European Journal of Medicinal Chemistry 46 (2011) 3900–3908

Contents lists available at ScienceDirect

European Journal of Medicinal Chemistry

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

Original article

Synthesis and cytotoxicity of 2-phenylquinazolin-4(3*H*)-one derivatives

Hee-Kyung Rhee [a], Ji Hye Yoo [a], Eunyoung Lee [a], Young Joo Kwon [a], Hang-Rhan Seo [b], Yun-Sil Lee [a], Hea-Young Park Choo [a,*]

[a] College of Pharmacy & Division of Life & Pharmaceutical Sciences, Ewha Womans University, Seoul 120-750, Korea
[b] Division of Radiation Effects, Korea Institute of Radiological and Medical Sciences, Seoul 139-706, Korea

ARTICLE INFO

Article history:
Received 30 November 2010
Received in revised form
17 May 2011
Accepted 24 May 2011
Available online 31 May 2011

Keywords:
2-Phenylquinazolin-4(3*H*)-one
Cytotoxicity
Cell cycle arrest

ABSTRACT

Thirty 2-phenylquinazolin-4(3*H*)-one derivatives were prepared and their cytotoxic activities were tested in five human tumor cell lines. Some compounds (**5e**, **5k**, **5t**, **6c** and **6f**) showed relatively high cytotoxic activity. Especially, compound **6c** showed the most cytotoxicity against all cell lines tested among the synthesized derivatives, and the inhibitory activity of **6c** against HeLa cell was higher than that of adriamycin. The putative mechanism of antitumor action in apoptotic cell death was cell cycle arrest in the G0/G1 phase by compounds **5k**, **5v**, **5m**, **6c**, and **6f** in HeLa cells. These compounds showed relatively high cytotoxicity in this cell type.

© 2011 Elsevier Masson SAS. All rights reserved.

1. Introduction

The quinazolinone moiety has been utilized extensively in medicinal chemistry and is considered to be a privileged structure [1,2] that show various pharmacological activities, such as antifungal [3], antibacterial [4,5], antimalarial [6], anti-inflammatory [7], anticonvulsant [8], antihypertensive [9] and anticancer activities [10,11]. 2-Styryl quinazolinone (**I**), shown in Fig. 1, is known to inhibit tubulin polymerization, while 2-methyl quinazolinone (**II**) inhibits the DNA repair enzyme poly(ADP-ribose) polymerase (PARP) [12,13]. Further, compounds connected quinazolinone to benzodithiazine rings (**III**) possess cancer cell growth-inhibitory properties [1]. Recently, quinazolinones linked to pyrrolobenzodiazepins (**V**) showed DNA binding ability, activation of caspase-3, cleavage of PARP and subsequent cell death [14]. The antiproliferative activity of some compounds (**VI**) involved cell cycle arrest in the G0/G1 phase [15,16].

Abnormal control of cell cycle is a result of cancer development [17]. In eukaryotic cells, cell cycle progression is modulated by sequential activation and inactivation of cyclin-dependent kinases (Cdks), which are associated with their respective cyclin subunits [18]. G1 progression and G1/S transition are regulated by Cdk4/Cdk6, which assemble with D-type cyclins during the mid-G1 phase, and by Cdk2, which later combines with cyclin E. The G2/M transition is regulated by Cdk2 in combination with cyclins A and B [19, 20]. The Cdk activity is modulated by the phosphorylation of Cdk [21]. In addition, the relative balance between the cellular concentrations of Cdk inhibitors, including the Ink4 (Inhibitors of CDK4) family and the Cip/Kip family, also regulates the cell cycle progression. The Ink4 proteins bind to Cdk4/Cdk6 and block the formation of Cdk4/6-cyclin complexes and high levels of Cip/Kip proteins inhibit Cdk2 activity [22]. However, these G1/S-associated regulators are frequently mutated and deregulated in various human cancers [23]. A recent study suggests that targeting G1-cell cycle regulators may be an effective strategy for possible therapeutic intervention in cancers [24].

In our continuous effort to study novel antitumor agents [25–30], we report the synthesis, cytotoxicity, and cell cycle arrest of quinazolinone derivatives in this paper.

2. Results and discussion

2.1. Chemistry

The synthesis of the quinazolinone derivatives **5a**–**v**, **6a**–**f**, and **7a**,**b** is outlined in Scheme 1 and Scheme 2.

The coupling reaction of anthranilamide with terephthalic acid monomethyl ester and EDCI afforded compound **1**, which upon cyclization and ester hydrolysis by treatment with 1 M NaOH yielded compound **2**. Compound **2** was coupled to *tert*-butyl 1-piperazine carboxylate using PyBop to give compound **3**. *N*-Boc

* Corresponding author. Tel.: +82 2 3277 3042; fax: +82 2 3277 2851.
E-mail address: hypark@ewha.ac.kr (H.-Y.P. Choo).

0223-5234/$ – see front matter © 2011 Elsevier Masson SAS. All rights reserved.
doi:10.1016/j.ejmech.2011.05.061

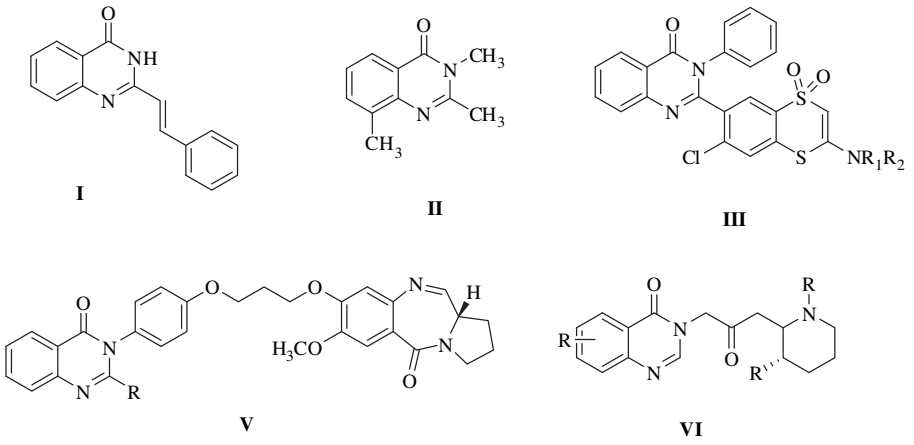
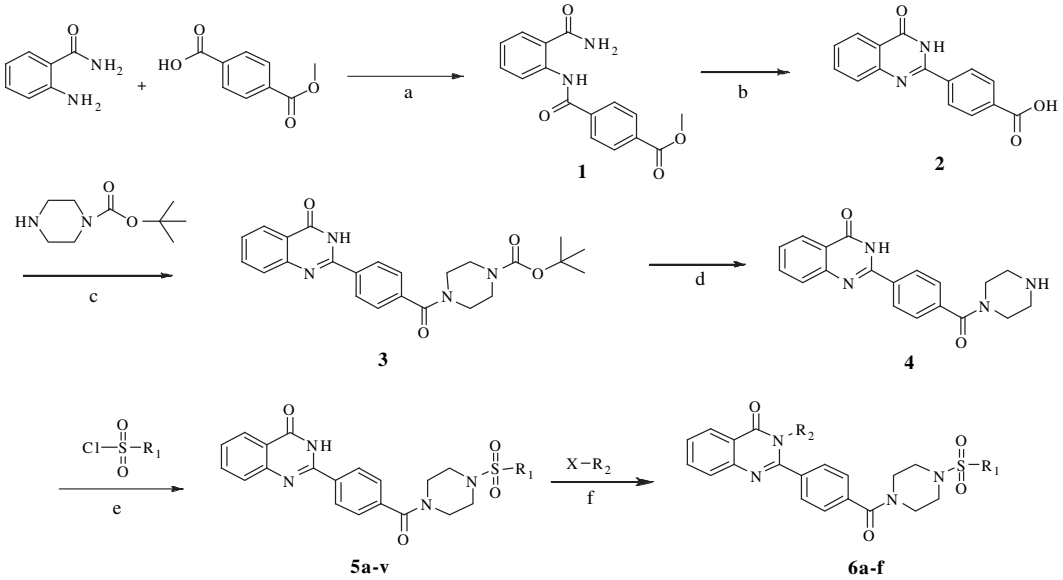


Fig. 1. Structures of quinazolinone derivatives.

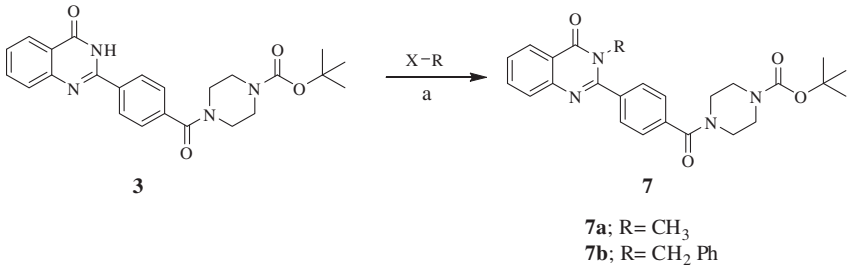
deprotection of compound **3** using HCl–dioxane gave compound **4**, which was treated with substituted sulfonyl chloride and sodium hydride to provide compounds **5a**–**v** by nucleophilic displacement. The final synthetic step involved *N*-methylation or *N*-benzylation with iodomethane or benzylbromide to afford the desired compounds **6a**–**f** and **7a**,**b**. Each individual synthesized compound was characterized by ^{1}H and ^{13}C NMR and high resolution MS. The structures of the prepared quinazolinone derivatives are illustrated in Table 1.

2.2. Cytotoxicity

The cytotoxicity of compounds synthesized is listed in Table 2. In the SAR analyses, the potency of compounds was enhanced when the electron-withdrawing nature of groups substituted on phenyl ring in R_1 position was increased; **5e** with electron-withdrawing NO_2 is more potent than **5b** with electron-donating OMe group in all cell lines except MDA-MB231 cell line; **5h** with electron-withdrawing CF_3 group is more potent than **5c** with electron-donating CH_3 group in all cell lines except HCT29 cell line; **5g** with strong electron-withdrawing F group is more potent than **5f** with week electron-withdrawing Cl group in all cell lines except HeLa cell line; **6c** is more potent than the **6f** with electron-donating OCH_3 group in all cell lines except HCT29 cell line. Although the SAR for the R_2 substituents could not be clearly deduced because of the small numbers of the compounds, among compounds tested, the SAR clearly shows that the potency of compounds increases with increasing size of the R_2 group; **5a** < **6a** in all cell lines, and **5a** < **6a** < **6b** in MDA-MB231 and HL-60 cell lines; **5b** < **6d** < **6e** < **6f** in all cell lines except HeLa cell line in **6e**. Based on the above points it may be worthwhile modifying more potent **6c** with electron-withdrawing R_1 group and **5e** with bulky R_2 group like 4-OCH_3 benzyl, may led to more potent compounds. The direct comparison of cytotoxicity between compounds synthesized in the present study and known simple 2-phenyl-4-quinazolinones derivatives [10–12] cannot be performed because the cell lines and positive controls used for cytotoxicity evaluation are different.



Scheme 1. a) EDCI, DMAP, DMF, rt, 20 h; b) 1 M NaOH, $CHCl_3$, rt, 20 h; c) PyBop, iPr_2Net, DMF, rt, 20 h; d) 4.0 M HCl in 1,4-dioxane, $CHCl_3$, rt, 3 h; e) NaH, DMF, 100 °C, 16 h; f) Iodomethane or benzylbromide, K_2CO_3, DMF, 100 °C, 16 h.



Scheme 2. a) Iodomethane or benzylbromide, K_2CO_3, DMF, 100 °C, 16 h.

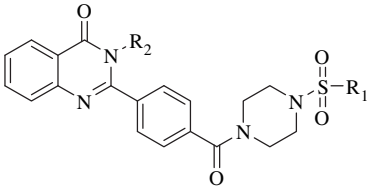
2.3. Cell cycle mechanism of cytotoxicity

Since HeLa cells are a good cell type for examining cell cycle distribution [31,32], we examined the cell cycle distribution in HeLa cells after treatment with some compounds (**5k**, **5v**, **5m**, **6c** and **6f**) that showed relatively high cytotoxicity to elucidate the mechanisms of their cytotoxicities. A high percent of sub G1 (apoptotic cell death) was found in the treatment of these compounds (**5m** > **6f** > **5k** > **6c** > **5v**) with concomitant increased G1 arrest (Tables 3 and 4). Actually, the G1 arrest ratio was similar for all compounds tested; therefore, a mechanism other than G1 arrest could be involved in the induction of apoptosis. However, when compounds **5e** and **5k** were evaluated by PARP-1 inhibition assay or antimitotic activity test, no activity was observed (data not shown).

3. Conclusion

Thirty 2-phenylquinazolin-4(3*H*)-one derivatives were synthesized and their cytotoxic activities were tested in five human tumor cell lines. Some compounds (**5e**, **5k**, **5t**, **6c** and **6f**) showed relatively high cytotoxic activity. The cell cycle distribution following treatment with compounds (**5k**, **5v**, **5m**, **6c** and **6f**) that showed relatively high cytotoxicity in HeLa cells was examined to elucidate the mechanisms of their cytotoxicities. A high percentage of sub G1 (apoptotic cell death) was found in the treatment with these compounds (**5m** > **6f** > **5k** > **6c** > **5v**) with concomitant increased G1 arrest.

Table 1
Structures of prepared quinazolinone derivatives.



5-6

Compound	R_1	R_2	Compound	R_1	R_2
5a	Phenyl	H	**5o**	2-naphtyl	H
5b	$4OCH_3$ phenyl	H	**5p**	8-quinolinyl	H
5c	$4\text{-}CH_3$ phenyl	H	**5q**	2-thiophenyl	H
5d	4-isopropyl phenyl	H	**5r**	methyl	H
5e	$4\text{-}NO_2$ phenyl	H	**5s**	Isopropyl	H
5f	4-Cl phenyl	H	**5t**	Butyl	H
5g	4-F phenyl	H	**5u**	cyclopropyl	H
5h	$4\text{-}CF_3$ phenyl	H	**5v**	cyclopentyl	H
5i	$3\text{-}CF_3$ phenyl	H	**6a**	Phenyl	Methyl
5j	$2\text{-}CF_3$ phenyl	H	**6b**	Phenyl	Benzyl
5k	Benzyl	H	**6c**	Phenyl	$4\text{-}OCH_3$ benzyl
5l	$4\text{-}CH_3$ benzyl	H	**6d**	$4\text{-}OCH_3$ phenyl	Methyl
5m	4-Cl benzyl	H	**6e**	$4\text{-}OCH_3$ phenyl	Benzyl
5n	1-naphtyl	H	**6f**	$4\text{-}OCH_3$ phenyl	$4\text{-}OCH_3$ benzyl

4. Experimental

4.1. Materials and methods

All the melting points of the synthesized compounds were determined in Pyrex capillaries using electrothermal digital melting point apparatus (Büchi) and were not corrected. ^{1}H NMR and ^{13}C NMR spectra were recorded on Varian Unity Inova 400 MHz NMR spectrometers, and Bruker Anance 400 MHz NMR spectrometer. The ^{1}H NMR data were reported as peak multiplicities: s for singlet; d for doublet; t for triplet; and m for multiplet. Coupling constants were recorded in Hertz. Infrared spectra were recorded on a Nocolet IS10 FT-IR. Mass spectral data were obtained on a Jeol

Table 2
Cytotoxicity of compounds against human tumor cell lines.

Compound	MTT assay, IC_{50} (μM)[a]				
	HeLa	HCT29	DU145	MDA-MB231	HL-60
2	>50	30.6 ± 7.5	28.1 ± 6.2	>50	11.7 ± 0.9
3	20.7 ± 10.7	20.7 ± 2.1	>50	8.5 ± 0.5	15.4 ± 1.1
4	>50	>50	24.3 ± 1.7	>50	16.7 ± 3.7
5a	8.9 ± 0.3	12.5 ± 3.7	7.1 ± 1.8	32.6 ± 1.4	14.3 ± 0.3
5b	>50	21.6 ± 6.9	27.0 ± 1.6	5.1 ± 0.6	7.5 ± 0.4
5c	23.5 ± 0.8	10.5 ± 2.2	18.1 ± 0.7	43.5 ± 1.7	8.4 ± 0.6
5d	17.2 ± 1.7	9.0 ± 2.3	16.2 ± 2.1	9.4 ± 0.3	2.6 ± 0.3
5e	20.0 ± 1.2	2.6 ± 0.1	25.2 ± 2.1	12.5 ± 0.5	2.0 ± 0.3
5f	18.0 ± 10.0	>50	>50	>50	13.6 ± 2.1
5g	35.4 ± 2.7	11.1 ± 5.3	35.0 ± 3.6	27.7 ± 1.0	10.9 ± 0.4
5h	13.4 ± 1.4	21.6 ± 4.4	14.9 ± 1.5	31.4 ± 1.6	6.5 ± 0.2
5i	9.3 ± 0.2	9.5 ± 0.1	14.1 ± 0.5	>50	23.5 ± 3.2
5j	8.3 ± 1.0	>50	24.7 ± 0.7	5.5 ± 0.3	14.1 ± 0.7
5k	9.1 ± 0.8	2.3 ± 0.4	7.7 ± 0.8	15.8 ± 0.5	18.7 ± 0.1
5l	9.0 ± 2.2	19.5 ± 8.3	29.6 ± 0.8	7.7 ± 0.1	16.7 ± 1.8
5m	4.4 ± 1.0	12.6 ± 0.6	27.1 ± 1.1	>50	>50
5n	11.7 ± 0.7	11.6 ± 6.1	9.9 ± 0.9	22.2 ± 1.8	7.0 ± 0.5
5o	13.3 ± 1.3	16.5 ± 1.4	27.8 ± 1.0	>50	26.6 ± 0.6
5p	11.1 ± 0.7	>50	15.6 ± 1.3	6.3 ± 0.4	14.6 ± 0.4
5q	>50	15.7 ± 3.5	21.3 ± 1.1	9.4 ± 0.4	2.2 ± 0.1
5r	>50	>50	20.0 ± 0.3	6.4 ± 1.2	11.6 ± 0.4
5s	11.0 ± 0.6	>50	17.4 ± 1.2	5.8 ± 0.7	7.5 ± 1.1
5t	17.3 ± 11.3	10.3 ± 0.4	17.9 ± 1.8	1.2 ± 0.2	14.9 ± 1.8
5u	>50	>50	6.0 ± 0.9	8.2 ± 0.6	10.8 ± 1.1
5v	11.2 ± 0.6	12.9 ± 1.6	4.8 ± 0.1	14.7 ± 1.5	11.2 ± 0.1
6a	14.1 ± 2.1	13.3 ± 1.7	10.4 ± 0.9	9.1 ± 0.3	5.9 ± 1.2
6b	20.1 ± 4.1	23.6 ± 0.4	15.3 ± 1.3	19.3 ± 2.3	4.2 ± 1.1
6c	2.9 ± 0.01	8.6 ± 0.1	2.5 ± 0.1	4.2 ± 0.4	2.6 ± 0.8
6d	23.7 ± 3.1	25.8 ± 0.5	21.5 ± 0.9	>50	5.9 ± 0.9
6e	34.2 ± 0.5	22.5 ± 0.3	16.0 ± 1.1	48.1 ± 1.0	6.1 ± 0.4
6f	16.5 ± 0.1	5.8 ± 0.1	5.8 ± 0.1	9.9 ± 0.9	3.8 ± 1.1
7a	15.5 ± 1.2	28.0 ± 0.5	17.2 ± 0.3	24.9 ± 0.5	9.5 ± 1.9
7b	21.6 ± 1.0	>50	>50	40.4 ± 0.8	2.9 ± 0.9
Adriamycin	3.7 ± 0.2	2.5 ± 0.2	1.9 ± 0.1	1.4 ± 0.2	0.8 ± 0.04

[a] Each data point represents mean ± SD from three different experiments performed in triplicate. "-" means non-tested. Cell lines used are as follows. HeLa; human cervix cancer cell line, HCT-29; human colon cancer cell line, DU145; human prostate cancer cell line, MDA-MB231; human breast cancer cell line, HL-60; human myeloid leukemic tumor cell line.

Table 3
2-phenylquinazolin-4(3H)-one derivatives enhanced cell death.

Compounds	Sub G1 phase	Enhanced ratio of cell death
Control	2.43 ± 0.70	
5k	17.14 ± 1.58[a]	7.04
5v	14.51 ± 2.62[a]	5.96
5m	21.27 ± 5.32[a]	8.74
6c	16.61 ± 3.72[a]	6.83
6f	17.74 ± 2.21[a]	7.29

HeLa Cells were treated with 10 μmol/L 2-phenylquinazolin-4(3H)-one derivatives for the 72 h.
[a] Statistical significance at $p < 0.05$.

JMS 700 high resolution mass spectrometer at the Korea Basic Science Institute (Daegu). Most of the reagents were purchased from Sigma–Aldrich Chemical Company, Merck Company and Ducksan Pure Chemical Company.

4.2. General procedure for preparation of 4-(2-carbamoylphenylcarbamoyl) benzoic acid (**1**)

Terephthalic acid monomethyl ester (500 mg, 2.77 mmol) and 1-ethyl-3-(3′-dimethylaminopropyl)carbodiimide (532 mg, 2.77 mmol) were mixed in 15 mL of *N*,*N*-dimethylformamide (DMF). This mixture was stirred at rt for 1 h and then 4-dimethylaminopyridine (678 mg, 5.55 mmol) and anthranilamide (378 mg, 2.77 mmol) were added. The mixture was stirred at rt for 20 h. The reaction mixture was acidified with 10% HCl and extracted with ethyl acetate. The organic phase was washed with 10% HCl, saturated sodium bicarbonate solution, and brine. The organic phase was dried over $MgSO_4$ and evaporated *in vacuo*.

White powder, 87% (716 mg), mp 207–209 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.112 (s, 1H), 8.702 (d, J = 8.2 Hz, 1H), 8.450 (s, 1H), 8.156 (d, J = 6.8 Hz, 2H), 8.071 (d, J = 7.4 Hz, 2H), 7.932 (d, J = 7.8 Hz, 1H), 7.892 (s, 1H), 7.617 (t, J = 7.9 Hz, 1H), 7.232 (t, J = 7.6 Hz, 1H), 3.906 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 171.09, 165.56, 163.48 (3C, carbonyl), 139.81, 138.62, 132.64, 132.45, 129.70 (two overlapping signals), 128.75, 127.36 (two overlapping signals), 122.99, 120.15, 119.29 (12C, aromatic), 52.46 (1C, −O−CH_3) IR (film) 3342, 2923, 1529, 1281, 1105, 717 cm^{-1}. HR-FABMS Calcd for $C_{16}H_{15}N_2O_4$ (M^++H): 299.1032, Found: 299.1035.

4.3. General procedure for preparation of 4-(4-oxo-3,4-dihydroquinazolin-2-yl)benzoic acid (**2**)

4-(2-Carbamoylphenylcarbamoyl)benzoic acid (**1**) (716 mg, 2.40 mmol) in chloroform (30 mL) was treated with 1 M NaOH solution. The mixture was strongly stirred at rt for 20 h. The aqueous layer was separated, washed with chloroform and then acidified with 2 M HCl. The resulting solid was filtered off and washed with water and chloroform.

Table 4
The increased G1 phase arrest by 2-phenylquinazolin-4(3H)-one derivatives.

Compounds	Rate of G1 phase	Fold induction of G1 phase
Control	48.6 ± 3.5	
5k	59.0 ± 1.0[a]	1.21
5v	58.4 ± 1.2[a]	1.20
5m	58.2 ± 2.7[a]	1.20
6c	57.7 ± 2.7[a]	1.19
6f	57.1 ± 0.3[a]	1.18

Flow cytometric analysis after PI staining was conducted following 36 h of 10 μmol/L 2-phenylquinazolin-4(3H)-one derivatives using HeLa cells.
[a] Statistical significance at $p < 0.05$.

White powder, 51% (325 mg), mp >300 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.682 (s, 1H), 8.299 (d, J = 6.8 Hz, 2H), 8.188 (d, J = 8.0 Hz, 1H), 8.097 (d, J = 7.0 Hz, 2H), 8.038 (s, 1H), 7.889 (t, J = 7.7 Hz, 1H), 7.790 (d, J = 7.6 Hz, 1H), 7.581 (t, J = 7.5 Hz, 1H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 166.72, 162.11 (2C, carbonyl), 151.69 (1C, quinazoline), 148.34, 136.42, 134.70, 133.07, 129.39 (two overlapping signals), 128.07 (two overlapping signals), 127.47, 126.99, 125.89, 121.10 (12C, aromatic). IR (film) 3500–2800 3152, 3032, 2920, 1686, 1449, 1304, 1280,942, 769 cm^{-1}. HR-FABMS Calcd for $C_{15}H_{11}O_3N_2$ (M^++H): 267.0770, Found: 267.0772.

4.4. General procedure for preparation of tert-butyl 4-(4-(4-oxo-3,4-dihydro quinazolin-2-yl)benzoyl)piperazine-1-carb-oxylate (**3**)

To a solution of 4-(4-Oxo-3,4-dihydroquinazolin-2-yl)benzoic acid (**2**) (320 mg, 1.20 mmol), *tert*-butyl 1-piperazine carboxylate (246 mg, 1.32 mmol), and benzotriazol-1-yl-oxytripyrrol-idinophosphonium hexafluorophosphate (688 mg, 1.32 mmol) in DMF (15 mL) was added N, N-diisopropylethylamine (420 μL, 2.40 mmol). This mixture was stirred at rt for 20 h. The reaction mixture was acidified with 10% HCl and extracted with ethyl acetate. The organic phase was washed with 10% HCl, saturated $NaHCO_3$ solution, and brine. The organic phase was dried over $MgSO_4$ and evaporated *in vacuo*.

White powder, 59% (307 mg), mp 248–250 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 11.620 (s, 1H), 8.353 (d, J = 7.8 Hz, 1H), 8.341 (d, J = 7.8 Hz, 2H), 7.850 (d, J = 7.8 Hz, 2H), 7.632 (d, J = 7.8 Hz, 2H), 7.567 (t, J = 6.9 Hz, 1H), 3.800–3.435 (m, 8H), 1.484 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.58, 163.52, 154.56 (3C, carbonyl), 150.66 (1C, quinazoline), 149.28, 138.48, 135.10, 134.23, 128.17, 127.80 (two overlapping signals), 127.69 (two overlapping signals), 127.27, 126.47, 121.00 (12C, aromatic), 80.52(1C, −O−C−), 29.72, 28.39 (two overlapping signals) (3C, $-CH_3$ ×3). IR (film) 3299, 2964, 2922, 2867, 1682, 1611, 1416, 1159, 1012, 851, 726 cm^{-1}. HR-FABMS Calcd for $C_{24}H_{27}O_4N_4$ (M^++H): 435.2032, Found: 435.2028.

4.5. General procedure for preparation of 2-(4-(piperazine-1-carbonyl)phenyl) quinazolin-4(3H)-one (**4**)

4M HCl in 1,4-dioxane (3 mL) was added to a solution of 4-(4-(4-oxo-3,4-dihydroquinazolin-2-yl)benzoyl)piperazine-1-carboxylate (3) (65 mg, 0.15 mmol) in chloroform (3 mL), and the reaction mixture was stirred at rt for 3 h. The solvent was removed *in vacuo*.

Pale brown solid, 100% (50 mg), mp >300 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.649 (s, 1H), 8.917 (s, 2H), 8.282 (d, J = 6.4 Hz, 2H), 8.188 (d, J = 8.0 Hz, 1H), 7.889 (t, J = 7.6 Hz, 1H), 7.772 (d, J = 8.2 Hz, 1H), 7.655 (d, J = 6.8 Hz, 2H), 7.578 (t, J = 7.6 Hz, 1H), 3.806–3.432 (m, 8H). ^{13}C NMR (100 MHz, DMSO- d_6): δ 168.46, 162.17 (2C, carbonyl), 151.64 (1C, quinazoline), 148.49, 137.53, 134.66, 133.83, 127.92(two overlapping signals), 127.49, 127.33(two overlapping signals), 126.83, 125.86, 121.04 (12C, aromatic), 42.36, (4C, piperazine). IR(film) 3386, 2926, 1660, 1599, 1438, 1282, 1119, 1008, 766 cm^{-1}. HR-FABMS Calcd for $C_{19}H_{19}N_4O_2$ (M^++H): 335.1508, Found: 335.1510.

4.6. General procedure for the preparation of 2-(4-(4-R_1-sulfonyl) piperazine -1-carbonyl)phenyl)quinazolin-4 (3H)-one (**5a-v**)

Sodium hydride (60% dispersion in mineral oil) (18 mg, 0.45 mmol) was added to a solution of 2-(4-(Piperazine-1-carbonyl)phenyl)quinazolin-4(3H)-one (**4**) (50 mg, 0.15 mmol) in DMF (10 mL), and the mixture was heated at 100 °C. Appropriate sulfonyl chloride (0.22 mmol) in DMF (3 mL) was added slowly to the reaction mixture. The mixture was stirred at 100 °C for 16 h. After cooling, saturated $NaHCO_3$ solution was added. The reaction

mixture was extracted with ethyl acetate and the organic phase was washed with brine. The organic phase was dried over $MgSO_4$ and evaporated *in vacuo*. The residue was washed with ethyl acetate/hexane (1:10) and purified by column chromatography (ethyl acetate) to provide 2-(4-(4-(substituted)-sulfonyl)piperazine-1-carbonyl)phenyl)quinazolin-4(3H)-one.

4.6.1. 2-(4-(4-(Phenylsulfonyl)piperazine-1-carbonyl)phenyl) quinazolin-4(3H)-one (**5a**)

Pale brown solid, 29% (21 mg), mp 211–213 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.339 (s, 1H), 8.327 (d, J = 8.0 Hz, 1H), 8.283 (d, J = 7.4 Hz, 2H), 7.839 (d, J = 3.2 Hz, 2H), 7.789 (d, J = 7.6 Hz, 2H), 7.692 (t, J = 6.5 Hz, 1H), 7.610 (t, J = 7.5 Hz, 2H), 7.557 (t, J = 8.0 Hz, 1H), 7.552 (d, J = 7.2 Hz, 2H), 3.913–3.010 (m, 8H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 168.43, 162.14(2C, carbonyl), 151.62 (1C, quinazoline), 148.53, 137.89, 135.11, 134.66, 133.69, 133.40, 129.55(two overlapping signals), 127.86(two overlapping signals), 127.49(two overlapping signals), 127.26(two overlapping signals), 126.82, 125.85, 121.06 (18C, aromatic). HR-FABMS Calcd for $C_{25}H_{23}O_4N_4S$ (M^++H): 475.1440, Found: 475.1443.

4.6.2. 2-(4-(4-(4-Methoxyphenylsulfonyl)piperazine-1-carbonyl) phenyl)quinazolin-4(3H)-one (**5b**)

Pale brown solid, 23% (18 mg), mp 170–172 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.480 (s, 1H), 8.327 (d, J = 8.0 Hz, 1H), 8.181 (d, J = 6.4 Hz, 2H), 7.837–7.824 (m, 2H), 7.710 (d, J = 6.8 Hz, 2H), 7.550 (t, J = 7.6 Hz, 1H), 7.542 (d, J = 7.6 Hz, 2H), 7.044 (d, J = 7.0 Hz, 2H), 3.899 (s, 3H), 3.552–2.957 (m, 8H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 168.41, 164.82, (2C, carbonyl) 162.87, (1C, quinazoline), 137.91, 134.63, 133.75, 129.78(two overlapping signals), 127.86(two overlapping signals), 127.26(two overlapping signals), 126.48(two overlapping signals), 125.86, 121.05, 114.68(two overlapping signals), (18C, aromatic), 56.44(1C, $-OCH_3$). IR (film) 2923, 2854, 1659, 1599, 1433, 1284, 1259, 1153, 929, 766, 732 cm^{-1}. HR-FABMS Calcd for $C_{26}H_{25}O_5N_4S$ (M^++H): 505.1546, Found: 505.1542.

4.6.3. 2-(4-(4-Tosylpiperazine-1-carbonyl)phenyl)quinazolin-4(3H)-one (**5c**)

White solid, 26% (19 mg), mp 242–245 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.414 (s, 1H), 8.328 (d, J = 7.8 Hz, 1H), 8.182 (d, J = 6.6 Hz, 2H), 7.837 (d, J = 4.8 Hz, 2H), 7.656 (d, J = 6.4 Hz, 2H), 7.547 (t, J = 4.2 Hz, 1H), 7.540 (d, J = 8.4 Hz, 2H), 7.380 (d, J = 8.4 Hz, 2H), 3.894–2.979 (m, 8H), 2.471 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_{36}$) δ 169.20, 162.46 (2C, carbonyl) 150.09 (1C, quinazoline), 144.25, 137.97, 136.65, 131.13, 134.34, 132.37, 129.98 (two overlapping signals), 129.98(two overlapping signals), 128.17, 128.00, 127.79(two overlapping signals), 127.42, 127.26, 126.57, 121.09 (18C, aromatic), 46.08(4C, piperazine), 21.59(1C, $-CH_3$). HR-FABMS Calcd for $C_{26}H_{25}O_4N_4S$ (M^++H): 489.1597, Found: 489.1595.

4.6.4. 2-(4-(4-(4-Isopropylphenylsulfonyl)piperazine-1-carbonyl) phenyl)quinazolin-4(3H)-one (**5d**)

Pale brown solid, 16% (13 mg), mp 208–211 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.522 (s, 1H), 8.330 (d, J = 8.0 Hz, 1H), 8.194 (d, J = 6.8 Hz, 2H), 7.837 (d, J = 4.8 Hz, 2H), 7.691 (d, J = 8.6 Hz, 2H), 7.556 (t, J = 7.4 Hz, 1H), 7.548 (d, J = 8.8 Hz, 2H), 7.425 (d, J = 7.6 Hz, 2H), 3.911–2.968 (m, 8H), 3.073–2.968 (m, 1H), 1.316 (d, J = 6.8 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.40, 163.43 (2C, carbonyl), 154.86 (1C, quinazoline), 150.48, 149.22, 137.82, 135.13, 134.42, 132.73, 128.17, 127.94(two overlapping signals), 127.88(two overlapping signals), 127.65(two overlapping signals), 127.45(two overlapping signals), 127.32, 126.45, 120.98, (18C, aromatic), 46.06 (4C, piperazine), 34.25(1C,-C-), 29.72, 23.65 (2C, $-CH_3 \times 2$). IR(film) 2962, 2926, 1680, 1598, 1431, 1284, 1165, 941, 773, 716 cm^{-1}. HR-FABMS Calcd for $C_{28}H_{29}O_4N_4S$ (M^++H): 517.1910, Found: 517.1907.

4.6.5. 2-(4-(4-(4-Nitrophenylsulfonyl)piperazine-1-carbonyl) phenyl)quinazolin-4(3H)-one (**5e**)

Yellow solid, 12% (9 mg), mp 140–142 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.237 (s, 1H), 8.440 (d, J = 7.2 Hz, 2H), 8.328 (d, J = 7.6 Hz, 1H), 8.173 (d, J = 8.4 Hz, 2H), 7.973 (d, J = 6.8 Hz, 2H), 7.835 (d, J = 3.8 Hz, 2H), 7.561 (t, J = 7.3 Hz, 1H), 7.545 (d, J = 8.4 Hz, 2H), 3.931–3.012 (m, 8H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.45, 163.51 (2C, carbonyl), 150.52 (1C, quinazoline), 150.44, 149.18, 141.65, 137.48, 137.48, 135.19, 128.90(two overlapping signals), 128.19, 127.88(two overlapping signals), 127.71(two overlapping signals), 127.39, 126.45, 124.64(two overlapping signals), 120.94 (18C, aromatic). IR(film) 3062, 2923, 2854, 1668, 1598, 1436, 1283, 1144, 1116, 943, 855, 968, 741, 708 cm^{-1}. HR-FABMS Calcd for $C_{25}H_{22}O_6N_5S$ (M^++H): 520.1291, Found: 520.1294.

4.6.6. 2-(4-(4-(4-Chlorophenylsulfonyl)piperazine-1-carbonyl) phenyl)quinazolin-4(3H)-one (**5f**)

Pale brown solid, 43% (32 mg), mp 273–275 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.277 (s, 1H), 8.334 (d, J = 8.0 Hz, 1H), 8.175 (d, J = 6.6 Hz, 2H), 7.838 (d, J = 4.4 Hz, 2H), 7.721 (d, J = 9.6 Hz, 2H), 7.574–7.520 (m, 5H), 3.910–2.886 (m, 8H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.38, 162.17 (2C, carbonyl), 151.66, (1C, quinazoline), 148.56, 138.37, 137.92, 134.63(two overlapping signals), 134.03, 133.69, 129.69(two overlapping signals), 129.43(two overlapping signals), 127.84(two overlapping signals), 127.51, 127.25(two overlapping signals), 127.09, 126.79, 125.85, 121.04, (18C, aromatic), 45.56, (4C, piperazine) IR(film) 3063, 2824, 2854, 1679, 1599, 1468, 1433, 1348, 1285, 1163,1091, 1010, 942, 762 cm^{-1}. HR-FABMS Calcd for $C_{25}H_{22}O_4N_4ClS$ (M^++H): 509.1050, Found: 509.1053.

4.6.7. 2-(4-(4-(4-Fluorophenylsulfonyl)piperazine-1-carbonyl) phenyl)quinazolin-4(3H)-one (**5g**)

Pale brown solid, 29% (21 mg), mp 217–220 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.621 (s, 1H), 8.329 (d, J = 8.0 Hz, 1H), 8.213 (d, J = 8.0 Hz, 2H), 7.841 (d, J = 4.4 Hz, 2H), 7.805 (d, J = 8.8 Hz, 2H), 7.561 (t, J = 8.2 Hz, 1H), 7.553 (d, J = 7.6 Hz, 2H), 7.284 (d, J = 4.2 Hz, 1H), 7.260 (d, J = 6.4 Hz, 1H), 3.904–2.957 (m, 8H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.43, 169.32,(2C, carbonyl), 163.54 (1C, quinazoline), 166.77, 164.25, 150.51, 149.23, 137.69, 136.62, 135.15, 134.50, 131.61, 130.50, 130.40, 128.18, 127.84, 127.73, 127.44, 127.33, 126.43, 120.62, 116.82, 116.60 (18C, aromatic), 47.07, 46.74, 46.07 (4C, piperazine), IR(film) 3065, 2921, 1662, 1631, 1595, 1431, 1283, 1171, 1155, 1008, 939, 765, 727 cm^{-1}. HR-FABMS Calcd for $C_{25}H_{22}O_4N_4FS$ (M^++H): 493.1346, Found: 493.1344.

4.6.8. 2-(4-(4-(4-(Trifluoromethyl)phenylsulfonyl)piperazine-1-carbonyl)phenyl)quinazolin-4(3H)-one (**5h**)

White solid, 33% (27 mg), mp 276–278 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.728 (s, 1H), 8.328 (d, J = 8.0 Hz, 1H), 8.221 (d, J = 6.6 Hz, 2H), 7.915–7.827 (m, 6H), 7.557–7.516 (m, 3H), 3.919–3.064 (m, 8H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.46, 163.63 (2C, carbonyl), 150.50 (1C, quinazoline), 149.22, 139.29, 137.54, 135.17(two overlapping signals), 134.55, 133.61, 128.21(two overlapping signals), 127.85(two overlapping signals), 127.77(two overlapping signals), 127.34, 126.56(two overlapping signals), 126.41(two overlapping signals), 124.21(18C, aromatic), 121.16(1C, CF_3), 46.01 (4C, piperazine). HR-FABMS Calcd for $C_{26}H_{22}O_4N_4F_3S$ (M^++H): 543.1314, Found: 543.1314.

4.6.9. 2-(4-(4-(3-(Trifluoromethyl)phenylsulfonyl)piperazine-1-carbonyl)phenyl)quinazolin-4(3H)-one (**5i**)

White solid, 30% (24 mg), mp 264–266 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.520 (s, 1H), 8.329 (d, J = 8.0 Hz, 1H), 8.203 (d, J = 6.6 Hz, 2H), 8.024 (s, 1H), 7.974–7.919 (m, 2H), 7.836 (d, J = 3.8 Hz, 2H), 7.770 (t, J = 8.0 Hz, 1H), 7.559–7.518 (m, 3H), 3.916–3.127 (m, 8H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 168.38, 162.16 (2C, carbonyl), 151.61 (1C, quinazoline), 148.58, 137.90, 136.67, 136.64, 133.69, 131.62, 131.27, 130.31, 130.16, 129.98, 127.84(two overlapping signals), 127.56, 126.27(two overlapping signals), 126.80, 125.84, 123.85 (18C, aromatic), 121.06(1C, $-CF_3$), 46.37, 45.52 (4C, piperazine). HR-FABMS Calcd for $C_{26}H_{22}O_4N_4F_3S$ (M^++H): 543.1314, Found: 543.1316.

*4.6.10. 2-(4-(4-(2-(Trifluoromethyl)phenylsulfonyl)piperazine-1-carbonyl)phenyl) quinazolin-4(3H)-one (**5j**)*

Pale brown solid, 15% (12 mg), mp 269–271 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.658 (s, 1H), 8.336 (d, J = 8.0 Hz, 1H), 8.231 (d, J = 8.4 Hz, 2H), 8.176–8.153 (m, 1H), 7.947–7.914 (m, 1H), 7.839–7.826 (m, 2H), 7.771–7.726 (m, 2H), 7.591 (d, J = 8.4 Hz, 2H), 7.561–7.534 (m, 1H), 3.870–3.317 (m, 8H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.57, 163.75 (2C, carbonyl), 150.63 (1C, quinazoline), 149.28, 137.82, 137.15, 135.14, 134.48, 133.17, 133.17, 132.38, 132.25, 128.85, 128.78, 128.37, 128.17, 128.04, 127.80, 127.46, 127.30, 126.43 (18C, aromatic), 120.95 (1C, CF_3), 45.58, (4C, piperazine). IR (film) 3062, 2923, 1662, 1622, 1599, 1435, 1283, 1144, 1118, 1007, 942, 856, 766 cm^{-1}. HR-FABMS Calcd for $C_{26}H_{22}O_4N_4F_3S$ (M^++H): 513.1314, Found: 543.1318.

*4.6.11. 2-(4-(4-(Benzylsulfonyl)piperazine-1-carbonyl)phenyl) quinazolin-4(3H)-one (**5k**)*

Pale brown solid, 27% (20 mg), mp 177–178 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.326 (s, 1H), 8.340 (d, J = 7.6 Hz, 1H), 8.191 (d, J = 7.6 Hz, 2H), 7.842 (d, J = 4.6 Hz, 2H), 7.566 (t, J = 8.2 Hz, 1H), 7.557 (d, J = 7.4 Hz, 2H), 7.463–7.411 (m, 5H), 4.269 (s, 2H), 3.769–3.045 (m, 8H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.44, 163.18 (2C, carbonyl), 150.41(1C, quinazoline), 149.17, 137.97, 135.15, 134.39, 130.66, 129.14, 128.97(two overlapping signals), 128.44(two overlapping signals), 128.17, 127.82(two overlapping signals), 127.59(two overlapping signals), 127.36, 126.49, 121.01 (18C, aromatic), 57.72 (1C, -N–CH_2–Ph), 45.93 (4C, piperazine). IR (film) 3062, 2923, 1669, 1597, 1438, 1144,942, 765, 707 cm^{-1}. HR-FABMS Calcd for $C_{26}H_{25}O_4N_4S$ (M^++H): 489.1597, Found: 489.1594.

*4.6.12. 2-(4-(4-(4-Methylbenzylsulfonyl)piperazine-1-carbonyl) phenyl)quinazolin-4(3H)-one (**5l**)*

Pale yellow solid,13% (10 mg), mp 190–193 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.058 (s, 1H), 8.341 (d, J = 7.8 Hz, 1H), 8.160 (d, J = 8.4 Hz, 2H), 7.841 (d, J = 4.4 Hz, 2H), 7.565–7.520 (m, 3H), 7.293–7.174 (m, 4H), 4.227 (s, 2H), 3.768–3.030 (m, 8H), 2.385 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.49, 163.59 (2C, carbonyl), 150.57, (1C, quinazoline), 149.24, 139.14, 137.95, 135.15, 134.40, 130.51(two overlapping signals), 129.66(two overlapping signals), 128.16, 127.77, 127.74(two overlapping signals), 127.33, 126.45, 125.28, 122.99, 120.94, (18C, aromatic), 57.37 (1C, SO_2-CH_2- **),** 46.13 (4C, piperazine), 21.28 (1C, $-CH_3$). HR-FABMS Calcd for $C_{27}H_{27}O_4N_4S$ (M^++H): 503.1753, Found: 503.1756.

*4.6.13. 2-(4-(4-(4-Chlorobenzylsulfonyl)piperazine-1-carbonyl) phenyl)quinazolin-4(3H)-one (**5m**)*

Pale yellow solid, 17% (13 mg), mp 210–214 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.881 (s, 1H), 8.342 (d, J = 8.0 Hz, 1H), 8.258 (d, J = 8.4 Hz, 2H), 7.846 (d, J = 3.6 Hz, 2H), 7.582–7.530 (m, 3H), 7.406–7.332 (m, 4H), 4.213 (s, 2H), 3.794–3.079 (m, 8H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.54, 163.53, (2C, carbonyl), 150.52(1C, quinazoline), 149.22, 138.88, 1387.79, 135.35, 135.16, 134.49, 131.93(two overlapping signals), 129.24(two overlapping signals), 127.80(two overlapping signals), 127.35(two overlapping signals), 126.90, 126.45, 120.96, 95.01, (18C, aromatic), 56.94(1C, SO_2-CH_2-)**.** HR-FABMS Calcd for $C_{26}H_{24}O_4N_4ClS$ (M^++H): 523.1207, Found: 523.1211.

*4.6.14. 2-(4-(4-(Naphthalen-1-ylsulfonyl)piperazine-1-carbonyl) phenyl)quinazolin-4(3H)-one (**5n**)*

White solid, 23% (18 mg), mp 257–260 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.840 (s, 1H), 8.741 (d, J = 8.8 Hz, 1H), 8.312 (d, J = 8.0 Hz, 1H), 8.243 (d, J = 7.4 Hz, 1H), 8.206 (d, J = 8.4 Hz, 2H), 8.138 (t, J = 7.2 Hz, 1H), 7.984 (t, J = 7.0 Hz, 1H), 7.844 (d, J = 6.8 Hz, 2H), 7.696 (t, J = 7.7 Hz, 1H), 7.648 (t, J = 7.2 Hz, 1H), 7.602 (t, J = 6.5 Hz, 1H), 7.549 (t, J = 4.0 Hz, 1H), 7.521 (d, J = 9.6 Hz, 2H), 3.839–3.178 (m, 8H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.39, 163.48 (2C, carbonyl) 150.52 (1C, quinazoline), 149.20, 137.81, 136.61, 135.12, 134.99, 134.46, 134.38, 132.10, 130.89, 129.14, 128.88, 128.42, 128.15, 127.81, 127.66, 127.36, 127.31, 127.11, 126.45, 124.86, 124.23, 120.95 (22C, aromatic), 45.60 (4C, piperazine). IR (film) 3074, 2921, 2854, 1664, 1632, 1438, 1284, 1161, 1131, 932, 767 cm^{-1}. HR-FABMS Calcd for $C_{29}H_{25}O_4N_4S$ (M^++H): 525.1597, Found: 525.1594.

*4.6.15. 2-(4-(4-(Naphthalen-2-ylsulfonyl)piperazine-1-carbonyl) phenyl)quinazolin-4(3H)-one (**5o**)*

Pale pink solid, 29% (23 mg), mp 217–220 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.967 (s, 1H), 8.346 (s, 1H), 8.303 (d, J = 8.0 Hz, 1H), 8.209 (d, J = 8.0 Hz, 2H), 8.031 (t, J = 8.0 Hz, 2H), 7.973 (d, J = 7.6 Hz, 1H), 7.824 (d, J = 3.6 Hz, 2H), 7.758 (d, J = 8.6 Hz, 1H), 7.725 (t, J = 7.5 Hz, 1H), 7.679 (t, J = 7.5Hz, 1H), 7.531–7.490 (m, 3H), 3.912–3.074 (m, 8H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.39, 163.64, (2C, carbonyl) 150.57 (1C, quinazoline), 149.23, 137.72, 135.10, 134.41, 132.55, 132.26, 129.60, 129.32, 129.23, 129.20, 128.14, 128.03, 127.87(two overlapping signals), 127.81(two overlapping signals), 127.72(two overlapping signals), 127.28, 126.41, 122.74, 120.92 (22C, aromatic), 46.09 (4C, piperazine). IR(film) 2924, 2854, 1658, 1622, 1460, 1434, 1283, 1158, 1011, 943, 855, 762, 717 cm^{-1}. HR-FABMS Calcd for $C_{29}H_{25}O_4N_4S$ (M^++H): 525.1597, Found: 525.1599.

*4.6.16. 2-(4-(4-(Quinolin-8-ylsulfonyl)piperazine-1-carbonyl) phenyl)quinazolin-4(3H)-one (**5p**)*

White solid, 21% (17 mg), mp 274–276 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.583 (s, 1H), 9.069 (d, J = 4.4 Hz, 1H), 8.515 (d, J = 7.4 Hz, 1H), 8.326 (d, J = 7.6 Hz, 1H), 8.287 (d, J = 8.4 Hz, 1H), 8.192 (d, J = 8.4 Hz, 2H), 8.086 (d, J = 8.4 Hz, 1H), 7.833 (d, J = 4.0 Hz, 2H), 7.669 (t, J = 7.8 Hz, 1H), 7.581–7.527 (m, 4H), 3.881–3.492 (m, 8H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.47, 163.50 (2C, carbonyl), 151.30 (1C, quinazoline), 150.61, 149.23, 144.10, 138.15, 136.59, 135.61, 135.12, 134.27, 133.82, 133.28(two overlapping signals), 129.09, 128.54, 128.14, 127.81(two overlapping signals), 127.66(two overlapping signals), 127.29, 126.45, 125.63, 122.25, 120.95 (23C, aromatic). HR-FABMS Calcd for $C_{28}H_{24}O_4N_5S$ (M^++H): 526.1549, Found: 526.1552.

*4.6.17. 2-(4-(4-(Thiophen-2-ylsulfonyl)piperazine-1-carbonyl) phenyl)quinazolin-4(3H)-one (**5q**)*

Pale brown solid, 15% (22 mg), mp 194–197 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.198 (s, 1H), 8.330 (d, J = 7.6 Hz, 1H), 8.279 (d, J = 8.8 Hz, 2H), 7.842 (d, J = 4.6 Hz, 2H), 7.693 (d, J = 5.2 Hz, 1H), 7.572–7.545(m, 4H), 7.208(t, J = 4.4 Hz, 1H), 3.949–3.803(m, 8H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.49, 169.33 (2C, carbonyl), 163.82 (1C, quinazoline), 150.65, 149.28, 137.67, 135.64, 135.13, 134.50, 132.91, 132.76, 128.16, 127.95, 127.85, 127.80, 127.46, 127.28, 126.40, 120.92, (16C, aromatic), 46.03 (4C, piperazine). IR (film) 3074, 2923, 2854, 1659, 1624, 1432, 1350, 1283, 1156, 1008, 939, 726 cm^{-1}. HR-FABMS Calcd for $C_{23}H_{21}O_4N_4S_2$ (M^++H): 481.1004, Found: 481.1005.

*4.6.18. 2-(4-(4-(Methylsulfonyl)piperazine-1-carbonyl)phenyl) quinazolin-4(3H)-one (**5r**)*

Pale brown solid, 11% (7 mg), mp 221–223 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.567 (s, 1H), 8.349 (d, J = 7.2 Hz, 1H), 8.247 (d,

J = 8.0 Hz, 2H), 7.849–7.833 (m, 2H), 7.645 (d, J = 7.8 Hz, 2H), 7.570–7.519 (m, 1H), 3.935–3.285 (m, 8H), 2.838 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.53, 163.23 (2C, carbonyl), 150.34 (1C, quinazoline), 149.17, 137.85, 135.16, 134.53, 127.93 (two overlapping signals), 127.67 (two overlapping signals), 127.40, 126.50, 121.01 (12C, aromatic), 46.18 (4C, piperazine), 35.95(1C, $-SO_2-CH_3$). IR (film) 3017, 2924, 1737, 1660, 1623, 1434, 1342, 1283, 1159, 941, 767 cm^{-1}. HR-FABMS Calcd for $C_{20}H_{21}O_4N_4S$ (M^++H): 413.1284, Found: 413.1279.

4.6.19. 2-(4-(4-(Isopropylsulfonyl)piperazine-1-carbonyl)phenyl) quinazolin-4(3H)-one (**5s**)

Pale brown solid, 10% (7 mg), mp: 168–172C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.323 (s, 1H), 8.347 (d, J = 8.4 Hz, 1H), 8.211 (d, J = 7.2 Hz, 2H), 7.844–7.828 (m, 2H), 7.620 (d, J = 8.4 Hz, 2H), 7.565–7.538 (m, 1H), 3.870–3.484 (m, 8H), 3.248–3.180 (m, 1H), 1.377 (d, J = 6.8 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.54, 163.25 (2C, carbonyl), 150.46 (1C, quinazoline), 149.19, 138.06, 135.14, 134.41, 128.18, 127.89(two overlapping signals), 127.69, 127.64, 127.36, 126.50, 121.00 (12C, aromatic), 53.73 (1C, $-SO_2$-C-), 46.39 (4C, piperazine), 16.74 (2C, CH_3 x2). HR-FABMS Calcd for $C_{22}H_{25}O_4N_4S$ (M^++H): 441.1597, Found: 441.1599.

4.6.20. 2-(4-(4-(Butylsulfonyl)piperazine-1-carbonyl)phenyl) quinazolin-4(3H)-one (**5t**)

Pale brown solid, 19% (13 mg), mp 220–222 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.145 (s, 1H), 8.348 (d, J = 8.0 Hz, 1H), 8.299 (d, J = 8.0 Hz, 2H), 7.851–7.836 (m, 2H), 7.637 (d, J = 8.4 Hz, 2H), 7.571–7.530 (m, 1H), 3.914–3.316 (m, 8H), 2.963 (t, J = 8.0 Hz, 2H), 1.850–1.773 (m, 2H), 1.519–1.426 (m, 2H), 0.987 (d, J = 7.4 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.65, 163.92 (2C, carbonyl), 150.72 (1C, quinazoline), 149.30, 137.86, 135.15, 134.52, 128.17, 127.93(two overlapping signals), 127.81(two overlapping signals), 127.30, 126.42, 120.93 (12C, aromatic), 49.64, (1C, SO_2-C-), 45.81 (4C, piperazine), 25.03, 21.72, 13.58 (3C, -C-C-C). HR-FABMS Calcd for $C_{23}H_{27}O_4N_4S$ (M^++H): 455.1753, Found: 455.1756.

4.6.21. 2-(4-(4-(Cyclopropylsulfonyl)piperazine-1-carbonyl)phenyl) quinazolin-4(3H)-one (**5u**)

Pale brown solid, 15% (10 mg), mp 247–249 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.443 (s, 1H), 8.349 (d, J = 8.0 Hz, 1H), 8.233 (d, J = 8.0 Hz, 2H), 7.847–7.831 (m, 2H), 7.641 (d, J = 7.4 Hz, 2H), 7.568–7.528 (m, 1H), 3.927–3.307 (m, 8H), 2.313–2.249 (m, 1H), 1.226–1.186 (m, 2H), 1.066–1.013 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.61, 163.81 (2C, carbonyl), 150.66 (1C, quinazoline), 149.28, 137.85, 135.16, 134.51, 128.17, 127.88 (two overlapping signals), 127.32 (two overlapping signals), 127.32, 126.42, 120.93 (12C, aromatic), 46.11 (4C, piperazine), 25.85 (**1C**, $-SO_2$-cyclopropyl), 4.50 (2C, cyclopropyl). HR-FABMS Calcd for $C_{22}H_{23}O_4N_4S$ (M^++H): 439.1440, Found: 439.1436.

4.6.22. 2-(4-(4-(Cyclopentylsulfonyl)piperazine-1-carbonyl) phenyl)quinazolin-4(3H)-one (**5v**)

Pale brown solid, 10% (7 mg), mp 140–142 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.735 (s, 1H), 8.347 (d, J = 8.0 Hz, 1H), 8.255 (d, J = 7.2 Hz, 2H), 7.847 (d, J = 4.4 Hz, 2H), 7.630 (d, J = 8.4 Hz, 2H), 7.581–7.520 (m, 1H), 3.889–3.342 (m, 8H), 3.499–3.427 (m, 1H), 2.045–1.983 (m, 4H), 1.858–1.773 (m, 2H), 1.690–1.615 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.56, 163.48(2C, carbonyl), 150.56(1C, quinazoline), 149.23, 138.00, 135.15, 134.44, 128.17, 127.87(two overlapping signals), 127.74(two overlapping signals), 127.34, 126.47, 120.98, (12C, aromatic), 46.20 (4C, piperazine), 60.71(1C, $-SO_2$-C-), 28.05, 25.63, (4C, -cyclopentyl). HR-FABMS Calcd for $C_{24}H_{27}O_4N_4S$ (M^++H): 467.1753, Found: 467.1756.

4.7. General procedure for preparation of 3-R_2-2-(4-(4-(R_1-phenylsulfonyl)piperazine-1-carbonyl)phenyl) quinazol-in-4(3H)-one (**6a-f**)

K_2CO_3 (23 mg, 0.17 mmol) was added to a solution of 2-(4-(4-R_1-sulfonyl)piperazine-1-carbonyl)phenyl)quinazolin-4(3H)-one (**5a** or **5b**) (40 mg, 0.08 mmol) in DMF (10 mL). Iodomethane or benzyl bromide (0.08 mmol) was added slowly to the reaction mixture. And then the mixture was stirred at 100 °C for 16 h. After cooling, the reaction mixture was extracted with ethyl acetate and the organic phase was washed with brine. The organic phase was dried over $MgSO_4$ and evaporated *in vacuo*.

4.7.1. 3-Methyl-2-(4-(4-(phenylsulfonyl)piperazine-1-carbonyl) phenyl)quinazolin-4(3H)-one (**6a**)

White solid, 39% (16 mg), mp 196–199 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.633 (d, J = 8.4 Hz, 2H), 8.185 (d, J = 8.2 Hz, 1H), 7.995 (d, J = 8.6 Hz, 1H), 7.856 (t, J = 7.6 Hz, 1H), 7.776 (d, J = 6.8 Hz, 2H), 7.680 (t, J = 7.5 Hz, 1H), 7.600–7.524 (m, 3H), 7.473 (d, J = 8.2 Hz, 2H), 4.287 (s, 3H), 3.892–3.982 (m, 8H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.30, 167.24, (2C, carbonyl), 158.92, (1C, quinazoline), 151.71, 139.98, 136.38, 135.45, 133.69, 133.28, 129.33, 128.67(two overlapping signals), 128.04, 127.73(two overlapping signals), 127.63, 127.25(two overlapping signals), 126.88, 123.53, 115.45 (**18C,** aromatic), 46.13 (4C, piperazine), 22.70 (1C, $-CH_3$**).** HR-FABMS Calcd for $C_{26}H_{25}N_4O_4S$ (M^++H): 489.1597, Found: 489.1601.

4.7.2. 3-Benzyl-2-(4-(4-(phenylsulfonyl)piperazine-1-carbonyl) phenyl)quinazolin-4(3H)-one (**6b**)

White solid, 70% (33 mg), mp 153–156 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.626 (d, J = 8.2 Hz, 2H), 8.239 (d, J = 8.4 Hz, 1H), 8.000 (d, J = 8.2 Hz, 1H), 7.864 (t, J = 7.6 Hz, 1H), 7.780 (d, J = 6.8 Hz, 2H), 7.684 (d, J = 7.5 Hz, 1H), 7.603–7.519 (m, 5H), 7.482 (d, J = 8.4 Hz, 2H), 7.447–7.365 (m, 3H), 5.768 (s, 2H), 3.884–3.018 (m, 8H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.27, 166.67 (2C, carbonyl), 158.87, (1C, quinazoline), 151.88, 139.95, 136.42, 136.32, 135.47, 133.79, 133.26, 129.33, 128.66, 128.63, 128.33, 128.20, 128.05, 127.72, 127.27, 126.91, 123.64, 115.46, (18C**,** aromatic), 68.54 (1C, $-CH_2$-Ph), 46.11 (4C, piperazine). IR(film) 3058, 2924, 2851, 1627, 15741498, 1419, 1351, 1286, 1109, 735 cm^{-1}. HR-FABMS Calcd for $C_{32}H_{29}N_4O_4S$ (M^++H): 565.1910, Found: 565.1912.

4.7.3. 3-Methyl-2-(4-(4-(4-methoxyphenylsulfonyl)piperazine-1-carbonyl)phenyl)quinazolin-4(3H)-one (**6d**)

White solid, 29% (12 mg), mp 153–156 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.631 (d, J = 8.4 Hz, 2H), 8.186 (d, J = 8.0 Hz, 1H), 7.995 (d, J = 8.4 Hz, 1H), 7.858 (t, J = 7.7 Hz, 1H), 7.705 (d, J = 7.0 Hz, 2H), 7.567 (t, J = 7.6 Hz, 1H), 7.475 (d, J = 7.6 Hz, 2H), 7.040 (d, J = 6.8 Hz, 2H), 4.290 (s, 3H), 3.904 (s, 3H), 3.861–2.983 (m, 8H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.26, 167.23, (2C, carbonyl), 163.37, (1C, quinazoline), 158.92, 151.69, 139.94, 136.44, 133.68, 129.89, 129.80, 128.65(two overlapping signals), 128.02, 127.24(two overlapping signals), 126.86, 123.53, 115.44, 114.48(two overlapping signals), 114.16, (18C**,** aromatic), 55.69,(1C, $-OCH_3$), 46.10, 45.43 (4C, piperazine), 30.92(1C, -N-CH3**).** HR-FABMS Calcd for $C_{27}H_{27}N_4O_5S$ (M^++H): 519.1702, Found: 519.1705.

4.7.4. 3-Benzyl-2-(4-(4-(4-methoxyphenylsulfonyl)piperazine-1-carbonyl)phenyl)quinazolin-4(3H)-one (**6e**)

White solid, 63% (30 mg), mp 153–156 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.629 (d, J = 8.4 Hz, 2H), 8.239 (d, J = 8.0 Hz, 1H), 8.001 (d, J = 7.8 Hz, 1H), 7.864 (t, J = 7.7 Hz, 1H), 7.716–7.678 (m, 2H), 7.584 (t, J = 8.0 Hz, 2H), 7.488 (d, J = 8.4 Hz, 2H), 7.448–7.345 (m, 4H), 7.043 (d, J = 7.8 Hz, 2H), 5.770 (s, 2H), 3.906 (s, 3H), 3.864–2.974 (m, 8H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.24, 166.66, (2C, carbonyl), 163.37,

(1C, quinazoline), 158.87, 151.87, 139.92, 136.46, 136.31, 133.78, 129.89, 128.66(two overlapping signals), 128.41, 128.33, 128.20, 128.04, 127.57, 127.38, 127.27, 126.90, 126.85, 126.70, 123.63, 115.45, 114.48(two overlapping signals), 114.16, (24C, aromatic), 68.53 (1C, -N–CH_2–Ph), 55.69 (1C, –OCH_3), 46.01 (4C, piperazine). IR (film) 2926, 2854, 1573, 1495, 1160, 730 cm^{-1}. HR-FABMS Calcd for $C_{33}H_{31}N_4O_5S$ (M^++H): 595.2015, Found: 595.2015.

4.8. General Procedure for preparation of tert-butyl 4-(4-(3-substituted-4-oxo-3,4-dihydroquinazolin-2-yl)benzoyl) piperazine-1-carboxylate (**7a-b**)

K_2CO_3 (41 mg, 0.3 mmol) was added to a solution of *tert*-Butyl 4-(4-(4-oxo-3,4-dihydroquinazolin-2-yl)benzoyl)piperazine-1-carboxylate (**3**) (65 mg, 0.15 mmol) in DMF (10 mL). Iodomethane or benzyl bromide (0.08 mmol) was added slowly to the reaction mixture. The mixture was then stirred at 100 °C for 16 h. After cooling, the reaction mixture was extracted with ethyl acetate and the organic phase was washed with brine. The organic phase was dried over $MgSO_4$ and evaporated *in vacuo*. The residue was washed with ethyl acetate/hexane (1: 10) and purified by column chromatography (ethyl acetate) to provide *tert*-Butyl 4-(4-(3-substituted-4-oxo-3,4-dihydroquinazolin-2-yl)benzoyl) piperazine-1-carboxylate.

4.8.1. tert-Butyl 4-(4-(3-methyl-4-oxo-3,4-dihydroquinazolin-2-yl) benzoyl)piperazine-1-carboxylate (**7a**)

White solid, 39% (16 mg), mp 175–177 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.671 (d, J = 8.4 Hz, 2H), 8.194 (d, J = 8.0 Hz, 1H), 8.011 (d, J = 8.4 Hz, 1H), 7.862 (t, J = 7.8 Hz, 1H), 7.568–7.519 (m, 3H), 4.306 (s, 3H), 3.774–3.436 (m, 8H), 1.479 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.43, 167.17, (2C, carbonyl), 159.01, (1C, quinazoline), 154.56, 151.69, 139.67, 137.07, 133.61, 128.63(two overlapping signals), 128.00, 127.17(two overlapping signals), 126.76, 123.48, 115.39 (12C**,** aromatic), 80.35(1C, -O-C-), 54.15,(1C, -N-CH_3), 43.65 (4C, piperazine), 28.36 (3C, –CH_3 x3 **).** IR(film) 2927, 2863, 1684, 1624, 1575, 1424, 1375, 1244, 1159, 1119, 1010, 971, 860, 761 cm^{-1}. HR-FABMS Calcd for $C_{25}H_{29}N_4O_4$ (M^++H): 449.2189, Found: 449.2186.

4.8.2. tert-Butyl 4-(4-(3-benzyl-4-oxo-3,4-dihydroquinazolin-2-yl) benzoyl) piperazine-1-carboxylate (**7b**)

White solid, 70% (33 mg), mp 162–163 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.663 (d, J = 8.4 Hz, 2H), 8.242 (d, J = 8.0 Hz, 1H), 8.016 (d, J = 8.4 Hz, 1H), 7.866 (t, J = 7.7 Hz, 1H), 7.595 (d, J = 7.8 Hz, 2H), 7.564 (t, J = 8.0 Hz, 3H), 7.452–7.355 (m, 3H), 5.786 (s, 2H), 3.772–3.450 (m, 8H), 1.480 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.43, 166.63 (2C, carbonyl), 158.99, (1C, quinazoline), 154.57, 151.90, 139.67, 137.12, 136.34, 133.74, 129.96, 128.67(two overlapping signals), 128.64, 128.30, 128.21, 128.04, 127.22(two overlapping signals), 126.82, 123.61, 115.44, (18C, aromatic), 80.37, (1C, -O-C-), 68.53, (1C, –CH_2-Ph), 43.73 (4C, piperazine), 28.37 (3C, –CH_3 **x3).** IR (film) 2970, 2925, 2860, 1574, 1626, 1574, 1422, 1245, 1183, 1007, 764 cm^{-1}. HR-FABMS Calcd for $C_{31}H_{33}N_4O_4$ (M^++H): 525.2502, Found: 525.2498.

4.9. Cytotoxicity assay

For the evaluation of cytotoxicity, five different cancer cell lines were used: HeLa; human cervix cancer cell line, HCT-29; human colon cancer cell line, DU145; human prostate cancer cell line, MDA-MB231; human breast cancer cell line, HL-60; human myeloid leukemic tumor cell line. Experiments were performed by methods previously described [33]. Cancer cells were cultured according to the supplier's instructions. Cells were seeded in 96-well plates at a density of 2–4 $\times 10^4$ cells per well and incubated overnight in 0.1 mL of media supplemented with 10% Fetal Bovine Serum (Hyclone, USA) in a 5% CO_2 incubator at 37 °C. On day 2, culture medium in each well was exchanged with 0.1 mL aliquots of medium containing graded concentrations of compounds. On day 4, 5 μL of the cell counting kit-8 solution (Dojindo, Japan) was added to each well and then incubated for additional 4 h under the same conditions. The absorbance of each well was determined by an Automatic Elisa Reader System (Bio-Rad 3550) at a 450 nm wavelength. For determination of the IC_{50} values, the absorbance readings at 450 nm were fitted to the four-parameter logistic equation. Adriamycin was purchased from Sigma and used as a positive control.

4.10. Cell cycle analysis

For cell cycle analysis, cells were fixed in 80% ethanol at 4 °C for at least 18 h. Next, the fixed cells were washed once with PBS-EDTA and then resuspended in 1 mL of PBS. After the addition of 10 μL each of propidium iodide (5 mg/mL) and RNase (10 mg/mL), the samples were incubated for 30min at 37 °C and then analyzed using a FACScan flow cytometer.

Acknowledgments

This work was supported by a grant (314-2008-1-E00306) from Korea Research Foundation.

References

[1] E. Pomarnacka, M. Maruszak, K. Langowska, P. Reszka, P.J. Bednarski, Arch. Pharm. 341 (2008) 485–490 (Weinheim).
[2] A.R. Khosropour, I. Mohammadpoor-Baltork, H. Ghorbankhani, Tetrahedron Lett. 47 (2006) 3561–3564.
[3] G. Grover, S.G. Kini, Eur. J. Med. Chem. 41 (2006) 256–262.
[4] A.K. Tiwari, A.K. Mishra, A. Bajpai, P. Mishra, R.K. Sharma, V.K. Pandey, V.K. Singh, Bioorg. Med. Chem. Lett. 16 (2006) 4581–4585.
[5] T.M. Abdel-Rahman, J. Heterocyclic Chem 43 (2006) 527–534.
[6] R. Suauki, H. Ishitani, Tetrahedron Lett. 40 (1999) 2175–2178.
[7] A. Kumar, S. Sharma, Archana,K. Bajaj, H. Panwar, T. Singh, V.K. Srivastava, Bioorg. Med.Chem. 11 (2003) 5293–5299.
[8] A. Mannschreck, H. Koller, G. Stunier, M.A. Davies, J. Traber, Eur. J. Med. Chem. 19 (1984) 381.
[9] V. Alagarsamy, U.S. Pathak, Bioorg. Med. Chem. 15 (2007) 3457–3462.
[10] S.L. Cao, Y.P. Feng, Y.Y. Jiang, S.Y. Liu, G.Y. Ding, R.T. Li, Bioorg. Med. Chem. Lett. 15 (2005) 1915–1917.
[11] Y. Xia, Z.Y. Yang, M.J. Hour, S.C. Kuo, P. Xia, K.F. Bastow, Y. Nakanishi, P. Namrpoothiri, T. Hackl, E. Hamel, H.K. Lee, Bioorg. Med. Chem. Lett. 11 (2001) 1193–1196.
[12] M.J. Hour, L.J. Huang, S.C. Kuo, Y. Xia, K. Bastow, Y. Nakanishi, E. Hamel, K.H. Lee, J. Med. Chem. 43 (2000) 4479–4487.
[13] R.J. Griffin, S. Srinivasan, K. Bowman, A.H. Calvert, N.J. Curtin, D.R. Newell, L.C. Pemberton, B.T. Golding, J. Med. Chem. 41 (1998) 5247–5256.
[14] A. Kamal, E. Vijaya Bharathi, M. Janaki Ramaiah, D. Dastagiri, J. Surendranadha Reddy, A. Viswanath, F. Sultana, S.N. Pushpavalli, M. Pal-Bhadra, H.K. Srivastava, G. Narahari Sastry, A. Juvekar, S. Sen, S. Zingde, Bioorg. Med. Chem. 18 (2010) 526–542.
[15] J. Slawinski, Z. Brzozowski, Eur. J. Med. Chem. 41 (2006) 1180–1189.
[16] M. Pines, I. Vlodavsky, A. Nagler, S. Yarkoni, WO2003059355 (2003).
[17] M. Malumbres, M. Barbacid, Nat. Rev. Cancer 9 (2009) 153–166.
[18] S.H. Lee, C. Park, C.Y. Jin, G.Y. Kim, S.K. Moon, J.W. Hyun, W.H. Lee, B.T. Choi, T.K. Kwon, Y.H. Yoo, Y.H. Choi, Biomed. Pharmacother. 62 (2008) 723–729.
[19] A. Koff, A. Giordano, D. Desai, K. Yamashita, J.W. Harper, S. Elledge, T. Nishimoto, D.O. Morgan, B.R. Franza, J.M. Roberts, Science 257 (1992) 1689–1694.
[20] D.O. Morgan, Annu. Rev. Cell Dev. Biol. 13 (1997) 261–291.
[21] P. Kaldis, Cell Mol. Life Sci. 55 (1999) 284–296.
[22] T. Sandal, Oncologist 7 (2002) 73–81.
[23] S.J. Freemantle, X. Liu, Q. Feng, F. Galimberti, S. Blumen, D. Sekula, S. Kitareewan, K.H. Dragnev, E. Dmitrovsky, J. Cell. Biochem. 102 (2007) 869–877.
[24] Q.Y. Yu, Y. Geng, P. Sicinski, Nature 411 (2001) 1017–1021.
[25] Y.P. H-Choo, M. Kim, S.K. Lee, S.W. Kim, I.K. Chung, Bioorg. Med. Chem. 10 (2002) 517–523.

[26] J.S. Kim, H.J. Lee, M.E. Suh, H.-Y.P. Choo, S.K. Lee, E.J. Lee, C. Kim, S.W. Park, Bioorg. Med. Chem. 12 (2004) 3683–3686.
[27] H.-J. Lee, J.S. Kim, M.-E. Suh, H.J. Park, S.K. Lee, H.-K. Rhee, H.J. Kim, E.-K. Seo, C. Kim, C.-O. Lee, H.-Y.P. Choo, Eur. J. Med. Chem. 42 (2007) 168–174.
[28] J.S. Kim, H.-K. Rhee, H.J. Park, I.-K. Lee, S.K. Lee, M.-E. Suh, C.-K. Ryu, H.-Y.P. Choo, Bioorg. Med. Chem. 15 (2007) 451–457.
[29] H.-K. Rhee, H.J. Park, S.K. Lee, C.O. Lee, H.Y.P. Choo, Bioorg. Med. Chem. 15 (2007) 1651–1658.
[30] H.-K. Rhee, S.Y. Lim, M.-J. Jung, Y. Kwon, M.-H. Kim, H.-Y.P. Choo, Bioorg. Med. Chem. 17 (2009) 7537–7541.
[31] M.L. Whitfield, G. Sherlock, A.J. Saldanha, J.I. Murray, C.A. Ball, K.E. Alexander, J.C. Matese, C.M. Perou, M.M. Hurt, P.O. Brown, D. Botstein, Mol. Biol. Cell. 13 (2002) 1977–2000.
[32] M.G. Cardenas, V.C. Blank, M. Marder, L.P. Roguin, Cancer Lett. 268 (2008) 146–157.
[33] D.H. Kang, J.S. Kim, M.J. Jung, E.S. Lee, Y. Jahng, Y. Kwon, Y. Na, Bioorg. Med. Chem. Lett. 18 (2008) 1520–1524.