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One-Pot Tandem Assembly of Amides, Amines, and Ketones: Synthesis of C4-Quaternary 3,4- and 1,4-Dihydroquinazolines

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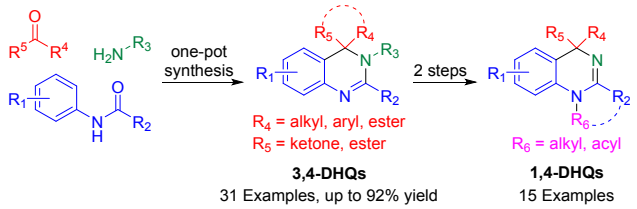


ABSTRACT: A multicomponent tandem assembly procedure for the synthesis of diverse C4-quaternary 3,4-dihydroquinazolines from amides, amines, and ketones has been developed. The one-pot reaction involves successive triflic anhydride mediated amide dehydration, ketimine addition, and Pictet-Spengler-like cyclization processes and affords products in up to 92% yield. Conversion of 3,4-dihydroquinazolines to the corresponding 1,4-dihydroquinazolines via a two-step N1 dealkylation and regioselective N3 functionalization protocol, including computational rationale for the observed regioselectivity, is also described.

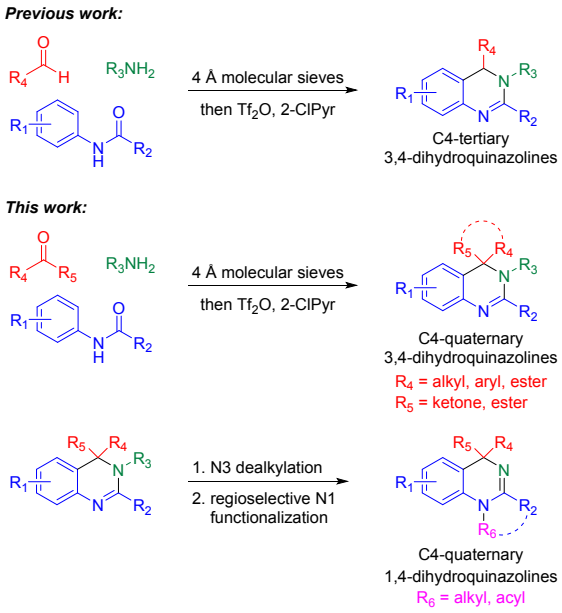
INTRODUCTION

Dihydroquinazolines (DHQs) are amidine-containing heterocycles found in natural products and in compounds of medicinal importance.[1] The DHQ motif exists in two forms which differ in the sites of saturation about the heterocyclic ring (e.g. the 1,4- and 3,4-dihydro forms), and in the absence of a substituent on one of the ring nitrogens, DHQ compounds may be found in both forms at equilibrium. The majority of known *N*-substituted DHQ syntheses focus on the production of compounds with a tertiary C4 center, the sole sp^3 hybridized carbon present in the scaffold. The synthesis of *N*-substituted DHQs bearing quaternary C4 centers has been much less explored, with literature reports of quaternary 1,4-DHQ scaffolds being particularly scant. Pioneering methods of *N*-substituted quaternary DHQ synthesis involved transformation of quinazolines via treatment with alkyl halides following metal-mediated quinazolinide anion generation to afford mixtures of 1,4- and 3,4-DHQs.[2] Alternatively, quaternary 3,4-DHQs have

been constructed from the corresponding tertiary counterparts through alkylation of select acidic substrates following deprotonation with NaH.[3] Other examples of quaternary 3,4-DHQ synthesis include addition of nitriles to functionalized hydroxymethylanilines in the presence of acids,[4] intramolecular attack of amidines onto tethered alkenes,[5] and Ugi multicomponent assembly,[6] among others.[7] A recent focus of quaternary DHQ synthesis has been for the construction of natural products hinckdentine A[8] and trigonoliimines A and B.[9] The quaternary 3,4-DHQ scaffold present in these alkaloids has been synthesized via intramolecular condensation reactions of aminomethylanilines bearing preassembled quaternary centers,[10] oxidation of tetrahydroquinazolines,[11] or Strecker assembly from o-ketoformanilides.[12] Separate methods have arisen for the synthesis of related DHQs bearing an additional heteroatom at the C4 center.[13]

Previously we reported the synthesis of 3,4-DHQs through a triflic anhydride-mediated tandem assembly process involving a key Pictet-Spengler-like annulation step (Scheme 1).[14] The reaction involved *in situ* generation of imines from aldehydes and amines, after which the imine became incorporated into the heterocyclic scaffold, with the starting aldehyde's carbon bulk making up the newly formed DHQ C4 carbon and its attached substituent (i.e. R_4). Whereas the use of imines in the reaction afforded compounds with tertiary C4 centers, an analogous reaction involving the installation of ketimines[15] would instead give rise to C4-quaternary 3,4-DHQs. Challenges for such a reaction were envisioned to mirror those of traditional Pictet-Spengler methods of quaternary center formation, namely difficulty in both the formation of ketiminium reaction intermediates and in cyclization to generate the new heterocyclic rings due to enhanced steric bulk and reduced electrophilicity of ketimines relative to imines.[16] However, overcoming these challenges would permit direct access to diverse quaternary members of this compound class. Herein we report a one-pot multicomponent synthesis of C4-quaternary 3,4-DHQs as well as selective conversion of 3,4-DHQs to the corresponding 1,4-DHQs.

Scheme 1. Synthesis of 3,4-DHQs and 1,4-DHQs



RESULTS AND DISCUSSION

The proposed synthesis of C4-quaternary 3,4-DHQs through a multicomponent tandem approach involved *in situ* ketimine generation from a ketone and an amine (Scheme 2). The reaction was anticipated to proceed via addition of the ketimine to an amide-derived reactive species such as **1a** or **1b** to form a ketiminium intermediate (e.g. **1c**), which would then undergo Pictet-Spengler-like cyclization to afford the quaternary product (e.g. **2**). Conditions developed by Movassaghi[17, 18] for the synthesis of aromatic heterocycles were selected to facilitate the conversion of amides to reactive pyridinium[18] (e.g. **1a**) and nitrilium[19] (e.g. **1b**) species through treatment with Tf_2O and a pyridine base. Ethyl benzoylformate was chosen as a ketone to test the proposed synthesis, as the ketone not only exhibits high electrophilicity required for ketimine formation, but it also contains an ester which would act as a useful reactive handle once incorporated into the DHQ scaffold. Initially, conditions similar to those previously used for the synthesis of 3,4-DHQs from aldehydes were investigated.[14] A mixture of amide **1**, benzylamine, and ethyl benzoylformate was stirred with molecular sieves in CH_2Cl_2 for 18 hours at room temperature followed by treatment with 2-chloropyridine (2-ClPyr) and Tf_2O at -41 °C. After warming to room temperature, the reaction stirred for an additional 24 hours to afford quaternary compound **2** in 72% yield (Table 1, entry 1).[20] The reaction yield was unchanged when 2-ClPyr and Tf_2O were instead added at -78 °C (entry 2). Variations in the pyridine base, including omission of a base (entries 3-8), revealed 2-fluoropyridine (2-FPyr) to provide higher yields of **2** (entry 3). The use of 2-FPyr with Tf_2O during amide dehydration is known to result in nitrilium formation (e.g. **1b**, Scheme 2),[19,21] which would presumably allow

for better access of the ketimine to initiate nucleophilic addition. Modifications to the solvent type did not increase reaction yield (entries 9 – 11), but changes in solvent volumes did have a measurable effect on the reaction outcome (entries 3, 12 - 14). As a general trend, reaction yields increased with increasing concentration of the amide so long as the amide was visibly soluble. The highest tested concentration where the amide was observed to be fully soluble resulted in 86% yield of **2** (entry 13), whereas a more concentrated reaction gave a lower product yield (entry 14). Interestingly, a similar product yield was observed when the base was exchanged with 2-ClPyr (entry 15) at the optimal reaction concentration, indicating generation of the nitrilium intermediate is not as crucial for high reaction yields when the rate of the bimolecular ketimine addition step is increased through solvent volume reduction. Lastly, increasing the reaction time following amide dehydration was not found to alter reaction yields (entry 16).

Scheme 2. C4-Quaternary 3,4-DHQ Tandem Assembly

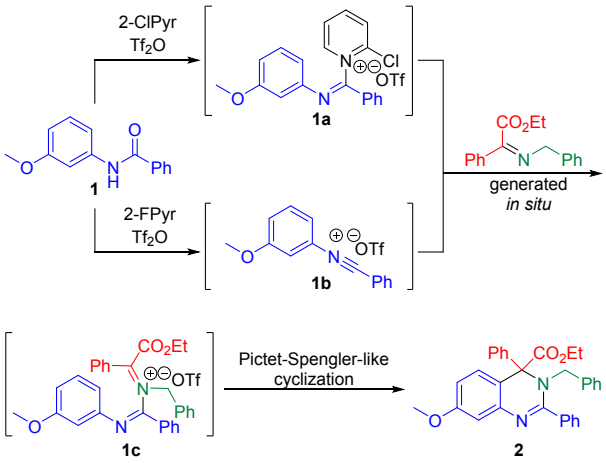
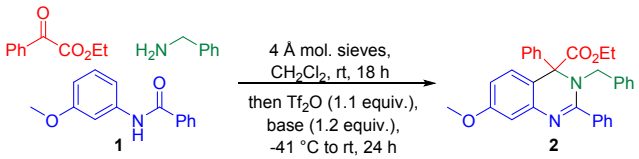


Table 1. Optimization of Reaction Conditions[a]



1 **2**

entry	base	solvent	conc. (M)[b]	yield (%)[c]
1	2-Chloropyridine	DCM	0.05	72
2[d]	2-Chloropyridine	DCM	0.05	72
3	2-Fluoropyridine	DCM	0.05	77
4	2,6-Dichloropyridine	DCM	0.05	50
5	Pentafluoropyridine	DCM	0.05	30
6	2-Methoxypyridine	DCM	0.05	71
7	Pyridine	DCM	0.05	46
8	None	DCM	0.05	41
9	2-Fluoropyridine	DCE	0.05	49
10	2-Fluoropyridine	$CHCl_3$	0.05	44
11	2-Fluoropyridine	toluene	0.05	61
12	2-Fluoropyridine	DCM	0.02	62
13	2-Fluoropyridine	DCM	0.20	86 (84)[e]
14	2-Fluoropyridine	DCM	0.50	64
15	**2-Chloropyridine**	**DCM**	**0.20**	**87 (85)[e]**
16[f]	2-Chloropyridine	DCM	0.20	86 (85)[e]

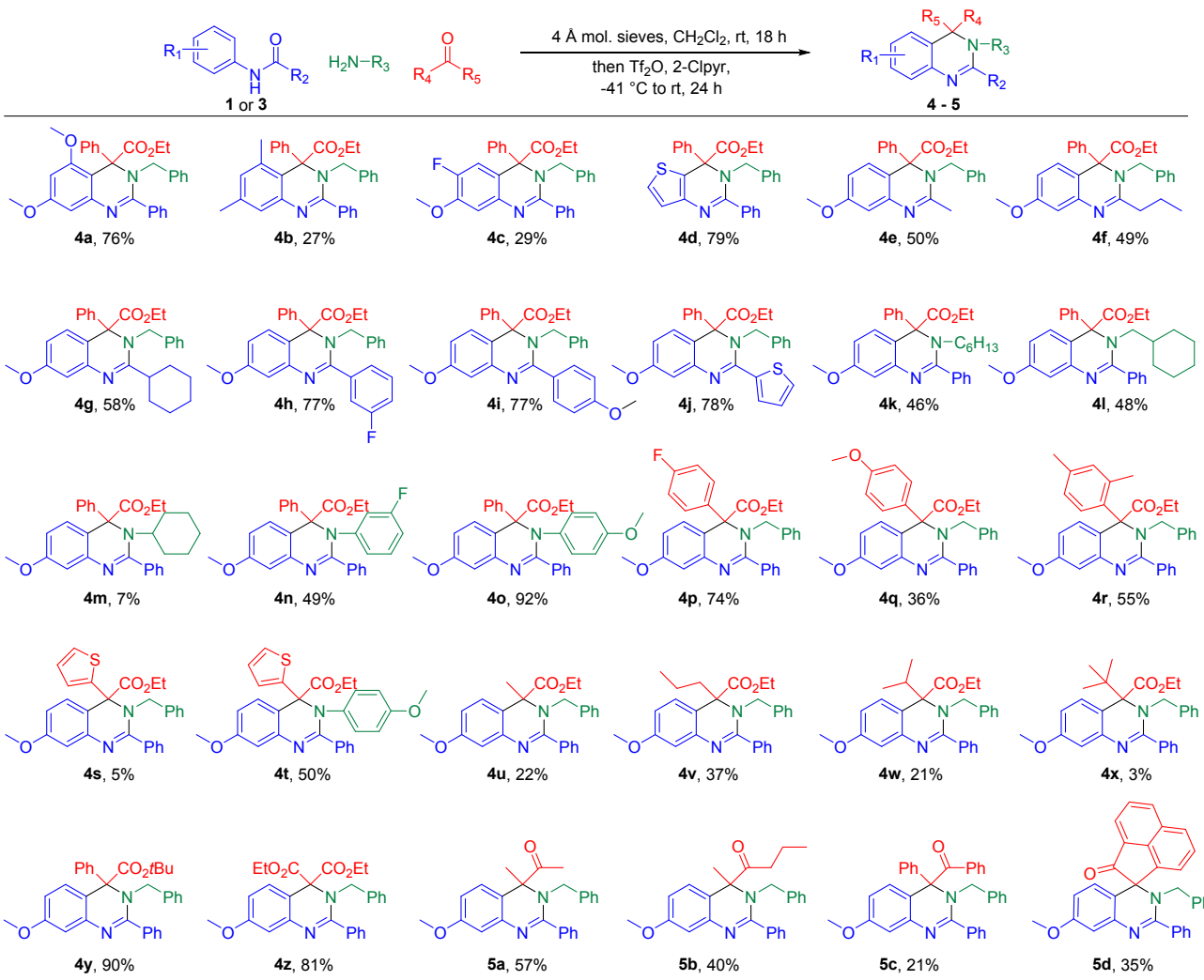
[a]Conditions: **1** (1.0 mmol), benzylamine (1.1 mmol), ethyl benzoylformate (1.1 mmol), 4 Å mol. sieves (1.0 g), CH_2Cl_2, rt, 18 hr; then base (1.2 mmol), Tf_2O (1.1 mmol), -41 °C; then rt, 24 h. [b]Amide concentration. [c]NMR yield with 1,3,5-trimethoxybenzene as internal standard. [d]Base and Tf_2O added at -78 °C. [e]Isolated yield. [f]48 h for final step.

With optimal reaction conditions identified, the reaction scope was then explored (Table 2). First, variations about the nucleophilic anilide portion of the starting amides were investigated. Higher yields were observed when using amides bearing electron rich anilides compared with electron poor anilides (compare **2** and **4a** to **4c**), a finding which aligns with prior observations that Pictet-Spengler-like cyclization is promoted by increases in electron density about the nucleophilic anilide ring.[14] However, increases in electron density through incorporation of groups that also added to steric bulk were found to negatively impact ring formation. The incorporation of a second methoxy group onto the starting anilide ring in the meta position provided a lower yield than if only a single meta-methoxy group was present (**4a** vs **2**). Likewise, the use of an amide with a 3,5-dimethyl anilide ring provided **4b** in only 27% yield. In general, incorporation of bulky groups about the heterocyclic scaffold which interact with the newly forming quaternary center led to lower reaction yields. Replacement of the anilide ring with the nucleophilic thiophene ring was also performed to afford heterocycle **4d** in good yields. The acyl portion of the amide was then varied (e.g. R_2) to demonstrate alkyl

(e.g. **4e** – **4g**) and aryl (e.g. **4h** – **4j**) group installation at this position. While all tested amide variants were converted to corresponding products, aromatic amides provided higher yields than the alkyl counterparts. Modulation of the amine component was also conducted, revealing that a range of alkyl and aryl amines are compatible with the reaction (e.g. **4k** – **4o**). However, the proximity of the nitrogen atom and its carbon bulk to the new quaternary center in the heterocyclic system makes it susceptible to steric effects, such that the use of a bulky amine like cyclohexylamine (e.g. **4m**) provides a low product yield.

Next, the ketone component was investigated (Table 2). First, different aryl keto esters were evaluated in the reaction (e.g. **4p** – **4r**). Electron deficient aryl groups were found to promote the reaction compared to electron rich arenes (e.g. **4p** vs **4q** and **4r**), with the enhancement of **4p** formation likely occurring due to increased electrophilicity of the Pictet-Spengler annulation precursor (e.g. **1c**, scheme 2). Replacement of the aryl group with a heteroaromatic thiophene ring resulted in the formation of **4s**, although the product was formed in a much lower yield than when using the aromatic counterparts. However, the quaternary center bearing the thiophene was installed in much higher yield when the amine component was changed to *p*-anisidine (e.g. PMP group in **4t**). Alkyl keto esters were also successfully used in the reaction (e.g. **4u** – **4x**), whereby reaction yields were observed to degrade as bulkiness of the alkyl group increased. Interestingly, incorporation of a *tert*-butyl ester (e.g. **4y**) had no negative effect on reaction yield, indicating that the bulky alkoxy group remains distal to reactive sites during the tandem assembly processes. Lastly, dual ester functionalities were readily installed from the use of a keto diester (e.g. **4z**). In addition to keto esters, the reaction was also found to tolerate diketones (e.g. **5a** – **5d**). Addition of alkyl diketones 2,3-butanedione and 2,3-hexanedione provided the corresponding DHQs bearing an alkyl group and a ketone at the quaternary center in moderate yields (e.g. **5a** and **5b**, respectively). Interestingly, while two possible regioisomer products were predicted to arise from the use of 2,3-hexanedione, the only product observed was that formed from ketimine generation at the more sterically accessible C2 carbonyl.[22] Aromatic functionalities were also installed at the quaternary center via treatment with benzil (e.g. **5c**) and with acenaphthoquinone (e.g. **5d**), the latter of which resulted in the formation of a *spiro* ring junction.

Table 2. Synthesis of Diverse C4-Quaternary 3,4-DHQs

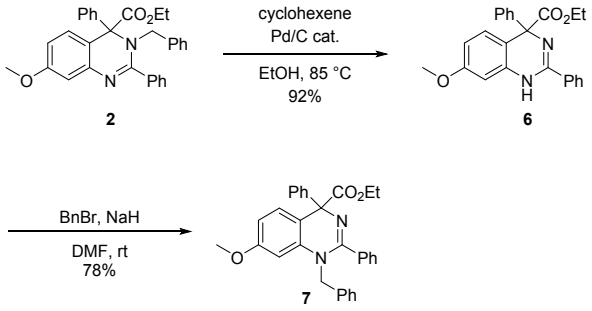


[a]Conditions: amide **1** or **3** (1.0 mmol), amine (1.1 mmol), ketone (1.1 mmol), 4 Å mol. sieves (1.0 g), CH_2Cl_2 (5.0 mL), rt, 18 h; then 2-ClPyr (1.2 mmol), Tf_2O (1.1 mmol), -41 °C; then rt, 24 h. Isolated yield.

Once the scope of the quaternary 3,4-DHQ synthesis had been explored, attention was turned towards the synthesis of 1,4-DHQs. Limited reports involving N1 functionalization of *N*-unsubstituted C4-quaternary DHQs describe alkylation through treatment with methyl iodide[23] and dimethyl sulfate.[4a, 24] In these studies, alkylation was performed with an excess of the alkylating agent, resulting in mixtures of N1 alkylation, N3 alkylation, and dialkylation. We sought to convert 3,4-DHQs prepared in our studies to the corresponding 1,4-DHQs via N3 dealkylation and subsequent N1 alkylation as a means of both accessing diverse 1,4-DHQs and for determining conditions which might afford regioselectivity during alkylation. To this end, compound **2** was selected to undergo transformation through

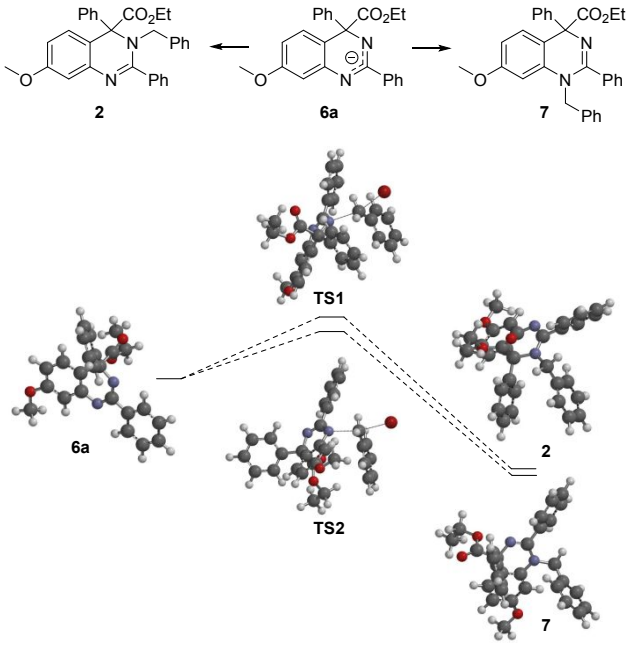
removal of the N3-benzyl substituent followed by alkylation with a benzyl halide (Scheme 3). The two-step reaction sequence was anticipated to afford **7**, the N1-benzyl regioisomer of **2**, and selectivity of the alkylation reaction was to be measured by observing the product ratio of **7** to **2**, resulting from N1 and N3 alkylation, respectively. The benzyl group was readily removed from **2** via hydrogenation to afford **6** in high yield. Alkylation of **6** with benzyl bromide after deprotonation with NaH then provided 1,4-DHQ **7** in 78% yield[20] without any of **2** being observed.

Scheme 3. Conversion of 3,4-DHQs to 1,4-DHQs



The alkylation of **6** with benzyl bromide was modelled in order to better understand the observed reaction regioselectivity (Scheme 4). The reaction involves initial deprotonation of **6** with NaH to generate anion **6a**; the approach of the alkyl halide towards the anion leads to transition states **TS1** and **TS2** in which the alkyl halide initiates bond formation with the N3 and N1 positions, respectively. DFT calculations of all compounds and transition states in DMF solution were performed at EDF2/6-31G* level of theory without symmetry constraints under SM8 continuum solvation model using Spartan'18 (Wavefunction, Inc.) software suite. Under this level of theory, both **2** and **7** were calculated to form exothermically (-105 and -113 kJ/mol, respectively) from the alkylation of **6a**. Interestingly, an activation energy of 72 kJ/mol in DMF was required to reach **TS1**, the transition state leading to **2**, whereas a lower activation energy of 55 kJ/mol in DMF was required to attain **TS2** en route to **7**. The difference of 17 kJ/mol between the corresponding transition states indicates the lower activation energy of **TS2** as the probable driving force for selective N1 alkylation of **6a**. Similar results of calculations were obtained for methyl iodide addition (C-PCM model, the activation energy difference of 11 kJ/mol favoring the N1-methyl analog of **7**),[25] whereas the addition of methyl bromide, based on the calculated data, should lead to a lower selectivity due to a smaller difference of the activation energies (4 kJ/mol). The computational data suggests functionalization of deprotonated quaternary DHQs should occur regioselectively at the N1 position through treatment with electrophiles of varying sizes.

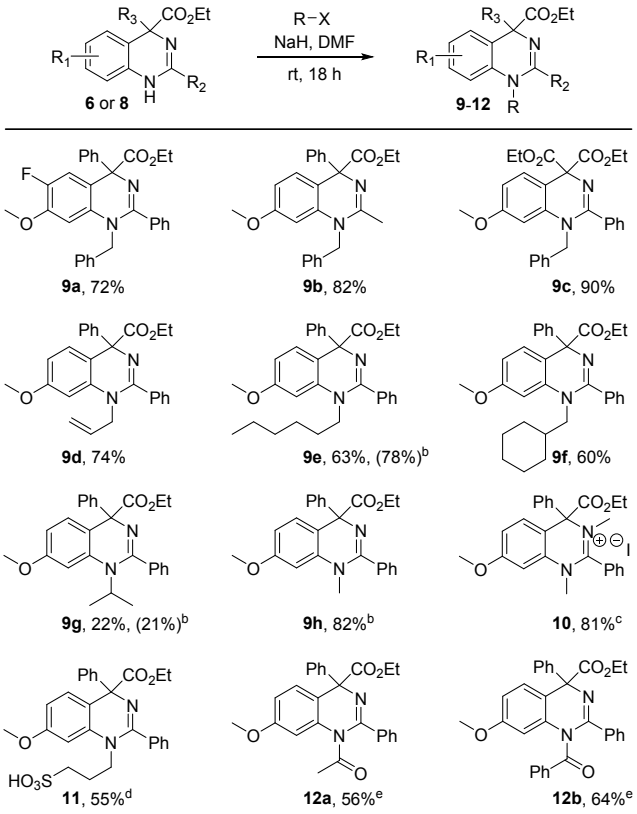
Scheme 4. Computational Rationale for Regioselective Alkylation



To explore the scope of 1,4-DHQ synthesis via regioselective functionalization, reactions involving combinations of various DHQs and electrophiles were investigated (Table 3). First, 3,4-DHQs **4c**, **4e**, and **4z**, which differ in the substituents installed around the parent scaffold, were subjected to hydrogenation conditions to afford the corresponding N3-dealkylated compounds (e.g. **8a** – **c**, respectively). Subsequently, each was treated with NaH and a slight excess of benzyl bromide (1.3 equivalents) to afford the anticipated N1-benzylated products in high yields (**9a** – **9c**). Next, the use of different alkyl halides was explored. Treatment of **6** with allyl bromide provided **9d** in 72% yield. Less reactive alkyl halides also resulted in formation of 1,4-DHQs, albeit in lower yields. A hexyl group was introduced through the use of 1-bromohexane to generate 63% of **9e**, while the cyclohexylmethyl group was installed in 60% yield (e.g. **9f**). The yield of **9e** was increased to 78% when 1.0 equivalent of 1-iodohexane was used, while a loss of yield was observed with the use of superstoichiometric amounts of the iodoalkane, presumably due to overalkylation. Conversely, treatment with the less reactive 1-chlorohexane resulted in formation of **9e** in less than 10% yield. Treatment with bulkier secondary alkyl halides 2-bromopropane and 2-iodopropane afforded **9g** in similar yields, which were lower than when using primary alkyl halides. Synthesis of N1-monomethylated product **9h**[22] in 82% yield was accomplished cleanly via treatment with 1.0 equivalent of methyl iodide with no N3-alkylated regioisomer being observed, a finding in agreement with the abovementioned computational data. Moreover, the use

of excess methyl iodide (3 equivalents) primarily afforded dialkylated dihydroquinazolinium salt **10**. In addition to alkyl halides, the use of electrophilic 1,3-propanesultone was also examined under the reaction conditions, leading to the generation of sulfonic acid **11** in 55% yield. Finally, acylation was performed through treatment with acid anhydrides or acid chlorides to generate N1-acylated products in moderate yields (e.g. **12a**[22] and **12b**).

Table 3. Scope of 1,4-DHQ Synthesis[a]

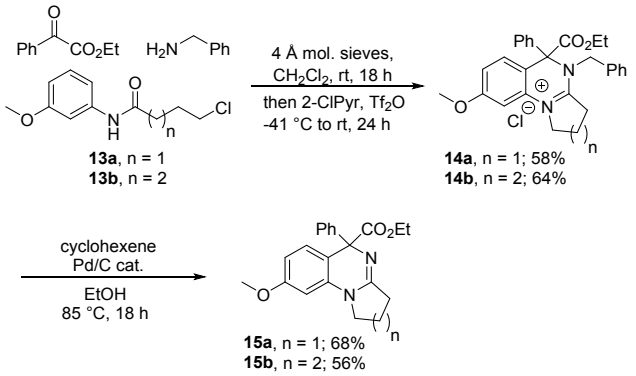


[a]Conditions: **6** or **8** (1.0 equiv.), NaH (1.2 equiv.), DMF, 0 °C, 30 min; then alkyl bromide (1.3 equiv.), rt, 18 h. Isolated yield. [b]Alkyl iodide (1.0 equiv.) used. [c]Methyl iodide (3.0 equiv.) used. [d]1,3-Propanesultone (2.0 equiv.) used instead of alkyl halide. [e]Acid chloride or acid anhydride (1.1 equiv.) used instead of alkyl halide.

Further exploration of quaternary 1,4-DHQ synthesis involved the installation of new fused rings about the N1-C2 portion of the scaffold (Scheme 5). Such ring systems were postulated to arise from tethered electrophiles at the C2 position that would undergo substitution by the N1 atom. Amides **13a** and **13b**, each bearing a chloroalkyl chain were constructed to test this hypothesis. The use of each in multicomponent 3,4-DHQ syntheses with ethyl benzoylformate

and benzylamine led to the assembly of multicyclic complexes **14a** and **14b** in which the halogen had been expelled via intramolecular cyclization. Whereas prior use of chloroalkyl electrophiles for intermolecular substitution was largely unsuccessful, providing low yields of 1,4-DHQs, the intramolecular substitution reactions worked very well. Removal of the N3-benzyl substituents via hydrogenation then afforded multicyclic adducts **15a** and **15b**, in which new 5 and 6 membered rings were incorporated, respectively.

Scheme 5. Synthesis of Fused Tricyclic 1,4-DHQs



CONCLUSIONS

In conclusion, we have developed an efficient one-pot procedure for the synthesis of C4-quaternary 3,4-DHQs via a Tf_2O-mediated tandem assembly of amides, amines, and ketones. We have also demonstrated conversion of 3,4-DHQs to 1,4-DHQs through a two-step procedure involving N3 dealkylation followed by regioselective N1 alkylation and acylation. The diverse functionalities installed about the ring systems through this chemistry are amenable to further synthetic manipulation, allowing for even greater future diversity about this heterocyclic scaffold.

EXPERIMENTAL SECTION

General Experimental Information. Reactions were carried out in flame-dried glassware under nitrogen atmosphere. All reactions were magnetically stirred and monitored by TLC on EMD Millipore silica gel $60F_{254}$ pre-coated glass plates using UV light (254 nm) to visualize the compounds. Column chromatography was carried out on SiliaFlash P60 (230 – 400 mesh) silica gel supplied by SiliCycle or on a Yamazen AKROS MPLC system using silica gel

columns supplied by Yamazen Corporation. Infrared spectra were recorded on an Agilent Technologies Cary 630 FT-IR spectrometer. Proton (^{1}H NMR) and carbon (^{13}C NMR) nuclear magnetic resonance spectra were recorded on a Bruker Avance III 400 MHz spectrometer. The chemical shifts are given in parts per million (ppm) on the delta (δ) scale. Tetramethylsilane (TMS) or the residual solvent peak was used as a reference value. High resolution mass spectra were recorded at the LSSU Cannabis Center of Excellence on an Agilent 1290 Ultra-High Pressure Liquid Chromatograph with a Time of Flight Mass Spectrometer (UHPLC-TOF). Melting points were obtained using a Mel-Temp capillary melting point apparatus and are uncorrected. 2-Chloropyridine and 2-fluoropyridine were dried over 4 Å molecular sieves; all other solvents and chemicals were purchased from commercial vendors and were used without additional purification. Amides **1**, **3a-e**, and **3h-j** were prepared as previously reported.[14]

General procedure for amide synthesis. To a mixture of an amine and triethylamine (TEA) in CH_2Cl_2, cooled to 0 °C in an ice bath, was added dropwise an appropriate acid chloride followed by 4-DMAP. The ice bath was removed, and the reaction stirred at room temperature under N_2 atmosphere for 18 h. The reaction mixture was washed with saturated $NaHCO_3$ solution (x3) and brine before being dried (Na_2SO_4) and concentrated. The crude product was then purified either by crystallization or chromatography.

General procedure for 3,4-DHQ synthesis: A mixture of amide, amine, aldehyde, and 4 Å molecular sieves (~1 g per mmol of amide) in CH_2Cl_2 was prepared and stirred for 18 h at room temperature under N_2 atmosphere. The reaction mixture was cooled to -41 °C in an acetonitrile/dry ice bath and was treated successively with 2-chloropyridine followed by Tf_2O. The reaction was then allowed to warm to room temperature and was stirred for 24 h. The molecular sieves were filtered from the reaction, and the filtrate was washed with saturated aqueous $NaHCO_3$ solution before being dried (Na_2SO_4) and concentrated. The crude mixture was then purified via chromatography.

General procedure for 3,4-DHQ debenzylation: To a mixture of 3,4-DHQ in EtOH and cyclohexene was added 10% Pd/C, and the reaction was heated to 85 °C in a sealed vial set in an aluminum block heater for 18 h. The mixture was cooled to room temperature and passed through a celite plug with EtOAc. The filtrate was concentrated, and the residue was purified via trituration or chromatography.

General procedure for 1,4-DHQ synthesis: To a suspension of NaH (60% dispersion in mineral oil) in DMF, cooled to 0 °C in an ice bath, was added *N*-unsubstituted 3,4-DHQ. The reaction stirred at 0 °C for 30 minutes before an alkyl halide or acid anhydride was added. The ice bath was removed, and the reaction was stirred at room temperature

for 18 h. The reaction was cooled in an ice bath and aqueous saturated $NaHCO_3$ solution was added. The mixture was extracted with CH_2Cl_2 (x3), and the pooled extracts were dried (Na_2SO_4) and concentrated. The remaining DMF was removed azeotropically *in vacuo* with toluene, and the resulting residue was purified by chromatography.

Ethyl 3-benzyl-7-methoxy-2,4-diphenyl-3,4-dihydroquinazoline-4-carboxylate (2). Prepared according to the general 3,4-DHQ synthesis protocol with **1** (0.227 g, 1.00 mmol), benzylamine (0.12 mL, 1.1 mmol), ethyl benzoylformate (0.18 g, 1.1 mmol), CH_2Cl_2 (5.0 mL), 2-chloropyridine (0.11 mL, 1.2 mmol), and Tf_2O (0.18 mL, 1.1 mmol). Following workup, the residue was purified by MPLC (0% - 1% MeOH in 95:5 CH_2Cl_2:ether as eluent) to afford the desired product (0.403 g, 85%) as a solid (m.p. = 133 - 136 °C). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60 – 7.47 (m, 2H), 7.40 – 7.30 (m, 2H), 7.26 – 7.16 (m, 3H), 7.20 – 7.09 (m, 3H), 6.98 – 6.86 (m, 3H), 6.85 (d, J = 2.0 Hz, 1H), 6.73 (d, J = 8.7 Hz, 1H), 6.64 – 6.51 (m, 3H), 4.83 (d, J = 17.0 Hz, 1H), 4.40 – 4.14 (m, 2H), 4.01 (d, J = 17.0 Hz, 1H), 3.73 (s, 3H), 1.21 (t, J = 7.1 Hz, 3H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 172.2, 160.2, 159.4, 143.3, 139.6, 138.8, 137.6, 130.5, 130.4, 128.5, 128.4, 128.0, 127.71, 127.65, 127.5, 126.02, 126.00, 118.6, 111.9, 107.4, 74.2, 62.1, 55.1, 52.0, 14.1; IR (neat): 3060, 2928, 1730, 1552, 1489, 1219, 1031 cm^{-1}; HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{31}H_{29}N_2O_3$ 477.2178; Found 477.2162.

Ethyl 3-benzyl-5,7-dimethoxy-2,4-diphenyl-3,4-dihydroquinazoline-4-carboxylate (4a). Prepared according to the general 3,4-DHQ synthesis protocol with **3a** (0.257 g, 1.00 mmol), benzylamine (0.12 mL, 1.1 mmol), ethyl benzoylformate (0.18 g, 1.1 mmol), CH_2Cl_2 (5.0 mL), 2-chloropyridine (0.11 mL, 1.2 mmol), and Tf_2O (0.18 mL, 1.1 mmol). Following workup, the residue was purified by MPLC (0% - 1% MeOH in 95:5 CH_2Cl_2:ether as eluent) to afford the desired product (0.383 g, 76%) as a solid (m.p. = 101 - 104 °C). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75 – 7.67 (m, 2H), 7.36 – 7.27 (m, 4H), 7.28 – 7.16 (m, 4H), 7.11 – 7.02 (m, 3H), 6.94 (d, J = 7.9 Hz, 2H), 6.55 (d, J = 2.4 Hz, 1H), 6.19 (d, J = 2.4 Hz, 1H), 4.62 (d, J = 17.4 Hz, 1H), 4.41 (d, J = 17.4 Hz, 1H), 3.96 (dq, J = 10.8, 7.1 Hz, 1H), 3.76 (s, 3H), 3.58 (dq, J = 10.8, 7.1 Hz, 1H), 3.54 (s, 3H), 1.05 (t, J = 7.2 Hz, 3H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 170.1, 160.6, 158.4, 155.8, 142.11, 142.07, 138.0, 136.8, 128.7, 128.1, 127.8, 127.7, 127.6, 127.5, 127.4, 126.5, 126.3, 108.1, 101.1, 96.8, 69.5, 61.4, 55.3, 55.2, 52.1, 13.7; IR (neat): 3058, 2935, 1735, 1597, 1552, 1213, 1150, 1042 cm^{-1}; HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{32}H_{31}N_2O_4$ 507.2284; Found 507.2282.

Ethyl 3-benzyl-5,7-dimethyl-2,4-diphenyl-3,4-dihydroquinazoline-4-carboxylate (4b). Prepared according to the general 3,4-DHQ synthesis protocol with **3b** (0.225 g, 1.00 mmol), benzylamine (0.12 mL, 1.1 mmol), ethyl benzoylformate (0.18 g, 1.1 mmol), CH_2Cl_2 (5.0 mL), 2-chloropyridine (0.11 mL, 1.2 mmol), and Tf_2O (0.18 mL, 1.1

mmol). Following workup, the residue was purified by flash chromatography (0% - 1% MeOH in 95:5 CH_2Cl_2:ether as eluent) followed by additional flash chromatography (20% EtOAc in hexanes as eluent) to afford the desired product (0.126 g, 27%) as an oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50 – 7.38 (m, 4H), 7.24 – 7.10 (m, 6H), 7.04 (d, J = 1.9 Hz, 1H), 6.97 – 6.88 (m, 3H), 6.68 (d, J = 2.0 Hz, 1H), 6.60 (dd, J = 8.0, 1.6 Hz, 2H), 4.71 (d, J = 17.1 Hz, 1H), 4.38 (dq, J = 10.8, 7.1 Hz, 1H), 4.23 (dq, J = 10.8, 7.1 Hz, 1H), 4.05 (d, J = 17.1 Hz, 1H), 2.28 (s, 3H), 1.60 (s, 3H), 1.31 (t, J = 7.1 Hz, 3H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 172.1, 158.0, 142.4, 140.6, 139.2, 138.4, 137.6, 137.0, 130.6, 129.8, 128.5, 128.1, 128.0, 127.9, 127.8, 127.5, 126.1, 126.0, 123.8, 122.6, 73.4, 62.2, 51.8, 21.6, 20.8, 14.1; IR (neat): 3062, 2920, 1730, 1593, 1556, 1448, 1217, 1027 cm^{-1}; HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{32}H_{31}N_2O_2$ 475.2386; Found 475.2383.

Ethyl 3-benzyl-6-fluoro-7-methoxy-2,4-diphenyl-3,4-dihydroquinazoline-4-carboxylate (4c). Prepared according to the general 3,4-DHQ synthesis protocol with **3c** (0.246 g, 1.00 mmol), benzylamine (0.12 mL, 1.1 mmol), ethyl benzoylformate (0.18 g, 1.1 mmol), CH_2Cl_2 (5.0 mL), 2-chloropyridine (0.11 mL, 1.2 mmol), and Tf_2O (0.18 mL, 1.1 mmol). Following workup, the residue was purified by flash chromatography (100:3:1 CH_2Cl_2:ether:MeOH as eluent) to afford the desired product (0.145 g, 29%) as an oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49 (dd, J = 6.5, 3.1 Hz, 2H), 7.34 – 7.29 (m, 2H), 7.27 – 7.21 (m, 3H), 7.22 – 7.12 (m, 3H), 6.99 – 6.87 (m, 4H), 6.60 – 6.50 (m, 3H), 4.81 (d, J = 16.9 Hz, 1H), 4.42 – 4.23 (m, 2H), 3.97 (d, J = 17.0 Hz, 1H), 3.88 (s, 3H), 1.28 (t, J = 7.1 Hz, 3H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 172.1, 159.0 (d, $^6J_{C\text{-}F}$ = 2 Hz), 149.5 (d, $^1J_{C\text{-}F}$ = 243 Hz), 148.2 (d, $^2J_{C\text{-}F}$ = 12 Hz), 139.10, 139.08, 138.9, 137.4, 130.5, 128.7 (d, $^3J_{C\text{-}F}$ = 5 Hz), 128.4, 128.1, 127.9, 127.8, 127.6, 126.14, 126.08, 118.0 (d, $^3J_{C\text{-}F}$ = 6 Hz), 116.5 (d, $^2J_{C\text{-}F}$ = 21 Hz), 108.4 (d, $^4J_{C\text{-}F}$ = 2 Hz), 73.9 (d, $^4J_{C\text{-}F}$ = 1 Hz), 62.3, 56.0, 52.1, 14.2; IR (neat): 3060, 2932, 1731, 1504, 1219, 1023 cm^{-1}; HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{31}H_{28}FN_2O_3$ 495.2084; Found 495.2086.

Ethyl 6-benzyl-5,7-diphenyl-1-thia-4,6-diaza-6,7-dihydroindene-7-carboxylate (4d). Prepared according to the general 3,4-DHQ synthesis protocol with **3d** (0.203 g, 1.00 mmol), benzylamine (0.12 mL, 1.1 mmol), ethyl benzoylformate (0.18 g, 1.1 mmol), CH_2Cl_2 (5.0 mL), 2-chloropyridine (0.11 mL, 1.2 mmol), and Tf_2O (0.18 mL, 1.1 mmol). Following workup, the residue was purified by flash chromatography (100:5 CH_2Cl_2:ether as eluent) to afford the desired product (0.356 g, 79%) as a solid (m.p. = 123 - 125 °C). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52 – 7.38 (m, 4H), 7.27 – 7.12 (m, 7H), 6.99 (d, J = 5.3 Hz, 1H), 6.97 – 6.85 (m, 3H), 6.55 (d, J = 6.7 Hz, 2H), 4.82 (d, J = 17.0 Hz, 1H), 4.43 – 4.26 (m, 2H), 4.03 (d, J = 17.0 Hz, 1H), 1.30 (t, J = 7.1 Hz, 3H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 171.6, 158.1, 145.3, 139.0, 138.8, 137.3, 130.0, 129.1, 128.6, 128.1, 127.9, 127.8, 127.6, 126.11, 126.09, 125.6, 123.6,

119.9, 73.5, 62.3, 52.0, 14.2; IR (neat): 3029, 2958, 1730, 1556, 1446, 1221, 1019 cm^{-1}; HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{28}H_{25}N_2O_2S$ 453.1637; Found 453.1635.

Ethyl 3-benzyl-7-methoxy-2-methyl-4-phenyl-3,4-dihydroquinazoline-4-carboxylate (4e). Prepared according to the general 3,4-DHQ synthesis protocol with **3e** (0.166 g, 1.00 mmol), benzylamine (0.12 mL, 1.1 mmol), ethyl benzoylformate (0.18 g, 1.1 mmol), CH_2Cl_2 (5.0 mL), 2-chloropyridine (0.11 mL, 1.2 mmol), and Tf_2O (0.18 mL, 1.1 mmol). Following workup, the residue was purified by flash chromatography (100:3:1 CH_2Cl_2:ether:MeOH as eluent) to afford the desired product (0.206 g, 50%) as an oil. ^1H NMR (400 MHz, $CDCl_3$) δ 7.37 – 7.31 (m, 2H), 7.19 – 7.05 (m, 6H), 6.94 – 6.89 (m, 2H), 6.73 (d, *J* = 2.6 Hz, 1H), 6.60 (d, *J* = 8.6 Hz, 1H), 6.52 (dd, *J* = 8.7, 2.7 Hz, 1H), 4.79 (d, *J* = 17.7 Hz, 1H), 4.33 – 4.14 (m, 3H), 3.80 (s, 3H), 2.22 (s, 3H), 1.23 (t, *J* = 7.1 Hz, 3H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 171.9, 160.3, 158.7, 142.8, 140.2, 138.2, 130.3, 130.1, 128.4, 128.2, 127.8, 126.6, 125.6, 118.4, 111.6, 106.5, 74.5, 62.1, 55.3, 52.2, 23.9, 14.1; IR (neat): 3060, 2980, 1730, 1590, 1562, 1493, 1215, 1198, 1151, 1027 cm^{-1}; HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{26}H_{27}N_2O_3$ 415.2022; Found, 415.2017.

***N*-(3-Methoxyphenyl)butanamide (3f)**. Prepared according to the general amide synthesis protocol with *m*-anisidine (1.12 mL, 10.0 mmol), TEA (1.70 mL, 12.2 mmol), butyryl chloride (1.13 mL, 11.0 mmol), 4-DMAP (0.012 g, 0.10 mmol), and CH_2Cl_2 (50 mL). After workup, the residue was purified by flash chromatography (20% EtOAc in hexanes as eluent) to afford the desired product (1.570 g, 82%) as a waxy solid (m.p. = 30 – 33 °C). ^1H NMR (400 MHz, $CDCl_3$) δ 8.65 (s, 1H), 7.33 (t, *J* = 2.2 Hz, 1H), 7.14 (t, *J* = 8.1 Hz, 1H), 7.07 (dt, *J* = 8.2, 1.3 Hz, 1H), 6.61 (ddd, *J* = 8.1, 2.5, 1.1 Hz, 1H), 3.69 (s, 3H), 2.31 (dd, *J* = 8.0, 7.0 Hz, 2H), 1.71 (h, *J* = 7.4 Hz, 2H), 0.93 (t, *J* = 7.4 Hz, 3H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 172.5, 160.0, 139.6, 129.5, 112.5, 109.9, 106.0, 55.1, 39.4, 19.2, 13.7. The NMR spectral data are consistent with those reported in the literature.[26]

Ethyl 3-benzyl-7-methoxy-4-phenyl-2-propyl-3,4-dihydroquinazoline-4-carboxylate (4f). Prepared according to the general 3,4-DHQ synthesis protocol with **3f** (0.193 g, 1.00 mmol), benzylamine (0.12 mL, 1.1 mmol), ethyl benzoylformate (0.18 g, 1.1 mmol), CH_2Cl_2 (5.0 mL), 2-chloropyridine (0.11 mL, 1.2 mmol), and Tf_2O (0.18 mL, 1.1 mmol). Following workup, the residue was purified by flash chromatography (100:5:1 CH_2Cl_2:ether:MeOH as eluent) to afford the desired product (0.217 g, 49%) as an oil. ^1H NMR (400 MHz, $CDCl_3$) δ 7.31 – 7.25 (m, 2H), 7.13 – 7.05 (m, 6H), 6.90 – 6.85 (m, 2H), 6.75 (d, *J* = 2.7 Hz, 1H), 6.59 (d, *J* = 8.7 Hz, 1H), 6.50 (dd, *J* = 8.7, 2.7 Hz, 1H), 4.82 (d, *J* = 18.0 Hz, 1H), 4.32 – 4.12 (m, 3H), 3.80 (s, 3H), 2.45 (ddd, *J* = 14.3, 10.1, 5.2 Hz, 1H), 2.35 (ddd, *J* = 14.3, 10.3, 6.2 Hz, 1H), 1.97 – 1.72 (m, 2H), 1.24 (t, *J* = 7.1 Hz, 3H), 0.95 (t, *J* = 7.4 Hz, 3H); $^{13}C\{^1H\}$ NMR (101 MHz,

$CDCl_3$) δ 172.1, 160.7, 160.3, 142.9, 140.4, 138.5, 130.4, 130.2, 128.2, 128.0, 127.6, 126.5, 125.5, 118.0, 111.6, 106.5, 74.2, 62.0, 55.3, 51.3, 38.0, 20.9, 14.13, 14.11; IR (neat): 3060, 2928, 1731, 1558, 1493, 1213, 1200, 1034 cm^{-1}; HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{28}H_{31}N_2O_3$ 443.2335; Found 443.2339.

***N*-(3-Methoxyphenyl)cyclohexanecarboxamide (3g)**. Prepared according to the general amide synthesis protocol with *m*-anisidine (1.12 mL, 10.0 mmol), TEA (1.70 mL, 12.2 mmol), cyclohexanecarbonyl chloride (1.47 mL, 11.0 mmol), 4-DMAP (0.012 g, 0.10 mmol), and CH_2Cl_2 (50 mL). After workup, the residue was purified by recrystallization from EtOAc and hexanes to afford the desired product (1.635 g, 70%) as a solid (m.p. = 94 – 97 °C). ^1H NMR (400 MHz, $CDCl_3$) δ 7.37 (t, *J* = 2.1 Hz, 1H), 7.22 – 7.13 (m, 2H), 6.94 (dd, *J* = 8.0, 2.1 Hz, 1H), 6.64 (dd, *J* = 8.3, 2.5 Hz, 1H), 3.80 (s, 3H), 2.22 (tt, *J* = 11.7, 3.5 Hz, 1H), 1.95 (dd, *J* = 12.7, 3.4 Hz, 2H), 1.88 – 1.78 (m, 2H), 1.75 – 1.65 (m, 1H), 1.54 (qd, *J* = 12.2, 10.7, 5.8 Hz, 2H), 1.38 – 1.17 (m, 3H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 174.4, 160.2, 139.4, 129.6, 111.6, 110.2, 105.2, 55.3, 46.7, 29.7, 25.7. The NMR spectral data are consistent with those reported in the literature.[27]

Ethyl 3-benzyl-2-cyclohexyl-7-methoxy-4-phenyl-3,4-dihydroquinazoline-4-carboxylate (4g). Prepared according to the general 3,4-DHQ synthesis protocol with **3g** (0.233 g, 1.00 mmol), benzylamine (0.12 mL, 1.1 mmol), ethyl benzoylformate (0.18 g, 1.1 mmol), CH_2Cl_2 (5.0 mL), 2-chloropyridine (0.11 mL, 1.2 mmol), and Tf_2O (0.18 mL, 1.1 mmol). Following workup, the residue was purified by flash chromatography (100:3:1 CH_2Cl_2:ether:MeOH as eluent) to afford the desired product (0.282 g, 58%) as an oil. ^1H NMR (400 MHz, $CDCl_3$) δ 7.28 (dd, *J* = 7.7, 2.0 Hz, 2H), 7.14 – 7.05 (m, 6H), 6.87 (dd, *J* = 7.7, 1.8 Hz, 2H), 6.73 (d, *J* = 2.6 Hz, 1H), 6.54 (d, *J* = 8.6 Hz, 1H), 6.47 (dd, *J* = 8.6, 2.7 Hz, 1H), 4.83 (d, *J* = 18.0 Hz, 1H), 4.31 – 4.07 (m, 3H), 3.80 (s, 3H), 2.36 (ddd, *J* = 11.5, 8.3, 3.2 Hz, 1H), 2.25 – 2.16 (m, 1H), 1.94 – 1.74 (m, 2H), 1.73 – 1.62 (m, 1H), 1.62 – 1.48 (m, 3H), 1.30 – 1.14 (m, 5H), 1.01 – 0.86 (m, 1H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 172.3, 163.6, 160.2, 143.2, 140.8, 139.0, 130.3, 130.1, 128.1, 128.0, 127.6, 126.4, 125.5, 118.1, 111.4, 106.8, 74.3, 61.9, 55.3, 50.9, 42.2, 31.4, 30.3, 26.6, 26.0, 25.8, 14.2; IR (neat): 2926, 1731, 1556, 1202, 1029 cm^{-1}; HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{31}H_{35}N_2O_3$ 483.2648; Found 483.2651.

Ethyl 3-benzyl-2-(*m*-fluorophenyl)-7-methoxy-4-phenyl-3,4-dihydroquinazoline-4-carboxylate (4h). Prepared according to the general 3,4-DHQ synthesis protocol with **3h** (0.246 g, 1.00 mmol), benzylamine (0.12 mL, 1.1 mmol), ethyl benzoylformate (0.18 g, 1.1 mmol), CH_2Cl_2 (5.0 mL), 2-chloropyridine (0.11 mL, 1.2 mmol), and Tf_2O (0.18 mL, 1.1 mmol). Following workup, the residue was purified by flash chromatography (20% EtOAc in hexanes as eluent) to afford the desired product (0.380 g, 77%) as a solid (m.p. = 124 - 127 °C). ^1H NMR (400 MHz, $CDCl_3$) δ

7.39 – 7.34 (m, 2H), 7.29 (d, J = 7.7 Hz, 1H), 7.24 – 7.11 (m, 5H), 7.00 – 6.87 (m, 4H), 6.84 (d, J = 2.6 Hz, 1H), 6.72 (d, J = 8.7 Hz, 1H), 6.63 – 6.55 (m, 3H), 4.75 (d, J = 16.9 Hz, 1H), 4.40 – 4.19 (m, 2H), 4.01 (d, J = 16.9 Hz, 1H), 3.78 (s, 3H), 1.26 (t, J = 7.1 Hz, 3H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 172.2, 162.3 (d, $^1J_{C\text{-}F}$ = 247 Hz), 160.3, 158.1 (d, $^4J_{C\text{-}F}$ = 2 Hz), 143.0, 139.5 (d, $^3J_{C\text{-}F}$ = 8 Hz), 138.6, 130.6, 129.8 (d, $^3J_{C\text{-}F}$ = 8 Hz), 128.6, 127.8, 127.7, 126.3, 126.1, 123.6 (d, $^4J_{C\text{-}F}$ = 3 Hz), 118.6, 115.6 (d, $^2J_{C\text{-}F}$ J = 21 Hz), 115.1 (d, $^2J_{C\text{-}F}$ = 23 Hz), 112.3, 107.5, 74.3, 62.3, 55.2, 52.0, 14.1; IR (neat): 2924, 1730, 1556, 1485, 1224, 1031 cm^{-1}; HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{31}H_{28}FN_2O_3$ 495.2084; Found 495.2090.

Ethyl 3-benzyl-7-methoxy-2-(*p*-methoxyphenyl)-4-phenyl-3,4-dihydroquinazoline-4-carboxylate (4i). Prepared according to the general 3,4-DHQ synthesis protocol with **3i** (0.257 g, 1.00 mmol), benzylamine (0.12 mL, 1.1 mmol), ethyl benzoylformate (0.18 g, 1.1 mmol), CH_2Cl_2 (5.0 mL), 2-chloropyridine (0.11 mL, 1.2 mmol), and Tf_2O (0.18 mL, 1.1 mmol). Following workup, the residue was purified by flash chromatography (100:10:1 CH_2Cl_2:ether:MeOH as eluent) to afford the desired product (0.389 g, 77%) as a foamy solid (m.p. = 60 - 64 °C). ^1H NMR (400 MHz, $CDCl_3$) δ 7.50 – 7.43 (m, 2H), 7.34 – 7.29 (m, 2H), 7.18 – 7.07 (m, 3H), 6.96 – 6.87 (m, 3H), 6.85 (d, J = 2.7 Hz, 1H), 6.77 (d, J = 8.8 Hz, 2H), 6.69 (d, J = 8.7 Hz, 1H), 6.61 – 6.54 (m, 3H), 4.87 (d, J = 17.0 Hz, 1H), 4.40 – 4.19 (m, 2H), 3.98 (d, J = 16.9 Hz, 1H), 3.78 (s, 3H), 3.71 (s, 3H), 1.26 (t, J = 7.1 Hz, 3H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 172.5, 160.2, 159.8, 159.3, 143.5, 139.7, 139.1, 130.6, 130.5, 130.1, 129.3, 128.4, 127.7, 127.6, 126.0, 126.0, 118.7, 113.5, 111.8, 107.3, 74.2, 62.1, 55.2, 52.0, 14.2; IR (neat): 3060, 2935, 1730, 1552, 1491, 1247, 1219, 1031 cm^{-1}; HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{32}H_{31}N_2O_4$ 507.2284; Found 507.2288.

Ethyl 3-benzyl-7-methoxy-4-phenyl-2-(2-thienyl)-3,4-dihydroquinazoline-4-carboxylate (4j). Prepared according to the general 3,4-DHQ synthesis protocol with **3j** (0.233 g, 1.00 mmol), benzylamine (0.12 mL, 1.1 mmol), ethyl benzoylformate (0.18 g, 1.1 mmol), CH_2Cl_2 (5.0 mL), 2-chloropyridine (0.11 mL, 1.2 mmol), and Tf_2O (0.18 mL, 1.1 mmol). Following workup, the residue was purified by flash chromatography (100:5 CH_2Cl_2:ether as eluent) to afford the desired product (0.377 g, 78%) as a solid (m.p. = 112 - 115 °C). ^1H NMR (400 MHz, $CDCl_3$) δ 7.35 – 7.31 (m, 2H), 7.25 (dd, J = 3.7, 1.2 Hz, 1H), 7.22 (dd, J = 5.1, 1.2 Hz, 1H), 7.19 – 7.10 (m, 3H), 6.99 – 6.94 (m, 3H), 6.87 – 6.83 (m, 2H), 6.74 – 6.70 (m, 2H), 6.67 (d, J = 8.6 Hz, 1H), 6.57 (dd, J = 8.7, 2.7 Hz, 1H), 5.06 (d, J = 17.2 Hz, 1H), 4.37 – 4.19 (m, 2H), 4.08 (d, J = 17.2 Hz, 1H), 3.77 (s, 3H), 1.25 (t, J = 7.1 Hz, 3H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 172.2, 160.3, 153.8, 143.2, 139.4, 138.8, 138.6, 130.6, 130.3, 128.6, 128.3, 127.9, 127.8, 127.4, 126.5,

126.3, 126.2, 119.1, 112.4, 107.6, 74.7, 62.3, 55.3, 52.4, 14.3; IR (neat): 3068, 2935, 1731, 1586, 1552, 1495, 1450, 1219, 1154, 1033 cm^{-1}; HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{29}H_{27}N_2O_3S$ 483.1742; Found 483.1740.

Ethyl 3-hexyl-7-methoxy-2,4-diphenyl-3,4-dihydroquinazoline-4-carboxylate (4k). Prepared according to the general 3,4-DHQ synthesis protocol with **1** (0.228 g, 1.00 mmol), hexylamine (0.15 mL, 1.1 mmol), ethyl benzoylformate (0.18 g, 1.1 mmol), CH_2Cl_2 (5.0 mL), 2-chloropyridine (0.11 mL, 1.2 mmol), and Tf_2O (0.18 mL, 1.1 mmol). Following workup, the residue was purified by MPLC (30% - 50% EtOAc in hexanes as eluent) to afford the desired product (0.215 g, 46%) as an oil. ^1H NMR (400 MHz, $CDCl_3$) δ 7.63 – 7.58 (m, 2H), 7.53 – 7.48 (m, 2H), 7.45 – 7.31 (m, 6H), 6.77 (d, J = 2.7 Hz, 1H), 6.70 (d, J = 8.7 Hz, 1H), 6.52 (dd, J = 8.7, 2.7 Hz, 1H), 4.39 – 4.23 (m, 2H), 3.76 (s, 3H), 3.33 (ddd, J = 15.5, 11.3, 4.9 Hz, 1H), 2.69 (ddd, J = 15.1, 11.6, 4.7 Hz, 1H), 1.28 (t, J = 7.1 Hz, 3H), 0.95 – 0.80 (m, 3H), 0.69 – 0.41 (m, 8H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 171.9, 160.2, 158.8, 143.3, 141.4, 137.7, 130.6, 130.5, 128.6, 128.33, 128.26, 127.9, 127.7, 118.0, 111.8, 107.1, 73.8, 62.1, 55.2, 49.4, 30.4, 29.5, 25.9, 22.0, 14.2, 13.7; IR (neat): 3060, 2928, 1731, 1552, 1489, 1217, 1033 cm^{-1}; HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{30}H_{35}N_2O_3$ 471.2648; Found 471.2650.

Ethyl 3-(cyclohexylmethyl)-7-methoxy-2,4-diphenyl-3,4-dihydroquinazoline-4-carboxylate (4l). Prepared according to the general 3,4-DHQ synthesis protocol with **1** (0.227 g, 1.00 mmol), cyclohexanemethylamine (0.14 mL, 1.1 mmol), ethyl benzoylformate (0.18 g, 1.1 mmol), CH_2Cl_2 (5.0 mL), 2-chloropyridine (0.11 mL, 1.2 mmol), and Tf_2O (0.18 mL, 1.1 mmol). Following workup, the residue was purified by MPLC (15% - 40% EtOAc in hexanes as eluent) followed by additional purification by MPLC (0% - 40% EtOAc in CH_2Cl_2 as eluent) to afford the desired product (0.233 g, 48%) as an oil. ^1H NMR (400 MHz, $CDCl_3$) δ 7.62 (d, J = 6.9 Hz, 2H), 7.47 – 7.40 (m, 2H), 7.38 – 7.26 (m, 6H), 6.82 – 6.65 (m, 2H), 6.50 (dd, J = 8.8, 2.7 Hz, 1H), 4.32 – 4.12 (m, 2H), 3.72 (s, 3H), 3.44 (dd, J = 15.1, 7.3 Hz, 1H), 2.63 (dd, J = 15.1, 5.0 Hz, 1H), 1.37 – 1.24 (m, 4H), 1.19 (t, J = 7.1 Hz, 3H), 0.91 – 0.82 (m, 1H), 0.75 – 0.53 (m, 3H), 0.15 – -0.09 (m, 3H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 172.1, 160.2, 159.4, 143.6, 141.0, 138.1, 131.2, 130.6, 128.61, 128.57, 128.4, 128.1, 127.8, 118.3, 111.7, 107.1, 74.2, 62.0, 55.2, 54.5, 37.4, 30.5, 30.4, 26.0, 25.8, 25.7, 14.1; IR (neat): 2924, 1731, 1551, 1489, 1217, 1150, 1031 cm^{-1}; HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{31}H_{35}N_2O_3$ 483.2648; Found 483.2641.

Ethyl 3-cyclohexyl-7-methoxy-2,4-diphenyl-3,4-dihydroquinazoline-4-carboxylate (4m). Prepared according to the general 3,4-DHQ synthesis protocol with **1** (0.227 g, 1.00 mmol), cyclohexylamine (0.13 mL, 1.1 mmol), ethyl benzoylformate (0.18 g, 1.1 mmol), CH_2Cl_2 (5.0 mL), 2-chloropyridine (0.11 mL, 1.2 mmol), and Tf_2O (0.18 mL, 1.1

mmol). Following workup, the residue was purified by flash chromatography (100:5:1 CH_2Cl_2:ether:MeOH as eluent) followed by additional flash chromatography (20% EtOAc in hexanes) to afford the desired product (0.034 g, 7%) as an oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62 – 7.51 (m, 4H), 7.43 – 7.31 (m, 6H), 6.79 – 6.66 (m, 2H), 6.50 (dd, J = 8.7, 2.7 Hz, 1H), 4.27 (qd, J = 7.1, 2.0 Hz, 2H), 3.77 (s, 3H), 2.86 (td, J = 11.3, 7.2 Hz, 1H), 1.85 – 1.74 (m, 1H), 1.43 – 1.33 (m, 1H), 1.30 – 1.20 (m, 5H), 1.10 – 0.99 (m, 2H), 0.78 – 0.42 (m, 4H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 171.7, 160.1, 158.7, 142.9, 141.6, 139.6, 130.8, 129.6, 128.6, 128.2, 127.8, 127.7, 118.4, 111.9, 107.1, 74.4, 63.0, 62.0, 55.3, 34.5, 33.4, 27.3, 27.1, 25.3, 14.1; IR (neat): 2924, 1733, 1541, 1489, 1264, 1141, 1036 cm^{-1}; HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{30}H_{33}N_2O_3$ 469.2491; Found 469.2485.

Ethyl 3-(*m*-fluorophenyl)-7-methoxy-2,4-diphenyl-3,4-dihydroquinazoline-4-carboxylate (4n). Prepared according to the general 3,4-DHQ synthesis protocol with **1** (0.227 g, 1.00 mmol), 3-fluoroaniline (0.11 mL, 1.1 mmol), ethyl benzoylformate (0.18 g, 1.1 mmol), CH_2Cl_2 (5.0 mL), 2-chloropyridine (0.11 mL, 1.2 mmol), and Tf_2O (0.18 mL, 1.1 mmol). Following workup, the residue was purified by flash chromatography (20% EtOAc in hexanes as eluent) followed by additional flash chromatography (100:3 CH_2Cl_2:ether as eluent) to afford the desired product (0.237 g, 49%) as a foamy oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73 – 7.57 (m, 2H), 7.29 – 7.03 (m, 8H), 6.94 (t, J = 1.5 Hz, 1H), 6.81 – 6.50 (m, 5H), 6.43 (tdd, J = 8.2, 2.5, 1.0 Hz, 1H), 4.42 – 4.23 (m, 2H), 3.81 (s, 3H), 1.25 (t, J = 7.1 Hz, 3H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 172.5, 161.7 (d, $^1J_{C\text{-}F}$ = 246 Hz), 160.2, 156.1, 143.7 (d, $^3J_{C\text{-}F}$ = 10 Hz), 142.9, 138.4, 137.3, 130.6, 129.8, 129.5, 129.0, 128.4 (d, $^3J_{C\text{-}F}$ = 9 Hz), 128.0, 127.8, 127.7, 125.6, 120.0, 116.8 (d, $^2J_{C\text{-}F}$ = 23 Hz), 112.7, 112.4 (d, $^2J_{C\text{-}F}$ = 21 Hz), 107.8, 74.6, 62.5, 55.3, 14.1; IR (neat): 3058, 2928, 1731, 1552, 1487, 1340, 1219, 1031 cm^{-1}; HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{30}H_{26}FN_2O_3$ 481.1927; Found 481.1930.

Ethyl 7-methoxy-3-(*p*-methoxyphenyl)-2,4-diphenyl-3,4-dihydroquinazoline-4-carboxylate (4o). Prepared according to the general 3,4-DHQ synthesis protocol with **1** (0.228 g, 1.00 mmol), *p*-anisidine (0.136 g, 1.1 mmol), ethyl benzoylformate (0.18 g, 1.1 mmol), CH_2Cl_2 (5.0 mL), 2-chloropyridine (0.11 mL, 1.2 mmol), and Tf_2O (0.18 mL, 1.1 mmol). Following workup, the residue was purified by flash chromatography (30% EtOAc in hexanes as eluent) to afford the desired product (0.454 g, 92%) as a solid (m.p. = 74 - 76 °C). ^{1}H NMR (400 MHz, $CDCl_3$, heated to 330 K) δ 7.63 – 7.56 (m, 2H), 7.23 – 7.17 (m, 2H), 7.16 – 7.03 (m, 6H), 6.92 (d, J = 2.6 Hz, 1H), 6.73 (broad s, 2H), 6.65 (d, J = 8.6 Hz, 1H), 6.58 (dd, J = 8.7, 2.6 Hz, 1H), 6.29 (d, J = 9.3 Hz, 2H), 4.29 (qq, J = 6.9, 3.7 Hz, 2H), 3.78 (s, 3H), 3.46 (s, 3H), 1.20 (t, J = 7.1 Hz, 3H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 172.4, 160.3, 157.2, 156.8, 143.5, 139.1, 138.0, 135.2, 131.0, 130.8, 129.7, 129.5, 128.5, 127.7, 127.5, 127.5, 119.8, 112.9, 112.3, 108.0, 74.8,

62.1, 55.3, 55.0, 14.1; IR (neat): 3060, 2958, 1731, 1508, 1351, 1245, 1228, 1033 cm^{-1}; HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{31}H_{28}N_2O_4$ 493.2127; Found 493.2125.

Ethyl 3-benzyl-4-(*p*-fluorophenyl)-7-methoxy-2-phenyl-3,4-dihydroquinazoline-4-carboxylate (4p). Prepared according to the general 3,4-DHQ synthesis protocol with **1** (0.227 g, 1.00 mmol), benzylamine (0.12 mL, 1.1 mmol), ethyl 4-fluorobenzoylformate (0.18 mL, 1.1 mmol), CH_2Cl_2 (5.0 mL), 2-chloropyridine (0.11 mL, 1.2 mmol), and Tf_2O (0.18 mL, 1.1 mmol). Following workup, the residue was purified by flash chromatography (100:5:2 CH_2Cl_2:ether:MeOH as eluent) to afford the desired product (0.366 g, 74%) as a solid (m.p. = 163 - 165 °C). ^1H NMR (400 MHz, $CDCl_3$) δ 7.60 – 7.50 (m, 2H), 7.31 – 7.22 (m, 5H), 7.01 – 6.89 (m, 3H), 6.85 (d, J = 2.7 Hz, 1H), 6.77 (t, J = 8.6 Hz, 2H), 6.69 (d, J = 8.7 Hz, 1H), 6.58 (dt, J = 8.8, 2.2 Hz, 3H), 4.86 (d, J = 17.0 Hz, 1H), 4.39 – 4.21 (m, 2H), 3.94 (d, J = 17.0 Hz, 1H), 3.79 (s, 3H), 1.26 (t, J = 7.1 Hz, 3H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 172.1, 162.4 (d, $^1J_{C\text{-}F}$ = 249 Hz), 160.4, 159.5, 143.4, 138.8, 137.5, 135.6 (d, $^4J_{C\text{-}F}$ = 3 Hz), 132.6 (d, $^3J_{C\text{-}F}$ = 8 Hz), 130.4, 128.8, 128.3, 127.8, 127.7, 126.3, 126.0, 118.3, 114.5 (d, $^2J_{C\text{-}F}$ = 22 Hz), 112.2, 107.6, 73.6, 62.4, 55.3, 52.3, 14.2; IR (neat): 3058, 2937, 1730, 1552, 1489, 1221, 1163, 1033 cm^{-1}; HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{31}H_{28}FN_2O_3$ 495.2084; Found 495.2078.

Ethyl 3-benzyl-7-methoxy-4-(*p*-methoxyphenyl)-2-phenyl-3,4-dihydroquinazoline-4-carboxylate (4q). Prepared according to the general 3,4-DHQ synthesis protocol with **1** (0.227 g, 1.00 mmol), benzylamine (0.12 mL, 1.1 mmol), ethyl 4-methoxybenzoylformate[28] (0.227 g, 1.1 mmol), CH_2Cl_2 (5.0 mL), 2-chloropyridine (0.11 mL, 1.2 mmol), and Tf_2O (0.18 mL, 1.1 mmol). Following workup, the residue was purified by flash chromatography (100:3:1 CH_2Cl_2:ether:MeOH as eluent) followed by additional flash chromatography (85:15:3 hexanes:EtOAC:TEA as eluent) to afford the desired product (0.183 g, 36%) as an oil. ^1H NMR (400 MHz, $CDCl_3$) δ 7.54 – 7.46 (m, 2H), 7.28 – 7.17 (m, 5H), 7.01 – 6.87 (m, 3H), 6.84 (d, J = 2.7 Hz, 1H), 6.75 (d, J = 8.7 Hz, 1H), 6.67 – 6.55 (m, 5H), 4.79 (d, J = 16.9 Hz, 1H), 4.42 – 4.19 (m, 2H), 3.99 (d, J = 16.9 Hz, 1H), 3.80 (s, 3H), 3.71 (s, 3H), 1.27 (t, J = 7.1 Hz, 3H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 172.6, 160.2, 159.5, 159.5, 143.4, 139.1, 137.6, 131.9, 131.6, 130.6, 128.6, 128.1, 127.8, 127.6, 126.1, 126.1, 118.7, 113.0, 112.0, 107.3, 73.7, 62.2, 55.3, 55.2, 52.1, 14.2; IR (neat): 2922, 1730, 1552, 1489, 1256, 1034 cm^{-1}; HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{32}H_{31}N_2O_4$ 507.2284; Found 507.2278.

Ethyl 3-benzyl-7-methoxy-2-phenyl-4-(2,4-xylyl)-3,4-dihydroquinazoline-4-carboxylate (4r). Prepared according to the general 3,4-DHQ synthesis protocol with **1** (0.228 g, 1.00 mmol), benzylamine (0.12 mL, 1.1 mmol), ethyl 2,4-dimethylbenzoylformate[28] (0.227 g, 1.1 mmol), CH_2Cl_2 (5.0 mL), 2-chloropyridine (0.11 mL, 1.2 mmol),

and Tf_2O (0.18 mL, 1.1 mmol). Following workup, the residue was purified by flash chromatography (100:5:2 CH_2Cl_2:ether:MeOH as eluent) followed by additional flash chromatography (30% EtOAc in hexanes as eluent) to afford the desired product (0.277 g, 55%) as a solid (m.p. = 146 - 149 °C). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70 – 7.63 (m, 2H), 7.38 – 7.24 (m, 3H), 7.14 (d, *J* = 7.9 Hz, 1H), 7.01 – 6.89 (m, 2H), 6.85 (t, *J* = 7.4 Hz, 2H), 6.76 (dd, *J* = 5.7, 3.0 Hz, 2H), 6.56 – 6.47 (m, 2H), 6.44 (d, *J* = 6.8 Hz, 2H), 4.94 (d, *J* = 16.3 Hz, 1H), 4.42 – 4.20 (m, 2H), 3.97 (d, *J* = 16.4 Hz, 1H), 3.76 (s, 3H), 2.21 (s, 3H), 1.71 (s, 3H), 1.25 (t, *J* = 7.1 Hz, 3H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 172.5, 160.1, 160.0, 142.3, 139.8, 138.6, 138.0, 137.8, 134.4, 133.7, 130.7, 129.7, 128.7, 128.4, 128.1, 127.3, 127.0, 126.2, 125.8, 118.5, 112.2, 107.5, 74.5, 62.2, 55.2, 52.7, 22.3, 20.8, 14.1; IR (neat): 3034, 2928, 1728, 1552, 1489, 1215, 1148, 1031 cm^{-1}; HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{33}H_{33}N_2O_3$ 505.2491; Found 505.2492.

Ethyl 3-benzyl-7-methoxy-2-phenyl-4-(2-thienyl)-3,4-dihydroquinazoline-4-carboxylate (4s). Prepared according to the general 3,4-DHQ synthesis protocol with **1** (0.229 g, 1.01 mmol), benzylamine (0.12 mL, 1.1 mmol), ethyl thiophene-2-glyoxylate[28] (0.204 g, 1.1 mmol), CH_2Cl_2 (5.0 mL), 2-chloropyridine (0.11 mL, 1.2 mmol), and Tf_2O (0.18 mL, 1.1 mmol). Following workup, the residue was purified by flash chromatography (100:5:1 CH_2Cl_2:ether:MeOH as eluent) followed by additional flash chromatography (85:15:5 cyclohexane:EtOAc:TEA) to afford the desired product (25.3 mg, 5%) as an oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 – 7.32 (m, 2H), 7.26 (dd, *J* = 5.1, 1.2 Hz, 1H), 7.24 – 7.16 (m, 3H), 7.10 (dd, *J* = 3.7, 1.2 Hz, 1H), 7.01 – 6.96 (m, 3H), 6.94 (d, *J* = 8.7 Hz, 1H), 6.87 (dd, *J* = 5.1, 3.7 Hz, 1H), 6.83 (d, *J* = 2.7 Hz, 1H), 6.78 – 6.72 (m, 2H), 6.62 (dd, *J* = 8.7, 2.7 Hz, 1H), 4.69 (d, *J* = 16.8 Hz, 1H), 4.38 – 4.16 (m, 3H), 3.81 (s, 3H), 1.28 (t, *J* = 7.1 Hz, 3H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 171.2, 160.5, 159.1, 144.5, 142.5, 138.6, 137.5, 130.1, 129.8, 128.5, 128.0, 127.7, 127.6, 127.5, 126.6, 126.3, 125.9, 118.4, 112.3, 107.7, 71.0, 62.6, 55.3, 52.2, 14.1; IR (neat): 3062, 2939, 1731, 1586, 1554, 1489, 1444, 1383, 1217, 1154, 1031 cm^{-1}; HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{29}H_{27}N_2O_3S$ 483.1742; Found 483.1746.

Ethyl 7-methoxy-3-(*p*-methoxyphenyl)-2-phenyl-4-(2-thienyl)-3,4-dihydroquinazoline-4-carboxylate (4t). Prepared according to the general 3,4-DHQ synthesis protocol with **1** (0.228 g, 1.00 mmol), *p*-anisidine (0.137 g, 1.11 mmol), ethyl thiophene-2-glyoxylate[28] (0.202 g, 1.10 mmol), CH_2Cl_2 (5.0 mL), 2-chloropyridine (0.11 mL, 1.2 mmol), and Tf_2O (0.18 mL, 1.1 mmol). Following workup, the residue was purified by MPLC (30% - 50% EtOAc in hexanes as eluent) to afford the desired product (0.251 g, 50%) as an oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56 – 7.50 (m, 2H), 7.20 – 7.11 (m, 4H), 7.02 – 6.98 (m, 2H), 6.90 (d, *J* = 8.7 Hz, 1H), 6.86 – 6.70 (m, 3H), 6.63 (dd, *J* = 8.7, 2.6 Hz, 1H), 6.41 (d, *J* = 8.9 Hz, 2H), 4.31 – 4.13 (m, 2H), 3.81 (s, 3H), 3.57 (s, 3H), 1.17 (t, *J* = 7.1 Hz, 3H); ^{13}C{^{1}H} NMR (101

MHz, $CDCl_3$) δ 170.8, 160.5, 157.5, 156.6, 143.7, 141.6, 136.8, 134.7, 130.2, 130.0, 129.4, 128.9, 128.7, 127.8, 127.5, 125.7, 118.7, 113.0, 112.8, 107.7, 71.4, 62.7, 55.4, 55.1, 14.0; IR (neat): 3060, 2960, 1735, 1651, 1508, 1489, 1351, 1247, 1033 cm^{-1}; HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{29}H_{27}N_2O_4S$ 499.1692; Found 499.1689.

Ethyl 3-benzyl-7-methoxy-4-methyl-2-phenyl-3,4-dihydroquinazoline-4-carboxylate (4u). Prepared according to the general 3,4-DHQ synthesis protocol with **1** (0.227 g, 1.00 mmol), benzylamine (0.12 mL, 1.1 mmol), ethyl pyruvate (0.12 mL, 1.1 mmol), CH_2Cl_2 (5.0 mL), 2-chloropyridine (0.11 mL, 1.2 mmol), and Tf_2O (0.18 mL, 1.1 mmol). Following workup, the residue was purified by MPLC (40% - 65% EtOAc in hexanes as eluent) to afford the desired product (0.091 g, 22%) as an oil. ^1H NMR (400 MHz, $CDCl_3$) δ 7.49 – 7.44 (m, 2H), 7.31 – 7.27 (m, 3H), 7.23 – 7.12 (m, 4H), 7.06 (dd, *J* = 8.0, 1.4 Hz, 2H), 6.82 (d, *J* = 2.7 Hz, 1H), 6.68 (dd, *J* = 8.6, 2.7 Hz, 1H), 4.81 (d, *J* = 17.6 Hz, 1H), 4.29 (d, *J* = 17.6 Hz, 1H), 4.16 (qd, *J* = 7.1, 5.5 Hz, 2H), 3.80 (s, 3H), 1.84 (s, 3H), 1.23 (t, *J* = 7.1 Hz, 3H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 172.9, 160.3, 160.2, 142.8, 139.6, 137.3, 128.8, 128.4, 128.3, 127.5, 126.8, 125.9, 125.8, 118.1, 112.3, 108.5, 65.6, 62.0, 55.3, 52.0, 24.3, 14.1; IR (neat): 3056, 2980, 1728, 1552, 1489, 1226, 1144, 1100, 1027 cm^{-1}; HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{26}H_{27}N_2O_3$ 415.2022; Found 415.2024.

Ethyl 3-benzyl-7-methoxy-2-phenyl-4-propyl-3,4-dihydroquinazoline-4-carboxylate (4v). Prepared according to the general 3,4-DHQ synthesis protocol with **1** (0.228 g, 1.01 mmol), benzylamine (0.12 mL, 1.1 mmol), ethyl 2-oxovalerate (0.16 mL, 1.1 mmol), CH_2Cl_2 (5.0 mL), 2-chloropyridine (0.11 mL, 1.2 mmol), and Tf_2O (0.18 mL, 1.1 mmol). Following workup, the residue was purified by MPLC (30% - 55% EtOAc in hexanes as eluent) to afford the desired product (0.170 g, 37%) as an oil. ^1H NMR (400 MHz, $CDCl_3$) δ 7.35 (dd, *J* = 6.6, 3.0 Hz, 2H), 7.25 – 7.18 (m, 3H), 7.15 – 7.03 (m, 5H), 6.88 (d, *J* = 8.6 Hz, 1H), 6.78 (d, *J* = 2.7 Hz, 1H), 6.63 (dd, *J* = 8.5, 2.7 Hz, 1H), 4.43 (s, 2H), 4.07 (dq, *J* = 10.8, 7.1 Hz, 1H), 3.87 (dq, *J* = 10.8, 7.1 Hz, 1H), 3.77 (s, 3H), 2.30 – 2.10 (m, 2H), 1.56 – 1.28 (m, 2H), 1.12 (t, *J* = 7.1 Hz, 3H), 0.78 (t, *J* = 7.3 Hz, 3H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 172.2, 160.0, 159.2, 142.8, 137.8, 137.5, 128.5, 128.2, 127.9, 127.5, 127.1, 126.9, 125.5, 116.1, 112.4, 108.6, 70.4, 61.8, 55.2, 52.2, 39.7, 16.9, 14.0, 13.8; IR (neat): 3062, 2928, 1728, 1554, 1493, 1232, 1142, 1031 cm^{-1}; HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{28}H_{31}N_2O_3$ 443.2335; Found 443.2337.

Ethyl 3-benzyl-4-isopropyl-7-methoxy-2-phenyl-3,4-dihydroquinazoline-4-carboxylate (4w). Prepared according to the general 3,4-DHQ synthesis protocol with **1** (0.228 g, 1.00 mmol), benzylamine (0.12 mL, 1.1 mmol), ethyl dimethylpyruvate (0.16 mL, 1.1 mmol), CH_2Cl_2 (5.0 mL), 2-chloropyridine (0.11 mL, 1.2 mmol), and Tf_2O (0.18 mL, 1.1 mmol). Following workup, the residue was purified by MPLC (14% - 35% EtOAc in hexanes as eluent) to

afford the desired product (0.092 g, 21%) as an oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31 – 7.23 (m, 2H), 7.22 – 7.12 (m, 3H), 7.10 – 6.97 (m, 5H), 6.84 (d, *J* = 2.7 Hz, 1H), 6.76 (d, *J* = 8.6 Hz, 1H), 6.65 (dd, *J* = 8.6, 2.7 Hz, 1H), 4.84 (d, *J* = 17.1 Hz, 1H), 4.26 (d, *J* = 17.2 Hz, 1H), 4.02 (dq, *J* = 10.8, 7.1 Hz, 1H), 3.81 (s, 3H), 3.70 (dq, *J* = 10.9, 7.2 Hz, 1H), 2.73 (hept, *J* = 6.8 Hz, 1H), 1.25 (d, *J* = 6.8 Hz, 3H), 1.02 (d, *J* = 6.8 Hz, 3H), 0.97 (t, *J* = 7.1 Hz, 3H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 170.9, 159.9, 158.9, 143.1, 138.1, 137.2, 128.7, 128.0, 127.8, 127.6, 126.8, 126.6, 126.3, 115.5, 111.9, 108.4, 74.0, 61.7, 55.2, 54.4, 39.3, 18.5, 17.5, 13.6; IR (neat): 3058, 2928, 1730, 1552, 1491, 1226, 1036 cm^{-1}; HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{28}H_{31}N_2O_3$ 443.2335; Found 443.2328.

Ethyl 3-benzyl-7-methoxy-2-phenyl-4-(*tert*-butyl)-3,4-dihydroquinazoline-4-carboxylate (4x). Prepared according to the general 3,4-DHQ synthesis protocol with **1** (0.227 g, 1.00 mmol), benzylamine (0.12 mL, 1.1 mmol), ethyl 3,3-dimethyl-2-oxobutanoate[29] (0.178 g, 1.1 mmol), CH_2Cl_2 (5.0 mL), 2-chloropyridine (0.11 mL, 1.2 mmol), and Tf_2O (0.18 mL, 1.1 mmol). Following workup, the residue was purified by flash chromatography (100:3:1 CH_2Cl_2:ether:MeOH as eluent) to afford the desired product (0.015 g, 3%) as an oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 – 7.31 (m, 2H), 7.21 – 7.13 (m, 3H), 7.05 – 6.99 (m, 3H), 6.93 – 6.86 (m, 3H), 6.71 – 6.68 (m, 2H), 5.05 (d, *J* = 17.6 Hz, 1H), 4.16 (d, *J* = 17.6 Hz, 1H), 4.04 (dq, *J* = 10.8, 7.1 Hz, 1H), 3.84 (s, 3H), 3.62 (dq, *J* = 10.9, 7.2 Hz, 1H), 1.26 (s, 9H), 0.87 (t, *J* = 7.1 Hz, 3H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 170.3, 159.7, 158.8, 143.5, 138.4, 136.9, 129.0, 128.3, 127.92, 127.91, 127.7, 126.6, 126.4, 115.5, 111.4, 108.2, 76.2, 61.3, 56.9, 55.3, 45.1, 26.3, 13.3; IR (neat): 2926, 1733, 1551, 1491, 1210, 1154, 1034 cm^{-1}; HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{29}H_{33}N_2O_3$ 457.2491; Found 457.2495.

***tert*-Butyl 3-benzyl-7-methoxy-2,4-diphenyl-3,4-dihydroquinazoline-4-carboxylate (4y)**. Prepared according to the general 3,4-DHQ synthesis protocol with **1** (0.227 g, 1.00 mmol), benzylamine (0.12 mL, 1.1 mmol), *tert*-butyl benzoylformate[30] (0.227 g, 1.1 mmol), CH_2Cl_2 (5.0 mL), 2-chloropyridine (0.10 mL, 1.2 mmol), and Tf_2O (0.18 mL, 1.1 mmol). Following workup, the residue was purified by flash chromatography (100:5:1 CH_2Cl_2:ether:MeOH as eluent) to afford the desired product (0.455 g, 90%) as a solid (m.p. = 147 - 150 °C). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54 – 7.47 (m, 2H), 7.40 – 7.35 (m, 2H), 7.26 – 7.21 (m, 3H), 7.19 – 7.10 (m, 3H), 6.97 – 6.87 (m, 3H), 6.84 (d, *J* = 2.7 Hz, 1H), 6.67 (d, *J* = 8.7 Hz, 1H), 6.59 – 6.53 (m, 3H), 4.80 (d, *J* = 17.0 Hz, 1H), 4.00 (d, *J* = 16.9 Hz, 1H), 3.81 (s, 3H), 1.45 (s, 9H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 171.3, 160.0, 159.5, 143.3, 140.0, 139.1, 137.6, 130.8, 130.7, 128.5, 128.3, 128.0, 127.8, 127.6, 127.5, 126.1, 126.0, 119.0, 111.8, 107.1, 83.2, 74.6, 55.3, 52.2, 28.0; IR

(neat): 3062, 2976, 1726, 1554, 1489, 1265, 1241, 1154, 1034 cm^{-1}; HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{33}H_{33}N_2O_3$ 505.2491; Found 505.2488.

Diethyl 3-benzyl-7-methoxy-2-phenyl-3,4-dihydroquinazoline-4,4-dicarboxylate (4z). Prepared according to the general 3,4-DHQ synthesis protocol with **1** (0.227 g, 1.00 mmol), benzylamine (0.12 mL, 1.1 mmol), diethyl ketomalonate (0.17 mL, 1.1 mmol), CH_2Cl_2 (5.0 mL), 2-chloropyridine (0.10 mL, 1.2 mmol), and Tf_2O (0.18 mL, 1.1 mmol). Following workup, the residue was purified by flash chromatography (25% EtOAc in hexanes as eluent) to afford the desired product (0.382 g, 81%) as a solid (m.p. = 141 - 143 °C). ^1H NMR (400 MHz, $CDCl_3$) δ 7.43 – 7.38 (m, 2H), 7.28 – 7.22 (m, 3H), 7.15 – 7.07 (m, 3H), 7.06 – 6.99 (m, 3H), 6.84 (d, *J* = 2.6 Hz, 1H), 6.72 (dd, *J* = 8.7, 2.7 Hz, 1H), 4.67 (s, 2H), 4.17 (dq, *J* = 10.8, 7.1 Hz, 2H), 3.93 (dq, *J* = 10.8, 7.1 Hz, 2H), 3.79 (s, 3H), 1.15 (t, *J* = 7.1 Hz, 6H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 168.9, 160.6, 158.4, 142.1, 137.7, 136.5, 128.9, 128.4, 128.2, 128.0, 127.6, 126.8, 126.7, 113.2, 112.7, 108.2, 74.5, 62.6, 55.3, 53.7, 13.8; IR (neat): 3064, 2880, 1735, 1558, 1493, 1254, 1224, 1034 cm^{-1}; HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{28}H_{29}N_2O_5$ 473.2076; Found 473.2072.

1-(3-Benzyl-7-methoxy-4-methyl-2-phenyl-3,4-dihydroquinazolin-4-yl)-1-ethanone (5a). Prepared according to the general 3,4-DHQ synthesis protocol with **1** (0.227 g, 1.00 mmol), benzylamine (0.12 mL, 1.1 mmol), 2,3-butanedione (0.10 mL, 1.1 mmol), CH_2Cl_2 (5.0 mL), 2-chloropyridine (0.11 mL, 1.2 mmol), and Tf_2O (0.18 mL, 1.1 mmol). Following workup, the residue was purified by MPLC (50% - 70% EtOAc in hexanes as eluent) to afford the desired product (0.220 g, 57%) as a solid (m.p. = 147 - 149 °C). ^1H NMR (400 MHz, $CDCl_3$) δ 7.59 – 7.44 (m, 2H), 7.29 (t, *J* = 3.2 Hz, 3H), 7.15 (dt, *J* = 13.4, 6.6 Hz, 3H), 7.01 (t, *J* = 7.7 Hz, 3H), 6.86 (d, *J* = 2.7 Hz, 1H), 6.69 (dd, *J* = 8.5, 2.7 Hz, 1H), 4.83 (d, *J* = 17.5 Hz, 1H), 4.23 (d, *J* = 17.5 Hz, 1H), 3.78 (s, 3H), 2.14 (s, 3H), 1.70 (s, 3H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 205.9, 160.7, 160.6, 143.4, 139.5, 137.1, 129.1, 128.5, 128.4, 127.7, 127.0, 125.8, 125.4, 117.6, 112.5, 109.0, 70.2, 55.3, 51.7, 24.6, 21.9, IR (neat): 3058, 2954, 1713, 1549, 1485, 1275, 1146, 1068, 1029 cm^{-1}; HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{25}H_{25}N_2O_2$ 385.1916; Found 385.1912.

1-(3-Benzyl-7-methoxy-4-methyl-2-phenyl-3,4-dihydroquinazolin-4-yl)-1-butanone (5b). Prepared according to the general 3,4-DHQ synthesis protocol with **1** (0.227 g, 1.00 mmol), benzylamine (0.12 mL, 1.1 mmol), 2,3-hexanedione (0.14 mL, 1.1 mmol), CH_2Cl_2 (5.0 mL), 2-chloropyridine (0.11 mL, 1.2 mmol), and Tf_2O (0.18 mL, 1.1 mmol). Following workup, the residue was purified by MPLC (0% - 20% EtOAc in hexanes as eluent) to afford the desired product (0.165 g, 40%) as a solid (m.p. = 117 - 119 °C). ^1H NMR (400 MHz, $CDCl_3$) δ 7.59 – 7.49 (m, 2H), 7.35 – 7.28 (m, 3H), 7.23 – 7.12 (m, 3H), 7.08 – 6.97 (m, 3H), 6.85 (d, *J* = 2.7 Hz, 1H), 6.69 (dd, *J* = 8.6, 2.7 Hz, 1H),

4.86 (d, J = 17.5 Hz, 1H), 4.22 (d, J = 17.5 Hz, 1H), 3.81 (s, 3H), 2.53 (ddd, J = 17.2, 7.8, 6.8 Hz, 1H), 2.40 (ddd, J = 17.2, 7.6, 6.5 Hz, 1H), 1.70 (s, 3H), 1.57 – 1.43 (m, 2H), 0.77 (t, J = 7.4 Hz, 3H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 208.5, 160.8, 160.5, 143.6, 139.7, 137.1, 129.1, 128.5, 128.4, 127.8, 126.9, 125.8, 125.4, 117.6, 112.4, 108.8, 70.0, 55.4, 51.7, 38.4, 21.9, 17.6, 13.6; IR (neat): 3058, 2924, 1713, 1552, 1489, 1273, 1146, 1029 cm^{-1}; HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{27}H_{29}N_2O_2$ 413.2229; Found 413.2230.

(3-Benzyl-7-methoxy-2,4-diphenyl-3,4-dihydroquinazolin-4-yl)phenylformaldehyde (5c). Prepared according to the general 3,4-DHQ synthesis protocol with **1** (0.228 g, 1.00 mmol), benzylamine (0.12 mL, 1.1 mmol), benzil (0.233 g, 1.1 mmol), CH_2Cl_2 (5.0 mL), 2-chloropyridine (0.11 mL, 1.2 mmol), and Tf_2O (0.18 mL, 1.1 mmol). Following workup, the residue was purified by MPLC (25% - 50% EtOAc in hexanes as eluent) to afford the desired product (0.108 g, 21%) as a solid (m.p. = 118 - 120 °C). ^1H NMR (400 MHz, $CDCl_3$) δ 7.67 – 7.60 (m, 2H), 7.50 – 7.43 (m, 2H), 7.43 – 7.34 (m, 3H), 7.31 – 7.16 (m, 8H), 6.94 – 6.88 (m, 1H), 6.88 – 6.81 (m, 4H), 6.50 (dd, J = 8.8, 2.7 Hz, 1H), 6.37 (d, J = 7.3 Hz, 2H), 4.65 (d, J = 16.9 Hz, 1H), 4.03 (d, J = 16.9 Hz, 1H), 3.75 (s, 3H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 198.9, 160.3, 159.9, 144.5, 138.7, 138.7, 137.5, 137.2, 131.7, 131.4, 129.7, 129.2, 128.9, 128.6, 128.1, 128.0, 127.9, 127.8, 127.5, 126.1, 126.0, 116.1, 112.1, 108.2, 78.5, 55.2, 52.7, IR (neat): 3062, 2932, 1679, 1582, 1549, 1487, 1277, 1156, 1033 cm^{-1}; HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{35}H_{29}N_2O_2$ 509.2229; Found 509.2224.

3'-Benzyl-7'-methoxy-2'-phenyl-3'*H*-spiro[acenaphthene-1,4'-quinazolin]-2-one (5d). Prepared according to the general 3,4-DHQ synthesis protocol with **1** (0.227 g, 1.00 mmol), benzylamine (0.12 mL, 1.1 mmol), acenaphthoquinone (0.201 g, 1.10 mmol), CH_2Cl_2 (5.0 mL), 2-chloropyridine (0.11 mL, 1.2 mmol), and Tf_2O (0.18 mL, 1.1 mmol). Following workup, the residue was purified by MPLC (45% - 65% EtOAc in hexanes as eluent) to afford the desired product (0.170 g, 35%) as a solid (m.p. = 126 - 129 °C). ^1H NMR (400 MHz, $CDCl_3$) δ 8.12 (d, J = 8.2 Hz, 1H), 7.95 (d, J = 7.0 Hz, 1H), 7.88 (d, J = 8.0 Hz, 1H), 7.73 (dd, J = 8.1, 7.0 Hz, 1H), 7.59 – 7.45 (m, 4H), 7.31 – 7.23 (m, 3H), 7.01 – 6.88 (m, 4H), 6.71 (d, J = 7.0 Hz, 2H), 6.30 (dd, J = 8.6, 2.7 Hz, 1H), 5.84 (d, J = 8.6 Hz, 1H), 4.25 (d, J = 16.4 Hz, 1H), 3.99 (d, J = 16.4 Hz, 1H), 3.72 (s, 3H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 201.7, 160.3, 159.5, 143.0, 142.0, 139.0, 137.6, 137.2, 132.0, 130.21, 130.16, 129.1, 128.8, 128.6, 128.3, 127.8, 127.5, 127.0, 126.9, 126.1, 125.7, 116.9, 112.1, 109.4, 73.1, 55.3, 52.5; IR (neat): 3027, 2926, 1724, 1552, 1489, 1344, 1275, 1150, 1031 cm^{-1}; HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{33}H_{25}N_2O_2$ 481.1916; Found 481.1920.

Ethyl 7-methoxy-2,4-diphenyl-3,4-dihydroquinazoline-4-carboxylate (6). Prepared according to the general 3,4-DHQ debenzylation protocol with **2** (2.182 g, 4.58 mmol), EtOH (8 mL), cyclohexene (20 mL), and 10% Pd/C (0.621 g). After workup, the residue was triturated with ether, and the solid was collected by filtration to afford the desired product (1.634 g, 92%) as a solid (m.p. = 159 - 161 °C). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 – 7.89 (m, 2H), 7.52 – 7.32 (m, 8H), 6.95 (d, J = 8.6 Hz, 1H), 6.91 (d, J = 2.7 Hz, 1H), 6.62 (dd, J = 8.6, 2.7 Hz, 1H), 6.13 (s, 1H), 4.42 – 4.20 (m, 2H), 3.83 (s, 3H), 1.27 (t, J = 7.1 Hz, 3H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 172.7, 160.2, 153.7, 143.8, 143.0, 135.2, 130.9, 129.5, 128.7, 128.6, 128.4, 127.5, 127.0, 116.2, 112.1, 108.6, 66.7, 62.4, 55.3, 14.2; IR (neat): 3358, 3060, 2976, 1728, 1593, 1560, 1465, 1208, 1103, 1023 cm^{-1}; HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{24}H_{23}N_2O_3$ 387.1709; Found 387.1715.

Ethyl 1-benzyl-7-methoxy-2,4-diphenyl-1,4-dihydroquinazoline-4-carboxylate (7). Prepared according to the general 1,4-DHQ synthesis protocol with **6** (83.3 mg, 0.22 mmol), benzyl bromide (29 μL, 0.29 mmol), NaH (11.0 mg, 0.28 mmol), and DMF (1.5 mL). After workup, the residue was purified by MPLC (31% - 52% EtOAc in hexanes as eluent) to afford the desired product (79.4 mg, 78%) as a solid (m.p. = 112 - 114 °C). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53 – 7.45 (m, 2H), 7.41 – 7.25 (m, 8H), 7.12 – 6.98 (m, 4H), 6.75 (d, J = 7.6 Hz, 2H), 6.61 (dd, J = 8.6, 2.4 Hz, 1H), 6.48 (d, J = 2.5 Hz, 1H), 4.79 (s, 2H), 4.35 (dq, J = 10.7, 7.1 Hz, 1H), 4.22 (dq, J = 10.8, 7.1 Hz, 1H), 3.70 (s, 3H), 1.26 (t, J = 7.1 Hz, 3H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 173.1, 159.5, 155.9, 144.3, 138.5, 136.8, 135.8, 129.5, 128.8, 128.8, 128.4, 127.9, 127.9, 127.14, 127.10, 126.5, 116.8, 108.2, 100.6, 69.2, 61.8, 55.2, 51.2, 14.2; IR (neat): 3058, 2924, 1728, 1612, 1504, 1366, 1210, 1029 cm^{-1}; HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{31}H_{29}N_2O_3$ 477.2178; Found 477.2174.

Ethyl 6-fluoro-7-methoxy-2,4-diphenyl-3,4-dihydroquinazoline-4-carboxylate (8a). Prepared according to the general 3,4-DHQ debenzylation protocol with **4c** (0.135 g, 0.41 mmol), EtOH (2 mL), cyclohexene (4 mL), and 10% Pd/C (0.094 g). The reaction mixture was passed through a silica plug (10% MeOH in EtOAc as eluent) instead of a celite plug, and the concentrated filtrate was purified by MPLC (10% ether in CH_2Cl_2 as eluent) to afford the desired product (0.082 g, 74%) as an oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 (dd, J = 7.9, 1.8 Hz, 2H), 7.50 – 7.32 (m, 8H), 6.98 (d, J = 8.2 Hz, 1H), 6.79 (d, J = 12.0 Hz, 1H), 6.13 (s, 1H), 4.39 – 4.21 (m, 2H), 3.90 (s, 3H), 1.27 (t, J = 7.1 Hz, 3H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 172.4, 153.2 (d, $^{6}J_{C\text{-}F}$ = 2 Hz), 149.7 (d, $^{1}J_{C\text{-}F}$ = 243 Hz), 148.1 (d, $^{2}J_{C\text{-}F}$ = 12 Hz), 142.4, 139.4 (d, $^{3}J_{C\text{-}F}$ = 3 Hz), 135.0, 130.9, 128.8, 128.7, 128.6, 127.3, 126.9, 115.7 (d, $^{3}J_{C\text{-}F}$ = 7 Hz), 115.6 (d, $^{2}J_{C\text{-}F}$ = 21 Hz), 109.5 (d, $^{4}J_{C\text{-}F}$ = 2 Hz), 66.4 (d, $^{4}J_{C\text{-}F}$ = 2 Hz), 62.6, 56.1, 14.1; IR (neat): 3379, 3060, 2976, 1731,

1599, 1497, 1476, 1444, 1228, 1094 cm^{-1}; HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{24}H_{22}FN_2O_3$ 405.1614; Found 405.1612.

Ethyl 1-benzyl-6-fluoro-7-methoxy-2,4-diphenyl-1,4-dihydroquinazoline-4-carboxylate (9a). Prepared according to the general 1,4-DHQ synthesis protocol with **8a** (65.5 mg, 0.16 mmol), benzyl bromide (25 µL, 0.21 mmol), NaH (8.0 mg, 0.20 mmol), and DMF (2.0 mL). After workup, the residue was purified by MPLC (32% - 53% EtOAc in hexanes as eluent) to afford the desired product (57.5 mg, 72%) as a solid (m.p. = 189 - 192 °C). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57 – 7.50 (m, 2H), 7.43 – 7.27 (m, 8H), 7.15 – 7.07 (m, 3H), 6.85 (d, J = 11.7 Hz, 1H), 6.79 (dd, J = 7.8, 1.8 Hz, 2H), 6.51 (d, J = 7.4 Hz, 1H), 4.82 (s, 2H), 4.34 (dq, J = 10.8, 7.1 Hz, 1H), 4.23 (dq, J = 10.8, 7.1 Hz, 1H), 3.73 (s, 3H), 1.27 (t, J = 7.1 Hz, 3H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 172.7, 156.0, 148.8 (d, $^1J_{C\text{-}F}$ = 242 Hz), 147.1 (d, $^2J_{C\text{-}F}$ = 12 Hz), 143.7, 136.6, 135.6, 133.8 (d, $^3J_{C\text{-}F}$ = 3 Hz), 129.7, 128.9, 128.6, 128.5, 128.1, 127.8, 127.4, 127.3, 126.6, 116.5 (d, $^3J_{C\text{-}F}$ = 6 Hz), 115.5 (d, $^2J_{C\text{-}F}$ = 21 Hz), 100.4 (d, $^4J_{C\text{-}F}$ = 2 Hz), 69.0, 61.9, 56.3, 51.7, 14.2; IR (neat): 3062, 2935, 1728, 1621, 1515, 1448, 1221, 1031 cm^{-1}; HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{31}H_{28}FN_2O_3$ 495.2084; Found 495.2089.

Ethyl 7-methoxy-2-methyl-4-phenyl-1,4-dihydroquinazoline-4-carboxylate (8b). Prepared according to the general 3,4-DHQ debenzylation protocol with **4e** (0.195 g, 0.47 mmol), EtOH (3 mL), cyclohexene (4 mL), and 10% Pd/C (0.098 g). After workup, the residue was purified by MPLC (8% - 35% MeOH in EtOAc as eluent) to afford the desired product (0.128 g, 84%) as an oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 – 7.28 (m, 5H), 6.94 (d, J = 8.6 Hz, 1H), 6.69 (s, 1H), 6.57 (dd, J = 8.6, 2.7 Hz, 1H), 5.63 (broad s, 1H), 4.36 – 4.18 (m, 2H), 3.79 (s, 3H), 2.17 (s, 3H), 1.26 (t, J = 7.1 Hz, 3H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 172.1, 160.3, 154.8, 142.8, 140.9, 129.8, 128.6, 128.4, 127.4, 114.0, 111.9, 106.1, 66.7, 62.5, 55.4, 21.7, 14.1; IR (neat): 3351, 2978, 1731, 1593, 1484, 1204, 1219, 1124, 1021 cm^{-1}; HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{19}H_{21}N_2O_3$ 325.1552; Found 325.1557.

Ethyl 1-benzyl-7-methoxy-2-methyl-4-phenyl-1,4-dihydroquinazoline-4-carboxylate (9b). Prepared according to the general 1,4-DHQ synthesis protocol with **8b** (70.0 mg, 0.22 mmol), benzyl bromide (33 µL, 0.28 mmol), NaH (10.5 mg, 0.26 mmol), and DMF (2.0 mL). After workup, the residue was purified by MPLC (0% - 1% MeOH in EtOAc as eluent) to afford the desired product (73.2 mg, 82%) as an oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 – 7.18 (m, 8H), 7.06 – 6.97 (m, 3H), 6.55 (dd, J = 8.6, 2.4 Hz, 1H), 6.28 (d, J = 2.5 Hz, 1H), 4.93 (d, J = 2.7 Hz, 2H), 4.28 (qq, J = 10.8, 7.1 Hz, 2H), 3.63 (s, 3H), 2.27 (s, 3H), 1.25 (t, J = 7.1 Hz, 3H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 173.1, 159.6, 153.0, 144.4, 138.4, 136.5, 129.1, 128.9, 127.8, 127.7, 127.3, 127.0, 125.8, 115.5, 107.4, 99.8, 68.6,

61.7, 55.2, 49.4, 22.4, 14.1; IR (neat): 3056, 2973, 1726, 1636, 1610, 1504, 1383, 1288, 1206, 1027 cm^{-1}; HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{26}H_{27}N_2O_3$ 415.2022; Found 415.2019.

Diethyl 7-methoxy-2-phenyl-3,4-dihydroquinazoline-4,4-dicarboxylate (8c). Prepared according to the general 3,4-DHQ debenzylation protocol with **4z** (0.205 g, 0.437 mmol), EtOH (2 mL), cyclohexene (4 mL), and 10% Pd/C (0.0.97 g). After workup, the residue was purified by MPLC (30% - 50% EtOAc in hexanes as eluent) to afford the desired product (0.128 g, 84%) as an oil. ^1H NMR (400 MHz, $CDCl_3$, 330 K) δ 7.89 (broad s, 2H), 7.64 – 7.30 (m, 4H), 6.88 (broad s, 1H), 6.70 (d, *J* = 8.0 Hz, 1H), 6.32 (broad s, 1H), 4.27 (qd, *J* = 7.1, 2.4 Hz, 4H), 3.79 (s, 3H), 1.27 (t, *J* = 7.1 Hz, 6H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 168.9, 161.0, 152.7, 143.9, 135.2, 130.9, 128.7, 126.9, 112.2, 109.9, 66.7, 62.8, 55.4, 14.0; IR (neat): 3353, 3060, 2980, 1730, 1620, 1478, 1249, 1210, 1049 cm^{-1}; HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{21}H_{23}N_2O_5$ 383.1607; Found 383.1612.

Diethyl 1-benzyl-7-methoxy-2-phenyl-1,4-dihydroquinazoline-4,4-dicarboxylate (9c). Prepared according to the general 1,4-DHQ synthesis protocol with **8c** (81.0 mg, 0.21 mmol), benzyl bromide (33 µL, 0.28 mmol), NaH (10.2 mg, 0.26 mmol), and DMF (2.0 mL). After workup, the residue was purified by MPLC (45% - 70% EtOAc in hexanes as eluent) to afford the desired product (90.0 mg, 90%) as an oil. ^1H NMR (400 MHz, $CDCl_3$) δ 7.55 – 7.47 (m, 2H), 7.40 – 7.30 (m, 4H), 7.27 – 7.08 (m, 5H), 6.64 (dd, *J* = 8.7, 2.4 Hz, 1H), 6.37 (d, *J* = 2.5 Hz, 1H), 4.82 (s, 2H), 4.28 (q, *J* = 7.1 Hz, 4H), 3.65 (s, 3H), 1.29 (t, *J* = 7.1 Hz, 6H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 169.6, 160.1, 156.8, 138.0, 136.8, 135.9, 129.7, 129.6, 128.6, 128.48, 128.45, 127.3, 126.3, 111.4, 108.7, 100.8, 70.7, 62.0, 55.2, 51.3, 14.1; IR (neat): 2983, 1733, 1616, 1508, 1374, 1269, 1219, 1053 cm^{-1}; HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{28}H_{29}N_2O_5$ 473.2076; Found 473.2073.

Ethyl 1-allyl-7-methoxy-2,4-diphenyl-1,4-dihydroquinazoline-4-carboxylate (9d). Prepared according to the general 1,4-DHQ synthesis protocol with **6** (85.8 mg, 0.22 mmol), allyl bromide (25 µL, 0.29 mmol), NaH (10.4 mg, 0.26 mmol), and DMF (2.0 mL). After workup, the residue was purified by MPLC (20% - 40% EtOAc in hexanes as eluent) to afford the desired product (70.1 mg, 74%) as a solid (m.p. = 106 - 109 °C). ^1H NMR (400 MHz, $CDCl_3$) δ 7.53 – 7.47 (m, 2H), 7.43 – 7.20 (m, 8H), 6.97 (d, *J* = 8.6 Hz, 1H), 6.64 (dd, *J* = 8.6, 2.4 Hz, 1H), 6.55 (d, *J* = 2.4 Hz, 1H), 5.47 (ddt, *J* = 17.2, 10.2, 5.0 Hz, 1H), 5.03 (dq, *J* = 10.6, 1.6 Hz, 1H), 4.97 (dq, *J* = 17.1, 1.6 Hz, 1H), 4.33 (dq, *J* = 10.8, 7.1 Hz, 1H), 4.27 – 4.16 (m, 3H), 3.79 (s, 3H), 1.26 (t, *J* = 7.1 Hz, 3H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 173.1, 159.6, 155.7, 143.9, 138.5, 135.8, 133.2, 129.5, 129.0, 128.7, 128.3, 127.9, 127.8, 127.0, 117.2, 117.1, 108.1,

100.6, 69.3, 61.6, 55.3, 49.9, 14.2; IR (neat): 3058, 2980, 1724, 1610, 1501, 1446, 1364, 1206, 1170, 1027 cm^{-1}; HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{27}H_{27}N_2O_3$ 427.2022; Found 427.2022.

Ethyl 1-hexyl-7-methoxy-2,4-diphenyl-1,4-dihydroquinazoline-4-carboxylate (9e). Prepared according to the general 1,4-DHQ synthesis protocol with **6** (86.0 mg, 0.22 mmol), 1-bromohexane (40 µL, 0.29 mmol), NaH (10.4 mg, 0.26 mmol), and DMF (2.0 mL). After workup, the residue was purified by MPLC (15% - 35% EtOAc in hexanes as eluent) to afford the desired product (65.7 mg, 63%) as an oil. ^1H NMR (400 MHz, $CDCl_3$) δ 7.53 – 7.47 (m, 2H), 7.42 – 7.19 (m, 8H), 6.95 (d, *J* = 8.5 Hz, 1H), 6.66 (dd, *J* = 8.5, 2.4 Hz, 1H), 6.62 (d, *J* = 2.4 Hz, 1H), 4.32 (dq, *J* = 10.8, 7.1 Hz, 1H), 4.21 (dq, *J* = 10.8, 7.1 Hz, 1H), 3.83 (s, 3H), 3.71 – 3.52 (m, 2H), 1.32 – 1.23 (m, 5H), 1.09 – 1.00 (m, 2H), 0.97 – 0.77 (m, 4H), 0.74 (t, *J* = 7.3 Hz, 3H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 173.2, 159.7, 156.3, 143.9, 138.5, 135.9, 129.5, 129.1, 128.9, 128.3, 127.79, 127.76, 127.0, 118.0, 107.8, 100.1, 69.3, 61.6, 55.4, 46.9, 31.2, 28.0, 25.8, 22.3, 14.2, 13.9; IR (neat): 3060, 2928, 1728, 1610, 1500, 1446, 1366, 1211, 1172, 1113, 1027 cm^{-1}; HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{30}H_{35}N_2O_3$ 471.2648; Found 471.2659.

Ethyl 1-(cyclohexylmethyl)-7-methoxy-2,4-diphenyl-1,4-dihydroquinazoline-4-carboxylate (9f). Prepared according to the general 1,4-DHQ synthesis protocol with **6** (85.3 mg, 0.22 mmol), bromomethyl cyclohexane (40 µL, 0.29 mmol), NaH (10.5 mg, 0.26 mmol), and DMF (2.0 mL). After workup, the residue was purified by MPLC (20% - 40% EtOAc in hexanes as eluent) to afford the desired product (64.4 mg, 60%) as an oil. ^1H NMR (400 MHz, $CDCl_3$) δ 7.46 (dd, *J* = 7.1, 2.6 Hz, 2H), 7.43 – 7.35 (m, 3H), 7.35 – 7.26 (m, 4H), 7.24 – 7.18 (m, 1H), 6.97 (d, *J* = 8.6 Hz, 1H), 6.68 (dd, *J* = 8.6, 2.4 Hz, 1H), 6.60 (d, *J* = 2.4 Hz, 1H), 4.33 (dq, *J* = 10.9, 7.1 Hz, 1H), 4.21 (dq, *J* = 10.9, 7.1 Hz, 1H), 3.85 (s, 3H), 3.48 (dd, *J* = 14.5, 6.0 Hz, 1H), 3.36 (dd, *J* = 14.5, 7.2 Hz, 1H), 1.55 – 1.20 (m, 8H), 1.09 – 0.73 (m, 4H), 0.54 (qd, *J* = 12.2, 3.3 Hz, 1H), 0.36 – 0.21 (m, 1H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 173.3, 159.6, 156.4, 144.1, 138.7, 136.0, 129.4, 129.3, 128.8, 128.3, 127.8, 127.7, 127.1, 117.8, 107.6, 100.2, 69.1, 61.7, 55.4, 53.2, 36.2, 30.5, 30.3, 26.1, 25.7, 14.2; IR (neat): 3058, 2920, 1726, 1610, 1502, 1446, 1372, 1202, 1172, 1027 cm^{-1}; HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{31}H_{35}N_2O_3$ 483.2648; Found 483.2655.

Ethyl 1-isopropyl-7-methoxy-2,4-diphenyl-1,4-dihydroquinazoline-4-carboxylate (9g). Prepared according to the general 1,4-DHQ synthesis protocol with **6** (77.0 mg, 0.20 mmol), 2-bromopropane (24 µL, 0.26 mmol), NaH (9.9 mg, 0.25 mmol), and DMF (2.0 mL). After workup, the residue was purified by MPLC (20% - 40% EtOAc in hexanes as eluent) to afford the desired product (17.9 mg, 21%) as an oil. ^1H NMR (400 MHz, $CDCl_3$) δ 7.63 – 7.58 (m, 2H), 7.43 – 7.33 (m, 5H), 7.33 – 7.27 (m, 2H), 7.26 – 7.20 (m, 1H), 6.91 (d, *J* = 8.6 Hz, 1H), 6.85 (d, *J* = 2.4 Hz, 1H), 6.66

(dd, J = 8.7, 2.4 Hz, 1H), 4.34 (dq, J = 10.8, 7.1 Hz, 1H), 4.20 (dq, J = 10.8, 7.1 Hz, 1H), 3.95 – 3.85 (m, 1H), 3.84 (s, 3H), 1.32 – 1.23 (m, 6H), 1.19 (d, J = 6.9 Hz, 3H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 173.3, 159.2, 158.2, 143.9, 139.2, 137.1, 129.6, 129.4, 128.6, 128.2, 127.9, 127.8, 127.0, 120.4, 107.9, 103.1, 69.4, 61.6, 55.4, 51.9, 22.6, 22.5, 14.2; IR (neat): 3060, 2978, 1726, 1612, 1500, 1333, 1210, 1047 cm^{-1}; HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{27}H_{29}N_2O_3$ 429.2178; Found 429.2173.

Ethyl 7-methoxy-1-methyl-2,4-diphenyl-1,4-dihydroquinazoline-4-carboxylate (9h). Prepared according to the general 1,4-DHQ synthesis protocol with **6** (84.8 mg, 0.22 mmol), methyl iodide (14 μL, 0.22 mmol), NaH (10.2 mg, 0.26 mmol), and DMF (1.5 mL). After workup, the residue was purified by MPLC (0% - 15% EtOAc in CH_2Cl_2 as eluent) to afford the desired product (72.0 mg, 82%) as a solid (m.p. = 181 - 184 °C). ^1H NMR (400 MHz, $CDCl_3$) δ 7.60 – 7.50 (m, 2H), 7.49 – 7.25 (m, 8H), 6.98 (d, J = 8.6 Hz, 1H), 6.69 (dd, J = 8.6, 2.4 Hz, 1H), 6.61 (d, J = 2.4 Hz, 1H), 4.37 (dq, J = 10.8, 7.1 Hz, 1H), 4.26 (dq, J = 10.7, 7.1 Hz, 1H), 3.87 (s, 3H), 3.16 (s, 3H), 1.29 (t, J = 7.1 Hz, 3H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 173.2, 159.9, 155.7, 143.7, 139.9, 135.6, 129.6, 129.0, 128.9, 128.3, 127.9, 127.7, 127.0, 116.5, 107.7, 99.1, 69.3, 61.6, 55.4, 36.0, 14.2; IR (neat): 3060, 2932, 1728, 1612, 1472, 1355, 1221, 1098, 1040 cm^{-1}; HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{25}H_{25}N_2O_3$ 401.1865; Found 401.1874.

4-(ethoxycarbonyl)-7-methoxy-1,3-dimethyl-2,4-diphenyl-1,4-dihydroquinazolin-3-ium iodide (10). Prepared according to the general 1,4-DHQ synthesis protocol with **6** (88.5 mg, 0.23 mmol), methyl iodide (43 μL, 0.69 mmol), NaH (10.6 mg, 0.27 mmol), and DMF (1.5 mL), with the reaction proceeding for 2 days. After workup, the residue was purified by MPLC (3% - 7% MeOH in 95:5 CH_2Cl_2:ether as eluent) to afford the desired product (101 mg, 81%) as an orange solid (m.p. = 106 - 110 °C). ^1H NMR (400 MHz, $CDCl_3$) δ 8.33 – 8.26 (m, 1H), 7.77 – 7.67 (m, 4H), 7.61 – 7.46 (m, 5H), 7.06 (d, J = 2.2 Hz, 1H), 6.92 – 6.81 (m, 2H), 4.47 (dq, J = 10.7, 7.1 Hz, 1H), 4.35 (dq, J = 10.8, 7.1 Hz, 1H), 3.95 (s, 3H), 3.62 (s, 3H), 2.64 (s, 3H), 1.32 (t, J = 7.2 Hz, 3H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 168.8, 162.4, 161.4, 136.1, 134.6, 132.8, 131.4, 130.8, 130.5, 130.30, 130.25, 129.4, 129.3, 128.4, 126.9, 115.8, 114.7, 102.4, 74.4, 64.0, 56.6, 41.1, 40.8, 14.1; IR (neat): 2935, 1735, 1616, 1504, 1226, 1018 cm^{-1}; HRMS (ESI-TOF) m/z: $[M-I]^+$ Calcd for $C_{26}H_{27}N_2O_3$ 415.2016; Found 415.2019.

Ethyl 1-[3-(hydroxymercaptohydroperoxy)propyl]-7-methoxy-2,4-diphenyl-1,4-dihydroquinazoline-4-carboxylate (11). Prepared according to the general 1,4-DHQ synthesis protocol with **6** (0.158 g, 0.41 mmol), 1,3-propanesultone (0.100 g, 0.82 mmol), NaH (20.1 mg, 0.50 mmol), and DMF (2.0 mL). During workup, the mixture was made acidic with the addition of 6M HCl solution and was extracted with CH_2Cl_2 (x6). After workup, the residue

was purified by MPLC (5% - 13% MeOH in CH_2Cl_2 as eluent) to afford the desired product (0.115 g, 55%) as a solid (m.p. = 226 - 227 °C). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67 – 7.45 (m, 5H), 7.38 – 7.19 (m, 6H), 6.99 (d, *J* = 8.8 Hz, 1H), 6.83 (dd, *J* = 8.8, 2.1 Hz, 1H), 4.41 – 4.23 (m, 2H), 4.19 – 3.95 (m, 2H), 3.84 (s, 3H), 2.05 – 1.85 (m, 2H), 1.67 – 1.53 (m, 2H), 1.26 (t, *J* = 7.1 Hz, 3H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 169.2, 161.4, 160.2, 138.4, 134.0, 133.1, 129.9, 129.2, 128.9, 128.7, 128.5, 127.1, 115.9, 115.6, 101.9, 67.3, 63.4, 56.6, 47.9, 46.8, 23.7, 14.1, IR (neat): 3055, 2982, 2736, 1737, 1616, 1504, 1221, 1152, 1031 cm^{-1}; HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{27}H_{29}N_2O_6S$ 509.1746; Found 509.1742.

Ethyl 1-acetyl-7-methoxy-2,4-diphenyl-1,4-dihydroquinazoline-4-carboxylate (12a). Prepared according to the general 1,4-DHQ synthesis protocol with **6** (73.0 mg, 0.19 mmol), acetic anhydride (20 µL, 0.21 mmol), NaH (9.3 mg, 0.23 mmol), and DMF (2.5 mL). After workup, the residue was purified by MPLC (20% - 40% EtOAc in hexanes as eluent) to afford the desired product (44.9 mg, 56%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95 – 7.87 (m, 2H), 7.53 – 7.40 (m, 4H), 7.40 – 7.26 (m, 5H), 7.02 (d, *J* = 8.6 Hz, 1H), 6.81 (dd, *J* = 8.7, 2.6 Hz, 1H), 4.36 – 4.21 (m, 2H), 3.87 (s, 3H), 1.62 (s, 3H), 1.24 (t, *J* = 7.1 Hz, 3H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 171.4, 168.1, 159.3, 157.0, 140.8, 136.6, 135.7, 131.4, 128.8, 128.3, 128.2, 127.8, 127.7, 127.0, 126.4, 112.0, 110.0, 71.9, 62.2, 55.6, 25.2, 14.1; IR (neat): 3058, 2933, 1728, 1700, 1618, 1493, 1277, 1228, 1027 cm^{-1}; HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{26}H_{25}N_2O_4$ 429.1814; Found 429.1822.

Ethyl 1-benzoyl-7-methoxy-2,4-diphenyl-1,4-dihydroquinazoline-4-carboxylate (12b). Prepared according to the general 1,4-DHQ synthesis protocol with **6** (76.8 mg, 0.20 mmol), benzoyl chloride (25 µL, 0.22 mmol), NaH (9.7 mg, 0.24 mmol), and DMF (2.5 mL). After workup, the residue was purified by MPLC (10% - 30% EtOAc in hexanes as eluent) to afford the desired product (62.5 mg, 64%) as a solid (m.p. = 179 - 182 °C). ^{1}H NMR (400 MHz, $CDCl_3$-*d*) δ 8.22 (d, *J* = 2.6 Hz, 1H), 7.42 – 7.28 (m, 7H), 7.21 – 7.01 (m, 5H), 6.90 (dd, *J* = 8.7, 2.6 Hz, 1H), 6.83 (dd, *J* = 8.2, 7.3 Hz, 2H), 6.43 (d, *J* = 7.3 Hz, 2H), 4.48 – 4.29 (m, 2H), 3.92 (s, 3H), 1.29 (t, *J* = 7.1 Hz, 3H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 172.1, 170.1, 159.7, 155.9, 141.1, 137.1, 136.6, 136.6, 131.0, 130.0, 128.4, 128.04, 128.01, 127.97, 127.9, 127.7, 127.1, 121.4, 112.1, 107.0, 71.5, 62.2, 55.6, 14.2; IR (neat): 3058, 2932, 1730, 1684, 1625, 1498, 1336, 1239, 1046 cm^{-1}; HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{31}H_{27}N_2O_4$ 491.1971; Found 491.1982.

4-Chloro-*N*-(3-methoxyphenyl)butanamide (13a). Prepared according to the general amide synthesis protocol with *m*-anisidine (1.20 mL, 10.2 mmol), TEA (1.70 mL, 12.2 mmol), 4-chlorobutyryl chloride (1.20 mL, 10.7 mmol), 4-DMAP (0.012 g, 0.10 mmol), and CH_2Cl_2 (50 mL). After workup, the residue was purified by flash chromatography

(60% EtOAc in hexanes as eluent) to afford the desired product (2.230 g, 98%) of the title compound as a solid (m.p. = 51 - 53 °C). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 – 7.25 (m, 2H), 7.21 (t, *J* = 8.1 Hz, 1H), 6.96 (d, *J* = 7.8 Hz, 1H), 6.67 (dd, *J* = 8.1, 2.5 Hz, 1H), 3.80 (s, 3H), 3.66 (t, *J* = 6.1 Hz, 2H), 2.55 (t, *J* = 7.0 Hz, 2H), 2.20 (p, *J* = 6.6 Hz, 2H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 170.0, 160.2, 138.9, 129.7, 111.9, 110.3, 105.5, 55.3, 44.4, 34.2, 27.9. The NMR spectral data are consistent with those reported in the literature.[31]

4-benzyl-5-(ethoxycarbonyl)-8-methoxy-5-phenyl-2,3,4,5-tetrahydro-1H-pyrrolo[1,2-a]quinazolin-10-ium chloride (14a). Prepared according to the general 3,4-DHQ synthesis protocol with **13a** (0.228 g, 1.00 mmol), benzylamine (0.12 mL, 1.1 mmol), ethyl benzoylformate (0.18 g, 1.1 mmol), CH_2Cl_2 (5.0 mL), 2-chloropyridine (0.11 mL, 1.2 mmol), and Tf_2O (0.18 mL, 1.1 mmol), with **13a** not being added to the reaction mixture until 1 hour prior to Tf_2O addition. Following workup, the residue was purified by MPLC (3% - 20% MeOH in CH_2Cl_2 as eluent) to afford the desired product (0.278 g, 58%) as an oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 – 7.34 (m, 2H), 7.33 – 7.23 (m, 3H), 7.18 – 7.11 (m, 3H), 6.95 – 6.85 (m, 4H), 6.77 (dd, *J* = 8.8, 2.4 Hz, 1H), 5.06 (d, *J* = 17.0 Hz, 1H), 4.85 (q, *J* = 8.6 Hz, 1H), 4.59 (d, *J* = 17.0 Hz, 1H), 4.48 (td, *J* = 9.7, 3.9 Hz, 1H), 4.43 – 4.25 (m, 2H), 3.93 (s, 3H), 3.64 (ddd, *J* = 18.4, 9.5, 4.2 Hz, 1H), 3.38 (ddd, *J* = 18.2, 9.9, 7.8 Hz, 1H), 2.70 – 2.45 (m, 2H), 1.27 (t, *J* = 7.1 Hz, 3H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 168.4, 166.1, 161.5, 136.2, 132.9, 131.91, 131.85, 130.8, 130.0, 128.7, 128.6, 128.0, 126.4, 114.4, 114.0, 101.3, 75.6, 63.9, 56.3, 55.3, 52.4, 34.0, 18.9, 14.0; IR (neat): 3066, 2920, 1737, 1634, 1508, 1224, 1018 cm^{-1}; HRMS (ESI-TOF) m/z: $[M-Cl]^+$ Calcd for $C_{28}H_{29}N_2O_3$ 441.2173; Found 441.2169.

Ethyl 12-methoxy-8-phenyl-2.7-diazatricyclo[7.4.0.0^{2,6}]trideca-1(13),6,9,11-tetraene-8-carboxylate (15a). Prepared according to the general 3,4-DHQ debenzylation protocol with **14a** (89.2 mg, 0.19 mmol), EtOH (1.0 mL), cyclohexene (2.0 mL), and 10% Pd/C (54.2 mg). After workup, the residue was purified by MPLC (2% - 5% MeOH in CH_2Cl_2 as eluent) to afford the desired product (44.8 mg, 68%) as a solid (m.p. = 143 - 146 °C). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 – 7.17 (m, 5H), 7.09 (d, *J* = 8.6 Hz, 1H), 6.60 (dd, *J* = 8.6, 2.5 Hz, 1H), 6.29 (d, *J* = 2.5 Hz, 1H), 4.34 – 4.19 (m, 2H), 3.81 (s, 3H), 3.71 – 3.66 (m, 2H), 2.92 – 2.70 (m, 2H), 2.24 – 2.05 (m, 2H), 1.24 (t, *J* = 7.1 Hz, 3H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 173.0, 159.9, 157.9, 144.6, 137.5, 129.7, 127.9, 127.6, 127.0, 113.1, 107.6, 98.3, 69.7, 61.8, 55.4, 47.4, 31.2, 19.6, 14.1; IR (neat): 3058, 2932, 1728, 1666, 1612, 1504, 1450, 1377, 1262, 1213, 1176, 1038 cm^{-1}; HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{21}H_{23}N_2O_3$ 351.1709; Found 351.1710.

5-Chloro-*N*-(3-methoxyphenyl)pentanamide (13b). Prepared according to the general amide synthesis protocol with *m*-anisidine (1.20 mL, 10.7 mmol), TEA (1.70 mL, 12.2 mmol), 5-chlorovaleroyl chloride (1.40 mL, 10.9 mmol),

4-DMAP (0.014 g, 0.11 mmol), and CH_2Cl_2 (50 mL). After workup, the residue was passed through a silica plug (60% EtOAc in hexanes as eluent) to afford the desired product (2.576 g, 99%) of the title compound as a solid (m.p. = 41 - 43 °C). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.16 (s, 1H), 7.32 (t, *J* = 2.1 Hz, 1H), 7.20 – 7.06 (m, 2H), 6.61 (dt, *J* = 7.8, 1.8 Hz, 1H), 3.66 (s, 3H), 3.43 (t, *J* = 6.3 Hz, 2H), 2.36 (t, *J* = 7.2 Hz, 2H), 1.85 – 1.66 (m, 4H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 170.6, 160.2, 139.0, 129.7, 111.8, 110.2, 105.5, 55.3, 44.6, 36.7, 31.9, 22.8. The NMR spectral data are consistent with those reported in the literature.[31]

5-benzyl-6-(ethoxycarbonyl)-9-methoxy-6-phenyl-1,2,3,4,5,6-hexahydropyrido[1,2-a]quinazolin-11-ium chloride (14b). Prepared according to the general 3,4-DHQ synthesis protocol with **13b** (0.242 g, 1.00 mmol), benzylamine (0.12 mL, 1.1 mmol), ethyl benzoylformate (0.18 g, 1.1 mmol), CH_2Cl_2 (5.0 mL), 2-chloropyridine (0.11 mL, 1.2 mmol), and Tf_2O (0.18 mL, 1.1 mmol), with **13b** not being added to the reaction mixture until 1 hour prior to Tf_2O addition. Following workup, the residue was purified by MPLC (3% - 15% MeOH in CH_2Cl_2 as eluent) to afford the desired product (0.316 g, 64%) as an oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.10 – 6.76 (m, 9H), 6.66 – 6.50 (m, 4H), 4.88 (d, *J* = 18.0 Hz, 1H), 4.46 (td, *J* = 12.1, 4.3 Hz, 1H), 4.24 (d, *J* = 18.1 Hz, 1H), 4.15 (dq, *J* = 10.9, 7.1 Hz, 1H), 4.04 (dq, *J* = 10.8, 7.1 Hz, 1H), 3.94 (d, *J* = 12.7 Hz, 1H), 3.68 (s, 3H), 3.11 (ddd, *J* = 17.4, 9.5, 6.6 Hz, 1H), 2.80 (dd, *J* = 19.1, 4.8 Hz, 1H), 2.21 – 2.08 (m, 1H), 1.91 – 1.61 (m, 3H), 1.00 (t, *J* = 7.1 Hz, 3H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 168.8, 164.0, 161.5, 135.5, 134.6, 133.1, 131.3, 130.5, 130.1, 128.8, 128.5, 127.7, 125.2, 116.2, 114.4, 101.5, 75.1, 64.0, 56.5, 53.8, 49.6, 30.0, 21.3, 18.1, 14.1; IR (neat): 2932, 1737, 1618, 1508, 1452, 1230, 1023 cm^{-1}; HRMS (ESI-TOF) m/z: $[M-Cl]^+$ Calcd for $C_{29}H_{31}N_2O_3$ 455.2329; Found 455.2325.

Ethyl 6-methoxy-9-phenyl-4a,10-diaza-2,3,4,9-tetrahydro-1*H*-phenanthrene-9-carboxylate (15b). Prepared according to the general 3,4-DHQ debenzylation protocol with **14b** (0.105 g, 0.22 mmol), EtOH (1.0 mL), cyclohexene (2.0 mL), and 10% Pd/C (55.6 mg). After workup, the residue was purified by MPLC (0% - 5% EtOAc in CH_2Cl_2 as eluent) to afford the desired product (44.0 mg, 56%) as a solid (m.p. = 121 - 124 °C). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 – 7.17 (m, 5H), 6.95 (d, *J* = 8.6 Hz, 1H), 6.60 (dd, *J* = 8.6, 2.4 Hz, 1H), 6.48 (d, *J* = 2.4 Hz, 1H), 4.34 – 4.14 (m, 2H), 3.79 (s, 3H), 3.64 – 3.45 (m, 2H), 2.85 – 2.67 (m, 2H), 1.97 – 1.72 (m, 4H), 1.23 (t, *J* = 7.1 Hz, 3H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 173.4, 159.7, 152.6, 144.2, 138.8, 129.1, 127.8, 127.6, 126.9, 115.5, 107.3, 98.4, 68.1, 61.6, 55.4, 45.1, 31.7, 23.1, 20.2, 14.2; IR (neat): 3055, 2943, 1728, 1634, 1610, 1506, 1446, 1282, 1210, 1176, 1027 cm^{-1}; HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{22}H_{25}N_2O_3$ 365.1865; Found 365.1861.

Associated Content

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org

^{1}H and ^{13}C NMR spectral data of all compounds (PDF).

Crystallography data for compounds **2** and **7** (CIF).

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Notes

The authors declare no competing financial interest.

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