Supplementary Information for:

One-pot, three-component Fischer indolisation–N-alkylation for rapid synthesis of 1,2,3-trisubstituted indoles

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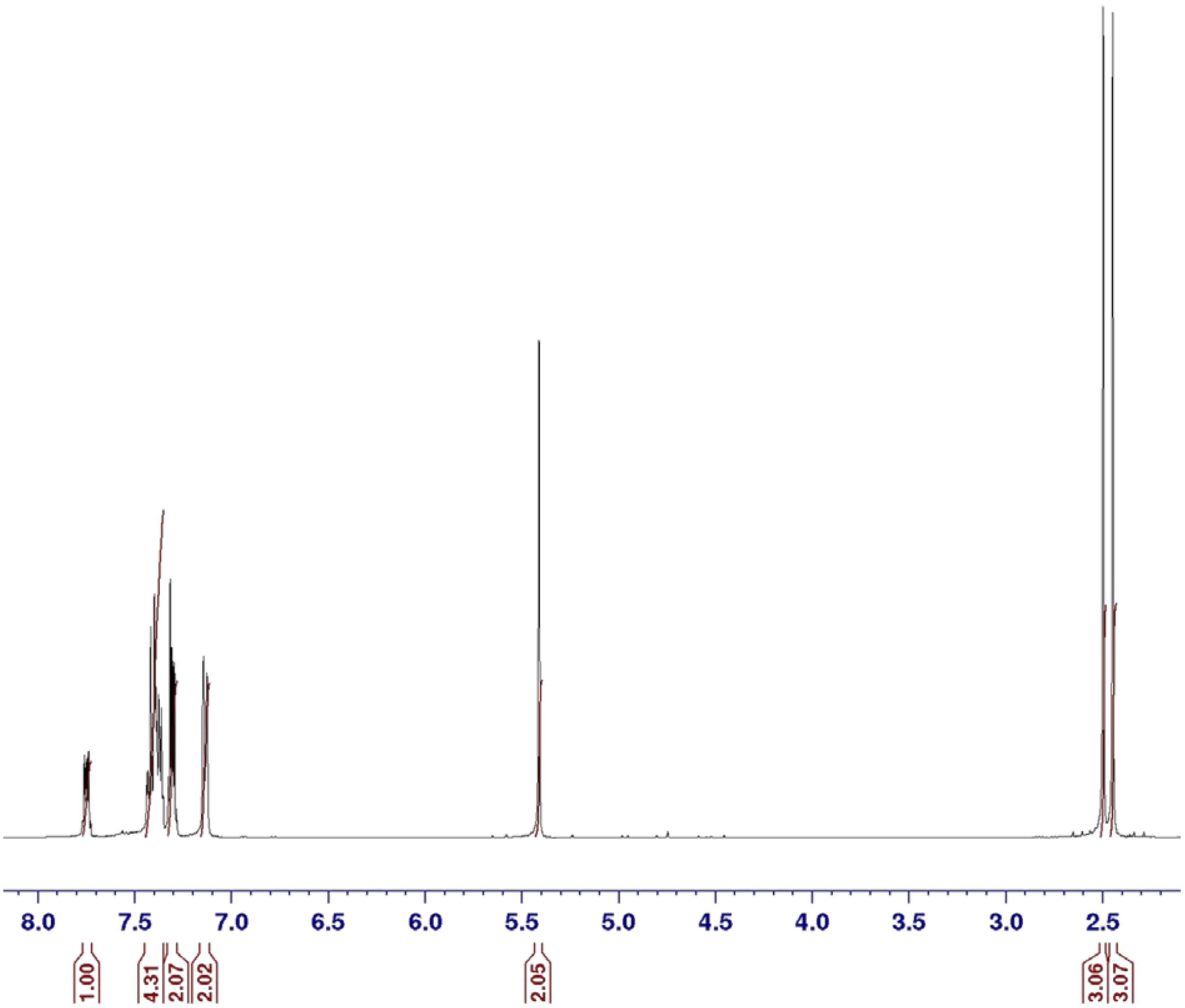
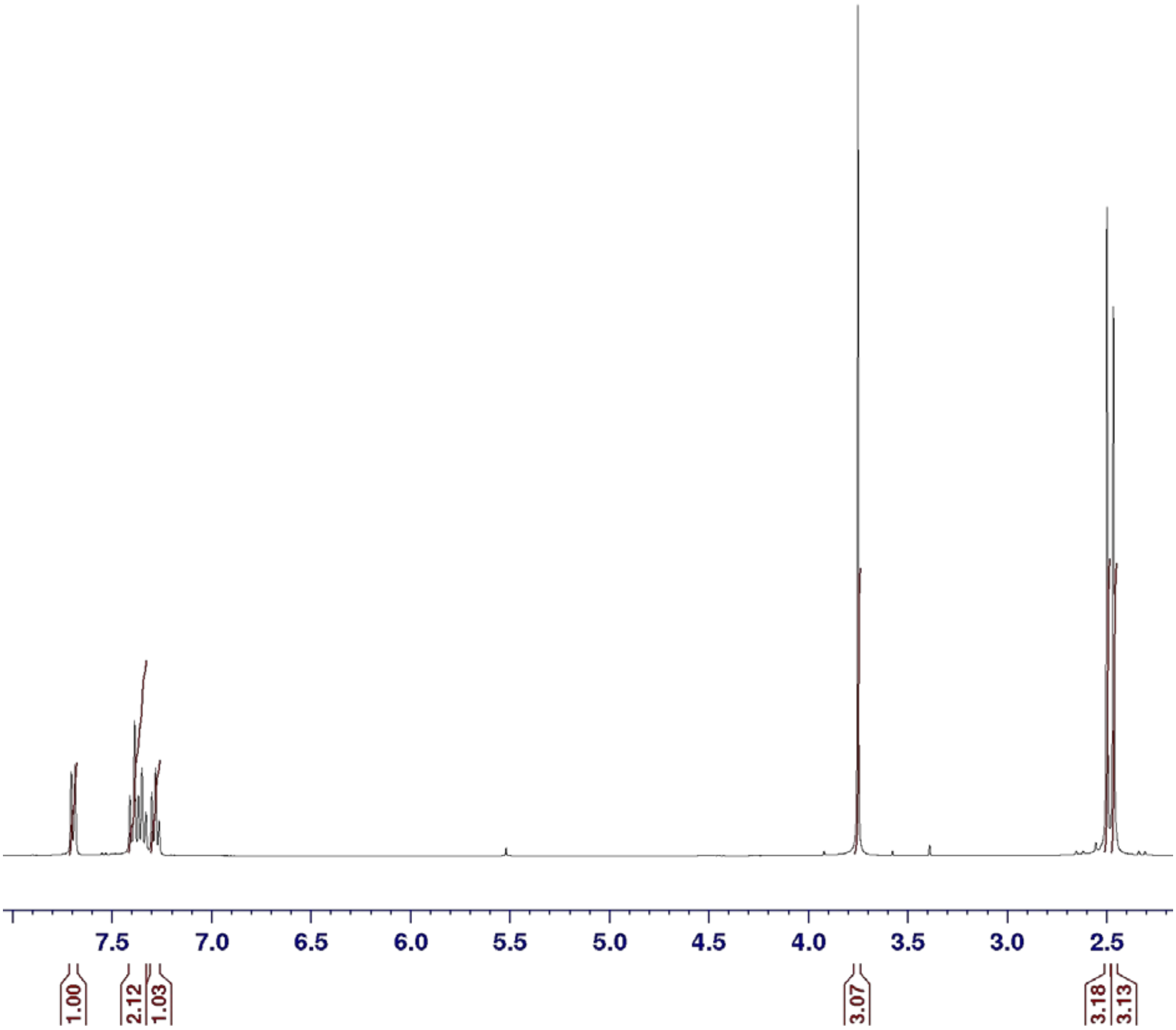
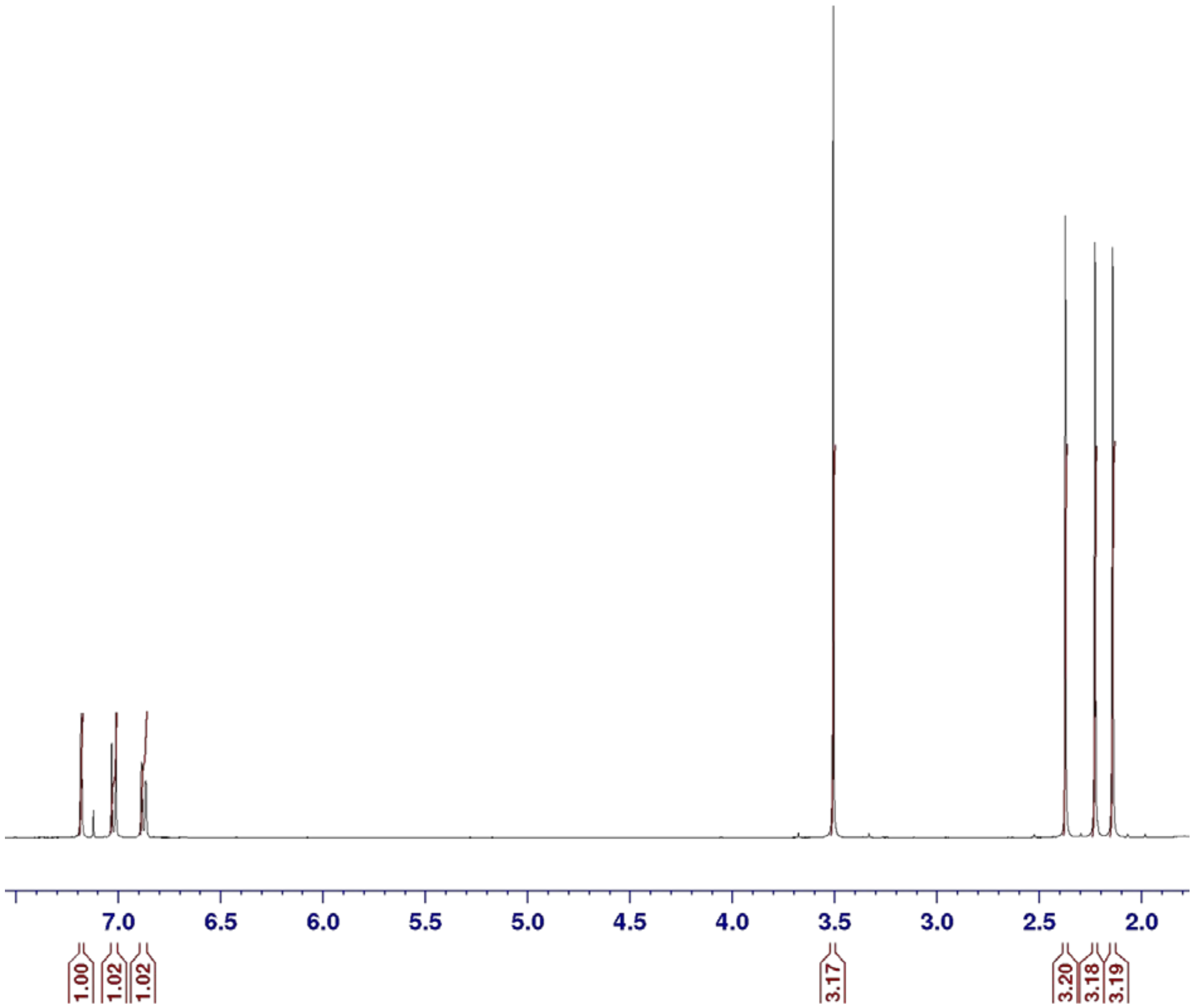
^{1}H NMR spectrum for 4a:



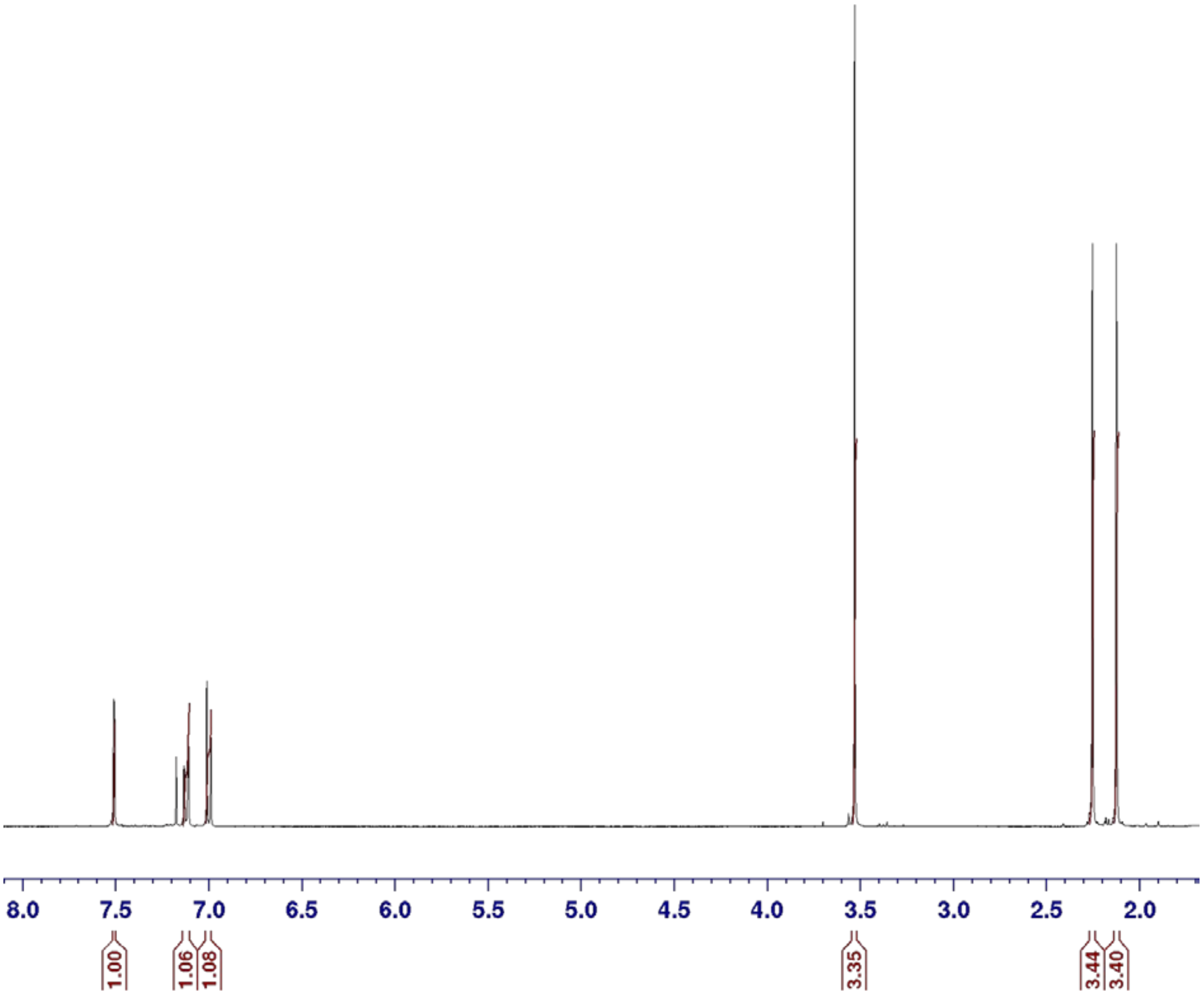
^{1}H NMR spectrum for 4b:



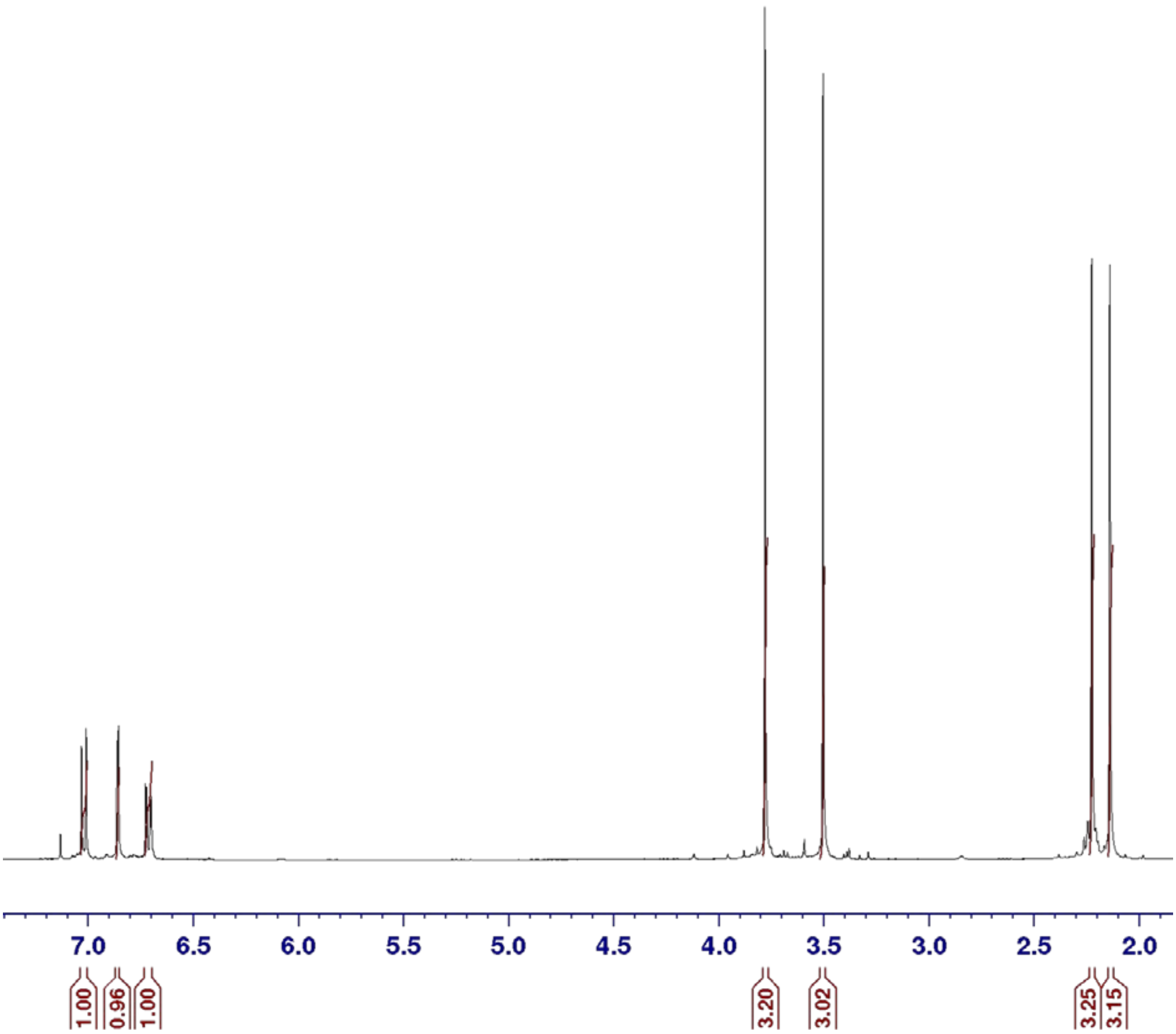
^{1}H NMR spectrum for 4c:



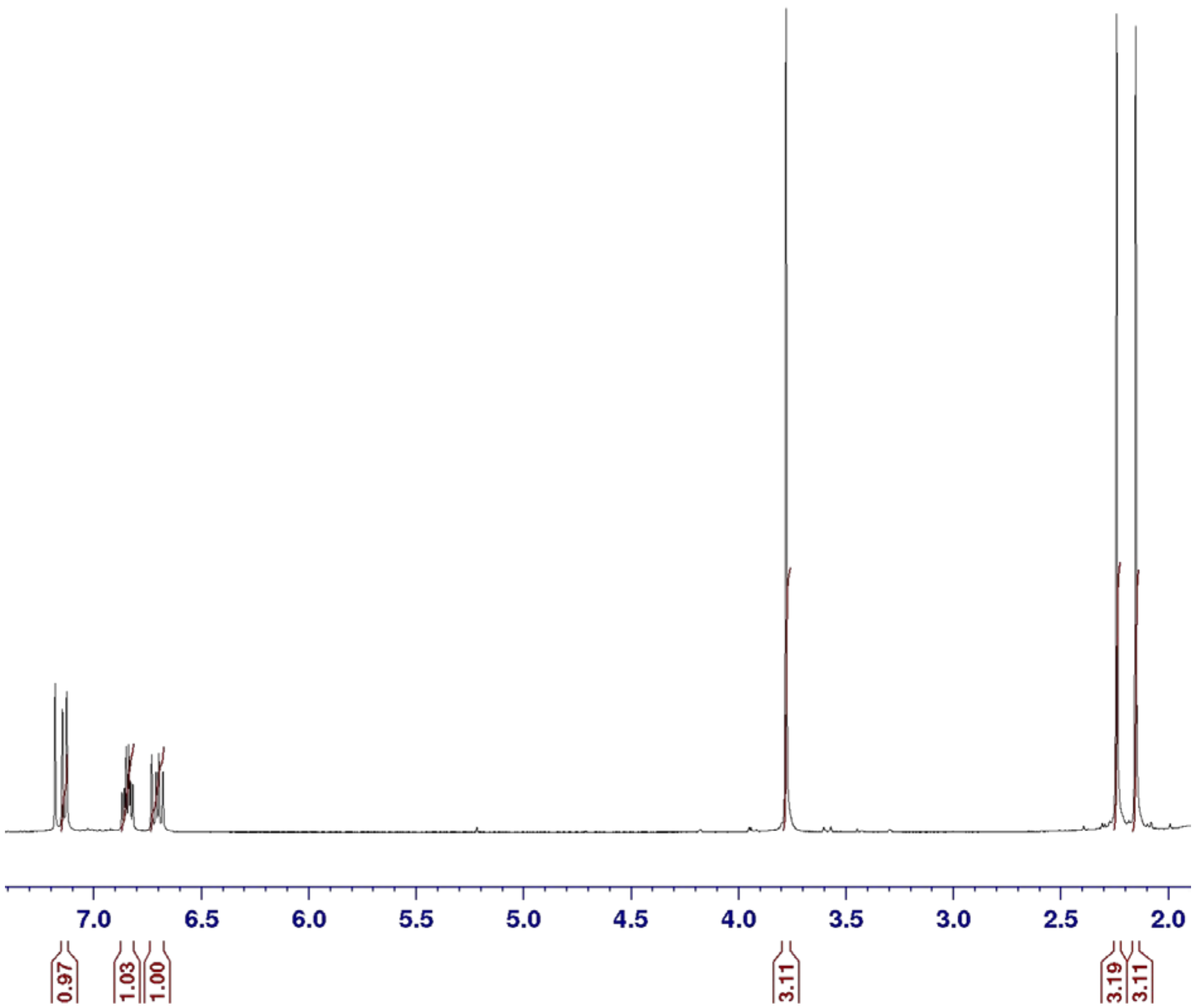
^{1}H NMR spectrum for 4d:



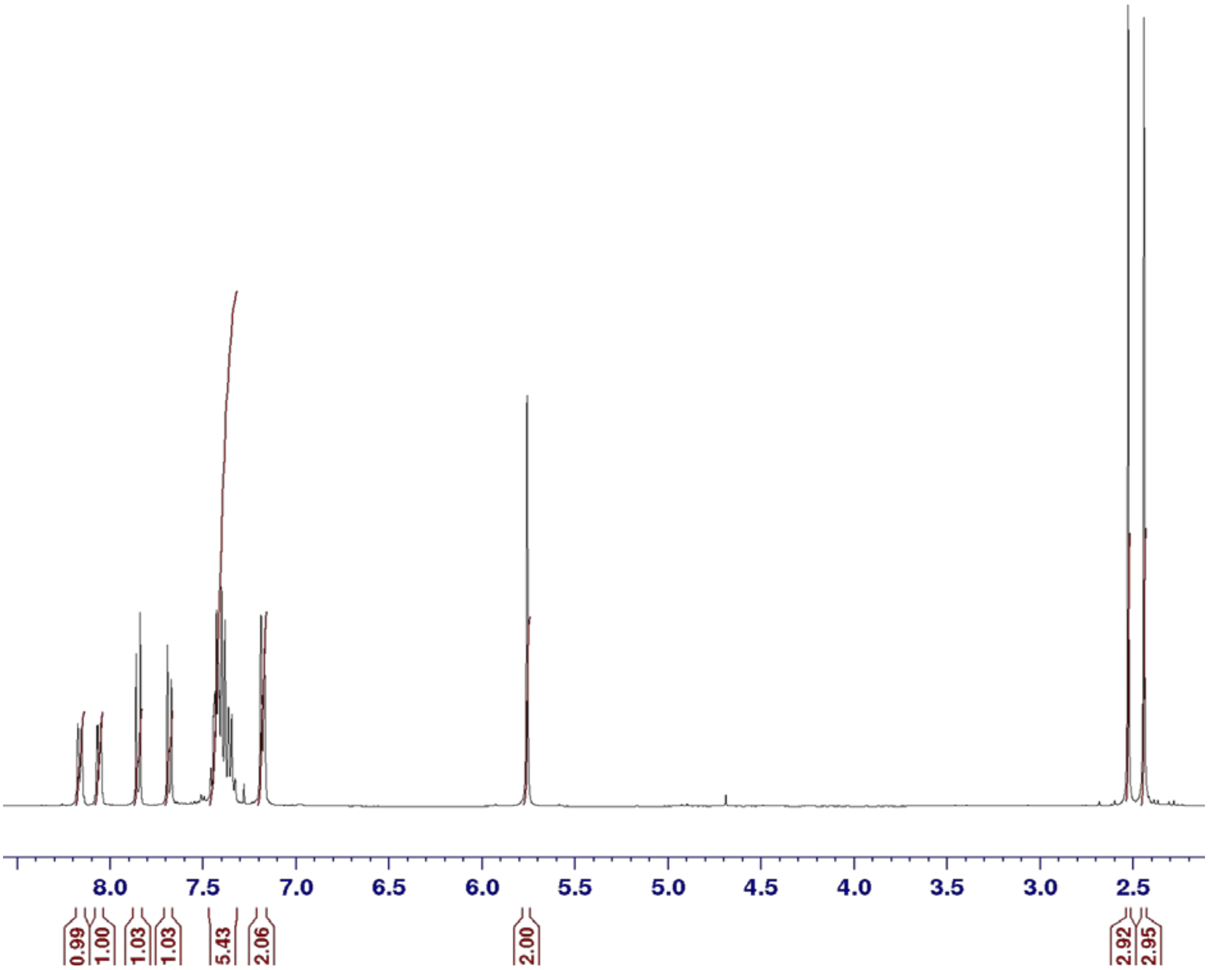
^{1}H NMR spectrum for 4e:



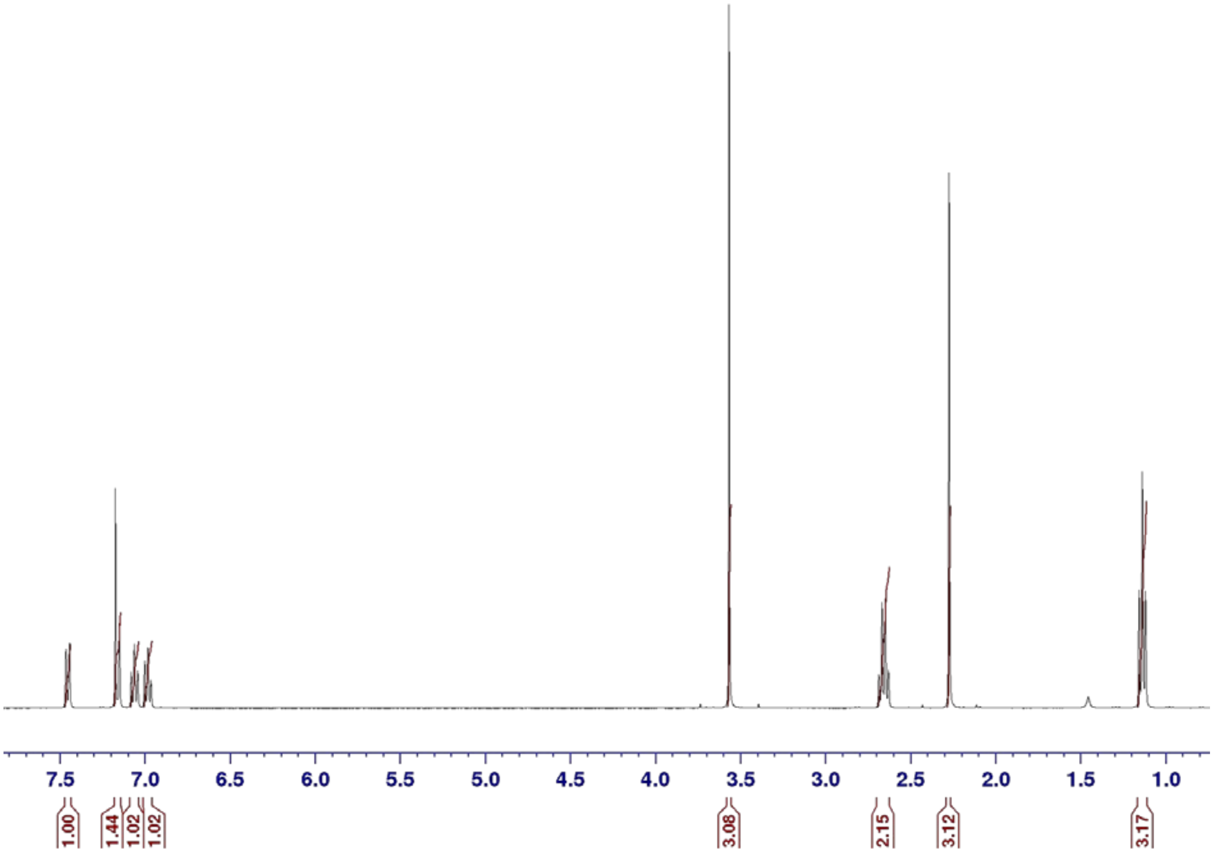
^{1}H NMR spectrum for 4f:



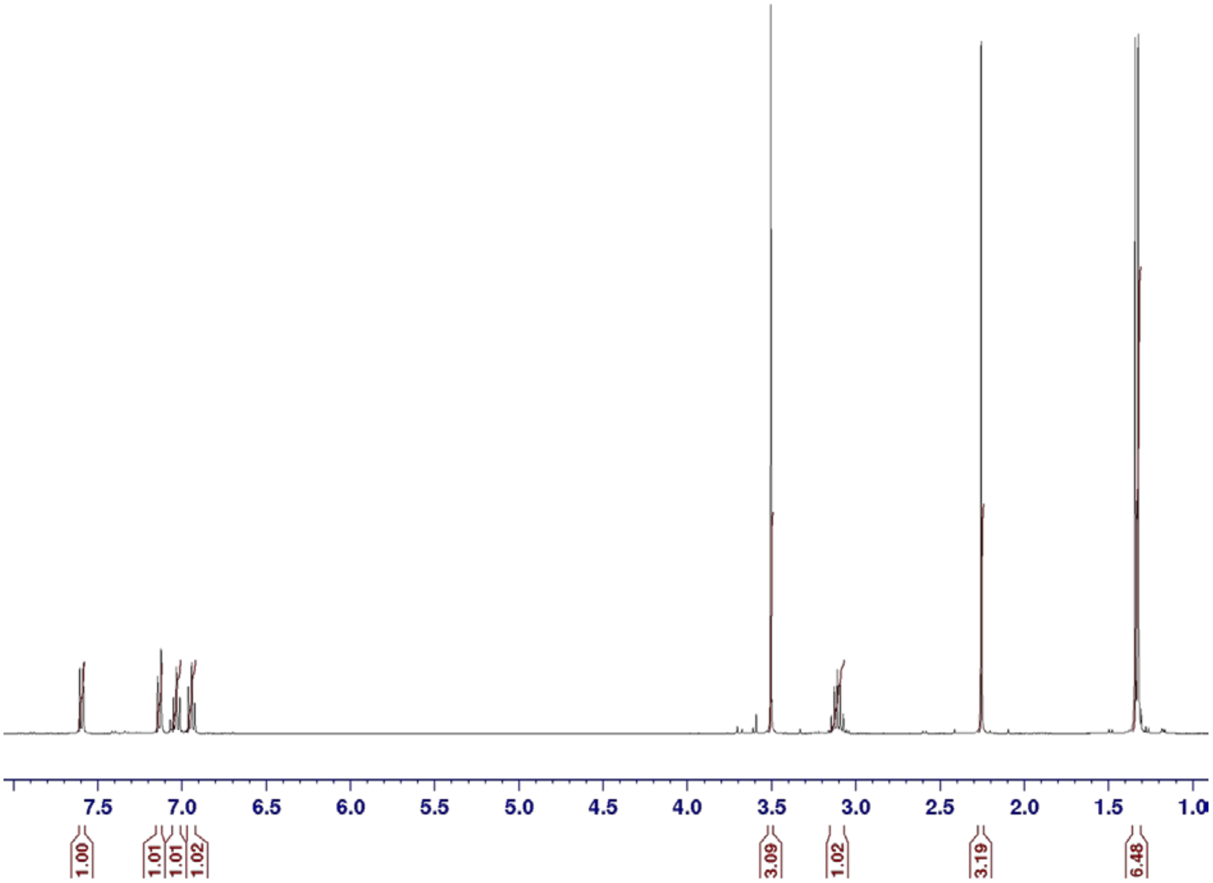
^{1}H NMR spectrum for 4g:



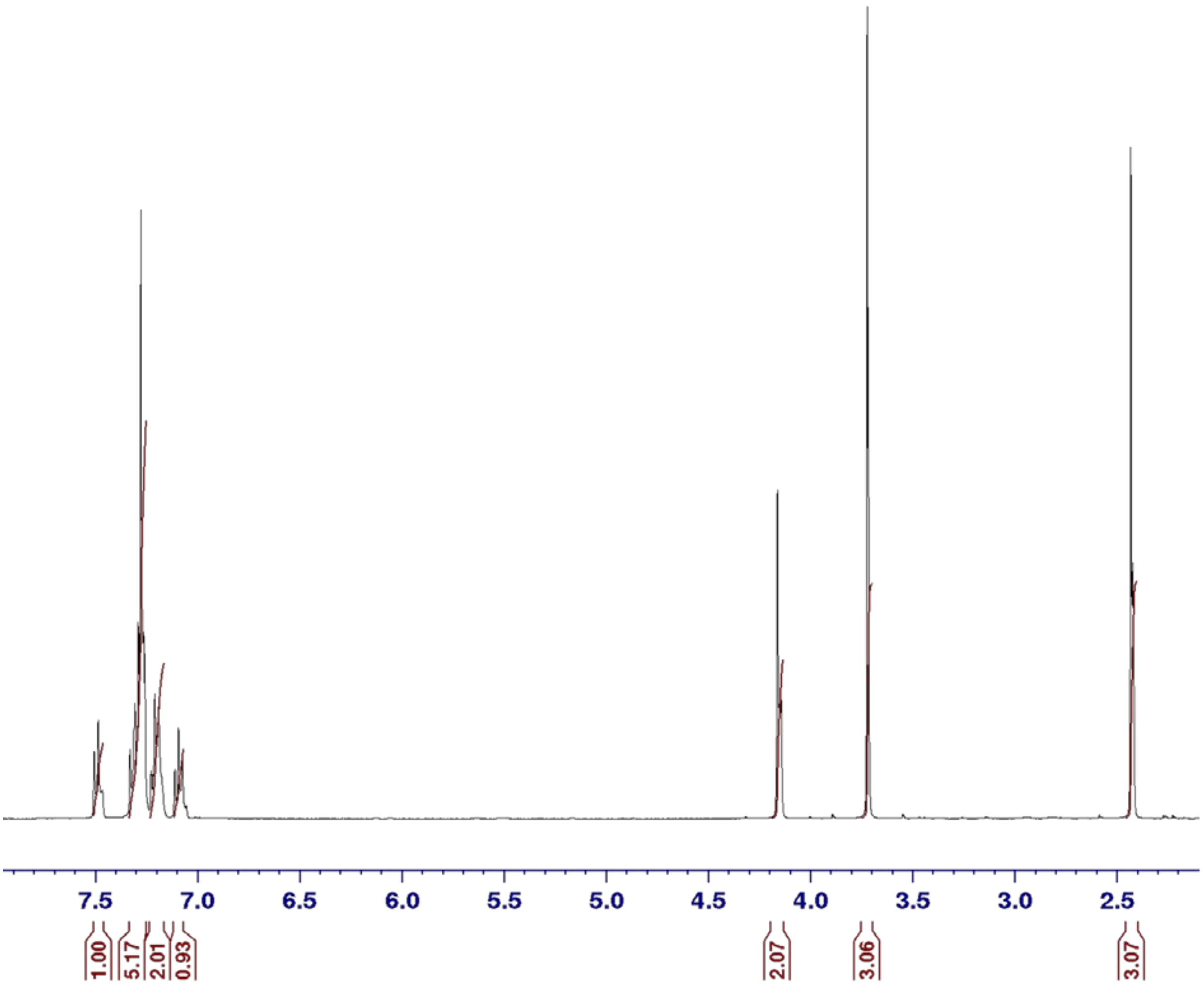
^{1}H NMR spectrum for 4h:



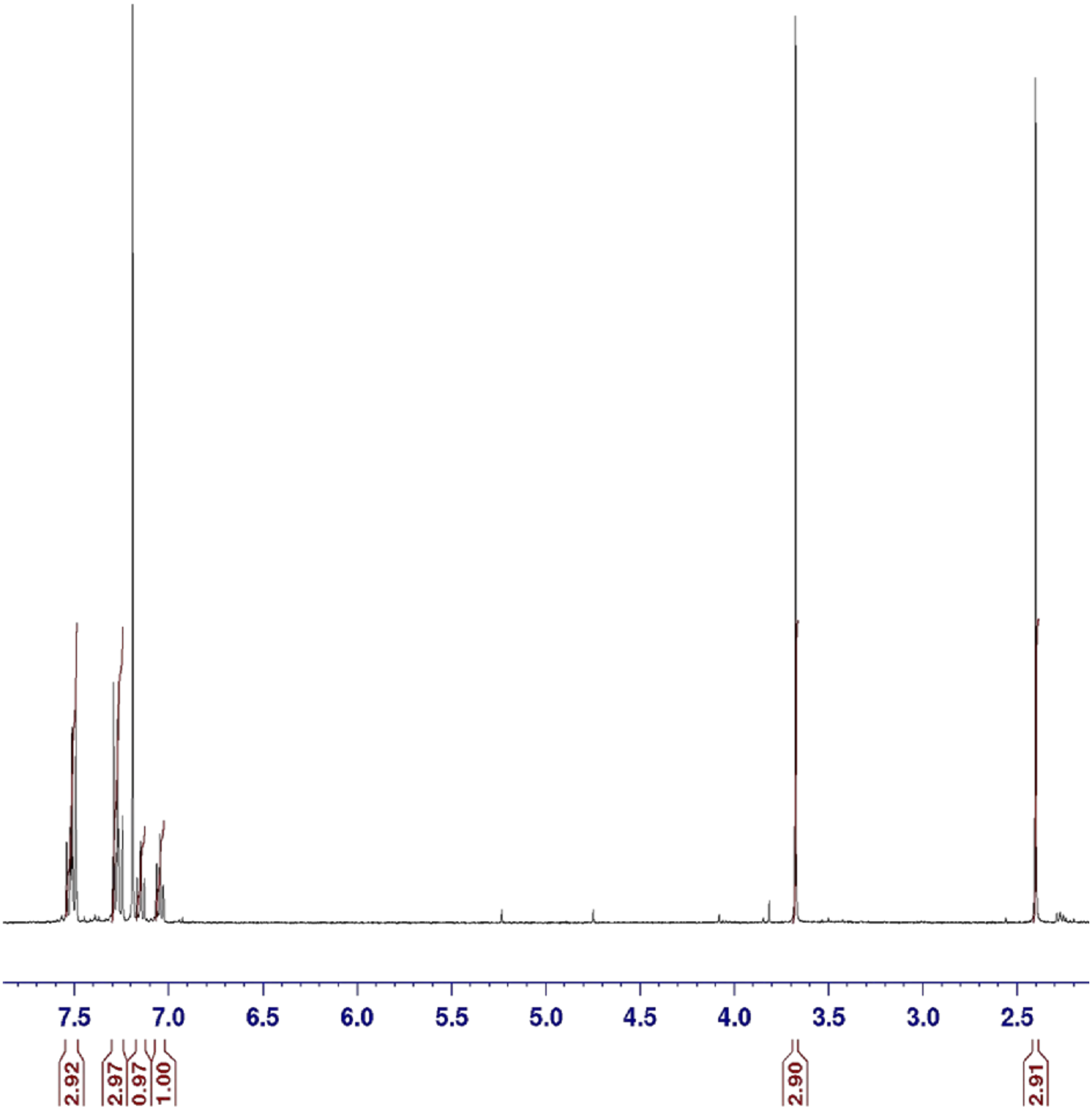
^{1}H NMR spectrum for 4i:



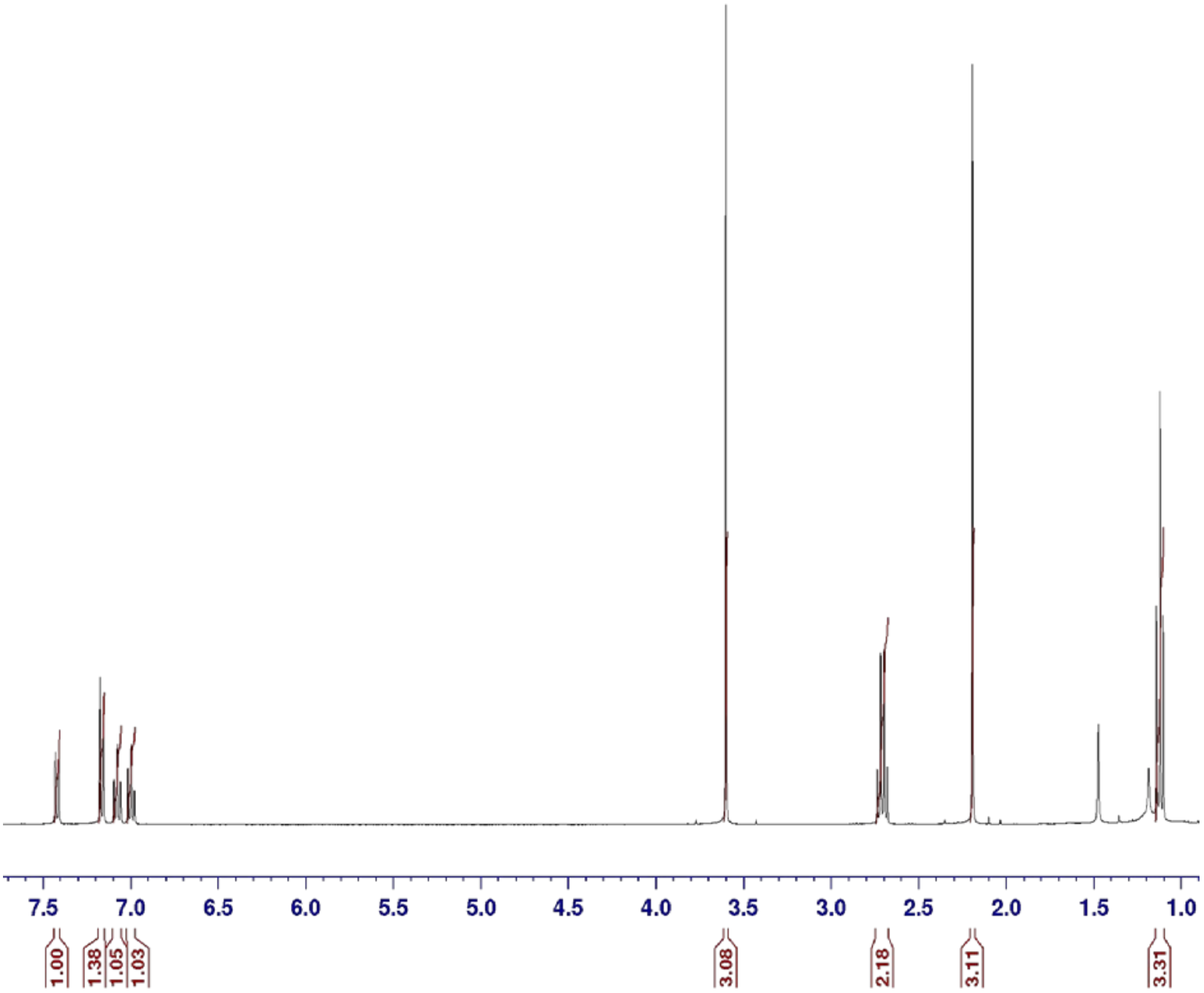
^{1}H NMR spectrum for 4j:



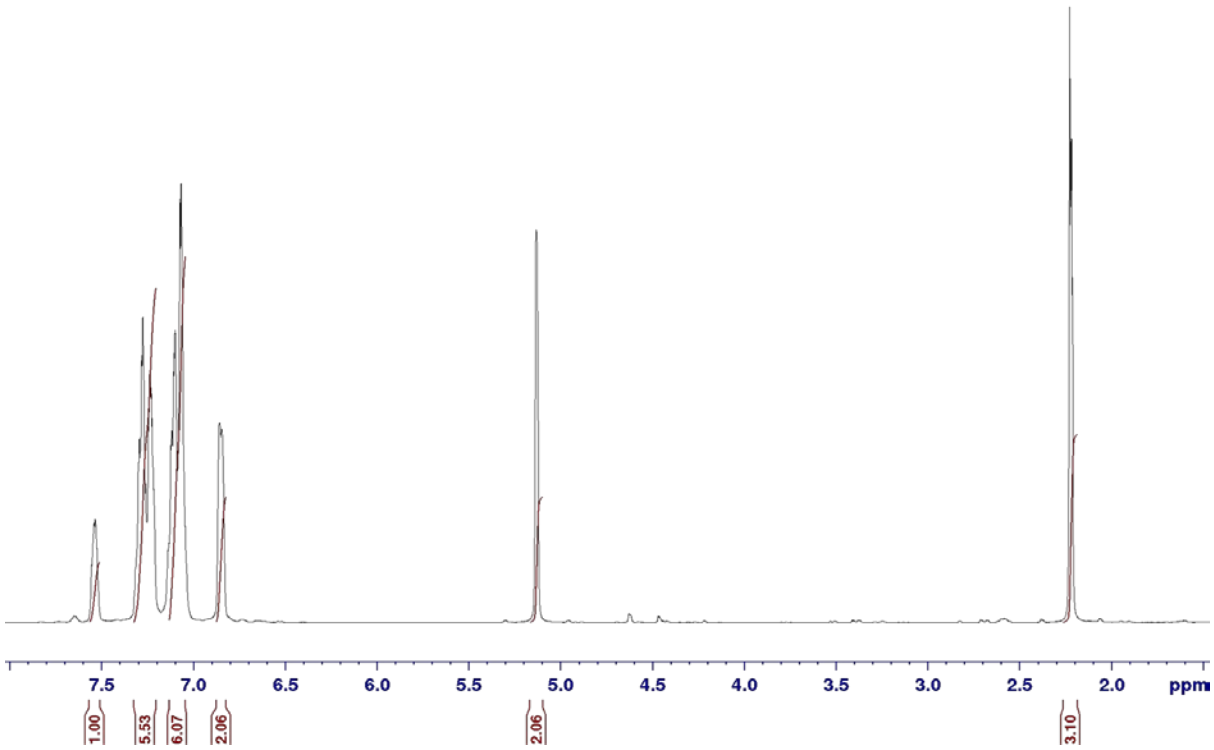
^{1}H NMR spectrum for 4k:



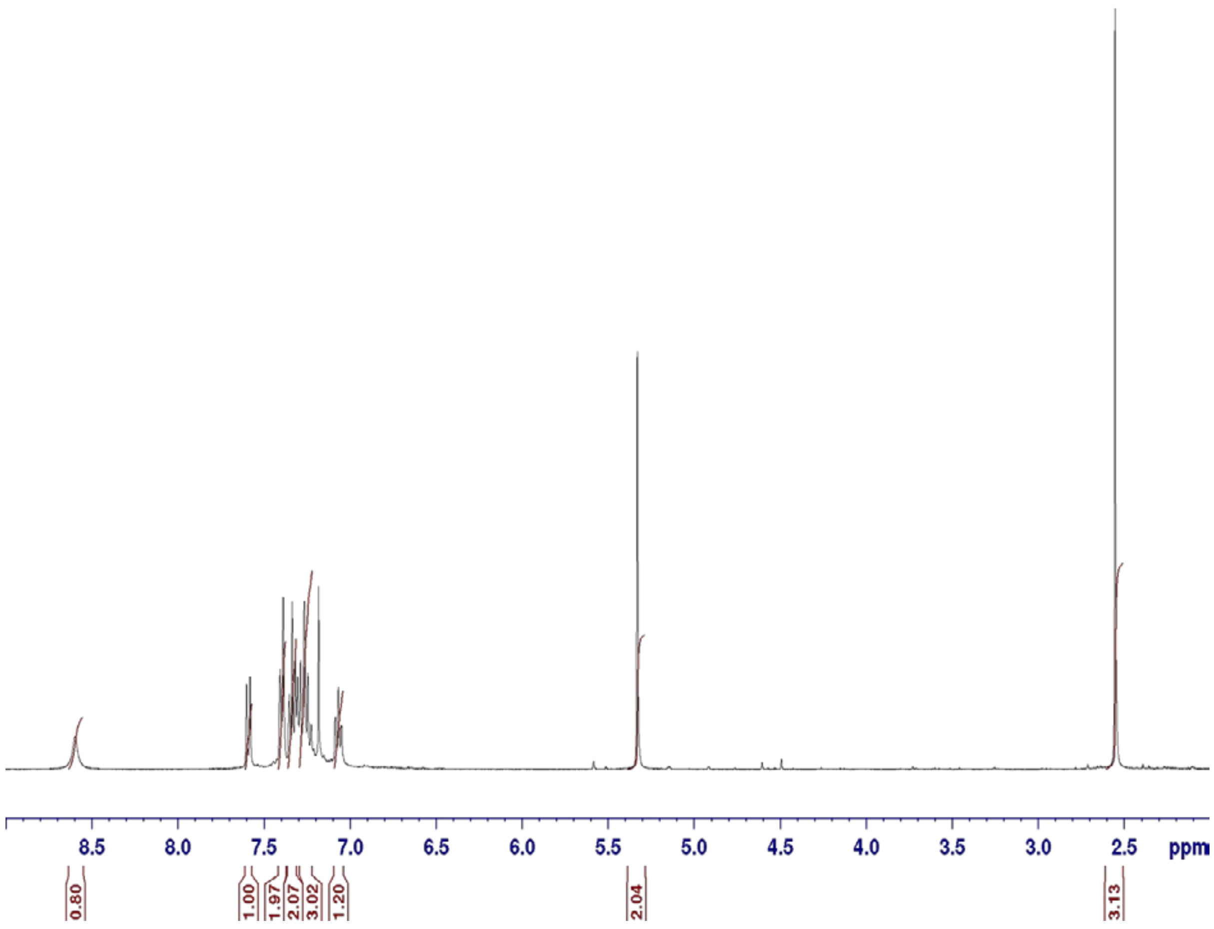
^{1}H NMR spectrum for 4l:

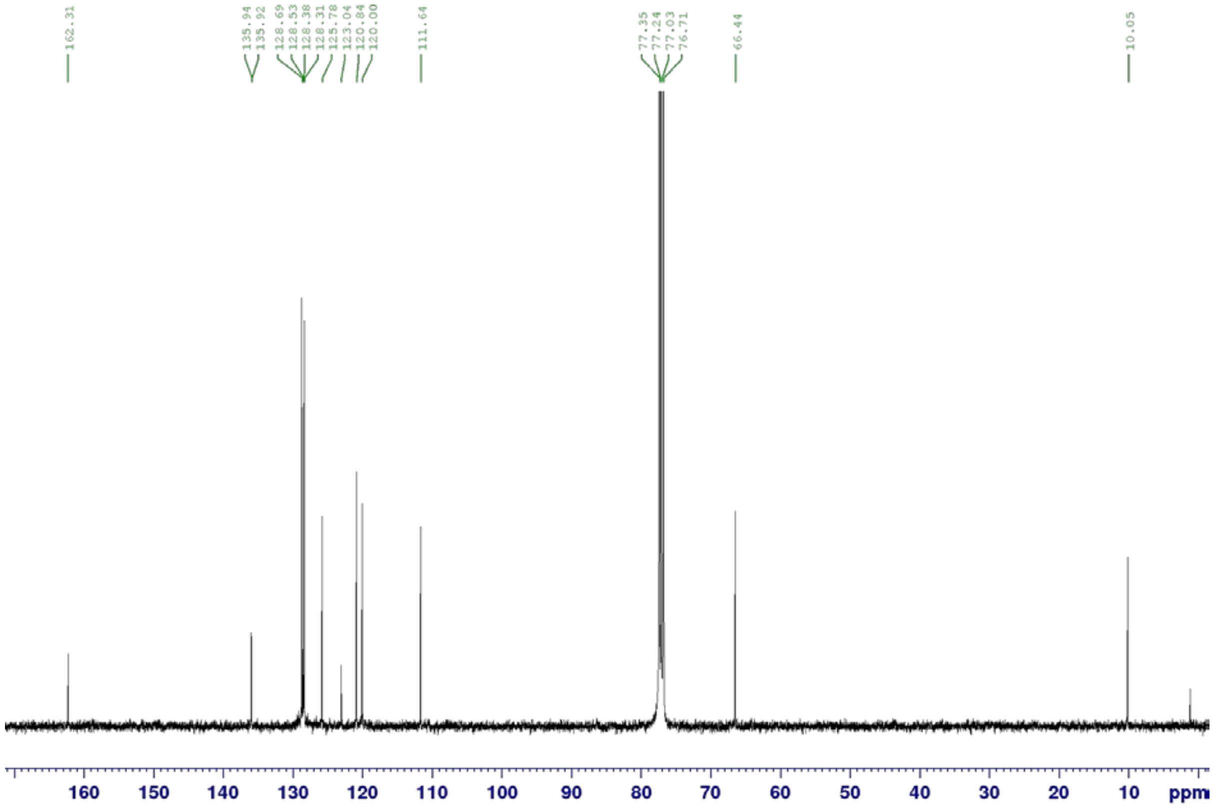


^{1}H NMR spectrum for 4m:

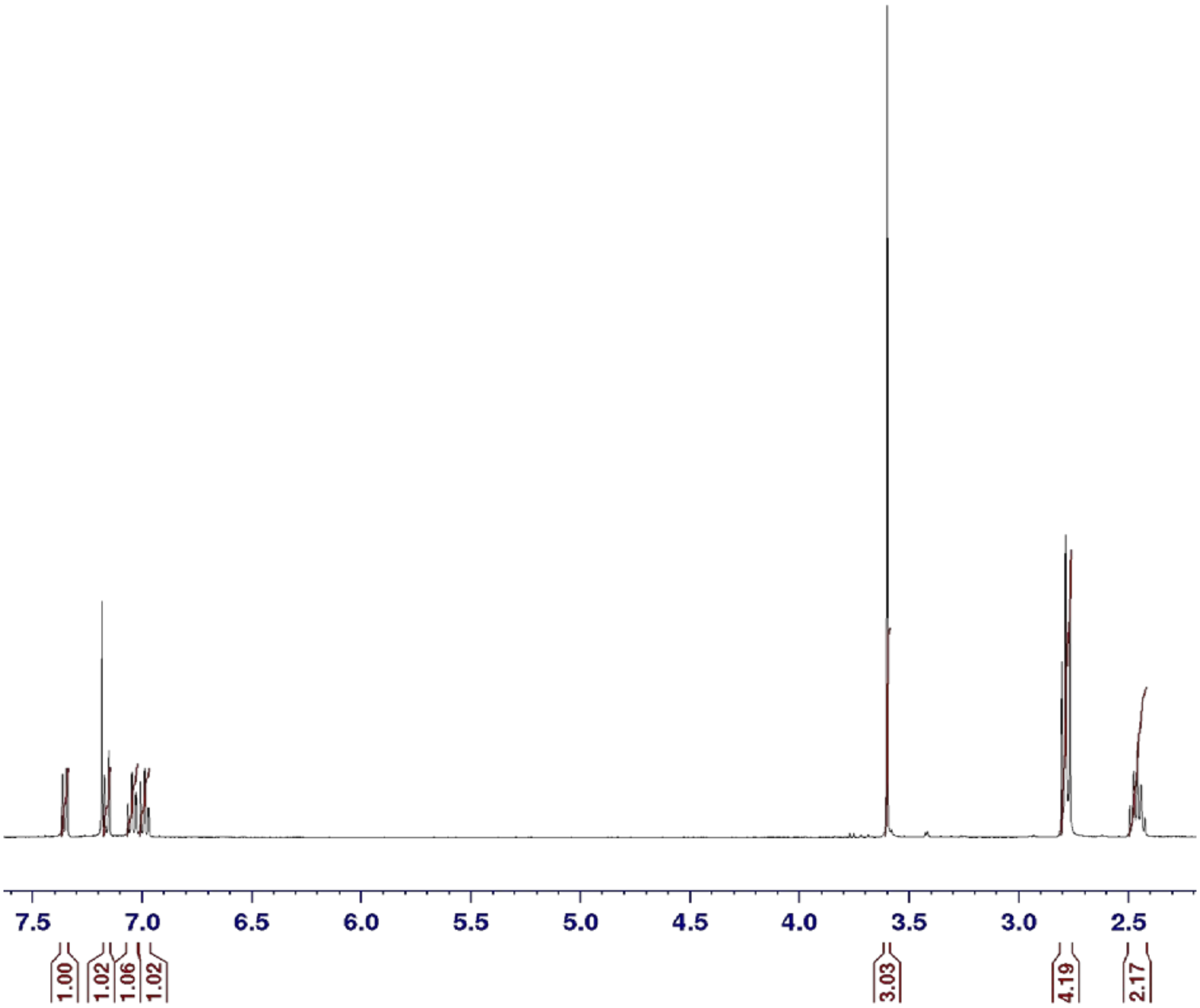


^{1}H and ^{13}C NMR spectra for 4n:

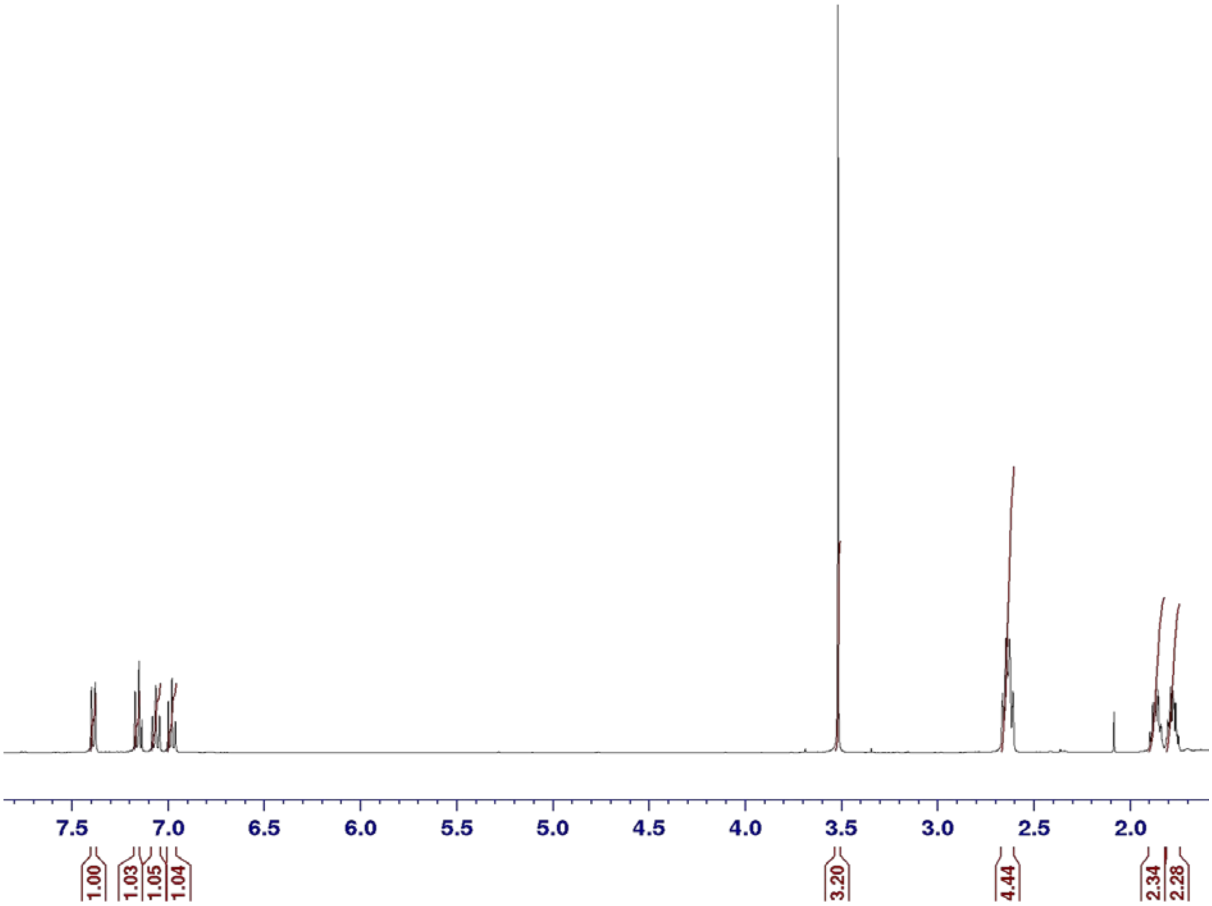




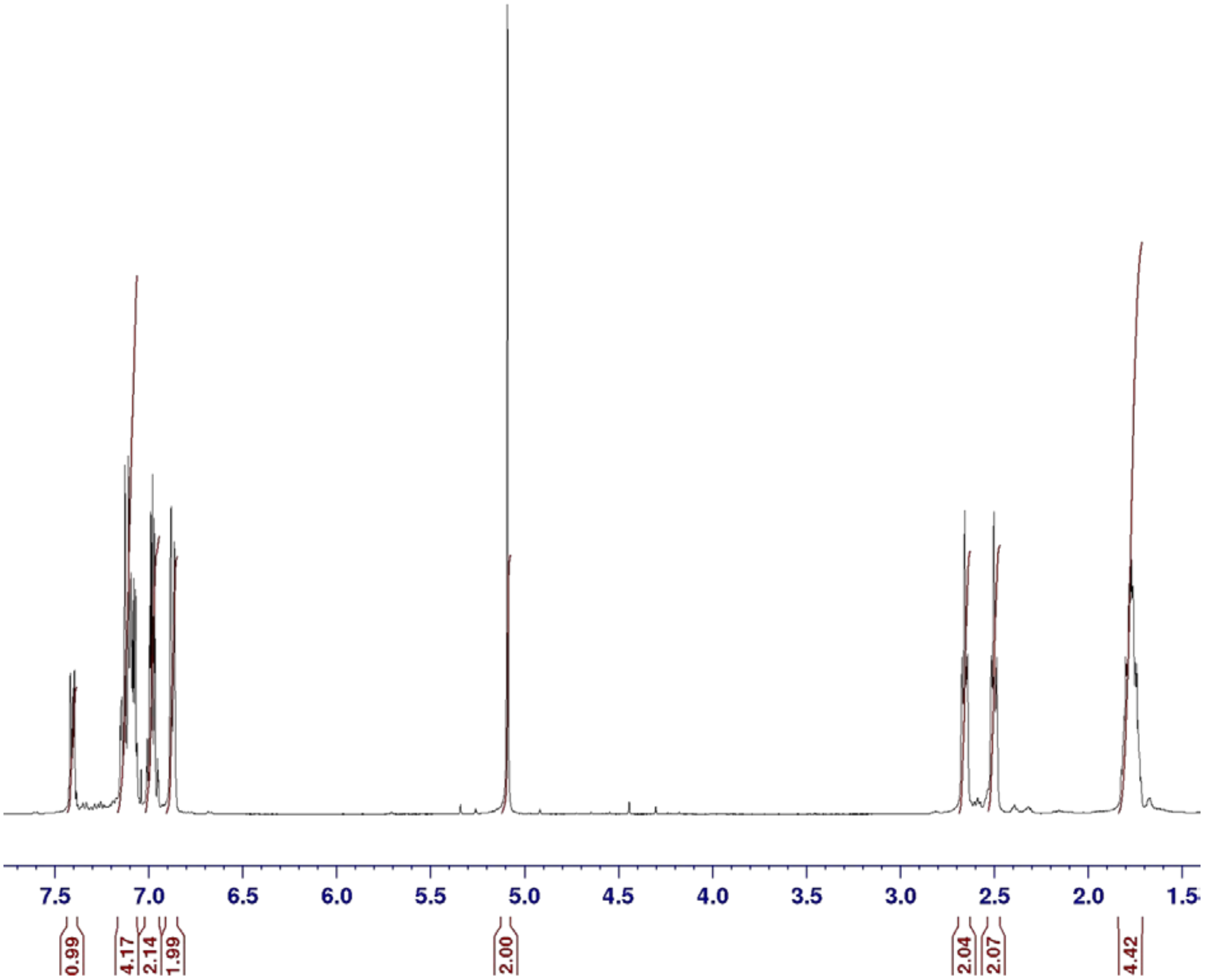
^{1}H NMR spectrum for 4o:



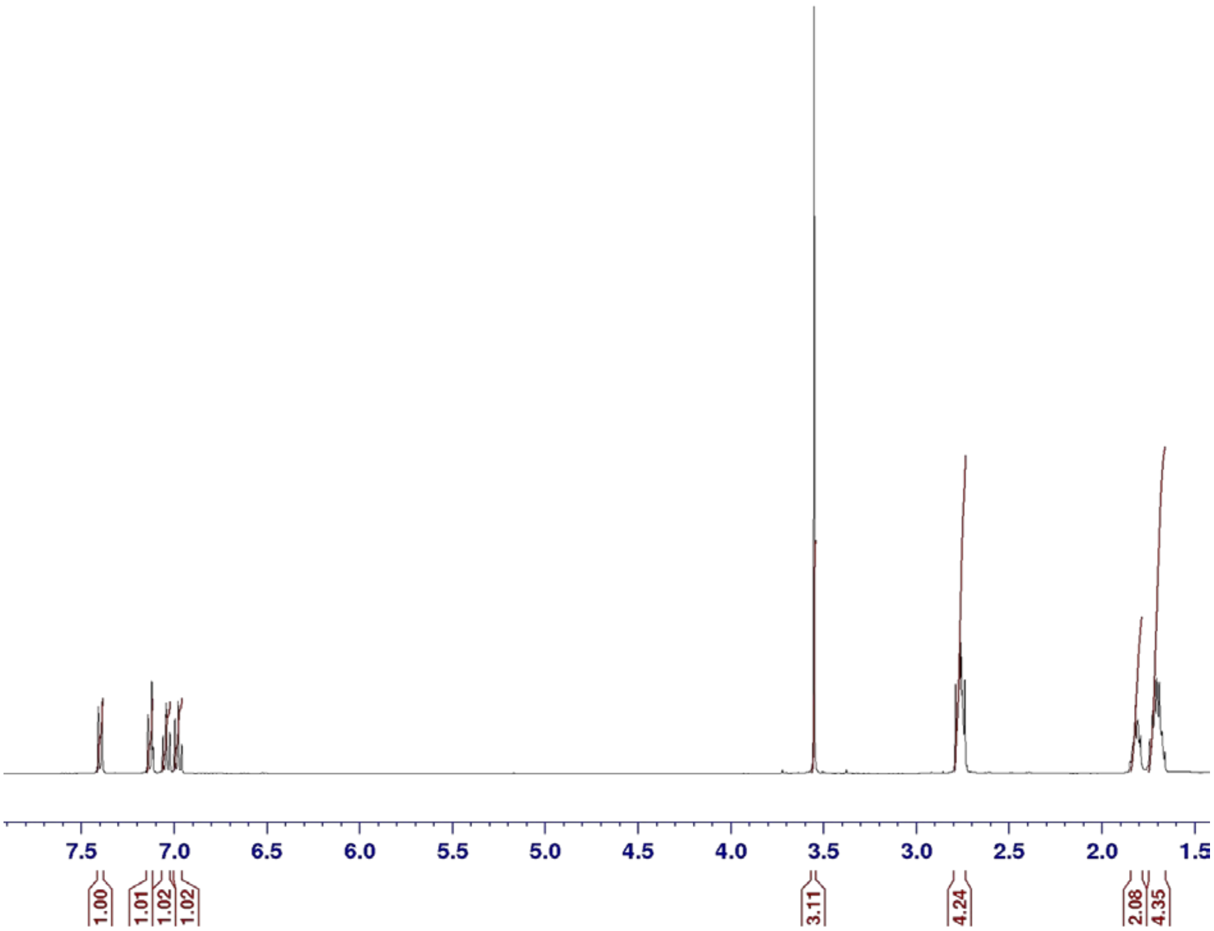
^{1}H NMR spectrum for 4p:



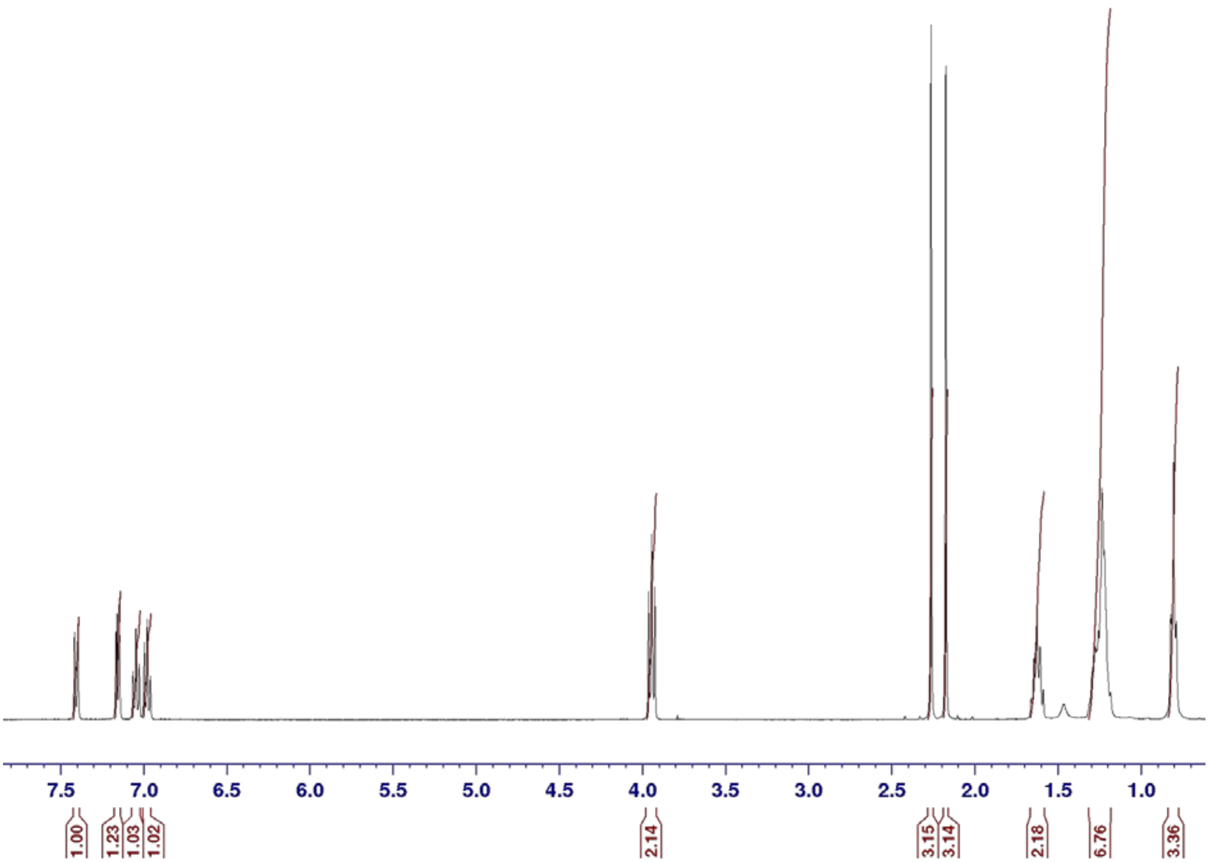
^{1}H NMR spectrum for 4q:

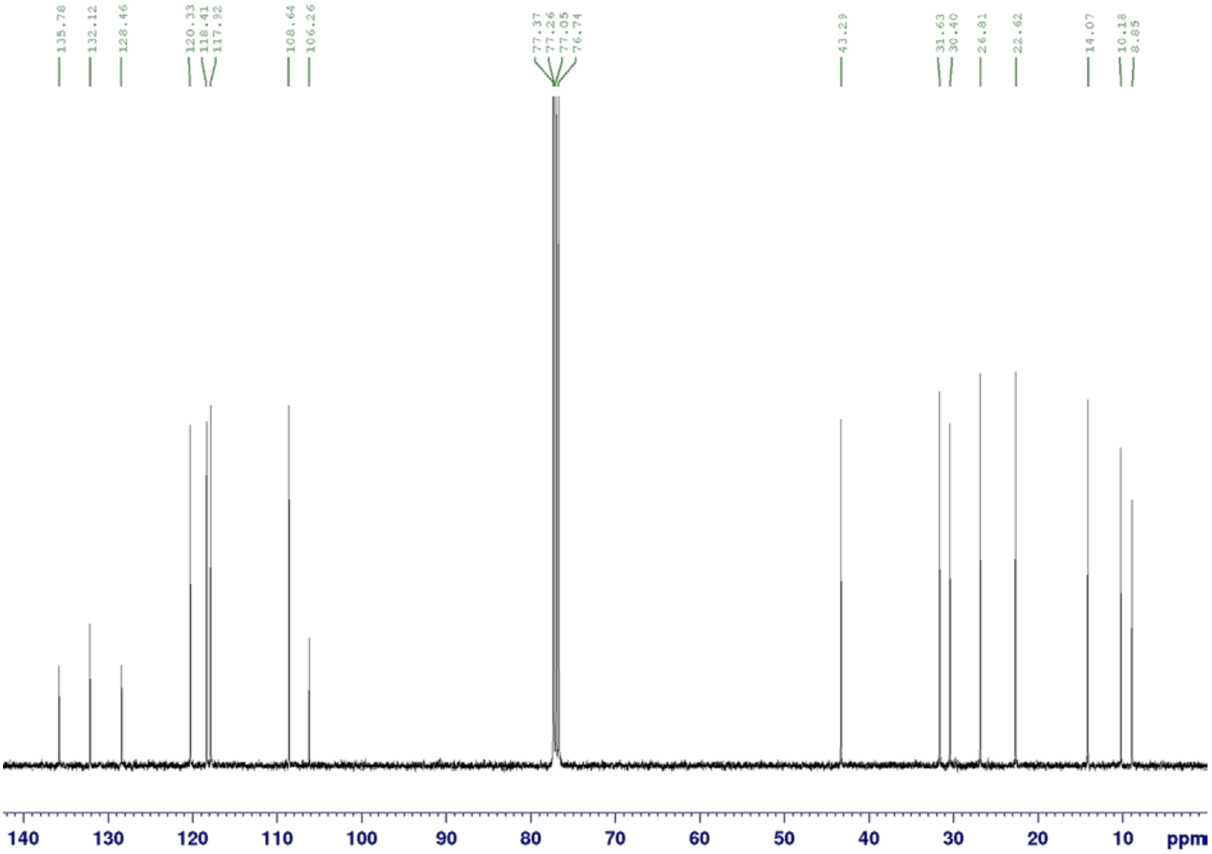


^{1}H NMR spectrum for 4r:

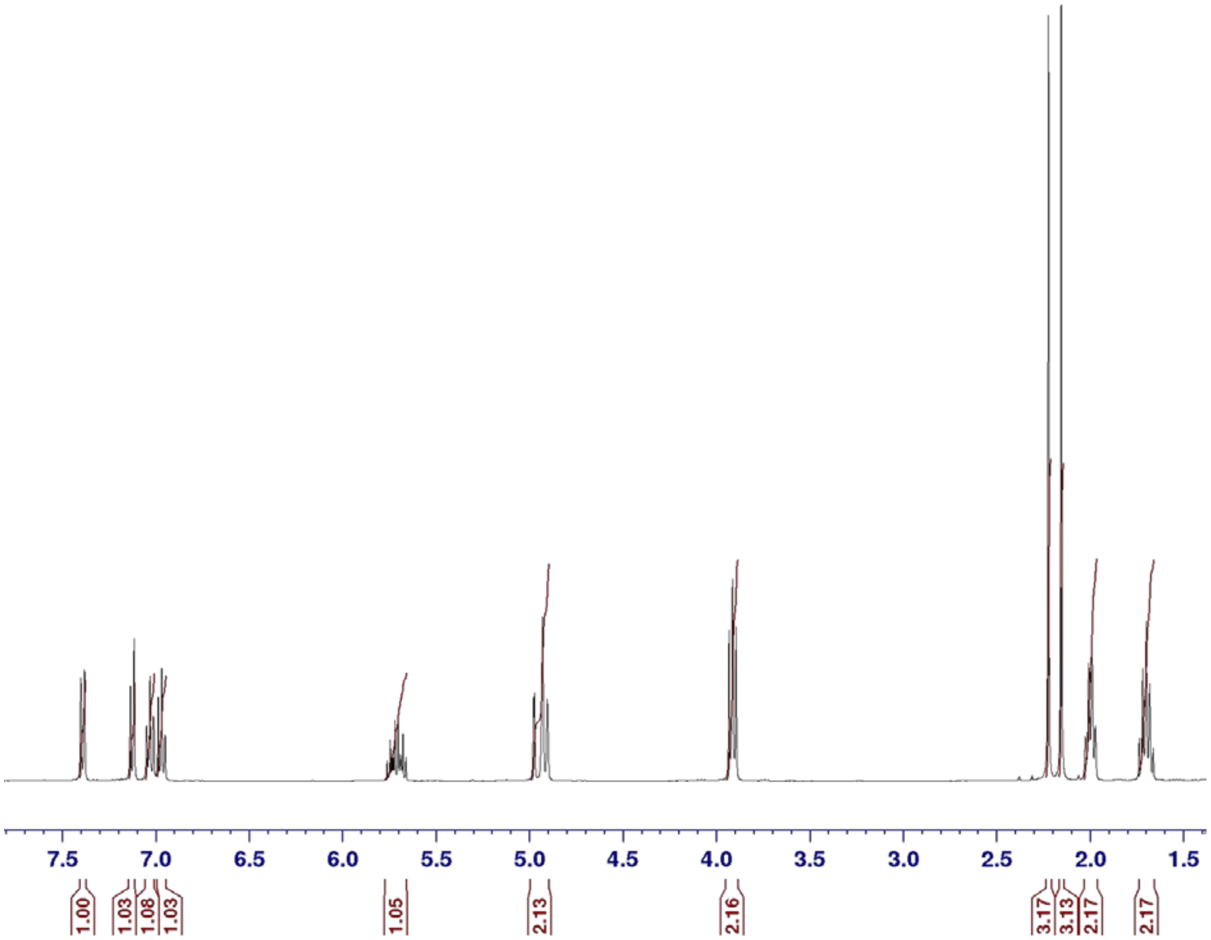


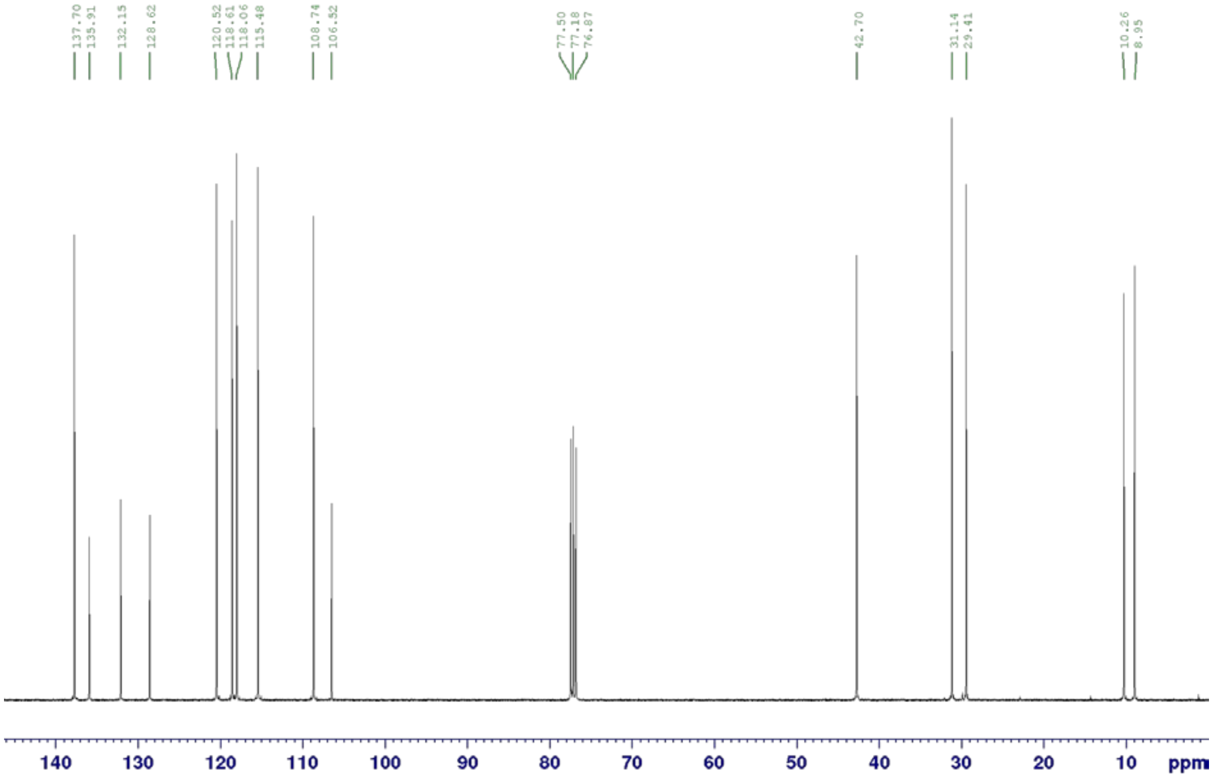
^{1}H and ^{13}C NMR spectra for 4s:



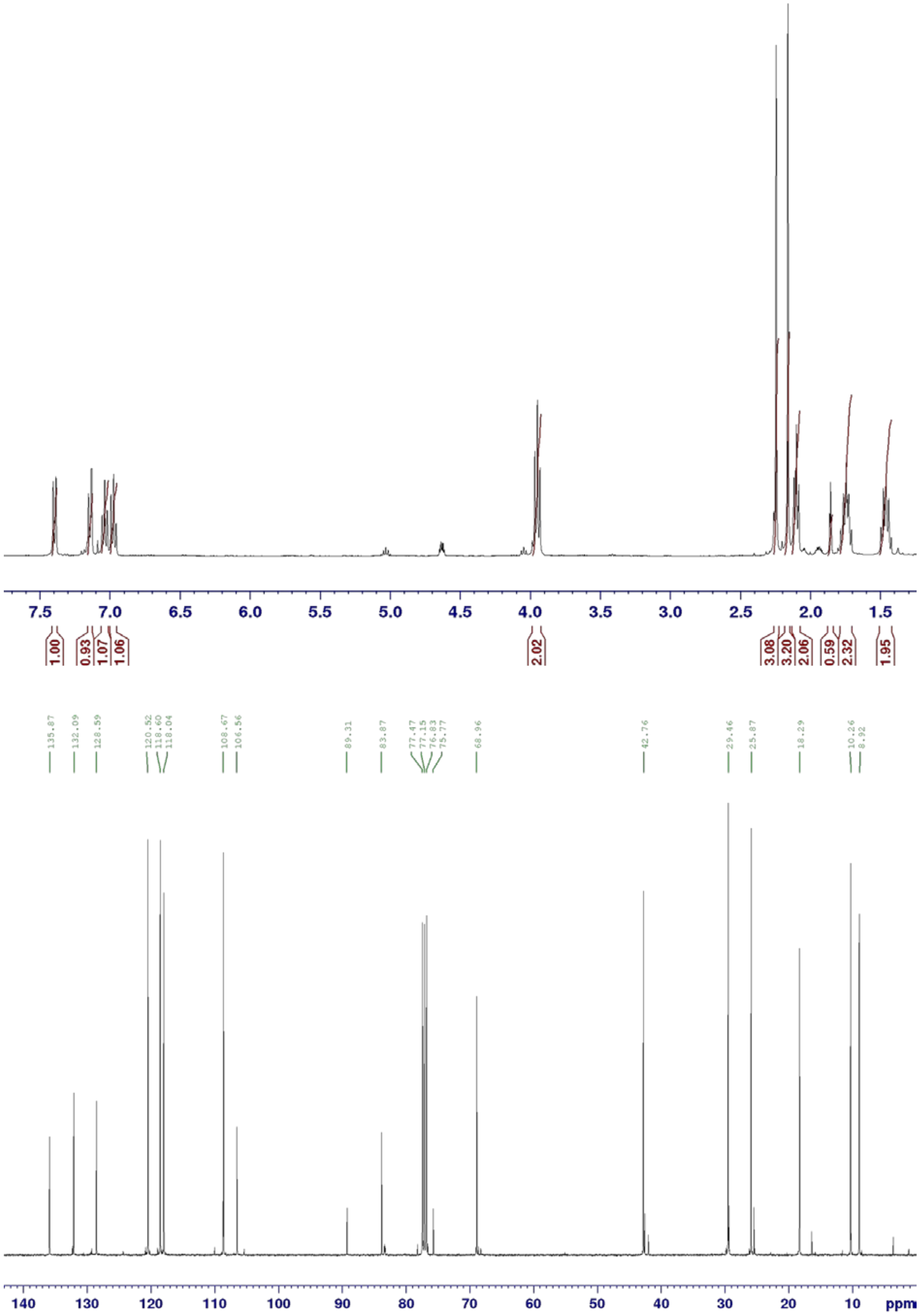


^{1}H and ^{13}C NMR spectra for 4t:

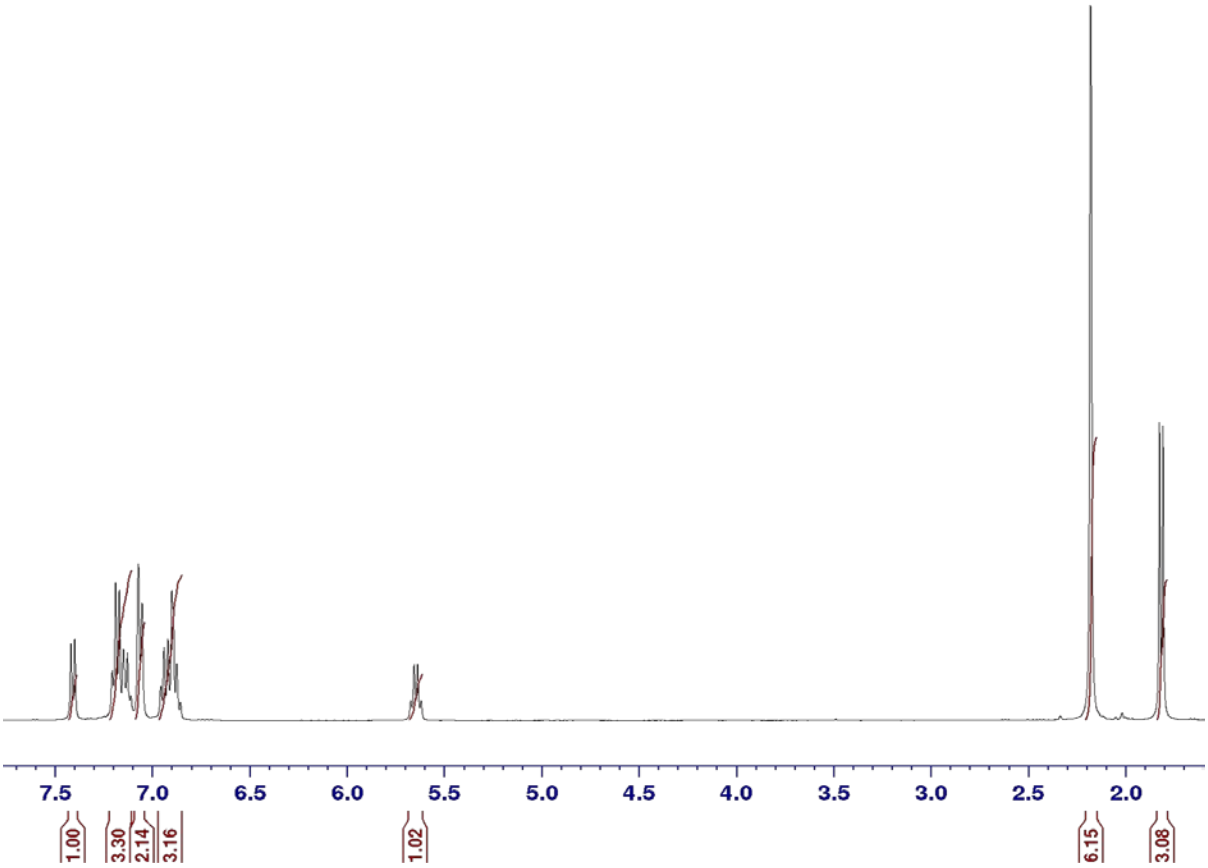


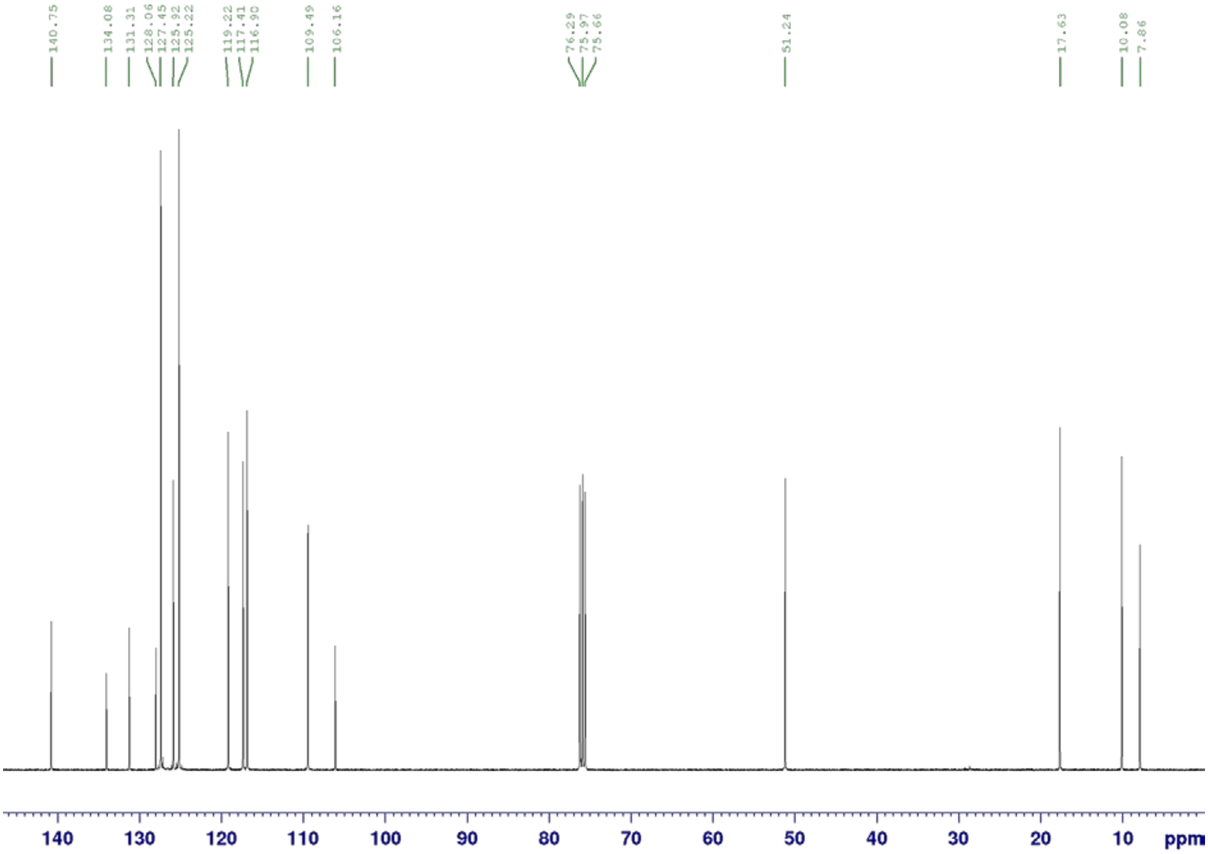


^{1}H and ^{13}C NMR spectra for 4u:

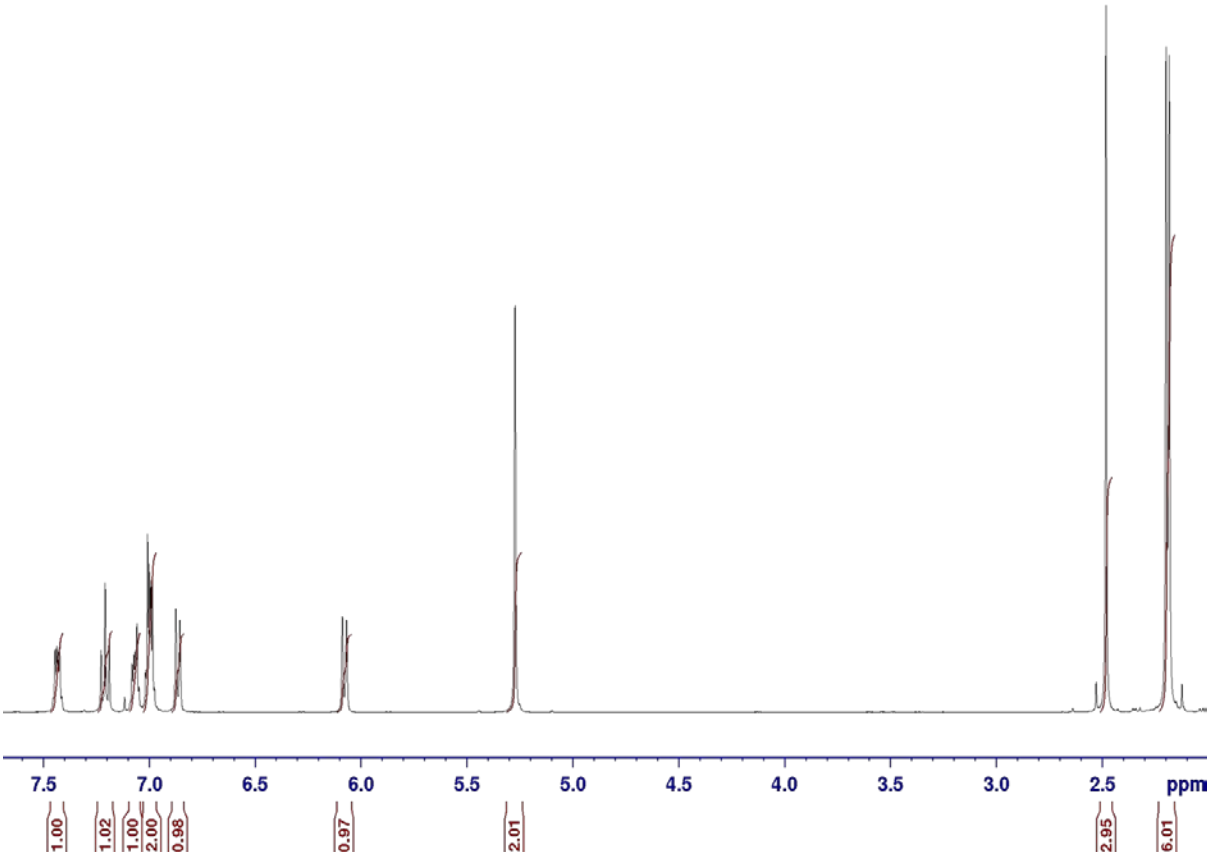


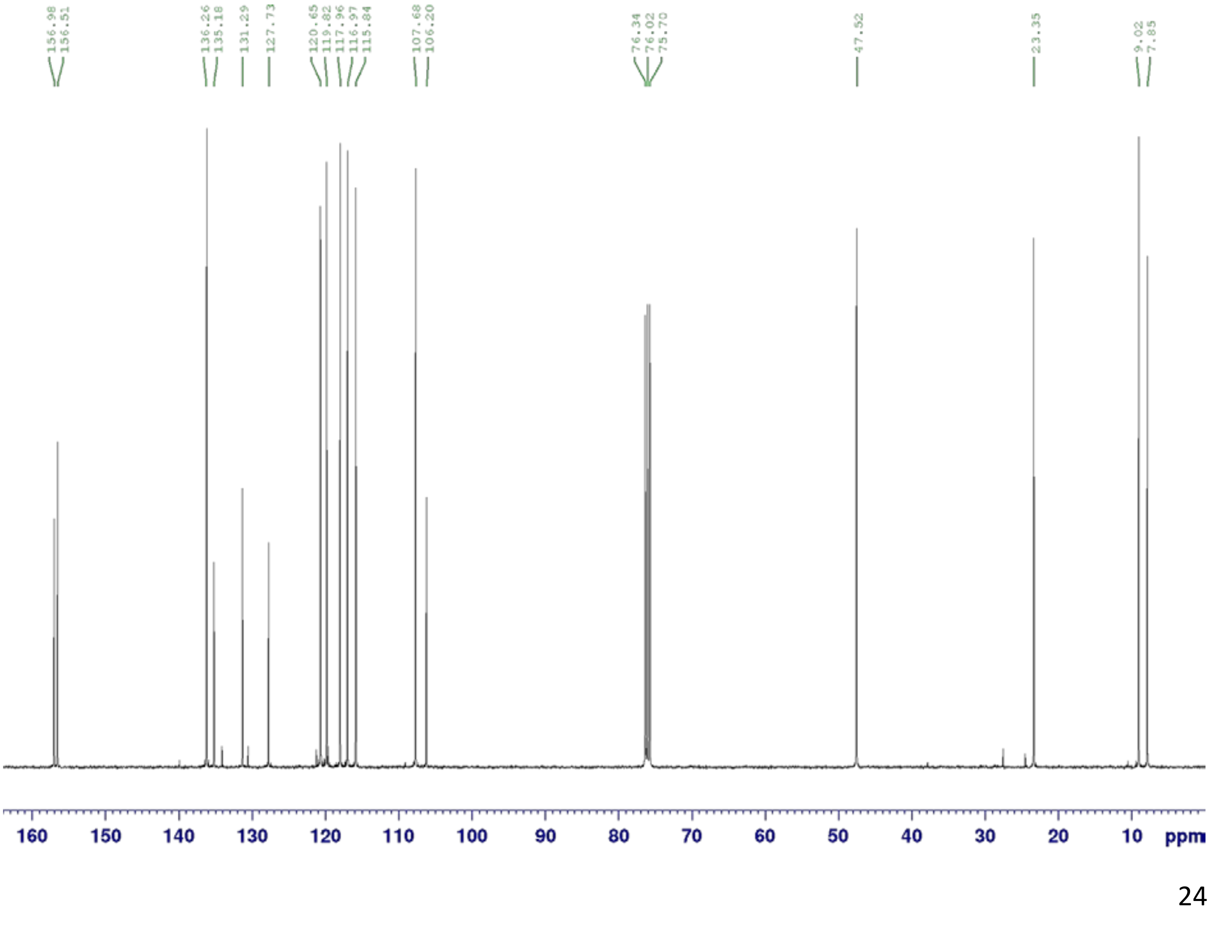
^{1}H and ^{13}C NMR spectra for 4v:



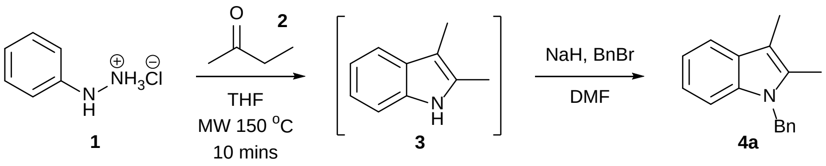


^{1}H and ^{13}C NMR spectra for 4w:





Quantitative analysis of one-pot and stepwise syntheses of 4a



Scheme S1 – Synthesis of indole ***4a*** *from hydrazine* ***1****, ketone* ***2*** *and benzyl bromide.*

The data included below derives from an attempt to quantitatively compare our one-pot Fischer indolisation–*N*-alkylation methodology with its stepwise counterpart. We have done this because we feel that it is often taken-as-read that one-pot, multi-step methodology is more effective than stepwise methodology, without any concrete evidence to validate this assumption.

We have made this comparison using our optimised, one-pot conditions for the synthesis of **4a**, and stepwise conditions that attempt to provide a *useful* benchmark (Scheme S1). Clearly, whichever conditions we chose for our stepwise reaction could serve to over-emphasise or downplay the differences between the two approaches (*e.g.* we could have chosen an overnight reflux for the Fischer indolisation to achieve the former, or we could have omitted intermediate chromatography to achieve the latter); consequently, we have opted for conditions that we consider to be both effective and representative of common, published practice.[1] As such, the stepwise conditions used here include an identical microwave-promoted Fischer indolisation protocol, but then differ from the one-pot approach through use of aqueous work up, silica gel chromatography of the intermediate 2,3-dimethylindole and standard, non-thermal indole *N*-alkylation.[1]

A comparison such as this clearly has its limitations beyond the choice of protocols – we only performed these analyses once, different workers will work with different efficiency at different tasks on different days, and invariably there is a degree of approximation in timing and measuring solvent use (*e.g.* what is the “right” length of time for a flask to reside on a rotary evaporator, or the “right” volume of solvent for washing up?). Nevertheless, we have attempted to be as thorough and consistent as possible (e.g. both processes were carried out by the same operator (AP) with identical equipment where appropriate) and we believe that the data we have collected offers a valid, interesting and useful comparison.

Stepwise Protocol:

Butanone (64 µL, 0.716 mmol, 1.05 eq.) was added to a stirred suspension of phenylhydrazine hydrochloride (99 mg, 0.682 mmol, 1 eq.) in THF (300 µL) in a thick-walled microwave tube. The tube was capped with a septum and heated to 150 °C using microwave irradiation (maximum power = 300 W; time to reach 150 °C = 3.5 minutes), then held at this temperature for 10 minutes. After cooling to room temperature, the reaction was partitioned between water (5 mL) and DCM (5 mL), the layers were separated and the aqueous phase was extracted with DCM (2 x 5 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure. The resulting crude product was purified by flash chromatography, eluting with 5% ethyl acetate in hexane, to give 2,3-dimethylindole (95 mg, 0.655 mmol, 96%). This was then dissolved in DMF (1.5 mL), and to this solution was added sodium hydride (31 mg of a 60% dispersion in mineral oil, 0.786 mmol, 1.2 eq. based on 1.0 eq. dimethylindole) then benzyl bromide (86 µL, 0.721 mmol, 1.1 eq. based on 1.0 eq. dimethylindole). The resulting mixture was stirred at room temperature for 1 hour, then quenched by dropwise addition of methanol and concentrated under reduced pressure. The crude indole was purified by flash chromatography, eluting with 3% ethyl acetate in hexane, to give 1-benzyl-2,3-dimethylindole (135 mg, 84% from phenylhydrazine·HCl) as a yellow oil.

One-pot Protocol

Butanone (64 µL, 0.716 mmol, 1.05 eq.) was added to a stirred suspension of phenylhydrazine hydrochloride (99 mg, 0.682 mmol, 1 eq.) in THF (300 µL) in a thick-walled microwave tube. The tube was capped with a septum and heated to 150 °C using microwave irradiation (maximum power = 300 W; time to reach 150 °C = 3.5 minutes), then held at this temperature for 10 minutes. After cooling to room temperature, sodium hydride (110 mg of a 60% dispersion in mineral oil, 2.51 mmol, 4 eq.) then DMF (500 µL) were cautiously added in small portions to the stirred reaction mixture, which was then recapped and heated to 80 °C using an oil bath. After 5 minutes, benzyl bromide (85 µL, 0.716 mmol, 1.05 eq.) was carefully added, and the resulting mixture was capped and stirred at 80 °C for 30 minutes, then quenched by dropwise addition of methanol and concentrated under reduced pressure. The crude indole was purified by flash chromatography, eluting with 3% ethyl acetate in hexane, to give 1-benzyl-2,3-dimethylindole (146 mg, 91% from phenylhydrazine·HCl) as a yellow oil.

Measurement of energy consumption was achieved using a domestic plug-in monitor (Prodigit Electronics model 2000MU).

	Stepwise	**One-pot**
Yield	84%, 0.573 mmol	91%, 0.621 mmol
Time	Prepare reaction 1 = 5 mins Total time in MW = 15 mins Work-up and concentrate = 44 minutes Chromatography (pre-packed column) = 36 mins Solvent evaporation on rotary evaporator = 20 mins Transfer and set up reaction 2 = 30 mins Reaction time = 60 mins Quench = 3 mins Rotavap = 15 mins Chromatography (column packed during evaporation) = 20 mins Concentrate = 20 mins **Total = 268 minutes**	Prepare reaction = 5 mins Total time in MW = 15 mins Addn of hydride = 3 mins Addn of DMF = 1 min Heat = 5 mins Addn of BnBr = 1 min Heat = 15 mins Quench = 3 mins Rotavap = 15 mins Chromatography (column packed during evaporation) = 20 mins Concentrate = 20 mins **Total = 103 minutes**
Solvent usage	Reaction 1: 0.3 mL THF Work-up (extraction, rinsing, transfer): 65 mL DCM Washing up: 130 mL acetone Column 1:Preparation – 150 mL hexane Running – 300 mL (hexane 285 mL and ethyl acetate 15 mL) Rinse column tubes – 120 mL acetone Washing up – 200 mL acetone Transfer: 5 mL DCM Reaction 2: 1.5 mL DMF Quench: 3 mL methanol Transfer/rinse: 10 mL (methanol 5 mL and acetone 5 mL) Washing up: 9 mL acetone Column 2:Preparation – 150 mL hexane Running – 250 mL (hexane 242.5 mL and ethyl acetate 7.5 mL) Rinse column tubes – 100 mL acetone Washing up – 200 mL acetone **Total = 1694 mL (2.96 L / mmol 4a)**	Reaction: 0.3 mL THF and 0.5 mL DMF Quench: 3 mL methanol Transfer/rinse: 10 mL (methanol 5 mL and acetone 5 mL) Washing up: 9 mL acetone Column: Preparation – 150 mL hexane Running – 250 mL (hexane 242.5 mL and ethyl acetate 7.5 mL) Rinse column tubes – 100 mL acetone Washing up – 200 mL acetone **Total = 723 mL (1.16 L / mmol 4a)**
Energy	MW 150 °C / 10 mins = 0.03 kWh Stirring / RT / 1 h = 0.01 kWh **Total = 0.04 kWh**	MW 150 °C / 10 mins = 0.03 kWh Stirring / 80 °C oil bath / 15 mins = 0.03 kWh **Total = 0.06 kWh**

Reference for Supplementary Information

1. A. Perry, K. Davis and L. West, *Org. Biol. Chem.*, 2018, **16**, 7245–7254.