ISSN 1068-1620, Russian Journal of Bioorganic Chemistry, 2016, Vol. 42, No. 4, pp. 428–433. © Pleiades Publishing, Ltd., 2016.

Antimicrobial Activities of Some Novel Thiazoles[1]

Saleh M. Al-Mousawi[a, 2], Moustafa Sherief Moustafa[b], and Esmaeil Al-Saleh[b]

[a] *Department of Chemistry, Faculty of Science, University of Kuwait, Safat, 13060 Kuwait*

[b] *Department of Biological Sciences, Faculty of Science, University of Kuwait, Safat, 13060 Kuwait*

Received December 25, 2015; in final form, February 2, 2016

Abstract—2-(4-Phenylthiazol-2(3*H*)-ylidene)-malononitrile was synthesized by treating 1-phenyl-2-thiocyanatoethanone with malononitrile. Reaction of 2-(4-phenylthiazol-2(3*H*)-ylidene)-malononitrile with hydrazine hydrate afforded 4-(4-phenylthiazol-2-yl)-1*H*-pyrazole-3,5-diamine, reaction with benzylidenemalononitrile yielded 2-(5-benzylidene-4-phenyl-5*H*-thiazol-2-ylidene)-malononitrile, and coupling with benzenediazonium chloride gave 2-(4-phenyl-5-phenylazo-3*H*-thiazol-2-ylidene)-malononitrile. Diaminopyrazole reacted with enaminonitrile to yield the 3-(4-phenylthiazol-2-yl)pyrazolo[1,5-a]pyrimidine-2,7-diamine. All synthesized compounds showed significant antimicrobial activities with MIC range of 5–750 μg/mL. The results demonstrated a correlation of the hydrophobicity of the compounds with their antimicrobial activity. The most potent antimicrobial compound was 2-(4-phenylthiazol-2(3*H*)-ylidene)-malononitrile.

Keywords: *thiazoles, aminopyrazoles, antimicrobial activities*

DOI: 10.1134/S1068162016040038

INTRODUCTION

In 1973, it has been reported [1] that arylhydrazone of mesoxalic acid dinitrile (**I**) reacts with hydrazine hydrate to yield 4-(aryldiazenyl)-1*H*-pyrazole-3,5-diamine (**II**) (Scheme 1). The derivatives of compound (**II**) have attracted attention for their potential as hair dyes [2, 3]. However, compound (**II**) and its derivatives have several other useful properties that can be exploited for commercial applications, e.g. the antimicrobial activity [4–6].

Thiazoles are also biologically important molecules, their antimicrobial activities [7–9] and other biological activities have been reported [10–13]. Despite numerous reports on thiazoles and their derivatives, the biological activities of arylazocyanomethyl thiazole derivatives have not been investigated. This was the objective of the present work. Also, the emergence of antibiotic resistant pathogens necessitates the discovery of new antimicrobial agents to control potential imminent health hazards.

Thiazole derivatives are prepared by treating haloketones with cyanothioacetamide [14–16]. Recently, it has been reported that reaction of thiocyanate (**III**) with malononitrile (**IV**) affords only 2-(4-phenylthiazol-2(3*H*)-ylidene)-malononitrile (**V**) [17–19] that may have potential pharmacological properties. In this endeavor, we report facile synthesis and antimicrobial activities of some interesting thiazoles including 2-(4-phenylthiazol-2(3*H*)-ylidene)malononitrile (**V**), 4-(4-phenylthiazol-2-yl)-1*H*-pyrazole-3,5-diamine (**VI**), 2-(5-benzylidene-4-phenyl-5*H*-thiazol-2-ylidene)-malononitrile (**VII**), and 2-(4-phenyl-5-phenylazo-3*H*-thiazol-2-ylidene)-malononitrile (**VIII**).

RESULTS AND DISCUSSION

Chemistry

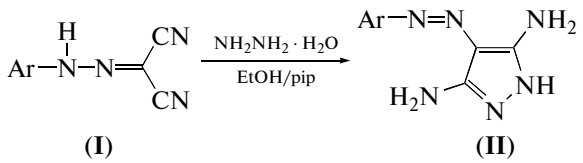
The synthesis of 2-(4-phenylthiazol-2(3*H*)-ylidene)-malononitrile (**V**) was achieved by the reaction of aryl thiocyanate (**III**) with malononitrile (**IV**) in the presence of piperidine as reported by Al-Mousawi et al. [17, 19]. Previously we have reported the synthesis of compound (**V**) by mixing (**III**) and malononitrile (**IV**) in the presence of chitozan as a heterogeneous ecofriendly catalyst but in the absence of a solvent, with similar yields [20]. In none of these synthetic attempts, 2-(2-thiocyanatoethylidene)malononitrile derivatives (**IX**) could be isolated as has been claimed by Abdelrazik et al. [20].

A new diaminopyrazole derivative (**VI**) was obtained via the reaction of thiazole (**V**) with hydrazine hydrate. Reaction of 2-(4-phenylthiazol-2(3*H*)-ylidene)malononitrile (**V**) with benzylidenemalononitrile in ethanolic piperidine solution afforded 2-(5-benzylidene-4-phenyl-5*H*-thiazol-2-ylidene)-malononitrile (**VII**). Coupling of 2-(4-phenylthiazol-2(3*H*)-ylidene)malononitrile (**V**) with benzenediazonium chloride gave 2-(5-phenylazo-3*H*-thiazol-2-ylidene)-malononitrile (**VIII**) in 85–90% yield (Scheme 2).

[1] The article is published in the original.

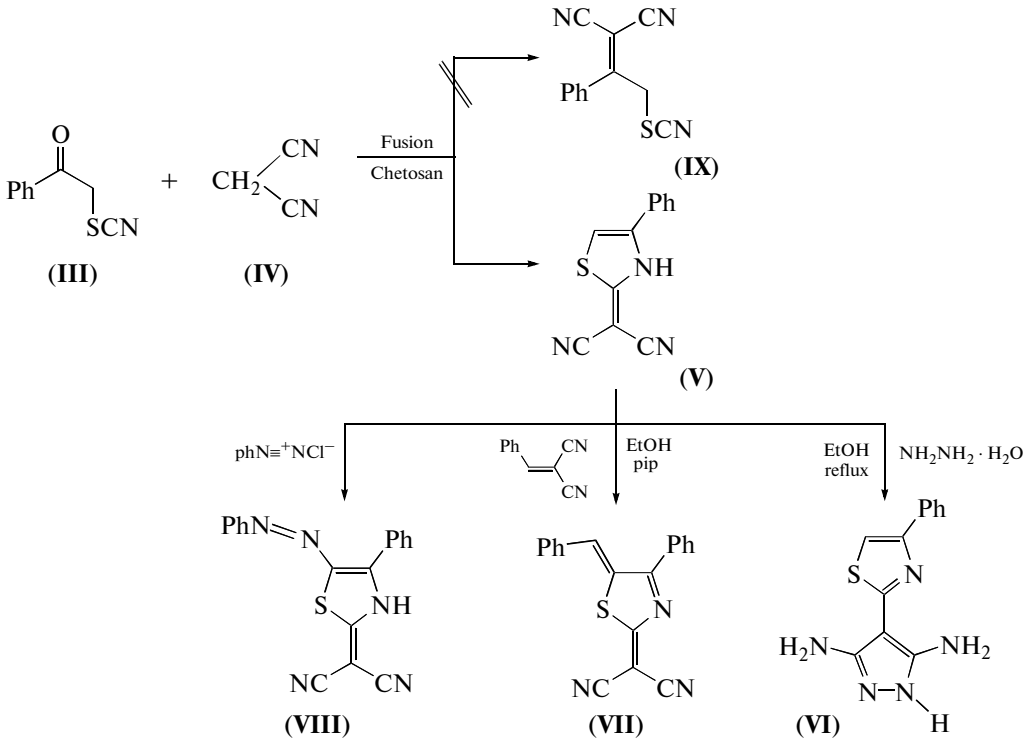
[2] Corresponding author: e-mail: salehalmousawi@hotmail.com.

Diaminopyrazole (**VI**) reacted with enaminonitrile (**IX**) to yield the 3-(4-phenylthiazol-2-yl)pyrazolo[1,5-a]pyrimidine-2,7-diamine (**X**) (Scheme 3). The 3-(4-phenylthiazol-2-yl)pyrazolo[1,5-a]pyrimidine-2,7-diamine (**X**) was concluded to be the product based on the results of X-ray crystallographic analyses (CCDC 795153) (Fig. 1) [21].



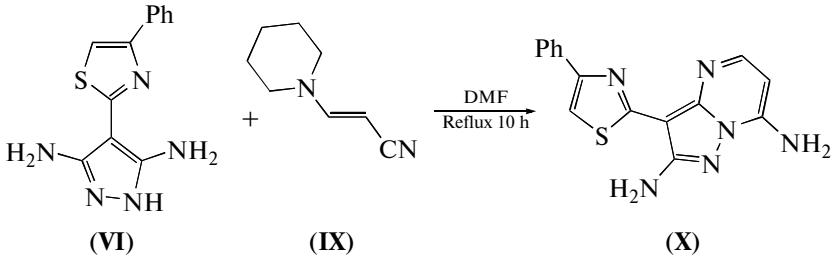
(**I**) (**II**)

Scheme 1. Synthesis of diaminopyrazole derivatives (**II**).



(**III**) (**IV**) (**IX**) (**V**) (**VIII**) (**VII**) (**VI**)

Scheme 2. Synthesis of thiazoles derivatives (**VI**–**VIII**).



(**VI**) (**IX**) (**X**)

Scheme 3. Synthesis of compound (**X**).

Antimicrobial Activity

The synthesized compounds were found to be active against all tested microbial strains. However, the potency of antimicrobial activity differed between the compounds. The inhibitory effects of the synthesized compounds were demonstrated by determination of the minimal inhibitory concentration (MIC) values and by the dose–response experiments. MICs for compounds (**V**–**VIII**) are shown in the table.

Compound (**V**) showed the MIC ranging between 5–15 μg/mL for the yeast *Candida albicans*, gram-positive, and gram-negative bacterial strains. The activity of compound (**V**) against *Bacillus* spp., *E. coli*, and *P. aeruginosa* was found to be more potent than that of such antibiotics as cefotaxime and nitrofurantoin (table). Compound (**VI**) was also more potent against all gram-negative bacteria when compared with nitrofurantoin. Compounds (**VI**) and (**VII**) showed higher tendency to inhibit gram-positive bacteria as compared with gram-negative bacteria. Thus, compounds (**V**) and (**VII**) exhibited higher tendency to inhibit gram-positive bacteria (compounds), while compound (**VI**) demonstrated higher inhibitory potentials against gram-negative bacteria. The apti-

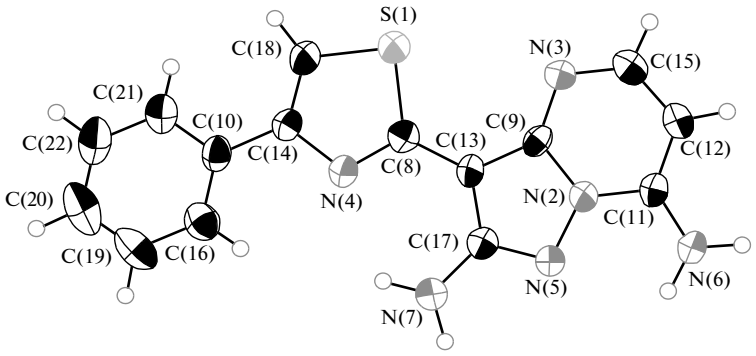


Fig. 1. Plot of the X-ray crystallographic data of 3-(4-phenylthiazol-2-yl)pyrazolo[1,5-*a*]pyrimidine-2,7-diamine (**X**).

tude of chemical compounds and antibiotics to restrain the growth of specific bacterial groups has been reported previously by Saene et al. [22]. Though, *E. coli*, *S. enterica*, and *P. aeruginosa* are gram-negative bacteria associated with Gamma Proteobacteria [23] and are expected to possess common genetic background implying similar behavior [24], the tested strains showed different responce towards the synthesized compounds. Similarly, though methicillin-resistant *Staphylococcus aureus* (MRSA) and *Bacillus* are gram-positive bacteria, MRSA strains show generally higher resistance to the tested compounds as compared to *Bacillus* strains. In addition, all synthesized compounds demonstrated antifungal activity that was the most potent for compounds (**V**) and (**VII**). The antimicrobial efficacy of the newly synthesized compounds was confirmed by comparison of their antimicrobial activity with that of well known antibiotics, such as cefotaxime, nitrofurantoin, penicillin, and piperacillin. The choice of these four antibiotics for comparison was based on the higher frequency of their usage in Kuwait and on the ability of these antibiotics to inhibit gram-positive and gram-negative bacteria.

The dose-response studies showed that the inhibitory effects were proportional to the amount of the compound added in the microbial culture. A pronounced linear relationship between bacterial growth and concentration was demonstrated by the hydrophilic compounds (**V**) and (**VI**) (Fig. 2, curve *1*). This may be due to their higher solubility in aqueous media implicating their faster transport through the bacterial cell wall. Conversely, compounds (**VII**) and (**VIII**) with their higher hydrophobic character showed a non-linear correlation between bacterial growth and their concentration (Fig. 3, curve *1*). An initial increase in the concentration of these compounds in the culture media resulted in an insignificant inhibitory effect. However, an addition of these compounds at a higher concentration resulted in instant inhibition of the bacterial growth (Fig. 3, curve *1*). The hydrophobicity of compounds (**VII**) and (**VIII**) could hinder their transport through bacterial cell wall leading to modest antibacterial activity (Fig. 3, curve *1*). However, an exposure of the tested bacteria to higher concentrations of compounds (**VII**) and (**VIII**) may induce alteration in pharmacodynamics and antimicrobial activity by binding to the cell wall receptors enhancing their toxicity for the microorganism. For example, an addition of compound (**VIII**) (0–450 μg/mL) in the culture media of *P. aeruginosa* resulted in an initial insignificant decrease in bacterial growth followed by a significant inhibition at the

Antimicrobial activity of compounds (**V**–**VIII**) and the reference compounds

Microorganism (number of strains)		MIC, μg/mL							
		(**V**)	(**VI**)	(**VII**)	(**VIII**)	Cefo	Nf	P	Pip
Gram-positive bacteria	*Bacillus* spp. ($n = 10$)	5–10	25–30	45–50	50–70	10	5	1	1
	MRSA ($n = 20$)	5–10	25–30	90–100	200–250	30	15	10	5
Gram- negative bacteria	*E. coli* ($n = 20$)	12.5	15–30	250–625	Nil	30	130	30	130
	P. aeruginosa ($n = 50$)	12.5	15–30	200–250	400–500	60	130	30	10
	S. enteric ($n = 25$)	12.5	15–30	250–500	625–750	5	130	5	5
Yeast	*C. albicans* ($n = 20$)	5–15	25–50	5–10	50–400	–	–	–	–

MRSA, methicillin-resistant *Staphylococcus aureus*; MIC, minimum inhibitory concentration; Cefo, Cefotaxime; Nf, Nitrofurantoin; P, Penicillin; Pip, Piperacillin.

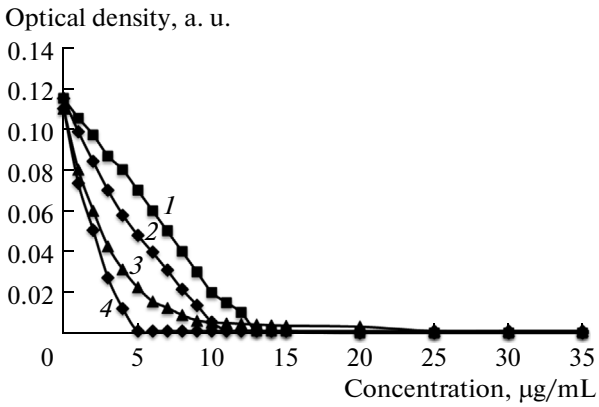


Fig. 2. Dose–response curves for 2-(4-phenylthiazol-2(3*H*)-ylidene)-malononitrile (**V**) and 4-(4-phenylthiazol-2-yl)-1*H*-pyrazole-3,5-diamine (**VI**) with MRSA and *P. aeruginosa*. *1*, compound (**V**) against *P. aeruginosa*; *2*, compound (**VI**) against *P. aeruginosa*; *3*, compound (**VI**) against MRSA; *4*, compound (**V**) against MRSA.

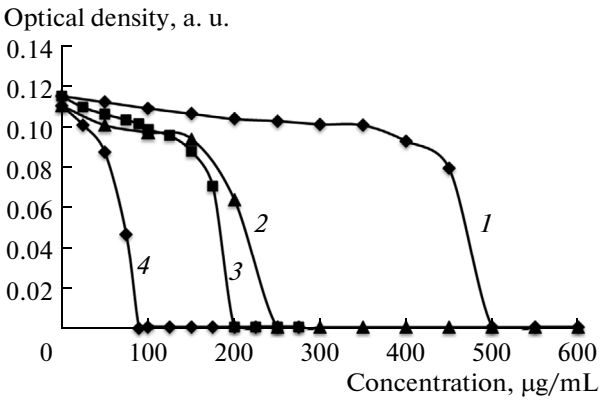


Fig. 3. Dose–response curves for 2-(5-benzylidene-4-phenyl-5*H*-thiazol-2-ylidene)-malononitrile (**VII**) and 2-(4-phenyl-5-phenylazo-3*H*-thiazol-2-ylidene)-malononitrile (**VIII**) with MRSA and *P. aeruginosa*. *1*, compound (**VIII**) against *P. aeruginosa*; *2*, compound (**VIII**) against MRSA; *3*, compound (**VII**) against *P. aeruginosa*; *4*, compound (**VII**) against MRSA.

higher concentration of 450 to 500 μg/mL (Fig. 3, curve *2*). Similar results were shown for MRSA (Fig. 3, curve *3*).

In conclusion, some of the synthetic products, in particular compound (**V**), showed higher broad-spectrum antibacterial and antifungal activities against tested microorganisms causing common hospital infections. Compound (**V**) was found to be the most potent antimicrobial agent followed by compounds (**VI**) and (**VII**), while the lowest activity was observed for compound (**VIII**). These compounds may be potentially useful drugs that can be explored further for their antimicrobial activity.

EXPERIMENTAL

General

Melting points reported are uncorrected and were determined with a Sanyo (Gallaenkamp) instrument. Infrared spectra in KBr pellets were recorded using a FT–IR 6300 (Jasco) instrument, absorption bands are reported as ν_{max}, cm^{-1}. ^1H and ^{13}C NMR spectra were determined using a Bruker DPX instrument at 400 MHz or 600 MHz for ^1H NMR and 100 MHz for ^{13}C NMR and DMSO-d_6 solutions with TMS as internal standards. Chemical shifts (δ) are reported in ppm. Mass spectra and accurate mass measurements were made using a GCMS DFS (Thermo) spectrometer with the EI (70 EV) mode. X-ray crystallographic structure determinations were performed using Rapid II (Rigaku) and X8 Prospector (Bruker) single crystal X-ray diffractometers. All X-ray crystal structure data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk. All reactions were monitored using TLC using ethyl acetate-petroleum ether (1 : 1, v/v) as an eluent and carried out until starting materials were completely consumed.

Phenylthiazol-2(3*H*)-ylidene)malononitrile (V). Method a: A solution of α-thiocyanatoketone (**III**) (1.77 g, 0.01 mol) and malononitrile (**IV**) (0.66 g, 0.01 mol) in ethanol (15 mL) containing piperidine (20 μL) was stirred at reflux for 3–4 h. The solid material was produced by pouring the reaction mixture into ice water and subsequent separation by filtration. Crystallization in DMF yielded green crystals in 82% yield. **Method b**: An equimolar mixture of α-thiocyanatoketone (**III**) and malononitrile (**IV**) with chitosan (15%) was heated for 15 min without any solvent. The reaction mixture was cooled and dissolved in ethanol. The solid material thus obtained was collected by filtration and crystallized from DMF to give green crystals. Yield 93%; mp 275–276°C; IR: 3147 (NH), 2210 (CN), 2175 (CN); ^1H NMR (400 MHz): 7.33 (s, 1H, CH), 7.45–7.49 (m, 3H, Ar-H), 7.71–7.72 (m, 2H, Ar-H), 13.23 (br, 1H, NH, D_2O exchangeable); ^{13}C NMR: 172.27, 143.70, 130.01, 129.12(2C), 128.92, 127.51 (2C), 127.64 117.75, 105.93 (2CN). MS: *m/z* (%) 225 (M^+, 100), 180 (20), 134 (45), 108 (10), 102 (15), 89 (15), 77 (10). Calcd. for $C_{12}H_7N_3S$ (225.27): C, 63.98; H, 3.13; N, 18.65; S, 14.23. Found: C, 63.94; H, 3.31; N; 18.45; S, 13.92.

4-(4-Phenylthiazol-2-yl)-1*H*-pyrazole-3,5-diamine (VI). An equimolar mixture of compound (**V**) and hydrazine monohydrate in DMF (10 mL) was stirred at reflux for 20 h. The mixture was cooled and poured into ice water. The solid product collected by filtration was crystallized from DMF to give light yellow crystals. Yield 78%; mp 322–323°C; IR: 3372, 3256 (NH_2), 3176, 3112 (NH_2), 3132 (NH); ^1H NMR (400 MHz): 5.39 (br, 4H, $2NH_2$, D_2O exchangeable), 7.31–7.46 (m, 3H, Ar-H), 7.75 (s, 1H, CH), 7.96–7.98 (m, 2H, Ar-H), 10.73 (br, 1H, NH, D_2O exchangeable); ^{13}C NMR:

166.29, 162.08, 152.30 (2C), 134.31, 128.69 (2C), 127.69, 125.89 (2C), 107.48, 87.97. MS: *m/z* (%) 257 (M^+, 100), 226 (10), 200 (5), 134 (35), 128 (10), 90 (10). Calcd. for $C_{12}H_{11}N_5S$ (257.31): C, 56.01; H, 4.31; N, 27.22; S, 12.41. Found: C, 55.80; H, 4.41; N; 26.88; S, 11.99.

2-(5-Benzylidene-4-phenylthiazol-2(5*H*)-ylidene)malononitrile (VII). An equimolar mixture of compound (**V**) and benzylidenemalononitrile in EtOH (20 mL) and piperidine (1 mL) was stirred under reflux for 3 h. The reaction mixture was cooled and poured into ice-water giving a solid which was collected by filtration and crystallized from EtOH to give the product as faint yellow crystals. Yield 77%; mp 280–282°C; IR: 22.7 (CN), 2179 (CN); ^{1}H NMR (600 MHz): 5.84 (s, 1H, CH), 7.15–7.42 (m, 10H, Ar-H); ^{13}C NMR: 169.07, 141.21, 140.04, 131.24, 130.57, 129.69, 129.21 (2C), 128.91 (2C), 128.45 (2C), 128.21, 127.94, 127.61 (2C), 124.62, 122.00, 117.17. MS: *m/z* (%) 313 (M^+, 80), 285 (10), 235 (90), 225 (100), 178 (10), 134 (60), 98 (20). Calcd. for $C_{19}H_{11}N_3S$ (313.38): C, 72.82; H, 3.54; N, 13.41; S, 10.23. Found: C, 12.94; H, 3.32; N; 13.31; S, 10.19.

2-(4-Phenyl-5-phenylazo-3*H*-thiazol-2-ylidene)malononitrile (VIII). A cold solution of benzenediazonium chloride (0.01 mol) was added to a solution of sodium nitrite (0.7 g in 10 mL H_2O) and a solution of aniline hydrochloride (0.93 g, 0.01 mol of aniline and concentrated HC1, 5 mL) with stirring at room temperature. The resulting solution was then added to a cold solution of compound (**V**) (2.25 g, 0.01 mol) in ethanol (50 mL) containing sodium acetate (2 g). The reaction mixtures was stirred for 1 h and filtered. The solid products were crystallized from EtOH to give red crystals. Yield 85%; mp 198–200°C; IR: 3180 (NH), 2216 (2CN); ^{1}H NMR (400 MHz): 5.03 (br, 1H, NH, D_2O exchangeable), 7.25–7.60 (m, 8H, Ar-H), 8.22–8.24 (m, 2H, Ar-H); ^{13}C NMR: 175.46, 147.29, 138.67, 131.79, 131.47, 130.73 (2C), 130.70 (2C), 129.59 (2C), 128.63 (2C), 127.05, 118.96, 117.71, 115.70 (2CN). MS: *m/z* (%) 329 (M^+, 100), 301 (20), 237 (15), 225 (25), 153 (5), 103 (20), 92 (25), 77 (65). Anal. calcd. for $C_{18}H_{11}N_5S$ (329.38): C, 65.64; H, 3.37; N, 21.26; S, 9.73. Found: C, 65.49; H, 3.51; N, 21.15; S, 9.39.

3-(4-Phenylthiazol-2-yl)pyrazolo[1,5-*a*]pyrimidine-2,7-diamine (X). A mixture of (**VI**) (2.57 g, 0.01 mol) and 3-(piperidin-1-yl)acrylonitrile (**IX**) (1.36 g, 0.01 mol) in DMF (10 mL) was stirred at reflux for 10 h. The reaction mixture was cooled and poured into ice water giving a solid which was collected by filtration and crystallized from DMF to give the product as yellow crystals. Yield 70%; mp 329–330°C; IR: 3443, 3305 (NH_2), 3355, 3263 (NH_2); ^{1}H NMR (400 MHz): 6.13 (d, 1H, J = 6.0, CH), 6.62 (br, 2H, NH_2, D_2O exchangeable), 7.33–7.47 (m, 3H, Ar-Hs), 7.61 (br, 2H, NH_2, D_2O exchangeable), 7.85 (s, 1H, thiazole-H), 8.01 (m, 2H, Ar-Hs), 8.07 (d, 1H, J = 6.0, CH); ^{13}C NMR: 160.59, 156.98, 152.22, 149.36, 147.14, 146.94, 134.31, 128.75 (2C), 127.72, 125.90 (2C), 109.66, 89.99, 88.59. MS: *m/z* (%) 308 (M^+, 100), 268 (30), 175 (5), 154 (5), 134 (30), 102 (5), 89(5), 77 (5). Calcd. for $C_{15}H_{12}N_6S$ (308.36): C, 58.43; H, 3.92; N, 27.25; S, 10.40. Found: C, 58.33; H, 3.79; N; 27.20; S, 10.37.

Antimicrobial Activity

Antimicrobial activity of the synthesized compounds was assessed using gram-positive bacteria (*Bacillus* spp. and methicillin-resistant *Staphylococcus aureus* (MRSA)), gram-negative bacteria (*E. coli*, *Pseudomonas aeruginosa*, and *Salmonella enterica*), and yeast (*Candida albicans*). Microdilution method was used as reported by James and Jean [25]. Briefly, the synthesized compounds at different concentrations in DMSO were added to shaked cultures of test strains (10 strains of *Bacillus* spp.; MRSA, *E. coli*, and *C. albicans* 20 strains each, 25 strains of *S. enterica*, and 50 strains of *P. aeruginosa*). Optical density (λ 600 nm) of the microbial cultures was measured in sterile 96 well plates using the LD400 (Beckman Coulter, USA) reader in the presence or absence (controls) of the experimental compounds at 37°C. The minimum inhibitory concentrations (MIC) of the compounds were calculated. For comparative studies, effect of antibiotics (cefotaxime, nitrofurantoin, penicillin, and piperacillin) on the growth of test microorganisms was examined and the results were used to determine MIC. In addition, the dose-response curves were built using the aforementioned method. All test microorganisms were isolated from medical samples collected from hospitals in Kuwait. The strains were identified by sequencing of the 16S [26] and 18S rRNA genes [27]. All experiments were conducted in triplicates.

ACKNOWLEDGMENTS

The authors are grateful Dr. Bivin Thomas for graphical assistance and to Kuwait University Research Administration for the financial support of project no. SC12/13. Analytical facilities were provided by the GFS projects no. GS 01/01, GS 01/03, GS 01/05, GS 02/10, and GS 03/08 and are greatly appreciated.

REFERENCES

1. Elnagdi, M.H. and Abd Allah, S.O., *J. Prakt. Chem.*, 1973, vol. 315, pp. 1009–1016.
2. Tsai, P.C. and Wang, I.J., *Dyes Pigments*, 2007, vol. 74, pp. 578–584.
3. Pi, C.T. and Wang, I.J., *Dyes Pigments*, 2004, vol. 64, pp. 259–264.
4. El-Gaby, M.S.A., Taha, N.M., Micky, J.A., and El-Sharief, M.A.M.Sh., *Acta Chimica Slovenica*, 2002, vol. 49, pp. 159–171.

5. Cottarel, G., PCT Int. Appl., no. WO 2009042270, 2009.
6. Shaikh, B.M., Konda, S.G., Chobe, S.S., Mandawad, G.G., Yemul, O.S. and Dawane, B.S., *J. Chem. Pharm. Res.*, 2011, vol. 3, pp. 435–443.
7. Sugumaran, M., Sethuvani, S., and Poornima, M., *Res. J. Pharm. Biol. Chem. Sci.*, 2012, vol. 3, pp. 625–631.
8. Schwartz, J.R., Saunders, C.W., Youngquist, R.S., Kelly, C.P., Domsic, J.K., Lucas, R.L., and Xu, J., *PCT Int. Appl.*, no. WO 2012058557 A2 20120503, 2012.
9. Gaikwad, N.D., Patil, S.V., and Bobade, V.D., *Bioorg. Med. Chem. Lett.*, 2012, vol. 22, pp. 3449–3454.
10. Vinay, V. and Lakshika, K.A., *Int. J. Res. Pharm. Sci.,* 2011, vol. 1, pp. 17–27.
11. Devprakash, B. and Udaykumar, A.A., *J. Pharm. Res.*, 2011, vol. 4, pp. 2436–2440.
12. Pandey, Y., Sharma, P.K., Kumar, N., and Singh, A., *Int. J. Pharm. Tech. Res.*, 2011, vol. 3, pp. 980–985.
13. Cunico, W., Gomes, C.R.B., and Vellasco, W.T., *Mini-Rev. Org. Chem.*, 2008, vol. 5, pp. 336–344.
14. Eldin, S.M., *Zeitschrift fuer Naturforschung, B: Chem. Sci.*, 1999, vol. 54, pp. 1589–1597.
15. Dyachenko, V.D., Chernega, A.N., and Dyachenko, S.V., *Russ. J. Gen. Chem.*, 2012, vol. 82, pp. 720–724.
16. Dyachenko, V.D., *Russ. J. Org. Chem.,* 2006, vol. 42, pp. 1085–1086.
17. Al-Mousawi, S.M., Moustafa, M.S., and Elnagdi, M.H., *Molecules*, 2011, vol. 16, pp. 3456–3468.
18. Al-Mousawi, S.M., Moustafa, M.S., and Elnagdi, M.H., *ARKIVOC,* 2010, vol. 2, pp. 224–232.
19. Ishiwata, Y., *Eur. Pat. Appl.*, no. EP1975204A220081001, 2008.
20. Abdelrazek, F.M., Salah, Abdellatif M., and Elbazza, Z.E., *Archiv der Pharmazie*, 1992, vol. 325, pp. 301–305.
21. Cambridge Crystallographic Data Centre, deposit no. CCDC 795153. www.ccdc.cam.ac.uk.
22. van Saene, R., Fairclough, S., and Petros, A., *Clin. Microbiol. Inf.*, 1998, vol. 4, pp. 56–57.
23. Koul, A., Arnoult, E., Lounis, N., Guillemont, J., and Andries, K., *Nature*, 2011, vol. 469, pp. 483–490.
24. Moellering, R.C., *Int. J. Antimicrob. Agents*, 2001, vol. 37, pp. 2–9.
25. James H.J. and Jean, C.L., *Antimicrob. Agents Chemother.*, 1975, vol. 8, pp. 610–611.
26. Kuske, C.R., Barns, S.M., and Busch, J.D., *Appl. Environ. Microbiol.*, 1997, vol. 63, pp. 3614–3621.
27. Zunaina, E., Wan, H.W.H., Chan, Y.Y., Nur, H.A.R., Balqis, K.S.K.A., Sabariah, O., Zainul, F.Z., and Manickam, R., *Ophthalmology*, 2008, vol. 8, pp. 7–11.