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Design, synthesis and antiviral activity of novel quinazolinones

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ABSTRACT

HIV-1 integrase (IN) is a validated therapeutic target for antiviral drug design. However, the emergence of viral strains resistant to clinically studied IN inhibitors demands the discovery of novel inhibitors that are structurally as well as mechanistically different. Herein, a series of quinazolinones were designed and synthesized as novel HIV-1 inhibitors. The new synthetic route provides a practical method for the preparation of 5-hydroxy quinazolinones. Primary bioassay results indicated that most of the quinazolinones possess anti-HIV activity, especially for compound **11b** with 77.5% inhibition rate at 10 μM emerged as a new active lead. Most of the synthesized compounds were also found to exhibit good anti-TMV activity, of which compound **9a** showed similar *in vivo* anti-TMV activity to commercial plant virucide Ribavirin. This work provides a new and efficient approach to evolve novel multi-functional antiviral agents by rational integration and optimization of previously reported antiviral agents.

1. Introduction

It was recently reported that there were 34.0 million (31.6 million–35.2 million) people living with HIV at the end of 2010, with 1.8 million (1.6 million–1.9 million) AIDS-related deaths and 2.7 million (2.4 million–2.9 million) new infections. The overall number of people living with HIV has increased as a result of new infections and the beneficial effects of the more widely available highly active anti-retroviral therapy (HAART), which employs a combinational use of drugs [1].

The currently FDA approved anti-HIV drugs belong to several different groups such as: nucleoside reverse transcriptase inhibitors (NRTIs), nucleotide reverse transcriptase inhibitors (NtRTIs), nonnucleoside reverse transcriptase inhibitors (NNRTIs), protease inhibitors (PIs), fusion inhibitors (FIs), co-receptor inhibitors (CRIs) and integrase inhibitors (INIs) [2].

Although the HAART has brought about a substantial decrease in the death rate and changed AIDS from a rapidly lethal disease into a chronic manageable condition, the retroviral infection can be only temporarily controlled but not eradicated since HIV-1 becomes almost undetectable in the plasma for more than two years, persisting in reservoirs. Furthermore, the HAART efficacy has been limited by the emergence of drug-resistant viral strains, drug-toxicity, the poor ability of patients to adhere to the prescribed therapy and costs, so a refining of the current therapies and the developing of new therapeutic paradigms are still warranted [3].

HIV-1 integrase (IN), the viral enzyme that catalyzes the integration of proviral cDNA into the host cell genome, has emerged as an attractive target for novel anti-AIDS agents [4–6]. Recently, raltegravir (MK-0518) (RAL, marketed as Isentress™ by Merck and Co.) was approved for clinical use by the FDA as a new HIV inhibitor targeting the viral integrase enzyme. Raltegravir disrupts the critical viral process of integration in which newly made viral DNA is inserted into the host cell chromosomal DNA [7]. Raltegravir is the first approved integrase inhibitor whereas other integrase inhibitors GS-9137 and S/GSK1349572 have reached clinical development (Fig. 1) [8,9]. Like other well-known diketo acid inhibitors, these compounds share two common structural chemotypes essential for the anti-integrase activity: a diketo acid chain able to interact with Mg^{2+} metal ions (marked in bold) and a properly oriented hydrophobic benzyl moiety (marked in dashed box) [10,11]. They selectively inhibit strand transfer reaction, suggesting that they bind at the IN/DNA interface, acting as "interfacial inhibitors" [12,13]. Despite the lack of detailed structural information about HIV-1 IN/DNA interactions, this speculative mechanism of action tends to be validated by the recent X-ray crystal structure of integrase from the

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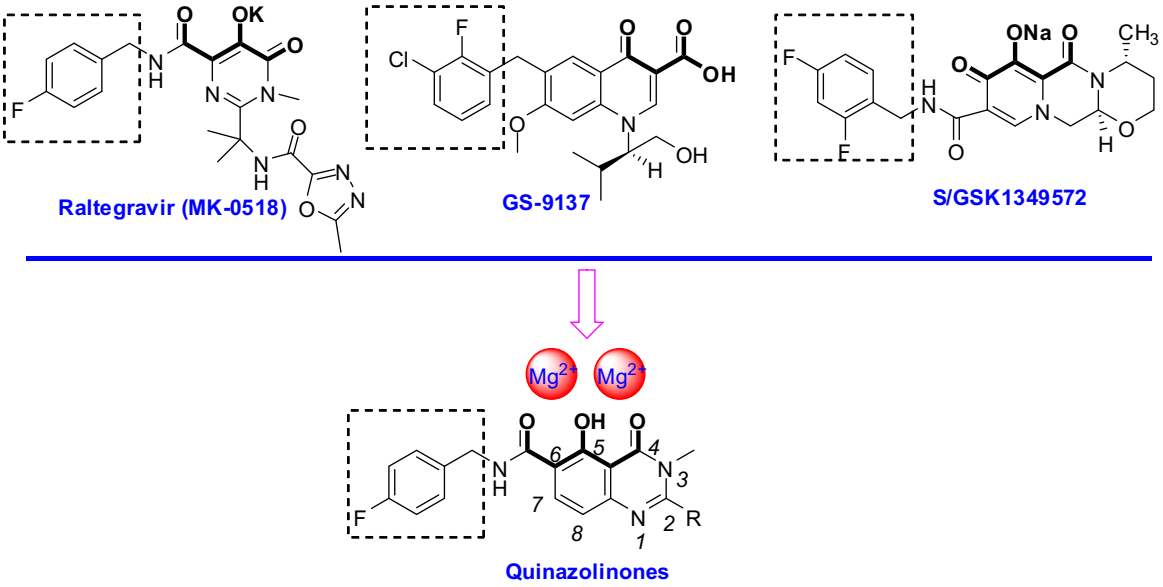


Fig. 1. Chemical structures of raltegravir (MK-0518), GS-9137, S/GSK1349572 and quinazolinones.

prototype foamy virus (PFV-1 IN) in complex with its cognate viral DNA and strand transfer inhibitors [14,15].

The quinazolinone nucleus and its derivatives have been extensively studied because of their wide range of pharmacological activities. As medicines, many of them display antifungal [16], antimicrobial [17], anti-HIV [18], antitubercular [19], anticancer [20], antiinflammatory [21], anticonvulsant [22], antidepressant [23], hypolipidemic [24], antiulcer [25], analgesic [26] or immunotropic activities [27] and are also known to act as thymidyalate synthase [28], poly(ADP-ribose) polymerase (PARP) [29], and protein tyrosine kinase [30] inhibitors. As pesticides, they are used as insecticides [31] and fungicides [32]. In light of the growing number of applications in recent years there has been an enormous increase in the interest among biologists and chemists in their synthesis and bioactivity of quinazoline derivatives. In our previous work in this area we reported that some of these compounds showed antiviral activities against TMV and CMV [33].

Taking into account the above findings, a series of new derivatives containing a quinazolinone core (quinazolinones, Fig. 1) were designed and synthesized as chelating agents for bivalent metal ions. We propose that the free hydroxyl and two carbonyl groups on the quinazolinones might sufficiently bind to the two metal cofactors in the IN active site, and the substituents on the amide portion could provide the interactions with the hydrophobic pocket of the enzyme. The obtained compounds were characterized and evaluated for their antiviral activity against HIV. As we have found that the quinazolinone derivatives possess anti-TMV activity [33], the synthesized new structural compounds also were evaluated for their anti-TMV activity. Herein, we report the synthesis, evaluation and SAR studies of these new structural quinazolinone derivatives.

2. Results and discussion

2.1. Chemistry

As shown in Scheme 1, treatment of substituted phenol **1** with pivaloyl chloride gave amido protected compound **2** in 96% yield. Methylation of **2** with dimethyl sulfate afforded hydroxyl protected compound **3**. Regioselectively metalation and then subsequent acylation of compound **3** gave acid **4** in 81% high yield. Treatment of acid **4** with ethyl chloroformate and methylamine afforded substituted benzamide **5**. Oxidation of compound **5** with potassium permanganate gave acid **6** in 84% high yield. Treatment of **6** with 4-fluorobenzylamine afforded substituted benzamide **7**. As compound **7** contains three acylamino groups and a methoxyl, the next regioselective deprotection was carried out at several different conditions. The best result is that treatment of compound **7** with 6 M hydrochloric acid solution gave the key intermediate **8** in 61% yield. Treatment of **8** with a variety of substituted aldehydes in the presence of *p*-toluenesulfonic acid afforded benzo-heterocycle compounds **9a**–**h**. Oxidation of compounds **9a**–**h** with I_2 gave methoxy quinazolinones **10a**–**h**. Demethylation of compounds **10a**–**h** with $AlCl_3$ afforded hydroxy quinazolinones **11a**–**h**.

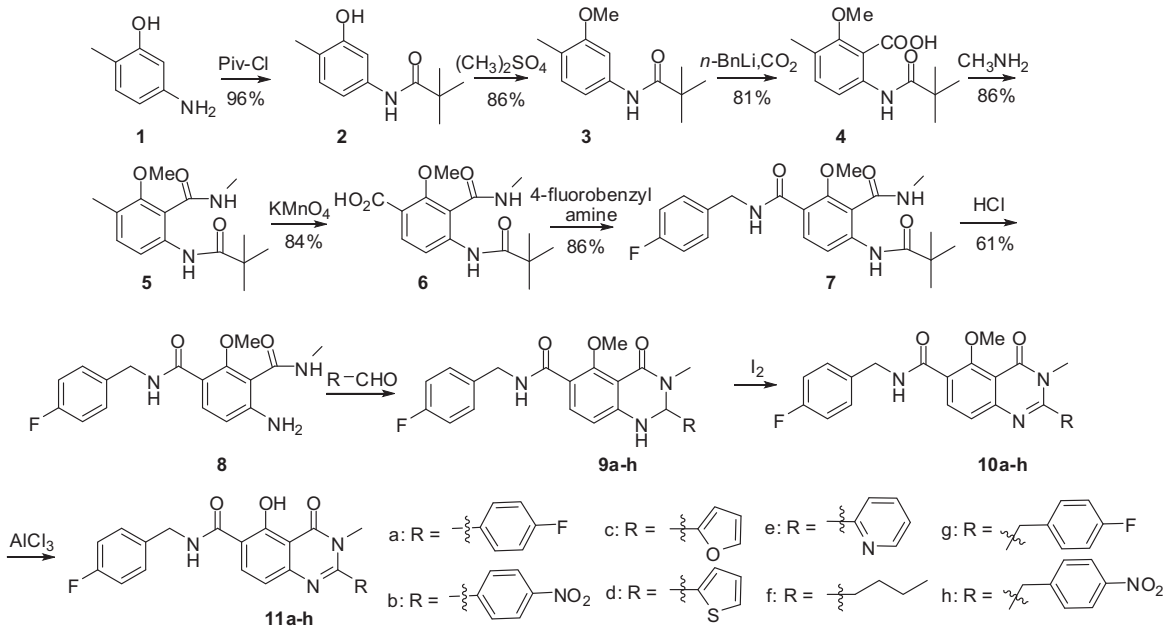
2.2. Anti-HIV activity

2.2.1. Cellular cytotoxicity screening

The cytotoxicity of compounds was evaluated by MTT (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide) assay method [34]. Briefly, TZM-bl cells were plated in 96-well plates and incubated for 18 h at 37 °C, followed by a second incubation for 48 h in the presence of the test compounds. MTT (20 μL at 5 mg/mL) was added to each well and incubated for 3 h at 37 °C. The plates were placed on a shaker for 10 min at room temperature and the OD_{550} measured using a Spectra MAX340 microplate reader (Molecular Devices) with a reference wave length at 690 nm.

2.2.2. Drug screening

The cell-based anti-HIV activity of the synthesized compounds was tested using our previously reported method [35]. Compounds were prepared from initial dimethyl sulfoxide (DMSO) stocks and plated as described. TZM-bl cells were seeded at concentration of 10^4 cells/well. The following day, samples and controls (AZT and MK-0518) were then added. Finally, the pseudotyped virus was added with final concentration of DMSO in all wells was maintained at 2%. The plates were incubated at 37 °C in a humidified CO_2 incubator for 48 h. Steady-glow substrate (Promega) was added directly to each well and cell lysis was allowed to proceed in the dark for 20 min. Luciferase activity was measured using the Envision microplate luminometer (PerkinElmer).



Scheme 1. Synthesis of compounds **11a**–**h**.

2.2.3. Biological evaluation of synthesized compounds against HIV

The first toxic testing toward TZM-bl cells indicated that all the synthesized compounds showed no toxic to TZM-bl cells at 10 μM.

The antiviral activity of the synthesized compounds at 10 μM was evaluated by using the above cell-based method. The commercial MK-0518 and AZT were used as positive controls. As shown in Table 1, most of synthesized compounds exhibited anti-HIV activity, especially compound **11b** with 77.5% inhibition rate emerged as new lead compound.

The 1,2-dihydrogen quinazolinones **9a**–**h** showed moderate to good activity against HIV, except for compound **9h**, which exhibited no activity. Comparing with **9a**–**h**, the 5-methoxy quinazolinones **10a**–**h** showed lower anti-HIV activity except for compounds **10d**–**f**. The structural difference between **10a**–**h** and **11a**–**h** lies in the 5-substituents. The 5-hydroxy quinazolinones **11a**–**h** showed significantly higher anti-HIV activity than 5-methoxy quinazolinones **10a**–**h** except for compounds **11e**,**f**. For the most important, the anti-HIV activity of compounds **11a**–**h** is also higher than that of 1,2-dihydrogen quinazolinones **9a**–**h** except for compounds **11c**,**e**. The above results suggest that the synergy effects are conspicuous for quinazolinone derivatives. It should be mentioned that, the 5-hydroxyl of quinazolinone, proposed to bind to the two metal cofactors in the IN active site, plays an important role in keeping high activity.

Among the synthesized compounds, 2-aryl-substituted quinazolinones **9a**,**b**, **10a** and **11a**,**b** exhibited relatively higher antiviral activity. However, the introduction of methylene at 2-position significantly decreased the antiviral activity (inhibition rate: **9g**,**h** < **9a**,**b**; **10g**,**h** < **10a**,**b**; **11g**,**h** < **11a**,**b**). The 2-heterocyclo-substituted quinazolinones **9c**–**e**, **10c**–**e** and **11d** also exhibited moderate antiviral activity but lower than corresponding 2-aryl-substituted quinazolinones **9a**,**b**, **10a** and **11a**,**b** except for compound **10e**. The *n*-butyl substituted compounds **9f** and **11f** almost showed no activity, whereas compound **10f** exhibited moderate antiviral activity. The above results indicate that the aryl-substituents at 2-position of quinazolinone are favorable for their antiviral activity.

Table 1
Anti-HIV activity of synthesized compounds **9a**–**h**, **10a**–**h** and **11a**–**h**.

Compd.	Inhibition (%)	Compd.	Inhibition (%)
9a	31.0	**10f**	19.1
9b	64.9	**10g**	−27.4
9c	8.1	**10h**	−33.8
9d	17.5	**11a**	68.4
9e	9.9	**11b**	77.5
9f	3.2	**11c**	−9.2
9g	15.6	**11d**	33.2
9h	−17.7	**11e**	−11.0
10a	27.6	**11f**	2.4
10b	−3.8	**11g**	49.5
10c	1.6	**11h**	29.0
10d	25.1	MK-0518	95.2
10e	44.6	AZT	98.1

2.3. Anti-TMV activity

In previous work, we have found that quinazolinone derivatives also possess anti-TMV activity. The synthesized new structural compounds also were evaluated for their anti-TMV activity using our previously reported method [36]. The commercial plant virucide Ribavirin was used as the control.

The primary *in vitro* bioassay results indicated that most of the tested compounds possess good *in vitro* anti-TMV activity (Table 2). Therefore, these compounds were further tested to investigate their antiviral activity *in vivo*.

As shown in Table 2, most of the tested compounds also exhibited good *in vivo* anti-TMV activity. The 2-aryl-substituted quinazolinone **9a** exhibited similar *in vivo* activity with commercial plant virucide Ribavirin, which showed 34.2% inactivation effect, 32.7% curative effect and 39.6% protection effect at 500 μg/mL. The tested compounds showed relatively higher protection and inactivation effects comparing with their corresponding curative effect. The 2-aryl-substituted quinazolinone **9b**, 2-heterocyclo-substituted quinazolinones **10d**,**e** and 2-benzyl substituted quinazolinones **10g** and **11h** showed moderate to good *in vivo* activity. Although the activity of tested quinazolinones is similar or slightly lower than Ribavirin, the novel chemical structure provides a new

Table 2
Anti-TMV activity of compounds **9a**–**e**, **10a**, **10c**–**e**, **10g**, **10h**, **11d** and **11h**.

Compd.	500 μg/mL			
	In vitro inhibition rate (%)	*In vivo*		
		Inactivation effect (%)	Curative effect (%)	Protection effect (%)
9a	24.2	30.4	26.3	28.9
9b	19.5	18.9	15	20.3
9c	7.5	8.2	0	0
9d	16.3	13.7	0	5.4
9e	0	15.2	0	8.7
10a	ND	13.3	8.2	7.4
10c	10	0	8.9	11.7
10d	0	20.4	9.4	12.7
10e	21.3	29.4	17.6	19.5
10g	21.2	10.6	15.2	17.7
10h	ND	0	0	12.4
11d	14.5	8.2	10.9	9.8
11h	18.4	12.7	13.3	16.8
Ribavirin	38.5	34.2	32.7	39.6

scaffold for exploring novel anti-TMV agents with different action mechanisms.

3. Conclusion

A series of novel structural quinazolinones have been prepared as HIV-1 inhibitors. The synthetic route provides a practical method for the preparation of 5-hydroxy quinazolinones. Bioassay results indicated that most of the quinazolinones possess anti-HIV activity, of which compound **11b** with 77.5% inhibition rate at 10 μM emerged as new active lead. In addition, the synthesized compounds were also tested their anti-TMV activity. Most of the tested compounds exhibited good anti-TMV activity, of which compound **9a** showed similar *in vivo* anti-TMV activity to commercial plant virucide Ribavirin. This work provides a novel approach to develop multi-functional antiviral agents from previously reported agents.

4. Experimental

4.1. General

The melting points were determined with an X-4 binocular microscope melting-point apparatus (Beijing Tech Instruments Co., Beijing, China) and were uncorrected. ^{1}H NMR spectra were obtained by using Bruker AV 400, Bruker AV300 and a Varian Mercury Plus 400 MHz spectrometer. Chemical shifts (δ) were given in parts per million (ppm) and measured downfield from internal tetramethylsilane. ^{13}C NMR spectra were recorded by using Bruker AV 400 (100 MHz) and Bruker AV 300 (75 MHz) with $CDCl_3$ or DMSO-d_6 as a solvent. Chemical shifts (δ) are reported in parts per million using the solvent peak. Elemental analyses were determined on a Yanaco C, H, N Corder MT-3 elemental analyzer. High-resolution mass spectra were obtained with an FT-ICR MS spectrometer (Ionspec, 7.0 T). All anhydrous solvents were dried and purified by standard techniques just before use.

4.2. N-(3-hydroxy-4-methylphenyl)pivalamide (**2**)

To a stirred solution of 5-amino-2-methylphenol (**1**) (20.0 g, 0.16 mol) and $NaHCO_3$ (41.0 g, 0.49 mol) in H_2O (350 mL) and ethyl acetate (450 mL) was added pivaloyl chloride (29.0 g, 0.24 mol) at 0 °C. The mixture was allowed to warm to room temperature and stirred for 2 h. After layer separation, the aqueous layer was extracted with ethyl acetate (2 × 100 mL). The combined organic layer was washed with saturated aq. $NaHCO_3$ solution (100 mL) and brine (100 mL), then dried with anhydrous $MgSO_4$ and concentrated in vacuo to afford compound **2** as a white solid (32.3 g, 96% yield). Mp 146–148 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.29 (s, 1H, OH), 7.89 (s, 1H, 6-H), 7.36 (br s, 1H, NH), 7.00 (d, J = 7.9 Hz, 1H, 4-H), 6.40 (d, J = 7.9 Hz, 1H, 3-H), 2.20 (s, 3H, ArCH_3), 1.33 (s, 9H, C$(CH_3)_3$); ^{13}C NMR (100 MHz, $CDCl_3$): δ 177.6, 155.7, 136.2, 130.4, 121.1, 110.3, 107.5, 39.7, 27.6, 15.7. Anal. Calcd. for $C_{12}H_{17}NO_2$: C, 69.54; H, 8.27; N, 6.76. Found: C, 69.58; H, 8.49; N, 6.65.

4.3. N-(3-methoxy-4-methylphenyl)pivalamide (**3**)

To a stirred solution of **2** (10.0 g, 48.3 mmol) in THF (250 mL) was added 70% NaH (2.5 g, 72.5 mmol). The mixture was stirred at room temperature for 30 min and refluxed for 2 h, then cooled to room temperature, and then dimethyl sulfate (12.2 g, 96.8 mmol) was added dropwise. The result solution was refluxed for another hour, then H_2O (20 mL) was added. The mixture was stirred at room temperature for 30 min and concentrated in vacuo. The residue was taken into ethyl acetate (300 mL), and washed with H_2O (100 mL) and brine (100 mL), then dried with anhydrous $MgSO_4$ and concentrated in vacuo. The residue was purified by column chromatography on silica gel to afford compound **3** as a white solid (9.2 g, 86%). Mp 124–126 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.49 (s, 1H, 6-H), 7.29 (br s, 1H, NH), 7.03 (d, J = 7.9 Hz, 1H, 4-H), 6.71 (dd, J = 7.9 Hz, 1.4 Hz, 1H, 3-H), 3.84 (s, 3H, OMe), 2.17 (s, 3H, ArCH_3), 1.32 (s, 9H, C$(CH_3)_3$); ^{13}C NMR (100 MHz, $CDCl_3$): δ 176.6, 157.9, 137.1, 130.2, 122.3, 110.9, 102.8, 55.4, 39.6, 27.7, 15.8. Anal. Calcd. for $C_{13}H_{19}NO_2$: C, 70.56; H, 8.65; N, 6.33. Found: C, 70.29; H, 8.77; N, 6.17.

4.4. 2-Methoxy-3-methyl-6-pivalamidobenzoic acid (**4**)

To a stirred solution of **3** (22.0 g, 0.1 mol) in THF (1.2 L) was added the solution of *n*-BuLi in hexane (146 mL, 0.22 mol) at 0 °C under N_2. The mixture was stirred at 0 °C for 10 h, then CO_2 was blown into the mixture. The mixture was allowed to warm to room temperature and stirred for 6 h, then concentrated in vacuo. The residue was taken into 10% KOH solution (500 mL) and extracted with ethyl acetate (2 × 150 mL). The aqueous layer was acidified with 6 N HCl solution to about pH = 2–3 at 0 °C, then extracted with ethyl acetate (3 × 200 mL). The extract was dried with anhydrous $MgSO_4$ and concentrated in vacuo to afford compound **4** as a yellow solid (21 g, 81%). Mp 93–95 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 12.29 (br s, 1H, COOH), 11.72 (br s, 1H, NH), 8.63 (d, J = 8.8 Hz, 1H, 4-H), 7.40 (d, J = 8.8 Hz, 1H, 3-H), 3.92 (s, 3H, OMe), 2.32 (s, 3H, ArCH_3), 1.34 (s, 9H, C$(CH_3)_3$); ^{13}C NMR (100 MHz, $CDCl_3$): δ 178.2, 168.1, 157.4, 141.6, 137.3, 124.5, 118.0, 107.9, 62.9, 40.5, 27.5, 15.5. Anal. Calcd. for $C_{14}H_{19}NO_4$: C, 63.38; H, 7.22; N, 5.28. Found: C, 63.18; H, 7.37; N, 5.16.

4.5. 2-Methoxy-N,3-dimethyl-6-pivalamidobenzamide (**5**)

To a stirred solution of **4** (7.0 g, 0.026 mol) and Et_3N (3.2 g, 0.032 mol) in THF (220 mL) was added ethyl chloroformate (5.0 g, 0.029 mol) at −15 °C. The mixture was stirred at −15 °C for 2 h, then 25% solution of methylamine in H_2O (7.9 g, 0.063 mol) was added dropwise. Another hour later, the mixture was allowed to warm to room temperature and stirred for 1 h, then stirred at 60 °C for 1 h, and then concentrated in vacuo. The residue was taken into ethyl acetate (300 mL), and washed with saturated aq. $NaHCO_3$ solution (100 mL), H_2O (100 mL) and brine (100 mL), then dried with anhydrous $MgSO_4$ and concentrated in vacuo to afford compound **5** as a yellow solid (6.3 g, 86%). Mp 105–107 °C; ^{1}H NMR

(400 MHz, $CDCl_3$): δ 11.50 (br s, 1H, NH), 8.36 (d, $J = 8.6$ Hz, 1H, 4-H), 7.80 (d, $J = 0.8$ Hz, 1H, CH_3NH), 7.23 (d, $J = 8.6$ Hz, 1H, 3-H), 3.69 (s, 3H, OMe), 3.02 (d, $J = 4.8$ Hz, 3H, NMe), 2.24 (s, 3H, ArCH_3), 1.32 (s, 9H, C(CH_3)$_3$); ^{13}C NMR (100 MHz, $CDCl_3$): δ 177.6, 168.0, 156.3, 139.2, 134.0, 125.5, 117.5, 114.0, 61.3, 40.1, 27.6, 26.6, 15.5. Anal. Calcd. for $C_{15}H_{22}N_2O_3$: C, 64.73; H, 7.97; N, 10.06. Found: C, 64.71; H, 8.12; N, 10.12.

4.6. 2-Methoxy-3-(methylcarbamoyl)-4-pivalamidobenzoic acid (**6**)

To a solution of **5** (25.0 g, 0.09 mol) and pyridine (33.4 g, 0.42 mol) in water (109 mL) was warily added $KMnO_4$ (42.6 g, 0.27 mol) in batches at 45–50 °C, then the mixture was stirred at 50 °C for 3 h. After cooling to room temperature, the 10% solution of sodium hydrosulfite in H_2O (100 mL) was added, then the mixture was filtered through a Celite pad (9 cm × 3 in) eluting with H_2O (150 mL) and then MeOH (150 mL). The filtrate was concentrated to 300 mL in vacuo and then acidified with 6 N HCl solution to about pH = 1–2 at 0 °C, then extracted with CH_2Cl_2 (3 × 150 mL). The extract was dried with anhydrous $MgSO_4$ and concentrated in vacuo. The residue was purified by column chromatography on silica gel to afford compound **6** as a white solid (23.3 g, 84%). Mp 192–194 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 11.59 (br s, 1H, NH), 8.59 (d, $J = 9.0$ Hz, 1H, 4-H), 8.11 (d, $J = 9.0$ Hz, 1H, 3-H), 7.54 (d, $J = 4.2$ Hz, 1H, CH_3NH), 3.90 (s, 3H, OMe), 3.06 (d, $J = 4.8$ Hz, 3H, NMe), 1.33 (s, 9H, C(CH_3)$_3$); ^{13}C NMR (100 MHz, $CDCl_3$): δ 178.2, 168.5, 167.0, 159.5, 145.8, 135.9, 117.2, 116.8, 114.9, 63.8, 40.5, 27.5, 26.8. Anal. Calcd. for $C_{15}H_{20}N_2O_5$: C, 58.43; H, 6.54; N, 9.09. Found: C, 58.38; H, 6.61; N, 9.04.

4.7. N^1-(4-fluorobenzyl)-2-methoxy-N^3-methyl-4-pivalamidoisophthalamide (**7**)

To a stirred solution of **6** (11.0 g, 0.036 mol) and Et_3N (4.3 g, 0.043 mol) in THF (300 mL) was added ethyl chloroformate (6.7 g, 0.086 mol) at −15 °C. The mixture was stirred at −15 °C for 1 h, then 4-fluorobenzylamine (10.7 g, 0.086 mol) was added dropwise. Another hour later, the mixture was allowed to warm to room temperature and stirred for 1 h, then stirred at 60 °C for 2 h, and then concentrated in vacuo. The residue was taken into ethyl acetate (400 mL), and washed with saturated aq. $NaHCO_3$ solution (100 mL), H_2O (100 mL) and brine (100 mL), then dried with anhydrous $MgSO_4$ and concentrated in vacuo. The residue was purified by column chromatography on silica gel to afford compound **7** as a white solid (12.7 g, 86%). Mp 134–136 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 11.22 (br s, 1H, NH), 8.46 (d, $J = 9.0$ Hz, 1H, 4-H), 8.05 (d, $J = 9.0$ Hz, 1H, 3-H), 7.70–7.78 (m, 1H, NH), 7.40–7.44 (m, 1H, NH), 7.28–7.35 (m, 2H, ArH), 7.01–7.05 (m, 2H, ArH), 4.56 (d, $J = 5.6$ Hz, 2H, ArCH_2), 3.69 (s, 3H, OMe), 3.02 (d, $J = 4.8$ Hz, 3H, NMe), 1.30 (s, 9H, C(CH_3)$_3$); ^{13}C NMR (100 MHz, $CDCl_3$): δ 177.9, 166.9, 164.5, 163.4, 161.0, 156.4, 143.6, 134.4, 134.2, 134.1, 129.6, 129.5, 121.0, 117.7, 115.7, 115.5, 114.8, 63.4, 43.2, 40.3, 27.5, 26.8. Anal. Calcd. for $C_{22}H_{26}FN_3O_4$: C, 63.60; H, 6.31; N, 10.11. Found: C, 63.61; H, 6.51; N, 10.15.

4.8. 4-Amino-N^1-(4-fluorobenzyl)-2-methoxy-N^3-methylisophthalamide (**8**)

The solution of **7** (6.0 g, 14.5 mmol) in 6 N HCl (240 mL) was refluxed for 1 h, then concentrated to 100 mL in vacuo, and then basified with $NaHCO_3$ to about pH = 9–10 at 0 °C, then extracted with ethyl acetate (3 × 100 mL). The extract was dried with anhydrous $MgSO_4$ and concentrated in vacuo. The residue was purified by column chromatography on silica gel to afford compound **8** as a slight yellow solid (2.9 g, 61%). Mp 170–172 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.92 (d, $J = 8.8$ Hz, 1H, 4-H), 7.80 (br s, 1H, NH), 7.32 (dd, $J = 5.5$, 8.1 Hz, 2H, ArH), 7.15 (br s, 1H, NH), 7.02 (t, $J = 8.6$ Hz, 2H, ArH), 6.51 (d, $J = 8.8$ Hz, 1H, 3-H), 5.90 (br s, 2H, NH_2), 4.58 (d, $J = 5.6$ Hz, 2H, ArCH_2), 3.67 (s, 3H, OMe), 2.97 (d, $J = 4.8$ Hz, 3H, NMe); ^{13}C NMR (100 MHz, DMSO-d_6): δ 166.0, 164.9, 157.1, 149.6, 143.0, 135.5, 131.8, 129.3, 129.3, 129.3, 115.0, 114.8, 111.2, 62.8, 62.4, 41.9, 27.0, 26.0; HRMS (ESI) calcd for $C_{17}H_{17}FN_3O_3$ $(M-H)^-$: 330.1259, found: 330.1257.

4.9. General procedure for the preparation of compounds **9a**–**h**

The solution of **8** (1.5 mmol), corresponding aldehyde (2.3 mmol), *p*-toluenesulfonic acid (0.3 mmol) and $MgSO_4$ (0.5 g) in ethanol (60 mL) was refluxed for 3 h, then concentrated in vacuo. The residue was taken into CH_2Cl_2 (100 mL), and washed with saturated aq. $NaHCO_3$ solution (100 mL), H_2O (100 mL) and brine (100 mL), then dried with anhydrous $MgSO_4$ and concentrated in vacuo. The residue was purified by column chromatography on silica gel to afford compounds **9a**–**h**.

4.9.1. N-(4-fluorobenzyl)-2-(4-fluorophenyl)-5-methoxy-3-methyl-4-oxo-1,2,3,4-tetrahydroquinazoline-6-carboxamide (**9a**)

Slight yellow solid, 92% yield; mp 181–183 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.26 (s, 1H, CONH), 8.03 (d, $J = 8.7$ Hz, 1H, ArH), 7.28–7.37 (m, 4H, ArH), 6.99–7.06 (m, 4H, ArH), 6.44 (d, $J = 8.7$ Hz, 1H, ArH), 5.66 (s, 1H, ArCH), 5.36 (s, 1H, ArNH), 4.56 (d, $J = 4.5$ Hz, 2H, ArCH_2), 3.85 (s, 3H, OMe), 2.92 (s, 3H, NMe); HRMS (ESI) calcd for $C_{24}H_{20}F_2N_3O_3$ $(M-H)^-$: 436.1478, found: 436.1477.

4.9.2. N-(4-fluorobenzyl)-5-methoxy-3-methyl-2-(4-nitrophenyl)-4-oxo-1,2,3,4-tetrahydroquinazoline-6-carboxamide (**9b**)

Yellow solid, 93% yield; mp: 215–217 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.29 (t, $J = 5.5$ Hz, 1H, NH), 8.06 (d, $J = 8.6$ Hz, 2H, ArH), 7.88 (d, $J = 8.7$ Hz, 1H, ArH), 7.45 (d, $J = 8.6$ Hz, 2H, ArH), 7.23 (dd, $J = 5.4$, 8.2 Hz, 2H, ArH), 6.92–6.99 (m, 3H, ArH, NH), 6.44 (d, $J = 8.7$ Hz, 1H, ArH), 5.64 (d, $J = 2.8$ Hz, 1H, NHCHN), 4.48–4.54 (m, 2H, ArCH_2), 3.83 (s, 3H, OMe), 3.02 (s, 3H, NMe); HRMS (ESI) calcd for $C_{24}H_{20}FN_4O_5$ $(M-H)^-$: 463.1423, found: 463.1430.

4.9.3. N-(4-fluorobenzyl)-2-(furan-2-yl)-5-methoxy-3-methyl-4-oxo-1,2,3,4-tetrahydroquinazoline-6-carboxamide (**9c**)

White solid, 88% yield; mp: 194–196 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.27 (s, 1H, NH), 8.07 (d, $J = 8.7$ Hz, 1H, ArH), 7.27–7.33 (m, 3H, OCHCH, ArH), 7.01 (t, $J = 8.6$ Hz, 2H, ArH), 6.52 (d, $J = 8.7$ Hz, 1H, ArH), 6.27 (s, 1H, CCHCH), 6.20 (d, $J = 3.1$ Hz, 1H, CHCHCH), 5.66 (d, $J = 2.7$ Hz, 1H, NHCHN), 5.46 (d, $J = 2.1$ Hz, 1H, ArNH), 4.52–4.64 (m, 2H, ArCH_2), 3.83 (s, 3H, OMe), 3.14 (s, 3H, NMe); HRMS (ESI) calcd for $C_{22}H_{19}FN_3O_4$ $(M-H)^-$: 408.1365, found: 408.1360.

4.9.4. N-(4-fluorobenzyl)-5-methoxy-3-methyl-4-oxo-2-(thiophen-2-yl)-1,2,3,4-tetrahydroquinazoline-6-carboxamide (**9d**)

White solid, 91% yield; mp: 230–231 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.29 (s, 1H, NH), 8.10 (d, $J = 8.7$ Hz, 1H, ArH), 7.32 (dd, $J = 8.0$, 5.7 Hz, 2H, ArH), 7.23 (d, $J = 5.0$ Hz, 1H, SCHCH), 6.93–7.04 (m, 4H, ArH, SC$CHCH$), 6.49 (d, $J = 8.7$ Hz, 1H, ArH), 5.92 (d, $J = 2.2$ Hz, 1H, NHCHN), 5.18 (s, 1H, ArNH), 4.53–4.64 (m, 2H, ArCH_2), 3.86 (s, 3H, OMe), 3.08 (s, 3H, NMe); HRMS (ESI) calcd for $C_{22}H_{19}FN_3O_3S$ $(M-H)^-$: 424.1137, found: 424.1136.

4.9.5. N-(4-fluorobenzyl)-5-methoxy-3-methyl-4-oxo-2-(pyridin-2-yl)-1,2,3,4-tetrahydroquinazoline-6-carboxamide (**9e**)

White solid, 79% yield; mp: 185–187 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.57 (d, $J = 4.2$ Hz, 1H, NCH), 8.20 (s, 1H, NH), 8.00 (d, $J = 8.7$ Hz, 1H, ArH), 7.65 (t, $J = 4.2$ Hz, 1H, NCCHCH), 7.22–7.31

(m, 4H, NCH*CHCH*, ArH), 7.00 (t, $J = 8.4$ Hz, 2H, ArH), 6.45 (d, $J = 8.7$ Hz, 1H, ArH), 5.75 (s, 1H, Ar*NH*), 5.64 (d, $J = 2.2$ Hz, 1H, NH*CH*N), 4.50–4.61 (m, 2H, ArCH_2), 3.82 (s, 3H, OMe), 3.20 (s, 3H, NMe); HRMS (ESI) calcd for $C_{23}H_{20}FN_4O_3$ $(M-H)^-$: 419.1525, found: 419.1528.

4.9.6. 2-Butyl-N-(4-fluorobenzyl)-5-methoxy-3-methyl-4-oxo-1,2,3,4-tetrahydroquinazoline-6-carboxamide (**9f**)

Colorless viscous liquid, 79% yield; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.29 (s, 1H, NH), 8.06 (d, $J = 8.6$ Hz, 1H, ArH), 7.29 (dd, $J = 12.1$, 6.4 Hz, 2H, ArH), 7.31 (t, $J = 8.5$, 16.9 Hz, 2H, ArH), 6.49 (d, $J = 8.6$ Hz, 1H, ArH), 5.22 (s, 1H, Ar*NH*), 4.54–4.60 (m, 3H, ArCH_2, NH*CH*N), 3.85 (s, 3H, OMe), 3.08 (s, 3H, NMe), 1.70–1.80 (m, 2H, CCH_2CH_2), 1.22–1.30 (m, 4H, $CCH_2CH_2CH_2$), 0.86 (m, 3H, CH_3CH_2); HRMS (ESI) calcd for $C_{22}H_{25}FN_3O_3$ $(M-H)^-$: 398.1885, found: 398.1886.

4.9.7. N,2-bis(4-fluorobenzyl)-5-methoxy-3-methyl-4-oxo-1,2,3,4-tetrahydroquinazoline-6-carboxamide (**9g**)

White solid, 50% yield; mp: 231–233 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.11 (d, $J = 8.4$ Hz, 1H, ArH), 7.64 (s, 1H, NH), 7.21–7.37 (m, 4H, ArH), 7.02 (t, $J = 5.1$ Hz, 4H, ArH), 6.44 (d, $J = 8.7$ Hz, 1H, ArCH_2), 4.76 (s, 1H, NH*CH*N), 4.68 (d, $J = 4.3$ Hz, 2H, ArCH_2), 4.60 (dd, $J = 6.4$, 11.0 Hz, 1H, Ar*NH*), 3.96 (s, 2H, ArCH_2), 3.84 (s, 3H, OMe), 3.09 (s, 3H, NMe); HRMS (ESI) calcd for $C_{25}H_{22}F_2N_3O_3$ $(M-H)^-$: 450.1635, found: 450.1640.

4.9.8. N-(4-fluorobenzyl)-5-methoxy-3-methyl-2-(4-nitrobenzyl)-4-oxo-1,2,3,4-tetrahydroquinazoline-6-carboxamide (**9h**)

Yellow solid, 71% yield; mp: 195–196 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.12–8.21 (m, 4H, ArH, NH), 7.33 (dd, $J = 8.4$, 5.5 Hz, 2H, ArH), 7.25–7.27 (m, 2H, ArH), 7.03 (t, $J = 8.6$ Hz, 2H, ArH), 6.49 (d, $J = 8.6$ Hz, 1H, ArH), 4.94 (s, 1H, Ar*NH*), 4.75–4.79 (m, 1H, NH*CH*N), 4.55–4.65 (m, 2H, ArCH_2NH), 3.85 (s, 3H, OMe), 3.10–3.20 (m, 2H, ArCH_2CH), 3.10 (s, 3H, NMe); HRMS (ESI) calcd for $C_{25}H_{23}FN_4NaO_5$ $(M+Na)^+$: 501.1545, found: 501.1539.

4.10. General procedure for the preparation of compounds **10a–h**

The solution of **9a–h** (1.0 mmol) and I_2 (3.0 mmol) in ethanol (60 mL) was refluxed for 1 h, then cooled to room temperature and stirred for 8 h, and then concentrated in vacuo. The residue was taken into CH_2Cl_2 (100 mL), and washed with 10% $Na_2S_2O_4$ solution (3×50 mL), H_2O (100 mL) and brine (100 mL), then dried with anhydrous $MgSO_4$ and concentrated in vacuo. The residue was purified by column chromatography on silica gel to afford compounds **10a–h**.

4.10.1. N-(4-fluorobenzyl)-2-(4-fluorophenyl)-5-methoxy-3-methyl-4-oxo-3,4-dihydroquinazoline-6-carboxamide (**10a**)

White solid, 92% yield; mp: 219–221 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.50 (d, $J = 8.7$ Hz, 1H, ArH), 8.35 (s, 1H, NH), 7.58–7.64 (m, 2H, ArH), 7.36 (dd, $J = 8.2$, 5.6 Hz, 2H, ArH), 7.22–7.27 (m, 3H, ArH), 7.05 (t, $J = 8.6$ Hz, 2H, ArH), 4.66 (d, $J = 5.6$ Hz, 2H, ArCH_2), 3.91 (s, 3H, OMe), 3.50 (s, 3H, NMe); HRMS (ESI) calcd for $C_{24}H_{18}F_2N_3O_3$ $(M-H)^-$: 434.1322, found: 434.1329.

4.10.2. N-(4-fluorobenzyl)-5-methoxy-3-methyl-2-(4-nitrophenyl)-4-oxo-3,4-dihydroquinazoline-6-carboxamide (**10b**)

Slight yellow solid, 87% yield; mp: 248–249 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.53 (d, $J = 8.7$ Hz, 1H, ArH), 8.43 (d, $J = 8.5$ Hz, 2H, ArH), 8.33 (s, 1H, NH), 7.82 (d, $J = 8.5$ Hz, 2H, ArH), 7.60 (d, $J = 8.7$ Hz, 1H, ArH), 7.37 (dd, $J = 5.6$, 8.2 Hz, 2H, ArH), 7.06 (t, $J = 8.6$ Hz, 2H, ArH), 4.67 (d, $J = 5.5$ Hz, 2H, ArCH_2), 3.92 (s, 3H, OMe), 3.49 (s, 3H, NMe); HRMS (ESI) calcd for $C_{24}H_{18}FN_4O_5$ $(M-H)^-$: 461.1267, found: 461.1269.

4.10.3. N-(4-fluorobenzyl)-2-(furan-2-yl)-5-methoxy-3-methyl-4-oxo-3,4-dihydroquinazoline-6-carboxamide (**10c**)

White solid, 87% yield; mp: 131–132 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.47 (d, $J = 8.7$ Hz, 1H, ArH), 8.34 (s, 1H, NH), 7.69 (s, 1H, O*CH*CH), 7.59 (d, $J = 8.7$ Hz, 1H, ArH), 7.35 (dd, $J = 8.3$, 5.5 Hz, 2H, ArH), 7.25 (s, 1H, CC*H*CH), 7.04 (t, $J = 8.6$ Hz, 2H, ArH), 6.64 (dd, $J = 1.2$, 2.8 Hz, 1H, CH*CH*CH), 4.65 (d, $J = 5.6$ Hz, 2H, ArCH_2), 3.84 (s, 3H, OMe), 3.77 (s, 3H, NMe); HRMS (ESI) calcd for $C_{22}H_{17}FN_3O_4$ $(M-H)^-$: 406.1209, found: 406.1207.

4.10.4. N-(4-fluorobenzyl)-5-methoxy-3-methyl-4-oxo-2-(thiophen-2-yl)-3,4-dihydroquinazoline-6-carboxamide (**10d**)

White solid, 92% yield; mp: 172–174 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.48 (d, $J = 8.7$ Hz, 1H, ArH), 8.34 (s, 1H, NH), 7.61 (d, $J = 5.1$, 1H, ArH), 7.59 (s, 1H, S*CH*), 7.57 (d, $J = 4.0$, 1H, SC*CH*), 7.36 (dd, $J = 5.5$, 8.4 Hz, 2H, ArH), 7.19 (dd, $J = 3.9$, 4.9 Hz, 1H, ArH), 7.05 (t, $J = 8.6$ Hz, 2H, ArH), 4.65 (d, $J = 5.6$ Hz, 2H, ArCH_2), 3.90 (s, 3H, OMe), 3.78 (s, 3H, NMe); HRMS (ESI) calcd for $C_{22}H_{17}FN_3O_3S$ $(M-H)^-$: 422.0980, found: 422.0985.

4.10.5. N-(4-fluorobenzyl)-5-methoxy-3-methyl-4-oxo-2-(pyridin-2-yl)-3,4-dihydroquinazoline-6-carboxamide (**10e**)

White solid, 87% yield; mp: 214–216 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.73 (d, $J = 4.6$ Hz, 1H, N*CH*), 8.50 (d, $J = 8.7$ Hz, 1H, ArH), 8.36 (s, 1H, NH), 7.88–7.97 (m, 2H, NC*CHCH*), 7.61 (d, $J = 8.7$ Hz, 1H, ArH), 7.48 (dd, $J = 5.1$, 6.1 Hz, 1H, NCH*CH*), 7.34 (dd, $J = 5.5$, 8.5 Hz, 2H, ArH), 7.05 (t, $J = 8.6$ Hz, 2H, ArH), 4.66 (d, $J = 5.6$ Hz, 2H, ArCH_2), 3.91 (s, 3H, OMe), 3.60 (s, 3H, NMe); HRMS (ESI) calcd for $C_{23}H_{18}FN_4O_3$ $(M-H)^-$: 4117.1368, found: 417.1369.

4.10.6. 2-Butyl-N-(4-fluorobenzyl)-5-methoxy-3-methyl-4-oxo-3,4-dihydroquinazoline-6-carboxamide (**10f**)

White solid, 71% yield; mp: 109–110 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.44 (d, $J = 8.7$ Hz, 1H, ArH), 8.34 (s, 1H, NH), 7.49 (d, $J = 8.7$ Hz, 1H, ArH), 7.35 (dd, $J = 8.1$, 5.7 Hz, 2H, ArH), 7.04 (t, $J = 8.6$ Hz, 2H, ArH), 4.64 (d, $J = 5.6$ Hz, 2H, ArCH_2), 3.85 (s, 3H, OMe), 3.60 (s, 3H, NMe), 2.81 (t, $J = 7.7$ Hz, 2H, CCH_2CH_2), 1.79–1.86 (m, 2H, $CCH_2CH_2CH_2$), 1.46–1.56 (m, 2H, $CH_2CH_2CH_3$), 1.01 (t, $J = 7.3$ Hz, 3H, CH_3CH_2); HRMS (ESI) calcd for $C_{22}H_{23}FN_3O_3$ $(M-H)^-$: 396.1729, found: 396.1735.

4.10.7. N,2-Bis(4-fluorobenzyl)-5-methoxy-3-methyl-4-oxo-3,4-dihydroquinazoline-6-carboxamide (**10g**)

White solid, 41% yield; mp: 181–182 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.48 (d, $J = 8.7$ Hz, 1H, ArH), 8.32 (s, 1H, NH), 7.55 (d, $J = 8.6$ Hz, 1H, ArH), 7.24–7.38 (m, 4H, ArH), 7.04 (t, $J = 7.9$ Hz, 4H, ArH), 4.65 (d, $J = 5.2$ Hz, 2H, ArCH_2), 4.20 (s, 2H, ArCH_2), 3.84 (s, 3H, OMe), 3.48 (s, 3H, NMe); HRMS (ESI) calcd for $C_{25}H_{20}F_2N_3O_3$ $(M-H)^-$: 448.1478, found: 448.1469.

4.10.8. N-(4-fluorobenzyl)-5-methoxy-3-methyl-2-(4-nitrobenzyl)-4-oxo-3,4-dihydroquinazoline-6-carboxamide (**10h**)

Slight yellow solid, 63% yield; mp: 234–236 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.49 (d, $J = 8.7$ Hz, 1H, ArH), 8.30 (s, 1H, NH), 8.24 (d, $J = 8.4$ Hz, 2H, ArH), 7.50 (dd, $J = 15.3$, 8.7 Hz, 3H, ArH), 7.35 (dd, $J = 5.7$, 8.2 Hz, 2H, ArH), 7.04 (t, $J = 8.6$ Hz, 2H, ArH), 4.65 (d, $J = 5.6$ Hz, 2H, ArCH_2), 4.32 (s, 2H, ArCH_2), 3.50 (s, 3H, NMe); HRMS (ESI) calcd for $C_{22}H_{20}FN_4O_5$ $(M-H)^-$: 475.1423, found: 475.1422.

4.11. General procedure for the preparation of compounds **11a–h**

To a stirred solution of **10a–h** (0.4 mmol) and $AlCl_3$ (1.2 mmol) in CH_2Cl_2 (60 mL) was added dropwise pyridine (4.8 mmol) at 30 °C under N_2. The mixture was refluxed for 28 h, then cooled to room

temperature and acidified with 0.5 N HCl solution to about pH = 1–2 at 0 °C, and then extracted with CH_2Cl_2 (3 × 50 mL). The extract was dried with anhydrous $MgSO_4$ and concentrated in vacuo. The residue was purified by column chromatography on silica gel to afford compounds **11a**–**h**.

*4.11.1. N-(4-fluorobenzyl)-2-(4-fluorophenyl)-5-hydroxy-3-methyl-4-oxo-3,4-dihydroquinazoline-6-carboxamide (**11a**)*

White solid, 74% yield; mp: 195–197 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 13.58 (s, 1H, OH), 8.60 (d, *J* = 8.7 Hz, 1H, ArH), 8.51 (s, 1H, NH), 7.62 (dd, *J* = 8.6, 5.2 Hz, 2H, ArH), 7.38 (dd, *J* = 8.3, 5.6 Hz, 2H, ArH), 7.23–7.30 (m, 3H, ArH), 7.04 (t, *J* = 17.3 Hz, 2H, ArH), 4.69 (d, *J* = 5.6 Hz, 2H, ArCH_2), 3.52 (s, 3H, NMe); HRMS (ESI) calcd for $C_{23}H_{16}F_2N_3O_3$ $(M-H)^-$: 420.1165, found: 420.1160.

*4.11.2. N-(4-fluorobenzyl)-5-hydroxy-3-methyl-2-(4-nitrophenyl)-4-oxo-3,4-dihydroquinazoline-6-carboxamide (**11b**)*

White solid, 80% yield; mp: 222–223 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 13.46 (s, 1H, OH), 8.64 (d, *J* = 8.7 Hz, 1H, ArH), 8.49 (s, 1H, NH), 8.44 (d, *J* = 8.5 Hz, 2H, ArH), 7.82 (d, *J* = 8.5 Hz, 2H, ArH), 7.38 (dd, *J* = 5.9, 8.0 Hz, 2H, ArH), 7.31 (d, *J* = 8.7 Hz, 1H, ArH), 7.05 (t, *J* = 8.6 Hz, 2H, ArH), 4.69 (d, *J* = 5.6 Hz, 2H, ArCH_2), 3.52 (s, 3H, NMe); HRMS (ESI) calcd for $C_{23}H_{16}FN_4O_5$ $(M-H)^-$: 447.1110, found: 447.1113.

*4.11.3. N-(4-fluorobenzyl)-2-(furan-2-yl)-5-hydroxy-3-methyl-4-oxo-3,4-dihydroquinazoline-6-carboxamide (**11c**)*

White solid, 58% yield; mp: 151–153 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 13.61 (s, 1H, OH), 8.59 (d, *J* = 8.7 Hz, 1H, ArH), 8.50 (s, 1H, NH), 7.70 (d, *J* = 1.4 Hz, 1H, OC*H*CH), 7.37 (dd, *J* = 8.6, 5.4 Hz, 2H, ArH), 7.27–7.33 (m, 2H, ArH, OCC*H*CH), 7.04 (t, *J* = 8.7 Hz, 2H, ArH), 6.66 (dd, *J* = 1.7, 3.5 Hz, 1H, CH*CH*CH), 4.69 (d, *J* = 5.7 Hz, 2H, ArCH_2), 3.82 (s, 3H, NMe); HRMS (ESI) calcd for $C_{21}H_{15}FN_3O_4$ $(M-H)^-$: 392.1052, found: 392.1058.

*4.11.4. N-(4-fluorobenzyl)-5-hydroxy-3-methyl-4-oxo-2-(thiophen-2-yl)-3,4-dihydroquinazoline-6-carboxamide (**11d**)*

White solid, 78% yield; mp: 158–160 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 13.56 (s, 1H, OH), 8.58 (d, *J* = 8.7 Hz, 1H, ArH), 8.49 (s, 1H, NH), 7.61 (dd, *J* = 5.0, 15.9 Hz, 2H, ArH), 7.37 (dd, *J* = 5.7, 8.0 Hz, 2H, S*CHCH*), 7.29 (d, *J* = 8.7 Hz, 1H, ArH), 7.20 (t, *J* = 4.3 Hz, 1H, SC*CH*), 7.04 (d, *J* = 8.6 Hz, 2H, ArH), 4.68 (d, *J* = 5.6 Hz, 2H, ArCH_2), 3.80 (s, 3H, NMe); HRMS (ESI) calcd for $C_{21}H_{15}FN_3O_3S$ $(M-H)^-$: 408.0824, found: 408.0828.

*4.11.5. N-(4-fluorobenzyl)-5-hydroxy-3-methyl-4-oxo-2-(pyridin-2-yl)-3,4-dihydroquinazoline-6-carboxamide (**11e**)*

White solid, 74% yield; mp: 185–187 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 13.71 (s, 1H, OH), 8.73 (d, *J* = 4.7 Hz, 1H, N*CH*), 8.61 (d, *J* = 8.7 Hz, 1H, ArH), 8.52 (s, 1H, NH), 7.92–7.97 (m, 2H, NC*CHCH*), 7.49 (dd, *J* = 6.5, 1.3 Hz, 1H, NCH*CH*), 7.38 (dd, *J* = 5.7, 8.2 Hz, 2H, ArH), 7.32 (d, *J* = 8.7 Hz, 1H, ArH), 7.05 (d, *J* = 8.6 Hz, 2H, ArH), 4.70 (d, *J* = 5.7 Hz, 2H, ArCH_2), 3.66 (s, 3H, NMe); HRMS (ESI) calcd for $C_{22}H_{16}FN_4O_3$ $(M-H)^-$: 403.1212, found: 403.1216.

*4.11.6. 2-Butyl-N-(4-fluorobenzyl)-5-hydroxy-3-methyl-4-oxo-3,4-dihydroquinazoline-6-carboxamide (**11f**)*

White solid, 72% yield; mp: 123–125 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 13.64 (s, 1H, OH), 8.55 (d, *J* = 8.7 Hz, 1H, ArH), 8.49 (s, 1H, NH), 7.36 (dd, *J* = 8.3, 5.6 Hz, 2H, ArH), 7.21 (d, *J* = 8.7 Hz, 1H, ArH), 7.03 (t, *J* = 8.6 Hz, 2H, ArH), 4.68 (d, *J* = 5.7 Hz, 2H, ArCH_2), 3.62 (s, 3H, NMe), 2.84 (t, *J* = 7.6 Hz, 2H, CCH_2CH_2), 1.79–1.87 (m, 2H, $CCH_2CH_2CH_2$), 1.47–1.58 (m, 2H, $CH_2CH_2CH_3$), 1.01 (t, *J* = 7.3 Hz, 3H, CH_3CH_2); HRMS (ESI) calcd for $C_{21}H_{21}FN_3O_3$ $(M-H)^-$: 382.1572, found 382.1578.

*4.11.7. N,2-bis(4-fluorobenzyl)-5-hydroxy-3-methyl-4-oxo-3,4-dihydroquinazoline-6-carboxamide (**11g**)*

White solid, 68% yield; mp: 172–174 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 13.55 (s, 1H, OH), 8.60 (d, *J* = 8.7 Hz, 1H, ArH), 8.47 (s, 1H, NH), 7.36 (t, *J* = 7.7 Hz, 1H, ArH), 7.23–7.29 (m, 3H, ArH), 7.04 (dd, *J* = 8.1, 16.2 Hz, 4H, ArH), 4.68 (d, *J* = 5.5 Hz, 2H, ArCH_2), 4.23 (s, 2H, ArCH_2), 3.50 (s, 3H, NMe); ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.8, 164.3, 163.4, 163.3, 161.0, 158.7, 156.2, 150.0, 138.5, 134.4, 130.0, 130.0, 129.4, 129.3, 117.6, 116.3, 116.1, 115.6, 115.4, 106.7, 43.1, 41.7, 30.4, 29.7; HRMS (ESI) calcd for $C_{24}H_{18}F_2N_3O_3$ $(M-H)^-$: 434.1322, found: 434.1326.

*4.11.8. N-(4-fluorobenzyl)-5-hydroxy-3-methyl-2-(4-nitrobenzyl)-4-oxo-3,4-dihydroquinazoline-6-carboxamide (**11h**)*

White solid, 71% yield; mp: 215–216 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 13.46 (s, 1H, OH), 8.60 (d, *J* = 8.7 Hz, 1H, ArH), 8.46 (s, 1H, NH), 8.24 (d, *J* = 8.5 Hz, 2H, ArH), 7.48 (d, *J* = 8.5 Hz, 2H, ArH), 7.36 (dd, *J* = 5.5, 8.2 Hz, 2H, ArH), 7.24 (d, *J* = 8.9 Hz, 1H, ArH), 7.03 (d, *J* = 8.6 Hz, 2H, ArH), 4.68 (d, *J* = 5.6 Hz, 2H, ArCH_2), 4.35 (s, 2H, ArCH_2), 3.53 (s, 3H, NMe); ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.6, 164.2, 158.7, 154.8, 149.7, 147.5, 141.5, 138.7, 134.4, 129.6, 129.4, 129.3, 124.3, 117.7, 116.3, 115.6, 115.4, 106.7, 43.1, 42.0, 30.5, 29.7; HRMS (ESI) calcd for $C_{24}H_{18}FN_4O_5$ $(M-H)^-$: 461.1267, found: 461.1261.

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Appendix A. Supplementary material

Supplementary data related to this article can be found online in the online version, at doi:10.1016/j.ejmech.2012.04.010.

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