Synthesis and Antibacterial Activity of Novel Schiff Bases of Thiosemicarbazone Derivatives With Adamantane Moiety

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Abstract

Increased bacterial resistance to antibiotics is a major threat to human health, and it is particularly important to develop novel antibiotic drugs. Here, we designed a series of Schiff base thiosemicarbazone derivatives containing an adamantane moiety, and carried out structural characterization of the compounds and *in vitro* antibacterial activity tests. Compound **7e** was as effective as the commonly-used antibiotic ampicillin against the Gram-negative bacterium *Escherichia coli*, and compound **7g** had a good inhibitory effect against Gram-positive *Bacillus subtilis*. These findings provide data for the development of better thiosemicarbazone antibacterial agents.

Introduction

In the past 30 years, only limited progress has been made in research into antibacterial drugs with new mechanisms and core structures [1–3]. Amoxicillin, norfloxacin, and ciprofloxacin are the commonest drugs used to treat bacterial infection, but are associated with severe side effects. Toxicity and bacterial resistance to the drugs play an important role in the failure of treatment [4, 5]. The development of antibacterial drugs with novel structures is very important research for clinical application [6].

Recently, considerable attention has been focused on substituted thiosemicarbazone derivatives because of their interesting biological activities. Compounds with a thiosemicarbazone structure are known to possess tranquilizing, muscle relaxing, psychoanaleptic, hypnotic, ulcerogenic, antidepressant, antibacterial, antifungal, analgesic, and anti-inflammatory properties [7–14]. Thiosemicarbazones are a type of Schiff base formed by condensation of thiosemicarbazide and an aldehyde or ketone. Studies have shown that changing the structure of the aldehydes and ketones or introducing different active groups on position N(4) can improve the antibacterial and anticancer activities of the compounds [15]. Therefore, synthesis of thiosemicarbazone compounds with various structures and study of their structure–activity relationships have important theoretical significance and potential practical application value.

Adamantane compounds have shown relatively good antivirus, antitumor, and anti-Parkinson's syndrome activities [16–21]. The introduction of adamantyl groups into the molecular structure of other compounds often enhances the biological activity of the compound. The adamantyl group has relatively good fat solubility, so can greatly increase the membrane permeability of a compound [22–25]. Much research has been carried out on thiosemicarbazone derivatives, but no work has been done screening adamantyl thiosemicarbazone derivatives for their antibacterial activity.

In this paper, novel adamantyl thiosemicarbazone derivatives were synthesized by the condensation of an adamantyl phenyl aldehyde with a thiosemicarbazide. The structures of the compounds were elucidated by infrared (IR), ^{1}H NMR, and ^{13}C NMR spectroscopies, and mass spectrometry. The activities of the compounds were screened *in vitro* against *Bacillus subtilis* (a Gram-positive bacterium) and

Escherichia coli (Gram-negative). To the best of our knowledge, this is the first report that thiosemicarbazone analogues having an adamantane moiety inhibit the growth of bacteria.

Results And Discussion

Chemistry

Scheme 1 shows the procedure for synthesis of novel Schiff base derivatives of thiosemicarbazones with an adamantane moiety (compounds **7a**–**h**). The Friedel-Crafts alkylation reaction of bromoadamantane and toluene in the presence of anhydrous potassium carbonate and palladium carbon was used to obtain 1-(*p*-toluene)adamantane (**2**). Compound **2** underwent free radical substitution reaction using NBS and BPO to yield benzyl bromide (**3**), followed by oxidation to give **4** [4-(1-adamantyl)benzaldehyde]. The aromatic amines **5a**–**h** were used to prepare the thiotoluamides **6a**–**h** in basic conditions. Finally, **4** was reacted with **6a**–**h** to produce thiosemicarbazone Schiff base derivatives **7a**–**h**.

The yields of all thiosemicarbazone products were 62–86%. The compounds obtained were stable in both the solid and solution states. Analytical data for these compounds were consistent with their composition. The structures of thiosemicarbazone compounds **7a-h** were confirmed on the basis of infrared (IR), ^{1}H nuclear magnetic resonance (NMR), ^{13}C NMR, and electrospray ionization mass spectral (ESI/MS) data, which showed their negative ion peaks $[M + H]^{+}$. In the infrared (IR) spectra, N-H, aromatic and aromatic C-Hs, C = N, C = C, C-N and C-O bands stretching vibrations were observed. N-H bands belonging to the thiosemicarbazone group were recorded around 3250 cm^{-1}. Aromatic and aliphatic C-H stretching bands appeared between 3190 cm^{-1} and 2910 cm^{-1}. C = N and C = C groups gave rise to the bands in the region 1600 – 1442 cm^{-1}. C-N and C-O bands were observed in the region 1287 – 1124 cm^{-1}. In the ^{1}H-NMR spectra, adamantyl group protons had peaks between 1.74 ppm and 2.07 ppm. The chemical shift values of aromatic ring protons were between 6.92 ppm and 8.37 ppm, depending on the substituent groups. The characteristic azomethine (-CH = N-) protons appeared between 6.77 ppm and 7.22 ppm. Besides, the characteristic N-H protons were seen at 9.93–11.91 ppm. In the ^{13}C-NMR spectra, aliphatic and aromatic carbons were observed between 21.05–56.56 ppm and 113.78-163.19 ppm, respectively. the azomethine (-CH = N-) and the thiocarbamoyl carbons were detected at 143.06- 143.93 ppm and 175.10-177.60 ppm, respectively. In Mass (MS) analysis, the mass spectral data were coherent with their molecular formulas.

Antimicrobial activity

The antibacterial activity of the synthesized compounds against *B. subtilis* (Gram-positive) and *E. coli* (Gram-negative) was evaluated using the disk inhibition method and the microdilution method to determine MICs [26–28]. Ampicillin was used as a positive control drug. The results are shown in Tables 1 and 2.

In the disk inhibition method (Table 1), a diameter of the inhibition zone is 20 mm or more indicates that the drug has a very strong antibacterial effect on the strain; the inhibition zone of 10–20 mm is

categorized as strong antibacterial effect; a diameter of 5–10 mm indicates a moderate antibacterial effect; and diameter of 5 mm or less indicates that there is little or no antibacterial effect of the compound on the strain [29].

Based on the growth inhibition response, the antibacterial inhibition of compounds **7a** and **7g** on *B. subtilis* with concentration of 8 μg/mL (22 mm) had very strong activity and other concentrations (10–20 mm) including strong activity.The antibacterial inhibition of compounds **7d** and **7h** on *B. subtilis* with concentrations of 1–8 μg/mL (10–20 mm) had strong activity, while compounds **7c** and **7e** with concentrations of 2–8 μg/mL (10–20 mm) indicated strong activity. The antibacterial inhibition of compounds **7b** and **7f** on *B. subtilis* with concentrations of 1–8 μg/mL (5–10 mm) had moderate activity. The antibacterial inhibition of compound **7a** and **7e** on *E. coli* with concentrations of 1–8 μg/mL (10–20 mm) had the best inhibitory effect, similar to the effect of positive control Ampicillin. Meanwhile compounds **7b-c** and **7g-h** with concentrations of 1–8 μg/mL (10–20 mm) had strong activity against *E. coli*, but compounds **7f** with concentrations of 1–2 μg/mL (5–10 mm) including moderate activity and concentrates of 4–8 μg/mL (10–20 mm) are categorized as strong activity.

Table 1
Antibacterial activity of compounds **7a-h** at different concentration

Comp.	**Diameter of inhibition zone of different strains(mm)**							
	***Escherichia coli* (μg/mL)**				***Bacillus subtilis* (μg/mL)**			
	1	**2**	**4**	**8**	**1**	**2**	**4**	**8**
7a	12	13	15	17	15	16	19	20
7b	10	11	13	14	6	7	8	9
7c	11	13	14	15	8	10	11	13
7d	12	13	14	16	10	11	13	14
7e	13	14	15	16	9	10	11	12
7f	8	9	10	11	7	8	9	10
7g	10	12	13	14	17	18	19	22
7h	8	10	11	13	10	12	13	15
Ampicillin	14	14.5	15	16	18	20	21	22
DMSO	-	-	-	-	-	-	-	-
Note:"-"represents sample no inhibitory effect on the strain. DMSO, dimethylsulfoxide.								

Table 2
Minimum inhibitory concentrations of compounds **7a**–**h** (μg/mL), mean ± standard deviation

Comp.	*E. coli*	*B. subtilis*
7a	8 ± 0.1	8 ± 0.02
7b	1 ± 0.3	4 ± 0.03
7c	1 ± 0.04	8 ± 0.3
7d	2 ± 0.1	4 ± 0.02
7e	1 ± 0.2	2 ± 0.1
7f	2 ± 0.03	4 ± 0.2
7g	2 ± 0.4	1 ± 0.01
7h	1 ± 0.02	8 ± 0.2
Ampicillin	50	50

The MIC values of the test derivatives indicate that most compounds exhibit good activity against gram-negative bacteria as shown in Table 2. Compounds **7b-d** bearing methoxy group on the phenyl had MIC 1–2 μg/mL for *E. coli* and slightly higher MIC for *B. subtilis.* While compound **7c** bearing no substituent had MIC 8 μg/mL for *E. coli* and *B. subtilis.* Meanwhile, derivatives **7e-g** with electron-withdrawing group had MIC 1–2 μg/mL for *E. coli* and almost similar MIC for *B. subtilis.* Compound **7h** bearing methyl group showed good antibacterial with MIC 1 μg/mL for *E. coli* compared with that of compound **7a**. From the MIC values as shown in Table 2, it could be easily inferred in general that with substitution on phenyl of thiosemicarbazone had antibacterial activity toward gram-negative bacteria.

Conclusions

In summary, we investigated the antibacterial activity of novel adamantyl thiosemicarbazones prepared by the reaction of benzaldehyde adamantane with different amine-substituted thiosemicarbazides. Of particular note, *in vitro* antibacterial activity tests showed that compound **7e** was as effective against *E. coli* (a Gram-negative bacterium) as ampicillin, while **7g** had good activity against the Gram-positive bacterium *B. subtilis*. These data lay a foundation for development of improved thiosemicarbazone antibacterial agents.

Materials And Methods

General

The starting materials which include 4-(1-adamantyl)benzaldehyde was prepared according to procedure described previously and other required chemicals were purchased from different commercial sources

and used without purification unless otherwise stated. The progress of reactions was monitored by using thin layer chromatography (TLC) with silica gel 60 aluminium-backed plates and the ^{1}H NMR and ^{13}C NMR spectra were recorded via Bruker spectrometer 400 MHz as dilute solutions in suitable deuterated solvent at 25°C. The chemical shifts were recorded on the δ-scale (ppm) using residual solvents as an internal standard (DMSO; ^{1}H 2.50, and $CHCl_3$; ^{1}H 7.26,). Coupling constant were calculated in Hertz (Hz) and multiplicities were labelled as s (singlet), d (doublet), t (triplet), q (quartet), quint (quintet) and the prefixes br (broad) or app (apparent) were used. IR spectra were recorded on a Specord 2000 spectrometer. Mass spectra were taken on the AB Sciex 6500 QTAP mass spectrometer. Melting points of synthesized compounds were determined by means of a Stuart™ melting point SMP3 apparatus.

Chemistry

General procedure for synthesis of derivatives 6a-h

The anilines (1.0 mmol) was dissolved in 20 mL of DMF, and NaOH (1.2 mmol) and CS_2 (1.0 mmol) were added. After reaction at room temperature for 2 h, hydrazine hydrate (3.0 mmol) was added, and the reaction was continued for 1 h. Cool to room temperature, pour the solution into crushed ice, filter with suction, and recrystallize the filter cake with ethanol to obtain intermediates **6a-h**.

N-(2-Fluorophenyl)hydrazinecarbothioamide (6a)

^{1}H NMR (400 MHz, DMSO-d_6) δ 9.34 (s, 1H), 8.08 (s, 1H), 7.19 (dq, J = 22.4, 7.7 Hz, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 180.44, 156.88, 154.46, 127.82, 127.72, 127.13, 126.39, 126.32, 124.16, 115.56; FT-IR (KBr, cm^{-1}): v(N-H) 3265.31, 3193.09, v(C-N) 1481.12, v(C=S) 1226.07.

N-(2-Methoxyphenyl)hydrazinecarbothioamide (6b)

^{1}H NMR (400 MHz, DMSO-d_6) δ 9.94 (s, 1H), 9.18 (s, 1H), 8.74 (s, 1H), 7.04 (s, 2H), 6.90 (s, 1H), 4.83 (s, 2H), 3.84 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 178.87, 149.87, 128.63, 124.26, 121.63, 120.16, 111.28, 56.3; FT-IR (KBr, cm^{-1}): v(N-H) 3313.47, 3193.43, v(C-N) 1457.01, v(C=S) 1238.42.

N-(3-Fluorophenyl)hydrazinecarbothioamide (6c)

^{1}H NMR (400 MHz, DMSO-d_6) δ 9.29 (s, 1H), 7.86 (s, 1H), 7.45 (s, 1H), 7.32 (s, 1H), 6.91 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 179.70, 141.72, 129.94, 119.24, 40.29; FT-IR (KBr, cm^{-1}) : v(N-H) 3291.84, 3193.52, v(C-N) 1456.99, v(C=S) 1224.76.

N-(3-Methoxyphenyl)hydrazinecarbothioamide (6d)

^{1}H NMR (400 MHz, DMSO-d_6) δ 9.14 (s, 1H), 7.49 (s, 1H), 7.20 (d, J = 7.1 Hz, 2H), 6.67 (d, J = 6.2 Hz, 1H), 4.78 (s, 2H), 3.73 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 159.55, 140.90, 129.28, 115.64, 109.96, 109.21, 55.54; FT-IR (KBr, cm^{-1}) : v(N-H) 3266.26, 3190.51, v(C-N) 1457.42, v(C=S) 1228.66.

N-Phenylhydrazinecarbothioamide (6e)

^{1}H NMR (400 MHz, DMSO-d_6) δ 9.11 (s, 1H), 7.66 (s, 2H), 7.42-7.22 (m, 2H), 7.17-7.05 (m, 1H), 4.81 (s, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 180.05, 139.79, 128.52, 124.49, 123.78; FT-IR (KBr, cm^{-1}) 3300.04, 3156.12, 1635.80, 1524.39, 1488.93, 1282.00, 1217.49, 1068.07, 971.13, 894.88, 735.19, 609.89.

N-(4-Fluorophenyl)hydrazinecarbothioamide (6f)

^{1}H NMR (400 MHz, DMSO-d_6) δ 9.72 (s, 1H), 9.12 (s, 1H), 7.55 (d, J = 37.9 Hz, 2H), 7.14 (dt, J = 17.5, 8.8 Hz, 2H), 4.78 (s, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 180.34, 136.14, 126.33, 115.13, 114.91; FT-IR (KBr, cm^{-1}) 3307.96, 3108.03, 1636.04, 1493.81, 1284.91, 1208.69, 905.59, 813.48, 502.85.

N-(4-Methoxyphenyl)hydrazinecarbothioamide (6g)

^{1}H NMR (400 MHz, DMSO-d_6) δ 9.40 (s, 1H), 8.96 (s, 1H), 7.37 (dd, J = 53.0, 8.5 Hz, 2H), 6.88 (t, J = 10.1 Hz, 2H), 4.70 (s, 2H), 3.73 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 180.45, 156.69, 132.72, 126.03,113.76,55.71; FT-IR (KBr, cm^{-1}) 3312.45, 3158.14, 1635.19, 1508.62, 1489.55, 1240.97, 1031.78, 829.78, 509.71.

N-(p-Tolyl)hydrazinecarbothioamide (6h)

^{1}H NMR (400 MHz, DMSO-d_6) δ 9.54 (s, 1H), 9.04 (s, 1H), 7.49 (d, J = 6.1 Hz, 2H), 7.10 (d, J = 8.1 Hz, 2H), 4.76 (s, 2H), 2.27 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 180.09 , 137.18 , 133.68 , 128.99 , 124.02 , 20.96; FT-IR (KBr, cm^{-1}) 3291.18, 3191.53, 1615.95, 1537.23, 1060.91, 806.74, 726.66, 441.48.

Synthesis of target compound 7a-h

4-(1-adamantyl)benzaldehyde (1.0 mmol) and thiosemicarbazone (**6a-h**) (1.2 mmol) were dissolved in ethanol (6 mL). Then two drops of acetic acid was added and the solution was refluxed for 3 h.

2-[4-(Adamantan-1-yl)benzylidene]-N-phenylhydrazine-1-carbothioamide (7a)

Light yellow solid, yield 62 %, m.p.178-180 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.91 (s, 1H), 9.93 (s, 1H), 8.13 (s, 1H), 7.80 (d, J = 8.3 Hz, 2H), 7.55 (t, J = 7.5 Hz, 1H), 7.41 (d, J = 8.3 Hz, 2H), 7.26 (dd, J = 24.5, 9.3 Hz, 3H), 2.06 (s, 3H), 1.88 (s, 6H), 1.74 (s, 6H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 127.92, 125.50, 124.39, 55.35, 42.91, 36.65, 28.79. FT-IR (KBr, cm^{-1}) 3298.94, 3141.85, 2899.12, 2846.27, 1621.21, 1545.86, 1221.97, 805.11,745.76; MS, m/z (%): 408.3 [M+H]$^+$.

2-[4-(Adamantan-1-yl)benzylidene]-N-(2-methoxyphenyl)hydrazine-1-carbothioamide (7b)

Light yellow solid, yield 60 %, m.p.187-189 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.89 (s, 1H), 10.00 (s, 1H), 8.36 (d, J = 7.3 Hz, 1H), 8.17 (d, J = 16.8 Hz, 1H), 7.72 (d, J = 8.3 Hz, 2H), 7.46 (d, J = 8.3 Hz, 2H), 7.24-

6.89 (m, 3H), 3.91 (s, 3H), 2.07 (s, 3H), 1.90 (d, *J* = 12.0 Hz, 6H), 1.75 (s, 6H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 151.41, 143.06, 127.53, 125.78, 123.50, 120.35, 56.56, 42.86, 39.44, 36.60, 28.74; FT-IR (KBr, cm^{-1}) 3154.70, 2899.16, 1599.45, 1235.88, 1193.39, 1031.00, 743.44; MS, m/z(%): 420.3 $[M+H]^+$.

2-[4-(Adamantan-1-yl)benzylidene]-N-(3-methoxyphenyl)hydrazine-1-carbothioamide(7c)

Light yellow solid, yield 79 %, m.p. 175-177 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.89 (s, 1H), 10.12 (s, 1H), 8.15 (s, 1H), 7.82 (d, *J* = 8.2 Hz, 2H), 7.63 (d, *J* = 11.3 Hz, 1H), 7.51-7.42 (m, 2H), 7.40 (d, *J* = 10.2 Hz, 1H), 7.03 (t, *J* = 8.8 Hz, 1H), 2.07 (s, 3H), 1.88 (s, 6H), 1.75 (s, 6H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 163.19, 153.66, 143.93, 128.05, 125.46, 121.50, 112.57, 42.86, 36.60; FT-IR (KBr, cm^{-1}) 3135.56, 2987.81, 2900.50, 2847.06, 1599.16, 1541.58, 1272.83, 1064.02, 548.94; MS, m/z (%): 408.3 $[M+H]^+$.

2-[4-(Adamantan-1-yl)benzylidene]-N-(4-methoxyphenyl)hydrazine-1-carbothioamide (7d)

Light yellow solid, yield 53 %, m.p.174-176 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.77 (s, 1H), 9.99 (s, 1H), 8.14 (s, 1H), 7.82 (d, *J* = 8.0 Hz, 2H), 7.41 (d, *J* = 8.0 Hz, 2H), 7.34-7.15 (m, 3H), 6.78 (d, *J* = 7.9 Hz, 1H), 3.77 (s, 3H), 2.07 (s, 3H), 1.88 (s, 6H), 1.74 (s, 6H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 159.49, 143.52, 129.18, 127.98, 125.46, 118.01, 111.53, 111.17, 55.64, 42.87, 36.60, 28.74; FT-IR (KBr, cm^{-1}) 3125.97, 2899.24, 2845.76, 1597.70, 1546.41, 1463.44, 1288.53, 767.71, 546.23, 448.62; MS, m/z (%): 420.3 $[M+H]^+$.

2-[4-(Adamantan-1-yl)benzylidene]-N-(2-fluorophenyl)hydrazine-1-carbothioamide (7e)

Light yellow solid, yield 49 %, m.p.170-171 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.68 (s, 1H), 9.95 (s, 1H), 8.11 (s, 1H), 7.81 (d, *J* = 8.4 Hz, 2H), 7.40 (d, *J* = 8.6 Hz, 4H), 6.93 (d, *J* = 8.9 Hz, 2H), 5.75 (s, 1H), 3.77 (s, 3H), 2.06 (s, 3H), 1.86 (d, *J* = 12.9 Hz, 6H), 1.74 (s, 6H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 176.31, 143.43, 128.48, 127.96, 126.07, 125.44, 42.88, 36.62, 28.76; FT-IR (KBr, cm^{-1}) 3138.58, 1198.23,803.73, 744.39, 493.02; MS, m/z (%): 390.1 $[M+H]^+$.

2-[4-(Adamantan-1-yl)benzylidene]-N-(3-fluorophenyl)hydrazine-1-carbothioamide (7f)

Light yellow solid, yield 50 %, m.p.188-190 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.79 (s, 1H), 10.06 (s, 1H), 8.13 (s, 1H), 7.82 (d, *J* = 8.3 Hz, 2H), 7.55 (dd, *J* = 8.8, 5.1 Hz, 2H), 7.41 (d, *J* = 8.4 Hz, 2H), 7.20 (t, *J* = 8.8 Hz, 2H), 2.07 (s, 3H), 1.89 (d, *J* = 9.0 Hz, 6H), 1.74 (s,6H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 176.72, 158.89, 143.56, 135.95, 128.49, 127.97, 125.44, 115.01, 42.87, 36.61, 28.75; FT-IR (KBr, cm^{-1}) 3155.17, 2900.14, 2845.94, 1526.22, 1508.51, 1196.02, 928.48, 836.46, 553.47, 499.03; MS, m/z (%): 408.3 $[M+H]^+$.

2-[4-(Adamantan-1-yl)benzylidene]-N-(4-fluorophenyl)hydrazine-1-carbothioamide (7g)

Light yellow solid, yield 57 %, m.p.177-179 °C; ^{1}H NMR (400 MHz,DMSO-d_6) δ 11.68 (s, 1H), 9.95 (s, 1H), 8.11 (s, 1H), 7.80 (s, 2H), 7.41 (s, 4H), 6.94 (s, 2H), 3.77 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 157.42,

143.23, 131.91, 127.90, 125.41, 113.78, 55.77, 42.92, 36.64, 28.78; FT-IR (KBr, cm^{-1}) 3135.42, 2980.90, 2899.64, 1608.72, 1532.53, 1510.61, 1233.24, 1014.33, 804.52, 548.38; MS, m/z (%): 420.3$[M+H]^+$.

2-[4-(Adamantan-1-yl)benzylidene]-N-(p-tolyl)hydrazine-1-carbothioamide (7h)

Light yellow solid, yield 89 %, m.p.196-197 °C; ^1H NMR (400 MHz, DMSO-d_6) δ 11.71 (s, 1H), 9.97 (s, 1H), 8.12 (s, 1H), 7.81 (d, J = 8.2 Hz, 2H), 7.42 (t, J = 9.5 Hz, 4H), 7.17 (d, J = 8.0 Hz, 2H), 2.31 (s, 3H), 2.06 (s, 3H), 1.88 (s, 6H), 1.74 (s, 6H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 143.30, 131.86, 128.96, 127.93, 126.09, 125.44, 42.87, 36.6, 28.75; FT-IR (KBr, cm^{-1}) 3132.79, 2896.53, 2845.57, 1532.84, 1492.85, 1264.08, 1201.14, 1176.71, 835.84, 449.53; MS, m/z (%): 404.4 $[M+H]^+$.

In vitro antibacterial activity evaluation

Minimum Inhibitory Concentration (MIC) assays using standard microdilution methods were carried out in 96-well microplates based on a modified procedure described previously according to the guidelines of the Clinical and Laboratory Standards Institute [30-31]. All compounds were prepared as 5 mg/mL solutions in dimethyl sulfoxide (DMSO) and were tested in a final concentration range of 1-8 μg/mL. MICs for the reference antibiotic Ampicillin against quality control strains were used to confirm the validity of the screen.

All experiments were performed in duplicate and repeated three times.

Declarations

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Authors' contributions Jiahui Zhu and Yan Xia performed all experiments, purified all compounds, analyzed the data and summarized the results. Jiahui Zhu tested all compounds for their antibacterial activity. Dongfeng Li and Guosheng Teng helped in the compiling the data of the manuscript. Yan Xia and Ruibin Hou conceived and designed this research and wrote the manuscript. All authors have contributed to the final version and approved the final manuscript.

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Compliance with ethical standards

Conflicts of interest All the authors declared no conflict of interest.

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Figures

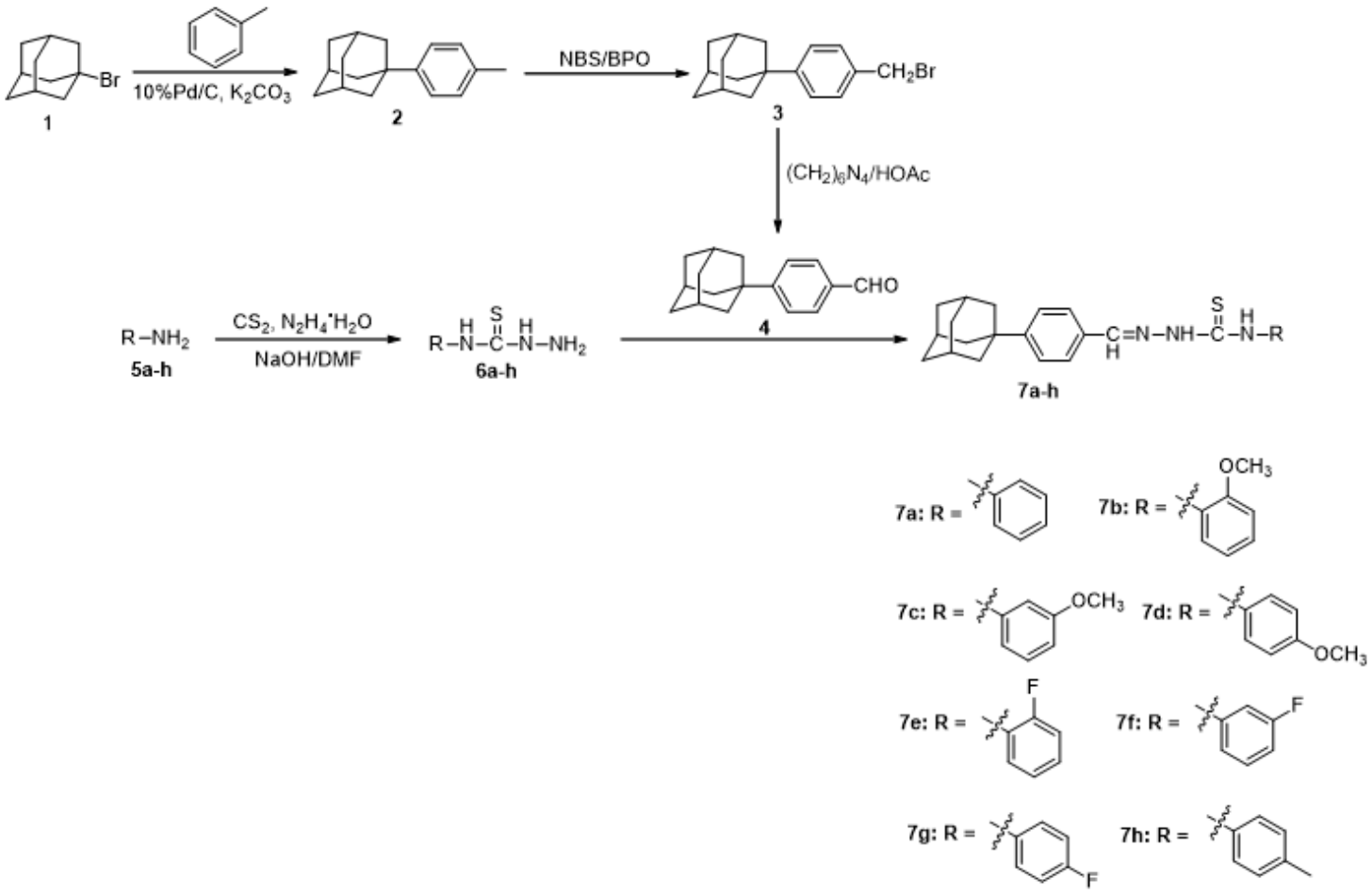

Figure 1

Synthetic procedures of compounds 7a-h.