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Graphical Abstract

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Metal-free Synthesis of Benzimidazo[1,2-*c*]quinazolin-6-ones with Indole and Benzenediamine Oxidized by I_2/TBHP

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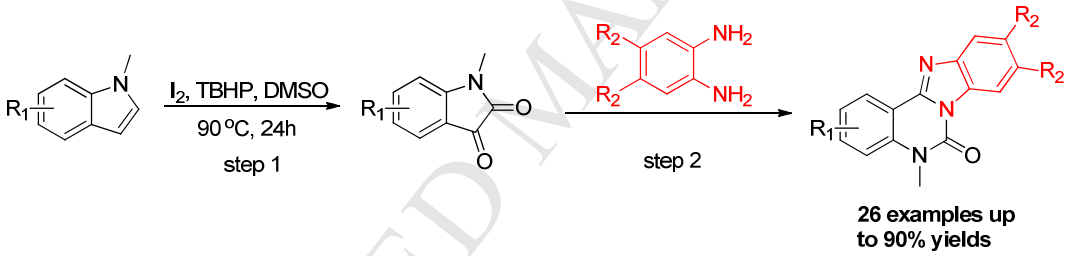
A variety of benzimidazo[1,2-*c*]quinazoline derivatives can be accessed in moderate to good yields under simple and metal-free reaction conditions using indoles and *o*-benzenediamines oxidized by iodine and TBHP. A TBHP oxidized ring expansion reaction mechanism that explains the synthesis of benzimidazo[1,2-*c*]quinazolines was reported.



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Metal-free Synthesis of Benzimidazo[1,2-*c*]quinazolin-6-ones with Indole and Benzenediamine Oxidized by I_2/TBHP

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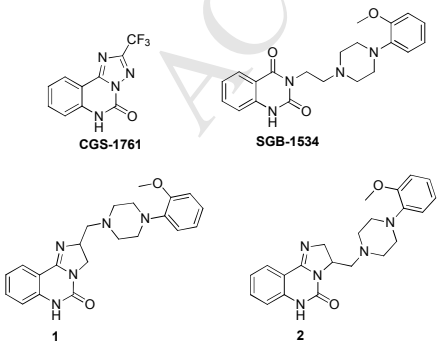
ABSTRACT

A variety of benzimidazo[1,2-*c*]quinazolin-6-ones derivatives can be accessed in moderate to good yields under simple and metal-free reaction conditions using indoles and *o*-benzenediamines oxidized by iodine and TBHP. This procedure works in reasonable yields for different indoles as well as *o*-benzenediamines thus may provide a good synthesis of quinazolinones. A TBHP oxidized ring expansion reaction mechanism that explains the synthesis of benzimidazo[1,2-*c*]quinazolin-6-ones were reported.

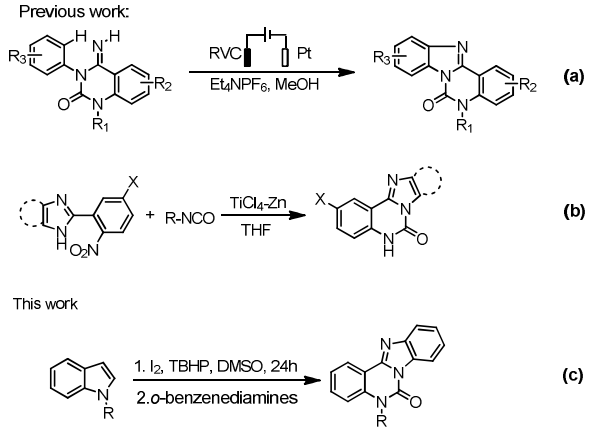
1. Introduction

Benzimidazole and quinazolinone derivatives exist widely in natural products. They are important heterocycles with diverse range of biological and medical activities such as antidiabetic, analgesic, antiviral, chemotherapeutic, antifungal, anti-parasitic anti-inflammatory, antihypertensive, anti-HIV, bronco-dilatory and anti-allergic. [1] Also in the early literatures, benzimidazo[1,2-*c*]quicnazoline and its derivatives have shown potential activities in pharmaceuticals. For example, they showed antihypertonic, antirheumatic, antianaphylactic, anti-asthmatic, tranquilizing, neurostimulating, and benzodiazepine binding activities. [2] (Scheme 1).



Scheme 1 Example of benzimidazo[1,2-c]quinazoline-6-ones.

For example, CGS-1761 was thought to have weak anxiolytic profiles. [3] The SGB-1534 has been found to have antihypertensive activities mediated via *α*-adrenoceptor and serotonic receptor anatgonismthat selectively antagonized the α_1-adrenoceptor. [4] Also compounds with the similar structure such as 2-[[4-(2-methoxyphenyl)-piperazin-1-yl]methyl]-2,3-dihydroimidazo[1,2-*c*]-quinazolin-5(6*H*)-one (3) and 3-[[4-(2-methoxyphenyl)piperazin-1-yl]methyl]-2,3-dihydroimidazo[1,2-*c*]-quinazolin-5(6*H*)-one (4) that selectively antagonized the *α*-1 adrenoceptor. [5] On this basis, we speculated that benzo-[4,5]imidazo[1,2-*c*]quinazolin-6(5*H*)-one and its derivatives had potential biological and medical activities.



Scheme 2 Preparation of benzimidazo[1,2-c]quinazolin-6-ones

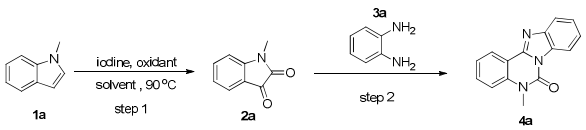
There have been some literatures that reported the methods for preparation of benzimidazo[1,2-*c*]quinazolin-6-ones. [6] Zhao reported a synthesis of pyridoimidazoles through transition-metal-catalyzed or hypervalent-iodine-mediated C-H/N-H cross-

coupling of *N*-arylamidines (Scheme 2a). [7] In the other report, a synthesis of quinazolines via the reductive cyclization by low-valent titanium reagent was proposed (Scheme 2b). [5] Based on the early literatures, an operationally simple and generally applicable strategy to access a variety of benzimidazo[1,2-*c*]quinazolin-6-ones with indoles and *o*-benzenediamines mediated by I_2/TBHP was reported (Scheme 2c).

2. Results and discussion

Our study was initiated by the reaction of *N*-methyl-indoles (0.5 mmol) in DMSO at 90 °C in the presence of I_2 and TBHP (2.5 mmol). After 24 hours, *o*-benzenediamine was added, and the reaction lasted for 30 min. The product could be obtained in 90% yield (Table 1, entry 1). In our design, the reaction would give quinoxaline, but finally 5-methylbenzo-[4,5]imidazo[1,2-*c*]quinazolin-6(5*H*)-one (**4a**) was obtained. The structure was determined by ^{1}H NMR, ^{13}C NMR and XRD (see supporting information). When the reaction was mediated by other iodine sources such as KI and NH_4I, the yield of 4a was decreased (Table 1, entries 3-4). Then we changed the oxidants, reaction temperatures, solvents and other reaction conditions (more details are shown in Supporting Information), no better results were revealed (Table 1 entries 5-13).

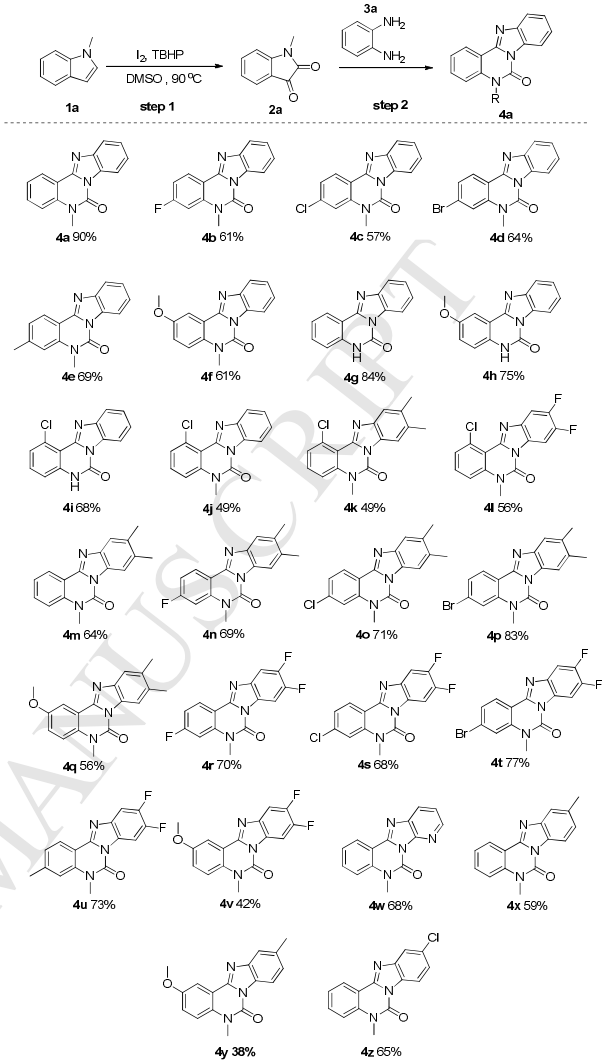
Table 1. Reaction Optimization[a].



Entry	Iodine(mmol)	Oxidant (mmol)	Solvent	Yield (%)[b]
1	I_2 (0.6)	TBHP (2.5)	DMSO	90
2	NH_4I (0.6)	TBHP (2.5)	DMSO	40
3	KI (0.6)	TBHP (2.5)	DMSO	36
4	I_2 (0.6)	BPO (2.5)	DMSO	44
5	I_2 (0.6)	Na_2S_2 (2.5)	DMSO	Trace
6	I_2 (0.6)	$(NH_4)_2S_2O_8$ (2.5)	DMSO	84
7	I_2 (0.6)	TBHP (2.5)	DMF	30
8	I_2 (0.6)	TBHP (2.5)	Toluene	54
9	I_2 (0.6)	TBHP (2.5)	1,4-dioxane	trace
10	I_2 (0.6)	TBHP (2.5)	DMSO	40[c]
11	I_2 (0.6)	TBHP (2.5)	DMSO	66[d]
12	I_2 (0.6)	TBHP (2.5)	DMSO	64[e]
13	I_2 (0.6)	TBHP (2.5)	DMSO	88[f]

[a] All reactions were carried out using 0.5 mmol **1a** in the solvent (5 ml) by first adding I_2 (0.6 mmol) and TBHP (2.5 mmol) at the 90 °C and stirring for 24 h, followed by adding **3a** (0.34 mol) and stirring until reaction finished. [b] Isolated yield. [c] Changed the temperature to 120 °C after added *o*-benzenediamine. [d] Reaction time of step 2 is 10 min. [e] Reaction proceeded in nitrogen. [f] Reaction proceeded in oxygen.

With the optimal reaction conditions in hand, we investigated the scope of the reaction by using different indoles and *o*-benzenediamines (Scheme 3). Generally, *N*-methyl-indoles bearing electron-donating groups gave similar yields with those bearing electron-withdrawing groups (**4b**-**4d**, **4e**-**4f**). It showed that the yield of reaction was uninfluenced by the electronic effect of the substituents on the indoles.

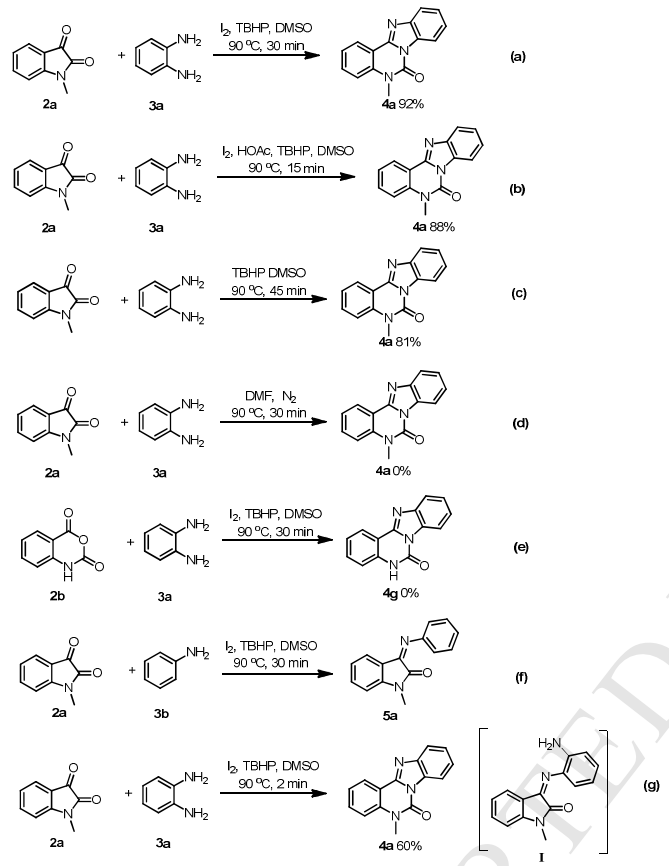


Scheme 3 Substrate scope of indoles and *o*-benzenediamines (All reactions were carried out by adding 0.5 mmol 1, 0.6 mmol I2 and 2.5 mmol TBHP to 6 ml DMSO at 90 °C, stirring for 24 hours, followed by adding 0.34 mmol 2 at 90 °C and stirring for 30 min).

It was worth noting that indoles proceeded smoothly in this reaction and provided the higher yields of the products than *N*-methyl-indoles (**4g**-**4i**). Steric hindrance also played an important role in this reaction. 4-Chloro-1-methyl-1*H*-indole (**4j**-**4l**) showed lower yields than 5-chloro-1-methyl-1*H*-indole (**4c**, **4o** and **4s**). Electron-donating groups and electron-withdrawing groups on the *o*-benzenediamines were tolerated. Intriguingly, *o*-benzenediamines with electron-donating groups (**4m**-**4q**) gave better yields than those with electron-withdrawing groups (**4r**-**4v**). Monosubstituted substituted *o*-benzenediamines (**4x**-**4z**) also proceeded well.

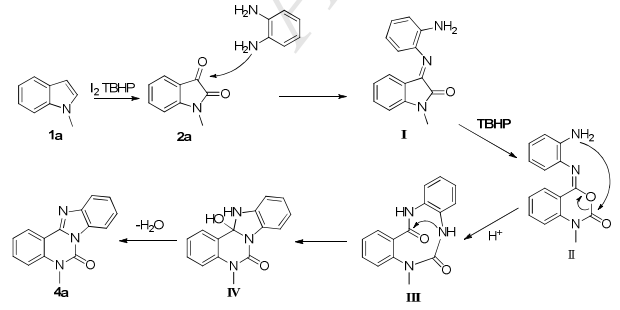
In order to better understand the mechanism of this reaction, several control experiments were performed in Scheme 4. Isatin **2a** was used under standard conditions, and a slightly high yield of **4a** was obtained, which indicated that isatin was an intermediate in the reaction. A faster reaction rate was received when acetic acid was added in, which showed that hydrogen ion influenced the reaction. One control experiment was conducted with TBHP as the only oxidant and a slightly high yield of **4a** was obtain, which showed that TBHP was crucial for the second step.

Then the **2a** reacted in the reaction condition without any oxidant, and no product **4a** was obtained. It was shown that oxidant played an important role in the reaction process. When isatoic anhydride **2b** was subjected to the reaction under the standard conditions, and no product was obtained. The result proved that isatin wasn't oxidized and the oxidant showed effect on other process. When aniline **3b** was used in the standard conditions and a trance amount of compound **5a** was obtained. It was indicated that nucleophilic reaction occurred with *o*-benzenediamine and isatin. Finally, the **2a** reacted for 2 minutes under the same reaction condition **Scheme (a)**. We found that the less yield of product **4a** was obtained and intermediate **I** was detected by crude HRMs.



Scheme 4 Control experiments

Based on the above result and the literatures, [8] a proposed reaction mechanism for the formation of benzimidazo[1,2-*c*]-quinazoline derivatives is illustrated in Scheme 5. First, indole 1a was oxidized to the isatin **2a**. Then nucleophilic reaction occurred with compound **2a** and *o*-benzenediamines and intermediate **I** was generated. Baeyer-Villiger oxidation was occurred on the intermediate **I** and generated intermediate **II**.



Scheme 5 Proposed reaction mechanism

Subsequently, intramolecular nucleophilic reaction of II afforded the intermediate **III**. The nitrogen atom attack to ketone and provides intermediate **IV.** Finally, along with intramolecular condensation reaction, the desired product **4a** was obtained.

3. Conclusions

In conclusion, we have found that benzimidazo[1,2-*c*]-quinazolin-6(5*H*)-ones could be synthesized with indoles **1** and *o*-benzenediamines **2** oxidized by I_2 and TBHP. This procedure worked in reasonable yields for different indoles as well as *o*-benzenediamines and thus might provide a convenient and metal-free synthesis of quinazolinone derivatives.

4. Experimental

4.1. General Information:

N-methyl-1*H*-indoles were prepared according to literature procedures. Other reagents were purchased from commercial suppliers and used without further purification. All reactions were carried out in air and using undistilled solvent, without any precautions to exclude air and moisture. All reactions were monitored by thin-layer chromatography (TLC). Chromatograms were visualized by fluorescence quenching with UV light at 254 nm and 365 nm. ^{1}H NMR spectra were recorded in $CDCl_3$ or d_6-DMSO on a Bruker Avance 300 spectrometer at 400 MHz and 500 MHz, and tetramethylsilane (TMS) served as internal standard. ^{13}C NMR spectra were run in the same instrument at 101 MHz, and 126 MHz. HRMS was recorded on a commercial apparatus (ESI Source).

4.2. Preparation of N-methyl-1H-indoles:

To a solution of indole (1.17 g, 10 mmol) and potassium hydroxide (2.8 g, 50 mmol) in anhydrous DMF (20 ml) was added iodomethane (2.13 g, 15 mmol). The reaction mixture was stirred at room temperature for 2 h. Then H_2O was added to the mixture. The water layer was extracted with EtOAc (50 ml × 3). The organic layer was combined and dried over Na_2SO_4. After filtration and evaporation, the residue was purified by silica gel chromatography (petroleum ether/ethyl acetate 8/1) to afford N-methyl-1*H*-indole (1.24 g, 94%).

4.3.General Procedure for the Reaction:

N-methyl indole (0.5 mmol), DMSO (5 ml) were added into reaction tube and stirred at 90 ^{o}C. Then the I_2 (0.6 mmol) and TBHP (2.5 mmol) were added into the reaction tube. After 24 hours the *o*-benzenediamine (0.34 mmol) was added into the mixture. The reaction was stopped until the $_o$-benzenediamine was completetly consumed as monitored by TLC analysis. After the completion of reaction, 5% $Na_2S_2O_3$ solution (30 mL) was added to the mixture. The mixture was extracted with EtOAc (3×20 ml) and the organic layer was dried by Na_2SO_4. Then the crude product was purified by silica gel chromatography (petroleum ether/ethyl acetate/ dichloromethane 3/1/1).

4.4. Characterization of Benzimidazo[1,2-c]quinazoline.

*4.4.1.*5-Methylbenzo[4,5]imidazo[1,2-*c*]quinazolin-6(5*H*)-one (**4a**)

Yield = 90%; white solid. Mp: 160-161 ^{o}C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.57 (d, *J* = 7.6 Hz, 1H), 8.49 (d, *J* = 7.6 Hz, 1H), 7.90 (d, *J* = 8.0 Hz, 1H), 7.65 (t, 1H), 7.52 (m, 4H), 3.19 (s, 3H).; ^{13}C NMR (101 MHz, $CDCl_3$) δ 147.0, 146.7, 143.5, 138.0, 132.4,

131.2, 125.7, 125.6, 124.3, 123.9, 119.3, 115.5, 114.5, 113.2, 30.5. ^{19}F NMR (376 MHz, $CDCl_3$) δ -103.76, -218.54. HRMS (ESI) calcd for $C_{15}H_{11}N_3O$ [(M + H)$^+$]: 250.0975; found, 250.0975.

4.4.2. 3-Fluoro-5-methylbenzo[4,5]imidazo[1,2-*c*]quinazolin-6(5*H*)-one (**4b**)

Yield = 61%; white solid. Mp: 188-190 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.52 (dd, *J* = 8.8, 6.4 Hz, 1H), 8.42 (d, *J* = 7.6 Hz, 1H), 7.85 (d, *J* = 7.6 Hz, 1H), 7.50-7.40 (m, 2H), 7.11-6.99 (m, 2H) 3.72 (s, 3H).; ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.3 (d, $^1J_{C,F}$ = 253 Hz, 1C), 146.9, 146.0, 143.7, 139.8 (d, $^3J_{C,F}$ = 10 Hz, 1C), 131.0, 127.9 (d, $^3J_{C,F}$ = 10 Hz, 1C), 125.6, 124.3, 119.3, 115.3, 111.7 (d, $^2J_{C,F}$ = 23 Hz, 1C), 109.8 (d, $^4J_{C,F}$ = 3 Hz, 1C), 102.2 (d, $^2J_{C,F}$ = 28 Hz, 1C), 30.7. HRMS (ESI) calcd for $C_{15}H_{10}FN_3O$ [(M +H)$^+$]: 268.0881; found, 268.0888.

4.4.3. 3-Chloro-5-methylbenzo[4,5]imidazo[1,2-*c*]quinazolin-6(5*H*)-one (**4c**)

Yield = 57%, white solid. Mp: 223-224 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.44 (dd, *J* = 8.4, 5.2 Hz, 2H), 7.86 (d, *J* = 8.0 Hz, 1H), 7.50-7.26 (m, 4H), 3.73 (s, 3H).; ^{13}C NMR (101 MHz, $CDCl_3$) δ 146.7, 145.9, 143.7, 138.8, 138.4, 131.1, 126.8, 125.7, 124.5, 124.2, 119.4, 115.4, 114.7, 111.8, 30.6. HRMS (ESI) calcd for $C_{15}H_{10}ClN_3O$ [(M +H)$^+$]: 284.0585; found, 284.0588.

4.4.4. 3-Bromo-5-methylbenzo[4,5]imidazo[1,2-*c*]quinazolin-6(5*H*)-one (**4d**)

Yield = 64%, white solid. Mp: 221-223 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.42 (d, *J* = 8.0 Hz, 1H), 8.37 (d, *J* = 8.4 Hz, 1H), 7.85 (dd, *J* = 1.2, 6.8 Hz, 1H), 7.50-7.41 (m, 4H), 3.73 (s, 3H).; ^{13}C NMR (101 MHz, $CDCl_3$) δ 146.6, 145.9, 143.5, 138.8, 131.1, 127.1, 126.8, 126.7, 125.7, 124.6, 119.4, 117.6, 115.4, 112.1, 30.6. HRMS (ESI) calcd for $C_{15}H_{10}BrN_3O$ [(M +H)$^+$]: 328.0080; found, 328.0088.

4.4.5. 3,5-Dimethylbenzo[4,5]imidazo[1,2-*c*]quinazolin-6(5*H*)-one (**4e**)

Yield = 80%, white solid. Mp: 269-271 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.47 (dd, *J* = 9.5, 8.0 Hz, 2H), 7.88(d, *J* = 8.0 Hz, 1H), 7.51-7.42 (m, 2H), 7.20 (d, *J* = 8.0, 1H), 7.09 (s, 1H), 3.76 (s, 3H), 2.48 (s, 3H).; ^{13}C NMR (126 MHz, $CDCl_3$) δ 147.1, 146.9, 143.5, 138.0, 131.1, 125.5, 125.5, 125.1, 124.0, 119.1, 115.4, 114.8, 110.6, 30.4, 22.3. HRMS (ESI) calcd for $C_{16}H_{13}N_3O$ [(M +H)$^+$]: 264.1131; found, 264.1138.
3N3O [(M +H)+]: 264.1131; found, 264.1138.

4.4.6. 2-Methoxy-5-methylbenzo[4,5]imidazo[1,2-*c*]quinazolin-6(5*H*)-one (**4f**)

Yield = 61%, white solid. Mp: 233-235 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.48 (d, *J* = 8.0 Hz, 1H), 7.92 (d, *J* = 3.0 Hz, 1H), 7.88 (d, *J* = 8.0 Hz, 1H), 7.51-7.42 (m, 2H), 7.26-7.16 (m, 2H), 3.94 (s, 3H), 3.74 (s, 3H).; ^{13}C NMR (126 MHz, $CDCl_3$) δ 156.0, 146.8, 146.6, 143.6, 132.0, 131.3, 125.5, 124.2, 121.3, 119.2, 116.0, 115.5, 113.8, 106.7, 56.0, 30.5. HRMS (ESI) calcd for $C_{16}H_{13}N_3O_2$ [(M +H)$^+$]: 280.1081; found, 280.1122.

4.4.7. Benzo[4,5]imidazo[1,2-*c*]quinazolin-6(5*H*)-one (**4g**)

Yield = 84%, white solid. Mp: >300 °C. ^{1}H NMR (400 MHz, d_6-DMSO) δ 11.97 (s, 1H), 8.38 (dd, *J* = 10.0, 8.0 Hz, 2H), 7.88 (d, *J* = 7.6 Hz, 1H), 7.68 (t, 1H), 7.52-7.36 (m, 4H).; ^{13}C NMR (101 MHz, d_6-DMSO) δ 148.1, 146.9, 144.0, 137.6, 132.7, 131.1, 125.5, 124.9, 124.1, 123.8, 119.6, 116.4, 115.2, 112.3. HRMS (ESI) calcd for $C_{14}H_9N_3O$ [(M +H)$^+$]: 236.0818; found, 236.0815.

4.4.8. 2-Methoxybenzo[4,5]imidazo[1,2-*c*]quinazolin-6(5*H*)-one (**4h**)

Yield = 75%, white solid. Mp: 292-294 °C. ^{1}H NMR (400 MHz, d_6-DMSO) δ 11.83 (s, 1H), 8.35 (d, *J* = 7.2 Hz, 1H), 7.84 (d, *J* = 7.6 Hz, 1H), 7.72 (d, *J* = 2.4 Hz, 1H), 7.49-7.24 (m, 4H), 3.86 (s, 3H).; ^{13}C NMR (101 MHz, d_6-DMSO) δ 155.7, 148.0, 146.6, 143.9, 131.6, 131.2, 125.5, 124.1, 121.6, 119.6, 118.0, 115.3, 112.8, 106.3, 56.1. HRMS (ESI) calcd for $C_{15}H_{11}N_3O_2$ [(M +H)$^+$]: 266.0924; found, 266.0918.

4.4.9. 1-Chlorobenzo[4,5]imidazo[1,2-*c*]quinazolin-6(5*H*)-one (**4i**)

Yield = 68%, white solid. Mp: >300 °C. ^{1}H NMR (400 MHz, d_6-DMSO) δ 12.09 (s, 1H), 8.39 (dd, *J* = 7.2, 1.6 Hz, 1H), 7.91 (d, *J* = 8.0 Hz, 1H), 7.58 (t, 1H), 7.49-7.34 (m, 5H).; ^{13}C NMR (101 MHz, d_6-DMSO) δ 146.5, 146.0, 143.8, 139.7, 132.4, 131.6, 130.4, 126.0, 125.6, 124.8, 120.1, 115.3, 115.3, 110.4. HRMS (ESI) calcd for $C_{14}H_8ClN_3O$ [(M +H)$^+$]: 270.0429; found, 270.0423.

4.4.10. 1-Chloro-5-methylbenzo[4,5]imidazo[1,2-*c*]quinazolin-6(5*H*)-one (**4j**)

Yield = 49%, white solid. Mp: 238-240 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.50 (d, *J* = 7.5 Hz, 1H), 8.01 (d, *J* = 8.0 Hz, 1H), 7.53-7.22 (m, 5H), 3.77 (s, 34H).; ^{13}C NMR (126 MHz, $CDCl_3$) δ 146.6, 144.4, 143.6, 139.7, 133.5, 131.1, 130.4, 126.6, 125.5, 124.9, 120.3, 115.4, 113.1, 111.8, 31.3. HRMS (ESI) calcd for $C_{15}H_{10}ClN_3O$ [(M + Na)$^+$]: 306.0405; fond, 306.0412.

4.4.11. 1-Chloro-5,9,10-trimethylbenzo[4,5]imidazo[1,2-*c*]quinazolin-6(5*H*)-one (**4k**)

Yield = 49%, white solid. Mp: 243-245 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.20 (s, 1H), 7.73 (s, 1H), 7.41-7.35 (m, 2H), 7.19 (dd, *J* = 8.0, 1.0 Hz, 1H), 3.74 (s, 3H), 2.43 (d, *J* = 6.0 Hz, 6H).; ^{13}C NMR (126 MHz, $CDCl_3$) δ 146.6, 143.5, 142.1, 139.5, 134.6, 134.4, 133.1, 130.6, 128.7, 126.4, 120.2, 115.3, 112.9, 111.9, 31.2, 20.6, 20.5. HRMS (ESI) calcd for $C_{17}H_{14}ClN_3O$ [(M + H)$^+$]: 312.0898; found, 312.0907.

4.4.12. 1-Chloro-9,10-difluoro-5-methylbenzo[4,5]imidazo[1,2-*c*]quinazolin-6(5*H*)-one (**4l**)

Yield = 56%, white solid. Mp: 266-268 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.38 (dd, *J* = 10.0, 7.9 Hz, 1H), 7.81 (dd, *J* = 10.0, 7.9 Hz, 1H), 7.59-7.49 (m, 2H), 7.34 (d, *J* = 8.0 Hz, 1H), 3.82 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 151.0 (dd, $^1J_{C,F}$ = 18, 249 Hz, 1C), 150.2 (dd, $^1J_{C,F}$ = 17, 249 Hz, 1C), 146.3, 145.8 (d, $^3J_{C,F}$ = 3 Hz, 1C) 139.7, 133.6, 131.6, 127.0, 125.8 (d, $^2J_{C,F}$ = 11 Hz, 1C), 113.3, 111.6, 107.8 (d, $^2J_{C,F}$ = 20 Hz, 1C), 104.1 (d, $^2J_{C,F}$ = 24 Hz, 1C), 31.5. ^{19}F NMR (376 MHz, $CDCl_3$) δ -137.65~ -137.91 (m, 2F). HRMS (ESI) calcd for $C_{15}H_8ClF_2N_3O$ [(M + H)$^+$]: 320.0397; found, 320.0402.

4.4.13. 5,9,10-Trimethylbenzo[4,5]imidazo[1,2-*c*]quinazolin-6(5*H*)-one (**4m**)

Yield = 64%, white solid. Mp: 221-223 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.53 (dd, *J* = 7.6, 1.2 Hz, 1H), 8.23 (s, 1H), 7.63-7.26 (m, 4H), 3.77 (s, 3H), 2.44 (d, *J* = 6.4 Hz, 6H).; ^{13}C NMR (400 MHz, $CDCl_3$) δ 147.1, 145.9, 142.1, 137.8, 134.6, 133.6, 131.9, 129.6, 125.5, 123.7, 119.4, 115.4, 114.4, 113.5, 30.4, 20.6.

HRMS (ESI) calcd for $C_{17}H_{16}N_3O$ [(M + H)$^+$]: 278.1288; found, 278.1300.

4.4.14. 3-Fluoro-5,9,10-trimethylbenzo[4,5]imidazo[1,2-*c*]quinazolin-6(5*H*)-one (**4n**)

Yield = 69%, white solid. Mp: 252-254 ^{o}C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.49 (dd, *J* = 8.8, 6.4 Hz, 1H), 8.16 (s, 1H), 7.58 (s, 1H), 7.09-6.97 (m, 2H), 3.71 (s, 3H), 2.43 (d, *J* = 7.6 Hz, 6H).; ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.1 (d, $^1J_{C, F}$ = 253 Hz, 1C), 146.9, 145.3, 142.0, 139.5 (d, $^3J_{C, F}$ = 11 Hz, 1C), 134.7, 133.7, 129.3, 127.7 (d, $^3J_{C, F}$ = 10 Hz, 1C), 119.3, 115.3, 111.6 (d, $^2J_{C, F}$ = 23 Hz, 1C), 111.3, 109.9 (d, $^4J_{C, F}$ = 2.2 Hz, 1C), 102.1 (d, $^2J_{C, F}$ = 28 Hz, 1C), 30.6, 20.5. ^{19}F NMR (376 MHz, $CDCl_3$) δ -104.53 (s, 1F). HRMS (ESI) calcd for $C_{17}H_{14}FN_3O$ [(M + H)$^+$]: 296.1194; found, 296.1203.

4.4.15. 3-Chloro-5,9,10-trimethylbenzo[4,5]imidazo[1,2-*c*]quinazolin-6(5*H*)-one (**4o**)

Yield = 71%, whitesolid. Mp: 267-279 ^{o}C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.40 (d, *J* = 8.4, 1H), 8.15 (s, 1H), 7.58(s, 1H), 7.32-7.26 (m, 2H), 3.72 (s, 3H), 2.43 (d, *J* = 7.6, 6H).; ^{13}C NMR (101 MHz, $CDCl_3$) δ 146.7, 145.1, 142.1, 138.6, 137.9, 134.9, 133.9, 129.4, 126.5, 124.0, 119.4, 115.3, 114.6, 112.0, 30.5, 20.6, 20.5. HRMS (ESI) calcd for $C_{17}H_{14}ClN_3O$ [(M + H)$^+$]: 312.0898; found, 312.0901.

4.4.16. 3-Bromo-5,9,10-trimethylbenzo[4,5]imidazo[1,2-*c*]quinazolin-6(5*H*)-one (**4p**)

Yield = 83%, white solid. Mp: 286-288 ^{o}C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.38 (d, *J* = 8.0 Hz, 1H), 8.18 (s, 1H), 7.61 (s, 1H), 7.50-7.46 (m, 2H), 3.74 (s, 3H), 2.44 (d, *J* = 7.2 Hz, 6H).; ^{13}C NMR (101 MHz, $CDCl_3$) δ 146.7, 145.1, 141.8, 138.7, 135.0, 134.1, 129.4, 127.0, 126.7, 126.3, 119.4, 117.6, 115.4, 112.3, 30.6, 29.7, 20.6. HRMS (ESI) calcd for $C_{17}H_{14}BrN_3O$ [(M + H)$^+$]: 356.0393; found, 356.0397.

4.4.17. 2-Methoxy-5,9,10-trimethylbenzo[4,5]imidazo[1,2-*c*]quinazolin-6(5*H*)-one (**4q**)

Yield = 56%, White solid. Mp: 242-245 ^{o}C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.21 (s, 1H), 7.91 (s, 1H), 7.61 (s, 1H), 7.22-7.13 (m, 2H), 3.93 (s, 3H), 3.73 (s, 3H), 2.43 (d, *J* = 7.0 Hz, 3H).; ^{13}C NMR (126 MHz, $CDCl_3$) δ 155.9, 146.8, 145.8, 134.7, 133.7, 131.9, 129.6, 121.0, 119.2, 115.9, 115.5, 113.9, 106.6, 56.0, 30.5, 20.6, 20.6. HRMS (ESI) calcd for $C_{18}H_{17}N_3O_2$ [(M +H)$^+$]: 308.1394; found, 308.1400.

4.4.18. 3,9,10-Trifluoro-5-methylbenzo[4,5]imidazo[1,2-*c*]quinazolin-6(5*H*)-one (**4r**)

Yield = 70%, white solid. Mp: 241-242 ^{o}C. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.54 (dd, *J* = 8.6, 6.4 Hz, 1H), 8.32 (dd, *J* = 9.6, 7.4 Hz, 1H), 7.65 (dd, *J* = 10.2, 7.0 Hz, 1H), 7.18-7.07(m, 2H), 3.78 (s, 3H).; ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.6 (d, $^1J_{C, F}$ = 254 Hz, 1C), 151.0 (dd, $^1J_{C, F}$ = 15, 246 Hz, 1C), 149.7 (dd, $^1J_{C, F}$ =15, 246 Hz, 1C), 147.4, 146.6, 139.8 (d, $^3J_{C, F}$ = 11 Hz, 1C), 139.3 (d, $^3J_{C, F}$ = 11 Hz, 1C), 128.0 (d, $^3J_{C, F}$ = 10 Hz, 1C), 126.2, 112.2 (d, $^2J_{C, F}$ = 23 Hz, 1C), 109.5 (d, $^4J_{C, F}$ = 2 Hz, 1C), 107.0 (d, $^3J_{C, F}$ = 20 Hz, 1C), 104.0 (d, $^3J_{C, F}$ = 24 Hz, 1C), 102.4 (d, $^3J_{C, F}$ = 28 Hz, 1C), 30.8. ^{19}F NMR (376 MHz, $CDCl_3$) δ -103.03 (s, 1F), -137.97~-138.85(m, 2F). HRMS (ESI) calcd for $C_{15}H_8F_3N_3O$ [(M + H)$^+$]: 304.0692; found, 304.0694.

4.4.19. 3-Chloro-9,10-difluoro-5-methylbenzo[4,5]imidazo[1,2-*c*]quinazolin-6(5*H*)-one (**4s**)

Yield = 68%, white solid. Mp: 293-295 ^{o}C ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.46 (d, J = 8.4 Hz, 1H), 8.33 (dd, J = 10.0, 7.6 Hz, 1H), 7.67 (dd, J = 10.0, 7.8 Hz, 1H), 7.42-7.40 (m, 2H), ^{13}C NMR (101 MHz, $CDCl_3$) δ 149.9 (d, $^1J_{C, F}$ = 260 Hz, 1C), 148.6 (d, $^1J_{C, F}$ = 217 Hz, 1C), 139.4 (d, $^3J_{C, F}$ = 10 Hz, 1C), 138.9 (d, $^3J_{C, F}$ = 11 Hz, 1C), 126.8, 126.5 (d, $^3J_{C, F}$ = 12 Hz, 1C), 124.6, 114.9, 111.5, 107.1 (d, $^2J_{C, F}$ = 20 Hz, 1C), 104.1 (d, $^2J_{C, F}$ = 24 Hz, 1C), 30.8. ^{19}F NMR (376 MHz, $CDCl_3$) δ -137.56~-138.24(m, 2F). HRMS (ESI) calcd for $C_{15}H_8ClF_2N_3O$ [(M + H)$^+$]: 320.397; found, 320.0402

4.4.20. 3-Bromo-9,10-difluoro-5-methylbenzo[4,5]imidazo[1,2-*c*]quinazolin-6(5*H*)-one (**4t**)

Yield = 77%, white solid. Mp: >300 ^{o}C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.41 (d, *J* = 6.8 Hz, 1H), 8.34 (dd, *J* = 6.0, 8.0 Hz, 1H), 7.68 (dd, *J* = 5.6, 8.0 Hz, 1H), 7.58-7.57 (m, 2H), 3.80 (s, 3H).; ^{13}C NMR (126 MHz, $CDCl_3$) δ 149.3 (dd, $^1J_{C, F}$ = 16, 243 Hz, 1C), 148.2 (dd, $^1J_{C, F}$ = 15, 236 Hz, 1C), 147.3, 140.2, 139.2 (d, $^3J_{C, F}$ = 9 Hz, 1C), 138.8, 130.6, 127.5, 127.2, 126.9, 117.9, 111.8, 107.1 (d, $^2J_{C, F}$ = 21 Hz, 1C), 104.1 (d, $^2J_{C, F}$ = 25 Hz, 1C), 30.8. ^{19}F NMR (376 MHz, $CDCl_3$) δ -137.87~-138.64 (m, 2F). HRMS (ESI) calcd for $C_{15}H_8BrF_2N_3O$ [(M +H)$^+$]: 363.9892; found, 363.9898.

4.4.21. 9,10-Difluoro-3,5-dimethylbenzo[4,5]imidazo[1,2-*c*]quinazolin-6(5*H*)-one (**4u**)

Yield = 73%, white solid. Mp: 279-281 ^{o}C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.39 (d, *J* = 8.4 Hz, 1H), 8.33 (dd, *J* = 7.2, 10.0 Hz, 1H), 7.65 (dd, *J* = 7.2, 10.0 Hz, 1H), 7.24-7.18 (m, 2H), 3.79 (s, 3H), 2.55 (s, 3H).; ^{13}C NMR (101 MHz, $CDCl_3$) δ 150.8 (dd, $^1J_{C, F}$ = 24, 258 Hz, 1C), 149.5 (dd, $^1J_{C, F}$ = 26, 246 Hz, 1C), 143.8, 138.0, 128.8, 126.5, 125.5 (d, $^3J_{C, F}$ = 12 Hz, 1C), 115.0, 110.7, 106.8 (d, $^2J_{C, F}$ = 20 Hz, 1C), 104.0 (d, $^2J_{C, F}$ = 24 Hz, 1C), 30.5, 29.7, 23.9, 22.4. ^{19}F NMR (376 MHz, $CDCl_3$) δ -138.26(d, 2F). HRMS (ESI) calcd for $C_{16}H_{11}F_2N_3O$ [(M + H)$^+$]: 300.0943; found, 300.0964.

4.4.22. 9,10-Difluoro-2-methoxy-5-methylbenzo[4,5] imidazo[1,2-*c*]quinazolin-6(5*H*)-one (**4v**)

Yield = 42%, white solid. Mp: 249-251 ^{o}C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.35 (dd, *J* = 10.0, 6.0 Hz, 1H), 7.93 (d, *J* = 2.5 Hz, 1H), 7.66 (dd, *J* = 10.0, 7.5 Hz, 1H), 7.32-7.26 (m, 2H), 3.94 (s, 3H), 3.79 (s, 3H).; ^{13}C NMR (126 MHz, $CDCl_3$) δ 156.2, 150.7 (dd, $^1J_{C, F}$ = 15, 246 Hz, 1C), 149.4 (d, $^1J_{C, F}$ = 15, 246 Hz, 1C), 148.0 (d, $^4J_{C, F}$ = 3 Hz, 1C), 146.4, 139.3 (d, $^3J_{C, F}$ = 11 Hz, 1C), 132.1, 126.6 (d, $^3J_{C, F}$ = 12 Hz, 1C), 121.7, 116.2, 113.6, 106.8 (d, $^2J_{C, F}$ = 20Hz, 1C), 106.7, 104.1 (d, $^2J_{C, F}$ = 25 Hz, 1C), 56.0, 30.7. ^{19}F NMR (376 MHz, $CDCl_3$) δ -137.82 (d, 2F). HRMS (ESI) calcd for $C_{16}H_{11}F_2N_3O_2$ [(M + H)$^+$]: 316.0892; found, 316.0891.

4.4.23 5-methylpyrido[3',2':4,5]imidazo[1,2-*c*]quinazolin-6(5*H*)-one (**4w**)

Yield= 68%, white solid. Mp: >300 ^{o}C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.75 (m, 2H), 8.71 (dd, *J* = 1.5, 8.0 Hz, 1H), 7.76 (m, 1H), 7.49 (m, 3H), 3.84 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 156.1, 148.9, 147.6, 146.7, 138.2, 133.3, 126.8, 124.3, 123.5, 119.2, 114.6, 113.0, 30.6. HRMS (ESI) calcd for $C_{14}H_{10}N_4O$ [(M + H)$^+$]: 251.0927; found, 251.0930

4.4.24. 5,10-dimethylbenzo[4,5]imidazo[1,2-*c*]quinazolin-6(5*H*)-one (**4x**)

Yield = 59%, white solid. Mp: 219-221 ^{o}C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.53 (dd, *J* = 1.5, 9.5 Hz, 1H), 8.32 (d, *J* = 10.5 Hz, 1H), 7.65 (s, 1H), 7.63 (m, 1H), 7.38 (m, 3H), 3.76 (s, 3H), 2.54 (s, 3H) ^{13}C NMR (101 MHz, $CDCl_3$) δ 147.0, 146.7, 144.0, 137.9, 135.5, 132.1, 129.2, 125.7, 125.6, 123.7,

119.2, 114.8, 114.4, 113.4, 30.4, 21.9, 21.8. HRMS (ESI) calcd for $C_{16}H_{13}N_3O$ [$(M+H)^+$]: 264.3013; found, 264.3020.

4.4.25. 2-methoxy-5,10-dimethylbenzo[4,5]imidazo[1,2-c]quinazolin-6(5H)-one (**4y**)

Yield = 38% white solid. Mp: 175-177 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.36 (m, 1H), 8.00 (m, 1H), 7.76 (m, 1H), 7.33 (m, 3H), 3.96 (s, 3H), 3.77 (s, 3H), 2.55 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 156.1, 146.8, 132.2, 127.1, 125.8, 121.4, 119.0, 118.7, 116.0, 115.5, 115.0, 107.0, 106.9, 56.1, 30.6, 21.9. HRMS (ESI) calcd for $C_{17}H_{15}N_3O_2$ [$(M+H)^+$]:294.3273; found, 294.3281.

4.4.26. 10-chloro-5-methylbenzo[4,5]imidazo[1,2-*c*]quinazolin-6(5*H*)-one (**4z**)

Yield = 65% white solid. Mp: 136-138 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.38 (d, *J* = 7.2 Hz, 1H), 8.22 (d, *J* = 8.0 Hz, 1H), 7.73 (d, *J* = 7.2 Hz, 1H), 7.62 (d, *J* = 10.7 Hz, 1H), 7.44 (d, *J* = 7.6 Hz, 1H), 7.25 (d, *J* = 7.6 Hz, 1H), 3.68 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 147.0, 146.6, 146.3, 138.0, 135.6, 134.6, 132.3, 129.2, 127.0, 125.8, 123.8, 119.2, 118.8, 115.4, 114.8, 114.5. HRMS (ESI) calcd for $C_{15}H_{10}ClN_3O$ [$(M+H)^+$]: 284.7194 found, 284.7196.

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6. Notes and references

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