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MEDICINAL CHEMISTRY RESEARCH

ORIGINAL RESEARCH

Synthesis and antimicrobial activities of 2-azetidinyl-4-quinazolinone derivatives of diclofenac analogue

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Abstract A new class of 2-azetidinyl-4-quinazolinones **6a–k** was synthesized by multi-step process, starting from 2-[2-(2,6-dichlorophenyl)amino]phenyl acetic acid **1**. Acid **1** was easily converted to acid chloride **2**, which on cyclization reaction with 5-bromo anthranilic acid yielded benzoxazinone **3**. The condensation reaction of **3** with benzene-1,4-diamine afforded 4-quinazolinone **4**. Finally the title compound **6a–k** was synthesized from 4-quinazolinone **4** by Schiff base formation **5a–k** with aromatic aldehyde and then cyclization reaction with chloroacetyl-chloride. The in vitro antimicrobial activity of compounds **5a–k** and **6a–k** were tested. These compounds showed pronounced antimicrobial activity when **4-Cl** and **4-OCH_3** groups were present.

Keywords Antimicrobial activity · 2-Azetidinone · Diclofenac · 4-Quinazolinone

Introduction

The synthetic studies of 4-quinazolinone derivatives have been presented due to the chemical and biological interest. 4-Quinazolinone derivatives possesses antibacterial, antifungal (Grover and Kini, 2006), hypolipidemic (Kurogi *et al.*, 1996), antitumor (Baek *et al.*, 2004), anti-inflammatory (Kumar *et al.*, 2007), antimalarial (Jiang *et al.*, 2005), CNS depressant, anticonvulsant (Jatav *et al.*, 2008), analgesic (Alagarsamy *et al.*, 2007), antitubercular (Mosaad *et al.*, 2004) and antiviral (Saleh *et al.*, 2002) activities. Schiff base has good antibacterial (Parekh *et al.*, 2005), antifungal (Gursoy *et al.*, 2005; Mishra *et al.*, 2005), antitubercular (Joshi *et al.*, 2008), antioxidant (Yuksek *et al.*, 2006), antitumor (Ren *et al.*, 2002) and pharmacological applications. β-Lactam (4-membered cyclic amide) ring structure constitutes the dominant class of agents currently employed for the chemotherapy of bacterial infections. Various 2-azetidinones have been reported to possess antibacterial (Halve *et al.*, 2006; Suryavanshi and Pai, 2006), antifungal (Havaldar and Khatri, 2006; Panwar *et al.*, 2006), anti-inflammatory (Gurupadayya *et al.*, 2008), anthelminthic (Srivastava *et al.*, 2004), antiviral (Pandey *et al.*, 2005) and anticonvulsant (Rajasekaran and Murugesan, 2005) activities.

Diclofenac is available as generic drug in a number of formulations. Over the counter use is approved in some countries for minor aches and pains and fever associated with common infections. In the United Kingdom, India and the United States, it may be supplied as either the sodium or potassium salt, in China most often as the sodium salt, while in some other countries only as the potassium salt. Diclofenac is often used to treat chronic pain associated with cancer, particularly if inflammation is also present. Diclofenac has been found to be effective against all strains of multi-drug resistant *Escherichia coli*. Therefore, it may be suggested that diclofenac has the capacity to treat UTI (uncomplicated urinary tract infections) caused by *E. coli* (Mazumdar *et al.*, 2006). The diclofenac analogue compounds displayed antibacterial (Dutta *et al.*, 2000), antimycobacterial (Sriram *et al.*, 2006), anti-inflammatory, analgesic, ulcerogenic, lipid peroxidation (Amir and Shikha, 2004; Bhandari *et al.*, 2008), antitumor (Barbaric *et al.*, 2007) and transthyretin amyloid fibril formation inhibitor (Oza *et al.*, 2002) activities.

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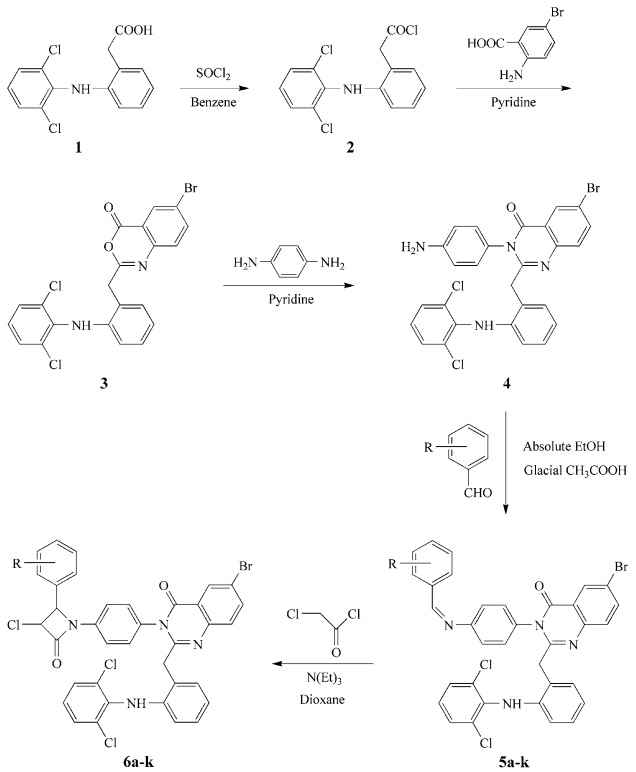
We have synthesized 2,3-disubstituted 4-quinazolinone derivatives in which C-2 position was occupied by 2-[(2,6-dichlorophenyl)amino]benzyl unit from lead molecule diclofenac and 3rd position was replaced with various substituted aryls (Patel and Lilakar, 2001), aryl acetamides (Patel and Chaudhari, 2006), 4-thiazolidinones (Patel and Patel, 2007a, b), 2-azetidinones (Patel and Patel, 2008) and aryl sulfonamides (Patel and Chaudhari, 2008). We observed that these synthesized compounds showed very good antimicrobial activity and henceforth we enhanced this work with diclofenac analogue of 4-quinazolinone **5a–k** and **6a–k**. The synthetic route is shown in Scheme 1. The structure of **5a–k** and **6a–k** was firmly established by elemental analyses, IR and NMR spectral data. Preliminary microbiological test showed that most of the compounds possessed good antimicrobial activity in vitro.

Results and discussion

Chemistry

We have synthesized a series of heterocyclic compounds, 2-[2-(2,6-dichlorophenyl) amino]benzyl-3-[4-(2-substitutedarylidene)aryl]-6-bromoquinazolin-4(3*H*)ones **5a–k** and 2-[2-(2,6-dichlorophenyl)amino]benzyl-3-{4-[4-(2-substituted-phenyl)-3-chloro-2-oxo-azetidinyl]aryl}-6-bromoquinazolin-4(3*H*)one **6a–k** as illustrated in Scheme 1. Structures of all the compounds were established on the basis of elemental analyses, IR, ^{1}H NMR and ^{13}C NMR spectral data. The required benzoxazinone **3** was prepared by the cyclization between 5-bromoanthranilic acid and 2-[(2,6-dichlorophenyl)amino]phenyl acetyl chloride **2** using pyridine (Gao *et al.*, 2007). Formation of the product was confirmed by a sharp band at 1695 cm^{-1} for C=O group along with a band at 1140 cm^{-1} for C–O–C stretching in IR spectrum. Compound **3** was converted to quinazolin-4(3*H*)one **4**, by its condensation with benzene-1,4-diamine (Laddha *et al.*, 2006). Insertion of the nitrogen atom of benzene-1,4-diamine in benzoxazinone ring was confirmed by the disappearance of C–O–C stretching band at 1140 cm^{-1} and also gave a strong C=O stretching vibration of quinazolinone at 1685 cm^{-1} instead in gave a band at 1695 cm^{-1} of benzoxazinone. Further confirmed by ^{13}C NMR spectrum, which showed C=O and C=N signals of quinazolinone at δ 160.4 ppm and δ 164.5 ppm, respectively. When compound **4** was treated with substituted aromatic aldehydes in the presence of glacial acetic acid as a catalyst, Schiff bases **5a–k** were formed (Archana *et al.*, 2002), which were confirmed by the presence of strong –N=CH– stretching vibration of Schiff bases at around 1632 cm^{-1} and ^{1}H NMR spectra showed singlet at around δ 6 ppm due to one proton of Schiff base. Further cyclization reaction of Schiff bases **5a–k** with chloroacetylchloride in presence of triethylamine as a catalyst at 0–5 °C gave the desired compounds azetidinyl-quinazolin-4(3*H*)ones **6a–k** (Halve *et al.*, 2006). IR spectra of compounds **6a–k** showed strong stretching vibration at around 1750 cm^{-1} due to C=O group of β-lactam ring. ^{1}H NMR spectra of **6a–k** showed doublet at around δ 3.35 ppm and δ 3.25 ppm equivalent to one proton due to >CH–Ar and >CH–Cl of β-lactam ring respectively.



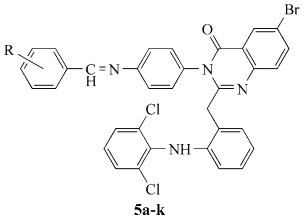
R = 2-NO_2, 3-NO_2, 2-OH, 4-OH, 2-Cl, 4-Cl, 4-OCH_3, 3,4,5-$(OCH_3)_3$, 2-OH-4-OCH_3, 4-$N(CH_3)_2$, 2-OH-4-$N(C_2H_5)_2$

Scheme 1 Protocol for the synthesis of compounds **5a–k** and **6a–k**

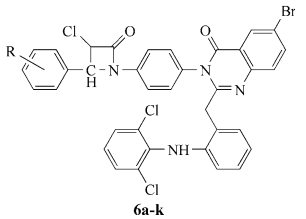
Antimicrobial activity

The results of preliminary antibacterial testing of the compounds **5a–k** and **6a–k** are shown in Tables 1 and 2. All these compounds were compared with control drug penicillin-G. It can be seen from the calculated potency that the Schiff base derivatives showed good antibacterial activity but when they were converted to 2-azetidinone derivatives, the results found different depending upon the substituents. Schiff bases **5e**, **5f**, **5g**, **5h** and **5i** possessed moderate activities (50–53.85%) against *Staphylococcus aureus* while 2-azetidinone derivatives **6e**, **6f**, **6g**, **6h** and **6i** displayed very good activities (58.33–66.67%) against *S. aureus*. On the other hand, Schiff bases **5f** and **5g** were found very active (59.79 and 63.91%, respectively) while

Table 1 Gram positive antibacterial activity of **5a–k** and **6a–k**



5a-k



6a-k

Compound	R	*S. aureus*				Potency (%)	*B. subtilis*				Potency (%)
		Std: Penicillin-G					Std: Penicillin-G				
		U_H	U_L	S_H	S_L		U_H	U_L	S_H	S_L	
5a	2-NO_2	3	2	12	7	28.43	5	3	15	9	36.00
5b	3-NO_2	3	1	12	6	29.73	3	2	15	9	24.99
5c	2-OH	5	3	12	7	42.87	5	3	15	9	36.00
5d	4-OH	4	3	12	8	34.85	4	2	15	8	30.50
5e	2-Cl	6	3	12	7	50.98	6	3	15	9	42.68
5f	4-Cl	6	4	12	8	50.88	9	5	15	8	59.79
5g	4-OCH_3	7	4	13	7	53.85	9	5	14	8	63.91
5h	3,4,5-$(OCH_3)_3$	6	3	12	7	50.98	8	4	15	8	53.33
5i	2-OH-4-OCH_3	6	4	12	6	50.00	7	4	15	9	47.81
5j	4-$N(CH_3)_2$	0	0	12	7	0	0	0	14	7	0
5k	2-OH-4-$N(C_2H_5)_2$	0	0	12	6	0	0	0	15	8	0
6a	2-NO_2	4	2	12	7	36.75	6	3	15	9	42.68
6b	3-NO_2	3	1	12	6	29.73	4	2	14	8	32.65
6c	2-OH	6	3	12	7	50.98	6	3	15	9	42.68
6d	4-OH	5	3	12	8	44.44	5	3	15	8	35.08
6e	2-Cl	8	4	12	7	65.76	6	3	15	8	41.48
6f	4-Cl	8	5	12	8	66.67	8	5	14	7	57.44
6g	4-OCH_3	8	4	13	7	60.94	8	4	14	8	57.14
6h	3,4,5-$(OCH_3)_3$	7	4	12	7	58.33	7	5	15	9	46.48
6i	2-OH-4-OCH_3	7	4	12	6	58.33	7	4	16	9	44.69
6j	4-$N(CH_3)_2$	0	0	12	7	0	0	0	15	9	0
6k	2-OH-4-$N(C_2H_5)_2$	0	0	12	6	0	0	0	15	9	0

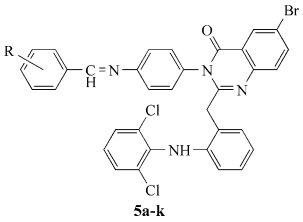
2-azetidinone derivatives **6f** and **6g** showed decreased activities (57.44 and 57.14%, respectively) against *Bacillus subtilis*. Schiff base derivatives **5d**, **5e**, **5f**, **5g** and **5h** showed moderate activities (44.44–52.88%) against *Pseudomonas aeruginosa* while 2-azetidinone derivatives **6d**, **6e**, **6f**, **6g** and **6h** exhibited very good activities (58.33–65.76%). Schiff base derivatives **5f**, **5g**, **5h** and **5i** showed moderate to very good activities (42.86–64.33%) as compared to 2-azetidinone derivatives **6f**, **6g**, **6h** and **6i** which showed moderate activities (50–53.33%) against *E. coli.* In addition, Schiff base **5g** (64.33%) was found very active than 2-azetidinone **6g** (53.33%); on the other hand, 2-azetidinones **6f** and **6i** exhibited higher activities (51.09 and 50%, respectively) than Schiff bases **5f** and **5i** (49.68 and 42.86%, respectively) against *E. coli*.

The results of antifungal testing of compounds **5a–k** and **6a–k** are shown in Table 3. The results of antifungal activity revealed that Schiff base derivatives **5f** and **5g** as well as 2-azetidinone derivatives **6f** and **6g** exhibited comparatively good activity (2 mm at 50 μg/mL and 3–5 mm at 100 μg/mL) against fungi *Candida albicans* as compared to control drug amphotericine-B. The remaining compounds showed moderate to poor activities.

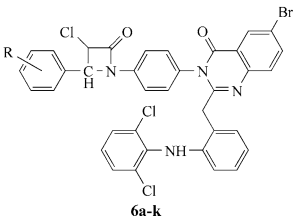
Conclusion

A series of 2-azetidinyl-4-quinazolinones **6a–k** exhibited comparatively good antimicrobial activity, most in case when they restrain chloro and methoxy group. Schiff base

Table 2 Gram negative antibacterial activity of **5a–k** and **6a–k**



5a-k



6a-k

Compound	R	*P. aeruginosa*				Potency (%)	*E. coli*				Potency (%)
		Std: Penicillin-G					Std: Penicillin-G				
		U_H	U_L	S_H	S_L		U_H	U_L	S_H	S_L	
5a	2-NO_2	4	2	13	8	35.33	4	2	14	8	32.65
5b	3-NO_2	3	1	12	8	33.92	3	1	14	8	28.39
5c	2-OH	4	2	12	8	38.83	5	3	14	7	36.74
5d	4-OH	5	2	12	7	44.55	4	2	14	7	31.50
5e	2-Cl	5	3	12	8	44.44	5	3	14	8	37.56
5f	4-Cl	6	3	13	7	46.93	7	5	14	8	49.68
5g	4-OCH_3	6	3	12	8	52.88	9	5	14	7	64.33
5h	3,4,5-$(OCH_3)_3$	5	2	12	8	47.09	7	4	14	7	50.00
5i	2-OH-4-OCH_3	4	2	12	8	38.83	6	4	14	7	42.86
5j	4-$N(CH_3)_2$	0	0	12	7	0	0	0	14	8	0
5k	2-OH-4-$N(C_2H_5)_2$	0	0	12	8	0	0	0	15	8	0
6a	2-NO_2	6	3	13	7	46.93	5	3	14	8	37.56
6b	3-NO_2	4	2	12	7	36.75	4	2	14	8	32.65
6c	2-OH	6	4	12	6	50.00	6	3	14	7	43.53
6d	4-OH	7	4	12	6	58.33	5	2	14	7	37.89
6e	2-Cl	7	4	12	7	58.33	6	3	14	8	44.56
6f	4-Cl	8	5	13	7	61.79	7	3	14	8	51.09
6g	4-OCH_3	8	4	12	7	65.76	8	4	15	8	53.33
6h	3,4,5-$(OCH_3)_3$	7	4	12	6	58.33	7	3	14	7	50.00
6i	2-OH-4-OCH_3	6	3	12	7	50.98	7	4	14	7	50.00
6j	4-$N(CH_3)_2$	0	0	12	6	0	0	0	14	8	0
6k	2-OH-4-$N(C_2H_5)_2$	0	0	12	6	0	0	0	15	8	0

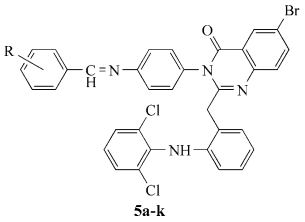
derivative with 4-methoxy group showed good activity against gram positive as well as gram negative bacteria among the series but the result seems different after cyclization of Schiff base to 2-azetidinone. It shows that the activity got increase against *S. aureus* and *P. aeruginosa*, while decrease against *B. subtilis* and *E. coli*. 2-Azetidinone derivatives with 2-chloro and 4-chloro group displayed good activity against *S. aureus*. 4-Chloro and 4-methoxy group containing 2-azetidinone derivatives possessed good activity against *P. aeruginosa*. Whereas Schiff base derivative with 4-methoxy group exhibited good activity against *B. subtilis* and *E. coli*. Schiff base as well as 2-azetidinone derivatives containing 4-chloro and 4-methoxy group showed good antifungal activity against *C. albicans*. 2-Azetidinone derivatives were found more active than that of Schiff base derivatives.

Experimental

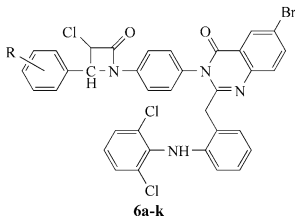
General

Melting points (m.p.) were determined in one-end-open capillary tubes on a Mel-Temp apparatus and are uncorrected. Infrared (IR) absorption spectra were recorded on Perkin-Elmer RX-1 FTIR spectrometer using potassium bromide (KBr) pellet and the wave numbers were given in cm^{-1}. The ^1H NMR spectra were recorded in deutero

Table 3 Antifungal activity (zone of inhibition in mm) of **5a–k** and **6a–k**



5a-k



6a-k

Compound	R	*C. albicans*	
		50 μg/mL	100 μg/mL
5a	2-NO_2	1	2
5b	3-NO_2	1	2
5c	2-OH	0	1
5d	4-OH	0	1
5e	2-Cl	1	2
5f	4-Cl	2	4
5g	4-OCH_3	2	3
5h	3,4,5-$(OCH_3)_3$	1	2
5i	2-OH-4-OCH_3	0	0
5j	4-$N(CH_3)_2$	0	1
5k	2-OH-4-$N(C_2H_5)_2$	0	0
6a	2-NO_2	1	2
6b	3-NO_2	1	2
6c	2-OH	0	0
6d	4-OH	0	0
6e	2-Cl	2	3
6f	4-Cl	2	5
6g	4-OCH_3	2	4
6h	3,4,5-$(OCH_3)_3$	1	2
6i	2-OH-4-OCH_3	0	1
6j	4-$N(CH_3)_2$	0	1
6k	2-OH-4-$N(C_2H_5)_2$	0	0
Amphotericine-B	–	4	9

chloroform ($CDCl_3$) on a Bruker Avance II 400 NMR spectrometer (400 MHz). The ^{13}C NMR spectra were recorded in deutero chloroform ($CDCl_3$) on a Bruker Avance II 400 NMR spectrometer operating at 100 MHz. The chemical shifts are reported in part per million (δ ppm) using tetramethylsilane (TMS) as an internal standard. The microanalyses were performed on a Perkin-Elmer 240C elemental analyzer. The purities of the compounds were checked by thin layer chromatography (TLC) using ready-made silica gel plates (Merck) and benzene:methanol (8:2) as a solvent system. The spots were developed in an iodine chamber and visualized under ultraviolet (UV) lamp. 2-[(2,6-Dichlorophenyl)amino]phenyl acetyl chloride **2** was synthesized by literature procedure (Furniss *et al.*, 1989).

Synthesis of 2-[2-(2,6-dichlorophenyl)amino]benzyl-6-bromo-3,1-benzoxazin-4(*H*)one (**3**)

A mixture of 2-[(2,6-dichlorophenyl)amino]phenyl acetyl chloride (**2**) (0.02 mol) and 5-bromo anthranilic acid (0.02 mol) in pyridine (40 mL) were stirred at 0–5 °C for 1 h, further stirred for 1 h at room temperature. A pasty mass obtained which was washed thoroughly with sodium bicarbonate (5%) to remove unreacted acid. A solid separated was filtered, dried and recrystallized from methanol to give (**3**). Yield = 55%, m.p. 194–198 °C; IR (KBr) cm^{-1}: 3445 (NH), 2928, 2852 (CH_2), 1695 (C=O of benzoxazinone), 1615 (C=N), 1320 (C–N), 1140 (C–O–C), 784 (C–Cl), 630 (C–Br); ^1H NMR ($CDCl_3$): δ 9.25 (s, 1H, NH), 6.15–7.58 (m,

10H, ArH), 3.58 (s, 2H, CH_2); ^{13}C NMR ($CDCl_3$): δ 164.3, 159.2, 148.5, 138.3, 138.1, 135.3, 135.2, 129.2, 129.1, 127.6, 127.4, 126.7, 124.1, 121.5, 121.2, 119.1, 118.5, 118.2, 32.5; Anal. Calcd. for $C_{21}H_{13}N_2O_2BrCl_2$: C, 52.97; H, 2.75; N, 5.88. Found: C, 52.95; H, 2.78; N, 5.85.

2-[2-(2,6-Dichlorophenyl)amino]benzyl-3-(4-aminoaryl)-6-bromoquinazolin-4(3*H*)ones (**4**)

A mixture of (**3**) (0.01 mol) and benzene-1,4-diamine (0.01 mol) in pyridine (20 mL) was refluxed on an oil bath for 5–6 h. After completion of the reaction, the oily mass obtained, which was slowly poured onto crushed ice-cold water contained concentrated HCl (36% 10 mL) with occasional stirring. The product obtained was filtered and washed several times with water. The crushed product was dried and crystallized from ethanol to provide (**4**). Yield = 58%, m.p. 209–211 °C; IR (KBr) cm^{-1}: 3505 (NH_2), 3438 (NH), 2922, 2849 (CH_2), 1685 (C=O of quinazolinone), 1613 (C=N), 1317 (C–N), 784 (C–Cl), 627 (C–Br); ^1H NMR ($CDCl_3$): δ 9.30 (s, 1H, NH), 6.30–7.60 (m, 14H, ArH), 5.73 (s, 2H, NH_2), 3.62 (s, 2H, CH_2); ^{13}C NMR ($CDCl_3$): δ 164.5, 160.4, 146.2, 144.1, 138.6, 136.4, 135.4, 132.4, 129.8, 129.5, 127.9, 127.8, 126.8, 124.7, 123.1, 122.8, 122.5, 121.8, 121.2, 119.1, 118.3, 116.6, 28.9; Anal. Calcd. for $C_{27}H_{19}ON4BrCl_2$: C, 57.27; H, 3.38; N, 9.89. Found: C, 57.22; H, 3.32; N, 9.83.

General procedure for the preparation of 2-[2-(2,6-dichlorophenyl)amino]benzyl-3-[4-(substitutedarylidene)aryl]-6-bromoquinazolin-4(3*H*)ones (**5a–k**)

A mixture of (**4**) (0.005 mol) and substituted aromatic aldehyde (0.005 mol) was taken in absolute ethanol (40 mL) and added few drops of glacial acetic acid. Then the mixture was refluxed for 4–6 h on water bath. The excess solvent was distilled off, poured in to ice cold water. The separated solid was filtered, washed and recrystallized from ethanol to provide (**5a–k**).

*2-[2-(2,6-Dichlorophenyl)amino]benzyl-3-[4-(2-nitroarylidene)aryl]-6-bromoquinazolin-4(3H)one (**5a**)*

Yield = 56%, m.p. 167–170 °C; IR (KBr) cm^{-1}: 3443 (NH), 2925, 2852 (CH_2), 1674 (C=O of quinazolinone), 1635 (N=CH), 1615 (C=N), 1542, 1360 (NO_2), 1342 (C–N), 785 (C–Cl), (C–Br); ^1H NMR ($CDCl_3$): δ 9.30 (s, 1H, NH), 6.55–7.84 (m, 18H, ArH), 6.20 (s, 1H, N=CH), 3.60 (s, 2H, CH_2); ^{13}C NMR ($CDCl_3$): δ 165.3, 161.2, 160, 148.8, 147.8, 146.3, 138.5, 136.5, 135.3, 135.2, 132.4, 132.3, 131.2, 130.1, 129.8, 129.4, 128.3, 127.8, 127.7, 126.8, 124.6, 124.1, 123.2, 122.9, 122.5, 121.7, 121.3, 119.2, 118.4, 28.6; Anal. Calcd. for $C_{34}H_{22}O_3N_5BrCl_2$: C, 58.39; H, 3.17; N, 10.01. Found: C, 58.31; H, 3.09; N, 9.96.

*2-[2-(2,6-Dichlorophenyl)amino]benzyl-3-[4-(3-nitroarylidene)aryl]-6-bromoquinazolin-4(3H)one (**5b**)*

Yield = 57%, m.p. 157–161 °C; IR (KBr) cm^{-1}: 3441 (NH), 2928, 2855 (CH_2), 1678 (C=O of quinazolinone), 1632 (N=CH), 1613 (C=N), 1545, 1358 (NO_2), 1340 (C–N), 787 (C–Cl), (C–Br); ^1H NMR ($CDCl_3$): δ 9.25 (s, 1H, NH), 6.53–7.85 (m, 18H, ArH), 6.17 (s, 1H, N=CH), 3.58 (s, 2H, CH_2); ^{13}C NMR ($CDCl_3$): δ 164.6, 162.1, 161.2, 148.7, 148.2, 146.4, 138.4, 136.6, 135.4, 135.3, 134.7, 132.4, 131.3, 129.8, 129.7, 129.3, 127.7, 127.6, 126.8, 126.2, 124.5, 123.3, 122.8, 122.7, 122.6, 121.8, 121.4, 119.1, 118.3, 28.5; Anal. Calcd. for $C_{34}H_{22}O_3N_5BrCl_2$: C, 58.39; H, 3.17; N, 10.01. Found: C, 58.35; H, 3.08; N, 9.98.

*2-[2-(2,6-Dichlorophenyl)amino]benzyl-3-[4-(2-hydroxyarylidene)aryl]-6-bromo quinazolin-4(3H)one (**5c**)*

Yield = 55%, m.p. 155–160 °C; IR (KBr) cm^{-1}: 3450 (NH), 3255 (OH), 2928, 2853 (CH_2), 1680 (C=O of quinazolinone), 1635 (N=CH), 1618 (C=N), 1335 (C–N), 784 (C–Cl), (C–Br); ^1H NMR ($CDCl_3$): δ 9.25 (s, 1H, NH), 6.57-7.86 (m, 18H, ArH), 6.15 (s, 1H, N=CH), 4.85 (s, 1H, OH), 3.62 (s, 2H, CH_2); ^{13}C NMR ($CDCl_3$): δ 164.2, 161.1, 160.2, 159.3, 148.8, 146.5, 138.6, 136.6, 135.5, 132.6, 132.5, 131.3, 130.6, 129.6, 129.2, 127.8, 127.6, 126.9, 124.3, 123.5, 122.7, 122.5, 121.7, 121.5, 121.3, 119.3, 118.5, 118.2, 116.3, 28.5; Anal. Calcd. for $C_{34}H_{23}O_2N_4BrCl_2$: C, 60.92; H, 3.46; N, 8.36. Found: C, 60.83; H, 3.37; N, 8.29.

*2-[2-(2,6-Dichlorophenyl)amino]benzyl-3-[4-(4-hydroxyarylidene)aryl]-6-bromo quinazolin-4(3H)one (**5d**)*

Yield = 57%, m.p. 163–165 °C; IR (KBr) cm^{-1}: 3448 (NH), 3245 (OH), 2918, 2852 (CH_2), 1673 (C=O of quinazolinone), 1630 (N=CH), 1615 (C=N), 1345 (C–N), 785 (C–Cl), (C–Br); ^1H NMR ($CDCl_3$): δ 9.28 (s, 1H, NH), 6.52–7.84 (m, 18H, ArH), 6.20 (s, 1H, N=CH), 4.88 (s, 1H, OH), 3.67 (s, 2H, CH_2); ^{13}C NMR ($CDCl_3$): δ 164.4, 160.8, 160.3, 159.5, 148.5, 146.3, 138.4, 136.7, 135.3, 132.5, 131.4, 130.6, 129.5, 129.3, 127.7, 127.5, 126.5, 126.4, 124.4, 123.6, 122.8, 122.7, 121.6, 121.4, 119.2, 118.3, 116.3, 28.6; Anal. Calcd. for $C_{34}H_{23}O_2N_4BrCl_2$: C, 60.92; H, 3.46; N, 8.36. Found: C, 60.85; H, 3.38; N, 8.31.

*2-[2-(2,6-Dichlorophenyl)amino]benzyl-3-[4-(2-chloroarylidene)aryl]-6-bromo quinazolin-4(3H)one (**5e**)*

Yield = 54%, m.p. 142–145 °C; IR (KBr) cm^{-1}: 3444 (NH), 2922, 2848 (CH_2), 1677 (C=O of quinazolinone), 1632 (N=CH), 1617 (C=N), 1335 (C–N), 787 (C–Cl), (C–Br); ^1H NMR ($CDCl_3$): δ 9.18 (s, 1H, NH), 6.57-7.87 (m, 18H, ArH), 6.25 (s, 1H, N=CH), 3.78 (s, 2H, CH_2); ^{13}C NMR ($CDCl_3$): δ 165.1, 161.2, 160.1, 148.7, 146.4, 138.3, 136.3, 135.4, 133.9, 133.4, 132.5, 132.3, 131.3, 130.6, 129.5, 129.2, 128.9, 127.9, 127.6, 127.2, 126.6, 124.7, 123.3, 122.8, 122.4, 121.5, 121.2, 119.3, 118.3, 29.1; Anal. Calcd. for $C_{34}H_{22}ON_4BrCl_3$: C, 59.28; H, 3.22; N, 8.13. Found: C, 59.24; H, 3.14; N, 8.08.

*2-[2-(2,6-Dichlorophenyl)amino]benzyl-3-[4-(4-chloroarylidene)aryl]-6-bromo quinazolin-4(3H)one (**5f**)*

Yield = 56%, m.p. 160–163 °C; IR (KBr) cm^{-1}: 3446 (NH), 2925, 2845 (CH_2), 1679 (C=O of quinazolinone), 1636 (N=CH), 1619 (C=N), 1332 (C–N), 783 (C–Cl), (C–Br); ^1H NMR ($CDCl_3$): δ 9.20 (s, 1H, NH), 6.51-7.85 (m, 18H, ArH), 6.28 (s, 1H, N=CH), 3.75 (s, 2H, CH_2); ^{13}C NMR ($CDCl_3$): δ 165, 162.2, 160.8, 148.5, 146.2, 138.5, 136.7, 136.6, 135.4, 132.3, 131.8, 131.3, 130.5, 129.6, 129.4, 128.7, 127.8, 127.6, 126.7, 124.3, 123.5, 122.7, 122.5, 121.5, 121.3, 119.1, 118.2, 28.7; Anal. Calcd. for $C_{34}H_{22}ON_4BrCl_3$: C, 59.28; H, 3.22; N, 8.13. Found: C, 59.28; H, 3.16; N, 8.06.

*2-[2-(2,6-Dichlorophenyl)amino]benzyl-3-[4-(4-methoxyarylidene)aryl]-6-bromo quinazolin-4(3H)one (**5g**)*

Yield = 62%, m.p. 161–164 °C; IR (KBr) cm^{-1}: 3425 (NH), 2920, 2840 (CH_2), 1670 (C=O of quinazolinone), 1628 (N=CH), 1610 (C=N), 1310 (C–N), 1196, 1100 (C–O–C), 778 (C–Cl), 630 (C–Br); ^1H NMR ($CDCl_3$): δ 9.30 (s, 1H, NH), 6.58–7.85 (m, 18H, ArH), 5.93 (s, 1H, N=CH), 3.80 (s, 3H, OCH_3), 3.60 (s, 2H, CH_2); ^{13}C NMR ($CDCl_3$): δ 164.8, 162.7, 161.2, 160.9, 148.2, 146.4, 138.3, 136.5, 135.3, 132.4, 131.4, 130.5, 129.5, 129.3, 127.7, 127.4, 126.5, 126.3, 124.4, 123.6, 122.5, 122.3, 121.7, 121.3, 119.2, 118.3, 114.5, 55.3, 28.4; Anal. Calcd. for $C_{35}H_{25}O_2N_4BrCl_2$: C, 61.42; H, 3.68; N, 8.19. Found: C, 61.33; H, 3.59; N, 8.13.

*2-[2-(2,6-Dichlorophenyl)amino]benzyl-3-[4-(3,4,5-trimethoxyarylidene)aryl]-6-bromo quinazolin-4(3H)one (**5h**)*

Yield = 59%, m.p. 150–155 °C; IR (KBr) cm^{-1}: 3430 (NH), 2923, 2845 (CH_2), 1675 (C=O of quinazolinone), 1630 (N=CH), 1615 (C=N), 1313 (C–N), 1195, 1105 (C–O-C), 780 (C–Cl), 632 (C–Br); ^1H NMR ($CDCl_3$): δ 9.32 (s, 1H, NH), 6.44–7.79 (m, 16H, ArH), 5.95 (s, 1H, N=CH), 3.85 (s, 6H, OCH_3), 3.68 (s, 3H, OCH_3), 3.63 (s, 2H, CH_2); ^{13}C NMR ($CDCl_3$): δ 164.2, 161.5, 160.2, 150.9, 148.4, 146.3, 141.5, 138.2, 136.5, 135.3, 132.3, 131.2, 129.5, 129.3, 128.1, 127.7, 127.5, 126.6, 124.4, 123.6, 122.6, 122.4, 121.7, 121.2, 119.3, 118.3, 106.6, 55.1, 54.6, 29.5; Anal. Calcd. for $C_{37}H_{29}O_4N_4BrCl_2$: C, 59.69; H, 3.93; N, 7.53. Found: C, 59.62; H, 3.84; N, 7.47.

*2-[2-(2,6-Dichlorophenyl)amino]benzyl-3-[4-(2-hydroxy-4-methoxyarylidene)aryl]-6-bromoquinazolin-4(3H)one (**5i**)*

Yield = 63%, m.p. 171–174 °C; IR (KBr) cm^{-1}: 3425 (NH), 3250 (OH), 2925, 2848 (CH_2), 1678 (C=O of quinazolinone), 1632 (N=CH), 1614 (C=N), 1317 (C–N), 1198, 1109 (C–O–C), 775 (C–Cl), 625 (C–Br); ^1H NMR ($CDCl_3$): δ 9.25 (s, 1H, NH), 6.49–7.73 (m, 17H, ArH), 5.85 (s, 1H, N=CH), 4.75 (s, 1H, OH), 3.91 (s, 3H, OCH_3), 3.65 (s, 2H, CH_2); ^{13}C NMR ($CDCl_3$): δ 164.9, 164.3, 162.1, 161.5, 160.8, 148.5, 146.4, 138.5, 136.5, 135.4, 132.4, 131.6, 131.4, 129.5, 129.3, 127.8, 127.5, 126.7, 124.2, 123.6, 122.9, 122.6, 121.6, 121.4, 119.2, 118.4, 110.8, 107.2, 102.1, 55.8, 28.6; Anal. Calcd. for $C_{35}H_{25}O_3N_4BrCl_2$: C, 60.02; H, 3.60; N, 8.00. Found: C, 59.94; H, 3.51; N, 7.94.

*2-[2-(2,6-Dichlorophenyl)amino]benzyl-3-[4-(4-N-dimethylaminoarylidene)aryl]-6-bromoquinazolin-4(3H)one (**5j**)*

Yield = 65%, m.p. 174–177 °C; IR (KBr) cm^{-1}: 3435 (NH), 2920, 2845 (CH_2), 1686 (C=O of quinazolinone), 1633 (N=CH), 1615 (C=N), 1317 (C–N), 784 (C–Cl), 614 (C–Br); ^1H NMR ($CDCl_3$): δ 9.20 (s, 1H, NH), 6.45–7.81 (m, 18H, ArH), 5.95 (s, 1H, N=CH), 3.62 (s, 2H, CH_2), 2.89 (s, 6H, N–$(CH_3)_2$); ^{13}C NMR ($CDCl_3$): δ 165.8, 161.4, 160.2, 151.8, 148.3, 146.5, 138.2, 136.4, 135.2, 132.5, 131.3, 130.1, 129.4, 129.3, 127.6, 127.5, 126.6, 124.6, 123.7, 123.3, 122.4, 122.2, 121.6, 121.4, 119.3, 118.2, 114.4, 41.1, 28.4; Anal. Calcd. for $C_{36}H_{28}ON_5BrCl_2$: C, 62.00; H, 4.05; N, 10.04. Found: C, 61.91; H, 3.96; N, 9.97.

*2-[2-(2,6-Dichlorophenyl)amino]benzyl-3-[4-(2-hydroxy-4-N-diethylaminoarylidene) aryl]-6-bromoquinazolin-4(3H)one (**5k**)*

Yield = 58%, m.p. 144–148 °C; IR (KBr) cm^{-1}: 3445 (NH), 3244 (OH), 2923, 2847 (CH_2), 1685 (C=O of quinazolinone), 1637 (N=CH), 1618 (C=N), 1316 (C–N), 785 (C–Cl), 620 (C–Br); ^1H NMR ($CDCl_3$): δ 9.23 (s, 1H, NH), 6.15–7.85 (m, 17H, ArH), 5.84 (s, 1H, N=CH), 3.57 (s, 2H, CH_2), 3.44 (q, 4H, N–$(CH_2)_2$), 1.28 (t, 6H, CH_3); ^{13}C NMR ($CDCl_3$): δ 164.9, 162.2, 161.5, 160.2, 153.3, 148.3, 146.3,

138.4, 136.4, 135.5, 132.5, 131.5, 131.3, 129.7, 129.6, 127.8, 127.5, 126.7, 124.3, 123.5, 122.6, 122.4, 121.6, 121.4, 119.3, 118.2, 108.2, 107.3, 99.1, 44.6, 28.9, 13.2; Anal. Calcd. for $C_{38}H_{32}O_2N_5BrCl_2$: C, 61.55; H, 4.35; N, 9.44. Found: C, 61.47; H, 4.26; N, 9.39.

General procedure for the preparation of 2-[2-(2,6-dichlorophenyl)amino]benzyl-3-{4-[4-(2-substitutedphenyl)-3-chloro-2-oxo-azetidinyl]aryl}-6-bromoquinazolin-4(3*H*)ones (**6a–k**)

A solution of (**5**) (0.0025 mol) in dry dioxane (20 mL) was added to a well-stirred mixture of chloroacetylchloride (0.0025 mol) and triethylamine (0.0025 mol) in dry dioxane at 0–5 °C. The reaction mixture was stirred for 10–12 h and kept for 2 days at room temperature. The product was isolated and recrystallized from ethanol to provide (**6a–k**).

*2-[2-(2,6-Dichlorophenyl)amino]benzyl-3-{4-[4-(2-nitrophenyl)-3-chloro-2-oxo-azetidinyl]aryl}-6-bromoquinazolin-4(3H)one (**6a**)*

Yield = 58%, m.p. 174–176 °C; IR (KBr) cm^{-1}: 3440 (NH), 2926, 2853 (CH_2), 1746 (C=O of azetidinone), 1682 (C=O of quinazolinone), 1613 (C=N), 1545, 1355 (NO_2), 1335 (C–N), 788 (C–Cl), (C–Br); ^1H NMR ($CDCl_3$): δ 9.25 (s, 1H, NH), 6.51–7.85 (m, 18H, ArH), 3.52 (s, 2H, CH_2), 3.32 (d, 1H, CH–Ar), 3.23 (d, 1H, CH–Cl); ^{13}C NMR ($CDCl_3$): δ 164.3, 162.6, 160.5, 147.3, 146.2, 138.4, 137.4, 137.3, 136.4, 135.3, 134.6, 132.3, 129.7, 129.5, 128.4, 127.9, 127.7, 127.6, 127.4, 126.7, 124.5, 123.5, 123.3, 121.7, 121.5, 121.2, 119.1, 118.3, 62.3, 55.4, 28.1; Anal. Calcd. for $C_{36}H_{23}O_4N_5BrCl_3$: C, 55.73; H, 2.99; N, 9.03. Found: C, 55.66; H, 2.91; N, 8.95.

*2-[2-(2,6-Dichlorophenyl)amino]benzyl-3-{4-[4-(3-nitrophenyl)-3-chloro-2-oxo-azetidinyl]aryl}-6-bromoquinazolin-4(3H)one (**6b**)*

Yield = 56%, m.p. 165–168 °C; IR (KBr) cm^{-1}: 3445 (NH), 2925, 2850 (CH_2), 1740 (C=O of azetidinone), 1680 (C=O of quinazolinone), 1615 (C=N), 1543, 1351 (NO_2), 1338 (C–N), 786 (C–Cl), 628 (C–Br); ^1H NMR ($CDCl_3$): δ 9.35 (s, 1H, NH), 6.53–7.87 (m, 18H, ArH), 3.48 (s, 2H, CH_2), 3.31 (d, 1H, CH–Ar), 3.22 (d, 1H, CH–Cl); ^{13}C NMR ($CDCl_3$): δ 164.2, 162.2, 160.3, 147.7, 146.5, 144.5, 138.5, 137.4, 136.5, 135.4, 133.2, 132.3, 129.6, 129.5, 129.4, 128.5, 127.6, 127.5, 126.9, 124.4, 123.5, 123.4, 121.8, 121.7, 121.6, 121.5, 119.3, 118.4, 62.6, 55.6, 28.6; Anal. Calcd. for $C_{36}H_{23}O_4N_5BrCl_3$: C, 55.73; H, 2.99; N, 9.03. Found: C, 55.67; H, 2.93; N, 8.99.

*2-[2-(2,6-Dichlorophenyl)amino]benzyl-3-{4-[4-(2-hydroxyphenyl)-3-chloro-2-oxo-azetidinyl]aryl}-6-bromoquinazolin-4(3H)one (**6c**)*

Yield = 55%, m.p. 163–167 °C; IR (KBr) cm^{-1}: 3448 (NH), 3250 (OH), 2923, 2852 (CH_2), 1753 (C=O of azetidinone), 1681 (C=O of quinazolinone), 1613 (C=N), 1338 (C–N), 785 (C–Cl), 625 (C–Br); ^1H NMR ($CDCl_3$): δ 9.28 (s, 1H, NH), 6.58–7.93 (m, 18H, ArH), 4.85 (s, 1H, OH), 3.63 (s, 2H, CH_2), 3.36 (d, 1H, CH–Ar), 3.28 (d, 1H, CH–Cl); ^{13}C NMR ($CDCl_3$): δ 164.5, 163.1, 160.9, 154.3, 146.4, 138.5, 137.5, 136.6, 135.4, 132.5, 130.8, 129.5, 129.2, 128.4, 128.3, 128.1, 127.8, 127.5, 126.8, 124.3, 123.4, 121.7, 121.5, 121.4, 121.2, 119.2, 118.3, 115.6, 61.7, 55.6, 28.7; Anal. Calcd. for $C_{36}H_{24}N_4O_3Cl_3Br$: C, 57.89; H, 3.24; N, 7.50. Found: C, 57.81; H, 3.16; N, 7.43.

*2-[2-(2,6-Dichlorophenyl)amino]benzyl-3-{4-[4-(4-hydroxyphenyl)-3-chloro-2-oxo-azetidinyl]aryl}-6-bromoquinazolin-4(3H)one (**6d**)*

Yield = 61%, m.p. 170–175 °C; IR (KBr) cm^{-1}: 3450 (NH), 3247 (OH), 2920, 2853 (CH_2), 1755 (C=O of azetidinone), 1675 (C=O of quinazolinone), 1618 (C=N), 1340 (C–N), 787 (C–Cl), 621 (C–Br); ^1H NMR ($CDCl_3$): δ 9.25 (s, 1H, NH), 6.55–7.90 (m, 18H, ArH), 4.90 (s, 1H, OH), 3.60 (s, 2H, CH_2), 3.35 (d, 1H, CH–Ar), 3.30 (d, 1H, CH–Cl); ^{13}C NMR ($CDCl_3$): δ 164.7, 162.3, 160.3, 156.5, 146.4, 138.5, 137.7, 136.7, 136.1, 135.3, 132.6, 129.4, 129.3, 128.5, 128.3, 127.6, 127.4, 126.5, 124.5, 123.7, 121.8, 121.7, 121.5, 119.1, 118.2, 115.7, 61.9, 55.8, 28.5; Anal. Calcd. for $C_{36}H_{24}N_4O_3Cl_3Br$: C, 57.89; H, 3.24; N, 7.50. Found: C, 57.85; H, 3.18; N, 7.45.

*2-[2-(2,6-Dichlorophenyl)amino]benzyl-3-{4-[4-(2-chlorophenyl)-3-chloro-2-oxo-azetidinyl]aryl}-6-bromoquinazolin-4(3H)one (**6e**)*

Yield = 63%, m.p. 157–160 °C; IR (KBr) cm^{-1}: 3448 (NH), 2923, 2850 (CH_2), 1740 (C=O of azetidinone), 1675 (C=O of quinazolinone), 1615 (C=N), 1330 (C–N), 784 (C–Cl), 635 (C–Br); ^1H NMR ($CDCl_3$): δ 9.28 (s, 1H, NH), 6.52–7.85 (m, 18H, ArH), 3.52 (s, 2H, CH_2), 3.36 (d, 1H, CH–Ar), 3.29 (d, 1H, CH–Cl); ^{13}C NMR ($CDCl_3$): δ 164.7, 163.2, 161.2, 146.5, 143.5, 138.3, 137.6, 136.3, 135.4, 132.4, 132.2, 129.6, 129.2, 128.6, 128.4, 128.3, 128.2, 127.8, 127.5, 126.7, 126.6, 124.7, 123.4, 121.7, 121.5, 121.3, 119.3, 118.4, 62.4, 54.3, 29.2; Anal. Calcd. for $C_{36}H_{23}O_2N_4BrCl_4$: C, 56.50; H, 3.03; N, 7.32. Found: C, 56.44; H, 2.94; N, 7.27.

*2-[2-(2,6-Dichlorophenyl)amino]benzyl-3-{4-[4-(4-chlorophenyl)-3-chloro-2-oxo-azetidinyl]aryl}-6-bromoquinazolin-4(3H)one (**6f**)*

Yield = 57%, m.p. 172–176 °C; IR (KBr) cm^{-1}: 3445 (NH), 2926, 2852 (CH_2), 1748 (C=O of azetidinone), 1685 (C=O of quinazolinone), 1612 (C=N), 1328 (C–N), 786 (C–Cl), 630 (C–Br); ^1H NMR ($CDCl_3$): δ 9.22 (s, 1H, NH), 6.50–7.87 (m, 18H, ArH), 3.55 (s, 2H, CH_2), 3.37 (d, 1H, CH–Ar), 3.28 (d, 1H, CH–Cl); ^{13}C NMR ($CDCl_3$): δ 164.7, 163.5, 160.2, 146.3, 141.5, 138.6, 137.7, 136.6, 135.4, 132.7, 132.4, 129.5, 129.4, 128.6, 128.5, 128.3, 127.8, 127.6, 126.7, 124.3, 123.4, 121.8, 121.5, 121.4, 119.2, 118.3, 62.1, 54.6, 29.3; Anal. Calcd. for $C_{36}H_{23}O_2N_4BrCl_4$: C, 56.50; H, 3.03; N, 7.32. Found: C, 56.46; H, 2.95; N, 7.28.

*2-[2-(2,6-Dichlorophenyl)amino]benzyl-3-{4-[4-(4-methoxyphenyl)-3-chloro-2-oxo-azetidinyl]aryl}-6-bromoquinazolin-4(3H)one (**6g**)*

Yield = 65%, m.p. 168–170 °C; IR (KBr) cm^{-1}: 3446 (NH), 2923, 2848 (CH_2), 1740 (C=O of azetidinone), 1685 (C=O of quinazolinone), 1618 (C=N), 1349 (C–N), 1205, 1104 (C–O–C), 778 (C–Cl), 630 (C–Br); ^1H NMR ($CDCl_3$): δ 9.35 (s, 1H, NH), 6.55–7.84 (m, 18H, ArH), 3.82 (s, 3H, OCH_3), 3.50 (s, 2H, CH_2), 3.36 (d, 1H, CH–Ar), 3.28 (d, 1H, CH–Cl); ^{13}C NMR ($CDCl_3$): δ 164.1, 163.5, 159.8, 158.5, 146.3, 138.4, 137.6, 136.5, 135.7, 135.3, 132.5, 129.7, 129.5, 128.3, 127.9, 127.4, 127.2, 126.5, 124.4, 123.5, 121.8, 121.6, 121.4, 119.1, 118.2, 114.3, 63.5, 56.4, 54.5, 28.6; Anal. Calcd. for $C_{37}H_{26}O_3N_4BrCl_3$: C, 58.40; H, 3.44; N, 7.36. Found: C, 58.32; H, 3.36; N, 7.28.

*2-[2-(2,6-Dichlorophenyl)amino]benzyl-3-{4-[4-(3,4,5-trimethoxyphenyl)-3-chloro-2-oxo-azetidinyl]aryl}-6-bromoquinazolin-4(3H)one (**6h**)*

Yield = 59%, m.p. 165–167 °C; IR (KBr) cm^{-1}: 3448 (NH), 2925, 2850 (CH_2), 1745 (C=O of azetidinone), 1675 (C=O of quinazolinone), 1613 (C=N), 1320 (C–N), 1189, 1095 (C–O–C), 780 (C–Cl), 632 (C–Br); ^1H NMR ($CDCl_3$): δ 9.28 (s, 1H, NH), 6.44–7.79 (m, 16H, ArH), 3.92 (s, 6H, OCH_3), 3.65 (s, 3H, OCH_3), 3.57 (s, 2H, CH_2), 3.34 (d, 1H, CH–Ar), 3.25 (d, 1H, CH–Cl); ^{13}C NMR ($CDCl_3$): δ 164.2, 162.4, 161.4, 150.5, 146.2, 138.3, 137.7, 137.5, 137.3, 136.4, 135.3, 132.3, 129.4, 129.3, 128.4, 127.5, 127.3, 126.6, 124.5, 123.6, 121.7, 121.6, 121.3, 119.3, 118.3, 104.3, 64.2, 56.6, 55.2, 54.5, 28.7; Anal. Calcd. for $C_{39}H_{30}O_5N_4BrCl_3$: C, 57.06; H, 3.68; N, 6.82. Found: C, 56.97; H, 3.59; N, 6.76.

*2-[2-(2,6-Dichlorophenyl)amino]benzyl-3-{4-[4-(2-hydroxy-4-methoxyphenyl)-3-chloro-2-oxo-azetidinyl]aryl}-6-bromoquinazolin-4(3H)one (**6i**)*

Yield = 54%, m.p. 184–188 °C; IR (KBr) cm^{-1}: 3435 (NH), 3248 (OH), 2928, 2852 (CH_2), 1748 (C=O of azetidinone), 1678 (C=O of quinazolinone), 1615 (C=N), 1316 (C–N), 1195, 1110 (C–O–C), 778 (C–Cl), 627 (C–Br); ^1H NMR ($CDCl_3$): δ 9.28 (s, 1H, NH), 6.45–7.75 (m, 17H, ArH), 4.81 (s, 1H, OH), 3.85 (s, 3H, OCH_3), 3.58 (s, 2H, CH_2), 3.36 (d, 1H, CH-Ar), 3.26 (d, 1H, CH-Cl); ^{13}C NMR ($CDCl_3$): δ 164.6, 162.2, 161.4, 160.1, 155.2, 146.3, 138.4, 137.6, 136.5, 135.3, 132.5, 129.4, 129.3, 129.2, 128.5, 127.8, 127.6, 126.6, 124.2, 123.5, 123.2, 121.7, 121.6, 121.4, 119.1, 118.3, 106.7, 101.8, 63.6, 57.1, 55.8, 28.7; Anal. Calcd. for $C_{37}H_{26}O_4N_4BrCl_3$: C, 57.20; H, 3.37; N, 7.21. Found: C, 57.12; H, 3.28; N, 7.15.

*2-[2-(2,6-Dichlorophenyl)amino]benzyl-3-{4-[4-(4-N-dimethylaminophenyl)-3-chloro-2-oxo-azetidinyl]aryl}-6-bromoquinazolin-4(3H)one (**6j**)*

Yield = 52%, m.p. 187–190 °C; IR (KBr) cm^{-1}: 3437 (NH), 2923, 2851 (CH_2), 1752 (C=O of azetidinone), 1686 (C=O of quinazolinone), 1614 (C=N), 1318 (C–N), 785 (C–Cl), 620 (C–Br); ^1H NMR ($CDCl_3$): δ 9.30 (s, 1H, NH), 6.50–7.83 (m, 18H, ArH), 3.50 (s, 2H, CH_2), 3.35 (d, 1H, CH–Ar), 3.30 (d, 1H, CH–Cl) 2.89 (s, 6H, N–$(CH_3)_2$); ^{13}C NMR ($CDCl_3$): δ 165.1, 163.3, 160.7, 147.6, 146.4, 138.3, 137.5, 136.5, 135.3, 133.2, 132.5, 129.6, 129.4, 128.4, 127.9, 127.8, 127.6, 126.6, 124.4, 123.6, 121.7, 121.5, 121.2, 119.2, 118.2, 114.1, 63.3, 56.3, 41.2, 28.6; Anal. Calcd. for $C_{38}H_{29}O_2N_5BrCl_3$: C, 58.97; H, 3.78; N, 9.05. Found: C, 58.89; H, 3.68; N, 8.96.

*2-[2-(2,6-Dichlorophenyl)amino]benzyl-3-{4-[4-(2-hydroxy-4-N-diethylamino phenyl)-3-chloro-2-oxo-azetidinyl]aryl}-6-bromoquinazolin-4(3H)one (**6k**)*

Yield = 67%, m.p. 158–162 °C; IR (KBr) cm^{-1}: 3446 (NH), 3247 (OH), 2924, 2848 (CH_2), 1750 (C=O of azetidinone), 1685 (C=O of quinazolinone), 1619 (C=N), 1317 (C–N), 784 (C–Cl), 625 (C–Br); ^1H NMR ($CDCl_3$): δ 9.25 (s, 1H, NH), 6.23–7.88 (m, 17H, ArH), 3.58 (s, 2H, CH_2), 3.42 (q, 4H, N–$(CH_2)_2$), 3.34 (d, 1H, CH–Ar), 3.28 (d, 1H, CH–Cl), 1.25 (t, 6H, CH_3); ^{13}C NMR ($CDCl_3$): δ 164.5, 162.5, 161.5, 154.9, 149.2, 146.4, 138.5, 137.6, 136.5, 135.4, 132.5, 129.7, 129.5, 129.2, 128.3, 127.7, 127.5, 126.6, 124.4, 123.3, 121.8, 121.5, 121.4, 120.4, 119.2, 118.1, 106.7, 98.7, 62.4, 55.6, 44.7, 28.9, 13.3; Anal. Calcd. for $C_{40}H_{33}O_3N_5BrCl_3$: C, 58.73; H, 4.07; N, 8.56. Found: C, 58.67; H, 3.98; N, 8.48.

Antimicrobial activity

The compounds **5a–k** and **6a–k** were tested for in vitro antimicrobial activity by cup-plate method (Barry, 1976). Antibacterial activity was screened against two gram positive bacteria (*Staphylococcus aureus* ATCC 9144 and *Bacillus subtilis* ATCC 6633), two gram negative bacteria (*Pseudomonas aeruginosa* ATCC 9027 and *Escherichia coli* ATCC 25922) whereas antifungal activity was screened against fungi *Candida albicans* ATCC 10231. Penicillin-G and Amphotericine-B were used as standard drugs. Microbial cultures were obtained from National Collection of Industrial Microorganisms (NCIM), National Chemical Laboratory, Pune. The potency of the compounds for antibacterial activity was calculated by using the following formula (Edwin and Marion, 1945) and antifungal activity was noted as the zone of inhibition only.

$$\text{Potency} = \{\text{antilog}\,[(D/B) \times I]\} \times M \times F$$

where F = dilution factor = 1 (same dilution used for standard and test); M = potency of standard = 100; $I = \log(S_H/S_L)$; $D = (U_H + U_L) - (S_H + S_L)$; $B = (U_H - U_L) + (S_H - S_L)$; S_H = zone of inhibition of standard at 100 μg/mL; S_L = Zone of inhibition of standard at 50 μg/mL; U_H = zone of inhibition of unknown at 100 μg/mL; U_L = zone of inhibition of unknown at 50 μg/mL.

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