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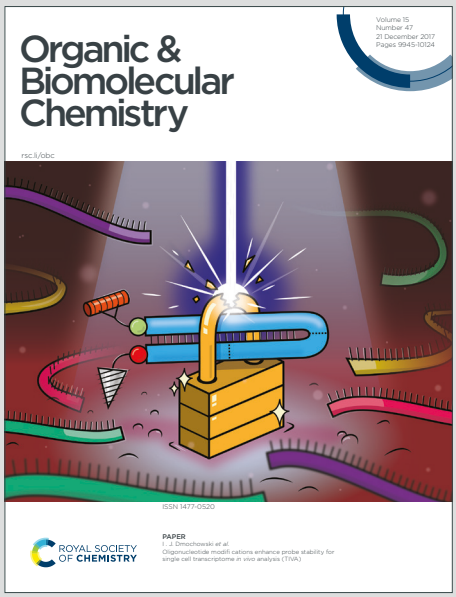

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TMSOTf-Catalyzed Synthesis of Substituted Quinazolines Using Hexamethyldisilazane as Nitrogen Source under Neat and Microwave Irradiation

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ABSTRACT: In this article, we report an efficient and mild synthetic route for the construction of substituted quinazolines from functionalized 2-aminobenzophenones with various benzaldehydes by *cat*. TMSOTf and hexamethyldisilazane (HMDS) under neat, metal-free and microwave irradiation condition in which the gaseous ammonia was formed *in situ*. This synthetic protocol provided the desired quinazolines with a broad substrate scope in good to excellent yields. Some structures were confirmed by X-ray single-crystal diffraction analysis.

Quinazoline is a privileged skeleton occurring commonly in many natural products,[1] some metal complex ligands[2] and various synthetic molecules with diverse pharmaceutical properties, including antibacterial,[3] anticancer,[4] anticonvulsant,[5] anti-inflammatory,[6] antiplasmodial,[7] antitumor,[8] antimicrobial,[9] antioxidant,[10] anti-HIV,[11] antitubercular[12] and as an α-adrenergic blocker.[13] Additionally, its derivatives have been applied as photochemotherapeutic agents,[14] DNA-gyrase, JAK2, PDE5 and EGFR (epidermal growth factor receptor) tyrosine kinase inhibitors[15] and CB2 receptor agonists.[16] Some quinazoline-based drugs are shown in Figure 1. Prazosin, an orally available sympatholytic drug is used for the treatment of hypertension, anxiety and post-traumatic stress disorder.[17] Vasicine is a quinazoline alkaloid isolated from *Adhatoda vasica* with bronchodilatory activity displayed both *in vivo* and *in vitro*.[18]

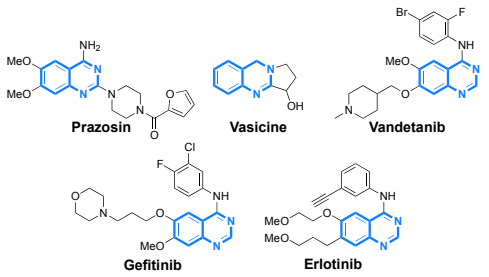

Figure 1. Examples of Bioactive Quinazoline-based Drugs

Vandetanib is the first FDA approved drug applied for the treatment of late-stage medullary thyroid cancer.[19] Gefitinib and Erlotinib demonstrated promising clinical activity acting as EGFR tyrosine kinase inhibitors,[20] and used for treating lung and pancreatic cancers.[21] Owing to many biologically active properties and pharmaceutically applications of quinazoline derivatives, the development of these compounds has evoked great interest.[22]

Numerous synthetic strategies were well-established for the construction of substituted quinazoline scaffold starting from various *ortho*-functionalized anilines, including 2-aminobenzyl alcohols,[23] 2-aminobenzoic acids,[24] 2-aminobenzonitriles,[25] 2-aminobenzylamines,[26] 2-

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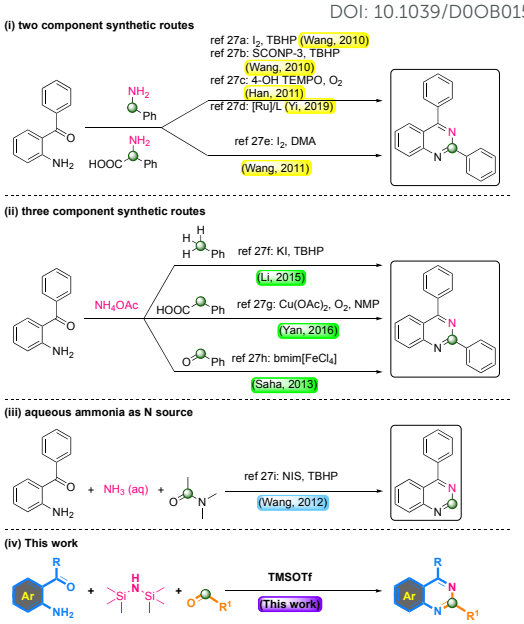
aminobenzaldehydes and 2-aminobenzophenones.[27] In additions to *ortho*-functionalized anilines, *o*-nitroacetophenone were used as raw materials for the synthesis of substituted quinazolines via a hydrogen-transfer strategy,[28] and non-substituted aniline were used as starting materials for the preparation of substituted quinazolines via a four-component intermolecular condensation method.[29] Among these, most popular synthetic routes for the preparation of functionalized quinazoline skeletons were performed from 2-aminobenzophenones with various N sources and diverse one carbon synthons. As illustrated in Scheme 1, a variety of synthetic protocols from 2-aminobenzophenone have been developed, including: (i) two components synthetic routes with benzylamine by using I_2/TBHP,[27a] SCONP-3/TBHP,[27b] 4-OH TEMPO/O_2,[27c] ruthenium catalytic system [Ru]/L,[27d] with α-amino acid catalyzed by I_2/TBHP oxidative decarboxylative amination,[27e] (ii) three components synthetic routes with ammonium acetate as N source with one carbon synthon obtained from benzylic carbon in KI/TBHP catalytic system,[27f] arylacetic acid by using $Cu(OAc)_2/O_2$/NMP,[27g] or aromatic aldehyde catalyzed by ionic liquid bmim[$FeCl_4$],[27h] and (iii) NH_4OAc as N source with DMA as one carbon synthon by the involvement of NIS/TBHP system.[27i] These methodologies were broadly established, considering their substrate generality, multistep procedure, requirement of inert atmosphere, stringent condition and involvement of expensive catalysts, ligands or additives. Due to the importance of quinazoline derivatives in biological and medicinal chemistry, the development of a facile, effective and environmentally benign protocol that is obtained from readily available starting materials and reagents would be highly desired.[30]

Hexamethyldisilazane (HMDS) is a stable, commercially available reagents used for the silylation reactions by utilizing various catalysts and high temperature to increase the silylating power.[31] In our previous work, the TMSOTf-catalyzed HMDS silylation carbohydrates which provided gaseous ammonia as the only by-product.[32] Therefore, TMSOTf/HMDS could be considered as an appropriate system to obtain ammonium as N source. Furthermore, based on our successful experience associated with the synthesis of quinoline skeletons under microwave irradiation condition.[33] Herein, we developed an effective and conventional synthetic protocol for the construction of quinazoline scaffold by using TMSOTf/HMDS catalytic system under neat and microwave irradiation condition, as illustrated in Scheme 1, equation (iv).

Scheme 1. Synthetic Methods For Developing Quinazolines from 2-Aminobenzophenone



Initially, the reaction of 2-aminobenzophenone (**1a**) with benzaldehyde (**2a**) and use of HMDS as N source were selected as model substrates under microwave irradiation to optimize the reaction conditions, as shown in Table 1. Based on the reported literature,[34] gaseous ammonia was found when the silylation of alcohol occurred in presence of nitromethane at room temperature. In entries 1-3, the formation of **3a** failed when we used EtOH as additive and $MeNO_2$ as solvent at rt and only 30% yield of product was obtained under heating. To the best of our knowledge, HMDS could be activated by various catalysts.[34] Therefore, we further changed the additive to Lewis acids for the generation of gaseous ammonia. In entries 4-9, some metal triflates were used such as AgOTf, $Fe(OTf)_2$, $Sn(OTf)_2$, $Fe(OTf)_3$, $Fe(OTf)_3$ and non-metal triflate TMSOTf catalyzed the formation of desired quinazoline **3a** under microwave irradiation resulting in high yields. Non-metal Lewis acids such as $InCl_3$ catalyzed the formation of **3a** in 45% yield, but $AlCl_3$ provided some unknown products (entries 10 and 11). Other Brønsted acids, including *p*-TsOH and TfOH were also investigated, but no reaction occurred with these (entries 12 and 13). Replacing the reaction solvents with DCM, MeCN and 1,4-dioxane, the yields showed that toluene was the best medium (entries 14-16). As we know, HMDS is a liquid reagent, we further examined its reaction properties in a solvent-free and neat condition, no obvious yield changes was observed (entry 17). Decreasing the reaction temperature from 150°C to 100°C showed that only 50% yield of **3a** was isolated and it turned complicated at room temperature (entries 18-19). Increasing the reaction temperature to 200°C demonstrated that the yield of **3a** was slightly lowered (entry 20). Considering the fact that conventional experimental operation resulted in the formation of unnecessary waste, conducting neat reaction condition served as a good reaction medium. Therefore, we think that non-metal TMSOTf catalyzed HMDS *in situ* generation of gaseous ammonia to synthesize quinazoline scaffold from 2-aminobenzophenone (**1a**) and benzaldehyde (**2a**) was the optimized reaction condition for conducting the experiments.

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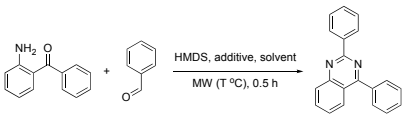
Table 1. Optimization of the Reaction Conditions[a]

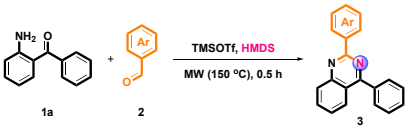


1a 2a 3a

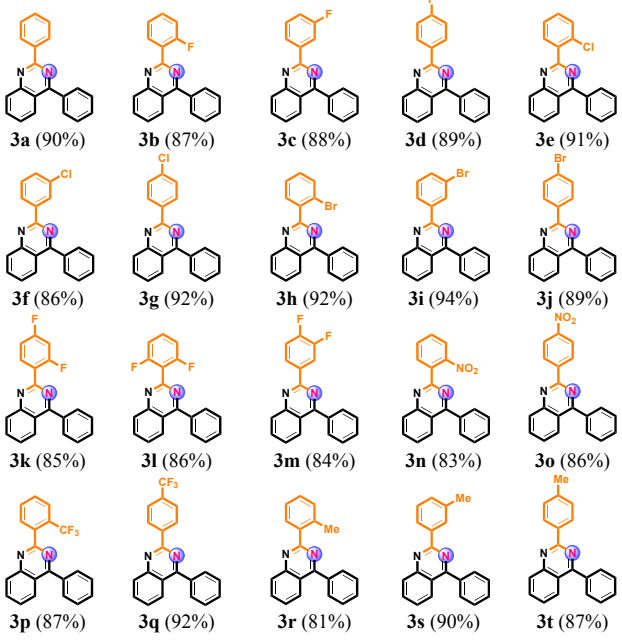
Entry	Additive	Solvent	Temperature (°C)	Yield (%)[b]
1	EtOH	$MeNO_2$	25	N.R.
2	--	$MeNO_2$	25	N.R.
3	--	$MeNO_2$	150	30
4	AgOTf	Toluene	150	87
5	$Fe(OTf)_2$	Toluene	150	85
6	$Sn(OTf)_2$	Toluene	150	86
7	$Fe(OTf)_3$	Toluene	150	84
8	$Bi(OTf)_3$	Toluene	150	88
9	TMSOTf	Toluene	150	88
10	$InCl_3$	Toluene	150	45
11	$AlCl_3$	Toluene	150	—[c]
12	*p*-TsOH	Toluene	150	N.R.
13	TfOH	Toluene	150	N.R.
14	TMSOTf	DCM	150	88
15	TMSOTf	MeCN	150	20
16	TMSOTf	1,4-Dioxane	150	60
17[d]	TMSOTf	--	150	90
18[d]	TMSOTf	--	100	50
19[d]	TMSOTf	--	25	—[c]
20[d]	TMSOTf	--	200	75

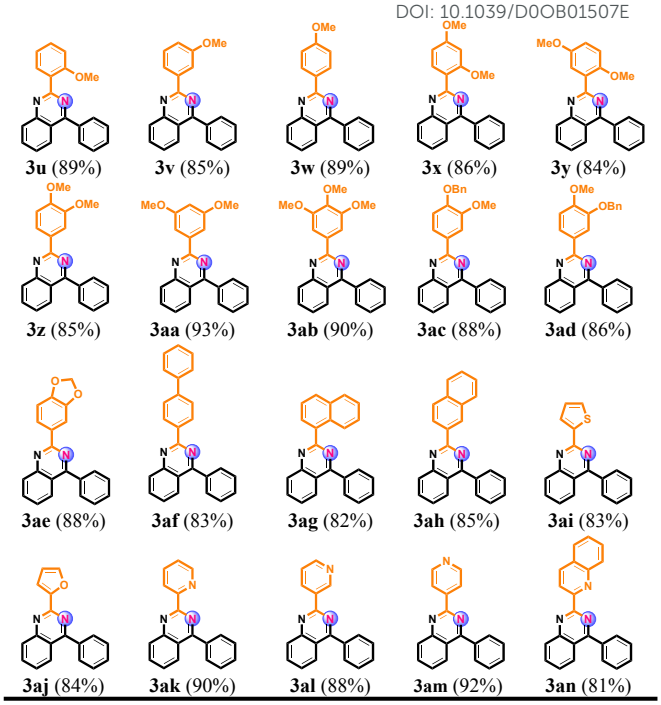
[a] Reaction conditions: **1a** (1.0 mmol), **2a** (1.05 mmol), HMDS (0.3 mL), additive (0.1 mmol), solvent (5 mL), MW, 0.5 h. [b] Isolated yields. [c] Complicated products were formed. [d] HMDS (0.5 mL).

Table 2. Substrate Scope of Aromatic Aldehydes 2[a,b]



1a 2 3



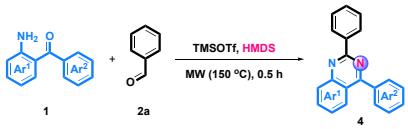


[a] Reaction conditions: **1a** (1.0 mmol), **2** (1.05 mmol), HMDS (1.0 mL), TMSOTf (0.1 mmol), MW, 0.5 h. [b] Isolated yields.

On the basis of the optimal reaction conditions in hand, **3a** was prepared at 90% yield. Next, the substrate scope of aromatic benzaldehyde **2** was investigated with 2-aminobenzophenone (**1a**) under optimized reaction conditions. As shown in Table 2, the aromatic benzaldehydes **2b-2q** with electron-withdrawing groups, such as -F, -Cl, -Br, $-NO_2$ and $-CF_3$ were well reacted with **1a** to afford corresponding products **3b-3q** in moderate to good yields. The reaction of **1a** with various electron-donating functional groups on aromatic benzaldehydes **2r-2ah** were conducted smoothly for the preparation of desired quinazolines **3r-3ah** resulting in good to excellent yields. Nevertheless, an array of heterocyclic carbaldehydes, such as 2-thiophenyl **2ai**, 2-furanyl **2aj**, 2-pyridyl **2ak**, 3-pyridyl **2al**, 4-pyridyl **2am** and 2-quinolinyl **2an** were also well tolerated and the corresponding quinazolines **3ai-3an** were obtained in modest yields.[35] The structures of **3c**, **3l**, **3w**, **3aa** and **3ab** were confirmed by single-crystal X-ray crystallography.[36]

We subsequently investigated the structural diversity of substituted 2-aminobenzophenones **1b-1o** by assessing the substitution effect on both the two aromatic rings. As shown in Table 3, the functional groups on Ar^1 and Ar^2 with a wide range of substitution were examined. The electron-withdrawing groups, (-F, -Cl, -Br and $-NO_2$), or electron-donating groups (methyl, methoxy) at Ar^1 or Ar^2 rings were appropriately managed in this synthetic protocol. The reaction of **1** with **2a** were conducted smoothly and the corresponding products **4a-4n** were isolated in moderate to good yields. The structures of **4h** was also confirmed by single-crystal X-ray crystallography.[36]

Table 3. Substrate Scope of 2-aminobenzophenones 1[a,b]



1 2a 4

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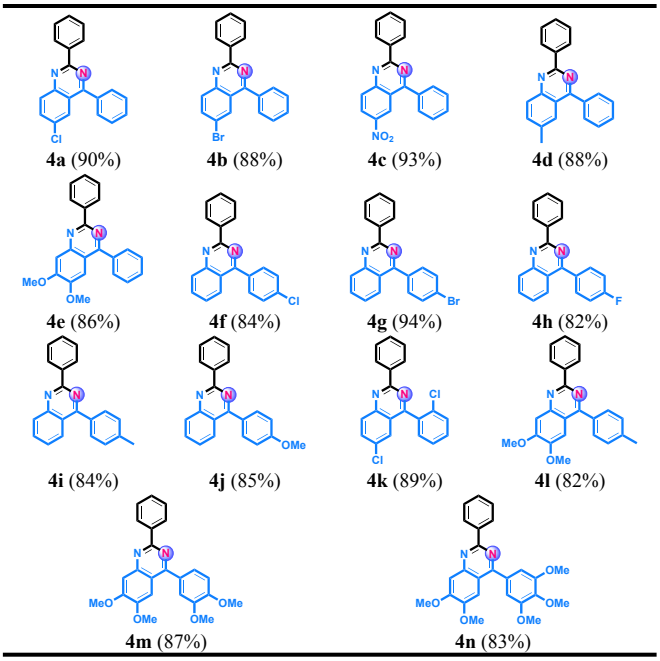
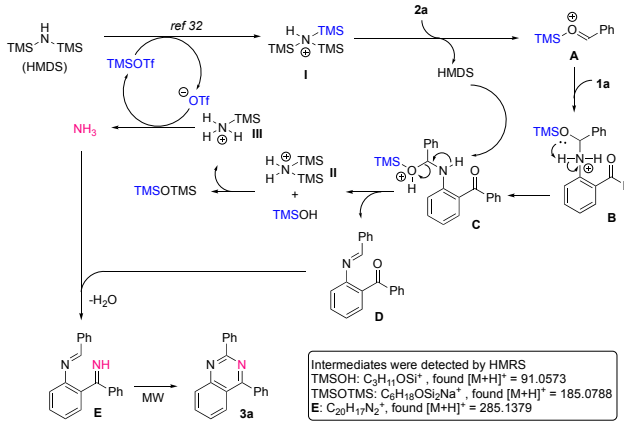


[a] Reaction conditions: **1** (1.0 mmol), **2a** (1.05 mmol), HMDS (1.0 mL), TMSOTf (0.1 mmol), MW, 0.5 h. [b] Isolated yields.

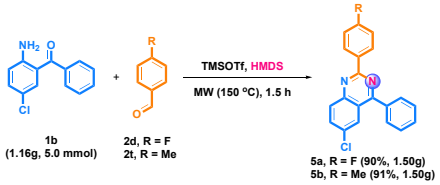
On the basis of the experimental results as shown in Tables 1-2, a plausible mechanism was speculated as demonstrated in Scheme 2. Initially, the system of TMSOTf and HMDS could form complex **I** with the releases of triflate anion. The reaction of benzaldehyde **2a** took place with **I** to generate oxonium **A**. Next, the intermolecular addition of 2-aminobenzophenone **1a** with intermediate **A** occurred to form intermediate **B**. The deprotonation of **C** was performed by the involvement of HMDS to afford intermediate **D**. At the same time, the complex **II** reacted with TMSOH to give the silylated product TMSOTMS ether and complex **III**, which could be further transformed to gaseous ammonia by triflate anion, and TMSOTf could be regenerated. Finally, the imination and oxidation of *in situ* ammonia with intermediate **D** to form **E** under microwave irradiation to obtain desired quinazoline **3a**. Notably, the *in situ* mass spectrometry analysis of TMSOH, TMSOTMS and intermediate **E** were detected.[37]

Scheme 2. Plausible Mechanism



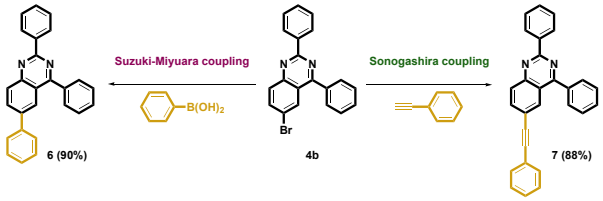
Furthermore, the gram-scale synthesis of quinazolines **5** is shown in Scheme 3.When the reaction scale of **1b** increased to 5.0 mmol (1.16 g) with the addition of **2d** (650 mg) and **2t** (630 mg) for conducting the TMSOTf-catalyzed intermolecular cyclization in 1.5 h, it was seen that the desired quinazolines **5a** and **5b** were isolated in 90% and 91% yields respectively. The results showed that the substituents on the substrates **1** and **2** did not influence the results in gram-scale synthesis.

Scheme 3. Gram-Scale Synthesis of Quinazolines 5



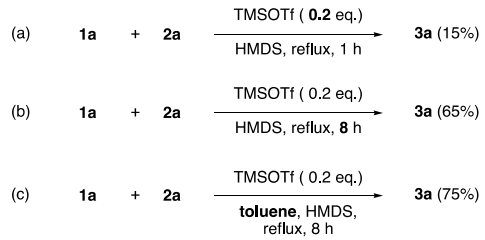
Interestingly, the quinazolines prepared from our synthetic protocol can smoothly undergo further synthetic modification, as illustrated in Scheme 4. The desired biaryl product **6** could be prepared *via* Suzuki-Miyaura coupling reaction of **4b** with phenylboronic acid. Nevertheless, $Pd(PPh_3)_4$/CuI-catalyzed Sonogashira coupling reaction of **4b** with phenylacetylene gave the alkynylated quinazoline **7** in a moderate yield.

Scheme 4. Synthetic Applications of Quinazolines



Notably, the preparation of **3a** from **1a** and **2a** by using a normal hot plate as a heating source was also examined in some control experiments, as shown in Scheme 5. It was noticed that increasing the amount of TMSOTf led to the isolation of our desired product **3a** in poor yield with recovered starting materials (eq. a). Additionally, to extend the reaction time from 1 h to 8 h, the reaction could afford **3a** with a significant growth (eq. b). When the reaction was performed in the presence of cosolvent, toluene and HMDS, the product yield increased by 10% (eq. c). On the basis of the findings observed in these control experiments and reported literatures, we can conclude that microwave irradiation is a better heating source than a normal hot plate for the preparation of substituted quinazoline scaffolds.[38]

Scheme 5. Control Experiments



In summary, we developed a methodology for TMSOTf-catalyzed HMDS *in situ* generation of gaseous ammonia for the synthesis of substituted quinazolines from functionalized 2-aminobenzophenones and aromatic aldehydes *via* a neat, metal-free under microwave irradiation reaction conditions. This protocol could afford substituted quinazolines in high yields by the involvement of quantitative ammonia through

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controlling the exact amounts of HMDS and catalytic amount of TMSOTf. The plausible mechanism was proposed. Some structures were confirmed by X-ray single-crystal diffraction analysis. Considering the functions of the quinazoline scaffold, further investigation of biological and medicinal activities will be conducted and published in due course.

EXPERIMENTAL SECTION

General Information. All reagents and solvents were commercially available and used without further purification. Reactions were routinely performed using the Discover SP system (CEM) in the sealed reaction vessels in standard mode with the temperature monitored using a vertically focused IR sensor. All reactions were monitored by TLC on silica gel 60 F254 (Merck) with detection by UV light. Column chromatography was performed using silica gel (200–300 mesh). Products in organic solvents were dried with anhydrous magnesium sulfate before concentration in vacuo. Melting points were determined with a MP-2D melting apparatus. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AVIII 500 spectrometer operating at 500 and at 125 MHz, respectively. Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, m = multiplet, br = broad), coupling constants (Hz) and integration. HRMS were obtained on a Waters LCT Premier XE (Waters Corp., Manchester, UK) instrument equipped with an electrospray source. The X-ray intensity data were measured at low temperature 100 K using Mo Kα radiation diffractometer equipped with a kappa geometry goniometer and corrected for absorption effects using the numerical method (SADABS).

General procedure for the synthesis of skeletons 3, 4 and 5: A mixture of 2-aminobenzophenones **1** (1.0 mmol), aromatic aldehydes **2** (1.05 mmol), trimethylsilyl trifluoromethanesulfonate (0.1 mmol) in hexamethyldisilazane (0.5 mL), in a dried 15 mL microwave vial at 25 °C. The mixture was subjected to a microwave irradiation instrument and stirred at 150 °C for 0.5 h (for gram-scale: 1.5 h). The consumption of the starting materials were confirmed by TLC. The reaction was cooled to 25 °C, the mixture of crude product was transferred to a 100 mL round bottom flask, and the solvent was concentrated. The residue was diluted with water (10 mL) and the mixture was extracted with CH_2Cl_2 (3 x 15 mL). The combined organic layers were washed with brine, dried, filtered and evaporated to afford crude product under reduced pressure. Purification on silica gel (hexanes/EtOAc = 10/1~4/1) afforded compounds **3a-3an**, **4a-4n** and **5a-5b**.

2,4-Diphenylquinazoline (***3a***).[30b] Yield = 90% (254 mg); White solid; mp = 118-119 °C (literature: 119-121 °C); **HRMS** (ESI, M^++H) calcd for $C_{21}H_{15}N_2$ 283.1230, found 283.1222; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 8.72 (d, J = 8.0 Hz, 2H), 8.17 (d, J = 8.5 Hz, 1H), 8.13 (d, J = 8.5 Hz, 1H), 7.93-7.85 (m, 3H), 7.64-7.58 (m, 3H), 7.57-7.49 (m, 4H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 168.26, 160.19, 151.95, 138.18, 137.64, 133.48, 130.46, 130.15 (2x), 129.87, 129.13, 128.63 (2x), 128.49 (4x), 126.95 (2x), 121.64.

2-(2-Fluorophenyl)-4-phenylquinazoline (***3b***).[22b] Yield = 87% (261 mg); Colorless solid; mp = 88-89 °C (literature: 90-92 °C); **HRMS** (ESI, M^++H) calcd for $C_{20}H_{14}FN_2$ 301.1136, found 301.1133; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 8.24-8.16 (m, 3H), 7.92 (t, *J* = 8.5 Hz, 1H), 7.89-7.86 (m, 2H), 7.62-7.57 (m, 4H), 7.48-7.44 (m, 1H), 7.30 (td, *J* = 1.0, 7.5 Hz, 1H), 7.23 (ddd, *J* = 1.0, 8.0, 11.0 Hz, 1H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 168.44, 161.32 (d, *J* = 253.0 Hz), 159.13 (d, *J* = 4.25 Hz), 151.74, 137.32, 133.71, 132.15, 131.41 (d, *J* = 8.375 Hz), 130.17 (2x), 129.99, 129.19, 128.59 (2x), 127.59, 127.37 (d, *J* = 10.125 Hz), 126.98, 124.11 (d, *J* = 3.625 Hz), 121.36, 116.81 (d, *J* = 22.125 Hz).

2-(3-Fluorophenyl)-4-phenylquinazoline (***3c***).[39] Yield = 88% (264 mg); Colorless solid; mp = 180-181 °C (literature: 160 °C); **HRMS** (ESI, M^++H) calcd for $C_{20}H_{14}FN_2$ 301.1136, found 301.1135; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 8.50 (d, *J* = 8.0 Hz, 1H), 8.42 (d, *J* = 10.5 Hz, 1H), 8.15 (t, *J* = 8.5 Hz, 2H), 7.92-7.88 (m, 3H), 7.62-7.60 (m, 3H), 7.57 (t, *J* = 7.0 Hz, 1H), 7.51-7.47 (m, 1H), 7.22-7.18 (m, 1H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 168.39, 163.22 (d, *J* = 243.125 Hz), 158.99 (d, *J* = 2.875 Hz), 151.86, 140.64 (d, *J* = 7.75 Hz), 137.45, 133.66 130.16 (2x), 130.01, 129.92 (d, *J* = 7.875 Hz), 129.18, 128.54 (2x), 127.31, 127.02, 124.23 (d, *J* = 2.375 Hz), 121.81, 117.30 (d, *J* = 21.125 Hz), 115.42 (d, *J* = 23.125 Hz). **Single-crystal X-ray diagram**: crystal of ***3c*** was grown by slow diffusion of EtOAc into a solution of ***3c*** in CH_2Cl_2 to yield colorless prisms. The compound crystallizes in the monoclinic crystal system, space group P 21/n, *a* = 10.3439(4) Å, *b* = 6.8286(2) Å, *c* = 20.1913(7) Å, *V* = 1412.80(8) Å^3, *Z* = 4, d_{calcd} = 1.407 Mg/m^3, *F*(000) = 620, 2θ range 3.152-27.101, *R* indices (all data) *R*1 = 0.0481, w*R*2 = 0.1140. CCDC number is 1996087.

2-(4-Fluorophenyl)-4-phenylquinazoline (***3d***).[39] Yield = 89% (267 mg); White solid; mp = 149-150 °C (literature: 149-150 °C); **HRMS** (ESI, M^++H) calcd for $C_{20}H_{14}FN_2$ 301.1136, found 301.1128; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 8.73-8.70 (m, 2H), 8.13 (t, *J* = 8.0 Hz, 2H), 7.90-7.87 (m, 3H), 7.62-7.58 (m, 3H), 7.54 (t, *J* = 8.0 Hz, 1H), 7.20 (t, *J* = 9.0 Hz, 2H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 168.35, 164.61 (d, *J* = 248.5 Hz), 159.26, 151.92, 137.56, 134.36 (d, *J* = 2.625 Hz), 133.60, 130.72 (d, *J* = 8.625 Hz, 2x), 130.12 (2x), 129.95, 129.03, 128.52 (2x), 127.00 (d, *J* = 2.8875 Hz, 2x), 121.54, 115.39 (d, *J* = 21.525 Hz, 2x).

2-(2-Chlorophenyl)-4-phenylquinazoline (***3e***).[40] Yield = 91% (288 mg); White solid; mp = 81-82 °C (literature: 93-94 °C); **HRMS** (ESI, M^++H) calcd for $C_{20}H_{14}ClN_2$ 317.0840, found 317.0831; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 8.20 (d, *J* = 10.0 Hz, 2H), 7.96-7.87 (m, 4H), 7.66-7.62 (m, 1H), 7.60-7.56 (m, 3H), 7.55-7.52 (m, 1H), 7.43-7.37 (m, 2H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 168.26, 161.29, 151.53, 138.45, 137.19, 133.80, 133.05, 131.78, 130.52, 130.18 (3x), 130.01, 129.10, 128.60 (2x), 127.77, 127.03, 126.84, 121.34.

2-(3-Chlorophenyl)-4-phenylquinazoline (***3f***).[30b] Yield = 86% (272 mg); White solid; mp = 126-127 °C (literature: 115-117 °C); **HRMS** (ESI, M^++H) calcd for $C_{20}H_{14}ClN_2$ 317.0840, found 317.0831; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 8.71 (s, 1H), 8.61-8.59 (m, 1H), 8.14 (t, *J* = 8.5 Hz, 2H), 7.91-7.87 (m, 3H), 7.62-7.60 (m, 3H), 7.56 (t, *J* = 8.0 Hz, 1H), 7.48-7.44 (m, 2H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 168.43, 158.83, 151.83, 140.04, 137.41, 134.62, 133.68, 130.40, 130.15 (2x), 130.02, 129.71, 129.15, 128.65, 128.54 (2x), 127.33, 127.02, 126.72, 121.80.

2-(4-Chlorophenyl)-4-phenylquinazoline (***3g***).[30b] Yield = 92% (291 mg); White solid; mp = 190-191 °C (literature: 187-188 °C); **HRMS** (ESI, M^++H) calcd for $C_{20}H_{14}ClN_2$ 317.0840, found 317.0836; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 8.65 (d, *J* = 8.5 Hz, 2H), 8.15-8.12 (m, 2H), 7.91-7.87 (m, 3H), 7.63-7.58 (m, 3H), 7.58-7.55 (m, 1H), 7.49 (d, *J* = 8.5 Hz, 2H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 168.42, 159.21, 151.91, 137.52,

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136.69, 133.68, 130.14 (2x), 130.00 (2x), 129.11, 128.70 (2x), 128.56 (2x), 127.19, 127.06, 121.71.

2-(2-Bromophenyl)-4-phenylquinazoline (***3h***). Yield = 92% (331 mg); White solid; mp = 76-77 °C; **HRMS** (ESI, M^++H) calcd for $C_{20}H_{14}BrN_2$ 361.0335, found 361.0326; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 8.22-8.19 (m, 2H), 7.95 (td, *J* = 1.0, 7.0 Hz, 1H), 7.91-7.88 (m, 3H), 7.74 (dd, *J* = 1.0, 8.5 Hz, 1H), 7.65 (td, *J* = 1.0, 7.0 Hz, 1H), 7.61-7.55 (m, 3H), 7.46 (td, *J* = 1.0, 7.5 Hz, 1H), 7.31 (td, *J* = 1.5, 7.0 Hz, 1H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 168.20, 162.13, 151.51, 140.32, 137.19, 133.84, 133.69, 131.73, 130.30, 130.20 (2x), 130.03, 129.11, 128.61 (2x), 127.80, 127.45, 127.07, 122.13, 121.36.

2-(3-Bromophenyl)-4-phenylquinazoline (***3i***).[30b] Yield = 94% (338 mg); White solid; mp = 135-136 °C (literature: 98-99 °C); **HRMS** (ESI, M^++H) calcd for $C_{20}H_{14}BrN_2$ 361.0335, found 361.0326; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 8.87 (s, 1H), 8.64 (d, *J* = 7.5 Hz, 1H), 8.14 (t, *J* = 9.0 Hz, 2H), 7.91-7.87 (m, 3H), 7.63-7.60 (m, 4H), 7.56 (t, *J* = 8.0 Hz, 1H), 7.39 (t, *J* = 8.0 Hz, 1H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 168.44, 158.69, 151.82, 140.26, 137.40, 133.69, 133.32, 131.55, 130.15 (2x), 130.02, 130.00, 129.16, 128.55 (2x), 127.35, 127.18, 127.02, 122.81, 121.80.

2-(4-Bromophenyl)-4-phenylquinazoline (***3j***).[30b] Yield = 89% (320 mg); White solid; mp = 193-194 °C (literature: 185-186 °C); **HRMS** (ESI, M^++H) calcd for $C_{20}H_{14}BrN_2$ 361.0335, found 361.0328; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 8.58 (d, *J* = 8.5 Hz, 2H), 8.15-8.12 (m, 2H), 7.92-7.87 (m, 3H), 7.65 (d, *J* = 8.5 Hz, 2H), 7.62-7.59 (m, 3H), 7.58-7.55 (m, 1H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 168.42, 159.28, 151.90, 137.50, 137.14, 133.69, 131.66 (2x), 130.24 (2x), 130.14 (2x), 130.01, 129.12, 128.56 (2x), 127.22, 127.06, 125.27, 121.74.

2-(2,4-Difluorophenyl)-4-phenylquinazoline (***3k***). Yield = 85% (270 mg); Colorless solid; mp = 109-110 °C; **HRMS** (ESI, M^++H) calcd for $C_{20}H_{13}F_2N_2$ 319.1041, found 319.1037; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 8.28 (ddd, *J* = 6.5, 8.5, 15.5 Hz, 1H), 8.18-8.15 (m, 2H), 7.92 (t, *J* = 7.0 Hz, 1H), 7.87-7.86 (m, 2H), 7.62-7.58 (m, 4H), 7.05-6.96 (m, 2H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 168.50, 162.88 (t, *J* = 11.125 Hz), 162.85 (dd, *J* = 11.875, 518.0 Hz), 158.28 (d, *J* = 4.875 Hz), 151.73, 137.23, 133.81, 133.46 (dd, *J* = 3.0, 9.75 Hz), 130.14 (2x), 130.06, 129.12, 128.61 (2x), 127.64, 127.00, 123.72 (dd, *J* = 3.625, 9.75 Hz), 121.33, 111.46 (dd, *J* = 3.625, 9.75 Hz), 105.02 (t, *J* = 25.5 Hz).

2-(2,6-Difluorophenyl)-4-phenylquinazoline (***3l***). Yield = 86% (273 mg); Colorless solid; mp = 117-118 °C; **HRMS** (ESI, M^++H) calcd for $C_{20}H_{13}F_2N_2$ 319.1041, found 319.1042; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 8.20 (d, *J* = 9.5 Hz, 2H), 7.98-7.94 (m, 1H), 7.87-7.82 (m, 2H), 7.69-7.65 (m, 1H), 7.61-7.55 (m, 3H), 7.43-7.37 (m, 1H), 7.08-7.01 (m, 2H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 168.85, 160.95 (d, *J* = 250.0 Hz), 161.90 (d, *J* = 250.0 Hz), 155.34, 151.51, 136.94, 133.96, 130.58 (t, *J* = 10.275 Hz), 130.13 (2x), 130.07, 129.11, 128.66 (2x), 128.17, 127.12, 121.70, 111.87 (d, *J* = 25.25 Hz, 2x), 111.87 (d, *J* = 14.625 Hz). **Single-crystal X-ray diagram**: crystal of ***3l*** was grown by slow diffusion of EtOAc into a solution of ***3l*** in CH_2Cl_2 to yield colorless prisms. The compound crystallizes in the triclinic crystal system, space group P -1, *a* = 7.8602(2) Å, *b* = 8.9830(2) Å, *c* = 11.3189(3) Å, *V* = 736.11(3) Å^3, *Z* = 2, d_{calcd} = 1.436 Mg/m^3, *F*(000) = 328, 2θ range 1.919-27.100°, *R* indices (all data) *R*1 = 0.0391, w*R*2 = 0.0874. CCDC number is 1994079.

2-(3,4-Difluorophenyl)-4-phenylquinazoline (***3m***). Yield = 84% (267 mg); White solid; mp = 180-181 °C; **HRMS** (ESI, M^++H) calcd for $C_{20}H_{13}F_2N_2$ 319.1041, found 319.1043; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 8.56-8.52 (m, 1H), 8.49-8.46 (m, 1H), 8.13 (d, *J* = 9.0 Hz, 2H), 7.92-7.85 (m, 3H), 7.62-7.55 (m, 4H), 7.28 (q, *J* = 9.6 Hz, 1H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 168.47, 158.16, 152.15 (d, *J* = 12.875, 152.15 Hz), 151.83, 150.52 (dd, *J* = 12.75, 245.75 Hz), 137.37, 135.40 (q, *J* = 3.375 Hz), 133.77, 130.12 (2x), 130.08, 129.08, 128.57 (2x), 127.33, 127.06, 124.95 (q, *J* = 3.25 Hz), 121.68, 117.47 (d, *J* = 18.75 Hz), 117.15 (d, *J* = 17.375 Hz).

2-(2-Nitrophenyl)-4-phenylquinazoline (***3n***).[30b] Yield = 83% (271 mg); Colorless solid mp = 159-160 °C (literature: 159-161 °C); **HRMS** (ESI, M^++H) calcd for $C_{20}H_{14}N_3O_2$ 328.1081, found 328.1081; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 8.22 (d, *J* = 7.5 Hz, 1H), 8.17 (d, *J* = 8.5 Hz, 1H), 8.14 (d, *J* = 8.5 Hz, 1H), 7.94-7.86 (m, 2H), 7.83-7.79 (m, 2H), 7.72-7.67 (m, 1H), 7.64-7.54 (m, 5H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 168.31, 158.74, 151.58, 150.08, 136.80, 133.90, 133.73, 132.09, 131.69, 130.14 (2x), 130.12, 129.96, 129.03, 128.54 (2x), 127.98, 127.04, 123.9, 121.45.

2-(4-Nitrophenyl)-4-phenylquinazoline (***3o***).[30b] Yield = 86% (281 mg); White solid; mp = 217-218 °C (literature: 200-201 °C); **HRMS** (ESI, M^++H) calcd for $C_{20}H_{14}N_3O_2$ 328.1081, found 328.1072; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 8.88 (d, *J* = 8.5 Hz, 2H), 8.35 (d, *J* = 8.5 Hz, 2H), 8.18 (t, *J* = 8.0 Hz, 2H), 7.95 (t, *J* = 8.0 Hz, 1H), 7.91-7.87 (m, 2H), 7.66-7.61 (m, 4H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 168.71, 157.94, 151.81, 149.13, 144.04, 137.21, 134.01, 130.24, 130.15 (2x), 129.43 (2x), 129.36, 128.66 (2x), 128.05, 127.14, 123.65 (2x), 121.96.

4-Phenyl-2-(2-(trifluoromethyl)phenyl)quinazoline (***3p***). Yield = 87% (305 mg); White solid; mp = 113-114 °C; **HRMS** (ESI, M^++H) calcd for $C_{21}H_{14}F_3N_2$ 351.1104, found 351.1094; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 8.21 (d, *J* = 8.5 Hz, 1H), 8.19 (d, *J* = 8.5 Hz, 1H), 7.97-7.92 (m, 2H), 7.90-7.86 (m, 2H), 7.85 (d, *J* = 8.0 Hz, 1H), 7.70-7.62 (m, 2H), 7.61-7.54 (m, 4H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 168.18, 161.75, 151.40, 139.02, 137.04, 133.91, 131.63, 130.15 (2x), 130.06, 129.10, 128.98, 128.82 (q, *J* = 30.4125 Hz), 128.76, 128.59 (2x), 127.83, 127.08, 126.82 (q, *J* = 5.0 Hz), 124.21 (q, *J* = 272.1875 Hz), 121.33.

4-Phenyl-2-(4-(trifluoromethyl)phenyl)quinazoline (***3q***).[30b] Yield = 92% (322 mg); White solid; mp = 120-121 °C (literature: 123-124 °C); **HRMS** (ESI, M^++H) calcd for $C_{21}H_{14}F_3N_2$ 351.1104, found 351.1096; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 8.82 (d, *J* = 8.0 Hz, 2H), 8.17 (t, *J* = 8.4 Hz, 2H), 7.95-7.87 (m, 3H), 7.74 (d, *J* = 8.0 Hz, 2H), 7.65-7.58 (m, 4H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 168.57, 158.81, 151.88, 141.51, 137.41, 133.80, 132.00 (q, *J* = 32.0 Hz), 130.16 (2x), 131.00, 129.28, 128.90 (2x), 128.61 (2x), 127.60, 127.09, 125.40 (q, *J* = 3.625 Hz, 2x), 123.16, 121.93.

4-Phenyl-2-(*o*-tolyl)quinazoline (***3r***).[39] Yield = 81% (240 mg); White solid; mp = 74-75 °C (literature: 73-75 °C); **HRMS** (ESI, M^++H) calcd for $C_{21}H_{17}N_2$ 297.1386, found 297.1378; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 8.17 (d, *J* = 8.5 Hz, 2H), 8.01-7.97 (m, 1H), 7.92 (t, *J* = 8.0 Hz, 1H), 7.88-7.84 (m, 2H), 7.62-7.56 (m, 4H), 7.38-7.31 (m, 3H), 2.68 (s, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 168.01, 163.38, 151.67, 138.81, 137.50, 137.39, 133.55, 131.23, 130.71, 130.12 (2x), 129.87, 129.19, 129.10, 128.53 (2x), 127.25, 126.95, 125.94, 121.01, 21.23.

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4-Phenyl-2-(*m*-tolyl)quinazoline (***3s***).[25b] Yield = 90% (266 mg); White solid; mp = 116-117 °C (literature: 113-114 °C); **HRMS** (ESI, M^++H) calcd for $C_{21}H_{17}N_2$ 297.1386, found 297.1378; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 8.52-8.48 (m, 2H), 8.16 (d, *J* = 8.0 Hz, 1H), 8.13 (d, *J* = 8.0 Hz, 1H), 7.97-7.87 (m, 3H), 7.63-7.58 (m, 3H), 7.55 (t, *J* = 7.5 Hz, 1H), 7.42 (t, *J* = 7.5 Hz, 1H), 7.32 (d, *J* = 7.5 Hz, 1H), 2.49 (s, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 168.30, 160.42, 151.98, 138.13, 137.70, 133.50, 131.32, 130.19 (2x), 129.89, 129.15, 129.14, 129.13, 128.52 (2x), 128.45, 127.01, 126.92, 125.90, 121.68, 21.55.

4-Phenyl-2-(*p*-tolyl)quinazoline (***3t***).[30b] Yield = 87% (258 mg); White solid; mp = 169-170 °C (literature: 164-165 °C); **HRMS** (ESI, M^++H) calcd for $C_{21}H_{17}N_2$ 297.1386, found 297.1384; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 8.61 (d, *J* = 8.5 Hz, 2H), 8.15 (d, *J* = 8.0 Hz, 1H), 8.11 (d, *J* = 8.0 Hz, 1H), 7.91-7.85 (m, 3H), 7.63-7.58 (m, 3H), 7.54-7.51 (m, 1H), 7.35 (d, *J* = 8.0 Hz, 2H), 2.46 (s, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 168.16, 160.29, 151.98, 140.66, 137.72, 135.47, 133.40, 130.15 (2x), 129.82, 129.25 (2x), 129.04, 128.60 (2x), 128.47 (2x), 126.95, 126.70, 121.56, 21.50.

2-(2-Methoxyphenyl)-4-phenylquinazoline (***3u***).[27j] Yield = 89% (278 mg); White solid; mp = 160-161 °C (literature: 160-165 °C); **HRMS** (ESI, M^++H) calcd for $C_{21}H_{17}N_2O$ 313.1335, found 313.1331; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 8.19 (d, *J* = 8.5 Hz, 1H), 8.13 (d, *J* = 8.5 Hz, 1H), 7.91-7.82 (m, 4H), 7.59-7.52 (m, 4H), 7.45-7.41 (m, 1H), 7.10 (td, *J* = 1.0, 7.5 Hz, 1H), 7.06 (d, *J* = 8.0 Hz, 1H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 168.08, 161.63, 157.73, 151.53, 137.43, 133.41, 131.65, 130.59, 130.06 (2x), 129.70, 129.23, 129.01, 128.44 (2x), 127.16, 126.84, 121.17, 120.68, 112.06.

2-(3-Methoxyphenyl)-4-phenylquinazoline (***3v***). Yield = 85% (265 mg); White solid; mp = 129-130 °C; **HRMS** (ESI, M^++H) calcd for $C_{21}H_{17}N_2O$ 313.1335, found 313.1327; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 8.34 (d, *J* = 7.5 Hz, 1H), 8.30 (s, 1H), 8.17 (d, *J* = 8.0 Hz, 1H), 8.13 (d, *J* = 8.0 Hz, 1H), 7.93-7.85 (m, 3H), 7.63-7.57 (m, 3H), 7.54 (t, *J* = 8.0 Hz, 1H), 7.46 (t, *J* = 8.0 Hz, 1H), 7.08 (dd, *J* = 2.0, 8.0 Hz, 1H), 3.96 (s, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 168.16, 159.94, 159.90, 151.90, 139.67, 137.60, 133.44, 130.16 (2x), 129.85, 129.46, 129.13, 128.45 (2x), 126.97, 126.92, 121.67, 121.26, 116.76, 113.35, 55.39.

2-(4-methoxyphenyl)-4-phenylquinazoline (***3w***).[30b] Yield = 89% (278 mg); Colorless solid; mp = 158-159 °C (literature: 158-160 °C); **HRMS** (ESI, M^++H) calcd for $C_{21}H_{17}N_2O$ 313.1335, found 313.1329; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 8.66 (d, *J* = 9.0 Hz, 2H), 8.10 (t, *J* = 8.5 Hz, 2H), 7.89-7.85 (m, 3H), 7.60-7.57 (m, 3H), 7.51 (t, *J* = 7.5 Hz, 1H), 7.04 (d, *J* = 9.0 Hz, 2H), 3.90 (s, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 168.14, 161.73, 160.02, 152.04, 137.76, 133.42, 130.91, 130.28 (2x), 130.13 (2x), 129.81, 128.91, 128.47 (2x), 126.98, 126.49, 121.38, 113.83 (2x), 55.35. **Single-crystal X-ray diagram**: crystal of ***3w*** was grown by slow diffusion of EtOAc into a solution of ***3w*** in CH_2Cl_2 to yield colorless prisms. The compound crystallizes in the orthorhombic crystal system, space group P b c a, *a* = 14.6384(3) Å, *b* = 6.90900(10) Å, *c* = 30.7229(7) Å, *V* = 3107.21(11) Å^3, *Z* = 8, d_{calcd} = 1.335 Mg/m^3, *F*(000) = 1312, 2*θ* range 2.877-65.073, *R* indices (all data) *R*1 = 0.0433, w*R*2 = 0.0997. CCDC number is 1988309.

2-(2,4-Dimethoxyphenyl)-4-phenylquinazoline (***3x***). Yield = 86% (294 mg); Colorless gum; **HRMS** (ESI, M^++H) calcd for $C_{22}H_{19}N_2O_2$ 343.1441, found 343.1434; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 8.15 (d, *J* = 8.5 Hz, 1H), 8.10 (d, *J* = 8.5 Hz, 1H), 7.94 (d, *J* = 8.5 Hz, 1H), 7.88-7.83 (m, 3H), 7.57-7.51 (m, 3H), 6.65-6.61 (m, 3H), 3.91 (s, 3H), 3.86 (s, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 167.90, 161.98, 161.27, 159.28, 151.64, 137.56, 133.28, 133.08, 130.05 (2x), 129.64, 128.92, 128.40 (2x), 126.82, 126.78, 122.08, 120.92, 104.90, 99.47, 55.99, 55.38.

2-(2,5-Dimethoxyphenyl)-4-phenylquinazoline (***3y***). Yield = 84% (287 mg); White solid; mp = 102-103 °C; **HRMS** (ESI, M^++H) calcd for $C_{22}H_{19}N_2O_2$ 343.1441, found 343.1435; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 8.19 (d, *J* = 8.5 Hz, 1H), 8.14 (d, *J* = 8.5 Hz, 1H), 7.92-7.87 (m, 1H), 7.86-7.82 (m, 2H), 7.60-7.53 (m, 4H), 7.45 (d, *J* = 3.0 Hz, 1H), 7.02-6.96 (m, 2H), 3.87 (s, 3H), 3.83 (s, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 168.14, 161.32, 153.66, 152.15, 151.54, 137.40, 133.45, 130.09 (2x), 129.98, 129.74, 129.04, 128.44 (2x), 127.25, 126.86, 121.23, 116.68, 116.20, 114.10, 56.98, 55.80.

2-(3,4-Dimethoxyphenyl)-4-phenylquinazoline (***3z***). Yield = 85% (291 mg); White solid; mp = 109-110 °C; **HRMS** (ESI, M^++H) calcd for $C_{22}H_{19}N_2O_2$ 343.1441, found 343.1433; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 8.34 (dd, *J* = 2.0, 8.5 Hz, 1H), 8.27 (d, *J* = 2.0 Hz, 1H), 8.14-8.07 (m, 2H), 7.90-7.84 (m, 3H), 7.62-7.57 (m, 3H), 7.52-7.48 (m, 1H), 7.00 (d, *J* = 8.5 Hz, 1H), 4.06 (s, 3H), 3.97 (s, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 168.10, 159.89, 151.97, 151.28, 148.95, 137.72, 133.43, 131.09, 130.12 (2x), 129.80, 128.88, 128.46 (2x), 126.98, 126.55, 122.17, 121.40, 111.16, 110.72, 56.00, 55.92.

2-(3,5-Dimethoxyphenyl)-4-phenylquinazoline (***3aa***). Yield = 93% (318 mg); Colorless solid; mp = 150-151 °C; **HRMS** (ESI, M^++H) calcd for $C_{22}H_{19}N_2O_2$ 343.1441, found 343.1433; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 8.16 (d, *J* = 8.5 Hz, 1H), 8.13 (d, *J* = 8.0 Hz, 1H), 7.92-7.86 (m, 5H), 7.63-7.58 (m, 3H), 7.57-7.53 (m, 1H), 6.63 (t, *J* = 2.0 Hz, 1H), 3.93 (s, 6H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 168.16, 161.00 (2x), 159.83, 151.91, 140.37, 137.63, 133.49, 130.25 (2x), 129.91, 129.21, 128.49 (2x), 127.07, 126.98, 121.77, 106.48 (2x), 103.36, 55.58 (2x). **Single-crystal X-ray diagram**: crystal of ***3aa*** was grown by slow diffusion of EtOAc into a solution of ***3aa*** in CH_2Cl_2 to yield colorless prisms. The compound crystallizes in the triclinic crystal system, space group P -1, *a* = 5.9542(2) Å, *b* = 10.6468(4) Å, *c* = 13.6281(5) Å, *V* = 834.81(5) Å^3, *Z* = 2, d_{calcd} = 1.362 Mg/m^3, *F*(000) = 360, 2*θ* range 1.976-27.103, *R* indices (all data) *R*1 = 0.0552, w*R*2 = 0.1237. CCDC number is 1996086.

4-Phenyl-2-(3,4,5-trimethoxyphenyl)quinazoline (***3ab***). Yield = 90% (335 mg); Colorless solid; mp = 200-201 °C; **HRMS** (ESI, M^++H) calcd for $C_{23}H_{21}N_2O_3$ 373.1547, found 373.1537; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 8.15 (d, *J* = 8.5 Hz, 1H), 8.11 (d, *J* = 8.5 Hz, 1H), 8.01 (s, 2H), 7.90-7.86 (m, 3H), 7.63-7.59 (m, 3H), 7.56-7.52 (m, 1H), 4.03 (s, 6H), 3.95 (s, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 168.18, 159.70, 153.29 (2x), 151.91, 140.40, 137.65, 133.67, 133.52, 130.14 (2x), 129.86, 129.02, 128.49 (2x), 127.01, 126.88, 121.53, 105.83 (2x), 60.92, 56.26 (2x). **Single-crystal X-ray diagram**: crystal of ***3ab*** was grown by slow diffusion of EtOAc into a solution of ***3ab*** in CH_2Cl_2 to yield colorless prisms. The compound crystallizes in the orthorhombic crystal system, space group P b c a, *a* = 14.2321(7) Å, *b* = 13.7476(6) Å, *c* = 19.4973(9) Å, *V* = 3814.8(3) Å^3, *Z* = 8, d_{calcd} = 1.297 Mg/m^3, *F*(000) = 1568, 2*θ* range 2.309-27.103, *R* indices (all data) *R*1 = 0.0608, w*R*2 = 0.1031. CCDC number is 1996497.

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2-(4-(Benzyloxy)-3-methoxyphenyl)-4-phenylquinazoline (***3ac***). Yield = 88% (368 mg); White solid; mp = 137-138 °C; **HRMS** (ESI, M^++H) calcd for $C_{28}H_{23}N_2O_2$ 419.1754, found 419.1745; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 8.30-8.26 (m, 2H), 8.12 (d, *J* = 8.5 Hz, 1H), 8.09 (d, *J* = 8.5 Hz, 1H), 7.88-7.84 (m, 3H), 7.62-7.58 (m, 3H), 7.53-7.47 (m, 3H), 7.40-7.36 (m, 2H), 7.33-7.29 (m, 1H), 7.03 (d, *J* = 8.5 Hz, 1H), 5.26 (s, 2H), 4.07 (s, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 168.10, 159.88, 151.97, 150.39, 149.56, 137.71, 136.87, 133.42, 131.50, 130.11 (2x), 129.80, 128.90, 128.52 (2x), 128.45 (2x), 127.83, 127.26 (2x), 126.98, 126.57, 122.04, 121.39, 113.32, 111.72, 70.80, 56.14.

2-(3-(Benzyloxy)-4-methoxyphenyl)-4-phenylquinazoline (***3ad***). Yield = 86% (359 mg); White solid; mp = 165-166 °C; **HRMS** (ESI, M^++H) calcd for $C_{28}H_{23}N_2O_2$ 419.1754, found 419.1747; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 8.39-8.33 (m, 2H), 8.10 (t, *J* = 8.5 Hz, 2H), 7.90-7.83 (m, 3H), 7.64-7.59 (m, 3H), 7.56 (d, *J* = 7.5 Hz, 2H), 7.50 (t, *J* = 8.0 Hz, 1H), 7.40 (t, *J* = 7.5 Hz, 2H), 7.32 (t, *J* = 7.5 Hz, 1H), 7.03 (d, *J* = 8.5 Hz, 1H), 5.32 (s, 2H), 3.97 (s, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 168.06, 159.87, 152.07, 151.98, 148.22, 137.80, 137.27, 133.46, 131.07, 130.24 (2x), 129.89, 128.98, 128.54 (2x), 128.51 (2x), 127.89, 127.76 (2x), 127.02, 126.59, 122.55, 121.43, 113.94, 111.32, 71.12, 56.07.

2-(Benzo[*d*][1,3]dioxol-5-yl)-4-phenylquinazoline (***3ae***).[40] Yield = 88% (287 mg); White solid; mp = 155-156 °C (literature: 169-170 °C); **HRMS** (ESI, M^++H) calcd for $C_{21}H_{15}N_2O_2$ 327.1128, found 327.1119; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 8.32 (d, *J* = 8.5 Hz, 1H), 8.21 (s, 1H), 8.10 (d, *J* = 8.5 Hz, 1H), 8.09 (d, *J* = 8.5 Hz, 1H), 7.90-7.82 (m, 3H), 7.62-7.57 (m, 3H), 7.50 (t, *J* = 8.0 Hz, 1H), 6.95 (d, *J* = 8.0 Hz, 1H), 6.04 (s, 2H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 168.05, 159.63, 151.93, 149.74, 148.03, 137.64, 133.44, 132.65, 130.11 (2x), 129.83, 128.91, 128.45 (2x), 126.94, 126.60, 123.55, 121.41, 108.77, 108.18, 101.34.

2-([1,1'-Biphenyl]-4-yl)-4-phenylquinazoline (***3af***). Yield = 83% (297 mg); Colorless solid; mp = 155-156 °C; **HRMS** (ESI, M^++H) calcd for $C_{26}H_{19}N_2$ 359.1543, found 359.1533; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 8.81 (d, *J* = 8.0 Hz, 2H), 8.19 (d, *J* = 8.0 Hz, 1H), 8.14 (d, *J* = 8.0 Hz, 1H), 7.95-7.87 (m, 3H), 7.80 (d, *J* = 8.0 Hz, 2H), 7.72 (d, *J* = 8.0 Hz, 2H), 7.66-7.60 (m, 3H), 7.55 (t, *J* = 7.5 Hz, 1H), 7.50 (t, *J* = 7.5 Hz, 2H), 7.40 (t, *J* = 7.0 Hz, 1H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 168.24, 159.93, 151.98, 143.06, 140.66, 137.64, 137.15, 133.49, 130.15 (2x), 129.87, 129.10 (3x), 128.77 (2x), 128.49 (2x), 127.56, 127.18 (2x), 127.14 (2x), 126.98, 126.92, 121.64.

2-(Naphthalen-1-yl)-4-phenylquinazoline (***3ag***).[22b] Yield = 82% (272 mg); White solid; mp = 124-125 °C (literature: 171-173 °C); **HRMS** (ESI, M^++H) calcd for $C_{24}H_{17}N_2$ 333.1386, found 333.1379; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 8.84 (d, *J* = 8.5 Hz, 1H), 8.29 (d, *J* = 7.5 Hz, 1H), 8.26 (d, *J* = 8.5 Hz, 1H), 8.22 (d, *J* = 8.5 Hz, 1H), 8.00 (d, *J* = 8.0 Hz, 1H), 7.98-7.90 (m, 4H), 7.67-7.52 (m, 7H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 168.41, 162.72, 151.68, 137.39, 136.49, 134.17, 133.71, 131.31, 130.20, 130.10 (2x), 129.90, 129.64, 129.11, 128.55 (2x), 128.40, 127.42, 127.00, 126.68, 126.05, 125.75, 125.27, 121.21.

2-(Naphthalen-2-yl)-4-phenylquinazoline (***3ah***).[25b] Yield = 85% (282 mg); White solid; mp = 172-173 °C (literature: 172-173 °C); **HRMS** (ESI, M^++H) calcd for $C_{24}H_{17}N_2$ 333.1386, found 333.1384; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 9.25 (s, 1H), 8.82 (dd, *J* = 1.5, 8.5 Hz, 1H), 8.21 (d, *J* = 8.5 Hz, 1H), 8.15 (d, *J* = 8.5 Hz, 1H), 8.08-8.03 (m, 1H), 7.99 (d, *J* = 8.5 Hz, 1H), 7.96-7.88 (m, 4H), 7.66-7.60 (m, 3H), 7.58-7.50 (m, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 168.39, 160.21, 152.04, 137.70, 135.57, 134.68, 133.60, 133.41, 130.22 (2x), 129.96, 129.28, 129.17, 128.98, 128.58 (2x), 128.14, 127.71, 127.08, 127.04, 126.96, 126.10, 125.58, 121.76.

4-Phenyl-2-(thiophen-2-yl)quinazoline (***3ai***).[30b] Yield = 83% (239 mg); Colorless solid; mp = 147-148 °C (literature: 146-147 °C); **HRMS** (ESI, M^++H) calcd for $C_{28}H_{13}N_2S$ 289.0794, found 289.0794; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 8.21 (d, *J* = 3.0 Hz, 1H), 8.08 (d, *J* = 8.5 Hz, 2H), 7.90-7.83 (m, 3H), 7.62-7.56 (m, 3H), 7.53-7.48 (m, 2H), 7.19 (t, *J* = 5.0 Hz, 1H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 168.38, 157.21, 151.83, 144.16, 137.25, 133.69, 130.16 (2x), 129.99, 129.78, 129.29, 128.69, 128.50 (2x), 128.20, 127.12, 126.69, 121.50.

2-(Furan-2-yl)-4-phenylquinazoline (***3aj***).[22b] Yield = 84% (228 mg); Colorless solid; mp = 174-175 °C (literature: 167-168 °C); **HRMS** (ESI, M^++H) calcd for $C_{18}H_{13}N_2O$ 273.1022, found 273.1020; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 8.15 (d, *J* = 8.5 Hz, 1H), 8.04 (d, *J* = 8.5 Hz, 1H), 7.88-7.79 (m, 3H), 7.69 (s, 1H), 7.58-7.53 (m, 3H), 7.52-7.47 (m, 2H), 6.60-6.57 (m, 1H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 168.73, 153.46, 152.72, 151.48, 145.16, 137.12, 133.80, 129.98 (2x), 129.93, 128.82, 128.46 (2x), 127.07, 126.90, 121.50, 114.13, 112.11.

4-Phenyl-2-(pyridin-2-yl)quinazoline (***3ak***).[35] Yield = 90% (255 mg); Colorless solid; mp = 179-180 °C (literature: 178-179 °C); **HRMS** (ESI, M^++H) calcd for $C_{19}H_{14}N_3$ 284.1182, found 284.1180; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 8.91 (d, *J* = 5.0 Hz, 1H), 8.75 (d, *J* = 8.0 Hz, 1H), 8.36 (d, *J* = 8.5 Hz, 1H), 8.14 (d, *J* = 8.0 Hz, 1H), 7.94-7.84 (m, 4H), 7.62-7.55 (m, 4H), 7.42-7.37 (m, 1H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 168.79, 159.08, 155.35, 151.97, 150.23, 137.36, 136.85, 133.72, 130.13 (2x), 129.94, 129.86, 128.50 (2x), 127.79, 126.92, 124.58, 124.32, 122.17.

4-Phenyl-2-(pyridin-3-yl)quinazoline (***3al***).[30b] Yield = 88% (249 mg); White solid; mp = 158-159 °C (literature: 143-144 °C); **HRMS** (ESI, M^++H) calcd for $C_{19}H_{14}N_3$ 284.1182, found 284.1180; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 9.88 (s, 1H), 8.93 (d, *J* = 8.0 Hz, 1H), 8.73 (d, *J* = 5.0 Hz, 1H), 8.15 (t, *J* = 7.5 Hz, 2H), 7.94-7.86 (m, 3H), 7.64-7.55 (m, 4H), 7.44 (dd, *J* = 5.0, 7.5 Hz, 1H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 168.54, 158.37, 151.83, 151.11, 150.34, 137.30, 135.82, 133.79, 133.66, 130.15 (2x), 130.10, 129.15, 128.57 (2x), 127.49, 127.07, 123.28, 121.87.

4-Phenyl-2-(pyridin-4-yl)quinazoline (***3am***). Yield = 92% (260 mg); White solid; mp = 162-163 °C; **HRMS** (ESI, M^++H) calcd for $C_{19}H_{14}N_3$ 284.1182, found 284.1175; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 8.79 (d, *J* = 6.0 Hz, 2H), 8.52 (d, *J* = 6.0 Hz, 2H), 8.17 (t, *J* = 9.0 Hz, 2H), 7.92 (t, *J* = 7.5 Hz, 1H), 7.89-7.85 (m, 2H), 7.63-7.58 (m, 4H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 168.65, 158.06, 151.74, 150.37 (2x), 145.43, 137.19, 133.85, 130.13 (3x), 129.34, 128.58 (2x), 127.97, 127.05, 122.36 (2x), 122.19.

4-Phenyl-2-(quinolin-2-yl)quinazoline (***3an***).[35] Yield = 81% (270 mg); White solid; mp = 171-172 °C (literature: 157-158 °C); **HRMS** (ESI, M^++H) calcd for $C_{23}H_{16}N_3$ 334.1339, found 334.1333; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 8.88 (d, *J* = 8.5 Hz, 1H), 8.46 (d, *J* = 9.0 Hz, 1H), 8.43 (d, *J* = 8.5 Hz, 1H), 8.36 (d, *J* = 8.5 Hz, 1H), 8.20 (d, *J* = 8.5 Hz, 1H), 7.99-7.93 (m, 3H), 7.89 (d, *J* = 8.0 Hz, 1H), 7.80-7.75 (m, 1H), 7.67-7.58 (m, 5H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 168.96, 159.32,

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155.50, 152.15, 148.40, 137.43, 136.96, 133.75, 131.04, 130.34 (2x), 130.19, 130.10, 129.52, 128.59 (2x), 128.56, 128.07, 127.40, 127.37, 127.00, 122.28, 121.58.

6-Chloro-2,4-diphenylquinazoline (***4a***).[25b] Yield = 90% (284 mg); White solid; mp = 194-195 °C (literature: 193-195 °C); **HRMS** (ESI, M^++H) calcd for $C_{20}H_{14}ClN_2$ 317.0840, found 317.0840; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 8.68 (dd, *J* = 1.5, 8.0 Hz, 2H), 8.11-8.09 (m, 2H), 7.88-7.86 (m, 2H), 7.81 (dd, *J* = 1.5, 9.0 Hz, 1H), 7.64-7.62 (m, 3H), 7.56-7.51 (m, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 167.51, 160.45, 150.49, 137.77, 137.11, 134.45, 132.57, 130.86, 130.73, 130.18, 130.03 (2x), 128.71 (2x), 128.66 (2x), 128.55 (2x), 125.75, 122.17.

6-Bromo-2,4-diphenylquinazoline (***4b***).[25b] Yield = 88% (317 mg); White solid; mp = 205-206 °C (literature: 204-205 °C); **HRMS** (ESI, M^++H) calcd for $C_{20}H_{14}BrN_2$ 361.0335, found 361.0328; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 8.69-8.67 (m, 2H), 8.26 (d, *J* = 2.0 Hz, 1H), 8.02 (d, *J* = 8.5 Hz, 1H), 7.94 (dd, *J* = 2.0, 8.5 Hz, 1H), 7.90-7.84 (m, 2H), 7.65-7.59 (m, 3H), 7.56-7.50 (m, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 167.40, 160.48, 150.69, 137.77, 137.08, 137.00, 130.94, 130.76, 130.20, 130.04 (2x), 129.07, 128.73 (2x), 128.68 (2x), 128.56 (2x), 122.66, 120.61.

6-Nitro-2,4-diphenylquinazoline (***4c***).[41] Yield = 93% (304 mg); White solid; mp = 246-247 °C (literature: 245-247 °C); **HRMS** (ESI, M^++H) calcd for $C_{20}H_{14}N_3O_2$ 328.1081, found 328.1085; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 9.06 (d, *J* = 2.5 Hz, 1H), 8.77-8.71 (m, 2H), 8.64 (dd, *J* = 2.5, 9.0 Hz, 1H), 8.26 (d, *J* = 9.0 Hz, 1H), 7.94-7.89 (m, 2H), 7.70-7.65 (m, 3H), 7.59-7.54 (m, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 170.45, 162.87, 154.50, 145.42, 137.10, 136.38, 131.71, 131.02, 130.95, 130.23 (2x), 129.21 (2x), 129.06 (2x), 128.73 (2x), 126.95, 124.25, 120.46.

6-Methyl-2,4-diphenylquinazoline (***4d***).[25b] Yield = 88% (260 mg); Colorless solid; mp = 173-174 °C (literature: 173-176 °C); **HRMS** (ESI, M^++H) calcd for $C_{21}H_{17}N_2$ 297.1386, found 297.1385; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 8.70-8.65 (m, 2H), 8.06 (d, *J* = 8.5 Hz, 1H), 7.91-7.85 (m, 3H), 7.72 (dd, *J* = 2.0, 8.5 Hz, 1H), 7.64-7.57 (m, 3H), 7.55-7.46 (m, 3H), 2.52 (s, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 167.52, 159.60, 150.56, 138.33, 137.89, 137.12, 135.74, 130.26, 130.10 (2x), 129.73, 128.86, 128.49 (6x), 125.59, 121.63, 21.86.

6,7-Dimethoxy-2,4-diphenylquinazoline (***4e***).[25b] Yield = 86% (294 mg); White solid; mp = 176-177 °C (literature: 176-178 °C); **HRMS** (ESI, M^++H) calcd for $C_{22}H_{19}N_2O_2$ 343.1441, found 343.1431; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 8.63 (d, *J* = 8.0 Hz, 2H), 7.89 (d, *J* = 7.5 Hz, 2H), 7.63-7.55 (m, 3H), 7.54-7.45 (m, 4H), 7.36 (s, 1H), 4.11 (s, 3H), 3.92 (s, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 165.16, 159.37, 155.66, 149.98, 149.92, 138.51, 138.23, 130.01, 129.77 (2x), 129.62, 128.59 (2x), 128.44 (2x), 128.24 (2x), 117.12, 107.40, 104.14, 56.41, 56.07.

4-(4-Chlorophenyl)-2-phenylquinazoline (***4f***).[25b] Yield = 84% (265 mg); White solid; mp = 154-155 °C (literature: 143-145 °C); **HRMS** (ESI, M^++H) calcd for $C_{20}H_{14}ClN_2$ 317.0840, found 317.0831; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 8.72-8.64 (m, 2H), 8.16 (d, *J* = 8.5 Hz, 1H), 8.07 (d, *J* = 8.5 Hz, 1H), 7.89 (t, *J* = 8.0 Hz, 1H), 7.84 (d, *J* = 8.5 Hz, 2H), 7.58 (d, *J* = 8.5 Hz, 2H), 7.56-7.49 (m, 4H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 167.00, 160.19, 152.03, 138.00, 136.25, 136.06, 133.66, 131.48 (2x), 130.58, 129.29, 128.81 (2x), 128.60 (2x), 128.53 (2x) , 127.17, 126.51, 121.44.

4-(4-Bromophenyl)-2-phenylquinazoline (***4g***).[25b] Yield = 94% (338 mg); White solid; mp = 159-160 °C (literature: 152-153 °C); **HRMS** (ESI, M^++H) calcd for $C_{20}H_{14}BrN_2$ 361.0335, found 361.0333; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 8.68 (d, *J* = 7.5 Hz, 2H), 8.16 (d, *J* = 8.5 Hz, 1H), 8.06 (d, *J* = 8.5 Hz, 1H), 7.89 (t, *J* = 7.5 Hz, 1H), 7.77 (d, *J* = 8.5 Hz, 2H), 7.74 (d, *J* = 8.5 Hz, 2H), 7.58-7.49 (m, 4H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 167.06, 160.20, 152.04, 137.99, 136.53, 133.67, 131.77 (2x), 131.71 (2x), 130.59, 129.30, 128.61 (2x), 128.53 (2x), 127.18, 126.49, 124.59, 121.40.

4-(4-Fluorophenyl)-2-phenylquinazoline (***4h***).[25b] Yield = 82% (246 mg); Colorless solid; mp = 140-141 °C (literature: 132-134 °C); **HRMS** (ESI, M^++H) calcd for $C_{20}H_{14}FN_2$ 301.1136, found 301.1132; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 8.69 (d, *J* = 8.5 Hz, 2H), 8.16 (d, *J* = 8.5 Hz, 1H), 8.09 (d, *J* = 8.5 Hz, 1H), 7.94-7.87 (m, 3H), 7.59-7.48 (m, 4H), 7.30 (t, *J* = 8.5 Hz, 2H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 167.33, 163.95 (d, *J* = 248.75 Hz), 160.19, 152.06, 138.08, 133.77 (d, *J* = 3.125 Hz), 133.62, 132.18 (d, *J* = 8.375 Hz, 2x), 130.56, 129.28, 128.62 (2x), 128.54 (2x), 127.13, 126.68, 121.55, 115.67 (d, *J* = 21.625 Hz, 2x). **Single-crystal X-ray diagram**: crystal of ***4h*** was grown by slow diffusion of EtOAc into a solution of ***4h*** in CH_2Cl_2 to yield colorless prisms. The compound crystallizes in the triclinic crystal system, space group P -1, *a* = 6.0455(5) Å, *b* = 11.0023(10) Å, *c* = 11.7294(10) Å, *V* = 714.87(11) Å^3, *Z* = 2, d_{calcd} = 1.395 Mg/m^3, *F*(000) = 312, 2θ range 2.009-27.096, *R* indices (all data) *R*1 = 0.0783, w*R*2 = 0.1408. CCDC number is 2002377.

2-Phenyl-4-(*p*-tolyl)quinazoline (***4i***).[25b] Yield = 84% (249 mg); Colorless solid; mp = 101-102 °C (literature: 126-127 °C); **HRMS** (ESI, M^++H) calcd for $C_{21}H_{17}N_2$ 297.1386, found 297.1385; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 8.73-8.68 (m, 2H), 8.19-8.12 (m, 2H), 8.91-8.86 (m, 1H), 7.81 (d, *J* = 8.0 Hz, 2H), 7.58-7.47 (m, 4H), 7.41 (d, *J* = 8.0 Hz, 2H), 2.51 (s, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 168.28, 160.21, 151.98, 140.14, 138.27, 134.88, 133.40, 130.41, 130.17 (2x), 129.23 (2x), 129.12, 128.64 (2x), 128.48 (2x), 127.07, 126.85, 121.71, 21.45.

4-(4-Methoxyphenyl)-2-phenylquinazoline (***4j***).[25b] Yield = 85% (265 mg); Colorless solid; mp = 105-106 °C (literature: 120-121 °C); **HRMS** (ESI, M^++H) calcd for $C_{21}H_{17}N_2O$ 313.1335, found 313.1338; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 8.72 (d, *J* = 7.5 Hz, 2H), 8.17 (d, *J* = 9.0 Hz, 1H), 8.14 (d, *J* = 8.5 Hz, 1H), 7.90 (d, *J* = 9.0 Hz, 2H), 7.88-7.84 (m, 1H), 7.57-7.49 (m, 4H), 7.12 (d, *J* = 8.5 Hz, 2H), 3.92 (s, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 167.62, 161.18, 160.08, 152.02, 138.28, 133.29, 131.81 (2x), 130.37, 130.12, 129.08, 128.59 (2x), 128.44 (2x), 126.98, 126.77, 121.57, 113.96 (2x), 55.40.

6-Chloro-4-(2-chlorophenyl)-2-phenylquinazoline (***4k***).[30a] Yield = 89% (312 mg); White solid; mp = 178-179 °C (literature: 172-173 °C); **HRMS** (ESI, M^++H) calcd for $C_{20}H_{13}Cl_2N_2$ 351.0450, found 351.0442; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 8.67-8.61 (m, 2H), 8.11 (d, *J* = 9.0 Hz, 1H), 7.82 (dd, *J* = 2.0, 9.0 Hz, 1H), 7.65-7.57 (m, 2H), 7.56-7.47 (m, 6H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 166.38, 160.70, 149.90, 137.66, 135.94, 134.87, 132.89, 132.79, 131.07, 130.84, 130.82, 130.79, 130.17, 128.76 (2x), 128.62 (2x), 127.05, 125.57, 122.82.

6,7-Dimethoxy-2-phenyl-4-(*p*-tolyl)quinazoline (***4l***). Yield = 82% (292 mg); White solid; mp = 168-169 °C; **HRMS** (ESI, M^++H) calcd for $C_{23}H_{21}N_2O_2$ 357.1598, found 357.1591; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 8.64 (d, *J* = 8.0 Hz, 2H), 7.79 (d,

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J = 7.5 Hz, 2H), 7.55-7.41 (m, 4H), 7.40-7.36 (m, 3H), 4.08 (s, 3H), 3.90 (s, 3H), 2.48 (s, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 165.06, 159.21, 155.45, 149.77, 139.67, 138.50, 135.32, 129.88, 129.68 (2x), 129.22 (2x), 128.34 (2x), 128.16 (2x), 117.02, 107.02, 107.29, 104.17, 56.29, 55.96, 21.37.

4-(3,4-Dimethoxyphenyl)-6,7-dimethoxy-2-phenylquinazoline (***4m***). Yield = 87% (350 mg); White solid; mp = 183-184 °C; **HRMS** (ESI, M^++H) calcd for $C_{24}H_{23}N_2O_4$ 403.1652, found 403.1643; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 8.62 (d, *J* = 8.5 Hz, 2H), 7.53-7.40 (m, 7H), 7.06 (d, *J* = 8.0 Hz, 1H), 4.09 (s, 3H), 3.99 (s, 3H), 3.98 (s, 3H), 3.92 (s, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 164.66, 159.21, 155.51, 150.39, 149.91, 149.83, 149.11, 138.48, 130.81, 129.97, 128.40 (2x), 128.17 (2x), 122.78, 116.98, 112.92, 110.87, 107.97, 104.25, 56.36, 56.07, 56.03, 56.01.

6,7-Dimethoxy-2-phenyl-4-(3,4,5-trimethoxyphenyl)quinazoline (***4n***). Yield = 83% (359 mg); White solid; mp = 196-197 °C; **HRMS** (ESI, M^++H) calcd for $C_{25}H_{25}N_2O_5$ 433.1758, found 433.1752; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 8.62 (d, *J* = 7.0 Hz, 2H), 7.54-7.47 (m, 3H), 7.46 (s, 1H), 7.42 (s, 1H), 7.11 (s, 2H), 4.11 (s, 3H), 3.97 (s, 3H), 3.95 (s, 6H), 3.94 (s, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 164.87, 159.27, 155.70, 153.39 (2x), 149.98, 149.95, 139.35, 138.37, 133.54, 130.09, 128.45 (2x), 128.23 (2x), 116.97, 107.42, 107.10 (2x), 104.13, 60.98, 56.44, 56.35 (2x), 56.13.

6-Chloro-2-(4-fluorophenyl)-4-phenylquinazoline (***5a***).[25b] Yield = 90% (1500 mg); White solid; mp = 189-190 °C; **HRMS** (ESI, M^++H) calcd for $C_{20}H_{13}ClFN_2$ 335.0746, found 335.0736; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 8.68 (dd, *J* = 2.5, 9.0 Hz, 2H), 8.08 (d, *J* = 2.5 Hz, 1H), 8.06 (d, *J* = 9.0 Hz, 1H), 7.86-7.84 (m, 2H), 7.81 (dd, *J* = 2.5, 9.0 Hz, 1H), 7.63-7.62 (m, 3H), 7.19 (t, *J* = 9.0 Hz, 2H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 167.58, 164.76 (d, *J* = 249.25 Hz), 159.50, 150.44, 136.99, 134.57, 133.94 (d, *J* = 2.625 Hz), 132.61, 130.74 (2x), 130.54 (d, *J* = 68.5 Hz, 2x), 129.99 (2x), 128.75 (2x), 125.79, 122.05, 115.50 (d, *J* = 21.375 Hz, 2x).

6-Chloro-4-phenyl-2-(*p*-tolyl)quinazoline (***5b***).[25b] Yield = 91% (1500 mg); White solid; mp = 203-204 °C; **HRMS** (ESI, M^++H) calcd for $C_{21}H_{16}ClN_2$ 331.0997, found 331.0993; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 8.57 (d, *J* = 8.5 Hz, 2H), 8.08 (d, *J* = 2.5 Hz, 1H), 8.07 (d, *J* = 8.5 Hz, 1H), 7.87-7.85 (m, 2H), 7.81-7.79 (m, 1H), 7.64-7.60 (m, 3H), 7.33 (d, *J* = 8.0 Hz, 2H), 2.45 (s, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 167.42, 160.54, 150.51, 141.03, 137.16, 135.05, 134.38, 132.29, 130.76, 130.14, 130.02 (2x), 129.33 (2x), 128.70 (2x), 128.62 (2x), 125.74, 122.07, 21.53.

2,4,6-triphenylquinazoline (***6***).[29] Pd(OAc)2 (5.6 mg, 2.5 mol %) and PPh_3 (13 mg, 5.0 mol %) were added to a solution of 6-bromo-2,4-diphenylquinazoline **4b** (1.0 mmol) in DME/EtOH (9/1, 10 mL) at reflux. Then Na_2CO_3 (159 mg, 1.5 mmol) and phenlboronic acid (1.1 mmol) were added to the solution directly. The reaction mixture was stirred at reflux for 18 h and cooled to rt, and the solvent was concentrated. The residue was diluted with water (10 mL), and the mixture was extracted with EtOAc (3 × 20 mL). The combined organic layers were washed with brine, dried, filtered, and evaporated to afford crude product. Purification on silica gel (hexanes/EtOAc = 10/1−6/1) afforded compounds **6**. Yield = 90% (322 mg); White solid; mp = 137-138 °C (literature: 143-145 °C); **HRMS** (ESI, M^++H) calcd for $C_{26}H_{19}N_2$ 359.1543, found 359.1541; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 8.73 (d, *J* = 8.0 Hz, 2H), 8.31 (d, *J* = 2.0 Hz, 1H), 8.24 (d, *J* = 8.5 Hz, 1H), 8.16 (d, *J* = 2.0, 8.5 Hz, 1H), 7.98-7.92 (m, 2H), 7.67-7.60 (m, 5H), 7.58-7.51 (m, 3H), 7.48 (t, *J* = 7.5 Hz, 2H), 7.40 (t, *J* = 7.5 Hz, 1H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 168.36, 160.13, 151.37, 139.98, 139.82, 138.16, 137.69, 133.19, 130.49, 130.18 (2x), 129.95, 129.60, 129.02 (2x), 128.64 (2x), 128.62 (2x), 128.52 (2x), 127.92, 127.36 (2x), 124.52, 121.85.

6-(4-methoxyphenyl)-2,4-diphenylquinazoline (***7***). $PdCl_2(PPh_3)_2$ (49 mg, 0.07 mmol) and CuI (26.5 mg, 0.14 mmol) dissolved in triethylamine (5 mL) and toluene (10 mL) at rt for 30 minutes. Then 6-bromo-2,4-diphenylquinazoline **4b** (1.0 mmol) dissolved in triethylamine (3 mL) and phenylacetylene (1.2 mmol) were added to the solution directly. The reaction mixture was stirred at reflux for 6 h and cooled to rt, and the solvent was concentrated. The residue was diluted with water (10 mL), and the mixture was extracted with EtOAc (3 × 20 mL). The combined organic layers were washed with brine, dried, filtered, and evaporated to afford crude product. Purification on silica gel (hexanes/EtOAc = 15/1−10/1) afforded compounds **7**. Yield = 88% (336 mg); White solid; mp = 191-192 °C; **HRMS** (ESI, M^++H) calcd for $C_{28}H_{19}N_2$ 383.1543, found 383.1533; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 8.71 (d, *J* = 8.0 Hz, 2H), 8.29 (s, 1H), 8.12 (d, *J* = 8.5 Hz, 1H), 7.98 (dd, *J* = 2.0, 8.5 Hz, 1H), 7.94-7.89 (m, 2H), 7.67-7.59 (m, 3H), 7.58-7.50 (m, 5H), 7.41-7.34 (m, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 167.96, 160.63, 151.48, 137.94, 137.39, 136.20, 131.69 (2x), 130.72, 130.19 (2x), 130.09 (2x), 129.32, 128.72 (3x), 128.68 (2x), 128.55 (2x), 128.43 (2x), 122.67, 122.09, 121.53, 91.30, 88.83.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1039/xxxxxxxxxx.

Detailed experimental procedures and spectroscopic data for all compounds and X-ray analysis data for **3c**, **3l**, **3w**, **3aa**, **3ab** and **4h** (PDF)

Accession Codes

CCDC 1988309, 1994079, 1996086, 1996087, 1996497 and 2002377 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by containing The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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REFERENCES

(1) (a) J. P. Michael *Nat. Prod. Rep*. 2004, **21**, 650-668; (b) J. P. Michael, *Nat. Prod. Rep*. 2008, **25**, 166-187.
(2) (a) D. J. Connolly, P. M. Lacey, M. McCarthy, C. P. Saunders, A. M. Carroll, R. Goddard and P. J. Guiry, *J. Org. Chem*. 2004, **69**, 6572-6589; (b) L. Hu, H. Xu, Q. Yang, Z. Deng, C. Yu and Y. Peng, *J. Organomet. Chem*. 2017, **843**, 20-25.
(3) (a) R. Tiwari and G. Chhabra, *Asian J. Chem*. 2010, **22**, 5981-5986; (b) P. P. Kung, M. D. Casper, K. L. Cook, L. Wilson-Lingard, L. M. Risen, T. A. Vickers, R. Ranken, L. B. Blyn, R. Wyatt, P. D. Cook and D. J. J. Ecker, *J. Med. Chem*. 1999, **42**, 4705-4713; (c) S. Jantova, K. Spirkova, S. Stankovsky and P. Duchonova, *Folia Microbiol* 1999, **44**, 187-190; (d) G. Grovera and S. G. Kini, *Eur. J. Med. Chem*. 2006, **41**, 256-262.
(4) (a) L. A. Doyle and D. D. Ross, *Oncogene* 2003, **22**, 7340-7358; (b) E. A. Henderson, V. Bavetsias, D. S. Theti, S. C. Wilson, R. Clauss and A. L. Jackman, *Bioorg. Med. Chem*. 2006, **14**, 5020-5042; (c) R. Gundla, R. Kazemi, R. Sanam, R. Muttineni, J. A. R. P. Sarma, R. Dayam and N. Neamati, *J. Med. Chem*. 2008, **51**, 3367-3377; (d) G. Marzaro, A. Guiotto and A. Chilin, 2012, **22**, 223-252.
(5) V. G. Ugale and S. B. Bari, *Eur. J. Med. Chem*. 2014, **80**, 447-501.
(6) (a) C. Balakumar, P. Lamba, D. P. Kishore, B. L. Narayana, K. V. Rao, K. Rajwinder, A. R. Rao, B. Shireesha and B. Narsaiah, *Eur. J. Med. Chem*. 2010, **45**, 4904-4913; (b) A. M. Alafeefy, A. A. Kadi, O. A. Al-Deeb, K. E. El-Tahir and N. A. Al-jaber, *Eur. J. Med. Chem*. 2010, **45**, 4947-4952.
(7) Y. Kabri, N. Azas, A. Dumetre, S. Hutter, M. Laget, P. Verhaeghe, A. Gellis and P. Vanelle, *Eur. J. Med. Chem*. 2010, **45**, 616-622.
(8) (a) A. S. El-Azab, M. A. Al-Omar, A. A. M. Abdel-Aziz, N. I. Abdel-Aziz, M. A. A. El-Sayed, A. M. Aleisa, M. M. Sayed-Ahmed and S. G. Abdel-Hamide, *Eur. J. Med. Chem*. 2010, **45**, 4188-4198; (b) M. N. Noolvi, H. M. Patel, V. Bhardwaj, A. Chauhan, *Eur. J. Med. Chem*. 2011, **46**, 2327-2346.
(9) E. Jafari, M. R. Khajouei, F. Hassanzadeh, G. H. Hakimelahi, G. A. Khodarahmi, *Res. Pharm. Sci*. 2016, **11**, 1-14.
(10) A. Kumar, P. Sharma, P. Kumari, B. L. Kalal, *Bioorg. Med. Chem. Lett*. 2011, **21**, 4353-4357.
(11) A. Machara, V. Lux, M. Kozisek, K. Grantz-Saskova, O. Stepanek, M. Kotora, K. Parkan, M. Pavova, B. Glass and P. Sehr, *J. Med. Chem*. 2016, **59**, 545-558.
(12) K. Waisser, J. Gregor, H. Dostal, J. Kunes, L. Kubicova, V. Klimesova and J. Kaustova, *Farmaco* 2001, **56**, 803-807.
(13) J. F. Mendes de Silva, M. Walters, S. Al-Damluji, C. R. Ganellin, *Bioorg. Med. Chem*. 2008, **16**, 7254-7263.
(14) P. Barraja, L. Caracausi, P. Diana, A. Montalbano, A. Carbone, A. Salvador, P. Brun, I. Castagliuolo, S. Tisi, F. Dall'Acqua, D. Vedaldi and G. Cirrincione, *ChemMedChem* 2011, **6**, 1238-1248.
(15) (a) S. Boyapati, U. Kulandaivelu, S. Sangu and M. R. Vanga, *Arch. Pharm*. 2010, **343**, 570-576; (b) S. H. Yang, D. B. Khadka, S. H. Cho, H. K. Ju, K. Y. Lee, H. J. Han, K. T. Lee and W. J. Cho, *Bioorg. Med. Chem*. 2011, **19**, 968-977; (c) Y. H. Kim, H. Choi, J. Lee, I. C. Hwang, S. K. Moon, S. J. Kim, H. W. Lee, D. S. Im, S. S. Lee, S. K. Ahn, S. W. Kim, C. K. Han, J. H. Yoon, K. J. Lee, N. S. Choi, *Bioorg. Med. Chem. Lett*. 2008, **18**, 6279-6282; (d) O. Cruz-Lopez, A. Conejo-Garcia, M. C. Nunez, M. Kimatrai, M. E. Garcia-Rubino, F. Morales, V. Gomez-Perez and J. M. Campos, *Curr. Med. Chem*. 2011, **18**, 943-963.
(16) R. Saari, J.-C. Törmä and T. Nevalainen, *Bioorg. Med. Chem*. 2011, **19**, 939-950.
(17) (a) B. Akduman and E. D. Crawford, *Urology* 2001, **58**, 49-54; (b) M. A. Raskind, E. R. Peskind, B. Chow, C. Harris, A. Davis-Karim, H. A. Holmes, K. L. Hart, M. McFall, T. A. Mellman, C. Reist, J. Romesser, R. Rosenheck, M.-C. Shih, M. B. Stein, R. Swift, T. Gleason, Y. Lu and G. D. Huang, *N. Engl. J. Med*. 2018, **378**, 507-517.
(18) O. P. Gupta, M. L. Sharma, B. J. Ghatak and C. K. Atal, *Indian J. Med. Res*. 1977, **66**, 680-691.
(19) A. Machara, V. Lux, M. Kozisek, K. Grantz-Saskova, O. Stepanek, M. Kotora, K. Parkan, M. Pavova, B. Glass and P. Sehr, *J. Med. Chem*. 2016, **59**, 545-558.
(20) C. Carmi, A. Cavazzoni, S. Vezzosi, F. Bordi, F. Vacondio, C. Silva, S. Rivara, A. Lodola, R. R. Alfieri, S. La Monica, M. Galetti, A. Ardizzoni, P. G. Petronimi and M. Mor, *J. Med. Chem*. 2010, **53**, 2038-2050.
(21) (a) W. Pao and V. A. *J. Clin. Oncol*. 2005, **23**, 2556-2568; (b) V. A. Miller, M. G. Kris, N. Shah, J. Patel, C. Azzoli, J. G. M. Kurg, W. Pao, N. Rizvi, B. Pizzo, L. Tyson, E. Venkatrman, L. Ben-Porat, N. Memoli, M. Zakowski, V. Rusch and R. T. Heelan, *J. Clin. Oncol*. 2004, **22**, 1103-1109.
(22) (a) W. Zhang, F. Guo, F. Wang, N. Zhao, L. Liu, J. Li and Z. Wang, *Org. Biomol. Chem*. 2014, **12**, 5752-5756; (b) J.-P. Lin, F.-H. Zhang and Y.-Q. Long, *Org. Lett*. 2014, **16**, 2822-2825; (c) Z.-C. Shen, P. Yang and Y. Tang, *J. Org. Chem*. 2016, **81**, 309-317; (d) Z. Lv, B. Wang, Z. Hu, Y. Zhou, W. Yu and J. Chang, *J. Org. Chem*. 2016, **81**, 9924-9930; (e) R. Prakash, B. R. Bora, R. C. Boruah and S. Gogoi, *Org. Lett*. 2018, **20**, 2297-2300.
(23) (a) Z. Chen, J. Chen, M. Liu, J. Ding, W. Gao, X. Huang and H. Wu, *J. Org. Chem*. 2013, **78**, 11342-11348; (b) L. Ye, L. Yu, L. Zhu and X. Xia, *Molecules* 2013, **18**, 13860-13869.
(24) A. Witt and J. Bergman, *Curr. Org. Chem*. 2003, **7**, 659-677.
(25) (a) M. Ramanathan, Y. H. Liu, S. M. Peng and S. T. Liu, *Org. Lett*. 2017, **19**, 5840-5843; (b) K. Hu, Q. Zhen, J. Gong, T. Cheng, L. Qi, Y. Shao and J. Chen, *Org. Lett*. 2018, **20**, 3083-3087.
(26) (a) C. U. Maheswari, G. S. Kumar, M. Venkateshwar, R. A. Kumar, M. L. Kantam and K. R. Reddy, *Adv. Synth. Catal*. 2010, **352**, 341-346; (b) H. Yuan, W. J. Yoo, H. Miyamura and S. Kobayashi, *Adv. Synth. Catal*. 2012, **354**, 2899-2904; (c) B. Han, X. L. Yang, C. Wang, Y. W. Bai, T. C. Pan, X. Chen and W. Yu, *J. Org. Chem*. 2012, **77**, 1136-1142; (d) T. Chatterjee, D. Kim and E. J. Cho, *J. Org. Chem*. 2018, **83**, 7423-7430.
(27) (a) J. Zhang, D. Zhu, C. Yu, C. Wan and Z. Wang, *Org. Lett*. 2010, **12**, 2841-2843; (b) J. Zhang, C. Yu, S. Wang, C. Wan and Z. Wang, *Chem. Commun*. 2010, **46**, 5244-5246; (c) B. Han, C. Wang, R.-F. Han, W. Yu, X.-Y. Duan, R. Fang and X.-L. Yang, *Chem. Commun*. 2011, **47**, 7818-7820; (d) P. T. K. Arachchige and C. S. Yi, *Org. Lett*. 2019, **21**, 3337-3341; (e) Y. Yan and Z. Wang, *Chem. Commun*. 2011, **47**, 9513-9515; (f) D. Zhao, Q. Shen and J.-X. Li, *Adv. Synth. Catal*. 2015, **357**, 339-344; (g) Y. Yan, M. Shi, B. Niu, X. Meng, C. Zhu, G. Liu, T. Chen and Y. Liu, *RSC Adv*. 2016, **6**, 36192-36197; (h) S. K. Panja and S. Saha, *RSC Adv*. 2013, **3**, 14495-14500; (i) Y. Yan, Y. Zhang, C. Feng, Z. Zha and Z. Wang, *Angew. Chem. Int. Ed*. 2012, **51**, 8077-8081; (j) S. Rachakonda, P. S. Pratap and M. V. B. Rao, *Synthesis* 2012, **44**, 2065-2069.
(28) (a) H. M. Wang, H. Chen, Y. Chen and G. J. Deng, *Org. Biomol. Chem*. 2014, **12**, 7792-7799; (b) L. Tang, P. F. Wang, Y. Fan, X. K. Yang, C. F. Wan and Z. G. Zha, *ChemCatChem* 2016, **8**, 3565-3569.
(29) J. Chen, D. Chang, F. Xiao and G.-J. Deng, *Green Chem*. 2018, **20**, 5459-5463.
(30) (a) R. Sarma and D. Prajapati, *Green Chem*. 2011, **13**, 718-722; (b) Z. H. Zhang, X. N. Zhang, L. P. Mo, Y. X. Li, F. P. Ma, *Green Chem*. 2012, **14**, 1502-1506.
(31) C. A. Bruynes and T. K. Jurriens, *J. Org. Chem*. 1982, **47**, 3966-3969.
(32) A. A. Joseph, V. P. Verma, X.-Y. Liu, C.-H. Wu, V. M.

View Article Online
DOI: 10.1039/D0OB01507E

Dhurandhare and C.-C. Wang, *Eur. J. Org. Chem*. 2012, 744-753.
(33) (a) C.-K. Chan, C.-Y. Lai, W.-C. Lo, Y.-T. Cheng, M.-Y. Chang and C.-C. Wang, *Org. Biomol. Chem*. 2020, **18**, 305-315; (b) C.-K. Chan, C.-Y. Lai and C.-C. Wang, *Synthesis* 2020, **52**, 1779-1794.
(34) S. T. Kadam and S. S. Kim, *Green Chem*. 2010, **12**, 94-98.
(35) E. Liang, Y. Wu, J. Chen, W. Xiong, J. Zhao, X. Yao, and X. Tang, *Tetrahedron* 2019, **75**, 130783.
(36) CCDC 1996087 (**3c**), 1994079 (**3l**), 1988309 (**3w**), 1996086 (**3aa**), 1996497 (**3ab**) and 2002377 (**4h**), contain the supplementary crystallographic data for this paper. This data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the CCDC, 12 Union Road, Cambridge CB2 1EZ, UK; fax: 44-1223-336033; e-mail: deposit@ccdc.cam.ac.uk).
(37) The HRMS data of TMSOH, TMSOTMS and intermediate **E** have been included in the Supporting Information.
(38) (a) T. Besson and C. W. Rees, *J. Chem. Soc., Perkin Trans. 1* 1996, 2857-2860; (b) M. Soukri, G. Guillaumet, T. Besson, D. Aziane, M. Aadil, E. M. Essassi and M. Akssira, *Tetrahedron Lett*. 2000, **41**, 5857-5860. (c) J. A. Seijas, M. P. Vázquez-Tato and M. M. Martínez, *Tetrahedron Lett*. 2000, **41**, 2215-2217; (d) T. Besson, J. Guillard and C. W. Rees, *Tetrahedron Lett*. 2000, **41**, 1027-1030; (e) F.-R. Alexandre, A. Berecibar, R. Wrigglesworth and T. Besson, *Tetrahedron* 2003, **59**, 1413-1419; (f) D. S. Yoon, Y. Han, T. M. Stark, J. C. Haber, B. T. Gregg and S. B. Stankovich, *Org. Lett*. 2004, **6**, 4775-4778; (g) D. Maitraie, T. Yakaiah, K. Srinivas, G. V. Reddy, S. Ravikanth, B. Narsaiah, P. S. Rao, K. Ravikumar and B. Sridhar, *J. Fluor.* Chem. 2006, **127**, 351-359; (h) V. Kumar, C. Mohan, M. Gupta and M. P. Mahajan, *Tetrahedron* 2005, **61**, 3533-3538; (i) S. Ferrini, F. Ponticelli and M. Taddei, *Org. Lett*. 2007, **9**, 69-72; (j) A. Chilin, G. Marzaro, S. Zanatta and A. Guiotto, *Tetrahedron Lett*. 2007, **48**, 3229-3231; (k) F. Portela-Cubillo, J. S. Scott and J. C. Walton, *J. Org. Chem*. 2009, **74**, 4934-4942.
(39) F. Wang, H. Wang, Q. Wang, S. Yu and X. Li, *Org. Lett*. 2016, **18**, 1306-1309.
(40) X. Wang, D. He, Y. Huang, Q. Fan, W. Wu and H. Jiang, *J. Org. Chem*. 2018, **83**, 5458-5466.
(41) M. Ramanathan and S.-T. Liu *J. Org. Chem*. 2017, **82**, 8290-8295.

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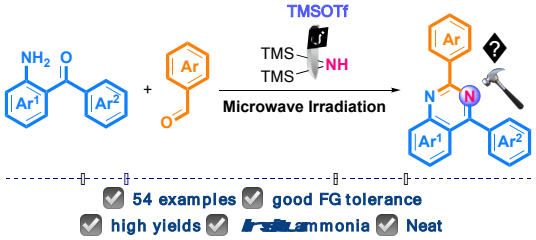

An efficient synthetic route for the synthesis of substituted quinazolines under neat, metal-free and microwave irradiation condition has been developed by using TMSOTf as an acid catalyst and HMDS as a nitrogen source.