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MEDICINAL CHEMISTRY RESEARCH

ORIGINAL RESEARCH

Dimeric 2-(2-chlorophenyl)-quinazolin-4-ones as potential antimicrobial agents

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Abstract 3-(Aryl)-2-(2-chlorophenyl)-6-{2-[2-(2-chlorophenyl)-4-oxo(3-hydroquinazolin-3yl)]ethyl}-3-hydroquinazolin-4-ones had been selected as target bio-active molecules. Several quinazoline derivatives were prepared by using anthranilic acid, acid chloride, 2-amino-ethanol, and different amines. Newly synthesized compounds were screened for their antibacterial and antifungal activities on *Escherichia coli*, *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Staphylococcus pyogenes*, *Candida albicans*, *Aspergillus niger*, and *Aspergillus clavatus*. The compounds **5e**, **5g**, and **5h** are shown to have excellent activity, while **5c**, **5d**, **5i**, **5k**, **5l** are shown to have very good activity against several strains of bacteria. The structures of the synthesized compounds were firmly established by well-defined spectral analysis techniques like IR, ^{1}H-NMR, ^{13}C-NMR, and Mass spectra.

Keywords Quinazolinone · Antimicrobial activity of quinazolinone moiety · Dimeric quinazolinone

Introduction

Since the last half of the 20th century, bacteria have developed resistance against currently available drugs and therefore it is an ongoing effort, for medicinal chemists to synthesize new chemotherapeutic agents. In continuation to this, compounds bearing heterocyclic nuclei have received much attention because of their chemotherapeutic value in the development of novel antimicrobials (Dahiya and Kumar, 2008). Quinazolines are heterocyclic compounds having wide spectrum medicinal values such as antihypertensive (Pandey and Bajpai, 2004), antiviral (Hess and Cronin, 1968) anti-inflammatory (Yadav and Shirude, 2006; Wand and Xia, 2003). The diverse pharmacological properties exhibited by quinazolones have been of much significance in recent years. 2,3-Disubstituted quinazolones have been demonstrated to be associated with antiviral (Pandey *et al.*, 1988) and antifungal activities (Tiwari *et al.*, 2006). In addition, some quinazolone derivatives containing sulphonamido group caused antihypertensive effect probably due to the initial reduction of blood volume because of Na^{+} depletion and subsequently on account of direct relaxation of arteriolar smooth muscle (Papsech and Schroeder, 1956). Some compounds were generally effective in lower blood pressure in the spontaneous hypertensive rats model and showed α-adrenergic blocking activity (Atkins and Nicolosi, 1979).

Looking to the medicinal importance of these compounds, this study is aimed to synthesize new bio-active molecules and screen them for antimicrobial activity (Desai and Moradia, 2007; Desai and Shah, 2001; Desai and Bhatt, 1995; Desai and Desai, 2005). The study reported in this article is in continuation of the previous work aimed at synthesizing bio-active heterocyclic entities (Desai and Desai, 2005; Desai and Undavia, 1998; Desai and Undavia, 1996; Desai and Bhavsar, 2008; Desai and Saxena, 2008; Desai and Baldaniya, 2009).

Nanda and his co-workers synthesized 3-(arylideneamino)-2-phenylquinazoline-4(3*H*)-ones, which were investigated for their antimicrobial 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. It was found that the incorporation of the

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3-arylideneamino substituent enhanced the antibacterial activity of the quinazolone system (Nanda *et al.*, 2007). On the basis of this, for the first time the authors have reported the dimeric quinazolinones and try to evaluate antimicrobial activity. Results of the antimicrobial activity clearly indicate that by introducing the dimeric structure of quinazoline, the activity was enhanced. It was report herein the synthesis of quinazolinones with a view to synthesize more potentially bio-active molecules.

This study is in conjunction with the ongoing programme of utilizing readily obtainable starting materials for the synthesis of heterocyclic systems (Madkour, 2002; Madkour *et al.*, 2001; Mahmoud and Madkour, 2001; Salem *et al.*, 2001; Madkour *et al.*, 1998; Madkour *et al.*, 1994 Madkour, 1993).

One of the most important features of (4*H*)-3,1-benzoxazinone chemistry is their use as key starting materials for further transformations. They are indeed useful intermediates in organic synthesis affording through reaction with nitrogen nucleophiles 4(3*H*)quinazolinones. This scaffold (**5**) is a part of the synthesis of new chemical entities in the form of antimicrobial agents. 3-(Aryl)-2-(2-chlorophenyl)-6-{2-[2-chlorophenyl)-4-oxo(3-hydro-quinazolin-3yl)]ethyl}hydroquinazolin-4-ones (**5a–l**) were synthesized in five steps. First step involves condensation of 2-amino benzoic acid with 2-chlorobenzoyl chloride to give 2-(2-chlorophenyl)benzo[*d*]1,3-oxazin-4-one (**1**). It was condensed with 2-amino ethyl alcohol to yield 2-(2-chlorophenyl)-3-(2-hydroxyethyl)-3-hydroquinazolin-4-one (**2**). Compound (**2**) was further condensed with 2-amino benzoic acid to give 2-amino-5-{2-[2-chlorophenyl)-4-oxo(3-hydroquinazolin-3-yl)ethyl} benzoic acid (**3**), which on further treatment with 2-chloro benzoyl chloride furnished 2-(2-chlorophenyl)-6-{2-[2-(2-chlorophenyl)-4-oxo-(3-hydroquinazolin-3-yl)]ethyl}benzo[*d*]1,3-oxozin-4-one (**4**). Finally, compound (**4**) on treatment with different aromatic amines yielded 2-(2-chlorophenyl)-5-{2-[2-(2-chlorophenyl)-4-oxo(3-hydroquinazolin-3-yl)]ethyl}-3-aryl-3-hydroquinazolin-4-ones (**5a–l**).

Results and discussion

The characterization of newly synthesized compounds of the series was carried out by IR, NMR, and Mass spectra and the data is discussed in the Experimental section.

^{13}C-NMR—Data

The final compound-**5g** has dimeric quinazolinone rings. The chemical shifts of the final compound carbons vary from $\delta = 164.0$ to 23.3 ppm. The carbon nuclei under the influence of a strong electronegative environment appears downfield, e.g., the C-2 and C-14 carbonyl, which are directly linked to the ring nitrogen, have a chemical shift value of $\delta = 161.4$ and 160.8 ppm, whereas the C-24 and C-30 are linked to one chlorine atom appears at the same $\delta = 130.8$ ppm. The carbons C-1 and C-15 which are attached on both sides of nitrogen atoms appeared at the same high value of $\delta = 164.0$ ppm, The chemical shift of the ring carbons at C-3 and C-13 are affected by the presence of the nearest carbonyl group and appeared at the same $\delta = 120.8$ ppm. The C-36 appeared at $\delta = 142.7$ ppm due to the strong electron withdrawing influence of nitro group. The methyl group attached to C-34 appeared at $\delta = 134.9$ ppm while the carbon of the methyl group C-37 appears at low value of $\delta = 23.3$ ppm. The C-34 which is attached to methyl group appeared at $\delta = 125.7$ ppm. The C-35 which is affected by the influence of the C-36 which is attached to nitro group and C-34 at methyl group appeared at $\delta = 125.7$ ppm. C-8 and C-16 which are present in the quinazolinone rings appeared at $\delta = 151.2$ and 148.4 ppm due to the nitrogen atmosphere on the nearest carbon atom. The carbon C-32 appeared at $\delta = 122.4$ ppm while the carbons C-19 and C-25 of the chloro benzene rings which are directly attached to quinazolinone rings appeared at the same value of $\delta = 123.0$ ppm. The carbons of the phenyl rings of quinazolinone nucleus appeared between $\delta = 122.4$ to 133.5 ppm, respectively. The carbons of the chloro benzene ring which are attached to the quinazolinone ring having equivalent carbons C-20 and C-26 appeared at $\delta = 127.5$ ppm. C-21 and C-27 appeared at $\delta = 127.0$, C-22 and C-28 appeared at $\delta = 131.6$ ppm, C-23 and C-29 appeared at 128.9, respectively. The carbon skeleton of compound-**5g** is described in Fig. 1.

Antimicrobial activity

For antibacterial activity, compounds **5b**, **5d**, **5i**, **5k**, and **5l** (R = 2-Cl-C_6H_4, 2,4-$(CH_3)_2$-C_6H_3, 3-NO_2-C_6H_4, 3,4-$(Cl)_2$-C_6H_3 and 2,6-$(Cl)_2$-4-NO_2-C_6H_2) are considered to

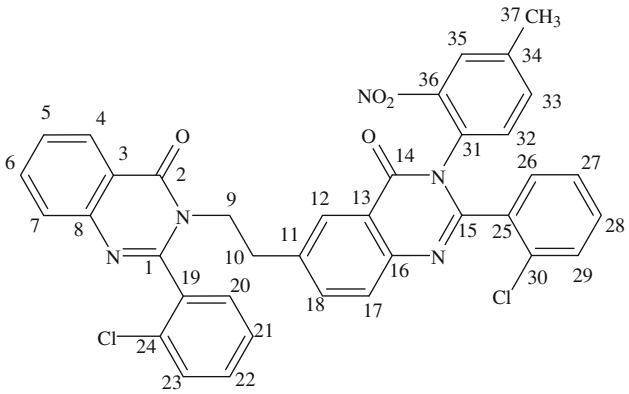


Fig. 1 Carbon skeleton of the compound-**5g**

be very good active against *S. pyogenes* as compared to the standard drug ampicillin, while compounds **5c**, **5f**, and **5j** (R = 2,3-$(CH_3)_2$-C_6H_3, 4-OCH_3-2-NO_2-C_6H_3, and 4-NO_2-C_6H_4) are considered as good active against *S. pyogenes*, while compounds **5e** (R = 2,5-$(CH_3)_2$-C_6H_3 and **5g** (R = 4-CH_3-2-NO_2-C_6H_3) are considered as excellent active against *S. pyogenes* and compound-**5h** considered as very excellent against *S. pyogenes* as compared to the standard drug ampicillin. Compounds **5b**, **5e**, **5f**, **5g**, **5h**, **5j**, and **5l** (R = 2-Cl-C_6H_4, 2,5-$(CH_3)_2$-C_6H_3, -4-OCH_3-2-NO_2-C_6H_3, 4-CH_3-2-NO_2-C_6H_3, 2-NO_2-C_6H_4, 4-NO_2-C_6H_4, and 2,6-$(Cl)_2$-4-NO_2-C_6H_2) are considered as good active against gram positive bacteria *S. aureus*, while **5d**, **5i**, and **5k** (R = 2,4-$(CH_3)_2$-C_6H_3, 3-NO_2-C_6H_4, 3,4-$(Cl)_2$-C_6H_3) are considered as very good active against *S. aureus* as compared to the standard drug ampicillin. Compounds **5c**, **5d**, **5i**, and **5k** (2,3$(CH_3)_2$-C_6H_3, 2,4-$(CH_3)_2$-C_6H_3, 3-NO_2-C_6H_4, and 3,4-$(Cl)_2$-C_6H_3) are considered as good active against gram negative *P.aeruginosa* bacteria as compared to the standard drug ampicillin, while compounds **5a**, **5e**, and **5h** (R = 4-Br-C_6H_4, 2,5-$(CH_3)_2$-C_6H_3 and 2-NO_2-C_6H_4) are considered as moderately active as compared to the standard drug ampicillin. Compounds **5e**, **5f**, **5h**, and **5j** (R = 2,5$(CH_3)_2$-C_6H_3, 4-OCH_3-2-NO_2-C_6H_3, 2-NO_2-C_6H_4, and 4-NO_2-C_6H_4) are considered good active against gram negative bacteria as compared to the standard drug ampicillin, while the compounds **5c**, **5d**, and **5i** (R = 2,3-$(CH_3)_2$-C_6H_3, 2,4$(CH_3)_2$-C_6H_3, and 3-NO_2-C_6H_4) are considered as very good active against *E. coli,* while compounds **5a**, **5g**, and **5k** (4-Br-C_6H_4,4-CH_3-2-NO_2-C_6H_3 and 3,4-$(Cl)_2$-C_6H_3) are considered as moderately active against *E.coli* as compared to the standard drug ampicillin. The antibacterial activity of the compounds was enhanced due to the introduction of nitro, chloro, and methyl groups in the dimeric structure of quinazolinone. The results of antibacterial studies are given in Table 1. For antifungal activity, it has been observed that compounds **5d**, **5f**, **5h**, and **5k** (R = 2,4$(CH_3)_2$-C_6H_3, 4-OCH_3-2-NO_2-C_6H_3, 2-NO_2-C_6H_4, 3,4-$(Cl)_2$-C_6H_3) are found to be excellent active against *C. albicans,* compound **5e** (R = 2,5-$(CH_3)_2$-C_6H_3) is considered as very good active against *C. albicans* as compared to the standard drug griseofulvin*,* while compounds **5b**, **5c**, **5g**, and **5j** (R = 2-Cl-C_6H_4, 2,3-$(CH_3)_2$-C_6H_3), 4-CH_3-2-NO_2-C_6H_3, 4-NO_2-C_6H_4) are considered as good active against *C.albicans*. Compounds **5b**, **5h**, and **5l** (R = 2-Cl-C_6H_4, 2-NO_2-C_6H_4, and 2,6-$(Cl)_2$-4-NO_2-C_6H_2) are considered as good active against *A.niger* as compared to the standard drug griseofulvin. Compounds

Table 1 Results of antibacterial and antifungal screening of the compounds (**5a–l**)

S. no.	–Ar	Minimum inhibitory concentration (MIC) ug/ml ±SD				Minimum inhibitory concentration (MIC) in 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
5a	-4-Br-C_6H_4	200 ± 4.50*	200 ± 3.78*	500 ± 4.04*	500 ± 4.04*	1000 ± 2.51*	500 ± 4.50*	1000 ± 3.05*
5b	-2-C1-C_6H_4	500 ± 4.72*	500 ± 3.05*	200 ± 3.05*	50 ± 2.51*	500 ± 4.04*	100 ± 3.51*	100 ± 4*
5c	-2,3-$(CH_3)_2$-C_6H_3	50 ± 4.93*	100 ± 4.04*	500 ± 4.04*	100 ± 4.50*	500 ± 4*	500 ± 4.35*	500 ± 3.78*
5d	-2,4-$(CH_3)_2$-C_6H_3	50 ± 34.04*	100 ± 4.58*	50 ± 3.78*	50 ± 4*	100 ± 4.58*	500 ± 3.60*	500 ± 3.05*
5e	-2,5-$(CH_3)_2$-C_6H_3	100 ± 3.78*	200 ± 4*	100 ± 3.05*	25 ± 1*	200 ± 4.04*	500 ± 4.50*	500 ± 3.60*
5f	-4-OCH_3-2-NO_2-C_6H_3	100 ± 4.04*	500 ± 3.46*	100 ± 2.51*	100 ± 3.51*	100 ± 4.50*	500 ± 4.58*	500 ± 4.04*
5g	-4-CH_3-2-NO_2-C_6H_3	200 ± 4.93*	500 ± 4.58*	100 ± 3.51*	25 ± 1*	500 ± 2.30*	1000 ± 4.04*	100 ± 4.04*
5h	-2-NO_2-C_6H_4	100 ± 4*	200 ± 3.60*	200 ± 4.04*	12.5 ± 1.32*	100 ± 3.21*	100 ± 3.05*	1000 ± 4.16*
5i	-3-NO_2-C_6H_4	50 ± 3.78*	100 ± 4.04*	50 ± 3*	50 ± 4.04*	1000 ± 3.51*	1000 ± 3.51*	100 ± 3*
5j	-4-NO_2-C_6H_4	100 ± 3.21*	500 ± 3.51*	200 ± 3.21*	100 ± 4.16*	500 ± 3.46*	500 ± 3.51*	500 ± 4.04*
5k	-3,4-$(C1)_2$-C_6H_3	200 ± 3.21*	100 ± 3.05*	50 ± 3.51*	50 ± 2.08*	100 ± 3.78*	500 ± 4.16*	100 ± 3.05*
51	-2,6-$(C1)_2$-4-NO_2-C_6H_2	500 ± 4.58*	500 ± 3.51*	100 ± 3.05*	50 ± 3.60*	500 ± 3.05*	100 ± 4*	100 ± 2.51*
	Ampicillin	100 ± 2.0*	100 ± 1.0*	250 ± 1.52*	100 ± 2.08*	–	–	–
	Griseofulvin	–	–	–	–	500 ± 0.57*	100 ± 1*	100 ± 1.15*

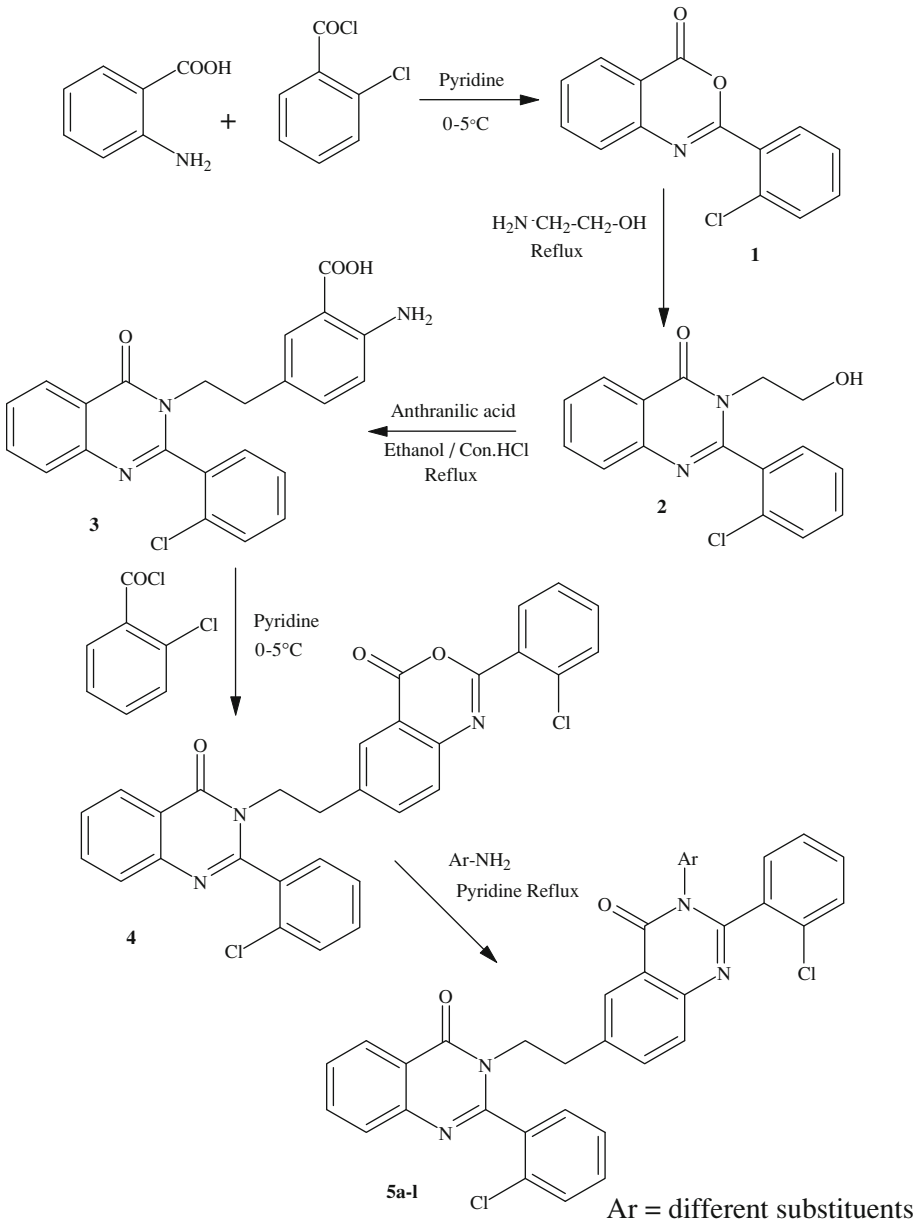
SD Standard deviation * $P \leq 0.0001$

5b, **5g**, **5i**, **5k**, and **5l** (R = 2-Cl-C_6H_4, 4-CH_3-2-NO_2-C_6H_3, 3-NO_2-C_6H_4, 3,4-$(Cl)_2$-C_6H_3, 2,6-$(Cl)_2$-4-NO_2-C_6H_2) are considered as good active against *A. clavatus* as compared to the standard drug griseofulvin. The enhancement of the activity of these compounds is due to the presence of nitro and chloro groups in the dimeric structure of quinazolinone.

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 are reported in ppm in reference to the 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 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 is used for distillation Scheme 1.

Scheme 1 Preparation of the compounds **5a–l**



Antibacterial activity

The newly synthesized compounds were screened for their antibacterial activity against gram positive bacteria *Staphylococcus aureus* (MTCC-96) and *Streptococcus pyogenes* (MTCC-442) and gram negative *Escherichia 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 (**5a**–**l**) were screened for their antibacterial activity in triplicate against *Escherichia coli*, *Staphylococcus aureus*, *Pseudomonas aeruginosa*, and *Streptococcus 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 (0.25, 0.05, 0.5, and 1 μg/ml) MIC against *E. coli*, *P. aeruginosa*, *S. aureus*, and *S. pyogenes*, respectively.

Antifungal activity

Same compounds were tested for antifungal activity in triplicate against *Candida albicans*, *Aspergillus nigerm*, and *Aspergillus 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 100 μg/ml MIC against all fungi used for the antifungal activity.

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.

Experimental

Preparation of 2-(2-chlorophenyl) benzo[*d*]1,3-oxazin-4-one (**1**) was synthesized according to the reported method (Desai NC and Undavia NK, 1996).

Preparation of 2-(2-chlorophenyl)-3-(2-hydroxyethyl)-3-hydroquinazolin-4-one (2)

2-Amino ethyl alcohol (0.02 mol) and compound (**1**) (0.01 mol) was refluxed for 4 h. The solution was poured into ice-cold water and then required amount of dilute hydrochloric acid (10%) was added to remove unreacted 2-amino ethyl alcohol. The solid product was filtered and washed with cold water. The resulting solid was recrystallized from ethanol (99%). m.p.: 178°C, yield: 65%; IR (KBr): 3335 cm^{-1} (O–H str.), 3110, 3065 (C–H str., aromatic ring), 2835 (C–H str., $–CH_2$ group), 1735(C=O str., amide group), 1652, 1615 (C=N, C=C str., quinazoline ring), 820 (C–Cl stretching); ^{1}H NMR ($CDCl_3$) : 6.79–7.85 (m, 8H, Ar–H), 3.20 (t, 2H, $O–CH_2$), 3.45 (t, 2H, $N–CH_2$); 4.2 (s, 1H, -OH); ^{13}C-NMR (δ Value): 41.5, 58.9, 120.8, 122.4, 123.0, 127.0, 127.4, 127.5, 128.8, 128.9, 130.8, 131.6, 133.5, 151.2, 161.4, 164.0; GCMS : *m/z* : 300.07 (M^+); Anal. Calc. for $C_{16}H_{13}ClN_2O_2$: C-63.90%, H-4.36%, N-9.32%. Found: C-63.25%, H-4.24%, N-9.84%.

Preparation of 2-amino-5-{2-[2-chlorophenyl)-4-oxo(3-hydroquinazolin-3-yl)] ethyl} benzoic acid (3)

A mixture of compound (**2**) (0.01 mol) and anthranilic acid (0.01 mol) in ethanol (50 ml) containing 2 ml of concentrated hydrochloric acid was heated under reflux for 10 h. Ethanol was distilled off. It was air dried and recrystallized from ethanol (99%). m.p.: 210°C, yield: 65%; IR (KBr): 3120, 3079 (C–H str., aromatic ring), 2835 (C–H str., $-CH_2$ group), 1705 (C=O str., acid group), 1740 (C=O str., amide group), 1655, 1606 (C=N, C=C, quinazoline ring), 1358(C–N str., quinazoline ring), 825(C–Cl stretching); ^{1}H NMR ($CDCl_3$): 11.21 (s, 1H, –COOH), 8.5 (s, 2H, $–NH_2$), 6.69–7.60 (m, 11H, Ar–H). 2.70 (t, 2H, $C–CH_2$), 3.39 (t, 2H, $N–CH_2$); ^{13}C-NMR (δ Value): 33.5, 43.1, 110.1, 116.1, 120.8, 122.4, 123.0, 127.0, 127.4, 127.5, 128.8, 128.9, 129.3, 130.0, 130.8, 131.6, 133.5, 133.7, 148.4, 151.2, 161.4, 164.0, 169.3; GCMS: *m/z*: 419.10 (M^+); Anal. Calc. for $C_{23}H_{18}ClN_3O_3$: C-65.79%, H-4.32%, N-10.01%. Found: C-65.56%, H-4.45%, N-10.08%.

Preparation of 2-(2-chlorophenyl)-6-{2-[2-(2-chlorophenyl)-4-oxo (3-hydroquinazolin-3-yl)] ethyl} benzo[d]1,3-oxazin-4-one **(4)**

Compound (**3**) (0.02 mol) was dissolved in pyridine (50 ml) by stirring slowly at room temperature. The solution was cooled to 0°C and 2-chlorobenzoyl chloride (0.01 mol) was slowly added dropwise to this solution with constant stirring. When the addition was completed, the reaction mixture was further stirred for 1 h at room temperature and set aside for 1 h. The pasty mass so obtained was diluted with water (50 ml) and treated with 5% sodium bicarbonate solution (50 ml) to remove any unreacted acid. When the effervescence ceased, it was filtered and washed with water to remove the adhered pyridine and the inorganic materials. The crude product was dried and recrystallized from ethanol. m.p.: 222°C, yield: 70%; IR (KBr): 3095, 3065(C–H str., aromatic ring), 2835(C–H str., $–CH_2$ group), 1716, 1730 (C=O str., amide group), 1655, 1606 (C=N, C=C, quinazoline ring), 1358(C–N str., quinazoline ring), 822(C–Cl stretching); ^{1}H NMR ($CDCl_3$): 6.62–7.88 (m, 15H, Ar–H). 2.61 (t, 2H, C–CH_2), 3.39(t, 2H, N–CH_2); ^{13}C-NMR (δ Value): 33.5, 43.1, 116.2, 120.8, 122.4, 123.0, 127.0, 127.4, 127.5, 128.8, 128.9, 130.5, 130.6, 130.8, 131.6, 132.5, 133.9, 134.2, 137.8, 151.2, 156.0, 159.4, 161.4, 164.0; GCMS: *m/z*: 540.40 (M^+); Anal. Calc. for $C_{30}H_{19}Cl_2N_3O_3$: C-66.67%, H-3.54%, N-7.77%. Found: C-66.69%, H-3.55%, N-7.82%.

General preparation of 2-(2-chlorophenyl)-6-{2-[2-(2-chlorophenyl)-4-oxo(3-hydroquinazolin-3-yl)]ethyl}-3-(aryl)-3-hydroquinazolin-4-ones **(5a–l)**

Compound (**4**) (0.01 mol) was taken in pyridine (30 ml) and substituted amine (0.01 mol) was added. The reaction mixture was refluxed for 5–6 h. The solution was poured onto crushed ice and few drops of concentrated hydrochloric acid was added. The product was filtered, washed with cold water, dried, and recrystallized from ethanol.

Physical constants and characterization of 3-(4-bromophenyl)-2-(2-chlorophenyl)-6-{2-[2-(2-chlorophenyl)-4-oxo(3-hydroquinazolin-3-yl)]ethyl}-3-hydroquinazolin-4-one **(5a)**

m.p.:176°C; yield: 75%; IR (KBr): 3095, 3065 (C–H str., aromatic ring), 2835 (C–H str., $–CH_2$ group), 1716, 1730 (C=O str., amide group), 1655, 1606, (C=N, C=C, quinazoline ring), 1358(C–N str., quinazoline ring), 1520 (N–O str., $–NO_2$ group), 832 (C–Cl stretching) 575 (C–Br stretching); ^{1}H NMR ($CDCl_3$): 6.91–7.85 (m, 19H, Ar–H). 2.61 (t, 2H, C–CH_2), 3.39 (t, 2H, N–CH_2); ^{13}C-NMR ($CDCl_3$) : 33.1, 43.1, 118.7, 120.7, 120.8, 122.3, 122.4, 123.0, 123.8, 127.0, 127.4, 127.5, 127.7, 128.8, 128.9, 130.8, 131.6, 131.7, 131.8, 132.4, 133.5, 138.0, 148.4, 151.2, 160.8, 161.4, 164.0; GCMS: *m/z*: 694.91 (100.0%). Anal. Calc. For $C_{36}H_{23}BrCl_2N_4O_2$: C-62.30%, H-3.39%, N-8.11%. Found: C-62.26%, H-3.33%, N-8.06%.

Physical constants and characterization of 2,3-bis(2-chlorophenyl)-6-{2-[2-(2-chlorophenyl)-4-oxo(3-hydroquinazolin-3-yl)]ethyl}-3-hydroquinazolin-4-one **(5b)**

m.p.:174°C; yield: 58%; IR (KBr): 3092, 3072 (C–H str., aromatic ring), 2831 (C–H str., $–CH_2$ group), 1714, 1738 (C=O str., amide group), 1651, 1611, (C=N, C=C, quinazoline ring), 1354 (C–N str., quinazoline ring), 1524 (N–O str., $–NO_2$ group), 832, 826 (C–Cl stretching); ^{1}H NMR ($CDCl_3$): 6.52–7.90 (m, 19H, Ar–H). 2.63 (t, 2H, C–CH_2), 3.37 (t, 2H, N–CH_2); ^{13}C-NMR ($CDCl_3$): 33.1, 43.1, 120.7, 120.8, 122.3, 122.4, 123.0, 125.8, 127.0, 127.1, 127.4, 127.5, 127.7, 128.8, 128.9, 129.0, 130.5, 130.8, 131.6, 132.4, 133.5, 135.7, 138.0, 148.2, 151.2,160.6, 161.4, 164.2; GCMS: *m/z*: 649.96 (100.0%) (M^+); Anal. Calc. For $C_{36}H_{23}Cl_3N_4O_2$: C-66.35%, H-3.22%, N-8.26%. Found: C-62.30%, H-3.16%, N-8.20%.

Physical constants and characterization of 3-(2,3-dimethylphenyl)-2-(2-chlorophenyl)-6-{2-[2-(2-chlorophenyl)-4-oxo(3-hydroquinazolin-3-yl)]ethyl}-3-hydroquinazolin-4-one **(5c)**

m.p.:197°C; yield: 56%; IR (KBr): 3085, 3068 (C–H str., aromatic ring), 2837 (C–H str., $–CH_2$ group), 1718, 1734 (C=O str., amide group), 1658, 1609, (C=N, C=C, quinazoline ring), 1354 (C–N str., quinazoline ring), 1522 (N–O str., $–NO_2$ group), 836 (C–Cl stretching); ^{1}H NMR ($CDCl_3$): 6.65–7.88 (m, 18H, Ar–H). 2.65 (t, 2H, C–CH_2), 3.39 (t, 2H, N–CH_2), 2.37 (s, 3H, Ar–CH_3), 2.33 (s, 3H, Ar–CH_3); ^{13}C-NMR ($CDCl_3$): 16.7, 21.8, 33.1, 43.1, 118.4, 120.7, 120.8, 122.3, 122.4, 123.0, 124.5, 125.9, 127.0, 127.4, 127.5, 127.7, 128.0, 128.8, 128.9, 130.8, 131.6, 132.4, 133.5, 135.4, 137.0, 138.0, 148.3, 151.2, 160.8, 161.1, 164.2; GCMS: *m/z*: 643.57 (100.0%) (M^+); Anal. Calc. For $C_{38}H_{28}Cl_2N_4O_2$: C-70.92%, H-4.38%, N-8.70%. Found: C-62.30%, H-3.16%, N-8.20%.

Physical constants and characterization of 3-(2,4-dimethylphenyl)-2-(2-chlorophenyl)-6-{2-[2-(2-chlorophenyl)-4-oxo (3-hydroquinazolin-3-yl)]ethyl}-3-hydroquinazolin-4-one **(5d)**

m.p.:210°C; yield: 62%; IR (KBr): 3094, 3068 (C–H str., aromatic ring), 2833 (C–H str., $–CH_2$ group), 1717, 1731

(C=O str., amide group), 1656, 1607, (C=N, C=C, quinazoline ring), 1359 (C–N str., quinazoline ring), 1521 (N–O str., $–NO_2$ group), 828 (C–Cl stretching); ^{1}H NMR ($CDCl_3$): 6.52–7.85 (m, 18H, Ar–H). 2.61 (t, 2H, C–CH_2), 3.30 (t, 2H, N–CH_2), 2.33 (s, 3H, Ar–CH_3), 2.28 (s, 3H, Ar–CH_3); GCMS: *m/z*: 643.57 (100.0%) (M^+); ^{13}C-NMR ($CDCl_3$): 19.5, 24.6, 33.1, 43.1, 120.7, 120.8, 121.4, 122.3, 122.4, 123.0, 126.2, 127.0, 127.4, 127.5, 127.7, 128.8, 128.9, 130.8, 131.1, 131.6, 132.4, 133.5, 133.9, 134.2, 138.0, 148.5, 151.2, 160.8, 161.3, 164.3; Anal. Calc. For $C_{38}H_{28}Cl_2N_4O_2$: C-70.92%, H-4.38%, N-8.70%. Found: C-62.30%, H-3.16%, N-8.20%.

Physical constants and characterization of 3-(2,5-dimethylphenyl)-2-(2-chlorophenyl)-6-{2-[2-(2-chlorophenyl)-4-oxo(3-hydroquinazolin-3-yl)]ethyl}-3-hydroquinazolin-4-one **(5e)**

m.p.:245°C; yield: 65%; IR (KBr): 3093, 3064 (C–H str., aromatic ring), 2831 (C–H str., –CH_2 group), 1719, 1736 (C=O str., amide group), 1657, 1613, (C=N, C=C, quinazoline ring), 1354 (C–N str., quinazoline ring), 1529 (N–O str., $–NO_2$ group), 839 (C–Cl stretching); ^{1}H NMR ($CDCl_3$): 6.57–7.84 (m, 18H, Ar–H). 2.55 (t, 2H, C–CH_2), 3.55 (t, 2H, N–CH_2), 2.40 (s, 3H, Ar–CH_3), 2.24 (s, 3H, Ar–CH_3); ^{13}C-NMR ($CDCl_3$): 19.2, 24.3, 33.1, 43.1, 120.7, 120.8, 121.2, 122.3, 122.4, 123.0, 124.5, 127.0, 127.4, 127.5, 127.7, 128.8, 128.9, 129.1, 130.8, 131.3, 131.6, 132.4, 133.5, 135.4, 135.6, 138.0, 148.6, 151.2, 160.8, 161.1, 164.4; GCMS: *m/z*: 643.57 (100.0%) (M^+); Anal. Calc. For $C_{38}H_{28}Cl_2N_4O_2$: C-70.92%, H-4.38%, N-8.70%. Found: C-62.30%, H-3.16%, N-8.20%.

Physical constants and characterization of 2-(2-chlorophenyl)-6-{2-[2-(2-chlorophenyl)-4-oxo(3-hydroquinazolin-3-yl)]ethyl}-3-(4-methoxy-2-nitrophenyl)-3-hydroquinazolin-4-one **(5f)**

m.p.:235°C; yield: 68%; IR (KBr): 3091, 3063 (C–H str., aromatic ring), 2836 (C–H str., –CH_2 group), 1719, 1733 (C=O str., amide group), 1654, 1609, (C=N, C=C, quinazoline ring), 1356 (C–N str., quinazoline ring), 1525 (N–O str., $–NO_2$ group), 836 (C–Cl stretching); ^{1}H NMR ($CDCl_3$) : 6.67–7.83 (m, 18H, Ar–H). 2.61 (t, 2H, C–CH_2), 3.39 (t, 2H, N–CH_2), 3.91 (s, 3H, –OCH_3); GCMS: *m/z*: 690.94 (100.0%) (M^+); ^{13}C-NMR ($CDCl_3$): 33.1, 43.1, 55.8, 110.1, 120.6, 120.7, 120.8, 122.3, 122.4, 123.0, 123.5, 125.6, 127.0, 127.4, 127.5, 127.7, 128.8, 128.9, 130.8, 131.6, 132.4, 133.5, 138.0, 143.4, 148.2, 151.2, 157.1, 160.8, 161.4, 164.2; Anal. Calc. For $C_{37}H_{25}Cl_2N_5O_5$: C-64.35%, H-3.14%, N-10.14%. Found: C-62.30%, H-3.16%, N-8.20%.

Physical constants and characterization of 2-(2-chlorophenyl)-6-{2-[2-(2-chlorophenyl)-4-oxo(3-hydroquinazolin-3-yl)]ethyl}-3-(4-methyl-2-nitrophenyl)-3-hydroquinazolin-4-one **(5g)**

m.p.:220°C; yield: 55%; IR (KBr): 3082, 3061 (C–H str., aromatic ring), 2838 (C–H str., –CH_2 group), 1719, 1738 (C=O str., amide group), 1653, 1608, (C=N, C=C, quinazoline ring), 1353 (C–N str., quinazoline ring), 1520 (N–O str., $–NO_2$ group), 830 (C–Cl stretching); ^{1}H NMR ($CDCl_3$): 6.71–7.89 (m, 18H, Ar–H). 2.61 (t, 2H, C–CH_2), 3.39 (t, 2H, N–CH_2), 2.25 (s, 3H, Ar–CH_3); GCMS: *m/z*: 674.54 (100.0%) (M^+); ^{13}C-NMR ($CDCl_3$): 23.3, 33.1, 43.1, 120.7, 120.8, 122.3, 122.4, 123.0, 125.7, 127.0, 127.4, 127.5, 127.7, 128.8, 128.9, 130.3, 130.8, 131.6, 132.4, 133.5, 134.9, 135.3, 138.0, 142.3, 148.2, 151.2, 160.6, 161.3, 164.1; Anal. Calc. For $C_{37}H_{25}BrCl_2N_5O_4$: C-65.88%, H-3.73%, N-10.38%. Found: C-62.30%, H-3.16%, N-8.20%.

Physical constants and characterization of 2-(2-chlorophenyl)-6-{2-[2-(2-chlorophenyl)-4-oxo(3-hydroquinazolin-3-yl)]ethyl}-3-(2-nitrophenyl)-3-hydroquinazolin-4-one **(5h)**

m.p.:198°C; yield: 63%; IR (KBr): 3098, 3063 (C–H str., aromatic ring), 2839 (C–H str., –CH_2 group), 1711, 1732 (C=O str., amide group), 1654, 1608, (C=N, C=C, quinazoline ring), 1357 (C–N str., quinazoline ring), 1522 (N–O str., $–NO_2$ group), 831 (C–Cl stretching); ^{1}H NMR ($CDCl_3$): 6.68–7.89 (m, 19H, Ar–H). 2.61 (t, 2H, C–CH_2), 3.34 (t, 2H, N–CH_2); GCMS: *m/z*: 660.51 (100.0%) (M^+); ^{13}C-NMR ($CDCl_3$): 33.1, 43.1, 120.7, 120.8, 122.3, 122.4, 122.5, 123.0, 124.1, 125.3, 127.0, 127.4, 127.5, 127.7, 128.8, 128.9, 130.8, 131.6, 132.4, 133.3, 133.5, 136.1, 138.0, 142.4, 148.1, 151.2, 160.5, 161.6, 164.3; Anal. Calc. For $C_{36}H_{23}Cl_2N_5O_4$: C-65.46%, H-3.51%, N-10.60%. Found: C-62.30%, H-3.16%, N-8.20%.

Physical constants and characterization of 2-(2-chlorophenyl)-6-{2-[2-(2-chlorophenyl)-4-oxo(3-hydroquinazolin-3-yl)]ethyl}-3-(3-nitrophenyl)-3-hydroquinazolin-4-one **(5i)**

m.p.:186°C; yield: 72%; IR (KBr): 3091, 3062 (C–H str., aromatic ring), 2832 (C–H str., –CH_2 group), 1711, 1736 (C=O str., amide group), 1652, 1607, (C=N, C=C, quinazoline ring), 1351(C–N str., quinazoline ring), 1523 (N–O str., $–NO_2$ group), 825 (C–Cl stretching); ^{1}H NMR ($CDCl_3$): 6.59–7.92 (m, 19H, Ar–H). 2.58 (t, 2H, C–CH_2), 3.32 (t, 2H, N–CH_2); GCMS: *m/z*: 6 (100.0%) (M^+); ^{13}C-NMR ($CDCl_3$): 33.1, 43.1, 114.5, 119.5, 120.7, 120.8, 122.3, 122.4, 123.0, 127.0, 127.4, 127.5, 127.7, 128.8,

128.9, 129.9, 130.8, 131.6, 132.4, 133.5, 133.6, 138.0, 148.1, 148.0, 151.2, 160.7, 161.4, 164.4; Anal. Calc. For $C_{36}H_{23}Cl_2N_5O_4$: C-65.46%, H-3.51%, N-10.60%. Found: C-62.30%, H-3.16%, N-8.20%.

Physical constants and characterization of 2-(2-chlorophenyl)-6-{2-[2-(2-chlorophenyl)-4-oxo(3-hydroquinazolin-3-yl)]ethyl}-3-(4-nitrophenyl)-3-hydroquinazolin-4-one **(5j)**

m.p.:230°C; yield: 68%; IR (KBr): 3090, 3061 (C–H str., aromatic ring), 2836 (C–H str., $–CH_2$ group), 1714, 1732 (C=O str., amide group), 1651, 1611, (C=N, C=C, quinazoline ring), 1353 (C–N str., quinazoline ring), 1522 (N–O str., $–NO_2$ group), 834 (C–Cl stretching); ^{1}H NMR ($CDCl_3$): 6.67–7.97 (m, 19H, Ar–H). 2.61 (t, 2H, C–CH_2), 3.37 (t, 2H, N–CH_2); GCMS: *m/z*: 660.51 (100.0%) (M^+); ^{13}C-NMR ($CDCl_3$): 33.1, 43.1, 120.7, 120.8, 122.3, 122.4, 122.5, 123.0, 124.1, 127.0, 127.4, 127.5, 127.7, 128.8, 128.9, 130.8, 131.6, 132.4, 133.5, 138.0, 138.8, 143.5, 148.6, 151.2, 160.4, 161.4, 164.3; Anal. Calc. For $C_{36}H_{23}Cl_2N_5O_4$: C-65.46%, H-3.51%, N-10.60%. Found: C-62.30%, H-3.16%, N-8.20%.

Physical constants and characterization of 3-(3,4-dichlorophenyl)-2-(2-chlorophenyl)-6-{2-[2-(2-chlorophenyl)-4-oxo(3-hydroquinazolin-3-yl)]ethyl}-3-hydroquinazolin-4-one **(5k)**

m.p.:235°C; yield: 62%; IR (KBr): 3092, 3061 (C–H str., aromatic ring), 2833 (C–H str., $–CH_2$ group), 1712, 1733 (C=O str., amide group), 1654, 1606, (C=N, C=C, quinazoline ring), 1355 (C–N str., quinazoline ring), 1529 (N–O str., $–NO_2$ group), 839 (C–Cl stretching); ^{1}H NMR ($CDCl_3$): 6.65–7.89 (m, 18H, Ar–H). 2.62 (t, 2H, C–CH_2), 3.41 (t, 2H, N–CH_2); GCMS: *m/z*: 684.41 (100.0%) (M^+); ^{13}C-NMR ($CDCl_3$): 33.1, 43.1, 120.7, 120.8, 121.1, 122.3, 122.4, 123.0, 123.4, 127.0, 127.4, 127.5, 127.7, 128.8, 128.9, 130.4, 130.8, 131.6, 132.2, 132.4, 133.5, 138.0, 148.4, 151.2, 160.8, 161.4, 164.0; Anal. Calc. For $C_{36}H_{22}Cl_4N_4O_2$: C-63.17%, H-3.24%, N-8.18%. Found: C-62.30%, H-3.16%, N-8.20%.

Physical constants and characterization of 3-(2,6-dichloro-4-nitrophenyl)2-(2-chlorophenyl)-6-{2-[2-(2-chlorophenyl)-4-oxo(3-hydroquinazolin-3-yl)]ethyl}-3-hydroquinazolin-4-one **(5l)**

m.p.:206°C; yield: 60%; IR (KBr): 3091, 3069 (C–H str., aromatic ring), 2834 (C–H str., $–CH_2$ group), 1711, 1731 (C=O str., amide group), 1654, 1609, (C=N, C=C, quinazoline ring), 1359 (C–N str., quinazoline ring), 1521 (N–O str., $–NO_2$ group), 831 (C–Cl stretching); ^{1}H NMR ($CDCl_3$): 6.62–7.87 (m, 17H, Ar–H). 2.58 (t, 2H, C–CH_2), 3.28 (t, 2H, N–CH_2); GCMS: *m/z*: 538.98 (100.0%) (M^+); ^{13}C-NMR ($CDCl_3$) : 33.1, 43.1, 120.7, 120.8, 122.3, 122.4, 122.5, 123.0, 127.0, 127.4, 127.5, 127.7, 128.8, 128.9, 130.8, 131.6, 132.4, 132.8, 133.5, 138.0, 145.1, 146.3, 148.2, 151.2, 160.9, 161.3, 164.2; Anal. Calc. For $C_{36}H_{21}Cl_4N_5O_4$: C-59.28%, H-2.90%, N-9.60%. Found: C-62.30%, H-3.16%, N-8.20%.

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