Synthesis of Some New Quinazoline Derivatives as Potential Anti-Infective Agents

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Abstract: A new series of the fused heterocyclic analogs 4-oxo-6-iodo-2-tolyl-3H-quinazoline were prepared and screened for their antimicrobial activity. Compounds 8, 11 and 12 showed remarkable broad spectrum antimicrobial activity. The fused heterocycles 14-oxo-6-iodo-2-tolyl-3H-quinazoline nucleus proved to contribute for antimicrobial activity. The detailed synthesis and their antimicrobial screening are reported.

[Menshawy A. Mohamed, Ahmed M. Alafeefy and Sami G. Abdel hamid. **Synthesis of Some New Quinazoline Derivatives as Potential Anti-Infective Agents.** *Life Sci J 2014;11(11):108-112]* (ISSN:1097-8135).
http://www.lifesciencesite.com.14

Key words: synthesis, 4-oxo-6-iodo-2-tolyl-3H-quinazoline, antimicrobial screening.

Introduction

The spread of antibiotic resistance among pathogenic bacteria has become a major problem for the clinical management of infectious diseases and has encouraged many of medicinal chemists to search for new antibacterial agents that are able to overcome multidrug-resistant mechanism that can be summarized in three major mechanisms: the first is destruction or modification of the antibiotic (e.g. production of -lactamases and aminoglycoside-inactivating enzymes), the second prevention of access to the target (e.g. alteration of permeability or efflux) and the third is alteration of the target site. These mechanisms of resistance in Gram-positive bacteria Staphylococcus *aureus*, and *Bacillus subitilis* can be mediated either via chromosomes or via plasmids[(1)].

The increasing incidence of infections caused by Gram-positive bacteria with acquired multidrug resistance and the challenge for development of new antibacterial has encourage many medicinal chemists to search for a new antibacterial agents other than analogs of existing antibiotics[(2)].

Due to the importance of quinazoline nucleus as antibacterial for resistant strains of gram positive and gram negative bacteria, a new focus has been made toward some quinazoline analogs for getting a new drug or a new lead for a new drug that can combat resistance of different bacterial strains[(3-10)].

A new series of 6-iodoquinazoline derivatives was synthesized and screened. In this work, the quinazoline analogs were designed to contain some functional groups which was believed to contribute to the antimicrobial activity such as –NHNHSO2-, -NHNH=CH- in addition to a collection of fused or connected heterocycles to the quinazoline ring such as tolyl, substituted phenyl. The new synthesized compounds were screened against Gram negative (*Escherichia coli and Salmonella typhi*), Gram positive bacteria (*S. aureus, B. subitilus*) and fungi (*C. albicans*).

Experimental

All melting points shown in (table 1) were taken in open capillaries and are uncorrected. Microanalysis were conducted on a Heraeus instrument, results are within ±0.4% of the theoretical values, Thin layer chromatography was performed on Merk 5x10 cm plates, percolated with silica gel GF_{254} using (EtOAc, hexane 1:10) as solvent system and short wavelength UV light for visualization. All fine chemicals and reagents used were purchased from Aldrich chemical Co. U.S.A. [1] HNMR were recorded on a Bruker 500 MHz spectrophotometer, Chemical shifts are in б(ppm) values downfield from Tetra methyl Siloxane as an internal standard. The following organisms were used in the antimicrobial screening. *Escherichia coli*, *Staphylococcus aureus*, Sarcina sp. *Bacillus subitilis* and *Candida albicans* [(11)].

The starting material 2-amino-5-iodobenzoic acid (2) was synthesized in 70% yield by adapting a reported procedure [(12).]

2-(4-methylbenzamido)-5-iodobenzoic acid (3)

A mixture of compound (2) 5-iodoanthranilic acid (2.63 g, 0.01mol) and p-tolylchloride (1.54 g, 0.01mol) in dry pyridine (15ml) was heated under reflux for

24h.The reaction mixture was cooled treated with icy hydrochloric acid. The separated solid was filtered, washed with water, dried and crystallized from ethanol (Table 1). ^{1}H NMR (500 MHz,$CDCl_3$-d_6), 3: δ 2.44(s,3H,methyl-H),7.302-7.317 (dd,2H J=7.5-Hz,tolyl-H).7.365- 7.391 (dd,1H,J=13-Hz,phenyl-H),8.066-8.083 (dd,1 H,J=13-Hz,phenyl-H), 8.159-8.175 (dd,2H J=7.5-Hz,tolyl-H), 8.54(s,1 H, phenyl-H), 9.25(s,1 H, COOH), 12.46(broad s,1 H, phNHCO) . ^{13}C NMR (500 MHz,$CDCl_3$-d_6) δ 21.00, 89.67, 118.46 (2), 128.43 (2), 128.81, 129.62 (2), 137.17 (2), 143.86, 145.32 (2), 146.53, 153.20, 167.55.6-iodo-2-p-tolyl-4H-benzo[d][1,3]oxazin-4-one (4)

A mixture of compound (3) 2-(4-methylbenzamido)-5-iodobenzoic acid (, 0.01mol) and acetic anhydride (15ml) was heated under reflux for 2h.The reaction mixture was concentrated, cooled and crystallized from ethanol (Table 1). ^{1}H NMR (500 MHz,$CDCl_3$-d_6), 4: δ 2.37(s,3H,methyl-H),7.414-7.430 (m,2H J=8-Hz,tolyl-H).7.500- 7.483 (dd,1H,J= 8.5-Hz,quinazoline-H), 8.084-8.100 (m,2H J=8-Hz,tolyl-H), 8.228-8.245 (dd,1 H,J=8-Hz,quinazoline-H, 8.388 (d,1 H, quinazoline--H). ^{13}C NMR (500 MHz,$CDCl_3$-d_6) δ 21.78, 91.90, 118.46,127.09, 128.43, 128.81, 129.62, 137.17, 143.86, 145.32, 146.53, 157.82, 158.22.

2-(4-methylbenzamido)-5-iodobenzohydrazide (5)

A mixture of compound (4) 6-iodo-2-p-tolyl-4H-benzo[d][1,3]oxazin-4-one (2.63 g, 0.01mol) and hydrazine hydrate 60% in water (0.03mol) in absolute ethanol (20ml) was heated under reflux for 1h.The reaction mixture was cooled. The separated solid was crystallized from ethanol (Table 1). ^{1}H NMR (500 MHz, DMSO-d_6), 5: δ 2.38(s,3H,methyl-H), 4.71(s,2H,NHNH2),7.361-7.376 (m,2H J=7.5-Hz,tolyl-H) 7.818-7.834 (m,2H J=7.5-Hz,tolyl-H), 7.848- 7.866 (d,1H,J= 9-Hz,phenyl-H), 8.090(s,1 H, phenyl--H), 8.451-8.469 (d,1 H,J=9-Hz,phenyl-H), 10.321(s,1 H, CONHNH2), 12.416 (s,1 H, phNHCO). ^{13}C NMR (500 MHz, DMSO-d_6) δ 21.00, 86.38, 122.15,126.94, 127.90, 129.45, 129.70, 131.38, 135.79, 138.89, 140.36, 142.37, 164.21, 165.91.

3-amino-2-(4-tolyl)-quinazolin-4(3H)-one (6)

Fusion of a mixture of compound (4) 6-iodo-2-p-tolyl-4H-benzo[d][1,3]oxazin-4-one (2.63 g, 0.01mol) and neat hydrazine hydrate 95% (0.03mol) for 30 min gave compound (6).The reaction mixture was washed with water, cooled. The separated solid was crystallized from ethanol (Table 1). ^{1}H NMR (500 MHz, DMSO-d_6), 6: δ 2.38(m,3H,methyl-H), δ 5.86-5.70(s,2H,NH2),7.274-7.290 (dd,2H J=8-Hz,tolyl-H). 7.486-7.503 (dd,,1H,J=8.5-Hz,quinazoline-H). 7.709-7.725 (dd,2H J=8-Hz,tolyl-H).8.096-8.110(dd,, 1H,J=8.5-Hz,quinazoline-H), 8.43(d, 1 H, quinazoline-H)). ^{13}C NMR (500 MHz, DMSO-d_6) δ 20.97, 91.55, 121.66, 127.92, 129.54, 129.68, 131.67,134.13, 139.45, 142.57, 145.90, 156.37, 160.00.

3-(benzylideneamino)-6-iodo-2-p-tolylquinazolin-4(3H)-one (7)

A mixture of 3-amino-2-(4-tolyl)-quinazolin-4(3H)-one (6) (3.55g, 0.01mol) and appropriate aldehyde (benzaldhyde) (0.01mol) in glacial acetic acid (15ml) was heated under reflux for 18h. The reaction mixture then cooled the obtained solid was filtered, washed with water, dried and crystallized from ethanol (l (Table 1). ^{1}HNMR (DMSO-d_6), 7: δ 2.4(s,3H,tolyl methyl-H), 7.2 (d,1H J=13-Hz, quinazoline- H)7.33-7.34(dd,2H J=16-Hz tolyl-H),7.44-7.45 (dd,2H J=14-Hz phenyl-H), 7.52-7.53 (dd,2H J=16-Hz tolyl-H), 8.09-8.10 (dd,2 H,J=14-Hz,phenyl-H), 8.11-8.23 (dd,1H J=12 Hz, quinazoline-H), 8.33(d,1 H,J=12 Hz, quinazoline-H) 8.48(s,1 H, N=CH).

3-(4-methoxybenzylideneamino)-6-iodo-2-p-tolylquinazolin-4(3H)-one (8)

A mixture of 3-amino-2-(4-tolyl)-quinazolin-4(3H)-one (6) (3.65g, 0.01mol) and appropriate aldehyde (p-methoxy benzaldhyde) (0.01mol) in glacial acetic acid (15ml) was heated under reflux for 18h. The reaction mixture then cooled the obtained solid was filtered, washed with water, dried and crystallized from ethanol (Table 1). ^{1}HNMR (DMSO-d_6), 8: δ 2.4(s,3H,tolyl methyl-H), 3.3 (s,3H,phenyl methoxy-H), 7.2 (d,1H J=13-Hz, quinazoline- H)7.34-7.35(dd,2H J=16-Hz tolyl-H),7.44-7.45 (dd,2H J=14-Hz phenyl-H), 7.52-7.53 (dd,2H J=16-Hz tolyl-H), 8.09-8.10 (dd,2 H,J=14-Hz,phenyl-H), 8.1-8.2 (dd,1H J=12 Hz, quinazoline-H), 8.33(d,1 H,J=12 Hz, quinazoline-H) 8.5(s,1 H, N=CH).

3-(2,4-dichlorobenzylideneamino)-6-iodo-2-p-tolylquinazolin-4(3H)-one (9)

A mixture of 3-amino-2-(4-tolyl)-quinazolin-4(3H)-one (6) (3.65g, 0.01mol) and appropriate aldehyde (2,4,-dichloro benzaldhyde) (0.01mol) in glacial acetic acid (15ml) was heated under reflux for 18h. The reaction mixture then cooled the obtained solid was filtered, washed with water, dried and crystallized from ethanol (Table 1). ^{1}HNMR (DMSO-d_6), 9: δ 2.4(s,3H,tolyl methyl-H), 7.28 (dd,1H,phenyl-H), 7.2 (d,1H J=13-Hz, quinazoline- H)7.354-7.369 (dd,2H J=15-Hz tolyl-H),7.651-7.660 (dd, H J=9-Hz phenyl-H), 7.606-7.621 (dd,2H J=15-Hz tolyl-H), 8.071-8.080 (d,1 H,J=9-Hz,phenyl-H), 7.806-7.820 (dd,1H J=15 Hz, quinazoline-H), 8.768-8.783(d,1 H,J=15 Hz, quinazoline-H) 8.58(s,1 H, N=CH).

3-(2,4,6-trimethoxybenzylideneamino)-6-iodo-2-p-tolylquinazolin-4(3H)-one (10)

A mixture of 3-amino-2-(4-tolyl)-quinazolin-4(3H)-one (6) (3.65g, 0.01mol) and appropriate aldehyde (2,4,6-trimethoxy benzaldhyde) (0.01mol) in glacial acetic acid (15ml) was heated under reflux for 18h. The reaction mixture then cooled the obtained solid was filtered, washed with water, dried and crystallized from ethanol (Table 1). ^{1}HNMR (DMSO-d_6), 10: δ 2.4(s,3H,tolyl methyl-H), 2.51(s,3H,phenyl methoxy-H)3.37 (s,6H,phenyl methoxy-H), 7.28-7.30 (d,2H J=16-Hz, phenyl- H), 7.528-7.539(dd,2H J=11-Hz tolyl-H), 7.545-7.555(dd,2H J=11-Hz tolyl-H),8.168-8.172 (dd,1H J=4-Hz, quinazoline- H), 8.185-8.189 (dd,2H J=4-Hz quinazoline- H), 8.09-8.10 (dd,2 H,J=14-Hz,phenyl-H), 8.1-8.2 (dd,1H J=12 Hz, quinazoline-H), 8.438-8.442(d,1 H,J=4 Hz, quinazoline-H) 11.160 (s,1 H, N=CH) ^{13}C NMR (500 MHz, DMSO-d_6) δ 20.97,39.47, 92.33, 122.41, 128.39, 128.46, 129.72, 130.38,134.61, 139.45, 140.13, 143.51, 145.91, 156.81, 158.25, 168.52.

3-(4-bromobenzene sulphonamido)-6-iodo-2-p-tolylquinazolin-4(3H)-one (11)

A mixture of compound 3-amino-2-(4-tolyl)-quinazolin-4(3H)-one (6) (0.365g, 0.001mol) and p-bromo benzene sulphonyl chloride (0.255 gm, 0.001mol)) in dry pyridine (15ml) was heated under reflux for 24h.The reaction mixture was cooled treated with icy hydrochloric acid. The separated solid was filtered, washed with water, dried and crystallized from ethanol (Table 1). ^{1}H NMR (500 MHz,$CDCl_3$-d_6), 11: δ2.38(s,1H, SO2-NH), 2.44(s,3H,tolyl methyl-H), 7.28-7.29 (m,1H J=12-Hz, quinazoline- H)7.35-7.37(dd,1H J=16-Hz tolyl-H),7.39-7.4 (dd,2H J=14-Hz phenyl-H), 7.51-7.52 (dd,2H J=16-Hz tolyl-H), 7.91-7.92 (dd,2 H,J=14-Hz,phenyl-H), 8.1-8.2 (dd,1H J=12 Hz, quinazoline-H), 8.39(d,1 H,J=12 Hz, quinazoline-H).

3-(4-nitrobenzene sulphonamido)-6-iodo-2-p-tolylquinazolin-4(3H)-one (12)

A mixture of compound 3-amino-2-(4-tolyl)-quinazolin-4(3H)-one (6) (0.365g, 0.001mol) and p-nitro benzene sulphonyl chloride (0.221 gm, 0.001mol)) in dry pyridine (15ml) was heated under reflux for 24h.The reaction mixture was cooled treated with icy hydrochloric acid. The separated solid was filtered, washed with water, dried and crystallized from ethanol (Table 1). ^{1}H NMR (500 MHz,$CDCl_3$-d_6), 12: δ2.3(s,1H, SO2-NH), 2.44(s,3H,methyl-H), 7.34-7.37 (m,2H J=12-Hz,tolyl-H, 1H J=16-Hz quinazoline-H) 7.46- 7.53 (dd,2H,J=12-Hz,tolyl-H),8.082-8.096 (dd,2 H,J=16-Hz,phenyl-H), 8.115-8.119 (dd,1H Hz, quinazoline-H), 8.082-8.098(dd,2 H J=16, phenyl-H), 8.4(d,1 H, quinazoline-H).

3-(benzene sulphonamido)-6-iodo-2-p-tolylquinazolin-4(3H)-one (13)

A mixture of compound 3-amino-2-(4-tolyl)-quinazolin-4(3H)-one (6) (0.365g, 0.001mol) and benzene sulphonyl chloride (0.2 ml, 0.001mol)) in dry pyridine (15ml) was heated under reflux for 24h.The reaction mixture was cooled treated with icy hydrochloric acid. The separated solid was filtered, washed with water, dried and crystallized from ethanol (Table 1). ^{1}H NMR (500 MHz,$CDCl_3$-d_6), 13: δ 2.39(s,1H, SO2-NH), 2.44(s,3H,tolyl methyl-H), 7.27-7.28 (m,1H J=12-Hz, quinazoline- H)7.38-7.39(dd,2H J=16-Hz tolyl-H),7.41-7.42 (dd,2H J=14-Hz phenyl-H), 7.52-7.53 (dd,2H J=16-Hz tolyl-H), 8.08-8.09 (dd,2 H,J=14-Hz,phenyl-H), 8.1-8.2 (dd,1H J=12 Hz, quinazoline-H), 8.38(d,1 H,J=12 Hz, quinazoline-H).

3-(4-methylbenzene sulphonamido)-6-iodo-2-p-tolylquinazolin-4(3H)-one (14)

A mixture of compound 3-amino-2-(4-tolyl)-quinazolin-4(3H)-one (6) (0.365g, 0.001mol) and p-methyl benzene sulphonyl chloride (0.19 gm, 0.001mol)) in dry pyridine (15ml) was heated under reflux for 24h.The reaction mixture was cooled treated with icy hydrochloric acid. The separated solid was filtered, washed with water, dried and crystallized from ethanol (Table 1). ^{1}H NMR (500 MHz,$CDCl_3$-d_6), 14: : δ2.39(s,1H, SO2-NH), 2.28(s,3H,phenyl methyl-H), 2.44(s,3H,tolyl methyl-H), 7.282-7.295 (m,1H J=13-Hz, quinazoline- H)7.357-7.373(dd,1H J=16-Hz tolyl-H),7.462-7.476 (dd,2H J=14-Hz phenyl-H), 7.514-7.531 (dd,1H J=16-Hz tolyl-H), 8.084-8.100 (dd,2H,J=16-Hz,tolyl-H),8.116-8.120 (dd,1 H,J=14-Hz,phenyl-H), 8.27-8.28 (dd,1H J=13 Hz, quinazoline-H), 8.4(d,1 H, quinazoline-H).

Antimicrobial testing

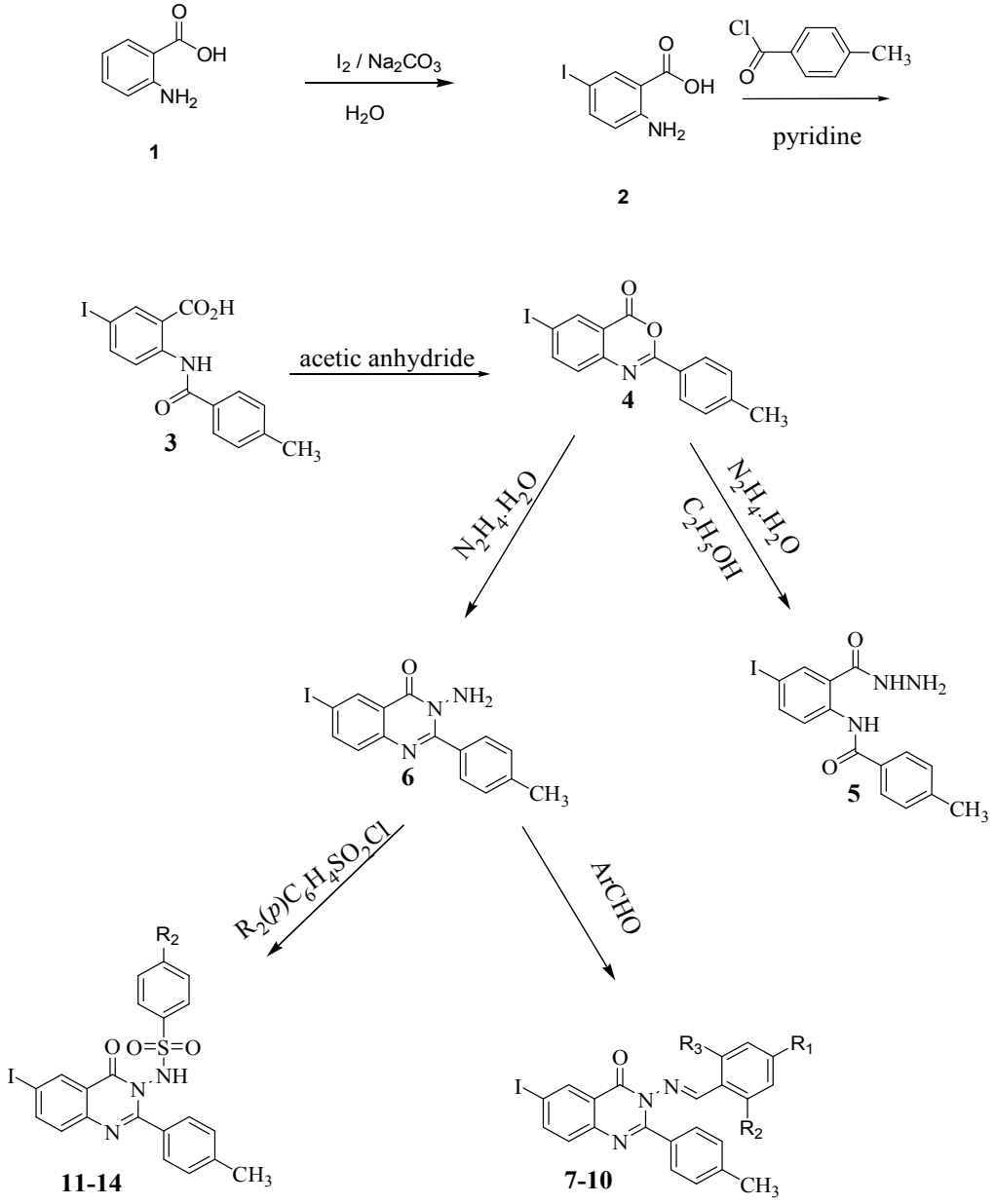
Nutrient agar plates were seeded using 0.1 of overnight cultures. Cylindrical plugs were removed from the agar plates using a sterile cork borer and 100 ul of the tested compound (1mg/ml DMSO) were added to the well in triplicates. Blank solvent was used as control. Plates inoculated with tested bacteria were incubated at 37˚c, while those of Fungi were incubated at 30˚c. Results were taken after 24hr of incubation and were recorded as average diameter of inhibition zone in mm.

Antimicrobial Screening

Most of the newly synthesized compounds were subjected to antimicrobial screening by in vitro cup-plate technique[11,13] using noroxin, erythromycin and nystatin as positive controls. Compunds 8,11 and 12 showed remarkable activity towards the Gram positive bacteria *S. Aureus* and *B. Subitilis* and the gram negative bacteria Escherichia coli and *Salmonella typhi* proved to be sensitive toward compounds 5,6,7,13 and 14. Moreover Compounds 8 and 13

showed very good activity toward the used fungi *C. albicans*.

As result the compounds 8, 11, and 12 proved to be the most active broad spectrum antimicrobial agents in this study (table 2). A close view to the structures of active compounds leads to that the remarkable antimicrobial activity was related to the compounds have a quinazoline skeleton attached to sulphamoyl moiety as in compounds 11,12 and 13 or a quinazoline skeleton attached to methoxy phenyl moiety as in compound 8 which open a new window to new leads for designing a prototype antimicrobial of quinazoline nucleus that will be a figure in the antimicrobial area future.



7 : R_1=H. R2=H R3=H **8 :** R_1=OCH_3 R2=H R3=H

9 : R_1=Cl. R2=Cl R3=H **10 :** R_1=OCH_3 R2=OCH_3 R3=OCH_3

.**11** R_2=Br. **12:**R_2=NO_2. **13 :** R_2=H. **14** R_2=CH_3

Table1: The physicochemical properties of new synthesized compounds.

No.	Compound	Solvent of crystallization	Melting point	Yield	Molecular Formula
1	3	Ethanol	224-226	70%	C15H12INO3
2	4	Dioxane	198-200	55%	C15H10INO2
3	5	Ethanol	243-244	60%	C15H14IN3O2
4	6	Ethanol	229-231	40%	C15H12IN3O
5	7	Ethanol	218-220	66%	C22H16IN3O
6	8	Ethanol	266-267	63%	C23H18IN3O2
7	9	Ethanol	283-284	65%	C22H14Cl2IN3O
8	10	Ethanol	296-298	72%	C25H22IN3O4
9	11	Acetic acid	222-224	67%	C21H15BrIN3O3S
10	12	Acetic acid	237-239	65%	C21H15IN4O5S
11	13	Acetic acid	223-225	54%	C21H16IN3O3S
12	14	Acetic acid	232-234	45%	C22H18IN3O3S

Table2: Antimicrobial screening results of the tested compounds at 1mg/ml concentration.

No.	Compound No.	B.subitilis	Sarcina sp.	S.aureus	S.typhi	E.coli	C.albicans
1	5	+	+	+	+	+	+
2	6	+	+	+	+	+	+
3	7	+	+	+	+	+	+
4	8	++	++	+	+	+	++
5	11	++	++	++	+	+	+
6	12	++	++	++	+	+	+
7	13	++	+	+	+	+	++
8	14	+	+	+	+	+	+
9	Noroxin	+++	+++	+++	++	++	NT
10	Erythromycin	+++	++	+++	++	++	NT
11	Nystatin	NT	NT	NT	NT	NT	++

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

Results and Discussion

The approach for getting the target compounds shown in scheme 1 achieved by using the starting material 5-iodo-2-amino benzoic acid (2) that was prepared according to a reported procedure () and allowed to react with 4-tolyl chloride to afford the amide derivative (3) that cyclized to the corresponding benzoxazone (4). That benzoxazone was reacted with hydrazine hydrate 60 % in absolute ethanol to produce the diamide derivative (5). However, the 3-amino-2-(4-tolyl)-quinazolin-4(3H)-one (6) derivative was obtained on boiling compound (4) with neat hydrazine hydrate 95 %. The 3-amio derivative (6) was reacted with certain aldehydes to produce the corresponding arylidene derivatives (7-10).in addition to condensation of 3-amino derivative with benzene sulphonyl chloride derivatives to afford compounds (11-14).

Acknowledgment

The authors extend their appreciation to the Deanship of Scientific Research at Salman bin Abdul-Aziz University, Grant No. 6.H.32, Alkharj, Saudi Arabia.

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6/1/2014