*Research Paper*

Journal of Chemical Research

# Utility of 3-(thiophen-2-yl)prop-2-enoyl isothiocyanate in heterocyclic synthesis

Journal of Chemical Research
1–8

DOI: 10.1177/1747519819862176
journals.sagepub.com/home/chl
SAGE

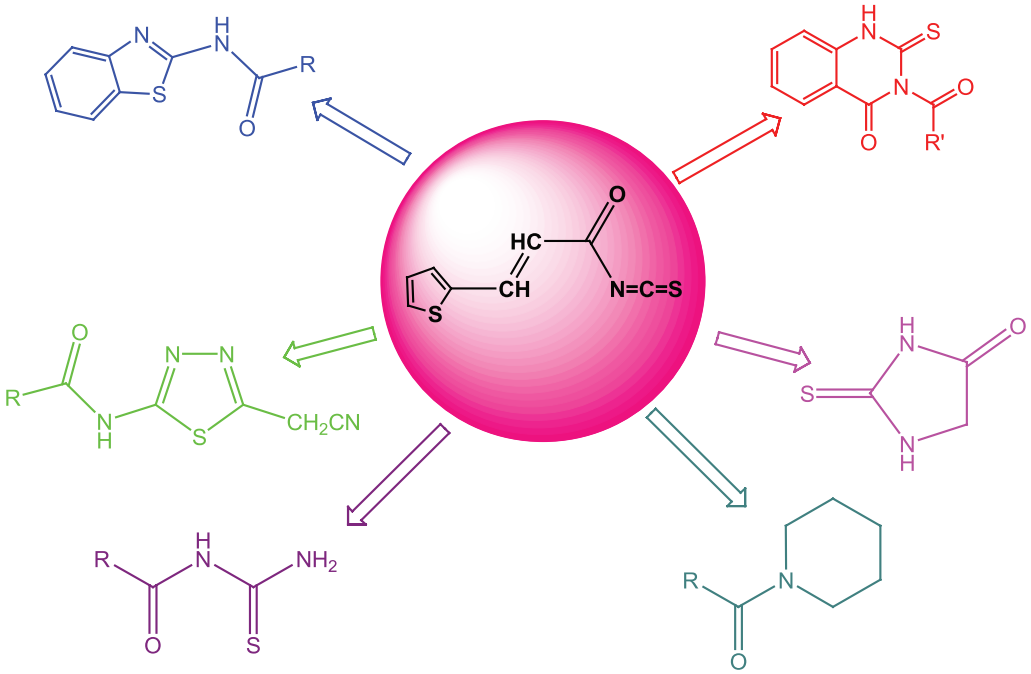
**Amira A El-Sayed, Saad R Atta-Allah and Magdy M Hemdan**

## Abstract

Convenient syntheses of quinazoline, benzothiazole, thiadiazole, imidazole, and thiourea derivatives starting from 3-(thiophen-2-yl)prop-2-enoyl isothiocyanate are described. The structures of the synthesized compounds are confirmed from their microanalytical and spectral data. Some of the products are examined for their antibacterial activity against Gram-positive and Gram-negative bacteria and fungi.

## Keywords

3-(thiophen-2-yl)prop-2-enoyl isothiocyanate, benzothiazoles, imidazoles, quinazolines, thiadiazoles, thioureas

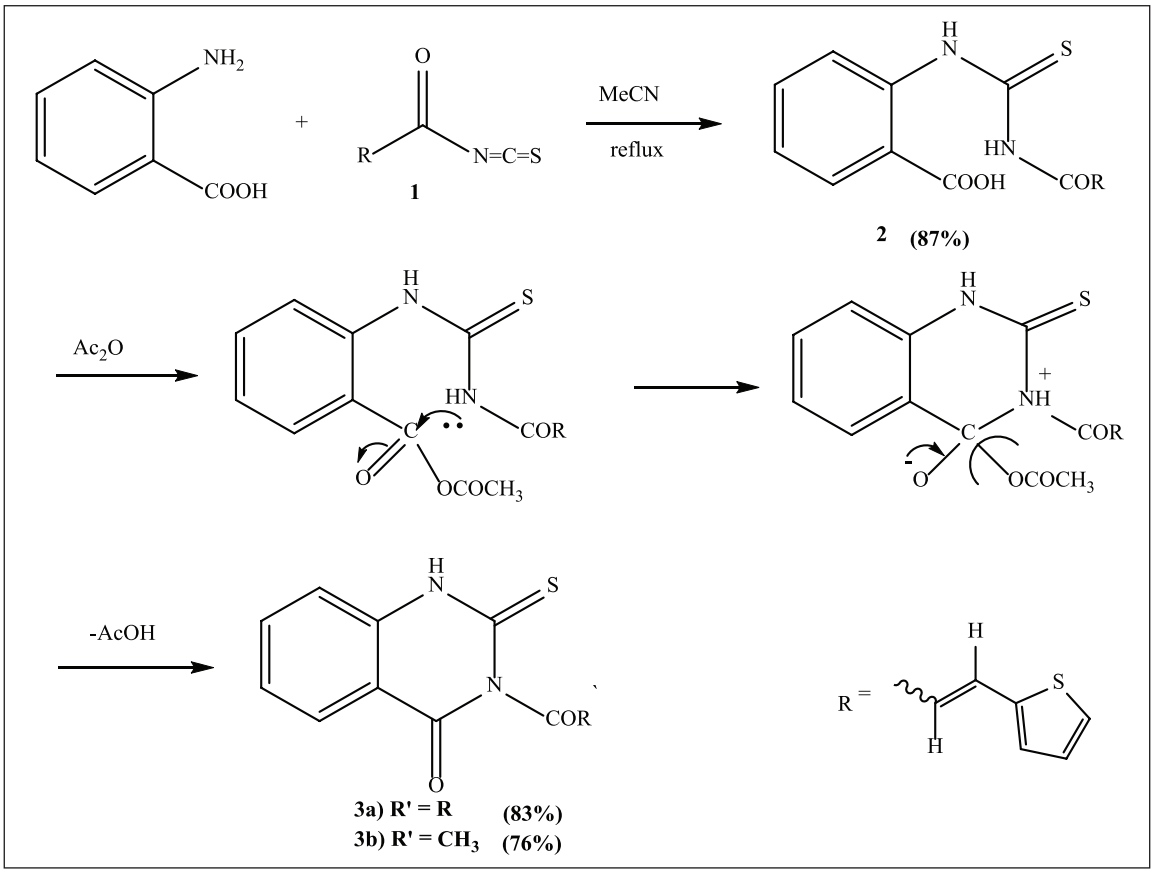



## Introduction

Extensive studies on the chemistry of aroyl isothiocyanates have established the value of these reagents as starting materials for the syntheses of a wide variety of heterocyclic compounds and thiourea derivatives.[1–11] Highly reactive α,β-unsaturated acyl isothiocyanates can be useful intermediates in organic synthesis, because their multiple bonds can participate in cyclization reactions.[12] In addition, intramolecular cyclization of α,β-unsaturated acylthioureas, formed in the reaction of α,β-unsaturated acyl isothiocyanates and amines, have been reported.[13–16] In this investigation, we utilized a heterocyclic α,β-unsaturated acyl isothiocyanate in order to synthesize several heterocyclic compounds expected to

Department of Chemistry, Faculty of Science, Ain Shams University, Cairo, Egypt

**Corresponding author:**
Amira A El-Sayed, Department of Chemistry, Faculty of Science, Ain Shams University, Abbasia, Cairo 11566, Egypt.
Email: amira_aa47@hotmail.com



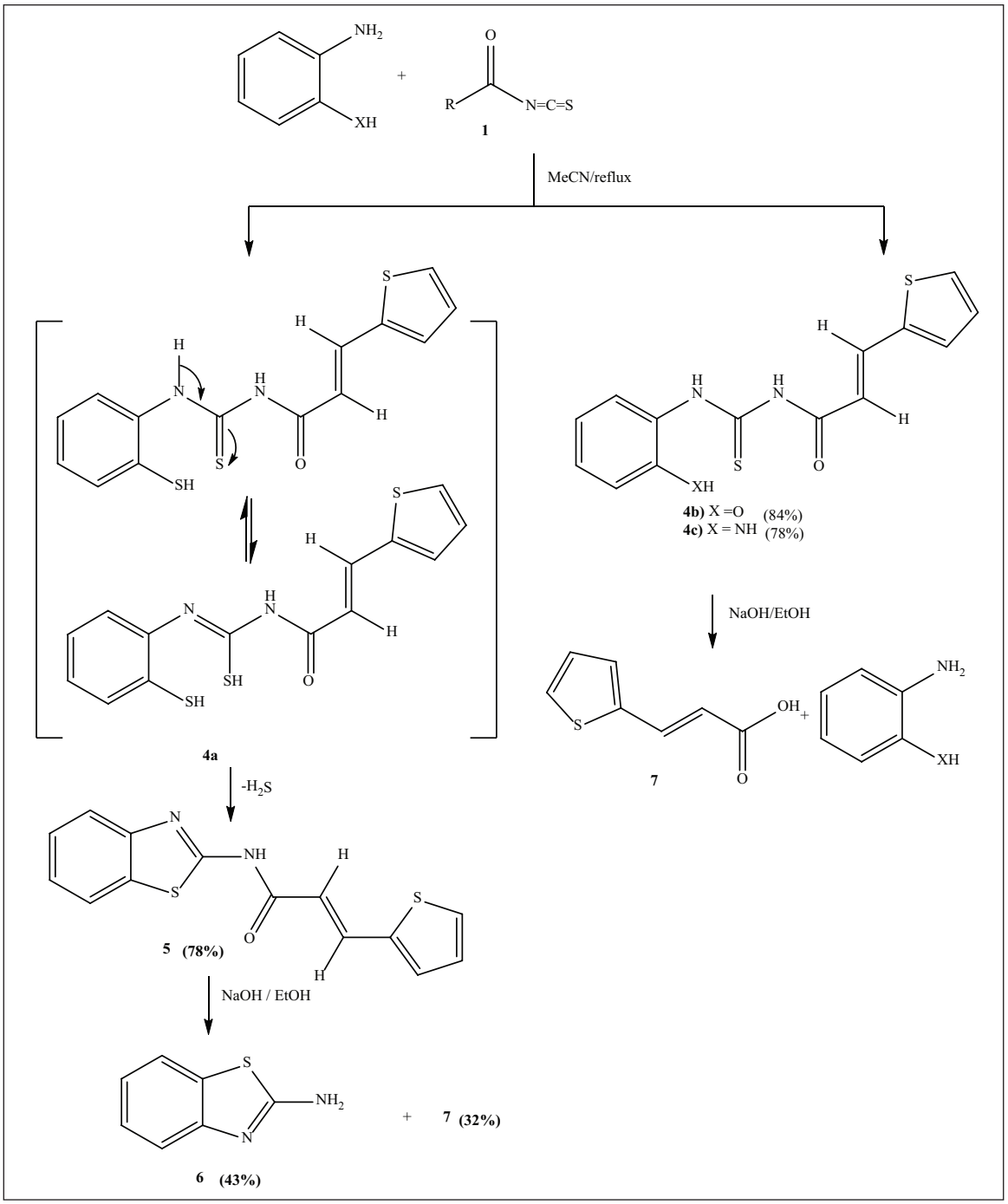

**Scheme 1.** Synthesis of quinazolines **3a,b**.

demonstrate antibacterial activity against Gram-positive and Gram-negative bacteria and fungi.

## Results and discussion

In the current study, transformations of 3-(thiophen-2-yl) prop-2-enoyl isothiocyanate (**1**)[7] has been performed, leading to the novel derivatives of quinazoline, benzothiazole, thiadiazole, imidazole, and thiourea derivatives. Thus, addition of an equimolar amount of anthranilic acid to a solution of 3-(thiophen-2-yl)prop-2-enoyl isothiocyanate (**1**) in boiling acetonitrile produced thiourea derivative **2**. Heating the adduct **2** in acetic anhydride for 1 h afforded quinazoline derivative **3a** (Scheme 1). Moreover, when compound **2** was heated in acetic anhydride for 3 h, quinazoline **3b** was obtained in a good yield. Compound **3b** has been also formed by heating quinazoline **3a** in acetic anhydride for 3 h. The infrared (IR) spectra of compounds **2** and **3** showed absorption frequencies for NH, CO, and C=S groups, as well as an absorption for the OH group of compound **2**. Their $^1$H NMR spectra displayed signals for aromatic protons besides NH protons in the downfield region that were exchangeable with $D_2O$. In addition, olefinic protons were observed for compounds **2** and **3a**. Inspection of the $^1$H NMR spectrum of compound **2** showed the existence of extra signals corresponding to olefinic as well as acidic protons, with an integration ratio of 70:30. This is good proof for its existence as a mixture of *E*/*Z* stereoisomers in the ratio 2:1. The second olefinic proton of the *Z*-isomer is hidden under the multiplets due to the aromatic signals. The higher ratio of the *E*-isomer compared with the *Z* counterpart could be attributed to its higher stability because of hindrance. On the contrary, compound **3a** exists exclusively as the *E*-isomer, since its configuration is based on the higher value of the CH=CH coupling constant ($J$=15.6 Hz). The mass spectra of the synthesized compounds revealed mass ions in accord with their proposed structures (see the experimental analysis section). The formation of quinazoline derivatives **3** obviously proceeds via cyclization of thiourea derivative **2** by removing a molecule of water.

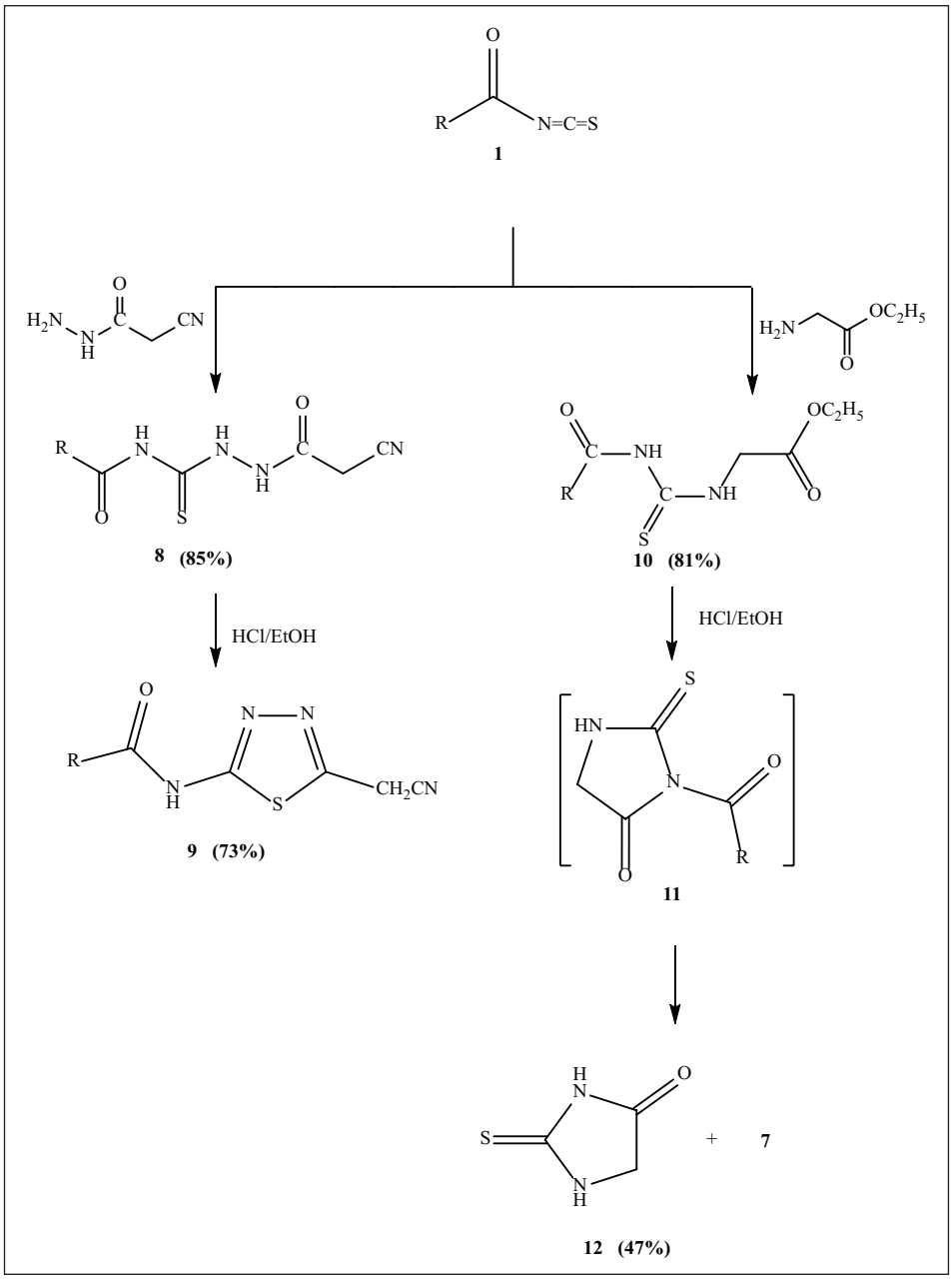
Treatment of isothiocyanate **1** with *o*-aminothiophenol in dry acetonitrile afforded benzothiazole derivative **5** in a good yield. However, the reaction of isothiocyanate **1** with *o*-aminophenol and/or *o*-phenylenediamine gave the open adducts **4b** and **4c**, respectively. Boiling compound **5** in ethanolic sodium hydroxide solution furnished a mixture of 2-amino-1,3-benzothiazole **6** and acrylic acid derivative **7**. On the contrary, compounds **4b** and **4c** produced acrylic acid derivative **7** on treatments with ethanolic sodium hydroxide (Scheme 2). The structures of compounds **4**–**7** were substantiated from their microanalytical and spectral data. Thus, their IR spectra showed bands correlating with their functional groups (see the experimental analysis section). Further support for the assigned structures of compounds **4**–**7** was gained from their $^1$H NMR spectra, which exhibit signals characteristic for aromatic protons and NH protons (compounds **4**–**6**) in addition to OH protons for compounds **4b** and **7** in the downfield region that were exchanged following a $D_2O$ shake. The configurational assignment of compounds **4**, **5**, and **7** as the *E*-configured isomers was based on the coupling constants of their olefinic protons, which were in




**Scheme 2.** Reactions of isothiocyanate **1** with *o*-aminothiophenol, *o*-aminophenol, and *o*-pheneylene diamine.

the expected range of *trans* isomers. The formation of compound **5** can be explained on the basis of nucleophilic attack of the amino group of the *o*-aminothiophenol on the isothiocyanato carbon atom of **1** producing non-isolable thiourea derivative **4a**, which then cyclizes to afford compound **5** via removal of $H_2S$. The highly nucleophilic character of the sulfur atom of the SH group is responsible for the ease of cyclization of **4a** in comparison to **4b** and **4c**. Compounds **6** and **7** were obtained as the result of amide hydrolysis of the corresponding compounds.

The interaction of isothiocyanate **1** and 2-cyanoacetohydrazide and/or ethyl glycinate HCl produced adducts **8** and **10**, respectively. Heating of the adduct **8** in ethanolic hydrochloric acid solution afforded thiadiazole derivative **9** in a good yield. On the contrary, refluxing of the compound **10** in ethanolic hydrochloric acid solution afforded a mixture of 2-thioxoimidazolidin-4-one (**12**) and acid **7** (Scheme 3). The IR spectra of compounds **8**–**10** and **12** showed absorption frequencies correlating with NH and CO groups, in addition to CN groups for compounds **8** and **9**. Their $^1$H NMR spectra displayed signals corresponding to $CH_2$ protons, while the NH protons were in the downfield region and were exchangeable with $D_2O$. The appearance of two doublet signals with higher coupling constants values, in the range ($J$=15.4–15.6 Hz), suggests the existence of compounds **8**, **9**, and **10** as the *E*-configured isomers. Further evidence for the assigned structures of the synthesized compounds **8**–**10** and **12** was gained from their mass spectral data, which revealed the




**Scheme 3.** Reactions of isothiocyanate **1** with 2-cyanoacetohydrazide and ethyl glycinate.

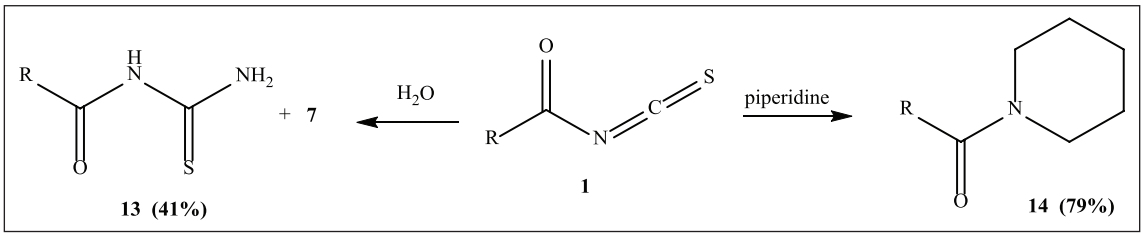
correct molecular ion peaks and some important peaks that were in accord with their proposed structures. The formation of compound **9** is understood to occur via cyclization of the open adduct **8** with removal of a molecule of water. Compound **12** is formed by acid-catalyzed hydrolysis of compound **10** through removal of an ethanol molecule to afford the non-isolable intermediate **11**, followed by hydrolysis.

Refluxing a solution of the isothiocyanate **1** in acetonitrile in the presence of a few drops of distilled water gave a mixture of thiourea derivative **13** and the acid **7**. On the contrary, the amide derivative **14** was obtained upon heating of a solution of **1** in acetonitrile in the presence of piperidine (Scheme 4). The assigned structures for compounds **13** and **14** were gained from their IR, which displayed NH, $NH_2$, and C=O absorptions for compound **13** and a C=O frequency for compound **14**. Analysis of the $^1$H NMR spectrum of compound **13** revealed its existence as a mixture of *E*/*Z* stereoisomers in the ratio of 2:1. The appearance of the two hydrogen atoms of the $NH_2$ group as two broad singlets was good evidence for their magnetic non-equivalence. This suggests the existence of compound **13** as its chelated form as shown in Scheme 5. The $^1$H NMR spectrum of compound **14** showed that it existed as the *E*-configured isomer (see the experimental analysis section).

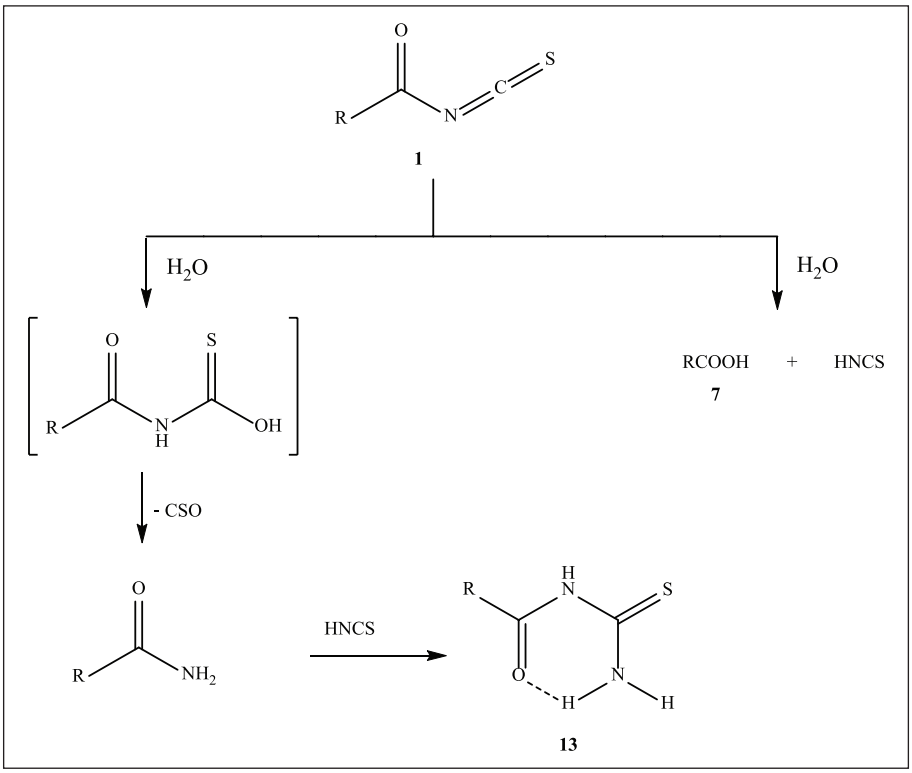
The mechanism of formation of compound **13** can be visualized as shown in Scheme 5. The formation of compound **14** is thought to occur via attack of the nitrogen atom of the piperidine molecule on the carbonyl group of **1**, followed by isothiocyanato group displacement.

## Antimicrobial activity

The prepared heterocyclic compounds **2**, **3**, **5**, **7**, **8**, and **9** were examined for their antibacterial activity against




**Scheme 4.** Formation of compounds **13** and **14**.




**Scheme 5.** The mechanism of formation of compound **13**.

Gram-positive bacteria (*Bacillus cereus* and *Staphylococcus aureus*), Gram-negative bacteria (*Escherichia coli* and *Pseudomonas aeruginosa*) and fungi (*Candida albicans* and *Aspergillus fumigatus*).[17,18] Compounds **2**, **3**, and **5** proved to be good antimicrobial agents, as shown in Table 1 and Figure 1.

## Experimental analysis

Melting points were measured on an electrothermal melting point apparatus and are uncorrected. The elemental analyses were recorded on a Perkin-Elemer 2400 CHN elemental analyzer (USA). The IR spectra were recorded on a FTIR Maltson (infinity series) spectrophotometer LABX (Canada) as KBr disks. The $^1$H NMR spectra were measured using a Varian Gemini 300-MHz spectrometer LABX (Canada), with chemical shifts (δ) expressed in ppm downfield from tetramethylsilane (TMS) as the internal standard, in DMSO-$d_6$. Mass spectra were determined on a Shimadzu GC-MSQP 1000 EX instrument (Japan) operating at 70 eV. Thin-layer chromatography (TLC) was run using TLC aluminum sheets coated with silica gel $F_{254}$ (Merck, England) to monitor the progress of all reactions and the homogeneity of the synthesized compounds. 3-(Thiophen-2-yl)prop-2-enoyl isothiocyanate (**1**) was synthesized as described in the literature.[7]

### *Reactions of isothiocyanate (**1**) with the different nucleophiles; general procedure*

To a solution of isothiocyanate **1** (3 mmol) in dry acetonitrile (30 mL) was added anthranilic acid (3 mmol). The reaction mixture was refluxed for 3 h and cooled to room temperature. The precipitated solid product was collected and recrystallized to give compound **2**. The same procedure was performed with *o*-aminothiophenol, *o*-aminophenol, *o*-phenylenediamine, 2-cyanoacetohydrazide, ethyl glycinate, distilled water, and piperidine. The progress of all reactions and the homogeneity of the synthesized compounds were monitored by TLC. The solid obtained for each reaction was recrystallized from a suitable solvent to give the corresponding compound.

*(E, Z)-2-(3-(3-(thiophen-2-yl)acryloyl)thioureido)benzoic acid* (**2**): Yellow crystals, 87%; m.p. 187–189 °C

**Table 1.** Antimicrobial Activity Data.

| Compound | Inhibition zone diameter (cm/gm sample) | | | | | |
|---|---|---|---|---|---|---|
| | *B. cereus* ($G^+$) | *S. aureus* ($G^+$) | *E. coli* ($G^-$) | *P. aeruginosa* ($G^-$) | *C. albicans* (fungi) | *A. fumigatus* (multicellular fungi) |
| **2** | 20 | 24 | 35 | 21 | 15 | 10 |
| **3** | 20 | 23 | 33 | 20 | 14 | 11 |
| **5** | 12 | 10 | 22 | 13 | 9 | 4 |
| **7** | 13 | 17 | 23 | 12 | 8 | 6 |
| **8** | 12 | 16 | 24 | 11 | 8 | 5 |
| **9** | 19 | 25 | 35 | 19 | 15 | 13 |
| **S** | 25 | 30 | 40 | 25 | – | – |
| **F** | – | – | – | – | 20 | 15 |

**S**: septrin DS (antibacterial agent); **F**: Fungistatin (antifungal agent); *B. cereus: Bacillus cereus; S. aureus: Staphylococcus aureus; E. coli: Escherichia coli; P. aeruginosa: Pseudomonas aeruginosa; C. albicans: Candida albicans; A. fumigatus: Aspergillus fumigatus*.

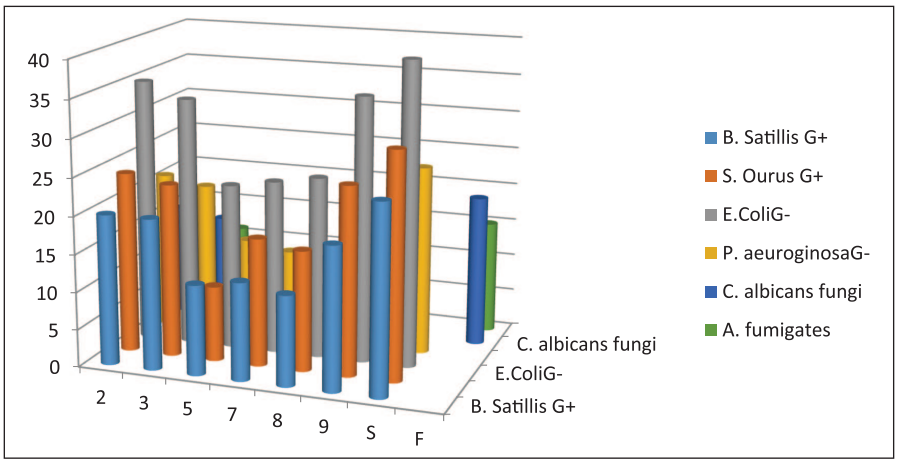



**Figure 1.** Graphical Representation of Antimicrobial Activity.

(EtOH); IR (KBr): 3400 (br. OH), 3272 (NH), 3052 (ArH), 1666 (CO), 1592 (C=C), 1162 (CS), 754 $cm^{-1}$ $\delta_{4H}$; $^1H$ NMR (300 MHz) (DMSO-*d*) δ 7.17 (m, 1H), 7.36 (t, 1H, *J* = 6.8 Hz), 7.54–7.64 (m, 2H), 7.80–7.97 (m, 2H), 8.10 (d, 1H, *J* = 7.6 Hz), 3.49 (br s, 1H, 1NH, exchangeable), For *the E*-isomer: 6.83 (d, 1H, CH=, *J* = 15.4 Hz), 7.94 (d, 1H, CH=, *J* = 15.4 Hz), 11.55 (br s, 1H, 1NH, exchangeable), 13.09 (br s, 1H, 1OH, exchangeable); For *Z*-isomer: 6.53 (d, 1H, CH=, *J* = 11.2 Hz), 7.76 (d, 1H, CH=, *J* = 4.8 Hz), 10.72 (br s, 1H, 1NH, exchangeable), 12.19 (br s, 1H, 1OH, exchangeable); MS (70 eV): *m/z* (%): 332 ($M^+$, absent), 314 ($M^+$-$H_2O$, 13), 298 ($M^+$-$H_2S$, 4), 171 (2), 162 (54), 146 (3), 137 (100), 119 (21), 109 (51), 92 (22), 65 (61), 63 (36); Anal. calcd for $C_{15}H_{12}N_2O_3S_2$ (332.40): C, 54.20; H, 3.64; N, 8.43; found C, 53.82; H, 3.51; N, 8.57.

*(E)-N-(3,1-benzothiazol-2-yl)-3-(thiophen-2-yl)acrylamide* (**5**): Colorless crystals, 78%; m.p. 245–247 °C (EtOH); IR (KBr) υ: 3236 (NH), 3067 (ArH), 1660 (CO), 1598 (C=C), 751 $cm^{-1}$ $\delta_{4H}$; $^1H$ NMR (300 MHz) (DMSO-*d*6) δ 6.71 (d, 1H, CH=, *J* = 15.4 Hz), 7.44 (d, 1H, CH=, *J* = 15.4 Hz), 7.18–8.00 (m, 7H, ArH), 12.51 (br s, 1H, 1NH, exchangeable); MS (70 eV): *m/z* (%): 286 ($M^+$, 11), 258 ($M^+$-CO, 6), 226 (2), 151 (3), 150 (8), 149 (28), 137 (99), 109 (100), 108 (28), 83 (12),65 (84); Anal. calcd for $C_{14}H_{10}N_2OS_2$ (286.37): C, 58.72; H, 3.52; N, 9.78; found C, 58.65; H, 3.16; N, 9.54.

*(E)-1-(2-hydroxyphenyl)-3-(3-(thiophen-2-yl)acryloyl) thiourea* (**4b**): Yellow crystals, 84%, m.p. 214–216 °C (EtOH); IR (KBr) υ: 3480 (br OH), 3334 (NH), 3038 (ArH), 1666 (CO), 1600, 1558 (C=C), 1198 (C=S), 740 $cm^{-1}$; $^1H$ NMR (300 MHz) (DMSO-*d*6) δ 6.83 (d, 1H, CH=, *J* = 15.6 Hz), 6.82 (m, 1H, ArH), 6.93 (d, 1H, *J* = 8.1 Hz), 7.05 (t, 1H, *J* = 7.2 Hz), 7.18 (t, 1H, *J* = 4.5, 3.6 Hz), 7.53 (d, 1H, *J* = 3.6 Hz), 7.76 (d, 1H, *J* = 4.8 Hz), 7.94 (d, 1H, CH=, *J* = 15.6 Hz), 8.56 (d, 1H, *J* = 8.4 Hz), 10.18 (br s, 1H, NHCS, exchangeable), 11.41 (br s, 1H, CONHCS, exchangeable), 12.93 (br s, 1H, 1OH, exchangeable); MS (70 eV): *m/z* (%): 304 ($M^+$, 4), 271 ($M^+$-SH, 9), 167 (4), 152 (6), 137 (100), 136 (7), 109 (64), 108 (15), 78 (18), 108 (28), 65 (59); Anal. calcd for $C_{14}H_{12}N_2O_2S_2$ (304.39): C, 55.24; H, 3.97; N, 9.20; found C, 55.37; H, 3.86; N, 8.96.

*(E)-1-(2-aminophenyl)-3-(3-(thiophen-2-yl)acryloyl) thiourea* (**4c**): Yellow crystals; 78%, m.p. 179–181 °C (EtOH); IR (KBr) υ: 3382, 3300, 3132 (NH), 3063 (ArH), 1674 (CO), 1612 (C=C), 1170 (C=S), 744 $cm^{-1}$ $\delta_{4H}$; $^1H$ NMR (300 MHz) (DMSO-*d*6) δ 5.01 (br s, 2H, $NH_2$, exchangeable), 6.59 (t, 1H, *J* = 8.1 Hz), 6.77 (d, 1H, *J* = 8.1 Hz), 6.83 (d, 1H, CH=, *J* = 15.6 Hz), 7.00 (t, 1H, *J* = 7.5 Hz), 7.14 (t, 1H, *J* = 3.9, 4.8 Hz), 7.31 (d, 1H, *J* = 7.8 Hz), 7.53 (m, 1H, *J* = 3.8 Hz),7.75 (d, 1H, *J* = 5.1 Hz), 7.92 (d, 1H, CH=, *J* = 15.3 Hz), 11.43 (br s, 1H, NHCS,

exchangeable), 11.99 (br. s, 1H, CONHCS, exchangeable); MS (70 eV): *m/z* (%): 303 ($M^+$, 6), 302 ($M^+$-H, 3), 270 ($M^+$-SH, 8), 269 (8), 153 (26), 152 (11), 150 (70), 137 (100), 134 (14), 133 (15), 109 (76), 108 (27),78 (11),65 (78); Anal. calcd for $C_{14}H_{13}N_3OS_2$ (303.40): C, 55.42; H, 4.32; N, 13.85; found C, 55.16; H, 4.09; N, 13.63.

*(E)-1-(2-cyanoacetyl)-4-(3-(thiophen-2-yl)acryloyl)thiosemicarbazide* (**8**): Pale yellow crystals, 85%, m.p. 210 °C (with decomposition), (EtOH); IR (KBr) υ: 3291, 3181, 3102 (NH), 3073, 3017 (ArH), 2930, 2903 (alkyl-H), 2260 (CN), 1679 (CO), 1614, (C=C), 1180 (C=S) $cm^{-1}$; $^1$H NMR (300 MHz) (DMSO-*d*6) δ 3.84 (s, 2H, $CH_2$), 6.75 (d, 1H, CH=, *J*=15.6 Hz), 7.13 (t, 1H, *J*=4.8, 3.9 Hz), 7.54 (d, 1H, *J*=3.0 Hz), 7.75 (d, 1H, *J*=5.4 Hz), 7.91 (d, 1H, CH=, *J*=15.6 Hz), 11.15 (br s, H, NHCS, exchangeable), 11.62 (br s, H, NHCO, exchangeable), 12.44 (br s, H, CONHCS, exchangeable); MS (70 eV): *m/z* (%): 294 ($M^+$,8), 276 ($M^+$-$H_2O$, 4), 249 (5), 235 (6), 209 (8), 154 (8), 137 (100), 109 (88), 99 (25), 65 (35); Anal. calcd for $C_{11}H_{10}N_4O_2S_2$ (294.35): C, 44.88; H, 3.42; N, 19.03; found C, 44.66; H, 3.19; N, 18.72.

*(E)-ethyl 2-(3-(3-(thiophen-2-yl)acryloyl)thioureido) acetate* (**10**): Colorless crystals, 81%, m.p. 162–164 °C, (EtOH); IR (KBr) υ: 3208, 3150 (NH), 3048 (ArH), 2973 (alkyl-H), 1750 ($CO_{ester}$), 1678 ($CO_{amide}$), 1616 (C=C), 1116 (C=S) $cm^{-1}$; $^1$H NMR (300 MHz) (DMSO-*d*6) δ 1.32 (t, 3H, $CH_3$, *J*=7.2), 4.27 (q, 2H, $OCH_2$, *J*=7.2), 4.45 (s, 2H, $NCH_2CO$), 6.19 (d, 1H, CH=, *J*=15.4 Hz), 7.09–7.44 (m, 3H), 7.92 (d, 1H, CH=, *J*=14.6 Hz), 8.68 (br s, 1H, NHCS, exchangeable), 11.08 (br s, H, CONHCSNH, exchangeable); MS (70 eV): *m/z* (%): 298 ($M^+$, 8), 253 ($M^+$-OEt, 1), 138 (9), 137 (100), 109 (34), 83 (39), 65 (31); Anal. calcd for $C_{12}H_{14}N_2O_3S_2$ (298.38): C, 48.30; H, 4.73; N, 9.39; found C, 48.41; H, 4.63; N, 9.11.

*(E/Z)-1-(3-(thiophen-2-yl)acryloyl)thiourea* (**13**): Colorless crystals, 41%, m.p. 222–224 °C, (EtOH); IR (KBr) υ: 3320, 3232, 3164 (NH), 3043 (ArH), 1684 (CO), 1590 (C=C), 1158 (C=S) $cm^{-1}$; $^1$H NMR (300 MHz) (DMSO-*d*6) δ 7.15 (t, 1H, *J*=3.9 Hz), 7.50 (d, 1H, *J*=3.3 Hz), 7.73 (d, 1H, *J*=4.5 Hz), 9.38, 9.77 (two br. s, 2H, $NH_2$, exchandeable), 11.13 (br s, 1H, CONHCS, exchangeable), For *E*-isomer: 6.74 (d, 1H, CH=, *J*=15.6 Hz), 7.84 (d, 1H, CH=, *J*=15.3 Hz), For *Z*-isomer: 6.60 (d, 1H, CH=, *J*=12.6 Hz), 8.04 (d, 1H, CH=, *J*=7.8 Hz); MS (70 eV): *m/z* (%): 212 ($M^+$, 34), 179 ($M^+$-SH, 10), 152 (2), 137 (100), 109 (57), 83 (4), 65 (47); Anal. calcd for $C_8H_8N_2OS_2$ (212.29): C, 45.26; H, 3.80; N, 13.20; found C, 44.88; H, 3.63; N, 12.86.

*(E)-1-(piperidin-1-yl)-3-(thiophen-2-yl)prop-2-en-1-one* (**14**): Colorless crystals, 79%, m.p. 244–246 °C, (EtOH); IR (KBr) υ: 3098 (ArH), 2940, 2860 (alkyl-H), 1630 (CO), 1574 (C=C) $cm^{-1}$; $^1$H NMR (300 MHz) (DMSO-*d*6) δ 1.37–1.72 (m, 6H, 3 $CH_2$-piperidyl), 3.43–3.62 (m, 4H, 2 $CH_2$-piperidyl), 6.94 (d, 1H, CH=, *J*=15.0 Hz), 7.12–7.18 (m, 1H, thienyl), 7.4.2–7.51 (m, 1H, thienyl), 7.64 (d, 1H, CH=, *J*=12.4 Hz), 7.65 (m, 1H, thienyl); MS (70 eV): *m/z* (%): 221 ($M^+$, 12), 137 (100), 109 (86), 83 (9), 65 (31); Anal. calcd for $C_{12}H_{15}NOS$ (221.32): C, 65.12; H, 6.83; N, 6.33; found C, 65.36; H, 6.71; N, 6.12.

## *Formation of compounds* **3a** *and* **3b**

A solution of compound **2** (1 g) in acetic anhydride (10 mL) was refluxed for 1 h. The solid product obtained was filtered off and recrystallized to give compound **3a**. Compound **3b** was obtained after 3 h of refluxing compound **2** in acetic anhydride. In addition, compound **3a** was refluxed in acetic anhydride for 3 h to afford **3b**.

*(E)-3-(3-(thiophen-2-yl)acryloyl)-2-thioxo-2,3-dihydroquinazolin-4(1H)-one* (**3a**): Colorless crystals 83%, m.p. 240–242 °C (EtOH); IR (KBr) υ: 3222, 3191, 3100 (NH), 3058 (ArH), 1685 (CO), 1622 (C=C), 1153 (CS), 746 $cm^{-1}$ $\delta_{4H}$; $^1$H NMR (300 MHz) (DMSO-*d*6) δ 6.73 (d, 1H, CH=, *J*=15.3 Hz), 7.17 (t, 1H, *J*=4.5 Hz),7.52 (t, 2H, *J*=7.2 Hz), 7.62 (d, 1H, *J*=7.8 Hz), 7.74 (d, 1H, *J*=4.8 Hz), 7.88 (d, 1H, *J*=5.8 Hz), 7.89 (d, 1H, CH=, *J*=15.6 Hz), 8.06 (d, 1H, *J*=7.8 Hz), 12.02 (br s, 1H, 1NH, exchangeable); MS (70 eV) *m/z* (%): 314 ($M^+$, 27), 205 (7), 177 (65), 145 (32), 137 (100), 120 (67), 109 (76), 103 (18), 83 (12), 65 (37); Anal. calcd for $C_{15}H_{10}N_2O_2S_2$ (314.38):C, 57.31; H, 3.21; N, 8.91; found C, 57.12; H, 2.97; N, 8.76.

*3-acetyl-2-thioxo-2,3-dihydroquinazolin-4(1H)-one* (**3b**): Colorless crystals, 76%, m.p. 269–271 °C (EtOH); IR (KBr) υ: 3211, 3197 (NH), 3062 (ArH), 2918 (alkyl-H), 1658 (CO), 1278 (CS), 766 $cm^{-1}$ $\delta_{4H}$; $^1$H NMR (300 MHz) (DMSO-*d*6) δ 2.14 (s, 3H, $CH_3CO$), 7.52 (t, 1H, *J*=8.1, 6.9 Hz), 7.59 (d, 1H, *J*=8.1 Hz),7.87 (t, 1H, *J*=6.9 Hz), 8.04 (d, 1H, *J*=7.8 Hz), 11.87 (br s, 1H, 1NH, exchangeable); MS (70 eV): *m/z* (%): 220 ($M^+$, 38), 221 ($M^+$+1, 6), 205 ($M^+$-$CH_3$, 7), 179 (18), 178 (100), 162 (54), 150 (46), 145 (38), 120 (67), 90 (74),63 (68); Anal. calcd for $C_{10}H_8N_2O_2S$ (220.25): C, 54.53; H, 3.66; N, 12.72; found C, 54.61; H, 3.48; N, 12.43.

## *Formation of compounds* **6** *and* **7**

A solution of compound **5** (1 g) in ethanol (30 mL) and 3-M sodium hydroxide (5 mL) was refluxed for 1 h. The reaction mixture was concentrated under vacuum and then cooled to room temperature. To an ice-cold solution of the reaction mixture was added 3-M hydrochloric acid. The precipitated solid was collected to give a mixture of compounds **6** and **7**, which were separated by fractional crystallization. A similar procedure was performed in the case reactions of compounds **4b** and **4c**.

*2-amino-3,1-benzothiazole* (**6**): Colorless crystals, 43%, m.p. 124–126 °C (m.p. 126–128 °C) [16] (light petroleum 60–80 °C); IR (KBr) υ: 3394, 3270 ($NH_2$), 3055 (ArH), 1642 (C=N), 741 $cm^{-1}$ $\delta_{4H}$; $^1$H NMR (300 MHz) (DMSO-*d*6) δ 6.99 (t, 1H, *J*=7.5, *J*=7.8 Hz), 7.19 (t, 1H, *J*=7.2 Hz, *J*=7.8 Hz), 7.32 (d, 1H, *J*=8.1 Hz), 7.40 (br s, 2H, $NH_2$, exchangeable), 7.63 (d, 1H, *J*=7.5 Hz); MS (70 eV) *m/z* (%): 150 ($M^+$, 100), 133 (2), 123 (23), 118 (5), 108 (5), 96 (26), 82 (5); Anal. calcd for $C_7H_6N_2S$ (150.20): C, 55.97; H, 4.03; N, 18.65; found C, 55.69; H, 3.81; N, 18.23.

*(E)-3-(thiophen-2-yl)acrylic acid* (**7**): Colorless crystals, 32%, m.p. 144–146 °C (m.p. 145–148 °C) [19] (EtOH); IR (KBr) υ: 3085–2584 (br OH), 3085 (ArH), 1675 (CO), 1614 (C=C) $cm^{-1}$; $^1$H NMR (300 MHz) (DMSO-*d*6) δ 6.17

(d, 1H, CH=, *J*=15.6 Hz), 7.12–7.15 (m, 1H, ArH), 7.50 (d, 1H, *J*=3.6 Hz),7.66–7.68 (m, 1H, ArH), 7.73 (d, 1H, CH=, *J*=15.9 Hz), 12.33 (br s, 1H, 1OH, exchangeable); MS (70 eV) *m/z* (%): 154 ($M^+$, 100), 137 (65), 121 (56), 109 (52), 97 (27), 65 (32); Anal. calcd for $C_7H_6O_2S$ (154.19): C, 54.53; H, 3.92; found C, 54.22; H, 3.67.

### *Formation of compounds* **9** *and* **12**

A solution of compound **8** or **10** (1 g) in ethanol (30 mL) and 3-M hydrochloric acid (5 mL) was refluxed for 2 h. The reaction mixture was evaporated in vacuo to *ca* half-volume. A solution of 10% sodium carbonate was added until effervescence ceased. The precipitated solid was filtered off and recrystallized to give compounds **9** or **12**.

*(E)-N-(5-(cyanomethyl)-1,3,4-thiadiazol-2-yl)-3-(thiophen-2-yl)acrylamide* (**9**): Pale yellow crystals, 73%, m.p. 296–298 °C, (dioxane); IR (KBr) υ: 3242, 3155, 3111 (NH), 3022 (ArH), 2909, 2830 (alkyl-H), 2250 (CN), 1670 (CO), 1611 (C=N), 1565 (C=C) $cm^{-1}$; $^1H$ NMR (300 MHz) (DMSO-*d*6) δ 4.52 (s, 2H, $CH_2$), 6.66 (d, 1H, CH=, *J*=15.6 Hz), 7.18 (dd, 1H, *J*=3.6, 4.8 Hz), 7.54 (d, 1H, *J*=3.6 Hz), 7.63 (d, 1H, *J*=4.8 Hz), 7.95 (d, 1H, CH=, *J*=15.3 Hz), 12.74 (br s, 1H, 1NH, exchangeable); MS (70 eV) *m/z* (%): 276 ($M^+$, 5), 243 (2), 152 (51), 139 (6), 134 (100), 124 (16), 109 (74), 83 (22); Anal. calcd for $C_{11}H_8N_4OS_2$ (276.34): C, 47.81; H, 2.92; N, 20.27; found C, 47.53; H, 2.76; N, 19.99.

*2-thioxoimidazolidin-4-one* (**12**): Buff crystals, 47%, m.p. 227–229 °C, (m.p. 229–231 °C) [20] (EtOH); IR (KBr): 3282, 3185 (NH), 2970, 2912, 2830 (alkyl-H), 1715 (CO), 1161 (C=S) $cm^{-1}$; $^1H$ NMR (300 MHz) (DMSO-*d*6) δ 4.07 (s, 2H, $CH_2$), 9.79 (br s, 1H, NHCS, exchangeable), 11.59 (br s, 1H, CONHCS, exchangeable); MS (70 eV): *m/z* (%): 116 ($M^+$, 100),88 ($M^+$-CO, 22), 83 ($M^+$-SH, 1) 72 (5), 60 (26); Anal. calcd for $C_3H_4N_2OS$ (116.14): C, 31.02; H, 3.47; N, 24.12; found C, 30.69; H, 3.24; N, 23.78.

## Microbacterial activity

The newly synthesized heterocyclic compounds listed in Table 1 were tested for their antibacterial activity against Gram-positive bacteria (*Bacillus cereus* and *Staphylococcus aureus*), Gram-negative bacteria (*Escherichia coli* and *Pseudomonas aeruginosa*), and fungi (*Candida albicans* and *Aspergillus fumigatus*) at a concentration of 100 μg/mL in dimethyl sulfoxide (DMSO). Nutrient agar and potato dextrose agars were used to culture the bacteria and fungi, respectively. The plates were inculcated by the bacteria or fungi and incubated for 24 h at 37 °C for bacteria and for 72 h at 28 °C for fungi, and then the inhibition zones of microbial growth surrounding the filter paper disk (5 mm) were measured in millimeters.

## Conclusion

The synthetic utilization of α,β-unsaturated acyl isothiocyanate is based on the different reactivities of both centers toward nucleophiles. It is observed from all the reactions mentioned that the nucleophilic attack proceeds at the isothiocyanato group rather than at the α,β-unsaturated system, which reflects the higher reactivity of the former. Compounds **2**, **3**, and **9** are the more active antimicrobial agents.

### Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

### Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

### ORCID iD

Amira A El-Sayed https://orcid.org/0000-0002-0840-4806

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