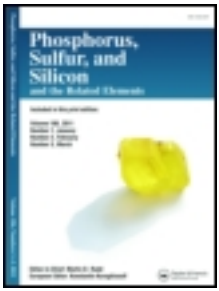

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Synthesis and Reactions of Some New Quinoline Thiosemicarbazide Derivatives of Potential Biological Activity

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Synthesis and Reactions of Some New Quinoline Thiosemicarbazide Derivatives of Potential Biological Activity

E. M. Keshk,[1] S. I. El-Desoky,[1] M. A. A. Hammouda,[1] A. H. Abdel-Rahman,[1] and A. G. Hegazi[2]
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*Quinoline-2-carbohydrazide (**3**) was reacted with aryl or alkyl isothiocyanates to give the corresponding quinoline thiosemicarbazides(**4a–e**). Cyclization of the substituted thiosemicarbazides with sodium hydroxide led to the formation of 5-(quinolin-2-yl)-2H-1, 2, 4-triazole-3(4H)-thiones (**5a–e**). Desulfurization of thiosemicarbazides by mercuric oxide gave 5-(quinolin-2-yl)-1, 3, 4-oxadiazol-2-amines (**6a–e**). Treatment of thiosemicarbazides with ethyl bromoacetate or α-bromopropionic acid yielded (Z)-N′-(3-substituted thiazolidin-4-oxo-2-ylidene) quinoline-2-carbohydrazides (**7a–d**), (**8a–d**), respectively. Treatment of thiosemicarbazides with chloroacetone furnished (Z)-N′-(4-methyl-3-substituted-thiazol-2(3H)-ylidene) quinoline-2-carbohydrazides (**9a–d**). Furthermore, the reaction of thiosemicarbazides with phosphorus oxychloride gave N-substituted-5-(quinolin-2-yl)-1,3,4-thiadiazol-2-amines (**10a–e**). All newly synthesized compounds were tested and evaluated for antimicrobial activity.*

Keywords Antimicrobial activity; oxadiazole; quinaldic acid; thiazole; thiadiazole; thiosemicarbazide; triazole

INTRODUCTION

Quinoline and its derivatives represent one of the most active classes of compounds possessing a wide spectrum of pharmacological properties.[1–8] Various thiosemicarbazides[9,10] and their cyclized products, e.g., triazoles,[11,12] oxadiazoles,[13,14] thiazolidinones,[15,16] thiazoles[17,18] and thiadiazoles[19,20] are also associated with a broad spectrum of biological properties.

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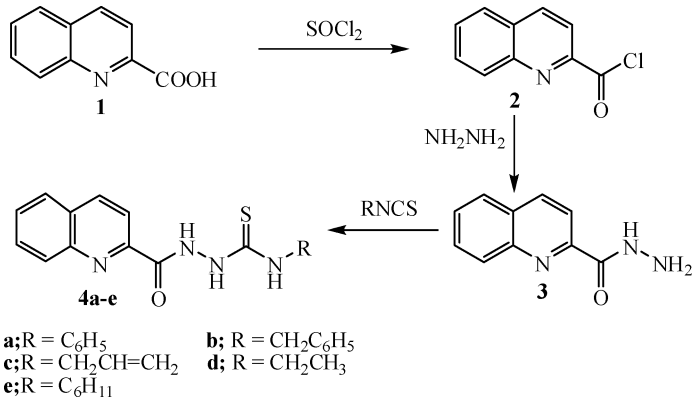
In continuation of our research on the synthesis of new heterocyclic compounds of potential biological interest,[21,22] this work deals with synthesis, characterization and biological evaluation of new compounds containing a quinoline nucleus combined with thiosemicarbazide, 1,2,4-triazole, 1,3,4-oxadiazole, thiazolidinone, thiazole, and 1,3,4-thiadiazole moieties, which are expected to possess high biological activity.

RESULTS AND DISCUSSION

Treatment of quinoline-2-carboxylic acid (quinaldic acid) **1** with thionyl chloride gave the corresponding acid chloride **2** which reacted with hydrazine hydrate affording quinoline -2-carbohydrazide **3**.[23]

The carbohydrazide **3** was reacted with isothiocyanate derivatives, namely, phenyl, benzyl, allyl, ethyl and cyclohexyl isothiocyanate to afford 1- (quinolin-2-yl-carbonyl) -4-substituted thiosemicarbazides **4a–e** (Scheme 1).

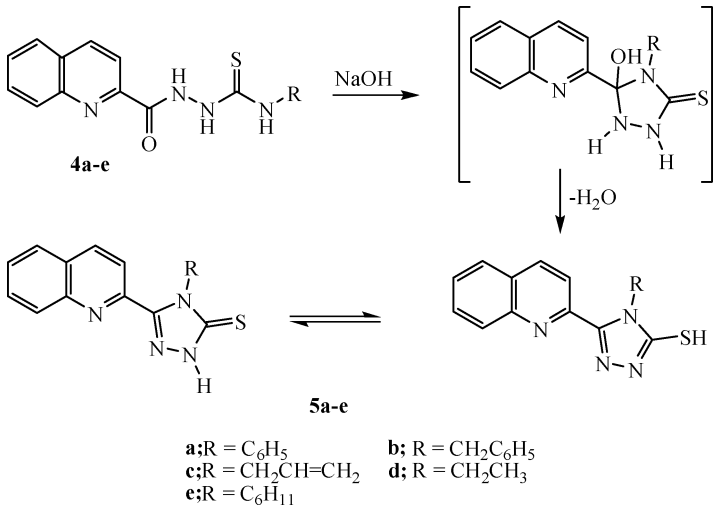


SCHEME 1

The structure of the products **4a-e** was assigned based on their elemental analyses and spectral data (Tables I and II). IR spectra of compounds **4a–e** showed the absorption bands of NH at 3288–3109 cm^{-1}, carbonyl group at 1692–1659 cm^{-1} in addition to the characteristic band of (—N—C═S) functions in the range 1265–1234 cm^{-1}. The ^1H NMR spectrum of compound **4a** for example, showed a multiplet signal at δ 7.12–8.60 due to the aromatic protons and a broad singlet signal at δ 9.80 due to the two NH protons of thiourea, in addition to a singlet signal at δ 10.85 due to the amide NH proton.

Cyclization of 4-substituted thiosemicarbazides **4a–e** was carried out by heating with aqueous sodium hydroxide solution 2*N* leading to the

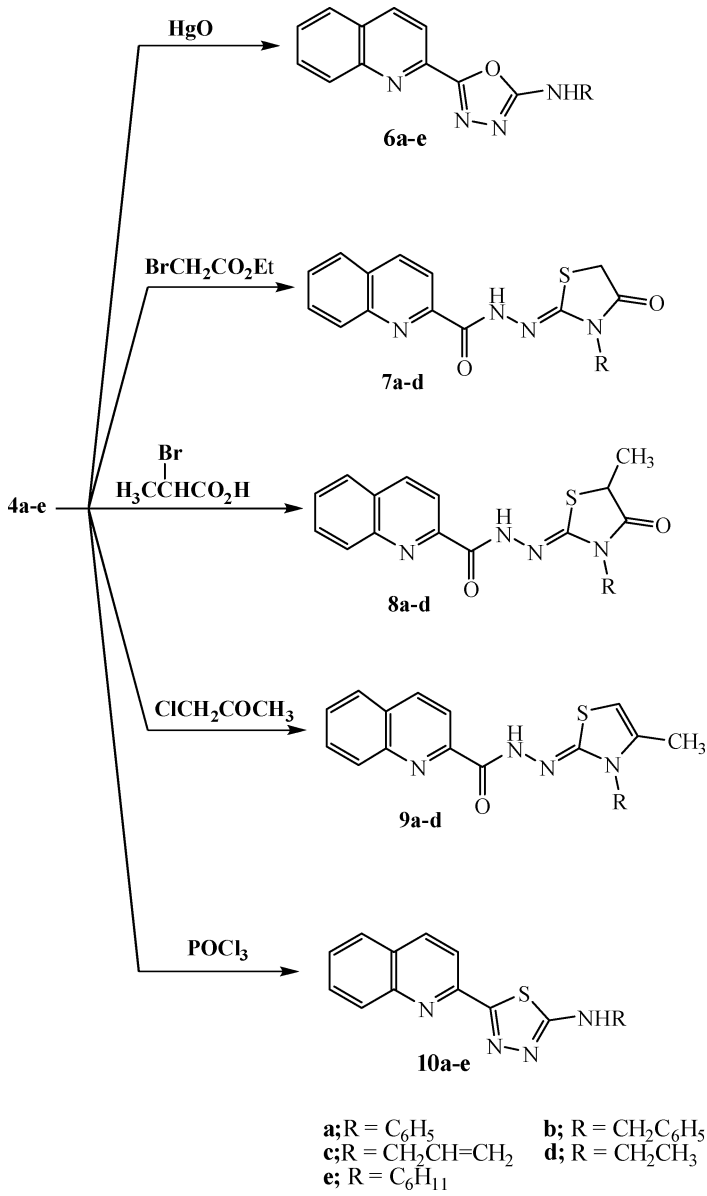
formation of 4-substituted-5-(quinolin-2-yl)-2*H*-1, 2, 4-triazole-3(4*H*)-thiones **5a–e** (Scheme 2).



SCHEME 2

The elemental analyses and spectral data of derivatives **5a–e** were compatible with the suggested structures. IR spectra of compounds **5a–e** showed absorption bands at 3172–3113 cm^{-1} (NH) and a stretching vibration band in the region of 1620–1613 cm^{-1} characteristic for the (C=N) of triazole ring. Meanwhile, the stretching frequency band of the carbonyl group was disappeared. In the solid state, compounds **5a–e** are present predominately in the thioxo form as it was shown by the (C=S) band at 1285–1270 cm^{-1} in the IR spectra of these compounds. The ^{1}H NMR spectra of the compounds **5a–e** revealed clearly the absence of the two NH singlet signals, and instead of that exhibited one singlet signal due to SH proton.

Desulphurization of thiosemicarbazides **4a–e** could be obtained by refluxing the thiosemicarbazide derivatives with yellow mercuric oxide in boiling ethanol to yield *N*-substituted-5-(quinolin-2-yl)-1, 3, 4-oxadiazol- 2-amines **6a–e** (Scheme 3). The structures of the products **6a–e** were conformed from the correct elemental analyses, IR, ^{1}H NMR, and ^{13}C NMR spectra. IR spectra of the 1, 3, 4-oxadiazoles **6a–e** lacked the absorption band of carbonyl group and instead exhibited stretching vibration bands of (NH) and (C=N) groups. ^{1}H NMR spectrum of compound **6d** as an example showed triplet and quartet signals at δ 1.30, 3.55 confirming the presence of an ethyl group in the product,



SCHEME 3

also singlet signal for NH proton at δ 5.80 ppm and the multiplet signal for aromatic protons at δ 7.20–8.30.

Treatment of compounds **4a–d** with ethyl bromoacetate in the presence of anhydrous sodium acetate, furnished the (*Z*) – *N*′-(3-

substituted thiazolidin-4-oxo-2-ylidene) quinoline-2-carbohydrazides **7a–d**. The structures of compounds **7a–d** were confirmed by elemental analyses and spectroscopic methods e.g. IR, ^{1}H NMR, and ^{13}C NMR spectra. IR spectra of compounds **7a–d** showed strong absorption bands at 1722–1703 cm^{-1} characteristic for the carbonyl group of thiazolidinone ring, which provided firm support for ring closure. The ^{1}H NMR spectrum of **7a** showed two types of signals, the two singlet signals at δ 4.26, 10.95 corresponding to protons of methylene group and proton of (NH) group respectively and the other type was multiplet signal characteristic for aromatic protons at δ 7.37–7.58. The lack of (C—S) stretching band at 1234 cm^{-1}as well as, the presence of amidic NH and absence of two singlet thiourea (NH) at 9.80 ppm confirm clearly the expected reaction between thiourea fragment and α-haloesters.

Meanwhile, treatment of compounds **4a–d** with α-bromopropionic acid gave (*Z*) – *N*′-(3-substituted thiazolidin-5-methyl-4-oxo-2-ylidene) quinoline-2-carbohydrazides **8a–d**. The structures of compounds **8a–d** were compatible with their elemental analyses and spectral data. ^{1}H NMR spectrum of compound **8a–d** showed clearly the quartet thiazolidinone CH proton in the region δ 4.23–4.53 whereas the doublet signal for CH_3 group was appeared in the region δ1.63–1.75. Also, the presence of only one singlet amidic signal for (NH) at δ 10.30–10.70 and lack thiourea protons in addition to (—N=C—S—CH) signal confirm the expected product in the form of carbonyl hydrazone thiazolidinone form.

On the other hand, treatment of substituted thiosemicarbazides **4a–d** with chloroacetone in the presence of anhydrous sodium acetate, furnished the corresponding (*Z*)-*N*′-(4-methyl-3-substituted-thiazol-2(3*H*)-ylidene) quinoline-2-carbohydrazides **9a–d**. The structure of compounds **9a–d** was in an agreement with their elemental analyses and spectral data. The ^{1}H NMR spectra of compounds **9a–d** revealed clearly the presence of singlet peak corresponding to methyl group, which confirm thiazole ring closure. For example, the ^{1}H NMR spectrum of compound **9d** showed the presence of the characteristic thiazole CH signal at δ 5.65 which corresponding to olefinic proton, beside one singlet signal at δ 2.10 for methyl group, also the triplet and quartet signals for ethyl group at δ 1.30 and 3.90.

Several procedures were reported for the dehydrative cyclization of substituted thiosemicarbazides to their 1, 3, 4-thiadiazole analogous utilizing a variety of dehydrating agents, e.g., sulfuric acid, phosphorus oxychloride or polyphosphoric acid. Accordingly, treatment of substituted thiosemicarbazides **4a–e** with phosphorus oxychloride yielded *N*-substituted-5-(quinolin-2-yl)-1,3,4-thiadiazol-2-amines **10a–e**. The structures of compounds **10a–e** were confirmed by elemental analyses and spectroscopic methods. For example, ^{1}H NMR

spectrum of compound **10b** showed in addition to the expected agreeable quinoline protons 7.29–8.46 ppm, also the absence of the characteristic amidic and thiourea NH protons at δ 10.60, 9.60, and 8.46, instead presence of one singlet amine (NH) at δ 8.67.

BIOLOGICAL STUDIES

Antimicrobial Activity

The antimicrobial activity of the newly synthesized compounds were tested and evaluated against gram positive bacteria (*Staphylococcus aureus*), gram negative bacteria (*Escherichia coli*) and yeast (*Candida*), and compared with respect to some reference antibiotics (Tetracycline and Ketoconazole). The obtained results are listed in Table III and Figures (1–7).

All microbial were affected by the tested chemical compound derivatives. Their activities varied according to structure of compounds and microbial strains; if compared with the reference antibiotics (Tetracycline and Ketoconazole).

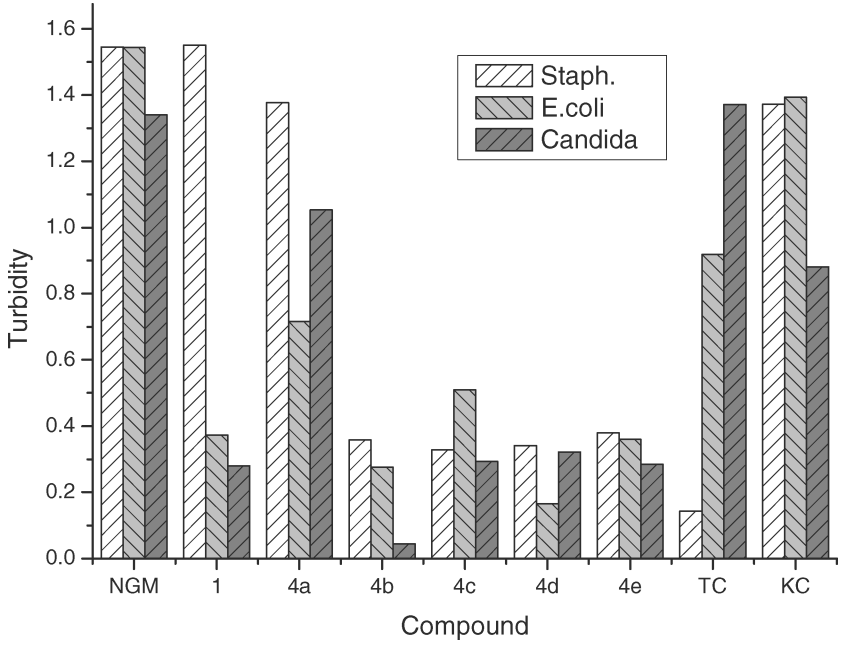


Figure 1 Antimicrobial activity of quinaldic acid **1** and compounds **4a–e** against the microbial strains, tetracycline (TC), and ketoconazole (KC).

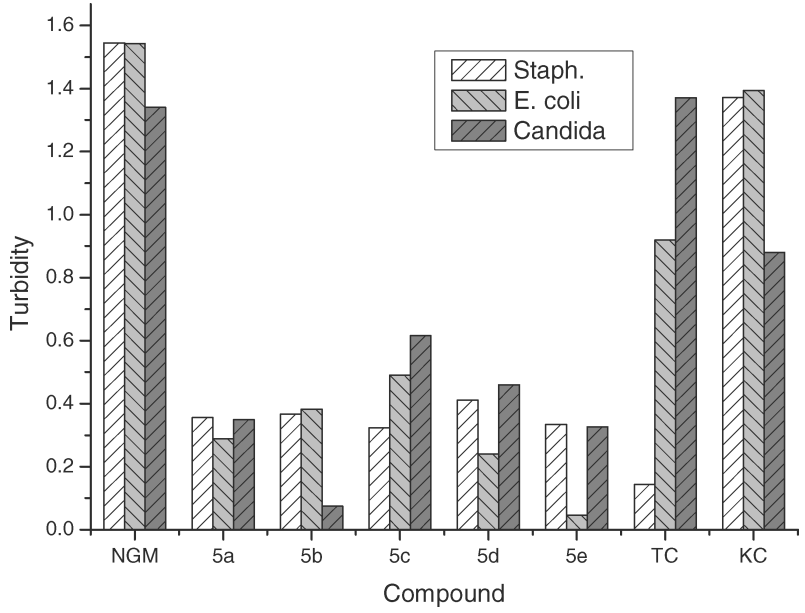


Figure 2 Antimicrobial activity of compounds **5a–e** against the microbial strains, tetracycline (TC), and ketoconazole (KC).

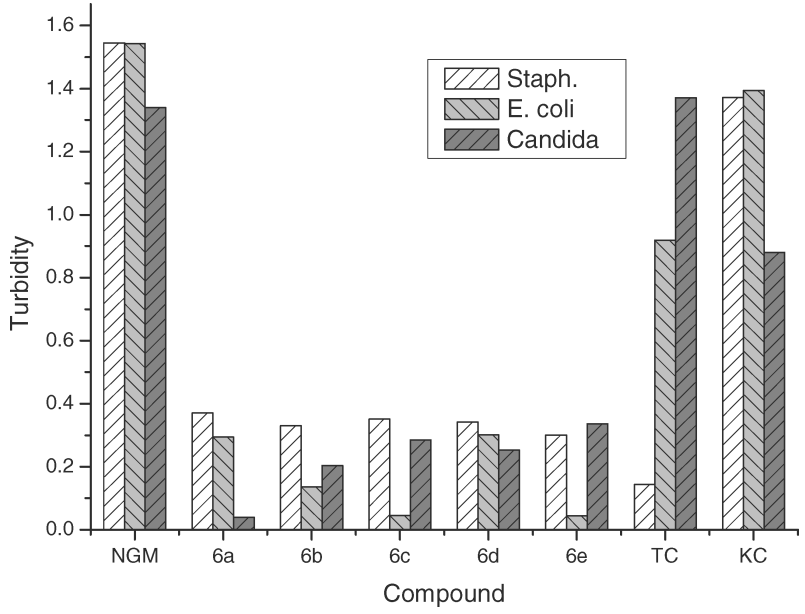


Figure 3 Antimicrobial activity of compounds **6a–e** against the microbial strains, tetracycline (TC), and ketoconazole (KC).

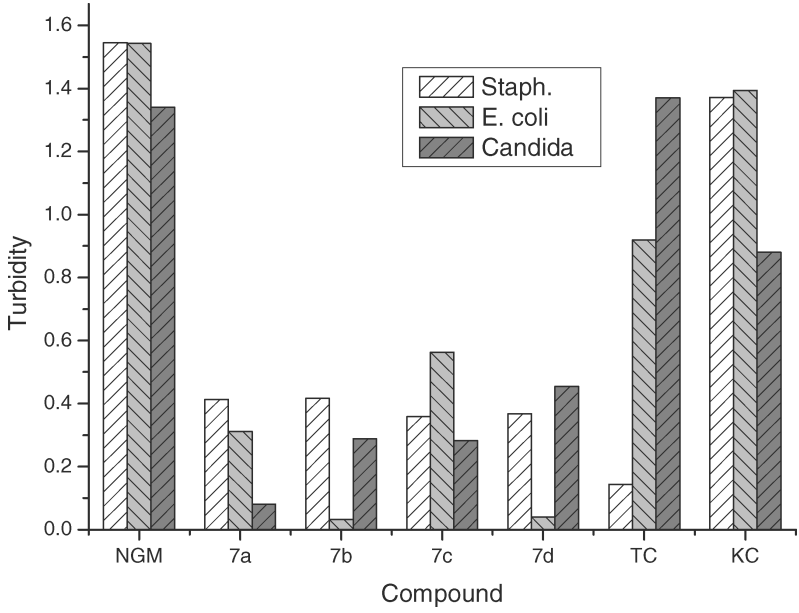


Figure 4 Antimicrobial activity of compounds **7a–d** against the microbial strains, tetracycline (TC), and ketoconazole (KC).

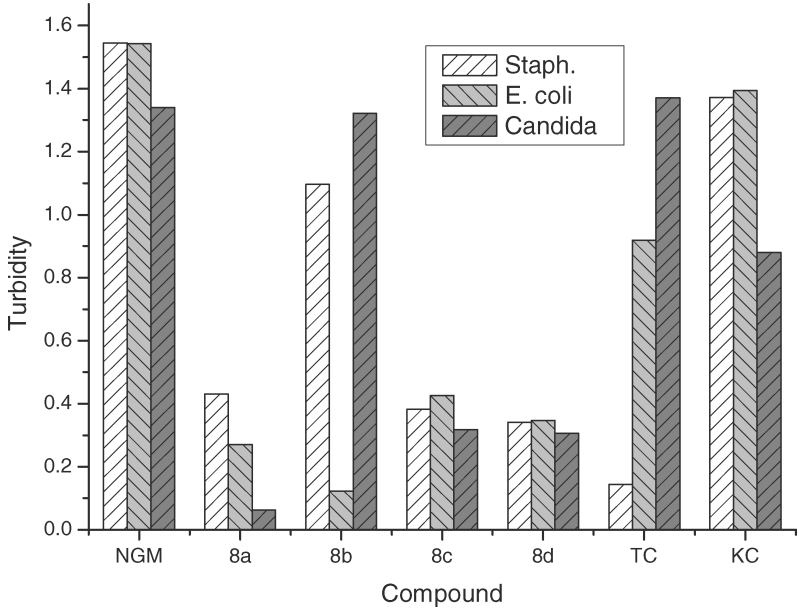


Figure 5 Antimicrobial activity of compounds **8a–d** against the microbial strains, tetracycline (TC), and ketoconazole (KC).

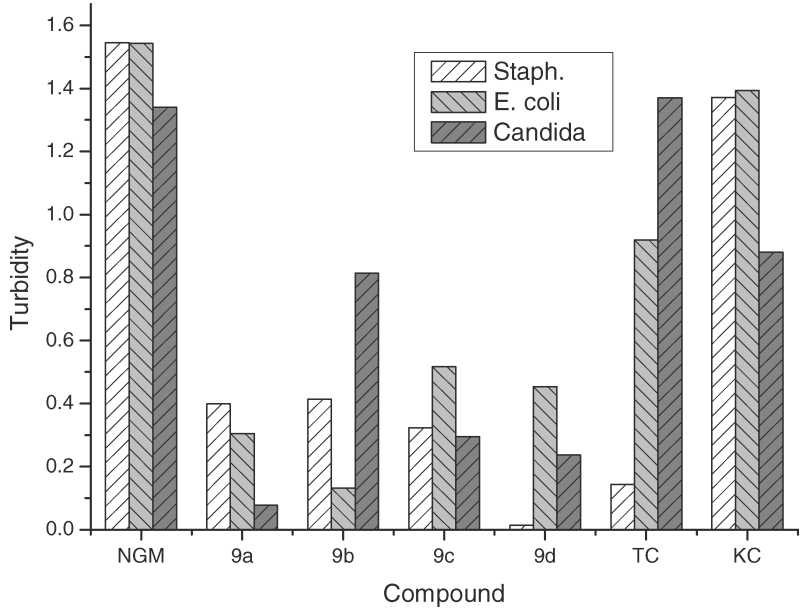


Figure 6 Antimicrobial activity of compounds **9a–d** against the microbial strains, tetracycline (TC), and ketoconazole (KC).

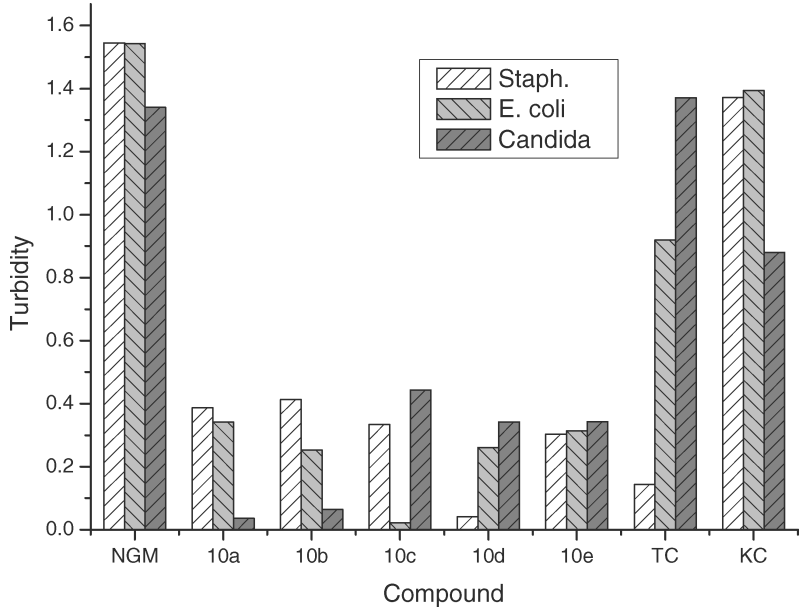


Figure 7 Antimicrobial activity of compounds **10a–e** against the microbial strains, tetracycline (TC), and ketoconazole (KC).

Concerning the antimicrobial activity against quinaldic acid and its derivatives, e.g., thiosemicarbazides and heterocyclic rings attached to quinoline moiety, it was evident that the quinaldic acid (**1**) did not show any effect against bacterial strains *Staphylococcus aurous*, while showed moderate activities against the other strains (*Escherichia coli* and *Candida*). The antimicrobial activity of compounds **4a–e** revealed that the compound **4d** showed the most potent activity against *E.coli*, while the compound **4b** is considered the best derivative against microbial strains *Staph., E.coli,* and*Candida*. These results indicated that these compounds might be interfering with the growth or metabolism of these microbial strains due to presence of the peptide group of the molecule. Moreover, the antimicrobial activity of compounds**4a–e** varies according to nature of the *N*-substituent on the thiouridyl moiety.

The antimicrobial activity of compounds **5a–e** showed that the activity against all used microbial strains increased in order: **5c** < **5b** < **5e**.

On the other hand, antimicrobial activity of compounds **6a–e** indicated that the compound **6e** showed the most potent activity against the used microbial strains *Staph.*, *E. coli*, while the compound **6a** exhibited the potent activity against *Candida*.

However, compounds **7a–d** exhibited antimicrobial activities against the strains *Staph.*, *E.coli*, and *Candida*; the derivative, which showed the least activity, was compound **7c**, while the most potent activity was obtained by derivative **7b**. The activity of compounds may be attributed to presence of the peptide group and the thiazolidinone ring. Compounds **8a–d**, which resembles the derivatives **7a–d** in structures, showed a different behavior where the antimicrobial activity against all the three microbial strains increased in order: **8d**< **8b** <**8a**.

The antimicrobial activity of compounds **9a–d** which also contain peptide group and thiazole ring against the three microbial strains *Staph., E.coli,* and *Candida* were decreased in order **9d** > **9a** > **9b**.

The last derivatives **10a–e** showed good effects and the activities of them increased in order: **10d** < **10a** < **10c**.

EXPERIMENTAL

Melting points are uncorrected. Elemental analyses were carried out in the Microanalytical Unit of the Faculty of Science, Cairo University. IR spectra were recorded on a Mattson 5000 FTIR spectrometer. ^{1}H NMR spectra were taken on a Jeol-Ex-270 MHz and Varian-Vx-300 MHz NMR spectrometer using TMS as an internal standard with

($\delta = 0$ ppm). ^{13}C NMR spectra were taken on Bruker WP 300 using TMS as an internal standard with ($\delta = 0$ ppm). The purity of the synthesized compounds was tested by thin-layer chromatography (TLC). The physical and spectral data of the newly compounds are listed in Tables I and II.

1-(Quinolin-2-yl-carbonyl)-4-substituted thiosemicarbazides (4a–e)—General Procedure

To a suspension of quinoline-2-carbohydrazide **3** (0.01 mol, 1.87 g) in dioxane (20 ml), the appropriate isothiocyanate (0.01 mol) was added. The reaction mixture was heated at 80°C with stirring for 2 h and left over night at room temperature. The solid so obtained was filtered off, dried, and crystallized from the proper solvent to give compounds **4a–e**.

4-Substituted-5-(quinolin-2-yl)-2*H*-1, 2, 4-triazole-3(4*H*)-thiones (5a–e)—General Procedure

A suspension of the appropriate thiosemicarbazide derivatives **4a–e** (0.01 mol) in sodium hydroxide (15 ml, 2 N) was refluxed under stirring for 10 h. The reaction mixture was neutralized with dilute hydrochloric acid after cooling. The precipitate obtained was filtered off, washed well with water, dried, and crystallized from the proper solvent to give compounds **5a–e**.

N-Substituted-5-(quinolin-2-yl)-1, 3, 4-oxadiazol- 2-amines (6a–e)—General Procedure

A mixture of the appropriate thiosemicarbazides **4a–e** (0.01 mol) and excess yellow mercuric oxide (0.015 mol) in ethanol (30 ml) was refluxed for 4–6 h. The reaction mixture was allowed to cool to room temperature (to allow the sedimentation of the black mercuric sulfide), was filtered and the mercuric sulfide was washed with ethanol. The filtrate and alcoholic washing were combined, treated with water until a permanent turbidity existed, and allowed to stand overnight. The product was separated, filtered off, dried, and crystallized from the proper solvent to give compounds **6a–e**.

TABLE I The Physical and Analytical Data of the Newly Synthesized Compounds

Compd. no.	m.p. °C (Yield %)	Color solvent of cryst.	Formula (mol. wt.)	Analysis calcd./found (%)			
				C	H	N	S
4a	178–180	Yellow	$C_{17}H_{14}N_4OS$	63.33	4.38	17.38	9.95
	(98)	Ethanol	(322.39)	63.50	4.50	17.20	9.80
4b	180–182	Yellow	$C_{18}H_{16}N_4OS$	64.26	4.79	16.65	9.53
	(90)	Ethanol	(336.41)	64.40	4.90	16.60	9.40
4c	198–200	Pale yellow	$C_{14}H_{14}N_4OS$	58.72	4.93	19.57	11.20
	(85)	Dioxane	(286.35)	58.60	4.80	19.50	11.25
4d	214–216	Pale brown	$C_{13}H_{14}N_4OS$	56.91	5.14	20.42	11.69
	(67)	Methanol	(274.34)	56.80	5.22	20.45	11.60
4e	206–208	Yellow	$C_{17}H_{20}N_4OS$	62.17	6.14	17.06	9.76
	(80)	Ethanol	(328.43)	62.30	6.00	17.01	9.70
5a	286–288	Pale brown	$C_{17}H_{12}N_4S$	67.08	3.97	18.41	10.53
	(70)	Ethanol	(304.37)	67.00	3.90	18.50	10.58
5b	284–286	Pale brown	$C_{18}H_{14}N_4S$	67.90	4.43	17.60	10.07
	(69)	Ethanol	(318.40)	68.00	4.50	17.70	10.04
5c	214–216	Yellow	$C_{14}H_{12}N_4S$	62.66	4.51	20.88	11.95
	(65)	Chloroform	(268.34)	62.51	4.60	20.80	12.00
5d	232–234	Yellow	$C_{13}H_{12}N_4S$	60.91	4.72	21.86	12.51
	(70)	Chloroform	(256.33)	60.80	4.80	21.90	12.55
5e	210–212	Pale Yellow	$C_{17}H_{18}N_4S$	65.78	5.84	18.05	10.33
	(68)	Acetone	(310.42)	65.90	5.70	18.00	10.40
6a	242–244	Colorless	$C_{17}H_{12}N_4O$	70.82	4.20	19.43	—
	(65)	Ethanol	(228.30)	70.70	4.30	19.50	—
6b	230–232	Pale Yellow	$C_{18}H_{14}N_4O$	71.51	4.69	18.53	—
	(60)	Ethanol	(302.33)	71.40	4.60	18.60	—
6c	154–156	Gray	$C_{14}H_{12}N_4O$	66.65	4.79	22.21	—
	(59)	Ethanol	(252.27)	66.50	4.90	22.25	—
6d	174–176	Gray	$C_{13}H_{12}N_4O$	64.99	5.03	23.32	—
	(58)	Acetone	(240.26)	65.20	5.10	23.40	—
6e	206–208	Colorless	$C_{17}H_{18}N_4O$	69.37	6.16	19.03	—
	(62)	Ethanol	(294.35)	69.50	6.20	19.00	—
7a	188–190	Yellow	$C_{19}H_{14}N_4O_2S$	62.97	3.89	15.46	8.85
	(85)	Ethanol	(362.41)	63.20	4.00	15.50	8.80
7b	208–210	Yellow	$C_{20}H_{16}N_4O_2S$	63.81	4.28	14.88	8.52
	(80)	Chloroform	(376.43)	64.00	4.40	14.80	8.60
7c	120–122	Yellow	$C_{16}H_{14}N_4O_2S$	58.88	4.32	17.17	9.82
	(75)	Ethanol	(326.37)	59.00	4.20	17.25	9.90
7d	166–168	Yellow	$C_{15}H_{14}N_4O_2S$	57.31	4.49	17.82	10.20
	(80)	Ethanol	(314.36)	57.20	4.60	17.90	10.25
8a	228–230	Pale Yellow	$C_{20}H_{16}N_4O_2S$	63.81	4.28	14.88	8.52
	(85)	Ethanol	(376.43)	63.70	4.40	14.80	8.45
8b	210–212	Colorless	$C_{21}H_{18}N_4O_2S$	64.60	4.65	14.35	8.21
	(83)	Acetone	(390.46)	64.74	4.70	14.38	8.25
8c	128–130	Pale yellow	$C_{17}H_{16}N_4O_2S$	59.98	4.74	16.46	9.42
	(80)	Ethanol	(340.40)	60.12	4.60	16.40	9.39

TABLE I The Physical and Analytical Data of the Newly Synthesized Compounds (Continued.)

Compd. no.	m.p. °C (Yield %)	Color solvent of cryst.	Formula (mol. wt.)	Analysis calcd./found (%)			
				C	H	N	S
8d	194–196	Buff	$C_{16}H_{16}N_4O_2S$	58.52	4.91	17.06	9.76
	(82)	Ethanol	(328.39	58.40	5.00	17.00	9.80
9a	136–138	Buff	$C_{20}H_{16}N_4OS$	66.65	4.47	15.54	8.90
	(84)	Acetone	(360.43)	66.52	4.60	15.60	8.95
9b	148–150	Olive	$C_{21}H_{18}N_4OS$	67.36	4.84	14.96	8.56
	(87)	Ethanol	(374.46)	67.41	4.70	15.00	8.60
9c	170–172	Pale brown	$C_{17}H_{16}N_4OS$	62.94	4.97	17.27	9.88
	(85)	Ethanol	(324.40)	63.00	5.20	17.30	9.92
9d	168–170	Yellow	$C_{16}H_{16}N_4OS$	61.52	5.16	17.93	10.26
	(82)	Ethanol	(312.39)	61.60	5.40	18.00	10.30
10a	292–294	Yellow	$C_{17}H_{12}N_4S$	67.08	3.97	18.41	10.53
	(67)	Ethanol	(304.37)	67.20	4.12	18.5	10.50
10b	220–222	Pale brown	$C_{18}H_{14}N_4S$	67.90	4.43	17.60	10.07
	(64)	Acetone	(318.40)	67.95	4.40	17.70	10.13
10c	198–200	Yellow	$C_{14}H_{12}N_4S$	62.66	4.51	20.88	11.95
	(66)	Ethanol	(268.34)	62.72	4.40	20.80	11.99
10d	226–228	Pale yellow	$C_{13}H_{12}N_4S$	60.91	4.72	21.86	12.51
	(65)	Ethanol	(256.33)	60.98	4.76	21.77	12.55
10e	186–188	Pale yellow	$C_{17}H_{18}N_4S$	65.78	5.84	18.05	10.33
	(63)	Chloroform	(310.42)	65.83	5.90	18.00	10.40

(*Z*)-*N*′-(3-Substituted thiazolidin-4-oxo-2-ylidene) quinoline-2-carbohydrazides (7a–d)—General Procedure

A mixture of the appropriate thiosemicarbazide derivatives **4a–d** (0.01 mol), ethyl bromoacetate (0.01 mol), and anhydrous sodium acetate (0.015 mol) in absolute ethanol (25 ml) was refluxed for 3 h. The reaction mixture was diluted with water after cooling and allowed to stand overnight, the solid obtained was filtered off, dried, and crystallized from the proper solvent to give compounds **7a–d**.

(*Z*)-*N*′-(3-Substituted thiazolidin-5-methyl-4-oxo-2-ylidene) quinoline-2-carbohydrazides (8a–d)—General Procedure

A mixture of the appropriate thiosemicarbazide derivatives **4a–d** (0.01 mol), α-bromopropionic acid (0.01 mol), and anhydrous sodium acetate (0.015 mol) in absolute ethanol (25 ml) was refluxed for 3 h. The reaction mixture was diluted with water after cooling and allowed to stand

TABLE II The Spectral Data of the Newly Synthesized Compounds

Compd. no.	IR (ν, cm^{-1})	^1H NMR (δ, ppm)	^{13}C NMR (δ, ppm)
4a	3253 (NH amidic), 3121 (NHCS), 1659 (C═O), 1234 (C═S)	(DMSO-d_6): 7.12–8.60 (m,11H, Ar-H), 9.80 (br.s, 2H, 2NH thiourea), 10.85 (br.s,1H, NH carboxamide)	—
4b	3288 (NH amidic), 3159 (NHCS), 2984, 2932 (CH aliph), 1691 (C═O), 1236 (C═S)	(DMSO-d_6): 4.80 (d, 2H, CH_2), 7.15–8.30 (m, 10H, Ar-H), 8.46 (m, 2H, H-4quinoline, NH thiourea), 9.60 (br.s, 1H, NH thiourea), 10.60 (br.s, 1H, NH carboxamide)	($CDCl_3$/DMSO-d_6): 46.9, 118.5, 126.4, 126.9, 127.7, 128.7, 129.1, 129.9, 137.3, 138.7, 145.8, 148.7, 162.9, 182.0
4c	3270 (NH amidic), 3165 (NHCS), 2983, 2933 (CH aliph), 1692 (C═O),1240 (C═S)	($CDCl_3$): 4.32 (t, 2H, CH_2 allyl), 5.21 (dd, 2H, CH_2 olefinic), 5.91 (m, 1H, CH═ olefinic), 6.75 (br.s, 1H, NH thiourea),7.67–7.90 (m, 3H, Ar-H), 8.15 (br.s, 1H, NH thiourea), 8.20–8.34 (m, 2H, Ar-H), 8.37 (d,1H, H- 4 quinoline), 10.05(br.s, 1H, NH carboxamide)	—
4d	3213 (NH amidic), 3149 (NHCS), 2968, 2925 (CH aliph), 1677 (C═O),1241 (C═S)	($CDCl_3$/DMSO-d_6): 1.20 (t, 3H, $CH_2\underline{CH_3}$), 3.60 (q, 2H, $\underline{CH_2}CH_3$), 7.60–8.25 (m, 6H, Ar-H), 8.40 (m, 1H, NH thiourea), 9.50 (s, 1H, NH thiourea), 10.50 (br. s, 1H, NH carboxamide)	($CDCl_3$/DMSO-d_6): 13.9, 40.3, 118.2, 127.7, 128.7, 129.1, 129.9, 137.1, 145.8, 148.3, 180.9
4e	3235 (NH amidic), 3109 (NHCS), 2930, 2850 (CH aliph), 1661 (C═O),1265 (C═S)	($CDCl_3$): 1.12–1.75 (m, 10 H, cyclohexyl), 4.26 (m, 1H, cyclohexyl), 6.86 (d, 1H, NH cyclohexyl), 7.62–8.32 (m, 6H, Ar-H.), 8.99 (br. s, 1H, NH thiourea), 10.52 (br. s, 1H, NH carboxamide)	—
5a	3142(NH), 1619 (C═N) , 1270 (C═S)	($CDCl_3$/DMSO-d_6): 7.20–8.40 (m, 11H, Ar-H), 14.20 (br.s, 1H, SH)	—

5b	3159(NH), 2959, 2818 (CH aliph), 1620 (C═N) , 1277 (C═S)	($CDCl_3$/DMSO-d_6): 6.10 (s, 2H, CH_2), 7.00–8.20 (m,11H, Ar-H), 14.05 (s, 1H, SH)	($CDCl_3$/DMSO-d_6): 46.8, 118.1, 125.7, 125.9, 126.4, 126.9, 127.8, 128.9, 135.7, 144.4, 145.2, 147.1, 168.4
5c	3172(NH), 2982, 2954 (CH aliph), 1613 (C═N) , 1284 (C═S)	(DMSO-d_6): 5.07- 5.13 (m, 2H, CH_2 allyl), 5.41 (dd, 2H, CH_2 olefinic) 5.98 (m, 1H, CH═ olefinic), 7.68 - 8.58 (m, 6H, Ar-H), 14.21 (br.s, 1H, SH)	—
5d	3113 (NH), 2962, 2942 (CH aliph), 1614 (C═N), 1280 (C═S)	(DMSO-d_6): 0.90 (t, 3H, $CH_2\underline{CH_3}$), 4.20 (q, 2H, $\underline{CH_2}CH_3$), 7.60–8.50 (m, 6H, Ar-H), 14.00 (br.s,1H, SH)	—
5e	3164 (NH), 2970, 2935 (CH aliph), 1618 (C═N), 1285 (C═S)	($CDCl_3$): 1.30–1.80 (m, 10H, cyclohexyl), 5.33 (m,1H, cyclohexyl), 7.58–8.90 (m,6H, Ar-H), 14.15 (br.s,1H, SH)	—
6a	3225 (NH), 1619 (C═N)	($CDCl_3$/DMSO-d_6): 7.00–8.40 (m,11H, Ar-H), 10.70 (br.s, 1H, NH)	—
6b	3216 (NH), 2982, 2913 (CH aliph), 1612 (C═N)	($CDCl_3$/DMSO-d_6): 4.50 (d, 2H, CH_2), 7.00–8.50 (m,12H, Ar-H, NH)	—
6c	3230 (NH), 2890 (CH aliph) , 1613 (C═N)	($CDCl_3$): 4.12–4.16 (m, 2H, CH_2allyl), 5.28 (dd, 2H, CH_2 olefinic), 5.99 (m, 1H, CH═ olefinic), 7.57–8.25 (m,7H, Ar-H, NH)	—
6d	3218 (NH), 2973, 2876 (CH aliph), 1621 (C═N)	($CDCl_3$): 1.30 (t, 3H,$CH_2\underline{CH_3}$), 3.55 (q, 2H, $\underline{CH_2}CH_3$), 5.80 (br.s, 1H, NH), 7.20–8.30 (m,6H, Ar-H)	($CDCl_3$): 17.9, 38.5, 118.9, 127.6, 128.2, 129.5, 137.0, 143.7, 147.6, 158.5, 164.2

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The Spectral Data of the Newly Synthesized Compounds *(Continued.)*

Compd. no.	IR (ν, cm^{-1})	^1H NMR (δ, ppm)	^{13}C NMR (δ, ppm)
6e	3248 (NH), 2929, 2854 (CH aliph), 1620 (C═N)	($CDCl_3$): 1.24–1.75 (m, 10H, cyclohexyl), 3.78 (m, 1H, cyclohexyl), 4.91 (d, 1H, NH), 7.56–8.24 (m, 6H, Ar-H)	—
7a	3298 (NH), 2983, 2953 (CH aliph), 1722, 1699 (C═O), 1620 (C═N)	(DMSO-d_6): 4.26 (s, 2H, CH_2 thiazolidinone ring), 7.37–8.59 (m,11H, Ar-H), 10.95 (br.s,1H, NH)	—
7b	3280 (NH), 2970, 2955 (CH aliph), 1705 (broad C═O), 1619 (C═N)	($CDCl_3$): 3.95 (s, 2H, CH_2 thiazolidinone ring), 5.00 (s, 2H, CH_2), 7.20 - 8.35 (m,11H, Ar-H), 10.35 (br.s,1H, NH)	($CDCl_3$): 32.9, 46.6, 118.8, 127.8, 128.520, 129.4, 130.3, 135.7, 137.7, 146.3, 149.0, 155.5, 160.2, 170.4
7c	3274 (NH), 2930(CH aliph), 1703 (broad C═O), 1614 (C═N)	($CDCl_3$): 3.95 (s, 2H, CH_2 thiazolidinone ring), 4.51 (t, 2H, CH_2allyl), 5.33 (dd, 2H, CH_2 olefinic), 5.97 (m, 1H, CH═ olefinic), 7.61–8.33 (m, 6H, Ar-H,), 10.34 (br.s,1H, NH)	—
7d	3265 (NH), 2950(CH aliph) 1706, 1680 (C═O), 1621(C═N)	($CDCl_3$): 1.30 (t, 3H,$CH_2\underline{CH_3}$), 3.90(q, 2H, $\underline{CH_2}CH_3$), 4.00 (s, 2H, CH_2 thiazolidinone ring), 7.20–8.30 (m, 6H, Ar-H), 10.30 (br.s,1H, NH)	($CDCl_3$): 12.4, 33.1, 38.7, 118.8, 127.7, 128.1, 129.4, 130.2, 137.7, 146.3, 149.1, 155.8, 160.2, 170.3
8a	3280 (NH), 2990 (CH aliph), 1718, 1697 (C═O), 1617 (C═N)	($CDCl_3$): 1.75 (d, 3H, CH_3), 4.35(q, 1H, methine proton of thiazolidinone ring), 7.00–8.30 (m,11H, Ar-H), 10.30 (br.s,1H, NH)	($CDCl_3$/DMSO-d_6): 19.5, 43.0, 118.8, 127.7, 128.2, 129.1, 129.7, 130.4, 132.4, 137.7, 146.3, 149.0, 157.6, 160.1, 174.2

8b	3261 (NH), 2970, 2910 (CH aliph), 1700 (broad C=O), 1610 (C=N)	($CDCl_3$): 1.63 (d, 3H, CH_3), 4.53 (q, 1H, methine proton of thiazolidinone ring), 5.05 (s, 2H, CH_2), 7.20–8.60 (m,11H, Ar-H), 10.70 (br.s,1H, NH)	($DMSO\text{-}d_6$): 18.8, 42.6, 45.6, 118.3, 127.3, 127.8, 128.3, 128.8, 129.4, 130.2, 135.6, 137.8, 145.8, 149.1, 159.7, 174.7
8c	3217 (NH), 2929(CH aliph), 1703 (broad C=O), 1615(C=N)	($CDCl_3$): 1.72 (d, 3H, CH_3), 4.23 (q, 1H, methine proton of thiazolidinone ring), 4.51 (t, 2H, CH_2 allyl), 5.32 (dd, 2H, CH_2 olefinic), 6.35 (m, 1H, CH= olefinic), 7.61–8.33 (m, 6H, Ar-H), 10.30 (br.s,1H, NH)	—
8d	3267 (NH), 2926(CH aliph), 1707 (broad C=O), 1616(C=N)	($CDCl_3/CF_3COOH$): 1.30 (t, 3H, $CH_2\underline{CH_3}$), 1.70 (d, 3H, CH_3), 3.85 (q, 2H, $\underline{CH_2}CH_3$), 4.25 (q, 1H, methine proton of thiazolidinone ring), 7.70–8.80 (m, 7H, Ar-H, NH)	—
9a	3353 (NH), 2919(CH aliph), 1696 (C=O) 1619 (C=N)	($CDCl_3$): 1.70 (s, 3H, CH_3), 5.60 (s, 1H, CH= proton of thiazole ring), 7.00–8.15 (m,12H, Ar-H, NH)	($CDCl_3$): 13.1, 91.2, 118.4, 121.7, 123.7, 127.3, 128.4, 129.3, 130.0, 130.5, 135.9, 136.5, 146.3, 147.8, 164.1
9b	3364 (NH), 2926 (CH aliph), 1687 (C=O), 1609 (C=N)	($CDCl_3$): 2.00 (s, 3H, CH_3), 5.20 (s, 2H, CH_2), 5.70 (s, 1H, CH= proton of thiazole ring),7.20–8.30 (m,11H, Ar-H), 10.05 (br.s,1H, NH)	($CDCl_3$): 14.4, 47.6, 93.9, 118.9, 126.7, 127.7, 128.7, 129.2, 129.7, 131.1, 136.3, 136.8, 137.3, 146.4, 149.9, 159.9, 166.8

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The Spectral Data of the Newly Synthesized Compounds *(Continued.)*

Compd. no.	IR (ν, cm^{-1})	^1H NMR (δ, ppm)	^{13}C NMR (δ, ppm)
9c	3278(NH), 2995(CH aliph), 1673 (C═O), 1608 (C═N)	($CDCl_3$): 2.12 (s, 3H, CH_3), 4.57 (t, 2H, CH_2 allyl), 5.19 (dd, 2H, CH_2 olefinic), 5.65 (s, 1H, CH═ proton of thiazole ring), 5.99 (m, 1H, CH═ olefinic), 7.57–8.35 (m, 6H, Ar-H), 10.03 (br.s,1H, NH)	—
9d	3362 (NH), 2952(CH aliph), 1677 (C═O), 1604 (C═N)	($CDCl_3$): 1.30 (t, 3H,$CH_2\underline{CH_3}$), 2.10 (s, 3H, CH_3), 3.90 (q, 2H, $\underline{CH_2}$ CH_3), 5.65 (s, 1H, CH═ proton of thiazole ring), 7.50–8.40 (m, 6H, Ar-H), 10.20 (br.s,1H, NH)	($CDCl_3$): 13.2, 13.9, 39.4, 93.3, 118.7, 127.5, 129.0, 129.5, 130.1, 135.7, 137.2, 146.2, 149.9, 159.7, 165.5
10a	3248 (NH), 1610 (C═N)	(DMSO-d_6): 7.04–8.53 (m,11H, Ar-H), 10.65 (br.s,1H, NH)	—
10b	3191(NH), 2953, 2927 (CH aliph), 1612 (C═N)	(DMSO-d_6): 4.59 (d, 2H, CH_2), 7.29–8.46 (m,11H, Ar-H), 8.67 (br.s,1H, NH)	—
10c	3220 (NH), 2934, 2895 (CH aliph), 1613 (C═N)	($CDCl_3$): 4.03 (t, 2H, CH_2 allyl), 5.27 (dd, 2H, CH_2 olefinic), 5.95 (m, 1H, CH═ olefinic), 7.06–8.46 (m, 6H, Ar-H), 8.6 (br.s, 1H, NH)	—
10d	3223 (NH), 2974, 2881 (CH aliph), 1609 (C═N)	(DMSO-d_6): 1.23 (t, 3H,$CH_2\underline{CH_3}$), 3.44 (q, 2H, $\underline{CH_2}CH_3$), 7.60–8.46 (m,7H, Ar-H, NH)	—
10e	3181 (NH), 2928, 2853 (CH aliph), 1600 (C═N)	($CDCl_3$): 1.26 -1.79 (m, 10H, cyclohexyl), 3.45 (br.s,1H, cyclohexyl), 5.61 (br.s, 1H, NH), 7.51–8.31 (m, 6H, Ar-H)	—

TABLE III Antimicrobial Activity of Newly Synthesized Compounds

Compd.	*Staph.*	*E. coli*	*Candida*
NGM	1.545 ± 0.137	1.543 ± 0.064	1.341± 0.081
1	1.551 ± 0.109	0.372 ± 0.027	0.280 ± 0.086
4a	1.377 ± 0.039	0.716 ± 0.094	1.053 ± 0.271
4b	0.358 ± 0.051	0.276 ± 0.076	0.044 ± 0.014
4c	0.328 ± 0.086	0.51 ± 0.048	0.293 ± 0.055
4d	0.341 ± 0.003	0.166 ± 0.035	0.322 ± 0.089
4e	0.379 ± 0.083	0.360 ± 0.111	0.285 ± 0.050
5a	0.356 ± 0.053	0.289 ± 0.070	0.344 ± 0.052
5b	0.366 ± 0.046	0.382 ± 0.079	0.075 ± 0.029
5c	0.323 ± 0.088	0.49 ± 0.036	0.616 ± 0.129
5d	0.411 ± 0.003	0.241± 0.099	0.460 ± 0.132
5e	0.334 ± 0.085	0.046 ± 0.005	0.326 ± 0.022
6a	0.370 ± 0.043	0.294 ± 0.068	0.039 ± 0.015
6b	0.330 ± 0.072	0.136 ± 0.012	0.203 ± 0.123
6c	0.351 ± 0.082	0.045 ± 0.008	0.285 ± 0.050
6d	0.342 ± 0.083	0.302 ± 0.096	0.252 ± 0.057
6e	0.301 ± 0.096	0.044 ± 0.005	0.336 ± 0.050
7a	0.413 ± 0.031	0.311 ± 0.064	0.081 ± 0.034
7b	0.417 ± 0.031	0.032 ± 0.006	0.289 ± 0.099
7c	0.359 ± 0.082	0.563 ± 0.091	0.283 ± 0.052
7d	0.367 ± 0.082	0.04 ± 0.003	0.454 ± 0.162
8a	0.430 ± 0.036	0.27 ± 0.074	0.063 ± 0.021
8b	1.096 ± 0.270	0.123 ± 0.009	1.322 ± 0.089
8c	0.382 ± 0.084	0.425 ± 0.070	0.318 ± 0.026
8d	0.341 ± 0.083	0.347 ± 0.082	0.306 ± 0.058
9a	0.399 ± 0.031	0.305 ± 0.065	0.077 ± 0.031
9b	0.414 ± 0.031	0.132 ± 0.006	0.814 ± 0.200
9c	0.323 ± 0.088	0.517 ± 0.077	0.295 ± 0.042
9d	0.014 ± 0.003	0.453 ± 0.115	0.237 ± 0.064
10a	0.387 ± 0.034	0.342 ± 0.064	0.036 ± 0.016
10b	0.413 ± 0.031	0.252 ± 0.089	0.065 ± 0.022
10c	0.334 ± 0.085	0.022 ± 0.008	0.443 ± 0.149
10d	0.041 ± 0.003	0.260 ± 0.115	0.342 ± 0.087
10e	0.304 ± 0.095	0.313 ± 0.055	0.343 ± 0.020
Tetracycline (50 μg/ml)	0.143 ± 0.032	0.919 ± 0.123	1.371 ± 0.034
Ketoconazole(50 μg/ml)	1.372 ± 0.106	1.394 ± 0.091	0.881± 0.253

NGM means the value of normal growth of microbial.

overnight, the solid obtained was filtered off, dried, and crystallized from the proper solvent to give compounds **8a–d.**

(*Z*)-*N*-(4-Methyl-3-substituted-thiazol-2(3*H*)-ylidene)quinoline-2-carbohydrazides (9a–d)—General Procedure

A mixture of the appropriate thiosemicarbazide derivatives **4a–d** (0.01mol), chloroacetone (0.01mol), and anhydrous sodium acetate

(0.015 mol) in absolute ethanol (25 ml) was refluxed for 3 h. The reaction mixture was diluted with water after cooling and allowed to stand overnight, the solid obtained was filtered off, dried, and crystallized from the proper solvent to give compounds **9a–d.**

N-Substituted-5-(quinolin-2-yl)-1,3,4-thiadiazol-2-amines (10a–e)—General Procedure

Phosphorus oxychloride (15 ml) was added to the appropriate thiosemicarbazides **4a–e** (0.01 mol), and the mixture was refluxed for 2–4 h. The mixture was evaporated in *vacuo*, and the residue was washed with diluted ammonium hydroxide solution and water. The solid obtained was filtered off, dried, and crystallized from the proper solvent to give compounds **10a–e**.

Antimicrobial Activity

Microbial Strains

Staphylococcus *aureus, Escherichia coli, and Candida* were isolated and identified in the section of Microbiology and Immunology, Department of Parasitology and Animal Diseases, National Research Centre Egypt.

Antimicrobial Assay

The Antimicrobial activity of the synthesized compounds was determined by dissolving all tested compounds in dimethyl sulfoxide (DMSO). Suspensions of the aforementioned microbial strains were prepared and adjusted by comparison against 0.5 McFarland turbidity standard (5×10^7 organisms/ml) tubes. The suspensions were further diluted to obtain a final of 5×10^6 organisms/ml. All microbial strains were cultured on nutrient broths for further microbial propagation.[24] The nutrient broth was inoculated by the (20 μg/ml) broth of incubated microbial strains, then added (40 μg/ml) of each tested chemical compounds. The tubes were incubated at 37°C for 24 h. The growth of control microbial strains, as well as inhibition of the microbial growth due to chemical compounds, was measured by Spectrophotometric assay as a turbidity at 420 nm wavelength. The mean value of inhibition was calculated from triple reading in each test subtracted from the solvent control. Broad spectrum antibiotics (Tetracycline and Ketoconazole) were used as standard for inhibition of tested microbial.

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