Med Chem Res (2012) 21:1577–1586
DOI 10.1007/s00044-011-9674-5

MEDICINAL CHEMISTRY RESEARCH

ORIGINAL RESEARCH

A clubbed quinazolinone and 4-thiazolidinone as potential antimicrobial agents

N. C. Desai · Amit M. Dodiya · Prashant N. Shihora

Received: 9 March 2011 / Accepted: 13 May 2011 / Published online: 28 May 2011

Abstract A series of *N*-{5-[(2-chlorophenyl)methylene]-2-(4-hydroxyphenyl]-4-oxo(1,3-thiazolidin-3-yl)}{4-[2-(4-methylphenyl)-4-oxo(3-hydroquinazolin-3-yl)]phenyl} carboxamides **(6a–n)** have been synthesized. All the synthesized compounds were screened for in vitro antibacterial and antifungal activities on *Escherichia coli, Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Staphylococcus pyogenes*, *Candida albicans*, *Aspergillus niger*, and *Aspergillus clavatus*. The structures of the compounds were elucidated by IR, ^{1}H NMR, ^{13}C NMR, and Mass spectra.

Keywords Quinazolinone · 4-Thiazolidinone · Antimicrobial activity

Introduction

4(3*H*)-Quinazolinones and its derivatives constitute an important class of heterocyclic compounds. In view of wide range of bioactivities, this group of compounds dwell an important role in medicinal and pesticide chemistry. Having a broad spectrum of pharmacological activities, they act as analgesic (Aly *et al.*, 2010; Terashima *et al.*, 1995), antimicrobial (Jatav *et al.*, 2006; Dahiya and Kumar, 2008), antitumor (El-azab *et al.*, 2010), anticancer (Giri *et al.*, 2010), antiinflammatory (Kumar and Rajput, 2009), anticonvulsant (Kashaw *et al.*, 2010), antidepressant (Ergenc *et al.*, 1991), hypolipidemic (Bekhit and Khalil, 1998), antiulcer (Hamel *et al.*, 1996), or immunotropic activities (Gursoy and Karali, 1995). They also work as thymidyalate synthase (Baek *et al.*, 1998), poly(ADP-ribose) polymerase (PARP) (Griffin *et al.*, 1998) and protein tyrosine kinase (Sumegi *et al.*, 2007) inhibitors. These compounds are also used as anti-HIV (Purohit *et al.*, 2003) and antiviral agents (Liu *et al.*, 1999) such as TMV, CMV inhibitors. With the inclining biological significance, synthesis, and bioactivity of quinazoline derivatives have gained momentum amongst the biologist and chemist in recent past. Our group has reported that some of these compounds showed antimicrobial activity (Desai and Dodiya, 2011). Nanda and his co-workers synthesized 3-(arylideneamino)-2-phenylquinazoline-4(3*H*)-ones, which were investigated for antibacterial activity against both gram-positive (*Staphylococcus aureus* 6571 and *Bacillus subtilis*) and gram-negative bacteria (*Escherichia coli* K12 and *Shigella dysenteriae 6*) using a turbidometric assay method (Nanda *et al.*, 2007). However, our group later found that the incorporation of 3-arylideneamino substituent enhanced the antibacterial activity of quinazolone system (Desai and Trivedi, 1993).

For a long time small heterocycle scaffold containing nitrogen, sulfur, and oxygen have been under investigation due to their important medicinal properties. Among these types of molecules, 4-thiazolidinones have displayed various important biological activities (Capan *et al.*, 1999; Vigorita *et al.*, 2001; Kavitha *et al.*, 2006; Ottana *et al.*, 2005; Kucukguzel *et al.*, 2006). Currently 4-thiazolidones are considered as a new class of antidiabetic (insulin-sensitising) drugs and potent aldose reductase inhibitors. In addition, they possess substantial potential for the treatment of diabetes complications like cataract, nephropathy, and neuropathy (Gerstein *et al.*, 2006). Based on the results, we have designed and synthesized a series of *N*-{5-[(2-chlorophenyl)methylene]-2-(4-hydroxyphenyl]-4-

N. C. Desai (✉) · A. M. Dodiya · P. N. Shihora
Medicinal Chemistry Division, Department of Chemistry, Bhavnagar University, Bhavnagar 364 002, India
e-mail: dnisheeth@rediffmail.com

oxo(1,3-thiazolidin-3-yl)}{4-[2-(4-methylphenyl)-4-oxo(3-hydroquinazolin-3-l)]phenyl}carboxamides (**6a**–**n**).

The condensation of 4-methylbenzoyl chloride and anthranilic acid in the presence of pyridine below 10°C gives 2-(4-methylphenyl) benzo[d]1,3-oxazin-4-one (**1**), which when reacted with benzocain gave ethyl 4-[2-(4-methylphenyl)-4-oxo-3-hydroquinazolin-3-yl]benzoate (**2**) by the removal of water molecule. Compound (**2**) on reaction with hydrazine hydrate furnished *N*-amino{4-[2-(4-methylphenyl)-4-oxo-(3-hydroquinazolin-3-yl)]phenyl}carboxamide (**3**). Compound (**3**) on condensation with various aromatic aldehydes yielded schiff bases *N*-[(1Z)-1-aza-2-(4-hydroxyphenyl)vinyl]{4-[2-(4-methylphenyl)-4-oxo-(3-hydroquinazolin-3-yl)]phenyl} (**4**).

Then, further it produced *N*-[2-(4-hydroxyphenyl)-4-oxo-(1,3-thiazolidin-3-yl)]{4-[2-(4-methylphenyl)-4-oxo-(3-hydroquinazolin-3-yl)] phenyl} carboxamide (**5**) by cycloaddition with mercaptoacetic acid in the presence of 1,4–dioxane which on condensation with different aryl aldehydes furnished *N*-{5-[(2-chlorophenyl)methylene]-2-(4-hydroxyphenyl]-4-oxo(1,3-thiazolidin-3-yl)}{4-[2-(4-methylphenyl)-4-oxo(3-hydroquinazolin-3-yl)] phenyl}-carboxamides (**6a**–**n**).

The structures of compounds synthesized were assigned on the basis of IR, ^{1}H NMR, ^{13}C NMR, and Mass spectra. These compounds were evaluated for their antimicrobial screening on different strains of bacteria and fungi (Scheme 1).

Results and discussion

IR data

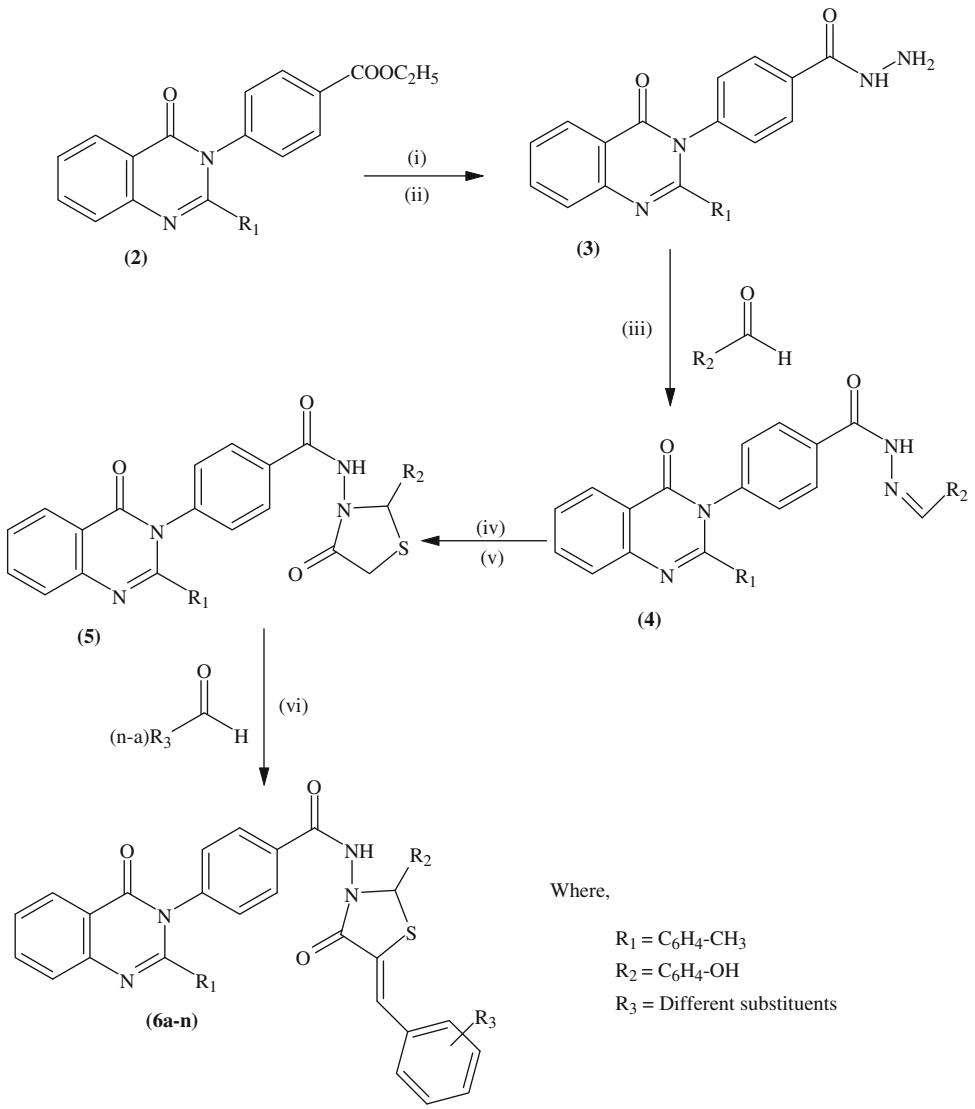
The IR spectrum of the title compound **6g** (molecular formula $C_{38}H_{27}N_5O_6S$, m.w. 681.17) has given vibrations at 3082 and 3061 cm^{-1} over the ranges which showed multiple weak absorption peaks corresponding to Qu–H and Ar–H stretching vibration. The absorption peak at 3315 cm^{-1} is due to the stretching vibration of secondary amine which is part of amide linkage. The absorption peak at 3230 cm^{-1} is due to the stretching vibration of hydroxyl group. The absorption peak at 3050 cm^{-1} is due to the stretching vibration of methylene group, while the absorption at 2838 cm^{-1} is due to the stretching vibration of aromatic –CH_3 group, while the absorption at 1462 cm^{-1} is due to the bending vibration of aromatic –CH_3 group. The strong absorptions at 1719 and 1738 cm^{-1} are due to the C=O stretching vibration and amide group, while the moderate intensity absorption at 1653 cm^{-1} corresponds to a C=N stretching vibration, and C=C linkage stretching vibration appeared at 1608 cm^{-1}. The presence of nitro group gives two vibrations, at the range of 1520 cm^{-1} –NO_2 group symmetric stretching vibration while at 1345 cm^{-1} –NO_2 group asymmetric stretching vibration. The absorption peak at 860 cm^{-1} is due to the bending vibration of methylene group. The absorption peak at 774 cm^{-1} indicates that mono substituted benzene ring is present.

^{1}H NMR data

It has been observed from the chemical structure of compound **6g** that different pairs of carbons, e.g., C-10 and C-15, C-11 and C-14, C-17 and C-21, C-18 and C-20, C-34 and C-38, C-35 and C-37 are attached to chemically equivalent protons, which appeared at $\delta = 7.71$, 7.28, 7.35, 7.76, 7.78, 6.63 ppm, respectively. The protons attached at C-13 position appeared as a singlet at $\delta = 2.34$ ppm due to the –CH_3 group. The proton of the hydroxy group appeared as singlet at 5.0 ppm. The proton attached to C-5 appeared as a multiplet at $\delta = 7.63$ ppm while the proton attached to C-6 appeared as a multiplet at $\delta = 7.70$ ppm. The proton attached to C-29 appeared as a multiplet at $\delta = 7.66$ ppm due to mutual coupling with protons attached to C-28 and C-30. The proton of the methylene group, which is attached to C-26 appeared as a singlet at $\delta = 4.6$ ppm. The proton of the secondary amine appeared as a singlet at $\delta = 8.4$ due to one side attachment with carbonyl group and another side with nitrogen atom. The proton of the C-30 appeared as a doublet at $\delta = 8.14$ ppm and C-32 appeared as a singlet at $\delta = 8.31$ ppm due to the influence of nitro group on nearest position. The protons of the quinazolinone ring which are attached to C-7 and C-8 appeared as a doublet at $\delta = 7.63$ and 8.03 ppm, respectively.

^{13}C NMR data

The chemical shifts of the final compound **6g** carbons vary from $\delta = 164.8$ to 24.3 ppm. The carbon nuclei under the influence of a strong electronegative environment appeared downfield, e.g., the C-2, C-22, and C-23 carbonyl, which are directly linked to the ring nitrogen atom has a chemical shift value of $\delta = 160.8$, 164.8, and 164.4 ppm, respectively. The carbon C-1 which is attached on both sides to nitrogen atoms appeared at the same high value of $\delta = 164.0$ ppm. The chemical shift of the ring carbons at C-3, C-19, and C-24 are affected by the presence of the nearest carbonyl group, appeared at the same $\delta = 120.8$, 129.8, and 129.3 ppm, respectively. The C-31 appeared at $\delta = 147.8$ ppm due to the strong electron withdrawing influence of nitro group, while C-36 appeared at $\delta = 147.8$ ppm due to the strong electron withdrawing influence of hydroxy group. The methyl group attached with the C-12 appeared at $\delta = 139.8$ ppm, while the carbon of the methyl group C-13 appeared at low value of



Scheme 1 Synthetic route of the title compounds. (i) NH_2-$NH_2{\cdot}H_2O$. (ii) Methanol, 6 h reflux. (iii) Methanol, 5 h reflux. (iv) $HSCH_2COOH$. (v) 1,4-dioxane, 6 h reflux. (vi) 1,4-dioxane, 8 h reflux

$\delta = 24.3$ ppm. The carbon of the methylene group C-26 appeared at $\delta = 125.2$ ppm. The carbon C-25 which is present in thiazolidine ring and which is attached on one side with nitrogen and on the other side with sulfur atom appeared at $\delta = 63.4$ ppm. The carbons of the 4-methyl phenyl ring which are attached to quinazolinone ring carbon at C-1 position having equivalent carbons like, C-10 and C-15 appeared at 126.0 ppm, while another equivalent carbon of this ring are C-11 and C-14 appeared at 129.1 ppm, respectively. The carbons of the phenyl ring, which is attached one side with amide group and another side to quinazolinone nucleus having equivalent carbons like, C-17 and C-21 appeared at 121.7 ppm, while C-18 and C-20 equivalent carbons appeared at 127.7 ppm. The 4-hydroxyphenyl ring with is attached with thiazoldine ring at C-25 position having equivalent carbons like C-34 and C-38 appeared at 129.1 ppm, while C-35 and C-37 appeared at 115.9 ppm. The carbons (C-27, C-28, C-29, C-30, and C-32) of the 3-nitrophenyl ring which is attached with methylene linkage appeared from 120.0 to 136.1 ppm, respectively. The carbons (C-3, C-4, C-5, C-6, C-7, and C-8) of the quinazolinone ring appeared from 120.8 to 151.2 ppm, respectively. The carbon numbering is described in Fig. 1.

Antimicrobial activity

For antibacterial activity, compounds **6b**, **6d**, **6f**, **6i**, and **6j** are considered to be good active against *E. coli*, while compounds **6m** and **6n** are considered as very good active against *E. coli*, while compounds **6c** and **6g** are considered as excellent active against *E. coli*. Compounds **6b**, **6g**, **6k**, and **6m** are considered as good active against *P.aeruginosa*, while compounds **6d** and **6e** are considered as very good active against *P. aeruginosa*. Compounds **6j** and **6l**

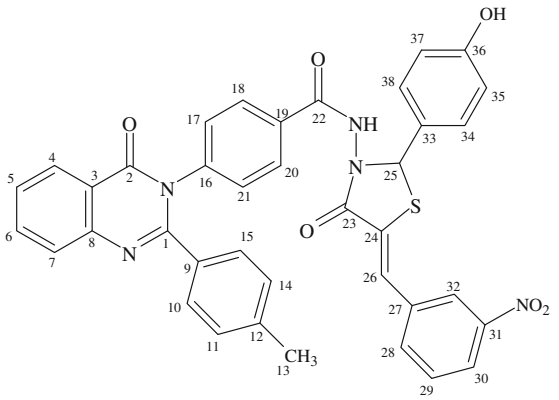


Fig. 1 Carbon numbering of the compound **6g**

are considered as good active against *S. aureus*, while compounds **6b**, **6d**, **6e**, **6f**, **6k**, and **6m** are considered as very good active against *S. aureus*, while compound **6g** is considered as excellent active. Compounds **6a**, **6c**, **6d**, **6h**, **6l**, and **6m** are considered as good active against *S. pyogenes*, while compound **6f** is considered as very good active against *S. pyogenes*. For the antifungal activity, compounds **6d**, **6e**, **6g**, and **6n** are considered as good active against *C. albicans*. Compounds **6b**, **6c**, **6g**, **6i**, and **6m** are considered as good active against *A. niger*. Compounds **6d**, **6f**, **6i**, and **6l** are considered as good active against *A. clavatus* The antibacterial and antifungal activities have been enhanced due to the incorporation of 4-thiazolidine in quinazoline ring followed by the substitution at 5th position of 4-thiazolidine ring system due to the Knoevenagel reaction of active methylene group present at 5th position. The discussion and comparison of antibacterial and antifungal activities have been compared with ampicillin and griseofulvin, respectively.

Antibacterial activity

For the antibacterial activity, the newly synthesized compounds were screened for their antibacterial activity against gram positive bacteria *S. aureus* (MTCC-96) and *Streptococcus pyogenes* (MTCC-442) and gram negative *E. coli* (MTCC-443) and *Pseudomonas aeruginosa* (MTCC-1688)]. Antibacterial activity was carried out by serial broth dilution method (Ghalem and Mohamed, 2009; Desai and Trivedi, 1993; Al-Bayati and Al-Mola, 2008). The standard strains used for the antimicrobial activity was procured from Institute of Microbial Technology, Chandigarh. The compounds **(6a–n)** were screened for their antibacterial activity in triplicate against *E. coli*, *S. aureus*, *P. aeruginosa*, and *S. pyogenes* at different concentrations of 1000, 500, 200, 100, 50, 25, 12.5 μg/ml as shown in (Table 1). The drugs which were found to be active in primary screening were similarly diluted to obtain 100, 50, 25, 12.5 μg/ml concentrations. 10 μg/ml suspensions were further inoculated on appropriate media and growth was noted after 24 and 48 h. The lowest concentration, which showed no growth after spot subculture was considered as MIC for each drug. The highest dilution showing at least 99% inhibition is taken as (MIC). The test mixture should contain 10^8 cells/ml. The standard drug used in this study was 'ampicillin' for evaluating antibacterial activity which showed (100, 100, 250, and 100 μg/ml) MIC against *E. coli*, *P. aeruginosa*, *S. aureus*, and *S. pyogenes*, respectively.

Antifungal activity

While for the antifungal activity, same compounds were tested for antifungal activity in triplicate against *Candida albicans*, *A. niger*, and *A. clavatus* at various concentrations of 1000, 500, 200, and 100 μg/ml as shown in (Table 1). The results were recorded in the form of primary and secondary screening. The synthesized compounds were diluted at 1000 μg/ml concentration, as a stock solution. The synthesized compounds which were found to be active in this primary screening were further tested in a second set of dilution against all microorganisms. The lowest concentration, which showed no growth after spot subculture was considered as (MIC) for each drug. The highest dilution showing at least 99% inhibition is taken as MIC. The test mixture should contain 10^8 spores/ml MIC. 'griseofulvin' was used as a standard drug for antifungal activity, which showed (500, 100, and 100 μg/ml) MIC against *C. albicans*, *A. niger*, and *A. clavatus*, respectively. The results of antimicrobial evaluation of derivatives (**6a–n**) are collected in (Table 1).

Statistical analysis

The standard deviation value is expressed in terms of ±SD. On the basis of the calculated value by using ANOVA method, it has been observed that the differences below 0.0001 level ($P \leq 0.0001$) were considered as statistically significant.

Materials and methods

All the required chemicals were purchased from E. Merck. IR spectra were recorded on Perkin Elmer FT–IR spectrophotometer. ^{1}H NMR and ^{13}C NMR spectra were recorded on Bruker DPX-40C instrument at 400 MHz. Chemical shifts were reported in ppm in reference to the

Table 1 Results of antibacterial and antifungal screening of the compounds (**6a–n**)

Sr. no.	$-R_3$	Minimum inhibitory concentration (MIC) in ug/ml ± SD				Minimum inhibitory concentration (MIC) ug/ml ± SD		
		E. coli MTCC 443	*P. aeruginosa* MTCC 1688	*S. aureus* MTCC 96	*S. pyogenes* MTCC 442	*C. albicans* MTCC 227	*A. niger* MTCC 282	*A. clavatus* MTCC 1323
6a	–H	200 ± 4.50*	500 ± 3.78*	500 ± 4.04*	100 ± 4.04*	500 ± 2.51*	1000 ± 4.50*	1000 ± 3.05*
6b	$-3,4,5-(OCH_3)_3$	100 ± 4.72*	100 ± 3.05*	100 ± 3.05*	200 ± 2.51*	1000 ± 4.04*	100 ± 3.51*	1000 ± 4*
6c	$-N(CH_3)_2$	25 ± 4.93*	200 ± 4.04*	1000 ± 4.04*	100 ± 4.50*	1000 ± 4*	100 ± 4.35*	500 ± 3.78*
6d	–2–OH–naphthyl	100 ± 4.04*	50 ± 4.58	100 ± 3.78*	100 ± 4*	100 ± 4.58*	1000 ± 3.60*	100 ± 3.05*
6e	–4–F	500 ± 3.78*	50 ± 4*	100 ± 3.05*	250 ± 1*	100 ± 4.04*	500 ± 4.50*	1000 ± 3.60*
6f	–4–OH	100 ± 4.04*	500 ± 3.46*	100 ± 2.51*	50 ± 3.51*	1000 ± 4.50*	1000 ± 4.58*	100 ± 4.04*
6g	$-3-NO_2$	25 ± 4.93*	100 ± 4.58*	50 ± 3.51*	500 ± 1*	100 ± 2.30*	100 ± 4.04*	500 ± 4.04*
6h	–2–Cl	200 ± 4*	500 ± 3.60*	500 ± 4.04*	100 ± 1.32*	1000 ± 3.21*	1000 ± 3.05*	1000 ± 4.16*
6i	$-4-OCH_3$	100 ± 3.78*	500 ± 4.04*	500 ± 3*	500 ± 4.04*	1000 ± 3.51*	100 ± 3.51*	100 ± 3*
6j	$-2-OH-4-OCH_3$	100 ± 3.21*	200 ± 3.51*	250 ± 3.21*	500 ± 4.16*	500 ± 3.46*	1000 ± 3.51*	500 ± 4.04*
6k	$-2-OCH_3$	500 ± 3.21*	100 ± 3.05*	100 ± 3.51*	500 ± 2.08*	500 ± 3.78*	500 ± 4.16*	500 ± 3.05*
6l	–2–OH–5–Br	500 ± 4.58*	500 ± 3.51*	250 ± 3.05*	100 ± 3.60*	500 ± 3.05*	1000 ± 4*	100 ± 2.51*
6m	$-2,6-(Cl)_2$	50 ± 4.04*	200 ± 2*	100 ± 3.53*	100 ± 2*	500 ± 3.78*	100 ± 3.60*	1000 ± 2*
6n	–4–Cl	50 ± 3*	100 ± 3.21*	500 ± 1.56*	500 ± 3.45*	100 ± 2.23*	1000 ± 3*	1000 ± 3*
Ampicillin		100 ± 2.0*	100 ± 1.0*	250 ± 1.52*	100 ± 2.08*	–	–	–
Griseofulvin		–	–	–	–	500 ± 0.57*	100 ± 1*	100 ± 1.15*

SD standard deviation, * $P \leq 0.0001$

residual solvent signal. Mass spectra were recorded on JEOL SX-102. Elemental analysis was performed by Perkin-Elmer 2400-CHN analyzer. Melting points were recorded on Gallenkamp apparatus and were left uncorrected. Aluminum coated TLC plates 60 F_{245} (E. Merck) were used for monitoring of reaction and purity of compounds. In the conventional method, compounds were synthesized by using Random synthesizer. Bookie Rotavapour was used for distillation.

Experimental

Synthesis of 1 and 2

2-(4-methylphenyl)benzo[*d*]1,3-oxazin-4-one **1** and 2-(4-methylphenyl)-3-(4-propanoylphenyl)-3-hydroquinazolin-4-one **2** have been synthesized as described previously (Pandey *et al.*, 2005).

Preparation of *N*-amino{4-[2-(4-methylphenyl)-4-oxo(3-hydroquinazolin-3-yl)]phenyl}carboxamide **(3)**

The intermediate compound **3** has been achieved by a mixture of 2-(4-methylphenyl)-3-(4-propanoylphenyl)-3-hydroquinazolin-4-one **2** (0.01 mol) and excess of hydrazine hydrate (99%, 0.015 mol) in methanol (40 ml) was added to a round bottom flask. The contents were refluxed for 6 h. After the reaction was completed, the reaction mixture was poured into crushed ice to afford dark brown precipitate. This was collected by filtration and washed with cold water. The resulting solid was recrystallized from ethanol (99%).

M.p.: 182°C, Yield 75%; IR (KBr): 3426 cm^{-1} (–N–H stretching, primary amine), 3311 cm^{-1} (N–H stretching, secondary amine), 3084, 3062 cm^{-1} (Qu–H and Ar–H stretching, aromatic ring), 2837 cm^{-1} (C–H stretching, $–CH_3$ group), 1713 cm^{-1} (C=O stretching, amide group), 1648, 1605 cm^{-1} (C=N, C=C stretching, aromatic ring), 1341 cm^{-1} (C–N stretching, quinazoline ring), 771 cm^{-1} (para-substitution of aromatic ring); ^1H NMR ($CDCl_3$): 7.0–7.9 (m, 12H, Ar–H), 8.0 (s, 1H, –CONH–), 2.3 (s, 3H, $Ar–CH_3$), 2.0(s, 2H, $–N–NH_2$); ^{13}C NMR: 21.3, 120.8, 124.5, 125.6, 126.6, 126.7, 127.3, 127.6, 129.1, 129.6, 130.3, 133.4, 136.1, 139.8, 148.7, 156.2, 160.6, 167.2. GCMS: *m/z*: 370.14 (M^+). Anal. calcd. for $C_{22}H_{18}N_4O_2$: C, 71.33; H, 4.89; N, 15.12. Found: C, 71.52; H, 4.60; N, 15.26.

Preparation of *N*-[(1Z)-1-aza-2-(4-hydroxyphenyl)vinyl]{4-[2-(4-methylphenyl)-4-oxo(3-hydroquinazolin-3-yl)]phenyl}carboxamide **(4)**

The intermediate compound **4** has been achieved by a mixture of *N*-amino{4-[2-(4-methylphenyl)-4-oxo(3-hydroquinazolin-3-yl)]phenyl}carboxamides **3** (0.01 mol)

and 4-hydroxybenzaldehyde (0.01 mol) (over a period of 10 min) in methanol (30 ml) was refluxed for 5 h. After the reaction was completed, the light brown schiff base comes out. This was collected by filtration. The resulting solid was recrystallized from methanol.

M.p.: 222°C, Yield 78%; IR (KBr): 3312 cm^{-1} (N–H stretching, secondary amine), 3233 cm^{-1} (O–H stretching, –OH group), 3081, 3065 cm^{-1} (Qu–H and Ar–H stretching, aromatic ring), 2832 cm^{-1} (C–H stretching, $–CH_3$ group), 1714 cm^{-1} (C=O stretching, amide group), 1644, 1603 cm^{-1} (C=N, C=C stretching, aromatic ring), 1344 cm^{-1} (C–N stretching, quinazoline ring), 774 cm^{-1} (ortho substitution of aromatic ring); ^{1}H NMR ($CDCl_3$): δ 6.8–7.9 (m, 16H, ArH), 8.1(s, 1H, –CONH–), 8.1 (s, 1H, –N=CH–), 5.0 (s, 1H, ArOH); ^{13}C NMR: 21.3, 116.0, 120.8, 124.5, 125.6, 126.3, 126.6, 126.7, 127.3, 128.4, 129.1, 129.6, 130.3, 130.6, 133.4, 136.1, 139.8, 146.8, 148.7, 156.2, 160.8, 163.2; GCMS: *m/z*: 474.17 (M^+). Anal. calcd. for $C_{29}H_{22}N_4O_3$:C, 76.09; H, 4.89; N, 8.87. Found: C, 76.29; H, 4.60; N, 8.60.

Preparation of *N*-[2-(4-hydroxyphenyl)-4-oxo(1,3-thiazolidin-3-yl)]{4-[2-(4-methylphenyl)-4-oxo(3-hydroquinazolin-3-yl)]-phenyl}carboxamide **(5)**

The synthesis of intermediate compound **5** has been achieved by a mixture of *N*-[(1Z)-1-aza-2-(4-hydroxyphenyl)vinyl]{4-[2-(4-methylphenyl)-4-oxo(3-hydroquinazolin-3-yl)]phenyl}carboxamides **4** (0.01 mol) and mercaptoacetic acid (0.011 mol) in 1:4 dioxane (40 ml) was refluxed for 6 h. After the reaction completed, the solution was poured into ice-cold aqueous solution of sodium bicarbonate to remove unreacted mercaptoacetic acid. The yellow to brown precipitate was filtered, and then washed with cold water. The resulting solid was recrystallized from ethanol (99%).

M.p.: 242°C, Yield 68%; IR (KBr): 3315 cm^{-1} (N–H stretching, secondary amine), 3230 cm^{-1} (O–H stretching, –OH group), 3081, 3065 cm^{-1} (Qu–H and Ar–H stretching, aromatic ring), 2835 cm^{-1} (C–H stretching, $–CH_3$ group), 1738, 1717 cm^{-1} (C=O stretching, amide group), 1648, 1605 cm^{-1} (C=N, C=C stretching, aromatic ring), 1341 cm^{-1} (C–N stretching, quinazoline ring), 776 cm^{-1} (ortho substitution of aromatic ring); ^{1}H NMR ($CDCl_3$): δ 6.6–7.9 (m, 16H, Ar–H), 8.0 (s, 1H, –CONH–), 5.9 (s, 1H, –N–CH–S), 4.9 (s, 1H, ArOH), 3.3 (s, 2H, –CO–CH–S). ^{13}C NMR ($CDCl_3$): δ 21.3, 32.4, 62.2, 115.7, 120.8, 124.5, 125.6, 126.6, 126.7, 127.0, 127.3, 127.6, 129.1, 129.6, 130.3, 133.4, 136.1, 139.8, 148.7, 156.2, 156.5, 160.6, 163.7, 164.9; GCMS: *m/z*: 648.14 (M^+). Anal. calcd. for $C_{31}H_{24}N_4O_4S$: C, 67.86; H, 4.40; N, 10.21. Found: C, 67.27; H, 4.86; N, 10.52.

General preparation of *N*-{5-[(aryl)methylene]-2-(4-hydroxyphenyl)-4-oxo(1,3-thiazolidin-3-yl)}{4-[2-(4-methylphenyl)-4-oxo(3-hydroquinazolin-3-yl)]phenyl}carboxamides **(6a–n)**

A mixture of a sodium methoxide solution of *N*-[2-(4-hydroxyphenyl)-4-oxo(1,3-thiazolidin-3-yl)] {4-[2-(4-methylphenyl)-4-oxo(3-hydroquinazolin-3-yl)]phenyl}carboxamide **5** (0.01 mol) and benzaldehyde (0.01 mol) in 1:4 dioxane (40 ml) was refluxed for 8 h. After the reaction was completed, the reaction mixture was pour into crushed ice to afford brown precipitate. This was collected by filtration, and then washed with cold water. The resulting solid was recrystallized from ethanol (99%).

Physical constants and characterization of N-{5-[(phenyl)methylene]-2-(4-hydroxyphenyl)-4-oxo(1,3-thiazolidin-3-yl)}{4-[2-(4-methylphenyl)-4-oxo(3-hydroquinazolin-3-yl)] phenyl}carboxamide **(6a)**

M.p.: 132°C, Yield 68%; IR (KBr): 3310 cm^{-1} (N–H stretching, secondary amine), 3230 cm^{-1} (O–H stretching, –OH group), 3120 cm^{-1} (C–H stretching, aromatic ring), 3052 (=CH stretching), 2900 cm^{-1} (C–H stretching, $–CH_3$ group), 1710, 1725 cm^{-1} (C=O stretching, amide group), 1630, 1610 cm^{-1} (C=N, C=C stretching, aromatic ring), 1345 cm^{-1} (C–N stretching, quinazoline ring), 920 cm^{-1} (ortho-substitution of aromatic ring), 864 (=CH bending); ^{1}H NMR ($CDCl_3$): δ 6.0–7.9 (m, 21H, Ar–H), 8.3 (s, 1H, –CONH–), 4.7 (s, 1H, –C=CH–Ar), 5.9 (s, 1H, –N–CH–S), 5.0 (s, 1H, Ar–OH); ^{13}C NMR ($CDCl_3$): δ 24.3, 63.4, 115.9, 120.8, 121.7, 122.4, 125.2, 125.6, 126.0, 126.4, 127.4, 127.7, 128.0, 128.7, 128.8, 129.1, 129.3, 129.8, 133.5, 134.5, 135.2, 136.1, 139.8, 151.2, 156.9, 160.8, 164.1, 164.3, 164.5; GCMS: *m/z*: 613.18 (M^+). Anal. calcd. for $C_{38}H_{28}N_4O_4S$: C-71.68%, H-4.43%, N-8.80%. Found: C-71.74%, H-4.49%, N-8.85%.

Physical constants and characterization of *N*-{5-[(3,4,5-trimethoxyphenyl)methylene]-2-(4-hydroxyphenyl)-4-oxo- (1,3-thiazolidin-3-yl)} {4-[2-(4-methylphenyl)-4-oxo(3-hydroquinazolin-3-yl)]phenyl}carboxamide **(6b)**

M.p.: 125°C, Yield 71%; IR (KBr): 3311 cm^{-1} (N–H stretching, secondary amine), 3231 cm^{-1} (O–H stretching, –OH group), 3122 cm^{-1} (C–H stretching, aromatic ring), 3061 (=CH stretching), 2902 cm^{-1} (C–H stretching, $–CH_3$ group), 1713, 1724 cm^{-1} (C=O stretching, amide group), 1632, 1611 cm^{-1} (C=N, C=C stretching, aromatic ring), 1346 cm^{-1} (C–N stretching, quinazoline ring), 1255 cm^{-1} (C–O stretching, ether group), 924 cm^{-1} (ortho-substitution of aromatic ring), 859 (=CH bending); ^{1}H NMR

($CDCl_3$): δ 6.1–7.9 (m, 18H, Ar–H), 8.4 (s, 1H, –CONH–), 4.9 (s, 1H, –C = CH–Ar), 5.9 (s, 1H, –N–CH–S), 5.1 (s, 1H, Ar–OH), 3.7 (s, 9H, Ar–OCH_3); ^{13}C NMR ($CDCl_3$): δ 24.3, 56.1, 56.4, 63.4, 103.8, 115.9, 120.8, 121.7, 122.4, 125.2, 125.6, 126.0, 127.4, 127.7, 128.8, 129.1, 129.3, 129.5, 129.8, 133..5, 134.5, 136.1, 138.4, 139.8, 150.7, 151.2, 156.9, 160.8, 164.2, 164.5, 164.6; GCMS: *m/z*: 726.21 (M^+). Anal. calcd. for $C_{41}H_{34}N_4O_7S$: C-67.75%, H-4.72%, N-7.71%. Found: C-67.81%, H-4.76%, N-7.75%.

Physical constants and characterization of *N*-{5-[(4-(dimethylamino)phenyl)methylene]-2-(4-hydroxyphenyl)-4-oxo(1,3-thiazolidin-3-yl)}{4-[2-(4-methylphenyl)-4-oxo(3-hydroquinazolin-3-yl)]phenyl}carboxamide **(6c)**

M.p.: 100°C, Yield 70%; IR (KBr): 3314 cm^{-1} (N–H stretching, secondary amine), 3232 cm^{-1} (O–H stretching, –OH group), 3124 cm^{-1} (C–H stretching, aromatic ring), 3056 (=CH stretching), 2903 cm^{-1} (C–H stretching, $-CH_3$ group), 1713 cm^{-1}, 1723 cm^{-1} (C=O stretching, amide group), 1632, 1612 cm^{-1} (C=N, C=C stretching, aromatic ring), 1347 cm^{-1} (C–N stretching, quinazoline ring), 926 cm^{-1} (ortho-substitution of aromatic ring), 857 (=CH bending); ^{1}H-NMR ($CDCl_3$): δ 6.6–7.9 (m, 20H, Ar–H), 8.2 (s, 1H, –CONH–), 4.6 (s, 1H, –C=CH–Ar), 5.9 (s, 1H, –N–CH–S), 5.0 (s, 1H, Ar–OH), 2.8 (s, 6H, Ar–$N(CH_3)_2$); ^{13}C NMR ($CDCl_3$): δ 24.3, 40.2, 63.4, 114.2, 115.9, 120.8, 121.7, 122.4, 124.7, 125.2, 125.6, 126.0, 127.3, 127.4, 127.7, 128.8, 129.1, 129.3, 129.8, 133.5, 134.5, 136.1, 139.8, 148.8, 151.2, 156.9, 160.7, 164.2, 164.4, 164.7; GCMS: *m/z*: 679.23 (M^+). Anal. calcd. for $C_{40}H_{53}N_5O_4S$: C-70.67%, H-4.89%, N-10.30%. Found: C-70.72%, H-4.93%, N-10.35%.

Physical constants and characterization of *N*-{5-[(1-hydroxy(2-naphthyl))methylene)]-2-(4-hydroxyphenyl)-4-oxo(1,3-thiazolidin-3-yl)}{4-[2-(4-methylphenyl)-4-oxo(3-hydroquinazolin-3-yl)]phenyl}-carboxamide **(6d)**

M.p.: 160°C, Yield 55%; IR (KBr): 3313 cm^{-1} (N–H stretching, secondary amine), 3233 cm^{-1} (O–H stretching, –OH group), 3124 (C–H stretching, aromatic ring), 3051 (=CH stretching), 2904 cm^{-1} (C–H stretching, $-CH_3$ group), 1713, 1725 cm^{-1} (C=O stretching, amide group), 1636, 1615 cm^{-1} (C=N, C=C stretching, aromatic ring), 1343 cm^{-1} (C–N stretching, quinazoline ring), 920 cm^{-1} (ortho substitution of aromatic ring), 863 (=CH bending); ^{1}H NMR ($CDCl_3$): δ 6.6–7.9 (m, 20H, Ar–H), 8.5 (s, 1H, –CONH–), 4.7 (s, 1H, –C=CH–Ar), 5.9 (s, 1H, –N–CH–S), 5.0 (s, 1H, Ar–OH), 5.1 (s, 1H, Ar–OH); ^{13}C NMR ($CDCl_3$): δ 24.3, 63.4, 115.9, 117.7, 117.8, 120.8, 121.7, 122.3, 122.4, 123.6, 125.2, 125.6, 126.0, 126.8, 127.4, 127.7, 128.5, 128.8, 129.1, 129.3, 129.8, 130.1, 131.9, 133.5, 134.5, 136.1, 139.8, 151.2, 155.8, 156.9, 160.6, 164.2, 164.3, 164.6; GCMS: *m/z*: 702.19 (M^+). Anal. calcd. for $C_{42}H_{30}N_4O_5S$: C-71.78%, H-4.30%, N-7.97%. Found: C-71.82%, H-4.34%, N-7.99%.

Physical constants and characterization of *N*-{5-[(4-fluorophenyl)methylene]-2-(4-hydroxyphenyl)-4-oxo(1,3-thiazolidin-3-yl)} {4-[2-(4-methylphenyl)-4-oxo(3-hydroquinazolin-3-yl)]phenyl}carboxamide **(6e)**

M.p.: 175°C, Yield 74%; IR (KBr): 3313 cm^{-1} (N–H stretching, secondary amine), 3231 cm^{-1} (O–H stretching, –OH group), 3123 cm^{-1} (C–H stretching, aromatic ring), 3045 (=CH stretching), 2906 cm^{-1} (C–H stretching, $-CH_3$ group), 1711, 1723 cm^{-1} (C=O stretching, amide group), 1634, 1616 cm^{-1} (C=N, C=C stretching, aromatic ring), 1344 cm^{-1} (C–N stretching, quinazoline ring), 1250 cm^{-1} (C–F stretching), 924 cm^{-1} (ortho substitution of aromatic ring), 860 (=CH bending); ^{1}H NMR ($CDCl_3$): δ 6.1–7.9 (m, 20H, Ar–H), 8.3 (s, 1H, –CONH–), 4.9 (s, 1H, –C = CH–Ar), 5.9 (s, 1H, –N–CH–S), 5.1 (s, 1H, Ar–OH); ^{13}C NMR ($CDCl_3$): δ 24.3, 63.4, 115.4, 115.9, 120.8, 121.7, 122.4, 125.2, 125.6, 126.0, 127.4, 127.7, 128.0, 128.8, 129.1, 129.3, 129.8, 130.8, 133.5, 134.5, 136.1, 139.8, 151.2, 156.9, 162.1, 160.5, 164.0, 164.2, 164.8; GCMS: *m/z*: 654.17 (M^+). Anal. calcd. for $C_{38}H_{27}FN_4O_4S$: C-69.71%, H-4.16%, N-8.56%. Found: C-69.76%, H-4.21%, N-8.60%.

Physical constants and characterization of *N*-{5-[(4-hydroxyphenyl)methylene]-2-(4-hydroxyphenyl)-4-oxo(1,3-thiazolidin-3-yl)} {4-[2-(4-methylphenyl)-4-oxo(3-hydroquinazolin-3-yl)]phenyl}carboxamide **(6f)**

M.p.: 255°C, Yield 65%; IR (KBr): 3317 cm^{-1} (N–H stretching, secondary amine), 3235 cm^{-1} (O–H stretching, –OH group), 3120 cm^{-1} (C–H stretching, aromatic ring), 3055 (=CH stretching), 2900 cm^{-1} (C–H stretching, $-CH_3$ group), 1715, 1727 cm^{-1} (C=O stretching, amide group), 1634, 1613 cm^{-1} (C=N, C=C stretching, aromatic ring), 1346 cm^{-1} (C–N stretching, quinazoline ring), 863 (=CH bending), 927 cm^{-1} (ortho substitution of aromatic ring); ^{1}H NMR ($CDCl_3$): δ 6.5–7.9 (m, 20H, Ar–H), 8.1 (s, 1H, –CONH–), 4.8 (s, 1H, –C = CH–Ar), 5.8 (s, 1H, –N–CH–S), 5.1 (s, 1H, Ar–OH), 5.0 (s, 1H, Ar–OH); ^{13}C NMR ($CDCl_3$): δ 24.3, 63.4, 115.8, 115.9, 120.8, 121.7, 122.4, 125.2, 125.6, 126.0, 127.4, 127.7, 127.8, 128.8, 129.1, 129.3, 129.8, 133.5, 134.5, 136.1, 139.8, 151.2, 156.9,

157.7, 164.0, 160.8, 164.4, 164.8; GCMS: *m/z*: 652.18 (M^+). Anal. calcd. for $C_{38}H_{28}N_4O_5S$: C-69.92%, H-4.32%, N-8.58%. Found: C-69.96%, H-4.38%, N-8.64%.

Physical constants and characterization of *N*-{5-[(3-nitrophenyl)methylene]-2-(4-hydroxyphenyl)-4-oxo(1,3-thiazolidin-3-yl)} {4-[2-(4-methylphenyl)-4-oxo(3-hydroquinazolin-3-yl)]phenyl}carboxamide **(6g)**

M.p.: 111°C, Yield 59%; IR (KBr): 3315 cm^{-1} (N–H stretching, secondary amine), 3230 cm^{-1} (O–H stretching, –OH group), 3083, 3061 cm^{-1} (Qu–H and Ar–H stretching, aromatic ring), 3050 (=CH stretching), 2838 cm^{-1} (C–H stretching, $–CH_3$ group), 1738, 1719 cm^{-1} (C=O stretching, amide group), 1653, 1608 cm^{-1} (C=N, C=C stretching, aromatic ring), 1520 cm^{-1} ($–NO_2$ group asymmetric stretching), 1345 cm^{-1} (C–N stretching, quinazoline ring), 1345 ($–NO_2$ group symmetric stretching), 860 (=CH bending), 774 cm^{-1} (ortho substitution of aromatic ring); ^{1}H NMR ($CDCl_3$): δ 6.0–7.9 (m, 20H, Ar–H), 8.4 (s, 1H, –CONH–), 4.6 (s, 1H, –C=CH–Ar), 5.9 (s, 1H, –N–CH–S), 5.0 (s, 1H, Ar–OH); ^{13}C NMR ($CDCl_3$): δ 24.3, 63.4, 115.9, 120.0, 120.8, 123.1, 121.7, 122.4, 125.2, 125.6, 126.0, 127.4, 127.7, 128.8, 129.1, 129.3, 129.6, 129.8, 132.5, 133.5, 134.5, 136.1, 139.8, 147.8, 151.2, 156.9, 160.8, 164.1, 164.3, 164.8; GCMS: *m/z*: 681.17 (M^+). Anal. calcd. for $C_{38}H_{27}N_5O_6S$: C-66.95%, H-3.99%, N-10.27%. Found: C-66.99%, H-3.97%, N-10.32%.

Physical constants and characterization of *N*-{5-[(2-chlorophenyl)methylene]-2-(4-hydroxyphenyl)-4-oxo(1,3-thiazolidin-3-yl)} {4-[2-(4-methylphenyl)-4-oxo(3-hydroquinazolin-3-yl)]phenyl}carboxamide **(6h)**

M.p.: 219°C, Yield 70%; IR (KBr): 3315 cm^{-1} (N–H stretching, secondary amine), 3234 cm^{-1} (O–H stretching, –OH group), 3120 cm^{-1} (C–H stretching, aromatic ring), 3053 (=CH stretching), 2909 cm^{-1} (C–H stretching, $–CH_3$ group), 1716, 1729 cm^{-1} (C=O stretching, amide group), 1636, 1607 cm^{-1} (C=N, C=C stretching, aromatic ring), 1349 cm^{-1} (C–N stretching, quinazoline ring), 866 (=CH bending), 920 cm^{-1} (ortho substitution of aromatic ring), 745 cm^{-1} (C–Cl stretching); ^{1}H NMR ($CDCl_3$): δ 6.0–7.9 (m, 20H, Ar–H), 8.3 (s, 1H, –CONH–), 4.7 (s, 1H, –C = CH–Ar), 5.8 (s, 1H, –N–CH–S), 5.1 (s, 1H, Ar–OH); ^{13}C NMR ($CDCl_3$): δ 24.3, 63.4, 115.9, 120.8, 121.7, 122.4, 125.2, 125.6, 126.0, 126.8, 127.4, 127.7, 127.8, 128.7, 128.8, 129.1, 129.3, 129.4, 129.8, 133.0, 31.1, 133..5, 134.5, 136.1, 139.8, 151.2, 156.9, 160.5, 164.2, 164.3, 164.7; GCMS: *m/z*: 670.14 (M^+). Anal. calcd. for $C_{38}H_{27}ClN_4O_4S$: C-68.00%, H-4.05%, N-8.35%. Found: C-68.05%, H-4.11%, N-8.39%.

Physical constants and characterization of *N*-{5-[(4-methoxyphenyl)methylene]-2-(4-hydroxyphenyl)-4-oxo(1,3-thiazolidin-3-yl)}{4-[2-(4-methylphenyl)-4-oxo(3-hydroquinazolin-3-yl)]phenyl}carboxamide **(6i)**

M.p.: 300°C, Yield 72%; IR (KBr): 3316 cm^{-1} (N–H stretching, secondary amine), 3238 cm^{-1} (O–H stretching, –OH group), 3120 cm^{-1} (C–H stretching, aromatic ring), 3048 (=CH stretching), 2903 cm^{-1} (C–H stretching, $–CH_3$ group), 1715, 1728 cm^{-1} (C=O stretching, amide group), 1635, 1615 cm^{-1} (C=N, C=C stretching, aromatic ring), 1349 cm^{-1} (C–N stretching, quinazoline ring), 862 (=CH bending), 926 cm^{-1} (ortho substitution of aromatic ring); ^{1}H NMR ($CDCl_3$): δ 6.1–7.9 (m, 18H, Ar–H), 8.4 (s, 1H, –CONH–), 4.7 (s, 1H, –C=CH–Ar), 5.8 (s, 1H, –N–CH–S), 5.0 (s, 1H, Ar–OH), 3.6 (s, 3H, Ar–OCH_3); ^{13}C NMR ($CDCl_3$): δ 24.3, 55.8, 63.4, 114.2, 115.9, 120.8, 121.7, 122.4, 125.2, 125.6, 126.0, 127.4, 127.5, 127.7, 128.8, 129.1, 129.3, 129.8, 133.5, 134.5, 136.1, 139.8, 151.2, 156.9, 159.8, 160.3, 164.0, 164.1, 164.5; GCMS: *m/z*: 666.19 (M^+). Anal. calcd. for $C_{39}H_{30}N_4O_5S$: C-70.25%, H-4.54%, N-8.40%. Found: C-70.30%, H-4.59%, N-8.46%.

Physical constants and characterization of *N*-{5-[(4-methoxy-2-hydroxyphenyl)methylene]-2-(4-hydroxyphenyl)-4-oxo(1,3-thiazolidin-3-yl)}{4-[2-(4-methylphenyl)-4-oxo(3-hydroquinazolin-3-yl)]phenyl}carboxamide **(6j)**

M.p.: 181°C, Yield 63%; IR (KBr): 3313 cm^{-1} (N–H stretching, secondary amine), 3234 cm^{-1} (O–H stretching, –OH group), 3120 cm^{-1} (C–H stretching, aromatic ring), 3059 (=CH stretching), 2903 cm^{-1} (C–H stretching, $–CH_3$ group), 1712, 1723 cm^{-1} (C=O stretching, amide group), 1632, 1614 cm^{-1} (C=N, C=C stretching, aromatic ring), 1340 cm^{-1} (C–N stretching, quinazoline ring), 858 (=CH bending), 923 cm^{-1} (ortho substitution of aromatic ring); ^{1}H NMR ($CDCl_3$): δ 6.6–7.9 (m, 20H, Ar–H), 8.4 (s, 1H, –CONH–), 4.8 (s, 1H, –C=CH–Ar), 5.9 (s, 1H, –N–CH–S); 5.1 (s, 1H, Ar–OH), 5.0 (s, 1H, Ar–OH), 3.7 (s, 3H, Ar–OCH_3). ^{13}C NMR ($CDCl_3$): δ 24.3, 55.8, 63.4, 101.9, 106.8, 108.8, 115.9, 120.8, 121.7, 122.4, 125.2, 125.6, 126.0, 127.4, 127.7, 128.8, 129.1, 129.3, 129.8, 133.5, 134.5, 136.1, 139.8, 151.2, 156.9, 159.3, 161.2, 160.6, 164.3, 164.5, 164.5; GCMS: *m/z*: 682.18 (M^+). Anal.

calcd. for $C_{39}H_{30}N_4O_6S$: C-68.61%, H-4.43%, N-8.21%. Found: C-68.66%, H-4.49%, N-8.26%.

Physical constants and characterization of *N*-{5-[(2-methoxyphenyl)methylene]-2-(4-hydroxyphenyl)-4-oxo(1,3-thiazolidin-3-yl)}{4-[2-(4-methylphenyl)-4-oxo(3-hydroquinazolin-3-yl)]phenyl}carboxamide **(6k)**

M.p.: 99°C. Yield 69%; IR (KBr): 3314 cm^{-1} (N–H stretching, secondary amine), 3233 cm^{-1} (O–H stretching, –OH group), 3122 cm^{-1} (C–H stretching, aromatic ring), 3051 (=CH stretching), 2903 cm^{-1} (C–H stretching, $–CH_3$ group), 1713, 1725 cm^{-1} (C=O stretching, amide group), 1630, 1613 cm^{-1} (C=N, C=C stretching, aromatic ring), 1346 cm^{-1} (C–N stretching, quinazoline ring), 863 (=CH bending), 921 cm^{-1} (ortho substitution of aromatic ring); ^{1}H NMR ($CDCl_3$): δ 6.1–7.9 (m, 18H, Ar–H), 8.3 (s, 1H, –CONH–), 4.7 (s, 1H, –C=CH–Ar), 5.9 (s, 1H, –N–CH–S), 5.1 (s, 1H, Ar–OH), 3.7 (s, 3H, Ar–OCH_3); ^{13}C NMR ($CDCl_3$): δ 24.3, 56.2, 63.4, 114.2, 114.9, 115.9, 120.8, 121.0, 121.7, 122.4, 125.2, 125.6, 126.0, 127.4, 127.7, 128.8, 129.0, 129.1, 129.3, 129.8, 133.5, 134.5, 136.1, 139.8, 151.2, 156.9, 157.6, 160.6, 164.2, 164.3, 164.6; GCMS: *m/z*: 666.74 (M^+). Anal. calcd. for $C_{39}H_{30}N_4O_5S$: C-70.25%, H-4.54%, N-8.40%. Found: C-70.29%, H-4.59%, N-8.46%.

Physical constants and characterization of *N*-{5-[(5-bromo-2-hydroxyphenyl)methylene]-2-(4-hydroxyphenyl)-4-oxo(1,3-thiazolidin-3-yl)}{4-[2-(4-methylphenyl)-4-oxo(3-hydroquinazolin-3-yl)]phenyl}-carboxamide **(6l)**

M.p.: 150°C, Yield 71%; IR (KBr): 3313 cm^{-1} (N–H stretching, secondary amine), 3234 cm^{-1} (O–H stretching, –OH group), 3120 (C–H stretching, aromatic ring), 3057 (=CH stretching), 2907 cm^{-1} (C–H stretching, $–CH_3$ group), 1718, 1727 cm^{-1} (C = O stretching, amide group), 1634, 1612 cm^{-1} (C=N, C=C stretching, aromatic ring), 1340 cm^{-1} (C–N stretching, quinazoline ring), 867 (=CH bending), 926 cm^{-1} (ortho substitution of aromatic ring), 556 cm^{-1} (C–Br stretching); ^{1}H NMR ($CDCl_3$): δ 6.3–8.1 (m, 19H, Ar–H), 8.5 (s, 1H, –CONH–), 4.7 (s, 1H, –C=CH–Ar), 5.8 (s, 1H, –N–CH–S), 5.1 (s, 1H, Ar–OH), 4.9 (s, 1H, Ar–OH); ^{13}C NMR ($CDCl_3$): δ 24.3, 63.4, 115.9, 115.6, 118.0, 118.7, 120.8, 121.7, 122.4, 125.2, 125.6, 126.0, 127.4, 127.7, 128.8, 129.1, 129.3, 129.8,131.3, 132.2, 133.5, 134.5, 136.1, 139.8, 151.2, 156.9, 157.3, 160.9, 164.1, 164.3, 164.6; GCMS: *m/z*: 730.09 (M^+). Anal. calcd. for $C_{38}H_{27}BrN_4O_5S$: C-62.38%, H-3.72%, N-7.66%. Found: C-62.42%, H-3.77%, N-7.71%.

Physical constants and characterization of *N*-{5-[(2,6-dichlorophenyl)methylene]-2-(4-hydroxyphenyl)-4-oxo(1,3-thiazolidin-3-yl)}{4-[2-(4-methyl- phenyl)-4-oxo(3-hydroquinazolin-3-yl)]phenyl}carboxamide **(6m)**

M.p.: 183°C, Yield: 72%; IR (KBr): 3319 cm^{-1} (N–H stretching, secondary amine), 3230 cm^{-1} (O–H stretching, –OH group), 3123 cm^{-1} (C–H stretching, aromatic ring), 3048 (=CH stretching), 2903 cm^{-1} (C–H stretching, $–CH_3$ group), 1716, 1728 cm^{-1} (C=O stretching, amide group), 1632, 1614 cm^{-1} (C=N, C=C stretching, aromatic ring), 1349 cm^{-1} (C–N stretching, quinazoline ring), 869 (=CH bending), 925 cm^{-1} (ortho substitution of aromatic ring), 752 cm^{-1} (C–Cl stretching); ^{1}H NMR ($CDCl_3$): δ 6.2–7.7 (m, 19H, Ar–H), 8.4 (s, 1H, –CONH–), 4.9 (s, 1H, –C=CH–Ar), 5.7 (s, 1H, –N–CH–S), 5.3 (s, 1H, Ar–OH); ^{13}C NMR ($CDCl_3$): δ 24.3, 63.4, 115.9, 120.8, 121.7, 122.4, 125.2, 125.6, 126.0, 126.8, 127.4, 127.7, 128.8, 129.1, 129.3, 129.8, 130.8, 132.5, 133.5, 134.5, 135.7, 136.1, 139.8, 151.2, 156.9, 160.8, 164.0,164.4, 164.8; GCMS: *m/z*: 704.15 (M^+). Anal. calcd. for $C_{36}H_{26}Cl_2N_4O_4S$: C-64.68%, H-3.71%, N-7.94%. Found: C-64.73%, H-3.76%, N-7.99%.

Physical constants and characterization of *N*-{5-[(4-chlorophenyl)methylene]-2-(4-hydroxyphenyl)-4-oxo(1,3-thiazolidin-3-yl)}{4-[2-(4-methylphenyl)-4-oxo(3-hydroquinazolin-3-yl)]phenyl}carboxamide **(6n)**

M.p.: 209°C, Yield: 68%; IR (KBr): 3317 cm^{-1} (N–H stretching, secondary amine), 3235 cm^{-1} (O–H stretching, –OH group), 3125 cm^{-1} (C–H stretching, aromatic ring), 3055 (=CH stretching), 2905 cm^{-1} (C–H stretching, $–CH_3$ group), 1716, 1728 cm^{-1} (C=O stretching, amide group), 1637, 1615 cm^{-1} (C=N, C=C stretching, aromatic ring), 1348 cm^{-1} (C–N stretching, quinazoline ring), 925 cm^{-1} (ortho substitution of aromatic ring), 859 (=CH bending), 742 cm^{-1} (C–Cl stretching); ^{1}H NMR ($CDCl_3$): δ 6.1–7.9 (m, 20H, Ar–H), 8.5 (s, 1H, –CONH–), 4.8 (s, 1H, –C=CH–Ar), 5.8 (s, 1H, –N–CH–S), 5.0 (s, 1H, Ar–OH); ^{13}C NMR ($CDCl_3$): δ 24.3, 63.4, 115.9, 120.8, 121.7, 122.4, 125.2, 125.6, 126.0, 127.4, 127.7, 127.8, 128.7, 128.8, 129.1, 129.3, 129.8, 133.3, 133.5, 134.5, 136.1, 139.8, 151.2, 156.9, 160.7, 164.2, 164.3, 164.7; GCMS: *m/z*: 670.14 (M^+). Anal. calcd. for $C_{38}H_{27}ClN_4O_4S$: C-68.00%, H-4.05%, N-8.35%. Found: C-68.06%, H-4.09%, N-8.41%.

Acknowledgment The authors express their sincere thanks to the Department of Chemistry and to Bhavnagar University, Bhavnagar for providing research facilities.

References

Al-Bayati FA, Al-Mola HF (2008) Antibacterial and antifungal activities of different parts of *Tribulus terrestris* L. growing in Iraq. J Zhejiang Univ Sci B 9:154–159. doi:10.1631/jzus.B0720251

Aly MM, Mohamed YA, Basyouni WM (2010) Synthesis of some new 4(3*H*)-quinazolinone-2-carboxaldehyde thiosemicarbazones and their metal complexes and a study on their anticonvulsant, analgesic, cytotoxic and antimicrobial activities. Eur J Med Chem 45:3365–3373. doi:10.1016/j.ejmech.2010.04.020

Baek DJ, Park YK, Heo HI, Lee MH, Yang ZY, Chio MH (1998) Synthesis of 5-substituted quinazolinone derivatives and their inhibitory activity in vitro. Bioorg Med Chem Lett 8:3287–3290

Bekhit AA, Khalil MA (1998) Synthesis benzopyrazolyl derivatives of quinazolinones. Pharmazie 1998(53):539–544

Capan G, Ulusoy N, Ergenc N (1999) New 6-phenylimidazo[2,1-b]thiazole derivatives: synthesis and antifungal activity. Monatsh Chem 130:1399–1407

Dahiya R, Kumar A (2008) Synthesis and biological activity of peptide derivatives of iodoquinazolinones/nitroimi-dazoles. Molecules 13:958–976

Desai NC, Trivedi PB (1993) Synthesis and antimicrobial activity of some heterocyclic compounds. Indian J Chem 33B:497–500

Desai NC, Dodiya A, Bhatt N, Kumar M (2011) Dimeric 2-(2-chlorophenyl)-quinazolin-4-ones as potential antimicrobial agents. Med Chem Res. doi:10.1007/s00044-011-9621-5

El-Azab AS, Al-Omar MA, Sayed-Ahmed MM, Abdel-Hamide SG (2010) Design, synthesis and biological evalua- tion of novel quinazoline derivatives as potential antitumor agents: molecular docking study. Eur J Med Chem 45:4188–4198

Ergenc N, Buyuktimkin S, Capan G, Baktir G, Rollas S (1991) synthesis and evaluation of some CNS depressant properties of 3-{2-[(5-aryl-1,3,4-oxadiazol-2-yl)amino]acetamido}-2-methyl-4(3H)-quinazolinones. Pharmazie 46:290–291

Gerstein HC, Yale JF, Harris SB, Issa M, Stewart JA, Dempsey E (2006) A randomized trial of adding insulin glargine vs. avoidance of insulin in people with Type 2 diabetes on either no oral glucose-lowering agents or submaximal doses of metformin and/or sulphonylureas. The Canadian INSIGHT (implementing new strategies with insulin glargine for hyperglycaemia treatment) study. Diabet Med 23:736–742

Ghalem BR, Mohamed B (2009) Antimicrobial evaluation of the oleoresin oil of *Pistacia vera* L. African J Pharm Pharmacol 3:92–96

Giri RS, Thaker HM, Giordano T, Chen B, Vasu KK (2010) Synthesis and evaluation of quinazolinone derivatives as inhibitors of NF-kB, AP-1 mediated transcription and eIF-4E mediated translational activation: inhibitors of multi-pathways involve in cancer. Eur J Med Chem 45:3558–3563

Griffin RJ, Srinivasan S, Bowman K, Calvert AH, Curtin NJ, Neweli DR (1998) Resistance-modifying agents. 5. Synthesis and biological properties of quinazolinone inhibitors of the DNA repair enzyme poly(ADP-ribose) polymerase (PARP). J Med Chem 41:5247–5256

Gursoy A, Karali N (1995) Synthesis and anticonvulsant activity of new acylthiosemicarbazides and thiazolidones. Farmaco 50:857–866

Hamel E, Lin CM, Plowman J, Wang HK, Lee KH, Paull KD (1996) Antitumor 2,3-dihydro-2-aryl-4(1H)-quinazolinone derivatives. Interactions with tubulin. Biochem Pharmacol 51:53–59

Jatav V, Jain SK, Kashaw SK, Mishra P (2006) Synthesis and Antimicrobial activity of novel 2-methyl-3-(1′3′4′-thiadiazoyl)-4-(3H)-quinazolinones. Indian J Pharm Sci 68:360–363

Kashaw SK, Kashaw V, Mishra P, Stables JP (2010) Synthesis, anticonvulsant and CNS depressant activity of some new bioactive 1-(4-substituted-phenyl)-3-(4-oxo-2-phenyl/ethyl-4H-quinazolin-3-yl)-urea. Eur J Med Chem 44:4335–4343

Kavitha CV, Basappa S, Nanjunda S, Mantelingu K, Shidhar MA (2006) Synthesis or new bioactive venlafaxine analogs: novel thiazolidin-4-ones as antimicrobials. Bioorg Med Chem 14:2290–2299

Kucukguzel G, Kocatepe A, Gulluce M (2006) Synthesis and biological activity of 4-thiazolidinones, thiosemicarbazides derived from diflunisal hydrazide. Eur J Med Chem 41:353–359

Kumar A, Rajput CS (2009) Synthesis and anti-inflammatory activity of newer quinazolin-4-one derivatives. Eur J Med Chem 44:83–90

Liu X, Huang RQ, Li HY, Yang Z (1999) Synthesis and bioactivity of O-(4-quinazolinyl) hydroximic thioesters (amides). Chin J Appl Chem 16:23–26

Nanda AK, Ganguli S, Chakraborty R (2007) Antibacterial activity of some 3-(Arylideneamino)-2-phenylquinazoline-4(3*H*)-ones: synthesis and preliminary QSAR studies. Molecules 12:2413–2426

Ottana R, Maccari R, Barreca ML, Rotondo A, Rossi A, Chiricosta G, Paola R (2005) 5-Arylidene-2-imino-4-thiazolidinones: design and synthesis of novel anti-inflammatory agents. Bioorg Med Chem 13:4243–4252

Pandey VK, Pathak LM, Mishra SK (2005) Synthesis and characterisation of isoquinolinyl quinazolines and a study of their antiviral and antifungal activities. Indian J Chem 44B:1940–1945

Purohit DM, Bhuva VR, Shah VH (2003) Synthesis of 5-arylaminosulpho-*N*-acetylanthranilic acid, 6-arylaminosulpho-2-methyl-3-amino/3-*N*-chloroacetamido/3-*N*-arylaminoacetamido-4-(3*H*)-quinazolones as potential anti-HIV anticancer and antimicrobial agents. Chemistry 1:233–245

Sumegi B, Hideg K, Kalai T (2007) Quinazolinone-derivatives and their use for preparation of pharmaceutical compositions having parp enzyme inhibitory effect [P]. US Pat. Appl. 20070042935, 22 Feb 2007

Terashima K, Shimamura H, Kawase A, Tanaka Y, Tanimura T, Kamisaki T, Ishizuka Y, Sato M (1995) Studies on antiulcer agents. IV: antiulcer effects of 2-benzylthio-5,6,7,8-tetrahydro-4(3*H*)-quinazolinones and related compounds. Chem Pharm Bull 43:2021–2023

Vigorita MG, Ottana R, Monforte F, Maccari R, Trovato A, Monforte MT (2001) Synthesis and antiinflamatory, analgesic activity of 3,3′-(1,2-ethandiyl)-bis[2-aryl-4-thiazolidinone]chiral compounds. Bioorg Med Chem Lett 11:2791–2794