ANNALES
UNIVERSITATIS MARIAE CURIE-SKŁODOWSKA
LUBLIN – POLONIA
VOL. XXIII, N 4, 2 SECTIO DDD 2010

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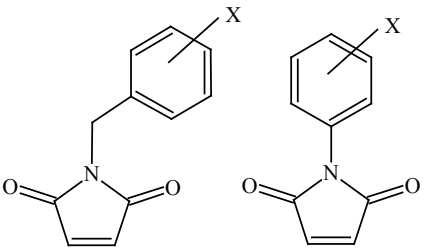
Synthesis and biological activity of derivatives of 1-bromo-17-azapentacyclo[6.6.5.$0^{2,7}$.$0^{9,14}$.$0^{15,19}$]nonadeca-2,4,6,9,11,13-heksaen-16,18-dione

Synteza i biologiczna aktywność pochodnych 1-bromo-17-azapentacyklo[6.6.5.$0^{2,7}$.$0^{9,14}$.$0^{15,19}$] nonadeca-2,4,6,9,11,13-heksaen-16,18-dionu

INTRODUCTION

N-substituted imides are known for their biological activity. For example, many N-arylmaleimides have antifungal and antibacterial properties [3, 8, 9]. This activity is related to the presence of double bond in an imide ring as well as the character of the substituents [3]. N-phenylmaleimides and N-benzylmaleimides (Fig. 1), which contain electron-donor groups, such as $–OCH_3$ and $–CH_3$ and electron withdrawing atoms like halogens are described as agents, which decrease the activity against Gram-negative bacteria (*E.coli*). It should be noticed that large groups like $–OC_4H_9$ do not produce this effect in their activity against Gram-positive bacteria (*S.aureus*). In the case of N-phenylsuccinimides, some nitrogenated substituents introduced in the imide ring can increase the activity of these compounds [3]. Generally, the imides with an alkyl substituent showed higher activities than their aromatic analogues, but structure-activity relation ships were not clearly established [9]. N-substituted imides can also act as potential anticancer agents [3, 5]. The best known compounds like mitonafide, amonafide and azonafide (Fig. 2) establish a class of antineoplastic agents and antifolate thymidylate synthase inhibitors [5]. Another imide derivative, aminoglutethimide (Fig. 3) is one of the best nonsteroidal drug which inhibits aromatase enzyme (cytochrome P450). It is used in the treatment of mammary gland carcinoma [5].

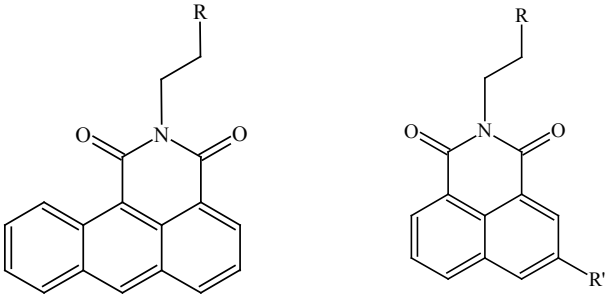


X:

H, 4-Cl, 3,4-diCl, 4-Me, 4-Et, 4-OMe, 4-OC_4H_9

Fig. 1. Structure of substituted N-phenylomaleimide and N-benzylmaleimide

We should point to the analgesic activity of cyclic imides. Many of them have better analgesic properties than aspirin or paracetamol with lower stomach problems characteristic of acetic-acid derivatives [4].



R = $N(CH_3)_2$: azonafide

R = $N(CH_3)_2$, R' = NO_2 : mitonafide

R = $N(CH_3)_2$, R' = NH_2 : amonafide

Fig. 2. Structure of azonafide, mitonafide and amonafide

Inspired by these reports we designed and synthesized 11 new derivatives of 1-bromo-17-azapen tacyclo[6.6.5.$0^{2,7}$.$0^{9,14}$.$0^{15,19}$]nonadeca-2,4,6,9,11,13-heksaen-16,18-dione (Scheme1).

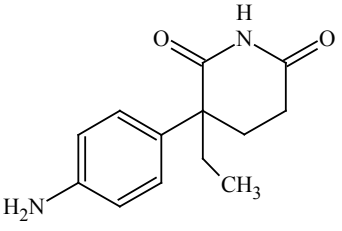
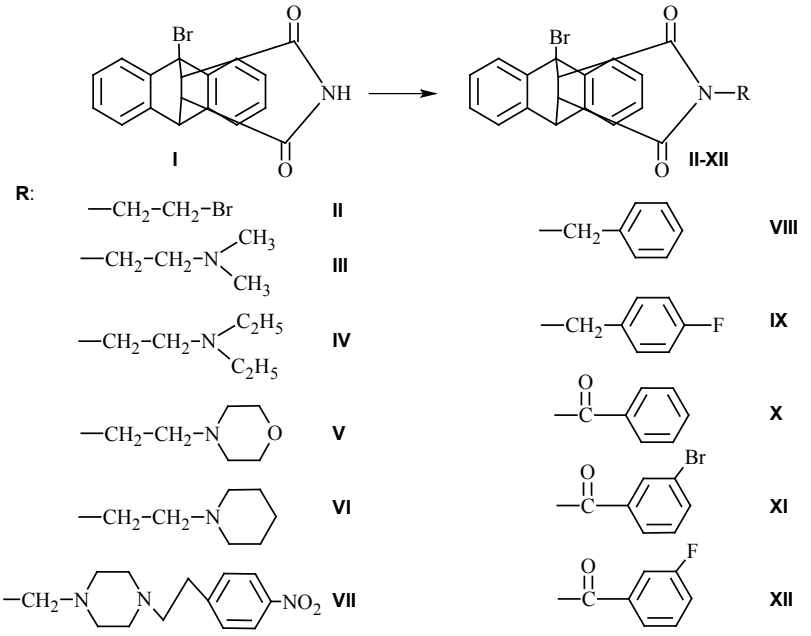


Fig. 3. Structure of aminoglutethimide

The starting compound **I** was synthesized according to the method described previously [6]. This compound was condensed with dibromoethane or dibromomethane in acetonitrile.

The second route were reactions of imide **I** with appropriate alkylamines and substituted chlorobenzyl and chlorobenzoyl derivatives in acetone.

Finally, twelve newly synthesized compounds, aminoalkyl, benzyl and benzoyl derivatives of 1-bromo-17-azapentacyclo[6.6.5.$0^{2,7}$.$0^{9,14}$.$0^{15,19}$]nonadeca-2,4,6,9,11,13-heksaen-16,18-dione were tested for their antimicrobial activity against five microbial species: *Staphylococcus aureus, Escherichia coli, Pseudomonas aeruginosa, Stenotrophomonas maltophilia and Candida albicans*. The chosen set of microorganisms was made up of representatives of species most popular in hospital infections. They all easily acquire resistance to antimicrobial agents.



Scheme 1. Method of preparation of compounds **II**–**XII**

They belong to three large groups of microorganisms, which differ in their structure, cell wall construction, mechanism of the pathogenicity and susceptibility to various antimicrobial agents [2].

S. aureus is a Gram-positive coccus, *E. coli, P. aeruginosa* and *S. maltophilia* are Gram-negative, rod shaped bacteria. *E. coli* is a popular enteric bacterium; the latter two rods are nonfermenters, common in hospital environment. *C. albicans* is a fungus (yeast). *C. albicans* is responsible for the over 90% of human infections caused by yeasts [7].

The chosen set of species provides a good model for screening of newly synthesized chemical compounds for antimicrobial activity.

EXPERIMENTAL DESIGN

Melting points were determined in open capillary in Electrothermal 9100 apparatus and were uncorrected. Nuclear magnetic resonance spectra of protons (^{1}H NMR) were recorded in $CDCl_3$ or DMSO-d_6 on a Bruker VMNRS300 operating at 300MHz. The chemical shift values were expressed in ppm (parts per million) relative to tetramethylsilane used as an internal standard and coupling constants *J* are given in Hz. The ESI MS were recorded on a Mariner Perspective – Biosystem instrument. Column chromatography was performed using 0.05–0.2 mm Kieselgel (70–325 mesh ASTM, Merck). Reactions were monitored by TLC on 0.2 mm thick Kieselgel G plates with 254 nm fluorescent indicator (Merck), eluted with 9.8:0.2 or 9.5:05 chloroform-methanol.

Synthesis of compound **II**

Compound **I** (0.01mol) was dissolved in acetonitrile (30mL), next anhydrous K_2CO_3 (0.01mol) and 1,2-dibromoethane (0.05mol) were added. The mixture was refluxed for 7 h. When the reaction was completed, the mixture was filtered off and the solvent was evaporated. The residue was purified by column chromatography (eluent: chloroform).

1-bromo-17-bromoethyl-17-azapentacyclo[6.6.5.0^{2,7}.0^{9,14}.0^{15,19}]nonadeca-2,4,6,9,11,13-heksaen-16, 18-dione (**II**)

$C_{20}H_{15}Br_2NO_2$; M = 461.15; 87%; m.p. 188.7-189.7°C, ^{1}H NMR (300MHz, $CDCl_3$) δ (ppm): 7.91(m,1H, Haromat), 7.73(m, 1H, Haromat), 7.39(m, 1H, Haromat), 7.26(m, 5H, Haromat), 4.82(d, *J* = 3.0, 1H, C8-H), 3.49(m, 3H, C15-H, C1'-H), 3.34(dd, *J* = 12.0, *J* = 8.7, 1H, C19-H), 2.62(t, *J* = 7.6, 2H, C2'-H); ESI MS(m/z): 100% = 461.0; 35% = 462.1; 98% = 463.1; 30% = 464.1 [L+H$^+$]

General procedure of preparing N-ethylamino derivatives of imide (**III–VI**)

The imide **I** was dissolved in acetone (30 mL), then powdered anhydrous K_2CO_3 (0.01 mol) and catalytic amount of 98% 1,8-diazabicyclo[5.4.0]undec-7-ene and an appropriate chloroalkylamine(0.01mol) were added. The reaction mixture was heated for 8–14 h, respectively. After the reaction completion, the inorganic residue was filtered off and the solvent was evaporated. The obtained compound was purified by column chromatography (eluent: chloroform or chloroform/methanol 50:0.2).

All new derivatives were converted to their hydrochlorides and crystallized from methanol.

1-bromo-17-[2-(dimethylamino)ethyl]-17-azapentacyclo[6.6.5.0^{2,7}.0^{9,14}.0^{15,19}]nonadeca-2,4,6,9,11,13-heksaen-16,18-dione (**III**)

$C_{22}H_{21}BrN_2O_2$*HCl; M = 425.32*HCl; 92%; m.p. 173-174,5°C, ^{1}H NMR (300MHz, DMSO-d_6) δ (ppm): 10.55(s, 1H, HCl), 7.79(m, 1H, Haromat), 7.56(m, 2H, Haromat), 7.31(m, 3H, Haromat), 7.26(m, 2H, Haromat), 4.92(d, *J* = 3.3, 1H, C8-H), 3.61(m, 1H, C15-H), 3.47(m, 1H, C19-H), 3.32(m, 2H, C1'-H), 2.62(m, 8H, C2'-H, -CH_3); ESI MS(m/z): 98% = 425.0; 50% = 426.1; 100% = 427.0; 40% = 428.1 [L+H$^+$],

1-bromo-17-[2-(diethylamino)ethyl]-17-azapentacyclo[6.6.5.$0^{2,7}$.$0^{9,14}$.$0^{15,19}$]nonadeca-2,4,6,9,11,13-heksaen-16,18-dione (**IV**)

$C_{24}H_{25}BrN_2O_2$*HCl; M = 453.37*HCl; 89%; m.p. 148-149,3°C, ^{1}H NMR (300MHz, DMSO-d_6) δ (ppm): 10.46(s, 1H, HCl), 7.79(m, 1H, Haromat), 7.56(m, 2H, Haromat), 7.30(m, 5H, Haromat), 4.93(d, *J* = 3.3, 1H, C8-H), 3.60(d, *J* = 8.4, 1H, C15-H), 3.51(dd, *J* = 11.7, *J* = 8.4, 1H, C19-H), 3.35(m, 2H, C1'-H), 3.00(m, 4H, -CH_2-), 2.37(m, 2H, C2'-H), 1.11(m, 6H, -CH_3); ESI MS(m/z): 100% = 453.1; 50% = 454.1; 99.% = 455.1; 38% = 456.1 [L+H^+],

1-bromo-17-(2-morpholin-4-ylethyl)-17-azapentacyclo[6.6.5.$0^{2,7}$.$0^{9,14}$.$0^{15,19}$]nonadeca-2,4,6,9,11,13-heksaen-16,18-dione (**V**)

$C_{24}H_{23}BrN_2O_3$*HCl; M = 467.35*HCl; 84%; m.p. 227-227,6°C, ^{1}H NMR (300MHz, DMSO-d_6) δ (ppm): 11.30(s, 1H, HCl), 7.79(m, 1H, Haromat), 7.56(m, 2H, Haromat), 7.29(m, 5H, Haromat), 4.92(d, *J* = 3.3, 1H, C8-H), 3.86(m, 2H, Hmorpholine), 3.75(m, 2H, Hmorpholine), 3.60(m, 1H, C15-H), 3.51(dd, *J* = 11.7, *J* = 8.4, 1H, C19-H), 3.37(m, 2H, C1'-H), 3.27(m, 2H, Hmorpholine), 2.91(m, 2H, Hmorpholine), 2.71(m, 2H, C2'-H); ESI MS(m/z): 100% = 467.1; 25% = 468.1; 98% = 469.1; 15% = 470.1 [L+H^+],

1-bromo-17-(2-piperidin-1-ylethyl)-17-azapentacyclo[6.6.5.$0^{2,7}$.$0^{9,14}$.$0^{15,19}$]nonadeca-2,4,6,9,11,13-heksaen-16,18-dione (**VI**)

$C_{25}H_{25}BrN_2O_2$*HCl; M = 465.38*HCl; 80%; m.p. 275-276,8°C, ^{1}H NMR (300MHz, DMSO-d_6) δ (ppm): 10.25(s, 1H, HCl), 7.79(m, 1H, Haromat), 7.56(m, 2H, Haromat), 7.30(m, 5H, Haromat), 4.92(d, *J* = 3.3, 1H, C8-H), 3.59(d, *J* = 8.4, 1H, C15-H), 3.49(dd, *J* = 11.7, *J* = 8.7, 1H, C19-H), 3.37(m, 2H, C1'-H), 3.25(m, 4H, Hpiperidine), 2.67(m, 2H, C2'-H), 1.69(m, 5H, Hpiperidine), 1.30(m, 1H, Hpiperidine); ESI MS(m/z): 100% = 465.1; 60% = 466.1; 99% = 467.1; 48% = 468.1 [L+H^+]

Synthesis of compound **VII**

Imide **I** (0.01mol) was dissolved in acetonitrile (30mL), next powdered anhydrous K_2CO_3 (0.01mol) and 1,1-dibromomethane (0.05mol) were added. The mixture was refluxed for 7h. When the reaction was completed, the mixture was filtered off and the solvent was evaporated. Next, the residue was dissolved in acetone (30mL) and 1-[2-(4-nitrophenyl)ethyl]piperazine hydrochloride (0.001mol), powdered anhydrous K_2CO_3 (0.01 mol), catalytic amount of KI were added. The reaction mixture was heated for 12 h. Then, an inorganic residue was filtered off and the solvent was evaporated. The obtained compound was purified by column chromatography (eluent: chloroform or chloroform/methanol 50:0.2).

Pure compound was converted to its hydrochloride and crystallized from methanol.

1-bromo-17-{[4-(4-nitrophenyl)piperazin-1-yl]methyl}-17-azapentacyclo[6.6.5.$0^{2,7}$.$0^{9,14}$.$0^{15,19}$] nonadeca-2,4,6,9,11,13-heksaen-16,18-dione (**VII**)

$C_{29}H_{25}BrN_4O_2$*HCl; M = 573.44*HCl; 68%; m.p. 148-149,48°C, ^{1}H NMR (300MHz, DMSO-d_6) δ (ppm): 10.95(s, 1H, HCl), 8.10(m, 2H, Haromat), 7.75(m, 1H, Haromat), 7.53(m, 2H, Haromat),

7.27(m, 3H, Haromat), 7.11(m, 1H, Haromat), 7.00(m, 2H, Haromat), 6.78(m, 1H, Haromat), 4.88(d, J = 3.3, 1H, C8-H), 4.10(s, 2H, C15-H, C19-H), 3.41(m, 4H, Hpiperazine), 3.26(m, 4H, Hpiperazine), 1.81(m, 2H, C1'-H); ESI MS(m/z): 98% = 573.1; 9% = 574.1; 100% = 575.1; 8% = 576.1 [L+H$^+$]

General procedure of preparing N-benzyl and N-benzoyl derivatives (**VIII**–**XII**)

Appropriate benzyl or benzoyl derivatives (0.01mol) were added to a mixture of imide (0.01mol), powdered anhydrous K_2CO_3 (0.01 mol) in acetone (30 mL). The reaction mixture was heated for 8–14 h. Then, an inorganic residue was filtered off and the solvent was evaporated. The obtained compounds were purified by crystallization from benzene.

17-benzyl-1-bromo-17-azapentacyclo[6.6.5.0^{2,7}.0^{9,14}.0^{15,19}]nonadeca-2,4,6,9,11,13-heksaen-16,18-dione (**VIII**)

$C_{25}H_{18}BrNO_2$; M = 444.32; 75%; m.p. 219-220°C, ^{1}H NMR (300MHz, $CDCl_3$) δ (ppm): 7.88(m, 1H, Haromat), 7.61(m, 1H, Haromat), 7.36(m, 2H, Haromat), 7.24(m, 1H, Haromat), 7.08(m, 6H, Haromat), 6.74(m, 2H, Haromat), 4.78(d, J = 3.3, 1H, C8-H), 4.30(m, 2H, -CH_2-benzyl), 3.95(d, J = 9.0, 1H, C15-H), 3.32(dd, J = 12.0, J = 8.4, 1H, C19-H); ESI MS(m/z): 100% = 466.1; 12% = 467.1; 93% = 468.1; 9% = 469.1 [L+Na$^+$],

1-bromo-17-(4-fluorobenzyl)-17-azapentacyclo[6.6.5.0^{2,7}.0^{9,14}.0^{15,19}]nonadeca-2,4,6,9,11,13-heksaen-16,18-dione (**IX**)

$C_{25}H_{17}BrFNO_2$l; M = 462.317; 83%; m.p. 230-232°C, ^{1}H NMR (300MHz, $CDCl_3$) δ (ppm): 7.88(m, 1H, Haromat), 7.59(m, 1H, Haromat), 7.36(m, 1H, Haromat), 7.25(m, 2H, Haromat), 7.13(m, 1H, Haromat), 7.02(m, 2H, Haromat), 6.78(m, 4H, Haromat), 4.77(d, J = 3.3, 1H, C8-H), 4.27(m, 2H, -CH_2-benzyl), 3.45(d, J = 8.7, 1H, C15-H), 3.31(dd, J = 12.0, J = 8.7, 1H, C19-H); ESI MS(m/z): 100% = 484.1; 8% = 485.0; 91% = 486.1; 9% = 487.1 [L+Na$^+$],

17-benzoyl-1-bromo-17-azapentacyclo[6.6.5.0^{2,7}.0^{9,14}.0^{15,19}]nonadeca-2,4,6,9,11,13-heksaen-16,18-dione (**X**)

$C_{25}H_{16}BrNO_3$l; M = 458.30; 84%; m.p. 247.6-250.5°C, ^{1}H NMR (300MHz, $CDCl_3$) δ (ppm): 7.91(m, 2H, Haromat), 7.55(m, 1H, Haromat), 7.43(m, 4H, Haromat), 7.30(m, 4H, Haromat), 6.76(m, 2H, Haromat), 4.92(d, J = 3.3, 1H, C8-H), 3.62(d, J = 9.0, 1H, C15-H), 3.52(dd, J = 12.3, J = 9.0, 1H, C19-H); ESI MS(m/z): 98% = 480.0; 30% = 481.0; 100% = 482.0; 30% = 483.0 [L+Na$^+$],

1-bromo-17-(3-florobenzoyl)-17-azapentacyclo[6.6.5.0^{2,7}.0^{9,14}.0^{15,19}]nonadeca-2,4,6,9,11,13-heksaen-16,18-dione (**XI**)

$C_{25}H_{15}BrFNO_3$; M = 476.29; 80%; m.p. 236.1-237.9°C, ^{1}H NMR (300MHz, $CDCl_3$) δ (ppm): 7.90(m, 2H, Haromat), 7.40(m, 4H, Haromat), 7.30(m, 4H, Haromat), 6.56(m, 2H, Haromat), 4.92(d, J = 3.3, 1H, C8-H), 3.63(d, J = 9.0, 1H, C15-H), 3.53(dd, J = 12.3, J = 9.0, 1H, C19-H); ESI MS(m/z): 99% = 498.0; 28% = 499.0; 100% = 500.0; 27% = 501.0 [L+Na$^+$],

1-bromo-17-(3-bromobenzoyl)-17-azapentacyclo[6.6.5.$0^{2,7}$.$0^{9,14}$.$0^{15,19}$]nonadeca-2,4,6,9,11,13-heksaen-16,18-dione (**XII**)

$C_{25}H_{15}Br_2NO_3$; M = 537.20; 70%; m.p. 143.4-146.5°C, ^{1}H NMR (300MHz, $CDCl_3$) δ (ppm): 7.90(m, 1H, Haromat), 7.75(m, 1H, Haromat), 7.27(m, 9H, Haromat), 4.80(d, *J* = 3.0, 1H, C8-H), 3.48(d, *J* = 8.7, 1H, C15-H), 3.37(dd, *J* = 12.0, *J* = 8.7, 1H, C19-H); ESI MS(m/z): 100% = 537.0; 30% = 538.0; 98% = 539.0; 27% = 540.0 [L+Na^+]

MICROBIOLOGY

O r g a n i s m s . The standard strains of *S. aureus* ATCC 25923, *E. coli* ATCC 25922, *P. aeruginosa* ATCC 27853 and *C. albicans* ATCC 14053 and one clinical isolate *S. maltophilia* CO2275 were used.

S c r e e n i n g f o r t h e a n t i m i c r o b i a l a c t i v i t y . The method according to CLSI (Clinical and Laboratory Standards Institute) directives was applied [1]. Compounds I–XII were tested to their bacteriostatic activity at high concentrations (512 mg/l). The tested substances were dissolved in DMSO and then the solutions were added to brain heart infusion broth (BHI-B) medium to the final concentration 512 mg/l. The bacteria were cultured on the plates with BHI agar (BHI-A) medium supplemented with 7% horse blood, at temperature 35–37 °C, in an aerobic atmosphere, for 18–24 hours. The fungal strain was cultured in the Sabouraud agar (SA), at the same temperature and atmosphere, but for at least 24 hours. The cultures which were in mid-logarithmic phase of growth were suspended in 0.9% NaCl solution to obtain 0.5 Mac Farland's optical density. 1.0–9.0 x 10^5 cells (0,1 ml of the prepared suspension) were added to sample tubes with 2 ml of BHI-B broth medium containing the tested substances. Samples were incubated at temperature 35 – 37°C for 24 - 48 hours. If after 48 h the growth was absent, the substance was noticed as potentially possessing antimicrobial activity.

In all experiments strains vitality controls and DMSO antimicrobial activity controls in the applied concentrations were performed.

RESULTS

The antimicrobial activities of the examined compounds are presented in the table 1.

In the experiments it appeared that all examined *P. aeruginosa* strains (the standard strain *P. aeruginosa* ATCC 27853 and twenty other clinical isolates, data non shown) were susceptible to DMSO in the applied concentration. Because of that, testing the activity of the compounds against *P. aeruginos*a was not possible in applied conditions and the obtained results were not reliable. The strains of other species displayed full growth in the presence of DMSO.

Among the examined compounds two (numbers III and IV) displayed bacteriostatic activity against Gram-positive bacteria as well and *C. albicans*. No inhibition of growth in the presence of other compounds was observed.

Table 1. Microbiological activity compounds number I–XII against bacteria and fungus strains

Chemical compound (512 μg/ml)	Microbiological activity against strains				
	S. aureus ATCC 25923	*E. coli* ATCC 25922	*P. aeruginosa* ATCC 27853	*S. maltophilia* CO2275	*C. albicans* ATCC 14053
DMSO control	-	-	+	-	-
I	-	-	ND	-	-
II	-	-	ND	-	-
III	+	-	ND	-	+
IV	+	-	ND	-	+
V	-	-	ND	-	-
VI	-	-	ND	-	-
VII	-	-	ND	-	-
VIII	-	-	ND	-	-
IX	-	-	ND	-	-
X	-	-	ND	-	-
XI	-	-	ND	-	-
XII	-	-	ND	-	-

ND – no data, strain susceptible to used concentration of DMSO

CONCLUSIONS

It appeared that the imides with nitrogenated substituents demonstrated increased biological activity comparing to the N-phenyl- and N-benzyl-imides, which may result from differences in the molecular size of these chemicals. The lack of activity of compounds III and IV against Gram-negative bacteria may be a result of poor permeability of the outer membrane for large molecules. The outer membrane is a part of the cell wall in Gram-negative but not Gram-positive bacteria.

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SUMMARY

We synthesized a series of eleven new derivatives of 1-bromo-17-azapentacyclo[6.6.5.$0^{2,7}$.$0^{9,14}$.$0^{15,19}$] nonadec-2,4,6,9,11,13-heksaen-16,18-dione and antibacterial activities *in vitro* was estimated towards Gram-positive, Gram-negative bacteria and yeast from the ATCC collection. We tried to perform modifications in order to maintain elements having influence on the biological activity. Despite it, in evaluated preliminary tests only two compounds (**III**–**IV**) showed activity towards *Staphylococcus aureus* and *Candida albicans*. Therefore, biological research will be executed for them in the nearest future. The main aim of the present investigation will be to assay the minimal inhibitory concentration (MIC), minimal bactericidal concentration (MBC) for these two tested compounds III and IV and tolerance of *C. albicans* standard and *S. aureus* strains, which occur as various phenotypes (MRSA, MSSA, VISA, hetero-VISA, VSSA).

Keywords: N-substituted imides, 1-bromo-17-azapentacyclo[6.6.5.$0^{2,7}$.$0^{9,14}$.$0^{15,19}$]nonadeca-2,4,6,9,11,13-heksaen-16,18-dione, antimicrobial activity

STRESZCZENIE

Ze swej aktywności biologicznej znane są zarówno niepodstawione, jak i podstawione cykliczne imidy. Wykazują działanie przeciwgrzybiczne, przeciwbakteryjne, insektobójcze, przeciwrakowe, jak i niektóre z nich przeciwbólowe, lepsze niż aspiryna czy paracetamol. Postanowiliśmy zsyntezować, bazując na doniesieniach literatury, i poddać wstępnym badaniom mikrobiologicznym serię nowych podstawionych pochodnych wybranego imidu. Pomimo że otrzymane związki w swojej budowie zawierają wszystkie elementy, dzięki którym powinny wykazywać działanie biologiczne, działanie to jest w kierunku bakterii Gram-ujemnych słabe. Jednakże dwa związki wykazały dobrą aktywność w kierunku bakterii Gram-dodatnich (*S. aureus*) i *C. albicans*, tym samym będą one poddane poszerzonym badaniom mikrobiologicznym. Celem dalszych analiz będzie oznaczenie wartości minimalnego stężenia hamującego (MIC), minimalnego stężenia bójczego (MBC), jak również tolerancji *Candida albicans* oraz różnych szczepów gronkowca złocistego (MRSA, MSSA, VISA, hetero-VISA, VSSA) na związki III oraz IV.

Słowa kluczowe: 1-bromo-17-azapentacyclo[6.6.5.$0^{2,7}$.$0^{9,14}$.$0^{15,19}$]nonadeca-2,4,6,9,11,13-heksaen-16,18-dion, aktywność mikrobiologiczna