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Pd(II)-catalyzed aerobic oxidative intramolecular hydroamination and C–H functionalization of *N*-alkynyl anilines for the synthesis of indole derivatives

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ABSTRACT

A Pd(II)-catalyzed aerobic oxidative approach to 2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indoles from simple *N*-alkynyl anilines through tandem intramolecular hydroamination and aryl C–H activation process has been developed. Molecular oxygen was used as the sole oxidant to recycle the Pd-catalysis. This protocol is attractive due to the available starting materials and the valuable products.

1. Introduction

2,3-Dihydro-1*H*-pyrrolo[1,2-*a*]indole (Fig. 1, **I**) is a core structure of many bioactive molecules and pharmaceuticals. It was early found to be naturally originated in microbial metabolites, mitomycin antibiotics (**II**).[1,2] Afterward, large numbers of bioactive compounds containing this skeleton have also been discovered and synthesized, ranging from antitumor antibiotic,[1–4] enzyme inhibitors (**III**),[5,6]r-eceptorantagonists[7,8] to antibacterial agents.[3,9] Due to the importance of these substituted dihydropyrrolo[1,2-*a*]indoles in biological application, the corresponding synthesis methods have gathered much interest of synthetic chemists. However, this special indole structure with two five-membered rings fused together by a C–N bond as a bridge make the synthesis more challenging than that of cyclano[*b*] indoles and usually need multiple steps.[10] Most of the strategies are based on the accomplishment of one cyclization of either the two five-membered rings, affording an indole or 1-phenylpyrrolidine, and followed by another cyclization.[11] In view of this limitation, a new protocol design to directly synthesize the ternary fused ring in one-step from easily available substrates is still attractive.

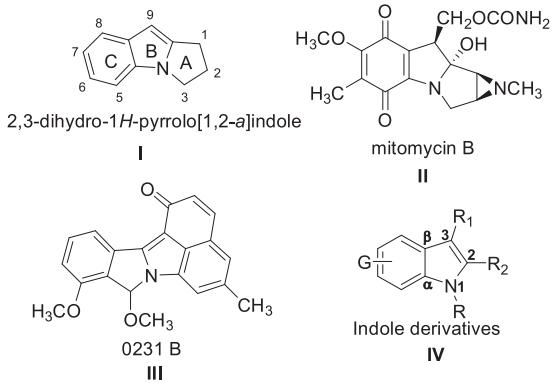

Fig. 1. 2,3-Dihydro-1*H*-pyrrolo[1,2-*a*]indole, and some bioactive compounds carrying this ternary fused ring parent nucleus.

Considering indole is the core backbone of these structures, a cascade reaction via indole construction may provide an alternative approach to 1*H*-pyrrolo[1,2-*a*]indoles. Recently, a variety of well-established methods for indole synthesis have been significantly developed. Based on the indole structures (Fig. 1, **IV**), there are several retrosynthetic disconnections, such as C_α–N_1,[12] N_1–C_2,[13] C_2–C_3,[14] C_β–C_3[15,16] via intramolecular reactions and C_2, C_3-explant[17] or a N_1, C_2, C_3-explant[18] via intermolecular reactions.[19] Among them, the C_2, C_3-explant strategy by the reaction of anilines with alkynes has been significantly studied. Since Larock and co-workers reported the palladium-catalyzed heteroannulation of internal alkynes with 2-iodoanilines,[20] a great deal of attention has been attracted to this intermolecular process due to the available

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substrates with high flexibility in substituents. As described by Glorius et al.,[15] indoles can be synthesized directly from enamines catalyzed by $Pd(OAc)_2$ by direct dual C–H bonds activation strategy. The coupling of simple anilines with alkynes to indoles has also been realized via Rh(II)-catalyzed oxidative cyclization by Fagnou and coworkers.[17b] Despite the significances of these approaches, stoichiometric amounts of $Cu(OAc)_2$were required as oxidant in these indole constructions. More recently, the Pd(II)-catalyzed synthesis of multi-substituted indoles from the simple amines and internal alkynes utilizing O_2 as the oxidant has been developed by the groups of Jiao[21] and Yoshikai,[16] respectively. However, it is noted that some special indole frameworks are difficult to construct due to the limited substrate scope of these internal alkynes in this method. On the basis of these results and our experience in this filed, we report here a new protocol to directly synthesize the 1*H*-pyrrolo[1,2-*a*]indoles by a cascade process from easily available substrates.

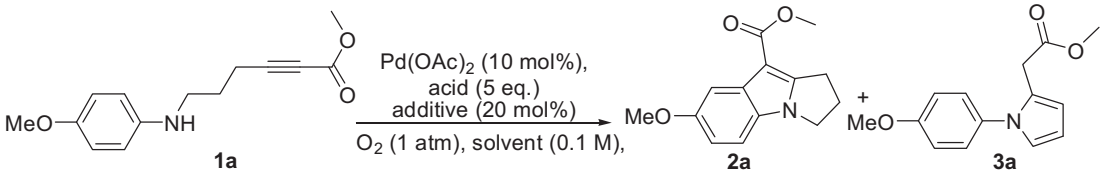
2. Results and discussion

According to our previous study, *para*-methoxy substituted aniline **1a** was selected as the model substrate for the conditions optimization (Table 1). Fortunately, the desired 1*H*-pyrrolo[1,2-*a*]indole product **2a** was obtained in 7% yield (entry 1, Table 1). Based on this result, a set of inorganic and organic oxidants in the presence of O_2 had been screened. However, no better yield was given with the serious decomposition of the starting material. When varying the solvent under the mild oxidative atmosphere of O_2 (1 atm), acetonitrile doubled the yield to 16% with a recovery of 46% starting material (entry 2). After the screening of different organic acids as well as some Lewis acids, benzoic acid was turned out to be the preferable choice with a yield of 38% (entries 3–7). In this regard, a PhCOOK in the place of benzoic acid was tested under a higher catalyst loading of 20 mol %, which gave the desired product in 30% yield (entry 8). In the presence of benzoic acid, PhCOOK reduced the reaction time markedly with a better outcome, which indicates that benzoate ion may play an important role in accelerating the reaction process (entry 9). The reaction at 110 °C consumed all substrate producing **2a** in 46% yield (entry 10). In a screening of the benzoate, PhCOOLi bearing a better solubility in acetonitrile was tested to be the best additive in this system at low temperature, and provided a more appealing output at same time (entries 11 and 12). The reaction in sealed tube exhibited best efficiency (entry 12, Table 1). It must also be noted that a very small amount of β-H elimination byproduct **3a** is conventionally observed and hardly avoided in this reaction.

With these optimized conditions in hand, the scope of this cascade transformation was investigated (Table 2). The unsubstituted aniline substrate **1b** afforded the desired 1*H*-pyrrolo[1,2-*a*] indoles product **2b** in 55% yield. A series of electron-rich substrates substituted with primary alkyl (**1c**), cyclic tertiary alkyl (**1h**), quaternary alkyl, (**1i**) and even a phenyl group (**1e**) at *para*-position of the benzene ring underwent well with moderate yields. It is noteworthy that a hydroxyl group was also tolerated in this reaction without protection giving **2g** in 50% yield, which has been reported to be a direct intermediate for the preparation of mitomycin.[1] When the electron donating groups were changed to the halides, the reaction produced the desired product with low yields (**2k** 35%, **2l** 31%). To our delight, other electron withdrawing substituents, such as trifluoromethyl, trifluoro methoxy, and acetyl, presented satisfied results in this protocol (**2n**, **2o**, **2p**). *ortho*-Substituted substrates, such as **1j** only afforded the product in 29% yield. If the substrate is substituted at the *meta*-position (**1d**, **1f**), the regioselectivity could not be controlled, although the total yields were higher than that of other substrate. The dimethyl substituted **1q** achieved a high efficiency (77%). Meanwhile, the substrates with a longer linker chain between nitrogen atom and alkynyl group were also investigated, however, only trace amount of products were observed.

To study the substitutional flexibility on the alkynyl terminal, we changed the ester group to phenyl group, but no product was detected under the standard conditions. This observation helpfully gave us an implicit on the mechanism that the Pd center may need the C=O double bond for tautomerization to turn over itself to *cis*-form after the *trans*-aminopalladation of alkynyl as a π Lewis acid.[13g,22] Therefore, a variety of alkynyl ketones were designed to

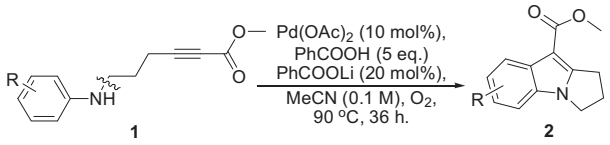
Table 1
Optimization of catalytic conditions[a,b]



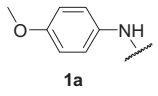
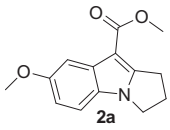
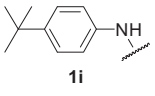
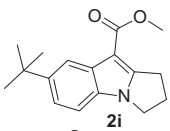
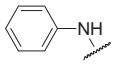
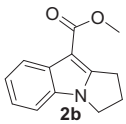
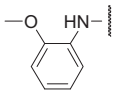
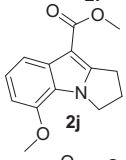
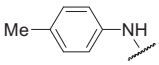
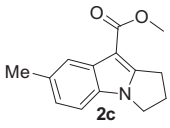
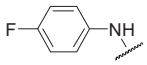
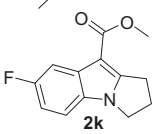
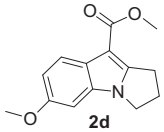
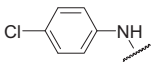
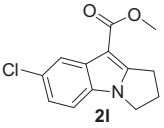
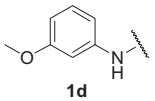
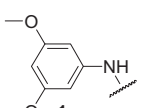
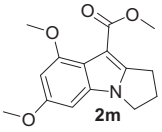
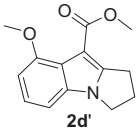
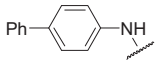
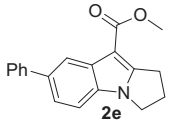
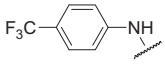
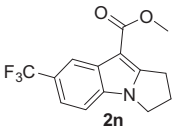
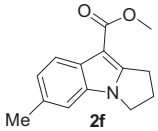
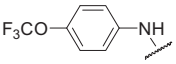
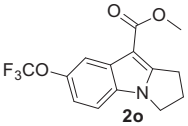
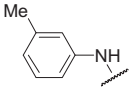
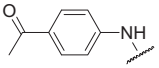
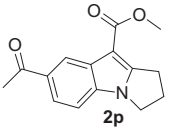
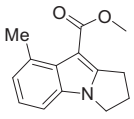
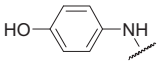
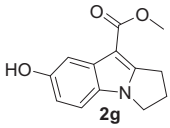
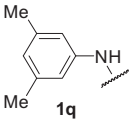
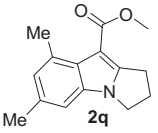
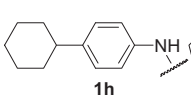
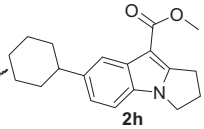
Entry	Solvent	Acid	Additive	*T* (°C)	Time (h)	Recovery of **1a** (%)	Yield of **2a** (%)
1[c]	DMA	PivOH		120	12	Massive	7
2[c]	CH_3CN	PivOH		100	40	46	16
3	CH_3CN	PivOH		100	40	52	25
4	CH_3CN	AcOH		100	40	60	8
5	CH_3CN	Phenol		100	40	76	6
6	CH_3CN	PhCOOH		100	40	32	38
7	CH_3CN	$FeCl_3$		100	40	<5	0
8[d]	CH_3CN		PhCOOK	100	40	36	30
9[d]	CH_3CN	PhCOOH	PhCOOLi	100	12	<10	37
10	CH_3CN[e]	PhCOOH	PhCOOLi	110	36	0	46
11	CH_3CN[e]	PhCOOH	PhCOOLi	100	36	0	45
12	**CH_3CN**[e]	**PhCOOH**	**PhCOOLi**	**90**	**36**	**0**	**52**
13	CH_3CN[e]	PhCOOH	PhCOOK	80	36	<5	45
14	CH_3CN[e]	PhCOOH	PhCOOLi	80	12	32	36
15	CH_3CN[e]	PhCOOH	PhCOOLi	60	36	60	20
16	CH_3CN	PhCOOH	PhCOOK	100	60	Massive	<10

[a] Reaction conditions: **1a** (0.15 mmol), $Pd(OAc)_2$ (0.015 mmol, 10 mol %), acid (0.75 mmol, 5 equiv), additive (0.03 mmol, 20 mol %), O_2 (1 atm), solvent (1.5 mL, 0.1 M).
[b] Isolated yields.
[c] Solvent: PivOH (4:1).
[d] 20 mol % catalyst was employed in this reaction.
[e] These reactions were carried out in sealed tube.

Table 2
Pd(II) catalytic synthesis of 2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indole ester derivatives by direct Ar–H bond activation utilizing O_2 as oxidant[a]



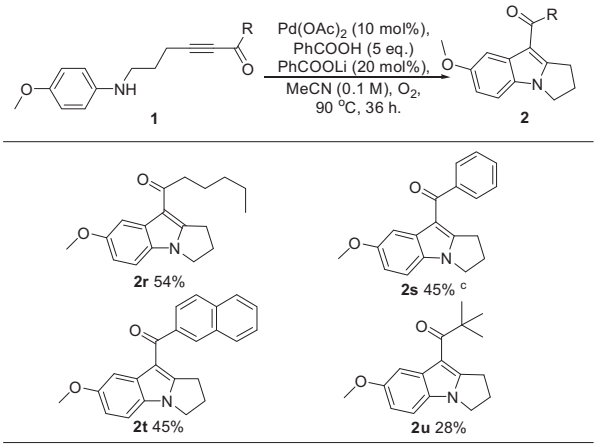
1 2

substrate	product	yield of **2**[b]	substrate	product	yield of **2**[b]
 **1a**	 **2a**	52%	 **1i**	 **2i**	42%
 **1b**	 **2b**	55%	 **1j**	 **2j**	29%[c]
 **1c**	 **2c**	49%	 **1k**	 **2k**	35% (**3k,** 22%)
 **2d**	38%		 **1l**	 **2l**	31% (**3l,** 18%)
 **1d**	71% (**3d**, 27%)		 **1m**	 **2m**	43%[d]
 **2d'**	33%				
 **1e**	 **2e**	50% (**3e**, 23%)	 **1n**	 **2n**	40%[c]
 **2f**	33%		 **1o**	 **2o**	44%
 **1f**	50%		 **1p**	 **2p**	50%
 **2f'**	17%				
 **1g**	 **2g**	50%[c]	 **1q**	 **2q**	**77%**
 **1h**	 **2h**	42%			

[a] Standard conditions (unless otherwise noted): **1** (0.15 mmol), $Pd(OAc)_2$ (0.015 mmol, 10 mol%), PhCOOH (0.75 mmol, 5 eq.), PhCOOLi (0.03 mmol, 20 mol%), O_2 (1 atm), MeCN (1.5 mL, 0.1 M), 90 °C (sealed) for 36 h.
[b] Isolated yields. The number in parentheses refers to isolated yield of byproduct **3**.
[c] This reaction was carried out at 110 °C.
[d] This reaction was carried out at 130 °C.

validate this speculation (Table 3). The reaction of **1r** performed well under the standard conditions and produced the desired product **2r** in 54% yield. Other alkynyl ketones were also examined. Substrates with both aryl and alkyl acyl groups on the alkynyl terminal reacted steadily under the optimal conditions, and provided **2r**, **2s**, and **2t** in moderate yields, respectively. In addition, no β-H elimination byproducts **3** were observed for these alkynyl ketone-type substrates.

Table 3
Pd(II) catalytic synthesis of 2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indole ketone derivatives by direct Ar–H bond activation utilizing O_2 as oxidant[a,b]



[a] Standard conditions (unless otherwise noted): **1** (0.15 mmol), $Pd(OAc)_2$ (0.015 mmol, 10 mol%), PhCOOH (0.75 mmol, 5 eq.), PhCOOLi (0.03 mmol, 20 mol%), O_2 (1 atm), MeCN (1.5 mL, 0.1 M), 90 °C (sealed) for 36 h.
[b] Isolated yields.
[c] This reaction was carried out at 110 °C.

Based on these above results, a proposed mechanism is outlined in Fig. 2. First, $Pd(OAc)_2$ plays as a Lewis acid to active the alkyne group, subsequent intramolecular hydroamination generated *trans*-nitropalladation intermediates **A**.[13g,22] Then intermediates **B** as the tautomer of **A** undergo rotation to generate the *cis*-form Pd(II) species **C**, followed by electrophilic aromatic palladation to form intermediates **D**.[23] Finally, reductive elimination of **D** yield **2**with the formation of Pd(0), which can be reoxidized to Pd(II) species by molecular oxygen to complete the catalytic cycle.[24] During this process, intermediates **E** could be generated from **B** under these acetic conditions and subsequently undergo β-H elimination[25] and aromatization to generate the byproducts **3**.

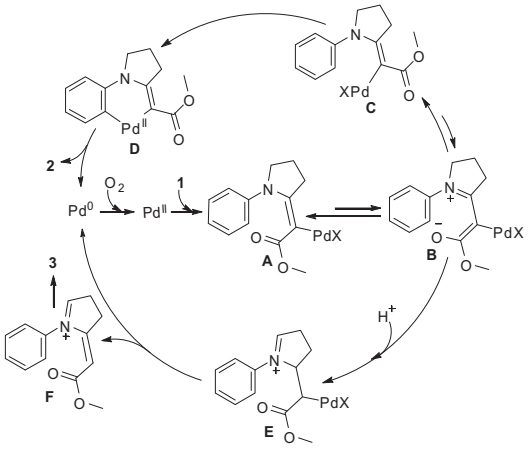


Fig. 2. Proposed mechanism for syntheses of 2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indole derivatives.

3. Conclusion

In summary, a methodology for the construction of 2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indole derivatives through a direct C–H bond functionalization strategy has been developed.[25] Molecular oxygen was used as the sole oxidant to recycle the Pd-catalysis. This protocol is attractive due to the available starting materials and the valuable products. A mechanism involving *trans*-aminopalladation, *ortho*-carbopalladation, and reductive elimination was proposed. However, the influence of electronic properties and a thermoinstability of substrates were also presented in this methodology. Research for a more efficient and stable catalytic system is undergoing in our lab.

4. Experimental section

4.1. General information

4.1.1. Analytical. Flash Column Chromatography was applied to obtain all reaction yields and performed on silica gel 300–400 mesh. NMR spectra were recorded on a Bruker AVIII-400 spectrometer. All ^1H NMR chemical shifts were reported in units parts per million referencing to the residual H-solvent signals by assigning $CHCl_3$ resonance as 7.26 ppm in $CDCl_3$ or DMSO resonance as 2.49 ppm in DMSO-d_6. All ^{13}C NMR chemical shifts (δ) were reported in units ppm by assigning $CHCl_3$ resonance as 77.0 ppm in $CDCl_3$ or DMSO resonance as 39.7 ppm in DMSO-d_6. All coupling constants (J) were reported in Hertz (Hz). High Resolution Mass Spectra were measured by APEX IV Fourier Transform Ion Cyclotron Resonance Mass Spectrometer in ESI Positive (showed a systematic error of about 0.0005). Melting points were recorded on Accurate Micro-Melting Point Measuring Instrument X-5B and are reported uncorrected. Infrared spectra were recorded on a Nicolet FTIR Spectrophotometer NEXUS-470. The wavenumbers (ν) of recorded IR signals are quoted in cm^{-1}.

4.1.2. Chemical. All substrates were directly synthesized according the reported methods and isolated through recrystallization and Flash Column Chromatography, The purities were confirmed by NMR. $Pd(OAc)_2$ was purchased from Strem Chemical. Unless otherwise noted, all commercially obtained reagents were used as received. MeCN was distilled in small scale with CaH_2 and stored under Argon. Reactions were carried in Schlenk tube or in sealed tube with a magnetic stirrer and all isolated yields were calculated based on the starting material **1**.

4.2. General experimental procedure for syntheses of 2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indoles (2)

To a 40 mL seal tube, **1**(0.15 mmol), $Pd(OAc)_2$ (3.4 mg, 0.015 mmol, 10 mol %), PhCOOH (91.5 mg, 0.75 mmol, 5 equiv) and PhCOOLi (3.8 mg, 0.03 mmol, 20 mol %) were added under O_2, the tube was added with MeCN (1.5 mL) via syringe and sealed up. The formed mixture was stirred at 90 °C under O_2 for 36 h as monitored by TLC. The solution was then cooled to room temperature, diluted with ethyl acetate (10 mL) and stirred with saturated Na_2CO_3 aqueous solution (10 mL) for 5 min. After separating, the aqueous portion was extracted with ethyl acetate (5 mL×3). The organic portions were combined, dried over $MgSO_4$, filtered, and evaporated under vacuum. The residue was purified through Flash Column Chromatography on silica gel to afford **2**.

*4.2.1. Methyl 7-methoxy-2,3-dihydro-1H-pyrrolo[1,2-a]indole-9-carboxylate (**2a**, Table 2).* Yellow solid, 52% yield; mp 109–110 °C; FTIR (neat, cm^{-1}): 3440, 2946, 2834, 1694, 1615, 1544, 1476, 1456, 1160, 811, 778; ^1H NMR (400 MHz, $CDCl_3$): δ 7.61 (s, 1H), 7.08 (d,

J=8.7 Hz, 1H), 6.81 (d, *J*=8.6 Hz, 1H), 4.01 (t, *J*=7.1 Hz, 2H), 3.88 (overlap, 6H), 3.21 (t, *J*=7.4 Hz, 2H), 2.64–2.51 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.93, 155.71, 152.93, 131.87, 127.79, 111.54, 110.49, 103.53, 98.77, 55.82, 50.61, 44.64, 26.49, 26.36; HRMS (ESI, positive): *m*/*z* calculated for $C_{14}H_{15}NO_3$ (H^+) 246.1130; $C_{14}H_{15}NO_3$ (Na^+) 268.0950, found: 246.1125, 268.0944.

*4.2.2. Methyl 2,3-dihydro-1H-pyrrolo[1,2-a]indole-9-carboxylate (**2b**, Table 2).* Yellow solid, 55% yield; mp 92–94 °C; FTIR (neat, cm^{-1}): 3466, 2946, 2888, 2851, 1739, 1684, 1612, 1545, 1480, 1455, 1206, 1105, 753; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.10 (dd, *J*=6.5, 1.6 Hz, 1H), 7.30–7.16 (m, 4H), 4.12 (t, *J*=7.6 Hz, 2H), 3.90 (s, 3H), 3.30 (t, *J*=7.6 Hz, 2H), 2.71–2.61 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.93, 152.87, 132.71, 130.94, 121.71, 121.61, 121.42, 109.80, 99.14, 50.68, 44.45, 26.61, 26.11; HRMS (ESI, positive): *m*/*z* calculated for $C_{13}H_{13}NO_2$ (H^+) 216.1024, found: 216.1019.

*4.2.3. Methyl 7-methyl-2,3-dihydro-1H-pyrrolo[1,2-a]indole-9-carboxylate (**2c**, Table 2).* Yellow solid, 49% yield; mp 151–152 °C; FTIR (neat, cm^{-1}): 3451, 2946, 2854, 1690, 1616, 1547, 1454, 1424, 1112, 810; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.90 (s, 1H), 7.13 (d, *J*=8.2 Hz, 1H), 7.02 (d, *J*=8.2 Hz, 1H), 4.08 (t, *J*=7.1 Hz, 2H), 3.89 (s, 3H), 3.27 (t, *J*=7.5 Hz, 2H), 2.63 (p, *J*=7.3 Hz, 2H), 2.48 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.03, 152.88, 131.19, 131.12, 131.05, 123.14, 121.24, 109.45, 98.63, 50.65, 44.50, 26.60, 26.20, 21.64; HRMS (ESI, positive): *m*/*z* calculated for $C_{14}H_{15}NO_2$ (H^+) 230.1181, found: 230.1176.

*4.2.4. Methyl 6-methoxy-2,3-dihydro-1H-pyrrolo[1,2-a]indole-9-carboxylate (**2d**, Table 2).* Light yellow solid, 38% yield; mp 134–135 °C; FTIR (neat, cm^{-1}): 3448, 2925, 1670, 1622, 1547, 1469, 1443, 1232, 1106, 818, 776; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.95 (d, *J*=8.7 Hz, 1H), 6.87 (dd, *J*=8.7, 2.1 Hz, 1H), 6.72 (d, *J*=1.8 Hz, 1H), 4.04 (t, *J*=7.1 Hz, 2H), 3.81–3.96 (overlap, 6H), 3.25 (t, *J*=7.5 Hz, 2H), 2.72–2.56 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.92, 156.12, 151.89, 133.33, 124.94, 122.03, 110.69, 99.02, 93.94, 55.73, 50.66, 44.31, 26.68, 26.01; HRMS (ESI, positive): *m*/*z* calculated for $C_{14}H_{15}NO_3$ (H^+) 246.1130, found: 246.1125.

*4.2.5. Methyl 8-methoxy-2,3-dihydro-1H-pyrrolo[1,2-a]indole-9-carboxylate (**2d′**, Table 2).* Light yellow solid, 33% yield; mp 179–180 °C; FTIR (neat, cm^{-1}): 3434, 2954, 2852, 1706, 1608, 1573, 1442, 1091, 765; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.14 (t, *J*=8.0 Hz, 1H), 6.87 (d, *J*=8.0 Hz, 1H), 6.68 (d, *J*=7.9 Hz, 1H), 4.09 (t, *J*=7.2 Hz, 2H), 3.98 (s, 3H), 3.86 (s, 3H), 3.28 (t, *J*=7.5 Hz, 2H), 2.68–2.56 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.22, 153.85, 152.49, 134.60, 122.86, 119.51, 103.36, 102.88, 99.36, 56.04, 51.21, 44.87, 27.26, 26.29; HRMS (ESI, positive): *m*/*z* calculated for $C_{14}H_{15}NO_3$ (H^+) 246.1130, found: 246.1125.

*4.2.6. Methyl 7-phenyl-2,3-dihydro-1H-pyrrolo[1,2-a]indole-9-carboxylate (**2e**, Table 2).* Yellow solid, 50% yield; mp 158–159 °C; FTIR (neat, cm^{-1}): 3434, 2993, 2946, 2858, 1687, 1545, 1465, 1443, 1107, 766; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.33 (s, 1H), 7.68 (d, *J*=7.5 Hz, 2H), 7.43 (t, *J*=7.0 Hz, 3H), 7.31 (t, *J*=7.3 Hz, 1H), 7.25 (d, *J*=8.5 Hz, 1H), 4.06 (t, *J*=7.2 Hz, 2H), 3.90 (s, 3H), 3.25 (t, *J*=7.5 Hz, 2H), 2.68–2.55 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.84, 153.46, 142.38, 135.13, 132.22, 131.47, 128.63, 127.52, 126.52, 121.44, 120.01, 110.03, 99.46, 50.72, 44.54, 26.62, 26.19; HRMS (ESI, positive): *m*/*z* calculated for $C_{19}H_{17}NO_2$ (H^+) 292.1338, found: 292.1332.

*4.2.7. Methyl 6-methyl-2,3-dihydro-1H-pyrrolo[1,2-a]indole-9-carboxylate (**2f**, Table 2).* Yellow solid, 33% yield; mp 155–156 °C; FTIR (neat, cm^{-1}): 2953, 2924, 2853, 1690, 1547, 1440, 1206, 1104, 810, 747; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.96 (d, *J*=8.1 Hz, 1H), 7.09–7.01 (m, 2H), 4.04 (t, *J*=6.9 Hz, 2H), 3.89 (s, 3H), 3.25 (t, *J*=7.5 Hz, 2H), 2.62 (p, *J*=7.4 Hz, 2H), 2.47 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.98, 152.33, 133.04, 131.53, 128.66, 123.19, 121.03, 109.89, 98.94, 50.64, 44.30, 26.62, 26.03, 21.63; HRMS (ESI, positive): *m*/*z* calculated for $C_{14}H_{15}NO_2$ (H^+) 230.1181, found: 230.1176.

*4.2.8. Methyl 8-methyl-2,3-dihydro-1H-pyrrolo[1,2-a]indole-9-carboxylate (**2f′**, Table 2).* Light yellow solid, 17% yield; mp 137–138 °C; FTIR (neat, cm^{-1}): 2957, 2921, 2851, 1698, 1527, 1490, 1438, 1187, 1091, 759; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.13–7.04 (m, 2H), 6.98 (d, *J*=6.8 Hz, 1H), 4.09 (t, *J*=7.1 Hz, 2H), 3.84 (s, 3H), 3.28 (t, *J*=7.5 Hz, 2H), 2.85 (s, 3H), 2.61 (p, *J*=7.3 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.56, 153.13, 133.38, 132.40, 129.36, 123.92, 121.94, 107.50, 100.24, 50.66, 44.67, 27.31, 26.13, 22.51; HRMS (ESI, positive): *m*/*z* calculated for $C_{14}H_{15}NO_2$ (H^+) 230.1181, found: 230.1176.

*4.2.9. Methyl 7-hydroxy-2,3-dihydro-1H-pyrrolo[1,2-a]indole-9-carboxylate (**2g**, Table 2).* White solid, 50% yield (under 110 °C); mp 269–270 °C; FTIR (neat, cm^{-1}): 3735, 3266, 2893, 1723, 1660, 1626, 1532, 1490, 1459, 1238, 1195, 1116, 869, 780; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.96 (s, Ar–OH, 1H), 7.31 (d, *J*=2.3 Hz, 1H), 7.17 (d, *J*=8.6 Hz, 1H), 6.62 (dd, *J*=8.6, 2.4 Hz, 1H), 4.05 (d, *J*=14.3 Hz, 2H), 3.74 (s, 3H), 3.12 (t, *J*=7.5 Hz, 2H), 2.54 (dd, *J*=14.5, 7.4 Hz, 2H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 164.97, 153.02, 152.89, 131.73, 126.96, 111.21, 111.19, 105.48, 97.25, 50.52, 44.71, 26.39, 26.26; HRMS (ESI, positive): *m*/*z* calculated for $C_{13}H_{13}NO_3$ (H^+) 232.0974; $C_{13}H_{13}NO_3$ (Na^+) 254.0793, found: 232.0968, 254.0788.

*4.2.10. Methyl 7-cyclohexyl-2,3-dihydro-1H-pyrrolo[1,2-a]indole-9-carboxylate (**2h**, Table 2).* Yellow solid, 42% yield; mp 147–148 °C; FTIR (neat, cm^{-1}): 3423, 2921, 2839, 1692, 1618, 1545, 1457, 1110, 783; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.95 (s, 1H), 7.17 (d, *J*=8.3 Hz, 1H), 7.08 (dd, *J*=8.3, 1.0 Hz, 1H), 4.07 (t, *J*=7.1 Hz, 2H), 3.90 (s, 3H), 3.26 (t, *J*=7.5 Hz, 2H), 2.69–2.57 (m, 3H), 1.99–1.72 (m, 5H), 1.58–1.22 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.04, 152.88, 141.89, 131.32, 131.15, 121.14, 119.08, 109.52, 98.84, 50.65, 45.02, 44.48, 35.14, 27.14, 26.63, 26.29, 26.20; HRMS (ESI, positive): *m*/*z* calculated for $C_{19}H_{23}NO_2$ (H^+) 298.1807, found: 298.1802.

*4.2.11. Methyl 7-tert-butyl-2,3-dihydro-1H-pyrrolo[1,2-a]indole-9-carboxylate (**2i**, Table 2).* Yellow solid, 42% yield; mp 158–160 °C; FTIR (neat, cm^{-1}): 3445, 2958, 2866, 1686, 1542, 1475, 1452, 1193, 1107, 784; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.16 (d, *J*=1.7 Hz, 1H), 7.29 (dd, *J*=8.5, 1.9 Hz, 1H), 7.18 (d, *J*=8.5 Hz, 1H), 4.06 (t, *J*=7.2 Hz, 2H), 3.90 (s, 3H), 3.26 (t, *J*=7.5 Hz, 2H), 2.67–2.57 (m, 2H), 1.42 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.04, 152.89, 144.79, 130.94, 130.91, 119.81, 117.51, 109.25, 98.96, 50.65, 44.48, 34.82, 31.94, 26.65, 26.23; HRMS (ESI, positive): *m*/*z* calculated for $C_{17}H_{21}NO_2$ (H^+) 272.1650, found: 272.1645.

*4.2.12. Methyl 5-methoxy-2,3-dihydro-1H-pyrrolo[1,2-a]indole-9-carboxylate (**2j**, Table 2).* White solid, 29% yield (under 110 °C); mp 150–152 °C; FTIR (neat, cm^{-1}): 3452, 2985, 2957, 2924, 2852, 1688, 1618, 1548, 1498, 1452, 1264, 792, 733; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.68 (d, *J*=8.1 Hz, 1H), 7.10 (t, *J*=8.0 Hz, 1H), 6.62 (d, *J*=7.8 Hz, 1H), 4.37 (t, *J*=7.2 Hz, 2H), 3.91 (s, 3H), 3.88 (s, 3H), 3.22 (t, *J*=7.6 Hz, 2H), 2.64–2.53 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.01, 152.54, 146.71, 132.61, 123.08, 122.09, 114.11, 102.44, 99.26, 55.42, 50.62, 47.69, 26.86, 25.84; HRMS (ESI, positive): *m*/*z* calculated for $C_{14}H_{15}NO_3$ (H^+) 246.1130; $C_{14}H_{15}NO_3$ (Na^+) 268.0950, found: 246.1125, 268.0944.

*4.2.13. Methyl 7-fluoro-2,3-dihydro-1H-pyrrolo[1,2-a]indole-9-carboxylate (**2k**, Table 2).* Yellow solid, 35% yield; mp 112–113 °C; FTIR (neat, cm^{-1}): 3435, 2985, 2954, 2924, 2856, 1687, 1628, 1546, 1454, 1118, 777; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.75 (dd, *J*=10.0, 2.5 Hz, 1H), 7.12 (dd, *J*=8.8, 4.4 Hz, 1H), 6.91 (td, *J*=9.0, 2.5 Hz, 1H),

4.08 (t, J=7.2 Hz, 2H), 3.88 (s, 3H), 3.27 (t, J=7.6 Hz, 2H), 2.71–2.59 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.58, 159.20 (d, J_{CF}=236.2 Hz), 154.14, 131.61 (d, J_{CF}=11.0 Hz), 129.26, 110.38 (d, J_{CF}=10.0 Hz), 109.80 (d, J_{CF}=26.4 Hz), 106.95 (d, J_{CF}=25.1 Hz), 99.44 (d, J_{CF}=4.3 Hz), 50.75, 44.74, 26.60, 26.33; ^{19}F NMR (376 MHz, $CDCl_3$): δ −121.94; HRMS (ESI, positive): m/z calculated for $C_{13}H_{12}FNO_2$ (H^+) 234.0930, found: 234.0925.

*4.2.14. Methyl 7-chloro-2,3-dihydro-1H-pyrrolo[1,2-a]indole-9-carboxylate (**2l**, Table 2).* Brown solid, 31% yield; mp 132–134 °C; FTIR (neat, cm^{-1}): 3456, 2953, 2924, 2852, 1681, 1615, 1542, 1488, 1455, 1206, 1108, 780; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.05 (s, 1H), 7.17–7.09 (m, 2H), 4.08 (t, J=7.2 Hz, 2H), 3.89 (s, 3H), 3.27 (t, J=7.5 Hz, 2H), 2.65 (p, J=7.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.46, 153.97, 131.83, 131.05, 127.51, 121.98, 121.00, 110.72, 99.05, 50.83, 44.67, 26.60, 26.19; HRMS (ESI, positive): m/z calculated for $C_{13}H_{12}ClNO_2$ (H^+) 250.0635, found: 250.0629.

*4.2.15. Methyl 6,8-dimethoxy-2,3-dihydro-1H-pyrrolo[1,2-a]indole-9-carboxylate (**2m**, Table 2).* Yellow solid, 43% yield (under 130 °C); mp 148–149 °C; FTIR (neat, cm^{-1}): 3434, 2992, 2937, 2840, 1708, 1623, 1579, 1504, 1450, 1210, 1098, 802; ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.32 (d, J=9.1 Hz, 2H), 4.01 (t, J=7.0 Hz, 2H), 3.94 (s, 3H), 3.83 (s, 6H), 3.23 (t, J=7.5 Hz, 2H), 2.64–2.53 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.10, 157.17, 154.44, 151.12, 134.73, 113.97, 99.44, 93.93, 86.04, 55.98, 55.61, 50.91, 44.60, 26.93, 26.31; HRMS (ESI, positive): m/z calculated for $C_{15}H_{17}NO_4$ (H^+) 276.1236; $C_{15}H_{17}NO_4$ (Na^+) 298.1055, found: 276.1230, 298.1050.

*4.2.16. Methyl 7-(trifluoromethyl)-2,3-dihydro-1H-pyrrolo[1,2-a]indole-9-carboxylate (**2n**, Table 2).* Yellow solid, 40% yield (under 110 °C); mp 135–136 °C; FTIR (neat, cm^{-1}): 3434, 2989, 2951, 2898, 2850, 1670, 1624, 1548, 1492, 1463, 1111, 826; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.38 (s, 1H), 7.41 (d, J=8.4 Hz, 1H), 7.27 (d, J=8.5 Hz, 1H), 4.12 (t, J=7.2 Hz, 2H), 3.91 (s, 3H), 3.29 (t, J=7.6 Hz, 2H), 2.73–2.62 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.31, 154.45, 133.98, 130.30, 126.58 (m), 123.88 (quint, J_{CF}=37.1 Hz), 119.06 (q, J_{CF}=4.2 Hz), 118.58 (q, J_{CF}=3.6 Hz), 109.99, 100.11, 50.91, 44.62, 26.62, 26.08; ^{19}F NMR (376 MHz, $CDCl_3$): δ −60.40; HRMS (ESI, positive): m/z calculated for $C_{14}H_{12}F_3NO_2$ (H^+) 284.0898; $C_{14}H_{12}F_3NO_2$ (Na^+) 306.0718, found: 284.0893, 306.0712.

*4.2.17. Methyl 7-(trifluoromethoxy)-2,3-dihydro-1H-pyrrolo[1,2-a]indole-9-carboxylate (**2o**, Table 2).* Yellow solid, 44% yield; mp 113–114 °C; FTIR (neat, cm^{-1}): 3434, 2983, 2856, 1670, 1628, 1546, 1460, 1285, 1257, 777; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.95 (s, 1H), 7.21 (d, J=8.7 Hz, 1H), 7.07 (d, J=8.7, 1H), 4.12 (t, J=7.2 Hz, 2H), 3.90 (s, 3H), 3.31 (t, J=7.5 Hz, 2H), 2.68 (p, J=7.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.42, 154.42, 144.55, 131.15, 120.79 (q, J_{CF}=255.6 Hz), 115.56, 114.20, 110.35, 99.78, 50.86, 44.75, 26.68, 26.28; ^{19}F NMR (376 MHz, $CDCl_3$): δ −57.96; HRMS (ESI, positive): m/z calculated for $C_{14}H_{12}F_3NO_3$ (H^+) 300.0848, found: 300.0842.

*4.2.18. Methyl 7-acetyl-2,3-dihydro-1H-pyrrolo[1,2-a]indole-9-carboxylate(**2p**, Table 2).* Yellow solid, 50% yield; mp 134–136 °C; FTIR (neat, cm^{-1}): 3451, 2949, 2851, 1693, 1671, 1608, 1546, 1455, 1112, 816, 784, 609; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.74 (s, 1H), 7.91 (d, J=8.5 Hz, 1H), 7.28 (d, J=8.2 Hz, 1H), 4.16 (t, J=7.1 Hz, 2H), 3.94 (s, 3H), 3.32 (t, J=7.5 Hz, 2H), 2.79–2.64 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 198.53, 165.45, 154.25, 135.16, 131.36, 130.41, 123.45, 122.00, 109.84, 100.56, 50.97, 44.63, 26.72, 26.68, 26.14; HRMS (ESI, positive): m/z calculated for $C_{15}H_{15}NO_3$ (H^+) 258.1130; $C_{15}H_{15}NO_3$ (Na^+) 280.0950, found: 258.1125, 280.0944.

*4.2.19. Methyl 6,8-dimethyl-2,3-dihydro-1H-pyrrolo[1,2-a]indole-9-carboxylate(**2q**, Table 2).* Light yellow solid, 77% yield; mp 139–141 °C; FTIR (neat, cm^{-1}): 3433, 2922, 1702, 1622, 1533, 1437, 1095, 828, 778; ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.87 (s, 1H), 6.82 (s, 1H), 4.05 (t, J=7.2 Hz, 2H), 3.83 (s, 3H), 3.27 (t, J=7.6 Hz, 2H), 2.81 (s, 3H), 2.65–2.54 (m, 2H), 2.41 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.63, 152.73, 133.77, 131.95, 131.73, 127.10, 125.62, 107.59, 99.98, 50.64, 44.52, 27.25, 26.12, 22.44, 21.31; HRMS (ESI, positive): m/z calculated for $C_{15}H_{17}NO_2$ (H^+) 244.1338; $C_{15}H_{17}NO_2$ (Na^+) 266.1157, found: 244.1332, 266.1152.

*4.2.20. 1-(7-Methoxy-2,3-dihydro-1H-pyrrolo[1,2-a]indol-9-yl) hexan-1-one(**2r**, Table 3).* White solid, 54% yield; mp 137–138 °C; FTIR (neat, cm^{-1}): 3420, 2959, 2927, 2855, 1628, 1575, 1530, 1484, 1450, 1260, 795; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.88 (d, J=1.9 Hz, 1H), 7.11 (d, J=8.7 Hz, 1H), 6.85 (dd, J=8.7, 2.2 Hz, 1H), 4.09 (t, J=7.2 Hz, 2H), 3.89 (s, 3H), 3.30 (t, J=7.4 Hz, 2H), 2.76 (t, J=7.4 Hz, 2H), 2.73–2.60 (m, 2H), 1.83–1.70 (m, 2H), 1.46–1.32 (m, 4H), 0.92 (t, J=6.7 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 195.63, 156.22, 151.60, 131.75, 127.84, 112.16, 110.30, 109.87, 104.39, 55.80, 44.39, 41.03, 31.88, 27.62, 26.52, 24.36, 22.70, 14.02; HRMS (ESI, positive): m/z calculated for $C_{18}H_{23}NO_2$ (H^+) 286.1807; $C_{18}H_{23}NO_2$ (Na^+) 308.1626, found: 286.1802, 308.1621.

*4.2.21. (7-Methoxy-2,3-dihydro-1H-pyrrolo[1,2-a]indol-9-yl)(phenyl)methanone (**2s**, Table 3).* Brown solid, 45% yield (under 110 °C); mp 151–152 °C; FTIR (neat, cm^{-1}): 3489, 3056, 2929, 2835, 1720, 1612, 1513, 1474, 1452, 1268, 801, 726, 702; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.71 (d, J=2.4 Hz, 1H), 7.69–7.61 (m, 2H), 7.55–7.41 (m, 3H), 7.16 (d, J=8.7 Hz, 1H), 6.87 (dd, J=8.7, 2.5 Hz, 1H), 4.08 (t, J=7.1 Hz, 2H), 3.86 (s, 3H), 2.74 (t, J=7.4 Hz, 2H), 2.56–2.44 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 192.08, 156.16, 153.72, 141.83, 132.14, 130.65, 128.28, 128.04, 127.87, 112.49, 110.64, 109.26, 103.86, 55.77, 44.82, 27.45, 26.80; HRMS (ESI, positive): m/z calculated for $C_{19}H_{17}NO_2$ (H^+) 292.1338, found: 292.1332.

*4.2.22. (7-Methoxy-2,3-dihydro-1H-pyrrolo[1,2-a]indol-9-yl)(naphthalen-2-yl)methanone (**2t**, Table 3).* Light yellow solid, 45% yield; mp 187–189 °C; FTIR (neat, cm^{-1}): 3445, 2961, 2936, 2836, 1606, 1500, 1440, 1421, 1045, 779; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.16 (s, 1H), 7.92 (t, J=9.0 Hz, 3H), 7.80 (d, J=8.1 Hz, 1H), 7.73 (d, J=2.0 Hz, 1H), 7.64–7.50 (m, 2H), 7.17 (d, J=8.7 Hz, 1H), 6.89 (dd, J=8.7, 2.0 Hz, 1H), 4.10 (t, J=7.0 Hz, 2H), 3.83 (s, 3H), 2.77 (t, J=7.3 Hz, 2H), 2.58–2.42 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 191.56, 156.32, 153.44, 139.12, 134.46, 132.65, 132.31, 128.77, 128.34, 128.18, 128.09, 127.87, 127.24, 126.53, 125.09, 112.54, 110.48, 109.61, 104.31, 55.78, 44.74, 27.46, 26.78; HRMS (ESI, positive): m/z calculated for $C_{23}H_{19}NO_2$ (H^+) 342.1494, found: 342.1489.

*4.2.23. 1-(7-Methoxy-2,3-dihydro-1H-pyrrolo[1,2-a]indol-9-yl)-2,2-dimethylpropan-1-one (**2u**, Table 3).* Light yellow solid, 28% yield; mp 148–150 °C; FTIR (neat, cm^{-1}): 3446, 2978, 2952, 2932, 2832, 1617, 1497, 1476, 1453, 1060, 858, 793; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.80 (d, J=2.4 Hz, 1H), 7.13 (d, J=8.7 Hz, 1H), 6.85 (dd, J=8.7, 2.3 Hz, 1H), 4.08 (t, J=7.1 Hz, 2H), 3.89 (s, 3H), 3.37 (t, J=7.3 Hz, 2H), 2.69–2.59 (m, 2H), 1.42 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 202.53, 155.69, 150.82, 132.03, 127.87, 111.50, 110.26, 108.38, 105.82, 55.87, 44.31, 42.82, 30.02, 27.20, 26.72; HRMS (ESI, positive): m/z calculated for $C_{17}H_{21}NO_2$ (H^+) 272.1650, found: 272.1645.

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Supplementary data

Supplementary data (starting material syntheses, characterization of byproduct representative **3a**, and copies of NMR spectra) associated with this article can be found in the online version. Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.tet.2013.01.031.

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