ChemInform Abstract: Novel 6,8-Dibromo-4(3H)quinazolinone Derivatives of Antibacterial and Antifungal Activities.

ARTICLE *in* CHEMINFORM · NOVEMBER 2010

Impact Factor: 0.74 · DOI: 10.1002/chin.201047155

6 AUTHORS, INCLUDING:

Sherein I. Abd El-Moez
National Research Center, Egypt
53 PUBLICATIONS **125** CITATIONS

European Journal of Medicinal Chemistry 45 (2010) 3311–3319

Contents lists available at ScienceDirect

European Journal of Medicinal Chemistry

journal homepage: http://www.elsevier.com/locate/ejmech

Original article

Novel 6,8-dibromo-4(3*H*)quinazolinone derivatives of anti-bacterial and anti-fungal activities

Mosaad S. Mohamed [a], Mohsen M. Kamel [b], Emad M.M. Kassem [b], Nageh Abotaleb [a], Sherein I. Abd El-moez [b], Marwa F. Ahmed [a,*]

[a] *Faculty of Pharmacy, Helwan University, Dokki, Cairo, Egypt*
[b] *National Research Centre, Dokki, Cairo 12, Egypt*

ARTICLE INFO

Article history:
Received 25 February 2010
Received in revised form
11 April 2010
Accepted 13 April 2010
Available online 20 April 2010

Keywords:
Ethyl-4-(6,8-dibromo-2-phenyl-4-oxo(4*H*)-quinazolin-3-yl)benzoate,benzoic acid hydrazide
Schiff bases
Thiazolidinones
Mannich beses
Oxadiazole
Pyrazols
Pyrrole
Urea and thiourea derivatives
Anti-bacterial
Anti-fungal

ABSTRACT

Starting from 4-(6,8-dibromo-2-phenyl-4-oxo-(4*H*)-quinazolin-3-yl)-benzoic acid ethyl ester (**II**) and its acid hydrazide **III**, a new series of Schiff bases **IV** and their cyclized products, thiazolidinones **V**, oxadiazole **VIII**, pyrazoles **X**–**XII**, pyrroles **XIII**–**XV** and other related products were synthesized. These compounds were screened for their anti-bacterial activity against Gram-positive bacteria (*Staphylococcus aureus*, *Legionella monocytogenes* and *Bacillus cereus*) and Gram-negative bacteria (*Escherichia coli*, *Pseudomonas aeruginosa* and *Salmonella typhimurium*) and anti-fungal activity (*Candida albicans* and *Aspergillus flavus*) using paper disc diffusion technique. The minimum inhibitory concentrations (MICs) of the compounds were also determined by agar streak dilution method. Among the synthesized compounds 2-(4-(2-phenyl-6,8-dibromo-4-oxo-(4*H*)quinazolin-3-yl)-*N*-ethylamido benzoic acid hydrazide **VIIa** was found to exhibits the most potent in vitro anti-microbial activity with the MICs of 1.56, 3.125, 1.56, 25, 25 and 25 μg/ml against *E. coli*, *S. typhimurium*, *L. monocytogenes*, *S. aureus*, *P. aeruginosa*, and *B. cereus* respectively. Compound 2-(4-(2-phenyl-6,8-dibromo-4-oxo-(4*H*)quinazolin-3-yl)-*N*-methyl thioamido benzoic acid hydrazide **VIIc** was found to exhibit the most potent in vitro anti-fungal activity with MICs 0.78 and 0.097 μg/ml against C. albicans and *A. flavus*.

1. Introduction

The rapid rise in bacterial resistance to the traditional antibiotics such as penicillin's [1] and tetracycline [2] has encouraged a continuing search for new classes of compounds with novel modes of anti-bacterial activity. The quinazolinones have emerged as anti-microbial agents of an immense interest because of their broad spectrum of in-vitro activity and their in-vivo chemotherapeutic activity [3,4]. Diverse examples of anti-microbial quinazolinones such as (structure 1) which exerted anti-bacterial effect against *Staphylococcus aureus* in a very low concentration [5], quinazolinone derivatives (structure 2) [6] and (structure 3) [7], showed potent anti-microbial activities. Also (structure 4) exhibited high in-vivo activity, low toxicity and good pharmacokinetic profile [8,9].

Quinazolin-4(3*H*)-ones with substitution at position 3, has been reported to be associated with anti-microbial properties [10–17]. Examples of these substitutions were substituted phenyl ring moieties [10,11], bridged phenyl rings [12,13], heterocyclic rings [14] and aliphatic systems [15,16]. On the other hand, diverse chemotherapeutic agents contain pharmacophores like Br, phenolic OH, and Cl substitutions, are reported to possess anti-microbial activities [17–19].

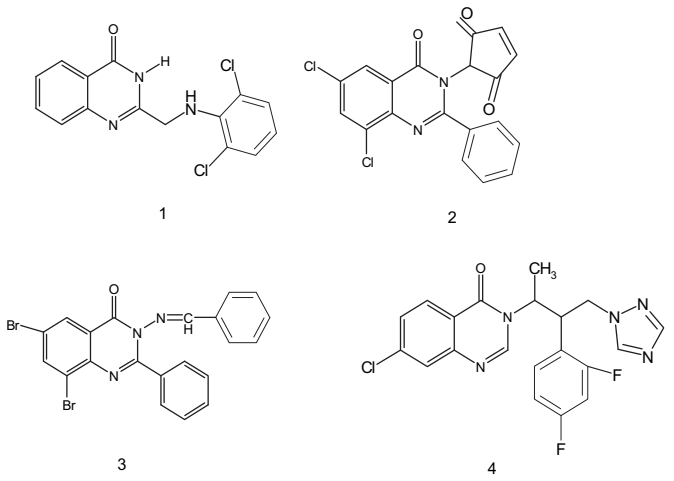
Based on these findings, and in continuation of our drug research program concerning synthesis of new safer and more biologically active quinazolinones [20–22], it was of interest to synthesize a new series of 6,8-dibromo-3-substituted phenyl-quinazoline-4(3*H*)-one derivatives with the hope to obtain more active and less toxic anti-microbial agents.

2. Chemistry

Synthesis of the desired compounds was achieved by allowing 6,8-dibromo-2-phenyl-4(*H*)-3,1-benzoxazin-4-one (**I**) [23] to undergo fusion with ethyl-*p*-aminobenzoate at 140 °C to give the intermediate ethyl-4-[6,8-dibromo-2-phenyl-4-oxo(4*H*)quinazolin-3-yl)-benzoate (**II**), which upon reaction with excess

* Corresponding author. Tel.: +20 0103875225.
E-mail address: marwafarag80@yahoo.com (M.F. Ahmed).

0223-5234/$ – see front matter © 2010 Elsevier Masson SAS. All rights reserved.
doi:10.1016/j.ejmech.2010.04.014



hydrazine hydrate afforded the corresponding 4-(6,8-dibromo-2-phenyl-4-oxo-(4*H*)-quinazoline-3-yl)-benzoic acid hydrazide (**III**) (Scheme 1).

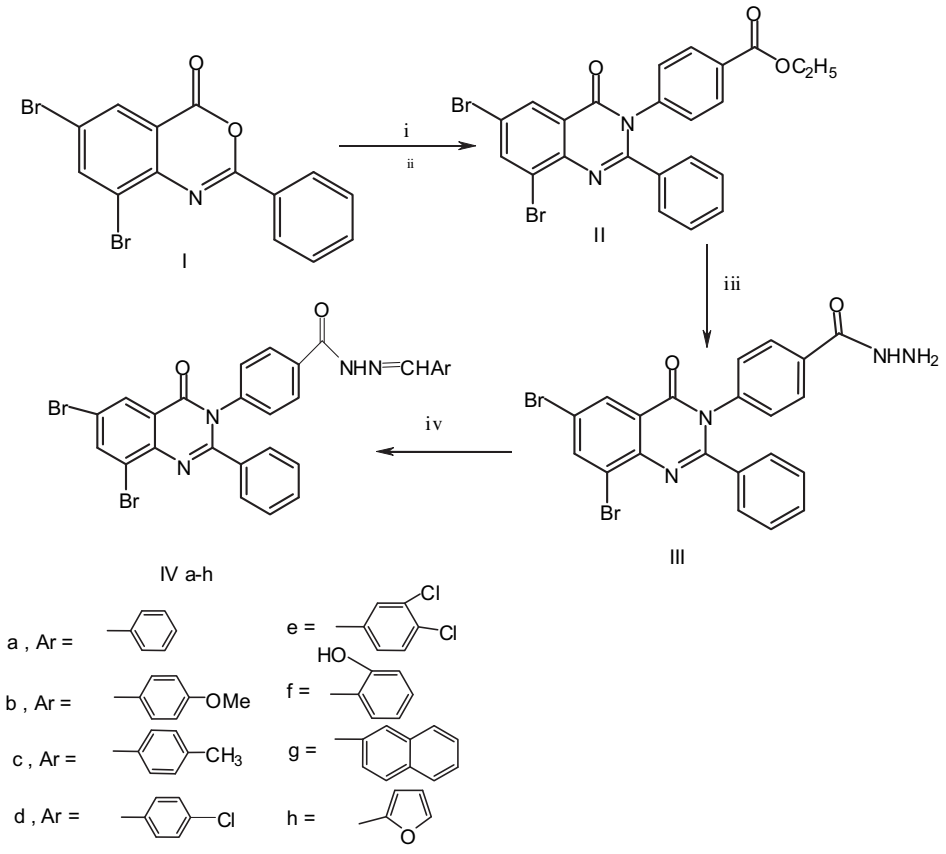
Assignments of structures **II** and **III** are based on correct elemental analyses. IR spectrum of compound **II** displayed absorption bands at 1700, 1684 cm^{-1} for two carbonyl groups. Its ^1H NMR spectrum showed a triplet signal at 1.3 ppm and quartet signal at 4.18 ppm which supported the presence of ethyl group. IR spectrum of compound **III** displayed absorption bands at 3312, 3132 cm^{-1} for (NH, NH_2) groups. The mass spectrum of **III** showed (*m*/*z*, R.I.): M^+ 512.2, 514.24, 516.2 (49%, 100%, 50%).

Reaction of **III** with different aromatic aldehydes, namely, benzaldehyde, *p*-anisaldehyde, *p*-tolualdehyde, *p*-chlorobenzaldehyde, 3, 4-dichlorobenzaldehyde, 2-hydroxybenzaldehyde, naphthalene-2-carboxaldehyde and/or furfural in glacial acetic acid, afforded the corresponding arylmethylidine-hydrazides (Schiff bases) **IVa**–**h**, respectively (Scheme 1).

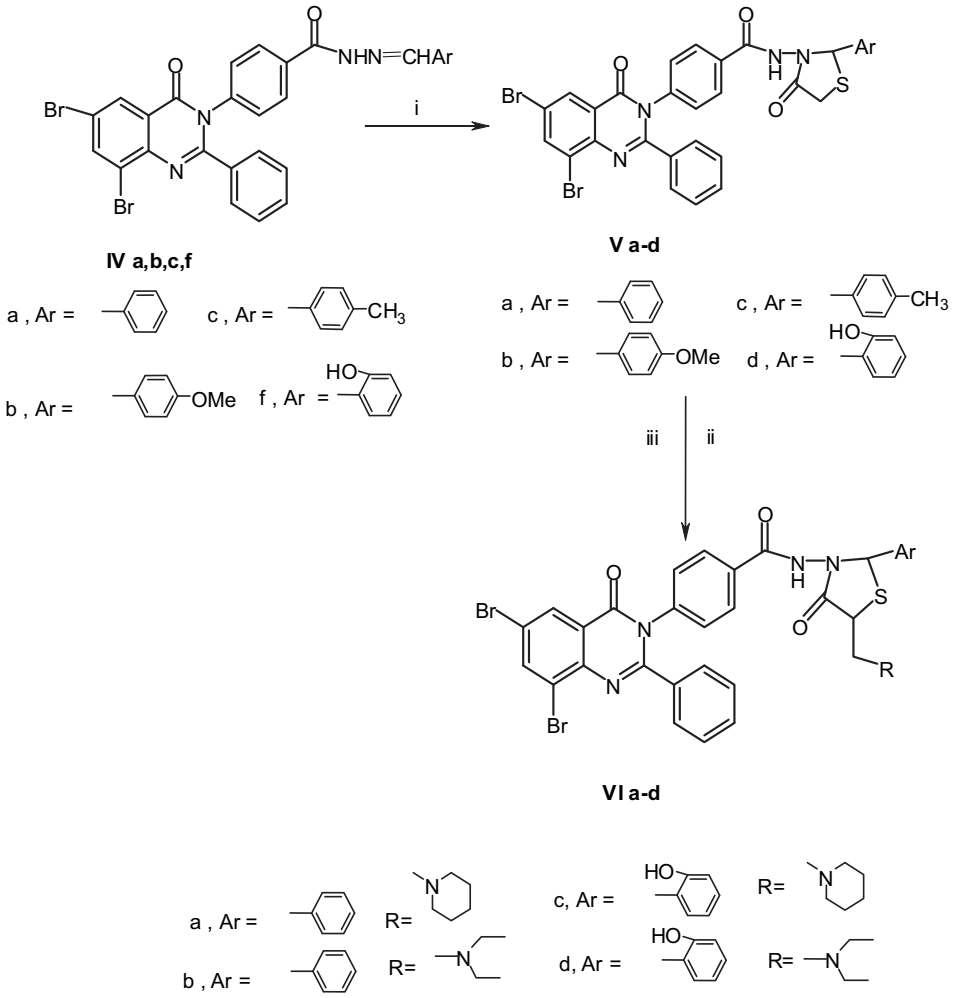
Compounds **IVa**–**h** gave correct values in elemental analyses. The ^1H NMR spectrum of compound **IVb** showed signal at 3.7 ppm of methoxy group and at 12.07 ppm (s, 1H, NH, exchangeable with D_2O). ^1H NMR spectrum of compound **IVc** showed signal at 2.5 ppm of methyl group and at 11.2 ppm (s, 1H, NH, exchangeable with D_2O). Mass spectrum of **IVf** showed (*m*/*z*, R.I.): M^+ 615.97, 617.97, 619.97 (4.1%, 8.3%, 4.4%).

Cyclocondensation of the Schiff bases **IVa**–**c** and **IVf** with mercapto acetic acid in glacial acetic acid [24] afforded the corresponding 4-[6,8-dibromo-2-phenyl-4-oxo(4*H*)quinazolin-3-yl]-*N*-(4-oxo-2-substituted thiazolidin-3-yl)-benzamides (**Va**–**d**), respectively (Scheme 2). Assignments of structures (**Va**–**d**) are based on correct elemental analyses. IR spectrum of compounds (**Va**–**d**) assigned for three carbonyl groups (2CO, cyclic amide) and (CONH). The ^1H NMR spectrum of compound **Va** showed signal at 3.70 ppm of CH_2, thiazolidinone ring, 5.90 ppm of CH of thiazolidinone ring, and at 11.2 ppm (s, 1H, NH, exchangeable with D_2O). Compounds (**Vb**, **c**) gave correct values in ^1H NMR spectra.

The quinazolinyl-thiazolidinones **Va**–**d** react with paraformaldehyde and secondary amines namely, piperidine and/or diethyl amine to give the corresponding Mannich bases, namely 4-[6,8-dibromo-2-phenyl-4-oxo(4*H*)-quinazolin-3-yl]-*N*-[4-oxo-3-diethylaminomethyl/(or piperidinomethyl)-2-phenyl(and/or 2-hydroxy phenyl)-thiazolidin-3-yl] benzamides (**VIa**–**d**) (Scheme 2).



Scheme 1. Reagent and conditions: (i) ethyl-*p*-aminobenzoate; (ii) fusion at 140 °C, sand bath for 1 h; (iii) $NH_2NH_2 \cdot H_2O$ in absolute ethanol, reflux, 6 h.; (iv) Ar-CHO in glacial acetic acid, reflux 5 h.



Scheme 2. Reagent and conditions: (i) thioglycolic acid in glacial acetic acid, reflux, 6 h; (ii) paraformaldehyde; (iii) diethyl amine and/or piperidine in dimethylformamid, refluxed, 6 h.

IR spectrum of compounds (**VIa**–**d**) assigned for three carbonyl groups (2CO, cyclic amide) and (CONH). The ^{1}H NMR spectrum of compound **Va** showed signal at 1.2 ppm triplet for $2CH_3$ of diethyl, at 3.8 ppm quartet for $2CH_2$ of diethyl, at 2.9 ppm $-CH_2-$N, 3.70 ppm of CH, thiazolidinone ring, 5.70 ppm of CH of thiazolidinone ring), and at 11.3 ppm (s, 1H, NH, exchangeable with D_2O). The ^{1}H NMR spectrum of compound **Vc** showed signals at 1.47 and 2.6 ppm for piperdine.

Also, condensation of the benzoic acid hydrazide **III** with phenyl (or ethyl) isocyanate and/or methyl isothiocyanate in pyridine, afforded the corresponding phenyl (or ethyl) hydrazine-carboxamides **VIIa**–**c** respectively, (Scheme 3).

Assignments of structures **VIIa**–**c** are based on correct elemental analyses. IR spectrum of all compounds revealed the presence of three NH groups. The ^{1}H NMR spectrum of compound **Va** showed signal at 1.1 ppm triplet for CH_3 of ethyl, at 3.1 ppm quartet for CH_2 of ethyl, at 5.01, 5.02 and 10.75 ppm (s, 3H, 3NH, exchangeable with D_2O). Compounds (**VIIb**, **c**) gave correct values in ^{1}H NMR spectra. The mass spectrum of **VIIb** showed (*m*/*z*, R.I.): M^+ 630.9, 630.9, 630.9 (4%, 8.5%, 3.9%).

On the other hand, heating of the acid hydrazide **III** with acetic anhydride, gave the corresponding methyl oxadiazole **VIII**, while its reaction with acetic anhydride in acetic acid afforded the corresponding acetyl hydrazide **IX**. (Scheme 3)

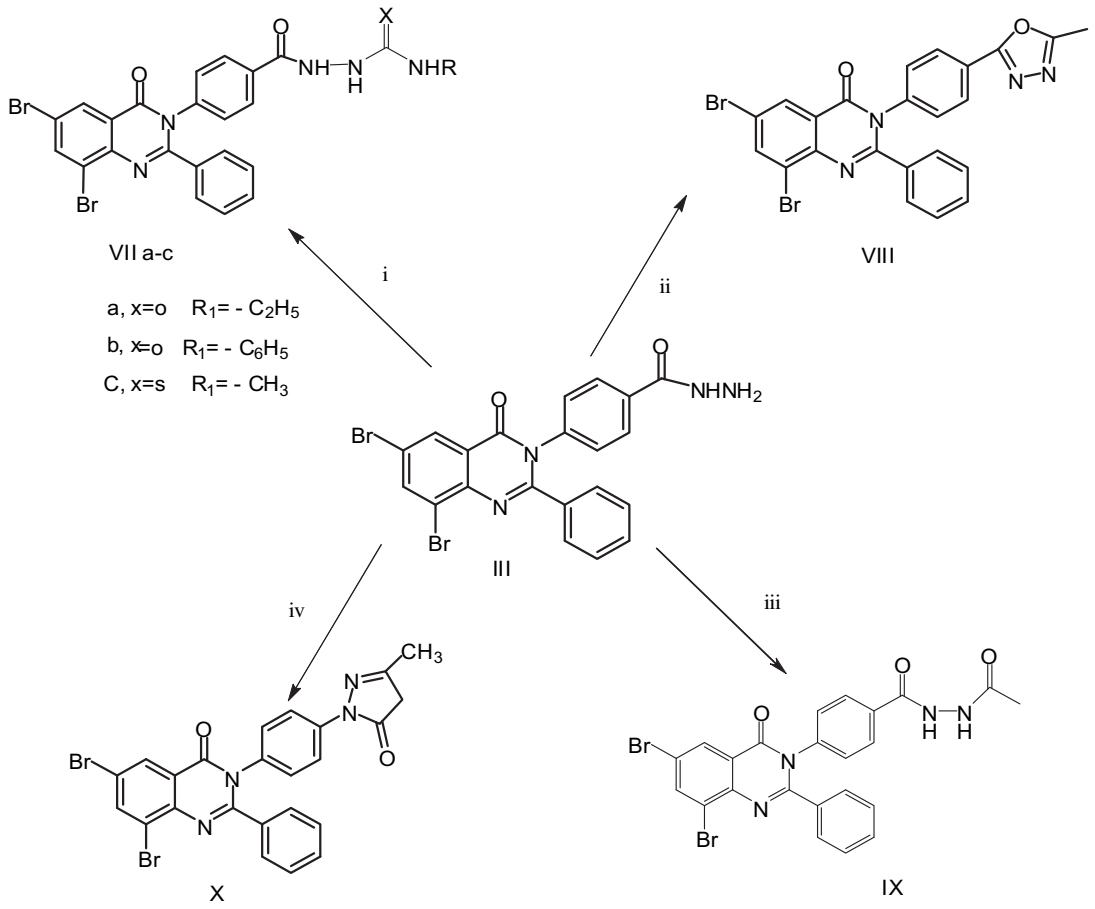
Compounds **VIII**–**IX** gave correct values in elemental analyses. IR spectrum of compound **VIII** revealed the presence of one carbonyl group at 1703 cm^{-1} and the absence of any absorption bands in the NH region. On the other hand IR spectrum of compound **IX** revealed the presence of three carbonyl groups 1730, 1710 and 1680 cm^{-1}, 2NH at 3285, 3280 cm^{-1}. The Mass spectra of compounds **VIII**, **IX** are in agreement with their structures.

Further, reaction of **III** with dikeonic esters or B-diketones, such as, ethylaceto-acetate, acetylacetone, and/or diethylmalonate, afforded the corresponding pyrazolyl-carbonyl phenyl quinazolinones **X**–**XII** respectively (Schemes 3 and 4).

Assignments of structures **X**–**XII** are based on correct elemental analyses. IR spectrum of compound **X** revealed the presence of two carbonyl groups at 1725 and 1680 cm^{-1} and the absence of any absorption bands in the NH region. IR spectrum of compound **XI** showed the presence of one carbonyl group at 1680 and the absence of any absorption bands in the NH region. Furthermore IR spectrum of compound **XII** revealed the presence of NH group at 3160 cm^{-1} and three carbonyl groups at 1720, 1715 and 1687 cm^{-1}. The ^{1}H NMR spectrum of compound **XII** showed signal at 3.2 ppm singlet for CH_2, pyrazolone group.

Reaction of the benzoic acid hydrazide **III** with the cyclic anhydrides, such as maleic anhydride, succinc anhydride and/or phthalic anhydride, gave the corresponding pyrrol-2,5-dione, pyrrolidin-2,5-dione, and/or 1,3-dioxoisoindoline derivatives **XIII**–**XV** respectively (Scheme 4).

Compounds **XIII**–**XV** gave correct values in elemental analyses. IR spectrum of compounds **XIII**–**XV** revealed the presence of NH group and four carbonyl groups. The ^{1}H NMR spectrum of



Scheme 3. Reagent and conditions: (i) iso/isothiocyanate in pyridine reflux, 5 h; (ii) acetic anhydride, reflux, 6 h; (iii) acetic anhydride in acetic acid, refluxed for 6 h; iv) ethylaceto acetate in ethanol, reflux 5 h.

compound **XIII** and **XIV** are in agreement with their structure. The mass spectrum of **XIII** showed (*m*/*z*, RI): M^+ 591.94, 593.94, 595.94 (10%, 20.3%, 9.9%). Mass spectrum of **XV** showed (*m*/*z*, RI): M^+ 593.95, 595.95, 597.95 (4%, 8.3%, 3.2%)

3. Biological evaluation

3.1. Materials and methods

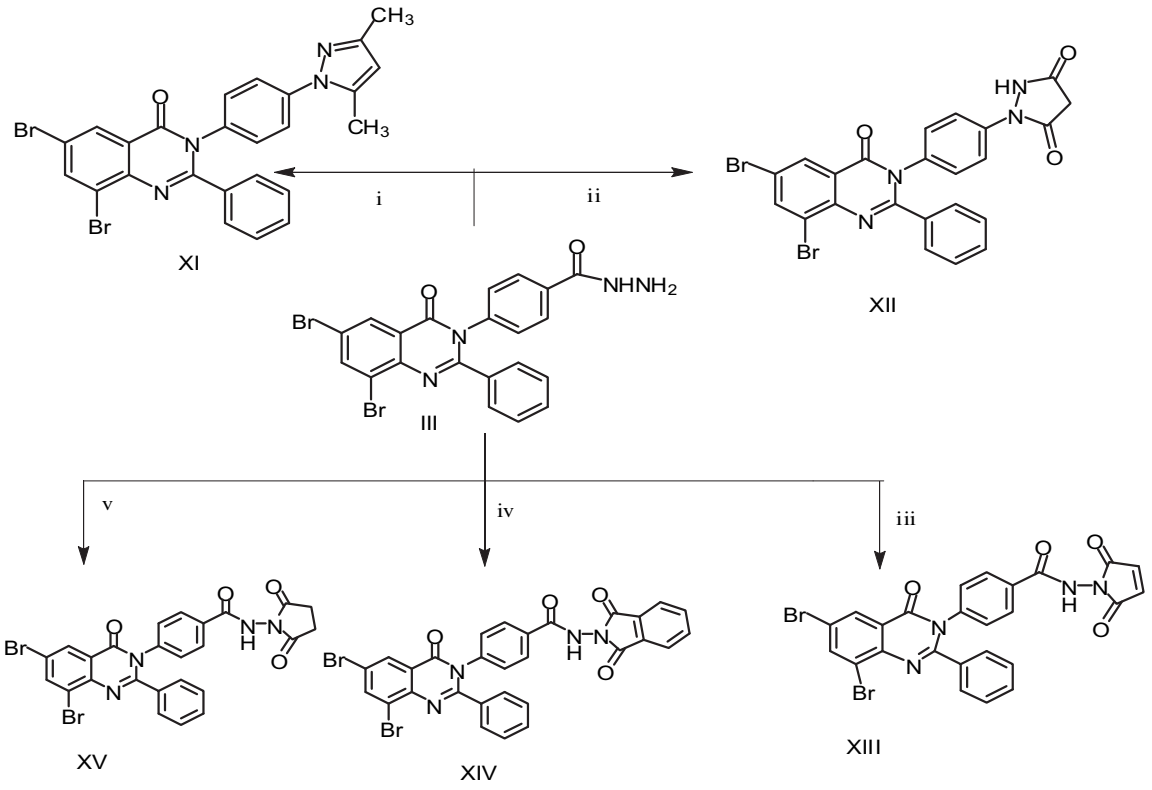
3.1.1. Antimicrobial activity

All the synthesized compounds were screened for anti-microbial activities by paper disc diffusion technique. The anti-bacterial activity of the synthesized compounds was tested against strains isolated from animal byproducts and were accused of being a direct cause of food intoxication in human. The strains include three Gram-positive bacteria (*S. aureus*, *Legionella monocytogenes* and *Bacillus cereus*) and three Gram-negative bacteria (*Escherichia coli, Pseudomonas aeruginosa* and *Salmonella typhimurium*) using Muller Hinton agar medium (Oxoid). The anti-fungal activities of the compounds were tested against two fungi (*Candida albicans* and *Aspergillus flavus*) using Sabouraud dextrose agar medium (Oxoid). The observed data on the anti-microbial activity of the synthesized compounds and standard drugs are given in Table 1.

4. Results and discussion

In this present work novel series of quinazolin-4(3*H*)-ones compounds were synthesized. Synthetic Schemes 1–4 illustrate the way used for the synthesis of target compounds. All the synthesized compounds were screened for their anti-bacterial activity against *S. aureus*, *L. monocytogenes*, *B. cereus*, *E. coli*, *P. aeruginosa* and *S. typhimurium* and anti-fungal activity against *C. albicans* and *A. flavus*. The minimum inhibitory concentrations (MIC) of all compounds were also determined. The anti-bacterial data (Table 1) revealed that all tested compounds of this investigation are moderate to good activity against all the tested pathogenic bacteria. As compared to the standard drug Ciprofloxacin with MICs 1.56, 0.39, 1.56, 1.56, 0.78 and 0.39 μg/ml against *E. coli*, *S. typhimurium*, *L. monocytogenes*, *S. aureus*, *P. aeruginosa*, and *B. cereus* respectively, 2-(4-(2-Phenyl-6,8-dibromo-4-oxo-(4*H*)quinazolin-3-yl)-*N*-ethylamido benzoic acid hydrazide **VIIa** showed very promising activity with MIC 1.56 μg/ml against both E. coli and *L. monocytogenes*. Compound **II** show significant anti-microbial activity against *S. aureus*, *S. typhimurium* with MICs 1.56 μg/ml and 3.125 μg/ml respevtively. Compound **VId** show potent anti-microbial activity against *S. typhimurium* with MIC 0.78 μg/ml. Also compounds **VIII**, **IVe** and **VIc** show potent anti-microbial activity against *B. cereus* with MIC 1.56 μg/ml.

The screening data of anti-fungal activity of these series of compounds shows wide range of anti-fungal activity. It is of interest that compound 2-(4-(2-Phenyl-6,8-dibromo-4-oxo-(4*H*)quinazolin-3-yl)-*N*-methyl thioamido benzoic acid hydrazide **VIIc** was found to exhibit the most potent in vitro anti-fungal activity with MICs of 0.78 and 0.097 μg/ml against *C. albicans* and *A. flavus*. which is even so much more potent than standard drug Fluconazole with MICs of 1.56 and 0.78 μg/ml against *C. albicans* and *A. flavus*.1.56. Also compounds **IVg** and **XIV** showed pronounced anti-fungal activity against *A. flavus* with MIC 0.39 μg/ml.Compound **VIb** and



Scheme 4. Reagent and conditions: (i) acetylacetone in ethanol, reflux 5 h; (ii) diethylmalonate in ethanol, reflux 5 h; (iii) maleic anhydride in ethanol, reflux 7 h; (iv) phthalic anhydride in ethanol, reflux 7 h; (v) succinic anhydride in ethanol, reflux 7 h.

Vb show potent anti-fungal activity against *A. flavus* with MIC 1.56 μg/ml.

The most potent anti-bacterial activity exhibited by compound **VIIa** might be due to the presence of N-ethylamido benzoic acid hydrazide moiety of the 2-phenyl substituted quinazolin-4(3*H*)-one.On the other hand the most potent anti-fungal activity exhibited by compound **VIIc** might be due to the presence of N-methyl thioamido benzoic acid hyrazide moiety of the 2-phenyl substituted quinazolin-4(3*H*)-one. It is interesting to note that a minor alteration in the molecular configuration of investigated compounds may have a pronounced effect on anti-microbial screening, e.g. compound **VIIc** having thioamido benzoic acid hyrazide moiety have so much more anti-fungal activity than **VIIa** and **VIIb** with ethylamido benzoic acid hydrazide and phenylamido benzoic acid hydrazide moieties respectively. On the other hand compounds **VIIa** and **VIIb** have more anti-bacterial activity than **VIIc**.

5. Conclusion

We have synthesized novel series of quinazolin-4(3*H*)-ones compounds to evaluate them on anti-microbial screen. The anti-microbial activity of the synthesized compounds may be due the presence of the versatile pharmacophores and bromine which might increase the lipophilic character of the molecule, which facilitate the crossing through the biological membrane of the micro-organism and thereby inhibit their growth. The data also revealed that presence of N-methyl thioamido benzoic acid hyrazide moiety of the 2-phenyl substituted quinazolin-4(3*H*)-one exerted more influence on the anti-fungal profile than ethylamido benzoic acid hydrazide and phenylamido benzoic acid hydrazide moieties which might be due to presence of sulphur atom which has anti-fungal properties [25].

6. Experimental

6.1. Chemistry

All melting points are uncorrected, elemental analyses were carried out in the micro analytical units of National Research Centre and Cairo University, Egypt. IR spectra were recorded on FT. IR spectrophotometer-Nexus 670-Nicolet, USA and Perkin Elmer-9712 spectrophotometer. ^{1}H NMR spectra were determined on a Varian-Gemmi-300 MHz and Joel-Ex270 MHz NMR spectrometer using TMS as an internal standard. Mass spectra were recorded on Finnegan Mat SSQ 7000 mode EI 70 ev (Thermo Inst. Sys. Inc., USA). Thin layer chromatography was carried out on silica gel 60 F254 (Merck) thin layer chromatography plates using a chloroform, petroleum ether, methanol mixture (7:4:1 v/v) as the mobile phase.

6.1.1. 2-Phenyl-6,8-dibromo-(4H)-3,1-benzoxazin-4-one (I)

This compound was prepared according to a reported method [23]. m.p. 178 °C.

6.1.2. Ethyl 4-(2-phenyl-6,8-dibromo-4-oxo-(4H)quinazolin-3-yl) benzoate (*II*)

A mixture of the benzoxazine I (3.8 g, 10 mmol) and ethyl-*p*-aminobenzoate (1.65 g; 10 mmol) was heated together upon fusion at 140 °C on sand bath for 1 h. After cooling, the crude mass was crystallized from ethanol twice to give white crystals of **II**. M.p. 194 °C, in 75% yield. Analysis for $C_{23}H_{16}Br_2N_2O_3$, M.wt (528.2) Calcd.: %C, 52.30; H, 3.05; N, 5.30. Found: % C, 52.50; H, 2.95; N, 5.10, IR (KBr, cm^{-1}): 3059(CH, aromatic), and 1700, 1684 (2CO). ^{1}H NMR (DMSO-d_6, δ ppm): 1.3 (t, J = 7.1 Hz, 3H, CH3, ethyl group), 4.18 (q, J = 7.13 Hz, 2H, CH_2, ethyl group), 7.26–7.73 (m, 9H, aromatic-H), 7.8 (s, 1H, H-7, Ar-H), and 8.2 (s, 1H, H-5, Ar-H).MS (*m*/*z*, R.I.): M^+ 525.95, 527.95, 529.95 (10.1%, 20.4%, 10.4%) and at *m*/*z* 108.2 (100%).

Table 1
Anti-microbial activity of the synthesized compounds.

Tested chemicals	In vitro activity-zone of inhibition in mm (MIC in μg/ml)							
	Tested strains							
	E. coli O157 (F)	*S. typhimurium* (3)	*L. monocytogenes* (A)	*S. aureus*	*P. aeruginosa* (C)	*B. cereus* (E)	*C. albicans*	*A. flavus*
II	11 (50)	16 (3.125)	14 (25)	17 (1.56)	12 (50)	9 (50)	−ve	10 (25)
III	10 (>50)	11(50)	11 (50)	10 (>50)	13 (25)	12 (25)	−ve	15 (18.5)
IVa	11(45)	10 (>50)	13 (35)	12 (25)	12 (50)	12 (30)	−ve	10 (25)
IVb	8 (>50)	10 (>50)	12 (50)	11 (50)	11(>50)	13 (35.5)	−ve	11 (25)
IVc	11(40)	15 (5)	13 (30)	12 (25)	15 (2.5)	11 (35)	−ve	12 (20)
IVd	12 (20)	10 (>50)	14 (30)	12 (25)	12 (20)	16 (5.5)	−ve	16 (12.5)
IVe	14 (25)	11(50)	13 (25)	14 (25)	14 (25)	17 (1.56)	11(25)	12 (19)
IVf	10 (50)	13 (30)	11 (50)	15 (12.5)	11(>50)	13 (25.5)	−ve	15 (10.5)
IVg	13 (25)	12 (50)	16 (3.125)	14 (25)	13 (25)	12 50)	13 (25)	26 (0.39)
IVh	9 (>50)	16 (5)	11 (>50)	13 (20)	8 (>50)	12 (50)	12 (25)	−ve
Va	10 (>50)	16 (4.1)	13 (32)	12 (25)	12 (35)	9 (50)	−ve	−ve
Vb	11 (45)	12 (40)	11 (>50)	10 (45)	11(50)	18 (1.9)	10 (25)	20 (1.56)
Vc	9 (>50)	15 (7)	10 (50)	10 (>50)	16 (10.1)	9 (50)	10 (30)	16 (12.5)
Vd	13 (30)	12 (50)	15 (15)	11 (45)	12 (35)	9 (>50)	−ve	−ve
VIa	11 (45)	11(50)	15 (13)	12 (30)	14 (10)	12 (25)	12 (35)	14 (20)
VIb	10 (>50)	10 (>50)	13 (25)	12 (25)	13 (25)	12 (30)	14 (12.5)	18 (1.56)
VIc	12 (35)	15 (12.5)	12 (50)	12 (50)	11(25)	16 (1.56)	15 (12.5)	16 (12.5)
VId	10 (50)	18 (0.78)	14 (12.5)	12 (25)	12 (50)	13 (25)	12(25)	14 (18)
VIIa	18 (1.56)	16 (3.125)	16 (1.56)	11(25)	12 (25)	13 (25)	−ve	16 (12.5)
VIIb	10 (50)	16 (3.2)	13 (30)	10 (50)	12 (50)	14 (12.5)	9 (50)	−ve
VIIc	11 (50)	12 (50)	11(>50)	10 (>50)	14 (25)	9 (>50)	22 (0.78)	38 (0.097)
VIII	14 (25)	12 (50)	15(12.5)	15 (12.5)	12 (50)	17 (1.56)	11 (25)	18 (9.5)
IX	9 (>50)	14 (30)	14 (35)	11 (40)	13 (25)	9 (>50)	−ve	22 (1.2)
X	8 (>50)	14 (30)	16 (6)	11 (40)	12 (50)	11 (>50)	9 (50)	20 (2.5)
XI	10 (50)	14 (20)	15 (12.5)	10 (50)	12 (30)	13 (25)	9 (50)	−ve
XII	9 (>50)	12 (50)	10 (>50)	9 (>50)	11(>50)	10 (>50)	−ve	18 (1.9)
XIII	9 (>50)	17 (2.9)	11 (>50)	9 (>50)	11(>50)	9 (50)	10 (25)	17 (4.5)
XIV	11(50)	11(>50)	10 (>50)	10 (>50)	11(>50)	16 (5.5)	9 (50)	25 (0.39)
XV	9 (>50)	18 (1.7)	12 (50)	9(>50)	11(>50)	9 (>50)	−ve	17 (3.5)
Ciprofloxacin (100 μg/ml)	18 (1.56)	20 (0.39)	17 (1.56)	18 (1.56)	19 (0.78)	20 (0.39)	–	–
Fluconazole (100 μg/ml)	–	–	–	–	–	–	18 (1.56)	22 (0.78)
DMSO	−ve	−ve	−ve	−ve	−ve	−ve	−ve	−ve

*6.1.3. 4-(2-Phenyl-6,8-dibromo-4-oxo-(4H)quinazolin-3-yl)-benzoic acid hydrazide(**III**)*

A solution of the ester derivative **II** (5.28 g; 10 mmol) and hydrazine hydrate 98% (1.6 g; 50 mmol) in absolute ethanol (20 mL) was refluxed for 6 h. Upon cooling, the formed precipitate was filtered off and recrystalized from ethanol to give the hydrazide derivative **III**. m.p. 240 °C, in 85% yield. Analysis for $C_{21}H_{14}Br_2N_4O_2$, M.wt. (514.17). Calcd.: %C, 49.05; H, 2.74; N, 10.90. Found: %C, 49.00; H, 2.69; N, 10.80. IR (KBr, cm^{-1}): 3312, 3132 (NH, NH_2), 3056 (CH, aromatic), 1712 (CO, quinazoline ring) and 1640 (CO, amide). ^1H NMR (DMSO-d_6, δ ppm): 4.9 (s, 2H, NH_2, exchangeable with D_2O), 7.40–7.8 (m, 9H, aromatic-H), 7.9 (s, 1H, H-7, Ar-H), 8.2 (s, 1H, H-5, Ar-H) and 10.00 (s, 1H, NH, exchangeable with D_2O). ^{13}C NMR (DMSO-d_6, δ ppm): 113.5 (C-5), 122.4 (C-7), 124.1 (C-2$^{\backslash\backslash}$,6$^{\backslash\backslash}$), 125.3 (C-3), 127.8 (C-4$^{\backslash\backslash}$) 128.2 (C-2$^{\backslash}$and C-6$^{\backslash}$), 129.3 (C-3$^{\backslash\backslash}$ andC-5$^{\backslash\backslash}$), 129.7 (C-1$^{\backslash}$,3$^{\backslash}$, 5$^{\backslash}$),), 131.3 (C-8), 132.9 (C-6$^{\backslash}$)137.6 (C-1$^{\backslash\backslash}$), 139 (C-6), 154 (C-4), 156 (C-1), 160 (C-2), and 167.8 (C=O). MS (*m*/*z*, R.I.): M^+ 512.2, 514.24, 516.2 (49%, 100%, 50%).

*6.1.4. 4-(2-Phenyl-6,8-dibromo-4-oxo-(4H)quinazolin-3-yl)benzoic acid (1-substituted meth(E)ylidene) hydrazides (**IVa**–**h**)*

General method: A mixture of compound **III** (5.14 g; 10 mmol) and the appropriate aldehyde, namely: benzaldehyde, *p*-anisaldehyde, *p*-tolualdehyde, *p*-chlorobenzaldehyde, 3,4-dichlorobenzaldehde, 2-hydroxybenzaldehyde, naphthalene-2-carboxaldehyde and/or furan-2-carboxaldehyde (20 mmol) in glacial acetic acid (30 mL), was refluxed for 5 h. The reaction mixture was cooled and adding ice water the formed precipitate was filtered off, washed with water and crystallized from the proper solvent to obtain the desired Schiff bases (**IVa**–**h**) respectively.

*6.1.5. 4-(2-Phenyl-6,8-dibromo-4-oxo-(4H)quinazolin-3-yl)benzoic acid (phenyl meth(E)ylidene) hydrazide (**IVa**)*

Crystallized from ethanol to give white crystals, m.p. 220 °C, in 70% yield. Analysis for $C_{28}H_{18}Br_2N_4O_2$, M.wt. (602.28). Calcd.: %C, 55.84; H, 3.01; N, 9.30. Found: 55.75; H, 2.98; N, 9.1. IR (KBr, cm^{-1}): 3360 (NH), 1710, 1683 (2CO) and 1594 (C=N). ^1H NMR (DMSO-d_6, δ ppm): 7.2–7.74(m, 14H, aromatic-H), 7.8 (s, 1H, H-7, Ar-H), 8.2 (s, 1H, H-5, Ar-H), 8.66(s, 1H, CH=N) and 12.00 (s, 1H, NH, exchangeable with D_2O). MS (*m*/*z*, R.I.): M^+ 599.95, 601.95, 603.95 (3.1%, 6.4%, 3.4%) and at *m*/*z* 323.4 (100%).

*6.1.6. 4-(2-Phenyl-6,8-dibromo-4-oxo-(4H)quinazolin-3-yl)benzoic acid (4-methoxy phenyl meth(E)ylidene) hydrazide (**IVb**)*

Crystallized from ethanol to give yellowish white crystals, m.p. 160 °C, in 79% yield. Analysis for $C_{29}H_{20}Br_2N_4O_3$, M.wt. (632.30). Calcd.: %C, 55.09; H, 3.19; N, 8.86. Found, %C, 54.97; H, 3.00; N, 8.56. IR (KBr, cm^{-1}): 3350 (NH), 1714, 1683 (2CO) and 1594 (C=N). ^1H NMR (DMSO-d_6, δ ppm): 3.7(3H, s, OCH_3), 7.2–7.6 (m, 13H, aromatic-H), 7.8 (s, 1H, H-7, Ar-H), 8.2 (s, 1H, H-5, Ar-H), 8.66(s, 1H, CH=N), and 12.07 (s, 1H, NH, exchangeable with D_2O).

*6.1.7. 4-(2-Phenyl-6,8-dibromo-4-oxo-(4H)quinazolin-3-yl)benzoic acid (4-methyl phenyl meth(E)ylidene) hydrazide (**IVc**)*

Crystallized from ethanol to give white crystals, m.p. 200 °C, in 80% yield (Analysis for $C_{29}H_{20}Br_2N_4O_2$, M.wt. (616.30). Calcd.: %C, 56.52; H, 3.27; N, 9.09. Found, %C, 56.49; H, 3.30; N, 8.97. IR (KBr, cm^{-1}): 3313 (NH), 1715, 1679 (2CO) and 1595 (C=N). ^1H NMR (DMSO-d_6, δ ppm): 2.5(3H, s, CH_3), 7.03–7.75 (m, 13H, aromatic-H), 7.8 (s, 1H, H-7, Ar-H), 8.2 (s, 1H, H-5, Ar-H), 8.8(s, 1H, CH=N), and 11.2 (s, 1H, NH, exchangeable with D_2O). ^{13}C NMR (DMSO-d_6,

δ ppm): 20.5 (CH_3), 113.5 (C-5), 124.2 (C-7), 125.3 (C-2$^{\prime\prime}$,6$^{\prime\prime}$), 126.4 (C-2$^{\prime\prime\prime}$ and C-6$^{\prime\prime\prime}$), 127.3 (C-3), 127.9 (C-4$^{\prime\prime}$) 128.2 (C-2$^{\prime}$and C-6$^{\prime}$), 129.5 (C-3$^{\prime\prime}$ andC-5$^{\prime\prime}$), 129.7(C-1$^{\prime}$,3$^{\prime}$, 5$^{\prime}$),), 130.1 (C-3$^{\prime\prime\prime}$ and C-5$^{\prime\prime\prime}$), 130.4 (C-1$^{\prime\prime\prime}$) 131.3 (C-8), 132.8 (C-6$^{\prime}$)137.6 (C-1$^{\prime\prime}$), 139 (C-6), 144.2 (C-4$^{\prime\prime\prime}$). 147.8 (-N=CH)., 154 (C-4), 156 (C-1), 160 (C-2), 162.8 (C=O), MS (*m*/*z*, R.I.): M^+ 613.99, 615.99, 617.99 (5.1%, 10.3%, 5.4%) and at *m*/*z* 498.7 (100%).

*6.1.8. 4-(2-Phenyl-6,8-dibromo-4-oxo-(4H)quinazolin-3-yl)benzoic acid (4-chloro phenyl meth(E)ylidene) hydrazide (**IVd**)*

Crystallized from ethanol to give white crystals, m.p. 180 °C, in 82% yield. Analysis for $C_{28}H_{17}Br_2ClN_4O_2$, M.wt. (636.72). Calcd.: %C, 52.82; H, 2.69; N, 8.80. Found, %C, 52.79; H, 2.60; N, 8.60. IR (KBr, cm^{-1}): 3415 (NH), 1710, 1680 (2CO) and 1600 (C=N). ^{1}H NMR (DMSO-d_6, δ ppm): 7.3–7.76 (m, 13H, aromatic-H), 7.8 (s, 1H, H-7, Ar-H), 8.2 (s, 1H, H-5, Ar-H), 8.8(s, 1H, CH=N), and 11.7 (s, 1H, NH, exchangeable with D_2O).

*6.1.9. 4-(2-Phenyl-6,8-dibromo-4-oxo-(4H)quinazolin-3-yl)benzoic acid (3,4-dichloro phenyl meth(E)ylidene) hydrazide (**IVe**)*

Crystallized from ethanol to give white crystals, m.p. 140 °C, in 82% yield. Analysis for $C_{28}H_{16}Br_2Cl_2N_4O_2$, M.wt. (671.17). Calcd.: %C, 52.82; H, 2.69; N, 8.80. Found, %C, 52.79; H, 2.60; N, 8.60. IR (KBr, cm^{-1}): 3320 (2NH), 1712, 1685 (2CO) and 1605 (C=N).

*6.1.10. 4-(2-Phenyl-6,8-dibromo-4-oxo-(4H)quinazolin-3-yl) benzoic acid (2-hydroxy phenyl meth(E)ylidene) hydrazide (**IVf**)*

Crystallized from ethanol to give yellowish white crystals, m.p. 154 °C, in 80% yield. Analysis for $C_{28}H_{18}Br_2N_4O_3$, M.wt. (618.28). Calcd.: %C, 54.39; H, 2.93; N, 9.06. Found, %C, 54.30; H, 2.70; N, 8.96. IR (KBr, cm^{-1}): 3310 (NH), 1710, 1680 (2CO) and 1600 (C=N). MS (*m*/*z*, R.I.): M^+ 615.97, 617.97, 619.97 (4.1%, 8.3%, 4.4%) and at *m*/*z* 500.3 (100%).

*6.1.11. 4-(2-Phenyl-6,8-dibromo-4-oxo-(4H)quinazolin-3-yl)-benzoic acid (naphthalene-2-yl meth(E)ylidene) hydrazide (**IVg**)*

Crystallized from ethanol to give white crystals, m.p. 145 °C, in 80% yield. Analysis for $C_{32}H_{20}Br_2N_4O_2$, M.wt. (652.33). Calcd.: %C, 58.92; H, 3.09; N, 8.59. Found, %C, 58.81; H, 3.00; N, 8.50. IR (KBr, cm^{-1}): 3400 (NH), 1712, 1681 (2CO) and 1595 (C=N). ^{1}H NMR (DMSO-d_6, δ ppm): 7.3–7.72 (m, 16H, aromatic-H), 7.8 (s, 1H, H-7, Ar-H), 8.2 (s, 1H, H-5, Ar-H), 8.7(s, 1H, CH=N), and 11.8 (s, 1H, NH, exchangeable with D_2O).

*6.1.12. 4-(2-Phenyl-6,8-dibromo-4-oxo-(4H)quinazolin-3-yl)-benzoic acid (furan-2-yl meth(E)ylidene) hydrazide (**IVh**)*

Crystallized from ethanol to give white crystals, m.p. 160 °C, in 75% yield. Analysis for $C_{26}H_{16}Br_2N_4O_3$, M.wt. (592.24). Calcd.: %C, 56.52; H, 3.27; N, 9.09. Found, %C, 56.49; H, 3.30; N, 8.97. IR (KBr, cm^{-1}): 3410 (NH), 1715, 1681 (2CO) and 1605 (C=N).

*6.1.13. 4-(2-Phenyl-6,8-dibromo-4-oxo-(4H)quinazolin-3-yl)-N-[4-oxo-2-(aryl) thiazolidin-3-yl]-benzamides (**Va–d**)*

General method: A mixture of compounds (**IVa–c,f**) (10 mmol) and thioglycolic acid (0.35 ml; 10 mmol) in glacial acetic acid (20 mL) was refluxed for 6 h. The excess solvent was evaporated under reduced pressure and the obtained residue was poured on crushed ice. The solid product was filtered off and washed with water to obtain the desired products **Va–d** respectively.

*6.1.14. 4-(2-Phenyl-6,8-dibromo-4-oxo-(4H)quinazolin-3-yl)-N-[4-oxo-2-phenyl thiazolidin-3-yl]benzamide (**Va**)*

Crystallized from ethanol to give white crystals, m.p. 188 °C, in 70% yield. Analysis for $C_{30}H_{20}Br_2N_4O_3S$, M.wt. (676.38). Calcd.: %C, 53.27; H, 2.98; N, 8.28. Found, %C, 53.20; H, 2.92; N, 8.22. IR (KBr, cm^{-1}): 3260 (NH), 3066(CH, aromatic), 2924 (CH-thiazolidinone), 1717, 1685 (2CO, cyclic amide), 1655 (CONH) and 1590 (C=N). ^{1}H NMR (DMSO-d_6, δ ppm): 3.70 (s, 2H, CH_2, thiazolidinone ring), 5.90 (s, 1H, CH of thiazolidinone ring), 7.5–7.9 (m, 14H, aromatic-H) 8.01 (s, 1H, H-7, Ar-H), 8.3 (s, 1H, H-5, Ar-H) and 11.2 (s, 1H, NH, exchangeable with D_2O).

*6.1.15. 4-(2-Phenyl-6,8-dibromo-4-oxo-(4H)quinazolin-3-yl)-N-[4-oxo-2-(4-methoxy phenyl) thiazolidin-3-yl]-benzamide (**Vb**)*

Crystallized from ethanol to give white crystals, m.p. 116 °C, in 75% yield. Analysis for $C_{31}H_{22}Br_2N_4O_4S$, M.wt. (706.40). Calcd.: %C, C, 52.71; H, 3.14; N, 7.93. Found, %C, 52.60; H, 3.00; N, 7.89. IR (KBr, cm^{-1}): 3363 (NH), 3066 (CH, aromatic), 2925 (CH-thiazolidinone), 1712, 1687 (2CO, cyclic amide), 1660 (CONH) and 1600 (C=N). ^{1}H NMR (DMSO-d_6, δ ppm): 3.34 (s, 2H, CH_2, thiazolidinone ring), 3.6 (s, 3H, OCH3), 5.90 (s, 1H, CH of thiazolidinone ring),, 7.5–8.0 (m, 13H, aromatic-H) 8.1 (s, 1H, H-7, Ar-H), 8.4 (s, 1H, H-5, Ar-H) and 11.27 (s, 1H, NH, exchangeable with D_2O). MS (*m*/*z*, R.I.): M^+ 703.97, 706.97, 709.97 (10.2%, 20.3%, 10.3%) and at *m*/*z* 438.1 (100%).

*6.1.16. 4-(2-Phenyl-6,8-dibromo-4-oxo-(4H)quinazolin-3-yl)-N-[4-oxo-2-(4-methyl phenyl) thiazolidin-3-yl]benzamide (**Vc**)*

Crystallized from ethanol to give white crystals, m.p. 120 °C, in 70% yield. Analysis for $C_{31}H_{22}Br_2N_4O_3S$, M.wt. (690.40). Calcd.: %C, C, 53.93; H, 3.21; N, 8.12. Found, %C, 53.88; H, 3.10; N, 8.07. IR (KBr, cm^{-1}): 3364(NH), 3067(CH, aromatic), 2924 (CH-thiazolidinone), 1698, 1685 (2CO, cyclic amide), 1662 (CONH) and 1600 (C=N). ^{1}H NMR (DMSO-d_6, δ ppm): 2.5 (s, 3H, CH3), 3.7 (s, 2H, CH_2, thiazolidinone ring), 5.90 (s, 1H, CH of thiazolidinone ring), 7.5–8.1 (m, 13H, aromatic-H) 8.2 (s, 1H, H-7, Ar-H), 8.45 (s, 1H, H-5, Ar-H), and 11.25 (s, 1H, NH, exchangeable with D_2O). MS (*m*/*z*, R.I.): M^+ 687.98, 689.98, 691.98 (1.3%, 2.8%, 1.3%) and at *m*/*z* 438.3 (100%).

*6.1.17. 4-(2-Phenyl-6,8-dibromo-4-oxo-(4H)quinazolin-3-yl)-N-[4-oxo-2-(2-hydroxy phenyl) thiazolidin-3-yl]benzamide (**Vd**)*

Crystallized from ethanol to give white crystals, m.p. 250 °C, in 65% yield. Analysis for $C_{30}H_{20}Br_2N_4O_4S$, M.wt. (692.38). Calcd.: %C, C, 52.04; H, 2.91; N, 8.09. Found, %C, 51.99; H, 2.80; N, 8.00. IR (KBr, cm^{-1}): 3360(NH), 3060(CH, aromatic), 2920 (CH, thiazolidinone), 1710, 1683 (2CO, cyclic amide), 1660 (CONH) and 1600 (C=N)

*4-(2-Phenyl-6,8-dibromo-4-oxo-(4H)quinazolin-3-yl)-N-[5-diethylamino and/or piperidinomethyl)-4-oxo-2-arylthiazolidin-3-yl]benzamides (**VIa–d**): Mannich bases*

General method: A mixture of compounds (**Va,d**), paraformaldehyde (0.045 g; 5 mmol) and the appropriate secondary amine (5 mmol) namely, diethyl amine and/or piperidine in DMF (20 mL) was refluxed for 6 h. The excess solvent was evaporated under vacuum and the obtained residue was poured on crushed ice. The solid product was filtered off and washed with water to obtain the desired products **VIa–d** respectively.

*6.1.19. 4-(2-Phenyl-6,8-dibromo-4-oxo-(4H)quinazolin-3-yl)-N-[4-oxo-2-phenyl-5-diethylaminomethyl thiazolidin-3-yl]benzamide (**VIa**)*

Crystallized from ethanol to give yellow crystals, m.p. 210 °C, in 60% yield. Analysis for $C_{35}H_{31}Br_2N_5O_3S$, M.wt. (690.40). Calcd.: %C, C, 55.20; H, 4.10 N, 9.20. Found, %C, 55.00; H, 4.00; N, 9.13. IR (KBr, cm^{-1}): 3363(NH), 3089(CH, aromatic), 1707, 1685 (2CO, cyclic amide), 1662 (CONH) and 1600 (C=N). ^{1}H NMR (DMSO-d_6, δ ppm): 1.2 (t, $J = 7.3$ Hz, 6H, $2CH_3$ of diethyl), 3.8 (q, $J = 7.2$ Hz, 4H, $2CH_2$ of diethyl), 2.9 (s, 2H, $-CH_2-$N), 3.7 (s, 1H, CH, thiazolidinone ring), 5.70 (s, 1H, CH of thiazolidinone ring), 7.5–8.1 (m, 14H, aromatic-H) 8.2 (s, 1H, H-7, Ar-H), 8.48 (s, 1H, H-5, Ar-H) and 11.3 (s, 1H, NH, exchangeable with D_2O).

*6.1.20. 4-(2-Phenyl-6,8-dibromo-4-oxo-(4H)quinazolin-3-yl)-N-[4-oxo-2-(2-hydroxyphenyl)-5-diethylaminomethylthiazolidin-3-yl] benzamide (**VIb**)*

Crystallized from ethanol to give brown crystals, m.p. 176 °C, in 60% yield. Analysis for $C_{35}H_{31}Br_2N_5O_4S$, M.wt. (690.40). Calcd.: %C, C, 54.07; H, 4.02; N, 9.01. Found, %C, 54.00; H, 3.90; N, 8.97. IR (KBr, cm^{-1}): 3360(NH), 3080(CH, aromatic), 1690, 1683 (2CO, cyclic amide), 1660 (CONH) and 1601 (C=N). MS (*m*/*z*, R.I.): M^+ 775, 577, 579 (2.3%, 4.8%, 2.3%) and at *m*/*z* 438.3 (100%).

*6.1.21. 4-(2-Phenyl-6,8-dibromo-4-oxo-(4H)quinazolin-3-yl)-N-[4-oxo-2-phenyl-5-piperdin-1-ylmethylthiazolidin-3-yl]benzamide (**VIc**)*

Crystallized from ethanol to give white crystals, m.p. 155 °C, in 64% yield. Analysis for $C_{36}H_{31}Br_2N_5O_3S$, M.wt. (773.54). Calcd.: %C, C, 55.90; H, 4.04; N, 9.05. Found, %C, 55.80; H, 4.00; N, 8.93. IR (KBr, cm^{-1}): 3356(NH), 3066(CH, aromatic), 1695, 1682 (2CO, cyclic amide), 1660 (CONH) and 1601 (C=N). ^{1}H NMR (DMSO-d_6, δ ppm): 1.47 (m, 6H, $3CH_2$ of piperdine), 2.6 (m, 4H, CH_2NCH_2 of piperdine), 2.8 (s, 2H, $-CH_2-$N), 3.73 (s, 1H, CH, thiazolidinone ring), 5.70 (s, 1H, CH of thiazolidinone ring), 7.5–8.0 (m, 14H, aromatic-H) 8.2 (s, 1H, H-7, Ar-H), 8.43 (s, 1H, H-5, Ar-H), and 11.3 (s, 1H, NH, exchangeable with D_2O).

*6.1.22. 4-(2-Phenyl-6,8-dibromo-4-oxo-(4H)quinazolin-3-yl)-N-[4-oxo-2-(2-hydroxyphenyl)-5-piperdin-1-ylmethylthiazolidin-3-yl] benzamide (**VId**)*

Crystallized from ethanol to give white crystals, m.p. 230 °C, in 65% yield. Analysis for $C_{36}H_{31}Br_2N_5O_4S$, M.wt. (789.54). Calcd.: %C, C, 54.76; H, 3.96; N, 8.87. Found, %C, 54.60; H, 3.90; N, 8.80. IR (KBr, cm^{-1}): 3350(NH), 3062(CH, aromatic), 1693, 1680 (2CO, cyclic amide), 1660 (CONH) and 1601 (C=N).

*6.1.23. 2-(4-(2-Phenyl-6,8-dibromo-4-oxo-(4H)quinazolin-3-yl)-N-substituted amido/(thioamido) benzoic acid hydrazides (**VIIa–c**)*

General method: a mixture of compound **III** (5.14 g; 10 mmol), the appropriate iso/isothiocyanate, namely: ethyl isocyanate, phenyl isocyanate and/or methyl isothiocyanate (10 mmol) in pyridine (20 ml) was refluxed for 5 h. The solvent was poured on crushed ice containing few drops HCl. The solid product was filtered off and washed with water to obtain the desired products **Va–c** respectively.

*6.1.24. 2-(4-(2-Phenyl-6,8-dibromo-4-oxo-(4H)quinazolin-3-yl)-N-ethylamido benzoic acid hydrazide (**VIIa**)*

Crystallized from ethanol to give white crystals, m.p. 120 °C, in 70% yield. Analysis for $C_{24}H_{19}Br_2N_5O_3$, M.wt. (585.25). Calcd.: %C, C, 49.25; H, 3.27; N, 11.97. Found, %C, 49.20; H, 3.19; N, 11.91. IR (KBr, cm^{-1}): 3313, 3270, 3200 (3NH), 3064 (CH-aromatic), 1709, 1669, 1659 (3CO). ^{1}H NMR (DMSO-d_6, δ ppm): 1.1 (t, $J = 7.2$ Hz, 3H, ethyl), 3.1 (q, $J = 7.4$ Hz, 2H, ethyl), 7.5–8.2 (m, 9H, aromatic-H), 8.4 (s, 1H, H-7, Ar-H), 8.9 (s, 1H, H-5, Ar-H), 5.01, 5.02 and 10.75 (s, 3H, 3NH, exchangeable with D_2O). ^{13}C NMR (DMSO-d_6, δ ppm): 15.5 (CH_3), 34.5 (CH_2) 113.7 (C-5), 123.9 (C-7), 125.1 (C-2$^{\prime\prime}$,6$^{\prime\prime}$),126.2 (C-3), 127.8 (C-4$^{\prime\prime}$) 128.2 (C-2$^{\prime}$and C-6$^{\prime}$), 129.3 (C-3$^{\prime\prime}$ andC-5$^{\prime\prime}$),129.7(C-1$^{\prime}$,3$^{\prime}$,5$^{\prime}$),), 131.8 (C-8), 132.9 (C-6$^{\prime}$)137.6 (C-1$^{\prime\prime}$), 139 (C-6), 154 (C-4), 156.3 (C-1), 160 (C-2), 162.8 (NHC = O), 167.8 (C=O).

*6.1.25. 2-(4-(2-Phenyl-6,8-dibromo-4-oxo-(4H)quinazolin-3-yl)-N-phenylamido benzoic acid hydrazide (**VIIb**)*

Crystallized from ethanol to give yellowish white crystals, m.p. 230 °C, yield (72%). Analysis for $C_{28}H_{19}Br_2N_5O_3$, M.wt. (633.29). Calcd.: %C, C, 53.10; H, 3.02; N, 11.06 Found, %C, 52.97; H, 2.96; N, 10.95. IR (KBr, cm^{-1}): 3282, 3275, 3200 (3NH), 3059 (CH-aromatic), 1710, 1662, 1660 (3CO). ^{1}H NMR (DMSO-d_6, δ ppm): 6.9–7.5 (m, 14H, aromatic-H), 7.7 (s, 1H, H-7, Ar-H), 8.5 (s, 1H, H-5, Ar-H), 5.01, 9.02 and 9.2 (s, 3H, 3NH, exchangeable with D_2O). MS (*m*/*z*, R.I.): M^+ 630.9, 630.9, 630.9 (4%, 8.5%, 3.9%) and at *m*/*z* 515.2 (100%).

*6.1.26. 2-(4-(2-Phenyl-6,8-dibromo-4-oxo-(4H)quinazolin-3-yl)-N-methyl thioamido benzoic acid hydrazide (**VIIc**)*

Crystallized from ethanol to give white crystals, m.p. 270 °C, in 70% yield. Analysis for $C_{23}H_{17}Br_2N_5O_2S$, M.wt. (587.29). Calcd.: %C, C, 47.04; H, 2.92; N, 11.92. Found, %C, 46.99; H, 2.90; N, 11.90. IR (KBr, cm^{-1}): 3282, 3263, 3200 (3NH), 3059 (CH-aromatic), 1682, 1660 (3CO), 1188 (C=S). ^{1}H NMR (DMSO-d_6, δ ppm): 2.5 (3, 3H, CH_3), 7.5–8.2 (m, 9H, aromatic-H), 8.4 (s, 1H, H-7, Ar-H), 8.9 (s, 1H, H-5, Ar-H), 4, 4.04 and 12.3 (s, 3H, 3NH, exchangeable with D_2O). MS (*m*/*z*, R.I.): M^+ 584.95, 586.95, 588.95 (5%, 10.5%, 5.4%) and at *m*/*z* 435.2 (100%).

*6.1.27. 2-Phenyl-6,8-dibromo-3-[4-(5-methyl-1,3,4-oxadiazol-2-yl) phenyl]-2-phenylquinazolin-4(3H)-one (**VIII**)*

A mixture of the hydrazide **III** (5.14 g; 10 mmol) and acetic anhydride (20 mL) was refluxed for 6 h. The precipitated solid formed upon cooling, was filtered and recrystalized from ethanol to give white crystals of **VIII**. M.p. 180 °C, in 75% yield. Analysis for $C_{23}H_{14}Br_2N_4O_2$, M.wt. (538.19). Calcd.: %C, C, 51.33; H, 2.62; N, 10.41 Found: %C, 51.24; H, 2.53; N, 10.38. IR (KBr, cm^{-1}): 3075 (CH-aromatic), 1703, (CO). ^{1}H NMR (DMSO-d_6, δ ppm): 2.7 (s, 3H, methyl), 7.9–8.2 (m, 9H, aromatic-H). 8.1 (s, 1H, H-7, Ar-H) and 8.6 (s, 1H, H-5, Ar-H), MS (*m*/*z*, RI): M^+ 535.95, 537.95, 539.95 (7%, 14.3%, 6.9%) and at *m*/*z* 23.01 (100%).

*6.1.28. N′-Acetyl-4-(2-phenyl-6,8-dibromo-4-oxo-(4H)quinazolin-3-yl)benzohydrazide (**IX**)*

A mixture of hydrazide **III** (5.14 g; 10 mmol), and a mixture of acetic anhydride (10 mL) and acetic acid (10 mL) was refluxed for 6 h. The precipitated solid formed upon cooling, was filtered and recrystalized from ethanol to give white crystals of **IX**. M.p. 170 °C, in 70% yield. Analysis for $C_{23}H_{16}Br_2N_4O_3$, M.wt. (556.21). Calcd.: %C, C, 49.67; H, 2.90; N, 10.07 Found: %C, 49.60; H, 2.83; N, 9.88. IR (KBr, cm^{-1}): 3285, 3280 (2NH), 3061 (CH-aromatic), 1730, 1710 and 1680 (3CO). ^{1}H NMR (DMSO-d_6, δ ppm): 2.3 (s, 3H, methyl), 7.5–7.9 (m, 9H, aromatic-H) 8.1 (s, 1H, H-7, Ar-H), 8.5 (s, 1H, H-5, Ar-H), 11, and 11.1 (s, 2H, 2NH, exchangeable with D_2O). MS (*m*/*z*, RI): M^+ 553.96, 555.96, 557.96 (10%, 20.3%, 9.9%) and at *m*/*z* 506.2 (100%).

*6.1.29. 2-Phenyl-6,8-dibromo-3-]4-(3-methyl-4,5-dihydro-5-oxopyrazolin-1-yl)carbonyl]phenyl quinazolin-4(3H)-one (**X**)*

A mixture of the hydrazide **III** (5.14 g; 10 mmol), and ethylaceto acetate (1.3 g; 10 mmol) in absolute ethanol (20 mL) was refluxed for 5 h. The precipitated solid formed upon cooling, was filtered and recrystalized from ethanol to give white crystals of **X**. M.p. 290 °C, in 70% yield. Analysis for $C_{24}H_{16}Br_2N_4O_2$, M.wt. (552.22). Calcd.: %C, C, 52.20; H, 2.92; N, 10.15. Found: %C, 52.07; H, 2.80; N, 10.09. IR (KBr, cm^{-1}): 3062 (CH-aromatic), 1725, 1680 (2CO). MS (*m*/*z*, RI): M^+ 549.96, 551.96, 553.96 (5%, 10.3%, 4.9%) and at *m*/*z* 105.2 (100%).

*6.1.30. 2-Phenyl-6,8-dibromo-3-]4-(3,5-dimethyl pyrazol-1-yl) carbonyl] phenylquinazolin-4(3H)-one (**XI**)*

A mixture of the hydrazide **III** (5.14 g; 10 mmol) and acetylacetone (1.04 g; 10 mmol) in absolute ethanol (20 mL) was refluxed for 5 h. The precipitated solid formed upon cooling, was filtered and recrystalized from ethanol to give white crystals of **XI**. M.p. 140 °C, in 70% yield. Analysis for $C_{25}H_{18}Br_2N_4O$, M.wt. (550.24). Calcd.: %C, C, 54.57; H, 3.30; N, 10.18. Found: %C, 54.43; H, 3.20; N, 10.03. IR (KBr, cm^{-1}): 3075 (CH-aromatic), 1680 (CO). MS (*m*/*z*, RI): M^+ 547.98, 549.98, 551.98 (8%, 17.1%, 8.3%) and at *m*/*z* 323.2 (100%).

*6.1.31. 2-Phenyl-6,8-dibromo-3-]4-(3,5-dioxopyrazol-(1H)-2-yl) carbonyl]phenyl quinazolin-4(3H)-one (**XII**)*

A mixture of hydrazide **III** (5.14 g; 10 mmol) and diethylmalonate (1.6 g; 10 mmol) in absolute ethanol (20 mL) was refluxed for 5 h. The precipitated solid formed upon cooling, was filtered and recrystalized from ethanol to give white crystals of **XII**. M.p. 210 °C, in 70% yield. Analysis for $C_{23}H_{14}Br_2N_4O_3$, M.wt. (554.19). Calcd.: %C, C, 49.85; H, 2.55; N, 10.11. Found: %C, 49.76; H, 2.42; N, 10.07. IR (KBr, cm^{-1}): 3160 (NH), 3073 (CH-aromatic), 1720, 1715, 1687 (3CO). ^{1}H NMR (DMSO-d_6, δ ppm): 3.2 (s, 2H, CH_2, pyrazolone), 7.5–8.0 (m, 9H, aromatic-H), 8.1 (s, 1H, H-7, Ar-H) and 8.2 (s, 1H, H-5, Ar-H), MS (*m*/*z*, RI): M^+ 551.94, 553.94, 555.94 (9.2%, 18.3%, 10%) and at *m*/*z* 396.2 (100%).

*6.1.32. 4-(2-Phenyl-6,8-dibromo-4-oxo-(4H)quinazolin-3-yl)-N-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)benzamide (**XIII**)*

A mixture of the hydrazide **III** (5.14 g; 10 mmol) and maleic anhydride (0.72 g; 10 mmol) in absolute ethanol (20 mL) was refluxed for 7 h. The precipitated solid formed upon cooling, was filtered and recrystalized from ethanol to give white crystals of **XIII**. M.p. 212 °C, in 70% yield. Analysis for $C_{25}H_{14}Br_2N_4O_4$, M.wt. (594.21). Calcd.: %C, C, 50.53; H, 2.37; N, 9.43. Found: %C, 50.40; H, 2.29; N, 9.37. IR (KBr, cm^{-1}): 3430 (NH), 3070 (CH-aromatic), 1780, 1770, 1710, 1680 (4CO). ^{1}H NMR (DMSO-d_6, δ ppm): 6.9–7.8 (m, 11H, aromatic-H) 7.9 (s, 1H, H-7, Ar-H), 8.1 (s, 1H, H-5, Ar-H), and 11.1 (s, 1H, NH, exchangeable with D_2O). MS (*m*/*z*, RI): M^+ 591.94, 593.94, 595.94 (10%, 20.3%, 9.9%) and at *m*/*z* 420.2 (100%).

*6.1.33. 4-(2-Phenyl-6,8-dibromo-4-oxo-(4H)quinazolin-3-yl)-N-(1,3-dioxoisoindolin-2-yl)benzamide (**XIV**)*

A mixture of the hydrazide **III** (5.14 g; 10 mmol), and phthalic anhydride (1.28 g; 10 mmol) in absolute ethanol (20 mL) was refluxed for 7 h. The formed precipitate upon cooling was filtered and recrystalized from ethanol to give white crystals of **XVI**. M.p. 294 °C in 72% yield. Analysis for $C_{29}H_{16}Br_2N_4O_4$, M.wt. (644.27). Calcd.: %C, C, 54.06; H, 2.50; N, 8.70. Found: %C, 53.92; H, 2.39; N, 8.57. IR (KBr, cm^{-1}): 3437 (NH), 3074 (CH-aromatic), 1775, 1770, 1710, 1680 (4CO). ^{1}H NMR (DMSO-d_6, δ ppm): 6.9–7.7 (m, 13H, aromatic-H), 7.87 (s, 1H, H-7, Ar-H), 8.1 (s, 1H, H-5, Ar-H) and 11.7 (s, 1H, NH, exchangeable with D_2O). MS (*m*/*z*, RI): M^+ 641.95, 643.95, 645.95 (1%, 2.3%, 1.2%) and at *m*/*z* 397.2 (100%).

*6.1.34. 4-(2-Phenyl-6,8-dibromo-4-oxo-(4H)quinazolin-3-yl)-N-(2,5-dioxopyrrolidin-1-yl)benzamide (**XV**)*

A mixture of the hydrazide **III** (5.14 g; 10 mmol), and succinic anhydride (0.71 g, 10 mmol) in absolute ethanol (20 mL) was refluxed for 7 h. The precipitated solid formed upon cooling, was filtered and recrystalized from ethanol to give white crystals of **XI**. M.p. 280 °C, in 60% yield. Analysis for $C_{25}H_{16}Br_2N_4O_4$, M.wt. (596.23). Calcd.: %C, C, 50.36; H, 2.70; N, 9.40. Found: %C, 50.20; H, 2.59; N, 9.37. IR (KBr, cm^{-1}): 3311 (NH), 3070 (CH-aromatic), 1773, 1760, 1710, 1680 (4CO). MS (*m*/*z*, RI): M^+ 593.95, 595.95, 597.95 (4%, 8.3%, 3.2%) and at *m*/*z* 113.2 (100%).

6.2. Antimicrobial screening

The anti-bacterial activity of the synthesized compounds was tested against strains isolated from animal byproducts and were accused of being a direct cause of food intoxication in human. The strains include three Gram-positive bacteria (*S. aureus*, *L. monocytogenes* and *B. cereus*) and three Gram-negative bacteria (*E. coli*, *P. aeruginosa* and *S. typhimurium*) using Muller Hinton agar medium (Oxoid). The anti-fungal activities of the compounds were tested against two fungi (*C. albicans* and *A. flavus*) using Sabouraud dextrose agar medium (Oxoid).

6.2.1. Paper disc diffusion technique

The sterilized medium [26] (autoclaved at 120 °C for 30 min) (40–50 °C) was inoculated (1 ml/100 ml of medium) with the suspension (105 cfu/ml) of the micro-organism (matched to 0.9 McFarland barium sulphate standard) and poured into a Petri dish to give a depth of 3–4 mm. The paper impregnated with the test chemicals (29 compounds) each dissolved in conc. (100 μg/ml in DMSO) was placed on the solidified medium. The plates were pre-incubated for 1 h at room temperature and incubated at 37–28 °C for 24–48 h for anti-bacterial and anti-fungal activities, respectively. Ciprofloxacin (10 μg/disc) and Fluconazole (10 μg/disc) were used as standard for anti-bacterial and anti-fungal activity, respectively. The observed inhibition zone is presented in Table 1.

6.2.2. Minimum inhibitory concentration (MIC)

MIC [27] of the compound was determined by agar streak dilution method. A stock solution of the synthesized compound (100 μg/ml) in DMSO was prepared and graded quantities of the test compounds were incorporated in specified quantity of molten sterile agar (Muller Hinton agar for anti-bacterial activity and Sabouraud dextrose agar medium for anti-fungal activity). A specified quantity of the medium (40–50 °C) containing the compound was poured into a Petri dish to give a depth of 3–4 mm and allowed to solidify.

Suspension of the micro-organism was prepared to contain approximately 105 cfu/ml and applied to plates with serially diluted compounds in DMSO to be tested and incubated at 37 °C for 24 and 48 h for bacteria and fungi, respectively. The MIC was considered to be the lowest concentration of the test substance exhibiting no visible growth of bacteria or fungi on the plate. The observed MIC is presented in Table 1.

References

[1] D. Nathwani, M.J. Wood, Drugs 45 (1993) 866–894.
[2] D. Schnappinger, W. Hillen, Arch. Microbiol. 165 (1996) 359–369.
[3] A.B.A. El-Gazzar, M.M. Youssef, A.M.S. Youssef, A.A. Abu-Hashem, F.A. Badria, Eur. J. Med. Chem. 44 (2009) 609–624.
[4] M.M. Said, M.M.M. Hussein, Bull. Fac. Pharm 32 (1994) 341–347.
[5] S. Jantova, S. Stankovsk, K. Spirakova, Biologica. Bratislava 59 (6) (2004) 741–752.
[6] Y. Zhou, D. Murphy, Z. Sun, V. Greogr, Tetrahedron Lett. 45 (2004) 8049–8051.
[7] P. Panneerselvam, B.A. Rather, D.R.S. Reddy, N.R. Kumar, Eur. J. Med. Chem. (France) 44 (5) (May 2009) 2328–2333.
[8] J. Bartroli, E. Turmo, M. Alguero, E. Bonsompte, M.L. Vericat, L. Conte, J. Ramis, M. Merlos, J. Garsia-Rafanell, J. Forn, J. Med. Chem. 41 (1998) 1869–1882.
[9] P.M. Chandrikaa, T. Yakaiahb, A. Raghu Ram Raoa, B. Narsaiahb, N. Chakra Reddyc, V. Sridharc, J. Venkateshwara Raoc, Eur. J. Med. Chem. 43 (2008) 846–852.
[10] P.N. Bhargava, S. Prakash, Indian J. Chem. 39B (1997) 18–22.
[11] T.M. Abdel-Rahman, Heterocycl. Commun 3 (1997) 535–538.
[12] P. Kumar, C. Nath, K.P. Bhargava, K. Shanker, Pharmazie 37 (1982) 802.
[13] T. Aono, S. Marui, F. Itoh, M. Yamooka, M. Nakao, Eur. Patent No. 735035, 1996.
[14] S.K. Pandey, A. Singh, A. Singh, Nizamuddin, Eur. J. Med. Chem. 44 (3) (2009) 1188–1197.
[15] M. Ishikawa, H. Azuma, Y. Eguchi, S. Ito, T. Naito, H. Ebisawa, I. Kotoku, J. Pharmacobio-Dyn. 5 (1982) 8.
[16] M.K. Ibrahim, J. Al-Azhar, Pharm. Sci. 22 (1998) 9–12.
[17] P. Mishra, P. Pannerselvam, S. Jain, J. Indian Chem. Soc. 72 (1995) 559–560.
[18] Y.D. Kulkarni, A. Rowhani, J. Indian Chem. Soc. 67 (1990) 46.
[19] P.N. MishraGupta, A.K. Shakya, J. Indian Chem. Soc. 68 (1991) 618–619.
[20] O.M. Fathalla, E.M.M. Kassem, N.M. Ibrahem, M.M. Kamel, Acta Pol. Pharm. Drug Res. 65 (1) (2008) 11–20.
[21] M.S. Mohamed, M.M. Kamel, E.M.M. Kassem, N. Abotaleb, S.M. Nofal, M. F. Ahmed, Acta Polon.Pharmaceutica – Drug Research 66 (2009) 487–500.
[22] M.S. Mohamed, M.M. Kamel, E.M.M. Kassem, N. Abotaleb, S.M. Nofal, M. F. Ahmed, Acta Polon Pharmaceutica – Drug Research 67 (2) (2010) 159–171.
[23] V. Alagarsamy, G. Muruganantham, R. Venkateshaperumal, Biol. Pharm. Bull. 26 (12) (2003) 1711–1714.
[24] P.B. Trivedi, N.K. Undavia, M.A. Dave, K.N. Bhatt, N.C. Desai, Ind. J. Chem. Sect. B 32 (4) (1993) 497–500.
[25] A.N. Lin, R.J. Reimer, D.M. Carter, J. Am. Acad. Dermatol. 18 (1988) 553–558.
[26] S.H. Gillespie, Medical Microbiology-Illustrated. Butterworth Heinemann Ltd., United Kingdom, 1994, 234–247.
[27] P.M. Hawkey, D.A. Lewis, Medical Bacteriology – a Practical Approach. Oxford University Press, United Kingdom, 1994, pp. 181–194.