Electronic Supplementary Material (ESI) for Green Chemistry.

ELECTRONIC SUPPORTING INFORMATION

Practical and Sustainable Preparation of Pyrrolo[2,3-*b*]indoles by Cu/Fe Catalyzed Intramolecular C(sp^2)−H Amination

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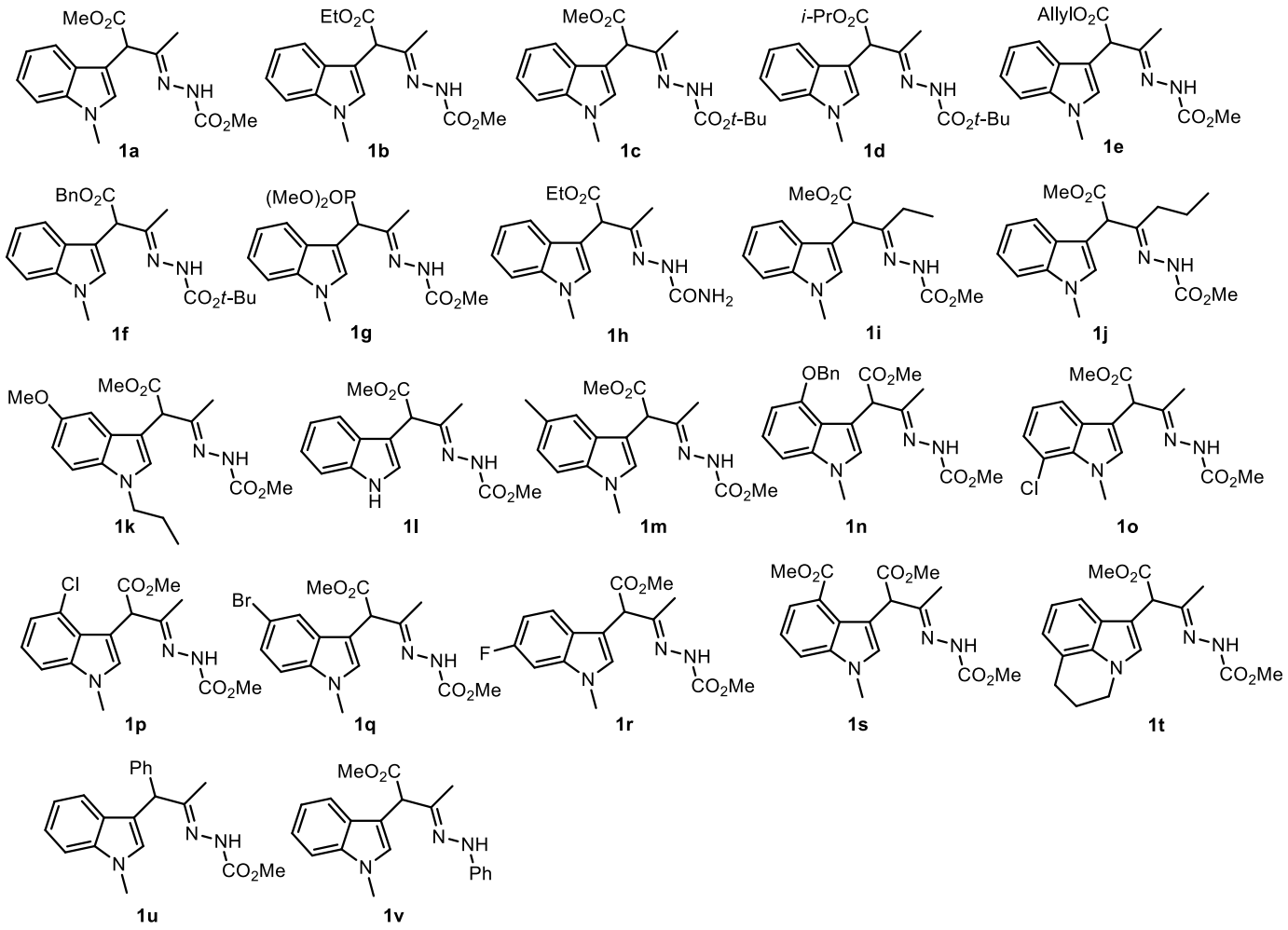
1. General Remarks

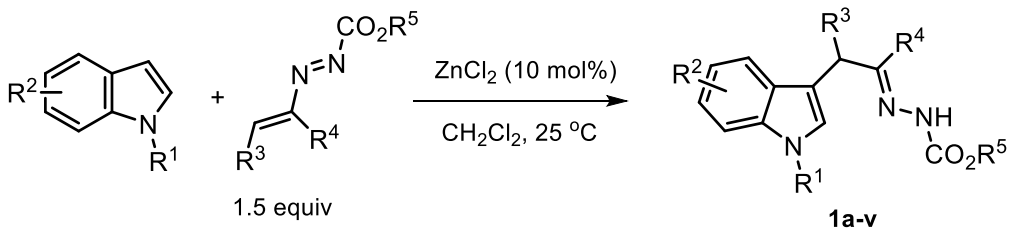
All the commercially available reagents and solvents were used without further purification. α-(Indol-3-yl)hydrazones **1a–v** were prepared according to our previously reported method with a slight modification.[1,2] Chromatographic purification of compounds was carried out on silica gel (60–200 μm). TLC analysis was performed on pre-loaded (0.25 mm) glass supported silica gel plates (Kieselgel 60); compounds were visualized by exposure to UV light and by dipping the plates in 1% $Ce(SO_4)\cdot 4H_2O$, 2.5% $(NH_4)_6Mo_7O_{24}\cdot 4H_2O$ in 10% sulphuric acid followed by heating on a hot plate. All ^{1}H NMR and ^{13}C NMR spectra were recorded at 400 and 100 MHz using DMSO-d_6 or $CDCl_3$ as solvent on a Bruker Ultrashield 400 spectrometer (Bruker, Billerica, MA, USA). Chemical shift (δ scale) are reported in parts per million (ppm) relative to the central peak of the solvent and are sorted in descending order within each group. The following abbreviations are used to describe peak patterns where appropriate: s = singlet, d = doublet, dd = doublet of doublet, dt = doublet of triplet, t = triplet, q = quartet, sept = septet, m = multiplet and br = broad signal. All coupling constants (J value) are given in Hertz [Hz]. High-resolution mass spectral (HRMS) analyses were performed using Orbitrap Exploris 240 Mass Spectrometers (Thermo Scientific) equipped with an ESI source. Melting points were determined in open capillary tubes and are uncorrected.

2. Synthesis and characterization of substrates

List of substrates **1a–v** prepared according to the general procedures.[1,2]

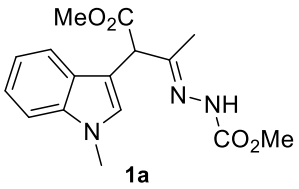


2.1. Procedure for the synthesis of α-(indol-3-yl)hydrazones **1a–v**[1,2]:



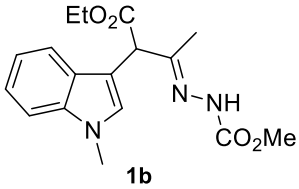
To a stirred mixture of indole (1 mmol) and azoalkene (1.5 mmol, 1.5 equiv) in dichloromethane (4 mL), zinc dichloride (13.6 mg, 0.1 mmol, 10 mol %) was added. After the disappearance of indole (0.25–18 h, TLC check), the solvent was removed and the crude mixture was purified by column chromatography on silica gel to afford, after crystallization, the α-(indol-3-yl)hydrazones **1** (23–95% yields).

2.2 Characterization of substrates



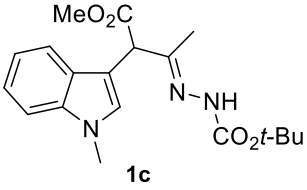
1a

Methyl 2-(4-methoxy-3-(1-methyl-1*H*-indol-3-yl)-4-oxobutan-2-lidene)hydrazinecarboxylate (1a): The chemical-physical data of compound **1a** are in agreement with those reported.[2]



1b

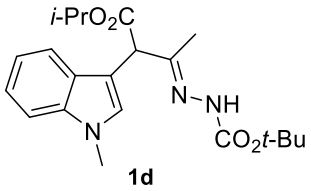
Methyl 2-(4-ethoxy-3-(1-methyl-1*H*-indol-3-yl)-4-oxobutan-2-ylidene)hydrazinecarboxylate (1b): The chemical-physical data of compound **1b** are in agreement with those reported.[2]



1c

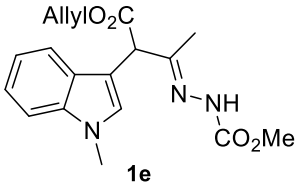
***tert*-Butyl 2-(4-methoxy-3-(1-methyl-1*H*-indol-3-yl)-4-oxobutan-2-ylidene)hydrazinecarboxylate (1c):** Compound **1c** was isolated by column chromatography (ethyl acetate/cyclohexane 35:65) in 60% yield (216.6 mg), 1 h; white solid; mp: 138−140 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.57 (br, 1H), 7.45 (d, J = 8.0 Hz, 1H), 7.41 (d, J = 8.4 Hz, 1H), 7.32 (s, 1H), 7.17−7.13 (m, 1H), 7.04−7.00 (m, 1H), 4.83 (s, 1H), 3.77 (s, 3H), 3.66 (s, 3H), 1.76 (s, 3H), 1.45 (s, 9H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 171.2, 153.0, 150.2, 136.5, 128.5, 126.8, 121.3, 118.9, 118.7, 109.8, 107.6, 79.1,

51.9, 51.3, 32.4, 28.1, 14.5. HRMS (ESI-Orbitrap, *m/z*): $[M+H]^+$ calcd for $C_{19}H_{25}N_3O_4$ 360.1918, found 360.1923.



1d

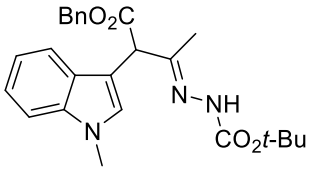
***tert*-Butyl 2-(4-isopropoxy-3-(1-methyl-1*H*-indol-3-yl)-4-oxobutan-2-ylidene)hydrazinecarboxylate: (1d):** The chemical-physical data of compound **1d** are in agreement with those reported.[2]



1e

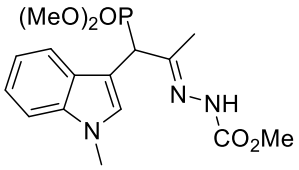
Methyl 2-(4-(allyloxy)-3-(1-methyl-1*H*-indol-3-yl)-4-oxobutan-2-ylidene)hydrazinecarboxylate: (1e):

The chemical-physical data of compound **1e** are in agreement with those reported.[2]



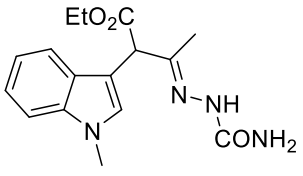
1f

***tert*-Butyl 2-(4-(benzyloxy)-3-(1-methyl-1*H*-indol-3-yl)-4-oxobutan-2-ylidene)hydrazinecarboxylate (1f):** The chemical-physical data of compound **1f** are in agreement with those reported.[2]



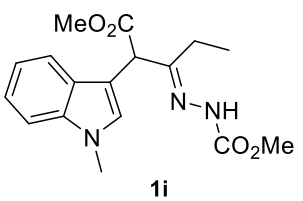
1g

Methyl 2-(1-(dimethoxyphosphoryl)-1-(1-methyl-1*H*-indol-3-yl)propan-2-ylidene)hydrazinecarboxylate: (1g): The chemical-physical data of compound **1g** are in agreement with those reported.[2]



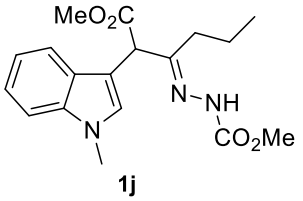
1h

Ethyl 3-(2-carbamoylhydrazono)-2-(1-methyl-1*H*-indol-3-yl)butanoate: (1h): The chemical-physical data of compound **1h** are in agreement with those reported.[2]



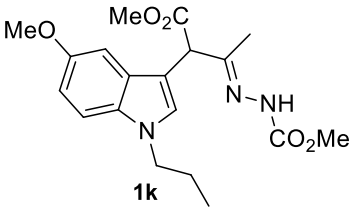
1i

Methyl 2-(1-methoxy-2-(1-methyl-1*H*-indol-3-yl)-1-oxopentan-3-ylidene)hydrazinecarboxylate: (1i): The chemical-physical data of compound **1i** are in agreement with those reported.[2]



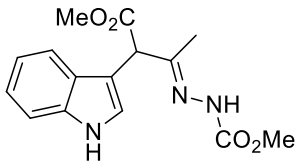
1j

Methyl 2-(1-methoxy-2-(1-methyl-1H-indol-3-yl)-1-oxohexan-3-ylidene)hydrazinecarboxylate: (1j): The chemical-physical data of compound **1j** are in agreement with those reported.[2]



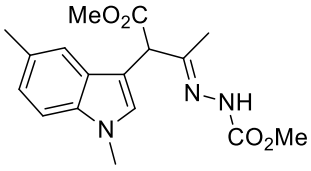
1k

Methyl 2-(4-methoxy-4-oxo-3-(1-propyl-1*H*-indol-3-yl)butan-2-ylidene)hydrazinecarboxylate: (1k): The chemical-physical data of compound **1k** are in agreement with those reported.[2]



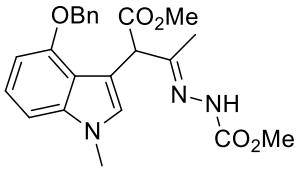
1l

Methyl 2-(3-(1*H*-indol-3-yl)-4-methoxy-4-oxobutan-2-ylidene)hydrazinecarboxylate: (1l): The chemical-physical data of compound **1l** are in agreement with those reported.[2]



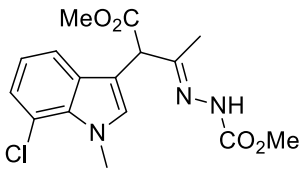
1m

Methyl 2-(3-(1,5-dimethyl-1*H*-indol-3-yl)-4-methoxy-4-oxobutan-2-ylidene)hydrazinecarboxylate: (1m): The chemical-physical data of compound **1m** are in agreement with those reported.[2]



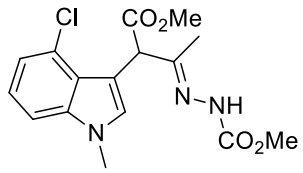
1n

Methyl 2-(3-(4-(benzyloxy)-1-methyl-1*H*-indol-3-yl)-4-methoxy-4-oxobutan-2-ylidene)hydrazinecarboxylate: (1n): The chemical-physical data of compound **1n** are in agreement with those reported.[2]



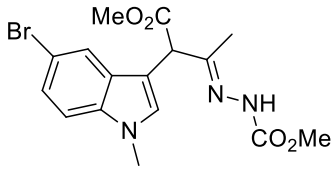
1o

Methyl 2-(3-(7-chloro-1-methyl-1*H*-indol-3-yl)-4-methoxy-4-oxobutan-2-ylidene)hydrazinecarboxylate: (1o): The chemical-physical data of compound **1o** are in agreement with those reported.[2]



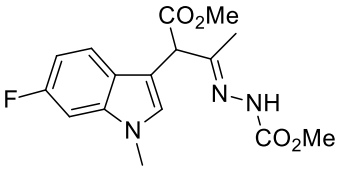
1p

Methyl 2-(3-(4-chloro-1-methyl-1*H*-indol-3-yl)-4-methoxy-4-oxobutan-2-ylidene)hydrazinecarboxylate: (1p): The chemical-physical data of compound **1p** are in agreement with those reported.[2]



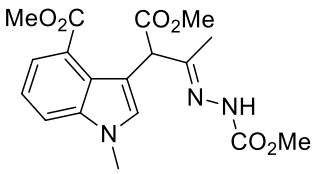
1q

Methyl 2-(3-(5-bromo-1-methyl-1*H*-indol-3-yl)-4-methoxy-4-oxobutan-2-ylidene)hydrazinecarboxylate: (1q): The chemical-physical data of compound **1q** are in agreement with those reported.[2]



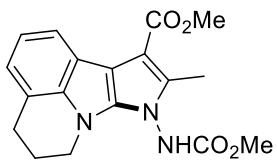
1r

Methyl 2-(3-(6-fluoro-1-methyl-1*H*-indol-3-yl)-4-methoxy-4-oxobutan-2-ylidene)hydrazinecarboxylate: (1r): The chemical-physical data of compound **1r** are in agreement with those reported.[2]



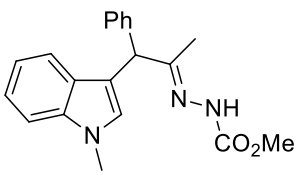
1s

Methyl 3-(1-methoxy-3-(2-(methoxycarbonyl)hydrazono)-1-oxobutan-2-yl)-1-methyl-1*H*-indole-4-carboxylate: (1s): The chemical-physical data of compound **1s** are in agreement with those reported.[2]



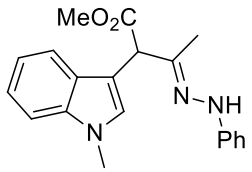
1t

Methyl 2-(3-(5,6-dihydro-4*H*-pyrrolo[3,2,1-*ij*]quinolin-1-yl)-4-methoxy-4-oxobutan-2-ylidene)hydrazinecarboxylate: (1t): The chemical-physical data of compound **1t** are in agreement with those reported.[2]



1u

Methyl 2-(1-(1-methyl-1*H*-indol-3-yl)-1-phenylpropan-2-ylidene)hydrazinecarboxylate: (1u): The chemical-physical data of compound **1u** are in agreement with those reported.[2]



1v

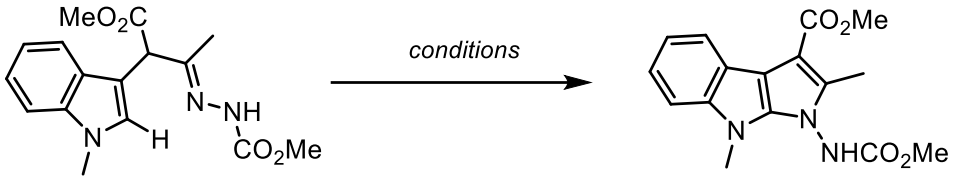
Methyl 2-(1-methyl-1*H*-indol-3-yl)-3-(2-phenylhydrazono)butanoate (1v): Compound **1v** was isolated by column chromatography (ethyl acetate/cyclohexane 30:70) in 64% yield (215.0 mg), 4 h; pale yellow solid; mp: 121−122 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.90 (s, 1H), 7.50 (d, *J* = 8.0 Hz, 1H), 7.41 (d, *J* = 8.0 Hz, 1H), 7.32 (s, 1H), 7.20–7.12 (m, 3H), 7.10–7.07 (m, 2H), 7.02–6.98 (m, 1H), 6.74–6.69 (m, 1H), 4.91 (s, 1H), 3.77 (s, 3H), 3.69 (s, 3H), 1.83 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 171.6, 146.3, 142.7, 136.6, 128.8, 128.4, 127.0, 121.2, 118.9, 118.8, 118.4, 112.4, 109.7, 108.3, 51.8, 51.3, 32.4, 14.1. HRMS (ESI-Orbitrap, *m/z*): $[M+H]^+$ calcd for $C_{20}H_{21}N_3O_2$ 336.1707, found: 336.1701.

3. Copper-Iron catalyzed Intramolecular C(sp^2)−H Amination

3.1 Preliminary optimization studies

Optimization of Reaction Conditions for the Intramolecular Oxidative Cyclization of 1a (Table S1). First, we tested the conversion of α-indolylhydrazone **1a** to 1-amino pyrrolo[2,3-*b*]indole **2a** using a combination of a palladium catalyst and an oxidant. To our delight, product **2a** was obtained in 90% yield in the presence of $Pd(OAc)_2$ (0.1 mmol) and AgOAc (2 equiv) in DCM at room temperature (entry 1). A further investigation of the process revealed that the palladium catalyst was not needed since both $Cu(OAc)_2{\cdot}H_2O$ (0.1 mmol) or $FeCl_3{\cdot}6H_2O$ (0.1 mmol) alone catalyze the reaction albeit with scarce yield and poor conversion (entries 2 and 3). On the other hand, we were pleased to find that the intramolecular C–N coupling was successful in the presence of catalytic amounts of both $Cu(OAc)_2{\cdot}H_2O$ and $FeCl_3{\cdot}6H_2O$ (82% yield, entry 4). A comparable yield of **2a** (76%) within a shorter reaction time was registered when the reaction was conducted in DCE at 50 °C (entry 5). Extra additives such as acid (PivOH) and base (K_2CO_3) gave inferior results (entries 6 and 7). Doubling the co-catalyst loading led to a slightly increase in the yield of **2a** (entry 8). A contextual reducing of the half the amount of catalyst (0.05 mmol) and doubling that of co-catalyst (0.1 mmol) did not lead to a significant improvement in yield (76%, entry 9). Other copper salts with different oxidation states (I, II) tested (e.g., CuO, $Cu(OTf)_2$, $CuCl_2$, CuI, and CuCl) in combination with $FeCl_3{\cdot}6H_2O$ co-catalyst also performed well (entries 10–14). Finally, different solvents were explored, and the best result was obtained when acetone/H_2O, or neat H_2O was used, albeit with slower conversion for the latter (entries 15–20). Based on these preliminary studies and considering the economic and environmental issue we decided to employ H_2O as a solvent for the transformation. Therefore, conditions involving 10 mol% of $Cu(OAc)_2{\cdot}H_2O$ and 5 mol% of $FeCl_3{\cdot}6H_2O$ in H_2O at room temperature were selected as base to further optimize this intramolecular C–H amination.

Table S1: Preliminary experiments[a]



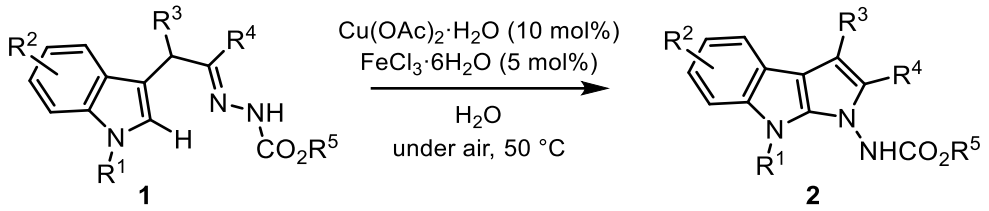
1a **2a**

entry	catalyst [equiv.]	co-catalyst [equiv.]	additive [equiv.]	solvent	t [h]	yield [%][b]
1[c]	$Pd(OAc)_2$ (0.1)	–	–	DCM	3	90
2	$FeCl_3 \cdot 6H_2O$ (0.1)	–	–	DCM	12	28[d,e]
3	$Cu(OAc)_2 \cdot H_2O$ (0.1)	–	–	DCM	12	33
4	$Cu(OAc)_2 \cdot H_2O$ (0.1)	$FeCl_3 \cdot 6H_2O$ (0.05)	–	DCM	5	82
5	$Cu(OAc)_2 \cdot H_2O$ (0.1)	$FeCl_3 \cdot 6H_2O$ (0.05)	–	DCE[f]	0.8	76
6	$Cu(OAc)_2 \cdot H_2O$ (0.1)	$FeCl_3 \cdot 6H_2O$ (0.05)	PivOH (5.0)	DCM	18	60
7	$Cu(OAc)_2 \cdot H_2O$ (0.1)	$FeCl_3 \cdot 6H_2O$ (0.05)	K_2CO_3 (2.0)	DCM	6	47
8	$Cu(OAc)_2 \cdot H_2O$ (0.1)	$FeCl_3 \cdot 6H_2O$ (0.1)	–	DCM	4	83
9	$Cu(OAc)_2 \cdot H_2O$ (0.05)	$FeCl_3 \cdot 6H_2O$ (0.1)	–	DCM	5	76
10	CuO (0.1)	$FeCl_3 \cdot 6H_2O$ (0.05)	–	DCM	4	83
11	$Cu(OTf)_2$ (0.1)	$FeCl_3 \cdot 6H_2O$ (0.05)	–	DCM	8	76
12	$CuCl_2$ (0.1)	$FeCl_3 \cdot 6H_2O$ (0.05)	–	DCM	12	82
13	CuI (0.1)	$FeCl_3 \cdot 6H_2O$ (0.05)	–	DCM	24	79
14	CuCl (0.1)	$FeCl_3 \cdot 6H_2O$ (0.05)	–	DCM	24	68
15	$Cu(OAc)_2 \cdot H_2O$ (0.1)	$FeCl_3 \cdot 6H_2O$ (0.05)	–	toluene	24	trace[d]
16	$Cu(OAc)_2 \cdot H_2O$ (0.1)	$FeCl_3 \cdot 6H_2O$ (0.05)	–	MeCN	1	35
17	$Cu(OAc)_2 \cdot H_2O$ (0.1)	$FeCl_3 \cdot 6H_2O$ (0.05)	–	MeOH	1	54
18	$Cu(OAc)_2 \cdot H_2O$ (0.1)	$FeCl_3 \cdot 6H_2O$ (0.05)	–	Me_2CO	1	57
19	$Cu(OAc)_2 \cdot H_2O$ (0.1)	$FeCl_3 \cdot 6H_2O$ (0.05)	–	H_2O(9)/ Me_2CO(1)	3	95[g]
20	$Cu(OAc)_2 \cdot H_2O$ (0.1)	$FeCl_3 \cdot 6H_2O$ (0.05)	–	H_2O	24	99[g]

[a]All reaction were performed on 0.2 mmol scale of **1a** in 2 mL of solvent (0.1 M) under air atmospher for the indicate time. [b]All yields refer to the isolated product after column chromatography, unless otherwise noted. [c]AgOAc (2.0 eq.) as an external oxidant was used. [d]The unreacted

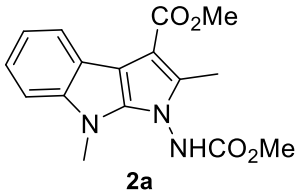
starting material was recovered. [e]38% Yield of **2a** with complete consumption of **1a** was observed with 1.0 equiv. of $FeCl_3·6H_2O$. [f]Performed at 50 °C. [g]Without column chromatography.

3.2 Procedure for the synthesis of products **2a–t**



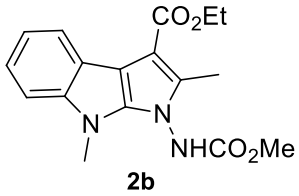
In a round-bottom flask, α-indolylhydrazone **1** (0.2 mmol), $Cu(OAc)_2·H_2O$ (0.02 mmol, 4.0 mg), $FeCl_3·6H_2O$ (0.01 mmol, 2.7 mg) and water (2 mL) were added. The aqueous suspension was stirred at 50 °C (oil bath) until consumption of the starting material (TLC check). Then, the reaction mixture was diluted with brine and extracted with ethyl acetate (3 x 10 mL). The organic phase was dried over anhydrous sodium sulphate and the solvent was removed under vacuum. The crude product was purified by crystallization or by flash chromatography on silica gel (cyclohexane/ethyl acetate) to give the corresponding product **2** (52-99% yields).

3.3 Characterization of products



2a

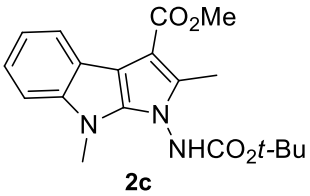
Methyl 1-((methoxycarbonyl)amino)-2,8-dimethyl-1,8-dihydropyrrolo[2,3-*b*]indole-3-carboxylate (2a)[2]: compound **2a** was obtained by simple extraction with ethyl acetate and crystallization from diethyl ether in 99% yield (62.8 mg), 3 h; pale brown solid; The chemical-physical data of compound **2a** are in agreement with those reported.[2] mp: 164–166 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.99 (br, 1H), 7.93 (dd, *J* = 8.0 Hz, 0.8 Hz, 1H), 7.44 (d, *J* = 8.0 Hz, 1H), 7.19–7.14 (m, 1H), 7.12–7.08 (m, 1H), 3.89 (s, 3H), 3.79 (s, 6H), 2.48 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 165.1, 156.2, 139.7, 136.5, 136.3, 120.6, 120.1, 119.7, 119.2, 109.5, 102.7, 102.1, 53.3, 50.9, 29.1, 10.2; HRMS (ESI-Orbitrap, *m/z*): $[M+H]^+$ Calcd for $C_{16}H_{18}N_3O_4$ 316.1292; Found 316.1288.



2b

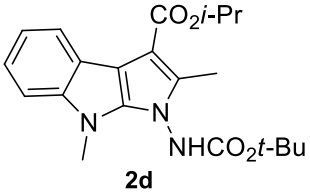
Ethyl 1-((methoxycarbonyl)amino)-2,8-dimethyl-1,8-dihydropyrrolo[2,3-*b*]indole-3-carboxylate (2b): compound **2b** was isolated by column chromatography (ethyl acetate/cyclohexane 40:60) in 71% yield (46.6 mg); 4 h; whitish solid; mp: 149−151 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.04 (br, 1H), 7.96 (d, *J* = 8.0 Hz, 1H), 7.45 (d, *J* = 8.0 Hz, 1H), 7.18–7.14 (m, 1H), 7.12–7.08 (m, 1H), 4.36 (q, *J* = 7.2 Hz, 2H), 3.81 (s, 3H), 3.79 (s, 3H), 2.49 (s, 3H), 1.42 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 164.6, 156.2, 139.7, 136.5, 136.6, 120.5, 120.1, 119.7, 119.1, 109.5, 102.6, 102.4, 59.3,

53.2, 29.1, 14.6, 10.2. HRMS (ESI-Orbitrap, *m/z*): $[M+H]^+$ calcd for $C_{17}H_{19}N_3O_4$ 330.1448, found 330.1452.



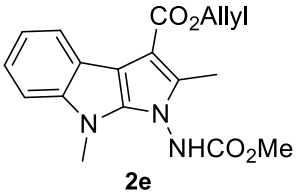
2c

Methyl 1-((*tert*-butoxycarbonyl)amino)-2,8-dimethyl-1,8-dihydropyrrolo[2,3-*b*]indole-3-carboxylate (2c): compound **2c** was isolated by simple extraction with ethyl acetate and crystallization from diethyl ether/petroleum ether in 92% yield (66.0 mg); 4 h; whitish solid; mp: 179–180 ; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.73 (br, 1H), 7.92 (d, *J* = 7.2 Hz, 1H), 7.44 (d, *J* = 8.0 Hz, 1H), 7.18–7.14 (m, 1H), 7.11–7.07 (m, 1H), 3.89 (s, 3H), 3.79 (s, 3H), 2.47 (s, 3H), 1.51 (s, 9H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 165.1, 154.7, 139.7, 136.5, 136.4, 120.5, 120.1, 119.6, 119.1, 109.4, 102.5, 101.8, 81.5, 50.8, 29.0, 27.8, 10.2. HRMS (ESI-Orbitrap, *m/z*): $[M+H]^+$ calcd for $C_{19}H_{23}N_3O_4$ 358.1761, found 358.1752.



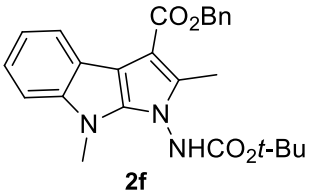
2d

Isopropyl 1-((*tert*-butoxycarbonyl)amino)-2,8-dimethyl-1,8-dihydropyrrolo[2,3-*b*]indole-3-carboxylate (2d): compound **2d** was obtained by simple extraction with ethyl acetate and crystallization from diethyl ether/petroleum ether in 97% yield (74.5 mg); 12 h; pale grey solid; mp: 152–154 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.73 (br, 1H), 7.96 (d, *J* = 7.6 Hz, 1H), 7.43 (d, *J* = 7.6 Hz, 1H), 7.17–7.07 (m, 2H), 5.19 (sept, *J* = 6.4 Hz, 2H), 3.79 (s, 3H), 2.45 (s, 3H), 1.51 (s, 3H), 1.40 (d, *J* = 6.0 Hz, 6H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 164.2, 154.7, 139.7, 136.5, 136.4, 120.4, 120.2, 119.7, 119.1, 109.4, 102.7, 102.6, 81.5, 66.4, 29.0, 27.8, 22.2, 10.4. HRMS (ESI-Orbitrap, *m/z*): $[M+H]^+$ calcd for $C_{21}H_{27}N_3O_4$ 386.2074, found 386.2077.



2e

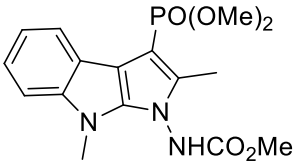
Allyl 1-((methoxycarbonyl)amino)-2,8-dimethyl-1,8-dihydropyrrolo[2,3-*b*]indole-3-carboxylate (2e): compound **2e** was isolated by column chromatography (ethyl acetate/cyclohexane 40:60) in 64% yield (49.2 mg); 20 h; white solid; mp: 134–136 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.06 (br, 1H), 7.94 (d, *J* = 8.0 Hz, 1H), 7.45 (d, *J* = 8.0 Hz, 1H), 7.18–7.14 (m, 1H), 7.10–7.06 (m, 1H), 6.19–6.10 (m, 1H), 5.46–5.40 (m, 1H), 5.32–5.29 (m, 1H), 4.87–4.86 (m, 2H), 3.80 (s, 3H), 3.79 (s, 3H), 2.49 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 164.2, 156.2, 139.7, 136.7, 136.3, 133.4, 120.6, 120.0, 119.7, 119.1, 117.9, 109.5, 102.6, 102.0, 63.9, 53.3, 29.1, 10.2. HRMS (ESI-Orbitrap, *m/z*): $[M+H]^+$ calcd for $C_{18}H_{19}N_3O_4$ 342.1448, found 342.1450.



2f

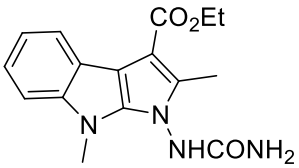
Benzyl 1-((*tert*-butoxycarbonyl)amino)-2,8-dimethyl-1,8-dihydropyrrolo[2,3-*b*]indole-3-carboxylate (2f): compound **2f** was obtained by simple extraction with ethyl acetate and crystallization from ethyl acetate/diethyl ether in 85% yield (74.1 mg); 20 h at 50 °C then 24 h to 70 °C;

brown solid; mp: 188–190 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.76 (br, 1H), 7.77 (d, *J* = 7.6 Hz, 1H), 7.50 (m, 2H), 7.43–7.40 (m, 3H), 7.38–7.34 (m, 1H), 7.11 (t, *J* = 7.6 Hz, 1H), 6.93 (t, *J* = 7.6 Hz, 1H), 5.41 (s, 2H), 3.78 (s, 3H), 2.47 (s, 3H), 1.50 (s, 9H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 164.4, 154.6, 139.6, 136.9, 136.8, 136.4, 128.5, 128.1, 127.9, 120.4, 120.0, 119.8, 119.0, 109.3, 102.6, 101.9, 81.5, 64.9, 29.0, 27.8, 10.2. HRMS (ESI-Orbitrap, *m/z*): $[M+H]^+$ calcd for $C_{25}H_{27}N_3O_4$ 434.2074, found 434.2082.



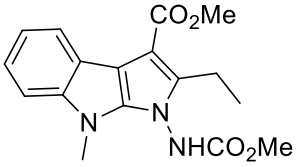
2g

Methyl (3-(dimethoxyphosphoryl)-2,8-dimethylpyrrolo[2,3-*b*]indol-1(8*H*)-yl)carbamate (2g): compound **2g** was obtained by simple extraction with ethyl acetate and crystallization from ethyl acetate/petroleum ether in 99% yield (72.5 mg); 12 h; brown solid; mp: 184–186 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.98 (br, 1H), 7.74 (d, *J* = 8.0 Hz, 1H), 7.45 (d, *J* = 8.0 Hz, 1H), 7.17–7.13 (m, 1H), 7.08 (t, *J* = 7.2 Hz, 1H), 3.80 (s, 3H), 3.78 (s, 3H), 3.65 (d, $^{3}J_{HP}$ = 8.4 Hz, 3H), 3.62 (d, $^{3}J_{HP}$ = 8.4 Hz, 3H), 2.40 (s,3 H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 156.3, 139.6, 137.8 (d, $^{2}J_{CP}$ = 26.2 Hz), 137.0 (d, $^{2}J_{CP}$ = 14.7 Hz), 120.5, 119.7, 119.3, 118.6, 109.6, 104.2 (d, $^{2}J_{CP}$ = 11.0 Hz), 93.4 (d, $^{1}J_{CP}$ = 215 Hz), 53.2, 51.8, 51.7, 29.1, 10.2. HRMS (ESI-Orbitrap, *m/z*): $[M+H]^+$ calcd for $C_{16}H_{20}N_3O_5P$ 366.1213, found 366.1216.



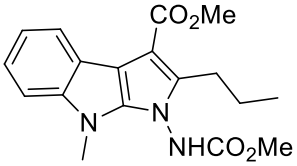
2h

Ethyl 2,8-dimethyl-1-ureido-1,8-dihydropyrrolo[2,3-*b*]indole-3-carboxylate (2h): compound **2h** was obtained by simple extraction with ethyl acetate and crystallization from diethyl ether in 85% yield (53.2 mg); 36 h; grey solid; mp: 240–242 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.55 (br, 1H), 7.95 (d, *J* = 7.6 Hz, 1H), 7.42 (d, *J* = 7.6 Hz, 1H), 7.13 (t, *J* = 7.2 Hz, 1H), 7.07 (t, *J* = 7.2 Hz, 1H), 6.55 (br, 2H), 4.35 (q, *J* = 6.8 Hz, 2H), 3.80 (s, 3H), 2.48 (s, 3H), 1.41 (t, *J* = 6.8 Hz, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 164.8, 157.6, 139.6, 137.3, 137.0, 120.3, 120.2, 119.6, 118.9, 109.3, 102.4, 101.9, 59.1, 29.0, 14.7, 10.4. HRMS (ESI-Orbitrap, *m/z*): $[M+H]^+$ calcd for $C_{16}H_{18}N_4O_3$ 315.1452, found 315.1454.



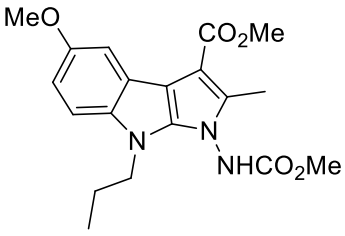
2i

Methyl 2-ethyl-1-((methoxycarbonyl)amino)-8-methyl-1,8-dihydropyrrolo[2,3-*b*]indole-3-carboxylate (2i): compound **2i** was isolated by column chromatography (ethyl acetate/cyclohexane 30:70) in 80% yield (52.6 mg); 4 h; pale yellow solid; mp: 188–190 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.10 (br, 1H), 7.94 (d, *J* = 8.0 Hz, 1H), 7.45 (d, *J* = 8.0 Hz, 1H), 7.19–7.15 (m, 1H), 7.12–7.08 (m, 1H), 3.90 (s, 3H), 3.81 (s, 3H), 3.78 (s, 3H), 3.06–2.97 (m, 1H), 2.87–2.78 (m, 1H), 1.14 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 164.8, 156.4, 142.3, 139.8, 136.2, 120.6, 120.1, 119.7, 119.1, 109.4, 102.7, 101.3, 53.2, 50.8, 29.0, 17.5, 14.0. HRMS (ESI-Orbitrap, *m/z*): $[M+H]^+$ calcd for $C_{17}H_{19}N_3O_4$ 330.1448, found 330.1441.



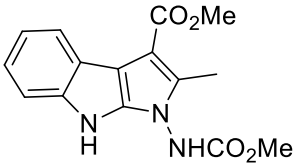
2j

Methyl 1-((methoxycarbonyl)amino)-8-methyl-2-propyl-1,8-dihydropyrrolo[2,3-*b*]indole-3-carboxylate (2j): compound **2j** was isolated by column chromatography (ethyl acetate/cyclohexane 30:70) in 85% yield (58.7 mg); 12 h; pale yellow solid; mp: 122–124 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.07 (br, 1H), 7.94 (d, *J* = 8.0 Hz, 1H), 7.45 (d, *J* = 8.0 Hz, 1H), 7.19–7.15 (m, 1H), 7.12–7.08 (m, 1H), 3.90 (s, 3H), 3.81 (s, 3H), 3.78 (s, 3H), 3.04–2.97 (m, 1H), 2.83–2.76 (m, 1H), 1.65–1.50 (m, 2H), 0.93 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 164.9, 156.3, 140.8, 139.8, 136.3, 120.6, 120.1, 119.7, 119.1, 109.4, 102.7, 101.9, 53.2, 50.8, 29.0, 25.9, 22.4, 13.7. HRMS (ESI-Orbitrap, *m/z*): $[M+H]^+$ calcd for $C_{18}H_{21}N_3O_4$ 344.1605, found 344.1609.



2k

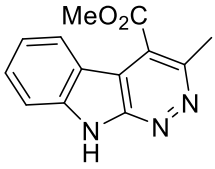
Methyl 5-methoxy-1-((methoxycarbonyl)amino)-2-methyl-8-propyl-1,8-dihydropyrrolo[2,3-*b*]indole-3-carboxylate (2k): compound **2k** was isolated by column chromatography (ethyl acetate/cyclohexane 40:60) in 99% yield (73.9 mg); 6 h; whitish solid; mp: 186–188 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.02 (br, 1H), 7.45 (d, *J* = 2.4 Hz, 1H), 7.36 (d, *J* = 8.8 Hz, 1H), 6.77 (dd, *J* = 8.8, 2.4 Hz, 1H), 4.23–4.04 (m, 2H), 3.89 (s, 3H), 3.79 (s, 6H), 2.46 (s, 3H), 1.75–1.58 (m, 2H), 0.82 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 165.0, 156.1, 153.3, 136.6, 136.4, 134.3, 120.5, 110.3, 109.0, 103.1, 102.8, 102.1, 55.3, 53.1, 50.8, 44.3, 23.1, 11.1, 10.2. HRMS (ESI-Orbitrap, *m/z*): $[M+H]^+$ calcd for $C_{19}H_{23}N_3O_5$ 374.1710, found 374.1715.



2l

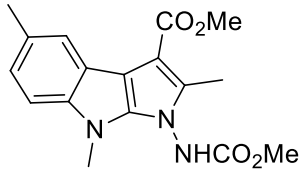
Methyl 1-((methoxycarbonyl)amino)-2-methyl-1,8-dihydropyrrolo[2,3-*b*]indole-3-carboxylate (2l)[2]**:** compound **2l** was isolated by column chromatography (ethyl acetate/cyclohexane 55:45) in 52% yield (31.1 mg); 12 h; white solid; for compound **2l**, a spontaneous ring enlargement reaction to azacarboline was observed[2]; ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.50 (br, 1H), 10.88 (br, 1H), 7.90–7.88 (m, 1H), 7.34–7.32 (m, 1H), 7.10–7.02 (m, 2H), 3.89 (s, 3H), 3.78 (s, 3H), 2.48 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 165.2, 155.7, 138.6, 137.3, 135.6, 120.9, 120.3, 119.5, 118.8, 111.7, 102.4, 102.0, 52.9, 50.7, 10.3. HRMS (ESI-Orbitrap, *m/z*): $[M+H]^+$ calcd for $C_{15}H_{15}N_3O_4$ 302.1135, found 302.1131.

During the course of the reaction, the following work-up, and the long standing in the presence or absence of DMSO-d_6 solution, the compound **2l** gives a partial conversion to azacarboline **5a**.



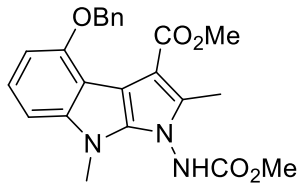
5a

Methyl 3-methyl-9*H*-pyridazino[3,4-*b*]indole-4-carboxylate (5a): The chemical-physical data of compound **5a** are in agreement with those reported.[2]



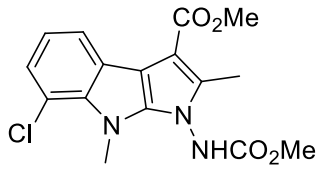
2m

Methyl 1-((methoxycarbonyl)amino)-2,5,8-trimethyl-1,8-dihydropyrrolo[2,3-*b*]indole-3-carboxylate (2m): compound **2m** was isolated by column chromatography (ethyl acetate/cyclohexane 40:60) in 93% yield (61.4 mg); 5 h; pale brown solid; mp: 201–203 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.00 (br, 1H), 7.72 (s, 1H), 7.32 (d, J = 8.4 Hz, 1H), 6.98 (dd, J = 8.4, 1.2 Hz, 1H), 3.89 (s, 3H), 3.80 (s, 3H), 3.74 (s, 3H), 2.47 (s, 3H), 2.42 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 165.1, 156.2, 138.2, 136.5, 136.2, 127.6, 121.8, 120.2, 119.7, 109.1, 102.4, 102.1, 53.2, 50.8, 29.1, 21.3, 10.2. HRMS (ESI-Orbitrap, *m/z*): $[M+H]^+$ calcd for $C_{17}H_{19}N_3O_4$ 330.1448, found 330.1449.



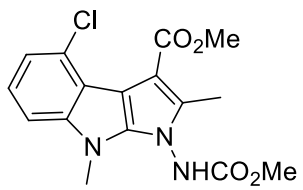
2n

Methyl 4-(benzyloxy)-1-((methoxycarbonyl)amino)-2,8-dimethyl-1,8-dihydropyrrolo[2,3-*b*]indole-3-carboxylate (2n): compound **2n** was obtained by simple extraction with ethyl acetate/diethyl ether and crystallization from ethyl acetate/diethyl ether in 96% yield (80.7 mg); 48 h; whitish solid; mp: 150–152 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.98 (br, 1H), 7.49–7.47 (m, 2H), 7.38–7.34 (m, 2H), 7.31–7.27 (m, 1H), 7.05–7.02 (m, 2H), 6.67–6.65 (m, 1H), 5.25 (s, 2H), 3.80 (s, 3H), 3.75 (s, 3H), 3.38 (s, 3H), 2.36 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 165.8, 156.3, 151.6, 140.9, 138.0, 135.5, 134.3, 128.3, 127.6, 127.5, 121.3, 110.6, 103.9, 102.7, 100.6, 69.3, 53.2, 50.3, 29.3, 10.1. HRMS (ESI-Orbitrap, *m/z*): $[M+H]^+$ calcd for $C_{23}H_{23}N_3O_5$ 422.1710, found 422.1708.



2o

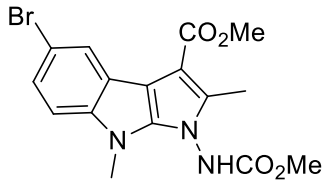
Methyl 7-chloro-1-((methoxycarbonyl)amino)-2,8-dimethyl-1,8-dihydropyrrolo[2,3-*b*]indole-3-carboxylate (2o): compound **2o** was obtained by simple extraction with ethyl acetate and crystallization from diethyl ether/petroleum ether in 97% yield (67.6 mg); 24 h; brownish solid; mp: 189–191 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.10 (br, 1H), 7.95 (dd, J = 7.6, 1.2 Hz, 1H), 7.15 (dd, J = 7.6, 1.2 Hz, 1H), 7.08 (t, J = 7.2 Hz, 1H), 4.12 (s, 3H), 3.89 (s, 3H), 3.80 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 164.8, 156.1, 137.9, 137.1, 134.4, 123.4, 122.5, 120.5, 119.0, 115.6, 102.9, 102.0, 53.3, 50.9, 32.2, 10.2. HRMS (ESI-Orbitrap, *m/z*): $[M+H]^+$ calcd for $C_{16}H_{16}ClN_3O_4$, 350.0902, found 350.0909.



2p

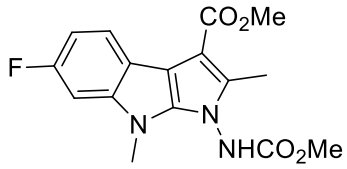
Methyl 4-chloro-1-((methoxycarbonyl)amino)-2,8-dimethyl-1,8-dihydropyrrolo[2,3-*b*]indole-3-carboxylate (2p): compound **2p** was obtained by simple extraction with ethyl acetate and crystallization from diethyl ether/petroleum ether in 99% yield (69.1 mg); 2 h; brownish solid; mp: 170–172 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.02 (br, 1H), 7.48–7.43 (m, 1H), 7.16–7.11 (m, 2H), 3.81 (s, 6H), 3.78 (s, 3H), 2.34 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 165.6, 156.3,

140.5, 137.0, 134.7, 123.7, 121.1, 120.2, 118.4, 108.4, 104.1, 100.0, 53.3, 50.7, 29.4, 10.0. HRMS (ESI-Orbitrap, *m/z*): $[M+H]^+$ calcd for $C_{16}H_{16}ClN_3O_4$, 350.0902, found 350.0911.



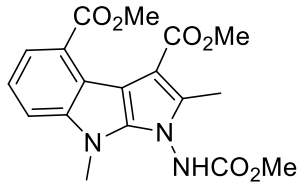
2q

Methyl 5-bromo-1-((methoxycarbonyl)amino)-2,8-dimethyl-1,8-dihydropyrrolo[2,3-*b*]indole-3-carboxylate (2q): compound **2q** was obtained by simple extraction with ethyl acetate and crystallization from diethyl ether in 98% yield (77.3 mg); 9 h; brownish solid; mp: 194–196 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.07 (br, 1H), 8.02 (d, J = 2.0 Hz, 1H), 7.46 (d, J = 8.4 Hz, 1H), 7.29 (dd, J = 8.8, 2.0 Hz, 1H), 3.89 (s, 3H), 3.79 (s, 6H), 2.48 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 164.8, 156.2, 138.4, 137.3, 137.0, 122.8, 121.7, 121.5, 111.7, 111.5, 102.0, 53.4, 51.1, 29.3, 10.3. HRMS (ESI-Orbitrap, *m/z*): $[M+H]^+$ calcd for $C_{16}H_{16}BrN_3O_4$, 394.0397, found 394.0404.



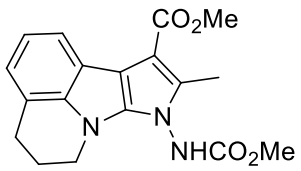
2r

Methyl 6-fluoro-1-((methoxycarbonyl)amino)-2,8-dimethyl-1,8-dihydropyrrolo[2,3-*b*]indole-3-carboxylate (2r): compound **2r** was obtained by simple extraction with ethyl acetate and crystallization from diethyl ether in 98% yield (65.4 mg); 8 h; brownish solid; mp: 200–202 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.07 (br, 1H), 7.88 (dd, J = 8.8 Hz, $^4J_{HF}$ = 6.0 Hz, 1H), 7.38 (dd, $^3J_{HF}$ = 10.8 Hz, J = 2.4 Hz, 1H), 6.96–6.91 (m, 1H), 3.89 (s, 3H), 3.80 (s, 3H), 3.77 (s, 3H), 2.47 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 165.0, 158.3 (d, $^1J_{CF}$ = 232.4 Hz), 156.2, 139.8 (d, $^3J_{CF}$ = 12.2 Hz), 136.3, 120.3 (d, $^3J_{CF}$ = 9.9 Hz), 116.8, 106.7 (d, $^2J_{CF}$ = 23.4 Hz), 102.5, 101.9, 96.8 (d, $^2J_{CF}$ = 26.9 Hz), 59.7, 53.3, 50.9, 29.4, 10.1. HRMS (ESI-Orbitrap, *m/z*): $[M+H]^+$ calcd for $C_{16}H_{16}FN_3O_4$, 334.1198, found 334.1201.



2s

Dimethyl 1-((methoxycarbonyl)amino)-2,8-dimethyl-1,8-dihydropyrrolo[2,3-*b*]indole-3,4-dicarboxylate (2s): compound **2s** was obtained by simple extraction with ethyl acetate and crystallization from diethyl ether in 99% yield (74.8 mg); 6 h; whitish solid; mp: 210–212 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.04 (br, 1H), 7.68 (d, J = 8.0 Hz, 1H), 7.39 (d, J = 8.0 Hz, 1H), 7.20 (t, J = 8.0 Hz, 1H), 3.83 (s, 3H), 3.81 (s, 3H), 3.75 (s, 3H), 3.72 (s, 3H), 2.36 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 168.8, 165.4, 156.3, 139.9, 137.8, 135.2, 123.0, 120.4, 119.5, 117.9, 113.0, 104.4, 101.9, 53.3, 51.4, 51.0, 29.2, 10.0. HRMS (ESI-Orbitrap, *m/z*): $[M+H]^+$ calcd for $C_{18}H_{19}N_3O_6$, 374.1347, found 374.1349.

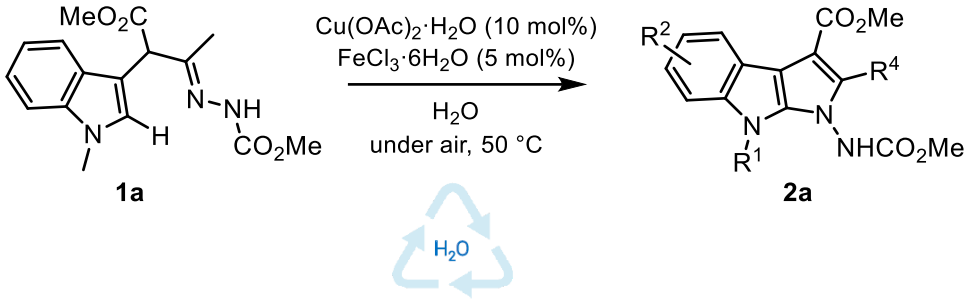


2t

Methyl 8-((methoxycarbonyl)amino)-9-methyl-4,5,6,8-tetrahydropyrrolo[3',2':4,5]pyrrolo[3,2,1-*ij*]quinoline-10-carboxylate (2t): compound **2t** was obtained by simple extraction with ethyl acetate and crystallization from diethyl ether in 97% yield (65.9 mg); 4 h; whitish solid; mp: 169–171 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.00 (br, 1H), 7.66 (d, J = 7.6 Hz, 1H), 6.98 (t, J = 7.6 Hz, 1H), 6.87 (d, J = 7.2 Hz, 1H), 4.32–4.27 (m, 1H), 4.09–4.02 (m, 1H), 3.89 (s, 3H), 3.79 (s, 3H), 2.93 (t, J = 6.0 Hz, 2H), 2.48 (s, 3H), 2.18–2.13 (m, 2H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 165.1, 156.2, 135.9, 135.9, 135.6, 121.5, 119.0, 118.4, 118.1, 117.2, 102.6, 102.1, 53.2, 50.8, 41.2, 23.9, 21.9, 10.1. HRMS (ESI-Orbitrap, *m/z*): $[M+H]^+$ calcd for $C_{18}H_{19}N_3O_4$, 342.1448, found 342.1451.

4. Recycling of the aqueous catalytic system

Recycling of $Cu(OAc)_2 \cdot H_2O/FeCl_3 \cdot 6H_2O$, and water in the intramolecular oxidative cyclization of **1a**.



In a round-bottom flask, α-indolylhydrazone **1a** (0.4 mmol), $Cu(OAc)_2 \cdot H_2O$ (0.04 mmol, 8.0 mg), $FeCl_3 \cdot 6H_2O$ (0.02 mmol, 5.4 mg) and water (4 mL) were added. The aqueous suspension was stirred at 50 °C (oil bath) until consumption of the starting material (TLC check). At the end, the reaction mixture was extracted with ethyl acetate (3 x 3 mL). The aqueous phase containing the catalyst system was re-used for the five runs with the catalyst activities indicated in the Table S2.

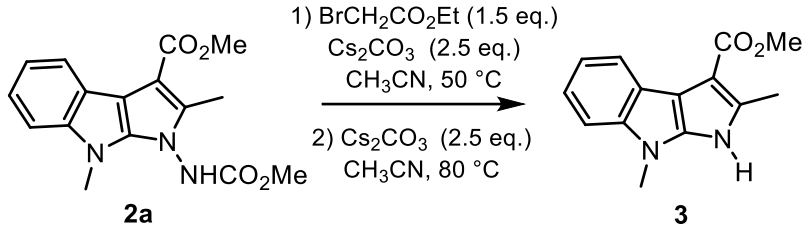
On the other hand, the collected organic phase was dried over anhydrous sodium sulphate and the solvent was removed under vacuum. The crude was purified by crystallization (for the first 3 cycles) or by flash chromatography on silica gel (cyclohexane/ethyl acetate 60:40 for the last 2 cycles) to give the corresponding product **2a** (Table S2).

Table S2. Recycling of the aqueous catalytic system.

Cycle	Yield (%)	Time (h)
Fresh	99	4
1st	99	4
2nd	82	6.5
3rd	81	24
4th	74	28
5th	52	48

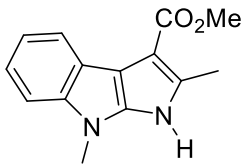
5. Synthetic transformations

5.1 Access to compound **3**



2a **3**

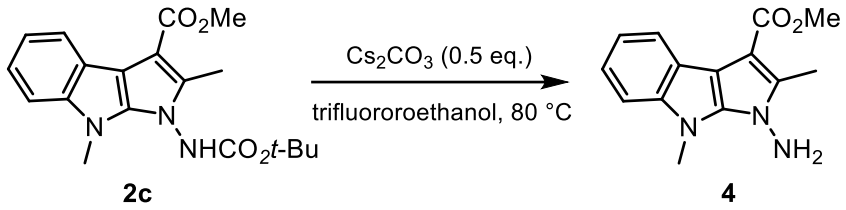
Compound **3** was prepared according to a modified version of the Magnus method.[3] To a solution of **2a** (63.1 mg, 0.2 mmol) in acetonitrile (5 mL), ethyl bromoacetate (0.033 mL, 0.3 mmol) and Cs_2CO_3 (162.9 mg, 0.5 mmol) were added. The mixture was stirred at 50 °C (oil bath) until the disappearance of the starting material (0.5 h). The solvent was removed under vacuum, water (5 mL) was added and the mixture was extracted with ethyl acetate (3 x 10 mL). The combined organic layer was dried over Na_2SO_4 and filtered. After the solvent was removed under reduced pressure, the residue was dissolved in acetonitrile (5 mL) and Cs_2CO_3 (162.9 mg, 0.5 mmol) was added. The mixture was stirred at 80 °C until TLC showed complete consumption of intermediate (1 h). The solvent was removed under vacuum, water (5 mL) was added and the mixture was extracted with ethyl acetate (3 x 10 mL). The collected organic phase was washed with brine, dried over Na_2SO_4 and filtered. After the solvent was removed under vacuum, the residue was purified by column chromatography (ethyl acetate) to afford compound **3** as a red solid (16.5 mg, 34% yield).



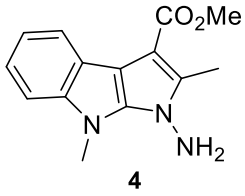
3

Methyl 2,8-dimethyl-1,8-dihydropyrrolo[2,3-*b*]indole-3-carboxylate (3): mp 88–90 °C (dec.); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.95 (br, 1H), 7.82 (d, *J* = 6.8 Hz, 1H), 7.37–7.30 (m, 3H), 4.02 (s, 3H), 3.71 (s, 3H), 2.34 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 179.8, 169.5, 165.7, 144.8, 135.7, 124.2, 123.8, 123.8, 120.3, 110.4, 101.5, 53.0, 32.9, 24.4. HRMS (ESI-Orbitrap, m/z): $[M+H]^+$ calcd for $C_{14}H_{14}N_2O_2$, 243.1128, found 234.1121.

5.2 Access to compound **4**

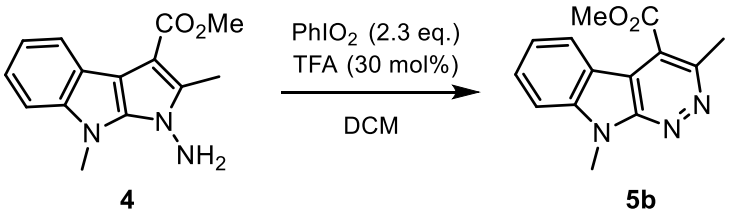


Compound **4** was prepared according to the literature procedure[4]. To a solution of **2c** (357.4 mg, 1.0 mmol) in trifluoroethanol (2 mL), CsOAc (96.0 mg, 0.5 mmol) was added. The mixture was stirred at 80 °C (oil bath) for 24 hours. Upon the completion of reaction (TLC check), the solvent was removed by vacuum and the residue was purified by column chromatography (ethyl acetate/cyclohexane 30:70) to afford compound **4** as a red solid (120.2 mg, 47% yield b.r.s.m.).



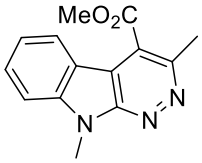
Methyl 1-amino-2,8-dimethyl-1,8-dihydropyrrolo[2,3-*b*]indole-3-carboxylate (4): mp 228–230 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.91–7.88 (m, 1H), 7.40–7.37 (m, 1H), 7.13–7.03 (m, 2H), 6.04 (s, 2H), 4.01 (s, 3H), 3.86 (s, 3H), 2.63 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 165.4, 139.9, 137.5, 137.3, 120.3, 119.9, 119.4, 118.6, 109.1, 102.2, 99.8, 50.5, 29.6, 10.6. HRMS (ESI-Orbitrap, m/z): $[M+H]^+$ calcd for $C_{14}H_{15}N_3O_2$, 258.1237, found 258.1243.

5.3 Access to compound **5b**[2]



To a solution of compound **4** (48.6 mg, 0.2 mmol) in dichloromethane, $PhIO_2$ (108.6 mg, 0.46 mmol) and trifluoroacetic acid (0.05 mL, 0.06 mmol) were added. The solution was stirred at room temperature for

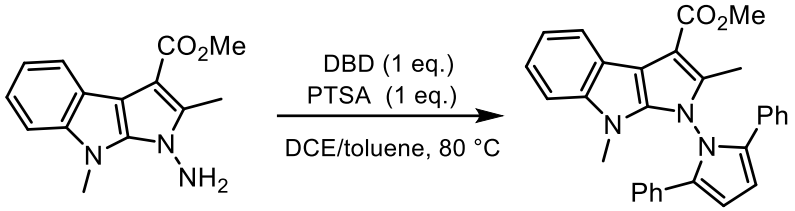
0.5 hour. After completion of the reaction (TLC check), the solvent was removed under vacuum and the residue was purified by column chromatography (ethyl acetate/cyclohexane 50:50) to afford compound **5b** as a yellow solid (27.6 mg, 54% yield).[2]



5b

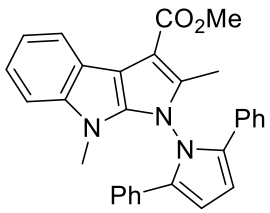
Methyl 3,9-dimethyl-9*H*-pyridazino[3,4-*b*]indole-4-carboxylate: (5b): The chemical-physical data of compound **5b** are in agreement with those reported.[2]

5.4 Access to compound **6**



4 **6**

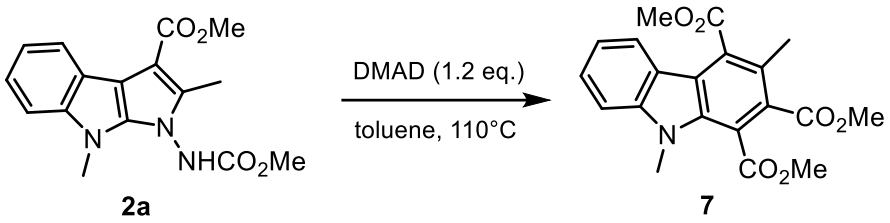
Compound **6** was prepared according to the literature procedure.[5] To a solution of compound **4** (48.6 mg, 0.2 mmol) in dichloroethane/toluene 1:1 (2 mL), 1,4-diphenylbutane-1,4-dione (47.7 mg, 0.2 mmol) and *p*-toluenesulfonic acid (34.4 mg, 0.2 mmol) were added. The solution was heated at 80°C for 48 hours. After the disappearance of the starting material (TLC check), the solvent was removed under vacuum and the residue was purified by column chromatography (ethyl acetate/cyclohexane/dichloromethane 20:80:10) to afford compound **6** as a colorless oil (37.7 mg, 41% yield).



6

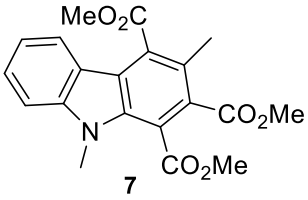
Methyl 1-(2,5-diphenyl-1*H*-pyrrol-1-yl)-2,8-dimethyl-1,8-dihydropyrrolo[2,3-*b*]indole-3-carboxylate(6): ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.97–7.95 (m, 1H), 7.83–7.81 (m, 1H), 7.47–7.43 (m, 1H), 7.38–7.36 (m, 1H), 7.25–7.15 (m, 7H), 7.05–7.03 (m, 3H), 6.87 (s, 2H), 3.90 (s, 3H), 3.29 (s, 3H), 2.23 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 164.7, 152.6, 139.9, 135.2, 135.0, 130.1, 129.8, 129.0, 128.9, 127.7, 127.5, 126.1, 123.4, 121.1, 120.1, 119.9, 119.6, 109.9, 109.2, 108.2, 103.5, 102.9, 51.1, 28.5, 10.3. HRMS (ESI-Orbitrap, m/z): $[M+H]^+$ calcd for $C_{30}H_{25}N_3O_2$, 460.2020, found 460.2013.

5.5 Access to compound **7**



2a **7**

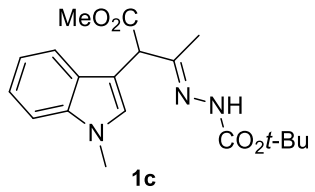
Compound **7** was prepared according to the literature procedure.[6] To a solution of **2a** (94.6 mg, 0.3 mmol) in toluene (1 mL) dimethyl acetylenedicarboxylate (0.049 mL, 0.36 mmol) was added and the reaction mixture was refluxed for 12 hours. After the disappearance of the starting material (TLC check), the solvent was removed under vacuum and the residue was purified by column chromatography (ethyl acetate/cyclohexane 40:60) to afford compound **7** as a red oil (64.3 mg, 58% yield).

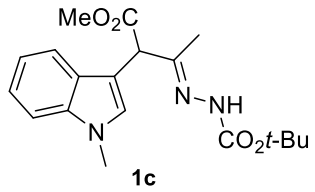


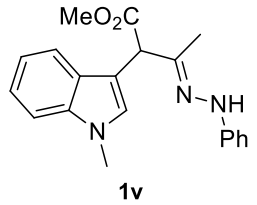
7

Trimethyl 3,9-dimethyl-9*H*-carbazole-1,2,4-tricarboxylate (7): ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.76 (d, J = 7.6 Hz, 1H), 7.73 (d, J = 8.4 Hz, 1H), 7.63–7.58 (m, 1H), 7.32–7.28 (m, 1H), 4.10 (s, 3H), 3.96 (s, 3H), 3.88 (s, 3H), 3.75 (s, 3H), 2.36 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 168.5, 167.8, 166.8, 142.8, 134.7, 129.9, 129.0, 128.0, 121.7, 121.0, 120.8, 120.5, 118.6, 116.3, 110.3, 53.2, 53.1, 52.8, 31.7, 16.2. HRMS (ESI-Orbitrap, m/z): $[M+H]^+$ calcd for $C_{20}H_{19}NO_6$, 370.1285, found 370.1279.

6. ^{1}H and ^{13}C NMR spectra



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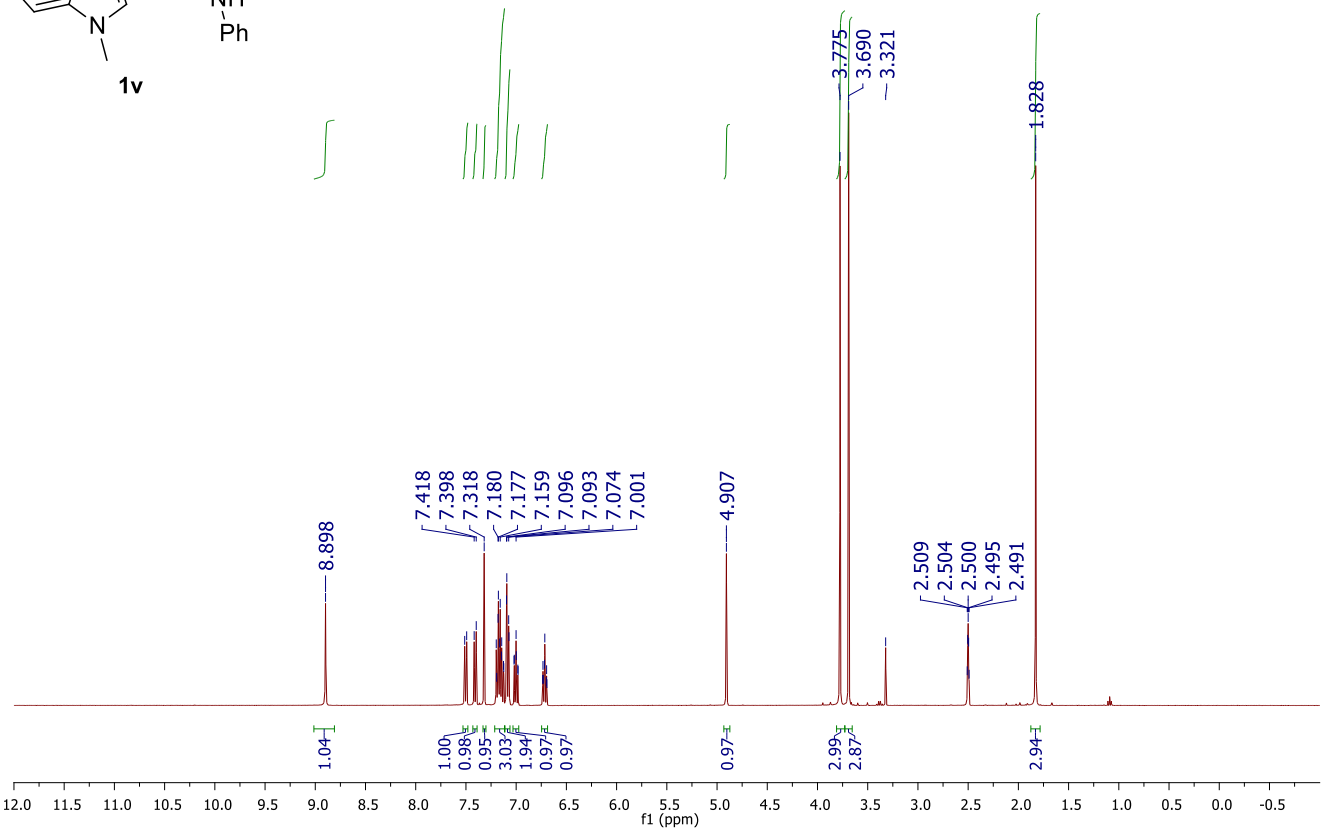
N
NH
Ph
N

1v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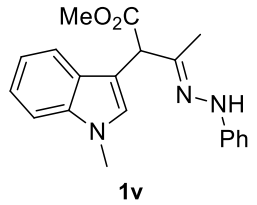
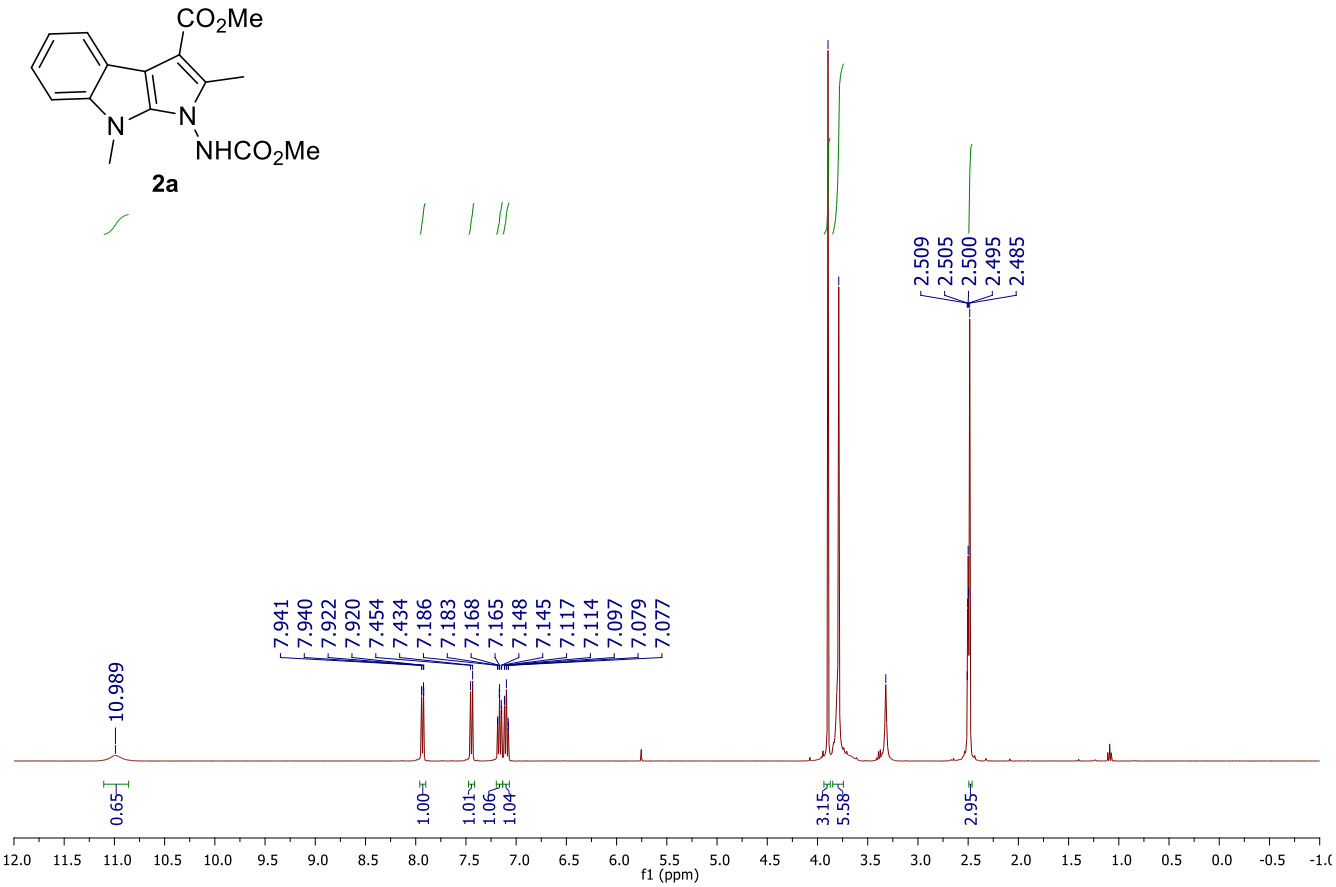
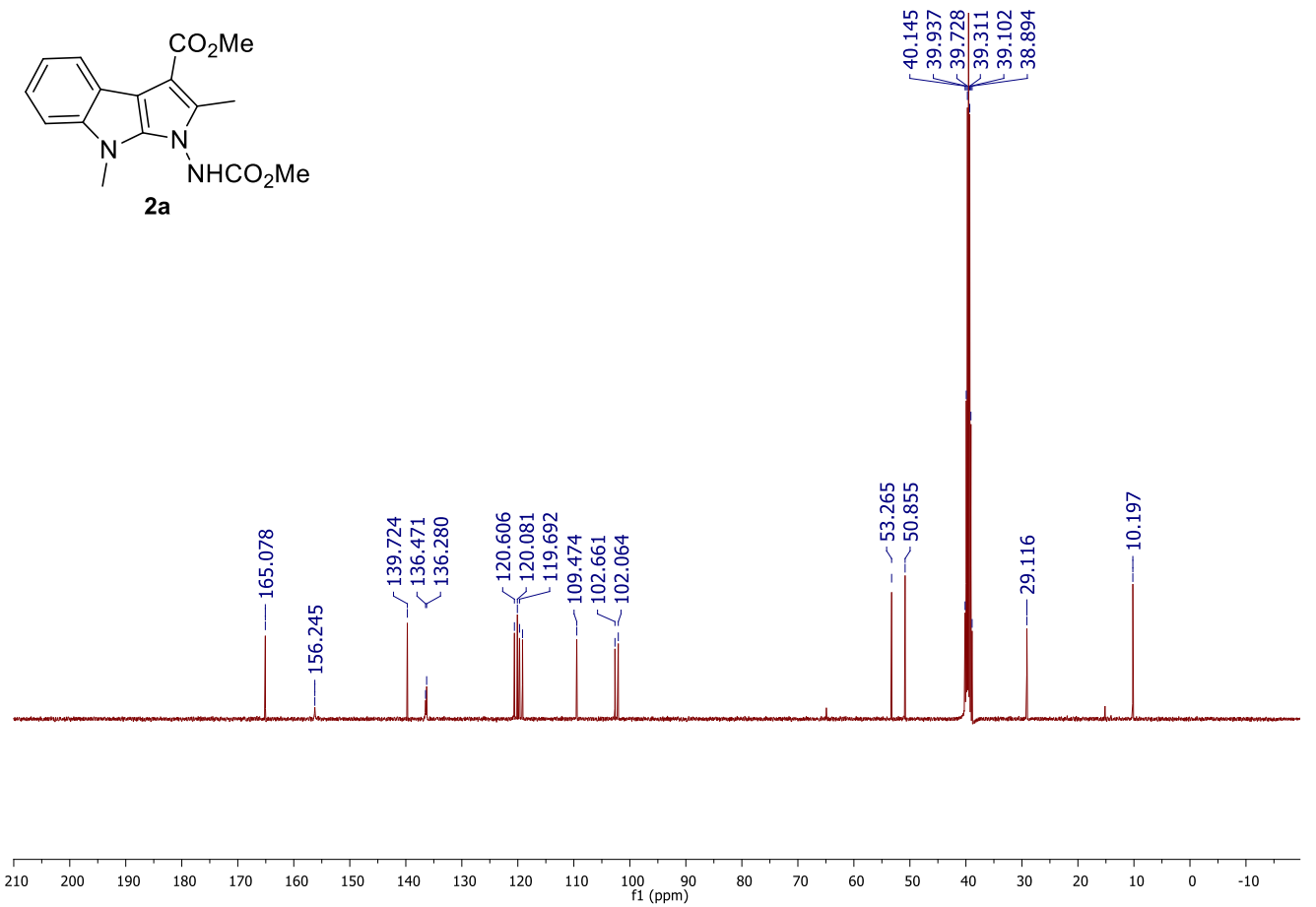
7.318
7.180
7.177
7.159
7.096
7.093
7.074
7.001
4.907
3.775
3.690
3.321
2.509
2.504
2.500
2.495
2.491
1.828
1.04
1.00
0.98
0.95
3.03
1.94
0.97
0.97
0.97
2.99
2.87
2.94
f1 (ppm)

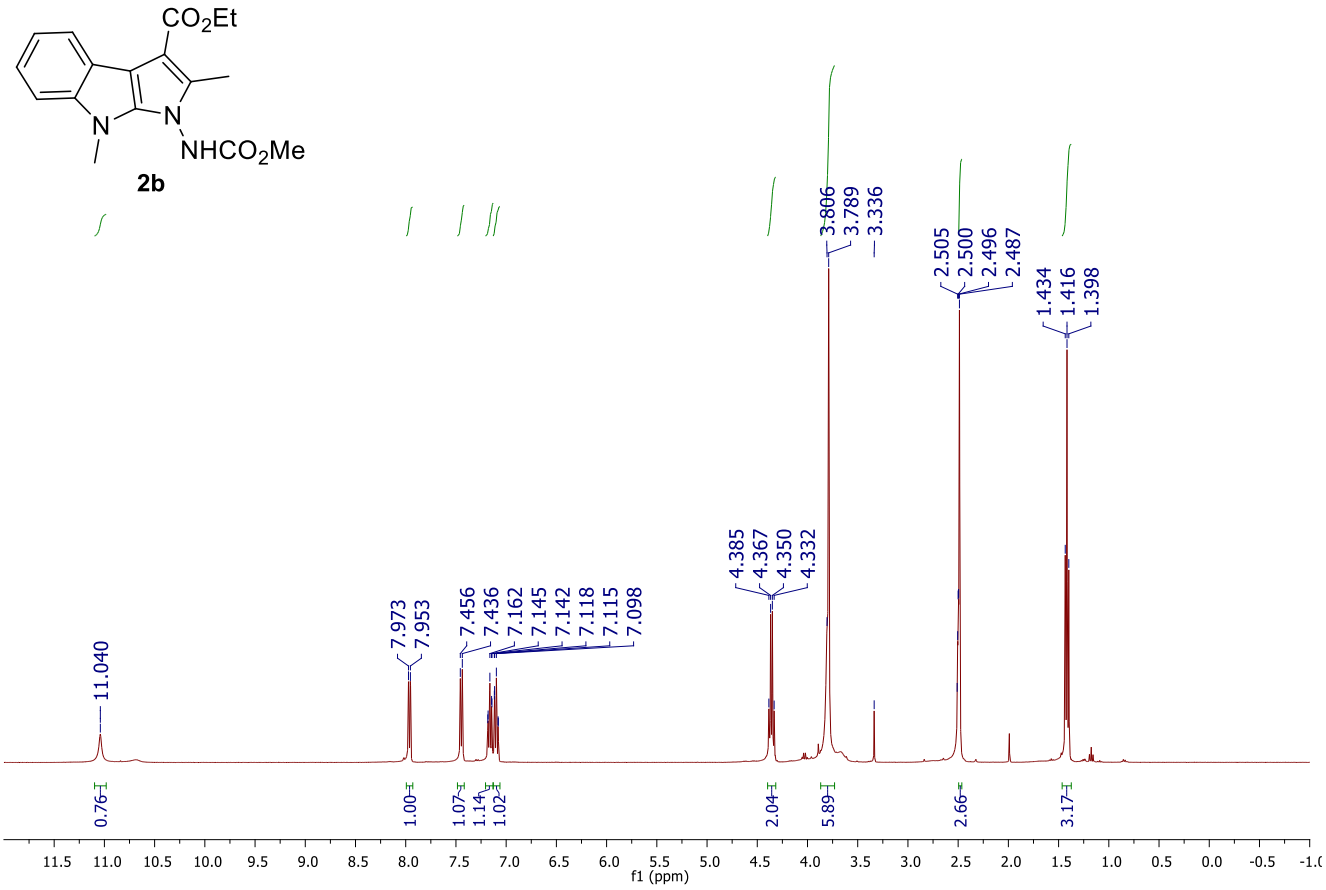

MeO2C
N
NH
Ph
N

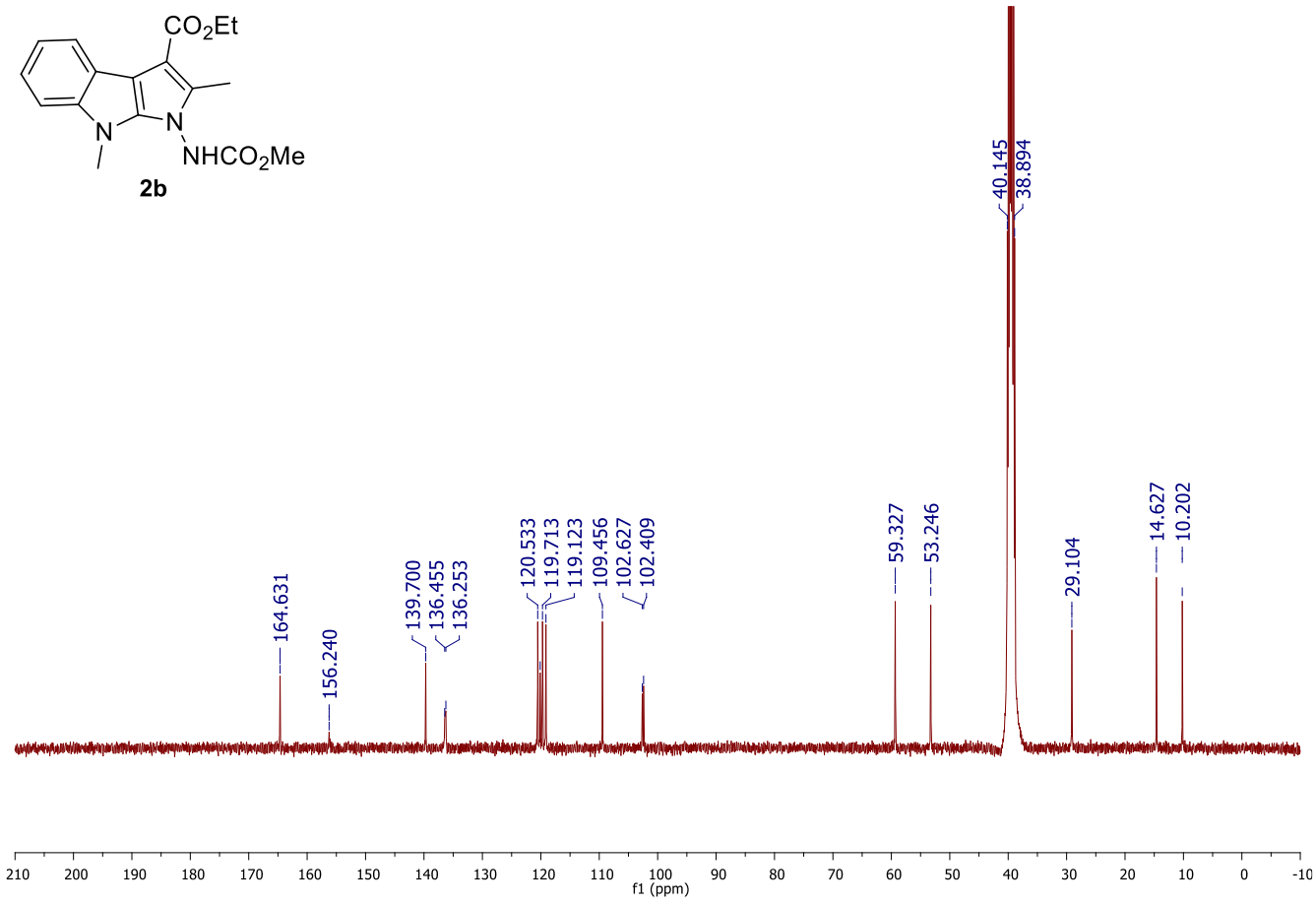
1v

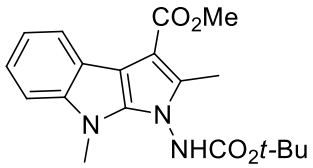
171.627
146.284
142.733
136.578
128.770
128.418
126.992
121.247
118.931
118.838
118.449
112.432
109.733
108.343
51.757
51.346
40.146
39.938
39.103
38.894
32.371
14.097
f1 (ppm)


CO2Me
N
N
NHCO2Me
2a
2.509
2.505
2.500
2.495
2.485
7.941
7.940
7.922
7.920
7.454
7.434
7.186
7.183
7.168
7.165
7.148
7.145
7.117
7.114
7.097
7.079
7.077
10.989
0.65
1.00
1.01
1.06
1.04
3.15
5.58
2.95
f1 (ppm)

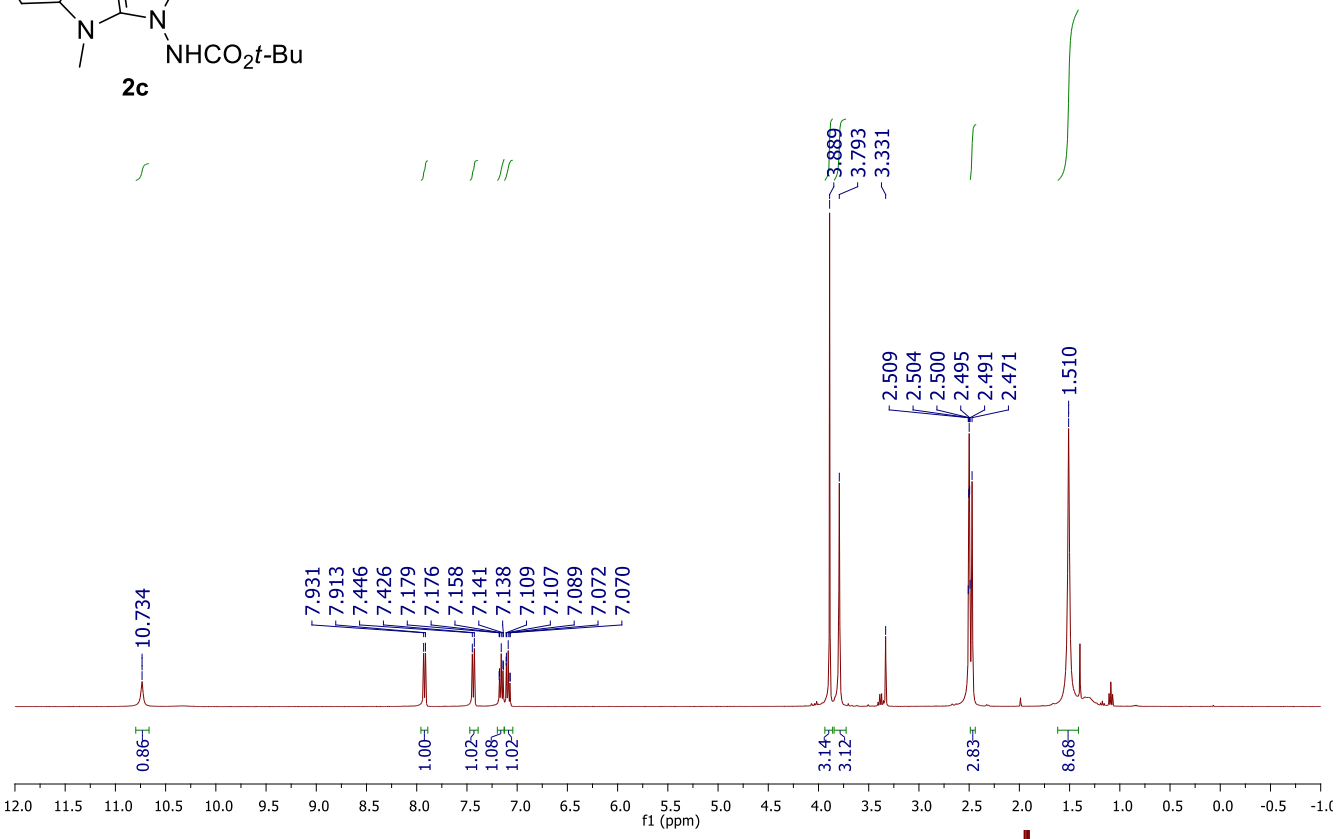

CO2Me
N
N
NHCO2Me
2a
40.145
39.937
39.728
39.311
39.102
38.894
165.078
156.245
139.724
136.471
136.280
120.606
120.081
119.692
109.474
102.661
102.064
53.265
50.855
29.116
10.197
f1 (ppm)

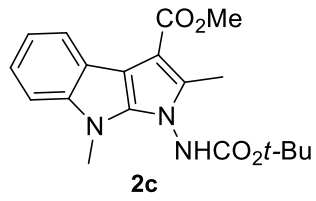

CO2Et
N
N
NHCO2Me
2b
11.040
7.973
7.953
7.456
7.436
7.162
7.145
7.142
7.118
7.115
7.098
4.385
4.367
4.350
4.332
3.806
3.789
3.336
2.505
2.500
2.496
2.487
1.434
1.416
1.398
0.76
1.00
1.07
1.14
1.02
2.04
5.89
2.66
3.17
f1 (ppm)


CO2Et
N
N
NHCO2Me
2b
164.631
156.240
139.700
136.455
136.253
120.533
119.713
119.123
109.456
102.627
102.409
59.327
53.246
40.145
38.894
29.104
14.627
10.202
f1 (ppm)


CO2Me
N
N
NHCO2t-Bu

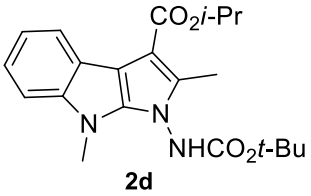
2c


10.734
7.931
7.913
7.446
7.426
7.179
7.176
7.158
7.141
7.138
7.109
7.107
7.089
7.072
7.070
3.889
3.793
3.331
2.509
2.504
2.500
2.495
2.491
2.471
1.510
0.86
1.00
1.02
1.08
1.02
3.14
3.12
2.83
8.68
f1 (ppm)


CO2Me
N
N
NHCO2t-Bu

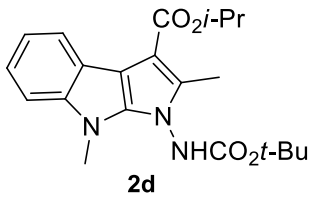
2c

165.1
154.7
139.7
136.5
136.4
120.5
120.1
119.6
119.1
109.4
102.5
101.8
81.5
50.8
40.1
38.9
29.0
27.8
10.2
f1 (ppm)


CO2i-Pr
N
N
NHCO2t-Bu

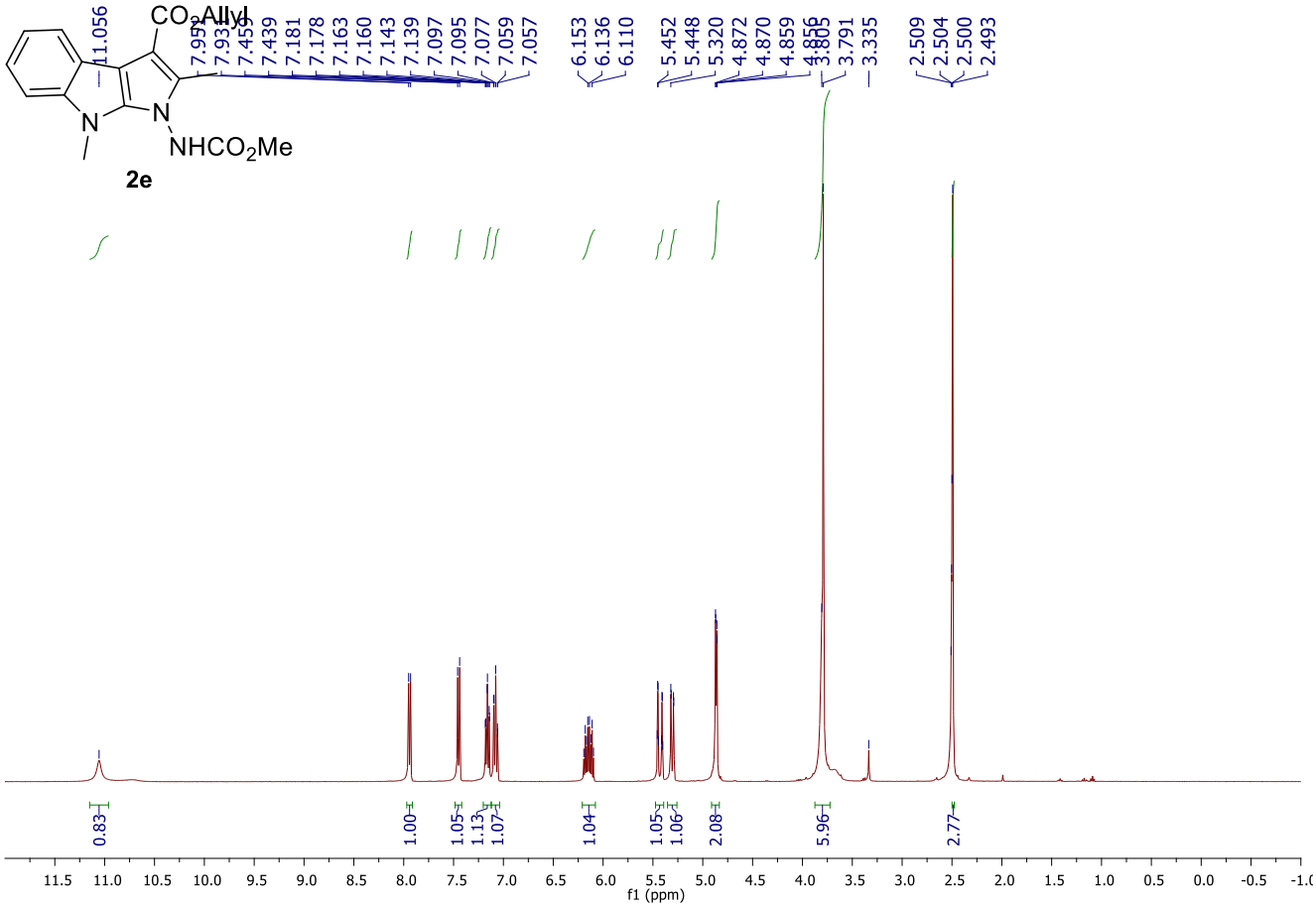
2d

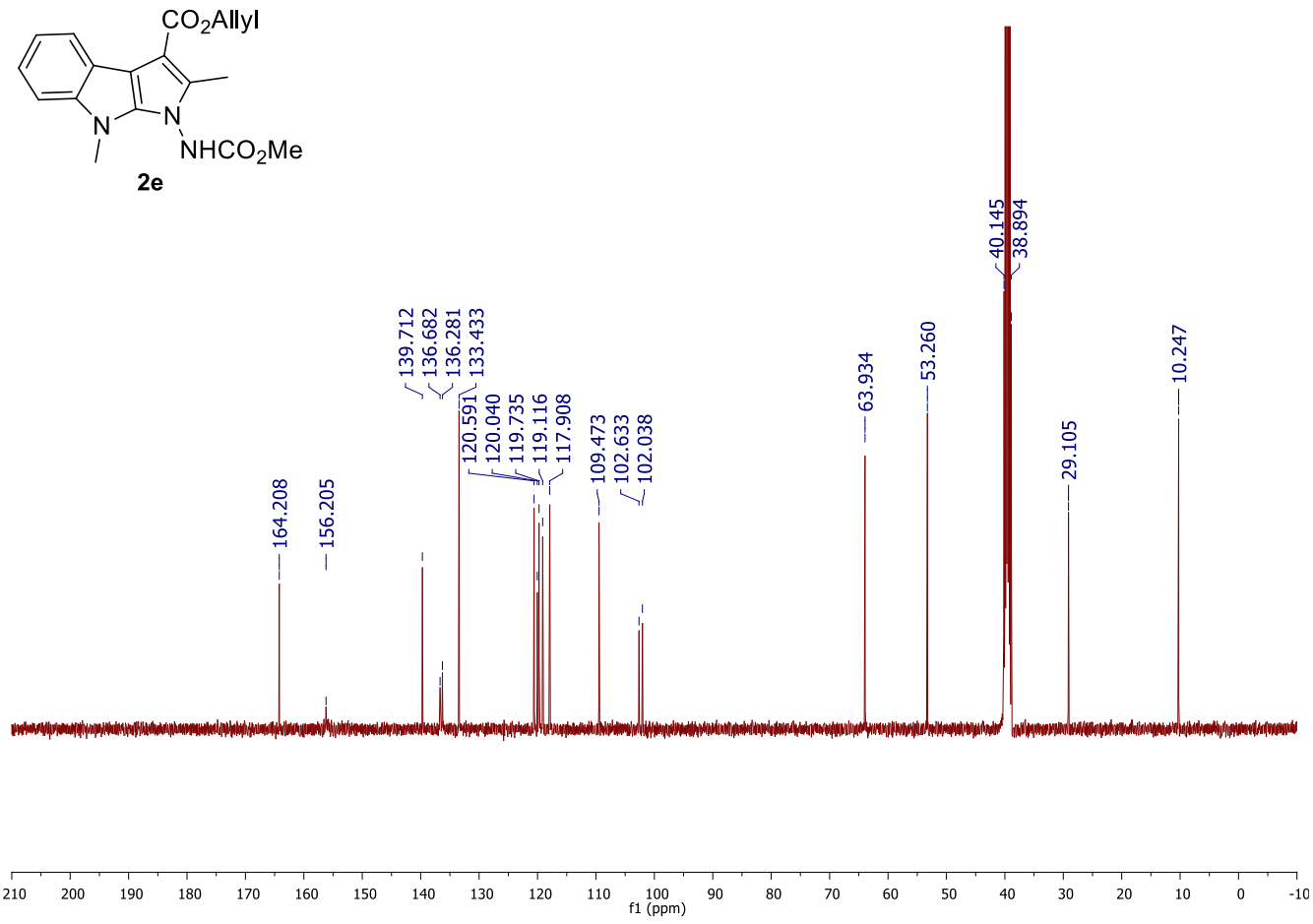
10.735
7.985
7.966
7.443
7.424
7.151
7.132
7.109
7.090
5.243
5.227
5.211
5.195
5.180
5.165
5.149
3.788
3.331
2.500
2.466
1.507
1.406
1.391
1.06
1.00
1.02
2.02
1.05
3.24
2.86
8.51
6.15
f1 (ppm)

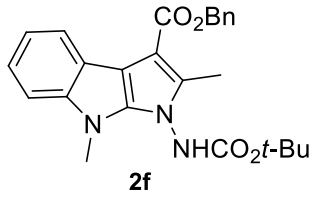

CO2i-Pr
N
N
NHCO2t-Bu

2d

164.240
154.724
139.664
136.462
136.403
120.401
119.735
119.053
109.389
102.700
102.577
81.461
66.385
28.984
27.834
22.182
10.245
f1 (ppm)

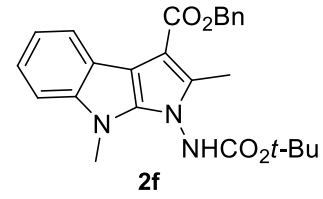

CO2Allyl
NHCO2Me
2e
11.056
7.995
7.933
7.455
7.439
7.181
7.178
7.163
7.160
7.143
7.139
7.097
7.095
7.077
7.059
7.057
6.153
6.136
6.110
5.452
5.448
5.320
4.872
4.870
4.859
3.805
3.791
3.335
2.509
2.504
2.500
2.493
0.83
1.00
1.05
1.13
1.07
1.04
1.05
1.06
2.08
5.96
2.77
f1 (ppm)


CO2Allyl
NHCO2Me
2e
164.208
156.205
139.712
136.682
136.281
133.433
120.591
120.040
119.735
119.116
117.908
109.473
102.633
102.038
63.934
53.260
40.145
38.894
29.105
10.247
f1 (ppm)


CO2Bn
N
N
NHCO2t-Bu

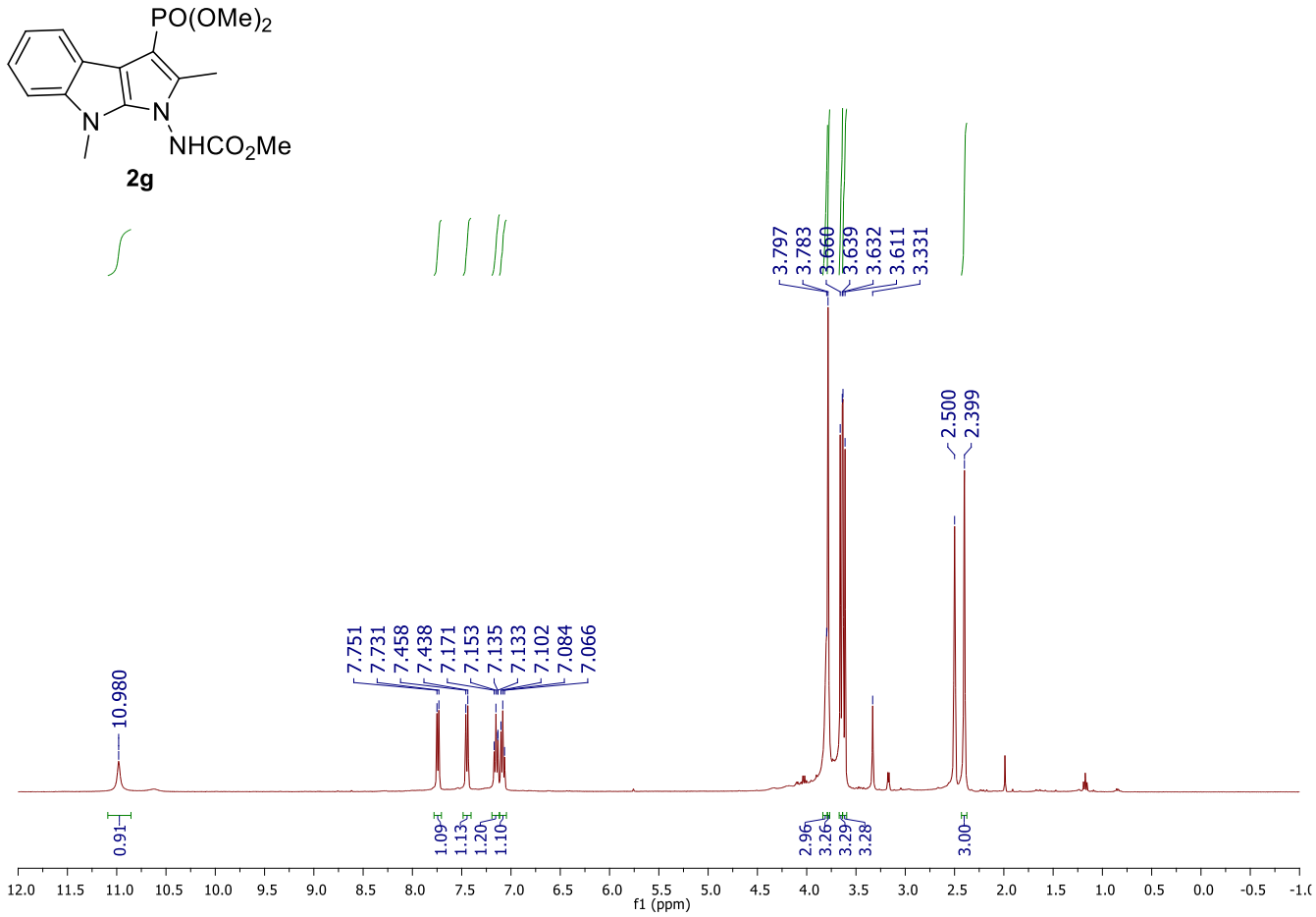
2f

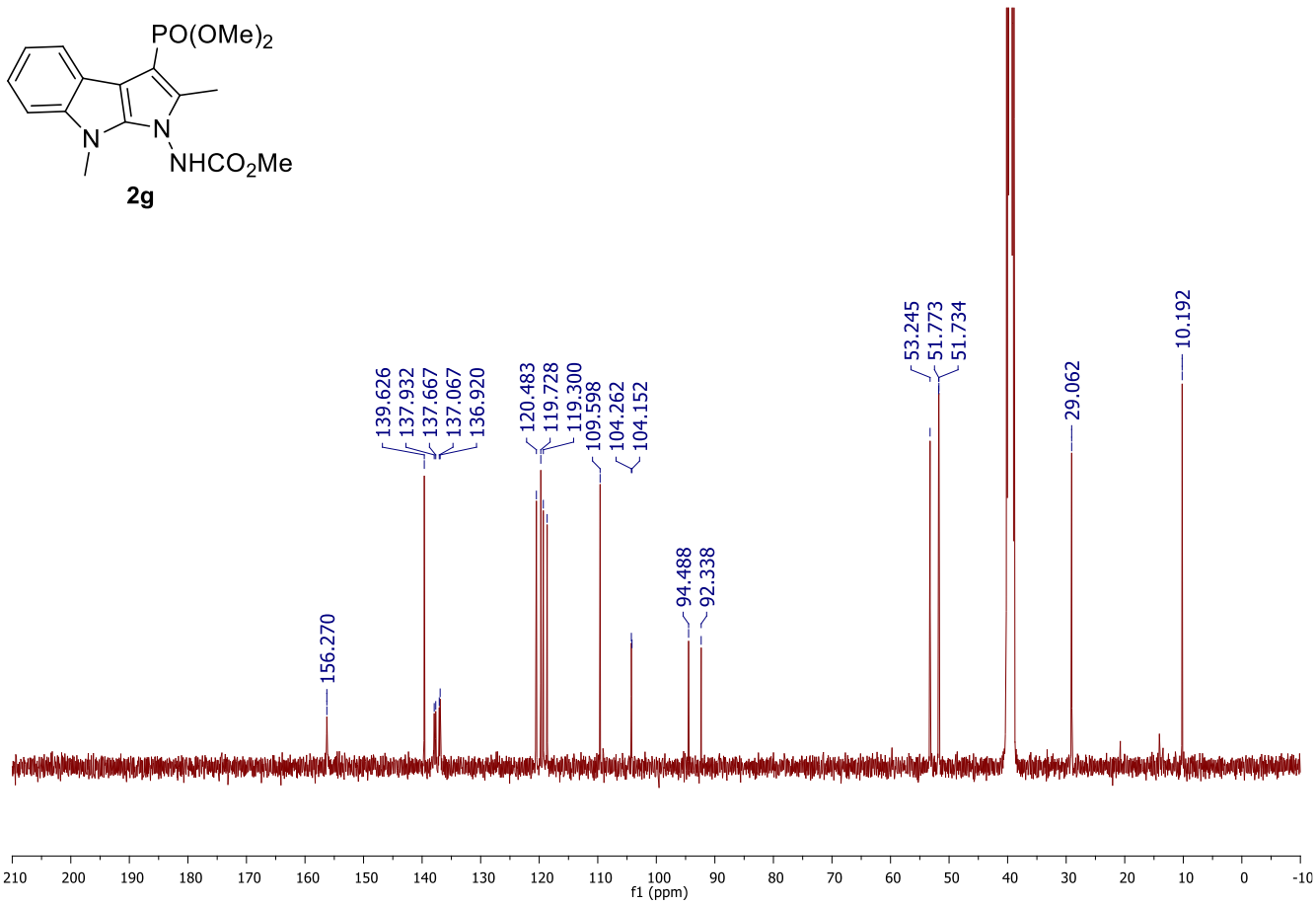
10.756
7.784
7.765
7.511
7.493
7.429
7.415
7.397
7.376
7.358
7.340
7.134
7.115
7.096
6.953
6.934
6.915
5.407
3.784
3.332
2.500
2.475
1.505
0.82
1.08
2.26
3.22
0.95
1.00
1.00
2.08
3.08
3.01
8.81
f1 (ppm)

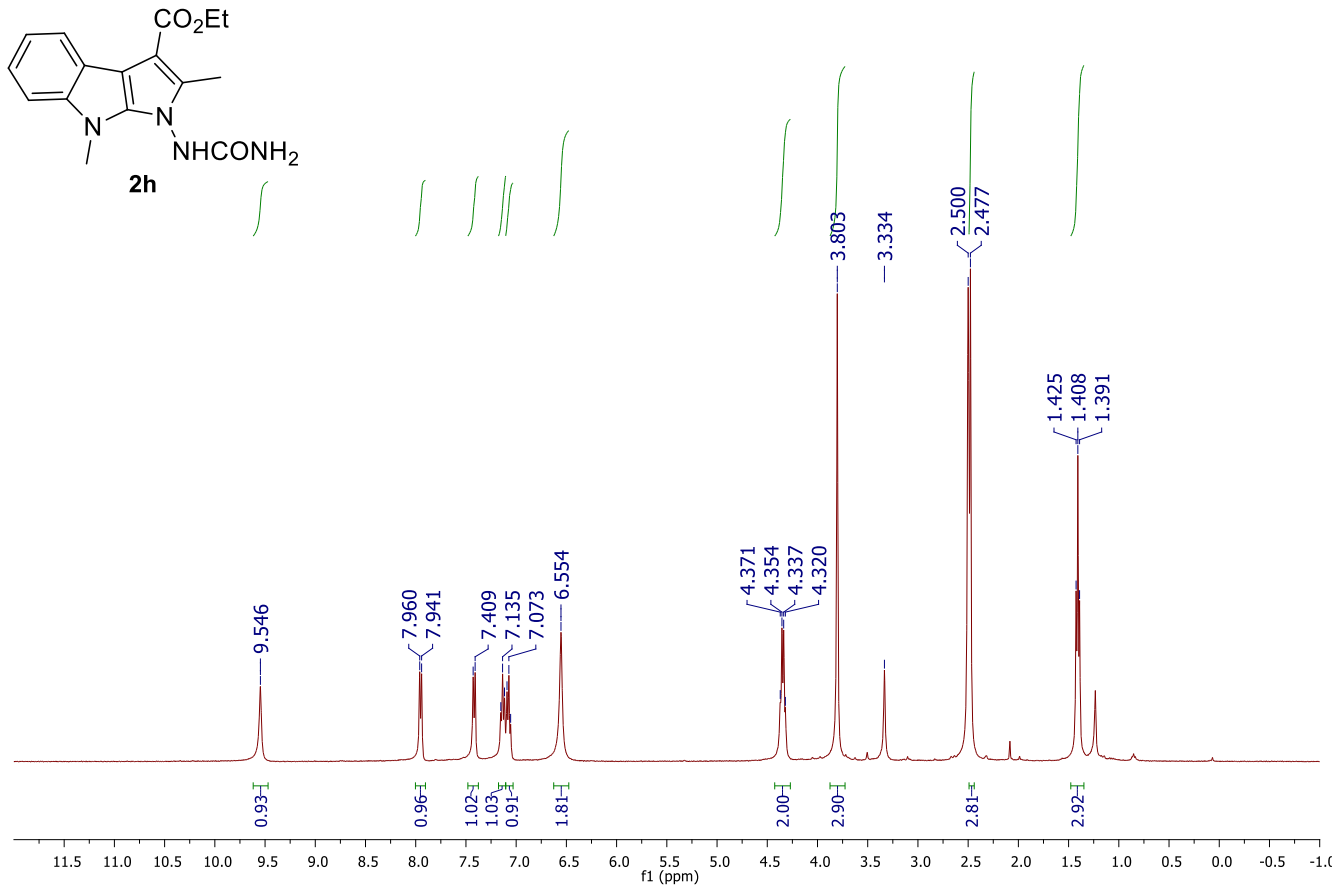

CO2Bn
N
N
NHCO2t-Bu

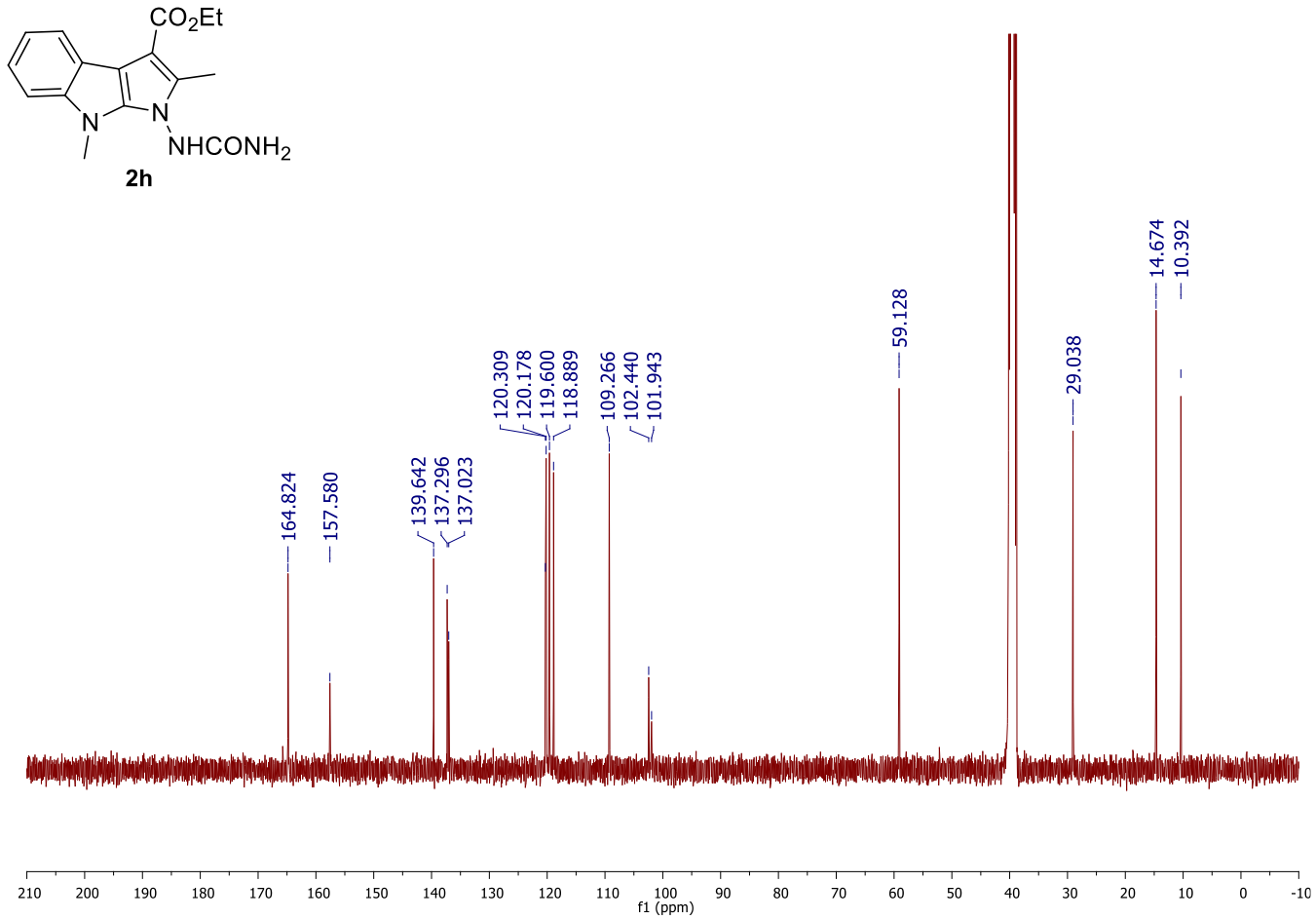
2f

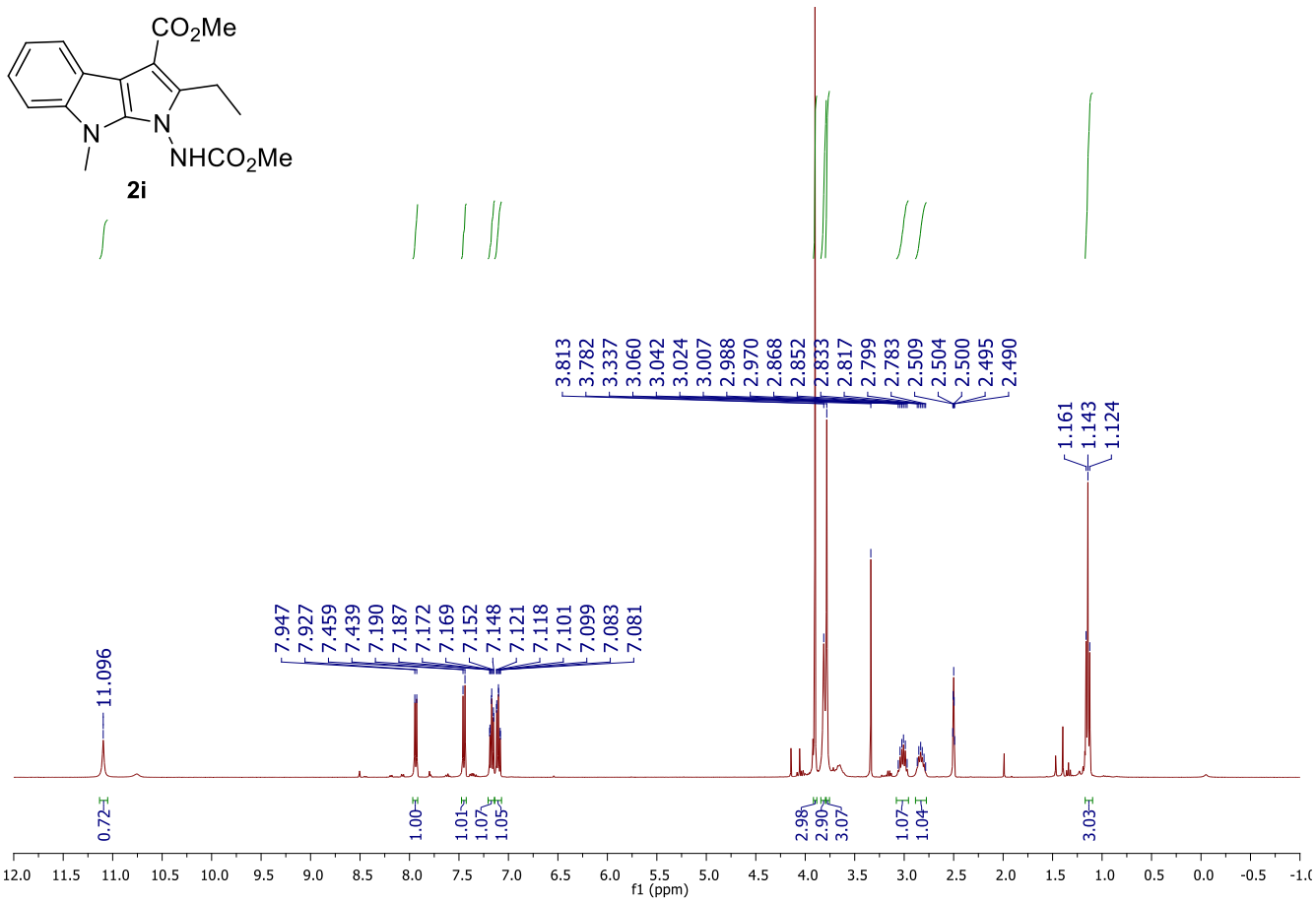
139.650
136.893
136.820
136.391
128.470
128.125
127.948
120.437
120.049
119.764
118.963
164.387
154.649
109.349
102.569
101.908
81.497
64.912
28.966
27.817
10.243
f1 (ppm)

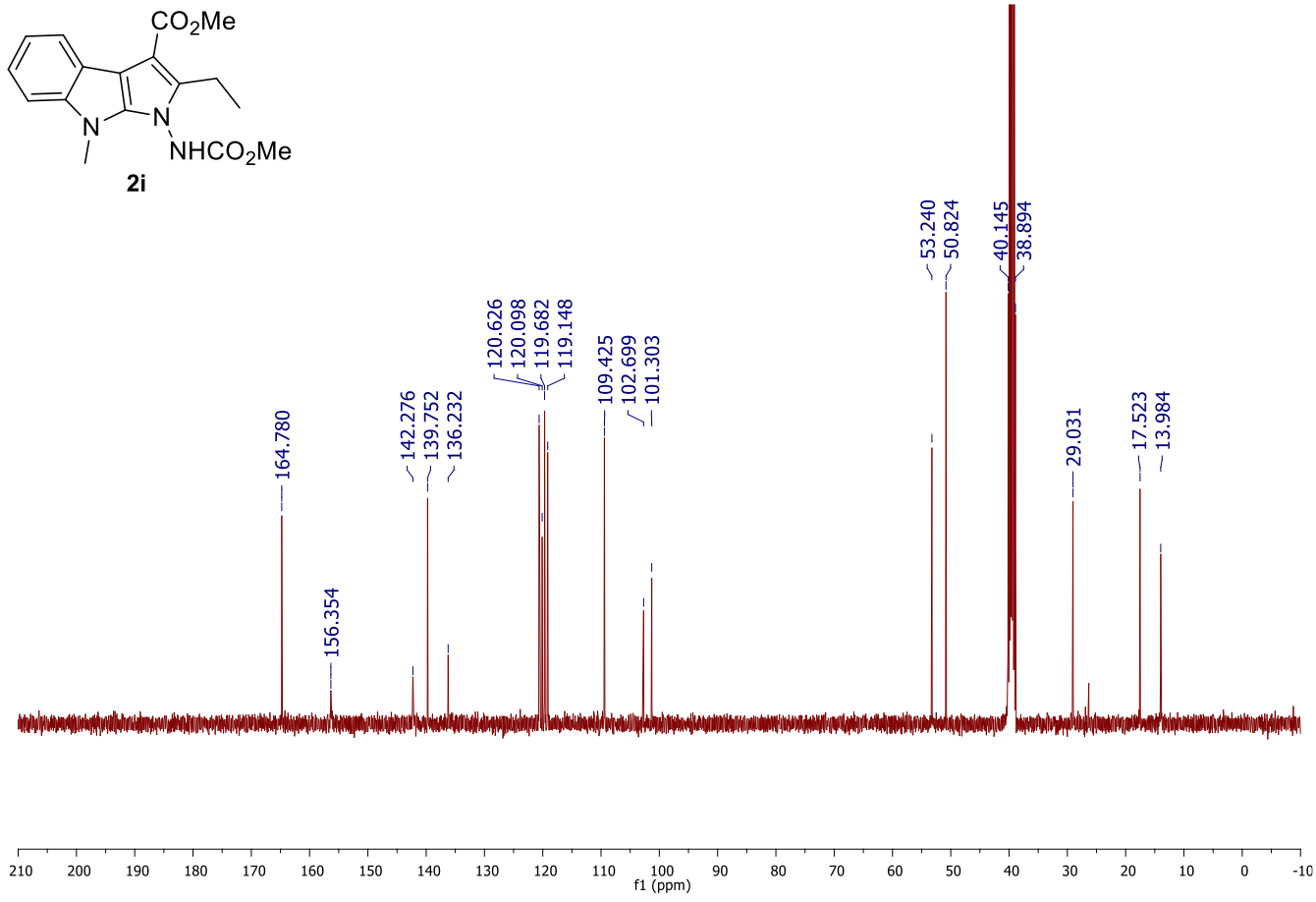

PO(OMe)2
N
N
NHCO2Me
2g
3.797
3.783
3.660
3.639
3.632
3.611
3.331
2.500
2.399
10.980
7.751
7.731
7.458
7.438
7.171
7.153
7.135
7.133
7.102
7.084
7.066
0.91
1.09
1.13
1.20
1.10
2.96
3.26
3.29
3.28
3.00
f1 (ppm)

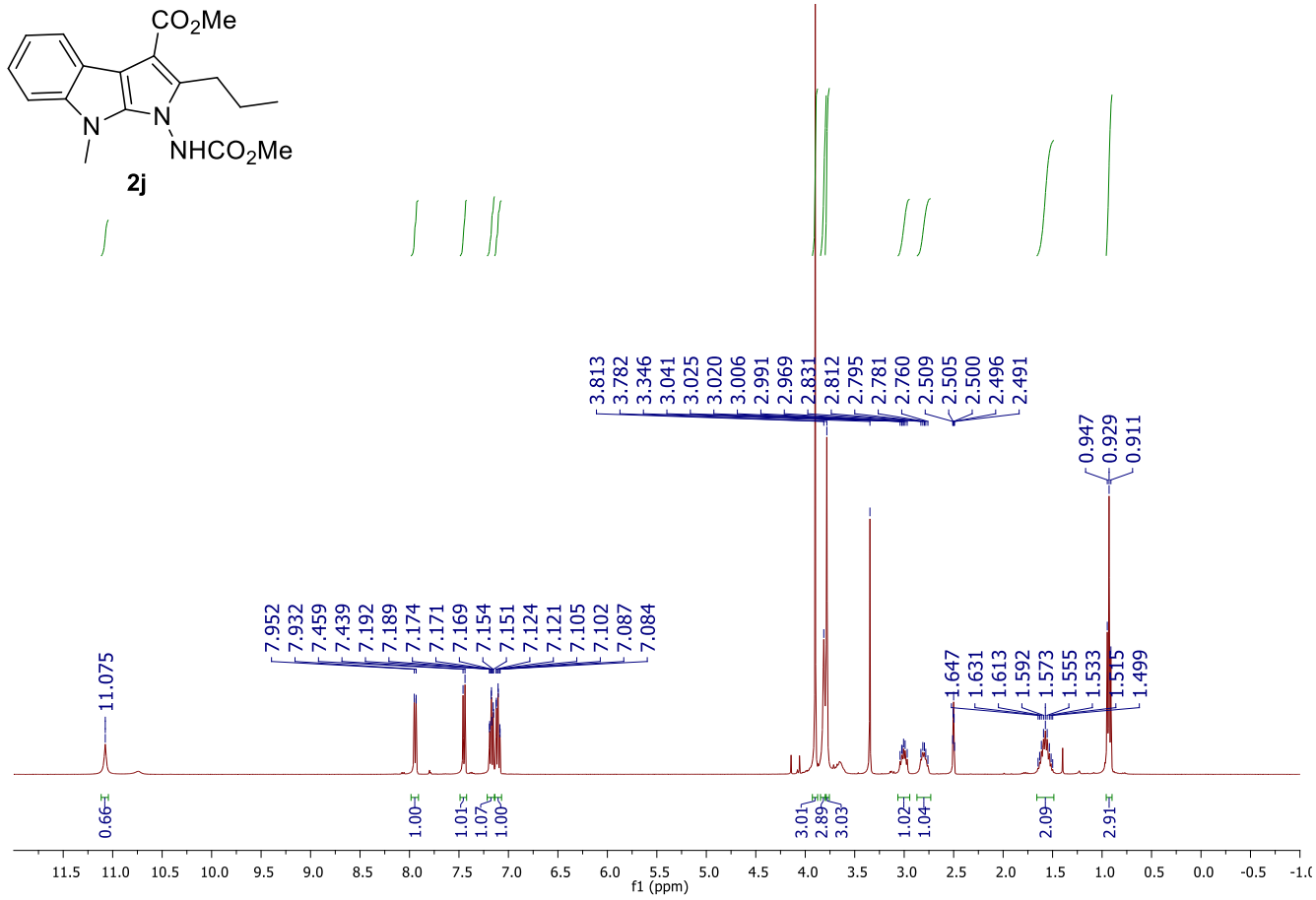

PO(OMe)2
N
N
NHCO2Me
2g
139.626
137.932
137.667
137.067
136.920
120.483
119.728
119.300
109.598
104.262
104.152
94.488
92.338
156.270
53.245
51.773
51.734
29.062
10.192
f1 (ppm)

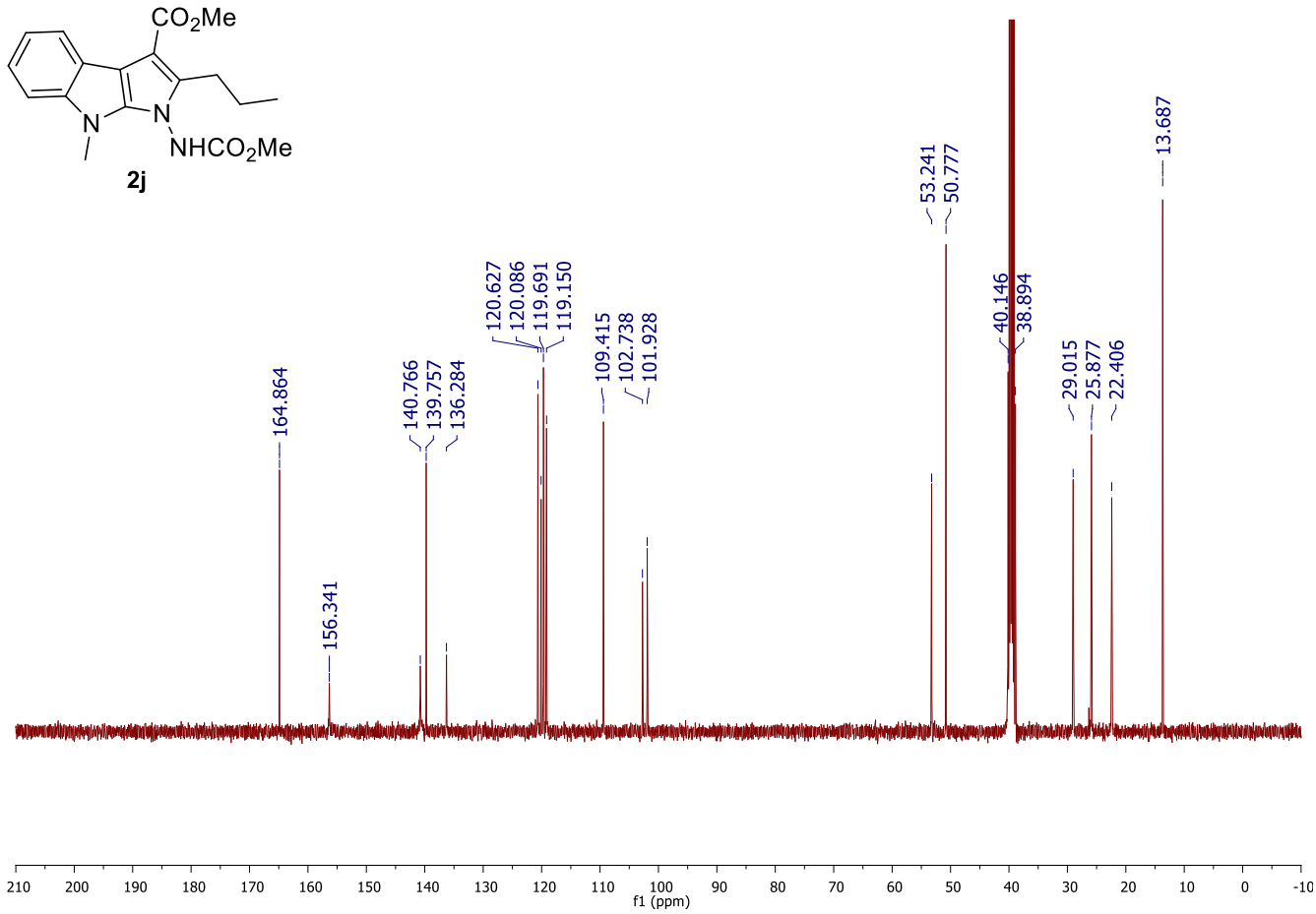

CO2Et
N
N
NHCONH2
2h
9.546
7.960
7.941
7.409
7.135
7.073
6.554
4.371
4.354
4.337
4.320
3.803
3.334
2.500
2.477
1.425
1.408
1.391
0.93
0.96
1.02
1.03
0.91
1.81
2.00
2.90
2.81
2.92
f1 (ppm)

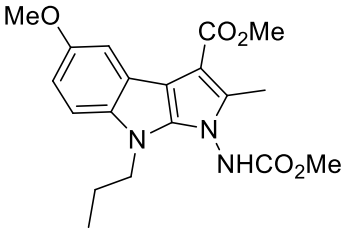

CO2Et
N
N
NHCONH2
2h
164.824
157.580
139.642
137.296
137.023
120.309
120.178
119.600
118.889
109.266
102.440
101.943
59.128
29.038
14.674
10.392
f1 (ppm)


CO2Me
N
N
NHCO2Me
2i
11.096
7.947
7.927
7.459
7.439
7.190
7.187
7.172
7.169
7.152
7.148
7.121
7.118
7.101
7.099
7.083
7.081
3.813
3.782
3.337
3.060
3.042
3.024
3.007
2.988
2.970
2.868
2.852
2.833
2.817
2.799
2.783
2.509
2.504
2.500
2.495
2.490
1.161
1.143
1.124
0.72
1.00
1.01
1.07
1.05
2.98
2.90
3.07
1.07
1.04
3.03
f1 (ppm)


CO2Me
N
N
NHCO2Me
2i
164.780
156.354
142.276
139.752
136.232
120.626
120.098
119.682
119.148
109.425
102.699
101.303
53.240
50.824
40.145
38.894
29.031
17.523
13.984
f1 (ppm)

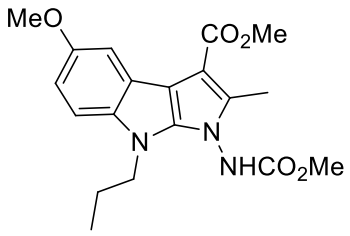

CO2Me
N
N
NHCO2Me
2j
11.075
7.952
7.932
7.459
7.439
7.192
7.189
7.174
7.171
7.169
7.154
7.151
7.124
7.121
7.105
7.102
7.087
7.084
3.813
3.782
3.346
3.041
3.025
3.020
3.006
2.991
2.969
2.831
2.812
2.795
2.781
2.760
2.509
2.505
2.500
2.496
2.491
1.647
1.631
1.613
1.592
1.573
1.555
1.533
1.515
1.499
0.947
0.929
0.911
0.66
1.00
1.01
1.07
1.00
3.01
2.89
3.03
1.02
1.04
2.09
2.91
f1 (ppm)


CO2Me
N
N
NHCO2Me
2j
164.864
156.341
140.766
139.757
136.284
120.627
120.086
119.691
119.150
109.415
102.738
101.928
53.241
50.777
40.146
38.894
29.015
25.877
22.406
13.687
f1 (ppm)


MeO
CO2Me
N
N
NHCO2Me

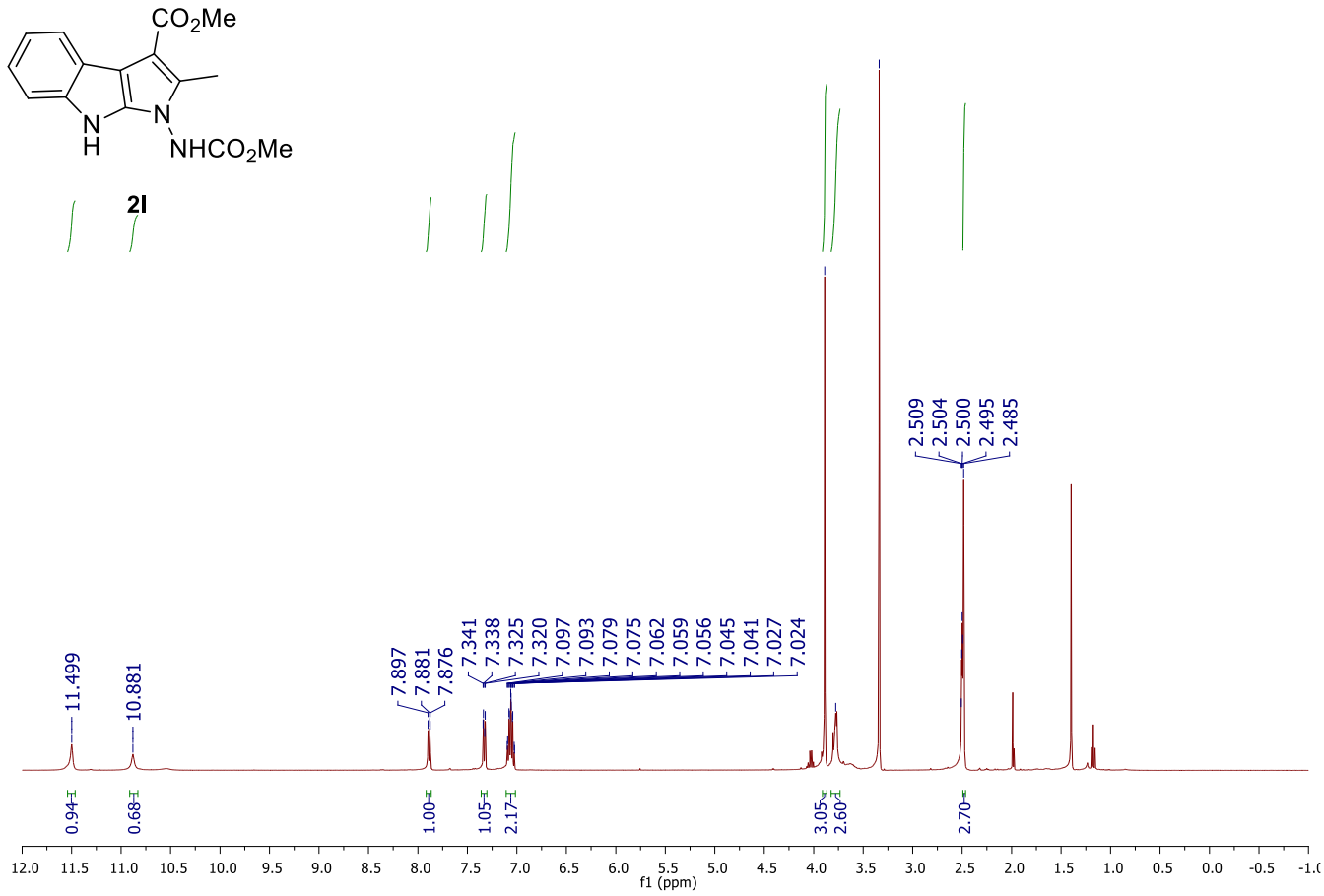
2k

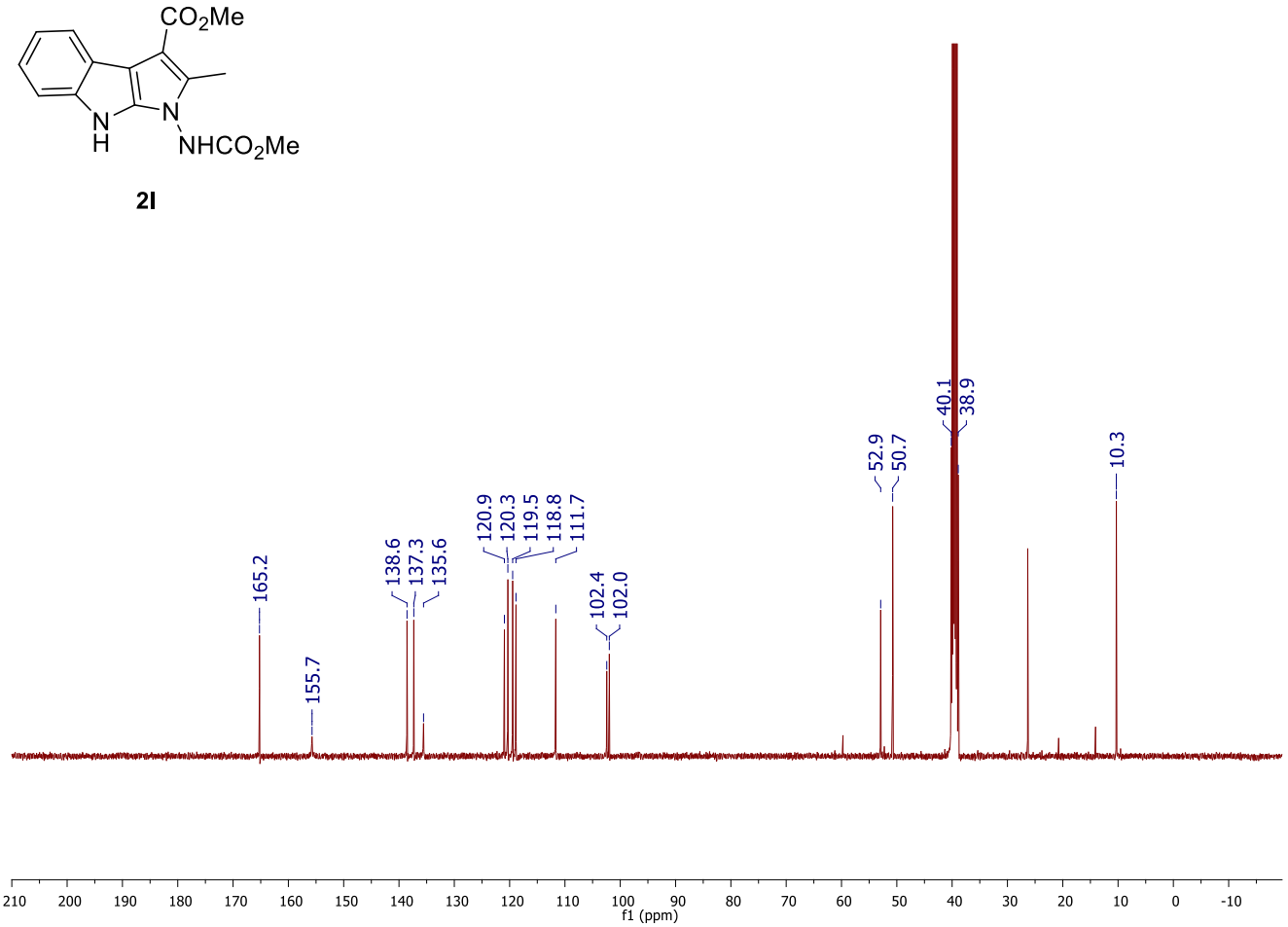
4.235
4.216
4.199
4.181
4.111
4.095
4.076
4.057
4.037
3.889
3.791
3.331
2.500
2.459
0.836
0.817
0.799
7.458
7.452
7.375
7.353
6.783
6.777
6.761
6.755
11.021
1.755
1.738
1.721
1.703
1.687
1.672
1.655
1.637
1.619
1.602
1.585
0.86
1.00
0.99
0.99
2.30
3.04
5.60
2.88
2.13
3.06
f1 (ppm)

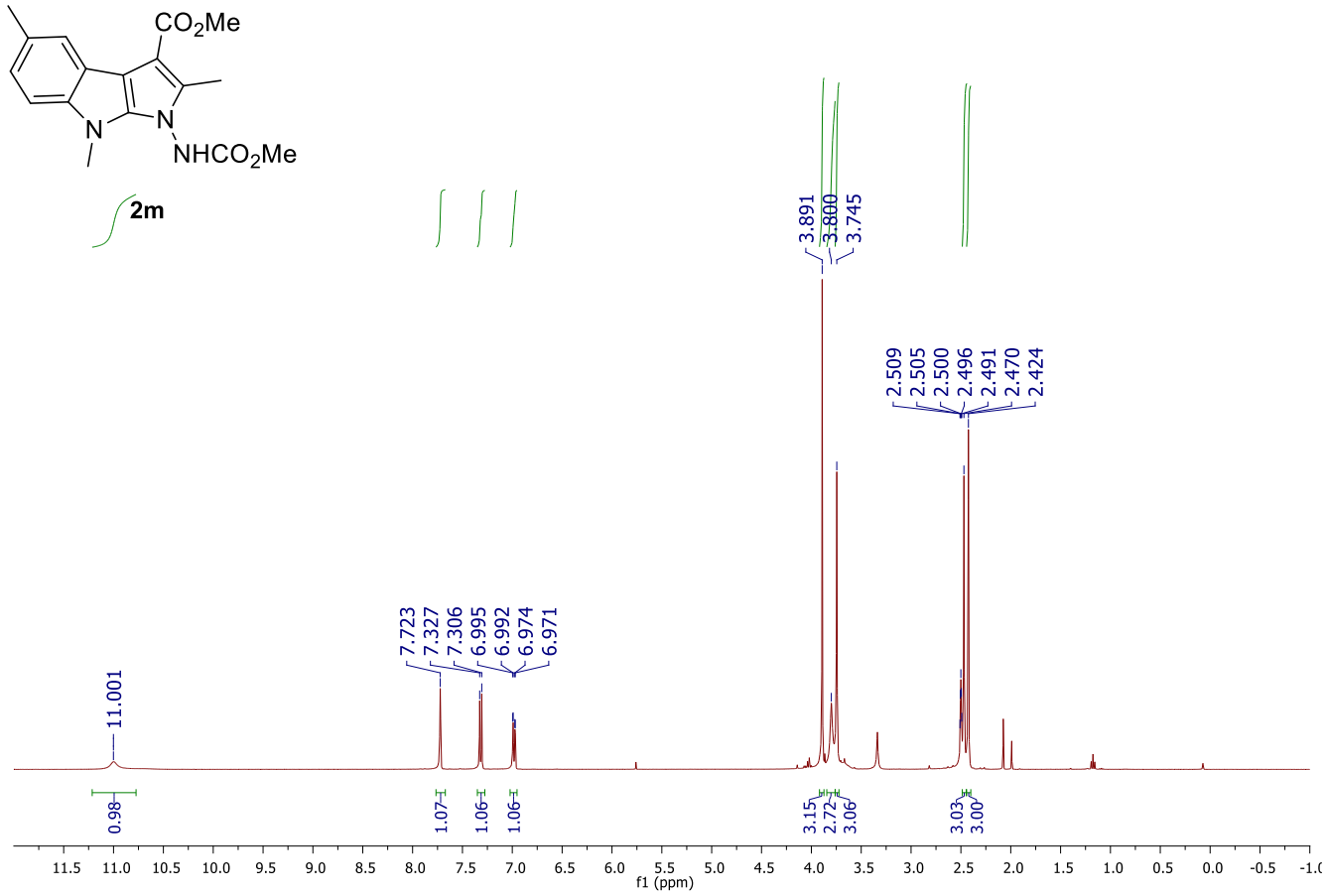

MeO
CO2Me
N
N
NHCO2Me

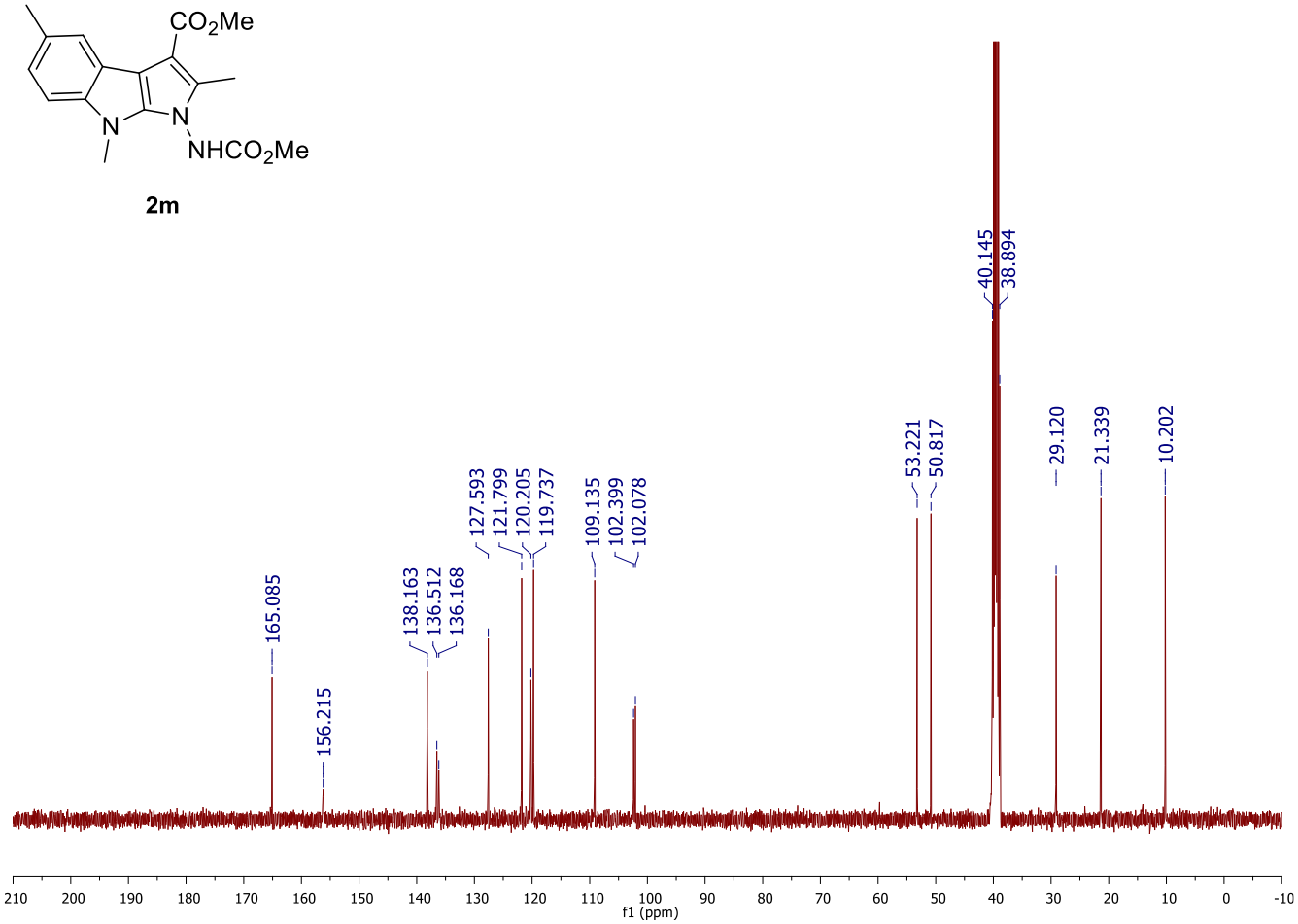
2k

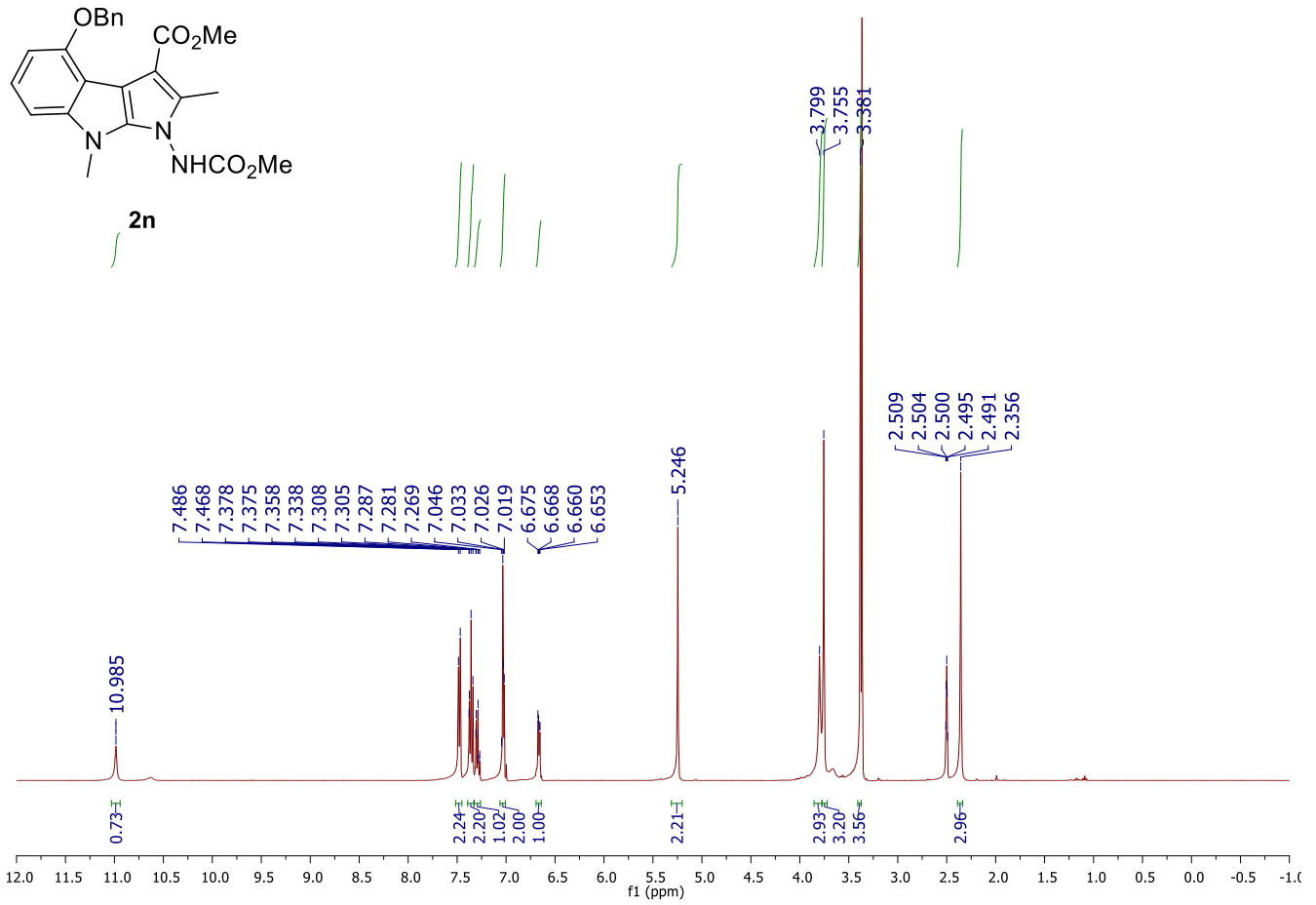
55.284
53.134
50.836
44.319
40.146
38.895
11.061
10.202
23.062
165.027
156.067
153.261
136.561
136.382
134.284
120.457
110.270
109.004
103.112
102.777
102.086
f1 (ppm)

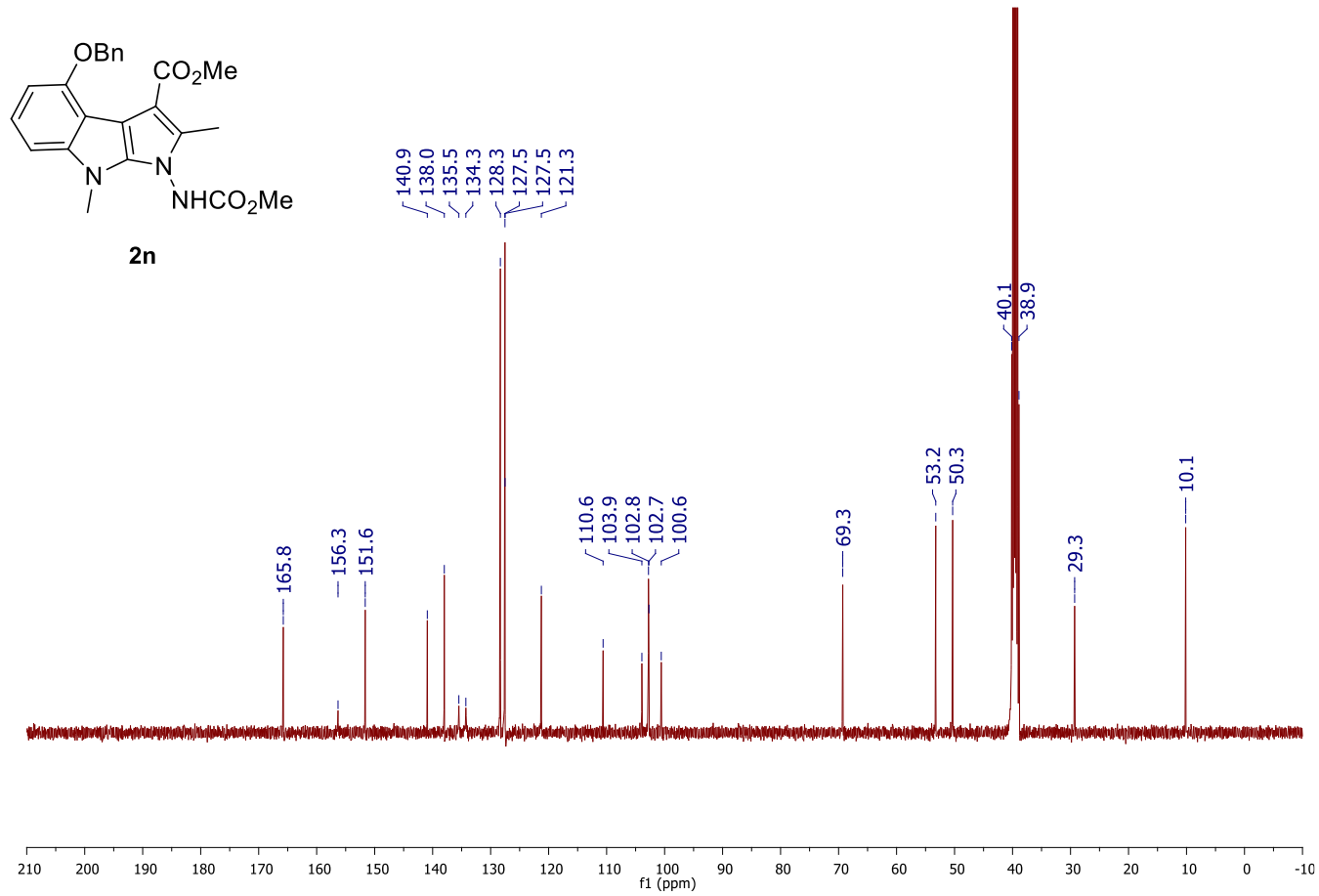

CO2Me
N
H
N
NHCO2Me
2l
11.499
10.881
7.897
7.881
7.876
7.341
7.338
7.325
7.320
7.097
7.093
7.079
7.075
7.062
7.059
7.056
7.045
7.041
7.027
7.024
2.509
2.504
2.500
2.495
2.485
0.94
0.68
1.00
1.05
2.17
3.05
2.60
2.70
f1 (ppm)

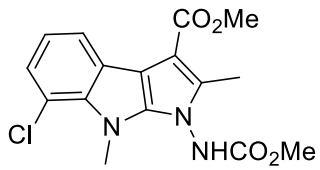

CO2Me
N
H
N
NHCO2Me
2l
165.2
155.7
138.6
137.3
135.6
120.9
120.3
119.5
118.8
111.7
102.4
102.0
52.9
50.7
40.1
38.9
10.3
f1 (ppm)


CO2Me
N
N
NHCO2Me
2m
3.891
3.800
3.745
2.509
2.505
2.500
2.496
2.491
2.470
2.424
7.723
7.327
7.306
6.995
6.992
6.974
6.971
11.001
0.98
1.07
1.06
1.06
3.15
2.72
3.06
3.03
3.00
f1 (ppm)


CO2Me
N
N
NHCO2Me
2m
40.145
38.894
53.221
50.817
29.120
21.339
10.202
165.085
156.215
138.163
136.512
136.168
127.593
121.799
120.205
119.737
109.135
102.399
102.078
f1 (ppm)

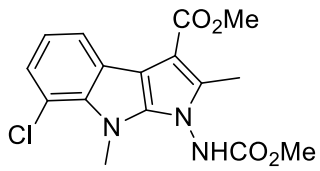

OBn
CO2Me
N
N
NHCO2Me
2n
3.799
3.755
3.381
2.509
2.504
2.500
2.495
2.491
2.356
5.246
7.486
7.468
7.378
7.375
7.358
7.338
7.308
7.305
7.287
7.281
7.269
7.046
7.033
7.026
7.019
6.675
6.668
6.660
6.653
10.985
0.73
2.24
2.20
1.02
2.00
1.00
2.21
2.93
3.20
3.56
2.96
f1 (ppm)


OBn
CO2Me
N
N
NHCO2Me
2n
140.9
138.0
135.5
134.3
128.3
127.5
127.5
121.3
165.8
156.3
151.6
110.6
103.9
102.8
102.7
100.6
69.3
53.2
50.3
40.1
38.9
29.3
10.1
f1 (ppm)


CO2Me
Cl
N
N
NHCO2Me

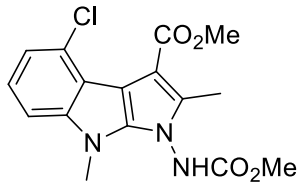
2o

11.110
7.966
7.947
7.164
7.145
7.100
7.081
7.061
4.121
3.893
3.808
3.338
2.500
2.481
0.87
1.00
1.19
0.94
3.32
3.34
2.59
2.71
f1 (ppm)


CO2Me
Cl
N
N
NHCO2Me

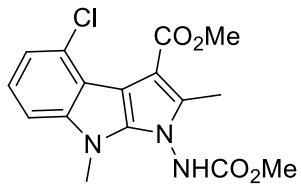
2o

164.761
156.079
137.927
137.086
134.547
123.444
122.518
120.467
119.016
115.607
102.942
101.954
53.329
50.948
40.146
38.895
32.229
10.192
f1 (ppm)


Cl
CO2Me
N
N
NHCO2Me

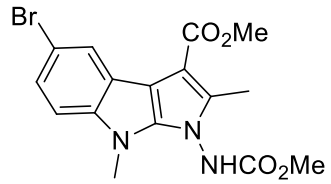
2p

11.021
7.479
7.467
7.460
7.452
7.445
7.433
7.160
7.141
7.132
7.125
7.113
3.814
3.779
3.324
2.508
2.504
2.500
2.496
2.492
2.341
0.63
1.00
2.06
6.12
3.03
3.00
f1 (ppm)

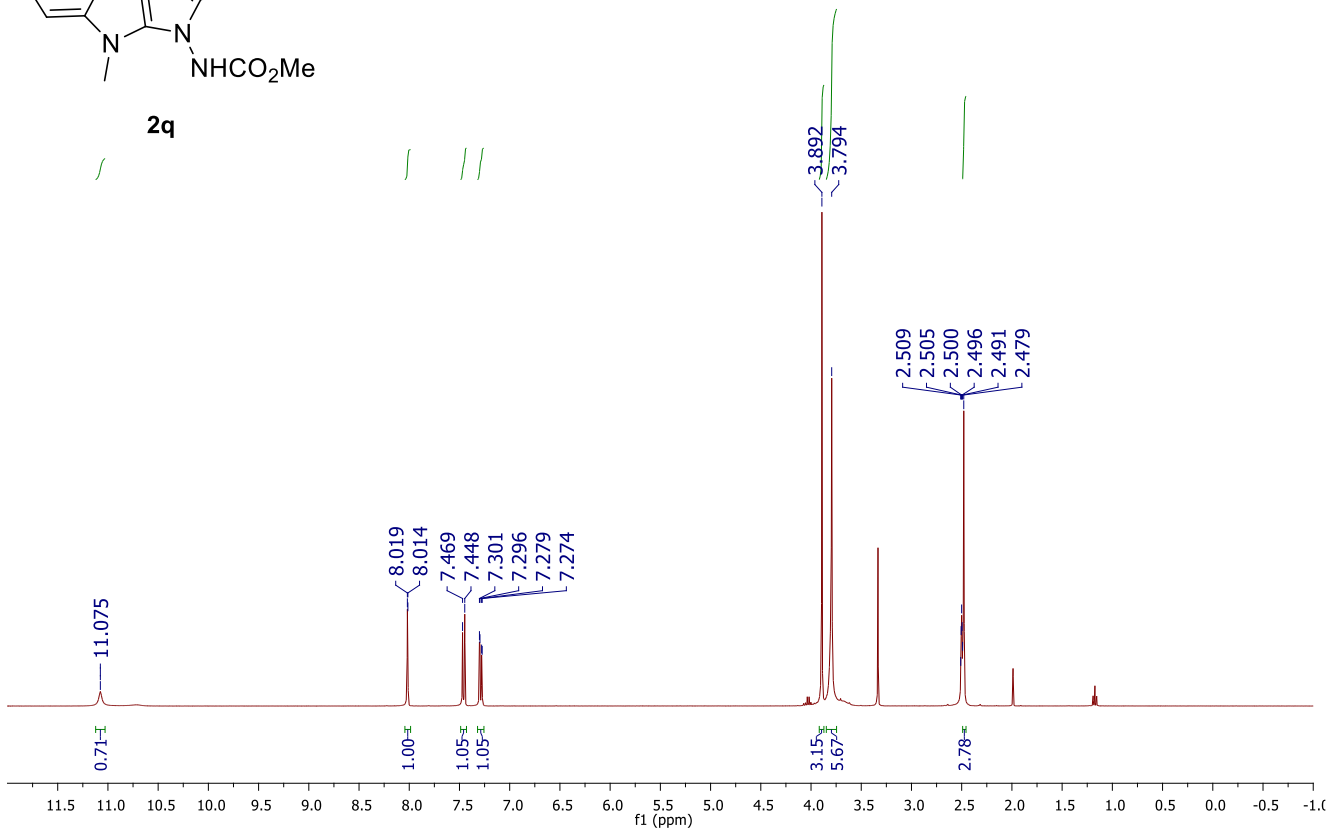

Cl
CO2Me
N
N
NHCO2Me

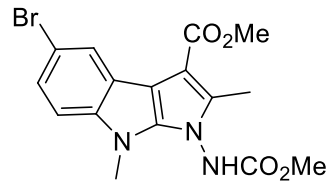
2p

165.555
156.256
140.491
136.969
134.656
123.680
121.068
120.184
108.430
104.079
100.041
53.293
50.701
29.368
10.045
f1 (ppm)


Br
CO2Me
N
N
NHCO2Me

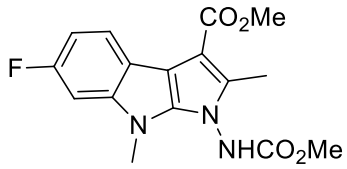
2q


11.075
8.019
8.014
7.469
7.448
7.301
7.296
7.279
7.274
3.892
3.794
2.509
2.505
2.500
2.496
2.491
2.479
0.71
1.00
1.05
1.05
3.15
5.67
2.78
f1 (ppm)


Br
CO2Me
N
N
NHCO2Me

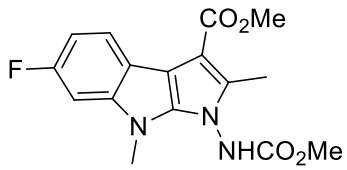
2q

164.8
156.2
138.4
137.3
137.0
122.8
121.7
121.5
111.7
111.5
102.0
53.4
51.1
40.1
38.9
29.3
10.3
f1 (ppm)


CO2Me
F
N
N
NHCO2Me

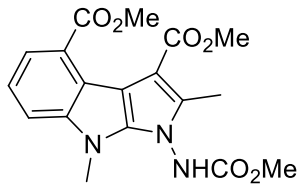
2r

11.066
7.900
7.885
7.878
7.864
7.395
7.389
7.368
7.363
6.964
6.958
6.942
6.940
6.936
6.934
6.918
6.912
3.888
3.803
3.772
3.363
2.509
2.504
2.500
2.495
2.491
2.473
0.74
0.99
0.98
0.99
3.00
2.80
2.95
2.56
f1 (ppm)


CO2Me
F
N
N
NHCO2Me

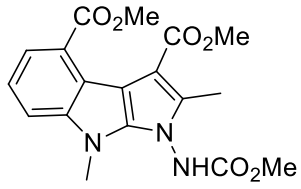
2r

164.964
159.452
157.128
156.199
139.906
139.784
136.323
120.384
120.285
116.770
106.862
106.628
102.458
101.885
96.892
96.623
59.742
53.281
50.893
40.146
38.894
29.402
10.137
f1 (ppm)


CO2Me
CO2Me
N
N
NHCO2Me

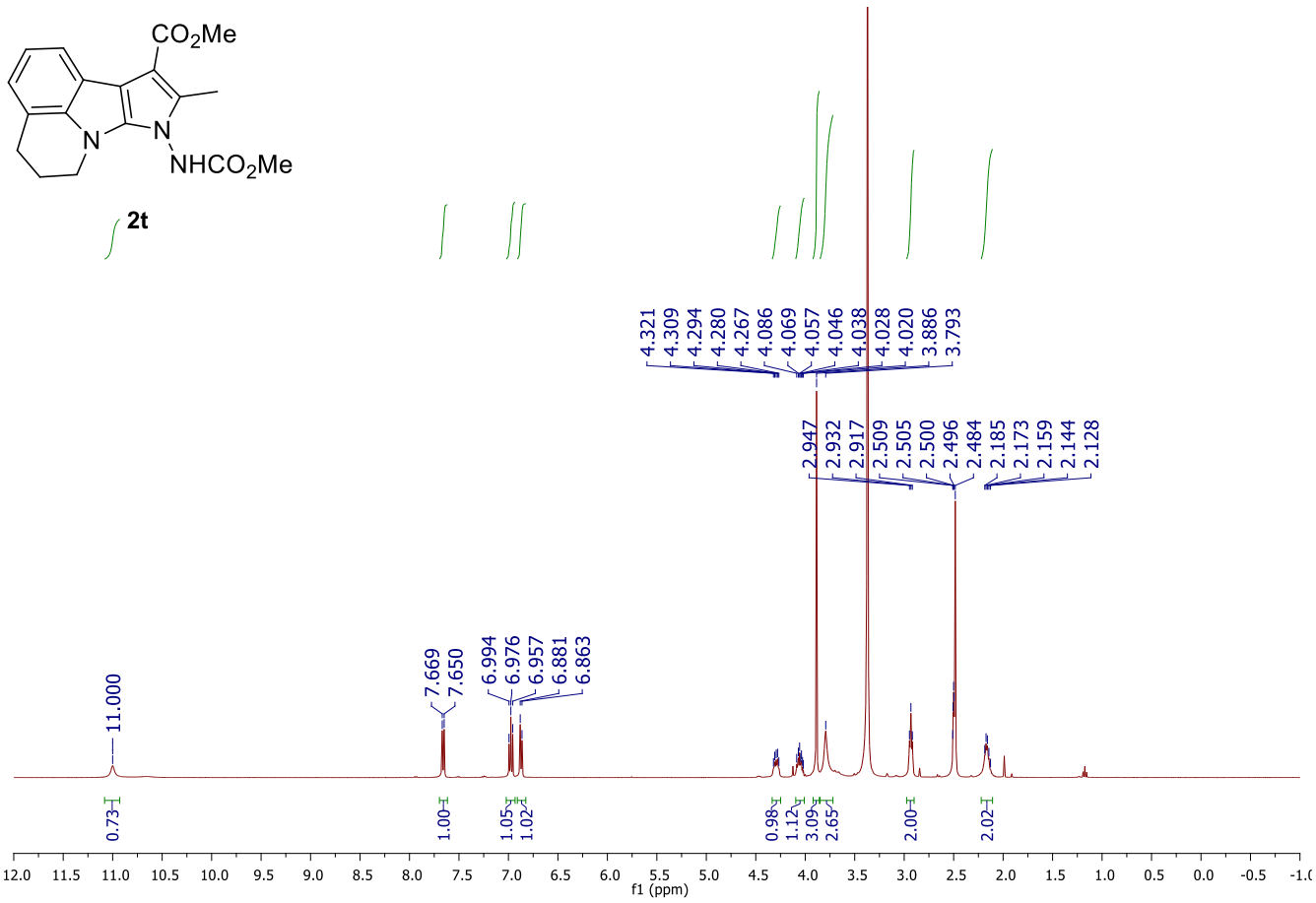
2s

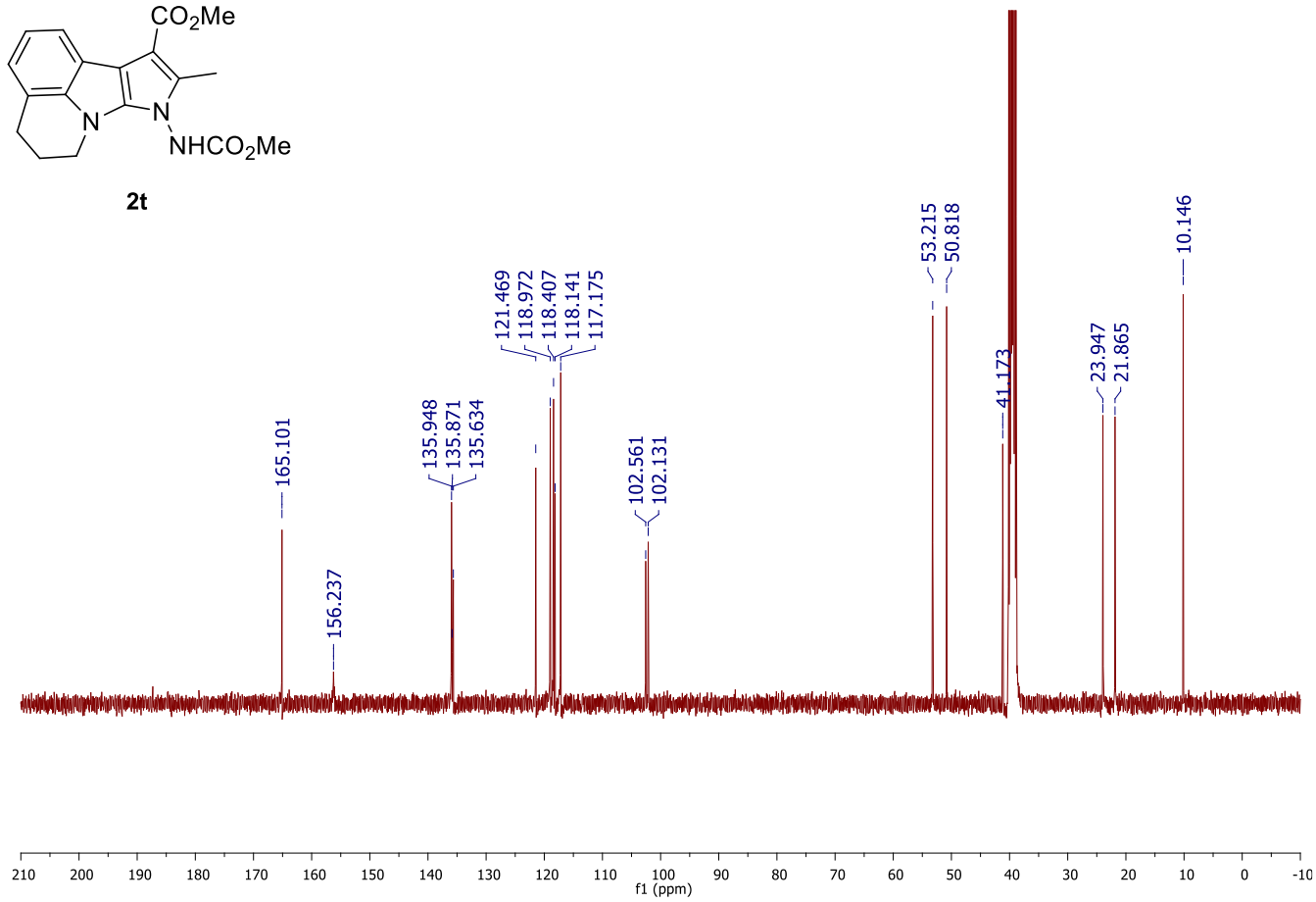
3.834
3.806
3.746
3.720
3.331
2.508
2.504
2.500
2.495
2.491
2.363
7.688
7.668
7.399
7.379
7.223
7.203
7.184
11.037
0.86
0.99
0.99
1.02
3.39
2.72
3.48
3.00
3.00
f1 (ppm)

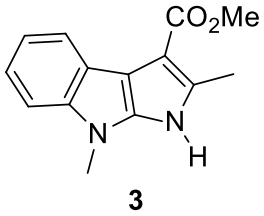

CO2Me
CO2Me
N
N
NHCO2Me

2s

40.1
39.9
39.1
38.9
53.3
51.4
51.0
10.0
29.2
123.0
120.4
119.5
117.9
113.0
168.8
165.4
139.9
137.8
135.2
104.4
101.9
156.3
f1 (ppm)

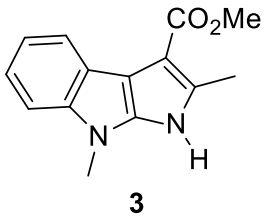

CO2Me
N
N
NHCO2Me
2t
4.321
4.309
4.294
4.280
4.267
4.086
4.069
4.057
4.046
4.038
4.028
4.020
3.886
3.793
2.947
2.932
2.917
2.509
2.505
2.500
2.496
2.484
2.185
2.173
2.159
2.144
2.128
11.000
7.669
7.650
6.994
6.976
6.957
6.881
6.863
0.73
1.00
1.05
1.02
0.98
1.12
3.09
2.65
2.00
2.02
f1 (ppm)


CO2Me
N
N
NHCO2Me
2t
165.101
156.237
135.948
135.871
135.634
121.469
118.972
118.407
118.141
117.175
102.561
102.131
53.215
50.818
41.173
23.947
21.865
10.146
f1 (ppm)


CO2Me
N
N
H

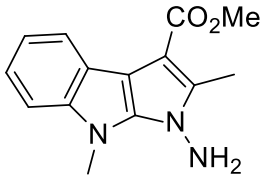
3

9.949
7.827
7.810
7.373
7.354
7.326
7.320
7.313
7.307
7.302
7.297
7.273
4.020
3.712
2.336
0.77
0.91
3.19
2.68
3.19
2.76
f1 (ppm)

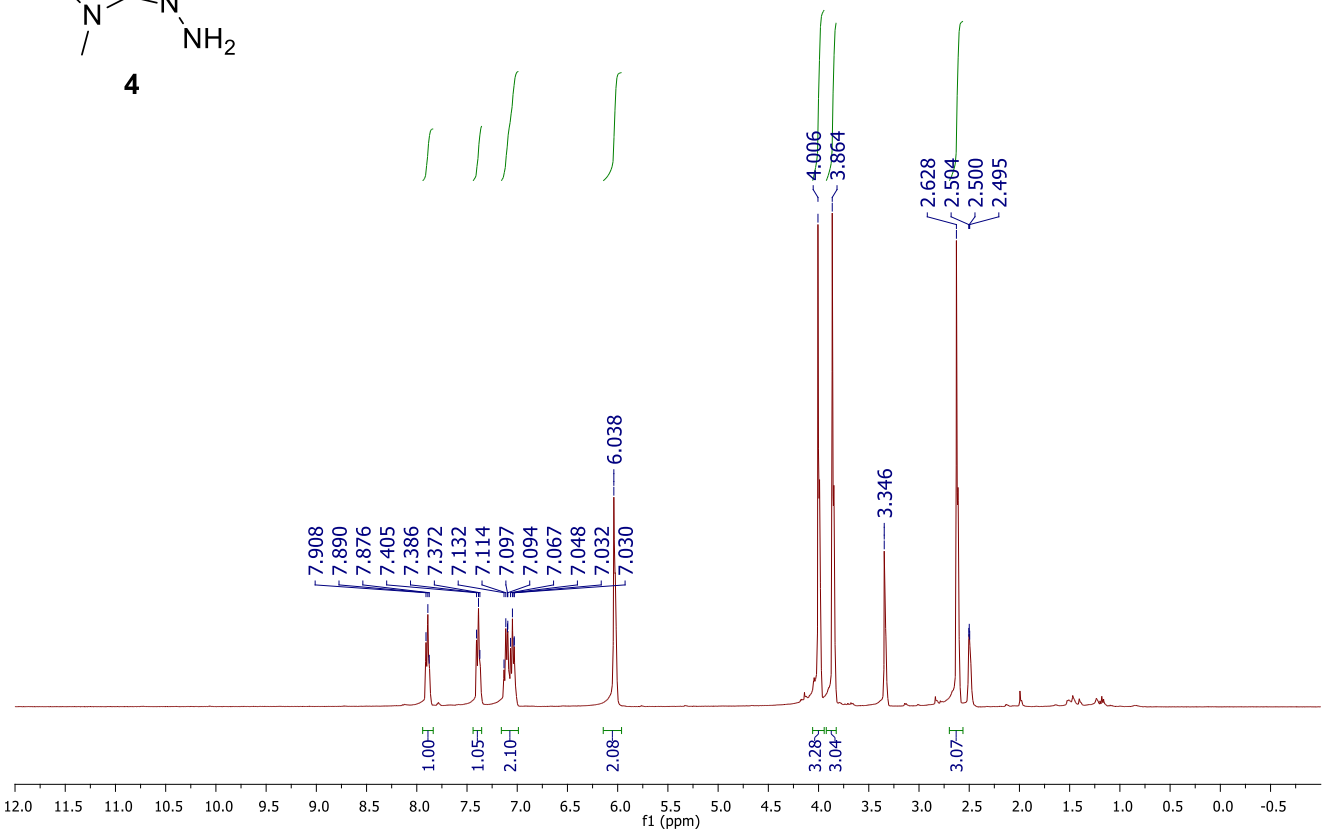

CO2Me
N
N
H

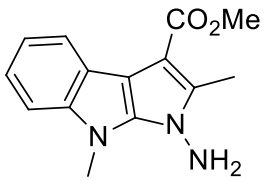
3

179.8
169.5
165.7
144.8
135.7
124.2
123.8
123.8
120.3
110.4
101.5
53.0
32.9
24.4
f1 (ppm)


CO2Me
N
N
NH2

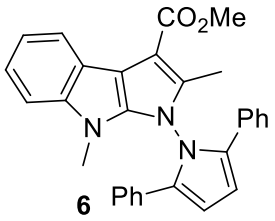
4


7.908
7.890
7.876
7.405
7.386
7.372
7.132
7.114
7.097
7.094
7.067
7.048
7.032
7.030
6.038
4.006
3.864
3.346
2.628
2.504
2.500
2.495
1.00
1.05
2.10
2.08
3.28
3.04
3.07
f1 (ppm)

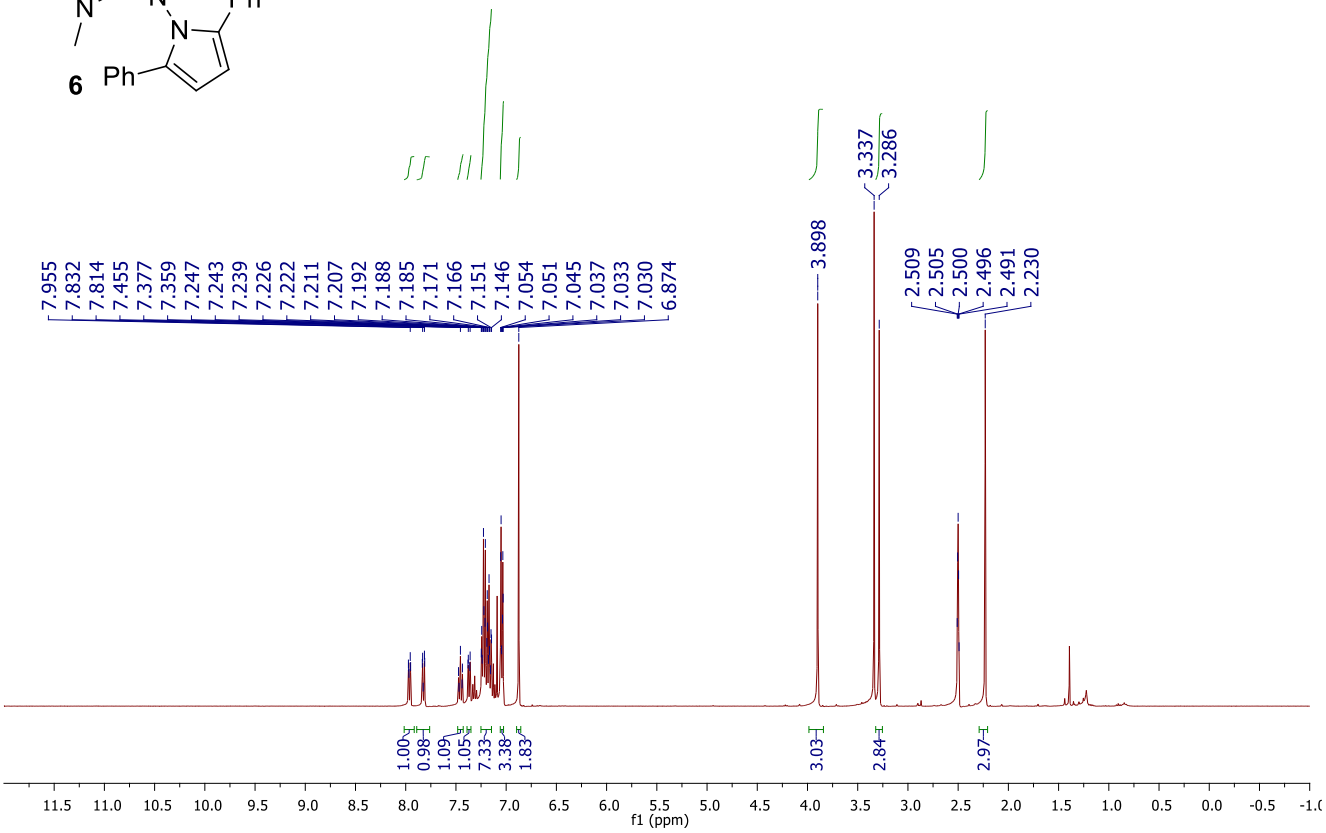

CO2Me
N
N
NH2

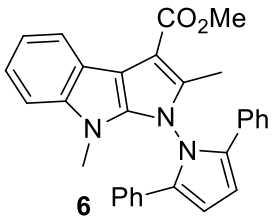
4

165.364
139.919
137.476
137.338
120.313
119.904
119.421
118.582
109.089
102.150
99.832
50.450
29.645
10.641
f1 (ppm)


CO2Me
N
N
N
Ph
Ph

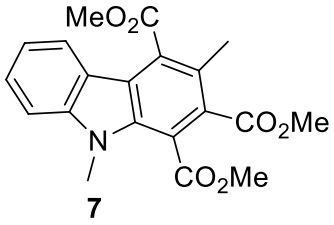
6


7.955
7.832
7.814
7.455
7.377
7.359
7.247
7.243
7.239
7.226
7.222
7.211
7.207
7.192
7.188
7.185
7.171
7.166
7.151
7.146
7.054
7.051
7.045
7.037
7.033
7.030
6.874
3.898
3.337
3.286
2.509
2.505
2.500
2.496
2.491
2.230
1.00
0.98
1.09
1.05
7.33
3.38
1.83
3.03
2.84
2.97
f1 (ppm)

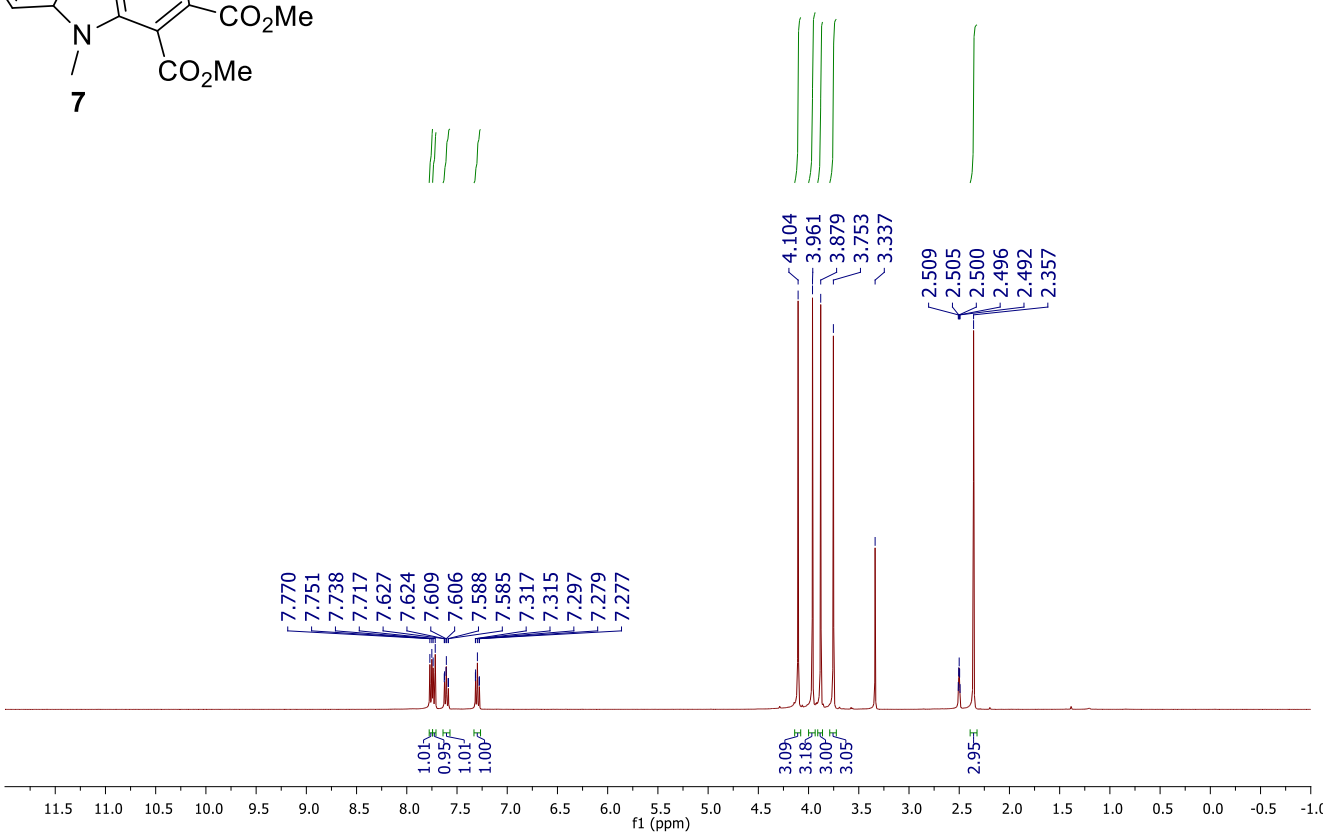

CO2Me
N
N
N
Ph
Ph

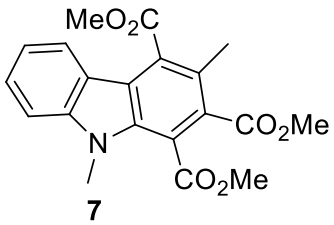
6

139.9
136.1
135.2
135.0
130.1
129.8
129.0
128.9
127.7
127.5
126.1
123.4
121.1
120.1
119.9
119.6
109.9
109.2
108.2
103.5
102.9
164.7
152.6
51.1
40.1
39.9
39.1
38.9
28.5
10.3
f1 (ppm)


MeO2C
CO2Me
N
CO2Me

7


4.104
3.961
3.879
3.753
3.337
2.509
2.505
2.500
2.496
2.492
2.357
7.770
7.751
7.738
7.717
7.627
7.624
7.609
7.606
7.588
7.585
7.317
7.315
7.297
7.279
7.277
1.01
0.95
1.01
1.00
3.09
3.18
3.00
3.05
2.95
f1 (ppm)


MeO2C
CO2Me
N
CO2Me

7

40.1
39.9
39.1
38.9
31.7
53.1
52.8
16.2
142.8
134.7
129.9
129.0
128.0
121.7
121.0
120.8
120.5
118.6
116.3
110.3
168.5
167.8
166.8
f1 (ppm)

7. First Pass CHEM21 green metrics toolkit

Reaction carried out on a gram scale. Typical procedure.

In a round-bottom flask, methyl 2-(4-methoxy-3-(1-methyl-1*H*-indol-3-yl)-4-oxobutan-2-lidene)hydrazinecarboxylate **1a** (3.15 mmol, 1 g), $Cu(OAc)_2 \cdot H_2O$ (0.315 mmol, 62.9 mg), $FeCl_3 \cdot 6H_2O$ (0.157 mmol, 42.4 mg) and water (30 mL) were added. The aqueous suspension was stirred at 50 °C (oil bath) until consumption of the starting material (12 h, TLC check). Then, the crude product that precipitates was collected on a Büchner funnel, washed with water (5 mL), and dried in air or a vacuum desiccator to give the corresponding product **2a** (0.933 g, 94% yields).

Summary of First Pass Metrics Toolkit

Yield, AE, RME, MI/PMI and OE

Reactant (Limiting Reactant First)	Mass (g)	MW	Mol	Catalyst	Mass (g)	Reagent	Mass (g)	Reaction solvent	Volume (cm^3)	Density ($g\ ml^{-1}$)	Mass (g)	Work up chemical	Mass (g)	Workup solvent	Volume (cm3)	Density ($g\ ml^{-1}$)	Mass (g)
1a	1,00	317,345	0,00315	$Cu(OAc)_2{\cdot}H_2O$	0,0629			H_2O	30,00	1,00	30,00			water	5,00	1,00	5,00
			#DIV/0!	$FeCl_3{\cdot}6H_2O$	0,0424						0,00						0,00
			#DIV/0!								0,00						0,00
			#DIV/0!								0,00						0,00
			#DIV/0!								0,00						0,00
			#DIV/0!								0,00						0,00
			#DIV/0!								0,00						0,00
Total	1,00	317,35			0,11		0,00				30,00		0,00				5,00

$$RME = \frac{mass\ of\ isolated\ product}{total\ mass\ of\ reactants} \times 100$$

$$AE = \frac{molecular\ weight\ of\ product}{total\ molecualr\ weight\ of\ reactants} \times 100$$

$$mass\ intensity = \frac{total\ mass\ in\ a\ process\ or\ process\ step}{mass\ of\ product}$$

$$OE = \frac{RME}{AE} \times 100$$

		Flag
Yield	93,9	93,9
Conversion	100,0	100,0
Selectivity	93,9	93,9
AE	99,4	
RME	93,3	OE 93,9
PMI total	38,7	
PMI Reaction	33,3	
reagents, catlyst	1,2	
PMI reaction solvents	32,2	
PMI Workup	5,4	
PMI Workup chemical	0,0	
PMI workup solvents	5,4	

	Mass	MW	Mol
Product 2a	0,933	315,329	0,0030
	mass		
Unreacted limiting reactant	0,00		

Solvents (First Pass)

		List solvents below
Preferred solvents	**water,** EtOH, nBuOH, AcOipr, AcOnBu, PhOMe, MeOH, tBuOH, BnOH, ethylene glycol, acetone, MEK, MIBK, **AcOEt,** sulfolane	**water**
Problematic solvents: (acceptable only if substitution does not offer advantages)	DMSO, cyclohexanone, DMPU, AcOH, Ac2O, Acetonitrile, AcOMe, THF, heptane, Me-cyclohexane, toluene, xylene, MTBE, **cyclohexane**, chlorobenzene, formic acid, pyridine, Me-THF	
Hazardous solvents: These solvents have significant health and/or safety concerns.	dioxane, pentane, TEA, diisopropyl ether, DME, DCM, DMF, DMA, NMP, methoxyethanol, hexane	
Highly hazardous solvents: The solvents which are agreed not to be used, even in screening	Et_2O, Benzene, CCl_4, chloroform, DCE, nitromethane, CS_2, HMPA	

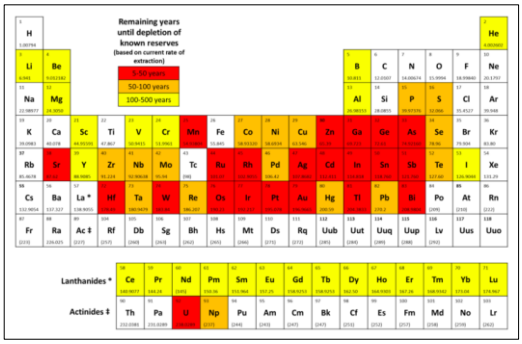
Catalyst/enzyme (First Pass)

		Tick
Catalyst or enzyme used, **or** reaction takes place without **any** catalyst/reagents.	Green Flag	X
Use of stoichiometric quantities of reagents	Amber Flag	
Use of reagents in excess	Red Flag	

		Tick
Facile recovery of catalyst/enzyme	Green Flag	X
catalyst/enzyme not recovered	Amber Flag	

Critical elements

Supply remaining	Flag colour	Note element
5-50 years	Red Flag	
50-500 years	Amber Flag	Cu
+500 years	Green Flag	



Energy (First Pass)

		Tick
Reaction run between 0 to 70°C	Green Flag	X
Reaction run between -20 to 0 or 70 to 140°C	Amber Flag	
Reaction run below -20 or above 140°C	Red Flag	

		Tick
Reaction run at reflux	Red Flag	
Reaction run 5°C or more below the solvent boiling point	Green Flag	X

Batch/flow

		Tick
Flow	Green Flag	
Batch	Amber Flag	X

Work Up

		List
quenching filtration centrifugation crystallisation Low temperature distillation/evaporation/ sublimation (<	Green Flag	filtration
solvent exchange, quenching into aqueous solvent	Amber Flag	
chromatography/ion exchange high temperature multiple recrystallisation	Red Flag	

Health & safety

	Red Flag	Amber Flag	Green Flag	List substances and H-codes	List substances and H-codes	List substances and H-codes
Highly explosive	H200, H201, H202, H203	H205, H220, H224	If no red or amber flagged H codes present then green flag	none	none	none
Explosive thermal runaway	H230, H240, H250	H241				
Toxic	H300, H310, H330	H301, H311, H331,				
Long Term toxicity	H340, H350, H360, H370, H372	H341, H351, H361, H371, H373				
Environmental implications	H400, H410, H411, H420	H401, H412				

Use of chemicals of environmental concern		List substances of very high concern
Chemical identified as Substances of Very High Concern by ChemSec which are utilised	Red Flag	none

8. References

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