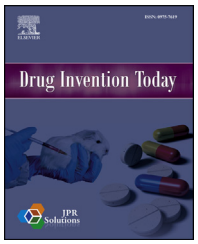
Available online at www.sciencedirect.com

SciVerse ScienceDirect

journal homepage: www.elsevier.com/locate/dit



Original Article

Antifungal activities of novel 1,2,3-benzotriazole derivatives synthesized by ultrasonic and solvent-free conditions

Muvvala S. Sudhir [a], *Ratnakaram Venkata Nadh* [b,*], *Sugreevu Radhika* [c]

[a] *Department of Chemistry, Sri Subbaraya and Narayana College, Narasaraopet 522 601, Andhra Pradesh, India*
[b] *School of Biotechnology, Vignan University, Guntur 522213, Andhra Pradesh, India*
[c] *Department of Pharmaceutical Chemistry, Chalapathi Institute of Pharmaceutical Sciences, Guntur 522034, Andhra Pradesh, India*

ARTICLE INFO

Article history:
Received 28 April 2013
Accepted 19 June 2013

Keywords:
1,2,3-Benzotriazoles
Ultrasonic
Solvent-free conditions
Antifungal activities
Nystatin

ABSTRACT

Objectives: To evaluate the antifungal activities of novel 1,2,3-benzotriazole derivatives synthesized by ultrasonic and solvent-free conditions.

Methods: Newer "1-(1H-benzo[d][1,2,3]triazole-1-carbonyl) derivatives" (5A–5P) were synthesized by using "1H–benzo[d][1,2,3]triazole" (1) as the starting material under ultrasonicated and solvent-free conditions. The resulting products were isolated and characterized by melting points and spectral studies. All the products were assayed for antifungal activity for various pathogenic fungi.

Results: Excellent antifungal activity was shown by derivative-5L against *Candida albicans* (MTCC – 3018) whereas other compounds have shown comparable activity. Except derivative-5P, all synthesized compounds have shown mild activity against *Candida glabrata* (MTCC – 3019). Towards *Aspergillus niger* (MTCC – 2638) and *Aspergillus flavus* (MTCC – 2737) most of the compounds were inactive and some were feebly active. All the synthesized derivatives were inactive against *Saccharomyces cerevisiae* (MTCC – 170). The Minimum Inhibitory Concentrations (MIC) of the most of the synthesized 1,2,3-benzotriazole derivatives for these fungi were found to be 62.5 μg/ml.

Conclusions: Some of the newer 1,2,3-benzotriazole derivatives synthesized under solvent-free and ultrasound irradiation with noteworthy advantages viz., shorter reaction times, operational simplicity, simple work-up, and eco-friendly nature, have shown antifungal activities against selected pathogenic strains. Attachment of phenyl or phenyl with electron withdrawing substituents to either nitrile or azo functional group can be attributed to the substantial antifungal activity of these benzotriazoles.

* *Corresponding author*. Tel.: +91 9441027105.
E-mail address: doctornadh@gmail.com (R. Venkata Nadh).

0975-7619/$ – see front matter
http://dx.doi.org/10.1016/j.dit.2013.06.004

1. Introduction

Although number of drugs are available in the market, but the need of discovering the new antimicrobial drugs with better pharmacokinetic profile and lesser toxicity has become the main objective in the field of medicinal chemistry, it is also due to the fast microbial resistance to the existing molecules.[1]

A large number of compounds containing benzotriazole system have been investigated because of their broad spectrum of biological activities which include analgesic, antibacterial, antifungal, antiparasitic, antiviral, anti-inflammatory, anticonvulsant, anti-nociceptive, DNA cleavage, herbicidal, antitubercular, antiemetic, protein kinase inhibition, respiratory syndrome protease inactivation, an active ester in the peptide synthesis and agonists of peroxisome proliferator activated receptors.[2,3] In addition to these considerable biological applications, benzotriazoles are important intermediates, protecting groups and final products in organic synthesis.[4]

A large number of organic reactions have been carried out in higher yield, shorter reaction time and milder condition under ultrasound irradiation. Large-scale use of organic solvents in synthesis causes environmental hazards. There were several advantages of performing syntheses in solvent-free media, such as, short reaction time, increased safety, and low cost.[2] In the present study, newer 1,2,3-benzotriazole derivatives were synthesized by ultrasonicated solvent-free conditions and their antifungal activities were evaluated.

2. Materials and methods

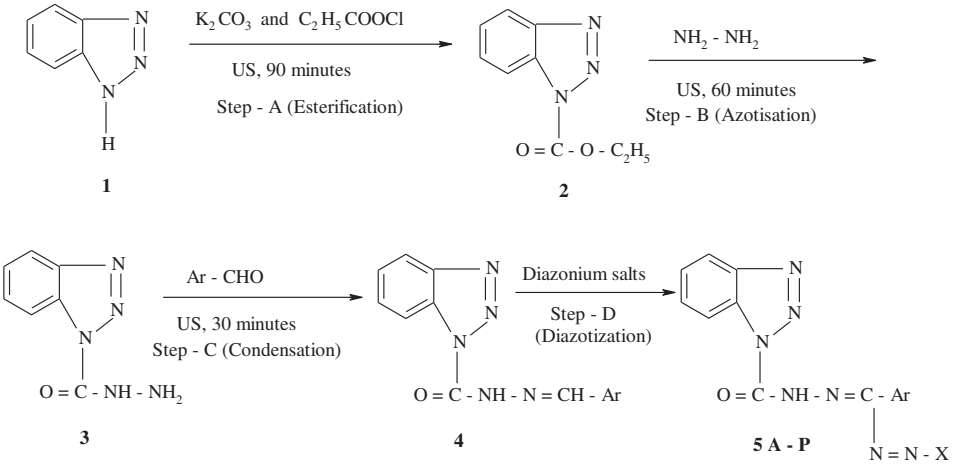
All organic solvents and chemicals were purchased from SD Fine Chemicals Ltd., Mumbai and were of analytical grade. For synthesis of benzotriazole derivatives, a 12 mm wide and 140 mm long probe (of a UP 400S ultrasonic processor) was immersed directly into the reaction mixture at room temperature. The operating frequency and the output power were 24 kHz and 240 W respectively. The synthesized compounds were characterized by spectral studies using Perkin Elmer 1600 series Fourier Transformer-Infrared Spectrophotometer in KBr-Pellet method; ^{1}H NMR spectra by Bruker 400 MHz NMR spectrometer (Bruker Bioscience, Billerica, MA, USA) in MeOD using TMS as internal standard.

2.1. Scheme for the synthesis of the compounds

By suitable modifications to the classical synthesis carried out by other workers viz., Asati et al,[5] Chitre et al,[6] Sukla and Srivatsava,[7] sixteen compounds were synthesized under ultrasonication and solvent-free conditions in four steps (Step A – esterification, Step B – azotisation, Step C – condensation, Step D – diazotization) as shown in Fig. 1.

2.2. Antifungal activity by disc diffusion method and MIC for fungi

All the synthesized compounds of present study were screened for *in-vitro* antifungal activity against five different strains of fungi i.e., *Aspergillus niger* MTCC – 2638, *Aspergillus flavus* MTCC – 2737, *Candida albicans* MTCC – 3018, *Candida glabrata* MTCC – 3019 and *Saccharomyces cerevisiae* MTCC – 170 by paper disc diffusion method.[8] Whatmann filter paper grade-1 discs of 5 mm diameter were sterilized by autoclaving for 15 min at 121 °C. The synthesized compounds were dissolved in DMSO at the concentration level of 100 μg/ml and the sterile discs were impregnated with these synthesized compounds. The nutrient agar of 20 ml was placed in flat bottomed Petri dish. When solidified 4 ml of second nutrient solution seeded with test fungi was poured evenly on to the first layer [40–48 °C, 15 lb/in^2]. As soon as the second layer was solidified,



5A – D: Ar = C_6H_5 ; 5E – H: Ar = C_4H_3O ; 5 I – L: Ar = $C_6H_4NO_2$ and 5M – P: Ar = C_6H_4Cl

5A, E, I, M: X = C_6H_5 ; 5B, F, J, N: X = $C_6H_4NO_2$; 5C, G, K, O: X = C_6H_4Cl and 5D, H, L, P: X = C_6H_4Br

Note : US = Ultrasonication

Fig. 1 – Scheme of Synthesis.