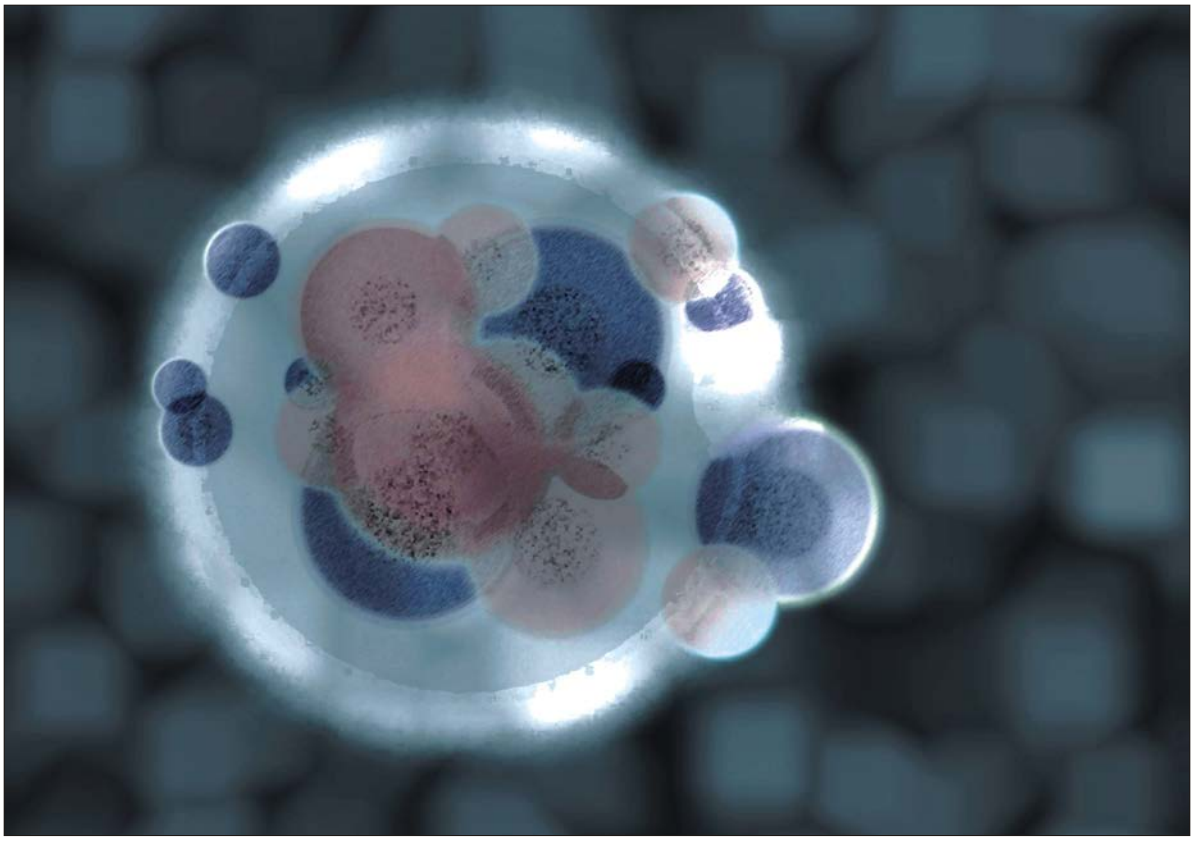

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New Quinazoline Related Derivatives with Antimicrobial Activity: Part II

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Abstract: A series of 2-(4-chlorophenyl)-6-iodoquinazoline carrying different acyclic or heterocyclic moieties were prepared and tested for their activity against certain strains of Gram negative bacteria, Gram positive bacteria and pathogenic Fungi. The results revealed that some of synthesized compounds displayed marked activity against some of the tested microorganisms

Key words: Synthesis, 6-Iodo-4(3*H*)quinazolin-4-one, antimicrobial activity

INTRODUCTION

The spread of antibiotic resistance among pathogenic bacteria has become a serious problem for the clinical management of infectious diseases and has resulted in a clear need for novel antibacterial agents other than analogs of existing antibiotics[1-5]. It was established that quinazolines and its derivatives have a strong and broad spectrum antimicrobial[6-10] and antifungal[11,12] activities. Furthermore, barbituric acid derivatives have been shown to interfere with nucleic acid biosynthesis[3]. In this study both moieties were gathered with or without oxygen bridge to detect, if the biological activity of these compounds will be enhanced or not through evaluation of the antibacterial activities of the produced compounds. In addition to the aforementioned derivatives, some other heterocyclic rings which add to the antimicrobial activity were linked to the quinazoline nucleus. The newly synthesized compounds were screened against certain strains of Gram negative bacteria, Gram positive bacteria and pathogenic Fungi.

MATERIALS AND METHODS

Interaction of 5-iodoanthranilic acid with 4-chlorobenzoylchloride in dimethylformamide yielded *N*-(4chlorobenzoyl)-5-iodoanthranilic acid (1), which was subsequently cyclized to the benzoxazine derivative (2) by heating with acetic anhydride. Condensation of (2) with formamide yielded the quinazoline derivative (3). The reaction of (3) with diethyl 2-bromomalonate yielded diethyl 2-[2-(4-chlorophenyl)-6-iodoquinazolin-4-yloxy]malonate (4). The reaction of (3) with a mixture of phosphorus oxychloride and phosphorus pentachloride yielded 2-(4-chlorophenyl)-4-chloro-6-iodoquinazoline (5). Refluxing (5) with diethyl malonate in ethanolic sodium ethoxide containing one drop 15-crown-5 yielded diethyl 2-[2-(4-chlorophenyl)-6-iodoquinazolin-4-yl]malonate (6). Condensation of (2) with hydroxylamine hydrochloride in dry pyridine yielded 2-(4-chlorophenyl)-3-hydroxy-6-iodo-4(3*H*)quinazolin-4-one (7), which was reacted with diethyl 2-bromomalonate to afford diethyl 2-[2-(4-chlorophenyl)-6-iodoquinazolin-3-yloxy]malonate (8). Reaction of compound 4, 6 and 8 with urea or thiourea in ethanolic sodium ethoxide yielded the corresponding cyclic derivatives 9(a, b), 10(a, b) and 11(a, b), respectively (scheme 1, Table 1 and 2).

The 4-chloro derivative (5) was reacted with sodium azide in acetic acid, ethyl anthranilate in pyridine and hydrazine hydrate in ethanol at room temperature to yield 5-(4-chlorophenyl)-9-iodo-1,2,3,4-tetrazolo-[1,5-c] quinazoline (12), 2-(4-chlorophenyl)-4-(2-ethoxy-carbonylphenylamino)-6-iodoquinazoline (13) and 2-(4-Chlorophenyl)-3-hydrazino-6-iodoquinazoline (14), respectively. The 4-hydrazino derivative (14) was allowed to react with some acid anhydrides to obtain the corresponding imido derivatives 15, 16 and 17 (scheme 2, Table 3 and 4).

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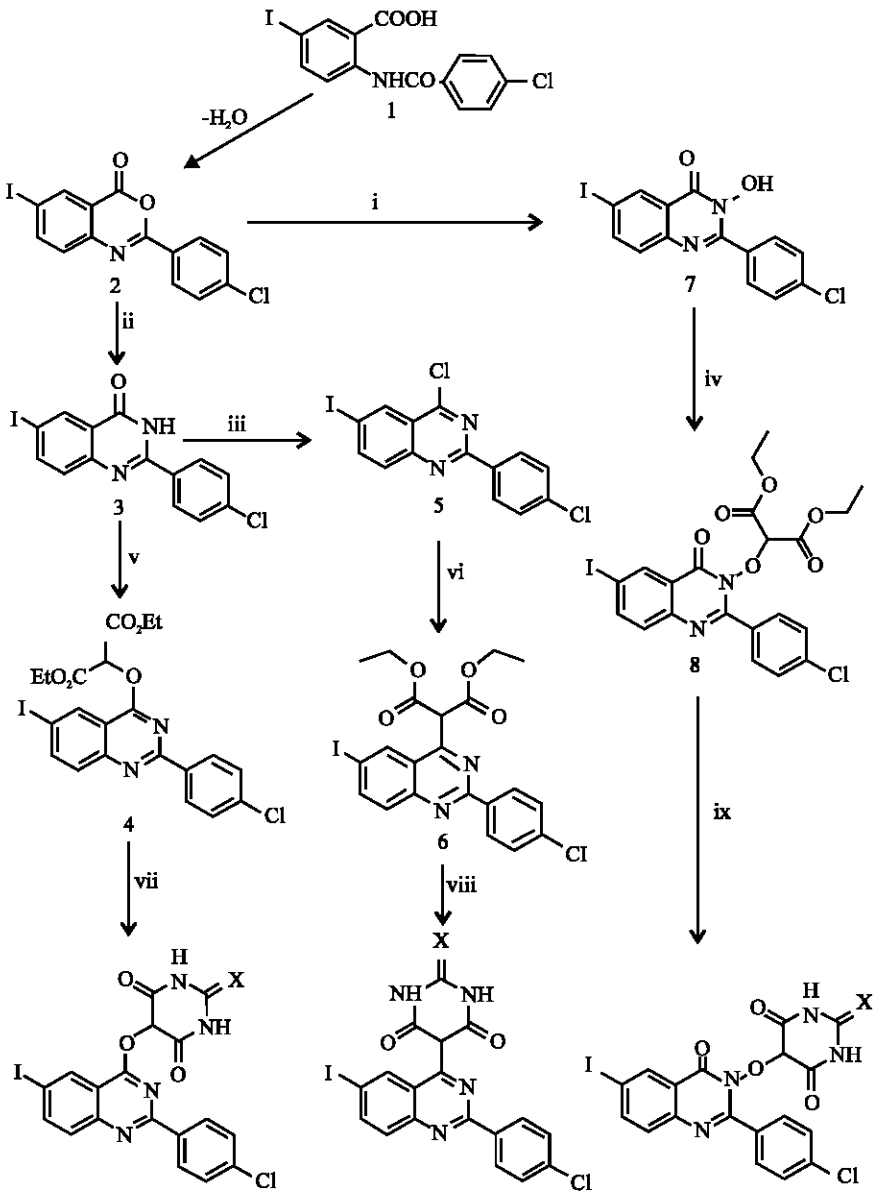
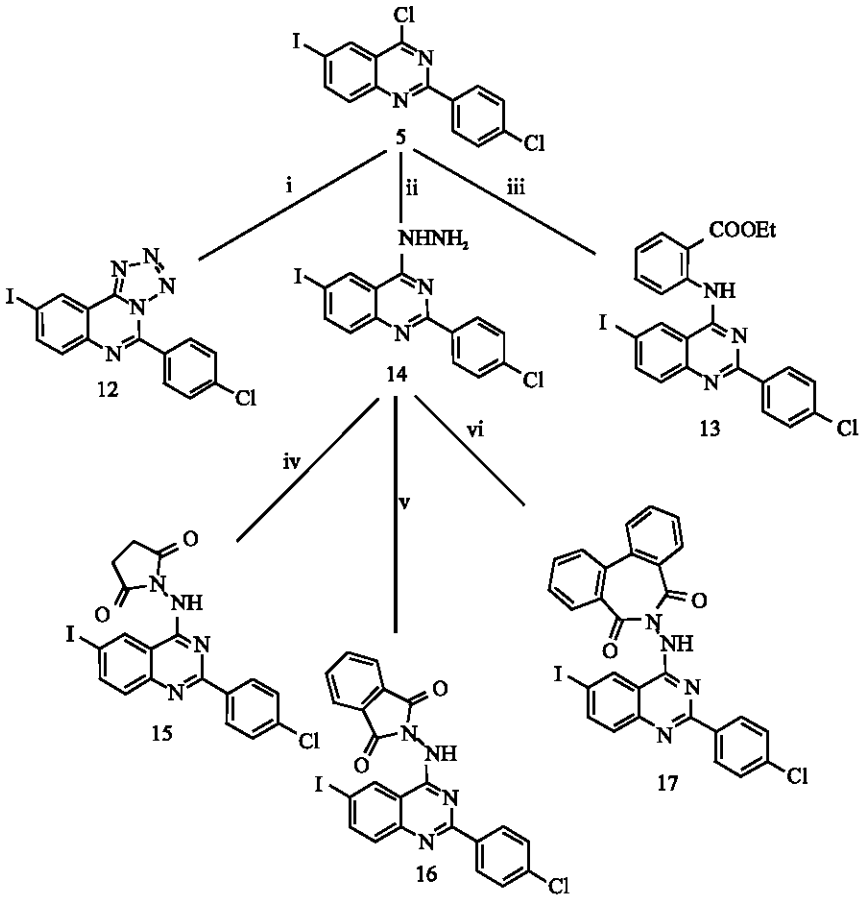


Scheme 1:

I)$NH_2OH.HCl$/pyridine. ii)$HCONH_2$. iii)$POCl_3/PCl_5$. iv,v)$BrCH(CO_2Et)_2/C_2H_5ONa$.
vi) $CH_2(CO_2Et)/C_2H_5ONa$/crown-5. vii,viii,ix) urea (thiourea)/C_2H_5ONa.

Chemistry: Melting points (°C) were determined on a Koffler apparatus and are uncorrected. IR spectra were obtained on a Pye Unicam SP 1200 spectrophotometer using Kbr wafer technique (υ, cm^{-1}). ^1H NMR spectra were recorded on a varian Gimine 200-MHZ, Brucker AC 200-MHZ and Brucker MAX 400-MHZ using TMS as an internal standard with chemical shifts (δ) expressed in ppm, the mass spectra were determined using MP model MS-5988 at 70 eV . The reactions and the purity of all compounds were checked by TLC using chloroform-n-hexane (9:1) as eluent.

N-(4-Chlorobenzoyl)-5-iodoanthranilic acid (1), 2-(4-chlorophenyl)-6-iodo-4*H*-3,1-benzoxazin-4-one (2) and 2-(4-chlorophenyl)-6-iodo-3,4-dihdroquinazolin-4-one (3) were prepared according to a reported procedures[13].



Scheme 2:

I)	sodium azide/ acetic acid.	ii)	hydrazine hydrate/ethanol absolute.
iii)	ethyl anthranilate/dry pyridine.	iv)	succinic anhydride / acetic acid
v)	phthalic anhydride/acetic acid.	vi)	diphenic anhydride / acetic acid

Diethyl 2-[2-(4-chlorophenyl)-6-iodoquinazolin-4-yloxy]malonate (4): A mixture of 2-(4-chlorophenyl)-6-iodo-3,4-dihdroquinazolin-4-one (3) (1.15 g, 0.003 mol), diethyl 2-bromomalonate (0.74 g, 0.0031 mol) and anhydrous potassium carbonate (1.0 g) in dry acetone (20 mL), was heated under reflux for 10 h and the reaction mixture was filtered while hot. The filtrate was evaporated under reduced pressure and the separated crude product was washed with water and crystallized from ethanol. M.P.: 142-4°C. Yield: 1.21 g (75.0%). IR: 1750 (C=O). ^{1}H NMR ($CDCl_3$): δ 1.3-1.4 (t, 6H, 2C*H*$_3$), 4.1-4.2 (q, 4H, 2C*H*$_2$), 4.9 (s, 1H, OC*H*), 7.3-8.2 (m, 7H, Ar-*H* and quinazoline-*H*). Ms: m/z (Rel. Int.); 540 (M^+, 61.52%), 542 (M^++ 2, 39.65%), 544 (M^++ 4, 6.71%). Analysis for $C_{21}H_{18}ClIN_2O_5$: % Calc. (Found); C 46.46 (46.8), H 3.36 (3.1), N 5.18 (5.5).

2-(4-Chlorophenyl)-4-chloro-6-iodo-quinazoline (5): A mixture of 2-(4-chlorophenyl)-6-iodo-3,4-dihydroquinazolin-4-one (3) (1.15 g, 0.003 mol), phosphorus oxychloride (5 ml) and phosphorus pentachloride (1.01 g) was heated under reflux for 2 h. The excess phosphorus oxychloride was removed under reduced pressure and crushed ice (20 g) was added to the residue. The separated solid was filtered, washed with water, dried and crystallized from benzene. M.P.: 156-8°C. Yield: 0.48 g (39.9%). IR: 1620 (C=N). ^{1}H NMR ($CDCl_3$): δ 7.4-8.2 (m, 7H, Ar-*H* and quinazoline-*H*). Ms: m/z (Rel. Int.); 400 (M^+, 37.2%), 402 (M^++ 2, 23.85%). Analysis for $C_{14}H_7Cl_2IN_2$: % Calc. (Found); C 41.93 (42.2), H 1.76 (2.0), N 6.99 (7.1).

Diethyl 2-[2-(4-chlorophenyl)-6-iodoquinazolin-4-yl]malonate (6): Diethylmalonate (1.6 g, 0.01 mol) was added dropwise to a solution of sodium ethoxide (0.7 g) containing one drop of 15-crown-5 in absolute ethanol (25 ml) and the mixture was stirred for 2 h at room temperature. 2-(4-Chlorophenyl)-4-chloro-6-iodoquinazoline 5 (4.0 g, 0.01 mol) was then added

Table 1: Melting points, molecular formulae and microanalytical data of compounds 9(a, b),. 10(a, b) and 11(a, b).

Comp.No.	X	M.P.(°C)	Mol. Formula	Analysis %Calcd. Found		
9a	O	200-2	$C_{18}H_{10}ClIN_4O_4$	C:	42.50	42.9
				H:	1.98	1.7
				N:	11.01	11.1
9b	S	187-9	$C_{18}H_{10}ClIN_4O_3S$	C:	41.20	41.6
				H:	1.92	1.7
				N:	10.68	10.7
10a	O	301-3	$C_{18}H_{10}ClIN_4O_3$	C:	43.88	43.8
				H:	2.05	2.0
				N:	11.37	11.3
10b	S	280-2	$C_{18}H_{10}ClIN_4O_2S$	C:	42.50	42.8
				H:	1.98	2.1
				N:	11.01	10.8
11a	O	237-9	$C_{18}H_{10}ClIN_4O_5$	C:	41.21	40.9
				H:	1.92	1.7
				N:	10.68	11.0
11b	S	214-6	$C_{18}H_{10}ClIN_4O_4S$	C:	39.98	40.0
				H:	1.86	1.7
				N:	10.36	10.7

portionwise and the mixture was refluxed for 5 h. The separated solid was filtered, washed with water, dried and crystallized from ethanol. M.P.: 146-8°C. Yield: 2.5 g (47.6%). IR: 3060 (Ar-CH), 2980 (Aliphatic-CH), 1750 (C=O), 1620 (C=N). ^{1}H NMR ($CDCl_3$): δ 1.2-1.3 (t, 6H, 2C*H*$_3$), 4.1-4.2 (q, 4H, 2C*H*$_2$), 4.54(s, 1H, C*H*) and 7.3-8.2(m, 7H, Ar-*H* and quinazoline-*H*). Analysis for $C_{21}H_{18}ClIN_2O_4$: % Calc.(Found); C 48.07 (47.9), H 3.46 (3.4), N 5.34 (5.1).

2-(4-Chlorophenyl)-3-hydroxy-6-iodo-4(3H)quinazolin-4-one (7): A mixture of 2-(4-chlorophenyl)-6-iodo-4*H*-3,1-benzoxazin-4-one 1 (3.83 g, 0.01 mol) and hydroxylamine hydrochloride (0.7 g, 0.01 mol) in dry pyridine (30 ml), was heated under reflux for 6 h and the reaction mixture was then concentrated to half its volume. The separated solid was filtered, washed with water and crystallized from ethanol. M.P.: 262-4°C. Yield: 2.0 g (50.17%). IR: 3500-3300 (OH), 1670 (CO),1620 (C=N). ^{1}H NMR ($CDCl_3$): δ 5.4 (s, 1H, O*H*), 7.3-8.3 (m, 7H, Ar-*H* and quinazoline-*H*). Analysis for $C_{14}H_8ClIN_2O_2$: % Calc.(Found); C 42.19 (42.4), H 2.02 (1.7), N 7.03 (6.9).

Diethyl 2-[2-(4-chlorophenyl)-6-iodoquinazolin-3-yloxy]malonate (8): Diethyl 2-bromomalonate (2.39 g, 0.01 mol) was slowly added to a mixture of 2-(4-chlorophenyl)-3-hydroxy-6-iodo-3,4-dihydroquinazolin-4-one 7 (3.99 g, 0.01 mol) and anhydrous potassium carbonate (2 g) in dry acetone (20 ml). The mixture was heated under reflux for 3 h and the mixture was filtered while hot. The filtrate was distilled under reduced pressure and the separated crude product was washed with water and crystallized from ethanol. M.P.: 131-3°C. Yield: 3.0 g (53.88%). IR: 3060 (Ar-CH), 2980 (Aliphatic-CH), 1750 (C=O), 1680 (C=O), 1620 (C=N). ^{1}H NMR ($CDCl_3$): δ 1.0-1.1 (t, 6H, 2C*H*$_3$), 4.2-4.3 (q, 4H, 2C*H*$_2$), 4.89 (s, 1H, OC*H*) and 7.3-8.3 (m, 7H, Ar-*H* and quinazoline-*H*). Analysis for $C_{21}H_{18}ClIN_2O_6$: % Calc. (Found); C 45.30 (45.4), H 3.26 (3.4), N 5.03 (5.4).

General methods for the synthesis of barbituric acid derivatives (9a,b), (10a,b) and (11a,b): A mixture of the appropriate diethyl ester (0.005 mol), urea or thiourea (0.01 mol) and sodium ethoxide (0.07 g, 0.01 mol) in absolute ethanol (15 ml) was refluxed with stirring for 5 h. On cooling, the mixture was neutralized with dil. hydrochloric acid and the separated solid was washed with water, dried and crystallized from ethanol to yield the products in 80 % yields (Table 1 and 2).

5-(4-Chlorophenyl)-9-iodo-1,2,3,4-tetrazolo-[1,5-c]-quinazoline (12): A mixture of 2-(4-chlorophenyl)-4-chloro-6-iodoquinazoline 5 (1.2 g, 0.003 mol) and sodium azide (0.19 g, 0.003 mol) in acetic acid (10 ml) was heated under reflux for 2 h. The solvent was then evaporated under vacuum and the separated solid was filtered, washed with water, dried and crystallized from ethanol. M.P.: > 300°C. Yield: 0.50 g (40.8 %). IR: 1620 (C=N). ^{1}H NMR ($CDCl_3$): δ 7.4-8.2 (m, 7H Ar-*H* and quinazolin-*H*). Analysis for $C_{14}H_7ClIN_5$: %Calc. (Found); C 41.25 (40.9), H 1.73 (1.6), N 17.18 (17.5).

Table 2: IR (ν, cm^{-1}) and ^{1}H NMR ($CDCl_3$, δ, ppm), data of compounds 9 (a, b), 10(a, b) and 11 (a, b)

Comp. No.	Data
9a	IR: 3250 (NH),1680 (C=O), 1670 (C=O)1620(C=N). ^{1}H NMR: 5.1 (s, 1H, OC*H*), 5.7-5.8 (bs, 2H, 2N*H*) and 7.3-8.6(m, 7H, Ar-*H* and quinazoline-*H*).
9b	IR: 3250 (NH),1680 (C=O),1670 (C=O),1620(C=N), 1240(C=S).1H NMR: 5.1 (s, 1H, OC*H*), 5.7-5.8 (bs, 2H, 2N*H*), 7.3-8.6 (m, 7H, Ar-H and quinazoline-*H*).
10a	IR: 3260 (NH), 1680 (C=O), 1620 (C=N). ^{1}H NMR: 4.66 (s, 1H, C*H*) 5.3-5.4(bs, 2H, 2N*H*), 7.4-8.2 (m, 7H, Ar-*H* and quinazoline-*H*).
10b	IR: 3260 (NH),1680 (C=O),1620 (C=N), 1240(C=S). ^{1}H NMR: 4.6 (s, 1H, C*H*) 5.3-5.4 (bs, 2H, 2N*H*), and 7.4-8.2 (m, 7H, Ar-*H* and quinazoline-*H*).
11a	IR: 3250 (NH),1680 (C=O),1670 (C=O),1620(C=N). ^{1}H NMR: 5.3 (s, 1H, OC*H*), 5.6-5.7 (bs, 2H, 2N*H*), 7.3-8.3 (m, 7H, Ar-*H* and quinazoline-*H*).
11b	IR: 3250 (NH),1680 (C=O), 1670 (C=O,1620 (C=N), 1240 (C=S). ^{1}H NMR: 5.3 (s, 1H, OC*H*), 5.6-5.7 (bs, 2H, 2N*H*), 7.3-8.3 (m, 7H, Ar *H* and quinazoline-*H*).

Table 3: Yield percentages, melting points, molecular formulae and microanalytical data compounds 15-17.

Comp. No.	Yield%	M.P.°C	Mol. Formula	Analysis %Calcd. Found
15	48	256-8	$C_{18}H_{12}ClIN_4O_2$	C: 45.17 45.2
				H: 2.53 2.3
				N: 11.70 11.5
16	55	281-3	$C_{22}H_{12}ClIN_4O_2$	C: 50.17 49.8
				H: 2.30 2.2
				N: 10.64 10.4
17	60	> 300	$C_{28}H_{16}ClIN_4O_2$	C: 55.79 55.6
				H: 2.68 2.3
				N: 9.29 9.4

Table 4: ^{1}H NMR (DMSO-d_6, δ, ppm) and Ms: m/z (Rel. Int.) data of compounds 15 and 17.

Comp.No.	Data
15	^{1}H NMR: 2.34-2.43 (m, 4H, CH_2CH_2), 7.4-8.2 (m, 7H, Ar-*H* and quinazoline-*H*), 9.8-10.0 (bs,1H, N*H*).
17	Ms: 602 (M^+, 6.25%), 604 (M^++ 2, 1.45%), 75(100%).

2-(4-Chlorophenyl)-4-(2-ethoxycarbonylphenylamino)-6-iodoquinazoline (13): A mixture of 2-(4-chlorophenyl)-4-chloro-6-iodoquinazoline 5 (1.2 g, 0.003 mol) and ethyl anthranilate (0.49 g, 0.003 mol) in dry pyridine (10 ml) was heated under reflux for 2 h. The solvent was then evaporated under vacuum and the separated solid was filtered, washed with water, dried and crystallized from ethanol. M.P.: 121-23°C. Yield: 1.0 g (62.9%). IR: 3180 (NH), 1750 (C=O). ^{1}H NMR ($CDCl_3$): δ 1.0-1.1 (t, 3H CH_2CH_3), 4.2-4.3 (q, 2H, CH_2CH_3), 7.2-8.4 (m, 11H, Ar-*H* and quinazoline-*H*), 11.1 (bs, 1H, N*H*). Analysis for $C_{23}H_{17}ClIN_3O_2$: % Calc. (Found); C 52.15 (52.3), H 3.23 (3.6), N 7.93 (7.5).

2-(4-Chlorophenyl)-4-hydrazino-6-iodoquinazoline(14): A mixture of 2-(4-chlorophenyl)-4-chloro-6-iodoquinazoline 5 (1.2 g, 0.003 mol) and 98% hydrazine hydrate (1 ml) in ethanol (10 ml) was stirred at room temperature for 30 minutes. On cooling, the separated solid was filtered and crystallized from ethanol. M.P.: > 300°C. Yield: 1.0 g (84%). IR: 3300, 3250 (NH_2), 3160 (NH), 1620 (C=N). ^{1}H NMR (DMSO-d_6): δ 5.2 (bs, 2H, NH_2), 7.8-8.6 (m, 7H, Ar-*H* and quinazoline-*H*), 9.8 (bs, 1H, N*H*). Analysis for $C_{14}H_{10}ClIN_4$: % Calc. (Found); C 42.40 (42.6), H 2.54 (2.6), N 14.13 (14.5).

General method for the synthesis of 2-(4-Chlorophenyl)-4-imidoamino-6-iodoquinazoline (15-17): A mixture of 2-(4-chlorophenyl)-4-hydrazino-6-iodo-quinazoline 14 (1.2 g, 0.003 mol) and the appropriate acid anhydride, in acetic acid (10 ml) was heated under reflux for 3 h. On cooling, the separated solid was filtered, washed with water and crystallized from acetic acid (Table 3 and 4).

Antimicrobial testing: All of the newly synthesized compounds (dissolved in dimethylformamide) were subjected to antimicrobial screening by determining the minimum inhibitory concentration (MIC) using the agar dilution technique[14].

The *in vitro* antimicrobial activity of the prepared compounds against the Gram negative bacteria (*Escherichia coli* ATCC 2592, *Pseudomonas aeruginosae* ATCC 27853), the Gram positive bacteria (*Staphylococcus aureus* ATCC 25923, *Bacillus subtillis* ATCC 6633) and the pathogenic Fungi (*Saccharomyces cerevisiae* ATCC 9763 and *Candida albicans* ATCC 1023) was determined by preparing suspensions of each microorganism to contain approximately 10^5-10^6 CFU (colony forming units)/well. The test compounds were applied to the wells at concentrations ranging from 200 to about 3.0 μg mL^{-1} in dimethylformamide solution, in addition to the 0 (control) and the standard Tetracycline. The plates were incubated for 24 h at 37°C in case of bacteria and 34°C for fungi, and growth was assessed by visual inspection. The minimum inhibitory concentration (MIC) was defined as the lowest concentration of inhibitor at which microbial growth was not apparent disregarding a single colony or a faint haze caused by the inoculum.

RESULTS

The MICs of the active compounds against the susceptible pathogenic organisms are presented in Table 5. It was found that all of the compounds had inhibitory activity only against *Staphylococcus aureus* and *Bacillus subtilis* and were inactive or presented a MIC more than 200 μg mL^{-1}. Compounds 9b, 10b and 11b showed the highest activity against these strains (MIC= 10.0 μg mL^{-1}) while 7, 9a, 10a and 11a (MIC = 20.0 μg mL^{-1}). Compounds 15, 16 and 17 (MIC = 50 μg mL^{-1}), compounds 5 and 12 (MIC = 100 μg mL^{-1}).

This category of compounds (9a, 9b, 10a, 10b, 11a and 11b) where the quinazoline nucleus attached to barbituric and thiobarbituric acid moieties at two different positions with or without oxygen bridge, such compounds contain two NH groups each one is surrounded by two C=O groups which enables them to attain many tautomeric forms that might be responsible for their activity. It was reported that some barbiturates and thiobarbiturates interfere with nucleic acid biosynthesis[3] leading to cell death, and so the inhibitory activities of such compounds could be attributed to some sort of synergism between both moieties.

Table 5: Antimicrobial activity (MIC, μg mL^{-1})

	Susceptible microorganisms	
Comp. No.	*Staphylococcus aureus*	*Bacillus subtilis*
7	20.00	20.00
9b,10b,11b	10.00	10.00
9a,10a,11a	20.00	20.00
15,16,17	50.00	50.00
Tetracycline	0.40	0.25

In conclusion, the present study revealed that the heterocyclic systems quinazolin-4-yloxy-barbituric acid 9a, quinazolin-4-yloxy-2-thiobarbituric acid 9b, quinazolin-3-yloxy-barbituric acid (10a), quinazolin-3-yloxy-2-thiobarbituric acid (10b), quinazolin-4-yl-barbituric acid 11a, quinazolin-4-yl-2-thiobarbituric acid 11b, 2-(4-chlorophenyl)-3-hydroxy-6-iodo-4(3*H*)quinazolin-4-one(7) and 2-(4-chlorophenyl)-4-imidoamino-6-iodoquinazoline (15-17) could be useful as a template for future development through modification or derivatization to design a more potent antimicrobial agents.

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