Alternative and efficient one-pot three-component synthesis of substituted 2-aryl-4-styrylquinazolines/4-styrylquinazolines from synthetically available 1-(2-aminophenyl)-3-arylprop-2-en-1-ones: characterization and evaluation of their antiproliferative activities†

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In this study, an alternative and efficient one-pot three-component synthesis approach to develop a new series of (*E*)-2-aryl-4-styrylquinazolines and (*E*)-4-styrylquinazolines is described. According to this approach, the target compounds were synthesized straightforward in high yields and in short reaction times from substituted 1-(2-aminophenyl)-3-arylprop-2-en-1-ones *via* its well-Cu(OAc)$_2$-mediated cyclocondensation reactions with aromatic aldehydes or its well-catalyst-free cyclocondensation reactions with trimethoxy methane (trimethyl orthoformate), and ammonium acetate under aerobic conditions. This is an operationally simple, valuable, and direct method to synthesize 2-aryl- and non-C2-substituted quinazolines containing a styryl framework at C4 position from cheap and synthetically available starting materials. All the synthesized compounds were submitted to the US National Cancer Institute for *in vitro* screening. The bromo- and chloro-substituted quinazolines **5c** and **5d** displayed a potent antitumor activity against all the tested subpanel tumor cell lines with IC$_{50}$ (MG-MID) values of 5.25 and 5.50 μM, and a low cytotoxic effect with LC$_{50}$ (MG-MID) values of 91.20 and 84.67 μM, respectively, indicating a low toxicity of these compounds to normal human cell lines, as required for potential antitumor agents.

1 Introduction

Quinazoline is regarded as a privileged scaffold found in many naturally existing and synthesized compounds and used as an effective template in medicinal chemistry for drug discovery.[1] Compounds bearing this fragment have shown remarkable and broad-spectrum biological and pharmacological activities such as antimicrobial,[2] antipsychotic,[3] antimalarial,[1d,4] anti-spasm,[1b] and anticancer[1a,c,5] activities. Fig. 1 shows some representative examples of known quinazoline-based drugs used for the treatment of several diseases.[1a,d,5b,6–10]

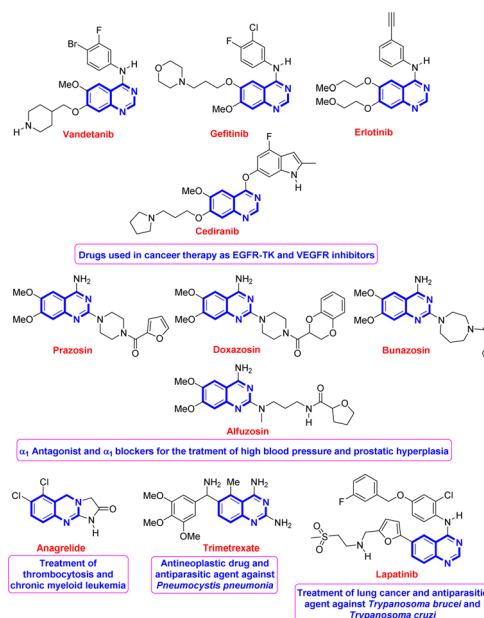Due to their wide-ranging biological and pharmacological properties, the synthesis of quinazoline derivatives has been
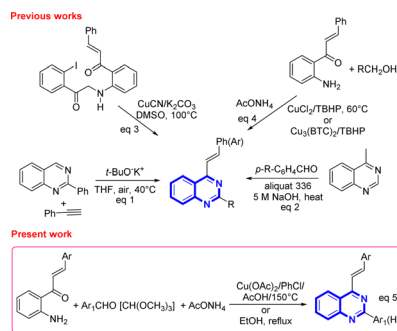
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Fig. 1 Representative drugs based on the quinazoline backbone.

Scheme 1 Recent approaches to the synthesis of substituted 4-styrylquinazolines.

extensively studied over the years. Regardless of efficiency and importance, most of the developed synthetic approaches involve either multiple steps or the use of special or not readily available starting materials or preliminary preparation of some intermediates.[11–19] Among them, the one-pot three-component cyclocondensation reaction between 2-aminoaryl ketones or 2-aminobenzonitriles and electrophilic reagents such as aromatic aldehydes or orthoesters, and amines or ammonium acetate under different reaction conditions is the most common way towards quinazoline derivatives.[20]

However, despite the existence of a myriad of compounds based on the quinazoline backbone, studies related to the synthesis and biological activities of 4-styrylquinazolines have been found to be scarce in the literature so far. These types of compounds are usually prepared by employing the direct *t*-BuOK-mediated stereoselective alkenylation of pre-formed quinazolines with unactivated terminal alkynes (Scheme 1, eqn (1)),[21] or by achieving the Knoevenagel-type condensation of preformed 4-methylquinazolines with aromatic aldehydes (Scheme 1, eqn (2)),[22] or through copper-catalyzed cyanation of 2-iodo-*N*-arylbenzamides with the subsequent rearrangement of the formed 2-cyano-*N*-arylbenzamides (Scheme 1, eqn (3)).[23]

In recent years, Satish and co-workers, in 2019, and Krishnan and co-workers, in 2022, have used copper(II) chloride or copper-based metal organic frameworks to promote the one-pot three-component oxidative amination of 2′-aminochalcones with methanol and primary alcohols and ammonium acetate in the presence of *tert*-butyl hydroperoxide affording substituted 4-styrylquinazolines (Scheme 1, eqn (4)).[24]

Our group has already reported the use of 2′-aminochalcones as valuable precursors for the straightforward synthesis of functionally diverse and structurally complex 4-styrylquinolines through the Friedländer reaction.[25] As part of an ongoing interest on the reactivity and synthetic utility of 2′-amino-chalcones, herein, we aimed to provide a simple, efficient, and alternative one-pot three-component synthesis approach of 2-aryl-4-styrylquinazolines and 4-styryl-quinazolines *via* Cu(OAc)$_2$-promoted and catalyst-free cyclocondensations of 1-(2-aminophenyl)-3-arylprop-2-en-1-ones with aromatic aldehydes or trimethyl orthoformate, and ammonium acetate under aerobic conditions (Scheme 1, eqn (5)).

2 Results and discussion

We have started using 2′-aminochalcone **1a**, benzaldehyde **2a** and ammonium acetate as the reaction model to set up the conditions for the designed 2-aryl-4-styrylquinazolines and 4-styrylquinazolines. The reactants were combined in 1.0/1.0/2.5 molar ratio, respectively, and reacted under different experimental conditions, as shown in Table 1. Initially, we tried to perform the reaction in refluxing ethanol under aerobic conditions without any catalyst; however, after 6 and 20 h of heating, only multiple spots on TLC controls were observed

Table 1 Initial trials for the one-pot three-component synthesis of 2-phenyl-4-styrylquinazoline **3a**

Entry[a]	Solvent	Catalyst/additive	T (°C)	t (h)	Yield (%)
1	EtOH	—	80	6	—
2	EtOH	—	80	20	—
3	EtOH	I$_2$ (5.0 mol%)	80	20	—
4	EtOH	I$_2$ (10 mol%)	80	20	—
5	EtOH	CAN (5.0 mol%)	80	7	—
6	EtOH	CAN (10.0 mol%)	80	10	—
7	EtOH	CoCl$_2$·2H$_2$O (5.0 mol%)	80	5	—
8	EtOH	CoCl$_2$·2H$_2$O (10.0 mol%)	80	10	—
9	Toluene	ZnCl$_2$ (5.0 mol%)	90	7	—
10	Toluene	ZnCl$_2$ (10.0 mol%)	110	10	—
11	AcOH	—	100	10	—
12	AcOH	—	115	10	—
13	PhCl	—	150	10	15
14[b]	PhCl/AcOH	—	150	8	27
15[c]	PhCl/DMSO	—	150	12	14
16	PhCl/AcOH	NiCl$_2$·6H$_2$O (5.0 mol%)	150	8	33
17	PhCl/AcOH	NiCl$_2$·6H$_2$O (10.0 mol%)	150	8	43
18	PhCl/AcOH	Cu(OAc)$_2$ (0.5 mol)	150	2	50
19	PhCl/AcOH	Cu(OAc)$_2$ (0.5 mmol)	120	4	36
20	PhCl/AcOH	Cu(OAc)$_2$ (1.0 mmol)	150	1	60
21	PhCl	Cu(OAc)$_2$ (1.0 mmol)	150	5	48
22[d]	PhCl/AcOH	Cu(OAc)$_2$ (1.0 mmol)	150	2	60
23[e]	PhCl/AcOH	Cu(OAc)$_2$ (1.0 mmol)	150	2	62
24[b]	**PhCl/AcOH**	**Cu(OAc)$_2$ (1.3 mmol)**	**150**	**1**	**81**
25	PhCl/AcOH	Cu(OAc)$_2$ (1.5 mmol)	150	4	72
26[f]	PhCl/AcOH	Cu(OAc)$_2$ (1.3 mmol)	150	3	68
27[g]	PhCl/AcOH	Cu(OAc)$_2$ (1.3 mmol)	150	1	80
28[h]	PhCl/AcOH	Cu(OAc)$_2$ (1.3 mmol)	150	1	—
29[i]	PhCl/AcOH	Cu(OAc)$_2$ (1.3 mmol)	150	1	—
30[j]	PhCl/AcOH	Cu(OAc)$_2$ (1.3 mmol)	150	1	—

[a] **1a** (1.0 mmol), **2a** (1.0 mmol), AcONH$_4$ (2.5 mmol). [b] PhCl (2 mL)/AcOH (three drops). [c] PhCl (2 mL)/DMSO (5 mol%). [d] PhCl (2 mL)/AcOH (0.5 mL). [e] PhCl (2 mL)/AcOH (1.0 mL). [f] AcONH$_4$ (2.0 mmol). [g] AcONH$_4$ (3.0 mmol). [h] NH$_4$I (2.5 mmol). [i] NH$_4$Cl (2.5 mmol). [j] (NH$_4$)$_2$SO$_4$ (2.5 mmol).

(entries 1 and 2). To evaluate the influence of catalysts/promoters on this transformation, molecular iodine, CAN, $CoCl_2 \cdot 2H_2O$, and $ZnCl_2$ were tested in ethanol (entries 3–8) and toluene (entries 9 and 10), but none of them was capable of performing the planed transformation. No reaction also occurred when glacial acetic acid (AcOH) was used as the catalyst and solvent (entries 11 and 12). A new compound was observed (TLC control) when the reaction was performed in chlorobenzene at 150 °C without any addition of catalyst (entry 13). After purification of the reaction mixture by column chromatography, the new product formed was obtained as a solid in 15% yield with recovery of starting 2′-aminochalcone **1a**. NMR analysis confirmed that this product was the expected 2-phenyl-4-styrylquinazoline **3a**.

Notably, the yield of **3a** practically doubled and the reaction time decreased in 2 h when AcOH (three drops) was added to the reaction mixture (entry 14). By contrast, introduction of an aprotic polar solvent such as DMSO to the reaction mixture had a negative effect and delivered **3a** in diminished yields (entry 15).

The above-mentioned experimental results showed that chlorobenzene as the solvent with a little amount of AcOH is the best basic medium to perform our model reaction, and we started combining with other catalysts/promoters. Therefore, we decided to evaluate the effect of $NiCl_2 \cdot 6H_2O$ (5.0–10.0 mol%) and $Cu(OAc)_2$ (0.5–1.0 mmol), running the reaction under aerobic conditions at 150 °C. We were pleased to find that the presence of these two salts has a significant influence on the **3a** yields (entries 16–20). Among these two salts, $Cu(OAc)_2$, in an equimolar ratio, was found to be the best in promoting the reaction, whereby **3a** was isolated in 60% yield after 1 h of heating (entry 20).
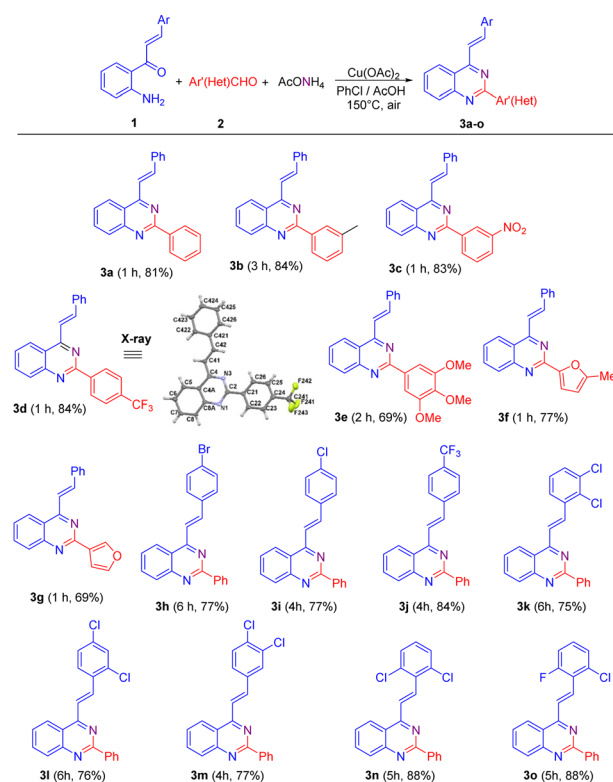
In this optimization process, it was also observed that a decrease in the amount of $Cu(OAc)_2$ and the temperature led to a drop in **3a** yield (entries 18 and 19). Without addition of AcOH, a significant reduction in the yield was also noticed (entry 21). Furthermore, an increase in the amount of AcOH had only a negligible effect on the reaction outcome, giving **3a** in similar yields to that obtained in entry 20 (entries 22 and 23). These results strongly suggested that equimolar amounts of $Cu(OAc)_2$ in combination with a catalytic amount of AcOH in chlorobenzene play an important role in this one-pot three-component transformation.

Encouraged by these results, we moved then to further optimize the reaction yield by evaluating the effect of temperature, reaction time and reactant/$Cu(OAc)_2$ molar ratios. Pleasingly, there was a significant improvement in **3a** yield when the reaction was performed using 1.3 mmol of $Cu(OAc)_2$ at 150 °C for 1 h without changing the initial molar ratios of reactants (1.0/1.0/2.5); under these conditions, the reaction was very clean and provided the desired product in 81% yield (entry 24). On the contrary, a significant drop in **3a** yield was noticed when the amount of $Cu(OAc)_2$ was increased to 1.5 mmol (entry 25), but especially when the amount of $AcONH_4$ was decreased to 2.0 mmol (entry 26). Additionally, increasing the amount of $AcONH_4$ from 2.5 to 3.0 mmol did not afford better results (entry 27), giving **3a** in a similar yield to that obtained in entry

24. Finally, when the model reaction was performed in the fixed molar ratios of reactants and conditions of entry 24, but using other ammonia sources such as NH_4I, NH_4Cl and $(NH_4)_2SO_4$ instead of $AcONH_4$, in each case, a complex mixture of compounds was noticed (entries 28–30). From these trials, it was concluded that the best conditions to perform this one-pot three-component transformation are those highlighted in entry 24 (Table 1).

Once the reaction conditions were established, they were applied to different substrates to explore the scope of this transformation. Initially, we studied the behavior of 2′-aminochalcone **1a** in its reaction with (hetero)aromatic aldehydes **2** (Scheme 2). Pleasingly, it was found that all the tested aldehydes reacted well with **1a** to produce the corresponding 2-aryl-4-styrylquinazolines **3** in good to excellent yields.

As shown in Scheme 2, benzaldehydes containing a weak electron-donating group at *meta* position (**2b**) or strong electron-withdrawing substituents at *meta* (**2c**) and *para* (**2d**) positions practically did not affect the reaction yields, affording the expected 4-styryl-2-arylquinazolines **3b–3d** in yields comparable to that obtained for **3a**. Nevertheless, the *meta*-methylbenzaldehyde **2b** exhibited a lower reactivity than that of its *meta*-nitro- and *para*-trifluoromethyl-substituted analogues **2c** and **2d**, and so a longer reaction time was necessary for substrate consumption.

Scheme 2 $Cu(AcO)_2$-promoted oxidative cyclocondensation of 2′-aminochalcones **1** with aromatic aldehydes **2** and ammonium acetate under aerobic conditions. The X-ray structure for **3d** is shown with thermal anisotropic ellipsoids at 50% probability. Experimental conditions: **1** (1.0 mmol), **2** (1.0 mmol), $AcONH_4$ (2.5 mmol), $Cu(OAc)_2$ (1.3 mmol), PhCl (2 mL), and AcOH (three drops).

Similarly, trisubstituted benzaldehydes such as 3,4,5-trimethoxybenzaldehyde **2e** and heteroaromatic aldehydes such as 5-methylfuran-2-carbaldehyde **2f** and furan-3-carbaldehyde **2g** proceeded successfully to come up with the expected products. However, in general, they exhibited lower efficiencies than their **2a–2d** analogues and afforded the corresponding quinazoline derivatives **3e–3g** in lower yields.

Next, we evaluated the reactivity of 2′-aminochalcones **1** containing one or two electron-withdrawing substituents at different positions on the benzene ring of the styryl fragment with benzaldehyde **2a** as the fixed electrophilic partner. It was found that both *para*-monosubstituted (**1h–1j**) and disubstituted (**1k–1o**) chalcones were successfully subjected to this transformation but required longer reaction times to afford the corresponding 2-aryl-4-styrylquinazolines **3h–3o** in yields of 75–88%. 2′-Aminochalcone with a trifluoromethyl group at the *para*-position **1j** gave a better yield (84%) than that of its *para*-halogen-substituted analogues **1h** (77%) and **1i** (77%). The reaction with dichloro-substituted chalcones **1k–1m** also reached completion within 4–6 h, producing the desired quinazolines **3k–3m** in similar yields to that obtained for *p*-bromo(chloro)-substituted analogues **3h** and **3i**.

Among the tested substituted 2′-aminochalcones **1**, 2,6-dichloro- (**1n**) and 2-chloro-6-fluoro- (**1o**) disubstituted derivatives afforded the corresponding 2-phenyl-4-styrylquinazolines **3n** and **3o** in the best yields (88%).
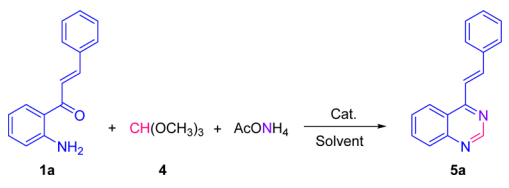
To broaden the scope of this one-pot three-component transformation, we then evaluated the reaction of 2′-aminochalcones **1** with ammonium acetate and trimethyl orthoformate **4** instead of aromatic aldehydes. Curiously, to the best of our knowledge, this transformation was not previously explored with the aim of assembling the non-substituted C2 4-styrylquinazoline core position.

As shown in Table 2, this one-pot three-component cyclo-condensation under the optimized conditions, using **1a** as the model substrate, occurs at a much lower rate than that of their 2-aryl-4-styrylquinazoline analogues **3**, affording the expected 4-styrylquinazoline **5a** in only 45% yield after 20 h of heating (entry 1). This unsatisfactory result prompted us to investigate again this transformation in more detail with respect to Cu(OAc)$_2$ loading, molar ratios of reactants, solvent, and temperature.

In this new optimization process, it was observed that an increase in the amount of **4** from 1.0 to 2.0–3.5 mmol without changing the reaction temperature and the molar ratio of Cu(OAc)$_2$, **1a**, and ammonium acetate had only a negligible influence on the **5a** yields (entries 2 and 3).

Nevertheless, the yield of **5a** was significantly improved (up to 60%) running the reaction with 3.5 mmol of **4** and reducing, at the same time, both the amount of Cu(OAc)$_2$ and the reaction temperature (entries 4–6). Similarly, performing the reaction using 3.5 mmol of **4** in PhCl at 150 and 100 °C in the absence of

Table 2 Optimization of the 4-styrylquinazoline **5a** synthesis from 2′-aminochalcone **1a**, trimethyl orthoformate **4** and ammonium acetate

Entry	Ratio 1a/4/AcONH$_4$	Solvent	Cu(OAc)$_2$ (mmol)	T (°C)	t (h)	Yield (%)
1	1.0 : 1.0 : 2.5	PhCl/AcOH	1.3 mmol	150	20	45
2	1.0 : 2.0 : 2.5	PhCl/AcOH	1.3 mmol	150	20	47
3	1.0 : 3.5 : 2.5	PhCl/AcOH	1.3 mmol	150	20	50
4	1.0 : 3.5 : 2.5	PhCl/AcOH	1.0 mmol	150	18	55
5	1.0 : 3.5 : 2.5	PhCl/AcOH	0.5 mmol	150	18	58
6	1.0 : 3.5 : 2.5	PhCl/AcOH	0.5 mmol	100	24	60
7	1.0 : 3.5 : 2.5	PhCl	—	150	18	55
8	1.0 : 3.5 : 2.5	PhCl	—	100	18	50
9	1.0 : 3.5 : 2.5	AcOH	—	110	10	—
10	1.0 : 3.5 : 2.5	AcOH	—	80	10	—
11	1.0 : 3.5 : 2.5	—	—	80	15	—
12	1.0 : 3.5 : 2.5	—	—	120	15	—
13	1.0 : 3.5 : 2.5	MeOH	—	65	25	63
14	1.0 : 3.5 : 2.5	EtOH	—	80	18	70
15	**1.0 : 3.5 : 3.0**	**EtOH**	**—**	**80**	**5**	**85**
16	1.0 : 3.0 : 3.0	EtOH	—	80	8	80
17	1.0 : 4.0 : 3.5	EtOH	—	80	4	83
18	1.0 : 4.0 : 3.5	EtOH	—	80	10	84
19	1.0 : 4.0 : 4.0	EtOH	—	80	10	82
20	1.0 : 3.5 : 2.5	*n*-BuOH	—	120	17	67

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$Cu(OAc)_2$ and AcOH had a little effect on the reaction outcome and delivered **3a** in diminished yields (entries 7 and 8). The desired product was not formed at all when AcOH was used as the catalyst and solvent (entries 9 and 10).

It would appear from these results that both $Cu(OAc)_2$ and AcOH are not necessary for the reaction to take place. Contrary to the report by Bath and coworkers,[20a] we found that the solvent nature plays an important role in this transformation. For example, the solvent-free trials at 80 and 120 °C did not afford the expected compound (entries 11 and 12).

In the light of the above-mentioned results, we decided to perform the planed transformation by simple heating in different polar solvents (methanol, ethanol, and *n*-butanol), evaluating the effect of reaction times and molar ratio of reactants (entries 13–20). The reaction proceeded in all three tested solvents, with ethanol as the best one/solvent for this transformation (entries 14–19). With ethanol as the solvent, the optimal molar ratio of reactants for the reaction was determined to be 1.0/3.5/3.0 (**1a** : **4** : $AcONH_4$); under these conditions, the reaction reached completion within 5 h, affording the desired product **5a** in 85% yield (entry 15). Other molar ratios of reactants did not afford better results even if the reaction time was extended to 8–18 h (entries 14 and 16–19).
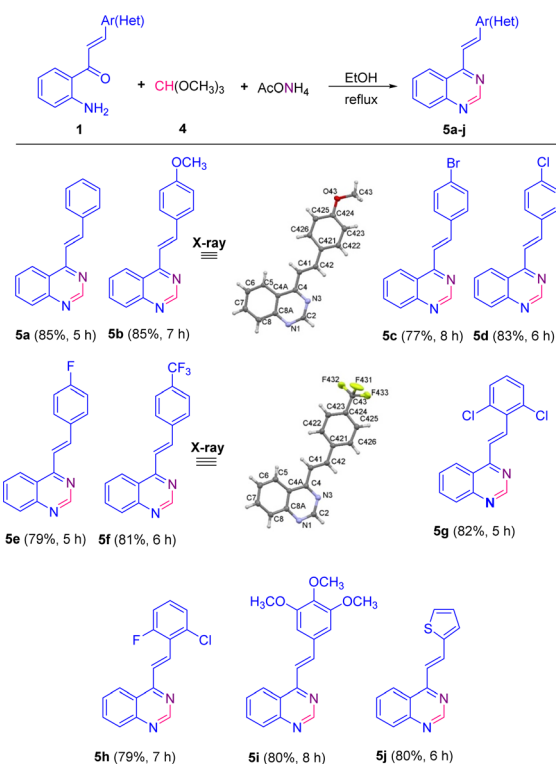
The scope of this catalyst-free one-pot three-component reaction with different substituted 2′-aminochalcones **1** was explored under the optimized conditions highlighted in entry 15, and the results are listed in Scheme 3. It was rewarding to find that chalcones **1a–i** containing substituents on the aromatic ring of the styryl fragment, regarding their electronic behavior, that is, both electron donating/withdrawing groups, and their substitution pattern (mono, di- or trisubstituted) were also successfully subjected to this transformation. As a result, the corresponding 4-styrylquinazoline derivatives **5a–i** were obtained in similar yields to that obtained for **5a**, regardless of the positions of substituents.
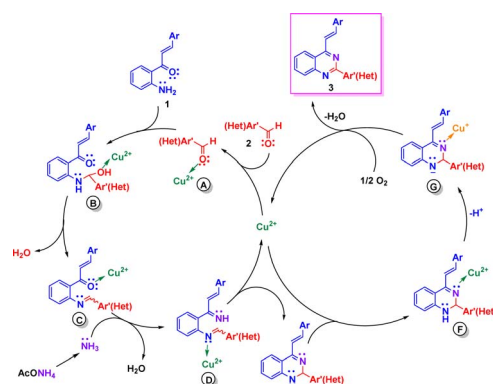
Among the *para*-halogenated 2′-aminochalcones **1c**, **1d**, and **1e**, and *para*-trifluoromethyl-substituted chalcone **1f**, chalcones **1d** and **1f** resulted to be the most reactive, giving the corresponding 4-styrylquinazolines **5d** and **5f** in yields of 83 and 81%, respectively. The *para*-bromo- (**1c**) and the *para*-fluoro- (**1e**) substituted 2′-aminochalcones also worked well in this transformation, though providing the 4-styrylquinazolines **5c** and **5e** in slightly inferior yields (77 and 79%, respectively).

No significant differences were noticed in the efficiencies of dihalogenated chalcones **1g** and **1h** with respect to trimethoxy-substituted chalcone **1i**; all three chalcones successfully produced the expected quinazolines **5g–5i** in yields of 82, 79 and 80%, respectively. Moreover, 2′-aminochalcone **1j** containing a thiophene ring in the vinyl fragment instead of the benzene ring also participated smoothly in this transformation, providing the corresponding quinazoline **5j** in a similar yield (80%).

Among all the tested 2′-aminochalcones **1**, the non-substituted and *para*-methoxy-substituted chalcones **1a** and **1b** showed the highest efficiencies and provided the

Scheme 3 Catalyst-free one-pot three-component synthesis of 4-styrylquinazolines **5**. The X-ray structures of **5b** and **5f** are shown with thermal anisotropic ellipsoids at 50% probability.

Scheme 4 Plausible mechanism leading to 2-aryl-4-styrylquinazolines **3**.

Scheme 5 Plausible mechanism leading to 4-styrylquinazolines **5**.

Table 3 Inhibitory concentration (IC$_{50}$, μM) and lethal concentration (LC$_{50}$, μM) of compounds **5c** and **5d** over all tested *in vitro* tumor cell lines[a]

Cancer panel cell line	5c [b] IC$_{50}$ (μM)	5c [b] LC$_{50}$ (μM)	5d [c] IC$_{50}$ (μM)	5d [c] LC$_{50}$ (μM)
Leukemia (I)				
CCRF-CEM	3.09	>100	3.72	>100
HL-60(TB)	2.45	>100	2.40	>100
K-562	3.24	>100	4.07	>100
MOLT-4	3.89	>100	12.02	>100
RPMI-8226	3.24	>100	NT[d]	NT
SR	3.24	>100	NT	NT
Non-small cell lung cancer (II)				
A549/ATCC	6.92	>100	5.75	>100
EKVX	2.95	>100	2.63	>100
HOP-62	5.50	>100	10.47	>100
NCI-H226	7.76	93.33	2.82	>100
NCI-H23	3.72	63.10	3.16	70.79
NCI-H322M	4.37	>100	3.47	69.18
NCI-H460	5.75	>100	8.51	>100
NCI-H522	4.79	77.62	10.72	>100
Colon cancer (III)				
COLO 205	5.62	45.71	3.72	43.65
HCC-2998	5.01	81.28	6.61	52.48
HCT-116	3.39	>100	3.72	52.48
HCT-15	2.51	>100	1.78	63.10
HT29	5.75	>100	5.37	63.10
KM12	3.02	>100	10.23	57.54
SW-620	3.16	>100	3.55	>100
CNS cancer (IV)				
SF-268	7.76	>100	9.12	>100
SF-295	14.79	>100	3.80	>100
SF-539	5.75	60.26	4.90	46.77
SNB-19	7.24	>100	10.72	52.48
SNB-75	2.24	>100	1.91	>100
U251	4.79	>100	4.37	64.57
Melanoma (V)				
LOX IMVI	3.63	41.69	4.17	47.86
MALME-3M	15.49	>100	22.91	>100
M14	6.17	>100	5.13	56.23
MDA-MB-435	4.07	>100	4.90	>100
SK-MEL-2	5.50	89.13	6.92	56.23
SK-MEL-28	13.18	>100	11.22	64.57
SK-MEL-5	9.33	54.95	10.47	47.86
UACC-257	31.62	>100	7.76	>100
UACC-62	5.25	58.88	4.47	58.88
Ovarian cancer (VI)				
IGROV1	17.38	>100	15.85	>100
OVCAR-3	2.51	74.13	3.47	>100
OVCAR-4	19.05	>100	10.23	>100
OVCAR-5	5.01	>100	4.57	>100
OVCAR-8	5.89	>100	5.50	97.72
NCI/ADR-RES	2.82	100.00	2.34	75.86
SK-OV-3	10.47	>100	5.50	>100
Renal cancer (VII)				
786-0	12.88	>100	8.51	>100
A498	16.60	>100	28.84	>100

Table 3 (*Contd.*)

Cancer panel cell line	5c [b] IC$_{50}$ (μM)	5c [b] LC$_{50}$ (μM)	5d [c] IC$_{50}$ (μM)	5d [c] LC$_{50}$ (μM)
ACHN	5.13	>100	4.57	>100
CAKI-1	3.63	>100	3.98	>100
RXF 393	4.79	>100	ND	NT
SN12C	3.72	>100	5.50	61.66
TK-10	19.05	>100	19.05	>100
UO-31	3.47	>100	4.37	>100
Prostate cancer (VIII)				
PC-3	5.62	>100	5.89	>100
DU-145	4.37	>100	6.03	>100
Breast cancer (IX)				
MCF7	2.45	>100	1.86	56.23
MDA-MB-231/ATCC	4.27	>100	11.75	>100
HS 578T	8.13	>100	9.33	>100
BT-549	3.09	75.86	2.63	44.67
T-47D	2.75	>100	2.69	>100
MDA-MB-468	2.09	32.36	1.91	27.54

[a] Data obtained from NCIs *in vitro* disease-oriented human tumor cell screen. [b] NSC 840315. [c] NSC 847835. [d] NT, not tested.

corresponding 4-styrylquinazolines **5a** and **5b** in the best yields (85%).

Finally, we also tried to use triethyl orthoacetate in reaction with 2′-aminochalcone **1a** and ammonium acetate to assemble the 2-methyl-substituted 4-styrylquinazoline core. The importance of this class of derivatives lies in their potential use as building blocks of more complex molecules due to the inherent reactivity of the methyl group that allows for further functionalization. Unfortunately, under the reaction conditions established for compounds **3** and **5**, the planned one-pot three-component cyclocondensation with triethyl orthoacetate did not occur. This may be due to its lower reactivity compared to that shown by trimethyl orthoformate and aromatic aldehydes.

The structures of the target compounds **3** and **5** were established mainly by a combined study of IR, HRMS and ^{1}H NMR and ^{13}C NMR spectra (see the Experimental section). In their IR spectra, the absence of any N–H stretching bands around 3275–3285 cm^{-1}, which are characteristic in the spectra of 2′-aminochalcone precursors **1**, was used for monitoring the formation of the quinazoline ring. Additionally, the IR spectra of **3** and **5** showed the characteristic absorption band at 961–973 cm^{-1} (for **3**) and 948–983 cm^{-1} (for **5**) attributed to a *trans*-disubstituted alkene. Additional supports for the expected structures were obtained from their mass-spectra. Compounds were identified based on the elemental composition of the protonated molecules and their product ions [M + H]$^+$, which confirmed their exact molecular weights (see Experimental section).

Based on literature reports,[17,20a,e] we propose tentative reaction mechanisms by which the formation of 2-aryl-4-styrylquinazolines **3** and 4-styrylquinazolines **5** could occur. The rationalization of mechanism for compounds **3** is depicted in Scheme 4. First, the carbonyl group of aromatic aldehydes **2** is activated by Cu(II) to give complex **A**. Nucleophilic attack of 2′-aminochalcone **1** onto activated aldehyde **A** followed by dehydration of the formed aminol **B** yields the imine intermediate **C** in which the carbonyl group is activated by Cu(II). Subsequent condensation of **C** with ammonia, generated from ammonium acetate, produces the diimine **D**, which upon intramolecular cycloaddition and release of Cu(II) afforded the dihydroquinazoline **E**. Then, Cu(II) coordinates with the imine nitrogen atom of **E** and produces the intermediate **F**, which upon deprotonation and reduction of Cu(II) to Cu(I) is transformed into the anion **G**.[17] Finally, after reoxidation of the Cu(I) complex to the Cu(II) complex, compounds **3** are released and the catalytic cycle would be closed.

The plausible mechanism for compounds **5** is illustrated in Scheme 5, which could imply the initial formation of methyl formimidate **A**, which is transformed into the final product **5** via two possible paths.[20a] Through path a, intermediate **A** by condensation with ammonia, generated from ammonium acetate, yields the methyl imino-formimidate **B**, which upon intramolecular cycloaddition produces the dihydroquinazoline **C**. Finally, **C** is transformed into the target compound **5** by loss of a molecule of methanol. Through path b, intermediate **A** reacts with ammonia via nucleophilic substitution affording the formimidamide **D**, which, in turn, upon intramolecular cycloaddition and subsequent dehydration of the formed dihydroquinazolin-4-ol **E** yields the target 4-styryquinazoline **5**.

The formation of the 4-styrylquinazoline scaffolds with 2-aryl-substituted and non-substituted at the C2 position was unambiguously confirmed by a detailed analysis of the ^{1}H, ^{13}C and 2D NMR spectra, which showed no signals arising from the H atoms of the amino group, neither were there any signals from the carbonyl group which had been present in the precursor chalcones **1**. Instead, the ^{13}C spectra of quinazolines **3** contained signals from two new quaternary aromatic C atoms at δ 153.7–160.4 (C2) and δ 161.1–162.3 (C4). In turn, the ^{1}H and ^{13}C spectra of the non-substituted at C2 styrylquinazolines **5** contained signals from a new Caryl-H unit (H2/C2) at δ 9.23–9.36 (singlet) and δ 153.6–155.0, and a new quaternary aromatic C atom at δ 161.4–162.4 (C4). As in the spectra of the precursor chalcones **1**, the ^{1}H spectra of **3** and **5** contained signals from the *trans* vinylic protons –CH$_A$=CH$_B$–, appearing as two doublets in the aromatic region at δ 7.91–8.29 and 8.32–8.80 (for **3**) and at δ 7.69–8.25 and 8.21–8.48 (for **5**), respectively.

Additionally, the molecular structures of representative compounds **3d**, **5b** and **5f** were unambiguously established by single-crystal X-ray diffraction analysis, and their structures are included in Schemes 2 and 3. Their X-ray crystal structures agree with the structural elucidation deduced from NMR analysis.

All the synthesized 2-aryl-4-styrylquinazolines **3** (15 compounds) and 4-styrylquinazolines **5** (10 compounds) were selected by the USA National Cancer Institute (NCI) to test their antitumor activities under the drug discovery program of the NCI (USA).[26] Two of them showed an average inhibition percentage higher than 70%, which corresponding to *para*-bromostyryl- (**5c**) (NSC 840315) and *para*-chlorostyryl- (**5d**) (NSC 847835) substituted quinazolines were so selected to determine their IC$_{50}$ and LC$_{50}$ at five concentrations at 10-fold dilution (100, 10, 1, 0.1 and 0.01 μM). The other twenty-three compounds proved to have limited activity or were totally inactive (see Tables 1S and 2S in the ESI†).

An overview of the substitution pattern of the tested compounds reveals that active compounds **5c** and **5d** belong to the non-substituted at C2 position 4-styryquinazolines,

Table 4 Median 50% inhibitory concentration (IC$_{50}$, μM) values of *in vitro* subpanel tumor cell lines

Comp.	Subpanel tumor cell lines[a]									MG-MID[b]
	I	II	III	IV	V	VI	VII	VIII	IX	
5c	3.19	5.22	4.07	7.10	10.47	9.02	8.66	4.99	3.80	**5.25**
5d	5.55	5.68	5.00	5.80	8.66	6.78	10.69	5.96	5.03	**5.50**

[a] I = leukemia; II = non-small cell lung cancer; III = colon cancer; IV = CNS cancer; V = melanoma; VI = ovarian cancer; VII = renal cancer; VIII = prostate cancer; IX = breast cancer. [b] IC$_{50}$ (μM) full panel mean graph midpoint (MG-MID) = the average sensitivity of all cell lines towards the test compound.

Table 5 Median 50% lethal concentration (LC$_{50}$, μM) values of *in vitro* subpanel tumor cell lines

Comp.	Subpanel tumor cell lines[a]									MG-MID[b]
	I	II	III	IV	V	VI	VII	VIII	IX	
5c	> 100	91.76	89.57	93.38	82.74	95.69	> 100	> 100	91.95	**91.20**
5d	> 100	87.66	61.76	77.30	73.16	96.23	94.52	> 100	71.41	**84.67**

[a] I = leukemia; II = non-small cell lung cancer; III = colon cancer; IV = CNS cancer; V = melanoma; VI = ovarian cancer; VII = renal cancer; VIII = prostate cancer; IX = breast cancer. [b] LC$_{50}$ (μM) full panel mean graph midpoint (MG-MID) = the average sensitivity of all cell lines towards the test compound.

suggesting that the presence of a phenyl or aryl substituent at C2 position has a detrimental effect on the antitumor activity.

The results obtained in this assay indicated that the two compounds under investigation (5c and 5d) exhibited remarkable antitumor activities against most of the tested subpanel tumor cell lines. Overall, both compounds showed practically the same pattern of sensitivity against some individual cell lines (Table 3), as well as a broad spectrum of antitumor activity (Table 4). Regarding the sensitivity against some individual cell lines, 5c and 5d proved to be very sensitive towards most of the tested subpanel tumor cell lines with IC_{50} values in the range of 1.78–31.62 μM. However, 5d displayed the best sensitivity profile against all the examined cancer cell lines with IC_{50} values in the range of 1.78–28.84 μM (Table 3). For these two compounds, the most sensitive cell lines are as follows: SNB-75 (CNS cancer, IC_{50} = 2.24 μM, for 5c), HCT-15 (colon cancer, IC_{50} = 1.78 μM, for 5d), SNB-75 (CNS cancer, IC_{50} = 1.91 μM, for 5d), and MCF7 and MDA-MB-468 (breast cancer, IC_{50} = 1.86 μM, for 5d, and IC_{50} = 2.09 and 1.91 μM, for 5c and 5d, respectively).

Regarding the broad spectrum of antitumor activity, the results also revealed that 5c and 5d showed effective growth inhibition with IC_{50} (MG-MID) values of 5.25 and 5.50 μM (Table 4), and a low cytotoxic effect with LC_{50} (MG-MID) values of 91.20 and 84.67 μM, respectively (Table 5), indicating the low toxicity of these compounds to normal human cell lines, as required for potential antitumor agents.

3 Conclusions

We have described an easy and efficient one-pot three-component synthetic protocol to afford, in high yields and short reaction times, 2-aryl-4-styrylquinolines and 4-styrylquinazolines from readily available 2′-aminochalcones. Easily available and cheap starting materials, operational simplicity, high yields, and a good functional group tolerance are the most significant features of this protocol, which make it a good alternative to previous methods for the synthesis of 2-aryl- and non-C2-substituted 4-styrylquinazolines.

Additionally, in contrast to other methodologies, the synthesis of non-C2-substituted 4-styrylquinazolines did not require the use of any catalyst. Quinazolines 3 and 5 were screened for their antitumor activity, with 4-bromostyrylquinazoline 5c and 4-chloro-styrylquinazoline 5d as the most active compounds with an IC_{50} value of 5 μM. They exhibited remarkable inhibitory action against all the tested subpanel tumor cell lines and a low cytotoxic profile; thus, they can be considered promising hits, especially bearing in mind their small size and potential for further structural modifications with the aim to improve both the potency and selectivity.

4 Experimental

All reagents and solvents were purchased from commercial sources and used without further purification. Monitoring of the reactions was performed using silica gel TLC plates (Merck silica gel 60 F254). Spots were visualized by UV light at 254 and 365 nm. Column chromatography was performed using Merck

Kieselgel (230–400 mesh) (ASTM). Melting points were determined using a MEL-TEMP 1201D capillary apparatus and are uncorrected. IR spectra were recorded using a Bruker Tensor 27 spectrometer (equipped with a platinum ATR cell). ^1H and ^{13}C NMR spectra were recorded at 25 °C using a Bruker Avance III 400 spectrometer, with $CDCl_3$ as the solvent. Chemical shifts (δ) and coupling constant (J) values are reported in ppm and Hz, respectively. Chemical shifts are relative to the solvent peak used as reference ($CDCl_3$: δ 7.26 for ^1H and δ 77.23 for ^{13}C). NMR multiplicity assignments: q = quartet, t = triplet, d = doublet, s = singlet, br = broad, m = multiplet. High-resolution mass spectra (HRMS) were recorded using either a Waters Micromass AutoSpect NT system (equipped with a direct inlet probe) operating at 70 eV or a Dionex Ultimate® 3000 chromatograph coupled with a LTQ Orbitrap XL™ Hybrid Ion Trap-Orbitrap Fourier Transform Mass Spectrometer with injection into HESI II in the positive mode. Elemental analyses were performed using a Vario Micro cube CHN/S analyzer and were within ±0.4 of theoretical values.

The single-crystal X-ray diffraction measurements of the suitable crystal of 3d, 5b and 5f were obtained using a Hampton Research Mounted CryoloopTM equipped with a Diffractometer Bruker D8 Venture (APEX 4) at Centro de Instrumentación Científico y Técnico" (CICT) in Universidad de Jaén (UJA), Spain, with a monochromator multilayer mirror, CCD rotation images, thick slices φ & θ scans, and a Mo INCOATEC high brilliance microfocus sealed tube as the X-ray source (λ = 0.71073 Å). The structures were solved by a direct method and refined by the full-matrix least-squares technique against F^2 in the isotropic-anisotropic approximation. Data collection: APEX4 v2021.10-0;80 (ref. 27) cell refinement: SAINT V8.40B;[28] data reduction: SAINT V8.37A;16 program(s) used to solve structure: SHELXT-2014/5; 81 (ref. 29) program(s) used to refine structure: SHELXL-2019/1;82 (ref. 30) software used to prepare material for publication: Wingx 2018.283 (ref. 31) and Mercury 3.10.3.84.[32]

It is important to mention that all compounds described in this paper were obtained as perfectly stable solid substances that could be stored without special precautions; however, some of them have been previously synthesized and reported as viscous liquids.[24a]

4.1 Synthesis of substituted (E)-4-styrylquinazolines 3 and 5

All reactions were performed using a Radley Carousel 12 PlusTM Reaction Station System with a stand, a stirring hotplate and an integral temperature controller.

4.1.1 General procedure for the synthesis of (E)-2-aryl-4-styrylquinazolines 3. In a 20 mL Radleys reaction tube, 2′-aminochalcones 1 (1.0 mmol), (hetero)aromatic aldehydes 2 (1.0 mmol), ammonium acetate (2.5 mmol) and copper acetate (1.3 mmol) were mixed in chlorobenzene (2.0 mL) and glacial acetic acid (three drops) at room temperature and then capped. The obtained suspensions were stirred magnetically at 150 °C until completion of the reactions (TLC monitored). Then, the crude mixtures were allowed to cool down to room temperature and extracted with dichloromethane (3 × 30 mL) followed by

washing with water (50 mL) and brine. In each case, the combined organic layers were dried over anhydrous sodium sulfate, and the solvents removed under reduced pressure. The resulting crude was purified by flash chromatography on silica gel using *n*-heptane–ethyl acetate mixtures as the eluent (10 : 1 to 8 : 1) to obtain the target compounds **3** as solid substances.

4.1.1.1 (E)-2-Phenyl-4-styrylquinazoline (3a). White solid; yield: 0.250 g (81%); m.p. 140–142 °C; R_f = 0.53 (9% ethyl acetate–*n*-heptane).

IR (ATR): $\bar{\nu}_{max}$ (cm^{-1}) 3026 (C_{sp^2}–H), 1628 (C=N), 1528 (C=C_{arom}), 973 (=C–H$_{trans}$).

NMR ^{1}H (400 MHz, CDCl$_3$): δ = 8.74–8.71 (m, 2H, H2′/H6′), 8.46 (d, *J* = 15.5 Hz, 1H, =CH$_B$), 8.30 (dd, *J* = 8.3, 1.4 Hz, 1H, H5), 8.10 (dd, *J* = 8.4, 1.2 Hz, 1H, H8), 7.97 (d, *J* = 15.5 Hz, 1H, H$_A$C=), 7.87 (ddd, *J* = 8.4, 6.9, 1.4 Hz, 1H, H7), 7.79–7.76 (m, 2H, H2/H6″), 7.61 (ddd, *J* = 8.3, 6.9, 1.3 Hz, 1H, H6), 7.60–7.55 (m, 2H, H3′/H5′), 7.55–7.50 (m, 1H, H4′), 7.49–7.45 (m, 2H, H3″/H5″), 7.44–7.39 (m, 1H, H4″).

NMR ^{13}C (100 MHz, CDCl$_3$): δ = 161.9 (C4), 160.2 (C2), 152.1 (C8a), 139.5 (=CH$_B$), 138.6 (C1′), 136.2 (C1″), 133.5 (C7), 130.4 (C4′), 129.6 (C4″), 129.4 (C8), 128.9 (C3″/C5″), 128.6 (C2′/C6′, C3′/C5′), 128.1 (C2″/C6″), 126.9 (C6), 123.9 (C5), 121.7 (C4a), 121.0 (H$_A$C=).

HPLC-ESI$^+$-QTOF-MS: *m/z* [M + H]$^+$ calcd for C$_{22}$H$_{16}$N$_2$: 309.1386; found: 309.1386.

Anal. calcd for C$_{22}$H$_{16}$N$_2$: C, 85.69; H, 5.23; N, 9.08. Found: C, 85.66; H, 5.20; N, 9.12.

4.1.1.2 (E)-4-Styryl-2-(m-tolyl)quinazoline (3b). Yellow solid; yield: 0.271 g (84%); m.p. 122–123 °C; R_f = 0.50 (12.5% ethyl acetate–*n*-heptane).

IR (ATR): $\bar{\nu}_{max}$ (cm^{-1}) 3064 (C_{sp^2}–H), 1629 (C=N), 1530 (C=C_{arom}), 968 (=C–H$_{trans}$), 704 and 690 (C_{arom}–H, benzene *m*-subst.).

NMR ^{1}H (400 MHz, CDCl$_3$): δ = 8.54–8.52 (m, 2H, H2′, H6′), 8.45 (d, *J* = 15.5 Hz, 1H, =CH$_B$), 8.30 (dd, *J* = 8.4, 1.4 Hz, 1H, H5), 8.10 (dd, *J* = 8.4, 1.3 Hz, 1H, H8), 7.97 (d, *J* = 15.5 Hz, 1H, H$_A$C=), 7.87 (ddd, *J* = 8.4, 6.9, 1.4 Hz, 1H, H7), 7.79–7.76 (m, 2H, H2″/H6″), 7.60 (ddd, *J* = 8.4, 6.9, 1.3 Hz, 1H, H6), 7.46 (dd, *J* = 8.4, 7.4 Hz, 1H, H5′), 7.43–7.39 (m, 3H, H3″/H5″, H4″), 7.34 (dt, *J* = 7.4, 1.9 Hz, 1H, H4′), 2.53 (s, 3H, 3′-CH$_3$).

NMR ^{13}C (100 MHz, CDCl$_3$): δ = 161.9 (C4), 160.4 (C2), 152.1 (C8a), 139.5 (=CH$_B$), 138.5 (C1′), 138.2 (C3′), 136.2 (C1″), 133.5 (C7), 131.3 (C4′), 129.6 (C8), 129.3 (C4″), 129.1 (C2′), 128.9 (C3″/C5″), 128.5 (C5′), 128.1 (C2″/C6″), 126.8 (C6), 125.9 (C6′), 123.9 (C5), 121.7 (C4a), 121.1 (H$_A$C=), 21.6 (3′-CH$_3$).

HPLC-ESI$^+$-QTOF-MS: *m/z* [M + H]$^+$ calcd for C$_{23}$H$_{18}$N$_2$: 323.1543, found: 323.1543.

Anal. calcd for C$_{23}$H$_{18}$N$_2$: C, 85.68; H, 5.63; N, 8.69. Found: C, 85.65; H, 5.68; N, 8.67.

4.1.1.3 (E)-2-(3-Nitrophenyl)-4-styrylquinazoline (3c). White solid; yield: 0.295 g (83%); m.p. 178–179 °C; R_f = 0.40 (12.5% ethyl acetate–*n*-heptane).

IR (ATR): $\bar{\nu}_{max}$ (cm^{-1}) 3070 (C_{sp^2}–H), 1631 (C=N), 1560 (C=C_{arom}), 1523 and 1346 (NO$_2$), 969 (=C–H$_{trans}$), 708 and 685 (C_{arom}–H, benzene *p*-subst.).

NMR ^{1}H (400 MHz, CDCl$_3$): δ = 9.54 (t, *J* = 1.9 Hz, 1H, H2′), 9.05 (dt, *J* = 7.8, 1.4 Hz, 1H, H6′), 8.44 (d, *J* = 15.5 Hz, 1H, =

CH$_B$), 8.35 (ddd, *J* = 8.2, 2.4, 1.9 Hz, 1H, H4′), 8.31 (dd, *J* = 8.4, 1.4 Hz, 1H, H5), 8.11–8.09 (m, 1H, H8), 7.95 (d, *J* = 15.5 Hz, 1H, H$_A$C=), 7.91 (ddd, *J* = 8.5, 7.0, 1.5 Hz, 1H, H7), 7.79–7.76 (m, 2H, H2″/H6″), 7.71 (t, *J* = 8.0 Hz, 1H, H5′), 7.66 (ddd, *J* = 8.4, 7.0, 1.4 Hz, 1H, H6), 7.50–7.46 (m, 2H, H3″/H5″), 7.45–7.41 (m, 1H, H4″).

NMR ^{13}C (100 MHz, CDCl$_3$): δ = 162.3 (C4), 157.8 (C2), 151.8 (C8a), 148.8 (C3′), 140.4 (C1′), 140.1 (=CH$_B$), 135.9 (C1″), 134.4 (C6′), 133.9 (C7), 129.9 (C4″), 129.4 (C8, C5′), 129.0 (C3″/C5″), 128.2 (C2″/C6″), 127.6 (C6), 124.8 (C4′), 123.9 (C5), 123.6 (C2′), 121.9 (C4a), 120.5 (H$_A$C=). HPLC-ESI$^+$-QTOF-MS: *m/z* [M + H]$^+$ calcd for C$_{22}$H$_{15}$N$_3$O$_2$: 354.1237, found: 354.1235.

Anal. calcd for C$_{22}$H$_{15}$N$_3$O$_2$: C, 74.78; H, 4.28; N, 11.89. Found: C, 74.77; H, 4.30; N, 11.87.

4.1.1.4 (E)-4-Styryl-2-(4-(trifluoromethyl)phenyl)quinazoline (3d). White solid; yield: 0.316 g (84%); m.p. 141–142 °C; R_f = 0.50 (12.5% ethyl acetate–*n*-heptane).

IR (ATR): $\bar{\nu}_{max}$ (cm^{-1}) 3024 (C_{sp^2}–H), 1632 (C=N), 1534 (C=C_{arom}), 1064 (C_{sp^3}–F), 961 (=C–H$_{trans}$), 858 (C_{arom}–H, benzene *p*-subst.).

NMR ^{1}H (400 MHz, CDCl$_3$): δ = 8.84–8.81 (m, 2H, H2′/H6′), 8.44 (d, *J* = 15.5 Hz, 1H, =CH$_B$), 8.32 (ddd, *J* = 8.3, 1.6, 0.6, 1H, H5), 8.10 (ddd, *J* = 8.5, 1.3, 0.6 Hz, 1H, H8), 7.96 (d, *J* = 15.5 Hz, 1H, H$_A$C=), 7.90 (ddd, *J* = 8.4, 6.9, 1.3 Hz, 1H, H7), 7.82–7.79 (m, 2H, H3′/H5′), 7.79–7.76 (m, 2H, H2″/H6″), 7.64 (ddd, *J* = 8.3, 6.9, 1.3 Hz, 1H, H6), 7.50–7.46 (m, 2H, H3″/H5″), 7.45–7.41 (m, 1H, H4″).

NMR ^{13}C (100 MHz, CDCl$_3$): δ = 162.1 (C4), 158.7 (C2), 151.9 (C8a), 141.9 (C1′), 139.8 (=CH$_B$), 136.0 (C1″), 133.7 (C7), 131.9 (d, *J* = 32.3 Hz, C4′), 129.8 (C4″), 129.4 (C8), 129.0 (C3″/C5″), 128.9 (C2′/C6′), 128.1 (C2″/C6″), 127.4 (C6), 125.4 (q, *J* = 3.7 Hz, C3′/C5′, 4″-CF$_3$), 123.9 (C5), 121.8 (C4a), 120.7 (H$_A$C=).

HPLC-ESI$^+$-QTOF-MS: *m/z* [M + H]$^+$ calcd for C$_{23}$H$_{15}$F$_3$N$_2$: 377.1260, found: 377.1257.

Crystals suitable for X-ray single-crystal diffraction were obtained from a hexane/ethyl acetate (8 : 1) solution, and the crystal data for **3d** were deposited at CCDC with deposition number 2349436:† chemical formula C$_{23}$H$_{15}$F$_3$N$_2$, Mr 376.37; orthorhombic, P2$_1$2$_1$2$_1$; 100 K, cell dimensions *a*, *b*, *c* (Å) 5.0188 (6), 13.9106 (15), 25.986 (3) α, β, γ (°) 90, 90, 90. *V* (Å^3) 1814.2 (4), *Z* = 4, *F*(000) = 776, Dx (Mg m^{-3}) = 1.38, Mo Kα, μ (mm^{-1}) = 0.10, crystal size (mm) = 0.32 × 0.05 × 0.04. Multi-scan absorption correction (SADABS2016/2), T_{min}, T_{max} 0.418, 0.746. No. of measured, independent and observed [*I* > 2σ(*I*)] reflections 15 905, 4131, 3355, R_{int} = 0.096, (sin θ/λ)$_{max}$ (Å^{-1}) = 0.650, θ values (°): θ$_{max}$ = 27.5, θ$_{min}$ = 2.1; Range *h* = −16→16, *k* = −18→18, *l* = −32→33, Refinement, R[*F*^{2} > 2σ(F^2)] = 0.087, wR(*F*^{2}) = 0.195, *S* = 1.19. No. of reflections 4131, No. of parameters 253, No. of restraints 0. Weighting scheme: *w* = 1/σ^2(F$_o$^{2}) + (0.0603P)^2 + 2.0297P where P = (F$_o$^{2} + 2F$_c$^{2})/3. (Δ/σ) < 0.001, Δρ$_{max}$, Δρ$_{min}$ (e Å^{-3}) 0.41, −0.43.

4.1.1.5 (E)-4-Styryl-2-(3,4,5-trimethoxyphenyl)quinazoline (3e). Yellow solid; yield: 0.275 g (69%); m.p. 152–153 °C; R_f = 0.26 (25% ethyl acetate–*n*-heptane).

IR (ATR): $\bar{\nu}_{max}$ (cm^{-1}) 2933 (C_{sp^2}–H), 1630 (C=N), 1441 (C=C_{arom}), 961 (=C–H$_{trans}$).

NMR ^{1}H (400 MHz, CDCl$_3$): δ = 8.39 (d, J = 15.4 Hz, 1H, =CH$_B$), 8.30 (ddd, J = 8.4, 1.3, 0.6 Hz, 1H, H5), 8.09 (ddd, J = 8.4, 1.2, 0.6 Hz, 1H, H8), 8.02 (s, 2H, H2′/H6′), 7.96 (d, J = 15.4 Hz, 1H, H$_A$C=), 7.88 (ddd, J = 8.4, 6.9, 1.3 Hz, 1H, H7), 7.76–7.73 (m, 2H, H2″/H6″), 7.60 (ddd, J = 8.4, 6.9, 1.2 Hz, 1H, H6), 7.50–7.45 (m, 2H, H3″/H5″), 7.44–7.40 (m, 1H, H4″), 4.07 (s, 6H, 3′-/5′-OCH$_3$), 3.96 (s, 3H, 4′-OCH$_3$).

NMR ^{13}C (100 MHz, CDCl$_3$): δ = 161.9 (C4), 159.7 (C2), 153.4 (C3′/C5′), 152.0 (C8a), 140.5 (C4′), 139.5 (=CH$_B$), 136.1 (C1″), 134.0 (C1′), 133.5 (C7), 129.6 (C4″), 129.3 (C8), 129.0 (C3″/C5″), 128.0 (C2″/C6″), 126.8 (C6), 123.9 (C5), 121.6 (C4a), 121.1 (H$_A$C=), 106.0 (C2′/C6′), 61.0 (4′-OCH$_3$), 56.3 (3′-/5′-OCH$_3$).

UHPLC-ESI-Orbitrap-MS: m/z [M + H]$^+$ calcd for C$_{25}$H$_{22}$N$_2$O$_3$: 399.17087, found: 399.17010.

Anal. calcd for C$_{25}$H$_{22}$N$_2$O$_3$: C, 75.36; H, 5.57; N, 7.03. Found: C, 75.40; H, 5.58; N, 7.01.

4.1.1.6   (E)-4-Styryl-2-(5-methylfuran-2-yl)quinazoline (3f). Yellow solid; yield: 0.241 g (77%); m.p. 171–172 °C; R_f = 0.33 (25% ethyl acetate–n-heptane).

IR (ATR): $\bar{\nu}_{max}$ (cm^{-1}) 2912 (C$_{sp^2}$–H), 1631 (C=N), 1547 (C=C$_{arom}$), 1198 (C–O), 966 (=C–H$_{trans}$). NMR ^{1}H (400 MHz, CDCl$_3$): δ = 8.33 (d, J = 15.5 Hz, 1H, =CH$_B$), 8.25 (dd, J = 8.3, 1.3 Hz, 1H, H5), 8.09 (dd, J = 8.4, 1.3 Hz, 1H, H8), 7.91 (d, J = 15.5 Hz, 1H, H$_A$C=), 7.84 (ddd, J = 8.5, 6.9, 1.5 Hz, 1H, H7), 7.75–7.73 (m, 2H, H2″/H6″), 7.56 (ddd, J = 8.3, 6.9, 1.3 Hz, 1H, H6), 7.48 (d, J = 3.1 Hz, 1H, H3′), 7.45–7.44 (m, 2H, H3″/H5″), 7.42–7.38 (m, 1H, H4″), 6.24 (dd, J = 3.1, 1.0 Hz, 1H, H4′), 2.52 (s, 3H, 5′-CH$_3$).

NMR ^{13}C (100 MHz, CDCl$_3$): δ = 162.3 (C4), 155.9 (C5′), 153.7 (C2), 151.7 (C8a), 151.5 (C2′), 139.8 (=CH$_B$), 136.0 (C1″), 133.7 (C7), 129.7 (C4″), 129.1 (C8), 128.9 (C3″/C5″), 128.1 (C2″/C6″), 126.5 (C6), 124.0 (C5), 121.4 (C4a), 120.6 (H$_A$C=), 115.5 (C3′), 108.8 (C4′), 14.3 (5′-CH$_3$). UHPLC-ESI-Orbitrap-MS m/z [M + H]$^+$ calcd for C$_{21}$H$_{16}$N$_2$O: 313.13409; found: 313.13345.

Anal. calcd for C$_{21}$H$_{16}$N$_2$O: C, 80.75; H, 5.16; N, 8.97. Found: C, 80.78; H, 5.13; N, 8.99.

4.1.1.7   (E)-4-Styryl-2-(furan-3-yl)quinazoline (3g). Yellow solid; yield: 0.206 g (69%); m.p. 175–176 °C; R_f = 0.35 (25% ethyl acetate–n-heptane).

IR (ATR): $\bar{\nu}_{max}$ (cm^{-1}) 3063 (C$_{sp^2}$–H), 1628 (C=N), 1535 (C=C$_{arom}$), 1150 (C–O), 966 (=C–H$_{trans}$). NMR ^{1}H (400 MHz, CDCl$_3$): δ = 8.46 (dd, J = 1.7, 0.8 Hz, 1H, H5′), 8.33 (d, J = 15.5 Hz, 1H, =CH$_B$), 8.26 (dd, J = 8.3, 1.5 Hz, 1H, H5), 8.01 (dd, J = 8.4, 1.3 Hz, 1H, H8), 7.92 (d, J = 15.5 Hz, 1H, H$_A$C=), 7.85 (ddd, J = 8.4, 6.9, 1.5 Hz, 1H, H7), 7.76–7.73 (m, 2H, H2″/H6″), 7.57 (ddd, J = 8.3, 6.9, 1.3 Hz, 1H, H6), 7.56 (t, J = 1.7 Hz, 1H, H2′), 7.48–7.44 (m, 2H, H3″/H5″), 7.43–7.39 (m, 1H, H4″), 7.28 (dd, J = 1.7, 0.8 Hz, 1H, H4′).

NMR ^{13}C (100 MHz, CDCl$_3$): δ = 162.0 (C4), 157.0 (C2), 151.9 (C8a), 145.1 (C5′), 143.8 (C2′), 139.5 (=CH$_B$), 136.1 (C1″), 133.5 (C7), 129.7 (C4″), 129.0 (C3″/C5″), 128.9 (C8), 128.1 (C2″/C6″), 127.9 (C3′), 126.6 (C6), 123.9 (C5), 121.6 (C4a), 120.7 (H$_A$C=), 109.9 (C4′).

HPLC-ESI$^+$-QTOF-MS: m/z [M + H]$^+$ calcd for C$_{20}$H$_{14}$N$_2$O: 299.1179; found: 299.1180.

Anal. calcd for C$_{20}$H$_{14}$N$_2$O: C, 80.52; H, 4.73; N, 9.39; O, 5.36. Found: C, 80.56; H, 4.70; N, 9.36.

4.1.1.8   (E)-4-(4-Bromostyryl)-2-phenylquinazoline (3h). Yellow solid; yield: 0.298 g (77%); m.p. 123–125 °C; R_f = 0.50 (9% ethyl acetate–n-heptane).

IR (ATR): $\bar{\nu}_{max}$ (cm^{-1}) 3022 (C$_{sp^2}$–H), 1629.26 (C=N), 1558 (C=C$_{arom}$), 967 (=C–H$_{trans}$), 816 (C$_{arom}$–H, benzene p-subst.), 659 (C$_{sp^2}$–Br).

NMR ^{1}H (400 MHz, CDCl$_3$): δ = 8.73–8.69 (m, 2H, H2′/H6′), 8.38 (d, J = 15.5 Hz, 1H, =CH$_B$), 8.27 (dd, J = 8.4, 1.4 Hz, 1H, H5), 8.10 (dd, J = 8.4, 1.3 Hz, 1H, H8), 7.95 (d, J = 15.5 Hz, 1H, H$_A$C=), 7.88 (ddd, J = 8.4, 6.8, 1.2 Hz, 1H, H7), 7.64–7.52 (m, 8H, H6, H3′/H5′, H4′, H2″/H6″, H3″/H5″).

NMR ^{13}C (100 MHz, CDCl$_3$): δ = 161.5 (C4), 152.1 (C8a), 138.2 (C1′), 138.3 (=CH$_B$), 134.6 (C1″), 133.5 (C7), 132.0 (C3″/C5″), 130.5 (C4′), 129.5 (C2″/C6″), 129.3 (C8), 128.6 (C2′/C6′, C3′/C5′), 126.7 (C6), 124.0 (C4″), 123.6 (C5), 121.5 (C4a), 121.0 (H$_A$C=).

UHPLC-ESI$^+$-Orbitrap-MS: m/z [M + H]$^+$ calcd for C$_{22}$H$_{15}$BrN$_2$, [^{79}Br]: 387.04926; found [^{79}Br]: 387.04919.

4.1.1.9   (E)-4-(4-Chlorostyryl)-2-phenylquinazoline (3i). Yellow solid; yield: 0.264 g (77%); m.p. 115–116 °C; R_f = 0.50 (9% ethyl acetate–n-heptane).

IR (ATR): $\bar{\nu}_{max}$ (cm^{-1}) 3059 (C$_{sp^2}$–H), 1629 (C=N), 1559 (C=C$_{arom}$), 968 (=C–H$_{trans}$), 817 (C$_{arom}$–H, benzene p-subst.), 686 (C$_{sp^2}$–Cl).

NMR ^{1}H (400 MHz, CDCl$_3$): δ = 8.72–8.69 (m, 2H, H2′/H6′), 8.39 (d, J = 15.4 Hz, 1H, =CH$_B$), 8.27 (dd, J = 8.4, 1.3 Hz, 1H, H5), 8.10 (dd, J = 8.4, 1.3 Hz, 1H, H8), 7.93 (d, J = 15.4 Hz, 1H, H$_A$C=), 7.88 (ddd, J = 8.4, 6.9, 1.3 Hz, 1H, H7), 7.71–7.68 (m, 2H, H2″/H6″), 7.61 (ddd, J = 8.3, 6.9, 1.3 Hz, 1H, H6), 7.58–7.54 (m, 2H, H3′/H5′), 7.54–7.50 (m, 1H, H4′), 7.45–7.42 (m, 2H, H3″/H5″).

NMR ^{13}C (100 MHz, CDCl$_3$): δ = 161.6 (C4), 160.2 (C2), 152.1 (C8a), 138.5 (C1′), 138.0 (=CH$_B$), 135.4 (C4″), 134.6 (C1″), 133.6 (C7), 130.5 (C4′), 129.4 (C8), 129.2 (C2″/C6″, C3″/C5″), 128.6 (C2′/C6′, C3′/C5′), 126.9 (C6), 123.7 (C5), 121.6 (C4a), 121.5 (H$_A$C=).

HPLC-ESI$^+$-QTOF-MS: m/z [M + H]$^+$ calcd for C$_{22}$H$_{15}$ClN$_2$, [^{35}Cl/^{37}Cl]: 343.0997/345.0975, found [^{35}Cl/^{37}Cl]: 343.0992/345.0979.

4.1.1.10   (E)-4-(4-Trifluoromethylstyryl)-2-phenylquinazoline (3j). Yellow solid; yield: 0.316 g (84%); m.p. 145–146 °C; R_f = 0.47 (9% ethyl acetate–n-heptane).

FTIR (ATR) $\bar{\nu}_{max}$ (cm^{-1}): 3063 (C$_{sp^2}$–H), 1637 (C=N), 1562 (C=C$_{arom}$), 1319 (C$_{sp^3}$–F), 969 (=C–H$_{trans}$), 831 (C$_{arom}$–H, benzene p-subst.).

NMR ^{1}H (400 MHz, CDCl$_3$): δ = 8.73–8.70 (m, 2H, H2′/H6′), 8.45 (d, J = 15.5 Hz, 1H, =CH$_B$), 8.29 (dd, J = 8.4, 1.4 Hz, 1H, H5), 8.11 (dd, J = 8.4, 1.3 Hz, 1H, H8), 8.03 (d, J = 15.5 Hz, 1H, H$_A$C=), 7.89 (ddd, J = 8.4, 6.9, 1.4 Hz, 1H, H7), 7.86 (d, J = 8.0 Hz, 2H, H2″/H6″), 7.72 (d, J = 8.0 Hz, 2H, H3″/H5″), 7.63 (ddd, J = 8.3, 6.9, 1.3 Hz, 1H, H6), 7.59–7.53 (m, 3H, H3′/H5′, H4′).

NMR ^{13}C (100 MHz, CDCl$_3$): δ = 161.2 (C4), 160.2 (C2), 152.2 (C8a), 139.5 (C1″), 138.3 (C1′), 137.6 (=CH$_B$), 133.7 (C7), 130.6 (C4′), 129.5 (C8), 129.3 (C4″), 128.6 (C3′/C5′, C2′/C6′), 128.1 (C2″/C6″), 127.1 (C6), 125.9 (q, J = 3.7 Hz, C3″/C5″, 4″-CF$_3$), 123.7 (C5), 123.4 (H$_A$C=), 121.7 (C4a).

UHPLC-ESI⁺-Orbitrap-MS: m/z [M + H]⁺ calcd for $C_{23}H_{15}F_3N_2$: 377.12582, found: 377.12656.

*4.1.1.11 (E)-4-(2,3-Dichlorostyryl)-2-phenylquinazoline (**3k**).* Yellow solid; yield: 0.283 g (75%); m.p. 163–165 °C; R_f = 0.34 (9% ethyl acetate–*n*-heptane).

IR (ATR): $\bar{\nu}_{max}$ (cm⁻¹) 3065 (C_{sp^2}–H), 1625 (C=N), 1556 (C=C_{arom}), 967 (=C–H$_{trans}$), 689 (C_{sp^2}–Cl).

NMR ¹H (400 MHz, CDCl₃): δ = 8.80 (d, J = 15.5 Hz, 1H, =CH$_B$), 8.74–8.71 (m, 2H, H2′/H6′), 8.26 (dd, J = 8.3, 1.3 Hz, 1H, H5), 8.11 (dd, J = 8.2, 1.3 Hz, 1H, H8), 7.91 (d, J = 15.5 Hz, 1H, H$_A$C=), 7.91–7.86 (m, 1H, H7), 7.77 (dd, J = 7.9, 1.5 Hz, 1H, H4″), 7.61 (ddd, J = 8.3, 6.9, 1.3 Hz, 1H, H6), 7.59–7.52 (m, 3H, H3′/H5′, H4′), 7.51 (dd, J = 7.9, 1.5 Hz, 1H, H6″), 7.30 (td, J = 7.9, 1.5 Hz, 1H, H5″).

NMR ¹³C (100 MHz, CDCl₃): δ = 161.3 (C4), 160.2 (C2), 152.2 (C8a), 138.3 (C1′), 136.9 (C1″), 135.5 (=CH$_B$), 134.0 (C3″), 133.7 (C7), 133.0 (C2″), 130.8 (C6″), 130.6 (C4′), 129.5 (C8), 128.6 (C2′/C6′, C3′/C5′), 127.4 (C5″), 127.1 (C6), 125.8 (C4″), 125.0 (H$_A$C=), 123.7 (C5), 121.7 (C4a). UHPLC-ESI⁺-Orbitrap-HRMS: m/z [M + H]⁺ calcd for $C_{22}H_{14}Cl_2N_2$, [³⁵Cl, ³⁵Cl]: 377.06068; found: [³⁵Cl, ³⁵Cl]: 377.06104.

*4.1.1.12 (E)-4-(2,4-Dichlorostyryl)-2-phenylquinazoline (**3l**).* Yellow solid; yield: 0.287 g (76%); m.p. 177–178 °C; R_f = 0.44 (9% ethyl acetate–*n*-heptane).

IR (ATR): $\bar{\nu}_{max}$ (cm⁻¹) 3025 (C_{sp^2}–H), 1626 (C=N), 1559 (C=C_{arom}), 968 (=C–H$_{trans}$), 692 (C_{sp^2}–Cl). NMR ¹H (400 MHz, CDCl₃): δ = 8.74 (dd, J = 15.5, 0.6 Hz, 1H, =CH$_B$), 8.73–8.71 (m, 2H, H2′/H6′), 8.25 (dd, J = 8.3, 1.4 Hz, 1H, H5), 8.11 (dd, J = 8.5, 1.3 Hz, 1H, H8), 7.92 (d, J = 15.5 Hz, 1H, H$_A$C=), 7.88 (ddd, J = 8.5, 6.9, 1.4 Hz, 1H, H7), 7.80 (d, J = 8.5 Hz, 1H, H6″), 7.61 (ddd, J = 8.3, 6.9, 1.3 Hz, 1H, H6), 7.58–7.52 (m, 3H, H3′/H5′, H4′), 7.51 (d, J = 2.1 Hz, 1H, H3″), 7.34 (ddd, J = 8.5, 2.1, 0.6 Hz, 1H, H5″).

NMR ¹³C (100 MHz, CDCl₃): δ = 161.3 (C4), 160.2 (C2), 152.2 (C8a), 138.3 (C1′), 135.5 (C2″, C4″), 134.3 (=CH$_B$), 133.6 (C7), 133.1 (C1″), 130.5 (C4′), 130.1 (C3″), 129.5 (C8), 128.6 (C2′/C6′, C3′/C5′), 128.4 (C6″), 127.5 (C5″), 127.1 (C6), 124.1 (H$_A$C=), 123.7 (C5), 121.7 (C4a).

UHPLC-ESI⁺-Orbitrap-HRMS: m/z [M + H]⁺ calcd for $C_{22}H_{14}Cl_2N_2$ [³⁵Cl, ³⁵Cl]: 377.06068; found: [³⁵Cl, ³⁵Cl]: 377.06061.

*4.1.1.13 (E)-4-(3,4-Dichlorostyryl)-2-phenylquinazoline (**3m**).* Yellow solid; yield: 0.290 g (77%); m.p. 174–175 °C; R_f = 0.47 (9% ethyl acetate–*n*-heptane).

IR (ATR): $\bar{\nu}_{max}$ (cm⁻¹) 3065 (C_{sp^2}–H), 1629 (C=N), 1557 (C=C_{arom}), 967 (=C–H$_{trans}$), 689 (C_{sp^2}–Cl). NMR ¹H (400 MHz, CDCl₃): δ = 8.71–8.68 (m, 2H, H2′/H6′), 8.32 (d, J = 15.4 Hz, 1H, =CH$_B$), 8.26 (dd, J = 8.5, 1.4 Hz, 1H, H5), 8.10 (dd, J = 8.5, 1.3 Hz, 1H, H8), 7.92 (d, J = 15.4 Hz, 1H, H$_A$C=), 7.88 (ddd, J = 8.4, 6.9, 1.4 Hz, 1H, H7), 7.84 (d, J = 2.0 Hz, 1H, H2″), 7.61 (ddd, J = 8.4, 6.9, 1.3 Hz, 1H, H6), 7.58–7.51 (m, 5H, H3′/H5′, H4′, H5″, H6″).

NMR ¹³C (100 MHz, CDCl₃): δ = 161.1 (C4), 160.1 (C2), 152.1 (C8a), 138.3 (C1′), 136.6 (=CH$_B$), 136.2 (C1″), 133.7 (C7), 133.4 (C3″), 133.2 (C4″), 130.9 (C5″), 130.6 (C4′), 129.5 (C8, C2″), 128.6 (C2′/C6′, C3′/C5′), 127.1 (C6, C6″), 123.7 (C5), 122.7 (H$_A$C=), 121.6 (C4a).

HPLC-ESI⁺-QTOF-MS: m/z [M + H]⁺, calcd for $C_{22}H_{14}Cl_2N_2$ [³⁵Cl, ³⁵Cl]: 377.0607, found: 377.0605; calcd [³⁵Cl, ³⁷Cl]: 379.0581, found: 379.0583; calcd [³⁷Cl, ³⁷Cl]: 380.0607, found: 380.0610.

*4.1.1.14 (E)-4-(2,6-Dichlorostyryl)-2-phenylquinazoline (**3n**).* Yellow solid; yield: 0.332 g (88%); m.p. 137–139 °C; R_f = 0.53 (9% ethyl acetate–*n*-heptane).

IR (ATR): $\bar{\nu}_{max}$ (cm⁻¹) 3058 (C_{sp^2}–H), 1626 (C=N), 1558 (C=C_{arom}), 975 (=C–H$_{trans}$), 687 (C_{sp^2}–Cl). NMR ¹H (400 MHz, CDCl₃): δ = 8.75–8.72 (m, 2H, H2′/H6′), 8.69 (d, J = 15.8 Hz, 1H, =CH$_B$), 8.29 (d, J = 15.8 Hz, 1H, H$_A$C=), 8.25 (dd, J = 8.3, 1.3 Hz, 1H, H5), 8.11| (dd, J = 8.4, 1.3 Hz, 1H, H8), 7.88 (ddd, J = 8.4, 6.9, 1.3 Hz, 1H, H7), 7.61 (ddd, J = 8.3, 6.9, 1.3 Hz, 1H, H6), 7.59–7.50 (m, 3H, H3′/H5′, H4′), 7.33 (ddd, J = 8.1, 1.4, 0.7 Hz, 1H, H3″), 7.27 (td, J = 8.5, 5.6 Hz, 1H, H4″), 7.15–7.10 (m, 1H, H5″).

NMR ¹³C (100 MHz, CDCl₃): δ = 161.4 (C4), 160.2 (C2), 152.2 (C8a), 138.4 (C1′), 135.2 (C2″/C6″), 133.6 (C7, C1″), 133.0 (=CH$_B$), 130.5 (C4′), 129.5 (C8), 129.4 (H$_A$C=), 129.3 (C4″), 128.9 (C3″/C5″), 128.6 (C2′/C6′, C3′/C5′), 127.1 (C6), 124.0 (C5), 121.9 (C4a).

UHPLC-ESI⁺-Orbitrap-HRMS: m/z [M + H]⁺ calcd for $C_{22}H_{14}Cl_2N_2$ [³⁵Cl, ³⁵Cl]: 377.06068; found: 377.06085.

*4.1.1.15 (E)-4-(2-Chloro-6-fluorostyryl)-2-phenylquinazoline (**3o**).* Yellow solid; yield: 0.318 (88%); m.p. > 141 °C (decomposition); R_f = 0.50 (9% ethyl acetate–*n*-heptane). IR (ATR): $\bar{\nu}_{max}$ (cm⁻¹) 3065 (C_{sp^2}–H), 1622 (C=N), 1557 (C=C_{arom}), 1210 (C_{sp^2}–F), 974 (=C–H$_{trans}$), 686 (C_{sp^2}–Cl).

NMR ¹H (400 MHz, CDCl₃): δ = 8.75–8.72 (m, 2H, H2′/H6′), 8.69 (d, J = 15.8 Hz, 1H, =CH$_B$), 8.29 (d, J = 15.8 Hz, 1H, H$_A$C=), 8.25 (da, J = 8.7 Hz, 1H, H5), 8.11 (dd, J = 8.4, 1.3 Hz, 1H, H8), 7.88 (ddd, J = 8.4, 6.9, 1.3 Hz, 1H, H7), 7.61 (ddd, J = 8.3, 6.9, 1.3 Hz, 1H, H6), 7.59–7.50 (m, 3H, H3′/H5′, H4′), 7.33 (dd, J = 8.1, 1.4 Hz, 1H, H3″), 7.27 (td, J = 8.1, 5.6 Hz, 1H, H4″), 7.15–7.10 (m, 1H, H5″).

NMR ¹³C (100 MHz, CDCl₃): δ = 162.1 (d, J = 255.2 Hz, C6″), 161.8 (C4), 160.1 (C2), 152.2 (C8a), 138.4 (C1′), 136.1 (d, J = 5.7 Hz, C2″), 133.6 (C7), 130.5 (C4′), 129.9 (d, J = 10.5 Hz, C4″), 129.7 (d, J = 2.3 Hz, =CH$_B$), 129.3 (C8), 128.6 (C2′/C6′, C3′/C5′), 128.0 (d, J = 14.5 Hz, H$_A$C=), 127.1 (C6), 126.1 (d, J = 3.1 Hz, C3″), 123.9 (C5), 123.2 (d, J = 14.0 Hz, C1″), 121.8 (C4a), 114.9 (d, J = 23.5 Hz, C5″).

UHPLC-ESI⁺-Orbitrap-MS: m/z [M + H]⁺ calcd for $C_{22}H_{14}ClFN_2$ [³⁵Cl]: 361.09015; found: 361.09078.

4.1.2 General procedure for the synthesis of (E)-4-styrylquinazolines 5. In a 20 mL Radleys reaction tube, 2′-aminochalcones **1** (1.0 mmol), trimethyl orthoformate **4** (3.5 mmol), and ammonium acetate (3.0 mmol) were mixed in ethanol (2.0 mL) at room temperature and then capped. The obtained suspensions were stirred magnetically at 80 °C until completion of the reactions (TLC monitored). Then, the crude mixtures were allowed to cool down to room temperature, and the excess of trimethyl orthoformate and ethanol was removed under reduced pressure. In each case, the residue was extracted with ethyl acetate (3 × 30 mL) followed by washing with water (30 mL) and brine. The combined organic layers were dried over anhydrous sodium sulfate, and the solvent was removed under

reduced pressure. The resulting crude was purified by flash chromatography on silica gel using n-heptane–ethyl acetate mixtures as the eluent $(8:1$ to $5:1)$ to obtain the target compounds **5** as solid substances.

4.1.2.1 (E)-4-(Styryl)quinazoline (5a). Yellow solid; yield: 0.197 g (85%); m.p. 94–96 °C; $R_f = 0.22$ (25% ethyl acetate–n-heptane).

IR (ATR): $\bar{\nu}_{max}$ (cm^{-1}) 3032 (C$_{sp^2}$–H), 1626 (C=N), 1557 (C=C$_{arom}$), 974 (=C–H$_{trans}$).

NMR ^{1}H (400 MHz, CDCl$_3$): δ = 9.29 (s, 1H, H2), 8.32 (dd, J = 8.4, 1.5 Hz, 1H, H5), 8.28 (d, J = 15.5 Hz, 1H, =CH$_B$), 8.05 (dt, J = 8.5, 1.3 Hz, 1H, H8), 7.93 (d, J = 15.5 Hz, 1H, H$_A$C=), 7.90 (ddd, J = 8.4, 6.9, 1.3 Hz, 1H, H7), 7.74–7.71 (m, 2H, H2′/H6′), 7.67 (ddd, J = 8.3, 6.9, 1.3 Hz, 1H, H6), 7.47–7.38 (m, 3H, H3′/H5′, H4′).

NMR ^{13}C (100 MHz, CDCl$_3$): δ = 162.1 (C4), 154.8 (C2), 151.2 (C8a), 139.9 (=CH$_B$), 135.9 (C1′), 133.6 (C7), 129.8 (C4′), 129.1 (C8), 129.0 (C2′/C6′), 128.1 (C3′/C5′), 127.5 (C6), 123.9 (C5), 123.1 (C4a), 120.5 (H$_A$C=).

HPLC-ESI$^+$-QTOF-MS: m/z [M + H]$^+$ calcd for C$_{16}$H$_{12}$N$_2$: 233.1073; found: 233.1076.

Anal. calcd for C$_{16}$H$_{12}$N$_2$: C, 82.73; H, 5.21; N, 12.06. Found: C, 82.77; H, 5.20; N, 12.03.

4.1.2.2 (E)-4-(4-Methoxystyryl)quinazoline (5b). Yellow solid; yield: 0.223 g (85%); m.p. 93–95 °C; $R_f = 0.22$ (25% ethyl acetate–n-heptane).

IR (ATR): $\bar{\nu}_{max}$ (cm^{-1}) 3033 (C$_{sp^2}$–H), 1622 (C=N), 1563 (C=C$_{arom}$), 978 (=C–H$_{trans}$).

NMR ^{1}H (400 MHz, CDCl$_3$): δ = 9.25 (s, 1H, H2), 8.30 (dd, J = 8.5, 1.6 Hz, 1H, H5), 8.25 (d, J = 15.4 Hz, 1H, =CH$_B$), 8.02 (dd, J = 8.5, 1.0 Hz, 1H, H8), 7.88 (ddd, J = 8.3, 6.9, 1.3 Hz, 1H, H7), 7.79 (d, J = 15.4 Hz, 1H, H$_A$C=), 7.70–7.66 (m, 2H, H2′/H6′), 7.64 (ddd, J = 8.4, 6.9, 1.4 Hz, 1H, H6), 6.98–6.95 (m, 2H, H3′/H5′), 3.86 (s, 3H, 4′–OCH$_3$).

NMR ^{13}C (100 MHz, CDCl$_3$): δ = 162.4 (C4), 161.1 (C4′), 151.1 (C8a), 154.8 (C2), 139.6 (=CH$_B$), 133.5 (C7), 129.7 (C2′/C6′), 129.0 (C8), 128.7 (C1′), 127.3 (C6), 123.9 (C5), 123.0 (C4a), 118.0 (H$_A$C=), 114.4 (C3′/C5′), 55.4 (4′-OCH$_3$).

HPLC-ESI$^+$-QTOF-MS: m/z [M + H]$^+$ calcd for C$_{17}$H$_{14}$N$_2$O: 263.1179; found: 263.1185.

Anal. calcd for C$_{17}$H$_{14}$N$_2$O: C, 77.84; H, 5.38; N, 10.68. Found: C, 77.84; H, 5.36; N, 10.65.

Crystals suitable for X-ray single-crystal diffraction were obtained from a hexane/ethyl acetate $(8:1)$ solution, and the crystal data for **5b** were deposited at CCDC with deposition number 2349524:† chemical formula C$_{17}$H$_{14}$N$_2$O, Mr 262.30; orthorhombic, $Pca2_1$; 100 K, cell dimensions a, b, c (Å) 24.6763(13), 3.9753(2), 13.3702(7), α, β, γ (°) 90, 90, 90. V (Å^3) 1311.56(12), $Z = 4$, $F(000) = 552$, Dx (Mg m^{-3}) = 1.328, Mo Kα, μ (mm^{-1}) = 0.084, crystal size (mm) = 0.10 × 0.06 × 0.04. Multiscan absorption correction (SADABS2016/2), T_{min}, T_{max} 0.6632, 0.7455. No. of measured, independent and observed [$I > 2\sigma(I)$] reflections 24 495, 2885, 2668, $R_{int} = 0.051$, (sin θ/λ)$_{max}$ (Å^{-1}) = 0.642, θ values (°): $\theta_{max} = 27.1$, $\theta_{min} = 2.2$; range $h = -31 \rightarrow 31$, $k = -5 \rightarrow 5$, $l = -17 \rightarrow 17$, refinement, $R[F^2 > 2\sigma(F^2)] = 0.031$, wR($F^2$) = 0.074, S = 1.05. No. of reflections 2885, no. of parameters 182, no. of restraints 1. Weighting scheme: $w = 1/$ $\sigma^2(F_o^2) + (0.0603P)^2 + 0.3624P$ where $P = (F_o^2 + 2F_c^2)/3$. $(\Delta/\sigma) <$ 0.001, $\Delta\rho_{max}$, $\Delta\rho_{min}$ (e Å^{-3}) 0.14, −0.18.

4.1.2.3 (E)-4-(4-Bromostyryl)quinazoline (5c). Yellow solid; yield: 0.240 g (77%); m.p. 150–152 °C; $R_f = 0.22$ (25% ethyl acetate–n-heptane).

IR (ATR): $\bar{\nu}_{max}$ (cm^{-1}) 3038 (C$_{sp^2}$–H), 1627 (C=N), 1563 (C=C$_{arom}$), 983 (=C–H$_{trans}$), 661 (C$_{sp^2}$–Br). NMR ^{1}H (400 MHz, CDCl$_3$): δ = 9.29 (s, 1H, H2), 8.31 (dd, J = 8.5, 1.3 Hz, 1H, H5), 8.22 (d, J = 15.5 Hz, 1H, =CH$_B$), 8.06 (dt, J = 8.4, 1.0 Hz, 1H, H8), 7.92 (d, J = 15.5 Hz, 1H, H$_A$C=), 7.91 (ddd, J = 8.4, 6.9, 1.4 Hz, 1H, H7), 7.68 (ddd, J = 8.3, 6.9, 1.3 Hz, 1H, H6), 7.61–7.56 (m, 4H, H2′/H6′, H3′/H5′).

NMR ^{13}C (100 MHz, CDCl$_3$): δ = 161.7 (C4), 154.8 (C2), 151.2 (C8a), 138.5 (=CH$_B$), 134.8 (C1′), 133.7 (C7), 132.2 (C3′/C5′), 129.4 (C2′/C6′), 129.2 (C8), 127.7 (C6), 124.0 (C4′), 123.8 (C5), 123.1 (C4a), 121.1 (H$_A$C=).

HPLC-ESI$^+$-QTOF-MS: m/z [M + H]$^+$ calcd for C$_{16}$H$_{11}$BrN$_2$ [^{79}Br]: 311.0178; found: 311.0177.

4.1.2.4 (E)-4-(4-Chlorostyryl)quinazoline (5d). Yellow solid; yield: 0.221 g (83%); m.p. 162–163 °C; $R_f = 0.22$ (25% ethyl acetate–n-heptane).

IR (ATR): $\bar{\nu}_{max}$ (cm^{-1}) 3058 (C$_{sp^2}$–H), 1626 (C=N), 1535 (C=C$_{arom}$), 977 (=C–H$_{trans}$), 682 (C$_{sp^2}$–Cl). NMR ^{1}H (400 MHz, CDCl$_3$): δ = 9.29 (s, 1H, H2), 8.30 (dd, J = 8.4, 1.7 Hz, 1H, H5), 8.23 (d, J = 15.5 Hz, 1H, =CH$_B$), 8.05 (dd, J = 8.5, 1.8 Hz, 1H, H8), 7.91 (ddd, J = 8.4, 6.9, 1.7 Hz, 1H, H7), 7.89 (d, J = 15.5 Hz, 1H, H$_A$C=), 7.67 (ddd, J = 8.4, 6.9, 1.6 Hz, 1H, H6), 7.67–7.63 (m, 2H, H2′/H6′), 7.43–7.40 (m, 2H, H3′/H5′).

NMR ^{13}C (100 MHz, CDCl$_3$): δ = 161.8 (C4), 154.8 (C2), 151.2 (C8a), 138.4 (=CH$_B$), 135.6 (C4′), 134.4 (C1′), 133.7 (C7), 129.2 (C2′/C6′, C3′/C5′), 129.1 (C8), 127.6 (C6), 123.8 (C5), 123.1 (C4a), 121.0 (H$_A$C=).

HPLC-ESI$^+$-QTOF-MS: m/z [M + H]$^+$ calcd for C$_{16}$H$_{11}$ClN$_2$ [^{35}Cl]: 267.0684; found [^{35}Cl]: 267.0685.

4.1.2.5 (E)-4-(4-Fluorostyryl)quinazoline (5e). Yellow solid; yield: 0.198 g (79%); m.p. 134–136 °C; $R_f = 0.22$ (25% ethyl acetate-n-heptane).

IR (ATR): $\bar{\nu}_{max}$ (cm^{-1}) 3031 (C$_{sp^2}$–H), 1628 (C=N), 1566 (C=C$_{arom}$), 1157 (C$_{sp^2}$–F), 969 (=C–H$_{trans}$). NMR ^{1}H (400 MHz, CDCl$_3$): δ = 9.28 (s, 1H, H2), 8.30 (dt, J = 8.8, 1.0 Hz, 1H, H5), 8.24 (d, J = 15.5 Hz, 1H, =CH$_B$), 8.04 (dd, J = 8.5, 1.0 Hz, 1H, H8), 7.90 (ddd, J = 8.4, 6.9, 1.3 Hz, 1H, H7), 7.84 (d, J = 15.5 Hz, 1H, H$_A$C=), 7.72–7.69 (m, 2H, H2′/H6′), 7.66 (ddd, J = 8.3, 6.9, 1.3 Hz, 1H, H6), 7.16–7.11 (m, 2H, H3′/H5′).

NMR ^{13}C (100 MHz, CDCl$_3$): δ = 163.6 (d, J = 251.3 Hz, C4′), 161.9 (C4), 154.8 (C2), 151.2 (C8a), 138.6 (=CH$_B$), 133.7 (C7), 132.1 (d, J = 2.2 Hz, C1′), 129.8 (d, J = 8.2 Hz, C2′/C6′), 129.1 (C8), 127.6 (C6), 123.8 (C5), 123.0 (C4a), 120.2 (d, J = 2.3 Hz, H$_A$C=), 116.1 (d, J = 22.0 Hz, C3′/C5′). HPLC-ESI$^+$-QTOF-MS: m/z [M + H]$^+$ calcd for C$_{16}$H$_{11}$FN$_2$: 251.097; found: 251.0978.

4.1.2.6 (E)-4-(4-(Trifluoromethyl)styryl)quinazoline (5f). Yellow solid; yield: 0.243 g (81%); m.p. 156–157 °C; $R_f = 0.26$ (25% ethyl acetate–n-heptane).

IR (ATR): $\bar{\nu}_{max}$ (cm^{-1}) 3039 (C$_{sp^2}$–H), 1629 (C=N), 1541 (C=C$_{arom}$), 1109 (C$_{sp^3}$–F), 973 (=C–H$_{trans}$). NMR ^{1}H (400 MHz, CDCl$_3$): δ = 9.32 (s, 1H, H2), 8.29 (d, J = 8.6 Hz, 1H, H5), 8.29 (d, J = 15.5 Hz, 1H, =CH$_B$), 8.08 (d, J = 8.52 Hz, 1H, H8), 8.00 (d, J

= 15.5 Hz, 1H, H$_A$C=), 7.93 (ddd, J = 8.4, 6.8, 1.4 Hz, 1H, H7), 7.82 (d, J = 8.1 Hz, 2H, H2'/H6'), 7.70 (ddd, J = 8.4, 6.9, 1.2 Hz, 1H, H6), 7.70 (d, J = 8.1 Hz, 2H, H3'/H5').

NMR ^{13}C (100 MHz, CDCl$_3$): δ = 161.4 (C4), 154.8 (C2), 151.3 (C8a), 139.3 (C1'), 138.0 (=CH$_B$), 133.8 (C7), 131.2 (d, J = 32.4 Hz, C4'), 129.2 (C8), 127.8 (C6), 128.1 (C2'/C6', C3'/C5'), 125.9 (q, J = 3.8 Hz, 4'-CF$_3$), 123.7 (C5), 123.1 (C4a), 122.9 (H$_A$C=).

HPLC-ESI$^+$-QTOF-MS: m/z [M + H]$^+$ calcd for C$_{17}$H$_{11}$F$_3$N$_2$: 301.0947; found: 301.0946.

Crystals suitable for X-ray single-crystal diffraction were obtained from a hexane/ethyl acetate (8 : 1) solution, and the crystal data for **5f** were deposited at CCDC with deposition number 2349522:† chemical formula C$_{17}$H$_{11}$F$_3$N$_2$, Mr 300.28; monoclinic, $P2_1/c$; 100 K, cell dimensions a, b, c (Å) 13.1299 (8), 13.2052 (9), 7.7725 (4) $α$, $β$, $γ$ (°) 90, 95.083 (2), 90. V (Å^3) = 1342.32 (14), Z = 4, F (000) = 616, Dx (Mg m^{-3}) = 1.49, Mo Kα, $μ$ (mm^{-1}) = 0.118, crystal size (mm) = 0.12 × 0.06 × 0.05. Multiscan absorption correction (SADABS2016/2), T_{min}, T_{max} 0.669, 0.746. No. of measured, independent and observed [$I > 2σ(I)$] reflections 30 816, 2951, 2229, R_{int} = 0.076, (sin $θ/λ$)$_{max}$ (Å^{-1}) = 0.642, $θ$ values (°): $θ_{max}$ = 27.1, $θ_{min}$ = 2.2; range h = −16 → 16, k = −16 → 16, l = −9 → 9, refinement, $R[F^2 > 2σ(F^2)]$ = 0.055, wR(F^2) = 0.132, S = 1.8. No. of reflections 2951, no. of parameters 199, no. of restraints 0. Weighting scheme: w = $1/σ^2(F_o^2)$ + $(0.0381P)^2$ + 1.6974P where P = $(F_o^2 + 2F_c^2)/3$. ($Δ/σ$) < 0.001, $Δρ_{max}$, $Δρ_{min}$ (e Å^{-3}) 0.52, −0.48.

4.1.2.7 (E)-4-(2,6-dichlorostyryl)quinazoline (5g). Yellow solid; yield: 0.247 g (82%); m.p. 154–156 °C; R_f = 0.30 (17% ethyl acetate–n-heptane).

IR (ATR): $\bar{v}_{max}$ (cm^{-1}) 3032 (C$_{sp^2}$–H), 1631 (C=N), 1538 (C=C$_{arom}$), 968 (=C–H$_{trans}$), 756 (C$_{sp^2}$–Cl). NMR ^{1}H (400 MHz, CDCl$_3$): δ = 9.36 (s, 1H, H2), 8.32 (d, J = 15.5 Hz, 1H, =CH$_B$), 8.25 (dd, J = 8.6, 1.4 Hz, 1H, H5), 8.11 (d, J = 15.5 Hz, 1H, H$_A$C=), 8.07 (dd, J = 8.5, 1.4 Hz, 1H, H8), 7.92 (ddd, J = 8.5, 6.9, 1.4 Hz, 1H, H7), 7.67 (ddd, J = 8.5, 6.9, 1.4 Hz, 1H, H6), 7.42 (d, J = 8.1 Hz, 2H, H3'/H5'), 7.22 (t, J = 8.1 Hz, 1H, H4').

NMR ^{13}C (100 MHz, CDCl$_3$): δ = 161.6 (C4), 155.0 (C2), 151.2 (C8a), 135.2 (C2'/C6'), 133.8 (C7), 133.5 (C1'), 133.4 (=CH$_B$), 129.4 (C4'), 129.3 (H$_A$C=), 129.1 (C8), 128.9 (C3'/C5'), 127.8 (C6), 124.0 (C5), 123.3 (C4a).

HPLC-ESI$^+$-QTOF-MS: m/z [M + H]$^+$ calcd for C$_{16}$H$_{10}$Cl$_2$N$_2$ [^{35}Cl]: 301.0294; found [^{35}Cl]: 301.0296.

4.1.2.8 (E)-4-(2-Chloro-6-fluorostyryl)quinazoline (5h). Beige solid; yield: 0.245 g (79%); m.p. 130–131 °C; R_f = 0.30 (17% ethyl acetate–n-heptane).

IR (ATR): $\bar{v}_{max}$ (cm^{-1}) 3038 (C$_{sp^2}$–H), 1625 (C=N), 1539 (C=C$_{arom}$), 1198 (C$_{sp^2}$–F), 970 (=C–H$_{trans}$), 757 (C$_{sp^2}$–Cl).

NMR ^{1}H (400 MHz, CDCl$_3$): δ = 9.35 (s, 1H, H2), 8.48 (d, J = 15.8 Hz, 1H, =CH$_B$), 8.28 (dt, J = 8.4, 1.2 Hz, 1H, H5), 8.25 (d, J = 15.8 Hz, 1H, H$_A$C=), 8.06 (dt, J = 8.5, 1.2 Hz, 1H, H8), 7.91 (ddd, J = 8.4, 6.9, 1.4 Hz, 1H, H7), 7.68 (ddd, J = 8.4, 6.9, 1.3 Hz, 1H, H6), 7.32–7.29 (m, 1H, H3'), 7.26 (td, J = 8.0, 5.4 Hz, 1H, H4'), 7.12 (dddd, J = 11.1, 8.1, 1.6, 0.6 Hz, 1H, H5').

NMR ^{13}C (100 MHz, CDCl$_3$): δ = 162.1 (d, J = 254.5 Hz, C6'), 161.9 (C4), 154.9 (C2), 151.2 (C8a), 136.2 (d, J = 5.2 Hz, C2'), 133.7 (C7), 130.1 (d, J = 3.0 Hz, =CH$_B$), 130.1 (d, J = 10.8 Hz, C4'), 129.1 (C8), 127.7 (d, J = 13.7 Hz, H$_A$C=), 127.6 (C6), 126.1

(d, J = 3.6 Hz, C3'), 124.0 (C5), 123.2 (C4a), 123.0 (d, J = 14.0 Hz, C1'), 119.9 (d, J = 23.5 Hz, C5').

HPLC-ESI$^+$-QTOF-MS: m/z [M + H]$^+$ calcd for C$_{16}$H$_{10}$ClFN$_2$ [^{35}Cl]: 285.0589; found [^{35}Cl]: 285.0591.

4.1.2.9 (E)-4-(3,4,5-Trimethoxystyryl)quinazoline (5i). Yellow solid; yield: 0.258 g (80%); m.p. 181–182 °C; R_f = 0.20 (33.3% ethyl acetate–n-heptane).

IR (ATR): $\bar{v}_{max}$ (cm^{-1}) 3040 (C$_{sp^2}$–H), 1625 (C=N), 1560 (C=C$_{arom}$), 972 (=C–H$_{trans}$).

NMR ^{1}H (400 MHz, CDCl$_3$): δ = 9.26 (s, 1H, H2), 8.32 (dt, J = 8.4, 1.4 Hz, 1H, H5), 8.21 (d, J = 15.4 Hz, 1H, =CH$_B$), 8.04 (dd, J = 8.4, 1.2 Hz, 1H, H8), 7.89 (ddd, J = 8.4, 6.9, 1.4 Hz, 1H, H7), 7.79 (d, J = 15.4 Hz, 1H, H$_A$C=), 7.66 (ddd, J = 8.4, 6.9, 1.4 Hz, 1H, H6), 6.94 (s, 2H, H2'/H6'), 3.95 (s, 6H, 3'-/5'-OCH$_3$), 3.91 (s, 3H, 4'-OCH$_3$).

NMR ^{13}C (100 MHz, CDCl$_3$): δ = 162.0 (C4), 154.8 (C3'/C5'), 153.6 (C2, C4'), 151.2 (C8a), 140.0 (=CH$_B$), 133.6 (C7), 131.4 (C1'), 129.1 (C8), 127.5 (C6), 123.9 (C5), 123.0 (C4a), 119.7 (H$_A$C=), 105.4 (C2'/C6'), 61.0 (4'-OCH$_3$), 56.3 (3'-/5'-OCH$_3$).

HPLC-ESI$^+$-QTOF-MS: m/z [M + H]$^+$ calcd for C$_{19}$H$_{18}$N$_2$O$_3$: 323.1390; found: 323.1391.

Anal. calcd for C$_{19}$H$_{18}$N$_2$O$_3$: C, 70.79; H, 5.63; N, 8.69. Found: C, 70.76; H, 5.60; N, 8.72.

4.1.2.10 (E)-4-(2-(Thiophen-2-yl)vinyl)quinazoline (5j). Yellow solid; yield: 0.191 g (80%); m.p. 74–75 °C; R_f = 0.30 (25% ethyl acetate–n-heptane).

IR (ATR): $\bar{v}_{max}$ (cm^{-1}) 3057 (C$_{sp^2}$–H), 1617 (C=N), 1534 (C=C$_{arom}$), 948 (=C–H$_{trans}$).

NMR ^{1}H (400 MHz, CDCl$_3$): δ = 9.25 (s, 1H, H2), 8.42 (d, J = 15.0 Hz, 1H, =CH$_B$), 8.27 (d, J = 8.4 Hz, 1H, H5), 8.03 (d, J = 8.3 Hz, 1H, H8), 7.89 (ddd, J = 8.3, 7.0, 1.3 Hz, 1H, H7), 7.69 (d, J = 15.0 Hz, 1H, H$_A$C=), 7.67–7.64 (m, 1H, H6), 7.40 (d, J = 5.1 Hz, 1H, H5'), 7.37 (d, J = 3.6 Hz, H3'), 7.11–7.09 (m, 1H, H4').

NMR ^{13}C (100 MHz, CDCl$_3$): δ = 161.8 (C4), 154.8 (C2), 151.1 (C8a), 141.4 (C2'), 133.6 (C7), 132.5 (=CH$_B$), 130.7 (C3'), 129.0 (C8), 128.3 (C4'), 127.8 (C5'), 127.5 (C6), 123.9 (C5), 122.9 (C4a), 119.4 (H$_A$C=).

HPLC-ESI$^+$-QTOF-MS: m/z [M + H]$^+$ calcd for C$_{14}$H$_{10}$N$_2$S: 239.0637; found: 239.0640.

Anal. calcd for C$_{14}$H$_{10}$N$_2$S: C, 70.56; H, 4.23; N, 11.76; S, 13.45. Found: C, 70.54; H, 4.22; N, 11.73; S, 13.41.

Data availability

The data supporting this article have been included as part of the ESI† (^{1}H and ^{13}C NMR spectra of compounds **3** and **5**). Growth inhibitory percentage (GI%) of compounds **3** over all tested *in vitro* tumor cell lines (Table 1S†). Growth inhibitory percentage (GI%) of compounds **5** over all tested *in vitro* tumor cell lines (Table 2S†). Crystallographic data for compounds **3d**, **5b** and **5f** have been deposited at CCDC with deposition numbers 2349436, 2349524, and 2349522, respectively.†

Author contributions

All authors declare that they have all participated in the execution and analysis of the paper and approved the final version.

Conflicts of interest

There are no conflicts to declare.

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