Article

Novel Adamantane Derivatives: Synthesis, Cytotoxicity and Antimicrobial Properties

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Abstract: Seventeen adamantane derivatives were synthesized according to facile condensation reaction protocols. Spectral analysis (^{1}H NMR and ^{13}C NMR) was applied to confirm the chemical structure of the obtained substances. The synthesized compounds were tested for in vitro antimicrobial activity against a panel of Gram-positive and Gram-negative bacterial strains and towards fungi from *Candida* spp. Among them, four derivatives numbered **9**, **14**, **15** and **19** showed the highest antibacterial potential with MIC = 62.5–1000 µg/mL with respect to all Gram-positive bacteria. *S. epidermidis* ATCC 12228 was the most susceptible among the tested bacterial strains and *C. albicans* ATCC 10231 among fungi. Additionally, the cytotoxicity for three derivatives was measured with the use of the MTT test on A549, T47D, L929 and HeLa cell lines. Our cytotoxicity studies confirmed that the tested substances did not cause statistically significant changes in cell proliferation within the range of the tested doses.

Keywords: adamantane derivatives; Schiff bases; hydrazide–hydrazone; biological activity; cytotoxicity; antimicrobial activity; antibacterial activity; antifungal activity

1. Introduction

Adamantane is an organic chemical compound belonging to polycyclic hydrocarbons. According to the review of the scientific literature, it can be stated that searching for new adamantane derivatives is currently a course of research adopted by many research groups around the world. The main reason for this state of affairs is the documented biological activity of many derivatives of this compound [1]. It is also very important that the introduction of the adamantane system to novel compounds usually results in an increase in lipophilicity. In turn, this may modify the bioavailability of synthesized substances and enlarge their therapeutic effect [1].

Adamantane derivatives display significant biological activity, including antiviral [1–6], antidiabetic [1,7–11], antibacterial [1,12–15], antimalarial [1,16,17], anticancer [1,18–21] activities and anti-inflammatory properties [1,22,23].

Many currently used drugs contain the adamantane system. Amantadine, rimantadine and tromantadine are examples of amine derivatives of adamantane with antiviral activity (Figure 1). Some adamantane derivatives, like vildagliptin or saxagliptin, show antidiabetic activity and are used to treat type 2 diabetes mellitus (T2DM) (Figure 2), whereas adapalene is known for its anti-inflammatory activity, and it is used in the treatment of acne (Figure 3) [1,11,22].

In recent years, scientists have also paid attention to the antimicrobial properties of adamantane derivatives [1] since bacterial resistance to commonly used antibacterial agents is rising, making the treatment of infections much more challenging than before [24,25].
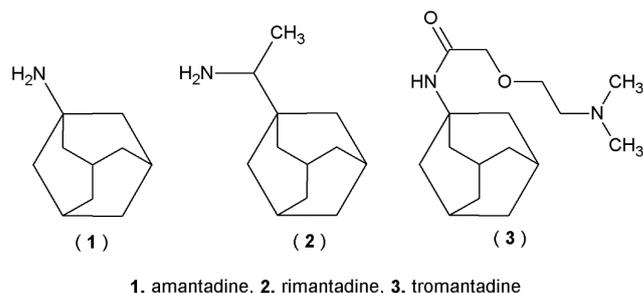
1. amantadine, 2. rimantadine, 3. tromantadine

Figure 1. Amine derivatives of adamantane with antiviral activity.
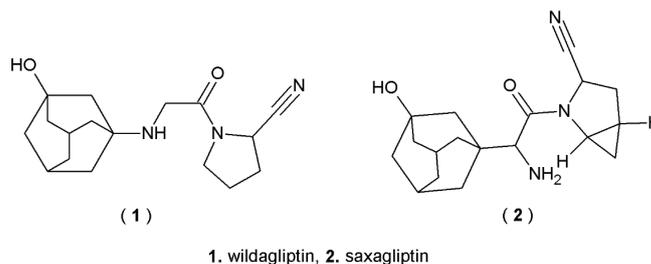

1. wildagliptin, 2. saxagliptin

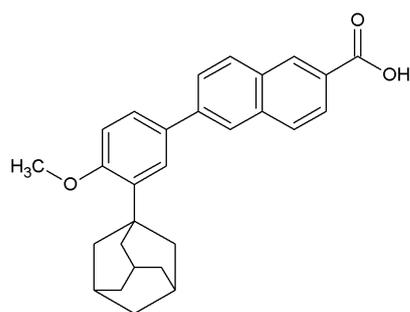**Figure 2.** Adamantane derivatives with antidiabetic activity.

Figure 3. Chemical structure of adapalene.

Al-Wahaibi et al. [14] synthesized interesting derivatives of isothiourea that contained the adamantane system. The obtained compounds showed significant antibacterial activity towards Gram-positive and Gram-negative bacteria. Additionally, synthesized derivatives highly decreased glucose levels in blood serum in comparison to gliclazide [14]. Pham et al. [15] obtained novel hydrazide–hydrazones with the 1-adamantane carbonyl moiety and tested the synthesized substances on some Gram-negative and Gram-positive bacteria, as well as the fungus *Candida albicans*. The screening results revealed that four compounds possess good antibacterial properties against Gram-positive bacteria and *C. albicans* in comparison with known antimicrobial reference substances [15]. According to the latest research, derivatives of adamantane are reported to also influence the biofilm formation of *E. faecalis*, *P. aeruginosa* and methicillin-resistant *S. aureus*, and their antimicrobial activity may be attributed to membranotropic activity [26–28].

For many years now, our research team has focused on the synthesis of novel compounds with a hydrazide–hydrazone moiety that display significant antimicrobial and anticancer activity [29,30]. According to our previous studies, hydrazide–hydrazones are promising antibacterial agents, especially against Gram-positive bacterial strains, and antifungal against the yeasts from *Candida* spp. [31–33].

Based on the facts presented above, which point to the interesting and broad biological activity of adamantane derivatives, we decided to synthesize novel Schiff bases and hydrazide–hydrazones containing the adamantane system and then establish their in vitro antimicrobial activity and test their cytotoxicity. Our goal was to investigate whether the connection of the adamantane system with a Schiff base or hydrazide–hydrazone moiety

would enhance or decrease its antibacterial and antifungal activity in comparison with our previously obtained results for other compounds from the same group.

2. Materials and Methods

2.1. Chemistry

Sigma-Aldrich (Munich, Germany) or Merck Co. (Darmstadt, Germany) were the manufacturers from whom all reagents and solvents were purchased. In order to confirm the purity of synthesized derivatives and to monitor the progress of the conducted reactions, we applied TLC chromatography on aluminum plates covered with silica gel (aluminum oxide 60 F-254, Merck Co.) with the chloroform–ethanol mixture 10:1 (*v/v*) used as the mobile phase. Spots on the chromatograms were detected by irradiation with UV light at λ = 254 nm. The Bruker Avance 300 and 600 apparatus (Bruker BioSpin GmbH, Ettlingen, Germany) were used to register the ^{1}H NMR and ^{13}C NMR spectra. The Fisher–Johns apparatus (Fisher Scientific, Dreieich, Germany) was used to establish melting temperatures of the novel derivatives of adamantane. The Perkin Elmer 2400 series II CHNS/O analyzer (Waltham, MA, USA) was used to perform elemental analysis of the obtained substances. The results were within $\pm 0.4\%$ of the theoretical value.

2.2. Experimental

2.2.1. General Method for the Synthesis of 3-Aminotricyclo[3.3.1.1^{3,7}]decan-1-ol Derivatives (**2**, **3**), Tricyclo[3.3.1.1^{3,7}]decan-1-amine Derivatives (**5–11**), 1-(Tricyclo[3.3.1.1^{3,7}]dec-1-yl)methanamine Derivatives (**13–17**)

A total of 0.2 g (1.2 mmol) of 3-aminotricyclo[3.3.1.1^{3,7}]decan-1-ol (**1**) or 0.2 g (1.3 mmol) of 1-adamantanylamine (**4**) or 0.2 g (1.2 mmol) of 1-adamantanemethylamine (**12**) was placed in a round-bottomed flask and dissolved in ethanol (5 mL, 96%) by heating under reflux. Then, appropriate amounts of various aldehydes or ketones (1.3 mmol) were added, and the mixture in the flask was heated under reflux for 3 h. After that, the solution was allowed to cool and was put into the refrigerator for 24 h. Subsequently, a precipitate appeared, and it was filtered off under reduced pressure, then dried and re-crystalized from ethanol (96%).

3-[(2,3-dimethoxybenzylidene)amino]tricyclo[3.3.1.1^{3,7}]decan-1-ol (**2**)

Cream solid; M.p.: 116 °C; Yield: 87%; ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm): 1.53–1.55 (d, *J* = 6.0 Hz, 2H, CH$_{2\text{-adamantane}}$), 1.58–1.61 (m, 8H, 4×CH$_{2\text{-adamantane}}$), 1.64–1.66 (d, *J* = 6.0 Hz, 2H, CH$_{2\text{-adamantane}}$), 2.24–2.26 (t, 2H, 2×CH$_{\text{adamantane}}$), 3.77 (s, 3H, OCH$_3$), 3.83 (s, 3H, OCH$_3$), 4.56 (s, 1H, OH), 7.08–7.10 (t, *J* = 6.0, 1H, ArH), 7.12–7.13 (d, *J* = 3.0 Hz, 1H, ArH), 7.41–7.43 (d, *J* = 6.0 Hz, 1H, ArH), 8.54 (s, 1H, =CH); ^{13}C NMR (150 MHz, DMSO-d_6) δ (ppm): 30.74 (2×CH$_{\text{adamantane}}$), 35.30 (CH$_{2\text{-adamantane}}$), 42.33 (2×CH$_{2\text{-adamantane}}$), 44.73 (2×CH$_{2\text{-adamantane}}$), 50.99 (CH$_{2\text{-adamantane}}$), 56.26 (C$_{\text{adamantane}}$), 60.98 (OCH$_3$), 61.66 (OCH$_3$), 68.30 (C$_{\text{adamantane}}$), 114.97, 118.21, 124.42, 130.40 (4×C$_{\text{ar}}$), 149.26 (=CH), 150.45, 153.05 (2×C$_{\text{ar}}$).

3-[(2,4-dimethoxybenzylidene)amino]tricyclo[3.3.1.1^{3,7}]decan-1-ol (**3**)

Yellow solid; M.p.: 86 °C; Yield: 96%; ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm): 1.51–1.53 (m, 4H, 2×CH$_{2\text{-adamantane}}$), 1.57–1.58 (d, *J* = 3.0 Hz, 6H, 3×CH$_{2\text{-adamantane}}$), 1.60–1.62 (d, *J* = 6.0 Hz, 2H, CH$_{2\text{-adamantane}}$), 2.22–2.24 (t, *J* = 3.0 Hz, 2H, 2×CH$_{\text{-adamantane}}$), 3.80 (s, 3H, OCH$_3$), 3.84 (s, 3H, OCH$_3$), 4.53 (s, 1H, OH), 6.55–6.56 (d, *J* = 3.0 Hz, 1H, ArH), 6.60–6.61 (d, *J* = 3.0 Hz, 1H, ArH), 7.76–7.78 (d, *J* = 3.0 Hz, 1H, ArH), 8.51 (s, 1H, =CH); ^{13}C NMR (150 MHz, DMSO-d_6) δ (ppm): 30.74 (2×CH$_{\text{adamantane}}$), 35.31 (CH$_{2\text{-adamantane}}$), 42.57 (2×CH$_{2\text{-adamantane}}$), 44.73 (2×CH$_{2\text{-adamantane}}$), 51.22 (CH$_{2\text{-adamantane}}$), 56.06 (C$_{\text{adamantane}}$), 60.55 (OCH$_3$), 61.66 (OCH$_3$), 68.34 (C$_{\text{adamantane}}$), 98.35, 106.37, 118.07, 127.75 (4×C$_{\text{ar}}$), 149.53 (=CH), 160.17, 162.95 (2×C$_{\text{ar}}$).

2-ethoxy-6-[(tricyclo[3.3.1.1^{3,7}]dec-1-ylimine)methyl]phenol (**5**)

Yellow solid; M.p.: 74 °C; Yield: 90%; ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm): 1.30–1.32 (t, *J* = 3.0 Hz, 3H, CH$_3$), 1.67–1.73 (m, 6H, 3×CH$_{2\text{-adamantane}}$), 1.81–1.82 (d, *J* = 3.0 Hz, 6H, 3×CH$_{2\text{-adamantane}}$), 2.14–2.16 (t, *J* = 3.0 Hz, 3H, 3×CH$_{\text{adamantane}}$), 3.99–4.03 (q, *J* = 3.0 Hz, *J* = 6.0 Hz, 2H, CH$_2$), 6.69–6.72 (t, *J* = 3.0 Hz, *J* = 6.0 Hz, 1H, ArH,), 6.95–6.97 (d, *J* = 6.0 Hz, 1H, ArH), 7.02–7.04 (d, *J* = 6.0 Hz, 1H, ArH), 8.53 (s, 1H, =CH), 14.76 (s, 1H, OH); ^{13}C NMR (150 MHz, DMSO-d_6) δ (ppm): 15.30 (CH$_3$), 29.26 (3×CH$_{\text{adamantane}}$), 36.12 (3×CH$_{2\text{-adamantane}}$), 42.82 (3×CH$_{2\text{-adamantane}}$), 56.84 (C$_{\text{adamantane}}$), 64.39 (CH$_2$), 116.51, 117.11, 118.61, 124.22 (4×C$_{\text{ar}}$), 148.02 (=CH), 154.61, 161.33 (2×C$_{\text{ar}}$).

2-ethoxy-4-[(tricyclo[3.3.1.1^{3,7}]dec-1-ylimine)methyl]phenol (**6**)

Yellow solid; M.p.: 118 °C; Yield: 21%; ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm): 1.05–1.07 (t, *J* = 3.0 Hz, 3H, CH$_3$), 1.61–1.69 (m, 6H, 3×CH$_{2\text{-adamantane}}$), 1.71–1.72 (d, *J* = 3.0 Hz, 6H, 3×CH$_{2\text{-adamantane}}$), 2.10–2.12 (t, *J* = 3.0 Hz, 3H, 3×CH$_{\text{adamantane}}$), 4.01–4.05 (q, *J* = 3.0 Hz, 2H, CH$_2$), 6.91–6.92 (d, *J* = 3.0 Hz, 1H, ArH), 7.11–7.13 (d, *J* = 3.0 Hz, 1H, ArH), 7.31 (s, 1H, ArH), 8.16 (s, 1H, =CH), 9.72 (s, 1H, OH); ^{13}C NMR (150 MHz, DMSO-d_6) δ (ppm): 15.23 (CH$_3$), 29.47 (3×CH$_{\text{adamantane}}$), 36.52 (3×CH$_{2\text{-adamantane}}$), 43.39 (3×CH$_{2\text{-adamantane}}$), 56.96 (C$_{\text{adamantane}}$), 64.19 (CH$_2$), 111.60, 115.76, 123.02, 128.01, 147.48 (5×C$_{\text{ar}}$), 148.10 (=CH), 154.74 (C$_{\text{ar}}$).

1-(2-nitrophenyl)-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-yl)methanimine (**7**)

Yellow solid; M.p.: 128 °C; Yield: 63%; ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm): 1.65–1.73 (m, 6H, 3×CH$_{2\text{-adamantane}}$), 1.74–1.75 (d, 6H, 3×CH$_{2\text{-adamantane}}$), 2.13 (m, 3H, 3×CH$_{\text{adamantane}}$), 7.67–7.70 (t, *J* = 3.0 Hz, 1H, ArH), 7.77–7.80 (t, *J* = 3.0 Hz, *J* = 6.0 Hz, 1H, ArH), 7.93–7.95 (d, *J* = 6.0 Hz, 1H, ArH), 8.02–8.03 (d, *J* = 3.0 Hz, 1H, ArH), 8.53 (s, 1H, =CH); ^{13}C NMR (150 MHz, DMSO-d_6) δ (ppm): 29.34 (3×CH$_{\text{adamantane}}$), 36.43 (3×CH$_{2\text{-adamantane}}$), 42.88 (3×CH$_{2\text{-adamantane}}$), 58.48 (C$_{\text{adamantane}}$), 124.60, 129.61, 131.27, 131.58, 133.89 (5×C$_{\text{ar}}$), 149.35 (=CH), 151.96 (C$_{\text{ar}}$).

1-(3-nitrophenyl)-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-yl)methanimine (**8**)

Yellow solid; M.p.: 110 °C; Yield: 47%; ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm): 1.66–1.68 (m, 3H, CH$_{2\text{-adamantane}}$), 1.72–1.74 (m, 3H, CH$_{2\text{-adamantane}}$), 1.78 (d, *J* = 3.0 Hz, 6H, 3×CH$_{2\text{-adamantane}}$), 2.14 (t, *J* = 3.0 Hz, 3H, 3×CH$_{\text{adamantane}}$), 7.73–7.76 (t, *J* = 3.0 Hz, *J* = 6.0 Hz, 1H, ArH), 8.18–8.19 (d, *J* = 3.0 Hz, 1H, ArH), 8.27–8.29 (m, 1H, ArH), 8.48 (s, 1H, =CH), 8.58–8.59 (m, 1H, ArH); ^{13}C NMR (150 MHz, DMSO-d_6) δ (ppm): 29.36 (3×CH$_{\text{adamantane}}$), 36.42 (3×CH$_{2\text{-adamantane}}$), 43.07 (3×CH$_{2\text{-adamantane}}$), 58.19 (C$_{\text{adamantane}}$), 121.88, 125.12, 130.73, 134.56, 138.98 (5×C$_{\text{ar}}$), 148.59 (=CH), 153.93 (C$_{\text{ar}}$).

1-(4-nitrophenyl)-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-yl)methanimine (**9**)

Orange solid; M.p.: 100 °C; Yield: 84%; ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm): 1.63–1.67 (m, 3H, CH$_{2\text{-adamantane}}$), 1.71–1.73 (m, 3H, CH$_{2\text{-adamantane}}$), 1.76–1.77 (d, *J* = 3.0 Hz, 6H, 3×CH$_{2\text{-adamantane}}$), 2.12–2.14 (t, *J* = 3.0 Hz, 3H, 3×CH$_{\text{adamantane}}$), 8.00–8.02 (d, *J* = 6.0 Hz, 2H, ArH), 8.28–8.30 (d, *J* = 6.0 Hz, 2H, ArH), 8.46 (s, 1H, =CH); ^{13}C NMR (150 MHz, DMSO-d_6) δ (ppm): 29.36 (3×CH$_{\text{adamantane}}$), 36.42 (3×CH$_{2\text{-adamantane}}$), 43.03 (3×CH$_{2\text{-adamantane}}$), 58.52 (C$_{\text{adamantane}}$), 124.30, 129.16, 142.99 (5×C$_{\text{ar}}$), 148.78 (=CH), 154.17 (C$_{\text{ar}}$).

1-(2-chloro-5-nitrophenyl)-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-yl)methanimine (**10**)

Yellow solid; M.p.: 100 °C; Yield: 95%; ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm): 1.68–1.70 (m, 3H, CH$_{2\text{-adamantane}}$), 1.72–1.74 (m, 3H, CH$_{2\text{-adamantane}}$), 1.80–1.81 (d, *J* = 3.0 Hz, 6H, 3×CH$_{2\text{-adamantane}}$), 2.14–2.16 (t, 3H, 3×CH$_{\text{adamantane}}$), 7.84–7.85 (d, *J* = 3.0 Hz, 1H, ArH), 8.27–8.29 (d, *J* = 3.0 Hz, 1H, ArH), 8.62 (s, 1H, =CH), 8.67–8.68 (d, *J* = 3.0 Hz, 1H, ArH); ^{13}C NMR (150 MHz, DMSO-d_6) δ (ppm): 29.33 (3×CH$_{\text{adamantane}}$), 36.33 (3×CH$_{2\text{-adamantane}}$), 42.91 (3×CH$_{2\text{-adamantane}}$), 59.05 (C$_{\text{adamantane}}$), 122.51, 126.28, 132.03, 135.01, 140.73 (5×C$_{\text{ar}}$), 147.15 (=CH), 150.19 (C$_{\text{ar}}$).

N-(tricyclo[3.3.1.1^{3,7}]dec-1-yl)tricyclo[3.3.1.1^{3,7}]decan-2-imine (**11**)

White solid; M.p.: 110 °C; Yield: 11%; ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm): 1.49–1.60 (m, 22H, 11×CH$_{2\text{-adamantane}}$), 1.96–1.98 (m, 5H, 5×CH$_{\text{adamantane}}$), 2.15–2.17 (m, 2H, 2×CH$_{\text{adamantane}}$).

1-(2-nitrophenyl)-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)methanimine (**13**)

Orange solid; M.p.: 44 °C; Yield: 33%; ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm): 1.68–1.71 (m, 12H, 6×CH$_{2\text{-adamantane}}$), 2.02–2.04 (t, *J* = 3.0 Hz, 3H, 3×CH$_{\text{adamantane}}$), 3.41 (s, 2H, CH$_2$), 7.58–7.60 (t, *J* = 3.0 Hz, 1H, ArH), 7.68–7.70 (t, *J* = 3.0 Hz, 1H, ArH), 7.83–7.85 (d, *J* = 6.0 Hz, 1H, ArH), 8.25–8.27 (d, *J* = 6.0 Hz, 1H, ArH), 8.58 (s, 1H, =CH).

1-(3-nitrophenyl)-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)methanimine (**14**)

Yellow solid; M.p.: 60 °C; Yield: 4%; ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm): 1.53–1.55 (d, *J* = 6.0 Hz, 6H, 3×CH$_{2\text{-adamantane}}$), 1.59–1.61 (m, 4H, 2×CH$_{2\text{-adamantane}}$), 1.66–1.68 (m, 2H, CH$_{2\text{-adamantane}}$), 1.93–1.95 (t, 3H, 3×CH$_{\text{-adamantane}}$), 3.27 (s, 2H, CH$_2$), 7.88–7.91 (t, *J* = 6.0 Hz, *J* = 3.0 Hz, 1H, ArH), 8.32–8.34 (d, *J* = 6.0 Hz, 1H, ArH), 8.51–8.53 (m, 1H, ArH), 8.68–8.70 (m, 1H, ArH), 10.14 (s, 1H, =CH); ^{13}C NMR (150 MHz, DMSO-d_6) δ (ppm): 28.35 (3×CH$_{\text{adamantane}}$), 34.58 (C$_{\text{adamantane}}$), 37.12 (3×CH$_{2\text{-adamantane}}$), 41.07 (3×CH$_{2\text{-adamantane}}$), 73.50 (CH$_2$), 124.53, 129.01, 131.42, 135.36, 137.64 (5×C$_{\text{ar}}$), 148.75 (=CH), 159.59 (C$_{\text{ar}}$).

1-(4-nitrophenyl)-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)methanimine (**15**)

Yellow solid; M.p.: 192 °C; Yield: 11%; ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm): 1.56 (d, *J* = 3.0 Hz, 6H, 3×CH$_{2\text{-adamantane}}$), 1.61–1.63 (m, 3H, CH$_{2\text{-adamantane}}$), 1.68–1.70 (m, 3H, CH$_{2\text{-adamantane}}$), 1.96 (m, 3H, 3xCH$_{\text{adamantane}}$), 3.31 (s, 2H, CH$_2$), 8.00–8.01 (d, *J* = 3.0 Hz, 2H, ArH), 8.30–8.32 (d, *J* = 6.0 Hz, 2H, ArH), 8.43 (s, 1H, =CH); ^{13}C NMR (150 MHz, DMSO-d_6) δ (ppm): 28.35 (3×CH$_{\text{adamantane}}$), 34.66 (C$_{\text{adamantane}}$), 37.11 (3×CH$_{2\text{-adamantane}}$), 41.07 (3×CH$_{2\text{-adamantane}}$), 73.73 (CH$_2$), 124.41, 129.29, 142.15 (5×C$_{\text{ar}}$), 148.92 (=CH), 159.87 (C$_{\text{ar}}$).

5-bromo-N-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)tricyclo[3.3.1.1^{3,7}]decan-2-imine (**16**)

White solid; M.p.: 158 °C; Yield: 54%; ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm): 1.50–1.52 (d, *J* = 6.0 Hz, 6H, 3×CH$_{2\text{-adamantane}}$), 1.60–1.69 (m, 10H, 5×CH$_{2\text{-adamantane}}$), 1.93–1.95 (m, 6H, 3×CH$_{2\text{-adamantane}}$), 2.16–2.17 (m, 1H, CH$_{\text{adamantane}}$), 2.22–2.24 (m, 1H, CH$_{\text{adamantane}}$), 2.34–2.39 (m, 1H, CH$_{\text{adamantane}}$), 2.44–2.46 (m, 3H, 3×CH$_{\text{adamantane}}$), 3.21 (s, 2H, CH$_2$); ^{13}C NMR (150 MHz, DMSO-d_6): 28.39 (CH$_{\text{adamantane}}$), 31.51 (3×CH$_{\text{adamantane}}$), 32.18 (C$_{\text{adamantane}}$), 34.13 (2×CH$_{2\text{-adamantane}}$), 36.07 (CH$_{\text{adamantane}}$), 37.24 (3×CH$_{2\text{-adamantane}}$), 42.49 (CH$_{\text{adamantane}}$), 46.82 (3×CH$_{2\text{-adamantane}}$), 48.83 (2×CH$_{2\text{-adamantane}}$), 50.03 (CH$_{2\text{-adamantane}}$), 61.94 (C$_{\text{adamantane}}$), 65.85 (CH$_2$), 173.61 (=C$_{\text{adamantane}}$).

5-hydroxy-N-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)tricyclo[3.3.1.1^{3,7}]decan-2-imine (**17**)

White solid; M.p.: 266 °C; Yield: 95%; ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm): 1.50–1.52 (d, *J* = 6.0 Hz, 6H, 3×CH$_{2\text{-adamantane}}$), 1.55–1.61 (m, 4H, 2×CH$_{2\text{-adamantane}}$), 1.61–1.65 (m, 2H, CH$_{2\text{-adamantane}}$), 1.65–1.74 (m, 10H, 5×CH$_{2\text{-adamantane}}$), 1.93–1.95 (m, 3H, 3×CH$_{\text{adamantane}}$), 2.15–2.17 (m, 3H, 3×CH$_{\text{adamantane}}$), 3.15 (s, 2H, CH$_2$), 4.56 (s, 1H, OH); ^{13}C NMR (150 MHz, DMSO-d_6) δ (ppm): 28.42 (CH$_{\text{adamantane}}$), 30.28 (3×CH$_{\text{adamantane}}$), 32.88 (C$_{\text{adamantane}}$), 34.13 (2×CH$_{2\text{-adamantane}}$), 37.29 (CH$_{\text{adamantane}}$), 38.23 (3×CH$_{2\text{-adamantane}}$), 41.00 (CH$_{\text{adamantane}}$), 44.74 (3×CH$_{2\text{-adamantane}}$), 45.14 (2×CH$_{2\text{-adamantane}}$), 46.20 (CH$_{2\text{-adamantane}}$), 62.05 (C$_{\text{adamantane}}$), 66.31 (CH$_2$), 175.89 (=C$_{\text{adamantane}}$).

2.2.2. Synthesis of Hydrazide of 1-Adamantanecarboxylic Acid (**19**)

The tricyclo[3.3.1.1^{3,7}]decane-1-carbonyl chloride (compound **18**, 1.0 mmol, 0.2g, CAS number: 2094-72-6) was placed in a round-bottomed flask and dissolved in ethanol (5 mL, 96%) by heating under reflux. Then, 1.1 mmol of 100% hydrazine hydrate was added, and the mixture was heated under reflux for 3 h. After that, the mixture was cooled and left in

the refrigerator for 24 h. The formed precipitate was filtered off under reduced pressure, dried and re-crystallized from ethanol (96%).

tricyclo[3.3.1.1^{3,7}]decane-1-carbohydrazide (**19**)

CAS Number: 81375-05-5; White powder; M.p.: 224 °C; Yield: 25%; ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm): 1.63–1.69 (m, 6H, 3×CH$_{2-adamantane}$), 1.80–1.82 (d, *J* = 6.0 Hz, 6H, 3×CH$_{2-adamantane}$), 1.95–1.97 (m, 3H, 3×CH$_{adamantane}$), 4.04 (s, 2H, NH$_2$), 9.13 (s, 1H, NH); ^{13}C NMR (150 MHz, DMSO-d_6) δ (ppm): 27.84 (3×CH$_{adamantane}$), 36.50 (3×CH$_{2-adamantane}$), 38.79 (3×CH$_{2-adamantane}$), 38.96 (C$_{adamantane}$), 178.85 (C=O).

Synthesis of Hydrazide–Hydrazones of 1-Adamantanecarbarboxylic Acid (**20–23**)

A total of 1.0 mmol (0.19 g) of hydrazide of 1-adamantanecarboxylic acid (**19**) was dissolved in a round-bottomed flask in ethanol (5 mL, 96%). Then 1.1 mmol of appropriate aldehyde or ketone was added, and the flask was heated under reflux for 3 h. The content of the flask was allowed to cool and was placed in the refrigerator for 24 h. The precipitate obtained was filtered off, dried and re-crystallized from ethanol (96%).

N-[(4-hydroxy-3-ethoxyphenyl)methylidene]tricyclo[3.3.1.1^{3,7}]decane-1-carbohydrazide (**20**)

Yellow solid; M.p.: 246 °C; Yield: 29%; ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm): 1.36–1.38 (t, *J* = 3.0 Hz, 3H, CH$_3$), 1.63–1.69 (m, 6H, 3×CH$_{2-adamantane}$), 1.81–1.82 (d, 6H, 3×CH$_{2-adamantane}$), 1.95–1.97 (t, 3H, 3CH$_{adamantane}$), 4.06–4.09 (q, *J* = 3.0 Hz, 2H, CH$_2$), 6.88–6.90 (d, *J* = 6.0 Hz, 1H, ArH), 7.23–7.25 (d, *J* = 9.0 Hz, 1H, ArH), 7.43 (s, 1H, ArH), 8.55 (s, 1H, =CH), 9.12 (s, 1H, OH), 9.66 (s, 1H, NH); ^{13}C NMR (150 MHz, DMSO-d_6) δ (ppm): 15.19 (CH$_3$), 28.03 (3×CH$_{adamantane}$), 36.58 (3×CH$_{2-adamantane}$), 38.98 (3×CH$_{2-adamantane}$), 56.48 (C$_{adamantane}$), 64.29 (CH$_2$), 111.90, 116.04, 123.75, 125.94 (4×C$_{ar}$), 147.56 (=CH), 150.57, 161.05 (2×C$_{ar}$), 176.38 (C=O).

N-[(2-chloro-5-nitrophenyl)methylidene]tricyclo[3.3.1.1^{3,7}]decane-1-carbohydrazide (**21**)

Orange solid; M.p.: 196 °C; Yield: 5%; ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm): 1.71–1.73 (m, 3H, CH$_{2-adamantane}$), 1.75–1.77 (m, 4H, 2×CH$_{2-adamantane}$), 1.90–1.91 (d, *J* = 3.0 Hz, 6H, 3×CH$_{2-adamantane}$), 2.06–2.08 (t, *J* = 3.0 Hz, 3H, 3×CH$_{adamantane}$), 7.60–7.61 (d, *J* = 3.0 Hz, 1H, ArH), 8.15–8.16 (d, *J* = 3.0 Hz, 1H, ArH), 8.33 (s, 1H, ArH), 8.54 (s, 1H, =CH), 10.34 (s, 1H, NH).

N-(5-bromotricyclo[3.3.1.1^{3,7}]dec-2-ylidene)tricyclo[3.3.1.1^{3,7}]decane-1-carbohydrazide (**22**)

Cream solid; M.p.: 160 °C; Yield: 7%; ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm): 1.57–1.69 (m, 8H, 4×CH$_{2-adamantane}$), 1.81–1.83 (d, *J* = 6.0 Hz, 6H, 3×CH$_{2-adamantane}$), 1.97–2.01 (m, 8H, 4×CH$_{2-adamantane}$), 2.13–2.17 (m, 1H, CH$_{adamantane}$), 2.22–2.26 (m, 1H, CH$_{adamantane}$), 2.36–2.39 (m, 1H, CH$_{adamantane}$), 2.44–2.47 (m, 3H, 3×CH$_{adamantane}$), 10.84 (s, 1H, NH); ^{13}C NMR (150 MHz, DMSO-d_6) δ (ppm): 28.03 (CH$_{adamantane}$), 32.03 (3×CH$_{adamantane}$), 34.77 (C$_{adamantane}$), 35.93 (2×CH$_{2-adamantane}$), 36.58 (CH$_{adamantane}$), 37.24 (3×CH$_{2-adamantane}$), 38.97 (CH$_{adamantane}$), 42.49 (3×CH$_{2-adamantane}$), 48.00 (2×CH$_{2-adamantane}$), 49.76 (CH$_{2-adamantane}$), 65.25 (C$_{adamantane}$), 168.24 (=C$_{adamantane}$), 176.39 (C=O).

N-(5-hydroxytricyclo[3.3.1.1^{3,7}]dec-2-ylidene)tricyclo[3.3.1.1^{3,7}]decane-1-carbohydrazide (**23**)

White solid; M.p.: 238 °C; Yield: 4%; ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm): 1.63–1.69 (m, 16H, 8×CH$_{2-adamantane}$), 1.80–1.82 (d, *J* = 6.0 Hz, 6H, 3×CH$_{2-adamantane}$), 1.96–1.98 (m, 6H, 6×CH$_{adamantane}$), 5.45 (s, 1H, OH), 9.12 (s, 1H, NH); ^{13}C NMR (150 MHz, DMSO-d_6) δ (ppm): 29.93 (CH$_{adamantane}$), 33.46 (3×CH$_{adamantane}$), 37.05 (C$_{adamantane}$), 38.09 (2×CH$_{2-adamantane}$), 38.42 (CH$_{adamantane}$), 44.30 (3×CH$_{2-adamantane}$), 44.83 (CH$_{adamantane}$), 45.30 (3×CH$_{2-adamantane}$), 45.90 (2×CH$_{2-adamantane}$), 47.07 (CH$_{2-adamantane}$), 65.98 (C$_{adamantane}$), 167.86 (=C$_{adamantane}$), 176.54 (C=O).

2.3. Antimicrobial Activity Assays
Microbiological Material and In Vitro Screening Method

The novel adamantane derivatives were screened for antimicrobial activity according to guidelines provided by EUCAST (European Committee on Antimicrobial Susceptibility

Testing) [34] and CLSI (Clinical and Laboratory Standards Institute) [35] against a panel of reference microorganisms from ATCC (American Type Culture Collection). The detailed assay procedures were described earlier by our research team [31–33].

2.4. Cytotoxicity

2.4.1. Cell Lines

The A549 (ECACC 86012804) and the T47D (ECACC 85102201) cell lines were purchased from ECACC (European Collection of Authenticated Cell Cultures) and maintained in DMEM growth medium (PAN Biotech GmbH, Aidenbach, Bayern, Germany), supplemented with 2 mM of glutamine, 10% Fetal Bovine Serum and antibiotics (1% of 100 U/L penicillin, 100 mg/mL streptomycin). The L929 (NCTC clone 929, ATCC® CCL-1™) and HeLa (ATCC® CCL-2™) cell lines came from ATCC (American Type Culture Collection) and were maintained in EMEM growth medium (PAN Biotech GmbH, Aidenbach, Bayern, Germany) supplemented with antibiotics (1% of 100 U/L penicillin, 100 mg/mL streptomycin) and with 5% and 10% FBS (Foetal bovine serum, (PAN Biotech GmbH, Aidenbach, Bayern, Germany), respectively. The cell lines were grown in tissue culture flasks (75 cm^2) and kept in a humidified atmosphere of 5% CO_2 at 37 °C. The examined cell lines were tested against mycoplasma contamination by microbiological assays.

2.4.2. MTT Analysis

In order to establish the cytotoxicity of the tested compounds (**7**, **10**, **21**), an indirect method was applied, i.e., the spectrophotometric measurement of the product concentration resulting from the reduction in the chemical compound by living cells (with functional mitochondria). The amount of colored product was directly proportional to the metabolic activity of the cell.

The principle of the examination relies on the ability of live cells, with intact mitochondrial membranes, to reduce water-insoluble yellow 3-(4,5-dimethyl-1,3-thiazol-2-yl)-2,5-diphenyl-2*H*-tetrazole bromide (MTT) to purple formazan, also insoluble in water. Therefore, L929, A549, HeLa and T47D cell lines were cultured for 24 h in 96-well plates so that they could adhere well to the basis. Then, 20 µL of the tested compounds marked as **7**, **10** and **21** (range 5–200 µM) were added to the cells. After 24 and 48 h of incubation, 10 µL of MTT was added to the cells. Then after 3 h, 100 µL of medium was withdrawn from each well and quenched with the same amount of DMSO (dimethyl sulfoxide). After 5 min of incubation, the absorbance at 570 nm was read off a BioTek model EPOCH ELISA plate reader. The absorbance values of the samples ranged from about 0.3 to about 1.2 and therefore were within the range of linearity of the Lambert–Beer law.
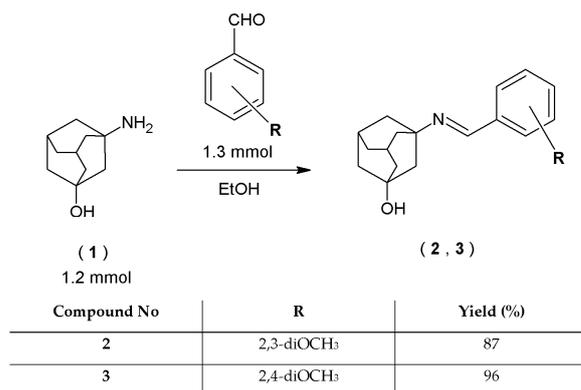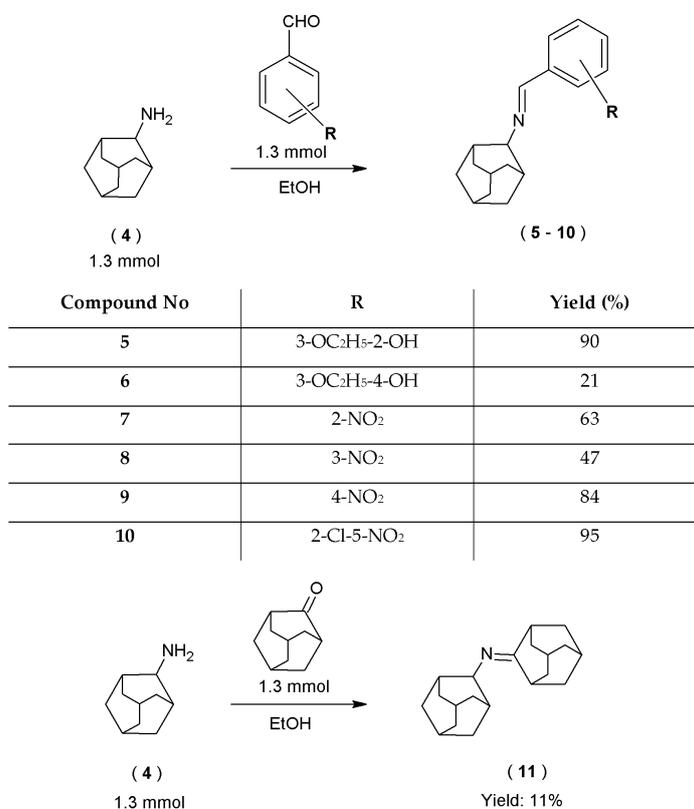
3. Results

3.1. Chemistry

As a starting compound for the synthesis in this research, we used the following adamantane derivatives: 3-aminotricyclo[3.3.1.1^{3,7}]decan-1-ol (**1**), tricyclo[3.3.1.1^{3,7}]decan-1-amine (**4**), 1-(tricyclo[3.3.1.1^{3,7}]dec-1-yl)methanamine (**12**) and tricyclo[3.3.1.1^{3,7}]decane-1-carbonyl chloride (**18**).

Two novel 3-aminotricyclo[3.3.1.1^{3,7}]decan-1-ol derivatives (**2**, **3**) were synthesized with the condensation reaction of 3-amineadamantane-1-ol (**1**) with substituted benzaldehydes. The reactions were carried out with the use of ethanol (96%) as a solvent (Scheme 1).

Novel 1-adamantanylamine derivatives (**5–11**) were synthesized with the condensation reaction of tricyclo[3.3.1.1^{3,7}]decan-1-amine (**4**) with six different appropriate substituted aromatic aldehydes and one ketone. As previously, the reactions were carried out with the use of ethanol (96%) as a solvent (Scheme 2).

Scheme 1. Synthesis of 3–amineadamantane–1–ol derivatives.

Compound No	R	Yield (%)
2	2,3-diOCH$_3$	87
3	2,4-diOCH$_3$	96

Compound No	R	Yield (%)
5	3-OC$_2$H$_5$-2-OH	90
6	3-OC$_2$H$_5$-4-OH	21
7	2-NO$_2$	63
8	3-NO$_2$	47
9	4-NO$_2$	84
10	2-Cl-5-NO$_2$	95

Scheme 2. Synthetic route to new 1–adamantylamine derivatives.

In the same synthetic way, but with the use of a different starting compound, novel 1-adamantylmethylamine derivatives (**13–17**) were synthesized. The 1-(tricyclo [3.3.1.1^{3,7}]dec-1-yl)methanamine (**12**) was dissolved in ethanol (96%) and subjected to the condensation reaction with three substituted benzaldehydes and two ketones (Scheme 3).

Novel hydrazide–hydrazones of 1-adamantanecarbarboxylic acid (**20–23**) were obtained with a two-stage synthetic method. Firstly, hydrazide of 1-adamantanylcarboxylic acid (**19**) was obtained with the reaction of tricyclo[3.3.1.1^{3,7}]decane-1-carbonyl chloride (**18**) with 100% hydrazine hydrate (Scheme 4). Subsequently, hydrazide of 1-adamantanecarboxylic acid (**19**) was subjected to the condensation reaction with two aromatic aldehydes and two ketones to obtain four novel hydrazide–hydrazones of 1-adamantanecarboxylic acid (**20–23**) (Scheme 5).

The chemical structure of all synthesized adamantane derivatives was confirmed with the analysis of the ^{1}H NMR and ^{13}C NMR spectra.

Compound No	R	Yield (%)
13	2-NO$_2$	33
14	3-NO$_2$	4
15	4-NO$_2$	11

Compound No	R	Yield (%)
16	Br	54
17	OH	95

Scheme 3. Synthesis scheme of 1-adamantylmethyl amine derivatives.

Scheme 4. The course of synthesis of the hydrazide of 1-adamantanecarboxylic acid.

Compound No	R	Yield (%)
20	3-OC$_2$H$_5$-4-OH	29
21	2-Cl-5-NO$_2$	5

Compound No	R	Yield (%)
22	Br	7
23	OH	4

Scheme 5. Route to the synthesis of hydrazide–hydrazones of 1-adamantanecarboxylic acid.

3.2. Antimicrobial Activity Assays

The screening results obtained in vitro indicated that few of the analyzed compounds displayed antimicrobial activity (Table 1). The majority of the compounds exhibited an antibacterial effect towards Gram-positive bacteria, except substances numbered **3**, **11**, **16** and **23**, which were inactive towards them. The sensitivity of the other substances was varied. In the case of active compounds, the Minimal Inhibitory Concentrations (MICs) and Minimal Bactericidal Concentrations (MBCs) against these bacteria were within the scope of 62.5 µg/mL to 1000 µg/mL and from 250 µg/mL to >1000 µg/mL, respectively. Among them, derivatives **9**, **14**, **15** and **19** showed the highest antibacterial potential with MIC = 62.5–1000 µg/mL towards all Gram-positive bacteria. *S. epidermidis* ATCC 12228 was the most susceptible to compound **9** (MIC = 62.5 µg/mL and MBC = 250 µg/mL, MBC/MIC = 4) with a bactericidal effect. Other compounds displayed a moderate or mild effect (MIC = 250–1000 µg/mL) or were inactive towards these bacteria.

Schiff bases numbered as **9** substituted with 4-nitrophenyl and **14** with 3-nitrophenyl moiety as well as hydrazide **19** also inhibited growth of all Gram-negative bacterial strains (MIC = 125–1000 µg/mL, MBC = 250 – > 1000 µg/mL). Among them, hydrazide of 1-adamantanecarboxylic acid **19** possessed the highest activity with a moderate effect (MIC = 125–500 µg/mL and similar MBC = 250–1000 µg/mL). This hydrazide showed a bactericidal effect towards all reference bacteria from this group (MBC/MIC = 1–4). The activity of other compounds was lower. Among these microorganisms, *B. bronchiseptica* ATCC 4617 was the most sensitive to the tested substances (MIC = 125–1000 µg/mL, MBC = 500 – > 1000 µg/mL), except to derivatives **2**, **3**, **10**, **11**, **22** and **23** (which had no activity). Moreover, Schiff base **5** substituted with 3-ethoxy-2-hydroxyphenyl and hydrazide **19** were slightly active against some rods from the *Enterobacteriaceae* family and *Pseudomonas aeruginosa* ATCC 9027, respectively.

The results included in Table 1 also indicated some antifungal effects of the tested compounds against yeasts from *Candida* spp. Most of these substances were active at MIC and MFC (Minimal Fungicidal Concentration), ranging from 62.5 µg/mL to 1000 µg/mL and from 125 µg/mL to >1000 µg/mL, respectively. The compounds showed mainly moderate or mild effects. The activity of one of them—the Schiff base numbered **5**, which was substituted with 3-ethoxy-2-hydroxyphenyl—was good (MIC = 62.5 µg/mL and MFC = 125 µg/mL, MFC/MIC = 2) towards *C. albicans* ATCC 10231 with a fungicidal effect. Compounds **5**, **9**, **14** and **15** exhibited a moderate fungicidal effect against all fungi (MIC = 62.5–500 µg/mL, MFC = 125–1000 µg/mL and MFC/MIC = 1–4). Compounds **2**, **8** and **10** had a slightly weaker effect. Moreover, derivatives **7**, **19** and **23** showed activity only towards some of yeasts. Compounds **16**, **20** and **22** had no anticandidal activity.

Table 1. The results of adamantane derivatives in vitro antimicrobial activity screening.

Species	MIC (MBC or MFC) [µg/mL] and {MBC/MIC or MFC/MIC} of Tested Compounds and Standard Antimicrobial Agents																			
	2	3	5	6	7	8	9	10	11	14	15	17	19	20	22	23	CIP/VA */NY **	NIT	CFX	APC
Gram-positive bacteria																				
Staphylococcus aureus ATCC 25923	-	-	-	-	-	-	125 (250) {2}	1000 (2000) {2}	-	250 (1000) {4}	500 (>1000) {>2}	1000 (>1000) {>1}	500 (1000) {2}	1000 (>1000) {>1}	-	-	0.48 (0.48) {1}	15.62 (15.62)	0.49	nd
Staphylococcus aureus ATCC 6538	-	-	-	-	-	1000 (1000) {1}	250 (>1000) {>4}	1000 (>1000) {>1}	-	1000 (>1000) {>1}	500 (>1000) {>2}	-	250 (1000) {4}		-	-	0.24 (0.24) {1}	15.62 (15.62)	0.98	nd
Staphylococcus aureus ATCC 43300	-	-	-	-	-	-	500 (1000) {2}		-	1000 (1000) {1}	1000 (>1000) {>1}	-	500 (500) {1}		-	-	0.24 (0.24) {1}	7.81 (15.62)	nd	nd
Staphylococcus epidermidis ATCC 12228	-	-	-	-	250 (1000) {4}	500 (1000) {2}	62.5 (250) {4}	500 (1000) {4}	-	500 (500) {1}	125 (500) {4}	1000 (>1000) {>1}	250 (1000) {4}	1000 (>1000) {>1}	-	-	0.12 (0.12) {1}	3.91 (7.81)	0.24	nd
Enterococcus faecalis ATCC 29212	-	-	1000 (>1000) {>1}	-	1000 (>1000) {>1}	-	500 (>1000) {>2}	-	-	1000 (>1000) {>1}	500 (>1000) {>2}	-	500 (1000) {2}		-	-	0.98 * (1.95) {2}	nd	nd	nd
Micrococcus luteus ATCC 10240	-	-	500 (1000) {2}	500 (>1000) {>2}	1000 (>1000) {>1}	1000 (>1000) {>1}	500 (500) {1}		-	500 (1000) {2}	500 (>1000) {>2}	1000 (1000) {1}	125 (500) {4}	500 (>1000) {>2}	1000 (>1000) {>1}	-	0.98 (1.95) {2}	62.5 (62.5)	0.98	nd
Bacillus subtilis ATCC 6633	1000 (>1000) {>1}	-	1000 (>1000) {>1}	1000 (>1000) {>1}	1000 (>1000) {>1}	500 (1000) {2}	250 (500) {2}	1000 (>1000) {>1}	-	500 (500) {1}	500 (>1000) {>2}	1000 (>1000) {>1}	250 (250) {1}	250 (500) {2}	-	-	0.03 (0.03) {1}	3.91 (3.91)	15.62	62.5
Bacillus cereus ATCC 10876	-	-	1000 (>1000) {>1}	-	-	1000 (>1000) {>1}	500 (>1000) {>2}	1000 (>1000) {>1}	-	500 (>1000) {>2}	1000 (>1000) {>1}	-	125 (250) {2}	500 (1000) {2}	-	-	0.06 (0.12) {2}	7.81 (15.62)	31.25	nd
Gram-negative bacteria																				
Bordetella bronchiseptica ATCC 4617	-	-	500 (1000) {2}	1000 (>1000) {>1}	1000 (>1000) {>1}	500 (>1000) {>2}	250 (1000) {4}	-	-	500 (1000) {2}	1000 (>1000) {>1}	500 (1000) {2}	125 (500) {4}	500 (1000) {2}	-	-	0.98 (0.98) {1}	125 (>1000)	nd	nd
Klebsiella pneumoniae ATCC 13883	-	-	-	-	-	-	1000 (>1000) {>1}	-	-	1000 (>1000) {>1}	-	-	500 (500) {1}	-	-	-	0.12 (0.24) {2}	15.62 (31.25)	nd	nd
Proteus mirabilis ATCC 12453	-	-	-	-	-	-	1000 (>1000) {>1}	-	-	1000 (>1000) {>1}	-	1000 (>1000) {>1}	500 (1000) {2}	-	-	-	0.03 (0.03) {1}	62.5 (125)	nd	nd
Salmonella typhimurium ATCC 14028	-	-	1000 (1000) {1}	-	-	-	1000 (>1000) {>1}	-	-	1000 (>1000) {>1}	-	-	500 (500) {1}	-	-	-	0.06 (0.06) {1}	31.25 (62.5)	nd	nd
Escherichia coli ATCC 25922	-	-	500 (1000) {2}	-	-	-	1000 (1000) {1}	-	-	1000 (>1000) {>1}	-	1000 (>1000) {>1}	250 (500) {2}	-	-	-	0.004 (0.008) {2}	7.81 (15.62)	nd	nd

Table 1. *Cont.*

| Species | MIC (MBC or MFC) [µg/mL] and {MBC/MIC or MFC/MIC} of Tested Compounds and Standard Antimicrobial Agents | | | | | | | | | | | | | | | | | | | |
	2	3	5	6	7	8	9	10	11	14	15	17	19	20	22	23	CIP/VA */NY **	NIT	CFX	APC
Pseudomonas aeruginosa ATCC 9027	-	-	-	-	-	-	1000 (>1000) {>1}	-	-	1000 (>1000) {>1}	-	1000 (>1000) {>1}	**125 (250) {2}**			-	0.48 (0.98) {2}	-	nd	nd
Candida albicans ATCC 2091	**500 (1000) {2}**	**1000 (1000) {1}**	**125 (250) {2}**	1000 (>1000) {>1}	**1000 (1000) {1}**	**250 (500) {2}**	**125 (500) {4}**	**500 (1000) {2}**	**1000 (1000) {1}**	**250 (250) {1}**	**250 (500) {2}**	**1000 (1000) {1}**	1000 (>1000) {>1}	-	-	1000 (>1000) {>1}	0.24 ** (0.24) {1}	na	na	na
Candida albicans ATCC 10231	**500 (500) {1}**	**1000 (1000) {1}**	**62.5 (125) {2}**	1000 (>1000) {>1}	**1000 (1000) {1}**	**250 (500) {2}**	**125 (250) {2}**	**500 (1000) {2}**	1000 (>1000) {>1}	**125 (250) {2}**	**250 (500) {2}**	1000 (>1000) {>1}	500 (>1000) {>2}	-	-	1000 (>1000) {>1}	0.48 ** (0.48) {1}	na	na	na
Candida parapsilosis ATCC 22019	**250 (1000) {4}**	**1000 (1000) {1}**	**250 (500) {2}**	1000 (>1000) {>1}	**1000 (1000) {1}**	**250 (500) {2}**	**250 (250) {1}**	**500 (1000) {2}**	1000 (>1000) {>1}	**125 (250) {2}**	**250 (500) {2}**	**1000 (1000) {1}**	1000 (>1000) {>1}	-	-	-	0.24 ** (0.48) {2}	na	na	na
Candida glabrata ATCC 90030	1000 (>1000) {>1}	1000 (>1000) {>1}	**250 (500) {2}**	-	-	**1000 (1000) {1}**	**250 (250) {1}**	**1000 (1000) {1}**	**1000 (1000) {1}**	**500 (500) {1}**	**500 (500) {1}**	**1000 (1000) {1}**	-	-	-	-	0.24 ** (0.48) {2}	na	na	na
Candida krusei ATCC 14243	**1000 (1000) {1}**	**1000 (1000) {1}**	**500 (1000) {2}**	1000 (>1000) {>1}	1000 (>1000) {>1}	**500 (1000) {2}**	**125 (500) {4}**	**500 (1000) {2}**	**1000 (1000) {1}**	**250 (250) {1}**	**250 (500) {2}**	**500 (1000) {2}**	125 (1000) {8}	-	-	1000 (>1000) {>1}	0.24 ** (0.24) {1}	na	na	na

'-', no activity; na, not applicable; nd, not determined. The standard antimicrobial agents used as reference substances: ciprofloxacin (CIP), nitrofurantoin (NIT), cefuroxime (CFX) and ampicillin (APC) for bacteria (except enterococci), vancomycin (VA *) for enterococci and nystatin (NY **) for fungi. Compounds with bactericidal (MBC/MIC ≤ 4) or fungicidal (MFC/MIC ≤ 4) effects are marked with bold font.

(The "Fungi" label spans the five Candida rows as a vertical row header.)

3.3. Cytotoxicity

The 24 and 48 h cultures of L929 cells with the compounds marked **7**, **10** and **21** showed that the most cytotoxic compounds were **10** at a dose of 100 μM during 24 h and 48 h of culture and **21**—at a dose of 100 μM during 48 h of culture. However, none of the tested compounds caused a cytotoxic effect below 50% (Tables 2 and 3, Figures S1–S6 in Supplementary Materials).

Table 2. The cell proliferation in % after 24 h exposition on studied compounds in L929 cell line.

Compound No/Concentration (μM)	7				10				21			
	Repeat:				Repeat:				Repeat:			
	No 1	No 2	No 3	No 4	No 1	No 2	No 3	No 4	No 1	No 2	No 3	No 4
control	91	104	89	95	87	112	103	96	101	94	96	103
5	96	104	101	97	100	106	118	109	98	96	109	104
10	94	89	96	92	95	81	103	107	96	91	93	111
25	97	97	78	61	74	72	64	69	87	96	94	85
50	66	64	55	63	79	86	78	89	59	85	53	51
100	76	87	66	68	54	47	59	62	79	84	85	91
150	81	84	98	91	88	79	94	92	86	88	93	99
200	76	79	98	89	85	73	77	69	80	97	99	101

Table 3. The cell proliferation in % after 48 h exposition on studied compounds in L929 cell line.

Compound No/Concentration (μM)	7				10				21			
	Repeat:				Repeat:				Repeat:			
	No 1	No 2	No 3	No 4	No 1	No 2	No 3	No 4	No 1	No 2	No 3	No 4
control	97	101	108	102	98	95	97	101	109	98	105	100
5	113	100	98	97	93	116	110	99	104	109	93	98
10	78	95	82	100	98	91	87	90	107	96	93	88
25	89	83	70	79	69	61	75	69	88	71	77	68
50	55	53	75	66	64	59	61	61	64	66	58	62
100	68	74	62	61	51	42	41	39	56	77	50	39
150	64	76	63	84	56	63	62	88	79	74	89	75
200	67	71	79	82	67	89	74	61	67	70	78	83

The 48 h culture of A549 with the tested compounds (**7**, **10**, **21**) showed that the best effect in promoting cytotoxicity was obtained with the use of compound **10** at a concentration of 25 and 150 μM and derivative **21** at a concentration of 100 μM but with no compound could be given the IC$_{50}$. On the other hand, during the 24 h culture of the A549 cell line, these compounds caused a slight increase in cell proliferation (Tables 4 and 5, Figures S7–S12 in Supplementary Materials).

The 24 h culture of T47D cells with the examined compounds (**7**, **10**, **21**) showed that the main antiproliferative effect was observed with compounds **7** at a dose of 25–50 μM and **21** at a dose of 25 μM. During the 48 h cell culture, only compound **21** at a dose of 25 μM caused such an effect. However, none of the tested compounds caused a cytotoxic effect below 50% (Tables 6 and 7, Figures S13–S18 in Supplementary Materials).

Table 4. The cell proliferation in % after 24 h exposition on studied compounds in A549 cell line.

| Compound No/Concentration (μM) | 7 | | | | 10 | | | | 21 | | | |
| | Repeat: | | | | Repeat: | | | | Repeat: | | | |
	No 1	No 2	No 3	No 4	No 1	No 2	No 3	No 4	No 1	No 2	No 3	No 4
control	106	93	100	112	105	89	93	101	95	113	103	102
5	94	88	96	97	105	100	101	88	97	103	112	94
10	93	96	104	100	102	93	88	91	94	98	99	103
25	94	73	85	87	93	98	100	84	96	87	88	78
50	93	81	75	67	94	106	114	125	101	112	98	96
100	86	75	98	76	88	101	102	98	101	94	93	74
150	101	89	83	79	103	87	96	96	87	81	89	80
200	73	78	96	74	83	89	97	74	82	89	84	85

Table 5. The cell proliferation in % after 48 h exposition on studied compounds in A549 cell line.

| Compound No/Concentration (μM) | 7 | | | | 10 | | | | 21 | | | |
| | Repeat: | | | | Repeat: | | | | Repeat: | | | |
	No 1	No 2	No 3	No 4	No 1	No 2	No 3	No 4	No 1	No 2	No 3	No 4
control	99	108	102	93	76	101	99	87	93	85	88	100
5	88	100	102	103	107	100	93	99	86	88	108	102
10	73	79	85	83	97	104	88	96	99	94	83	97
25	76	71	94	101	88	67	87	86	78	59	77	89
50	67	79	89	88	68	73	87	81	97	81	74	63
100	54	65	68	89	78	98	78	99	89	71	62	88
150	78	67	63	68	72	89	57	61	89	91	78	84
200	87	79	76	85	88	92	70	67	75	81	77	74

Table 6. The cell proliferation in % after 24 h exposition on studied compounds in T47D cell line.

| Compound No/Concentration (μM) | 7 | | | | 10 | | | | 21 | | | |
| | Repeat: | | | | Repeat: | | | | Repeat: | | | |
	No 1	No 2	No 3	No 4	No 1	No 2	No 3	No 4	No 1	No 2	No 3	No 4
control	117	107	98	105	102	107	95	92	88	94	112	101
5	123	104	101	97	100	86	85	91	82	96	110	104
10	112	89	68	92	85	81	83	84	96	80	83	84
25	79	67	60	76	89	103	69	64	59	74	65	58
50	83	64	75	63	89	67	107	97	83	83	97	104
100	87	84	101	88	94	119	78	86	79	95	104	79
150	76	84	98	104	88	79	94	92	63	78	81	85
200	67	74	78	91	98	98	101	113	72	97	99	81

During the 24 and 48 h of cultures of the HeLa cell line, it was shown that all tested compounds did not significantly inhibit cell proliferation. The only exception was compound **10** at a dose of 25 μM during 48 h culture, which resulted in a decrease in proliferation of approximately 60% (Tables 8 and 9, Figures S19–S24 in Supplementary Materials).

Table 7. The cell proliferation in % after 48 h exposition on studied compounds in T47D cell line.

Compound No/Concentration (µM)	7				10				21			
	Repeat:				Repeat:				Repeat:			
	No 1	No 2	No 3	No 4	No 1	No 2	No 3	No 4	No 1	No 2	No 3	No 4
control	78	108	102	78	96	93	87	100	98	83	104	101
5	98	91	98	84	87	100	109	87	89	94	88	102
10	102	102	95	98	93	94	98	81	86	94	83	100
25	73	84	94	86	88	106	87	85	51	59	89	77
50	67	79	89	88	91	101	89	107	87	92	68	63
100	87	73	43	81	112	104	78	99	89	102	87	83
150	68	71	75	68	102	97	75	88	73	69	71	84
200	74	78	76	85	94	92	84	72	75	81	86	94

Table 8. The cell proliferation in % after 24 h exposition on studied compounds in HeLa cell line.

Compound No/Concentration (µM)	7				10				21			
	Repeat:				Repeat:				Repeat:			
	No 1	No 2	No 3	No 4	No 1	No 2	No 3	No 4	No 1	No 2	No 3	No 4
control	89	107	98	105	98	78	95	101	78	96	101	97
5	98	79	103	111	100	96	75	78	89	78	84	101
10	84	96	98	82	85	83	88	101	96	87	93	96
25	96	73	-	87	64	72	93	78	59	84	76	68
50	61	77	53	58	69	79	84	101	94	85	87	107
100	74	76	84	87	94	81	74	86	90	97	74	88
150	81	65	98	78	71	69	89	91	106	92	81	73
200	78	93	71	89	66	89	71	90	78	73	99	75

'-', Not registered.

Table 9. The cell proliferation in % after 48h exposition on studied compounds in HeLa cell line.

Compound No/Concentration (µM)	7				10				21			
	Repeat:				Repeat:				Repeat:			
	No 1	No 2	No 3	No 4	No 1	No 2	No 3	No 4	No 1	No 2	No 3	No 4
control	97	101	96	103	89	101	93	98	87	101	90	87
5	101	76	89	97	91	-	88	94	81	106	107	96
10	91	89	87	91	74	68	76	98	87	77	82	97
25	77	73	67	63	69	51	47	68	76	87	93	63
50	81	70	79	75	94	101	99	87	96	84	68	56
100	78	86	100	78	87	98	82	91	76	85	91	76
150	71	97	64	78	86	97	101	83	75	76	88	84
200	89	84	87	101	95	101	103	87	82	97	88	85

'-', Not registered.

The above study indicates that the compounds designated as **7**, **10** and **21** do not have strong antiproliferative properties against cancer cells.

4. Discussion

4.1. Chemistry

The chemical syntheses described in the current research enabled us to obtain seventeen novel adamantane derivatives not described in the scientific literature so far, i.e., two derivatives of 3-aminotricyclo[3.3.1.1^{3,7}]decan-1-ol (**2**,**3**), seven derivatives of tricyclo [3.3.1.1^{3,7}]decan-1-amine (**5–11**), five derivatives of 1-(tricyclo[3.3.1.1^{3,7}]dec-1-yl)methanamine (**13–17**) and four adamantanecarboxylic acid derivatives with a hydrazide–hydrazone moi-

ety (**20–23**). Compounds **2, 3, 5–11, 13–17** and **20–23** were synthesized based on a typical condensation reaction between the amine group of one compound and the carbonyl group of another substance. For the synthesis of the above-mentioned derivatives, we used the following starting materials: 1.2 mmol of 3-aminotricyclo[3.3.1.1^{3,7}]decan-1-ol (**1**) or 1.3 mmol of 1-adamantanylamine (**4**) or 1.2 mmol of 1-adamantanemethylamine (**12**) or 1.0 mmol of hydrazide of 1-adamantanecarboxylic acid (**19**) and an appropriate amount of aldehydes or ketones.

The yields of the condensation reaction were different for each of the obtained derivatives, and they varied significantly. The yields of the synthesis depended on the aldehydes or ketones used for the synthesis. The lack of a catalyst used in our research may also have contributed to the low efficiency of the reactions performed. A review of the literature shows that the addition of a few drops of glacial acetic acid is usually used to obtain substances based on condensation reactions [36].

The yields of the performed reactions were within the scope of 4–96%. The highest yield of 96% was found in the synthesis of 3-[(2,4-dimethoxybenzylidene)amino]tricyclo[3.3.1.1^{3,7}]decan-1-ol (**3**), whereas the lowest yield of 4% was found for 1-(3-nitrophenyl)-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)methanimine (**14**) and *N*-(5-hydroxytricyclo[3.3.1.1^{3,7}]dec-2-ylidene)tricyclo[3.3.1.1^{3,7}]decane-1-carbohydrazide (**23**).

4.2. NMR Spectra Analysis

The analysis of the ^{1}H NMR and ^{13}C NMR spectra made it possible to identify and confirm the chemical structure of the obtained substances and the correctness of their synthesis.

The derivatives of 3-aminotricyclo[3.3.1.1^{3,7}]decan-1-ol (**2,3**) on the ^{1}H NMR spectra possessed a characteristic singlet signal for the proton of the =CH group at δ 8.51–8.54 ppm. On the ^{13}C NMR spectra, the signal for the carbon atom of the =CH group appeared at δ 149.26 ppm (**2**) and 149.53 ppm (**3**). The presence of this signal both on the ^{1}H NMR and ^{13}C NMR confirmed the correctness of the synthesis. For the derivatives (**2,3**), on the ^{1}H NMR spectra, a singlet signal for the proton of hydroxyl group was found at δ 4.53–4.56 ppm.

In the case of the derivatives of tricyclo[3.3.1.1^{3,7}]decan-1-amine (**5–10**), on the ^{1}H NMR spectra, a singlet signal for the proton of the =CH group was present in the range of δ 8.16–8.62 ppm. The carbon atom of =CH on the ^{13}C NMR spectra for these substances (**5–10**) appeared in the range of δ 147.15–149.35 ppm.

The correctness of the synthesis of the novel derivatives of 1-(tricyclo[3.3.1.1^{3,7}]dec-1-yl)methanamine (**13–15**) was confirmed with the ^{1}H NMR spectroscopy based on the presence of singlet signals for a proton of CH$_2$ and the =CH group, which appeared at δ 3.15–3.41 ppm and δ 8.43–10.14 ppm, respectively. The carbon atoms of CH$_2$ and the =CH group of compounds **13–15** gave signals on the ^{13}C NMR spectra in the range of δ 65.85–73.73 ppm (CH$_2$) and δ 148.75–148.92 ppm (=CH). For compound **16,** we found a characteristic signal for =C$_{adamantane}$ at δ 173.61 ppm because this condensation reaction was carried out with ketone.

On the ^{1}H NMR spectra of the hydrazide of 1-adamantanecarboxylic acid (**19**), we found characteristic singlet signals for protons that corresponded to the NH (δ 9.13 ppm) and NH$_2$ groups (δ 4.04 ppm). On the ^{13}C NMR spectra for this compound, signals for carbon atoms were found in the expected range of chemical shift.

The hydrazide–hydrazones of 1-adamantanecarboxylic acid (**20–21**) obtained in the reaction with aldehydes possessed two typical signals for this class of compounds on the ^{1}H NMR spectra. One singlet signal for the proton of the =CH group was found in the range of δ 7.94–9.13 ppm, and the other singlet signal for the proton of the NH group was found at δ 9.12–10.84 ppm. On the ^{13}C NMR spectra for compounds **20–21**, a signal for the carbon atom of the =CH group appeared around δ 147 ppm, whereas for derivatives **22–23,** signals for =C$_{adamantane}$ were found at δ 168.24 ppm (compound **22**) and δ 167.86 ppm (compound **23**).

Signals for other aliphatic and aromatic fragments of obtained substances on the ^{1}H NMR and ^{13}C NMR spectra were found at the expected values of chemical shift.

The examples of the ^{1}H NMR spectra of the synthesized adamantane derivatives are presented in Supplementary Materials (Figures S25–S27).

4.3. Antimicrobial Activity Assays

Our research goal was to investigate the effect of the incorporation of the adamantane system into novel Schiff bases and hydrazide–hydrazone compounds. Unfortunately, the combination of adamantane and Schiff bases or a hydrazide-hydrazone moiety did not provide the expected significant enhancement in antibacterial activity against Gram-positive bacterial strains in comparison with previously reported hydrazone compounds [31–33]. Only selected adamantane derivatives synthesized by our research group were active against all tested Gram-positive bacteria (Schiff bases **9**, **14**, **15** and hydrazide **19**).

However, the antibacterial activity towards Gram-negative bacterial strains shown by the newly synthesized adamantane derivatives described in this research is not so common in the scientific literature devoted to the antibacterial activity profile of hydrazide–hydrazones [31–33].

Although, in the case of antifungal activity, the results were better than expected even though they were much lower than for reference substances. For the activity of hydrazide–hydrazones that were previously reported by our research team, the antifungal activity was moderate, whereas in this research, it is worth underlining, especially compound **5** with a 3-ethoxy-2-hydroxyphenyl substituent, which showed the lowest value of MIC towards *C. albicans* ATCC 10231 (MIC = 62.5 μg/mL, MBC = 125 μg/mL, MBC/MIC = 2). Other synthesized adamantane derivatives also influence the growth of yeasts from *Candida* spp.

According to literature findings, the adamantane derivatives synthesized by Orzeszko et al. [12,13] and Pham et al. [15], similar to the compounds synthesized by our research group, also displayed interesting activity toward *Candida albicans* and a few species of Gram-positive bacteria.

After the analysis of the structure–antibacterial and structure–antifungal activity relationships of the obtained derivatives, it is clear that among hydrazide–hydrazones (**20–23**), the substitution of the NH$_2$ group in hydrazide **19** resulted in a decrease in both antibacterial and antifungal activity. The free amino group of hydrazide **19** promoted activity against Gram-positive bacterial strains. Among Schiff bases (**2**, **3**, **5–11**, **13–17**), the substitution of the phenyl ring with the electron-withdrawing group—the nitro group at positions 3 (compound **14**) and 4 (compound **9**, **15**)—was the most beneficial substitution for an increase in antibacterial activity. The presence of two electron donating groups in the phenyl ring—two methoxy groups at positions 2 and 3 (compound **2**), 2 and 4 (compound **3**), as well as the adamantanyl (**11**) moiety—decreased the antibacterial potential of the synthesized adamantane derivatives. In the case of antifungal activity, there was no direct connection between the presence of electron-donating or electron-withdrawing groups at the phenyl ring and the bioactivity. The activity increased when in the structure of the Schiff base there was a 3-ethoxy-2-hydroxyphenyl (**5**) or 4-nitrophenyl (**9**) substituent. *Staphylococcus epidermidis* ATCC 12228 and *Candida albicans* ATCC 10231 were the most sensitive microorganisms towards tested adamantane derivatives.

4.4. Cytotoxicity

In our study, the cytotoxicity results of the tested compounds (**7**, **10**, **21**) showed that the newly synthesized derivatives of adamantane did not cause statistical changes in cell proliferation within the range of the tested doses.

Our results were like those obtained by Pham et al. [36] in both experiments; the A549 and HeLa cell lines showed similar cell viability with the use of adamantane derivatives [36]. The lack of a negative effect on fibroblasts (L929 line) means that these compounds can be considered for further tests in the antiviral or antibacterial direction, and this negative

effect does not prejudge their potential as antiproliferative compounds in relation to other types of cancer.

In our study, we selected only the three most popular types of cancer in Poland (cervical cancer, breast cancer and lung cancer). Therefore, further research is needed to check the exact cytotoxicity of these compounds in relation to other types of cancer. Hassan et al. [37], for instance, have shown that some adamantane derivatives were effective for hepatocellular carcinoma [37]. Turk-Erbul et al. [38] showed the effectiveness of adamantane derivatives against lung cancer lines, but these were completely different derivatives than those used in our experiment [38]. Therefore, further research in this direction should be performed.

5. Conclusions

In this research, we managed to synthesize and establish the chemical structure of novel adamantane derivatives. The obtained substances were subjected to antimicrobial activity screening. Only a few of the synthesized derivatives showed some antimicrobial activity, especially derivatives **9** and **14**, towards all reference microorganisms. Additionally, all Gram-positive and Gram-negative bacteria were sensitive to substance **19**. In turn, compound **15** was active towards all Gram-positive bacteria. Moreover, reference yeasts belonging to *Candida* spp. were sensitive to the majority of the tested adamantane derivatives. The bacteria and yeasts included in these studies constitute a natural, opportunistic or pathogenic microflora of the human body. Therefore, it seems practical to use these compounds, with some future structure modification, in the prevention and treatment of infections caused by the selected microorganisms, especially fungi. Additionally, cytotoxicity studies confirmed that the tested substances did not cause statistically significant changes in cell proliferation within the range of the tested doses.

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