# Synthesis, Antimicrobial, and Antiinflammatory Activities of Novel 2-(1-Adamantyl)-5-substituted-1,3,4-oxadiazoles and 2-(1-Adamantylamino)-5-substituted-1,3,4-thiadiazoles

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Original article

# Synthesis, antimicrobial, and anti-inflammatory activities of novel 2-(1-adamantyl)-5-substituted-1,3,4-oxadiazoles and 2-(1-adamantylamino)-5-substituted-1,3,4-thiadiazoles

Adnan A. Kadi [a], Nasser R. El-Brollosy [a], Omar A. Al-Deeb [a], Elsayed E. Habib [b], Tarek M. Ibrahim [c], Ali A. El-Emam [a,*]

[a] *Department of Pharmaceutical Chemistry, P. O. Box 2457, College of Pharmacy, King Saud University, Riyadh 11451, Saudi Arabia*
[b] *Department of Microbiology, Faculty of Pharmacy, University of Mansoura, Mansoura 35516, Egypt*
[c] *Department of Pharmacology and Toxicology, Faculty of Pharmacy, University of Mansoura, Mansoura 35516, Egypt*

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**Abstract**

Reaction of 1-adamantanecarbonyl chloride with certain carboxylic acid hydrazides in pyridine yielded the corresponding *N*-acyl adamantane-1-carbohydrazide derivatives **3a–j**, which were cyclized to the corresponding 2-(1-adamantyl)-5-substituted-1,3,4-oxadiazoles **4a–j** *via* heating with phosphorus oxychloride. Treatment of 1-adamantylisothiocyanate with some carboxylic acid hydrazides in ethanol yielded the corresponding 1-acyl-4-(1-adamantyl)-3-thiosemicarbazides **7a–g**, which were cyclized to the corresponding 2-(1-adamantylamino)-5-substituted-1,3,4-thiadiazole derivatives **8a–g**. Compounds **4a–j**, **7a–g**, and **8a–g** were tested for *in vitro* activities against a panel of Gram-positive and Gram-negative bacteria and the yeast-like pathogenic fungus *Candida albicans*. Several derivatives produced good or moderate activities particularly against the tested Gram-positive bacteria *Bacillus subtilis*. Meanwhile, compounds **4i** and **8g** displayed marked antifungal activity against *C. albicans*. In addition, the *in vivo* anti-inflammatory activity of the synthesized compounds was determined using the carrageenin-induced paw oedema method in rats. The oxadiazole derivatives **4c**, **4g**, **4i** and **4j** produced good dose-dependent anti-inflammatory activity.


*Keywords:* 1-Adamantyl derivatives; 1,3,4-Oxadiazoles; 1,3,4-Thiadiazoles; Anti-inflammatory activity; Antimicrobial activity

## 1. Introduction

Derivatives of adamantane have long been known for their antiviral activity against Influenza A [1–5] and HIV viruses [6–8]. Several adamantane derivatives were also associated with central nervous [9–12], antimicrobial [13–16], and anti-inflammatory activities [15–19]. In addition, several 1,3,4-oxadiazole derivatives were reported to possess significant antibacterial [20–24] and anti-inflammatory activities [25–27]. Moreover, 1,3,4-thiadiazole nucleus constitutes the active part of several biologically active compounds, including antibacterial [28–30], antimycotic [31,32] and anti-inflammatory agents [33–35]. In an earlier work [16], we reported the synthesis and potent anti-inflammatory and analgesic activities of series of 3-(1-adamantyl)-4-substituted-1,2,4-triazoline-5-thiols and their related derivatives. Recently, we reported the anti-inflammatory and antimicrobial activities of novel series of 3-(1-adamantyl)-substituted-1,2,4-triazoline-5-thiones and 2-(1-adamantyl)-1,3,4-oxadiazolin-5-thiones, carrying an acetic or propionic acid moiety [8,17]. In continuation to our interest in the chemical and pharmacological properties of adamantane derivatives, we report herein the synthesis,

* Corresponding author. Tel.: +966 1 4677350; fax: +966 1 4676220.
*E-mail address:* elemam5@hotmail.com (A.A. El-Emam).

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antimicrobial, and anti-inflammatory activities of a new series of 2-(1-adamantyl)-5-substituted-1,3,4-oxadiazoles and 2-(1-adamantylamino)-5-substituted-1,3,4-thiadiazoles.

## 2. Chemistry

The starting material 1-adamantanecarbonyl chloride **1** was obtained *via* the reaction of 1-adamantane carboxylic acid with thionyl chloride [36]. The reaction of **1** with various carboxylic acid hydrazides **2a–j** in pyridine yielded the corresponding *N*-acyl derivatives **3a–j** in high yields. Compounds **3a–j** were cyclized by heating with phosphorus oxychloride for 1 h to yield the corresponding 2-(1-adamantyl)-5-substituted-1,3,4-oxadiazoles **4a–j**. Compounds **4a–j** were also independently prepared in 85–95% yields by the reaction of the carboxylic acid hydrazides **2a–j** with 1-adamantane carboxylic acid in the presence of phosphorus oxychloride (Scheme 1, Table 1).

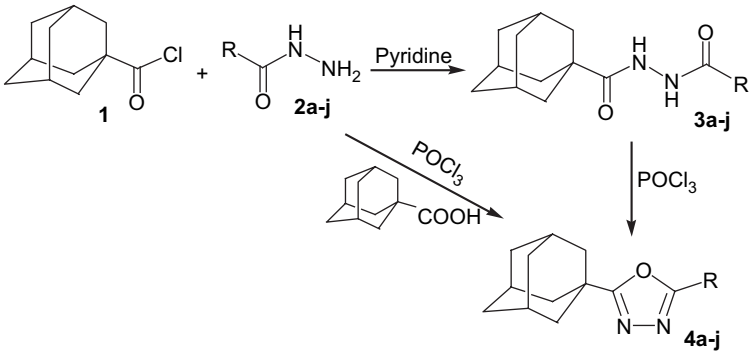
1-Adamantylisothiocyanate **6** was obtained from the commercially available 1-adamantylamine **5** *via* treatment with carbon disulphide and potassium hydroxide [37]. The reaction of **6** with various carboxylic acid hydrazides in ethanol yielded the corresponding 1-acyl-4-(1-adamantyl)-3-thiosemicarbazides **7a–g**. Cyclization of compounds **7a–g** was achieved by the action of sulphuric acid at room temperature to yield the corresponding 2-(1-adamantylamino)-5-substituted-1,3,4-thiadiazole derivatives **8a–g** (Scheme 2, Table 1). The structures of all the newly synthesized compounds were confirmed by elemental analyses in addition to the IR, $^{1}$H NMR, $^{13}$C NMR, and mass spectral data which were in full agreement with their structures.

## 3. Biological testing

### 3.1. In vitro antimicrobial activity

The synthesized compounds were tested for their *in vitro* antimicrobial activity against a panel of standard strains of the Gram-positive bacteria (*Staphylococcus aureus* IFO 3060 and *Bacillus subtilis* IFO 3007), the Gram-negative bacteria (*Escherichia coli* IFO 3301 and *Pseudomonas aeuroginosa* IFO 3448), and the yeast-like pathogenic fungus *Candida albicans* IFO 0583. The primary screening was carried out using the agar disc-diffusion method [38] using Müller–Hinton agar medium. The results of the preliminary antimicrobial testing of compounds **4a–j**, **7a–g** and **8a–g** (200 μg/disc), the broad spectrum antibacterial antibiotic Ampicillin trihydrate (100 μg/disc) and the antifungal drug Clotrimazole (100 μg/disc) are shown in Table 2. The results revealed that they showed varying degrees of inhibition against the tested microorganisms. In general, the best antibacterial activity was displayed by compounds **4g**, **4i**, **7a**, **7e**, **7f**, **8c** and **8e**, and the Gram-positive bacteria *B. subtilis* is considered the most sensitive among the tested microorganisms. Compounds **4g**, **7e**, **8c** and **8c** showed good activity against Gram-positive bacteria *S. aureus* (inhibition zone $> 15$ mm), while compounds **4i** and **8b** were moderately active (inhibition zone 11–16 mm). Compounds **4g**, **4i**, **7a**, **7e**, **7f**, **8c** and **8e** showed strong activity against *B. subtilis*, while compounds **4b**, **4c**, **4d**, **4h**, **7b** and **7c** were moderately active. Compounds **7a**, **7e** and **8e** produced good activity against the Gram-negative bacteria *E. coli*, while compounds **4g**, **4i**, **8a** and **8c** were moderately active. The inhibitory activity against the tested Gram-negative bacteria *P. aeuroginosa* was significantly lower than the other tested microorganisms, only compounds **4i**, **7e** and **8e** were moderately active, while the other compounds were either weakly active or completely inactive (inhibition zone $\leq 10$ mm). None of the tested compounds were found to be superior to the Clotrimazole against *C. albicans*, only compounds **4i**, **7g** and **8g** produced marked activity. The minimal inhibitory concentration (MIC) for the most active compounds **4g**, **4i**, **7a**, **7e**, **7f**, **7g**, **8c**, **8e** and **8g** against the same microorganism used in the primary screening was calculated using the microdilution susceptibility method in Müller–Hinton Broth and Sabouraud Liquid Medium [39]. The MIC of the most active compounds, the antibacterial antibiotic Ampicillin trihydrate and the antifungal drug Clotrimazole which are shown in Table 3, were in accordance with the results obtained in the primary screening.

In general, the antibacterial activity seemed to be dependent on the nature of substituents rather the basic skeleton of the molecules. Within the oxadiazole series **4a–j**, it was noticed that the substituents at position 5 has great influence on the antibacterial activity, the highest activity was observed with the 3,4-dimethoxyphenyl (**4g**) and the 2-thienyl (**4i**) derivatives. Meanwhile, the 4-halophenyl derivatives (**4b**, **4c**



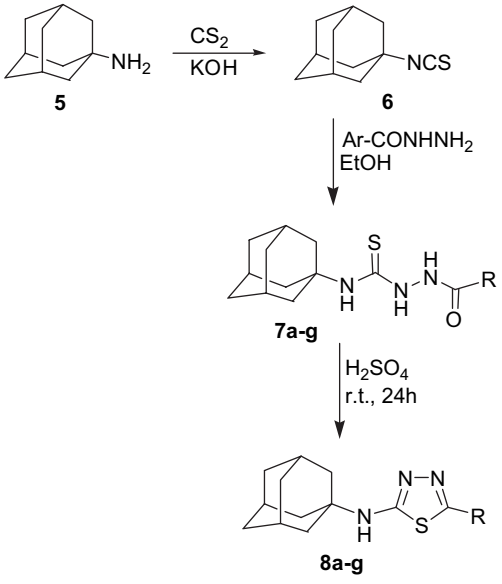

Scheme 1.

Table 1
Crystallization solvents, melting points, yield percentages, molecular formulae, and molecular weights of compounds **4a–j**, **7a–g** and **8a–g**

| Compound | R | Crystallization solvent | M.p. (°C) | Yield[a] (%) | Mol. formula (Mol. wt.) |
|---|---|---|---|---|---|
| **4a** | $C_6H_5$ | EtOH/$H_2O$ | 108–110 | 82 (88) | $C_{18}H_{20}N_2O$ (280.36) |
| **4b** | 4-$FC_6H_4$ | EtOH | 149–151 | 85 (91) | $C_{18}H_{19}FN_2O$ (298.35) |
| **4c** | 4-$ClC_6H_4$ | EtOH | 178–180 | 85 (90) | $C_{18}H_{19}ClN_2O$ (314.81) |
| **4d** | 4-$BrC_6H_4$ | EtOH/$CHCl_3$ | 188–190 | 83 (88) | $C_{18}H_{19}BrN_2O$ (359.26) |
| **4e** | 4-$NO_2C_6H_4$ | EtOH/$CHCl_3$ | 238–240 | 85 (91) | $C_{18}H_{19}N_3O_3$ (325.36) |
| **4f** | 3,5-$(NO_2)_2C_6H_3$ | EtOH | 200–202 | 88 (93) | $C_{18}H_{18}N_4O_5$ (370.36) |
| **4g** | 3,4-$(OCH_3)_2C_6H_3$ | EtOH/$H_2O$ | 145–147 | 82 (89) | $C_{20}H_{24}N_2O_3$ (340.42) |
| **4h** | 2-Cl,4-$NO_2C_6H_3$ | EtOH/$H_2O$ | 153–155 | 86 (88) | $C_{18}H_{18}ClN_3O_3$ (359.81) |
| **4i** | 2-Thienyl | EtOH/$H_2O$ | 110–112 | 80 (85) | $C_{16}H_{18}N_2OS$ (286.39) |
| **4j** | 1-Adamantyl | EtOH/$H_2O$ | 318–320 | 88 (95) | $C_{22}H_{30}N_2O$ (338.49) |
| **7a** | $C_6H_5$ | EtOH/$H_2O$ | 189–191 | 77 | $C_{18}H_{23}N_3OS$ (329.46) |
| **7b** | 4-$FC_6H_4$ | EtOH | 162–164 | 81 | $C_{18}H_{22}FN_3OS$ (347.45) |
| **7c** | 4-$ClC_6H_4$ | EtOH | 190–192 | 83 | $C_{18}H_{22}ClN_3OS$ (363.90) |
| **7d** | 4-$BrC_6H_4$ | EtOH | 195–197 | 85 | $C_{18}H_{22}BrN_3OS$ (408.36) |
| **7e** | 4-$NO_2C_6H_4$ | EtOH/$H_2O$ | 190–192 | 85 | $C_{18}H_{22}N_4O_3S$ (374.46) |
| **7f** | 2-Thienyl | EtOH | 188–190 | 75 | $C_{16}H_{21}N_3OS_2$ (335.49) |
| **7g** | 1-Adamantyl | EtOH | 210–212 | 85 | $C_{22}H_{33}N_3OS$ (387.58) |
| **8a** | $C_6H_5$ | EtOH/$H_2O$ | 169–171 | 69 | $C_{18}H_{21}N_3S$ (311.44) |
| **8b** | 4-$FC_6H_4$ | EtOH/$H_2O$ | 227–229 | 72 | $C_{18}H_{20}FN_3S$ (329.43) |
| **8c** | 4-$ClC_6H_4$ | EtOH/$H_2O$ | 262–264 | 72 | $C_{18}H_{20}ClN_3S$ (345.89) |
| **8d** | 4-$BrC_6H_4$ | EtOH/$CHCl_3$ | 280–282 | 74 | $C_{18}H_{20}BrN_3S$ (390.34) |
| **8e** | 4-$NO_2C_6H_4$ | EtOH/$CHCl_3$ | 263–265 | 79 | $C_{18}H_{20}N_4O_2S$ (356.44) |
| **8f** | 2-Thienyl | EtOH/$H_2O$ | 223–225 | 66 | $C_{16}H_{19}N_3S_2$ (317.47) |
| **8g** | 1-Adamantyl | EtOH/$H_2O$ | 238–240 | 82 | $C_{22}H_{31}N_3S$ (369.57) |

[a] The figures shown in parentheses represent the yields obtained by method B.

and **4d**) were more active than their phenyl analog (**4a**). The nitrophenyl derivatives **4e** and **4f** were completely inactive. In the acyclic thiosemicarbazide derivatives **7a–g**, the highest activity was observed with the phenyl, 4-nitrophenyl and 2-thienyl derivatives, whereas, the halophenyl and 1-adamantyl derivatives were almost inactive. In the adamantylaminothiadiazole series, it seems that the presence of 4-fluoro, chloro or nitrophenyl moieties enhance the activity particularly against *S. aureus*. In addition, marked antifungal activity was only observed in the diadamantyl derivatives **4j**, **7g** and **8g** and the 2-thienyl derivative **4i**, which may be attributed to their high lipophilicity.




Scheme 2.

### 3.2. Acute anti-inflammatory activity

The acute anti-inflammatory activity of the synthesized compounds was determined following the carrageenin-induced paw oedema method in rats [40]. Each compound was tested in three dose levels: 20, 40 and 60 mg/kg. The results of the anti-inflammatory activity of the synthesized compounds and the well-known anti-inflammatory drug Indomethacin (10 mg/kg) are shown in Table 4. The majority of the oxadiazole derivatives **4a–j**, and to a less extent the thiadiazole derivatives **8a–g** showed significant dose-dependent anti-inflammatory activity. The best activity was observed with the oxadiazole derivatives **4c**, **4g**, **4i** and **4j** which displayed strong dose-dependent inhibition of carrageenin-induced oedema producing >50% inhibition at 60 mg/kg dose. Meanwhile, the oxadiazole derivatives **4a**, **4b** and the thiadiazole derivatives **8a**, **8b**, **8c**, **8f** and **8g** were found moderately active producing <50% inhibition of carrageenin-induced oedema. The oxadiazole derivatives **4d**, **4e**, **4f**, and **4h**, the thiadiazole derivatives **8d** and **8e** and all the thiosemicarbazide derivatives **7a–g** were practically inactive.

The structure–anti-inflammatory activity relationship of the synthesized compounds revealed that the activity is dependent on the basic molecular skeleton; most of the cyclic oxadiazoles and to a lesser extent the thiadiazoles are active whereas the acyclic thiosemicarbazides are generally inactive. In the oxadiazole series, it seemed that 4-chlorphenyl, 3,4-dimethoxyphenyl,

Table 2
Antimicrobial activity of compounds **4a–j**, **7a–g** and **8a–g** (200 μg/8 mm disc), the broad spectrum antibacterial drug Ampicillin (100 μg/8 mm disc) and the antifungal drug Clotrimazole (100 μg/8 mm disc) against *Staphylococcus aureus* IFO 3060 (SA), *Bacillus subtilis* IFO 3007 (BS), *Escherichia coli* IFO 3301 (EC), *Pseudomonas aeuroginosa* IFO 3448 (PA), and *Candida albicans* IFO 0583 (CA)

| Compound | Diameter of growth inhibition zone (mm) | | | | |
|---|---|---|---|---|---|
| | SA | BS | EC | PA | CA |
| **4a** | – | – | – | – | – |
| **4b** | – | 12 | – | – | – |
| **4c** | – | 13 | 10 | – | – |
| **4d** | – | 14 | – | – | – |
| **4e** | – | – | – | – | – |
| **4f** | – | – | – | – | – |
| **4g** | 18 | 24 | 12 | – | – |
| **4h** | – | 14 | 10 | 10 | – |
| **4i** | 14 | 18 | 11 | 12 | 16 |
| **4j** | – | – | – | – | 10 |
| **7a** | – | 22 | 16 | – | – |
| **7b** | – | 13 | – | – | – |
| **7c** | – | 13 | – | – | – |
| **7d** | – | 10 | – | – | – |
| **7e** | 20 | 24 | 19 | 15 | – |
| **7f** | – | 18 | 10 | – | – |
| **7g** | – | – | – | – | 16 |
| **8a** | – | – | 12 | – | – |
| **8b** | 14 | 10 | 10 | – | – |
| **8c** | 18 | 16 | 12 | – | – |
| **8d** | – | – | – | – | – |
| **8e** | 16 | 18 | 17 | 12 | – |
| **8f** | – | 10 | – | – | – |
| **8g** | – | – | – | – | 18 |
| Ampicillin | 19 | 18 | 16 | 15 | NT |
| Clotrimazole | NT | NT | NT | NT | 21 |

–: Inactive (inhibition zone < 10 mm). NT: not tested.

2-thienyl and 1-adamantyl moieties enhance the activity, while the nitrophenyl moieties diminished the activity.

There are in fact a high number of enzyme/receptors involved in the inflammatory process. Without specific tests it is quite difficult to hypothesize a mechanism of action, they may exert their action *via* inhibition of the cyclooxygenase enzymes like other nonsteroidal anti-inflammatory agents. In addition, the recently reported activity of some adamantane derivatives as selective inhibitors of 11β-hydroxysteroid dehydrogenase type 1 (11β-HSD1) [41,42] should be taken in consideration. The 11β-hydroxysteroid dehydrogenase type 1 converts cortisone to the active glucocorticoid cortisol, which is responsible for various metabolic disorders including water retention, thus the inhibition of 11β-HSD1 would result in increasing intracellular cortisone level.

Table 3
The minimal inhibitory concentration (MIC, μg/ml) of compounds **4g**, **4i**, **7a**, **7e**, **7f**, **7g**, **8c**, **8e**, and **8g**, the broad spectrum antibacterial drug Ampicillin and the antifungal drug Clotrimazole against *Staphylococcus aureus* IFO 3060 (SA), *Bacillus subtilis* IFO 3007 (BS), *Escherichia coli* IFO 3301 (EC), *Pseudomonas aeuroginosa* IFO 3448 (PA), and *Candida albicans* IFO 0583 (CA)

| Compound | Minimal inhibitory concentration (MIC, μg/ml) | | | | |
|---|---|---|---|---|---|
| | SA | BS | EC | PA | CA |
| **4g** | 2 | 0.5 | ND | ND | ND |
| **4i** | ND | 2 | ND | ND | 2 |
| **7a** | ND | 1 | 4 | ND | ND |
| **7e** | 1 | 0.5 | 2 | ND | ND |
| **7f** | ND | 4 | ND | ND | ND |
| **7g** | ND | ND | ND | ND | 4 |
| **8c** | 2 | ND | ND | ND | ND |
| **8e** | 2 | 2 | 1 | ND | ND |
| **8g** | ND | ND | ND | ND | 2 |
| Ampicillin | 1 | 0.5 | 2 | 2 | ND |
| Clotrimazole | ND | ND | ND | ND | 2 |

ND: not determined.

Table 4
Anti-inflammatory effect of intraperitoneal injection of various doses of compounds **4a–j, 7a–g**, **8a–g** and Indomethacin (10 mg/kg) against carrageenin-induced paw oedema in rats

| Compound | % Reduction of paw oedema from control[a] | | |
|---|---|---|---|
| | 20 mg/kg | 40 mg/kg | 60 mg/kg |
| Control[b] | – | – | – |
| **4a** | 23.16* ± 4.03 | 31.28* ± 6.12 | 34.50* ± 4.80 |
| **4b** | 11.72* ± 5.81 | 29.15* ± 5.16 | 38.62 ± 4.80 |
| **4c** | 34.50* ± 6.31 | 44.66* ± 4.18 | 50.71* ± 4.12 |
| **4d** | 11.60* ± 5.63 | 13.15* ± 7.23 | 13.01 ± 8.29 |
| **4e** | 9.92* ± 7.01 | 13.56* ± 5.16 | 12.08 ± 7.92 |
| **4f** | 4.16 ± 7.20 | 5.22 ± 7.07 | 3.66 ± 6.30 |
| **4g** | 36.73* ± 2.0 | 53.61* ± 3.16 | 70.20* ± 1.72 |
| **4h** | 19.69 ± 2.27 | 21.65 ± 3.71 | 19.34 ± 5.31 |
| **4i** | 35.95* ± 4.81 | 49.77* ± 4.13 | 63.72* ± 2.04 |
| **4j** | 44.27* ± 4.19 | 68.97* ± 1.63 | 71.52* ± 3.10 |
| **7a** | 2.32 ± 6.90 | 1.80 ± 8.34 | – |
| **7b** | – | – | – |
| **7c** | 9.11 ± 7.91 | – | – |
| **7d** | – | 2.34 ± 6.82 | – |
| **7e** | 0.76 ± 6.88 | – | – |
| **7f** | 0.96 ± 7.23 | 2.16 ± 8.01 | |
| **7g** | 11.34* ± 8.62 | 13.08 ± 7.29 | 10.12 ± 7.82 |
| **8a** | 19.69* ± 5.35 | 34.05* ± 4.80 | 33.53 ± 6.21 |
| **8b** | 18.02* ± 4.31 | 35.55* ± 3.02 | 39.35* ± 6.92 |
| **8c** | 21.63* ± 3.90 | 37.02* ± 2.08 | 37.11* ± 4.81 |
| **8d** | 12.51* ± 7.90 | 13.38 ± 7.40 | 14.16 ± 7.81 |
| **8e** | 9.11 ± 7.15 | 10.10 ± 7.70 | 10.74 ± 8.02 |
| **8f** | 15.43* ± 5.90 | 28.62* ± 4.72 | 37.52* ± 3.62 |
| **8g** | 31.60* ± 5.12 | 39.65* ± 2.90 | 44.14* ± 4.18 |
| Indomethacin (10 mg/kg) | 60.4* ± 2.24 | 60.4* ± 2.24 | 60.4* ± 2.24 |

*Significantly different from control at $p < 0.05$.
[a] Results are expressed as mean ± S.E.M. ($n = 5$) and compared with Students "*t*" test.
[b] The group was injected with 1 ml of 0.5% aqueous carboxymethyl cellulose solution.

## 4. Experimental protocols

All melting points (°C, uncorrected) were determined using a Gallenkamp melting point apparatus. Infra red spectra were recorded in KBr discs using Jasco FT/IR 460 Plus spectrometer. NMR spectra were obtained on a Bruker AC 500 Ultra Shield NMR spectrometer at 500 MHz for $^{1}$H and 125 MHz for $^{13}$C, the chemical shifts are expressed in $\delta$ (ppm) downfield from tetramethylsilane (TMS). Electron impact mass spectra were recorded on a Shimadzu GC–MS-QP 5000 instrument. Elemental analyses (C, H, N, S) were in full agreement with the proposed structures within ±0.4% of the theoretical

values. The bacterial strains and *C. albicans* fungus were obtained from the Institute of fermentation of Osaka (IFO), Osaka, Japan. The reference drugs Ampicillin trihydrate (CAS 7177-48-2), Clotrimazole (CAS 23593-75-1) and Indomethacin (CAS 53-86-1) were obtained from Sigma–Aldrich Chemie GmbH, Taufkirchen, Germany. The Sprague–Dawley rats were purchased from local animal house (Abu-Rawash, Giza, Egypt). The animal experiments for the determination of the anti-inflammatory activity were carried out in agreement with the pertinent legal and ethical standards of the international guidelines.

### 4.1. 2-(1-Adamantyl)-5-substituted-1,3,4-oxadiazoles (4a–j)

*Method A*: A mixture of 1-adamantanecarbonyl chloride **1** (1.99 g, 0.01 mol) and the appropriate carboxylic acid hydrazide **2a–j** (0.01 mol), in dry pyridine (10 ml), was heated under reflux for 30 min. On cooling, the mixture was poured onto cold water (50 ml) and stirred for 10 min. The separated solid was filtered, washed thoroughly with cold water and dried to yield the *N*-acyl adamantane-1-carbohydrazide derivatives **3a–j** in 90–95% yields. The products were pure enough to be used in the next step without further purification. The appropriate compounds **3a–j** were added to phosphorus oxychloride (6 ml) and the mixture was heated under reflux for 1 h. On cooling, crushed ice (50 g) was added cautiously and the mixture was stirred for 30 min. The separated crude product was filtered, washed with water then with saturated sodium hydrogen carbonate solution and finally with water, dried and crystallized from ethanol to yield compounds **4a–j** in 80–88% overall yields. *Method B*: A mixture of the appropriate carboxylic acid hydrazides **2a–j** (0.01 mol), 1-adamantane carboxylic acid (1.8 g, 0.01 mol) and phosphorus oxychloride (8 ml) was heated under reflux for 1 h. On cooling, crushed ice (50 g) was added cautiously and the mixture was stirred for 30 min. The separated crude product was filtered, washed with water then with saturated sodium hydrogen carbonate solution and finally with water, dried and crystallized from ethanol to yield compounds **4a–j** in 85–95% yields. Compound **4a**: $^1$H NMR ($CDCl_3$): $\delta$ 1.77 (s, 6H, Adamantane-H), 2.06 (s, 9H, Adamantane-H), 7.58–7.62 (m, 3H, Ar-H), 7.99 (d, 2H, Ar-H, $J = 6.7$ Hz). $^{13}$C NMR: $\delta$ 27.76, 34.32, 36.26, 39.41 (Adamantane-C), 125.21, 126.25, 132.29 (Ar-C), 163.24 (Oxadiazole C-5), 172.34 (Oxadiazole C-2). MS *m/z* (Rel. Int.): 280 ($M^+$, 100), 223 (19), 135 (63), 105 (58), 91 (29), 77 (74), 41 (82). Compound **4b**: $^1$H NMR ($CDCl_3$): $\delta$ 1.77 (s, 6H, Adamantane-H), 2.06 (s, 9H, Adamantane-H), 7.42–7.46 (m, 2H, Ar-H), 8.06–8.08 (m, 2H, Ar-H). $^{13}$C NMR: $\delta$ 27.61, 34.31, 36.16, 39.47 (Adamantane-C), 117.0, 120.78, 129.57, 129.64 (Ar-C), 163.24 (Oxadiazole C-5), 172.54 (Oxadiazole C-2). MS *m/z* (Rel. Int.): 289 ($M^+$, 100), 232 (17), 135 (73), 95 (19), 91 (32), 41 (75). Compound **4c**: $^1$H NMR ($CDCl_3$): $\delta$ 1.77 (s, 6H, Adamantane-H), 2.06 (s, 9H, Adamantane-H), 7.66 (d, 2H, Ar-H, $J = 8.0$ Hz), 8.0 (d, 2H, Ar-H, $J = 8.0$ Hz). $^{13}$C NMR: $\delta$ 27.62, 34.31, 36.22, 39.42 (Adamantane-C), 123.31, 126.04, 128.11, 132.63 (Ar-C), 163.24 (Oxadiazole C-5), 172.41 (Oxadiazole C-2). MS *m/z* (Rel. Int.): 316 ($M^+ + 2$, 39), 314 ($M^+$, 100), 257 (7), 223 (8), 139 (48), 135 (81), 111 (25), 91 (30), 41 (54). Compound **4d**: $^1$H NMR ($CDCl_3$): $\delta$ 1.81 (s, 6H, Adamantane-H), 2.15 (s, 9H, Adamantane-H), 7.64 (d, 2H, Ar-H, $J = 8.1$ Hz), 7.92 (d, 2H, Ar-H, $J = 8.1$ Hz). $^{13}$C NMR: $\delta$ 27.74, 34.45, 36.29, 39.96 (Adamantane-C), 123.26, 125.99, 128.23, 132.28 (Ar-C), 163.56 (Oxadiazole C-5), 172.85 (Oxadiazole C-2). MS *m/z* (Rel. Int.): 360 ($M^+ + 2$, 44), 358 (46), 303 (3), 301 (4), 223 (6), 185 (19), 183 (22), 157 (11), 155 (12), 135 (100), 91 (27), 41 (65). Compound **4e**: $^1$H NMR ($CDCl_3$): $\delta$ 1.79 (s, 6H, Adamantane-H), 2.08 (s, 9H, Adamantane-H), 7.61–7.72 (m, 2H, Ar-H), 8.33–8.53 (m, 2H, Ar-H). $^{13}$C NMR: $\delta$ 27.10, 33.15, 36.80, 39.82 (Adamantane-C), 125.15, 128.20, 141.95, 145.10 (Ar-C), 163.25 (Oxadiazole C-5), 173.05 (Oxadiazole C-2). MS *m/z* (Rel. Int.): 325 ($M^+$, 66), 268 (10), 175 (6), 150 (13), 135 (100), 91 (48), 41 (92). Compound **4f**: $^1$H NMR ($CDCl_3$): $\delta$ 1.80 (s, 6H, Adamantane-H), 2.12 (s, 9H, Adamantane-H), 8.99 (s, 1H, Ar-H), 9.0 (s, 2H, Ar-H). $^{13}$C NMR: $\delta$ 27.53, 34.23, 36.71, 39.42 (Adamantane-C), 123.27, 127.11, 128.01, 149.31 (Ar-C), 161.93 (Oxadiazole C-5), 173.63 (Oxadiazole C-2). MS *m/z* (Rel. Int.): 370 ($M^+$, 100), 313 (17), 195 (16), 175 (14), 135 (62), 105 (22), 91 (32), 41 (98). Compound **4g**: $^1$H NMR ($CDCl_3$): $\delta$ 1.77 (s, 6H, Adamantane-H), 2.04 (s, 9H, Adamantane-H), 3.74 (s, 3H, $OCH_3$), 3.77 (s, 3H, $OCH_3$), 6.82–7.03 (m, 3H, Ar-H). $^{13}$C NMR: $\delta$ 27.95, 33.85, 35.91, 39.02 (Adamantane-C), 57.32 ($OCH_3$), 58.90 ($OCH_3$), 114.32, 117.61, 123.73, 131.82, 146.73, 149.20 (Ar-C), 162.91 (Oxadiazole C-5), 172.80 (Oxadiazole C-2). MS *m/z* (Rel. Int.): 340 ($M^+$, 62), 283 (11), 135 (100), 91 (72), 41 (79). Compound **4h**: $^1$H NMR ($CDCl_3$): $\delta$ 1.67–1.87 (m, 6H, Adamantane-H), 1.99–2.08 (m, 9H, Adamantane-H), 8.28–8.50 (m, 3H, Ar-H). $^{13}$C NMR: $\delta$ 27.57, 34.41, 36.10, 38.95 (Adamantane-C), 123.16, 126.51, 128.66, 130.94, 132.80, 149.66 (Ar-C), 161.10 (Oxadiazole C-5), 173.37 (Oxadiazole C-2). MS *m/z* (Rel. Int.): 361 ($M^+ + 2$, 16), 359 ($M^+$, 44), 304 (15), 302 (14), 184 (15), 135 (100), 91 (26), 41 (94). Compound **4i**: $^1$H NMR ($CDCl_3$): $\delta$ 1.76 (s, 6H, Adamantane-H), 2.04 (s, 9H, Adamantane-H), 7.27–7.29 (m, 1H, Thiophene-H), 7.79–7.93 (m, 2H, Thiophene-H). $^{13}$C NMR: $\delta$ 27.60, 34.17, 36.13, 38.99 (Adamantane-C), 125.56, 129.33, 130.43, 131.67 (Thiophene-C), 160.34 (Oxadiazole C-5), 171.23 (Oxadiazole C-2). MS *m/z* (Rel. Int.): 286 ($M^+$, 67), 229 (14), 151 (13), 135 (88), 111 (33), 83 (100), 47 (89), 41 (65). Compound **4j**: $^1$H NMR ($CDCl_3$): $\delta$ 1.79 (s, 12H, Adamantane-H), 2.09 (s, 18H, Adamantane-H). $^{13}$C NMR: $\delta$ 27.70, 34.20, 36.27, 39.79 (Adamantane-C), 171.99 (Oxadiazole-C). MS *m/z* (Rel. Int.): 338 ($M^+$, 100), 281 (19), 203 (13), 175 (5), 135 (81), 41 (74).

### 4.2. 1-Acyl-4-(1-adamantyl)-3-thiosemicarbazides (7a–g)

A mixture of the carboxylic acid hydrazide (0.01 mol) and 1-adamantylisothiocyanate (1.93 g, 0.01 mol), in ethanol (10 ml) was heated under reflux for 4 h. On cooling, the precipitated crystalline solid was filtered, washed with cold ethanol, dried and crystallized from ethanol to yield compounds **7a–g** in 75–85% yields. Compound **7a**: $^1$H NMR

(DMSO-$d_6$): δ 1.63 (s, 6H, Adamantane-H), 2.04 (s, 3H, Adamantane-H), 2.20 (s, 6H, Adamantane-H), 7.49–7.59 (m, 3H, Ar-H), 7.89 (d, 2H, Ar-H, $J = 8.1$ Hz), 9.15 (s, 1H, NH), 10.33 (s, 1H, NH). $^{13}$C NMR: 29.45, 36.47, 39.96, 41.36 (Adamantane-C), 128.03, 128.91, 132.38, 132.89 (Ar-C), 161.32 (C=O), 166.21 (C=S). MS *m/z* (Rel. Int.): 329 ($M^+$, 2), 311 (8), 295 (12), 194 (19), 193 (42), 135 (100), 105 (75), 79 (46), 77 (76), 41 (48). Compound **7b**: $^1$H NMR (DMSO-$d_6$): δ 1.63 (s, 6H, Adamantane-H), 2.06 (s, 3H, Adamantane-H), 2.16 (s, 6H, Adamantane-H), 7.32–7.36 (m, 2H, Ar-H), 7.55–7.69 (d, 2H, Ar-H), 9.13 (s, 1H, NH), 10.35 (s, 1H, NH). $^{13}$C NMR: 29.15, 36.37, 39.69, 41.35 (Adamantane-C), 128.14, 128.16, 131.36, 136.02 (Ar-C), 163.62 (C=O), 165.65 (C=S). MS *m/z* (Rel. Int.): 347 ($M^+$, 2), 313 (9), 193 (27), 194 (12), 154 (23), 135 (100), 123 (82), 95 (62), 79 (42), 41 (43). Compound **7c**: $^1$H NMR (DMSO-$d_6$): δ 1.63 (s, 6H, Adamantane-H), 2.04 (s, 3H, Adamantane-H), 2.19 (s, 6H, Adamantane-H), 7.57 (d, 2H, Ar-H, $J = 8.0$ Hz), 7.90 (d, 2H, Ar-H, $J = 8.0$ Hz), 9.14 (s, 1H, NH), 10.40 (s, 1H, NH). $^{13}$C NMR: 29.31, 36.38, 39.89, 41.32 (Adamantane-C), 129.01, 129.98, 131.74, 137.17 (Ar-C), 162.03 (C=O), 165.24 (C=S). MS *m/z* (Rel. Int.): 365 ($M^+ + 2$, 1), 363 ($M^+$, 3), 345 (4), 329 (6), 212 (19), 193 (44), 141 (54), 139 (93), 135 (100), 113 (29), 111 (71), 93 (51), 79 (63), 41 (59). Compound **7d**: $^1$H NMR (DMSO-$d_6$): δ 1.63 (s, 6H, Adamantane-H), 2.04 (s, 3H, Adamantane-H), 2.19 (s, 6H, Adamantane-H), 7.72 (d, 2H, Ar-H, $J = 8.1$ Hz), 7.82 (d, 2H, Ar-H, $J = 8.1$ Hz), 9.14 (s, 1H, NH), 10.40 (s, 1H, NH). $^{13}$C NMR: 29.45, 36.37, 39.84, 41.32 (Adamantane-C), 126.14, 130.15, 131.95, 136.23 (Ar-C), 162.95 (C=O), 165.39 (C=S). MS *m/z* (Rel. Int.): 409 ($M^+ + 2$, 1), 407 ($M^+$, 1), 375 (7), 373 (8), 193 (14), 185 (44), 183 (43), 157 (23), 155 (24), 135 (100), 81 (34), 79 (69), 41 (44). Compound **7e**: $^1$H NMR (DMSO-$d_6$): δ 1.63 (s, 6H, Adamantane-H), 2.05 (s, 3H, Adamantane-H), 2.21 (s, 6H, Adamantane-H), 8.04 (d, 2H, Ar-H, $J = 8.0$), 8.30 (d, 2H, Ar-H, $J = 8.0$), 9.20 (s, 1H, NH), 10.14 (s, 1H, NH). $^{13}$C NMR: 29.23, 36.15, 39.79, 41.53 (Adamantane-C), 125.71, 129.30, 131.63, 138.17 (Ar-C), 163.02 (C=O), 166.19 (C=S). MS *m/z* (Rel. Int.): 374 ($M^+$, 2), 356 (9), 340 (11), 338 (15), 239 (15), 220 (26), 193 (37), 181 (19), 150 (56), 135 (100), 93 (36), 79 (37), 41 (76). Compound **7f**: $^1$H NMR (DMSO-$d_6$): δ 1.63 (s, 6H, Adamantane-H), 2.04 (s, 3H, Adamantane-H), 2.19 (s, 6H, Adamantane-H), 7.18–7.27 (m, 1H, Thiophene-H), 7.65–7.88 (m, 2H, Thiophene-H), 9.14 (s, 1H, NH), 10.35 (s, 1H, NH). $^{13}$C NMR: 29.13, 36.72, 39.89, 41.38 (Adamantane-C), 128.11, 129.81, 132.04, 137.23 (Thiophene-C), 161.16 (C=O), 166.37 (C=S). MS *m/z* (Rel. Int.): 335 ($M^+$, 2), 301 (13), 193 (18), 142 (31), 135 (92), 111 (100), 83 (24), 79 (41), 41 (86). Compound **7g**: $^1$H NMR (DMSO-$d_6$): δ 1.63–1.68 (m, 12H, Adamantane-H), 1.81 (s, 3H, Adamantane-H), 1.83 (m, 3H, Adamantane-H), 1.97–2.14 (m, 12H, Adamantane-H), 9.15 (s, 1H, NH), 9.73 (s, 1H, NH). $^{13}$C NMR: 29.14, 29.41, 36.34, 36.44, 38.78, 39.62, 40.55, 41.41 (Adamantane-C), 162.13 (C=O), 165.98 (C=S). MS *m/z* (Rel. Int.): 387 ($M^+$, 1), 252 (13), 237 (12), 163 (15), 193 (15), 135 (100), 93 (24), 79 (38), 41 (64).

### *4.3. 2-(1-Adamantylamino)-5-aryl-1,3,4-thiadiazoles (**8a–g**)*

Sulphuric acid (98%) (6 ml) was added dropwise to the appropriate substituted thiosemicarbazides **7a–g** (1.0 g) and the mixture was stirred at room temperature for 24 h. The resulted homogenous mixture was poured onto crushed ice (100 g), neutralized with ammonium hydroxide solution. The separated precipitate was filtered, washed with water, dried and crystallized to yield compounds **8a–g** in 66–82% yields. Compound **8a**: $^1$H NMR (DMSO-$d_6$): δ 1.66 (s, 6H, Adamantane-H), 2.0–2.08 (m, 9H, Adamantane-H), 7.43–7.81 (m, 6H, Ar-H and NH). $^{13}$C NMR: 29.14, 35.22, 36.38, 41.37 (Adamantane-C), 125.52, 126.80, 129.72, 131.38 (Ar-C), 162.26 (Thiadiazole-C), 166.27 (Thiadiazole-C). MS *m/z* (Rel. Int.): 311 ($M^+$, 13), 295 (13), 208 (20), 161 (11), 149 (15), 135 (85), 121 (22), 105 (31), 91 (29), 77 (100), 41 (96). Compound **8b**: $^1$H NMR (DMSO-$d_6$): δ 1.67 (s, 6H, Adamantane-H), 1.96–2.16 (m, 9H, Adamantane-H), 7.35–7.95 (m, 5H, Ar-H and NH), 7.55–7.69 (d, 2H, Ar-H), 9.13 (s, 1H, NH), 10.35 (s, 1H, NH). $^{13}$C NMR: 28.07, 35.42, 39.02, 41.06 (Adamantane-C), 118.71, 128.95, 130.02, 131.63 (Ar-C), 162.61 (Thiadiazole-C), 166.82 (Thiadiazole-C). MS *m/z* (Rel. Int.): 329 ($M^+$, 8), 314 (9), 208 (17), 135 (100), 107 (72), 95 (62), 79 (42), 41 (44). Compound **8c**: $^1$H NMR (DMSO-$d_6$): δ 1.62 (s, 6H, Adamantane-H), 1.93–2.04 (s, 9H, Adamantane-H), 7.42 (d, 2H, Ar-H, $J = 8.0$ Hz), 7.75 (d, 2H, Ar-H, $J = 8.0$ Hz). $^{13}$C NMR: 28.02, 35.31, 37.90, 41.0 (Adamantane-C), 124.52, 128.91, 129.55, 136.77 (Ar-C), 161.92 (Thiadiazole-C), 166.29 (Thiadiazole-C). MS *m/z* (Rel. Int.): 347 ($M^+ + 2$, 2), 3645 ($M^+$, 7), 330 (21), 208 (21), 135 (100), 124 (13), 111 (28), 79 (63), 41 (59). Compound **8d**: $^1$H NMR (DMSO-$d_6$): δ 1.65 (s, 6H, Adamantane-H), 1.99–2.08 (m, 9H, Adamantane-H), 7.67–7.79 (m, 6H, Ar-H & NH). $^{13}$C NMR: 28.21, 34.17, 36.72, 41.63 (Adamantane-C), 124.15, 127.23, 129.91, 133.45 (Ar-C), 162.36 (Thiadiazole-C), 166.59 (Thiadiazole-C). MS *m/z* (Rel. Int.): 391 ($M^+ + 2$, 4), 389 ($M^+$, 4), 375 (7), 373 (8), 241 (13), 239 (13), 208 (23), 201 (14), 199 (15), 183 (30), 181 (18), 157 (22), 155 (23), 149 (14), 135 (100), 91 (35), 79 (54), 41 (73). Compound **8e**: $^1$H NMR (DMSO-$d_6$): δ 1.66 (s, 6H, Adamantane-H), 1.97–2.07 (s, 3H, Adamantane-H), 7.93–8.38 (m, 5H, Ar-H and NH). $^{13}$C NMR: 29.32, 36.24, 36.32, 41.18 (Adamantane-C), 124.90, 126.50, 127.58, 137.21 (Ar-C), 162.51 (Thiadiazole-C), 167.03 (Thiadiazole-C). MS *m/z* (Rel. Int.): 356 ($M^+$, 3), 341 (13), 297 (18), 208 (33), 206 (14), 166 (28), 135 (100), 121 (12), 91 (54), 79 (55), 41 (83). Compound **8f**: $^1$H NMR (DMSO-$d_6$): δ 1.65 (s, 6H, Adamantane-H), 1.96–2.08 (m, 9H, Adamantane-H), 7.31–7.78 (m, 4H, Thiophene-H and NH). $^{13}$C NMR: 29.31, 35.23, 36.29, 41.24 (Adamantane-C), 125.99, 127.77, 128.64, 129.51 (Thiophene-C), 161.42 (Thiadiazole-C), 165.87 (Thiadiazole-C). MS *m/z* (Rel. Int.): 317 ($M^+$, 5), 301 (27), 208 (12), 183 (13), 167 (21), 151 (15), 135 (100), 127 (20), 111 (42), 93 (43), 79 (57), 41 (91). Compound **8g**: $^1$H NMR (DMSO-$d_6$): δ 1.65–1.72 (m, 12H, Adamantane-H), 1.95–2.14 (m, 18H, Adamantane-H), 7.95 (s, 1H, NH). $^{13}$C NMR: 29.14, 29.41, 36.34, 36.44, 38.78, 39.62, 40.55, 41.41 (Adamantane-C),

162.13 (Thiadiazole-C), 165.98 (Thiadiazole-C). MS *m/z* (Rel. Int.): 369 ($M^+$, 3), 353 (21), 235 (20), 208 (20), 149 (15), 135 (100), 93 (50), 79 (61), 41 (76).

### 4.4. Determination of in vitro antimicrobial activity

The primary screening was carried out using the agar disc-diffusion method using Müller–Hinton agar medium. Sterile filter paper discs (8 mm diameter) were moistened with the compound solution in dimethylsulphoxide of specific concentration (200 μg/disc), the antibacterial antibiotic 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 was measured after 24 h in case of bacteria and 48 h in case of *C. albicans*. The minimal inhibitory concentration (MIC) for the compounds **4g**, **4i**, **7a**, **7e**, **7f**, **7g**, **8c**, **8e** and **8g** against the same microorganisms used in the primary screening was carried out using the microdilution susceptibility method in Müller–Hinton Broth and Sabouraud Liquid Medium. The compounds, Ampicillin trihydrate and Clotrimazole were dissolved in dimethylsulphoxide at concentration of 128 μg/ml. The two-fold dilutions of the solution were prepared (128, 64, 32,…, 0.5 μg/ml). The microorganism suspensions at $10^6$ CFU/ml (colony forming unit/ml) concentrations were inoculated to the corresponding wells. The plates were incubated at 37 °C for 24 and 48 h for the bacteria and *C. albicans*, respectively. The MIC values were determined as the lowest concentration that completely inhibited visible growth of the microorganism as detected by unaided eye.

### 4.5. Determination of in vivo anti-inflammatory activity

Male Sprague–Dawley rats weighing 150–200 g were maintained at room temperature (20–23 °C). The animals were randomly divided into 74 groups each of five animals. The animals were housed with food and water *ad libitum* and allowed to be accustomed to their environment for two days before the testing. Each group was injected with the specific dose of test compound (20, 40, and 60 mg/kg), or Indomethacin (10 mg/kg) intraperitoneally as a uniform suspension in 1 ml of 0.5% aqueous carboxymethyl cellulose solution, 1 h before injection of 0.1 ml of carrageenin (1% solution in normal saline) into the plantar tissue of the right hind paw. The left hind paw was injected with 0.1 ml of normal saline solution. Four hours after carrageenin injection, the volume of paw oedema (ml) was determined using water plethysmometer. The percentage protection against inflammation was calculated as follows:

$$\frac{V_c - V_d}{V_c} \times 100$$

Where $V_c$ is the mean percentage increase in paw volume in the absence of the test compound (control) and $V_d$ is the mean percentage increase in paw volume after injection of the test compound. The values are expressed as the mean ± S.E.M. Statistical significance between the control and treated groups was performed using the Students "*t*" test.

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