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## Synthesis of Some New Substituted 2-Mercaptoquinazoline Analogs as Potential Antimicrobial Agents

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#### Synthesis of Some New Substituted 2-Mercaptoquinazoline Analogs as Potential Antimicrobial Agents

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A new series of substituted 2-mercapto-3-(4-chlorophenyl)-6-iodo-3H-quinazolin-4ones was prepared and screened for antimicrobial activity. Compounds 11, 13, 17, and 18 showed a remarkably broad spectrum of antimicrobial activity and could be useful as templates for further development through modification or derivatization to design more potent antimicrobial agents. A detailed synthesis of new 2mercaptoquinazolinones and their antimicrobial screening are reported.

Keywords Synthetic chemistry; 2-quinazolines; 1,3,4-oxadiazoles; 1,3,4-thiadiazoles; condensations; antimicrobial agent

#### INTRODUCTION

It was established that quinazolinones have a powerful and broad antimicrobial activity against different species of pathogenic gram negative and positive bacteria. In the present investigation, thioquinazoline analogs were designed to contain some moieties, which are believed to contribute to antimicrobial activity, such as  $-CH_2CN-$ , -CO-CH=CH-Ar,  $CH_2CO-Ar$ , and  $-CH_2-CONH-Ar$ , in addition to a series of heterocycles connected to the quinazoline ring, such as 1,3,4-oxadiazole and thiadiazole.<sup>1-4</sup> The new compounds were screened against Gram negative bacteria (*Escherichia coli*), Gram positive bacteria (*Staphylococcus aureus*, *Bacillus subitilis*), and fungi (*Saccharomyces cerevisiae*, *Candida albicans*).

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#### MATERIALS AND METHODS

All melting points were determined in open Barnistead Electrothermal capillaries and are uncorrected. Microanalyses were performed on a Heraeus instrument: results are within  $\pm 0.4\%$  of the theoretical values. TLC was performed on Merck (Darmstädt, Germany) 5 × 10 cm plates, which were precoated with silica gel GF<sub>254</sub> using short wavelength UV light for visualization (CHCl<sub>3</sub>, methanol 10:1) (Upland, USA). All of the fine chemicals and reagents used were purchased from Aldrich (Wisconsin, USA). <sup>1</sup>H NMR spectra were recorded on a Varian Gemini 200 spectrometer. Chemical shifts are given in  $\delta$  (ppm) values downfield from Me<sub>4</sub>Si as an internal standard. IR spectra were recorded on a Pye Unicam SP 100 instrument using KBr pellets. Mass spectra were recorded using an HP MS-5988 apparatus. The following organisms were used in the antimicrobial screening: *E. coli* ATCC 10536, *Staphylococcus aureus* ATCC 06538, *Bacillus subitilis* ATCC 6633, *Saccharomyces cerevisiae* ATCC 9763, and *Candida albicans* ATCC 1023.

#### SYNTHESIS

#### 2-Thioxo-3-(4-chlorophenyl)-6-iodo-3H-quinazolin-4-one (1)

A mixture of iodoanthranilic acid (2.63 g, 0.01 mol) and *p*-chlorophenylisothiocyanate (2.03 g, 0.012 mol) in ethanol (50 mL) was heated under reflux for 4 h. The reaction mixture was then cooled to r.t., and the solvent was evaporated under vacuum. The obtained residue was washed with petroleum ether (40:60), filtered, dried, and recrystallized from ethanol to give 1 (Table I, II). <sup>1</sup>H NMR (DMSO-d<sub>6</sub>),  $\delta$  7.41 (d, J = 7.5 Hz, 1H, Quin-H), 7.52 (d, J = 8.5 Hz, 2H, Ar-H), 7.65 (d, J = 8.5 Hz, 2H, Ar-H), 8.11 (dd, J = 2.0, 7.5 Hz, 1H, Quin-H), 8.31 (d, J = 2.0 Hz, 1H, Quin-H), 12.88 (br s, 1H, NH).

#### 2-Alkylmercapto-3-(4-chlorophenyl)-6-iodo-3*H*-quinazolin-4-ones (2a–d)

To a solution of 2-mercapto-3-(4-chlorophenyl)-6-iodo-3H-quinazolin-4one (1) (4.14 g, 0.01 mol) in dry acetone (50 mL), anhydrous potassium carbonate (2.0 g) was added, followed by the addition of either methyl iodide, ethyl iodide, propyl iodide, or butyl iodide (0.015 mol). The reaction mixture was heated under reflux for 20 h, filtered while hot, and the filtrate was concentrated in vacuo to give the crude product, which was recrystallized from the respective solvent (Table I, II). Downloaded by [Temple University Libraries] at 04:29 16 November 2014

						Analysis	
					Re	quired/(Found	(
Compound	Solvent	M.P. (°C)	Yield (%)	Molecular Formula	C%	%Н	N%
1	EtOH	320–321	75	$C_{14}H_8CIIN_2OS$ 414.65	(40.73) 40.55	(2.03) 1.94	(30.61) 30.61
2a	EtOH	180 - 181	80	$C_{15}H_{10}CIIN_2OS$ 428.68	(42.19) 42.03	(2.26) 2.35	(6.71) 6.53
$2\mathbf{b}$	EtOH	172 - 174	72	$C_{16}H_{12}CIIN_2OS 442.70$	(43.65) 43.41	(2.91) 2.73	(6.51) 6.33
2c	EtOH	161 - 163	69	$C_{17}H_{14}CIIN_2OS 456.73$	(44.62) 44.71	(3.17) 3.09	(6.34) 6.31
2d	EtOH	150 - 152	65	$C_{18}H_{16}ClIN_2OS$ 470.75	(46.09) 45.92	(3.32) 3.43	(5.81) 5.95
3a	Dioxane	220 - 222	60	$\mathrm{C_{21}H_{14}ClIN_2OS}$ 504.77	(49.82) 49.97	(2.61) 2.80	(5.71) 5.55
3b	Dioxane	200 - 202	55	$C_{21}H_{13}Cl_2IN_2OS$ 539.22	(46.91) 46.78	(2.61) 2.43	(5.01) 5.20
3c	Dioxane	245 - 246	51	$C_{21}H_{13}CIIN_3O_3S$ 549.77	(45.61) $45.88$	(2.51) 2.38	(7.88) 7.64
4a	EtOH	80 - 82	65	$C_{22}H_{14}CIIN_2O_2S$ 532.78	(49.41) 49.60	(2.81) 2.65	(5.49) 5.26
4b	EtOH	200 - 202	56	$C_{22}H_{13}CIIN_3O_4S~577.78$	(45.48) 45.73	(2.52) 2.27	(7.12) 7.27
<b>4</b> c	EtOH	310 - 312	59	$C_{22}H_{13}ClBrIN_2O_2S$ 611.68	(43.42) 43.20	(2.31) 2.14	(4.61) 4.58
4d	EtOH	170 - 172	66	$C_{23}H_{16}ClIN_2O_3S$ 562.81	(49.31) 49.08	(3.02) 2.87	(4.88) 4.99
0	MeOH	275 - 276	46	$C_{16}H_9CIIN_3OS 453.68$	(42.21) 42.36	(1.89) 2.00	(9.55) 9.26
9	EtOH	170 - 171	75	$C_{18}H_{14}CIIN_2O_3S$ 500.74	(43.51) 43.17	(2.99) 2.88	(5.71) 5.59
7	EtOH, Dioxane	235 - 236	70	$C_{16}H_{12}ClIN_4O_2S$ 486.71	(39.22) 39.48	(2.61) 2.49	(11.31) 11.51
8	MeOH	240 - 241	65	$C_{18}H_{15}ClIN_3O_3S$ 515.75	(42.09) 41.92	(2.74) 2.93	(8.01) 8.15
6	Dioxane	180 - 181	46	$C_{18}H_{13}CIIN_3O_2S$ 497.74	(43.76) 43.44	(2.85) 2.63	(8.19) 8.44
10	Dioxane	270 - 272	45	$C_{24}H_{14}BrClN_5O_3S$ 694.73	(41.73) 41.49	(2.21) 2.03	(10.31) 10.68
11	EtOH, Dioxane	230 - 231	55	$C_{23}H_{17}ClIN_5O_2S_2621.90$	(44.61) 44.42	(2.51) 2.76	(11.51) 11.26
12	MeOH-Dioxane	>330	60	$C_{19}H_{12}CIIN_4O_4S$ 554.5	(41.31) 41.14	(2.39) 2.18	(10.31) 10.10
13	EtOH-CHCl <sub>3</sub>	165 - 167	62	$C_{21}H_{16}CIIN_4O_2S$ 550.5	(45.91) 45.79	(2.81) 2.93	(10.01) 10.17
14	Dioxane	170 - 172	65	$C_{20}H_{14}CIIN_4O_2S$ 536.5	(43.23) 43.46	(2.81) 2.55	(10.31) 10.14
15	EtOH-Dioxane	190 - 192	73	$C_{19}H_{16}ClIN_4O_3S$ 542.78	(42.31) 42.02	(3.12) 2.97	$(10.19)\ 10.32$
16	AcOH	230 - 232	70	$C_{17}H_{12}ClIN_4O_3S$ 514.72	(39.51) 39.67	(2.71) 2.35	(11.04) 10.88
17	EtOH	217 - 218	43	$C_{17}H_{10}CIIN_4O_2S$ 496.71	(41.01) 41.11	(2.26) 2.03	(11.04) 11.28
18	EtOH	235 - 236	49	${ m C}_{17}{ m H}_{10}{ m ClIN}_4{ m OS}_2512.77$	(39.71) $39.82$	(2.12) 1.97	(11.13) 10.93

TABLE I Physicochemical Properties of the New Synthesized Compounds

**2a:** <sup>1</sup>H NMR (DMSO-d<sub>6</sub>):  $\delta$  2.61 (s, 3H, C<u>H</u><sub>3</sub>-S), 7.41 (d, J = 7.5 Hz, 1H, Quin-H), 7.52 (d, J = 8.5 Hz, 2H, Ar-H), 7.65 (d, J = 8.5 Hz, 2H, Ar-H), 8.10 (dd, J = 2.0, 7.5 Hz, 1H, Quin-H), 8.32 (d, J = 2.0 Hz, 1H, Quin-H).

**2b:** <sup>1</sup>H NMR (DMSO-d<sub>6</sub>):  $\delta$  1.17 (t, J = 7.0 Hz, 3H, S-CH<sub>2</sub>-CH<sub>3</sub>), 3.25 (q, J = 7.0 Hz, 2H, S-CH<sub>2</sub>-CH<sub>3</sub>), 7.40 (d, J = 7.5 Hz, 1H, Quin-H), 7.51 (d, J = 8.5 Hz, 2H, Ar-H), 7.64 (d, J = 8.5 Hz, 2H, Ar-H), 8.12 (dd, J = 2.0, 7.5 Hz, 1H, Quin-H), 8.32 (d, J = 2.0 Hz, 1H, Quin-H).

**2c:** <sup>1</sup>H NMR (DMSO-d<sub>6</sub>):  $\delta$  0.94 (t, J = 7.0 Hz, 3H, S-CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>C<u>H</u><sub>3</sub>), 1.62–1.69 (m, 2H, S-CH<sub>2</sub>C<u>H</u><sub>2</sub>CH<sub>3</sub>), 3.21 (t, J = 7.0 Hz, 2H, S-C<u>H</u><sub>2</sub>-CH<sub>2</sub>CH<sub>3</sub>), 7.41 (d, J = 7.5 Hz, 1H, Quin-H), 7.52 (d, J = 8.5 Hz, 2H, Ar-H), 7.65 (d, J = 8.5 Hz, 2H, Ar-H), 8.18 (dd, J = 2.0, 7.5 Hz, 1H, Quin-H), 8.33 (d, J = 2.0 Hz, 1H, Quin-H).

**2d:** <sup>1</sup>H NMR (DMSO-d<sub>6</sub>):  $\delta$  0.89 (t, J = 7.0 Hz, 3H, S-CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>C<sub>H<sub>2</sub></sub>, 1.32–1.38 (m, 2H, S-CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>), 1.58–1.67 (m, 2H, S-CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>), 3.14 (t, J = 7.0 Hz, 2H, S-CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>), 7.41 (d, J = 7.5 Hz, 1H, Quin-H), 7.53 (d, J = 8.5 Hz, 2H, Ar-H), 7.60 (d, J = 8.5 Hz, 2H, Ar-H), 8.10 (dd, J = 2.0, 7.5 Hz, 1H, Quin-H), 8.31 (d, J = 2.0 Hz, 1H, Quin-H).

#### 3-(4-Chlorophenyl)-6-iodo-2-(arylmethylthio)-4-(3*H*)quinazolines (3a–c)

A mixture of 1 (4.14 g, 0.01 mol), benzyl bromide, or 4-substituted benzyl bromide (0.015 mol), and anhydrous  $K_2CO_3$  (2.0 g) in acetone (50 mL) was heated under reflux for 12 h. The reaction mixture was filtered while hot, the filtrate was evaporated in vacuo, and the obtained solid was recrystallized from the respective solvent (Table I, II).

**3a:** <sup>1</sup>H NMR (DMSO-d<sub>6</sub>):  $\delta$  4.41 (s, 2H, CH<sub>2</sub>Ph), 7.28–7.64(m, 10H, Ar-H and Quin-H), 8.14 (dd, J = 2.0, 7.5 Hz, 1H, Quin-H), 8.34 (d, J = 2.0 Hz, 1H, Quin-H).

**3b:** <sup>1</sup>H NMR (DMSO-d<sub>6</sub>):  $\delta$  4.44 (s, 2H, CH<sub>2</sub>Ph), 7.16–7.69 (m, 9H, Ar-H and Quin-H), 8.14 (dd, J = 2.0, 7.5 Hz, 1H, Quin-H), 8.34 (d, J = 2.0 Hz, 1H, Quin-H).

**3c:** <sup>1</sup>H NMR (DMSO-d<sub>6</sub>):  $\delta$  4.46 (s, 2H, CH<sub>2</sub>-Ph), 7.25–8.04 (m, 9H, Ar-H and Quin-H), 8.13 (dd, J = 2.0, 7.5 Hz, 1H, Quin-H), 8.34 (d, J = 2.0 Hz, 1H, Quin-H).

Compound	IR Data, $\nu$ (cm <sup>-1</sup> )	MS Data, m/z
1	3160 (NH), 1685 (C=O)	$414 (M^+, 6.97\%), 416 (M + 2, 2.36\%), 345 (25.55\%), 347 (9.52\%)$
2a	3030 (Ar-CH), 2950 (aliph. CH), 1690 (C=O), 1050 (C-S)	$\begin{array}{c} 428(\mathrm{M}^+,38.85),430(\mathrm{M}+2,15.61\%),\\ 413(1.17\%),381(14.58\%),383\\ (6.38\%),317(17.34\%),216(23.97\%) \end{array}$
2b	3020 (Ar-CH), 2976 (aliph-CH), 1690 (C=O), 1060 (C-S)	$\begin{array}{l} 442(M^+,41.81\%),444(M+2,\\ 15.13\%),381(16.71\%),383(6.71\%),\\ 317(15.61\%),216(21.81\%) \end{array}$
2c	3050 (Ar-CH), 2980 (aliph-CH), 1688 (C=O), 1055 (C-S)	$\begin{array}{c} 456\ (\mathrm{M}^+, 36.85\%), 458\ (\mathrm{M}+2,\\ 14.21\%), 381\ (29.61\%), 383\\ (13.61\%), 317\ (14.61\%), 216\\ (29.30\%)\end{array}$
2d	3060 (Ar-CH), 2995, (aliph-CH), 1690 (C=O), 1050 (C-S)	$\begin{array}{c} 470 \ (M^+ \ 34.81), \ 4.72 \ (M+2, \ 14.81\%), \\ 413 \ (2.21\%), \ 381 \ (19.81\%), \ 383 \\ (8.21\%), \ 317 \ (19.65\%), \ 216 \ (25.61\%) \end{array}$
3a	3050 (Ar-CH), 2996 (aliph-CH), 1685 (C=O), 1640 (C=N), 1050 (C=S)	$\begin{array}{c} 504 \ (M^+, \ 4.44\%), \ 406 \ (M+2, \ 2.81\%), \\ 413 \ (9.31\%), \ 415 \ (3.14\%), \ 91 \ (100\%) \end{array}$
3b	3060 (Ar-CH), 2995 (aliph-CH), 1690 (C=O), 1645 (C + N), 1050 (C=S)	$\begin{array}{c} 538(M^+,26.25\%),540(M+2,\\ 15.72\%),542(M+4,2.91\%),413\\ (1.03\%),125(39.03\%),127(13.01\%) \end{array}$
4a	3050 (Ar-CH), 2995 (aliph-CH), 1715, 1690 (2C=O), 1640 (C=N), 1075 (C-S)	$532 (M^+, 13.61\%), 534 (M + 2, 4.61\%), 455 (26.51\%), 457 (8.71\%), 427 (32.21\%), 429 (11.03\%), 413 (4.07\%)$
4b	3050 (Ar-CH), 2990 (aliph-CH), 1710, 1685 (2C=O), 1630 (C=N), 1070 (C-S)	$577 \ (\mathrm{M}^+, 9.91\%), \ 579 \ ((\mathrm{M}+2), \ 3.31\%), \\ 455 \ (4.21\%), \ 457 \ (1.52\%), \ 427 \\ (8.21\%), \ 429 \ (2.915), \ 413 \ (1.01\%)$
4c	3040 (Ar-CH), 2985 (ALIPH-CH), 1685 (C=O), 1650 (C=N), 1050 (C-S)	$\begin{array}{c} 610 \ (\mathrm{M}+, 26.925), \ 612 \ (\mathrm{M}+2, \\ 37.61\%), \ 614 \ (\mathrm{M}+4, 9.4\%), \ 557 \\ (6.35\%), \ 579 \ (2.21\%), \ 427 \ (18.61\%), \\ 429 \ (6.3\%), \ 413 \ (11.32\%) \end{array}$
5	3060 (Ar-CH), 2992 (aliph-CH), 1685 (C=O), 2250 (C=N), 1640 (C=N), 1060 (C-S)	$\begin{array}{c} 453\ (\mathrm{M}^+,15.61\%),455\ (\mathrm{M}+2,6.91\%),\\ 427\ (7.61\%),429\ (2.57\%),413\\ (19.21\%)\end{array}$
6	3050 (Ar-CH), 2900 (aliph-CH), 1745, 1695 (2C=O)	$\begin{array}{c} 500\ (\mathrm{M^{+}},18.74\%),502\ (\mathrm{M}+2,7.34\%)\\ 455\ (21.23\%),457\ (8.21\%),427\\ (10.21\%),413\ (21.2\%) \end{array}$
7	3400, 3290 (NH <sub>2</sub> ), 3200 (NH), 3050 (Ar-CH), 2990 (aliph-CH), 1735, 1695 (2C=O)	$\begin{array}{c} 486 \ (M^+, \ 15.31\%), \ 488 \ (M+2, \ 6.1\%), \\ 413 \ (3.62\%) \end{array}$
8	3500 (OH), 3210 (NH), 3040 (Ar-CH), 2990 (aliph-CH), 1700, 1685 (2C=O), 1060 (C-S)	$515~(M^+,~9.71\%),~517~(M+2,~3.21\%),\\ 455~(79.12\%),~427~(31.04\%),~413\\ (30.38)$

TABLE II IR and Mass Spectral Data of the New Synthesized Compounds

Compound	IR Data, $\nu$ (cm <sup>-1</sup> )	MS Data, m/z
9	3150 (NH), 3040 (Ar-CH), 2995 (aliph-CH), 1700, 1690 (2C=O), 1620 (C=N), 1070 (C-S)	$\begin{array}{c} 497\ (M^{+}, 39.61\%), 599\ (M+2, 13.61),\\ 413\ (1.2\%)\end{array}$
10	3250 (2NH), 3040 (Ar-CH), 2990 (aliph-CH), 1700, 1690, 1620 (3C=O), 1620 (C=N), 1080 (C-5)	$\begin{array}{l} 593 \ (\mathrm{M}^+,  15.61\%),  597 \ (\mathrm{M}+2, \\ 20.61\%),  599 \ (4.92\%),  455 \ (3.61\%), \\ 457 \ (1.21\%),  427 \ (9.33\%),  429 \\ (3.21\%),  413 \ (6.01\%) \end{array}$
11	3460, 3320 (2NH), 3060 (ar-CH), 2990 (aliph-CH), 1700, 1685 (2C=O)	$\begin{array}{l} 621 \ (M^+, \ 31.32\%), \ 623 \ (M+2, \\ 15.11\%), \ 455 \ (68.32\%), \ 427 \\ (29.09\%), \ 413 \ (23.38\%) \end{array}$
12	3250 (NH), 3050 (Ar-CH), 2995 (aliph-CH), 1700–1685 (4C=O), 1640 (C=N)	$\begin{array}{c} 554 \ (M^+, \ 34.321\%), \ 556 \ (M+2, \\ 12.12\%), \ 455 \ (35.21\%), \ 427 \\ (12.03\%), \ 413 \ (1.32\%) \end{array}$
13	3060 (Ar-CH), 2990 (aliph-CH), 1700, 1685 (2C=O), 1645 (C=N), 1070 (C-S)	$\begin{array}{c} 550 \ (M^+, 29.56\%), \ 552 \ (M+2, 9.51\%); \\ 455 \ (21.31\%), \ 457 \ (7.07\%), \ 427 \\ (19.61\%), \ 429 \ (6.52\%), \ 413 \ (3.10\%) \end{array}$
14	3050 (Ar-CH), 2995 (aliph-CH), 1700, 1690 (2C=O), 1650 (C=N), 1055 (C-S)	$\begin{array}{c} 536 \ (M^+,  18.36\%),  538 \ (M+2,  6.4\%), \\ 455 \ (33.21\%),  457 \ (10.90\%),  427 \\ (13.21\%),  429 \ (4.40\%),  413 \ (13.21\%) \end{array}$
15	3250 (NH), 3060 (Ar-CH), 2995 (aliph-CH), 1700, 1690 (2C=O), 1650 (C=N), 1055 (C-S)	$542 \ (M^+, \ 39.12\%), \ 544 \ (M+2, \\ 12.91\%), \ 413 \ (23.21\%)$
16	3390, 3250 (2NH), 3055 (Ar-CH), 2995 (aliph-CH), 1725–1700, 1690 (3C=O), 2800–2700 (aldehydic-H), 1655 (C=N), 1060 (C-S)	$\begin{array}{c} 514 \ (M^+,  21.34\%),  516 \ (M+2, \\ 7.21\%),  413 \ (1.21\%) \end{array}$
17	3050 (ar-CH), 2995 (aliph-CH), 1690 (C=O), 1640 (C=N), 1070 (C-S)	$\begin{array}{l} 496 \ (\mathrm{H^+}, 31.34\%), 498 \ (\mathrm{M}+2,\\ 12.31\%), 427 \ (19.25\%), 429 \ (6.41\%),\\ 413 \ (1.91\%) \end{array}$
18	3060 (Ar-CH), 2990 (aliph-CH), 1685 (C=O), 1640 (C=N), 1050 (C=S)	$\begin{array}{c} 512 \ (M^+, \ 36.24\%), \ 514 \ (M+2, \\ 14.69\%), \ 413 \ (19.21\%) \end{array}$

 TABLE II IR and Mass Spectral Data of the New Synthesized

 Compounds (Continued)

#### 3-(4-Chlorophenyl)-6-iodo-2-(arylcarbonylmethylthio)-4(3*H*)-quinazolinones (4a–c)

A mixture of 1 (4.14 g, 0.01 mol), the appropriate 4-substituted phenacyl bromide (0.01 mol), and anhydrous  $K_2CO_3$  (2.0 g) in acetone (50 mL) was heated under reflux for 24 h. The reaction mixture was filtered while hot, and the filtrate was concentrated under reduced pressure and then

cooled to r.t. The obtained solid was filtered, dried, and recrystallized from the respective solvent (Table I, II).

**4a:** <sup>1</sup>H NMR (DMSO-d<sub>6</sub>):  $\delta$  4.71 (s, 2H, CH<sub>2</sub>CO), 7.37–7.86 (m, 10H, Ar-H and Quin-H), 8.10 (dd, J = 2.0, 7.5 Hz, 1H, Quin-H), 8.33 (d, J = 2.0 Hz, 1H, Quin-H).

**4d:** <sup>1</sup>H NMR (DMSO-d<sub>6</sub>):  $\delta$  3.73 (s, 3H, OC<u>H</u><sub>3</sub>), 4.68 (s, 2H, C<u>H</u><sub>2</sub>CO), 7.31–7.75 (m, 9H, Ar-H and Quin-H), 8.10 (dd, J = 2.0, 8.5 Hz, 1H, Quin-H), 8.32 (d, J = 2.0 Hz, 1H, Quin-H).

#### 2-Cyanomethylthio-3-(4-chlorophenyl)-4-oxo-6-iodo-3*H*-quinazoline (5)

To a solution of 2-mercapto-3-(4-chlorophenyl)-6-iodo-3*H*-quinazolin-4one (1) (4.14 g, 0.01 mol) in dry acetone (40 mL), anhydrous potassium carbonate (2.0 g) was added followed by the addition of 2chloroacetonitrile (1.1 g, 0.015 mol) The reaction mixture was refluxed for 8 h, and filtered while hot, and the filtrate was concentrated in vacuo to give the crude product, which was recrystallized from methanol. <sup>1</sup>H NMR (DMSO-d<sub>6</sub>):  $\delta$  4.25 (s, 2H, C<u>H</u><sub>2</sub>CN), 7.43 (d, *J* = 7.5 Hz, 1H, Quin-H), 7.53 (d, *J* = 8.5 Hz, 2H, Ar-H), 7.66 (d, *J* = 8.5 Hz, 2H, Ar-H), 8.12 (dd, *J* = 2.0, 7.5 Hz, 1H, Quin-H), 8.31 (d, *J* = 2.0 Hz, 1H, Quin-H).

#### 2-(Ethoxycarbonylmethyl)thio-3-(4-chlorophenyl)-4-oxo-6-iodo-3*H*-quinazoline (6)

A mixture of 2-mercapto-3-(4-chlorophenyl)-4-oxo-6-iodo-3*H*-quinazoline 1 (4.14 g, 0.01 mol), ethylbromoacetate (0.015 mol), and anhydrous potassium carbonate (2.0 g) in dry acetone (50 mL) was heated under reflux for 8 h. The solvent was evaporated, and the obtained residue was recrystallized from ethanol. <sup>1</sup>H NMR (DMSO-d<sub>6</sub>):  $\delta$  1.30 (t, *J* = 10.0 Hz, 3H, C<u>H</u><sub>3</sub>CH<sub>2</sub>-), 4.14 (s, 2H, C<u>H</u><sub>2</sub>CO), 4.39 (q, *J* = 10.0 Hz, 2H, CH<sub>3</sub>C<u>H</u><sub>2</sub>-), 7.41 (d, *J* = 7.5 Hz, 1H, Quin-H), 7.52 (d, *J* = 8.5 Hz, 2H, Ar-H), 7.66 (d, *J* = 8.5 Hz, 2H, Ar-H), 8.11 (dd, *J* = 2.0, 7.5 Hz, 1H, Quin-H), 8.31 (d, *J* = 2.0 Hz, 1H, Quin-H).

#### 2-[(3-(4-Chlorophenyl)-4-oxo-6-iodo-3*H*-quinazoline-2-yl)thio]acetylhydrazine (7)

A solution of the ester 6 (5 g, 0.01 mol) and hydrazine (85%, 5 mL) in ethanol (50 mL) was heated under reflux for 3 h. The solvent was evaporated, the obtained residue was washed with water

(50 mL), dried, and recrystallized from ethanol/dioxane (1:1). <sup>1</sup>H NMR (DMSO-d<sub>6</sub>):  $\delta$  3.96 (s, 2H, CH<sub>2</sub>CO), 4.30 (br s, 2H, NH<sub>2</sub>), 7.40 (d, J = 7.5 Hz, 1H, Quin-H), 7.52 (d, J = 8.5 Hz, 2H, Ar-H), 7.65 (d, J = 8.5 Hz, 2H, Ar-H), 8.10 (dd, J = 2.0, 7.5 Hz, 1H, Quin-H), 8.32 (d, J = 2.0 Hz, 1H, Quin-H), 9.4 (br s, 1H, NH).

#### *N*-(2-Hydroxyethyl)-2-[(3-(4-chloro)phenyl-4-oxo-6-iodo-3*H*-quinazolin-2-yl)thio]acetamide (8)

A solution of ester **6** (5 g, 0.01 mol) and 2-aminoethanol (1.2 g, 0.02 mol) in ethanol (50 mL) was heated under reflux for 3 h. The precipitated solid was filtered while hot, dried, and recrystallized from methanol. <sup>1</sup>H NMR (DMSO-d<sub>6</sub>):  $\delta$  2.71 (m, 2H, CH<sub>2</sub>CH<sub>2</sub>-), 3.45 (m, 2H, CH<sub>2</sub>CH<sub>2</sub>), 3.76 (br s, 1H, OH), 4.01 (s, 2H, CH<sub>2</sub>CO), 7.40 (d, J = 7.5 Hz, 1H, Quin-H), 7.52 (d, J = 8.5 Hz, 2H, Ar-H), 7.66 (d, J = 8.5 Hz, 2H, Ar-H), 8.31 (d, J = 2.0 Hz, 1H, Quin-H), 9.27 (br s, 1H, NH).

#### 2-[(2-Oxopyrrolidin-3-yl)thio]-3-(4-chlorophenyl)-4-oxo-6-iodo-3*H*-quinazoline (9)

A suspension of compound **8** (0.51 g, 0.001 mol) in conc.  $H_2SO_4$  (10 mL) was stirred at r.t. for 6 h. The reaction mixture was poured onto ice, stirred for 15 min, and neutralized with 30% aqueous NaOH. The solid was filtered off, washed with water, dried, and recrystallized from dioxane. <sup>1</sup>H NMR (DMSO-d<sub>6</sub>):  $\delta$  1.96 (m, 2H, pyrrolidine-H), 2.56 (m, 2H, pyrrolidine-H), 3.41 (m, 1H, pyrrolidine-H), 7.41 (d, J = 7.5 Hz, 1H, Quin-H), 7.52 (d, J = 8.5 Hz, 2H, Ar-H), 7.65 (d, J = 8.5 Hz, 2H, Ar-H), 8.11 (dd, J = 2.0, 7.5 Hz, 1H, Quin-H), 8.31 (d, J = 2.0 Hz, 1H, Quin-H), 8.9 (br s, 1H, NH).

#### (*E*)-*N*'-(5-Bromo-2-oxoindolin-3-ylidene)-2-[3-(4-chlorophenyl)-6-iodo-4-oxo-3,4-dihydroquinazolin-2-ylthio]acetohydrazide (10)

A mixture of compound **7** (2.43 g, 0.005 mol) and 4-bromoisatin (1.16 g, 0.005 mol) in 20 mL of glacial acetic acid was heated under reflux for 18 h. The reaction mixture was cooled to r.t., poured onto crushed ice, and the separated solid was filtered off and recrystallized from dioxane. <sup>1</sup>H NMR (DMSO-d<sub>6</sub>):  $\delta$  3.89 (s, 2H, S-C<u>H</u><sub>2</sub>CO), 7.20–7.71 (m, 9H, Ar-H

and Quin-H), 8.32 (d, J = 2.0 Hz, 1H, Quin-H), 8.91 (s, 1H, NH), 9.61 (s, 1H, NHCO).

#### N<sup>1</sup>-[(3-(4-chlorophenyl)-4-oxo-6-iodo-3*H*-quinazolin-2-yl)thioacetyl]-N<sup>3</sup>-phenylthiosemicarbazide (11)

A mixture of 2-[(3-(4-chlorophenyl)-4-oxo-6-iodo-3*H*-quinazoline-2-yl)thio]acetylhydrazine **7** (4.86 g, 0.01 mol) and phenylisothiocyanate (1.62 g, 0.012 mol) in dioxane (30 mL) was heated under reflux for 18 h. The solid was filtered, dried, and recrystallized to give **11**. <sup>1</sup>H NMR (DMSO-d<sub>6</sub>):  $\delta$  4.21 (s, 2H, CH<sub>2</sub>CO), 7.21–7.67 (m, 10H, Ar-H and Quin-H), 8.11 (dd, J = 2.0, 7.5 Hz, 1H, Quin-H), 8.33 (d, J = 2.0 Hz, 1H, Quin-H), 8.62 (br s, 1H, NH), 9.51 (b rs, 2H, NH).

#### 2-[3,5-Dioxopyrazolidin-1-yl)carbonylmethyl-thio]-4-(3-chlorophenyl)-4-oxo-6-iodo-3*H*-quinazoline (12)

To a solution of sodium ethoxide (made of 0.198 g sodium and 20 mL absolute ethanol) was added freshly distilled diethylmalonate (0.68 g, 0.004 mol) followed by the addition of compound **7** (1.36 g, 0.003 mol). The reaction mixture was heated for 5 h, the solvent was evaporated under reduced pressure, and the crude was acidified with 10% hydrochloric acid. The precipitate formed was filtered off, washed with cold water, and then recrystallized from methanol/dioxane (1:1). <sup>1</sup>H NMR (DMSO-d<sub>6</sub>):  $\delta$  3.47 (s, 2H, COC<u>H<sub>2</sub></u>CO), 3.95 (s, 2H, S-C<u>H<sub>2</sub></u>CO), 7.41 (d, J = 7.5 Hz, 1H, Quin-H), 7.52 (d, J = 8.5 Hz, 2H, Ar-H), 7.66 (d, J = 8.5 Hz, 2H, Ar-H), 8.11 (dd, J = 2.0, 7.5 Hz, 1H, Quin-H), 8.33 (d, J = 2.0 Hz, 1H, Quin-H), 9.7 (s, 1H, N<u>H</u>CO-).

#### 2-[(3,5-Dimethylpyrazol-yl)carbonylmethylthio]-3-(4-chlorophenyl)-4-oxo-3*H*-quinazoline (13)

Acetylacetone (1.5 g, 0.015 mol) was added to a solution of compound **7** (4.86 g, 0.01 mol) in ethanol (30 mL). The reaction mixture was heated under reflux for 10 h. The solvent was then removed under reduced pressure, and the residue was recrystallized from ethanol/chloroform (1:1). <sup>1</sup>H NMR (DMSO-d<sub>6</sub>):  $\delta$  2.79 (s, 6H, CH<sub>3</sub>), 4.11 (s, 2H, SCH<sub>2</sub>CO), 7.21–707 (m, 6H, Ar-H, Quin-H and pyrazole-H), 8.11 (dd, J = 2.0, 7.5 Hz, 1H, Quin-H), 8.31 (d, J = 2.0 Hz, 1H, Quin-H).

#### 2-[(3-Methyl-5-oxo-4,5-dihydropyrazol-1yl)carbonylmethylthio]-3-(4-chlorophenyl)-4-oxo-6-iodo-3*H*-quinazoline (14)

Ethylacetoacetate (2.0 g, 0.015 mol) was added to a solution of compound **7** (4.86 g, 0.01 mol) in ethanol (30 mL). The reaction mixture was heated under reflux for 8 h. The solvent was then removed under reduced pressure, and the residue was recrystallized from dioxane. <sup>1</sup>H NMR (DMSO-d<sub>6</sub>):  $\delta$  2.56 (s, 3H, CH<sub>3</sub>), 4.13 (s, 2H, S-CH<sub>2</sub>CO), 4.47 (s, 2H, CH<sub>2</sub>CO), 7.42 (d, J = 7.5 Hz, 1H, Quin-H), 7.53 (d, J = 8.5 Hz, 2H, Ar-H), 7.68 (d, J = 8.5 Hz, 2H, Ar-H), 8.10 (dd, J = 2.0, 7.5 Hz, 1H, Quin-H), 8.31 (d, J = 2.0 Hz, 1H, Quin-H).

#### *N*-Ethoxymethine-*N'*-[2(3-(4-chlorophenyl)-4-oxo-6-iodo-3*H*-quinazolin-2-yl)thioacetyl]hydrazine (15)

A mixture of **7** (2.43 g, 0.005 mol) and triethylorthoformate (10 mL) was heated under reflux for 30 min. The reaction mixture was filtered while hot and then cooled to r.t. The solid formed was filtered off, dried, and recrystallized from ethanol/dioxane (1:1). <sup>1</sup>H NMR (DMSO-d<sub>6</sub>):  $\delta$  1.31 (t, J = 7.0 Hz, 3H, CH<sub>3</sub>), 3.96 (q, J = 7.0 Hz, 2H, CH<sub>2</sub>), 4.16 (s, 2H, S-CH<sub>2</sub>CO), 7.41 (d, J = 7.5 Hz, 1H, Quin-H), 7.54 (d, J = 8.5 Hz, 2H, Ar-H), 7.67 (d, J = 8.5 Hz, 2H, Ar-H), 8.13 (dd, J = 2.0, 7.5 Hz, 1H, Quin-H), 8.31 (d, J = 2.0 Hz, 1H, Quin-H), 9.96 (s, 1H, CH=N), 10.08 (br s, 1H, NH).

#### *N*-Formyl-*N*-(2-(3-(4-chlorophenyl)-4-oxo-6-iodo-3*H*-quinazolin-2-yl)-thioacetyl]-hydrazine (16)

A solution of compound **7** (1.22, 0.003 mol) in formic acid (15 mL) was heated under reflux for 30 min. The solid separated upon cooling to r.t. was filtered off, washed with petroleum ether (50 mL), dried, and recrystallized from acetic acid. <sup>1</sup>H NMR (CDCl<sub>3</sub>):  $\delta$  4.17 (s, 2H, -S-C<u>H</u><sub>2</sub>CO), 7.41 (d, J = 7.5 Hz, 1H, Quin-H), 7.52 (d, J = 8.5 Hz, 2H, Ar-H), 7.64 (d, J = 8.5 Hz, 2H, Ar-H), 8.10 (dd, J = 2.0, 7.5 Hz, 1H, Quin-H), 8.33 (d, J = 2.0 Hz, 1H, Quin-H), 8.21 (br s, 1H, NH), 9.13 (br s, 1H, NH), 9.82 (s, 1H, CHO).

#### 2-[(1,3,4-Oxadiazol-2-yl)methylthio]-3-(4-chlorophenyl)-4-oxo-6-iodo-3*H*-quinazoline (17)

#### Method A

To a solution of 16 (0.514 g, 0.001 mol) in xylene (50 mL), phosphorus pentaoxide (2.0 g) was added. The reaction mixture was refluxed for 3 h and filtered, and the residue was recrystallized from dioxane.

#### Method B

Compound **15** (0.985 g, 0.002 mol) was heated at 210°C for 30 min. The reaction product was purified by preparative TLC on silica gel using chloroform/ethylacetate (90:10) as an eluent to give **17**. <sup>1</sup>H NMR (DMSO-d<sub>6</sub>):  $\delta$  4.13 (s, 2H, S-C<u>H</u><sub>2</sub>-), 7.42 (d, J = 7.5 Hz, 1H, Quin-H), 7.54 (d, J = 8.5 Hz, 2H, Ar-H), 7.64 (d, J = 8.5 Hz, 2H, Ar-H), 7.88 (s, 1H, oxadiazole-H), 8.17 (dd, J = 2.0, 7.5 Hz, 1H, Quin-H), 8.31 (d, J = 2.0 Hz, 1H, Quin-H).

#### 2-[(1,3,4-Thiadiazol-2-yl)methylthio]-3-(4-chlorophenyl)-4-oxo-6-iodo-3*H*-quinazoline (18)

To a solution of **16** (0.514 g, 0.001 mol) in xylene (50 mL), phosphorus pentasulfide (2.0 g) was added. The reaction mixture was refluxed for 1 h and filtered. From the filtrate, the solvent was evaporated, and the residue was treated with dimethylsulfoxide (10 mL) and filtered. The clear filtrate was poured onto ice and stirred. The solid was filtered off, washed with water, dried, and recrystallized from ethanol to afford **18**. <sup>1</sup>H NMR (DMSO-d<sub>6</sub>):  $\delta$  4.15 (s, 2H, S-CH<sub>2</sub>-), 7.43 (d, J = 7.5 Hz, 1H, Quin-H), 7.52 (d, J = 8.5 Hz, 2H, Ar-H), 7.66 (d, J = 8.5 Hz, 2H, Ar-H), 8.16 (dd, J = 2.0, 7.5 Hz, 1H, Quin-H), 8.10 (s, 1H, thiadiazole-H), 8.33 (d, J = 2.0 Hz, 1H, Quin-H).

#### **RESULTS AND DISCUSSION**

#### Chemistry

The synthetic strategy to obtain target compounds 1-18 is shown in Schemes 1 and 2. The starting material 2-mercapto-3-(4chlorophenyl)-4-oxo-6-iodo-3*H*-quinazoline was prepared by reacting 5-iodoanthranilic acid with 4-chlorophenylisothiocyanate in boiling ethanol. The 2-sulfhydryl group of 1 was alkylated with a series of alkylhalides, benzyl halides, phenacylhalides, and chloroacetonitrile to produce compounds **2a–d**, **3a–c**, **4a–f**, and **5**, respectively (Scheme 1). Further alkylation of 1 using ethylbromoacetate in boiling acetone containing anhydrous potassium carbonate afforded the target ester  ${\bf 6}$  (Scheme 1). $^{6,7}$ 

The ester group in **6** was reacted with hydrazine hydrate or ethanolamine to produce hydrazide **7** and the corresponding amide **8**, which, upon treatment with conc. sulfuric acid, was cyclodehydrated to produce 2-oxo-pyrrolidine **9** (Scheme 1). Acetic acid hydrazide **7** was reacted with isatin to produce -S-[2-oxo-3-indolinylidene)acetic acid hydrazide derivative **10**. Again acid hydrazide **7** was reacted with phenylisothiocyanate to afford the phenyl thiosemicarboazide derivative **11**.<sup>8</sup> Condensation of hydrazide **7** with diethylmalonate, acetylacetone, or ethylacetoacetate in ethanol furnished products, which gave analytical data compatible with 3-oxo-5-pyrazolono, 3,5-dimethylpyrazolo, and 3-methyl-5-pyrazolono derivatives **12**, **13**, and **14**, respectively (Scheme 2).<sup>9,10</sup>

Hydrazide **7** was reacted with triethylorthoformate or formic acid to produce the compound **15** or *N*-formyl derivative **16**, respectively (Scheme 2). Heating compound **15** afforded 1,3,4-oxadiazole **17**, while *N*-formyl derivative **16** was cyclodehydrated using  $P_2O_5$  or  $P_2S_5$  to give a compound, which proved to be identical to **17** in addition to the 1,3,4thiadiazole **18**, respectively (Scheme 2).<sup>11,12</sup>

#### Antimicrobial Screening

Antimicrobial Testing. Nutrient agar plates were seeded using 0.1 mL overnight cultures. Cylindrical plugs were removed from the agar plate using a sterile cork borer, and 100  $\mu$ L of the tested compounds (1 mg/mL DMSO) were added to the well in triplicates. A blank solvent was used as a control. Plates inoculated with tested bacteria were incubated at 37°C, while those of fungi were incubated at 30°C. Results (Table III) were taken after 24 h of incubation and were recorded as the average diameter of the inhibition zone in mm.<sup>5</sup>

All newly synthesized compounds were subjected to antimicrobial screening by the in vitro cup-plate technique using ampicillin, streptomycin, and nystatin as positive controls. Compounds 13, 14, 17, and 18 showed remarkable activity toward Gram negative bacteria *E. coli*.

Gram positive bacteria *S. aureus* and *B. subtilis* were proven to be sensitive toward compounds **9**, **10**, **12**, **17**, and **18**. Compounds **3c**, **4b**, **11**, and **18** showed remarkable activity toward the fungi *S. cerevisiae* and *C. albicans* used. A close examination of the structures of the active compounds revealed that the antimicrobial activity was confined to compounds that were connected with different heterocyclic rings.



**SCHEME 1** 



**SCHEME 2** 

Compound	E. coli	S. aureus	B. subitilis	S. cerevisica	C. albicans
1	_	_	_	+	+
2a	+	_	+	_	+
2b	_	+	_	_	+ + +
2c	_	_	_	_	+
2d	+	+	_	_	_
3a		—	—	—	+
3b		—	—	—	+
3c		+ + +	—	+ + +	++
4a		—	+	—	_
4b	++	—	—	+	+
<b>4c</b>	+	_	—	—	—
4d	+	+	—	—	—
5	+	_	—	+	++
6	—	++	++	—	+
7	_	+	_	—	++
8	_	_	+	+	_
9	—	+ + +	+ + +	—	—
10	_	++	++	—	_
11	+	+	+	++	++
12	++	+ + +	++	++	_
13	+ + +	++	++	+	+
14	+ + +	+	+	++	_
15	+	+	_	+	_
16	+	+	+	+	_
17	+ + +	++	++	+	++
18	+ + +	++	+ + +	++	++
Ampicillin	+++	+ + +	+ + +	NT	NT
Streptomycin Nystatin	+ + + NT	++ NT	$^{+++}_{\rm NT}$	$\begin{array}{c} \text{NT} \\ +++ \end{array}$	$\begin{array}{c} \mathbf{NT} \\ +++ \end{array}$

 TABLE III Antimicrobial Screening Results of the Tested

 Compounds at 1 mg/mL Concentration

—, Inactive (inhibition zone < 10 mm); +, moderate active (inhibition zone 10–15 mm); ++, active (inhibition zone 15–20 mm); +++, remarkable activity (inhibition zone >20 mm); NT = not tested.

In conclusion, the present study revealed that compounds 11, 13, 17, and 18 could be useful as templates for further development through modification or derivatization to design more potent antimicrobial agents.

#### REFERENCES

- [1] H. K. Misra and A. K. Sen Gupta, Pharmazie, 37, 254 (1982).
- [2] M. A. Aziza, M. W. Nassar, S. G. Abdel-Hamide, A. E. El-Hakim, and A. S. El-Azab, Ind. J. Heterocycl. Chem., 6, 25 (1996).

- [3] S. G. Abdel-Hamide, Saudi Pharm. J., 9, 72 (2001).
- [4] M. A. Aziza, M. W. Nassar, S. G. Abdel-Hamide, A. E. El-Hakim, and A. S. El-Azab, Az. J. Pharm. Sci., 21, 65 (1989).
- [5] J. G. Colle, J. P. Duguid, A. G. Fraser, and B. P. Marmion, In *Practical Medical Microbiology*, T. J. Macki and J. E. McCartney, Eds., 13th ed, p. 527–596 (Churchill Livingstone, London 1989).
- [6] M. A. Al-Omar, S. G. Abdel-Hamide, H. A. Al-Khamees, and H. H. El-Subbagh, Saudi Pharm. J., 12, 63 (2004).
- [7] S. G. Abdel-Hamide, A. E. El-Hakim, and R. M. Abdel-Rahman, Ind. J. Heterocycl. Chem., 5, 219 (1996).
- [8] M. M. Ghorab, S. G. Abdel-Hamide, G. M. Ali, and H. S. El-Sayed, Pestic. Sci., 48, 31 (1996).
- [9] M. S. Mohamed, M. K. Ibrahim, M. A. Ahmed, and S. G. Abdel-Hamide, J. Biol. Sci., 4, 504 (2004).
- [10] A. M. Mahmoud, H. A. El-Sherief, G. M. El-Nagger, and A. E. Abdel-Rahman, *Indian J. Chem.*, **22B**, 491 (1983).
- [11] M. A. Al-Omar, A. S. El-Azab, M. A. El-Obeid, and S. G. Abdel-Hamide; J. Saudi Chem. Soc., 10, 113 (2006).
- [12] M. A. Aziza, M. W. Nassar, S. G. Abdel-Hamide, A. E. El-Hakim, and A. S. El-Azab, Az. J. Pharm. Sci., 16, 125 (1995).