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Catalytic sp^3 C−H Oxidation of Peptides and Their Analogues by Radical Cation Salts: From Glycine Amides to Quinolines

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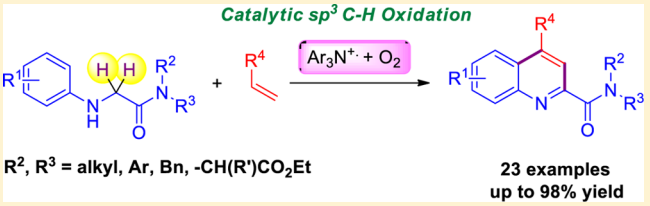
Supporting Information

ABSTRACT: A catalytic α-sp^3 C−H oxidation of peptides and glycine amides was achieved under radical cation salt catalysis in the presence of O_2, producing a series of substituted quinolines. The scope of this reaction shows good functional group tolerance and high efficiency of the oxidative functionalization.



With the study of the properties and functions of natural and non-natural amino acids, great efforts have been devoted to synthesis and modification of amino acids.[1] Since natural amino acids are relatively cheap and accessible, the development of a method for the direct modification of natural amino acids would provide a convenient way to access diverse new amino acids and peptides, which potentially have biological activities. Besides classical methods of functionalization of amino acid derivatives, such as α-functionalization with a strong base,[2] α-bromination by NBS,[3] Claisen rearrangements,[4] and UV photolysis,[5] Li and other groups recently developed a direct α-C−H functionalization of amino acids and peptides, which provided a more convenient way to synthesize amino acid derivatives.[6] Furthermore, Mancheño and Hu provided an efficient route to quinolines using glycine derivatives via tandem cross dehydrogenative coupling (CDC) reaction.[7] However, in these elegant transformations, excess quantities of the oxidants (such as DDQ, TEMPO oxoammonium, and peroxides) are needed, which increases the amount of organic or inorganic byproducts and causes an environmental impact as a result.

Over one century ago, the famous Wurster's Red and Blue salts were prepared in 1879.[8] Since then a great variety of persistent and isolable radical cation salts have been prepared.[9] Among them, aminium radical cation salts, tris(2,4-dibromophenyl)aminium hexachloroantimonate (TDBPA$^{+\bullet}$), and the commercially available tris(4-bromophenyl)aminium hexachloroantimonate (TBPA$^{+\bullet}$), have been widely used to achieve selective and highly efficient transformations, such as Diels−Alder reactions, rearrangements, couplings, etc.[10] In these transformations, radical cation salts were used as **single electron oxidants** to obtain one electron from an electron-rich substrate, producing a radical cation intermediate that undergoes further transformations (see Figure 1A).[10,11] However, no report involving their ability to initiate **aerobic oxidation** of a C−H bond was established.

Recently, we report for the first time a catalytic α-C−H oxidation of glycine esters using triarylaminium radical cation salts as an efficient initiator to prompt aerobic oxidation of an α-sp^3 C−H bond.[12] In this reaction, triarylaminium radical cation salts can react with O_2 to generate a distonic peroxide radical cation, followed by H-abstraction reaction from substrates to achieve α-sp^3 C−H bond activation (see Figure 1B). So we wondered whether our catalytic system could be applied to more general substrates and whether this catalytic α-C−H bond activation could be further extended to peptides and their analogues. Li et al. have reported that glycine esters, unlike glycine amides, did not undergo the CDC reaction with alkynes and arylboronic acids,[6b] which suggested that substituent effect significantly affects the CDC reaction. Herein, we wish to report a novel method for modifying glycine amides and peptides through direct reaction at α-C−H bonds, to provide an access to the quinoline skeleton in a catalytic CDC process.

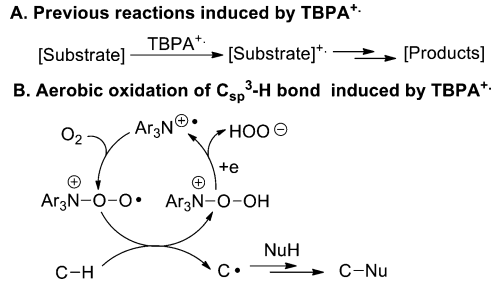


Figure 1. Different reaction patterns induced by radical cation salts.

We started our study with the radical cation salts initiated CDC reaction of *N*-methyl-2-(*p*-tolylamino)acetamide (**1a**) with styrene (**2a**) in the presence of 10 mol % of TBPA$^{+\bullet}$ and 10 mol % $InCl_3 \cdot 4H_2O$ under open air. The reaction gave a moderate yield of the desired product **3a** (Table 1, entry 1).[13] If the reaction solution was performed under O_2 (1 atm), after

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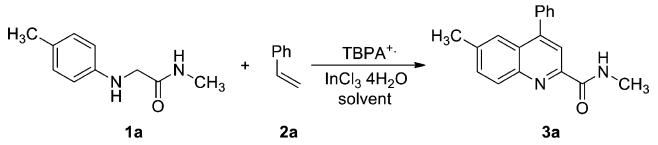
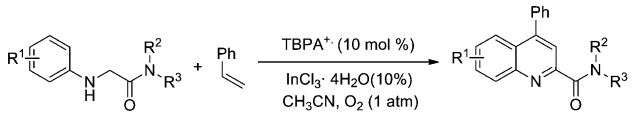
Table 1. Optimization of Reaction Conditions in the Transformation of 1a into 3a



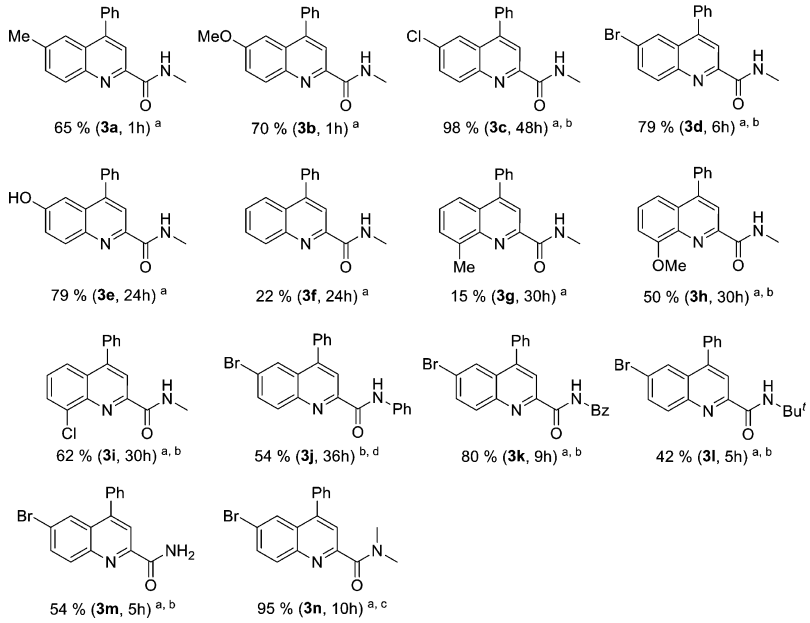
entry	$InCl_3{\cdot}H_2O$ (mol %)	$TBPA^{+\bullet}$ (mol %)	T (°C)	O_2 or air	solvent	t (h)[a]	yield (%)[b]
1	10	10	65	air	CH_3CN	3	64
2	10	10	65	O_2	CH_3CN	40 min	65
3	none	10	65	air	CH_3CN	3	41
4	none	10	65	O_2	CH_3CN	3	42
5	10	none	65	air	CH_3CN	24	NR
6	10	none	65	O_2	CH_3CN	24	NR
7	10	10	65	O_2	CH_2Cl_2	40 min	12
8	10	10	65	O_2	$CHCl_3$	40 min	36
9	10	10	65	O_2	$ClCH_2CH_2Cl$	40 min	46
10	10	1	65	O_2	CH_3CN	1	trace
11	10	5	65	O_2	CH_3CN	1	17
12	10	10	rt	O_2	CH_3CN	3	32
13	10	10	0	O_2	CH_3CN	24	14
14	**10**	**10**	**40**	**O_2**	**CH_3CN**	**80 min**	**69**
15[c]	10	10	40		CH_3CN	24	trace

[a]Monitored by TLC. [b]Detected by crude ^1H NMR based on **1a**. [c]Under argon atmosphere.

Scheme 1. Transformation of *N*-Phenylglycine Amides into Quinoline-2-carboxamides



products (isolated yields %)



[a]Below 40 °C. [b]20 mol % $TBPA^{+\bullet}$ added. [c]15 mol % $TBPA^{+\bullet}$ added. [d]Under refluxing.

only 40 min a 65% yield was reached (entry 2). In the absence of $InCl_3{\cdot}4H_2O$, the starting materials could also be completely consumed, but only poor yields were obtained under air or O_2, respectively, together with some unidentified oxidation products (entries 3 and 4). However, no product was detected in the absence of $TBPA^{+\bullet}$, which implied that the Lewis acid could only accelerate the reaction between glycine amide and styrene instead of initiating it (entries 5 and 6). Solvent optimization efforts showed that acetonitrile was a better solvent, probably because $InCl_3{\cdot}4H_2O$ has a higher solubility in acetonitrile (entries 7−9 compared to entry 2). Reducing the catalyst loading to 5 and 1 mol % led to decrease in the yields (entries 10 and 11). Lower reaction temperature decreased the reaction rate and the yield (entries 12 and 13). Below 40 °C,

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the best result was obtained using acetonitrile as a solvent (entry 14). We also tried the model reaction in the absence of O_2 (entry 15), and only a trace of the desired product was generated, which implied that O_2 is crucial to the C−H bond oxidation.

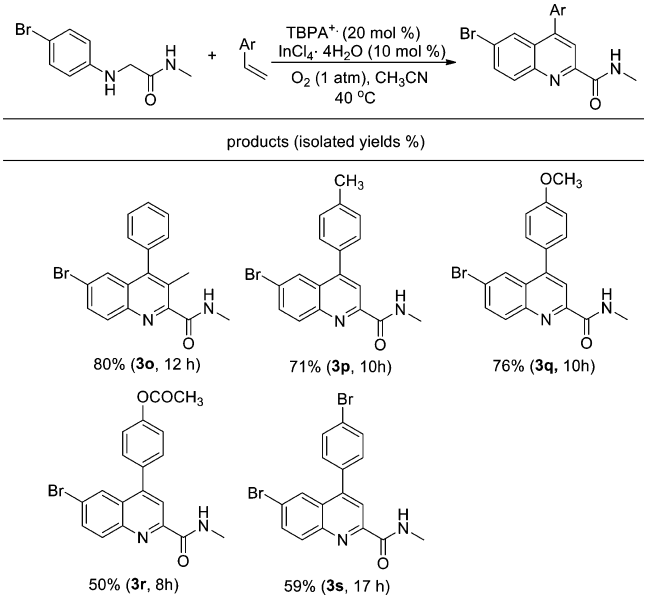
Under the best reaction conditions established, the generality of this catalytic CDC reaction was investigated. We used styrene as a nucleophile to test the substituent effect on glycine amides, and the results are compiled in Scheme 1. Glycine amides with electron-donating groups afforded the quinoline products in good yields (**3a** and **3b**). When glycine amides with electron-withdrawing groups were employed, higher catalyst loading was needed and good to excellent yields were obtained after prolonged reaction time (**3c** and **3d**). Electron-donating groups make the substrate easier to be oxidized, and some nonidentified oxidation products were observed by crude ^{1}H NMR. Interestingly, a phenolic hydroxyl group could also be tolerated, producing the desired product in good yield, which suggested good functional group tolerance of the standard oxidation conditions (**3e**). In the absence of a *para*-substituent at the aniline, the quinoline products **3f−i** were isolated in lower yields together with some unidentified products. Most likely coupling at the *para*-position of the aniline moiety of the starting *N*-phenylglycine amide would provide undesired byproducts.[14]

Other *N*-(4-bromophenyl)glycine amides were then tested. The corresponding *N*-phenyl amide gave the desired product **3j** in medium yield, and *N*-benzylamide with another active benzyl sp^3 C−H bond could also be tolerated, producing the **3k** product in 80% yield, which suggested that site-specific activation of glycine amides and peptides could be achieved via the current methods. Steric hindrance has a deleterious effect on reaction efficiency, as bulky amide reacted to form the desired product **3l** in 42% yield. We also found that a primary amide group does not affect the efficiency of the reaction, giving a medium yield of **3m**. According to Li's report, the CDC reaction does not work when glycine amides without hydrogen on the amide nitrogen are employed.[6b] The current method could also be applied to these kinds of amides, showing good functional group tolerance.

To further extend the scope of our protocol, we next turned our attention to various alkenes other than styrene (Scheme 2). Styrene derivatives with electron-donating groups gave better results than electron-withdrawing groups (**3o**, **3p**, **3q** vs **3s**), but the acetoxy group decreased the yield due to its decomposition under oxidation conditions (**3r**).

Next, other aliphatic olefins were employed in this reaction. When cyclopentadiene was used, a mixture of two polycyclic quinolines (Scheme 3, **4a** and **4a′**) was isolated in medium yields (ratio = 1.6:1), one of the components of which (**4a′**) was identified by single crystal X-ray structure analysis.[15] It is well-known that cyclopentadiene could undergo the Diels−Alder cyclodimerization to yield the [4 + 2] adduct under SET oxidation conditions,[10a] which further reacted with glycine amides, generating the tandem DA/imino DA/aromatization products; however when cyclohexadiene was used instead of cyclopentadiene, no such polycyclic adduct was found (Scheme 3). Besides the normal quinoline product **5** was isolated in 27% yield, a phenanthridine derivative **6** (formed through aromatization of **5**) was obtained. This reaction might open a new potential way to synthesize phenanthridine derivatives, and further investigations and applications were still under way in this laboratory.

Scheme 2. Reaction of *N*-(4-Bromophenyl)glycine Amides with Styrenes



Having succeeded in the catalytic functionalization of glycine amides, we decided to apply this methodology to more challenging substrates. Because of the diverse existence of peptides in nature, we focused on the catalytic functionalization of dipeptides. To our delight, glycine derived dipeptides reacted smoothly with styrene, affording the quinolines in good yield (Scheme 4, **7a** and **7b**). It is worth mentioning that the functionalization occurred exclusively at the N-terminus of the dipeptides without any scrambling on other amino acid moieties.

On the basis of the results that we obtained, a plausible pathway was presented (Scheme 5). Glycine amide was oxidized by TBPA$^{+\bullet}$ in the presence of O_2, yielding a glycine imine intermediate, which readily reacted with alkenes catalyzed by $InCl_3{\cdot}4H_2O$ (Povarov reaction).[16] The corresponding tetrahydroquinoline intermediate was further oxidized and aromatized to quinolines. More details of the mechanism are currently under investigation in this laboratory.

In summary, we demonstrated that an efficient radical cation salt prompted sp^3 C−H oxidaiton of glycine amides and peptides. Different from reported CDC reactions, only catalytic amounts of triarylaminium radical cation salts can efficiently induce this reaction, avoiding addition of excess oxidants. This method might potentially open a new way to achieve CDC reactions and also make a contribution to research in radical cation chemistry. The mild reaction conditions, good functional group tolerance, and high efficiency of the oxidative functionalization make the present transformation attractive for future applications.

EXPERIMENTAL SECTION

Typical Procedure for TBPA$^{+\bullet}$-Induced Reaction of Glycine amides and Styrenes. A solution of **1** (0.5 mmol), **2** (1.25 mmol) and $InCl_3{\cdot}4H_2O$ (10 mol %) in CH_3CN (5 mL) was mixed fully and then flushed with O_2 (flushing was continued until the reaction was complete), followed by addition of TBPA$^{+\bullet}$ (10 mol % based on **1**) under certain temperature. After completion as monitored by TLC, the reaction was quenched with sodium carbonate/methanol solution. The mixture was poured into a separatory funnel with the addition of excess DCM, and then the crude organic solution was extracted three

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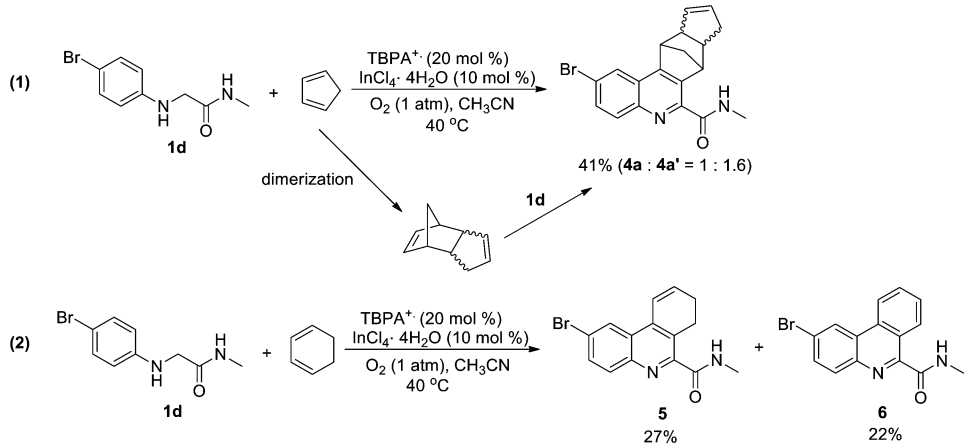
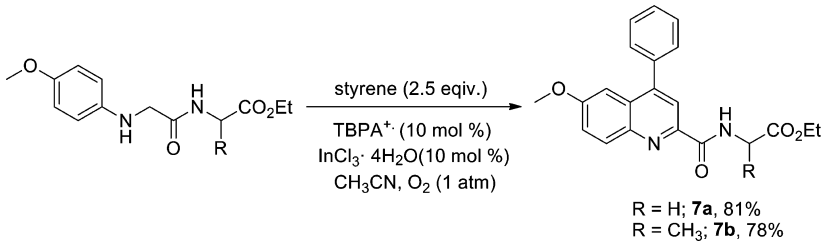
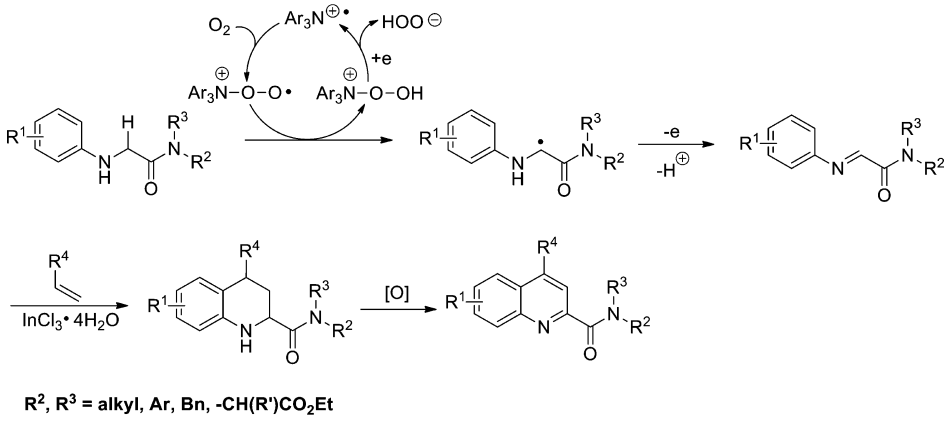
Scheme 3. Reactions of *N*-(4-Bromophenyl)glycine Amides with Cyclic 1,3-Dienes



Scheme 4. Catalytic Transformations of Dipeptide Esters



Scheme 5. Plausible Rationale for the α-sp^3 C−H Activation of *N*-Phenylglycine Amides and Their Transformation into 4-Phenylquinoline-2-carboxamides



times with water to remove inorganic salts. The organic phase was then dried over anhydrous magnesium sulfate and filtered, and the solvent was removed under reduced pressure. The products were separated by silica gel column chromatography using petroleum ether/acetone (v/v 10:1) to afford the products.

***N*,6-Dimethyl-4-phenylquinoline-2-carboxamide (3a).** Compound **3a** was isolated in 65% yield (89.7 mg, colorless crystal); mp 168.0−170.0 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.20 (s, *NH*, 1H), 8.15 (s, 1H), 7.96 (d, J = 8.5 Hz, 1H), 7.65 (s, 1H), 7.51 (d, J = 8.5 Hz, 1H), 7.45 (s, 5H), 3.04 (d, J = 5.1 Hz, 3H), 2.41 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.3, 149.1, 148.5, 145.7, 138.1, 137.9, 132.2, 129.6, 129.6, 128.6, 128.5, 127.7, 124.6, 119.1, 26.2, 22.0; EI-MS m/z (relative intensity, %) 276 (20.6%), 247 (5.4%), 219 (100%), 204 (14.0%); HRMS (ESI, ion trap) calcd for $C_{18}H_{16}N_2O$ + H$^+$, 277.1341, found 277.1351.

6-Methoxy-*N*-methyl-4-phenylquinoline-2-carboxamide (3b).[7b] Compound **3b** was isolated in 70% yield (102.2 mg, colorless crystal); mp 171.0−174.0 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.30−8.19 (m, 2H), 8.02 (dd, J = 9.2, 3.0 Hz, 1H), 7.59−7.44 (m, 4H), 7.43−7.36 (m, 1H), 7.28−7.20 (m, 2H), 3.79 (s, 3H), 3.10 (d, J = 4.8 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.4, 158.9, 148.3, 147.2, 143.1, 138.0, 131.4, 129.3, 128.9, 128.7, 128.5, 122.6, 119.4, 103.5, 55.5, 26.2; EI-MS m/z (relative intensity, %) 292 (22.0%), 263 (6.2%), 235 (100%), 191 (18.3%); HRMS (ESI, ion trap) calcd for $C_{18}H_{16}N_2O_2$ + H$^+$, 293.1290, found 293.1289.

6-Chloro-*N*-methyl-4-phenylquinoline-2-carboxamide (3c).[7b] Compound **3c** was isolated in 98% yield (145.0 mg, colorless crystal); mp 206.0−208.0 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.21 (s, 1H), 8.16 (s, *NH*, 1H), 8.01 (d, J = 9.0 Hz, 1H), 7.87 (d, J = 2.2 Hz, 1H), 7.62 (dd, J = 9.0, 2.3 Hz, 1H), 7.51−7.41 (m, 5H), 3.04 (d, J = 5.0 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.8, 149.6, 149.3, 145.5, 137.0, 134.0, 131.6, 130.8, 129.4, 128.9, 128.4, 124.8, 124.7, 119.8, 26.2; EI-MS m/z (relative intensity, %) 298 (8.7%), 296 (28.6%), 269 (3.4%), 267 (9.1%), 241 (34.0%), 239 (100%), 204 (31.3%), 203 (32.3%); HRMS (ESI, ion trap) calcd for $C_{17}H_{13}ClN_2O$ + H$^+$, 297.0795, found 297.0808.

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6-Bromo-*N*-methyl-4-phenylquinoline-2-carboxamide (3d). Compound **3d** was isolated in 79% yield (134.3 mg, colorless crystal); mp 231.0−235.0 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.28 (d, J = 1.6 Hz, 1H), 8.23 (s, *NH*, 1H), 8.12 (d, J = 2.0 Hz, 1H), 8.05−7.99 (m, 1H), 7.84 (dt, J = 9.0, 2.0 Hz, 1H), 7.60−7.48 (m, 5H), 3.12 (d, J = 5.3 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.8, 149.7, 149.2, 145.7, 137.0, 133.5, 133.4, 131.6, 129.6, 128.9, 128.8, 128.2, 122.3, 119.8, 26.2; EI-MS m/z (relative intensity, %) 342 (22.2%), 340 (22.1%), 313 (6.3%), 311 (7.2%), 285 (98.9%), 283 (100%), 204 (39.9%), 203 (48.9%); HRMS (ESI, ion trap) calcd for $C_{17}H_{13}BrN_2O$ + H^+, 341.0290, found 341.0299.

6-Hydroxy-*N*-methyl-4-phenylquinoline-2-carboxamide (3e). Compound **3e** was isolated in 79% yield (109.8 mg, colorless crystal); mp 238.0−240.0 °C; ^{1}H NMR (400 MHz, DMSO) δ 10.27 (s, *OH*, 1H), 8.82 (d, *NH*, J = 4.8 Hz, 1H), 8.05 (d, J = 9.1 Hz, 1H), 7.89 (d, J = 1.9 Hz, 1H), 7.67−7.49 (m, 5H), 7.42 (dd, J = 9.1, 2.5 Hz, 1H), 7.21−7.15 (m, 1H), 2.89 (dd, J = 4.8, 1.6 Hz, 3H); ^{13}C NMR (101 MHz, DMSO) δ 164.9, 157.3, 146.9, 146.8, 141.9, 137.7, 131.6, 129.2, 128.9, 128.7, 128.5, 123.0, 118.6, 106.2, 26.1; EI-MS m/z (relative intensity, %) 278 (31.0%), 249 (10.5%), 235 (9.0%), 221 (100%), 190 (12.1%), 165 (9.1%); HRMS (ESI, ion trap) calcd for $C_{17}H_{14}N_2O_2$ + H^+, 279.1134, found 279.1145.

***N*-Methyl-4-phenylquinoline-2-carboxamide (3f).**[7b] Compound **3f** was isolated in 22% yield (28.8 mg, colorless ail); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.32 (s, *NH*, 1H), 8.29 (s, 1H), 8.16 (d, J = 8.3 Hz, 1H), 7.99 (d, J = 8.3 Hz, 1H), 7.81−7.73 (m, 1H), 7.62−7.47 (m, 6H), 3.13 (d, J = 5.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.2, 150.0, 149.4, 147.1, 137.7, 130.0, 129.9, 129.6, 128.6, 127.8, 127.7, 126.0, 119.0, 26.3, one ^{13}C signal lost for overlap; EI-MS m/z (relative intensity, %) 262 (34.0%), 231 (18.4%), 205 (100%), 190 (20.8%), 176 (13.5%), 105 (15.6%); HRMS (ESI, ion trap) calcd for $C_{17}H_{14}N_2O$ + H^+, 263.1184, found 263.1180.

***N*,8-Dimethyl-4-phenylquinoline-2-carboxamide (3g).** Compound **3g** was isolated in 15% yield (20.7 mg, colorless oil); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.32 (s, *NH*, 1H), 8.28 (s, 1H), 7.83 (d, J = 8.4 Hz, 1H), 7.62 (d, J = 6.9 Hz, 1H), 7.58−7.42 (m, 4H), 7.38−7.34 (m, 1H), 6.94−6.91 (m, 1H), 3.16 (d, J = 5.1 Hz, 3H), 2.89 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.5, 150.2, 147.9, 146.1, 138.2, 137.6, 132.5, 130.0, 129.6, 128.5, 127.5, 125.6, 124.0, 118.8, 26.3, 18.4; EI-MS m/z (relative intensity, %) 276 (28.1%), 247 (8.7%), 219 (100%), 189 (16.2%); HRMS (ESI, ion trap) calcd for $C_{18}H_{16}N_2O$ + H^+, 277.1341, found 277.1355.

8-Methoxy-*N*-methyl-4-phenylquinoline-2-carboxamide (3h). Compound **3h** was isolated in 50% yield (73.0 mg, colorless crystal); mp 152.0−155.0 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.24 (s, *NH*, 1H), 8.22 (s, 1H), 7.51−7.37 (m, 7H), 7.04 (d, J = 7.6 Hz, 1H), 4.04 (s, 3H), 3.04 (d, J = 5.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.3, 155.6, 150.0, 148.3, 139.1, 138.0, 129.6, 129.0, 128.6, 128.5, 128.0, 119.8, 117.8, 108.0, 56.2, 26.2; EI-MS m/z (relative intensity, %) 292 (18.9%), 291 (18.3%), 235 (60.7%), 233 (100%), 204 (27.1%), 203 (24.5%); HRMS (ESI, ion trap) calcd for $C_{18}H_{16}N_2O_2$ + H^+, 293.1290, found 293.1301.

8-Chloro-*N*-methyl-4-phenylquinoline-2-carboxamide (3i). Compound **3i** was isolated in 62% yield (91.8 mg, colorless crystal); mp 178.0−180.0 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.39 (s, *NH*, 1H), 8.34 (s, 1H), 7.90 (t, J = 7.2 Hz, 2H), 7.60−7.44 (m, 6H), 3.15 (d, J = 5.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.8, 150.8, 149.5, 143.3, 137.4, 134.3, 129.0, 129.6, 129.2, 128.9, 128.7, 127.5, 125.1, 119.9, 26.4; EI-MS m/z (relative intensity, %) 298 (6.0%), 296 (19.9%), 269 (3.2%), 267 (11.9%), 241 (32.0%), 239 (100%), 204 (31.4%); HRMS (ESI, ion trap) calcd for $C_{17}H_{13}ClN_2O$ + H^+, 297.0795, found 297.0805.

6-Bromo-*N*,4-diphenylquinoline-2-carboxamide (3j). Compound **3j** was isolated in 54% yield (108.5 mg, colorless crystal); mp 225.0−227.0 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.20 (s, *NH*, 1H), 8.39 (s, 1H), 8.19−8.09 (m, 2H), 7.88 (t, J = 8.2 Hz, 3H), 7.57 (q, J = 7.7 Hz, 5H), 7.44 (t, J = 7.9 Hz, 2H), 7.20 (t, J = 7.4 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 161.8, 149.7, 145.5, 137.7, 136.9, 133.7, 131.7, 129.6, 129.5, 129.1, 129.1, 129.0, 128.9, 128.2, 124.5, 122.7, 119.8, one ^{13}C signal lost for overlap; EI-MS m/z (relative intensity, %) 404 (78.8%), 402 (80.7%), 285 (90.1%), 283 (100%), 203 (70.9%), 176 (21.6%); HRMS (ESI, ion trap) calcd for $C_{22}H_{15}BrN_2O$ + H^+, 403.0446, found 403.0455.

***N*-Benzyl-6-bromo-4-phenylquinoline-2-carboxamide (3k).** Compound **3k** was isolated in 80% yield (172.0 mg, colorless crystal); mp 256.0−257.0 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.59 (t, *NH*, J = 5.5 Hz, 1H), 8.34 (s, 1H), 8.14 (d, J = 2.1 Hz, 1H), 8.01 (d, J = 9.0 Hz, 1H), 7.83 (dd, J = 9.0, 2.1 Hz, 1H), 7.62−7.49 (m, 5H), 7.44 (d, J = 7.1 Hz, 2H), 7.39 (t, J = 7.4 Hz, 2H), 7.33 (dd, J = 8.3, 6.0 Hz, 1H), 4.77 (d, J = 6.1 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.1, 149.5, 149.3, 145.7, 138.2, 137.0, 133.5, 131.7, 129.5, 129.0, 128.9, 128.8, 128.1, 127.9, 127.6, 122.4, 120.0, 43.7; EI-MS m/z (relative intensity, %) 418 (22.2%), 416 (19.7%), 375 (22.9%), 373 (24.2%), 285 (41.5%), 283 (47.4%), 204 (22.4%), 203 (31.9%), 106 (100%); HRMS (ESI, ion trap) calcd for $C_{23}H_{17}BrN_2O$ + Na^+, 439.0422, found 439.0429.

6-Bromo-*N*-(*tert*-butyl)-4-phenylquinoline-2-carboxamide (3l). Compound **3l** was isolated in 42% yield (80.2 mg, colorless crystal); mp 216−220.0 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.29 (s, 1H), 8.20 (s, *NH*, 1H), 8.12 (s, 1H), 8.05 (d, J = 9.0 Hz, 1H), 7.84 (dd, J = 9.0, 2.0 Hz, 1H), 7.53 (dd, J = 17.9, 7.6 Hz, 5H), 1.57 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.3, 150.6, 149.2, 145.6, 137.1, 133.3, 131.6, 129.4, 128.9, 128.8, 128.7, 128.1, 122.2, 119.6, 51.1, 28.8; EI-MS m/z (relative intensity, %) 384 (38.4%), 382 (40.9%), 369 (93.8%), 367 (93.8%), 284 (89.2%), 282 (100%), 203 (76.2%); HRMS (ESI, ion trap) calcd for $C_{20}H_{19}BrN_2O$ + H^+, 383.0759, found 383.0759.

6-Bromo-4-phenylquinoline-2-carboxamide (3m). Compound **3m** was isolated in 54% yield (88.0 mg, colorless crystal); mp 240.0−242.0 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.29 (s, 1H), 8.15 (d, J = 2.1 Hz, 1H), 8.05−8.07 (m, 3H), 7.86 (dd, J = 9.0, 2.2 Hz, 1H), 7.62−7.49 (m, 5H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.7, 149.0, 145.8, 136.9, 133.6, 132.5, 131.8, 129.5, 129.0, 128.9, 128.1, 125.6, 122.7, 119.9; EI-MS m/z (relative intensity, %) 328 (4.1%), 326 (4.7%), 306 (25.1%), 304 (28.1%), 201 (18.9%), 199 (19.3%), 186 (96.2%), 184 (100%), 173 (20.0%), 171 (22.2%); HRMS (ESI, ion trap) calcd for $C_{16}H_{11}BrN_2O$ + Na^+, 348.9953, found 348.9955.

6-Bromo-*N*,*N*-dimethyl-4-phenylquinoline-2-carboxamide (3n). Compound **3n** was isolated in 95% yield (168.1 mg, colorless crystal); mp 207.0−209.0 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07 (d, J = 2.1 Hz, 1H), 8.02 (d, J = 9.0 Hz, 1H), 7.81 (dd, J = 9.0, 2.2 Hz, 1H), 7.66 (s, 1H), 7.54−7.47 (m, 5H), 3.19 (s, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.6, 154.0, 148.8, 145.6, 136.7, 133.3, 131.6, 129.3, 128.9, 128.8, 127.8, 127.6, 121.8, 121.4, 39.0; EI-MS m/z (relative intensity, %) 356 (43.9%), 354 (43.1%), 299 (20.0%), 297 (20.6%), 285 (96.1%), 283 (100%), 204 (32.6%), 203 (44.9%); HRMS (ESI, ion trap) calcd for $C_{18}H_{15}BrN_2O$ + H^+, 355.0446, found 355.0459.

6-Bromo-*N*,3-dimethyl-4-phenylquinoline-2-carboxamide (3o). Compound **3o** was isolated in 80% yield (141.6 mg, colorless crystal); mp 195.0−198.0 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.27 (s, *NH*, 1H), 8.22 (s, 1H), 8.02 (d, J = 9.0 Hz, 1H), 7.82 (dd, J = 9.0, 2.1 Hz, 1H), 7.69 (d, J = 2.0 Hz, 1H), 7.46−7.31 (m, 3H), 7.20 (d, J = 7.3 Hz, 1H), 3.13 (d, J = 5.1 Hz, 3H), 2.03 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.9, 149.7, 149.3, 145.4, 136.4, 135.8, 133.6, 131.6, 130.5, 129.5, 128.9, 128.2, 126.0, 122.4, 26.3, 20.0; EI-MS m/z (relative intensity, %) 356 (39.8%), 354 (40.8%), 299 (100%), 297 (97.2%), 217 (37.1%), 203 (12.6%); HRMS (ESI, ion trap) calcd for $C_{18}H_{15}BrN_2O$ + H^+, 355.0446, found 355.0440.

6-Bromo-*N*-methyl-4-(*p*-tolyl)quinoline-2-carboxamide (3p). Compound **3p** was isolated in 71% yield (125.7 mg, colorless crystal); mp 197.0−200.0 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.28 (s, 1H), 8.25 (s, *NH*, 1H), 8.16 (d, J = 2.1 Hz, 1H), 8.01 (d, J = 9.0 Hz, 1H), 7.82 (dd, J = 9.0, 2.2 Hz, 1H), 7.42 (d, J = 8.2 Hz, 2H), 7.37 (d, J = 8.0 Hz, 2H), 3.13 (d, J = 5.1 Hz, 3H), 2.49 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.9, 149.7, 149.3, 145.7, 139.0, 134.1, 133.4, 131.6, 129.6, 129.4, 128.9, 128.2, 122.2, 119.8, 26.3, 21.3; EI-MS m/z (relative intensity, %) 356 (40.8%), 354 (40.7%), 299 (96.3%), 297 (100%), 217 (27.3%), 203 (20.0%); HRMS (ESI, ion trap) calcd for $C_{18}H_{15}BrN_2O$ + H^+, 355.0446, found 355.0447.

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6-Bromo-4-(4-methoxyphenyl)-*N*-methylquinoline-2-carboxamide (3q). Compound **3q** was isolated in 76% yield (140.6 mg, colorless crystal); mp 185.0−188.0 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.26−8.24 (m, 2H), 8.17 (s, 1H), 7.99 (d, J = 9.0 Hz, 1H), 7.81 (d, J = 9.0 Hz, 1H), 7.46 (d, J = 8.4 Hz, 2H), 7.09 (d, J = 8.4 Hz, 2H), 3.92 (s, 3H), 3.12 (d, J = 5.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.8, 160.2, 149.6, 148.9, 145.7, 133.3, 131.5, 130.8, 129.2, 128.9, 128.1, 122.1, 119.6, 114.3, 55.4, 26.2; EI-MS m/z (relative intensity, %) 372 (33.4%), 370 (32.6%), 315 (100%), 313 (98.7%), 203 (13.5%); HRMS (ESI, ion trap) calcd for $C_{18}H_{15}BrN_2O_2$ + H^+, 371.0395, found 371.0400.

4-(6-Bromo-2-(methylcarbamoyl)quinolin-4-yl)phenyl Acetate (3r). Compound **3r** was isolated in 50% yield (99.5 mg, colorless crystal); mp 171.0−173.0 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.27 (s, 1H), 8.23 (s, *NH*, 1H), 8.13 (d, J = 2.1 Hz, 1H), 8.01 (d, J = 9.0 Hz, 1H), 7.84 (dd, J = 9.0, 2.1 Hz, 1H), 7.54 (d, J = 8.6 Hz, 2H), 7.31 (d, J = 8.6 Hz, 2H), 3.12 (d, J = 5.1 Hz, 3H), 2.38 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.2, 164.7, 151.1, 149.5, 148.1, 145.6, 134.4, 133.5, 131.6, 130.6, 128.6, 127.8, 122.5, 122.1, 119.8, 26.3, 21.2; EI-MS m/z (relative intensity, %) 400 (20.2%), 398 (20.5%), 358 (43.6%), 356 (45.8%), 301 (99.6%), 299 (100%), 219 (15.8%), 190 (23.8%); HRMS (ESI, ion trap) calcd for $C_{19}H_{15}BrN_2O_3$ + H^+, 399.0344, found 399.0354.

6-Bromo-4-(4-bromophenyl)-*N*-methylquinoline-2-carboxamide (3s). Compound **3s** was isolated in 59% yield (123.3 mg, colorless crystal); mp 256.0−258.0 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.26 (s, 1H), 8.21 (s, *NH*, 1H), 8.05 (d, J = 2.0 Hz, 1H), 8.03 (d, J = 9.0 Hz, 1H), 7.85 (dd, J = 9.0, 2.0 Hz, 1H), 7.71 (d, J = 8.3 Hz, 2H), 7.39 (d, J = 8.4 Hz, 2H), 3.13 (d, J = 5.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.6, 149.6, 147.8, 145.6, 135.8, 133.6, 132.1, 131.7, 131.0, 128.4, 127.7, 123.4, 122.6, 119.7, 26.3; EI-MS m/z (relative intensity, %) 422 (11.4%), 420 (22.5%), 418 (11.0%), 365 (52.0%), 363 (100%), 361 (52.3%), 203 (27.9%); HRMS (ESI, ion trap) calcd for $C_{17}H_{12}Br_2N_2O$ + H^+, 418.9395, found 418.9406.

2-Bromo-*N*-methyl-7a,10,10a,11-tetrahydro-7*H*-7,11-methanocyclopenta[*j*]phenanthridine-6-carboxamide (4a and 4a′). Compound **4a** and **4a′** was isolated in 41% yield as a mixture of two isomers (75.4 mg, colorless crystal, ratio 1:1.6). **4a′**: mp 176.0−178.0 °C. **Major product**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.21 (s, *NH*, 1H), 8.05 (d, J = 2.0 Hz, 1H), 7.87 (s, 1H), 7.70 (d, J = 1.9 Hz, 1H), 5.38 (dd, J = 5.4, 2.2 Hz, 1H), 4.81 (dd, J = 5.5, 1.7 Hz, 1H), 4.73 (d, J = 3.8 Hz, 1H), 3.90 (d, J = 4.0 Hz, 1H), 3.77−3.70 (m, 1H), 3.28−3.15 (m, 1H), 3.06 (d, J = 5.2 Hz, 3H), 2.26−2.08 (m, 1H), 2.02−1.89 (m, 2H), 1.38−1.22 (m, 1H). **Minor product**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.26 (s, 1H), 7.99 (d, J = 2.0 Hz, 1H), 7.89 (s, 1H), 7.68 (d, J = 1.9 Hz, 1H), 5.13 (dd, J = 5.4, 2.2 Hz, 1H), 4.85 (dd, J = 5.5, 1.8 Hz, 1H), 4.68 (d, J = 4.0 Hz, 1H), 3.93 (d, J = 3.8 Hz, 1H), 3.81−3.65 (m, 1H), 3.29−3.14 (m, 1H), 3.07 (d, J = 5.2 Hz, 3H), 2.26−2.08 (m, 1H), 2.03−1.89 (m, 2H), 1.80−1.61 (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.8, 165.7, 156.5, 153.0, 144.7, 144.4, 143.5, 140.2, 137.5, 132.3, 132.3, 132.1, 131.8, 131.7, 130.9, 130.2, 127.5, 126.8, 126.1, 126.0, 121.5, 121.4, 54.1, 53.9, 51.4, 51.3, 47.3, 46.7, 45.8, 45.3, 41.2, 41.1, 34.0, 33.8, 25.9, 25.8, one ^{13}C signal lost for overlap; EI-MS m/z (relative intensity, %) 370 (41.1%), 368 (41.8%), 304 (34.2%), 302 (35.4%), 247 (74.3%), 245 (100%), 166 (26.2%), 164 (26.2%); HRMS (ESI, ion trap) calcd for $C_{19}H_{17}BrN_2O$ + H^+, 369.0603, found 369.0593.

2-Bromo-*N*-methyl-7,8-dihydrophenanthridine-6-carboxamide (5) and 2-Bromo-*N*-methylphenanthridine-6-carboxamide (6). Compound **5** and **6** was isolated as a mixture (77.2 mg). **5**: mp 169.0−171.0 °C; Mixture of two products; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.52 (d, J = 8.4 Hz, 1H), 8.61 (d, J = 1.9 Hz, 1H), 8.45 (d, J = 8.3 Hz, 1H), 8.10 (t, J = 14.6 Hz, 3H), 7.91 (d, J = 8.7 Hz, 1H), 7.88−7.80 (m, 1H), 7.80−7.70 (m, 3H), 7.67 (dd, J = 9.0, 1.9 Hz, 1H), 7.07 (d, J = 9.9 Hz, 1H), 6.62−6.52 (m, 1H), 3.53 (t, J = 8.6 Hz, 2H), 3.12 (d, J = 5.1 Hz, 3H), 3.05 (d, J = 5.1 Hz, 3H), 2.37 (ddt, J = 10.9, 8.0, 4.0 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.8, 166.3, 149.8, 148.3, 143.7, 140.3, 138.2, 136.6, 132.4, 132.3, 132.1, 131.7, 131.4, 131.2, 129.0, 128.5, 128.1, 126.6, 125.7, 124.9, 124.2, 122.7, 121.7, 121.6, 121.2, 26.4, 26.2, 22.6, 22.5, one 13C signal lost for overlap; EI-MS m/z (relative intensity, %) **5**: 318 (22.9%), 316 (23.0%), 259 (95.8%), 257 (100%); **6**: 316 (17.8%), 314 (16.5%), 259 (97.6%), 257 (100%); HRMS (ESI, ion trap) calcd for **5** ($C_{15}H_{13}BrN_2O$ + H^+), 317.0290, found 317.0282; **6** ($C_{15}H_{11}BrN_2O$ +H^+), 315.0133, found 315.0138.

Ethyl *N*-[(6-Methoxy-4-phenylquinolin-2-yl)carbonyl] Aminoacetate (7a). Compound **7a** was isolated in 81% yield (147.4 mg, colorless crystal); mp 226.0−229.0 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.69 (t, J = 5.5 Hz, *NH*, 1H), 8.19 (s, 1H), 8.08 (d, J = 9.2 Hz, 1H), 7.60−7.46 (m, 5H), 7.42 (dd, J = 9.2, 2.7 Hz, 1H), 7.24 (d, J = 2.6 Hz, 1H), 4.34 (d, J = 5.7 Hz, 2H), 4.28 (q, J = 7.1 Hz, 2H), 3.81 (s, 3H), 1.33 (t, J = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.9, 165.0, 159.0, 148.2, 146.4, 143.2, 138.0, 131.7, 129.3, 129.0, 128.7, 128.5, 122.7, 119.4, 103.4, 61.5, 55.5, 41.5, 14.2; EI-MS m/z (relative intensity, %) 364 (29.0%), 318 (18.3%), 291 (25.4%), 235 (100%), 234 (81.1%), 191 (22.8%), 190 (13.2%); HRMS (ESI, ion trap) calcd for $C_{21}H_{20}N_2O_4$ + Na^+, 387.1321, found 387.1310.

***N*-[(6-Methoxy-4-phenylquinolin-2-yl)carbonyl]-2-aminopropionate (7b).** Compound **7b** was isolated in 78% yield (147.4 mg, colorless crystal); mp 211.0−213.0 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.71 (d, J = 7.9 Hz, *NH*, 1H), 8.19 (s, 1H), 8.12 (t, J = 7.5 Hz, 1H), 7.62−7.47 (m, 5H), 7.42 (dd, J = 9.2, 2.8 Hz, 1H), 7.23 (d, J = 2.7 Hz, 1H), 4.86 (p, J = 7.2 Hz, 1H), 4.27 (q, J = 7.1 Hz, 2H), 3.81 (s, 2H), 1.61 (d, J = 7.2 Hz, 3H), 1.33 (t, J = 7.2 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.9, 164.3, 159.0, 148.2, 146.5, 143.2, 138.0, 131.7, 129.3, 129.0, 128.7, 128.5, 122.6, 119.4, 103.4, 61.5, 55.5, 48.2, 18.6, 14.2; EI-MS m/z (relative intensity, %) 378 (22.1%), 335 (8.8%), 305 (59.9%), 262 (15.2%), 235 (75.6%), 234 (100%), 191 (22.8%), 190 (12.4%); HRMS (ESI, ion trap) calcd for $C_{22}H_{22}N_2O_4$ + Na^+, 401.1477, found 401.1463.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Copies of all ^{1}H NMR and ^{13}C NMR spectra of all compounds. Crystallographic data of products **4a** and **5** in CIF format. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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