

Electrochemical synthesis of 4-quinazolinone derivatives mediated by acetic acid

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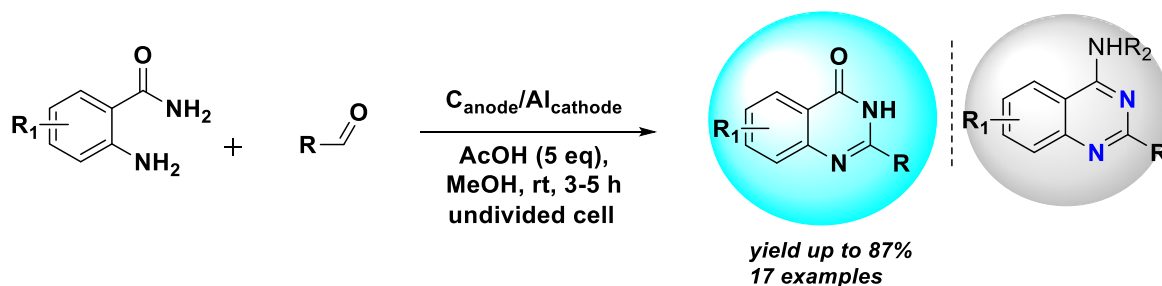
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Abstract

The acid-catalyzed cyclization of 2-aminobenzamides into 4-quinazolines was achieved using a combination of carbon and aluminum electrodes under electrochemical conditions. Overall, the method offers large substrate scope with good functional group tolerance using acetic acid as an inexpensive electrolyte. Quinazolin-4(3H)-one and 2-methylquinazolin-4(3H)-one derivatives were also prepared under similar electrochemical conditions. The transformations occurred at room temperature with moderate to good yields. A few of the quinazolin-4(3H)-one cores were successfully transformed into compounds similar to known anticancer drugs.



- Mild reaction conditions
- Room Temperature
- Milligram to gram scale reactions
- High Yielding
- Important intermediates for biologically active compounds

Keywords: 4-Quinazolinone, electrochemical reactions, scalable, room temperature

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Introduction

Nitrogen-containing heterocycles have attracted significant attention from researchers due to their diverse utility in various fields involving pharmaceuticals, agrochemicals, polymers and natural products.¹⁻⁴ For example, quinazolinone derivatives, which are nitrogen-containing six-membered heterocycles, can be found in a wide range of pharmaceuticals and natural products.⁵⁻⁹ In particular, the quinoline-4(3*H*)-one ring system is common in various pharmaceuticals and natural products (see Figure 1).¹⁰⁻¹²

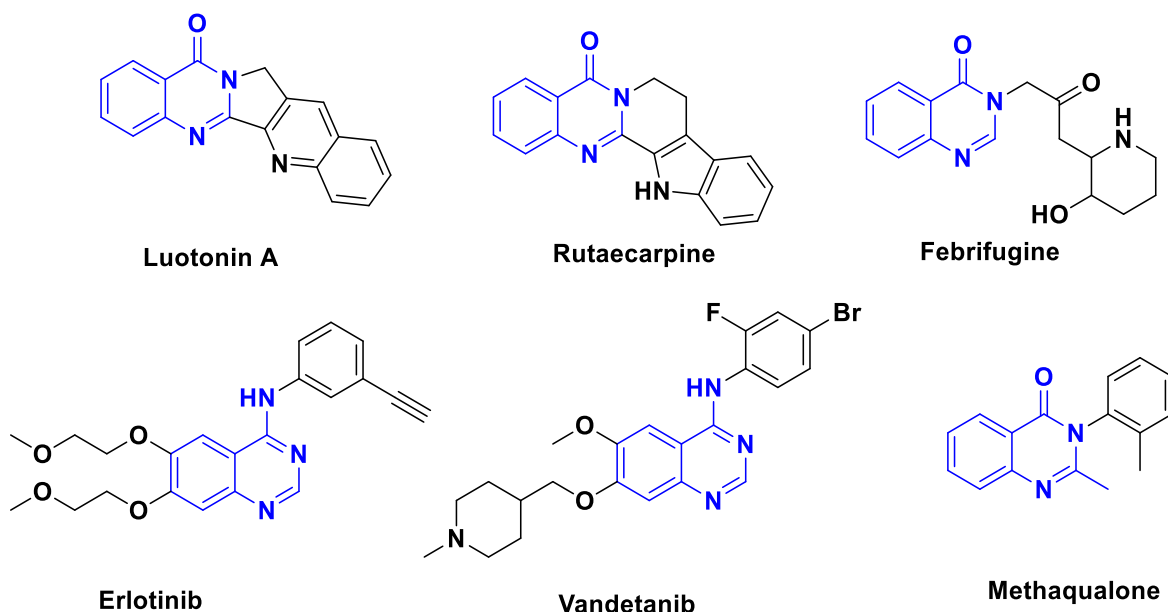
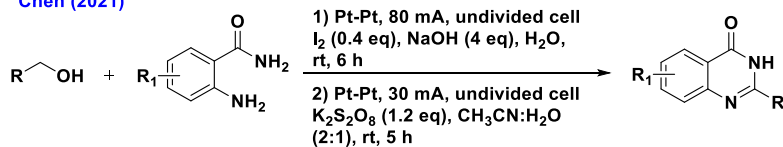


Figure 1. Active pharmaceutical agents and natural products containing quinazolinone structures.

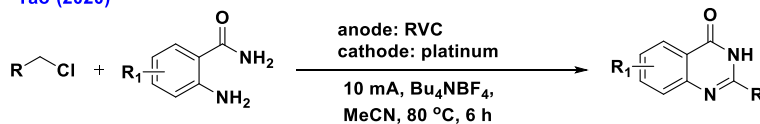
There are various chemical methods known in the literature to prepare quinazolinone starting from 2-aminobenzamides, but each process has their own limitations, like high temperatures and the use of transition metals. A few electrochemical methods have also been reported for the synthesis of 4-quinazolinones starting from 2-aminobenzamides (See scheme 1). Recently, Chen *et al.* have reported the electrochemical synthesis of 4-quinazolinones, but there are a very few reports of utilization of the said method to prepare quinazolin-4(3*H*)-ones and 2-methylquinazolin-4(3*H*)-ones which are important scaffolds in anticancer drugs.¹³ Yao *et al.* have also utilized various substituted benzyl chlorides to couple with 2-amino benzamides to prepare 4-quinazolinones at high temperatures.¹⁴ In addition, Wang *et al.* have described the synthesis of quinazolinone derivatives at high reaction temperatures.¹⁵ We thus envisioned the synthesis of 4-quinazolinones from 2-aminobenzamides by using an aluminum and carbon electrode system and acetic acid as an electrolyte though an oxidative cyclization in an undivided cell. To our pleasant surprise, it worked well to provide several valuable heterocyclic systems. This electrochemical method is thus quite useful to synthesize quinazolin-4(3*H*)-one and 2-methylquinazolin-4(3*H*)-one derivatives in very good yields at room temperature and under mild reaction conditions.

Previous Work

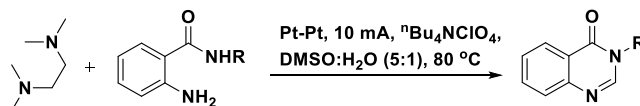
Chen (2021)



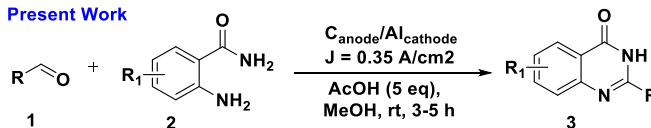
Yao (2020)



Wang (2020)



Present Work

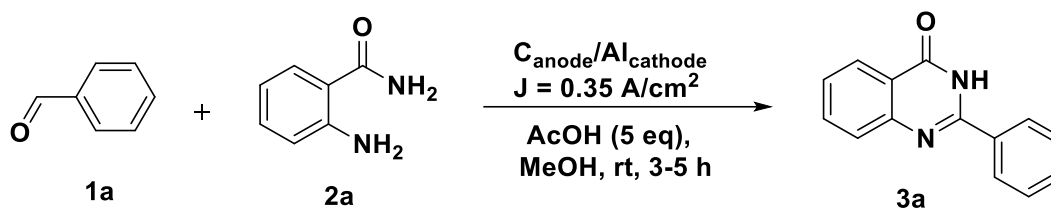


Scheme 1. Earlier literature reports and our present work.¹³⁻¹⁵

Results and Discussion

In earlier work, we synthesized benzoxazoles, benthiazoles and benzimidazoles by using aluminum and carbon as the electrode system, acetic acid as an electrolyte and acetonitrile/methanol as the solvent.¹⁶⁻¹⁸ Performing research on similar lines we electrochemically reacted benzaldehyde (**1a**) and 2-aminobenzamide (**2a**) in acetonitrile and after 3 h obtained 41% conversion (as per LCMS analysis). Encouraged by this result we screened a number of solvents (as listed in Table-1). We observed that polar protic solvent like methanol and ethanol facilitated the reaction and that increasing the ratio of methanol in the presence of acetonitrile led to a decrease in reaction time.

We have observed that by using acetonitrile as a solvent, the reaction did not move to full conversion, even after stirring for 24 h (entry 1a). Of interest was that an increase in the ratio of methanol to acetonitrile, appeared to improve the conversion rate. We also screened some polar aprotic solvents like DMSO, tetrahydrofuran and acetone, but did not observe any conversion in DMSO and tetrahydrofuran, whereas only 7% conversion was observed in acetone (entries 2-9). Furthermore, we obtained 86% conversion after 3 h, when methanol was used exclusively as a solvent (entry 10). The polar solvent would appear to facilitate the Schiff base formation leading to better conversion.¹⁹ Apart from methanol, promising results were also observed in ethanol for which 69% conversion was attained; however, by decreasing the polarity of the alcohols by using propanol only 39% conversion was observed after 3 h. Another advantage of having a polar solvent was the better solubility of the starting materials. All these electrochemical conversions were carried out through an electrochemical reactor prepared from a 5v mobile phone charger. In addition, a carbon rod (0.2 mm diameter) and aluminum wires were used as electrodes. Furthermore, a current of 0.35 A/cm² was passed through the reaction for 3h to carry out these electrochemical conversions in good yield.

Table 1. Screening conditions for solvents

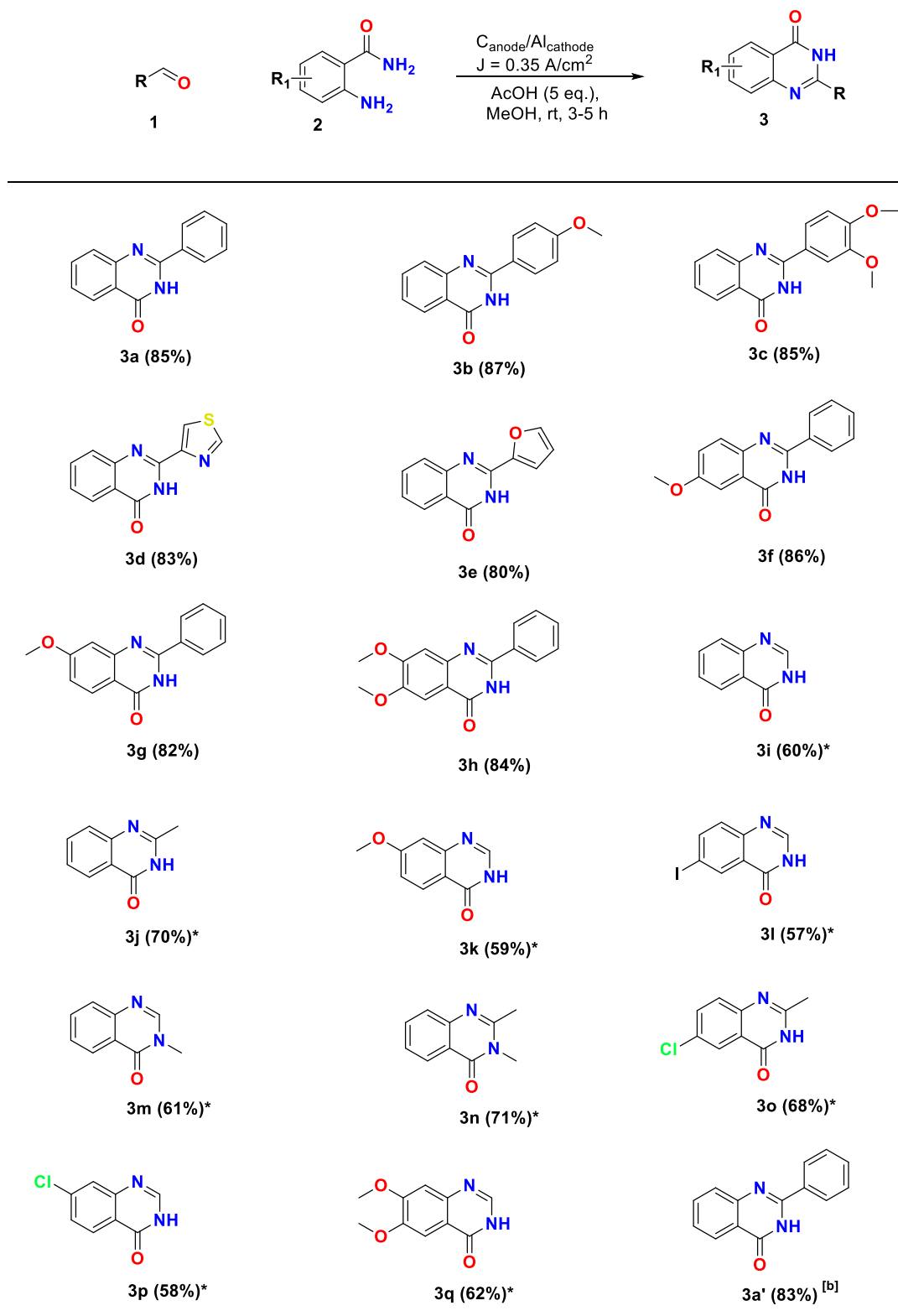
Entry	Solvent	Conversion (%)	Time (h)
1	Acetonitrile	41	3
1a	Acetonitrile	62	24
2	Acetonitrile: Methanol (4:1)	49	3
3	Acetonitrile: Methanol (1:1)	51	3
4	Acetonitrile: Methanol (1:2)	57	3
5	Ethanol	69	3
6	Tetrahydrofuran	No Conversion	3
7	DMSO	No Conversion	3
8	<i>n</i> -propanol	39	3
9	Acetone	7	3
10	Methanol	86	3

As a control reaction, we reacted **1a** and **2a** in methanol, using aluminum as cathode and carbon as anode with 5 equivalents of acetic acid without passing electric current through the system. After stirring this reaction for 3 h, the majority of non-cyclized starting materials were observed in the reaction. When we did the reaction without using acetic acid, we again observed mostly starting materials after 3 hours, with no trace of cyclized product being formed. Thus, it was confirmed that electric current and acetic acid were both required for the reaction to initiate. Acetic acid was used both as an accelerant for the Schiff base formation and an electrolyte and could easily be removed from the reaction mixture through a simple workup after the reaction was deemed complete.

With these optimized conditions in hand, we next turned our attention to exploring the substrate scope and generality of the method with differently substituted 2-aminobenzamides and aldehydes. As a result, we synthesized various substituted 4-quinazolinone in 58-87% yields (see Table 2). All these reactions were performed with equimolar ratio of aldehyde and 2-aminobenzamides. For example, aromatic aldehydes were coupled with 2-aminobenzamides to yield **3a** and **3c**, both in 85% yield, and **3b** in 87% yield respectively. Heteroaromatic aldehydes also successfully participated in the electrochemical reaction to yield **3d** and **3e** in 83% and 80% respectively. It should be noted that 4- and 5- substituted 2-aminobenzamides are very commonly utilized in the synthesis of anticancer drugs.²⁰ To this end, 4-methoxy-2-aminobenzamide, 5-methoxy-2-aminobenzamide and 4,5-dimethoxy-2-aminobenzamide were coupled with benzaldehyde to give as outcome products **3f**, **3g** and **3h** which were isolated in 86%, 82% and 84% yield respectively. Although the yield of **3f** was found to be slightly greater than the **3g** and **3h**, it would be difficult to attribute this to the electron-rich benzamide system (as compared to **3g** and **3h**) as the yield difference falls within experimental error.

We then turned our attention to the synthesis of quinazolin-4(3*H*)-one and 2-methylquinazolin-4(3*H*)-one derivatives. To this end, 1, 3, 5-trioxane and paraldehyde were coupled with 2-amino benzamides to afford **3i** and **3j** in 60% and 70% yield respectively. Substituted 2-amino-benzamides were also coupled with 1,3,5-trioxane to afford substituted quinazolin-4(3*H*)-one derivatives compounds **3k**, **3l** and **3p**, **3q** in 59%, 57%, 58% and 62% yield, respectively. Similarly, chloro-substituted 2-aminobenzamide was coupled with paraldehyde to provide substituted 2-methylquinazolin-4(3*H*)-one **3o**, and 2-amino-*N*-methylbenzamide was reacted with paraldehyde and 1,3,5-trioxane to synthesize **3m** and **3n** in 61% and 71% yield respectively. We observed that in the reactions where we coupled 1,3,5-trioxane or paraldehyde with different 2-aminobenzamides it was required to increase the reaction time to 5 h to allow the reactions to go to completion. This increase in reaction time might be because of the use of the stable trimer forms of formaldehyde and acetaldehyde which require a longer time for Schiff base formation followed by cyclization.

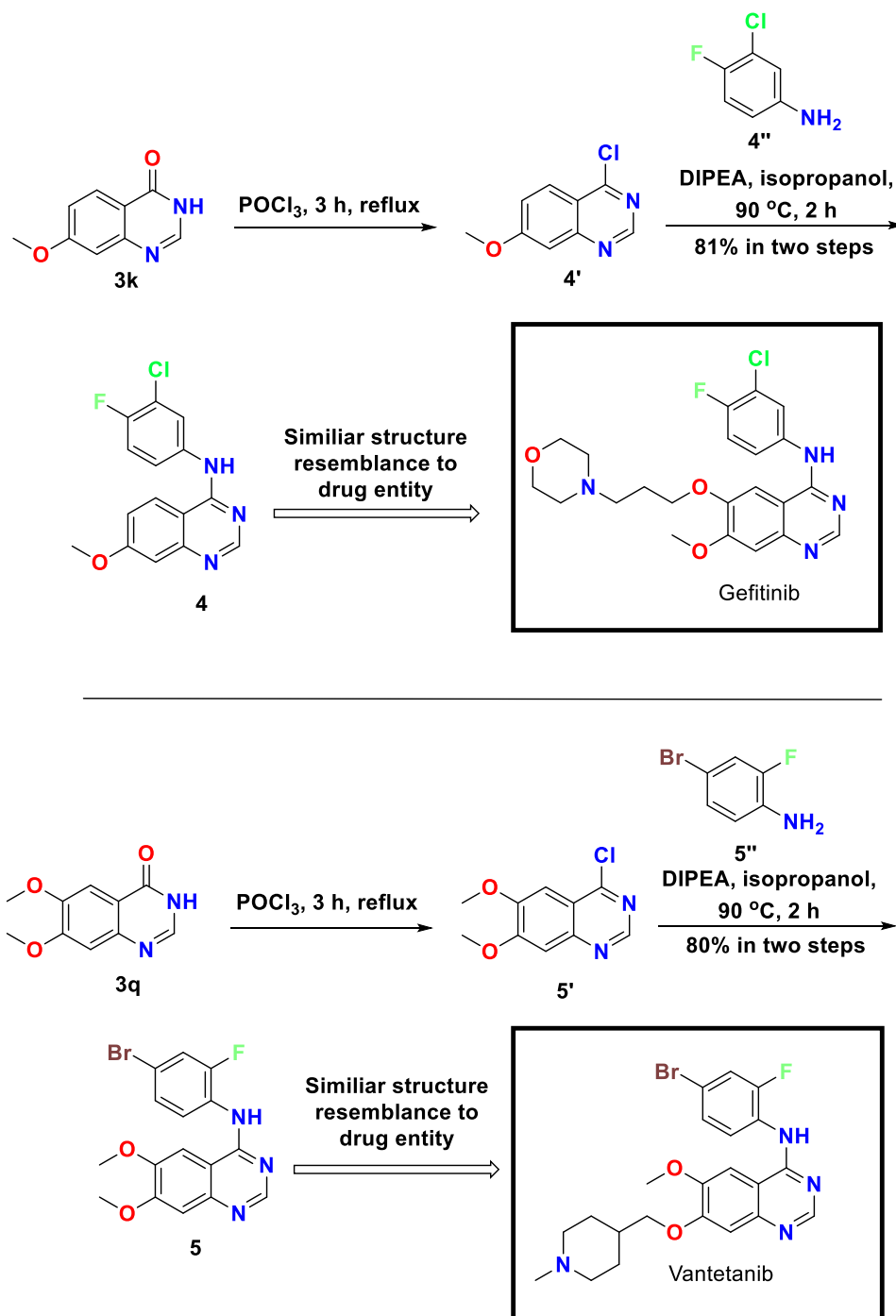
We also tried to demonstrate in a few examples how the products could be further utilized to prepare various anti-cancer drug molecules. To this goal, utilizing the same electrochemical method, we synthesized substituted *N*-phenyl-7-methoxyquinazolin-4-amines **4** and **5** (from **3k** and **3q** as shown in Scheme-2) as compounds which are similar in structure to the marketed drugs, Gefitinib and Vantetinib. To this end, **3k** and **3q** were heated at reflux in POCl₃ for 3 hours to give chloro intermediates (**4'** and **5'**) which were reacted with different anilines at 90°C in isopropanol solvent to give **4** and **5** in 81% and 80% yield over two steps respectively.

Table 2. Substrate scope of (benz)aldehydes and 2-aminobenzamides utilized for the electrochemical synthesis of substituted 4-quinazolinones

[a] Conditions: Undivided cell, C anode/Al cathode, HOAc (5 equiv.), Methanol, RT, 3h.

*Time = 5 h

[b] Conditions for 5g scale reaction: Undivided cell, C anode/Al cathode, HOAc (5 equiv.), Methanol, RT, 5h.

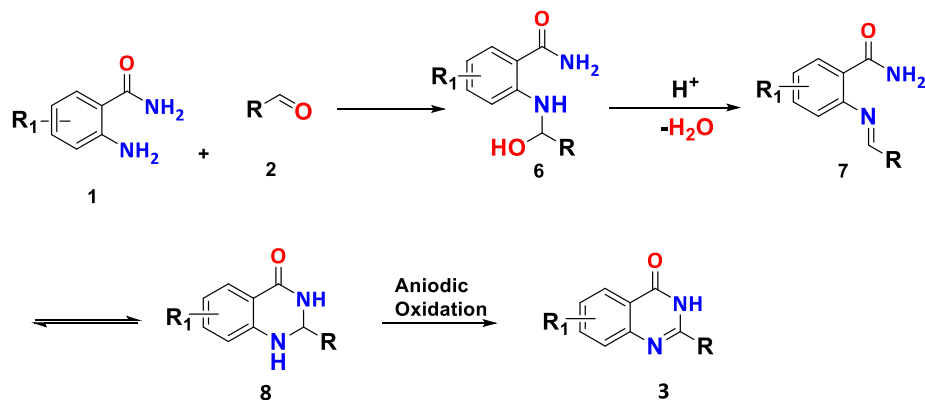


Scheme 2. Extension of materials **3k** and **3q** into **4** and **5** bearing resemblance to common anticancer drugs.

We have also carried out scale up reactions by reacting benzaldehyde (**1a**) and 2-amino benzamide (**1b**) to prepare compound **3a'** in 5 g scale. While we increased the scale of the reaction, no drastic change in yield was experienced; however, the reaction time was increased to 5 h to ensure the reaction went to completion. This process proved well across variety of substrates and scale of reactions.

Finally, in terms of an overall reaction sequence, the process is thought to begin with the acid-catalyzed reaction between the substituted 2-aminobenzamide **1** and a differently substituted aldehyde **2** to form hemiaminal intermediate **6**, which dehydrates under the acidic conditions to provide imine intermediate **7**.

Imine **7** and cyclized compound **8** are interconvertible, with **8** then finally undergoing anodic oxidation to afford the desired product **3**.



Conclusions

An easy, scalable and robust electrochemical method is developed to synthesize various 4-quinazolinone derivatives by reacting various (benz)aldehydes with substituted 2-aminobenzamides using acetic acid as an electrolyte. This method was utilized to synthesize substituted quinazolin-4(3*H*)-one and 2-methylquinazolin-4(3*H*)-one derivatives. All these moieties are very important in the recent drug discovery because of their pharmacological importance. Scale up of the reaction was also carried out to check the feasibility and scalability of the reactions.

Experimental Section

General Method. All reagents were purchased from commercial sources (Sigma-Aldrich, Angene and TCI) and were used without further purification. Acetonitrile was dried over P₂O₅ before use. Methanol was used without drying. The reactions were monitored using pre-coated thin-layer chromatography (TLC) plates (Merck, silica gel 60 F254, 0.25 mm) and compounds were visualized either under ultraviolet light (254 nm) or by staining with iodine. Silica gel (100 - 200 and 230-400 mesh) was used for column chromatography. ¹H and ¹³C NMR spectra were recorded on Bruker Advance 400 instrument operating at 400 MHz (¹H), 101 MHz (¹³C). Chemical shifts (δ) are in ppm and referenced to TMS as an internal standard (δ 0.00 for ¹H NMR) or DMSO-*d*₆/CDCl₃ (δ 77.0 ppm for ¹³C NMR); coupling constants (J) are quoted in Hz. All ¹H- NMR had moisture observed at δ 1.5 – 1.6 for CDCl₃ and δ 3.3 for DMSO-*d*₆. LCMS was recorded on WATERS ACQUITY H Class with PDA and SQ DETECTOR instrument.

Experimental procedure for compounds 3a-3q

General procedure for the synthesis of 4-quinazolinones

2-Aminobenzamide (1.0 equiv.), aldehyde (1.0 equiv.) and MeOH were added in an undivided cell. The reaction mixture was stirred at room temperature for 5 minutes followed by addition of acetic acid (5.0 equiv.). The cell was equipped with carbon anode and aluminum cathode and electrolyzed using constant current of ~0.35 A.cm⁻² at room temperature while stirring for 3 h, whilst the reaction mixture was monitored

by LCMS and TLC. Upon complete consumption of starting material, electrolysis was terminated. Reaction mixture was concentrated under reduced pressure, diluted with water (10 mL) and extracted with ethyl acetate (3×15 mL). The combined organic layer was dried over Na₂SO₄ and concentrated using rotary evaporator. The so obtained crude material was purified by flash chromatography on silica gel using a solvent mixture of ethyl acetate and hexane.

2-Phenylquinazolin-4(3H)-one (3a). As per the general procedure, 2-aminobenzamide (100 mg, 0.73 mmol), benzaldehyde (77 mg, 0.73 mmol), acetic acid (0.20 mL, 3.5 mmol), MeOH (5 mL) produced **3a**²¹ as a white solid, mp 220–222 °C; Lit mp 223 °C²¹ (170 mg, 85%). ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.51–7.56 (m, 4H), 7.75 (d, *J* = 8.1 Hz, 1H), 7.85 (t, *J* = 7.6 Hz, 1H), 8.17 (t, *J* = 8.7 Hz, 3H), 12.56 (s, 1H). ¹³C NMR (100 MHz, DMSO-*d*₆) 121.48, 126.33, 127.04, 127.99, 129.07, 128.24, 131.85, 133.21, 135.05, 149.23, 152.779, 162.69. LCMS (*m/z*): 223.2 [M+H]⁺.

2-(4-Methoxyphenyl)quinazolin-4(3H)-one (3b). As per the general procedure, 2-aminobenzamide (100 mg, 0.73 mmol), 4-methoxy benzaldehyde (109 mg, 0.73 mmol), acetic acid (0.2 mL, 3.5 mmol), MeOH (5 mL) produced **3b**²² as a white solid, mp 241–243 °C; Lit mp 245–247 °C²² (184 mg, 87%). ¹H NMR (400 MHz, DMSO-*d*₆) δ 3.85 (s, 3H), 7.09 (d, *J* = 8.6 Hz, 2H), 7.49 (t, *J* = 7.5 Hz, 1H), 7.71 (d, *J* = 8.1 Hz, 1H), 7.96 – 7.78 (m, 1H), 8.13 (d, *J* = 7.9 Hz, 1H), 8.20 (d, *J* = 8.5 Hz, 2H), 12.43 (s, 1H). ¹³C NMR (100 MHz, DMSO-*d*₆) 55.92, 114.46, 121.16, 125.26, 126.290, 126.58, 127.75, 135.21, 149.40, 152.31, 129.91, 162.76, 162.33. LCMS (*m/z*): 253.37 [M+H]⁺.

2-(3,4-Dimethoxyphenyl)quinazolin-4(3H)-one (3c). As per the general procedure, 2-aminobenzamide (100 mg, 0.73 mmol), 3,4-dimethoxy benzaldehyde (122 mg, 0.73 mmol), acetic acid (0.2 mL, 3.5 mmol), MeOH (5 mL) produced **3c**²³ as a white solid, mp 252–255 °C; Lit mp 250–252 °C²³ (175 mg, 85%). ¹H NMR (400 MHz, DMSO-*d*₆) δ 3.87 (d, *J* = 14.3 Hz, 6H), 7.12 (d, *J* = 8.5 Hz, 1H), 7.49 (t, *J* = 7.5 Hz, 1H), 7.72 (d, *J* = 8.1 Hz, 1H), 7.91 – 7.78 (m, 3H), 8.14 (d, *J* = 8.1 Hz, 1H), 12.46 (s, 1H). ¹³C NMR (100 MHz, DMSO-*d*₆) 56.16, 111.18, 111.85, 121.17, 121.62, 125.23, 126.30, 126.59, 127.79, 135.32, 149.03, 149.39, 152.07, 152.30, 162.81. LCMS (*m/z*): 283.2 [M+H]⁺.

2-(Thiazol-4-yl)quinazolin-4(3H)-one (3d). As per the general procedure, 2-aminobenzamide (100 mg, 0.73 mmol), thiazole-4-carboxaldehyde (83 mg, 0.73 mmol), acetic acid (0.2 mL, 3.5 mmol), MeOH (5 mL) produced **3d** as a white solid, mp 160–163 °C (155 mg, 83%). ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.53 (t, *J* = 7.5 Hz, 1H), 7.74 (d, *J* = 8.1 Hz, 1H), 7.85 (t, *J* = 7.6 Hz, 1H), 8.16 (d, *J* = 7.8 Hz, 1H), 8.69 (d, *J* = 2.0 Hz, 1H), 9.32 (d, *J* = 2.0 Hz, 1H), 12.10 (s, 1H). ¹³C NMR (100 MHz, DMSO-*d*₆) 122.02, 124.21, 126.49, 127.17, 127.79, 135.11, 147.65, 149.17, 149.33, 156.05, 161.64. LCMS (*m/z*): 230.13 [M+H]⁺.

2-(Furan-2-yl)quinazolin-4(3H)-one (3e). As per the general procedure, 2-aminobenzamide (100 mg, 0.73 mmol), 2-furaldehyde (70 mg, 0.73 mmol), acetic acid (0.2 mL, 3.5 mmol), MeOH (5 mL) produced **3e**²⁴ as white solid, mp 222–225 °C; Lit mp 220–223 °C²⁴ (150 mg, 80%). ¹H NMR (400 MHz, DMSO-*d*₆) δ 6.81 (s, 1H), 7.54 (d, *J* = 8.5 Hz, 1H), 7.68 (q, *J* = 6.0, 1H), 7.75 (d, *J* = 8.6 Hz, 1H), 7.86 (d, *J* = 8.3 Hz, 1H), 8.05 (d, *J* = 8.3 Hz, 1H), 8.18 (d, *J* = 8.3 Hz, 1H), 12.57 (s, 1H). ¹³C NMR (100 MHz, DMSO-*d*₆) 112.98, 114.96, 121.62, 126.40, 126.93, 127.71, 135.10, 144.48, 146.56, 147.05, 149.13, 162.03. LCMS (*m/z*): 212.13 [M+H]⁺.

6-Methoxy-2-phenylquinazolin-4(3H)-one (3f). As per the general procedure, 2-amino-5-methoxybenzamide (100 mg, 0.60 mmol), Benzaldehyde (64 mg, 0.60 mmol), acetic acid (0.2 mL, 3.5 mmol), MeOH (5 mL) produced **3f**²⁵ as a white solid, mp 252–255 °C; Lit mp 249–251 °C²⁵ (131 mg, 86%). ¹H NMR (400 MHz, DMSO-*d*₆) δ 3.92 (s, 3H), 8.19 (d, *J* = 7.0 Hz, 2H), 7.47 (dd, *J* = 9.0, 2.8 Hz, 1H), 7.48–7.57 (m, 4H), 7.72 (d, *J* = 8.9 Hz, 1H). ¹³C NMR (100 MHz, DMSO-*d*₆) 56.13, 106.35, 122.26, 124.59, 127.96, 129.05, 129.71, 131.52, 133.26, 143.68, 150.57, 158.22, 162.50. LCMS (*m/z*): 253.27 [M+H]⁺.

7-Methoxy-2-phenylquinazolin-4(3H)-one (3g). As per the general procedure, 2-amino-4-methoxybenzamide (100 mg, 0.60 mmol), Benzaldehyde (64 mg, 0.60 mmol), acetic acid (0.2 mL, 3.5 mmol), MeOH (5 mL) produced **3g**²⁶ as a white solid, mp 236–238 °C; Lit mp 235–236 °C²⁶ (125 mg, 82%). ¹H NMR (400 MHz, DMSO-*d*₆) δ 3.92 (s, 3H), 7.11 (d, *J* = 8.0, 1H), 7.19 (s, 1H), 7.47–7.61 (m, 3H), 8.04 (d, *J* = 8.0, 1H), 8.19 (d, *J* = 6.8 Hz, 2H), 12.41 (s, 1H). ¹³C NMR (100 MHz, DMSO-*d*₆) 56.19, 108.97, 114.88, 116.65, 127.91, 128.20, 129.05, 131.86, 133.19, 151.41, 153.37, 162.25, 164.65. LCMS (*m/z*): 253.22 [M+H]⁺.

6,7-Dimethoxy-2-phenylquinazolin-4(3H)-one (3h). As per the general procedure, 2-amino-4,5-dimethoxybenzamide (100 mg, 0.51 mmol), benzaldehyde (95 mg, 0.89 mmol), acetic acid (0.2 mL, 3.5 mmol) MeOH (5 mL) produced **3h**²⁷ obtained as a white solid, mp 303–305 °C; Lit mp 307–309 °C²⁷ (121 mg, 84%). ¹H NMR (400 MHz, DMSO-*d*₆) δ 3.90 (s, 3H), 3.94 (s, 3H), 7.23 (s, 1H), 7.49–7.57 (m, 4H), 8.18 (d, *J* = 6.8 Hz, 1H), 12.43 (s, 1H). ¹³C NMR (100 MHz, DMSO-*d*₆) 105.45, 108.73, 114.46, 127.91, 129.03, 131.49, 133.33, 145.29, 149.09, 151.26, 155.22, 163.02. LCMS (*m/z*): 283.25 [M+H]⁺.

Quinazolin-4(3H)-one (3i). As per the general procedure, 2-aminobenzamide (100 mg, 0.74 mmol), 1, 3, 5-trioxane (99 mg, 1.1 mmol), acetic acid (0.2 mL, 3.5 mmol), MeOH (5 mL) produced **3i**²⁸ obtained as an off-white solid mp 222–224 °C; Lit mp 218–220 °C²⁸ (65 mg, 60%). ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.55 (d, *J* = 8.5 Hz, 1H), 7.68 (d, *J* = 8.3 Hz, 1H), 7.81–7.84 (m, 1H), 8.09–8.14 (m, 2H), 12.26 (s, 1H). ¹³C NMR (100 MHz, DMSO-*d*₆) 123.12, 126.29, 127.16, 127.68, 134.72, 145.84, 149.24, 161.20. LCMS (*m/z*): 147.03 [M+H]⁺.

2-Methylquinazolin-4(3H)-one (3j). As per the general procedure, 2-aminobenzamide (100 mg, 0.74 mmol), paraldehyde (145 mg, 1.1 mmol), acetic acid (0.2 mL, 3.5 mmol) MeOH (5 mL) produced **3j**²⁹ obtained as a white solid, mp 240–243 °C; Lit mp 239–241 °C²⁹ (82 mg, 70%). ¹H NMR (400 MHz, DMSO-*d*₆) δ 2.35 (s, 3H), 7.48 (d, *J* = 8.5 Hz, 1H), 7.59 (d, *J* = 7.6 Hz, 1H), 7.88–7.76 (m, 1H), 8.09 (d, *J* = 6.8 Hz, 1H), 12.24 (s, 1H). ¹³C NMR (100 MHz, DMSO-*d*₆) 121.09, 126.11, 126.26, 127.02, 134.68, 149.43, 154.69, 162.16. LCMS (*m/z*): 161.08 [M+H]⁺.

7-Methoxyquinazolin-4(3H)-one (3k). As per the general procedure, 2-amino-4-methoxybenzamide (100 mg, 0.60 mmol), 1, 3, 5-trioxane (81 mg, 0.90 mmol), acetic acid (0.2 mL, 3.5 mmol) MeOH (5 mL) produced **3k**³⁰ as a white solid, mp 254–256 °C; Lit mp 257–259 °C³⁰ (63 mg, 59%). ¹H NMR (400 MHz, DMSO-*d*₆) δ 3.98 (s, 3H), 7.10 (d, *J* = 6.8 Hz, 2H), 8.00–8.07 (m, 2H), 12.1 (s, 1H). ¹³C NMR (100 MHz, DMSO-*d*₆) 56.15, 108.83, 116.64, 127.91, 146.46, 151.45, 160.75, 164.37. LCMS (*m/z*): 177.02 [M+H]⁺.

6-Iodoquinazolin-4(3H)-one (3l). As per the general procedure, 2-amino-5-iodobenzamide (100 mg, 0.38 mmol), 1, 3, 5-trioxane (52 mg, 0.58 mmol), acetic acid (0.2 mL, 3.5 mmol) MeOH (5 mL) produced **3l**³¹ as a white solid, mp 272–274 °C; Lit mp 270–272 °C³¹ (59 mg, 57%). ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.47 (d, *J* = 8.5 Hz, 1H), 8.11 (dd, *J* = 8.6, 2.1 Hz, 1H), 8.14 (s, 1H), 8.39 (d, *J* = 2.1 Hz, 1H), 12.42 (s, 1H). ¹³C NMR (100 MHz, DMSO-*d*₆) 92.26, 124.89, 129.89, 134.59, 143.10, 146.54, 148.49, 159.88. LCMS (*m/z*): 273.10 [M+H]⁺.

3-Methylquinazolin-4(3H)-one (3m). As per the general procedure, 2-amino-*N*-methylbenzamide (100 mg, 0.67 mmol), 1, 3, 5-trioxane (90 mg, 1.0 mmol), acetic acid (0.2 mL, 3.5 mmol) MeOH (5 mL) produced **3m**³² as a white solid, mp 102–104 °C; Lit mp 103–105 °C³² (65 mg, 61%). ¹H NMR (400 MHz, DMSO-*d*₆) δ 3.52 (s, 3H), 7.56 (ddd, *J* = 8.1, 7.1, 1.2 Hz, 1H), 7.69 (dd, *J* = 8.2, 1.1 Hz, 1H), 7.84 (ddd, *J* = 8.5, 7.1, 1.6 Hz, 1H), 8.18 (dd, *J* = 7.9, 1.5 Hz, 1H), 8.40 (s, 1H). ¹³C NMR (100 MHz, DMSO-*d*₆) 33.98, 121.90, 126.30, 127.37, 127.57, 134.55, 148.55, 148.88, 161.10. LCMS (*m/z*): 160.9 [M+H]⁺.

2,3-Dimethylquinazolin-4(3H)-one (3n). As per the general procedure, 2-amino-*N*-methylbenzamide (100 mg, 0.67 mmol), paraldehyde (132 mg, 1.00 mmol), acetic acid (0.2 mL, 3.5 mmol) MeOH (5 mL) produced **3n**³³ as a white solid, mp 110–112 °C; Lit mp 111–113 °C³³ (83 mg, 71%). ¹H NMR (400 MHz, DMSO-*d*₆) δ 2.67 (s, 3H), 3.54 (s, 3H), 7.48 (t, *J* = 7.5 Hz, 1H), 7.58 (d, *J* = 8.1 Hz, 1H), 7.78 (dd, *J* = 15.3, 1.6 Hz, 1H), 8.10 (dd, *J* = 8.0, 1.5

Hz, 1H). ^{13}C NMR (100 MHz, DMSO- d_6) 23.60, 31.00, 120.16, 126.53, 126.60, 126.81, 134.56, 147.46, 156.11, 161.71. LCMS (m/z): 175.05 [M+H] $^+$.

6-Chloro-2-methylquinazolin-4(3H)-one (3o). As per the general procedure, 2-amino-5-chlorobenzamide (100 mg, 0.59 mmol), paraldehyde (116 mg, 0.88 mmol), acetic acid (0.2 mL, 3.5 mmol) MeOH (5 mL) produced **3o**³⁴ as a white solid, mp 285–287 °C; Lit mp 287–289 °C³⁴ (78 mg, 68%). ^1H NMR (400 MHz, DMSO- d_6) δ 2.36 (s, 3H), 7.60 (d, J = 8.7 Hz, 1H), 7.80 (dd, J = 8.7, 2.6 Hz, 1H), 8.01 (d, J = 2.5 Hz, 1H), 12.39 (s, 1H). ^{13}C NMR (100 MHz, DMSO- d_6) 21.92, 122.32, 125.10, 130.49, 134.76, 129.28, 148.11, 155.38, 161.17. LCMS (m/z): 194.09 [M+H] $^+$.

7-Chloroquinazolin-4(3H)-one (3p). As per the general procedure, 2-amino-4-chlorobenzamide (100 mg, 0.59 mmol), 1, 3, 5-trioxane (79 mg, 0.88 mmol), acetic acid (0.2 mL, 3.5 mmol) MeOH (5 mL) produced **3p**³⁵ as a white solid, mp 252–254 °C; Lit mp 251–253 °C³⁵ (62 mg, 58%). ^1H NMR (400 MHz, DMSO- d_6) δ 7.57 (dd, J = 8.5, 2.0 Hz, 1H), 7.74 (d, J = 2.0 Hz, 1H), 8.17 – 8.09 (m, 2H), 12.32 (s, 1H). ^{13}C NMR (100 MHz, DMSO- d_6) 118.04, 125.79, 128.42, 130.36, 139.36, 147.41, 150.32, 161.04. LCMS (m/z): 180.09 [M+H] $^+$.

6,7-Dimethoxyquinazolin-4(3H)-one (3q). As per the general procedure, 2-amino-4,5-dimethoxybenzamide (100 mg, 0.51 mmol), 1, 3, 5-trioxane (79 mg, 0.88 mmol), acetic acid (0.2 mL, 3.5 mmol) and MeOH (5 mL) produced **3q**³⁶ obtained as white solid, mp 294–296 °C; Lit mp 296–298 °C³⁶ (72 mg, 62%). ^1H NMR (400 MHz, DMSO- d_6) δ 3.85 (s, 3H), 3.89 (s, 3H), 7.11 (s, 1H), 7.42 (s, 1H), 7.98 (s, 1H), 12.32 (s, 1H). ^{13}C NMR (100 MHz, DMSO- d_6) 56.15, 56.39, 105.35, 108.45, 116.06, 144.32, 145.34, 149.00, 154.91, 160.53. LCMS (m/z): 207.1 [M+1] $^+$.

Synthesis of 2-Phenylquinazolin-4(3H)-one (3a') on larger scale. 2-Aminobenzamide (6.41 g, 47.1 mmol), benzaldehyde (5 g, 47.1 mmol) and MeOH (100 mL) were added in an undivided cell. The reaction mixture was stirred at room temperature for 5 minutes followed by addition of acetic acid (13.42 mL, 235.0 mmol). The cell was equipped with carbon anode and aluminum cathode and electrolyzed using constant current of ~ 0.35 A.cm $^{-2}$ at room temperature while stirring for 5 h, whilst the reaction mixture was monitored by LCMS and TLC. Upon complete consumption of starting material, electrolysis was terminated. Reaction mixture was concentrated under reduced pressure, diluted with water (50 mL) and extracted with ethyl acetate (3 \times 40 mL). The combined organic layer was dried over Na $_2$ SO $_4$ and concentrated using rotary evaporator. The so obtained crude material was purified by flash chromatography on silica gel using a solvent mixture of ethyl acetate and hexane to afford **3a'**²¹ as a white solid, mp 220–222 °C; Lit mp 223–225 °C²¹ (9.0 g, 86%). ^1H NMR (400 MHz, DMSO- d_6) δ 7.51–7.56 (m, 4H), 7.75 (d, J = 8.1 Hz, 1H), 7.85 (t, J = 7.6 Hz, 1H), 8.17 (t, J = 8.7 Hz, 3H), 12.56 (s, 1H). ^{13}C NMR (100 MHz, DMSO- d_6) 121.48, 126.33, 127.04, 127.99, 129.07, 128.24, 131.85, 133.21, 135.05, 149.23, 152.78, 162.69. LCMS (m/z): 223.2 [M+H] $^+$.

Synthesis of compounds 4 and 5

4-Chloro-7-methoxyquinazoline (4'). To a solution of 7-methoxyquinazolin-4(3H)-one (200 mg, 1.14 mmol) in POCl $_3$ (4 mL) was cooled to 0 °C. Reaction mixture was refluxed for 3 h. The progress of the reaction was monitored by TLC. After completion of reaction, the reaction mixture was evaporated under reduced pressure and residue was co-evaporated twice with dichloromethane and dried under reduced pressure to afford 4-chloro-7-methoxyquinazoline as brown liquid, which was utilized in next step without any purification.

N-(3-Chloro-4-fluorophenyl)-7-methoxyquinazolin-4-amine (4). To a 0 °C cooled solution of 4-chloro-7-methoxyquinazoline (0.22 g, 1.1 mmol) in isopropanol (4 mL) was added DIPEA (1.46 g, 11.3 mmol) followed by addition of 3-chloro-4-fluoroaniline (197 mg, 1.36 mmol). Reaction mixture was stirred at 90 °C for 2 h. After completion of reaction (monitored by TLC), the reaction mixture was diluted with water (10 mL) and extracted with ethyl acetate (3 \times 10 mL). The combined organic layer was washed with brine solution (10 mL) and dried over anhydrous sodium sulphate. The solvent was evaporated under reduced pressure. The crude

residue was purified by combi-flash column chromatography using 0-15% EtOAc/heptane as eluent to afford *N*-(3-chloro-4-fluorophenyl)-7-methoxyquinazolin-4-amine (0.28 g, 81% over two steps). **Compound-4**: ^1H NMR (400 MHz, $\text{DMSO-}d_6$) δ 3.99 (s, 3H), 7.34 (s, 1H), 7.49-7.57 (m, 2H), 7.73 (s, 1H), 8.05 (dd, $J = 8.5, 2.0$ Hz, 1H), 8.84 (d, $J = 2.0$ Hz, 2H), 8.92 (s, 1H), 11.54 (bs, 1H). ^{13}C NMR (100 MHz, $\text{DMSO-}d_6$) 56.81, 100.89, 107.83, 117.43, 119.56, 125.79, 127.10, 127.57, 134.59, 141.86, 151.61, 154.40, 156.85, 159.63, 165.35. LCMS (m/z): 302.0 $[\text{M}-1]^+$.

4-Chloro-6,7-dimethoxyquinazoline (5'). A solution of 6,7-dimethoxyquinazolin-4(3*H*)-one (200 mg, 0.97 mmol) in POCl_3 (4 mL) was cooled to 0 °C, after which the reaction mixture was heated at reflux for 3 h. The progress of the reaction was monitored by TLC. After completion of reaction, the reaction mixture solvent was evaporated under reduced pressure and the residue was co-evaporated twice with dichloromethane and dried under reduced pressure to afford 4-chloro-6,7-dimethoxyquinazoline as a brown liquid, which was utilized directly in the next step without any further purification.

***N*-(4-Bromo-2-fluorophenyl)-6,7-dimethoxyquinazolin-4-amine (5)**. To a 0 °C cooled solution of 4-chloro-6,7-dimethoxyquinazoline (0.22 g, 0.97 mmol) in isopropanol (4 mL) was added DIPEA (1.27 g, 9.79 mmol), followed by addition of 4-bromo-2-fluoroaniline (223 mg, 1.18 mmol). The reaction mixture was stirred at 90 °C for 2 h. After completion of reaction (monitored by TLC), the reaction mixture was diluted with water (10 mL) and extracted with ethyl acetate (3 \times 10 mL). The combined organic layer was washed with brine solution (10 mL) and dried over anhydrous sodium sulphate. The solvent was evaporated under reduced pressure. The crude residue was purified by combi-flash column chromatography using 0-15% EtOAc/heptane as eluent to afford *N*-(4-bromo-2-fluorophenyl)-6,7-dimethoxyquinazolin-4-amine (0.29 g, 80% over two steps). **Compound 5**: ^1H NMR (400 MHz, $\text{DMSO-}d_6$) δ 4.01 (s, 6H), 7.35 (s, 1H), 7.52-7.59 (m, 2H), 7.78 (dd, $J = 8.5, 2.0$ Hz, 1H), 8.24 (s, 1H), 8.80 (s, 1H), 11.42 (bs, 1H). ^{13}C NMR (100 MHz, $\text{DMSO-}d_6$) 57.00, 57.44, 100.46, 104.52, 107.65, 120.65, 124.72, 128.44, 130.68, 136.65, 149.41, 150.81, 156.08, 157.02, 158.63, 159.36. LCMS (m/z): 378.1 $[\text{M}+1]^+$.

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Supplementary Material

For experimental procedures, NMR spectra and characterization of compounds please see Supporting Information file.

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