Abstract: The reaction of 1-adamantyl isothiocyanate 4 with the various cyclic secondary amines yielded the corresponding N-(1-adamantyl)carbothioamides 5a–e, 6, 7, 8a–c and 9. Similarly, the reaction of 4 with piperazine and trans-2,5-dimethylpiperazine in 2:1 molar ratio yielded the corresponding N,N'-bis(1-adamantyl)piperazine-1,4-dicarbothioamides 10a and 10b, respectively. The reaction of N-(1-adamantyl)-4-ethoxycarbonylpiperidine-1-carbothioamide 8c with excess hydrazine hydrate yielded the target carbohydrazide 11, in addition to 4-(1-adamantyl)thiosemicarbazide 12 as a minor product. The reaction of the carbohydrazide 11 with methyl or phenyl isothiocyanate followed by heating in aqueous sodium hydroxide yielded the 1,2,4-triazole analogues 14a and 14b. The reaction of the carbohydrazide 11 with various aromatic aldehydes yielded the corresponding N'-arylideneamino derivatives 15a–g. The compounds 5a–e, 6, 7, 8a–c, 9, 10a, 10b, 14a,
14b and 15a–g were tested for in vitro antimicrobial activity against certain strains of pathogenic Gram-positive and Gram-negative bacteria and the yeast-like fungus Candida albicans. The compounds 5c, 5d, 5e, 6, 7, 10a, 10b, 15a, 15f and 15g showed potent antibacterial activity against one or more of the tested microorganisms. The oral hypoglycemic activity of compounds 5c, 6, 8b, 9, 14a and 15b was determined in streptozotocin (STZ)-induced diabetic rats. Compound 5c produced significant reduction of serum glucose levels, compared to gliclazide.

**Keywords:** adamantane derivatives; carbothioamides; antimicrobial activity; hypoglycemic activity

1. Introduction

Derivatives of adamantane have long been known for their multifarious pharmacological activities. The incorporation of an adamantyl moiety into several molecules results in compounds with relatively high lipophilicity, which in turn can modify the biological availability of these molecules. The adamantyl-bearing compound are more lipophilic than their des-adamantyl analogues. Beyond increasing the partition coefficient, the adamantyl group positively modulates the therapeutic index of many experimental compounds through a variety of mechanisms [1,2]. After the discovery of amantadine in 1960 as potent antiviral drug for the treatment of Influenza A infection [3–5] and as antiparkinsonian drug [6,7], adamantane derivatives attracted the attention of several scientists as potential chemotherapeutic agents. Further studies based on amantadine resulted in the discovery of more potent antiviral drugs as Rimantadine [8] and Tromantadine [9]. Several adamantane derivatives were also proved to possess marked inhibitory activity against human immunodeficiency viruses (HIV) [10–13]. 6-[3-(1-Adamantyl)-4-hydroxyphenyl]-2-naphthalene carboxylic acid (CD437), a synthetic retinoid derivative, was developed as a potent inducer of apoptosis in human head and neck squamous cell carcinoma [14]. Several adamantane derivatives were recognized as potent bactericidal and fungicidal agents [15–25]. In addition, the adamantane-based drugs, Vildagliptin [26] and Saxagliptin [27] are members of a new class of oral hypoglycemic agents known as dipeptidyl peptidase IV (DPP-IV) inhibitors, which were approved for the treatment of type 2 diabetes. Adamantane derivatives constitutes the major class of 11β-hydroxysteroid dehydrogenase type 1 (11β-HSD1) inhibitor, which are considered important therapy for controlling non-insulin-dependent diabetes, hyperglycemia, obesity, insulin resistance, hyperlipidemia, hypertension and other symptoms associated with excessive body cortisol [28–30]. Moreover, anti-inflammatory activity was reported to several adamantane-containing molecules [19–22,31–33]. In view of the reported chemotherapeutic and hypoglycemic activities of the N-(1- and 2-adamantyl)carboxamides [29,34–36] and the diverse biological activities of several N-(substituted)carbothioamides [37,38], it was of interest to synthesize series of N-(1-adamantyl)carbothioamide derivatives, structurally-related to the previously reported adamantane derivatives, for evaluation as antimicrobial and hypoglycemic agents.
2. Results and Discussion

2.1. Chemical Synthesis

1-Adamantyl isothiocyanate 4, required as starting material, was prepared in good yield via modification of the previously described methods [39,40]. Thus, 1-adamantylamine 1 was reacted with carbon disulfide and trimethylamine, in ethanol, to yield the dithiocarbamate salt 2, followed by addition of di-tert-butyl dicarbonate (Boc₂O) to yield the intermediate 3, which was converted to the target product 4 via stirring with catalytic amount of 4-dimethylaminopyridine (DMAP). 1-Adamantyl isothiocyanate 4 was reacted with the cyclic secondary amines namely, 1-substituted piperazines, morpholine, pyrrolidine, 4-substituted piperidines and 1,2,3,4-tetrahydroisoquinoline, in boiling ethanol, to yield the corresponding N-(1-adamantyl)carbothioamides 5a–e, 6, 7, 8a–c and 9, respectively. The reaction was found to proceed smoothly and the products were precipitated from the reaction mixture in good yields after two hours. 1-Adamantyl isothiocyanate 4 was similarly reacted with piperazine and trans-2,5-dimethylpiperazine in 2:1 molar ratio to yield the corresponding N,N'-bis(1-adamantyl)piperazine-1,4-dicarbothioamide derivatives 10a and 10b in high yields (Scheme 1, Table 1). The structures of compounds 5a–e, 6, 7, 8a–c, 9, 10a and 10b were confirmed by elemental analyses, in addition to the ¹H-NMR, ¹³C-NMR, and ESI-MS mass spectral data which were in full agreement with their structures, in addition to the X-ray spectrum of compound 9 [41].

Scheme 1. Synthesis of the target N-(1-adamantyl)carbothioamides 5a–e, 6, 7, 8a–c, 9, 10a and 10b.
Table 1. Crystallization solvents, melting points, yield percentages, molecular formulae and molecular weights of compounds 5a–e, 6, 7, 8a–c, 9, 10a, 10b, 14a, 14b and 15a–g.

| Comp. No. | R                | Cryst. Solv. | Mp (°C) | Yield (%) | Molecular Formula (Mol. Wt.) |
|-----------|------------------|--------------|---------|-----------|-----------------------------|
| 5a        | C₂H₅            | EtOH         | 150–152 | 77        | C₁₇H₂₉N₃S (307.50)          |
| 5b        | COOC₂H₅        | EtOH         | 121–123 | 68        | C₁₉H₂₉N₃O₂S (351.51)       |
| 5c        | C₆H₅            | EtOH         | 174–176 | 91        | C₂₁H₂₉N₃S (355.54)         |
| 5d        | 2-CH₃OC₆H₄     | EtOH         | 137–139 | 95        | C₂₂H₃₁N₃O₂S (385.57)       |
| 5e        | C₆H₅CH₂        | EtOH         | 146–148 | 95        | C₂₂H₃₁N₃S (369.57)         |
| 6         | -               | EtOH         | 139–141 | 88        | C₁₈H₂₄N₂OS (280.43)        |
| 7         | -               | EtOH         | 175–177 | 74        | C₁₅H₂₄N₂S (264.43)         |
| 8a        | H               | EtOH         | 145–147 | 78        | C₁₅H₂₄N₂S (264.43)         |
| 8b        | C₆H₅            | EtOH         | 137–139 | 90        | C₂₂H₃₀N₂S (354.55)         |
| 8c        | COOC₂H₅        | EtOH         | 166–168 | 78        | C₁₉H₂₉N₂O₂S (350.52)       |
| 9         | -               | EtOH         | 147–149 | 88        | C₂₀H₂₆N₂S (326.5)          |
| 10a       | H               | DMF          | 227–229 | 89        | C₂₆H₄₀N₄S₂ (472.75)        |
| 10b       | CH₃             | DMF          | 232–234 | 92        | C₂₈H₄₄N₄S₂ (500.81)        |
| 14a       | CH₃             | EtOH         | 200–202 | 38        | C₁₉H₂₆N₂S (391.6)          |
| 14b       | C₆H₅            | DMF          | >300    | 44        | C₂₁H₃₁N₂S (453.67)         |
| 15a       | 2-OH            | EtOH         | 196–198 | 65        | C₂₂H₃₂N₂O₂S (440.6)        |
| 15b       | 3,4-Cl₂        | EtOH/CHCl₃  | 237–237 | 61        | C₂₆H₃₂Cl₂N₂O₂S (493.49)   |
| 15c       | 2,6-Cl₂        | EtOH         | 199–201 | 54        | C₂₄H₃₀Cl₂N₂O₂S (493.49)   |
| 15d       | 3,4-(OCH₃)₂     | EtOH         | 154–156 | 48        | C₂₆H₃₂O₂N₄S (484.65)       |
| 15e       | 3,4,5-(OCH₃)₃  | EtOH         | 128–130 | 43        | C₂₆H₃₂O₄N₄O₄S (514.68)     |
| 15f       | 2-OH-5-OCH₃    | EtOH/CHCl₃  | 170–172 | 44        | C₂₅H₃₁N₂O₂S (470.63)       |
| 15g       | 3-OCH₂H₅-4-OH   | EtOH/CHCl₃  | 194–196 | 58        | C₂₅H₃₁O₂N₄O₄S (484.65)     |

N-(1-Adamantyl)-4-ethoxycarbonylpiperidine-1-carbothioamide 8c was reacted with excess hydrazine hydrate, in ethanol, at reflux temperature, to get the target carbohydrazide derivative 11. On monitoring the reaction with thin layer chromatography (TLC), it was observed that the target product was formed after few minutes in addition to a minor product which was further identified as 4-(1-adamantyl)thiosemicarbazide 12. It was also observed that prolongation of the reaction time results in higher ratios of the side product 12. The reaction time was optimized at 20 min to yield 72% of 11 and 18% of 12. The formation of the side product could be explained as a result of hydrazinolysis of the thiocarboxamide function of the major product 11. The structure of the side product 12 was assigned based on the ¹H-NMR and ¹³C-NMR data, in addition to ESI-MS mass spectra and elemental analyses.

The reaction of the carbohydrazide 11 with equimolar amount of methyl or phenyl isothiocyanate, in ethanol for 6 h yielded the intermediate 1,4-disubstituted-3-thiosemicarbazides 13a or 13b. Dehydrative cyclization of compounds 13a and 13b was achieved by heating in 10% aqueous sodium hydroxide solution for 2 h, followed by acidification with hydrochloric acid to yield the target 1,2,4-triazole derivatives 14a and 14b in 38% and 44% overall yields, respectively. Attempted reaction of the carbohydrazide 11 with various aromatic aldehydes via prolonged heating in ethanol yielded fair yields of the corresponding arylideneamino derivatives. On the other hand, carrying out the reaction in the higher boiling solvent N,N-dimethylformamide (DMF) greatly improved the yield. Thus, the reaction of...
the carbohydrazide 11 with certain aromatic aldehydes via heating in DMF for two hours yielded the target compounds 15a–g in relatively higher yields (43%–71%).

The structures of compounds 11, 12, 14a, 14b and 15a–g (Scheme 2, Table 1) were confirmed by elemental analyses, in addition to the ¹H-NMR, ¹³C-NMR, and ESI-MS mass spectral data, which were in full agreement with their structures.

Scheme 2. Synthesis of the target N-(1-adamanty)carbothioamides 14a,b and 15a–h.

2.2. In Vitro Antimicrobial Activity

The synthesized compounds 5a–e, 6, 7, 8a–c, 9, 10a, 10b, 14a, 14b and 15a–g were tested for in vitro inhibitory activity against the standard pathogenic strains of the Institute of fermentation of Osaka (IFO) namely; *Staphylococcus aureus* IFO 3060, *Bacillus subtilis* IFO 3007, *Micrococcus luteus* IFO 3232 (Gram-positive bacteria), *Escherichia coli* IFO 3301, *Pseudomonas aeruginosa* IFO 3448 (Gram-negative bacteria), and the yeast-like pathogenic fungus *Candida albicans* IFO 0583. The primary screening was carried out using the agar disc-diffusion method using Müller-Hinton agar medium [42]. The results of the preliminary antimicrobial screening of the synthesized compounds (200 μg/disc), the antibacterial antibiotics Ampicillin trihydrate, Gentamicin (100 μg/disc) and the potent antifungal drug Clotrimazole
(100 μg/disc) and the calculated log \( P \) values (Clog \( P \)) of the tested compounds (calculated using the CS ChemOffice Ultra version 8.0, CambridgeSoft, Cambridge, MA, USA) are presented in Table 2.

Table 2. Antimicrobial activity of compounds 5a–e, 6, 7, 8a–c, 9, 10a, 10b, 14a, 14b and 15a–g (200 μg/8 mm disc), the broad spectrum antibacterial drugs Gentamicin (100 μg/8 mm disc), Ampicillin (100 μg/8 mm disc) and the antifungal drug Clotrimazole (100 μg/8 mm disc) against \textit{Staphylococcus aureus} IFO 3060 (SA), \textit{Bacillus subtilis} IFO 3007 (BS), \textit{Micrococcus luteus} IFO 3232 (ML), \textit{Escherichia coli} IFO 3301 (EC), \textit{Pseudomonas aeruginosa} IFO 3448 (PA), and \textit{Candida albicans} IFO 0583 (CA).

| Comp. No. | Clog \( P \) | Diameter of Growth Inhibition Zone (mm) \( ^a \) |
|-----------|---------------|-----------------------------------------|
| 5a        | 4.32          | -                                       |
| 5b        | 4.32          | -                                       |
| 5c        | 4.77          | 20 (8) \( ^b \) 24 (2) \( ^b \) 16 15 14 - |
| 5d        | 4.79          | 19 (4) \( ^b \) 22 (4) \( ^b \) 17 12 - - |
| 5e        | 5.52          | 15 19 (8) \( ^b \) 12 15 12 - - |
| 6         | 3.23          | 22 (2) \( ^b \) 20 (1) \( ^b \) 19 (4) \( ^b \) 15 12 - |
| 7         | 4.06          | 18 (8) \( ^b \) 20 (2) \( ^b \) 18 (4) \( ^b \) 15 13 - |
| 8a        | 4.62          | 12 14 12 - - - |
| 8b        | 6.03          | 16 16 14 - - - |
| 8c        | 4.01          | 12 13 - - - |
| 9         | 5.48          | - - - - - - |
| 10a       | 6.86          | 25 (32) \( ^b \) 28 (16) \( ^b \) 20 (32) \( ^b \) 18 16 - |
| 10b       | 7.90          | 26 (32) \( ^b \) 24 (8) \( ^b \) 23 (32) \( ^b \) 19 (64) \( ^b \) 12 - |
| 14a       | 3.40          | - - - - - - |
| 14b       | 5.29          | - - - - - - |
| 15a       | 5.07          | 18 (16) \( ^b \) 22 (2) \( ^b \) 15 12 - - |
| 15b       | 5.77          | 12 12 - - - - |
| 15c       | 4.70          | 14 17 12 - - - |
| 15d       | 4.41          | - - - - - - |
| 15e       | 4.03          | - - - - - - |
| 15f       | 5.14          | 22 (8) \( ^b \) 27 (1) \( ^b \) 19 (8) \( ^b \) 13 11 11 |
| 15g       | 4.79          | 19 (8) \( ^b \) 25 (2) \( ^b \) 18 (8) \( ^b \) 12 12 13 |
| Gentamicin| 6.86          | 25 (2) \( ^b \) 25 (2) \( ^b \) 18 (2) \( ^b \) 20 (0.5) \( ^b \) 19 (1) \( ^b \) NT |
| Ampicillin| 7.90          | 23 (2) \( ^b \) 21 (0.5) \( ^b \) 19 (2) \( ^b \) 17 (2) \( ^b \) 16 (2) \( ^b \) NT |
| Clotrimazole | 5.07         | NT NT NT NT NT 21 (2) \( ^b \) |

\( ^a \) (-): Inactive (inhibition zone < 10 mm); (NT): Not tested; \( ^b \) The figures shown in parentheses represent the MIC values (μg/mL).

The antimicrobial activity results revealed that the tested compounds exhibited various degrees of inhibition against the tested microorganisms. Potent antibacterial activity was displayed by the compounds 5c–e, 6, 7, 10a, 10b, 15a, 15f and 15g which produced growth inhibition zones ≥ 18 mm against one or more of the tested bacteria. In addition, the derivatives 8a, 8b and 15c showed moderate activity (growth inhibition zones 14–17 mm), the derivatives 8c and 15b produced weak activity (growth
inhibition zones 10–13 mm) and the derivatives 5a, 5b, 9, 14a, 14b, 15d and 15e were practically inactive (growth inhibition zones < 10 mm) against the tested microorganisms.

The Gram-positive bacteria *Bacillus subtilis* and *Staphylococcus aureus* and to a lesser extent *Micrococcus luteus* are considered the most sensitive among the tested microorganisms. Meanwhile, the activity against the tested Gram-negative bacteria was generally lower than that of the Gram-positive bacteria, only compound 10a and 10b were found strongly active against *Escherichia coli* and moderately or weakly active against *Pseudomonas aeruginosa*. The inhibitory activity of the compounds against *Candida albicans* was rather lower than their antibacterial activity, only compounds 15f and 15g displayed marginal activity compared to Clotrimazole. In addition, the antimicrobial activity of the compounds were not correlated to their lipophilicity.

The *N*-(1-adamantyl)carbothioamides 5c–e, 6, 7 and 8a–c showed marked activity against the tested Gram-positive bacteria and weak to moderate activity against the tested Gram-negative bacteria, in addition to the absence of antifungal activity. The antibacterial activity was dependent on the nature of the precursor cyclic secondary amine. Among the piperazine derivatives 5a–e, the 4-aryl and benzyl derivatives 5c, 5d and 5e were highly active and the ethyl and the ethoxycarbonyl derivatives 5a and 5b were inactive. The morpholine and pyrrolidine derivatives 6 and 7 were highly active against the Gram-positive bacteria and retained moderate activity against *Escherichia coli* and weak activity against *Pseudomonas aeruginosa*. The antibacterial activity of the piperidine derivatives 8a–c was lower than their morpholine and pyrrolidine analogues with moderate to weak activity against the tested Gram-positive bacteria. The tetrahydroisoquinoline derivative 9 totally lacked antimicrobial activity.

The *N*,*N'*-bis(1-adamantyl)piperazine-1,4-dicarbothioamides 10a and 10b exhibited potent broad-spectrum antibacterial activity against the tested Gram-positive bacteria and *Escherichia coli* in addition moderate activity and weak activity against *Pseudomonas aeruginosa*. The *N*-(1-adamantyl)piperidine-4-(5-mercapto-4-phenyl-1,2,4-triazol-3-yl)-1-carbothioamides 14a and 14b totally lacked antimicrobial activity. Concerning the antimicrobial activity of the *N*'-(arylidene)piperidine-4-carboxyhydrazides 15a–g, it was observed that the activity mainly dependent on the arylidene moiety. The phenolic derivatives 15a, 15f and 15g displayed potent antibacterial activity against the tested Gram-positive bacteria and endowed marginal activity against *Candida albicans*.

The minimal inhibitory concentrations (MIC) [43] for the most active compounds 5c, 5d, 5e, 6, 7, 10a, 10b, 15a, 15f and 15g which are shown in Table 2, were in accordance with the results obtained in the primary screening. Despite the potent broad-spectrum antibacterial activity of compounds 10a and 10b, the MIC values were higher than expected. The high MIC values of compounds 10a and 10b may be attributed high lipophilicity and the poor water solubility in the aqueous Müller-Hinton Broth and Sabouraud Liquid Medium.

2.3. In Vivo Hypoglycemic Activity

The oral hypoglycemic activity of compounds 5c, 6, 8b, 9, 14a and 15b was determined in streptozotocin (STZ)-induced diabetic rats. The compounds were tested at 10 and 20 mg/kg dose levels. The diabetogenic effect of STZ is the direct result of irreversible damage to the pancreatic beta cells, resulting in degranulation and loss of insulin secretion [44,45].
The results of oral hypoglycemic activity compounds 5c, 6, 8b, 9, 14a and 15b (10 and 20 mg/kg) and the potent hypoglycemic drug gliclazide in STZ-induced diabetic rats (10 mg/kg) are listed in Table 3. The highest activity was shown by compound 5c, which produced significant strong dose-independent reduction of serum glucose levels in STZ-induced diabetic rats, compared to gliclazide at 10 mg/kg dose level (Potency ratio 92.48%). Compound 6 displayed good hypoglycemic at 20 mg/kg dose level and weak activity at 10 mg/kg dose level.

Table 3. Oral hypoglycemic activity of compounds 5c, 6, 8b, 9, 14a, 15b (10 and 20 mg/kg) and gliclazide (10 mg/kg) in STZ-induced diabetic rats.

| Treatment | Results |
|-----------|---------|
|           | $C_0$ (mg/dL) | $C_{24}$ (mg/dL) | % Glucose Reduction |
| Group 1 c | 302.6 ± 11.64 | 287.2 ± 16.85 | 5.09% |
| Group 2 d | 295.4 ± 17.52 | 183.0 ± 13.38 | 38.05% |
| 5c (10 mg/kg) | 291.6 ± 15.23 | 189.0 ± 22.16 * | 35.19% (92.48) |
| 5c (20 mg/kg) | 319.6 ± 7.85 | 207.0 ± 13.84 * | 35.23% (46.30) |
| 6 (10 mg/kg) | 283.8 ± 11.16 | 263.8 ± 16.66 | 7.05% (18.52) |
| 6 (20 mg/kg) | 296.6 ± 12.92 | 196.0 ± 9.67 * | 33.92% (44.58) |
| 8b (10 mg/kg) | 264.2 ± 5.49 | 257.4 ± 9.45 | 2.57% (6.75) |
| 8b (20 mg/kg) | 303.3 ± 16.35 | 291.2 ± 8.18 | 4.05% (5.32) |
| 9 (10 mg/kg) | 282.8 ± 13.90 | 275.8 ± 15.52 | 2.48% (6.52) |
| 9 (20 mg/kg) | 276.2 ± 14.17 | 264.6 ± 7.35 | 4.20% (5.52) |
| 14a (10 mg/kg) | 274.8 ± 14.59 | 277.4 ± 7.19 | 0.95% (2.50) |
| 14a (20 mg/kg) | 286.4 ± 24.56 | 271.4 ± 21.85 | 5.24% (6.89) |
| 15b (10 mg/kg) | 282.0 ± 14.21 | 287.8 ± 13.37 | −2.06% |
| 15b (20 mg/kg) | 293.2 ± 15.66 | 286.8 ± 17.16 | 2.18% (2.87) |

* Results are expressed as mean ± S.E.M. (n = 5); b The figures shown in parentheses are the relative potency compared with gliclazide; c Treated with a single oral dose of 0.5% (w/v) aqueous CMC solution (5 mL/kg); d Treated with 10 mg/kg gliclazide in 0.5% (w/v) aqueous CMC; * Significant difference at $p < 0.01$ compared with the corresponding control.

The hypoglycemic activity of the tested N-adamantyl carbothioamides 5c, 6, 8b, 9, 14a and 15c greatly influenced by the nature of the carbothioamide moiety. The piperazine and morpholine carbothioamides 5c and 6 retained good potency, while the corresponding piperidine and tetrahydroisoquinoline analogs 8b, 9, 14a and 15c were almost inactive.

2.4. Oral Acute Toxicity Testing of Compound 5c

The method of Litchfield and Wilcoxon was adopted for measuring the acute oral toxicity of compound 5c which possessed the highest hypoglycemic activity [46]. The oral LD$_{50}$ of compound 5c in normal albino mice was found to be 298 ± 15.50 mg/kg. The oral LD$_{50}$ of gliclazide was reported to be >3000 mg/kg in mice [47]. Although the oral acute toxicity of compound 5c is higher than that of gliclazide, the compound induces its hypoglycemic activity at safe doses.
3. Experimental Section

3.1. General

Melting points (°C) were measured in open glass capillaries using a Branstead 9100 Electrothermal melting point apparatus and are uncorrected. NMR spectra were obtained on a Bruker AC 500 Ultra Shield NMR spectrometer (Fällanden, Switzerland) operating at 500.13 MHz for $^1$H and 125.76 MHz for $^{13}$C, the chemical shifts are expressed in $\delta$ (ppm) downfield from tetramethylsilane (TMS) as internal standard; coupling constants ($J$) are expressed in Hz. Electrospray ionization mass spectra (ESI-MS) were recorded on an Agilent 6410 Triple Quad tandem mass spectrometer at 4.0 and 3.5 kV for positive and negative ions, respectively. Elemental analyses (C, H, N & S) were in agreement with the proposed structures within ±0.4% of the theoretical values. Monitoring the reactions and checking the purity of the final products were carried out by thin layer chromatography (TLC) using silica gel precoated aluminum sheets (60 F254, Merck) and visualization with ultraviolet light (UV) at 365 and 254 nm. The bacterial strains and Candida albicans fungus were obtained from the Institute of Fermentation of Osaka (IFO), Osaka, Japan. The reference drugs Ampicillin trihydrate (CAS 7177-48-2), Gentamicin sulfate (CAS 1405-41-0), Clotrimazole (CAS 23593-75-1) and Gliclazide (CAS 21187-98-4) were purchased from Sigma-Aldrich Chemie GmbH, Taufkirchen, Germany. The Sprague-Dawley rats and the normal albino mice were purchased from local animal house (Abu-Rawash, Giza, Egypt). The animal experiments for the determination of the hypoglycemic activity and acute toxicity were carried out in agreement with the pertinent legal and ethical standards of the international guidelines.

3.2. Synthesis of N-(1-Adamantyl)-4-substituted piperazine-1-carbothioamides 5a–e, N-(1-Adamantyl)morpholine-4-carbothioamide 6, N-(1-Adamantyl)pyrrolidine-1-carbothioamide 7, N-(1-Adamantyl)-4-substituted piperidine-1-carbothioamides 8a–e and N-(1-Adamantyl)-1,2,3,4-tetrahydroisoquinoline-2-carbothioamide 9

A mixture of 1-adamantyl isothiocyanate 4 (387 mg, 2 mmol) and 2.0 mmol of the appropriate cyclic secondary amine (1-substituted piperazines, morpholine, pyrrolidine, piperidine, 4-phenylpiperidine, ethyl isonipecotate or 1,2,3,4-tetrahydroisoquinoline), in ethanol (15 mL), was heated under reflux for 2 h. On cooling, the precipitated crude product were filtered, washed with cold ethanol, dried, and crystallized from ethanol.

5a: $^1$H-NMR (DMSO-$d_6$): $\delta$ 1.0 (t, 3H, CH$_2$CH$_3$, $J$ = 7.0 Hz), 1.62 (s, 6H, Adamantane-H), 1.97–2.03 (m, 3H, Adamantane-H), 2.24 (s, 6H, Adamantane-H), 2.32 (s, 4H, Piperazine-H), 3.34 (q, 2H, CH$_2$CH$_3$, $J$ = 7.0 Hz), 3.68 (s, 4H, Piperazine-H), 4.04 (q, 2H, CH$_2$CH$_3$, $J$ = 7.0 Hz), 6.57 (s, 1H, NH). $^{13}$C-NMR: $\delta$ 11.90 (CH$_3$CH$_2$), 29.06, 39.15, 39.97, 40.90 (Adamantane-C), 47.18 (CH$_2$CH$_3$), 51.35, 52.14 (Piperazine-C), 180.21 (C=S). ESI-MS, m/z: 308.3 (M+H)$^+$.

5b: $^1$H-NMR (DMSO-$d_6$): $\delta$ 1.18 (t, 3H, CH$_2$CH$_3$, $J$ = 7.0 Hz), 1.58–1.62 (m, 6H, Adamantane-H), 1.78 (s, 3H, Adamantane-H), 2.25 (s, 6H, Adamantane-H), 3.34–3.39 (m, 4H, Piperazine-H), 3.73 (s, 4H, Piperazine-H), 4.04 (q, 2H, CH$_2$CH$_3$, $J$ = 7.0 Hz), 6.57 (s, 1H, NH). $^{13}$C-NMR: $\delta$ 14.54 (CH$_3$CH$_2$), 29.09,
36.08, 39.06, 40.06 (Adamantane-C), 46.72, 53.84 (Piperazine-C), 60.69 (CH·CH₃), 154.63 (C=O), 180.53 (C=S). ESI-MS, m/z: 352.4 (M+H)+.

5c: ¹H-NMR (DMSO-d₆): δ 1.63 (s, 6H, Adamantane-H), 1.96–2.05 (s, 3H, Adamantane-H), 2.27 (s, 6H, Adamantane-H), 3.16–3.20 (m, 4H, Piperazine-H), 3.84–3.88 (m, 4H, Piperazine-H), 6.64 (s, 1H, NH), 6.77–6.80 (m, 1H, Ar-H), 6.92–6.94 (m, 2H, Ar-H), 7.21–7.24 (m, 2H, Ar-H). ¹³C-NMR: δ 29.08, 36.08, 46.96 (Adamantane-C), 47.66, 53.80 (Piperazine-C), 115.15, 118.82, 128.95, 150.48 (Ar-C), 180.53 (C=S). ESI-MS, m/z: 356.4 (M+H)+.

5d: ¹H-NMR (CDCl₃): δ 1.58–1.66 (m, 6H, Adamantane-H), 1.90–2.05 (s, 3H, Adamantane-H), 2.24 (s, 6H, Adamantane-H), 2.34 (s, 4H, Piperazine-H), 3.49 (s, 2H, CH₂), 3.70 (s, 4H, Piperazine-H), 6.52 (s, 1H, NH), 7.27–7.34 (m, 5H, Ar-H). ¹³C-NMR: δ 29.06, 36.07, 39.05, 40.91 (Adamantane-C), 47.29, 53.18 (Piperazine-C), 55.44 (OCH₃), 111.38, 118.36, 121.10, 123.51, 140.48, 152.24 (Ar-C), 180.49 (C=S). ESI-MS, m/z: 386.4 (M+H)+.

5e: ¹H-NMR (DMSO-d₆): δ 1.62 (s, 6H, Adamantane-H), 1.97–2.03 (s, 3H, Adamantane-H), 2.24 (s, 6H, Adamantane-H), 2.34 (s, 4H, Piperazine-H), 3.49 (s, 2H, CH₂), 3.70 (s, 4H, Piperazine-H), 6.52 (s, 1H, NH), 7.27–7.34 (m, 5H, Ar-H). ¹³C-NMR: δ 29.06, 36.07, 39.05, 40.91 (Adamantane-C), 47.29, 53.18 (Piperazine-C), 55.44 (OCH₃), 111.38, 118.36, 121.10, 123.51, 140.48, 152.24 (Ar-C), 180.49 (C=S). ESI-MS, m/z: 370.4 (M+H)+.

6: ¹H-NMR (DMSO-d₆): δ 1.63 (s, 6H, Adamantane-H), 1.97–2.05 (s, 3H, Adamantane-H), 2.26 (s, 6H, Adamantane-H), 3.57 (s, 4H, Morpholine-H), 3.67 (s, 4H, Morpholine-H), 6.52 (s, 1H, NH), 7.27–7.34 (m, 5H, Ar-H). ¹³C-NMR: δ 25.52, 54.50 (Pyrrolidine-C), 29.83, 36.37, 41.99, 42.14 (Adamantane-C), 176.68 (C=S). ESI-MS, m/z: 281.3 (M+H)+.

7: ¹H-NMR (CDCl₃): δ 1.68–1.73 (m, 7H, 3 Adamantane-H & 4 Pyrrolidine-H), 1.98–2.02 (m, 3H, Adamantane-H), 2.09–2.12 (s, 3H, Adamantane-H), 2.22–2.23 (m, 6H, Adamantane-H), 3.55–3.57 (m, 4H, Pyrrolidine-H), 4.98 (s, 1H, NH). ¹³C-NMR: δ 25.52, 54.50 (Pyrrolidine-C), 29.83, 36.37, 41.99, 42.14 (Adamantane-C), 176.68 (C=S). ESI-MS, m/z: 265.3 (M+H)+.

8a: ¹H-NMR (CDCl₃): δ 1.52–1.66 (m, 12H, Piperidine & Adamantane-H), 2.04 (s, 3H, Adamantane-H), 2.22–2.23 (m, 6H, Adamantane-H), 3.65 (t, 4H, Piperidine-H, J = 5.5 Hz), 5.14 (s, 1H, NH). ¹³C-NMR: δ 23.83, 25.38, 48.46 (Piperidine-C), 29.65, 36.45, 42.02, 43.77 (Adamantane-C), 179.75 (C=S). ESI-MS, m/z: 279.3 (M+H)+.

8b: ¹H-NMR (CDCl₃): δ 1.57–1.68 (m, 8H, 6 Adamantane-H & 2 Piperidine-H), 1.89–1.90 (m, 1H, Piperidine-H), 2.10 (s, 3H, Adamantane-H), 2.23–2.24 (m, 6H, Adamantane-H), 2.65–2.71 (m, 2H, Piperidine-H), 2.91–2.97 (m, 2H, Piperidine-H), 3.18–3.22 (m, 2H, Piperidine-H), 5.23 (s, 1H, NH), 7.12–7.16 (m, 3H, Ar-H), 7.22–7.25 (m, 2H, Ar-H). ¹³C-NMR: δ 29.23, 42.71, 48.12 (Piperidine-C), 29.78, 32.88, 36.46, 42.0 (Adamantane-C), 126.55, 126.78, 128.49, 145.04 (Ar-C), 179.99 (C=S). ESI-MS, m/z: 355.4 (M+H)+.
8c: $^1$H-NMR (CDCl$_3$): $\delta$ 1.18 (t, 3H, CH$_2$C$_3$, $J = 7.0$ Hz), 1.50–2.21 (m, 4H, Piperidine-H), 1.58–1.62 (m, 6H, Adamantane-H & 2 Piperidine-H), 2.04 (s, 3H, Adamantane-H), 2.25–2.27 (m, 6H, Adamantane-H), 2.47–2.58 (m, 1H, Piperidine-H), 3.0–3.14 (m, 2H, Piperidine-H), 4.06 (q, 2H, CH$_2$CH$_3$, $J = 7.0$ Hz), 5.18 (s, 1H, NH). $^{13}$C-NMR: $\delta$ 14.21 (CH$_2$C$_3$), 29.74, 36.41, 40.60, 41.91 (Adamantane-C), 35.53, 43.76, 46.63 (Piperidine-C), 66.6 (CH$_2$CH$_3$), 174.17 (C=O), 180.14 (C=S).

9: $^1$H-NMR (CDCl$_3$): $\delta$ 1.50–2.21 (m, 8H, 6 Adamantane-H & 2 Piperidine-H), 2.04 (s, 3H, Adamantane-H), 2.25–2.27 (m, 6H, Adamantane-H), 2.47–2.58 (m, 1H, Piperidine-H), 3.0–3.14 (m, 2H, Piperidine-H), 4.06 (q, 2H, CH$_2$CH$_3$, $J = 7.0$ Hz), 5.18 (s, 1H, NH). $^{13}$C-NMR: $\delta$ 14.21 (CH$_2$C$_3$), 29.74, 36.41, 40.60, 41.91 (Adamantane-C), 35.53, 43.76, 46.63 (Piperidine-C), 66.6 (CH$_2$CH$_3$), 174.17 (C=O), 180.14 (C=S).

3.3. Synthesis of N,N'-Bis(1-adamantyl)piperazine-1,4-dicarbothioamide 10a and trans-N,N'-Bis(1-adamantyl)-2,5-dimethylpiperazine-1,4-dicarbothioamide 10b

A mixture of 1-adamantyl isothiocyanate 4 (774 mg, 4 mmol) and anhydrous piperazine or trans-2,5-dimethylpiperazine (2.0 mmol), in ethanol (20 mL), was heated under reflux for 2 h. On cooling, the precipitated crude product were filtered, washed with cold ethanol, dried, and crystallized from DMF.

10a: $^1$H-NMR (CDCl$_3$): $\delta$ 1.25–1.45 (m, 12H, Adamantane-H), 1.49–1.66 (m, 6H, Adamantane-H), 1.87–2.09 (m, 12H, Adamantane-H), 3.08 (s, 8H, Piperazine-H), 9.81 (s, 2H, NH). $^{13}$C-NMR: $\delta$ 27.98, 35.44, 40.08, 41.98 (Adamantane-C), 51.38, 52.08 (Piperazine-C), 179.98 (C=S). ESI-MS, $m/z$: 471.4 (M–H, 100)$^-$. 

10b: $^1$H-NMR (CDCl$_3$): $\delta$ 0.86 (d, 6H, CH$_3$, $J = 5.0$ Hz), 1.08–1.23 (m, 12H, Adamantane-H), 1.46–1.47 (m, 6H, Adamantane-H), 1.86–2.09 (m, 12H, Adamantane-H), 2.25–2.66 (m, 2H, Piperazine-H), 3.43–3.54 (m, 2H, Piperazine-H), 3.70–3.76 (m, 2H, Piperazine-H), 9.83 (s, 2H, NH). $^{13}$C-NMR: $\delta$ 14.15 (CH$_3$), 28.14, 35.41, 41.38, 42.70 (Adamantane-C), 50.32, 57.41 (Piperazine-C), 180.01 (C=S). ESI-MS, $m/z$: 499.5 (M–H, 100)$^-$. 

3.4. Synthesis of 1-(1-Adamantylthiocarbamoyl)piperidine-4-carbohydrazide 11 and 4-(1-Adamantyl)-3-thiosemicarbazide 12

Hydrazine hydrate (98%, 10 mL) was added to a hot solution of compound 8c (3.5 g, 0.01 mol) in ethanol (20 mL) and the mixture was heated under reflux with stirring for 20 min. On cooling, the precipitated crude product was filtered, washed with cold ethanol, dried and crystallized from water to yield 2.42 g (72%) of compound 11. The filtrate was evaporated under reduced pressure and the residue was crystallized from water to yield 0.4 gm (18%) of compound 12.

11: Mp. 216–217 °C. $^1$H-NMR (DMSO-$d_6$): $\delta$ 1.55–1.96 (m, 10H, 6 Adamantane-H & 4 Piperidine-H), 2.06–2.18 (m, 9H, Adamantane-H), 2.32 (m, 1H, Piperidine-H), 2.68–2.92 (m, 4H, Piperidine-H), 5.50 (d, 2H, NH$_2$, $J = 9.5$ Hz), 8.08 (t, 1H, NH, $J = 9.5$ Hz), 8.36 (s, 1H, NH). $^{13}$C-NMR: $\delta$ 28.0, 36.05, 40.75,
44.95 (Adamantane-C), 30.85, 41.35, 48.0 (Piperidine-C), 172.80 (C=O), 181.88 (C=S). ESI-MS, m/z: 337.3 (M+H, 100)⁺.

12: Mp. 195–197 °C. ¹H-NMR (DMSO-d₆): δ 1.64–2.02 (m, 6H, Adamantane-H), 2.12–2.18 (m, 9H, Adamantane-H), 4.50 (d, 2H, NH₂, J = 10.5 Hz), 7.42 (t, 1H, NH, J = 10.5 Hz), 8.36 (s, 1H, NH). ¹³C-NMR: δ 28.99, 35.95, 39.85, 51.91 (Adamantane-C), 179.08 (C=S). ESI-MS, m/z: 226.2 (M+H, 100)⁺.

3.5. Synthesis of N-(1-Adamantyl)piperidine-4-(5-mercapto-4-phenyl-1,2,4-triazol-3-yl)-1-carbothioamide 14a,b

A mixture of 1-(1-adamantylthiocarbamoyl)piperidine-4-carbohydrazide 11 (673 mg, 2 mmol), methyl or phenyl isothiocyanate (2 mmol), in ethanol (10 mL), was heated under reflux for 6 h. The solvent was then distilled off in vacuo to yield the crude products 13a,b which were used in the second step without further purification.

Aqueous sodium hydroxide solution (10%, 10 mL) was added to the crude product 13a or 13b and the mixture was heated under reflux for 2 h, then filtered hot. The filtrate was acidified with 37% HCl to pH 1–2 and the precipitated crude products 14a,b were filtered, washed with water and crystallized.

14a: ¹H-NMR (DMSO-d₆): δ 1.67–1.69 (m, 9H, Adamantane-H), 1.92–2.16 (m, 10H, 6 Adamantane-H & 4 Piperidine-H), 2.22–2.24 (m, 1H, Piperidine-H), 2.62–2.64 (m, 4H, Piperidine-H), 3.42 (s, 3H, CH₃), 8.30 (s, 1H, NH), 9.88 (s, 1H, SH). ¹³C-NMR: δ 22.50 (CH₃), 28.92, 36.08, 39.88, 41.90 (Adamantane-C), 27.80, 35.05, 51.30 (Piperidine-C), 163.52, 179.95 (Triazole C-3 & C-5), 180.23 (C=S). ESI-MS, m/z: 390.4 (M−H, 100)⁻.

14b: ¹H-NMR (DMSO-d₆): δ 1.64–1.65 (m, 9H, Adamantane-H), 2.01–2.06 (m, 6H, Adamantane-H), 2.16–2.22 (m, 5H, Piperidine-H), 2.51–2.52 (m, 4H, Piperidine-H), 7.14–7.51 (m, 5H, Ar-H), 8.32 (s, 1H, NH), 9.63 (s, 1H, SH). ¹³C-NMR: δ 28.94, 35.88, 39.87, 40.03 (Adamantane-C), 28.98, 35.95, 53.31 (Piperidine-C), 124.80, 124.86, 128.18, 139.0 (Ar-C), 161.50, 180.50 (Triazole C-3 & C-5), 181.90 (C=S). ESI-MS, m/z: 452.4 (M−H, 100)⁻.

3.6. Synthesis of 1-[(1-Adamantyl)thiocarbamoyl]-N’-(arylidene)piperidine-4-carbohydrazides 15a–g

A mixture of 1-(1-adamantylthiocarbamoyl)piperidine-4-carbohydrazide 11 (673 mg, 2 mmol), the appropriate aromatic aldehyde (2 mmol), in DMF (6 mL), was heated under reflux for 2 h. On cooling, water (10 mL) was gradually added with stirring and the mixture was allowed to stand for 1 h. The precipitated crude products were filtered, washed with water, dried and crystallized.

15a: ¹H-NMR (DMSO-d₆): δ 1.65–1.67 (m, 9H, Adamantane-H), 1.95–2.40 (m, 15H, 6 Adamantane-H & 9 Piperidine-H), 6.83–6.89 (m, 2H, Ar-H), 7.21–7.23 (m, 1H, Ar-H), 7.47 (s, 1H, NH), 7.68–7.70 (m, 1H, Ar-H), 8.32 (s, 1H, NH), 8.39 (s, 1H, OH), 11.27 (s, 1H, CH=N). ¹³C-NMR: δ 29.01, 35.91, 39.03, 40.98 (Adamantane-C), 30.63, 40.03, 52.92 (Piperidine-C), 116.12, 119.35, 120.29, 125.84, 131.07, 156.51 (Ar-C), 138.50 (CH=N), 162.0 (C=O), 174.54 (C=S). ESI-MS, m/z: 439.4 (M−H, 100)⁻.
3.7. Determination of the in Vitro Antimicrobial Activity (Agar Disc-Diffusion Method)

Sterile filter paper discs (8 mm diameter) were moistened with the compound solution in dimethylsulphoxide of specific concentration (200 μg/disc), the antibacterial antibiotics Gentamicin and Ampicillin trihydrate (100 μg/disc) and the antifungal drug Clotrimazole (100 μg/disc) were carefully
placed on the agar culture plates that had been previously inoculated separately with the microorganisms. The plates were incubated at 37 °C, and the diameter of the growth inhibition zones were measured after 24 h in case of bacteria and 48 h in case of *Candida albicans*.

### 3.8. Determination of the Minimal Inhibitory Concentration (MIC)

Compounds 5c, 5d, 5e, 6, 7, 10a, 10b, 15f and 15g Gentamicin and Ampicillin trihydrate were dissolved in dimethylsulphoxide at concentration of 128 μg/mL. The twofold dilutions of the solution were prepared (128, 64, 32, ..., 0.5 μg/mL). The microorganism suspensions at 106 CFU/mL (colony forming unit/mL) concentrations were inoculated to the corresponding wells. The plates were incubated at 36 °C for 24 h. The MIC values were determined as the lowest concentration that completely inhibited visible growth of the microorganism as detected by unaided eye.

### 3.9. Determination of the in Vivo Hypoglycemic Activity

*Animals*: Locally bred male Sprague-Dawley rats (250 ± 30 g body weight) were obtained from Abu Rawash, Giza, Egypt. The rats were housed in wire-bottomed cages at 22 ± 2 °C. A standard pellet diet and tap water were supplied *ad libitum*. The animals were acclimatized to these conditions for 15 days before the experiment.

*Induction of experimental diabetes*: Rats were fasted for 16 h before the induction of diabetes with STZ (Sigma Chemical Co., St. Louis, MO, USA). The animals were injected intraperitoneally with 0.22–0.25 mL of a freshly prepared solution STZ (60 mg/mL in 0.01 M citrate buffer, pH 4.5) at a final dose of 60 mg/kg body weight. Only rats with serum glucose levels greater than 250 mg/dL were used in experiments.

*Design of the experiment*: Uniform suspensions of the compounds 5c, 6, 8b, 9, 14a and 15b and the oral hypoglycemic drug gliclazide (positive control) in 0.5% (w/v) aqueous carboxymethyl cellulose (CMC) solution were prepared at specific concentration of 10 mg/mL in case of the test compounds and gliclazide. 48 h post STZ injection, the hypoglycemic activity of the compounds 5c, 6, 8b, 9, 14a and 15b was assessed, the diabetic rats were fasted for 16 h and divided into 14 groups each of 5 animals (n = 5) and the serum glucose level was determined for each group and considered as initial fasting serum glucose (C0). Group 1, which served as the negative diabetic control group, received only a single oral dose of 0.5% (w/v) aqueous CMC solution (5 mL/kg). Groups 2 was treated with 10 mg/kg gliclazide in 0.5% (w/v) aqueous CMC (positive control). Groups 3–14 were treated with either a single oral dose of the 10 or 20 mg/kg of the test compounds. All treatments were administered by oral gavage. 24 h after treatment, the blood samples were collected and the serum glucose level (C24) was determined for each group.

*Determination of serum glucose*: Blood samples from the tail vein were collected, allowed to clot, centrifuged at 2000 r.p.m. for 10 min. The serum was separated and used in the same day for the measurement of serum glucose levels using commercial glucose oxidase (GO) assay kit (Sigma-Aldrich Co., St. Louis, MO, USA). Blood glucose levels were expressed in mg/dL as mean ± SEM. The data were statistically analyzed using ANOVA with Tukey’s multiple comparison test. The values of *p* < 0.01 were considered as significant. The percentage of serum glucose reduction for each group was calculated in relation to the initial serum glucose level as follows:
% Serum glucose reduction = \[(C_0 - C_{24}/C_0)\] × 100

where \(C_0\) is the mean initial fasting serum glucose level, \(C_{24}\) is the mean serum glucose level 24 h after treatment.

3.10. Determination of the Oral Acute Toxicity of Compound 5c

Freshly prepared suspensions of compound 5c in concentrations of 1%, 3%, 4%, 6%, 8% and 12% in 0.5% aqueous carboxymethyl cellulose solution were prepared. Each compound was given to six groups each of 6 normal albino mice of both sexes by oral intubation in doses of 250, 500, 750, 1000, 1250 and 1500 mg/kg. The percentage mortality was recorded 24 h after compound administration and the oral lethal dose LD50 was calculated.

4. Conclusions

In this study, series of \(N\)-(1-adamantyl)carbothioamides were synthesized and their \textit{in vitro} antimicrobial activity was determined. Compounds 5c, 5d, 5e, 6, 7, 10a, 10b, 15a, 15f and 15g displayed marked antibacterial activity. In addition, the \textit{in vivo} oral hypoglycemic activity of compounds 5a–e, 6, 7, 8a–c, 10a, 10b, 14a, 14b and 15a–g was determined in streptozotocin (STZ)-induced diabetic rats. Compound 5c produced significant hypoglycemic activity compared gliclazide at a safe dose. The active compounds are considered to be good candidates as newer antibacterial and hypoglycemic agents, further studies such as molecular docking for the exploration of the mechanism of their biological activity are required for optimization of the activity are being undertaken.

Supplementary Materials

Supplementary materials can be accessed at: http://www.mdpi.com/1420-3049/20/05/8125/s1.

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Author Contributions

Ebtehal S. Al-Abdullah and Ali A. El-Emam designed the study; Hanaa M. Al-Tuwaijri, Monirah A. Al-Alshaikh, Ebtehal S. Al-Abdullah and Ali A. El-Emam synthesized the intermediate and target compounds and performed the interpretation of spectral data; Hanan M. Hassan conducted the hypoglycemic activity testing; Elsayed E. Habib performed the antimicrobial testing. All the authors participated in the preparation of the manuscript.

Conflicts of Interest

The authors declare no conflicts of interest in this study.
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Sample Availability: Samples of the all compounds are available from the correspondent author.

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