http://www.pjbs.org

PJBS

ISSN 1028-8880

Pakistan Journal of Biological Sciences

ANSInet
Asian Network for Scientific Information
308 Lasani Town, Sargodha Road, Faisalabad - Pakistan

Pakistan Journal of Biological Sciences 7 (7): 1262-1268, 2004
ISSN 1028-8880

New Quinazoline Related Derivatives with Antimicrobial Activity: Part I

S.M. Mosaad, [1]K.I. Mohammed, [1]M.A. Ahmed and [1]S.G. Abdel-Hamide
Department of Pharmaceutical Organic Chemistry, Faculty of Pharmacy, Helwan University, Cairo, Egypt
[1]Department of Pharmaceutical Chemistry, Faculty of Pharmacy, Al-Azhar University, Cairo, Egypt

Abstract: A new series of anthranilic acid derivatives were prepared through reaction of 2-(4-chlorophenyl)-6-iodo-4(*H*)-3,1-benzoxazine 3 with some amines. Reaction of {2-(4-chlorophenyl)-3-amino-6-iodo-3,4-dihydro-quinazolin-4-one} 6 and {2-(4-chlorobenzoyl-amino)-5-iodobenzoic acid hydrazide} 7 with some aldehydes and acid anhydrides was also reported. The structures of the new compounds were confirmed by microanalyses and spectral data. Some compounds showed promising antibacterial activities against *Staphylococcus aureus* and *Bacillus subtilis*. Compounds 5h and 5K showed the highest activity (MIC = 12.5 μg ml^{-1}), compound 12 a (MIC = 20.0 μg ml^{-1}), compounds 5 a-g, 5 I, 5 j, 6 r, 9 a-h, (MIC = 50 μg ml^{-1}) and compounds 8 g, 12 b, 12 c, (MIC = 100 μg ml^{-1}).

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

INTRODUCTION

Quinazoline analogs have been reported to be biologically versatile compounds possessing a variety of activities including antimicrobial potency[1,2]. As a continuation of previous efforts[3-6] aiming to locate new, active, quinazoline containing, antimicrobial agents with enhanced potency, a new series of 6-iodoquinazoline derivatives was synthesized and screened. In the present investigation, the quinazoline analogs were designed to contain some functional groups which are believed to contribute to antimicrobial activity such as –CONH-NH-R and –CO-NR-CO-[7,8], in addition to some heterocycles connected to the quinazoline ring such as thiazoline and imidazoline[9,10]. The new synthesized compounds were screened against certain strains of gram negative, gram positive bacteria and pathogenic fungi.

MATERIALS AND METHODS

The starting material 3 was prepared via a reported procedure[5]. Trials to prepare 4 via the reaction of 3 with a variety of aliphatic or aromatic primary amines ended with failure. The reaction was tried by prolonged boiling in ethanol, pyridine, or acetic acid containing fused sodium acetate and by fusion in the absence of solvents. In all cases the reaction afforded the diamides 5a-r (Scheme 1 and Table 1). Attempts to cyclize the diamide to the corresponding 4(3*H*)quinazolin-4-one by heating with acetic anhydride, polyphosphoric acid or with a mixture of benzenesulphonyl chloride and phosphorus oxychloride, failed to give the target compounds and the 3, 1-benzoxazin-4-one 3 was obtained instead. The structure of the isolated diamide derivatives was proved by elemental analyses (Table 1) and spectral data (Table 2).

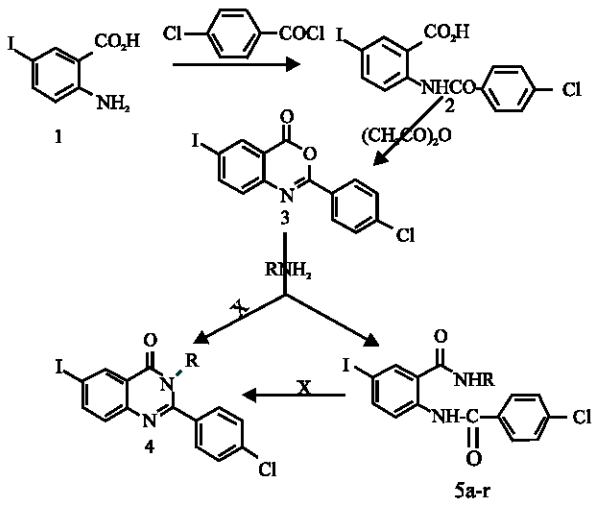
Reaction of 3 with excess boiling hydrazine hydrate afforded 2-(4-chlorophenyl)-3-amino-6-iodo-3, 4-dihydroquinazolin-4-one 6. On the other hand, reaction of 3 with hydrazine hydrate in boiling ethanol yielded 2-(4-chlorobenzoylamino)-5-iodobenzoic acid hydrazide 7.

Compounds 6 and 7 were then reacted with certain aromatic aldehydes to yield the corresponding arylidenes 8 a-h, 9 a-h, respectively. The arylidene derivatives 8a and 9a were then reacted with thioglycolic acid in toluene in the presence of sodium acetate to yield the corresponding chiral thiazolidine analogs 10 and 11, respectively. It is noteworthy to report that the chirality of compounds 10 and 11 is not considered herein. Compound 3 was also reacted with benzoic acid hydrazide, its 4-amino analogue and nicotinic acid hydrazide, independently, in pyridine to yield the corresponding 2-(4-chlorophenyl)-3-aroylamino-6-iodo-3, 4-dihydroquinazolin-4-ones 12a, 12b and 12c, respectively (Scheme 2).

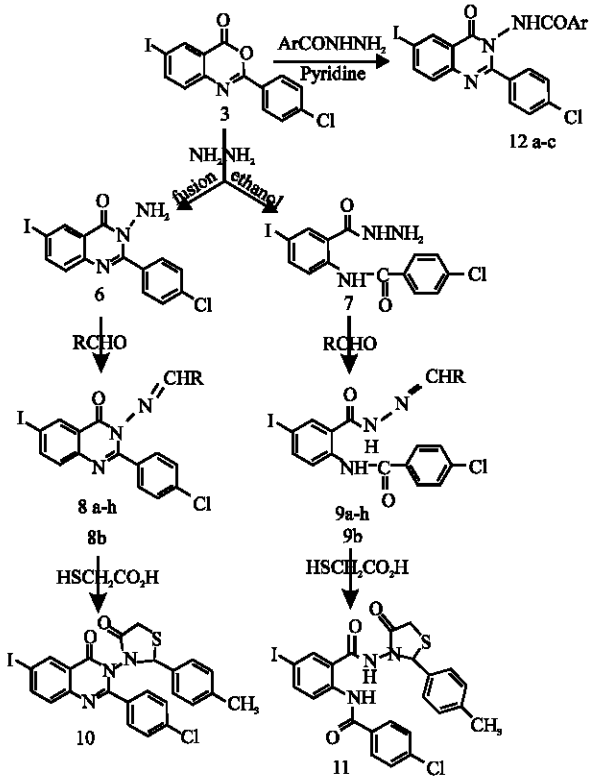
The reaction of 6 with equimolar amount of benzoyl chloride in pyridine yielded the corresponding amide, which was identical with compound 12 a. When benzoyl chloride was used in excess, the corresponding 3-*N*, *N*-dibenzoylamino derivative 13 was obtained. Interaction of 6 with succinic anhydride or phthalic anhydride by heating in acetic acid in the presence of anhydrous sodium acetate yielded the corresponding imido derivatives 14 or 15, respectively (Scheme 3).

Corresponding Author: S.M. Mosaad, Department of Pharmaceutical Organic Chemistry, Faculty of Pharmacy, Helwan University, Cario Egypt
S.G. Abdel-Hamide, Pharmaceutical Chemistry Department, Faculty of Pharmacy, King Saud University, P.O. Box 2457, Riyadh 11451, Saudi Arabia E-mail: eisa1424@yahoo.com

Scheme 1

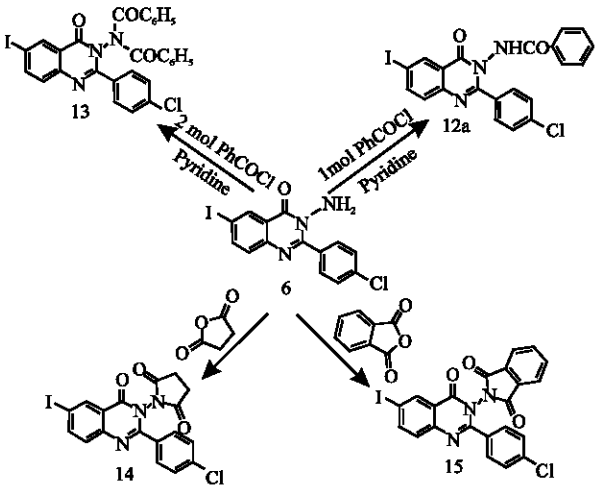


Scheme 2



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 (chemical shifts δ, ppm). Mass spectra

Scheme 3



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.

2-(4-Chlorobenzoylamino)-5-iodo-*N*-substituted-benzamides 5a-r: A mixture of 2-(4-chlorophenyl)-6-iodo-4*H*-3, 1-benzoxazin-4-one 3 (3.8 g, 0.01 mol) and the appropriate aliphatic or aromatic amine (0.03 mol) in ethanol (20 ml) was heated under reflux for 3 h. The solvent was then removed under reduced pressure and the obtained solid was washed with water and crystallized from the appropriate solvent (Table 1 and 2).

2-(4-Chlorophenyl)-3-amino-6-iodo-3, 4-dihydroquinazolin-4-one 6: A mixture of 2-(4-chlorophenyl)-6-iodo-4*H*-3, 1-benzoxazin-4-one 3 (1.15 g, 0.003) and 98% hydrazine hydrate (5 ml) was heated under reflux for 3 h. On cooling, the separated solid was washed with water and crystallized from ethanol. M.P.: 240-2°C. Yield: 0.81 g (70.5%). IR: 3350, 3300 (NH_2), 1680 (C=O). ^1H NMR($CDCl_3$, δ ppm): 5.7-5.8 (bs, 2H, NH_2) and 7.4-8.5 (m, 7H, Ar-*H* and quinazoline-*H*). Analysis for $C_{14}H_9ClIN_3O$:% Calc. (Found); C 42.29 (41.9), H 2.28 (2.6), N 10.57 (10.8).

2-(4-Chlorobenzoylamino)-5-iodobenzoic acid hydrazide 7: A mixture of 2-(4-chlorophenyl)-6-iodo-4*H*-3, 1-benzoxazin-4-one 3 (1.15 g, 0.003 mol) and 98% hydrazine hydrate (0.75 g, 0.015 mol) in ethanol (10 ml) was reflexed for 2 h. The solvent was evaporated under reduced pressure and the obtained solid was washed with water, dried and crystallized from ethanol. M.P.: 220-2°C. Yield: 0.8 g (64.16%). IR: 3350, 3300 (NH_2), 3250 (NH), 1680 (C=O), 1670 (C=O), 1620 (C=N). ^1H NMR (DMSO-d_6, δ ppm): 5.7-5.8 (bs, 2H, (NH_2), 7.5-8.3 (m, 7H, Ar-*H*),

Table 1: Crystallization solvents, yield percentages, melting points, molecular formula and microanalytical data of compounds 5 a-r

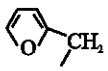
Comp. no.	R	Cryst. Solv.	Yield (%)	M.P.(°C)	Mol. Formula	Analysis (%)	Calcd.	Found
5a	CH_3	EtOH	90	270-2	$C_{15}H_{12}ClIN_2O_2$	C:	43.45	43.1
						H:	2.92	2.8
						N:	6.76	7.1
5b	C_2H_5	EtOH	90	235-7	$C_{16}H_{14}ClIN_2O_2$	C:	44.83	44.5
						H:	3.29	3.4
						N:	6.54	6.5
5c	C_3H_7(*n*)	EtOH	90	220-2	$C_{17}H_{16}ClIN_2O_2$	C:	46.12	46.5
						H:	3.64	3.5
						N:	6.33	6.6
5d	C_3H_7(*iso*)	EtOH	95	220-2	$C_{17}H_{16}ClIN_2O_2$	C:	46.12	46.2
						H:	3.64	4.0
						N:	6.33	6.1
5e	C_4H_9(*n*)	EtOH	90	190-2	$C_{18}H_{18}ClIN_2O_2$	C:	47.34	47.5
						H:	3.97	4.3
						N:	6.13	5.8
5f	C_4H_9(*iso*)	EtOH	95	180-2	$C_{18}H_{18}ClIN_2O_2$	C:	47.34	47.1
						H:	3.97	4.2
						N:	6.13	5.9
5g		EtOH	85	205-7	$C_{19}H_{14}ClIN_2O_3$	C:	47.47	47.8
						H:	2.94	3.0
						N:	5.83	5.6
5h	4-BrC_6H_4	AcOH	50	252-4	$C_{20}H_{13}BrClIN_2O_2$	C:	43.24	43.6
						H:	2.36	2.6
						N:	5.04	5.2
5i	4-ClC_6H_4	EtOH	50	170-2	$C_{20}H_{13}Cl_2IN_2O_2$	C:	47.00	46.7
						H:	2.56	2.8
						N:	5.48	5.6
5j	2,6-$Cl_2C_6H_3$	AcOH	42	195-7	$C_{20}H_{12}Cl_3IN_2O_2$	C:	44.03	43.8
						H:	2.22	2.1
						N:	5.13	5.1
5k	3-HOC_6H_4	AcOH	45	265-7	$C_{20}H_{14}ClIN_2O_3$	C:	48.76	59.1
						H:	2.86	2.8
						N:	5.69	6.0
5l	4-HOC_6H_4	AcOH	55	280-2	$C_{20}H_{14}ClIN_2O_3$	C:	48.76	48.5
						H:	2.86	2.8
						N:	5.69	5.9
5m	2-$CH_3C_6H_4$	EtOH	68	202-4	$C_{21}H_{16}ClIN_2O_2$	C:	51.40	51.5
						H:	3.29	3.2
						N:	5.71	6.0
5n	2-$COCH_3C_6H_4$	EtOH	70	281-3	$C_{22}H_{16}ClIN_2O_3$	C:	50.94	51.0
						H:	3.11	2.8
						N:	5.40	5.1
5o	4-$COCH_3C_6H_4$	EtOH	72	197-9	$C_{22}H_{16}ClIN_2O_3$	C:	50.94	51.3
						H:	3.11	2.7
						N:	5.40	5.5
5p	4-$H_2NSO_2C_6H_4$	EtOH	53	214-6	$C_{20}H_{15}ClIN_3O_4S$	C:	43.22	43.5
						H:	2.72	2.5
						N:	7.56	7.6
5q	4-$AcNHSO_2C_6H_4$	AcOH	51	270-2	$C_{22}H_{17}ClIN_3O_5S$	C:	44.20	44.2
						H:	2.87	2.8
						N:	7.03	6.7
5r	4-$EtOCOC_6H_4$	EtOH	55	220-2	$C_{23}H_{18}ClIN_2O_4$	C:	50.34	50.1
						H:	3.31	3.2
						N:	5.10	4.9

Table 2: ^{1}H NMR ($CDCl_3$, δ, ppm) data of compounds 5 (c, e, m and p)

Comp. no.	δ, ppm
5c	^{1}HNMR: 0.9-1.0 (t, 3*H*, CH_3), 1.55-1.65 (m, 2H, $CH_3CH_2CH_2$), 3.2- 3.3 (q, 2H, CH_2NH), 7.5-8.4 (m, 7H, Ar-*H*), 8.85 (bs, 1H, CON*H*), 12.5(bs, 1H, 1N*H*CO).
5e	^{1}H NMR: 0.9-1.0 (t, 3H, CH_3), 1.44-1.54 (m, 2H, CH_3CH_2), 1.5-1.7 (m, 2H, CH_2CH_2), 3.2-3.34 (q, 2H, CH_2NH), 7.5-8.4 (m, 7H, Ar-*H*), 8.9 (bs, 1H, CON*H*), 12.5 (bs, 1H, N*H*CO),
5m	^{1}H NMR: 2.3 (s, 3H, Ar-CH_3), 7.4-8.4 (m, 11H, Ar-*H*), 9.0 (bs, 1H, CON*H*), 12.5 (bs, 1H, N*H*CO).
5p	^{1}H NMR: 3.2 (bs, 2H, SO_2NH_2), 7.5-8.4 (m, 11H, Ar-*H*), 10.8 (bs, 1H, CON*H*), 11.4 (bs, 1H, N*H*CO).

Table 3: Yield percentages, melting points, molecular formula and microanalytical data of compounds 8 a-h

Comp. no.	Ar	Yield (%)	M.P.(°C)	Mol. Formula	Analysis (%) Calcd.	Found
8a	C_6H_5	75	205-7	$C_{21}H_{13}ClIN_3O$	C:	51.93	52.0
					H:	2.70	2.6
					N:	8.65	8.8
8b	4-$CH_3C_6H_4$	70	205-7	$C_{22}H_{15}ClIN_3O$	C:	52.98	53.0
					H:	3.03	3.2
					N:	8.41	8.3
8c	2-ClC_6H_4	75	270-2	$C_{21}H_{12}Cl_2IN_3O$	C:	48.49	48.6
					H:	2.33	2.3
					N:	8.08	8.2
8d	2-FC_6H_4	77	240-2	$C_{21}H_{12}ClFIN_3O$	C:	50.07	50.1
					H:	2.40	2.6
					N:	8.34	8.2
8e	4-ClC_6H_4	75	264-6	$C_{21}H_{12}Cl_2IN_3O$	C:	48.49	48.4
					H:	2.33	2.1
					N:	8.08	8.1
8f	4-$CH_3OC_6H_4$	70	245-7	$C_{22}H_{15}ClIN_3O_2$	C:	51.24	51.3
					H:	2.93	3.0
					N:	8.15	7.9
8g	3,4-$(CH_3O)_2C_6H_3$	70	256-7	$C_{23}H_{17}ClIN_3O_3$	C:	50.62	50.9
					H:	3.14	3.3
					N:	7.70	7.9
8h	C_6H_5CH=CH	70	248-0	$C_{23}H_{15}ClIN_3O$	C:	53.98	53.9
					H:	2.95	3.2
					N:	8.21	8.1

Table 4: ^{1}H NMR(DMSO-d_6, δ, ppm) data of compounds 8(a, b and f)

Comp. no.	δ, ppm
8a	^{1}H NMR: 7.3-8.3 (m,12H, Ar-*H* and quinazoline-*H*), 9.25 (s, 1H, C*H*=N).
8b	^{1}H NMR: 2.4 (s,3H, Ar-CH_3), 7.2-8.3 (m,11H, Ar-*H* and quinazoline-*H*), 9.25 (s, 1H, C*H*=N).
8f	^{1}H NMR: 3.8 (s, 3H, OCH_3), 7.2-8.3 (m, 11H, Ar-*H* and quinazoline-*H*), 9.25 (s, 1H, C*H*=N).

Table 5: Yield percentages, melting points, molecular formula and Microanalytical data of compounds 9 a-h

Comp. no.	Ar	Yield (%)	M.P. (°C)	Mol. Formula	Analysis (%) Calcd.	Found
9a	C_6H_5	78	175-7	$C_{21}H_{15}ClIN_3O_2$	C:	50.07	50.4
					H:	3.00	2.9
					N:	8.34	7.9
9b	4-$CH_3C_6H_4$	70	264-6	$C_{22}H_{17}ClIN_3O_2$	C:	51.04	51.2
					H:	3.31	3.1
					N:	8.12	8.4
9c	2-ClC_6H_4	75	260-2	$C_{21}H_{14}Cl_2IN_3O_2$	C:	46.87	46.7
					H:	2.62	3.0
					N:	7.81	7.9
9d	2-FC_6H_4	80	273-5	$C_{21}H_{14}ClFIN_3O_2$	C:	48.35	48.0
					H:	2.70	2.6
					N:	8.05	8.1
9e	4-ClC_6H_4	75	251-3	$C_{21}H_{14}Cl_2IN_3O_2$	C:	46.87	46.9
					H:	2.62	3.1
					N:	7.81	8.2
9f	4-$CH_3OC_6H_4$	70	261-3	$C_{22}H_{17}ClIN_3O_3$	C:	49.51	49.3
					H:	3.21	3.3
					N:	7.87	7.9
9g	3,4-$(CH_3O)_2C_6H_3$	70	276-8	$C_{23}H_{19}ClIN_3O_4$	C:	49.00	49.0
					H:	3.40	3.5
					N:	7.45	7.4
9h	C_6H_5CH=CH	70	287-9	$C_{23}H_{17}ClIN_3O_2$	C:	52.15	52.3
					H:	3.23	3.4
					N:	7.93	7.6

Table 6: ^{1}H NMR (DMSO-d_6, δ, ppm) of compounds 9 b and 9 f

Comp. no.	δ, ppm
9b	^{1}H NMR: 2.4 (s, 3H, Ar-CH_3), 7.3-8.2 (m,11H, Ar-*H*), 9.25 (s, 1H, N=C*H*), 11.7-11.9 (bs, 1H, N*H*CO), 12.1 (bs, 1H, N*H*CO).
9f	^{1}H NMR : 3.8 (s, 3H, OCH_3), 7.6-8.5 (m, 11H, Ar-*H*), 9.25 (s, 1H, N=C*H*), 11.7-11.9 (bs, 1H, N*H*CO), 12.0-12.1 (bs, 1H, N*H*CO).

Table 7: Melting points, molecular formula and microanalytical data of compounds 12 a-c

Comp. no.	Ar	M.P. (°C)	Mol. Formula	Analysis (%) Calcd.	Found
12a	phenyl	196-8	$C_{21}H_{13}ClIN_3O_2$	C:	50.27	49.9
				H:	2.61	2.7
				N:	8.38	8.5
12b	4-amino-phenyl	170-2	$C_{21}H_{14}ClIN_4O_2$	C:	48.81	49.0
				H:	2.73	3.0
				N:	10.84	11.0
12c	3-pyridyl	160-2	$C_{20}H_{12}ClIN_4O_2$	C:	47.79	47.9
				H:	2.41	2.5
				N:	11.15	11.0

Table 8: IR (υ, cm^{-1}), ^1H NMR (δ, ppm) and Ms: m/z (Rel. Int.) data of compounds 12 a-c

Comp. no.	Data
12a	IR: 3220 (NH), 1690(C=O), 1680 (C=O). ^1H NMR ($CDCl_3$): 7.2-8.3 (m, 12H, Ar-*H* and quinazoline-*H*), 12.4 (bs, 1H, N*H*C=O).
12b	IR: 3360, 3320 (NH_2), 3210 (NH), 1685 (C=O), 1670 (C=O). ^1H NMR (DMSO-d_6): 5.5-5.6 (bs, 2H, NH_2), 6.64-8.3 (m, 11H, Ar-*H* and quinazoline-*H*), 12.4 (bs, 1H, N*H*CO).
12c	IR: 3180 (NH), 1690 (C=O), 1680 (C=O). ^1H NMR (DMSO-d_6): 7.3-9.1 (m, 11H, Ar-*H* and quinazoline-*H*), 12.4 (bs, 1H, N*H*) Ms: m/z (Rel. Int.) 502(M^+, 11.19%), 504 (M^++2, 2.7%),106 (100%).

Table 9: Melting points, molecular formula and microanalytical data of compounds 14 and 15

Comp. no.	M.P.(°C)	Mol. Formula	Analysis (%) Calcd.	Found
14	287-9	$C_{18}H_{11}ClIN_3O_3$	C:	45.07	45.2
			H:	2.31	2.3
			N:	8.76	8.5
15	273-5	$C_{22}H_{11}ClIN_3O_3$	C:	50.07	50.0
			H:	2.10	2.2
			N:	7.96	8.2

Table 10: IR (υ, cm^{-1}), ^1H NMR(DMSO-d_6, δ, ppm) and Ms: m/z (Rel. Int.) data of compounds 14 and 15

Comp. no.	Data
14	^1H NMR: 2.7-2.9 (m, 4H, CH_2CH_2), 7.2-8.3 (m, 7H, Ar-*H* and quinazoline-*H*). Ms: 527(16.86%), 529 (4.11%), 75 (100%).
15	IR: 1700 (C=O), 1680 (C=O). ^1H NMR: 7.2-8.3 (m, 11H, Ar-*H* and quinazoline-*H*).

10.3-10.4 (t, 1H, N*H*NH_2), 12.1(bs, N*H*CO). Analysis for $C_{14}H_{11}ClIN_3O_2$:% Calc. (Found); C 40.46 (40.8), H 2.67 (2.5), N 10.11 (10.4).

2-(4-Chlorophenyl)-3-(arylideneamino)-6-iodo-3,4-dihydroquinazolin-4-ones 8a-g: A mixture of 2-(4-chlorophenyl)-3-amino-3, 4-dihydroquinazolin-4-one 6 (3.98 g, 0.01 mol) and the appropriate aldehyde (0.01 mol) in acetic acid (20 ml) was heated under reflux for 2 h. On cooling, the separated solid was filtered, washed with water, dried and crystallized from acetic acid (Table 3 and 4).

***N*-Arylidene-2-(4-chlorobenzoylamino)-5-iodobenzoic acid hydrazide 9a-g:** A mixture of 2-(4-chlorobenzoylamino)-5-iodobenzoic acid hydrazide 7 (4.16 g, 0.01 mol) and the appropriate aldehyde (0.01 mol) in acetic acid (20 ml) was heated under reflux for 2 h. On cooling, the separated solid was filtered, washed with water, dried and crystallized from acetic acid (Table 5 and 6).

2-(4-Chlorophenyl)-3-[2-(4-methylphenyl)-4-oxo-1,3-thiazolidin-3-yl]-6-iodo-3,4-dihydroquinazolin-4-one10: A mixture of 2-(4-chlorophenyl)-3-(4-methylbenzylidene)-6-iodo-3,4-dihydroquinazoline-4-one 8b (0.55 g, 0.001 mol) and thioglycolic acid (0.18 g, 0.002 mol) and anhydrous sodium acetate (1.0 g) in dry toluene (10 ml), was reflexed for 10 h and the mixture was then filtered while hot. The filtrate was evaporated under reduced pressure and the obtained solid was crystallized from methanol. M.P.: 220-2°C. Yield: 0.2 g (34.85%). IR: 1700 (C=O),1680 (C=O). ^1H NMR ($CDCl_3$, δ ppm): 2.5 (s, 3H, Ar-CH_3), 3.5 (s, 2H, SCH_2), 6.1 (s, 1H, SC*H*), 7.2-8.3 (m, 11 Ar-*H* and quinazoline-H). Ms: m/z (Rel. Int.): 573(M^+, 0.74%), 575(M^++2, 0.25%), 381(100%), 383(33%). Analysis for $C_{24}H_{17}ClIN_3O_2S$:% Calc. (Found); C 50.23 (50.6), H 2.99 (3.3), N 7.32 (7.0).

***N*-[2-(4-Methylphenyl)-4-oxo-1,3-thiazolidin-3-yl]-2-(4-chlorobenzoyl-amino)-5-iodobenzamide 11:** A mixture of *N*-(4-methylbenzylidene)-2-(4-chlorobenzoylamino)-5-iodobenzoic acid hydrazide 9b (0.517 g, 0.001 mol),

thioglycolic acid (0.18 g, 0.002 mol) and anhydrous sodium acetate (1.0 g) in dry toluene (10 ml), was reflexed for 12 h and the mixture was then filtered while hot. The filtrate was distilled under reduced pressure and the obtained solid was crystallized from methanol. M.P.: 144-6°C. Yield: 0.23 g (38.85%). IR: 3250 (NH), 3150 (NH), 1685 (C=O), 1680 (C=O), 1665 (C=O). ^{1}H NMR (CD_3OD, δ ppm): 2.5 (s, 3H, Ar-C*H*$_3$), 3.5 (s, 2H, SC*H*$_2$), 6.1 (s, 1H, SC*H*), 7.2-8.3 (m, 11H Ar-*H*), 11.7 (bs, 1H CON*H*) and 12.1 (bs, 1H, N*H*CO). Analysis for $C_{24}H_{19}ClIN_3O_3S$:% Calc. (Found); C 48.70 (49.1), H 3.24 (3.2), N 7.10 (7.0).

2-(4-Chlorophenyl)-3-aroylamino-6-iodo-3,4-dihydroquinazolin-4-ones 12 a-c: A mixture of 2-(4-chlorophenyl)-6-iodo-4*H*-3, 1-benzoxazin-4-one 3 (1.15 g, 0.003 mol) and the appropriate acid hydrazide (0.003 mol) in dry pyridine (10 ml), was heated under reflux for 5 h. On cooling, the solvent was removed under reduced pressure and the remaining residue was treated with cold dil. hydrochloric acid. The separated solid was filtered, washed with water, dried and crystallized from acetic acid to yield compounds 12 a-c in 60% yields (Table 7 and 8).

2-(4-Chlorophenyl)-3-benzoylamino-6-iodo-3,4-dihydroquinazolin-4-one 12a: Benzoyl chloride (0.145 g, 0.001 mol) was added dropwise to a solution of 2-(4-chlorophenyl)-3-amino-6-iodo-3,4-dihydroquinazolin-4-one 6 (0.4 g, 0.001 mol) in dry pyridine and the reaction mixture was warmed for 10 min. On cooling, the pyridine layer was removed by decantation and the residue was treated with dil. hydrochloric acid, washed with water, filtered and crystallized from acetic acid. M.P.: 196-8°C. Yield: 0.4 g (80%). IR: 3300-200 (NH), 1710 (C=O), 1680 (C=O). Ms: m/z (Rel. Int.): 501 (M^+, 28.5%), 503 (M^++2, 8.4%). Analysis for $C_{21}H_{13}ClIN_3O_2$:% Calc. (Found); C 50.27 (50.3), H 2.61 (3.0), N 8.38 (8.7).

2-(4-Chlorophenyl)-3-(*N*,*N*-dibenzoylamino)-6-iodo-3,4-dihydroquinazolin-4-one 13: Benzoyl chloride (0.29 g, 0.002 mol) was added dropwise to a solution of 2-(4-chlorophenyl)-3-amino-6-iodo-3,4-dihydroquinazolin-4-one 6 (0.4 g, 0.001 mol) in dry pyridine and the reaction mixture was reflexed for 30 min. On cooling, the pyridine layer was removed by decantation and the residue was treated with dil. hydrochloric acid, washed with water, filtered and crystallized from acetic acid. M.P.: > 300°C. Yield: 0.3 g (49.5%). IR: 1710 (C=O), 1680 (C=O). Ms: m/z (Rel. Int.): 605 (M^+, 1.44%), 607 (M^++2, 0.3%). Analysis for $C_{28}H_{17}ClIN_3O_3$:% Calc. (Found); C 55.51 (55.3), H 2.83 (3.0), N 6.94 (6.6).

2-(4-Chlorophenyl)-3-imido-6-iodo-3,4-dihydroquinazolin-4-ones 14 and 15: A mixture of 2-(4-chlorophenyl)-3-amino-6-iodo-3,4-dihydroquinazolin-4-one 6 (3.98 g, 0.01 mol), the appropriate acid anhydride (0.01 mol) and anhydrous sodium acetate (0.5 g) in acetic acid (50 ml) was reflexed for 5 h. On cooling the separated solid was filtered, washed with water and crystallized from acetic acid to afford compounds 14 and 15 in 60% yields (Table 9 and 10).

Antimicrobial testing: All of the newly synthesized compounds were subjected to antimicrobial screening by determining the minimum inhibitory concentration (MIC) using the agar dilution technique[11].

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 subtilis* 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 as a solution in DMF to the wells at concentrations ranging from 200 to about 3.0 μg ml^{-1} in addition to the standard Tetracycline and the 0 (control). 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.

RESULTS AND DISCUSSION

The MICs of the active compounds against the susceptible organisms are presented in Table 11. It was found that all of the compounds had inhibitory activity only against *Staphylococcus aureus* and *Bacillus subtilis* and were inactive against other microorganisms are presented in (Table 11). Compounds 5 h and 5 K showed the highest activity against these strains (MIC = 12.5 μg ml^{-1}) while 12a (MIC = 20.0 μg ml^{-1}). Compounds 5a-g, 5i, 5j, 5l-r, 9a-g, (MIC = 50 μg ml^{-1}).

Table 11: Antimicrobial activity (MIC μg ml^{-1})

	Susceptible microorganisms	
Comp. no.	*Staphylococcus aureus*	*Bacillus subtilis*
5 (a-g, I, j, l-r)	50.0	50.00
5 (h, k)	12.5	12.50
9 a-g	50.0	50.00
12 a	20.0	20.00
Tetracycline	0.4	0.25

It is worth to mention that the inhibitory activity of compounds 5h, 5k and 12a might be attributed to their ability to chelate some metals necessary for the living microorganism, each compound bears 3 adjacent electron rich centers, or their ability to penetrate cell walls after intramolecular hydrogen bonding, otherwise the antibacterial activity of the remaining compounds seems to be sporadic with no apparent pattern and thus making it difficult to correlate with structural requirements.

ACKNOWLEDGMENT

The authors are grateful to Dr. Soliman I. Fooda, Assoc. Prof. of Microbiology, Faculty of Pharmacy, Al-Azhar University for carrying out the antimicrobial testing.

REFERENCES

1. Pandeya, S.N., D. Sriram, G. Nath and E. De Clercq, 1999. Synthesis, antibacterial, antifungal and anti-HIV evaluation of a Schiff and Mannich bases of isatin derivatives with 3-amino-3-methylmercaptoquinazoline-4-(3*H*)-one. Pharm. Acta Helv., 74: 11-17.
2. Misra, H.K. and A.K.S. Gupta, 1982. Synthesis and evaluation of substituted 4 (3*H*) quinazoline derivatives for antimicrobial and anticholinesterase activity. Pharmazie, 37: 254-256.
3. Abdel-Hamide, S.G., 2001. Synthesis of some new qunazolines and their antimicrobial screening. Saudi Pharm. J., 9: 72-84.
4. Abdel-Hamide, S.G., 1999. Synthesis and biological activity of 4-substituted quinazolines. Indian J. Heterocyclic Chem., 9: 63-68.
5. Mosaad, S.M., K.I. Mohammed, M.A. Ahmed and S.G. Abdel-Hamide, 2004. Synthesis of certain new 6-iodoquinazolines as potential antitubercular agents. J. Applied Sci., 4: 302-307.
6. Mohamed, Y.A., M.A. Aziza, F.M. Salama and A. Alafify, 1992. Some new quinazolines with antibacterial activity. J. Serb. Chem. Soc., 57: 29-34.
7. Korolkovas, A., 1988. Essentials of Medicinal Chemistry. 2nd Edn. John Willey and Sons, New York, pp: 720-721.
8. Hamad, A.S. and M.E. Azab, 2001. Synthesis and biological activity of 4-some quinazoline derivatives. Boll Chem. Farm., 140: 233-237.
9. Nawrocka, W. and J.J. Stanko, 2002. Antimicrobial 4 (3*H*) Quinazolinones. Part III. Boll. Chim. Farm., 140: 84-91.
10. Neil, V.H., S. Christopher and B. Keith, 1990. Antifolate and antibacterial actvity of 5- substituted 2, 4- diaminoquinazolines. J. Med. Chem., 33: 434-444.
11. Colle, J.G., J.P. Duguid, A.G. Fraser and B.P. Marmion, 1989. Mackie and McCartney, Practical Medical Microbiology, 13th Edn., Churchill Livingstone, london, U.K.