β-Nitroacrylates as Useful Building Blocks for the Synthesis of Alkyl Indole-2-Carboxylates

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Abstract: Polyfunctionalized alkyl indole 2-carboxylates can be easily synthesized starting form β-nitroacrylates and *o*-bromoanilines through an addition–elimination process followed by an intramolecular palladium-catalyzed Heck reaction.

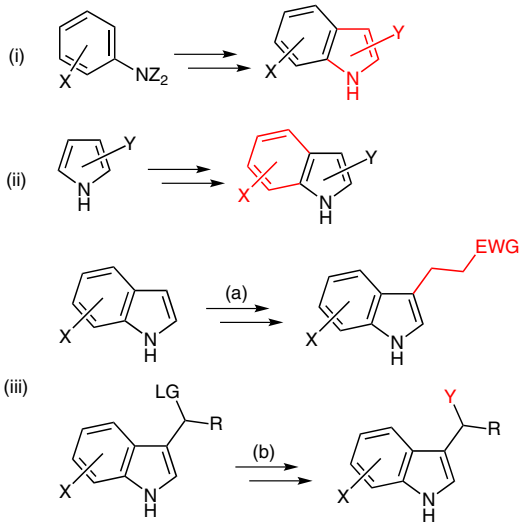
Key words: indoles, Heck reaction, β-nitroacrylates, cyclization, Michael addition

Over the years, several synthetic methods have been proposed that can be used to access functionalized indole systems.[1] This continuous interest reflects the importance of this heterocyclic system due to its presence in numerous synthetic and naturally occurring molecules.[2] The main synthetic tactics used for preparing functionalized indoles can be classified as: (i) construction of a pyrrole system onto a benzene precursor,[3] (ii) benzannulation of pyrroles,[4] and (iii) derivatization of a preformed indole core, usually by C-3 Friedel–Crafts reaction in combination with electron-poor alkenes (a),[5] or by the functionalization of the benzylic position via alkylideneindolenine intermediates (b)[6] (Scheme 1).

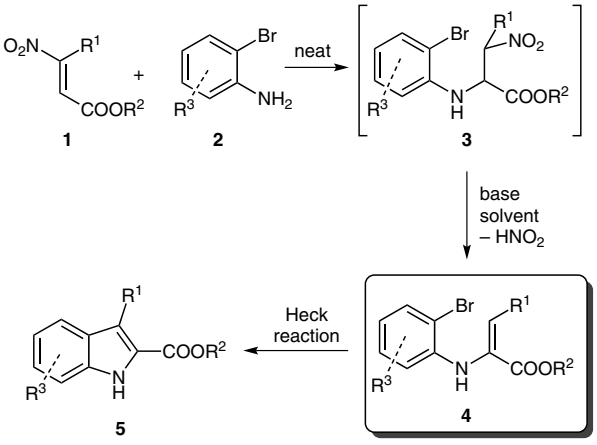
In this context, pathway (i) has been the most investigated and, recently, efforts have been directed towards metal-catalyzed ring construction, which ensures mild reaction conditions and the possibility of introducing a variety of functionalities into the indole ring.[7] Although some important goals have been reached, further drawbacks need to be overcome, and the identification of new substrates that can be easily converted into functionalized indoles remains a research topic of great interest.

In this regard, following our ongoing studies on β-nitroacrylate chemistry,[8] we have disclosed a novel and simple one-pot synthesis of α-enamino esters **4** that can be directly transformed into alkyl indole-2-carboxylates **5** by palladium-catalyzed Heck reaction (Scheme 2).[9]

The thus-obtained indole derivatives **5**, or their acid form (R^2 = H), belong to an important sub-class of indoles that are widely used as strategic intermediates for the synthesis of important biologically active molecules,[10] however, despite their importance, only a few synthetic methods have been reported. Among them, the Japp–Klingemann reaction followed by Fischer rearrangement (A),[11] and the Hemetsberger–Knittel indole synthesis (B) (Scheme 3)[12] are two of the most well-known methods; however, both these approaches have important limitations. The former approach is rather complex, requiring the preparation of



Scheme 1 Common synthetic approaches for the synthesis of functionalized indoles



Scheme 2 Our synthetic approach

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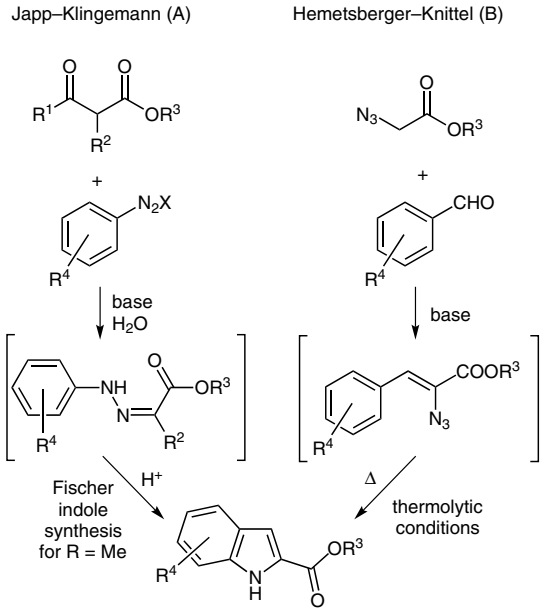
the appropriate β-keto esters and the arendiazonium salts, and harsh acidic reaction conditions are needed to promote the Fischer cyclization. On the other hand, the Hemetsberger–Knittel synthesis entails the use of hazardous azidoacetates, restricting functionalization to the benzene ring and usually furnishing the indoles in very low yields.



Scheme 3 Japp–Klingemann/Fischer (A) and Hemetsberger–Knittel (B) approaches

In this regard, our synthetic strategy, which exploits the high reactivity of β-nitroacrylates **1** in combination with *o*-bromoanilines **2**, represents a novel, convenient and alternative strategic approach.

To optimize our protocol, we first studied the aza-Michael reaction and were pleased to observe complete conversion of **1a** and **2a** into **3a** at 70 °C (24 h), under solvent-free conditions (Table 1). We then treated crude **3a** with a range of bases and solvents, obtaining the best yield of **4a** (87%) by using two equivalents of TBD on polymer[13] in MeCN (Table 1, entry 3).

Having optimized the synthesis of **4a**, we extended our protocol to prepare title compounds **5a**–**j** by submitting crude **4a**–**j**, which were readily obtained by TBD-filtration and solvent evaporation, to the Kondo reaction conditions,[9a] obtaining, in all cases, good overall yields of indoles (Table 2).

In conclusion, our approach provides simple access to functionalized alkyl indole-2-carboxylates, which are useful synthetic intermediates.[14] By the appropriate selection of β-nitroacrylate and *o*-bromoaniline precursors, it is possible to introduce different substituents onto the benzene ring, modify the ester moiety, and introduce several functionalities onto the C-3 alkyl chain. Furthermore, thanks to the simple conditions used to prepare intermediates **4**, the whole process involves just one aqueous work-up and a single chromatographic purification.

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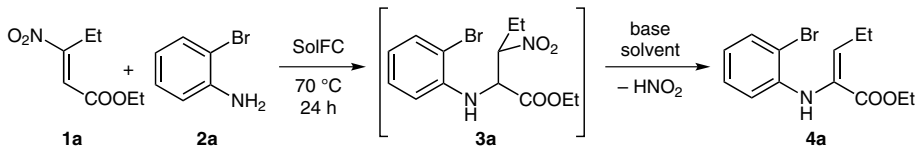
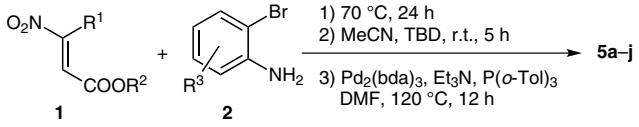
Table 1 Optimization Studies

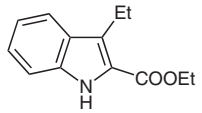
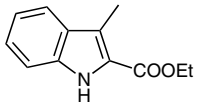
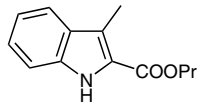
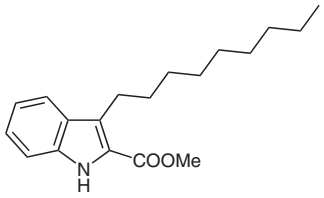
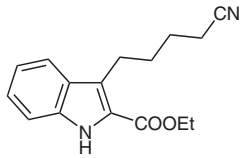
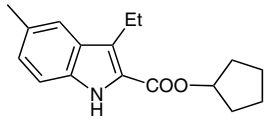
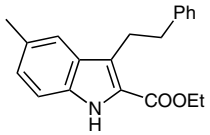
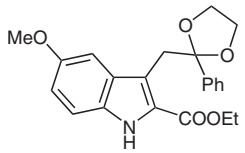
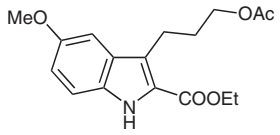
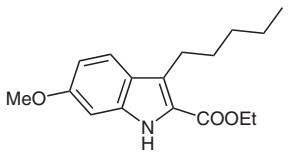


Entry	Base (equiv)	Solvent	Time (h)	Yield of **4a** (%)[a]
1	TBD on polymer (1)	MeCN	9	41
2	TBD on polymer (1.5)	MeCN	9	67
3	TBD on polymer (2)	MeCN	5	87
4	KF/Al_2O_3 (2)	MeCN	5	31
5	carbonate on polymer (2)	MeCN	5	43
6	TMG (2)	MeCN	3	77
7	TBD on polymer (2)	CPME	5	–
8	TBD on polymer (2)	CH_2Cl_2	5	81
9	TBD on polymer (2)	EtOAc	5	9

[a] Yield of pure isolated product.

Table 2 Preparation of Indole-2-carboxylic Acid Esters **5**



Indole **5**		Yield (%)[a]
5a		60 (52)[b]
5b		56
5c		50
5d		44
5e		59
5f		51
5g		55
5h		51
5i		49
5j		47

[a] Yield of pure isolated product.
[b] Heck reaction conditions: Microwave, 190 °C, MeCN, 1.5 h.

References and Notes

(1) (a) Gribble, G. W. *Contemp. Org. Synth.* **1994**, 145. (b) Gribble, G. W. *J. Chem. Soc., Perkin Trans. 1* **2000**, 1045. (c) Humphrey, G. R.; Kuethe, J. T. *Chem. Rev.* **2006**, *106*, 2875.

(2) (a) Faulkner, D. J. *Nat. Prod. Rep.* **2002**, *19*, 1. (b) Saxton, J. E. In *The Alkaloids*; Cordell, G. A., Ed.; Academic Press: New York, **1998**. (c) Sundberg, R. J. In *Indoles*; Academic Press: New York, **1997**. (d) Saxton, J. E. *Nat. Prod. Rep.* **1997**, *14*, 559.

(3) (a) Robinson, B. In *The Fischer Indole Synthesis*; Wiley-Interscience: New York, **1982**. (b) Dalpozzo, R.; Bartoli, G. *Curr. Org. Chem.* **2005**, *9*, 163. (c) Thyagarajan, B. S.; Hillard, J. B.; Reddy, K. V.; Majumdar, K. C. *Tetrahedron Lett.* **1974**, 1999. (d) Baudin, J.-B.; Comménil, M.-G.; Julia, S. A.; Lorne, R.; Mauclaire, L. *Bull. Soc. Chim. Fr.* **1996**, *133*, 329. (e) Houlihan, W. J.; Parrino, V. A.; Uike, Y. *J. Org. Chem.* **1981**, *46*, 4511. (f) Gassman, P. G.; Gruetzmacher, G.; Van Bergen, T. J. *J. Am. Chem. Soc.* **1973**, *95*, 6508.

(4) (a) Palmieri, A.; Gabrielli, S.; Lanari, D.; Vaccaro, L.; Ballini, R. *Adv. Synth. Catal.* **2011**, *353*, 1425. (b) Hosmane, R. S.; Hiremath, S. P.; Schneller, S. W. *J. Chem. Soc., Perkin Trans. 1* **1973**, 2450. (c) Andrews, J. F. P.; Jackson, P. M.; Moody, C. J. *Tetrahedron* **1993**, *49*, 7353. (d) Barluenga, J.; Vazquez-Villa, H.; Ballestreros, A.; Gonzalez, J. M. *Adv. Synth. Catal.* **2005**, *347*, 526. (e) Attanasi, O. A.; Favi, G.; Filippone, P.; Lillini, S.; Mantellini, F.; Spinelli, D.; Stenta, M. *Adv. Synth. Catal.* **2007**, *349*, 907. (f) Muratake, H.; Natsume, M. *Heterocycles* **1990**, *31*, 683. (g) Katritzky, A. R.; Ledoux, S.; Nair, S. K. *J. Org. Chem.* **2003**, *68*, 5728.

(5) (a) Ballini, R.; Clemente, R. R.; Palmieri, A.; Petrini, M. *Adv. Synth. Catal.* **2006**, *348*, 191. (b) Bartoli, G.; Bosco, M.; Giuli, S.; Giuliani, A.; Lucarelli, L.; Marcantoni, E.; Sambri, L.; Torregiani, E. *J. Org. Chem.* **2005**, *70*, 1941. (c) Bandini, M.; Melloni, A.; Tommasi, S.; Umani-Ronchi, A. *Synlett* **2005**, 1199. (d) Bandini, M.; Eichholzer, A. *Angew. Chem. Int. Ed.* **2009**, *48*, 9608.

(6) Palmieri, A.; Petrini, M.; Shaikh, R. R. *Org. Biomol. Chem.* **2010**, *8*, 1259.

(7) (a) Larock, R. C.; Yum, E. K.; Refvik, M. D. *J. Org. Chem.* **1998**, *63*, 7652. (b) Nazaré, M.; Schneider, C.; Lindenschmidt, A.; Will, D. W. *Angew. Chem. Int. Ed.* **2004**, *43*, 4526. (c) Arcadi, A.; Bianchi, G.; Marinelli, F. *Synthesis* **2004**, 610. (d) Kothandaraman, P.; Mothe, S. R.; Toh, S. S. M.; Chan, P. W. H. *J. Org. Chem.* **2011**, *76*, 7633. (e) Nanjo, T.; Tsukano, C.; Takemoto, Y. *Org. Lett.* **2012**, *14*, 4270.

(8) (a) Ballini, R.; Gabrielli, S.; Palmieri, A. *Curr. Org. Chem.* **2010**, *14*, 65. (b) Ballini, R.; Gabrielli, S.; Palmieri, A. *Synlett* **2010**, 2468. (c) Palmieri, A.; Gabrielli, S.; Ballini, R. *Adv. Synth. Catal.* **2010**, *352*, 1485. (d) Palmieri, A.; Gabrielli, S.; Cimarelli, C.; Ballini, R. *Green Chem.* **2011**, *13*, 3333. (e) Gabrielli, S.; Palmieri, A.; Panmand, D. S.; Lanari, D.; Vaccaro, L.; Ballini, R. *Tetrahedron* **2012**, *68*, 8231. (f) Gabrielli, S.; Ballini, R.; Palmieri, A. *Monatsh. Chem.* **2013**, *144*, 509. (g) Palmieri, A.; Gabrielli, S.; Ballini, R. *Green Chem.* **2013**, *15*, 2344.

(9) (a) Yamazaki, K.; Kondo, Y. *Chem. Commun.* **2002**, 210. (b) Yamazaki, K.; Nakamura, Y.; Kondo, Y. *J. Org. Chem.* **2003**, *68*, 6011.

(10) (a) Rosauer, K. G.; Ogawa, A. K.; Willoughby, C. A.; Ellsworth, K. P.; Geissler, W. M.; Myers, R. W.; Deng, Q.; Chapman, K. T.; Harris, G.; Moller, D. E. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 4385. (b) Parrish, J. P.; Kastrinsky, D. B.; Stauffer, F.; Hedrick, M. P.; Hwang, I.; Boger, D. L. *Bioorg. Med. Chem.* **2003**, *11*, 3815. (c) Boger, D. L.; Boyce, C. W. *J. Org. Chem.* **2000**, *65*, 4088. (d) Dai, Y.;

Guo, Y.; Guo, J.; Pease, L. J.; Li, J.; Marcotte, P. A.; Glaser, K. B.; Tapang, P.; Albert, D. H.; Richardson, P. L.; Davidsen, S. K.; Michaelides, M. R. *Bioorg. Med. Chem.* **2003**, *13*, 1897.

(11) (a) Japp, F. R.; Klingemann, F. *Ber. Dtsch. Chem. Ges.* **1887**, *20*, 2942. (b) Delfourne, E.; Roubin, C.; Bastide, J. *J. Org. Chem.* **2000**, *65*, 5476. (c) Meyer, M. D.; Kruse, L. I. *J. Org. Chem.* **1984**, *49*, 3195.

(12) (a) Knittel, D. *Synthesis* **1985**, 186. (b) Hemetsberger, H.; Knittel, D. *Monatsh. Chem.* **1972**, *103*, 194. (c) Venable, J. D.; Cai, H.; Chai, W.; Dvorak, C. A.; Grice, C. A.; Jablonowski, J. A.; Shah, C. R.; Kwok, A. K.; Ly, K. S.; Pio, B.; Wei, J.; Desai, P. J.; Jiang, W.; Nguyen, S.; Ling, P.; Wilson, S. J.; Dunford, P. J.; Thurmond, R. L.; Lovenberg, T. W.; Karlsson, L.; Carruthers, N. I.; Edwards, J. P. *J. Med. Chem.* **2005**, *48*, 8289.

(13) The 1,5,7-triazabicyclo[4.4.0]dec-5-ene (TBD) bound to polystyrene (3 mmol/g) was purchased from Sigma–Aldrich (01961-5G-F) and used directly without any manipulation.

(14) **Synthesis of Indoles 5; General Procedure:** *o*-Bromoaniline **1** (0.5 mmol) and β-nitroacrylate **2** (0.5 mmol) were stirred at 70 °C for 24 h, then MeCN (3 mL) and TBD (1 mmol, 333 mg) were added and the resulting solution was stirred at r.t. for 5 h. Finally, after TBD filtration (washing with EtOAc) and solvent evaporation, the crude material **4** was dissolved in DMF (4 mL), treated with $Pd_2(dba)_3$ (32 mg, 0.034 mmol), P(*o*-Tol)$_3$ (42 mg, 0.138 mmol), Et_3N (0.96 mL, 6.9 mmol), and heated at 110 °C for 12 h. After cooling, the reaction was quenched with 2 M HCl (10 mL), extracted with Et_2O (3 × 30 mL) and the organic extracts were dried over Na_2SO_4. After filtration and solvent evaporation at reduced pressure, the crude indole **5** was purified by flash chromatography (hexane–EtOAc).

Ethyl 3-Ethyl-1*H*-indole-2-carboxylate (5a): White solid; mp 91–93 °C. IR (Nujol): 747, 1257, 1673, 3329 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.29 (t, *J* = 7.7 Hz, 3 H), 1.44 (t, *J* = 7.3 Hz, 3 H), 3.14 (q, *J* = 7.7 Hz, 2 H), 4.43 (q, *J* = 7.3 Hz, 2 H), 7.14 (t, *J* = 7.7 Hz, 1 H), 7.32 (t, *J* = 8.1 Hz, 1 H), 7.38 (d, *J* = 7.7 Hz, 1 H), 7.70 (d, *J* = 8.1 Hz, 1 H), 8.78 (br s, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.7, 15.7, 18.3, 60.9, 111.9, 120.1, 121.0, 123.0, 125.7, 127.1, 127.9, 136.2, 162.7. MS (EI, 70 eV): *m*/*z* (%) = 217 (100) [M]$^+$, 202, 188, 171, 170, 156, 143, 128, 115, 101, 89, 77, 63, 51, 39, 29. Anal. Calcd for $C_{13}H_{15}NO_2$ (217.26): C, 71.87; H, 6.96; N, 6.45. Found: C, 71.91; H, 7.00; N, 6.41.

Ethyl 3-Methyl-1*H*-indole-2-carboxylate (5b): Pale-orange solid; mp 128–130 °C. IR (Nujol): 744, 780, 1257, 1683, 3326 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.45 (t, *J* = 7.3 Hz, 3 H), 2.63 (s, 3 H), 4.44 (q, *J* = 7.3 Hz, 2 H), 7.08–7.44 (m, 3 H), 7.68 (d, *J* = 8.1 Hz, 1 H), 8.73 (br s, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 10.1, 14.7, 60.9, 111.8, 120.1, 120.4, 121.0, 123.6, 125.8, 128.8, 136.0, 162.9. MS (EI, 70 eV): *m*/*z* (%) = 203 [M]$^+$, 174, 157 (100), 129, 102, 77, 51, 29. Anal. Calcd for $C_{12}H_{13}NO_2$ (203.24): C, 70.92; H, 6.45; N, 6.89. Found: C, 70.98; H, 6.48; N, 6.86.

Propyl 3-Methyl-1*H*-indole-2-carboxylate (5c): Pale-yellow solid; mp 102–105 °C. IR (Nujol): 744, 780, 1242, 1682, 3328 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.06 (t, *J* = 7.3 Hz, 3 H), 1.77–1.89 (m, 2 H), 2.62 (s, 3 H), 4.33 (t, *J* = 6.8 Hz, 2 H), 7.14 (t, *J* = 7.3 Hz, 1 H), 7.29–7.40 (m, 2 H), 7.67 (d, *J* = 8.1 Hz, 1 H), 8.70 (br s, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 10.2, 10.9, 22.4, 66.6, 111.8, 120.1, 120.3, 121.0, 123.7, 125.8, 128.8, 136.1, 163.1. MS (EI, 70 eV): *m*/*z* (%) = 217 [M]$^+$, 174, 157 (100), 129, 102, 77, 51, 41, 29. Anal. Calcd for $C_{13}H_{15}NO_2$ (217.26): C, 71.87; H, 6.96; N, 6.45. Found: C, 71.84; H, 6.93; N, 6.47.

Methyl 3-Nonyl-1*H*-indole-2-carboxylate (5d): White solid; mp 65–67 °C. IR (Nujol): 749, 1250, 1675, 3326 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.88 (t, *J* = 6.8 Hz, 3 H), 1.07–1.43 (m, 12 H), 1.62–1.73 (m, 2 H), 3.06–3.14 (m, 2 H), 3.95 (s, 3 H), 7.11–7.16 (m, 1 H), 7.28–7.40 (m, 2 H), 7.69 (dd, *J* = 0.9, 9.0 Hz, 1 H), 8.75 (br s, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.4, 22.9, 24.9, 29.6, 29.8, 29.9, 30.0, 31.3, 32.2, 51.9, 111.9, 120.1, 121.2, 123.0, 125.8, 126.0, 128.2, 136.2, 163.1. MS (EI, 70 eV): *m*/*z* (%) = 301 [M]$^+$, 242, 188 (100), 156, 128. Anal. Calcd for $C_{19}H_{27}NO_2$ (301.42): C, 75.71; H, 9.03; N, 4.65. Found: C, 75.74; H, 9.05; N, 4.64.

Ethyl 3-(4-Cyanobutyl)-1*H*-indole-2-carboxylate (5e): White solid; mp 115–117 °C. IR (Nujol): 752, 1021, 1250, 1697, 2248, 3374 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.44 (t, *J* = 7.3 Hz, 3 H), 1.67–1.78 (m, 2 H), 1.81–1.92 (m, 2 H), 2.36 (t, *J* = 6.8 Hz, 2 H), 3.17 (t, *J* = 7.3 Hz, 2 H), 4.43 (q, *J* = 7.3 Hz, 2 H), 7.12–7.18 (m, 1 H), 7.29–7.42 (m, 2 H), 7.66 (d, *J* = 8.1 Hz, 1 H), 8.81 (br s, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.7, 17.3, 23.9, 25.3, 29.9, 61.1, 112.1, 120.0, 120.5, 120.8, 123.5, 124.0, 125.9, 128.0, 136.1, 162.4. MS (EI, 70 eV): *m*/*z* (%) = 270 [M]$^+$, 224, 202, 197, 156 (100), 128, 101, 77, 29. Anal. Calcd for $C_{16}H_{18}N_2O_2$ (270.33): C, 71.09; H, 6.71; N, 10.36. Found: C, 71.06; H, 6.70; N, 10.40.

Cyclopentyl 3-Ethyl-5-methyl-1*H*-indole-2-carboxylate (5f): White solid; mp 113–115 °C. IR (Nujol): 783, 799, 1255, 1679, 3314 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.26 (t, *J* = 7.7 Hz, 3 H), 1.58–2.06 (m, 8 H), 2.45 (s, 3 H), 3.06 (q, *J* = 7.7 Hz, 2 H), 5.44–5.50 (m, 1 H), 7.14 (dd, *J* = 1.3, 8.5 Hz, 1 H), 7.24–7.28 (m, 1 H), 7.45 (s, 1 H), 8.61 (br s, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 15.8, 18.4, 21.8, 24.0, 33.2, 77.8, 111.6, 120.2, 123.5, 126.1, 127.6, 128.1, 129.4, 134.5, 162.7. MS (EI, 70 eV): *m*/*z* = 271 [M]$^+$, 203, 188, 186, 185 (100), 170, 142, 115, 41 Anal Calcd. for $C_{17}H_{21}NO_2$ (271.35): C, 75.25; H, 7.80; N, 5.16. Found: C, 75.29; H, 7.82; N, 5.13.

Ethyl 5-Methyl-3-phenethyl-1*H*-indole-2-carboxylate (5g): White solid; mp 132–134 °C. IR (Nujol): 755, 779, 798, 1601, 1678, 3309 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.44 (t, *J* = 7.3 Hz, 3 H), 2.47 (s, 3 H), 2.91–2.99 (m, 2 H), 3.34–3.41 (m, 2 H), 4.41 (q, *J* = 7.3 Hz, 2 H), 7.13–7.33 (m, 7 H), 7.41 (s, 1 H), 8.75 (br s, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.8, 21.8, 27.4, 37.6, 60.9, 111.7, 120.2, 123.6, 123.8, 126.1, 127.7, 128.2, 128.5, 128.8, 129.6, 134.5, 142.6, 162.7. MS (EI, 70 eV): *m*/*z* (%) = 307 [M]$^+$, 216 (100), 170, 142, 115, 91, 65, 39, 29. Anal. Calcd for $C_{20}H_{21}NO_2$ (307.39): C, 78.15; H, 6.89; N, 4.56. Found: C, 78.19; H, 6.91; N, 4.53.

Ethyl 5-Methoxy-3-[(2-phenyl-1,3-dioxolan-2-yl)methyl]-1*H*-indole-2-carboxylate (5h): White solid; mp 144–146 °C. IR (Nujol): 752, 762, 779, 1022, 1258, 1539, 1668, 3326 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.37 (t, *J* = 7.3 Hz, 3 H), 3.68–3.85 (m, 9 H), 4.27 (q, *J* = 7.3 Hz, 2 H), 6.96 (dd, *J* = 2.5, 8.5 Hz, 1 H), 7.11 (d, *J* = 2.5 Hz, 1 H), 7.22–7.30 (m, 4 H), 7.36–7.42 (m, 2 H), 8.72 (br s, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.6, 36.5, 55.9, 60.8, 64.9, 102.9, 110.7, 112.4, 117.0, 117.7, 125.8, 126.2, 127.9, 129.5, 131.2, 142.9, 154.4, 162.5. MS (EI, 70 eV): *m*/*z* (%) = 381 [M]$^+$, 232, 186, 149 (100), 105, 77. Anal. Calcd for $C_{22}H_{23}NO_5$ (381.42): C, 69.28; H, 6.08; N, 3.67. Found: C, 69.32; H, 6.10; N, 3.66.

Ethyl 3-(3-Acetoxypropyl)-5-methoxy-1*H*-indole-2-carboxylate (5i): Pale-yellow solid; mp 74–76 °C. IR (Nujol): 782, 1220, 1674, 1732, 3327 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.42 (t, *J* = 7.3 Hz, 3 H), 1.97–2.07 (m, 2 H), 2.05 (s, 3 H), 3.11–3.18 (m, 2 H), 3.87 (s, 3 H), 4.12 (t, *J* = 6.8 Hz, 2 H), 4.41 (q, *J* = 7.3 Hz, 2 H), 6.97–7.04 (m,

2 H), 7.27 (d, *J* = 8.5 Hz, 1 H), 8.73 (br s, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.7, 21.3, 21.4, 29.7, 56.0, 61.0, 64.5, 101.0, 113.0, 117.3, 123.2, 124.1, 128.4, 131.4, 154.6, 162.4, 171.4. MS (EI, 70 eV): *m*/*z* (%) = 319 $[M]^+$, 259, 231, 213, 186 (100), 158, 115, 43. Anal. Calcd for $C_{17}H_{21}NO_5$ (319.35): C, 63.94; H, 6.63; N, 4.39. Found: C, 63.98; H, 6.65; N, 4.37.

Ethyl 6-Methoxy-3-pentyl-1*H*-indole-2-carboxylate (5j): White solid; mp 108–110 °C. IR (Nujol): 781, 1247, 1671, 3311 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.89 (t, *J* = 6.8 Hz, 3 H), 1.33–1.39 (m, 4 H), 1.41 (t, *J* = 7.3 Hz, 3 H), 1.61–1.71 (m, 2 H), 3.02–3.07 (m, 2 H), 3.85 (s, 3 H), 4.40 (q, *J* = 7.3 Hz, 2 H), 6.76–6.82 (m, 2 H), 7.52–7.55 (m, 1 H), 8.61 (br s, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.3, 14.7, 22.8, 25.0, 31.0, 32.2, 55.7, 60.6, 93.7, 111.5, 122.0, 122.2, 122.8, 126.3, 137.1, 159.2, 162.2. MS (EI, 70 eV): *m*/*z* (%) = 289 $[M]^+$, 243, 232, 216, 204, 186 (100), 160, 158, 115, 89, 41, 29. Anal. Calcd for $C_{17}H_{23}NO_3$ (289.37): C, 70.56; H, 8.01; N, 4.84. Found: C, 70.60; H, 8.00; N, 4.82.

