Uses of 2-(Thiophene-2-carbonylcarbamothioylthio)acetic Acid as a Good Synthon for Construction of Some New Thiazole and Annulated Thiazole Derivatives

Heba Kamal Abd El-Mawgoud,* a Saad Ramadan Atta-Allah, b and Magdy Mohamed Hemdan b

a Department of Chemistry, Faculty of Women for Arts, Science and Education, Ain Shams University; Heliopolis, Cairo 11767, Egypt; and b Department of Chemistry, Faculty of Science, Ain Shams University; Abbasiya, Cairo 11566, Egypt.

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The reaction of thiophene-2-carbonyl isothiocyanate 2 with thioglycolic acid gave 2-(thiophene-2-carbonylcarbamothioylthio)acetic acid 3. Compound 3 was subjected to some selected reactions with sulphuric acid as well as benzaldehyde, piperonal and isatin under different reaction conditions. The products obtained were new derivatives of thiazole and annulated thiazole derivatives bearing thiophene moiety in some cases. The structures of the new synthesized compounds were confirmed on the basis of their microanalytical and spectral properties. Some compounds were tested for their antimicrobial activity against six selected microorganisms using the standard antibacterial Gentamycin and antifungal Ketoconazole as references.

Key words thiophene-2-carbonyl isothiocyanate; thiazole; fused thiazole; indole; antimicrobial activity

Isothiocyanates serve as good synthon for construction of many condensed heterocyclic systems1–11 such as thiazoles, thiadiazoles, triazoles, benzimidazoles, dithiolane, fused oxazolines, triazines, and oxazines.

1,3-Thiazolidine-4-one derivatives are a class of important heterocycles that have attracted considerable attention because of their biological properties such as antibacterial, antifungal12–14 antiinflammatory,15,16 antiproliferative activity against human colon cancer,17 anti-human immunodeficiency virus (HIV),18–22 anti-tubercular,23,24 cyclooxygenase (COX-2) inhibitors,25 potent PTP1B inhibitors,26 anticonvulsant,27 and antitumor activity.28 Based on these considerations, our interest was focused on synthesizing new fused heterocyclic compounds including thiazolidine moiety with suitable substituents. The biological activity of some of the synthesized compounds has been screened.

Results and Discussion

Thiophene-2-carbonyl isothiocyanate 2 was prepared by the reaction of thiophene-2-carbonyl chloride 1 with ammonium thiocyanate in a dry acetonitrile at room temperature.1–3 A solution of isothiocyanate 2 in acetonitrile was treated with an equivalent amount of thioglycolic acid to give 2-(thiophene-2-carbonylcarbamothioylthio)acetic acid 3 in a high yield. The spectroscopic data of compound 3 agree with its proposed structure. Its IR spectrum showed absorption bands due to –OH, N–H amide, C=O and C=S groups. The 1H-NMR spectrum displayed singlet signal of methylene protons in addition to thiophene protons, as well as broad singlet signals for NH and OH protons in the down field region which were exchanged with D2O. Heating of compound 3 with concentrated sulphuric acid at 100°C afforded the 1,3-thiazolidin-4-one derivative 4. On the other hand, compound 4 was also obtained by refluxing 2-thioxo-1,3-thiazolidin-4-one 29 with the acid chloride 1 in pyridine (identical melting point (mp), mixed mp and TLC) (Chart 1). Structure of compound 4 was elucidated on the basis of its microanalytical and spectral data (cf. experimental).

Reagents and conditions: (i) NH4SCN, dry MeCN, stirring at r.t 15 min.; (ii) Dry MeCN, stirring at r.t 2 h; (iii) H2SO4, water bath 30 min.; (iv) Pyridine, reflux 1 h.

Chart 1.
The reaction of compound 3 with benzaldehyde and/or piperonal in pyridine for 2 h afforded 5-arylidene-3-(thiophen-2-ylcarbonyl)-2-thioxo-1,3-thiazolidin-4-one derivatives 6a and 6b, respectively. Thionation of compounds 6a and b was achieved using Lawesson’s reagent in dioxane, which gave the 1,3-thiazolidine-2,4-dithione derivatives 7a and b, respectively. Refluxing of compounds 7a and b with hydrazine hydrate in ethanol for 2 h produced thiazolotriazole derivatives 8a and b. On the other hand, compounds 8a and b were obtained from the reaction of the arylimine derivatives 6a and b with hydrazine hydrate in ethanol for 4 h (identical mp, mixed mp and TLC) (Chart 2). The spectral properties of the new products 6–8 agree with their proposed structures (cf. Experimental).

On the other hand, when the reaction of compound 3 with benzaldehyde and/or piperonal was carried out in glacial acetic acid and in presence of catalytic amount of anhydrous sodium acetate for 3 h, 5-substituted-2-thioxo-1,3-thiazolidin-4-one derivatives 9a and 9b were obtained, respectively. Moreover, compounds 9a and b were also obtained by the reaction of 2-thioxo-1,3-thiazolidin-4-one 5 with benzaldehyde and/or piperonal in boiling glacial acetic acid and in presence

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**Chart 2.**

Reagents and conditions: (i) Benzaldehyde or piperonal, pyridine, reflux 2 h; (ii) Lawesson’s reagent, dioxane, reflux 1.5 h; (iii) N₂, EtOH, reflux 2 h; (iv) 4 h; EtOH; (v) Benzaldehyde or piperonal, glacial AcOH / AcONa, reflux 3 h; (vi) Aldehyde, glacial AcOH / AcONa, reflux 1 h; (vii) Compound (1), pyridine, reflux 1 h.

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**Chart 3.**

Reagents and conditions: (i) Iodesin, pyridine, reflux 2 h; (ii) N₂, EtOH, reflux 4 h; (iii) 4 h; (iv) Ac₂O, reflux 1 h; (v) Iodesin, glacial AcOH / AcONa, reflux 3 h; (vi) Iodesin, glacial AcOH / AcONa, reflux 1 h; (vii) Compound (1), pyridine, reflux 1 h.
of anhydrous sodium acetate for 1 h (identical mp, mixed mp and TLC). The reaction of compounds 9a and b with Lawesson's reagent in dioxane afforded the 5-substituted-1,3-thiazolidine-2,4-dithione derivatives 10a and 10b, respectively. Refluxing of compounds 10a and b with hydrazine hydrate in ethanol for 2 h yielded 5-substituted-5H-pyrazolo[3,4-d]-[1,3]thiazole-5-thione derivatives 11a and b. Furthermore, compounds 11a and b were also obtained by heating of compounds 9a and b with hydrazine hydrate in ethanol for 4 h (identical mp, mixed mp and TLC). Formation of compounds 11a and b involving initial conjugated addition of hydrazine to 9a and b or to 10a and b and subsequent ring closure onto the (thio) carbonyl function, followed by two successive dehydrogenation steps to give the pyrazolo[3,4-d][1,3]thiazole-5-thione derivatives 11a and b. Reaction of the 1,3-thiazolidin-4-one derivatives 9a and b with thiopehene-2-carbonyl chloride 1 in boiling pyridine for 1 h gave compounds 6a and b (Chart 2).

The structures of the new synthesized compounds were established on the basis of their microanalytical and spectroscopic data, as explained in the experimental part. The appearance of only one singlet signal for the absorption of alkene−H in the 1H-NMR of compounds 6a and b−10a and b makes us unable to predict which isomer E or Z is the actual stereo-isomer of the given compound, but we are sure that there is no mixture of E or Z stereoisomer.

Further aspect of reactivity of compound 3 was gained by its reaction with isatin in pyridine to give thiazolidine derivative 12 in a good yield. However, reaction of compound 3 with isatin in glacial acetic acid and in the presence of a catalytic amount of fused sodium acetate produced thiazolidine derivative 15. Refluxing of solutions of compounds 12 and 15 in ethanol with hydrazine hydrate afforded thiazolopyrimidine derivatives 13 and 16, respectively. The formation of the latter derivatives is regarded as cyclocondensation reaction of hydrazine molecule with compounds 12 and 15, followed by removal of thiophene-2-carbonyl hydrazide in case of its reaction with compound 12. On the other hand, heating of compounds 12 and 15 in acetic anhydride gave mono- and diacetylated products 14 and 17, respectively (Chart 3). The structures of compounds 12−17 were established on the basis of their microanalytical and spectral data (cf. Experimental).

Experimental

Melting points of the reaction products were determined in open capillary tubes on an electrothermal melting point apparatus and were uncorrected. The elemental analyses were performed on a PerkinElmer 2400 CHN elemental analyzer. The Fourier transform (FT)-IR were recorded on a PerkinElmer Model 297 Infrared spectrometer using the KBr wafer technique. The 1H-NMR spectra were measured on a Varian Gemini 300 MHz spectrometer, with chemical shift (δ) expressed in ppm downfield with tetramethylsilane (TMS) as internal standard, in dimethyl sulfoxide (DMSO)-d6. MS were obtained on a Shimadzu GC-MSQP 1000 EX instrument operating at 70 eV. TLC was run using TLC aluminium sheets silica gel F254 (Merck, Germany). It was used in the monitoring of the progress of all reactions and in the checking of the homogeneity of the synthesized compounds. The antimicrobial activity was studied at the Regional Center for Mycology and Biotechnology at Al-Azhar University, Egypt.

A solution of thiophene-2-carbonyl isothiocyanate (3 mmol, 0.26 g) in concentrated sulfuric acid (5 mL) was heated on a water bath for ½ h. After cooling, the reaction mixture was added onto ice cold water. The solid product formed was collected by filtration, dried and recrystallized from ethanol to give 4. Dark brown crystals; yield 54%; mp 154−156°C. 1H-NMR (DMSO-d6): δ 8.34−7.64 (3H, thiophene protons, m), 12.91 (OH, exchangeable with D2O, br s). 13C-NMR (DMSO-d6): δ 170.95 (C=O, C=O), 152.51 (C=C), 129.24 (C=S) cm−1. MS (70 eV) m/z (γ): 246 (M+, 1), 121 (15), 153 (1.57), 133 (2.81), 111 (100), 83 (50.4). Anal. Calc. for C5H5NOS2 (246.32): C, 39.49; H, 2.07; N, 5.76. Found: C, 39.71; H, 1.98; N, 5.61.

A solution of 2-thioxo-1,3-thiazolidin-4-one 5 (1 mmol, 0.13 g) and thiophene-2-carbonyl chloride 1 (1 mmol, 0.11 mL) in pyridine (10 mL) was refluxed for 1 h. After cooling, the reaction mixture was added onto ice cold water. The solid product formed was collected by filtration, dried and recrystallized from ethanol to give 4. Yield 67%.

General Procedure for the Preparation of Compounds 6a, 6b, and 12

A solution of compound 3 (1 mmol, 0.26 g) and benzaldehyde, piperonal or isatin (1 mmol) in pyridine (15 mL) was heated under reflux for 2 h. After cooling, the reaction mixture was added onto ice cold water. The solid product formed was collected by filtration, dried and recrystallized from ethanol to give the corresponding compounds 6a, 6b, and 12.
respectively.

1,4-dioxane (20 mL) was heated under reflux for 1.5 h. After cooling, the solid product formed was filtered off, dried and recrystallized from ethanol to give 7a, 7b, 10a, and 10b, respectively.

5-Benzylidene-3-(thiophen-2-ylcarbothioyl)-1,3-thiazolidine-2,4-dithione (7a)

Brown crystals; yield 58.5%; mp 120–122°C. 1H-NMR (DMSO-d_6): δ 7.35 (1H=CH=H), 7.37–7.45 (5H, phenyl protons, m), 7.55–7.66 (3H, thiophene protons, m). IR (KBr) v: 3063, 3032 (C=H_arom), 1566 (C=C), 1223 (C=S) cm⁻¹. MS (70 eV) m/z (%): 363 (M⁺, 58.13), 331 (100), 127 (9.34). Anal. Calcd for C₁₁H₁₀NS₂: C, 46.38; H, 3.70; S, 37.66. Found: C, 46.92; H, 3.59; S, 37.6. 5-(1,3-Benzodioxol-5-ylmethylidene)-3-(thiophen-2-ylcarbothioyl)-1,3-thiazolidine-2,4-dithione (7b)

Brick red crystals; yield 62%; mp 208–210°C. 1H-NMR (DMSO-d_6): δ 5.48 (2H, CH₂, s), 6.05 (1H=CH=H), 6.86–7.30 (3H, Ar-H, m), 7.45–8.04 (3H, thiophene protons, m). IR (KBr) v: 3071, 2916, 2851 (C=H_arom), 1570 (C=C), 1234 (C=S) cm⁻¹. MS (70 eV) m/z (%): 407 (M⁺, 10.10), 389 (100), 324 (7.19), 286 (0.77), 280 (5.95), 277 (5.83), 261 (1.73), 181 (10.1), 180 (9.34). Anal. Calcd for C₁₁H₉NS₂: C, 48.25; H, 2.72; N, 3.36. Found: C, 47.43; H, 2.17; N, 3.6. 5-Benzylidene-1,3-thiazolidine-2,4-dithione (10a)

Reddish brown crystals, yield 72%; mp 145–147°C (lit.31 198°C). 1H-NMR (DMSO-d_6): δ 6.85–7.31 (5H, Ar-H, m), 7.64 (1H=CH=H), 13.93 (1H, NH, exchangeable, brs). IR (KBr) v: 3100 (N=H), 3060 (C=H_arom), 1597 (C=C), 1258 (C=S) cm⁻¹. MS (70 eV) m/z (%): 237 (M⁺, 100). Anal. Calcd for C₁₀H₁₀NS₂: C, 47.12; H, 3.09; N, 18.29. Found: C, 47.40; H, 3.89; N, 18.3. 5-(1,3-Benzodioxol-5-ylmethylidene)-1,3-thiazolidine-2,4-dithione (10b)

Reddish brown crystals; yield 78%; mp 210–212°C. 1H-NMR (DMSO-d_6): δ 6.02 (2H, CH₂, s), 6.11–7.32 (3H, Ar-H, m), 7.77 (1H=CH=H), 13.80 (1H, NH, exchangeable, brs). IR (KBr) v: 3441 (N=H_arom), 3051 (C=H_arom), 2874 (C=H_arom), 1570 (C=C), 1238 (C=S), 1099 (C=O) cm⁻¹. MS (70 eV) m/z (%): 281 (M⁺, 34.21), 178 (3.36), 147 (7.15), 134 (2.05), 103 (3.12), 76 (10.15), 56 (100). Anal. Calcd for C₁₀H₉NS₂: 281.37 (C, 46.95; H, 2.51; N, 4.98. Found: C, 47.18; H, 2.59; N, 5.11.

General Procedure for the Preparation of Compounds

7-Benzylidene-3-(thiophen-2-yl)5H,7H-1,3-thiazolo[4,3-c]-1,2,4-triazole-5-thione (8a)

Buff crystals; yield 47%; mp 155–157°C. 1H-NMR (DMSO-d_6): δ 7.18 (1H=CH=H), 7.21–7.36 (5H, phenyl protons, m), 7.99–8.02 (3H, thiophene protons, m). 1C-NMR (DMSO-d_6): δ 226, 147.9, 134.7, 132.9, 131.8, 128.6, 128.2, 127.4, 127.3, 127.1, 125.1. IR (KBr) v: 3063 (C=H_arom), 1601 (C=N), 1558 (C=C), 1265 (C=S) cm⁻¹. MS (70 eV) m/z (%): 327 (M⁺, 18.15), 303 (8.63), 134 (2.47), 83 (4.22), 77 (100). Anal. Calcd for C₁₁H₁₀NS₂: 327.43 (C, 55.02; H, 2.77; N, 12.83. Found: C, 54.81; H, 2.82; N, 12.71. 7-(1,3-Benzodioxol-5-ylmethylidene)-3-(thiophen-2-yl)-5H,7H-[1,3]thiazolo[4,3-c]-1,2,4-triazole-5-thione (8b)

Buff crystals; yield 49.5%; mp 164–166°C. 1H-NMR (DMSO-d_6): δ 5.91 (2H, CH₂, s), 6.03 (2H, =CH=H), 6.69–6.97 (3H, Ar-H, m), 7.14–7.31 (3H, thiophene protons, m). IR (KBr) v: 3070 (C=H_arom), 2920, 2851 (C=H_arom), 1609 (C=N), 1520 (C=C), 1242 (C=S) cm⁻¹. MS (70 eV) m/z (%): 371 (M⁺, 16.88), 368 (100), 343 (3.39), 295 (2.17), 288 (1.92), 121 (3.69), 83 (21.23), 76 (19.72). Anal. Calcd for C₁₁H₉NS₂: 371.44 (C, 51.73; H, 2.44; N, 11.31. Found: C, 51.85; H, 2.38; N, 11.19. 3-Phenyl-5H-pyrazolo[3,4-d][1,3]thiazole-5-thione (11a)

Grey crystals; yield 45%; mp 162–164°C. 1H-NMR (DMSO-d_6): δ 7.23–7.40 (5H, Ar-H, m). 1C-NMR (DMSO-d_6): δ 226, 163.4, 132.7, 129.6, 128.6, 128.2, 127.4, 117.6. IR (KBr) v: 3050 (C=H_arom), 1636 (C=N), 1261 (C=S) cm⁻¹. Anal. Calcd for C₁₁H₁₀NS₂: 313.3 (C, 46.6; H, 3.73; N, 18.2). Found: C, 46.0; H, 3.7; N, 18.17.
v: 3071 (C–H amide), 2897 (C–H alkyl), 1618 (C=C), 1260 (C–S), 1246 (C=S), 1107 (C–O) cm$^{-1}$. MS (70 eV) $m/z$ (%): 275 (M$^+$, 9.30), 247 (17.54), 199 (1.40), 185 (9.18), 154 (0.85), 135 (100), 121 (18.28), 90 (32.32), 76 (52.55). Anal. Caled for C$_{15}$H$_{10}$N$_2$O$_4$S$_2$: C, 52.01; H, 2.91; N, 8.09. Found: C, 51.37; H, 2.28; N, 8.09.

**General Procedure for the Preparation of Compounds 9a, 9b, and 15**

**Method A**

A solution of compound 3 (1 mmol, 0.26 g) with benzaldehyde, piperonal or isatine (1 mmol) in glacial acetic acid (15 mL) in presence of anhydrous sodium acetate (3 mmol, 0.25 g) was heated under reflux for 4 h. After cooling, a solid product obtained was filtered off, dried and recrystallized from ethanol to give 9a, 9b, and 15, respectively.

**Method B**

A solution of rhodanine (1 mmol, 0.13 g) with benzaldehyde, piperonal or isatine (1 mmol) in glacial acetic acid (15 mL) in presence of anhydrous sodium acetate (3 mmol, 0.25 g) was heated under reflux for 1 h. After cooling, the solid product formed was filtered off, dried and recrystallized from ethanol to give 9a, 9b, and 15, respectively.

6-Hydroxy-1,3-thiazolo[4,5-d]pyridazin-3-ylidene-2-thiol (16)

Brown crystals; yield 54.5%; mp 221–223°C. 1H-NMR (DMSO-$d_6$) $\delta$: 7.60–7.72 (4H, Ar-H, m), 6.79–7.46 (4H, indole-H, m). IR (KBr) $\nu$: 3154 (N–H amide), 3059 (C–H arom), 1698 (C–O), 1612 (C–N=O), 1589 (C=C), 1235 (C–O) cm$^{-1}$. MS (70 eV) $m/z$ (%): 258 (M$^+$, 100). Anal. Caled for C$_{15}$H$_{10}$N$_2$O$_4$S$_2$: C, 51.55; H, 1.57; N, 21.86. Found: C, 51.74; H, 1.64; N, 22.02.

**General Procedure for the Preparation of Compounds 14 and 17**

A solution of compound 12 or 15 (1 mmol) in acetic anhydride (5 mL) was heated under reflux for 1 h. After cooling, the solid product formed was filtered off, dried and recrystallized from ethanol to give the corresponding compounds 14 and 17.

1-Acetyl-3-[4-oxo-3-(thiophen-2-ylcarbonyl)-2-thioxo-1,3-thiazolidin-5-ylidene]-1,3-dihydro-2H-indol-2-one (14)

Reddish brown crystals; yield 82%; mp 244–246°C. 1H-NMR (DMSO-$d_6$) $\delta$: 6.14 (2H, CH$_2$, s), 7.08–7.18 (3H, Ar-H, m), 7.57 (1H=CH, s), 13.74 (1H, NH, exchangeable, br, s). IR (KBr) $\nu$: 3154 (N–H amide), 2938, 2854 (C–H alkyl), 1689 (C=O), 1581 (C=I), 1260 (C–S), 1097 (C–O) cm$^{-1}$. MS (70 eV) $m/z$ (%): 258 (M$^+$, 100), 178 (27.64), 87 (2.38). Anal. Caled for C$_{15}$H$_{10}$N$_2$O$_4$S$_2$: C, 51.62; H, 1.38; N, 6.63. Found: C, 54.42; H, 3.11; N, 6.19.

**Antimicrobial Activity**

Some of the new synthesized compounds were tested for their antimicrobial activity against different microorganisms representing Gram-positive bacteria (Staphylococcus aureus and Bacillus subtilis), Gram-negative bacteria (Escherichia coli and Proteus vulgaris) using the standard antibiotic Gentamycin (MIC 4 μg/mL) as reference and fungi (Aspergillus fumigatus and Candida albicans) using the standard antibiotic Ketoconazole (MIC 100 μg/mL).

The Susceptibility tests were performed according to NCCLS recommendations (National Committee for Clinical Laboratory Standards, 1993). Screening tests regarding the inhibition zone were carried out by the well diffusion method. The inoculum suspension was prepared from colonies grown overnight on an agar plate and inoculated into Mueller–Hinton broth (fungi using malt broth). A sterile swab was immersed in the suspension and used to inoculate Mueller–Hinton agar plates (fungi using malt agar plates). The compounds were

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dissolved in dimethyl sulfoxide (DMSO) at concentration of 10mg/mL. The inhibition zone was measured around each well after 24h at 37°C. Controls using DMSO were adequately done, the mean zone of inhibition in mm beyond well diameter 6mm produced on a range of pathogenic microorganisms results are depicted in Table 1.

The results indicated that two synthesized compounds 3 and 4 showed high antimicrobial activity against the examined Gram-positive bacteria *Staphylococcus aureus*, and only one compound 4 showed high antimicrobial activity against the examined Gram-positive bacteria *Bacillus subtilis*. On the other hand, five compounds 6a, 7a, 7b, 8a, and 14 showed moderate antimicrobial activity against the examined Gram-positive bacteria *Staphylococcus aureus* as well as five compounds 3, 7b, 8a, 12, and 14 showed moderate antimicrobial activity against the examined Gram-positive bacteria *Bacillus subtilis*. Furthermore, it is clear also from the results that the synthesized compounds 7b, 8a, and 14 showed moderate antimicrobial activity against the both examined Gram-positive bacteria *Staphylococcus aureus and Bacillus subtilis*.

Also, the results revealed that four compounds 3, 4, 7a, and 7b showed high antimicrobial activity against the examined Gram-negative bacteria *Proteus vulgaris*. On the other hand, five compounds 3, 4, 6a, 7a, and 7b, and four compounds 6a, 8a, 12, and 14 showed moderate antimicrobial activity against the examined Gram-negative bacteria *Escherichia coli* and *Proteus vulgaris*, respectively. Only one compound 6a showed moderate antimicrobial activity against the both examined Gram-negative bacteria *Escherichia coli* and *Proteus vulgaris*, as shown in Table 1.

In addition, one compound 3 showed very high antifungal activity against the examined fungi *Aspergillus fumigatus*, while three compounds 3, 4 and 6a showed high antifungal activity against the examined fungi *Candida albicans*. Only compound 4 showed moderate antifungal activity against the examined fungi *Aspergillus fumigatus*, as well as only one compound 13 showed moderate antifungal activity against *Candida albicans*, as shown in Table 1.

In conclusion, results of antimicrobial activity revealed that the synthesised compounds showed moderate and/or high antimicrobial activity against the examined bacteria and fungi, respectively.

**Conflict of Interest** The authors declare no conflict of interest.

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| Compound | Gram-positive bacteria | Gram-negative bacteria | Fungi |
|----------|------------------------|------------------------|-------|
|          | *Staphylococcus aureus* | *Bacillus subtilis* | *Aspergillus fumigatus* | *Candida albicans* |
|          | RCMB 010010 | RCMB 015 | RCMB 0052 | RCMB 00208 | RCMB 005003 |
| 3        | 19 | 15 | 16 | 18 | 22 | 20 |
| 4        | 20 | 17 | 15 | 17 | 15 | 17 |
| 6a       | 13 | 12 | 13 | 15 | 12 | 18 |
| 6b       | 10 | 9 | NA | NA | NA | NA |
| 7a       | 13 | 12 | 14 | 18 | NA | NA |
| 7b       | 15 | 16 | 13 | 17 | NA | NA |
| 8a       | 13 | 14 | 12 | 14 | NA | 10 |
| 8b       | 11 | 12 | 10 | NA | NA | 12 |
| 12       | 12 | 14 | 12 | 14 | NA | NA |
| 13       | 10 | 9 | 11 | 12 | NA | 14 |
| 14       | 14 | 13 | 12 | 14 | NA | NA |
| Gentamycin | 24 | 26 | 30 | 25 | — | — |
| Ketoconazole | — | — | — | — | — | 17 |
|          |          |          |          |          | 20 |

*a Zone of inhibition: 0–12 mm (low); 13–16 mm (moderate); 17–20 mm (high); >20 mm (very high); NA = No activity; Well diameter of the hole=6.0 mm (100 µL was tested); RCMB: Regional Center for Mycology and Biotechnology.*
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