Microwave Assisted Synthesis of Fused Thiazoles in Multicomponent System and Their *in vitro* Antitumor, Antioxidant, and Antimicrobial Activities

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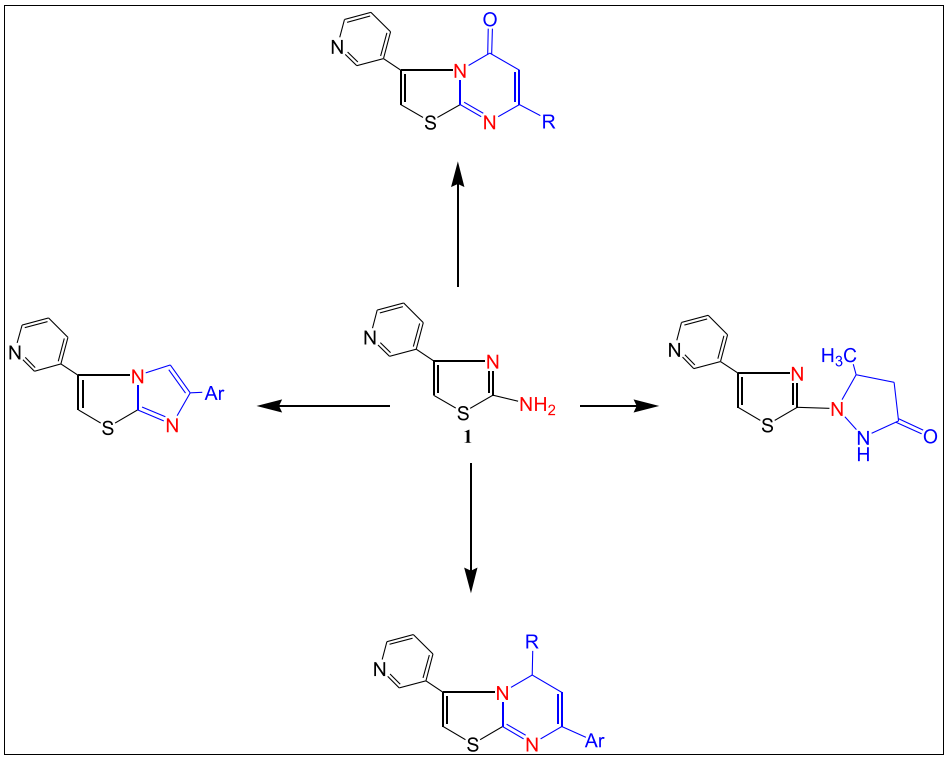
Received February 5, 2016
DOI 10.1002/jhet.2671
Published online 00 Month 2016 in Wiley Online Library (wileyonlinelibrary.com).



A novel series of thiazolopyrimidines, thiazolopyrimidinones, imidazolothiazoles, and 1-thiazole-5-pyrazolone was synthesized under microwave irradiation. Most of the synthesized compounds were screened *in vitro* antitumor, antioxidant, and antimicrobial activities.

INTRODUCTION

Heterocycles containing a thiazole ring system are found to exhibit a wide spectrum of biological activities. Antimicrobial activity of thiazoles has been extensively studied by many researchers [1,2]. Organic compounds bearing thiazoles of different pharmacodynamic moieties have anti-inflammatory, antiviral, antitumor, herbicides, and fungicides activities [3–8]. Also, thiazole and thiadiazole analogs have been proposed as a novel promising class of adenosines A_1 and A_3 receptor antagonists [9]. Thiazole derivatives were described as inhibitor of vascular endothelial growth factor receptors I and III [10]. Triazolyl thiazole series were reported as cdk5/p25 inhibitors, potentially useful for the treatment of Alzheimer's disease [11].

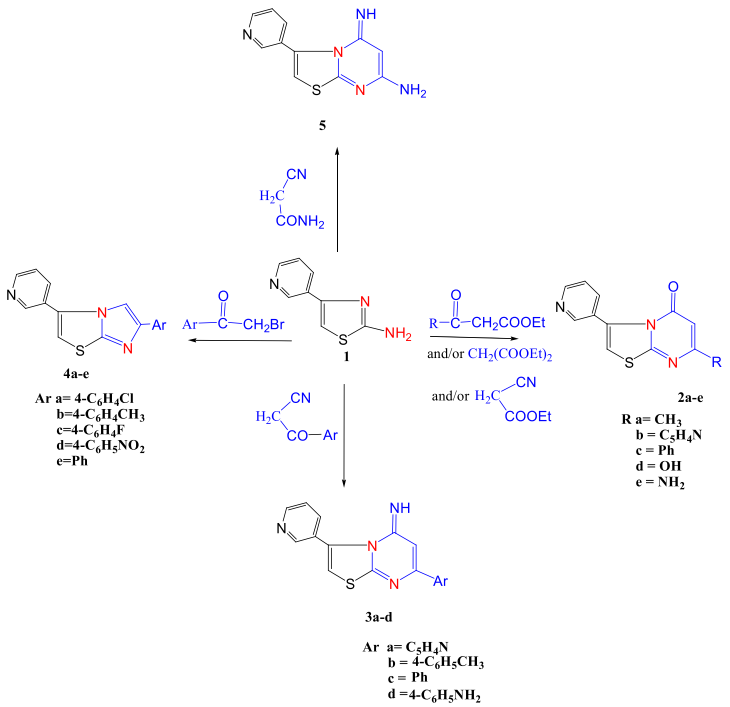
In view of these facts and in continuing effort to find synergistic cytotoxic activities, we report herein novel heterocyclic moieties fused with the thiazole ring with the hope that such moieties represent another biologically active scaffold with higher cytotoxic activity [12–14]. The present work aims to synthesize novel thiazolopyrimidines, thiazolopyrimidinones, imidazolothiazoles, and 1-thiazole-5-pyrazolone derivatives expected to have antioxidant, antitumor, and antimicrobial activities.

RESULTS AND DISCUSSION

Chemistry. The synthetic methodology followed for the target compounds is outlined in Schemes 1–3. Synthesis of compounds containing condensed rings and/or more than one heterocyclic nucleus is gaining more and more popularity because of their specific use in medicine.

The condensation of 4-(pyridine-3-yl) thiazol-2-amine (**1**) [15] with some active methylene compounds, ketoesters, diethylmalonate, and ethyl cyanoacetate, in acetic acid, gave 7-substituted-3-(pyridine-3-yl)-5*H*-thiazolo[3,2-*a*]pyrimidin-

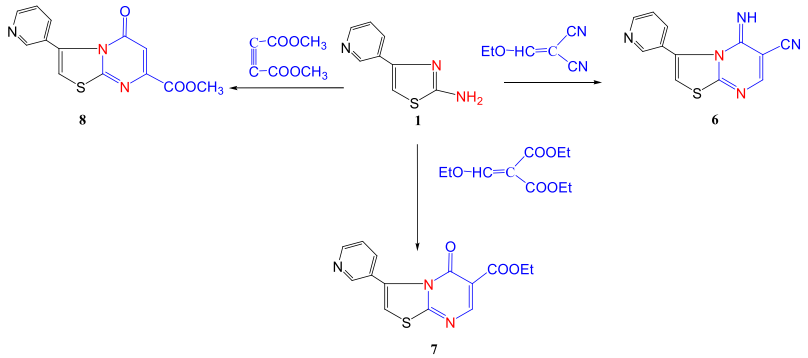
Scheme 1. Synthesis of Thiazolopyrimidinone derivatives **(2a-e)**, thiazolopyrimidin-5-imine derivatives **(3a-d,5)** and imidazolothiazole derivatives **(4a-e)**. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]



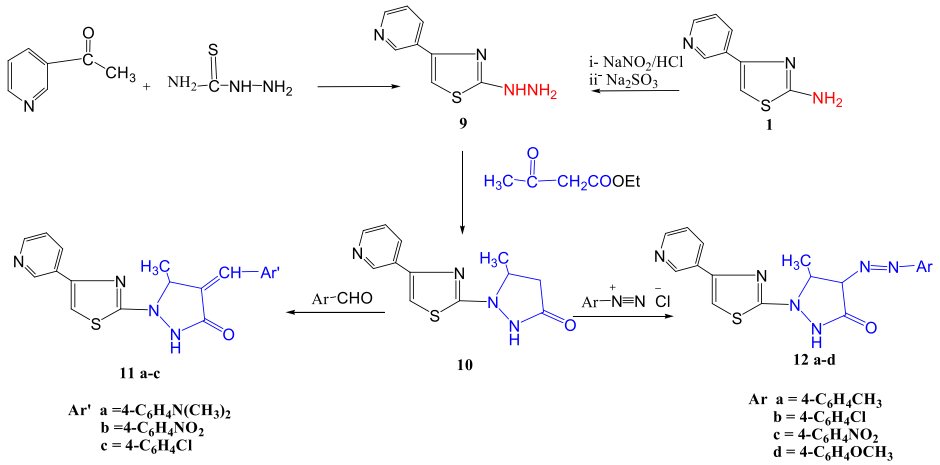
5-ones **2a–e** (Scheme 1) in 65–76% yields. The structure of compounds **2a–e** was proved on the basis of analytical and spectral data. IR spectrum for compound **2e** showed bands at ν 705–708 cm^{-1} (C–S), ν 1629–1645 cm^{-1} (C=O), and ν 3436 cm^{-1} (NH_2). The IR spectrum for compound **2d** showed ν 3275 cm^{-1} (OH). The ^1H NMR spectra of compounds **2a–e** showed the presence of a singlet at δ 7.12–7.23 ppm (thiazole ring proton), a singlet at δ 7.17–7.41 ppm (pyrimidine ring proton), a singlet at δ 2.41 ppm (CH_3 proton) for compound **2a**, a broad peak at δ 6.51 ppm (OH proton) for compound **2d,** a singlet at δ 5.63 (NH_2 proton), which disappeared on D_2O exchange for compound **2e**, and multiplets at δ 7.28–9.21 ppm corresponding to heteroaromatic protons.

Condensation of compound **1** with ketonitrile derivatives gave 7-substituted-3-(pyridine-3-yl)-5*H*-thiazolo [3,2-*a*] pyrimidin-5-amine **3a–d** (Scheme 1) in 64–68% yields. The IR spectra showed bands at ν 702–709 cm^{-1} (C–S) and broad bands at ν 3220–3233 cm^{-1} (NH). The ^1H NMR spectra of compounds **3a–d** showed the presence of a singlet at δ 7.15–7.39 ppm (thiazole ring proton), a singlet at δ 7.23–7.41 ppm (pyrimidine ring proton), a singlet at δ 4.82 ppm (NH_2 protons), which disappeared by mixing with

Scheme 2. Synthesis of thiazolopyrimidin-5-imine derivatives **(6,8)** and Thiazolopyrimidinone **(7)**. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]



Scheme 3. Synthesis of 4-arylidene-1- thiazole-3- pyrazolone **(11a-c)** and 4-(aryldiazenyl)-1- thiazole-3- pyrazolone **12a-d**. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]



D_2O for compound **3d,** a singlet at δ 2.37 ppm (CH_3 proton) for compound **3b**, and multiplets at δ 7.33–9.12 ppm corresponding to aromatic and heteroaromatic protons.

The condensation of compound **1** with phenacyl bromides gave 6-(4-aryl)-3-(pyridine-3-yl)imidazo[2,1-*b*]thiazole **4a–e** (Scheme 1) in 67–76% yields. The IR spectra showed bands at ν 679–683 cm^{-1} (C–S) and bands at ν 1600–1626 cm^{-1} (C=N). The ^{1}H NMR spectra of compounds **4a–e** showed the signals for all expected protons.

Similarly, the condensation of compound **1** with cyanoacetamide gave 5-imino-3-(pyridine-3-yl)-5*H*-thiazolo [3,2-*a*] pyrimidin-7-amine **5** (Scheme 1) in a yield of 71%. The structure of **5** was confirmed by various spectroscopic techniques including IR, NMR, and mass spectral data as well as microanalysis (see Experimental section for details).

Reaction of 4-(pyridine-3-yl) thiazol-2-amine (**1**) with ethoxymethylene malononitrile and ethoxymethylene diethylmalonate gave 5-imino-3-(pyridine-3-yl)-5*H*-thiazolo [3,2-*a*]pyrimidin-6-carbonitrile **6** and ethyl-5-oxo-3-(pyridine-3-yl)-5*H*-thiazolo [3,2-*a*]pyrimidin-6-carboxylate **7** (Scheme 2) in 65% and 62% yields, respectively. The IR spectra of compounds **6** and **7** showed bands at ν 677 and ν 724 cm^{-1} (C–S), respectively, a band at ν 2210 cm^{-1} (C=N) for compound **6**, and two bands at ν 1635 and ν 1735 cm^{-1} (C=O of pyrimidinone and C=O of ester group), respectively, for compound **7**. The ^{1}H NMR spectra of compounds **6** and **7** showed the presence of a singlet at δ 7.11 and 7.13 ppm (thiazole ring proton), respectively, a singlet at δ 7.24 and 7.21 ppm (pyrimidine ring proton), respectively, and multiplets at δ 7.41–9.06 and 7.32–9.08 ppm, respectively, corresponding to heteroaromatic protons. Also, compound **7** showed triplet at δ 1.35 ppm (CH_3 proton) and a quartet CH_2 at δ 3.95 ppm for ethyl protons.

Condensation of **1** with acetylene dimethyl carboxylate gave ethyl-5-oxo-3-(pyridine-3-yl)-5*H*-thiazolo[3,2-*a*]pyrimidin-7-methylcarboxylate (**8**; Scheme 2) in 70% yield. The IR spectrum of compound **8** showed a band at ν 707 cm^{-1} (C–S) and two bands at ν 1662 and ν 1725 cm^{-1} (C=O of pyrimidinone and C=O of ester group, respectively). The ^{1}H NMR spectrum of compound **8** showed the presence of a singlet at δ 7.13 ppm (thiazole ring proton), a singlet at δ 7.16 ppm (pyrimidine ring proton), a singlet at δ 3.16 ppm (CH_3 proton), and multiplets at δ 7.36–9.30 corresponding to heteroaromatic protons (see Experimental section for details).

Treatment of compound **1** with nitrous acid followed by reduction with sodium sulfite in water gave 2-hydrazino-4-(pyridine-3-yl)-1,3-thiazole (**9**; Scheme 3), which could be also obtained by the reaction of 3-acetylpyridine with thiosemicarbazide in absolute ethanol. The reaction of compound **9** with ethylacetoacetate gave 3-methyl-1-[4-(pyridin-3-yl)thiazol-2-yl]-1*H*-pyrazol-5(4*H*)-one (**10**; Scheme 3). The reactivity of the active methylene group was tested by reaction of **10** with some aromatic aldehydes and diazonium salts of some aromatic amines to give (*Z*) -4- arylidene-5-methyl-1-(4-(pyridine-3-yl)thiazol-2-yl)pyrazolidine-3-ones **11a–c** and 5-methyl-4-(aryldiazenyl)-1-(4-(pyridine-3-yl)thiazol-2-yl)pyrazolidine-3-ones **12a–d**, respectively, (Scheme 3) in good yields. The IR spectra of compounds **11a–c** showed bands at ν 756–781 cm^{-1} (C–S), ν 3340–3410 (NH), and ν 1656–1689 (C=O). The ^{1}H NMR spectra of compounds **11a–c** showed the presence of singlet at δ 6.85–6.89 ppm (thiazole ring protons), singlet at δ 2.21 ppm (CH_3 protons), a singlet at δ 6.98–6.99 ppm (=CH protons), singlet at δ 9.69–9.88 ppm (NH of pyrazolone ring protons), multiplets at δ 7.35–9.14 corresponding to aromatic and heteroaromatic protons, and a singlet at δ 2.75 ppm ($N(CH_3)_2$ protons) for compound **11a**. On the other hand, the IR spectra of compounds **12a–d** showed bands at ν 727–767 cm^{-1} (C–S), ν 3383–3401 (NH), ν 1656–1689 (C=O), and ν 1650–1659 (N=N). The ^{1}H NMR spectra of compounds **12a–d** showed the presence of a singlet at δ 6.86–6.92 ppm (thiazole ring protons), a singlet at δ 6.93–6.99 ppm (pyrazolone ring protons), a singlet

Table 1

The reaction time and yield for compounds **2–8** produced by both traditional and microwave procedures.

	Time		Yield (%)	
Product	Microwave (120–130°C, min)	Conventional heating (reflux, h)	Microwave irradiation	Conventional heating
2a	15	4	90	76
2b	20	4	89–92	69
2c	20	4	92	67
2d	20	4	87–89	72
2e	20	4	90–92	65
3a	15	5	90–93	68
3b	25	5	90–92	65
3c	20	5	88–91	68
3d	20	5	83	64
4a	15	6	91–92	69
4b	20	6	86–88	70
4c	25	8	82	67
4d	15	8	81–84	72
4e	25	6	85	76
5	20	4	88	71
6	15	5	83–85	65
7	15	5	75	62
8	25	4	85–87	70

at δ 2.21 ppm (CH_3 protons), a singlet at δ 9.61–9.98 ppm (NH of pyrazolone ring protons), and multiplets at δ 7.33–9.31 corresponding to aromatic and heteroaromatic protons. They also showed two singlets at δ 2.32 and 3.41 ppm (CH_3 and OCH_3 protons) that resonated for compounds **12a** and **12d,** respectively (see Experimental section for details).

Microwave irradiation technique as a source of energy was used. Under this technique, interesting results were obtained in which the reaction time was reduced from 4–8 h to only few minutes (15–25 min) and the yields were increased from 62–76% to 75–93%. Also, the products obtained are more pure than that obtained by conventional heating procedure (Table 1).

PHARMACOLOGY

Antitumor activity. The newly synthesized compounds **4a–e** were chosen as prototypes for screening against a panel of two human cancer cell lines HEPG2 (liver cancer) and MCF7 (breast cancer). Primary anticancer assay was performed in accordance with the protocol of National Cancer Institute, Cairo University, Egypt, according to Sulforhodamine B (SRB) assay [16].

Results and discussion. Antitumor activities of compounds **4a–4e** were measured by the use of SRB assay against human cancer cell lines HEPG2 (liver cancer) and MCF7 (breast cancer). These results were summarized in Table 2 and represented in Figures 1 and 2. The overall results indicated that compounds **4a–e** have nearly the same antitumor activity with IC50 that ranged from 22.10–30.70 µg/mL through induction of apoptosis in MCF7 (breast cancer) cell line and ranged

Table 2

IC50 for compound **4** tested on breast and liver cancer.

	IC50 (µg/mL)	
Product	Breast cancer	Liver cancer
4a	22.10	21.50
4b	19.70	22.00
4c	29.20	39.10
4d	22.40	11.80
4e	30.70	22.60
Standard-DOX	MCF7-DOX (4.40)	HEPG2-DOX (3.10)

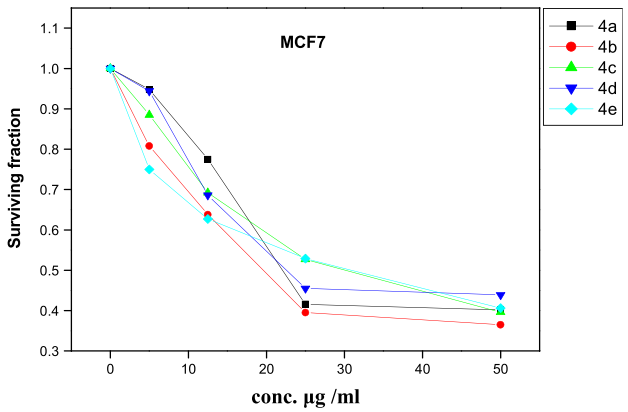


Figure 1. IC50 of compounds **4a–e** tested on MCF7 for breast cancer. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

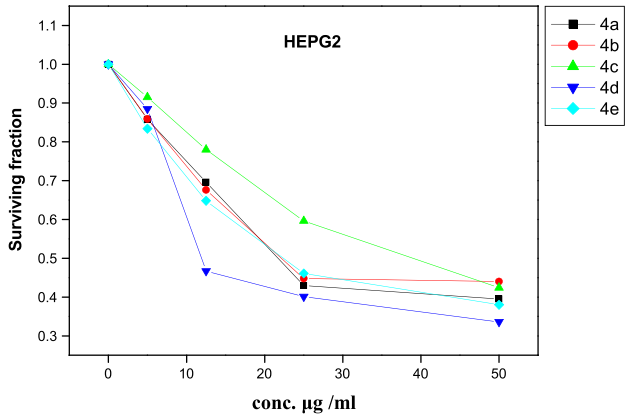


Figure 2. IC50 of compounds **4a–e** tested on HEPG2 for liver cancer. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

from 11.80–39.10 µg/mL through induction of apoptosis in HEPG2 (liver cancer) cell line. The highest antitumor activity was detected with compound **4b** (IC50 = 19.70 µg/mL) in MCF7 breast cancer cell line, suggesting that it might be a potential alternative agent for human breast cancer therapy. Compound **4d** has the most antitumor activity (IC50 = 11.80 µg/mL) through induction of apoptosis in HEPG2 cancer cell line, suggesting that it might be a potential alternative agent for human hepatic cancer therapy. Compound **4c** has the lowest antitumor activity (IC50 = 39.10 µg/mL) apoptosis in HEPG2 cancer cell line.

Antioxidant screening. Because antioxidants are gaining attention as a potential means of treating a large number of life style diseases like cancer, the 1,1-phenyl-2-picrylhydrazyl (DPPH) radical has been widely used to test the ability of compounds to scavenge radical. Briefly, the assay measures the decreases in absorbance of the DPPH radicals at a characteristic wave length after 60 min incubation of the DPPH radical with different concentrations (from 5 to 50 µg/mL) of the antioxidant compounds according to the method of Brand-Williams *et al.* [17]. The absorbance of the reaction mixture was recorded at $\lambda = 517$ nm using a UV visible spectrometer (Genway 6305). L-ascorbic acid (vitamin C) was used as a standard antioxidant (positive control). Results are expressed as the percentage of the DPPH-free radical scavenging at (five concentrations) each value is expressed as the average of three experiments per concentration ± SD.

Materials and Methods. *1,1-Phenyl-2-picrylhydrazyl radical scavenging assay.* The antioxidant activities of the tested compounds were measured by using DPPH radical scavenging assay with L-ascorbic acid as reference drug [16]. Each tested sample and L-ascorbic acid (50 µg) were dissolved in dimethyl sulfoxide (DMSO) (1 mL). The dissolved sample (250 mL) was added to 1 mL DPPH/DMSO solution (6 µg/50 mL), and the total volume was adjusted to 3 mL with DMSO. An equal amount of DMSO was used as a control. The mixture was mixed and incubated for 30 min in the dark at room temperature. Absorbance was measured using a spectrophotometer at 517 nm. DPPH radical scavenging % = 1 ×)a sample/a control 100). Serial dilutions 5–50 µg/mL of each compound were measured by the same assay to obtain the IC50 according to Brand-Williams *et al.* [17].

Results and discussion. The free radical scavenging activity for the tested compounds is shown in Table 3 and represented in Figures 3–5. Compound **4a** has the most potent antioxidant activity with IC50 (3.99) and was found to be close to the value from the standard drug possibly because of the presence of chlorine atom in the aryl group. The IC50 values of compounds **2a–d** exhibited good scavenging activity against the DPPH radical that ranged from 60–77% with IC50 range of 4.18–5.59 µg/mL. The values were found to be slightly

Table 3

Percentage of free radical scavenging activity (DPPH radical) obtained for the tested compounds.

Product	Decrease of DPPH absorbance % (Conc. = 100 µg/mL)	IC50 (µg/mL)
2a	76.62	5.00
2b	76.43	5.59
2c	65.17	4.83
2d	67.81	4.18
2e	59.92	8.06
3a	45.09	8.24
3b	68.53	5.54
3c	77.15	4.89
3d	67.81	5.88
4a	76.81	3.99
4b	53.63	10.0
4c	64.55	4.36
4d	65.89	6.33
4e	58.79	7.99
5	62.54	6.30
6	56.65	8.30
7	57.2	8.40
8	55.17	8.34
9	43.96	8.38
10	59.77	7.42
11a	45.09	8.24
11b	61.68	6.30
11c	59.77	7.37
12a	75.88	6.00
12b	55.17	8.34
12c	77.81	5.88
12d	76.62	5.00
Ascorbic acid*	82	3.20

DPPH, 1,1-phenyl-2-picrylhydrazyl.
*Antioxidant reference standard.

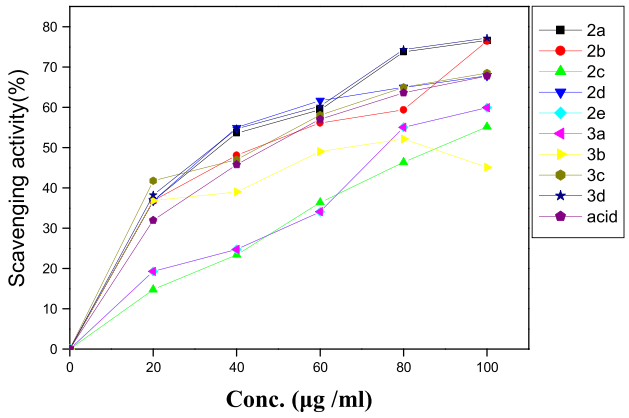


Figure 3. Scavenging antioxidant percentage of compounds **2a–e** and **3a–d**. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

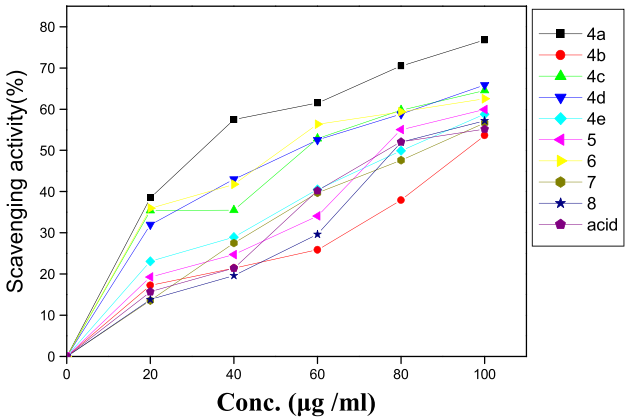


Figure 4. Scavenging antioxidant percentage of compounds **4a–e**, **5**, **6**, **7**, and **8**. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

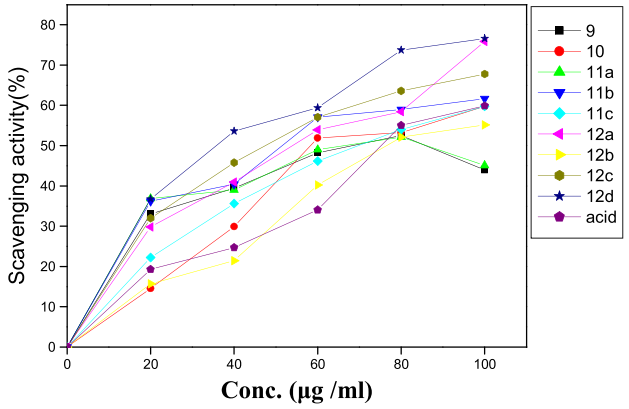


Figure 5. Scavenging antioxidant percentage of compounds **9**, **10**, **11a–c**, and **12a–d**. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

higher than the values for the standard ascorbic acid (IC50, 3.2 µg/mL). Compounds **3b–d** exhibited higher antioxidant activity (with effective radical scavengers 68%, 66%, and 67%, respectively) than compound **3a** (with effective radical scavengers as 45%) compared with the standard, ascorbic acid. The IC50 values for compounds **4a–e** indicated that compounds showed antioxidant activity in the order **4a** > **4c** > **4d** > **4e** > **4b**. Compounds **5–10** and **11a–c** exhibited moderate scavenging activity against the DPPH radical that ranged from 43.9–62.5% with IC50 in the range of 6.3–8.38 µg/mL. The compound **5** and **11b** were considerably more effective radical scavengers 62% with IC50 of 6.3 µg/mL. Compounds **12a–d** also exhibited moderate antioxidant activity. The IC50 values of compounds **12a–d** showed the same antioxidant activity in the range of 5–8 µg/mL.

Antimicrobial evaluation. Through history, there has been a continual battle between humans and the multitude of microorganisms that cause infection and disease. Diseases caused by microbial infection are serious menaces to the health of human beings and after, have connection to some other diseases whenever the body system gets debilitated. During the 20th century, vaccines for bacterial toxins and many other common acute viral infections were developed and made widely available. Thiazole is an important class of heterocycles that has been found in many potent biologically active molecules as sulfathiazole, fentiozoc, and meloxicom. Our ongoing research in the field of the synthesis and antimicrobial activities of medicinally important new compounds has included fused thiazole compounds as new examples in this domain.

Antimicrobial assay. An aliquot of 0.1 mL of each bacterial strain was inoculated and spread on nutrient agar, while 0.1 mL of the yeast was spread on sabouraud agar slopes. Antimicrobial activities of the synthesized compounds were tested *in vitro* against different types of bacteria and one fungal strain by the cut-plug method [18]. The assay plates were inoculated with 100 mL containing the diluted inoculums (107 CFU/mL) of each tested organism that were spread on the corresponding media. After solidification, the wells were made, and 10 mg of the synthesized chemicals was dissolved in 1 mL DMSO and inserted in the wells. Nutrient agar plates were incubated at 37°C for 24 h, while sabouraud agar plates were incubated at 25°C for 48 h. The zones of inhibition around the wells were measured, and the average based on three replies was recorded. For reference drugs miphinicol at a concentration of 1 mg/mL for Gram-positive bacteria, Keflex was used as standard for Gram-negative bacteria at a concentration of 1 mg/mL, and Flucoral was used as standard for fungi at a concentration of 1 mg/mL, and amikacin was used as standard at a concentration of 1 mg/mL for *Candida albicans.*

Results and discussion. Compounds **2a–e** and **4a–e** were screened for their *in vitro* antibacterial activities against *Staphylococcus aureus*, *Bacillus subtilis* (Gram

Table 4

Diameters of inhibition zones (mm) of newly synthesized compounds against different tested bacteria and fungi on nutrient agar at 30°C after 24 h.

Product	*Bacillus subtilis*	*Escherichia coli*	*Pseudomonas aeruginos*a	*Staphylococcus aureus*	*Candida albicans*	*Asbergillus nigar*
2a	–	–	–	–	–	11
2b	–	11	–	–	–	12
2c	11	11	–	11	–	11
2d	–	–	–	–	–	–
2e	–	11	–	–	–	–
4a	–	11	–	–	–	–
4b	–	–	–	–	–	–
4c	–	–	–	–	–	–
4d	–	14	–	13	–	11
4e	11	13	–	14	–	11
St.	31.5	30	37.5	32	25.0	23

St., standard, which is miphinicol at conc. 1 mg/mL for gram-positive bacteria, while Keflex was used as standard for gram-negative bacteria at conc. 1 mg/mL. Flucoral was used as standard for fungi at conc. 1 mg/mL. Amikacin was tested as standard at conc. 1 mg/mL for *Candida albicans*. The sensitivity of microorganisms to the tested compounds is identified in the following manner. Highly sensitive = inhibition zone: 15–20 mm; moderately sensitive = inhibition zone: 10–15 mm; slightly sensitive = inhibition zone: 1–10 mm; not sensitive = inhibition zone: 0 mm; each result represents the average of triplicate readings.

positive), *Pseudomonas aeruginosa, Escherichia coli* (Gram negative), *Candida albicans*, and *Asbergillus nigar* (fungi).

The results obtained are recorded in Table 4. In general, these compounds showed a relatively moderate activity against Gram-positive and Gram-negative bacteria as well as against yeast. These activities can be revealed by the diameter of their inhibition zones. From the bioactivity data of the synthesized compounds, it was inferred that compounds **2c** and **4e** showed the highest activity than other compounds. On the other hand, compounds **2d**, **4b**, and **4c** showed no antimicrobial activity for the tested organisms. Compounds **2b** and **4d** were found to have slight or moderate activity, while compounds **2a, 2e**, and **4a** showed a moderate activity with only one organism (*A. nigar*) and (*E. coli*), respectively. It is worth mentioning that minor change in molecular configuration of the tested compounds profoundly influences the microbial activity. The present study was focused on the determination of minimum inhibitory concentration (MIC) for compounds **2c** and **4e**. The present data show that the most sensitive organism to the tested sample **2c** is *B. subtilis* and *E. coli* that showed (MIC) value of 250 and 180, respectively, while the most sensitive organisms to **4e** are *B. subtilis* and *S. aureus* that showed MIC values of 250 and 125, respectively, compared with others (Table 5).

CONCLUSION

Novel heterocycles having 1,3-thiazole ring system have been synthesized under microwave irradiation conditions. The synthesized compounds were tested for their antioxidant activity radical scavenging activities against the DPPH using L-ascorbic as reference drug. Compounds **4a–e** were evaluated for their *in vitro* cytotoxicity against human liver cell line (HEGP2) and human breast cell line (MCF7). Also, compounds **2a–e** and **4a–e** were screened for their *in vitro* antibacterial activity against *S. aureus*, *B. subtilis* (Gram positive), *P. aeruginosa, E. coli* (Gram negative), *C. albicans*, and *A. nigar* (fungi). The synthesized compounds could be considered as a useful template for future development or modification to obtain more potent and selective reagents.

Table 5

MIC for **2c** and **4e** against tested microorganisms (MIC) μg/mL.

Product	*Bacillus subtilis*	*Escherichia coli*	*Pseudomonas aeruginos*a	*Staphylococcus aureus*	*Candida albicans*	*A. nigar*
2c	250	180	–	500	–	1000
4e	250	500	–	125	–	1000
St.	31.25	62.5	62.5	31.25	31.25	1000

All the dilutions of both samples and standards were performed by double-fold dilution.
MIC, minimal inhibitory concentration.

EXPERIMENTAL

General. Melting points were recorded on a Gallenkamp melting point apparatus and are reported uncorrected. Infrared spectra were recorded on Perkin–Elmer Fourier transform infrared spectroscopy 1430 spectrophotometer (Waltham, MA, USA) using the KBr disk technique. The ^{1}H NMR spectra were recorded on a Bruker AC spectrometer (300 MHz, Billerica, MA, USA) at 25°C in hexadeuterated dimethyl sulfoxide (DMSO-d_6) with trimethylsilyl as an internal standard, and chemical shifts are reported in ppm as δ values. Reactions were conducted under microwave irradiation in closed vessels with magnetic stirring in a Synthos 3000 (Anton Paar, Graz, Austria) microwave with dual magnetrons system and with maximum power of 1000 W. Mass spectra were measured on a Finnigan MAT 8222 EX mass spectrometer at 70 eV. Absorbance was measured using a Jenway 6305 spectrophotometer (Staffordshire, UK). Microanalyses were performed on Perkin–Elmer 2400 elemental analyzer at microanalytical center at Cairo University. Reaction progress was monitored by thin layer chromatography (TLC) using benzene/acetone (2/1 by volume) as eluent. The strains under study were obtained from Al-Azhar University, fermentation biotechnology, and applied microbiology (Farm-BAM). Bacteria were cultured on nutrient agar, and the fungus was cultured on sabouraud agar slopes. Antimicrobial activities of the synthesized compounds were tested *in vitro* on nutrient agar at 30°C, after 24 h by the cut-plug method according to Pridham *et al.* [18].

General procedure for the synthesis of compounds 2, 3, 5, and 8. A mixture of 4-(pyridine-3-yl) thiazol-2-amine (**1**; 1.0 g, 5.6 mmol), ketoester or ketonitrile (5.6 mmol), diethylmalonate (0.88 g), ethyl cyanoacetate (0.63 g), cyanoactamide (0.47 g), and dimethylacetylene dicarboxylate (0.78 g), in ethanol (20 ml) containing a catalytic amount of piperidine, was refluxed for 3–4 h. On completion of reaction, monitored by TLC, the reaction mixture was cooled to room temperature, and the separated solid was filtered and washed with methanol to obtain compounds **2**, **3**, **5**, and **8.**

7-Methyl-3-(pyridin-3-yl)-5H-thiazolo[3,2-a]pyrimidin-5-one (2a). M.p. 190–192°C; IR (KBr) υ/cm^{-1} = 3057 (Ar-H), 2940 (Aliph-H), 1631 (C=O), 706 (C–S). ^{1}H NMR (DMSO-d_6): δ ppm = 2.41 (s, 3H, CH_3), 7.13 (s, 1H, CH of thiazole), 7.17 (s, 1H, CH of pyrimidine), 7.28–9.00 (m, 4H, Ar-H). MS m/z (%): 242 (M − 1; 26), 177 (53), 114 (25), 84 (100), 73 (50), 60 (81). *Anal.* for $C_{12}H_9N_3OS$ (243.284) Calcd.: C 59.24; H 3.73; N 17.27; S 13.18%, Found: C 59.95; H 3.39; N 17.62; S 13.61%.

3,7-Di(pyridin-3-yl)-5H-thiazolo[3,2-a]pyrimidin-5-one (2b). M.p. 250–252°C; IR (KBr) υ/cm^{-1} = 3175 (Ar-H), 2854 (Aliph-H), 1632 (C=O), 705 (C–S). ^{1}H NMR (DMSO-d_6): δ ppm = 7.21 (s, 1H, CH of thiazole), 7.32 (s, 1H, CH of pyrimidine), 7.47–9.12 (m, 8H, Ar-H). MS m/z (%): 306 (20), 295 (51), 208 (71), 177 (31), 123 (51), 106 (60), 84 (100). *Anal.* for $C_{16}H_{10}N_4OS$ (306.342) Calcd.: C 62.73; H 3.29; N 18.29; S 10.47%, Found: C 63.43; H 3.74; N 8.83; S 10.82%.

7-Phenyl-3-(pyridin-3-yl)-5H-thiazolo[3,2-a]pyrimidin-5-one (2c) yield 67%. M.p. 245–247°C; IR (KBr) υ/cm^{-1} = 3166 (Ar-H), 2853 (Aliph-H), 1635 (C=O), 708 (C–S). ^{1}H NMR (DMSO-d_6): δ ppm = 7.18 (s, 1H, CH of thiazole), 7.25 (s, 1H, CH of pyrimidine), 7.32–9.08 (m, 9H, Ar-H). MS m/z (%): 306 (M + 1, 10), 248 (205), 209 (1000), 176 (11), 134 (21), 105 (41). *Anal.* for $C_{17}H_{11}N_3OS$ (305.354) Calcd.: C 66.87; H 3.63; N 13.76; S 10.50%, Found: C 66.24; H 3.12; N, 13.28; S 10.18%.

7-Hydroxy-3-(pyridin-3-yl)-5H-thiazolo[3,2-a]pyrimidin-5-one (2d). M.p. 245–247°C; IR (KBr) υ/cm^{-1} = 3275 (OH), 3059 (Ar-H), 2943 (Aliph-H), 1629 (C=O), 707 (C–S). ^{1}H NMR (DMSO-d_6): δ ppm = 7.12 (s, 1H, CH of thiazole), 7.35 (s, 1H, CH of pyrimidine), 7.39–9.21 (m, 4H, Ar-H), 6.51 (s, 1H, OH). MS m/z (%): 243 (M − 2, 11), 227 (23), 209 (46), 177 (100), 135 (62), 105 (75). *Anal.* for $C_{11}H_7N_3O_2S$ (245.257) Calcd.: C 53.87; H 2.88; N 17.13; S 13.07%, Found: C 53.21; H 2.14; N 17.71; S 13.71%.

5-Amino-3-(pyridin-3-yl)-5,6-dihydrothiazolo[3,2-a]pyrimidin-7-one (2e). M.p. 205–207°C; IR (KBr) υ/cm^{-1} = 3436 (NH_2), 3130 (Ar-H), 2966 (Aliph-H), 1645 (C=O), 705 (C–S). ^{1}H NMR (DMSO-d_6): δ ppm = 7.23 (s, 1H, CH of thiazole), 7.41 (s, 1H, CH of pyrimidine), 7.47–9.21 (m, 4H, Ar-H), 5.63 (s, exch., 2H, NH_2). MS m/z (%):244 (M, 12), 226 (24), 209 (61), 177 (100), 135 (57), 104 (47). *Anal.* for $C_{11}H_{10}N_4OS$ (244.272) Calcd.: C 53.64; H 4.09; N 22.75; S 13.02%, Found: C 53.99; H 4.46; N 22.32; S 13.39%.

3,7-Di-(pyridin-3-yl)-5H-thiazolo[3,2-a]pyrimidin-5-amine (3a). M.p. 155–157°C; IR (KBr) υ/cm^{-1} = 3220 (NH), 3118 (Ar-H), 2974 (Aliph-H), 706 (C–S). ^{1}H NMR (DMSO-d_6): δ ppm = 7.21 (s, 1H, CH of thiazole), 7.23 (s, 1H, CH of pyrimidine), 7.33–9.12 (m, 4H, Ar-H), 9.82 (s, H, NH). MS m/z (%): 306 (M − 1, 27), 296 (78), 289 (28), 177 (100), 135 (47), 106 (41). *Anal.* for $C_{16}H_{13}N_5S$ (307.373) Calcd.: C 53.87; H 2.88; N 17.13; S 13.07%, Found: C 53.25; H 2.46; N 17.64; S 13.41%.

3-(Pyridin-3-yl)-7-p-tolyl-5H-thiazolo[3,2-a]pyrimidin-5-amine (3b). M.p. 193–195°C; IR (KBr) υ/cm^{-1} = 3225 (NH), 3017 (Ar-H), 2928 (Aliph-H), 709 (C–S). ^{1}H NMR (DMSO-d_6): δ ppm = 2.37(s, 3H, CH_3), 7.15 (s, 1H, CH of thiazole), 7.32 (s, 1H, CH of pyrimidine), 7.35–9.02 (m, 8H, Ar-H), 9.69 (s, H, NH). ^{13}C NMR (DMSO-d_6) δ (ppm): 22.2 (CH_3), 43.8 (C-NH_2), 103.6 (C5 of thiazole), 123.1 (C3 of pyrimidine), 148.7 (C4 of thiazole), 149.1 (C4 of thiazole), 123.6, 128.3, 129.0, 129.8, 130.5, 132.6, 135.6, 146.8, 148.0

(Caromatic). MS m/z (%): 320 (M, 21), 286 (13), 202 (47), 177 (18), 135 (62), 119 (100), 91 (76). *Anal.* for $C_{18}H_{16}N_4S$ (320.411) Calcd.: C 67.47; H 5.03; N 17.49; S 10.01%, Found: C 67.91; H 5.43; N 17.84; S 10.43%.

7-Phenyl-3-(pyridin-3-yl)-5H-thiazolo[3,2-a]pyrimidin-5-amine (3c). M.p. 240–242°C; IR (KBr) $\upsilon/cm^{-1} = 3233$ (NH_2), 3154 (Ar-H), 2954 (Aliph-H), 702 (C–S). ^1H NMR (DMSO-d_6): δ ppm = 7.21 (s, 1H, CH of thiazole), 7.39 (s, 1H, CH of pyrimidine), 7.41–9.11 (m, 9H, Ar-H), 9.75 (s, H, NH). MS m/z (%): 306 (22), 286 (55), 209 (15), 177 (26), 135 (48), 105 (48), 91 (19). *Anal.* for $C_{17}H_{14}N_4S$ (306.094) Calcd.: C 66.64; H 4.61; N 18.29; S 10.47%, Found: C 66.16; H 4.23; N 18.73; S 10.89%.

7-(4-Aminophenyl)-3-(pyridin-3-yl)-5H-thiazolo[3,2-a]pyrimidin-5-amine (3d). M.p. 270–273°C; IR (KBr) $\upsilon/cm^{-1} = 3331$ (NH_2), 3230 (NH), 3154 (Ar-H), 2943 (Aliph-H), 707 (C–S). ^1H NMR (DMSO-d_6): δ ppm = 4.82 (s, 2H, NH_2), 7.39 (s, 1H, CH of thiazole), 7.41 (s, 1H, CH of pyrimidine), 7.48–9.12 (m, 8H, Ar-H), 9.62 (s, H, NH). MS m/z (%): 320 (M − 1, 12), 316 (65), 286 (62), 177 (100), 135 (51), 105 (22), 91 (26). *Anal.* for $C_{17}H_{15}N_5S$ (321.105) Calcd.: C 63.69; H 4.80; N 21.89; S 9.98%, Found: C 63.29; H 4.45; N 21.38; S 9.31%.

5-Imino-3-(pyridin-3-yl)-5H-thiazolo[3,2-a]pyrimidin-7-amine (5). M.p. 188–190°C; IR(KBr) $\upsilon/cm^{-1} = 3215$ (NH), 3302 (NH_2), 3129 (Ar-H), 2959 (Aliph-H), 705 (C–S).^1H NMR (DMSO-d_6): δ ppm = 4.98 (s, 2H, NH_2), 7.25 (s, 1H, CH of thiazole), 7.37 (s, 1H, CH of pyrimidine), 7.39–9.03 (m, 4H, Ar-H), 9.55 (s, H, NH). MS m/z (%): 243 (M, 34), 227 (45), 209 (26), 177 (100), 135 (79), 105 (27), 91 (17). *Anal.* for $C_{11}H_9N_5S$ (243.058) Calcd.: C 54.31; H 3.73; N 28.79; S 13.18%, Found: C 54.81; H 3.99; N 28.36; S 13.82%.

Methyl 5-oxo-3-(pyridin-3-yl)-5H-thiazolo[3,2-a]pyrimidine-7-carboxylate (8). M.p. 135–136°C; IR (KBr) $\upsilon/cm^{-1} = 3064$ (Ar-H), 2952 (Aliph-H), 1725 (C=O of ester), 1662 (C=O of pyrimidinone), 707 (C–S). ^1H NMR (DMSO-d_6): δ ppm = 3.16 (s, 3H, CH_3), 7.13 (s, 1H, CH of thiazole), 7.16 (s, 1H, CH of pyrimidinone), 7.36–9.30 (m, 4H, Ar-H). MS m/z (%): 287 (34), 227 (45), 209 (26), 177 (100), 135 (79), 105 (28), 91 (16). *Anal.* for $C_{13}H_9N_3O_3S$ (287.036) Calcd.: C 55.80; H 3.68; N 13.95; S 10.64%, Found: C 55.39; H 3.99; N 13.48; S 10.17%.

General procedure for the synthesis of compounds 4, 6, and **7**. A mixture of 4-(pyridine-3-yl) thiazol-2-amine (**1**; 1.0 g, 5.6 mmol), phenacyl bromide (5.6 mmol), ethoxymethylenemalononitrile (0.68 g), or ethoxymethylene diethylmalonate (1.2 g), in ethanol (20 mL), was refluxed for 5–8 h. On completion of the reaction, monitored by TLC, the reaction mixture was cooled to room temperature, and the separated solid was filtered and washed with methanol to obtain compounds **4**, **6**, and **7.**

6-(4-Chlorophenyl)-3-(pyridin-3-yl)imidazo[2,1-b]thiazole (4a). M.p. 230–233°C; IR (KBr) $\upsilon/cm^{-1} = 3157$ (Ar-H), 2940 (Aliph-H), 1626 (C=N), 679 (C–S). ^1H NMR (DMSO-d_6): δ ppm = 6.87 (s, 1H, CH of thiazole), 6.99 (s, 1H, CH of imidazole), 7.36–9.23 (m, 8H, Ar-H). MS m/z (%): 311 (24), 274 (50.00), 261 (69), 249 (86), 190 (100), 177 (20), 121 (31), 82 (57). *Anal.* for $C_{16}H_{10}ClN_3S$ (311.028) Calcd.: C 61.64; H 3.23; Cl 11.37; N 13.48; S 10.28%, Found: C 61.99; H 3.73; Cl 11.87; N 13.83; S 10.75%.

3-(Pyridin-3-yl)-6-p-tolylimidazo[2,1-b]thiazole (4b). M.p. 245–247°C; IR (KBr) $\upsilon/cm^{-1} = 3066$ (Ar-H), 2934 (Aliph-H), 1608 (C=N), 680 (C–S). ^1H NMR (DMSO-d_6): δ ppm = 2.44 (s, 3H, CH_3), 6.50 (s, 1H, CH of thiazole), 6.68 (s, 1H, CH of imidazole), 7.4–9.30 (m, 8H, Ar-H). MS m/z (%): 291 (M, 46), 286 (51), 264 (14), 208 (54), 177 (36), 135 (16), 119 (100), 91 (53). *Anal.* for $C_{17}H_{13}N_3S$ (291.083) Calcd.: C 70.08; H 4.50; N 14.42; S 11.00%, Found: C 70.85; H 4.11; N 14.11; S 11.41%.

6-(4-Fluorophenyl)-3-(pyridin-3-yl)imidazo[2,1-b]thiazole (4c). M.p. 200–202°C; IR (KBr) $\upsilon/cm^{-1} = 3168$ (Ar-H), 2983 (Aliph-H), 1600 (C=N), 679 (C–S). ^1H NMR (DMSO-d_6): δ ppm = 6.91 (s, 1H, CH of thiazole), 6.98 (s, 1H, CH of imidazole), 7.33–9.32 (m, 8H, Ar-H). MS m/z (%): 295 (M, 26), 272 (35), 244 (14), 216 (54), 177 (75), 123 (100), 95 (51), 75 (26). *Anal.* for $C_{16}H_{10}FN_3S$ (295.058) Calcd.: C 65.07; H 3.41; N 14.23; S 10.86%, Found: C 65.73; H 3.01; N 14.86; S 10.36%.

6-(4-Nitrophenyl)-3-(pyridin-3-yl)imidazo[2,1-b]thiazole (4d). M.p. 210–212°C; IR (KBr) $\upsilon/cm^{-1} = 3073$ (Ar-H), 2940 (Aliph-H), 1607 (C=N), 683 (C–S).^1H NMR (DMSO-d_6): δ ppm = 6.79 (s, 1H, CH of thiazole), 6.98 (s, 1H, CH of imidazole), 7.19–9.11 (m, 8H, Ar-H). MS m/z (%): 322 (M, 45), 190 (55), 177 (36), 135 (26), 123 (75), 80 (52). *Anal.* for $C_{16}H_{10}N_3SF$ (322.052) Calcd.: C 59.62; H 3.13; N 17.38; S 9.95%, Found: C 59.11; H 3.54; N 17.92; S 9.51%.

6-Phenyl-3-(pyridin-3-yl)imidazo[2,1-b]thiazole (4e). M.p. 235–236°C; IR (KBr) $\upsilon/cm^{-1} = 3064$ (Ar-H), 2936 (Aliph-H), 1603 (C=N), 686 (C–S). ^1H NMR (DMSO-d_6): δ ppm = 6.82 (s, 1H, CH of thiazole), 6.98 (s, 1H, CH of imidazole), 7.14–9.00 (m, 4H, Ar-H). MS m/z (%): 277 (M, 34), 238 (46), 208 (26), 190 (38) 177 (46), 135 (19), 105 (100), 77 (45). *Anal.* for $C_{16}H_{11}N_3S$ (277.067) Calcd.: C 69.29; H 4.00; N 15.15; S 11.56%, Found: C 69.72; H 4.41; N 15.61; S 11.97%.

5-Imino-3-(pyridin-3-yl)-5H-thiazolo[3,2-a]pyrimidine-6-carbonitrile (6). M.p. 213–215°C; IR (KBr) $\upsilon/cm^{-1} = 3055$ (Ar-H), 2210 (CN), 677 (C–S). ^1H NMR (DMSO-d_6): δ ppm = 7.11 (s, 1H, CH of thiazole), 7.24 (s, 1H, CH of pyrimidine), 7.41–9.06 (m, 4H, Ar-H), 9.32 (s,

1H, NH). MS m/z (%): 253 (M, 56), 226 (50), 208 (65), 177 (100), 135 (26), 91 (26). *Anal.* for $C_{12}H_7N_5S$ (253.042) Calcd.: C 56.90; H 2.79; N 27.65; S 12.66%, Found: C 56.24; H 2.12; N 27.21; S 12.12%.

Ethyl 5-oxo-3-(pyridin-3-yl)-5H-thiazolo[3,2-a]pyrimidine-6-carboxylate (7). M.p. 177–179°C; IR(KBr) υ/cm^{-1} = 3078 (Ar-H), 2987 (Aliph-H), 1735 (CO of ester), 1635 (C=O of pyrimidinone), 724 (C–S). ^{1}H NMR (DMSO-d_6): δ ppm = 1.35 (t, 3H, CH_3), 3.95 (q, 2H, CH_2, J = 7 Hz), 7.13 (s, 1H, CH of thiazole), 7.21 (s, 1H, CH of pyrimidinone), 7.32–9.08 (m, 4H, Ar-H). MS m/z (%): 301 (M, 44), 297 (64), 268 (15), 209 (25), 177 (79), 105 (100), 91 (27). *Anal.* for $C_{14}H_{11}N_3O_3S$ (301.052) Calcd.: C 55.80; H 3.68; N 13.95; S 10.64%, Found: C 55.31; H 3.42; N 13.43; S 10.23%.

General procedure for the synthesis of 1-(4-(pyridin-3-yl) thiazol-2-yl) hydrazine (9). The synthesis of compound **9** was achieved by methods A and B in 64% and 75% yields, respectively. The obtained compound by both methods has the same m.p. Its spectroscopic data were identical.

Method (A). A mixture of acetyl pyridine (1.89 g, 1.0 mmol) and thiosemicarbazide (1.82 g, 2.0 mmol) in absolute ethanol (50 mL) was heated under reflux for 8 h. After evaporation of ethanol, the residue was treated with aqueous Na_2CO_3 (60 mL, 20%). The precipitate was filtered off, washed with water, and crystallized from aqueous ethanol (50%) to give compound **9**.

Method (B). A solution of sodium nitrite (0.651 g, 9.4 mmol) in H_2O (7 mL) was gradually added to a cold solution (0°C) of 4-(pyridine-3-yl) thiazol-2-amine (**1**; 1.0 g, 5.6 mmol) in conc. HCl (20 mL) and H_2O (12 mL) with stirring for a few minutes filter the solution rapidly and slowly added to an ice-cold-stirred solution of sodium sulfite (4.1 g, 5.6 mmol) (90% sodium sulfite, 100 mL of H_2O containing 4.0 g of NaOH). The precipitate was filtered off, washed with water, and crystallized from aqueous ethanol (50%) to give compound **9**.

M.p. 135–136°C.; IR (KBr) υ/cm^{-1} = 3442 (NH_2), 3324 (NH), 3055 (Ar-H), 2997 (Aliph-H), 724 (C–S). ^{1}H NMR (DMSO-d_6): δ ppm = 7.11 (s, 1H, CH of thiazole), 5.14 (s, 2H, NH_2), 7.32–9.00 (m, 4H, Ar-H), 11.91 (s, 1H, NH). MS m/z (%): 192 (13), 185 (29), 167 (9), 177 (32), 115 (26), 97 (40). *Anal.* for $C_8H_8N_4S$ (192.047) Calcd.: C 49.98; H 4.19; N 29.14; S 16.68%, Found: C 49.32; H 4.51; N 29.65; S 16.19%.

Synthesis of 5-methyl-1-(4-(pyridin-3-yl) thiazol-2-yl) pyrazolidin-3-one (10). A mixture of 1-(4-(pyridin-3-yl) thiazol-2-yl) hydrazine (**9**; 1.92 g, 1.0 mmol) and ethylacetoacetate (1.29 g, 1.0 mmol) in absolute ethanol (20 mL) was heated under reflux for 3 h. After evaporation of ethanol, the precipitate was filtered off, washed with cold ethanol, and crystallized from ethanol to give **10**. Yield 82%, m.p. 174–176°C; IR (KBr) υ/cm^{-1} = 3309 (NH), 3095 (Ar-H), 2996 (Aliph-H), 1676 (C=O), 745 (C–S). ^{1}H NMR (DMSO-d_6): δ ppm = 2.21 (s, 3H, CH_3), 3.85 (s, 2H, CH_2 of pyrazolone), 6.91 (s, 1H, CH of thiazole), 7.32–9.15 (m, 4H, Ar-H), 9.77 (s, 1H, NH). MS m/z (%): 260 (M, 82), 236 (40), 219 (25), 209 (17), 197 (21), 183 (30), 97 (11). *Anal.* for $C_{12}H_{12}N_4OS$ (260.073) Calcd.: C 55.37; H 4.65; N 21.52; S 12.32%, Found: C 55.82; H 4.99; N 21.89; S 12.61%.

General procedure for the synthesis of 4-arylidene-5-methyl-1-(4-(pyridine-3-yl) thiazol-2-yl) pyrazolidine-3-one (11). A mixture of 5-methyl-1-(4-(pyridin-3-yl) thiazol-2-yl) pyrazolidin-3-one (**10**; 2.6 g, 1.0 mmol) and aromatic aldehydes (1.0 mmol) was fused in an oil bath at 120–130°C for 2 h. The reaction mixture was cooled, and methanol (5 mL) was added to give colored solid. The solid was filtered, washed with cold methyl alcohol, and crystallized from ethanol to the pure products.

4-(4-(Dimethylamino)benzylidene)-5-methyl-1-(4-(pyridin-3-yl)thiazol-2-l)pyrazolidin-3-one (11a). Yield 74%, m.p. 217–219°C; IR (KBr) υ/cm^{-1} = 3340 (NH), 3055 (Ar-H), 2987 (Aliph-H), 1665 (C=O), 776 (C–S). ^{1}H NMR (DMSO-d_6): δ ppm = 2.21 (s, 3H, CH_3 of pyrazolone), 2.75 (s, 6H, $N(CH_3)_2$), 6.86 (s, 1H, CH of thiazole), 6.99 (s, 1H, =CH), 7.54–9.21 (m, 8H, Ar-H), 9.69 (s, 1H, NH). MS m/z (%): 391 (M, 35%), 350 (40), 259 (46), 208 (17), 197 (33), 185 (28), 91 (22). *Anal.* for $C_{21}H_{21}N_5OS$ (391.147) Calcd.: C 64.43; H 5.41; N 17.89; S 8.19%, Found: C 64.88; H 5.82; N,17.43; S 8.53%.

4-(4-Nitrobenzylidene)-5-methyl-1-(4-(pyridin-3-yl) thiazol-2-yl) pyrazolidin-3-one (11b). Yield 74%, m.p. 169–171°C; IR (KBr) υ/cm^{-1} = 3310 (NH), 3087 (Ar-H), 2998 (Aliph-H), 1689 (C=O), 756 (C–S). ^{1}H NMR (DMSO-d_6): δ ppm = 2.21 (s, 3H, CH_3 of pyrazolone), 6.89 (s, 1H, CH of thiazole), 6.99 (s, 1H, =CH), 7.54–9.14 (m, 8H, Ar-H), 9.71 (s, 1H, NH). MS m/z (%): 393 (M, 23), 368 (55), 355 (41), 287 (46), 156 (100), 147 (37), 90 (90). *Anal.* for $C_{19}H_{15}N_5O_3S$ (393.09) Calcd.: C 58.01; H 3.84; N 17.80; S 8.15%, Found: C 58.84; H 3.29; N 17.25; S 8.58%.

4-(4-Chlorobenzylidene)-5-methyl-1-(4-(pyridin-3-yl)thiazol-2-yl) pyrazolidin-3-one (11c). Yield 78%, m.p. 182–184°C; IR (KBr) υ/cm^{-1} = 3410 (NH), 3092 (Ar-H), 2987 (Aliph-H), 1656 (C=O), 781 (C–S). ^{1}H NMR (DMSO-d_6): δ ppm = 2.21(s, 3H, CH_3 of pyrazolone), 6.85 (s, 1H, CH of thiazole), 6.98 (s, 1H, =CH), 7.35–9.13 (m, 8H, Ar-H), 9.88 (s, 1H, NH). MS m/z (%): 382 (M, 77), 368 (16), 353 (15), 313 (33), 293 (17), 144 (27), 127 (100), 91 (24). *Anal.* for $C_{19}H_{15}ClN_4OS$ (382.066) Calcd.: C 59.60; H 3.95; Cl 9.26; N 14.63; S 8.37%, Found: C 59.02; H 3.36; Cl 9.21; N 14.99; S 8.74%.

General procedure for the synthesis of (5-methyl-4-(aryldiazenyl)-1-(4-(pyridine-3-yl) thiazol-2-yl) pyrazolidine-3-one

(**12**). An aqueous solution of sodium nitrite (0.7 g, 10.0 mmol) was added to a solution of aryl amine [10.0 mmol in concentrated HCl (5 mL)] and cooled at 0°C. The cold diazonium salt solution was added dropwise with stirring over 30 min to an iced solution of 5-methyl-1-(4-(pyridin-3-yl) thiazol-2-yl) pyrazolidin-3-one (**10**; 2.6 g, 10.0 mmol) in pyridine (10 mL). The precipitated dye was filtered, washed with water several times, dried, and crystallized from ethanol to give pure **12**.

5-Methyl-1-(4-(pyridin-3-yl)thiazol-2-yl)-4-(p-tolyldiazenyl) pyrazolidin-3-one (12a). Yield 71%, m.p. 235–236°C; IR (KBr) $\upsilon/cm^{-1} = 3383$ (NH), 3099 (Ar-H), 2999 (Aliph-H), 1662 (C=O), 1650 (N=N), 727 (C–S). ^{1}H NMR (DMSO-d_6): δ ppm = 2.21 (s, 3H, CH_3 of pyrazolone), 2.32 (s, 3H, CH_3), 6.87 (s, 1H, CH of thiazole), 6.94 (s, 1H, CH of pyrazolone), 7.33–9.12 (m, 8H, Ar-H), 9.92 (s, 1H, NH). MS m/z (%): 387 (M, 55), 365 (21), 348 (16), 299 (25), 144 (100), 129 (50), 90 (38). *Anal.* for $C_{19}H_{18}N_6OS$ (378.126) Calcd.: C 60.30; H 4.79; N 22.21; S 8.47%, Found: C 60.91; H 4.16; N 22.91; S 8.01%.

4-(4-Chlorophenyl)diazenyl)-5-methyl-1-(4-(pyridin-3-yl) thiazol-2-yl)pyrazolidin-3-one (12b). Yield 56%, m.p. 224–226°C; IR (KBr) $\upsilon/cm^{-1} = 3391$ (NH), 3099 (Ar-H), 2973 (Aliph-H), 1667 (C=O), 1655 (N=N), 734 (C–S). ^{1}H NMR (DMSO-d_6): δ ppm = 2.21 (s, 3H, CH_3 of pyrazolone), 6.92 (s, 1H, CH of thiazole), 6.94 (s, 1H, CH of pyrazolone), 7.33–9.31 (m, 8H, Ar-H), 9.98 (s, 1H, NH). MS m/z (%): 398 (M, 36), 386 (33), 335 (42), 263 (100), 141 (21), 127 (35), 95 (46). *Anal.* for $C_{18}H_{15}ClN_6OS$ (398.072) Calcd.: C 54.20; H 3.79; Cl 8.89; N 21.07; S 8.04%, Found: C 54.99; H 3.32; Cl 8.34; N 21.71; S 8.55%.

5-Methyl-4-(4-nitrophenyl)diazenyl)-1-(4-(pyridin-3-yl) thiazol-2-yl)pyrazolidin-3-one (12c). Yield 69%, m.p. 234–236°C; IR (KBr) $\upsilon/cm^{-1} = 3401$(NH), 3056 (Ar-H), 2959 (Aliph-H), 1669 (C=O), 1659 (N=N), 767 (C–S). ^{1}H NMR (DMSO-d_6): δ ppm = 2.21 (s, 3H, CH_3 of pyrazolone), 6.86 (s, 1H, CH of thiazole), 6.93 (s, 1H, CH of pyrazolone), 7.33–9.23 (m, 8H, Ar-H), 9.61 (s, 1H, NH). MS m/z (%): 409 (M, 45), 389 (26), 325 (41), 254 (57), 144 (100), 129 (50), 91 (43). *Anal.* for $C_{18}H_{15}N_7O_3S$ (409.096) Calcd.: C 52.80; H 3.69; N 23.95; O 11.72; S 7.83%, Found: C 52.21; H 3.98; N 23.35; S 7.32%.

4-((4-Methoxyphenyl)diazenyl)-5-methyl-1-(4-(pyridin-3-yl)thiazol-2-yl) pyrazolidin-3-one (12d). Yield 64%, m.p. 179–181°C; IR (KBr) $\upsilon/cm^{-1} = 3382$ (NH), 3080 (Ar-H), 2994 (Aliph-H), 1661 (C=O), 1657 (N=N), 751 (C–S). ^{1}HNMR (DMSO-d_6): δ ppm = 2.21 (s, 3H, CH_3 of pyrazolone), 3.41 (s, 3H, OCH_3), 6.91 (s, 1H, CH of thiazole), 6.99 (s, 1H, CH of pyrazolone), 7.11–9.15 (m, 8H, Ar-H), 9.83 (s, 1H, NH). MS m/z (%): 392 (M − 2, 34), 379 (46), 313 (92), 291 (21), 185 (62), 144 (33), 115 (34), 97 (54). *Anal.* for $C_{19}H_{18}N_6O_2S$ (394.121) Calcd.: C 57.85; H 4.60; N 21.31; S 8.13%, Found: C 57.32; H 4.11; N 21.89; S 8.61%.

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