Adamantane-Isothiourea Hybrid Derivatives: Synthesis, Characterization, In Vitro Antimicrobial, and In Vivo Hypoglycemic Activities

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Academic Editor: Diego Muñoz-Torrero
Received: 14 April 2017; Accepted: 27 April 2017; Published: 29 April 2017

Abstract: A new series of adamantane-isothiourea hybrid derivatives, namely 4-arylmethyl (Z)-N′-(adamantan-1-yl)-morpholine-4-carbothioimidates 7a–e and 4-arylmethyl (Z)-N′-(adamantan-1-yl)-4-phenylpiperazine-1-carbothioimidates 8a–e were prepared via the reaction of N-(adamantan-1-yl)morpholine-4-carbothioamide 5 and N-(adamantan-1-yl)-4-phenylpiperazine-1-carbothioamide 6 with benzyl or substituted benzyl bromides, in acetone, in the presence of anhydrous potassium carbonate. The structures of the synthesized compounds were confirmed by 1H-NMR, 13C-NMR, electrospray ionization mass spectral (ESI-MS) data, and X-ray crystallographic data. The in vitro antimicrobial activity of the new compounds was determined against certain standard strains of pathogenic bacteria and the yeast-like pathogenic fungus Candida albicans. Compounds 7b, 7d and 7e displayed potent broad-spectrum antibacterial activity, while compounds 7a, 7c, 8b, 8d and 8e were active against the tested Gram-positive bacteria. The in vivo oral hypoglycemic activity of the new compounds was carried on streptozotocin (STZ)-induced diabetic rats. Compounds 7a, 8ab, and 8b produced potent dose-independent reduction of serum glucose levels, compared to the potent hypoglycemic drug gliclazide.

Keywords: synthesis; adamantane; isothiourea; carbothioimidate; antimicrobial activity; hypoglycaemic activity

1. Introduction

The adamantane nucleus was recognized early as an essential pharmacophore in various pharmacologically-active drugs. The incorporation of an adamantyl moiety into various bioactive molecules results in compounds with relatively high lipophilicity which, in turn, modifies the bioavailability and modulates their therapeutic efficacies [1,2]. Amantadine, the first adamantane-based drug, was approved for the treatment of Influenza A infection [3–5] and as an anti-Parkinsonian drug [6]. Further studies based on amantadine resulted in the development of the potent antiviral drugs rimantadine [7] and tromantadine [8]. Numerous adamantane-based analogues were proved to possess significant inhibitory activity against human immunodeficiency viruses (HIV) [9–12]. The synthetic retinoid derivative CD437 was developed as a potent inducer of apoptosis in human head and neck squamous cell carcinoma [13]. Potent bactericidal and fungicidal activities were reported for several
adamantane derivatives, including SQ109, which was approved for use against drug-susceptible and drug-resistant TB strains [14]. SQ109 also showed excellent inhibitory activity against Helicobacter pylori-related duodenal ulcers and carcinomas, and Candida glabrata [15]. The adamantane-based drugs, vildagliptin [16], and saxagliptin [17] are currently used as oral hypoglycemic agents for the treatment of type 2 diabetes acting via inhibition of dipeptidyl peptidase IV (DPP-IV). Moreover, the adamantane derivatives MK-544 [18], PF-877423 [19], and AZD6925 [20] were recently developed as 11β-hydroxysteroid dehydrogenase type 1 (11β-HSD1) inhibitors as drug candidates for the treatment of non-insulin-dependent diabetes and obesity [21] (Figure 1).

![Figure 1. Biologically-active adamantane-based derivatives.](image)

On the other hand, several compounds containing an isothiourea moiety were reported to possess significant antiviral [22], histamine-H3 antagonistic [23,24], calcium channel antagonistic [25], anticancer [26], antibacterial [27], and nitric oxide synthase inhibitory [28,29] activities.

In view of the diverse pharmacological properties of adamantane and isothiourea derivatives, and following our previous studies on the chemical and biological properties of adamantane derivatives [10,30–33], we report herein the synthesis and characterization of novel adamantane derivatives containing an isothiourea moiety as potential antimicrobial and/or hypoglycemic agents.

2. Results and Discussion

2.1. Chemical Synthesis

The key starting material 1-adamantyl isothiocyanate 4 was prepared in good yield via our previously described methods [33]. The reaction of 1-adamantylamine 1 with carbon disulphide and trimethylamine, in ethanol, yielded the dithiocarbamate salt 2, which was reacted with di-tert-butyl dicarbonate (Boc₂O) to yield the intermediate 3. The intermediate 3 was stirred with catalytic amount of 4-dimethylaminopyridine (DMAP) to furnish the target product 4. The reaction of 1-adamantyl isothiocyanate 4 with morpholine and 1-phenylpiperazine, in boiling ethanol, yielded the corresponding N-(adamantan-1-yl)morpholine-4-carbothioamide 5 and N-(adamantan-1-yl)-4-phenylpiperazine-1-carbothioamide 6, respectively [33]. The carbothioamides 5 and 6 were reacted with benzyl or substituted benzyl bromides, in acetone, in the presence of anhydrous potassium carbonate to yield the corresponding S-arylmethyl derivatives 7a–e and 8a–e, respectively, in good yields (Scheme 1, Table 1). The structures of the target compounds 7a–e and 8a–e were confirmed by
elemental analyses (Table S1), in addition to the $^1$H-NMR and $^{13}$C-NMR, and electrospray ionization mass spectral (ESI-MS) data, which were in full agreement with their structures. The ESI-MS data showed the correct positive ions (M + H)$^+$ ions for all compounds. In addition, compounds 7d and 8d were subjected to single crystal X-ray studies.

![Scheme 1. Synthetic approach for the target compounds 7a–e and 8a–e.](image)

### Table 1. Crystallization solvents, melting points, yield percentages, molecular formulae, and molecular weights of compounds 7a–e and 8a–e.

| Comp. No. | R  | Cryst. Solv. | M.p. (°C) | Yield (%) | Mol. Formula (Mol. Wt.) |
|-----------|----|-------------|-----------|-----------|-------------------------|
| 7a        | H  | EtOH/H2O    | 108–110   | 91        | C$_{22}$H$_{29}$N$_3$O$_3$S (370.35) |
| 7b        | 4-Cl | EtOH      | 92–94    | 76        | C$_{22}$H$_{28}$BrN$_3$S (480.11) |
| 7c        | 4-Br | EtOH       | 98–100   | 85        | C$_{22}$H$_{29}$BrN$_3$S (490.45) |
| 7d        | 4-NO$_2$ | EtOH | 118–120  | 95        | C$_{22}$H$_{28}$N$_6$O$_2$S (415.55) |
| 7e        | 3,5-(CF$_3$)$_2$ | EtOH/H$_2$O | 106–108  | 72        | C$_{28}$H$_{35}$N$_3$S (506.55) |
| 8a        | H  | EtOH/H$_2$O | 137–139  | 88        | C$_{28}$H$_{34}$N$_4$O$_2$S (445.66) |
| 8b        | 4-Cl | EtOH       | 153–155  | 90        | C$_{28}$H$_{33}$ClN$_3$S (480.11) |
| 8c        | 4-Br | EtOH       | 140–142  | 92        | C$_{28}$H$_{33}$BrN$_3$S (524.56) |
| 8d        | 4-NO$_2$ | EtOH | 145–147  | 96        | C$_{28}$H$_{34}$N$_6$O$_2$S (506.66) |
| 8e        | 3,5-(CF$_3$)$_2$ | EtOH/H$_2$O | 113–115  | 75        | C$_{28}$H$_{34}$F$_3$N$_5$S (581.66) |

2.2. Crystallographic Studies

The single crystal X-ray crystallographic data of compounds 7d and 8d are summarized in Table 2. Compound 7b crystallizes in the centrosymmetric monoclinic space group $P2_1/c$ with one molecule in the asymmetric unit ($Z = 4$). The ORTEP (Oak Ridge Thermal Ellipsoid Plot) is shown in Figure 2. The morpholine ring adopts a chair conformation and the mean planes of the nitrophenyl and morpholine rings make a dihedral angle of 52.55 (5). The conformation about the N1=C11 imine bond is Z (cis) configuration. The crystal packing is mainly controlled by intermolecular C-H . . . O hydrogen bonding (Figure 3).

### Table 2. Single-crystal X-ray crystallographic data of compounds 7d and 8d.

| Data             | Compound 7d                     | Compound 8d                     |
|------------------|--------------------------------|--------------------------------|
| Formula          | C$_{28}$H$_{33}$N$_4$O$_2$S     | C$_{28}$H$_{33}$N$_4$O$_2$S     |
| Formula weight   | 415.55                         | 490.66                         |
| Temperature (K)  | 293                            | 293                            |
| Wavelength (Å)   | 0.71073                        | 0.71073                        |
| Crystal system   | Monoclinic                     | Orthorhombi                    |
Table 2. Cont.

| Data                        | Compound 7d          | Compound 8d          |
|-----------------------------|----------------------|----------------------|
| Space group                 | $P2_1/c$             | $P2_12_12_1$         |
| $a$, $b$, $c$ (Å)           | 6.9204 (5), 29.775 (3), 10.2725 (10) | 6.9426 (9), 9.6472 (12), 39.086 (5) |
| V (Å$^3$)                   | 2116.7 (3)           | 2617.8 (6)           |
| Z                           | 4                    | 4                    |
| Radiation type              | Mo Kα                | Mo Kα                |
| $\mu$ (mm$^{-1}$)           | 0.18                 | 0.16                 |
| No. of reflections          | 11033                | 25091                |
| No. of unique reflections/obs. reflections | 3718/2253            | 4609/1447            |
| No. of parameters           | 262                  | 318                  |
| No. of restraints           | 0                    | 0                    |
| $\Delta \rho_{\text{max}}, \Delta \rho_{\text{min}}$ (e Å$^{-3}$) | 0.28, −0.21          | 0.44, −0.40          |
| $T_{\text{min}}, T_{\text{max}}$ | 0.939, 0.989         | 0.924, 0.957         |
| $R_{\text{int}}$           | 0.073                | 0.526                |
| Crystal size (mm)           | 0.35 × 0.11 × 0.06   | 0.85 × 0.21 × 0.05   |
| $R[F^2 > 2\sigma(F^2)], wR(F^2), S$ | 0.052, 0.192, 0.65 | 0.128, 0.296, 1.02  |
| CCDC number                 | 1525183              | 1523432              |

Figure 2. ORTEP diagram of compound 7d drawn at 40% ellipsoids for non-hydrogen atoms.

Figure 3. Molecular packing of compound 7d viewed hydrogen bonds, which are drawn as dashed lines.
Compound 8b crystallizes in the orthorhombic space group \(P2_12_12_1\) with one molecule in the asymmetric unit \((Z = 4)\). The ORTEP is shown Figure 4. The piperazine ring also adopts a chair conformation with a dihedral angle of 39.25 (4). The conformation about the N1A=C11A imine bond is \(Z\) (cis) configuration. The crystal packing is mainly controlled by intermolecular C-H…S hydrogen bonding (Figure 5).

![Molecular packing of compound 8d](image)

**Figure 4.** ORTEP diagram of compound 8d drawn at 40% ellipsoids for non-hydrogen atoms.

![Molecular packing of compound 8d](image)

**Figure 5.** Molecular packing of compound 8d viewed hydrogen bonds, which are drawn as dashed lines.

### 2.3. In Vitro Antimicrobial Activity

The newly synthesized compounds 7a–e and 8a–e were tested for their in vitro growth inhibitory activity against the standard bacterial strains of the American type culture collection ATCC, *Staphylococcus aureus* ATCC 6571, *Bacillus subtilis* ATCC 5256, *Micrococcus luteus* ATCC 27141 (Gram-positive bacteria), *Escherichia coli* ATCC 8726, *Pseudomonas aeruginosa* ATCC 27853 (Gram-negative bacteia), and the yeast-like pathogenic fungus *Candida albicans* MTCC 227. The preliminary antimicrobial activity testing was carried out using the semi-quantitative agar-disc diffusion method with Müller-Hinton agar medium [34]. The outcomes of the preliminary antimicrobial screening of compounds 7a–e, 8a–e (200 \(\mu\)g/disc), the antibacterial antibiotics gentamicin sulphate, ampicillin trihydrate and the antifungal drug clotrimazole (100 \(\mu\)g/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 shown in Table 3.
The main features of the results of the antimicrobial activity testing revealed that the tested compounds generally displayed marked antibacterial and marginal antifungal activities against the tested microorganisms, the antibacterial activity against the Gram-positive bacteria was higher than the activity against the Gram-negative bacteria, and the compound lipophilicity had no influence on their activity. In addition, the Gram-positive bacteria *S. aureus* and *B. subtilis* are more sensitive than *M. luteus*, and the Gram-negative bacteria *P. aeruginosa* was more resistant than *E. coli*. Potent antibacterial activity was shown by compounds 7a–e, 8d and 8e which produced growth inhibition zones ≥ 20 mm against one or more of the tested microorganisms. In the morpholine derivatives 7a–e, compounds 7b, 7d and 7e retained good broad spectrum antibacterial activity; while compound 7a displayed good activity against the Gram-positive bacteria and medium activity against *E. coli* (inhibition zones 15–19 mm). The optimum activity was achieved by 7e which was highly active against all the tested bacterial strains. In the piperazine derivatives 8a–c, compounds 8b, 8d and 8e showed high activity against the tested Gram-positive bacteria, while compounds 8a and 8c showed medium activity against the tested Gram-positive bacteria and weak activity (growth inhibition zones 10–14 mm) against the tested Gram-negative bacteria. The activity against yeast-like pathogenic fungus *C. albicans* of the tested compounds was rather lower than that against the tested bacterial strains. Compound 8d showed medium inhibitory activity, compounds 7b, 7d, 8a, 8b, 8c and 8e showed weak activity and compounds 7a, 7c and 7e were practically inactive (growth inhibition zones < 10 mm).

Table 3. Antimicrobial activity of compounds 7a–e and 8a–e (200 μg/8 mm disc), the broad-spectrum antibacterial drugs gentamicin sulphate, ampicillin trihydrate and the antifungal drug clotrimazole (100 μg/8 mm disc) against *Staphylococcus aureus* ATCC 6571 (SA), *Bacillus subtilis* ATCC 5256 (BS), *Micrococcus luteus* ATCC 27141 (ML), *Escherichia coli* ATCC 8726 (EC), *Pseudomonas aeruginosa* ATCC 27853 (PA) and the yeast-like pathogenic fungus *Candida albicans* MTCC 227 (CA).

| Comp. No. | Clog P | Diameter of Growth Inhibition Zone (mm) | SA | BS | ML | EC | PA | CA |
|-----------|--------|----------------------------------------|----|----|----|----|----|----|
| 7a        | 5.584  | 22 (b)                                 | 21 (4) | 20 (4) | 18 (16) | 14 (64) | - |
| 7b        | 6.297  | 24 (4)                                 | 28 (0.5) | 22 (4) | 22 (20) | 15 (32) | 11 (>128) |
| 7c        | 6.447  | 22 (4)                                 | 18 (16) | 14 (64) | 13 (128) | 12 (128) | - |
| 7d        | 5.327  | 31 (0.5)                               | 32 (0.25) | 28 (0.5) | 22 (1) | 18 (4) | 14 (32) |
| 7e        | 7.350  | 33 (0.25)                              | 34 (0.25) | 28 (1) | 24 (2) | 20 (4) | - |
| 8a        | 7.130  | 18 (8)                                 | 18 (8) | 14 (128) | 12 (<128) | 10 (>128) | 10 (>128) |
| 8b        | 7.843  | 21 (8)                                 | 24 (2) | 16 (32) | 16 (64) | 12 (>128) | 13 (64) |
| 8c        | 7.993  | 17 (32)                                | 19 (8) | 14 (64) | 11 (>128) | 10 (>128) | 12 (128) |
| 8d        | 6.873  | 24 (1)                                 | 28 (1) | 20 (2) | 18 (2) | 14 (4) | 16 (16) |
| 8e        | 8.896  | 28 (1)                                 | 31 (0.5) | 22 (2) | 19 (4) | 18 (8) | 14 (64) |
| Gentamicin sulfate | 27 (1) | 26 (2)                                 | 20 (2) | 22 (0.5) | 21 (0.5) | NT |
| Ampicillin trihydrate | 22 (2) | 23 (1)                                 | 20 (2) | 16 (8) | 16 (8) | NT |
| Clotrimazole | NT      | NT                                     | NT | NT | NT | 21 (4) |

(a): inactive (inhibition zone < 10 mm), b Figures shown in parentheses represent the MIC values (μg/mL), NT: not tested.

From the above results, it could be concluded that the antibacterial activity of the morpholine derivatives 7a–e is generally superior to their *N*-phenylpiperazine analogues. In addition, the presence of the electron-withdrawing substituents NO2 and CF3 (compounds 7d, 7e, 8d and 8e) greatly enhanced the antibacterial activity. Unlike the antibacterial activity, the *N*-phenylpiperazine analogues 8a–e were generally more active than the morpholine analogues 7a–e against *C. albicans*. The values of the minimal inhibitory concentration (MIC) in Müller-Hinton Broth [35] for the tested compounds (Table 3) were correlated to the results obtained in the preliminary screening.

2.4. In Vivo Hypoglycemic Activity

The oral hypoglycaemic activity of compounds 7a–c and 8a–c was determined in streptozotocin (STZ)-induced diabetic rats. STZ induces its hyperglycemic activity via irreversible damage to the
pancreatic beta cells, resulting in loss of insulin secretion [36,37]. The compounds were tried in 10 and 20 mg/kg dose levels. The dose levels (10 and 20 mg/kg) were determined after pilot experiments which showed that increasing the dose to 30 mg/kg was found to produce toxic central nervous manifestations in the form of severe symmetric convulsions. The hypoglycemic activity testing experiment (animal treatments, induction of experimental diabetes, and measurement of serum glucose level) was carried out following the previously reported protocols [32,33]. The results of the oral hypoglycemic activity of compounds 7a–c, 8a–c (10 and 20 mg/kg), and the potent hypoglycemic drug gliclazide in STZ-induced diabetic rats (10 mg/kg) are shown in Table 4.

The optimum hypoglycemic activity was attained by compounds 7a, 8a, and 8b which produced potent dose-independent reduction of serum glucose levels, compared to gliclazide at 10 mg/kg dose level (Potency ratio 71.08, 75.13 and 79.04%, respectively). Compound 7b showed medium dose-dependent hypoglycemic activity and compound 8c showed weak activity at 10 mg/kg dose level without significant increase in the activity at 20 mg/kg dose level. Despite the high activity of the bis(3,5-trifluormethyl) derivative 7e (Potency ratio 82.32%), increasing the dose produced toxic central nervous manifestations. Similarly, compound 8e showed toxic manifestations at 10 and 20 mg/kg doses.

The hypoglycemic activity of the tested compounds revealed that the piperazine derivatives 8a–e are generally more active than their morpholine analogues 7a–e. In addition, the aryl substituents greatly influenced the hypoglycemic activity and toxicity. The optimum activity was attained by the phenyl derivatives (7a, 8a) and to a lesser extent the chlorophenyl derivatives (7b, 8b). The bis(3,5-trifluormethyl) derivatives were generally toxic.

Table 4. Oral hypoglycemic activity of compounds 7a–c, 8a–c (10 and 20 mg/kg), and gliclazide (10 mg/kg) in STZ-induced diabetic rats.

| Treatment | C0 (mg/dL) a | C24 (mg/dL) a | % Glucose Reduction b |
|-----------|--------------|--------------|-----------------------|
| Group 1 c | 302.8 ± 11.64| 290.2 ± 18.22| 4.16%                 |
| Group 1 d | 299.2 ± 16.50| 171.6 ± 12.32| 42.65%                |
| 7a (10 mg/kg) | 304.8 ± 13.26| 212.4 ± 12.16*| 30.31% (71.08)        |
| 7a (20 mg/kg) | 300.6 ± 11.65| 134.6 ± 9.75*| 55.22% (64.74)        |
| 7b (10 mg/kg) | 288.9 ± 12.15| 245.2 ± 19.25*| 15.13% (35.47)        |
| 7b (20 mg/kg) | 294.8 ± 9.08| 201.5 ± 9.60*| 31.65% (37.13)        |
| 7c (10 mg/kg) | 284.8 ± 19.55| 281.2 ± 7.19 | 1.26% (2.69)          |
| 7c (20 mg/kg) | 280.6 ± 21.64| 286.8 ± 19.02| 2.75% (1.37)          |
| 7d (10 mg/kg) | 278.1 ± 16.24| 282.2 ± 27.20| −1.47%                |
| 7d (20 mg/kg) | 302.6 ± 22.25| 299.8 ± 18.80| 0.93% (1.08)          |
| 7e (10 mg/kg) | 306.2 ± 15.20| 198.7 ± 19.10*| 35.12% (82.32)        |
| 7e (20 mg/kg) |                | Toxic        |                       |
| 8a (10 mg/kg) | 294.6 ± 11.30| 200.2 ± 9.88*| 32.04% (75.13)        |
| 8a (20 mg/kg) | 290.6 ± 8.60| 108.4 ± 11.05*| 62.70% (73.30)        |
| 8b (10 mg/kg) | 301.4 ± 9.06| 199.8 ± 10.01*| 33.71% (79.04)        |
| 8b (20 mg/kg) | 296.0 ± 11.02| 144.6 ± 10.01*| 51.15% (59.96)        |
| 8c (10 mg/kg) | 320.5 ± 22.05| 277.6 ± 16.20| 13.39% (31.38)        |
| 8c (20 mg/kg) | 313.5 ± 18.60| 269.9 ± 20.12| 13.91% (16.30)        |
| 8d (10 mg/kg) | 295.0 ± 22.45| 289.2 ± 25.28| 1.97% (4.61)          |
| 8d (20 mg/kg) | 304.5 ± 27.50| 309.0 ± 25.95| −1.48                 |
| 8e (10 mg/kg) | 286.6 ± 13.22| 178.2 ± 16.04*| 37.82% (88.68)        |
| 8e (20 mg/kg) |                | Toxic        |                       |

a 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.
3. Materials and Methods

3.1. General

Melting points (°C, uncorrected) were measured in open glass capillaries using a Branstead 9100 electrothermal melting point apparatus (Thermo Fisher Scientific, Waltham, MA, USA). Nuclear magnetic resonance (NMR) spectra were obtained on a Bruker Ascend 700 NMR spectrometer (Fällanden, Switzerland) at 700.17 MHz for $^1$H and 176.08 MHz for $^{13}$C, using CDCl$_3$ as the solvent. The chemical shifts are expressed in δ (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 (Agilent Technologies, Santa Clara, CA, USA) at 4.0 kV for positive ions. Elemental analyses (C, H, N, and S) were in agreement with the proposed structures within ±0.4% of the theoretical values (Table S1). 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 F$_{254}$; Merck Schuchardt, Darmstadt, Germany), and visualization with ultraviolet light (UV) at 365 and 254 nm. The reference drugs gentamicin sulfate (CAS 1405-41-0), ampicillin trihydrate (CAS 7177-48-2), clotrimazole (CAS 23593-75-1) and gliclazide (CAS 21187-98-4), and streptozotocin (CAS 18883-66-4) were purchased from Sigma-Aldrich Chemie GmbH, Taufkirchen, Germany. The Sprague-Dawley rats were purchased from local animal house. The commercial glucose oxidase (GO) assay kit (Sigma-Aldrich Co., St. Louis, MO, USA) were used for measurement of serum glucose levels. The animal experiments for the determination of the hypoglycemic activity were performed in accordance with the guidelines provided by the Experimental Animal Laboratory (EAL) and approved by the Animal Care and Use Committee (ACUC) of the College of Pharmacy, King Saud University (Saudi Arabia). The X-ray crystallographic data of compound 8c was recently described [38].

3.2. Synthesis of 4-Arylmethyl (Z)-N’-(Adamantan-1-yl)-Morpholine-4-Carbothioimidates 7a–e and 4-Arylmethyl (Z)-N’-(Adamantan-1-yl)-4-Phenylpiperazine-1-Carbothioimidates 8a–e

The appropriate arylmethyl bromide (2 mmol) and anhydrous potassium carbonate (276 mg, 2 mmol) were added to a solution of N-(adamantan-1-yl)morpholine-4-carbothioamide 5 (560 mg, 2 mmol) or N-(adamantan-1-yl)-4-phenylpiperazine-1-carbothioamide 6 (711 mg, 2 mmol), in anhydrous acetone (15 mL), and the mixture was heated under reflux for 4 h. The solvent was then distilled off in vacuo and the resulting residues were washed with water (20 mL), dried, and crystallized from ethanol or aqueous ethanol.

**Benzyl (Z)-N’-(adamantan-1-yl)-morpholine-4-carbothioimidate 7a:** $^1$H-NMR: δ 1.61–1.66 (m, 6H, adamantane-H), 1.85 (m, 6H, adamantane-H), 2.0 (s, 3H, adamantane-H), 3.20–3.21 (m, 4H, morpholine-H), 3.65–3.72 (m, 4H, morpholine-H), 3.90 (s, 2H, benzylic CH$_2$), 7.07–7.19 (m, 5H, Ar-H). $^{13}$C-NMR: δ 29.02, 29.80, 35.96, 54.18 (adamantane-C), 37.06 (benzylic CH$_2$), 49.66, 66.42 (morpholine-C), 125.60, 126.44, 127.90, 140.02 (Ar-C), 154.46 (C=N). ESI-MS, m/z: 372.3 (M + H)$^+$.

**4-Chlorobenzyl (Z)-N’-(adamantan-1-yl)-morpholine-4-carbothioimidate 7b:** $^1$H-NMR: δ 1.62–1.65 (m, 6H, adamantane-H), 1.84 (m, 6H, adamantane-H), 2.0 (s, 3H, adamantane-H), 3.20–3.22 (m, 4H, morpholine-H), 3.65–3.72 (m, 4H, morpholine-H), 6.99 (d, 2H, Ar-H, $J$ = 7.5 Hz), 7.14 (d, 2H, Ar-H, $J$ = 7.5 Hz). $^{13}$C-NMR: δ 29.26, 29.80, 35.96, 54.18 (adamantane-C), 37.06 (benzylic CH$_2$), 49.66, 66.42 (morpholine-C), 127.65, 128.65, 133.0, 138.04 (Ar-C), 154.24 (C=N). ESI-MS, m/z: 393.4 (M + H)$^+$, 405.4 (M + 2 + H)$^+$.

**4-Bromobenzyl (Z)-N’-(adamantan-1-yl)-morpholine-4-carbothioimidate 7c:** $^1$H-NMR: δ 1.63–1.69 (m, 6H, adamantane-H), 1.84 (m, 6H, adamantane-H), 2.01 (s, 3H, adamantane-H), 3.25–3.30 (m, 4H, morpholine-H), 3.69–3.74 (m, 4H, morpholine-H), 3.91 (s, 2H, benzylic CH$_2$), 7.17 (d, 2H, Ar-H, $J$ = 7.5 Hz), 7.45 (d, 2H, Ar-H, $J$ = 7.5 Hz). $^{13}$C-NMR: δ 29.59, 29.94, 36.57, 54.69 (adamantane-C), 37.76
(benzylic CH₂), 49.70, 66.85 (morpholine-C), 121.0, 130.51, 137.26, 146.91 (Ar-C), 156.46 (C=N). ESI-MS, m/z (Rel. Int.): 449.4 (M + 2 + H, 100)*, 451.4 (M + 2 + H, 98)*.

4-Nitrobenzyl (Z)-N′-(adamantan-1-yl)-morpholine-4-carbothioimidate 7d: ¹H-NMR: δ 1.62 (s, 6H, adamantane-H), 1.77–1.79 (m, 6H, adamantane-H), 1.98–2.0 (m, 3H, adamantane-H), 3.24–3.30 (m, 4H, morpholine-H), 3.69–3.72 (m, 4H, morpholine-H), 4.02 (s, 2H, benzylic CH₂), 7.42 (d, 2H, Ar-H, J = 8.2 Hz), 8.21 (d, 2H, Ar-H, J = 8.2 Hz). ¹³C-NMR: δ 29.58, 29.84, 36.44, 54.79 (adamantane-C), 37.53 (benzylic CH₂), 49.79, 66.78 (morpholine-C), 123.76, 129.64, 146.07, 146.91 (Ar-C), 156.71 (C=N). ESI-MS, m/z: 416.2 (M + H)⁺.

3,5-Bis(trifluoromethyl)benzyl (Z)-N′-(adamantan-1-yl)-morpholine-4-carbothioimidate 7e: ¹H-NMR: δ 1.53–1.56 (m, 12H, adamantane-H), 1.85–1.87 (m, 3H, adamantane-H), 3.10–3.12 (m, 4H, piperazine-H), 3.30–3.33 (m, 4H, piperazine-H), 3.97 (s, 2H, benzylic CH₂), 7.12–7.16 (m, 5H, Ar-H). ¹³C-NMR: δ 29.16, 29.66, 35.25, 54.85 (adamantane-C), 36.41 (benzylic CH₂), 49.76, 66.20 (morpholine-C), 120.76, 122.72, 130.39, 142.78 (Ar-C), 124.89 (CF₃), 148.37 (C=N). ESI-MS, m/z: 507.2 (M + H)⁺.

Benzyl (Z)-N′-(adamantan-1-yl)-4-phenylpiperazine-1-carbothioimidate 8a: ¹H-NMR: δ 1.69 (s, 6H, adamantane-H), 1.74 (s, 6H, adamantane-H), 2.0 (s, 3H, adamantane-H), 2.88–2.92 (m, 4H, piperazine-H), 3.02–3.06 (m, 4H, piperazine-H), 3.98 (s, 2H, benzylic CH₂), 6.84–7.04 (m, 5H, Ar-H), 7.12–7.16 (m, 5H, Ar-H). ¹³C-NMR: δ 29.10, 29.96, 35.68, 53.98 (adamantane-C), 46.90, 48.18 (piperazine-C), 36.90 (benzylic CH₂), 114.28, 119.90, 126.92, 128.24, 129.0, 130.58, 139.94, 149.26 (Ar-C), 152.0 (C=N). ESI-MS, m/z: 446.3 (M + H)⁺.

4-Chlorobenzyl (Z)-N′-(adamantan-1-yl)-4-phenylpiperazine-1-carbothioimidate 8b: ¹H-NMR: δ 1.71–1.76 (m, 12H, adamantane-H), 2.15–2.17 (m, 3H, adamantane-H), 2.63–2.65 (m, 4H, piperazine-H), 3.22–3.24 (m, 4H, piperazine-H), 3.98 (s, 2H, benzylic CH₂), 6.89–6.91 (m, 3H, Ar-H), 6.95–6.96 (m, 2H, Ar-H), 7.29–7.33 (m, 4H, Ar-H). ¹³C-NMR: δ 29.17, 29.71, 35.51, 53.07 (adamantane-C), 48.65, 48.10 (piperazine-C), 36.39 (benzylic CH₂), 115.55, 116.13, 119.89, 128.49, 129.16, 129.45, 130.57, 150.31 (Ar-C), 151.27 (C=N). ESI-MS, m/z: 380.2 (M + H, 100)*, 382.2 (M + 2 + H, 37)*.

4-Bromobenzyl (Z)-N′-(adamantan-1-yl)-4-phenylpiperazine-1-carbothioimidate 8c: ¹H-NMR: δ 1.65 (s, 6H, adamantane-H), 1.86 (s, 6H, adamantane-H), 2.02–2.03 (m, 3H, adamantane-H), 2.36–2.37 (m, 4H, piperazine-H), 3.43–3.44 (m, 4H, piperazine-H), 3.95 (s, 2H, benzylic CH₂), 6.92–7.93 (m, 1H, Ar-H), 7.00–7.01 (m, 2H, Ar-H), 7.18 (d, 2H, Ar-H, J = 7.0 Hz), 7.29–7.33 (m, 2H, Ar-H), 7.44 (d, 2H, Ar-H, J = 7.0 Hz). ¹³C-NMR: δ 29.95, 36.58, 42.98, 54.70 (adamantane-C), 48.96, 49.17 (piperazine-C), 37.77 (benzylic CH₂), 116.20, 119.97, 120.94, 129.22, 130.59, 131.54, 137.33, 149.26 (Ar-C), 151.29 (C=N). ESI-MS, m/z (Rel. Int.): 524.4 (M + H, 98)*, 526.4 (M + 2 + H, 100)* [38].

4-Nitrobenzyl (Z)-N′-(adamantan-1-yl)-4-phenylpiperazine-1-carbothioimidate 8d: ¹H-NMR: δ 1.53 (s, 6H, adamantane-H), 1.72 (s, 6H, adamantane-H), 1.91 (s, 3H, adamantane-H), 3.16–3.18 (m, 4H, piperazine-H), 3.30–3.33 (m, 4H, piperazine-H), 3.97 (s, 2H, benzylic CH₂), 6.80–6.89 (m, 3H, Ar-H), 7.18–7.29 (m, 2H, Ar-H), 7.36 (d, 2H, Ar-H, J = 8.0 Hz), 8.08 (d, 2H, Ar-H, J = 8.0 Hz). ¹³C-NMR: δ 29.65, 29.90, 36.52, 54.86 (adamantane-C), 37.54 (benzylic CH₂), 43.03, 49.12 (piperazine-C), 116.21, 120.05, 123.72, 129.21, 129.66, 146.14, 146.94, 148.09 (Ar-C), 151.22 (C=N). ESI-MS, m/z: 491.2 (M + H)⁺.

3,5-Bis(trifluoromethyl)benzyl (Z)-N′-(adamantan-1-yl)-4-phenylpiperazine-1-carbothioimidate 8e: ¹H-NMR: δ 1.58 (s, 6H, adamantane-H), 1.69 (s, 6H, adamantane-H), 1.95–1.97 (m, 3H, adamantane-H), 3.29–3.31 (m, 4H, piperazine-H), 3.40–3.42 (m, 4H, piperazine-H), 4.04 (s, 2H, benzylic CH₂), 6.93–7.02 (m, 3H, Ar-H), 7.29 (s, 1H, Ar-H), 7.32–7.34 (m, 2H, Ar-H), 7.78 (s, 2H, Ar-H). ¹³C-NMR: δ 29.80, 35.51, 36.44, 54.80 (adamantane-C), 37.31 (benzylic CH₂), 49.0, 49.13 (piperazine-C), 116.28, 120.12, 129.16, 129.24, 131.44, 131.63, 141.30, 147.50 (Ar-C), 124.04 (CF₃), 151.19 (C=N). ESI-MS, m/z: 582.2 (M + H)⁺.
3.3. Crystal Growth and Single Crystal X-ray Study

Single crystals suitable for X-ray analysis were obtained by slow evaporation of CHCl₃:EtOH (1:1; 5 mL) solution of compounds 7d and 8d at room temperature. Data were collected on a Bruker APEX-II D8 Venture area diffractometer, equipped with graphite monochromatic Mo Kα radiation (λ = 0.71073 Å) at 100 K. Unit cell measurement, data collection, integration, scaling, and absorption corrections for the crystals were conducted using Bruker Apex II software [39]. Data reduction was done by Bruker SAINT suite [40]. The crystal structures were solved by the full matrix least squares method using SHELXL 2014 [41]. Absorption correction was applied using SADABS program [42]. ORTEP (Oak Ridge Thermal Ellipsoid Plot) was generated using Mercury 3.5.1 Cambridge Crystallographic Data Centre (CCDC) program [43].

4. Conclusions

In this study, new adamantane-linked isothiourea derivatives were synthesized and their in vitro antimicrobial and in vivo hypoglycemic activities were determined. Compounds 7b, 7d, and 7e displayed potent broad-spectrum antibacterial activity, while compounds 7a, 7c, 8b, 8d, and 8e were active against the tested Gram-positive bacteria. The tested compounds were generally inactive against the yeast-like pathogenic fungus Candida albicans. The in vivo oral hypoglycemic activity of the synthesized compounds was determined in streptozotocin (STZ)-induced diabetic rats. Compounds 7a, 8a, and 8b produced potent dose-independent reduction of serum glucose levels compared to gliclazide at 10 mg/kg dose level (potency ratios of 71.08%, 75.13%, and 79.04%, respectively). The active compounds are considered to be good candidates as newer antibacterial and hypoglycemic agents, though, further studies including toxicity testing and molecular docking for the exploration of the mechanism of their biological activity are required for optimization of the activity which are being undertaken.

Supplementary Materials: Supplementary materials (the experimental details of the determination of in vitro antimicrobial activity, in vivo hypoglycemic activity and microanalytical data) are available online.

Acknowledgments: The authors would like to thank the Deanship of Scientific Research, Princess Nourah Bint Abdulrahman University for funding this study (Research Project No. 37-S-173).

Author Contributions: L.H.A.-W. and A.A.E.-E. synthesized and characterized the target compounds and prepared the single crystals. H.M.H. performed the in vivo hypoglycemic testing, A.M.A.-K. conceived the antimicrobial testing. H.A.G. carried out the X-ray analysis. All authors discussed the contents of the manuscript and approved the submission.

Conflicts of Interest: The authors declare no conflict of interest.

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Sample Availability: Samples of all compounds are available from the correspondent author.