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Original article

Synthesis and biological evaluation of novel 2-(2-arylmethylene) hydrazinyl-4-aminoquinazoline derivatives as potent antitumor agents

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ABSTRACT

Two series of novel 2-(2-arylmethylene)hydrazinyl-4-aminoquinazoline derivatives were synthesized and evaluated for their cytotoxicity against H-460, HT-29, HepG2 and SGC-7901 cancer cell lines *in vitro*. Most compounds displayed moderate to excellent activity, with IC_{50} values ranging from 0.015 to 4.09 μM against all tested cell lines, respectively. The most promising compound **9p** (*E*)-2-(2-((1-(2,3-dichlorobenzyl)-1*H*-imidazol-2-yl)methylene)hydrazinyl)-*N*-(1-methylpiperidin-4-yl)quinazolin-4-amine with IC_{50} values of 0.031 μM, 0.015 μM, 0.53 μM and 0.58 μM, which was 4- to 224 times more active than references **10** and Iressa, had emerged as a lead for further structural modifications.

1. Introduction

Although development of novel targeted antitumor drugs have obtained important progress in recent years, cancer remains the major leading cause of death in the world due to drug resistance or undesirable toxic effects. Discovering antitumor activity of old drugs which have little side effects would be a promising approach to develop more effective antitumor agents. The worldwide used immunostimulatory agent Chloroquine (CQ) has recently aroused increasing attention owing to its unexpected cytotoxicity against different human cancer cell lines [1–4] (Fig.1). Its analogue **10** [5,6] was also reported for its significant anti-angiogenesis activity in chick embryo chorioallantoic membrane (CAM) assay [7].

Prompted by the outstanding cytotoxicity of CQ and compound **10**, we recently reported a series of 2-arylvinyl-4-aminoquinolines as well as their antitumor activity against four cancer cell lines (H-460, HT-29, HepG2 and SGC-7901) [8]. This study indicated that most compounds possessed promising cytotoxicity superior to **10**, and the improvement of activity depended strongly on the substituents at 2-positon and aliphatic amino groups at 4-positon of quinoline skeleton.

According to the previous structure–activity relationships (SARs) of 2-substituted-4-aminoquinolines [8], two series of novel 2-(2-arylmethylene)hydrazinyl-4-aminoquinazoline derivatives were newly designed based on bioisosterism theory, which was supposed to be practicable since 4-aminoquinazoline has been an attractive pharmacological skeleton present in many antitumor drugs, such as Iressa and Tarceva [9]. For the purpose of providing potential hydrogen bond to improve their activity, methylenehydrazinyl group as a linker was incorporated between quinazoline core and 2-aryl moieties to generate compounds **6a**–**6n**. To our knowledge, there never has been any studies about quinazoline derivatives with 2-(2-arylmethylene)hydrazinyl groups so far. Furthermore, in view of excellent antitumor activity of aryl imidazoles [10–12], compounds **9a**–**9p** with 1-benzyl-1*H*-imidazolyl groups instead of the substituted phenyl groups of **6a**–**6n** were synthesized to provide more effective antitumor agents. All target compounds were evaluated for their antitumor activity *in vitro* against four typical cancer cell lines (H-460, HT-29, HepG2 and SGC-7901 cell lines) and some of them showed promising cytotoxicity.

2. Results and discussion

2.1. Chemistry

2-(2-Arylmethylene)hydrazinyl-4-aminoquinazoline derivatives **6a**–**6n** were prepared as shown in Scheme 1. Commercially available 2-aminobenzoic acid condensed with urea at 160 °C for 12 h to get quinazoline-2,4-diol **2** as a white crystal, which was

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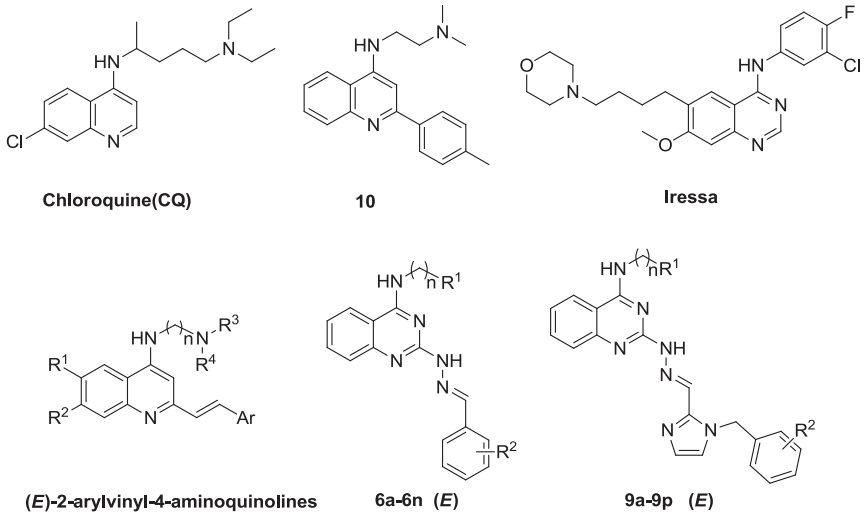


Fig. 1. Structures of CQ, CQ derivatives, Iressa and target compounds.

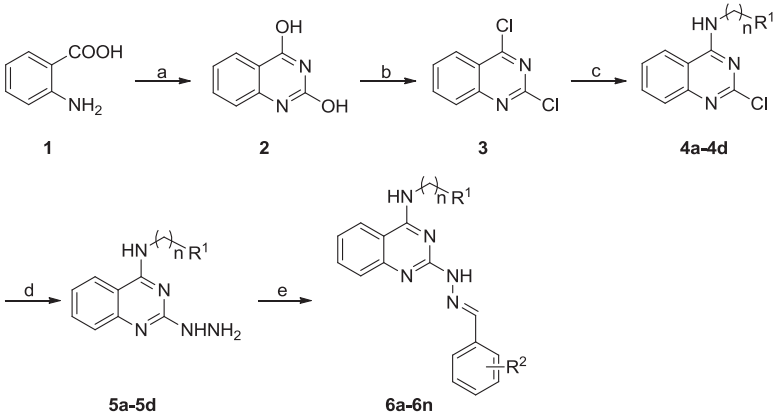
further treated with phosphoryl chloride in the presence of diisopropylethylamine (DIPEA) to provide 2,4-dichloroquinazoline **3** in 95% yield [13]. 2-Chloro-4-aminoquinazolines **4a**–**4d** were obtained *via* alkylation reaction of corresponding aliphatic amines with compound **3** in THF at room temperature, using triethylamine as an acid-binding agent [14]. Subsequently, compounds **4a**–**4d** were refluxed in 80% hydrazine hydrate to give rise to 2-hydrazinyl-4-aminoquinazolines **5a**–**5d** [15,16]. Finally, target compounds **6a**–**6n** were afforded by a classical condensation reaction of **5a**–**5d** and substituted benzaldehyde [16].

Further synthesis of 2-(2-((1-benzyl-1*H*-imidazol-2-yl)methylene)hydrazinyl)-4-aminoquinazoline derivatives **9a**–**9p** was outlined in Scheme 2. Intermediates **7a**–**7d** were prepared *via* alkylation of substituted benzyl chloride with imidazole in the presence of potassium carbonate in *N*,*N*-dimethylformamide (DMF). Treatment of **7a**–**7d** with *n*-butyllithium and DMF at −78 °C under nitrogen protection to afford key intermediates **8a**–**8d** [17,18]. Target compounds **9a**–**9p** were obtained from **5a**–**5d** and **8a**–**8d** in a similar manner as described for compounds **6a**–**6n**. All products were purified by silica gel chromatography.

The chemical structures of target compounds were determined by MS, ^{1}H NMR and ^{13}C NMR spectra. For the representative compound **6d**, the ^{1}H NMR spectrum indicated the chemical shift of NH–N = at $\delta = 10.73$ ppm and the N=CH appeared at $\delta = 8.15$ ppm were both in the form of singlet peak. Furthermore, the spatial configuration of compound **6d** perchlorate was identified by single crystal X-ray diffraction study. The ORTEP view of the structure shows that the molecule adopts an *E* configuration with respect to the N=CH double bond, as shown in Fig. 2.

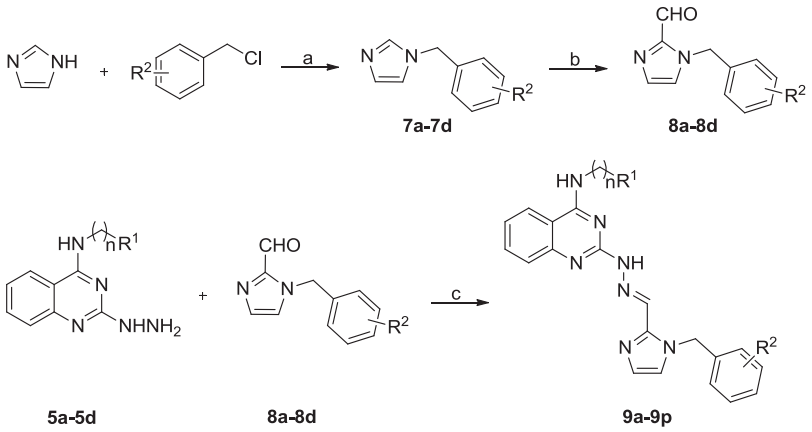
2.2. Cytotoxicity against tumor cells

All compounds **6a**–**6n** and **9a**–**9p** were evaluated for their cytotoxicity *in vitro* against four typical cancer cell lines including



6a: n = 2, R^1 = dimethylamino, R^2 = 4-chloro
6b: n = 2, R^1 = dimethylamino, R^2 = 4-fluoro
6c: n = 2, R^1 = dimethylamino, R^2 = 2-chloro-4-fluoro
6d: n = 3, R^1 = dimethylamino, R^2 = 4-chloro
6e: n = 3, R^1 = dimethylamino, R^2 = 4-fluoro
6f: n = 3, R^1 = dimethylamino, R^2 = 2-chloro-4-fluoro
6g: n = 3, R^1 = *N*-morpholino, R^2 = 4-chloro
6h: n = 3, R^1 = *N*-morpholino, R^2 = 4-fluoro
6i: n = 3, R^1 = *N*-morpholino, R^2 = 2-hydroxy
6j: n = 3, R^1 = *N*-morpholino, R^2 = 3-hydroxy
6k: n = 0, R^1 = *N*-methylpiperidin-4-yl, R^2 = 4-chloro
6l: n = 0, R^1 = *N*-methylpiperidin-4-yl, R^2 = 4-fluoro
6m: n = 0, R^1 = *N*-methylpiperidin-4-yl, R^2 = 2-chloro-4-fluoro
6n: n = 0, R^1 = *N*-methylpiperidin-4-yl, R^2 = 2,5-dimethoxy

Scheme 1. Reagents and conditions: (a) urea, 160 °C, 12 h; (b) $POCl_3$/diisopropylethylamine, 90 °C, 6 h; (c) $NH_2(CH_2)nR^1$/THF/TEA, 30 °C, 15 min; (d) EtOH/80% $NH_2NH_2{\cdot}H_2O$, 80–100 °C, 1 h; (e) ArCHO/Toluene, r.f., 2–3 h.



9a: n = 2, R^1 = dimethylamino, R^2 = H
9b: n = 2, R^1 = dimethylamino, R^2 = 4-methyl
9c: n = 2, R^1 = dimethylamino, R^2 = 4-fluoro
9d: n = 2, R^1 = dimethylamino, R^2 = 2,3-dichloro
9e: n = 3, R^1 = dimethylamino, R^2 = H
9f: n = 3, R^1 = dimethylamino, R^2 = 4-methyl
9g: n = 3, R^1 = dimethylamino, R^2 = 4-fluoro
6h: n = 3, R^1 = dimethylamino, R^2 = 2,3-dichloro
9i: n = 3, R^1 = *N*-morpholino, R^2 = H
9j: n = 3, R^1 = *N*-morpholino, R^2 = 4-methyl
9k: n = 3, R^1 = *N*-morpholino, R^2 = 4-fluoro
9l: n = 3, R^1 = *N*-morpholino, R^2 = 2,3-dichloro
9m: n = 0, R^1 = *N*-methylpiperidin-4-yl, R^2 = H
9n: n = 0, R^1 = *N*-methylpiperidin-4-yl, R^2 = 4-methyl
9o: n = 0, R^1 = *N*-methylpiperidin-4-yl, R^2 = 4-fluoro
9p: n = 0, R^1 = *N*-methylpiperidin-4-yl, R^2 = 2,3-dichloro

Scheme 2. Reagents and conditions: (a) K_2CO_3/DMF, 50 °C, 2 h; (b) i) *n*-BuLi/THF, −78 °C, 1 h, ii) DMF, −78 °C, 1 h, r.t., 2 h; (c) Toluene, r.f., 2–3 h.

non-small-cell lung cancer cell line (H-460), human colorectal cancer cell line (HT-29), human liver cancer cell line (HepG2) and human stomach cancer cell line (SGC-7901) by the 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay, taking compound **10** and Iressa as references. The results expressed as IC_{50} were summarized in Tables 1 and 2. The IC_{50} values are the average of at least three independent experiments.

As shown in Table 1, compounds **6a**–**6n** showed good to excellent cytotoxic activity and encouragingly, nine of them were more active against all tested cell lines than the lead compound **10** and Iressa, with IC_{50} values ranging from 0.023 to 4.09 μM. Compound **6k**, with 4-chlorophenyl group at 2-position and 1-methylpiperidin-4-amino group at 4-position exhibited the most potent cytotoxicity, while the corresponding compounds **6l**–**6n** containing fluoro or methoxy group instead of chloro group caused only a weaker or negative improvement in pharmacological activity compared to references, as can be seen from the comparison of **6a**–**6c** as well. It is interesting to note that all compounds except for **6f** exhibited better selectivity for HT-29 cell line than others, which have the makings of good drugs for colorectal cancer.

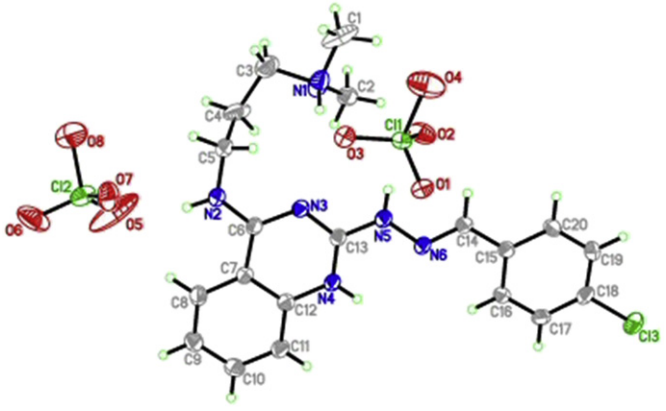


Fig. 2. ORTEP diagram showing the X-ray crystal structure of compound **6d** perchlorate.

Further analysis revealed that amino groups at 4-position of quinazoline ring had a notable influence on cytotoxicity. 4-Cycloamino analogues **6k**–**6m** exhibited superior activity to **6a**–**6j** bearing chain amino groups, respectively. Compared to dimethylamino group, the introduction of morpholino group at the terminal of chain amino moiety resulted in a certain decrease in activity (**6d** *vs*. **6g**, **6e** *vs*. **6h**).

Compounds **9a**–**9p** with 1-benzyl-1*H*-imidazolyl moieties were also examined for cytotoxicity, which yielded eleven compounds with remarkable IC_{50} values ranging from 0.015 to 3.68 μM against all tested cell lines, as listed in Table 2. As expected, the introduction of 1-benzyl-1*H*-imidazolyl moieties produced the improved activity than that of substituted phenyl groups, which resulted in about 2–12 times more active as compared between **9o** and **6l**. In addition, substituents on the benzyl had a major effect on the activity, with following rank order of potency: *H* < 4-methyl < 4-F < 2,3-dichloro. Turning to the effect of 4-aliphatic amino groups, 1-methylpiperidin-4-amino group made an enormous contribution to cytotoxicity, as demonstrated by the most prominent compound **9p** with IC_{50} values of 0.031 μM, 0.015 μM, 0.53 μM and 0.58 μM, which was 4- to 224 times better than references **10** and Iressa.

3. Conclusion

In summary, two series of novel 2-(2-arylmethylene)hydrazinyl-4-aminoquinazoline derivatives were synthesized and evaluated for their cytotoxicity against four human cancer cell lines (H-460, HT-29, HepG2 and SGC-7901). The pharmacological results were identical with our design decision and most compounds displayed moderate to excellent cytotoxic activity against one or more cancer cell lines owning to the introduction of methylenehydrazinyl fragment. Moreover, both substituents (R^2) on arylmethylene moieties at 2-position and 1-methylpiperidin-4-amino group on 4-

Table 1
Cytotoxicity of **6a**–**6n** against H-460, HT-29, HepG2 and SGC-7901 cell lines *in vitro*.

Compd.	*n*	R^1	R^2	IC_{50} (μmol/L) ± SD			
				H-460	HT-29	HepG2	SGC-7901
6a	2		4-Cl	3.25 ± 0.42	0.21 ± 0.07	0.37 ± 0.005	0.97 ± 0.21
6b	2		4-F	5.68 ± 0.82	1.53 ± 0.02	1.82 ± 0.17	4.10 ± 0.64
6c	2		2-Cl, 4-F	1.76 ± 0.091	0.33 ± 0.042	0.68 ± 0.011	1.68 ± 0.35
6d	3		4-Cl	1.49 ± 0.25	0.27 ± 0.007	0.55 ± 0.012	1.73 ± 0.26
6e	3		4-F	4.09 ± 0.23	0.87 ± 0.02	0.88 ± 0.07	2.76 ± 0.13
6f	3		2-Cl, 4-F	1.80 ± 0.12	1.15 ± 0.17	0.67 ± 0.05	1.66 ± 0.24
6g	3		4-Cl	4.00 ± 0.74	0.61 ± 0.03	1.74 ± 0.09	3.55 ± 0.46
6h	3		4-F	5.87 ± 0.62	2.19 ± 0.41	4.02 ± 0.50	6.77 ± 0.37
6i	3		2-OH	2.95 ± 0.35	2.08 ± 0.52	3.83 ± 0.28	3.21 ± 0.86
6j	3		3-OH	4.67 ± 0.29	6.32 ± 1.14	6.49 ± 0.58	4.90 ± 0.46
6k	0		4-Cl	0.21 ± 0.08	0.023 ± 0.03	0.17 ± 0.09	1.32 ± 0.29
6l	0		4-F	2.64 ± 0.32	1.41 ± 0.28	1.95 ± 0.05	1.76 ± 0.11
6m	0		2-Cl, 4-F	0.61 ± 0.05	0.27 ± 0.04	1.12 ± 0.62	1.63 ± 0.16
6n	0		2,5-diOMe	4.76 ± 0.27	2.83 ± 0.22	7.17 ± 1.41	4.24 ± 0.75
10				3.52 ± 0.31	1.35 ± 0.06	2.06 ± 0.39	4.92 ± 0.58
Iressa				5.59 ± 0.62	3.36 ± 0.24	6.42 ± 0.75	10.26 ± 2.13

position of the quinazoline skeleton were important for optimal cytotoxicity. This encouraging research provides a valuable leading compound **9** with IC_{50} values of 31 nM and 15 nM against H-460 and HT-29 cell lines, and highlights the potential for further development of novel 4-aminoquinazolines.

4. Experimental protocols

4.1. Chemistry

All melting points were obtained on a Büchi Melting Point B-540 apparatus (Büchi Labortechnik, Flawil, Switzerland) and were uncorrected. Mass spectra (MS) were taken in ESI mode on Agilent 1100 LC-MS (Agilent, Palo Alto, CA, USA). Proton (1H) nuclear magnetic resonance spectroscopy were performed using Bruker ARX-300, 300 MHz spectrometers (Bruker Bioscience, Billerica, MA, USA) with TMS as an internal standard. Unless otherwise noted, all the materials were obtained from commercially available sources and were used without further purification.

*4.1.1. Quinazoline-2,4-diol (**2**)*

A mixture of 2-aminobenzoic acid (68.5 g, 0.5 mol) and urea (210 g, 3.5 mol) was stirred at 160 °C for 12 h. After cooling to 100 °C, water (250 mL) was added and stirred for 1 h. The reaction mixture was cooled to room temperature, filtered and washed with water to afford title compound **2** (72 g, 89%) as a gray-white solid.

*4.1.2. 2,4-Dichloroquinazoline (**3**)*

Quinazoline-2,4-diol **2** (48.6 g, 0.3 mol) was added to a stirred solution of $POCl_3$ (200 mL) at room temperature, and then DIPEA (77.6 g, 0.3 mol) was added dropwise to the mixture. The reaction mixture was heated to 90 °C for 6 h. The mixture was concentrated under reduced pressure. The residue was poured into ice water (500 mL), stirred at room temperature for 1 h and separated by filtration to give title compound **3** (56.7 g, 95%).

*4.1.3. General procedure for preparation of 2-chloro-4-aminoquinazolines (**4a**–**4d**)*

Triethylamine (7.6 g, 0.075 mol) and corresponding aliphatic amine (0.05 mol) were successively added to a solution of 2,4-dichloroquinazolin **3** (10.0 g, 0.05 mol) in THF (80 mL). After stirring at 30 °C for 15 min, excess THF was removed under reduced pressure. The residue was poured into water (200 mL), separated by filtration to give compounds **4a**–**4d** (80–100%) as pale or light pink solids.

*4.1.4. General procedure for preparation of 2-hydrazinyl-4-aminoquinazolines (**5a**–**5d**)*

A solution of 2-chloro-4-aminoquinazoline **4** (0.02 mol) in EtOH (10 mL) was added dropwise to a stirred hydrazine monohydrate

Table 2
Cytotoxicity of **9a**–**9p** against H-460, HT-29, HepG2 and SGC-7901 cell lines *in vitro*.

Compd.	*n*	R^1	R^2	IC_{50} (μmol/L) ± SD			
				H-460	HT-29	HepG2	SGC-7901
9a	2		H	9.65 ± 2.38	2.62 ± 0.17	9.60 ± 1.82	4.30 ± 0.26
9b	2		4-Me	4.20 ± 0.11	1.41 ± 0.26	2.98 ± 0.35	2.75 ± 0.21
9c	2		4-F	1.05 ± 0.36	0.93 ± 0.14	3.06 ± 0.063	2.42 ± 0.52
9d	2		2,3-diCl	0.87 ± 0.08	0.26 ± 0.05	0.67 ± 0.02	1.85 ± 0.19
9e	3		H	4.67 ± 0.64	1.98 ± 0.22	4.04 ± 0.64	2.13 ± 0.20
9f	3		4-Me	1.69 ± 0.26	2.44 ± 0.18	3.68 ± 0.47	2.60 ± 0.33
9g	3		4-F	0.64 ± 0.15	0.63 ± 0.09	2.86 ± 0.23	3.51 ± 0.41
9h	3		2,3-diCl	0.43 ± 0.07	0.36 ± 0.05	0.85 ± 0.14	1.17 ± 0.32
9i	3		H	4.03 ± 0.45	2.84 ± 0.36	4.80 ± 0.72	3.96 ± 0.31
9j	3		4-Me	3.76 ± 0.18	3.16 ± 0.27	3.19 ± 0.41	3.02 ± 0.20
9k	3		4-F	2.47 ± 0.28	0.93 ± 0.08	2.21 ± 0.44	1.92 ± 0.13
9l	3		2,3-diCl	0.91 ± 0.22	0.72 ± 0.16	1.25 ± 0.34	2.66 ± 0.28
9m	0		H	1.03 ± 0.07	0.75 ± 0.09	1.42 ± 0.10	1.38 ± 0.35
9n	0		4-Me	0.77 ± 0.23	0.20 ± 0.03	1.23 ± 0.27	0.96 ± 0.52
9o	0		4-F	0.21 ± 0.09	0.65 ± 0.15	0.98 ± 0.26	0.78 ± 0.16
9p	0		2,3-diCl	0.031 ± 0.03	0.015 ± 0.006	0.53 ± 0.11	0.58 ± 0.23
10				3.52 ± 0.31	1.35 ± 0.06	2.06 ± 0.39	4.92 ± 0.58
Iressa				5.59 ± 0.62	3.36 ± 0.24	6.42 ± 0.75	10.26 ± 2.13

(50 mL) at 80 °C. The mixture was stirred under reflux for 1 h and cooled to room temperature. After filtration, the aqueous layer was extracted with n-butyl alcohol and the combined organic layer was washed with brine, and dried over Na_2SO_4. The solvent was removed under reduced pressure to afford title compounds **5a**–**5d** (82–88%) as pale solids.

*4.1.5. General procedure for preparation of compounds **6a**–**6n***

A mixture of 2-hydrazinyl-4-aminoquinazoline **5** (1 mmol) and substituted benzaldehyde (1 mmol) in benzene (5 mL) was stirred under reflux for 2–3 h, then the solvent was removed under reduced pressure. Ether (5 mL) was added to reaction mixture at room temperature and stirred for 30 min. The precipitate was collected by filtration and purified by silica gel chromatography (MeOH:CH_2Cl_2 = 15:1) to afford title compounds **6a**–**6n** (65–80%) as yellow solids.

*4.1.5.1. (E)-N^1-(2-(2-(4-Chlorobenzylidene)hydrazinyl)quinazolin-4-yl)-N^2,N^2-dimethylethane-1,2-diamine (**6a**).* Yellow solid, 72% yield. mp 148–152 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ: 8.58 (1H, s), 8.16 (2H, d, J = 9.3 Hz), 7.73 (2H, d, J = 8.4 Hz), 7.64 (1H, t, J = 7.5 Hz), 7.50 (3H, t, J = 8.4 Hz), 7.23 (1H, t, J = 7.5 Hz), 3.82 (2H, s), 3.04 (2H, s), 2.60 (6H, s). ^{13}C NMR (151 MHz, DMSO-d_6) δ: 160.95, 134.83, 133.64, 133.55, 129.27, 128.53, 123.84, 122.53, 112.56, 57.27, 44.28, 37.50. MS (ESI) m/z: 369.0, 371.0 (M^+).

*4.1.5.2. (E)-N^1-(2-(2-(4-Fluorobenzylidene)hydrazinyl)quinazolin-4-yl)-N^2,N^2-dimethylethane-1,2-diamine (**6b**).* Yellow solid, 68% yield. mp 133–135 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ: 8.50 (1H, s), 8.18 (1H, s), 8.14 (1H, d, J = 7.8 Hz), 7.76 (2H, dd, J = 8.4, 5.7 Hz), 7.63 (1H, t, J = 7.5 Hz), 7.49 (1H, d, J = 8.2 Hz), 7.34–7.17 (3H, m), 3.79 (2H, q), 2.93 (2H, t), 2.52 (6H, s). ^{13}C NMR (151 MHz, DMSO-d_6) δ: 163.67, 162.04, 160.84, 133.43, 132.42, 128.88, 124.68, 123.69, 122.35, 116.14, 112.44, 57.48, 44.55, 37.77. MS (ESI) m/z: 353.1, 354.0 (M^+).

*4.1.5.3. (E)-N^1-(2-(2-(2-Chloro-4-fluorobenzylidene)hydrazinyl)quinazolin-4-yl)-N^2,N^2-dimethylethane-1,2-diamine (**6c**).* Yellow solid,

65% yield. mp 126–129 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ: 10.98 (1H, s), 8.51 (1H, s), 8.12–8.03 (3H, m), 7.58 (1H, t, J = 8.1, 7.2 Hz), 7.47 (1H, dd, J = 9.0, 2.4 Hz), 7.42 (1H, d, J = 8.1 Hz), 7.29 (1H, td, J = 8.7, 2.7 Hz), 7.18 (1H, t, J = 8.4, 7.2 Hz), 3.67 (2H, q), 2.56 (2H, t), 2.24 (6H, s). MS (ESI) m/z: 387.0, 389.0 (M^+).

*4.1.5.4. (E)-N^1-(2-(2-(4-Chlorobenzylidene)hydrazinyl)quinazolin-4-yl)-N^3,N^3-dimethylpropane-1,3-diamine (**6d**).* Yellow solid, 76% yield. mp 140–144 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ: 10.73 (1H, s), 8.28 (1H, t, J = 5.4 Hz), 8.15 (1H, s), 8.08 (1H, d, J = 7.8 Hz), 7.69 (2H, d, J = 8.4 Hz), 7.57 (1H, t, J = 8.1 Hz), 7.44 (3H, q, J = 8.1, 8.4 Hz), 7.16 (1H, t, J = 8.1 Hz), 3.58 (2H, q), 2.38 (2H, t), 2.19 (6H, s), 1.88–1.79 (2H, p). MS (ESI) m/z: 382.7, 384.7 (M^+).

*4.1.5.5. (E)-N^1-(2-(2-(4-Fluorobenzylidene)hydrazinyl)quinazolin-4-yl)-N^3,N^3-dimethylpropane-1,3-diamine (**6e**).* Yellow solid, 71% yield. mp 163–166 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ: 10.72 (1H, s), 8.21 (1H, t), 8.15 (1H, s), 8.04 (1H, d, J = 8.1 Hz), 7.72 (2H, dd, J = 8.7, 5.7 Hz), 7.57 (1H, t, J = 8.1,7.2 Hz), 7.41 (1H, d, J = 8.1 Hz), 7.25 (2H, t, J = 9.0, 8.7 Hz), 7.15 (1H, t, J = 7.8, 7.2 Hz), 3.57 (1H, q), 2.35 (2H, t), 2.18 (6H, s), 1.88–1.78 (2H, p). MS (ESI) m/z: 366.8, 367.8 (M^+).

*4.1.5.6. (E)-N^1-(2-(2-(2-Chloro-4-fluorobenzylidene)hydrazinyl)quinazolin-4-yl)-N^3,N^3-dimethylpropane-1,3-diamine (**6f**).* Yellow solid, 69% yield. mp 120–123 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ: 11.01 (1H, s), 8.51 (1H, s), 8.23 (1H, t), 8.06 (2H, t, J = 8.4 Hz), 7.58 (1H, t, J = 8.1 Hz), 7.48 (1H, dd, J = 9.0, 2.7 Hz), 7.42 (1H, d, J = 8.1 Hz), 7.30 (1H, td, J = 8.7, 2.7 Hz), 7.18 (1H, t, J = 8.1 Hz), 3.56 (2H, q), 2.33 (2H, t), 2.16 (6H, s), 1.87–1.77 (2H, p). MS (ESI) m/z: 400.7, 402.6 (M^+).

*4.1.5.7. (E)-2-(2-(4-Chlorobenzylidene)hydrazinyl)-N-(3-morpholinopropyl)quinazolin-4-amine (**6g**).* Yellow solid, 72% yield. mp 177–180 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ: 10.81 (1H, s), 8.15 (2H, s), 8.08 (1H, d, J = 8.1 Hz), 7.69 (2H, d, J = 8.7 Hz), 7.58 (1H, td, J = 7.2 Hz), 7.50–7.40 (3H, m, J = 8.7, 7.8 Hz), 7.17 (1H, t, J = 6.9 Hz), 3.57 (6H, t), 2.44–2.33 (6H, m), 1.92–1.79 (2H, p). MS (ESI) m/z: 425.1, 427.1 (M^+).

*4.1.5.8. (E)-2-(2-(4-Fluorobenzylidene)hydrazinyl)-N-(3-morpholinopropyl)quinazolin-4-amine (**6h**).* Yellow solid, 68% yield. mp 173–176 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ: 12.24 (1H, s), 9.61 (1H, s), 8.41 (1H, d, J = 7.8 Hz), 8.35 (1H, s), 8.02 (2H, dd, J = 8.1, 6.0 Hz), 7.90 (1H, d, J = 8.4 Hz), 7.81 (1H, t, J = 7.2 Hz), 7.44 (1H, t, J = 7.5 Hz), 7.34 (2H, t, J = 8.4 Hz), 3.65 (6H, s), 2.62 (6H, s), 2.04–1.90 (2H, p). MS (ESI) m/z: 409.0, 410.0 (M^+).

*4.1.5.9. (E)-2-(2-(2-Hydroxybenzylidene)hydrazinyl)-N-(3-morpholinopropyl)quinazolin-4-amine (**6i**).* Yellow solid, 65% yield. mp 235–238 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ: 12.28 (1H, s), 11.11 (1H, s), 8.24 (2H, s), 8.08 (1H, d, J = 8.1 Hz), 7.60 (1H, t, J = 7.8 Hz), 7.36 (2H, q, J = 8.4, 7.5 Hz), 7.20 (2H, q, J = 14.4, 6.9 Hz), 6.95–6.81 (2H, m), 3.62 (2H, q), 3.57 (4H, t), 2.44 (2H, t), 2.34 (4H, t), 1.92–1.77 (2H, p). ^{13}C NMR (151 MHz, DMSO-d_6) δ: 161.14, 158.02, 157.07, 142.31, 133.44, 130.28, 129.99, 125.64, 123.64, 122.38, 120.05, 119.65, 116.99, 112.82, 66.92, 56.94, 54.16, 26.21. MS (ESI) m/z: 407.0, 408.0 (M^+).

*4.1.5.10. (E)-2-(2-(3-Hydroxybenzylidene)hydrazinyl)-N-(3-morpholinopropyl)quinazolin-4-amine (**6j**).* Yellow solid, 67% yield. mp 128–130 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ: 12.11 (1H, s), 9.72 (1H, s), 9.42 (1H, s), 8.35 (1H, d, J = 8.1 Hz), 8.25 (1H, s), 7.80 (2H, d), 7.42 (1H, t, J = 7.5 Hz), 7.33 (1H, s), 7.28 (2H, d, J = 5.1 Hz), 6.89 (1H, t, J = 5.1 Hz), 3.63 (6H, s), 2.89 (1H, s), 2.73 (1H, s), 2.56 (4H, s), 1.98–1.88 (2H, p). MS (ESI) m/z: 407.0, 408.0 (M^+).

*4.1.5.11. (E)-2-(2-(4-Chlorobenzylidene)hydrazinyl)-N-(1-methylpiperidin-4-yl)quinazolin-4-amine (**6k**).* Yellow solid, 78% yield. mp 189–193 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ: 10.91 (1H, s), 8.19 (1H, d, J = 7.8 Hz), 8.14 (1H, s), 7.86 (1H, d, J = 7.2 Hz), 7.70 (2H, d, J = 8.1 Hz), 7.58 (1H, t, J = 7.6 Hz), 7.45 (3H, q, J = 8.4 Hz), 7.17 (1H, t, J = 7.2 Hz), 4.29–4.11 (1H, m), 2.96 (2H, d), 2.31 (3H, s), 2.18 (2H, t), 1.99 (2H, d), 1.76 (2H, q). ^{13}C NMR (151 MHz, DMSO-d_6) δ: 160.13, 157.00, 135.12, 133.30, 133.11, 129.17, 128.31, 125.41, 123.74, 121.97, 112.63, 54.80, 47.67, 45.85, 30.97. MS (ESI) m/z: 394.8, 396.9 (M^+).

*4.1.5.12. (E)-2-(2-(4-Fluorbenzylidene)hydrazinyl)-N-(1-methylpiperidin-4-yl)quinazolin-4-amine (**6l**).* Yellow solid, 74% yield. mp 178–182 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ: 10.85 (1H, s), 8.20 (1H, d, J = 8.1 Hz), 8.16 (1H, s), 7.92 (1H, d, J = 7.2 Hz), 7.74 (2H, dd, J = 8.7, 5.7 Hz), 7.59 (1H, t, J = 7.2 Hz), 7.45 (1H, d, J = 8.1 Hz), 7.26 (2H, t, J = 9.0, 8.7 Hz), 7.17 (1H, t, J = 7.2 Hz), 4.27–4.15 (1H, m), 3.01 (2H, d), 2.35 (3H, s), 2.27 (2H, t), 2.01 (2H, d), 1.81 (2H, q). MS (ESI) m/z: 379.0, 380.0 (M^+).

*4.1.5.13. (E)-2-(2-(2-Chloro-4-fluorobenzylidene)hydrazinyl)-N-(1-methylpiperidin-4-yl)quinazolin-4-amine (**6m**).* Yellow solid, 71% yield. mp 155–158 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ: 11.01 (1H, s), 8.50 (1H, s), 8.20 (1H, d, J = 8.4 Hz), 8.09 (1H, dd, J = 8.7, 6.6 Hz, 1H), 7.86 (1H, d, J = 7.5 Hz), 7.59 (1H, t, J = 8.1 Hz), 7.49 (1H, dd, J = 8.7, 2.4 Hz), 7.43 (1H, d, J = 8.1 Hz), 7.31 (1H, td, J = 8.4, 2.4 Hz), 7.18 (1H, t, J = 7.8 Hz), 4.26–4.10 (1H, m), 2.92 (2H, d), 2.27 (3H, s), 2.10 (2H, t), 1.98 (2H, d), 1.74 (2H, q). MS (ESI) m/z: 413.2, 415.2 (M^+).

*4.1.5.14. (E)-2-(2-(2,5-Dimethoxybenzylidene)hydrazinyl)-N-(1-methylpiperidin-4-yl)quinazolin-4-amine (**6n**).* Yellow solid, 76% yield. mp 160–163 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ: 10.83 (1H, s), 8.41 (1H, s), 8.18 (1H, d, J = 8.1 Hz), 7.83 (1H, d, J = 7.5 Hz), 7.56 (1H, t, J = 7.2 Hz), 7.47 (1H, d, J = 3.0 Hz), 7.39 (1H, d, J = 8.1 Hz), 7.14 (1H, t, J = 7.5 Hz), 7.00 (1H, d, J = 9.0 Hz), 6.90 (1H, dd, J = 9.0, 3.0 Hz), 4.29–4.15 (1H, m), 3.80 (3H, s), 3.78 (3H, s), 2.89 (2H, d), 2.22 (3H, s), 2.10–1.90 (4H, m), 1.71 (2H, q). MS (ESI) m/z: 421.2, 422.2 (M^+).

*4.1.6. 1-substituted benzyl-1H-imidazoles (**7a**–**7d**)*

A mixture of potassium carbonate (15.2 g, 0.11 mol), imidazole (6.8 g, 0.1 mol) in DMF (60 mL) was stirred for 20 min, then substituted benzyl chloride (0.11 mol) was added dropwise to the solution. The reaction mixture was stirred at 50 °C for 2 h and poured into water (250 mL). The aqueous layer was extracted with CH_2Cl_2 and the combined organic layer was washed with water repeatedly, and dried over Na_2SO_4. The solvent was removed under reduced pressure to afford title compounds **7a**–**7d** as pale yellow oils.

*4.1.7. 1-substituted benzyl-1H-imidazole-2-carbaldehydes (**8a**–**8d**)*

n-Butyllithium (40 mmol) (16 mL of a 2.5 mol/dm^{-3} solution in hexanes) was added dropwise to a stirred solution of 1-substituted benzyl-1*H*-imidazole **7** (30 mmol) in dry THF (60 mL) under nitrogen at −78 °C. The mixture was stirred for 1 h, then DMF (100 mmol) was added dropwise. The mixture was then allowed to warm to ambient temperature and stirred for a further 2 h. The reaction was quenched with saturated ammonium chloride (50 mL). The aqueous layer was extracted with ether and the combined organic layer washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The residue was chromatographed (petroleum ether/ethyl acetate) to yield the title compounds **8a**–**8d** (23–49%) as colorless or white solids.

*4.1.8. General procedure for preparation of compounds **9a**–**9p***

A mixture of 2-hydrazinyl-4-aminoquinazoline **5** (1 mmol) and 1-substituted benzyl-1*H*-imidazole-2-carbaldehyde **8** (1 mmol) in

benzene (5 mL) was stirred under reflux for 2–3 h. Then the solvent was removed under reduced pressure. Ether (5 mL) was added to reaction mixture at room temperature and stirred for 30 min. The precipitate was collected by filtration and purified by silica gel chromatography (MeOH:CH_2Cl_2 = 12:1) to afford title compounds **9a**–**9p** (58–76%) as yellow solids.

*4.1.8.1. (E)-N^1-(2-(2-((1-Benzyl-1H-imidazol-2-yl)methylene)hydrazinyl)quinazolin-4-yl)-N^2,N^2-dimethylethane-1,2-diamine (**9a**).* Yellow solid, 56% yield. mp 102–105 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ: 10.91 (1H, s), 8.13 (2H, d), 8.07 (1H, d, J = 8.4 Hz), 7.62–7.52 (3H, m), 7.43 (1H, s), 7.38 (1H, d, J = 8.2 Hz), 7.32–7.24 (3H, m), 7.18 (1H, t, J = 8.1 Hz), 7.02 (1H, s), 5.78 (2H, s), 3.62 (2H, q), 2.63 (2H,t), 2.29 (6H, s). MS (ESI) m/z: 415.1, 416.1 (M^+).

*4.1.8.2. (E)-N^1-(2-(2-((1-(4-Methylbenzyl)-1H-imidazol-2-yl)methylene)hydrazinyl)quinazolin-4-yl)-N^2,N^2-dimethylethane-1,2-diamine (**9b**).* Yellow solid, 65% yield. mp 101–104 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ: 10.89 (1H, s), 8.09 (3H, t, J = 8.4 Hz), 7.59 (1H, t, J = 7.2 Hz), 7.48 (2H, d, J = 7.8 Hz), 7.41 (1H, s), 7.38 (1H, d, J = 8.1 Hz), 7.17 (1H, t, J = 7.5 Hz), 7.08 (2H, d, J = 7.8 Hz), 6.99 (1H, s), 5.75 (2H, s), 3.59 (2H, q), 2.47 (2H, t), 2.22 (3H, s), 2.14 (6H, s). MS (ESI) m/z: 427.6, 428.6 (M^+).

*4.1.8.3. (E)-N^1-(2-(2-((1-(4-Fluorobenzyl)-1H-imidazol-2-yl)methylene)hydrazinyl)quinazolin-4-yl)-N^2,N^2-dimethylethane-1,2-diamine (**9c**).* Yellow solid, 61% yield. mp 107–1110 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ: 10.99 (1H, s), 8.31 (1H, t), 8.17 (2H, d, J = 8.4 Hz), 7.77 (2H, dd, J = 8.1, 6.0 Hz), 7.61 (1H, t, J = 8.1 Hz), 7.51 (1H, s), 7.41 (1H, d, J = 7.8 Hz), 7.20–7.12 (3H, m, J = 8.7, 7.8 Hz), 7.03 (1H, s), 5.77 (2H, s), 3.61 (2H, q), 2.50 (2H, t), 2.16 (6H, s). MS (ESI) m/z: 433.0, 434.0 (M^+).

*4.1.8.4. (E)-N^1-(2-(2-((1-(2,3-Dichlorobenzyl)-1H-imidazol-2-yl)methylene)hydrazinyl)quinazolin-4-yl)-N^2,N^2-dimethylethane-1,2-diamine (**9d**).* Yellow solid, 72% yield. mp 116–118 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ: 10.84 (1H, s), 8.15 (1H, s), 8.03 (1H, d, J = 8.1 Hz), 7.96 (1H, t), 7.56 (2H, t, J = 7.8 Hz), 7.33 (2H, q, J = 8.4, 7.8, 3.3 Hz), 7.26 (1H, s), 7.15 (1H, t, J = 7.5 Hz), 7.08 (1H, s), 6.83 (1H, d, J = 7.2 Hz), 6.00 (2H, s), 3.53 (2H, q), 2.41 (2H, t), 2.10 (6H, s). MS (ESI) m/z: 482.9, 484.7 (M^+).

*4.1.8.5. (E)-N^1-(2-(2-((1-Benzyl-1H-imidazol-2-yl)methylene)hydrazinyl)quinazolin-4-yl)-N^3,N^3-dimethylpropane-1,3-diamine (**9e**).* Yellow solid, 73% yield. mp 105–107 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ: 10.89 (1H, s), 8.18 (1H, t), 8.10 (1H, s), 8.04 (1H, d, J = 8.1 Hz), 7.59 (3H, q, J = 8.1, 6.6 Hz), 7.44 (1H, s), 7.38 (1H, d, J = 8.1 Hz), 7.32–7.23 (3H, m, J = 7.2, 6.6 Hz), 7.17 (1H, t, J = 8.1 Hz), 7.00 (1H, s), 5.83 (2H, s), 3.49 (2H, q), 2.17 (2H, t), 2.10 (6H, s), 1.76–1.66 (2H, p). MS (ESI) m/z: 428.8, 429.8 (M^+).

*4.1.8.6. (E)-N^1-(2-(2-((1-(4-Methylbenzyl)-1H-imidazol-2-yl)methylene)hydrazinyl)quinazolin-4-yl)-N^3,N^3-dimethylpropane-1,3-diamine (**9f**).* Yellow solid, 69% yield. mp 159–162 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ: 10.90 (1H, s), 8.22 (1H, t), 8.10 (1H, s), 8.07 (1H, d, J = 8.1 Hz), 7.59 (1H, t, J = 7.8 Hz), 7.50 (2H, d, J = 7.8 Hz), 7.41 (1H, s), 7.38 (1H, d, J = 8.1 Hz), 7.17 (1H, t, J = 7.8 Hz), 7.09 (2H, d, J = 7.8 Hz), 6.99 (1H, s), 5.76 (2H, s), 3.51 (2H, q), 2.21 (5H, t), 2.13 (6H, s), 1.79–1.66 (2H, p). MS (ESI) m/z: 443.2, 444.2 (M^+).

*4.1.8.7. (E)-N^1-(2-(2-((1-(4-Fluorobenzyl)-1H-imidazol-2-yl)methylene)hydrazinyl)quinazolin-4-yl)-N^3,N^3-dimethylpropane-1,3-diamine (**9g**).* Yellow solid, 58% yield. mp 118–121 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ: 10.90 (1H, s), 8.51 (1H, s), 8.17 (1H, s), 8.07 (1H, d, J = 8.4 Hz), 7.60–7.56 (2H, dd, J = 7.8 Hz), 7.38–7.32 (2H, m, J = 8.1 Hz), 7.29 (1H, s), 7.22–7.14 (3H, m, J = 8.1, 7.8 Hz), 7.10 (1H, s), 5.77 (2H, s), 3.51 (2H, q), 2.19 (2H, t), 2.11 (6H, s), 1.77–1.65 (2H, p). MS (ESI) m/z: 447.1, 448.1 (M^+).

*4.1.8.8. (E)-N^1-(2-(2-((1-(2,3-Dichlorobenzyl)-1H-imidazol-2-yl)methylene)hydrazinyl)quinazolin-4-yl)-N^3,N^3-dimethylpropane-1,3-diamine (**9h**).* Yellow solid, 65% yield. mp 128–132 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ: 10.89 (1H, s), 8.22 (1H, t), 8.16 (1H, s), 8.05 (1H, d, J = 8.1 Hz), 7.56 (2H, q, J = 7.8, 5.1 Hz), 7.34 (2H, q, J = 7.8, 7.2 Hz), 7.28 (1H, s), 7.15 (1H, t, J = 7.8 Hz), 7.08 (1H, s), 6.87 (1H, d, J = 6.3 Hz), 5.99 (2H, s), 3.45 (2H, q), 2.18 (2H, t), 2.09 (6H, s), 1.77–1.63 (2H, p). ^{13}C NMR (151 MHz, DMSO-d_6) δ: 211.94, 161.09, 157.35, 143.35, 139.11, 133.16, 132.67, 130.72, 130.29, 129.90, 129.20, 126.22, 124.12, 123.54, 122.29, 112.96, 57.69, 49.15, 45.86, 27.08. MS (ESI) m/z: 497.6, 499.6 (M^+).

*4.1.8.9. (E)-2-(2-((1-Benzyl-1H-imidazol-2-yl)methylene)hydrazinyl)-N-(3-morpholinopropyl)quinazolin-4-amine (**9i**).* Yellow solid, 71% yield. mp 123–125 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ: 10.94 (1H, s), 8.17 (1H, t), 8.09 (2H, d), 7.65–7.55 (3H, m), 7.44 (1H, s), 7.38 (1H, d, J = 8.1 Hz), 7.33–7.23 (3H, m), 7.18 (1H, t, J = 7.8 Hz), 7.00 (1H, s), 5.83 (2H, s), 3.62–3.50 (6H, m), 2.35–2.17 (6H, m), 1.81–1.68 (2H, p). MS (ESI) m/z: 471.2, 472.2 (M^+).

*4.1.8.10. (E)-2-(2-((1-(4-Methylbenzyl)-1H-imidazol-2-yl)methylene)hydrazinyl)-N-(3-morpholinopropyl)quinazolin-4-amine (**9j**).* Yellow solid, 68% yield. mp 133–135 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ: 10.94 (1H, s), 8.23 (1H, t), 8.12 (2H, d, J = 7.8 Hz), 7.59 (1H, t, J = 7.2 Hz), 7.50 (2H, t), 7.39 (2H, d), 7.17 (1H, t, J = 8.4 Hz), 7.09 (2H, d, J = 7.8 Hz), 6.99 (1H, s), 5.76 (s, 2H), 3.60–3.50 (6H, m), 2.27 (4H, s), 2.23 (5H, s), 1.80–1.68 (2H, p). ^{13}C NMR (151 MHz, DMSO-d_6) δ: 211.95, 161.23, 157.64, 151.89, 142.68, 137.48, 135.93, 134.16, 133.08, 129.59, 129.11, 125.99, 124.70, 123.90, 122.23, 112.94, 66.90, 56.88, 54.08, 49.90, 26.16, 21.41. MS (ESI) m/z: 485.1, 486.0 (M^+).

*4.1.8.11. (E)-2-(2-((1-(4-Fluorobenzyl)-1H-imidazol-2-yl)methylene)hydrazinyl)-N-(3-morpholinopropyl)quinazolin-4-amine (**9k**).* Yellow solid, 64% yield. mp 110–114 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ: 10.96 (1H, s), 8.29 (1H, t), 8.15 (2H, d), 7.75 (2H, t, J = 7.8, 6.0 Hz), 7.59 (1H, t, J = 7.5 Hz), 7.49 (1H, s), 7.39 (1H, d, J = 8.4 Hz), 7.19 (1H, t, J = 7.8 Hz), 7.13 (2H, t, J = 8.7 Hz), 7.01 (1H, s), 5.79 (2H, s), 3.59 (2H, q), 3.54 (4H, t), 2.28 (4H, s), 2.22 (2H, t), 1.75 (2H, p). ^{13}C NMR (151 MHz, DMSO-d_6) δ: 212.09, 161.26, 157.63, 151.87, 142.62, 135.21, 133.34, 132.78, 131.54, 131.43, 129.64, 125.99, 124.04, 123.84, 122.27, 116.03, 115.75, 113.00, 66.89, 56.87, 54.08, 49.27, 26.15. MS (ESI) m/z: 489.0, 490.0 (M^+).

*4.1.8.12. (E)-2-(2-((1-(2,3-Dichlorobenzyl)-1H-imidazol-2-yl)methylene)hydrazinyl)-N-(3-morpholinopropyl)quinazolin-4-amine (**9l**).* Yellow solid, 76% yield. mp 160–164 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ: 10.85 (1H, s), 8.15 (1H, s), 8.11 (1H, t), 8.05 (1H, d, J = 7.8 Hz), 7.56 (2H, t, J = 7.8, 6.3 Hz), 7.35 (1H, d, J = 9.0 Hz), 7.29 (1H, t, J = 8.4 Hz), 7.25 (1H, s), 7.15 (1H, t, J = 7.8 Hz), 7.07 (1H, s), 6.87 (1H, d, J = 6.6 Hz), 6.00 (2H, s), 3.53 (4H, t), 3.45 (2H, q), 2.27 (4H, s), 2.21 (2H, t), 1.77–1.64 (2H, p). MS (ESI) m/z: 539.0, 541.9 (M^+).

*4.1.8.13. (E)-2-(2-((1-Benzyl-1H-imidazol-2-yl)methylene)hydrazinyl)-N-(1-methylpiperidin-4-yl)quinazolin-4-amine (**9m**).* Yellow solid, 69% yield. mp 172–175 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ: 10.95 (1H, s), 8.18 (1H, d, J = 8.4 Hz), 8.09 (1H, s), 7.81 (1H, d, J = 7.8 Hz), 7.67 (2H, d, J = 6.6 Hz), 7.59 (1H, t, J = 8.1 Hz), 7.46 (1H, s), 7.37 (1H, d, J = 7.8 Hz), 7.27 (3H, t, J = 7.8, 7.5 Hz), 7.16 (1H, t, J = 8.1 Hz), 6.98 (s, 1H), 5.84 (s, 2H), 4.22 (1H, s), 2.66 (2H, s), 2.07 (3H, s), 1.78 (2H, s), 1.63 (4H, s). MS (ESI) m/z: 441.2, 442.1 (M^+).

*4.1.8.14. (E)-2-(2-((1-(4-Methylbenzyl)-1H-imidazol-2-yl)methylene) hydrazinyl)-N-(1-methylpiperidin-4-yl)quinazolin-4-amine (**9n**).* Yell ow solid, 74% yield. mp 167–170 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ: 10.92 (1H, s), 8.22 (1H, d, J = 8.1 Hz), 8.10 (1H, s), 7.89 (1H, d, J = 7.8 Hz), 7.58 (1H, t, J = 7.8 Hz), 7.52 (2H, d, J = 7.8 Hz), 7.42 (1H, s), 7.38 (1H, d, J = 8.4 Hz), 7.16 (1H, t, J = 7.5 Hz), 7.09 (2H, d, J = 7.8 Hz), 6.98 (1H, s), 5.75 (2H, s), 4.22 (1H, s), 2.73 (2H, t), 2.22 (3H, s), 2.12 (3H, s), 1.81 (2H, t), 1.77–1.61 (4H, q). ^{13}C NMR (151 MHz, DMSO-d_6) δ: 211.96, 160.65, 157.68, 152.04, 142.55, 137.66, 135.91, 133.38, 132.81, 129.72, 129.49, 129.39, 125.92, 124.05, 122.11, 112.84, 54.96, 49.86, 47.61, 46.30, 31.59, 21.42. MS (ESI) m/z: 455.1, 456.1 (M^+).

*4.1.8.15. (E)-2-(2-((1-(4-Fluorobenzyl)-1H-imidazol-2-yl)methylene) hydrazinyl)-N-(1-methylpiperidin-4-yl)quinazolin-4-amine (**9o**).* Yel low solid, 63% yield. mp 135–138 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ: 10.89 (1H, s), 8.21 (1H, d, J = 8.4 Hz), 8.16 (1H, s), 7.91 (1H, d, J = 8.1 Hz), 7.75 (2H, dd, J = 7.8 Hz), 7.61 (1H, t, J = 8.1 Hz), 7.44 (1H, s), 7.40 (1H, d, J = 8.4 Hz), 7.17 (1H, t, J = 7.8 Hz), 7.12 (2H, t, J = 9.0, 8.7 Hz), 6.99 (1H, s), 5.86 (2H, s), 4.23 (1H, s), 2.68 (2H, t), 2.08 (3H, s), 1.80 (2H, s), 1.64 (4H, s). MS (ESI) m/z: 459.1, 460.1 (M^+).

*4.1.8.16. (E)-2-(2-((1-(2,3-Dichlorobenzyl)-1H-imidazol-2-yl)methylene)hydrazinyl)-N-(1-methylpiperidin-4-yl)quinazolin-4-amine (**9p**).* Yellow solid, 67% yield. mp 154–157 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ: 10.91 (1H, s), 8.14 (2H, d, J = 5.4 Hz), 7.74 (1H, d, J = 7.8 Hz), 7.59 (2H, t, J = 7.8, 6.6 Hz), 7.35 (2H, d, J = 8.3 Hz), 7.19 (1H, s), 7.19 (1H, t, J = 7.8, 7.2 Hz), 7.04 (1H, s), 6.02 (2H, s), 4.09 (1H, s), 2.67 (2H, s), 2.06 (3H, s), 1.78 (2H, t), 1.61 (4H, q). MS (ESI) m/z: 509.4, 511.4 (M^+).

4.2. Cytotoxicity assay in vitro

The cytotoxic activity of compounds **6a**–**6n** and **9a**–**9p** was evaluated with non-small-cell lung cancer cell line (H-460), human colorectal cancer cell line (HT-29), human liver cancer cell line (HepG2) and stomach cancer cell line (SGC-7901) by the MTT method *in vitro*, with compound **10** and Iressa as references. The cancer cells were cultured in minimum essential medium (MEM) supplemented with 10% fetal bovine serum (FBS).

Approximately 4×10^3 cells, suspended in MEM medium, were plated onto each well of a 96-well plate and incubated in 5% CO_2 at 37 °C for 24 h. The test compounds were added to the culture medium at the indicated final concentrations and the cell cultures were continued for 72 h. Fresh MTT was added to each well at a final concentration of 5 μg/mL and incubated with cells at 37 °C for 4 h. The formazan crystals were dissolved in 100 μL DMSO per each well, and the absorbency at 492 nm (for the absorbance of MTT formazan) and 630 nm (for the reference wavelength) was measured with the ELISA reader. All of the compounds were tested twice in each of the cell lines. The results expressed as IC_{50} (inhibitory concentration of 50%) were the averages of two determinations and were calculated by using the Bacus Laboratories Incorporated Slide Scanner (Bliss) software.

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Appendix A. Supplementary material

Supplementary material associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.ejmech.2012.05.039

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