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SYNTHESIS AND BIOLOGICAL ACTIVITY OF A NOVEL SERIES OF 17-AZAPENTACYCLO [6.6.5.$0^{2,7}$.$0^{9,14}$.$0^{15,19}$]NONADECA-2,4,6,9,11,13-HEXAEN-16,18-DIONE DERIVATIVES

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Abstract: In the search for novel antimicrobial agents, a series of new derivatives – N-substituted imides were prepared. All of the compounds were characterized by ^{1}H NMR and ESI MS spectra. These derivatives were tested for antimicrobial activity. Microorganisms used in this study included aerobic and facultative anaerobic bacteria such as *Staphylococcus aureus*, *Escherichia coli*, *Stenotrophomonas maltophilia*, and obligatory anaerobes such as *Bacteroides fragilis*, *Bacteroides thetaiotaomicron* and *Propionibacterium acnes*. Moreover, *Candida albicans* yeast was used. For representatives of all species the MICs of the investigated compounds were determined. Most of investigated derivatives had no antimicrobial activity (MIC > 512 mg/L) except the derivative **22** which showed slight activity against Gram-positive aerobes and anaerobes.

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

The main objective of this study was to expand research of antimicrobial activity of 1-bromo-17-azapentacyclo[6.6.5.$0^{2,7}$.$0^{9,14}$.$0^{15,19}$]nonadeca-2,4,6,9,11,13-hexaen-16,18-dione and determine the activity of next derivatives with different substituents in positions 1 and/or 8. It is known that N-substituted imides such as maleimides and related compounds: acrylamides such as isohematinic acid, a natural antibiotic produced by *Actinoplanes philippinensis* or *Phyllanthus sellowianus*, butenolides and thalidomide (Fig. 1) showed antibacterial and antifungal activity (1–7). N-substituted imides can also be treated as potential anticancer agents (1, 8). We mentioned in earlier paper (9) that compounds like mitonafide, amonafide and azonafide compose a class of antineoplastic agents and also antifolate thymidylate synthase inhibitors (8, 10) and aminoglutethimide, which is one of the best nonsteroidal drugs that inhibits aromatase enzyme (cytochrome P450) and is used in the treatment of mammary carcinoma (8).

Therefore, it was assumed that compounds having maleimides residue in the molecule may possess some interesting biological activity. It is also known that compounds containing short amine fragments exhibit antibacterial and antifungal activity (11, 12). In light of this information, we have decided to continue study on the microbial activity of imide condensed with short amine.

Our preliminary microbiology evaluations showed that two derivatives: 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-hexaen-16,18-dione (**A**) and 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-hexaen-16,18-dione (**B**) in high concentration have bacteriostatic activity against Gram-positive bacteria as well as *C. albicans* (9). The present study tests for these two compounds have been extended to quantitative determination of minimal inhibitory concentration (MIC) for investigated microorganisms. More-

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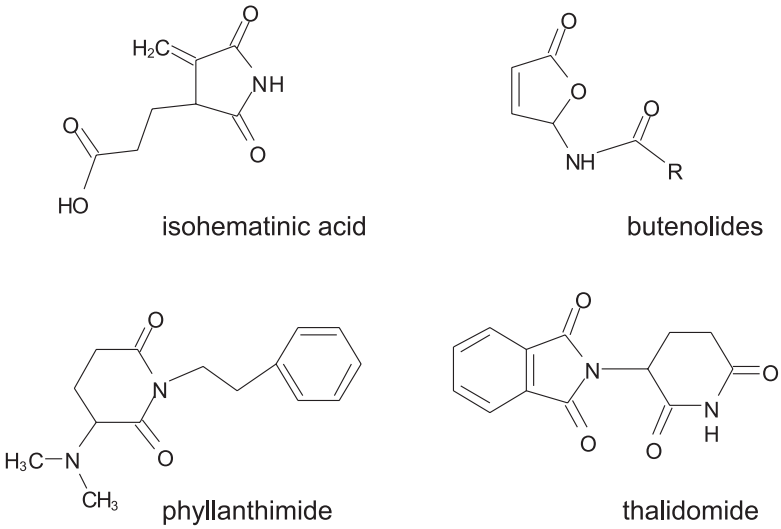


Figure 1. Structures of biologically active N-substituted imides

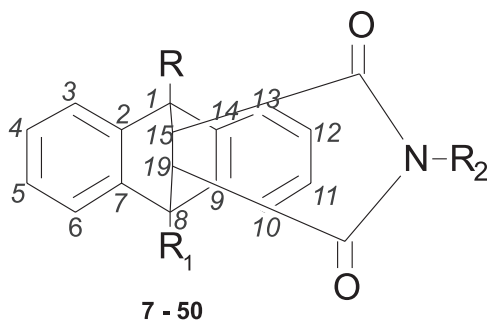


Figure 2. The numbering of carbon atoms of 17-azapentacyclo[6.6.5.$0^{2,7}$.$0^{9,14}$.$0^{15,19}$] nonadeca-2,4,6,9,11,13-hexaen-16,18-diones used in description of ^{1}H NMR

over, representatives of obligatory anaerobes such as *P. acnes, B. thetaiotaomicron* and *B. fragilis* were included.

In the aim to broaden the search area of the compounds with potential microbial activity, we synthesized 44 new compounds – derivatives of 17-azapentacyclo[6.6.5.$0^{2,7}$.$0^{9,14}$.$0^{15,19}$]nonadeca-2,4,6,9,11,13-hexaen-16,18-dione.

The starting compounds **1–6** were synthesized according to the method described previously (13–17). Next, imides **1–6** were condensed with appropriate chloroalkylamines and substituted chlorobenzyl and chlorobenzoyl derivatives in acetone.

All new compounds were also tested for their antimicrobial activity against four microbial species: *Staphylococcus aureus, Escherichia coli, Stenotrophomonas maltophilia* and *Candida albicans* and some (**7**, **8**, **18**, **19**, **22**, **27**, **28**, **41**, **42**, **46**, **47**) against *Propionibacterium acnes, Bacteroides thetaiotaomicron* and *Bacteroides fragilis*.

The chosen set of microorganisms includes Gram-positive cocci, enterobacteria and not fermenting rods as well as yeast. The chosen species, except *S. maltophilia* are frequent human hospital as well as community acquired pathogens. These organisms differ substantially in their biology and susceptibility to antimicrobial compounds. Similarly, investigated anaerobes represent normal flora and they are opportunistic pathogens. Aerobes and anaerobes differ in their susceptibility to antimicrobials as well as Gram-positive and Gram-negative bacteria. *C. albicans* is representing fungi, which are usually much more resistant to antimicrobial agents than bacteria.

EXPERIMENTAL

Chemistry

Melting points were determined in capillaries in an Electrothermal 9100 apparatus and were uncorrected. The proton nuclear magnetic resonance spectra (^{1}H-NMR) were recorded in DMSO-d_6 on a Bruker VMNRS300 apparatus operating at 300 MHz. Chemical shift values (δ) were expressed in ppm (parts per million) in relation to tetramethylsilane as an internal standard and coupling constants *J* are given in Hz. Mass spectral ESI (Electrospray Ionization) measurements were carried out on a

Mariner Perspective – Biosystem instrument with TOF detector. The spectra were obtained in the positive ion mod with a declustering potential 140–300 V. Chromatographic columns were filled with Merck Kieselgel 0.05–0.2 mm reinst (70–325 mesh ASTM) silica gel. Reactions were monitored by TLC on silica gel (plates with 254 nm fluorescent indicator, layer thickness 0.2 mm, Kieselgel G., Merck), eluted with 9.8:0.2 or 9.5:0.5 (v/v) chloroform-methanol eluents.

General procedure of preparing N-alkylamino derivatives (7–12, 18–22, 27–31, 41–50)

The appropriate imide (**1**– **7**) 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 (DBU) and an appropriate chloroalkylamine *(*0.01 mol) 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, v/v).

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

1-Hydroxymethyl-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-hexaen-16,18-dione (7)

Yield: 72%; white powder, m.p. 276.7–279.5°C (from EtOH/$(Et)_2O$); ^{1}H NMR (300 MHz, DMSO-d_6 + TMS, δ, ppm): 2.61 (8H, m, C1'-H, -CH_3), 3.30 (4H, m, C15-H, C19-H, C2'-H), 4.72 (1H, m, C8-H), 4.84 (2H, s, -CH_2-OH), 5.36 (1H, s, -OH), 7.18 (6H, m, Ar-H), 7.46 (1H, m, Ar-H), 7.69 (1H, m, Ar-H), 10.42 (1H, s, HCl); MS (m/z): 100% = 377.1, 48% = 378.2 [L+H^+].

1-Hydroxymethyl-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-hexaen-16,18-dione (8)

Yield: 68%; white powder, m.p. 269.0–271.4°C (from EtOH/$(Et)_2O$); ^{1}H NMR (300 MHz, DMSO-d_6 + TMS, δ, ppm): 1.10 (6H, t, CH_3, *J* = 7.2 Hz), 2.29 (2H, m, C1'-H), 2.99 (4H, m, -CH_2), 3.32 (4H, m, C15-H, C19-H, C2'-H), 4.73 (1H, s, C8-H), 4.89 (2H, s, -CH_2-OH), 5.37 (1H, s, -OH), 7.20 (6H, m, Ar-H), 7.46 (1H, m, Ar-H), 7.69 (1H, m, Ar-H), 10.46 (1H, s, HCl); MS (m/z): 100% = 405.2, 48% = 406.2 [L+H^+].

1-Hydroxymethyl-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-hexaen-16,18-dione (9)

Yield: 76%; white powder, m.p. 273.2–275.7°C (from EtOH/$(Et)_2O$); ^{1}H NMR (300 MHz, DMSO-d_6 + TMS, δ, ppm): 2.56 (2H, m, C1'-H), 2.87 (2H, m, morpholine), 3.31 (6H, m, C15-H, C19-H, C2'-H, morpholine), 3.78 (4H, m, morpholine), 4.72 (1H, s, C8-H), 4.83 (2H, s, -CH_2-OH), 5.34 (1H, s, -OH), 7.18 (6H, m, Ar-H), 7.46 (1H, m, Ar-H), 7.69 (1H, m, Ar-H), 10.99 (1H, s, HCl); MS (m/z): 100% = 419.2 [L+H^+].

1-Hydroxymethyl-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-hexaen-16,18-dione (10)

Yield: 66%; white powder, m.p. 304.8–307.8°C (from EtOH/$(Et)_2O$); ^{1}H NMR (300 MHz, DMSO-d_6 + TMS, δ, ppm): 1.31 (1H, m, piperidine), 1.69 (5H, m, piperidine), 2.42 (2H, m, C1'-H), 2.65 (2H, m, piperidine), 3.28 (6H, m, C15-H, C19-H, C2'-H, piperidine), 4.72 (1H, s, C8-H), 4.84 (2H, s, -CH_2-OH), 5.37 (1H, s, -OH), 7.19 (6H, m, Ar-H), 7.45 (1H, m, Ar-H), 7.69 (1H, m, Ar-H), 10.99 (1H, s, HCl); MS (m/z): 100% = 417.3 [L+H^+].

1-Hydroxymethyl-17-[3-(dimethylamino)propyl]-17-azapentacyclo[6.6.5.$0^{2,7}$.$0^{9,14}$.$0^{15,19}$] nonadeca-2,4,6,9,11,13-hexaen-16,18-dione (11)

Yield: 77%; white powder, m.p. 256.9–258.2°C (from EtOH/$(Et)_2O$); ^{1}H NMR (300 MHz, DMSO-d_6 + TMS, δ, ppm): 1.10 (2H, m, C2'-H), 2.60 (6H, s, -CH_3), 3.05 (2H, t, C1'-H, *J* = 6.9 Hz), 3.29 (4H, m, C15-H, C19-H, C3'-H), 4.73 (1H, s, C8-H), 4.84 (2H, m, -CH_2-OH), 5.35 (1H, m, -OH), 7.16 (4H, m, Ar-H), 7.26 (2H, m, Ar-H), 7.45 (1H, m, Ar-H), 7.69 (1H, m, Ar-H), 9.77 (1H, s, HCl); MS (m/z): 100% = 391.2, 62% = 392.3 [L+H^+].

N-{3-[1-(Hydroxymethyl)-16,18-dioxo-17-azapentacyclo[6.6.5.$0^{2,7}$.$0^{9,14}$.$0^{15,19}$]nonadeca-2,4,6,9,11,13-hexaen-17-yl]propyl}acetamide (12)

Yield: 63%; white powder, m.p. 256.9–258.2°C (from EtOH/$(Et)_2O$); ^{1}H NMR (300 MHz, DMSO-d_6 + TMS, δ, ppm): 0.81 (2H, m, C2'-H), 1.76 (3H, s, -$COCH_3$), 2.58 (2H, m, C3'-H), 2.94 (2H, t, C1'-H, *J* = 7.0 Hz), 3.25 (2H, m, C15-H, C19-H), 4.70 (1H, s, C8-H), 4.83 (2H, s, -CH_2-OH), 7.15 (6H, m, Ar-H), 7.45 (1H, m, Ar-H), 7.56 (1H, m, Ar-H), 7.68 (1H, m, NH); MS (m/z): 100% = 427.2, 8% = 428.2 [L+Na^+].

1,8-Dichloro-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-hexaen-16,18-dione (18)

Yield: 70%; white powder, m.p. 262.0–264.5°C (from EtOH/$(Et)_2O$); ^{1}H NMR (300 MHz, DMSO-d_6 + TMS, δ, ppm): 2.62 (8H, m, C1'-H, -CH_3), 3.32 (2H, m, C2'-H), 3.70 (2H, s, C15-H, C19-H), 7.45 (4H, m, Ar-H), 7.63 (2H, m, Ar-H), 7.82 (2H, m, Ar-H), 10.10 (1H, s, HCl); MS (m/z): 100% = 415.1, 68% = 417.1 [L+H$^+$].

1,8-Dichloro-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-hexaen-16,18-dione (**19**)

Yield: 68%; white powder, m.p. 238.5–240.6°C (from EtOH/$(Et)_2O$); ^{1}H NMR (300 MHz, DMSO-d_6 + TMS, δ, ppm): 1.10 (6H, m, -CH_3), 2.40 (2H, m, C1'-H), 3.01 (4H, m, -CH_2-), 3.38 (2H, m, C2'-H), 3.70 (2H, s, C15-H, C19-H), 7.44 (2H, m, Ar-H), 7.48 (2H, m, Ar-H), 7.63 (2H, m, Ar-H), 7.83 (2H, m, Ar-H), 10.19 (1H, s, HCl); MS (m/z): 100% = 443.1, 68% = 445.1 [L+H$^+$].

1,8-Dichloro-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-hexaen-16,18-dione (**20**)

Yield: 69%; white powder, m.p. 287.2–289.5°C (from EtOH/$(Et)_2O$); ^{1}H NMR (300 MHz, DMSO-d_6 + TMS, δ, ppm): 2.93 (2H, m, C1'-H), 3.39 (6H, m, C2'-H, morpholine), 3.63 (2H, m, morpholine), 3.69 (2H, s, C15-H, C19-H), 3.88 (2H, m, morpholine), 7.43 (2H, m, Ar-H), 7.47 (2H, m, Ar-H), 7.63 (2H, m, Ar-H), 7.82 (2H, m, Ar-H), 10.39 (1H, *s*, HCl); MS (m/z): 100% = 457.2, 58% = 459.2 [L+H$^+$].

1,8-Dichloro-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-hexaen-16,18-dione (**21**)

Yield: 68%; white powder, m.p. 268.6–271.4°C (from EtOH/$(Et)_2O$); ^{1}H NMR (300 MHz, DMSO-d_6 + TMS, δ, ppm): 1.32 (1H, m, piperidine), 1.68 (4H, m, piperidine), 2.68 (2H, m, C1'-H), 3.31 (7H, m, piperidine, C2'-H), 3.70 (2H, s, C15-H, C19-H), 7.46 (4H, m, Ar-H), 7.63 (2H, m, Ar-H), 7.83 (2H, m, Ar-H), 9.66 (1H, s, HCl); MS (m/z): 100% = 455.2, 82% = 457.2 [L+H$^+$].

1,8-Dichloro-17-[3-(dimethylamino)propyl]-17-azapentacyclo[6.6.5.0^{2,7}.0^{9,14}.0^{15,19}] nonadeca-2,4,6,9,11,13-hexaen-16,18-dione (**22**)

Yield: 74%; white powder, m.p. 255–257.5°C (from EtOH/$(Et)_2O$); ^{1}H NMR (300 MHz, DMSO-d_6 + TMS, δ, ppm): 1.13 (2H, m, C2'-H), 2.61 (6H, s, -CH_3), 3.11 (2H, t, C1'-H, *J* = 7.0 Hz), 3.31 (2H, m, C3'-H), 3.65 (2H, s, C15-H, C19-H), 7.47 (4H, m, Ar-H), 7.65 (2H, m, Ar-H), 7.82 (2H, m, Ar-H), 9.67 (1H, s, HCl); MS (m/z): 100% = 429.1, 68% = 431.1 [L+H$^+$].

1-Acetyl-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-hexaen-16,18-dione (**27**)

Yield: 72%; white powder, m.p. 162.7–166.0°C (from EtOH/$(Et)_2O$); ^{1}H NMR (300 MHz, DMSO-d_6 + TMS, δ, ppm): 2.62 (6H, s, -CH_3), 2.83 (3H, s, -$COCH_3$), 3.25 (2H, m, C1'-H), 3.31 (2H, m, C2'-H), 3.46 (1H, dd, C19-H, *J* = 11.4 Hz, *J* = 8.4 Hz), 4.16 (1H, d, C8-H, *J* = 8.4 Hz), 4.83 (1H, d, C15-H, *J* = 3.3 Hz), 7.03 (1H, m, Ar-H), 7.17 (2H, m, Ar-H), 7.25 (3H, m, Ar-H), 7.59 (1H, m, Ar-H), 7.65 (1H, m, Ar-H), 10.27 (1H, s, HCl); MS (m/z): 100% = 389.2, 5% = 390.2 [L+H$^+$].

1-Acetyl-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-hexaen-16,18-dione (**28**)

Yield: 64%; white powder, m.p. 233.6–236.0°C (from EtOH/$(Et)_2O$); ^{1}H NMR (300 MHz, DMSO-d_6 + TMS, δ, ppm): 1.09 (6H, t, -CH_3, *J* = 7.0 Hz), 2.19 (2H, m, C1'-H), 2.83 (3H, s, -$COCH_3$), 3.01 (4H, m, -CH_2-), 3.31 (2H, m, C2'-H), 3.47 (1H, dd, C19-H, *J* = 11.4 Hz, *J* = 8.4 Hz), 4.16 (1H, d, C8-H, *J* = 8.4 Hz), 4.83 (1H, d, C15-H, *J* = 3.0 Hz), 7.04 (1H, m, Ar-H), 7.23 (5H, m, Ar-H), 7.57 (1H, m, Ar-H), 7.65 (1H, m, Ar-H), 10.00 (1H, s, HCl); MS (m/z): 100% = 417.2, 23% = 418.2 [L+H$^+$].

1-Acetyl-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-hexaen-16,18-dione (**29**)

Yield: 72%; white powder, m.p. 191.7–194.2°C (from EtOH/$(Et)_2O$); ^{1}H NMR (300 MHz, DMSO-d_6 + TMS, δ, ppm): 2.82 (3H, s, -$COCH_3$), 2.92 (2H, m, C1'-H), 3.34 (5H, m, C2'-H, morpholine), 3.47 (1H, dd, C19-H, *J* = 11.7 Hz, *J* = 8.4 Hz), 3.65 (2H, m, morpholine), 3.87 (2H, m, morpholine), 4.16 (1H, d, C8-H, *J* = 8.4 Hz), 4.83 (1H, d, C15-H, *J* = 3.3 Hz), 7.03 (1H, m, Ar-H), 7.22 (5H, m, Ar-H), 7.59 (1H, m, Ar-H), 7.65 (1H, m, Ar-H), 10.55 (1H, s, HCl); MS (m/z): 100% = 431.2, 10% = 432.2 [L+H$^+$].

1-Acetyl-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-hexaen-16,18-dione (**30**)

Yield: 68%; white powder, m.p. 209.1–211.7°C (from EtOH/$(Et)_2O$); ^{1}H NMR (300 MHz, DMSO-d_6 + TMS, δ, ppm): 1.28 (3H, m, piperidine), 1.71 (5H, m, piperidine), 2.83 (3H, s, -$COCH_3$), 3.31 (6H, m, piperidine, C1'-H, C2'-H), 3.47 (1H, dd, C19-H, *J* =

11.7 Hz, *J* = 8.4 Hz), 4.16 (1H, d, C8-H, *J* = 8.4 Hz), 4.83 (1H, d, C15-H, *J* = 3.3 Hz), 7.02 (1H, m, Ar-H), 7.19 (2H, m, Ar-H) 7.26 (3H, m, Ar-H), 7.59 (1H, m, Ar-H), 7.65 (1H, m, Ar-H), 9.41 (1H, s, HCl); MS (m/z): 100% = 429.2, 15% = 430.2 [L+H$^+$].

1-Acetyl-17-[3-(dimethylamino)propyl]-17-azapentacyclo[6.6.5.0^{2,7}.0^{9,14}.0^{15,19}]nonadeca-2,4,6,9,11,13-hexaen-16,18-dione (**31**)

Yield: 74%; white powder, m.p. 254.0–256.9°C (from EtOH/$(Et)_2O$); ^{1}H NMR (300 MHz, DMSO-d_6 + TMS, δ, ppm): 1.05 (2H, m, C2'-H), 2.60 (6H, s, -CH_3), 2.83 (3H, s, -$COCH_3$), 3.02 (2H, t, C1'-H, *J* = 7.2 Hz), 3.27 (2H, m, C3'-H), 3.42 (1H, dd, C19-H, *J* = 11.4 Hz, *J* = 8.4 Hz), 4.13 (1H, d, C8-H, *J* = 8.7 Hz), 4.83 (1H, m, C15-H), 7.04 (1H, m, Ar-H), 7.20 (3H, m, Ar-H), 7.26 (2H, m, Ar-H), 7.58 (1H, m, Ar-H), 7.68 (1H, m, Ar-H), 9.69 (1H, s, HCl); MS (m/z): 100% = 403.2, 20% = 404.2 [L+H$^+$].

1-(Chloromethyl)-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-hexaen-16,18-dione (**41**)

Yield: 70%; white powder, m.p. 269.0–272.6°C (from EtOH/$(Et)_2O$); ^{1}H NMR (300 MHz, DMSO-d_6 + TMS, δ, ppm): 2.63 (8H, s, -CH_3, C1'H), 3.39 (4H, m, C2'-H, C19-H, C15-H), 4.81 (1H, *d*, C8-H, *J* = 3.0 Hz), 5.11 (2H, *m*, -CH_2-Cl), 7.25 (6H, *m*, Ar-H), 7.52 (1H, *m*, Ar-H), 7.64 (1H, *m*, Ar-H), 10.21 (1H, *s*, HCl); MS (m/z): 100% = 395.1, 80% = 397.2 [L+H$^+$].

1-(Chloromethyl)-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-hexaen-16,18-dione (**42**)

Yield: 64%; white powder, m.p. 238.0–241.0°C (from EtOH/$(Et)_2O$); ^{1}H NMR (300 MHz, DMSO-d_6 + TMS, δ, ppm): 1.10 (6H, *t*, -CH_3, *J* = 7.2 Hz), 2.30 (2H, *m*, C1'-H), 3.01 (4H, m, -CH_2-), 3.49 (4H, m, C2'-H, C19-H, C15-H), 4.81 (1H, d, C8-H, *J* = 3.3 Hz), 5.11 (2H, m, -CH_2-Cl), 7.24 (6H, m, Ar-H), 7.53 (1H, m, Ar-H), 7.64 (1H, m, Ar-H), 10.17 (1H, s, HCl); MS (m/z): 100% = 423.1, 80% = 425.2 [L+H$^+$].

1-(Chloromethyl)-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-hexaen-16,18-dione (**43**)

Yield: 68%; white powder, m.p. 248.6–251.0°C (from EtOH/$(Et)_2O$); ^{1}H NMR (300MHz, DMSO-d_6 + TMS, δ, ppm): 2.62 (2H, m, C1'-H), 2.91 (2H, m, morpholine), 3.44 (6H, *m*, C2'-H, morpholine, C19-H, C15-H), 3.67 (2H, m, morpholine), 3.87 (2H, m, morpholine), 4.80 (1H, d, C8-H, *J* = 2.7 Hz), 5.11 (2H, m, -CH_2-Cl), 7.25 (6H, m, Ar-H), 7.51 (1H, m, Ar-H), 7.64 (1H, m, Ar-H), 10.75 (1H, s, HCl); MS (m/z): 100% = 437.1, 70% = 439.2 [L+H$^+$].

1-(Chloromethyl)-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-hexaen-16,18-dione (**44**)

Yield: 58%; white powder, m.p. 271.2–274.0°C (from EtOH/$(Et)_2O$); ^{1}H NMR (300 MHz, DMSO-d_6 + TMS, δ, ppm): 1.28 (1H, m, piperidine), 1.70 (4H, m, piperidine), 2.39 (2H, m, C2'-H), 2.72 (2H, m, piperidine), 3.30 (5H, m, piperidine, C1'-H), 3.42 (2H, m, C19-H, C15-H), 4.81 (1H, d, C8-H, *J* = 3.0 Hz), 5.11 (2H, m, -CH_2-Cl), 7.24 (6H, *m*, Ar-H), 7.52 (1H, m, Ar-H), 7.64 (1H, m, Ar-H), 9.73 (1H, s, HCl); MS (m/z): 100% = 435.2, 55% = 437.2 [L+H$^+$].

1-(Chloromethyl)-17-[3-(dimethylamino)propyl]-17-azapentacyclo[6.6.5.0^{2,7}.0^{9,14}.0^{15,19}] nonadeca-2,4,6,9,11,13-hexaen-16,18-dione (**45**)

Yield: 70%; white powder, m.p. 167.0–170.0°C (from EtOH/$(Et)_2O$); ^{1}H NMR (300 MHz, DMSO-d_6 + TMS, δ, ppm): 1.11 (2H, m, C2'-H), 2.61 (6H, s, -CH_3), 3.06 (2H, t, C1'-H, *J* = 6.9 Hz), 3.31 (2H, m, C3'-H), 3.39 (2H, m, C19-H, C15-H), 4.80 (1H, d, C8-H, *J* = 3.0 Hz), 5.11 (2H, m, -CH_2-Cl), 7.27 (6H, m, Ar-H), 7.51 (1H, m, Ar-H), 7.63 (1H, m, Ar-H), 9.73 (1H, s, HCl); MS (m/z): 100% = 409.1, 55% = 411.1 [L+H$^+$].

1-(Methoxymethyl)-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-hexaen-16,18-dione (**46**)

Yield: 67%; white powder, m.p. 170.6–172.0°C (from EtOH/$(Et)_2O$); ^{1}H NMR (300 MHz, DMSO-d_6 + TMS, δ, ppm): 2.61 (8H, s, -CH_3, C1'H), 3.35 (4H, m, C2'-H, C19-H, C15-H), 3.62 (3H, s, -O-CH_3), 4.67 (2H, s, -CH_2-O-), 4.80 (1H, m, C8-H), 7.19 (6H, m, Ar-H), 7.46 (2H, m, Ar-H), 10.44 (1H, s, HCl); MS (m/z): 100% = 391.1, 48% = 392.2 [L+H$^+$].

1-(Methoxymethyl)-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-hexaen-16,18-dione (**47**)

Yield: 64%; white powder, m.p. 216.0–219.0°C (from EtOH/$(Et)_2O$); ^{1}H NMR (300 MHz, DMSO-d_6 + TMS, δ, ppm): 1.10 (6H, t, -CH_3, *J* = 7.4 Hz), 2.27 (2H, m, C1'-H), 3.00 (4H, m, -CH_2-), 3.29 (4H, m, C2'-H, C19-H, C15-H), 3.62 (3H, s, -O-CH_3), 4.67 (2H, s, -CH_2-O-), 4.76 (1H, d, C8-H, *J* = 2.4 Hz)), 7.18 (5H, m, Ar-H), 7.26 (1H, m, Ar-H), 7.47 (2H, m, Ar-H), 10.05 (1H, s, HCl); MS (m/z): 100% = 419.2, 48% = 420.3 [L+H$^+$].

1-(Methoxymethyl)-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-hexaen-16,18-dione (**48**)

Yield: 78%; white powder, m.p. 225.5–228.0°C (from EtOH/$(Et)_2O$); ^{1}H NMR (300 MHz, DMSO-d_6 + TMS, δ, ppm): 2.60 (2H, m, C1'-H), 2.88 (2H, m, morpholine), 3.37 (6H, m, C2'-H, morpholine, C19-H, C15-H), 3.62 (3H, s, -O-CH_3), 3.68 (2H, m, morpholine), 3.86 (2H, m, morpholine), 4.71 (3H, m, -CH_2-O-, C8-H), 7.19 (6H, m, Ar-H), 7.46 (2H, m, Ar-H), 10.84 (1H, s, HCl); MS (m/z): 100% = 433.2, 40% = 434.3 [L+H$^+$].

1-(Methoxymethyl)-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-hexaen-16,18-dione (**49**).

Yield: 58%; white powder, m.p. 176.0–179.6°C (from EtOH/$(Et)_2O$); ^{1}H NMR (300 MHz, DMSO-d_6 + TMS, δ, ppm): 1.30 (1H, m, piperidine), 1.67 (5H, m, piperidine), 2.44 (2H, m, piperidine), 2.65 (2H, m, C1'-H) 3.25 (2H, m, piperidine), 3.33 (4H, m, C19-H, C15-H, C2'), 3.62 (3H, s, -O-CH_3), 4.67 (2H, s, -CH_2-O-), 4.75 (1H, d, C8-H, *J* = 2.4 Hz), 7.17 (5H, m, Ar-H), 7.25 (1H, m, Ar-H), 7.47 (2H, m, Ar-H), 10.41 (1H, s, HCl); MS (m/z): 100% = 431.2, 63% = 432.3 [L+H$^+$].

1-(Methoxymethyl)-17-[3-(dimethylamino)propyl]-17-azapentacyclo[6.6.5.0^{2,7}.0^{9,14}.0^{15,19}] nonadeca-2,4,6,9,11,13-hexaen-16,18-dione (**50**)

Yield: 70%; white powder, m.p. 146.2–148.8°C (from EtOH/$(Et)_2O$); ^{1}H NMR (300 MHz, DMSO-d_6 + TMS, δ, ppm): 1.09 (2H, m, C2'-H), 2.58 (6H, s, -CH_3), 3.05 (2H, t, C1'-H, *J* = 7.2 Hz), 3.32 (4H, m, C3'-H, C19-H, C15-H), 3.62 (3H, s, -O-CH_3), 4.67 (2H, m, -CH_2-O-), 4.75 (1H, m, C8-H), 7.19 (5H, m, Ar-H), 7.29 (1H, m, Ar-H), 7.45 (2H, m, Ar-H), 9.57 (1H, s, HCl); MS (m/z): 100% = 405.2, 40% = 406.3 [L+H$^+$].

General procedure of preparing N-benzyl and N-benzoyl derivatives (**13–17, 23–26, 32–40**)

An appropriate benzyl or benzoyl derivative (0.01 mol) were added to a mixture of imide (0.01 mol), 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-hydroxymethyl-17-azapentacyclo[6.6.5.0^{2,7}.0^{9,14}.0^{15,19}]nonadeca-2,4,6,9,11,13-hexaen-16,18-dione (**13**).

Yield: 73%; white powder, m.p. 230.0–232.7°C (from EtOH/$(Et)_2O$); ^{1}H NMR (300 MHz, DMSO-d_6 + TMS, δ, ppm): 3.37 (2H, s, C15-H, C19-H), 4.24 (2H, m, -CH_2-benzyl), 4.74 (1H, s, C8-H), 4.83 (2H, m, -CH_2-OH), 5.32 (1H, m, -OH), 6.25 (2H, m, Ar-H), 7.15 (4H, m, Ar-H), 7.45 (1H, m, Ar-H), 7.69 (1H, m, Ar-H); MS (m/z): 100% = 418.1, 4% = 419.1 [L+Na$^+$].

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

Yield: 78%; white powder, m.p. 238.8–240.6°C (from EtOH/$(Et)_2O$); ^{1}H NMR (300 MHz, DMSO-d_6 + TMS, δ, ppm): 3.32 (1H, m, C19-H), 3.39 (1H, m, C15-H), 4.28 (2H, s, -CH_2-benzyl), 4.74 (1H, d, C8-H, *J* = 3.3 Hz), 4.95 (1H, d, -CH_2-OH, *J* = 11.7 Hz), 5.10 (1H, d, -CH_2-OH, *J* = 11.7 Hz), 6.63 (2H, m, Ar-H), 6.79 (2H, m, Ar-H), 7.01 (2H, m, Ar-H), 7.14 (2H, m, Ar-H), 7.20 (2H, m, Ar-H), 7.36 (1H, m, Ar-H), 7.58 (1H, m, Ar-H); MS (m/z): 100% = 436.1, 4% = 437.1 [L+Na$^+$].

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

Yield: 58%; white powder, m.p. 239.0–240.0°C (from EtOH/$(Et)_2O$); ^{1}H NMR (300 MHz, DMSO-d_6 + TMS, δ, ppm): 3.39 (2H, m, C15-H, C19-H), 4.38 (2H, s, -CH_2-benzyl), 4.75 (1H, m, C8-H), 4.81 (2H, m, -CH_2-OH), 5.34 (1H, t, -OH, *J* = 3.9 Hz), 6.51 (1H, d, H aromatic, *J* = 8.7 Hz), 7.18 (6H, m, Ar-H), 7.44 (1H, m, Ar-H), 7.68 (1H, m, Ar-H), 7.94 (2H, m, Ar-H); MS (m/z): 100% = 463.2, 4% = 464.2 [L+Na$^+$].

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

Yield: 68%; white powder, m.p. 122.4–123.9°C (from EtOH/$(Et)_2O$); ^{1}H NMR (300 MHz, DMSO-d_6 + TMS, δ, ppm): 3.51 (1H, m, C19-H), 3.59 (1H, d, C15-H, *J* = 9.0 Hz), 4.86 (1H, d, C8-H, *J* = 3.0 Hz), 5.00 (1H, d, -CH_2-OH, *J* = 12.0 Hz), 5.14 (1H, d, -CH_2-OH, *J* = 12.0 Hz), 6.77 (2H, m, Ar-H), 7.19 (1H, m, Ar-H), 7.24 (1H, m, Ar-H), 7.28 (1H, m, Ar-H), 7.39 (4H, m, Ar-H), 7.47 (1H, m, Ar-H), 7.55 (1H, m, Ar-H), 7.64 (1H, m, Ar-H); MS (m/z): 100% = 432.2, 4% = 433.2 [L+Na$^+$].

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

Yield: 78%; white powder, m.p. 125.3–126.5°C (from EtOH/$(Et)_2O$); ^{1}H NMR (300 MHz, DMSO-d_6 + TMS, δ, ppm): 3.41 (2H, s, C15-H, C19-H), 4.79 (1H, s, C8-H), 5.72(1H, m, -CH_2-OH), 7.21 (4H, m, Ar-H), 7.27 (1H, m, Ar-H), 7.36 (2H, m, Ar-H), 7.43 (1H, m, Ar-H), 7.56 (1H, m, Ar-H), 7.71 (1H, m, Ar-H), 7.97 (1H, d, Ar-H, *J* = 5.1 Hz), 8.17 (1H, m, Ar-H); MS (m/z): 100% = 512.0, 3% = 513.0 [L+Na^+].

17-Benzyl-1,8-dichloro-17-azapentacyclo [6.6.5.$0^{2,7}$.$0^{9,14}$.$0^{15,19}$]nonadeca-2,4,6,9,11,13-hexaen-16,18-dione (**23**)

Yield: 52%; white powder, m.p. 262.0–263.1°C (from EtOH/$(Et)_2O$); ^{1}H NMR (300 MHz, DMSO-d_6 + TMS, δ, ppm): 3.71 (2H, s, C15-H, C19-H), 4.28 (2H, s, -CH_2-benzyl), 6.29 (1H, d, Ar-H, *J* = 6.6 Hz), 7.12 (3H, m, Ar-H), 7.43 (4H, m, Ar-H), 7.59 (2H, m, Ar-H), 7.80 (2H, m, Ar-H); MS (m/z): 100% = 456.1, 45% = 458.1 [L+Na^+].

1,8-Dichloro-17-(4-fluorobenzyl)-17-azapentacyclo[6.6.5.$0^{2,7}$.$0^{9,14}$.$0^{15,19}$]nonadeca-2,4,6,9,11,13-hexaen-16,18-dione (**24**)

Yield: 76%; white powder, m.p. 247.5–250.0°C (from EtOH/$(Et)_2O$); ^{1}H NMR (300 MHz, DMSO-d_6 + TMS, δ, ppm): 3.69 (2H, s, C15-H, C19-H), 4.26 (2H, s, -CH_2-benzyl), 6.37 (2H, m, Ar-H), 6.94 (2H, m, Ar-H), 7.38 (2H, m, Ar-H), 7.45 (2H, m, Ar-H), 7.56 (2H, m, Ar-H), 7.81 (2H, m, Ar-H); MS (m/z): 100% = 474.1, 43% = 476.1 [L+Na^+].

1,8-Dichloro-17-(4-nitrobenzyl)-17-azapentacyclo[6.6.5.$0^{2,7}$.$0^{9,14}$.$0^{15,19}$]nonadeca-2,4,6,9,11,13-hexaen-16,18-dione (**25**)

Yield: 54%; white powder, m.p. 239.0–240.0°C (from EtOH/$(Et)_2O$); ^{1}H NMR (300 MHz, DMSO-d_6 + TMS, δ, ppm): 3.73 (2H, s, C15-H, C19-H), 4.43 (2H, s, -CH_2-benzyl), 6.58 (2H, d, Ar-H, *J* = 8.7 Hz), 7.43 (4H, m, Ar-H), 7.59 (2H, m, Ar-H), 7.81 (2H, m, Ar-H), 7.98 (2H, d, Ar-H, *J* = 8.4 Hz); MS (m/z): 100% = 501.0, 47% = 503.0 [L+Na^+].

17-Benzoyl-1,8-dichloro-17-azapentacyclo[6.6.5.$0^{2,7}$.$0^{9,14}$.$0^{15,19}$]nonadeca-2,4,6,9,11,13-hexaen-16,18-dione (**26**)

Yield: 45%; white powder, m.p. 287.4–289.2°C (from EtOH/$(Et)_2O$); ^{1}H NMR (300 MHz, DMSO-d_6 + TMS, δ, ppm): 3.90 (2H, s, C15-H, C19-H), 7.46 (2H, m, Ar-H), 7.67 (2H, m, Ar-H), 7.74 (1H, m, Ar-H), 7.83 (7H, m, Ar-H); MS (m/z): 98% = 470.1, 43% = 472.1 [L+Na^+].

17-Benzyl-1-acetyl-17-azapentacyclo[6.6.5.$0^{2,7}$.$0^{9,14}$.$0^{15,19}$]nonadeca-2,4,6,9,11,13-hexaen-16,18-dione (**32**)

Yield: 72%; white powder, m.p. 256.4–257.7°C (from EtOH/$(Et)_2O$); ^{1}H NMR (300 MHz, DMSO-d_6 + TMS, δ, ppm): 2.82 (3H, s, -$COCH_3$), 3.47 (1H, dd, C19-H, *J* = 12.0, *J* = 9.0 Hz), 4.20 (3H, m, C8-H, -CH_2-benzyl), 4.81 (1H, m, C15-H), 6.37 (2H, m, Ar-H), 7.09 (1H, m, Ar-H), 7.12 (5H, m, Ar-H), 7.25 (3H, m, Ar-H), 7.56 (1H, m, Ar-H), 7.67 (1H, m, Ar-H); MS (m/z): 100% = 430.3, 9% = 431.3 [L+Na^+].

1-Acetyl-17-(4-fluorobenzyl)-17-azapentacyclo[6.6.5.$0^{2,7}$.$0^{9,14}$.$0^{15,19}$]nonadeca-2,4,6,9,11,13-hexaen-16,18-dione (**33**).

Yield: 78%; white powder, m.p. 233.7–235.6°C (from EtOH/$(Et)_2O$); ^{1}H NMR (300MHz, DMSO-d_6 + TMS, δ, ppm): 2.82 (3H, s, -$COCH_3$), 3.45 (1H, dd, C19-H, *J* = 12.0, *J* = 8.7 Hz), 4.16 (3H, m, C8-H, -CH_2-benzyl), 4.81(1H, d, C15-H, *J* = 3.3 Hz), 6.44 (2H, m, Ar-H), 6.93 (2H, m, Ar-H), 7.00 (1H, m, Ar-H), 7.12 (2H, m, Ar-H), 7.20 (3H, m, Ar-H), 7.57 (1H, m, Ar-H), 7.63 (1H, m, Ar-H); MS (m/z): 100% = 448.2, 9% = 449.2 [L+Na^+].

1-Acetyl-17-(4-nitrobenzyl)-17-azapentacyclo[6.6.5.$0^{2,7}$.$0^{9,14}$.$0^{15,19}$]nonadeca-2,4,6,9,11,13-hexaen-16,18-dione (**34**).

Yield: 65%; white powder, m.p. 205.7–207.0°C (from EtOH/$(Et)_2O$); ^{1}H NMR (300 MHz, DMSO-d_6 + TMS, δ, ppm): 2.82 (3H, s, -$COCH_3$), 3.50 (1H, dd, C19-H, *J* = 11.7, *J* = 8.7 Hz), 4.22 (1H, d, C8-H, *J* = 9.0 Hz), 4.36 (2H, s, -CH_2-benzyl), 4.83 (1H, d, C15-H, *J* = 3.0 Hz), 6.62 (2H, d, Ar-H, *J* = 8.7 Hz), 7.03 (2H, d, Ar-H, *J* = 7.2 Hz), 7.18 (5H, m, Ar-H), 7.64 (2H, m, Ar-H), 7.98 (2H, d, Ar-H, *J* = 8.7 Hz); MS (m/z): 100% = 475.1, 9% = 476.2 [L+Na^+].

17-Benzoyl-1-acetyl-17-azapentacyclo[6.6.5.$0^{2,7}$.$0^{9,14}$.$0^{15,19}$]nonadeca-2,4,6,9,11,13-hexaen-16,18-dione (**35**).

Yield: 52%; white powder, m.p. 227.0–228.3°C (from EtOH/$(Et)_2O$); ^{1}H NMR (300 MHz, DMSO-d_6 + TMS, δ, ppm): 2.78 (3H, s, -$COCH_3$), 3.68 (1H, m, C19-H), 4.41 (1H, d, C8-H, *J* = 8.7 Hz), 4.75 (1H, d, C15-H, *J* = 3.0 Hz), 6.80 (2H, m, Ar-H), 7.00 (1H, m, Ar-H), 7.19 (4H, m, Ar-H), 7.42 (2H, m, Ar-H), 7.55 (2H, m, Ar-H), 7.69 (1H, m, Ar-H), 7.85 (1H, m, Ar-H); MS (m/z): 60% = 444.2 [L+Na^+].

17-Benzyl-1-methyl-17-azapentacyclo[6.6.5.$0^{2,7}$.$0^{9,14}$.$0^{15,19}$]nonadeca-2,4,6,9,11,13-hexaen-16,18-dione (**36**).

Yield: 78%; white powder, m.p. 178.0–180.0°C (from EtOH/$(Et)_2O$); ^1H NMR (300 MHz, DMSO-d_6 + TMS, δ, ppm): 2.17 (3H, s, -CH_3), 3.03 (1H, d, C15-H, *J* = 8.7 Hz), 3.39 (1H, m, C19-H), 4.24 (2H, s, CH_2-benzyl), 4.79 (1H, d, C8-H, *J* = 3.0 Hz), 6.25 (2H, m, Ar-H), 7.09 (3H, m, Ar-H), 7.19 (6H, m, Ar-H), 7.40 (1H, m, Ar-H), 7.47 (1H, m, Ar-H); MS (m/z): 100% = 402.1, 9% = 403.1 [L+Na^+].

1-Methyl-17-(4-fluorobenzyl)-17-azapentacyclo [6.6.5.$0^{2,7}$.$0^{9,14}$.$0^{15,19}$]nonadeca-2,4,6,9,11,13-hexaen-16,18-dione (**37**).

Yield: 80%; white powder, m.p. 190.4–191.9°C (from EtOH/$(Et)_2O$); ^1H NMR (300 MHz, DMSO-d_6 + TMS, δ, ppm): 2.16 (3H, s, -CH_3), 3.02 (1H, d, C15-H, *J* = 8.7 Hz), 3.38 (1H, dd, C19-H, *J* = 11.7, *J* = 8.4 Hz), 4.22 (2H, m, -CH_2-benzyl), 4.78 (1H, d, C8-H, *J* = 3.0 Hz), 6.30 (2H, m, Ar-H), 6.80 (2H, t, Ar-H, *J* = 8.7 Hz), 7.19 (6H, m, Ar-H), 7.39 (1H, m, Ar-H), 7.49 (1H, m, Ar-H); MS (m/z): 100% = 420.2, 19% = 421.2 [L+Na^+].

1-Methyl-17-(4-nitrobenzyl)-17-azapentacyclo [6.6.5.$0^{2,7}$.$0^{9,14}$.$0^{15,19}$]nonadeca-2,4,6,9,11,13-hexaen-16,18-dione (**38**).

Yield: 65%; white powder, m.p. 205.7–207.0°C (from EtOH/$(Et)_2O$); ^1H NMR (300 MHz, DMSO-d_6 + TMS, δ, ppm): 2.17 (3H, s, -CH_3), 3.06 (1H, d, C15-H, *J* = 8.7 Hz), 3.42 (1H, dd, C19-H, *J* = 11.7, *J* = 8.4 Hz), 4.39 (2H, s, -CH_2-benzyl), 4.80 (1H, d, C8-H, *J* = 3.0 Hz), 6.49 (2H, d, Ar-H, *J* = 8.7 Hz), 7.21 (6H, m, Ar-H), 7.40 (1H, m, Ar-H), 7.49 (1H, m, Ar-H), 7.93 (2H, m, Ar-H); MS (m/z): 100% = 447.1, 13% = 448.2 [L+Na^+].

17-Benzoyl-1-methyl-17-azapentacyclo[6.6.5.$0^{2,7}$.$0^{9,14}$.$0^{15,19}$]nonadeca-2,4,6,9,11,13-hexaen-16,18-dione (**39**).

Yield: 72%; white powder, m.p. 197.2–198.8°C (from EtOH/$(Et)_2O$); ^1H NMR (300 MHz, DMSO-d_6 + TMS, δ, ppm): 2.18 (3H, s, -CH_3), 3.24 (1H, d, C15-H, *J* = 9.0 Hz), 3.60 (1H, dd, C19-H, *J* = 11.7, *J* = 8.7 Hz), 4.88 (1H, d, C8-H, *J* = 3.0 Hz), 6.74 (2H, d, Ar-H, *J* = 7.5 Hz), 7.22 (2H, m, Ar-H), 7.41 (7H, m, Ar-H), 7.53 (1H, m, Ar-H), 7.70 (2H, m, Ar-H); MS (m/z): 100% = 416.1, 6% = 417.1 [L+Na^+].

1-Methyl-17-(4-fluorobenzoyl)-17-azapentacyclo[6.6.5.$0^{2,7}$.$0^{9,14}$.$0^{15,19}$]nonadeca-2,4,6,9,11,13-hexaen-16,18-dione (**40**).

Yield: 68%; white powder, m.p. 197.2–198.8°C (from EtOH/$(Et)_2O$); ^1H NMR (300 MHz, DMSO-d_6 + TMS, δ, ppm): 2.18 (3H, s, -CH_3), 3.23 (1H, d, C15-H, *J* = 8.7 Hz), 3.60 (1H, dd, C19-H, *J* = 12.0, *J* = 8.7 Hz), 4.88 (1H, d, C8-H, *J* = 3.3 Hz), 6.44 (1H, m, Ar-H), 6.89 (1H, m, Ar-H), 7.22 (2H, m, Ar-H), 7.39 (6H, m, Ar-H), 7.54 (2H, m, Ar-H); MS (m/z): 100% = 434.1, 7% = 435.1 [L+Na^+].

Microbiology

Organisms

The standard strains of *S. aureus* ATCC 25923, *E. coli* ATCC 25922, *C. albicans* ATCC 14053, *P. acnes* ATCC6919, *B. thetaiotaomicron* ATCC29741, *B. fragilis*ATCC 25285 and one clinical isolate *S. maltophilia* CO2275 were used.

Screening for the antimicrobial activity

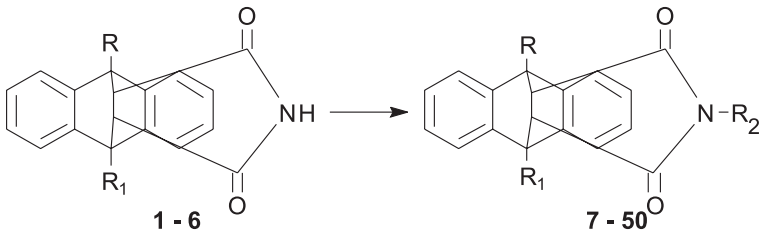
The method according to CLSI (Clinical and Laboratory Standards Institute) directives was applied (18). The compounds **7–50** and **A, B** were tested for their bacteriostatic activity, initially at the high concentrations (512 mg/L), and if bacteriostatic effect was observed, the concentrations were diminished.

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 h. Anaerobes were cultured

Table 1. Antimicrobial activity of biologically active compounds.

Compound	MIC (mg/L) value for:						
	S. aureus ATCC 25923	*E. coli* ATCC 25922	*S. maltophilia* CO 2275	*B. fragilis* ATCC 25285	*B. thetaiotaomicron* ATCC 29741	*P. acnes* ATCC 6919	*C. albicans* ATCC 14053
A	512	> 512	> 512	> 512	> 512	256	512
B	512	> 512	> 512	> 512	> 512	> 512	512
22	512	> 512	> 512	> 512	> 512	256	> 512



1 R = CH_2OH; R_1 = H **4** R = CH_3; R_1 = H
2 R = Cl; R_1 = Cl **5** R = CH_2Cl; R_1 = H
3 R = $COCH_3$; R_1 = H **6** R = CH_2OCH_3; R_1 = H

Compd.	R	R_1	R_2	Compd.	R	R_1	R_2
7	CH_2OH	H	$-(CH_2)_2N(CH_3)_2$	**29**	$COCH_3$	H	$-(CH_2)_2NC_4H_8O$
8	CH_2OH	H	$-(CH_2)_2N(C_2H_5)_2$	**30**	$COCH_3$	H	$-(CH_2)_2NC_5H_{10}$
9	CH_2OH	H	$-(CH_2)_2NC_4H_8O$	**31**	$COCH_3$	H	$-(CH_2)_3N(CH_3)_2$
10	CH_2OH	H	$-(CH_2)_2NC_5H_{10}$	**32**	$COCH_3$	H	$-CH_2C_6H_5$
11	CH_2OH	H	$-(CH_2)_3N(CH_3)_2$	**33**	$COCH_3$	H	$-CH_2C_6H_4F$
12	CH_2OH	H	$-(CH_2)_3NHCOCH_3$	**34**	$COCH_3$	H	$-CH_2C_6H_4NO_2$
13	CH_2OH	H	$-CH_2C_6H_5$	**35**	$COCH_3$	H	$-COC_6H_5$
14	CH_2OH	H	$-CH_2C_6H_4F$	**36**	CH_3	H	$-CH_2C_6H_5$
15	CH_2OH	H	$-CH_2C_6H_4NO_2$	**37**	CH_3	H	$-CH_2C_6H_4F$
16	CH_2OH	H	$-COC_6H_5$	**38**	CH_3	H	$-CH_2C_6H_4NO_2$
17	CH_2OH	H	$-COC_6H_4Br$	**39**	CH_3	H	$-COC_6H_5$
18	Cl	Cl	$-(CH_2)_2N(CH_3)_2$	**40**	CH_3	H	$-COC_6H_4F$
19	Cl	Cl	$-(CH_2)_2N(C_2H_5)_2$	**41**	CH_2Cl	H	$-(CH_2)_2N(CH_3)_2$
20	Cl	Cl	$-(CH_2)_2NC_4H_8O$	**42**	CH_2Cl	H	$-(CH_2)_2N(C_2H_5)_2$
21	Cl	Cl	$-(CH_2)_2NC_5H_{10}$	**43**	CH_2Cl	H	$-(CH_2)_2NC_4H_8O$
22	Cl	Cl	$-(CH_2)_3N(CH_3)_2$	**44**	CH_2Cl	H	$-(CH_2)_2NC_5H_{10}$
23	Cl	Cl	$-CH_2C_6H_5$	**45**	CH_2Cl	H	$-(CH_2)_3N(CH_3)_2$
24	Cl	Cl	$-CH_2C_6H_4F$	**46**	CH_2OCH_3	H	$-(CH_2)_2N(CH_3)_2$
25	Cl	Cl	$-CH_2C_6H_4NO_2$	**47**	CH_2OCH_3	H	$-(CH_2)_2N(C_2H_5)_2$
26	Cl	Cl	$-COC_6H_5$	**48**	CH_2OCH_3	H	$-(CH_2)_2NC_4H_8O$
27	$COCH_3$	H	$-(CH_2)_2N(CH_3)_2$	**49**	CH_2OCH_3	H	$-(CH_2)_2NC_5H_{10}$
28	$COCH_3$	H	$-(CH_2)_2N(C_2H_5)_2$	**50**	CH_2OCH_3	H	$-(CH_2)_3N(CH_3)_2$

Scheme 1. Synthesis of compounds **7–50**

in Schaedler agar with 5% of sheep blood in 35–37°C for 48 h in anaerobic atmosphere. The fungal strain was cultured in the Sabouraud agar (SA), at the same temperature and atmosphere, but for at least for 24 h. 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 and in the case of anaerobes 1.0 in the same scale. Samples of 1.0–9.0 × 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. For anaerobes, all media were prereduced. Samples were incubated at 35–37°C for 24–48 h and in the case of anaerobes for 48–60 h. If after 48 h (60 h for anaerobes) the growth was absent, the substance was noticed as potentially possessing antimicrobial activity.

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

RESULTS AND CONCLUSION

We have synthesized a series of 44 new derivatives of 17-azapentacyclo[6.6.5.$0^{2,7}$.$0^{9,14}$.$0^{15,19}$]nonadeca-2,4,6,9,11,13-hexaen-16,18-dione (Scheme

1). For all compounds the structures were established by ^{1}H NMR and ESI MS spectra. They were also tested for antimicrobial activity against a selection of Gram-positive cocci, Gram-negative bacteria and yeast from the ATCC collection and some derivatives were tested against anaerobic bacteria.

Most of the investigated compounds had no antimicrobial activity and do not inhibit growth even at the concentration 512 mg/L.

Among the examined compounds only one, compound **22,** displayed some antimicrobial activity. It was active against Gram-positive cocci represented by *S. aureus*. The compound inhibited the growth of bacteria at a concentration 512 mg/L. A similar result was obtained for the derivatives described earlier: **A** and **B** (9). They also inhibited the growth of bacteria at a concentration 512 mg/L. Moreover, they inhibited the growth of yeasts at a concentration 512 mg/L. Results of MIC values of these three compounds are presented in Table 1.

It is interesting that in imide arrangement of these derivatives at position 1 the halogen atom can be found. In other derivatives this position is occupied by $–CH_3$, $-CH_2OH$, $-CH_2Cl$, $-CH_2OCH_3$, and $-COCH_3$ substituents. It is worth noting also that elements linking these compounds are short aliphatic amines: dimethylethylamine and diethylethyl amine. It can be assumed that they do not have a decisive influence here. They can be found also in some other derivatives which do not show any activity. Active are only those, which in the imide system contain –Cl or –Br atoms.

Additionally, slightly higher antimicrobial activity of investigated derivatives **A** and **22** was observed against Gram-positive anaerobic bacteria (MIC = 256 mg/L). They had no activity against Gram-negative aerobes as well as anaerobes (MIC > 512 mg/L).

Structure-activity analysis of the synthesized compounds for antimicrobial activity indicates that derivatives with electron-withdrawing group, as in compounds **A**, **B** and **22** seem to be more effective than derivatives having electron-donating group at position 1 of imide arrangement.

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