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SYNTHESIS AND ANTIMICROBIAL EVALUATIONS OF SOME NOVEL DERIVATIVES OF BENZIMIDAZOLE

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ABSTRACT

N-Acyliminium reagents derived from benzimidazole have been successfully used in reactions with active methylene nucleophiles. A series of cyclic enaminoketones or dimedone were selectively amidoalkylated at the α-carbon atom of the enaminone. The new 2-substituted derivatives of 2,3-dihydrobenzimidazole are interesting both from synthetic point of view and as potential bioactive compounds.

All the synthesized benzimidazole derivatives were assayed for antimicrobial activity using standardized tests (DM and DDM) against seven strains microorganisms. Eight compounds displayed antimicrobial activity against *Staphylococcus aureus*, *Enterobacter aerogenes, Candida albicans*.

Key words: *N-acyliminium ions; enaminones; antimicrobial activity*

INTRODUCTION

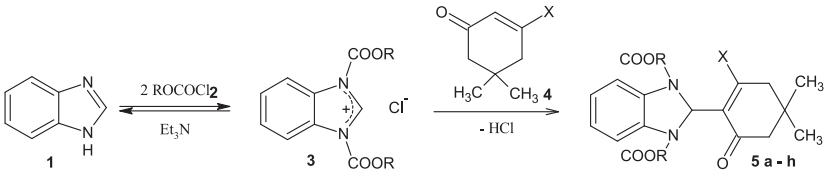
The α-amidoalkylation of carbon nucleophiles with *N*-acyliminium compounds is a long-established method for C–C bond formation [1–2]. This reaction can be used for the synthesis of various heterocyclic derivatives.

Benzimidazole ring is an important heterocyclic pharmacophore in drug discovery. Benzimidazoles are regarded as a promising class of bioactive heterocyclic compounds that exhibit a range of biological activities – antiviral [3–4], antitumor [5–6], anticancer [7], antimicrobial activity against *Staphylococcus aureus*, *Bacillus subtilis, Escherichia coli* and *Candida albicans* [8], antibacterial activity against *Staphylococcus aureus, Escherichia coli, Enterococcus faecalis* and fundicidal activity against *Candida albicans* and *Asperigillus* [9–11]. Benzimidazoles are potential enterovirus inhibitors [12].

The last several years we used successfully adducts of cyclic imines and acyl chlorides as electrophilic reagents in an intermolecular α-amidoalkylation reaction toward aromatics and methylene active carbonyl compounds [13–16].

RESULTS AND DISSCUSSION

A series of cyclic enamino ketones or dimedone **4** were selectively amidoalkylated with *N*-acyliminium compounds **3** derived from benzimidazole **1**. Enaminones, as defined by Greenhill, are monoenamines of 1,3-dicarbonyl compounds [17] and they combine the ambident electrophilicity of enones with the ambident nucleophilicity of enamines.



R = Me, Et

X = OH, NHR_1

R_1 = Me, Et, Pr, Ph, Bz, $C_6H_5CH_2CH_2$, 4-$ClC_6H_4CH_2$, 3,4-$(MeO)_2C_6H_3CH_2CH_2$

Scheme 1.

To determine the influence of the acyl component, we initially studied the reactions of two different N-acyliminium compounds **3** with enaminones **4**. The reactions were carried out for 1 h at r.t. in 1,2-dichloroethane. The substituents R_1 were varied in a series of enaminones. The yields were from 11% (R = C_2H_5, X = CH_3NH) to 87% (R = CH_3, X = C_6H_5NH) and all of the studied examples proceeded regioselectively at the α-carbon of the enaminone as indicated by the disappearance of the characteristic vinyl signal in the ^{1}H-NMR spectra.

All the synthesized benzimidazole derivatives were evaluated for antimicrobial activity. Antimicrobial effects were assessed in standard disk diffusion method according to recommendations of CLSI [18] and agar well diffusion method [19]. For second test a wells were prepared in the agar plates with the help of sterile borer (ø 6 mm). The effect of compound to be tested was determined by measuring the diameter of zone of inhibition. All experiments were done three times and mean value was presented. All newly synthesized compounds to be tested were dissolved in DMSO to 0.4% and DMSO was used as negative control. In resent investigation effects were estimated for two Gram positive strains (*Enterococcus faecalis*; *Staphylococcus aureus*), four Gram negative strains (*Escherichia coli*; *Enterobacter aerogenes*; *Salmonella abony*; *Pseudomonas aeruginosa*) and one yeast strain (*Candida albicans*).

The following strains were used in this study: *Escherichia coli* ATCC 25922; *Enterobacter aerogenes* ATCC 25029; *Salmonella abony* ATCC 6017; *Pseudomonas aeruginosa* ATCC 27853; *Enterococcus faecalis* ATCC 29212; *Staphylococcus aureus* ATCC 33592 (MRSA); *Candida albicans* ATCC 10231.

The following agar media were used for the antimicrobial test: Mueller-Hinton agar (*S. aureus, P. aeruginosa, E. coli, E. aerogenes, S. abony*, *E. faecalis*) and Saboraud-dextrose (*C. albicans*). All the culture media were prepared and treated according to the manufacturer guidelines.

There was no inhibition observed for used strains except for *E. aerogenes, S. aureus* and *C. albicans*. Tested compounds have more bacteriostatic than bactericidal effect on *E. aerogenes*. Clear bactericidal effect on *S. aureus* has **5c**. Data of antimicrobial effects of tested compounds are presented in table 1.

Table 1. *Antimicrobial effects of synthesized benzimidazole derivatives*

Compound / Strain			Zone of inhibition, ø mm					
			E. aerogenes		*S. aureus*		*C. albicans*	
5	**R**	**X**	**DDM**	**DM**	**DDM**	**DM**	**DDM**	**DM**
a	C_2H_5	$NHCH_2CH_2C_6H_5$	NI	12	NI	NI	NI	NI
b	C_2H_5	$NHCH_2C_6H_5$	NI	I	NI	NI	NI	10
c	C_2H_5	NHC_3H_7	NI	13	NI	13	NI	NI
d	C_2H_5	NHC_2H_5	NI	12	NI	NI	NI	NI
e	C_2H_5	$NHCH_3$	NI	12	NI	NI	NI	NI
f	CH_3	$NHCH_2C_6H_5$	NI	NI	NI	NI	NI	12
g	C_2H_5	OH	NI	13	NI	NI	NI	NI
h	CH_3	OH	NI	11	NI	NI	NI	NI

DDM – disc diffusion method, 80 μg; DM – agar well diffusion method, 200 μg; NI – no inhibition; I (intermediate sensitivity) – slight growth inhibition

We didn't find observable prevalence in the effects of tested compounds neither for Gram negative nor for Gram positive microorganisms included in this study.

Results which we obtained from two methods were different. Some of possible reasons for this may be the different amount of the compounds which applied in test or particular characteristics of the compounds or solvent. It seems that agar well diffusion test will be more appropriate to use for further investigation of antimicrobial activity of benzimidazole derivatives with suitable for bioassay solvents.

In conclusion, the scope of application of the intermolecular reaction of α-amidoalkilation has been successfully expanded. A series of cyclic enamino ketones were selectively amidoalkylated at the α-carbon atom in reactions with acyliminium reagents derived from benzimidazole.

Eight of synthesized benzimidazole derivatives displayed antimicrobial activity against three strains microorganisms. For some of the compounds was registered clear bactericidal effect on *Staphylococcus aureus*, bacteriostatic effect against *Enterobacter aerogenes* and antimicotyc activity against *Candida albicans*.

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