

The Bartoli Indole Synthesis on Solid Supports

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Supporting Information

¹H NMR: Bruker DP 300 (300 MHz), Bruker DP 400 (400 MHz); δ = 2.50 ppm for [D₅] dimethylsulfoxide, 3.31 ppm for [D₃] methanol, 7.26 ppm for CHCl₃. Description of signals: s = singlet, bs = broad singlet, d = doublet, t = triplet, q = quartet, m = multiplet, mc = centered multiplet, dd = doublet of doublet, ddd = doublet of dd, dt = doublet of triplets, dq = doublet of quartets, tt = triplet of triplets. The spectra were analyzed according to first order. All couplings constants are absolute values. Abbreviations for signals: Ar-H = Ar, Naph = napthyl, Tol = toluyl. ¹³C NMR: Bruker DP 300 (75 MHz), Bruker DP 400 (100 MHz); δ = 39.52 ppm for perdeuterodimethylsulfoxide, 77.16 ppm for deuteriochloroform, 49.00 for perdeuteromethanol. The signal structure was analyzed by DEPT and described as follows: + = primary or tertiary C-atom (positive signal), - = secondary C-atom (negative signal), q = quaternary C-atom (no signal). IR (infrared-spectroscopy): Perkin Elmer FT-IR 1750. The substances were dissolved in distilled dichloromethane. The resins were measured as KBr pellets on a Bruker IFS88 IR. ps = polystyrene. MS (mass spectroscopy): EI-HRMS (electronic ionization – high resolution mass spectroscopy): Kratos MS 50 (70 eV) and Thermo Quest Finnigan MAT 95 XL (70 eV). GC (gas chromatography) analytical: Hewlett-Packard HP 5890 Serie II 12 m \times 0.25 mm capillary column HP I (carrier gas N₂). TLC (Thin layer chromatography): Silica gel coated aluminium plates (Merck, silica gel 60, F₂₅₄). Detection under UV-light at 254 nm, displayed with molybdato phosphate (5% phosphor molybdic acid in ethanol, dipping solution), potassium permanganate (0.45 g potassium permanganate and 2.35 g of sodium carbonate in 90 ml of water, dipping solution). Elemental analysis: elementar vario EL at the Mikroanalytisches Labor des Instituts für Organische Chemie der Universität Bonn. Descriptions without nominated temperature were done by room temperature (rt). Solid materials (except resins) were powdered. Chemicals, solvents, reagents and chemicals were purchased from Aldrich, Fluka, Janssen, and Merck. Merrifield resin (1-2% cross-linked, 200-400 mesh) was obtained from CalBioChem-NovaBioChem with loading = 1.06 g·mol⁻¹. In order to get the molecular mass of the resin and to calculate the elemental analysis the following calculation has to be performed:

$$\text{molar mass}_{\text{new}} = \frac{1000}{\text{Loading}_{\text{old}}} - (\text{molar mass}_{\text{Sub}} - \text{molar mass}_{\text{Add}})$$

Formula 1: Formula for the Calculation of the Molar Mass of a Derivatized Resin

Solvents for reactions for organometallic and other sensitive materials (benzene, ether, tetrahydrofuran, dichloromethane) were distilled under argon. All resins were washed sequentially by using a vacuum reservoir connected to a sintered glass frit. Cleavage was conducted using Teflon tubes with a frit connected to a vacuum line or with a glass pipette filled with glass wool or just paper-filtered. Evaporation of the solvent was achieved using a rota vapor and/or high vacuum (ca. 0.1 mbar).

general washing procedure

(methanol, THF, pentane, dichloromethane) three times
(methanol, DMF, pentane, THF) once
(pentane, dichloromethane, pentane) two times

General Procedure for the Attachment of benzoic acids to Merrifield resin:

In a three-necked round bottom flask equipped with a mechanical stirrer was suspended 9.7 g (30 mmol) of cesium carbonate in DMF and stirred for 10 min. The nitro benzoic acid (30 mmol) was added and the mixture was stirred again for 10 min. Then 10 g (10.6 mmol, loading 1.06 mmol/g) of Merrifield resin were added to this mixture, which was stirred for 24 h at 50° C. The mixture was allowed to come to room temperature. The resin was filtered off and washed with water. After general washing procedure the resin was dried under high vacuum.

General Procedure for the Formation of Resin-bound Indoles:

1.0 g of resin **3** (0.90 mmol, loading 0.90 mmol/g) was suspended in 10 ml of abs. THF under argon. The mixture was cooled to – 40 °C and 3 mmol of the Grignard reagent was added, while the color changed into deep red to brown. The mixture allowed to come to 0° C. The resin was hydrolyzed with sat. aqueous ammonium chloride solution and filtered off. Then the resin was washed with water and after the general washing procedure. It was dried under high vacuum.

General Cleavage Protocol:

1 g of the resin was placed with 10 ml abs. THF in a 50 ml round bottom flask. A 30% solution of sodium methylate in methanol (1 ml) was added to the mixture, which was shaked for 3 h on a shaker. The mixture was filtered, the filtrate was hydrolyzed with water and extracted two times with diethyl ether and then two times with ethyl acetate. After drying with magnesium sulfate, the product was evaporated under reduced pressure.

The products were purified by column chromatography (silica, cyclohexane:ethyl acetate, 3:1). Nitro benzoic acids were isolated according the same procedure, however they were dissolved using hydrochloric acid instead of water.

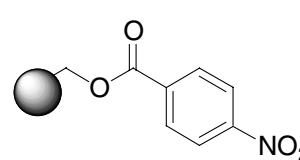
Heck Reaction:

For the Heck reaction, 1.04 g (0.9 mmol/g) of 7-bromo-2,3-dimethyl-1*H*-indol-6-carbonyloxymethyl polystyrene (**11e**), 23.6 mg (0.1 mmol) of palladium acetate and 145 mg (0.55 mmol) of triphenylphosphine were suspended in 12 ml DMF under argon. Then, 0.20 ml (1.0 mmol) of triethylamine and 2.60 ml (2.0 mmol) were added to the mixture. The mixture was heated under shaking for 24 h at 105 °C. The resin was filtrated and washed with water and then according to the general washing procedure. The resin was dried under high vacuum. The product was purified after cleavage by column chromatography (silica, cyclohexane:ethyl acetate, 3:1).

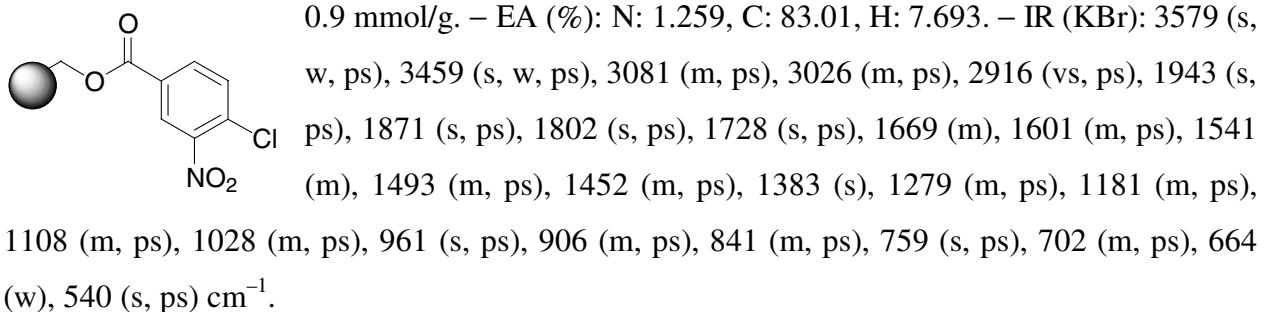
Suzuki Reaction:

For the Suzuki reaction, 1.01 g (0.9 mmol/g) of 7-bromo-2,3-dimethyl-1*H*-indol-6-carbonyloxymethyl polystyrene (**11e**), 83.2 mg (0.072 mmol) of tetrakis(triphenylphosphine) palladium and 358 mg (0.5 mmol) of 4-*t*-butyl phenylboronic acid were suspended in 10 ml of DMF under argon conditions. To this mixture, a solution of 308 mg (3.0 mmol) of sodium carbonate in 1 ml water was added. The mixture was heated under shaking for two days at 75 °C. The resin was filtrated and washed first with sat. aqueous ammonium acetate solution and then according to the general washing procedure. The resin was dried under high vacuum. The product was purified after cleavage by column chromatography (silica, cyclohexane:ethyl acetate, 3:1).

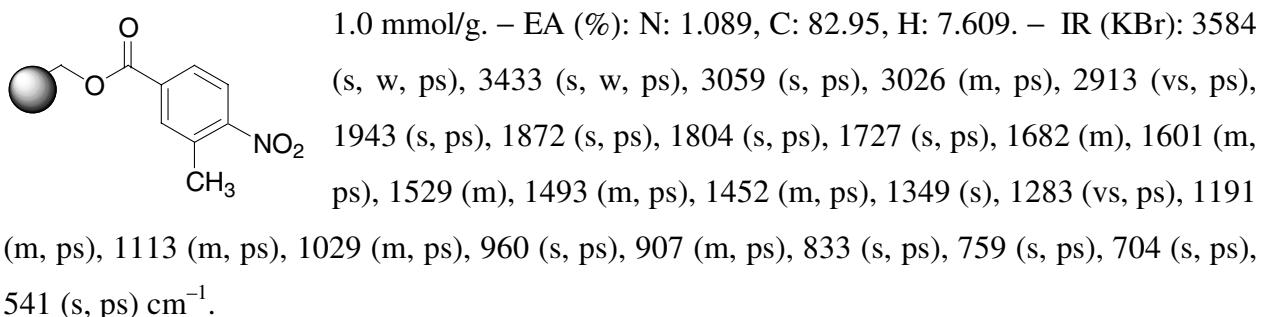
p-Nitrophenylcarbonyloxymethyl polystyrene (**3a**): Loading: 0.9 mmol/g. □

 -EA (%): N: 1.088, C: 85.97, H: 7.225. - IR (KBr): 3577 (s, w, ps), 3430 (s, ps), 3059 (s, ps), 3026 (m, ps), 2922 (vs, ps), 1944 (s, ps), 1872 (s, ps), 1805 (s, ps), 1728 (s, ps), 1680 (s), 1601 (s, ps), 1529 (m), 1493 (m, ps), 1452 (m, ps), 1346 (s), 1271 (m, ps), 1181 (s, ps), w 1100 (s, ps), 1015 (s, ps), 963 (s, ps), 906 (s, ps), 855 (m, ps), 758 (s, ps), 699 (s, ps), 540 (s, ps) cm⁻¹.

4-Chloro-3-nitrophenylcarbonyloxymethyl polystyrene (**3b**): Loading:



3-Methyl-4-nitrophenylcarbonyloxymethyl polystyrene (**3c**): Loading:



4-Fluoro-3-nitrophenylcarbonyloxymethyl polystyrene (**3d**): IR (KBr): 3649 (m, w, ps), 3442 (s, w, ps), 3060 (s, ps), 3028 (m, ps), 2930 (vs, ps), 1944 (s, ps), 1873 (s, ps), 1804 (s, ps), 1729 (vs, ps), 1603 (s, ps), 1543 (s), 1493 (m, ps), 1452 (m, ps), 1283 (vs, ps), 1147 (m, ps), 1106 (vs, ps), 1028 (m, ps), 964 (s, ps), 907 (m, ps), 841 (s, ps), 761 (s, ps), 702 (s, ps), 629 (m), 541 (vs, ps) cm^{-1} .

4-Nitrobenzoic acid : 87%. – ^1H NMR (400 MHz, CD_3OD): δ = 8.23 (d, 3J = 9.04 Hz, 2 H, 2(6)-H), 8.31 (d, 3J = 9.04 Hz, 2 H, 3(5)-H), 13.59 (bs, 1 H, OH). – ^{13}C NMR (100 MHz, CD_3OD): δ = 124.5 (+, C-3(5)), 131.9 (+, C-2(6)), 137.6 (q, C-1), 151.9 (q, C-4), 167.6 (q, CO_2). – IR (CH_2Cl_2): ν = 3448 (OH), 1607 (arene), 1532 (NO_2). – MS (EI), m/z (%) = (M^+ , 100), 150 (5), 137 (8), 121 (25), 109 (7), 93 (2), 81 (5), 75(8), 65 (20), 63 (2), 51 (4). – HRMS: calcd: 167.0219, found: 167.0217.

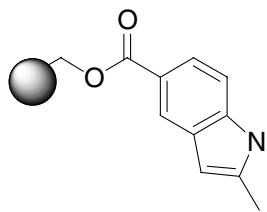
4-Chloro-3-methyl-benzoic acid : 91%. – ^1H NMR (400 MHz, CD_3OD): δ = 7.35 (d, 3J = 8.85, 1 H, 5-H), 8.21 (dd, 3J = 8.85, 4J = 2.15 Hz, 1 H, 6-H), 8.37 (d, 4J = 2.15 Hz, 1 H, 2-H), 12.90 (bs, 1 H, COOH). – ^{13}C NMR (100 MHz, CD_3OD): δ = 114.9 (+, C-2), 124.3 (q, C-1), 127.7 (+, C-5), 130.7 (q, C-4), 136.4 (+, C-6), 157.2 (q, C-3), 167.7 (q, CO_2). – IR (CH_2Cl_2): ν = 3492 (OH), 1618 (arene), 1538 (NO_2), 1357 (C-Cl). – MS (EI), m/z (%) = 201/203 (M^+ , 100), 171 (40), 115 (32), 99 (100), 75 (30), 63 (20). – HRMS: calcd 200.9829, found: 200.9827.

3-Methyl-4-nitro-benzoic acid : 89%. – ^1H NMR (400 MHz, CD_3OD): δ = 2.54 (s, 3 H, CH_3), 7.94 (dd, 3J = 8.34, 4J = 1.77 Hz, 1 H, 6-H), 8.03 (s, 1 H, 2-H), 8.04 (d, 3J = 8.34 Hz, 1 H, 5-H), 13.51 (bs, 1 H, COOH). – ^{13}C NMR (100 MHz, CD_3OD): δ = 19.0 (+, CH_3), 124.5 (+, C-5), 128.0 (+, C-6), 132.7 (q, C-3), 133.4 (+, C-2), 134.5 (q, C-1), 151.5 (q, C-4), 165.8 (q, CO_2). – IR (CH_2Cl_2): ν = 3692 (OH), 1602 (arene), 1550 (NO_2). – MS (EI), m/z (%) = 181 (M^+ , 35), 164 (100), 136 (17), 107 (15), 77 (50), 65 (30). – HRMS: calcd 181.0375, found 181.0374.

4-Fluoro-3-methyl-benzoic acid : 96%. – ^1H NMR (400 MHz, CD_3OD): δ = 7.53 (dd, 3J = 10.74, $^3J_{\text{HF}}$ = 8.67 Hz, 1 H, 5-H), 8.34 (m, 1 H, 6-H), 8.66 (dd, 3J = 7.35 Hz, 4J = 2.26 Hz, 1 H, 2-H), 13.53 (bs, 1 H, COOH). – ^{13}C NMR (100 MHz, CD_3OD): δ = 119.9 (+, J = 22.1 Hz, C-5), 128.6 (+, J = 1.2 Hz, C-2), 129.4 (q, J = 3.6 Hz, C-1), 137.8 (+, J = 10.2 Hz, C-6), 138.5 (q, J = 6.6 Hz, C-3), 159.2 (q, J = 268.1 Hz, C-4), 166.5 (q, CO_2). IR (CH_2Cl_2): ν = 3697 (OH), 1606 (arene), 1557 (NO_2). – MS (EI), m/z (%) = 185 (M^+ , 100), 168 (10), 15 (23), 139 (5), 127 (5), 122 (15), 110 (5), 99 (15), 93 (10), 83 (50), 75 (10), 57 (15). – HRMS: calcd 185.0124, found: 185.0124.

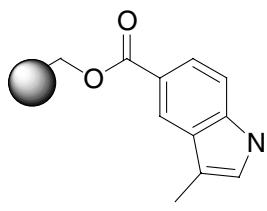
1H-indole-5-carbonyloxymethyl polystyrene (8a): Loading: 0.9 mmol/g. – EA (%): N: 1.098, C: 81.46, H: 7.362. – IR (KBr): 3303 (vs, w), 3060 (s, ps), 3026 (m, ps), 2924 (vs, ps), 1943 (s, ps), 1872 (s, ps), 1803 (s, ps), 1717 (vs, ps), 1603 (s, ps), 1494 (m, ps), 1453 (m, ps), 1375 (m), 1272 (s, ps), 1178 (m, ps), 1103 (vs, ps), 1029 (m, ps), 908 (m, ps), 847 (m, ps), 766 (s, ps), 705 (m, ps) cm^{-1} .

2-Methyl-1H-indole-5-carboxyloxymethyl polystyrene (8b): Loading: 0.8 mmol/g. – EA



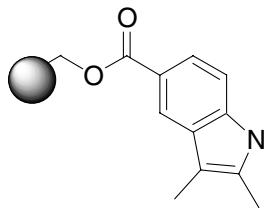
(%)
N: 1.006, C: 80.09, H: 7.379. – IR (KBr): 3638 (vs, w), 3059 (s, ps), 3026 (m, ps), 2924 (vs, ps), 1944 (s, ps), 1873 (s, ps), 1803 (s, ps), 1721 (vs, ps), 1603 (s, ps), 1493 (m, ps), 1452 (m, ps), 1376 (m), 1271 (vs, ps), 1099 (vs, ps), 1029 (m, ps), 965 (m, ps), 906 (m, ps), 843 (s, ps), 763 (s, ps), 700 (m, ps), 544 (vs, ps) cm^{-1} .

3-Methyl-1H-indole-5-carboxyloxymethyl polystyrene (8c): Loading: 0.9 mmol/g. – EA (%)



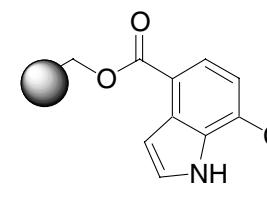
N: 0.999, C: 78.60, H: 7.587. IR (KBr): 3591 (vs, w), 3059 (m, ps), 3028 (m, ps), 2913 (vs, ps), 1943 (s, ps), 1872 (s, ps), 1804 (m, ps), 1720 (m, ps), 1665 (m), 1602 (s, ps), 1493 (m, ps), 1453 (m, ps), 1376 (m), 1272 (vs, ps), 1177 (m), 1102 (s, ps), 1028 (m, ps), 966 (m, ps), 906 (m, ps), 845 (m, ps), 768 (s, ps), 704 (m, ps), 549 (vs, ps) cm^{-1} .

2,3-Dimethyl-1H-indole-5-carboxyloxymethyl polystyrene (8d): Loading:



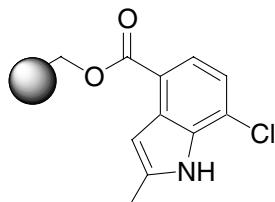
0.9 mmol/g. – EA (%): N: 1.110, C: 81.70, H: 7.634. – IR (KBr): 3645 (vs, w), 3296 (vs, w), 3060 (m, ps), 3026 (m, ps), 2928 (vs, ps), 1942 (s, ps), 1872 (s, ps), 1803 (m, ps), 1721 (vs, ps), 1601 (s, ps), 1531 (m), 1493 (m, ps), 1452 (m, ps), 1373 (m), 1269 (vs, ps), 1174 (m), 1099 (vs, ps), 1028 (s, ps), 963 (m, ps), 907 (m, ps), 843 (s, ps), 759 (s, ps), 700 (m, ps), 544 (m, ps) cm^{-1} .

7-Chloro-1H-indole-4-carboxyloxymethyl polystyrene (9a): Loading: 0.6 mmol/g. – EA (%)



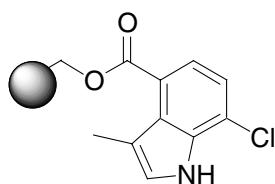
N: 0.694, C: 81.61, H: 7.148. – IR (KBr): 3575 (vs, w), 3304 (vs, w), 3026 (s, ps), 2913 (vs, ps), 1944 (s, ps), 1873 (s, ps), 1804 (s, ps), 1724 (s, ps), 1665 (m), 1601 (s, ps), 1494 (m, ps), 1452 (m, ps), 1371 (s), 1282 (vs, ps), 1029 (vs, ps), 907 (m, ps), 843 (m, ps), 763 (s, ps), 705 (m, ps) cm^{-1} .

7-Chloro-2-methyl-1H-indole-4-carboxyloxymethyl polystyrene (**9b**): Loading:



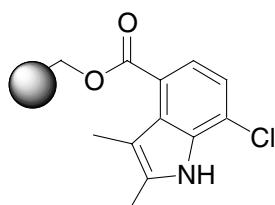
0.9 mmol/g. – EA (%): N: 1.076, C: 77.57, H: 7.325. – IR (KBr): 3575 (vs, w), 3060 (s, w), 3027 (m, ps), 2928 (vs, ps), 1944 (s, ps), 1872 (s, ps), 1804 (s, ps), 1718 (s, ps), 1667 (s), 1601 (s, ps), 1493 (m, ps), 1452 (m, ps), 1376 (s), 1279 (s, ps), 1163 (s), 1104 (m), 1029 (s, ps), 906 (m, ps), 842 (m, ps), 760 (s, ps), 701 (m, ps), 543 (vs, ps) cm^{-1} .

7-Chloro-3-methyl-1H-indole-4-carboxyloxymethyl polystyrene (**9c**): Loading: 0.4 mmol/g.



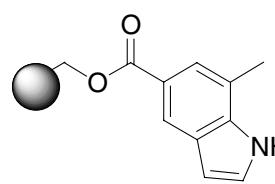
– EA (%): N: 0.544, C: 79.53, H: 7.587. – IR (KBr): 3583 (vs, w), 3058 (m, w), 3026 (m, ps), 2913 (vs, ps), 1943 (s, ps), 1872 (s, ps), 1804 (m, ps), 1722 (s, ps), 1665 (s), 1601 (s, ps), 1547 (m), 1493 (m, ps), 1452 (m, ps), 1372 (s), 1283 (vs, ps), 1180 (m), 1155 (m), 1102 (m), 1028 (m, ps), 978 (m), 906 (m, ps), 842 (m, ps), 759 (s, ps), 703 (m, ps), 546 (vs, ps) cm^{-1} .

7-Chloro-2,3-dimethyl-1H-indole-4-carboxyloxymethyl polystyrene (**9d**): Loading:



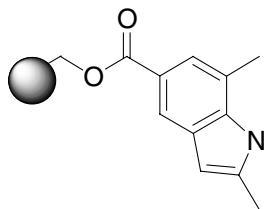
0.9 mmol/g. – EA (%): N: 1.269, C: 78.97, H: 7.292. – IR (KBr): 3647 (vs, w), 3290 (vs, w), 3058 (m, w), 3025 (m, ps), 2924 (vs, ps), 1942 (s, ps), 1869 (s, ps), 1802 (s, ps), 1724 (s, ps), 1669 (s), 1601 (m, ps), 1558 (m), 1493 (m, ps), 1452 (m, ps), 1377 (m), 1282 (vs, ps), 1175 (m), 1155 (w), 1105 (s), 1028 (m, ps), 979 (m), 907 (m, ps), 839 (m, ps), 822 (m), 762 (s, ps), 702 (m, ps), 537 (vs, ps) cm^{-1} .

7-Methyl-1H-indole-5-carboxyloxymethyl polystyrene (**10a**): Loading: 0.9 mmol/g. –



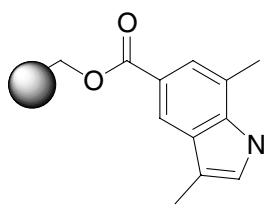
EA (%): N: 1.125, C: 82.22, H: 7.440. – IR (KBr): 3304 (vs, w), 3060 (s, ps), 3026 (m, ps), 2924 (vs, ps), 1944 (s, ps), 1873 (s, ps), 1804 (s, ps), 1721 (vs, ps), 1603 (s, ps), 1545 (s), 1494 (m, ps), 1452 (m, ps), 1373 (s), 1258 (m, ps), 1187 (m, ps), 1104 (s, ps), 1029 (vs, ps), 906 (m, ps), 843 (m, ps), 769 (s, ps), 703 (m, ps) cm^{-1} .

*2,7-Dimethyl-1*H*-indole-5-carbonyloxymethyl polystyrene* **(10b):** Loading:



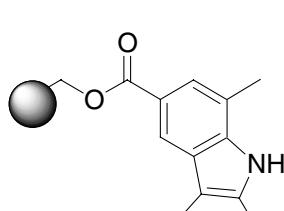
0.7 mmol/g. – EA (%): N: 1.939, C: 78.69, H: 7.322. – IR (KBr): 3654 (vs, w), 3306 (vs, ps), 3027 (vs, ps), 2929 (vs, ps), 1944 (s, ps), 1873 (s, ps), 1803 (s, ps), 1715 (vs, ps), 1601 (s, ps), 1493 (m, ps), 1452 (m, ps), 1375 (vs), 1100 (s, ps), 1029 (vs, ps), 907 (m, ps), 843 (m, ps), 765 (s, ps), 702 (m, ps), 548 (vs, ps) cm^{-1} .

*3,7-Dimethyl-1*H*-indole-5-carbonyloxymethyl polystyrene* **(10c):** Loading:



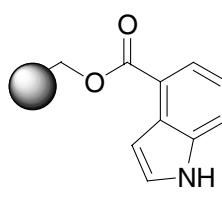
0.9 mmol/g. – EA (%): N: 1.073, C: 78.42, H: 7.695. – IR (KBr): 3626 (vs, w), 3026 (m, ps), 2912 (vs, ps), 1943 (s, ps), 1871 (s, ps), 1804 (s, ps), 1720 (m, ps), 1665 (m), 1602 (s, ps), 1543 (m), 1494 (m, ps), 1453 (m, ps), 1375 (m), 1256 (s), 1181 (m), 1102 (m, ps), 1068 (m), 1029 (m, ps), 967 (m), 907 (m, ps), 842 (m, ps), 821 (m), 761 (s, ps), 706 (m, ps), 568 (vs, ps) cm^{-1} .

*2,3,7-Trimethyl-1*H*-indole-5-carbonyloxymethyl polystyrene* **(10d):** Loading:

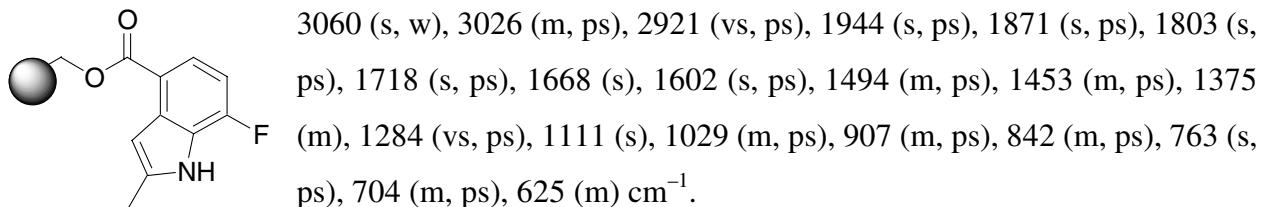


0.9 mmol/g. – EA (%): N: 1.089, C: 82.95, H: 7.609. – IR (KBr): 3648 (vs, w), 3304 (vs, w), 3060 (m, ps), 3025 (m, ps), 2922 (vs, ps), 1943 (s, ps), 1871 (s, ps), 1804 (m, ps), 1716 (vs, ps), 1602 (m, ps), 1513 (s), 1493 (m, ps), 1453 (m, ps), 1374 (s), 1289 (s), 1258 (m, ps), 1182 (m), 1104 (s, ps), 1028 (m, ps), 963 (s, ps), 907 (m, ps), 842 (m, ps), 760 (s, ps), 702 (m, ps), 538 (m, ps) cm^{-1} .

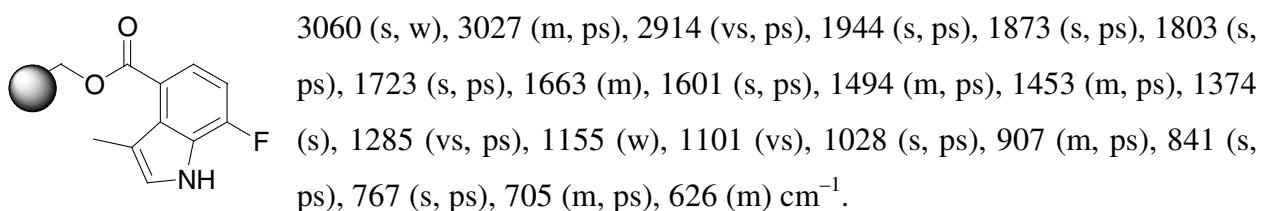
*7-Fluoro-1*H*-indole-4-carbonyloxymethyl polystyrene* **(11a):** IR (KBr): 3575 (vs, w), 3304 (vs, w), 3026 (s, ps), 2913 (vs, ps), 1944 (s, ps), 1873 (s, ps), 1804 (s, ps), 1724 (s, ps), 1665 (m), 1601 (s, ps), 1494 (m, ps), 1452 (m, ps), 1371 (s), 1282 (vs, ps), 1029 (vs, ps), 907 (m, ps), 843 (m, ps), 763 (s, ps), 705 (m, ps), 652 (m) cm^{-1} .



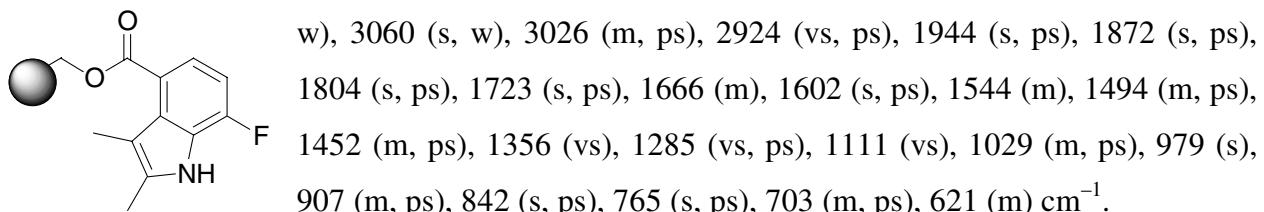
*7-Fluoro-2-methyl-1*H*-indole-4-carboxyloxymethyl polystyrene (11b): IR (KBr): 3303 (vs, w),*



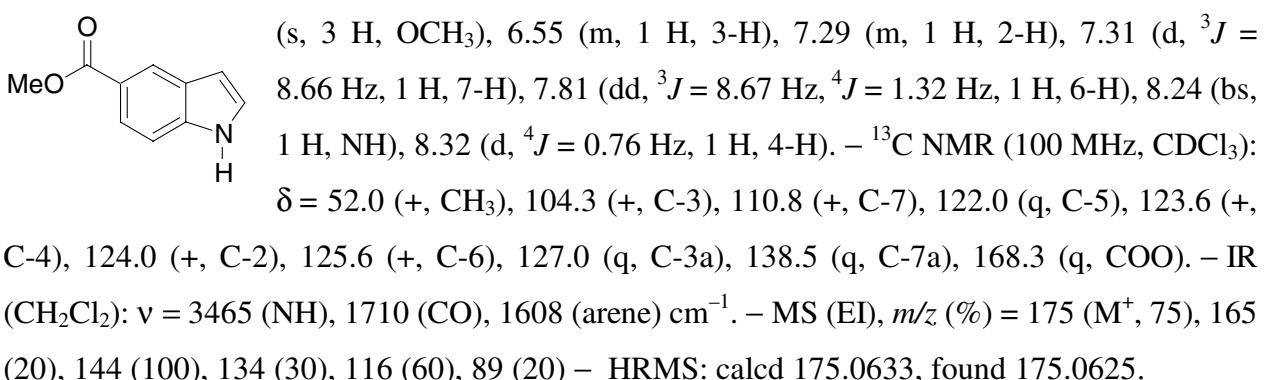
*7-Fluoro-3-methyl-1*H*-indole-4-carboxyloxymethyl polystyrene (11c): IR (KBr): 3291 (vs, w),*



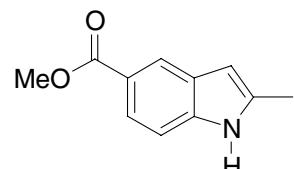
*7-Fluoro-2,3-dimethyl-1*H*-indole-4-carboxyloxymethyl polystyrene (11d): IR (KBr): 3304 (vs, w),*



*1*H*-Indole-5-carboxylic acid methyl ester (12a): 15%. – ^1H NMR (400 MHz, CDCl_3): δ = 3.83*

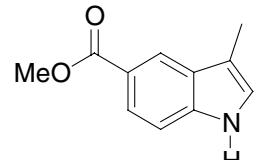


2-Methyl-1*H*-indole-5-carboxylic acid methyl ester (12b): 28%. – ^1H NMR (400 MHz, CDCl_3):



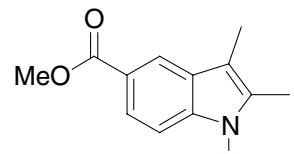
δ = 2.46 (s, 3 H, CCH_3), 3.92 (s, 3 H, OCH_3), 6.31 (m, 1 H, 3-H), 7.29 (d, 3J = 8.46 Hz, 1 H, 7-H), 7.81 (dd, 3J = 8.46, 4J = 1.64 Hz, 1 H, 6-H), 8.03 (bs, 1 H, NH), 8.27 (s, 1 H, 4-H). – ^{13}C NMR (100 MHz, CDCl_3): δ = 13.9 (+, C2CH_3), 51.9 (+, OCH_3), 101.9 (+, C-3), 109.9 (+, C-7), 111.3 (q, C-5), 122.7 (+, C-4), 122.8 (+, C-6), 131.6 (q, C-3a), 136.6 (q, C-2), 138.9 (q, C-7a), 168.4 (q, COO). – IR (CH_2Cl_2): ν = 3457 (NH), 1708 (CO), 1608 (arene) cm^{-1} . – MS (EI), m/z (%) = 189 (M^+ , 40), 165 (65), 158 (45), 134 (100), 106 (20). – HRMS: calcd 189.0790, found 189.0793.

3-Methyl-1*H*-indole-5-carboxylic acid methyl ester (12c): 32%. – ^1H NMR (400 MHz, CDCl_3):



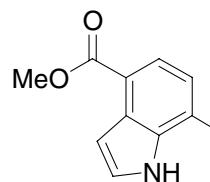
δ = 2.37 (d, 4J = 1.01 Hz, 3 H, C3CH_3), 3.94 (s, 3 H, OCH_3), 7.03 (m, 1 H, 2-H), 7.34 (dd, 3J = 8.59, 4J = 0.51 Hz, 1 H, 7-H), 7.90 (dd, 3J = 8.59, 4J = 1.64 Hz, 1 H, 6-H), 8.05 (bs, 1 H, NH), 8.36 (s, 1 H, 4-H). – ^{13}C NMR (100 MHz, CDCl_3): δ = 9.7 (+, C3CH_3), 52.0 (+, OCH_3), 110.7 (+, C-7), 113.5 (q, C-3), 121.5 (q, C-5), 122.2 (+, C-2), 122.9 (+, C-4), 123.5 (+, C-6), 128.2 (q, C-3a), 139.0 (q, C-7a), 168.4 (q, COO). – IR (CH_2Cl_2): ν = 3468 (NH), 1709 (CO), 1606 (arene) cm^{-1} . – MS (EI), m/z (%) = 189 (M^+ , 95), 164 (25), 158 (100), 130 (65), 103 (22), 77 (20). – HRMS: calcd 189.0790, found 189.0783.

2,3-Dimethyl-1*H*-indole-5-carboxylic acid methyl ester (12d): 13%. – ^1H NMR (400 MHz,

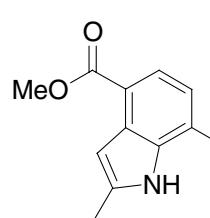


CDCl_3): δ = 2.25 (s, 3 H, C3CH_3), 2.37 (s, 3 H, C2CH_3), 3.93 (s, 3 H, OCH_3), 7.24 (dd, 3J = 8.46 Hz, 4J = 0.50 Hz, 1 H, 7-H), 7.81 (dd, 3J = 8.46, 4J = 1.64 Hz, 1 H, 6-H), 7.89 (bs, 1 H, NH), 8.23 (s, 1 H, 4-H). – ^{13}C NMR (100 MHz, CDCl_3): δ = 8.5 (+, C3CH_3), 11.7 (+, C2CH_3), 51.9 (+, OCH_3), 108.8 (q, C-3), 109.7 (+, C-7), 114.0 (q, C-5), 121.1 (+, C-4), 122.7 (+, C-6), 129.3 (q, C-3a), 132.1 (q, C-1), 138.1 (q, C-7a), 168.6 (q, COO). – IR (CH_2Cl_2): ν = 3459 (NH), 1707 (CO), 1607 (arene) cm^{-1} . – MS (EI), m/z (%) = 203 (M^+ , 100), 188 (30), 172 (70), 144 (50). – HRMS: calcd 203.0946, found 203.0937.

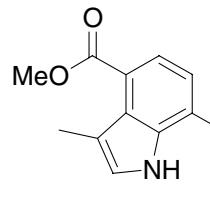
7-Chloro-1H-indole-4-carboxylic acid methyl ester (13a): 15%. – ^1H NMR (400 MHz, CDCl_3):

 δ = 3.98 (s, 3 H, OCH_3), 5.30 (s, 1 H, 3-H), 7.23 (m, 1 H, 6-H), 7.40 (m, 1 H, 2-H), 8.23 (d, 3J = 8.08 Hz, 1 H, 5-H), 8.55 (bs, 1 H, NH). – ^{13}C -NMR (100 MHz, CDCl_3): δ = 52.0 (+, OCH_3), 105.5 (+, C-3), 120.7 (q, C-4), 121.0 (+, C-5), 121.9 (q, C-7), 124.4 (+, C-2), 126.9 (+, C-6), 128.9 (q, C-3a), 134.0 (q, C-7a), 167.5 (q, COO). – IR (CH_2Cl_2): ν = 3457 (NH), 1713 (CO), 1567 (arene) cm^{-1} . – MS (EI), m/z (%) = 209/211 (M^+ , 70), 178 (100), 150 (50). – HRMS: calcd 209.0244, found 209.0245.

7-Chloro-2-methyl-1H-indole-4-carboxylic acid methyl ester (13b): 19%. – ^1H NMR (400 MHz,

 CDCl_3): δ = 2.51 (s, 3 H, C_2CH_3), 3.97 (s, 3 H, OCH_3), 6.88 (m, 1 H, 3-H), 7.13 (d, 3J = 8.08 Hz, 1 H, 6-H), 7.78 (d, 3J = 8.08 Hz, 1 H, 5-H), 8.34 (bs, 1 H, NH). – ^{13}C NMR (100 MHz, CDCl_3): δ = 14.2 (+, C_2CH_3), 52.2 (+, OCH_3), 103.7 (+, C-3), 119.7 (q, C-4), 120.2 (+, C-5), 121.1 (q, C-3a), 124.3 (+, C-6), 130.5 (q, C-7), 134.3 (q, C-7a), 139.0 (q, C-2), 168.1 (q, COO). – IR (CH_2Cl_2): ν = 3449 (NH), 1716 (CO), 1573 (arene) cm^{-1} . – MS (EI), m/z (%) = 223/225 (M^+ , 100), 192 (95), 164 (35), 158 (5), 128 (15), 102 (5). – HRMS: calcd 223.0400, found 223.0402.

7-Chloro-3-methyl-1H-indole-4-carboxylic acid methyl ester (13c): 11%. – ^1H NMR (400 MHz,

 CDCl_3): δ = 2.41 (s, 3 H, C_3CH_3), 3.96 (s, 3 H, OCH_3), 7.14 (m, 1 H, 2-H), 7.19 (d, 3J = 8.08 Hz, 1 H, 6-H), 7.59 (d, 3J = 8.08 Hz, 1 H, 5-H), 8.34 (bs, 1 H, NH). – ^{13}C NMR (100 MHz, CDCl_3): δ = 13.5 (+, C_3CH_3), 52.0 (+, OCH_3), 114.1 (q, C-3), 120.5 (+, C-5), 121.0 (q, C-4), 123.1 (q, C-7), 123.4 (+, C-2), 125.8 (+, C-6), 126.9 (q, C-3a), 134.9 (q, C-7a), 168.3 (q, COO). – IR (CH_2Cl_2): ν = 3460 (NH), 1720 (CO), 1617 (arene) cm^{-1} . – MS (EI), m/z (%) = 223/225 (M^+ , 100), 208 (10), 192 (55), 163 (70), 128 (20), 117 (5), 101 (7), 95 (5), 75 (5), 57 (5). – HRMS: calcd 223.0400, found 223.0399.

*7-Chloro-2,3-dimethyl-1*H*-indole-4-carboxylic acid methyl ester (13d):* 37%. – ^1H NMR (400 MHz, CDCl_3): δ = 2.29 (s, 3 H, C3CH_3), 2.42 (s, 3 H, C2CH_3), 3.94 (s, 3 H, OCH_3), 7.09 (d, 3J = 8.08 Hz, 1 H, 6-H), 7.50 (d, 3J = 8.08 Hz, 1 H, 5-H), 8.16 (bs, 1 H, NH). – ^{13}C NMR (100 MHz, CDCl_3): δ = 11.7 (+, C3CH_3), 12.2 (+, C2CH_3), 52.0 (+, OCH_3), 109.4 (q, C-3), 119.4 (+, C-5), 119.8 (q, C-4), 122.1 (q, C-7), 123.1 (+, C-6), 129.0 (q, C-3a), 131.0 (q, C-2), 134.8 (q, C-7a), 168.6 (q, COOMe). – IR (CH_2Cl_2): ν = 3451 (NH), 1718 (CO), 1619 (arene) cm^{-1} . – MS (EI), m/z (%) = 237/239 (M^+ , 75), 222 (25), 206 (40), 177 (100), 149 (20), 115 (20). – HRMS: calcd 237.0557, found 237.0559.

*7-Methyl-1*H*-indole-5-carboxylic acid methyl ester (14a):* 37%. – ^1H NMR (400 MHz, CDCl_3): δ = 2.53 (s, 3 H, C7CH_3), 3.93 (s, 3 H, OCH_3), 6.65 (dd, 3J = 3.15, 4J = 2.02 Hz, 1 H, 3-H), 7.25 (dd, 3J = 3.15, 4J = 2.52 Hz, 1 H, 2-H), 7.72 (s, 1 H, 6-H), 8.23 (bs, 1 H, NH), 8.27 (s, 1 H, 4-H). – ^{13}C NMR (100 MHz, CDCl_3): δ = 16.7 (+, C7CH_3), 51.9 (+, OCH_3), 104.8 (+, C-3), 120.1 (q, C-5), 121.9 (+, C-4), 122.4 (q, C-7), 123.8 (+, C-2), 125.2 (+, C-6), 127.2 (q, C-3a), 138.3 (q, C-7a), 168.5 (q, COO). – IR (CH_2Cl_2): ν = 3467 (NH), 1708 (CO), 1608 (arene) cm^{-1} . – MS (EI), m/z (%) = 189 (M^+ , 75), 158 (100), 130 (60), 103 (15), 77 (17). – HRMS: calcd 189.0790, found 189.0792.

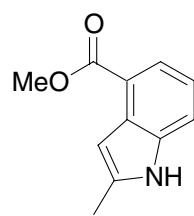
*2,7-Dimethyl-1*H*-indole-5-carboxylic acid methyl ester (14b):* 12%. – ^1H NMR (400 MHz, CDCl_3): δ = 2.48 (d, 4J = 0.88 Hz, 3 H, C2CH_3), 2.49 (s, 3 H, C7CH_3), 3.91 (s, 3 H, OCH_3), 6.31 (q, 4J = 1.01 Hz, 1 H, 3-H), 7.65 (q, 4J = 0.84 Hz, 1 H, 6-H), 7.94 (bs, 1 H, NH), 8.12 (s, 1 H, 4-H). – ^{13}C NMR (100 MHz, CDCl_3): δ = 13.9 (+, C2CH_3), 16.7 (+, C7CH_3), 51.9 (+, OCH_3), 102.4 (+, C-3), 119.2 (q, C-5), 120.7 (+, C-4), 122.0 (q, C-7), 123.0 (+, C-6), 128.3 (q, C-3a), 136.2 (q, C-2), 138.5 (q, C-7a), 168.6 (q, COO). – IR (CH_2Cl_2): ν = 3692 (NH), 1789 (CO), 1550 (arene) cm^{-1} . – MS (EI), m/z (%) = 203 (M^+ , 65), 179 (65), 172 (70), 148 (100), 135 (20). – HRMS: calcd 203.0946, found 203.0937.

*3,7-Dimethyl-1*H*-indole-5-carboxylic acid methyl ester (14c):* 12%. – ^1H NMR (400 MHz, CDCl_3): δ = 2.36 (d, 4J = 0.89 Hz, 3 H, C3CH₃), 2.49 (s, 3 H, C7CH₃), 3.93 (s, 3 H, OCH₃), 7.02 (s, 1 H, 2-H), 7.71 (s, 1 H, 6-H), 8.13 (bs, 1 H, NH), 8.22 (s, 1 H, 4-H). – ^{13}C NMR (100 MHz, CDCl_3): δ = 9.8 (+, C3CH₃), 16.6 (+, C7CH₃), 51.9 (+, OCH₃), 113.8 (q, C-3), 120.0 (+, C-4), 121.5 (q, C-5), 122.6 (+, C-2), 123.6 (+, C-6), 127.7 (q, C-7), 129.5 (q, C-3a), 138.7 (q, C-7a), 168.6 (q, COO). – IR (CH_2Cl_2): ν = 3469 (NH), 1707 (CO), 1614 (arene) cm^{-1} . – MS (EI), m/z (%) = 203 (M⁺, 100), 172 (95), 144 (50), 135 (30). – HRMS: calcd 203.0946, found 203.0939.

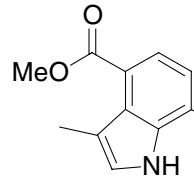
*2,3,7-Trimethyl-1*H*-indole-5-carboxylic acid methyl ester (14d):* 13%. – ^1H NMR (400 MHz, CDCl_3): δ = 2.17 (s, 3 H, C3CH₃), 2.24 (s, 3 H, C7CH₃), 2.39 (s, 3 H, C3CH₃), 3.92 (s, 3 H, OCH₃), 7.64 (s, 1 H, 6-H), 7.74 (bs, 1 H, NH), 8.10 (s, 1 H, 4-H). – ^{13}C NMR (100 MHz, CDCl_3): δ = 8.6 (+, C3CH₃), 11.7 (+, C2CH₃), 16.5 (+, C7CH₃), 51.9 (+, OCH₃), 109.2 (q, C-3), 114.7 (q, C-5), 119.0 (+, C-4), 121.2 (q, C-7), 123.1 (+, C-6), 128.8 (q, C-2), 129.5 (q, C-3a), 137.7 (q, C-7a), 168.8 (q, COO). – IR (CH_2Cl_2): ν = 3460 (NH), 1707 (CO), 1550 (arene) cm^{-1} . – MS (EI), m/z (%) = 217 (M⁺, 10), 166 (45), 135 (100), 107 (15), 77 (20). – HRMS: calcd 217.1103, found 217.1106.

*7-Fluoro-1*H*-indole-4-carboxylic acid methyl ester (15a):* 18%. – ^1H NMR (400 MHz, CDCl_3): δ = 3.98 (s, 3 H, OCH₃), 6.94 (dd, 3J = 10.35, $^3J_{\text{HF}}$ = 8.31 Hz, 1 H, 5-H), 7.22 (ddd, J = 5.55, 3.28, 2.27 Hz, 1 H, 2-H), 7.37 (dd, J = 2.78, 2.91 Hz, 1 H, 3-H), 7.89 (dd, J = 8.31, 7.80 Hz, 1 H, 3-H), 8.50 (bs, 1 H, NH). – ^{13}C NMR (100 MHz, CDCl_3): δ = 51.9 (+, OCH₃), 105.2 (+, J = 1.8 Hz, C-3), 106.8 (+, J = 17.4 Hz, C-6), 124.7 (q, J = 13.0 Hz, C-4), 125.1 (+, J = 7.6 Hz, C-2), 126.8 (+, C-5), 129.5 (q, C-7a), 131.6 (q, C-3a), 152.5 (q, J = 251.7 Hz, C-7), 167.3 (q, COOMe). – ^{19}F NMR (300 MHz, CDCl_3): δ = -128.39 (s, F). – IR (CH_2Cl_2): ν = 3463 (NH), 1712 (CO), 1580 (arene) cm^{-1} . – MS (EI), m/z (%) = 193 (M⁺, 85), 183 (5), 169 (7), 162 (100), 138 (5), 134 (40), 107 (12), 81 (5). – HRMS: calcd 193.0529, found 193.0539.

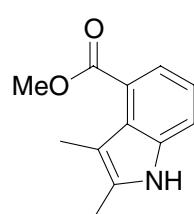
*7-Fluoro-2-methyl-1*H*-indole-4-carboxylic acid methyl ester (15b):* 19%. – ^1H NMR (400 MHz,

 CDCl_3): δ = 2.51 (d, 3J = 0.76 Hz, 3 H, C2CH₃), 3.96 (s, 3 H, OCH₃), 6.85 (dd, 3J = 10.36, $^3J_{\text{HF}}$ = 8.34 Hz, 1 H, 5-H), 6.89 (m, 1 H, 3-H), 7.82 (dd, J = 8.34, 4.80 Hz, 1 H, 6-H), 8.19 (bs, 1 H, NH). – ^{13}C NMR (100 MHz, CDCl_3): δ = 13.9 (+, C2CH₃), 51.8 (+, OCH₃), 103.3 (+, J = 1.8 Hz, C-3), 106.0 (+, J = 17.6 Hz, C-6), 117.0 (q, J = 3.2 Hz, C-4), 124.4 (q, C-7a), 126.8 (+, C-5), 133.0 (q, C-3a), 138.4 (q, C-2), 151.5 (q, J = 250.5 Hz, C-7), 167.5 (q, COO). – ^{19}F NMR (300 MHz, CDCl_3): δ = -129.17 (s, 1 F). – IR (CH_2Cl_2): ν = 3455 (NH), 1710 (CO), 1582 (arene) cm^{-1} . – MS (EI), m/z (%) = 207 (M⁺, 80), 176 (100), 148 (62). – HRMS: calcd 207.0696, found 207.0693.

*7-Fluoro-3-methyl-1*H*-indole-4-carboxylic acid methyl ester (15c):* 20%. – ^1H NMR (400 MHz,

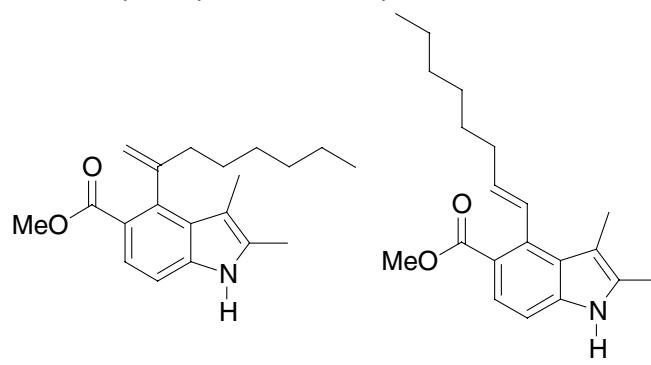
 CDCl_3): δ = 2.42 (d, 3J = 0.95 Hz, 3 H, C3CH₃), 3.95 (s, 3 H, OCH₃), 6.89 (dd, 3J = 10.17, $^3J_{\text{HF}}$ = 8.29 Hz, 1 H, 5-H), 7.12 (m, 1 H, 2-H), 7.64 (dd, J = 8.23, 5.08 Hz, 1 H, 6-H), 8.29 (bs, 1 H, NH). – ^{13}C NMR (100 MHz, CDCl_3): δ = 13.5 (+, C3CH₃), 51.9 (+, OCH₃), 106.1 (+, J = 17.4 Hz, C-6), 114.0 (q, J = 1.8 Hz, C-3), 121.5 (q, C-4), 124.1 (+, J = 7.2 Hz, C-2), 125.0 (+, C-5), 126.9 (q, J = 19.1 Hz, C-7a), 152.0 (q, J = 249.5 Hz, C-7), 168.1 (q, COOMe). – ^{19}F NMR (300 MHz, CDCl_3): δ = -130.34 (s, 1 F). – IR (CH_2Cl_2): ν = 3455 (NH), 1718 (carbonyl), 1572 (arene) cm^{-1} . – MS (EI), m/z (%) = 207 (M⁺, 100), 192 (10), 176 (60), 147 (75), 136 (5), 128 (10), 101 (7), 87 (7). – HRMS: calcd 207.0696, found 207.0701.

*7-Fluoro-2,3-dimethyl-1*H*-indole-4-carboxylic acid methyl ester (15d): 14%. – ¹H NMR*



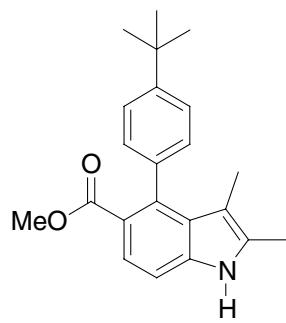
(400 MHz, CDCl₃): δ = 2.20 (d, ³J = 0.38 Hz, 3 H, C3CH₃), 2.32 (s, 3 H, C2CH₃), 3.84 (s, 3 H, OCH₃), 6.70 (dd, ³J = 10.10, ³J_{HF} = 8.34 Hz, 1 H, 5-H), 7.45 (dd, J = 8.34, 5.05 Hz, 1 H, 6-H), 7.99 (bs, 1 H, NH). – ¹³C NMR (100 MHz, CDCl₃): δ = 11.5 (+, J = 1.2 Hz, C3CH₃), 15.4 (+, C2CH₃), 51.9 (+, OCH₃), 105.3 (+, J = 17.2 Hz, C-6), 109.3 (q, J = 1.8 Hz, C-3), 119.5 (q, C-4), 123.8 (+, J = 7.6 Hz, C-5), 126.9 (q, J = 19.1 Hz, C-7a), 130.1 (q, C-2), 134.7 (q, C-3a), 151.3 (q, J = 248.7 Hz, C-7), 168.4 (q, COOMe). – ¹⁹F NMR (300 MHz, CDCl₃): δ = -131.33 (s, 1 F). – IR (CH₂Cl₂): ν = 3457 (NH), 1718 (CO), 1572 (arene) cm⁻¹. – MS (EI), m/z (%) = 221 (M⁺, 82), 206 (25), 190 (50), 161 (100), 115 (10). – HRMS: calcd 221.0852, found 221.0854.

*4-(1-Hexyl-vinyl)-2,3-dimethyl-1*H*-indole-5-carboxylic acid methyl ester (15f) and 2,3-dimethyl-4-oct-1-enyl-1*H*-indole-5-carboxylic acid methyl ester (15g): Inseparable mixture of both regio isomers (f,g). 18 %. – ¹H NMR*



(400 MHz, CDCl₃): δ = 0.78 (m, 6 H, CH₂CH₃ f+g), 2.25 (s, 3 H, C3CH₃), 1.16-1.36 (m, 17 H, CH₂), 1.91 (m, 2 H, CH₂), 2.13, 2.15 (s, 2 × 3 H, C3CH₃ f+g), 2.31 (s, 6 H, C2CH₃ f+g), 2.33 (m, 1 H, CH₂), 3.78, 3.81 (s, 2 × 3 H, OCH₃ f+g), 4.98 (s, 1 H, C_q=CHH), 5.31 (s, 1 H, C_q=CHH), 5.40-5.61 (m, 1 H, CHCH₂, g), 7.05 (d, 1 H, CHCH, f), 7.24-7.30 (m, 2 H, Ar-H), 7.60-7.68 (m, 2 H, Ar-H), 7.87, 7.90 (bs, 2 × 1 H, NH, f+g). – ¹³C NMR (100 MHz, CDCl₃): δ = 8.6, 8.9 (+, C3CH₃, f+g), 12.3 (+, C2CH₃, f+g), 14.5, 14.5 (+, CH₂CH₃ f+g), 23.0, 23.1 (-, CH₂CH₃, f+g), 29.0, 29.6, 29.8, 31.9, 32.2, 32.6, 32.9 (-, 7 × CH₂, f+g), 38.2 (-, C_q-CH₂CH₂, f), 52.0, 52.1(+, OCH₃, f+g), 108.5, 108.6 (+, C-3, f+g), 112.7 (-, C_qCH₂, f), 116.0, 116.4 (q, C-7, f+g), 119.8 (q, C-5, f), 121.6 (q, C-5, g), 128.7 (+, CH₂CHCH₂, g), 125.4, 129.7 128.3 (+, C-6, f+g), 132.5 (+, C-2, f+g), 134.9, 135.5 (q, C-4, f+g), 149.0 (q, C-7a, f+g), 168.7, 169.5 (q, COOMe, f+g). – IR (CH₂Cl₂): ν = 3457 (NH), 1708 (CO), 1609 (arene) cm⁻¹. – MS (EI), m/z (%) = 313 (M⁺, 100), 282 (15), 254 (10), 242 (35), 228 (10), 216 (20), 211 (15), 182 (10), 164 (5), 130 (5). – HRMS: calcd 313.2042, found 313.2044.

*4-(4-tert-Butyl-phenyl)-2,3-dimethyl-1*H*-indole-5-carboxylic acid methyl ester (15h): 15 %. –*



¹H NMR (400 MHz, CDCl₃): δ = 1.40 (s, 9 H, *t*-Bu), 2.25 (s, 3 H, C3CH₃), 2.32 (s, 3 H, C2CH₃), 3.63 (s, 3 H, OCH₃), 7.30 (m, 2 H, Ar-H), 7.48 (m, 3 H, Ar-H), 7.65 (bs, 1 H, NH), 7.75 (d, ³J = 8.33 Hz, 1 H, 4-H). – *¹³C NMR* (100 MHz, CDCl₃): δ = 8.6 (+, C3CH₃), 11.9 (+, C2CH₃), 31.6 (+, *t*-Bu), 35.1 (q, *t*-Bu), 51.6 (+, OCH₃), 108.2 (q, C-7), 114.9 (q, C-3), 116.6 (+, C-5), 121.5 (+, C-6), 121.6 (q, C-2), 125.4 (+, C-2',6'), 126.5 (q, C-1'), 127.0 (q, C-7a), 128.9 (+, C-3',5'), 135.0 (q, C-4'), 150.2 (q, C-3a), 169.0 (q, COOMe). – *IR* (CH₂Cl₂): ν = 3453 (NH), 1715 (CO), 1612 (arene) cm⁻¹. – *MS* (EI), *m/z* (%) = 335 (M⁺, 25), 322 (25), 307 (65), 283 (100), 268 (90), 251 (50), 226 (10), 203 (10), 196 (7), 167 (10), 149 (10), 135 (25), 111 (7), 97 (10), 83 (7), 57 (15). – *HRMS*: calcd 335.1885, found 335.1885.