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A novel strategy to the synthesis of 4-anilinoquinazoline derivatives

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ABSTRACT

A novel approach to prepare 4-anilinoquinazoline derivatives based on the transformation of indoline-2,3-dione to formamidine was developed. The processes with this approach are simple, efficient, and environmentally friendly. The efficiency of this approach was evaluated by synthesizing 17 4-anilinoquinazolines and comparing the obtained yields with those achievable through conventional synthetic methods. It was the first time that compounds **8d**, **8e**, **8h**, and **13b**–**f** were synthesized. The characteristics of the IR and the UV spectra of these compounds and the effects of their substituents on the spectra were observed.

1. Introduction

4-Anilinoquinazolines are a class of potentially high selective anticancer agents for their strong ability to inhibit several receptor tyrosine kinases,[1] such as EGFR, NGFR, and VEGFR-2, which often over-expresses or deregulates in many solid tumors. These small molecules can competitively fit into the ATP binding pocket of tyrosine kinase domain.[2–4] Among 4-anilinoquinazolines, PD153035 (**1**) was firstly reported as a selective specific EGFR tyrosine kinase inhibitor in 1994.[5] Then more similar molecules were reported and approved as anticancer drugs successively, such as Erlotinib (**2**, Tarceva), Gefitinib (**3**, Iressa), and Canertinib (**4**) (Fig. 1).

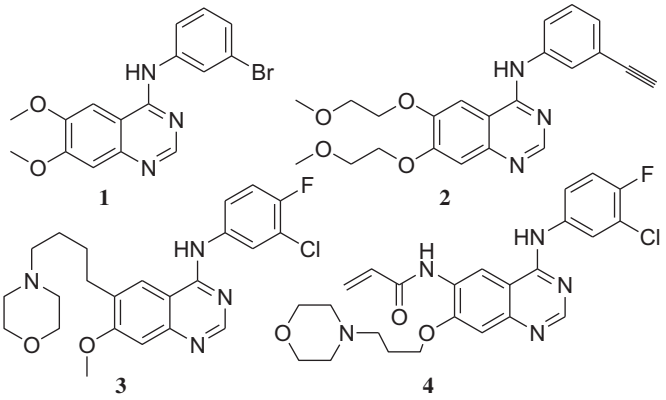

Fig. 1. Structures of tyrosine kinase inhibitors.

Despite the widespread utility of this class of compounds, the reported synthetic methods often require multi-steps and harsh conditions. The starting materials used in the reported methods are mainly substituted benzaldehydes (Scheme 1). The yields of the processes are not satisfactory.[6–8] The key intermediate of the synthetic routes is either substituted quinazolin-4(3*H*)-one or substituted *N*′-(2-cyanophenyl)-*N*,*N*-dimethylformamidine. Two common steps in these procedures are nitration and reduction. The nitration process needs to proceed at low temperature (no higher than 5 °C) with a large amount of concentrated sulfuric acid.[9] Thus restrictive control is required in adding reagents into sulfuric acid to keep the temperature under 5 °C. Nevertheless, the yield of the nitration is not satisfactory. Although there are several different ways to reduce the nitro group, the disappointing yields and difficult purification steps discouraged many researchers.[10,11] Hydrogenation process is a good choice to reduce the nitro group, however, the application of precious metal catalyst undoubtedly increases the cost of the product.[12] In addition, a complex setup is necessary regarding safety when using hydrogen. Therefore, a safe, efficient, environmentally friendly, and universal pathway to synthesize 4-anilinoquinazolines is highly demanded. In this paper a novel approach for fulfilling these requirements to prepare 4-anilinoquinazolines is disclosed.

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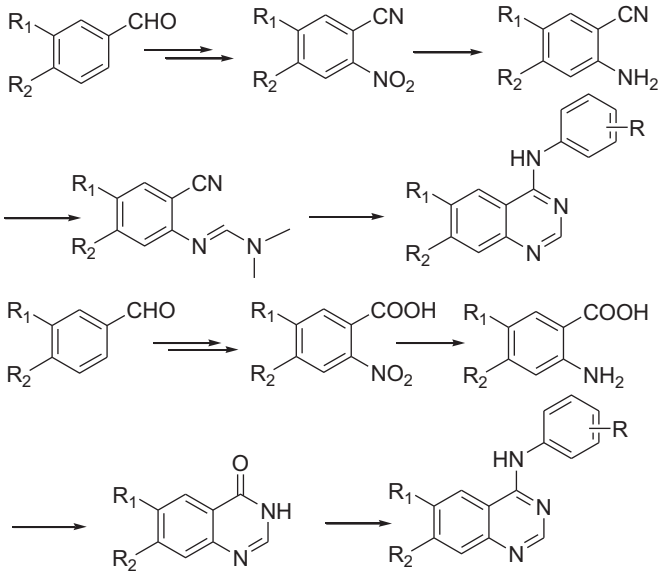
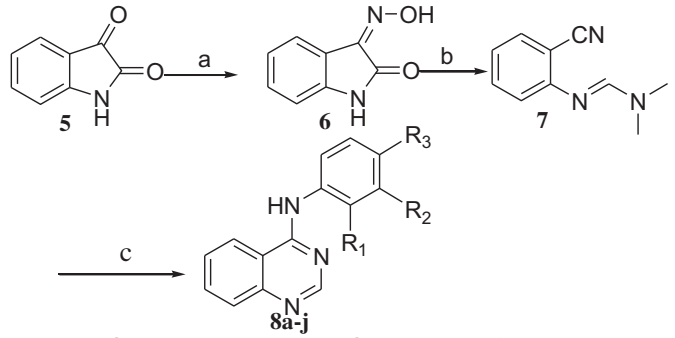


Scheme 1. Current general synthetic approaches.

2. Result and discussion

Substituted benzaldehydes were used as starting material in literature to synthesize 4-anilinoquinazolines. Both steps of nitration and reduction were needed to synthesize the key intermediate formamidine or quinazolin-4(3*H*)-one. To avoid these steps, we developed a new synthetic approach. Indole-2,3-dione (**5**, a cheap industrial scale product) was chosen as starting material. It underwent condensation with hydroxylamine hydrochloride followed by heated in the solution of DMF and $POCl_3$ to form compound **7**.[13] Finally, compound **7** reacted with substituted anilines to produce the target compounds **8a**–**j** (Scheme 2).[14,15] This route also avoided synthesizing anthranilonitrile and using DMF/DMA.



8a:R_1=H,R_2=H,R_3=H; **8b**:R_1=H,R_2=Cl,R_3=F;
8c:R_1=H,R_2=H,R_3=OH; **8d**:R_1=H,R_2=MeO,R_3=H;
8e:R_1=F,R_2=H,R_3=H; **8f**:R_1=H,R_2=H,R_3=F;
8g:R_1=Cl,R_2=H,R_3=H; **8h**:R_1=Cl,R_2=H,R_3=Cl;
8i:R_1=H,R_2=H,R_3=Br; **8j**:R_1=H,R_2=Br,R_3=H;

Scheme 2. Synthesis of compound **8a**–**j**. Reagents and conditions: (a) $HONH_3Cl$, H_2O, CH_3COONa, reflux, 30 min, 98%; (b) $POCl_3$, DMF, Na_2CO_3, H_2O, 0 °C to rt to 70 °C, 4 h, 88%; (c) amine derivatives, CH_3COOH, reflux, 3 h, 85–93%.

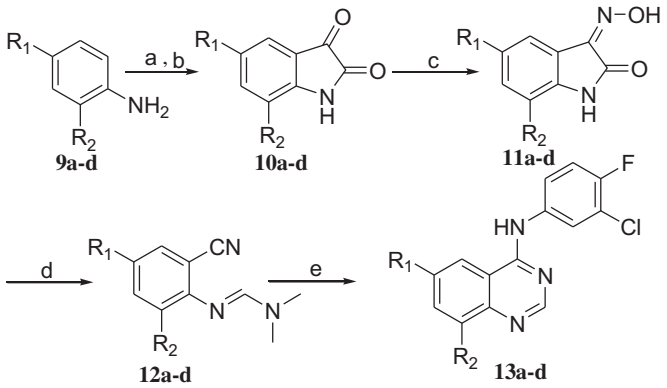
The synthesis of the key intermediate **7** was reported in 2010 with a low yield and in-sufficient purification process. To enhance product yield and facilitate the purification process, we investigated this reaction thoroughly. It was found that the main factors influencing the yield and purity of compound **7** were the reaction time and the ratio of compound **6** to $POCl_3$. As shown in Table 1, under the optimized conditions, ratio of $POCl_3$ to compound **6** is 1.5 to 1 and reaction time is 4 h, compound **7** was obtained with a high yield (88%) and a simple common work up procedure.

Table 1
Optimization of the reaction time and the ratio of **6** to $POCl_3$

6/$POCl_3$	Time				
	1 h	2 h	3 h	4 h	5 h
1:1	3%	10%	17%	20%	21%
1:1.2	10%	23%	35%	43%	40%
1:1.5	10%	26%	57%	88%	85%
1:1.8	—	—	—	—	—
1:2	—	—	—	—	—

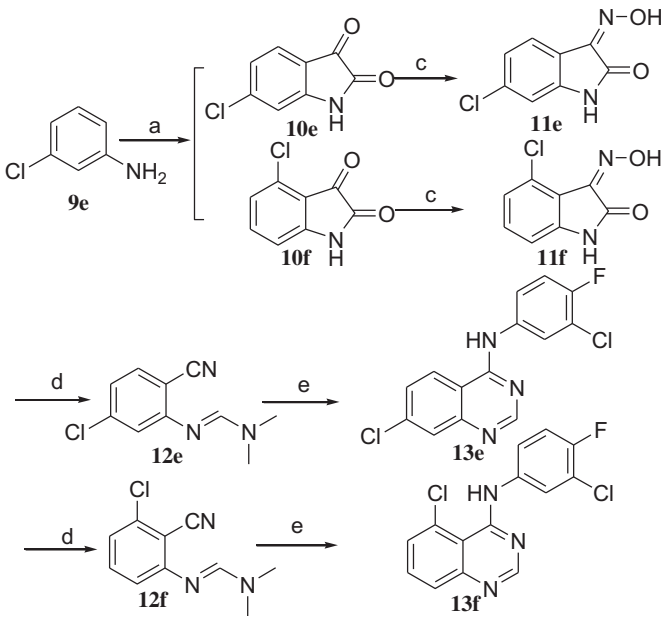
'——' Complex reaction mixture was obtained, and it was difficult to be purified.

After compound **7** was successfully obtained, 10 different substituted 4-anilinoquinazolines were synthesized (Scheme 2). To further evaluate our new approach, six different 5,6,7,8-substituted 4-anilinoquinazolines were synthesized (Schemes 3 and 4) with two more steps comparing with Scheme 2. Different substituted



13a:R_1=NO_2, R_2=H; **13b**:R_1=F, R_2=H;
13c:R_1=CH_3, R_2=H; **13d**:R_1=H, R_2=Cl;

Scheme 3. The synthesis of **13a**–**d**. Reagents and conditions: (a) $HONH_3Cl$, Cl_3CCHO, Na_2SO_4, H_2O, reflux, 1 h; (b) 95% of H_2SO_4, 65 °C, 1 h; (c) $HONH_3Cl$, H_2O, CH_3COONa, reflux, 30 min; (d) $POCl_3$, DMF, Na_2CO_3, H_2O, 0 °C to rt to 70 °C, 4 h; (e) 3-chloro-4-fluorobenzenamine, CH_3COOH, reflux, 3 h.

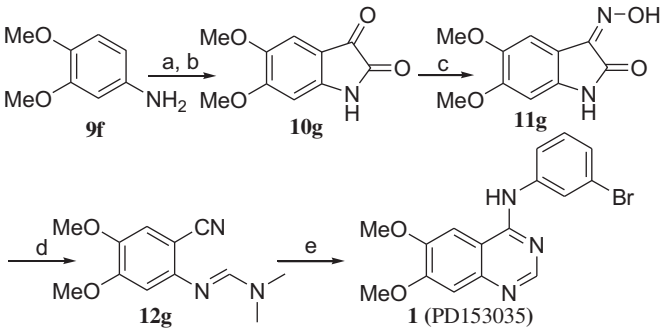


Scheme 4. The synthesis of **13e** and **13f**. Reagents and conditions: (a) $HONH_3Cl$, Cl_3CCHO, Na_2SO_4, H_2O, reflux, 1 h; (b) 95% of H_2SO_4, 65 °C, 1 h; (c) $HONH_3Cl$, H_2O, CH_3COONa, reflux, 30 min; (d) $POCl_3$, DMF, Na_2CO_3, H_2O, 0 °C to rt to 70 °C, 4 h; (e) 3-chloro-4-fluorobenzenamine, CH_3COOH, reflux, 3 h.

anilines (**9a**–**e**) were used as starting materials to synthesize isatin derivatives with the following two steps. Compounds **9a**–**e** firstly reacted with chloral hydrate and hydroxylamine hydrochloride to produce anilide derivatives. Then Beckmann rearrangement was carried out in 95% of H_2SO_4 to form compounds **10a**–**f**.[16] The rest steps were similar to Scheme 2. The yields of anilide derivatives were affected by the substituent groups of anilines used in the process. Generally, aniline with electron-drawing group gives a higher yield of aniline derivatives than that with electron-donating group. More by-product produced by more active amine. It was observed that the yield of **10c** (60.7%) was lower than the yield of other compound **10**. In addition, the efficiency of the new strategy was also practiced by synthesizing compound **5** with the above procedure. A total yield of 77.8% was obtained.

It is well known that aromatic ring with *ortho*- and *para*-directing group can form two products when an electrophilic substitution occurs on benzene ring. It is approved in this work at Beckmann rearrangement step b (Scheme 4), when 3-chlorobenzeneamine was used as starting material. Compounds **10e** and **10f** were formed and the ratio of **10e** to **10f** was approximately 1 to 1 by comparing the peak area of HPLC (The spectrum of HPLC is in Supplementary data.). After the whole process, the target compounds **13e** and **13f** were obtained with total yields of 23.7% and 26.1%, respectively.

PD153035 (**1**), one of the star molecule in 4-anilinoquinazoline family, is a selective specific EGFR tyrosine kinase inhibitor reported in 1994 for the first time. To further evaluate the developed strategy in this work, PD153035 (**1**) was synthesized through five steps using 3,4-dimethoxybenzenamine (**9f**) as starting material.[17] The yield of the anilide derivative obtained with **9f**, which has two electron-donating groups on the benzene ring, was lower than other compounds at reflux condition. To increase the yield of the intermediate, reaction temperature was lowered while the ratio of material in the system was also adjusted. High yield (90%) of anilide derivative was achieved at 70 °C. Consequently, 50.1% total yield of compound **1** was obtained (Scheme 5).



Scheme 5. The synthesis of PD153035 (**1**). Reagents and conditions: (a) $HONH_3Cl$, Cl_3CCHO, Na_2SO_4, H_2O, 70 °C, 1 h; (b) 95% of H_2SO_4, 65 °C, 2 h; (c) $HONH_3Cl$, H_2O, CH_3COONa, reflux, 30 min; (d) $POCl_3$, DMF, Na_2CO_3, H_2O, 0 °C to rt to 70 °C, 4 h; (e) 3-bromobenzenamine, CH_3COOH, reflux, 3 h.

In summary, 17 different substituted 4-anilinoquinazolines were synthesized successfully, of which compounds **8d, 8e**, **8h**, and **13a**–**g** were firstly synthesized in public literature. To verify the efficiency of our new approach, overall yields of the final products from this work along with those obtained with different routes reported in literature are listed in Table 2. It reveals that the overall yields of final products obtained through three steps with starting compound **5** are more than 70%, which are higher than those reported in literature using anthranilonitrile or anthranilic acid as starting material; The overall yields of the final products **8a**–**j**, using aniline as starting material, are in the range of 57–64%, which are comparable to the range reported in literature. The yields of **13a**, **13b**, **13d**, and **1** are in the range of 50–61%. The yield of **13c** is lower due to the electron-donating effect of the methyl groups on the quinazoline ring. The yields of **13e** and **13f** are approximately half of other products due to co-existence of two isomers of **10e** and **10f** in the process.

Table 2
Overall yields comparison

Compounds	Literature	Isolated (%)	
		From **5**	From aniline
8a	46.7%,[7] 79.2%,[18] 67%[19]	76.6	60
8b	—	79.9	62.2
8c	71%[20]	73.3	57
8d	—	75.6	58.8
8e	—	81.9	63.7
8f	65.1%[21]	82.7	64.3
8g	72.1%[22]	81.1	63.1
8h	—	78.5	61.1
8i	34.6%,[7] 78.2%[18]	73.3	57
8j	33.1%[7]	80.2	62.2
13a	72.3%,[11] 59.8%[23]	—	61.1
13b	—	—	53.8
13c	—	—	41.9
13d	—	—	54.6
13e	—	—	23.7
13f	—	—	26.1
1	55%,[24] 40%[25]	—	50.1

'——' The synthetic yields were not reported.

Following the new approach, the key intermediates **7** and **12a**–**g** can be produced by simple, efficient, and environmentally friendly processes. Purification process after each step can be done easily due to the high yield of target compound in each step. Extraction or column separation is not required. A simple precipitation process by controlling pH is performed followed by filtration. The preparation of compounds **5** and **10a**–**g** from aniline derivatives followed the method reported in the literature.[16] Compounds **10a**–**g**, **5**, and hydroxylamine hydrochloride are dissolved in water and kept refluxing for 30 min to produce the intermediates **11a**–**g** and **6** with yields in the range of 88–98%. This is a green reaction that no organic solvents are used. Once compounds **11a**–**g** and **6** are obtained, the key intermediates **12a**–**g** and **7** can be synthesized according to the conditions listed in Table 1. Finally, compounds **7** and **12a**–**g** react with corresponding substituted anilines to produce target compounds **8a**–**j**, **13a**–**f**, and **1**.

Previous studies reported the NMR and mass spectra of compounds of group **8** and compound **1** that were successfully synthesized. With the new approach developed in this work, compounds **8d**, **8e**, **8h**, and **13b**–**f** were successfully synthesized for the first time. Therefore, IR and UV spectra of these compounds were investigated and the effects of the substituent groups on such spectra were summarized. The common features of IR spectra of this kind of compounds include a sharp absorption peak in 3100–3500 cm^{-1} region generated from secondary amine and a smaller absorption peak in 3000–3100 cm^{-1} region rose from the benzene. Another common absorption peak of this group compounds is a single sharp peak in 1620–1700 cm^{-1} region from vibration of C=N bond.

The characteristics of IR spectra among the different compounds in this group originates from the different substituent groups, which have their own vibration frequencies, such as hydroxyl group of **8c** at 3240.25 cm^{-1}, methoxyl group of **8d** and **1** at 1155.80 cm^{-1} and 1151.27 cm^{-1}, nitro group of **13a** at 1533.45 cm^{-1}, and methyl group of **13c** at 3041.11 cm^{-1}. The bonds with halogen atoms exhibit specific absorption peaks and the substituent positions of halogen on benzene ring also influence their bond vibration frequencies. The common absorption peaks of **8a**–**j** in 735–770 cm^{-1} region represent the four successive hydrogens on the quinazoline ring. The common absorption peaks in 800–900 cm^{-1} of **13a**–**c**, which

all have a substituent at 6 positions, correspond to two successive hydrogens and a single hydrogen on quinazoline rings. The feature absorption peaks of **13e** are similar to **13a**–**c**. The feature peaks of **13d** and **13e** are in 710–850 cm^{-1}, corresponding to three successive hydrogens on quinazoline rings.

Two main common absorption peaks of those compounds in UV spectra are presented in the regions of 210–220 nm and 320–340 nm. The other two peaks appear in the regions of 235–250 nm and 280–290 nm and the sizes of the peaks depend on the position of the substituent groups. A substituent at *ortho*-position on aniline ring of **8a**–**j** causes the peak in the region of 280–290 nm larger than other positions, while a substituent at *para*-position results in the peak in the region of 235–250 nm lager. When a substituent at *meta*-position, the peaks in the regions of 235–240 nm and 280–290 nm are so small that only two main peaks in the regions of 210–220 nm and 320–330 nm are observed. When a substituent on quinazoline rings of **13a**–**g**, the UV feature peaks are similar to that on aniline ring. The substituent at *meta*-position causes the peak in the region of 280–290 nm smaller than at other positions.

3. Conclusion

A novel synthetic approach to produce 4-anilinoquinazolines with cheap starting material was developed. The processes with this approach are simple, efficient, and environmental friendly. Nitration and reduction steps are eliminated. No other organic solvents were used in this approach except of DMF and CH_3COOH. Seventeen 4-anilinoquinazolines were successfully synthesized and the overall yields of the target products were higher than the corresponding ones with conventional routes reported in literature. The synthesis of compounds **8e**, **8d**, **8h**, **13b**–**f** and IR and UV spectra of these compounds along with the effects of their substituent groups on the spectra were reported for the first time in public literature.

4. Experimental sections

4.1. General

All chemicals and solvents were analytical grade and used without further purification. Analytical TLC was performed on precoated silica gel plates (HG/T2354-92). Melting points were determined on an X-5 micro melting point apparatus and were uncorrected. The UV spectra were recorded on a 2600UV/VIS spectrophotometer using methanol as blank. The IR spectra were recorded on an FT-IR spectrometer (Spectrum Two); ^1H NMR spectra were recorded at 400 MHz on a Bruker Avance-400 MHz spectrometer with TMS as an internal standard; chemical shifts were given in parts per million (ppm) and coupling constants in hertz (Hz). Mass spectra were performed on LTQ-XL with direct sample injection; HRMS were performed on Agilent Technologies 6520B accurate-Mass Q-TOF LC/MS. Elemental analysis was performed on a Vario EL III CHNOS analyzer.

4.2. General procedure for the synthesis of 5 and 10a–g

(a) A 500 ml, three-necked, round-bottomed flask fitted with a condenser and a thermometer was charged with chloral hydrate (16.50 g, 0.1 mol) and 220 ml of water. Then anhydrous sodium sulfate (15.00 g), aniline derivative (0.1 mol), HCl solution (5.2%, 70 ml), and hydroxylamine hydrochloride (20.81 g, 0.3 mol, in 95 ml of water) were added in successively. After being heated to reflux for 1 h, the reaction mixture was cooled to room temperature. The intermediate compound (anilide derivative) was collected by filtration and dried, which was used for next step without further purification.

(b) A 100 ml, three-necked, round-bottomed flask fitted with a thermometer was charged with concentrated sulfuric acid (10 equiv). After heating to 50 °C with stirring, the dried product (1 equiv) from the above step was added in over a period of 20 min. The resulting solution was heated to 65 °C and kept for 1 h and then cooled down to room temperature with an ice bath. The precipitate was filtered out and dried to get the target compounds.

*4.2.1. Indoline-2,3-dione (**5**).* The dried product from the above step (15.4 g, 0.095 mol) was added into concentrated sulfuric acid (50 ml) in a period of 20 min at 50 °C. Then the resulted mixture was heated to 65 °C and kept for 1 h. The mixture was poured into ice water. The precipitate in the mixture was filtered out and dried. Red crystal solid of 11.51 g was obtained with a yield of 77.8%. Mp 189–192 °C; IR (KBr): 3192.19, 1728.52, 1616.46, 1461.23, 1401.93, 770.77 cm^{-1}; UV–vis (CH_3OH), λ/nm: 210, 242, 297 nm; ^1H NMR (400 MHz, $CDCl_3$): δ 11.09 (s, 1H), 7.13 (t, 1H), 7.42 (t, 1H), 7.76 (d, 1H), 7.83 (d, 1H); ESI-MS for $C_8H_5NO_2$ $[M+H]^+$: calcd: 148.13, found: 148.08. Anal. Calcd for $C_8H_5NO_2$: C, 65.31; H, 3.43; N, 9.52. Found: C, 65.27; H, 3.44; N, 9.53.

*4.2.2. 5-Nitroindoline-2,3-dione (**10a**).* The dried product from the above step (20.5 g, 0.098 mol) was added into concentrated sulfuric acid (53 ml) in a period of 20 min at 50 °C. Then the resulted mixture was heated to 65 °C and kept for 1 h. The mixture was poured into ice water. The precipitate in the mixture was filtered out and dried. Pale yellow crystal solid of 14.74 g was obtained with a yield of 76.4%. Mp 254–257 °C; IR (KBr): 3334.61, 3095.36, 1770.03, 1751.21, 1619.29, 1533.45, 1470.52, 1336.55, 903.33, 852.46 cm^{-1}; UV–vis (CH_3OH), λ/nm: 210, 321 nm; ^1H NMR (400 MHz, $CDCl_3$): δ 10.74 (s, 1H), 8.25 (d, 1H), 7.97 (s, 1H), 7.69 (d, 1H); ESI-MS for $C_8H_4N_2O_4$ $[M+H]^+$: calcd: 193.13, found: 193.08. Anal. Calcd for $C_8H_4N_2O_4$: C, 50.01; H, 2.10; N, 14.58. Found: C, 50.05; H, 2.06; N, 14.56.

*4.2.3. 5-Fluoroindoline-2,3-dione (**10b**).* The dried product from the above step (17.1 g, 0.095 mol) was added into concentrated sulfuric acid (50 ml) in a period of 20 min at 50 °C. Then the resulted mixture was heated to 65 °C and kept for 1 h. The mixture was poured into ice water. The precipitate in the mixture was filtered out and dried. Red solid of 12.35 g was obtained with a yield of 74.4%. Mp 221–224 °C; IR (KBr): 3446.51, 3068.88, 1738.77, 1724.51, 1620.63, 1488.17, 1141.15, 890.43, 847.51 cm^{-1}; UV–vis (CH_3OH), λ/nm: 215, 249, 295 nm; ^1H NMR (400 MHz, $CDCl_3$): δ 10.91 (s, 1H), 7.63 (d, 1H), 7.57 (s, 1H), 6.95 (d, 1H); ESI-MS for $C_8H_4NO_2F$ $[M+H]^+$: calcd: 166.12, found: 166.08. Anal. Calcd for $C_8H_4NO_2F$: C, 58.19; H, 2.44; N, 8.48. Found: C, 58.21; H, 2.39; N, 8.51.

*4.2.4. 5-Methylindoline-2,3-dione (**10c**).* The dried product from the above step (14.1 g, 0.08 mol) was added into concentrated sulfuric acid (43 ml) in a period of 20 min at 50 °C. Then the resulted mixture was heated to 65 °C and kept for 1 h. The mixture was poured into ice water. The precipitate in the mixture was filtered out and dried. Red solid of 9.83 g was obtained with a yield of 60.7%. Mp 168–171 °C; IR (KBr): 3458.06, 2996.94, 2923.95, 1747.00, 1716.05, 1628.01, 1604.41, 1492.00, 1437.81, 900.35, 812.40 cm^{-1}; UV–vis (CH_3OH), λ/nm: 216, 246, 300 nm; ^1H NMR (400 MHz, CD_3OD): δ 7.40 (d, J=8.0 Hz, 1H), 7.36 (s, 1H), 6.82 (d, J=8.0 Hz, 1H), 2.30 (s, 3H); ESI-MS for $C_9H_7NO_2$ $[M+H]^+$: calcd: 162.15, found: 162.08. Anal. Calcd for $C_9H_7NO_2$: C, 67.06; H, 4.38; N, 8.69. Found: C, 67.12; H, 4.08; N, 8.59.

*4.2.5. 7-Chloroindoline-2,3-dione (**10d**).* The dried product from the above step (18.5 g, 0.094 mol) was added into concentrated

sulfuric acid (50 ml) in a period of 20 min at 50 °C. Then the resulted mixture was heated to 65 °C and kept for 1 h. The mixture was poured into ice water. The precipitate in the mixture was filtered out and dried. Red solid of 14.17 g was obtained with a yield of 77.9%. Mp 152–154 °C; IR (KBr): 3456.09, 3076.51, 1771.23, 1746.61, 1614.52, 1529.23, 1475.12, 1434.67, 768.5, 734.2 cm^{-1}; UV–vis (CH_3OH), λ/nm: 218, 245, 300 nm; ^1H NMR (400 MHz, CD_3OD): δ 7.60 (d, J=8.1 Hz, 1H), 7.50 (d, J=7.4 Hz, 1H), 7.33–7.29 (m, 2H); ESI-MS for $C_8H_4NO_2Cl$ $[M+H]^+$: calcd: 182.57, found: 182.08. Anal. Calcd for $C_8H_4NO_2Cl$: C, 52.91; H, 2.22; N, 7.71. Found: C, 52.83; H, 2.10; N, 7.81.

*4.2.6. 6-Chloroindoline-2,3-dione (**10e**).* The dried product from the above step (16.2 g, 0.09 mol) was added into concentrated sulfuric acid (48 ml) in a period of 20 min at 50 °C. Then the resulted mixture was heated to 65 °C and kept for 1 h. The mixture was poured into ice water. The precipitate in the mixture was filtered out and dried. Crude red solid of 13.2 g was obtained. The crude product (6.5 g) was purified by column chromatography over silica gel (using petroleum ether/EtOAc=8:1) to afford **10e** as a red solid 2.91 g with a yield of 32.5%. Mp 238–241 °C; IR (KBr): 3460.23, 3106.31, 1756.24, 1732.80, 1615.04, 1589.10, 1436.88, 875.8, 838.97, 602.13 cm^{-1}; UV–vis (CH_3OH), λ/nm: 213, 251, 300 nm; ^1H NMR (400 MHz, CD_3OD): δ 7.52 (d, J=8.0 Hz, 1H), 7.11 (dd, J=8.0, 1.4 Hz, 1H), 6.97 (d, J=1.3 Hz, 1H); ESI-MS for $C_8H_4NO_2Cl$ $[M+H]^+$: calcd: 182.57, found: 182.08. Anal. Calcd for $C_8H_4NO_2Cl$: C, 52.91; H, 2.22; N, 7.71. Found: C, 52.80; H, 2.06; N, 7.79.

*4.2.7. 4-Chloroindoline-2,3-dione (**10f**).* The dried product from the above step (16.2 g, 0.09 mol) was added into concentrated sulfuric acid (48 ml) in a period of 20 min at 50 °C. Then the resulted mixture was heated to 65 °C and kept for 1 h. The mixture was poured into ice water. The precipitate in the mixture was filtered out and dried. Crude red solid of 13.2 g was obtained. The crude product (6.5 g) was purified by column chromatography over silica gel (using petroleum ether/EtOAc=8:1 and 6:1) to afford **10f** as a red solid 3.04 g with a yield of 34.6%. Mp 261–263 °C; IR (KBr): 3456.21, 3177.04, 1739.98, 1723.19, 1609.78, 1587.28, 1470.69, 1439.48, 788.70, 674.95 cm^{-1}; UV–vis (CH_3OH), λ/nm: 218, 243, 306 nm; ^1H NMR (400 MHz, CD_3OD): δ 7.51 (t, J=8.0 Hz, 1H), 7.05 (d, J=8.2 Hz, 1H), 6.86 (d, J=7.9 Hz, 1H); ESI-MS for $C_8H_4NO_2Cl$ $[M+H]^+$: calcd: 182.57, found: 182.08. Anal. Calcd for $C_8H_4NO_2Cl$: C, 52.91; H, 2.22; N, 7.71. Found: C, 52.58; H, 2.16; N, 7.72.

*4.2.8. General procedure for 5,6-dimethoxyindoline-2,3-dione (**10g**).*

(a) A 250 ml, three-necked, round-bottomed flask fitted with a condenser and a thermometer was charged with chloral hydrate (3.2 g, 0.019 mol) and 100 ml of water. Then anhydrous sodium sulfate (45.5 g), 3,4-dimethoxybenzenamine (2.62 g, 0.017 mol), HCl solution (5.2%, 30 ml), and hydroxylamine hydrochloride (3.9 g, 0.056 mol, in 20 ml of water) were added in successively. After being heated to 70 °C for 1 h, the reaction mixture was cooled to room temperature. The intermediate compound (anilide derivative) was collected by filtration and dried, which was used for next step without further purification.

(b) A 50 ml, three-necked, round-bottomed flask fitted with a thermometer was charged with concentrated sulfuric acid solution (9 ml). After heating to 50 °C with stirring, the dried product (3.6 g, 0.016 mol) from the above step was added in over a period of 20 min. The resulting solution was heated to 65 °C and kept for 1 h and then cooled down to room temperature with an ice bath. The precipitate was filtered out and the filtrate was extracted with ethyl acetate (40 ml×3). The organic phase was dried over anhydrous sodium sulfate and evaporated under reduced pressure, giving the compound **10g** as red solid.

Red solid; 2.58 g, 73% yield. Mp 246–249 °C; IR (KBr): 3432.93, 2946.11, 1767.8, 1743.78, 1621.81, 1496.42, 1467.08, 1198.89, 865.61 cm^{-1}; UV–vis (CH_3OH), λ/nm: 211, 267, 321 nm; ^1H NMR (400 MHz, CD_3OD): δ 7.08 (s, 1H), 6.55 (s, 1H), 3.94 (s, 3H), 3.79 (s, 3H); ESI-MS for $C_{10}H_9NO_4$ $[M+H]^+$: calcd: 208.17, found: 208.08. Anal. Calcd for $C_{10}H_9NO_4$: C, 57.97; H, 4.37; N, 6.76. Found: C, 57.88; H, 4.32; N, 6.59.

4.3. General procedure for the synthesis of compounds 6 and 11a–g

*4.3.1. 3-(Hydroxyimino)indolin-2-one (**6**).* A mixture of compound **5** (10.00 g, 0.068 mol) and hydroxylamine hydrochloride (5.00 g, 0.072 mol) in water (100 ml) was heated to reflux for 30 min, then sodium acetate (5 g) was added in and the solution was continued to reflux for another 30 min. The mixture was cooled down to room temperature. The solid was filtered out and dried to obtain a yellow solid **6**, which was pure enough for the next reaction; 10.81 g, 98% yield. Mp 219–221 °C.

*4.3.2. Compounds **11a–g**.* A mixture of compound **10a–g** (0.01 mol) and hydroxylamine hydrochloride (0.013 mol) in water (20 ml) was heated to reflux for 30 min, then sodium acetate (1.5 g) was added and the solution was continued to reflux for another 30 min. The mixture was cooled down to room temperature. The solid was filtered out and dried for the next step. The obtained yields were all in the range of 88% and 97%.

4.4. General procedure for the synthesis of compounds 7 and 12a–g

*4.4.1. 3-(2-Cyanophenyl)-1,1-dimethylurea (**7**).* Compound **6** (5.02 g, 0.031 mol) was added in slowly to the mixture of $POCl_3$ (4.3 ml, 0.046 mol) and DMF (20 ml) that was iced to 0 °C. The resulting mixture was stirred at room temperature for 10 min followed by heated to 70 °C for 4 h. The reaction mixture was cooled down and poured into water (100 ml). The unsolvable substance was filtered out. Then sodium carbonate solution (10%) was added into the solution to adjust the pH to 7. Thirty minutes later, the precipitate was filtered out and dried. Yellow solid **7** of 4.72 g was obtained with 88% yield, which was pure enough for the next reaction. Mp 145–148 °C.

*4.4.2. Compounds **12a–f**.* Compounds **11a–f** (1.0 equiv) was added in slowly to the mixture of $POCl_3$ (1.5 equiv) and DMF (8 ml) that was iced to 0 °C. The resulting mixture was stirred at room temperature for 10 min and then heated to 70 °C for 4 h. The reaction mixture was cooled down and poured into water (50 ml). The unsolvable substance was filtered out. Then sodium carbonate solution (10%) was added into the solution to adjust the pH to 7. Thirty minutes later, the precipitate was filtered out and dried to result the target compounds **12a–f**, respectively. The yields were all in the range of 80% and 85%.

*4.4.3. 3-(2-Cyano-4,5-dimethoxyphenyl)-1,1-dimethylurea (**12g**).* Compound **11g** (2.0 g, 0.009 mol) was added in slowly to the mixture of $POCl_3$ (1.3 ml, 0.014 mol) and DMF (8 ml) that was iced to 0 °C. The resulting mixture was stirred at room temperature for 10 min and then heated to 70 °C for 4 h. The reaction mixture was cooled down and poured into water (50 ml). The unsolvable substance was filtered out. Then sodium carbonate solution (10%) was added into the solution to adjust the pH to 7. The aqueous phase was extracted with ethyl acetate (30 ml×3) and then the organic phase was extracted with water (50 ml×3) to remove DMF. The

solvents were removed in vacuo giving a brown liquid product without further purification for the next step.

4.5. General procedure for the synthesis of compounds 8a–j, 13a–f, and PD153035 (1)

A mixture of compound **7** (1.0 equiv), **12a**–**g** (1.0 equiv), and different derivatives of aniline (1.0 equiv) in acetic acid (15 equiv) was heated to reflux for 3 h. The mixture was poured into the ice water. Twenty minutes later, the precipitate was filtered out and washed three times with water. The solid was dried to result in the target compounds.

*4.5.1. N-Phenylquinazolin-4-amine (**8a**).* The title compound was obtained in 89.7% yield, by condensing **7** (1.72 g, 0.01 mol) with aniline (0.93 g, 0.01 mol), as a white solid of 1.98 g. Mp 251–253 °C; IR (KBr): 3294.98, 3060.70, 1664.21, 1599.51, 1556.40, 1500.16, 1436.01, 756.96, 694.62 cm^{-1}; UV–vis (CH_3OH), λ/nm: 207, 239, 329 nm; ^1H NMR (400 MHz, CD_3OD): δ 8.50 (s, 1H), 8.39 (d, J=7.8 Hz, 1H), 7.89–7.84 (m, 1H), 7.79 (d, J=7.9 Hz, 1H), 7.73 (s, 1H), 7.66–7.61 (m, 1H), 7.50 (s, 2H), 7.41 (s, 2H), 7.19 (d, J=7.4 Hz, 1H); ESI-MS for $C_{14}H_{11}N_3$ $[M+H]^+$: calcd: 222.25, found: 222.08. Anal. Calcd for $C_{14}H_{11}N_3$: C, 75.99; H, 5.01; N, 18.99. Found: C, 75.68; H, 5.11; N, 18.45.

*4.5.2. N-(3-Chloro-4-fluorophenyl)quinazolin-4-amine (**8b**).* The title compound was obtained in 92.7% yield, by condensing **7** (1.72 g, 0.01 mol) with 3-chloro-4-fluorobenzenamine (1.47 g, 0.01 mol), as a white solid of 2.53 g. Mp 225–227 °C; IR (KBr): 3352.33, 3044.28, 1679.76, 1605.64, 1579.51, 1495.22, 1423.78, 1060.05, 872.70, 813.54, 761.49, 678.39 cm^{-1}; UV–vis (CH_3OH), λ/nm: 216, 243, 329 nm; ^1H NMR (400 MHz, CD_3OD): δ 8.58 (s, 1H), 8.37 (d, J=8.3 Hz, 1H), 8.06 (dd, J=6.7, 2.6 Hz, 1H), 7.88 (t, J=7.6 Hz, 1H), 7.81 (d, J=8.2 Hz, 1H), 7.81–7.59 (m, 3H), 7.27 (t, J=9.0 Hz, 1H); ESI-MS for $C_{14}H_9N_3ClF$ $[M+H]^+$: calcd: 274.69, found: 274.08. Anal. Calcd for $C_{14}H_9N_3ClF$: C, 61.43; H, 3.31; N, 15.35. Found: C, 61.86; H, 3.01; N, 15.40.

*4.5.3. 4-(Quinazolin-4-ylamino)phenol (**8c**).* The title compound was obtained in 85.1% yield, by condensing **7** (1.72 g, 0.01 mol) with 4-aminophenol (1.09 g, 0.01 mol), as a brown solid of 2.01 g. Mp 217–219 °C; IR (KBr): 3433.41, 3240.25, 3094.13, 1656.92, 1618.36, 1586.07, 1494.86, 1446.14, 1359.70, 1232.90, 818.41, 803.69, 773.79 cm^{-1}; UV–vis (CH_3OH), λ/nm: 210, 244, 332 nm; ^1H NMR (400 MHz, CD_3OD): δ 8.41 (s, 1H), 8.32 (d, J=8.2 Hz, 1H), 7.84 (t, J=7.5 Hz, 1H), 7.75 (d, J=8.2 Hz, 1H), 7.60 (t, J=7.5 Hz, 1H), 7.44 (d, J=8.5 Hz, 3H), 6.85 (d, J=8.5 Hz, 2H); ESI-MS for $C_{14}H_{11}N_3O$ $[M+H]^+$: calcd: 238.25, found: 238.08. Anal. Calcd for $C_{14}H_{11}N_3O$: C, 70.87; H, 4.67; N, 17.71. Found: C, 70.87; H, 4.39; N, 17.13.

*4.5.4. N-(3-Methoxyphenyl)quinazolin-4-amine (**8d**).* The title compound was obtained in 87.7% yield, by condensing **7** (1.72 g, 0.01 mol) with 3-methoxybenzenamine (1.23 g, 0.01 mol), as a white solid of 2.20 g. Mp 153–158 °C; IR (KBr): 3260.91, 3090.48, 2935.00, 2834.59, 1623.55, 1601.60, 1571.51, 1498.91, 1452.52, 1356.10, 1155.80, 1053.61, 875.75, 818.55, 771.51 cm^{-1};UV–vis (CH_3OH), λ/nm: 216, 332 nm; ^1H NMR (400 MHz, CD_3OD): δ 8.44 (s, 1H), 8.30 (d, J=8.2 Hz, 1H), 7.77 (d, J=7.9 Hz, 1H), 7.70 (d, J=8.1 Hz, 1H), 7.54 (t, J=7.6 Hz, 1H), 7.36 (s, 1H), 7.22 (d, J=6.4 Hz, 3H), 6.69 (dt, J=6.4, 2.4 Hz, 1H), 3.74 (s, 3H); ESI-MS for $C_{15}H_{13}N_3O$ $[M+H]^+$: calcd: 252.28, found: 252.08; HRMS for $C_{15}H_{13}N_3O$ $[M+H]^+$: calcd: 252.2833, found: 252.1126. Anal. Calcd for $C_{15}H_{13}N_3O$: C, 71.69; H, 5.21; N, 16.72. Found: C, 71.97; H, 5.01; N, 16.61.

*4.5.5. N-(2-Fluorophenyl)quinazolin-4-amine (**8e**).* The title compound was obtained in 95.1% yield, by condensing **7** (1.72 g, 0.01 mol) with 2-fluorobenzenamine (1.11 g, 0.01 mol), as a white solid of 2.28 g. Mp 167–170 °C; IR (KBr): 3067.19, 1620.17, 1599.04, 1571.53, 1500.84, 1454.18, 1407.94, 771.00, 745.94 cm^{-1}; UV–vis (CH_3OH), λ/nm: 215, 289, 320 nm; ^1H NMR (400 MHz, CD_3OD): δ 8.40 (s, 1H), 8.31 (d, J=8.3 Hz, 1H), 7.84 (d, J=7.1 Hz, 1H), 7.77 (d, J=8.3 Hz, 1H), 7.61 (dd, J=14.0, 6.7 Hz, 2H), 7.29 (s, 1H), 7.25–7.20 (m, 2H), 5.45 (s, 1H); ESI-MS for $C_{14}H_{10}N_3F$ $[M+H]^+$: calcd: 240.24, found: 240.08; HRMS for $C_{14}H_{10}N_3F$ $[M+H]^+$: calcd: 240.2478, found: 240.0928. Anal. Calcd for $C_{14}H_{10}N_3F$: C, 70.28; H, 4.21; N, 17.56. Found: C, 70.41; H, 4.12; N, 17.26.

*4.5.6. N-(4-Fluorophenyl)quinazolin-4-amine (**8f**).* The title compound was obtained in 95.8% yield, by condensing **7** (1.72 g, 0.01 mol) with 4-fluorobenzenamine (1.11 g, 0.01 mol), as a white solid of 2.29 g. Mp 205–208 °C; IR (KBr): 3059.51, 1623.16, 1572.80, 1530.73, 1495.57, 1420.66, 1397.73, 832.88, 818.32, 765.95 cm^{-1}; UV–vis (CH_3OH), λ/nm: 219, 235, 332 nm; ^1H NMR (400 MHz, CD_3OD): δ 8.51 (s, 1H), 8.38 (d, J=8.3 Hz, 1H), 7.88 (t, J=7.6 Hz, 1H), 7.80 (d, J=8.3 Hz, 1H), 7.76–7.71 (m, 3H), 7.65 (t, J=7.6 Hz, 1H), 7.16 (t, J=8.7 Hz, 2H); ESI-MS for $C_{14}H_{10}N_3F$ $[M+H]^+$: calcd: 240.24, found: 240.08. Anal. Calcd for $C_{14}H_{10}N_3F$: C, 70.28; H, 4.21; N, 17.56. Found: C, 70.42; H, 4.15; N, 17.15.

*4.5.7. N-(2-Chlorophenyl)quinazolin-4-amine (**8g**).* The title compound was obtained in 94.1% yield, by condensing **7** (1.72 g, 0.01 mol) with 2-chlorobenzenamine (1.47 g, 0.01 mol), as a white solid. 2.41 g, mp 114–117 °C; IR (KBr): 3436.45, 3039.16, 1621.61, 1601.29, 1588.12, 1496.67, 1445.93, 749.35, 673.30 cm^{-1}; UV–vis (CH_3OH), λ/nm: 214, 288, 317 nm; ^1H NMR (400 MHz, CD_3OD): δ 8.42 (s, 1H), 8.35 (d, J=8.3 Hz, 1H), 7.90 (t, J=7.3 Hz, 1H), 7.81 (d, J=8.2 Hz, 1H), 7.66 (t, J=7.9 Hz, 3H), 7.56 (d, J=7.9 Hz, 1H), 7.42 (t, J=7.1 Hz, 1H), 7.34 (t, J=7.1 Hz, 1H); ESI-MS for $C_{14}H_{10}N_3Cl$ $[M+H]^+$: calcd: 256.70, found: 256.08. Anal. Calcd for $C_{14}H_{10}N_3Cl$: C, 65.76; H, 3.94 N, 16.43. Found: C, 65.81; H, 3.84; N, 16.01.

*4.5.8. N-(2,4-Dichlorophenyl)quinazolin-4-amine (**8h**).* The title compound was obtained in 91.1% yield, by condensing **7** (1.72 g, 0.01 mol) with 2,4-dichlorobenzenamine (1.62 g, 0.01 mol), as a white solid of 2.65 g. Mp 225–228 °C; IR (KBr): 3360.25, 3034.22, 1683.39, 1595.30, 1572.07, 1502.43, 1475.91, 873.77, 812.35, 763.62, 677.32 cm^{-1}; UV–vis (CH_3OH), λ/nm: 210, 244, 331 nm; ^1H NMR (400 MHz, CD_3OD): δ 8.41 (s, 1H), 8.32 (d, J=8.2 Hz, 1H), 7.84 (t, J=7.5 Hz, 1H), 7.75 (d, J=8.2 Hz, 1H), 7.60 (t, J=7.5 Hz, 1H), 7.44 (d, J=8.5 Hz, 3H), 6.85 (d, J=8.5 Hz, 2H); ESI-MS for $C_{14}H_9N_3Cl_2$ $[M+H]^+$: calcd: 291.14, found: 291.08; HRMS for $C_{14}H_9N_3Cl_2$ $[M+H]^+$: calcd: 291.1469, found: 291.0266. Anal. Calcd for $C_{14}H_9N_3Cl_2$: C, 57.95; H, 3.12; N, 14.48. Found: C, 57.45; H, 3.34; N, 14.31.

*4.5.9. N-(4-Bromophenyl)quinazolin-4-amine (**8i**).* The title compound was obtained in 85.0% yield, by condensing **7** (1.72 g, 0.01 mol) with 4-bromobenzenamine (1.72 g, 0.01 mol), as a white solid of 2.55 g. Mp 232–234 °C; IR (KBr): 3298.71, 3058.55, 1621.16, 1598.79, 1571.46, 1497.46, 1455.38, 809.61, 767.53, 499.65 cm^{-1}; UV–vis (CH_3OH), λ/nm: 210, 238, 332 nm; ^1H NMR (400 MHz, CD_3OD): δ 8.55 (s, 1H), 8.38 (d, J=8.1 Hz, 1H), 7.90–7.85 (m, 1H), 7.80 (d, J=8.0 Hz, 1H), 7.77–7.74 (m, 2H), 7.64 (dd, J=11.2, 4.1 Hz, 1H), 7.55–7.52 (m, 2H), 5.48 (s, 1H); ESI-MS for $C_{14}H_{10}N_3Br$ $[M+H]^+$: calcd: 301.15, found: 301.08. Anal. Calcd for $C_{14}H_{10}N_3Br$: C, 56.02; H, 3.35; N, 13.99. Found: C, 56.39; H, 3.02; N, 13.90.

*4.5.10. N-(3-Bromophenyl)quinazolin-4-amine (**8j**).* The title compound was obtained in 93.3% yield, by condensing **7** (1.72 g, 0.01 mol) with 3-bromobenzenamine (1.72 g, 0.01 mol), as a white solid of 2.80 g. Mp 195–198 °C; IR (KBr): 3284.28, 3113.63, 1621.95, 1597.18, 1568.89, 1501.23, 1477.64, 862.22, 797.30, 587.41 cm^{-1};

UV–vis (CH_3OH), λ/nm: 213, 330 nm; ^1H NMR (400 MHz, CD_3OD): δ 8.60 (s, 1H), 8.40 (d, *J*=8.3 Hz, 1H), 8.14 (s, 1H), 7.89 (t, *J*=7.6 Hz, 1H), 7.79 (dd, *J*=16.4, 6.0 Hz, 2H), 7.65 (t, *J*=7.6 Hz, 1H), 7.32 (d, *J*=5.5 Hz, 2H), 5.49 (s, 1H); ESI-MS for $C_{14}H_{10}N_3Br$ $[M+H]^+$: calcd: 301.15, found: 301.08. Anal. Calcd for $C_{14}H_{10}N_3Br$: C, 56.02; H, 3.35; N, 13.99. Found: C, 56.37; H, 3.06; N, 13.91.

*4.5.11. N-(3-Chloro-4-fluorophenyl)-6-nitroquinazolin-4-amine (**13a**).* The title compound was obtained in 91.2% yield, by condensing **12a** (2.17 g, 0.01 mol) with 3-chloro-4-fluorobenzenamine (1.47 g, 0.01 mol), as a yellow solid of 2.90 g. Mp 279–281 °C; IR (KBr): 3307.68, 3096.44, 1625.21, 1587.82, 1573.43, 1595.99, 1538.13, 1435.48, 1340.91, 875.17, 848.54, 809.04 cm^{-1}; UV–vis (CH_3OH), λ/nm: 218, 240, 359; ^1H NMR (400 MHz, CD_3OD): δ 9.51 (d, *J*=2.2 Hz, 1H), 8.70 (s, 1H), 8.63 (dd, *J*=9.2, 2.3 Hz, 1H), 8.09 (dd, *J*=6.6, 2.5 Hz, 1H), 7.95 (d, *J*=9.2 Hz, 1H), 7.74 (dd, *J*=7.9, 3.8 Hz, 1H), 7.30 (t, *J*=8.9 Hz, 1H); ESI-MS for $C_{14}H_8N_4O_2ClF$ $[M+H]^+$: calcd: 319.69, found: 319.08. Anal. Calcd for $C_{14}H_8N_4O_2ClF$: C, 52.76; H, 2.53; N, 17.58. Found: C, 52.01; H, 2.61; N, 17.48.

*4.5.12. N-(3-Chloro-4-fluorophenyl)-6-fluoroquinazolin-4-amine (**13b**).* The title compound was obtained in 93.2% yield, by condensing **12b** (1.90, 0.01 mol) with 3-chloro-4-fluorobenzenamine (1.47 g, 0.01 mol), as a white solid of 2.71 g. Mp 225–228 °C; IR (KBr): 3303.48, 3035.25, 1672.97, 1613.01, 1577.05, 1495.78, 1420.65, 1328.01, 887.64, 873.21, 844.79, 810.61 cm^{-1}; UV–vis (CH_3OH), λ/nm: 213, 286, 337; ^1H NMR (400 MHz, CD_3OD): δ 8.58 (s, 1H), 8.16 (dd, *J*=9.6, 2.7 Hz, 1H), 8.07 (dd, *J*=6.7, 2.6 Hz, 1H), 7.87 (dd, *J*=9.2, 5.3 Hz, 1H), 7.72 (dd, *J*=8.4, 2.8 Hz, 2H), 7.27 (t, *J*=9.0 Hz, 1H), 5.49 (s, 1H); HRMS for $C_{14}H_8N_3ClF_2$ $[M+H]^+$: calcd: 292.6830, found: 292.0446. Anal. Calcd for $C_{14}H_8N_3ClF_2$: C, 57.64; H, 2.76; N, 14.41. Found: C, 57.55; H, 2.48; N, 14.56.

*4.5.13. N-(3-Chloro-4-fluorophenyl)-6-methylquinazolin-4-amine (**13c**).* The title compound was obtained in 88.9% yield, by condensing **12c** (1.86 g, 0.01 mol) with 3-chloro-4-fluorobenzenamine (1.47 g, 0.01 mol), as a yellow solid of 2.55 g. Mp 223–224 °C; IR (KBr): 3330.07, 3041.11, 1677.04, 1618.89, 1572.27, 1498.63, 1440.12, 1236.07, 880.78, 829.95, 657.94 cm^{-1}; UV–vis (CH_3OH), λ/nm: 220, 289, 335; ^1H NMR (400 MHz, CD_3OD): δ 8.54 (s, 1H), 8.19 (s, 1H), 8.05 (dd, *J*=6.7, 2.6 Hz, 1H), 7.75–7.69 (m, 3H), 7.27 (t, *J*=8.9 Hz, 1H), 2.58 (s, 3H); HRMS for $C_{15}H_{11}N_3ClF$ $[M+H]^+$: calcd: 288.7192, found: 288.0694. Anal. Calcd for $C_{15}H_{11}N_3ClF$: C, 62.62; H, 3.85; N, 14.60. Found: C, 62.25; H, 3.58; N, 14.63.

*4.5.14. 8-Chloro-N-(3-chloro-4-fluorophenyl)quinazolin-4-amine (**13d**).* The title compound was obtained in 90.1% yield, by condensing **12d** (2.06 g, 0.01 mol) with 3-chloro-4-fluorobenzenamine (1.47 g, 0.01 mol), as a white solid of 2.78 g. Mp 261–263 °C; IR (KBr): 3290.11, 3077.87, 1694.13, 1603.57, 1571.84, 1500.01, 1483.22, 1279.80, 871.7, 835.27, 790.94, 720.57 cm^{-1}; UV–vis (CH_3OH), λ/nm: 215, 291, 330; ^1H NMR (400 MHz, CD_3OD): δ 8.59 (s, 1H), 8.31 (s, 1H), 8.07 (d, *J*=4.2 Hz, 1H), 7.94 (d, *J*=7.1 Hz, 1H), 7.75–7.69 (m, 1H), 7.28 (t, *J*=8.9 Hz, 2H), 5.49 (s, 1H); HRMS for $C_{14}H_8N_3Cl_2F$ $[M+H]^+$: calcd: 309.1373, found: 309.0174. Anal. Calcd for $C_{14}H_8N_3Cl_2F$: C, 54.57; H, 2.62; N, 13.64. Found: C, 54.36; H, 2.55; N, 13.70.

*4.5.15. 7-Chloro-N-(3-chloro-4-fluorophenyl)quinazolin-4-amine (**13e**).* The title compound was obtained in 89.6% yield, by condensing **12e** (0.83 g, 0.004 mol) with 3-chloro-4-fluoro benzenamine (0.58 g, 0.004 mol), as a white solid of 1.08 g. Mp 198–201 °C; IR (KBr): 3395.78, 3117.85, 1620.2, 1574.8, 1501.71, 1448.09, 1298.29, 876.22, 817.22, 701.25 cm^{-1}; UV–vis (CH_3OH), λ/nm: 215, 286, 334; ^1H NMR (400 MHz, CD_3OD): δ 8.58 (s, 1H), 8.54 (s, 1H), 8.36 (d, *J*=8.9 Hz, 1H), 8.04 (dd, *J*=6.5, 2.9 Hz, 1H), 7.79–7.76 (m, 1H), 7.68 (dd, *J*=6.0, 2.5 Hz, 1H), 7.62 (d, *J*=8.9 Hz, 1H), 7.27 (t, *J*=4.3 Hz, 1H); ESI-MS for $C_{14}H_8N_3Cl_2F$ $[M+H]^+$: calcd: 309.13, found: 309.08. Anal. Calcd for $C_{14}H_8N_3Cl_2F$: C, 54.57; H, 2.62; N, 13.64. Found: C, 54.55; H, 2.36; N, 13.69.

*4.5.16. 5-Chloro-N-(3-chloro-4-fluorophenyl)quinazolin-4-amine (**13f**).* The title compound was obtained in 92.1% yield, by condensing **12f** (0.83 g, 0.004 mol) with 3-chloro-4-fluorobenzenamine (0.58 g, 0.004 mol), as a white solid of 1.15 g. Mp 168–172 °C; IR (KBr): 3393.77, 3119.57, 1620.82, 1574.52, 1501.99, 1425.33, 1264.46, 880.81, 817.43, 797.48 cm^{-1}; UV–vis (CH_3OH), λ/nm: 213, 281, 339; ^1H NMR (400 MHz, CD_3OD): δ 8.54 (s, 1H), 8.05 (dd, *J*=6.7, 2.6 Hz, 1H), 7.76 (d, *J*=2.2 Hz, 2H), 7.70–7.67 (m, 1H), 7.62 (dd, *J*=6.1, 4.1 Hz, 1H), 7.28 (t, *J*=8.9 Hz, 2H); HRMS for $C_{14}H_8N_3Cl_2F$ $[M+H]^+$: calcd: 309.1373, found: 309.0173. Anal. Calcd for $C_{14}H_8N_3Cl_2F$: C, 54.57; H, 2.62; N, 13.64. Found: C, 54.63; H, 2.56; N, 13.58.

*4.5.17. PD153035 (**1**).* The title compound was obtained in 90.2% yield, by condensing **12g** (the crude brown liquid) with 3-bromobenzenamine (1.54 g, 0.009 mol), as a white solid of 2.02 g. Mp 247–249 °C; IR (KBr): 3350.23, 3007.13, 1690.02, 1598.99, 1579.96, 1515.84, 1472.68, 878.37, 788.69, 550.12 cm^{-1}; UV–vis (CH_3OH), λ/nm: 223, 251, 333; ^1H NMR (400 MHz, CD_3OD): δ 8.51 (s, 1H), 8.07 (s, 1H), 7.79 (s, 1H), 7.75–7.70 (m, 1H), 7.35–7.29 (m, 2H), 7.18 (s, 1H), 5.49 (s, 1H), 4.03 (s, 3H), 4.01 (s, 3H); HRMS for $C_{16}H_{14}N_3Br$ $[M+H]^+$: calcd: 329.2066, found: 329.0051. Anal. Calcd for $C_{16}H_{14}N_3Br$: C, 58.55; H, 4.29; N, 12.80. Found: C, 58.48; H, 4.19; N, 12.91.

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Supplementary data

Supplementary data associated with this article can be found in the online version, at http://dx.doi.org/10.1016/j.tet.2013.12.028. These data include MOL files and InChiKeys of the most important compounds described in this article.

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