

4th INTERNATIONAL
BAU DRUG DESIGN
CONGRESS
ULUSLARARASI
BAU İLAÇ GELİŞTİRME
KONGRESİ



BAU TIP

BAHÇEŞEHİR ÜNİVERSİTESİ TIP FAKÜLTESİ

OCTOBER/EKİM
13 - 15
2016

BAHÇEŞEHİR
UNIVERSITY
SCHOOL OF
MEDICINE
ISTANBUL
TURKEY

Novel Methods and Emerging Targets in
Drug Discovery & Patented Drug Development

ABSTRACT BOOK

www.baudrugdesign.com

COORDINATOR OF CONGRESS

Assoc. Prof. Dr. Serdar DURDAĐI
Department of Biophysics
School of Medicine, Bahçeşehir University
Istanbul, Turkey

SCIENTIFIC ORGANIZATION COMMITTEE

Prof. Dr. Canan ATILGAN
Prof. Ozlem Tastan BISHOP
Prof. Dr. Henry J DUFF
Prof. Dr. Yavuz ERGUN
Prof. Dr. Burak ERMAN
Prof. Dr. Thomas MAVROMOUSTAKOS
Prof. Dr. Sergei NOSKOV
Prof. Dr. Manthos G. PAPADOPOULOS
Prof. Dr. Philip SEEMAN
Prof. Dr. Claudiu SUPRAN
Prof. Dr. Aykut UREN
Prof. Dr. Esin Aki-YALCIN
Prof. Dr. Ismail YALCIN
Assoc. Prof. Dr. Gulay BULUT
Assoc. Prof. Dr. Serdar DURDAGI
Assoc. Prof. Dr. Elif OZKIRIMLI
Assoc. Prof. Dr. Cenk SESAL
Assist. Prof. Dr. Umit AKBEY
Assist. Prof. Dr. Abdulilah ECE
Assist. Prof. Dr. Mustafa GUZEL

Bilge Eren^a, Özge Yılmaz^a, Gülçin Çetin^b and Cihan Darcan^b

^aDepartment of Chemistry, Faculty of Science and Arts, Bilecik Şeyh Edebali University, Bilecik, 11210, Turkey

^bDepartment of Molecular Biology and Genetics, Faculty of Science and Arts, Bilecik Şeyh Edebali University, Bilecik, 11210, Turkey

E-mail: bilge.eren@bilecik.edu.tr

Background: Benzimidazolium salts include biologically active benzimidazole ring and are the structural analogue of ionic liquids (ILs) [1]. Some benzimidazolium salts and their metal complexes containing alkyl, aryl or silyl groups showed remarkable antibacterial, antifungal [2-4] and anticancer [5] effects. Since a variety of 2-unsubstituted imidazolium or benzimidazolium derivatives have been synthesized as carbene precursors and used for catalytic and microbiological purposes [3,4], there is not any study related to the 2-arylsubstituted benzimidazolium derivatives. In our previous works, we have reported the synthesis of 2-arylbenzimidazoles by various methods [6-8]. In order to enhance the efficacy of them in the biological systems, it is very important to overcome the insolubility problem in water. For this reason, we have focused on the 1,3-dialkyl halide salts of 2-arylbenzimidazoles in the present work.

Methods: 1-Methyl-2-arylbenzimidazole derivatives were synthesized by using the previously reported method [6]. Novel **1,3-dialkyl-2-arylbenzimidazolium salts were synthesized via the N-alkylation of 1-methyl-2-arylbenzimidazole derivatives with various alkyl halides in CEM-Mars6 multimode microwave system (120 W) by using small amounts of DMF. Reactions were monitored by TLC.** Structures of the products were confirmed by using 300 MHz ¹H-¹³C NMR and FT-IR spectroscopic techniques. Antimicrobial activities of all synthesized compounds have been measured from DMSO solutions using microbroth tube dilution (NCCSL standards) and disc diffusion methods. MICs for each synthesized substances were investigated against *S. aureus* (ATCC 6535), *B. subtilis* (IMG 22), *E. coli* (W3110) *P. vulgaris* (NRRLB 2643) and *Candida albicans* (clinical isolate).

Results: We have already reported the microwave assisted synthesis of 1-methyl-2-arylbenzimidazole derivatives **1-7** before [6]. In the recent study N-alkylation of them with alkylhalides **under microwave conditions** afforded us 1,3-dialkyl-2-arylbenzimidazolium salts **8-28** which are the structural analogues of 1,3-dialkylimidazolium ionic liquids **29** (Figure 1). The yields in the range of 4-71 % under classical heating increased to the range of 64-96 % under microwave conditions. **Considering the reactions repeated by classical heating, the reaction times were decreased 3-6 hours to 5-35 minutes by microwaves.** MIC values of newly synthesized benzimidazolium salts **8-28 (1.95->1500 µg/ml)** are remarkably smaller than starting benzimidazoles **1-7 (62.5->1500 µg/ml)** on studied microorganisms. While they have little effect on gram-negative bacteria, they have remarkable effects on gram-positive and eukaryotic microorganisms. Especially **16, 18, 24, 25 and 27** were found to be the most effective compounds inhibiting the growth of both gram (+) bacteria and eukaryote.

Conclusions: It is the first report that describes the microwave assisted synthesis and antimicrobial activity of **2-arylsubstituted benzimidazolium salts**. The microwave method is advantageous regarding the usage of mild conditions and small amounts of solvent, easy purification and achieving high yields in short times. This study demonstrates that newly synthesized benzimidazolium salts (**especially compounds 16, 18, 24, 25 and 27**) have remarkable effects on microorganisms, especially in gram (+) bacteria and eukaryotes compared to benzimidazoles. Also, compounds 11 and 12 has considerable antifungal properties. Thus, the synthesized substances in this study may help in the treatment of fungal and bacterial diseases in developing pharmaceuticals.

Keywords: Benzimidazol, Benzimidazolium salts, Microwave, Antimicrobial, Antibacterial