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N-Heterocyclic Carbene-Catalyzed Annulation of Cyclic β-Enamino Esters with Enals: Access to Functionalized Indolo[2,3-a]quinolizidines

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Abstract: A novel synthetic approach to functionalized indolo[2,3-*a*]quinolizidines is developed *via* an N-heterocyclic carbene (NHC)-catalyzed annulation of cyclic *β*-enamino esters **1** with enals **2**. This methodology offers a pathway for quick and efficient construction of indolo[2,3-a]quinolizidine skeleton which is a core structure of many natural products with diverse bioactivities.

Indolo[2,3-*a*]quinolizidine skeleton is recognized as the privileged structure of numerous naturally occurring indole alkaloids with significant bioactivities (Figure 1). [1]Their structural diversity and complexity have attracted much attention from organic chemists and considerable efforts have been made toward the synthesis of these polycyclic molecules.[1b, 1d, 2] Notwithstanding, development of novel and general synthetic approaches to diverse functionalized indolo[2,3-a]quinolizidines is still highly desired.

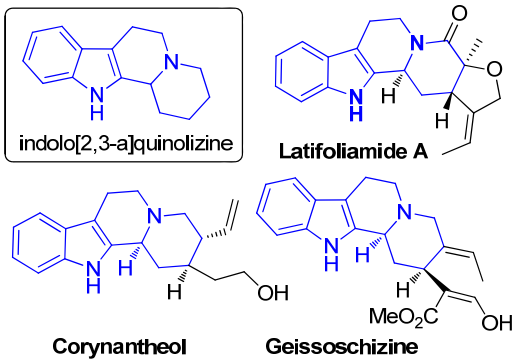
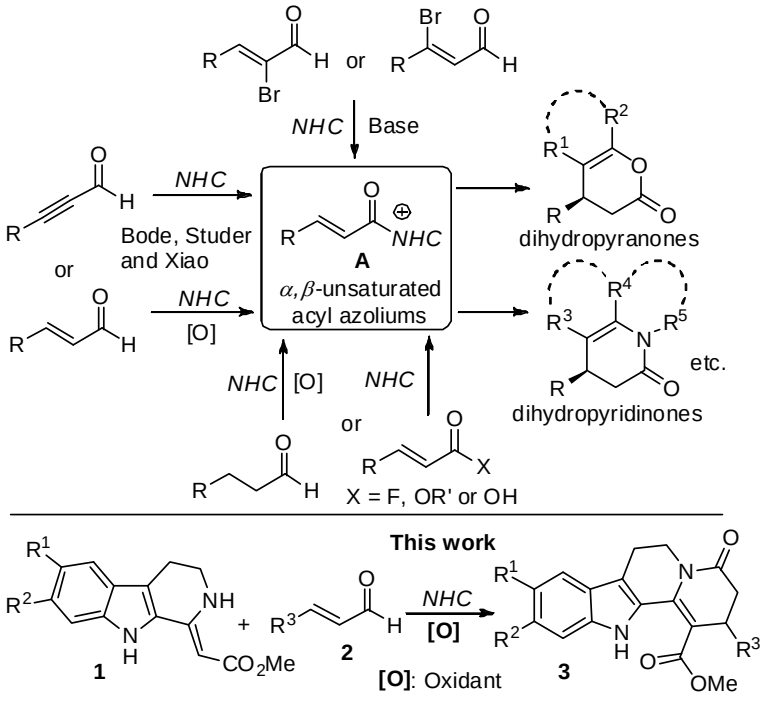


Figure 1. Representative natural products containing indolo[2,3-*a*]quinolizidine skeleton.

Over the past decade, N-Heterocyclic carbenes (NHCs) have been intensively investigated as versatile organocatalysts to promote a variety of unconventional chemical transformations of different aldehydes. [3] In recent years, *α*,*β*-unsaturated acyl azoliums have emerged as new reactive intermediates to enabled a wealth of

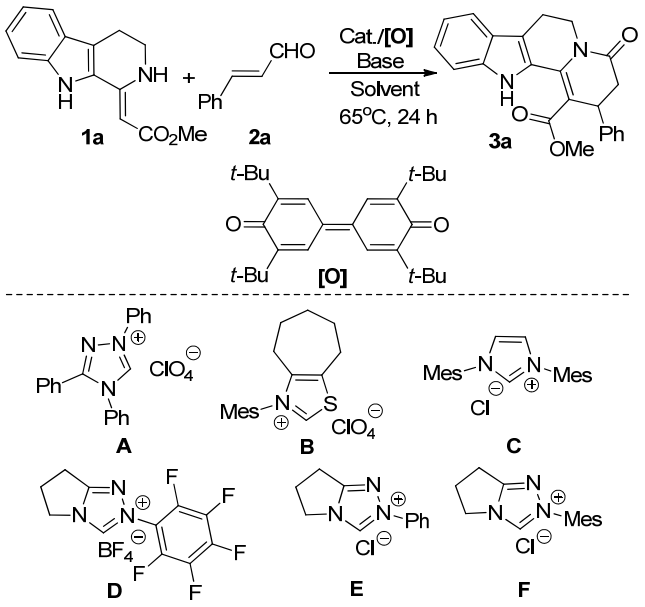
reactions with a range of nucleophiles which were firstly discovered by Zeitler in 2006.[4] More recently, Bode[5], Studer[6] and Xiao[7] independently reported NHC-catalyzed annulations of ynal[8] or enal[8e, 9]-derived α,β-unsaturated acyl azoliums with various stable enols to afford functionalized dihydropyranones (Scheme 1). Bode also described the elegant work of the reactions between α,β-unsaturated acyl azoliums and enamines to give diverse dihydropyridinones (Scheme 1). [10] Notably, α,β-unsaturated acyl azoliums can be equally generated from other various types of precursors under different conditions including α-bromoenals,[11] β-bromoenals,[12] saturated aldehydes,[13] α,β-unsaturated acyl fluorides,[14] α,β-unsaturated esters,[15] and α,β-unsaturated carboxylic acids or their anhydrides (Scheme 1).[16] Along with the discovery of diverse precursors for the generation of α,β-unsaturated acyl azoliums, development of novel nucleophiles suitable for this reaction system is still in demand. Cyclic β-enamino esters **1** have been proved as good nucleophiles and useful building blocks in the construction of bioactive compounds with highly complex skeletons.[17] To test their feasibility of serving as nucleophiles to react with α,β-unsaturated acyl azoliums and as our ongoing program to develop novel NHC-involved methodologies for the synthesis of heterocyclic compounds,[8c, 8e, 18] we combined cyclic β-enamino esters **1** with enals **2** under NHC/[O] condition in order to get indolo[2,3-a]quinolizidines **3**. Herein we wish to report the results.



Scheme 1. NHC-catalyzed reactions involving α,β-unsaturated acyl azolium intermediates.

To verify our hypothesis, a set of experiments were carried out to evaluate the feasibility of the reaction between cyclic *β*-enamino ester **1a** (1.0 equiv.) and enal **2a** (2.5 equiv.) (Table 1). Initially, the efficiency of some carbene precursors (15 mol %) was examined in the presence of DBU (1.0 equiv.) and commonly used quinone oxidant (1.1 equiv.) (entries 1-3). None of precursors **A-F** were suitable for this reaction in THF while precursors **E** and **F** were found effective in toluene although resulting in low yields. Then, after careful screening of other bases (entries 4-8), DIPEA was established as the optimal base which afforded desired product **3a** in 76% yield (entry 8). Further survey of solvents did not lead to improved yield of **3a**, and therefore, the optimal reaction condition was established as that shown in entry 8. [19]

Table 1. Optimization of the reaction conditions. [a]



Entry	Catalyst	Base	Solvent	Yield[b]
1	**A-F**	DBU	THF	0[c]
2	**E**	DBU	PhMe	25
3	**F**	DBU	PhMe	30
4	**F**	*t*-BuOK	PhMe	0
5	**F**	Cs_2CO_3	PhMe	42
6	**F**	K_2CO_3	PhMe	14
7	**F**	NEt_3	PhMe	35
8	**F**	**DIPEA**	**PhMe**	**76**
9	**F**	DIPEA	DCM	59
10	**F**	DIPEA	1,2-DCE	37
11	**F**	DIPEA	DMF	0
12	**F**	DIPEA	MeCN	0

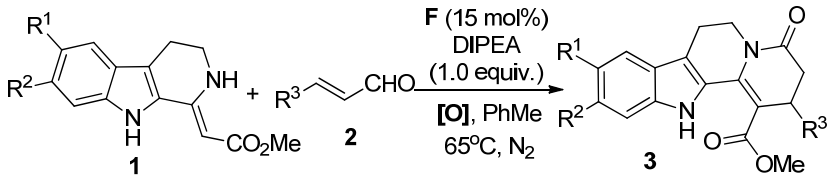
[a] All reactions were performed in a sealed tube on a 0.25 mmol scale with 1.0 equiv. of **1a**, 2.5 equiv. of **2a**, 1.1 equiv. of quionone oxidant **[O]**, 15mol% of a carbene precursor, 1.0 equiv. of a base and 200 mg of 4 Å MS in an anhydrous solvent (4 mL) at 65 °C for 24 h under N_2.

[b] Isolated yields based on **1a**.

[c] Low conversion of the reactions. DBU = 1,8-diazabicyclo[5.4.0]-undec-7-ene; Mes = 2,4,6-$(CH_3)_3C_6H_2$; DIPEA = *N*,*N*-diisopropylethylamine.

With the optimal reaction conditions in hand, we moved on to explore the reaction scope (Table 2). Initially, a variety of aryl enals **2** were used to test the generality of this reaction (entries 2-15). Enals **2b-m** except **2d** with different substituents on the phenyl rings were found suitable for this reaction, but resulting in comparatively lower yields than **2a** (entries 2-13). 2-Methyl substituted phenyl enal **2d** (entry 4) and 1-naphthyl enal **2n** (entry 14) failed to afford the desired products perhaps owing to the steric effect of the more hindered 2-methyl phenyl and 1-naphthyl groups respectively. Heteroaromatic-substituted enal **2o** was tolerant for this protocol but with significantly reduced yield (entry 15). Unfortunately, the reaction of aliphatic substituted enal **2p** did not work (entry 16). Subsequently, several cyclic *β*-enamino esters **1b-g** with different R^1 and R^2 substituents were examined (entries 17-22). Gratifyingly, the reactions of **1b-g** with enal **2a** afforded the corresponding products in moderate to good yields. It seemed that electron-donating groups on the phenyl ring of substrates **1** were favorable for this reaction (entries 19 and 20).

Table 2. Scope of the reaction.[a]

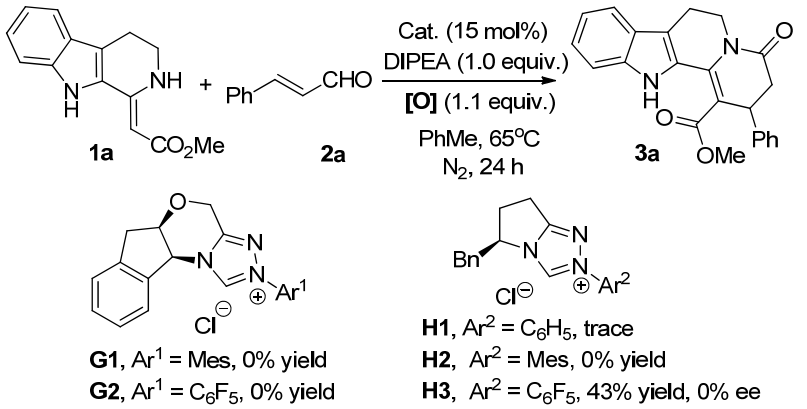


Entry	R^1, R^2, **1**	R^3, **2**	Time (h)	**3**, Yield (%)[b]
1	H, H, **1a**	Ph, **2a**	24	**3a**, 76
2	H, H, **1a**	(2-F)Ph, **2b**	20	**3b**, 40
3	H, H, **1a**	(2-Cl)Ph, **2c**	12	**3c**, 60
4	H, H, **1a**	(2-Me)Ph, **2d**	72	-, trace
5	H, H, **1a**	(2-OMe)Ph, **2e**	24	**3d** 52
6	H, H, **1a**	(3-F)Ph, **2f**	24	**3e**, 33
7	H, H, **1a**	(3-Cl)Ph, **2g**	24	**3f**, 53
8	H, H, **1a**	(3-Me)Ph, **2h**	36	**3g**, 45
9	H, H, **1a**	(4-F)Ph, **2i**	12	**3h**, 51
10	H, H, **1a**	(4-Cl)Ph, **2j**	12	**3i**, 61
11	H, H, **1a**	(4-Br)Ph, **2k**	48	**3j**, 28
12	H, H, **1a**	(4-Me)Ph, **2l**	24	**3k**, 65
13	H, H, **1a**	(4-OMe)Ph, **2m**	24	**3l**, 72
14	H, H, **1a**	1-Naphthyl, **2n**	72	-, 0
15	H, H, **1a**	2-Furyl, **2o**	10	**3m**, 30
16	H, H, **1a**	$Ph(CH_2)_2$, **2p**	24	-. 0
17	Cl, H, **1b**	Ph, **2a**	12	**3n**, 50
18	Br, H, **1c**	Ph, **2a**	10	**3o**, 41
19	Me, H, **1d**	Ph, **2a**	14	**3p**, 68
20	OMe, H, **1e**	Ph, **2a**	12	**3q**, 81
21	H, F, **1f**	Ph, **2a**	15	**3r**, 58
22	H, Cl, **1g**	Ph, **2a**	12	**3s**, 37

[a] All reactions were performed in a sealed tube on a 0.25 mmol scale with 1.0 equiv. of **1**, 2.5 equiv. of **2**, 1.1 equiv. of quionone oxidant **[O]**, 15mol% of **F**, 1.0 equiv. of DIPEA and 200 mg of 4 Å MS in anhydrous toluene (4 mL) at 65 °C under N_2.

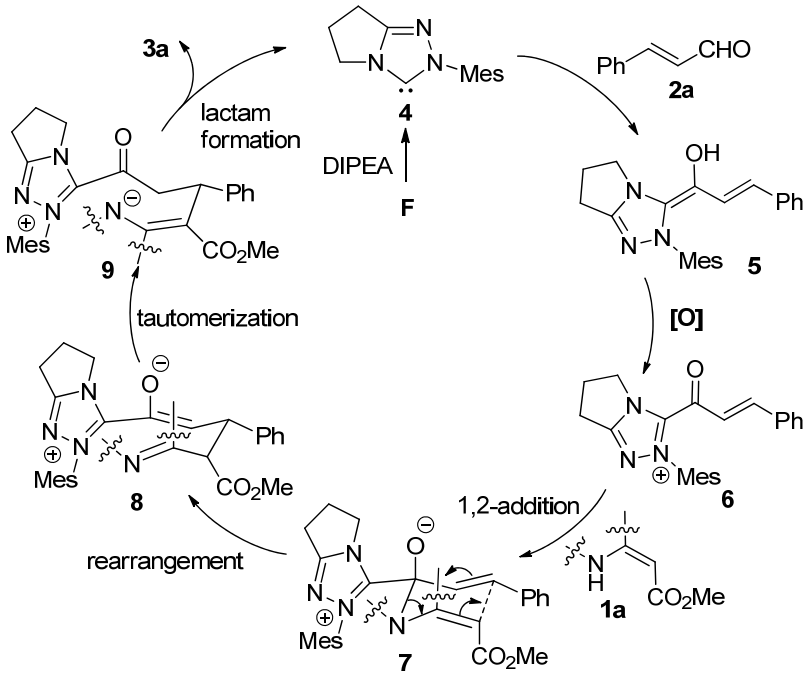
[b] Isolated yields based on **1**.

Several commonly used chiral carbene precursors **G1**-**2** and **H1**-**3** were then applied for a preliminary enantioselective study of this reaction (Scheme 2). However, most of these chiral carbene precursors were not suitable for this reaction while only **H3** resulted in 43% yield but 0% e.e. value.



Scheme 2. A preliminary enantioselective study.

A plausible reaction mechanism is proposed in Scheme 3. The combination of enal **2a** with NHC **4** generated upon deprotonation of carbene precursor **F** with DIPEA affords Breslow intermediate **5**, which is oxidized to α,β-unsaturated acyl azolium **6**. Then, 1,2-addition[10] of cyclic enamino ester **1a** to intermediate **6** followed by a Claisen rearrangement affords enolate **8**. The tautomerization of **8** and subsequent lactam formation give product **3a** and regenerate NHC **4** for next catalytic cycle.



Scheme 3. Proposed mechanism.

In conclusion, we have described a novel synthetic strategy for the synthesis of functionalized indolo[2,3-a]quinolizidine derivatives *via* an NHC-catalyzed annulation of cyclic *β*-enamino esters with enals. The indolo[2,3-a]quinolizidine core is frequently found as a privileged structure of numerous natural products and medicines, and therefore the resulting products might be used for further bioactivity study. Investigation of the reactions between cyclic *β*-enamino esters and *α,β*-unsaturated acyl azoliums derived from other precursors as well as development of an enantioselective synthetic protocol are currently undergoing in our laboratory.

Experimental section

General Methods. All reactions were carried out under an atmosphere of nitrogen in dry glassware, and were monitored by analytical thin-layer chromatography (TLC), which was visualized by ultraviolet light (254 nm). All solvents were obtained from commercial sources and were purified according to standard procedures. Purification of the products was accomplished by flash chromatography using silica gel (200~300 mesh). Substrates **1** were prepared according to a known method.[20] All NMR spectra were recorded on Bruker spectrometers, running at 300 MHz for ^{1}H and 75 MHz for ^{13}C respectively . Chemical shifts (δ) and coupling constants (J) are reported in ppm and Hz respectively. The solvent signals were used as references (residual $CHCl_3$ in $CDCl_3$: δ_H = 7.26 ppm, δ_c = 77.0 ppm). The following abbreviations are used to indicate the multiplicity in NMR spectra: s (singlet); d (doublet); t (triplet); q (quartet); m (multiplet). High resolution mass spectrometry (HRMS) was recorded on TOF perimer for ES^+ or ES^-. The e.e. value was determined via chiral HPLC analysis (Diacel Chiral pack IB, *n*-hexane/enthanol/diethylamine = 90/10/0.1).

General experimental procedure for the synthesis of products 3

To an oven-dried 15 mL glass cylindrical pressure vessel was charged with enal **1** (0.625 mmol), cyclic enamino ester **2** (0.25 mmol), quinone oxidant (112 mg, 0.275mmol), carbene precursor **F** (10 mg, 0.0375 mmol) and 200 mg of 4 Å MS under N_2 atmosphere. Then anhydrous toluene (3 mL) was added followed by addition of DIPEA (32 mg, 0.25 mmol) and the vessel was immediately sealed tightly. The resulting mixture was stirred at 65^{o}C for a period of time. After completion of the reaction as monitored by TLC, the mixture was cooled to room temperature. The solvent was evaporated under reduced pressure and the residue was purified by chromatography on silica gel to afford the product **3**.

3a, white solid, MP: 217–218°C. ^{1}H NMR (300MHz, $CDCl_3$): δ 12.25 (brs, 1H), 7.61 (d, J = 8.0, 1H), 7.49 (d, J = 8.3 Hz, 1H), 7.14-7.37 (m, 7H), 5.21 (m, 1H), 4.53 (dd, J = 5.4, 3.2 Hz, 1H), 3.81 (s, 3H), 3.25 (m, 1H), 2.96-3.04 (m, 4H). ^{13}C NMR (75MHz, $CDCl_3$): δ 169.2, 168.7, 142.2, 140.2, 136.9, 128.8, 127.0, 126.6, 125.8, 125.4, 124.9, 120.1, 119.5, 119.2, 112.2, 107.7, 52.5, 40.9, 38.8, 37.8, 20.9. HRMS (ESI) calcd for $C_{23}H_{19}N_2O_3$ $(M-H)^-$: 371.1396, found 371.1404. IR (KBr): v 3414, 1687, 1668, 1560, 1371, 1332, 1232, 1223, 1195, 1178, 1163, 1124, 756 cm^{-1}.

3b, yellow solid, MP: 228–229°C. ^{1}H NMR (300MHz, $CDCl_3$): δ 12.28 (brs, 1H), 7.59 (d, J = 8.0 Hz, 1H), 7.48 (d, J = 8.3 Hz, 1H), 7.33 (m, 1H), 7.07-7.17 (m, 2H), 6.98-7.07 (m, 3H), 5.23 (m, 1H), 4.81 (m, 1H), 3.77 (s, 3H), 3.24 (m, 1H), 2.99-3.03 (m, 2H), 2.93-2.98 (m, 2H). ^{13}C NMR (75MHz, $CDCl_3$): δ 169.1, 168.6, 160.8 (d, J = 246.1 Hz, 1C), 143.0, 137.1, 128.9 (d, J = 8.4 Hz, 1C), 127.5 (d, J = 3.9 Hz, 1C), 127.1, 126.9, 125.6, 125.5 (d, J = 58.4 Hz, 1C), 124.2 (d, J = 3.5 Hz, 1C), 120.2, 119.6, 119.4, 115.9 (d, J = 22.2 Hz, 1C), 112.3, 106.4, 52.5, 41.0, 37.4, 32.3 (d, J = 3.1 Hz, 1C), 21.0. HRMS (ESI) calcd for $C_{23}H_{18}N_2O_3F$ $(M-H)^-$: 389.1301, found 389.1313. IR (KBr): v 3417, 1695, 1668, 1614, 1564, 1371, 1332, 1236, 1201, 1174, 1159 cm^{-1}.

3c, yellow solid, MP: 233–234°C. ^{1}H NMR (300MHz, $CDCl_3$): δ 12.31 (brs, 1H), 7.60 (d, J = 8.0 Hz, 1H), 7.48 (d, J = 8.3 Hz, 1H), 7.41 (m, 1H), 7.34 (m, 1H), 7.12-7.20 (m, 3H), 7.06 (m, 1H), 5.25 (m, 1H), 4.90 (dd, J = 6.3, 2.6 Hz, 1H), 3.75 (s, 3H), 3.30 (m, 1H), 2.97-3.05 (m, 2H), 2.93-2.97 (m, 2H). ^{13}C NMR (75MHz, $CDCl_3$): δ 169.0, 168.5, 143.2, 137.0, 133.6, 130.0, 128.6, 127.3, 127.1, 125.7, 125.6, 124.9, 120.2, 119.6, 119.4, 115.4, 112.3, 106.9, 52.7, 41.1, 36.7, 35.8, 21.0. HRMS (ESI) calcd for $C_{23}H_{18}N_2O_3Cl$ $(M-H)^-$: 405.1006, found 405.1016. IR (KBr): v 3414, 1693, 1670, 1562, 1371, 1332, 1284, 1236, 1199, 1178, 1157, 1126 cm^{-1}.

3d, yellow solid, MP: 193–194°C. ^{1}H NMR (300MHz, $CDCl_3$): δ 12.22 (brs, 1H), 7.58 (d, J = 7.9 Hz, 1H), 7.47 (d, J = 8.3 Hz, 1H), 7.31 (m, 1H), 7.21 (m, 1H), 7.14 (m, 1H), 6.99 (dd, J = 7.5, 2.4 Hz, 1H), 6.88 (d, J = 7.9 Hz, 1H), 6.82 (t, J = 7.4 Hz, 1H), 5.21 (m, 1H), 4.78 (m, 1H), 3.89 (s, 3H), 3.75 (s, 3H) , 3.24 (m, 1H), 2.98-3.04 (m, 3H), 2.83 (dd, J = 15.9, 6.7 Hz, 1H). ^{13}C NMR (75MHz, $CDCl_3$): δ 169.5, 169.4, 157.0, 142.5, 136.9, 128.3, 127.3, 126.6, 126.0, 125.3, 125.1, 120.4, 120.1, 119.5, 118.9, 112.2, 110.7, 107.7, 55.3, 52.5, 40.8, 36.7, 32.9, 21.0. HRMS (ESI) calcd for $C_{24}H_{21}N_2O_4$ $(M-H)^-$: 401.1501, found 401.1511. IR (KBr): v 3417, 1689, 1670, 1558, 1365, 1257, 1246, 1220, 1170, 1159, 1122, 754 cm^{-1}.

3e, yellow solid, MP: 181–182°C. ^{1}H NMR (300MHz, $CDCl_3$): δ 12.25 (brs, 1H), 7.59 (d, J = 8.0 Hz, 1H), 7.47 (d, J = 8.3 Hz, 1H), 7.27-7.35 (m, 2H), 7.14 (m, 1H), 6.97 (m, 1H), 6.88-6.95

(m, 2H), 5.21 (m, 1H), 4.49 (dd, J = 5.9, 2.6 Hz, 1H), 3.80 (s, 3H), 3.20 (m, 1H), 2.86-3.28 (m, 4H). ^{13}C NMR (75MHz, $CDCl_3$): δ 169.0, 168.5, 163.1 (d, $J_{C\text{-}F}$ = 246.4 Hz, 1C), 142.9 (d, $J_{C\text{-}F}$ = 6.9 Hz, 1C), 142.6, 136.9, 130.3 (d, $J_{C\text{-}F}$ = 8.4 Hz, 1C), 125.7, 125.6, 124.9, 122.3 (d, $J_{C\text{-}F}$ = 2.7 Hz, 1C), 120.2, 119.6, 119.5, 114.1 (d, $J_{C\text{-}F}$ = 21.1 Hz, 1C), 113.8 (d, $J_{C\text{-}F}$ = 22.1 Hz, 1C), 112.3, 107.1, 52.6, 41.0, 38.7, 37.8, 21.0. HRMS (ESI) calcd for $C_{23}H_{18}N_2O_3F$ $(M\text{-}H)^-$: 389.1301, found 389.1310. IR (KBr): v 3419, 1699, 1670, 1614, 1587, 1568, 1365, 1332, 1234, 1219, 1174, 1159 cm^{-1}.

3f, yellow solid, MP: 149–150°C. ^{1}H NMR (300MHz, $CDCl_3$): δ 12.27 (brs, 1H), 7.58 (d, J = 8.0 Hz, 1H), 7.47 (d, J = 8.3Hz, 1H), 7.34 (m, 1H), 7.19-7.23 (m, 2H), 7.14-7.16 (m, 2H), 7.07 (m, 1H), 5.21 (m, 1H), 4.48 (dd, J = 6.0, 2.4 Hz, 1H), 3.80 (s, 3H), 3.21 (m, 1H), 2.90-3.03 (m, 2H), 2.85-2.97 (m, 2H). ^{13}C NMR (75MHz, $CDCl_3$): δ 168.9, 168.4, 142.7, 142.4, 137.0, 134.7, 130.1, 127.3, 127.0, 125.7, 125.6, 124.9, 124.8, 120.2, 119.6, 119.5, 112.3, 106.9, 52.6, 41.0, 38.8, 37.8, 21.0. HRMS (ESI) calcd for $C_{23}H_{19}N_2O_3ClNa$ $(M+Na)^+$: 429.0982, found 429.0976. IR (KBr): v 3419, 1695, 1668, 1593, 1560, 1516, 1367, 1332, 1282, 1255, 1205, 1178, 1157, 1122 cm^{-1}.

3g, yellow solid, MP: 196–197°C. ^{1}H NMR (300MHz, $CDCl_3$): δ 12.26 (brs, 1H), 7.58 (d, J = 8.0 Hz, 1H), 7.46 (d, J = 8.3 Hz, 1H), 7.32 (m, 1H), 7.12-7.20 (m, 2H), 6.97-7.04 (m, 3H), 5.21 (m, 1H), 4.48 (dd, J = 5.4, 2.9 Hz, 1H), 3.79 (s, 3H), 3.19 (m, 1H), 2.96-3.02 (m, 2H), 2.91-2.96 (m, 2H), 2.30 (s, 3H). ^{13}C NMR (75MHz, $CDCl_3$): δ 169.3, 168.9, 142.2, 139.9, 138.3, 136.9, 128.6, 127.9, 127.5, 125.9, 125.4, 125.0, 123.6, 120.1, 119.5, 119.1, 112.2, 107.9, 52.6, 40.9, 38.9, 37.8, 21.5, 21.0. HRMS (ESI) calcd for $C_{24}H_{21}N_2O_3$ $(M\text{-}H)^-$: 385.1552, found 385.1563. IR (KBr): v 3417, 1689, 1670, 1558, 1510, 1369, 1330, 1282, 1261, 1220, 1205, 1188, 1172, 1124, 748 cm^{-1}.

3h, yellow solid, MP: 191–192°C. ^{1}H NMR (300MHz, $CDCl_3$): δ 12.23 (brs, 1H), 7.58 (d, J = 8.0 Hz, 1H), 7.46 (d, J = 8.3 Hz, 1H), 7.32 (m, 1H), 7.12-7.18 (m, 3H), 6.95-7.00 (m, 2H), 5.21 (m, 1H), 4.48 (m, 1H), 3.79 (s, 3H), 3.19 (m, 1H), 2.95-3.00 (m, 2H), 2.90-2.99 (m, 2H). ^{13}C NMR (75MHz, $CDCl_3$): δ 169.1, 168.6, 162.0 (d, $J_{C\text{-}F}$ = 245.6 Hz, 1C), 142.4, 136.9, 135.8 (d, $J_{C\text{-}F}$ = 3.1 Hz, 1C), 128.2 (d, $J_{C\text{-}F}$ = 8.1 Hz, 1C), 125.8, 125.6, 124.9, 120.2, 119.6, 119.4, 115.7 (d, $J_{C\text{-}F}$ = 21.4 Hz, 1C), 112.3, 107.6, 52.6, 41.0, 38.9, 37.3, 21.0. HRMS (ESI) calcd for $C_{23}H_{18}N_2O_3F$ $(M\text{-}H)^-$: 389.1301, found 389.1311. IR (KBr): v 3419, 1695, 1668, 1560, 1506, 1369, 1332, 1232, 1176, 1157, 1112 cm^{-1}.

3i, yellow solid, MP: 201–202°C. ^{1}H NMR (300MHz, $CDCl_3$): δ 12.26 (brs, 1H), 7.60 (d, J = 8.0 Hz, 1H), 7.48 (d, J = 8.3 Hz, 1H), 7.26-7.36 (m, 3H), 7.12-7.18 (m, 3H), 5.21 (m, 1H), 4.48

(m,1H), 3.80 (s, 3H), 3.21 (m, 1H), 2.90-3.01 (m, 4H). ^{13}C NMR (75MHz, $CDCl_3$): δ 169.1, 168.5, 142.5, 138.8, 136.8, 132.9, 128.9, 128.1, 125.7, 125.6, 124.9, 120.2, 119.6, 119.5, 112.3, 107.2, 52.6, 41.0, 38.8, 37.5, 21.0. HRMS (ESI) calcd for $C_{23}H_{18}N_2O_3Cl$ $(M-H)^-$: 405.1006, found 405.1014. IR (KBr): ν 3414, 1695, 1668, 1616, 1560, 1369, 1330, 1232, 1197, 1176, 1112, 742 cm^{-1}.

3j, yellow solid, MP: 202–203°C. ^{1}H NMR (300MHz, $CDCl_3$): δ 12.24 (brs, 1H), 7.59 (d, J = 8.0 Hz, 1H), 7.47 (d, J = 8.3 Hz, 1H), 7.40 (d, J = 8.4 Hz, 2H), 7.32 (m, 1H), 7.12-7.17 (m, 1H), 7.07 (d, J = 8.4 Hz, 2H), 5.20 (m, 1H), 4.45 (m, 1H), 3.79 (s, 3H), 3.18 (m, 1H), 2.84-3.02 (m, 4H). ^{13}C NMR (75MHz, $CDCl_3$): δ 169.0, 168.5, 142.6, 139.3, 137.0, 132.0, 128.5, 125.7, 125.6, 124.9, 120.9, 120.2, 119.6, 119.5, 112.3, 107.1, 52.6, 41.0, 38.7, 37.5, 21.0. HRMS (ESI) calcd for $C_{23}H_{19}N_2O_3BrNa$ $(M+Na)^+$: 473.0477, found 473.0490. IR (KBr): ν 3423, 1697, 1670, 1556, 1510, 1373, 1334, 1276, 1259, 1220, 1159, 1174, 1161, 1124, 746 cm^{-1}.

3k, yellow solid, MP: 172–173°C. ^{1}H NMR (300MHz, $CDCl_3$) : δ 12.24 (brs, 1H), 7.59 (d, J = 8.0 Hz, 1H), 7.46 (d, J = 8.3 Hz, 1H), 7.30 (m, 1H), 7.13 (m, 1H), 7.06-7.10 (m, 4H), 5.21 (m, 1H), 4.47 (dd, J = 5.5, 3.0 Hz, 1H), 3.79 (s, 3H), 3.15-3.25 (m, 1H), 2.97-3.04 (m, 2H), 2.86-2.96 (m, 2H), 2.30 (s, 3H). ^{13}C NMR (75MHz, $CDCl_3$): δ 169.3, 168.9, 142.2, 137.0, 136.9, 136.6, 129.5, 126.5, 125.9, 125.4, 125.0, 120.1, 119.5, 119.1, 112.2, 108.0, 52.6, 40.9, 38.9, 37.5, 21.01, 20.96. HRMS (ESI) calcd for $C_{24}H_{21}N_2O_3$ $(M-H)^-$: 385.1552, found 385.1561. IR (KBr): ν 3412, 1695, 1668, 1560, 1369, 1332, 1232, 1197, 1176, 1157, 1114 cm^{-1}.

3l, yellow solid, MP: 159–160°C. ^{1}H NMR (300MHz, $CDCl_3$): 12.23 (brs, 1H), 7.58 (d, J = 8.0 Hz, 1H), 7.46 (d, J = 8.3 Hz, 1H), 7.32 (m, 1H), 7.10-7.16 (m, 3H), 6.82 (d, J = 8.7 Hz, 2H), 5.22 (m, 1H), 4.46 (dd, J = 5.5, 2.9 Hz, 1H), 3.79 (s, 3H), 3.77 (s, 3H), 3.18 (m, 1H), 2.96-3.05 (m, 2H), 2.84-2.93 (m, 2H). ^{13}C NMR (75MHz, $CDCl_3$): δ 169.3, 168.9, 158.6, 142.0, 136.9, 132.0, 127.7, 125.9, 125.4, 124.9, 120.1, 119.5, 119.1, 114.2, 112.2, 108.2, 55.2, 52.5, 40.9, 38.9, 37.1, 20.9. HRMS (ESI) calcd for $C_{24}H_{21}N_2O_4$ $(M-H)^-$: 401.1501, found 401.1510. IR (KBr): ν 3414, 1689, 1670, 1560, 1510, 1377, 1246, 1220, 1180, 1157, 1126 cm^{-1}.

3m, yellow solid, MP: 189–190°C. ^{1}H NMR (300MHz, $CDCl_3$): δ 12.26 (brs, 1H), 7.57 (d, J = 8.0 Hz, 1H), 7.45 (d, J = 8.3 Hz, 1H), 7.28-7.33 (m, 2H), 7.13 (m, 1H), 6.25 (dd, J = 3.1, 1.9 Hz, 1H), 6.06 (d, J = 3.2 Hz, 1H), 5.27 (m, 1H), 4.57 (d, J = 4.5 Hz, 1H), 3.88 (s, 3H), 3.12 (m, 1H), 2.95-3.08 (m, 3H), 2.84 (m, 1H). ^{13}C NMR (75MHz, $CDCl_3$): δ 168.9, 153.7, 142.5, 142.2, 136.9, 125.9, 125.5, 124.9, 120.2, 119.6, 119.5, 112.0, 110.2, 105.8, 105.6, 52.7, 41.6, 38.4, 35.8, 21.0.

HRMS (ESI) calcd for $C_{23}H_{19}N_2O_3$ $(M-H)^-$: 371.1396, found 371.1404. IR (KBr): *v* 3414, 1697, 1670, 1560, 1367, 1330, 1282, 1230, 1203, 1184, 1159, 1138, 1120, 740 cm^{-1}.

3n, yellow solid, MP: 208–209°C. ^1H NMR (300MHz, $CDCl_3$): δ 12.39 (brs, 1H), 7.55 (d, J = 1.7 Hz, 1H), 7.38 (d, J = 8.7 Hz, 1H), 7.23-7.32 (m, 4H), 7.17-7.20 (m, 2H), 5.20 (m, 1H), 4.51 (dd, J = 5.3, 3.0 Hz, 1H), 3.79 (s, 3H), 3.18 (m, 1H), 2.92-2.97 (m, 4H). ^{13}C NMR (75MHz, $CDCl_3$): δ 169.3, 168.7, 141.9, 139.9, 135.1, 128.9, 127.2, 126.7, 125.9, 125.8, 125.7, 118.9, 118.4, 113.4, 108.6, 52.7, 40.8, 38.8, 37.9, 20.9. HRMS (ESI) calcd for $C_{23}H_{18}N_2O_3Cl$ $(M-H)^-$: 405.1006, found 405.1016. IR (KBr): *v* 3412, 1695, 1670, 1616, 1570, 1371, 1321, 1284, 1234, 1197, 1178, 1157, 1116 cm^{-1}.

3o, yellow solid, MP: 192–193°C. ^1H NMR (300MHz, $CDCl_3$): δ 12.39 (brs, 1H), 7.72 (s, 1H), 7.36-7.40 (m, 2H), 7.27-7.33 (m, 2H), 7.17-7.23 (m, 3H), 5.20 (m, 1H), 4.52 (m, 1H), 3.79 (s, 3H), 3.20 (m, 1H), 2.90-3.00 (m, 4H). ^{13}C NMR (75MHz, $CDCl_3$): δ 169.3, 168.7, 141.9, 140.0, 135.3, 128.9, 128.2, 127.2, 126.9, 126.7, 122.1, 118.3, 113.7, 113.3, 108.7, 52.7, 40.8, 38.8, 37.9, 20.9. HRMS (ESI) calcd for $C_{23}H_{19}N_2O_3BrNa$ $(M+Na)^+$: 473.0477, found 473.0492. IR (KBr): *v* 3414, 1695, 1668, 1570, 1371, 1321, 1286, 1236, 1195, 1178, 1116 cm^{-1}.

3p, yellow solid, MP: 211–212°C. ^1H NMR (300MHz, $CDCl_3$): δ 12.23 (brs, 1H), 7.36 (d, J = 8.8 Hz, 1H), 7.27-7.31 (m, 2H), 7.18-7.22 (m, 3H), 6.99 (dd, J = 8.9, 2.4 Hz, 1H), 6.94 (d, J = 2.0 Hz, 1H), 5.19 (m, 1H), 4.51 (dd, J = 5.1, 2.8 Hz, 1H), 3.87 (s, 3H), 3.77 (s, 3H), 3.19 (m, 1H), 2.94-2.98 (m, 4H). ^{13}C NMR (75MHz, $CDCl_3$): δ 169.3, 168.8, 154.5, 142.4, 140.3, 132.4, 128.8, 127.0, 126.7, 126.3, 125.2, 118.6, 117.1, 113.2, 107.4, 99.7, 55.7, 52.5, 41.0, 38.9, 37.9, 21.1. HRMS (ESI) calcd for $C_{24}H_{21}N_2O_3$ $(M-H)^-$: 385.1552, found 385.1559. IR (KBr): v3414, 1693, 1668, 1556, 1496, 1371, 1327, 1257, 1244, 1217, 1193, 1178, 1159, 1143, 1122 cm^{-1}.

3q, yellow solid, MP: 210–211°C. ^1H NMR (300MHz, $CDCl_3$): δ 12.23 (brs, 1H), 7.36 (d, J = 8.9 Hz, 1H), 7.27-7.31 (m, 2H), 7.18-7.24(m, 3H), 6.99 (dd, J = 8.9, 2.4 Hz, 1H), 6.94 (d, J = 2.1 Hz, 1H), 5.20 (m, 1H), 4.50 (dd, J = 5.4, 3.1 Hz, 1H), 3.87 (s, 3H), 3.78 (s, 3H), 3.19 (m, 1H), 2.90-2.99 (m, 4H). ^{13}C NMR (75MHz, $CDCl_3$): δ 169.3, 168.8, 154.5, 142.4, 140.3, 132.4, 128.8, 127.0, 126.7, 126.4, 125.2, 118.6, 117.1, 113.2, 107.4, 99.7, 55.7, 52.5, 41.0, 38.9, 37.9, 21.1. HRMS (ESI) calcd for $C_{24}H_{21}N_2O_4$ $(M-H)^-$: 401.1501, found 401.1496. IR (KBr): *v* 3414, 1693, 1668, 1556, 1369, 1244, 1217, 1178, 1122 cm^{-1}.

3r, yellow solid, MP: 245–246°C. ^1H NMR (300MHz, $CDCl_3$): δ 12.34 (brs, 1H), 7.50 (dd, J =

8.7, 5.4 Hz, 1H), 7.23-7.32 (m, 2H), 7.17-7.22 (m, 3H), 7.12 (dd, J = 9.6, 2.1 Hz, 1H), 6.91 (m, 1H), 5.20 (m, 1H), 4.51 (m, 1H), 3.78 (s, 3H), 3.19 (m, 1H), 2.94-2.99 (m, 4H). ^{13}C NMR (75MHz, $CDCl_3$): δ 169.3, 168.8, 161.9 (d, $J_{C\text{-}F}$ = 242.3 Hz, 1C), 142.0, 140.1, 137.0 (d, $J_{C\text{-}F}$ = 13.0 Hz, 1C), 128.8, 127.1, 126.7, 121.8, 120.7 (d, $J_{C\text{-}F}$ = 10.5 Hz, 1C), 119.34, 119.33, 109.7 (d, $J_{C\text{-}F}$ = 25.5Hz, 1C), 107.8, 98.1 (d, $J_{C\text{-}F}$ = 26.0 Hz, 1C), 52.6, 40.8, 38.8, 37.9, 21.0. HRMS (ESI) calcd for $C_{23}H_{18}N_2O_3F$ $(M\text{-}H)^-$: 389.1301, found 389.1314. IR (KBr): v 3419, 1693, 1670, 1624, 1558, 1379, 1359, 1232, 1222, 1197, 1180, 1159, 1147, 1122, 1111 cm^{-1}.

3s, yellow solid, MP: 178–179°C. ^{1}H NMR (300MHz, $CDCl_3$): δ 12.35 (brs, 1H), 7.47-7.50 (m, 2H), 7.27-7.32 (m, 2H), 7.17-7.24 (m, 3H), 7.10 (dd, J = 8.5, 2.1 Hz, 1H), 5.21 (m, 1H), 4.51 (dd, J = 5.3, 3.3 Hz, 1H), 3.78 (s, 3H), 3.18 (m, 1H), 2.93-2.99 (m, 4H). ^{13}C NMR (75MHz, $CDCl_3$): δ 169.3, 168.7, 141.9, 140.0, 137.0, 131.2, 128.8, 127.1, 126.7, 126.6, 123.6, 121.1, 120.5, 119.1, 112.0, 108.3, 52.7, 40.8, 38.8, 37.9, 20.9. HRMS (ESI) calcd for $C_{23}H_{18}N_2O_3Cl$ $(M\text{-}H)^-$: 405.1006, found 405.1001. IR (KBr): v 3414, 1697, 1670, 1616, 1560, 1363, 1246, 1176, 1157, 1197, 1120 cm^{-1}.

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