

# Iron-Catalyzed C—H Insertions: Organometallic and Enzymatic Carbene Transfer Reactions

Katharina J. Hock, Anja Knorrscheidt, Renè Hommelsheim, Junming Ho, Martin J. Weissenborn, Rene M. Koenigs

Submitted date: 21/03/2018 • Posted date: 21/03/2018

Licence: CC BY-NC-ND 4.0

Citation information: Hock, Katharina J.; Knorrscheidt, Anja; Hommelsheim, Renè; Ho, Junming; Weissenborn, Martin J.; Koenigs, Rene M. (2018): Iron-Catalyzed C—H Insertions: Organometallic and Enzymatic Carbene Transfer Reactions. ChemRxiv. Preprint.

C—H insertion reactions with organometallic and enzymatic catalysts based on earth-abundant iron complexes remain one of the major challenges in organic synthesis. In this report, we describe the development and application of these iron-based catalysts in the reaction of two different carbene precursors with N-heterocycles for the first time. While FeTPPCI showed excellent reactivity in the Fe(III) state with diazoacetonitrile, the highest activities of the YfeX enzyme could be achieved upon heme-iron reduction to Fe(II) with both diazoacetonitrile and ethyl diazoacetate. This highlights unexpected and subtle differences in reactivity of both iron catalysts. Deuterium labeling studies indicated a C—H insertion pathway and a marked kinetic isotope effect. This transformation features mild reaction conditions, excellent yields or turnover numbers with broad functional group tolerance, including gram-scale applications giving a unique access to functionalized N-heterocycles.

## File list (2)

manuscript.pdf (1.14 MiB)

[view on ChemRxiv](#) • [download file](#)

SI.pdf (6.01 MiB)

[view on ChemRxiv](#) • [download file](#)

# Iron-catalyzed C—H insertions: organometallic and enzymatic carbene transfer reactions

Katharina J. Hock,<sup>[a]</sup> Anja Knorrscheidt,<sup>[b,c]</sup> Renè Hommelsheim,<sup>[a]</sup> Junming Ho,<sup>[d]</sup> Martin J. Weissenborn,<sup>\*[b,c]</sup> and Rene M. Koenigs<sup>\*[a]</sup>

[a] Institute of Organic Chemistry, RWTH Aachen University, Landoltweg 1, 52074 Aachen, Germany, E-mail: [rene.koenigs@rwth-aachen.de](mailto:rene.koenigs@rwth-aachen.de), [www.koenigslab.rwth-aachen.de](http://www.koenigslab.rwth-aachen.de)

[b] Leibniz Institute of Plant Biochemistry, Weinberg 3, 06120 Halle (Saale), Germany, E-mail: [martin.weissenborn@ipb-halle.de](mailto:martin.weissenborn@ipb-halle.de)

[c] Martin-Luther-University Halle-Wittenberg, Institute of Chemistry, 06099 Halle (Saale), Germany

[d] School of Chemistry, University of Sydney, Sydney NSW 2006, Australia.

## Abstract

C—H insertion reactions with organometallic and enzymatic catalysts based on earth-abundant iron complexes remain one of the major challenges in organic synthesis. In this report, we describe the development and application of these iron-based catalysts in the reaction of two different carbene precursors with *N*-heterocycles for the first time. While FeTPPCI showed excellent reactivity in the Fe(III) state with diazoacetonitrile, the highest activities of the YfeX enzyme could be achieved upon heme-iron reduction to Fe(II) with both diazoacetonitrile and ethyl diazoacetate. This highlights unexpected and subtle differences in reactivity of both iron catalysts. Deuterium labeling studies indicated a C—H insertion pathway and a marked kinetic isotope effect. This transformation features mild reaction conditions, excellent yields or turnover numbers with broad functional group tolerance, including gram-scale applications giving a unique access to functionalized *N*-heterocycles.

## Main

The C—H bond belongs to the most common groups in organic molecules and is typically considered unreactive towards functionalization reactions. Its direct modification would allow the most atom-economic and streamlined synthesis of functional molecules. C—H insertion reactions of diazo compounds are a modern strategy to construct highly functionalized molecules from simple and readily available precursors.<sup>1-3</sup> While state-of-the-art C—H functionalization reactions with diazoalkanes greatly depend on the application of precious metals such as rhodium, iridium, palladium or ruthenium, the application of earth-abundant non-precious metals, like cobalt, manganese or iron, in C—H functionalization reactions is still in its infancy.<sup>4-6</sup>

In recent years, iron-heme based catalysts – organometallic and enzymatic – have been employed for a diverse set of transformations of diazo compounds such as cyclopropanations, N—H, S—H, O—H, Si—H and B—H insertions as well as carbonyl-olefinations.<sup>4-7</sup> The C—H insertion reactions of iron-heme containing organometallic and enzymatic catalysts, have only been reported with azides in amination reactions.<sup>7</sup> To the best of our knowledge these catalysts have not been reported in C—H insertion reactions with diazo alkanes.

The major research focus on C—H insertion reactions with the diazoalkanes is on donor-acceptor substituted derivatives that allow simple handling and access to a broad variety of available precious metal catalysts.<sup>8</sup> Diazoacetonitrile was never considered being an appropriate synthon in C—H functionalization reactions although it would pave the way to prepare substituted acetonitriles in a single step. This can be attributed to lack of procedures for handling of this highly explosive diazo compound.<sup>9,10</sup> In particular, the insertion reaction of diazoacetonitrile into indole derivatives would enable a two-step synthesis of valuable tryptamine and alkaloid precursors.

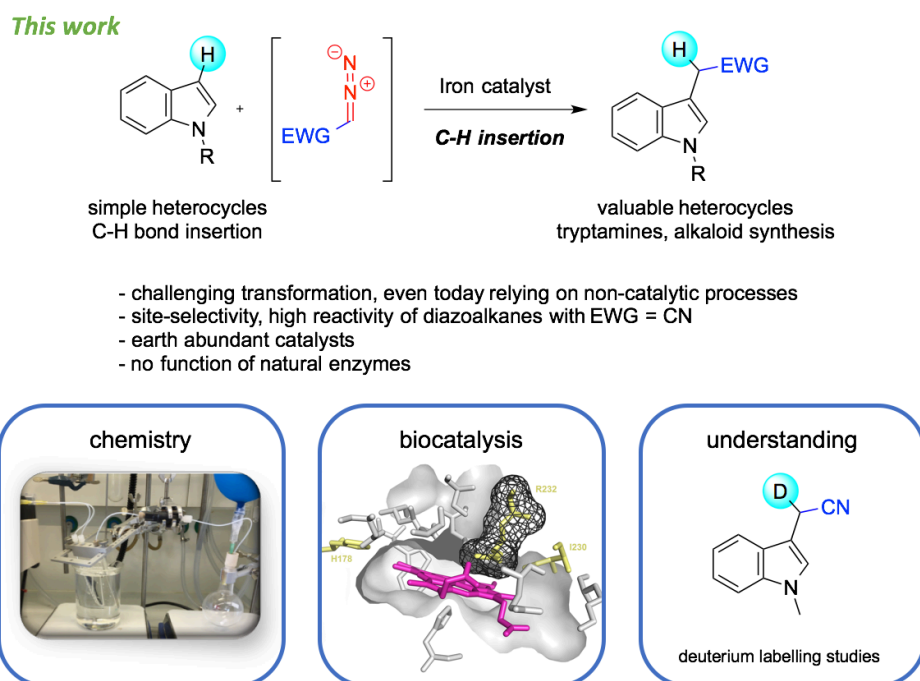
In classic organic synthesis, tryptamines can be most readily prepared either by decarboxylation of tryptophan and its derivatives<sup>11,12</sup> or in a three-step synthesis starting with the Mannich reaction of indole followed by quaternization of the amine and final nucleophilic

substitution with cyanide to yield 1*H*-Indole-3-acetonitrile (41% yield over 3 steps).<sup>13,14</sup> This key building block can be readily reduced to yield tryptamines in high yields.

The reaction of indole heterocycles with acceptor-only diazo compounds has only been studied with Rh(II) or Cu(I) catalysts and ethyl diazoacetate (EDA).<sup>15-19</sup> Currently available catalysts either suffer from low yielding reactions or provide – as in the case of Cu(I) catalysts – the cyclopropanation product of indole, which delivers the 3-substituted indole upon ring-opening.<sup>17</sup> Approaches by Woo and co-workers with FeTPPCL<sup>20</sup> as catalyst for the C—H insertion reaction of EDA and indole resulted in no product formation.<sup>21</sup>

While the biocatalytic construction of C—C bonds with diazo compounds via C—H activation has been shown with Mn-, Co- or Ir-substituted heme-proteins, naturally occurring iron-heme containing enzymes could not catalyze this reaction-type yet.<sup>22-24</sup>

As part of our ongoing studies towards highly reactive diazo alkanes,<sup>25,26</sup> we envisioned the C—H insertion reactions of diazoacetonitrile with non-precious metal catalysts. In this work, we describe iron-catalyzed C—H insertion reactions with bio- and organometallic catalysts, showcase the efficiency in 38 examples – including gram-scale synthesis – and investigate the reaction mechanism by deuterium labeling studies.



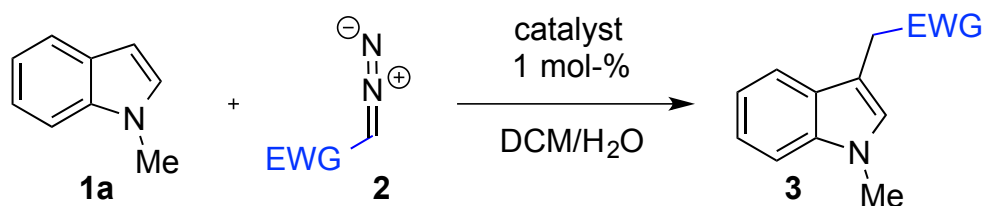
**Scheme 1.** C—H functionalization of indole heterocycles.

## Results and discussion

**Organometallic C—H insertion.** We initiated our investigations towards C—H activation reactions of diazoalkanes by studying a range of organometallic iron catalysts in the reaction of *N*-methyl indole with diazo acetonitrile. The latter was generated in continuous-flow to reduce safety hazards associated to this diazo compound.<sup>27</sup> To our surprise, the reaction of *N*-methyl indole with diazoacetonitrile was highly efficient with different organometallic iron catalysts (table 1, entry 1-7). FeTPPCI showed the best isolated yields of 92% and performed much better than the respective Fe(II) catalyst. The reduction of FeTPPCI by addition of Na<sub>2</sub>S<sub>2</sub>O<sub>4</sub> also resulted in significantly reduced product yield.

We subsequently investigated different alternative routes relying on the *in situ* generation of diazoacetonitrile. However, neither in a one-pot protocol nor a slow release protocol the desired product could be isolated in satisfactory yield and purity (yields for: slow release reaction: 43%, one-pot: 57%).<sup>28</sup> The reactivity of diazoacetonitrile is in striking contrast to the reaction of EDA, which provided only trace amounts of the desired reaction product (table 1, entry 8-12).

The natural iron containing prosthetic group hemein was tested thereafter for its activity in C—H insertion reactions; yet, the desired reaction product could only be isolated in reduced yield in the case of diazoacetonitrile.

**Table 1.** Reaction optimization.

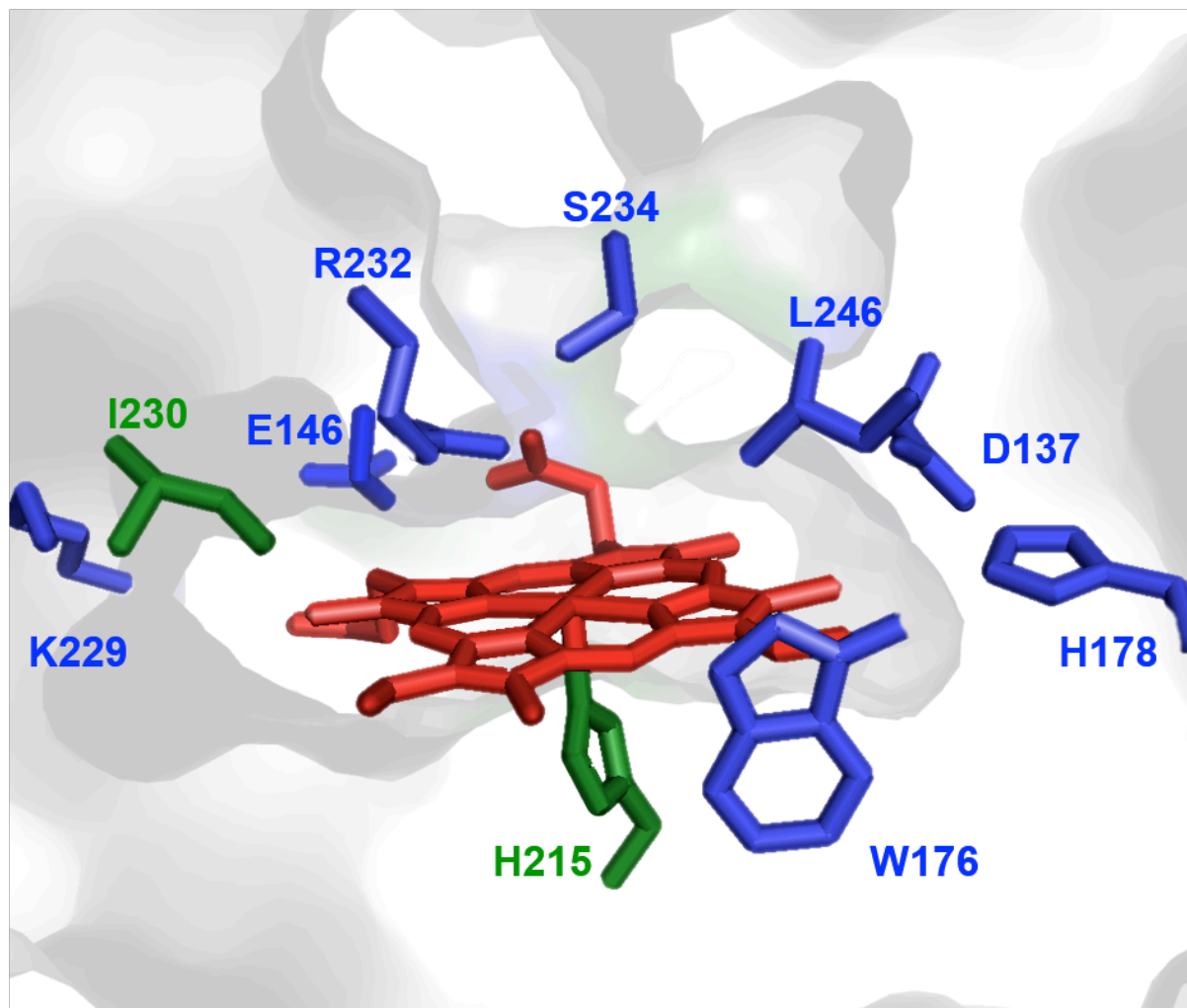
#	catalyst	additive	EWG	diazoalkane	product	% yield
1	FeTPP (1 mol-%)		CN	<b>2a</b>	<b>3aa</b>	54%
2	FePC (1 mol-%)		CN	<b>2a</b>	<b>3aa</b>	41%
3	FeTPPCI (1 mol-%)		CN	<b>2a</b>	<b>3aa</b>	92%
4	FeTPPCI (1 mol-%)	10 mol-% Na <sub>2</sub> S <sub>2</sub> O <sub>4</sub>	CN	<b>2a</b>	<b>3aa</b>	51%
5	FeTPPCI (1 mol-%)	1 eq Na <sub>2</sub> S <sub>2</sub> O <sub>4</sub>	CN	<b>2a</b>	<b>3aa</b>	10%
6	Hemin-Cl (1 mol-%)		CN	<b>2a</b>	<b>3aa</b>	47%
7	Hemin-Cl (1 mol-%)	10 mol-% Na <sub>2</sub> S <sub>2</sub> O <sub>4</sub>	CN	<b>2a</b>	<b>3aa</b>	19%
8	FeTPP (1 mol-%)		CO <sub>2</sub> Et	<b>2b</b>	<b>3ab</b>	no rct.
9	FeTPPCI (1 mol-%)		CO <sub>2</sub> Et	<b>2b</b>	<b>3ab</b>	traces
10	FeTPPCI (1 mol-%)	10 mol-% Na <sub>2</sub> S <sub>2</sub> O <sub>4</sub>	CO <sub>2</sub> Et	<b>2b</b>	<b>3ab</b>	no rct.
11	Hemin-Cl (1 mol-%)		CO <sub>2</sub> Et	<b>2b</b>	<b>3ab</b>	no rct.
12	Hemin-Cl (1 mol-%)	10 mol-% Na <sub>2</sub> S <sub>2</sub> O <sub>4</sub>	CO <sub>2</sub> Et	<b>2b</b>	<b>3ab</b>	no rct.

*reaction conditions:* a solution of amino acetonitrile hydrochloride (0.8 M, 4 eq) in water, and a solution of NaNO<sub>2</sub> (0.96 M, 4.8 eq) in water are added via syringe pump at a flow rate of 50  $\mu$ L/min for each syringe into a microreactor (LTF-MRT MX, 200 $\mu$ L volume) heated to 55  $^{\circ}$ C. The outlet of the reactor is added to a reaction vessel containing 0.4 mmol **1a**, 1 mol-% catalyst in 0.1 mL DCM and stirred for 2h. Isolated yields are reported.

**Biocatalytic C—H insertion.** Encouraged by the observed reactivity of organometallic iron-heme complexes and in particular by the activity of the natural cofactor heme, we decided to investigate heme-containing enzymes that could serve as a biocatalytic alternative in this C—H functionalization reaction.

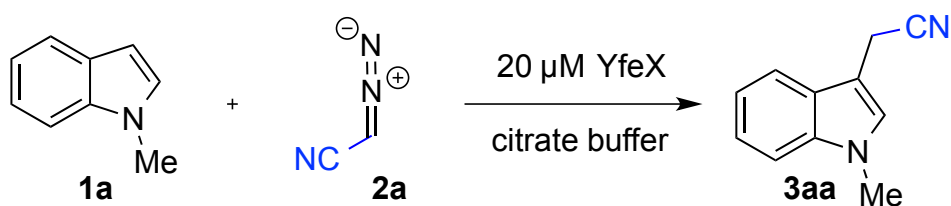
In initial studies, we had shown that P450<sub>BM3</sub> (from *Bacillus megaterium*) or P450<sub>NOR</sub> (from *Histoplasma capsulatum*) had lower activities toward C—H insertions than the *E. coli* enzyme YfeX.<sup>28</sup> YfeX had been used in previous studies to perform carbonyl olefination reactions in the absence of triphenylphosphine or arsine – though with modest turnovers.<sup>29</sup> Due to its *E. coli* origin YfeX shows remarkable expression rates and possesses a high stability at room temperature. YfeX wildtype showed TON of 37 at four hours reaction time in the reaction of diazoacetonitrile and *N*-methyl indole in the absence of oxygen. In striking difference to the organometallic experiments, we found the best reactivity by adding 5 mM of the reducing

agent  $\text{Na}_2\text{S}_2\text{O}_4$ . This indicates that the biocatalytic reactions are catalyzed by Fe(II) rather than Fe(III).



**Figure 2.** Active site residues of YfeX that were investigated in a focused mutant library. The green amino acids showed the most dominant effects. PDB: 5GT2.

As a proof of principle, we next tested a focused library of eleven YfeX variants. Active site residues from the distal site in proximity to the iron have been picked and changed for alanine.<sup>30</sup> The best variant I230A improved the TON twofold from 37 to more than 80, thereby clearly demonstrating the influence of the protein scaffold as well as its ability to be engineered. The mutation of the proximal axial ligand H215A caused the expected decrease in activity. Removal of the anionic aspartic acid D143 to alanine resulted in a substantial loss in activity.



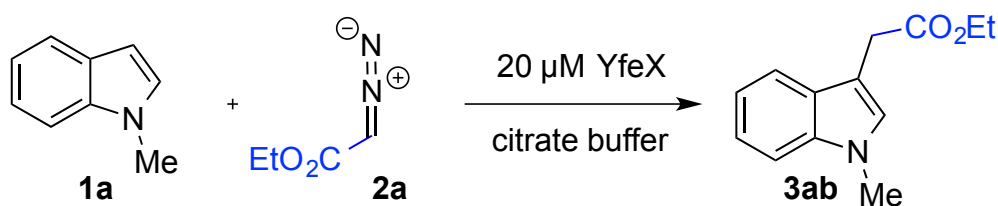
**Table 2.** Enzymatic activity of YfeX variants in C—H insertion reactions with *N*-methyl indole **1a** and diazo acetonitrile.

#	catalyst	<b>3aa</b> [ $\mu\text{M}$ ] <sup>[a]</sup>	TON <sup>[c]</sup>
1	YfeX WT	748	37 (51)
2	YfeX R232A	941	47 (66)
3	YfeX D143A	337	17 (20)
4	YfeX D137A	957 <sup>[b]</sup>	48 (56)
5	YfeX H178A	1232 <sup>[b]</sup>	62 (69)
6	YfeX H215A <sup>[e]</sup>	278	14 <sup>[e]</sup>
7	YfeX I230A	1607	80 (94)
8	YfeX S234A	995	50 (50)
9	YfeX L246A	898	45 (106)
10	YfeX E146A	601 <sup>[b]</sup>	30 (39)
11	YfeX K229A	1263	63 (68)

*reaction conditions:* Reactions were performed in an anaerobic 100 mM citrate buffer (pH = 7) with 50 mM *N*-methyl indole, 50 mM diazo acetonitrile, 5 mM Na<sub>2</sub>S<sub>2</sub>O<sub>4</sub> and 20  $\mu\text{M}$  catalyst for 4 h at 30 °C. [a] Mean values from three replicates  $\pm$  17 % standard deviation, conversions were based on GC analysis [b] 26 – 29 % standard deviation. [c] TON = **3aa**  $\mu\text{M}$ /20  $\mu\text{M}$  YfeX variant. In brackets the extrapolation to 100 % heme loading. [e] apoYfeX.

Further investigations focused on the insertion reaction of *N*-methyl indole with EDA. In striking contrast to the organometallic iron porphyrine catalysts, YfeX proved to be an excellent catalyst for this transformation under reductive conditions (50 mM Na<sub>2</sub>S<sub>2</sub>O<sub>4</sub>). The best variant showed 211 TON under optimized conditions. These observations are in sharp contrast to the reaction with diazoacetonitrile and highlights differences in the reactivity of both diazo compounds as well as their catalysts. In additional experiments, we could demonstrate this C—H insertion reaction in a whole-cell setup with YfeX WT enzyme and could achieve a high TON of 236.



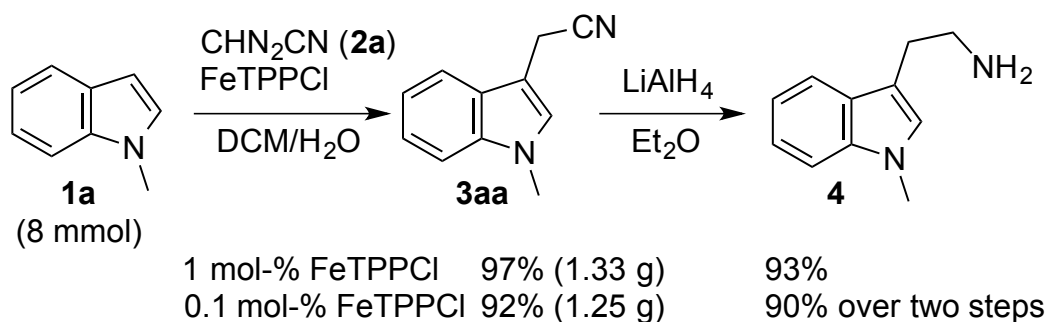


**Table 3.** Enzymatic activity of purified YfeX variants and the whole cell system in the C—H insertion reaction of *N*-methyl indole and ethyl diazoacetate.

#	catalyst	<b>3ab</b> [ $\mu\text{M}$ ] <sup>[d]</sup>	TON <sup>[e]</sup>
1	YfeX WT	1208	60 (82)
2	YfeX R232A	1243	62 (87)
3	YfeX D143A	1397	70 (83)
4	YfeX I230A	1699	85 (100)
5	YfeX I230A <sup>[a]</sup>	211	211 (248)
6	<i>E. coli</i> (BL21) pCA24N-YfeX WT <sup>[b]</sup>	1652	236 (320) <sup>[f]</sup>
7	<i>E. coli</i> (BL21) pCA24N <sup>[b, c]</sup>	33	-

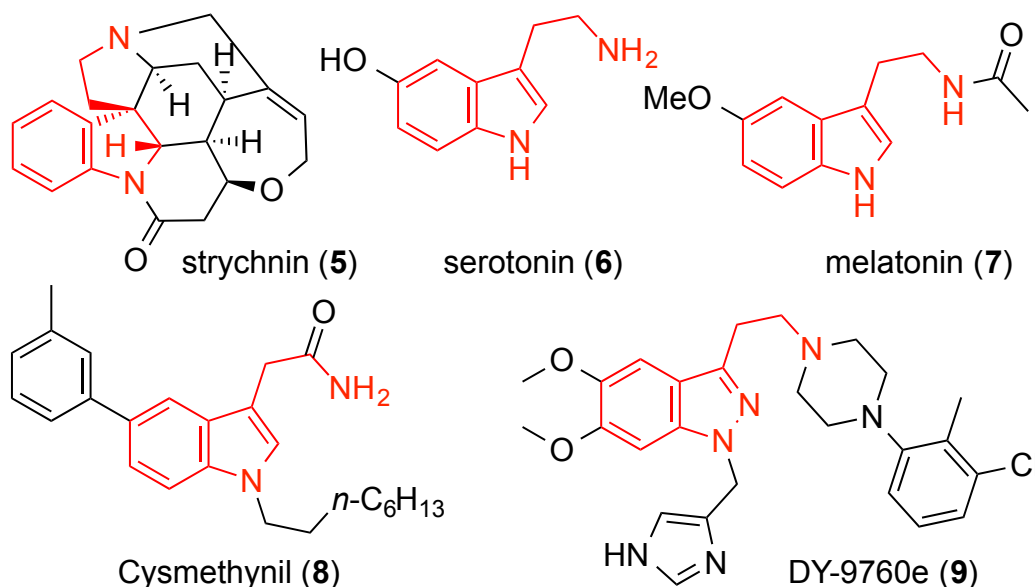
*reaction conditions:* Reactions were performed in an anaerobic 100 mM citrate buffer (pH = 7) with 50 mM *N*-methyl indole, 50 mM diazo acetonitrile, 50 mM  $\text{Na}_2\text{S}_2\text{O}_4$  and 20  $\mu\text{M}$  catalyst for 4 h at 30 °C. [a] 1  $\mu\text{M}$  YfeX WT concentration. [b] Whole cell biocatalyst, OD = 30. [c] Empty pCA24N vector (control). [d] Mean values from three replicates  $\pm$  12 % standard deviation, conversions were based on GC analysis. [e] TON = **3ab**  $\mu\text{M}/20 \mu\text{M}$  [or 1  $\mu\text{M}$ ] YfeX variant. In brackets the extrapolation to 100 % heme loading. [f] TON = **3ab**  $\mu\text{M}/7 \mu\text{M}$ .

**Application of the organometallic C—H insertion reaction.** We probed the organometallic protocol in a short synthesis of a tryptamine derivative, which would enable a streamlined synthesis of indole alkaloids. Starting with 8 mmol of *N*-methyl indole (**1a**), we could demonstrate that this protocol can be readily applied to the gram-scale synthesis of **3aa** in excellent yield and catalyst loadings as low as 0.1 mol-%. Reduction with  $\text{LiAlH}_4$  provides the tryptamine derivative (**4**) in a two-step synthesis and total yield of 90% over two steps, which is superior over classical routes (scheme 2).



**Scheme 2.** Gram-scale reaction and application in the synthesis of tryptamine.

This process thus allows the rapid synthesis of valuable tryptamines that are a privileged motif in biological and pharmaceutical research (figure 3);<sup>31-34</sup> an example is Cysmethynil (**8**), which is an inhibitor of isoprenylcysteine methyl transferase.<sup>32,33</sup> Their closely related analogues, the indazol-3-yl ethane amines, are privileged scaffolds in many drugs, such as DY-9760e (**9**), which is used for the treatment of ischemia.<sup>34</sup>



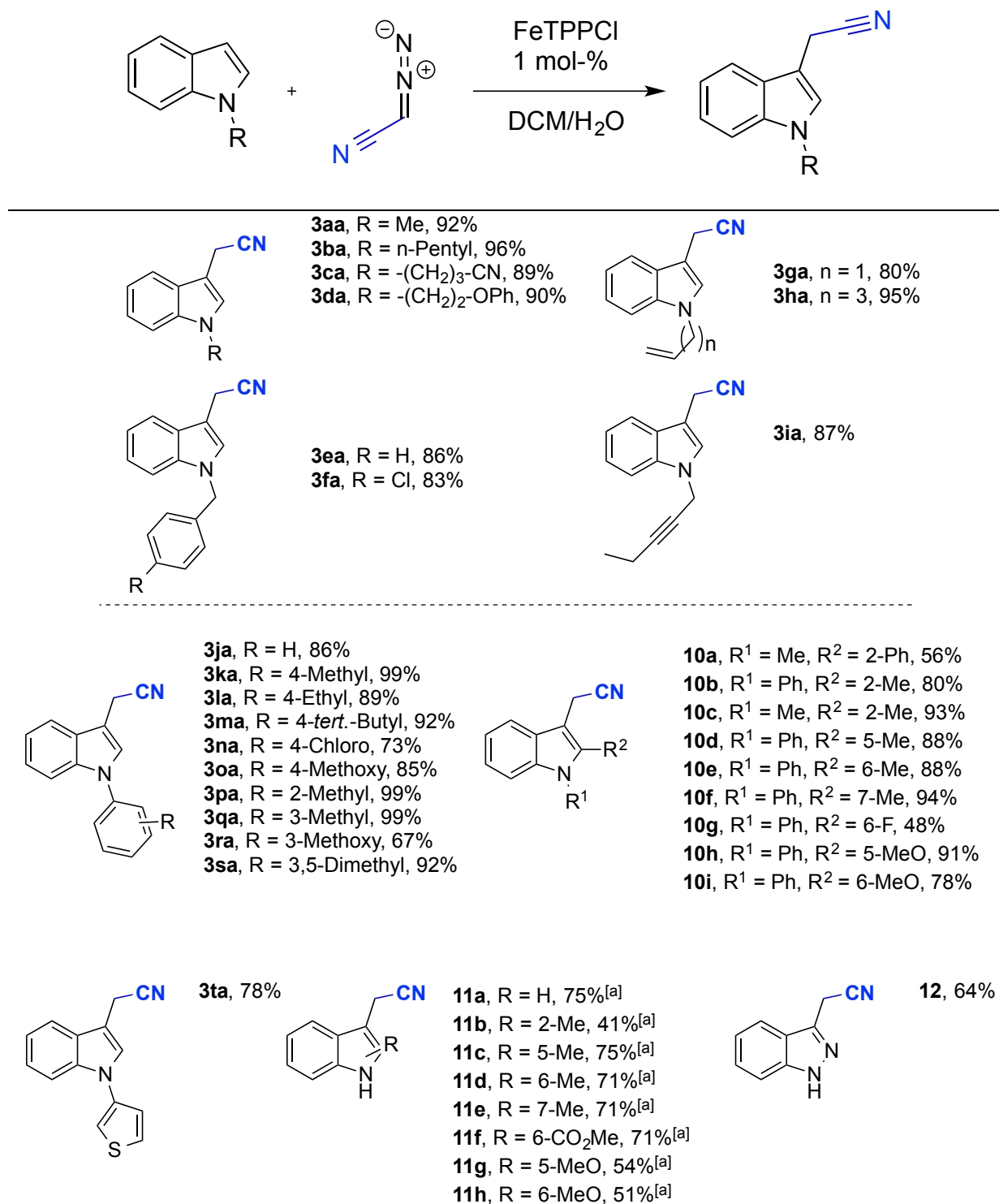
**Figure 3.** Occurrence of tryptamines in natural products and biologically active compounds.

In further studies, we examined the applicability of this newly developed method and probed different *N*-alkylated indoles. To our delight these indoles reacted smoothly under the present reaction conditions, providing the desired reaction products in very good to excellent yields. A broad variety of functional groups were well tolerated such as double and triple bonds, nitriles or ethers; no cyclopropanation or cyclopropenation byproducts were observed (table 4, **3ga-ia**). Further investigations focused on *N*-aryl substituted indoles, which reacted to the desired 1-aryl-3-acetonitrile indoles (table 4, **3ja-3ta**) with yields of up to 99%. We examined a range of substituents to probe the influence of electronic and steric effects. Electron-withdrawing, electron-donating and halogen substituents in the *para*-, *meta*- and *ortho*-position of the aromatic ring were tolerated and only a negligible effect on the reaction with diazoacetonitrile was observed. Sulfur containing heterocycles also proved compatible providing the 3-substituted indole in moderate yields (**3ta**). It should be noted that *N*-

heterocyclic substrates (e.g. *N*-(pyrimidin-2-yl)-indole) did not react under the present reaction conditions. We also investigated *Boc*-protected indole, however, we did not observe the formation of the desired product.

We then decided to investigate unprotected indoles, which would give a direct one-step access to building blocks that allow simple functionalization. These investigations would reveal insight into the reaction mechanism and show, whether C—H or N—H insertion is preferred. To our delight, unprotected indole reacted to the desired 1*H*-3-acetonitrile indole in 62% yield, without formation of the *N*-alkylation product. Even with a large excess of diazoacetonitrile (8 eq.), no N—H insertion was observed. Increasing the addition time of diazoacetonitrile from 10 to 20 min improved the reaction and the product was isolated in 75 % yield. Encouraged by these observations, we investigated a variety of core-substituted indoles, both without a masking group at the indole nitrogen and with the corresponding *N*-substituted derivatives. Aliphatic substituents at the indole core were well tolerated and the corresponding alkyl-substituted 3-acetonitrile indoles were isolated in good yields. Electron withdrawing groups, such as esters or fluorine, are tolerated, though the products were obtained only in moderate yields (table 4, entries **10** and **11**). Remarkably, indazole readily underwent the C—H insertion reaction and the desired product **12** was isolated in good yield, which marks the first example of C—H functionalization reactions of indazole with diazo compounds. It should be noted that 7-aza-indole did not provide the desired reaction product. Blocking the 3-position of indole as in 3-methyl-1-phenyl indole resulted in no reaction, which indicates that the C—H insertion takes place in the 3-position of indole exclusively.

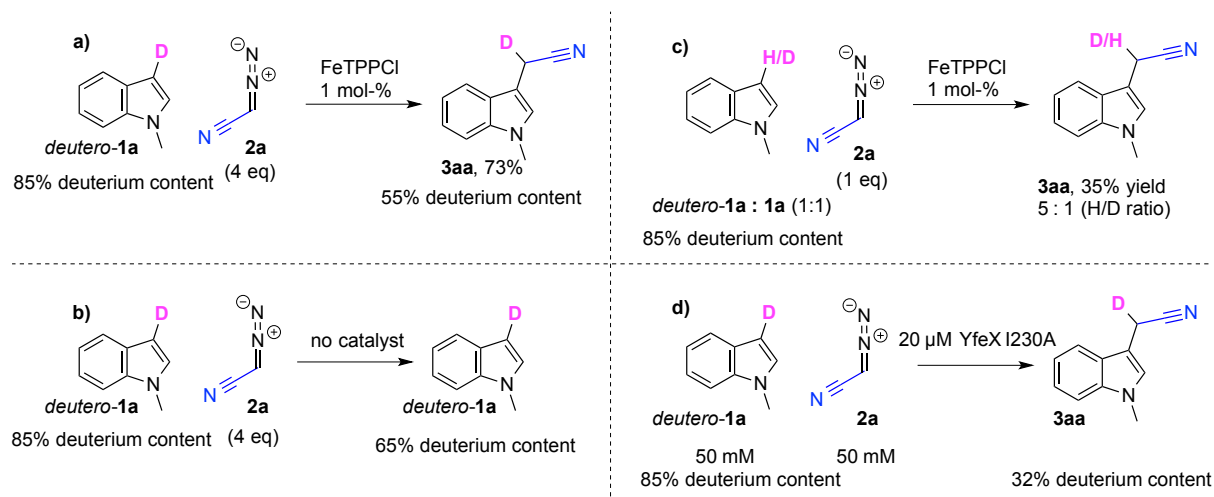
**Table 4.** Reaction scope of substituted *N*-alkyl and *N*-aryl indoles.



*Reaction conditions:* diazoacetonitrile (0.8 M, 4 eq) in water was added at a flow over a period of 10 minutes to a solution of indole derivative (0.4 mmol), 1 mol-% FeTPPCL in 0.1 mL DCM and stirred for 2h. Isolated yields are reported. <sup>[a]</sup> addition of diazoacetonitrile over a period of 20 minutes.

**Mechanistic studies.** We decided to study the reaction mechanism of the C—H insertion reaction for a better understanding of the observed reactivity. We tested FeTPPCI with 3-deutero-*N*-methyl indole (*deutero-1a*) under standard reaction conditions and were able to isolate *deutero-3aa* with good yields. NMR analysis revealed a 55 % incorporation of deuterium in the benzylic position (Scheme 3a). To further elucidate the drop of deuterium label during the reaction, we suggested a D/H exchange reaction in the slightly acidic reaction mixture (pH = 6.5) prior to the insertion reaction. We conducted the experiment under otherwise identical conditions without catalyst and examined the crude mixture by NMR spectroscopy. This experiment revealed an erosion of deuterium label to 65% under the present reaction conditions. This indicates, that the loss of deuterium label can indeed be driven by a D/H exchange reaction prior to the insertion reaction (Scheme 3b). Finally, we investigated a competition reaction of *N*-methyl indole (**1a**) and 3-deutero-*N*-methyl indole (*deutero-1a*) using only 1 eq. of diazoacetonitrile and could observe a ratio of 5 : 1 of **3aa** : *deutero-3aa* (Scheme 3c), which indicates that a proton transfer is the rate-limiting step. This observation is in striking contrast to previously reported copper catalyzed reactions of indole with EDA, in which a) no deuterium is incorporated in the reaction product and b) no kinetic isotope effect was observed.<sup>17</sup> To investigate, whether the biocatalyst behaves in a similar manner, we tested the enzymatic reaction with 3-deutero-*N*-methyl indole (*deutero-1a*), which revealed a deuterium incorporation of 32%. In absence of a enzyme, the deuterium label eroded to be 80% under neutral reaction conditions (pH = 7.0).

The above observations are indicating at an insertion reaction mechanism into the C-H/C-D bond at the C3-position of indole, which marks the first example of iron-catalyzed C-H insertion reactions of diazo compounds from both the organometallic and enzymatic perspective.



**Scheme 3.** Deuterium labelling experiments of the iron catalyzed reaction of indole with diazoacetone nitrile: a) organometallic transformation with 3-deutero-*N*-methyl indole; b) background reaction in the absence of catalyst; c) competition experiment for the determination of the kinetic isotope effect; d) enzymatic transformation with 3-deutero-*N*-methyl indole using the most active YfeX variant I230A.

## Conclusion.

We have discovered a novel reactivity of organometallic and enzymatic iron porphyrin catalysts, which enables the insertion reaction of diazoalkanes into the C—H bond of *N*-heterocycles. This work demonstrates that diazoacetone nitrile can be regarded as a “cyanomethyl” transfer reagent for the selective introduction of an acetonitrile moiety into the C3 position of indole and indazole heterocycles in up to 99% yield with broad functional group tolerance in a single step. This reaction was showcased in 38 examples and proved reliable on gram-scale to prepare tryptamine analogues with broad general applicability ranging from drug discovery and approved drugs to total synthesis. Besides the organometallic studies, we herein show the first example of iron-protein catalyzed C—H insertions of diazoalkanes utilizing a focused mutant library of the heme-protein YfeX. The reaction was also demonstrated in whole cells overexpressing YfeX with turnover numbers as high as 236. In contrast to the organometallic catalyst, YfeX was able to convert both, diazoacetone nitrile and ethyl diazoacetate, respectively, to the C—H insertion product.

Mechanistic investigations with deuterium labelled indole revealed a marked kinetic isotope effect and suggest a C—H insertion mechanism.

## Methods

### FeTPPCI catalyzed C—H insertion reaction

Two stock solutions were prepared in thoroughly degassed water: a) aqueous solution of amino acetonitrile hydrochloride (1.6 M) b) aqueous solution of sodium nitrite (1.92 M). The stock solutions were transferred into two syringes and placed in a syringe pump. The syringes were connected via PTFE tubing to a microreactor (LTF-MRT MX, 200  $\mu$ L volume) heated to 55 °C with an internal volume of 0.2 mL. Then, the tubing was passed through an ice bath to cool down the reaction mixture and the cold solution of diazoacetonitrile was added over a period of ten minutes to a mixture of FeTPPCI (1 mol-%) and indole derivative (0.4 mmol, 1 eq) that were dissolved in 0.1 mL of thoroughly degassed DCM. The resulting mixture was stirred an additional 2 h at room temperature. The aqueous phase was extracted with DCM (three times) and the combined organic layers were dried with Na<sub>2</sub>SO<sub>4</sub>. The solvent was removed under reduced pressure and the residue was purified by column chromatography on silica gel (pentane: diethyl ether 20:1 -> 1:1) to afford the desired product.

### YfeX catalyzed C—H insertion reactions

**Diazoacetonitrile:** Diazoacetonitrile was freshly prepared for each experiment. A degassed aqueous solution of amino acetonitrile hydrochloride (1 M) was stirred at 0 °C. Sodium nitrite was added to obtain a 1.2 M reaction mixture. After 5 min the reaction mixture was stirred for 10 min at room temperature, followed by further 5 min on ice cooling for an easier handling and a direct addition of the diazo acetonitrile component to the C—H insertion reaction mixture. C—H insertion reactions with the YfeX variants were performed in 2.5 ml Rotilabo® sample vials (Carl Roth, Karlsruhe, DE) with a final volume of 400  $\mu$ L in 100 mM citrate buffer (pH = 7). The reaction mixture consisted of 20  $\mu$ M YfeX, freshly prepared 50 mM diazo

acetonitrile, 50 mM *N*-methyl indole, 5 mM Na<sub>2</sub>S<sub>2</sub>O<sub>4</sub> and 5 % DMSO as degassed cosolvent and was saturated with N<sub>2</sub>. After a reaction time of 4 h at 30 °C and 600 rpm the products were extracted using 400 µL MTBE with 0,005 % ethyl benzoate and centrifuged at 8400 rpm for 3 min. The organic phase was analyzed by GC/MS.

**Ethyl diazoacetate:** C–H insertion reactions with the YfeX variants were performed in 2.5 ml Rotilabo® sample vials (Carl Roth, Karlsruhe, DE) with a final volume of 400 µl in 100 mM citrate buffer (pH = 7). The reaction mixture consisted of 20 µM/1 µM YfeX, 50 mM ethyl diazoacetate, 50 mM *N*-methyl indole, 50 mM Na<sub>2</sub>S<sub>2</sub>O<sub>4</sub> and 10 % DMSO as degassed cosolvent and was saturated with N<sub>2</sub>. After a reaction time of 4 h at 30 °C and 600 rpm, the products were extracted using 400 µL MTBE with 0,005 % ethyl benzoate and centrifuged at 8400 rpm for 3 min. The organic phase was analyzed by GC/MS.

## References

- 1 Davies, H. M. L. & Manning, J. R. Catalytic C–H functionalization by metal carbenoid and nitrenoid insertion. *Nature* **451**, 417-424 (2008).
- 2 Ford, A. *et al.* Modern Organic Synthesis with  $\alpha$ -Diazocarbonyl Compounds. *Chem. Rev.* **115**, 9981-10080 (2015).
- 3 Doyle, M. P., Duffy, R., Ratnikov, M. & Zhou, L. Catalytic Carbene Insertion into C–H Bonds. *Chem. Rev.* **110**, 704-724 (2010).
- 4 Bauer, I. & Knölker, H.-J. Iron Catalysis in Organic Synthesis. *Chem. Rev.* **115**, 3170-3387 (2015).
- 5 Zhu, S.-F. & Zhou, Q.-L. Iron-catalyzed transformations of diazo compounds. *Natl. Sci. Rev.* **1**, 580-603 (2014).
- 6 Shang, R., Ilies, L. & Nakamura, E. Iron-Catalyzed C–H Bond Activation. *Chem. Rev.* **117**, 9086-9139 (2017).
- 7 Brandenberg, O. F., Fasan, R. & Arnold, F. H. Exploiting and engineering hemoproteins for abiological carbene and nitrene transfer reactions. *Curr. Opin. Biotechnol.* **47**, 102-111 (2017).
- 8 Davies, H. M. L. & Morton, D. Guiding principles for site selective and stereoselective intermolecular C-H functionalization by donor/acceptor rhodium carbenes. *Chem. Soc. Rev.* **40**, 1857-1869 (2011).
- 9 Curtius, T. Diazoacetonitrile. *Ber. Dtsch. Chem. Ges.* **31**, 2489-2492 (1898).
- 10 Phillips, D. D. & Champion, W. C. An explosion during the preparation of diazoacetonitrile. *J. Am. Chem. Soc.* **78**, 5452 (1956).
- 11 S. Takano, T. N., K. Ogasawawa, . Efficient Synthesis of Tryptamine. *Heterocycles* **6**, 1167-1171 (1977).
- 12 M. Eckstein, S. M., A. Terczynska, M. Adamus. Process for preparing tryptamine hydrochloride. PL130769 (1984).
- 13 Pierce, L. T., Cahill, M. M. & McCarthy, F. O. Synthesis of novel 3,4-diaryl-5-aminopyrazoles as potential kinase inhibitors. *Tetrahedron* **67**, 4601-4611 (2011).
- 14 Tsotinis, A. *et al.* Mapping the Melatonin Receptor. 7. Subtype Selective Ligands Based on  $\beta$ -Substituted N-Acyl-5-methoxytryptamines and  $\beta$ -Substituted N-Acyl-5-methoxy-1-methyltryptamines. *J. Med. Chem.* **49**, 3509-3519 (2006).



- 15 Wenkert, E. *et al.* Reactions of ethyl diazoacetate with thianaphthene, indoles, and benzofuran. *J. Org. Chem.* **42**, 3945-3949 (1977).
- 16 Sandtorv, A. H. Transition Metal-Catalyzed C-H Activation of Indoles. *Adv. Synth. Catal.* **357**, 2403-2435 (2015).
- 17 Delgado-Rebollo, M., Prieto, A. & Pérez, P. J. Catalytic Functionalization of Indoles by Copper-Mediated Carbene Transfer. *ChemCatChem* **6**, 2047-2052 (2014).
- 18 Sarkar, M., Daw, P., Ghatak, T. & Bera, J. K. Amide-Functionalized Naphthyridines on a RhII–RhII Platform: Effect of Steric Crowding, Hemilability, and Hydrogen-Bonding Interactions on the Structural Diversity and Catalytic Activity of Dirhodium(II) Complexes. *Chem. Eur. J.* **20**, 16537-16549 (2014).
- 19 Özüdüru, G., Schubach, T. & Boysen, M. M. K. Enantioselective Cyclopropanation of Indoles: Construction of All-Carbon Quaternary Stereocenters. *Org. Lett.* **14**, 4990-4993 (2012).
- 20 TPP = meso-tetraphenyl porphyrine.
- 21 Baumann, L. K., Mbuvi, H. M., Du, G. & Woo, L. K. Iron Porphyrin Catalyzed N–H Insertion Reactions with Ethyl Diazoacetate. *Organometallics* **26**, 3995-4002 (2007).
- 22 Sreenilayam, G., Moore, E. J., Steck, V. & Fasan, R. Metal Substitution Modulates the Reactivity and Extends the Reaction Scope of Myoglobin Carbene Transfer Catalysts. *Adv. Synth. Catal.* **359**, 2076-2089 (2017).
- 23 Dydio, P. *et al.* An artificial metalloenzyme with the kinetics of native enzymes. *Science* **354**, 102-106, (2016).
- 24 Key, H. M., Dydio, P., Clark, D. S. & Hartwig, J. F. Abiological catalysis by artificial haem proteins containing noble metals in place of iron. *Nature* **534**, 534-537, (2016).
- 25 Hock, K. J., Mertens, L. & Koenigs, R. M. Rhodium catalyzed synthesis of difluoromethyl cyclopropanes. *Chem. Commun.* **52**, 13783-13786 (2016).
- 26 Hock, K. J., Spitzner, R. & Koenigs, R. M. Towards nitrile-substituted cyclopropanes - a slow-release protocol for safe and scalable applications of diazo acetonitrile. *Green Chem.* **19**, 2118-2122 (2017).
- 27 To minimize risks while working with this diazo compound, diazo acetonitrile was prepared in continuous-flow by mixing an aqueous solution of amino acetonitrile hydrochloride with an aqueous solution of sodium nitrite (microreactor: Little Things Factory MR Lab MX, tubing 0.8 mm ID, back pressure regulator 20 psi) at 55 °C, residence time 1 min. The outlet of the microreactor was added into a consecutive batch transformation containing 1-methyl indole and the respective metal catalyst. NMR studies revealed quantitative formation of diazo acetonitrile.
- 28 For details, see supporting information.
- 29 Weissenborn, M. J. *et al.* Enzyme-Catalyzed Carbonyl Olefination by the E. coli Protein YfeX in the Absence of Phosphines. *ChemCatChem* **8**, 1636-1640 (2016).
- 30 Liu, X. *et al.* Crystal structure and biochemical features of dye-decolorizing peroxidase YfeX from Escherichia coli O157 Asp143 and Arg232 play divergent roles toward different substrates. *Biochem. Biophys. Res. Commun.* **484**, 40-44 (2017).
- 31 Cooke, A. J. *et al.* TrkA kinase inhibitors, compositions and methods thereof. WO2016054807 (2016).
- 32 Winter-Vann, A. M. *et al.* A small-molecule inhibitor of isoprenylcysteine carboxyl methyltransferase with antitumor activity in cancer cells. *Proc. Natl. Acad. Sci. U. S. A.* **102**, 4336-4341 (2005).
- 33 Go, M.-L. *et al.* Amino Derivatives of Indole As Potent Inhibitors of Isoprenylcysteine Carboxyl Methyltransferase. *J. Med. Chem.* **53**, 6838-6850 (2010).
- 34 Fukunaga, K. *et al.* DY-9760e, a Novel Calmodulin Inhibitor, Exhibits Cardioprotective Effects in the Ischemic Heart. *Cardiovasc. Ther.* **24**, 88-100 (2006).

## **Acknowledgements**

R.M.K. thanks for support from the Excellence Initiative of the German federal and state governments and the Fonds der Chemischen Industrie (Sachkostenbeihilfe) for financial support. M.J.W and A.K. thank the BMBF („Biotechnologie 2020+ Strukturvorhaben: Leibniz Research Cluster“, 031A360B) for generous funding. The authors thank Niels Borlinghaus who performed the YfeX mutagenesis. J.H. thanks the Australian Research Council for financial support (Grant DE160100807) and the Australia National Computational Infrastructure (NCI) and Intersect Australia Ltd. for generous allocation of computational resources.

## **Author Contributions**

K.J.H, A.K. and R. H. performed the experiments. K.J.H., J. H., M.J.W. and R.M.K. participated in the discussions, supervised the project and wrote the manuscript. K.J.H. and R. M. K. conceived the idea of iron catalyzed C-H insertion reactions. R.M.K. organized the research.

## **Additional Information**

Supplementary information and chemical compound information are available.

## **Competing Financial Interests statement**

The authors declare no competing financial interest.

manuscript.pdf (1.14 MiB)

[view on ChemRxiv](#) • [download file](#)

---

# Supporting information

## Iron-catalyzed C—H insertions: organometallic and enzymatic carbene transfer reactions

Katharina J. Hock,<sup>[a]</sup> Anja Knorrscheidt,<sup>[b]</sup> Renè Hommelsheim,<sup>[a]</sup> Junming Ho,<sup>[c]</sup> Martin J. Weissenborn,<sup>\*[b]</sup> and Rene M. Koenigs<sup>\*[a]</sup>

[a] Institute of Organic Chemistry, RWTH Aachen University, Landoltweg 1, 52074 Aachen, Germany, E-mail: [rene.koenigs@rwth-aachen.de](mailto:rene.koenigs@rwth-aachen.de), [www.koenigslab.rwth-aachen.de](http://www.koenigslab.rwth-aachen.de)

[b] Leibniz Institute of Plant Biochemistry, Weinberg 3, 06120 Halle (Saale), Germany, E-mail: [martin.weissenborn@ipb-halle.de](mailto:martin.weissenborn@ipb-halle.de)

[c] Dr. Junming Ho, School of Chemistry, University of Sydney, Sydney NSW 2006, Australia.

## Table of contents

<b>SUPPORTING INFORMATION</b>	<b>1</b>
<b>GENERAL INFORMATION</b>	<b>3</b>
<b>IMPORTANT SAFETY NOTE</b>	<b>4</b>
<b>REACTION OPTIMIZATION DATA</b>	<b>5</b>
<b>EXPERIMENTAL PROCEDURES</b>	<b>6</b>
<b>EXPERIMENTAL PROCEDURES OF BIO</b>	<b>10</b>
<b>ANALYTICAL DATA</b>	<b>12</b>
Indole starting materials	12
Products	12
References	26

## General Information

Unless otherwise noted, all commercially available compounds were used as provided without further purification. Chemicals used in this manuscript were purchased from Sigma Aldrich, Alfa Aesar and Fluorochem. Amino acetonitrile hydrochloride used in this manuscript was purchased from Alfa Aesar and Fluorochem, though it can be readily synthesized on 50 mmol scale in a single step starting from formaldehyde, ammonium hydroxide and sodium cyanide, followed by precipitation of the hydrochloride salt with 69% yield.<sup>i</sup>

Solvents used in reactions were p.A. grade. All reactions were performed under Argon atmosphere using degassed solvents. Solvents for chromatography were technical grade and distilled prior to use. Analytical thin-layer chromatography (TLC) was performed on Macherey-Nagel silica gel aluminium plates with F-254 indicator, visualised by irradiation with UV light. Column chromatography was performed using silica gel Merck 60 (particle size 0.063 – 0.2 mm). Solvent mixtures are understood as volume/volume. <sup>1</sup>H-NMR, <sup>19</sup>F-NMR and <sup>13</sup>C-NMR were recorded on a Varian AV600 or AV400 spectrometer in CDCl<sub>3</sub>. Data are reported in the following order: chemical shift (δ) in ppm; multiplicities are indicated br (broadened singlet), s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet); coupling constants (J) are in Hertz (Hz). HRMS data were recorded on a ThermoFisher Scientific LTQ Orbitrap XL using ESI ionization or on a Finnigan MAT 95 using EI ionization at 70 eV. IR spectra were recorded on a Perkin Elmer-100 spectrometer and are reported in terms of frequency of absorption (cm<sup>-1</sup>).

The following equipment was utilized for the continuous-flow generation of diazo acetonitrile: Syringe pump: Chemyx Inc. Model Fusion 710. Micromixer: Little Things Factory, MR Lab MX. PTFE tubing: CS Chromatographie PTFE tubing, Art Nr. 590515, 1/16" AD, 0.8 mm ID, max pressure 37 bar. Back pressure regulator: IDEX back pressure assembly, 20 psi

GC/MS measurements were performed on a Shimadzu GCMS-QP2010 Ultra with a secondary electron multiplier as detector, an OPTIMA 5MS column (25 m x 0.20 mm, 0.20 μm film, Macherey-Nagel, DE) and helium as carrier gas with a linear velocity of 38.4 cm/s. Quantification was ensured with the help of ethyl benzoate as an internal standard. For separation the following program was used: 250 °C injection temperature, 200 °C ion source temperature, 290 °C interface temperature, 70 °C column oven temperature, 15 °C/min gradient to 150 °C, 30 °C/min to 200 °C, 100 °C/min gradient to 300 °C and hold for 2 min. All measurements were performed in triplicates and integration was accomplished by a selected ion monitoring mode, besides the deuterium labelling experiments. In these experiments a total ion current was used for quantification.

Optical density was measured at 600 nm with an Ultrospec 10 cell density meter (Amersham Biosciences, GB).

BCA Assay was measured at 560 nm with a TECAN infinite F200 pro (Grödig, AUT). For the Pyridine Hemochromagen Assay the absorbance at 557 nm was measured using a Jasco V-560 UV/VIS spectrophotometer (Tokyo, JPN).

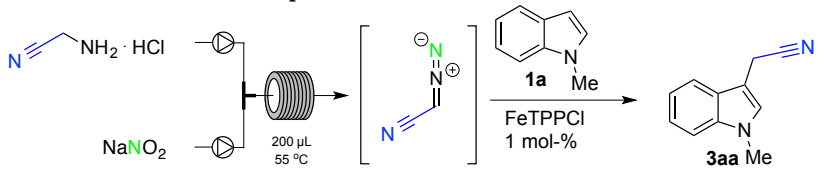
### **Important safety note**

*Safety hazards of diazo acetonitrile, described within this manuscript, have not been investigated. However, it should be noted this particular diazo compound was reported to be highly explosive.*

*Handling of diazo compounds should only be done in a well-ventilated fume cupboard using an additional blast shield. No incidents occurred handling of diazoalkanes during the preparation of this manuscript, yet the reader should be aware of carcinogenicity and explosiveness of the herein described diazo compounds. General safety precautions when working with diazomethane and its derivatives should be followed. Any reactions described in this manuscript should not be performed without strict risk assessment and proper safety precautions.*

## Reaction Optimization data

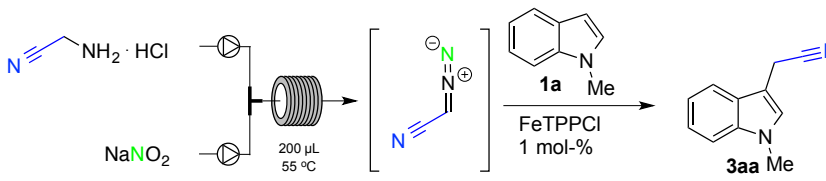
**Table S1.** Reaction optimization.



# <sup>[a]</sup>	Equivalents Amine/Nitrite	Conc.	Addition time	yield <sup>[b]</sup>
1	2/2.4	0.8 M	10 min	56%
2	4/4.8	0.8 M	10 min	71%
3	4/4.8	0.4 M	10 min	63%
4	4/4.8	1.6 M	10 min	92%
5	4/4.8	1.6 M	20 min	79%
6	4/4.8	1.6 M	5 min	72%

[a] *reaction conditions*: a solution of amino acetonitrile hydrochloride in water, and a solution of NaNO<sub>2</sub> in water are added via syringe pump at a equal flow rate for both syringes into a microreactor (LTF-MRT MX, 200 µL volume attached to a back pressure regulator 20 psi) heated to 55 °C and added after it has been cooled to 0 °C to a reaction vessel containing 0.4 mmol **1a**, 1mol-% FeTPPCL in 0.1 mL DCM. The flow rate is adjusted depending on the concentrations to the addition time noted. [b] Isolated yields.

**Table S2.** Solvent Screen.

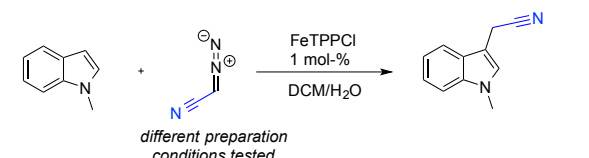


# <sup>[a]</sup>		yield <sup>[b]</sup>
1	DCM	92%
2	CHCl <sub>3</sub>	84%
3	EtOAc	66%
4	THF	66%
5	MeCN	51%
6	toluene	65%
7	pentane	75%

[a] *reaction conditions*: a solution of amino acetonitrile hydrochloride (1.6 M, 4 eq) in water, and a solution of NaNO<sub>2</sub> (1.92 M, 4.8 eq) in water are added via syringe pump at a flow rate of 100 µL/min for each syringe into a microreactor (LTF-MRT MX, 200 µL volume attached to a back pressure regulator 20 psi) heated to 55 °C and added after it has been cooled to 0 °C to a reaction vessel containing 0.4 mmol **1a**, 1mol-% FeTPPCL in 0.1 mL the solvent indicated. [b] isolated yields.



**Table S3.** Comparison of yields for different routes to prepare diazo acetonitrile.



*different preparation conditions tested*

# <sup>[a]</sup>	yield
One-pot protocol	57% <sup>[b]</sup>
Slow-release protocol	43% <sup>[b]</sup>
Flow protocol	92%

[a] reaction conditions: please see the experimental procedures; [b] product contains small amounts of impurities.

## Experimental Procedures

### Standard procedure for the C-H Insertion reactions

Two stock solutions were prepared in thoroughly degassed water: a) aqueous solution of amino acetonitrile hydrochloride (1.6 M) b) aqueous solution of sodium nitrite (1.92 M). The stock solutions were transferred into two syringes and placed in a syringe pump. The syringes were connected via PTFE tubing to a microreactor (LTF-MRT MX, 200  $\mu$ L volume) heated to 55 °C with an internal volume of 0.2 mL. Then, the tubing was passed through an ice bath to cool down the reaction mixture and the cold solution of diazo acetonitrile was added over a period of ten minutes to a mixture of FeTPPCL (1 mol-%) and indole derivative (0.4 mmol, 1 eq) that were dissolved in 0.1 mL of thoroughly degassed DCM. The resulting mixture was stirred an additional 2 h at room temperature. The aqueous phase was extracted with DCM (three times) and the combined organic layers were dried with Na<sub>2</sub>SO<sub>4</sub>. The solvent was removed under reduced pressure and the residue was purified by column chromatography on silica gel (pentane: diethyl ether 20:1 -> 1:1) to afford the desired product.

### Procedure for the gram-scale C-H insertion reaction

Two stock solutions were prepared in thoroughly degassed water: a) aqueous solution of amino acetonitrile hydrochloride (1.6 M, 20 mL) b) aqueous solution of sodium nitrite (1.92 M, 20 mL). The stock solutions were transferred into two syringes and placed in a syringe pump. The syringes were connected via PTFE tubing to a micromixer heated to 55 °C with an internal volume of 0.2 mL. Then, the tubing was passed through an ice bath to cool down the reaction mixture and the cold solution of diazo acetonitrile was added (0.1 mL/min flowrate per syringe) to a mixture of FeTPPCL (1 mol-%) and indole derivative (8 mmol, 1eq) that were dissolved in 2 mL of thoroughly degassed DCM. The resulting mixture was stirred an additional 2 h at room temperature. The aqueous phase was extracted with dichloromethane (three times) and the combined organic layers were dried with Na<sub>2</sub>SO<sub>4</sub>. The solvent was removed under reduced

pressure and the residue was purified by column chromatography on silica gel (pentane: diethyl ether 20:1 -> 2:1) to afford the desired product.

#### **Procedure for the slow-release reaction**

FeTPPCL (1 mol-%), amino acetonitrile hydrochloride (4eq) and *N*-methyl indole (0.4 mmol, 1eq) were dissolved in 0.1 mL of DCM and 1 mL of thoroughly degassed water under argon atmosphere. NaNO<sub>2</sub> (4.8 eq) was dissolved in 1 mL degassed water and added via syringe pump over 10 h at room temperature. The resulting mixture was stirred additional 2 h at room temperature. The aqueous phase was extracted with DCM (three times) and the combined organic layers were dried with Na<sub>2</sub>SO<sub>4</sub>. The solvent was removed under reduced pressure and the residue was purified by column chromatography on silica gel (pentane: diethyl ether 20:1 -> 2:1) to afford the desired product.

#### **Procedure for the batch reaction**

FeTPPCL (1 mol-%), amino acetonitrile hydrochloride (4eq), NaNO<sub>2</sub> (4.8 eq) and *N*-methyl indole (0.4 mmol, 1eq) were dissolved in 0.1 mL of DCM and 2 mL of thoroughly degassed water under argon atmosphere. The resulting mixture was stirred for 2 h at room temperature. The aqueous phase was extracted with DCM (three times) and the combined organic layers were dried with Na<sub>2</sub>SO<sub>4</sub>. The solvent was removed under reduced pressure and the residue was purified by column chromatography on silica gel (pentane: diethyl ether 20:1-> 2:1) to afford the desired product.

#### **Synthesis of *N*-alkyl indoles**

Indole (1 eq) was dissolved in DMF (5 mL per mmol indole) and sodium hydride (1.5 eq) was slowly added at 0 °C. The resulting mixture was stirred for 30 min, then the alkyl bromide was added and stirred over night. Ethyl acetate (20 mL per mmol indole) was added and the organic layer was extracted two times with brine, dried over Na<sub>2</sub>SO<sub>4</sub>, concentrated in vacuo. The residue was purified by column chromatography in silica gel (hexane: ethyl acetate 80:1) to yield the *N*-alkyl indoles.

#### **Synthesis of *N*-aryl indoles**

Indole (1 eq), CuI (10 mol-%), *trans*-1,2-diamino cyclohexane (20 mol-%) and aryl bromide (1.5 eq) was dissolved in saturated aq. K<sub>2</sub>CO<sub>3</sub> solution (5 mL per mmol indole) and heated to 90 °C over night under air. Ethyl acetate was added, the phases separated and the aqueous layer was extracted two times with ethyl acetate. The combined organic phases were dried over Na<sub>2</sub>SO<sub>4</sub>, concentrated in vacuo and purified by column chromatography on silica gel (hexane: ethyl acetate 80:1) to yield the *N*-aryl indoles.

#### **Synthesis of 3-deuterated *N*-methyl indole**

3-deuterated *N*-methyl indole was prepared in analogy to the literature procedure.<sup>ii</sup> 600 mg *N*-methyl indole were dissolved in 5 mL CD<sub>3</sub>OD and 5 mol-% of HNTf<sub>2</sub> was added. The reaction mixture was stirred at RT for 30 minutes. Then D<sub>2</sub>O and hexanes were added. The organic layer was dried over Na<sub>2</sub>SO<sub>4</sub> and evaporated to yield 3-deuterated *N*-methyl indole in quantitative yield (85% deuterium incorporation from <sup>1</sup>H-NMR).

### Plasmid Isolation

The plasmids were isolated using the Invisorb® Spin Plasmid Mini Two (500) (Stratec molecular, Berlin, DE). 5 ml of Lysogenic broth (LB) medium, containing 50 µg/ml chloramphenicol, were inoculated with one colony carrying the desired plasmid from a selective agar plate and incubated at 37 °C overnight. The plasmids were isolated as prescribed in the manufacturer's manual. The concentration of purified plasmids was determined by absorbance measurements at 260 nm with a TECAN infinite F200 pro (Grödig, AUT).

### Mutant generation via QuikChange™

Amino acid mutations were generated by using the QuikChange™ Site-Directed Mutagenesis Kit (Agilent Technologies, Santa Clara, US) as recommended by the manufacturer using the pCA24N-YfeX plasmid as template DNA.

**Table S4. Sequences of primers used for QuikChange® Mutagenesis.**

YfeX Mutant	Sequence (5'-3')	Sequence (3'-5')
R232A	GCTGAAGATTGTTGCCAGAGCCTGCCGTAC	GTACGGCAGGCTCTGGGCAACAATCTTCAGC
W176A	GTGTTTGTCCAGCGTGCGGAACACAACCTGAAGCAG	CTGCTTCAGGTTGTGTTCCGCACGCTGGACAAACAC
H215A	CCGGAACCTCTGCCCTCACCCGC	GCGGGTGAGGGCAGAGGTTTCCGG
E146A	CTTTGTTGACGGTACGGCAAACCCGGCGGGTGAAG	CTTCACCCGCCGGGTTTGCCGTACCGTCAACAAAG
I230A	GCAAAGGGCTGAAGGCTGTTGCCAGAGCCTG	CAGGCTCTGGCGAACAGCCTTCAGCCCTTTGC
D137A	GTTGGGTTGAAGAGCGTGCCCTGAGCGGCTTTGTTG	CAACAAAGCCGCTCAGGGCAGCTCTTCAACCCAAC
H178A	GTCCAGCGTTGGGAAGCAAACCTGAAGCAGCTC	GAGCTGCTTCAGGTTTGCTTCCCAACGCTGGAC
K229A	GATGGCAAAGGGCTGGCGATTGTTGCCAGAGC	GCTCTGGCGAACAATCGCCAGCCCTTTGCCATC
L246A	GTGGCACTCACGGTGCGTACTTCTGCGCCTAC	GTAGGCGCAGAAGTACGCACCGTGAGTGCCAC
S234A	GATTGTTGCCAGGCCCTGCCGTACGGCAC	GTGCCGTACGGCAGGGCCTGGCGAACAATC

### Expression and Purification

For expression of the YfeX gene and its corresponding mutants chemocompetent *E. coli* BL21 (DE3) cells were transformed with the plasmid pCA24N-YfeX by heat shock. Freshly-plated transformants were grown overnight in Terrific broth (TB) medium containing 50 µg·ml<sup>-1</sup> chloramphenicol. 2 ml of the pre-cultures were used to inoculate 400 ml TB autoinduction medium containing 50 µg·ml<sup>-1</sup> chloramphenicol. Cells were incubated at 37 °C on shakers at 120 rpm. After 4 h of cultivation, aqueous solutions of FeCl<sub>3</sub>/5-aminolevulinic acid (100 µM final concentration) were added, the temperature was reduced to 30 °C and the cells were incubated for further 16.5 h. Cells were harvested by centrifugation (3000 x g, 20 min, 4 °C). The supernatant was discarded and the pellets were resuspended in binding buffer (50 mM KPi, pH = 7.4, 200 mM NaCl). Cells were lysed by sonication (Bandelin Sonoplus HD3100: 6x30 s, 70 % amplitude, pulse mode) and the lysate was incubated with hemin (600 µM final concentration) at room temperature for 30 min with a final DMSO concentration of 2 %. The cell debris was removed by centrifugation for 45 min at 4 °C and 6000 x g. Excess of hemin and DMSO was removed during the protein purification steps. The proteins exhibiting a Hexahistidin-Tag were purified by IMAC (immobilized metal ion affinity chromatography) using 1 mL His GraviTrap TALON columns (GE Healthcare Europe GmbH, Freiburg, DE). The purification was performed with washing buffer consisting of 50 mM Kpi (pH = 7.4), 200 mM NaCl and 5 mM imidazole. The YfeX variants were finally

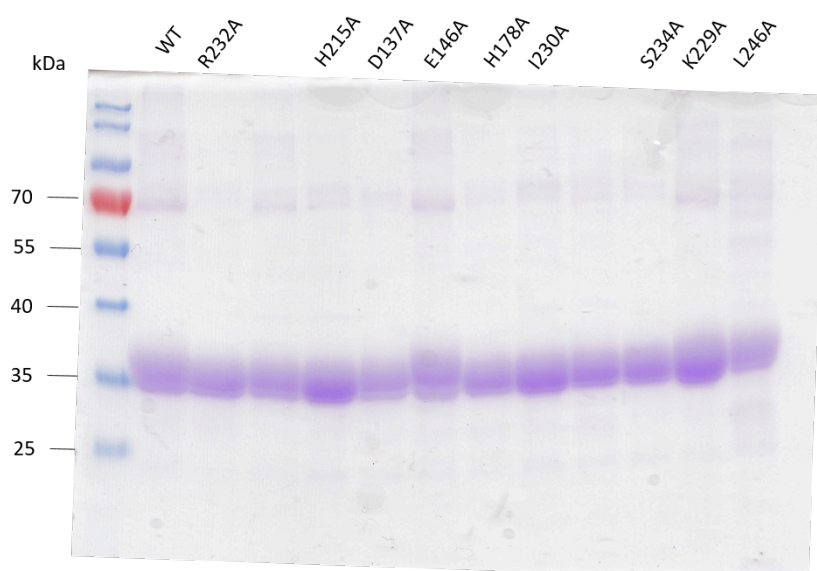
eluted by the addition of elution buffer (50 mM Kpi (pH = 7.4), 200 mM NaCl and 250 mM imidazole). PD-10 desalting columns (GE Healthcare Europe GmbH, Freiburg, DE) were used for buffer exchange of the pooled elution fractions, yielding the purified YfeX proteins in 50 mM KPi (pH = 7.4) and 10 % glycerol (v/v), which were flash-frozen in liquid N<sub>2</sub> and stored at -20 °C. Protein amounts were determined in triplicates using the Pierce™ BCA Protein Assay Kit (Thermo Scientific, Rockford, US) and the Pyridine Hemochromagen Assay (reduced form,  $\epsilon = 34.7 \text{ mM}^{-1}\text{cm}^{-1}$ ) was used for quantifying the heme b amount.<sup>1</sup>

**Table S5.** Heme b loading of YfeX variants.

#	YfeX variants	Percentage heme b loading [%] <sup>[a]</sup>
1	WT	74
2	R232A	71
3	W176A	-[b]
4	H215A	-[c]
5	E146A	77
6	I230A	85
7	D137A	86
8	H178A	89
9	K229A	92
10	F248A	94
11	L246A	42
12	S234A	103

[a] Calculated from BCA/Pyridine Hemochromagen Assay, mean values from two replicates  $\pm$  8 % standard deviation. [b] Insufficient expression. [c] ApoYfeX.<sup>1</sup>

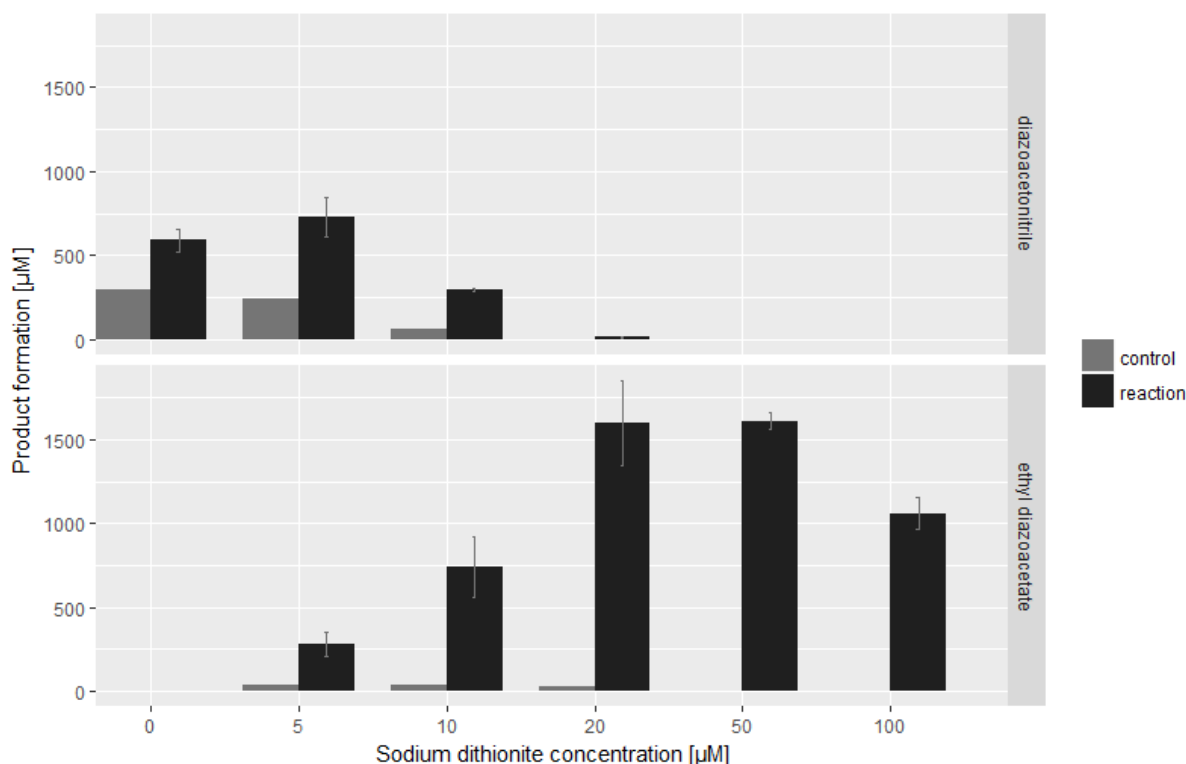
**Figure S1.** SDS PAGE analysis (12 %) of YfeX variants.



## Experimental Procedures of bio

### Optimization of reaction parameters

Trials for the optimization of the reaction conditions, through the method Design of Experiments (DoE), were accomplished with the help of the software MODDE pro (version 11.0.1.1878, Sartorius Stedium Biotech, Umeå, SE) by varying the concentration of the diazo component, the *N*-methyl indole, the pH value and a selection of different buffer systems. The optimized conditions were applied for each enzymatic C–H insertion reaction and are described in the corresponding sections. The influence of Na<sub>2</sub>S<sub>2</sub>O<sub>4</sub> in combination with different diazo compounds was investigated in detail and is shown in figure S2.



**Figure S2.** C–H insertion of *N*-methyl indole (50 mM) and the corresponding diazo component (50 mM) with varying Na<sub>2</sub>S<sub>2</sub>O<sub>4</sub> concentrations (20 µM YfeX WT, 4 h, 30 °C).

### Standard procedure of diazoacetonitrile for enzymatic bioconversions

The diazoacetonitrile was freshly prepared for each experiment. A degassed aqueous solution of amino acetonitrile hydrochloride (1 M) was stirred at 0 °C. Sodium nitrite was added to obtain an 1.2 M reaction mixture. After 5 min the reaction mixture was stirred for another 10 min at room temperature, followed by further 5 min on ice enabling an easier handling and a direct addition of the diazoacetonitrile component to the C–H insertion reaction mixture.

### Enzymatic C–H Insertion reactions with diazoacetonitrile

C–H insertion reactions with the YfeX variants were performed in 2.5 ml Rotilabo® sample vials (Carl Roth, Karlsruhe, DE) with a final volume of 400 µl (100 mM citrate buffer, pH = 7). The reaction mixture consisted of 20 µM YfeX, 50 mM freshly prepared diazoacetonitrile, 50 mM *N*-methyl indole, 5 mM Na<sub>2</sub>S<sub>2</sub>O<sub>4</sub> and 5 % DMSO as degassed

cosolvent and was saturated with N<sub>2</sub>. After an incubation time of 4 h at 30 °C and 600 rpm shaking velocity the products were extracted using 400 µL MTBE with 0,005 % ethyl benzoate and a centrifugation step at 6400 x g for 3 min. The organic phase was analyzed by GC/MS.

#### Enzymatic C–H Insertion reactions with ethyl diazoacetate

C–H insertion reactions with the YfeX variants were performed in 2.5 ml Rotilabo® sample vials (Carl Roth, Karlsruhe, DE) with a final volume of 400 µl (100 mM citrate buffer, pH = 7). The reaction mixture consisted of 20 µM/1 µM YfeX, 50 mM ethyl diazoacetate, 50 mM *N*-methyl indole, 50 mM Na<sub>2</sub>S<sub>2</sub>O<sub>4</sub> and 10 % DMSO as degassed cosolvent and was saturated with N<sub>2</sub>. After an incubation time of 4 h at 30 °C and 600 rpm shaking velocity, the products were extracted using 400 µL MTBE with 0,005 % ethyl benzoate and a centrifugation step at 6400 x g for 3 min. The organic phase was analyzed by GC/MS.

#### Whole cell C–H Insertion reactions

Biotransformation were performed in 2.5 ml Rotilabo® sample vials (Carl Roth, Karlsruhe, DE) in a final volume of 400 µl using resuspended *E. coli* cells (BL21) overexpressing YfeX WT at OD<sub>600</sub> = 30 in degassed 100 mM citrate buffer (pH = 7). The reaction mixture consisted of 50 mM ethyl diazoacetate, 50 mM *N*-methyl indole, 50 mM Na<sub>2</sub>S<sub>2</sub>O<sub>4</sub> and 10 % DMSO as degassed co-solvent and was saturated with N<sub>2</sub>. After an incubation time of 4 h at 30 °C and 600 rpm shaking velocity, the products were extracted using 400 µL MTBE with 0.005 % ethyl benzoate and a centrifugation step at 6400 x g for 10 min. The organic phase was analyzed by GC/MS. For calculation of the turnover number the protein was isolated as earlier described and the protein concentration was measured using the BCA Assay yielding an end concentration in the reaction vial of 7 µM.

#### Enzymatic deuterium labelling experiments

*Deutero-1a* was prepared according to the standard enzymatic C–H insertion procedure by using *deutero-1a* as starting material. The background D/H exchange was determined in absence of the catalyst. Following the previous mentioned extraction protocol and evaporation of the MTBE, the D/H ratio was measured by NMR analysis.

#### C–H Insertion reactions with heme proteins besides YfeX

The heme proteins P450<sub>BM3</sub> (*Bacillus megaterium*) and P450<sub>NOR</sub> (*Histoplasma capsulatum*) were also tested as catalysts for the C–H insertion reactions with diazoacetonitrile and ethyl diazoacetate. The reactions were performed according to the previously described enzymatic C–H insertion reaction procedure with 50 mM *N*-methyl indole, 50 mM diazo component and 20 mM Na<sub>2</sub>S<sub>2</sub>O<sub>4</sub>. Reactions were performed in unique runs.

**Table S6. C–H Insertion reactions with P450 enzymes.**

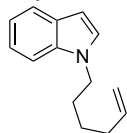
#	catalyst	Diazo component	Product formation [µM]	TON
1	P450 <sub>BM3</sub> <sup>[a]</sup>	Diazoacetonitrile	2.4	0.2
2	P450 <sub>NOR</sub> <sup>[b]</sup>	Diazoacetonitrile	2.5	0.1
3	P450 <sub>BM3</sub> <sup>[a]</sup>	Ethyl diazoacetate	3.1	0.3
4	P450 <sub>NOR</sub> <sup>[b]</sup>	Ethyl diazoacetate	39.9	1.8

<sup>[a]</sup> Protein concentration = 10 µM, <sup>[b]</sup> protein concentration = 22 µM.

## Analytical data

### Indole starting materials

#### 1-(Hex-5-en-1-yl)-1H-indol



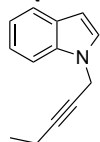
**<sup>1</sup>H NMR** (600 MHz, CDCl<sub>3</sub>):  $\delta$  = 7.62 (dt,  $J$  = 7.9, 1.0 Hz, 1H), 7.33 (dq,  $J$  = 8.2, 0.9 Hz, 1H), 7.19 (ddd,  $J$  = 8.2, 7.0, 1.2 Hz, 1H), 7.11 – 7.05 (m, 2H), 6.47 (dd,  $J$  = 3.1, 0.9 Hz, 1H), 5.75 (ddt,  $J$  = 17.0, 10.2, 6.7 Hz, 1H), 5.02 – 4.91 (m, 2H), 4.11 (t,  $J$  = 7.1 Hz, 2H), 2.13 – 2.02 (m, 2H), 1.89 – 1.78 (m, 2H), 1.41 (tt,  $J$  = 10.2, 6.5 Hz, 2H) ppm.

**<sup>13</sup>C NMR** (151 MHz, CDCl<sub>3</sub>):  $\delta$  = 138.2, 135.9, 128.59, 127.7, 121.3, 120.9, 119.2, 114.9, 109.3, 100.9, 46.2, 33.3, 29.6, 26.2 ppm.

**MS** (EI): 199.2 ([M]<sup>+</sup>, 100%).

**IR** (KBr): 3059, 2926, 2860, 2327, 2101, 1884, 1638, 1510, 1459, 1316, 1225, 997, 909, 735 cm<sup>-1</sup>.

#### 1-(Pent-3-yn-1-yl)-1H-indol



**<sup>1</sup>H NMR** (600 MHz, CDCl<sub>3</sub>):  $\delta$  = 7.64 (dt,  $J$  = 7.9, 1.0 Hz, 1H), 7.42 (dq,  $J$  = 8.2, 0.9 Hz, 1H), 7.26 – 7.19 (m, 2H), 7.13 (ddd,  $J$  = 8.0, 7.1, 1.0 Hz, 1H), 6.52 (dd,  $J$  = 3.2, 0.9 Hz, 1H), 4.85 (t,  $J$  = 2.3 Hz, 2H), 2.26 – 2.17 (m, 2H), 1.14 (t,  $J$  = 7.5 Hz, 3H) ppm.

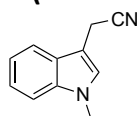
**<sup>13</sup>C NMR** (151 MHz, CDCl<sub>3</sub>):  $\delta$  = 135.7, 128.8, 127.2, 121.6, 120.9, 119.6, 109.4, 101.4, 87.2, 73.3, 36.2, 13.7, 12.4 ppm.

**MS** (EI): 183.2 ([M]<sup>+</sup>, 100%), 167.1 ([M-CH<sub>3</sub>]<sup>+</sup>, 11%), 154.1 ([M-C<sub>2</sub>H<sub>5</sub>]<sup>+</sup>, 12%).

**IR** (KBr): 3427, 3048, 2975, 2305, 2100, 1888, 1736, 1462, 1316, 1191, 1013, 736 cm<sup>-1</sup>.

## Products

#### 2-(1-methyl-1H-indol-3-yl)acetonitrile (3aa)



Compound **3aa** was prepared according to the general procedure and was obtained after column chromatography (pentane : diethyl ether 20:1 → 2:1) as a solid in 92% yield (63 mg).

**mp.**: 56-58 °C.

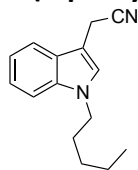
**<sup>1</sup>H NMR** (600 MHz, CDCl<sub>3</sub>):  $\delta$  = 7.58 (d,  $J$  = 7.9 Hz, 1H), 7.34 (d,  $J$  = 8.3 Hz, 1H), 7.32 – 7.26 (m, 1H), 7.18 (ddd,  $J$  = 7.9, 6.8, 1.0 Hz, 1H), 7.09 (s, 1H), 3.83 (s, 2H), 3.78 (s, 3H) ppm.

**<sup>13</sup>C NMR** (151 MHz, CDCl<sub>3</sub>):  $\delta$  = 137.0, 127.3, 126.4, 122.4, 118.2, 118.1, 109.6, 102.9, 32.8, 14.3 ppm.

**HRMS** (ESI): mass found: 171.09161, calculated mass for C<sub>11</sub>H<sub>11</sub>N<sub>2</sub><sup>+</sup>: 171.09167.

**IR** (KBr): 3814, 2926, 2344, 2245, 2105, 1911, 1724, 1609, 1465, 1351, 1250, 1130, 1056, 906, 741 cm<sup>-1</sup>.

### 2-(1-pentyl-1H-indol-3-yl)acetonitrile (3ba)



Compound **3ba** was prepared according to the general procedure and was obtained after column chromatography (pentane : diethyl ether 20:1 → 4:1) as a yellowish oil in 96% yield (87 mg).

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>): δ = 7.60 – 7.52 (m, 1H), 7.40 – 7.30 (m, 1H), 7.31 – 7.22 (m, 1H), 7.19 – 7.10 (m, 2H), 4.08 (t, *J* = 7.0 Hz, 2H), 3.82 (s, 2H), 1.82 (p, *J* = 7.0 Hz, 2H), 1.45 – 1.18 (m, 4H), 0.94 – 0.82 (m, 3H) ppm.

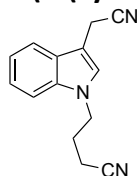
**<sup>13</sup>C NMR** (101 MHz, CDCl<sub>3</sub>): δ = 136.4, 126.4, 126.2, 122.2, 119.5, 118.3, 118.2, 109.8, 102.8, 46.4, 29.9, 29.0, 22.2, 14.3, 13.9 ppm.

**MS** (EI): 226.1 ([M]<sup>+</sup>, 100%), 200.2 ([M-CN]<sup>+</sup>, 18%), 169.1 ([M-C<sub>4</sub>H<sub>9</sub>]<sup>+</sup>, 36%).

**IR** (KBr): 3838, 2928, 2340, 2092, 1875, 1621, 1456, 1362, 1170, 1013, 920, 739 cm<sup>-1</sup>.

**EA** Anal. Calcd. for C<sub>15</sub>H<sub>11</sub>N<sub>2</sub>: C, 79.61; H, 8.02; N, 12.38. Found: C, 79.29; H, 7.82; N, 12.28.

### 4-(3-(cyanomethyl)-1H-indol-1-yl)butanenitrile (3ca)



Compound **3ca** was prepared according to the general procedure and was obtained after column chromatography (pentane : diethyl ether 20:1 → 0 : 100) as a colorless oil in 89% yield (79 mg).

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>): δ = 7.58 (dt, *J* = 7.9, 1.0 Hz, 1H), 7.36 (dd, *J* = 8.3, 1.0 Hz, 1H), 7.29 (ddd, *J* = 8.2, 6.9, 1.2 Hz, 1H), 7.19 (ddd, *J* = 7.9, 7.0, 1.1 Hz, 1H), 7.12 (s, 1H), 4.29 (t, *J* = 6.4 Hz, 2H), 3.82 (s, 2H), 2.73 – 2.24 (m, 2H), 2.24 – 2.14 (m, 2H) ppm.

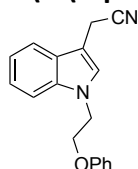
**<sup>13</sup>C NMR** (151 MHz, CDCl<sub>3</sub>) δ 136.2, 126.6, 125.9, 122.9, 120.2, 118.6, 117.9, 109.4, 104.2, 44.3, 26.0, 14.6, 14.3 ppm.

**HRMS** (ESI): mass found: 223.10939, calculated mass for C<sub>14</sub>H<sub>13</sub>N<sub>3</sub>: 223.11095.

**MS** (EI): 223.2 ([M]<sup>+</sup>, 100%), 169.1 ([M-C<sub>2</sub>H<sub>4</sub>CN]<sup>+</sup>, 77%).

**IR** (KBr): 3636, 3338. 2942, 2328, 2248, 1899, 1615, 1553, 1465, 1360, 1243, 1169, 1016, 916, 743 cm<sup>-1</sup>.

### 2-(1-(2-phenoxyethyl)-1H-indol-3-yl)acetonitrile (3da)



Compound **3da** was prepared according to the general procedure and was obtained after column chromatography (pentane : diethyl ether 20:1 → 1:1) as a colorless oil in 90% yield (99 mg).

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>): δ = 7.61 – 7.53 (m, 1H), 7.45 – 7.37 (m, 1H), 7.34 – 7.15 (m, 5H), 7.00 – 6.91 (m, 1H), 6.88 – 6.79 (m, 2H), 4.49 (t, *J* = 5.4 Hz, 2H), 4.25 (t, *J* = 5.5 Hz, 2H), 3.81 (s, 2H) ppm.

**<sup>13</sup>C NMR** (101 MHz, CDCl<sub>3</sub>): δ = 158.0, 136.5, 129.5, 126.9, 126.6, 122.5, 121.3, 119.9, 118.3, 118.1, 114.4, 109.6, 103.6, 66.6, 45.7, 14.3 ppm.

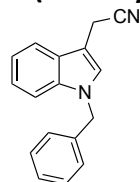


**MS** (EI): 276.1 ( $[M]^+$ , 83%), 169.1 ( $[M-(CH_2-OPh)]^+$ , 100%).

**IR** (KBr): 3870, 3452, 3051, 2932, 2665, 2324, 2251, 2102, 1904, 1593, 1473, 1364, 1236, 1049, 904, 745  $cm^{-1}$ .

**EA** Anal. Calcd for  $C_{18}H_{16}N_2O$ : C, 78.24; H, 5.84; N, 10.14. Found: C, 77.66; H, 5.90; N, 10.09.

### 2-(1-benzyl-1*H*-indol-3-yl)acetonitrile (**3ea**)



Compound **3ea** was prepared according to the general procedure and was obtained after column chromatography (pentane : diethyl ether 20:1  $\rightarrow$  4:1) as a colorless solid in 86% yield (85 mg).

**mp.**: 92-94  $^{\circ}C$ .

**$^1H$  NMR** (400 MHz,  $CDCl_3$ ):  $\delta$  = 7.66 – 7.52 (m, 1H), 7.38 – 6.99 (m, 9H), 5.28 (s, 2H), 3.83 (s, 2H) ppm.

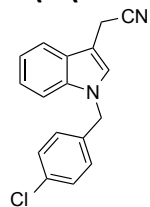
**$^{13}C$  NMR** (101 MHz,  $CDCl_3$ ):  $\delta$  = 136.9, 136.7, 128.8, 127.8, 126.8, 126.6, 122.6, 119.9, 118.3, 118.1, 110.1, 103.7, 50.1, 14.3 ppm.

**MS** (EI): 246.1 ( $[M]^+$ , 100%), 220.1 ( $[M-CN]^+$ , 48%).

**IR** (KBr): 3456, 3024, 2651, 2241, 2172, 2083, 1945, 1739, 1452, 1361, 1214, 1020, 905, 730  $cm^{-1}$ .

**EA** Anal. Calcd for  $C_{17}H_{14}N_2$ : C, 82.90; H, 5.73; N, 11.37. Found: C, 82.57; H, 5.88; N, 11.19.

### 2-(1-(4-chlorobenzyl)-1*H*-indol-3-yl)acetonitrile (**3fa**)



Compound **3fa** was prepared according to the general procedure and was obtained after column chromatography (pentane : diethyl ether 20:1  $\rightarrow$  4:1) as a yellowish oil in 83% yield (93 mg).

**$^1H$  NMR** (600 MHz,  $CDCl_3$ ):  $\delta$  = 7.84 – 7.47 (m, 1H), 7.40 – 7.12 (m, 6H), 7.09 – 7.00 (m, 2H), 5.27 (s, 2H), 3.84 (s, 2H) ppm.

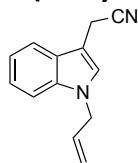
**$^{13}C$  NMR** (151 MHz,  $CDCl_3$ ):  $\delta$  = 136.6, 135.4, 133.7, 129.0, 128.1, 126.7, 126.5, 122.8, 120.1, 118.4, 118.0, 110.0, 104.0, 49.5, 14.3 ppm.

**MS** (EI): 282.1 ( $[M]^+$ , 28%), 280.1 ( $[M]^+$ , 78%), 127.0 ( $[CH_2-(C_6H_4Cl)]^+$ , 35%), 125.0 ( $[CH_2-(C_6H_4Cl)]^+$ , 100%).

**IR** (KBr): 3053, 2921, 2670, 2324, 2252, 2099, 1899, 1606, 1475, 1347, 1170, 1092, 805, 740  $cm^{-1}$ .

**EA** Anal. Calcd for  $C_{17}H_{13}ClN_2$ : C, 72.73; H, 4.67; N, 9.98. Found: C, 72.18; H, 4.67; N, 10.68.

### 2-(1-allyl-1H-indol-3-yl)acetonitrile (3ga)



Compound **3ga** was prepared according to the general procedure and was obtained after column chromatography (pentane : diethyl ether 20:1 → 4:1) as a yellowish oil in 80% yield (63 mg).

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>): δ = 7.60 – 7.52 (m, 1H), 7.33 (dt, *J* = 8.3, 1.0 Hz, 1H), 7.29 – 7.23 (m, 1H), 7.17 (ddd, *J* = 8.0, 6.9, 1.1 Hz, 1H), 7.12 (d, *J* = 1.1 Hz, 1H), 5.97 (ddt, *J* = 17.1, 10.2, 5.5 Hz, 1H), 5.22 (dq, *J* = 10.2, 1.4 Hz, 1H), 5.10 (dq, *J* = 17.1, 1.6 Hz, 1H), 4.70 (dt, *J* = 5.5, 1.6 Hz, 2H), 3.82 (d, *J* = 1.0 Hz, 2H) ppm.

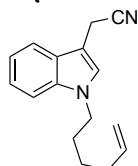
**<sup>13</sup>C NMR** (101 MHz, CDCl<sub>3</sub>): δ = 136.5, 132.9, 126.6, 126.3, 122.4, 119.8, 118.2, 117.7, 110.0, 103.4, 48.8, 14.3 ppm.

**HRMS** (ESI): mass found: 196.09964, calculated mass for C<sub>13</sub>H<sub>12</sub>N<sub>2</sub>: 196.10005.

**MS** (EI): 196.1 ([M]<sup>+</sup>, 23%), 170.1 ([M-CN]<sup>+</sup>, 21%), 156.1 ([M-allyl]<sup>+</sup>, 40%).

**IR** (KBr) 3814, 2909, 2339, 2094, 1869, 1636, 1448, 1359, 1174, 927, 741 cm<sup>-1</sup>.

### 2-(1-hex-5-en-1-yl-1H-indol-3-yl)acetonitrile (3ha)



Compound **3ha** was prepared according to the general procedure and was obtained after column chromatography (pentane : diethyl ether 20:1 → 4:1) as a colorless oil in 95% yield (90 mg).

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>): δ = 7.67 – 7.51 (m, 1H), 7.37 – 7.30 (m, 1H), 7.29 – 7.20 (m, 1H), 7.20 – 7.11 (m, 1H), 7.11 (s, 1H), 5.75 (ddt, *J* = 17.0, 10.2, 6.7 Hz, 1H), 5.13 – 4.93 (m, 2H), 4.09 (t, *J* = 7.1 Hz, 2H), 3.82 (s, 2H), 2.21 – 2.00 (m, 2H), 1.83 (p, *J* = 7.3 Hz, 2H), 1.47 – 1.35 (m, 2H) ppm.

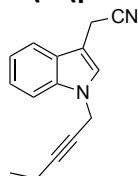
**<sup>13</sup>C NMR** (101 MHz, CDCl<sub>3</sub>): δ = 138.0, 136.3, 126.4, 126.2, 122.2, 119.6, 118.2, 115.0, 109.78, 102.9, 46.2, 33.2, 29.6, 26.1, 14.3 ppm.

**MS** (EI): 238.2 ([M]<sup>+</sup>, 23%), 212.2 ([M-CH<sub>2</sub>CN]<sup>+</sup>, 21%), 169.1 ([M-hexenyl]<sup>+</sup>, 40%).

**IR** (KBr) 3839, 2918, 2339, 2092, 1859, 1634, 1442, 1367, 1174, 1003, 914, 743 cm<sup>-1</sup>.

**EA Anal.** Calcd for C<sub>16</sub>H<sub>18</sub>N<sub>2</sub>: C, 80.63; H, 7.61; N, 11.75. Found: C, 79.91; H, 7.43; N, 12.43.

### 2-(1-(pent-2-yn-1-yl)-1H-indol-3-yl)acetonitrile (3ia)



Compound **3ia** was prepared according to the general procedure and was obtained after column chromatography (pentane : diethyl ether 20:1 → 4:1) as a colorless oil in 87% yield (77 mg).

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>): δ = 7.75 – 7.51 (m, 1H), 7.47 – 7.37 (m, 1H), 7.34 – 7.23 (m, 2H), 7.23 – 7.05 (m, 1H), 4.87 – 4.75 (m, 2H), 3.81 (s, 2H), 2.85 – 1.91 (m, 2H), 1.13 (dd, *J* = 7.6 Hz, 3H) ppm.

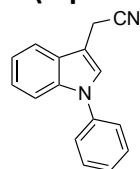
**<sup>13</sup>C NMR** (101 MHz, CDCl<sub>3</sub>): δ = 136.1, 126.8, 125.8, 122.5, 120.0, 118.3, 118.1, 109.8, 103.5, 87.7, 72.8, 36.2, 14.3, 13.6, 12.3 ppm.

**MS** (EI): 222.2 ([M]<sup>+</sup>, 100%), 193.1 ([M-Et]<sup>+</sup>, 11%).

**IR** (KBr) 3857, 3416, 2976, 2924, 2324, 2247, 2093, 1919, 1714, 1611, 1466, 1346, 1249, 1177, 1016, 743 cm<sup>-1</sup>;

**EA** Anal. Calcd for C<sub>10</sub>H<sub>8</sub>F<sub>3</sub>NO<sub>2</sub>: C, 79.61; H, 8.02; N, 12.38. Found: C, 79.29; H, 7.82; N, 12.28.

### 2-(1-phenyl-1*H*-indol-3-yl)acetonitrile (**3ja**)



Compound **3ja** was prepared according to the general procedure and was obtained after column chromatography (pentane : diethyl ether 20:1 → 4:1) as a colorless oil in 86% yield (80 mg).

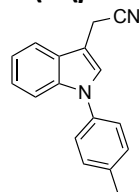
**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>): δ = 7.65 (dd, *J* = 7.9, 1.0 Hz, 1H), 7.59 – 7.52 (m, 3H), 7.51 – 7.47 (m, 2H), 7.43 – 7.37 (m, 2H), 7.32 – 7.28 (m, 1H), 7.27 – 7.21 (m, 1H), 3.90 (s, 2H) ppm.

**<sup>13</sup>C NMR** (101 MHz, CDCl<sub>3</sub>): δ = 139.1, 136.2, 129.7, 127.1, 126.9, 126.4, 124.3, 123.2, 120.7, 118.4, 117.9, 110.9, 105.6, 14.3 ppm.

**HRMS** (ESI): mass found: 233.10728, calculated mass for C<sub>16</sub>H<sub>13</sub>N<sub>2</sub><sup>+</sup>: 233.10732.

**IR** (KBr) 3056, 2922, 2251, 1908, 1597, 1485, 1372, 1216, 913, 741 cm<sup>-1</sup>.

### 2-(1-(*p*-tolyl)-1*H*-indol-3-yl)acetonitrile (**3ka**)



Compound **3ka** was prepared according to the general procedure and was obtained after column chromatography (pentane : diethyl ether 20:1 → 4:1) as a yellowish oil in 99% yield (97 mg).

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>): δ = 7.66 – 7.60 (m, 1H), 7.56 – 7.47 (m, 1H), 7.39 – 7.27 (m, 5H), 7.29 – 7.19 (m, 2H), 3.88 (s, 2H), 2.43 (s, 3H) ppm.

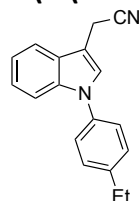
**<sup>13</sup>C NMR** (101 MHz, CDCl<sub>3</sub>): δ = 136.8, 136.5, 136.4, 130.2, 127.0, 126.5, 124.3, 123.1, 120.5, 118.3, 117.9, 110.9, 105.2, 21.0, 14.3 ppm.

**HRMS** (ESI): mass found: 246.11424, calculated mass for C<sub>17</sub>H<sub>14</sub>N<sub>2</sub>: 246.11570.

**MS** (EI): 246.1 ([M]<sup>+</sup>, 100%), 220.1 ([M-CN]<sup>+</sup>, 28%).

**IR** (KBr) 3415, 3042, 2919, 2250, 1900, 1609, 1514, 1456, 1372, 1301, 1227, 1129, 1016, 923, 820 cm<sup>-1</sup>.

### 2-(1-(4-ethylphenyl)-1*H*-indol-3-yl)acetonitrile (**3la**)



Compound **3la** was prepared according to the general procedure and was obtained after column chromatography (pentane : diethyl ether 20:1 → 4:1) as a yellowish oil in 89% yield (93 mg).

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>): δ = 7.66 – 7.58 (m, 1H), 7.56 – 7.49 (m, 1H), 7.45 – 7.30 (m, 5H), 7.29 – 7.17 (m, 2H), 3.88 (s, 2H), 2.73 (q, *J* = 7.6 Hz, 2H), 1.30 (t, *J* = 7.6 Hz, 3H) ppm.

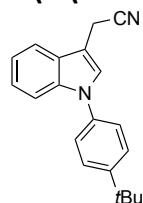
**<sup>13</sup>C NMR** (101 MHz, CDCl<sub>3</sub>): δ = 143.1, 136.7, 136.4, 129.0, 127.0, 126.5, 124.3, 123.1, 120.5, 118.3, 117.9, 110.9, 105.2, 28.4, 15.5, 14.3 ppm.

**HRMS** (ESI): mass found: 260.13044, calculated mass for C<sub>18</sub>H<sub>16</sub>N<sub>2</sub>: 260.13135.

**MS** (EI): 260.2 ([M]<sup>+</sup>, 100%), 245.2 ([M-CN]<sup>+</sup>, 29%).

**IR** (KBr) 3853, 3428, 2042, 2964, 2661, 2324, 2252, 2096, 1996, 1909, 1731, 1608, 1514, 1457, 1371, 1306, 1225, 1127, 1016, 838, 743 cm<sup>-1</sup>.

### 2-(1-(4-*tert*-butyl-phenyl)-1*H*-indol-3-yl)acetonitrile (**3ma**)



Compound **3ma** was prepared according to the general procedure and was obtained after column chromatography (pentane : diethyl ether 20:1 → 4:1) as a colorless solid in 92% yield (106 mg).

**mp.**: 93-94 °C.

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>): δ = 7.68 – 7.61 (m, 1H), 7.57 – 7.50 (m, 3H), 7.42 – 7.37 (m, 2H), 7.35 (s, 1H), 7.29 – 7.19 (m, 2H), 3.89 (s, 2H), 1.38 (s, 9H) ppm.

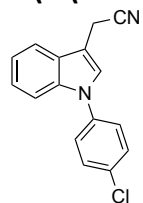
**<sup>13</sup>C NMR** (101 MHz, CDCl<sub>3</sub>): δ = 150.0, 136.4, 136.3, 127.0, 126.5, 123.9, 123.1, 120.6, 118.3, 117.9, 111.0, 105.2, 34.6, 31.3, 14.3 ppm.

**MS** (EI): 246.1 ([M]<sup>+</sup>, 100%), 220.1 ([M-CN]<sup>+</sup>, 28%).

**IR** (KBr) 3302, 2942, 2250, 2082, 1909, 1725, 1602, 1480, 1368, 1232, 1118, 1014, 836, 736 cm<sup>-1</sup>.

**EA Anal.** Calcd for C<sub>20</sub>H<sub>20</sub>N<sub>2</sub>: C, 83.30; H, 6.99; N, 9.71. Found: C, 82.60; H, 6.84; N, 9.63.

### 2-(1-(4-chlorophenyl)-1*H*-indol-3-yl)acetonitrile (**3na**)



Compound **3na** was prepared according to the general procedure and was obtained after column chromatography (pentane : diethyl ether 20:1 → 4:1) as a colorless solid in 73% yield (78 mg).

**mp.**: 93-95 °C.

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>): δ = 7.67 – 7.60 (m, 1H), 7.49 (d, *J* = 8.7 Hz, 3H), 7.44 – 7.38 (m, 2H), 7.33 (d, *J* = 1.2 Hz, 1H), 7.32 – 7.19 (m, 3H), 3.88 (s, 2H) ppm.

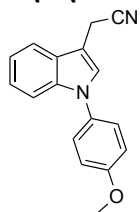
**<sup>13</sup>C NMR** (101 MHz, CDCl<sub>3</sub>): δ = 137.6, 136.1, 129.8, 126.1, 125.5, 123.5, 121.0, 118.5, 117.7, 110.7, 106.1, 14.3 ppm.

**HRMS** (ESI): mass found: 266.06029, calculated mass for C<sub>16</sub>H<sub>11</sub>ClN<sub>2</sub>: 266.06108.

**MS** (EI): 268.1 ([M]<sup>+</sup>, 35%), 266.1 ([M]<sup>+</sup>, 100%), 242.1 ([M-CN]<sup>+</sup>, 9%); 240.1 ([M-CN]<sup>+</sup>, 24%).

**IR** (KBr) 3823, 3452, 3058, 2921, 2660, 2244, 2080, 1912, 1736, 1592, 1494, 1455, 1365, 1291, 1227, 1090, 1012, 833, 731  $\text{cm}^{-1}$ .

**2-(1-(4-methoxyphenyl)-1H-indol-3-yl)acetonitrile (3oa)**



Compound **3oa** was prepared according to the general procedure and was obtained after column chromatography (pentane : diethyl ether 20:1  $\rightarrow$  2:1) as a yellowish oil in 85% yield (76 mg).

**$^1\text{H}$  NMR** (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 7.65 – 7.58 (m, 1H), 7.48 – 7.41 (m, 1H), 7.40 – 7.35 (m, 2H), 7.30 (s, 1H), 7.28 – 7.18 (m, 3H), 7.10 – 6.99 (m, 2H), 3.88 (s, 2H), 3.87 (s, 3H) ppm.

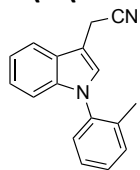
**$^{13}\text{C}$  NMR** (101 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 158.5, 136.7, 132.0, 126.7, 125.9, 123.0, 120.4, 118.2, 117.9, 114.7, 110.8, 104.9, 55.5, 14.3 ppm.

**HRMS** (ESI): mass found: 262.10965, calculated mass for  $\text{C}_{17}\text{H}_{14}\text{N}_2\text{O}$ : 262.11061.

**MS** (EI): 262.2 ( $[\text{M}]^+$ , 100%), 247.1 ( $[\text{M}-\text{CH}_3]^+$ , 17%), 236.2 ( $[\text{M}-\text{CN}]^+$ , 13%), 222.2 ( $[\text{M}-(\text{CH}_2-\text{CN})]^+$ , 21%).

**IR** (KBr) 3429, 3055, 2939, 2837, 2251, 1891, 1730, 1617, 1510, 1458, 1369, 1293, 1237, 1138, 1026, 832, 740  $\text{cm}^{-1}$ .

**2-(1-(2-methyl-phenyl)-1H-indol-3-yl)acetonitrile (3pa)**



Compound **3pa** was prepared according to the general procedure and was obtained after column chromatography (pentane : diethyl ether 20:1  $\rightarrow$  4:1) as a yellowish solid in 99% yield (97 mg).

**mp.**: 85-87  $^{\circ}\text{C}$ .

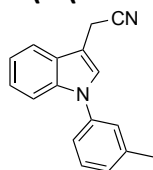
**$^1\text{H}$  NMR** (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 7.71 – 7.61 (m, 1H), 7.45 – 7.35 (m, 2H), 7.34 – 7.16 (m, 5H), 7.17 – 7.00 (m, 1H), 3.90 (s, 2H), 2.06 (s, 3H) ppm.

**$^{13}\text{C}$  NMR** (101 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 137.5, 137.4, 135.7, 131.2, 128.5, 128.0, 127.0, 126.8, 126.2, 122.9, 120.3, 118.1, 118.0, 111.0, 104.6, 17.6, 14.4 ppm.

**MS** (EI): 246.1 ( $[\text{M}]^+$ , 100%), 220.1 ( $[\text{M}-\text{CN}]^+$ , 41%), 206.0 ( $[\text{M}-(\text{CH}_2-\text{CN})]^+$ , 20%).

**IR** (KBr) 3452, 2922, 2249, 1737, 1594, 1494, 1462, 1369, 1311, 1226, 1008, 910, 744  $\text{cm}^{-1}$ . **EA** Anal. Calcd. for  $\text{C}_{17}\text{H}_{14}\text{N}_2$ : C, 82.90; H, 5.73; N, 11.37. Found: C, 82.68; H, 5.87; N, 11.26.

**2-(1-(3-methyl-phenyl)-1H-indol-3-yl)acetonitrile (3qa)**



Compound **3qa** was prepared according to the general procedure and was obtained after column chromatography (pentane : diethyl ether 20:1  $\rightarrow$  4:1) as a colorless solid in 99% yield (97 mg).

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>): δ = 7.65 – 7.60 (m, 1H), 7.58 – 7.51 (m, 1H), 7.45 – 7.33 (m, 2H), 7.30 – 7.14 (m, 5H), 3.88 (s, 2H), 2.44 (s, 3H) ppm.

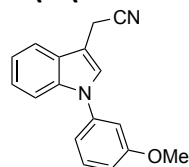
**<sup>13</sup>C NMR** (101 MHz, CDCl<sub>3</sub>): δ = 139.8, 139.0, 136.2, 129.4, 127.6, 127.1, 126.5, 124.9, 123.1, 121.3, 120.6, 118.3, 117.9, 111.0, 105.4, 21.42, 14.37 ppm.

**HRMS** (ESI): mass found: 246.11447, calculated mass for C<sub>17</sub>H<sub>14</sub>N<sub>2</sub>: 246.11570.

**MS** (EI): 246.2 ([M]<sup>+</sup>, 100%), 220.2 ([M-CN]<sup>+</sup>, 21%).

**IR** (KBr) 3416, 3051, 2918, 2251, 1721, 1641, 1599, 1490, 1461, 1369, 1307, 1228, 1185, 1129, 1013, 906, 786, 743 cm<sup>-1</sup>.

### 2-(1-(3-methoxy-phenyl)-1H-indol-3-yl)acetonitrile (3ra)



Compound **3ra** was prepared according to the general procedure and was obtained after column chromatography (pentane : diethyl ether 20:1 → 2:1) as a yellowish oil in 67% yield (70 mg).

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>): δ = 7.66 – 7.56 (m, 2H), 7.41 (t, *J* = 8.1 Hz, 1H), 7.37 (s, 1H), 7.32 – 7.19 (m, 2H), 7.10 – 7.02 (m, 1H), 7.01 (t, *J* = 2.3 Hz, 1H), 6.91 (ddd, *J* = 8.3, 2.5, 0.9 Hz, 1H), 3.88 (s, 2H), 3.86 (s, 3H) ppm.

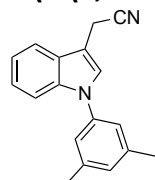
**<sup>13</sup>C NMR** (101 MHz, CDCl<sub>3</sub>): δ = 160.5, 140.2, 136.2, 130.4, 127.1, 126.4, 123.3, 120.8, 118.3, 117.8, 116.5, 112.4, 111.0, 110.2, 105.6, 55.5, 14.3 ppm.

**HRMS** (ESI): mass found: 262.10947, calculated mass for C<sub>17</sub>H<sub>14</sub>N<sub>2</sub>O: 262.11061.

**MS** (EI): 262.2 ([M]<sup>+</sup>, 100%), 236.1 ([M-CN]<sup>+</sup>, 27%).

**IR** (KBr) 2937, 2257, 2094, 1896, 1757, 1593, 1467, 1205, 1036, 746 cm<sup>-1</sup>.

### 2-(1-(3,5-dimethyl-phenyl)-1H-indol-3-yl)acetonitrile (3sa)



Compound **3sa** was prepared according to the general procedure and was obtained after column chromatography (pentane : diethyl ether 20:1 → 4:1) as a yellowish solid in 92% yield (86 mg).

**mp.**: 95-97°C.

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>): δ = 7.61 (dt, *J* = 7.7, 1.0 Hz, 1H), 7.55 (dd, *J* = 8.1, 1.1 Hz, 1H), 7.35 (s, 1H), 7.31 – 7.18 (m, 2H), 7.08 (s, 2H), 7.01 (s, 1H), 3.88 (s, 2H), 2.39 (s, 6H) ppm.

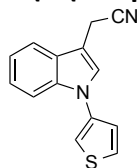
**<sup>13</sup>C NMR** (101 MHz, CDCl<sub>3</sub>): δ = 139.5, 138.9, 136.2, 128.5, 127.1, 126.5, 122.0, 120.5, 118.2, 117.9, 111.1, 105.2, 21.3, 14.3 ppm.

**MS** (EI): 260.0 ([M]<sup>+</sup>, 100%), 234.1 ([M-CN]<sup>+</sup>, 33%).

**IR** (KBr) 3749, 3453, 3018, 2923, 2610, 2244, 2180, 2069, 2044, 1983, 1913, 1739, 1601, 1468, 1366, 1220, 1013, 833, 726 cm<sup>-1</sup>.

**EA Anal.** Calcd for C<sub>18</sub>H<sub>16</sub>N<sub>2</sub>: C, 83.04; H, 6.19; N, 10.76. Found: C, 82.04; H, 6.03; N, 10.76.

### 2-(1-(thiophen-3-yl)-1*H*-indol-3-yl)acetonitrile (**3ta**)



Compound **3ta** was prepared according to the general procedure and was obtained after column chromatography (pentane : diethyl ether 20:1 → 2:1) as a colorless solid in 78% yield (74 mg).

**<sup>1</sup>H NMR** (600 MHz, CDCl<sub>3</sub>): δ = 7.62 (dd, *J* = 8.1, 3.2 Hz, 1H), 7.56 (dd, *J* = 8.7, 3.2 Hz, 1H), 7.47 (d, *J* = 3.2 Hz, 1H), 7.36 (s, 1H), 7.34 – 7.19 (m, 4H), 3.89 (s, 2H) ppm.

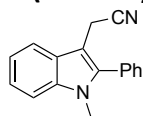
**<sup>13</sup>C NMR** (151 MHz, CDCl<sub>3</sub>): δ = 137.7, 136.5, 126.8, 126.5, 126.4, 123.5, 123.4, 120.8, 118.3, 117.8, 115.4, 111.0, 105.4, 14.3 ppm.

**HRMS** (ESI): mass found: 238.05573, calculated mass for C<sub>14</sub>H<sub>10</sub>N<sub>2</sub>S: 238.05647.

**MS** (EI): 238.1 ([M]<sup>+</sup>, 100%), 212.1 ([M-CN]<sup>+</sup>, 24%).

**IR** (KBr) 3107, 2915, 2248, 1897, 1612, 1547, 1461, 1408, 1225, 1129, 852, 738 cm<sup>-1</sup>.

### 2-(1-methyl-2-phenyl-1*H*-indol-3-yl)acetonitrile (**10a**)



Compound **10a** was prepared according to the general procedure and was obtained after column chromatography (pentane : diethyl ether 20:1 → 2:1) as a colorless solid in 56% yield (55 mg).

**mp.**: 65-67°C.

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>): δ = 7.74 – 7.70 (m, 1H), 7.57 – 7.45 (m, 3H), 7.43 – 7.36 (m, 3H), 7.31 (ddd, *J* = 8.2, 6.9, 1.2 Hz, 1H), 7.23 (ddd, *J* = 8.0, 7.0, 1.2 Hz, 1H), 3.71 (s, 2H), 3.62 (s, 3H) ppm.

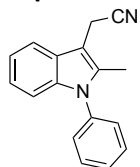
**<sup>13</sup>C NMR** (101 MHz, CDCl<sub>3</sub>): δ = 139.2, 137.0, 130.4, 130.2, 128.9, 128.8, 126.3, 122.5, 120.3, 118.2, 109.7, 101.1, 30.9, 13.8 ppm.

**MS** (EI): 246.1 ([M]<sup>+</sup>, 100%), 220.1 ([M-CN]<sup>+</sup>, 19%), 169.1 ([M-Ph]<sup>+</sup>, 13%).

**IR** (KBr) 3423, 3052, 2938, 2247, 1731, 1613, 1465, 1410, 1360, 1238, 1017, 912, 743 cm<sup>-1</sup>.

**EA** Anal. Calcd for C<sub>17</sub>H<sub>14</sub>N<sub>2</sub>: C, 82.90; H, 5.73; N, 11.37. Found: C, 82.37; H, 5.68; N, 11.29.

### 2-(2-methyl-1-phenyl-1*H*-indol-3-yl)acetonitrile (**10b**)



Compound **10b** was prepared according to the general procedure and was obtained after column chromatography (pentane : diethyl ether 20:1 → 4:1) as a brown solid in 80% yield (79 mg).

**mp.**: 87-89 °C.

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>): δ = 7.71 – 7.43 (m, 4H), 7.37 – 7.28 (m, 2H), 7.21 – 7.01 (m, 3H), 3.83 (s, 2H), 2.28 (s, 3H) ppm.

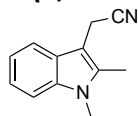
**<sup>13</sup>C NMR** (101 MHz, CDCl<sub>3</sub>): δ = 137.37, 137.31, 134.5, 129.5, 128.1, 128.0, 126.6, 122.0, 120.4, 118.0, 117.2, 110.2, 100.8, 13.2, 10.9 ppm.

**HRMS** (ESI): mass found: 246.11429, calculated mass for C<sub>17</sub>H<sub>14</sub>N<sub>2</sub>: 246.11570.

**MS** (EI): 246.1 ( $[M]^+$ , 100%), 231.2 ( $[M-CH_3]^+$ , 38%), 220.1 ( $[M-CN]^+$ , 28%).

**IR** (KBr): 3059, 2915, 2329, 2241, 2097, 1931, 1589, 1492, 1368, 1211, 1017, 742, 698  $cm^{-1}$ .

### 2-(1,2-dimethyl-1*H*-indol-3-yl)acetonitrile (**10c**)



Compound **10c** was prepared according to the general procedure and was obtained after column chromatography (pentane : diethyl ether 20:1  $\rightarrow$  2:1) as a colorless solid in 93% yield (69 mg).

**mp.**: 111-113  $^{\circ}C$ .

**$^1H$  NMR** (400 MHz,  $CDCl_3$ ):  $\delta$  = 7.60 – 7.51 (m, 1H), 7.27 (d,  $J$  = 8.1 Hz, 1H), 7.23 – 7.18 (m, 1H), 7.18 – 7.09 (m, 1H), 3.76 (s, 2H), 3.66 (s, 3H), 2.41 (s, 3H) ppm.

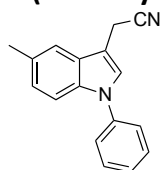
**$^{13}C$  NMR** (101 MHz,  $CDCl_3$ ):  $\delta$  = 136.4, 134.2, 126.3, 121.4, 119.7, 118.1, 117.2, 108.9, 99.2, 29.6, 13.1, 10.3 ppm.

**MS** (EI): 184.1 ( $[M]^+$ , 100%), 169.0 ( $[M-CH_3]^+$ , 12%), 158.1 ( $[M-CN]^+$ , 13%).

**IR** (KBr): 3048, 2920, 2242, 2108, 1922, 1739, 1611, 1568, 1470, 1430, 1367, 1253, 1128, 1012, 907, 739  $cm^{-1}$ .

**EA** Anal. Calcd for  $C_{12}H_{12}N_2$ : C, 78.23; H, 6.57; N, 15.21. Found: C, 78.00; H, 6.49; N, 15.15.

### 2-(5-methyl-1-phenyl-1*H*-indol-3-yl)acetonitrile (**10d**)



Compound **10d** was prepared according to the general procedure and was obtained after column chromatography (pentane : diethyl ether 20:1  $\rightarrow$  4:1) as a yellowish oil in 88% yield (87 mg).

**$^1H$  NMR** (400 MHz,  $CDCl_3$ ):  $\delta$  = 7.62 – 7.32 (m, 8H), 7.14 – 7.06 (m, 1H), 3.85 (s, 2H), 2.48 (s, 3H) ppm.

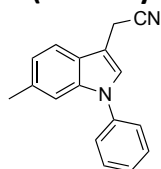
**$^{13}C$  NMR** (101 MHz,  $CDCl_3$ ):  $\delta$  = 139.2, 134.6, 130.2, 129.6, 127.4, 126.6, 126.3, 124.8, 124.1, 118.0, 110.6, 105.1, 21.4, 14.3 ppm.

**HRMS** (ESI): mass found: 246.11442, calculated mass for  $C_{17}H_{14}N_2$ : 246.11570.

**MS** (EI): 246.1 ( $[M]^+$ , 100%), 220.2 ( $[M-CN]^+$ , 20%), 206.2 ( $[M-C_2H_5]^+$ , 6%).

**IR** (KBr) 3353, 3039, 2916, 2662, 2329, 2252, 2098, 1884, 1593, 1494, 1376, 1227, 1141, 908, 735  $cm^{-1}$ .

### 2-(6-methyl-1-phenyl-1*H*-indol-3-yl)acetonitrile (**10e**)



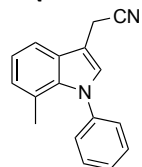
Compound **10e** was prepared according to the general procedure and was obtained after column chromatography (pentane : diethyl ether 20:1  $\rightarrow$  4:1) as a colorless oil in 88% yield (87 mg).

**$^1H$  NMR** (400 MHz,  $CDCl_3$ ):  $\delta$  = 7.60 – 7.43 (m, 5H), 7.41 – 7.28 (m, 3H), 7.06 (dd,  $J$  = 8.2, 1.3 Hz, 1H), 3.86 (s, 2H), 2.45 (s, 3H) ppm.



**<sup>13</sup>C NMR** (101 MHz, CDCl<sub>3</sub>): δ = 139.2, 136.6, 133.3, 129.6, 126.7, 125.8, 125.0, 124.4, 122.4, 118.0, 117.9, 110.7, 105.4, 21.8, 14.4 ppm.  
**MS** (EI): 46.2 ([M]<sup>+</sup>, 100%), 220.2 ([M-CN]<sup>+</sup>, 28%).  
**IR** (KBr) 3856, 3422, 3045, 2917, 2325, 2251, 2095, 1891, 1727, 1597, 1498, 1452, 1375, 1229, 1122, 1025, 913, 800, 762 cm<sup>-1</sup>.  
**EA** Anal. Calcd for C<sub>17</sub>H<sub>14</sub>N<sub>2</sub>: C, 82.90; H, 5.73; N, 11.37. Found: C, 81.79; H, 5.69; N, 11.48.

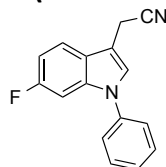
### 2-(7-methyl-1-phenyl-1*H*-indol-3-yl)acetonitrile (**10f**)



Compound **10f** was prepared according to the general procedure and was obtained after column chromatography (pentane : diethyl ether 20:1 → 2:1) as a yellowish oil in 94% yield (92 mg).

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>): δ = 7.56 – 7.42 (m, 4H), 7.40 – 7.31 (m, 2H), 7.16 (s, 1H), 7.12 (t, *J* = 7.6 Hz, 1H), 6.98 (d, *J* = 7.1 Hz, 1H), 3.85 (s, 2H), 1.99 (s, 3H) ppm.  
**<sup>13</sup>C NMR** (151 MHz, CDCl<sub>3</sub>): δ = 140.8, 136.0, 129.0, 128.7, 128.1, 127.9, 127.3, 125.6, 120.6, 116.1, 104.7, 19.5, 14.3 ppm.  
**HRMS** (ESI): mass found: 246.0114548355, calculated mass for C<sub>17</sub>H<sub>14</sub>N<sub>2</sub>: 246.11570.  
**MS** (EI): 246.1 ([M]<sup>+</sup>, 100%), 220.1 ([M-CN]<sup>+</sup>, 12%), 206.1 ([M-CH<sub>2</sub>CN]<sup>+</sup>, 12%).  
**IR** (KBr): 3343, 3050, 2922, 2669, 2327, 2253, 2099, 1896, 1591, 1496, 1420, 1365, 1075, 910, 753 cm<sup>-1</sup>.

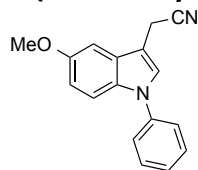
### 2-(6-fluoro-1-phenyl-1*H*-indol-3-yl)acetonitrile (**10g**)



Compound **10g** was prepared according to the general procedure and was obtained after column chromatography (pentane : diethyl ether 20:1 → 4:1) as a brown solid in 48% yield (48 mg).

**mp.**: 117-119 °C.  
**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>): δ = 7.58 – 7.48 (m, 3H), 7.46 – 7.42 (m, 2H), 7.42 – 7.36 (m, 1H), 7.34 (s, 1H), 7.20 (dd, *J* = 9.8, 2.1 Hz, 1H), 7.04 – 6.93 (m, 1H), 3.86 (s, 2H) ppm.  
**<sup>13</sup>C NMR** (101 MHz, CDCl<sub>3</sub>): δ = 138.7, 129.8, 127.2, 126.8, 124.2, 119.3 (d, *J* = 10.1 Hz), 117.6, 109.6 (d, *J* = 24.6 Hz), 97.5 (d, *J* = 27.1 Hz), 14.3 ppm.  
**<sup>19</sup>F NMR** (376 MHz, CDCl<sub>3</sub>): δ = -118.69 ppm.  
**MS** (EI): 250.1 ([M]<sup>+</sup>, 100%), 224.2 ([M-CN]<sup>+</sup>, 56%).  
**IR** (KBr) 3384, 3065, 2919, 2328, 2246, 2078, 1957, 1736, 1601, 1490, 1370, 1195, 1103, 967, 804, 751, 691 cm<sup>-1</sup>.  
**EA** Anal. Calcd. for C<sub>16</sub>H<sub>11</sub>FN<sub>2</sub>: C, 76.79; H, 4.43; N, 11.19. Found: C, 76.15; H, 4.63; N, 11.02.

### 2-(5-methoxy-1-phenyl-1*H*-indol-3-yl)acetonitrile (10h)



Compound **10h** was prepared according to the general procedure and was obtained after column chromatography (pentane : diethyl ether 20:1 → 2:1) as a colorless solid in 91% yield (95 mg).

**mp.:** 127-130 °C.

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>): δ = 7.53 – 7.40 (m, 5H), 7.39 – 7.30 (m, 2H), 7.02 (d, *J* = 2.4 Hz, 1H), 6.91 (dd, *J* = 9.0, 2.4 Hz, 1H), 3.88 (s, 3H), 3.85 (s, 2H) ppm.

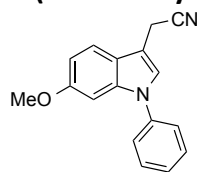
**<sup>13</sup>C NMR** (101 MHz, CDCl<sub>3</sub>): δ = 154.8, 139.2, 131.3, 129.7, 127.6, 126.7, 124.0, 117.8, 114.9, 113.4, 111.9, 105.1, 99.9, 55.8, 14.4 ppm.

**MS** (EI): 262.1 ([M]<sup>+</sup>, 100%), 247.1 ([M-CH<sub>3</sub>]<sup>+</sup>, 32%).

**IR** (KBr): 3450, 3059, 2930, 2844, 2240, 2089, 1883, 1739, 1596, 1483, 1236, 1035, 784 cm<sup>-1</sup>.

**EA** Anal. Calcd for C<sub>17</sub>H<sub>14</sub>N<sub>2</sub>O: C, 77.84; H, 5.38; N, 10.68. Found: C, 78.03; H, 5.29; N, 10.64.

### 2-(6-methoxy-1-phenyl-1*H*-indol-3-yl)acetonitrile (10i)



Compound **10i** was prepared according to the general procedure and was obtained after column chromatography (pentane : diethyl ether 20:1 → 2:1) as a yellowish oil in 78% yield (74 mg).

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>): δ = 7.63 – 7.44 (m, 5H), 7.37 (ddt, *J* = 8.6, 6.6, 1.4 Hz, 1H), 7.24 (d, *J* = 0.9 Hz, 1H), 7.00 (d, *J* = 2.2 Hz, 1H), 6.89 (dd, *J* = 8.7, 2.2 Hz, 1H), 3.84 (s, 2H), 3.81 (s, 3H) ppm.

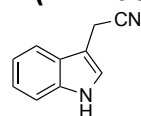
**<sup>13</sup>C NMR** (101 MHz, CDCl<sub>3</sub>): δ = 157.3, 139.2, 137.1, 129.7, 126.8, 125.4, 124.2, 121.4, 119.0, 117.9, 110.6, 105.6, 94.4, 55.7, 14.4 ppm.

**HRMS** (ESI): mass found: 262.10980, calculated mass for C<sub>17</sub>H<sub>14</sub>N<sub>2</sub>O: 262.11061.

**MS** (EI): 262.1 ([M]<sup>+</sup>, 36%), 77.3 ([Ph]<sup>+</sup>, 100%).

**IR** (KBr): 3307, 3053, 2942, 2323, 2252, 2097, 1884, 1745, 1602, 1493, 1453, 1379, 1283, 1223, 1119, 1027, 912, 735 cm<sup>-1</sup>.

### 2-(1*H*-indol-3-yl)acetonitrile (11a)



Compound **11a** was prepared according to the general procedure with the addition time of diazo acetonitrile being 20 min and was obtained after column chromatography (pentane : diethyl ether 20:1 → 1:1) as a colorless oil in 75% yield (47 mg).

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>): δ = 8.19 (s, 1H), 7.60 (d, *J* = 7.9 Hz, 1H), 7.41 (d, *J* = 8.2 Hz, 1H), 7.32 – 7.25 (m, 1H), 7.23 (s, 1H), 7.22 – 7.12 (m, 1H), 3.85 (s, 2H) ppm.

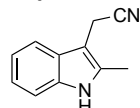
**<sup>13</sup>C NMR** (101 MHz, CDCl<sub>3</sub>): δ = 136.2, 125.9, 122.9, 122.7, 120.2, 118.1, 118.0, 111.5, 104.7, 14.4 ppm.

**HRMS** (ESI): mass found: 179.05832, calculated mass for  $C_{10}H_8N_2Na^+$ : 179.05797.

**IR** (KBr) 3397, 2912, 2677, 2341, 2099, 1771, 1624, 1427, 1347, 1229, 1081, 917, 744  $cm^{-1}$ .

The NMR data is in correspondence with the literature<sup>iii</sup>

### 2-(2-methyl-1H-indol-3-yl)acetonitrile (**11b**)



Compound **11b** was prepared according to the general procedure with the addition time of diazo acetonitrile being 20 min and was obtained after column chromatography (pentane : diethyl ether 20:1  $\rightarrow$  1:1) as a colorless oil in 41% yield (28 mg).

**$^1H$  NMR** (400 MHz,  $CDCl_3$ ):  $\delta$  = 7.93 (s, 1H), 7.63 – 7.45 (m, 1H), 7.37 – 7.27 (m, 1H), 7.19 – 7.08 (m, 2H), 3.74 (s, 2H), 2.43 (s, 3H) ppm.

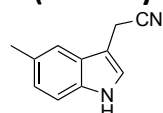
**$^{13}C$  NMR** (101 MHz,  $CDCl_3$ ):  $\delta$  = 134.9, 132.5, 127.2, 121.91, 120.1, 117.3, 110.4, 12.9, 11.6 ppm.

**HRMS** (ESI): mass found: 170.08341, calculated mass for  $C_{11}H_{10}N_2$ : 170.08440.

**MS** (EI): 170.1 ( $[M]^+$ , 100%), 155.1 ( $[M-CH_3]^+$ , 40%), 144.1 ( $[M-CN]^+$ , 34%).

**IR** (KBr) 3900, 3384, 3037, 2917, 2855, 2247, 2081, 1927, 1740, 1619, 1527, 1450, 1296, 1216, 1045, 912, 743  $cm^{-1}$ .

### 2-(5-methyl-1H-indol-3-yl)acetonitrile (**11c**)



Compound **11c** was prepared according to the general procedure with the addition time of diazo acetonitrile being 20 min and was obtained after column chromatography (pentane : diethyl ether 20:1  $\rightarrow$  1:1) as a colorless solid in 71% yield (48 mg).

**mp.**: 90-92  $^{\circ}C$ .

**$^1H$  NMR** (400 MHz,  $CDCl_3$ ):  $\delta$  = 8.05 (s, 1H), 7.36 (d,  $J$  = 0.9 Hz, 1H), 7.31 – 7.22 (m, 1H), 7.19 – 7.15 (m, 1H), 7.07 (dd,  $J$  = 8.3, 1.5 Hz, 1H), 3.80 (s, 2H), 2.46 (s, 3H) ppm.

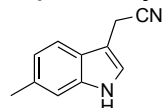
**$^{13}C$  NMR** (101 MHz,  $CDCl_3$ ):  $\delta$  = 134.5, 129.6, 126.2, 124.5, 122.7, 118.1, 117.6, 111.1, 104.2, 21.4, 14.3 ppm.

**MS** (EI): 170.1 ( $[M]^+$ , 100%), 55.1 ( $[M-CH_3]^+$ , 18%), 144.1 ( $[M-CN]^+$ , 36%).

**IR** (KBr): 3418, 2918, 2250, 2097, 2051, 1883, 1739, 1582, 1467, 1411, 1228, 1049, 917, 801  $cm^{-1}$ .

**EA Anal.** Calcd for  $C_{11}H_{10}N_2$ : C, 77.62; H, 5.92; N, 16.46. Found: C, 77.61; H, 5.85; N, 16.57.

### 2-(6-methyl-1H-indol-3-yl)acetonitrile (**11d**)



Compound **11d** was prepared according to the general procedure with the addition time of diazo acetonitrile being 20 min and was obtained after column chromatography (pentane : diethyl ether 20:1  $\rightarrow$  1:1) as a colorless solid in 71% yield (48 mg).

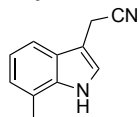
**mp.**: 117-119  $^{\circ}C$ .

**$^1H$  NMR** (400 MHz,  $CDCl_3$ ):  $\delta$  = 8.03 (s, 1H), 7.45 (d,  $J$  = 8.1 Hz, 1H), 7.22 – 7.10 (m, 2H), 7.09 – 6.90 (m, 1H), 3.80 (s, 2H), 2.46 (s, 3H) ppm.

**$^{13}C$  NMR** (101 MHz,  $CDCl_3$ ):  $\delta$  = 136.7, 132.8, 123.8, 122.04, 122.00, 118.1, 117.6, 111.3, 104.5, 21.6, 14.4 ppm.

**HRMS** (ESI): mass found: 170.08355, calculated mass for  $C_{11}H_{10}N_2$ : 170.08440.  
**MS** (EI): 170.1 ( $[M]^+$ , 100%), 155.1 ( $[M-CH_3]^+$ , 18%), 144.1 ( $[M-CN]^+$ , 31%).  
**IR** (KBr) 3407, 2917, 2862, 2252, 2078, 1895, 1739, 1619, 1556, 1451, 1400, 1343, 1232, 1084, 1050, 803  $cm^{-1}$ .

### 2-(7-methyl-1*H*-indol-3-yl)acetonitrile (**11e**)



Compound **11e** was prepared according to the general procedure with the addition time of diazo acetonitrile being 20 min and was obtained after column chromatography (pentane : diethyl ether 20:1  $\rightarrow$  1:1) as a brown solid in 72% yield (49 mg).

**mp.**: 126-127  $^{\circ}C$ .

**$^1H$  NMR** (400 MHz,  $CDCl_3$ ):  $\delta$  = 8.09 (s, 1H), 7.46 – 7.39 (m, 1H), 7.25 – 7.19 (m, 1H), 7.17 – 7.02 (m, 2H), 3.82 (s, 2H), 2.49 (s, 3H) ppm.

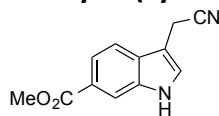
**$^{13}C$  NMR** (101 MHz,  $CDCl_3$ ):  $\delta$  = 135.8, 125.5, 123.3, 122.3, 120.7, 120.4, 118.1, 115.7, 105.2, 16.5, 14.5 ppm.

**HRMS** (ESI): mass found: 170.08316, calculated mass for  $C_{11}H_{10}N_2$ : 170.08440.

**MS** (EI): 170.1 ( $[M]^+$ , 100%), 155.1 ( $[M-CH_3]^+$ , 16%), 144.1 ( $[M-CN]^+$ , 34%).

**IR** (KBr) 3827, 3361, 2917, 2856, 2323, 2252, 2102, 1911, 1740, 1616, 1440, 1347, 1225, 1095, 915, 828, 784, 742  $cm^{-1}$ .

### methyl 3-(cyanomethyl)-1*H*-indole-6-carboxylate (**11f**)



Compound **11f** was prepared according to the general procedure with the addition time of diazo acetonitrile being 20 min and was obtained after column chromatography (pentane : diethyl ether 9:1  $\rightarrow$  1:2) as a yellowish solid in 40% yield (34 mg).

**mp.**: 149-150  $^{\circ}C$ .

**$^1H$  NMR** (400 MHz,  $CDCl_3$ ):  $\delta$  = 8.51 (s, 1H), 8.15 (s, 1H), 7.86 (dd,  $J$  = 8.4, 1.4 Hz, 1H), 7.60 (dt,  $J$  = 8.4, 0.7 Hz, 1H), 7.42 – 7.38 (m, 1H), 3.93 (s, 3H), 3.85 (s, 2H) ppm.

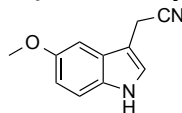
**$^{13}C$  NMR** (101 MHz,  $CDCl_3$ ):  $\delta$  = 167.7, 135.5, 129.3, 125.9, 124.7, 121.2, 117.7, 113.8, 105.2, 52.0, 14.3 ppm.

**HRMS** (EI): mass found: 214.07365, calculated mass for  $C_{12}H_{10}N_2O_2$ : 214.07423.

**MS** (EI): 214.1 ( $[M]^+$ , 97%), 183.1 ( $[M-OCH_3]^+$ , 100%), 155.2 ( $[M-CO_2Me]^+$ , 52%).

**IR** (KBr) 3826, 3330, 2940, 2247, 2084, 1912, 1688, 1422, 1324, 1210, 1089, 970, 899, 833, 768, 678  $cm^{-1}$ .

### 2-(5-methoxy-1*H*-indol-3-yl)acetonitrile (**11g**)



Compound **11g** was prepared according to the general procedure with the addition time of diazo acetonitrile being 20 min and was obtained after column chromatography (pentane : diethyl ether 9:1  $\rightarrow$  1:1) as a colorless oil in 54% yield (40 mg).

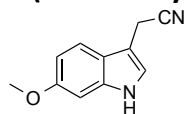
**$^1H$  NMR** (400 MHz,  $CDCl_3$ ):  $\delta$  = 8.08 (s, 1H), 7.37 – 7.23 (m, 1H), 7.18 (dd,  $J$  = 2.6, 1.3 Hz, 1H), 7.01 – 6.97 (m, 1H), 6.90 (ddd,  $J$  = 8.8, 2.6, 0.8 Hz, 1H), 3.86 (s, 3H), 3.79 (s, 2H) ppm.

**$^{13}C$  NMR** (101 MHz,  $CDCl_3$ ):  $\delta$  = 154.5, 131.2, 126.3, 123.3, 118.1, 113.2, 112.3, 104.3, 99.6, 55.8, 14.4 ppm.

**HRMS** (EI): mass found: 186.07896, calculated mass for C<sub>11</sub>H<sub>10</sub>N<sub>2</sub>O: 186.07931.

**IR** (KBr) 3401, 2944, 2832, 2250, 2075 1736, 1586, 1475, 1295, 1216, 1046, 919, 905 cm<sup>-1</sup>.

### 2-(6-methoxy-1*H*-indol-3-yl)acetonitrile (**11h**)



Compound **11h** was prepared according to the general procedure with the addition time of diazo acetonitrile being 20 min and was obtained after column chromatography (pentane : diethyl ether 9:1 → 1:1) as a colorless solid in 51% yield (38 mg).

**mp.**: 112-113°C.

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>): δ = 8.00 (s, 1H), 7.44 (d, *J* = 8.6 Hz, 1H), 7.14 – 7.07 (m, 1H), 6.96 – 6.61 (m, 2H), 3.84 (s, 3H), 3.79 (s, 2H) ppm.

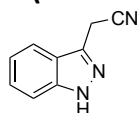
**<sup>13</sup>C NMR** (101 MHz, CDCl<sub>3</sub>): δ = 157.0, 121.4, 120.3, 118.7, 110.3, 94.8, 55.6, 14.4 ppm.

**HRMS** (ESI): mass found: 186.07834, calculated mass for C<sub>11</sub>H<sub>10</sub>N<sub>2</sub>O: 186.07931.

**MS** (EI): 186.0 ([M]<sup>+</sup>, 100%), 171.0 ([M-CH<sub>3</sub>]<sup>+</sup>, 81%), 160.0 ([M-CN]<sup>+</sup>, 23%).

**IR** (KBr) 3797, 3355, 2934, 2652, 2246, 2075, 1876, 1740, 1623, 1450, 1341, 1193, 1149, 1014, 807 cm<sup>-1</sup>.

### 2-(1*H*-indazol-3-yl)acetonitrile (**13**)



Compound **12** was prepared according to the general procedure and was obtained after column chromatography (pentane : diethyl ether 9:1 → 1:1) as a colorless solid in 64% yield (40 mg).

**mp.**: 80-81 °C

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>): δ = 8.08 (s, 1H), 7.69 (dq, *J* = 8.8, 1.0 Hz, 1H), 7.65 (dt, *J* = 8.5, 1.1 Hz, 1H), 7.32 (ddd, *J* = 8.8, 6.6, 1.1 Hz, 1H), 7.12 (ddd, *J* = 8.5, 6.6, 0.9 Hz, 1H), 5.36 (s, 2H) ppm.

**<sup>13</sup>C NMR** (101 MHz, CDCl<sub>3</sub>): δ = 149.7, 127.2, 123.1, 122.9, 122.4, 120.1, 117.5, 113.2, 40.8 ppm.

**HRMS** (ESI): mass found: 157.06328, calculated mass for C<sub>9</sub>H<sub>7</sub>N<sub>3</sub>: 157.06400.

**MS** (EI): 157.1 ([M]<sup>+</sup>, 23%), 131.2 ([M-CN]<sup>+</sup>, 5%).

**IR** (KBr) 3749, 3616, 3447, 3121, 2988, 2642, 2286, 2105, 2038, 1989, 1916, 1739, 1624, 1515, 1371, 1293, 1214, 1143, 913, 749 cm<sup>-1</sup>.

## References

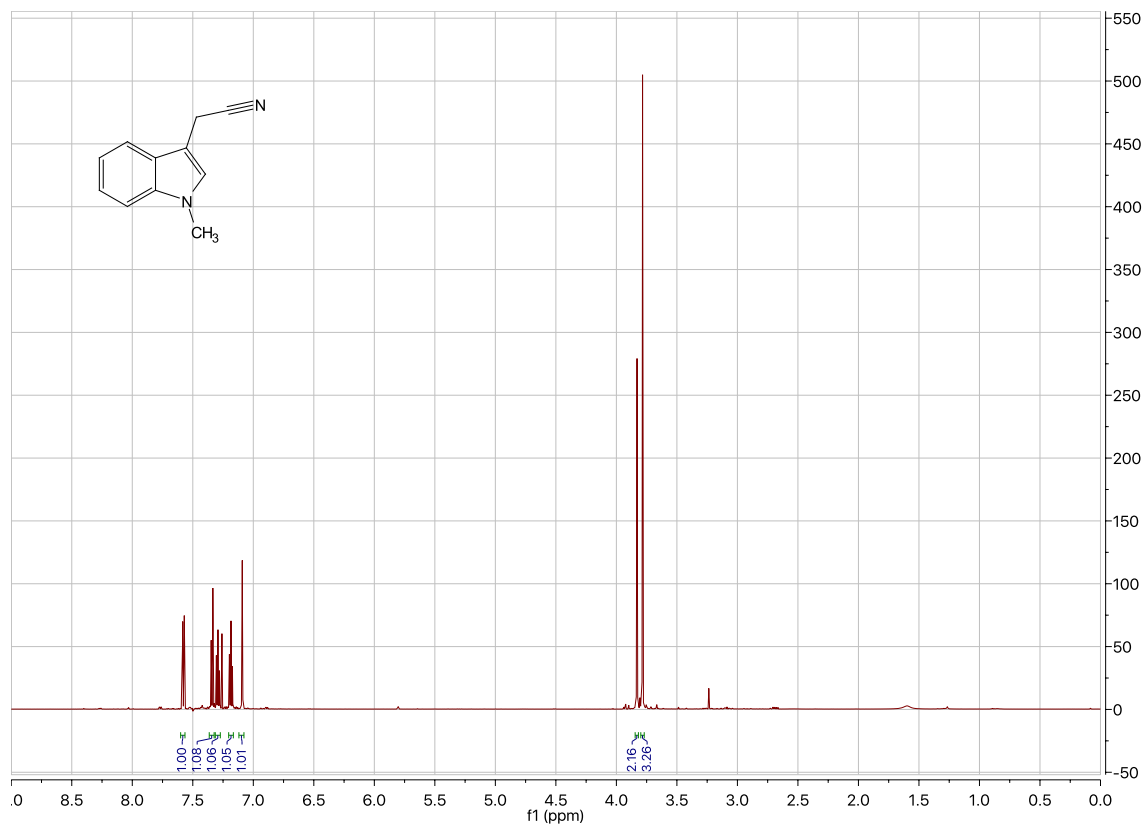
<sup>i</sup> B. Binkowski, L. P. Encell, M. Hall, M. B. Robers, M. R. Slater, K. V. Wood, M. G. Wood, (Promega Corporation), 2012, WO2012061530.

<sup>ii</sup> D. V. Patil, S. W. Kim, Q. H. Nguyen, H. Kim, S. Wang, T. Hoang, S. Shin, *Angew. Chem. Int. Ed.* **2017**, 56, 3670.

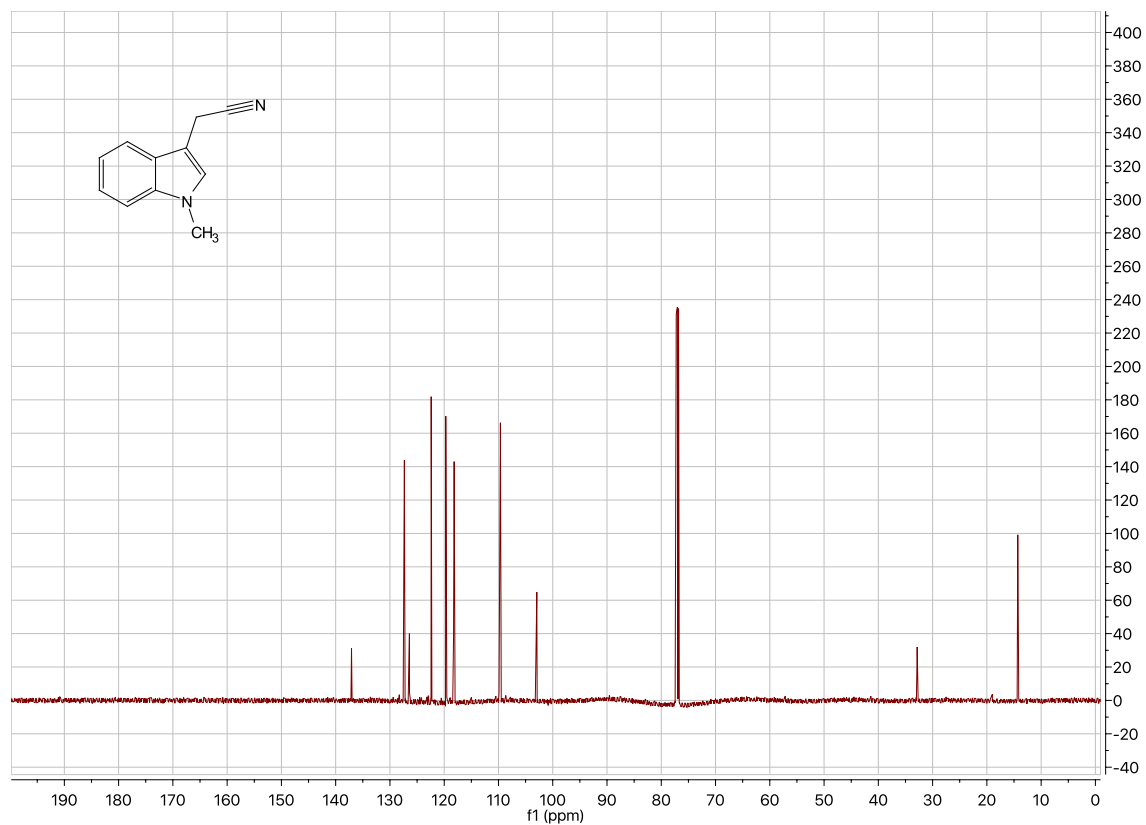
<sup>iii</sup> L. T. Pierce, M. M. Cahill, F. O. McCarthy, *Tetrahedron* **2011**, 67, 4601.

## 2-(1-methyl-1H-indol-3-yl)acetonitrile (3aa)

<sup>1</sup>H NMR (600 MHz, CDCl<sub>3</sub>)

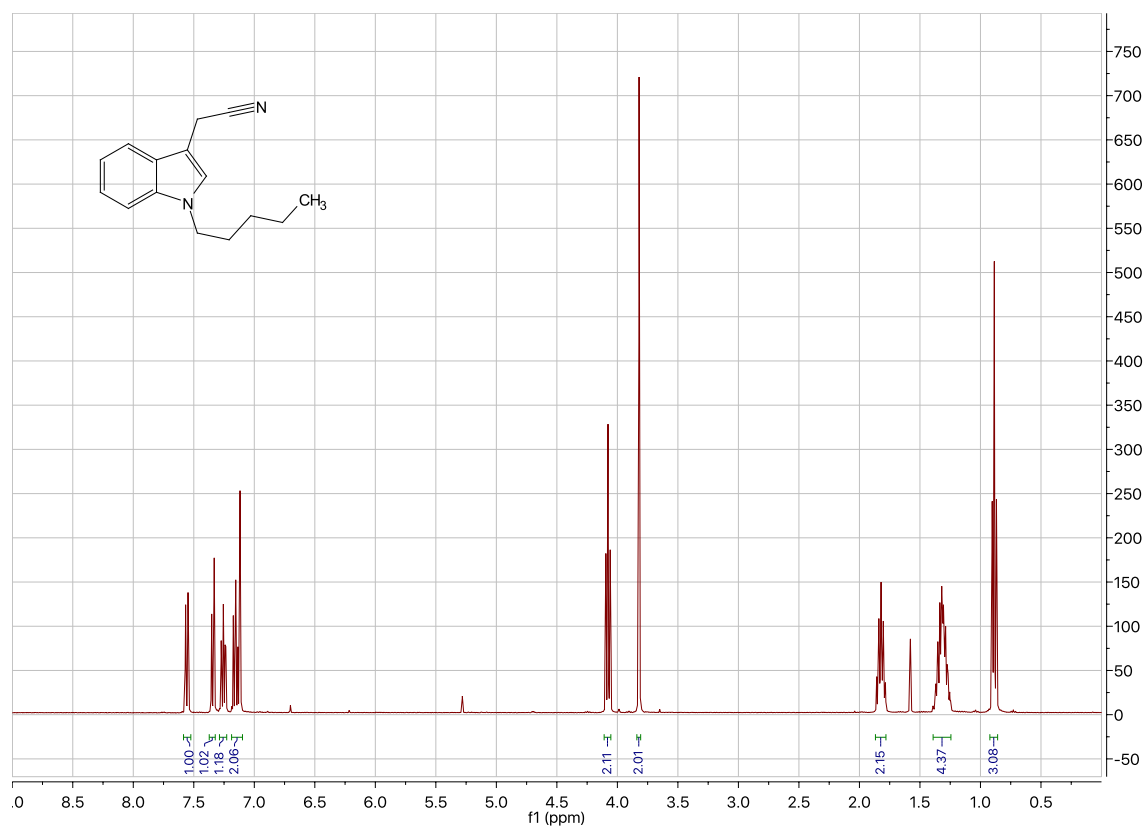


<sup>13</sup>C NMR (151 MHz, CDCl<sub>3</sub>)

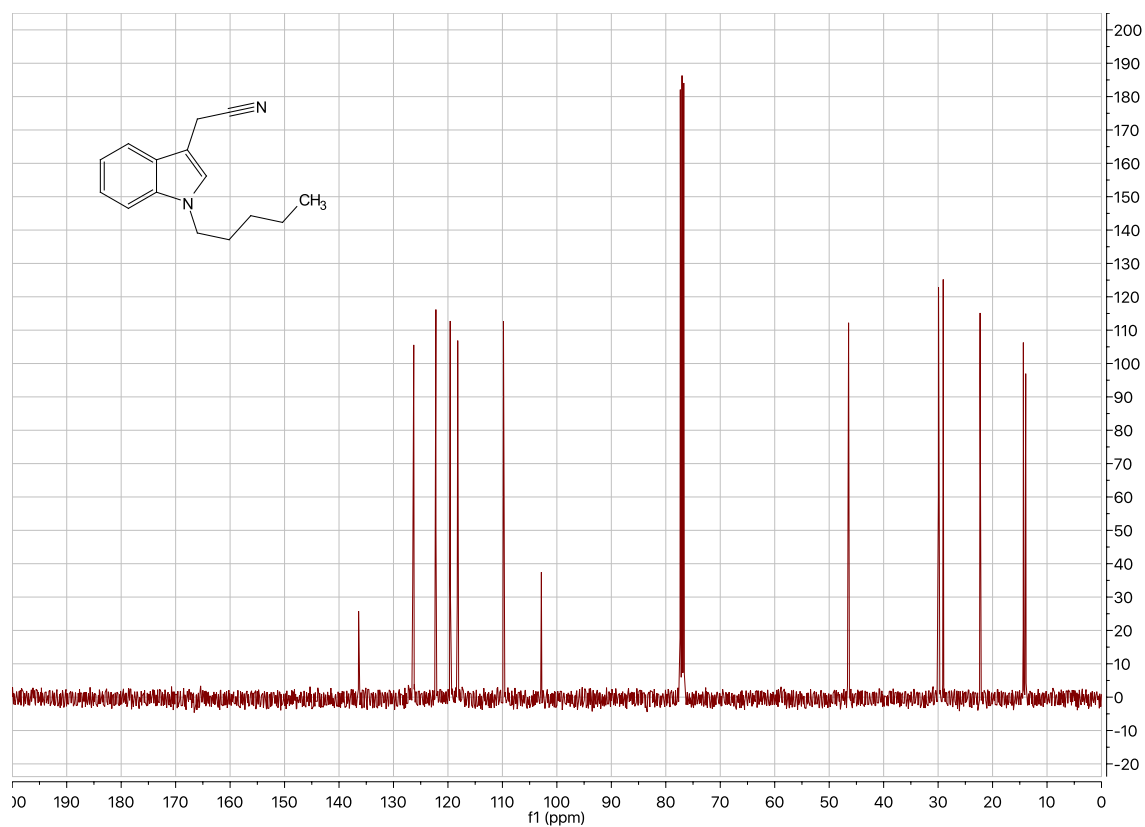


## 2-(1-pentyl-1H-indol-3-yl)acetonitrile (3ba)

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )

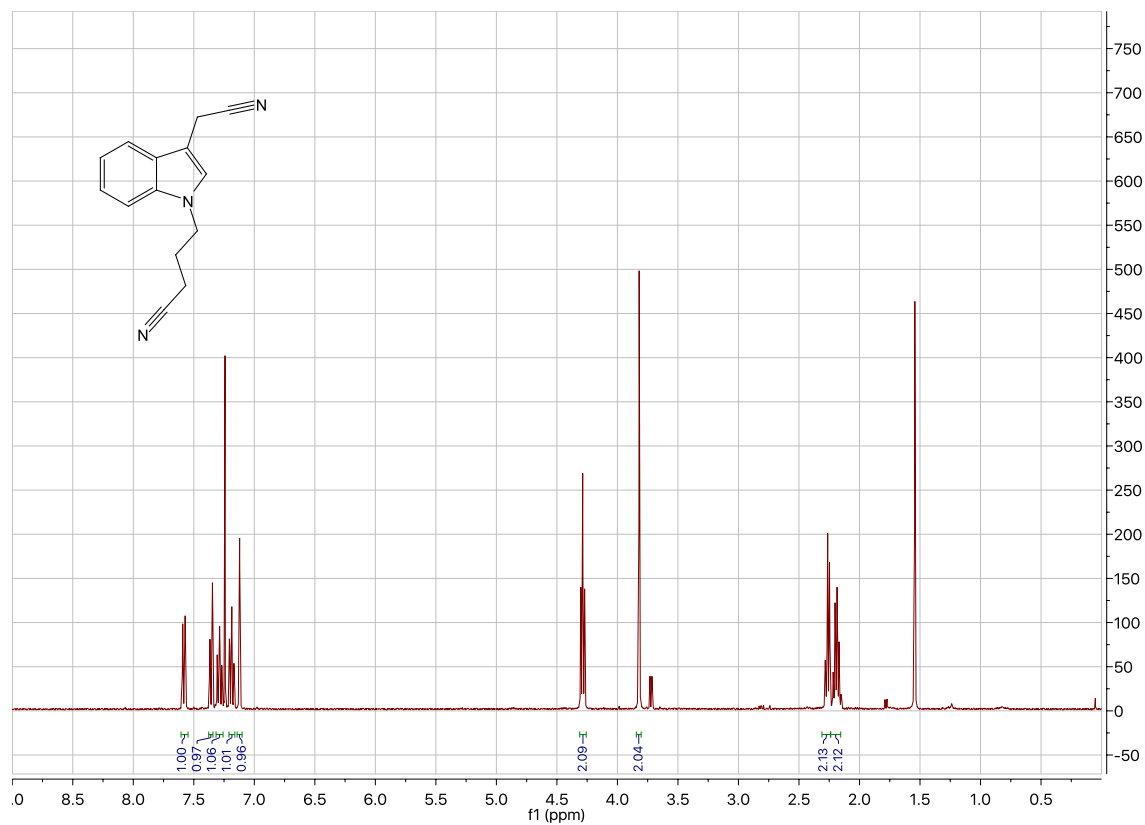


$^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ )

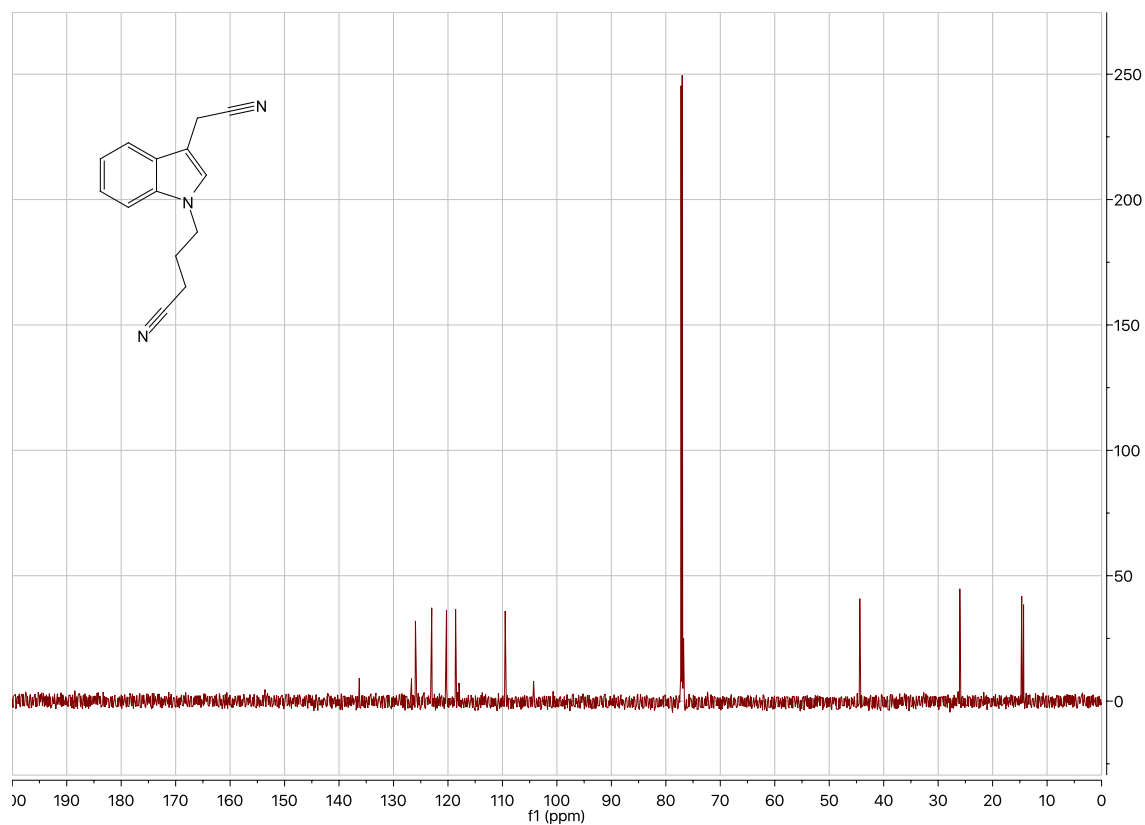


# 4-(3-(cyanomethyl)-1H-indol-1-yl)butanenitrile (3ca)

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )



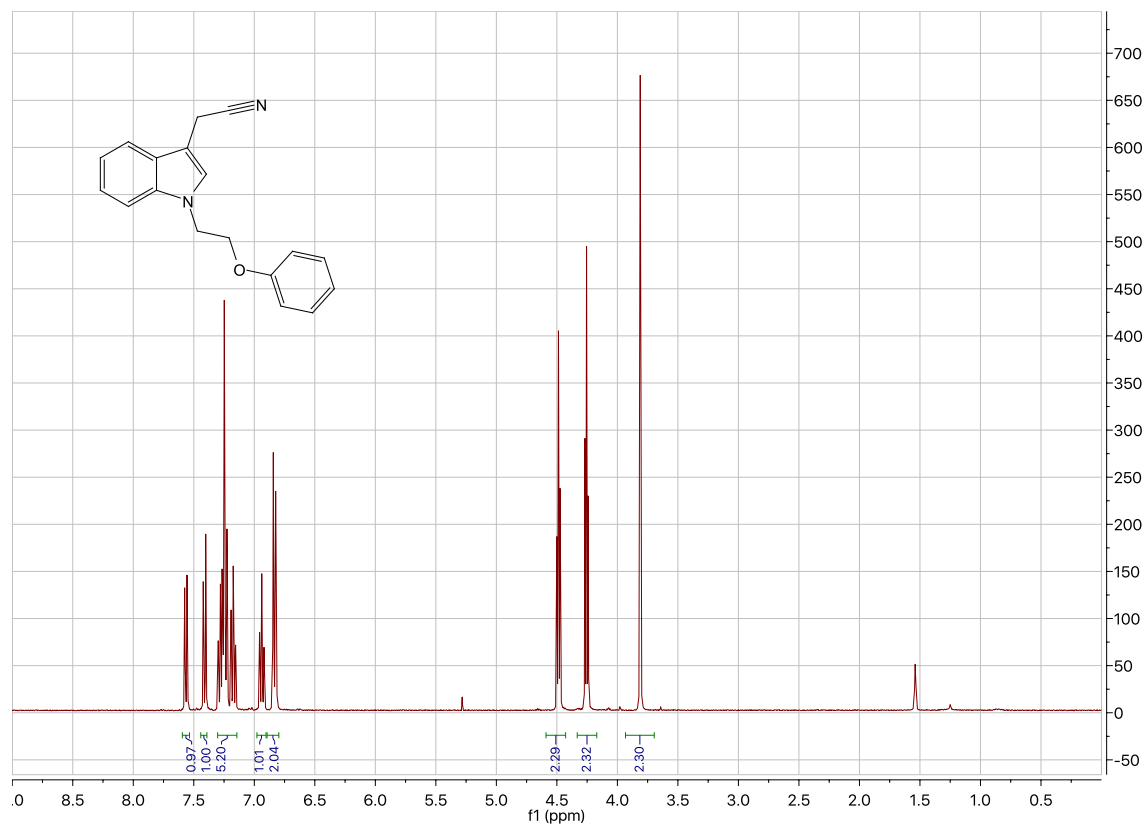
$^{13}\text{C}$  NMR (151 MHz,  $\text{CDCl}_3$ )



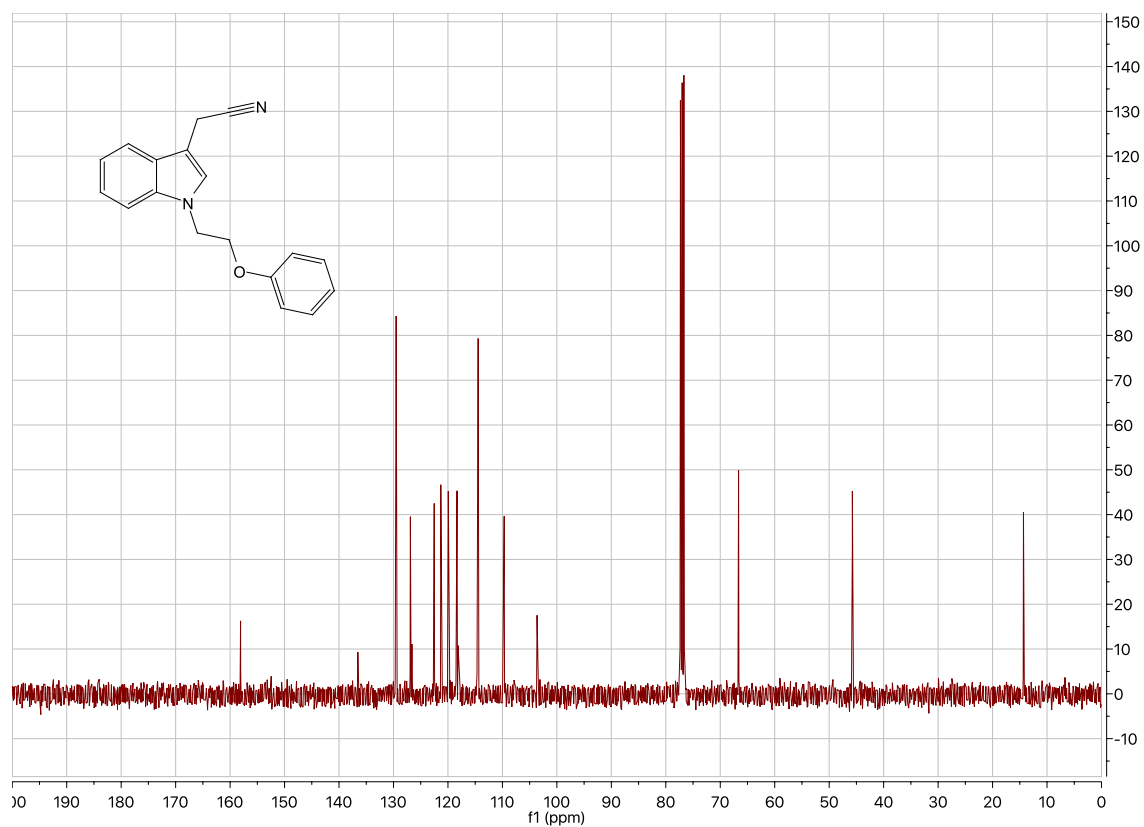


## 2-(1-(2-phenoxyethyl)-1H-indol-3-yl)acetonitrile (3da)

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )

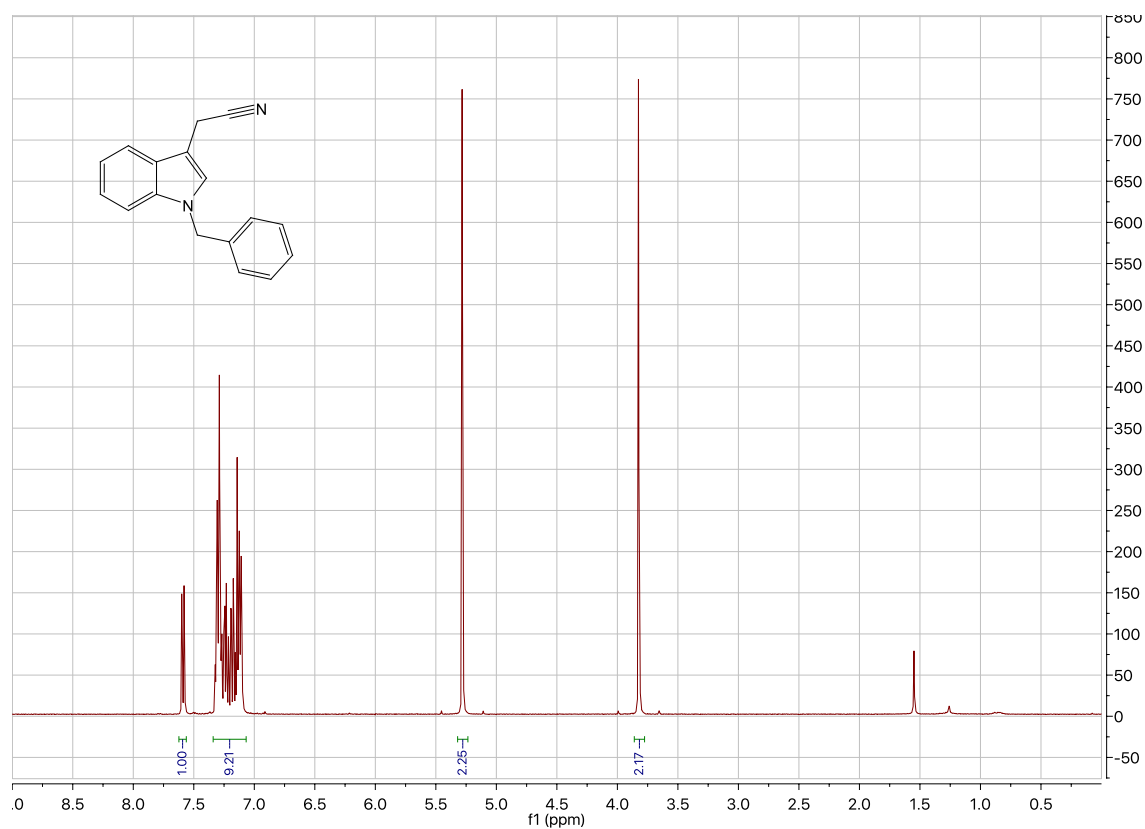


$^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ )

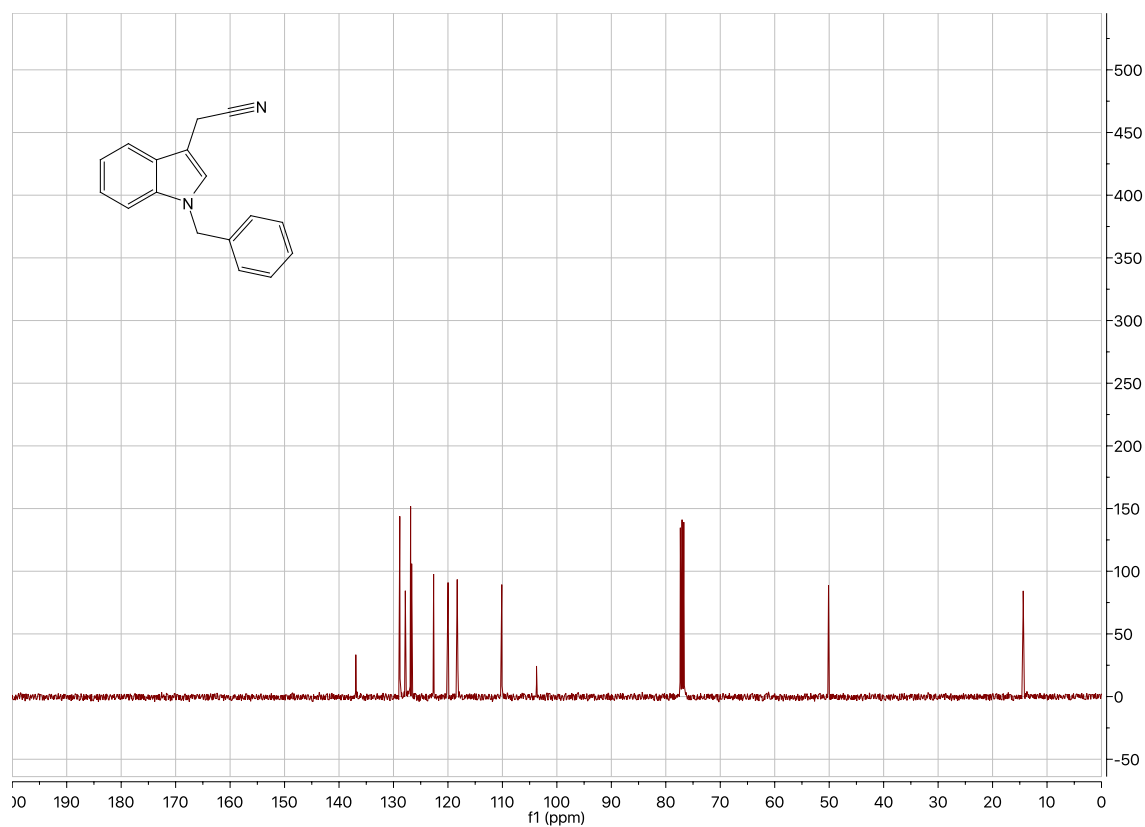


## 2-(1-benzyl-1H-indol-3-yl)acetonitrile (3ea)

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )

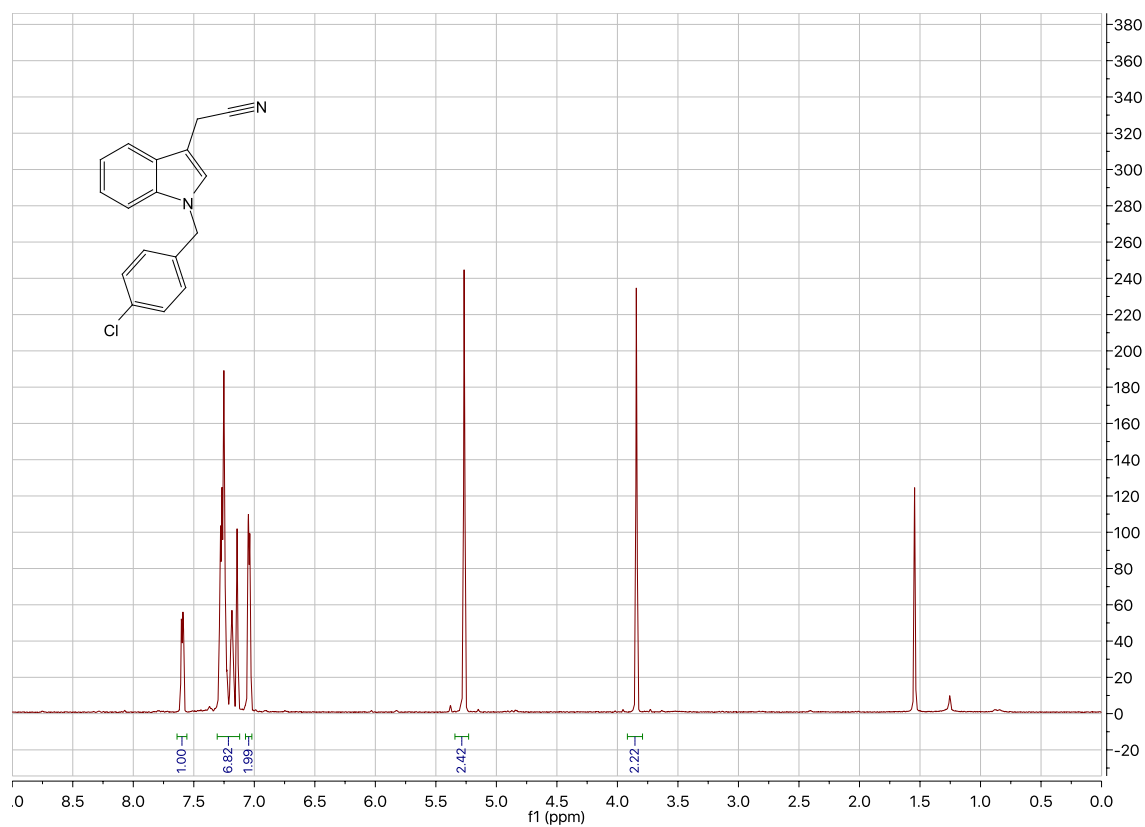


$^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ )

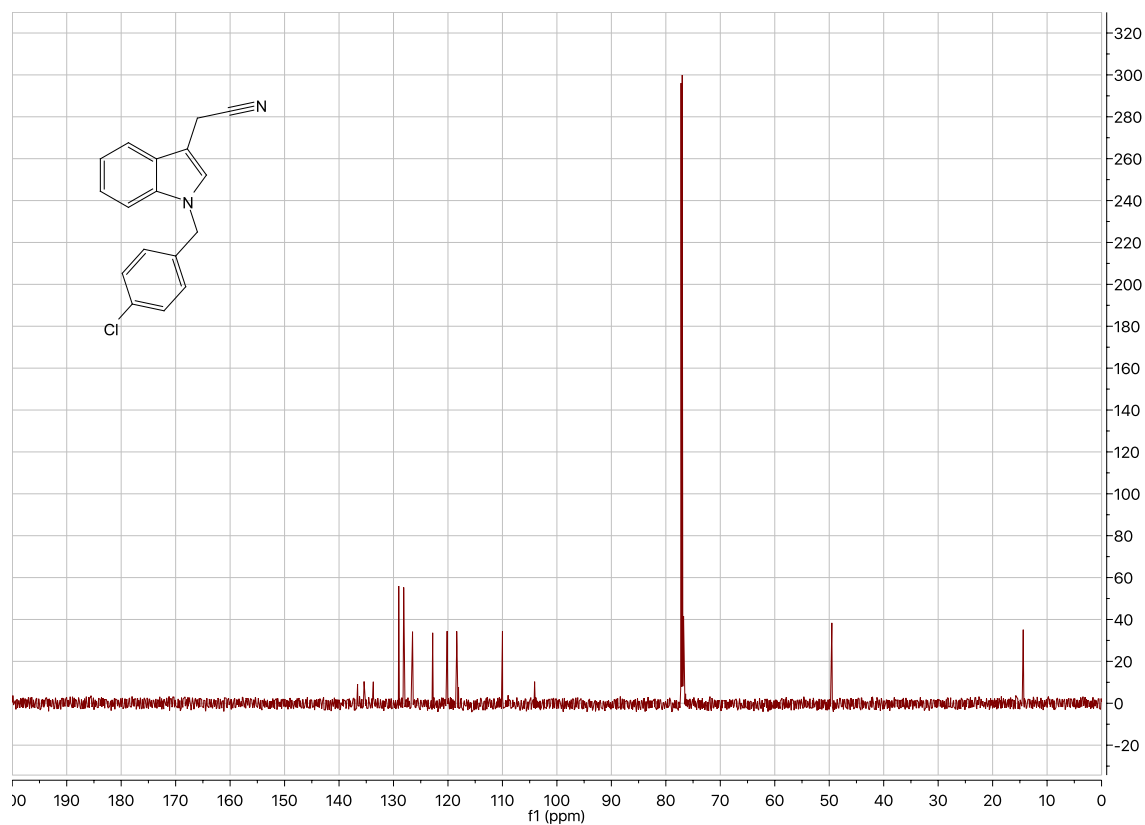


**2-(1-(4-chlorobenzyl)-1H-indol-3-yl)acetonitrile (3fa)**

<sup>1</sup>H NMR (600 MHz, CDCl<sub>3</sub>)

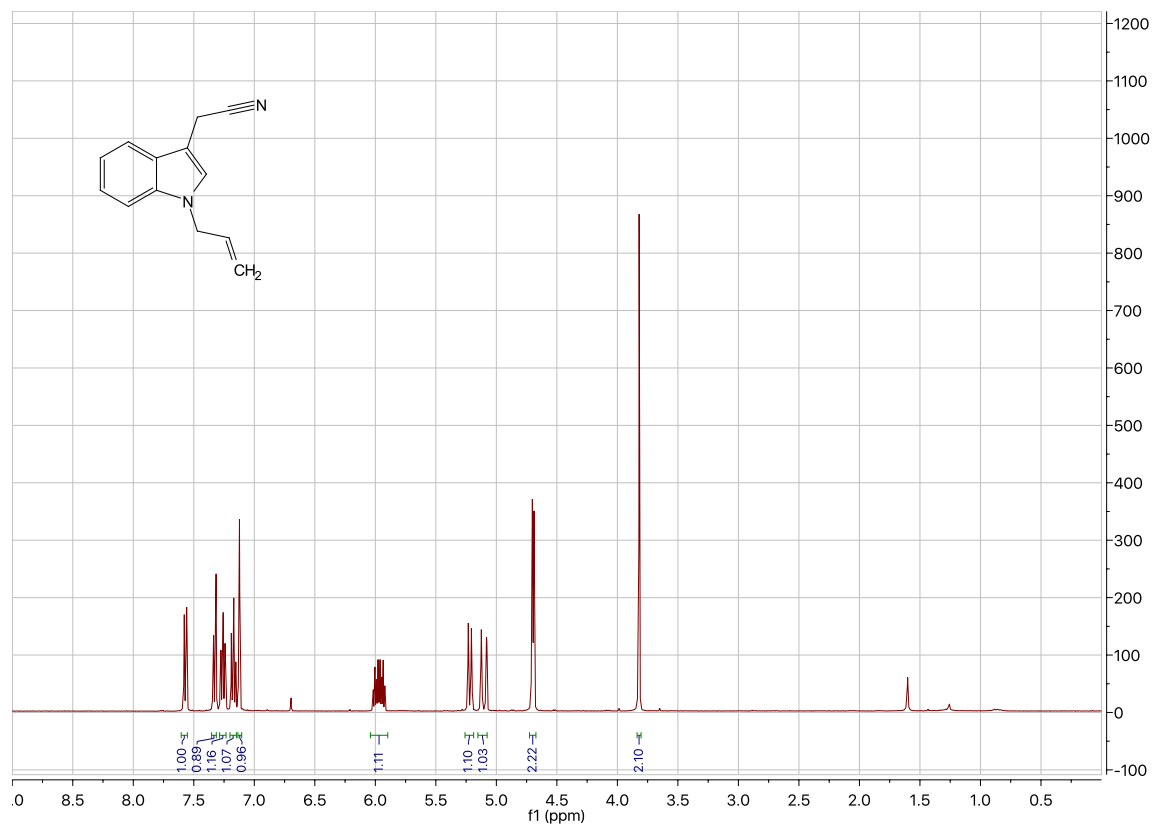


<sup>13</sup>C NMR (151 MHz, CDCl<sub>3</sub>)

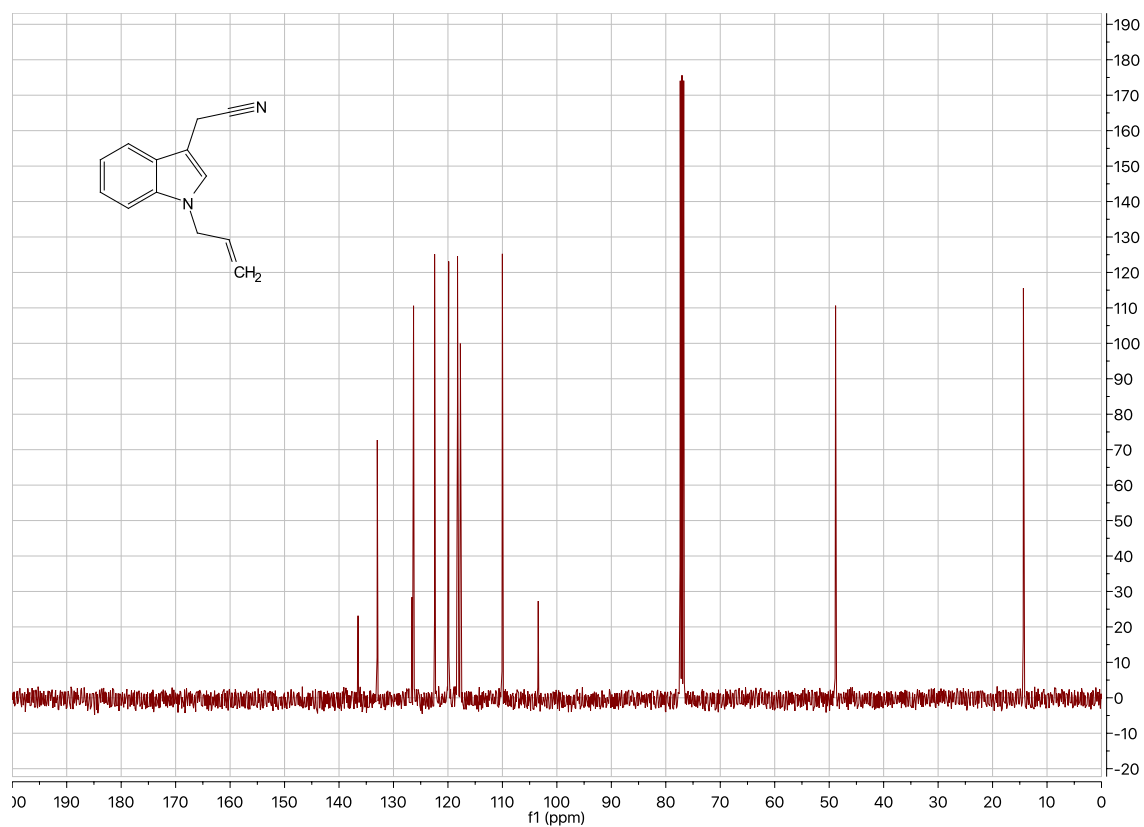


## 2-(1-allyl-1H-indol-3-yl)acetonitrile (3ga)

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )

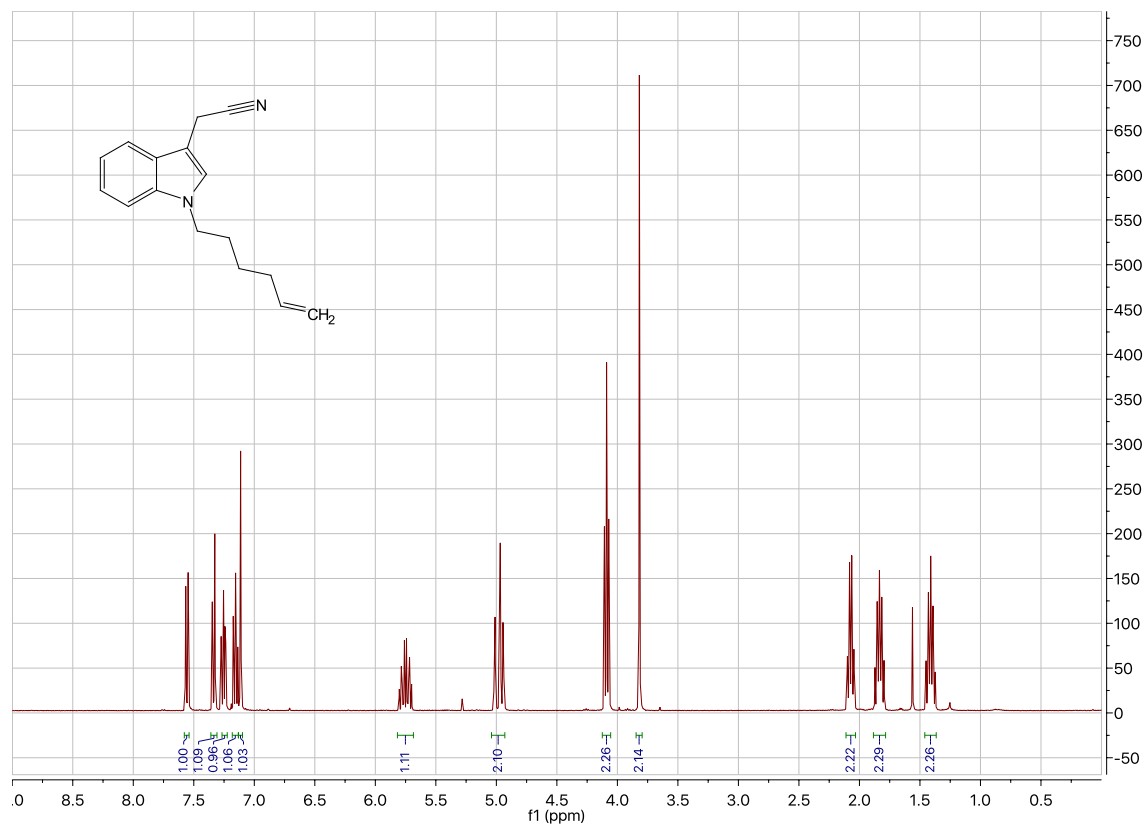


$^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ )

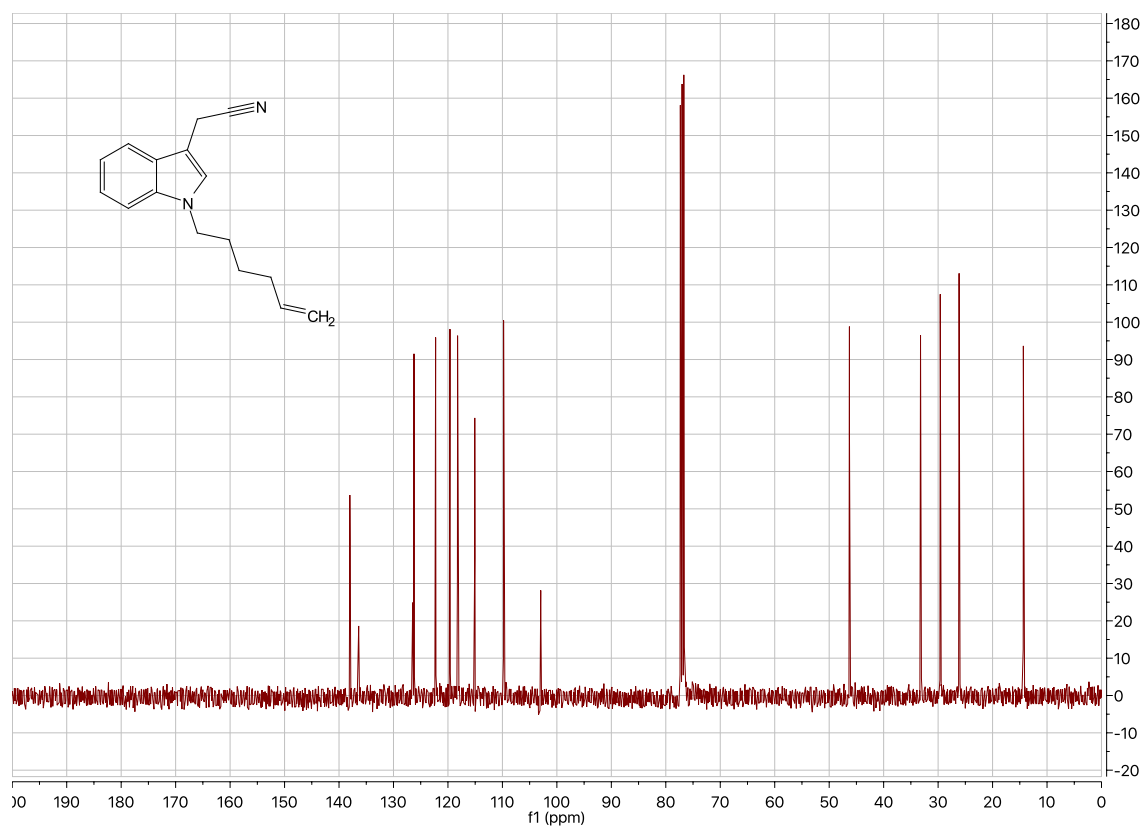


**2-(1-hex-5-en-1-yl-1H-indol-3-yl)acetonitrile (3ha)**

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)

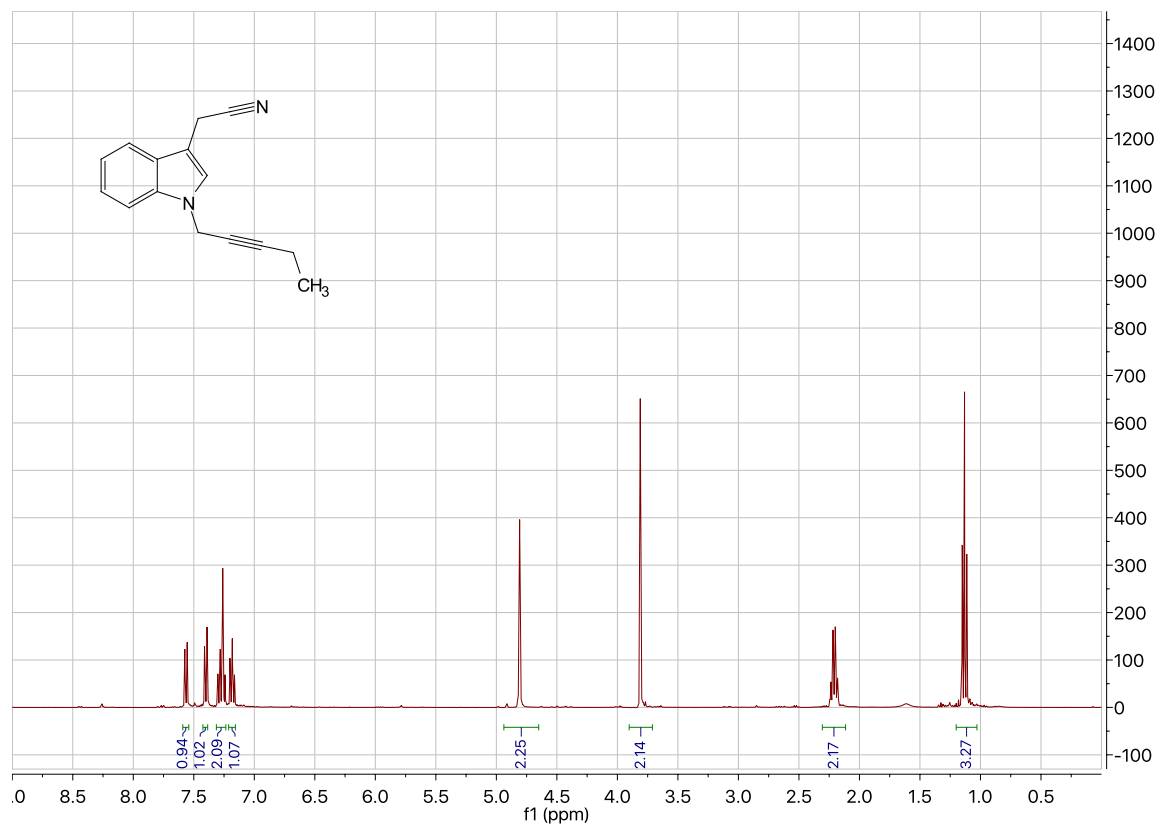


<sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>)

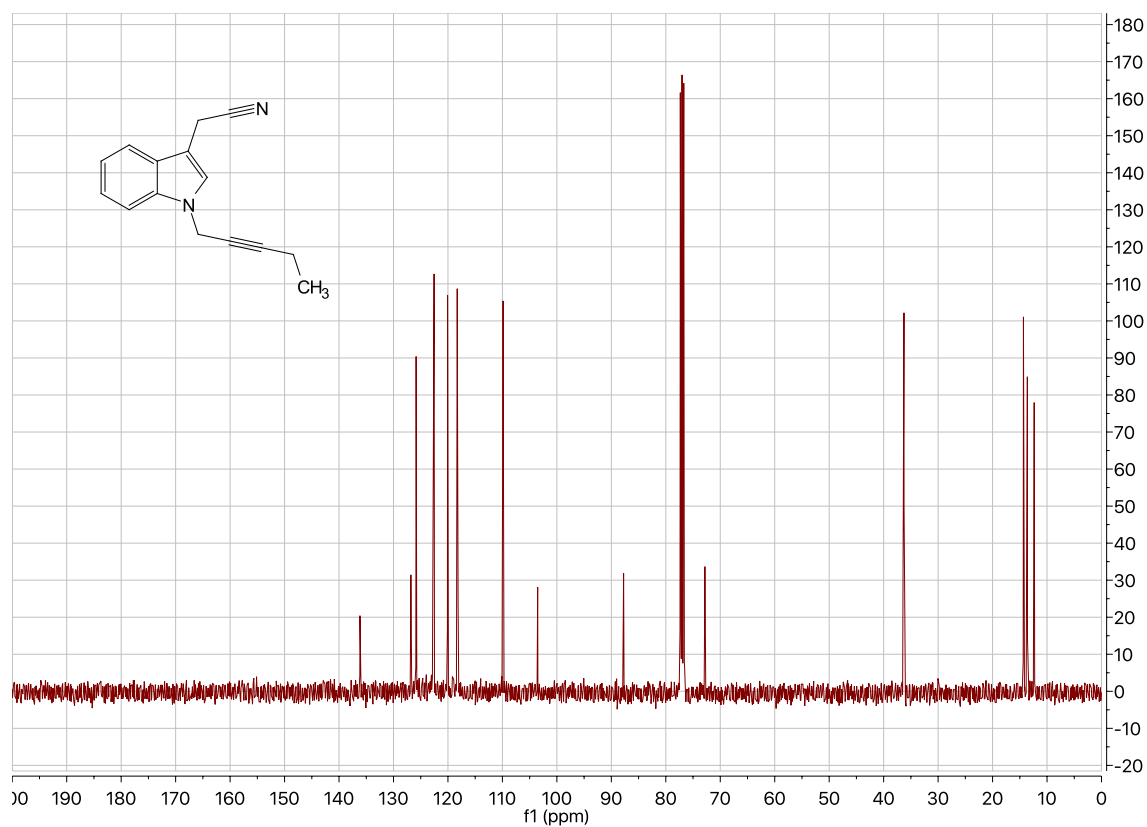


**2-(1-(pent-2-yn-1-yl)-1H-indol-3-yl)acetonitrile (3ia)**

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)

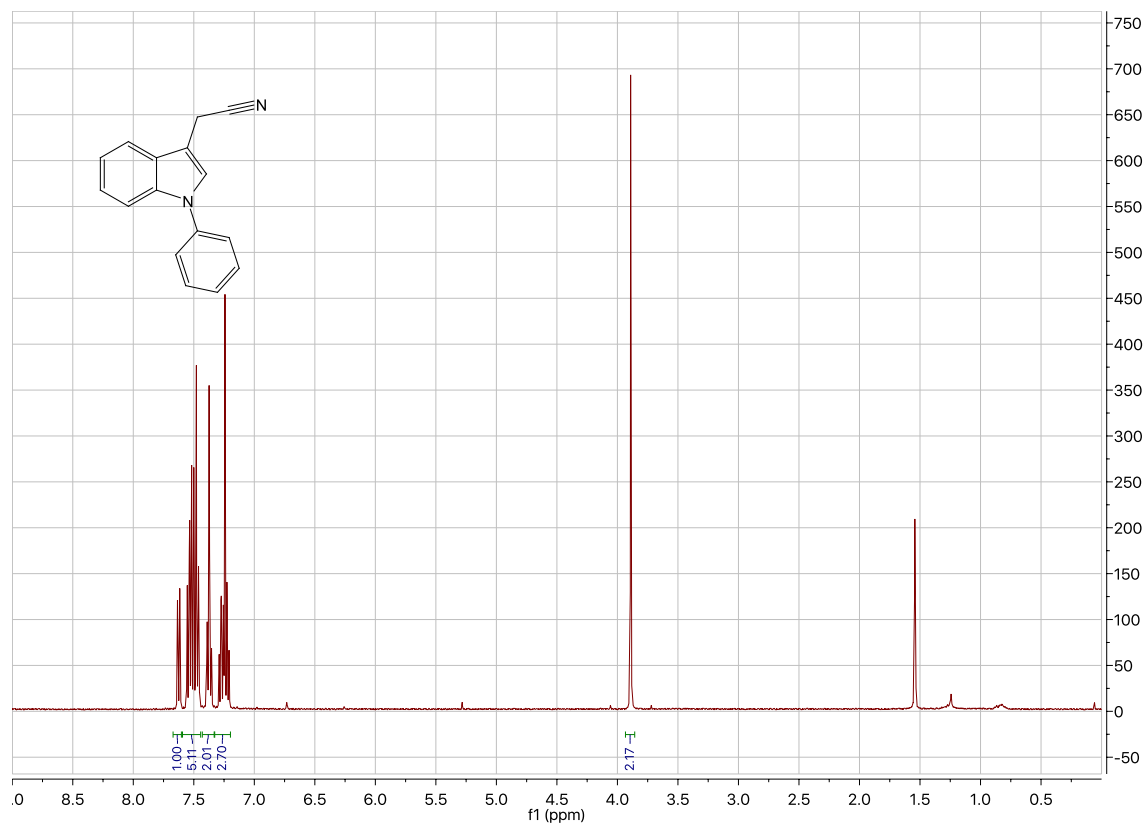


<sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>)

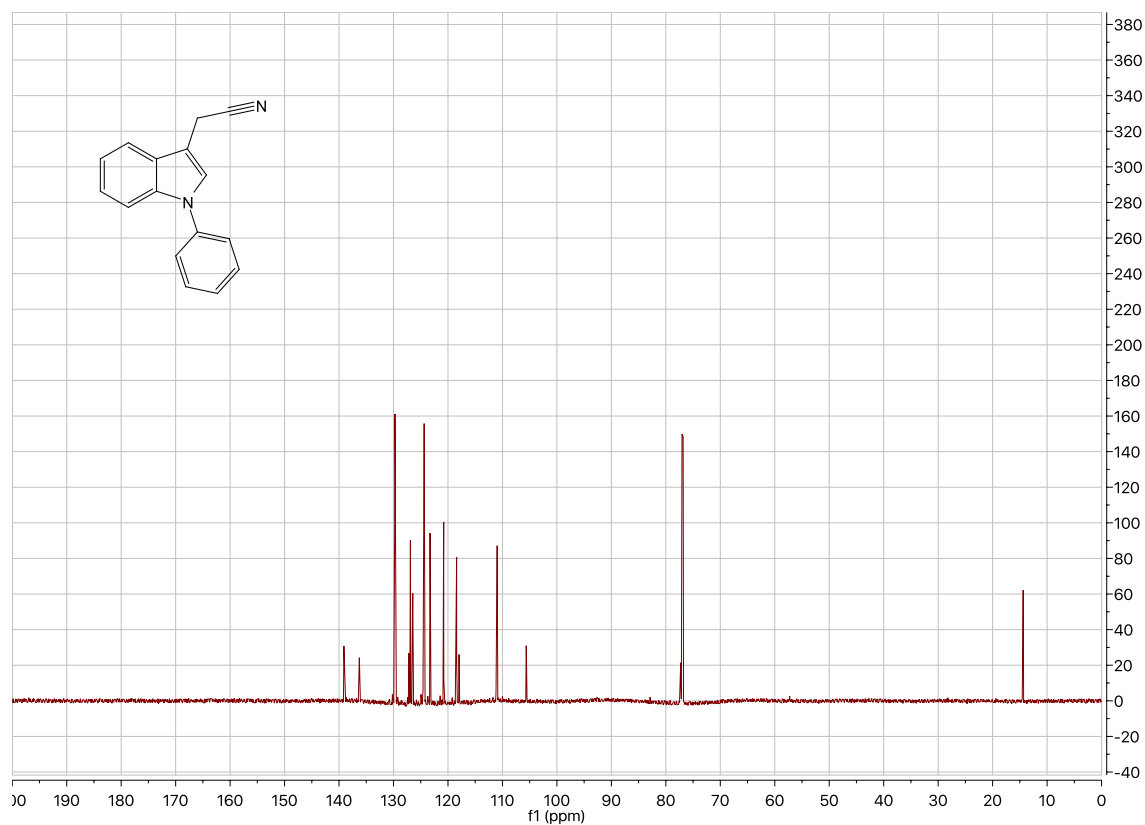


## 2-(1-phenyl-1H-indol-3-yl)acetonitrile (3ja)

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )

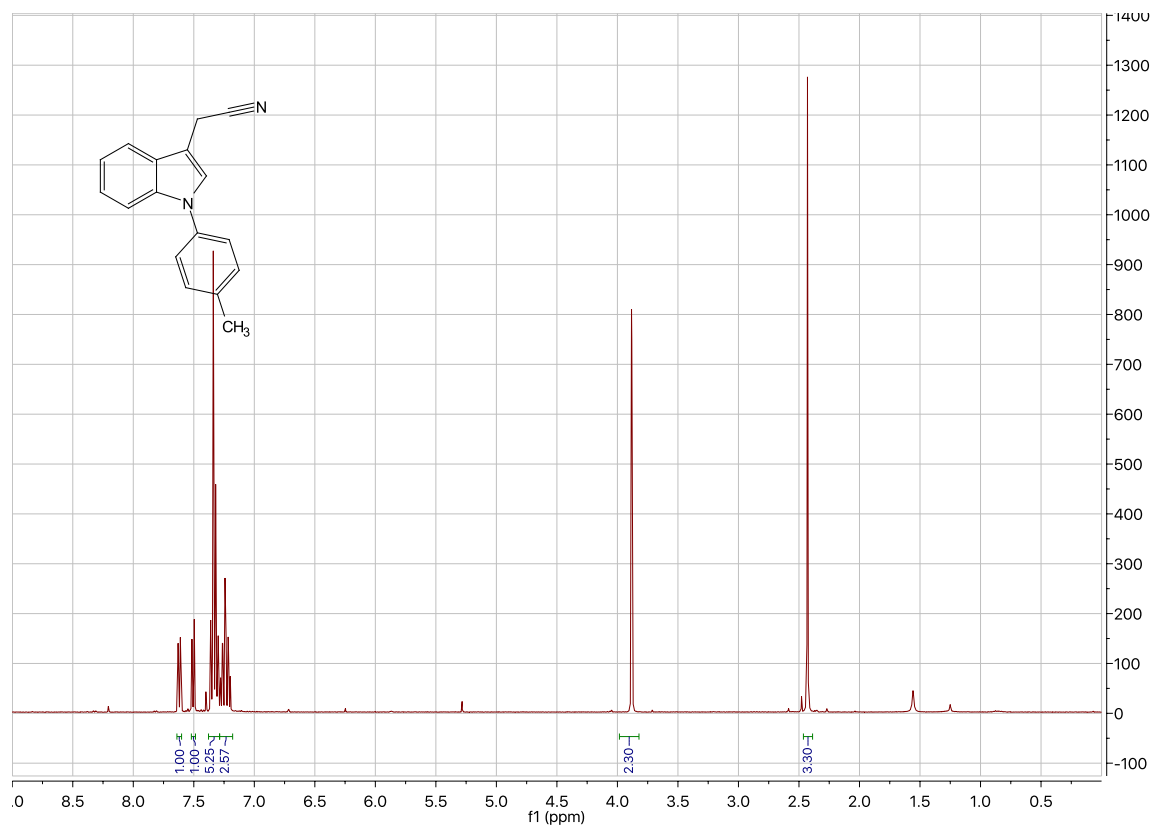


$^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ )

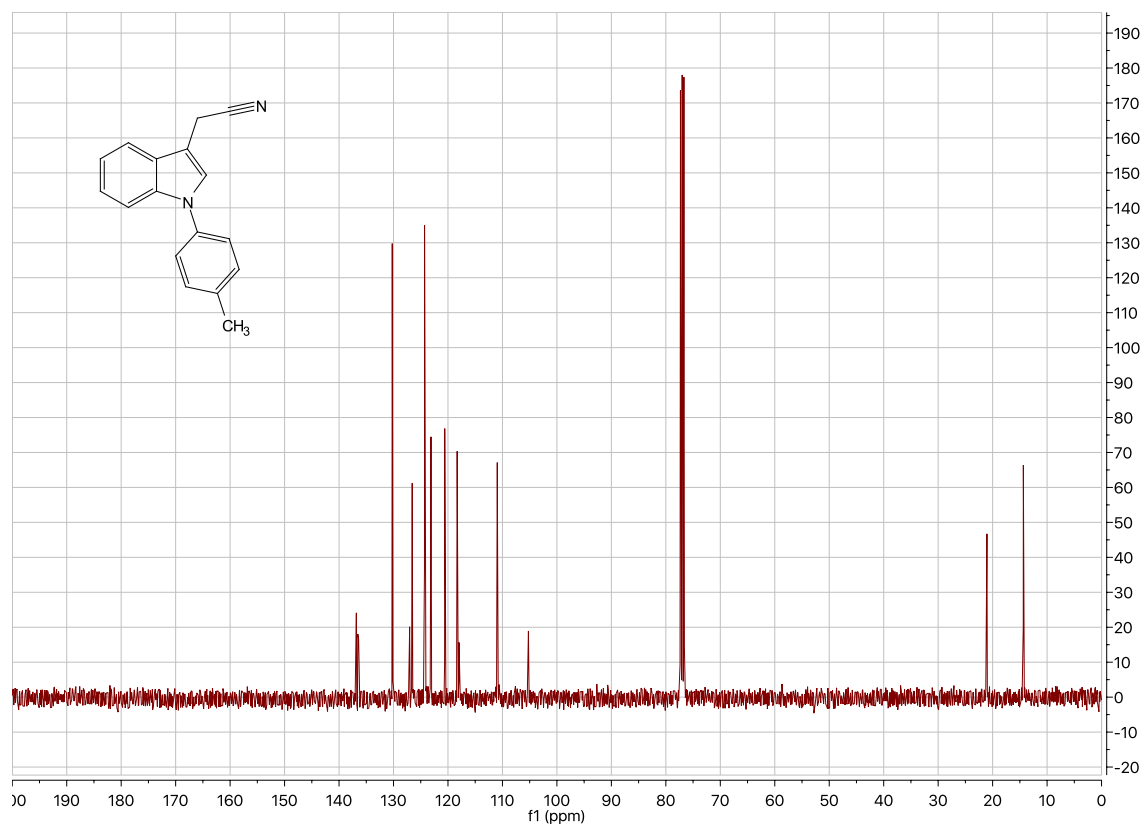


## 2-(1-(*p*-tolyl)-1*H*-indol-3-yl)acetonitrile (3ka)

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)



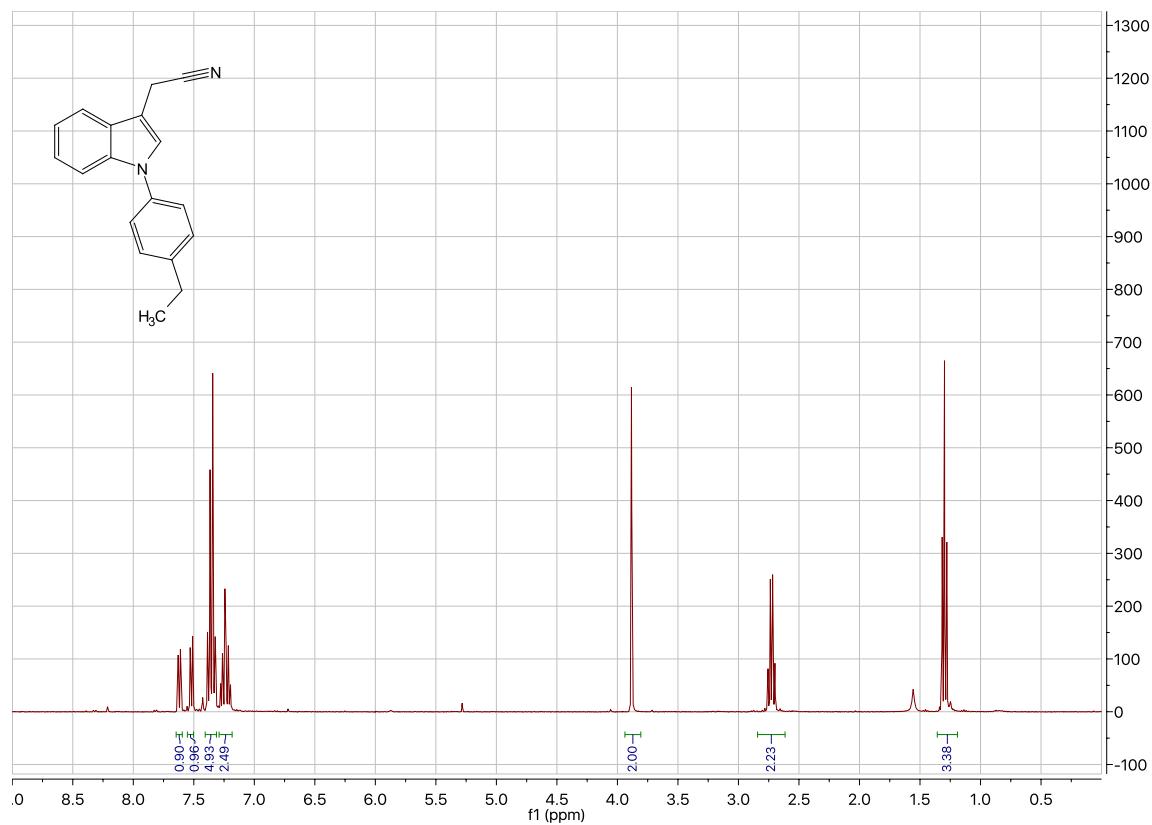
<sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>)



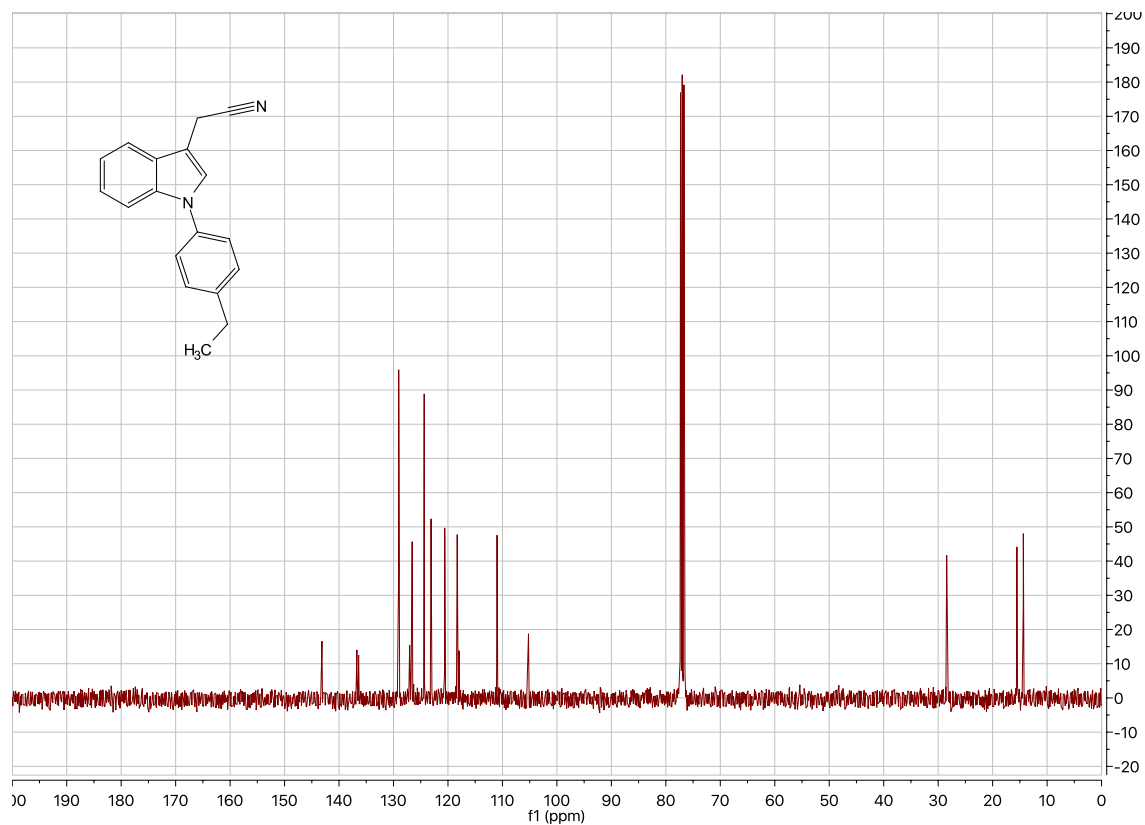


## 2-(1-(4-ethylphenyl)-1H-indol-3-yl)acetonitrile (3la)

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )

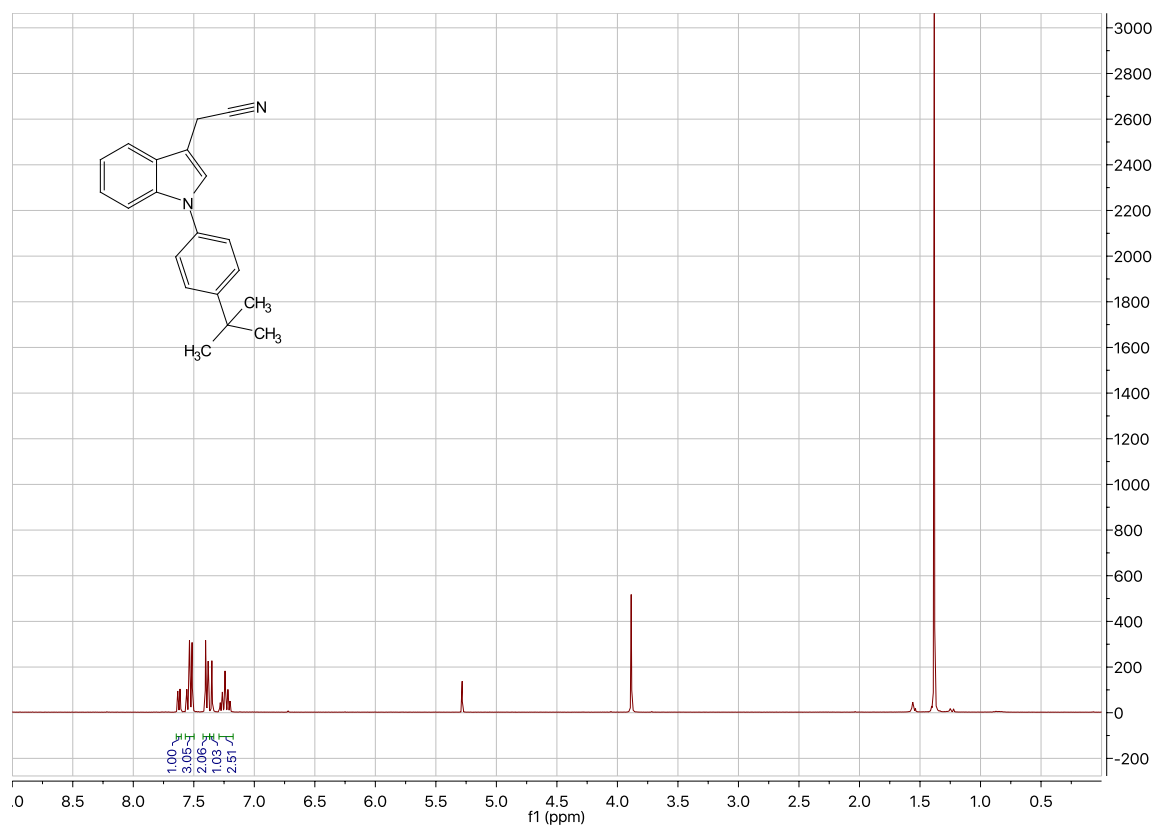


$^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ )

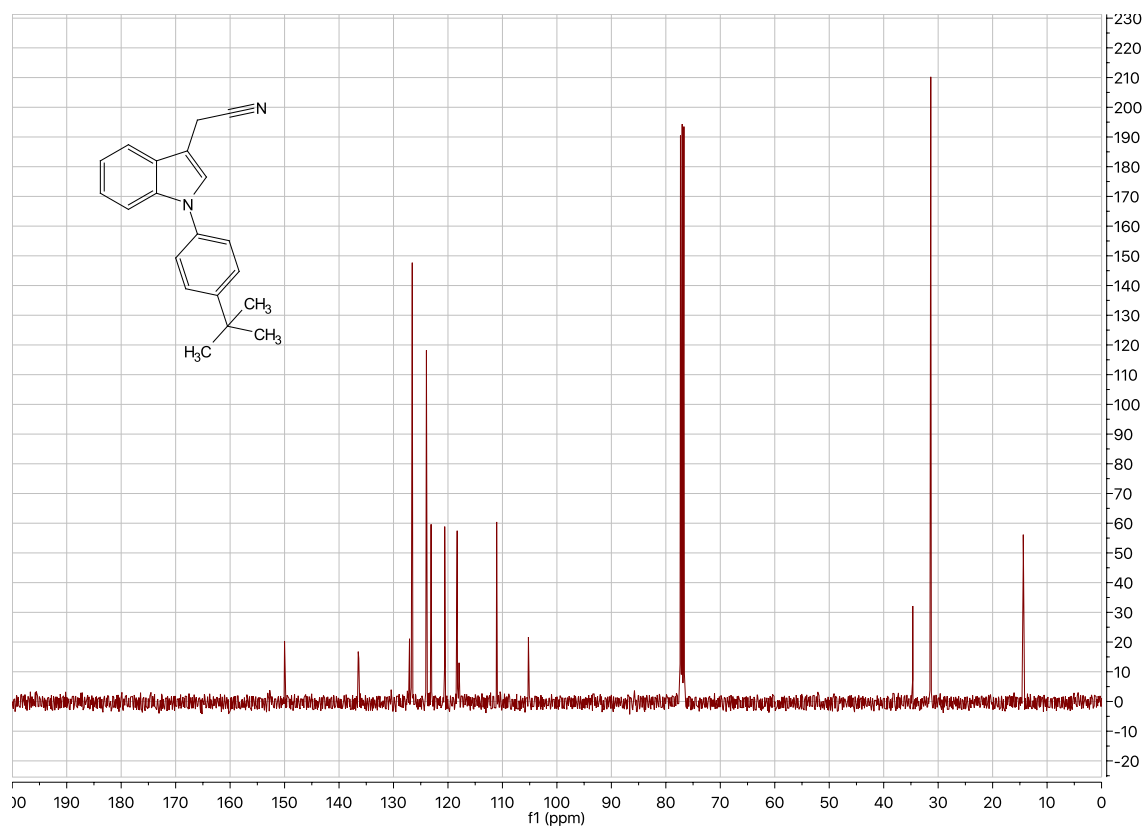


## 2-(1-(4-*tert*-butyl-phenyl)-1*H*-indol-3-yl)acetonitrile (3ma)

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )

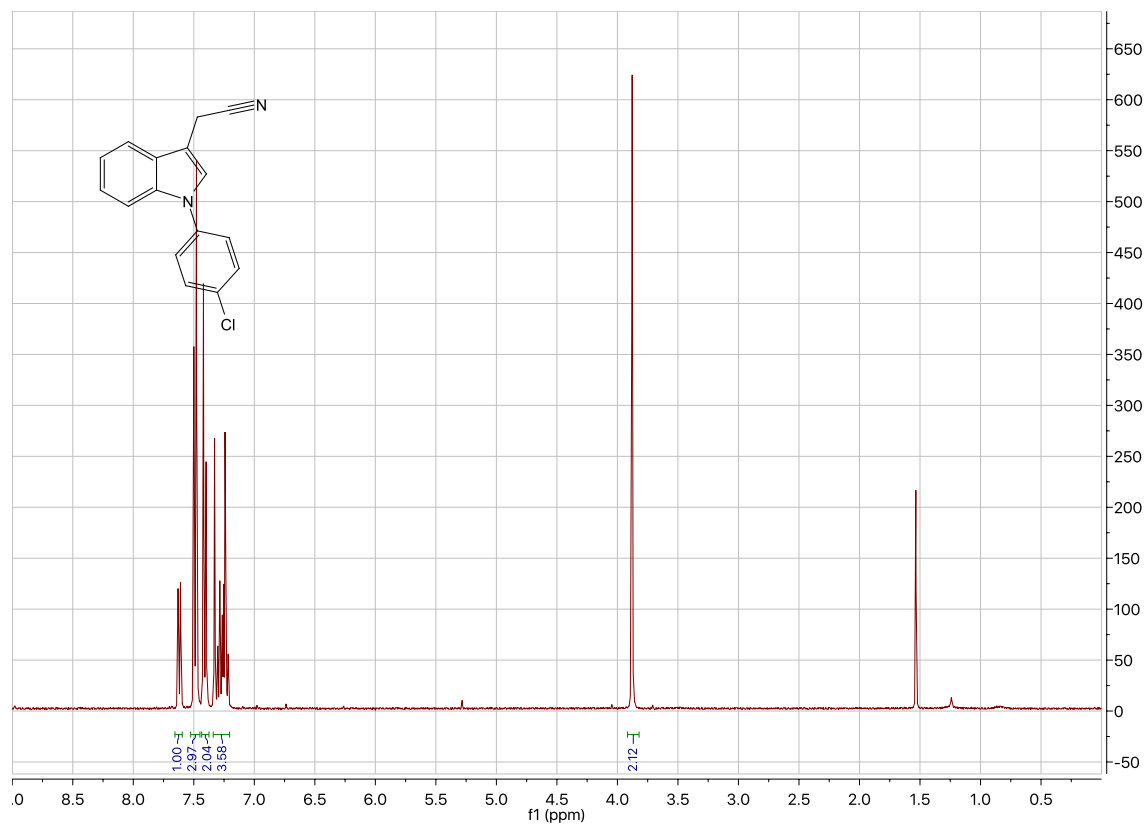


$^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ )

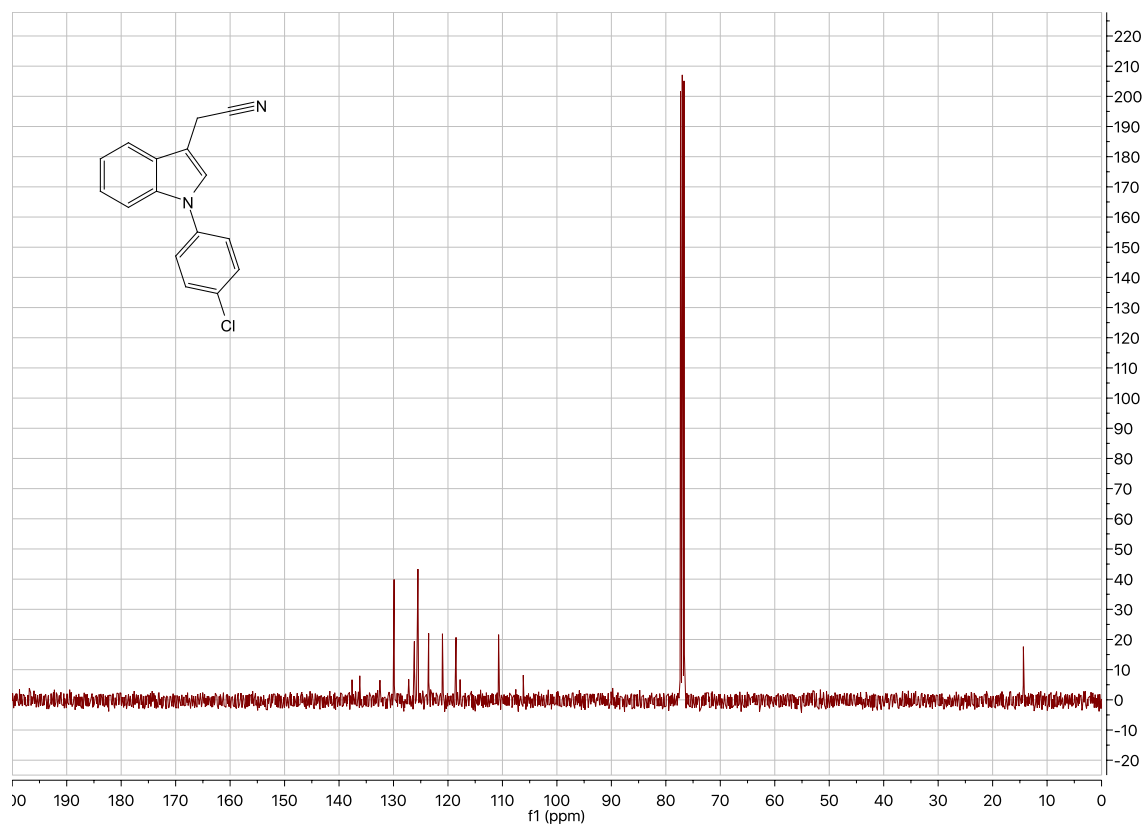


**2-(1-(4-chlorophenyl)-1H-indol-3-yl)acetonitrile (3na)**

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)

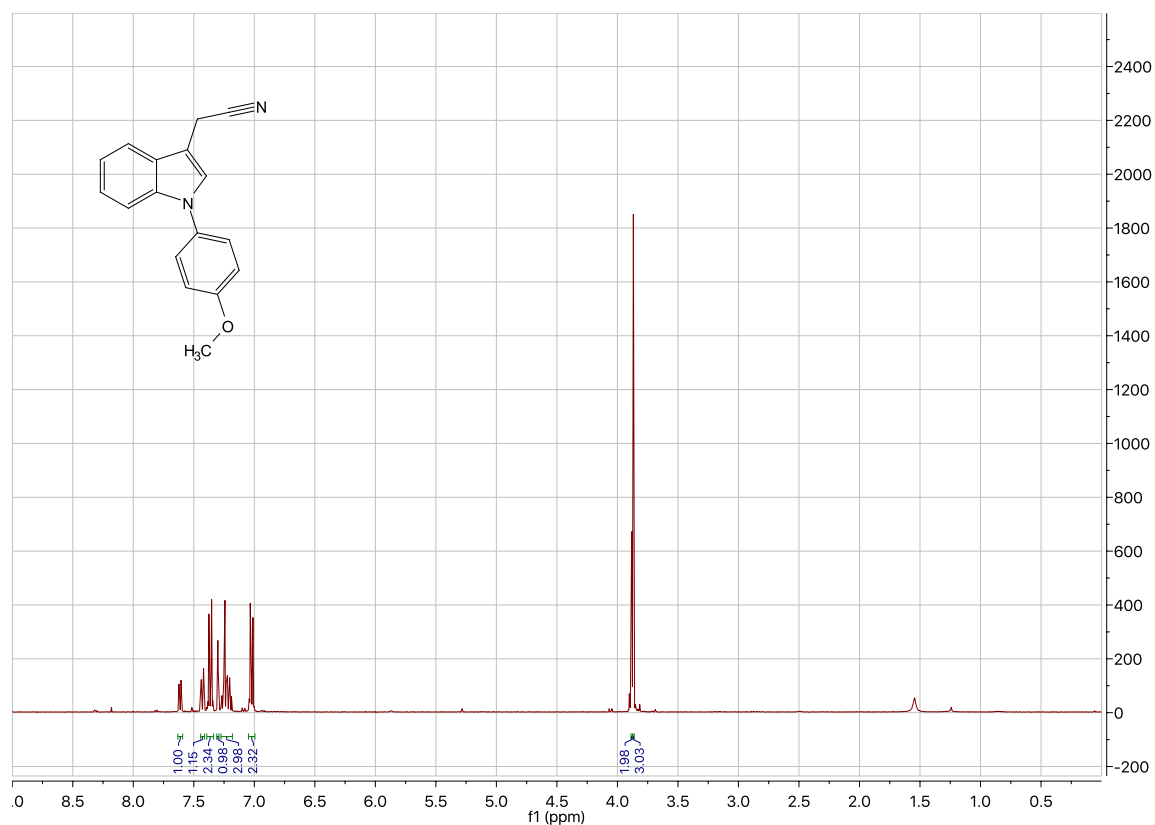


<sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>)

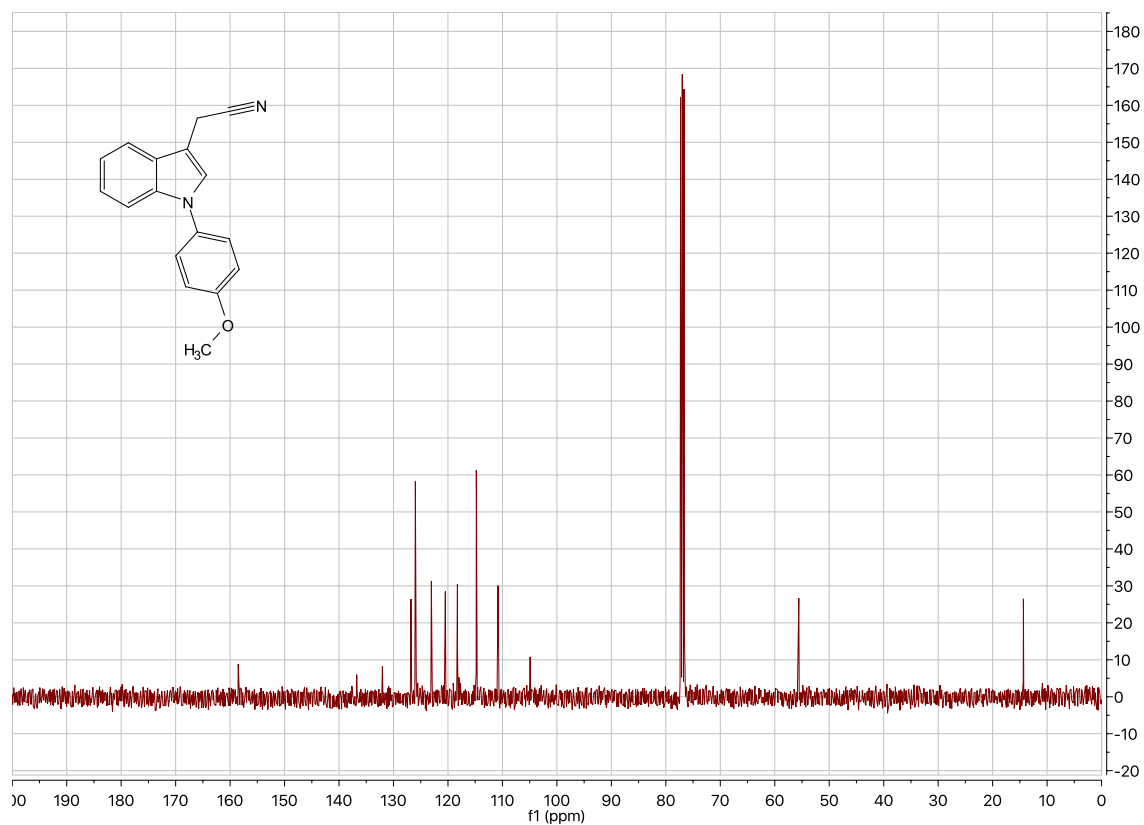


## 2-(1-(4-methoxyphenyl)-1H-indol-3-yl)acetonitrile (3oa)

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )

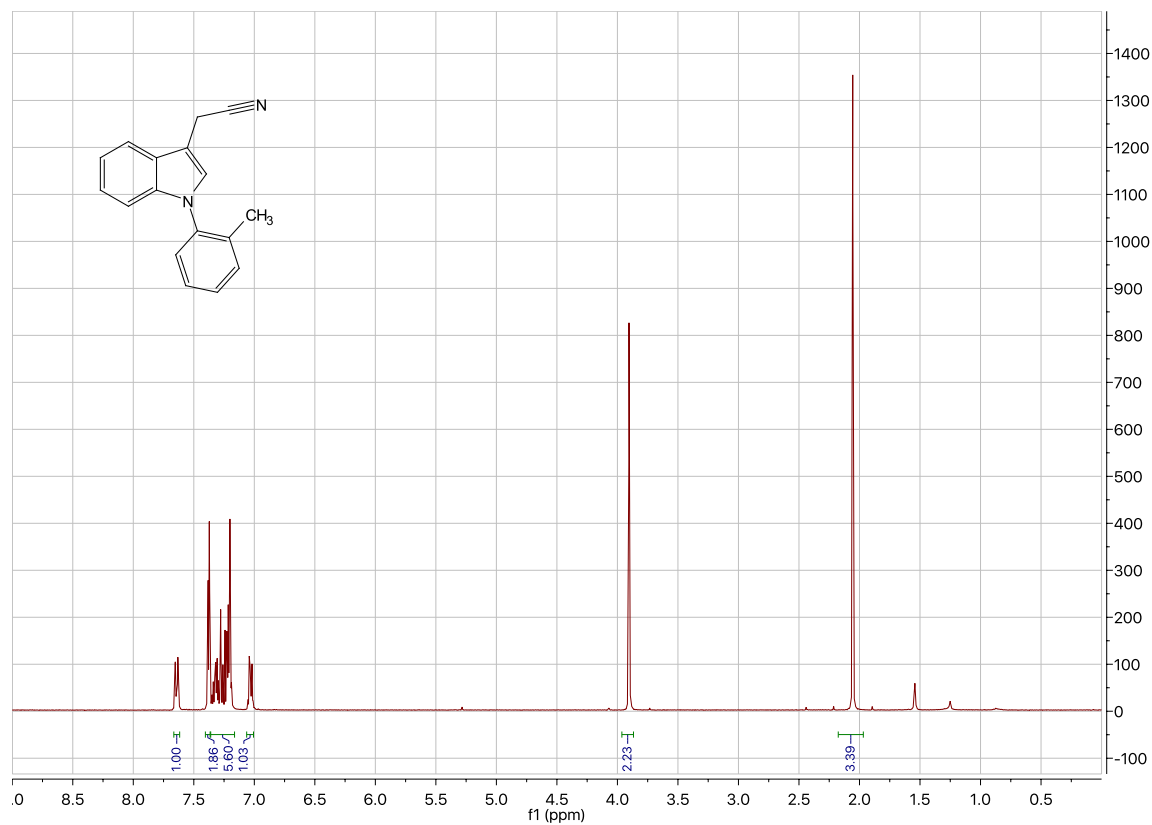


$^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ )

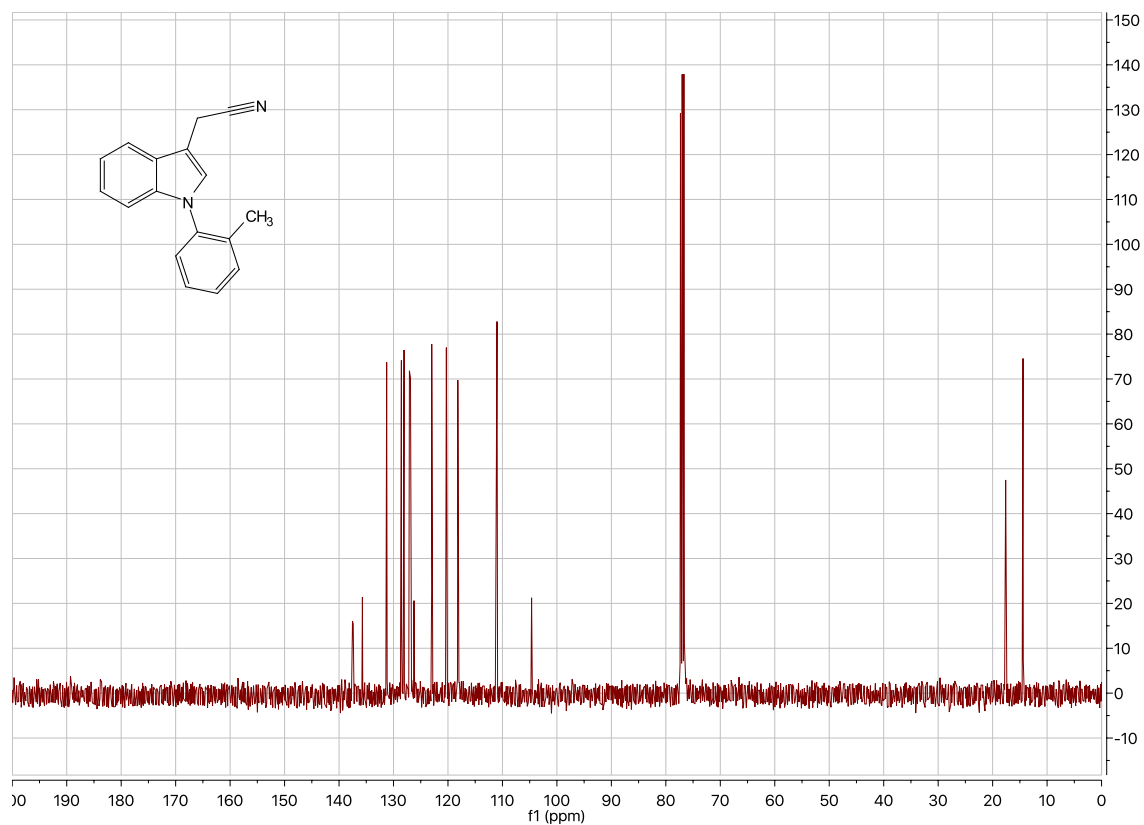


## 2-(1-(2-methyl-phenyl)-1H-indol-3-yl)acetonitrile (3pa)

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)

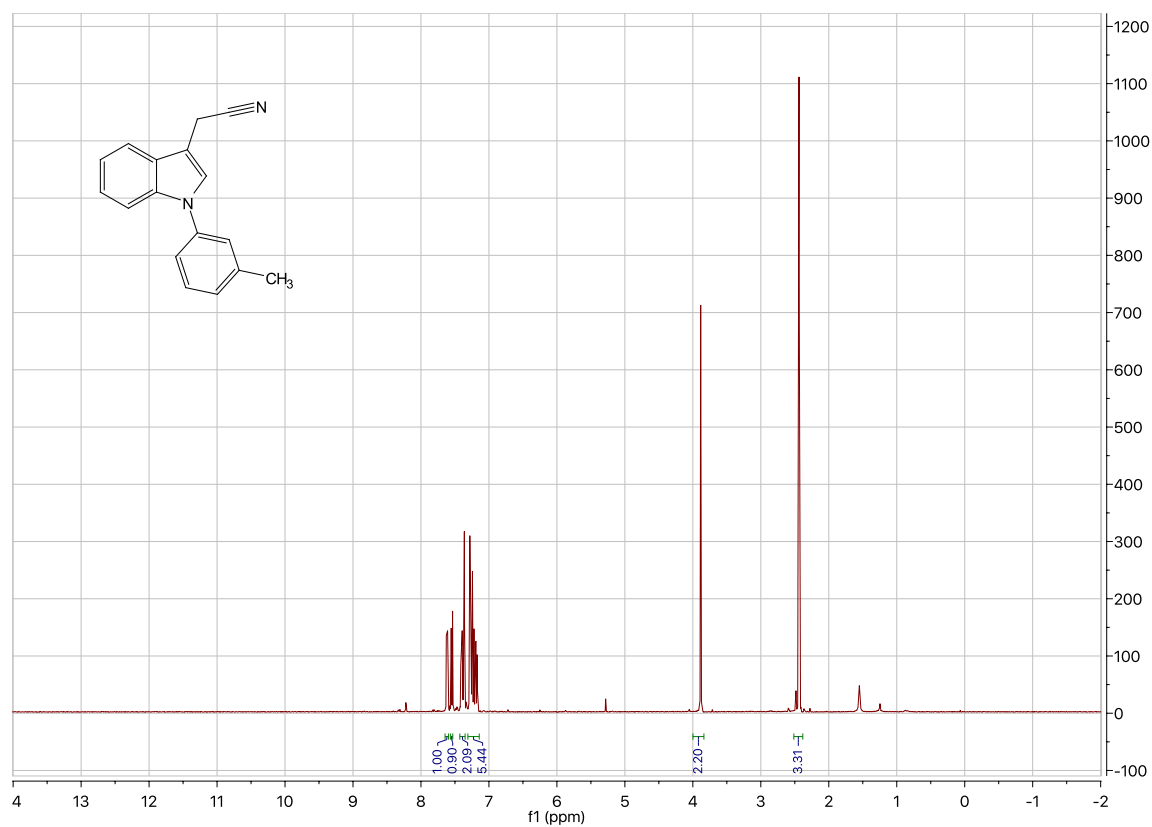


<sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>)

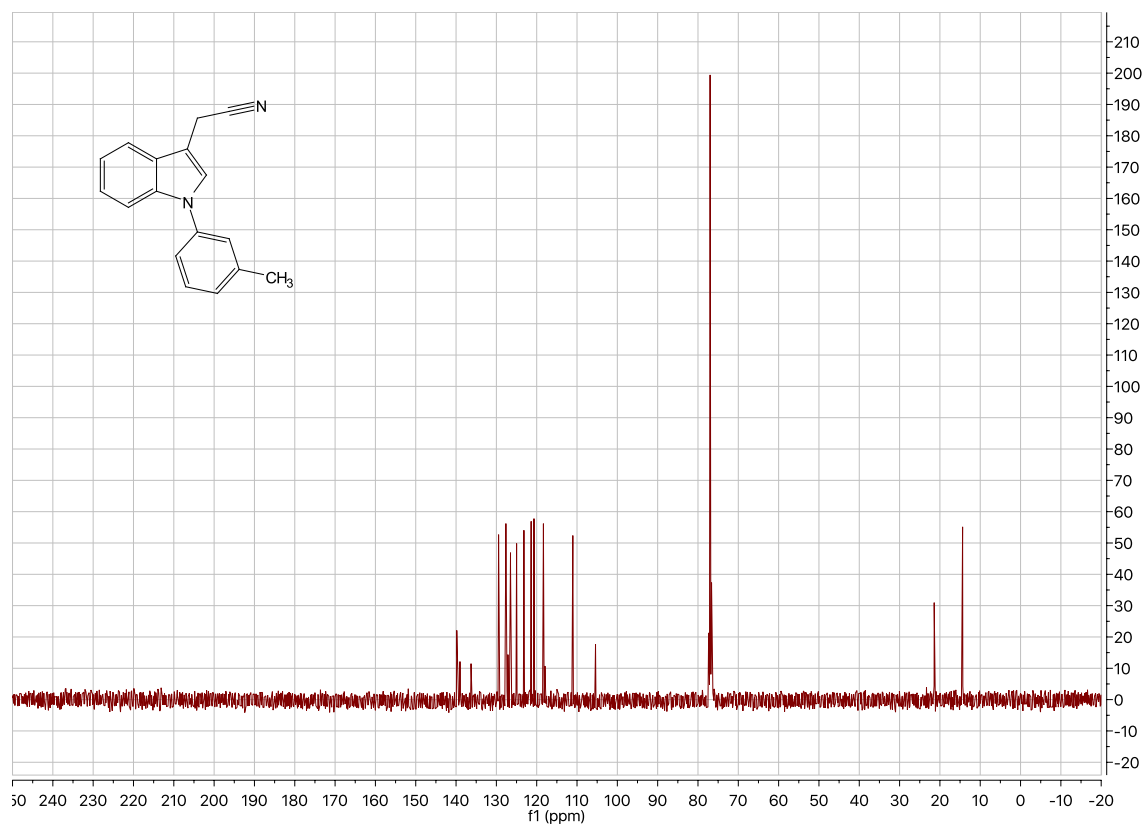


## 2-(1-(3-methyl-phenyl)-1*H*-indol-3-yl)acetonitrile (3qa)

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)

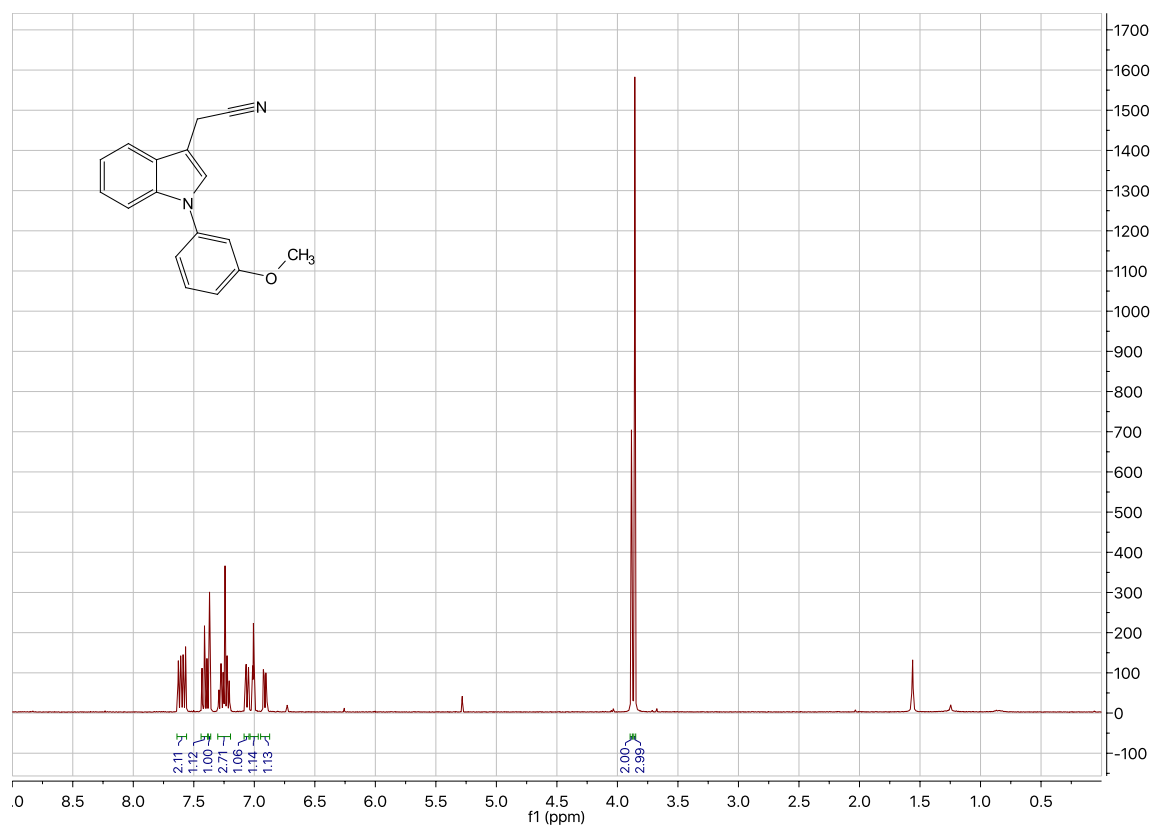


<sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>)

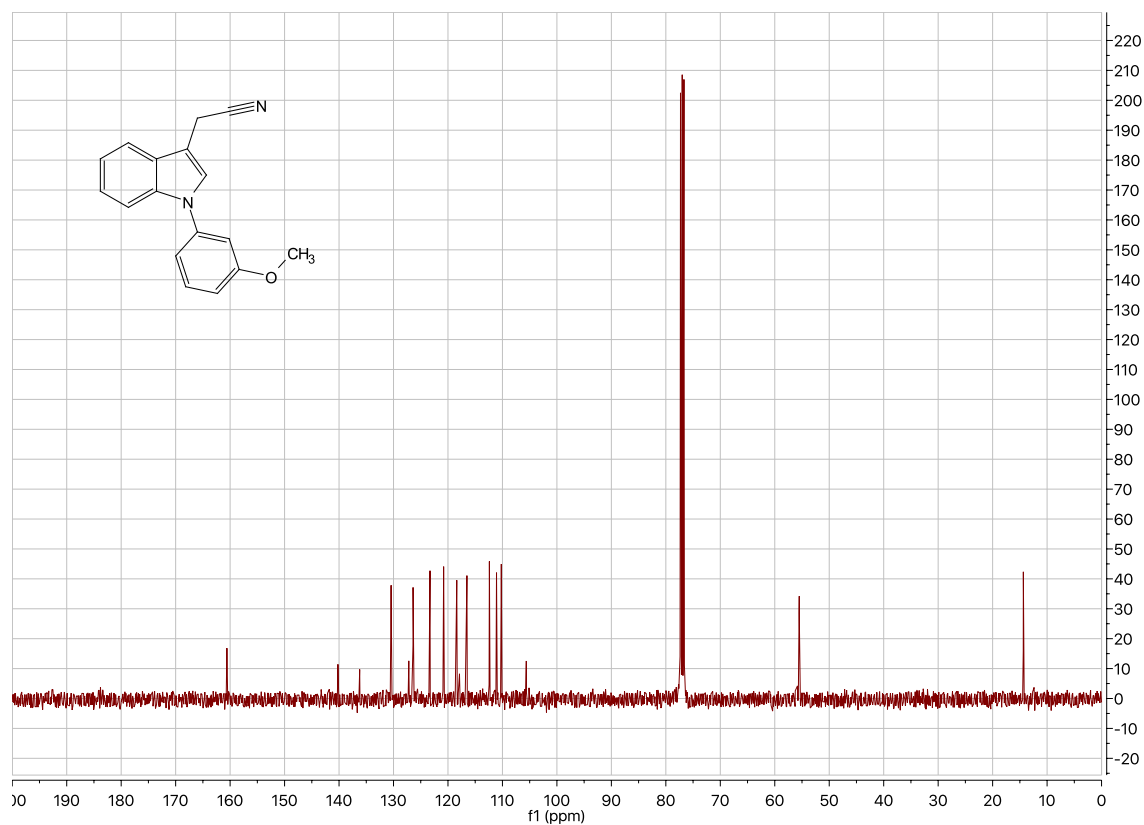


## 2-(1-(3-methoxy-phenyl)-1*H*-indol-3-yl)acetonitrile (3ra)

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )

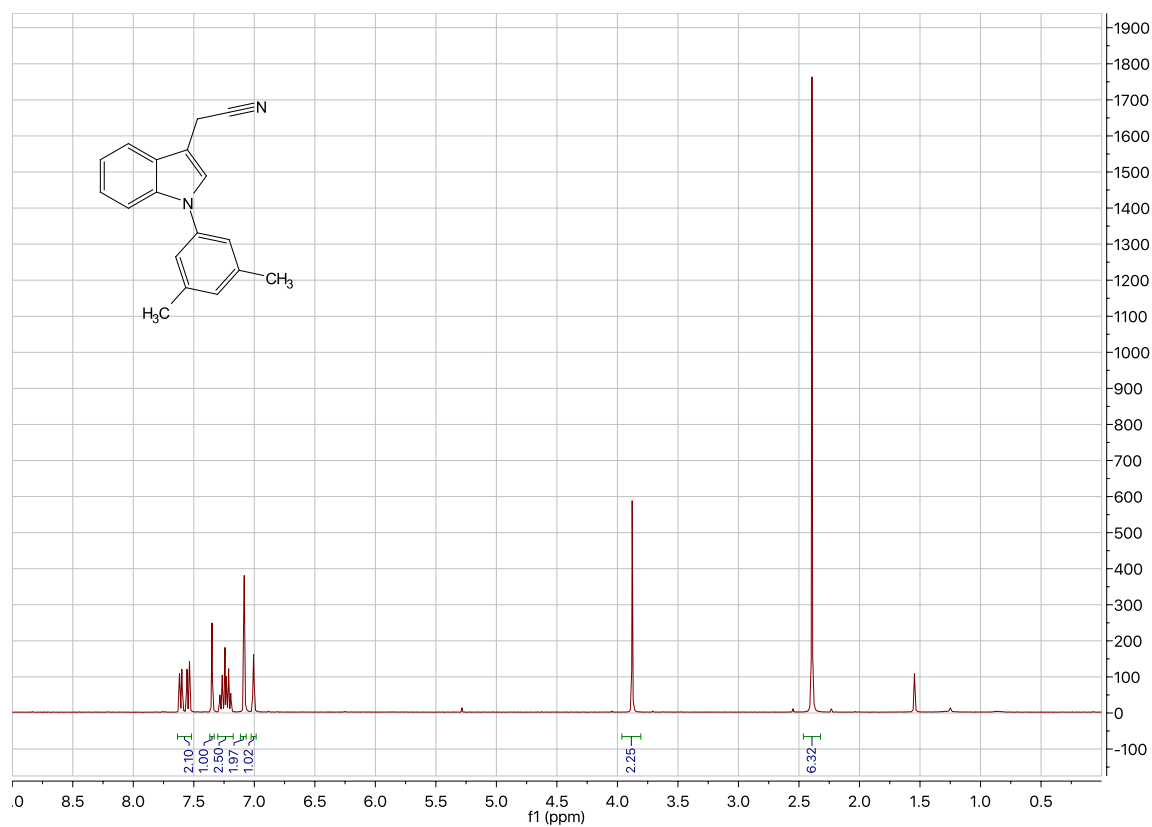


$^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ )

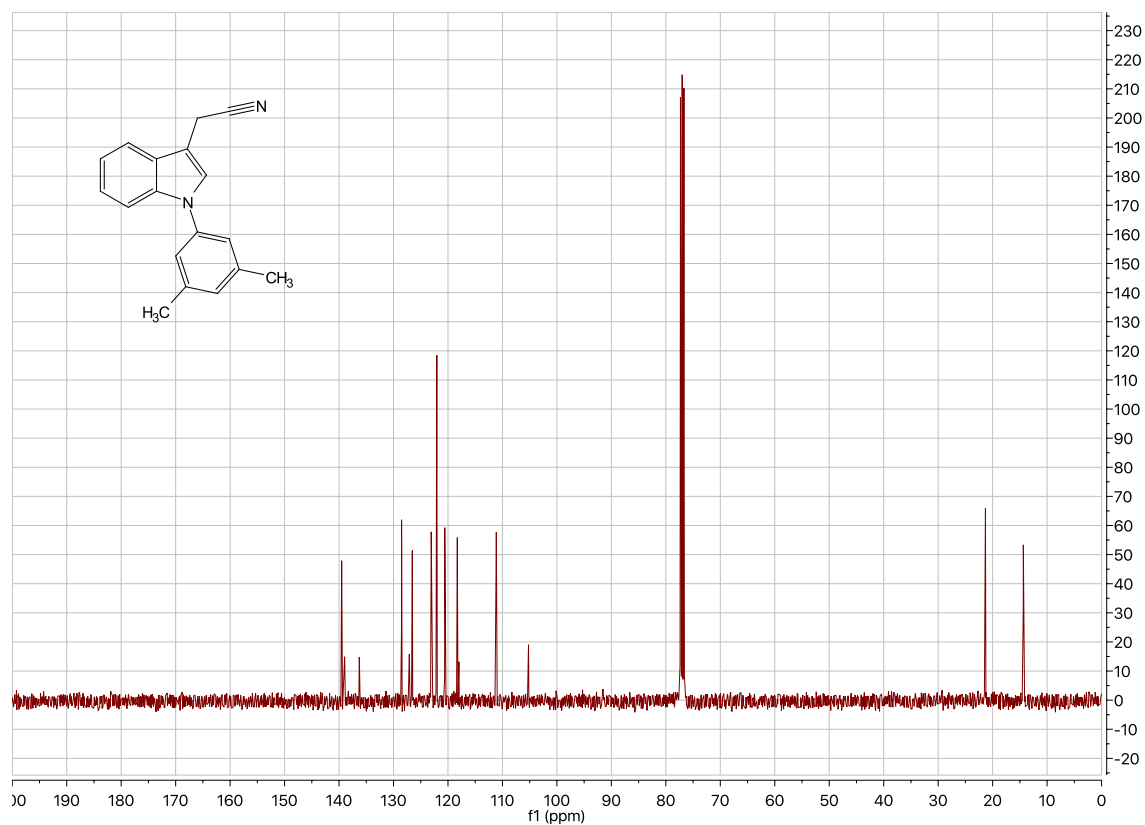


## 2-(1-(3,5-dimethyl-phenyl)-1H-indol-3-yl)acetonitrile (3sa)

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )



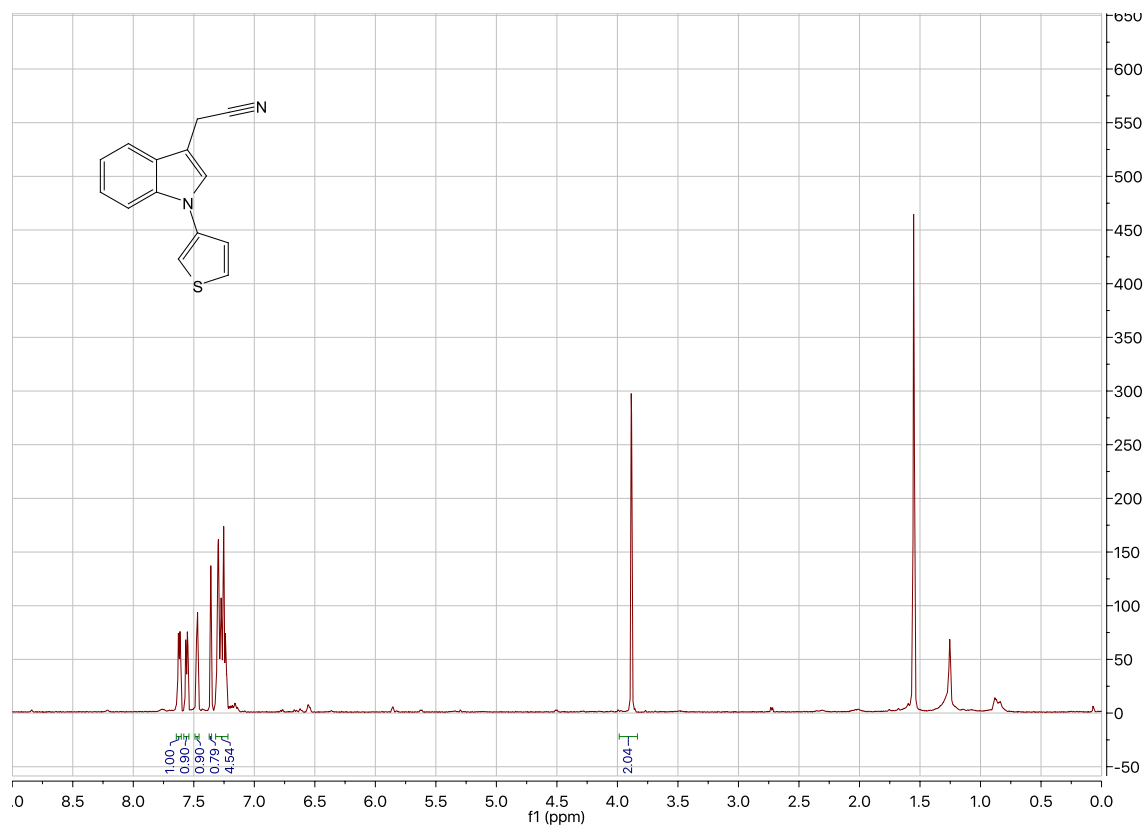
$^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ )



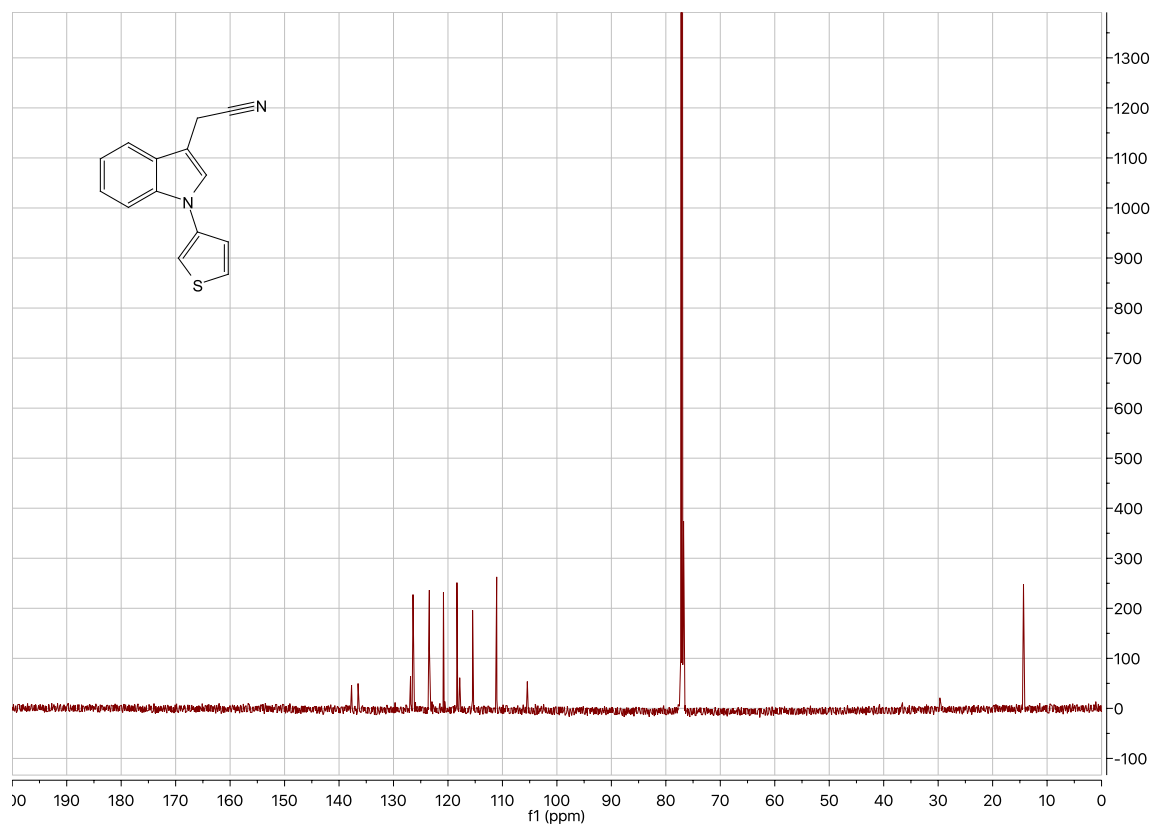


## 2-(1-(thiophen-3-yl)-1H-indol-3-yl)acetonitrile (3ta)

$^1\text{H}$  NMR (600 MHz,  $\text{CDCl}_3$ )

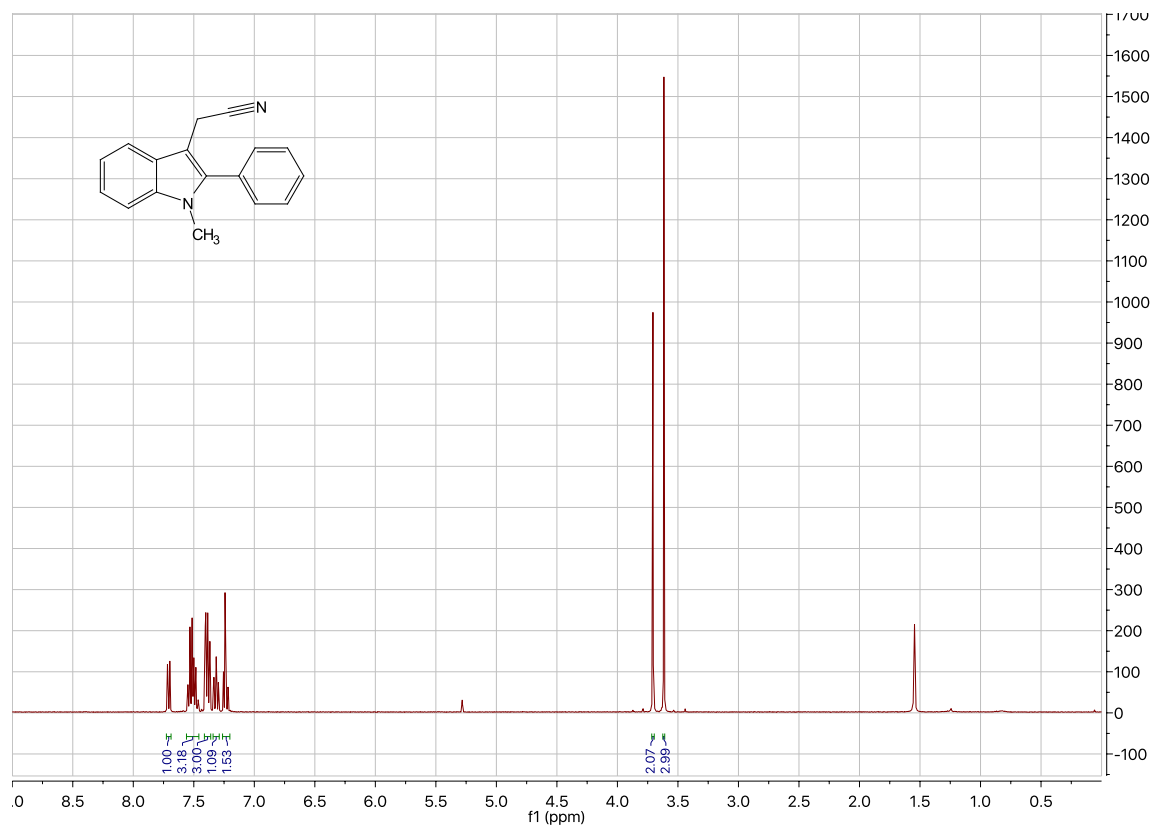


$^{13}\text{C}$  NMR (151 MHz,  $\text{CDCl}_3$ )

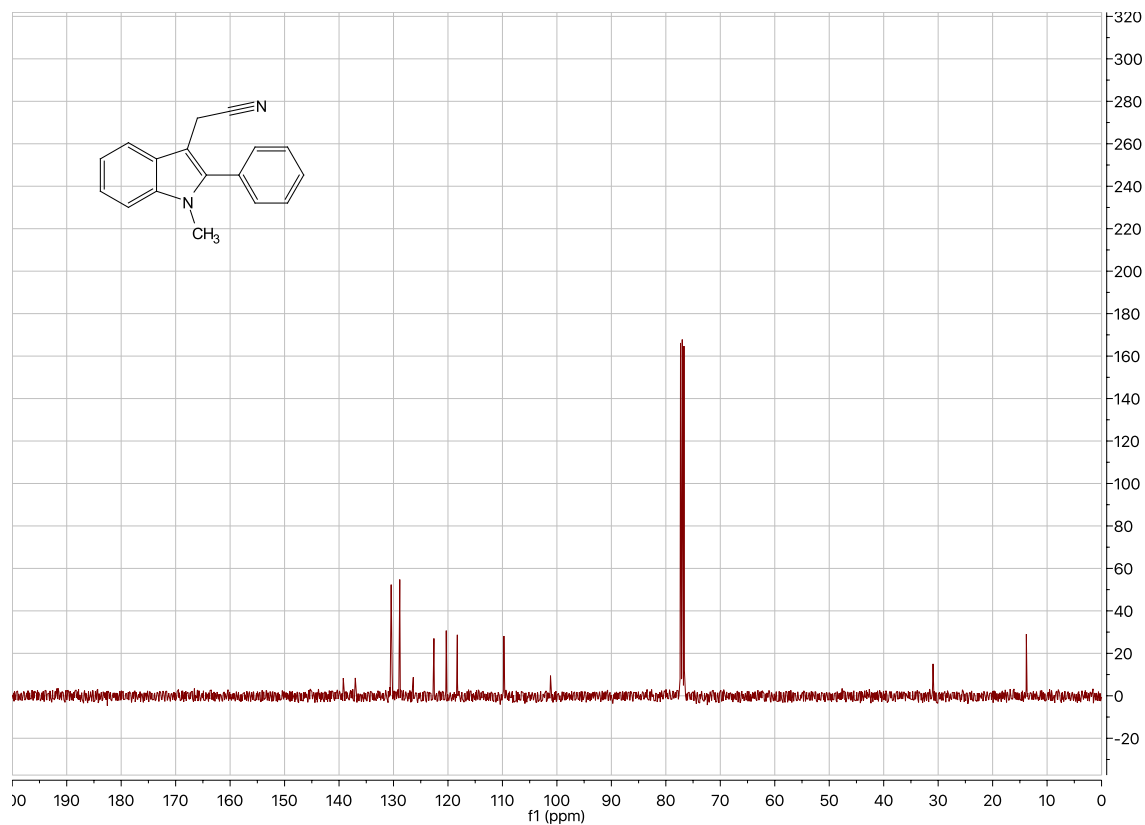


## 2-(1-methyl-2-phenyl-1*H*-indol-3-yl)acetonitrile (10a)

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )

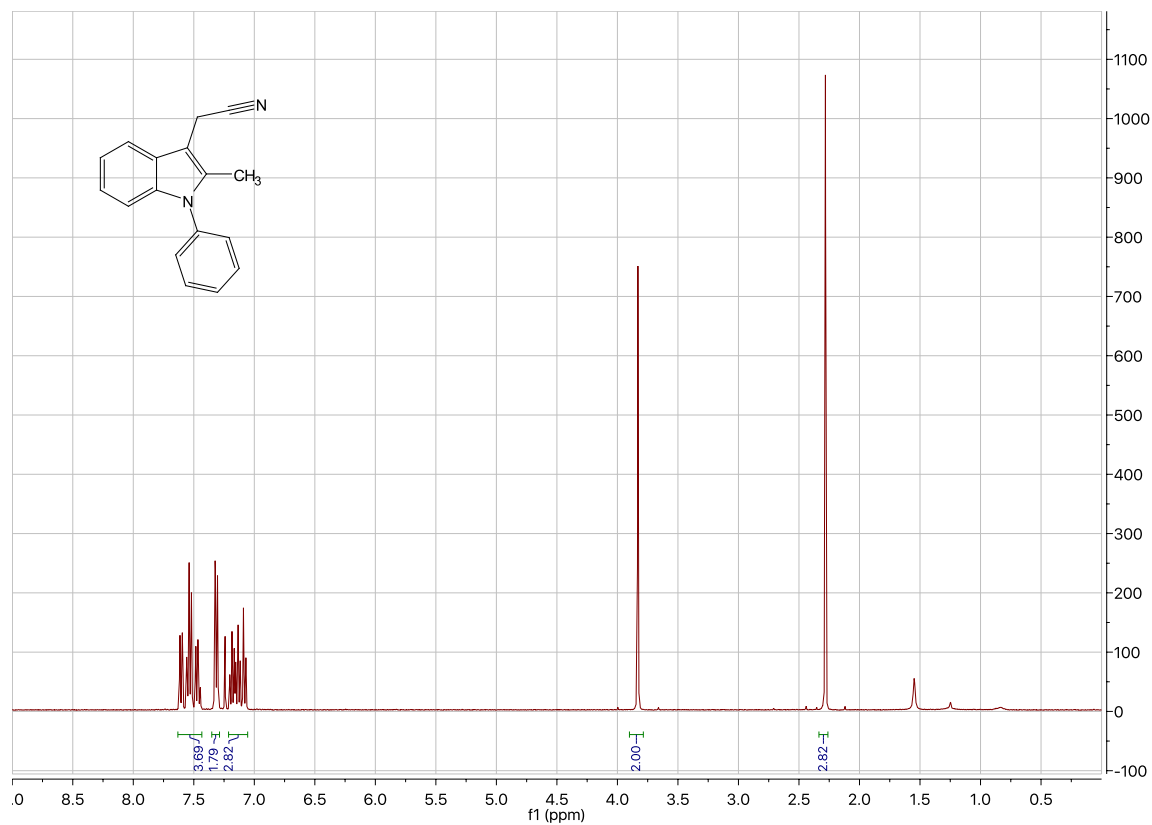


$^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ )

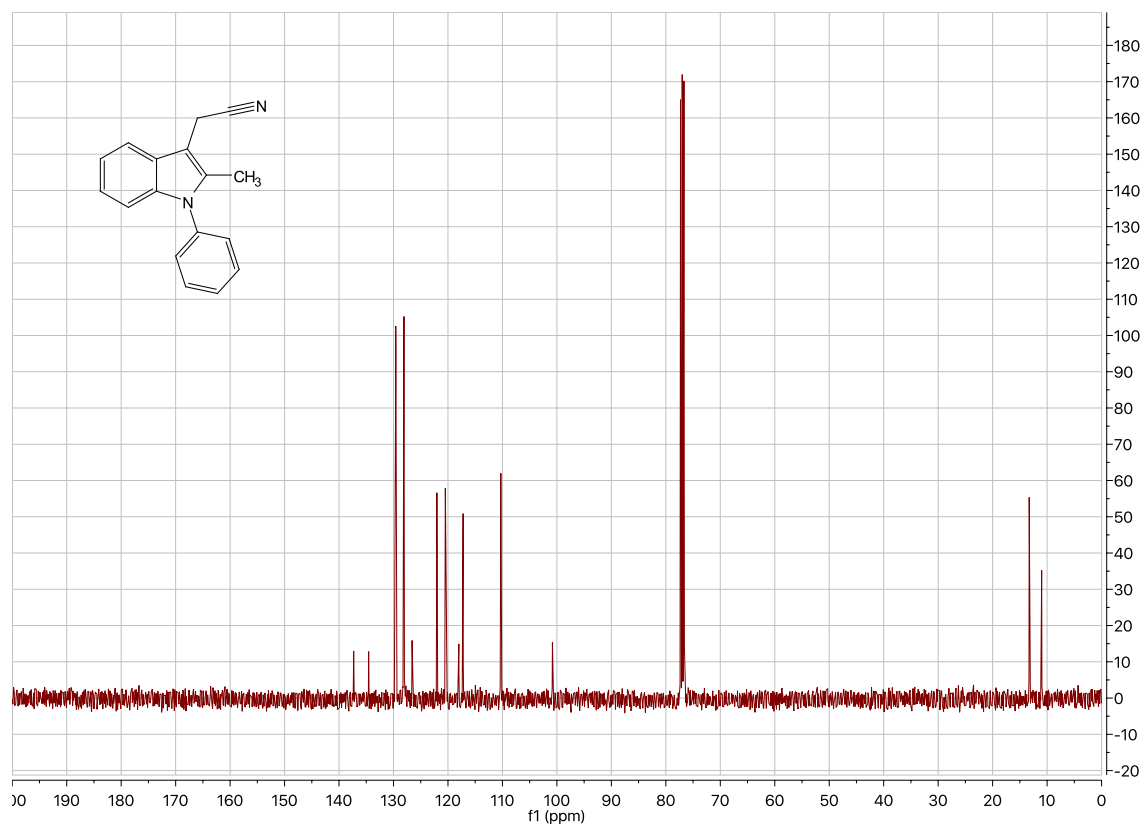


## 2-(2-methyl-1-phenyl-1*H*-indol-3-yl)acetonitrile (10b)

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )

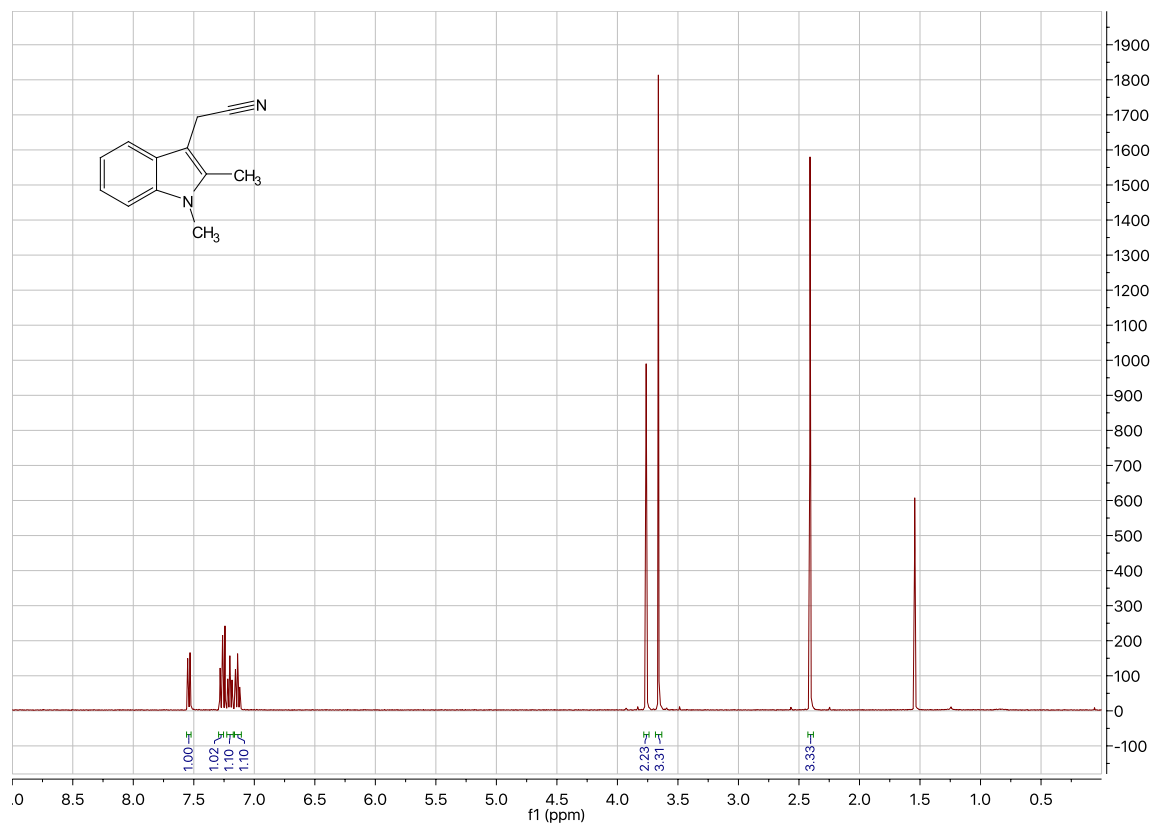


$^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ )

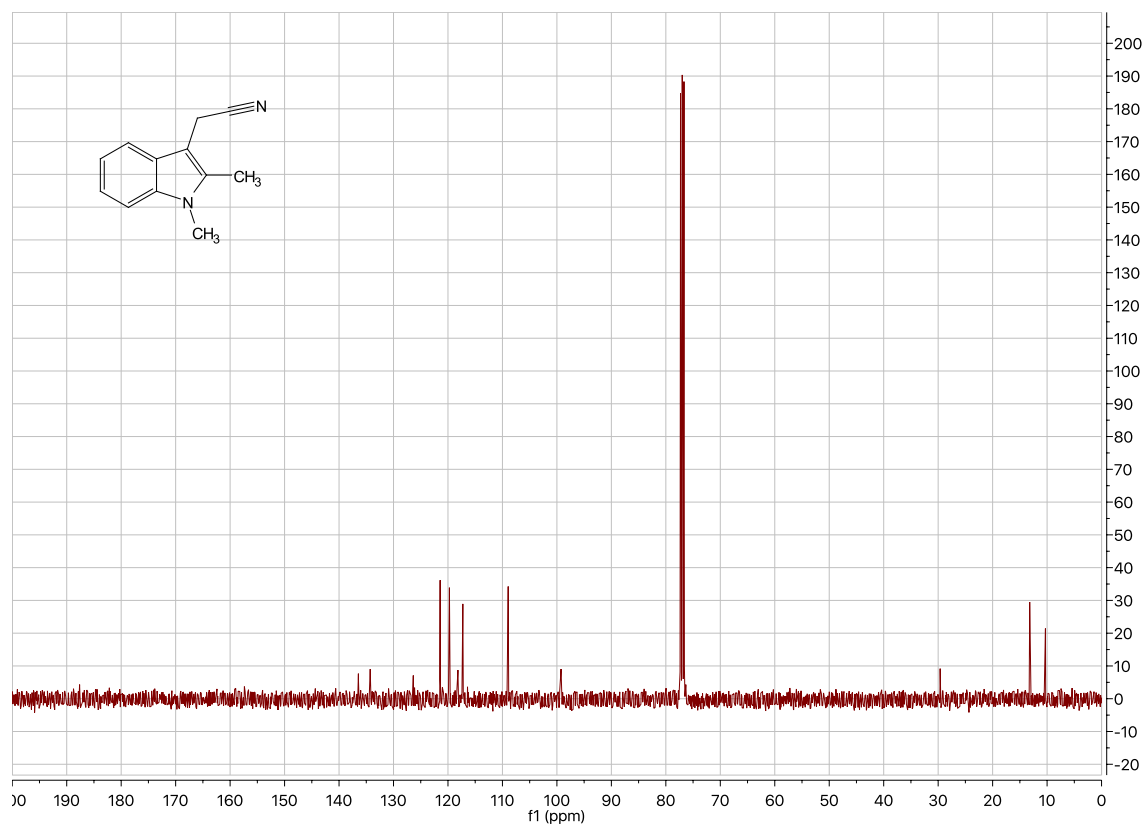


## 2-(1,2-dimethyl-1*H*-indol-3-yl)acetonitrile (10c)

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )

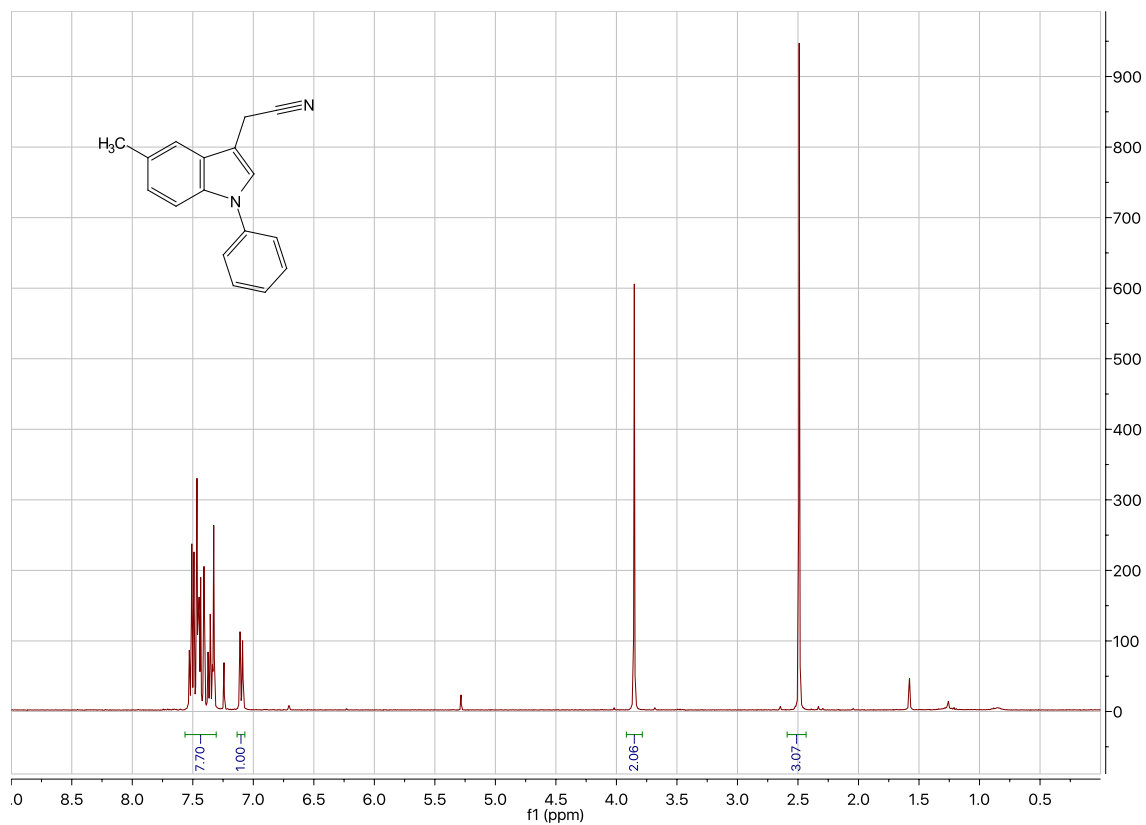


$^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ )

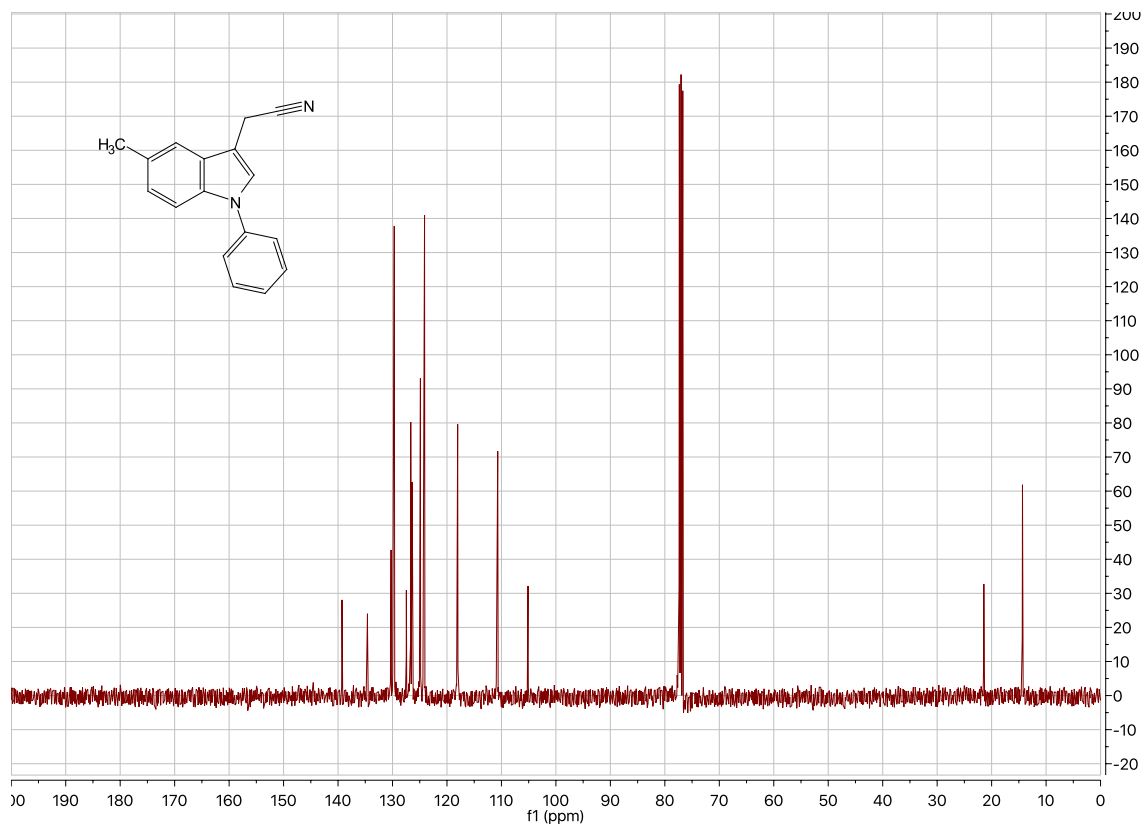


## 2-(5-methyl-1-phenyl-1*H*-indol-3-yl)acetonitrile (10d)

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)

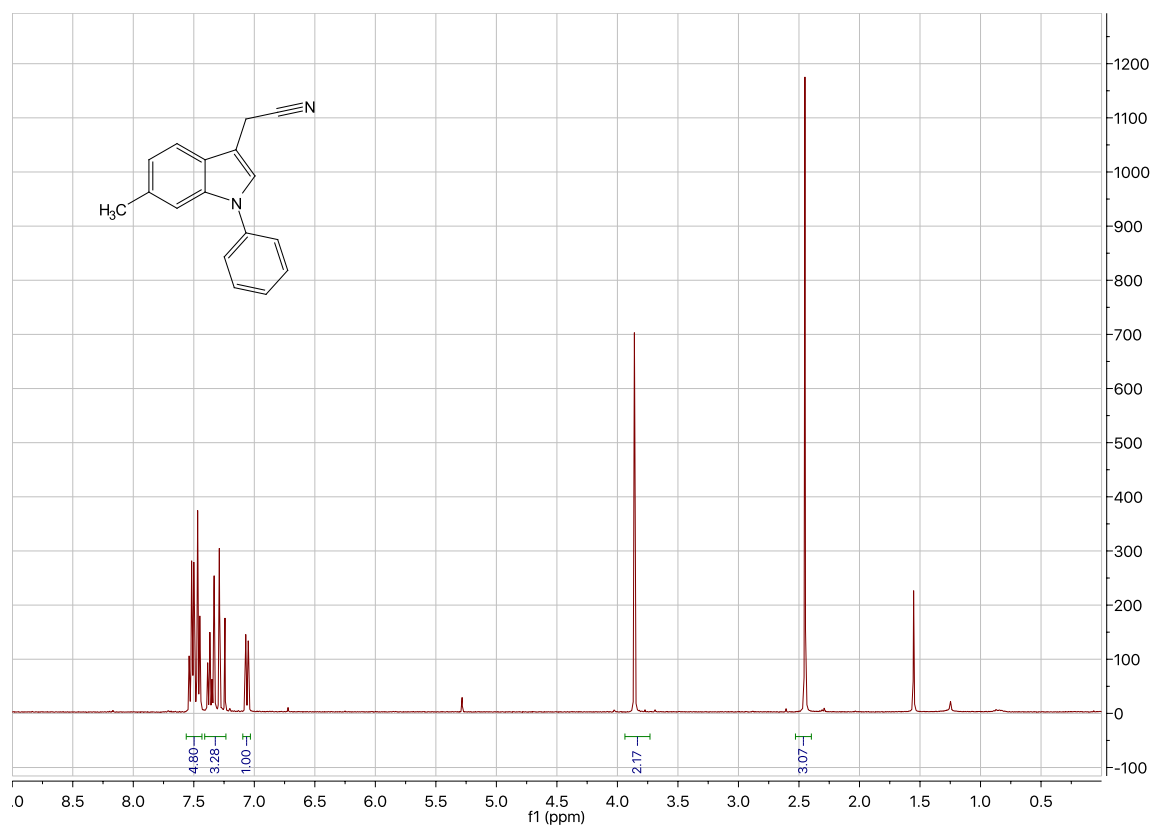


<sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>)

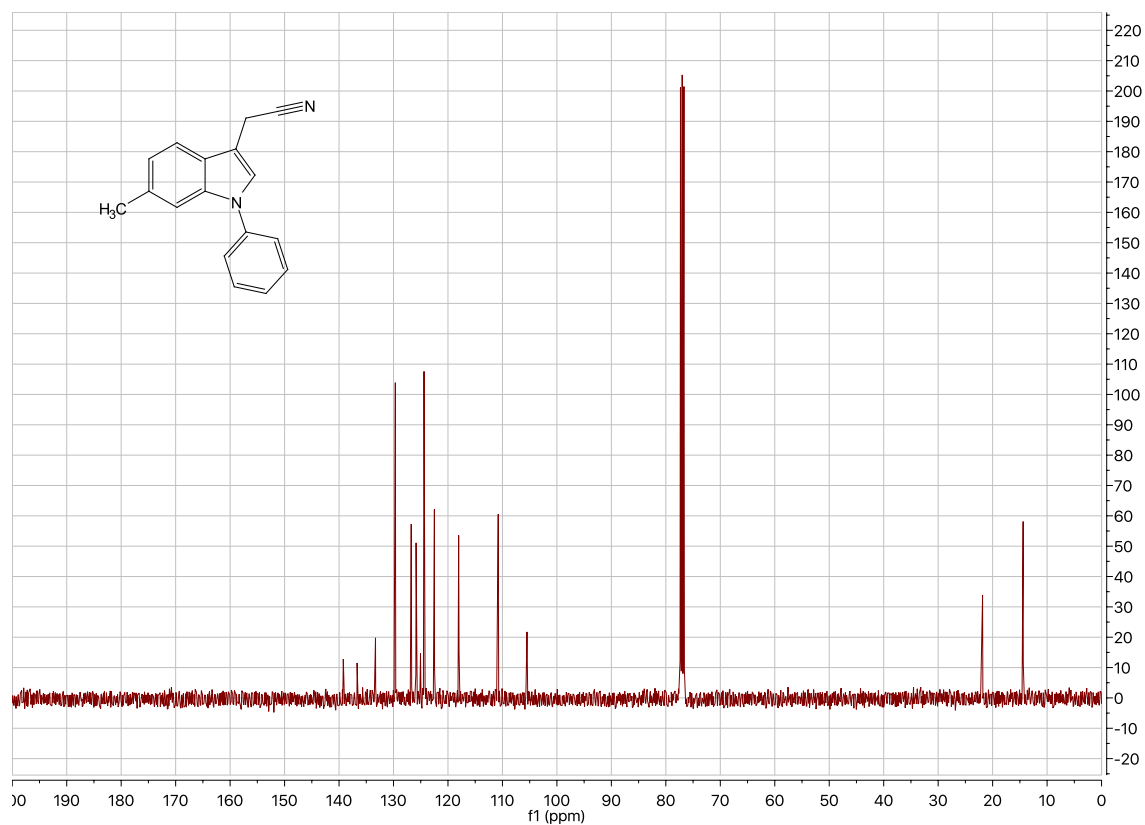


## 2-(6-methyl-1-phenyl-1*H*-indol-3-yl)acetonitrile (10e)

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)

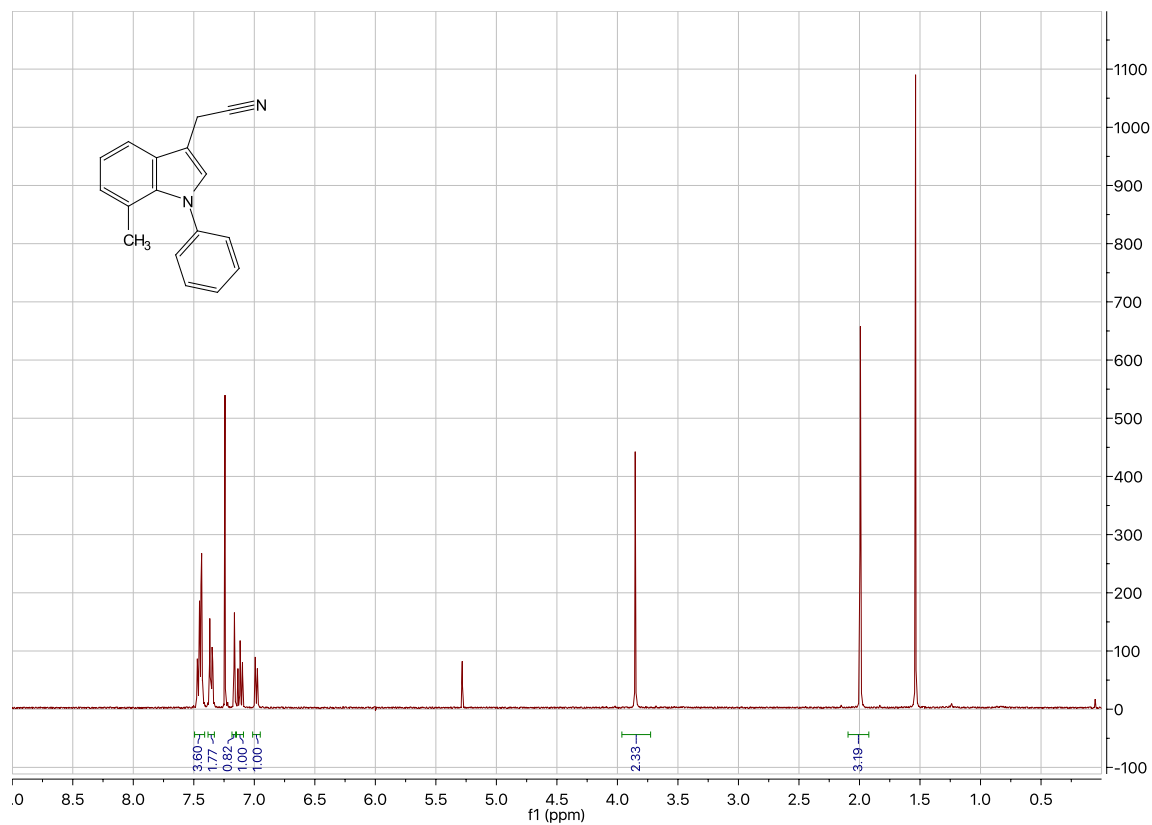


<sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>)

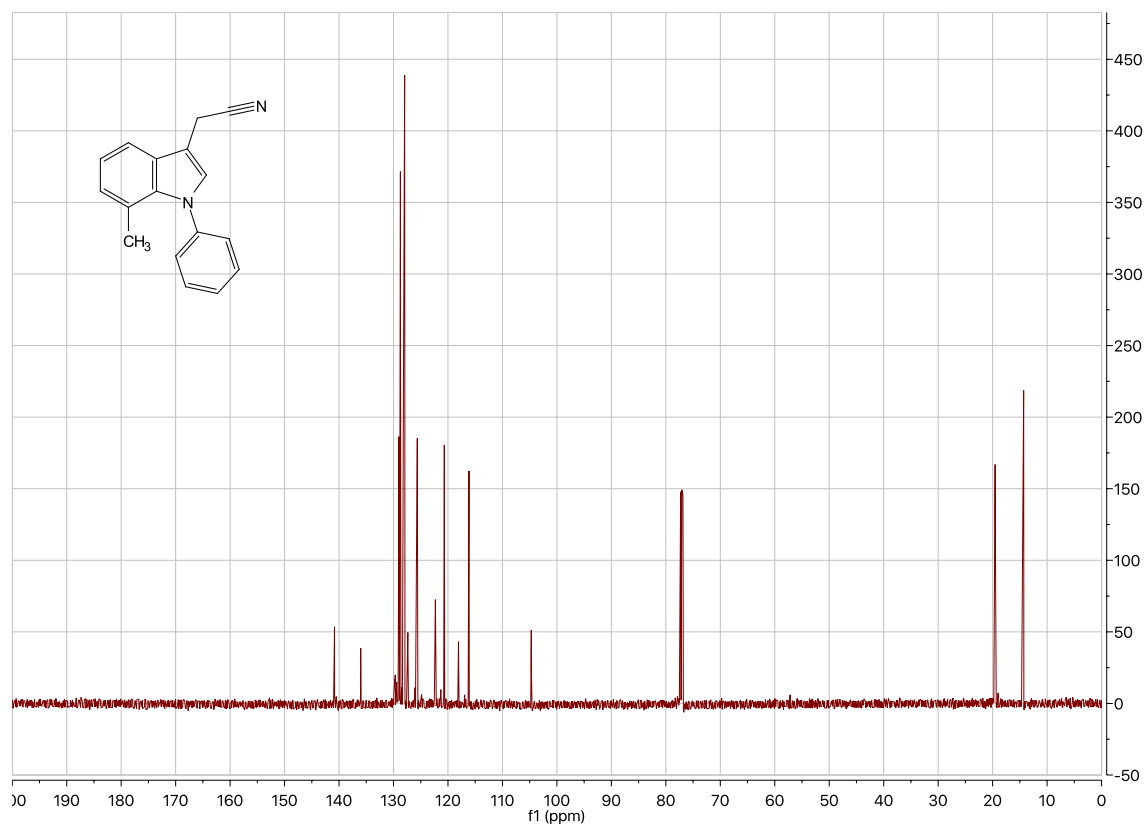


## 2-(7-methyl-1-phenyl-1*H*-indol-3-yl)acetonitrile (10f)

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)

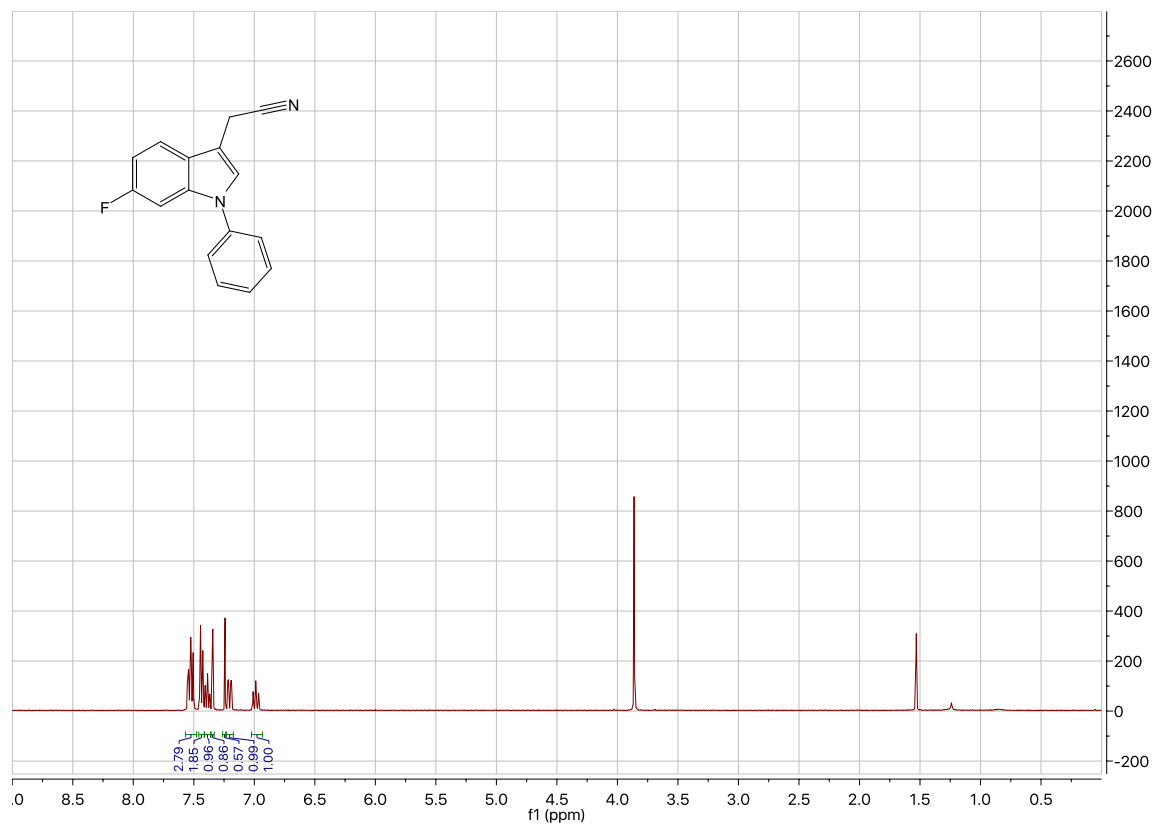


<sup>13</sup>C NMR (151 MHz, CDCl<sub>3</sub>)

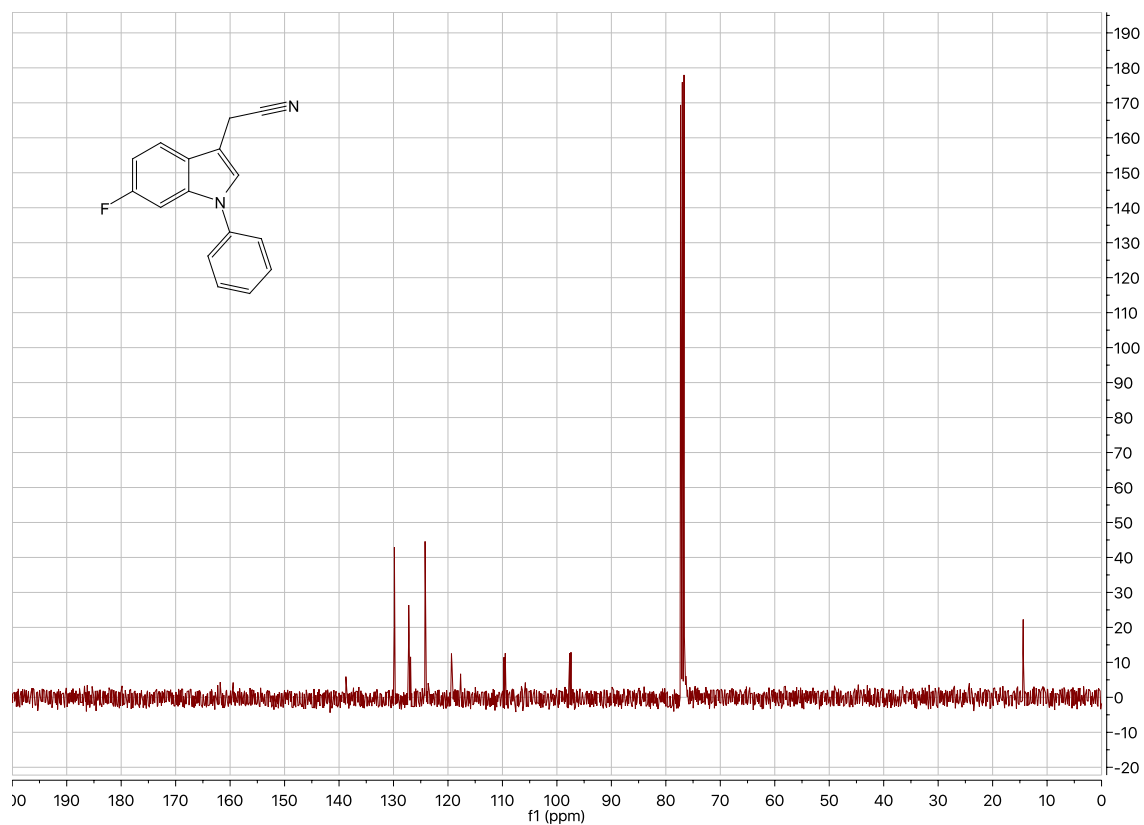


**2-(6-fluoro-1-phenyl-1H-indol-3-yl)acetonitrile (10g)**

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)

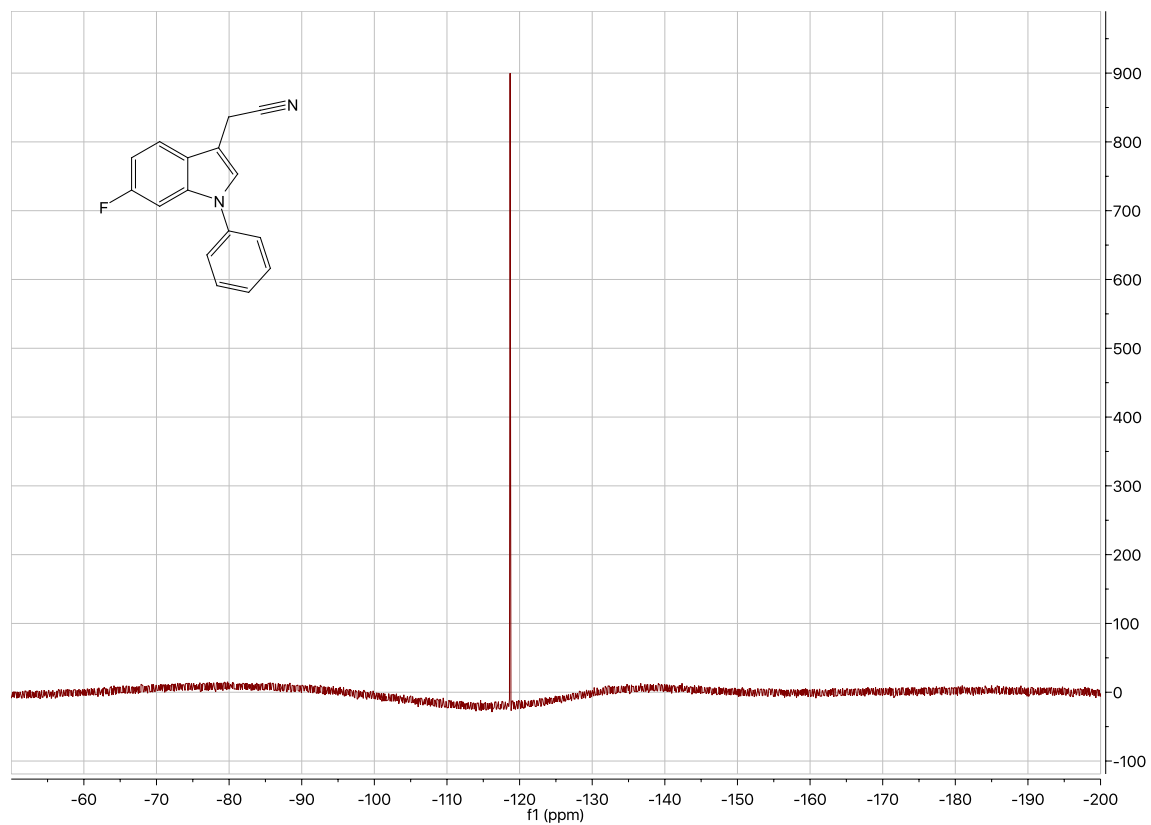


<sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>)



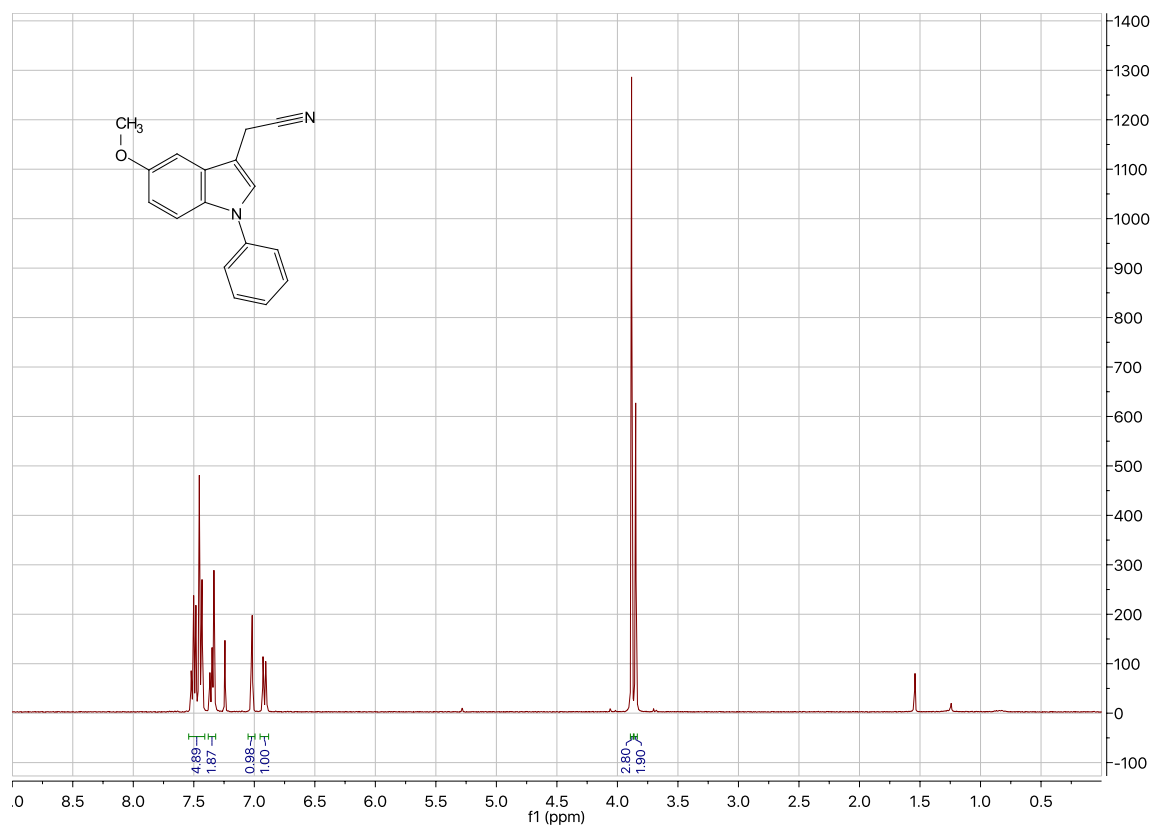


$^{19}\text{F}$  NMR (376 MHz,  $\text{CDCl}_3$ )

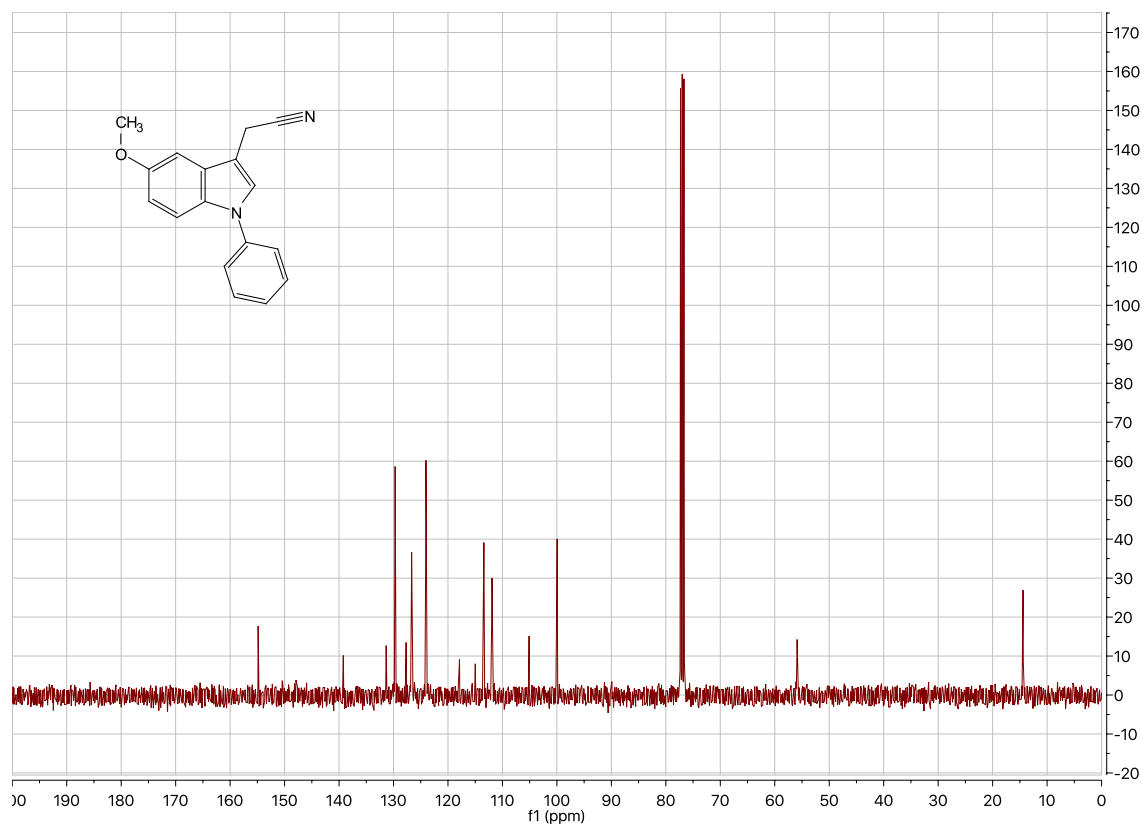


**2-(5-methoxy-1-phenyl-1*H*-indol-3-yl)acetonitrile (10h)**

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)

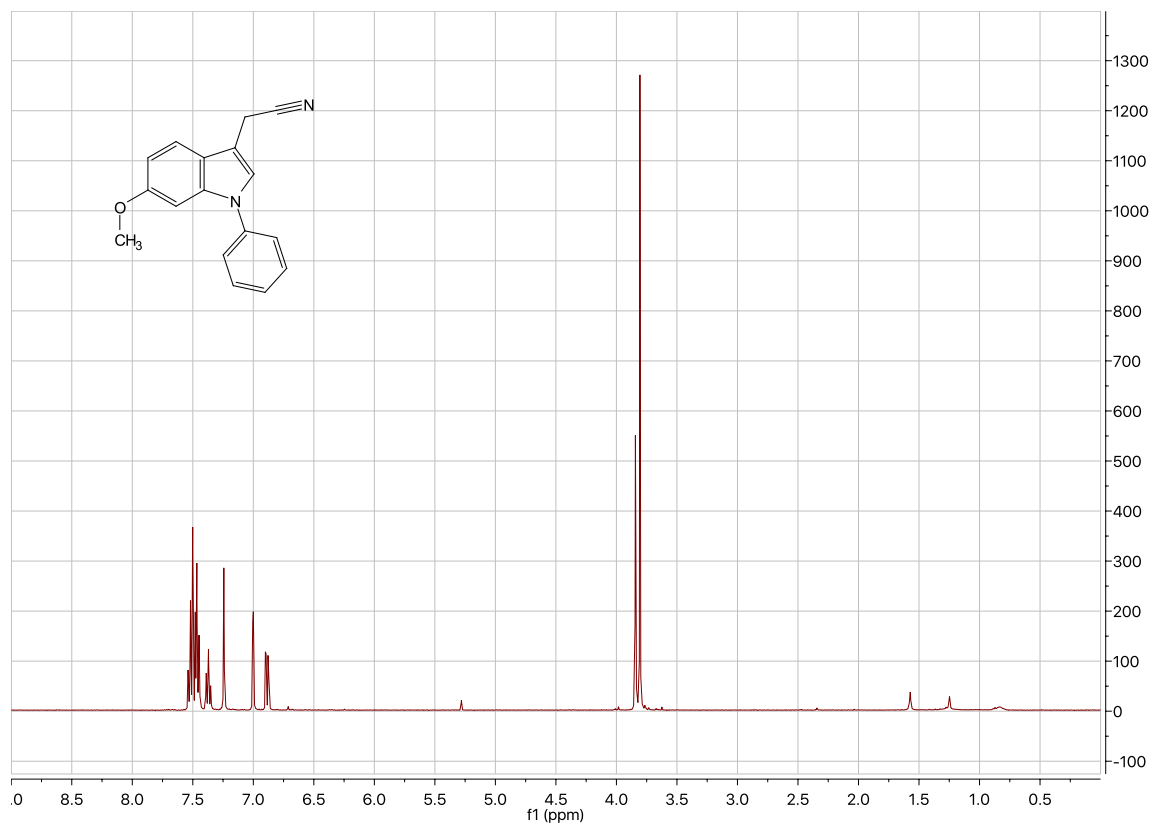


<sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>)

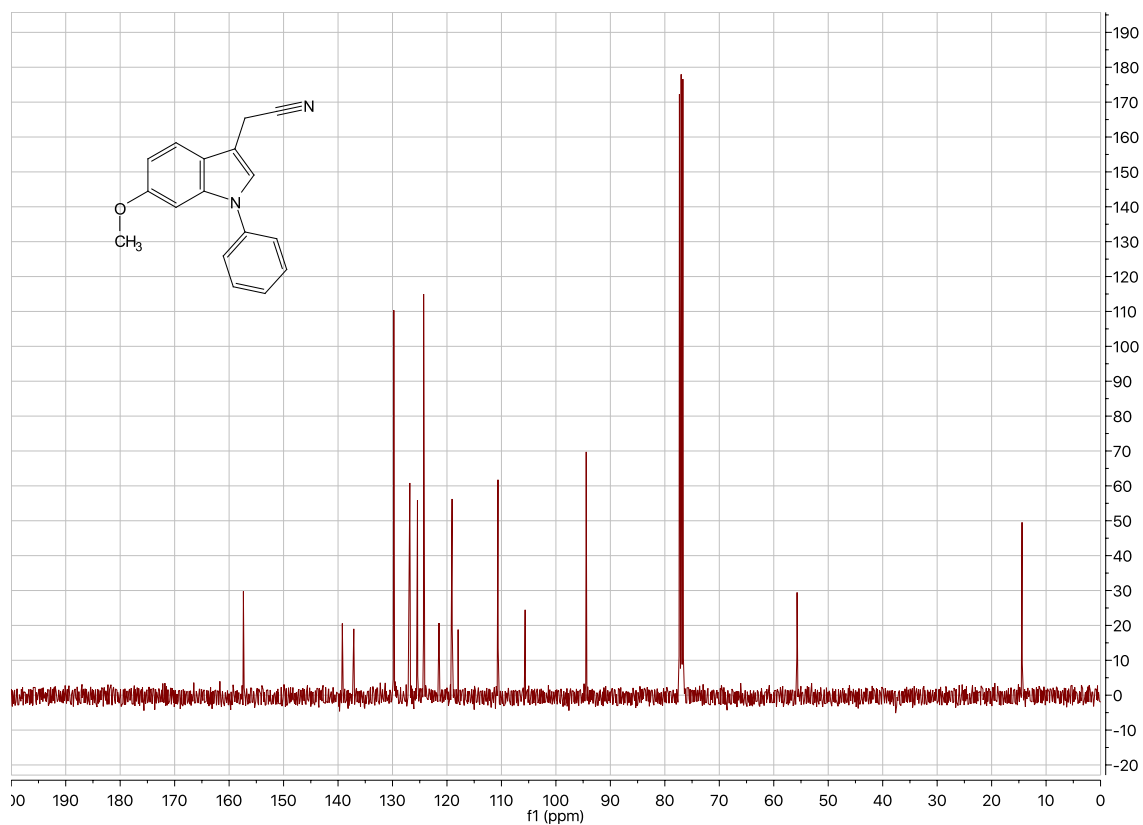


**2-(6-methoxy-1-phenyl-1*H*-indol-3-yl)acetonitrile (10i)**

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)

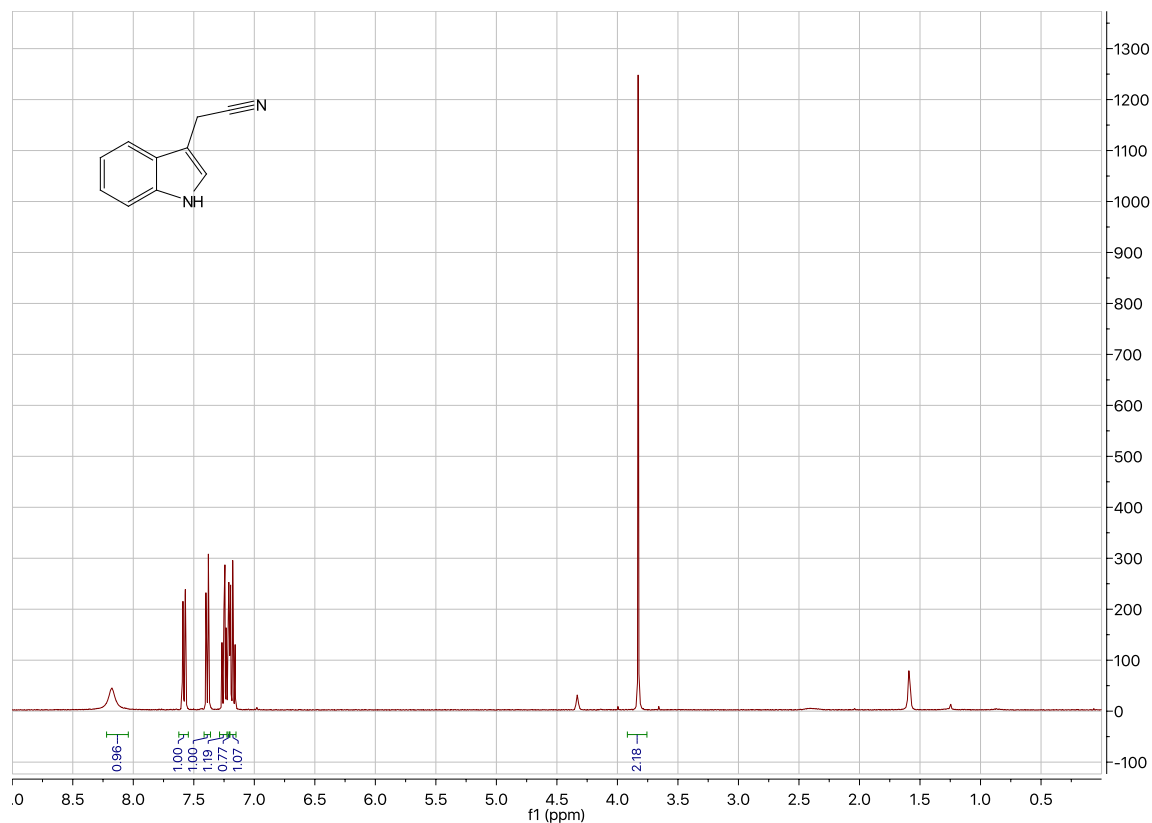


<sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>)

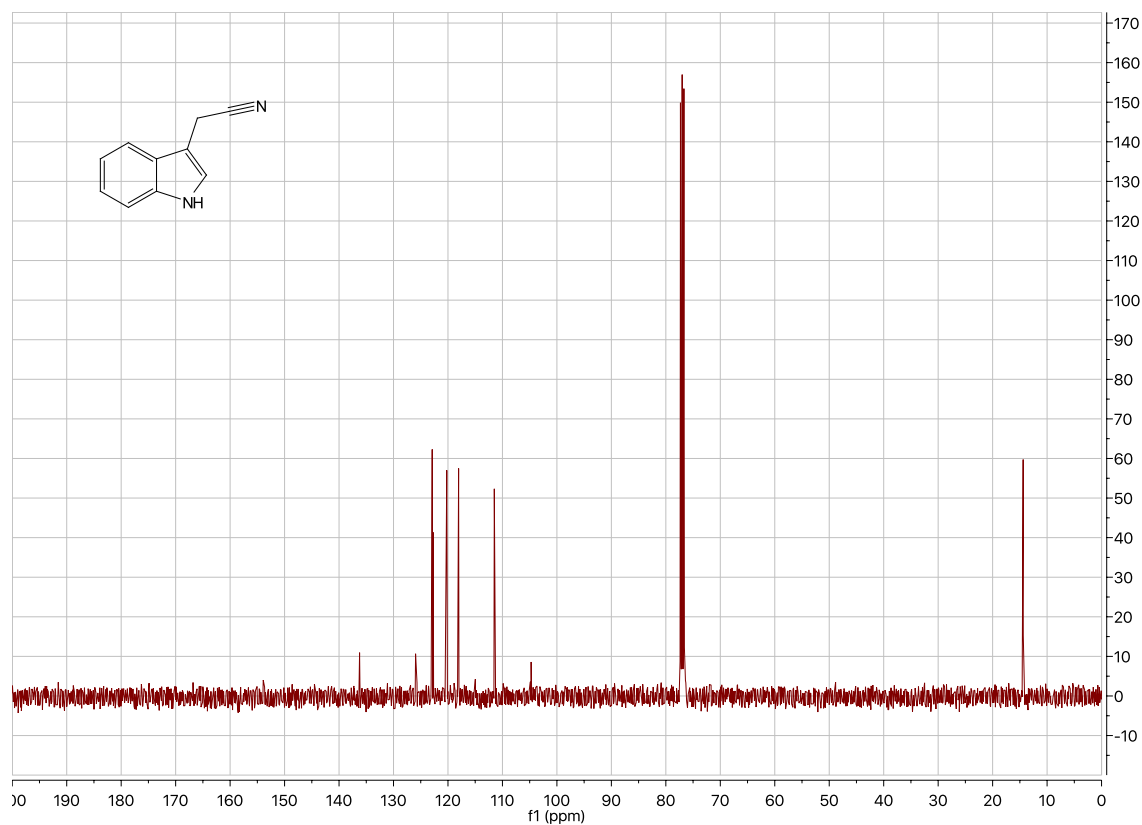


## 2-(1*H*-indol-3-yl)acetonitrile (11a)

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)

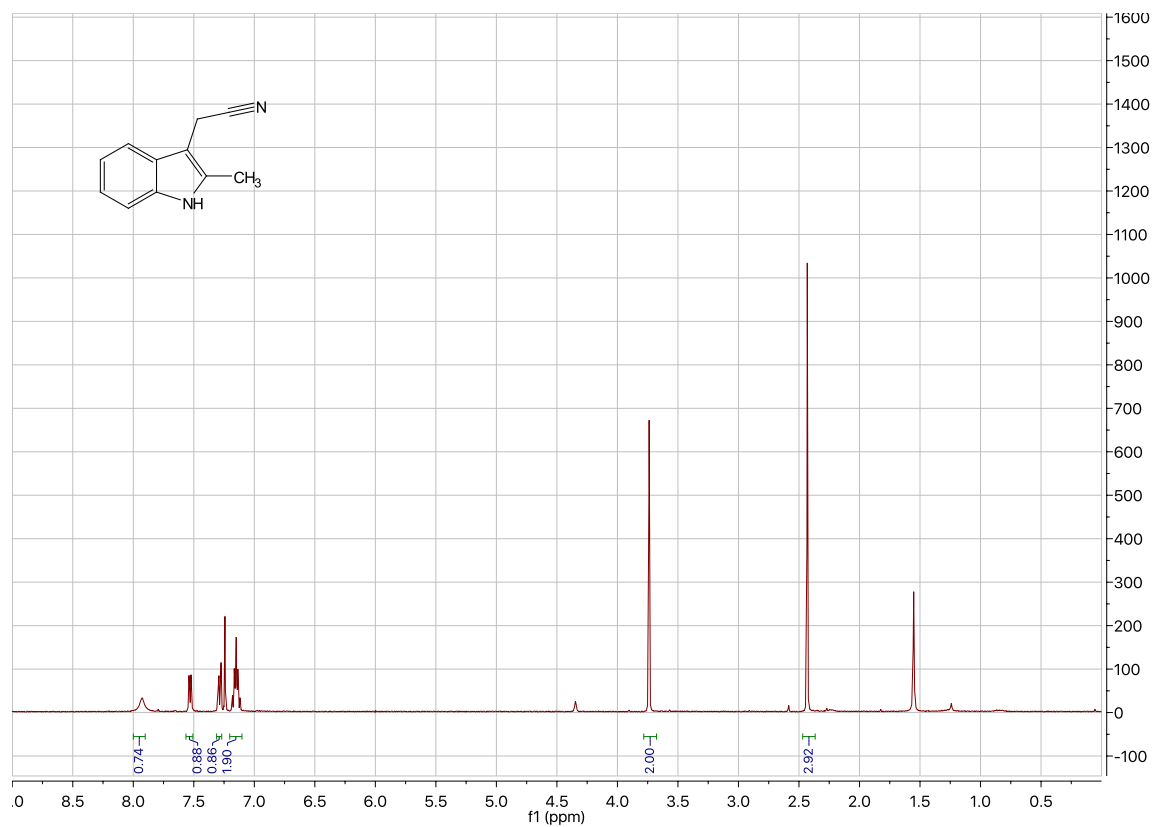


<sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>)

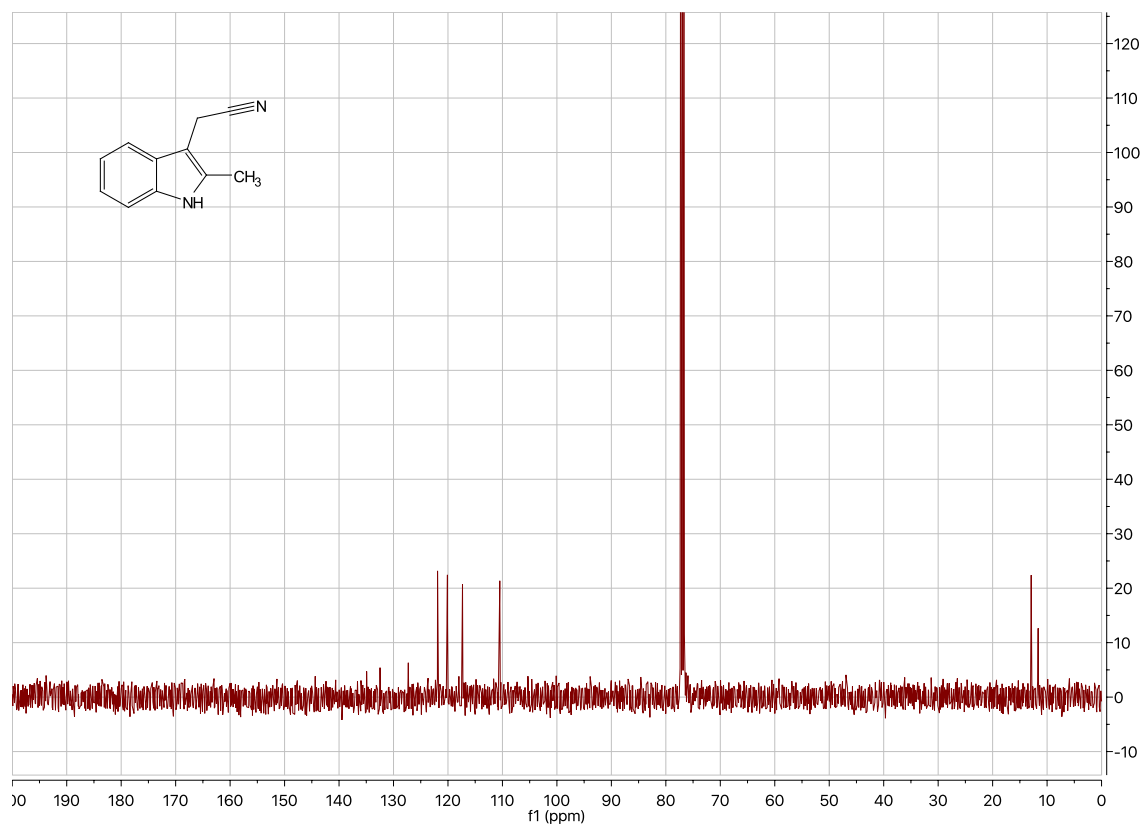


## 2-(2-methyl-1H-indol-3-yl)acetonitrile (11b)

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )

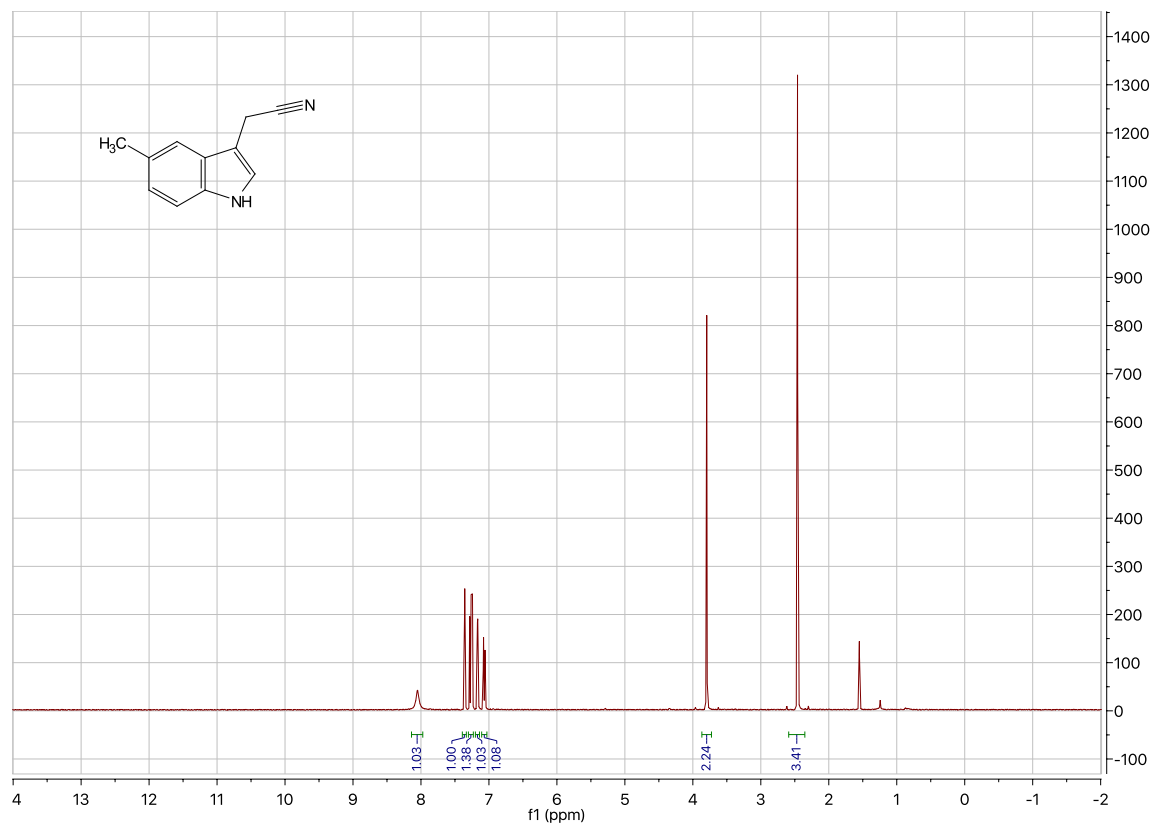


$^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ )

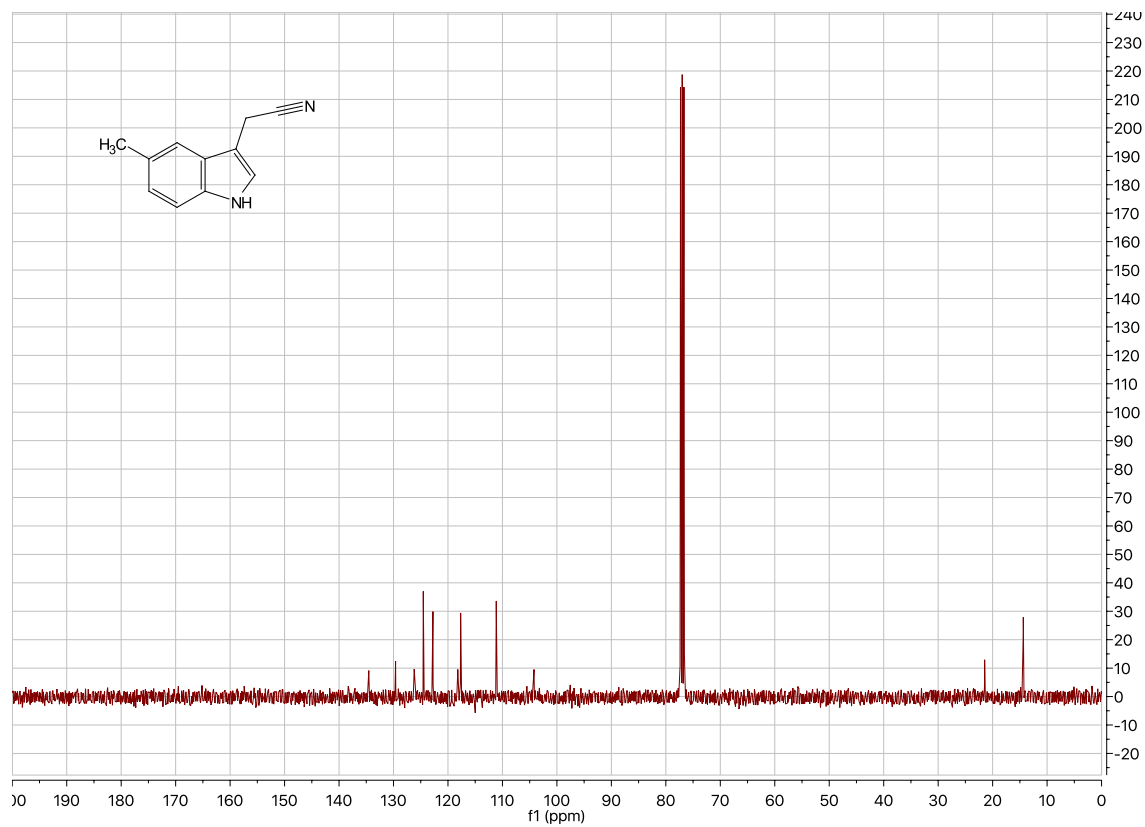


## 2-(5-methyl-1*H*-indol-3-yl)acetonitrile (11c)

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)

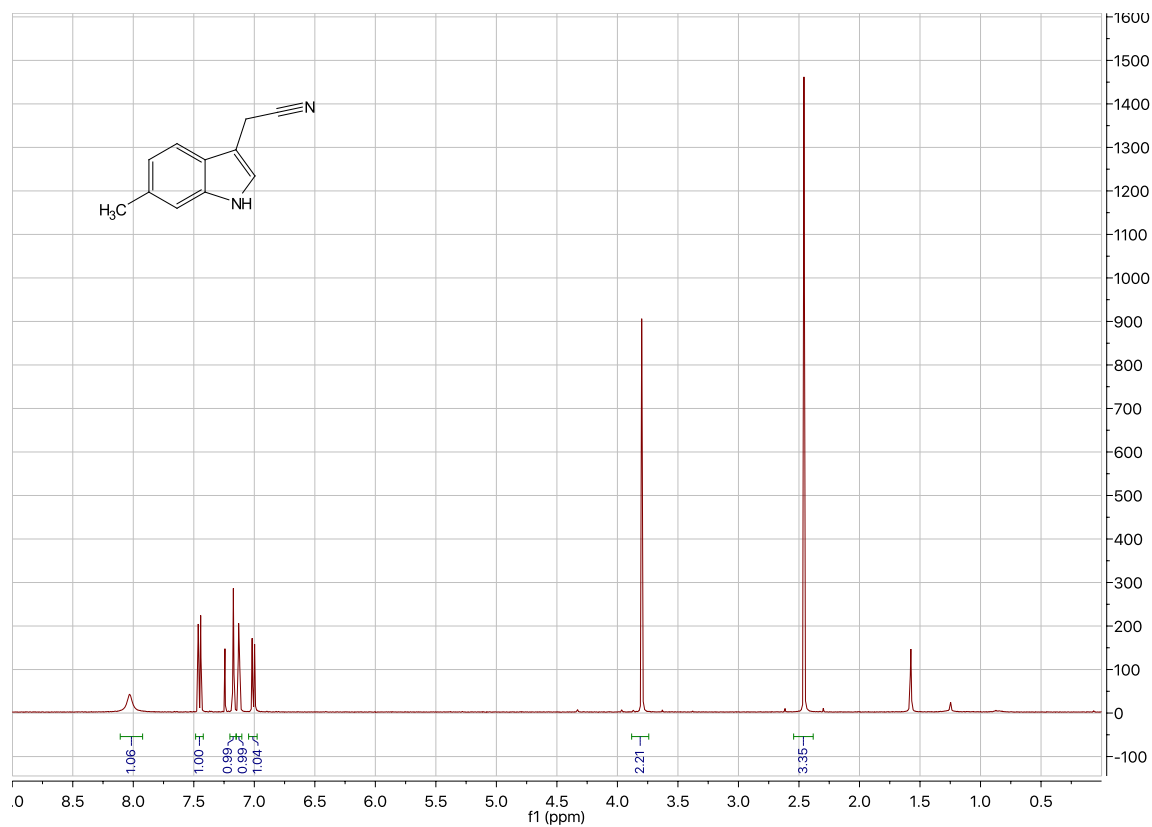


<sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>)

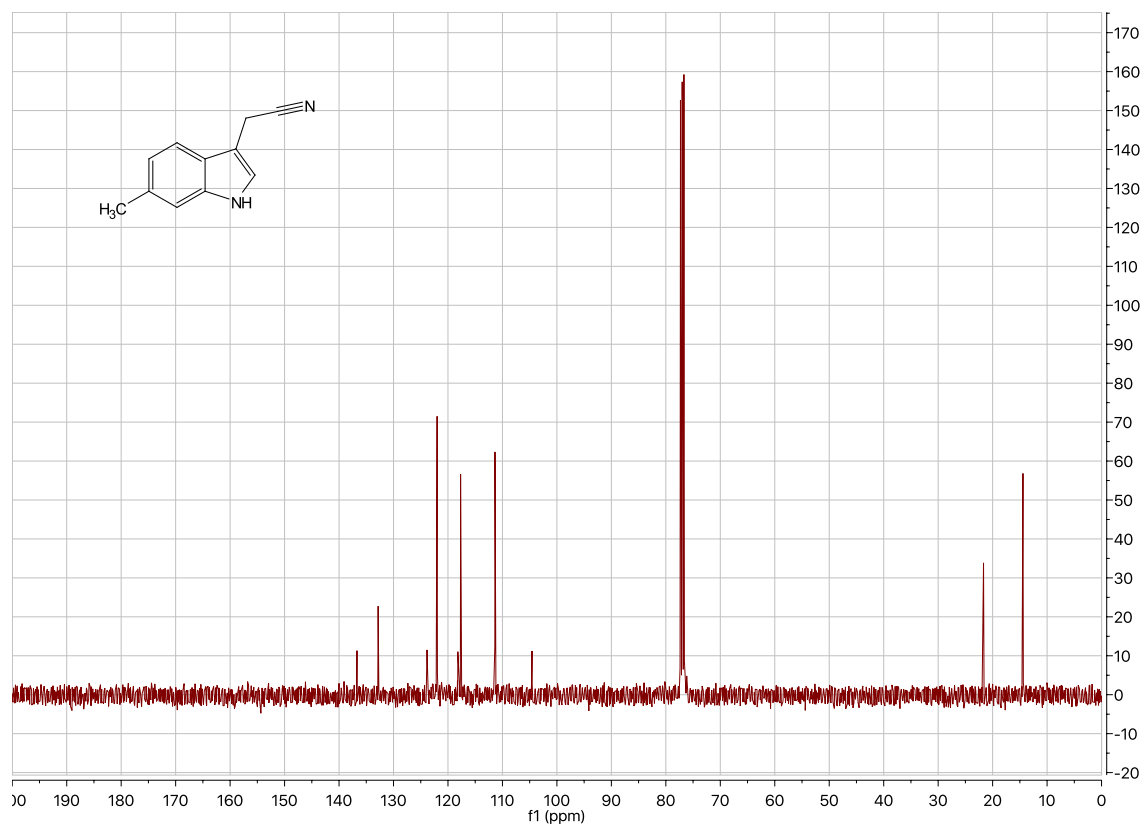


## 2-(6-methyl-1H-indol-3-yl)acetonitrile (11d)

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )

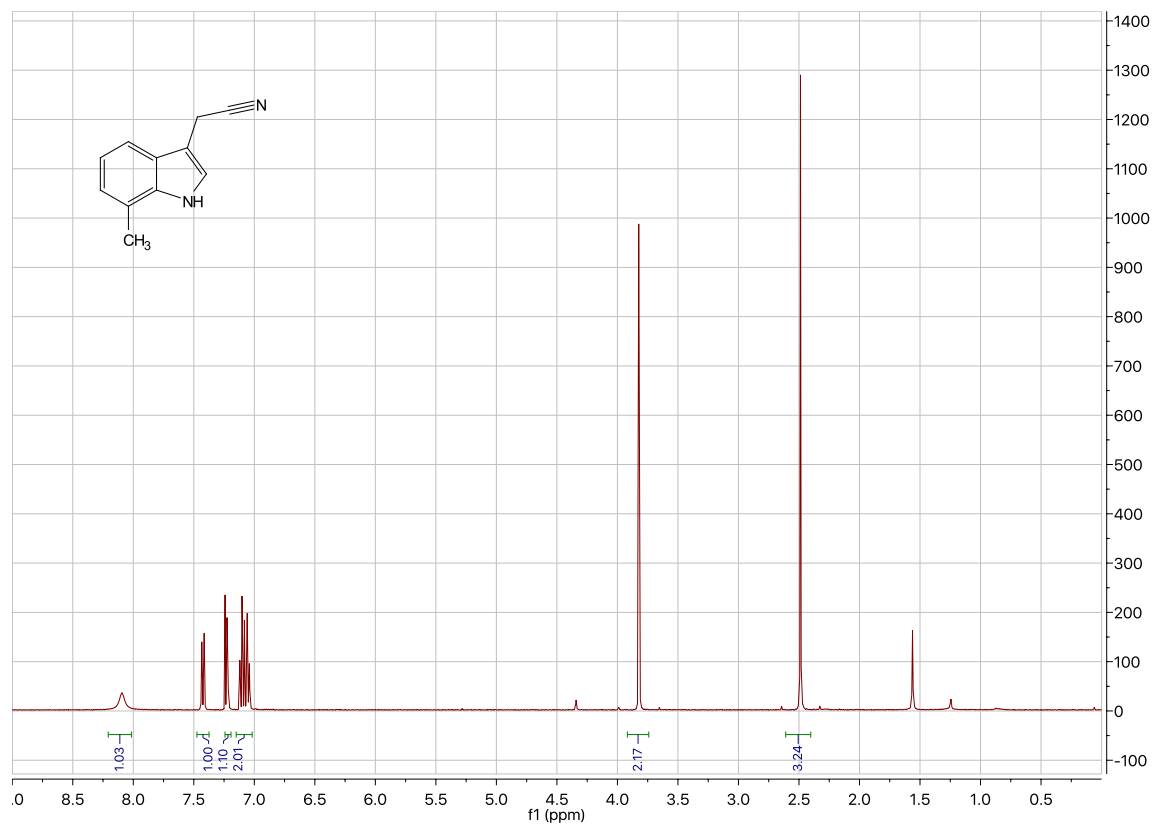


$^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ )

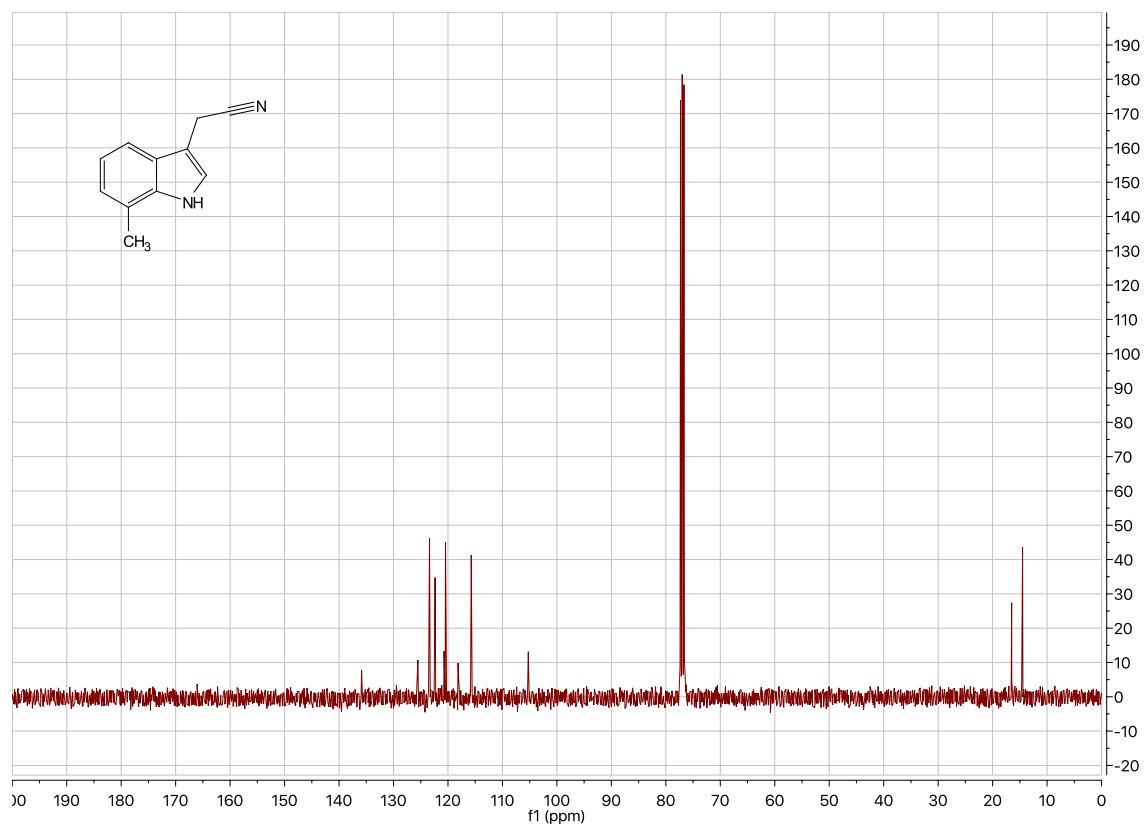


## 2-(7-methyl-1H-indol-3-yl)acetonitrile (11e)

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )



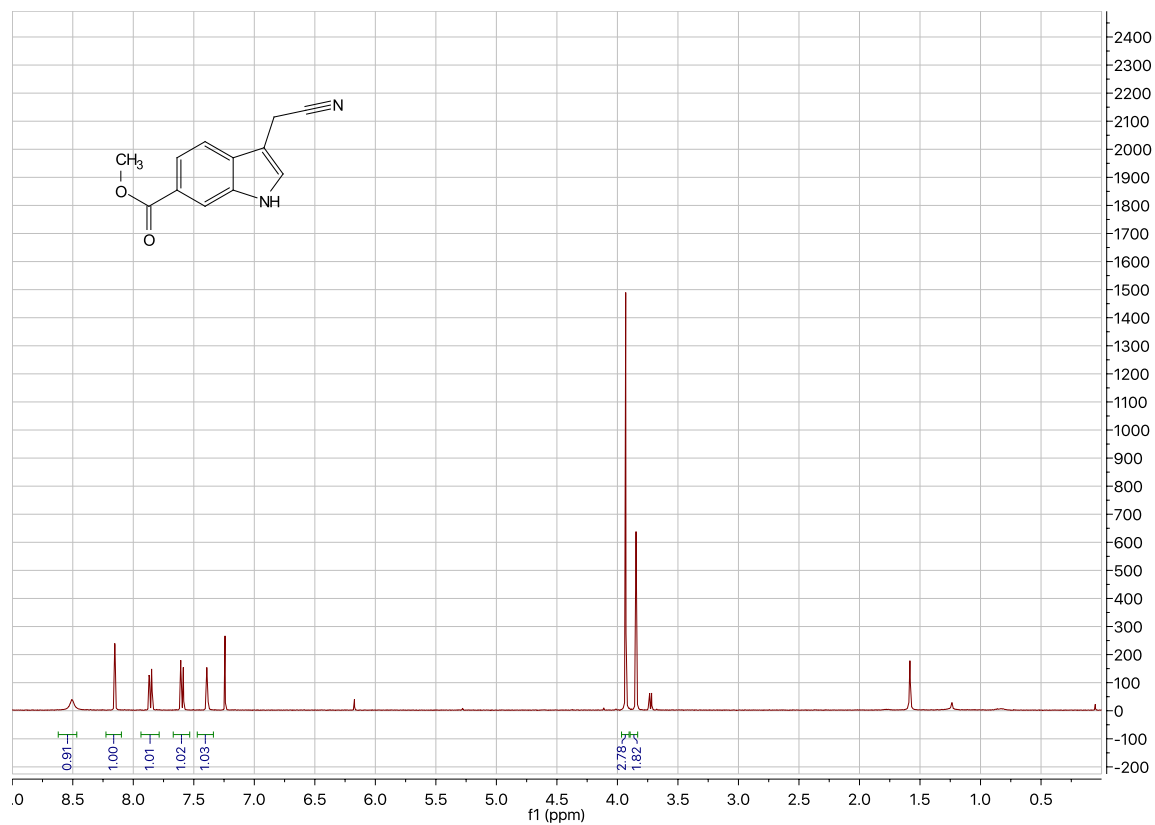
$^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ )



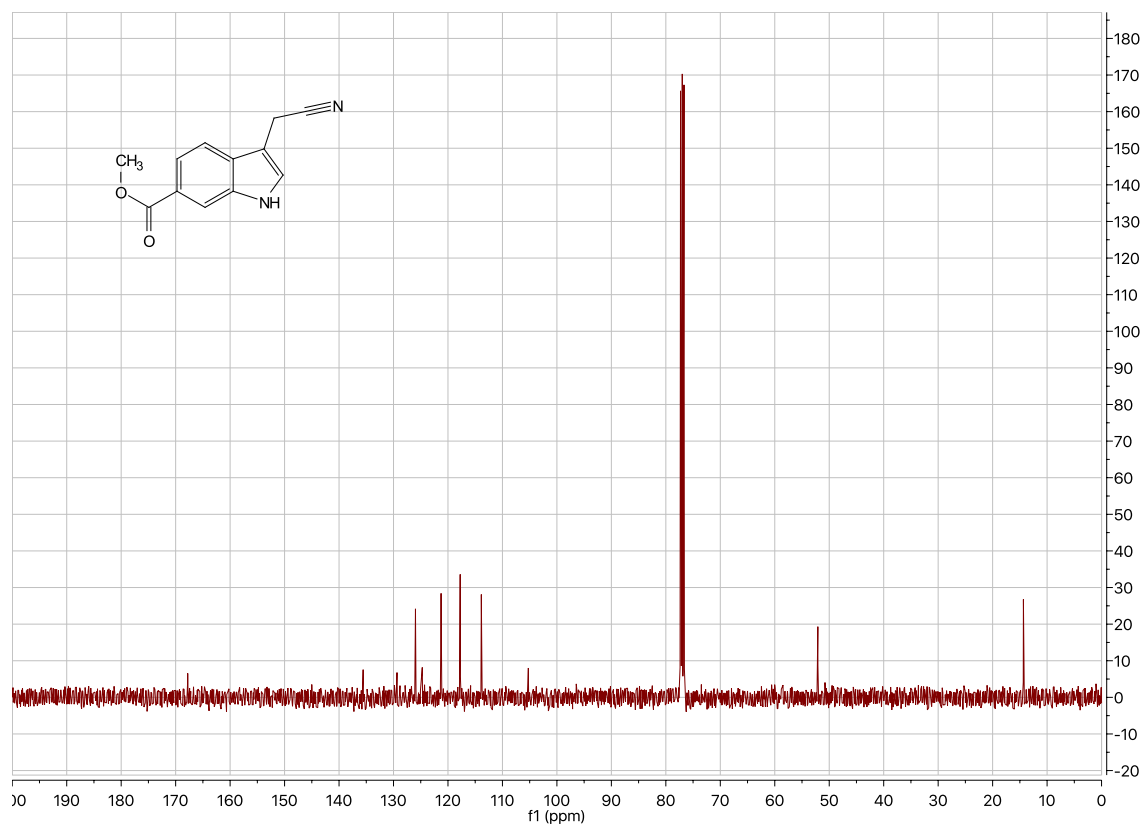


**methyl 3-(cyanomethyl)-1*H*-indole-6-carboxylate (11f)**

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)

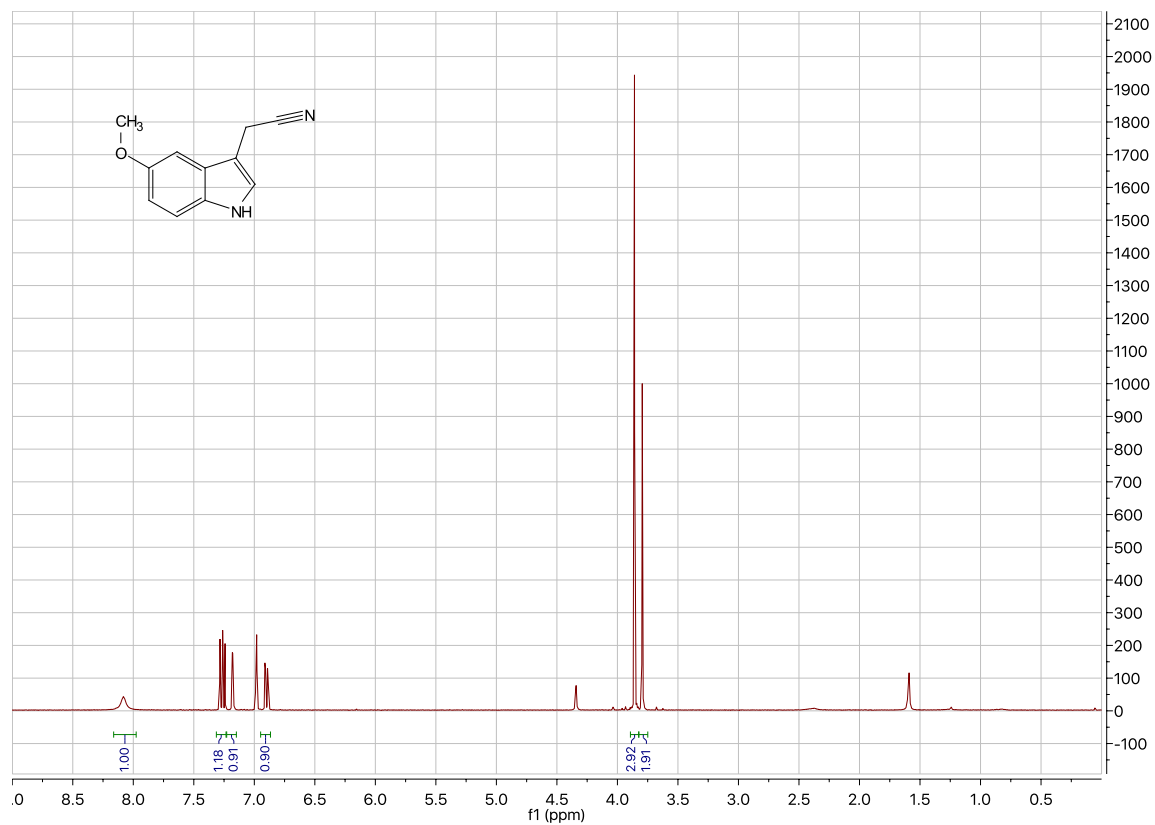


<sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>)

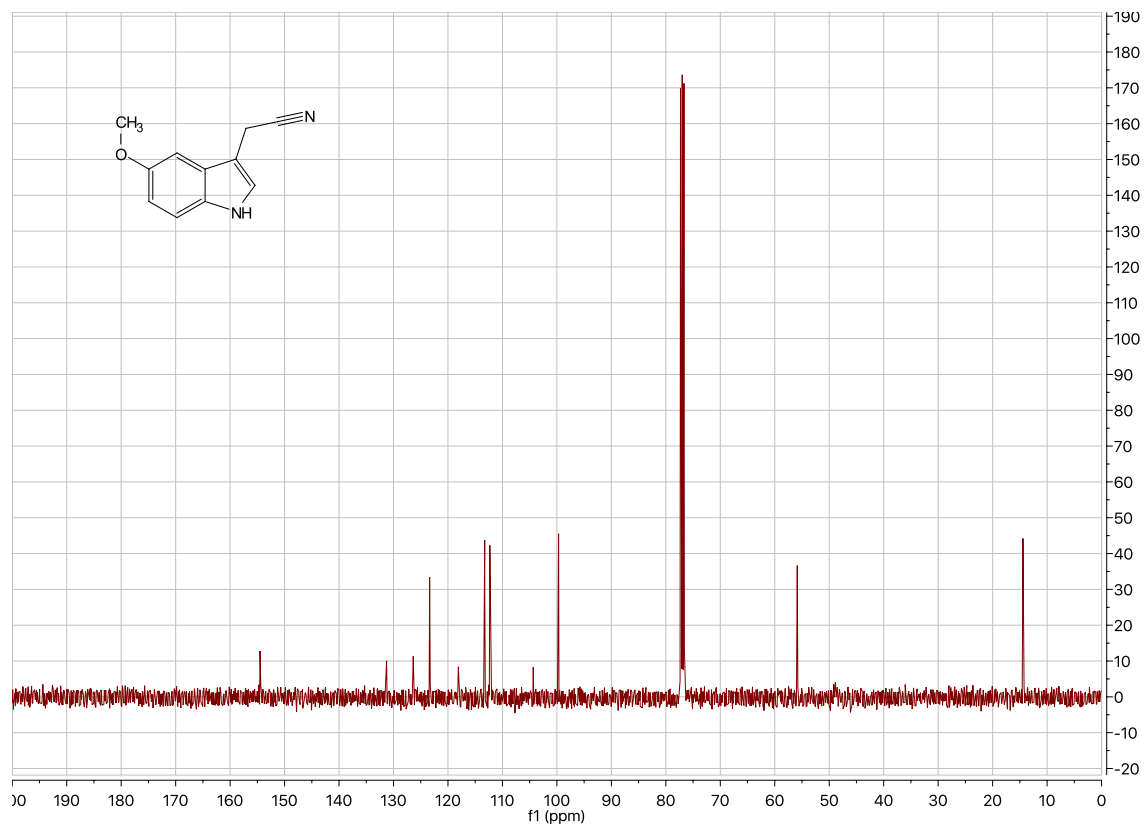


## 2-(5-methoxy-1H-indol-3-yl)acetonitrile (11g)

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )

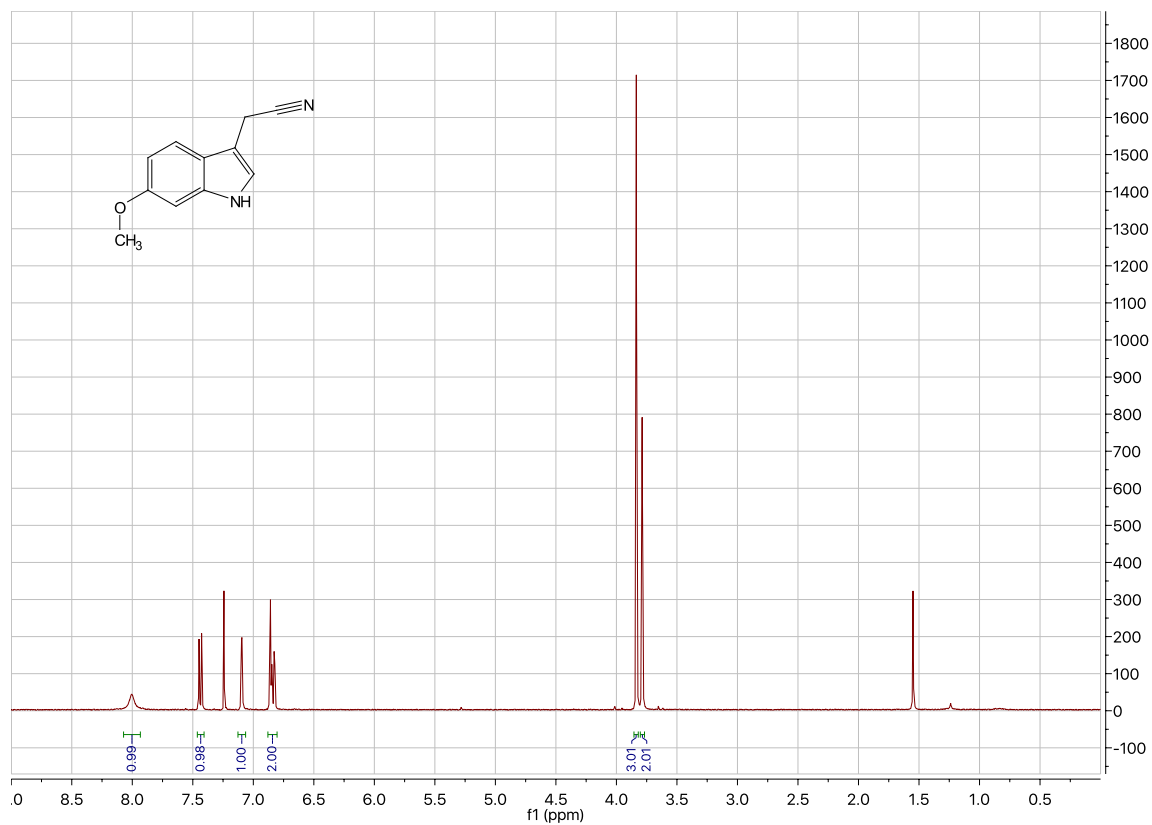


$^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ )

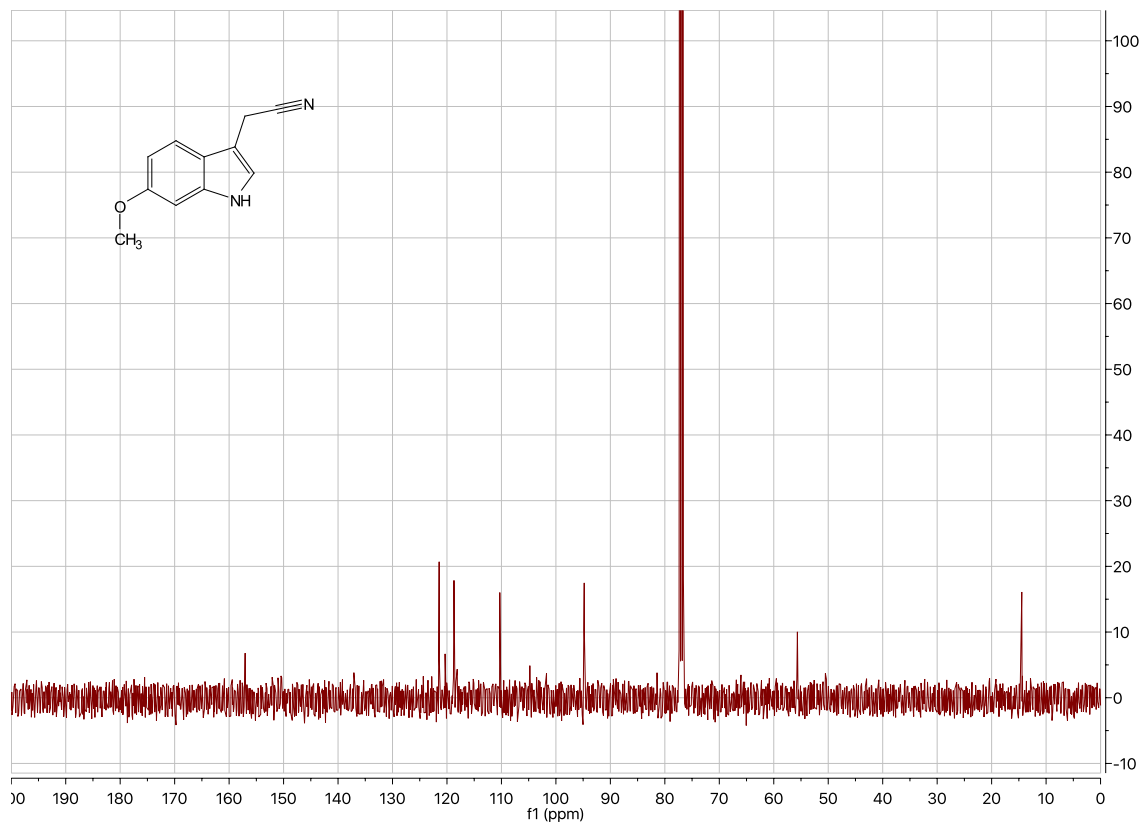


## 2-(6-methoxy-1H-indol-3-yl)acetonitrile (11h)

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )

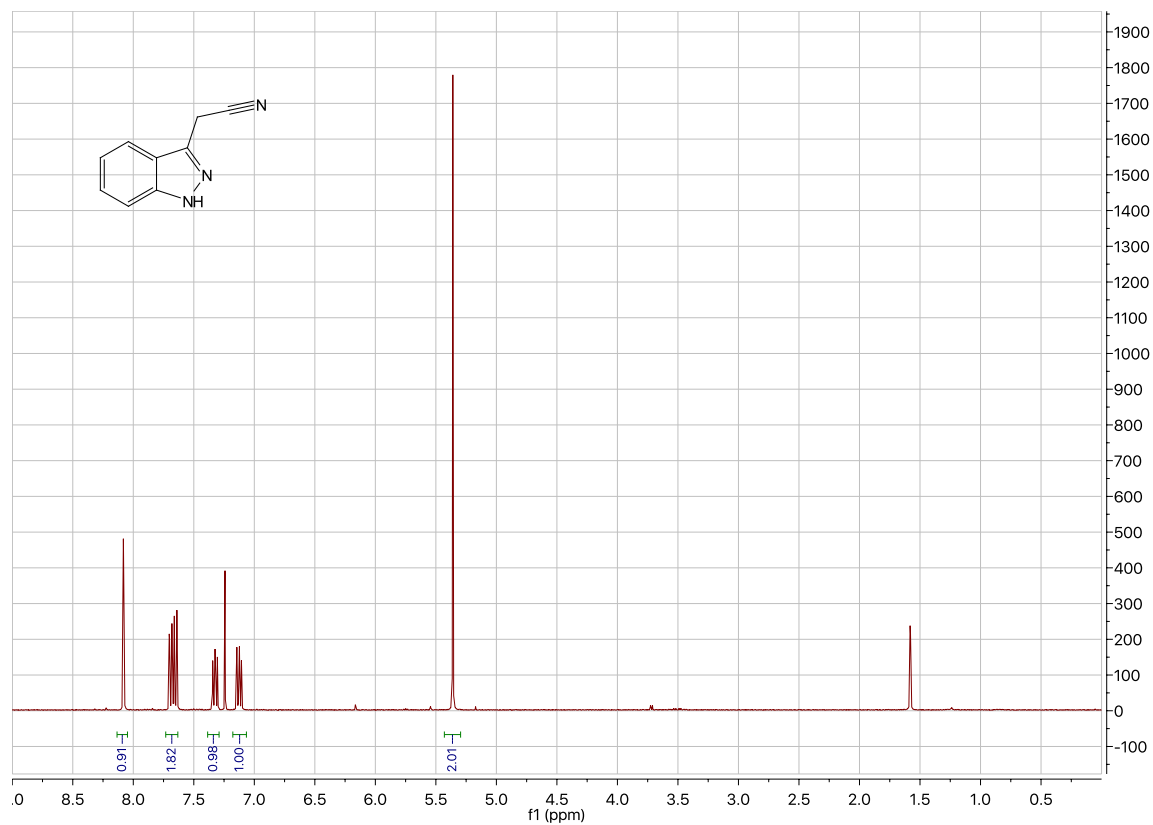


$^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ )

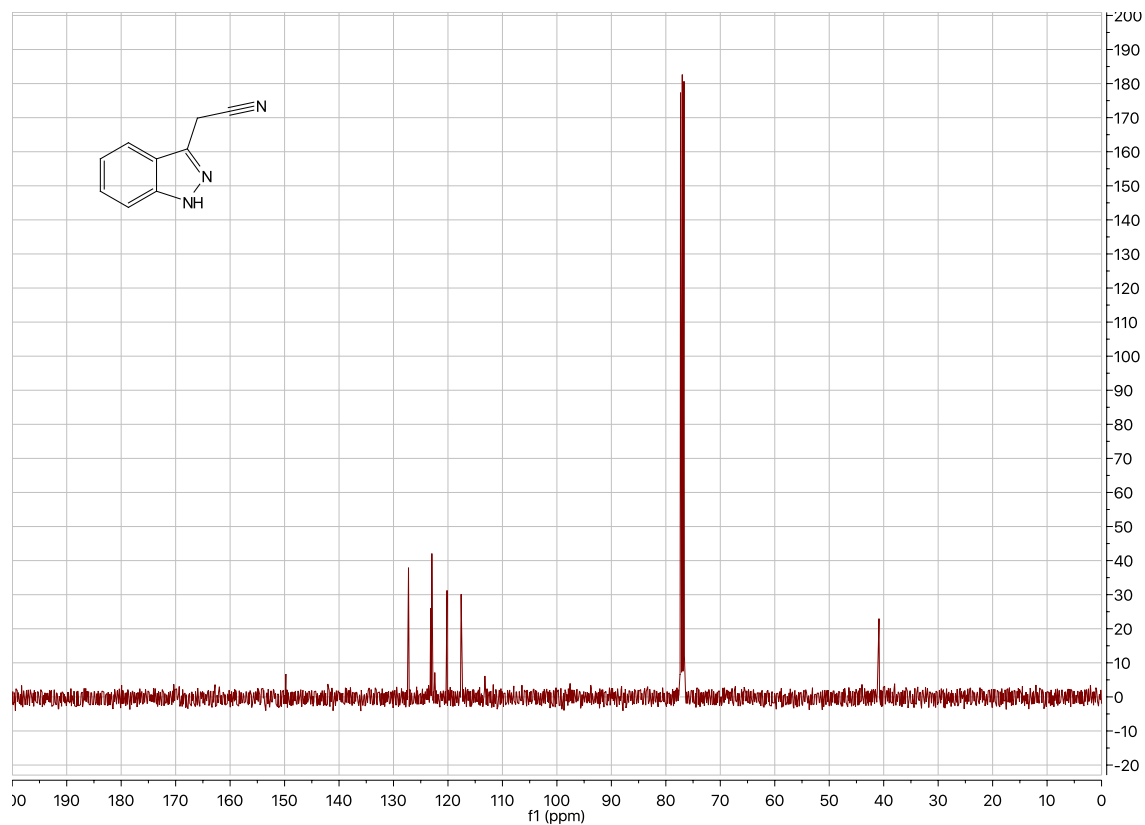


## 2-(1*H*-indazol-3-yl)acetonitrile (12)

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)



<sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>)



Sl.pdf (6.01 MiB)

[view on ChemRxiv](#) • [download file](#)

---