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EXPEDIENT SYNTHESIS OF 3,4-DIHYDROQUINAZOLINES *VIA* TANDEM ADDITION—CONJUGATE ADDITION CYCLIZATION OF CARBODIIMIDES BEARING A MICHAEL ACCEPTOR†

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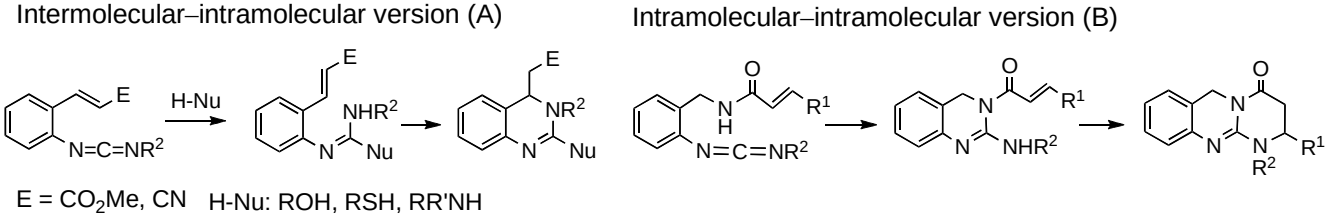
Abstract – Michael acceptor-possessing *N*-phenylcarbodiimides, which were prepared by an aza-Wittig reaction of the corresponding functionalized iminophosphoranes with aromatic and aliphatic isocyanates, reacted with enolate carbon-nucleophiles of active methylene compounds *via* the tandem cumulene addition—hetero (NH) Michael addition cyclization, to provide 2,3,4-trisubstituted 3,4-dihydroquinazolines. It was also found that 2-aminoquinolines and 2-amino-3,4-dihydroquinolines were competitively formed in some cases. Based on these observations, possible mechanistic pathways leading to these heterocycles are proposed.

INTRODUCTION

Quinazolines and quinazolinones are important classes of nitrogen-containing heterocycles, and their derivatives occur widely in natural products and synthetic drugs.[1] They are known to exhibit a diverse range of biological and pharmacological properties[2] such as central nervous system depressant and stimulant activities,[2] as well as antiparkinsonian,[2] anticancer,[3] antidiabetic,[4] antiinflammatory,[5] antimicrobial,[6] anticonvulsant,[7] antibacterial,[8] antimalarial,[9] antiallergy,[10] and analgesic properties.[11] Because quinazoline and quinazolinone derivatives display such biologically and pharmacologically rich properties, a number of synthetic methods to generate these compounds have been developed.[1,12,13] However, further advances in terms of new, efficient, and more general methods for the synthesis of these heterocyclic compounds are always desired.[13]

†This paper is dedicated to Professor Dr. Albert Padwa on the occasion of his 75th birthday.

The present method is based on our own, previously developed protocol involving a carbodiimide-mediated tandem nucleophilic addition—conjugate addition cyclization methodology (A)[14] and its intramolecular–intramolecular version (B)[15] involving the tandem reaction for the synthesis of 2,3,4-tri- or 2,3-disubstituted 3,4-dihydroquinazoline and 1,2,3,6-tetrahydro-*4H*-pyrimido[2,1-*b*]-quinazolin-4-one derivatives (Scheme 1). The first step of the reaction involves the addition of a hetero nucleophile such as an alcohol, thiol, or amine to one of the carbodiimide cumulene bonds, followed by an intramolecular hetero-conjugate addition by the newly formed NH moiety to form a dihydroquinazoline ring.[14] In the present study, we extended this tandem method to the reaction involving a carbon nucleophile, anticipating this to be a new route to synthesize 3,4-dihydroquinazolines having carbon substituents at the 2-, 3-, and 4-positions.[16] This is a valid investigation because of the important biological and pharmacological properties of these compounds.[1-11,16,17] Here we report our results on the above tandem methodology (A) involving the addition of a carbon nucleophile, particularly an enolate anion of an active methylene compound, to produce 3,4-dihydroquinazolines. We also observed the formation of quinoline compounds as alternative heterocyclic products in some cases. An entire pathway to produce these heterocycles will also be discussed.



Scheme 1

RESULTS AND DISCUSSION

In the previous work,[14,16,18] 3,4-dihydroquinazolines were synthesized essentially from three components, i.e., *ortho*-nitrocinnamic acid, isocyanate, and a nucleophile, *via* the key carbodiimide intermediates (*via* 1. reduction, 2. esterification, 3. azidation, 4. Staudinger reaction, 5. aza-Wittig reaction, and 6. nucleophilic addition).[14,18] In the present work, we took advantage of a more convergent synthesis of 2-R^3, 3-R^2, 4-R^1CH_2-trisubstituted 3,4-dihydroquinazolines from four components *via* the reactions indicated in Figure 1. The Heck coupling of 2-iodoaniline (**1**) with acrylonitrile (R^1 = CN) and methyl acrylate (R^1 = CO_2Me) afforded compounds **2** in good yields (Scheme 2, (a)). The Kirsanov reaction of **2** with triphenylphosphine yielded iminophosphoranes **3** quantitatively (Scheme 2, (b)). The aza-Wittig reaction of iminophosphoranes **3** with a variety of isocyanates **4** gave the functionalized carbodiimides **5** in good-to-excellent yields (Table 1).

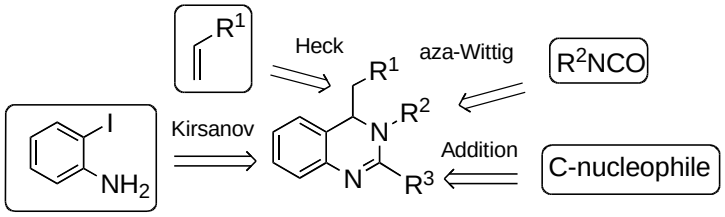
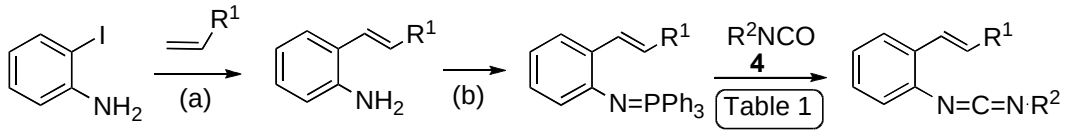


Figure 1. Convergent synthesis of 2,3,4-trisubstituted 3,4-dihydroquinazolines from four components



1

2A 70%
2B 94%

3A 94%
3B 92%

5

A: R^1 = CN **B**: R^1 = CO_2Me

(a) $Pd(OAc)_2$ (5 mol%), PPh_3 (10 mol%), Et_3N (1.4 equiv) / MeCN, 80 ¡C, 6–9 h

(b) PPh_3 (1.2 equiv), C_2Cl_6 (1.2 equiv), Et_3N (2.4 equiv) / CH_2Cl_2, rt, 1 h

Scheme 2. Preparation of functionalized carbodiimides 5 starting from 2-iodoaniline (**1**)

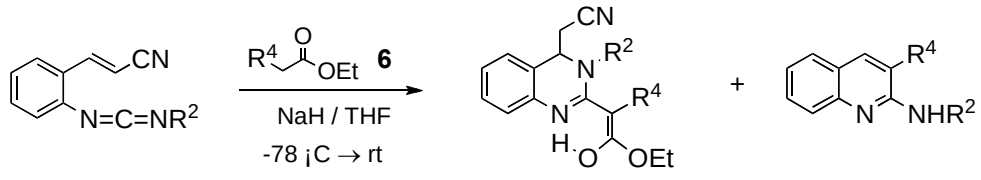
Table 1. Preparation of carbodiimides **5** *via* the aza-Wittig reaction of iminophosphoranes **3** with isocyanates **4**

R^1 = CN (**5A**)					R^1 = CO_2Me (**5B**)				
Run	**4**	R^2	Conditions	Yield (%) **5A**	Run	**4**	R^2	Conditions	Yield (%) **5B**
1	**4a**	Ph	CH_2Cl_2, rt, 2 h	**5Aa**/97	1	**4a**	Ph	CH_2Cl_2, rt, 1 h	**5Ba**/96
2	**4b**	*p*-Tol	CH_2Cl_2, rt, 2 h	**5Ab**/80	2	**4b**	*p*-Tol	CH_2Cl_2, rt, 1 h	**5Bb**/93
3	**4c**	*p*-$MeOC_6H_4$	CH_2Cl_2, rt, 7 h	**5Ac**/85	3	**4c**	*p*-$MeOC_6H_4$	CH_2Cl_2, rt, 4 h	**5Bc**/81
4	**4d**	Bn	CH_2Cl_2, rt, 5 h	**5Ad**/84	4	**4d**	Bn	CH_2Cl_2, rt, 8 h	**5Bd**/99
5	**4e**	^{n}Pr	$(CH_2Cl)_2$, 80 °C, 10 h	**5Ae**/90	5	**4e**	^{n}Pr	$(CH_2Cl)_2$, 80 °C, 5 h	**5Be**/92
6	**4f**	^{i}Pr	$(CH_2Cl)_2$, 70 °C, 9 h	**5Af**/91	6	**4f**	^{i}Pr	$(CH_2Cl)_2$, 70 °C, 8 h	**5Bf**/92
7	**4g**	^{c}Hex	Toluene, 110 °C, 5 h	**5Ag**/97	7	**4g**	^{c}Hex	$(CH_2Cl)_2$, 80 °C, 11 h	**5Bg**/99
8	**4h**	^{t}Bu	$(CH_2Cl)_2$, 80 °C, 11 h	**5Ah**/60	8	**4h**	^{t}Bu	$(CH_2Cl)_2$, 80 °C, 54 h	**5Bh**/86
					9	**4i**	Allyl	$(CH_2Cl)_2$, 80 °C, 6 h	**5Bi**/95

When carbodiimides **5Aa–e** bearing an acrylonitrile moiety (R^1 = CN) were allowed to react with enolate generated from diethyl malonate (**6a**), dihydroquinazolines **7a–e** were obtained as exclusive products, as expected (Table 2a). In contrast, in the reaction of **5Ah** (R^2 = ^{t}Bu) with **6a**, 2-(*t*-butylamino)quinoline-3-carboxylic ethyl ester (**8h**) was formed as the sole product instead of the expected product **7h**. The same tendency was observed in the reactions of **5Aa–h** with cyanoacetate (**6b**) (Table 2b). Namely, dihydroquinazolines **9a–g** were preferentially formed when the substituent R^2 was relatively less bulky, whereas the predominant formation of 2-(*t*-butylamino)quinoline-3-carbonitrile (**10h**) was observed in the reaction of **5Ah** involving the bulky ^{t}Bu group. The fact that formation of

dihydroquinazolines **7h**/**9h** was not observed can be ascribed to the steric hindrance caused by the bulky ^{t}Bu group on the nitrogen encountered in the aza-Michael addition cyclization step (Scheme 3). Unsurprisingly, all the dihydroquinazolines **7** and **9** obtained exist exclusively in the enol forms rather than the keto forms, which were indicated by spectroscopic data (IR, ^{1}H- and ^{13}C-NMR).[16a]

Table 2. Reaction of carbodiimides **5A** with malonate **6a**/cyanoacetate **6b** to give dihydroquinazolines **7**/**9** and quinolines **8**/**10**



5A

6a R^4 = CO_2Et **7** R^4 = CO_2Et **8** R^4 = CO_2Et

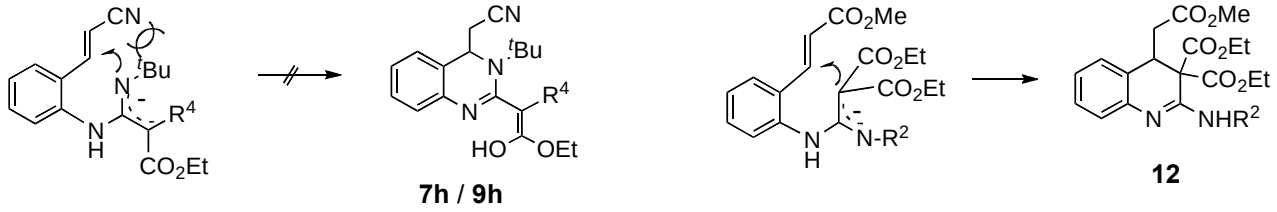
6b R^4 = CN **9** R^4 = CN **10** R^4 = CN

Table 2a. Reaction with **6a** (R^4 = CO_2Et)

Run	R^2	Time (h)	Product/Yield (%) **7**	**8**
1	Ph	4	**7a**/95	
2	*p*-Tol	3	**7b**/99	
3	*p*-$MeOC_6H_4$	4	**7c**/93	
4	Bn	3	**7d**/76	
5	^{n}Pr	1.5	**7e**/55	
6	^{t}Bu	25		**8h**/48

Table 2b. Reaction with **6b** (R^4 = CN)

Run	R^2	Time (h)	Product/Yield (%) **9**	**10**
1	Ph	6.5	**9a**/85	
2	*p*-Tol	4	**9b**/92	
3	*p*-MeO C_6H_4	3	**9c**/98	
4	Bn	3	**9d**/99	
5	^{n}Pr	6	**9e**/70	
6	^{i}Pr	2	**9f**/98	
7	^{c}Hex	7	**9g**/94	
8	^{t}Bu	24		**10h**/55

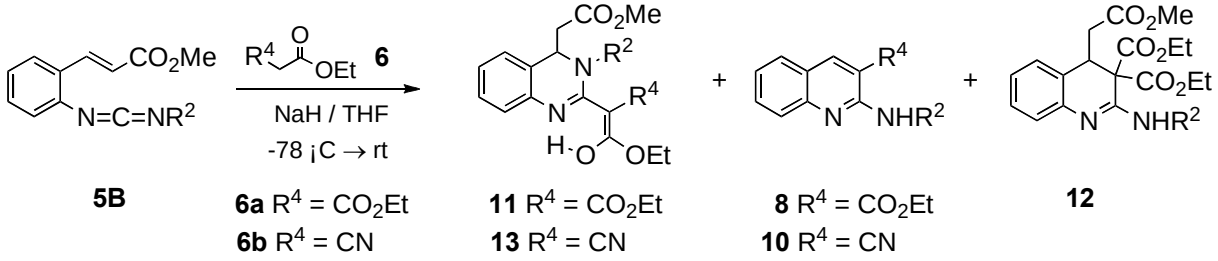


7h / 9h **12**

Scheme 3

In a similar way, the reaction of carbodiimides **5B** with cyanoacetate **6b** afforded dihydroquinazolines **13a**,**c**–**g**,**i** almost exclusively and the reaction of **5Bh** (R^2 = ^{t}Bu) with **6b** predominantly yielded quinoline-3-carbonitrile **10h** (Table 3b). In contrast, the reaction of carbodiimides **5B** with malonate **6a** showed similar but somewhat different product distributions (Table 3a). The reactions of entries **a**, **c**–**e** and **i** produced corresponding dihydroquinazolines **11a**,**c**–**e**,**i** and quinolines **8a**,**c**–**i**, while the formation of quinolines **8f**–**h** and dihydroquinolines **12f**–**h** in place of **11f**–**h** was observed when the substituent R^2 was relatively bulky (^{i}Pr, ^{c}Hex, or ^{t}Bu) (Scheme 3).

Table 3. Reaction of carbodiimides **5B** with malonate **6a**/cyanoacetate **6b** to give dihydroquinazolines **11**/**13** and quinolines **8**,**12**/**10**



5B **6a** R^4 = CO_2Et **6b** R^4 = CN **11** R^4 = CO_2Et **13** R^4 = CN **8** R^4 = CO_2Et **10** R^4 = CN **12**

Table 3a. Reaction with **6a** (R^4 = CO_2Et)

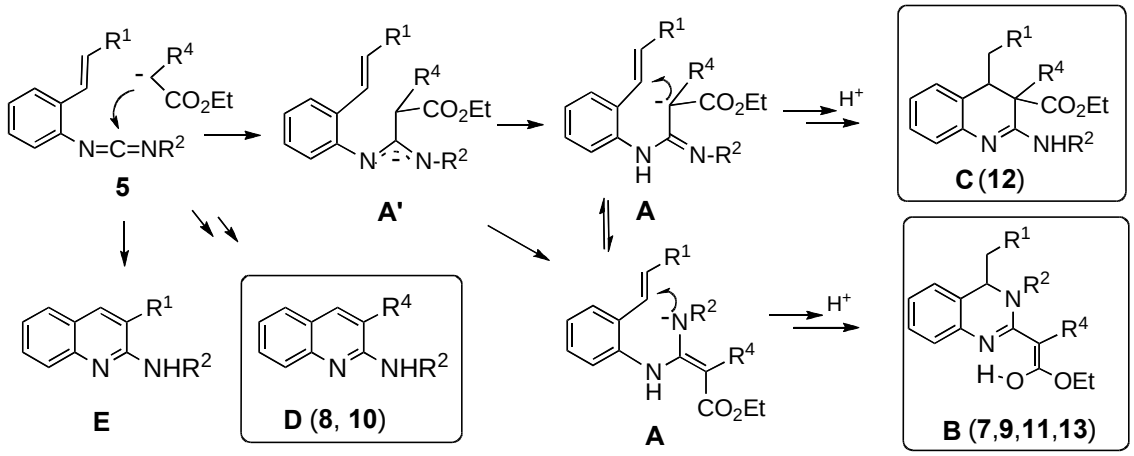
Run	R^2	Time (h)	Product/Yield (%) **11**	**8**	**12**
1	Ph	1	**11a**/51	**8a**/25	
2	*p*-$MeOC_6H_4$	2.5	**11c**/66	**8c**/27	
3	Bn	0.5	**11d**/57	**8d**/18	
4	^{n}Pr	1	**11e**/55	**8e**/4	
5	^{i}Pr	1		**8f**/18	**12f**/23
6	^{c}Hex	19		**8g**/63	**12g**/26
7	^{t}Bu	20		**8h**/44	**12h**/29
8	Allyl	5.5	**11i**/79	**8i**/13	

Table 3b. Reaction with **6b** (R^4 = CN)

Run	R^2	Time (h)	Product/Yield (%) **13**	**10**
1	Ph	2	**13a**/88	
2	*p*-$MeOC_6H_4$	0.5	**13c**/74	
3	Bn	6	**13d**/62	
4	^{n}Pr	17	**13e**/98	
5	^{i}Pr	48	**13f**/83	**10e**/5
6	^{c}Hex	17	**13g**/72	
7	^{t}Bu	24		**10h**/55
8	Allyl	0.5	**13i**/88	

MECHANISTIC CONSIDERATION

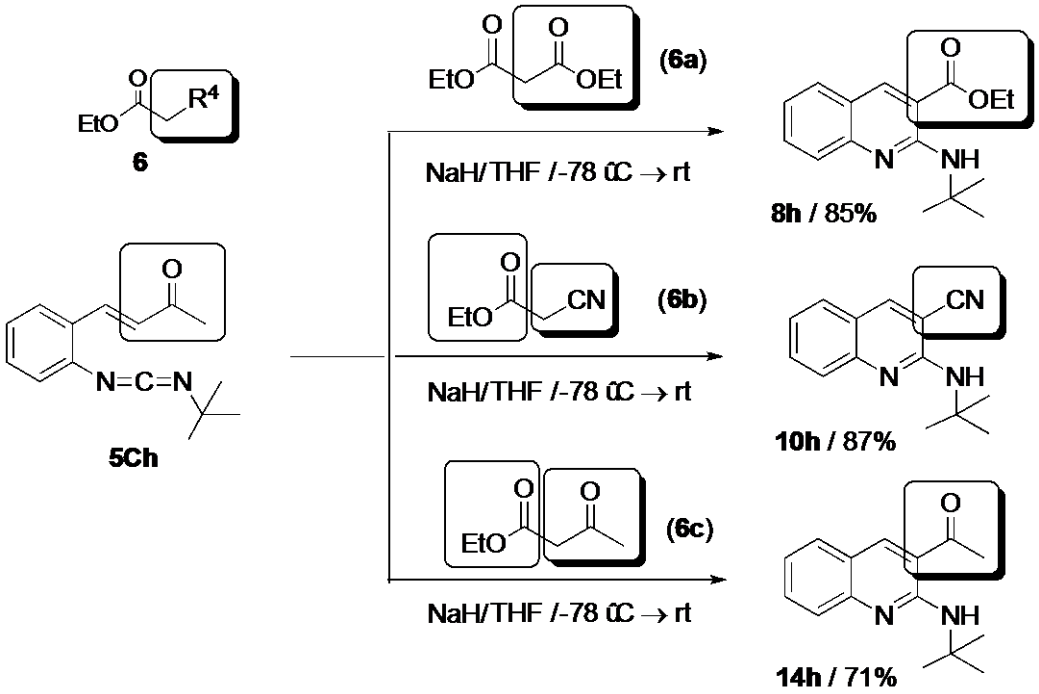
As shown in Scheme 4, the formation of dihydroquinazoline **B** and dihydroquinoline **C** can readily be understood. The enolate anion attacks the carbodiimide cumulene carbon of **5** to give the intermediate **A** *via* proton migration from **A'**, which undergoes N- and C-Michael addition to give, after tautomerization, dihydroquinazoline **B** and dihydroquinoline **C**, respectively. However, the formation of 2-aminoquinoline **D** is rather unusual. It is known that carbodiimide **5** readily undergoes 6π-electrocyclization on heating to give, after re-aromatization by proton shift, 2-aminoquinoline **E**[18] in which the R^1 group (CO_2Me or CN) undoubtedly originates from the carbodiimide **5**. In the present case, however, the obtained 2-aminoquinoline **D** possesses an R^4 group (CO_2Et or CN), which must have originated from the added



Scheme 4

nucleophile. This raises the question of how 2-aminoquinoline **D** was formed.

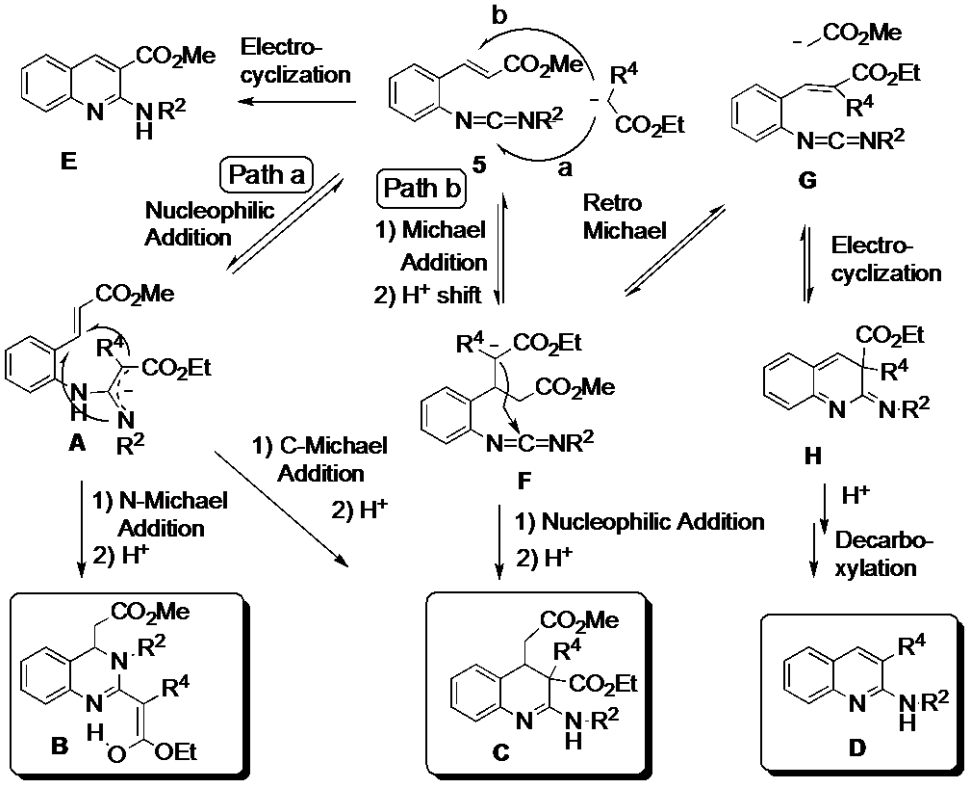
In the reaction between carbodiimide **5A** (R^1 = CN) and cyanoacetate (**6b**) (R^4 = CN), the quinolines **E** and **D** are the same (R^1 = R^4 = CN) and the electrocyclization route for the formation of **D** can not be excluded. To confirm that the R^4 group in **D** originates from the R^4 group in the nucleophile, we performed the reactions illustrated in Scheme 5, wherein we selected the carbodiimide **5Ch** (R^2 = ^{t}Bu) with an acetyl group in R^1 since predominant formation of **D** (**8**, **10**) was observed only when the R^2-substituent was a bulky group such as the ^{t}Bu group (see Tables 2 and 3). As a result, the reactions of **5Ch** with the enolate anions of **6a**, **6b**, and **6c** all produced the corresponding quinolines (**8h**, **10h**, **14h**) in good yields. This clearly shows that the ethyl acetate, acetonitrile, and acetone moieties (R^4C) in the quinolines originate from those in the enolates **6a–c** (R^4CH_2), respectively, with concurrent removal of the ethoxy carbonyl group from **6** and the acetonyl group (R^1C) from the substrate **5Ch**, as observed above. On the basis of these observations, we propose Scheme 6, which illustrates the entire pathway for the formation of these heterocycles.



Scheme 5

The reaction is initiated by nucleophilic attack at the two possible electrophilic centers, giving the intermediate **A** *via path a* or the intermediate **F** *via path b*. As described above in Scheme 4, the intramolecular N-Michael addition from **A** affords the dihydroquinazoline **B** (**7**, **9**, **11**, **13**). In contrast, the dihydroquinazoline **B** was scarcely formed when the substituent R^2 was a bulky ^{t}Bu group or even an ^{i}Pr or a ^{c}Hex group in the reaction of **5B** (R^1 = CO_2Me, bulkier than CN) with diethyl malonate (**6a**). This is consistent with the observation that cyclization by R^2N-attack on **A** to give dihydroquinazoline **B** is less

favored for steric reasons. Instead, in these cases only C-Michael addition/cyclization occurred to give the dihydroquinoline **C** (**12f**–**h**). The alternative pathway to produce the dihydroquinoline **C** from the intermediate **F** is also possible. The formation of the 2-aminoquinoline **D** (**8**, **10**, **14**) is proved by the existence of the intermediate **F** formed and *vice versa*. When the substituent R^2 is bulky and even R^4 is relatively bulky (CO_2Et), the intermediate **A** scarcely cyclizes to give **B** and **C**, and the equilibrated **F** in basic conditions undergoes retro-Michael reaction and electrocyclization to give **H** *via* **G**. Work-up of the reaction mixture predominantly furnishes the 2-aminoquinoline **D** after decarboxylation.



Scheme 6. Probable pathways for the formation of heterocycles

In conclusion, we have developed a functionalized carbodiimide-mediated tandem carbon-nucleophilic addition—conjugate addition cyclization methodology, for the synthesis of 3,4-dihydroquinazolines having carbon substituents at the 2-, 3-, and 4-positions. Furthermore, we have elucidated the mechanism by which these nitrogen heterocycles are formed.

EXPERIMENTAL

Preparation of methyl 2-aminocinnamate (2B) *via* the Mizoroki–Heck cross coupling: Triethylamine (4.4 mL, d 0.73, 32 mmol) and methyl acrylate (9.0 mL, d 0.96, 0.11 mol) were added to a mixture of 2-iodoaniline (4.99 g, 22.8 mmol), palladium acetate (256 mg, 1.14 mmol, 5 mol%), and triphenylphosphine (598 mg, 2.28 mmol) in acetonitrile (35 mL) at 0 °C with stirring. The reaction

mixture was heated at 80 °C for 9 h. After being cooled to room temperature, the reaction mixture was filtered and water was added to the filtrate. The mixture was extracted with AcOEt, washed with saturated aqueous NaCl, dried over $MgSO_4$ and concentrated under reduced pressure. Column chromatography of the residue on silica gel (AcOEt/hexane = 1/4) gave **2B** (3.73 g, 94%) as yellow crystals.

Preparation of methyl 3-[2-(triphenylphosphoranylidene)amino]phenylpropenoate (3B): Triphenylphosphine (3.61 g, 13.7 mmol) and hexachloroethane (3.25 g, 13.7 mmol) were added to a solution of **2B** (2.03 g, 11.4 mmol) in dichloromethane (30 mL) with stirring. After the mixture being cooled to 0 °C, triethylamine (3.8 mL, d 0.73, 27 mmol) was added and the reaction mixture was stirred at room temperature for 1 h. Removal of the solvent and column chromatography of the residue on silica gel (AcOEt/hexane = 1/4) gave **3B** (4.62 g, 92%) as yellow crystals.

Preparation of (*E*)-*N*-[2-(2-methoxycarbonylethenyl)phenyl]-*N'*-phenylcarbodiimide (5Ba)[16a]: Phenyl isocyanate (0.270 mL, d 1.10, 2.50 mmol) was added to a solution of iminophosphorane **3B** (1.10 g, 2.51 mmol) in dichloromethane (30 mL) at room temperature with stirring. After being stirred for 1 h, the solvent was removed under reduced pressure and the residue was purified by column chromatography on silica gel (AcOEt/hexane = 1/4) gave **5Ba** (0.670 g, 96%) as a colorless viscous oil (lit.[16a] mp 54 °C). ^{1}H-NMR (270.0 MHz, $CDCl_3$) δ 3.80 (s, 3H), 6.51 (d, J = 16.2 Hz, 1H), 7.14–7.59 (m, 9H), 8.14 (d, J = 16.2 Hz, 1H); IR, neat/NaCl (cm^{-1}) 2144 (NCN), 1718 (CO), 1622.

Typical procedure for the reaction of carbodiimides 5 with enolate carbon-nucleophiles: Ethyl cyanoacetate (**6b**) (0.040 mL, d 1.06, 0.375 mmol) was added to a suspension of NaH (40%, 22.5 mg, 0.375 mmol) in THF (1 mL) with stirring at -78 °C under an atmosphere of argon. After 0.5 h, a solution of carbodiimide **5Be** (74.0 mg, 0.303 mmol) in THF (3 mL) was added at -78 °C. The reaction mixture was warmed to room temperature with stirring for 17 h and quenched with saturated aqueous NH_4Cl, extracted with AcOEt three times. The organic layer was washed with water and brine, dried over $MgSO_4$ and concentrated under reduced pressure. Column chromatography of the residue on silica gel (AcOEt/hexane = 1/2) gave **13e** (0.106 g, 98%) as colorless crystals.

2,3,4-Trisubstituted 3,4-dihydroquinazolines (7, 9, 11, and 13)

Diethyl 2-[4-(cyanomethyl)-3-phenyl-3,4-dihydroquinazolin-2-yl]propanedioate (7a): Colorless solid; mp 68–70 °C; ^{1}H-NMR (500.0 MHz, $CDCl_3$) δ 1.16 (t, J = 7.1 Hz, 6H), 2.84 (dd, J = 8.5, 16.9 Hz, 1H), 3.08 (dd, J = 6.3, 16.9 Hz, 1H), 3.75–3.99 (m, 4H), 4.99 (dd, J = 6.3, 8.5 Hz, 1H), 7.08–7.18 (m, 4H), 7.22–7.33 (m, 4H), 7.38 (dd, J = 7.7, 7.7 Hz, 1H), 12.2 (s, 1H); ^{13}C-NMR (125.65 MHz, $CDCl_3$) δ 14.1 (CH_3 x2), 23.4 (CH_2), 59.7 (CH), 60.0 (CH_2 x2), 83.9 (C), 116.2 (CH), 116.6 (C), 121.6 (C), 124.0 (CH), 124.3 (CH x2), 125.9 (CH x2), 129.1 (CH x2), 130.0 (CH), 133.1 (C), 144.1 (C), 155.5 (C), 168.1 (C x2); IR, KBr (cm^{-1}) 3494, 2985, 2245, 1697, 1620, 1566; HRMS-ESI (*m/z*) [M + Na]$^+$ Calcd for $C_{23}H_{23}N_3O_4Na$: 428.1581, Found: 428.1586.

Diethyl 2-[4-(cyanomethyl)-3-(4-tolyl)-3,4-dihydroquinazolin-2-yl]propanedioate (7b): Colorless solid; mp 85–87 °C; ^{1}H-NMR (500.0 MHz, $CDCl_3$) δ 1.08 (t, *J* = 7.1 Hz, 6H), 2.21 (s, 3H), 2.73 (dd, *J* = 8.2, 16.9 Hz, 1H), 2.97 (dd, *J* = 6.4, 16.9 Hz, 1H), 3.67–3.92 (m, 4H), 4.89 (dd, *J* = 6.4, 8.2 Hz, 1H), 6.89–7.09 (m, 7H), 7.28 (dd, *J* = 7.7, 7.7 Hz, 1H), 12.13 (s, 1H); ^{13}C-NMR (125.65 MHz, $CDCl_3$) δ 14.0 (CH_3 x2), 20.7 (CH_3), 23.3 (CH_2), 59.77 (CH), 59.82 (CH_2 x2), 83.4 (C), 116.0 (CH), 116.6 (C), 121.5 (C), 123.9 (CH), 124.3 (CH x2), 125.8 (CH), 129.5 (CH x2), 129.8 (CH), 133.1 (C), 135.9 (C), 141.6 (C), 155.6 (C), 168.1 (C x2); IR, KBr (cm^{-1}) 3541, 3502, 3055, 2985, 2908, 2252, 1682, 1620, 1574; HRMS-ESI (*m/z*) $[M + Na]^+$ Calcd for $C_{24}H_{25}N_3O_4Na$: 442.1737, Found: 442.1738.

Diethyl 2-[4-(cyanomethyl)-3-(4-methoxyphenyl)-3,4-dihydroquinazolin-2-yl]propanedioate (7c): Colorless solid; mp 52–56 °C; ^{1}H-NMR (500.0 MHz, $CDCl_3$) δ 1.17 (t, *J* = 7.1 Hz, 6H), 2.80 (dd, *J* = 8.1, 16.9 Hz, 1H), 3.04 (dd, *J* = 6.5, 16.9 Hz, 1H), 3.77 (s, 3H), 3.80–3.99 (m, 4H), 4.90 (dd, *J* = 6.5, 8.1 Hz, 1H), 6.82 (d, *J* = 8.9 Hz, 2H), 7.09–7.16 (m, 3H), 7.18 (d, *J* = 8.9 Hz, 2H), 7.37 (dd, *J* = 7.6, 7.6 Hz, 1H), 12.18 (s, 1H); ^{13}C-NMR (125.65 MHz, $CDCl_3$) δ 14.1 (CH_3 x2), 23.5 (CH_2), 55.4 (CH_3), 59.9 (CH_2 x2), 60.2 (CH), 83.2 (C), 114.2 (CH x2), 116.1 (CH), 116.7 (C), 121.5 (C), 124.0 (CH), 125.8 (CH), 126.3 (CH x2), 129.9 (CH), 133.2 (C), 137.2 (C), 155.8 (C), 157.7 (C), 168.2 (C x2); IR, KBr (cm^{-1}) 3525, 3062, 2978, 2252, 1704, 1620, 1574, 756; HRMS-ESI (*m/z*) $[M + Na]^+$ Calcd for $C_{24}H_{25}N_3O_5Na$: 458.1686, Found: 458.1687.

Diethyl 2-[4-(cyanomethyl)-3-benzyl-3,4-dihydroquinazolin-2-yl]propanedioate (7d): Colorless powder; mp 39–41 °C; ^{1}H-NMR (500.0 MHz, $CDCl_3$) δ 1.36 (t, *J* = 7.1 Hz, 6H), 2.60 (dd, *J* = 7.9, 16.7 Hz, 1H), 2.83 (dd, *J* = 6.3, 16.7 Hz, 1H), 4.25–4.32 (m, 4H), 4.35 (d, *J* = 14.6 Hz, 1H), 4.53 (dd, *J* = 6.3, 7.9 Hz, 1H), 4.83 (d, *J* = 14.6 Hz, 1H), 6.79 (d, *J* = 7.5 Hz, 1H), 7.04 (dd, *J* = 7.5, 7.5 Hz, 1H), 7.07 (d, *J* = 7.9 Hz, 1H), 7.09–7.13 (m, 2H), 7.24–7.30 (m, 3H), 7.32 (dd, *J* = 7.9, 7.9 Hz, 1H), 11.8(s, 1H); ^{13}C-NMR (125.65 MHz, $CDCl_3$) δ 14.6 (CH_3 x2), 21.4 (CH_2), 53.2 (CH), 56.0 (CH_2), 60.1 (CH_2 x2), 78.3 (C), 116.0 (CH), 116.7 (C), 120.9 (C), 124.6 (CH), 125.3 (CH), 128.3 (CH x2), 128.6 (CH), 129.0 (CH x2), 129.8 (CH), 133.2 (C), 134.9 (C), 159.7 (C), 168.9 (C x2); IR, KBr (cm^{-1}) 3386, 3201, 3132, 3047, 2985, 2939, 2252, 1720, 1697, 1550, 1450, 1389, 1335, 1065; HRMS-ESI (*m/z*) $[M + Na]^+$ Calcd for $C_{24}H_{25}N_3O_4Na$: 442.1737, Found: 442.1738.

Diethyl 2-[4-(cyanomethyl)-3-propyl-3,4-dihydroquinazolin-2-yl]propanedioate (7e): Colorless crystals; mp 85–87 °C; ^{1}H-NMR (600.1 MHz, $CDCl_3$) δ 0.73 (t, *J* = 7.3 Hz, 3H), 1.35 (t, *J* = 7.1 Hz, 6H), 1.50–1.70 (m, 2H), 2.64 (dd, *J* = 8.2, 16.8 Hz, 1H), 2.80 (dd, *J* = 6.0, 16.8 Hz, 1H), 3.30 (ddd, *J* = 4.2, 8.1, 14.1 Hz, 1H), 3.49 (ddd, *J* = 6.7, 8.1, 14.1 Hz, 1H), 4.20–4.30 (m, 4H), 4.73 (dd, *J* = 6.0, 8.2 Hz, 1H), 7.07 (d, *J* = 7.8 Hz, 1H), 7.18 (dd, *J* = 7.5, 7.5 Hz, 1H), 7.23 (d, *J* = 7.5 Hz, 1H), 7.37 (dd, *J* = 7.8, 7.8 Hz, 1H), 11.82 (s, 1H); ^{13}C-NMR (150.9 MHz, $CDCl_3$) δ 10.6 (CH_3), 14.6 (CH_3 x2), 21.7 (CH_2), 21.9 (CH_2), 54.4 (CH), 54.6 (CH_2), 60.0 (CH_2 x2), 78.0 (C), 116.1 (CH), 116.7 (C), 120.9 (C), 124.7 (CH), 125.5

(CH), 130.0 (CH), 133.3 (C), 159.4 (C), 168.9 (C x2); IR, KBr (cm^{-1}) 3456, 3078, 2978, 2931, 2252, 1705, 1558, 1065, 771; HRMS-ESI (*m/z*) $[M + Na]^+$ Calcd for $C_{20}H_{25}N_3O_4Na$: 394.1737, Found: 394.1737.

Ethyl 2-cyano-2-[4-(cyanomethyl)-3-phenyl-3,4-dihydroquinazolin-2-yl]ethanoate (9a): Colorless solid; mp 198.5–200.6 °C; ^{1}H-NMR (500.0 MHz, $CDCl_3$) δ 1.31 (t, *J* = 7.1 Hz, 3H), 2.87 (dd, *J* = 8.6, 16.6 Hz, 1H), 3.03 (dd, *J* = 5.8, 16.6 Hz, 1H), 4.18–4.28 (m, 2H), 4.97 (dd, *J* = 5.8, 8.6 Hz, 1H), 7.14 (d, *J* = 7.9 Hz, 1H), 7.18–7.23 (m, 2H), 7.29–7.38 (m, 3H), 7.40–7.47 (m, 3H), 12.20 (s, 1H); ^{13}C-NMR (125.65 MHz) δ 14.3 (CH_3), 24.7 (CH_2), 60.3 (CH), 60.9 (CH_2), 62.8 (C), 115.9 (C), 116.3 (CH), 116.4 (C), 120.6 (C), 125.1 (CH), 125.6 (CH x2), 126.3 (CH), 128.0 (CH), 130.1 (CH x2), 130.3 (CH), 132.2 (C), 143.3 (C), 157.8 (C), 170.3 (C); IR, KBr (cm^{-1}) 3471, 3062, 2978, 2939, 2360, 2198, 1658, 1574, 1296, 1134, 756; HRMS-ESI (*m/z*) $[M + Na]^+$ Calcd for $C_{21}H_{18}N_4O_2Na$: 381.1322, Found: 381.1323.

Ethyl 2-cyano-2-[4-(cyanomethyl)-3-(4-tolyl)-3,4-dihydroquinazolin-2-yl]ethanoate (9b): Colorless solid; mp 209.4–210.8 °C; ^{1}H-NMR (500.0 MHz, $CDCl_3$) δ 1.30 (t, *J* = 7.1 Hz, 3H), 2.36 (s, 3H), 2.85 (dd, *J* = 8.5, 16.8 Hz, 1H), 3.01 (dd, *J* = 5.8, 16.8 Hz, 1H), 4.22 (q, *J* = 7.1 Hz, 2H), 4.92 (dd, *J* = 5.8, 8.5 Hz, 1H), 7.13 (d, *J* = 8.0 Hz, 1H), 7.16–7.25 (m, 6H), 7.42 (dd, *J* = 7.4, 7.4 Hz, 1H), 12.18 (s, 1H); ^{13}C-NMR (125.65 MHz) δ 14.3 (CH_3), 21.1 (CH_3), 24.6 (CH_2), 60.4 (CH), 60.8 (CH_2), 62.4 (C), 115.9 (C), 116.2 (CH), 116.5 (C), 120.5 (C), 125.0 (CH), 125.5 (CH x2), 126.2 (CH), 130.2 (CH), 130.6 (CH x2), 132.2 (C), 138.1 (C), 140.8 (C), 157.8 (C), 170.4 (C); IR, KBr (cm^{-1}) 3479, 3093, 3039, 2985, 2954, 2931, 2198, 1736, 1658, 1612, 1574, 1288, 1273, 1134, 1041; HRMS-ESI (*m/z*) $[M + Na]^+$ Calcd for $C_{22}H_{20}N_4O_2Na$: 395.1478, Found: 395.1478.

Ethyl 2-cyano-2-[4-(cyanomethyl)-3-(4-methoxyphenyl)-3,4-dihydroquinazolin-2-yl]ethanoate (9c): Colorless crystals; mp 197.6–199.1 °C; ^{1}H-NMR (500.0 MHz, $CDCl_3$) δ 1.29 (t, *J* = 7.1 Hz, 3H), 2.84 (dd, *J* = 8.2, 16.7 Hz, 1H), 2.99 (dd, *J* = 6.0, 16.7 Hz, 1H), 3.80 (s, 3H), 4.21 (q, *J* = 7.1 Hz, 2H), 4.89 (dd, *J* = 6.0, 8.2 Hz, 1H), 6.92 (d, *J* = 9.0 Hz, 2H), 7.13 (d, *J* = 8.0 Hz, 1H), 7.16–7.21 (m, 2H), 7.24 (d, *J* = 9.0 Hz, 2H), 7.41 (dd, *J* = 8.0, 8.0 Hz, 1H), 12.19 (s, 1H); ^{13}C-NMR (125.65 MHz, $CDCl_3$) δ 14.3 (CH_3), 24.5 (CH_2), 55.4 (CH_3), 60.5 (CH), 60.7 (CH_2), 61.9 (C), 115.0 (CH x 2), 116.0 (C), 116.1 (CH), 116.5 (C), 120.4 (C), 124.9 (CH), 126.1 (CH), 127.4 (CH x2), 130.2 (CH), 132.2 (C), 136.0 (C), 157.9 (C), 159.1 (C), 170.4 (C); IR, KBr (cm^{-1}) 3494, 3055, 2978, 2934, 2915, 2206, 1658, 1619, 1773, 1295, 1126; HRMS-ESI (*m/z*) $[M + Na]^+$ Calcd for $C_{22}H_{20}N_4O_3Na$: 411.1428, Found: 411.1429.

Ethyl 2-cyano-2-[4-(cyanomethyl)-3-benzyl-3,4-dihydroquinazolin-2-yl]ethanoate (9d): Colorless solid; mp 50.6–52.9 °C; ^{1}H-NMR (500.0 MHz, $CDCl_3$) δ 1.35 (t, *J* = 7.0 Hz, 3H), 2.59 (dd, *J* = 7.8, 16.6 Hz, 1H), 2.70 (dd, *J* = 6.5, 16.6 Hz, 1H), 4.22–4.30 (m, 2H), 4.59 (dd, *J* = 6.5, 7.8 Hz, 1H), 4.79 (d, *J* = 15.1 Hz, 1H), 5.42 (d, *J* = 15.1 Hz, 1H), 6.90 (d, *J* = 7.6 Hz, 1H), 7.02–7.12 (m, 2 H), 7.15–7.21 (m, 2H), 7.25–7.37 (m, 4H), 11.95 (s, 1H); ^{13}C-NMR (125.65 MHz) δ 14.3 (CH_3), 22.8 (CH_2), 54.3 (CH), 56.7 (CH_2), 59.2 (C), 60.7 (CH_2), 115.8 (CH), 115.9 (C), 118.9 (C), 120.3 (C), 125.0 (CH), 125.5 (CH), 128.1

(CH x2), 128.6 (CH), 128.9 (CH x2), 130.0 (CH), 132.2 (C), 134.4 (C), 159.1 (C), 170.3 (C); IR, KBr (cm^{-1}) 3487, 3062, 3039, 2978, 2931, 2252, 2198, 1736, 1658, 1574, 1273, 1134, 756; HRMS-ESI (*m/z*) $[M + Na]^+$ Calcd for $C_{22}H_{20}N_4O_2Na$: 395.1478, Found: 395.1478.

Ethyl 2-cyano-2-[4-(cyanomethyl)-3-propyl-3,4-dihydroquinazolin-2-yl]ethanoate (9e): Colorless needles; mp 140.2–141.0 °C; ^{1}H-NMR (500.0 MHz, $CDCl_3$) δ 0.89 (t, *J* = 7.3 Hz, 3H), 1.35 (t, *J* = 7.1 Hz, 3H), 1.65–1.91 (m, 2H), 2.64 (dd, *J* = 8.5, 16.6 Hz, 1H), 2.72 (dd, *J* = 5.9, 16.6 Hz, 1H), 3.60 (ddd, *J* = 5.1, 9.8, 14.8 Hz, 1H), 4.07 (ddd, *J* = 6.2, 9.5, 14.8 Hz, 1H), 4.26 (q, *J* = 7.1 Hz, 2H), 4.68 (dd, *J* = 5.9, 8.3 Hz, 1H), 7.05 (d, *J* = 7.6 Hz, 1H), 7.20 (ddd, *J* = 0.9, 7.5, 7.5 Hz, 1H), 7.25 (d, *J* = 7.5 Hz, 1H), 7.39 (ddd, *J* = 1.5, 7.6, 7.6 Hz, 1H), 11.97 (s, 1H); ^{13}C-NMR (125.65 MHz, $CDCl_3$) δ 10.6 (CH_3), 14.4 (CH_3), 22.4 (CH_2), 23.6 (CH_2), 55.5 (CH_2), 56.7 (CH), 58.8 (C), 60.7 (CH_2), 115.8 (C), 115.9 (CH), 118.9 (C), 120.2 (C), 124.9 (CH), 125.7 (CH), 130.1 (CH), 132.5 (C), 158.7 (C), 170.5 (C); IR, KBr (cm^{-1}) 3240, 3201, 3062, 2978, 2931, 2191, 1658, 1620, 1574, 1273, 764; HRMS-ESI (*m/z*) $[M + Na]^+$ Calcd for $C_{18}H_{20}N_4O_2Na$: 347.1478, Found: 347.1478.

Ethyl 2-cyano-2-[4-(cyanomethyl)-3-isopropyl-3,4-dihydroquinazolin-2-yl]ethanoate (9f): Colorless solid; mp 70–71 °C; ^{1}H-NMR (500.0 MHz, $CDCl_3$) δ 1.12 (d, *J* = 6.6 Hz, 3H), 1.35 (t, *J* = 7.1 Hz, 3H), 1.55 (d, *J* = 6.6 Hz, 3H), 2.59 (dd, *J* = 5.7, 16.6 Hz, 1H), 2.65 (dd, *J* = 9.1, 16.6 Hz, 1H), 4.27 (q, *J* = 7.1 Hz, 2H), 4.69 (sept, *J* = 6.6 Hz, 1H), 4.79 (dd, *J* = 5.7, 9.1 Hz, 1H), 7.06 (d, *J* = 7.6 Hz, 1H), 7.22 (dd, *J* = 7.6, 7.6 Hz, 1H), 7.29 (d, *J* = 7.6 Hz, 1H), 7.39 (dd, *J* = 7.6, 7.6 Hz, 1H), 11.88 (s, 1H); ^{13}C-NMR (125.65 MHz, $CDCl_3$) δ 14.4 (CH_3), 21.0 (CH_3), 22.1 (CH_3), 23.7 (CH_2), 49.0 (CH), 54.4 (CH), 59.6 (C), 60.6 (CH_2), 115.9 (C), 116.0 (CH), 118.8 (C), 121.4 (C), 125.2 (CH), 125.5 (CH), 130.0 (CH), 132.6 (C), 160.0 (C), 170.3 (C); IR, KBr (cm^{-1}) 3479, 3240, 2985, 2191, 1666, 1612, 1566, 1288; HRMS-ESI (*m/z*) $[M + Na]^+$ Calcd for $C_{18}H_{20}N_4O_2Na$: 347.1478, Found: 347.1482.

Ethyl 2-cyano-2-[4-(cyanomethyl)-3-cyclohexyl-3,4-dihydroquinazolin-2-yl]ethanoate (9g): Colorless solid; mp 103–106 °C; ^{1}H-NMR (500.0 MHz, $CDCl_3$) δ 1.06–1.21 (m, 1H), 1.36 (t, *J* = 7.1 Hz, 3H), 1.28–1.62 (m, 5H), 1.66–1.80 (m, 2H), 1.89–1.99 (m, 1H), 2.34–2.47 (m, 1H), 2.57 (dd, *J* = 5.5, 16.6 Hz, 1H), 2.64 (dd, *J* = 9.2, 16.6 Hz, 1H), 4.18–4.33 (m, 3H), 4.81 (dd, *J* = 5.5, 9.2 Hz, 1H), 7.05 (d, *J* = 7.6 Hz, 1H), 7.21 (dd, *J* = 7.6, 7.6 Hz, 1H), 7.29 (d, *J* = 7.6 Hz, 1H), 7.34 (dd, *J* = 7.6, 7.6 Hz, 1H), 11.87 (s, 1H); ^{13}C-NMR (125.65 MHz, $CDCl_3$) δ 14.4 (CH_3), 23.8 (CH_2), 24.9 (CH_2), 25.5 (CH_2), 25.6 (CH_2), 31.7 (CH_2), 32.6 (CH_2), 50.0 (CH), 59.5 (C), 60.6 (CH_2), 62.3 (CH), 115.9 (C), 116.0 (CH), 118.6 (C), 121.4 (C), 125.1 (CH), 125.5 (CH), 130.0 (CH), 132.6 (C), 160.0 (C), 170.4 (C); IR, KBr (cm^{-1}) 3487, 2931, 2854, 2198, 1650, 1620, 1574, 1288; HRMS-ESI (*m/z*) $[M + Na]^+$ Calcd for $C_{21}H_{24}N_4O_2Na$: 387.1791, Found: 388.1791.

Diethyl 2-[4-(methoxycarbonylmethyl)-3-phenyl-3,4-dihydroquinazolin-2-yl]propanedioate (11a): Colorless crystals; mp 40–42 °C; ^{1}H-NMR (600.1 MHz, $CDCl_3$) δ 1.16 (t, *J* = 7.1 Hz, 6H), 2.90 (dd, *J* =

9.8, 16.2 Hz, 1H), 3.13 (dd, *J* = 4.7, 16.2 Hz, 1H), 3.69 (s, 3H), 3.74–3.95 (m, 4H), 5.25 (dd, *J* = 4.7, 9.8 Hz, 1H), 7.04 (dd, *J* = 7.7, 7.7 Hz, 1H), 7.08–7.13 (m, 3H), 7.22–7.33 (m, 5H), 12.18 (s, 1H); ^{13}C-NMR (150.90 MHz, $CDCl_3$) δ 14.2 (CH_3 x2), 39.2 (CH_2), 52.0 (CH_3), 59.2 (CH), 59.8 (CH_2 x2), 82.9 (C), 116.0 (CH), 123.7 (CH), 123.9 (CH x2), 124.0 (C), 125.3 (CH), 125.8 (CH), 128.9 (CH x2), 129.1 (CH), 133.1 (C), 144.5 (C), 156.6 (C), 168.4 (C x2), 170.7 (C); IR, neat/NaCl (cm^{-1}) 3348, 2985, 1743, 1658, 1481, 1250, 1057, 756; HRMS-ESI (*m/z*) $[M + H]^+$ Calcd for $C_{24}H_{27}N_2O_6$: 439.1869, Found: 439.1864.

Diethyl 2-[4-(methoxycarbonylmethyl)-3-(4-methoxyphenyl)-3,4-dihydroquinazolin-2-yl]propanedioate (11c): Colorless crystals; mp 40–43 ºC; ^{1}H-NMR (500.0 MHz, $CDCl_3$) δ 1.16 (t, *J* = 7.1 Hz, 6H), 2.87 (dd, *J* = 9.8, 16.1 Hz, 1H), 3.09 (dd, *J* = 4.9, 16.1 Hz, 1H), 3.68 (s, 3H), 3.76 (s, 3H), 3.78–3.96 (m, 4H), 5.13 (dd, *J* = 4.9, 9.8 Hz, 1H), 6.79 (d, *J* = 9.0 Hz, 2H), 7.04 (dd, *J* = 7.6, 7.6 Hz, 1H), 7.09 (d, *J* = 7.6 Hz, 2H), 7.15 (d, *J* = 9.0 Hz, 2H), 7.30 (dd, *J* = 7.6, 7.6 Hz, 1H), 12.11 (s, 1H); ^{13}C-NMR (125.65 MHz, $CDCl_3$) δ 14.2 (CH_3 x2), 39.4 (CH_2), 51.9 (CH_3), 55.4 (CH_3), 59.6 (CH), 59.7 (CH_2 x2), 82.3 (C), 114.0 (CH x2), 115.9 (CH), 123.6 (CH), 123.8 (C), 125.7 (CH), 125.8 (CH x2), 129.0 (CH), 133.2 (C), 137.7 (C), 156.9 (C), 157.3 (C), 168.5 (C x2), 170.7 (C); IR, KBr (cm^{-1}) 3456, 3062, 2978, 2908, 1736, 1620, 1574, 1250, 1072, 756; HRMS-ESI (*m/z*) $[M + Na]^+$ Calcd for $C_{25}H_{28}N_2O_7Na$: 491.1789, Found: 491.1789.

Diethyl 2-[3-benzyl-4-(methoxycarbonylmethyl)-3,4-dihydroquinazolin-2-yl]propanedioate (11d): Colorless solid; mp 126.6–129.2 °C; ^{1}H-NMR (500.0 MHz, $CDCl_3$) δ 1.34 (t, *J* = 7.0 Hz, 6H), 2.51 (dd, *J* = 6.4, 16.5 Hz, 1H), 2.95 (dd, *J* = 7.6, 16.5 Hz, 1H), 3.70 (s, 3H), 4.20–4.29 (m, 4H), 4.32 (d, *J* = 14.3 Hz, 1H), 4.76 (dd, *J* = 6.6, 7.6 Hz, 1H), 4.79 (d, *J* = 14.3 Hz, 1H), 6.67 (d, *J* = 7.0 Hz, 1H), 6.92–6.98 (m, 1H), 7.03 (d, *J* = 7.6 Hz, 1H), 7.08–7.14 (m, 2H), 7.18–7.30 (m, 4H), 11.67 (s, 1H); ^{13}C-NMR (125.65 MHz, $CDCl_3$) δ 14.5 (CH_3 x2), 37.5 (CH_2), 51.8 (CH_3), 52.9 (CH), 55.9 (CH_2), 59.6 (CH_2 x2), 77.2 (C), 115.7 (CH), 123.3 (C), 124.3 (CH), 124.7 (CH), 128.1 (CH), 128.4 (CH x2), 128.5 (CH x2), 128.7 (CH), 133.5 (C), 135.7 (C), 160.4 (C), 168.9 (C x2), 171.0 (C); IR, KBr (cm^{-1}) 3209, 3062, 2954, 2924, 1736, 1674, 1466, 1296; HRMS-ESI (*m/z*) $[M + Na]^+$ Calcd for $C_{25}H_{28}N_2O_6Na$: 475.1840, Found: 475.1840.

Diethyl 2-[4-(methoxycarbonylmethyl)-3-propyl-3,4-dihydroquinazolin-2-yl]propanedioate (11e): Colorless solid; mp 54.4–56.6 °C; ^{1}H-NMR (500.0 MHz, $CDCl_3$) δ 0.69 (t, *J* = 7.3 Hz, 3H), 1.31 (t, *J* = 7.1 Hz, 6H), 1.49–1.70 (m, 2H), 2.59 (dd, *J* = 7.6, 16.5 Hz, 1H), 2.87 (dd, *J* = 6.6, 16.5 Hz, 1H), 3.30 (ddd, *J* = 4.3, 8.3, 13.9 Hz, 1H), 3.43 (ddd, *J* = 7.9, 8.9, 13.9 Hz, 1H), 3.68 (s, 3H), 4.15–4.26 (m, 4H), 4.95 (dd, *J* = 6.6, 7.5 Hz, 1H), 7.03 (d, *J* = 7.9 Hz, 1H), 7.09 (dd, *J* = 7.4, 7.4 Hz, 1H), 7.13 (d, *J* = 7.4 Hz, 1H), 7.28 (dd, *J* = 7.9, 7.9 Hz, 1H), 11.59 (s, 1H); ^{13}C-NMR (125.65 MHz, $CDCl_3$) δ 10.7 (CH_3), 14.6 (CH_3 x2), 21.8 (CH_2), 37.9 (CH_2), 51.9 (CH_3), 53.8 (CH), 54.4 (CH_2), 59.7 (CH_2 x2), 77,2 (C), 115.8 (CH), 123.3 (C), 124.3 (CH), 125.0 (CH), 128.9 (CH), 133.6 (C), 160.2 (C), 169.0 (C x2), 171.0 (C); IR, KBr (cm^{-1}); 3456, 3248, 3209, 2970, 2939, 1712, 1311, 1072, 767; HRMS-ESI (*m/z*) $[M + Na]^+$ Calcd for

$C_{21}H_{28}N_2O_6Na$: 427.1840, Found: 427.1840.

Diethyl 2-[4-(methoxycarbonylmethyl)-3-(prop-2-enyl)-3,4-dihydroquinazolin-2-yl]propanedioate (11i): Colorless crystals; mp 81.0–83.0 °C; ^{1}H-NMR (500.0 MHz, $CDCl_3$) δ 1.32 (t, *J* = 7.1 Hz, 6H), 2.56 (dd, *J* = 7.3, 16.5 Hz, 1H), 2.86 (dd, *J* = 6.8, 16.5 Hz, 1H), 3.68 (s, 3H), 3.86 (dd, *J* = 8.6, 14.7 Hz, 1H), 4.08–4.14 (m, 1H), 4.17–4.27 (m, 4H), 5.01 (dd, *J* = 6.8, 7.3 Hz, 1H), 5.28 (d, *J* = 10.1 Hz, 1H), 5.35 (d, *J* = 17.0 Hz, 1H), 5.54–5.68 (m, 1H), 7,03 (d, *J* = 7.8 Hz, 1H), 7.07–7.10 (m, 2H), 7.25–7.31 (m, 1H), 11.62 (s, 1H); ^{13}C-NMR (125.65 MHz, $CDCl_3$) δ 14.5 (CH_3 x2), 37.7 (CH_2), 51.8 (CH), 52.7 (CH_3), 54.9 (C), 55.3 (CH_2), 59.8 (CH_2 x2), 115.8 (CH), 120.5 (CH_2), 123.2 (C), 124.4 (CH), 125.1 (CH), 128.9 (CH), 132.8 (CH), 133.7 (C), 160.1 (C), 168.9 (C x2), 170.9 (C); IR, KBr (cm^{-1}) 3440, 2985, 1736, 1604, 1550, 1304, 1157, 1080, 763; HRMS-ESI (*m/z*) $[M + Na]^+$ Calcd for $C_{21}H_{26}N_2O_6Na$: 425.1689, Found: 425.1677.

Ethyl 2-cyano-2-[4-(methoxycarbonylmethyl)-3-phenyl-3,4-dihydroquinazolin-2-yl]ethanoate (13a): Colorless crystals; mp 178–179 °C (lit.[16a] 179 °C); ^{1}H-NMR (500.0 MHz, $CDCl_3$) δ 1.31 (t, *J* = 7.1 Hz, 3H), 2.80 (dd, *J* = 8.4, 15.0 Hz, 1H), 3.01 (dd, *J* = 6.5, 15.0 Hz, 1H), 3.72 (s, 3H), 4.23 (q, *J* = 7.1 Hz, 2H), 5.18 (dd, *J* = 6.5, 8.4 Hz, 1H), 7.09–7.14 (m, 3H), 7.23–7.30 (m, 3H), 7.32–7.42 (m, 3H), 12.07 (s, 1H); ^{13}C-NMR (125.65 MHz, $CDCl_3$) δ 14.4 (CH_3), 40.3 (CH_2), 52.3 (CH_3), 60.3 (CH), 60.6 (CH_2), 62.7 (C), 116.1 (CH), 116.9 (C), 123.2 (C), 124.7 (CH), 125.0 (CH x2), 125.9 (CH), 127.2 (CH), 129.4 (CH), 129.7 (CH x2), 132.2 (C), 143.7 (C), 158.5 (C), 170.2 (C), 170.4 (C).

Ethyl 2-cyano-2-[4-(methoxycarbonylmethyl)-3-(4-methoxyphenyl)-3,4-dihydroquinazolin-2-yl]-ethanoate (13c): Colorless crystals; mp 116.6–120.2 °C; ^{1}H-NMR (500.0 MHz, $CDCl_3$) δ 1.31 (t, *J* = 7.1 Hz, 3H), 2.78 (dd, *J* = 8.5, 15.1 Hz, 1H), 2.98 (dd, *J* = 6.4, 15.1 Hz, 1H), 3.71 (s, 3H), 3.79 (s, 3H), 4.22 (q, *J* = 7.1 Hz, 2H), 5.09 (dd, *J* = 6.4, 8.5 Hz, 1H), 6.89 (d, *J* = 9.0 Hz, 2H), 7.08–7.12 (m, 3H), 7.16 (d, *J* = 9.0 Hz, 2H), 7.30–7.37 (m, 1H), 12.05 (s, 1H); ^{13}C-NMR (125.65 MHz, $CDCl_3$) δ 14.4 (CH_3), 40.2 (CH_2), 52.2 (CH_3), 55.4 (CH_3), 60.3 (C), 60.5 (CH), 60.7 (CH_2), 114.8 (CH x2), 116.0 (CH), 117.1 (C), 123.0 (C), 124.6 (CH), 125.8 (CH), 126.8 (CH x2), 129.3 (CH), 132.3 (C), 136.6 (C), 158.57 (C), 158.59 (C), 170.2 (C), 170.6 (C); IR, KBr (cm^{-1}) 3464, 2978, 2954, 2206, 1736, 1574; HRMS-ESI (*m/z*) $[M + Na]^+$ Calcd for $C_{23}H_{23}N_3O_5Na$: 444.1535, Found: 444.1530.

Ethyl 2-cyano-2-[3-benzyl-4-(methoxycarbonylmethyl)-3,4-dihydroquinazolin-2-yl]ethanoate (13d): Colorless crystals; mp 123.2–124.7 °C; ^{1}H-NMR (500.0 MHz, $CDCl_3$) δ 1.35 (t, *J* = 7.1 Hz, 3H), 2.45 (dd, *J* = 5.8, 15.5 Hz, 1H), 2.77 (dd, *J* = 9.0, 15.5 Hz, 1H), 3.75 (s, 3H), 4.22–4.32 (m, 2H), 4.59 (d, *J* = 14.9 Hz, 1H), 4.76 (dd, *J* = 5.8, 9.0 Hz, 1H), 5.39 (d, *J* = 14.9 Hz, 1H), 6.76 (d, *J* = 7.7 Hz, 1H), 6.99–7.04 (m, 2H), 7.09–7.17 (m, 2H), 7.20–7.30 (m, 4H), 11.75 (s, 1H); ^{13}C-NMR (125.65 MHz, $CDCl_3$) δ 14.5 (CH_3), 38.8 (CH_2), 52.3 (CH), 54.5 (CH_3), 57.1 (CH_2), 58.9 (C), 60.5 (CH_2), 115.7 (CH), 119.4 (C), 122.9 (C), 124.81 (CH), 124.83 (CH), 128.21 (CH x2), 128.24 (CH), 128.7 (CH x2), 129.1 (CH), 132.5 (C), 135.2

(C), 159.8 (C), 170.4 (C), 170.6 (C); IR, KBr (cm^{-1}) 3448, 2985, 2946, 2198, 1735; HRMS-ESI (*m/z*) [M + Na]$^+$ Calcd for $C_{23}H_{23}N_3O_4Na$: 428.1581, Found: 428.1577.

Ethyl 2-cyano-2-[4-(methoxycarbonylmethyl)-3-propyl-3,4-dihydroquinazolin-2-yl]ethanoate (13e): Colorless solid; mp 108.4–110.4 °C; ^{1}H-NMR (500.0 MHz, $CDCl_3$) δ 0.82 (t, *J* = 7.3 Hz, 3H), 1.35 (t, *J* = 7.2 Hz, 3H), 1.60–1.81 (m, 2H), 2.56 (dd, *J* = 7.3, 15.3 Hz, 1H), 2.72 (dd, *J* = 7.4, 15.3 Hz, 1H), 3.48–3.56 (m, 1H), 3.71 (s, 3H), 4.00–4.16 (m, 1H), 4.25 (q, *J* = 7.2 Hz, 2H), 4.86 (dd, *J* = 7.3, 7.4 Hz, 1H), 7.01 (d, *J* = 7.8 Hz, 1H), 7.10–7.25 (m, 2H), 7.31 (dd, *J* = 7.8, 7.8 Hz, 1H), 11.80 (s, 1H); ^{13}C-NMR (125.65 MHz, $CDCl_3$) δ 10.7 (CH_3), 14.4 (CH_3), 22.3 (CH_2), 39.4 (CH_2), 52.2 (CH_3), 55.5 (CH_2), 56.7 (CH), 58.4 (C), 60.4 (CH_2), 115.7 (CH), 119.3 (C), 122.7 (C), 124.7 (CH), 125.2 (CH), 129.2 (CH), 132.7 (C), 159.3 (C), 170.3 (C), 170.7 (C); IR, KBr (cm^{-1}) 3456, 2970, 2198, 1736, 1574, 1373, 1273, 764; HRMS-ESI (*m/z*) [M + Na]$^+$ Calcd for $C_{19}H_{23}N_3O_4Na$: 380.1581, Found: 380.1581.

Ethyl 2-cyano-2-[3-isopropyl-4-(methoxycarbonylmethyl)-3,4-dihydroquinazolin-2-yl]ethanoate (13f): Colorless oil; ^{1}H-NMR (300.0 MHz, $CDCl_3$) δ 1.12 (d, *J* = 6.6 Hz, 3H), 1.35 (t, *J* = 7.1 Hz, 3H), 1.48 (d, *J* = 6.6 Hz, 3H), 2.55 (dd, *J* = 5.8, 15.2 Hz, 1H), 2.64 (dd, *J* = 9.0, 15.2 Hz, 1H), 3.65 (s, 3H), 4.21–4.35 (m, 2H), 4.64 (sept, *J* = 6.6 Hz, 1H), 4.96 (dd, *J* = 5.7, 9.0 Hz, 1H), 7.01 (d, *J* = 7.9 Hz, 1H), 7.12 (dd, *J* = 7.5, 7.5 Hz, 1H), 7.21 (d, *J* = 7.5 Hz, 1H), 7.30 (dd, *J* = 7.9, 7.9 Hz, 1H), 11.73 (s, 1H); ^{13}C-NMR (75.45 MHz, $CDCl_3$) δ 14.5 (CH_3), 20.8 (CH_3), 22.2 (CH_3), 39.6 (CH_2), 49.0 (CH), 52.0 (CH_3), 54.2 (CH), 58.9 (C), 60.4 (CH_2), 115.7 (CH), 119.4 (C), 123.8 (C), 124.8 (CH), 125.2 (CH), 129.1 (CH), 132.8 (C), 160.6 (C), 170.1 (C), 170.6 (C); IR, neat/NaCl (cm^{-1}) 3448, 3109, 2978, 2900, 2198, 1728, 1658, 1574, 1288, 1103; HRMS-ESI (*m/z*) [M + Na]$^+$ Calcd for $C_{19}H_{23}N_3O_4Na$: 380.1581, Found: 380.1587.

Ethyl 2-cyano-2-[3-cyclohexyl-4-(methoxycarbonylmethyl)-3,4-dihydroquinazolin-2-yl]ethanoate (13g): Colorless crystals; mp 102.1–105.2 °C; ^{1}H-NMR (500.0 MHz, $CDCl_3$) δ 1.06–1.21 (m, 1H), 1.24–1.42 (m, 2H), 1.36 (t, *J* = 7.1 Hz, 3H), 1.47–1.76 (m, 5H), 1.83–1.96 (m, 1H), 2.21–2.30 (m, 1H), 2.55 (dd, *J* = 5.7, 15.2 Hz, 1H), 2.61 (dd, *J* = 9.1, 15.2 Hz, 1H), 3.65 (s, 3H), 4.16 (tt, *J* = 3.6, 11.6 Hz, 1H), 4.21–4.32 (m, 2H), 4.99 (dd, *J* = 5.7, 9.1 Hz, 1H), 7.00 (d, *J* = 7.8 Hz, 1H), 7.11 (dd, *J* = 7.6, 7.6 Hz, 1H), 7.19 (d, *J* = 7.6 Hz, 1H), 7.29 (dd, *J* = 7.8, 7.8 Hz, 1H), 11.72 (s, 1H); ^{13}C-NMR (125.65 MHz, $CDCl_3$) δ 14.5 (CH_3), 24.9 (CH_2), 25.6 (CH_2), 25.7 (CH_2), 31.3 (CH_2), 32.7 (CH_2), 39.7 (CH_2), 50.0 (CH), 52.0 (CH_3), 59.0 (C), 60.4 (CH_2), 62.3 (CH), 115.8 (CH), 119.2 (C), 123.9 (C), 124.7 (CH), 125.2 (CH), 129.1 (CH), 132.9 (C), 160.7 (C), 170.2 (C), 170.6 (C); IR, KBr (cm^{-1}) 2931, 2198, 1743, 1574, 1489, 1450, 1373, 1288, 1103, 764; HRMS-ESI (*m/z*) [M + Na]$^+$ Calcd for $C_{22}H_{27}N_3O_4Na$: 420.1899, Found: 420.1894.

Ethyl 2-cyano-2-[4-(methoxycarbonylmethyl)-3-(prop-2enyl)-3,4-dihydroquinazolin-2-yl]ethanoate (13i): Colorless crystals**;** mp 147.8–149.8 °C; ^{1}H-NMR (500.0 MHz, $CDCl_3$) δ 1.35 (t, *J* = 7.12, 3H), 2.53

(dd, *J* = 7.4, 15.3 Hz, 1H), 2.70 (dd, *J* = 7.4, 15.3 Hz, 1H), 3.70 (s, 3H), 4.22–4.29 (m, 1H), 4.26 (q, *J* = 7.2 Hz, 2H), 4.52 (dd, *J* = 6.1, 15.5 Hz, 1H), 4.91 (dd, *J* = 7.4, 7.4 Hz, 1H), 5.30 (dd, *J* = 1.0, 10.1 Hz, 1H), 5.36 (dd, *J* = 1.0, 17.0 Hz, 1H), 5.74–5.84 (m, 1 H), 7.00–7.34 (m, 4H), 11.73 (s, 1H); ^{13}C-NMR (125.65 MHz, $CDCl_3$) δ 14.5 (CH_3), 39.2 (CH_2), 52.2 (CH_3), 54.8 (CH), 56.5 (CH_2), 58.5 (C), 60.5 (CH_2), 115.8 (CH), 119.5 (C), 120.7 (CH_2), 122.7 (C), 124.8 (CH), 125.4 (CH), 129.2 (CH), 132.4 (CH), 132.7 (C), 159.6 (C), 170.2 (C), 170.6 (C); IR, KBr (cm^{-1}) 2985, 2198, 1728, 1620, 1581, 1496, 1434, 1373, 1273, 1103, 1034, 764; HRMS-ESI (*m/z*) $[M + Na]^+$ Calcd for $C_{19}H_{21}N_3O_4Na$: 378.1430, Found: 378.1425.

Dihydroquinolines (12)

Diethyl 2-(isopropylamino)-4-(methoxycarbonylmethyl)quinoline-3,3(4*H*)-dicarboxylate (12f): Colorless oil; ^{1}H-NMR (500.0 MHz, $CDCl_3$) δ 1.02 (t, *J* = 7.1 Hz, 3H), 1.27 (d, *J* = 6.3 Hz, 3H), 1.28 (d, *J* = 6.3 Hz, 3H), 1.31 (t, *J* = 7.1 Hz, 3H), 2.41 (dd, *J* = 9.8 , 15.8 Hz, 1H), 2.58 (dd, *J* = 3.9, 15.8 Hz, 1H), 3.60 (s, 3H), 3.96–4.06 (m, 2H), 4.11 (dd, *J* = 3.9, 9.8 Hz, 1H), 4.24–4.35 (m, 2H), 4.36–4.43 (m, 1H), 6.42 (d, *J* = 6.9 Hz, 1H), 6.87 (dd, *J* = 7.4, 7.4 Hz, 1H), 7.03 (d, *J* = 7.8 Hz, 1H), 7.09–7.17 (m, 2H); ^{13}C-NMR (125.65 MHz, $CDCl_3$) δ 13.6 (CH_3), 13.8 (CH_3), 22.1 (CH_3), 22.6 (CH_3), 35.7 (CH_2), 39.3 (CH), 42.6 (CH), 51.6 (CH_3), 60.3 (C), 62.3 (CH_2), 62.8 (CH_2), 122.3 (CH), 123.6 (CH), 126.6 (C), 127.2 (CH), 128.2 (CH), 143.8 (C), 150.6 (C), 165.7 (C), 168.6 (C), 171.8 (C); IR, neat/NaCl (cm^{-1}) 3394, 3062, 2978, 2877, 1736, 1581, 1242, 1165; HRMS-ESI (*m/z*) $[M + H]^+$ Calcd for $C_{21}H_{29}N_2O_6$: 405.2020, Found: 405.2022.

Diethyl 2-(cyclohexylamino)-4-(methoxycarbonylmethyl)quinoline-3,3(4*H*)-dicarboxylate (12g): Colorless oil; ^{1}H-NMR (500.0 MHz, $CDCl_3$) δ 1.02 (t, *J* = 7.1 Hz, 3H), 1.24–1.35 (m, 3H), 1.32 (t, *J* = 7.2 Hz, 3H), 1.40–1.51 (m, 2H), 1.57–1.66 (m, 1H), 1.68–1.78 (m, 2H), 2.00–2.15 (m, 2H), 2.41 (dd, *J* = 9.9, 15.7 Hz, 1H), 2.57 (dd, *J* = 3.9, 15.7 Hz, 1H), 3.59 (s, 3H), 3.95–4.06 (m, 2H), 4.11 (dd, *J* = 3.9, 9.9 Hz, 1H), 4.12–4.18 (m, 1H), 4.23–4.35 (m, 2H), 6.55 (d, *J* = 7.2 Hz, 1H), 6.86 (dd, *J* = 7.4, 7.4 Hz, 1H), 7.02 (d, *J* = 7.8 Hz, 1H), 7.08–7.16 (m, 2H); ^{13}C-NMR (125.65 MHz, $CDCl_3$) δ 13.6 (CH_3), 13.8 (CH_3), 24.5 (CH_2 x2), 25.9 (CH_2), 32.1 (CH_2), 32.7 (CH_2), 35.7 (CH_2), 39.3 (CH), 49.0 (CH), 51.6 (CH_3), 60.3 (C), 62.3 (CH_2), 62.8 (CH_2), 122.3 (CH), 123.6 (CH), 126.6 (C), 127.2 (CH), 128.2 (CH), 143.9 (C), 150.6 (C), 165.7 (C), 168.6 (C), 171.8 (C); IR, neat/NaCl (cm^{-1}) 3386, 3062, 2978, 2931, 2854, 1743, 1612, 1581, 1234; HRMS-ESI (*m/z*) $[M + H]^+$ Calcd for $C_{24}H_{33}N_2O_6$: 445.2333, Found: 445.2336.

Diethyl 2-(*tert*-butylamino)-4-(methoxycarbonylmethyl)quinoline-3,3(4*H*)-dicarboxylate (12h): Colorless oil; ^{1}H-NMR (500.0 MHz, $CDCl_3$) δ 1.02 (t, *J* = 7.1 Hz, 3H), 1.31 (t, *J* = 7.2 Hz, 3H), 1.51 (s, 9H), 2.41 (dd, *J* = 10.0 Hz, 15.9 Hz, 1H), 2.63 (dd, *J* = 3.7, 15.9 Hz, 1H), 3.61 (s, 3H), 3.96–4.12 (m, 2H), 4.07 (dd, *J* = 3.7, 10.0 Hz, 1H), 4.22–4.34 (m, 2H), 6.34 (s, 1H), 6.85 (dd, *J* = 7.4, 7.4 Hz, 1H), 7.02 (d, *J* = 7.7 Hz, 1H), 7.09 (d, *J* = 7.4 Hz, 1H), 7.13 (dd, *J* = 7.7, 7.7 Hz, 1H); ^{13}C-NMR (125.65 MHz, $CDCl_3$) δ

13.6 (CH_3), 13.8 (CH_3), 28.6 (CH_3 x3), 35.8 (CH_2), 39.3 (CH), 51.6 (CH_3), 52.2 (C), 60.4 (C), 62.2 (CH_2), 62.7 (CH_2), 122.2 (CH), 123.8 (CH), 126.4 (C), 127.1 (CH), 128.1 (CH), 143.9 (C), 149.6 (C), 166.0 (C), 168.7 (C), 171.9 (C); IR, neat/NaCl (cm^{-1}) 3386, 3062, 2970, 1743, 1581, 1219, 1111; HRMS-ESI (*m/z*) $[M + Na]^+$ Calcd for $C_{22}H_{30}N_2O_6Na$: 441.1996, Found: 441.1994.

2-Aminoquinolines (8, **10**, and **14)**

Ethyl 2-(phenylamino)quinoline-3-carboxylate (8a): Yellow needles; mp 124–125 °C; ^{1}H-NMR (500.0 MHz, $CDCl_3$) δ 1.42 (t, *J* = 6.9 Hz, 3H), 4.38 (q, *J* = 6.9 Hz, 2H), 7.06 (dd, *J* = 7.4, 7.4 Hz, 1H), 7.29 (dd, *J* = 7.4, 7.4 Hz, 1H), 7.38 (dd, *J* = 7.8, 7.8 Hz, 2H), 7.66 (dd, *J* = 7.8, 7.8 Hz, 1H), 7.70 (d, *J* = 7.8 Hz, 1H), 7.80 (d, *J* = 7.8 Hz, 1H), 7.98 (d, *J* = 7.8 Hz, 2H), 8.65 (s, 1H), 10.29 (s, 1H, NH); ^{13}C-NMR (125.65 MHz, $CDCl_3$) δ 14.2 (CH_3), 61.6 (OCH_2), 110.5 (C), 119.9 (CH x2), 122.3 (CH), 122.3 (C), 123.2 (CH), 126.8 (CH), 128.7 (CH x2), 128.7 (C), 132.3 (C), 140.2 (C), 142.3 (CH), 149.6 (C), 152.5 (C), 167.1 (CO); IR, KBr (cm^{-1}) 3316, 3276, 2978, 1698; MS-EI (*m/z*) 292 [M^+, 91%], 291 [M^+ -H, 100%].

Ethyl 2-(4-methoxyphenylamino)quinoline-3-carboxylate (8c): Yellow crystals; mp 79.7–80.5 °C; ^{1}H-NMR (500.0 MHz, $CDCl_3$) δ 1.47 (t, *J* = 7.1 Hz, 3H), 3.83 (s, 3H), 4.45 (q, *J* = 7.1 Hz, 2H), 6.93 (d, *J* = 9.0 Hz, 2H), 7.25 (dd, *J* = 7.9, 7.9 Hz, 1H), 7.63 (dd, *J* = 7.8, 7.8 Hz, 1H), 7.67 (d, *J* = 7.9 Hz, 1H), 7.74 (d, *J* = 7.9 Hz, 1H), 7.85 (d, *J* = 9.0 Hz, 2H), 8.75 (s, 1H), 10.13 (s, 1H, NH); ^{13}C-NMR (125.65 MHz, $CDCl_3$) δ 14.3 (CH_3), 55.6 (CH_3), 61.6 (CH_2), 110.4 (C), 114.0 (CH x2), 121.8 (CH x2), 122.2 (C), 123.0 (CH), 126.7 (CH), 128.8 (CH), 132.4 (CH), 133.4 (C), 142.4 (CH), 149.9 (C), 152.8 (C), 155.2 (C), 167.2 (C); IR, KBr (cm^{-1}) 3309, 3271, 2978, 2931, 2839, 1689, 1604, 1211; HRMS-ESI (*m/z*) $[M + H]^+$ Calcd for $C_{19}H_{19}N_2O_3$: 322.1396, Found: 323.1392.

Ethyl 2-(benzylamino)quinoline-3-carboxylate (8d): Yellow oil; ^{1}H-NMR (500.0 MHz, $CDCl_3$) δ 1.42 (t, *J* = 7.1 Hz, 3H), 4.38 (q, *J* = 7.1 Hz, 2H), 4.87 (d, *J* = 5.2 Hz, 2H), 7.20 (dd, *J* = 7.3, 7.3 Hz, 1H), 7.24–7.28 (m, 1H), 7.34 (dd, *J* = 7.5, 7.5 Hz, 2H), 7.45 (d, *J* = 7.5 Hz, 2H), 7.58–7.70 (m, 3H), 8.29 (t, *J* = 5.2 Hz, 1H, NH), 8.67 (s, 1H); ^{13}C-NMR (125.65 MHz, $CDCl_3$) δ 14.3 (CH_3), 45.0 (CH_2), 61.2 (CH_2), 110.2 (C), 121.7 (C), 122.2 (CH), 126.3 (CH), 127.0 (CH), 127.9 (CH x2), 128.5 (CH x2), 129.0 (CH), 132.3 (CH), 139.7 (C), 142.3 (CH), 150.5 (C), 155.3 (C), 167.1 (C); IR, neat/NaCl (cm^{-1}) 3371, 3062, 3032, 2978, 2931, 2862, 1697, 1612, 1527, 1288; HRMS-ESI (*m/z*) $[M + H]^+$ Calcd for $C_{19}H_{19}N_2O_2$: 307.1441, Found: 307.1440.

Ethyl 2-(propylamino)quinoline-3-carboxylate (8e)[19]: ^{1}H-NMR (500.0 MHz, $CDCl_3$) δ 1.05 (t, *J* = 7.4 Hz, 3H), 1.44 (t, *J* = 7.1 Hz, 3H), 1.74 (qt, *J* = 7.4, 7.4 Hz, 2H), 3.57–3.63 (m, 2H), 4.40 (q, *J* = 7.1 Hz, 2H), 7.17 (dd, *J* = 7.9, 7.9 Hz, 1H), 7.58 (dd, *J* = 7.9, 7.9 Hz, 1H), 7.62 (d, *J* = 7.9 Hz, 1H), 7.64 (d, *J* = 7.9 Hz, 1H), 7.97 (brs, 1H, NH), 8.64 (s, 1H); IR, neat/NaCl (cm^{-1}) 3386, 3055, 2924, 1743, 1604, 1458; HRMS-ESI (*m/z*) $[M + H]^+$ Calcd for $C_{15}H_{19}N_2O_2$: 259.1441, Found: 259.1440.

Ethyl 2-(isopropylamino)quinoline-3-carboxylate (8f): Yellow oil; ^{1}H-NMR (500.0 MHz, $CDCl_3$) δ

1.32 (d, *J* = 6.4 Hz, 6H), 1.44 (t, *J* = 7.1 Hz, 3H), 4.39 (q, *J* = 7.1 Hz, 2H), 4.53 (septd, *J* = 6.3, 6.4 Hz, 1H), 7.16 (dd, *J* = 7.9, 7.9 Hz, 1H), 7.57 (dd, *J* = 7.9, 7.9 Hz, 1H), 7.60 (d, *J* = 7.9 Hz, 1H), 7.62 (d, *J* = 7.9 Hz, 1H), 7.83 (d, *J* = 6.3 Hz, 1H, NH), 8.62 (s, 1H); ^{13}C-NMR (125.65 MHz, $CDCl_3$) δ 14.3 (CH_3), 22.8 (CH_3 x2), 41.9 (CH), 61.1 (CH_2), 110.0 (C), 121.3 (C), 121.8 (CH), 126.2 (CH), 129.0 (CH), 132.2 (CH), 142.2 (CH), 150.8 (C), 154.9 (C), 167.2 (C); IR, neat/NaCl (cm^{-1}) 3371, 3055, 2970, 2931, 1697, 1527, 1288, 1203; HRMS-ESI (*m/z*) $[M + H]^+$ Calcd for $C_{15}H_{19}N_2O_2$: 259.1441, Found: 259.1439.

Ethyl 2-(cyclohexylamino)quinoline-3-carboxylate (8g): Yellow oil; ^{1}H-NMR (500.0 MHz, $CDCl_3$) δ 1.21–1.84 (m, 8H), 1.44 (t, *J* = 7.2 Hz, 3H), 2.04–2.18 (m, 2H), 4.23–4.33 (m, 1H), 4.39 (q, *J* = 7.2 Hz, 2H), 7.14 (dd, *J* = 7.6, 7.6 Hz, 1H), 7.56 (dd, *J* = 7.6, 7.6 Hz, 1H), 7.59 (d, *J* = 7.6 Hz, 1H), 7.62 (d, *J* = 7.6 Hz, 1H), 7.94 (d, *J* = 7.4 Hz, 1H, NH), 8.62 (s, 1H); ^{13}C-NMR (125.65 MHz, $CDCl_3$) δ 14.3 (CH_3), 24.8 (CH_2 x2), 26.0 (CH_2), 32.9 (CH_2 x2), 48.5 (CH), 61.1 (CH_2), 110.0 (C), 121.3 (C), 121.7 (CH), 126.1 (CH), 128.9 (CH), 132.2 (CH), 142.2 (CH), 150.8 (C), 154.9 (C), 167.2 (C); IR, neat/NaCl (cm^{-1}) 3371, 2931, 1697, 1527, 1458, 1288, 1203, 1072, 748; HRMS-ESI (*m/z*) $[M + H]^+$ Calcd for $C_{18}H_{23}N_2O_2$: 299.1760, Found: 299.1760.

Ethyl 2-(*tert*-butylamino)quinoline-3-carboxylate (8h): Yellow oil; ^{1}H-NMR (500.0 MHz, $CDCl_3$) δ 1.43 (t, *J* = 7.1 Hz, 3H), 1.58 (s, 9H), 4.38 (q, *J* = 7.1 Hz, 2 H), 7.15 (dd, *J* = 8.0, 8.0 Hz, 1H), 7.56 (dd, *J* = 8.0, 8.0 Hz, 1H), 7.59 (d, *J* = 8.0 Hz, 1H), 7.63 (d, *J* = 8.0 Hz, 1H), 7.98 (s, 1H, NH), 8.61 (s, 1H); ^{13}C-NMR (125.65 MHz, $CDCl_3$) δ 14.3 (CH_3), 29.0 (CH_3 x3), 51.4 (C), 61.1 (CH_2), 110.3 (C), 121.0 (C), 121.7 (CH), 126.4 (CH), 128.9 (CH), 132.0 (CH), 141.9 (CH), 150.3 (C), 155.0 (C), 167.4 (C); IR, neat/NaCl (cm^{-1}) 3363, 2962, 1697, 1535, 1403, 1365, 1288, 1203, 1080; HRMS-ESI (*m/z*) $[M + H]^+$ Calcd for $C_{16}H_{21}N_2O_2$: 273.1598, Found: 273.1597.

Ethyl 2-(prop-2-enylamino)quinoline-3-carboxylate (8i): Yellow oil; ^{1}H-NMR (300.0 MHz, $CDCl_3$) δ 1.44 (t, *J* = 7.1, 3H), 4.31 (dddd, *J* = 1.5, 1.7, 3.8, 5.4 Hz, 2H), 4.40 (q, *J* = 7.1 Hz, 2H), 5.17 (ddt, *J* = 1.5, 3.3, 10.2 Hz, 1H), 5.32 (ddt, *J* = 1.7, 3.3, 17.2 Hz, 1H), 6.08 (ddt, *J* = 5.4, 10.2, 17.2 Hz, 1H), 7.15–7.21 (m, 1H), 7.55–7.67 (m, 3H), 8.05 (t, *J* = 3.8 Hz, 1H), 8.65 (s, 1H); ^{13}C-NMR (75.45 MHz, $CDCl_3$) δ 14.3 (CH_3), 43.3 (CH_2), 61.2 (CH_2), 110.2 (C), 115.6 (CH_2), 121,6 (C), 122.2 (CH), 126.2 (CH), 129.0 (CH), 132.3 (CH), 135.3 (CH), 142.2 (CH), 150.5 (C), 155.3 (C), 167.1 (C); IR, neat/NaCl (cm^{-1}) 3379, 2924, 2854, 1728, 1697, 1535, 1458, 1288, 1088, 1026, 802; HRMS-ESI (*m/z*) $[M + H]^+$ Calcd for $C_{15}H_{17}N_2O_2$: 257.1290, Found: 257.1285.

2-(Isopropylamino)quinoline-3-carbonitrile (10e): Yellow oil; ^{1}H-NMR (300.0 MHz, $CDCl_3$) δ 1.32 (d, *J* = 6.5 Hz, 6H), 4.51 (sept, *J* = 6.5 Hz, 1H), 5.05 (s, 1H, NH), 7.16 (dd, *J* = 7.9, 7.9 Hz, 1H), 7.51–7.71 (m, 3H), 8.21 (s, 1H); ^{13}C-NMR (150.9 MHz, $CDCl_3$) δ 22.7 (CH_3 x2), 42.9 (CH), 95.8 (C), 116.6 (C), 121.0 (C), 123.2 (CH), 126.9 (CH), 128.1 (CH), 132.8 (CH), 143.8 (CH), 149.6 (C), 153.2 (C); IR, neat/NaCl (cm^{-1}) 3425, 3055, 2970, 2222, 1620, 1527, 1203, 756; HRMS-ESI (*m/z*) $[M + H]^+$ Calcd for

$C_{13}H_{14}N_3$: 212.1182, Found: 212.1179.

2-(*tert*-Butylamino)quinoline-3-carbonitrile (10h): Yellow crystals; mp 124.9–125.3 °C; ^{1}H-NMR (500.0 MHz, $CDCl_3$) δ 1.58 (s, 9H), 5.12 (s, 1H, NH), 7.24 (dd, *J* = 8.0, 8.0 Hz, 1H), 7.56 (d, *J* = 8.0 Hz, 1H), 7.61 (dd, *J* = 8.0, 8.0 Hz, 1H), 7.68 (d, *J* = 8.0 Hz, 1H), 8.16 (s, 1H); ^{13}C-NMR (125.65 MHz, $CDCl_3$) δ 28.9 (CH_3 x3), 52.6 (C), 96.3 (C), 116.7 (C), 120.6 (C), 123.1 (CH), 127.2 (CH), 127.9 (CH), 132.5 (CH), 143.4 (CH), 149.1 (C), 153.2 (C); IR, KBr (cm^{-1}) 3416, 2912, 2200, 1602, 1512, 1408, 1354, 1198, 750; HRMS-EI (*m/z*) Calcd for $C_{14}H_{15}N_3$: 225.1266, Found: 225.1259.

3-Acetyl-2-(*tert*-butylamino)quinoline (14h): Yellow crystals; mp 128.3–129.1 °C; ^{1}H-NMR (270.0 MHz, $CDCl_3$) δ 1.58 (s, 9H), 2.67 (s, 3H), 7.11–7.16 (m, 1H), 7.53–7.62 (m, 3H), 8.41 (s, 1H), 8.63 (s, 1H); ^{13}C-NMR (67.80 MHz, $CDCl_3$) δ 27.7 (CH_3), 29.0 (CH_3 x3), 51.4 (C), 116.8 (C), 120.7 (C), 121.8 (CH), 126.4 (CH), 129.0 (CH), 132.5 (CH), 143.0 (CH), 150.5 (C), 154.7 (C), 200.2 (C); IR, KBr (cm^{-1}) 3264, 3052, 2948, 1652, 1572, 1536, 1446, 1378, 1346, 1270, 1190, 1138, 908, 728; HRMS-EI (*m/z*) Calcd for $C_{15}H_{18}N_2O$: 242.1419, Found: 242.1420; Anal. Calcd for $C_{15}H_{18}N_2O$: C, 74.35; H, 7.49; N, 11.56. Found: C, 73.99; H, 7.60; N, 11.28.

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