Supporting Information:

Pd/Cu-free Magnetic Cobalt Catalyst for C-N cross Coupling Reactions: Synthesis of Abemaciclib and Fedratinib

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Experimental

2.1. General remarks

All the chemicals used were bought from Aldrich Chemical Company or Merck. The ^{1}H and ^{13}C NMR spectra were documented in $CDCl_3$ on Bruker Avance, 400 MHz and 100 MHz respectively. The Perkin-Elmer FT-IR spectrophotometer was applied for recording the FT-IR spectra. Transmission Electron Micrographs (TEM) were gotten using Philips CM-200. SEM images were recorded using FE-SEM JSM-7600F. A Bruker AXSDB Xray diffractometer using Cu Kα radiations was used to record the X-ray diffractogram (XRD) were recorded in 2 theta range of 10-80°.

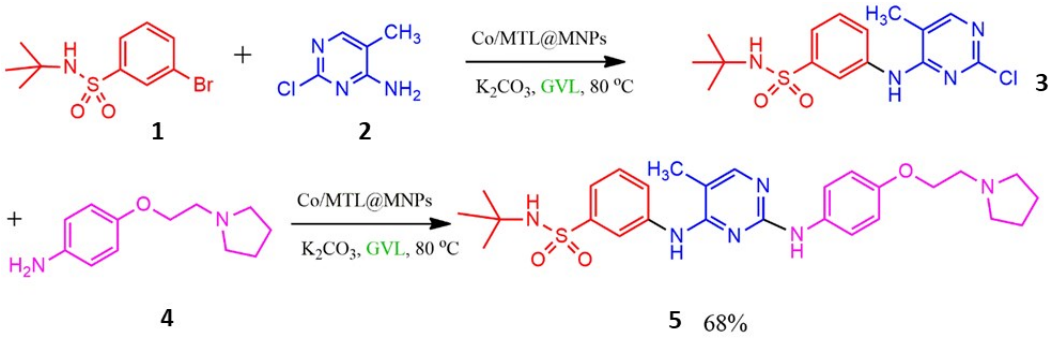
2.2. Synthesis of catalyst

For the synthesis of magnetic nanoparticles, ammonical solution (30 mL, 24 mL water and 6 mL NH_4OH) of $FeSO_4$ (2.4 g) and $Fe_2(SO_4)_3$ (7 g) was dispersed in deionized water (50 mL) and ultrasonicated for 30 min to get a stable ferrofluid. The obtained magnetic nanoparticles (MNPs) were filtered, washed with deionized water (3×10 mL), methylene chloride (3×10 mL) and dried under vacuum. For the coating of various edible natural ligands (mannitol, sorbitol, xylitol, tartaric acid, malic acid and citric acid) over the surface of MNPs, the mixture of MNPs and ligand (0.2 g) was stirred in deionized water (10 mL) at 60 °C for 7 h. Brown precipitates of ligand@MNPs were separated magnetically, washed with deionized water (3×10 mL) and dried under vacuum. Finally, for the immobilization of cobalt species onto ligand@MNPs, $CoCl_2.6H_2O$ (0.2 g) solvated on ethanol were added into the dispersed solution of ligand@MNPs (1 g) in ethanol (10 mL) and stirred for 3 h at room temperature. The Co-ligand@MNPs was separated magnetically and washed successively with ethanol (3×25 mL) and deionized water (3×25 mL). Finally, it was dried under vacuum at room temperature to get the final catalyst as dark brown powder.

2.3. General procedure for the C-N cross-coupling reaction catalyzed by Co-MTL@MNPs

A mixture of aryl halide (1 mmol), amine (1.2 mmol), K_2CO_3 (4 eq.) and Co-MTL@MNPs (10 mg, 0.22 mol% Co); mannitol was identified as the best ligand) in gamma-valerolactone (GVL) (5 mL) was stirred in a round bottom flask (50 mL) at room temperature till the completion of reaction (monitored by TLC). After that, the catalyst was removed via external magnet and washed with EtOAc (3×5 mL) followed by deionized water (3×10 mL). It was dried under vacuum for 2 h. The organic fraction was washed with brine solution and dried over anhydrous Mg_2SO_4. Finally, the product was obtained by the removal of the solvent under reduced pressure, the yield of product was evaluated by using gas chromatography applying decane as internal standard; the product was purified through silica gel chromatography using EtOAc-pet ether.

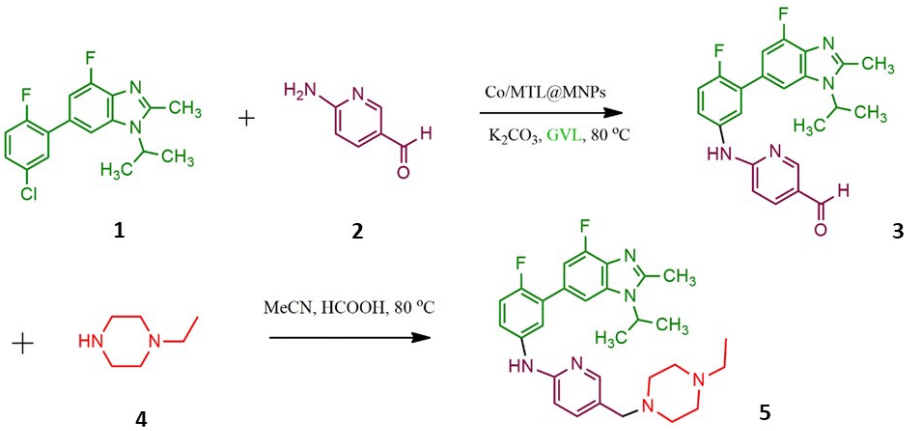
2.4. Synthesis procedure for Fedratinib preparation via C-N coupling reaction catalyzed by Co-MTL@MNPs



A mixture of **1** (3-bromo-N-(tert-butyl)benzenesulfonamide) (0.5 mmol, 146.5 mg), 2-chloro-5-methylpyrimidin-4-amine (0.6 mmol, 86.2 mg), K_2CO_3 (4 eq.) and Co-MTL@MNPs (10 mg, 0.22 mol% Co) in gamma-valerolactone (GVL) (5 mL) was stirred in a round bottom flask (50 mL) at 80 ℃ till the completion of reaction (18 h, monitored by TLC). Next, the reaction mixture was cooled to room temperature. The catalyst was removed by external magnet and washed with EtOAc (3×5 mL) followed by deionized water (3×10 mL). After extraction with ethyl acetate, the product was purified by flash column chromatography using EtOAc-pet.ether (65 % yield). The product was applied in next reaction as precursor.

In next step, A mixture of **3** (N-(tert-butyl)-3-((2-chloro-5-methylpyrimidin-4-yl)amino)benzenesulfonamide) (0.3 mmol, 106 mg) and 4-(2-(pyrrolidin-1-yl)ethoxy)aniline (0.31 mmol, 63.9 mg) K_2CO_3 (4 eq.) and Co-MTL@MNPs (0.1 g, 1.84 mol% Co) in gamma-valerolactone (GVL) (5 mL) was stirred in a round bottom flask (50 mL) at 80℃ till the completion of reaction (24 h, monitored by TLC). After that, the reaction mixture was cooled to room temperature. The catalyst was removed by external magnet and washed with EtOAc (3×5 mL) followed by deionized water (3×10 mL). After extraction with ethyl acetate, the product was purified by flash column chromatography (73 % yield).

Synthesis procedure for Abemaciclib preparation via C-N coupling reaction catalyzed by Co-MTL@MNPs



The compound **1** (6-(5-chloro-2-fluorophenyl)-4-fluoro-1-isopropyl-2-methyl-1H-benzo[d]imidazole) was prepared according to the method reported in literature based on the Suzuki coupling. In the following, A mixture of **1** (160.1 mg, 0.5 mmol), **2** 6-aminonicotinaldehyde (0.6 mmol, 73.2 mg), K_2CO_3 (4 eq.) and Co-MTL@MNPs (10 mg, 0.22 mol% Co) in gamma-valerolactone (GVL) (5 mL) was stirred in a round bottom flask (50 mL) at 80 ℃ till the completion of reaction (24 h, monitored by TLC). Next, the reaction mixture was cooled to room temperature. The catalyst was removed by external magnet and washed with EtOAc (3×5 mL) followed by deionized water (3×10 mL). After extraction with ethyl acetate, the product (**3**) was purified by flash column chromatography using EtOAc-pet. ether (71 % yield). The mixture of **3** (162.4

mg, 0.4 mmol), **4** (1-ethylpiperazine) (57.1 mg, 0.5 mmol), Formic acid (4.6 mg, 0.1 mmol), trimethyl orthoformate ($CH(OCH_3)_3$) (10.6 mg, 0.5 mmol), in acetonitrile (5 mL) was stirred in a round bottom flask (50 mL) at 80 ℃ till the completion of reaction (4 h, monitored by TLC). The reaction mixture was cooled to room temperature. After extraction with ethyl acetate, the product (**5**) was purified by flash column chromatography (56 % yield).

The characterization of reused catalyst:

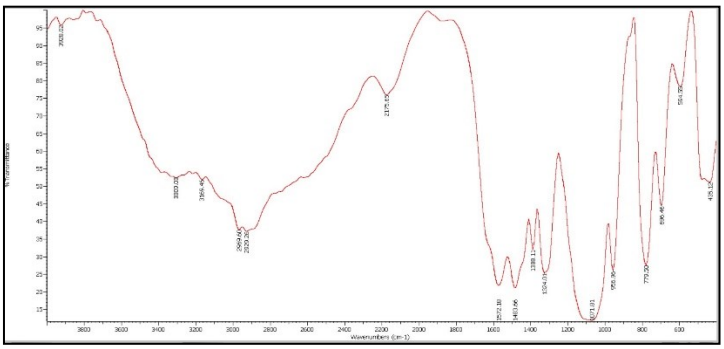


Figure 1S. The FT-IR spectra of reused catalyst

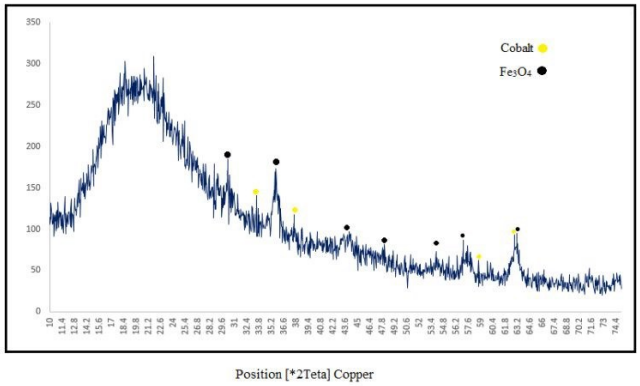


Figure 2S. The XRD pattern of reused catalyst

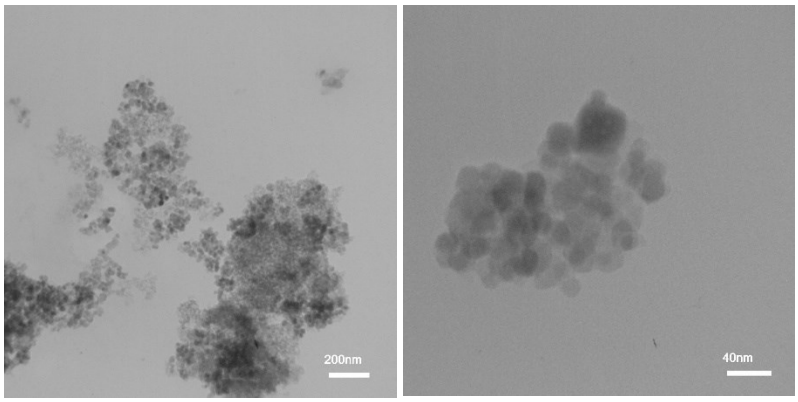


Figure 3S. The TEM images of the reused catalyst

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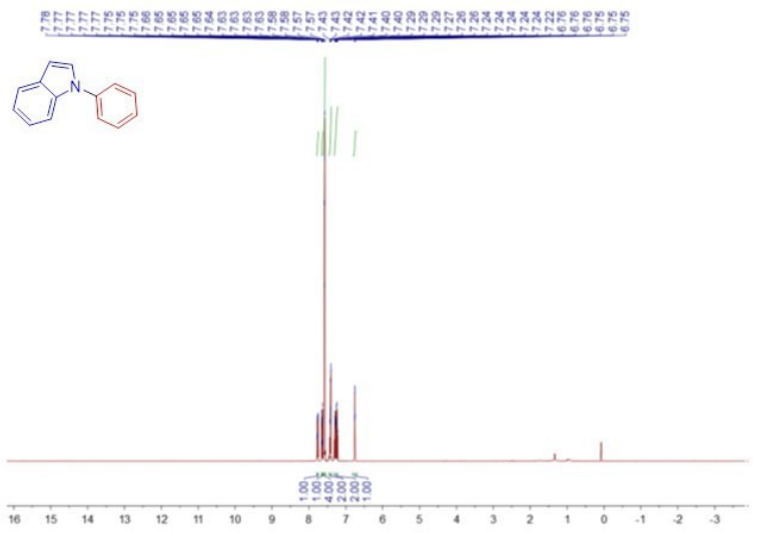

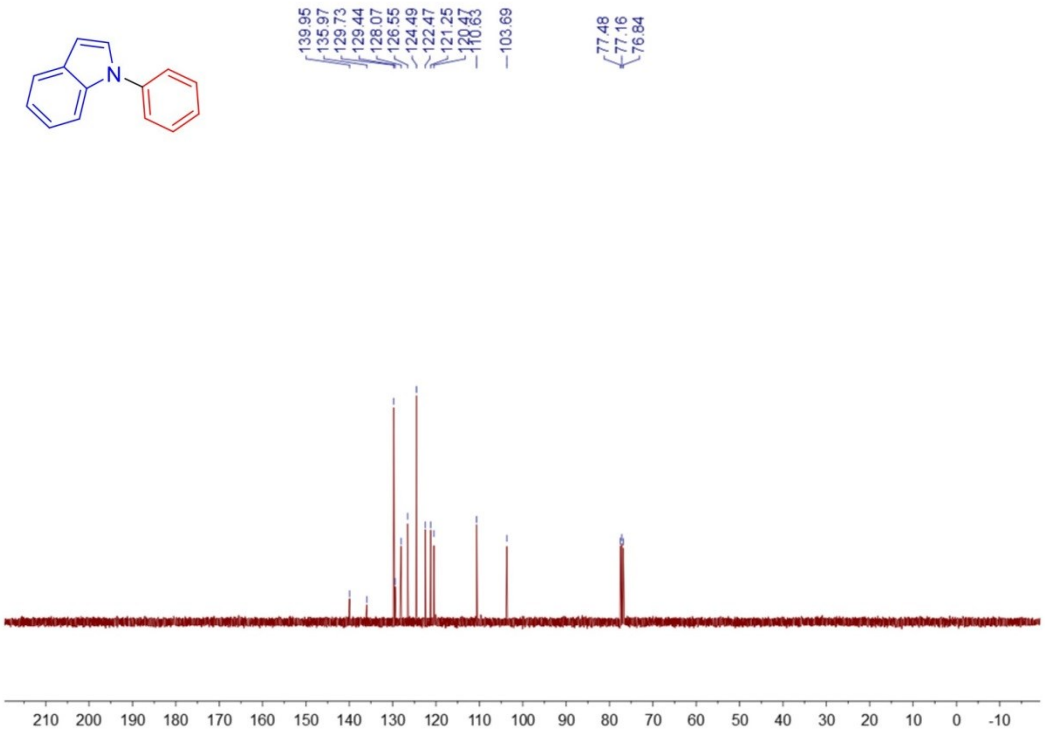

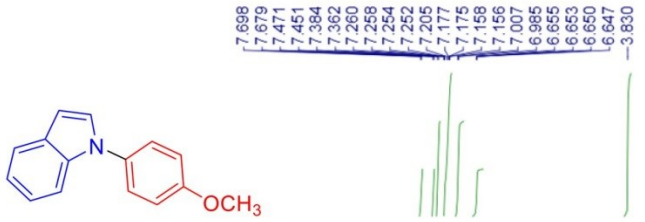
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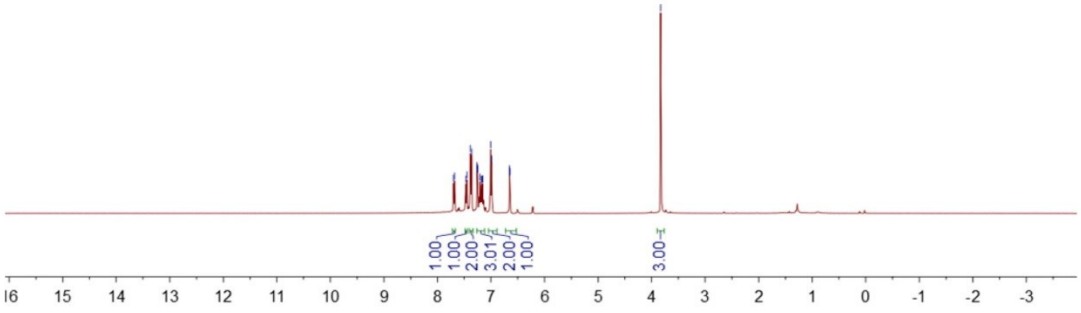
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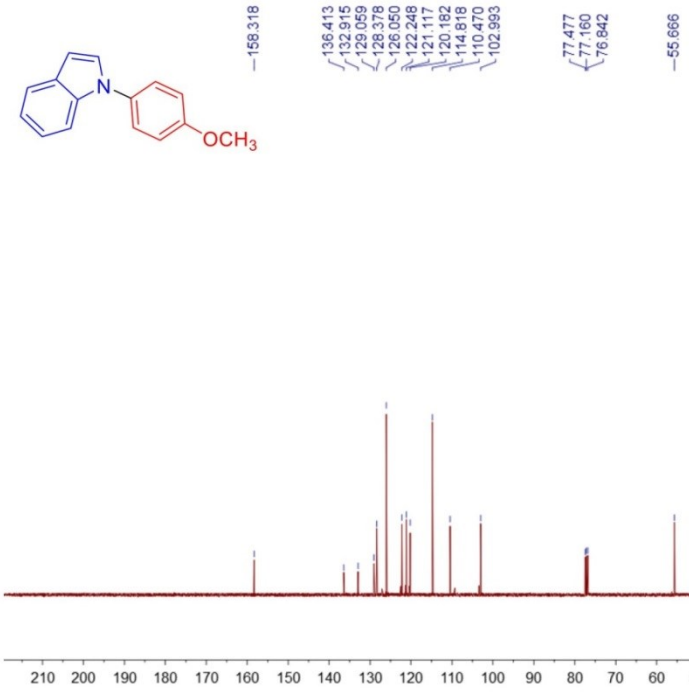
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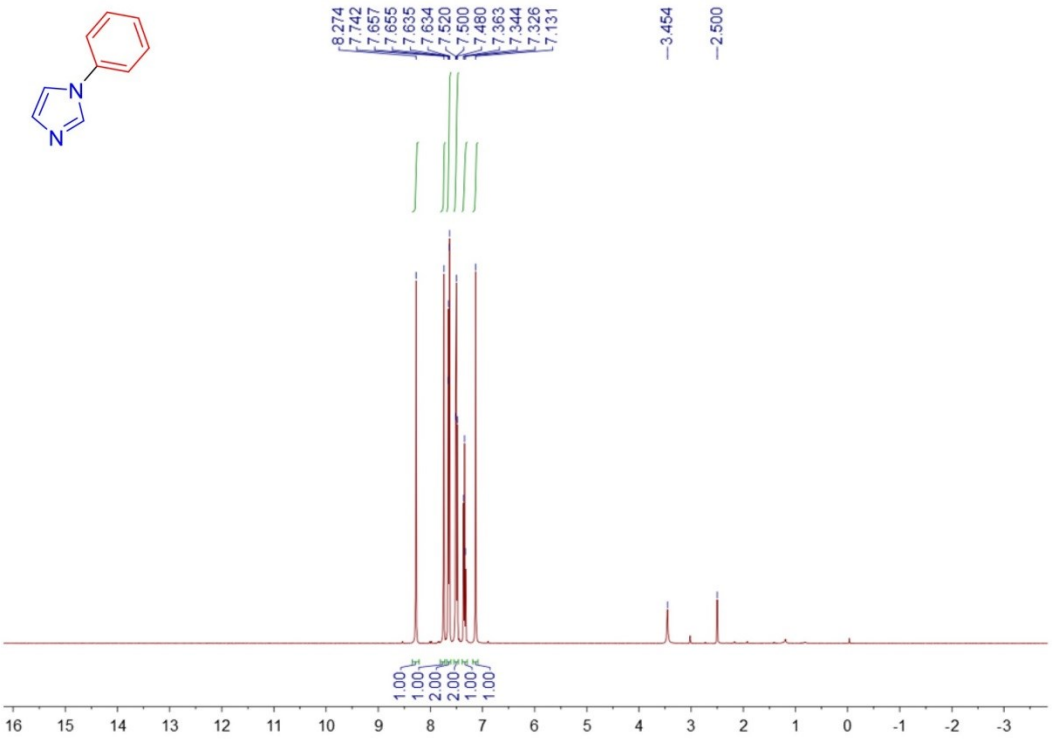
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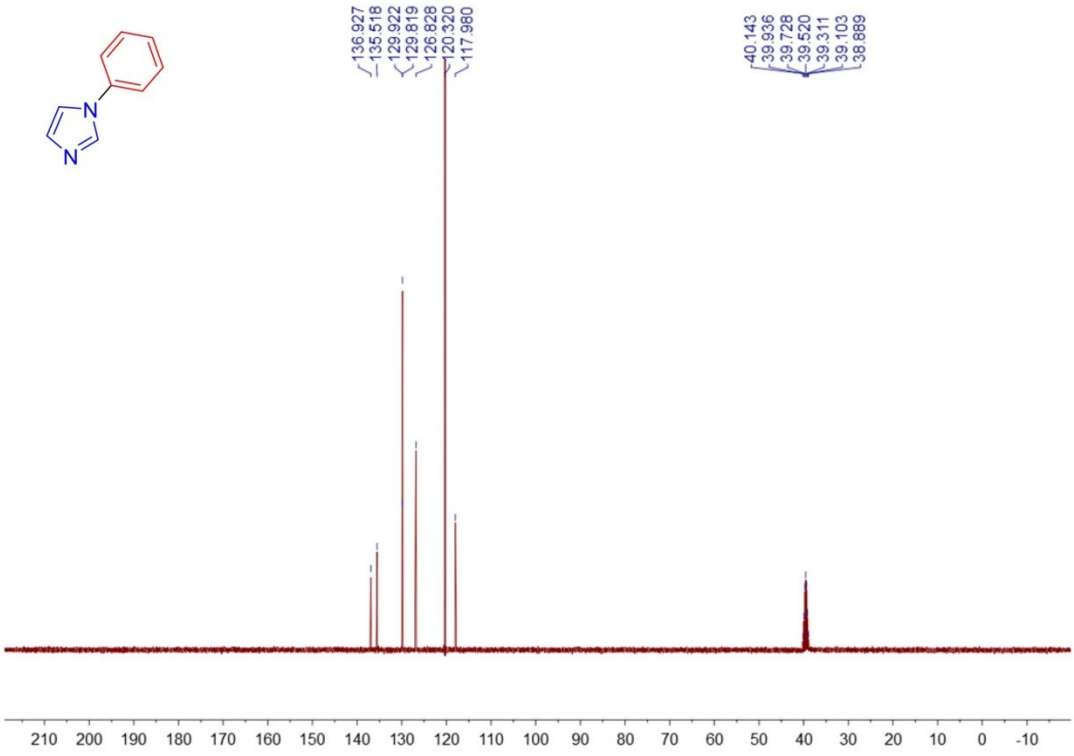
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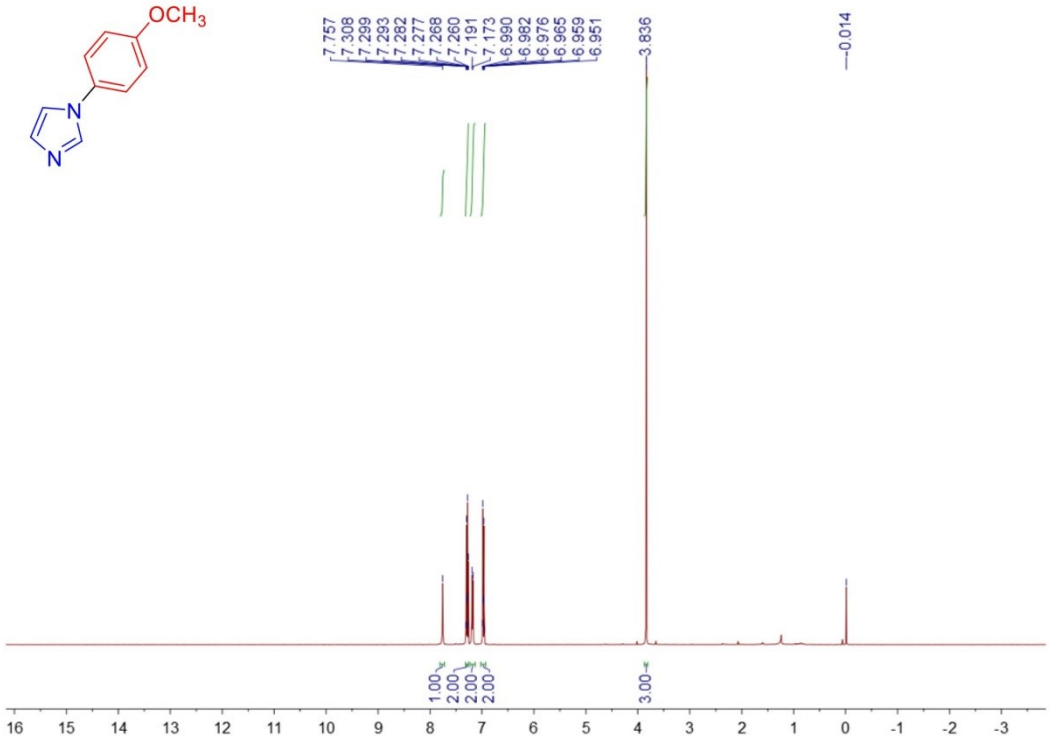
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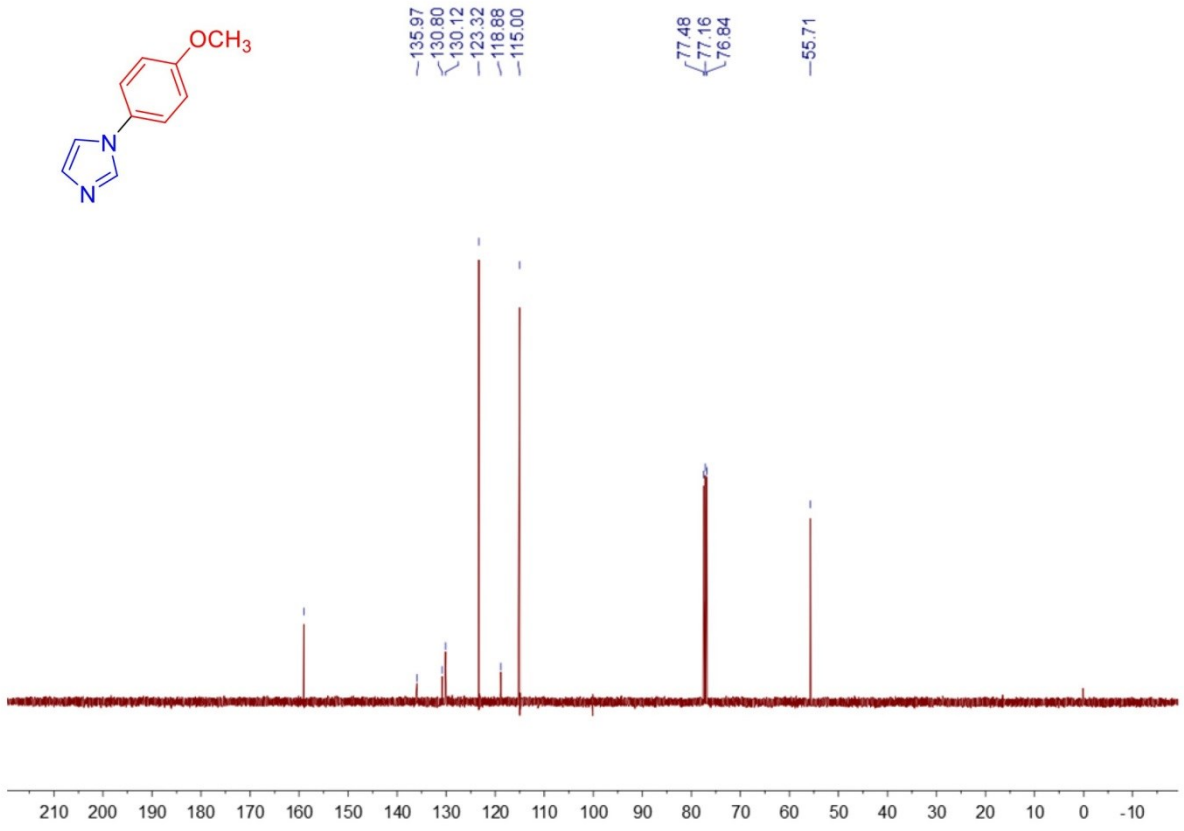
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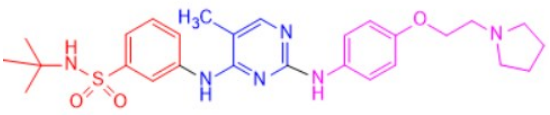

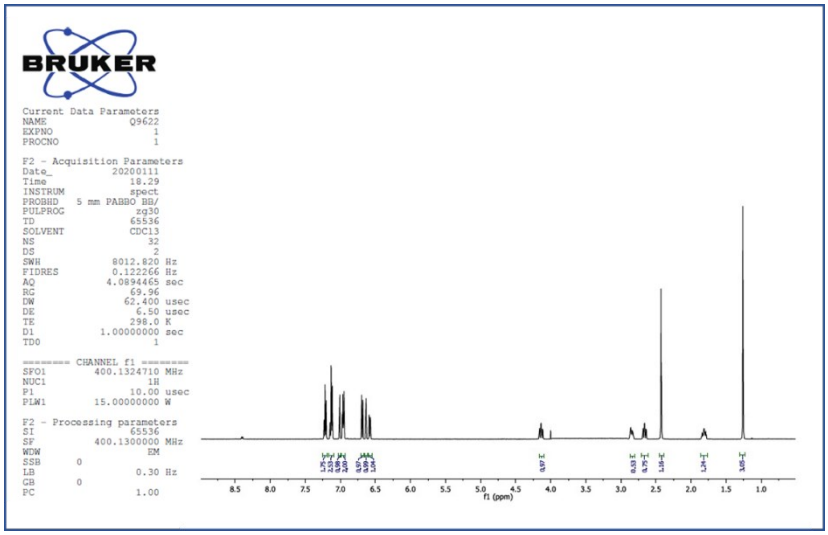

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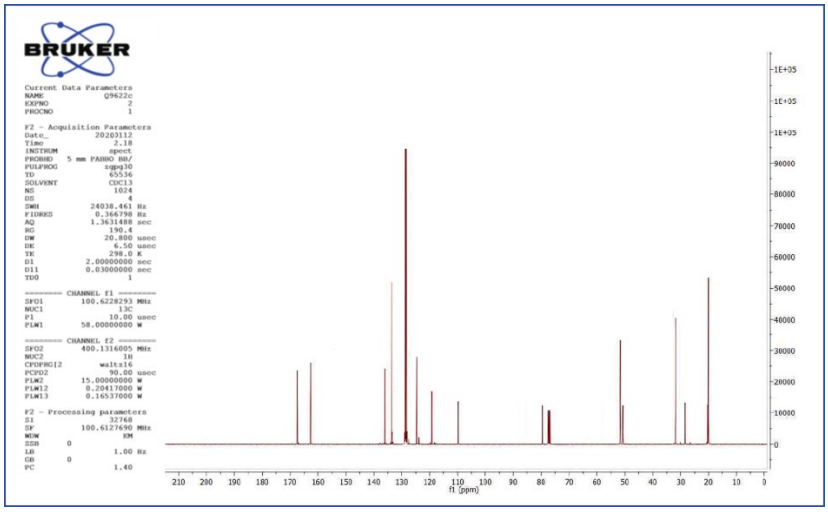

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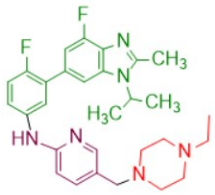

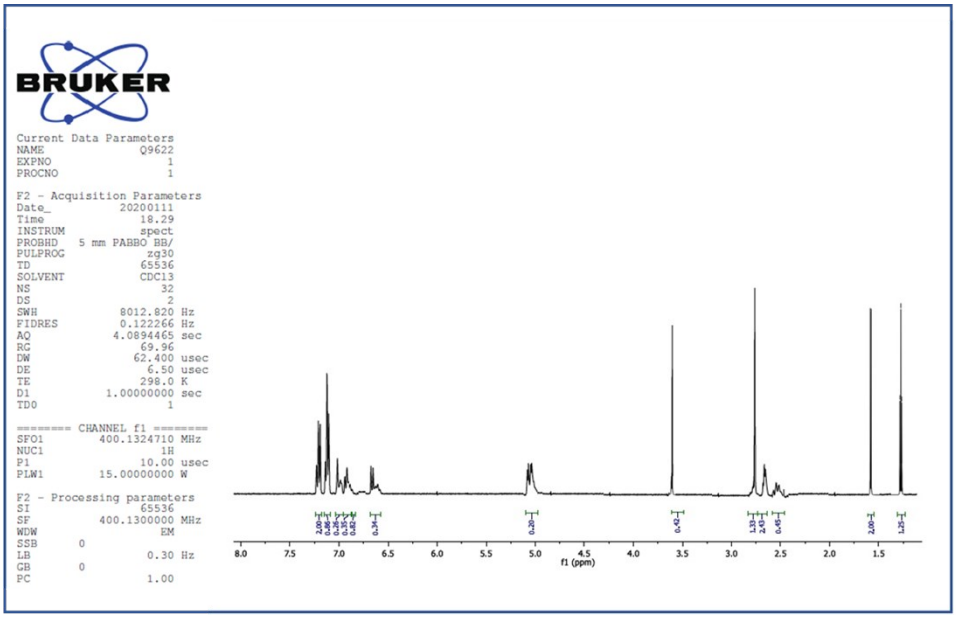

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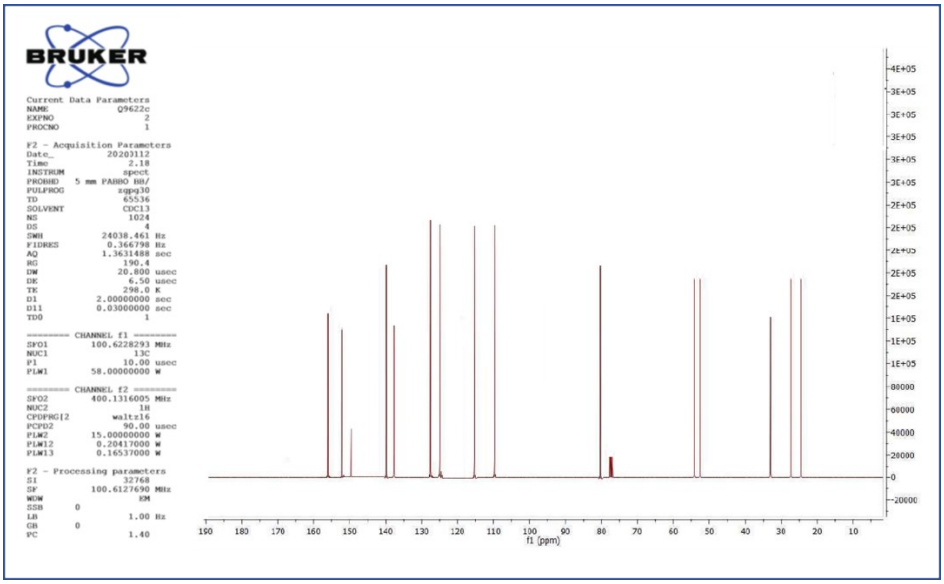

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