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Short communication

Synthesis and *in vitro* antitumor activities of novel 4-anilinoquinazoline derivatives

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ABSTRACT

A series of 6, 7-dialkoxy-4-anilinoquinazolines were designed, synthesized by substituting different heterocycles on 6-position and a variety of anilines on 4-position of the quinazoline. These novel quinazoline compounds were screened for their cytotoxic effect on epidermal growth factor receptor overexpressing skin epidermoid carcinoma cell line (A431), by using nonoverexpressing tumor cells as negative control (breast adeno carcinoma cell line MCF-7). 2-Butyl-4-chloro-1-{3-[7-methoxy-4-(3-(trifluoromethyl)phenylamino)quinazolin-6-yloxy]-propyl}-1*H*-imidazole-5-carboxaldehyde (**30**) and 2-butyl-4-chloro-1-{3-[4-(3-iodophenyl amino)-7-methoxyquinazolin-6-yloxy]propyl}-1*H*-imidazole-5-carboxaldehyde (**33**) were found to be more potent against A431 cell line (IC_{50} 3.5 and 3 μM) and their activities are comparable to gefitinib. Insilico docking experiments with human EGFR Tyrosine kinase domain (PDB id-2gs2) indicated that **33** docks at the same position as that of gefitinib involving Val702, Ala719, Ser696, and Lys721.

1. Introduction

At present, wide range of cytotoxic drugs with different mechanisms of action are used to treat human cancer, either alone or in combination. Also many compounds are in different phases of clinical trials. The main draw back of these cytotoxic drugs is, they do not discriminate between cancerous and normal cell types and are accompanied by toxic side effects that are often cumulative and dose limiting.

Growth factor signaling pathways have been a main focus of research for novel targeted anticancer agents because of their fundamental role in regulating key cellular functions including cell-proliferation, differentiation, metastasis and survival. An important mediator of growth factor signaling pathways is the epidermal growth factor receptor (EGFR).

A significant proportion of human tumors overexpresses growth factor receptor tyrosine kinase enzymes of the erbB family (which also includes erbB2 [HER2], erbB3 [HER3] and erbB4 [HER4]), and this overexpression is associated with poor prognosis of the disease [1–3]. Inhibitors of growth factor signaling through these pathways, especially erbB1 and erbB2, have been identified as potential anticancer drugs [4].

The most potent and selective EGFR-TK inhibitors reported to date are 4-anilinoquinazolines and related 4-anilinopyrido[*d*]pyrimidines [5–8]. Of several candidate compounds synthesized and tested, gefitinib (**1**) was the first EGFR-TKI to be approved by US FDA for treatment of patients with nonsmall-cell-lung cancer (NSCLC), and later erlotinib (**2**) (Fig. 1), which belongs to same class, was approved by US FDA for treating patients with NSCLC and pancreatic cancer. Therefore, the design and development of molecules that specifically inhibit the function of EGFR-TK function in cancer cells is an attractive approach for the development of new cancer therapeutic agents.

Recently it has been observed that, a subgroup of gefitinib and erlotinib treated patients with NSCLC were identified to have somatic mutations in TK domain of erbB1 mostly in exons 19 and 21, [9,10], these comprise small in-frame deletions around the ATP binding site of TK domain. However, the cells containing an activating mutation are interestingly more sensitive to erbB1 inhibition [11]. In contrast, a secondary mutation has been observed in gefitinib and erlotinib-responsive advanced NSCLC patients. This mutation resulted threonine to methionin change at position 790 in the kinase domain of erbB1 (T790M) and this unlikely mutation is reported to have resistance to gefitinib and erlotinib treatment [12].

Now focus is on developing molecules with multiple kinase inhibition, in particular erbB1 and erbB2 [13,14]. Recently Heymach has reported the synthesis of quinazoline compound ZD6474 which was a highly potent inhibitor of vascular endothelial growth factor and EGFR [15].

The main objective of the present investigation is, to make novel 6,7-disubstituted-4-anilinoquinazoline compounds by incorporating variety of anilines at 4-position of quinazoline and variety of

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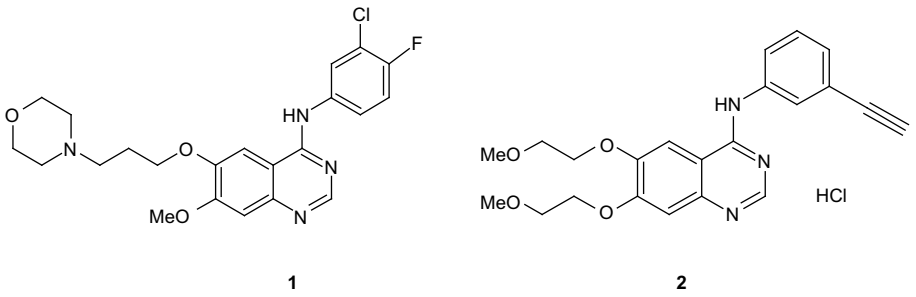


Fig. 1. Chemical structures of EGFR-TKIs.

heterocycles with different polarity at 6-position of quinazoline ring and check their anticancer activities in comparison with gefitinib. Further, these compounds may be looked into as inhibitors of other kinase enzymes.

2. Results and discussion

2.1. Chemistry

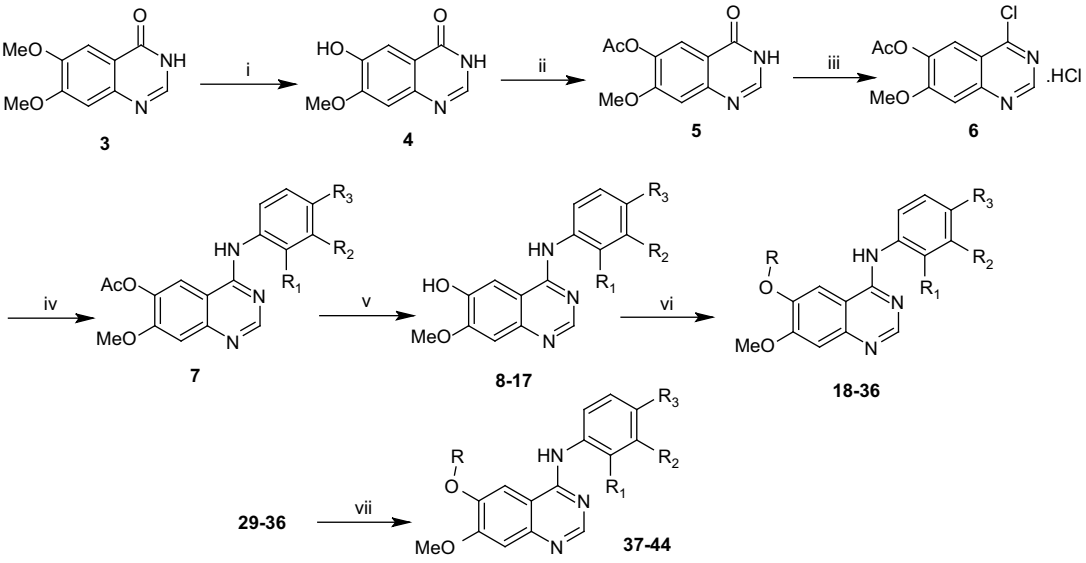
The synthesis of title compounds (**18**–**44**, Scheme 1) involves construction of a crucial basic skeleton 3,4-dimethoxy-quinazolin-4(3*H*)-one (**3**). We have prepared this compound on large scale in highly efficient way [16]. Selective demethylation of 6-methoxy group of compound **3** was done using methanesulphonic acid and L-methionine [17,18] to get demethylated product **4**, followed by O-protection using aceticanhydride to get compound **5**, which was then treated with thionyl chloride and DMF [19] to get chloro derivative **6** and then coupled with substituted anilines (Table 1) in DMF at 80 °C and quenched in ice-water to get 4-anilinoquinazoline derivatives **7** along with small amount of deacetylated product, may be due to the labile nature of acetate group in water. Without characterizing, compound **7** was deacetylated using aq. ammonia to get compounds **8**–**17**. These compounds were then alkylated with the corresponding alkyl halides (**46**–**48**) using potassium carbonate in DMF to get crude products **18**–**36**, which was further purified by using silica gel column chromatography to get pure material of title compounds **18**–**36**. The aldehyde group reduction of compounds **29**–**36** were carried out using sodium borohydride in methanol at 20 °C and the crude products isolated were recrystallized from methanol to get pure products **37**–**44**.

The side chain **46** was prepared by reacting the imidazole derivative (**45**) [20] and 1-bromo-3-chloropropane in presence of potassium carbonate (Scheme 2). Similarly, the other two side chains **47** and **48** were prepared by reacting 1-bromo-3-chloropropane and 2-mercapto benzothiozole/2-mercapto benzoxazole. The synthesized compounds were characterized by IR, ^{1}H NMR, ^{13}C NMR and mass spectroscopy.

2.2. Anticancer activity

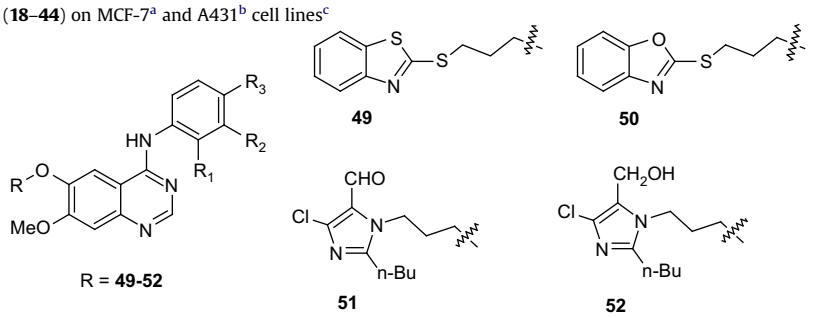
All the compounds **18**–**44** were evaluated for cytotoxic properties on EGFR overexpressing skin epidermoid carcinoma cell line (A431) with gefitinib as a standard. Inhibition of cell-proliferation was measured by MTT assay. The most potent compounds found in this assay were tested against breast adeno carcinoma cell line (negative control, MCF-7) [21]. The inhibitory potency (IC_{50}) of compounds **18**–**44** are given in Table 1. The IC_{50} values are the average of at least three independent experiments.

Previously reported work demonstrated that several anilines bearing halogens were suitable for inhibiting EGFR-TK [5]. A variety of side chains on 6-position with different anilines on 4-position of the quinazoline were synthesized (Table 1). In case of compounds



Scheme 1. Synthetic pathway of **18**–**44**, where R, R_1, R_2, and R_3, are as described in Table 1. Reagents and conditions: (i) methanesulphonic acid/L-methionine/130 °C for 30 h; (ii) aceticanhydride/pyridine/100 °C for 4 h; (iii) $SOCl_2$/DMF/reflux for 2 h; (iv) substituted aniline/DMF/80 °C for 1 h; (v) ammonia/methanol/reflux for 2 h; (vi) alkyl halide/K_2CO_3/DMF/130 °C for 2 h; (vii) $NaBH_4$/methanol/20 °C for 10 min.

Table 1
Cytotoxic effect of title compounds (**18**–**44**) on MCF-7[a] and A431[b] cell lines[c]



Compound	R	R_1	R_2	R_3	Cell based assays [IC_{50} (μM) ± SEM][d]	
					MCF-7	A431
1					12.05 ± 0.65	1.0 ± 1.00
18	**49**	H	Cl	F	NT	5.37 ± 0.34
19	**49**	H	CF_3	H	35.90 ± 2.16	4.05 ± 0.23
20	**49**	C_2H_5	H	Br	NT	5.87 ± 0.34
21	**49**	H	H	OCH_3	NT	14.17 ± 0.84
22	**49**	H	H	CH_3	NT	14.25 ± 0.79
23	**50**	H	Cl	F	36.95 ± 2.24	4.05 ± 0.25
24	**50**	H	CF_3	H	37.26 ± 2.20	4.03 ± 0.23
25	**50**	H	H	OCF_3	NT	9.08 ± 0.51
26	**50**	C_2H_5	H	Br	NT	17.25 ± 0.99
27	**50**	H	H	OCH_3	NT	13.06 ± 0.71
28	**50**	H	H	CH_3	NT	12.09 ± 0.66
29	**51**	H	Cl	F	NT	5.02 ± 0.26
30	**51**	H	CF_3	H	38.83 ± 2.23	3.51 ± 0.20
31	**51**	C_2H_5	H	Br	NT	6.56 ± 0.36
32	**51**	H	H	OCH_3	NT	13.99 ± 0.87
33	**51**	H	I	H	32.65 ± 1.84	3.00 ± 0.16
34	**51**	H	Br	H	NT	6.44 ± 0.37
35	**51**	H	F	H	NT	12.00 ± 0.73
36	**51**	H	C≡CH	H	NT	10.05 ± 0.57
37	**52**	H	Cl	F	NT	5.99 ± 0.35
38	**52**	H	CF_3	H	NT	8.28 ± 0.49
39	**52**	C_2H_5	H	Br	NT	10.57 ± 0.59
40	**52**	H	H	OCH_3	NT	20.02 ± 1.16
41	**52**	H	I	H	NT	9.95 ± 0.57
42	**52**	H	Br	H	NT	8.20 ± 0.45
43	**52**	H	F	H	NT	17.69 ± 0.99
44	**52**	H	C≡CH	H	NT	10.03 ± 0.58

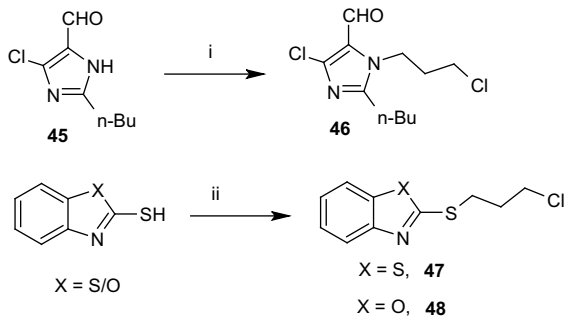
[a] Breast adeno carcinoma cell line.
[b] Skin epidermoid carcinoma cell line.
[c] Determined by MTT assay; NT, not tested.
[d] Mean of three independent experiments ± mean standard error.

bearing alkyl-thiobenzothiazole side chain (**18**–**22**) at 6-position of quinazoline ring and electron withdrawing groups on aniline (**19**, $IC_{50} = 4.05$ μM) substituted at 4-position of quinazolone skeleton were found to be more potent. The electron donating groups on aniline ring was observed to be less potent (**21**, $IC_{50} = 14.17$ μM). Similarly, when alkyl-thiobenzothiazole side chain was replaced with alkylthiobenzoxazole (**23**–**28**), we observed similar effect as discussed above.

In case of compounds bearing substituted imidazole side chain (**29**–**36**) exhibited good inhibitory properties. Compounds **30** and **33** were found to be most potent and showed IC_{50} values 3.51 and 3.00 μM, respectively. When the aldehyde group on imidazole ring of compounds **29**–**36** was reduced to alcohol, we found decrease in inhibitory activity (**37**–**44**). For example, compound **38** was 2.3-fold less potent than **30**. Similarly, between compounds **33** and **41**, 3.3-fold loss of activity was observed.

Furthermore, we have screened most potent compounds (**19**, **23**, **24**, **30**, **33**) on EGFR nonoverexpressing tumor cells (MCF-7) which was earlier used as negative control and growth inhibition was assessed by using the MTT assay. These compounds showed ~10-fold less activity on MCF-7 compared to EGFR overexpressing cell line (A431). Among the several compounds synthesized, we found that compounds **30** and **33** have showed comparable activity with that of gefitinib.

In order to get an insight whether these compounds act through EGFR-TKI pathway, we have docked most active (**33**) and inactive (**26** and **40**) compounds (Figs. 2–5), using autodock tool [22,23] in human EGFR Tyrosine kinase domain (PDB id-2gs2).



Scheme 2. Synthesis of **46**–**48**. Reagents and conditions: (i) 1-Bromo-3-chloropropane/acetone/K_2CO_3/60 °C for 2 h; (ii) 1-bromo-3-chloropropane/toluene/K_2CO_3/60 °C for 1 h.

Docking analysis revealed that compound **33** and gefitinib binds to EGFR at the same position involving Val702, Ala719, Ser696, Lys721 and many other amino acids. But least active compounds **40** and **26** (Fig. 5) showed that even though they bind in the similar location as that of gefitinib, the amino acids to which they interacted were different except a few (viz., Met769 and Ala719). Thus, insilico experiments corroborate well with *in vitro* results.

3. Conclusion

We have synthesized novel 4-anilinoquinazoline derivatives and tested for their anticancer activity on A431 and MCF-7 cell lines. Compounds **30** and **33** were identified as most potent having IC_{50} values 3.51 and 3.00 μM, respectively. In case of compounds bearing alkyl-thiobenzothiazole side chain (**18**–**22**) at 6-position of quinazoline ring and electron withdrawing groups on aniline (**19**, $IC_{50} = 4.05$ μM) substituted at 4-position of quinazolone skeleton were found to be more potent. The electron donating groups on aniline ring was observed to be less potent (**21**, $IC_{50} = 14.17$ μM). Compounds **30** and **33** showed ~10-fold more potency on A431 cell line compared to MCF-7 cell line, indicating the possibility of acting through EGFR-TKI pathway. Further insilico experiments indicated that **33** docks in EGFR-TK domain at the same position as that of gefitinib involving Val702, Ala719, Ser696, and Lys721.

4. Experimental

4.1. Chemistry

4.1.1. General methods/instruments

All the starting materials and reagents were obtained from commercial source and were used without further purification. IR spectra were recorded on a Nicolet Avatar 320 FT-IR spectrometer. ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$/DMSO-d_6 at 200 MHz on a Bruker A G Spectrometer. All the chemical shifts are reported in δ units and downfield from TMS as internal standard. Mass spectra were recorded using GCMS-QP2010S (Direct probe) and on Q-TOF micro™ AMPS MAX 10/6A system. Melting points were recorded on Acro Steel Pvt. Ltd. melting point apparatus and are uncorrected.

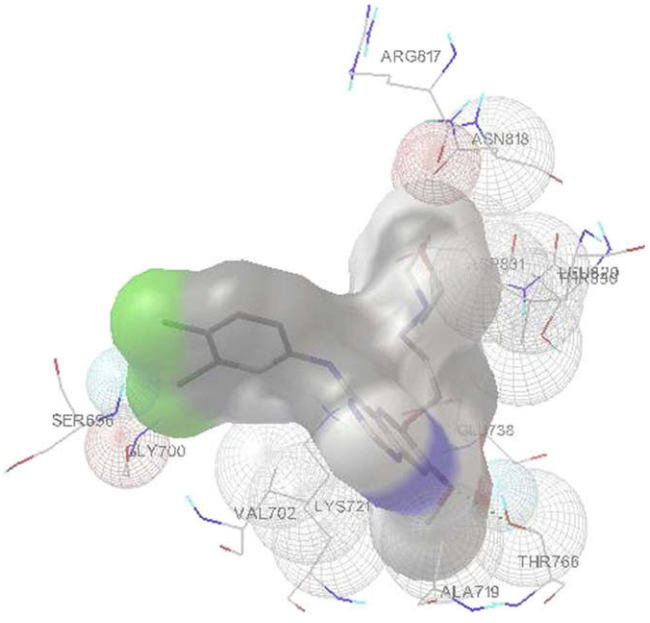


Fig. 2. Docking of gefitinib with human EGFR-TK domain (PDB id-2gs2).

4.1.2. Preparation of intermediates

*4.1.2.1. 7-Hydroxy-6-methoxy-quinazolin-4(3*H*)-one (**4**).* To a stirred solution of **3** (420 g, 2 mol) in methanesulphonic acid (2.5 L) was added DL-methionine (500 g, 3.3 mol). The reaction mixture was heated to 120 °C and stirred for about 25–30 h. The completion of the reaction was monitored by TLC. After the completion of the reaction, cooled to RT, quenched in ice-water and pH was adjusted to ~9 with 40% aq. NaOH. The precipitate was filtered, washed with water (500 mL) and finally dried at 60–70 °C to obtain **4** as grey solid (390 g, yield = quantitative); GC–MS (*m*/*z*): 192 (M^+).

*4.1.2.2. 7-Methoxy-4-oxo-3,4-dihydroquinazolin-6-yl-acetate (**5**).* To a stirred solution of **4** (390 g, 1.88 mol) and aceticanhydride (2 L) was added pyridine (400 mL). The reaction mass was heated to 100 °C and stirred for about 4 h. Cooled the reaction mixture to RT and quenched in ice-water by keeping the temperature 30–35 °C. The solid was filtered and air dried for 2 h and then dried at 60 °C to obtain **5** as grey colored solid (250 g, yield = 53%); GC–MS (*m*/*z*): 234 (M^+).

*4.1.2.3. 4-Chloro-7-methoxy-quinazolin-6-yl-acetate (**6**).* To a stirred solution of **5** (250 g, 1.06 mol) and thionyl chloride (2 L) was added DMF (10 mL) slowly. The reaction mixture was heated to reflux and stirred for about 2 h. Excess thionyl chloride was distilled off and the reaction mixture was quenched in ice with efficient stirring. The precipitate was filtered, washed with ice-water (100 mL) and dissolved the crude material in chloroform (1 L) and filtered to remove insolubles. Organic layer was concentrated under vacuum to obtain **6** as light yellow solid (250 g, yield = 93%).

4.1.3. General procedure for the preparation of compounds (**8**–**17**)

To a stirred solution of **6** (1 mol) and DMF (10 vol) was added substituted aniline (1.5 mol). The reaction mass was heated to 80 °C and stirred for about 1 h. The reaction mass was quenched in ice-water, filtered the solid to get **7**. The slightly wet material **7** was suspended in methanol (10 vol) and added 25% ammonia solution (0.4 vol) with efficient stirring. The reaction mass was heated to reflux and stirred for about 2 h. The reaction mixture was cooled to RT and filtered. Washed with chilled methanol (1/2 vol) and dried at 50–60 °C to obtain title product with yields ranging from 70 to 80%.

*4.1.3.1. 7-Methoxy-4-{[4-(trifluoromethoxy)phenyl]amino}quinazolin-6-ol (**8**).* Using compound **6** and 4-(trifluoromethoxy)aniline as starting materials, **8** was obtained as brown solid in 70% yield; m.p. 217–219 °C; GC–MS (*m*/*z*): 351(M^+).

*4.1.3.2. 7-Methoxy-4-{[3-(trifluoromethyl)phenyl]amino}quinazolin-6-ol (**9**).* Using compound **6** and 3-trifluoromethyl aniline as starting materials, **9** was obtained as brown solid in 80% yield; m.p. 274 °C; GC–MS (*m*/*z*): 335 (M^+).

*4.1.3.3. 4-[(3-Chloro-4-fluorophenyl)amino]-7-methoxy-quinazolin-6-ol (**10**).* Using compound **6** and 3-chloro-4-fluoroaniline as starting materials, **10** was obtained as brown solid in 75% yield; m.p. 285 °C; GC–MS (*m*/*z*): 319 (M^+).

*4.1.3.4. 4-[(4-Bromo-2-ethylphenyl)amino]-7-methoxy-quinazolin-6-ol (**11**).* Using compound **6** and 4-bromo-2-ethylaniline as starting materials, **11** was obtained as brown solid in 78% yield; m.p. 215 °C; GC–MS (*m*/*z*): 373 (M^+).

*4.1.3.5. 7-Methoxy-4-[(4-methoxyphenyl)amino]quinazolin-6-ol (**12**).* Using compound **6** and *p*-anisidine as starting materials, **12** was obtained as brown solid in 70% yield; m.p. 244 °C; GC–MS (*m*/*z*): 297 (M^+).

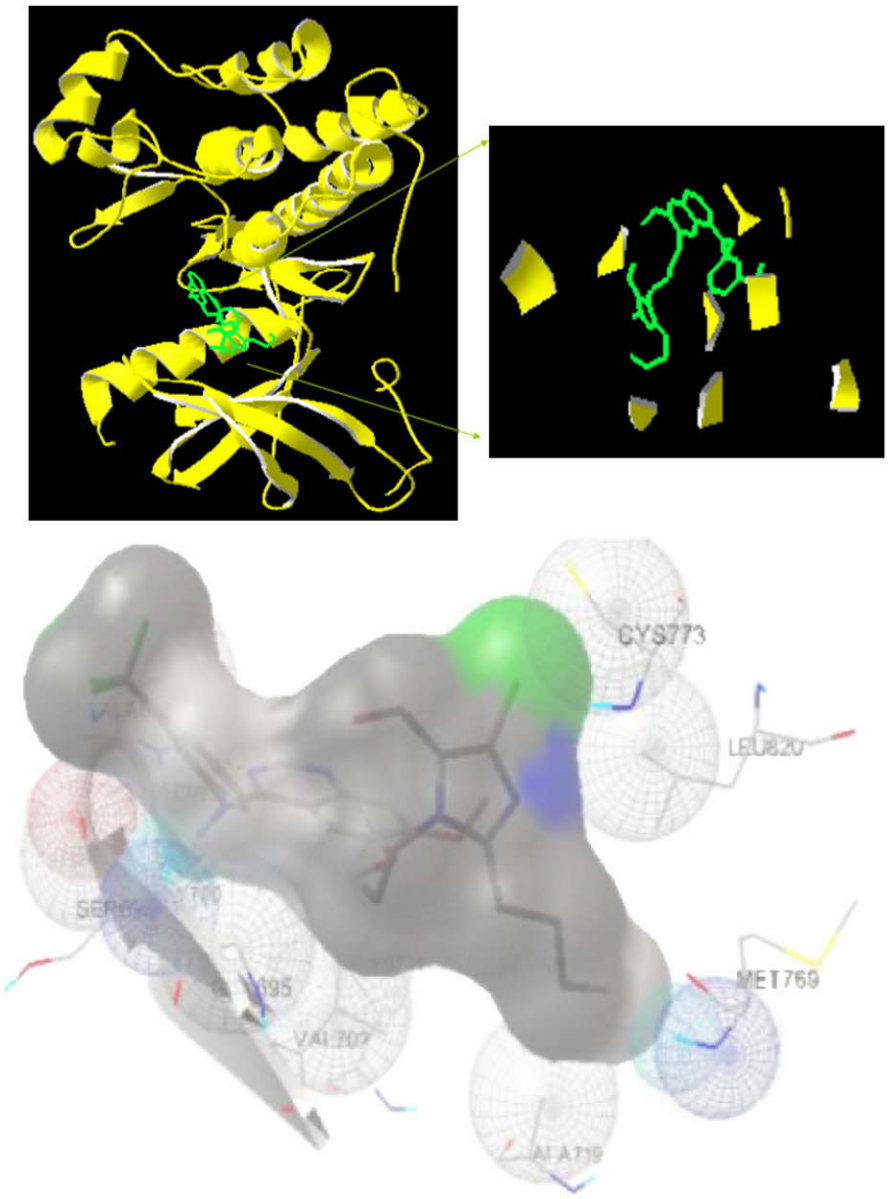


Fig. 3. Docking of compound **33** with human EGFR-TK domain (PDB id-2gs2).

*4.1.3.6. 7-Methoxy-4-[(4-methylphenyl)amino]quinazolin-6-ol (**13**).* Using compound **6** and 4-methylaniline as starting materials, **13** was obtained as brown solid in 72% yield; m.p. 254–255 °C; GC–MS (*m*/*z*): 281 (M^+).

*4.1.3.7. 4-[(3-Iodophenyl)amino]-7-methoxy-quinazolin-6-ol (**14**).* Using compound **6** and 3-iodoaniline as starting materials, **14** was obtained as brown solid in 75% yield; m.p. 263–265 °C; GC–MS (*m*/*z*): 393 (M^+).

*4.1.3.8. 4-[(3-Bromophenyl)amino]-7-methoxy-quinazolin-6-ol (**15**).* Using compound **6** and 3-bromoaniline as starting materials, **15** was obtained as brown solid in 75% yield; m.p. 272 °C; GC–MS (*m*/*z*): 345 (M^+).

*4.1.3.9. 4-[(3-Fluorophenyl)amino]-7-methoxy-quinazolin-6-ol (**16**).* Using compound **6**and 3-fluoroaniline as starting materials, **16** was obtained as brown solid in 75% yield; m.p. 268–270 °C; GC–MS (*m*/*z*): 285 (M^+).

*4.1.3.10. 4-[(3-Ethynylphenyl)amino]-7-methoxy-quinazolin-6-ol (**17**).* Using compound **6** and 3-ethynylaniline as starting materials, **17** was obtained as brown solid in 78% yield; m.p. 252–254 °C; GC–MS (*m*/*z*): 291 (M^+).

4.1.4. Synthesis of side chain intermediates

*4.1.4.1. 2-Butyl-4-chloro-1-(3-chloropropyl)-1*H*-imidazole-5-carboxaldehyde (**46**).* To a stirred solution of imidazole compound (**45**) (46.5 g, 0.25 mol), potassium carbonate (69 g, 0.5 mol) and acetone (400 mL) was added 1-bromo-3-chloropropane (39.2 g, 0.25 mol). The reaction mixture was heated to 60 °C and stirred for about 2 h. Completion of the reaction was monitored by TLC. The reaction mixture was cooled to RT, inorganics were filtered and organic solvent was concentrated under vacuum to obtain product as light yellow liquid (46.5 g, 70% yield); ^{1}H NMR ($CDCl_3$, 200 MHz,): δ 0.96 (t, $J = 7.2$ and 7.4 Hz, 3H), 1.43 (m, 2H), 1.77 (m, 2H), 2.24 (m, 2H), 2.74 (t, $J = 7.2$ and 8.2 Hz, 2H), 3.58 (t, $J = 5.8$ and 6.0 Hz, 2H), 4.38 (t, $J = 7.2$ and 7.4 Hz, 2H), 9.71 (s, 1H); GC–MS (*m*/*z*): 262 (M^+).

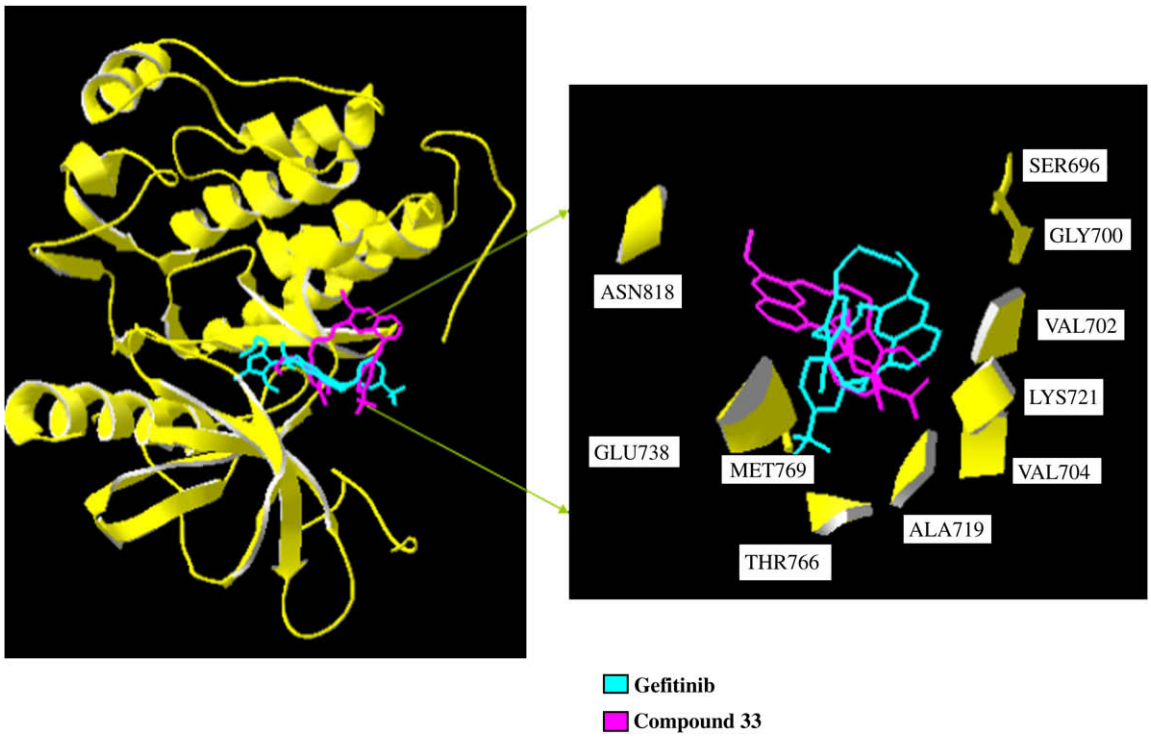


Fig. 4. An overlap of both gefitinib and compound **33** in human EGFR-TK domain (PDB id-2gs2).

*4.1.4.2. 2-[(3-Chloropropyl)thio]benzothiazole (**47**).* To a stirred solution of 2-mercapto benzothiazole (25 g, 0.15 mol) and powdered potassium carbonate (41 g, 0.30 mol) in toluene (100 mL) was added 1-bromo-3-chloropropane (47 g, 0.30 mol). The reaction mass was heated to 60 °C and stirred for about 1 h. Cooled to room temperature, inorganics were filtered and organic solvent was concentrated under vacuum to obtain crude material. It was then recrystallized from hexane to get pure product (25 g, yield = 69%); ^{1}H NMR ($CDCl_3$, 200 MHz): δ 2.31 (m, 2H), 3.49 (t, J = 6.8 Hz, 2H), 3.70 (t, J = 6.2 Hz, 2H), 7.29 (t, J = 7.8 Hz, 1H), 7.40 (t, J = 8.0 Hz, 1H), 7.74 (d, J = 7.8 Hz, 1H), 7.86 (d, J = 8.0 Hz, 1H); GC–MS (m/z): 243 (M^+).

*4.1.4.3. 2-[(3-Chloropropyl)thio]benzoxazole (**48**).* To a stirred 2-mercapto benzoxazole (25 g, 0.16 mol) and powdered potassium carbonate (45 g, 0.32 mol) in toluene (100 mL) was added 1-bromo-3-chloropropane (25 g, 0.16 mol). The reaction mass was heated to 60 °C and stirred for about 1 h. Cooled to room temperature, inorganics were filtered and toluene was concentrated under vacuum to get crude material, which was then recrystallized from hexane to obtain pure product (25 g, yield = 67%); ^{1}H NMR ($CDCl_3$, 200 MHz): δ 2.34 (m, 2H), 3.46 (t, J = 6.8 Hz, 2H), 3.72 (t, J = 6.2 Hz, 2H), 7.13–7.29 (m, 2H), 7.43 (dd, J = 2.2 and 6.8 Hz, 1H), 7.60 (dd, J = 2.2 and 6.8 Hz, 1H); GC–MS (m/z): 227 (M^+).

*4.1.5. General procedure for the preparation of final compounds (**18–36**)*

To a stirred solution of 6-hydroxyquinazoline compound (**8–17**) (5.7 mmol) and powdered potassium carbonate (14.2 mmol) in DMF (10 vol) was added side chain (alkyl halide, **46–48**) (6.3 mmol). The reaction mixture was heated to 130 °C and stirred for about 2 h. Completion of the reaction was monitored by TLC.

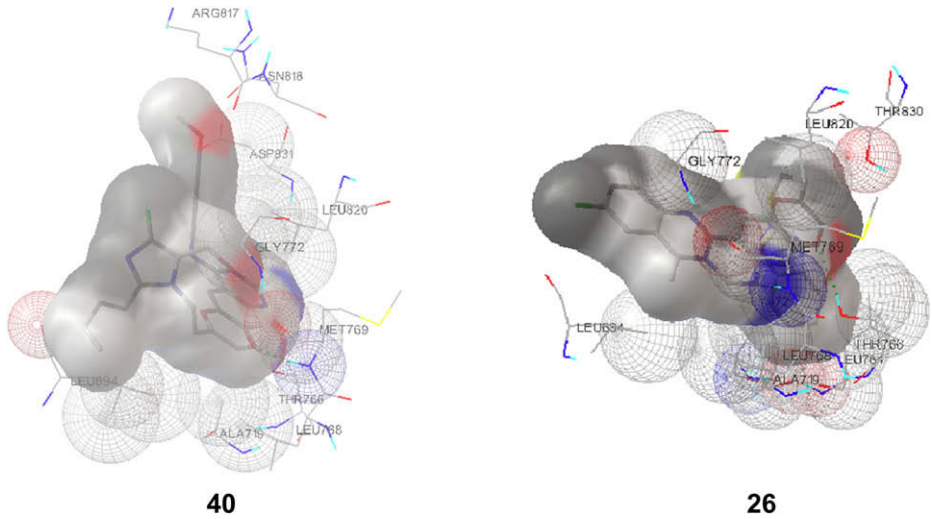


Fig. 5. Docking of compounds **26** and **40** with human EGFR-TK domain (PDB id-2gs2).

The reaction mass was cooled to RT, filtered and organic solvent was concentrated under vacuum. The residue obtained was dissolved in ethyl acetate and washed with water. Finally organic solvent was dried over sodium sulphate and concentrated to obtain crude material, which was further purified by column chromatography to get pure material of title compounds **18–36** with yields ranging from 60 to 75%.

4.1.5.1. 6-[3-(Benzothiazol-2-ylthio)propoxy]-N-*(3-chloro-4-fluorophenyl)-7-methoxyquinazo-lin-4-amine (**18**).* Using **10** and **47** as starting materials, compound **18** was obtained as pale yellow solid in 70% yield; m.p. 173–176 °C; IR (KBr): 756, 848, 995, 1064, 1145, 1211, 1242, 1346, 1473, 1504, 1577, 1624, 2923, 3128, 3301 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 2.37 (m, 2H), 3.52 (t, $J = 6.6$ Hz, 2H), 3.97 (s, 3H), 4.17 (t, $J = 5.8$ Hz, 2H), 7.08–7.17 (m, 2H), 7.32–7.39 (m, 3H), 7.47–7.53 (m, 1H), 7.62 (br s, 1H), 7.02–7.88 (m, 3H), 8.65 (s, 1H); ^{13}C NMR ($CDCl_3$, 200 MHz): δ 28.94, 30.48, 56.24, 67.22, 100.88, 108.16, 117.20, 117.65, 121.05, 121.49, 121.60, 124.09, 124.60, 126.26, 135.95, 147.95, 148.80, 152.00, 153.00, 153.50, 155.50, 156.00, 157.50, 165.00, 166.50; GC–MS (*m*/*z*): 527 (M^+).

4.1.5.2. 6-[3-(Benzothiazol-2-ylthio)propoxy]-7-methoxy-N-*[3-(trifluoromethyl)phenyl]quinazo-lin-4-amine (**19**).* Using **9** and **47** as starting materials, compound **19** was obtained as off-white solid in 70% yield; m.p. 92–95 °C; IR (KBr): 756, 848, 995, 1064, 1122, 1234, 1326, 1427, 1450, 1508, 1581, 1627, 2927, 3282 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 2.41 (m, 2H), 3.55 (t, $J = 6.6$ Hz, 2H), 3.98 (s, 3H), 4.23 (t, $J = 6$ Hz, 2H), 7.15–7.53 (m, 6H), 7.69–7.79 (m, 3H), 7.94–8.01 (m, 2H), 8.68 (s, 1H); ^{13}C NMR ($CDCl_3$, 200 MHz): δ 28.33, 29.83, 55.66, 66.48, 100.49, 107.39, 108.10, 113.00, 117.64, 119.60, 119.89, 120.51, 120.85, 124.05, 125.72, 128.91, 134.50, 138.50, 139.60, 147.70, 148.00, 151.20, 152.50, 152.92, 154.75, 156.10; HRMS (*m*/*z*): Calculated for $C_{26}H_{21}N_4O_2S_2F_3$ $(M + H)^+ = 543.1136$, found = 543.1125.

4.1.5.3. 6-[3-(Benzothiazol-2-ylthio)propoxy]-N-*(4-bromo-2-ethylphenyl)-7-methoxyquinazolin-4-amine (**20**).* Using **11** and **47** as starting materials, compound **20** was obtained as off-white solid in 68% yield; m.p. 204–207 °C; IR (KBr): 756, 999, 1064, 1176, 1238, 1330, 1427, 1473, 1500, 1581, 1620, 2962, 3058, 3300 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 1.22 (t, $J = 7.4$ and 7.6 Hz, 3H), 2.46 (m, 2H), 2.62 (q, $J = 7.4$ and 7.6 Hz, 2H), 3.59 (t, $J = 6.6$ Hz, 2H), 4.00 (s, 3H), 4.24 (t, $J = 6$ Hz, 2H), 6.92 (s, 1H), 7.03 (s, 1H), 7.24–7.49 (m, 6H), 7.69–7.78 (m, 2H), 8.57 (s, 1H); ^{13}C NMR ($CDCl_3$, 200 MHz): δ 13.17, 23.86, 28.42, 29.67, 55.69, 66.75, 100.67, 107.59, 108.00, 120.45, 120.89, 123.91, 125.60, 127.12, 129.24, 131.29, 133.95, 134.10, 135.10, 136.00, 137.80, 138.00, 139.80, 140.00, 147.12, 152.55, 153.41, 157.12; GC–MS (*m*/*z*): 581 (M^+).

4.1.5.4. 6-[3-(Benzothiazol-2-ylthio)propoxy]-7-methoxy-N-*(4-methoxyphenyl)quinazoline-4-amine (**21**).* Using **12** and **47** as starting materials, compound **21** was obtained as pale yellow solid in 60% yield; m.p. 123–126 °C; IR (KBr): 555, 756, 825, 999, 1026, 1072, 1245, 1342, 1434, 1512, 1581, 1627, 2923, 3325 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 2.41 (m, 2H), 3.55 (t, $J = 6.6$ Hz, 2H), 3.82 (s, 3H), 3.98 (s, 3H), 4.21 (t, $J = 6.2$ Hz, 2H), 6.93 (d, $J = 8.8$ Hz, 2H), 7.10 (s, 1H), 7.21 (s, 1H), 7.29–7.39 (m, 2H), 7.50 (d, $J = 8.8$ Hz, 2H), 7.69–7.80 (m, 2H), 8.59 (s, 1H); ^{13}C NMR ($CDCl_3$, 200 MHz): δ 28.32, 29.68, 54.98, 55.58, 66.46, 101.18, 107.18, 108.49, 113.76, 120.49, 120.83, 123.95, 124.12, 125.68, 130.95, 135.00, 146.74, 147.82, 152.80, 153.77, 154.35, 156.24, 156.68, 167.20; GC–MS (*m*/*z*): 504 (M^+).

4.1.5.5. 6-[3-(Benzothiazol-2-ylthio)propoxy]-7-methoxy-N-*(4-methylphenyl)quinazolin-4-amine (**22**).* Using **13** and **47** as starting materials, compound **22** was obtained as pale yellow solid in 65% yield; m.p. 104–106 °C; IR (KBr): 509, 756, 856, 999, 1068, 1242, 1427, 1515, 1577, 1627, 2927, 3100, 3300 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 2.35 (s, 3H), 2.44 (m, 2H), 3.57 (t, $J = 6.6$ Hz, 2H), 3.98 (s, 3H), 4.23 (t, $J = 6.2$ Hz, 2H), 7.08 (s, 1H), 7.20 (d, $J = 8.4$ Hz, 2H), 7.22 (s, 1H), 7.29–7.39 (m, 3H), 7.51 (d, $J = 8.4$ Hz, 2H), 7.69–7.80 (m, 2H); ^{13}C NMR ($CDCl_3$, 200 MHz): δ 20.42, 28.37, 29.74, 55.62, 66.56, 100.97, 107.20, 108.32, 120.47, 120.89, 122.05, 123.93, 125.65, 129.06, 133.38, 134.50, 135.55, 145.25, 146.80, 147.30, 153.20, 154.60, 156.21, 163.00; GC–MS (*m*/*z*): 488 (M^+).

4.1.5.6. 6-[3-(Benzoxazol-2-ylthio)propoxy]-N-*(3-chloro-4-fluorophenyl)-7-methoxy-quinazolin-4-amine (**23**).* Using **10** and **48** as starting materials, compound **23** was obtained as pale yellow solid in 70% yield; m.p. 63–67 °C; IR (KBr): 547, 744, 852, 1002, 1068, 1134, 1251, 1334, 1427, 1500, 1577, 1624, 2927, 3070, 3300 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 2.42 (m, 2H), 3.50 (t, $J = 6.6$ Hz, 2H), 3.98 (s, 3H), 4.21 (t, $J = 6.2$ Hz, 2H), 7.09–7.18 (m, 2H), 7.21–7.24 (m, 3H), 7.38–7.40 (m, 1H), 7.50–7.57 (m, 3H), 7.90 (m, 1H), 8.66 (s, 1H); HRMS (*m*/*z*): Calculated for $C_{25}H_{20}N_4O_3SFCl$ $(M + H)^+ = 511.1007$, found = 511.1022.

4.1.5.7. 6-[3-(Benzoxazol-2-ylthio)propoxy]-7-methoxy-N-*[3-(trifluoromethyl)phenyl]quinazolin- 4-amine (**24**).* Using **9** and **48** as starting materials, compound **24** was obtained as off-white solid in 70% yield; m.p. 147–149 °C; IR (KBr): 586, 744, 848, 1006, 1068, 1118, 1238, 1326, 1446, 1504, 1581, 1624, 2927, 3012, 3300 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 2.42 (m, 2H), 3.51 (t, $J = 6.6$ Hz, 2H), 3.98 (s, 3H), 4.22 (t, $J = 6$ Hz, 2H), 7.16–7.23 (m, 4H), 7.37–7.53 (m, 4H), 7.73 (s, 1H), 7.96–8.02 (m, 2H), 8.70 (s, 1H); HRMS (*m*/*z*): Calculated for $C_{26}H_{21}N_4O_3SF_3$ $(M + H)^+ = 527.1364$, found = 527.1343.

4.1.5.8. 6-[3-(Benzoxazol-2-ylthio)propoxy]-7-methoxy-N-*[4-(trifluoromethoxy)phenyl]quinazo-lin-4-amine (**25**).* Using **8** and **48** as starting materials, compound **25** was obtained as off-white solid in 60% yield; m.p. 90–94 °C; IR (KBr): 520, 663, 744, 929, 1068, 1141, 1270, 1342, 1434, 1512, 1585, 1627, 2935, 3070, 3224, 3300 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 2.42 (m, 2H), 3.51 (t, $J = 6.6$ Hz, 2H), 3.98 (s, 3H), 4.23 (t, $J = 6$ Hz, 2H), 7.16–7.24 (m, 6H), 7.37–7.42 (m, 1H), 7.49–7.53 (m, 1H). 7.67 (s, 1H), 7.74 (d, $J = 9$ Hz, 2H), 8.66 (s, 1H); ^{13}C NMR ($CDCl_3$, 200 MHz): δ 30.88, 31.18, 58.29, 69.45, 105.32, 109.72, 111.19, 112.51, 120.00, 120.56, 123.63, 125.84, 126.59, 126.93, 141.09, 144.10, 146.20, 149.49, 150.41, 154.10, 155.15, 156.15, 156.84, 158.53, 167.00; GC–MS (*m*/*z*): 542 (M^+).

4.1.5.9. 6-[3-(Benzoxazol-2-ylthio)propoxy]-N-*(4-bromo-2-ethylphenyl)-7-methoxy-quinazolin-4-amine (**26**).* Using **11** and **48** as starting materials, compound **26** was obtained as off-white solid in 70% yield; m.p. 187–190 °C; IR (KBr): 740, 856, 1002, 1064, 1130, 1211, 1242, 1388, 1427, 1500, 1581, 1620, 2927, 2962, 3058, 3300 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 1.22 (t, $J = 7.4$ &7.6 Hz, 3H), 2.45 (m, 2H), 2.63 (q, $J = 7.4$ and 7.6 Hz, 2H), 3.53 (t, $J = 6.6$ Hz, 2H), 3.99 (s, 3H), 4.23 (t, $J = 6$ Hz, 2H), 7.06 (br s, 2H), 7.20–7.28 (m, 3H), 7.37–7.54 (m, 5H), 8.57 (s, 1H); ^{13}C NMR ($CDCl_3$, 200 MHz): δ 13.18, 23.88, 28.34, 28.34, 55.66, 66.67, 100.98, 107.60, 108.28, 109.35, 117.80, 119.10, 123.54, 123.86, 127.14, 129.24, 131.31, 134.77, 140.00, 141.25, 147.90, 148.11, 151.00, 153.45, 154.75, 156.78, 164.0; GC–MS (*m*/*z*): 565 (M^+).

4.1.5.10. 6-[3-(Benzoxazol-2-ylthio)propoxy]-7-methoxy-N-*(4-methoxyphenyl)quinazolin-4-amine (**27**).* Using **12** and **48** as starting materials, compound **27** was obtained as pale yellow solid in 65% yield; m.p. 138–140 °C; IR (KBr): 555, 744, 856, 925, 1033, 1068, 1134, 1238, 1431, 1508, 1577, 1620, 2923, 3060, 3250 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 2.45 (m, 2H), 3.53 (t, $J = 6.8$ Hz, 2H), 3.82 (s, 3H), 3.99 (s, 3H), 4.25 (t, $J = 6.2$ Hz, 2H), 6.94 (d, $J = 9$ Hz, 2H), 7.10 (s, 1H), 7.22–7.29 (m, 4H), 7.38–7.42 (m, 1H), 7.49–7.55 (m, 3H), 8.60 (s, 1H); ^{13}C NMR ($CDCl_3$, 200 MHz): δ 28.30, 28.35, 55.00, 55.61, 66.52,

101.05, 107.43, 108.10, 109.38, 113.82, 117.80, 123.57, 123.90, 124.06, 130.90, 141.15, 144.90, 145.78, 146.50, 147.85, 153.45, 154.10, 155.85, 156.20; GC–MS (*m*/*z*): 488 (M^+).

*4.1.5.11. 6-[3-(Benzoxazol-2-ylthio)propoxy]-7-methoxy-*N*-(4-methylphenyl)quinazolin-4-amine (**28**).* Using **13** and **48** as starting materials, compound **28** was obtained as pale yellow solid in 65% yield; m.p. 107–110 °C; IR (KBr): 744, 860, 933, 1068, 1134, 1242, 1427, 1515, 1577, 1627, 2927, 3344 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 2.35 (s, 3H), 2.46 (m, 2H), 3.53 (t, $J = 6.8$ Hz, 2H), 3.99 (s, 3H), 4.26 (t, $J = 6.2$ Hz, 2H), 7.11 (s, 1H), 7.18–7.26 (m, 5H), 7.35–7.42 (m, 2H), 7.50–7.54 (m, 3H), 8.62 (s, 1H); ^{13}C NMR ($CDCl_3$, 200 MHz): δ 20.39, 28.35, 28.35, 55.61, 66.63, 101.03, 107.51, 108.31, 109.36, 117.83, 121.95, 123.55, 123.88, 129.08, 133.85, 135.80, 141.25, 147.00, 147.80, 151.20, 153.36, 154.55, 156.50, 164.0; GC–MS (*m*/*z*): 472 (M^+).

*4.1.5.12. 2-Butyl-4-chloro-1-{3-[4-(3-chloro-4-fluorophenylamino)-7-methoxyquinazolin-6-yloxy]propyl}-1*H*-imidazole-5-carboxaldehyde (**29**).* Using **10** and **46** as starting materials, compound **29** was obtained as yellow solid in 70% yield; m.p. 103–105 °C; IR (KBr): 543, 852, 1068, 1141, 1215, 1280, 1384, 1427, 1500, 1577, 1624, 1662, 2927, 2950, 3363 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 0.93 (t, $J = 7.2$ Hz, 3H), 1.37 (m, 2H), 1.76 (m, 2H), 2.31 (m, 2H), 2.71 (t, $J = 7.4$ and 8.0 Hz, 2H), 4.00 (s, 3H), 4.36 (m, 4H), 7.17 (t, $J = 8.8$ Hz, 1H), 7.43 (s, 1H), 7.62–7.69 (m, 1H), 8.02 (dd, $J = 2.6$ and 6.6 Hz, 1H), 8.22 (s, 1H), 8.66 (s, 1H), 9.69 (s, 1H); HRMS (*m*/*z*): Calculated for $C_{26}H_{26}N_5O_3Cl_2F$ $(M + H)^+ = 546.1475$, found = 546.1466.

*4.1.5.13. 2-Butyl-4-chloro-1-{3-[7-methoxy-4-(3-(trifluoromethyl) phenylamino)quinazolin-6-yloxy]propyl}-1*H*-imidazole-5-carboxaldehyde (**30**).* Using **9** and **46** as starting materials, compound **30** was obtained as yellow solid in 70% yield; m.p. 86–89 °C; IR (KBr): 698, 852, 1006, 1068, 1122, 1234, 1326, 1431, 1508, 1581, 1624, 1662, 2931, 2950, 3300 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 0.93 (t, $J = 7.2$ Hz, 3H), 1.39 (m, 2H), 1.78 (m, 2H), 2.33 (m, 2H), 2.71 (t, $J = 7.6$ and 8.0 Hz, 2H), 4.00 (s, 3H), 4.35 (m, 4H), 7.27 (s, 1H), 7.36–7.56 (m, 3H), 8.13–8.17 (m, 2H), 8.42 (s, 1H), 8.70 (s, 1H), 9.70 (s, 1H); HRMS (*m*/*z*): Calculated for $C_{27}H_{27}N_5O_3ClF_3$ $(M + H)^+ = 562.1833$, found = 562.1821.

*4.1.5.14. 1-{3-[4-(4-Bromo-2-ethylphenylamino)-7-methoxyquinazolin-6-yloxy]propyl}-2-butyl-4-chloro-1*H*-imidazole-5-carboxaldehyde (**31**).* Using **11** and **46** as starting materials, compound **31** was obtained as yellow solid in 75% yield; m.p. 111–114 °C; IR (KBr): 555, 856, 1006, 1064, 1141, 1245, 1276, 1384, 1423, 1500, 1581, 1620, 1662, 2931, 2958, 3236 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 0.91 (t, $J = 7.2$ and 7.4 Hz, 3H), 1.24 (t, $J = 7.6$ Hz, 3H), 1.37 (m, 2H), 1.72 (m, 2H), 2.32 (m, 2H), 2.67 (m, 4H), 4.00 (s, 3H), 4.19 (t, $J = 6.2$ and 6.4 Hz, 2H), 4.44 (t, $J = 7.2$ and 7.4 Hz, 2H), 7.25 (m, 2H), 7.41–7.47 (m, 4H), 8.56 (s, 1H), 9.65 (s, 1H); HRMS (*m*/*z*): Calculated for $C_{27}H_{31}N_5O_3BrCl$ $(M + H)^+ = 600.1377$, found = 600.1377.

*4.1.5.15. 2-Butyl-4-chloro-1-{3-[7-methoxy-4-(4-methoxyphenylamino)quinazolin-6-yloxy]propyl}-1*H*-imidazole-5-carboxaldehyde (**32**).* Using **12** and **46** as starting materials, compound **32** was obtained as pale yellow solid in 65% yield; m.p. 118–122 °C; IR (KBr): 551, 852, 1033, 1064, 1141, 1238, 1384, 1469, 1512, 1577, 1624, 1662, 2931, 2958, 3278 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 0.91 (t, $J = 7.2$ Hz, 3H), 1.37 (m, 2H), 1.73 (m, 2H), 2.29 (m, 2H), 2.73 (t, $J = 7.4$ and 8.0 Hz, 2H), 3.83 (s, 3H), 3.98 (s, 3H), 4.20 (t, $J = 6.4$ Hz, 2H), 4.41 (t, $J = 7.2$ and 7.6 Hz, 2H), 6.95 (d, $J = 8.8$ Hz, 2H), 7.23 (s, 1H), 7.34 (s, 1H), 7.60 (d, $J = 8.8$ Hz, 2H), 7.92 (s, 1H), 8.61 (s, 1H), 9.69 (s, 1H); ^{13}C NMR (DMSO-d_6, 200 MHz): δ 13.49, 22.32, 26.03, 29.38, 29.50, 42.39, 55.42, 55.97, 65.62, 102.20, 108.09, 109.10, 114.26, 124.05, 124.15, 131.67, 144.20, 147.40, 147.50, 154.10, 154.60, 155.10, 156.80, 157.20, 177.99; GC–MS (*m*/*z*): 523 (M^+).

*4.1.5.16. 2-Butyl-4-chloro-1-{3-[4-(3-iodophenylamino)-7-methoxyquinazolin-6-yloxy] propyl}-1*H*-imidazole-5-carboxaldehyde (**33**).* Using **14** and **46** as starting materials, compound **33** was obtained as off-white solid in 75% yield; m.p. 91–94 °C; IR (KBr): 586, 767, 852, 1002, 1064, 1234, 1280, 1388, 1427, 1469, 1508, 1569, 1624, 1674, 2927, 2958, 3209, 3328 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 0.93 (t, $J = 7.2$ Hz, 3H), 1.36 (m, 2H), 1.74 (m, 2H), 2.32 (m, 2H), 2.71 (t, $J = 7.6$ and 8.0 Hz, 2H), 4.01 (s, 3H), 4.23 (m, 4H), 7.13 (t, $J = 8.0$ Hz, 1H), 7.43 (br s, 1H), 7.47 (d, $J = 8.0$ Hz, 1H), 7.85 (d, $J = 8.0$ Hz, 1H), 8.19 (s, 1H), 8.24 (s, 1H), 8.69 (s, 1H), 9.71 (s, 1H); HRMS (*m*/*z*): Calculated for $C_{26}H_{27}N_5O_3ClI$ $(M + H)^+ = 620.0925$, found = 620.0951.

*4.1.5.17. 1-{3-[4-(3-Bromophenylamino)-7-methoxyquinazolin-6-yloxy] propyl}-2-butyl-4-chloro-1*H*-imidazole-5-carboxaldehyde (**34**).* Using **15** and **46** as starting materials, compound **34** was obtained as off-white solid in 75% yield; m.p. 83–85 °C; IR (KBr): 775, 852, 1006, 1064, 1238, 1388, 1427, 1508, 1569, 1624, 1662, 2927, 2958, 3328 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 0.93 (t, $J = 7.0$ Hz, 3H), 1.39 (m, 2H), 1.76 (m, 2H), 2.32 (m, 2H), 2.71 (t, $J = 8.0$ Hz, 2H), 4.01 (s, 3H), 4.36 (m, 4H), 7.28 (m, 2H), 7.44 (s, 1H), 7.77 (m, 1H), 8.12 (s, 1H), 8.24 (s, 1H), 8.70 (s, 1H), 9.71 (s, 1H); HRMS (*m*/*z*): Calculated for $C_{26}H_{27}N_5O_3BrCl$ $(M + H)^+ = 572.1064$, found = 572.1071.

*4.1.5.18. 2-Butyl-4-chloro-1-{3-[4-(3-fluorophenylamino)-7-methoxyquinazolin-6-yloxy] propyl}-1*H*-imidazole-5-carboxaldehyde (**35**).* Using **16** and **46** as starting materials, compound **35** was obtained as off-white solid in 70% yield; m.p. 81–83 °C; IR (KBr): 586, 678, 775, 852, 1006, 1064, 1141, 1245, 1276, 1388, 1427, 1508, 1577, 1620, 1662, 2931, 2958, 3332 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 0.93 (t, $J = 7.2$ Hz, 3H), 1.36 (m, 2H), 1.74 (m, 2H), 2.31 (m, 2H), 2.71 (t, $J = 7.6$ and 8.0 Hz, 2H), 4.00 (s, 3H), 4.36 (m, 4H), 6.84 (dt, $J = 2.0$ and 8.0 Hz, 1H), 7.35 (dd, $J = 8.0$ Hz, 1H), 7.45(s, 1H), 7.51 (d, $J = 8.0$ Hz, 1H), 7.84 (m, 1H), 8.31 (s, 1H), 8.70 (s, 1H), 9.70 (s, 1H); HRMS (*m*/*z*): Calculated for $C_{26}H_{27}N_5O_3ClF$ $(M + H)^+ = 512.1864$, found = 512.1857.

*4.1.5.19. 2-Butyl-4-chloro-1-{3-[4-(3-ethynylphenylamino)-7-methoxyquinazolin-6-yloxy]propyl}-1*H*-imidazole-5-carboxaldehyde (**36**).* Using **17** and **46** as starting materials, compound **36** was obtained as off-white solid in 70% yield; m.p. 122–125 °C; IR (KBr): 590, 790, 856, 1006, 1068, 1145, 1249, 1388, 1431, 1512, 1581, 1624, 1662, 2110, 2927, 3220, 3315 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 0.92 (t, $J = 7.2$ Hz, 3H), 1.36 (m, 2H), 1.74 (m, 2H), 2.32 (m, 2H), 2.70 (t, $J = 7.4$ and 8.0 Hz, 2H), 3.10 (s, 1H), 4.10 (s, 3H), 4.29 (t, $J = 6.8$ Hz, 2H), 4.41 (t, $J = 7.4$ and 7.8 Hz, 2H), 7.29–7.43 (m, 3H), 7.85 (d, $J = 7.8$ Hz, 1H), 7.97 (s, 1H), 8.19 (s, 1H), 8.68 (s, 1H), 9.71 (s, 1H); HRMS (*m*/*z*): Calculated for $C_{28}H_{28}N_5O_3Cl$ $(M + H)^+ = 518.1959$, found = 518.1946.

*4.1.6. General procedure for the preparation of final compounds (**37**–**44**)*

To a stirred solution of aldehyde (**29**–**36**) (2 mmol) in methanol (10 vol) was added sodium borohydride (1 mmol) by keeping the temperature of the reaction mixture 15–20 °C. After the complete addition of sodium borohydride, the reaction mixture was stirred for 10 min and then pH of the reaction mixture was adjusted to 1–2 using 25% aq. HCl, stirred for 10 min and then basified to pH 9–10 using 25% ammonia solution. The precipitate obtained was filtered and recrystallized from methanol to obtain pure material of title compounds **37**–**44** with yields ranging from 85 to 95%.

*4.1.6.1. Preparation of {2-butyl-4-chloro-1-[3-(4-(3-chloro-4-fluorophenylamino)-7-methoxy-quinazolin-6-yloxy)propyl]-1*H*-imidazol-5-yl} methanol (**37**).* By reducing aldehyde group of compound **29**,

compound **37** was obtained as white solid in 90% yield; m.p. 184–187 °C; IR (KBr): 543, 844, 999, 1049, 1215, 1249, 1431, 1500, 1581, 1627, 2927, 2950, 3160, 3450, 3640 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 0.84 (t, $J = 7.2$ Hz, 3H), 1.34 (m, 2H), 1.59 (m, 2H), 2.04–2.41 (m, 2H), 2.55 (t, $J = 8.0$ Hz, 2H), 4.0 (s, 3H), 4.11–4.24 (m, 4H), 4.69 (s, 2H), 7.10 (s, 1H), 7.15 (t, $J = 8.8$ Hz, 1H), 7.54–7.62 (m, 1H), 7.78 (br s, 1H), 7.93 (dd, $J = 2.8$ and 6.6 Hz, 1H), 8.64 (s, 1H); ^{13}C NMR (DMSO-d_6, 200 MHz): δ 13.41, 21.66, 25.27, 29.31, 29.32, 51.15, 55.89, 65.12, 102.53, 107.15, 108.63, 116.22, 116.65, 122.20, 122.27, 123.38, 125.50, 125.15, 131.10, 136.61, 146.98, 147.78, 152.64, 154.43, 155.99; GC–MS (m/z): 548 (M^+).

*4.1.6.2. {2-Butyl-4-chloro-1-[3-(7-methoxy-4-(3-(trifluoromethyl)phenylamino)quinazolin-6-yloxy)propyl]-1*H*-imidazol-5-yl}methanol (**38**).* By reducing aldehyde group of compound **30**, compound **38** was obtained as white solid in 90% yield; m.p. 170–173 °C; IR (KBr): 698, 933, 1010, 1076, 1130, 1238, 1326, 1431, 1496, 1581, 1627, 2935, 2960, 3143, 3300, 3640 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 0.74 (t, $J = 7.0$ and 7.4 Hz, 3H), 1.17 (m, 2H), 1.51 (m, 2H), 2.29 (m, 2H), 2.45 (t, $J = 7.6$ and 8.0 Hz, 2H), 3.91 (s, 3H), 4.10 (m, 4H), 4.64 (s, 2H), 7.17 (s, 1H), 7.32–7.50 (m, 3H), 8.02 (br s, 2H), 8.61 (s, 2H); ^{13}C NMR ($CDCl_3$, 200 MHz): δ 13.45, 21.68, 25.32, 29.31, 29.54, 51.23, 55.94, 65.32, 102.76, 107.37, 108.85, 117.69, 119.21, 121.50, 125.22, 127.20, 128.00, 128.70, 129.52, 140.40, 146.89, 147.20, 147.89, 152.62, 154.55, 156.01; GC–MS (m/z): 563 (M^+).

*4.1.6.3. 1-{3-[4-(4-Bromo-2-ethylphenylamino)-7-methoxyquinazolin-6-yloxy]propyl}-2-butyl-4-chloro-1*H*-imidazol-5-yl}methanol (**39**).* By reducing aldehyde group of compound **31**, compound **39** was obtained as white solid in 95% yield; m.p. 96–100 °C; IR (KBr): 864, 1006, 1064, 1249, 1396, 1431, 1469, 1581, 1627, 2931, 2958, 3217, 3640 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 0.79 (t, $J = 7.2$ Hz, 3H), 1.07 (t, $J = 7.4$ Hz, 3H), 1.21 (m, 2H), 1.56 (m, 2H), 2.26 (m, 2H), 2.58 (m, 4H), 3.98 (s, 3H), 4.15 (m, 4H), 4.42 (br s, 2H), 7.23–7.27 (m, 2H), 7.47–7.56 (m, 2H), 8.03 (s, 1H), 8.45 (s, 1H); ^{13}C NMR (DMSO-d_6, 200 MHz): δ 13.49, 13.85, 21.70, 23.90, 25.34, 29.32, 29.51, 51.17, 56.14, 65.53, 103.80, 104.19, 107.71, 119.72, 125.20, 129.22, 130.38, 131.36, 135.56, 142.10, 143.52, 146.84, 148.14, 151.44, 151.44, 155.14, 158.47; GC–MS (m/z): 602 (M^+).

*4.1.6.4. {2-Butyl-4-chloro-1-[3-(7-methoxy-4-(4-methoxyphenylamino) quinazolin-6-yloxy) propyl]-1*H*-imidazol-5-yl}methanol (**40**).* By reducing aldehyde group of compound **32**, compound **40** was obtained as white solid in 85% yield; m.p. 86–89 °C; IR (KBr): 550, 860, 1029, 1064, 1238, 1388, 1431, 1574, 1598, 1624, 2930, 2958, 3310, 3640 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 0.88 (t, $J = 7.2$ Hz, 3H), 1.27–1.42 (m, 4H), 1.64 (m, 2H), 2.57 (t, $J = 7.4$ and 8.0 Hz, 2H), 3.77 (s, 3H), 3.86 (s, 3H), 4.14 (m, 2H), 4.29 (m, 2H), 4.66 (s, 2H), 6.83 (d, $J = 8.4$ Hz, 2H), 7.13 (s, 1H), 7.60 (d, $J = 8.4$ Hz, 2H), 7.82 (s, 1H), 8.25 (s, 1H); HRMS (m/z): Calculated for $C_{27}H_{32}N_5O_4Cl$ $(M + H)^+ = 526.2221$, found = 526.2216.

*4.1.6.5. {2-Butyl-4-chloro-1-[3-(4-(3-iodophenylamino)-7-methoxyquinazolin-6-yloxy) propyl]-1*H*-imidazol-5-yl}methanol (**41**).* By reducing aldehyde group of compound **33**, compound **41** was obtained as white solid in 95% yield; m.p. 123–126 °C; IR (KBr): 586, 771, 852, 1002, 1060, 1238, 1388, 1427, 1469, 1508, 1573, 1624, 2927, 3190, 3300, 3640 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 0.82 (t, $J = 7.2$ Hz, 3H), 1.26 (m, 2H), 1.56 (m, 2H), 2.33 (m, 2H), 2.52 (t, $J = 7.4$ and 8.2 Hz, 2H), 3.96 (s, 3H), 4.14 (m, 4H), 4.67 (s, 2H), 7.09 (t, $J = 8.2$ Hz, 1H), 7.21 (s, 1H), 7.45 (d, $J = 8.2$ Hz, 1H), 7.75 (d, $J = 8.2$ Hz, 1H), 7.99 (s, 1H), 8.13 (s, 1H), 8.64 (s, 1H); ^{13}C NMR (DMSO-d_6, 200 MHz): δ 13.48, 21.70, 25.31, 29.32, 29.33, 51.22, 55.93, 65.24, 102.69, 107.33, 108.81, 121.01, 125.19, 125.50, 129.69, 130.37, 131.50, 141.00, 146.80, 147.10, 147.79, 152.71, 154.43, 155.94; GC–MS (m/z): 622 (M^+).

*4.1.6.6. {1-[3-(4-(3-Bromophenylamino)-7-methoxyquinazolin-6-yloxy) propyl]-2-butyl-4-chloro-1*H*-imidazol-5-yl}methanol (**42**).* By reducing aldehyde group of compound **34**, compound **42** was obtained as white solid in 95% yield; m.p. 117–121 °C; IR (KBr): 771, 1002, 1068, 1242, 1388, 1431, 1508, 1573, 1596, 1624, 2927, 3190, 3310, 3641 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 0.81 (t, $J = 7.2$ Hz, 3H), 1.56 (m, 2H), 1.93 (m, 2H), 2.33 (m, 2H), 2.52 (t, $J = 7.4$ and 8.2 Hz, 2H), 3.96 (s, 3H), 4.14 (m, 4H), 4.67 (s, 2H), 7.22–7.25 (m, 3H), 7.68 (s, 1H), 8.00 (s, 1H), 8.05 (s, 1H), 8.64 (s, 1H); ^{13}C NMR (DMSO-d_6, 200 MHz): δ 13.46, 21.69, 25.32, 29.31, 29.55, 51.23, 55.94, 65.31, 102.76, 107.37, 108.85, 120.43, 121.12, 123.89, 125.19, 125.53, 130.29, 141.22, 146.89, 147.10, 147.84, 152.68, 154.49, 155.96; GC–MS (m/z): 575 (M^+).

*4.1.6.7. {2-Butyl-4-chloro-1-[3-(4-(3-fluorophenylamino)-7-methoxyquinazolin-6-yloxy) propyl]-1*H*-imidazol-5-yl}methanol (**43**).* By reducing aldehyde group of compound **35**, compound **43** was obtained as white solid in 85% yield; m.p. 96–100 °C; IR (KBr): 582, 678, 771, 856, 1002, 1141, 1249, 1388, 1431, 1512, 1577, 1624, 2931, 3197, 3310, 3629 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 0.82 (t, $J = 7.0$ Hz, 3H), 1.26 (m, 2H), 1.65 (m, 2H), 2.34 (m, 2H), 2.53 (t, $J = 8.0$ Hz, 2H), 3.96 (s, 3H), 4.16 (m, 4H), 4.68 (s, 2H), 6.83 (t, $J = 8.0$ Hz, 1H), 7.21 (s, 1H), 7.32 (dd, $J = 8.0$ Hz, 1H), 7.44 (d, $J = 8.0$ Hz, 1H), 7.73 (br d, 1H), 8.15 (br s, 1H), 8.62 (s, 1H); ^{13}C NMR (DMSO-d_6, 200 MHz): δ 13.46, 21.69, 25.31, 29.32, 29.54, 51.21, 55.92, 65.29, 102.78, 107.16, 108.24, 108.76, 109.23, 109.65, 117.36, 125.19, 129.72, 129.91, 141.42, 146.90, 147.83, 152.59, 154.48, 156.03, 164.36; GC–MS (m/z): 514 (M^+).

*4.1.6.8. {2-Butyl-4-chloro-1-[3-(4-(3-ethynylphenylamino)-7-methoxyquinazolin-6-yloxy) propyl]-1*H*-imidazol-5-yl}methanol (**44**).* By reducing aldehyde group of compound **36**, compound **44** was obtained as white solid in 85% yield; m.p. 103–106 °C; IR (KBr): 590, 786, 1010, 1068, 1145, 1249, 1388, 1431, 1512, 1581, 1624, 1662, 2110, 2927, 3286, 3630 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 0.84 (t, $J = 7.2$ Hz, 3H), 1.28 (m, 2H), 1.59 (m, 2H), 2.35 (m, 2H), 2.54 (t, $J = 7.4$ and 8.2 Hz, 2H), 3.09 (s, 3H), 3.95 (s, 3H), 4.22 (m, 4H), 4.68 (s, 2H), 7.20–7.38 (m, 3H), 7.77 (d, $J = 7.8$ Hz, 1H), 7.88 (s, 1H), 8.11 (br s, 1H), 8.59 (s, 1H); ^{13}C NMR (DMSO-d_6, 200 MHz): δ 13.49, 21.70, 25.31, 29.33, 29.35, 51.19, 55.96, 65.27, 80.56, 84.00, 102.84, 106.84, 108.50, 121.60, 122.63, 124.84, 125.00, 125.50, 126.49, 128.87, 139.56, 146.00, 146.80, 147.84, 152.52, 154.52, 156.20; GC–MS (m/z): 520 (M^+).

4.2. Biological assay

4.2.1. In vitro *growth inhibition assay*

The cells were maintained in Dulbecco's Modified Eagle's Medium (DMEM) [Sigma-Aldrich Inc., USA] supplemented with 10% fetal bovine serum [Sigma Chemical Co., USA] in a CO_2 incubator. The cytotoxicity of the compounds was measured by MTT assay [24]. The cells were plated in a 96-well plate at the density of 5000 cells/well (A431) and 8000 cells/well for MCF-7. After 24 h, cell culture media was replaced with DMEM containing 0.1% FBS and the cells were treated with different concentrations of the compounds (0.01–50 μM). The cells were later incubated for 72 h. The cytotoxicity was measured by adding 5 mg/mL of MTT [Sigma-Aldrich Inc., USA] to each well and incubated for another 3 h. The purple formazan crystals were dissolved by adding 100 μL of DMSO to each well. The absorbance was read at 570 nm in a spectrophotometer [Spectra Max 340]. The cell death was calculated as follows:

$$\text{Cell dealth} = 100 - [(\text{test absorbance}/\text{control absorbance}) \times 100]$$

The test result is expressed as the concentration of a test compound which inhibits the cell growth by 50% (IC_{50}).

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Appendix Supplementary data

^{1}H NMR, ^{13}C NMR, mass spectra of compounds **18**–**44** and **46**–**48** are available free of charge via Internet at http://www.sciencedirect.org. Supplementary data associated with this article can be found in the online version at doi:10.1016/j.ejmech.2008.07.023.

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