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(54) **BORON-CONTAINING SMALL MOLECULES**

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A61K 31/69 (2006.01)
C07F 5/04 (2006.01)

(52) **U.S. Cl.** **514/64; 558/288**

(58) **Field of Classification Search** 514/64;
558/288

See application file for complete search history.

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(57) **ABSTRACT**

This invention relates to compounds useful for treating fungal infections, more specifically topical treatment of onychomycosis and/or cutaneous fungal infections. This invention is directed to compounds that are active against fungi and have properties that allow the compound, when placed in contact with a patient, to reach the particular part of the skin, nail, hair, claw or hoof infected by the fungus. In particular the present compounds have physiochemical properties that facilitate penetration of the nail plate.

12 Claims, 12 Drawing Sheets

FIGURE 1A

| | MIC (ug/mL) | | | | | | | |
|----|------------------------|-----------------|--------------------|-------------------------|------------------------|----------------------|----------------|------------------------------|
| | C. albicans ATCC 90028 | C. albicans F56 | C. neoformans F285 | A. fumigatus ATCC 13073 | T. mentagrophytes F311 | S. cerevisiae ANA309 | T. rubrum F296 | T. rubrum F296 w/ 5% keratin |
| C1 | 1 | 2 | 2 | 1 | 2 | 0.5 | 1 | 1 |
| C2 | 2 | 0.5 | 1 | 2 | 4 | | 8 | 8 |
| C3 | 16 | 32 | 32 | 16 | 16 | 4 | 32 | |
| C4 | 64 | 64 | > 64 | 32 | 32 | 8 | 32 | |
| C5 | 4 | 8 | 2 | 2 | 4 | 0.25 | 4 | |
| C6 | 8 | 16 | 8 | 16 | 16 | 64 | 16 | |
| C7 | > 64 | > 64 | > 64 | > 64 | 32 | 4 | 64 | |
| C8 | 2 | 2 | 8 | 2 | 4 | 2 | 8 | |
| C9 | > 64 | > 64 | > 64 | > 64 | 64 | >64 | 64 | |

FIGURE 1B

| | | | | | | | | |
|-----|-----|-----|------|------|------|-------|----|---|
| C10 | 0.5 | 0.5 | 0.25 | 0.25 | ≤0.5 | <0.06 | 1 | 2 |
| C11 | 32 | 32 | 32 | 32 | 2 | 2 | 4 | |
| C12 | 256 | | | | | >64 | | |
| C13 | 16 | | | | | 2 | 16 | |
| C16 | 32 | | | | | 8 | 16 | |
| C17 | 64 | 64 | 64 | 16 | 4 | 16 | 8 | |
| C18 | | | | | | 2 | | |
| C19 | | | | | | 0.5 | 8 | |
| C20 | | | | | | 8 | | |
| C21 | | | | | | 4 | | |
| C22 | | | | | | >64 | | |
| C23 | | | | | | >64 | | |

FIGURE 1C

| | | | | | | | | |
|-----|--|--|--|--|--|-------|---|--|
| | | | | | | | | |
| C24 | | | | | | 16 | | |
| C25 | | | | | | >64 | | |
| C26 | | | | | | >64 | | |
| C27 | | | | | | >64 | | |
| C28 | | | | | | <0.06 | 4 | |
| C31 | | | | | | 8 | | |

EXAMPLE 2A

| Fungus | Broth used | MIC ($\mu\text{g/mL}$) | | | | |
|------------------------------------|------------------------------------|--------------------------|------------|-------------|-------------|--------------|
| | | (C10) | Ciclopirox | Terbinafine | Fluconazole | Itraconazole |
| <i>A. fumigatus</i> ATCC 13073 | RPMI | 0.25 | nt | nt | >64 | 0.25 |
| <i>C. albicans</i> ATCC 90028 | RPMI | 1 | 0.5 | nt | 0.25 | ≤ 0.12 |
| <i>C. albicans</i> F56 | RPMI | 0.5 | nt | nt | >64 | 0.25 |
| <i>C. glabrata</i> ATCC 90030 | RPMI + MOPs | ≤ 0.5 | ≤ 0.5 | 64 | nt | ≤ 0.5 |
| <i>C. krusei</i> ATCC 44507 | RPMI + MOPs | 1 | ≤ 0.5 | 64 | nt | ≤ 0.5 |
| <i>C. neoformans</i> F285 | RPMI | 0.25 | nt | nt | 2 | ≤ 0.12 |
| <i>C. parapsilosis</i> ATCC 22019 | RPMI + MOPs | ≤ 0.5 | ≤ 0.5 | ≤ 0.5 | nt | ≤ 0.5 |
| <i>C. tropicalis</i> ATCC 13803 | RPMI + MOPs | ≤ 0.5 | ≤ 0.5 | 256 | nt | 1 |
| <i>E. floccosum</i> ATCC 52066 | RPMI + MOPs | ≤ 0.5 | ≤ 0.5 | ≤ 0.5 | nt | ≤ 0.5 |
| <i>F. solani</i> ATCC 36031 | RPMI + MOPs | ≤ 0.5 | 4 | 64 | nt | >256 |
| <i>M. furfur</i> ATCC 44344 | Urea | 1 | ≤ 0.5 | 2 | nt | ≤ 0.5 |
| <i>M. pachydermatis</i> ATCC 96746 | Urea | 1 | ≤ 0.5 | ≤ 0.5 | nt | ≤ 0.5 |
| <i>M. sympodialis</i> ATCC 44031 | Urea | 1 | ≤ 0.5 | ≤ 0.5 | nt | ≤ 0.5 |
| <i>M. audouinii</i> ATCC 42558 | RPMI + MOPs | 2 | 1 | ≤ 0.5 | nt | ≤ 0.5 |
| <i>M. canis</i> ATCC 10214 | RPMI + MOPs | 2 | ≤ 0.5 | ≤ 0.5 | nt | ≤ 0.5 |
| <i>M. gypseum</i> ATCC 24103 | RPMI + MOPs | 2 | ≤ 0.5 | ≤ 0.5 | nt | ≤ 0.5 |
| <i>T. mentagrophytes</i> F311 | RPMI + MOPs | 1 | 0.5 | ≤ 0.5 | 32 | ≤ 0.12 |
| <i>T. rubrum</i> F296 | RPMI + MOPs | 1 | 1 | ≤ 0.5 | 1 | ≤ 0.12 |
| <i>T. rubrum</i> F296 | RPMI + MOPs + 5% keratin powder | 2 | 1 | nt | 1 | nt |
| <i>T. tonsurans</i> ATCC 28942 | RPMI + MOPs | 2 | ≤ 0.5 | ≤ 0.5 | nt | ≤ 0.5 |

nt = not tested

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