Full Paper

Synthesis and Antibacterial Activity of 4-Aryl-2-(1-substituted ethylidene)thiazoles

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(*E*)-4-Aryl-2-[2-(1-substituted ethylidene)hydrazinyl]thiazoles and (*Z*)-3-substituted-4-aryl-2-[(*E*)-(1-phenylethylidene)hydrazono]-2,3-dihydrothiazoles were synthesized by the reaction of (substituted ethylidene)hydrazinecarbothioamides with ω-bromoacetophenones. The characterization of this new class of compounds was performed using different spectroscopic tools. The structure of (*Z*)-3-benzyl-4-(4-bromophenyl)-2-[(*E*)-(1-phenylethylidene)hydrazono]-2,3-dihydrothiazole **6e** was unambiguously confirmed by single-crystal X-ray crystallography. Compounds **5a–e**, **5i**, **6e**, **6g**, and **6i** were screened for their *in vitro* antibacterial activity against different strains of microorganisms; most of the tested compounds exhibited promising antibacterial activity against some organisms compared to ciprofloxacin and sulbactam penicillin. Compounds **5e**, **5i**, **6e**, **6g**, and **6i** exhibited several-fold significant antibacterial activity against the Gram-positive bacteria *Staphylococcus aureus*, better than ciprofloxacin, with minimum inhibitory concentration values ranging from 0.05 to 0.4 μg/mL. The rest of the tested compounds gave significant antibacterial activities against different Gram-negative bacterial strains.

Keywords: Antibacterial activity / ω-Bromoacetophenones / Heterocyclizations / (Substituted ethylidene)-hydrazinecarbothioamides / Thiazole derivatives

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Introduction

Thiazole derivatives are one of the most intensively investigated classes of aromatic five membered heterocycles. Thiazole nuclei have attracted continuing interest over the years due to numerous pharmacological applications and varied biological activities, such as antimicrobial [1–5], antiinflammatory [1, 4–6], antihypertensive [5–7], anticonvulsant [8], antifungal [9–14], antibacterial [12, 14–16], anticancer [17–21], and anti-HIV [4–6, 22–24].

Phenyl and substituted phenylthiazoles are common features of a wide range of biologically active products [25]. Studies have shown thiazole analogs to be potent and orally bioavailable antiviral agents for the inhibition of hepatitis B virus replication [26], and nitazoanide is widely used as antiparasitic agent [27].

On the other hand, thiosemicarbazones reacted with cyclization reagents such as ethyl chloroacetate, ethyl-2-chloroacetoacetate, and 2-bromoacetophenone to give substituted thiazolidinone and thiazoline derivatives [28–31].

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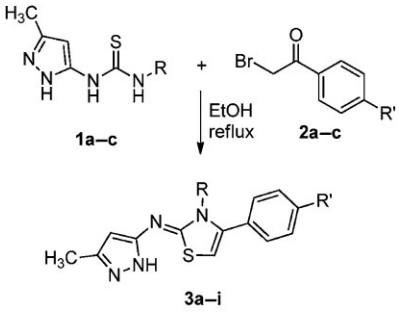


1: **a**, R = Ph; **b**, R = $PhCH_2$; **c**, R = Allyl
2: **a**, R' = H; **b**, R' = Br; **c**, R' = Ph
3: **a**, R = Ph, R' = H; **b**, R = $PhCH_2$, R' = H; **c**, R = Allyl, R' = H;
d, R = Ph, R' = Br; **e**, R = $PhCH_2$, R' = Br; **f**, R = Allyl, R' = Br;
g, R = R' = Ph; **h**, R = $PhCH_2$, R' = Ph; **i**, R = Allyl, R' = Ph

Scheme 1. (Thiazol-2-yl)pyrazol-5-amines from pyrazolylthioureas and ω-bromoacetophenones.

Condensation of thiosemicarbazones with α-bromopropylantipyryl ketone gave antipyrylthiazolyl and antipyrylthiazolonylhydrazones, respectively [32].

Recently, we reported that *N*-substituted (thiazole-2-yl) pyrazol-5-amine derivatives **3a–i** were obtained via condensation of pyrazolylthioureas **1a–c** with phenacyl bromides **2a–c** (Scheme 1) [33].

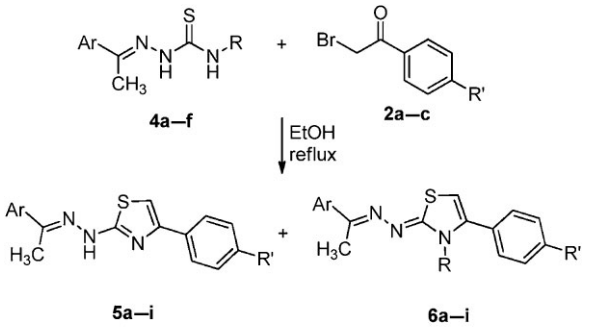
Encouraged by the above reports, it was planned to synthesize new di- and tri-substituted thiazoles containing a phenyl or *p*-bromophenyl moiety at position-4 and an aromatic heterocyclic ethylidenehydrazonyl group at position-2 of the thiazole ring with the evaluation of their antibacterial activity.

Results and discussion

Reactions of thiosemicarbazones with ω-bromoacetophenones

Treatment of thiosemicarbazones **4a–c** with one molar equivalent of ω-bromoacetophenones **2a–c** in ethanol at reflux resulted in the formation of (*E*)-4-aryl-2-[2-(1-substituted ethylidene)hydrazinyl]thiazoles **5a–i**, whereas the reaction of **4d–f** with **2a–c** afforded (*Z*)-3-substituted-4-aryl-2-[(*E*)-(1-phenylethylidene)hydrazono]-2,3-dihydrothiazoles **6a–i** in 66–90% yield (Scheme 2).

Elemental analyses and mass spectra clearly revealed that the products were formed by the addition of one molecule of **2a–c** to one molecule of **4a–f** with elimination of one molecule of HBr and another of H_2O. There are possibilities for the formation of various isomers **7–10** (Schemes 3–5). Compounds **4a–f** may react either with their sulfur atom or N-2 as nucleophilic sites. It is probable that all products observed are formed from one of the three labile (1:1) adducts (**A–C**) of thiosemicarbazones **4a–f** to ω-bromoacetophenones **2a–c** (Schemes 3–5).



2: **a**, R' = H; **b**, R' = Br; **c**, R' = Ph
4: **a**, Ar = Ph, R = H; **b**, Ar = Furan-2-yl, R = H;
c, Ar = Pyridin-3-yl, R = H; **d**, Ar = R = Ph;
e, Ar = Ph, R = $PhCH_2$; **f**, Ar = Ph, R = Allyl
5: **a**, Ar = Ph, R' = H; **b**, Ar = Furan-2-yl, R' = H;
c, Ar = Pyridin-3-yl, R' = H; **d**, Ar = Ph, R' = Br;
e, Ar = Furan-2-yl, R' = Br; **f**, Ar = Pyridin-3-yl, R' = Br;
g, Ar = R' = Ph; **h**, Ar = Furan-2-yl, R' = Ph;
i, Ar = Pyridin-3-yl, R' = Ph
6: **a**, Ar = R = Ph, R' = H; **b**, Ar = Ph, R = $PhCH_2$, R' = H;
c, Ar = Ph, R = Allyl, R' = H; **d**, Ar = R = Ph, R' = Br;
e, Ar = Ph, R = $PhCH_2$, R' = Br; **f**, Ar = Ph, R = Allyl, R' = Br;
g, Ar = R = R' = Ph; **h**, Ar = Ph, R = $PhCH_2$, R' = Ph;
i, Ar = Ph, R = Allyl, R' = Ph

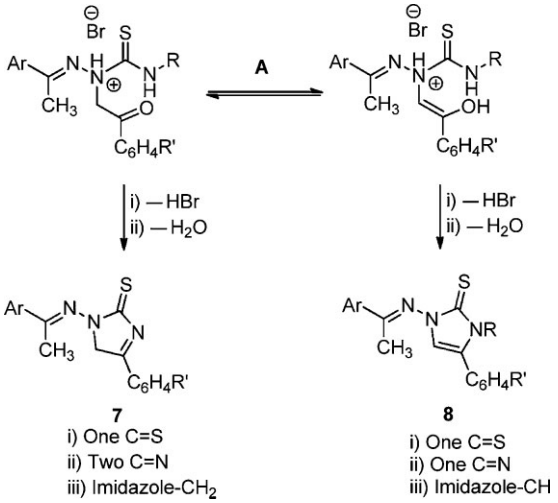
Scheme 2. Reaction of thiosemicarbazones **4a–f** with ω-bromoacetophenones **2a–c**.

Products **7** and **8** might form, if the reaction precedes via intermediate (**A**) (Scheme 3).

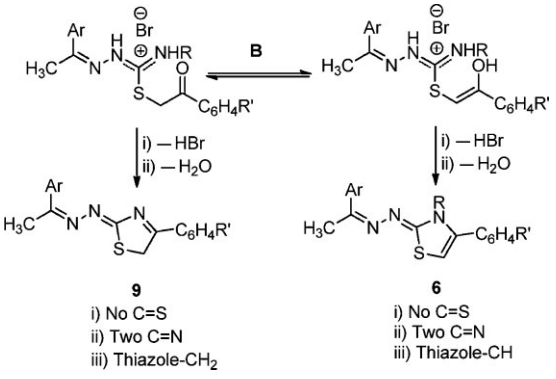
Intermediate (**B**) afforded the products **6** and **9** via SH and imine group or SH and N^2H (Scheme 4).

Products **5** and **10** might form during the intermediate (**C**) (Scheme 5).

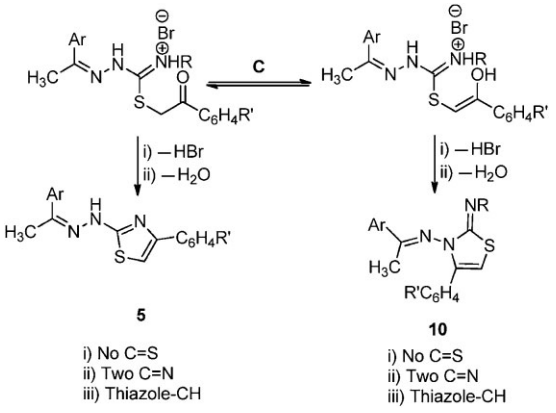
To illustrate the structure elucidation of compounds **5a–i**, we chose compound **5d**. IR spectrum showed a broad band at



Scheme 3. Alternative structures via intermediate **A**.



Scheme 4. Alternative structures via intermediate **B**.



Scheme 5. Alternative structures via intermediate **C**.

3290 cm^{-1} due to NH, a sharp band at 1635 cm^{-1} that was assigned to C=N vibration, in addition to bands at 1600 and 1585 cm^{-1} for the aromatic C=C.

The ^1H NMR spectrum of **5d** showed one methyl group at $\delta_H = 2.44$, nine protons at $\delta_H = 6.68–7.88$ due to aryl groups and NH at $\delta_H = 11.89$ ppm. From ^{13}C NMR data, structures with C=S double bonds such as **7** and **8** can be immediately ruled out, the two C=X ^{13}C-chemical shifts are too far up-field for a C=S. These signals must represent two C=N, one at $\delta_C = 163.51$ ppm, due to thiazole-C-2 and the other at $\delta_C = 159.55$ ppm, for acyclic C=N. The structure of **5d** was provided by ^{13}C NMR spectrum which exhibited signals at $\delta_C = 14.22$, 105.63, and 142.31 ppm, corresponding to CH_3, thiazole-CH and thiazole-C-4, respectively.

In addition, in the ^1H NMR of compound **5d** hydrazine-N^2H is regularly shifted down-field at $\delta_H = 11.89$ ppm, close to that found in the related systems (10.70–13.10 ppm) [34], compared with thiazole-exocyclic-NH in the alternative structure **10**.

Further evidence for the products **5a–i** comes from 2D NMR correlation. For example, in **5g**, HMBC and HSQC

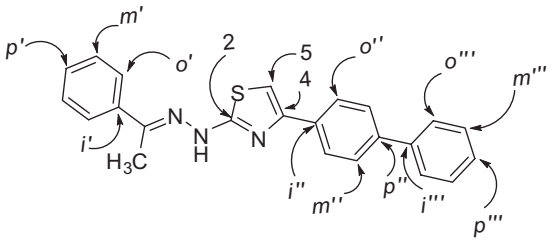


Figure 1. The structure of compound **5g**.

analyses were performed (Fig. 1). The methyl group signal $\delta_H = 2.22$ ppm gives a weak COSY correlation to the two-proton doublet at $\delta_H = 7.28$ ppm, which was assigned as H-*o*′, and gives HSQC correlation with the attached carbon at $\delta_H = 14.77$ which was assigned as CH_3.

The H-*o*′ gives HMBC correlation with the carbon at $\delta_C = 159.61$ ppm, which was indicated as acyclic-C=N, that means the phenyl and methyl group are geminal to each other and attached by acyclic-C=N. Furthermore, the signal at $\delta_C = 106.33$ gives HSQC correlation with one-proton singlet at $\delta_H = 7.34$ ppm, which was assigned as H-5. The signal at $\delta_C = 144.87$ ppm also gives HMBC correlation with H-5, which was assigned as C-4.

The aromatic protons at $\delta_H = 7.54$, 7.46, and 7.37 ppm give correlation with each other and were assigned as H-*o*‴, H-*m*‴, and H-*p*‴, respectively, and with the two doublet-protons at $\delta_H = 7.61$ and 7.55 ppm, which were assigned as H-*o*″ and H-*m*″, respectively. These two doublets give HSQC with carbons at $\delta_C = 130.33$ and 129.51 ppm, assigned as C-*o*″ and C-*m*″, respectively; in addition, the signal at $\delta_C = 144.87$ ppm, assigned as C-4 gives strong HMBC correlation with protons at $\delta_H = 7.61$ (H-*o*″) and 7.34 (H-5), which indicate the bi-phenyl group attached to the thiazole-C-4.

This fascinating versatility in the reaction of (substituted ethylidene)hydrazinecarbothioamides **4a–c** with **2a–c** justifies further investigation to prove the structure of **5a–i** and study the reactivity of ω-bromoacetophenones **2a–c** towards *N*-substituted-2-(1-phenylethylidene)hydrazinecarbothioamides **4d–f**.

By refluxing equimolar amounts of the reactants in ethanol as solvent, compounds **6a–i** were obtained as crystalline solids in 66–88% yield (Scheme 2).

The IR spectrum of **6e** as an example did not reveal any absorption due to the NH group, but show three absorption bands, one at 1635 cm^{-1} which was assigned to C=N and two bands at 1605, 1580 cm^{-1} due to Ar–C=C. The ^1H NMR of compound **6e** revealed three singlets at $\delta_H = 2.38$, 4.98, and 7.06 ppm, for CH_3, benzyl-CH_2 and thiazole-CH, respectively, in addition to aromatic protons.

Also, the ^{13}C NMR spectrum of **6e** showed signals at $\delta_C = 163.14$ (thiazole-C-2), 159.18 (acyclic-C=N), and

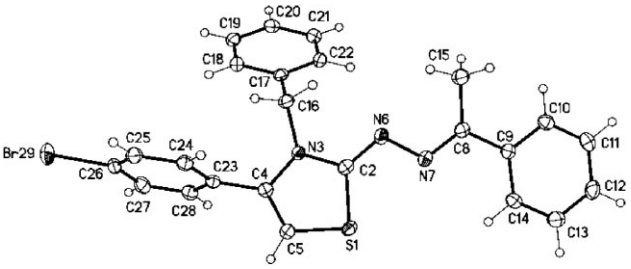


Figure 2. Molecular structure of **6e** in the crystal (one of the two crystallographic independent molecules, parameters are drawn at 50% probability level). The crystallographic numbering does not reflect the systematic IUPAC numbering.

142.80 ppm (thiazole-C-2). The ^{13}C NMR data of **6e** are in line with ^{1}H NMR data insofar as the distinctive appearance of carbon signals representing CH_3 at $\delta_C = 13.98$, benzyl-CH_2 and thiazole-CH resonated at $\delta_C = 42.44$ and 105.44 ppm, respectively. The molecular formulae of **6a–i** are supported by the mass spectra, which gave the predicted molecular ion peak.

Moreover, the structure of **6e** has been unambiguously confirmed by a single crystal X-ray structure analysis (Fig. 2 and Tables S1–7 in the Supporting Information). It revealed the presence of (*Z*)-3-benzyl-4-(4-bromophenyl)-2-[(*E*)-1-(phenylethylidene)hydrazono]-2,3-dihydrothiazole **6e**, which confirms a *cisoid* geometry with respect to C4-N3, C33-N32, and *transoid* geometry with respect to C2-N6, C31-N35 (note that the crystallographic numbering dose not correspond to IUPAC numbering rules). S1 to C15, C16, C23, and S30 to C44, C45, C52 are nearly coplanar. Due to steric encumbering, there is a substantial twisting of phenyl and benzyl groups out of the plane of the thiazole moiety.

Antibacterial activity

Nine chemically synthesized compounds **5a–e**, **5i**, **6e**, **6g**, and **6i** were screened for their *in vitro* antibacterial activity against different strains of microorganisms including *Escherichia coli*, *Klebsiella pneumoniae*, and *Pseudomonas aeruginosa* as examples of Gram-negative bacteria and *Staphylococcus aureus* as an example of Gram-positive bacteria. The antibacterial activities of the tested compounds were assayed using ciprofloxacin (Sigma, USA) and sulbactam penicillin (Pfizer) as reference antibiotics by determining the minimum inhibitory concentration (MIC) by broth agar dilution method according to Clinical Laboratory Standards Institute procedures [35]. The diameter of the zones of inhibition (mm) are given in (Table 1), the MICs (μg/mL) of the tested compounds are recorded (Table 2). The results indicated that most of the tested compounds exhibited promising antibacterial activity against some organisms compared to ciprofloxacin and sulbactam penicillin.

Compounds **5a**, **5c**, **5d**, **5i**, and **6e** exhibited significant antibacterial activity against Gram-negative bacteria, *E. coli* better than or equal to the activity of ciprofloxacin with MIC values ranging from 0.05 to 1 μg/mL. Moreover, compounds **5a**, **5d**, **5e**, **5i**, **6e**, **6g**, and **6i** revealed promising antibacterial activity against Gram-negative bacteria, *K. pneumoniae* better than ciprofloxacin with MIC values ranging from 0.02 to 0.4 μg/mL. Also compounds **5a**, **5c**, **5d**, **5i**, **6e**, and **6g** displayed remarkable antibacterial activity against Gram-negative bacteria, *P. aeruginosa* better than ciprofloxacin with MIC values ranging from 0.2 to 1 μg/mL. On the other hand, compounds **5e**, **5i**, **6e**, **6g**, and **6i** exhibited several folds significant antibacterial activity against Gram-positive bacteria, *S. aureus* better than ciprofloxacin with MIC values ranging from 0.05 to 0.4 μg/mL.

From the above-mentioned results, it appears that the presence of the phenyl ring in thiosemicarbazones **4** is essential for the antibacterial activity of this class of compounds against different types of Gram-negative bacteria (compounds **5a** and **5d**). Replacement of the phenyl ring in thiosemicarbazones with the furayl group (compounds **5b** and **5e**) or with the pyridyl group (compounds **5c** and **5i**) are associated with decreasing antibacterial activity against different types of Gram-negative bacteria. On the other hand, thiazole derivatives (**5e** and **5i**) gathering the furayl group or pyridyl group with the presence of *para*-disubstituted aryl (bromo or phenyl group) have promising antibacterial activity against Gram-positive bacteria, *S. aureus*. Substitution on the *N*- of the thiazole with either benzyl, phenyl and allyl groups (compounds **6e**, **6g**, and **6i**) was associated with increasing antibacterial activity against Gram-positive bacteria, *S. aureus*, but has a little effect on the antibacterial activity against Gram negative bacteria.

In conclusion, 2-(1-substituted ethylidene)hydrazinecarbothioamides **4a–f** are multi-dentate nucleophiles allowing for the formation of thiazole derivatives with ω-bromoacetophenones **2a–c**. Thus, thiaheterocycles *N*-(CS)-*N* + −CO−CH_2Br mode of cyclization is favored. Compounds **5a–5e**, **5i**, **6e**, **6g**, and **6i** were screened for their *in vitro* antibacterial activity against different strains of microorganisms.

Experimental

Chemistry

Melting points were determined using open glass capillaries on a Gallenkamp melting point apparatus (Weiss-Gallenkamp, Loughborough, UK), and are uncorrected. The IR spectra were recorded from potassium bromide disks with a Shimadzu 408 (Shimadzu Corporation, Kyoto, Japan). NMR spectra (400 MHz for ^{1}H, 100 MHz for ^{13}C) were observed in DMSO-d_6 on Bruker AM400 spectrometer (Bruker BioSpin, Karlsruhe, Germany) with tetramethylsilane as the internal standard. The ^{13}C signals were assigned with the aid of DEPT 135/90 experiments. Mass spectra

Table 1. The diameter of the zone of inhibition (mm) of the tested compounds **5a–e**, **5i**, **6e**, **6g**, **6i**, ciprofloxacin, and sulbactam penicillin.

Test compounds	Organisms	Diameter of inhibition zone (mm)				
		2 (μg/mL)	8 (μg/mL)	32 (μg/mL)	128 (μg/mL)	512 (μg/mL)
5a	*Staphylococcus aureus*	0	0	0	0	0
	Escherichia coli	6	7	7	8	10
	Klebsiella pneumoniae	6	7	7	8	9
	Pseudomonas aeruginosa	5	7	8	9	10
5b	*Staphylococcus aureus*	0	0	0	0	0
	Escherichia coli	2	3	7	7	10
	Klebsiella pneumoniae	0	4	5	6	8
	Pseudomonas aeruginosa	0	2	7	8	8
5c	*Staphylococcus aureus*	0	0	0	8	12
	Escherichia coli	6	6	7	8	10
	Klebsiella pneumoniae	4	5	6	7	13
	Pseudomonas aeruginosa	3	6	7	8	9
5d	*Staphylococcus aureus*	0	0	3	6	8
	Escherichia coli	5	6	6	7	8
	Klebsiella pneumoniae	5	6	7	8	10
	Pseudomonas aeruginosa	5	7	8	9	10
5e	*Staphylococcus aureus*	0	2	6	7	8
	Escherichia coli	0	2	6	7	8
	Klebsiella pneumonia	4	5	6	7	8
	Pseudomonas aeruginosa	0	0	2	8	10
5i	*Staphylococcus aureus*	5	6	7	8	8
	Escherichia coli	3	3	4	4	5
	Klebsiella pneumonia	4	4	5	6	6
	Pseudomonas aeruginosa	3	4	4	5	6
6e	*Staphylococcus aureus*	4	5	5	6	8
	Escherichia coli	4	4	5	6	6
	Klebsiella pneumonia	4	4	5	5	6
	Pseudomonas aeruginosa	4	4	6	7	8
6g	*Staphylococcus aureus*	5	6	7	8	8
	Escherichia coli	1	2	3	4	5
	Klebsiella pneumonia	4	5	5	6	7
	Pseudomonas aeruginosa	0	5	5	6	7
6i	*Staphylococcus aureus*	6	6	7	8	9
	Escherichia coli	3	4	6	7	8
	Klebsiella pneumoniae	4	5	5	6	6
	Pseudomonas aeruginosa	0	0	0	1	3
Ciprofloxacin	*Staphylococcus aureus*	5	10	15	17	20
	Escherichia coli	5	6	8	8	9
	Klebsiella pneumoniae	13	18	23	25	30
	Pseudomonas aeruginosa	8	21	29	32	40
Sulbactam penicillin	*Staphylococcus aureus*	5	8	10	13	18
	Escherichia coli	5	7	13	14	15
	Klebsiella pneumoniae	0	3	7	12	15
	Pseudomonas aeruginosa	0	1	5	8	10

(70 eV, electron impact mode) were recorded on Finnigan MAT 312 (Germany) instrument. TLC was performed on analytical Merck 9385 silica aluminum sheets (Kieselgel 60) with Pf_{254} indicator; TLC's were viewed at $\lambda_{max} = 254$ nm. Elemental analyses were carried out at the Microanalytical Center, Cairo University, Egypt.

Starting materials

2-(1-Substituted ethylidene)hydrazinecarbothioamides **4a–f** were prepared by the reaction of thiosemicarbazide or 4-substituted thiosemicarbazides with the proper ketones according to published procedures [36, 37]. ω-Bromoacetophenones **2a–c** were prepared according to Nobuta and Salama procedures [38, 39].

Products

A solution of 2-(substituted ethylidene)hydrazinecarbothioamides **4a–c** (0.1 mol), *N*-substituted-2-(1-phenylethylidene)hydrazinecarbothioamides **4d–f** (0.1 mol) in 10 mL ethanol was added dropwise to (0.1 mol) ω-bromoacetophenones **2a–c** in 10 mL ethanol and the reaction mixture was gently refluxed with stirring until the (substituted ethylidene)hydrazinecarbothioamides had disappeared (monitored by TLC). The resulting

Table 2. MICs of test compounds **5a-e**, **5i**, **6e**, **6g**, **6i**, ciprofloxacin, and sulbactam penicillin in (μg/mL).

Pseudomonas aeruginosa	*Klebsiella pneumoniae*	*Escherichia coli*	*Staphylococcus aureus*	Test compound
5a	>512	0.1	0.02	0.2
5b	>512	2.6	2.3	2.2
5c	>512	0.2	2.7	0.7
5d	5.1	0.05	0.4	0.2
5e	0.05	2.8	0.4	5.5
5i	0.06	0.2	0.08	0.4
6e	0.4	0.08	0.04	0.7
6g	0.06	2.5	0.1	1
6i	0.06	1	0.02	>512
Ciprofloxacin	1.5	0.2	0.6	1.6
Sulbactam penicillin	2.2	1.1	4.2	4.3

precipitate was filtered off, washed with ethanol, and recrystallized to give pure crystals of **5a–i** and **6a–i**.

*(E)-4-Phenyl-2-[2-(1-phenylethylidene)hydrazinyl]thiazole (**5a**):* Colorless crystals (0.264 g, 90%), mp 286–288°C (ethanol). IR (KBr) ν = 3290 (NH), 1635 (C=N), 1605, 1595 cm^{-1} (Ar-C=C); ^1H NMR (DMSO-d_6): δ_H = 2.35 (s, 3H, CH_3), 7.11–7.42 (m, 7H, Ar-CH, thiazole-CH), 7.73–7.80 (m, 4H, Ar-CH), 11.46 ppm (br s, 1H, NH); ^{13}C NMR (DMSO-d_6): δ_C = 14.88 (CH_3), 104.2 (thiazole-CH), 127.23, 127.46, 128.19, 128.39, 129.21, 129.28 (Ar-CH), 131.44, 135.71 (Ar-C), 142.39 (thiazole-C-4), 158.23 (acyclic-C=N), 162.61 (thiazole-C-2); MS (EI): *m/z* 293 (M^+, 100), 216 (25), 278 (16), 118 (56), 97 (33), 77 (45). *Anal. calcd. for* $C_{17}H_{15}N_3S$ (293.39): C, 69.59; H, 5.15; N, 14.32; S, 10.93. *Found*: C, 69.71; H, 4.99; N, 14.49; S, 11.11.

*(E)-4-Phenyl-2-[2-(1-furan-2-yl)ethylidene)hydrazinyl]thiazole (**5b**):* Colorless crystals (0.200 g, 71%), mp 262–264°C (ethanol); IR (KBr) ν = 3285 (NH), 1635 (C=N), 1600, 1595 cm^{-1} (Ar-C=C); ^1H NMR (DMSO-d_6): δ_H = 2.33 (s, 3H, CH_3), 6.11 (m, 1H, furan-CH), 6.81 (m, 2H, furan-CH, thiazole-CH), 7.21 (m, 1H, furan-CH), 7.23–7.86 (m, 5H, Ar-CH), 11.21 ppm (br s, 1H, NH); ^{13}C NMR (DMSO-d_6): δ_C = 13.12 (CH_3), 105.11 (thiazole-CH), 110.22, 112.23 (furan-CH), 127.53, 128.16, 129.31 (Ar-CH), 136.61 (Ar-C), 141.21 (furan-CH), 142.14 (thiazole-C-4), 151.22 (furan-C), 159.22 (acyclic-C=N), 163.44 ppm (thiazole-C-2); MS (EI): *m/z* 283 (M^+, 21), 206 (100), 181 (36), 167 (12), 108 (44), 97 (22), 77 (36). *Anal. calcd. for* $C_{15}H_{13}N_3OS$ (283.35): C, 63.58; H, 4.62; N, 14.83; S, 11.32. *Found*: C, 63.73; H, 4.49; N, 14.71; S, 11.45.

*(E)-4-Phenyl-2-[2-(1-pyridin-3-yl)ethylidene)hydrazinyl]thiazole (**5c**):* Colorless crystals (0.218 g, 74%), mp 225–227°C (ethanol); IR (KBr): ν = 3285 (NH), 1635 (C=N), 1605, 1585 cm^{-1} (Ar-C=C); ^1H NMR (DMSO-d_6): δ_H = 2.46 (s, 3H, CH_3), 6.69–7.52 (m, 6H, Ar-CH, thiazole-CH), 7.58 (m, 1H, pyridin-CH), 8.28 (m, 1H, pyridin-CH), 8.68 (m, 1H, pyridin-CH), 8.98 (m, 1H, pyridin-CH), 12.22 ppm (br s, 1H, NH); ^{13}C NMR (DMSO-d_6): δ_C = 13.58 (CH_3), 105.12 (thiazole-CH), 128.29, 129.11, 129.48 (Ar-CH), 137.74 (Ar-C), 142.19 (thiazole-C-4), 142.21 (pyridin-C), 142.78, 143.44, 150.89, 153.33 (pyridine-CH), 159.13 (acyclic-C=N), 163.24 ppm (thiazole-C-2); MS (EI): *m/z* 294 (M^+, 25), 274 (32), 97 (55), 119 (64), 77 (100). *Anal. calcd. for* $C_{16}H_{14}N_4S$ (294.37): C, 65.28; H, 4.79; N, 19.03; S, 10.89. *Found*: C, 65.16; H, 4.89; N, 18.99; S, 10.77.

*(E)-4-(4-Bromophenyl)-2-[2-(1-phenylethylidene)hydrazinyl]thiazole (**5d**):* Colorless crystals (0.297 g, 80%), mp 264–266°C (ethanol); IR (KBr): ν = 3290 (NH), 1635 (C=N), 1600, 1585 cm^{-1} (Ar-C=C); ^1H NMR (DMSO-d_6): δ_H = 2.44 (s, 3H, CH_3), 6.68–7.88 (m, 10H, Ar-CH, thiazole-CH), 11.89 ppm (br s, 1H, NH); ^{13}C NMR (DMSO-d_6): δ_C = 14.22 (CH_3), 105.63 (thiazole-CH), 126.23 (Ar-C-Br), 127.21, 127.61, 128.39, 128.45, 129.28 (Ar-CH), 136.33, 141.11 (Ar-C), 142.31 (thiazole-C-4), 159.55 (acyclic-C=N), 163.51 ppm (thiazole-C-2); MS (EI): *m/z* 371/373 (M^+, 21), 291 (100), 216 (18), 118 (52), 97 (77), 77 (28). *Anal. calcd. for* $C_{17}H_{14}BrN_3S$ (372.28): C, 54.85; H, 3.79; N, 11.29; S, 8.61. *Found*: C, 55.01; H, 3.91; N, 11.14; S, 8.74.

*(E)-4-(4-Bromophenyl)-2-[2-(1-furan-2-yl)ethylidene)-hydrazineyl]thiazole (**5e**):* Yellow crystals (0.246 g, 68%), mp 270–272°C (ethanol); IR (KBr): ν = 3285 (NH), 1630 (C=N), 1605, 1595 cm^{-1} (Ar-C=C); ^1H NMR (DMSO-d_6): δ_H = 2.33 (s, 3H, CH_3), 6.18 (m, 1H, furan-CH), 6.89 (m, 2H, furan-CH, thiazole-CH), 7.21 (m, 1H, furan-CH), 7.24–7.86 (m, 4H, Ar-CH), 11.32 ppm (br, s, 1H, NH); ^{13}C NMR (DMSO-d_6): δ_C = 14.12 (CH_3), 106.22 (thiazole-CH), 110.32, 112.29 (furan-CH), 126.12 (Ar-C-Br), 128.88, 129.35 (Ar-CH), 141.18 (Ar-C), 141.28 (furan-CH), 142.64 (thiazole-C-4), 151.24 (furan-C), 159.28 (acyclic-C=N), 163.14 ppm (thiazole-C-2); MS (EI): *m/z* 361/363 (M^+, 24), 281 (100), 209 (32), 108 (41), 97 (25), 77 (77). *Anal. calcd. for* $C_{15}H_{12}BrN_3OS$ (362.24): C, 49.73; H, 3.43; N, 11.60; S, 8.85. *Found*: C, 49.66; H, 3.61; N, 11.75; S, 8.66.

*(E)-4-(4-Bromophenyl)-2-[2-(1-(pyridin-3-yl)ethylidene)-hydrazinyl]thiazole (**5f**):* Colorless crystals (0.272 g, 73%), mp 242–244°C (ethanol); IR (KBr): ν = 3285 (NH), 1630 (C=N), 1600, 1595 cm^{-1} (Ar-C=C); ^1H NMR (DMSO-d_6): δ_H = 2.45 (s, 3H, CH_3), 6.89–7.55 (m, 5H, Ar-CH, thiazole-CH), 7.68 (m, 1H, pyridin-CH), 8.38 (m, 1H, pyridin-CH), 8.48 (m, 1H, pyridin-CH), 8.99 (m, 1H, pyridin-CH), 12.20 ppm (br s, 1H, NH); ^{13}C NMR (DMSO-d_6): δ_C = 14.18 (CH_3), 105.82 (thiazole-CH), 125.66 (Ar-C-Br), 129.11, 129.48 (Ar-CH), 137.74 (Ar-C), 142.49 (thiazole-C-4), 142.55 (pyridin-C), 142.78, 143.49, 151.33, 152.83 (pyridine-CH), 159.22 (acyclic-C=N), 163.54 ppm (thiazole-C-2); MS (EI): *m/z* 372/374 (M^+, 100), 292 (23), 192 (19), 179 (16), 119 (33), 97 (78), 77 (44). *Anal. calcd. for* $C_{16}H_{13}BrN_4S$ (373.27): C, 51.48; H, 3.51; N, 15.01; S, 8.59. *Found*: C, 51.66; H, 3.49; N, 15.16; S, 8.72.

*(E)-4-(4-Biphenyl-4-yl)-2-[2-(1-phenylethylidene)hydrazinyl]thiazole (**5g**):* Colorless crystals (0.310 g, 84%), mp 258–260°C (ethanol); IR (KBr): ν = 3295 (NH), 1635 (C=N), 1600, 1585 cm^{-1} (Ar-C=C); ^1H NMR (DMSO-d_6): δ_H = 2.22 (s, 3H, CH_3), 7.28 (d, J = 8.20, 2H, Ar-H-*o*'), 7.34 (s, 1H, thiazole-CH), 7.37 (t, J = 7.10, 1H, Ar-H-*p*'"), 7.46 (t, J = 7.6, 2H, Ar-H-*m*'"), 7.54 (d, J = 7.0, 2H, Ar-H-*o*'"), 7.55 (d, J = 6.8, 2H, Ar-H-*m*"), 7.57 (t, J = 7.3, 3H, Ar-H-*m*',*p*'), 7.61 (d, J = 7.8, 2H, Ar-H-*o*"), 11.26 (br, s, 1H, NH); ^{13}C NMR (DMSO-d_6): δ_C = 14.77 (CH_3), 106.33 (thiazole-CH), 126.74 (C-*m*'), 126.96 (C-*o*'"), 127.68 (C-*p*'"), 127.76 (C-*p*"), 128.09 (C-*i*'), 128.78 (C-*m*'"), 129.13 (C-*m*"), 129.51 (C-*o*'), 130.33 (C-*o*"), 131.65 (C-*p*'), 136.58 (C-*i*"), 139.34 (C-*i*'"), 144.87 (thiazole-C-4), 159.61 (acyclic-C=N), 163.48 (thiazole-C-2);MS (EI): *m/z* 369 (M^+), 210 (15), 152 (20), 118 (36), 97 (42), 77 (100). *Anal. calcd. for* $C_{23}H_{19}N_3S$ (369.48): C, 74.77; H, 5.18; N, 11.37; S, 8.68. *Found*: C, 74.61; H, 5.30; N, 11.24; S, 8.75.

*(E)-4-(4-Biphenyl-4-yl)-2-[2-(1-furan-2-yl)ethylidene)-hydrazineyl]thiazole (**5h**):* Pale brown crystals (0.284 g, 79%), mp 210–212°C (ethanol); IR (KBr): ν = 3290 (NH), 1633 (C=N), 1600, 1585 cm^{-1} (Ar-C=C); ^1H NMR (DMSO-d_6): δ_H = 2.34 (s, 3H, CH_3), 6.11 (m, 1H, furan-CH), 6.87 (m, 2H, furan-CH, thiazole-CH), 7.22 (m, 1H, furan-CH), 7.24–7.89 (m, 9H, Ar-CH), 11.76 ppm (br s, 1H, NH); ^{13}C NMR (DMSO-d_6): δ_C = 14.94 (CH_3), 106.12 (thiazole-CH), 111.12, 112.45 (furan-CH), 126.35, 127.77, 128.26, 129.35, 130.85 (Ar-CH), 136.61, 139.22, 141.18 (Ar-C), 141.08 (furan-CH), 142.22 (thiazole-C-4), 151.12 (furan-C), 159.08 (acyclic-C=N), 163.11 ppm (thiazole-C-2); MS (EI): *m/z* 359 (M^+, 37), 206 (16), 344 (24), 97 (62), 94 (14), 77 (100). *Anal. calcd. for* $C_{21}H_{17}N_3OS$ (359.44): C, 70.17; H, 4.77; N, 11.69; S, 8.92. *Found*: C, 69.98; H, 4.69; N, 11.85; S, 8.88.

*(E)-4-(4-Biphenyl-4-yl)-2-[2-(1-pyridin-3-yl)ethylidene)-hydrazineyl]thiazole (**5i**):* Yellow crystals (0.244 g, 66%), mp 278–280°C (ethanol); IR (KBr): ν = 3285 (NH), 1630 (C=N), 1600, 1590 cm^{-1} (Ar-C=C); ^1H NMR (DMSO-d_6): δ_H = 2.45 (s, 3H, CH_3), 6.89–7.95 (m, 10H, Ar-CH, thiazole-CH), 7.99 (m, 1H, pyridin-CH), 8.11 (m, 1H, pyridin-CH), 8.28 (m, 1H, pyridin-CH), 9.02 (m, 1H, pyridin-CH), 11.99 ppm (br s, 1H, NH); ^{13}C NMR (DMSO-d_6): δ_C = 14.18 (CH_3), 105.92 (thiazole-CH), 126.33, 127.86, 129.11, 130.68, 131.23 (Ar-CH), 131.55, 137.14, 139.77 (Ar-C), 142.69 (thiazole-C-4), 142.75 (pyridin-C), 142.78, 144.09, 151.13, 152.45 (pyridine-CH), 159.52 (acyclic-C=N), 163.68 ppm (thiazole-C-2); MS (EI): *m/z* 370 (M^+, 26), 217 (19), 153 (22), 192 (15), 178 (27), 97 (100) 77 (51). *Anal. calcd. for* $C_{22}H_{18}N_4S$ (370.47): C, 71.32; H, 4.90; N, 15.12; S, 8.66. *Found*: C, 71.44; H, 5.08; N, 15.26; S, 8.55.

*(Z)-3,4-Diphenyl-2-[(E)-(1-phenylethylidene)hydrazono]-2,3-dihydrothiazole (**6a**):* Colorless crystals (0.303 g, 82%), mp 310–312°C (ethanol); IR (KBr): ν = 1630 (C=N), 1600, 1585 cm^{-1} (Ar-C=C); ^1H NMR (DMSO-d_6): δ_H = 2.49 (s, 3H, CH_3), 7.23 (s, 1H, thiazole-CH), 7.24–7.56 (m, 6H, Ar-CH), 7.66–7.82 ppm (m, 9H, Ar-CH); ^{13}C NMR (DMSO-d_6): δ_C = 14.50 (CH_3), 105.28 (thiazole-CH), 126.02, 126.60, 127.07, 127.98, 128.11, 128.34, 128.55, 128.97, 129.21 (Ar-CH), 130.64, 137.94, 138.76 (Ar-C), 142.39 (thiazole-C-4), 159.33 (acyclic-C=N), 163.44 ppm (thiazole-C-2); MS (EI): *m/z* 369 (M^+, 21), 292 (16), 174 (55), 118 (26), 77 (100). *Anal. calcd. for* $C_{23}H_{19}N_3S$ (369.48): C, 74.77; H, 5.18; N, 11.37; S, 8.68. *Found*: C, 74.86; H, 5.06; N, 11.43; S, 8.51.

*(Z)-3-Benzyl-4-phenyl-2-[(E)-(1-phenylethylidene)hydrazono]-2,3-dihydro-thiazole (**6b**):* Colorless crystals (0.337 g, 88%), mp 278–280°C (ethanol); IR (KBr): ν = 1625 (C=N), 1600, 1585 cm^{-1} (Ar-C=C); ^1H NMR (DMSO-d_6): δ_H = 2.38 (s, 3H, CH_3), 4.89 (s, 2H, CH_2), 6.99 (s, 1H, thiazole-CH), 7.22–7.45 (m, 6H, Ar-CH), 7.55–7.78 ppm (m, 9H, Ar-CH); ^{13}C NMR (DMSO-d_6): δ_C = 14.44 (CH_3), 42.51 (CH_2), 105.28 (thiazole-CH), 126.12, 126.44, 127.28, 127.66, 128.23, 128.31, 128.25, 128.53, 129.28 (Ar-CH), 131.42, 137.88, 139.16 (Ar-C), 141.89 (thiazole-C-4), 158.68 (acyclic-C=N), 162.94 ppm (thiazole-C-2); MS (EI): *m/z* 383 (M^+, 100), 306 (25), 257 (18), 118 (36), 77 (86). *Anal. calcd. for* $C_{24}H_{21}N_3S$ (383.51): C, 75.16; H, 5.52; N, 10.96; S, 8.36. *Found*: C, 74.99; H, 5.44; N, 11.03; S, 8.52.

*(Z)-3-Allyl-4-phenyl-2-[(E)-(1-phenylethylidene)hydrazono]-2,3-dihydro-thiazole (**6c**):* Colorless crystals (0.233 g, 70%), mp 246–248°C (ethanol); IR (KBr): ν = 2195 (Ali-H), 1635 (C=N), 1605, 1585 cm^{-1} (Ar-C=C); ^1H NMR (DMSO-d_6): δ_H = 2.31 (s, 3H, CH_3), 4.49 (br, 2H, allyl-CH_2N), 5.11–5.28 (m, 2H, allyl-CH_2=), 5.60–5.78 (m, 1H, allyl-CH=), 7.12 (s, 1H, thiazole-CH), 7.21–7.34 (m, 6H, Ar-CH), 7.44–7.54 (m, 4H, Ar-CH); ^{13}C NMR (DMSO-d_6): δ_C = 14.44 (CH_3), 45.77 (allyl-CH_2N), 106.18 (thiazole-CH), 116.71 (allyl-CH_2=), 126.69, 127.77, 128.21, 128.87, 129.21, 130.22 (Ar-CH), 131.54, 137.88 (Ar-C), 135.71 (allyl-CH=), 142.19 (thiazole-C-4), 158.89 (acyclic-C=N), 162.98 ppm (thiazole-C-2); MS (EI): *m/z* 333 (M^+, 100), 256 (22), 232 (28), 118 (62), 77 (56). *Anal. calcd. for* $C_{20}H_{19}N_3S$ (333.45): C, 72.04; H, 5.74; N, 12.60; S, 9.62. *Found*: C, 71.96; H, 5.82; N, 12.71; S, 9.76.

*(Z)-3-Phenyl-4-(4-bromophenyl)-2-[(E)-(1-phenylethylidene)hydrazono]-2,3-dihydrothiazole (**6d**):* Colorless crystals (0.345 g, 77%), mp 123–125°C (ethanol); IR (KBr): ν = 3110 (Ar-H), 2285 (Ali-H), 1635 (C=N), 1600, 1565 cm^{-1} (Ar-C=C); ^1H NMR (DMSO-d_6): δ_H = 2.51 (s, 3H, CH_3), 6.69–7.02 (m, 4H, Ar-CH), 7.18 (s, 1H, thiazole-CH), 7.22–7.86 (m, 5H, Ar-CH), 7.88–8.02 ppm (m, 5H, Ar-CH); ^{13}C NMR (DMSO-d_6): δ_C = 14.43 (CH_3), 106.08 (thiazole-CH), 126.11 (Ar-C-Br), 126.61, 127.47, 128.92, 128.55, 128.74, 129.51, 130.66, 134.22 (Ar-CH), 137.94, 138.76, 141.23 (Ar-C), 142.29 (thiazole-C-4), 158.88 (acyclic-C=N), 163.56 ppm (thiazole-C-2); MS (EI): *m/z* 447/449 (M^+, 100), 367 (16), 216 (33), 118 (62), 98 (14), 77 (34). *Anal. calcd. for* $C_{23}H_{18}BrN_3S$ (448.38): C, 61.61; H, 4.05; N, 9.37; S, 7.15. *Found*: C, 61.76; H, 4.15; N, 9.24; S, 7.28.

*(Z)-3-Benzyl-4-(4-bromophenyl)-2-[(E)-(1-phenylethylidene)hydrazono]-2,3-dihydrothiazole (**6e**):* Orange crystals (0.374 g, 81%), mp 136–138°C (ethanol); IR (KBr): ν = 2290 (Ali-H), 1635 (C=N), 1605, 1580 cm^{-1} (Ar-C=C); ^1H NMR (DMSO-d_6): δ_H = 2.38 (s, 3H, CH_3), 4.98 (s, 2H, CH_2), 6.97–7.02 (m, 4H, Ar-CH), 7.06 (s, 1H, thiazole-CH), 7.22–7.82 (m, 5H, Ar-CH), 7.86–8.12 ppm (m, 5H, Ar-CH); ^{13}C NMR (DMSO-d_6): δ_C = 13.98 (CH_3), 42.44 (CH_2), 105.98 (thiazole-CH), 125.23 (Ar-C-Br), 126.55, 127.68, 128.66, 128.99, 128.56, 128.25, 129.56, 131.38 (Ar-CH), 137.38, 139.16, 141.55 (Ar-C), 142.80 (thiazole-C-4), 159.18 (acyclic-C=N), 163.14 ppm (thiazole-C-2); MS (EI): *m/z* 461/463 (M^+, 22), 370 (100), 306 (19), 154 (33), 118 (23), 91 (24), 77 (73). *Anal. calcd. for* $C_{24}H_{20}BrN_3S$ (462.40): C, 62.34; H, 4.36; N, 9.09; S, 6.93. *Found*: C, 62.51; H, 4.44; N, 8.93; S, 7.02.

(Z)-3-Allyl-4-(4-bromophenyl)-2-[(E)-(1-phenylethylidene)-hydrazono]-2,3-dihydrothiazole ***(6f)****:* Colorless crystals (0.272 g, 66%), mp 120–122°C (ethanol); IR (KBr): ν = 2190 (Ali-CH), 1635 (C=N), 1600, 1580 cm^{-1} (Ar-C=C); ^1H NMR (DMSO-d_6): δ_H = 2.25 (s, 3H, CH_3), 4.51 (br, 2H, allyl-CH_2N), 5.21–5.38 (m, 2H, allyl-CH_2=), 5.55–5.71 (m, 1H, allyl-CH=), 6.98 (s, 1H, thiazole-CH), 7.05–7.78 (m, 5H, Ar-CH), 7.88-8.03 ppm (m, 4H, Ar-CH); ^{13}C NMR (DMSO-d_6): δ_C = 14.02 (CH_3), 44.88 (allyl-CH_2N), 105.28 (thiazole-CH), 115.86 (allyl-CH_2=), 126.03 (Ar-C-Br), 126.69, 127.77, 128.21, 129.14, 131.56 (Ar-CH), 139.08, 140.25 (Ar-C), 135.55 (allyl-CH=), 141.89 (thiazole-C-4), 159.11 (acyclic-C=N), 162.88 ppm (thiazole-C-2); MS (EI): *m/z* 411/413 (M^+, 22), 331 (100), 176 (42), 138 (29), 118 (20), 77 (41). *Anal. calcd. for* $C_{20}H_{18}BrN_3S$ (412.35): C, 58.26; H, 4.40; N, 10.19; S, 7.78. *Found*: C, 58.21; H, 4.22; N, 10.29; S, 7.92.

(Z)-3-Phenyl-4-(biphenyl-4-yl)-2-[(E)-(1-phenylethylidene)-hydrazono]-2,3-dihydrothiazole ***(6g)****:* Colorless crystals (0.369 g, 83%), mp 276–278°C (ethanol); IR (KBr): ν = 3115 (Ar-H), 1635 (C=N), 1605, 1585 cm^{-1} (Ar-C=C); ^1H NMR (DMSO-d_6): δ_H = 2.42 (s, 3H, CH_3), 6.69–7.02 (m, 4H, Ar-CH), 7.11 (s, 1H, thiazole-CH), 7.32–7.86 (m, 5H, Ar-CH), 7.66–8.12 ppm (m, 10H, Ar-CH); ^{13}C NMR (DMSO-d_6): δ_C = 14.33 (CH_3), 105.68 (thiazole-CH), 126.22, 126.44, 127.41, 127.35, 128.52, 128.65, 128.74, 129.50, 131.62, 134.22, 136.22 (Ar-CH), 135.24, 136.14, 137.16, 139.24, 141.23 (Ar-C), 141.99 (thiazole-C-4), 159.58 (acyclic-C=N), 163.06 ppm (thiazole-C-2); MS (EI): *m/z* 445 (M^+, 100), 292 (68), 152 (25), 215 (44), 118 (31), 97 (16), 77 (26). *Anal. calcd. for* $C_{29}H_{23}N_3S$ (445.58): C, 78.17; H, 5.20; N, 9.43; S, 7.20. *Found*: C, 78.28; H, 5.35; N, 9.26; S, 7.09.

(Z)-3-Benzyl-4-(biphenyl-4-yl)-2-[(E)-(1-phenylethylidene)-hydrazono]-2,3-dihydrothiazole ***(6h)****:* Colorless crystals (0.353 g, 77%), mp 172–174°C (ethanol); IR (KBr): ν = 2295 (Ali-H), 1630 (C=N), 1605, 1585 cm^{-1} (Ar-C=C); ^1H NMR (DMSO-d_6): δ_H = 2.21 (s, 3H, CH_3), 4.91 (s, 2H, CH_2), 6.93 (s, 1H, thiazole-CH), 7.08–7.12 (m, 4H, Ar-CH), 7.22–7.78 (m, 5H, Ar-CH), 7.66–7.99 ppm (m, 10H, Ar-CH); ^{13}C NMR (DMSO-d_6): δ_C = 14.05 (CH_3), 42.14 (CH_2), 105.22 (thiazole-CH), 126.22, 126.34, 127.45, 127.66, 128.22, 128.24, 128.54, 129.55, 131.42, 134.33, 135.08 (Ar-CH), 136.11, 137.08, 137.26, 138.14, 141.33 (Ar-C), 142.25 (thiazole-C-4), 158.78 (acyclic-C=N), 162.77 ppm (thiazole-C-2); MS (EI): *m/z* 459 (M^+, 23), 382 (100), 306 (66), 206 (17), 118 (23), 77 (26). *Anal. calcd. for* $C_{30}H_{25}N_3S$ (459.60): C, 78.40; H, 5.48; N, 9.14; S, 6.98. *Found*: C, 78.28; H, 5.56; N, 8.99; S, 7.12.

(Z)-3-Allyl-4-(biphenyl-4-yl)-2-[(E)-(1-phenylethylidene)-hydrazono]-2,3-dihydrothiazole ***(6i)****:* Pale yellow crystals (0.296 g, 73%), mp 154–156°C (ethanol); IR (KBr): ν = 2195 (Ali-H), 1625 (C=N), 1600, 1585 cm^{-1} (Ar-C=C); ^1H NMR (DMSO-d_6): δ_H = 2.18 (s, 3H, CH_3), 4.42 (br, 2H, allyl-CH_2N), 5.11–5.38 (m, 2H, allyl-CH_2=), 5.50–5.56 (m, 1H, allyl-CH=), 6.98 (s, 1H, thiazole-CH), 7.15–7.23 (m, 4H, Ar-CH), 7.44–7.86 (m, 5H, Ar-CH), 7.66–7.87 ppm (m, 5H, Ar-CH); ^{13}C NMR (DMSO-d_6): δ_C = 14.09 (CH_3), 45.08 (allyl-CH_2N), 105.45 (thiazole-CH), 116.71 (allyl-CH_2=), 126.69, 127.77, 128.21, 128.36, 129.14, 129.36, 131.56, 133.25 (Ar-CH), 134.64, 138.22, 138.18, 140.86 (Ar-C), 135.66 (allyl-CH=), 142.09 (thiazole-C-4), 158.72 (acyclic-C=N), 162.91 ppm (thiazole-C-2); MS (EI): *m/z* 409 (M^+, 100), 256 (32), 153 (24), 118 (20), 231 (13), 178 (22), 77 (46). *Anal. calcd. for* $C_{26}H_{23}N_3S$ (409.55): C, 76.25; H, 5.66; N, 10.26; S, 7.83. *Found*: C, 76.33; H, 5.52; N, 10.12; S, 7.69.

Single crystal X-ray structure determination of ***6e****:* Suitable crystals were obtained by recrystallization from absolute ethanol. The single-crystal X-ray diffraction study were carried out on a Bruker Apex Duo diffractometer at 120(2) K using MoKα radiation (λ = 0.71073 Å). Direct Methods (SHELXS-97) [40] were used for structure solution and refinement was carried out using SHELXL-97 [40] (full-matrix least-squares on F^2). Hydrogen atoms were localized by difference electron density determination and refined using a riding model. A semi-empirical absorption correction was applied.

Compound 6e: $C_{24}H_{20}BrN_3S$, M_r = 462.40 g/mol, orange crystals, crystal size 0.24 × 0.12 × 0.04 mm, triclinic, space group P-1 (2) (No. 2), a = 10.2011(4) Å, b = 10.8581(4) Å, c = 20.8815(7) Å, α = 89.155(2)°, β = 80.010(2)°, γ = 63.132(2)°, V = 2026.63(13) $Å^{-3}$, Z = 4, D_{calc} = 1.515 Mgm^{-3}, μ = 2.147 mm^{-1}, T = 120(2) K, 19334 reflections, 9193 unique [R_{int} = 0.023], $2\theta_{max}$ = 55°, 525 parameters, R_1 [for 7522 I > 2σ(I)] = 0.029, wR2 (all data) = 0.064, S = 1.03, largest diff. peak and hole = 0.489/−0.281 eA^{-3}.

Antibacterial screening [35, 41]

Biological activity

Compounds **5a–e**, **5i**, **6e**, **6g**, and **6i** were screened for their *in vitro* antibacterial activity against *P. aeruginosa*, *E. coli* (ATCC 25922), *K. pneumonia* (as Gram-negative bacteria) and *S. aureus* (ATCC 19433) (as Gram-positive organism). Bacterial strains were supplied from department of Microbiology, Faculty of Pharmacy, El-Minia University. Suspension of each microorganism was prepared at 10^6 CFU/mL (colony forming units/mL) concentrations and inoculated into the corresponding wells. The tested compounds, as well as ciprofloxacin (Sigma, USA) and sulbactam penicillin (Pfizer) were dissolved in DMF to an initial concentration of 10 mg/mL and dilutions of the test compounds were prepared at concentrations 512, 128, 32, 8, 2 μg/mL.

Preparation of the inoculated media [42]

All strains were cultured on Muller–Hinton agar medium, which was supplied from Oxoid Chemical Co. UK, and prepared according to the instructions of the manufacturers. The media were molten on a water bath, inoculated with 0.5 mL of the culture of the specific microorganism and poured into sterile Petri dishes to form a layer of about 3–4 mm thickness. The layer was allowed to cool and harden.

With the aid of a cork-borer, cups of about 10 mm diameter were done.

Agar diffusion technique [35]

Different concentrations of the tested compounds in DMF were inoculated separately into the corresponding wells in the agar medium. All plates were incubated at 37°C for 24–48 h. The incubation chamber was kept sufficiently humid. At the end of the incubation period, the MICs were determined and it was defined to be the intercept of the graph of the logarithm concentrations versus the diameter of the inhibition zones.

*Crystallographic data (excluding structure factors) for the structures reported in this work have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. 918755 (**6e**). Copies of the data can be obtained free of charge on application to*

The Director, CCDC, 12 Union Road, Cambridge DB2 1EZ, UK (Fax: int. code +(1223)336-033; e-mail: deposit@ccdc.cam.ac.uk).

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