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NUCLEOPHILIC AROYLATION ON FLUOROQUINAZOLINES CATALYZED BY *N*-HETEROCYCLIC CARBENES

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Abstract – We report on the synthesis of 7-benzoyl- and 7-heteroaroylquinazolines from 7-fluoroquinazolines and aromatic aldehydes by *N*-heterocyclic carbene (NHC)-catalyzed nucleophilic aromatic substitution, showing that the NHC derived from 1,3-dimethylimidazolium iodide outperformed those originating from other azolium (e.g., thiazolium and triazolium) salts. Additionally, the developed methodology allowed the preparation of 5- and 8-aroylquinazolines from the corresponding fluoroquinazolines.

INTRODUCTION

Quinazoline derivatives have been attracting increased attention due to their well-pronounced biological (e.g., anti-malaria,[1] antitumor,[2] anti-inflammatory,[3,4] and anti-hypertensive)[5] activity, as exemplified by Afatinib and Elotinib, both of which are tyrosine kinase inhibitors used for cancer treatment.[6] Further examples include Prazosin (anti-hypertensive),[7] Afloqualone (peripherally acting muscle relaxant),[8] and KF31327 – a prospective drug for heart disease treatment.[9] Thus, the synthesis of novel quinazoline derivatives is of great importance to the discovery of bioactive substances.

PVHD121, a quinazoline derivative previously prepared in our research group from 4-chloroquinazoline by *N*-heterocyclic carbene (NHC)-catalyzed nucleophilic aroylation followed by a Grignard reaction,[10] was found to exhibit strong antiproliferative activity in random screenings.[11] Specifically, the NHC-catalyzed aroylation used in the above synthesis relied on the umpolung of aromatic aldehydes to afford 4-aroylquinazolines via S_NAr.

The first NHC-catalyzed reaction, namely, the dimerization of benzaldehyde (benzoin condensation) in the presence of thiamine hydrochloride as a catalyst precursor, was reported by Ukai *et al.* in 1943.[12] In such reactions, the NHC induces aldehyde dipole inversion (umpolung) by reacting with the carbonyl group to afford the Breslow intermediate that behaves as an acyl anion equivalent. Thus, the above

reactivity of NHCs allows aldehyde carbonyls to react with electrophiles, with this type of reaction being mediated exclusively by NHCs and the cyanide ion.[13,14] This has attracted increased amounts of attention in recent years.

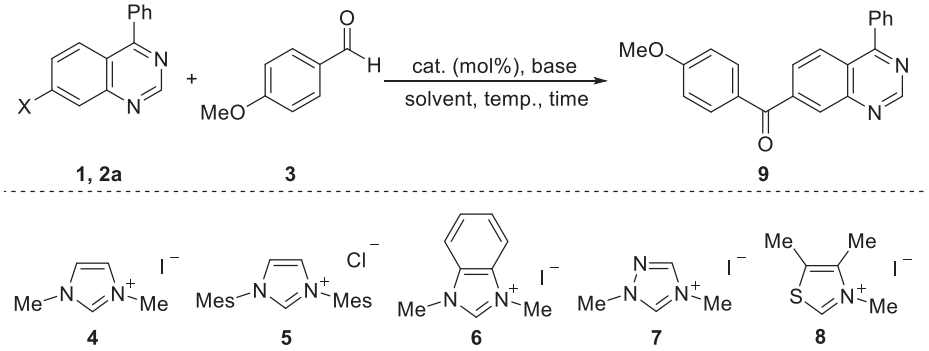
In addition to the well-known umpolung transformations such as benzoin condensation[12,14] and Stetter reaction,[15] numerous other NHC-catalyzed reactions have been reported to date, e.g., transesterification,[16] ring-opening polymerization,[17] and the homoenolate reaction.[18] Previously, we reported on the use of the NHC-catalyzed aroylation of Cl- and sulfonyl substituted *N*-heteroarenes,[19] arylimidoyl chlorides,[20] and electron-deficient 4-fluorobenzenes[21] to afford keto derivatives, demonstrating the applicability of this transformation to a variety of *N*-heteroarenes. However, in these examples, the heteroarene substitution positions were limited to the carbons of those imine moieties bearing a leaving group, with any substitution at those carbon atoms not adjacent to the nitrogen atoms being unknown. In the case of quinazoline, only aroylation at C2 and C4 imine carbons has been reported. To the best of our knowledge, the electrophilic substitution-based aroylation of the fused benzene ring of the quinazoline framework has only been reported for the 6-position of quinazoline-2,4-dione.[22] To bridge the above gap, we herein report on the first example of NHC-catalyzed nucleophilic aroylation at the fused benzene ring of quinazolines.

RESULTS AND DISCUSSION

The aroylation conditions were initially investigated for the reaction of 7-halogeno-4-phenylquinazolines with 4-methoxybenzaldehyde **3** (Table 1). To this end, 4-phenyl-substituted derivatives were chosen as substrates to prevent any undesired reactions with the carbon at position 4 of the quinazoline core, which is highly susceptible to nucleophilic attack. Based on the successful examples described in previous reports,[19] the optimal reaction conditions were investigated. Thus, the reaction of chloride **1** in the presence of dimethylimidazolium iodide **4** (10 mol%, NHC precursor) and NaH (base) in DMF at room temperature for 4 h, afforded the desired ketone **9**, albeit with a low yield (entry 1). However, when fluoroquinazoline **2a** was used under the same conditions, **9** was obtained with a significantly increased yield of 88% (entry 2). Screening identified DMF as the best solvent, with the use of NMP, DMSO, THF, and 1,4-dioxane leading to lower yields (entries 3−6). Additionally, we investigated the NHC precursor scope by testing azolium salts **5**–**8**, revealing that no target product was obtained when dimesitylimidazolium salt **5** was used instead of **4** (entry 7), which was ascribed to the bulkiness of the Breslow intermediate *N*-substituents impeding the nucleophilic attack. In the case of dimethylbenzimidazolium salt **6** and dimethyltriazolium salt **7**, ketone **9** was obtained in yields of 6% and 2%, respectively (entries 8 and 9), whereas no target product was obtained in the case of trimethylthiazolium salt **8** (entry 10). The above results indicated that the Breslow intermediate produced

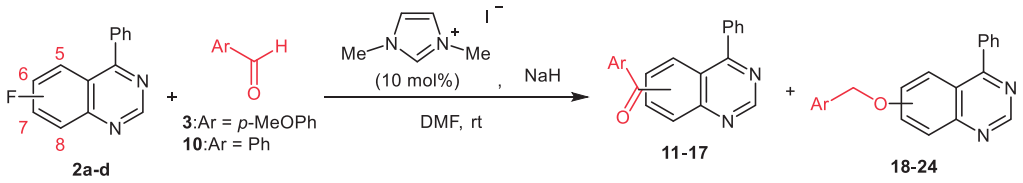
from precursor **4** exhibited the highest nucleophilicity. Moreover, we attempted to further optimize the reaction by base screening (DBU, KHMDS, and NaOBu^t), showing that NaH was the best choice (entries 11–13). Next, we examined the effects of catalyst loading (5–20 mol%; entries 14–16), demonstrating that the high yields observed for 5 and 15 mol% of **4** (entries 14 and 15) decreased at an elevated loading of 20 mol% (entry 16). All the reactions were performed using 1 mmol of the starting quinazolines. The catalyst loading for subsequent investigation was set to 10 mol% (22 mg of **4**) due to the difficulty of weighing smaller amounts of the highly hygroscopic imidazolium.

Table 1. Optimization of reaction conditions



Entry	Substrate	X	Cat. (mol%)	Solvent	Base	Temp.	Time (h)	Yield (%)	Recovery (%)
1	**1**	Cl	**4** (10)	DMF	NaH	rt	4	36	-
2	**2a**	F	**4** (10)	DMF	NaH	rt	4	88	-
3	**2a**	F	**4** (10)	NMP	NaH	rt	4	81	8
4	**2a**	F	**4** (10)	DMSO	NaH	rt	4	63	-
5	**2a**	F	**4** (10)	THF	NaH	reflux	4	25	-
6	**2a**	F	**4** (10)	1,4-dioxane	NaH	reflux	4	3	76
7	**2a**	F	**5** (10)	DMF	NaH	rt	7	-	45
8	**2a**	F	**6** (10)	DMF	NaH	rt	7	2	43
9	**2a**	F	**7** (10)	DMF	NaH	rt	7	6	44
10	**2a**	F	**8** (10)	DMF	NaH	rt	7	-	46
11	**2a**	F	**4** (10)	DMF	DBU	rt	4	-	87
12	**2a**	F	**4** (10)	DMF	KHMDS	rt	4	18	63
13	**2a**	F	**4** (10)	DMF	NaOBu^t	rt	4	50	-
14	**2a**	F	**4** (5)	DMF	NaH	rt	4	88	-
15	**2a**	F	**4** (15)	DMF	NaH	rt	4	82	-
16	**2a**	F	**4** (20)	DMF	NaH	rt	4	73	-

Table 2. Aroylation of 4-phenylquinazolines



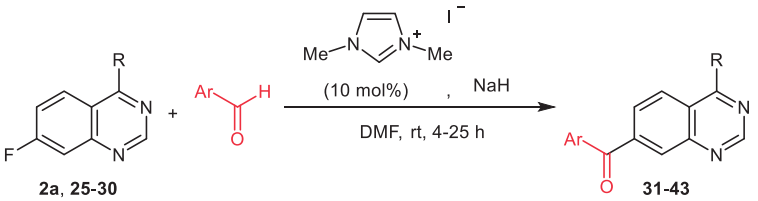
Entry	Substrate	Time (h)	Ketone (Yield)	Ether (Yield)	Recovery (%)
1	5-F (**2b**)	21	**11** (27%)	**18** (15%)	26
2	6-F (**2c**)	21	**12** (-)	**19** (21%)	40
3	8-F (**2d**)	21	**13** (9%)	**20** (16%)	41
4	5-F (**2b**)	24	**14** (13%)	**21** (9%)	40
5	6-F (**2c**)	24	**15** (-)	**22** (-)	59
6	7-F (**2a**)	4	**16** (74%)	**23** (-)	-
7	8-F (**2d**)	24	**17** (-)	**24** (-)	65

Next, we aroylated 5-, 6-, and 8-fluoroquinazolines **2b–d** with **3** to investigate the effect of leaving group position (Table 2), showing that although **2b** and **2d** afforded the desired ketones **11** and **13** in 27% and 9% yields, respectively (entries 1 and 3), no desired product was obtained from 6-fluoroquinazoline **2c** (entry 2). Notably, the above aroylations were accompanied by the formation of ethers **18–20**, which was ascribed to the reaction of the substrate with the 4-methoxybenzyl alcohol produced from **3** via Cannizzaro reaction. Although all the reactions were performed using a dry solvent under an argon atmosphere, this undesired reaction can be attributed to an existence of a small amount of water introduced along with hygroscopic sodium hydride and **4** during weighing. The aroylation of **2b** and **2a** with benzaldehyde afforded the desired ketones **14** and **16** in 13% and 74% yields, respectively (entries 4 and 6), whereas no target ketones were obtained in the case of **2c** and **2d** (entries 5 and 7).

These results show that the 5-fluoro substrate **2b** and the 7-fluoro substrate **2a** are more susceptible to substitution than the 6-fluoro substrate **2c** and the 8-fluoro substrate **2d**. This tendency can be explained by the stability of the reaction intermediates. The Meisenheimer complexes from **2b** and **2a** have resonance forms with a negative charge on one of the nitrogen atoms, whereas the complexes from **2c** and **2d** do not have the same type of resonance forms. In addition, the lower yields of the 5-aroylated products, relative to the 7-aroylated products, can be attributed to the bulkiness of the phenyl group at the peri-position. This hampers any nucleophilic attack at position 5.

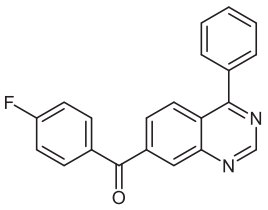
Once we had determined the optimal reaction conditions, we explored the reaction of 4-substituted quinazolines with various aromatic aldehydes (Table 3).

Table 3. Aroylation of 4-substituted quinazolines

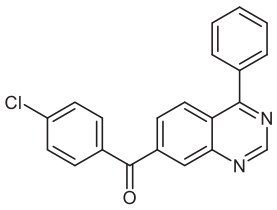


2a, **25-30** **31-43**

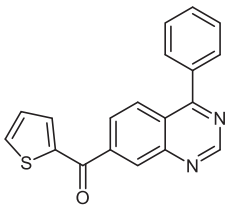
25: R = *p*-MeOPh **28**: R = *p*-PhPh
26: R = *p*-CF_3Ph **29**: R = OMe
27: R = *p*-CNPh **30**: R = benzoyl



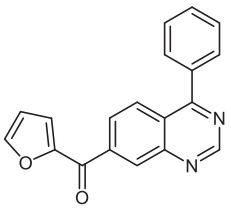
31: 4 h, 13%



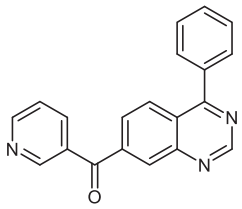
32: 4 h, 36%



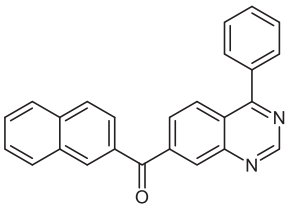
33: 4 h, 73%



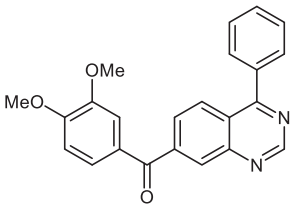
34: 25 h, 32%



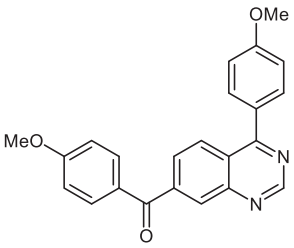
35: 21 h, 35%



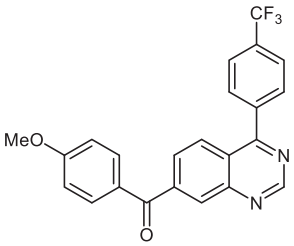
36: 22 h, 56%



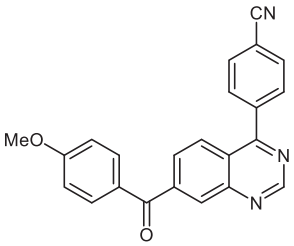
37: 20 h, 71%



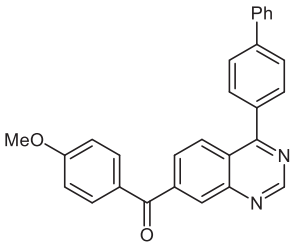
38: 4 h, 87%



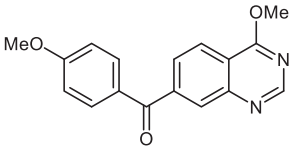
39: 4 h, 83%



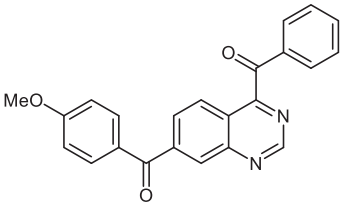
40: 9 h, 90%



41: 9 h, 77%



42: 4 h, 42%



43: 7 h, 79%

The reaction of **2a** with 4-fluoro- and 4-chlorobenzaldehydes provided ketones **31** and **32**, respectively, albeit with a low yield. Formyl heterocycles (thiophen-2-carbaldehyde, furfural, and pyridine-3-carboxaldehyde) were also tolerated, affording ketones **33**–**35** in moderate to low yields. We found that 2- naphthaldehyde and 3,4-dimethoxybenzaldehyde afforded ketones **36** and **37**, respectively, in moderate yields. On the other hand, aroylation with aliphatic aldehydes proved unsuccessful, affording

a complex product mixture. As expected, the Breslow intermediates originating from those aromatic aldehydes bearing electron-donating groups and electron-rich heteroarene carboaldehydes proved to be better nucleophiles than those derived from aromatic aldehydes bearing electron-withdrawing groups, leading to higher product yields. The one exception to this was furfural, which has a less stable furan ring. Finally, we explored the scope of quinazoline substituents at the 4-position, revealing that the reaction of the 4-aryl-substituted quinazolines bearing electron-donating or electron-withdrawing groups on the phenyl group (**25**–**28**) with **3** afforded the desired ketones **38**–**41** in moderate yields. The aroylation of 4-methoxyquinazoline **29** proceeded, producing a moderate yield, whereas that of 4-dimethylamino-7-fluoroquinazoline did not proceed (the starting materials were recovered). The dimethylamino group with a strong electron donating effect increases the electron density of the quinazoline, impeding the nucleophilic substitution. Although aroylations of 7-fluoro-4-methylquinazoline, 4-cyano-7-fluoroquinazoline, and 7-fluoro-4-phenylthioquinazoline were attempted, the reaction systems became complicated, such that the formation of target ketones could not be confirmed. It is believed that 7-fluoro-4-methylquinazoline behaved similarly to an active methylene compound because of the electron-withdrawing effect of the pyrimidine ring, affording a complex reaction mixture. The cyano group and the phenylthio group at position 4 of the quinazoline core are thought to act as leaving groups, causing undesired reactions. Quinazoline **30**, bearing a benzoyl group, afforded the desired ketone **43** in 79% yield.

CONCLUSION

In summary, we successfully introduced aroyl groups onto the fused benzene moiety of quinazolines at the C5, C7, and C8 positions by means of NHC-catalyzed nucleophilic aroylation, showing that the electrophilicities of quinazoline C7, C5, C8, and C6 positions decrease in the stated order. Importantly, novel 5-, 7-, and 8-aroylquinazolines were synthesized from quinazolines bearing a fluorine leaving group via S_NAr reactions with various aromatic aldehydes. The biological activities of these products will be separately reported in the future.

EXPERIMENTAL

Chemicals were supplied by WAKO Pure Chemical Industries, Ltd., Kanto Chemical Co. Inc, Tokyo Chemical Industry Co., Ltd., or Sigma-Aldrich, and were used without further purification. All reactions were performed under an argon atmosphere and with stirring unless otherwise noted. Column chromatography was performed on Merck Silica Gel 60 plates using dichloromethane or ethyl acetate and *n*-hexane as eluents. TLC experiments were carried out on Merck Silica Gel 60-F254 plates.

The ^{1}H or ^{13}C nuclear magnetic resonance (NMR) spectra were recorded on a JEOL JNM-ECA500 NMR spectrometer (500 MHz), JEOL JNM-EXC 300 NMR spectrometer (300 MHz) or Bruker AVANCE (400 MHz) using TMS and $CDCl_3$ as internal standards. The ^{1}H NMR and ^{13}C NMR spectra data were as follows: chemical shift (ppm), integration, multiplicity (s. singlet; d, doublet; t, triplet; q, quartet, m, multiplet), coupling constants (*J*) in Hz assignment. MS data were measured using 3-nitrobenzyl alcohol as a matrix on JEOL JMS-700 (FAB). Electrospray ionization-mass spectrometer (ESI-MS) spectra were recorded on a JEOL JMS-T100LC instrument and are reported as the mass-to-charge ratio (*m*/*z*). The melting points were measured using an AS ONE ATM-02 apparatus.

7-Chloro-4-phenylquinazoline (**1**)

A mixture of 4,7-dichloroquinazoline (1.68 g, 8.4 mmol), phenylboronic acid (1.09 g, 9.0 mmol), potassium carbonate (3.06 g, 22.1 mol) and 3 mol% of tetrakis(triphenylphosphine)palladium(0) (0.416 g, 0.36 mmol) in toluene (20 mL) was refluxed for 8 h, and poured into ice water. Then, the reaction mixture was extracted with CH_2Cl_2, washed with brine, and dried over Na_2SO_4. The residue was filtered, evaporated, and purified by silica gel column chromatography (*n*-hexane: EtOAc = 3:1) to afford compound **1** as a white solid (1.30 g, 64%); mp 113-114 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.36 (s, 1H), 8.11 (d, *J* = 2.0 Hz, 1H), 8.08 (d, *J* = 9.2 Hz, 1H), 7.77-7.74 (m, 2H), 7.60-7.54 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.4, 155.6, 151.7, 140.0, 136.7, 130.3, 129.9, 128.8, 128.7, 128.6, 127.9, 121.5; HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{14}H_{10}ClN_2$ + H: 241.0533; found: 241.0520.

7-Fluoro-4-phenylquinazoline (**2a**)

A mixture of 4-chloro-7-fluoroquinazoline (1.45 g, 7.94 mmol), phenylboronic acid (1.16 g, 9.50 mmol), potassium carbonate (2.77 g, 20.0 mol) and 3 mol% of tetrakis(triphenylphosphine)palladium(0) (0.268 g, 0.23 mmol) in toluene (20 mL) was refluxed for 8 h, and poured into ice water. Then, the reaction mixture was extracted with CH_2Cl_2, washed with brine, and dried over Na_2SO_4. The residue was filtered, evaporated, and purified by silica gel column chromatography (*n*-hexane: EtOAc = 3:1) to afford a compound **2a** as a white solid (1.14 g, 64%); mp 96-97 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.35 (s, 1H), 8.16 (dd, *J* = 9.2, 6.0 Hz, 1H), 7.78-7.71 (m, 3H), 7.63-7.53 (m, 3H), 7.58 (t, *J* = 3.2 Hz, 3H), 7.41-7.35 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 168.2, 165.4 (d, *J* = 256.5 Hz), 155.6, 152.8 (d, *J* = 13.7 Hz), 136.8, 130.2, 130.0 (d, *J* = 10.1 Hz), 129.8, 128.7, 120.4, 118.2 (d, *J* = 25.3 Hz), 112.6 (d, *J* = 20.2 Hz); HRMS (FAB): *m*/*z* $[M + H]^+$ calcd for $C_{14}H_{10}FN_2$: 225.0828; found: 225.0845.

5-Fluoro-4-phenylquinazoline (**2b**)

A mixture of 4-chloro-5-fluoroquinazoline (0.688 g, 3.76 mmol), phenylboronic acid (0.551 g, 4.52 mmol), potassium carbonate (1.30 g, 9.62 mol) and 3 mol% of tetrakis(triphenylphosphine)palladium(0)

(0.131 g, 0.113 mmol) in toluene (6 mL) was refluxed for 3 h, and poured into ice water. Then, the reaction mixture was extracted with CH_2Cl_2, washed with brine, and dried over Na_2SO_4. The residue was filtered, evaporated, and purified by silica gel column chromatography (*n*-hexane: EtOAc = 3:1) to afford compound **2b** as a yellow solid (0.680 g, 81%); mp 87-88 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.35 (s, 1H), 7.94 (d, *J* = 4.4 Hz, 1H), 7.84 (td, *J* = 8.1, 5.4 Hz, 1H), 7.66-7.63 (m, 2H), 7.53-7.46 (m, 3H), 7.24 (ddd, *J* = 10.9, 7.7, 1.0 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 166.1 (d, *J* = 4.3 Hz), 157.5 (d, *J* = 261.5 Hz), 154.6 (d, *J* = 1.4 Hz), 152.2, 139.6 (d, *J* = 3.6 Hz), 133.9 (d, *J* = 10.1 Hz), 129.7, 129.0 (d, *J* = 3.6 Hz), 127.9, 125.2 (d, *J* = 4.3 Hz), 114.2 (d, *J* = 12.3 Hz), 113.0 (d, *J* = 21.7 Hz); HRMS (FAB): *m*/*z* $[M + H]^+$ calcd for $C_{14}H_{10}FN_2$: 225.0828; found: 225.0817.

6-Fluoro-4-phenylquinazoline (**2c**)

A mixture of 4-chloro-6-fluoroquinazoline (0.725 g, 3.93 mmol), phenylboronic acid (0.581 g, 4.77 mmol), potassium carbonate (1.41 g, 10.2 mol) and 3 mol% of tetrakis(triphenylphosphine)palladium(0) (0.137 g, 0.119 mmol) in toluene (15 mL) was refluxed for 3 h, and poured into ice water. Then, the reaction mixture was extracted with CH_2Cl_2, washed with brine, and dried over Na_2SO_4. The residue was filtered, evaporated, and purified by silica gel column chromatography (*n*-hexane: EtOAc = 3:1) to afford compound **2c** as a colorless solid (0.838 g, 94%); mp 81-82 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.36 (s, 1H), 7.84 (dd, *J* = 9.2, 5.5 Hz, 1H), 7.80-7.66 (m, 4H), 7.61-7.57 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.8 (d, *J* = 5.8 Hz), 160.6 (d, *J* = 250.7 Hz), 154.1 (d, *J* = 2.9 Hz), 148.2, 136.6, 131.6 (d, *J* = 8.7 Hz), 130.2, 129.6, 128.8, 124.0 (d, *J* = 23.0 Hz), 123.6 (d, *J* = 8.7 Hz), 110.3 (d, *J* = 23.1 Hz); HRMS (FAB): *m*/*z* $[M + H]^+$ calcd for $C_{14}H_{10}FN_2$: 225.0828; found: 225.0845.

8-Fluoro-4-phenylquinazoline (**2d**)

A mixture of 4-chloro-8-fluoroquinazoline (0.628 g, 3.44 mmol), phenylboronic acid (0.506 g, 4.14 mmol), potassium carbonate (1.20 g, 8.68 mol) and 3 mol% of tetrakis(triphenylphosphine)palladium(0) (0.113 g, 0.0978 mmol) in toluene (15 mL) was refluxed for 3 h, and poured into ice water. Then, the reaction mixture was extracted with CH_2Cl_2, washed with brine, and dried over Na_2SO_4. The residue was filtered, evaporated, and purified by silica gel column chromatography (*n*-hexane: EtOAc = 3:1) to afford compound **2d** as a white solid (0.747 g, 97%); mp 75-76 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.41 (s, 1H), 7.92 (d, *J* = 7.3 Hz, 1H), 7.77-7.76 (m, 2H), 7.59-7.54 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.0 (d, *J* = 2.9 Hz), 157.1(d, *J* = 258.7 Hz), 154.4 (d, *J* = 1.4 Hz), 141.3 (d, *J* = 13.0 Hz), 136.5, 130.1, 129.7, 128.4, 127.1 (d, *J* = 7.2 Hz), 124.1(d, *J* = 2.2 Hz), 122.6 (d, *J* = 5.1 Hz), 117.3 (d, *J* = 18.8 Hz); HRMS (FAB): *m*/*z* $[M + H]^+$ calcd for $C_{14}H_{10}FN_2$: 225.0828; found: 225.0825.

7-Fluoro-4-(4-methoxyphenyl)quinazoline (**25**)

A mixture of 4-chloro-7-fluoroquinazoline (0.225 g, 1.23 mmol), 4-methoxyphenylboronic acid (0.229 g, 1.51 mmol), potassium carbonate (0.452 g, 3.27 mol) and 3 mol% of tetrakis(triphenylphosphine)palladium(0) (43.8 mg, 0.0391 mmol) in toluene (5 mL) was refluxed for 3 h, and poured into ice water. Then, the reaction mixture was extracted with CH_2Cl_2, washed with brine, and dried over Na_2SO_4. The residue was filtered, evaporated, and purified by silica gel column chromatography (*n*-hexane: EtOAc = 3:1) to afford compound **25** as a yellow solid (0.307 g, 98%); mp 122-123 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.31 (s, 1H), 8.21 (dd, *J* = 9.5, 6.5 Hz, 1H), 7.76 (dd, *J* = 6.5, 2.1 Hz, 2H), 7.70 (dd, *J* = 9.5, 2.1 Hz, 1H), 7.42-7.33 (m, 1H), 7.10 (dd, *J* = 6.5, 2.1 Hz, 2H), 3.92 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.6, 165.2 (d, *J* = 256.5 Hz), 161.4, 155.6, 152.9 (d, *J* = 13.8 Hz), 131.6, 130.1 (d, *J* = 10.1 Hz), 129.2, 120.3, 118.0 (d, *J* = 25.3 Hz), 114.2, 112.6 (d, *J* = 20.2 Hz), 55.4; HRMS (FAB): *m*/*z* $[M + H]^+$ calcd for $C_{15}H_{12}FN_2O$: 254.0855; found: 254.0830.

7-Fluoro-4-(4-(trifluoromethyl)phenyl)quinazoline (**26**)

A mixture of 4-chloro-7-fluoroquinazoline (0.198 g, 1.08 mmol), 4-(trifluoromethyl)phenylboronic acid (0.2521 g, 1.33 mmol), potassium carbonate (0.369 g, 2.67 mol) and 3 mol% of tetrakis(triphenylphosphine)palladium(0) (39.1 mg, 0.0338 mmol) in toluene (5 mL) was refluxed for 3 h, and poured into ice water. Then, the reaction mixture was extracted with CH_2Cl_2, washed with brine, and dried over Na_2SO_4. The residue was filtered, evaporated, and purified by silica gel column chromatography (*n*-hexane: EtOAc = 3:1) to afford compound **26** as a yellow solid (0.275 g, 87%); mp 97-98 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.39 (s, 1H), 8.09 (dd, *J* = 9.3, 5.8 Hz, 1H), 7.91-7.84 (m, 4H), 7.77 (dd, *J* = 9.3, 2.4 Hz, 1H), 7.46-7.39 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.2, 165.3 (d, *J* = 213.1 Hz), 155.5, 153.0 (d, *J* = 13.7 Hz), 140.2, 132.2 (d, *J* = 33.2 Hz), 130.2, 129.4 (d, *J* = 10.1 Hz), 125.7 (d, *J* = 4.3 Hz), 123.8 (q, *J* = 273.1 Hz), 120.2, 118.8 (d, *J* = 25.3 Hz), 112.9 (d, *J* = 21.0 Hz); HRMS (FAB): *m*/*z* $[M + H]^+$ calcd for $C_{15}H_{10}F_4N_2$: 293.0702; found: 293.0739.

7-Fluoro-4-(4-cyanophenyl)quinazoline (**27**)

A mixture of 4-chloro-7-fluoroquinazoline (0.512 g, 2.80 mmol), 4-cyanophenylboronic acid (0.455 g, 3.10 mmol), potassium carbonate (1.00 g, 7.25 mol) and 3 mol% of tetrakis(triphenylphosphine)palladium(0) (0.113 g, 0.0978 mmol) in toluene (15 mL) was refluxed for 24 h, and poured into ice water. Then, the reaction mixture was extracted with EtOAc, washed with brine, and dried over Na_2SO_4. The residue was filtered, evaporated, and purified by silica gel column chromatography (*n*-hexane: EtOAc = 3:1) to afford compound **27** as a yellow solid (0.145 g, 21%); mp 192-193 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.39 (s, 1H), 8.07-8.02 (dd, 1H), 7.89 (m, 4H), 7.81-7.76 (dd,

1H), 7.47-7.41 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.0 (d, J = 259.1 Hz), 165.6, 155.5, 153.0 (d, J = 14.4 Hz), 141.1, 132.5, 130.6, 129.0 (d, J = 10.8 Hz), 120.0, 119.1 (d, J = 25.2 Hz), 118.1, 114.1, 113.1(d, J = 20.4 Hz); HRMS (FAB): m/z $[M + H]^+$ calcd for $C_{15}H_9FN_3$: 250.0781; found: 250.0769.

4-(Biphenyl-4-yl)-7-fluoroquinazoline (**28**)

A mixture of 4-chloro-7-fluoroquinazoline (0.516 g, 2.83 mmol), 4-biphenylboronic acid (0.621 g, 3.13 mmol), potassium carbonate (1.018 g, 7.37 mol) and 3 mol% of tetrakis(triphenylphosphine)palladium(0) (0.114 g, 0.0986 mmol) in toluene (15 mL) was refluxed for 7 h, and poured into ice water. Then, the reaction mixture was extracted with EtOAc, washed with brine, and dried over Na_2SO_4. The residue was filtered, evaporated, and purified by silica gel column chromatography (*n*-hexane: EtOAc = 3:1) to afford compound **28** as a white solid (0.714 g, 84%); mp 152-153 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.37 (s, 1H), 8.26 (dd, J = 9.2, 6.3 Hz, 1H), 7.81-7.87 (m, 4H), 7.75 (dd, J = 9.5, 2.6 Hz, 1H), 7.68-7.70 (m, 2H), 7.51 (t, J = 7.7 Hz, 2H), 7.41-7.44 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.8, 165.4 (d, J = 256.7 Hz), 155.6, 152.9 (d, J = 14.4 Hz), 143.2, 140.1, 135.7, 130.4, 130.0 (d, J = 10.8 Hz), 129.0, 128.0, 127.4, 127.2, 120.4, 118.3 (d, J = 25.2 Hz), 112.7 (d, J = 19.2 Hz); HRMS (FAB): m/z $[M + H]^+$ calcd for $C_{20}H_{14}FN_3$: 301.1141; found: 301.1118.

7-Fluoro-4-methoxyquinazoline (**29**)

A mixture of 4-chloro-7-fluoroquinazoline (0.651 g, 3.57 mmol) and sodium methoxide (0.289 g, 5.35 mmol) in MeOH (10 mL) mixture was heated at reflux for 2 h. The reaction mixture was then cooled to room temperature, and the solvent was removed in vacuo. The orange residue was purified by silica column chromatography (CH_2Cl_2) to afford compound **29** as a white solid (0.634 g, 71%); mp 84-85 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.72 (s, 1H), 8.08-8.03 (m, 1H), 7.47 (dt, J = 9.7, 1.2 Hz, 1H), 7.24-7.18 (m, 1H), 4.11 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.1, 165.2 (d, J = 217.5 Hz), 155.4, 152.5 (d, J = 13.7 Hz), 126.0 (d, J = 10.1 Hz), 116.7 (d, J = 24.6 Hz), 113.3, 111.8 (d, J = 21.0 Hz), 54.2; HRMS (FAB): m/z $[M + H]^+$ calcd for $C_9H_8FN_2O$: 179.0621; found: 179.0646.

General Procedure for the Synthesis of Ketones (Table 1)

Under an atmosphere of argon, base (1.6 mmol) was added to the mixture of 7-chloro-4-phenylquinazoline (0.242 g, 1.0 mmol) or 7-fluoro-4-phenylquinazoline (0.224 g, 1.0 mmol), imidazolium iodide (0.05-0.20 mmol) and *p*-anisaldehyde (0.14 mL, 1.1 mmol) in solvent (10 mL). The mixture was stirred for 4-7 h at room temperature or reflux tempureture. The reaction mixture was poured into ice water, extracted with EtOAc, washed with brine, and dried over Na_2SO_4. The residue was filtered, evaporated, purified by silica gel column chromatography (*n*-hexane: EtOAc = 3:1) to afford (4-methoxyphenyl)(4-phenylquinazolin-7-yl)methanone (**9**).

(4-Methoxyphenyl)(4-phenylquinazolin-7-yl)methanone (**9**); Table 1, Entry 2

White solid (0.271 g, 88%); mp 176-177 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.45 (s, 1H), 8.39 (d, *J* = 1.7 Hz, 2H), 8.26 (d, *J* = 8.6 Hz, 1H), 7.98 (dd, *J* = 8.6, 1.7 Hz, 1H), 7.92 (dd, *J* = 6.9, 2.1 Hz, 2H), 7.83-7.82 (m, 2H), 7.62-7.59 (m, 3H), 7.00 (dt, *J* = 9.4, 2.1 Hz, 2H), 3.91 (s 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 194.1, 168.5, 163.8, 155.4, 150.6, 142.6, 136.7, 132.8, 130.5, 130.4, 130.0, 129.1, 128.8, 127.6, 127.5, 124.3, 113.9, 55.6; HRMS (FAB): *m*/*z* $[M + H]^+$ calcd for $C_{22}H_{17}N_2O_2$: 341.1290; found: 341.1293.

General Procedure for the Synthesis of Ketones and Ethers (Table 2)

Under an atmosphere of argon, sodium hydride (67.7 mg, 1.6 mmol) was added to the mixture of quinazoline compound (1.0 mmol), 1,3-dimethylimidazolium iodide (21.8 mg, 0.10 mmol) and *p*-anisaldehyde or benzaldehyde (1.1 mmol) in DMF (10 mL). The mixture was stirred for 4-24 h at room temperature. The reaction mixture was poured into ice water, extracted with EtOAc, washed with brine, and dried over Na_2SO_4. The residue was filtered, evaporated, purified by silica gel column chromatography (*n*-hexane: EtOAc = 3:1) to afford products.

Reaction of 5-fluoro-4-phenylquinazoline 2b with *p*-anisaldehyde 3

(4-Methoxyphenyl)(4-phenylquinazolin-5-yl)methanone (**11**)

Yellow solid (92.7 mg, 27%); mp 129-130 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.38 (s, 1H), 8.27 (d, *J* = 8.6 Hz, 1H), 7.99 (t, *J* = 7.7 Hz, 1H), 7.76 (d, *J* = 6.9 Hz, 1H), 7.29-7.27 (m, 2H), 7.20-7.01 (5H), 6.68 (d, *J* = 9.2 Hz, 2H), 3.83 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 193.8, 168.3, 163.4, 154.4, 151.6, 139.3, 138.9, 132.8, 131.3, 131.1, 130.6, 129.9, 129.7, 129.3, 128.2, 121.6, 113.4, 55.5; HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{22}H_{17}N_2O_2Na$: 363.1109; found: 363.1097.

5-(4-Methoxybenzyloxy)-4-phenylquinazoline (**18**)

Colorless solid (51.3 mg, 15%); mp 137-138 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.28 (s, 1H), 7.83-7.80 (m, 1H), 7.71 (d, *J* = 8.6 Hz, 1H), 7.49-7.47 (m, 2H), 7.30-7.28 (m, 3H), 7.02 (d, *J* = 8.0 Hz, 1H), 6.78-6.71 (m, 4H), 4.87 (s, 2H), 3.80 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.5, 159.1, 155.4, 154.0, 152.7, 141.7, 134.2, 128.5, 128.4, 128.4, 127.4, 121.0, 115.8, 113.6, 108.1, 70.4, 55.2; HRMS (FAB): *m*/*z* $[M + H]^+$ calcd for $C_{22}H_{19}N_2O_2$: 343.1447; found: 347.1442.

Reaction of 6-fluoro-4-phenylquinazoline 2c with *p*-anisaldehyde 3

6-(4-Methoxybenzyloxy)-4-phenylquinazoline (**19**)

Colorless solid (73.2 mg, 21%); mp 119-120 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.26 (s, 1H), 8.03 (d, *J* = 9.2 Hz, 1H), 7.72-7.70 (m, 2H), 7.63 (dt, *J* = 9.2, 1.4 Hz, 1H), 7.57 (dd, *J* = 4.6, 1.1 Hz, 3H), 7.42 (d, *J* = 2.9 Hz, 1H), 7.33 (d, *J* = 8.6 Hz, 2H), 6.92 (d, *J* = 8.0 Hz, 2H), 5.03 (s, 2H), 3.83 (s, 3H); ^{13}C NMR (125

MHz, $CDCl_3$) δ 166.6, 159.7, 157.3, 152.9, 147.3, 137.4, 130.4, 129.8, 129.6, 129.3, 128.7, 128.0, 127.0, 124.0, 114.1, 105.7, 70.1, 55.3; HRMS (FAB): *m*/*z* $[M + H]^+$ calcd for $C_{22}H_{19}N_2O_2$: 343.1447; found: 347.1436.

Reaction of 8-fluoro-4-phenylquinazoline 2d with *p*-anisaldehyde 3

(4-Methoxyphenyl)(4-phenylquinazolin-8-yl)methanone (13)

Colorless solid (30.6 mg, 9%); mp 147-148 °C; ^1H NMR (500 MHz, $CDCl_3$) δ 9.32 (s, 1H), 8.27 (d, *J* = 8.3 Hz, 1H), 7.93 (d, *J* = 7.7 Hz, 1H), 7.87-7.80 (m, 4H), 7.69 (t, *J* = 7.7 Hz, 1H), 7.61 (t, *J* = 2.6 Hz, 3H), 6.94 (t, *J* = 8.3 Hz, 2H), 3.88 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 195.1, 168.6, 164.0, 154.9, 149.0, 139.4, 137.0, 132.6, 132.2, 130.6, 130.3, 130.0, 128.8, 128.7, 127.0, 123.0, 113.8, 55.5; HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{22}H_{17}N_2O_2Na$: 363.1109; found: 363.1133.

8-(4-Methoxybenzyloxy)-4-phenylquinazoline (20)

Yellow solid (53.1 mg, 16%); mp 119-120 °C; ^1H NMR (500 MHz, $CDCl_3$) δ 9.26 (s, 1H), 8.03 (d, *J* = 9.7 Hz, 1H), 7.70 (dd, *J* = 7.4, 2.3 Hz, 2H), 7.63 (dd, *J* = 9.2, 2.9 Hz, 1H), 7.57-7.56 (m, 3H), 7.42 (d, *J* = 2.3 Hz, 1H), 7.33 (d, *J* = 8.6 Hz, 2H), 6.93-6.91 (m, 2H), 5.03 (s, 2H), 3.82 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.6, 159.6, 157.3, 152.9, 147.3, 137.4, 130.4, 129.8, 129.6, 129.3, 128.7, 127.9, 127.0, 123.9, 114.1, 105.7, 70.1, 55.3; HRMS (FAB): *m*/*z* $[M + H]^+$ calcd for $C_{22}H_{19}N_2O_2$: 343.1447; found: 347.1451.

Reaction of 5-fluoro-4-phenylquinazoline 2b with benzaldehyde 10

Phenyl(4-phenylquinazolin-5-yl)methanone (14)

Brown solid (41.0 mg, 13%); mp 112-113 °C; ^1H NMR (500 MHz, $CDCl_3$) δ 9.38 (s, 1H), 8.29 (dd, *J* = 8.3, 1.1 Hz, 1H), 8.01 (dd, *J* = 8.3, 7.2 Hz, 1H), 7.80 (dd, *J* = 7.4, 1.1 Hz, 1H), 7.44-7.41 (m, 1H), 7.30 (tt, *J* = 7.4, 1.4 Hz, 1H), 7.20-7.17 (m, 4H), 7.14-7.09 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 195.2, 168.2, 154.5, 151.6, 139.3, 138.6, 137.3, 132.92, 132.90, 131.8, 130.2, 129.5, 128.7, 128.4, 128.1, 121.6; HRMS (FAB): *m*/*z* $[M + H]^+$ calcd for $C_{21}H_{15}N_2O$: 311.1184; found: 311.1220.

5-(Benzyloxy)-4-phenylquinazoline (21)

Yellow solid (26.6 mg, 9%); mp 69-70 °C; ^1H NMR (500 MHz, $CDCl_3$) δ 9.30 (d, *J* = 6.3 Hz, 1H), 7.83 (t, *J* = 8.3 Hz, 1H), 7.73 (d, *J* = 8.0 Hz, 1H), 7.50 (dd, *J* = 7.4, 1.7 Hz, 2H), 7.31-7.29 (m, 3H), 7.21 (td, *J* = 13.6, 6.3 Hz, 3H), 7.03 (d, *J* = 8.0 Hz, 1H), 6.82 (d, *J* = 8.0 Hz, 2H), 4.95 (s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.5, 155.3, 154.0, 152.7, 141.7, 135.3, 134.2, 128.6, 128.4, 128.2, 127.6, 127.5, 126.8, 121.1, 115.8, 108.1, 70.6; HRMS (FAB): *m*/*z* $[M + H]^+$ calcd for $C_{21}H_{17}N_2O$: 312.1263; found: 312.1280.

Reaction of 7-fluoro-4-phenylquinazoline 2a with benzaldehyde 10

Phenyl(4-phenylquinazolin-7-yl)methanone (16)

White solid (0.239 g, 74%); mp 141-142 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.46 (s, 1H), 8.44 (d, *J* = 1.4 Hz, 1H), 8.28 (d, *J* = 8.6 Hz, 1H), 8.05 (dd, *J* = 8.6, 1.4 Hz, 1H), 7.92-7.81 (m, 4H), 7.69-7.51 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 195.5, 168.6, 155.5, 150.6, 141.7, 136.6, 136.5, 133.2, 131.3, 130.4, 130.2, 130.0, 128.8, 128.57, 127.7, 127.4, 124.6; HRMS (FAB): *m*/*z* $[M + H]^+$ calcd for $C_{21}H_{15}N_2O$: 311.1184; found: 311.1189.

General Procedure for the Synthesis of Ketones (Table 3)

Under an atmosphere of argon, sodium hydride (71.3 mg, 1.6 mmol) was added to the mixture of quinazoline compound (1.0 mmol), 1,3-dimethylimidazolium iodide (22.2 mg, 0.10 mmol) and aldehyde (1.1 mmol) in DMF (10 mL). The mixture was stirred for 4 to 20 h at room temperature. The reaction mixture was poured into ice water, extracted with EtOAc, washed with brine, and dried over Na_2SO_4. The residue was filtered, evaporated, purified by silica gel column chromatography (*n*-hexane: EtOAc = 3:1) to afford desired product.

(7-Fluoroquinazolin-4-yl)(phenyl)methanone (30)

Yellow solid (0.603 g, 86%); mp 83-84 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.50 (s, 1H), 7.97-7.95 (m, 2H), 7.89 (d, *J* = 8.0 Hz, 1H), 7.70-7.63 (m, 3H), 7.54-7.51 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 192.4, 163.9, 157.3 (d, *J* = 261.5 Hz), 153.9, 141.8 (d, *J* = 13.2 Hz), 134.9, 134.7, 130.6, 128.8, 128.6 (d, *J* = 7.2 Hz), 123.2, 121.6 (d, *J* = 4.8 Hz), 118.5 (d, *J* = 18.0 Hz); HRMS (FAB): *m*/*z* $[M + H]^+$ calcd for $C_{15}H_{11}FN_2O$: 253.0777; found: 253.0762.

(4-Fluorophenyl)(4-phenylquinazolin-7-yl)methanone (31)

White solid (40%, 0.133 g); mp 148-149 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.47 (s, 1H), 8.41 (d, *J* = 1.7 Hz, 1H), 8.29 (d, *J* = 8.6 Hz, 1H), 8.03-7.94 (m, 3H), 7.84-7.82 (m, 2H), 7.64-7.62 (m, 3H), 7.22 (t, *J* = 8.6 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 194.0, 167.7 (d, *J* = 218.3 Hz), 155.6, 150.6, 141.6, 136.6, 133.0, 132.9, 131.1, 130.5, 130.0, 128.8, 127.9, 127.3, 124.6, 116.0, 115.8; HRMS (FAB): *m*/*z* $[M + H]^+$ calcd for $C_{21}H_{14}FN_2O$: 329.1078; found: 329.1084.

(4-Chlorophenyl)(4-phenylquinazolin-7-yl)methanone (32)

White solid (0.124 g, 36%); mp 178-179 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.47 (s, 1H), 8.40 (s, 1H), 8.29 (d, *J* = 8.6 Hz, 1H), 8.03 (s, 1H), 7.87 (d, *J* = 6.3 Hz, 2H), 7.84-7.82 (m, 2H), 7.63 (t, *J* = 3.2 Hz, 3H), 7.52 (d, *J* = 8.6 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 194.4, 168.7, 155.6, 150.6, 141.4, 139.9, 134.8,

134.0, 131.6, 131.2, 130.5, 130.0, 129.0, 128.8, 127.9, 127.3, 124.7; HRMS (FAB): *m*/*z* $[M + H]^+$ calcd for $C_{21}H_{14}ClN_2O$: 345.0795; found: 345.0810.

(4-Phenylquinazolin-7-yl)(thiophen-2-yl)methanone (33)

White solid (0.254 g, 73%); mp 135-136 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.47 (s, 1H), 8.58 (d, *J* = 1.4 Hz, 1H), 8.29 (d, *J* = 8.6 Hz, 1H), 8.03 (dd, *J* = 8.6, 1.4 Hz, 1H), 7.85-7.76 (m, 4H), 7.64-7.59 (m, 3H), 7.22 (dd, *J* = 4.8, 4.1 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 186.9, 168.6, 155.5, 150.6, 142.8, 142.2, 136.6, 135.6, 135.4, 130.4, 130.1, 130.0, 128.8, 128.3, 127.9, 127.0, 124.5; HRMS (FAB): *m*/*z* $[M + H]^+$ calcd for $C_{19}H_{13}N_2OS$: 317.0749; found: 317.0766.

Furan-2-yl(4-phenylquinazolin-7-yl)methanone (34)

Brown solid (0.103 g, 32%); mp 147-148 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.48 (s, 1H), 8.76 (s, 1H), 8.28 (d, *J* = 8.6 Hz, 1H), 8.12 (dd, *J* = 8.6, 1.7 Hz, 1H), 7.87-7.79 (m, 3H), 7.62 (dd, *J* = 3.7, 2.6 Hz, 3H), 7.41 (d, *J* = 3.4 Hz, 1H), 6.68 (q, *J* = 1.7 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 181.1, 168.7, 155.4, 152.0, 150.6, 147.9, 141.2, 136.5, 130.6, 130.5, 130.0, 128.8, 127.7, 127.1, 124.7, 121.6, 112.7; HRMS (FAB): *m*/*z* $[M + H]^+$ calcd for $C_{19}H_{13}N_2O_2$: 301.0977; found: 301.1003.

(4-Phenylquinazolin-7-yl)(pyridin-3-yl)methanone (35)

Yellow solid (0.110 g, 35%); mp 197-198 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.48 (s, 1H), 9.11 (s, 1H), 8.90 (d, *J* = 4.0 Hz, 1H), 8.45 (s, 1H), 8.32 (d, *J* = 8.6 Hz, 1H), 8.22 (d, *J* = 7.4 Hz, 1H), 8.07 (dd, *J* = 8.6, 1.7 Hz, 1H), 7.83 (q, *J* = 3.2 Hz, 2H), 7.63 (t, *J* = 3.2 Hz, 3H), 7.52 (q, *J* = 4.2 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 194.0, 168.8, 155.8, 153.6, 151.1, 150.6, 140.7, 137.3, 136.5, 132.3, 131.7, 130.6, 130.0, 128.9, 128.2, 127.0, 125.0, 123.6; HRMS (FAB): *m*/*z* $[M + H]^+$ calcd for $C_{20}H_{14}N_3O$: 312.1137; found: 312.1132.

Naphthalen-2-yl(4-phenylquinazolin-7-yl)methanone (36)

White solid (0.206 g, 56%); mp 177-178 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.48 (s, 1H), 8.51 (s, 1H), 8.36 (s, 1H), 8.32 (d, *J* = 8.6 Hz, 1H), 8.09 (d, *J* = 8.6 Hz, 1H), 8.04-7.99 (m, 2H), 7.94 (t, *J* = 8.6 Hz, 2H), 7.85 (dd, *J* = 6.3, 2.3 Hz, 2H), 7.66-7.58 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 195.6, 168.7, 155.6, 150.7, 142.2, 136.7, 135.6, 133.8, 132.6, 132.2, 131.2, 130.4, 130.0, 129.6, 128.8, 128.8, 127.9, 127.8, 127.6, 127.1, 125.4, 124.6; HRMS (FAB): *m*/*z* $[M + H]^+$ calcd for $C_{25}H_{17}N_2O$: 361.1341; found: 361.1316.

(3,4-Dimethoxyphenyl)(4-phenylquinazolin-7-yl)methanone (37)

Yellow solid (0.263 g, 71%); mp 147-148 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.46 (s, 1H), 8.41 (d, *J* = 1.4 Hz, 1H), 8.28 (d, *J* = 9.3 Hz, 1H), 7.98 (dd, *J* = 8.6, 1.7 Hz, 1H), 7.85-7.82 (m, 2H), 7.63-7.60 (m, 4H),

7.46 (dd, *J* = 8.6, 2.1 Hz, 1H), 6.92 (d, *J* = 8.6 Hz, 1H), 3.98 (d, *J* = 3.4 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 194.2, 168.5, 155.4, 153.7, 150.5, 149.3, 142.6, 136.6, 130.4, 130.4, 129.9, 129.2, 128.7, 127.6, 127.5, 126.1, 124.3, 111.7, 109.8, 56.1, 56.0; HRMS (FAB): *m*/*z* $[M + H]^+$ calcd for $C_{23}H_{19}N_2O_3$: 371.0555; found: 371.0585.

(4-Methoxyphenyl)(4-(4-methoxyphenyl)quinazolin-7-yl)methanone (38)

White solid (0.322 g, 87%); mp 189-190 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.40 (s, 1H), 8.37 (d, *J* = 1.7 Hz, 1H), 8.31 (d, *J* = 8.6 Hz, 1H), 7.98 (dd, *J* = 8.6, 1.7 Hz, 1H), 7.93 (dd, *J* = 6.9, 2.1 Hz, 2H), 7.83 (dd, *J* = 6.5, 2.1 Hz, 2H), 7.13 (dd, *J* = 6.5, 2.1 Hz, 2H), 7.00 (dd, *J* = 6.9, 2.1 Hz, 2H), 3.92 (d, *J* = 5.5 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 194.2, 167.9, 163.8, 161.5, 155.4, 150.6, 142.4, 132.8, 131.8, 130.5, 129.2, 129.1, 127.7, 127.3, 124.3, 114.2, 113.9, 55.6, 55.5; HRMS (FAB): *m*/*z* $[M + H]^+$ calcd for $C_{23}H_{19}N_2O_3$: 370.1317; found: 370.1334.

(4-Methoxyphenyl)(4-(4-(trifluoromethyl)phenyl)quinazolin-7-yl)methanone (39)

White solid (0.345 g, 83%); mp 147-148 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.48 (s, 1H), 8.43 (d, *J* = 1.4 Hz, 1H), 8.19 (d, *J* = 8.6 Hz, 1H), 8.03-7.87 (m, 7H), 7.01 (dd, *J* = 6.9, 2.1 Hz, 2H), 3.92 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 193.9, 167.0, 163.9, 155.4, 150.6, 142.9, 140.1, 132.8, 132.2 (d, *J* = 32.5 Hz), 130.6, 130.3, 129.0, 128.0, 126.9, 125.8 (d, *J* = 3.6 Hz), 124.0, 123.8 (q, *J* = 272.4 Hz), 113.9, 55.6; HRMS (FAB): *m*/*z* $[M + H]^+$ calcd for $C_{23}H_{16}F_3N_2O_2$: 409.1164; found: 409.1158.

4-(7-(4-Methoxybenzoyl)quinazolin-4-yl)benzonitrile (40)

Yellow solid (0.143 g, 90%); mp 216-217 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.51-9.48 (s, 1H), 8.45-8.43 (d, 1H), 8.16-8.13 (d, 1H), 8.04-8.01 (dd, 1H), 7.93 (m, 6H), 7.03-7.00 (m, 1H), 3.92 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 193.9, 166.4, 164.1, 155.4, 150.8, 143.2, 141.0, 132.9, 132.6, 130.8, 130.7, 129.0, 128.3, 126.7, 126.9, 118.2, 114.3, 114.0, 55.7; HRMS (FAB): *m*/*z* $[M + H]^+$ calcd for $C_{23}H_{16}N_3O_2$: 366.1243; found: 366.1247.

(4-(Biphenyl-4-yl)quinazolin-7-yl)(4-methoxyphenyl)methanone (41)

Colorless solid (0.373 g, 77%); mp 174-175 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.46 (s, 1H), 8.41 (s, 1H), 8.34 (d, *J* = 9.2 Hz, 1H), 8.01 (d, *J* = 8.6 Hz, 1H), 7.94-7.92 (m, 4H), 7.84 (d, *J* = 8.0 Hz, 2H), 7.70 (d, *J* = 8.6 Hz, 2H), 7.50 (t, *J* = 7.7 Hz, 2H), 7.43-7.40 (m, 1H), 7.01 (d, *J* = 8.6 Hz, 2H), 3.91 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$); δ 194.2, 168.2, 163.9, 155.5, 150.6, 143.3, 142.6, 140.1, 135.6, 132.8, 130.6, 130.6, 129.2, 129.0, 128.0, 127.6, 127.6, 127.5, 127.3, 124.4, 113.9, 55.6; HRMS (FAB): *m*/*z* $[M + H]^+$ calcd for $C_{28}H_{21}N_2O_2$: 417.1603; found 417.1585.

(4-Methoxyphenyl)(4-methoxyquinazolin-7-yl)methanone (**42**)

White solid (0.126 g, 42%); mp 163-164 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.83 (s, 1H), 8.24-8.18 (m, 2H), 7.91-7.83 (m, 3H), 6.94 (dd, *J* = 6.9, 2.1 Hz, 2H), 4.18 (s, 3H), 3.86 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 194.4, 167.0, 163.7, 155.2, 150.2, 142.6, 132.7, 129.3, 129.2, 127.0, 124.0, 118.1, 113.8, 55.5, 54.5; HRMS (FAB): *m*/*z* $[M + H]^+$ calcd for $C_{17}H_{15}N_2O_3$: 295.0643; found: 295.0681.

(4-Benzoylquinazolin-7-yl)(4-methoxyphenyl)methanone (**43**)

Yellow solid (0.145 g, 79%); mp 131-132 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.37 (s, 1H), 8.21 (dd, *J* = 8.6, 1.1 Hz, 1H), 8.00-7.97 (m, 3H), 7.83 (d, *J* = 8.6 Hz, 2H), 7.76 (t, *J* = 7.7 Hz, 1H), 7.68 (d, *J* = 7.4 Hz, 1H), 7.53 (t, *J* = 7.7 Hz, 2H), 6.94 (d, *J* = 9.2 Hz, 2H), 3.88 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$); δ 194.5, 192.7, 164.3, 164.2, 154.1, 149.1, 139.6, 135.0, 134.7, 133.1, 132.7, 130.7, 130.4, 128.8, 128.2, 127.4, 121.8, 113.9, 55.4; HRMS (FAB): *m*/*z* $[M + H]^+$ calcd for $C_{23}H_{17}N_2O_3$: 369.1239; found: 369.1240

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