# A convergent microwave assisted synthesis of 4-amino-*N*-(4-oxo-2-substituted-4*H*-quinazolin-3-yl)benzenesulfonamide derivatives

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**Abstract**

An optimization of Grimmel's method under microwave irradiation is reported here for the first time to synthesize 4-amino-*N*-(4-oxo-2-substituted-4*H*-quinazolin-3-yl)benzenesulfonamide derivatives. The method was successfully applied for the synthesis of 2-alkyl and 2-aryl substituted derivatives. However, unexpected results were obtained when the same protocol was applied for 2-styryl-substituted quinazolinones. 2-Styrylquinazolinone derivatives were then synthesized via benzoxazinones under microwave irradiation. Subsequently, the effect of various bases (e.g. $Et_3N$, NMM, DMAP, DIPEA) on the efficiency of cyclization to quinazolinone was investigated. The use of microwave irradiation allows significant rate enhancements and better yields compared to conventional conditions.

**Keywords:** Quinazolinone, Grimmel's method, microwave, sulfonamide, 2-styrylquinazolinone

## Introduction

4(3*H*)-Quinazolinone core and its 2,3-disubstituted derivatives form an important class of compounds, as they are found in a wide range of compounds exhibiting a broad spectrum of pharmacological properties.[1]

In 1946, Grimmel reported the synthesis of quinazolinones by heating *N*-acetylanthranilic acids with anilines in toluene or xylene in the presence of condensing agents such as phosphorus trichloride, phosphorus oxychloride, or thionyl chloride.[2] Since his report, the method has frequently been used for the synthesis of diverse range of quinazolinones.[3] Therefore, we

intended to synthesize 4-amino-*N*-(4-oxo-2-substituted-4*H*-quinazolin-3-yl)benzenesulfonamide derivatives (**1**, Figure 1.) using Grimmel's conditions.

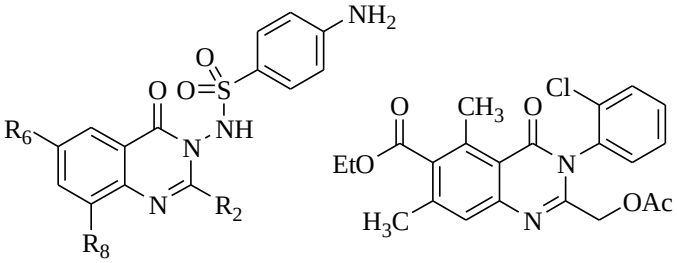



**Figure 1**

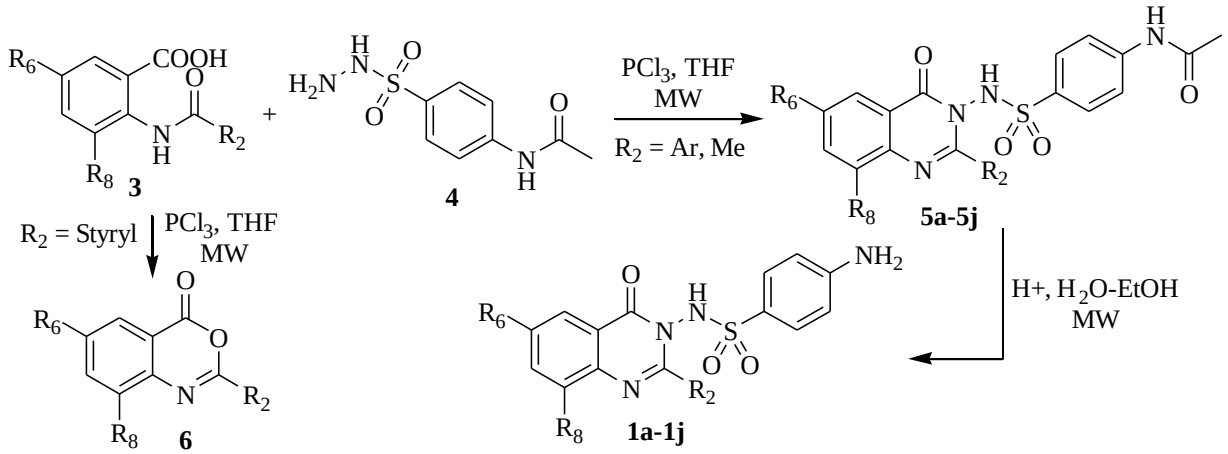
## Results and Discussion

Recently, Xue, S. *et al*.[4] have modified Grimmel's method for the synthesis of 2-acetoxymethyl-3-aryl-4-quinzolinones (**2**, Figure 1.) by varying solvents (MeCN, MDC, THF) and amount of $PCl_3$ (2 equivalent) under mild reaction conditions (50 °C). In their paper, they suggested that lower solubility of intermediates in toluene might be contributed to the low yield (15%), when toluene was used as a solvent (110 °C). Interestingly, when we applied the same protocol to *N*-acetylanthranilic acid (**3a**, $R_2$=$CH_3$, $R_6$=$R_8$=H) and 4-acetamidobenzenesulfonyl hydrazide[5] (**4**), good amount (67%) of quinazolinone product (**5a**, $R_2$=$CH_3$, $R_6$=$R_8$=H) was generated, despite of the fact that, both the starting materials were insoluble in toluene. This observation rules out the hypothesis suggested by Xue *et al*.[4] Furthermore, quinazolinone product was not detected, when **3a** and **4** were reacted using 2 equivalent of $PCl_3$ in MeCN at 50 °C.[4] This unexpected result encouraged us to further explore this reaction. When the same reaction was further heated to reflux for 5 h, desired product **5a** was isolated in 73% yield. We envisaged that the use of microwave irradiation could further improve the yield and reduce the reaction time. Therefore, the reaction conditions were optimized under microwave irradiation by changing power level, solvents and amount of $PCl_3$ (Table 1). The best results were obtained when THF and 1 equivalent of $PCl_3$ were employed at 350 W (Table 1, Entry 8). All the quinazolinone derivatives (**5a-5j**) containing methyl or aryl substitutions at 2$^{nd}$ position were synthesized using this protocol (Scheme 1). Subsequent hydrolysis of **5a-5j** under acidic condition using microwave irradiation (140 W) leads to the formation of desired products, 4-amino-*N*-(4-oxo-2-methyl/aryl-substituted quinazolin-3(4*H*)-yl)benzenesulfonamide (**1a-1j**). The reaction time and yield for the various substitutions used are represented in Table 2.

**Table 1.** Optimization of reaction conditions for the synthesis of 4-amino-*N*-(4-oxo-2-methylquinazolin-3(4*H*)-yl)benzenesulfonamide (**1a**)

| Entry | Solvent | Mol. eq. of $PCl_3$ | Power level (W) | Reaction time (min) | Yield (%) |
|---|---|---|---|---|---|
| 1 | Toluene | 0.34 | 280 | 30 | 10 |
| 2 | $CH_2Cl_2$ | 0.5 | 280 | 30 | 41 |
| 3 | $CH_3CN$ | 0.5 | 280 | 14 | 80 |
| 4 | $CH_3CN$ | 1.0 | 280 | 11 | 87 |
| 5 | THF | 0.5 | 280 | 12 | 85 |
| 6 | THF | 1.0 | 280 | 10 | 89 |
| 7 | THF | 2.0 | 280 | 9 | 78 |
| 8 | THF | 1.0 | 350 | 8 | 92 |
| 9 | THF | 1.0 | 420 | 7 | 85 |




**Scheme 1**

Interestingly, when we applied above optimized conditions to 2-cinnamamidobenzoic acid (**3k**, $R_2$=styryl, $R_6$=$R_8$=H) and **4**, (*E*)-2-styryl-4*H*-benzo[*d*][1,3]oxazin-4-one (**6k**, $R_2$=styryl, $R_6$=$R_8$=H) was generated as a major product (80%) (Scheme 1). The same reaction was repeated under conventional heating using toluene as a solvent, although the result was same. Moreover, Xue *et al.* have also reported the formation of small amount of benzoxazinone and regarded it as a plausible intermediate.[4] However, in our case even after extended heating, no further conversion of benzoxazinone (**6k**) to corresponding quinazolinone was observed. It suggests that benzoxazinone may not be a reactive intermediate, but it may be considered as a byproduct. After getting the unproductive results, we looked up other reported methods to access 2-styrylquinazolinones.

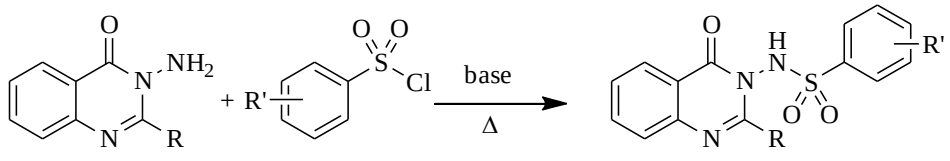
**Table 2.** Synthesis of 4-amino-*N*-(4-oxo-2-methyl/aryl-substituted quinazolin-3(4*H*)-yl)benzenesulfonamides (**1a-1j**) under microwave irradiation

| Compound | $R_2$ | $R_6$ | $R_8$ | Step – I[a] | | Step – II[b] | |
|---|---|---|---|---|---|---|---|
| | | | | Reaction time[c] | Yield[d] (%) | Reaction time[c] | Yield[d] (%) |
| **1a** | $CH_3$ | H | H | 8 | 92 | 1 | 78 |
| **1b** | $CH_3$ | Br | H | 7 | 83 | 2 | 75 |
| **1c** | $CH_3$ | Br | Br | 6 | 85 | 3 | 74 |
| **1d** | $C_6H_5$ | $NO_2$ | H | 10 | 89 | 1 | 79 |
| **1e** | $C_6H_5$ | H | H | 9 | 91 | 1 | 76 |
| **1f** | $C_6H_5$ | Br | H | 8 | 88 | 2 | 74 |
| **1g** | $C_6H_5$ | Br | Br | 6 | 84 | 3 | 73 |
| **1h** | 4-Cl-$C_6H_4$ | H | H | 9 | 86 | 2 | 75 |
| **1i** | 4-Cl-$C_6H_4$ | Br | H | 8 | 90 | 2 | 72 |
| **1j** | 4-Cl-$C_6H_4$ | Br | Br | 7 | 85 | 4 | 70 |

[a] Step – I: Synthesis of Quinazolinones at 350 W. [b] Step – II: Hydrolysis at 140 W. [c] Reaction time is in minutes. [d] Isolated yield after recrystallization.

The general method for the synthesis of 2-styryl-substituted quinazolin-4(3*H*)-ones is the Knoevenagel condensation of 2-methyl-substituted quinazolinones with aromatic aldehydes under basic[6] or acidic[7] conditions. However, this method did not give satisfactory results and the reactions were not always reproducible in our hands, might be due to the interference of sulfonamide group. These unexpected results prompted us to search for a new convergent method to synthesize quinazolinone derivatives, which could tolerate both styryl and 4-acetamidobenzenesulfonamide groups at 2nd & 3rd positions respectively.

To date, only few examples of 3-sulfonamide-substituted quinazolinones (**7**) are reported. One of the reported synthetic routes involves the sulfonylation of 3-aminoquinazolinones (**8**) with arylsulfonyl chlorides in refluxing benzene or ethanol in the presence of a base, such as pyridine or NaOH (Scheme 2).[8] 3-Aminoquinazolinones (**8**) can easily be prepared from corresponding benzoxazinones.[8a]

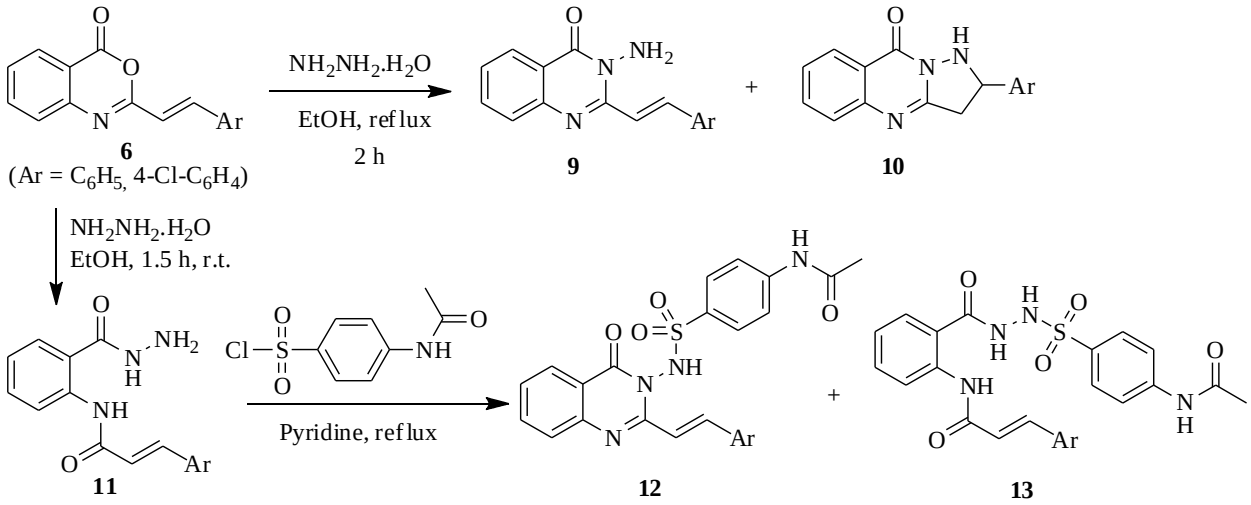



**8** **7**

**Scheme 2**

In case, when R is styryl substituent (Scheme 2), the key intermediate (*E*)-3-amino-2-styrylquinazolin-4(3*H*)-one (**9**) was difficult to prepare in good yield due to simultaneous formation of Michael adduct[9] (**10**) (Scheme 3). However, we managed to synthesize *N*-(2-(hydrazinecarbonyl)phenyl)cinnamamide (**11**) in 80% yield (Scheme 3). Further, sulfonylation of **11** with 4-acetamidobenzenesulfonyl chloride in presence of pyridine afforded the required product **12** in just 10% yield along with tetramide **13** (50%), which could be further cyclized[10] to **12**. However, this method suffers from certain drawbacks such as requiring multistep procedure, complex experimental processes and lower yields.




**Scheme 3**

Therefore, a new strategy had been planned, where (*E*)-2-styryl-4*H*-benzo[*d*][1,3]oxazin-4-ones (**6**) and **4** would condense to give the desired quinazolinones (**12**).

Recently, Zhou and Gregor *et al.* developed an excellent general method for the synthesis of 3-sulfonamide-substituted quinazolinone derivatives by condensation of benzoxazinones (**6**) and substituted sulfonyl hydrazides under solvent free conditions at 130 °C.[11] However, this method was not recommended on a larger scale (>0.2 mmol) due to the potential uncontrollable decomposition of the sulfonyl hydrazides. They have suggested that, a stepwise process using DMF as a solvent might have the potential for a safe scale-up. A pilot reaction was therefore attempted using equivalent amount of benzoxazinone (**6k**, Ar=phenyl, $R_6$=$R_8$=H) and 4-acetamidobenzenesulfonyl hydrazide (**4**) in anhydrous DMF. Initially, the mixture was shaken at room temperature[11] for 3 days, but tetramide (**13a**, Ar=phenyl, $R_6$=$R_8$=H) formation was not detected. Furthermore, upon heating this mixture for 24 h at 80 °C,[11] a mixture of **13a** (45%) and cyclized product (**12a**, Ar=phenyl, $R_6$=$R_8$=H) (20%) was isolated. Subsequently, we investigated the effect of microwave irradiation on the reaction rate as well as yield of the cyclized product.

Upon heating the equivalent amounts of **6k** and **4** in DMF under the microwave irradiation (455 W), some improvement was observed in the yield (45%) of cyclized product (**12a**).

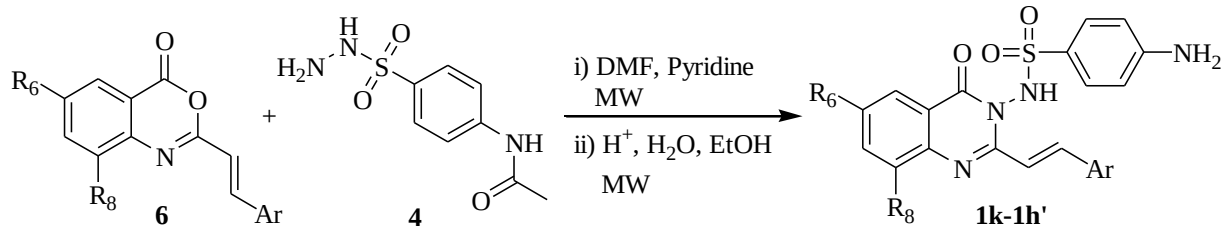
However, when pyridine was used as a solvent, formation of tetramide (**13a**) was considerably lower but the reaction required quite longer time to complete, as well as more decomposition of **4** was observed. Moreover, it was envisaged that the yield of the desired quinazolinones (**12**) could be increased with the increase in equivalents of **4**, as it decomposes during the reaction. Therefore, it was thought worthwhile to optimize the reaction conditions by varying the reactant ratio and molecular equivalents of pyridine. The optimized reaction condition involving 1.3 equivalent of **4** and 0.2 equivalent of pyridine, resulted in 60% isolated yield of **12a** (entry 3, Table 3). We envisioned that cyclization of tetramide leading to quinazolone **12a** was presumably promoted by pyridine. Therefore, it was decided to investigate effect of various bases e.g. triethyl amine ($Et_3N$), *N*-methyl morpholine (NMM), 4-(dimethylamino)pyridine (DMAP), *N*,*N*-diisopropylethylamine (DIPEA), on the efficiency of cyclization, hoping to identify an ideal combination that could optimize the reaction condition and contribute eventually to higher conversion of quinazolone. As shown in Table 3, a comparable yield of **12** was observed when $Et_3N$ or NMM was used as a base. When DMAP or DIPEA was used as a base, a little decomposition of benzoxazinones to corresponding *N*-acylanthranilic acids was observed, which led to the lower yield of **12**. All other quinazolinone derivatives were synthesized using 1.3 equivalents of **4** in presence of 0.2 equivalent of pyridine under microwave irradiation at 455 W (Table 4). Once the quinazolinones were synthesized, their hydrolysis to (*E*)-4-amino-*N*-(4-oxo-2-substituted styrylquinazolin-3(4*H*)-yl)benzenesulfonamide (**1k-1h'**) was not a difficult task. The hydrolysis was carried out under acidic condition using microwave irradiation at 140W (Scheme 4).

**Table 3.** Synthesis of (*E*)-*N*-(4-(*N*-(4-oxo-2-styrylquinazolin-3(4*H*)-yl)sulfamoyl)phenyl) acetamide under microwave irradiation (455 W)

| Entry | Solvent | 3° amine (mol. eq.) | Mol. eq. of **4** | Isolated yield (%) | | Reaction time (min) |
|---|---|---|---|---|---|---|
| | | | | Tetramide | Quinazolinone | |
| 1 | DMF | – | 1 | 25 | 45 | 6 |
| 2 | – | Pyridine (Ex.)[a] | 1 | 03 | 40 | 15 |
| 3 | DMF | Pyridine (0.2) | 1.3 | 08 | 60 | 7 |
| 4 | DMF | $Et_3N$ (0.2) | 1.3 | 08 | 56 | 7 |
| 5 | DMF | NMM (0.2) | 1.3 | 07 | 58 | 7 |
| 6 | DMF | DMAP (0.2) | 1.3 | 05 | 47 | 6 |
| 7 | DMF | DIPEA (0.2) | 1.3 | 04 | 43 | 6 |

[a] Ex. :- Excess




**Scheme 4**

**Table 4.** Synthesis of (*E*)-4-amino-*N*-(4-oxo-2-substituted styrylquinazolin-3(4*H*)-yl)benzenesulfonamides (**1k-1h'**) under microwave irradiation

| Compound | Ar | $R_6$ | $R_8$ | Step – I[a] | | Step – II[b] | |
|---|---|---|---|---|---|---|---|
| | | | | Reaction time[c] | Yield[d] | Reaction time[c] | Yield[d] |
| **1k** | $C_6H_5$ | H | H | 7 | 60 | 3 | 83 |
| **1l** | 4-OMe-$C_6H_4$ | H | H | 8 | 58 | 2 | 78 |
| **1m** | 2-$NO_2$-$C_6H_4$ | H | H | 7 | 45 | 2 | 80 |
| **1n** | 3-$NO_2$-$C_6H_4$ | H | H | 7 | 61 | 2 | 82 |
| **1o** | 4-$NO_2$-$C_6H_4$ | H | H | 6 | 49 | 2 | 80 |
| **1p** | 4-Cl-$C_6H_4$ | H | H | 6 | 61 | 3 | 85 |
| **1q** | 4-Me-$C_6H_4$ | H | H | 7 | 58 | 3 | 84 |
| **1r** | 2,3,4-Tri-OMe-$C_6H_2$ | H | H | 9 | 29 | 2 | 74 |
| **1s** | $C_6H_5$ | Br | H | 8 | 62 | 3 | 85 |
| **1t** | 4-OMe-$C_6H_4$ | Br | H | 8 | 64 | 2 | 77 |
| **1u** | 2-$NO_2$-$C_6H_4$ | Br | H | 6 | 47 | 2 | 79 |
| **1v** | 3-$NO_2$-$C_6H_4$ | Br | H | 6 | 60 | 3 | 81 |
| **1w** | 4-$NO_2$-$C_6H_4$ | Br | H | 7 | 55 | 2 | 87 |
| **1x** | 4-Cl-$C_6H_4$ | Br | H | 9 | 65 | 4 | 72 |
| **1y** | 4-Me-$C_6H_4$ | Br | H | 7 | 55 | 3 | 84 |
| **1z** | 2,3,4-Tri-OMe-$C_6H_2$ | Br | H | 7 | 32 | 2 | 73 |
| **1a'** | $C_6H_5$ | Br | Br | 7 | 63 | 4 | 71 |
| **1b'** | 4-OMe-$C_6H_4$ | Br | Br | 9 | 59 | 3 | 75 |
| **1c'** | 2-$NO_2$-$C_6H_4$ | Br | Br | 8 | 45 | 3 | 73 |
| **1d'** | 3-$NO_2$-$C_6H_4$ | Br | Br | 7 | 40 | 3 | 80 |
| **1e'** | 4-$NO_2$-$C_6H_4$ | Br | Br | 7 | 50 | 3 | 76 |
| **1f'** | 4-Cl-$C_6H_4$ | Br | Br | 10 | 52 | 5 | 70 |
| **1g'** | 4-Me-$C_6H_4$ | Br | Br | 7 | 54 | 4 | 81 |
| **1h'** | 2,3,4-Tri-OMe-$C_6H_2$ | Br | Br | 8 | 30 | 3 | 74 |

[a] Step – I: Synthesis of Quinazolinone ring at 455 W. [b] Step – II: Hydrolysis at 140 W. [c] Reaction time is in minutes.[d] Isolated yield after column chromatographic purification is in % .

## Conclusions

In summary, an efficient method for the synthesis of 2-methyl and 2-aryl-substituted 3-(4-aminobenzenesulfonamido)quinazolin-4(3*H*)-one derivatives by optimization of Grimmel's conditions under microwave irradiation has been developed. The results showed that Grimmel's method can not be applied for the synthesis of 2-styryl-substituted quinazolinones as it exclusively forms corresponding benzoxazinone. In addition, a convergent method for the synthesis of quinazolin-4(3*H*)-ones under microwave irradiation has been developed, which can tolerate both styryl and 4-acetamidobenzenesulfonamide groups at 2nd & 3rd positions respectively. This method can be used on a larger scale.[11] The use of even a small amount of pyridine and microwave irradiation can facilitate cyclization of tetramide to corresponding quinazolinone. It also provides an alternative route for the synthesis of various biologically active 3-substituted-2-styrylquinazolin-4(3*H*)-ones.

## Experimental Section

**General.** Column chromatographic separations were carried out on silica gel (60-120 mesh). Progress of the reaction was monitored on alumina supported pre-coated silica gel 60 $F_{254}$ Thin layer chromatography (TLC) plates (E-Merck, India) with Ultraviolet light and $I_2$ vapors as detecting agents followed by spraying with *Draggendorff* reagent. The elemental analyses (C, H and N) were performed with a model Elemental Vario EL analyzer. The $^1$H NMR and $^{13}$C NMR spectra were recorded on a Bruker (400 MHz) instrument using DMSO-$d_6$ as a solvent as well as an internal reference standard. The mass spectra (ESI) were recorded on a Shimadzu LC-MS 2010 eV mass spectrophotometer in acetonitrile. Melting points are uncorrected. All the microwave assisted reactions were carried out at atmospheric pressure using a multimode microwave reactor (Microwave Synthesis System, Model: Cata-R, Catalyst$^{TM}$ Systems, Pune-India) with attachment of glass vessel prolonged by a reflux condenser with constant stirring, whereby microwaves are generated by magnetron at a frequency of 2450 MHz having an output energy range of 140 to 700 Watts, and the temperature was monitored with an external flexible probe.

**General procedure for the synthesis of 4-amino-*N*-(2-alkyl/aryl-4-oxoquinazolin-3(4*H*)-yl)benzenesulfonamide derivatives (1a-1j)**

**Step–I: Synthesis of *N*-(4-(*N*-(4-oxo-2-methyl/aryl substituted quinazolin-3(4*H*)-yl)sulfamoyl)phenyl)acetamides (5a-5j)**

In a two-necked round bottomed flask fitted with a device condenser, *N*-acetylbenzenesulfonyl hydrazide (2 mmol), and appropriate *N*-acylanthranilic acid (2 mmol) were taken in 5 mL THF. To the above stirred mixture, a solution of phosphorus trichloride (2 mmol) in 2 mL THF was added drop-wise, over a period of 15 min. The resulting suspension was then irradiated in

microwave oven for an appropriate time with a power of 350 W (Table 2, Step – I). After cooling to room temperature, the reaction mixture was poured into 20 mL ice-cold water and neutralized with saturated sodium bicarbonate solution. The solid product thus obtained was filtered, washed with distilled water and recrystallized from ethanol.

**Step–II: Hydrolysis of 5a-5j**

**Caution**: All the reactions shown here were performed in an open reflux system. It is not recommended, to perform the reactions in a sealed vessel due to the possibility of generation of high pressure, as the reaction involves the use of HCl.

The product obtained in step – I (**5a-5j**) (1 mmol) was taken in a two-necked round bottomed flask containing 10 mL 50 % HCl solution in 10 mL ethanol. The mixture was then irradiated under microwave for an appropriate time (Table 2, Step – II) with a power of 140 W. The clear solution thus obtained was cooled, diluted with 20 mL distilled water and pH was adjusted to 8 using saturated $NaHCO_3$ solution. The precipitated product was filtered, washed with distilled water and recrystallized from ethanol.

**Note**: It is recommended to use co-solvent such as ethanol in order to avoid bumping of reaction mass during microwave irradiation.

**4-Amino-*N*-(2-methyl-4-oxoquinazolin-3(4*H*)-yl)benzenesulfonamide (1a).** Mp 216-218 °C. $^1$H NMR (400 MHz, DMSO-$d_6$): δ 2.49 (s, 3H), 6.14 (s, 2H), 6.54 (d, *J*=8.8 Hz, 2H), 7.35 (d, *J*=8.8 Hz, 2H), 7.57 (t, *J*=7.6 Hz, 1H), 7.61 (dd, *J*=8.0, 1.2 Hz, 1H), 7.82 (t, *J*=8.0 Hz, 1H), 7.91 (dd, *J*=8.0, 1.2 Hz, 1H), 10.82 (s, 1H). $^{13}$C NMR (100 MHz, DMSO-$d_6$): δ 22.48, 113.06, 121.03, 123.69, 126.80, 127.17, 127.30, 130.20, 135.51, 146.51, 154.19, 157.41, 159.42. MS (ESI) (*m/z*): 330.9 $[M+H]^+$. Anal. Calcd. for $C_{15}H_{14}N_4O_3S$: C, 54.53; H, 4.27; N, 16.96. Found: C, 54.54; H, 4.24; N, 16.91.

**4-Amino-*N*-(6-bromo-2-methyl-4-oxoquinazolin-3(4*H*)-yl)benzenesulfonamide (1b).** Mp 185-188 °C. $^1$H NMR (400 MHz, DMSO-$d_6$): δ 2.51 (s, 3H), 6.01 (s, 2H), 6.60 (d, *J*=8.8 Hz, 2H), 7.35 (d, *J*=8.8 Hz, 2H), 7.57 (dd, *J*=10.4, 2.2 Hz, 1H), 7.51 (d, *J*=10.4 Hz, 1H), 8.31 (d, *J*=2.1, 1H), 10.81 (s, 1H). $^{13}$C NMR (100 MHz, DMSO-$d_6$): δ 22.6, 113.1, 119.8, 123.7, 126.9, 127.2, 123.3, 130.2, 135.5, 156.5, 155.0, 157.3, 159.2. MS (ESI) (*m/z*): 409.2, 411.2 $[M]^+$. Anal. Calcd. for $C_{15}H_{13}BrN_4O_3S$: C, 44.02; H, 3.20; N, 13.69. Found: C, 44.06; H, 3.22; N, 13.60.

**4-Amino-*N*-(6,8-dibromo-2-methyl-4-oxoquinazolin-3(4*H*)-yl)benzenesulfonamide (1c).** Mp 211-212 °C. $^1$H NMR (400 MHz, DMSO-$d_6$): δ 2.55 (s, 3H), 5.89 (s, 2H), 6.56 (d, *J*=8.8 Hz, 2H), 7.35 (d, *J*=8.8 Hz, 2H), 8.19 (d, *J*=1.2 Hz, 1H), 8.51 (d, *J*=1.2, 1H), 10.19 (s, 1H). $^{13}$C NMR (100 MHz, DMSO-$d_6$): δ 21.81, 110.1, 121.7, 125.0, 126.8, 129.1, 130.1, 133.1, 137.2, 152.1, 158.9, 162.2, 163.6. MS (ESI) (*m/z*): 488.3, 490.3, 492.3 $[M]^+$. Anal. Calcd. for $C_{15}H_{12}Br_2N_4O_3S$: C, 36.91; H, 2.48; N, 11.48. Found: C, 36.86; H, 2.53; N, 11.52.

**4-Amino-*N*-(6-nitro-4-oxo-2-phenylquinazolin-3(4*H*)-yl)benzenesulfonamide (1d).** Mp 208-210 °C. $^1$H NMR (400 MHz, DMSO-$d_6$): δ 6.42 (s, 2H), 6.77 (d, *J*=8.4 Hz, 2H), 7.38 (d, *J*=7.6 Hz, 1H), 7.44 (t, *J*=7.6 Hz, 2H), 7.53 (d, *J*=8.4 Hz, 2H), 7.64 (d, *J*=7.6 Hz, 2H), 7.84 (d, *J*=8.4 Hz, 1H), 8.39 (d, *J*=8.4 Hz, 1H), 8.53 (s, 1H), 10.89 (s, 1H). $^{13}$C NMR (100 MHz, DMSO-$d_6$): δ

121.5, 123.0, 123.5, 128.2, 128.6, 128.8, 129.2, 129.5, 130.2, 135.7, 138.0, 155.3, 159.4, 163.5, 167.1. MS (ESI) (*m/z*): 438.2 $[M+H]^+$. Anal. Calcd. for $C_{20}H_{15}N_5O_5S$: C, 54.92; H, 3.46; N, 16.01. Found: C, 54.96; H, 3.42; N, 16.04.

**4-Amino-*N*-(4-oxo-2-phenylquinazolin-3(4*H*)-yl)benzenesulfonamide (1e).** Mp 167-168 °C. $^1$H NMR (400 MHz, DMSO-$d_6$): δ 6.14 (s, 2H), 6.57 (d, *J*=8.4 Hz, 2H), 7.35-7.42 (m, 5H), 7.57-7.61 (m, 3H), 7.69 (t, *J*=7.6 Hz, 1H), 7.75 (d, *J*=8.0 Hz, 1H), 8.21 (d, *J*=7.6 Hz, 1H), 10.81 (s, 1H). $^{13}$C NMR (100 MHz, DMSO-$d_6$): δ 121.1, 122.1, 123.4, 125.9, 125.2, 127.8, 129.1, 130.1, 131.1, 132.2, 136.4, 139.3, 157.2, 160.3, 161.9, 163.7. MS (ESI) (*m/z*): 393.5 $[M+H]^+$. Anal. Calcd. for $C_{20}H_{16}N_4O_3S$: C, 61.21; H, 4.11; N, 14.28. Found: C, 61.18; H, 4.14; N, 14.32.

**4-Amino-*N*-(6-bromo-4-oxo-2-phenylquinazolin-3(4*H*)-yl)benzenesulfonamide (1f).** Mp 213-215 °C. $^1$H NMR (400 MHz, DMSO-$d_6$): δ 6.12 (s, 2H), 6.58 (d, *J*=8.4 Hz, 2H), 7.36-7.43 (m, 5H), 7.62 (d, *J*=8.0 Hz, 2H), 7.69 (d, *J*=7.6 Hz, 1H), 7.82 (d, *J*=7.6 Hz, 1H), 8.24 (s, 1H), 10.81 (s, 1H). $^{13}$C NMR (100 MHz, DMSO-$d_6$): δ 120.6, 125.5, 125.6, 125.9, 127.8, 130.1, 131.6, 131.9, 132.5, 135.5, 136.3, 137.8, 157.1, 157.2, 159.4, 165.8. MS (ESI) (*m/z*): 471.2, 473.2 $[M]^+$. Anal. Calcd. for $C_{20}H_{15}BrN_4O_3S$: C, 50.97; H, 3.21; N, 11.89. Found: C, 50.94; H, 3.25; N, 11.93.

**4-Amino-*N*-(6,8-dibromo-4-oxo-2-phenylquinazolin-3(4*H*)-yl)benzenesulfonamide (1g).** Mp 220-221 °C. $^1$H NMR (400 MHz, DMSO-$d_6$): δ 6.11 (s, 2H), 6.59 (d, *J*=8.4 Hz, 2H), 7.36-7.44 (m, 5H), 7.63 (d, *J*=8.4 Hz, 2H), 8.27 (s, 1H), 8.39 (s, 1H), 10.85 (s, 1H). $^{13}$C NMR (100 MHz, DMSO-$d_6$): δ 117.2, 121.1, 125.1, 125.9, 128.3, 129.0, 131.1, 131.3, 131.7, 132.4, 135.3, 138.1, 158.1, 160.1, 161.3, 165.8. MS (ESI) (*m/z*): 548.3, 550.3, 552.3 $[M]^+$. Anal. Calcd. for $C_{20}H_{14}Br_2N_4O_3S$: C, 43.66; H, 2.56; N, 10.18. Found: C, 43.62; H, 2.58; N, 10.19.

**4-Amino-*N*-[2-(4-chlorophenyl)-4-oxoquinazolin-3(4*H*)-yl]benzenesulfonamide (1h).** Mp 176-178 °C. $^1$H NMR (400 MHz, DMSO-$d_6$): δ 6.11 (s, 2H), 6.50 (d, *J*=8.4 Hz, 2H), 7.52-7.55 (m, 3H), 7.63-7.68 (m, 3H), 7.71 (d, *J*=7.6 Hz, 1H), 7.89 (d, *J*=8.0 Hz, 2H), 8.15 (d, *J*=7.2 Hz, 1H), 10.85 (s, 1H). $^{13}$C NMR (100 MHz, DMSO-$d_6$): δ 120.2, 122.8, 123.7, 126.8, 127.3, 127.9, 129.8, 130.8, 131.2, 131.2, 136.9, 137.8, 155.8, 159.1, 162.1, 168.2. MS (ESI) (*m/z*): 426.8, 428.8 $[M]^+$. Anal. Calcd. for $C_{20}H_{15}ClN_4O_3S$: C, 56.27; H, 3.54; N, 13.12. Found: C, 56.32; H, 3.52; N, 13.10.

**4-Amino-*N*-[6-bromo-2-(4-chlorophenyl)-4-oxoquinazolin-3(4*H*)-yl]benzene-sulfonamide (1i).** Mp 188-189 °C. $^1$H NMR (400 MHz, DMSO-$d_6$): δ 6.12 (s, 2H), 6.51 (d, *J*=8.4 Hz, 2H), 7.55 (d, *J*=8.4 Hz, 2H), 7.65-7.68 (m, 3H), 7.80 (d, *J*=7.6 Hz, 1H), 7.93 (d, *J*=8.4 Hz, 2H), 8.17 (s, 1H), 10.79 (s, 1H). $^{13}$C NMR (100 MHz, DMSO-$d_6$): δ 120.3 122.5, 125.2, 129.0, 130.1, 130.5, 131.8, 132.8, 133.0, 135.8, 137.8, 138.1, 158.7, 160.1, 162.1, 168.0. MS (ESI) (*m/z*): 503.9, 505.9, 507.9 $[M]^+$. Anal. Calcd. for $C_{20}H_{14}BrClN_4O_3S$: C, 47.49; H, 2.79; N, 11.08. Found: C, 47.52; H, 2.83; N, 11.02.

**4-Amino-*N*-[6,8-dibromo-2-(4-chlorophenyl)-4-oxoquinazolin-3(4*H*)-yl]benzene sulfonamide (1j).** Mp 182-185 °C. $^1$H NMR (400 MHz, DMSO-$d_6$): δ 6.15 (s, 2H), 6.52 (d, *J*=8.4 Hz, 2H), 7.56 (d, *J*=8.4 Hz, 2H), 7.69 (d, *J*=8.2 Hz, 2H), 7.96 (d, *J*=8.2 Hz, 2H), 8.21 (d, *J*=2.4 Hz, 1H), 8.55 (d, *J*=2.4 Hz, 1H), 11.02 (s, 1H). $^{13}$C NMR (100 MHz, DMSO-$d_6$): δ 118.1,

122.5, 123.5, 126.2, 128.1, 129.2, 130.5, 130.8, 133.1, 137.0, 137.3, 138.2, 159.5, 160.2, 162.6, 163.3. MS (ESI) (*m/z*): 582.6, 584.6, 586.6, 588.6 $[M]^+$. Anal. Calcd. for $C_{20}H_{13}Br_2ClN_4O_3S$: C, 41.09; H, 2.24; N, 9.58. Found: C, 41.12; H, 2.27; N, 9.61.

**General experimental procedure for the synthesis of (*E*)-4-amino-*N*-(4-oxo-2-substituted styrylquinazolin-3(4*H*)-yl)benzenesulfonamide (1k-1h')**

**Step–I: Synthesis of (*E*)-*N*-(4-(*N*-(4-oxo-2-styryl-substituted quinazolin-3(4*H*)-yl)sulfamoyl)phenyl)acetamide (12k-h')**

The benzoxazinone (**6k-h'**) (2 mmol) and 4-acetamidobenzenesulfonyl hydrazide (**4**) (2.6 mmol) were taken in a solution of DMF (0.5 mL) and pyridine (0.4 mmol) contained in a two-neck round bottomed flask fitted with a device condenser. The mixture was then heated under microwave irradiation at 455 W for an appropriate time (Table 4, Step – I). After cooling, the reaction mass was dissolved in ethyl acetate (40 mL) and washed with distilled water (20 mL), dil. HCl (2 X 20 mL), aq. $NaHCO_3$ (2 X 20 mL) and distilled water (20 mL) sequentially by liquid–liquid extraction. The organic layer was dried and the resulting crude product was further purified by column chromatography.

**Step–II: Hydrolysis of 12k-h'.**

**Caution**: All the reactions shown here were performed in an open reflux system. It is not recommended to perform the reactions in a sealed vessel due to the possibility of generation of high pressure, as the reaction involves the use of HCl.

The product obtained in step – I (**12k-h'**) (1 mmol) was taken in a two-necked round bottomed flask containing 50 % HCl solution (10 mL) and ethanol (10 mL). The mixture was heated under microwave irradiation at 140 W for an appropriate time (Table 4, Step – II). After cooling to room temperature, the reaction mixture was filtered, diluted with distilled water (100 mL) and neutralized with saturated $NaHCO_3$ solution. The precipitated product was filtered and recrystallized from ethanol.

**Note**: It is recommended to use co-solvent such as ethanol in order to avoid bumping of reaction mass during microwave irradiation.

**4-Amino-*N*-(4-oxo-2-styrylquinazolin-3(4*H*)-yl)benzenesulfonamide (1k).** Mp 232-235 °C. $^1$H NMR (400 MHz, DMSO-$d_6$): δ 6.15 (s, 2H), 6.56 (d, *J*=8.4 Hz, 2H), 6.64 (d, *J*=15.6 Hz, 1H), 7.19 (t, *J*=7.6, 1H), 7.44-7.81 (m, 10H), 8.01 (dd, *J*=8, 1.2 Hz, 1H), 10.83 (s, 1H). $^{13}$C NMR (100 MHz, DMSO-$d_6$): δ 112.11, 119.88, 122.24, 124.19, 126.64, 127.63, 127.98, 128.05, 128.13, 128.56, 130.53, 132.86, 136.40, 138.86, 146.25, 147.25, 153.64, 160.32. MS (ESI) (*m/z*): 419.5 $[M+H]^+$. Anal. Calcd. for $C_{22}H_{18}N_4O_3S$: C, 63.14; H, 4.34; N, 13.39. Found: C, 62.96; H, 4.29; N, 13.46.

**4-Amino-*N*-(2-(4-methoxystyryl)-4-oxoquinazolin-3(4*H*)-yl)benzenesulfonamide (1l).** Mp 252-256 °C. $^1$H NMR (400 MHz, DMSO-$d_6$): δ 3.91 (s, 3H), 6.03 (s, 2H), 6.54 (d, *J*=8.4 Hz, 2H), 6.58 (d, *J*=16 Hz, 1H), 6.75 (d, *J*=8.8, 2H), 7.17 (t, *J*=8 Hz, 1H), 7.52 (d, *J*=8.4 Hz, 2H), 7.56-7.60 (m, 3H), 7.71 (d, *J*=16 Hz, 1H), 7.78 (t, *J*=7.6, 1H), 8.25 (dd, *J*=8, 1.2 Hz, 1H), 11.23

(s, 1H). $^{13}$C NMR (100 MHz, DMSO-$d_6$): δ 57.04, 112.11, 114.06, 120.79, 122.24, 124.19, 126.49, 127.63, 128.05, 128.56, 128.76, 130.53, 136.40, 137.63, 146.25, 147.25, 153.64, 160.22, 160.32. MS (m/z): 449.5 $[M+H]^+$. Anal. Calcd. for $C_{23}H_{20}N_4O_4S$: C, 61.59; H, 4.49; N, 12.49. Found: C, 61.71; H, 4.55; N, 12.38.

**4-Amino-*N*-(2-(2-nitrostyryl)-4-oxoquinazolin-3(4*H*)-yl)benzenesulfonamide (1m).** Mp 289-291 °C. $^1$H NMR (400 MHz, DMSO-$d_6$): δ 6.18 (s, 2H), 6.58 (d, *J*=11.2 Hz, 2H), 7.15 (d, *J*=15.6 Hz, 1H), 7.51-7.57 (m, 2H), 7.63-7.75 (m, 5H), 7.89 (t, *J*=7.2 Hz, 1H), 8.02-8.14 (m, 3H), 11.42 (s, 1H). $^{13}$C NMR (100 MHz, DMSO-$d_6$): δ 112.11, 122.24, 122.66, 124.19, 127.14, 127.22, 127.63, 128.05, 128.56, 129.07, 130.14, 130.15, 130.53, 131.62, 136.40, 146.25, 147.25, 147.98, 153.64, 160.32. MS (ESI) (*m/z*): 464.4 $[M+H]^+$. Anal. Calcd. for $C_{22}H_{17}N_5O_5S$: C, 57.01; H, 3.70; N, 15.11. Found: C, 56.88; H, 3.66; N, 15.00.

**4-Amino-*N*-(2-(3-nitrostyryl)-4-oxoquinazolin-3(4*H*)-yl)benzenesulfonamide (1n).** Mp 275-278 °C. $^1$H NMR (400 MHz, DMSO-$d_6$): δ 6.54 (s, 2H), 6.71 (d, *J*=8.4 Hz, 2H), 7.22 (d, *J*=16.4 Hz, 1H), 7.53-7.66 (m, 4H), 7.72-7.84 (m, 3H), 8.11-8.33 (m, 3H), 8.48 (s, 1H), 11.46 (s, 1H). $^{13}$C NMR (100 MHz, DMSO-$d_6$): δ 112.11, 119.53, 121.83, 122.24, 124.19, 124.32, 125.29, 127.63, 128.05, 128.56, 130.53, 133.78, 136.07, 136.40, 139.41, 146.25, 146.92, 147.25, 153.64, 160.32. MS (ESI) (*m/z*): 464.3 $[M+H]^+$. Anal. Calcd. for $C_{22}H_{17}N_5O_5S$: C, 57.01; H, 3.70; N, 15.11. Found: C, 57.15; H, 3.75; N, 15.18.

**4-Amino-*N*-(2-(4-nitrostyryl)-4-oxoquinazolin-3(4*H*)-yl)benzenesulfonamide (1o).** Mp 321-326 (d) °C. $^1$H NMR (400 MHz, DMSO-$d_6$): δ 6.43 (s, 2H), 6.69 (d, *J*=8.4 Hz, 2H), 7.14 (d, *J*=15.6 Hz, 1H), 7.54-7.69 (m, 5H), 7.88 (d, *J*=8.8 Hz, 2H), 7.99-8.13 (m, 2H), 8.24 (d, *J*=8.8 Hz, 2H), 11.50 (s, 1H). $^{13}$C NMR (100 MHz, DMSO-$d_6$): δ 112.11, 121.26, 122.24, 123.70, 124.19, 127.63, 128.05, 128.27, 128.56, 130.53, 136.40, 137.87, 139.96, 146.25, 147.25, 148.28, 153.64, 160.32. MS (ESI) (*m/z*): 464.8 $[M+H]^+$. Anal. Calcd. for $C_{22}H_{17}N_5O_5S$: C, 57.01; H, 3.70; N, 15.11. Found: C, 57.16; H, 3.67; N, 15.03.

**4-Amino-*N*-(2-(4-chlorostyryl)-4-oxoquinazolin-3(4*H*)-yl)benzenesulfonamide (1p).** Mp 312-315 °C. $^1$H NMR (400 MHz, DMSO-$d_6$): δ 6.38 (s, 2H), 6.58 (d, *J*=8.4 Hz, 2H), 6.91 (d, *J*=16 Hz, 1H), 7.18 (dt, *J*=7.6, 1.3 Hz, 1H), 7.53-7.61 (m, 6H), 7.77-7.80 (m, 2H), 8.32 (dd, *J*=7.6 Hz, 2H), 11.38 (s, 1H). $^{13}$C NMR (100 MHz, DMSO-$d_6$): δ 112.11, 121.42, 122.24, 124.19, 127.33, 127.63, 128.05, 128.56, 129.68, 130.53, 132.70, 134.47, 136.40, 137.60, 146.25, 147.25, 153.64, 160.32. MS (ESI) (*m/z*): 452.8, 454.8 $[M]^+$. Anal. Calcd. for $C_{22}H_{17}ClN_4O_3S$: C, 58.34; H, 3.78; N, 12.37. Found: C, 58.21; H, 3.82; N, 12.43.

**4-Amino-*N*-(2-(4-methylstyryl)-4-oxoquinazolin-3(4*H*)-yl)benzenesulfonamide (1q).** Mp 269-272 °C. $^1$H NMR (400 MHz, DMSO-$d_6$): δ 2.36 (s, 3H), 6.11 (s, 2H), 6.55 (d, *J*=8.4 Hz, 2H), 6.69 (d, *J*=16 Hz, 1H), 7.19 (t, *J*=7.6, 1H), 7.32-7.40 (m, 4H), 7.62 (dd, *J*=7.6, 1.3 Hz, 1H), 7.71-7.80 (m, 4H), 8.02 (d, *J*=7.6 Hz, 1H), 10.87 (s, 1H). $^{13}$C NMR (100 MHz, DMSO-$d_6$): δ 20.48, 112.11, 120.62, 122.24, 124.19, 127.63, 127.73, 127.86, 128.05, 128.56, 130.53, 132.38, 136.40, 136.86, 141.55, 146.25, 147.25, 153.64, 160.32. MS (ESI) (*m/z*): 433.3 $[M+H]^+$. Anal. Calcd. for $C_{23}H_{20}N_4O_3S$: C, 63.87; H, 4.66; N, 12.95. Found: C, 64.02; H, 4.71; N, 12.88.

**4-Amino-*N*-(4-oxo-2-(3,4,5-trimethoxystyryl)quinazolin-3(4*H*)-yl)benzenesulfonamide (1r).** Mp 219-221 °C. $^1$H NMR (400 MHz, DMSO-$d_6$): δ 3.88 (s, 3H), 3.90 (s, 6H), 6.07 (s, 2H), 6.52-6.56 (m, 3H), 6.92 (s, 2H), 7.04 (t, *J*=7.6 Hz, 1H), 7.47-7.50 (m, 3H), 7.6 (t, *J*=7.6 Hz, 1H), 7.81 (d, *J*=16 Hz, 1H), 8.18 (d, *J*=7.6 Hz, 1H), 11.25 (s, 1H). $^{13}$C NMR (100 MHz, DMSO-$d_6$): δ 61.10, 66.28, 103.68, 112.11, 119.50, 122.24, 124.19, 127.63, 128.05, 128.56, 130.21, 130.53, 136.40, 141.46, 141.56, 146.25, 147.25, 152.57, 153.64, 160.32. MS (ESI) (*m/z*): 509.8 $[M+H]^+$. Anal. Calcd. for $C_{25}H_{24}N_4O_6S$: C, 59.04; H, 4.76; N, 11.02. Found: C, 58.91; H, 4.82; N, 11.11.

**4-Amino-*N*-(6-bromo-4-oxo-2-styrylquinazolin-3(4*H*)-yl)benzenesulfonamide (1s).** Mp 274-277 °C. $^1$H NMR (400 MHz, DMSO-$d_6$): δ 6.27 (s, 2H), 6.61 (d, *J*=8.4 Hz, 2H), 6.65 (d, *J*=15.6 Hz, 1H), 7.45- 7.65 (m, 8H), 7.79-7.84 (m, 2H), 8.15 (s, 1H), 11.12 (s, 1H). $^{13}$C NMR (100 MHz, DMSO-$d_6$): δ 112.11, 119.19, 119.88, 123.44, 123.91, 124.19, 126.64, 127.98, 128.13, 130.53, 131.73, 132.86, 138.86, 139.28, 147.23, 147.49, 153.64, 159.41. MS (ESI) (*m/z*): 496.3, 498.3 $[M]^+$. Anal. Calcd. for $C_{22}H_{17}BrN_4O_3S$: C, 53.13; H, 3.45; N, 11.26. Found: C, 53.00; H, 3.49; N, 11.31.

**4-Amino-*N*-(6-bromo-2-(4-methoxystyryl)-4-oxoquinazolin-3(4*H*)-yl)benzenesulfonamide (1t).** Mp 290-292 °C. $^1$H NMR (400 MHz, DMSO-$d_6$): δ 3.93 (s, 3H), 6.30 (s, 2H), 6.59 (d, *J*=8.4 Hz, 2H), 6.72 (d, *J*=8.8 Hz, 2H), 6.77 (d, *J*=16 Hz, 1H), 7.44 (d, *J*=8.4 Hz, 2H), 7.55 (d, *J*=8.8 Hz, 2H), 7.61-7.65 (m, 2H), 7.80 (d, *J*=8 Hz, 1H), 8.26 (s, 1H), 11.35 (s, 1H). $^{13}$C NMR (100 MHz, DMSO-$d_6$): δ 57.04, 112.11, 114.06, 119.19, 120.79, 123.44, 123.91, 124.19, 126.49, 128.76, 130.53, 131.73, 137.63, 139.28, 147.23, 147.49, 153.64, 159.41, 160.22. MS (ESI) (*m/z*): 526.6, 528.6 $[M]^+$. Anal. Calcd. for $C_{23}H_{19}BrN_4O_4S$: C, 52.38; H, 3.63; N, 10.62. Found: C, 52.50; H, 3.60; N, 12.71.

**4-Amino-*N*-(6-bromo-2-(2-nitrostyryl)-4-oxoquinazolin-3(4*H*)-yl)benzenesulfonamide (1u).** Mp 329-334 (d) °C. $^1$H NMR (400 MHz, DMSO-$d_6$): δ 6.49 (s, 2H), 6.69 (d, *J*=8.4 Hz, 2H), 7.18 (d, *J*=15.6 Hz, 1H), 7.55 (d, *J*=8.4 Hz, 2H), 7.71-7.74 (m, 2H), 7.86-7.97 (m, 4H), 8.08- 8.12 (m, 2H), 11.43 (s, 1H). $^{13}$C NMR (100 MHz, DMSO-$d_6$): δ 112.11, 119.19, 122.66, 123.44, 123.91, 124.19, 127.14, 127.22, 129.07, 130.14, 130.15, 130.53, 131.62, 131.73, 139.28, 147.23, 147.49, 147.98, 153.64, 159.41. MS (ESI) (*m/z*): 542.6, 544.6 $[M]^+$. Anal. Calcd. for $C_{22}H_{16}BrN_5O_5S$: C, 48.72; H, 2.97; N, 12.91. Found: C, 48.88; H, 3.02; N, 13.01.

**4-Amino-*N*-(6-bromo-2-(3-nitrostyryl)-4-oxoquinazolin-3(4*H*)-yl)benzenesulfonamide (1v).** Mp 312-317 (d) °C. $^1$H NMR (400 MHz, DMSO-$d_6$): δ 6.56 (s, 2H), 6.72 (d, *J*=8.4 Hz, 2H), 7.24 (d, *J*=16.4 Hz, 1H), 7.56 (d, *J*=8.4 Hz, 2H), 7.77-7.80 (m, 2H), 7.94-8.00 (m, 2H), 8.11 (s, 1H), 8.24=8.27 (m, 2H), 8.50 (s, 1H), 11.47 (s, 1H). $^{13}$C NMR (100 MHz, DMSO-$d_6$): δ 112.11, 119.19, 119.53, 121.83, 123.44, 123.91, 124.19, 124.32, 125.29, 130.53, 131.73, 133.78, 136.07, 139.28, 139.41, 146.92, 147.23, 147.49, 153.64, 159.41. MS (ESI) (*m/z*): 542.2, 544.2 $[M]^+$. Anal. Calcd. for $C_{22}H_{16}BrN_5O_5S$: C, 48.72; H, 2.97; N, 12.91. Found: C, 48.61; H, 2.93; N, 12.84.

**4-Amino-*N*-(6-bromo-2-(4-nitrostyryl)-4-oxoquinazolin-3(4*H*)-yl)benzenesulfonamide (1w).** Mp > 350 °C. $^1$H NMR (400 MHz, DMSO-$d_6$): δ 6.45 (s, 2H), 6.70 (d, *J*=8.4 Hz, 2H), 7.16 (d, *J*=16 Hz, 1H), 7.54 (d, *J*=8.4 Hz, 2H), 7.72 (d, *J*=7.6 Hz, 1H), 7.86-7.93 (m, 4H), 8.09 (s, 1H),

8.35 (d, *J*=8.8 Hz, 2H), 11.51 (s, 1H). $^{13}$C NMR (100 MHz, DMSO-$d_6$): δ 112.11, 119.19, 121.26, 123.44, 123.70, 123.91, 124.19, 128.27, 130.53, 131.73, 137.87, 139.28, 139.96, 147.23, 147.49, 148.28, 153.64, 159.41. MS (ESI) (*m/z*): 542.5, 544.5 $[M]^+$. Anal. Calcd. for $C_{22}H_{16}BrN_5O_5S$: C, 48.72; H, 2.97; N, 12.91. Found: C, 48.90; H, 2.99; N, 12.97.

**4-Amino-*N*-(6-bromo-2-(4-chlorostyryl)-4-oxoquinazolin-3(4*H*)-yl)benzene-sulfonamide (1x).** Mp >350 °C. $^1$H NMR (400 MHz, DMSO-$d_6$): δ 6.39 (s, 2H), 6.59 (d, *J*=8.4 Hz, 2H), 6.96 (d, *J*=16 Hz, 1H), 7.56-7.63 (m, 5H), 7.74 (d, *J*=8, 1H), 7.74 (d, *J*=8.4, 2H), 7.87 (d, *J*=8, 1H), 8.37 (s, 1H), 11.44 (s, 1H). $^{13}$C NMR (100 MHz, DMSO-$d_6$): δ 112.11, 119.19, 121.42, 123.44, 123.91, 124.19, 127.33, 129.68, 130.53, 131.73, 132.70, 134.47, 137.60, 139.28, 147.23, 147.49, 153.64, 159.41. MS (ESI) (*m/z*): 529.7 531.7, 533.7 $[M]^+$. Anal. Calcd. for $C_{22}H_{16}BrClN_4O_3S$: C, 49.69; H, 3.03; N, 10.54. Found: C, 49.80; H, 2.98; N, 10.61.

**4-Amino-*N*-(6-bromo-2-(4-methylstyryl)-4-oxoquinazolin-3(4*H*)-yl)benzene-sulfonamide (1y).** Mp 311-313 °C. $^1$H NMR (400 MHz, DMSO-$d_6$): δ 2.36 (s, 3H), 6.13 (s, 2H), 6.56 (d, *J*=8.4 Hz, 2H), 6.71 (d, *J*=16 Hz, 1H), 7.35 (d, *J*=8, 2H), 7.41 (d, *J*=8.4 Hz, 2H), 7.68-7.73 (m, 3H), 7.79 (d, *J*=16 Hz, 1H), 7.84 (d, *J*= 7.6 Hz, 1H), 8.14 (s, 1H), 10.98 (s, 1H). $^{13}$C NMR (100 MHz, DMSO-$d_6$): δ 20.48, 112.11, 119.19, 120.62, 123.44, 123.91, 124.19, 127.73, 127.86, 130.53, 131.73, 132.38, 136.86, 139.28, 141.54, 147.23, 147.49, 153.64, 159.41. MS (ESI) (*m/z*): 511.6, 513.6 $[M]^+$. Anal. Calcd. for $C_{23}H_{19}BrN_4O_3S$: C, 54.02; H, 3.74; N, 10.96. Found: C, 53.89; H, 3.78; N, 11.05.

**4-Amino-*N*-(6-bromo-2-(3,4,5-trimethoxystyryl)-4-oxoquinazolin-3(4*H*)-yl)benzene-sulfonamide (1z).** Mp 258-260 °C. $^1$H NMR (400 MHz, DMSO-$d_6$): δ 3.87 (s, 3H), 3.89 (s, 6H), 6.10 (s, 2H), 6.53-6.57 (m, 3H), 6.94 (s, 2H), 7.51 (d, *J*=8.4 Hz, 2H), 7.56 (d, *J*=8 Hz, 1H), 7.79-7.84 (m, 2H), 8.25 (s, 1H), 11.32 (s, 1H). $^{13}$C NMR (100 MHz, DMSO-$d_6$): δ 61.10, 66.28, 103.68, 112.11, 119.19, 119.50, 123.44, 123.91, 124.19, 130.21, 130.53, 131.73, 139.28, 141.46, 141.56, 147.23, 147.49, 152.57, 153.64, 159.41. MS (ESI) (*m/z*): 587.2, 589.2 $[M]^+$. Anal. Calcd. for $C_{25}H_{23}BrN_4O_6S$: C, 51.11; H, 3.95; N, 9.54. Found: C, 51.00; H, 4.01; N, 9.43.

**4-Amino-*N*-(6,8-dibromo-4-oxo-2-styrylquinazolin-3(4*H*)-yl)benzene-sulfonamide (1a').** Mp 281-283 (d) °C. $^1$H NMR (400 MHz, DMSO-$d_6$): δ 6.29 (s, 2H), 6.58-6.63 (m, 3H), 7.41-7.45(m, 5H), 7.58 (dd, *J*=7.6, 1.2 Hz, 2H), 7.96 (d, *J*=16 Hz, 1H), 8.21 (d, *J*=2 Hz, 1H), 8.37 (d, *J*=2 Hz, 1H), 11.15 (s, 1H). $^{13}$C NMR (100 MHz, DMSO-$d_6$): δ 112.11, 118.58, 119.88, 122.69, 124.19, 125.06, 126.62, 127.97, 128.13, 130.53, 131.82, 132.89, 138.84, 142.46, 152.86, 153.64, 159.36, 159.93. MS (ESI) (*m/z*): 574.4, 576.4, 578.4 $[M]^+$. Anal. Calcd. for $C_{22}H_{16}Br_2N_4O_3S$: C, 45.85; H, 2.80; N, 9.72. Found: C, 46.02; H, 2.84; N, 9.63.

**4-Amino-*N*-(6,8-dibromo-2-(4-methoxystyryl)-4-oxoquinazolin-3(4*H*)-yl)benzene-sulfon-amide (1b').** Mp 304-309 (d) °C. $^1$H NMR (400 MHz, DMSO-$d_6$): δ 3.91 (s, 3H), 6.32 (s, 2H), 6.63 (d, *J*=8.4 Hz, 2H), 6.70-6.74 (m, 3H), 7.47 (d, *J*=8.4 Hz, 2H), 7.58 (d, *J*=8.8, 2H), 7.88 (d, *J*=16.4 Hz, 1H), 8.18 (d, *J*=2 Hz, 1H), 8.32 (d, *J*=2 Hz, 1H), 11.37 (s, 1H). $^{13}$C NMR (100 MHz, DMSO-$d_6$): δ 57.04, 112.11, 114.06, 118.58, 120.79, 122.69, 124.19, 125.06, 126.49, 128.76, 130.53, 131.82, 137.63, 142.46, 152.86, 153.64, 159.36, 159.93, 160.22. MS (ESI) (*m/z*): 604.1,

606.1, 608.1 $[M]^+$. Anal. Calcd. for $C_{23}H_{18}Br_2N_4O_4S$: C, 45.56; H, 2.99; N, 9.24. Found: C, 45.72; H, 2.95; N, 9.16.

**4-Amino-*N*-(6,8-dibromo-2-(2-nitrostyryl)-4-oxoquinazolin-3(4*H*)-yl)benzene-sulfonamide (1c').** Mp 339-345 (d) °C. $^1$H NMR (400 MHz, DMSO-$d_6$): δ 6.51 (s, 2H), 6.72 (d, *J*=8.4 Hz, 2H), 7.13 (d, *J*=15.6 Hz, 1H), 7.58 (d, *J*=8.4 Hz, 2H), 7.74 (t, *J*=7.6 Hz, 1H), 7.89 (t, *J*=7.6 Hz, 1H), 8.00-8.05 (m, 2H), 8.13 (d, *J*=8 Hz, 1H), 8.24 (d, *J*=2 Hz, 1H), 8.42 (d, *J*=2 Hz, 1H), 11.44 (s, 1H). $^{13}$C NMR (100 MHz, DMSO-$d_6$): δ 112.11, 118.58, 122.66, 122.69, 124.19, 125.06, 127.14, 127.22, 129.07, 130.14, 130.15, 130.53, 131.62, 131.82, 142.46, 147.98, 152.86, 153.64, 159.36, 159.93. MS (ESI) (*m/z*): 619.5, 621.5, 623.5 $[M]^+$. Anal. Calcd. for $C_{22}H_{15}Br_2N_5O_5S$: C, 42.53; H, 2.43; N, 11.27. Found: C, 42.65; H, 2.39; N, 11.18.

**4-Amino-*N*-(6,8-dibromo-2-(3-nitrostyryl)-4-oxoquinazolin-3(4*H*)-yl)benzene-sulfonamide (1d').** Mp 321-326 (d) °C. $^1$H NMR (400 MHz, DMSO-$d_6$): δ 6.58 (s, 2H), 6.76 (d, *J*=8.4 Hz, 2H), 7.19 (d, *J*=16 Hz, 1H), 7.59 (d, *J*=8.8 Hz, 2H), 7.79 (d, *J*=7.2 Hz, 1H), 8.11 (d, *J*=16 Hz, 1H), 8.27-8.32 (m, 3H), 8.45 (d, *J*=2 Hz, 1H), 8.57 (s, 1H), 11.51(s, 1H). $^{13}$C NMR (100 MHz, DMSO-$d_6$): δ 112.11, 118.58, 119.53, 121.83, 122.69, 124.19, 124.32, 125.06, 125.29, 130.53, 131.82, 133.78, 136.07, 139.41, 142.46, 146.92, 152.86, 153.64, 159.36, 159.93. MS (ESI) (*m/z*): 619.2, 621.2, 623.2 $[M]^+$. Anal. Calcd. for $C_{22}H_{15}Br_2N_5O_5S$: C, 42.53; H, 2.43; N, 11.27. Found: C, 42.42; H, 2.46; N, 11.41.

**4-Amino-*N*-(6,8-dibromo-2-(4-nitrostyryl)-4-oxoquinazolin-3(4*H*)-yl)benzene-sulfonamide (1e').** Mp >350 °C. $^1$H NMR (400 MHz, DMSO-$d_6$): δ 6.47 (s, 2H), 6.73 (d, *J*=8.4 Hz, 2H), 7.11 (d, *J*=15.6 Hz, 1H), 7.57 (d, *J*=8.4 Hz, 2H), 7.99-8.04 (m, 3H), 8.23 (d, *J*=2 Hz, 1H), 8.36 (d, *J*=7.6 Hz, 2H), 8.41 (d, *J*=2 Hz, 1H), 11.53(s, 1H). $^{13}$C NMR (100 MHz, DMSO-$d_6$): δ 112.11, 118.58, 121.26, 122.69, 123.70, 124.19, 125.06, 128.27, 130.53, 131.82, 137.87, 139.96, 142.46, 148.28, 152.86, 153.64, 159.36, 159.93. MS (ESI) (*m/z*): 619.5, 621.5, 623.2 $[M]^+$. Anal. Calcd. for $C_{22}H_{15}Br_2N_5O_5S$: C, 42.53; H, 2.43; N, 11.27. Found: C, 42.60; H, 2.38; N, 11.43.

**4-Amino-*N*-(6,8-dibromo-2-(4-chlorostyryl)-4-oxoquinazolin-3(4*H*)-yl)benzenesulfonamide (1f').** Mp >350 °C. $^1$H NMR (400 MHz, DMSO-$d_6$): δ 6.41 (s, 2H), 6.63 (d, *J*=8.4 Hz, 2H), 6.89 (d, *J*=16 Hz, 1H), 7.59-7.62 (m, 4H), 7.78 (d, *J*=16 Hz, 1H), 7.89 (d, *J*=8.8 Hz, 2H), 8.20 (d, *J*=2 Hz, 1H), 8.36 (d, *J*=2 Hz, 1H), 11.47(s, 1H). $^{13}$C NMR (100 MHz, DMSO-$d_6$): δ 112.11, 118.58, 121.42, 122.69, 124.19, 125.06, 127.33, 129.68, 130.53, 131.82, 132.70, 134.47, 137.61, 142.46, 152.86, 153.64, 159.36, 159.93. MS (ESI) (*m/z*): 608.6, 610.6, 612.6, 614.6 $[M]^+$. Anal. Calcd. for $C_{22}H_{15}Br_2ClN_4O_3S$: C, 43.27; H, 2.48; N, 9.17. Found: C, 43.11; H, 2.51; N, 9.26.

**4-Amino-*N*-(6,8-dibromo-2-(4-methylstyryl)-4-oxoquinazolin-3(4*H*)-yl)benzene-sulfonamide (1g').** Mp 316-323 (d) °C. $^1$H NMR (400 MHz, DMSO-$d_6$): δ 2.39 (s, 3H), 6.15 (s, 2H), 6.59 (d, *J*=8.4 Hz, 2H), 6.66 (d, *J*=16 Hz, 1H), 7.37 (d, *J*=8.4 Hz, 2H), 7.45 (d, *J*=8.4 Hz, 2H), 7.79 (d, *J*=8.4 Hz, 2H), 7.94 (d, *J*=16 Hz, 1H), 8.19 (d, *J*=2 Hz, 1H), 8.37 (d, *J*=2 Hz, 1H), 10.99 (s, 1H). $^{13}$C NMR (100 MHz, DMSO-$d_6$): δ 20.48, 112.11, 118.58, 120.62, 122.69, 124.19, 125.06, 127.73, 127.86, 130.53, 131.82, 132.38, 136.86, 141.55, 142.46, 152.86, 153.64, 159.36, 159.93. MS (ESI) (*m/z*): 588.1, 590.1, 592.1 $[M]^+$. Anal. Calcd. for $C_{23}H_{18}Br_2N_4O_3S$: C, 46.80; H, 3.07; N, 9.49. Found: C, 46.67; H, 3.13; N, 9.62.

**4-Amino-*N*-(6,8-dibromo-4-oxo-2-(3,4,5-trimethoxystyryl)quinazolin-3(4*H*)-yl)benzene-sulfonamide (1h').** Mp 273-277 (d) °C. $^1$H NMR (400 MHz, DMSO-$d_6$): δ 3.88 (s, 3H), 3.89 (s, 6H), 6.12 (s, 2H), 6.61 (d, *J*=8.4 Hz, 2H), 6.45 (d, *J*=16.4 Hz, 1H), 7.00 (s, 2H), 7.54 (d, *J*=8.4 Hz, 2H), 7.99 (d, *J*=16.4 Hz, 1H), 8.04 (d, *J*=2 Hz, 1H), 8.28 (d, *J*=2 Hz, 1H),11.35 (s, 1H). $^{13}$C NMR (100 MHz, DMSO-$d_6$): δ 61.10, 66.28, 103.68, 112.11, 114.46, 114.56, 118.58, 119.50, 122.69, 124.19, 125.06, 130.21, 130.53, 131.82, 142.46, 152.57, 152.86, 153.64, 159.36, 159.93. MS (ESI) (*m/z*): 664.5, 666.5, 668.5 $[M]^+$. Anal. Calcd. for $C_{25}H_{22}Br_2N_4O_6S$: C, 45.06; H, 3.33; N, 8.41. Found: C, 45.20; H, 3.29; N, 8.53.

**(*E*)-3-(4-Chlorophenyl)-*N*-(2-(hydrazinecarbonyl)phenyl)acrylamide (11).** Mp 164-166 °C. $^1$H NMR (400 MHz, DMSO-$d_6$): δ 4.63 (s, 2H), 6.86 (d, *J*=15.6 Hz, 1H), 7.16 (t, *J*=7.6 Hz, 1H), 7.48-7.53 (m, 3H), 7.59 (d, *J*=15.6 Hz, 1H),7.69 (d, *J*=7.2 Hz, 1H), 7.76 (d, *J*=8 4 Hz, 2H), 8.50 (d, *J*=8 Hz, 1H),10.05 (s, 1H), 11.41(s, 1H). $^{13}$C NMR (100 MHz, DMSO-$d_6$): δ 120.9, 121.4, 123.4, 123.8, 128.1, 129.4, 130.3, 132.1, 134.0, 134.9, 139.1, 140, 163.8, 167.7. MS (ESI) (*m/z*): 315.7, 317.7 $[M]^+$. Anal. Calcd. for $C_{16}H_{14}ClN_3O_2$: C, 60.86; H, 4.47; N, 13.31. Found: C, 60.89; H, 4.32; N, 13.27.

***N*-(2-(2-(4-Acetamidophenylsulfonyl)hydrazinecarbonyl)phenyl)cinnamamide (13).** Mp 192-195 °C. $^1$H NMR (400 MHz, DMSO-$d_6$): δ 1.91 (s, 3H), 6.63 (d, *J*=15.6 Hz, 1H), 7.20 (t, *J*=7.6 Hz, 1H), 7.44-7.56 (m, 5H), 7.65-7.73 (m, 5H), 7.79 (d, *J*=8.4 Hz, 2H) 8.32(d, *J*=8.4 Hz, 1H) 9.90 (s, 1H), 10.22 (s, 1H),10.41 (s, 1H) 10.89 (s, 1H). $^{13}$C NMR (100 MHz, DMSO-$d_6$): δ 24.62,111.0, 113.9, 116.8, 118.6, 119.6, 126.3, 128.4, 129.3, 129.4, 133.5, 134.1,135. 3, 137.1, 139.8, 142.2, 142.4, 158.6, 160.2, 164.7. MS (ESI) (*m/z*): 479.5 $[M+H]^+$. Anal. Calcd. for $C_{24}H_{22}N_4O_5S$: C, 60.24; H, 4.63; N, 11.71. Found: C, 60.36; H, 4.76; N, 11.58.

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