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Radical Cation Salt Promoted Catalytic Aerobic sp^3 C−H Oxidation: Construction of Quinoline Fused Lactones and Lactams

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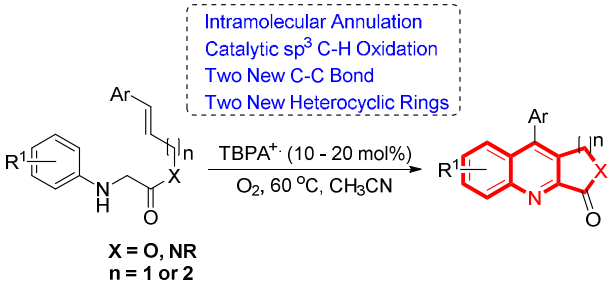
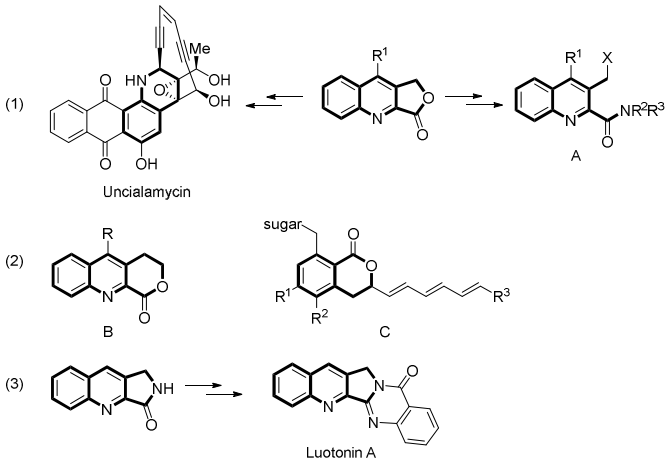


Abstract: A direct construction of quinoline fused lactones and lactams was achieved by sp^3 C−H bond oxidation of *N*-aryl glycine esters and amides under catalytic radical cation salt induced conditions. These polycyclic products are formed in a single step from readily accessible starting materials, and this method provides a new synthetic approach to this class of heterocycles.

Heterocycle fused lactones and lactams represent interesting classes of natural and synthetic

compounds which display a wide range of biological properties. Therefore, the development of streamlined protocols which allow access these valuable molecules from relatively simple starting materials is a worthwhile endeavor. For example, derivatives of furo[3,4-b]quinolin-3(1*H*)-one have been used to synthesize quinoline-2-carboxamides **A**, which represent promising new radioligands for the molecular imaging of the 18kDa translocator protein (TSPO).[1] Furthermore, the group of Nicolaou has employed a lactone fused analog towards their synthesis of enediyne antibiotic, *uncialamycin*. (Figure 1, eq. 1).[2] Quinoline fused 2-pyran-1-one system **B** can be perceived as a class of analogs of the dihydroisocoumarin glucosides **C**, which have been extracted from the fungus Cephalosporium sp. AL031, and exhibited antibacterial and fungicidal properties. (Figure 1, eq. 2) [3] Additionally, quinoline fused lactams are key intermediates to *luotonin A*, a cytotoxic alkaloid isolated from the Chinese medicinal plant *Peganum nigellastrum*, which is active against murine leukaemia cell line P-388 with an IC50 value of 1.8 $mg \cdot mL^{-1}$. (Figure 1, eq. 3) [4]

Figure 1. Heterocycles Fused Lactone and Lactam

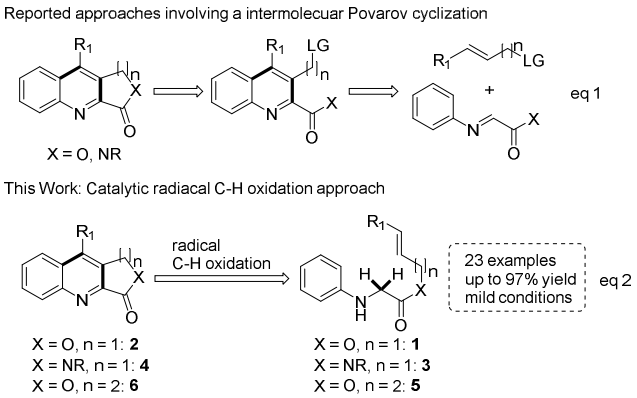


Quinoline-fused variants are important members of these classes of heterocycles, and several research groups have established protocols which to construct these scaffolds. Nevertheless, the

development of new catalytic approaches still remains an active field of research, and efforts are validated by the multitude of possible synthetic and biological applications. A stepwise approach toward these heterocycles is usually employed where quinoline formation occurs prior to a final lacton- or lactamization (Figure 2, eq. 1). [1f, 3b, 4b] For example, van de Weghe reported an elegant approach involving a tandem intermolecular Povarov cyclization/lactonization or lactamization. [2c] However, this method requires a tedious synthetic route to obtain the desired starting materials which suffers from low yields. We hypothesized that both the heteroaromatic ring and either the lactone or lactam ring could be constructed via intramolecular process involving the C−H oxidation/functionalization of readily accessible linear starting materials using the catalytic radical chemistry developed in our laboratory[5] (Figure 2, eq. 2). This would represent a highly efficient approach which could inspire new synthetic disconnections in the synthesis of heterocycles.

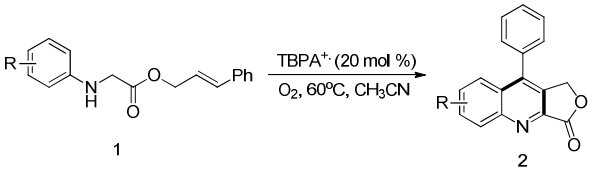
Recently, we reported a catalytic radical cation initiated C−H functionalization of glycine derivatives with styrenes to build quinoline skeletons. [5] This method represented a novel approach to CDCs (cross dehydrogenative couplings), avoiding using excess quantities of the oxidants (such as DDQ, TEMPO oxoammonium, and peroxides).[6] Preliminary results obtained during testing the intramolecular variant, suggested that our hypothesis concerning a one step construction of quinoline fused lactones and lactams was indeed feasible. Herein, report a novel method for the direct formation of heterocycles fused lactones and lactams by catalytic aerobic oxidation of glycine derivatives **1**.

Figure 2. Synthetic Disconnections in the Synthesis of Quinoline Fused Lactones and Lactams



We found that previously reported optimal conditions [5a] employing 20 mol % of $TBPA^{+\bullet}$ (tris(4-bromophenyl)aminium hexachloroantimonate), O_2 (1 atm) and at 60 °C led to efficient formation of the desired quinoline fused lactone **2**. With these conditions in hand we applied them to a diverse array of *N*-aryl glycine cinnamyl ester derivatives, and the results are compiled in Table 1.

Table 1. Intramolecular Cyclization of *N*-Aryl Glycine Cinnamyl Esters[a]

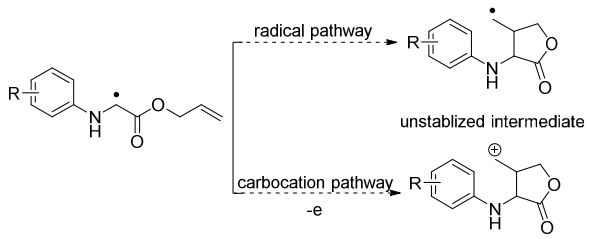


Entry	R	time (h)	product	yield (%) [b]
1	*p*-Br	72	**2a**	92
2	*p*-Cl	72	**2b**	97
3	*p*-F	72	**2c**	72
4	H	36	**2d**	49
5	*p*-Me	12	**2e**	91 [c]
6	*p*-MeO	12	**2f**	85 [c]
7	*p*-OH	24	**2g**	83 [c]
8	*o*-Me	36	**2h**	20

[a] Reaction conditions: **1** (0.5 mmol), $TBPA^{+\cdot}$ (20 mol %), O_2 (1 atm), 60 °C. [b] Isolated yield. [c] The reaction was carried out in the presence of 10 mol % $TBPA^{+\cdot}$.

This study revealed that substituted *N*-aryl glycine cinnamyl esters containing both electron-withdrawing and -donating groups were transformed to the desired products in moderate to excellent yields. However, electron-withdrawing groups were found to cause a decrease in reaction rate (entries 1-3), presumably the electron-withdrawing groups increasing the difficulty of oxidation. In the absence of a substituent on the *para*-position of aniline a diminution of yields results was obtained (entries 4 and 8). This is in accordance with our previously reported intermolecular variant. [5]. One reason for the yield attenuation observed is that coupling can occur at the *para*-position of aniline during oxidation.[7] A free phenol group was also tolerated, leading to the desired product in 83% yield, thus implying that these mild oxidation condition are amenable to the synthesis of more complicated compounds without tedious requiring protection-deprotection of fragile functional groups (entry 7). The reaction conditions were also tested using *N*-aryl glycine allyl esters, however no desired product was isolated, suggesting that radical or carbocation intermediate stability is crucial for the success of this reaction (Scheme 1).

Scheme 1. Reaction of Glycine Allyl Esters



To determine the generality of this protocol, we turned our attention toward the construction of quinoline fused lactams using the optimized conditions (Table 2). All tested *N*-aryl glycine cinnamyl amides exhibited good reactivity, affording the quinoline fused lactams in good to excellent yields. Bulky amide *N*-protecting groups, including *t*-butyl and *i*-propyl gave better results than the corresponding *n*-butyl analogs (entries 1 vs. 2 and 3). This might be due to the fact

that large *N*-groups provide a larger population of the reactive rotamer (Scheme 2). When the group is large, the cinnamyl group is closer to the desired reactive radical, which is in favor of intramolecular annulation. The substituent effect on cinnamyl group was also compared, and the result shows that electron-donating group increased the annulation yields (entries 4 and 5). Otherwise, electron-withdrawing group (4-Br) reduced the yields to 66% and 70% repectively (entries 6-7), which supported the existence of electron-deficient intermediate. One reviewer presented a reasonable reason for the substituent effect in Table 2, and we agree with him. The results in Table 1 shows that increasing electron donation on the *N*-aryl group of the glycine esters accelerates the reaction, presumably due to the rate limiting step is sp^3 C-H bond oxidation, not the cyclization. However, when a powerful electron-donating group is connected on aniline, the oxidation process is no longer rate limiting, and increased electron donation on the cinnamyl group renders alkene more nucleophilic, accelerating closure to the electron deficient radical **A** (Scheme 4). All this results supported that an electron transfer may indeed be the pathway to radical intermediate **A**.The reaction of *N,N*-dicinnamyl amide also occurred smoothly leaving one *N*-cinnamyl group unchanged (entry 9). This implies that the C−H bond adjacent to the aniline nitrogen is more active than the C−H bond adjacent to amide group, due to higher resonance stabilization. Even the benzyl C−H bond adjacent to amide nitrogen does not disturb the oxidation process, showing good selectivity under the oxidation conditions (entry 8).

Scheme 2. Rotamerization of Glycine Amide

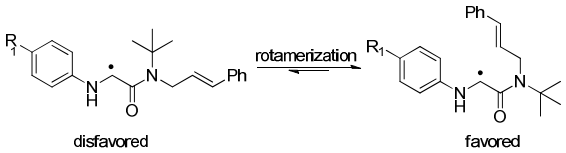
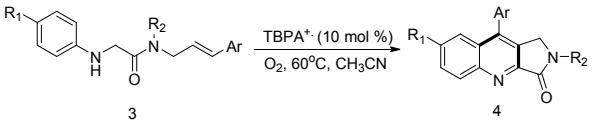


Table 2. Intramolecular Cyclization of Glycine Amide [a]



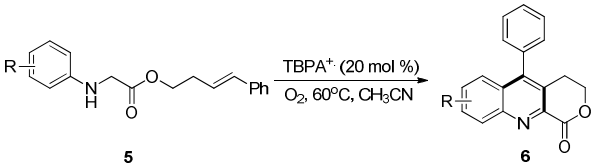
3 4

entry	R^1	R^2	Ar	time (h)	product	yield (%) [b]
1	*p*-OMe	*n*-Bu	Ph	20	**4a**	72
2	*p*-OMe	*t*-Bu	Ph	12	**4b**	93
3	*p*-OMe	*i*-Pr	Ph	19	**4c**	83
4	*p*-OMe	Ph	Ph	20	**4d**	70
5	*p*-OMe	Ph	*p*-$MeOC_6H_4$	12	**4e**	94
6	*p*-OMe	Ph	*p*-BrC_6H_4	24	**4f**	66
7	*p*-OMe	2,4-dimethylphenyl	*p*-BrC_6H_4	24	**4g**	70
8	*p*-OMe	CH_2Ph	Ph	16	**4h**	70
9	*p*-OMe	cinnamyl	Ph	14	**4i**	64
10	Br	*t*-Bu	Ph	24	**4j**	62

[a)] Reaction conditions: **3** (0.5 mmol), $TBPA^{+\cdot}$ (10 mol %), O_2 (1 atm), 60 °C [b)] Isolated yield

Having succeeded in constructing quinoline fused five-membered lactones and lactams, we wanted to explore the possibility of formation of six-member lactones (Table 3). The results show that the desired 3,4-dihydro-1*H*-pyrano[3,4-*b*]quinolin-1-one skeleton can also be built efficiently. The substituent on aniline does not affect the efficiency of the reaction, providing the polycyclic products in high yields.

Table 3. Construction of Six-membered Lactones [a]



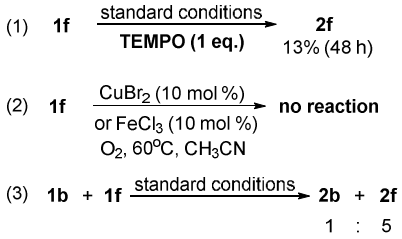
5 6

entry	R	time (h)	product	yield (%) [b]
1	*p*-Br	72	**6a**	97
2	*p*-Cl	72	**6b**	75 [d]
3	*p*-OCH_3	72	**6c**	92 [c]
4	*p*-OH	24	**6d**	83 [c]
5	*o*- OCH_3	36	**6e**	49 [c]

[a] Table Footnote. Reaction conditions: **3** (0.5 mmol), $TBPA^{+\cdot}$ (20 mol %), O_2 (1 atm), 60 °C. [b] Isolated yield. [c] The reaction was carried out in the presence of 10 mol % $TBPA^{+\cdot}$. [d] Under refluxing.

To probe the reaction mechanism, some control experiments were conducted (Scheme 3). In the presence of radical inhibitor TEMPO (1 equivalent), the reaction was inhibited and only 13% of the desired product was isolated after 48 hours (eq. 1), which suggested that radical intermediates might be involved. Other oxidants, such as Cu(II) and Fe(III), were used to initiate this reaction, but no reaction occurred, implying that $TBPA^{+\cdot}$ is crucial to induce the oxidation of the sp^3 C-H bond in glycine derivatives (eq. 2). A rate study was conducted to confirm the electronic effects on glycine esters. The standard reaction conditions were applied to the mixture of **1b** and **1f** (eq. 3). The ratio of the desired products is 1:5 (**2b**:**2f**), showing that electron-donating groups accelerated the oxidation of the sp^3 C-H bond. These results also supported the involvement of electron-deficient intermediate.

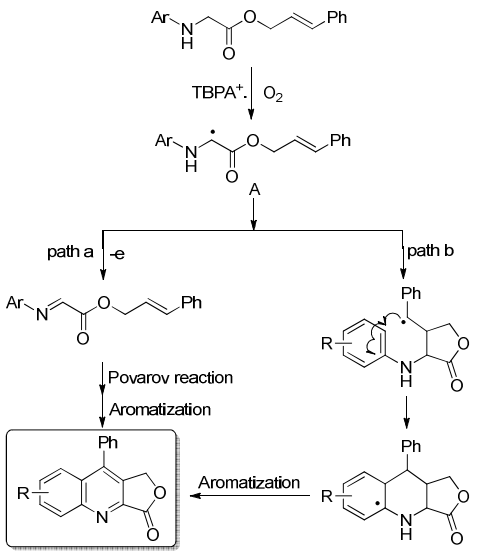
Scheme 3. Control Experiments



Based on the results of our group and others, [5,7] a plausible mechanism was proposed (Scheme 4). The sp^3 C−H bond adjacent to anilino group was oxidized by $TBPA^{+\bullet}$ in the presence of O_2, yielding a radical intermediate **A**, which can be further oxidized to the corresponding glycine

imine (Scheme 2, path a). Then a radical cation salt induced Povarov reaction can occur [8] to provide the quinoline derivatives. However, another pathway might also be operative (Scheme 2, path b). The radical intermediate **A** adds to the double bond directly, followed by radical addition to the phenyl group. After further oxidation and aromatization, the quinolino lactones or lactams are afforded. At this stage, two different pathways cannot be fully ruled out.

Scheme 4. Proposed Mechanism of Radical Cation Prompted Intramolecular Annulation



In conclusion, we have demonstrated an efficient synthesis of quinoline fused lactones and lactams using a radical cation salt prompted sp^3 C−H aerobic oxidation. The catalytic aerobic oxidation of glycine esters and amides was screened for a broad range of substrates. This approach provides one step access to these biologically and synthetically relevant core structures from simple starting materials. The mild reaction conditions, good functional group tolerance and the high efficiency will allow for further application in the synthesis of complicated natural products.

Experimental Section

Typical Procedure for $TBPA^{+\cdot}$ Induced Reaction of *N*-aryl glycine cinnamyl esters

A solution of **1** (0.5 mmol) in CH_3CN (5 ml) was mixed fully and then flushed with O_2 (keep flushing until the reaction completed), followed by addition of $TBPA^{+\cdot}$ (20 mol %) under 60 °C. After completion monitored by TLC (by UV visualization), the reaction was quenched by addition of saturated Na_2CO_3 in MeOH (10 ml) solution. The mixture was poured into a separator funnel with the addition of excess DCM (10 ml), and then the crude organic solution was extracted three times with water to remove inorganic salts. The organic phase was then dried over anhydrous magnesium sulfate, filtered, and the solvent was removed under reduced pressure. The products were separated by silica gel column chromatography eluted with petroleum ether/acetone (v/v 10:1) to afford the products.

7-Bromo-9-phenylfuro[3,4-*b*]quinolin-3(1*H*)-one (2a)

Compound **2a** was isolated in 92% yield (156 mg, colorless crystal); mp 168-171 °C; R_f value: 0.20 (v_{PE} : $v_{acetone}$ = 8:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.27 (d, *J* = 9.1 Hz, 1H), 8.04 (d, *J* = 2.1 Hz, 1H), 7.91 (dd, *J* = 9.1, 2.1 Hz, 1H), 7.73 – 7.58 (m, 3H), 7.50 – 7.41 (m, 2H), 5.40 (s, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.2, 149.2, 144.6, 143.1, 134.3, 133.1, 132.8, 129.9, 129.5, 128.9, 128.7, 127.9, 125.5, 124.2, 67.7; **EI-MS** *m/z* (relative intensity, %): 341 (99.3%), 339 (100%), 312 (12.6%), 310 (11.9%), 284 (64.7%), 282 (68.0%), 232 (11.3%), 216 (19.2%), 203 (39.3%), 176 (16.4%); **IR** (KBr, neat, cm^{-1}) ν 3057, 2965, 2915, 2851, 1779, 1574, 1482, 1439, 1378, 1262, 1134, 1049, 1006; **HRMS** (ESI): Calc'd for $C_{17}H_{10}BrNO_2 + H^+$, 339.9973; found, 339.9976.

7-Chloro-9-phenylfuro[3,4-*b*]quinolin-3(1*H*)-one (2b)

Compound **2b** was isolated in 97% yield (143 mg, colorless crystal); mp 154-158 °C; R_f value: 0.20 (v_{PE} : $v_{acetone}$ = 8:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.35 (d, *J* = 9.1 Hz, 1H), 7.86 (d, *J* = 2.2 Hz, 1H),

7.77 (dd, *J* = 9.1, 2.3 Hz, 1H), 7.68 – 7.58 (m, 3H), 7.45 (dd, *J* = 7.8, 1.6 Hz, 2H), 5.40 (s, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.1, 148.7, 144.3, 143.0, 135.6, 133.1, 132.7, 132.5, 131.5, 129.7, 129.4, 128.7, 128.3, 124.4, 67.7; **EI-MS** *m/z* (relative intensity, %): 297 (12.8%), 295 (45.8%), 268 (5.0%), 266 (12.9%), 240 (20.1%), 238 (52.1%), 203 (11.3%), 85 (64.6%), 71 (74.3%), 57 (100%); **IR** (KBr, neat, cm^{-1}) ν 3051, 2920, 2848, 1774, 1676, 1486, 1447, 1368, 1342, 1270, 1132, 1054, 1008; **HRMS** (ESI): Calc'd for $C_{17}H_{10}ClNO_2 + H^+$, 296.0478; found, 296.0488.

7-Fluoro-9-phenylfuro[3,4-*b*]quinolin-3(1*H*)-one (2c)

Compound **2c** was isolated in 97% yield (100 mg, colorless crystal); mp 150-152 °C; R_f value: 0.20 (v_{PE} : $v_{acetone}$ = 8:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.42 (dd, *J* = 9.2, 5.6 Hz, 1H), 7.76 – 7.56 (m, 4H), 7.56 – 7.39 (m, 3H), 5.41 (s, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.3, 162.3 (d, *J* = 253.1 Hz), 147.7, 143.9 (d, *J* = 2.9 Hz), 143.3 (d, *J* = 6.4 Hz), 134.0 (d, *J* = 9.6 Hz), 133.0 (d, *J* = 9.4 Hz), 129.7, 129.5, 129.1, 129.0, 128.6, 121.4 (d, *J* = 26.5 Hz), 109.1 (d, *J* = 23.7 Hz), 67.6; **EI-MS** *m/z* (relative intensity, %): 279 (79.7%), 250 (29.6%), 234 (12.2%), 222 (100%); **IR** (KBr, neat, cm^{-1}) ν 2919, 2854, 1769, 1705, 1634, 1578, 1507, 1458, 1225, 1126, 1048, 1013; **HRMS** (ESI): Calc'd for $C_{17}H_{10}FNO_2 + H^+$, 280.0774; found, 280.0786.

9-Phenylfuro[3,4-*b*]quinolin-3(1*H*)-one (2d)

Compound **2d** was isolated in 49% yield (64 mg, colorless oil); R_f value: 0.20 (v_{PE} : $v_{acetone}$ = 8:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.43 (d, *J* = 8.5 Hz, 1H), 7.92 (d, *J* = 8.5 Hz, 1H), 7.86 (ddd, *J* = 8.4, 6.8, 1.4 Hz, 1H), 7.70 – 7.56 (m, 4H), 7.46 (dd, *J* = 7.8, 1.6 Hz, 2H), 5.40 (s, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.6, 150.6, 144.2, 143.9, 133.5, 132.2, 131.3, 130.6, 129.5, 129.3, 129.3, 128.8, 127.8, 125.7, 67.7; **EI-MS** *m/z* (relative intensity, %): 261 (100%), 241 (19.9%), 232 (24.5%), 216 (17.3%), 204 (91.7%), 121 (46.6%); **IR** (KBr, neat, cm^{-1}) ν 2953, 2926, 2847, 1775, 1578, 1458, 1112, 1056;

HRMS (ESI): Calc'd for $C_{17}H_{11}NO_2 + H^+$, 262.0868; found, 262.0876.

7-Methyl-9-phenylfuro[3,4-*b*]quinolin-3(1*H*)-one (2e)

Compound **2e** was isolated in 91% yield (125 mg, colorless crystal); mp 142-143 °C; R_f value: 0.20 (v_{PE} : $v_{acetone}$ = 8:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.31 (dd, *J* = 8.6, 2.7 Hz, 1H), 7.67 (d, *J* = 8.7 Hz, 1H), 7.65 – 7.54 (m, 4H), 7.49 – 7.41 (m, 2H), 5.35 (s, 2H), 2.51 (s, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 168.8, 149.3, 143.3, 142.9, 140.0, 133.7, 133.1, 132.5, 131.0, 129.4, 129.3, 128.8, 127.9, 124.3, 67.8, 22.1; **IR** (KBr, neat, cm^{-1}) ν 3051, 2920, 2848, 1781, 1578, 1505, 1447, 1375, 1132, 1048, 1021; **HRMS** (ESI): Calc'd for $C_{18}H_{13}NO_2 + H^+$, 276.1025; found, 276.1026.

7-Methoxy-9-phenylfuro[3,4-*b*]quinolin-3(1*H*)-one (2f)

Compound **2f** was isolated in 85% yield (124 mg, colorless oil); R_f value: 0.20 (v_{PE} : $v_{acetone}$ = 8:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.33 (d, *J* = 9.3 Hz, 1H), 7.68 – 7.54 (m, 3H), 7.54 – 7.42 (m, 3H), 7.10 (d, *J* = 2.7 Hz, 1H), 5.35 (s, 2H), 3.81 (s, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 169.0, 160.1, 147.0, 141.9, 141.7, 133.9, 133.1, 132.9, 129.5, 129.4 (two ^{13}C), 128.6, 123.9, 102.9, 67.7, 55.6; **IR** (KBr, neat, cm^{-1}) ν 3058, 2927, 2854, 1774, 1617, 1505, 1460, 1420, 1368, 1290, 1224, 1126, 1047, 1021; **HRMS** (ESI): Calc'd for $C_{18}H_{13}NO_3 + H^+$, 292.0974; found, 292.0980.

7-Hydroxy-9-phenylfuro[3,4-*b*]quinolin-3(1*H*)-one (2g)

Compound **2g** was isolated in 83% yield (115 mg, colorless crystal); mp 218.0−220.0 °C; R_f value: 0.20 (v_{PE} : $v_{acetone}$ = 3:1); ^{1}H NMR (400 MHz, d_6-acetone) δ 8.17 (d, *J* = 9.2 Hz, 1H), 7.70 – 7.52 (m, 6H), 7.17 (d, *J* = 2.6 Hz, 1H), 5.43 (s, 1H); ^{13}C NMR (101 MHz, d_6-acetone) ^{13}C NMR (101 MHz, CD_3OD) δ 169.4, 159.2, 146.8, 142.5, 141.7, 135.0, 134.5, 133.5, 130.5, 123.0, 129.9, 129.8, 124.2, 107.0, 68.3; **EI-MS** *m/z* (relative intensity, %): 277 (100%), 248 (17.0%), 220 (88.6%); **IR** (KBr, neat, cm^{-1}) ν 3445, 3051, 2914, 2848, 1761, 1610, 1518, 1460, 1387, 1244, 1126, 1047, 1014; **HRMS** (ESI):

Calc'd for $C_{17}H_{11}NO_3 + H^+$, 278.0817; found, 278.0828.

5-Methyl-9-phenylfuro[3,4-*b*]quinolin-3(1*H*)-one (2h)

Compound **2h** was isolated in 20% yield (28 mg, colorless oil); R_f value: 0.20 (v_{PE} : $v_{acetone}$ = 8:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64 (d, *J* = 8.5 Hz, 1H), 7.58 (d, *J* = 6.7 Hz, 1H), 7.55 – 7.41 (m, 4H), 7.39 – 7.33 (m, 2H), 5.27 (s, 2H), 2.84 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.9, 149.8, 143.8, 142.9, 139.5, 133.9, 132.1, 130.5, 129.3, 129.1, 129.0, 128.8, 127.8, 123.6, 67.61, 18.6; **EI-MS** *m/z* (relative intensity, %): 275 (100%), 241 (49.0%), 229 (63.0%), 202 (24.3%), 166 (36.4%), 120 (87.6%); **IR** (KBr, neat, cm^{-1}) ν 2967, 2911, 2855, 1769, 1486, 1260, 1076, 1013; **HRMS** (ESI): Calc'd for $C_{18}H_{13}NO_2 + H^+$, 276.1025; found, 276.1030.

2-Butyl-7-methoxy-9-phenyl-1*H*-pyrrolo[3,4-*b*]quinolin-3(2*H*)-one (4a)

Compound **4a** was isolated in 72% yield (125 mg, colorless crystal); mp 180−183 °C; R_f value: 0.20 (v_{PE} : $v_{acetone}$ = 4:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.29 (d, *J* = 9.3 Hz, 1H), 7.66 – 7.52 (m, 3H), 7.48 (d, *J* = 6.8 Hz, 2H), 7.40 (dd, *J* = 9.3, 2.0 Hz, 1H), 7.01 (s, 1H), 4.32 (s, 2H), 3.76 (s, 3H), 3.68 (t, *J* = 7.5 Hz, 2H), 1.64 (dt, *J* = 15.2, 7.6 Hz, 2H), 1.44 – 1.30 (m, 2H), 0.93 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.4, 158.8, 148.8, 145.6, 141.5, 134.7, 132.3, 129.1, 128.9, 128.8, 128.6, 122.2, 103.4, 55.4, 47.1, 42.8, 30.1, 20.0, 13.7; **EI-MS** *m/z* (relative intensity, %): 346 (100%), 294 (43.2%), 265 (25.5%), 250 (42.9%), 214 (13.3%); **IR** (KBr, neat, cm^{-1}) ν 3051, 2959, 2927, 2861, 1702, 1617, 1578, 1512, 1460, 1414, 1264, 1224, 1119, 1028; **HRMS** (ESI): Calc'd for $C_{22}H_{22}N_2O_2 + H^+$, 347.1760; found, 347.1761.

2-(*tert*-Butyl)-7-methoxy-9-phenyl-1*H*-pyrrolo[3,4-*b*]quinolin-3(2*H*)-one (4b)

Compound **4b** was isolated in 93% yield (161 mg, colorless crystal); mp 172-176 °C; R_f value: 0.20 (v_{PE} : $v_{acetone}$ = 4:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.19 (d, *J* = 9.3 Hz, 1H), 7.57 – 7.43 (m, 3H), 7.40 –

7.34 (m, 2H), 7.32 (dd, *J* = 9.3, 2.6 Hz, 1H), 6.93 (t, *J* = 6.7 Hz, 1H), 4.29 (s, 2H), 3.67 (s, 3H), 1.49 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.7, 158.7, 149.8, 145.7, 141.3, 134.7, 132.3, 129.1, 128.8, 128.8, 128.7, 128.4, 122.1, 103.3, 55.3, 55.0, 45.4, 27.8; **EI-MS** *m/z* (relative intensity, %): 346 (26.1%), 331 (22.8%), 290 (21.6%), 173 (88.5%), 171 (100%), 151 (51.1%),108 (62.8%); **IR** (KBr, neat, cm^{-1}) ν 3051, 2979, 2920, 1695, 1584, 1493, 1447, 1395, 1264, 1224; **HRMS** (ESI): Calc'd for $C_{22}H_{22}N_2O_2 + H^+$, 347.1760; found, 347.1768.

2-Isopropyl-7-methoxy-9-phenyl-1*H*-pyrrolo[3,4-*b*]quinolin-3(2*H*)-one (4c)

Compound **4c** was isolated in 83% yield (138 mg, colorless crystal); mp 177-179 °C; R_f value: 0.20 (v_{PE} : $v_{acetone}$ = 4:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.31 (d, *J* = 9.3 Hz, 1H), 7.66 – 7.53 (m, 3H), 7.47 (d, *J* = 6.8 Hz, 2H), 7.42 (dd, *J* = 9.3, 2.5 Hz, 1H), 7.01 (d, *J* = 2.4 Hz, 1H), 4.85 (m, 1H), 4.27 (s, 2H), 3.77 (s, 3H), 1.29 (d, *J* = 6.8 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.8, 158.8, 149.1, 145.6, 141.6, 134.7, 132.3, 129.1, 128.8, 128.8, 128.7, 128.6, 122.2, 103.3, 55.3, 43.0, 42.1, 20.4; **EI-MS** *m/z* (relative intensity, %): 332 (100%), 317 (65.1%), 303 (16.8%), 290 (23.0%), 261 (13.8%), 246 (48.5%); **IR** (KBr, neat, cm^{-1}) ν 3051, 2973, 2927, 1696, 1624, 1505, 1460, 1414, 1230, 1119, 1028; **HRMS** (ESI): Calc'd for $C_{21}H_{20}N_2O_2 + H^+$, 333.1603; found, 333.1611.

7-Methoxy-2,9-diphenyl-1*H*-pyrrolo[3,4-*b*]quinolin-3(2*H*)-one (4d)

Compound **4d** was isolated in 70% yield (128 mg, colorless crystal); mp 232−233 °C; R_f value: 0.20 (v_{PE} : $v_{acetone}$ = 4:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.31 (d, *J* = 9.3 Hz, 1H), 7.87 (dd, *J* = 8.7, 1.0 Hz, 2H), 7.69 – 7.55 (m, 3H), 7.51 (dd, *J* = 8.0, 1.4 Hz, 2H), 7.41 (ddd, *J* = 15.3, 9.0, 1.9 Hz, 3H), 7.20 – 7.11 (m, 1H), 7.03 (d, *J* = 2.7 Hz, 1H), 4.77 (s, 2H), 3.78 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.5, 159.2, 148.4, 146.1, 141.7, 139.3, 134.6, 132.5, 129.3, 129.2, 129.1, 129.1, 128.8, 128.1, 125.0, 122.7, 119.5, 103.4, 55.5, 48.1; **EI-MS** *m/z* (relative intensity, %): 366 (100%), 337 (24.8%), 293 (7.9%), 247

(11.1%), 204 (9.7%), 71 (38.8%), 57 (53.8%); **IR** (KBr, neat, cm^{-1}) ν 3058, 2927, 2842, 1702, 1610, 1505, 1460, 1382, 1296, 1244, 1171, 1028; **HRMS** (ESI): Calc'd for $C_{24}H_{18}N_2O_2 + H^+$, 367.1447; found, 367.1460.

7-Methoxy-9-(4-methoxyphenyl)-2-phenyl-1,2-dihydro-3*H*-pyrrolo[3,4-*b*]quinolin-3-one (4e)

Compound **4e** was isolated in 94% yield (186 mg, colorless crystal); R_f value: 0.20 (v_{PE} : $v_{acetone}$ = 4:1); mp 227−230 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.31 (d, *J* = 9.2 Hz, 1H), 7.89 (d, *J* = 7.7 Hz, 2H), 7.46 – 7.37 (m, 5H), 7.23 – 7.06 (m, 4H), 4.79 (s, 2H), 3.95 (s, 3H), 3.80 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.5, 160.1, 159.0, 148.3, 145.9, 141.6, 139.2, 132.3, 130.2, 129.4, 129.0, 128.2, 126.5, 124.9, 122.5, 119.3, 114.7, 103.4, 55.4 (two ^{13}C), 48.1; **EI-MS** *m/z* (relative intensity, %): 396 (8.7%), 353 (20.7%), 266 (18.9%), 201 (26.3%), 158 (59.3%), 147 (100%), 121 (30.5%); **IR** (KBr, neat, cm^{-1}) ν 3058, 2926, 2847, 1705, 1613, 1507, 1450, 1394, 1295, 1239, 1176, 1133, 1027; **HRMS** (ESI): Calc'd for $C_{25}H_{20}N_2O_3 + H^+$, 397.1552; found, 397.1561.

9-(4-Bromophenyl)-7-methoxy-2-phenyl-1,2-dihydro-3*H*-pyrrolo[3,4-*b*]quinolin-3-one (4f)

Compound **4f** was isolated in 66% yield (147mg, colorless crystal); mp 225-229 °C; R_f value: 0.20 (v_{PE} : $v_{acetone}$ = 4:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.26 (d, J = 8.8 Hz, 1H), 7.84 (d, J = 7.6 Hz, 2H), 7.79 (d, J = 6.9 Hz, 2H), 7.49 – 7.32 (m, 5H), 7.22 – 7.11 (m, 1H), 6.96 (s, 1H), 4.72 (s, 2H), 3.79 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.1, 159.3, 148.2, 145.9, 140.4, 139.1, 133.4, 132.6, 132.4, 130.6, 129.1, 128.8, 128.0, 125.0, 123.5, 122.8, 119.3, 103.0, 55.5, 47.9; **EI-MS** *m/z* (relative intensity, %): 446 (26.5%), 444 (27.0%), 417 (6.2%), 415 (6.8%), 365 (2.0%), 289 (2.5%), 203 (3.5%), 183 (6.9%), 161 (2.7%), 149 (3.7%), 147 (3.3%), 77 (7.7%), 44 (100%); **IR** (KBr, neat, cm^{-1}) ν 3058, 2918, 2853, 2224, 1708, 1622, 1589, 1496, 1470, 1391, 1305, 1232, 1173, 1139, 1067, 1028;

HRMS (ESI): Calc'd for $C_{24}H_{17}BrN_2O_2 + H^+$, 445.0552; found, 445.0541.

9-(4-Bromophenyl)-2-(2,4-dimethylphenyl)-7-methoxy-1,2-dihydro-3*H*-pyrrolo[3,4-*b*]quinoli n-3-one (4g)

Compound **4f** was isolated in 70% yield (166mg, colorless crystal); mp 231-233 °C; R_f value: 0.20 (v_{PE} : $v_{acetone}$ = 4:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.37 (d, *J* = 8.6 Hz, 1H), 7.72 (d, *J* = 6.2 Hz, 2H), 7.48 (d, *J* = 8.0 Hz, 1H), 7.38-7.37 (m, 2H), 7.12 (s, 2H), 7.10 – 6.99 (m, 2H), 4.63 (s, 2H), 3.82 (s, 3H), 2.33 (s, 3H), 2.23 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.5, 159.4, 148.1, 145.9, 140.5, 138.4, 135.7, 134.1, 133.5, 132.7, 132.5, 132.0, 130.5, 129.3, 128.6, 127.5, 126.7, 123.4, 122.9, 103.1, 55.6, 50.5, 21.0, 18.2; **EI-MS** *m/z* (relative intensity, %): 474 (5.9%), 472 (6.3%), 268 (13.6%), 184 (3.7%), 169 (2.2%), 167 (2.0%), 139 (3.5%), 77 (4.6%), 71 (10.8%), 44 (100%); **IR** (KBr, neat, cm^{-1}) ν 2919, 2853, 1708, 1622, 1589, 1510, 1457, 1411, 1239, 1028; **HRMS** (ESI): Calc'd for $C_{26}H_{21}BrN_2O_2$ + H^+, 473.0865; found, 473.0874.

2-Benzyl-7-methoxy-9-phenyl-1*H*-pyrrolo[3,4-*b*]quinolin-3(2*H*)-one (4h)

Compound **4h** was isolated in 70% yield (133 mg, colorless crystal); mp 212−214 °C; R_f value: 0.20 (v_{PE} : $v_{acetone}$ = 4:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.30 (d, *J* = 9.3 Hz, 1H), 7.60 – 7.46 (m, 3H), 7.40 (m, 3H), 7.27 (m, 5H), 6.97 (s, 1H), 4.86 (s, 2H), 4.20 (s, 2H), 3.75 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.5, 158.9, 148.3, 145.6, 141.7, 136.4, 134.5, 132.3, 129.0, 128.9, 128.8, 128.8, 128.7, 128.2, 127.7, 122.3, 103.4, 55.4, 47.0, 46.7; **EI-MS** *m/z* (relative intensity, %): 380 (33.9%), 330 (29.4%), 315 (17.3%), 246 (17.7%), 161 (20.1%), 71 (70.5%), 57 (100%); **IR** (KBr, neat, cm^{-1}) ν 3052, 2926, 1705, 1620, 1577, 1507, 1457, 1408, 1218, 1028; **HRMS** (ESI): Calc'd for $C_{25}H_{20}N_2O_2 + H^+$, 381.1603; found, 381.1609.

2-Cinnamyl-7-methoxy-9-phenyl-1*H*-pyrrolo[3,4-*b*]quinolin-3(2*H*)-one (4i)

Compound **4i** was isolated in 64% yield (130 mg, colorless crystal); mp 242−246 °C; R_f value: 0.20 (v_{PE} : $v_{acetone}$ = 4:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.31 (d, *J* = 9.3 Hz, 1H), 7.63 – 7.49 (m, 3H), 7.49 – 7.38 (m, 3H), 7.38 – 7.16 (m, 5H), 7.00 (d, *J* = 2.4 Hz, 1H), 6.59 (d, *J* = 15.8 Hz, 1H), 6.23 (dt, *J* = 15.6, 6.6 Hz, 1H), 4.47 (d, *J* = 6.2 Hz, 2H), 4.33 (s, 2H), 3.76 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.3, 158.9, 148.4, 145.6, 141.7, 136.0, 134.6, 133.8, 132.3, 129.1, 129.0, 128.9, 128.8, 128.7, 128.5, 127.9, 126.4, 123.6, 122.3, 103.4, 55.3, 46.8, 45.2; **EI-MS** *m/z* (relative intensity, %): 406 (100%), 345 (24.0%), 291 (60.2%), 247 (56.4%), 219 (13.6%), 204 (36.0%), 168 (38.4%); **IR** (KBr, neat, cm^{-1}) ν 2960, 2919, 2847, 1698, 1613, 1500, 1408, 1288, 1218 1028; **HRMS** (ESI): Calc'd for $C_{27}H_{22}N_2O_2 + H^+$, 407.1760; found, 407.1771.

7-Bromo-2-(tert-butyl)-9-phenyl-1H-pyrrolo[3,4-*b*]quinolin-3(2*H*)-one (4j)

Compound **4j** was isolated in 62% yield (122 mg, colorless crystal); mp 239−242 °C; R_f value: 0.20 (v_{PE} : $v_{acetone}$ = 4:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.31 (d, *J* = 9.0 Hz, 1H), 7.78 – 7.66 (m, 2H), 7.66 – 7.55 (m, 3H), 7.43 (d, *J* = 6.6 Hz, 2H), 4.43 (s, 2H), 1.59 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.2, 152.3, 148.0, 142.3, 133.7, 133.7, 132.4, 130.6, 129.2, 128.8, 128.7, 128.1, 124.3, 121.3, 55.3, 45.4, 27.7; **EI-MS** *m/z* (relative intensity, %): 396 (0.1%), 394 (0.1%), 326 (80.0%), 279 (9.0%), 234 (16.7%), 232 (16.4%), 167 (38.1%), 149 (100%); **IR** (KBr, neat, cm^{-1}) ν 3056, 2966, 2918, 2849, 1697, 1596, 1490, 1442, 1389, 1262, 1082, 1024; **HRMS** (ESI): Calc'd for $C_{21}H_{19}BrN_2O + H^+$, 395.0759; found, 395.0759.

7-Bromo-5-phenyl-3,4-dihydro-1*H*-pyrano[3,4-*b*]quinolin-1-one (6a)

Compound **6a** was isolated in 97% yield (172 mg, colorless crystal); mp 162-166 °C; R_f value: 0.20 (v_{PE} : $v_{acetone}$ = 5:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.25 (d, *J* = 9.0 Hz, 1H), 7.83 (d, *J* = 9.0 Hz, 1H), 7.70 (s, 1H), 7.65 – 7.53 (m, 3H), 7.36 – 7.25 (m, 2H), 4.55 (t, *J* = 5.8 Hz, 2H), 3.04 (t, *J* = 5.7 Hz, 2H);

^{13}C NMR (101 MHz, $CDCl_3$) δ 162.8, 146.4, 146.0, 143.4, 134.1, 133.7, 132.8, 130.0, 129.6, 129.2, 129.1, 128.0, 124.1, 66.9, 26.6; **EI-MS** *m/z* (relative intensity, %): 355 (99.1%), 353 (100%), 297 (34.1%), 295 (35.2%), 230 (23.5%), 216 (48.2%); **IR** (KBr, neat, cm^{-1}) ν 3058, 2953, 2920, 1741, 1486, 1290, 1178; **HRMS** (ESI): Calc'd for $C_{18}H_{12}BrNO_2 + H^+$, 354.0130; found, 354.0140.

7-Chloro-5-phenyl-3,4-dihydro-1*H*-pyrano[3,4-*b*]quinolin-1-one (6b)

Compound **6b** was isolated in 75% yield (116 mg, colorless crystal); mp 170-171 °C; R_f value: 0.20 (v_{PE} : $v_{acetone}$ = 5:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.23 (d, *J* = 9.0 Hz, 1H), 7.61 (d, *J* = 9.0 Hz, 1H), 7.57 – 7.46 (m, 3H), 7.44 (s, 1H), 7.23 (d, *J* = 7.5 Hz, 2H), 4.47 (t, *J* = 5.8 Hz, 2H), 2.96 (t, *J* = 5.7 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.8, 146.1, 146.1, 143.2, 135.5, 134.1, 132.7, 131.0, 130.0, 129.2, 129.1, 129.1, 124.6, 66.8, 26.5; **EI-MS** *m/z* (relative intensity, %): 311 (33.0%), 309 (100%), 266 (4.0%), 264 (12.4%), 253 (25.2%), 251 (82.4%), 230 (25.4%), 216 (50.5%); **IR** (KBr, neat, cm^{-1}) ν 3058, 2920, 2848, 1738, 1486, 1283, 1178, 1087, 1021; **HRMS** (ESI): Calc'd for $C_{18}H_{12}ClNO_2 + H^+$, 310.0635; found, 310.0641.

7-Methoxy-5-phenyl-3,4-dihydro-1*H*-pyrano[3,4-*b*]quinolin-1-one (6c)

Compound **6c** was isolated in 92% yield (140 mg, colorless oil); R_f value: 0.20 (v_{PE} : $v_{acetone}$ = 5:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.29 (d, *J* = 9.3 Hz, 1H), 7.57 (dq, *J* = 14.1, 6.9 Hz, 3H), 7.41 (dd, *J* = 9.2, 2.2 Hz, 1H), 7.31 (d, *J* = 7.0 Hz, 2H), 6.75 (d, *J* = 2.0 Hz, 1H), 4.53 (t, *J* = 5.7 Hz, 2H), 3.74 (s, 3H), 3.00 (t, *J* = 5.7 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.4, 160.0, 144.9, 144.3, 140.5, 135.2, 132.9, 130.2, 129.5, 129.1, 129.0, 128.7, 123.0, 103.3, 66.9, 55.4, 26.6; **EI-MS** *m/z* (relative intensity, %): 305 (100%), 247 (40.9%), 232 (34.9%), 204 (26.3%); **IR** (KBr, neat, cm^{-1}) ν 3051, 2920, 2848, 1741, 1617, 1493, 1460, 1414, 1296, 1224, 1172, 1087, 1028; **HRMS** (ESI): Calc'd for $C_{19}H_{15}NO_3 + H^+$, 306.1130; found, 306.1141.

7-Hydroxy-5-phenyl-3,4-dihydro-1*H*-pyrano[3,4-*b*]quinolin-1-one (6d)

Compound **6d** was isolated in 83% yield (121 mg, colorless crystal); mp 210-212 °C; R_f value: 0.20 (v_{PE} : $v_{acetone}$ = 2:1); ^{1}H NMR (400 MHz, d_6-acetone) δ 8.12 (d, *J* = 9.1 Hz, 1H), 7.70 – 7.54 (m, 3H), 7.48 (d, *J* = 9.1 Hz, 1H), 7.41 (d, *J* = 7.7 Hz, 2H), 6.81 (s, 1H), 4.55 (t, *J* = 5.7 Hz, 2H), 3.01 (t, *J* = 5.7 Hz, 2H); ^{13}C NMR (101 MHz, d_6-acetone) δ 166.1, 161.6, 147.5, 146.8, 144.1, 139.1, 136.0, 133.8, 133.6, 132.9, 132.4, 132.0, 126.1, 110.0, 70.2, 30.0; **EI-MS** *m/z* (relative intensity, %): 291 (92.7%), 246 (14.3%), 233 (100%), 204 (16.3%); **IR** (KBr, neat, cm^{-1}) ν 3451, 3058, 2920, 2848, 1729, 1617, 1467, 1244, 1184, 1021; **HRMS** (ESI): Calc'd for $C_{18}H_{13}NO_3 + H^+$, 292.0974; found, 292.0978.

9-Methoxy-5-phenyl-3,4-dihydro-1*H*-pyrano[3,4-*b*]quinolin-1-one (6e)

Compound **6e** was isolated in 49% yield (75 mg, colorless oil); R_f value: 0.20 (v_{PE} : $v_{acetone}$ = 5:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62 – 7.44 (m, 3H), 7.35 – 7.18 (m, 3H), 7.10 – 7.06 (m, 2H), 4.52 (t, *J* = 5.8 Hz, 1H), 4.11 (s, 1H), 3.01 (t, *J* = 5.7 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.7, 156.5, 146.5, 141.7, 140.3, 135.2, 129. 8, 129.7, 129.2, 128.9, 128.7, 117.4, 107.6, 66.8, 56.1, 26.7; **EI-MS** *m/z* (relative intensity, %): 304 (100%), 276 (18.8%), 258 (52.0%), 230 (33.3%); **IR** (KBr, neat, cm^{-1}) ν 3182, 2914, 2848, 1735, 1624, 1512, 1211, 1159, 1021; **HRMS** (ESI): Calc'd for $C_{19}H_{15}NO_3 + H^+$, 306.1130; found, 306.1144.

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Supporting Information. Copies of all ^{1}H NMR and ^{13}C NMR spectra of all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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