# Synthesis and antimicrobial activity of novel 5-(1-adamantyl)-2-aminomethyl-4-substituted-1,2,4-triazoline-3-thiones

**ARTICLE** *in* EUROPEAN JOURNAL OF MEDICINAL CHEMISTRY · AUGUST 2013

Impact Factor: 3.45 · DOI: 10.1016/j.ejmech.2013.07.024 · Source: PubMed

European Journal of Medicinal Chemistry 68 (2013) 96–102

Contents lists available at ScienceDirect

European Journal of Medicinal Chemistry

journal homepage: http://www.elsevier.com/locate/ejmech

Original article

# Synthesis and antimicrobial activity of novel 5-(1-adamantyl)-2-aminomethyl-4-substituted-1,2,4-triazoline-3-thiones

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ARTICLE INFO

*Article history:*
Received 21 December 2012
Received in revised form
30 April 2013
Accepted 15 July 2013
Available online 8 August 2013

*Keywords:*
Adamantane derivatives
1,2,4-triazoles
*N*-Mannich bases
Antimicrobial activity

ABSTRACT

The reaction of 5-(1-adamantyl)-4-substituted-1,2,4-triazoline-3-thione **5a**,**b** and **10a**,**b** with formaldehyde solution and various primary aromatic amines or 1-substituted piperazines yielded the corresponding *N*-Mannich bases **6a**–**o**, **7a**–**g** and **11a**–**i**. The newly synthesized *N*-Mannich bases **6a**–**o**, **7a**–**g** and **11a**–**i** were tested for *in vitro* inhibitory activities against a panel of Gram-positive and Gram-negative bacteria and the yeast-like pathogenic fungus *Candida albicans*. The compounds **6j**, **6l**, **6m**, **7a**, **7b**, **7c**, **7d**, **7f**, **11a**, **11b**, **11c**, **11d**, **11e**, **11f**, **11h** and **11i** displayed moderate to good activity against the tested Gram-positive bacteria, while compounds **7c**, **11c**, **11d**, **11f** and **11h** showed potent broad spectrum antibacterial activity. None of the newly synthesized compounds were proved to possess marked activity against *C. albicans*.



## 1. Introduction

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. In almost all cases, an adamantyl-bearing compound will be more lipophilic than the des-adamantyl analogue. Beyond increasing partition coefficient, the adamantyl group positively modulates the therapeutic index of many experimental compounds through a variety of mechanisms [1,2]. Derivatives of adamantane have long been known for their antiviral activity against Influenza A [3–6] and HIV viruses [7–9]. Several adamantane derivatives were also associated with central nervous [10–12], hypoglycemic [13,14], antimicrobial [15–20] and anti-inflammatory activities [17–23]. In addition, several 1,2,4-triazoles and their *N*-Mannich bases were identified as potent antimicrobial agents [24–29]. In continuation to our interest in the chemical and pharmacological properties of adamantane derivatives [7,17–21,30], we report herein the synthesis and antimicrobial activity of new series of 5-(1-adamantyl)-4-substituted-1,2,4-triazole *N*-Mannich bases.

## 2. Results and discussion

### 2.1. Chemistry

The starting material adamantane-1-carbohydrazide **3** was prepared starting with adamantane-1-carboxylic acid **1** *via* esterification with methanol to yield the corresponding methyl ester **2**, which was reacted with hydrazine to yield **3** [21]. The reaction of **3** with methyl or 4-chlorophenylisothiocyanate yielded the intermediate 1-(1-adamantylcarbonyl)-4-substituted thiosemicarbazides **4a**,**b**, which were cyclized to the corresponding 5-(1-adamantyl)-4-substituted-1,2,4-triazoline-3-thiones **5a**,**b** *via* heating in 10% aqueous sodium hydroxide for 2 h [19,21]. Compounds **5a**,**b** were reacted with primary aromatic amines and formaldehyde solution in ethanol to yield the corresponding *N*-Mannich bases **6a**–**o** in good yields. The reaction was carried out by heating the reactants in ethanol for 15 min to enhance the solubility of compounds **5a**,**b**. On monitoring the reaction with thin layer chromatography (TLC), the starting compounds **5a**,**b** disappeared completely after 15 min and the products were precipitated after addition of water to the reaction mixture. The *N*-Mannich bases 5-(1-adamantyl)-4-(methyl or 4-chlorophenyl)-2-(4-substituted-1-piperazinylmethyl)-1,2,4-triazoline-3-thiones **7a**–**g** were similarly prepared *via* the reaction of compounds **5a**,**b** with the corresponding 1-substituted piperazine

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http://dx.doi.org/10.1016/j.ejmech.2013.07.024

and formaldehyde solution in 48–85% yields (Scheme 1, Table 1). The structures of compounds **6a**–**o** and **7a**–**g** were confirmed by elemental analyses in addition to the $^{1}$H NMR, $^{13}$C NMR, and ESI-MS mass spectral data which were in full agreement with their structures, in addition to the X-ray spectra of compounds **7a** [31] and **7b** [32].

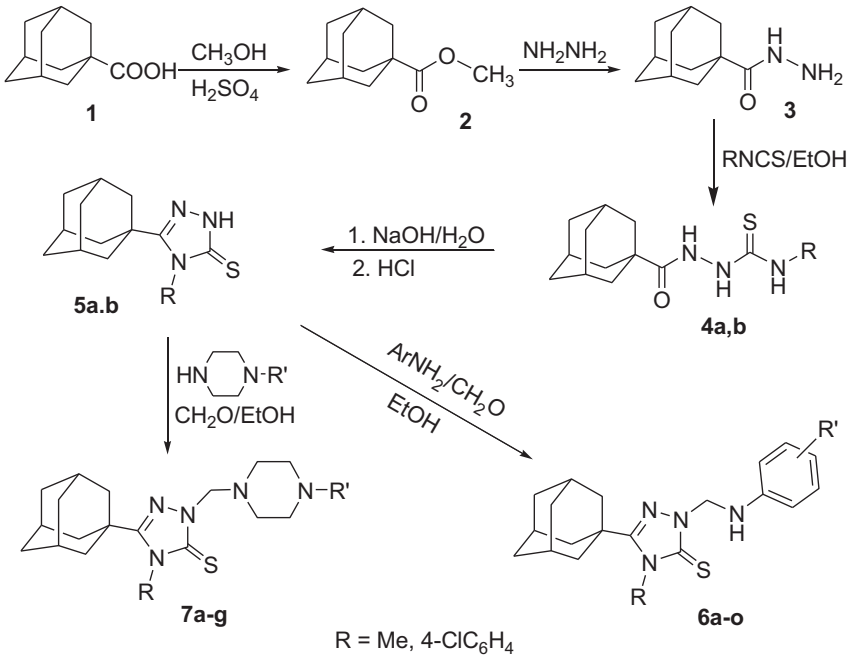
5-(1-Adamantyl)-4-amino-1,2,4-triazoline-3-thione **9** was prepared according to the previously reported method of El-Emam et al. [33] *via* the condensation of adamantane-1-carbohydrazide **3** with carbon disulphide in ethanolic potassium hydroxide to yield the corresponding potassium *N*′-(1-adamantylcarbonyl) dithiocarbazate **8**, which was subsequently heated with hydrazine to yield the target compound **9** in good overall yield. Compound **9** was condensed with 2-hydroxybenzaldehyde or 4-hydroxy benzaldehyde in ethanol by heating under reflux for 5 h to yield the target arylideneamino derivatives **10a**,**b** in 79% and 82% yields, respectively [18]. The piperazinomethyl *N*-Mannich bases **11a**–**i** were similarly prepared *via* the reaction of compounds **10a**,**b** with the corresponding 1-substituted piperazine and formaldehyde solution in 38–85% yields (Scheme 2, Table 1). The structures of compounds **11a**–**i** were confirmed by elemental analyses in addition to the $^{1}$H NMR, $^{13}$C NMR, and ESI-MS mass spectral data which were in full agreement with their structures, in addition to the X-ray spectra of compounds **11e** [34] and **11f** [35] which showed the existence of the imine bond of these derivatives in the *E* (*trans*) stereoisomers.

### 2.2. In vitro antimicrobial activity

The newly synthesized compounds **6a**–**o**, **7a**–**g** and **11a**–**i** were tested for their *in vitro* growth inhibitory activity against the standard 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 aeuroginosa* 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 [36].

The results of the preliminary antimicrobial testing of compounds **6a**–**o**, **7a**–**g** and **11a**–**i** (200 μg/disc), the antibacterial antibiotics Ampicillin trihydrate, Gentamicin (100 μg/disc) and the 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 shown in Table 2. The results revealed that the tested compounds showed varying degrees of inhibition against the tested microorganisms. In general, strong activity was displayed by the compounds **6j**, **6l**, **6m**, **7a**, **7b**, **7c**, **7d**, **7f**, **11a**, **11b**, **11c**, **11d**, **11e**, **11f**, **11h** and **11i**, which produced growth inhibition zones ≥18 mm against one or more of the tested microorganisms. Meanwhile, the compounds **6g**, **6h**, **6k**, **7e** and **11g** showed moderate activity (growth inhibition zones 14–17 mm), the compounds **6a**, **6b**, **6f**, **6n** and **7g** (growth inhibition zones 10–13 mm) and compounds **6c**, **6d**, **6e**, **6i** and **6o** were practically inactive (growth inhibition zones ≤10 mm) against the tested microorganisms. The Gram-positive bacteria *B. subtilis* and to a lesser extent *S. aureus* and *M. luteus* are considered the most sensitive among the tested microorganisms. The activity against the tested Gram-negative bacteria was generally lower than that against the Gram-positive bacteria, compound **7c** was strongly active against *E. coli*, while only compound **7c** was strongly active against *P. aeuroginosa*. The inhibitory activity of the compounds against *C. albicans* was rather lower than their antibacterial activity, only compound **6m** exhibited marginal activity. The minimal inhibitory concentrations (MIC) [37] for the most active compounds **6j**, **6l**, **6m**, **7a**, **7b**, **7c**, **7d**, **7f**, **11a**, **11b**, **11c**, **11d**, **11e**, **11f**, **11h** and **11i**, which are shown in Table 2, were in accordance with the results obtained in the primary.

In general, the antibacterial activity seemed to be dependent on the nature of substituents rather than basic skeleton of the molecules. Within the 5-(1-adamantyl)-4-(methyl or 4-chlorophenyl)-2-arylaminomethyl-1,2,4-triazoline-3-thiones **6a**–**o** (Table 2), it was observed that the antibacterial activity is not dependent on the lipophilicity, and the 4-methyl derivatives **6a**–**d** were generally inactive as well as their corresponding 4-(4-chlorophenyl) analogues **6e**, **6g**, **6i**, and **6o**. The substituents on the 2-arylaminomethyl moiety greatly influenced the antimicrobial




**Scheme 1.** Synthesis of compounds **6a**–**o** and **7a**–**g**.

**Table 1**
Recrystallization solvents, melting points, yield percentages, molecular formulae, molecular weights and microanalytical data of compounds **6a**–**o**, **7a**–**g** and **11a**–**i**.

| Comp. no. | R | R′ | Cryst. solvent | M.p. (°C) | Yield (%) | Mol. formula (mol. wt.) | Analysis: % calcd. (found) | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | C | H | N | S |
| **6a** | $CH_3$ | H | EtOH | 166–8 | 71 | $C_{20}H_{26}N_4S$ (354.51) | 67.76 (67.51) | 7.39 (7.44) | 15.80 (15.69) | 9.04 (9.02) |
| **6b** | $CH_3$ | 4-F | EtOH | 142–4 | 64 | $C_{20}H_{25}FN_4S$ (372.5) | 64.49 (64.26) | 6.76 (6.81) | 15.04 (15.12) | 8.61 (8.52) |
| **6c** | $CH_3$ | 4-Br | EtOH | 199–201 | 92 | $C_{20}H_{25}BrN_4S$ (433.41) | 55.42 (55.40) | 5.81 (5.81) | 12.93 (12.90) | 7.40 (7.33) |
| **6d** | $CH_3$ | 4-OEt | EtOH | 127–9 | 77 | $C_{22}H_{30}N_4OS$ (398.56) | 66.30 (66.31) | 7.59 (7.64) | 14.06 (13.90) | 8.05 (7.98) |
| **6e** | 4-$ClC_6H_4$ | H | EtOH | 133–5 | 76 | $C_{25}H_{27}ClN_4S$ (451.03) | 66.57 (66.58) | 6.03 (6.21) | 12.42 (12.34) | 7.11 (7.10) |
| **6f** | 4-$ClC_6H_4$ | 2-F | EtOH | 121–3 | 68 | $C_{25}H_{26}ClFN_4S$ (469.02) | 64.02 (63.92) | 5.59 (5.62) | 11.95 (11.93) | 6.84 (6.82) |
| **6g** | 4-$ClC_6H_4$ | 4-F | EtOH | 169–71 | 83 | $C_{25}H_{26}ClFN_4S$ (469.02) | 64.02 (63.91) | 5.59 (5.63) | 11.95 (11.88) | 6.84 (6.84) |
| **6h** | 4-$ClC_6H_4$ | 2-Cl | EtOH | 184–6 | 88 | $C_{25}H_{26}Cl_2N_4S$ (485.47) | 61.85 (61.82) | 5.40 (5.44) | 11.54 (11.30) | 6.60 (6.56) |
| **6i** | 4-$ClC_6H_4$ | 4-Br | EtOH | 193–5 | 90 | $C_{25}H_{26}BrClN_4S$ (529.92) | 56.66 (56.66) | 4.95 (5.06) | 10.57 (10.38) | 6.05 (5.98) |
| **6j** | 4-$ClC_6H_4$ | 2-$CF_3$ | EtOH | 112–4 | 55 | $C_{26}H_{26}ClF_3N_4S$ (519.02) | 60.17 (60.01) | 5.05 (5.09) | 10.79 (10.75) | 6.18 (6.14) |
| **6k** | 4-$ClC_6H_4$ | 3-$CF_3$ | EtOH | 128–30 | 52 | $C_{26}H_{26}ClF_3N_4S$ (519.02) | 60.17 (59.82) | 5.05 (5.24) | 10.79 (10.65) | 6.18 (6.01) |
| **6l** | 4-$ClC_6H_4$ | 4-$CF_3$ | EtOH | 127–9 | 60 | $C_{26}H_{26}ClF_3N_4S$ (519.02) | 60.17 (59.89) | 5.05 (5.22) | 10.79 (10.50) | 6.18 (6.08) |
| **6m** | 4-$ClC_6H_4$ | 2,6-$F_2$ | EtOH | 172–4 | 63 | $C_{25}H_{25}ClF_2N_4S$ (487.01) | 61.66 (61.67) | 5.17 (5.18) | 11.50 (11.23) | 6.58 (6.52) |
| **6n** | 4-$ClC_6H_4$ | 3,5-$Cl_2$ | EtOH | 200–2 | 92 | $C_{25}H_{25}Cl_3N_4S$ (519.92) | 57.75 (57.38) | 4.85 (4.98) | 10.78 (10.50) | 6.17 (6.17) |
| **6o** | 4-$ClC_6H_4$ | 4-OEt | EtOH | 183–5 | 80 | $C_{27}H_{31}ClN_4OS$ (495.08) | 65.50 (65.33) | 6.31 (6.46) | 11.32 (11.12) | 6.48 (6.45) |
| **7a** | $CH_3$ | $C_6H_5$ | EtOH | 150–2 | 75 | $C_{24}H_{33}N_5S$ (423.62) | 68.05 (67.75) | 7.85 (8.02) | 16.53 (16.50) | 7.57 (7.56) |
| **7b** | $CH_3$ | 2-$CH_3OC_6H_4$ | EtOH | 150–2 | 81 | $C_{25}H_{35}N_5OS$ (453.64) | 66.19 (65.98) | 7.78 (7.90) | 15.44 (15.42) | 7.07 (6.99) |
| **7c** | $CH_3$ | 3-$CF_3C_6H_4$ | EtOH/$H_2O$ | 186–8 | 56 | $C_{25}H_{32}F_3N_5S$ (491.62) | 61.08 (61.20) | 6.56 (6.55) | 14.25 (14.10) | 6.52 (6.45) |
| **7d** | 4-$ClC_6H_4$ | $C_2H_5$ | EtOH/$H_2O$ | 113–5 | 48 | $C_{25}H_{34}ClN_5S$ (472.09) | 63.60 (63.44) | 7.26 (7.48) | 14.83 (14.65) | 6.79 (6.70) |
| **7e** | 4-$ClC_6H_4$ | $C_6H_5$ | EtOH | 206–8 | 85 | $C_{29}H_{34}ClN_5S$ (520.13) | 66.97 (66.68) | 6.59 (6.71) | 13.46 (13.32) | 6.16 (6.11) |
| **7f** | 4-$ClC_6H_4$ | 2-$CH_3OC_6H_4$ | EtOH | 201–3 | 80 | $C_{30}H_{36}ClN_5OS$ (550.16) | 65.49 (65.33) | 6.60 (6.80) | 12.73 (12.65) | 5.83 (5.67) |
| **7g** | 4-$ClC_6H_4$ | $CH_2C_6H_5$ | EtOH/$H_2O$ | 123–5 | 62 | $C_{30}H_{36}ClN_5S$ (534.16) | 67.46 (67.25) | 6.79 (6.90) | 13.11 (13.0) | 6.00 (5.87) |
| **11a** | 2-OH | $C_2H_5$ | EtOH | 165–7 | 38 | $C_{26}H_{36}N_6OS$ (480.67) | 64.97 (65.01) | 7.55 (7.70) | 17.48 (17.30) | 6.67 (6.50) |
| **11b** | 2-OH | $COOC_2H_5$ | EtOH/$H_2O$ | 124–6 | 48 | $C_{27}H_{36}N_6O_3S$ (524.68) | 61.81 (61.65) | 6.92 (7.01) | 16.02 (15.85) | 6.11 (6.10) |
| **11c** | 2-OH | $C_6H_5$ | EtOH | 192–4 | 78 | $C_{30}H_{36}N_6OS$ (528.71) | 68.15 (67.94) | 6.86 (7.10) | 15.90 (15.78) | 6.06 (5.98) |
| **11d** | 2-OH | 2-$CH_3OC_6H_4$ | EtOH | 188–90 | 82 | $C_{31}H_{38}N_6O_2S$ (558.74) | 66.64 (66.55) | 6.86 (6.90) | 15.04 (14.92) | 5.74 (5.74) |
| **11e** | 2-OH | $CH_2C_6H_5$ | EtOH/$H_2O$ | 164–6 | 38 | $C_{31}H_{38}N_6OS$ (542.74) | 68.60 (68.24) | 7.06 (7.22) | 15.48 (15.50) | 5.91 (5.82) |
| **11f** | 4-OH | $C_2H_5$ | EtOH | 163–5 | 44 | $C_{26}H_{36}N_6OS$ (480.67) | 64.97 (64.66) | 7.55 (7.63) | 17.48 (17.22) | 6.67 (6.65) |
| **11g** | 4-OH | $COOC_2H_5$ | EtOH/$H_2O$ | 139–41 | 51 | $C_{27}H_{36}N_6O_3S$ (524.68) | 61.81 (61.43) | 6.92 (7.05) | 16.02 (15.89) | 6.11 (6.10) |
| **11h** | 4-OH | $C_6H_5$ | EtOH/$CHCl_3$ | 200–2 | 85 | $C_{30}H_{36}N_6OS$ (528.71) | 68.15 (68.0) | 6.86 (6.99) | 15.90 (15.76) | 6.06 (6.04) |
| **11i** | 4-OH | 2-$OCH_3C_6H_4$ | EtOH/$CHCl_3$ | 192–4 | 80 | $C_{31}H_{38}N_6O_2S$ (558.74) | 66.64 (66.32) | 6.86 (7.02) | 15.04 (14.87) | 5.74 (5.68) |

activity, the trifluoromethylphenyl and the 2,6-difluorophenyl substituents were optimistic within their 4-(4-chlorophenyl) derivatives. Meanwhile, the 4-bromophenyl, 4-ethoxyphenyl and to a lesser extent the 3,5-dichlorophenyl substituents were not favorable for antimicrobial activity.

The replacement of the 2-arylaminomethyl moiety with a 4-substituted-1-piperazinylmethyl (compounds **7a**–**g**) greatly enhanced the antibacterial activity and in contrary to the arylaminomethyl derivatives **6a**–**o**, the 4-methyl derivatives **7a**–**c** displayed higher antibacterial activity than their 4-(4-chlorophenyl) analogues despite their lower lipophilicity. In addition, the antibacterial activity of the 4-phenylpiperazin-1-yl, 4-(2-methoxyphenyl)piperazin-1-yl and 4-(3-trifluormethylphenyl)piperazin-1-yl derivatives were superior to their 4-ethylpiperazin-1-yl and 4-benzylpiperazin-1-yl analogues. In addition, the 3-trifluormethylphenyl analogue **7c** displayed broad spectrum antibacterial activity against the tested Gram-positive and Gram-negative bacteria.

The replacement of the methyl or 4-chlorophenyl substituents in compounds **7a**–**g** with 2- or 4-hydroxybenzylideneamino substituents (compounds **11a**–**i**) greatly enhanced the antibacterial activity. It was observed that neither the position of the phenolic OH group nor the lipophilicity of the compounds has influence on the antibacterial activity. Although derivatives **11a**–**i** showed moderate to good level of activity, a 4-ethoxycarbonylpiperazin-1-yl substituent is detrimental for antibacterial activity of this class of compounds.

## 3. Conclusion

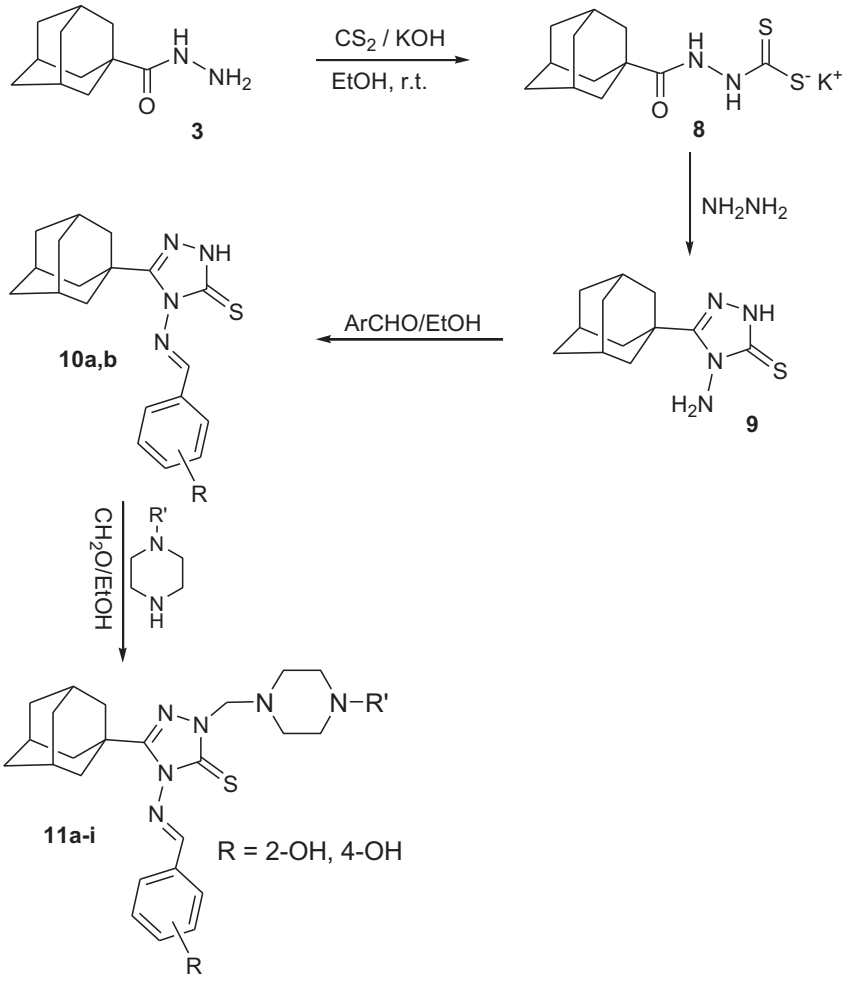
In this study, new *N*-Mannich bases of 5-(1-adamantyl)-4-substituted-1,2,4-triazoline-3-thiones were synthesized and their antimicrobial activity was determined. The newly synthesized compounds **6j**, **6l**, **6m**, **7a**, **7b**, **7c**, **7d**, **7f**, **11a**, **11b**, **11c**, **11d**, **11e**, **11f**, **11h** and **11i** displayed promising antibacterial activity compared to known antibacterial drugs. Though, the active compounds are considered as good candidates for newer antibacterial agents. The mechanism of the biological activity needs further investigations, which are in progress.

## 4. Experimental protocols

Melting points (°C) were measured in open glass capillaries using a Branstead 9001 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 Hertz. 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. Monitoring the reactions and checking the purity of the final products were carried out by thin layer chromatography (TLC) using silica gel precoated aluminium sheets (60 $F_{254}$, Merck) and visualization with ultraviolet light (UV) at 365 and 254 nm. 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) and Clotrimazole (CAS 23593-75-1) were obtained from Sigma–Aldrich Chemie GmbH, Taufkirchen, Germany.

### *4.1. 5-(1-Adamantyl)-2-arylaminomethyl-4-(methyl or 4-chlorophenyl)-1,2,4-triazoline-3-thiones (**6a**–**o**)*

A mixture of **5a** or **5b** (1.0 mmol), the appropriate primary aromatic amine (1.0 mmol) and 37% formaldehyde solution (1 mL), in ethanol (8 mL), was heated under reflux for 15 min when a clear




**Scheme 2.** Synthesis of compounds **11a–i**.

solution was obtained. Stirring was continued for 12 h at room temperature and the mixture was allowed to stand overnight. Cold water (5 mL) was added and the reaction mixture was stirred for 20 min. The precipitated crude products were filtered, washed with water, dried, and recrystallized from ethanol. **6a**: $^1$H NMR ($CDCl_3$): $\delta$ 1.67–1.78 (m, 6H, Adamantane–H), 2.04–2.25 (m, 9H, Adamantane–H), 3.79 (s, 3H, $CH_3$), 5.89 (s, 1H, NH), 6.18 (s, 2H, $CH_2$), 6.78–6.96 (m, 3H, Ar–H), 7.20 (t, 2H, Ar–H, $J$ = 7.0 Hz). $^{13}$C NMR: $\delta$ 27.82, 33.62, 35.16, 38.93 (Adamantane–C), 33.50 ($CH_3$), 65.0 ($CH_2$), 114.25, 119.11, 129.21, 145.04 (Ar–C), 156.71 (Triazole C-5), 167.95 (C=S). ESI-MS, $m/z$ (Rel. Int.): 355.2 (M + H, 100)$^+$. **6b**: $^1$H NMR ($CDCl_3$): $\delta$ 1.75–1.83 (m, 6H, Adamantane–H), 2.05 (s, 6H, Adamantane–H), 2.18 (s, 3H, Adamantane–H), 3.79 (s, 3H, $CH_3$), 5.74 (s, 1H, NH), 6.12 (s, 2H, $CH_2$), 6.96–7.09 (m, 4H, Ar–H). $^{13}$C NMR: $\delta$ 27.80, 33.65, 36.28, 38.93 (Adamantane–C), 33.50 ($CH_3$), 65.37 ($CH_2$), 115.52, 115.71, 140.0, 156.50 (Ar–C), 156.79 (Triazole C-5), 168.0 (C=S). ESI-MS, $m/z$ (Rel. Int.): 373.2 (M + H, 100)$^+$. **6c**: $^1$H NMR ($CDCl_3$): $\delta$ 1.75–1.83 (m, 6H, Adamantane–H), 2.04 (s, 6H, Adamantane–H), 2.12 (s, 3H, Adamantane–H), 3.77 (s, 3H, $CH_3$), 5.76 (s, 1H, NH), 6.12 (s, 2H, $CH_2$), 7.26 (d, 2H, Ar–H, $J$ = 7.5 Hz), 7.40 (d, 2H, Ar–H, $J$ = 7.5 Hz). $^{13}$C NMR: $\delta$ 27.80, 33.69, 35.78, 38.91 (Adamantane–C), 33.69 ($CH_3$), 64.98 ($CH_2$), 112.24, 116.74, 131.79, 145.62 (Ar–C), 156.82 (Triazole C-5), 168.14 (C=S). ESI-MS, $m/z$ (Rel. Int.): 434.1 (M + H + 2, 98)$^+$, 432.1 (M + H, 100)$^+$. **6d**: $^1$H NMR ($CDCl_3$): $\delta$ 1.54 (t, 3H, $CH_2C\boldsymbol{H}_3$, $J$ = 7.5 Hz), 1.75–1.84 (m, 6H, Adamantane–H), 2.05 (s, 6H, Adamantane–H), 2.17 (s, 3H, Adamantane–H), 3.81 (s, 3H, $CH_3$), 4.07 (q, 2H, $C\boldsymbol{H}_2CH_3$, $J$ = 7.5 Hz), 5.73 (s, 1H, NH), 6.11 (s, 2H, $CH_2$), 6.78 (d, 2H, Ar–H, $J$ = 7.0 Hz), 6.89 (d, 2H, Ar–H, $J$ = 7.0 Hz). $^{13}$C NMR: $\delta$ 15.17 ($CH_2\boldsymbol{C}H_3$), 27.83, 33.70, 35.20, 38.94 (Adamantane–C), 33.60 ($CH_3$), 63.80 ($\boldsymbol{C}H_2CH_3$), 64.49 ($CH_2$), 115.37, 116.71, 139.15, 141.06 (Ar–C), 156.63 (Triazole C-5), 167.88 (C=S). ESI-MS, $m/z$ (Rel. Int.): 399.1 (M + H, 100)$^+$. **6e**: $^1$H NMR ($CDCl_3$): $\delta$ 1.68–1.70 (m, 6H, Adamantane–H), 1.86 (s, 6H, Adamantane–H), 1.97 (s, 3H, Adamantane–H), 5.83 (s, 1H, NH), 6.27 (s, 2H, $CH_2$), 6.75–6.86 (m, 2H, Ar–H), 7.19–7.41 (m, 5H, Ar–H), 7.54–7.64 (m, 2H, Ar–H). $^{13}$C NMR: $\delta$ 27.72, 33.62, 36.06, 39.88 (Adamantane–C), 65.14 ($CH_2$), 114.41, 114.93, 129.19, 129.93, 131.13, 134.80, 136.30, 146.51 (Ar–C), 156.89 (Triazole C-5), 169.62 (C=S). ESI-MS, $m/z$ (Rel. Int.): 453.1 (M + H + 2, 29)$^+$, 451.1 (M + H, 100)$^+$. **6f**: $^1$H NMR ($CDCl_3$): $\delta$ 1.74–1.86 (m, 9H, Adamantane–H), 1.96 (s, 6H, Adamantane–H), 6.02 (s, 1H, NH), 6.24 (s, 2H, $CH_2$), 6.94–7.24 (m, 5H, Ar–H), 7.36–7.56 (m, 3H, Ar–H). $^{13}$C NMR: $\delta$ 27.76, 36.46, 39.22, 39.82 (Adamantane–C), 68.42 ($CH_2$), 115.28, 115.90, 117.28, 125.30, 128.24, 129.95, 131.0, 132.22, 134.20, 155.82 (Ar–H), 157.22 (Triazole C-5), 170.10 (C=S). ESI-MS, $m/z$ (Rel. Int.): 471.2 (M + H + 2, 29)$^+$, 469.2 (M + H, 100)$^+$. **6g**: $^1$H NMR ($CDCl_3$): $\delta$ 1.82–1.85 (m, 9H, Adamantane–H), 1.97 (s, 6H, Adamantane–H), 5.82 (s, 1H, NH), 6.21 (s, 2H, $CH_2$), 6.94–7.05 (m, 3H, Ar–H), 7.21–7.25 (m, 2H, Ar–H), 7.54–7.56 (m, 3H, Ar–H). $^{13}$C NMR: $\delta$ 27.70, 36.04, 39.84, 39.88 (Adamantane–C), 65.47 ($CH_2$), 115.79, 116.53, 129.95, 131.09, 134.75, 136.34, 143.0, 156.84 (Ar–H), 157.0 (Triazole C-5), 169.69 (C=S). ESI-MS, $m/z$ (Rel. Int.): 471.2 (M + H + 2, 34)$^+$, 469.2 (M + H, 100)$^+$. **6h**: $^1$H NMR ($CDCl_3$): $\delta$ 1.83–1.87 (m, 9H, Adamantane–H), 1.97 (s, 6H, Adamantane–H), 5.64–5.67 (m, 3H, $CH_2$ & NH), 6.76 (t,

**Table 2**
Antimicrobial activity of compounds **6a**–**o**, **7a**–**g** and **11a**–**i** (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 *Staphylococcus aureus* IFO 3060 (*SA*), *Bacillus subtilis* IFO 3007 (*BS*), *Micrococcus luteus* IFO 3232 (ML), *Escherichia coli* IFO 3301 (*EC*), *Pseudomonas aeuroginosa* IFO 3448 (*PA*), and *Candida albicans* IFO 0583 (*CA*).

| Comp. no. | Clog *P* | Diameter of growth inhibition zone (mm)[a] | | | | | |
|---|---|---|---|---|---|---|---|
| | | *SA* | *BS* | *ML* | *EC* | *PA* | *CA* |
| **6a** | 4.88 | – | 12 | – | – | – | – |
| **6b** | 5.33 | 12 | 12 | – | – | – | – |
| **6c** | 6.05 | – | – | – | – | – | – |
| **6d** | 5.51 | – | – | – | – | – | – |
| **6e** | 7.65 | – | – | – | – | – | – |
| **6f** | 8.09 | 11 | 12 | 12 | – | – | – |
| **6g** | 8.09 | 14 | 16 | 12 | – | – | – |
| **6h** | 8.66 | 16 | 11 | – | – | – | – |
| **6i** | 8.81 | – | – | – | – | – | – |
| **6j** | 9.06 | 17 | 19 (16)[b] | 14 | 12 | 11 | – |
| **6k** | 9.06 | 16 | 16 | 17 | – | – | – |
| **6l** | 9.06 | 16 | 22 (8)[b] | 18 (16)[b] | 14 | 11 | – |
| **6m** | 8.34 | 18 | 20 (8)[b] | 17 | 14 | 11 | 13 |
| **6n** | 9.48 | 12 | 13 | 11 | – | – | – |
| **6o** | 8.28 | – | – | – | – | – | – |
| **7a** | 5.14 | 19 (8)[b] | 18 (16)[b] | 14 | – | – | – |
| **7b** | 5.05 | 22 (4)[b] | 20 (4)[b] | 19 (16)[b] | 11 | – | – |
| **7c** | 6.32 | 30 (0.5)[b] | 33 (0.5)[b] | 28 (4)[b] | 19 (16)[b] | 21 (8)[b] | – |
| **7d** | 6.20 | 14 | 18 (8)[b] | 15 | – | – | – |
| **7e** | 7.91 | 16 | 17 | 14 | – | – | – |
| **7f** | 7.82 | 18 (16)[b] | 18 (16)[b] | 16 | – | – | – |
| **7g** | 8.83 | 11 | 12 | 11 | – | – | – |
| **11a** | 4.97 | 26 (1)[b] | 30 (0.5)[b] | 24 (2)[b] | 16 | 11 | – |
| **11b** | 6.51 | 18 (4)[b] | 19 (4)[b] | 16 | – | – | – |
| **11c** | 6.67 | 22 (8)[b] | 25 (4)[b] | 18 (16)[b] | 14 | 12 | – |
| **11d** | 6.58 | 28 (0.5)[b] | 33 (0.5)[b] | 25 (2)[b] | 18 (8)[b] | 12 | – |
| **11e** | 7.59 | 19 (2)[b] | 21 (2)[b] | 17 | 11 | 11 | – |
| **11f** | 4.97 | 30 (1)[b] | 29 (1)[b] | 25 (2)[b] | 17 | 13 | – |
| **11g** | 6.51 | 17 | 16 | 14 | – | – | – |
| **11h** | 6.67 | 22 (4)[b] | 22 (4)[b] | 19 (16)[b] | 16 | – | – |
| **11i** | 6.58 | 30 (1)[b] | 29 (1)[b] | 18 (16)[b] | 16 | 14 | – |
| **Gentamicin** | | 26 (2)[b] | 25 (2)[b] | 18 (2)[b] | 20 (0.5)[b] | 19 (1)[b] | NT |
| **Ampicillin** | | 23 (2)[b] | 21 (0.5)[b] | 19 (2)[b] | 17 (2)[b] | 16 (2)[b] | NT |
| **Clotrimazole** | | 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).

1H, Ar–H, $J$ = 7.0 Hz), 7.21–7.24 (m, 3H, Ar–H), 7.29–7.31 (m, 1H, Ar–H), 7.37–7.44 (m, 1H, Ar–H), 7.47–7.54 (m, 2H, Ar–H). $^{13}$C NMR: δ 27.71, 36.04, 39.88, 39.90 (Adamantane–C), 67.78 ($CH_2$), 113.50, 119.37, 120.17, 127.82, 129.38, 129.92, 131.03, 134.70, 136.32, 141.43 (Ar–H), 156.680 (Triazole C-5), 169.65 (C=S). ESI-MS, *m*/*z* (Rel. Int.): 487.2 (M + H + 2, 71)$^+$, 485.2 ($M^+$, 100). **6i**: $^1$H NMR ($CDCl_3$): δ 1.77–1.85 (m, 9H, Adamantane–H), 1.97 (s, 6H, Adamantane–H), 5.85 (s, 1H, NH), 6.22 (s, 2H, $CH_2$), 7.21–7.25 (m, 4H, Ar–H), 7.51–7.56 (m, 4H, Ar–H). $^{13}$C NMR: δ 27.70, 36.03, 39.83, 39.87 (Adamantane–C), 65.15 ($CH_2$), 116.32, 116.77, 129.96, 131.08, 131.89, 134.72, 136.37, 145.58 (Ar–C), 157.03 (Triazole C-5), 169.79 (C=S). ESI-MS, *m*/*z* (Rel. Int.): 533.1 (M + H + 2, 28)$^+$, 531.1 (M + H, 100)$^+$. **6j**: $^1$H NMR ($CDCl_3$): δ 1.73–1.77 (m, 9H, Adamantane–H), 1.86–1.94 (m, 6H, Adamantane–H), 5.54–5.62 (m, 3H, $CH_2$ & NH), 6.78–6.81 (m, 1H, Ar–H), 6.95–7.14 (m, 3H, Ar–H), 7.32–7.47 (m, 4H, Ar–H). $^{13}$C NMR: δ 27.69, 29.71, 36.03, 39.88 (Adamantane–C), 57.71 ($CH_2$), 114.28, 115.20, 118.32, 125.88, 126.68, 129.93, 131.0, 133.22, 134.64, 136.34, 143.08 (Ar–C & $CF_3$), 156.84 (Triazole C-5), 169.77 (C=S). ESI-MS, *m*/*z* (Rel. Int.): 521.2 (M + H + 2, 33)$^+$, 519.2 (M + H, 100)$^+$. **6k**: $^1$H NMR ($CDCl_3$): δ 1.67–1.70 (m, 3H, Adamantane–H), 1.78–1.83 (m, 6H, Adamantane–H), 1.95–1.97 (m, 6H, Adamantane–H), 5.64–5.84 (m, 3H, $CH_2$ & NH), 6.77–6.79 (m, 1H, Ar–H), 7.01–7.19 (s, 3H, Ar–H), 7.20 (d, 2H, Ar–H, $J$ = 8.5 Hz), 7.53 (d, 2H, Ar–H, $J$ = 8.5 Hz). $^{13}$C NMR: δ 27.71, 28.98, 36.04, 39.90 (Adamantane–C), 57.86 ($CH_2$), 114.36, 114.75, 114.75, 118.88, 129.71, 131.01, 133.55, 134.70, 136.14, 150.87, 152.78 (Ar–C & $CF_3$), 156.66 (Triazole C-5), 169.61 (C=S). ESI-MS, *m*/*z* (Rel. Int.): 521.2 (M + H + 2, 30)$^+$, 519.2 (M + H, 100)$^+$. **6l**: $^1$H NMR ($CDCl_3$): δ 1.77–1.86 (m, 9H, Adamantane–H), 1.97 (s, 6H, Adamantane–H), 5.84 (s, 2H, $CH_2$), 6.24 (s, 1H, NH), 7.21–7.25 (m, 4H, Ar–H), 7.55–7.65 (m, 4H, Ar–H), $^{13}$C NMR: δ 27.68, 36.02, 36.09, 39.86 (Adamantane–C), 64.94 ($CH_2$), 114.14, 114.42, 126.44, 129.98, 131.06, 134.67, 136.42, 147.91, 149.06 (Ar–C & $CF_3$), 157.16 (Triazole C-5), 169.92 (C=S). ESI-MS, *m*/*z* (Rel. Int.): 521.2 (M + H + 2, 38)$^+$, 519.2 (M + H, 100)$^+$. **6m**: $^1$H NMR ($CDCl_3$): δ 1.66–1.82 (m, 9H, Adamantane–H), 1.87–2.04 (m, 6H, Adamantane–H), 5.72 (s, 2H, $CH_2$), 5.80 (s, 1H, NH), 6.71–6.91 (m, 2H, Ar–H), 7.17–7.35 (m, 3H, Ar–H), 7.49–7.68 (m, 2H, Ar–H). $^{13}$C NMR: δ 27.73, 35.81, 36.02, 39.81 (Adamantane–C), 66.38 ($CH_2$), 111.91, 121.0, 129.90, 130.95, 131.14, 135.16, 136.12, 156.65 (Ar–C), 156.11 (Triazole C-5), 169.65 (C=S). ESI-MS, *m*/*z* (Rel. Int.): 489.2 (M + H + 2, 37)$^+$, 487.2 (M + H, 100)$^+$. **6n**: $^1$H NMR ($CDCl_3$): δ 1.68–1.87 (m, 9H, Adamantane–H), 1.98–2.04 (m, 6H, Adamantane–H), 5.75 (s, 2H, $CH_2$), 6.21 (s, 1H, NH), 6.87–6.99 (m, 1H, Ar–H), 7.20–7.29 (m, 4H, Ar–H), 7.54–7.56 (m, 2H, Ar–H). $^{13}$C NMR: δ 27.71, 36.04, 39.84, 39.89 (Adamantane–C), 65.51 ($CH_2$), 113.73, 119.75, 129.98, 131.03, 135.25, 136.38, 147.17, 148.63 (Ar–C), 156.89 (Triazole C-5), 170.20 (C=S). ESI-MS, *m*/*z* (Rel. Int.): 523.1 (M + H + 4, 34)$^+$, 521.1 (M + H + 2, 89)$^+$, 519.1 (M + H, 100)$^+$. **6o**: $^1$H NMR ($CDCl_3$): δ 1.42 (t, 3H, $CH_2C\boldsymbol{H}_3$, $J$ = 7.5 Hz), 1.80–1.84 (m, 9H, Adamantane–H), 1.95 (s, 6H, Adamantane–H), 4.0 (q, 2H, $C\boldsymbol{H}_2CH_3$, $J$ = 7.5 Hz), 5.77 (s, 1H, NH), 6.19 (s, 2H, $CH_2$), 6.81–7.05 (m, 2H, Ar–H), 7.20–7.32 (m, 3H, Ar–H), 7.52–7.55 (m, 3H, Ar–H). $^{13}$C NMR: δ 14.99 ($CH_2\boldsymbol{C}H_3$), 27.71, 35.92, 36.02, 39.84 (Adamantane–C), 63.87 ($\boldsymbol{C}H_2CH_3$), 65.80 ($CH_2$), 115.39, 115.88, 116.71, 129.90, 131.14, 134.38, 134.88, 152.86 (Ar–C), 157.05 (Triazole C-5), 169.52 (C=S). ESI-MS, *m*/*z* (Rel. Int.): 497.2 (M + H + 2, 30)$^+$, 495.2 (M + H, 100)$^+$.

### 4.2. 5-(1-Adamantyl)-4-(methyl or 4-chlorophenyl)-2-(4-substituted-1-piperazinylmethyl)-1,2,4-triazoline-3-thiones (**7a**–**g**)

A mixture of **5a** or **5b** (1.0 mmol), the appropriate *N*-substituted piperazine (1.0 mmol) and 37% formaldehyde solution (1.0 mL), in ethanol (8 mL), was heated under reflux for 15 min when a clear solution was obtained. Stirring was continued for 12 h at room temperature and the mixture was allowed to stand overnight. Cold water (5 mL) was added and the reaction mixture was stirred for 20 min. The precipitated crude products were filtered, washed with water, dried, and recrystallized from ethanol or aqueous ethanol. **7a** [31]: $^1$H NMR ($CDCl_3$): δ 1.77–1.84 (m, 6H, Adamantane–H), 2.14 (s, 6H, Adamantane–H), 2.27 (s, 3H, Adamantane–H), 3.05 (s, 4H, Piperazine–H), 3.27 (s, 4H, Piperazine–H), 3.82 (s, 3H, $CH_3$), 5.20 (s, 2H, $CH_2$), 6.85–6.93 (m, 3H, Ar–H), 7.25–7.33 (m, 2H, Ar–H). $^{13}$C NMR: δ 27.84, 33.97, 36.31, 39.02 (Adamantane–C), 31.58 ($CH_3$), 49.34, 50.40 (Piperazine–C), 69.23 ($CH_2$), 116.27, 119.86, 129.10, 151.33 (Ar–C), 156.31 (Triazole C-5), 169.53 (C=S). ESI-MS, *m*/*z* (Rel. Int.): 424.2 (M + H, 100)$^+$. **7b** [32]: $^1$H NMR ($CDCl_3$): δ 1.52–1.71 (m, 6H, Adamantane–H), 2.0 (s, 6H, Adamantane–H), 2.04 (s, 3H, Adamantane–H), 3.03–3.07 (m, 8H, Piperazine–H), 3.71 (s, 3H, $CH_3$), 3.85 (s, 3H, $OCH_3$), 5.27 (s, 2H, $CH_2$), 6.76–6.77 (m, 1H, Ar–H), 6.84–6.92 (m, 3H, Ar–H). $^{13}$C NMR: δ 27.85, 35.07, 36.33, 38.96 (Adamantane–C), 33.95 ($CH_3$), 50.55, 50.79 (Piperazine–C), 55.23 ($OCH_3$), 69.40 ($CH_2$), 110.90, 118.24, 120.91, 123.03, 141.24, 152.17 (Ar–C), 156.20 (Triazole C-5), 169.50 (C=S). ESI-MS, *m*/*z* (Rel. Int.): 454.2 (M + H, 100)$^+$. **7c**: $^1$H NMR ($CDCl_3$): δ 1.76–1.84 (m, 6H, Adamantane–H), 2.07 (s, 6H, Adamantane–H), 2.13 (s, 3H, Adamantane–H), 2.98 (s, 4H, Piperazine–H), 3.24 (s, 4H, Piperazine–H), 3.80 (s, 3H, $CH_3$), 5.19 (s, 2H, $CH_2$), 7.03–7.10 (m, 3H, Ar–H), 7.32–7.35 (m, 1H, Ar–H). $^{13}$C NMR: δ 27.82, 35.10, 36.29, 39.02 (Adamantane–C), 33.98 ($CH_3$), 48.79, 50.21 (Piperazine–C), 69.15 ($CH_2$), 112.33, 115.89, 118.83, 123.21,

125.38, 129.54, 151.38 (Ar–C & $CF_3$), 156.38 (Triazole C-5), 169.58 (C=S). ESI-MS, *m/z* (Rel. Int.): 492.2 $(M + H, 100)^+$. **7d**: $^1$H NMR ($CDCl_3$): $\delta$ 1.16 (t, 3H, $CH_3$, $J = 7.0$ Hz), $\delta$ 1.76–1.88 (m, 6H, Adamantane–H), 2.07 (s, 6H, Adamantane–H), 2.02 (s, 3H, Adamantane–H), 2.50 (q, 2H, C***H***$_2$CH$_3$, $J = 7.0$ Hz), 2.68–3.02 (m, 8H, Piperazine–H), 5.10 (s, 2H, $CH_2$), 6.88 (d, 2H, Ar–H, $J = 8.0$ Hz), 7.34 (d, 2H, Ar–H, $J = 8.0$ Hz). $^{13}$C NMR: $\delta$ 12.10 ($CH_3$), 27.87, 34.69, 36.50, 38.09 (Adamantane–C), 49.44 (***C***H$_2$CH$_3$), 54.30, 56.36 (Piperazine–C), 68.06 ($CH_2$), 119.52, 128.40, 130.88, 133.0 (Ar–C), 156.04 (Triazole C-5), 165.66 (C=S). ESI-MS, *m/z* (Rel. Int.): 474.3 $(M + H + 2, 38)^+$, 472.3 $(M + H, 100)^+$. **7e**: $^1$H NMR ($CDCl_3$): $\delta$ 1.76–1.84 (m, 6H, Adamantane–H), 2.04 (s, 6H, Adamantane–H), 2.22 (s, 3H, Adamantane–H), 2.98 (s, 4H, Piperazine–H), 3.02 (s, 4H, Piperazine–H), 5.22 (s, 3H, $CH_2$), 6.75–6.89 (m, 4H, Ar–H), 6.90–7.02 (m, 3H, Ar–H), 7.36 (d, 2H, Ar–H, $J = 7.5$ Hz). $^{13}$C NMR: $\delta$ 27.66, 33.56, 35.32, 38.82 (Adamantane–C), 50.22, 50.68 (Piperazine–C), 69.80 ($CH_2$), 113.92, 117.80, 127.50, 129.30, 129.92, 131.08, 133.90, 150.20 (Ar–C), 157.01 (Triazole C-5), 170.25 (C=S). ESI-MS, *m/z* (Rel. Int.): 522.3 $(M + H + 2, 39)^+$, 520.3 $(M + H, 100)^+$. **7f**: $^1$H NMR ($CDCl_3$): $\delta$ 1.57–1.70 (m, 6H, Adamantane–H), 1.87 (s, 6H, Adamantane–H), 1.97 (s, 3H, Adamantane–H), 3.12 (s, 8H, Piperazine–H), 3.88 (s, 3H, $OCH_3$), 5.26 (s, 2H, $CH_2$), 6.65–7.03 (m, 4H, Ar–H), 7.22–7.29 (m, 2H, Ar–H), 7.54–7.56 (m, 2H, Ar–H). $^{13}$C NMR: $\delta$ 27.75, 35.88, 36.09, 38.92 (Adamantane–C), 50.58, 50.85 (Piperazine–C), 55.25 ($OCH_3$), 69.63 ($CH_2$), 110.22, 118.27, 120.94, 123.18, 129.90, 130.88, 131.11, 135.22, 136.20, 141.16 (Ar–C), 152.14 (Triazole C-5), 171.20 (C=S). ESI-MS, *m/z* (Rel. Int.): 552.3 $(M + H + 2, 34)^+$, 550.3 $(M + H, 100)^+$. **7g**: $^1$H NMR ($CDCl_3$): $\delta$ 1.70–1.77 (m, 6H, Adamantane–H), 1.98 (s, 6H, Adamantane–H), 2.02 (s, 3H, Adamantane–H), 2.88 (s, 4H, Piperazine–H), 2.98 (s, 4H, Piperazine–H), 3.56 (s, 2H, PhC***H***$_2$), 5.04 (s, 2H, $CH_2$), 6.88–7.42 (m, 5H, Ar–H), 7.56–7.68 (m, 4H, Ar–H). $^{13}$C NMR: $\delta$ 27.88, 35.68, 35.02, 38.98 (Adamantane–C), 48.90, 52.05 (Piperazine–C), 61.98 (Ph***C***H$_2$), 70.88 ($CH_2$), 126.80, 127.32, 127.98, 129.22, 129.89, 130.20, 132.02, 136.02 (Ar–C), 153.04 (Triazole C-5), 171.28 (C=S). ESI-MS, *m/z* (Rel. Int.): 536.2 $(M + H + 2, 33)^+$, 534.2 $(M + H, 100)^+$.

### 4.3. 5-(1-Adamantyl)-4-[E-(2- or 4-hydroxybenzylideneamino)]-2-(4-substituted-1-piperazinylmethyl)-1,2,4-triazoline-3-thiones (***11a–i***)

A mixture of **10a** or **10b** (1.0 mmol), the appropriate *N*-substituted piperazine (1.0 mmol) and 37% formaldehyde solution (1 mL), in ethanol (8 mL), was heated under reflux for 15 min when a clear solution was obtained. Stirring was continued for 12 h at room temperature and the mixture was allowed to stand overnight. Cold water (5 mL) was added and the reaction mixture was stirred for 20 min. The precipitated crude products were filtered, washed with water, dried, and recrystallized from ethanol or aqueous ethanol. **11a**: $^1$H NMR (DMSO-$d_6$): $\delta$ 0.95 (t, 3H, $CH_3$, $J = 7.0$ Hz), 1.70–1.72 (m, 6H, Adamantane–H), 2.03 (s, 3H, Adamantane–H), 2.09 (s, 6H, Adamantane–H), 2.32–2.38 (m, 6H, Piperazine–H & C***H***$_2$CH$_3$), 2.72–2.75 (m, 4H, Piperazine–H), 5.05 (s, 2H, $CH_2$), 6.98–7.03 (m, 2H, Ar–H), 7.44–7.47 (m, 1H, Ar–H), 7.92–7.94 (m, 1H, Ar–H), 9.85 (s, 1H, CH=N), 10.50 (br. s, 1H, OH). $^{13}$C NMR: $\delta$ 11.78 ($CH_3$), 27.19, 34.72, 35.93, 38.11 (Adamantane–C), 49.77 (***C***H$_2$CH$_3$), 51.54, 52.15 (Piperazine–C), 68.54 ($CH_2$), 116.77, 118.28, 119.78, 126.64, 134.44, 158.58 (Ar–C), 154.18 (Triazole C-5), 162.0 (C=S), 162.80 (CH=N). ESI-MS, *m/z* (Rel. Int.): 504.1 $(M + H + Na, 100)^+$, 481.1 $(M + H, 14)^+$. **11b**: $^1$H NMR (DMSO-$d_6$): $\delta$ 1.14 (t, 3H, $CH_3$, $J = 7.0$ Hz), 1.69–1.70 (m, 6H, Adamantane–H), 2.02 (s, 3H, Adamantane–H), 2.08 (s, 6H, Adamantane–H), 2.69 (s, 4H, Piperazine–H), 3.36 (s, 4H, Piperazine–H), 3.99 (q, 2H, C***H***$_2$CH$_3$, $J = 7.0$ Hz), 5.09 (s, 2H, $CH_2$), 6.97–7.03 (m, 2H, Ar–H), 7.43–7.47 (m, 1H, Ar–H), 7.92 (d, 1H, Ar–H, $J = 6.5$ Hz), 9.85 (s, 1H, CH=N), 10.50 (br. s, 1H, OH). $^{13}$C NMR: $\delta$ 14.48 ($CH_3$), 27.18, 34.71, 35.92, 38.06 (Adamantane–C), 49.76, 56.0 (Piperazine–C), 60.66 (***C***H$_2$CH$_3$), 68.63 ($CH_2$), 116.76, 118.27, 119.77, 126.64, 134.43, 158.57 (Ar–C), 154.50 (Triazole C-5), 154.29 (C=O), 162.05 (C=S), 162.86 (CH=N). ESI-MS, *m/z* (Rel. Int.): 548.3 $(M + H + Na, 100)$, 525.3 $(M + H, 6)^+$. **11c**: $^1$H NMR (DMSO-$d_6$): $\delta$ 1.69–1.70 (m, 6H, Adamantane–H), 2.02 (s, 3H, Adamantane–H), 2.08 (s, 6H, Adamantane–H), 2.51 (s, 4H, Piperazine–H), 3.13 (s, 4H, Piperazine–H), 5.14 (s, 2H, $CH_2$), 6.75–6.78 (m, 1H, Ar–H), 6.91–7.03 (m, 5H, Ar–H & OH), 7.18–7.21 (m, 2H, Ar–H), 7.44–7.46 (m, 1H, Ar–H), 7.93–7.95 (m, 1H, Ar–H), 9.86 (s, 1H, CH=N). $^{13}$C NMR: $\delta$ 27.10, 34.72, 35.91, 38.08 (Adamantane–C), 48.24, 49.87 (Piperazine–C), 68.48 ($CH_2$), 115.53, 116.77, 118.27, 118.90, 119.81, 126.64, 128.84, 134.48, 150.96, 162.04 (Ar–C), 154.28 (Triazole C-5), 158.58 (C=S), 162.85 (CH=N). ESI-MS, *m/z* (Rel. Int.): 552.3 $(M + H + Na, 100)^+$, 529.2 $(M + H, 11)^+$. **11d**: $^1$H NMR ($CDCl_3$): $\delta$ 1.79 (s, 6H, Adamantane–H), 2.13 (s, 9H, Adamantane–H), 3.11 (s, 8H, Piperazine–H), 3.88 (s, 3H, $OCH_3$), 5.26 (s, 2H, $CH_2$), 6.87–6.89 (m, 1H, Ar–H), 6.95–7.11 (m, 5H, Ar–H), 7.45–7.51 (m, 2H, Ar–H), 9.64 (s, 1H, CH=N), 10.48 (s, 1H, OH). $^{13}$C NMR: $\delta$ 27.79, 35.34, 36.30, 38.87 (Adamantane–C), 50.66, 50.82 (Piperazine–C), 55.28 ($OCH_3$), 69.76 ($CH_2$), 110.91, 116.09, 117.56, 118.29, 120.12, 120.94, 123.15, 133.65, 134.67, 141.18, 152.19, 160.11 (Ar–C), 154.29 (Triazole C-5), 164.16 (C=S), 169.37 (CH=N). ESI-MS, *m/z* (Rel. Int.): 582.5 $(M + H + Na, 100)^+$, 559.4 $(M + H, 6)^+$. **11e** [34]: $^1$H NMR (DMSO-$d_6$): $\delta$ 1.71 (br. s, 6H, Adamantane–H), 2.04 (s, 3H, Adamantane–H), 2.09 (s, 6H, Adamantane–H), 2.37 (br. s, 4H, Piperazine–H), 2.72 (s, 4H, Piperazine–H), 3.49 (s, 2H, PhC***H***$_2$), 5.16 (s, 2H, $CH_2$), 6.98–7.03 (m, 2H, Ar–H), 7.23–7.32 (m, 5H, Ar–H), 7.44–7.47 (m, 2H, Ar–H), 9.85 (s, 1H, CH=N), 10.50 (br. s, 1H, OH). $^{13}$C NMR: $\delta$ 27.18, 34.73, 35.92, 38.10 (Adamantane–C), 49.93, 52.47 (Piperazine–C), 62.08 (Ph***C***H$_2$), 68.69 ($CH_2$), 116.77, 118.28, 119.80, 126.68, 126.85, 128.09, 128.82, 134.44, 138.01, 158.56 (Ar–C), 154.20 (Triazole C-5), 162.01 (C=S), 162.85 (CH=N). ESI-MS, *m/z* (Rel. Int.): 566.5 $(M + H + Na, 19)^+$, 543.5 $(M + H, 100)^+$. **11f** [35]: $^1$H NMR ($CDCl_3$): $\delta$ 1.18 (t, 3H, $CH_3$, $J = 6.5$ Hz), 1.69–1.76 (m, 6H, Adamantane–H), 1.95 (s, 6H, Adamantane–H), 2.03 (s, 3H, Adamantane–H), 2.56 (q, 2H, C***H***$_2$CH$_3$, $J = 6.5$ Hz), 2.85–3.90 (m, 8H, Piperazine–H), 5.18 (s, 2H, $CH_2$), 6.75 (d, 2H, Ar–H, $J = 8.0$ Hz), 7.67 (d, 2H, Ar–H, $J = 8.0$ Hz), 9.21 (s, 1H, CH=N). $^{13}$C NMR: $\delta$ 11.11 ($CH_3$), 27.84, 35.09, 36.48, 38.39 (Adamantane–C), 49.50 (***C***H$_2$CH$_3$), 52.29, 58.43 (Piperazine–C), 68.56 ($CH_2$), 116.53, 123.49, 130.87, 161.53 (Ar–C), 154.94 (Triazole C-5), 163.34 (C=S), 164.65 (CH=N). ESI-MS, *m/z* (Rel. Int.): 504.1 $(M + H + Na, 100)^+$, 481.1 $(M + H, 5)^+$. **11g**: $^1$H NMR ($CDCl_3$): $\delta$ 1.26 (t, 3H, $CH_3$, $J = 7.0$ Hz), 1.77 (s, 6H, Adamantane–H), 2.08 (s, 6H, Adamantane–H), 2.14 (s, 3H, Adamantane–H), 2.84 (s, 4H, Piperazine–H), 3.53 (s, 4H, Piperazine–H), 4.15 (q, 2H, C***H***$_2$CH$_3$, $J = 7.0$ Hz), 5.18 (s, 2H, $CH_2$), 6.96 (d, 2H, Ar–H, $J = 8.0$ Hz), 7.75 (d, 2H, Ar–H, $J = 8.0$ Hz), 9.58 (s, 1H, CH=N). $^{13}$C NMR: $\delta$ 14.62 ($CH_3$), 27.85, 35.36, 36.50, 38.60 (Adamantane–C), 43.67, 50.32 (Piperazine–C), 58.56 (***C***H$_2$CH$_3$), 69.20 ($CH_2$), 116.23, 124.48, 130.95, 160.65 (Ar–C), 155.50, 155.76 (C=O & Triazole C-5), 163.18 (C=S), 164.16 (CH=N). ESI-MS, *m/z* (Rel. Int.): 547.3 $(M + H + Na, 100)^+$, 525.3 $(M + H, 2)^+$. **11h**: $^1$H NMR ($CDCl_3$): $\delta$ 1.78 (s, 6H, Adamantane–H), 2.09 (s, 6H, Adamantane–H), 2.14 (s, 3H, Adamantane–H), 3.08 (s, 4H, Piperazine–H), 3.25 (s, 4H, Piperazine–H), 5.25 (s, 2H, $CH_2$), 6.90–6.98 (m, 6H, Ar–H & OH), 7.28–7.31 (m, 2H, Ar–H), 7.72 (d, 2H, Ar–H, $J = 8.0$ Hz), 9.52 (s, 1H, CH=N). $^{13}$C NMR: $\delta$ 27.86, 35.38, 36.52, 38.62 (Adamantane–C), 49.50, 50.53 (Piperazine–C), 69.10 ($CH_2$), 116.28, 116.56, 120.28, 124.70, 129.18, 130.97, 151.22, 160.20 (Ar–C), 155.47 (Triazole C-5), 163.07 (C=S), 164.42 (CH=N). ESI-MS, *m/z* (Rel. Int.): 552.3 $(M + H + Na, 100)^+$, 529.2 $(M + H, 4)^+$. **11i**: $^1$H NMR ($CDCl_3$): $\delta$ 1.74 (s, 6H, Adamantane–H), 1.96 (s, 3H, Adamantane–H), 2.04 (s, 6H, Adamantane–H), 2.92 (s, 4H, Piperazine–H), 3.06 (s, 4H, Piperazine–H), 3.75 (s, 3H, $OCH_3$), 5.02 (s, 2H, $CH_2$), 6.68–7.04 (m, 5H, Ar–H & OH), 7.22–7.28 (m, 2H, Ar–H), 7.68 (d, 2H, Ar–H,

$J = 8.0$ Hz), 9.56 (s, 1H, CH═N). $^{13}$C NMR: $\delta$ 27.66, 35.38, 36.50, 38.96 (Adamantane–C), 50.20, 50.53 (Piperazine–C), 56.54 ($OCH_3$), 70.02 ($CH_2$), 115.0, 116.20, 119.92, 121.98, 124.22, 128.98, 131.20, 142.55, 145.28, 160.22 (Ar–C), 155.60 (Triazole C-5), 160.78 (C═S), 164.40 (CH═N). ESI-MS, *m*/*z* (Rel. Int.): 582.3 $(M + H + Na, 100)^+$, 559.3 $(M + H, 9)^+$.

### 4.4. Determination of 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 was measured after 24 h in case of bacteria and 48 h in case of *C. albicans*.

### 4.5. Determination of the minimal inhibitory concentration (MIC)

Compounds **6j**, **6l**, **6m**, **7a**, **7b**, **7c**, **7d**, **7f**, **11a**, **11b**, **11c**, **11d**, **11e**, **11f**, **11h** and **11i**, Gentamicin, Ampicillin trihydrate and Clotrimazole 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. The MIC values were determined as the lowest concentration that completely inhibited visible growth of the microorganism as detected by unaided eye.

## Acknowledgements

The authors would like to extend their appreciation to the Deanship of Scientific Research at King Saud University for funding this research through the research group project No. RGP-VPP-274.

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