Journal de Mycologie Médicale (2015) 25, 50—56

Available online at ScienceDirect www.sciencedirect.com

Elsevier Masson France EM|consulte www.em-consulte.com

ORIGINAL ARTICLE/ARTICLE ORIGINAL

Synthesis and fungistatic activity of aryl aldoxime derivatives

Synthèse et activité fongistatique des dérivés d'aryle aldoxime

W. Marek Gołębiewski *, M. Cyrta, A. Michalczyk

Institute of Industrial Organic Chemistry, Annopol 6, 03-236 Warsaw, Poland

Received 19 August 2014; received in revised form 9 October 2014; accepted 30 October 2014
Available online 8 November 2014

KEYWORDS
Fungicides;
Oxime ethers;
Oxime esters;
Dermatophytes;
Lipophilicity

Summary
Objective. — The antifungal activity of 13 arylaldoxime ester and ether derivatives was tested against 4 dermatophytes *Trichophyton mentagrophytes* (TM), *Microsporum canis* (MC); *M. cookei*, *and M. gypseum*.
Materials and methods. — Structures of all new compounds prepared from aryl aldehydes were established by spectral means. The tests were performed on the Sabouraud Dextrose Agar (SDA) substrate. The sensitivity of the dermatophyte strains towards oxime derivatives was established by determining MIC and MFC values.
Results. — The tested compounds showed a moderate fungicidal activity reaching 100% inhibition rate at 1% concentration. The activity against *M. canis* of 4 derivatives was higher than the activity of a reference drug clotrimazole.
Conclusion. — A novel group of biologically active compounds was introduced. Simple aldoxime derivatives can be developed into a new class of antifungals.

MOTS CLÉS
Fongicides ;
Éthers d'oximes ;
Esters d'oximes ;
Les dermatophytes ;
La lipophilie

Résumé
Objectif. — L'activité antifongique des 13 esters et éther dérivés d'arylaldoxime a été testée contre 4 dermatophytes *Trichophyton mentagrophytes*, *Microsporum canis*, *M. cookei*, et *M. gypseum*.
Matériels et méthodes. — Les structures de tous les nouveaux composés préparés à partir d'aldéhydes aryliques ont été établies en utilisant des méthodes spectrales. Les essais ont été réalisés sur le substrat de Sabouraud Dextrose Agar (SDA). La sensibilité des souches de dermatophytes vis à vis des dérivés d'oxime a été établi par le calcul des valeurs de MIC et MFC.

* Corresponding author.
E-mail address: golebiewski@ipo.waw.pl (W. Marek Gołębiewski).

http://dx.doi.org/10.1016/j.mycmed.2014.10.026
1156-5233/

Résultats. — Les composés testés ont montré une activité fongicide modérée pour atteindre le taux d'inhibition de 100 % à une concentration de 1 %. L'activité contre *M. canis* de 4 dérivés était supérieure à l'activité du clotrimazole, le médicament de référence.
Conclusion. — Un nouveau groupe de composés biologiquement actifs a été présenté. Des dérivés simples d'aldoxime peuvent être développés comme nouvelle classe de composés antifongiques.

Introduction

Biological activity of Schiff bases derived from aromatic carbonyl compounds is known. Several benzo-1,3-dioxolealdoxime ethers show pyrethrum synergist activities against test *Tribolium castaneum* insect [23]. Alpha-azolylmethyl-alpha-aryl-substituted benzaldoxime derivatives display fungicidal activity against the *Candida* strains causing infections in humans and other animals [17]. Vanillin oxime-alkanoates showed in vitro antifungal activity against three phytopathogenic fungi *Macrophomina phaseolina*, *Rhizoctonia solani* and *Sclerotium rolfsii*, which was significantly higher than that of vanillin or its oxime.

We have been interested in synthesis and properties of aryl aldehydes Schiff bases for some time. Several salicylaldehyde hydrazones showed a moderate fungicidal and bactericidal activity [5]. The aldoxime derivatives were a subject of our recent patent application [6] concerning antifungal activity against plant pathogens. There is a continuous need for new selective protection agents due to appearance of growing pathogens resistance. In continuation of our work on aryl aldehydes Schiff bases we undertook the synthesis of new oxime derivatives as potentially biologically active compounds. Herein, we present results of our research on preparation and biological screening of several aryl aldoxime ethers and esters against dermatophytes *Trichophyton mentagrophytes* (TM), *Microsporum canis* (MC); *M. cookei*, and *M. gypseum (MG)*. *T. mentagrophytes* and *M. canis* are zoophilic fungal species infecting skin, hair and nails. *M. cookei* and *M. gypseum* are geophilic fungal species of a worldwide distribution, which cause skin infections in animals and humans, particularly children and rural workers during warm humid weather.

Dermatophytoses are most often treated with the imidazole derivatives such as clotrimazole, ketoconazole, bifonazole, econazole, miconazole or triazole derivatives such as fluconazole, itraconazole, which interfere with fungal ergosterol synthesis by inhibiting lanosterol 14-demethylase [14,22]. These strong systemic antifungal drugs are usually effective to cure the disease, but they often have side effects, growing pathogen resistance is observed and more immunosuppressed patients are at risk for these infections. Other frequently applied drugs include griseofulvin (spirocyclohexenodione derivative), allylamine derivatives (terbinafine), [8], short and medium-chain fatty acids such as formic, propionic, lactic, tartaric and citric acids [19], thiazole derivatives [2], 1,3,4-thiadiazole derivatives [13], dihaloquinolinols [3,4] or simple sodium pyrithione (sodium 2-pyridinethiol-1-oxide) [15]. The other agents are derivatives of natural quartenized polysaccharide chitosan [18], essential oils and various organic extracts [1,20].

Material and methods

Test organisms

Fungi *T. mentagrophytes* ATCC 9533, *M. gypseum* ATCC 6231, *M. cookei* ATCC 13275 were obtained from American Type Culture Collection (ATCC collection). The test strains were maintained on Sabouraud's Dextrose Agar (SDA) (Oxoid, UK) slants of pH 5.6, were stored in refrigerator at 4 °C and were transferred every 6—8 weeks to a fresh medium.

Fungicidal testing

Determination of minimum inhibitory concentration (MIC) and minimum fungicide concentration (MFC) for dermatophytes

The aim of this experiment was to determine the sensitivity of fungi to various concentrations of the test compounds and to determine the minimal concentrations (MIC) of the test compounds which completely inhibit the visible growth of fungi on the agar medium and to find the minimal fungicidal concentrations (MFC) values which kill 100% of a particular fungus. The test was performed on the Sabouraud Dextrose Agar (SDA) substrate in concentration range from 0.25% to 2%. Acetone solutions of test compounds were applied in an amount of 1 mL to the surface of agar-solidified medium on Petri dishes and then uniformly distributed and allowed to evaporate the solvent under aseptic conditions. Thereafter, the plates were loaded with mycelial discs (5 mm diameter) cut from homogeneous 5—7-day-old cultures of fungi grown on a SDA medium. As a control acetone was applied to the agar medium followed by mycelia discs after evaporation of acetone. The test was performed in three replications. As a reference, clotrimazole was used. As the value of minimum inhibitory concentration (MIC) the concentration of a compound limiting the fungus colony growth to 7 mm, i.e. 2 mm beyond the diameter of the incorporated inoculum, was adopted. Fungal inocula considered as negative (no growth) in the MIC test were incorporated into solid medium (SDA) without the addition of the test compounds and were incubated at the optimum temperature and time for the growth of the test fungi. As the value of the minimum fungicidal concentration (MFC), the concentration of compound causing total lack of growth of a fungus (macroscopic evaluation) was adopted.

Synthesis of tested compounds

Reagent grade chemicals were used without further purification unless otherwise noted. Spectra were obtained as follows: IR spectra on a JASCO FTIR-420 spectrometer, ^{1}H NMR