), (C), (AA), (AB), (K), (R), (I), (II), (III), (IV), (V), and (VI) .

127. The method of claim 126, further comprising administering to the subject an antifungal agent in combination with the compound.

128. The method of claim 126, wherein the compound and the antifungal agent are administered simultaneously.

129. The method of claim 126, wherein the compound and the antifungal agent are administered sequentially.

130. The method of claim 126, further comprising identifying the subject as a subject in need of treatment for a fungal infection.

131. The method of claim 126, wherein the subject is a human.

FIGURE 1A

FORMULA (A) COMPOUNDS

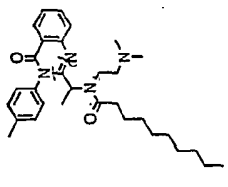
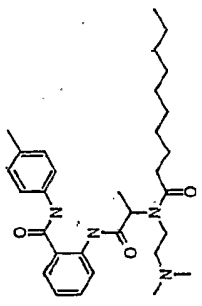
Counter	Structure	SampleID	Parent	Compound Class	C. albicans LOG IC50 (uM)	Result	C. albicans STAT IC50 (uM)	Result	C. albicans MIC (ug/ml)	Result	C. albicans Overnight Growth Inhibtion (%)	Result	C. albicans Phenotype Rating	Result
1		3151	3151	A	0.571uM .826uM		3.68uM 6.574uM		>64ug/ml >64ug/ml		- 61.79% - 15.16% 66.16%		2__Phenotype 5__Phenotype 5__Phenotype 5__Phenotype	
2		270270	3151	A	4.660uM		4.730uM		8ug/ml		- 9.87% - 3.71%		2*__Phenotype 2*__Phenotype	

FIGURE 1A

3		3145	3151	A	0.571uM	2.4uM	>64ug/ml	42.83%	4__Phenotype
4		2000	3151	A	0.805uM	6.32uM	>64ug/ml	10.2%	4__Phenotype
5		2771	3151	A	1.117uM	>20uM	>64ug/ml	29.58%	4__Phenotype
6		270320	3151	A	3.888uM	12.601uM	>64ug/ml	51.99% 56.42%	5__Phenotype 5__Phenotype
7		261093	3151	A	>20uM	>20uM			5__Phenotype
8		261092	3151	A	>20uM	>20uM			5__Phenotype

FIGURE 1A

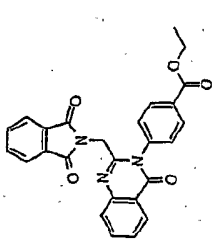
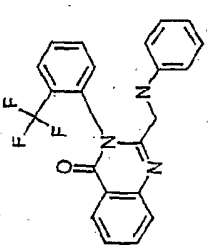
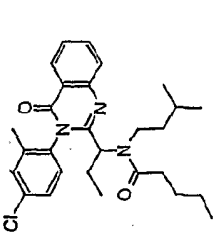
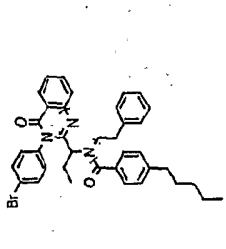
										5__Phenotype
9		261090	3151	A	>20uM	>20uM				5__Phenotype
10		261087	3151	A	>20uM	>20uM				5__Phenotype
11		4636	3151	A	>20uM	>20uM	9.19%			5__Phenotype
12		3787	3151	A	0.325uM	5.07uM	- 15.93%	>64ug/ml		5__Phenotype
13		3152	3151	A	1.23uM	7.57uM			64-	5__Phenotype

FIGURE 1A

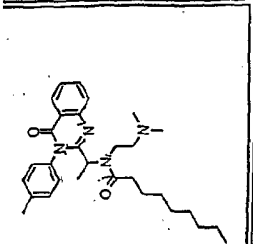
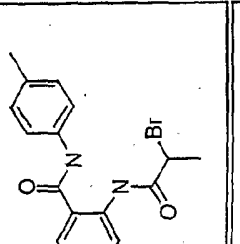
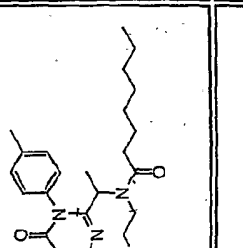
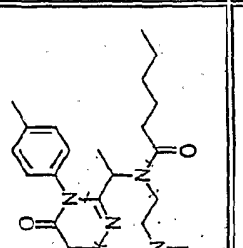
				1.23uM		32ug/ml 64-32ug/ml			
14		2069	3151	A	0.73uM	>64ug/ml	17.62uM		5__Phenotype
15		261251	3151	A	>20uM		>20uM		5__Phenotype
16		270319	3151	A	3.993uM	>64ug/ml	>20uM	97.97% 102.82%	5__Phenotype 5__Phenotype
17		270318	3151	A	>20uM	>64ug/ml	>20uM	97.11% 97.61%	5__Phenotype 5__Phenotype
18		261252	3151	A	>20uM		>20uM		5__Phenotype

FIGURE 1A

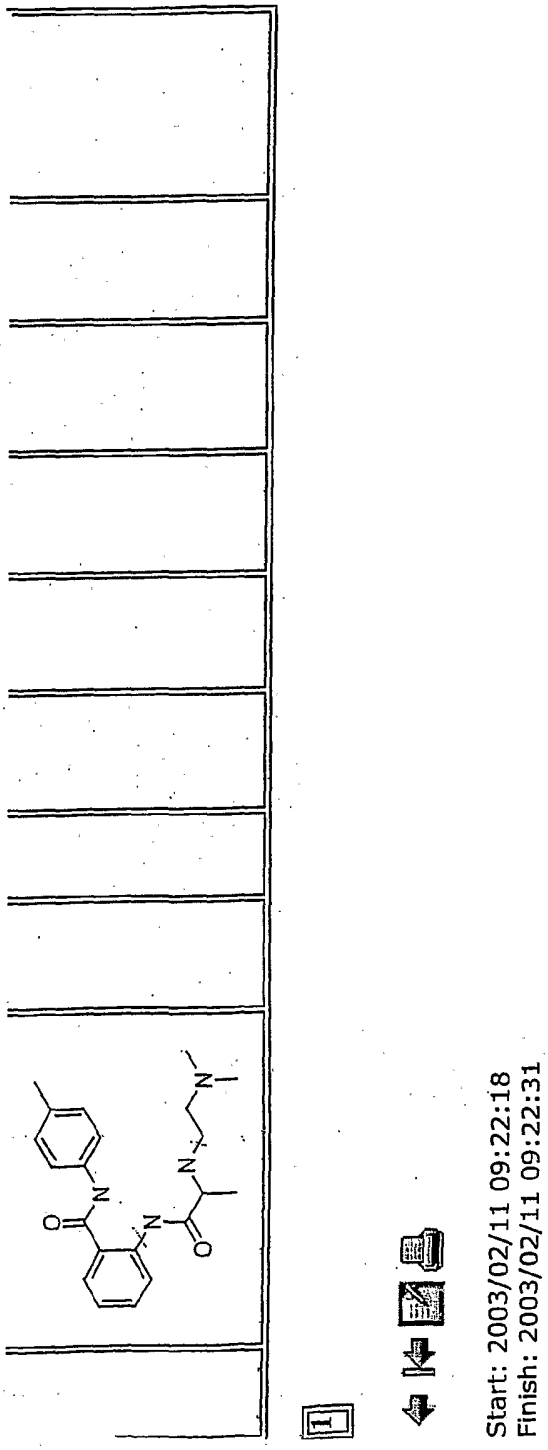


FIGURE 1A

FORMULA (O) COMPOUNDS

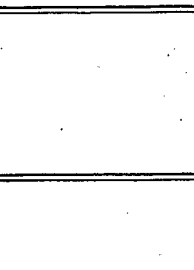
				Result	Result	Result	Result	Result
Counter	Structure	SampleID	Batch	C. albicans LOG IC50 (uM)	C. albicans STAT IC50 (uM)	C. albicans MIC (ug/ml)	C. albicans Overnight Growth Inhibtion (%)	C. albicans Phenotype Rating
1		261082	EMPTY Container	1.46uM	>20uM	32ug/ml		1__Phenotype
		261082	VIALB1-000000025088					
2		26547	VIRTUL-000000011710	1.76uM	8.86uM	>64ug/ml	81.5%	2__Phenotype

FIGURE 1A

	26547	VIALB1-00000025006	3.18uM	>20uM	64ug/ml			2__Phenotype	
3	261083	EMPTY Container							
	261083	VIALB1-00000025089							
4	27307	VIRTUL-00000011710	3.92uM	> 20uM	>64ug/ml	87.14%		2__Phenotype	
	27307	VIALB1-00000025008	6.51uM	>20uM	>64ug/ml			2__Phenotype	
5	261080	EMPTY Container							
	261080	VIALB1-00000025086	7.88uM	>20uM	>64ug/ml			4__Phenotype	
6	261077	EMPTY Container							

FIGURE 1A

		VIALB1-00000025083							4__Phenotype
	261077	EMPTY Container	8.28uM	>20uM	>64ug/ml				5__Phenotype
7	261081	VIALB1-00000025087							
		EMPTY Container	13.438uM	>20uM	>64ug/ml				
8	261081	VIALB1-00000025026							
	84366	EMPTY Container	18.79uM	>20uM	>64ug/ml				
9	261079	VIALB1-00000025085							
	261079	EMPTY Container	>20uM	>20uM					
10	261088								

FIGURE 1A

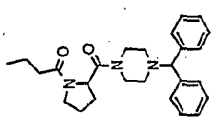
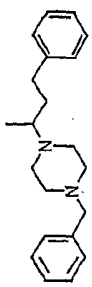
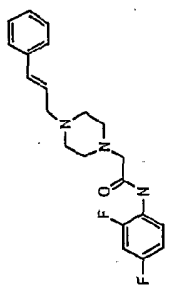
			5__Phenotype							
			19.4%							
			>20uM							
			>20uM							
	VIALB1-00000025093									
	261088									
11	3629		VIRTUL-000000011710							
	3629		VIALB1-00000024963							
			5__Phenotype							
			3.14% 2.6%							
			nullug/ml							
			18.73uM							
			>20uM							
	VIALB1-00000025007		AFCh3-000000008422							
	27297									
12	27297									
			2__Phenotype							
			>64ug/ml							
			>20uM							
			>20uM							
	VIALB1-00000025025		EMPTY Container							
	84365									
13	84365									
			5__Phenotype							
			>64ug/ml							
			>20uM							
			>20uM							
	EMPTY Container									
	89083									
14										

FIGURE 1A

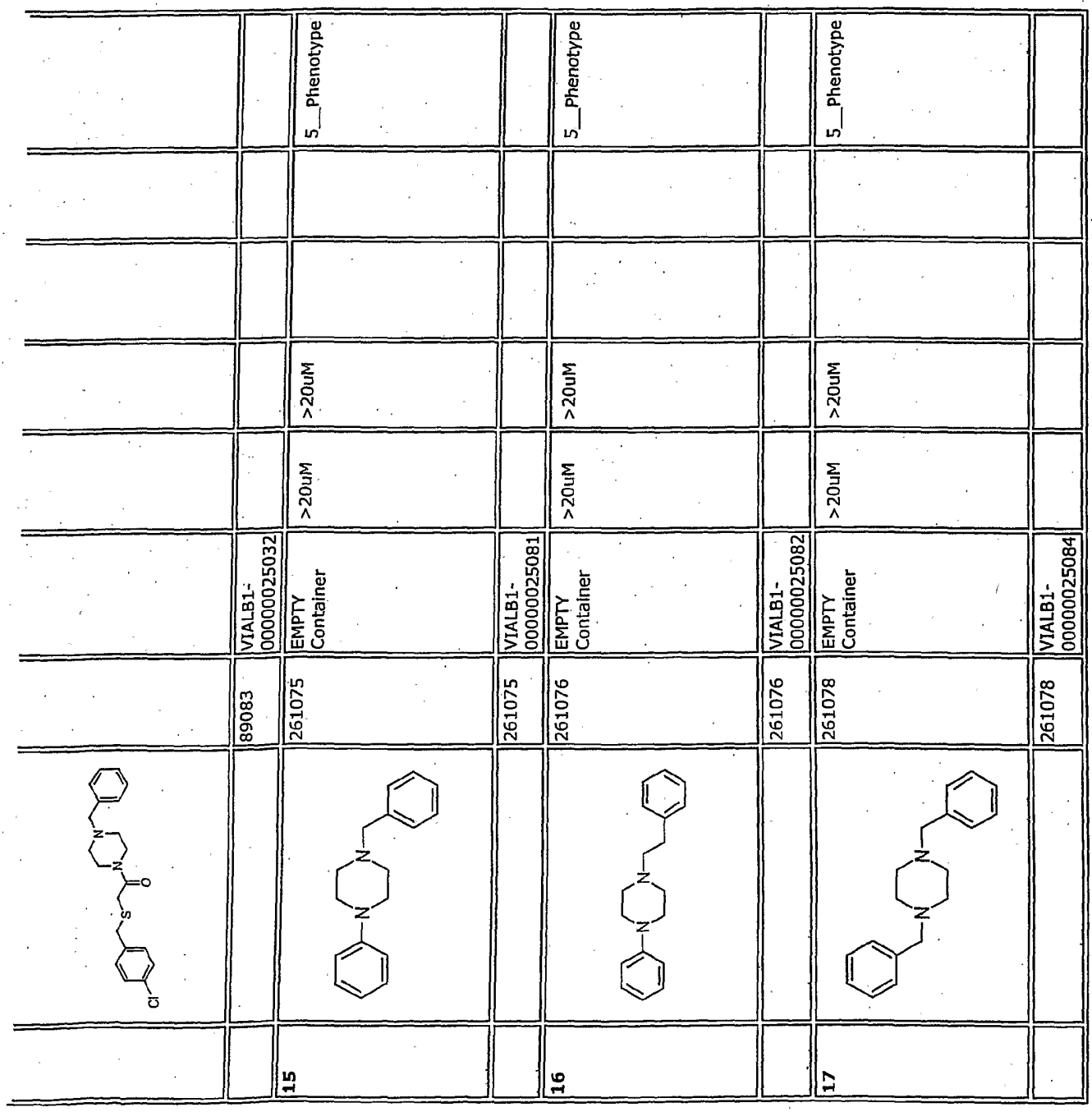

89083
VIALB1-00000025032
5__Phenotype
>20uM
>20uM
15
261075
261075
VIALB1-00000025081
5__Phenotype
>20uM
>20uM
16
261076
261076
VIALB1-00000025082
5__Phenotype
>20uM
>20uM
17
261078
261078
VIALB1-00000025084
EMPTY Container
EMPTY Container
EMPTY Container
Cl

FIGURE 1A

FORMULA (L) COMPOUNDS

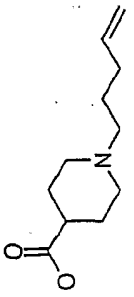
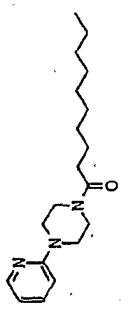
Counter	Structure	SampleID	Compound Class	Result C. albicans LOG IC50 (uM)	Result C. albicans STAT IC50 (uM)	Result C. albicans MIC (ug/ml)	Result C. albicans Overnight Growth Inhibtion (%)	Result C. albicans Phenotype Rating
1		261014	L	0.000uM	20.00uM	0ug/ml	0% 0%	0__Phenotype
2		261013	L	0.350uM	16.36uM	64ug/ml	88.25% 94.75%	1__Phenotype

FIGURE 1A

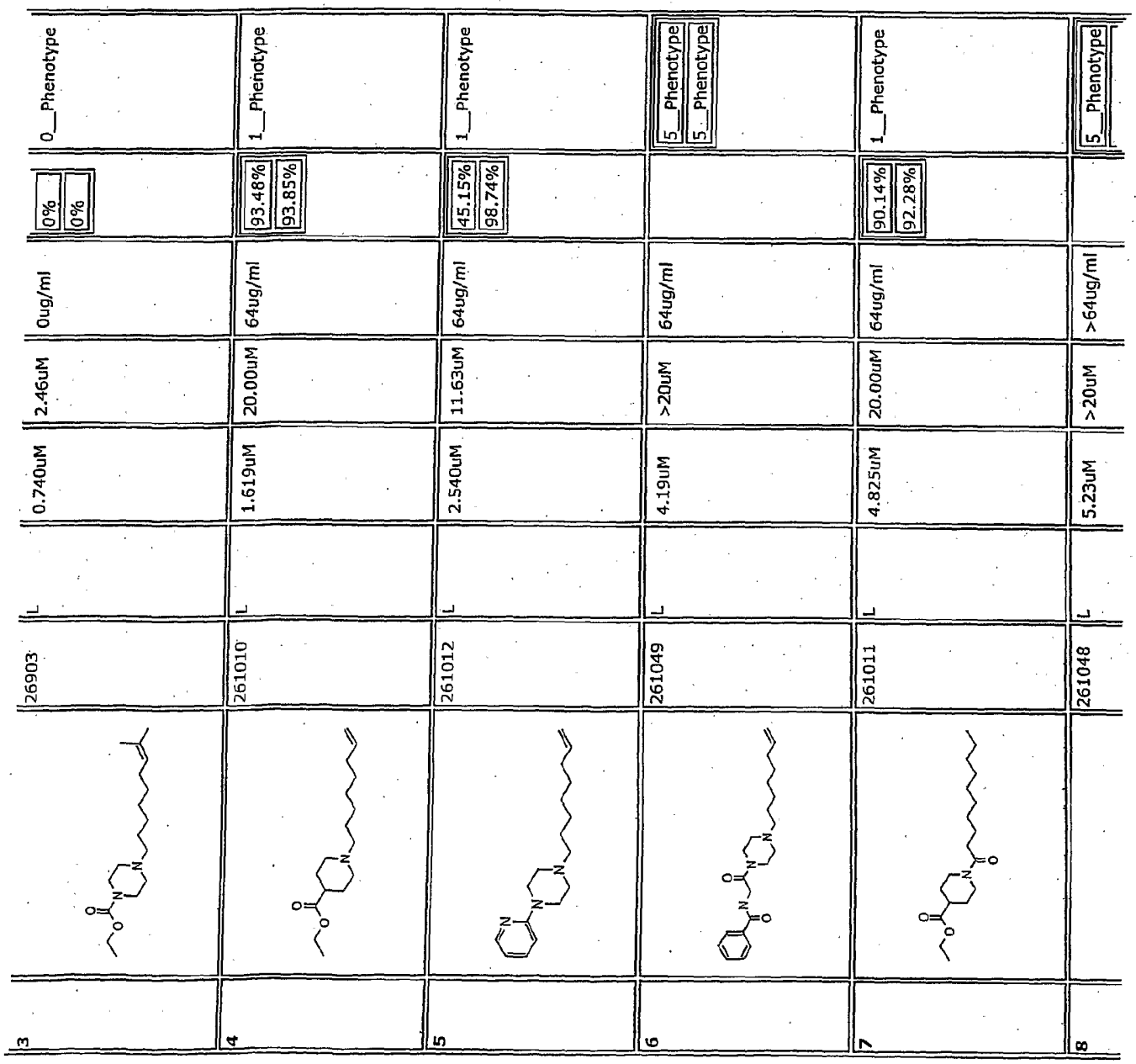

3
26903
L
0.740uM
2.46uM
0ug/ml
0%
0%
0__Phenotype
4
261010
L
1.619uM
20.00uM
64ug/ml
93.48%
93.85%
1__Phenotype
5
261012
L
2.540uM
11.63uM
64ug/ml
45.15%
98.74%
1__Phenotype
6
261049
L
4.19uM
>20uM
64ug/ml
5__Phenotype
5__Phenotype
7
261011
L
4.825uM
20.00uM
64ug/ml
90.14%
92.28%
1__Phenotype
8
261048
L
5.23uM
>20uM
>64ug/ml
5__Phenotype

FIGURE 1A

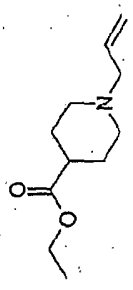
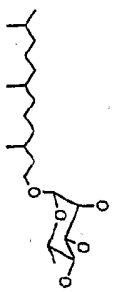
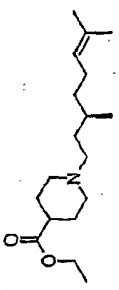
							5__Phenotype	
9		261009	L	20.000uM	20.00uM	0ug/ml	0% 0%	0__Phenotype
10		261008	L	20.000uM	20.00uM	0ug/ml	0% 0%	0__Phenotype
11		261037	L	>20uM	>20uM			5__Phenotype 5__Phenotype
12		94065	L					
13		261038	L					

FIGURE 1A

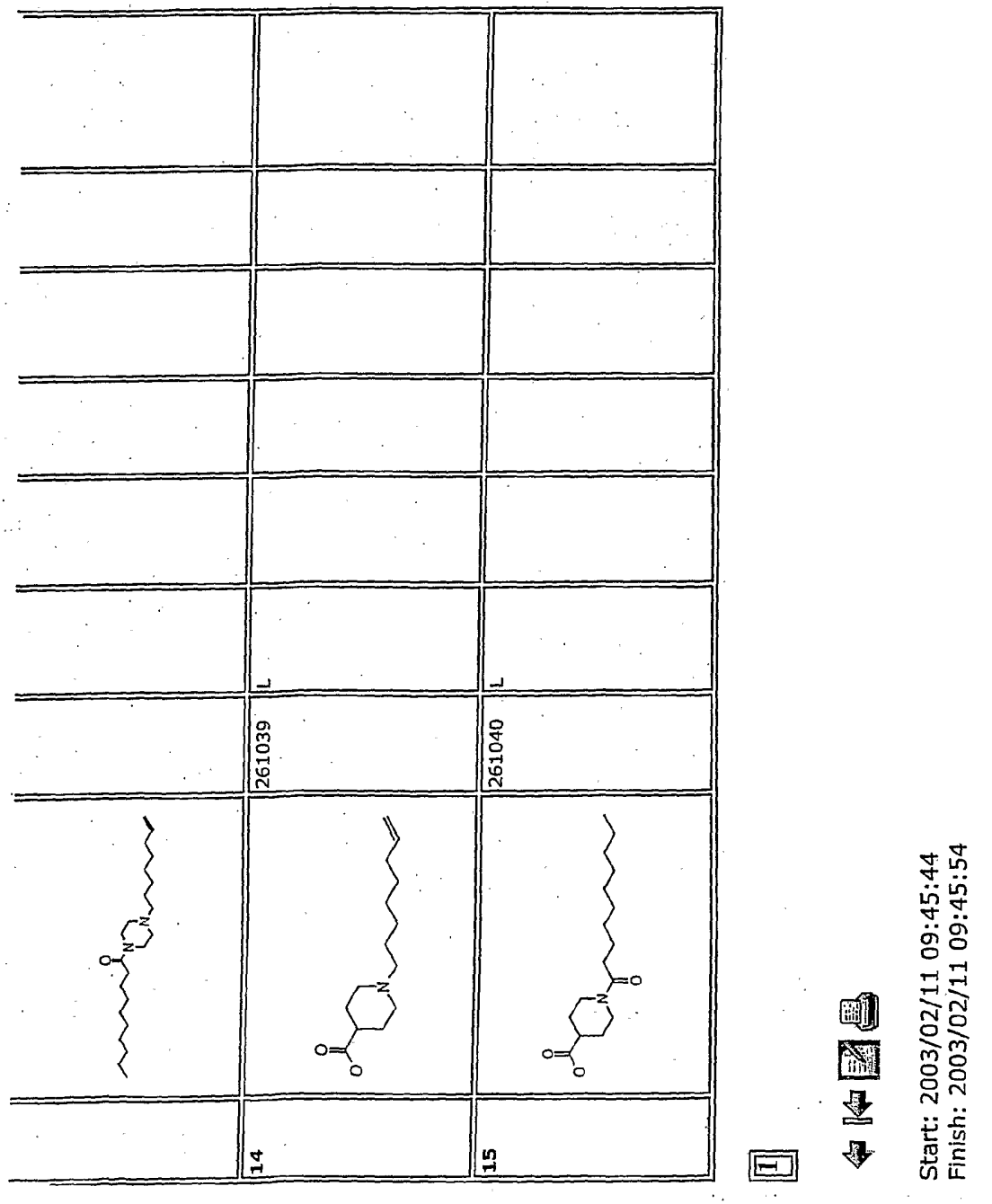
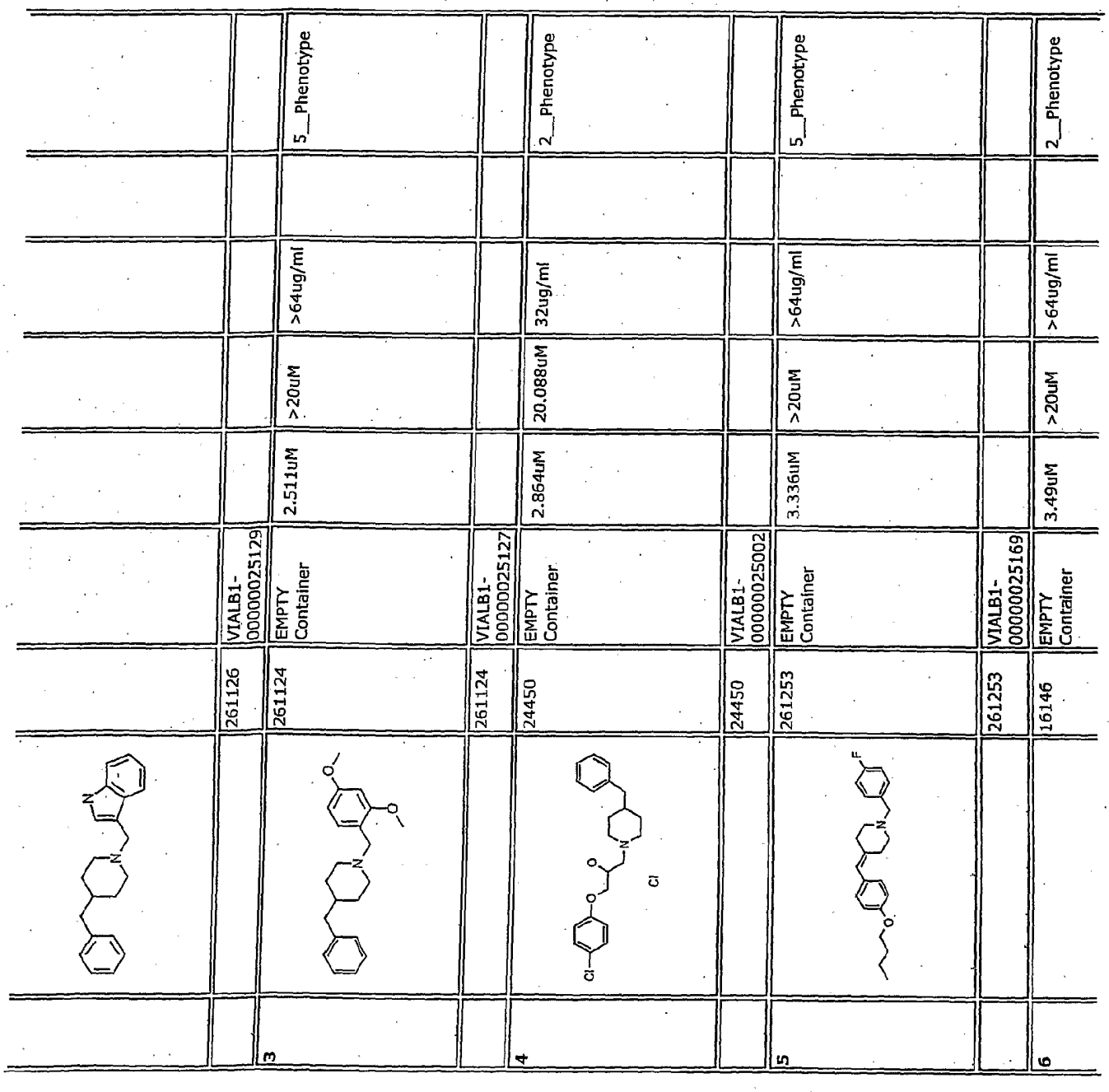

14
261039
L
15
261040
L
1
Start: 2003/02/11 09:45:44
Finish: 2003/02/11 09:45:54

FIGURE 1A

FORMULA (E) COMPOUNDS

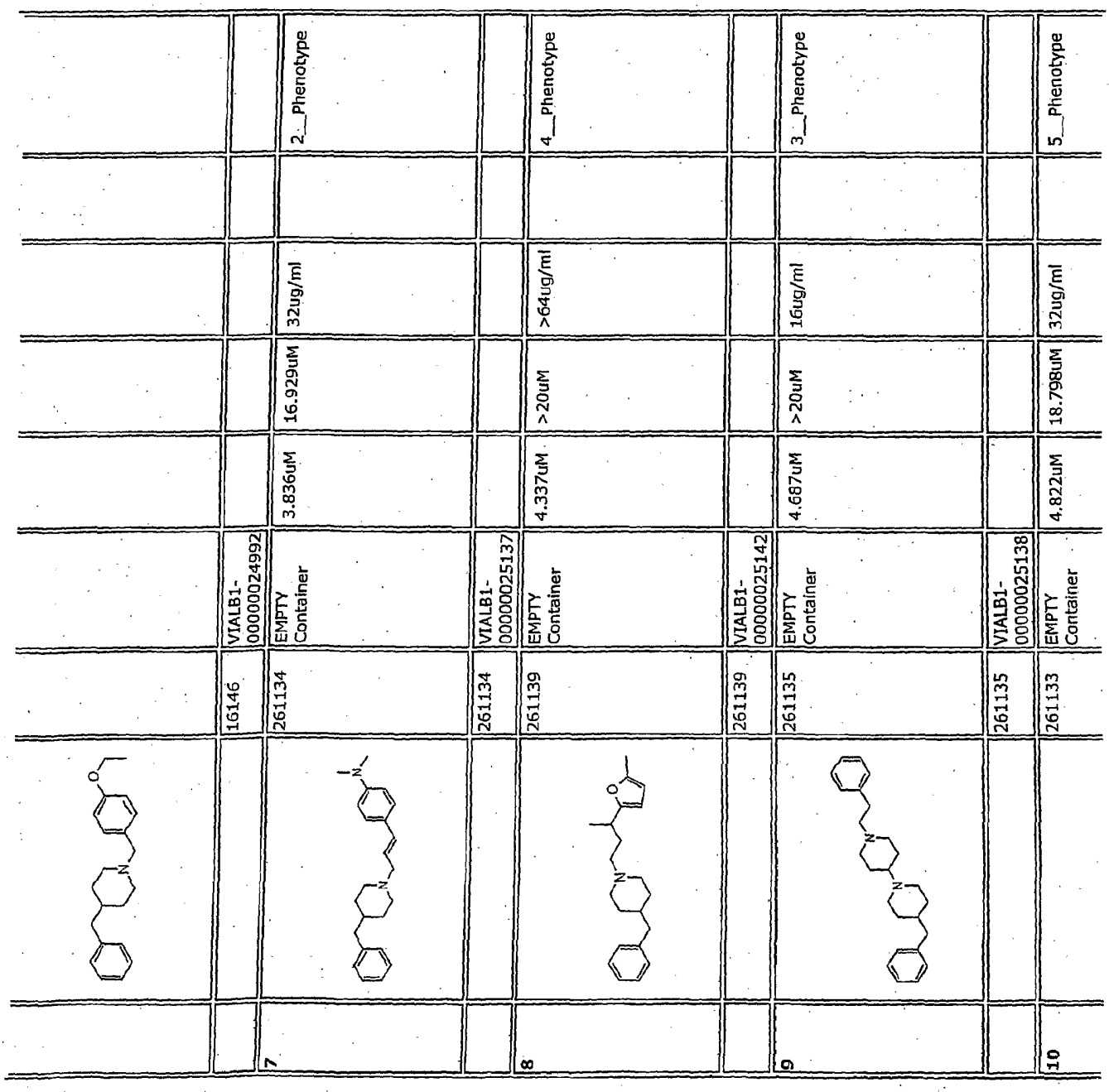
	Counter	Structure	SampleID	Batch	Result C. albicans LOG IC50 (uM)	Result C. albicans STAT IC50 (uM)	Result C. albicans MIC (ug/ml)	Result C. albicans Overnight Growth Inhibtion (%)	Result C. albicans Phenotype Rating
	1		84755	Error : 12752	1.178uM				
			84755	VIALB1-00000025029					
			84755	EMPTY Container		8.988uM	16ug/ml		2*__Phenotype
	2		261126	EMPTY Container	1.369uM	>20uM	>64ug/ml		2*__Phenotype

FIGURE 1A



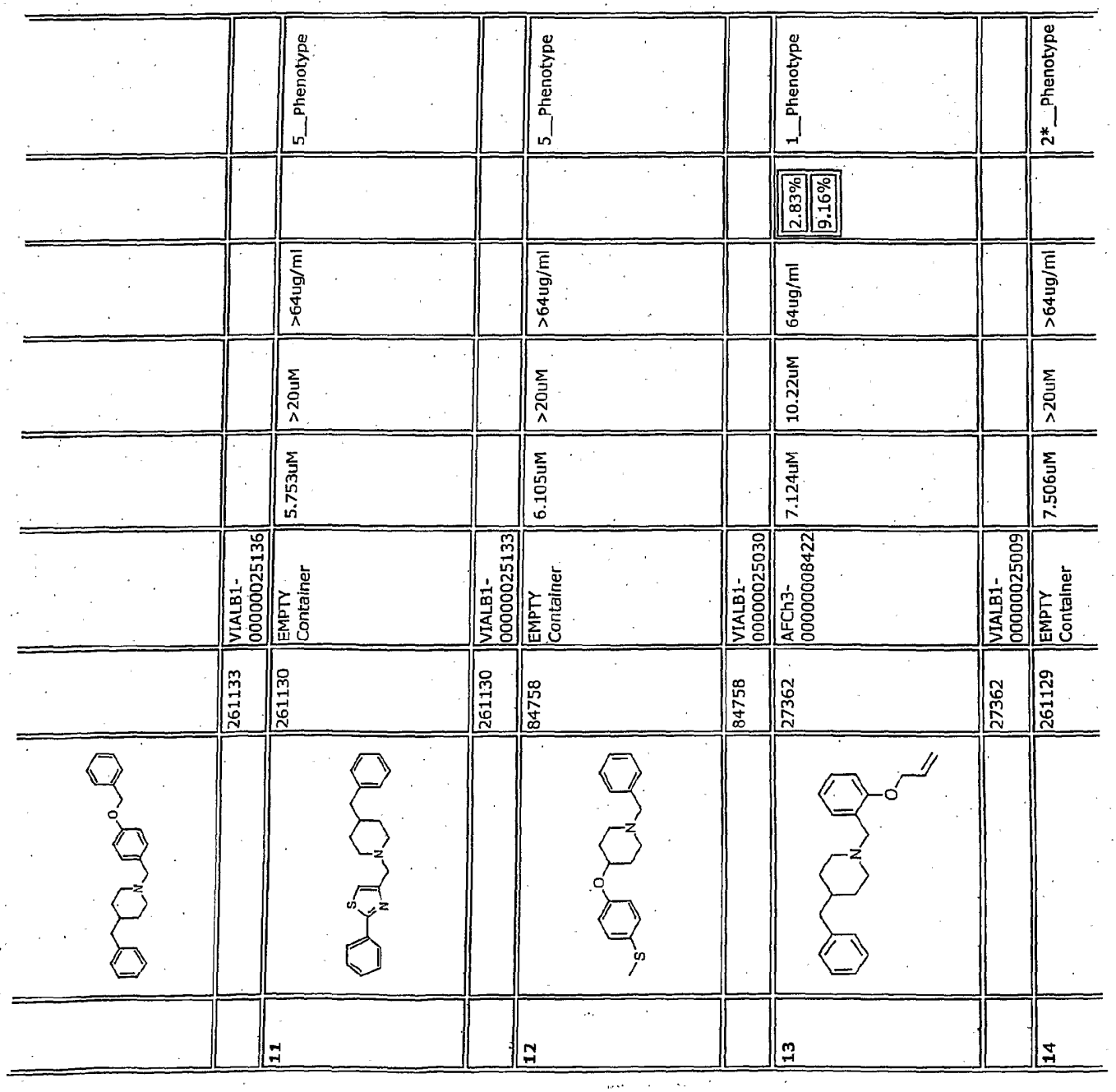
									5__Phenotype
		VIALB1-00000025129							
	261126	EMPTY Container	2.511uM	>20uM	>64ug/ml				
3	261124								5__Phenotype
		VIALB1-00000025127							
	261124	EMPTY Container	2.864uM	20.088uM	32ug/ml				
4	24450								2__Phenotype
		VIALB1-00000025002							
	24450	EMPTY Container	3.336uM	>20uM	>64ug/ml				
5	261253								5__Phenotype
		VIALB1-00000025169							
	261253	EMPTY Container	3.49uM	>20uM	>64ug/ml				
6	16146								2__Phenotype

FIGURE 1A



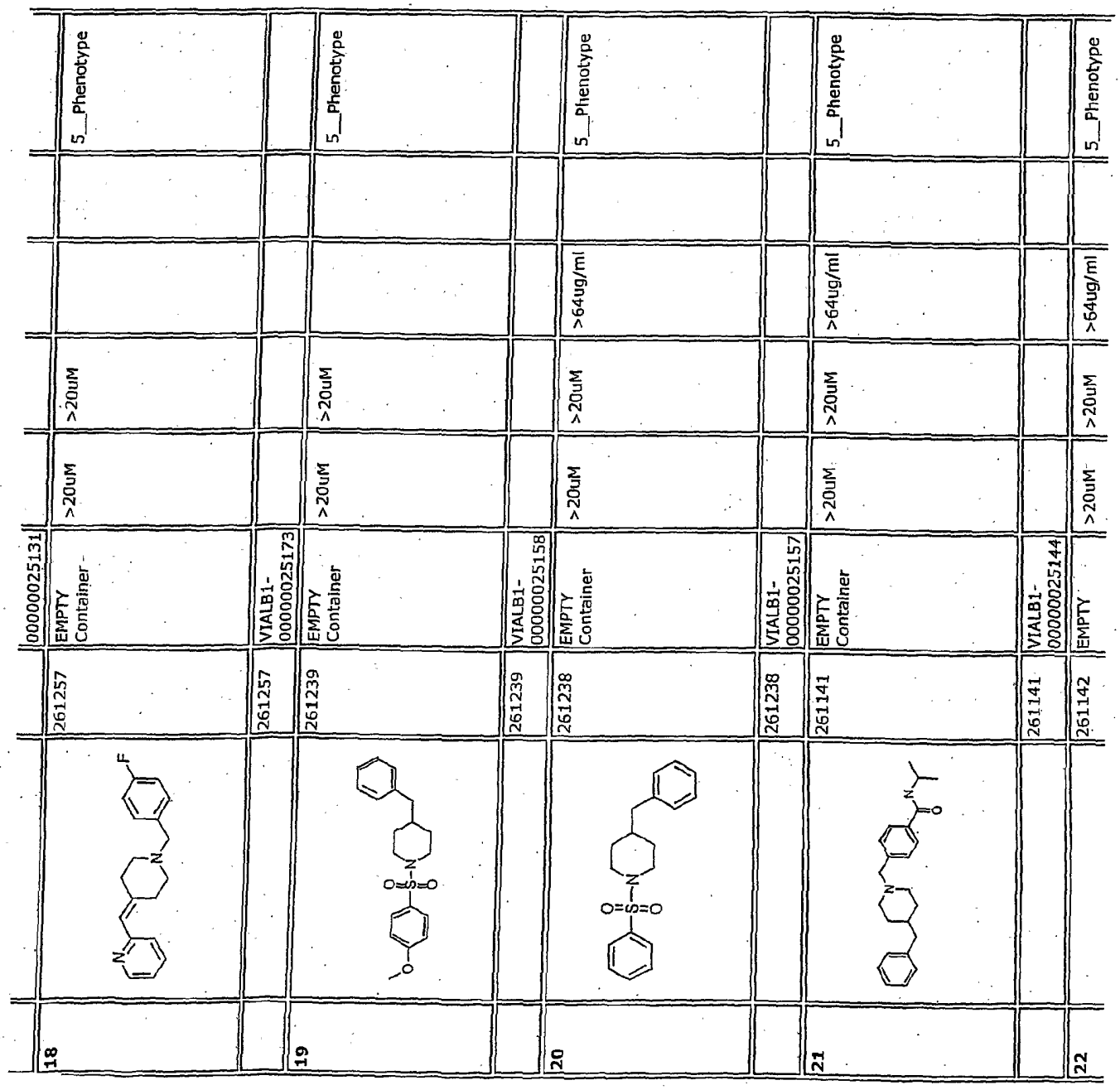
7		16146	VIALB1-000000024992					
		261134	EMPTY Container	3.836uM	16.929uM	32ug/ml	2__Phenotype	
		261134	VIALB1-000000025137					
8		261139	EMPTY Container	4.337uM	>20uM	>64ug/ml	4__Phenotype	
		261139	VIALB1-000000025142					
9		261135	EMPTY Container	4.687uM	>20uM	16ug/ml	3__Phenotype	
		261135	VIALB1-000000025138					
10		261133	EMPTY Container	4.822uM	18.798uM	32ug/ml	5__Phenotype	

FIGURE 1A



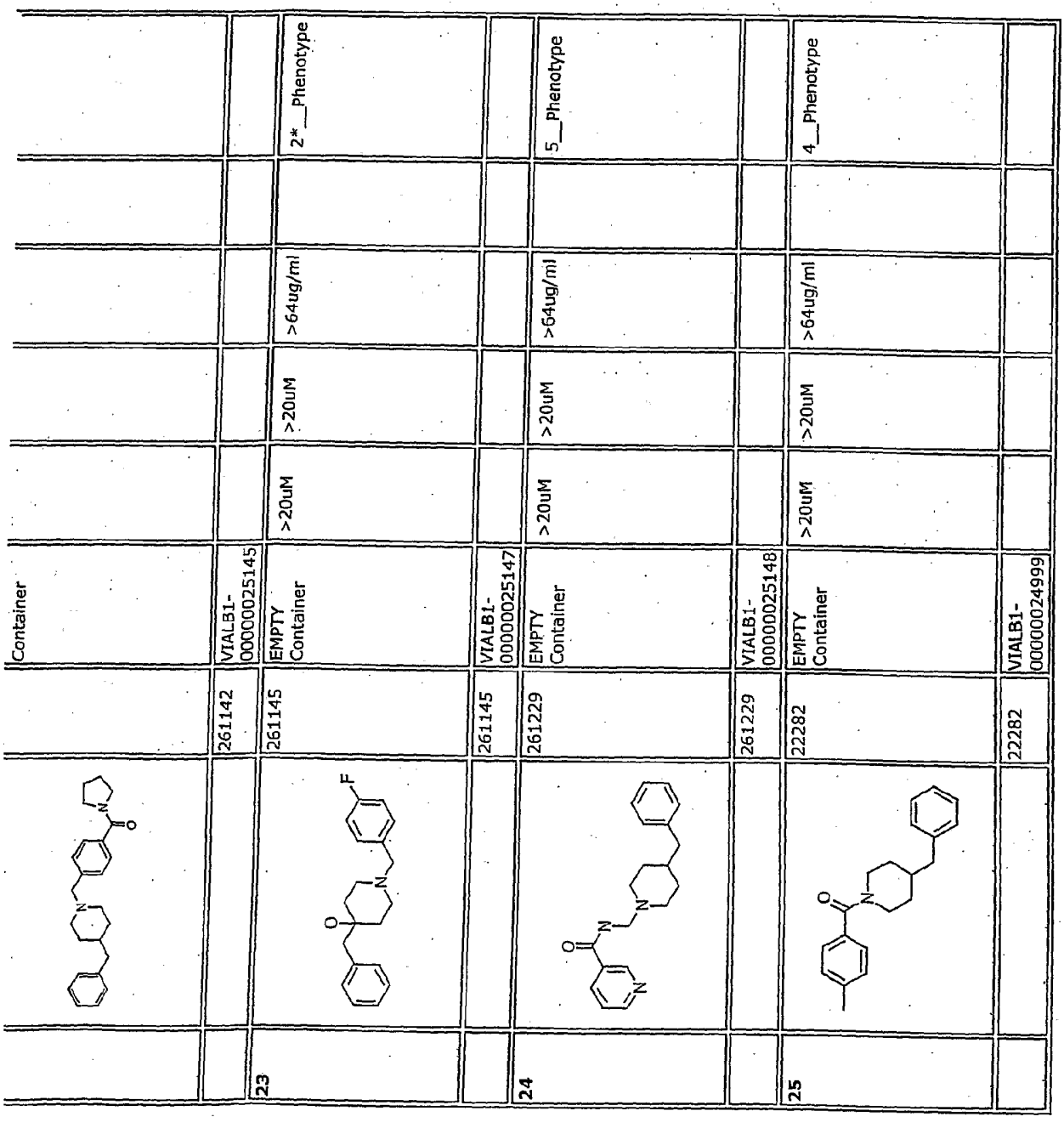
11		261133	VIALB1-00000025136						
		261130	EMPTY Container	5.753uM	> 20uM	>64ug/ml		5__Phenotype	
		261130	VIALB1-00000025133						
12		84758	EMPTY Container	6.105uM	> 20uM	>64ug/ml		5__Phenotype	
		84758	VIALB1-00000025030						
13		27362	AFCh3-00000008422	7.124uM	10.22uM	64ug/ml	2.83% 9.16%	1__Phenotype	
		27362	VIALB1-00000025009						
14		261129	EMPTY Container	7.506uM	> 20uM	>64ug/ml		2*__Phenotype	

FIGURE 1A



		000000025131						
18		261257	EMPTY Container	>20uM	>20uM			5__Phenotype
		261257	VIALB1-000000025173					
19		261239	EMPTY Container	>20uM	>20uM			5__Phenotype
		261239	VIALB1-000000025158					
20		261238	EMPTY Container	>20uM	>64ug/ml			5__Phenotype
		261238	VIALB1-000000025157					
21		261141	EMPTY Container	>20uM	>64ug/ml			5__Phenotype
		261141	VIALB1-000000025144					
22		261142	EMPTY	>20uM	>64ug/ml			5__Phenotype

FIGURE 1A



		Container					
	261142	VIALB1-00000025145	>20uM	>64ug/ml	>20uM	2*__Phenotype	
23	261145	EMPTY Container	>20uM	>64ug/ml	>20uM	2*__Phenotype	
	261145	VIALB1-00000025147					
	261229	EMPTY Container	>20uM	>64ug/ml	>20uM	5__Phenotype	
24	261229	VIALB1-00000025148					
	22282	EMPTY Container	>20uM	>64ug/ml	>20uM	4__Phenotype	
25	22282	VIALB1-00000024999					

FIGURE 1A

FORMULA (C) COMPOUNDS

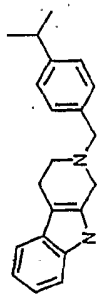
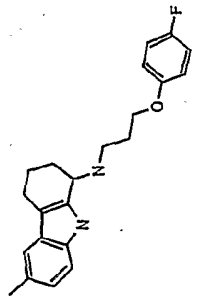
Counter	Structure	SampleID	Parent	Compound Class	C. albicans LOG IC50 (uM)	Result	C. albicans STAT IC50 (uM)	Result	C. albicans MIC (ug/ml)	Result	C. albicans Overnight Growth Inhibition (%)	Result	C. albicans Phenotype Rating	Result
1		17462	17462	C	1.668uM 3.306uM		9.967uM >20uM		>64ug/ml		57.78% 66.65%		1_Phenotype 5_Phenotype 5_Phenotype	
2		15079	17462	C	1.357uM 1.938uM		2.79uM 8.198uM		4ug/ml 8ug/ml		- 51.12% - 12.93% 94.24% 94.56%		1_Phenotype 5_Phenotype 5_Phenotype	

FIGURE 1A

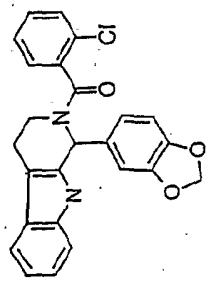
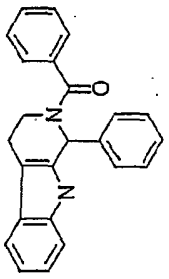
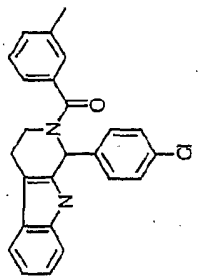
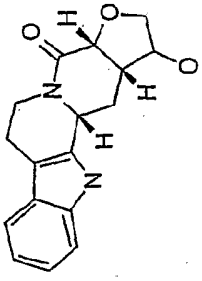
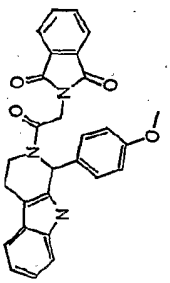
3		385416	17462	C	1.48uM	7.57uM	>64ug/ml	- 19.3% - 11.22%	5__Phenotype 5__Phenotype
4		305756	17462	C	0.845uM 5.77uM	14.07uM >20uM	>64ug/ml >64ug/ml	- 42.78% - 6.91% - 4.52% 2.51%	5__Phenotype 5__Phenotype 5__Phenotype 5__Phenotype
5		261112	17462	C	>20uM	>20uM			5__Phenotype
6		261110	17462	C	>20uM	>20uM			5__Phenotype
7		261109	17462	C	0.923uM	>20uM	>64ug/ml		5__Phenotype
8		76912	17462	C	5.2uM	17.22uM	>64ug/ml		5__Phenotype

FIGURE 1A

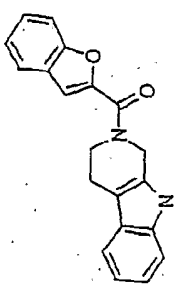
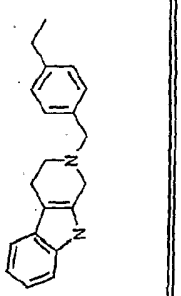
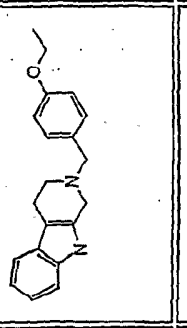
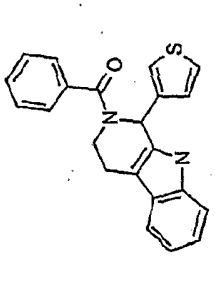
							19.94% - 5.73%	5__Phenotype	
9		76403	17462	C	>20uM	>20uM		5__Phenotype	
10		17802	17462	C	7.98uM	>20uM	>64ug/ml	9.72%	5__Phenotype
11		17454	17462	C	10.58uM	>20uM	>64ug/ml	19.31%	5__Phenotype
12		4951	17462	C	1.032uM	18.8uM	>64ug/ml	32.57%	5__Phenotype
13		261115	17462	C	>20uM	>20uM			5__Phenotype

FIGURE 1A

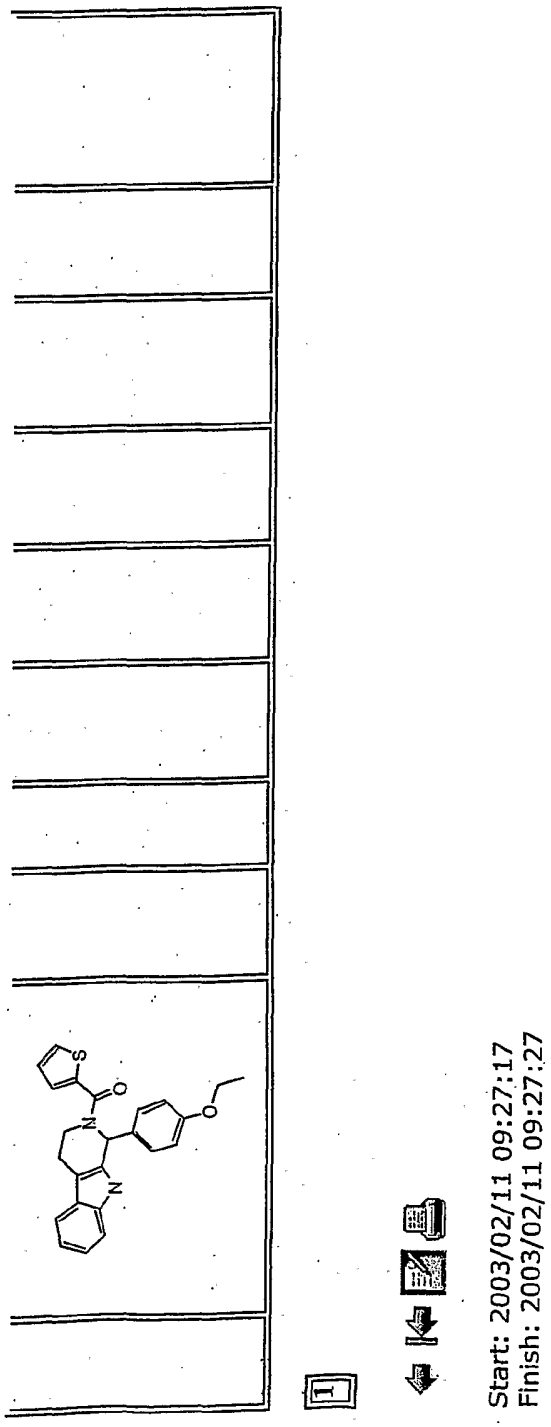


FIGURE 1A

FORMULA (AA) COMPOUNDS

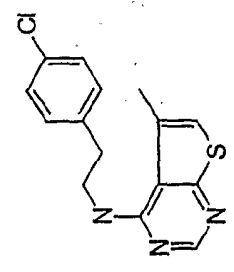
	Structure	SampleID	AA Batch	Result C. albicans LOG IC50 (uM)	Result C. albicans STAT IC50 (uM)	Result C. albicans MIC (ug/ml)	Result C. albicans Overnight Growth Inhibtion (%)	Result C. albicans Phenotype Rating
Counter								
1		261965	VIALB2-00000034833	0.107uM	4.075uM	>64ug/ml	50.81%	2__Phenotype
		261965	VIALB1-00000023144	0.32uM	2.087uM	>64ug/ml	40.045%	1__Phenotype
2		413079	VIALB1-00000039230	0.364uM	>20uM	>64ug/ml		3*__Phenotype

FIGURE 1A

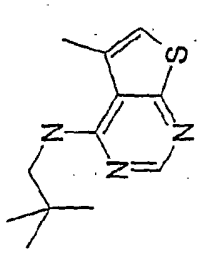
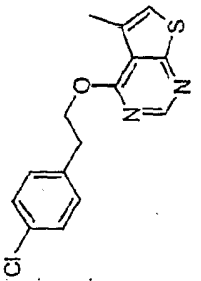
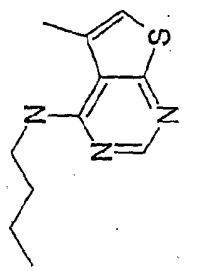
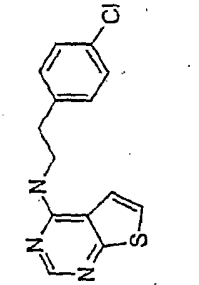
							1__Phenotype	
							8.25%	
						64-32ug/ml		
					14.177uM			
				0.551uM				
		VIALB1-00000036204						
	401848							
3								
							4__Phenotype	
						>64ug/ml		
					>20uM			
				0.608uM				
		VIALB1-00000039226						
	413075							
4								
							3__Phenotype	
						64ug/ml		
					>20uM			
				0.666uM				
		VIALB1-00000039229						
	413078							
5								
							2__Phenotype	
						>64ug/ml	21.13% 25.89%	
					>20uM			
				0.730uM				
		VIALB1-00000037204						
	404980							
6								
							5__Phenotype	
						>64ug/ml	-	
					>20uM			
				2.15uM				
		VIALB2-00000032047						
	284558							
7								

FIGURE 1A

							24.32% 4.67%	5__Phenotype
	284558	VIALB1-00000030451	2.82uM	>20uM	>64ug/ml	- 17.47% - 11.88%	5__Phenotype 5__Phenotype	
8	272502	VIALB1-00000031916	2.45uM	>20uM	>64ug/ml	- 28.01% - 15.55%	5__Phenotype 5__Phenotype	
9	413077	VIALB1-00000039228	2.529uM	>20uM	>64ug/ml		5__Phenotype	
10	385617	VIALB1-00000030466	3.16uM	>20uM	>64ug/ml	- 34.48% -13%	5__Phenotype 5__Phenotype	
11	413051	VIALB1-00000038670	5.729uM	>20uM	>64ug/ml		5__Phenotype	

FIGURE 1A

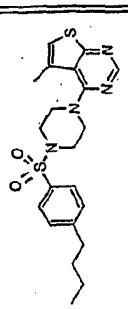
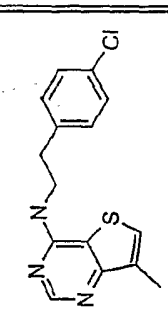
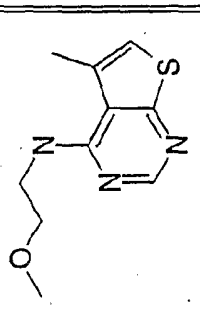
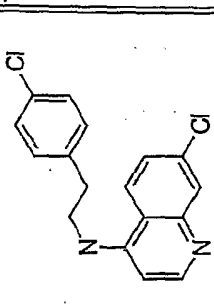
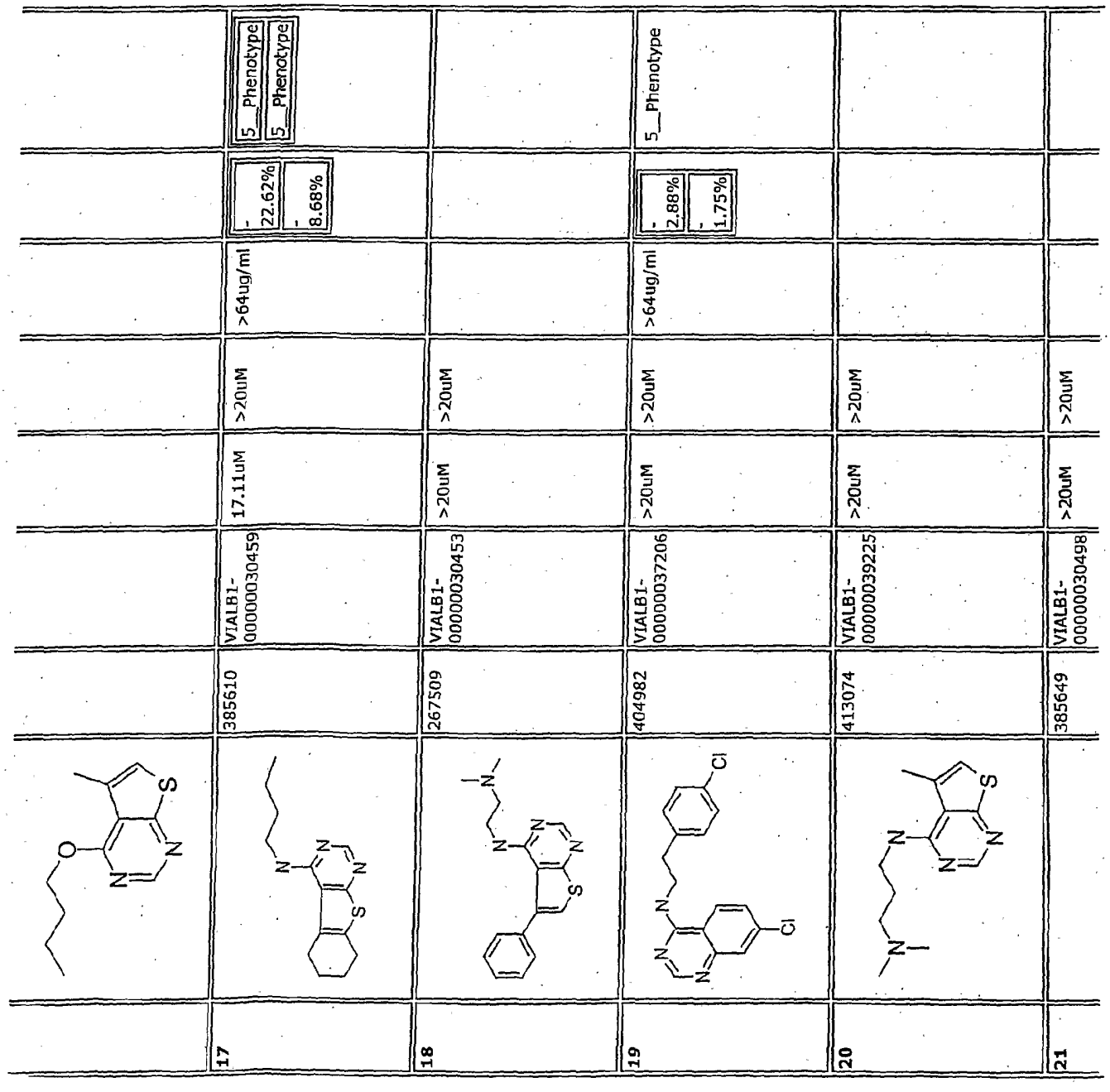
						5__Phenotype 5__Phenotype		
					- 19.84% 6.21%			
					>64ug/ml			
					>20uM			
				5.73uM				
			VIALB1-00000031797					
		292832						
12								
						5__Phenotype		
					25.73% 35.21%			
					>64ug/ml			
					>20uM			
				5.903uM				
			VIALB1-00000037205					
		404981						
13								
						5__Phenotype		
					>64ug/ml			
					>20uM			
				9.717uM				
			VIALB1-00000039224					
		413073						
14								
						5__Phenotype		
					43.81%			
					>64ug/ml			
					>20uM			
				15.530uM				
			VIALB1-00000034834					
		386311						
15								
						5__Phenotype		
					64ug/ml			
					>20uM			
				16.762uM				
			VIALB1-00000039231					
		413080						
16								

FIGURE 1A



17	385610	VIALB1-000000030459	17.11uM	>20uM	>64ug/ml	- 22.62% - 8.68%	5_Phenotype 5_Phenotype	
18	267509	VIALB1-000000030453	>20uM	>20uM				
19	404982	VIALB1-000000037206	>20uM	>20uM	>64ug/ml	- 2.88% - 1.75%	5_Phenotype	
20	413074	VIALB1-000000039225	>20uM	>20uM				
21	385649	VIALB1-000000030498	>20uM	>20uM				

stepC.isp

FIGURE 1A

								5__Phenotype
							1.95%	
						>64ug/ml		
					>20uM			
				>20uM				
			VIALB1-00000034835					
		386312						
	22							
								5__Phenotype
							- 0.95%	
						>64ug/ml		
					>20uM			
				>20uM				
			VIALB1-00000034836					
		386313						
	23							
								5__Phenotype
							- 0.08%	
						>64ug/ml		
					>20uM			
				>20uM				
			VIALB1-00000034837					
		386314						
	24							
								5__Phenotype
						>20uM		
				>20uM				
			VIALB1-00000037203					
		404979						
	25							

FIGURE 1A

FORMULA (AB) COMPOUNDS

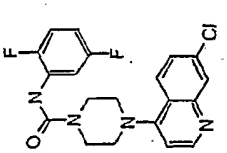
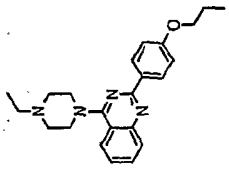
Counter	Structure	SampleID	Compound Class	Result C. albicans LOG IC50 (uM)	Result C. albicans STAT IC50 (uM)	Result C. albicans MIC (ug/ml)	Result C. albicans Overnight Growth Inhibtion (%)	Result C. albicans Phenotype Rating
1		269136	AB	0.709uM	6.158uM	>64ug/ml	22.985%	3_Phenotype
2		280043	AB	2.91uM	15.1uM	32ug/ml	10.28% 33.31%	5_Phenotype 5_Phenotype

FIGURE 1A

3	385411	AB	4.06uM	>20uM	>64ug/ml	- 28.89% - 19.5%	5_Phenotype 5_Phenotype	
4	292731	AB	4.33uM	>20uM	64ug/ml	- 0.24% 17.48%	5_Phenotype 5_Phenotype	
5	292587	AB	12.52uM	>20uM	>64ug/ml	- 7.83% 11.56%	5_Phenotype 5_Phenotype	
6	279968	AB	13.27uM	>20uM	64ug/ml	- 1.68% 24.44%	5_Phenotype 5_Phenotype	
7	385650	AB	>20uM	>20uM				
8	266809	AB	>20uM	>20uM				

FIGURE 1A

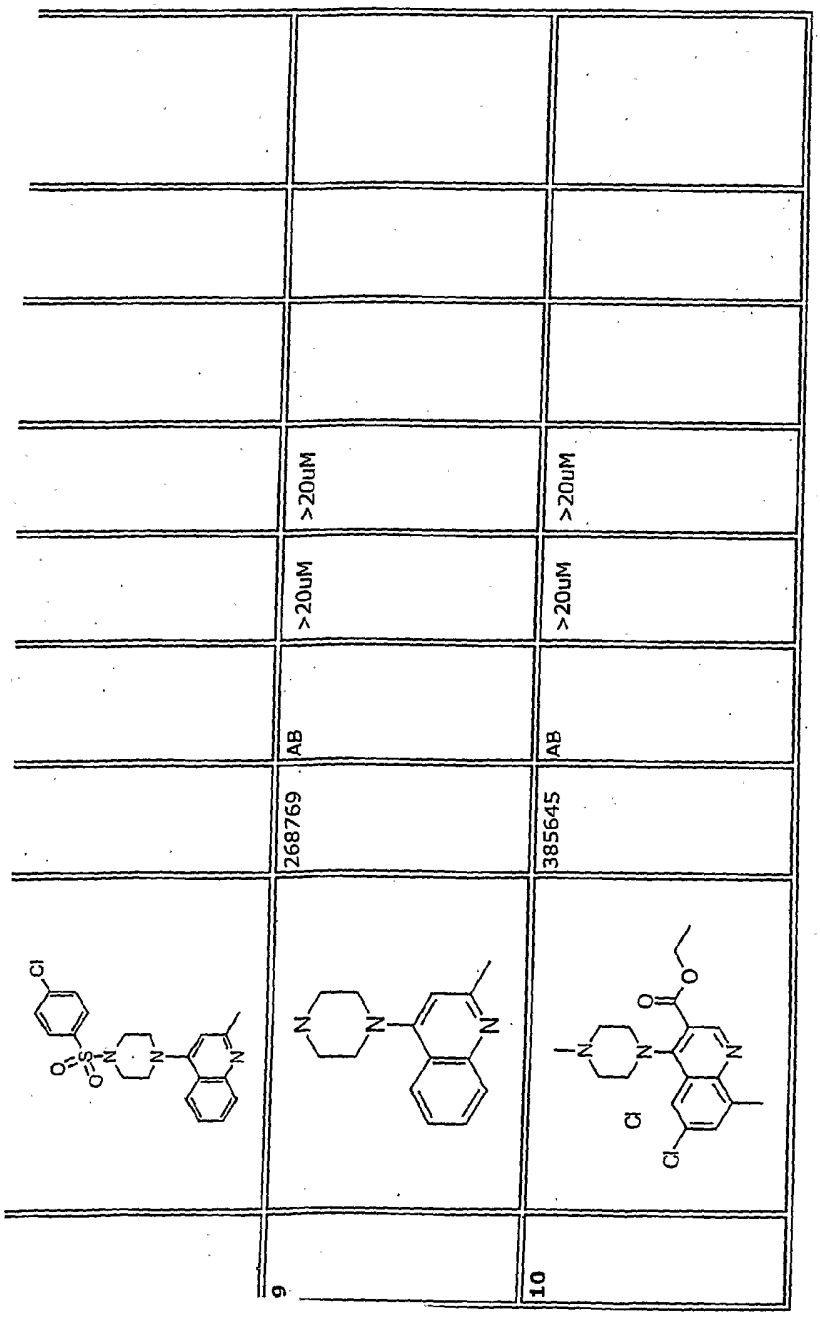

9
268769
AB
>20uM
>20uM
10
385645
AB
>20uM
>20uM
Start: 2003/02/11 10:00:43
Finish: 2003/02/11 10:00:50

FIGURE 1A

FORMULA (K) COMPOUNDS

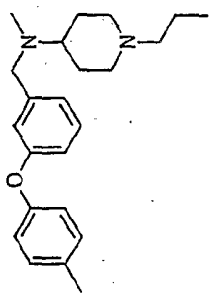
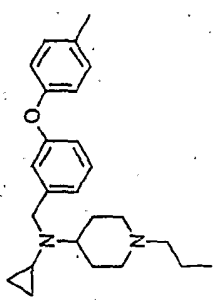
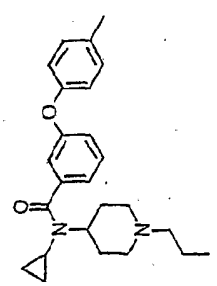
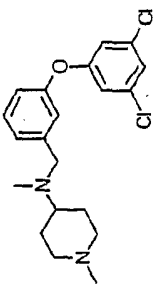
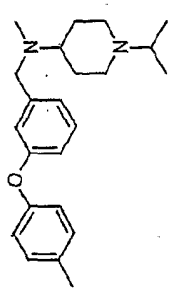
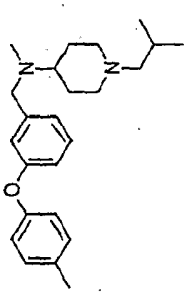
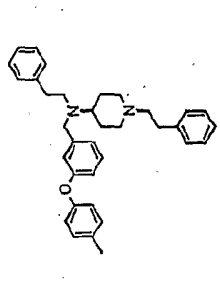
Counter	Structure	SampleID	Compound Class	Result	C. albicans LOG IC50 (uM)	Result	C. albicans STAT IC50 (uM)	Result	C. albicans MIC (ug/ml)	Result	C. albicans Overnight Growth Inhibition (%)	Result	C. albicans Phenotype Rating
1		270273	K		0.26uM 0.482uM		1.83uM 3.16uM		64ug/ml 64ug/ml		12.11% 19.54% 89.32% 96.12%		1__Phenotype 2__Phenotype 2__Phenotype
2		270408	K		0.37uM		1.12uM		64ug/ml		73.45% 85.92%		1__Phenotype

FIGURE 1A

3		270410	K	0.57uM	5.26uM	64ug/ml	52.29% 77.65%	1__Phenotype
4		261122	K	0.59uM	3.63uM	8ug/ml		2__Phenotype
5		270274	K	0.698uM	4.18uM	>64ug/ml	- 6.45% -5.4%	2*__Phenotype 2*__Phenotype
6		270275	K	0.773uM	4.46uM	64ug/ml	5.07% 15.58%	2__Phenotype 2__Phenotype
7		270309	K	0.941uM	14.593uM	>64ug/ml	- 36.32% - 22.38%	2__Phenotype 2__Phenotype
8		261121	K	0.99uM	4.44uM	4ug/ml		1__Phenotype

...ation

FIGURE 1A

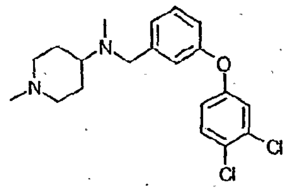
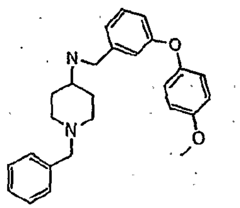
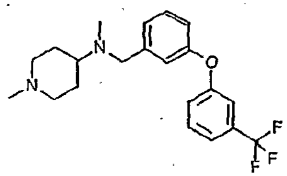
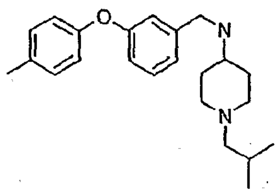
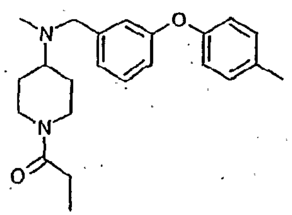
								
9		261003	K	1.112uM	1.95uM	32ug/ml	90.66% 94.36%	2__Phenotype
10		261241	K	1.214uM	10.97uM	16ug/ml		2__Phenotype
11		270315	K	1.282uM	>20uM	64- 32ug/ml	- 50.06% - 1.83%	2__Phenotype 2__Phenotype
12		270403	K	1.29uM	19.21uM	>64ug/ml	14.43% 54.02%	5__Phenotype
13		261033	K	1.305uM	>20uM			1__Phenotype

FIGURE 1A

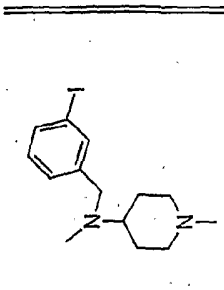
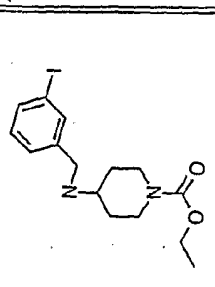
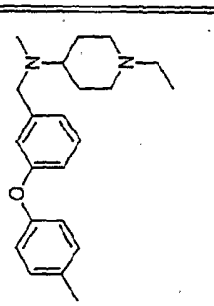
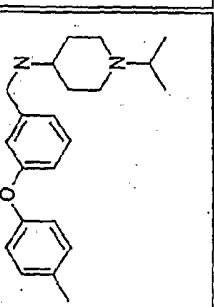
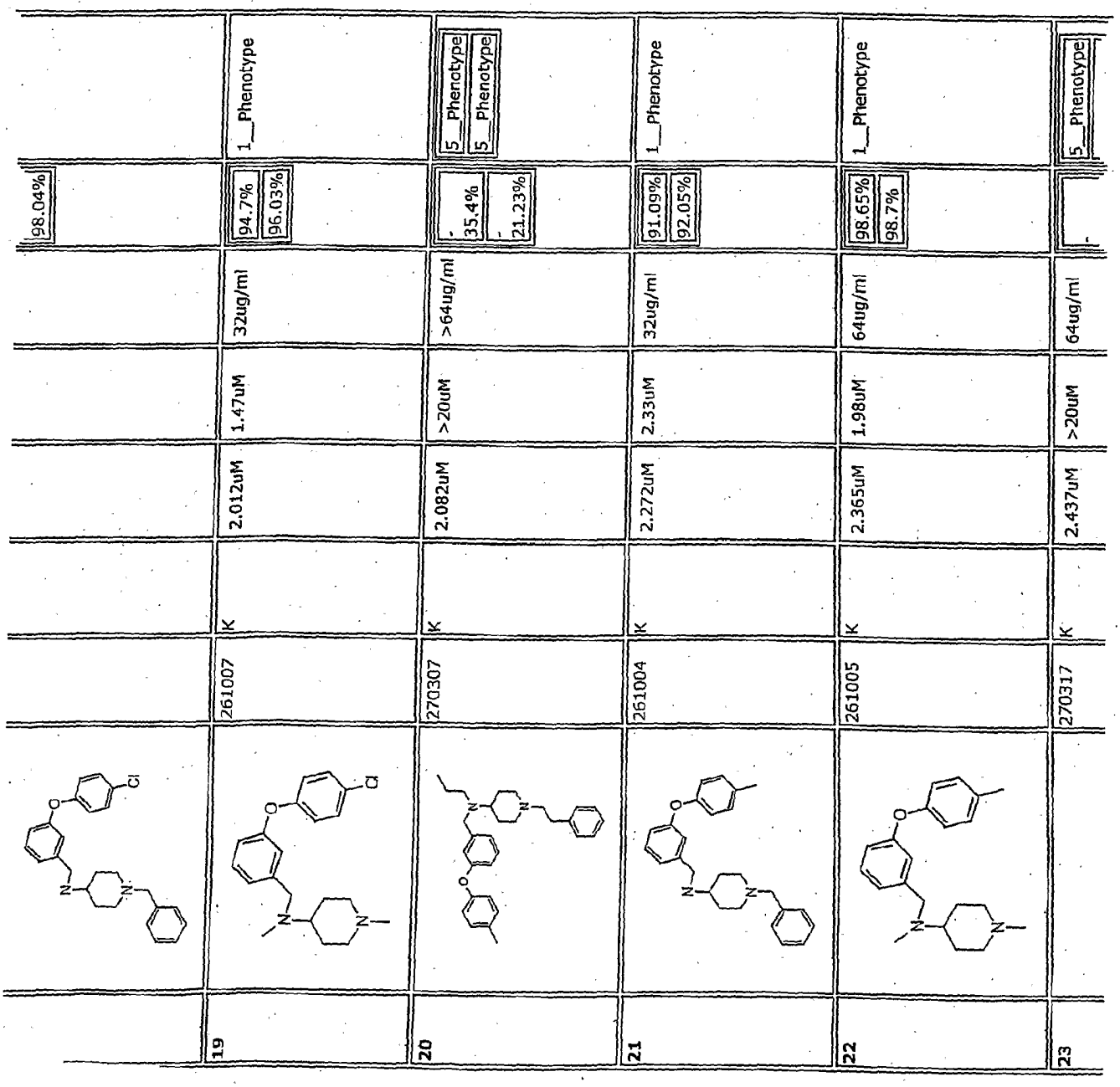
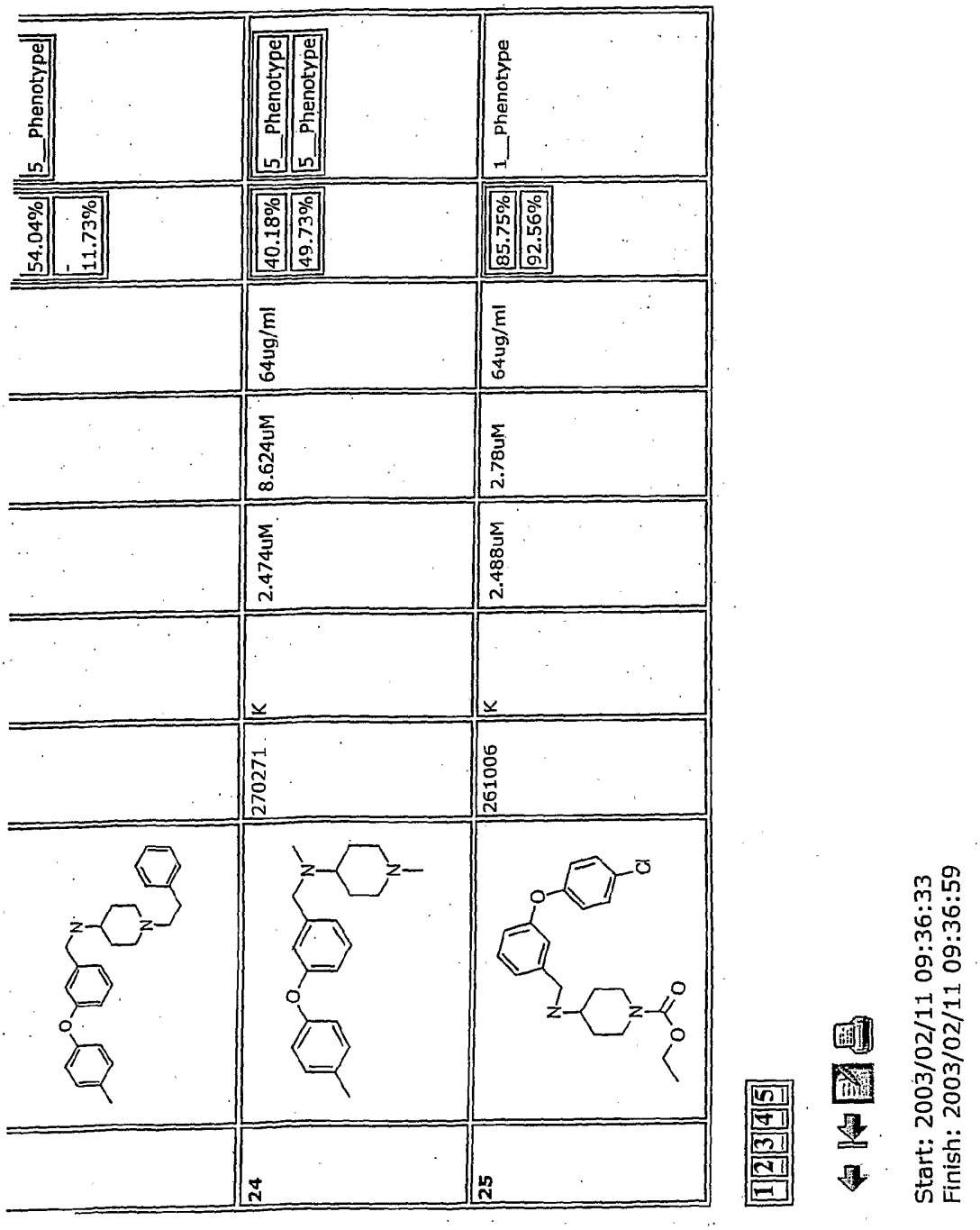
14		261119	K	1.31uM	5.49uM	4ug/ml		2__Phenotype	
15		261034	K	1.3734uM	>20uM			1__Phenotype	
16		270272	K	1.759uM	6.778uM	64-32ug/ml	12.54% 24.03%	5__Phenotype 5__Phenotype	
17		270314	K	1.821uM	>20uM	>64ug/ml	- 50.79% - 2.76%	5__Phenotype 5__Phenotype	
18		261002	K	1.863uM	1.72uM	16ug/ml	92.42%	1__Phenotype	

FIGURE 1A



							98.04%	
19	261007	K	2.012uM	1.47uM	32ug/ml	1__Phenotype	94.7% 96.03%	
20	270307	K	2.082uM	>20uM	>64ug/ml	5__Phenotype 5__Phenotype	- 35.4% - 21.23%	
21	261004	K	2.272uM	2.33uM	32ug/ml	1__Phenotype	91.09% 92.05%	
22	261005	K	2.365uM	1.98uM	64ug/ml	1__Phenotype	98.65% 98.7%	
23	270317	K	2.437uM	>20uM	64ug/ml	5__Phenotype	-	

FIGURE 1A


5__Phenotype
54.04%
-
11.73%
5__Phenotype
40.18%
49.73%
5__Phenotype
5__Phenotype
1__Phenotype
85.75%
92.56%
64ug/ml
64ug/ml
8.624uM
2.78uM
2.474uM
2.488uM
K
K
270271
261006
24
25
1 2 3 4 5
Start: 2003/02/11 09:36:33
Finish: 2003/02/11 09:36:59

Applicant(s): Microbia, Inc.
FIGURE 1A

Class K - AFDD

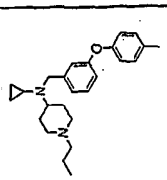
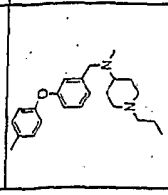
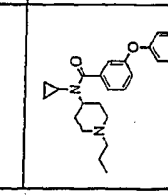
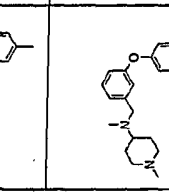
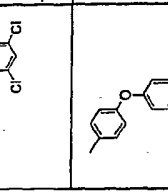
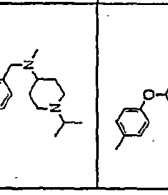
MOLSTRUCTURE	LIC50 (uM)	SIC50 (uM)	MIC (ug/ml)	Phenotype	Source
	0.37	1.12	64	1	microbia synthesized
	0.482	3.16	64	2	microbia synthesized
	0.57	5.26	64	1	microbia synthesized
	0.59	3.63	8	2	microbia synthesized
	0.698	4.185	>64	2*	microbia synthesized
	0.773	4.462	64	2	microbia synthesized

FIGURE 1A

Class K - AFDD

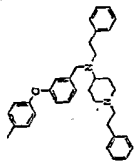
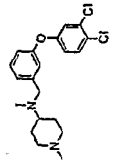
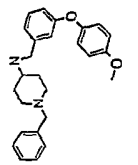
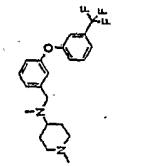
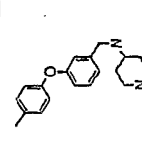
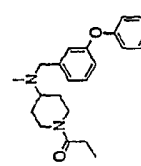
MOLSTRUCTURE	LIC50 (uM)	SIC50 (uM)	MIC (ug/ml)	Phenotype	Source
	0.941	14.593	>64	2	micobia synthesized
	0.99	4.44	4	1	micobia synthesized
	1.11	1.95	32	2	micobia synthesized
	1.214	10.97	16	2	micobia synthesized
	1.282	>20		2	micobia synthesized
	1.29	19.2	>64	5	micobia synthesized

FIGURE 1A

Class K - AFDD

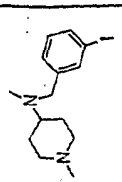
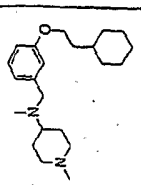
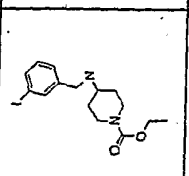
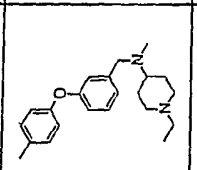
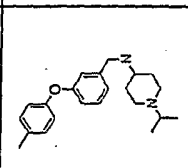
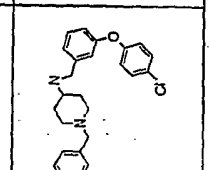
MOLSTRUCTURE	LIC50 (uM)	SIC50 (uM)	MIC (ug/ml)	Phenotype	Source
	1.305	>20		1	micobia synthesized
	1.31	5.49	4	2	micobia synthesized
	1.3734	>20		1	micobia synthesized
	1.759	6.778		5	micobia synthesized
	1.821	>20	>64	5	micobia synthesized
	1.86	1.72	16	1	micobia synthesized

FIGURE 1A

Class K - AFDD

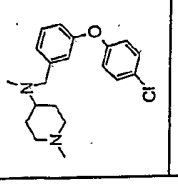
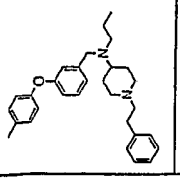
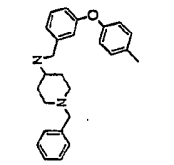
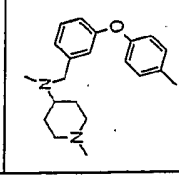
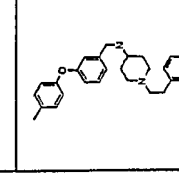
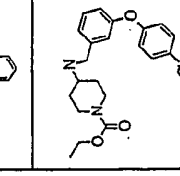
MOLSTRUCTURE	LIC50 (uM)	SIC50 (uM)	MIC (ug/ml)	Phenotype	Source
	2.01	1.47	32	1	micobia synthesized
	2.082	>20	>64	5	micobia synthesized
	2.27	2.33	32	1	micobia synthesized
	2.37	1.98	64	1	micobia synthesized
	2.437	>20	64	5	micobia synthesized
	2.49	2.78	64	1	micobia synthesized

FIGURE 1A

Class K - AFDD

MOLSTRUCTURE	LIC50 (uM)	SIC50 (uM)	MIC (ug/ml)	Phenotype	Source
	2.63	15.8	64	4	micobia synthesized
	2.747	8.624	64	5	micobia synthesized
	3.122	6.972	64	5	micobia synthesized
	3.126	17.269	>64	5	micobia synthesized
	3.397	>20	32	2	micobia synthesized
	3.57	>20	64	5	micobia synthesized

FIGURE 1A

Class K - AFDD

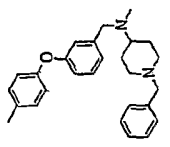
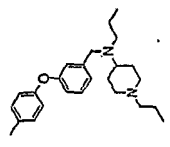
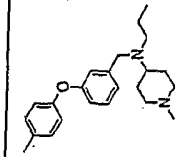
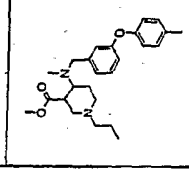
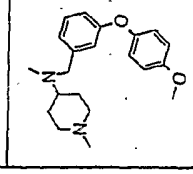
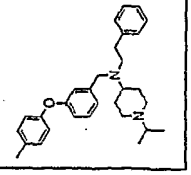
MOLSTRUCTURE	LIC50 (uM)	SIC50 (uM)	MIC (ug/ml)	Phenotype	Source
	3.704	8.826	>64	5	micobia synthesized
	3.82	9.57	64	5	micobia synthesized
	3.831	7.14	64	5	micobia synthesized
	3.88	17.28	>64	5	micobia synthesized
	3.97	2.41	64	5	micobia synthesized
	4.195	12.74	32	5	micobia synthesized

FIGURE 1A

Class K - AFDD

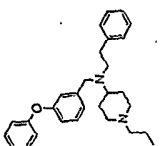
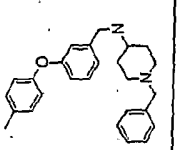
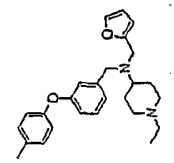
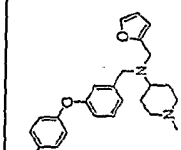
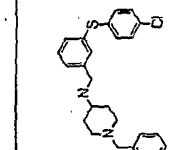
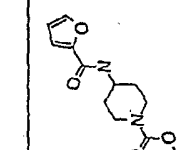
MOLSTRUCTURE	LIC50 (uM)	SIC50 (uM)	MIC (ug/ml)	Phenotype	Source
	4.269	17.545	>64	5	micobia synthesized
	4.273	>20	32	5	micobia synthesized
	4.43	9.207		5	micobia synthesized
	4.81	8.196		5	micobia synthesized
	4.838	>20		5	micobia synthesized
	5.629	>20		1	micobia synthesized

FIGURE 1A

Class K - AFDD

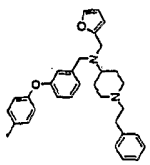
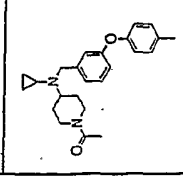
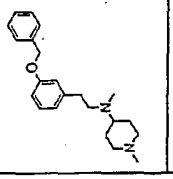
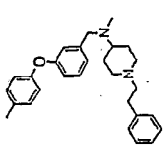
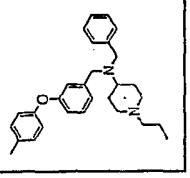
MOLSTRUCTURE	LIC50 (uM)	SIC50 (uM)	MIC (ug/ml)	Phenotype	Source
	5.658	>20	>64	5	micobia synthesized
	5.667	>20	>64	5	micobia synthesized
	5.69	20.34	>64	5	micobia synthesized
	5.92	>20	64	4	micobia synthesized
	6.07	15.232	64	5	micobia synthesized
	6.682	11.897	>64	5	micobia synthesized

FIGURE 1A

Class K - AFDD

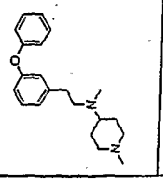
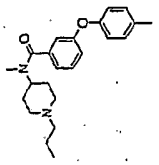
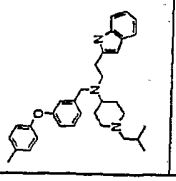
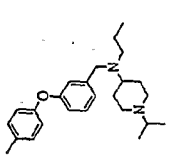
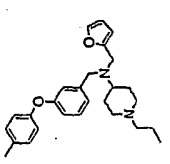
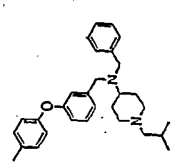
MOLSTRUCTURE	LIC50 (uM)	SIC50 (uM)	MIC (ug/ml)	Phenotype	Source
	6.76	>20	>64	5	micobia synthesized
	6.91	19.99	>64	5	micobia synthesized
	6.948	14.048	>64	2	micobia synthesized
	7.553	>20	>64	5	micobia synthesized
	7.589	15.523	64	5	micobia synthesized
	9.73	>20	>64	5	micobia synthesized

FIGURE 1A

Class K - AFDD

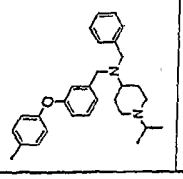
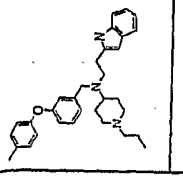
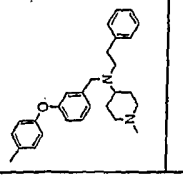
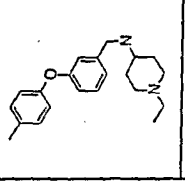
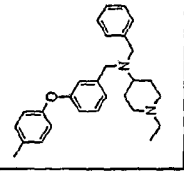
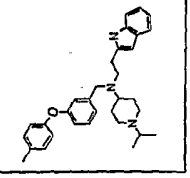
MOLSTRUCTURE	LIC50 (uM)	SIC50 (uM)	MIC (ug/ml)	Phenotype	Source
	9.851	13.605		5	micobia synthesized
	10.217	17.316	32	5	micobia synthesized
	10.697	20.6	16	5	micobia synthesized
	10.746	>20	64	5	micobia synthesized
	11.75	16.74	32	5	micobia synthesized
	11.886	17.624	8	5	micobia synthesized

FIGURE 1A

Class K - AFDD

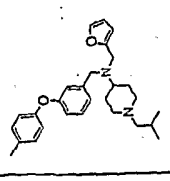
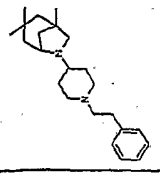
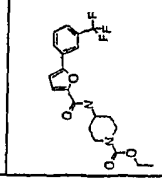
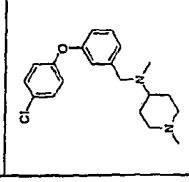
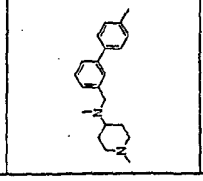
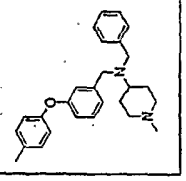
MOLSTRUCTURE	LIC50 (uM)	SIC50 (uM)	MIC (ug/ml)	Phenotype	Source
	11.894	>20	>64	5	microbia synthesized
	12.01	>20	64	5	purchased from chembridge
	12.352	>20		1	microbia synthesized
	12.58	6.43	32	2	purchased from chembridge
	12.7	>20	16	5	microbia synthesized
	13.121	17.34		5	microbia synthesized

FIGURE 1A

Class A - APUU

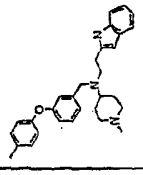
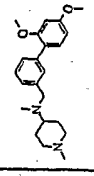
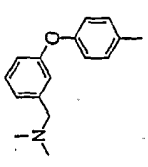
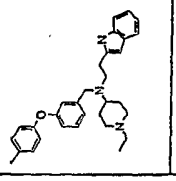
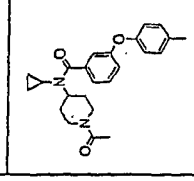
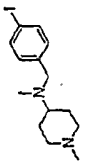
MOLSTRUCTURE	LIC50 (uM)	SIC50 (uM)	MIC (ug/ml)	Phenotype	Source
	14.318	>20	16	5	micobia synthesized
	16.09	>20	>64	5	micobia synthesized
	17.82	25	64	5	micobia synthesized
	17.973	>20	64	5	micobia synthesized
	19.07	>20	>64	5	micobia synthesized
	19.14	>20	64	5	micobia synthesized

FIGURE 1A

Class K - AFDD

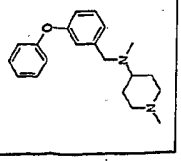
MOLSTRUCTURE	LIC50 (uM)	SIC50 (uM)	MIC (ug/ml)	Phenotype	Source
	>20	14.88		5	micobia synthesized

FIGURE 1A

FORMULA (R) COMPOUNDS

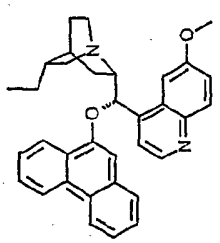
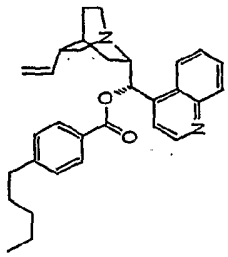
				Result	Result	Result	Result	Result
Counter	Structure	SampleID	Compound Class	C. albicans LOG IC50 (uM)	C. albicans STAT IC50 (uM)	C. albicans MIC (ug/ml)	C. albicans Overnight Growth Inhibtion (%)	C. albicans Phenotype Rating
1		270380	R	0.74uM 2.156uM	1.05uM >20uM	>64ug/ml >64ug/ml	15.01% 46.54% 46.81% 50.37%	1__Phenotype 2__Phenotype
2		270363	R	1.061uM	>20uM	>64ug/ml	19.56%	5__Phenotype

FIGURE 1A

3		270366	R	1.101uM 4.5uM 9.129uM	0.224uM 3.33uM 13.675uM	32ug/ml 64ug/ml >64ug/ml	3.8% 5.96% 13.68% 19.07% 22.72%	3__Phenotype 4__Phenotype 5__Phenotype		
4		270367	R	1.19uM 1.926uM	0.796uM >20uM	>64ug/ml >64ug/ml	13.12% 29.86% 35.35%	4__Phenotype 4__Phenotype		
5		261096	R	1.57uM	21.91uM	>64ug/ml		5__Phenotype		
6		270364	R	2.300uM	>20uM	>64ug/ml	22.72%	5__Phenotype		
7		261058	R	2.71uM	20.31uM	>64ug/ml		4__Phenotype 4__Phenotype		
8		261099	R	3.04uM	9.58uM	32ug/ml		4__Phenotype		

FIGURE 1A

			3.78uM	16.45uM	64-32ug/ml		5__Phenotype
9	261056	R	4.9uM	>20uM	>64ug/ml		5__Phenotype 5__Phenotype
10	11088	R	9.296uM	9.74uM	64ug/ml	22.54% 69.02%	2__Phenotype
11	270377	R	13.24uM	10.7uM	>64ug/ml	-9.6% 13.22%	4__Phenotype
12	261097	R	16.43uM	>20uM	32ug/ml		5__Phenotype
13	270394	R	>20uM	>20uM		-	

FIGURE 1A

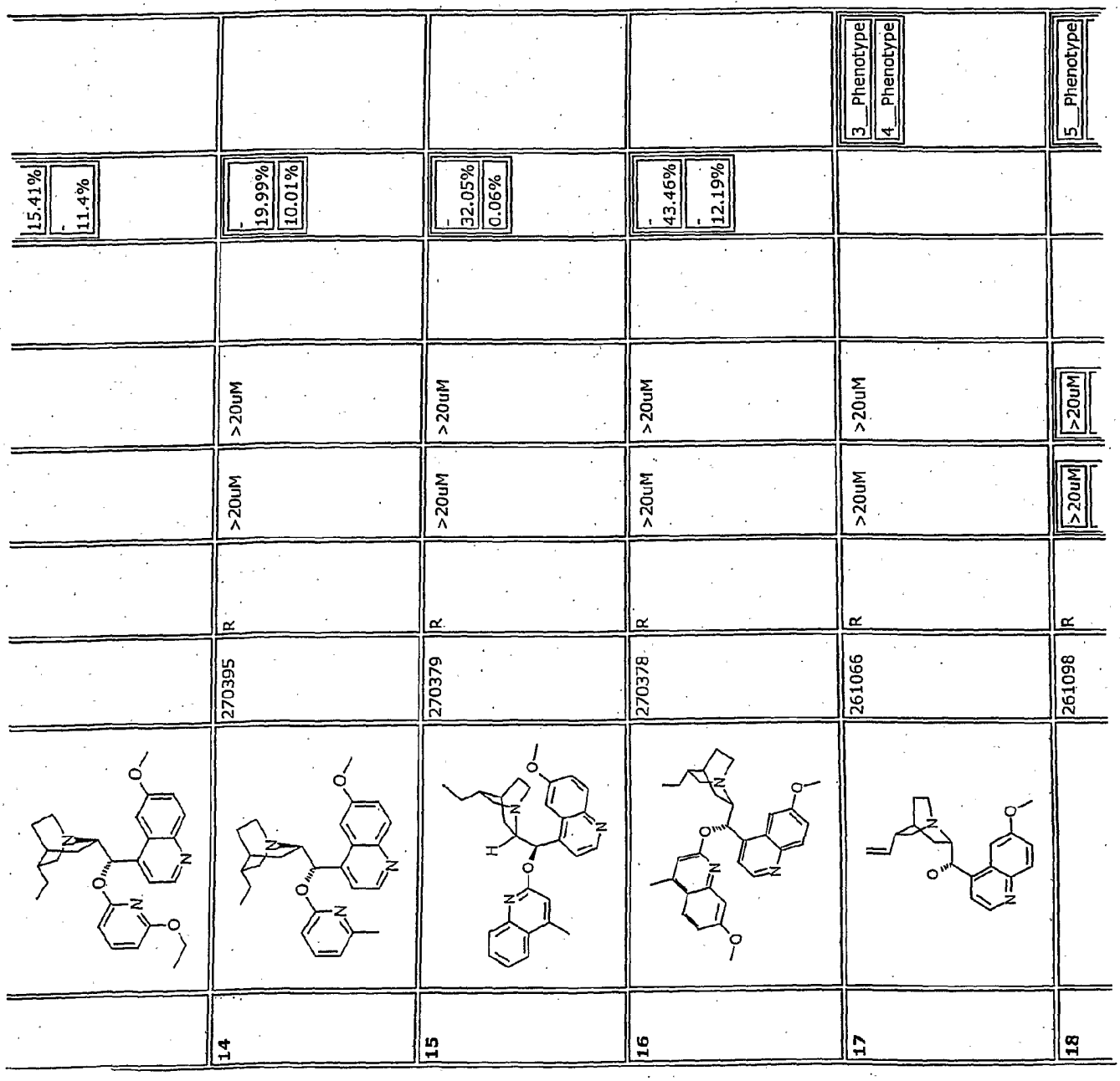
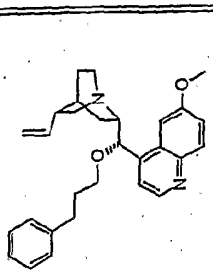
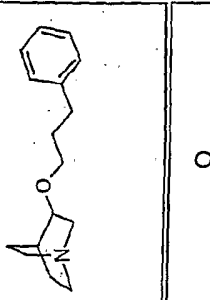
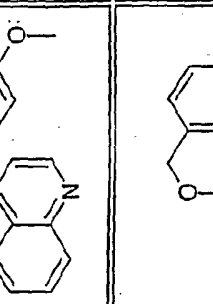
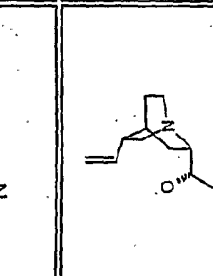

15.41%
- 11.4%
>20uM
>20uM
270395
R
14
- 19.99%
10.01%
>20uM
>20uM
270379
R
15
- 32.05%
0.06%
>20uM
>20uM
270378
R
16
- 43.46%
- 12.19%
3__Phenotype
4__Phenotype
>20uM
>20uM
261066
R
17
5__Phenotype
>20uM
>20uM
261098
R
18

FIGURE 1A

				>20uM	>20uM		5__Phenotype
19		261100	R	>20uM	>20uM		5__Phenotype
20		261061	R	>20uM	>20uM		5__Phenotype 5__Phenotype
21		261062	R	>20uM	>20uM		5__Phenotype 5__Phenotype
22		261063	R	>20uM	>20uM		5__Phenotype 5__Phenotype
23		261064	R	>20uM	>20uM		5__Phenotype

stanC.isp

FIGURE 1A

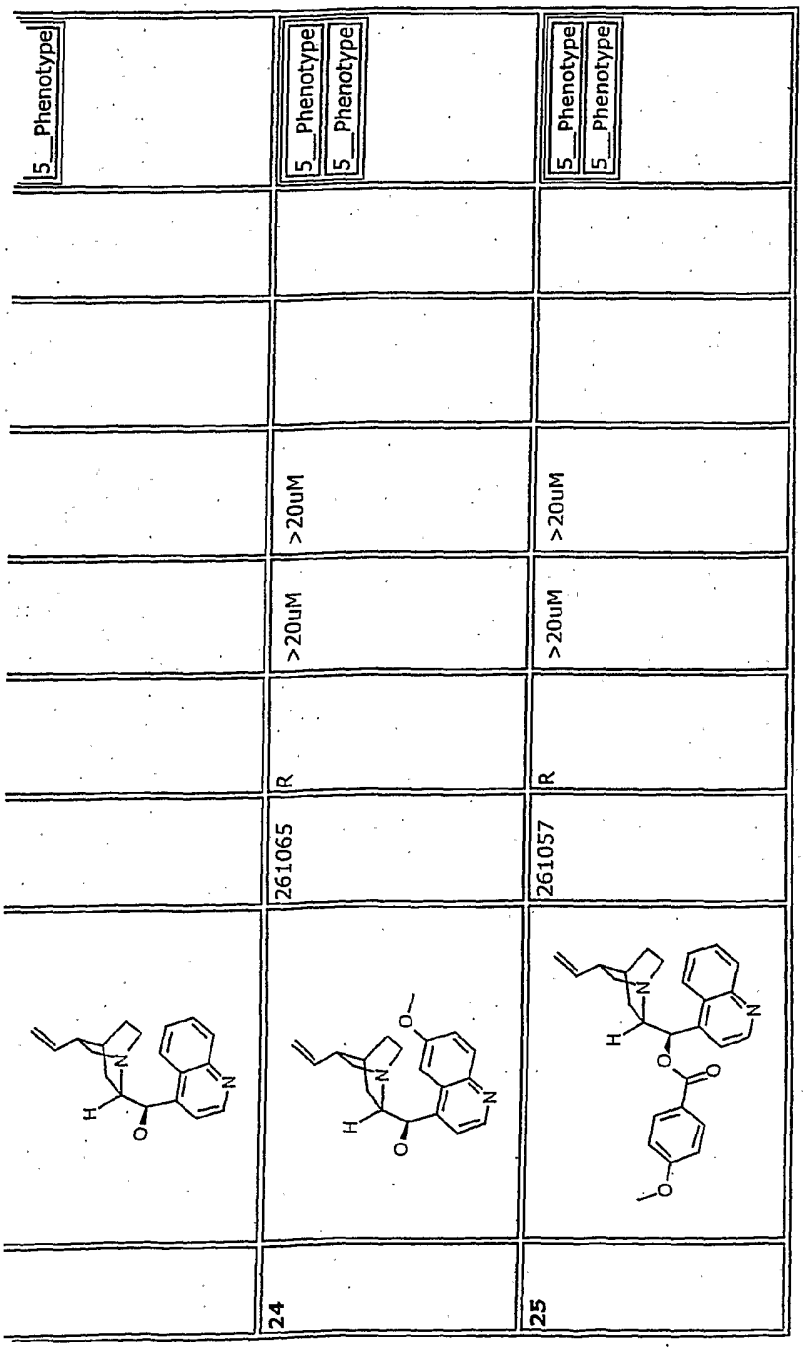
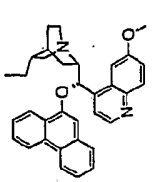
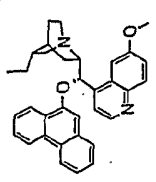
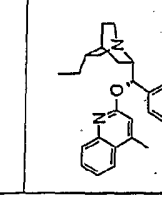
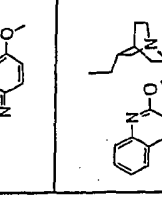
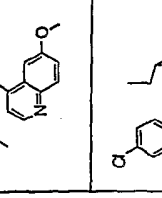
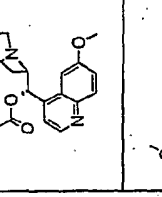

5_Phenotype
24
261065
R
>20uM
>20uM
>20uM
25
261057
R
>20uM
>20uM
>20uM
1 2
Start: 2003/02/11 09:49:41
Finish: 2003/02/11 09:49:56

FIGURE 1A

Class R -AFDD

MOLSTRUCTURE	LIC50 (uM)	SIC50 (uM)	MIC (ug/ml)	Phenotype	Comments
	0.74	1.05	65	1	Aldrich
	1.06	>20	65	5	Microbia synthesized
	1.101	0.224	32	3	Aldrich
	4.5	3.33	65	4	Aldrich
	1.19	>20	65	4	Aldrich
	1.57	21.91	65	5	Microbia synthesized

2/21/2003

Microbia Inc Confidential

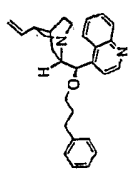
FIGURE 1A

Class R -AFDD

MOLSTRUCTURE	LIC50 (uM)	SIC50 (uM)	MIC (ug/ml)	Phenotype	Comments
	2.30	>20	65	5	Microbia synthesized
	2.71	20.31	65	4	Microbia synthesized
	3.04	9.58	64-32	5	Microbia synthesized
	4.90	>20	65	5	Microbia synthesized
	9.296	9.74	64	2	Chembridge Screening Library
	13.24	10.7	65	4	Microbia synthesized

FIGURE 1A

Class R -AFDD

MOLSTRUCTURE	LIC50 (uM)	SIC50 (uM)	MIC (ug/ml)	Phenotype	Comments
	16.43	>20	32	5	Microbia synthesized

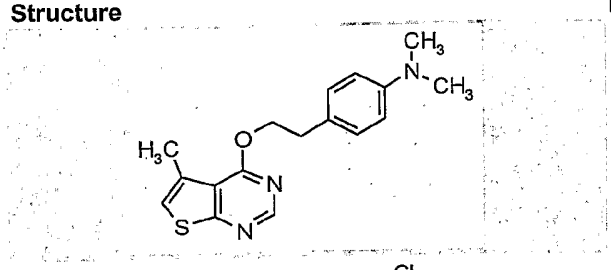
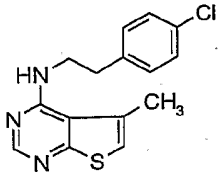
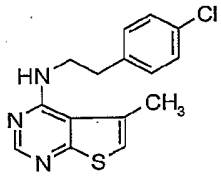
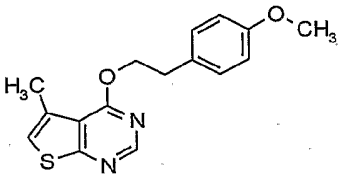
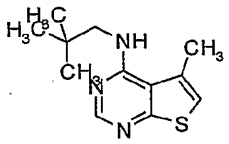
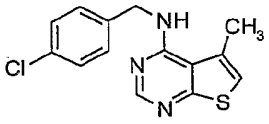
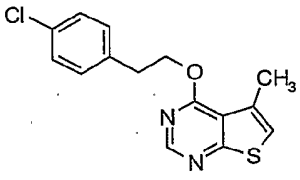
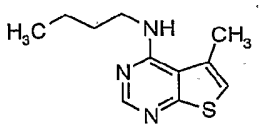
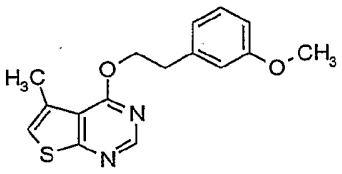
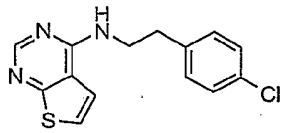
Structure	C.albicans LOG IC50 (uM)
	0.023 uM
	0.107 uM
	0.32 uM
	0.28 uM
	0.364 uM
	0.551 uM
	0.608 uM
	0.666 uM

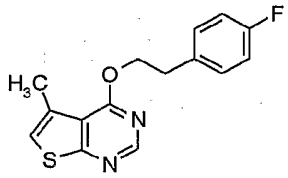
Fig 1B



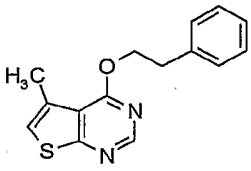
0.7 uM



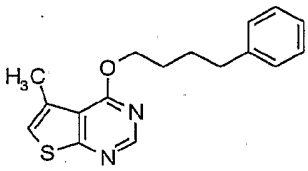
0.730 uM



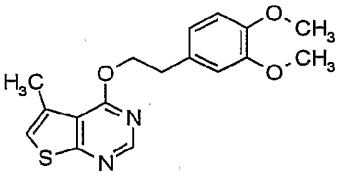
0.84 uM



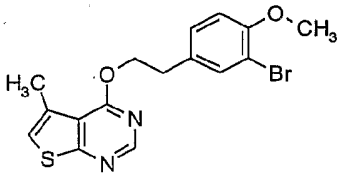
1.2 uM



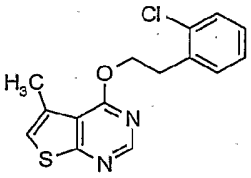
1.2 uM



1.27 uM

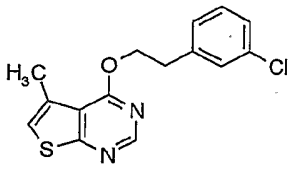


1.920 uM

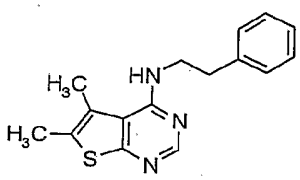


1.94 uM

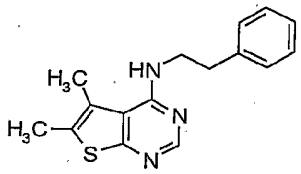
Fig 1B (cont.)



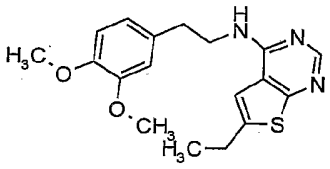
1.94 uM



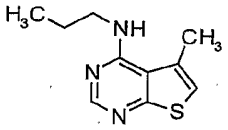
2.15 uM



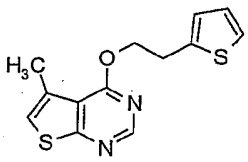
2.82 uM



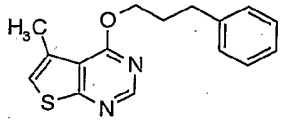
2.45 uM



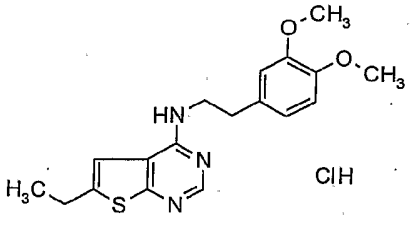
2.529 uM



2.73 uM

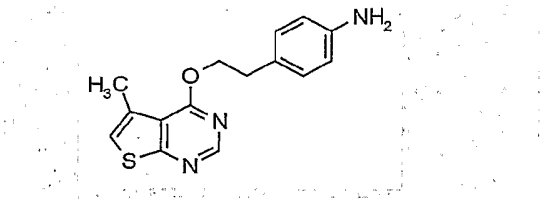


3.1 uM

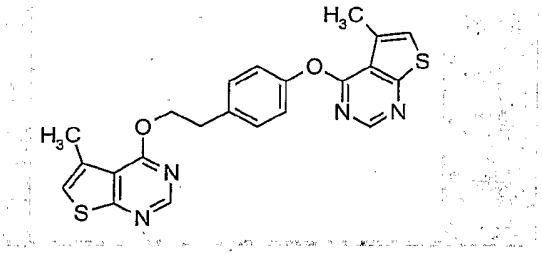


3.16 uM

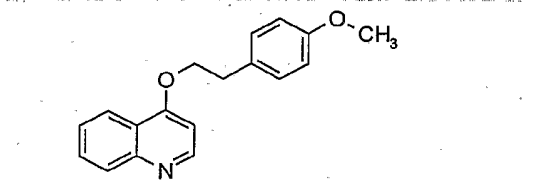
Fig 1B (cont.)



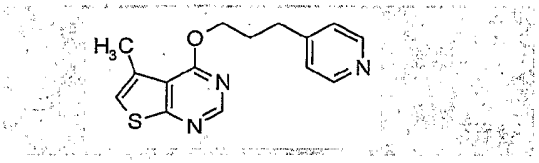
3.4 uM



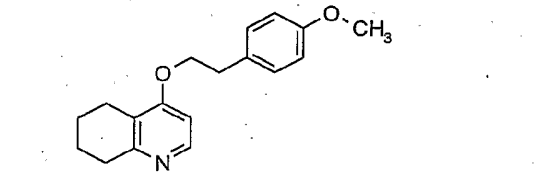
3.4 uM



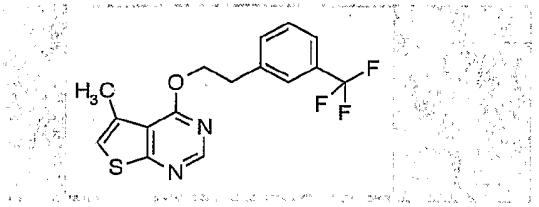
3.508 uM



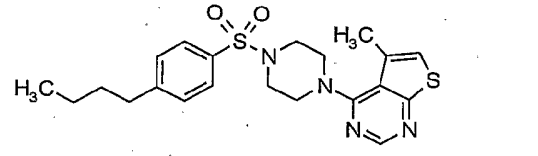
3.6 uM



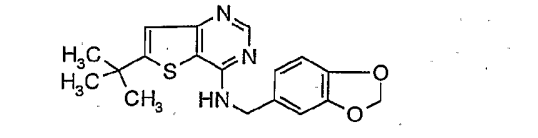
4.028 uM



5.1 uM

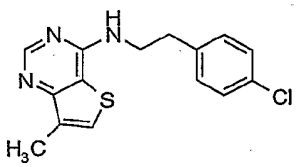


5.729 uM

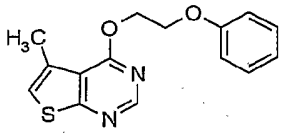


5.73 uM

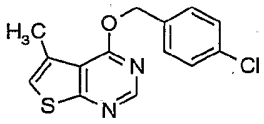
Fig 1B (cont.)



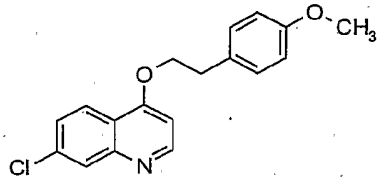
5.903 uM



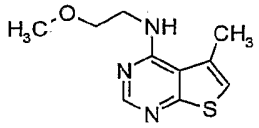
6.57 uM



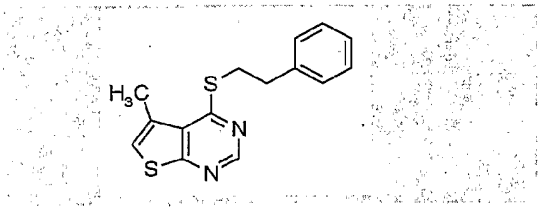
6.6 uM



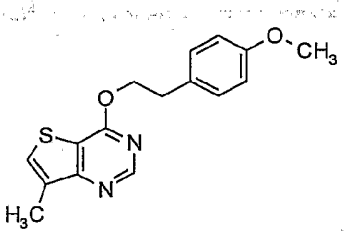
7.82 uM



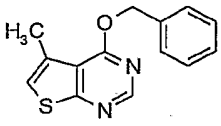
9.717 uM



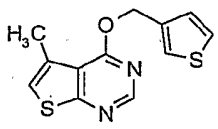
10.7 uM



13.16 uM

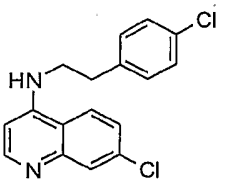


13.8 uM

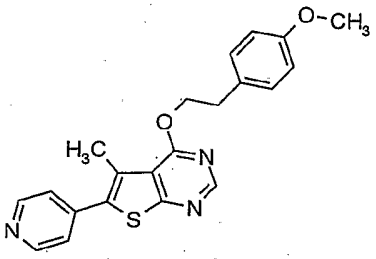


14.9 uM

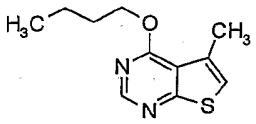
Fig 1B (Cont.)



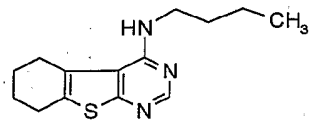
15.530 uM



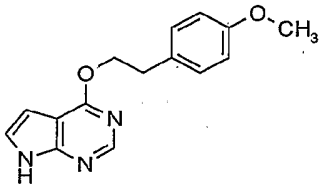
16.3 uM



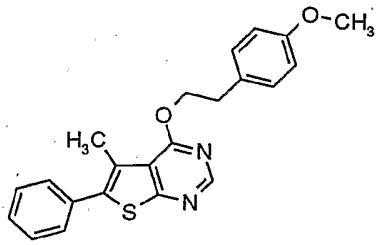
16.762 uM



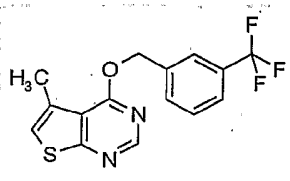
17.11 uM



17.717 uM



20 uM



20.4 uM

Fig 1B (Cont.)

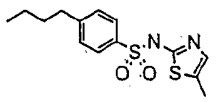
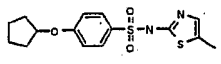
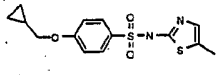
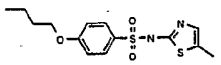
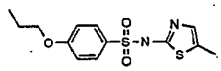
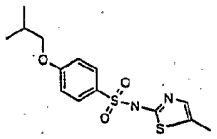
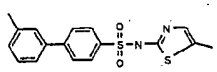
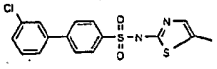
MOLSTRUCTURE	C. albicans LOG IC50 (uM)	C. albicans STAT IC50 (uM)	C. albicans MIC (ug/ml)	C. albicans Overnight Growth Inhibtion (%)	C. albicans Phenotype Rating	Mammalian Cytotoxicity LD50 (uM)
	0.028	0.712	>64	47	1*	>1000
	0.11	>20	>64	52.87	1*	
	0.1335	3.773	>64	10.35	1*	
	0.055	2.947	>64	33.13	1*	>1000
	0.065	4.94	>64	15.28	1*	>1000
	0.187	4.747	>64	19.78	1*	
	0.507	>20	>64	16.61	1*	
	0.211	>20	>64	11.16	3*	

Fig 2

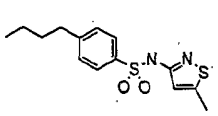
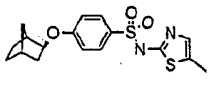
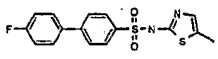
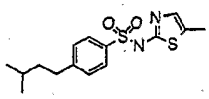
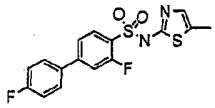
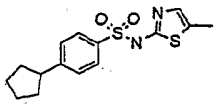
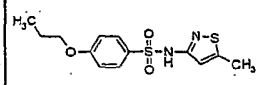
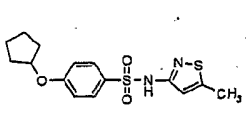
	0.0004	0.62	>64	54.67	1	
	0.39	>20	>64	23.2	3	
	0.0977	19.7	>64	18.25	1*	
	0.018	1.8	>64	5.17	1*	
	0.018	0.527	>64	-5.29	1*	
	0.044	0.108	>64	24.45	1*	
	0.001uM	0.97uM				
	0.016uM	>20uM				

Fig 2 (Cont)

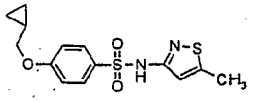
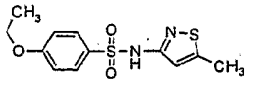
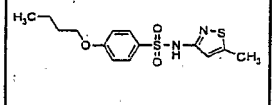
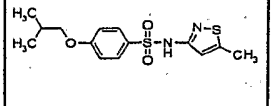
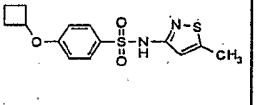
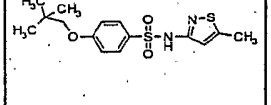
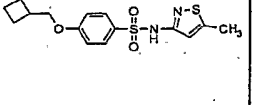
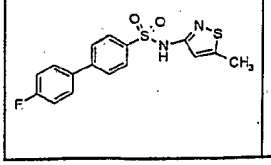
	0.002uM	>20uM				
	0.012uM	>20uM				
	0.0007uM	0.77uM				
	0.001uM	1.37uM				
	0.019uM	4.7uM				
	0.025uM	5.2uM				
	0.0005uM	1uM				
	0.003uM	1.2uM				

Fig 2 (cont.)

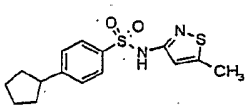
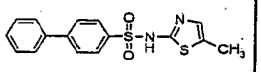
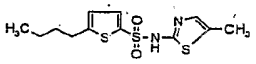
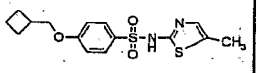
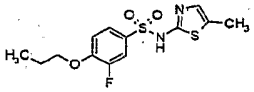
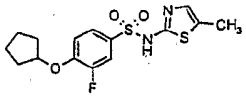
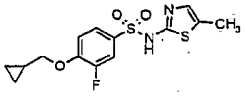
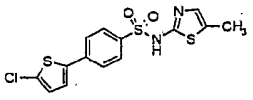
	<20 uM					
	<20 uM					
	0.149uM	11.074uM				
	<20 uM					
	0.045uM	>20uM				
	0.087uM	>20uM				
	0.036uM	>20uM				
	0.017uM	>20uM				

Fig 2 (cont)

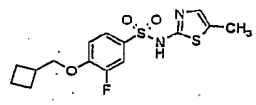
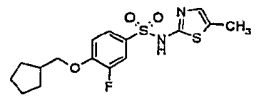
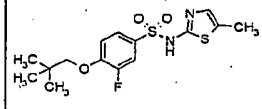
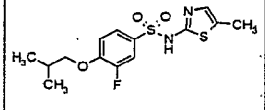
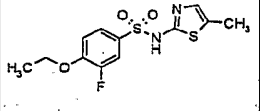
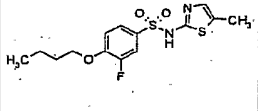
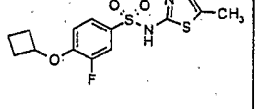
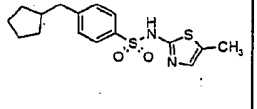
	<20 uM	>20uM				
	0.25uM	>20uM				
	<20 uM	>20uM				
	0.294uM	>20uM				
	0.7uM	>20uM				
	0.151uM	>20uM				
	0.018uM	>20uM				
	0.028uM	8.4uM				

Fig 2 (cont.)

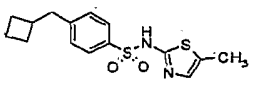
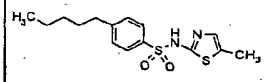
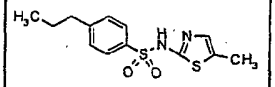
	0.0217uM	8.2uM				
	0.011uM	2.4uM				
	<20 uM					

Fig 2. (cont.)

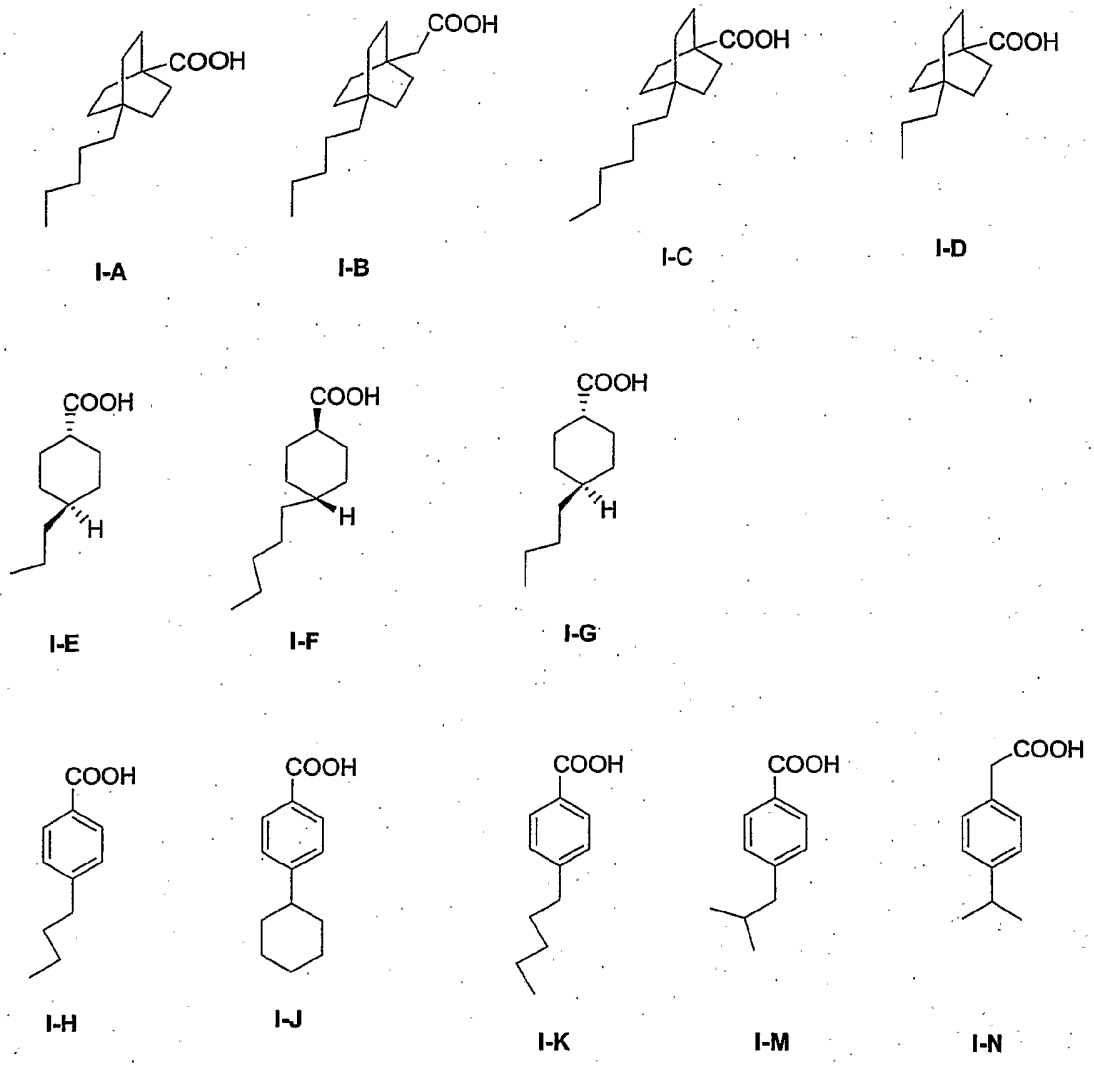

COOH
I-A
COOH
I-B
COOH
I-C
COOH
I-D
COOH
H
I-E
COOH
H
I-F
COOH
H
I-G
COOH
I-H
COOH
I-J
COOH
I-K
COOH
I-M
COOH
I-N

Fig. 3

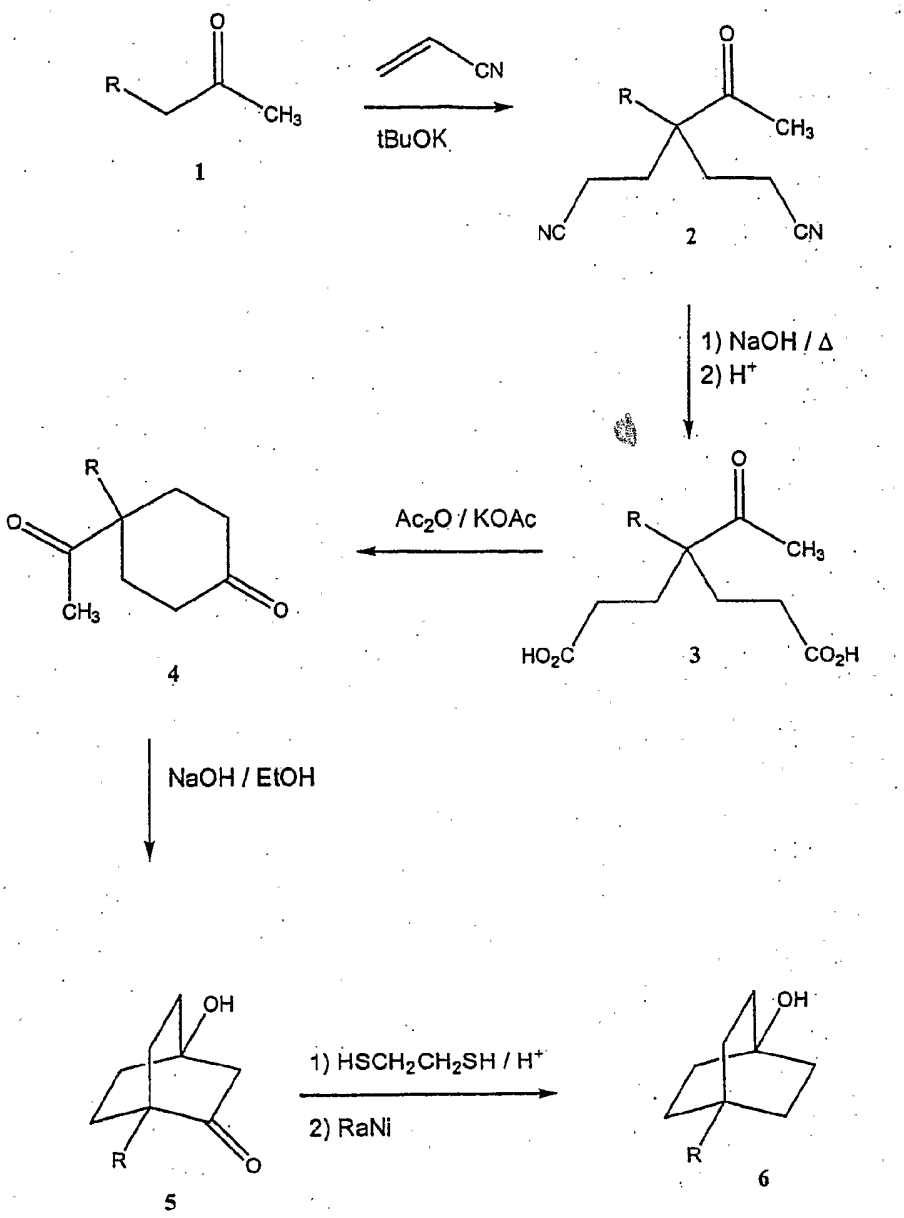

R
O
CH3
1
CN
tBuOK
NC
CN
2
1) NaOH / Δ
2) H+
HO2C
CO2H
3
Ac2O / KOAc
4
NaOH / EtOH
OH
5
1) HSCH2CH2SH / H+
2) RaNi
6

Fig. 4

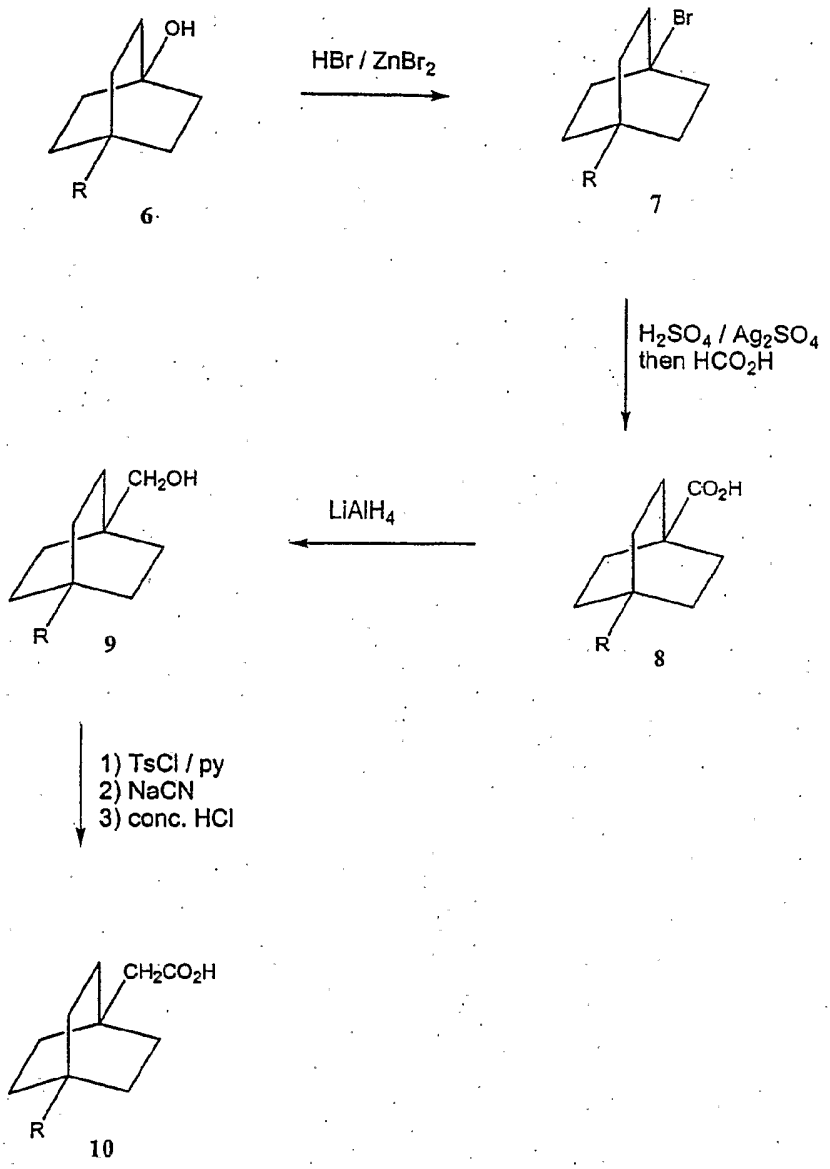

OH
HBr / ZnBr2
Br
R
6
7
H2SO4 / Ag2SO4
then HCO2H
CH2OH
LiAlH4
CO2H
R
9
8
1) TsCl / py
2) NaCN
3) conc. HCl
CH2CO2H
R
10

Fig. 5

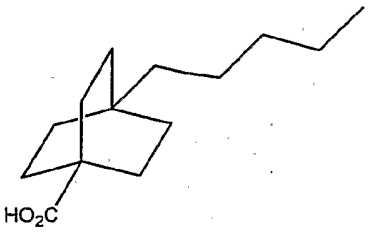
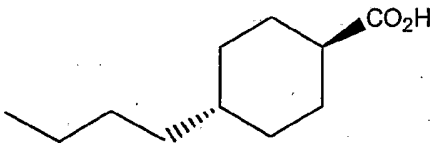
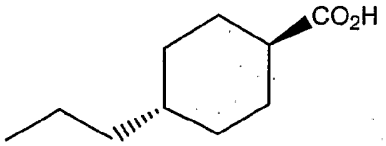
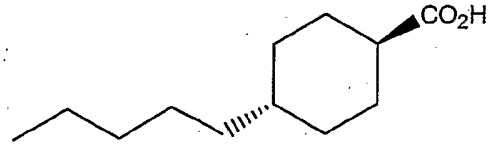
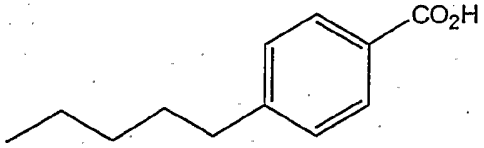
Structure of anti-invasin	C. albicans LOG IC_{50} (uM)	C. albicans STAT IC_{50} (uM)	C. albicans Phenotype rating	Source
	0.00049	1.26	3	Aldrich Chemical Company http://www.sigmaaldrich.com/
	0.0023	>20	1	TCI Americas http://www.tciamerica.com/
	0.055	>20	1	TCI Americas http://www.tciamerica.com/
	0.003	0.24	1	Avocado http://www.alfa.com/
	0.061	1.07	1	Aldrich Chemical Company http://www.sigmaaldrich.com/

Fig. 6

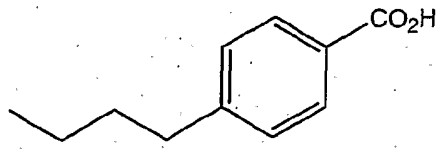
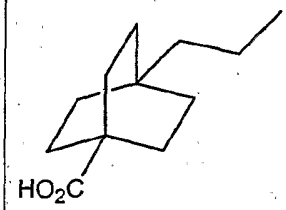
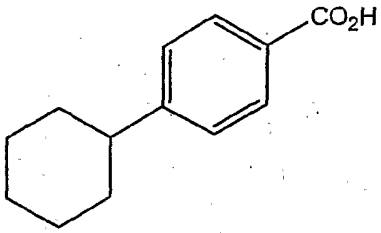
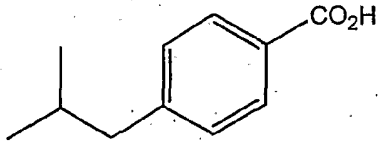
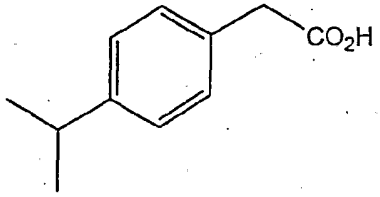
Structure of anti-invasin	C. albicans LOG IC_{50} (uM)	C. albicans STAT IC_{50} (uM)	C. albicans Phenotype rating	Source
	0.22	0.84.	5	Aldrich Chemical Company http://www.sigmaaldrich.com/
	0.28	3.8	2	ChemBridge http://chembridge.com/
	0.60	>20	ND	TCI Americas http://www.tciamerica.com/
	1.6	>20	ND	TCI Americas http://www.tciamerica.com/
	10	>20	ND	Lancaster Synthesis http://www.lancastersynthesis.com/

Fig. 6

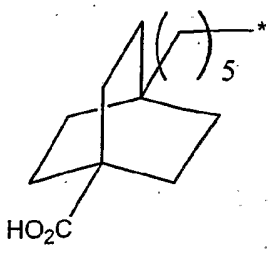
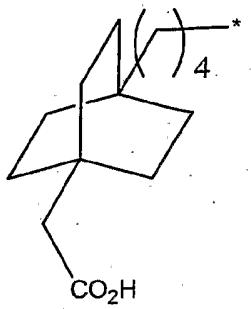
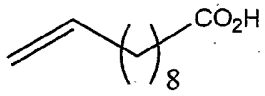
Structure of anti-invasin	C. albicans LOG IC_{50} (uM)	C. albicans STAT IC_{50} (uM)	C. albicans Phenotype rating	Source
	0.005	0.20	1	Specs and Biospecs http://www.specs.net/
	0.005	0.36	1	Specs and Biospecs http://www.specs.net/
	1.6	13	5	Undecylenic acid (for comparison purposes)

Fig. 6