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(54) Title: METHODS AND COMPOSITIONS FOR TREATING FUNGAL INFECTIONS

(57) Abstract: Phenylboronic acid and water soluble derivatives thereof and related boronic acid compounds are used for treating fungal and bacterial infections.

METHODS AND COMPOSITIONS FOR TREATING FUNGAL INFECTIONS

Field of the Invention

[001] The present invention relates to methods and compositions for treating fungal infections, and more particularly, dermatophytoses or onchomycosis of the fingernail and the toenail, as well as fungal infections in plants.

Background of the Invention

[002] Many fungal infections, or mycoses, of humans and animals affect only the outer layers of skin. Although these infections may be sometimes difficult to cure, they are not considered dangerous. Most cutaneous infections are caused by the homogeneous group of keratinophilic fungi known as dermatophytes. The dermatophyte *Trichophyton rubrum* is the major cause of tinea pedis and onychomycosis. Fungal infections of the mucous membranes are caused primarily by *Candida albicans*, usually affecting the mouth and the vaginal and anal regions.

[003] Fungal infections sometimes follow the use of antibiotics, which kill non-pathogenic as well as pathogenic bacteria, thereby providing a clear field for fungal invasion. Opportunistic fungal infection occurs when a fungus enters a compromised host, such as a patient suffering from AIDS.

[004] Dermatophytoses of the fingernails and toenails, in contrast to those at other body sites, are particularly difficult to eradicate with drug treatment, particularly with topical treatment. This is the consequence of factors that are intrinsic to the nail such as the hard, protective nail plate, sequestration of pathogens between the nail bed and plate, and slow growth of the nail, as well as the relatively poor efficacy of the early pharmacologic agents.

[005] "Onychomycosis" has traditionally referred to a non-dermatophytic infection of the nail. Onychomycosis is now used as a general term to denote any fungal nail infection.

Tinea unguium specifically describes a dermatophytic invasion of the nail plate. Despite the clearly diseased appearance associated with this condition, onychomycosis is all too often regarded as merely a cosmetic problem of relatively minor importance that is hardly worth treating. This belief may have been fostered by the adverse effects and long courses of medication associated with some of the earlier antifungal agents.

[006] However, onychomycosis can have significant negative effects on patients' emotional, social, and occupational functioning. Affected patients may be embarrassed in social and work situations, where they may feel unclean, and are unwilling to permit their hands and feet to be seen. Patients may fear that they will transmit their infection to family members, friends, or coworkers, fears that can lead to diminished self-esteem and avoidance of close relationships. Some patients experience discomfort that prevents them from carrying out tasks such as prolonged standing, writing, or typing.

[007] Onychomycosis in immunocompromised patients, such as those infected with human immunodeficiency virus, can pose a more serious health problem. Not only does this infection serve as a constant reminder to the patient of his or her own deteriorated condition, but the possibility exists of transfer of a very high titer of fungal pathogens to another body site.

[008] The dermatophyte species that most often causes onychomycosis in North America and parts of Europe are *T. rubrum*, *T. metagrophytes*, and *Epidermophyton floccosum*. The first two are much more often implicated than *E. floccosum*. Both dermatophytes and non-dermatophytes, especially *Candida Sp.*, have been identified as etiologic agents of onychomycosis.

[009] Contact with the source of infection constitutes a risk factor. Several factors unique to modern life have resulted in an increased prevalence of onychomycosis,

including wearing of shoes, especially tight, high-heeled shoes; the increased use by large numbers of people of damp spaces such as locker rooms and gymnasiums; the declining health of the aging American population, and the increased number of immunocompromised patients through disease (HIV) or therapeutic agents (immunosuppressive therapies associated with cancer or posttransplantation, and the extensive use of broad-spectrum antibiotics). Other factors that increase the risk of onychomycosis are direct trauma to the nail, including that resulting from certain tic disorders (nail biting).

[0010] Treatment of onychomycosis has been attempted for many generations, but success has been limited. Because of the perception that the lesions had a superficial cause, the earliest remedies were topical. However, topical drugs such as the imidazoles, the allylamines, and the pyridone cyclopiroxolamine proved to be generally ineffective against fungal infections of the nails because of their inability to penetrate the entire nail unit and eradicate the infection. Only recently, when the fungal nature of these infections was appreciated, have systemically active drugs been available for treating onychomycosis.

[0011] Many currently available antifungal agents require a long duration of therapy, sometimes for over one year, in order to completely treat the onychomycosis. Griseofulvin has limited efficacy because its activity is limited to dermatophytes and a prolonged duration of therapy is required for maximum efficacy. Ketoconazole cannot be used for long-term cure of onychomycosis because of the occurrence of side effects and significant drug interactions. Other previously used drugs include itraconazole, fluconazole, and terbinafine.

[0012] Additionally, serious damage is done to crops each year by fungal infections of plants such as smuts, rusts, ergot, and mildews.

[0013] Botrytis bunch rot has long been a problem in vineyards. High nitrogen fertilization predisposed grapevines

to infection by *Botritis cinerea* and increased disease severity. *In vitro* results of tests of a number of fungicides were described by R=Houma et al. in *Journal of Plant Pathology* **80(2):** 1998, abstracts of papers. Of the fungicides tested, Vinchlozoline, Chlorothalonil, and Dichlofluanide were effective in completely terminating conidia. Iprodione and Procymedone were apparently confronted with the problem of fungal resistance. Folpel, copper and chlorothalonil were not able to control mycelial growth as effectively as conidial germination.

[0014] Several *Fusarium* species occurring worldwide on cereals as causal agents of "head blight" of small grain cereals and "ear rot" of corn, can accumulate mycotoxins in infected kernels. Besides being damaging to the cereal crops, some of these mycotoxins are dangerous to animal and/or human health. The main groups of *Fusarium* toxins commonly recognized in grains are trichothecenes: including T-2 toxin (T2), diacetoxyscirpenol, deoxynivalenol, fusarenone X, and nivalenol; zearalenones, primarily zaearalenone; and fumonisins, in particular fumonisin B_1. Additionally, moniliformin, beauvericine, and fusaproliferin were also found in *Fusarium* infected cereal ears.

[0015] Boronic acids, such as phenylboronic acids, have been known to inhibit acid lipase. This property of phenyl boronic acids has been exploited for disrupting the epithelial barrier function to enhance penetration of topically applied active ingredients, as disclosed in Thronfeldt et al., U.S. Patent No. 6,190,894.

[0016] Boric acid and certain phenyl boronic acids are also inhibitors of certain beta-lactamases. Shoichet et al., in U.S. Patent Nos. 6,075,014 and 6,184,363, disclose that a number of phenyl boronic acids are effective against bacteria resistant to beta-lactam antibiotics as a result of porin mutations. These compounds, or pharmaceutically acceptable salts, are antibacterial by themselves, although at higher

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