ANNEXURE A

Supplementary Information

INHIBITION OF MONOAMINE OXIDASE BY SELECTED C-5 AND C-6 SUBSTITUTED ISATIN ANALOGUES

Supplementary Information

Chromatograms of the HPLC analyses of the synthesized compounds

Chromatograms are indicated at 210, 254 and 300 nm respectively.

INHIBITION OF MONOAMINE OXIDASE BY SELECTED C5- AND C6-SUBSTITUTED ISATIN ANALOGUES

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Supplementary Material

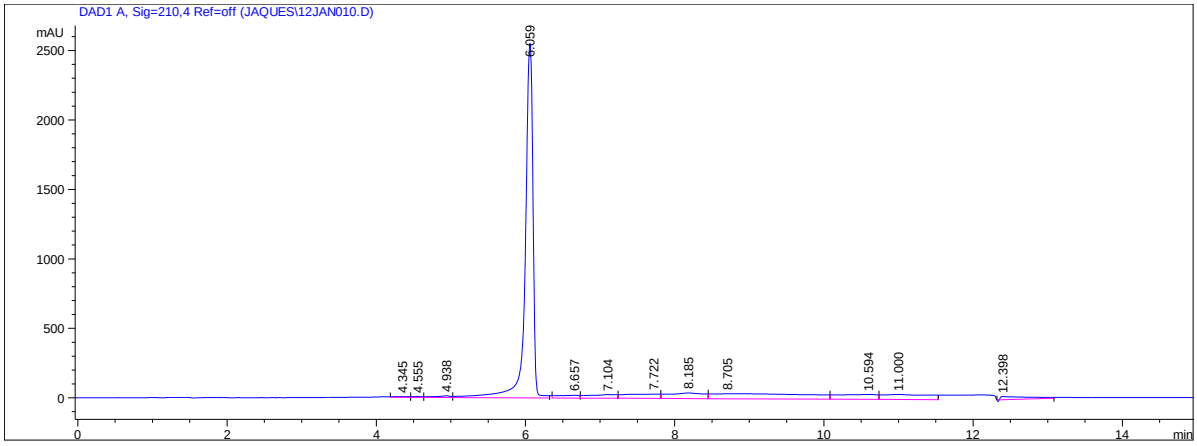
S1: HPLC traces of the following new/unknown compounds

- 5-Benzyloxyisatin (**9a**)
- 6-Benzyloxyisatin (**9b**)
- 5-(2-Phenylethyl)isatin (**9c**)
- 6-(2-Phenylethyl)isatin (**9d**)
- 5-Phenoxyisatin (**9e**)
- 6-Phenoxyisatin (**9f**)
- 5-Phenylisatin (**9g**)
- 6-Phenylisatin (**9h**)
- 5-(4-Phenylbutyl)isatin (**9i**)
- 5-(4-Chlorophenoxy)isatin (**9j**)

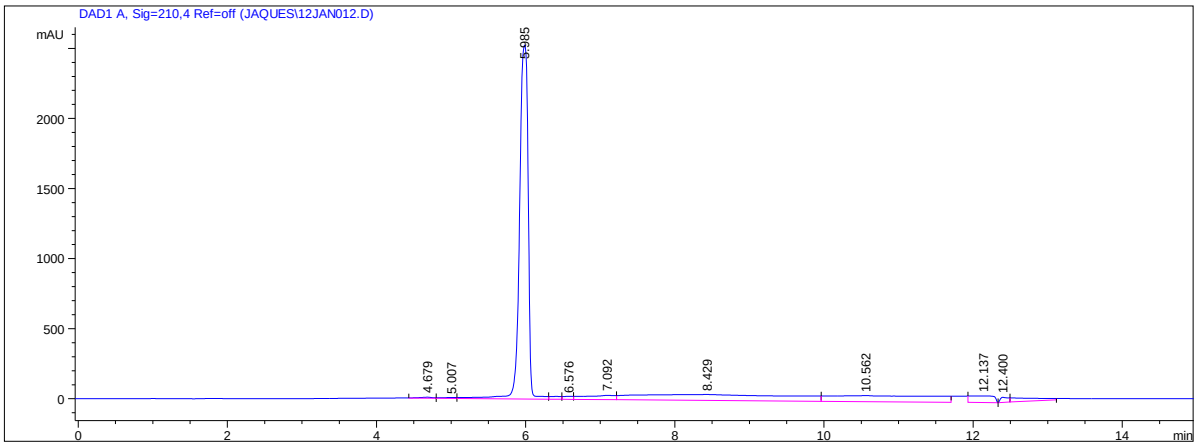
Method: To determine the purity of the previously unreported compounds (**9a**–**j**), HPLC analyses were carried out. HPLC analyses were performed with an Agilent 1100 HPLC system equipped with a quaternary pump and an Agilent 1100 series diode array detector. A Venusil XBP C18 column (4.60 × 150 mm, 5 µm) was used and the mobile phase consisted initially of 30% acetonitrile and 70% MilliQ water at a flow rate of 1 mL/min. At the start of each HPLC run a solvent gradient program was initiated by linearly increasing the composition of the acetonitrile in the mobile phase to 85% acetonitrile over a period of 5 min. Each HPLC run lasted 15 min

and a time period of 5 min was allowed for equilibration between runs. A volume of 20 µL of solutions of the test compounds in acetonitrile (1 mM) was injected into the HPLC system and the eluent was monitored at wavelengths of 210, 254 and 300 nm.

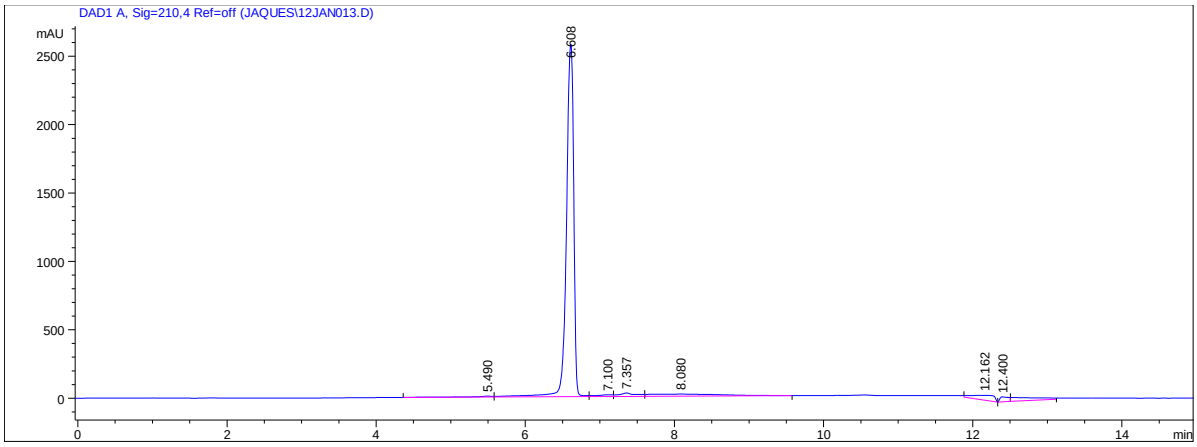
5-Benzyloxyisatin (9a)



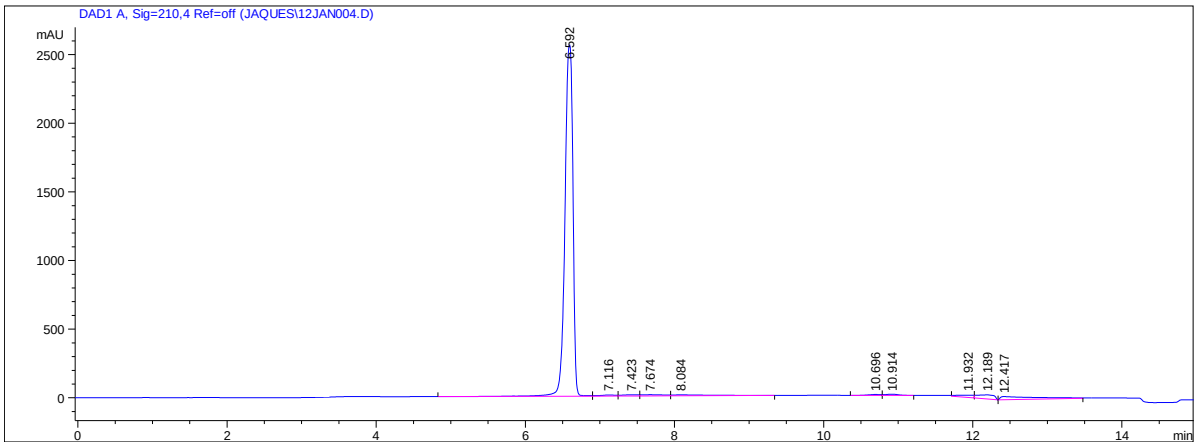
6-Benzyloxyisatin (9b)



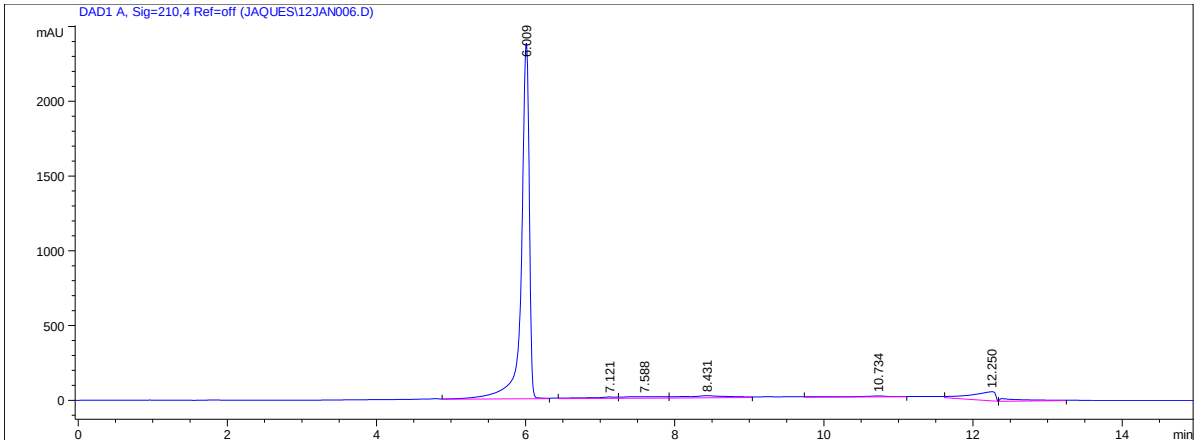
5-(2-Phenylethyl)isatin (9c)



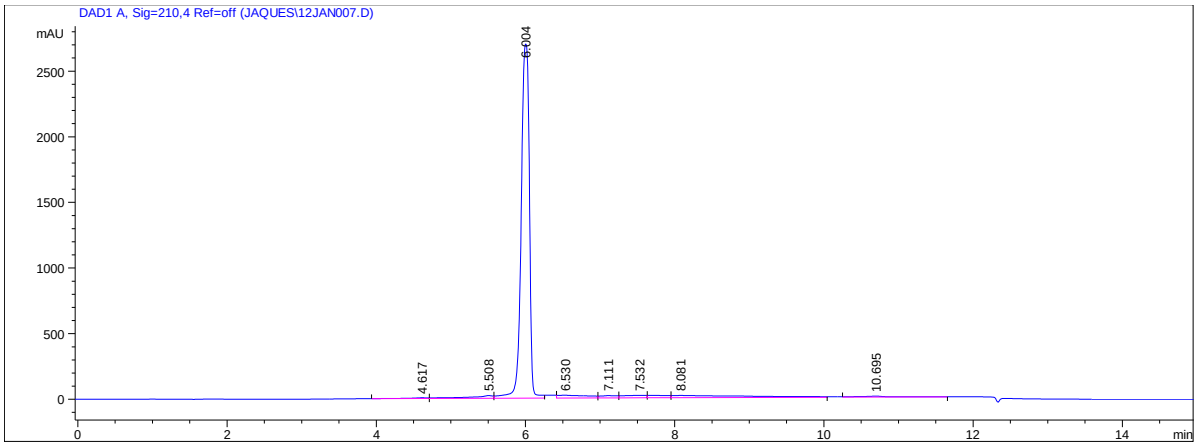
6-(2-Phenylethyl)isatin (9d)



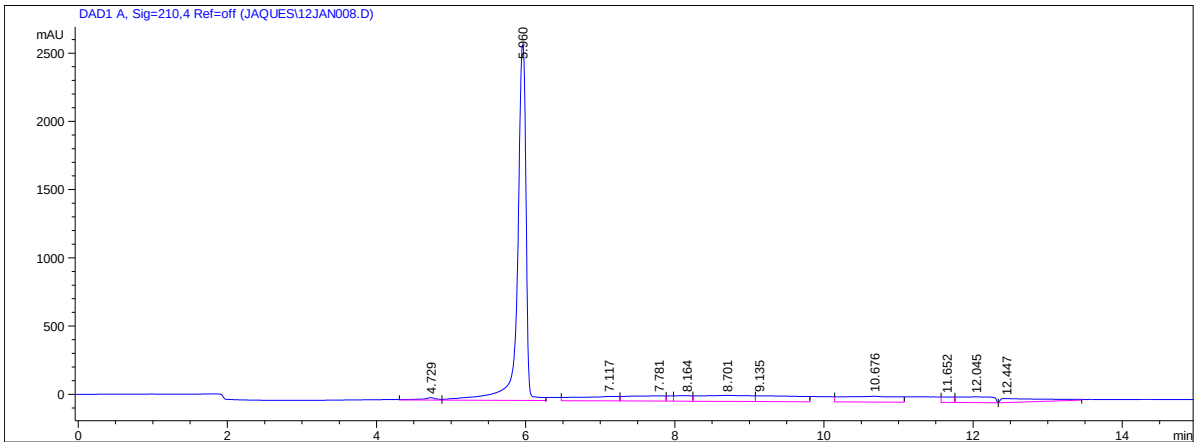
5-Phenoxyisatin (9e)



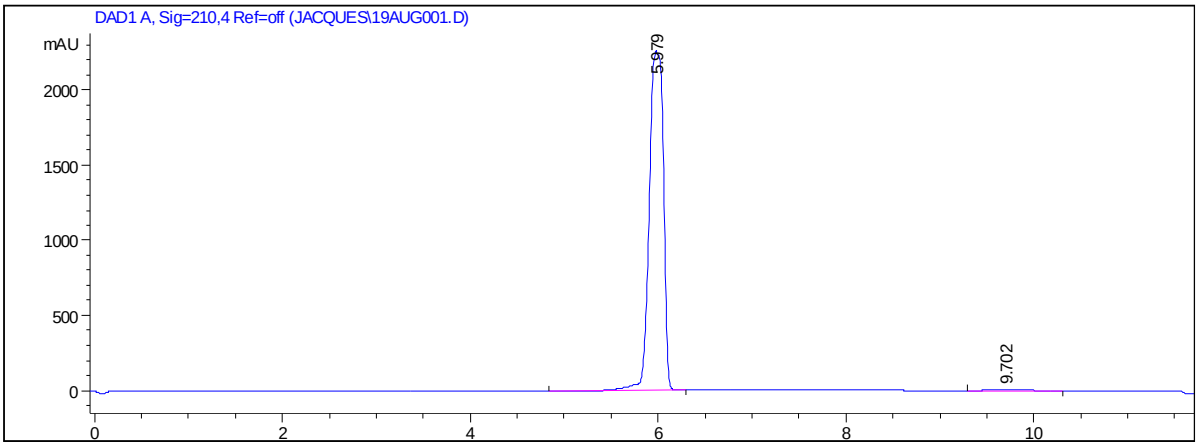
6-Phenoxyisatin (9f)



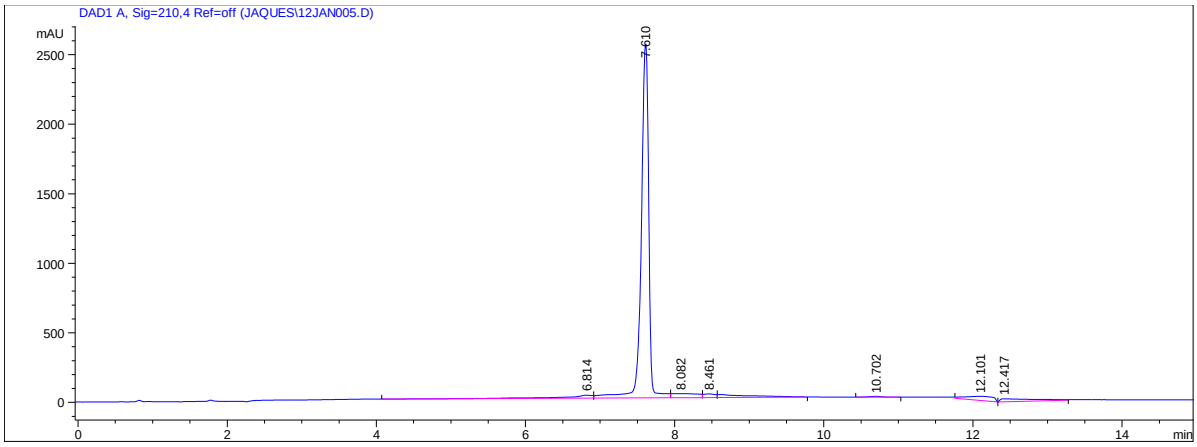
5-Phenylisatin (9g)



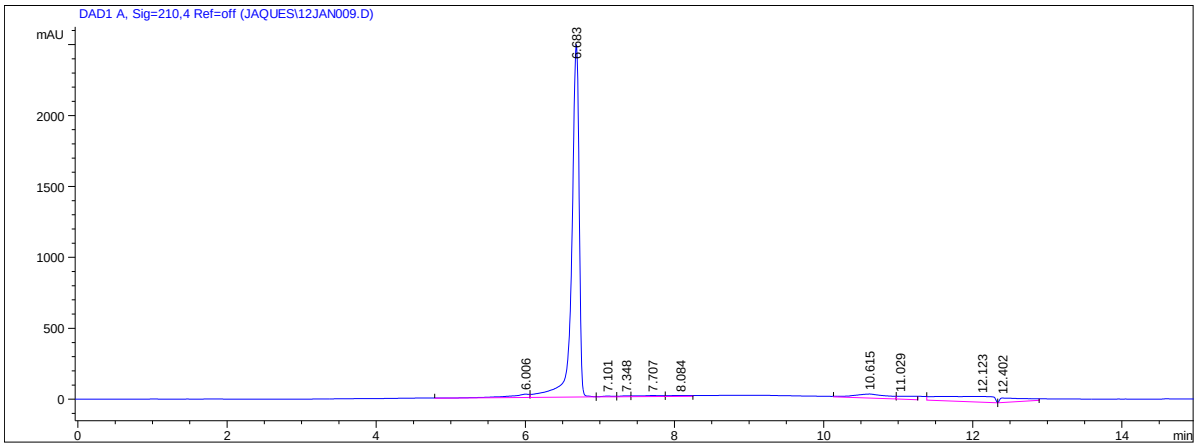
6-Phenylisatin (9h)



5-(4-Phenylbutyl)isatin (9i)



5-(4-Chlorophenoxy)isatin (9j)



S2: ^{1}H NMR and ^{13}C NMR spectra of the following new/unknown compounds

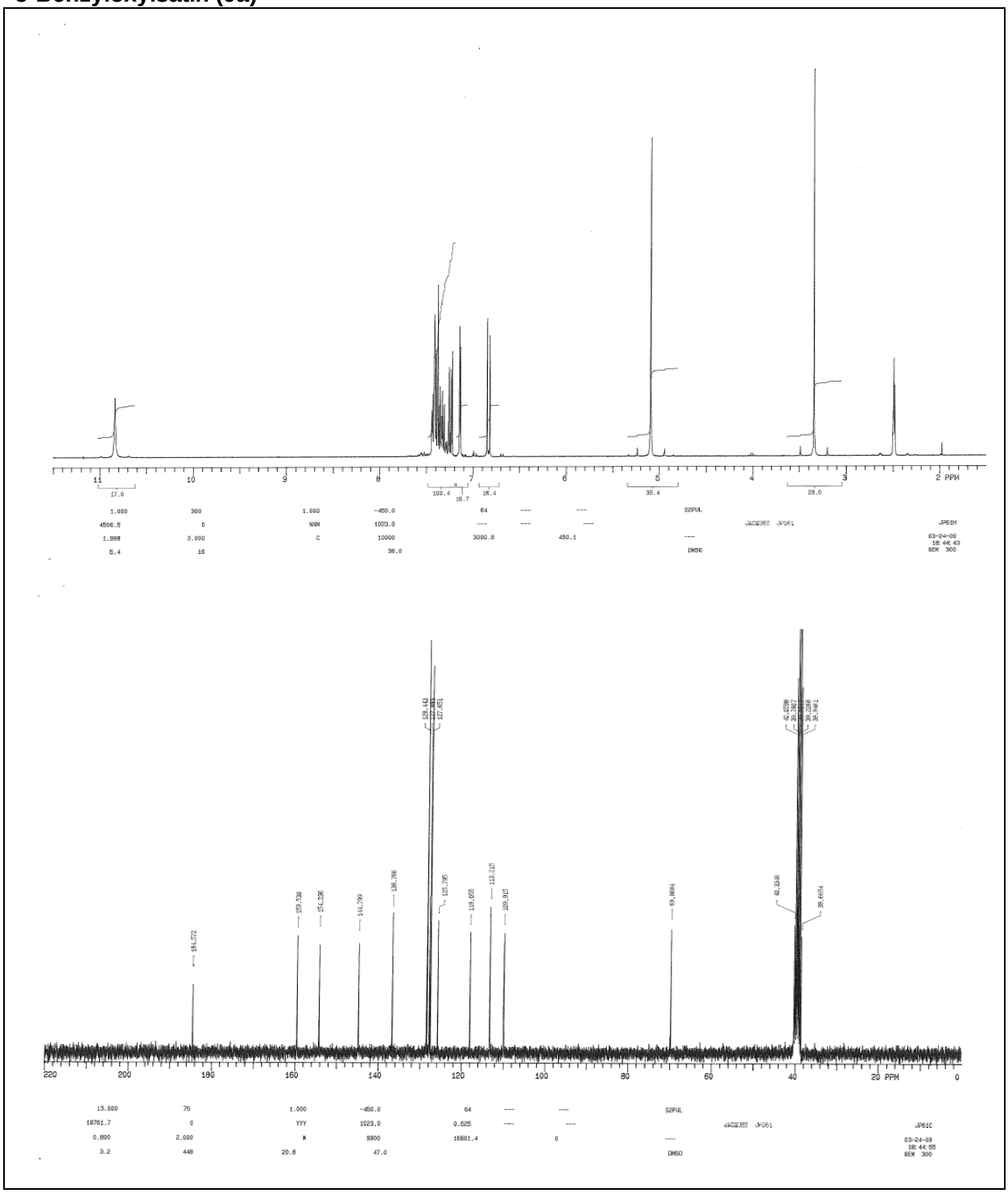
- 5-Benzyloxyisatin (**9a**)
- 6-Benzyloxyisatin (**9b**)
- 5-(2-Phenylethyl)isatin (**9c**)
- 6-(2-Phenylethyl)isatin (**9d**)
- 5-Phenoxyisatin (**9e**)
- 6-Phenoxyisatin (**9f**)
- 5-Phenylisatin (**9g**)
- 6-Phenylisatin (**9h**)

- 5-(4-Phenylbutyl)isatin (**9i**)
- 5-(4-Chlorophenoxy)isatin (**9j**)

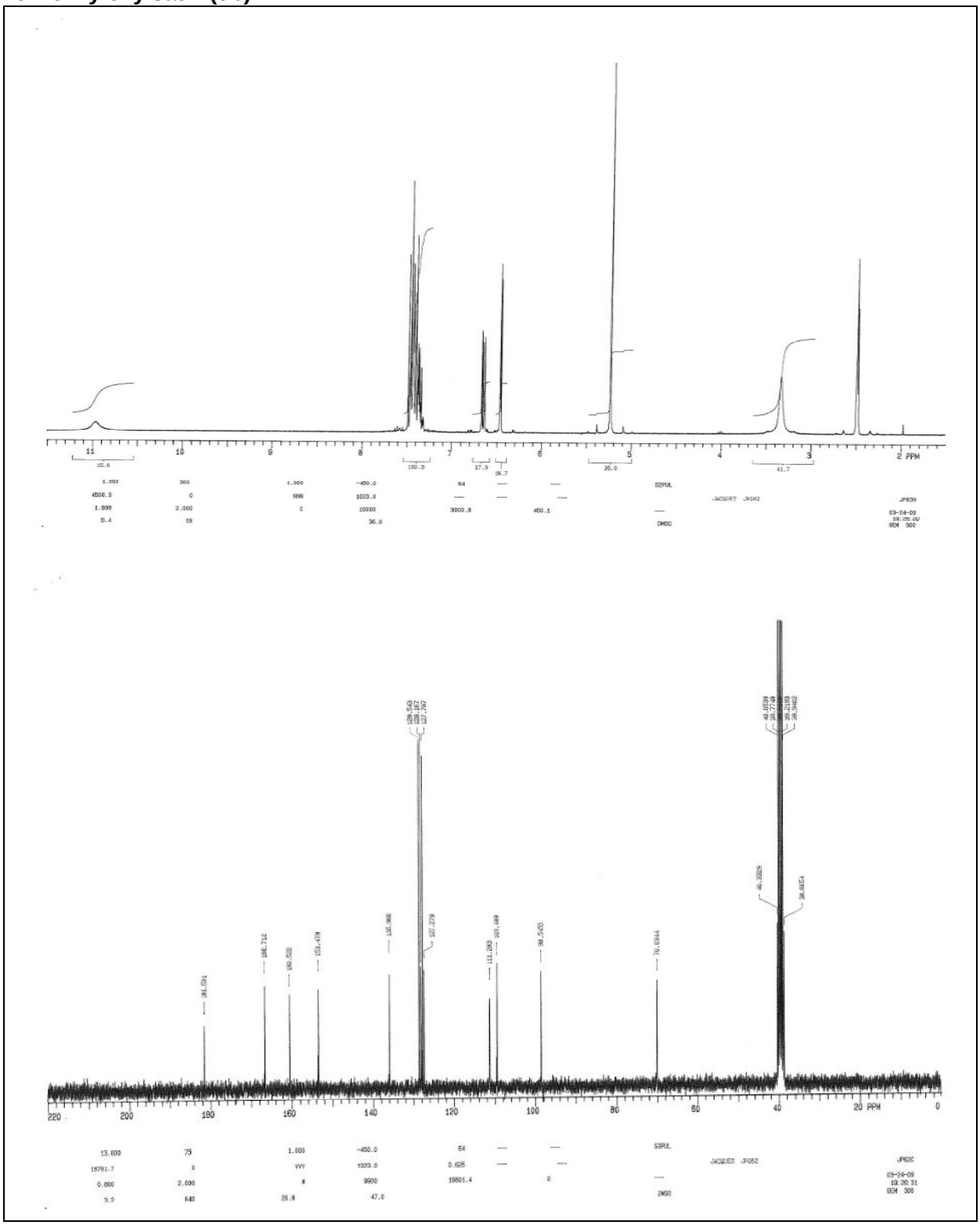
Proton (^{1}H) and carbon (^{13}C) NMR spectra were recorded on a Varian Gemini 300 spectrometer at frequencies of 300 MHz and 75 MHz, respectively, and on a Bruker Avance III 600 spectrometer at frequencies of 600 MHz and 150 MHz, respectively. All NMR measurements were conducted in DMSO-d*6*.

^{1}H-NMR and ^{13}C-NMR

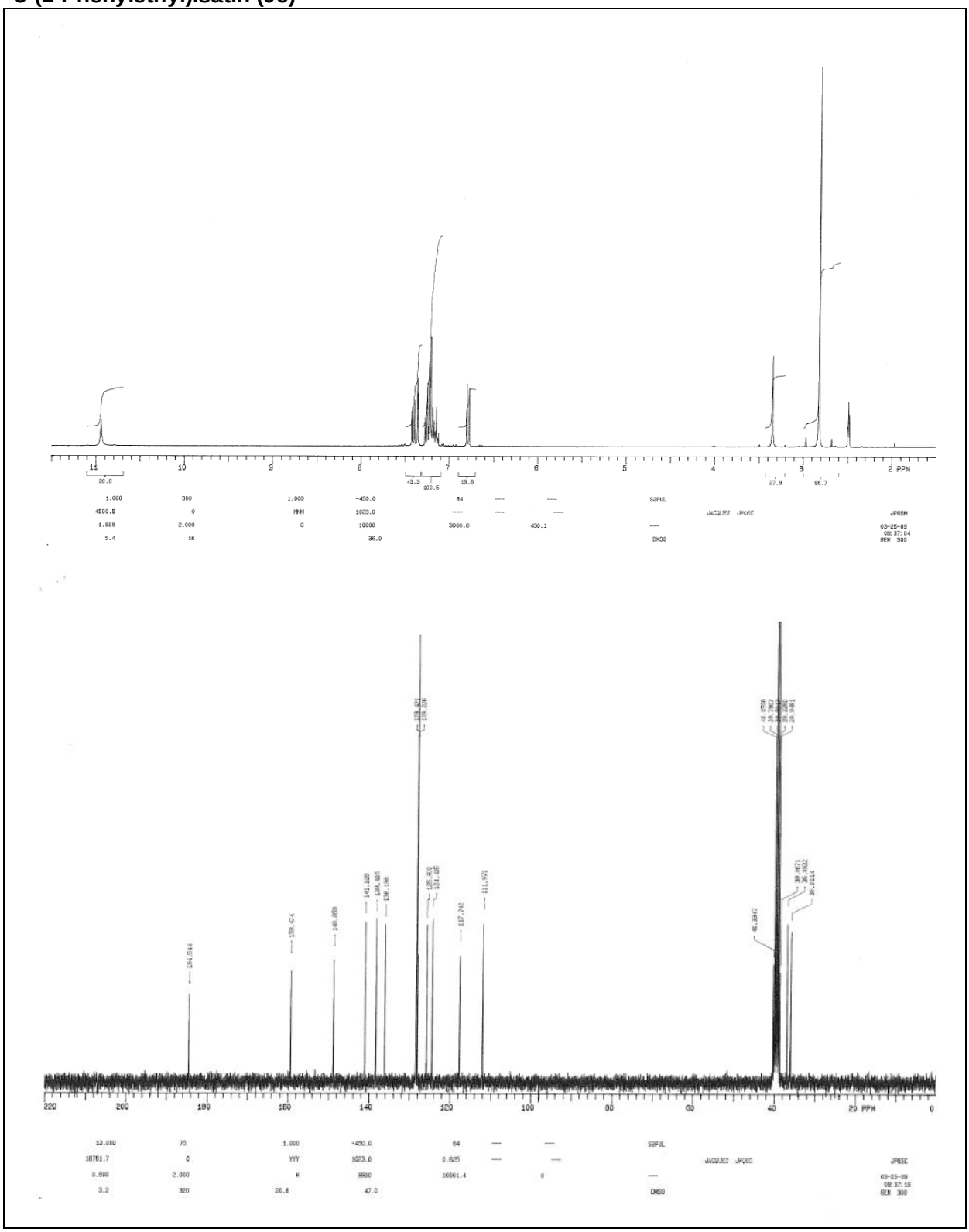
5-Benzyloxyisatin (9a)



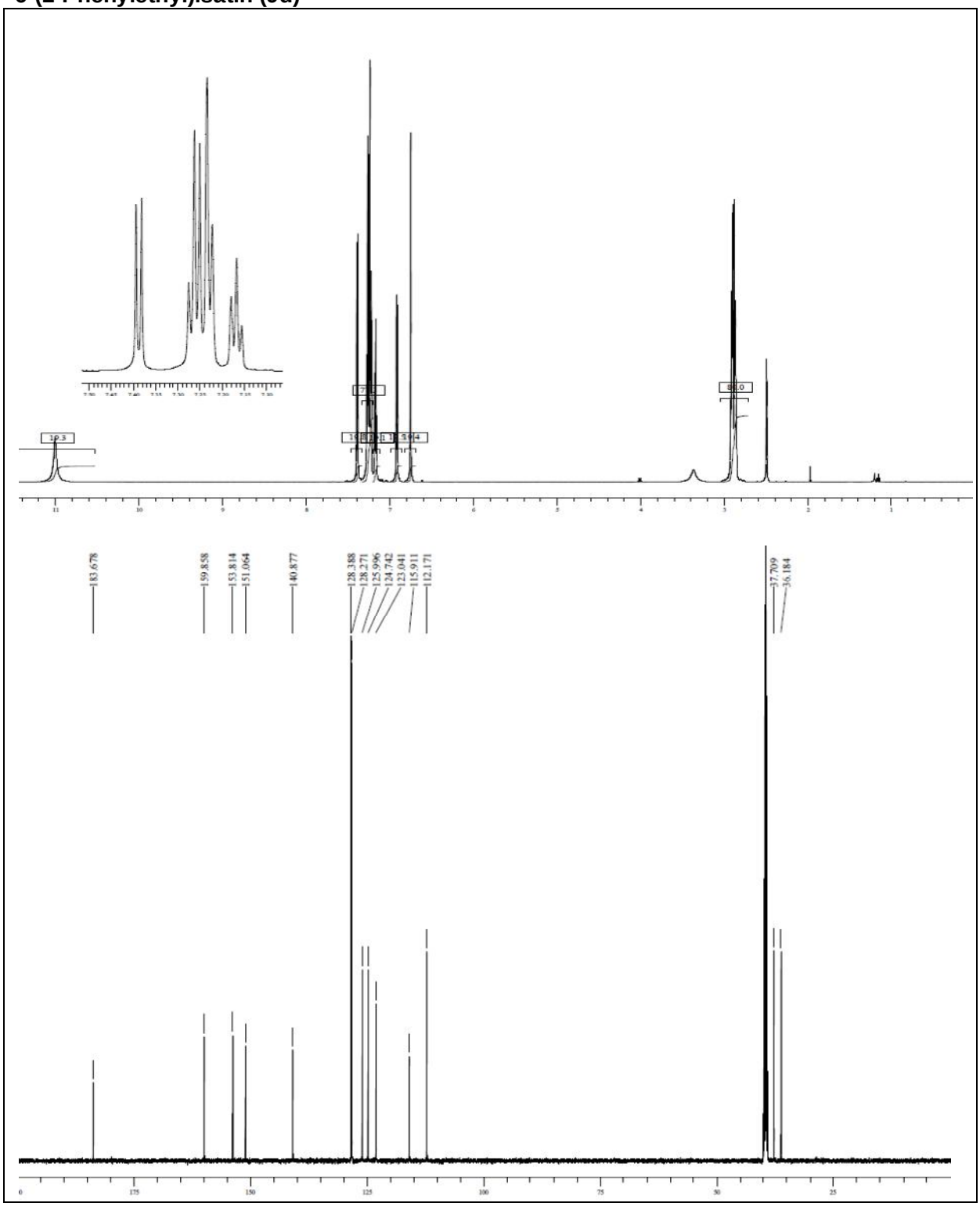
6-Benzyloxyisatin (9b)



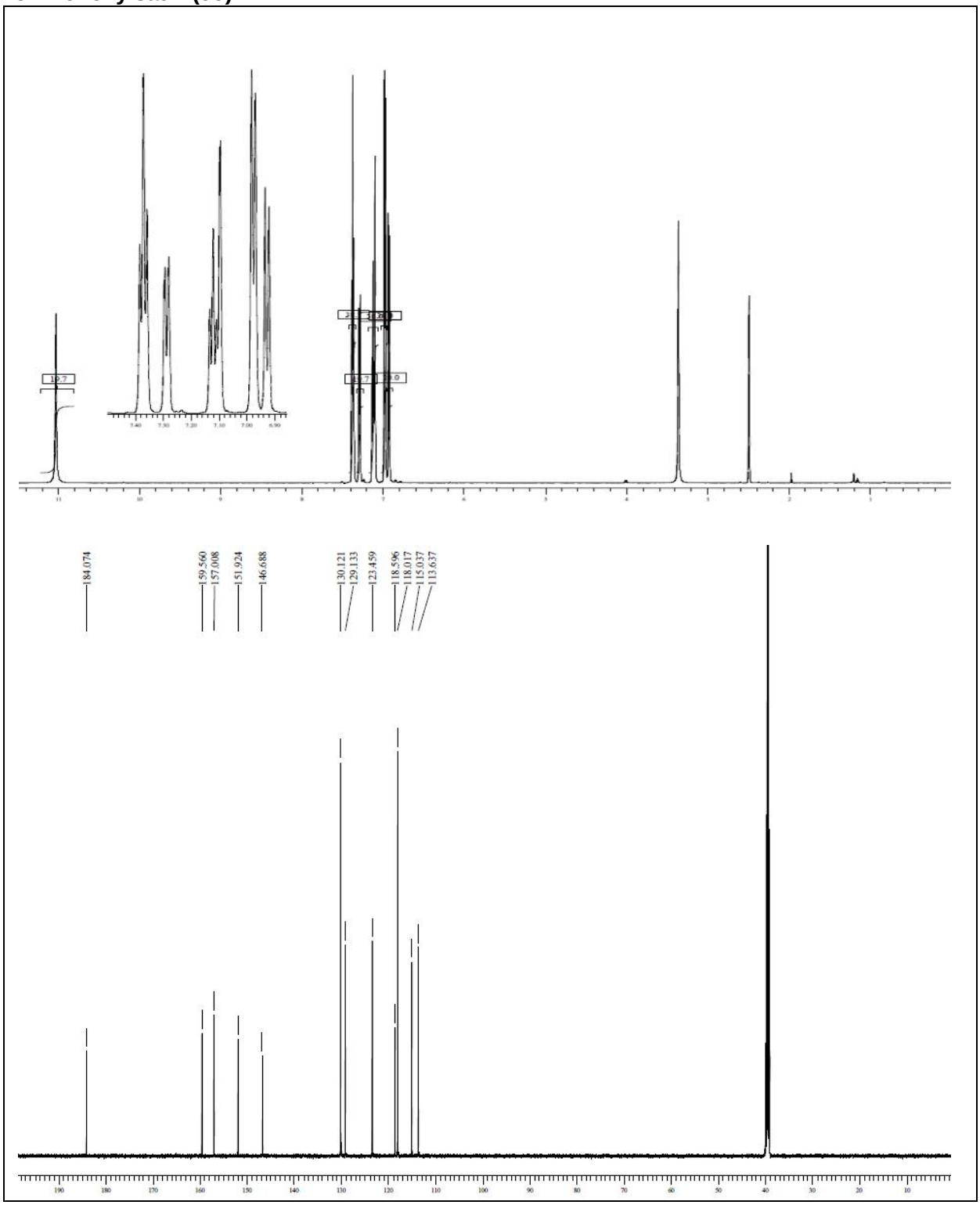
5-(2-Phenylethyl)isatin (9c)



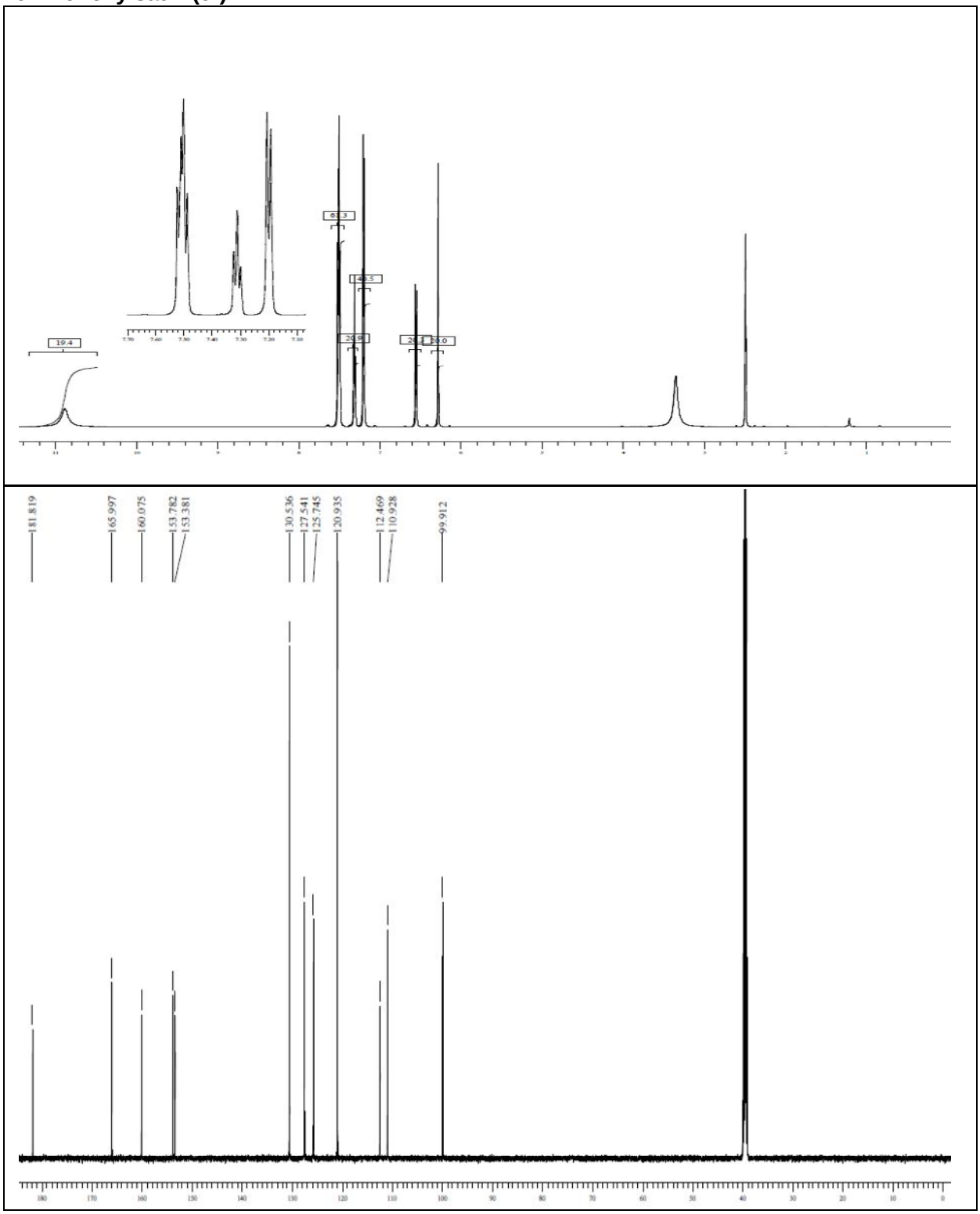
6-(2-Phenylethyl)isatin (9d)



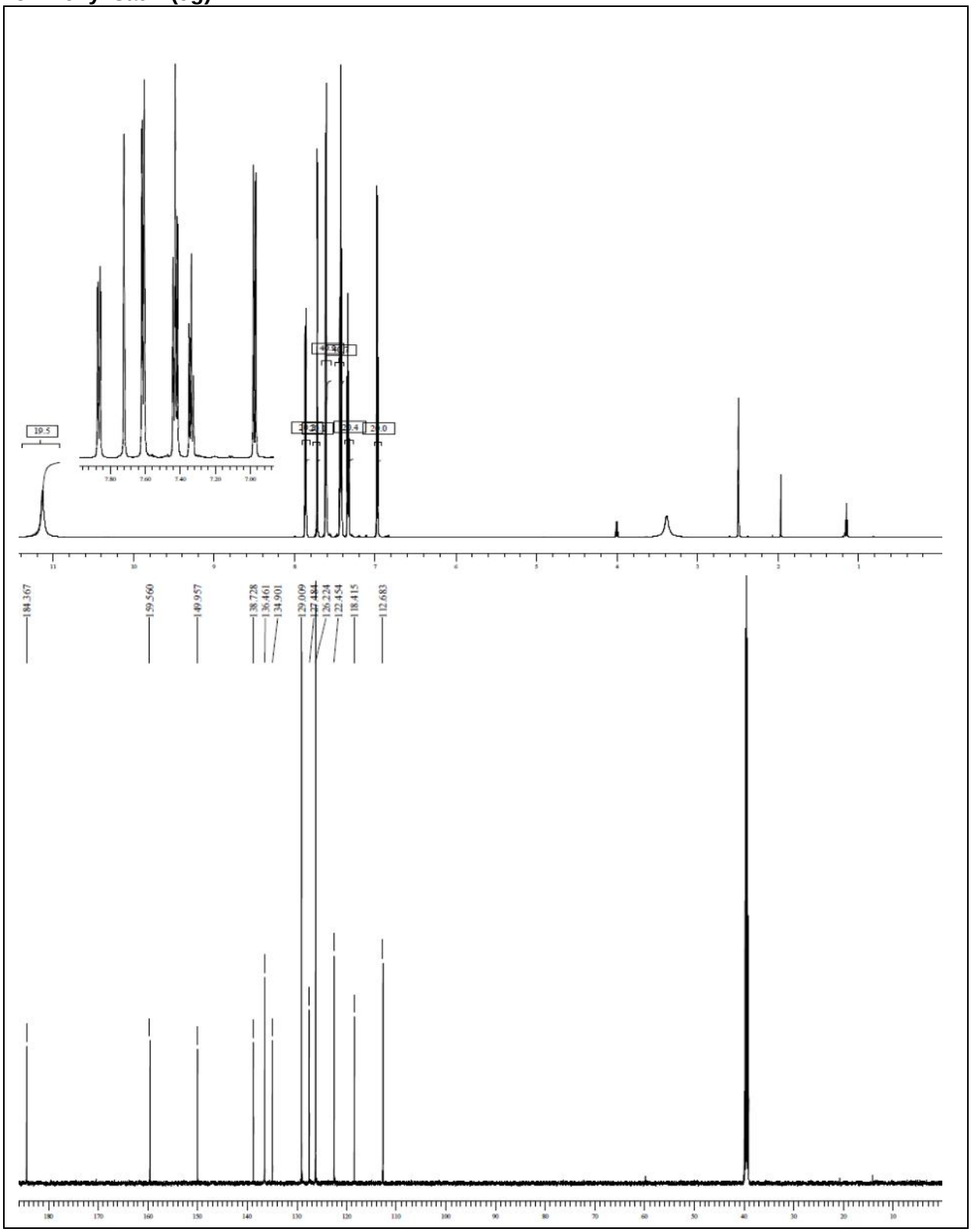
5-Phenoxyisatin (9e)



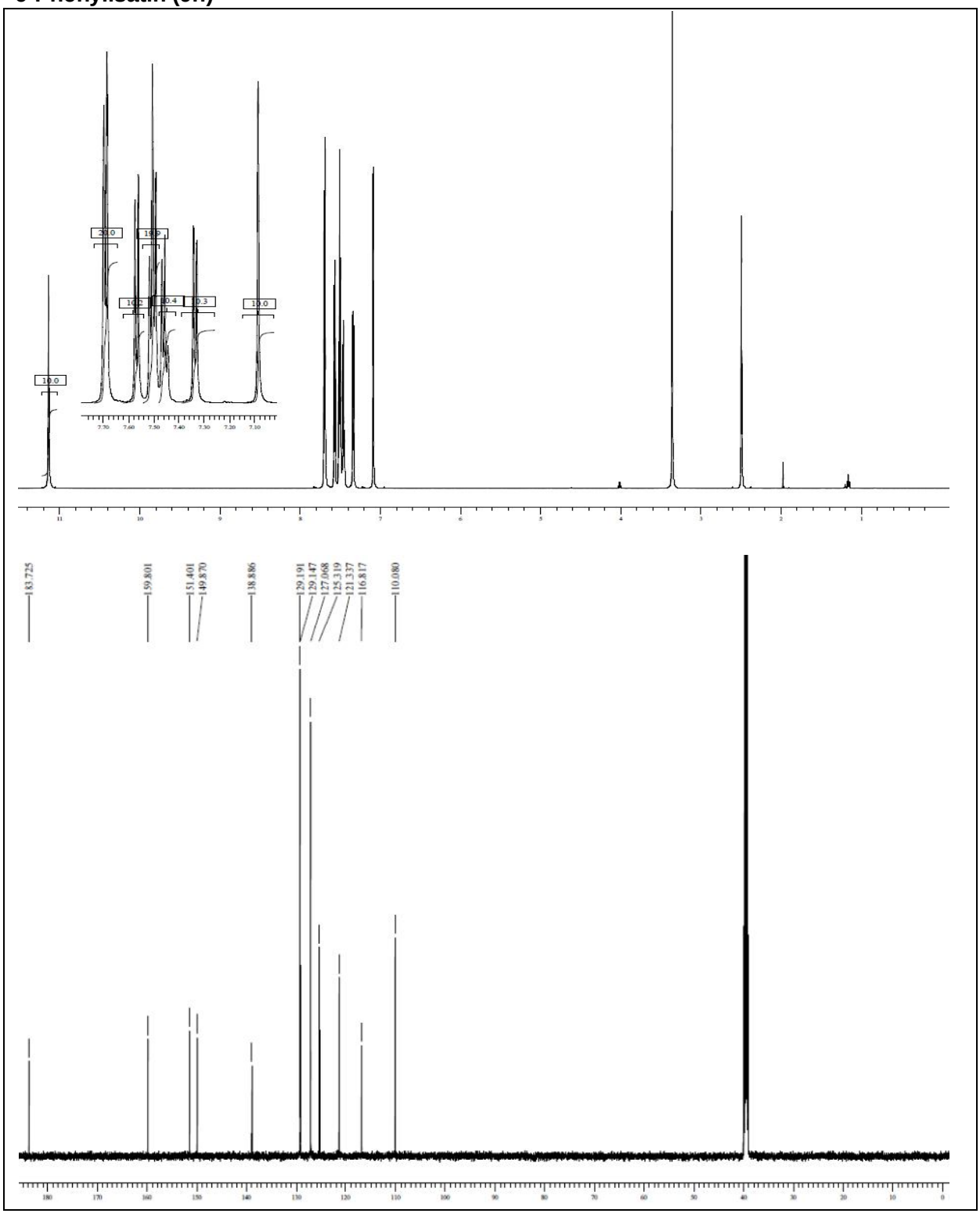
6-Phenoxyisatin (9f)



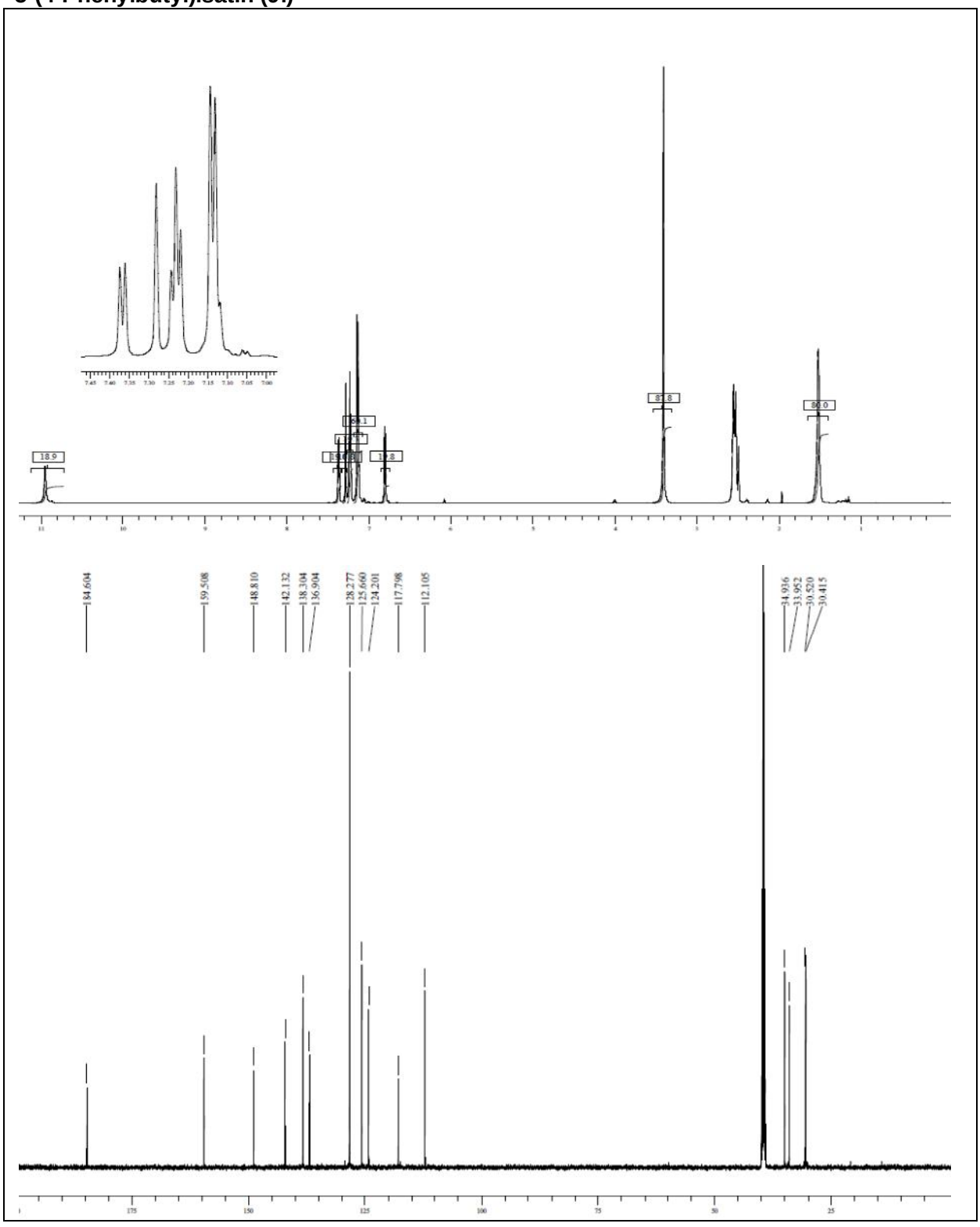
5-Phenylisatin (9g)



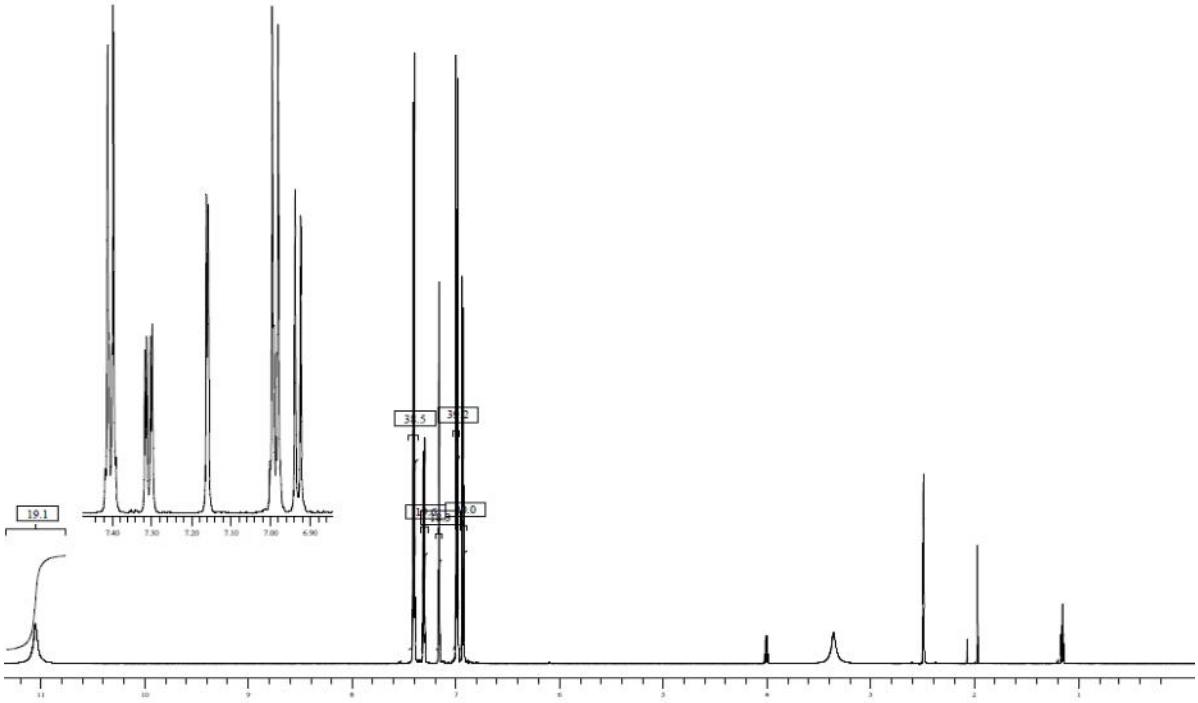
6-Phenylisatin (9h)

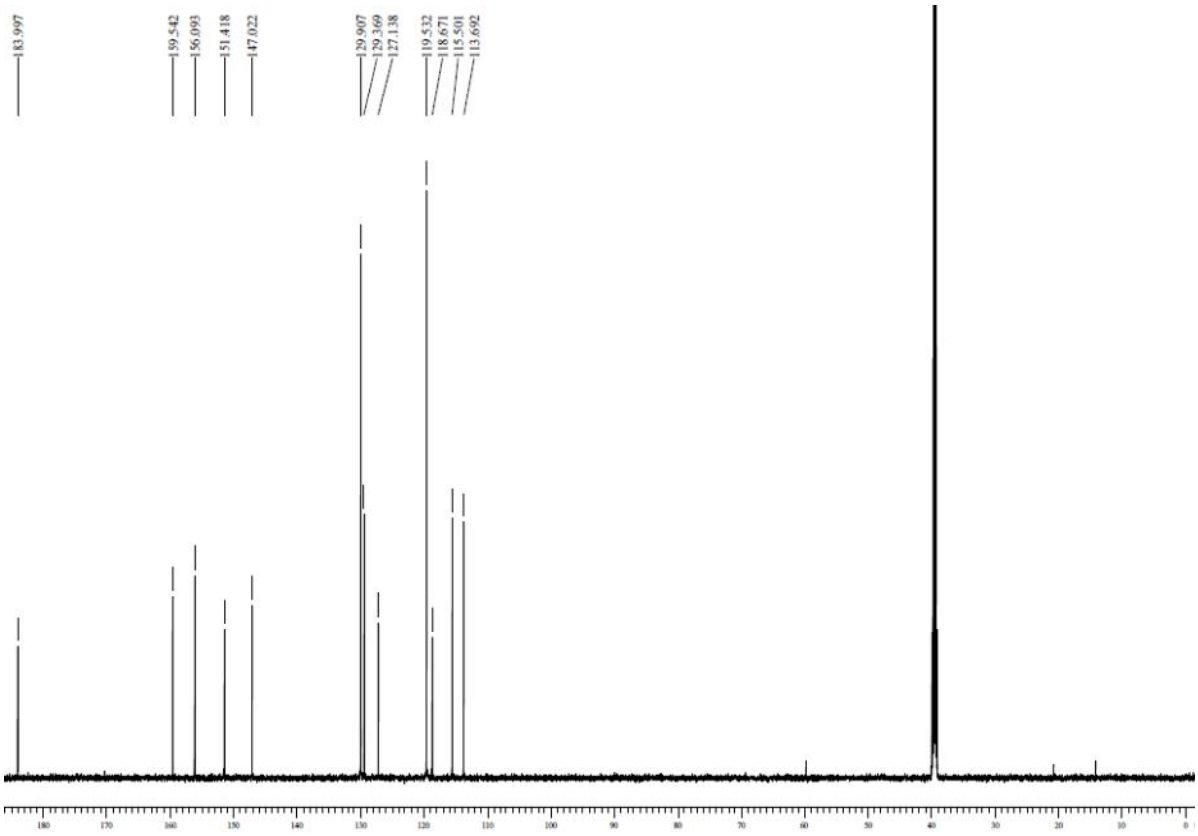


5-(4-Phenylbutyl)isatin (9i)

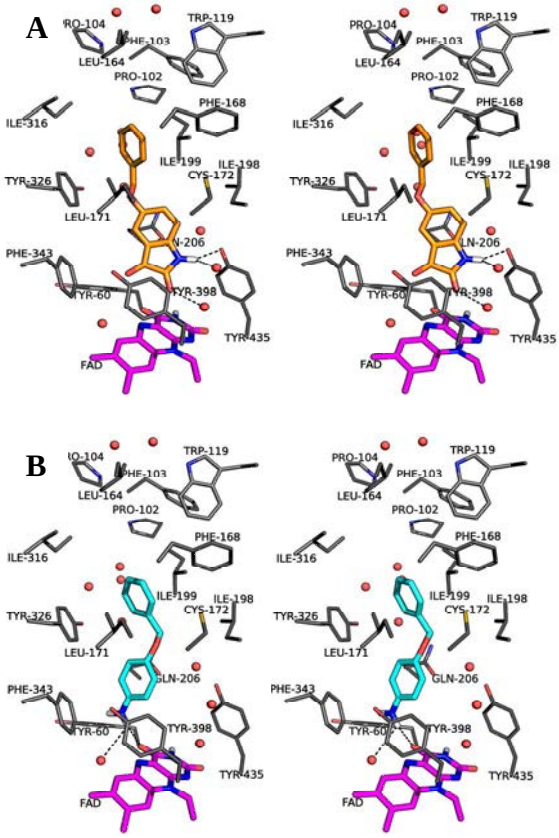


5-(4-Chlorophenoxy)isatin (9j)

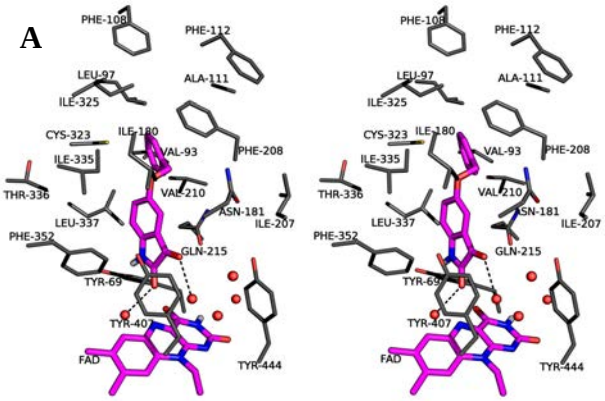


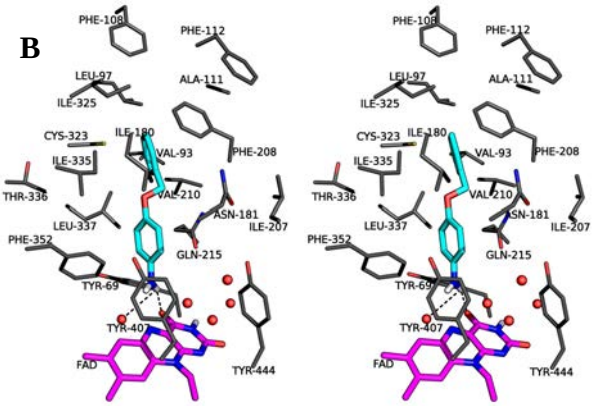


S3: Stereoview of the best ranked docking solution for the binding of isatin analogue 9a (orange colored, Top) aniline analogue 10 (cyan colored, Bottom) in the active site of MAO-B (2V5Z.pdb).[22] The illustrations were generated with PyMOL.[38]

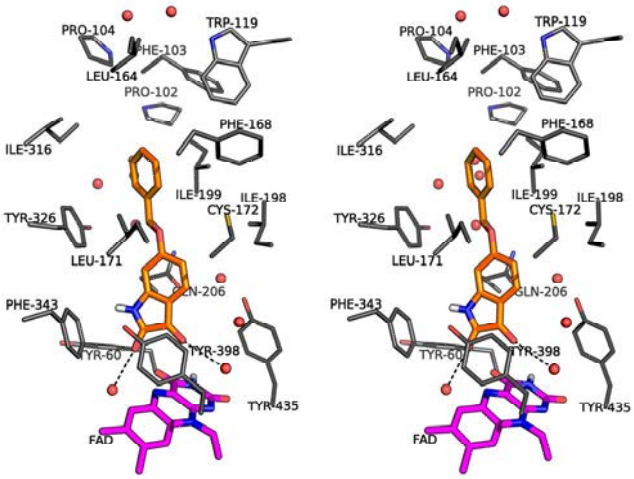


S4: Stereoview of the best ranked docking solution for the binding of isatin analogue 9a (magenta colored, Top) aniline analogue 10 (cyan colored, Bottom) in the active site of MAO-A (2Z5X.pdb).[3] The illustrations were generated with PyMOL.[38]





S5: Stereoview of the best ranked docking solution for the binding of isatin analogue 9b (orange colored) in the active site of MAO-B (2V5Z.pdb).[22] The illustrations were generated with PyMOL.[38]



ANNEXURE B

Supplementary Information

INHIBITION OF MONOAMINE OXIDASE BY C5-SUBSTITUTED PHTHALIMIDE ANALOGUES

Supplementary Information

Chromatograms of the HPLC analyses of the synthesized compounds

Chromatograms are indicated at 210, 254 and 300 nm respectively.

INHIBITION OF MONOAMINE OXIDASE BY C5-SUBSTITUTED PHTHALIMIDE ANALOGUES

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Pharmaceutical Chemistry, School of Pharmacy, North-West University, Private Bag X6001, Potchefstroom, 2520, South Africa.

SUPPLEMENTARY MATERIAL

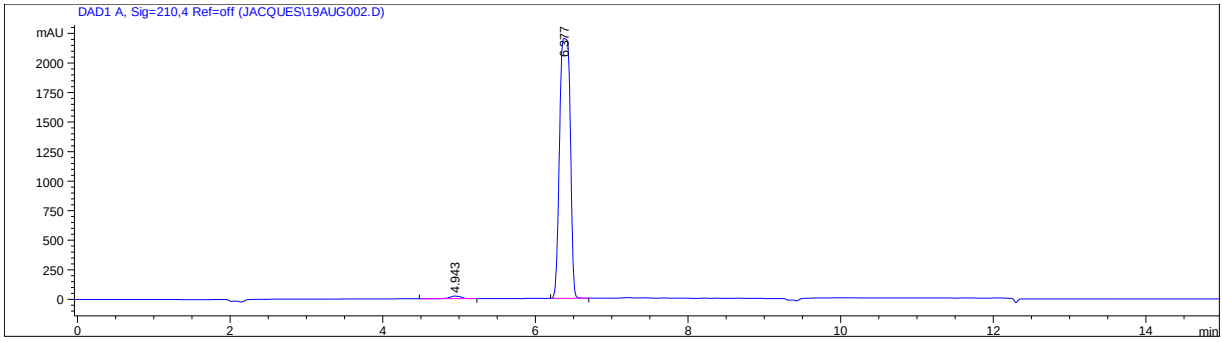
S1: HPLC traces of the following new/unknown compounds

- 5-Phenoxyphthalimide (**5a**)
- 5-Benzyloxyphthalimide (**5b**)
- 5-(2-Phenylethoxy)phthalimide (**5c**)
- 5-(3-Phenylpropoxy)phthalimide (**5d**)
- 5-{[(2E)-3-Phenylprop-2-en-1-yl]oxy}phthalimide (**5e**)
- 5-(Naphthalen-2-yloxy)phthalimide (**5f**)
- 5-(4-Bromobenzyloxy)phthalimide (**5g**)
- 5-[2-(4-Bromophenyl)ethoxy]phthalimide (**5h**)
- 5-(4-Bromophenoxy)phthalimide (**5i**)

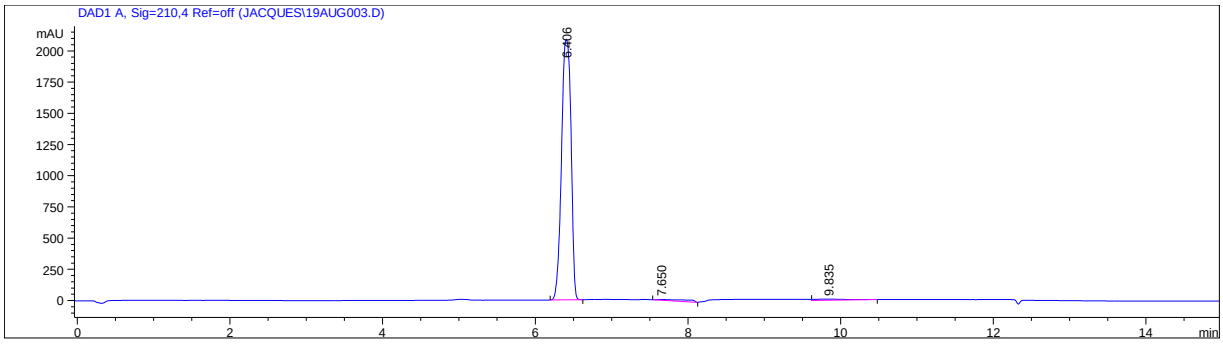
Method: To determine the purity of the previously unreported compounds (**5a**–**i**), HPLC analyses were carried out. HPLC analyses were performed with an Agilent 1200 HPLC system equipped with a quaternary pump and an Agilent 1200 series diode array detector. A Venusil XBP C18 column (4.60 × 150 mm, 5 µm) was used and the mobile phase consisted initially of 30% acetonitrile and 70% MilliQ water at a flow rate of 1 mL/min. At the start of each HPLC run a solvent gradient program was initiated by linearly increasing the composition of the acetonitrile in the mobile phase to 85% acetonitrile over a period of 5 min. Each HPLC run lasted 15 min and a time period of 5 min was allowed for equilibration between runs. A volume of 20 µL of

solutions of the test compounds in acetonitrile (1 mM) was injected into the HPLC system and the eluent was monitored at wavelengths of 210, 254 and 300 nm.

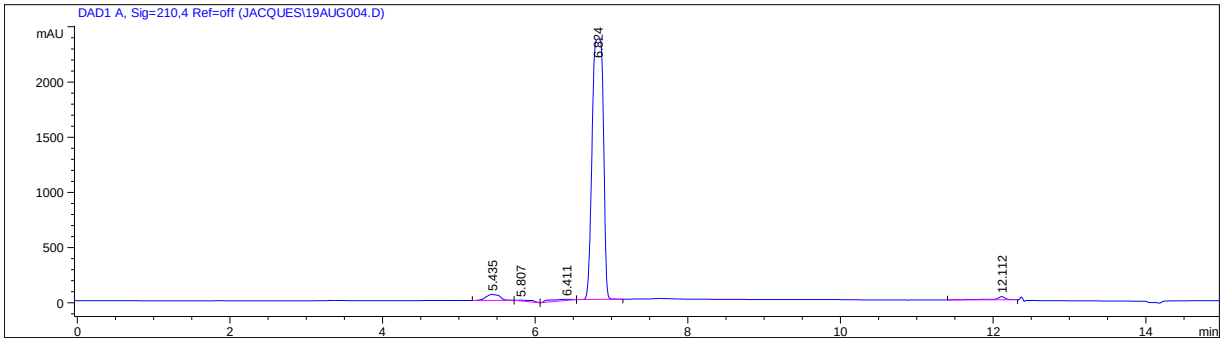
5-Phenoxyphthalimide (5a)



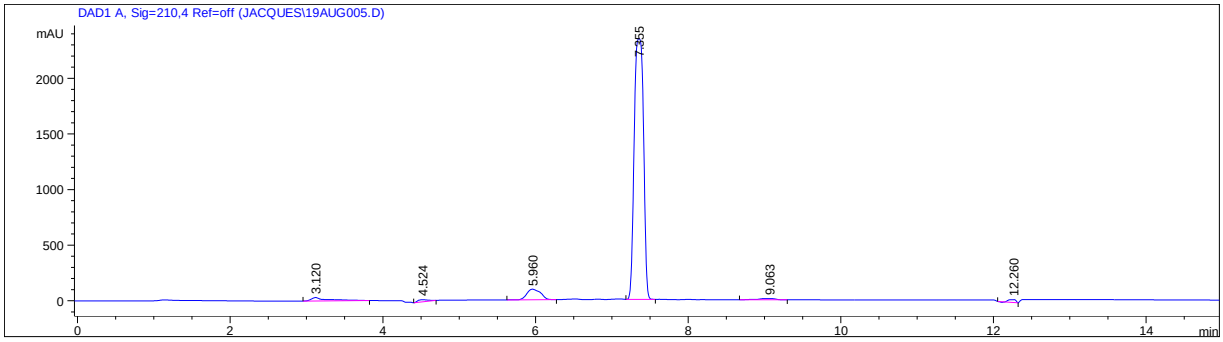
5-Benzyloxyphthalimide (5b)



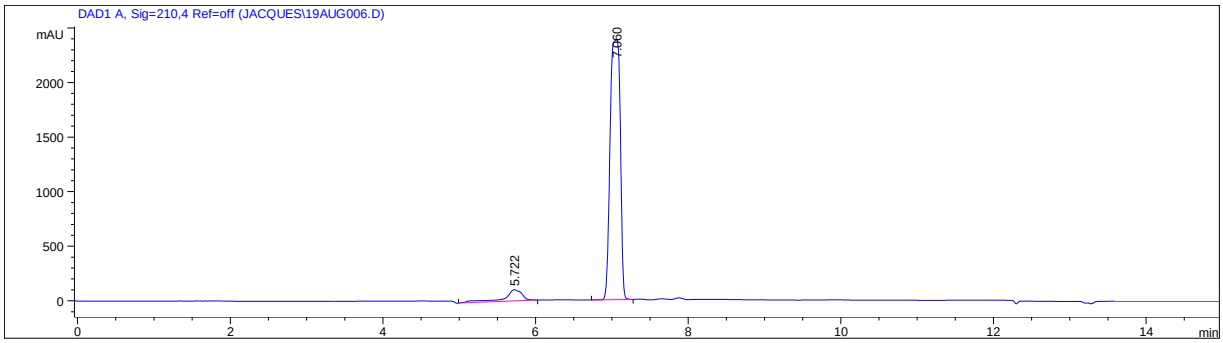
5-(2-Phenylethoxy)phthalimide (5c)



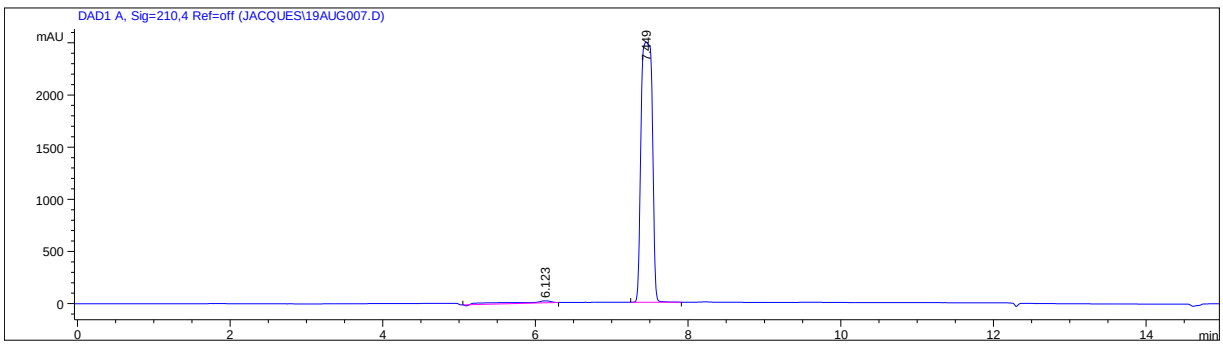
5-(3-Phenylpropoxy)phthalimide (5d)



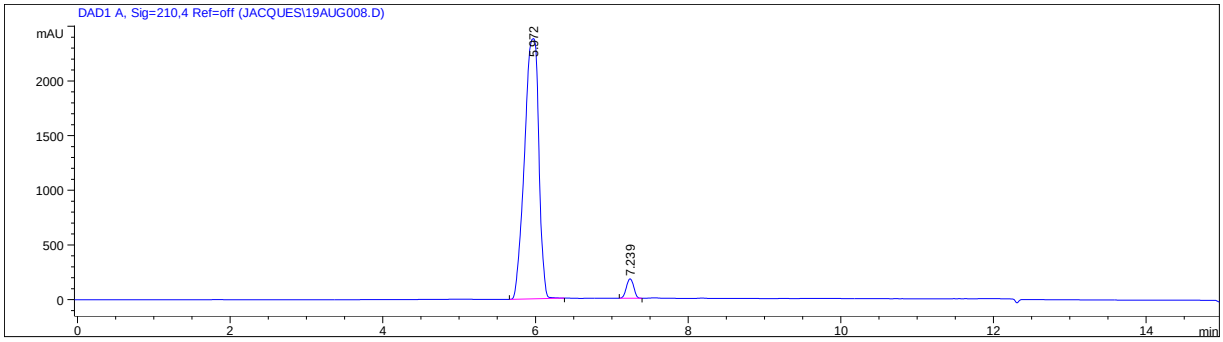
5-{[(2E)-3-Phenylprop-2-en-1-yl]oxy}phthalimide (5e)



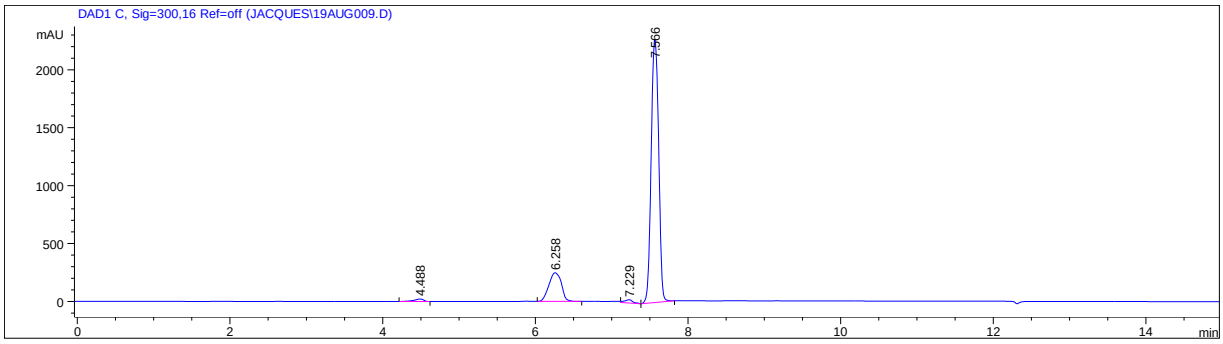
5-(Naphthalen-2-yloxy)phthalimide (5f)



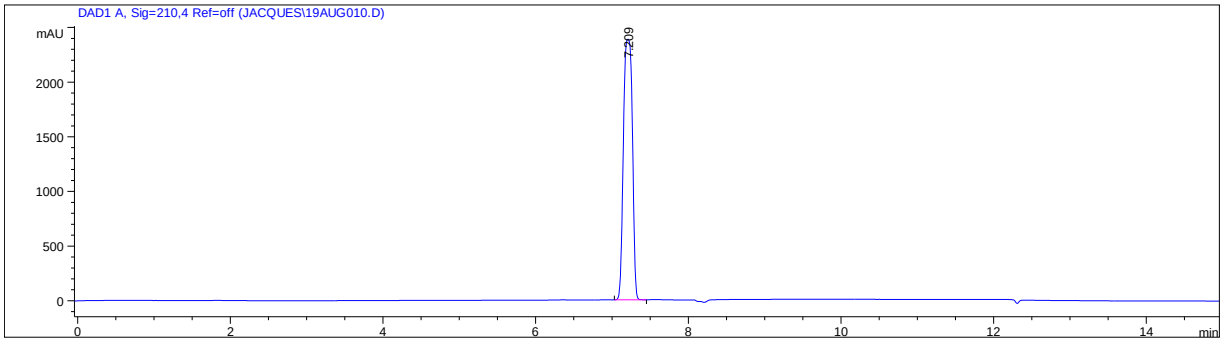
5-(4-Bromobenzyloxy)phthalimide (5g)



5-[2-(4-Bromophenyl)ethoxy]phthalimide (5h)



5-(4-Bromophenoxy)phthalimide (5i)

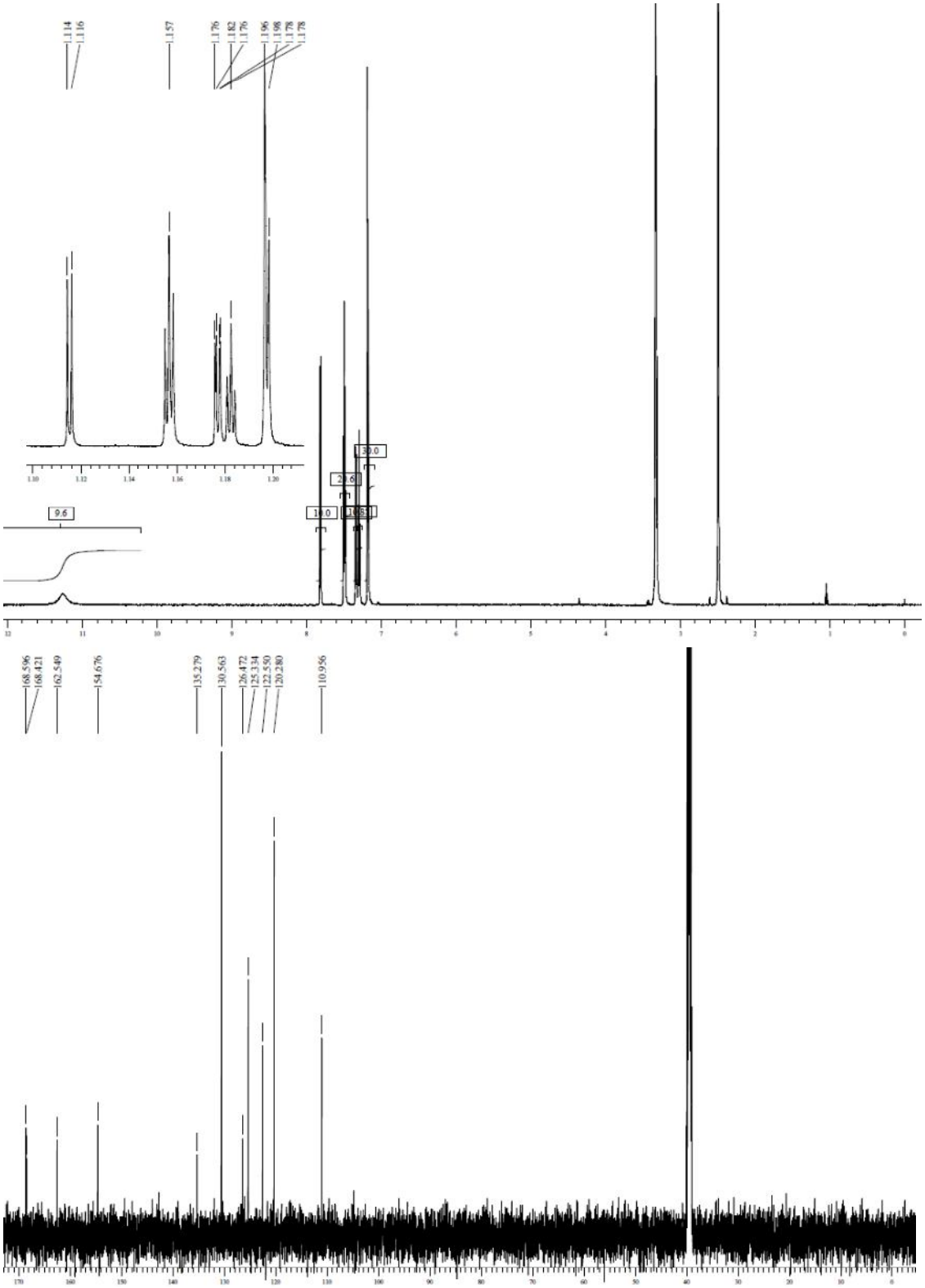


S2: ^{1}H NMR spectra of the following new/unknown compounds

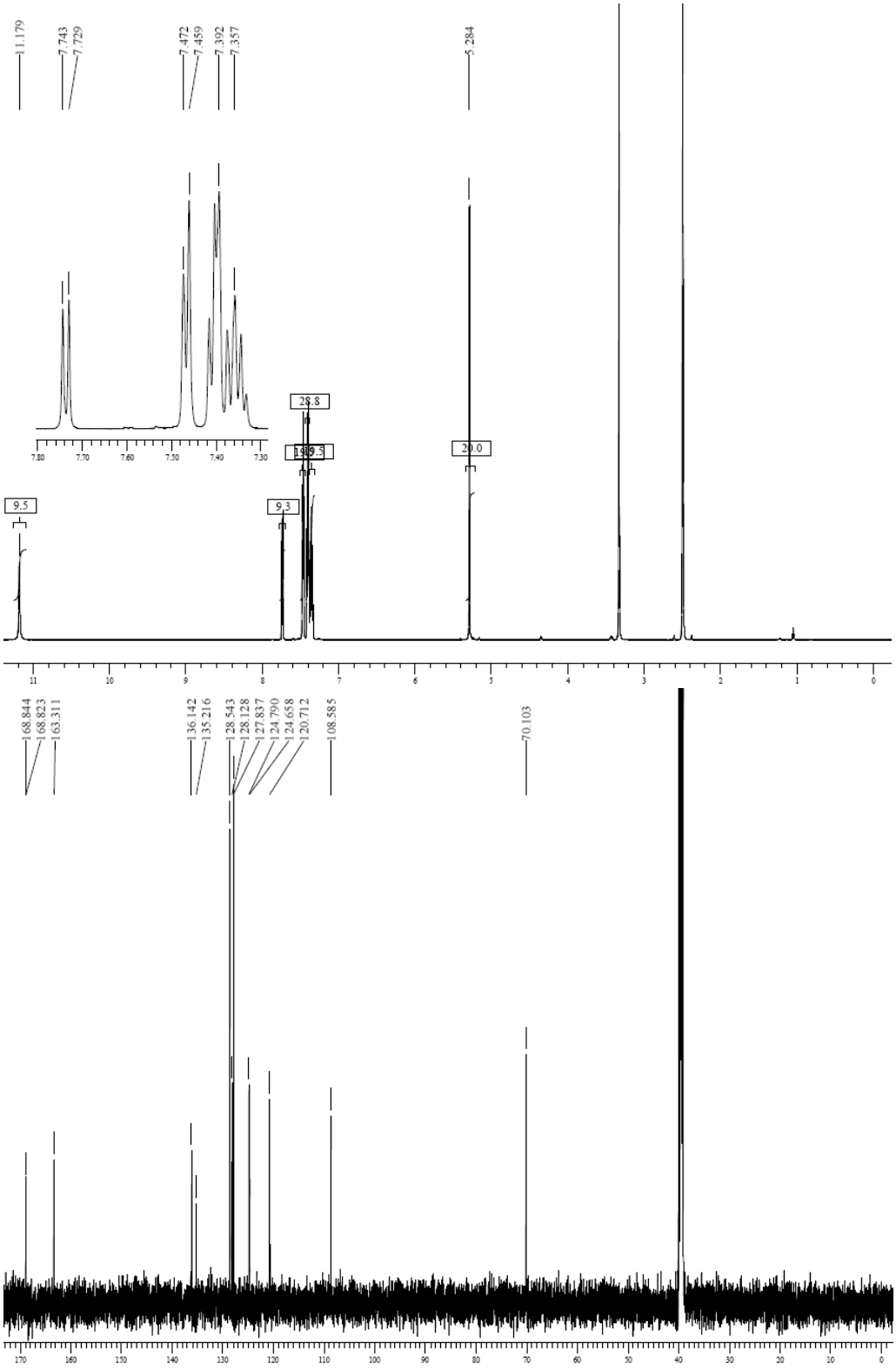
- 5-Phenoxyphthalimide (**5a**)
- 5-Benzyloxyphthalimide (**5b**)
- 5-(2-Phenylethoxy)phthalimide (**5c**)
- 5-(3-Phenylpropoxy)phthalimide (**5d**)
- 5-{[(2E)-3-Phenylprop-2-en-1-yl]oxy}phthalimide (**5e**)
- 5-(Naphthalen-2-yloxy)phthalimide (**5f**)
- 5-(4-Bromobenzyloxy)phthalimide (**5g**)
- 5-[2-(4-Bromophenyl)ethoxy]phthalimide (**5h**)
- 5-(4-Bromophenoxy)phthalimide (**5i**)

Proton (^{1}H) and carbon (^{13}C) NMR spectra were recorded on a Bruker Avance III 600 spectrometer at frequencies of 600 MHz and 150 MHz, respectively. All NMR measurements were conducted in DMSO-d*6*.

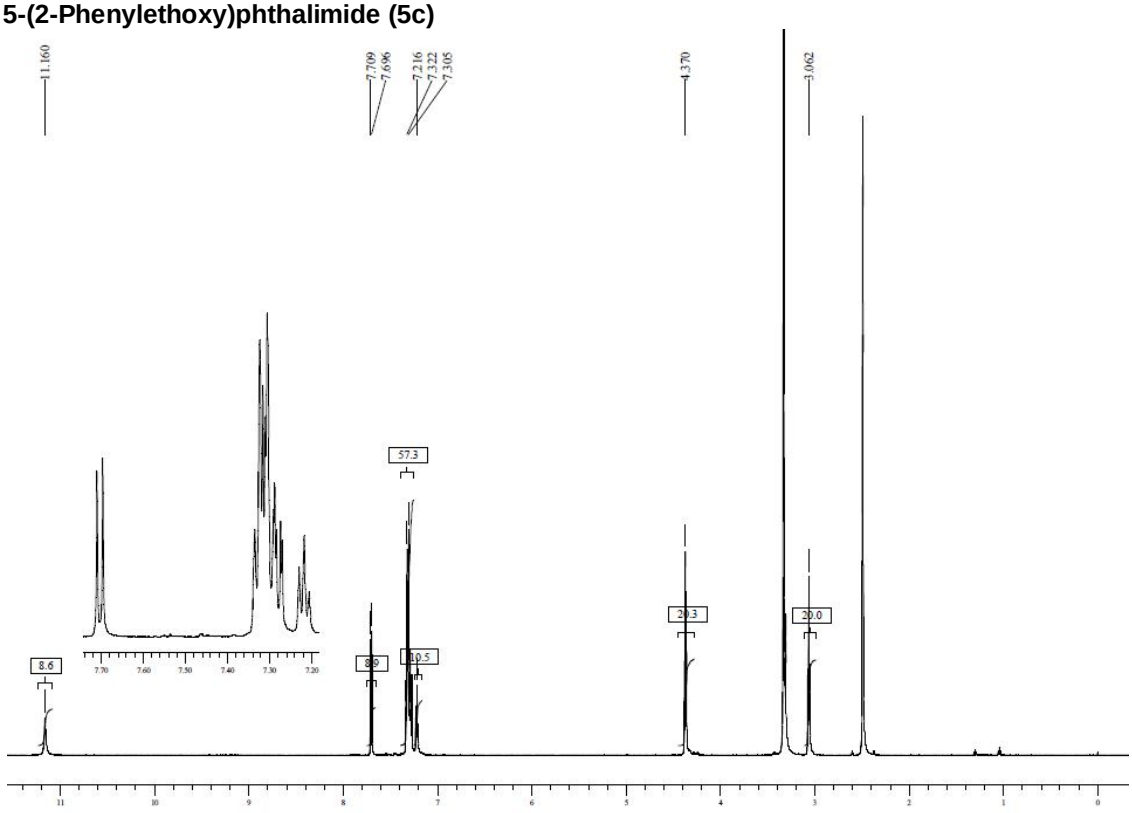
5-Phenoxyphthalimide (5a)

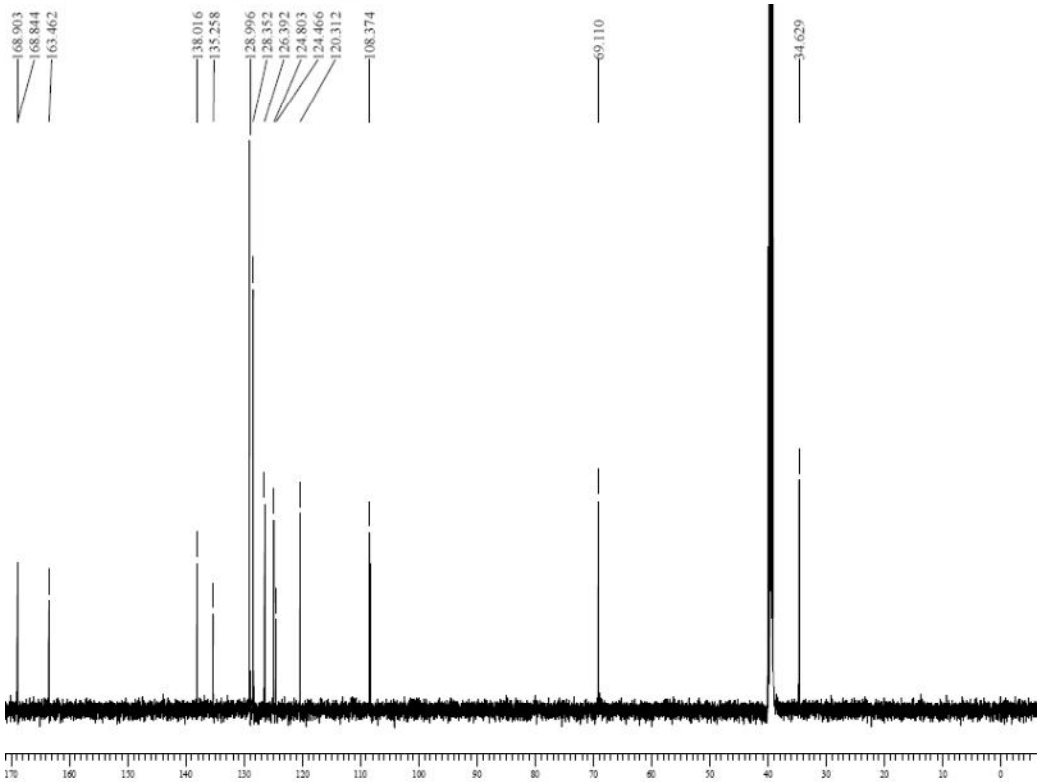


5-Benzyloxyphthalimide (5b)

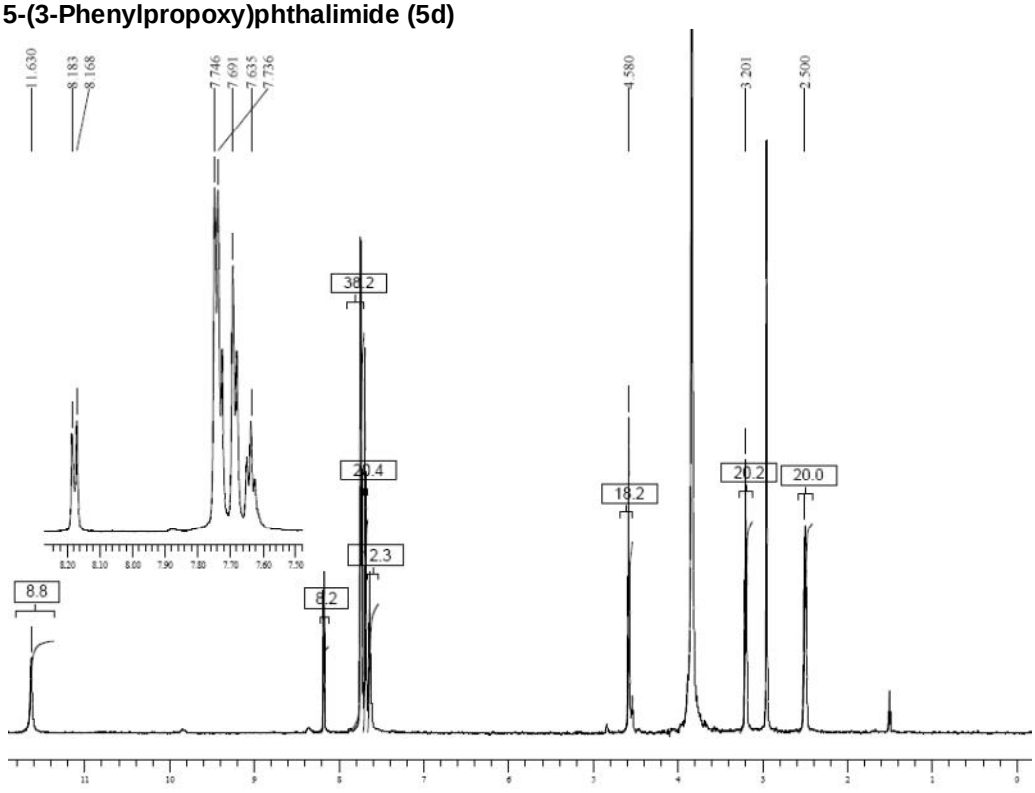


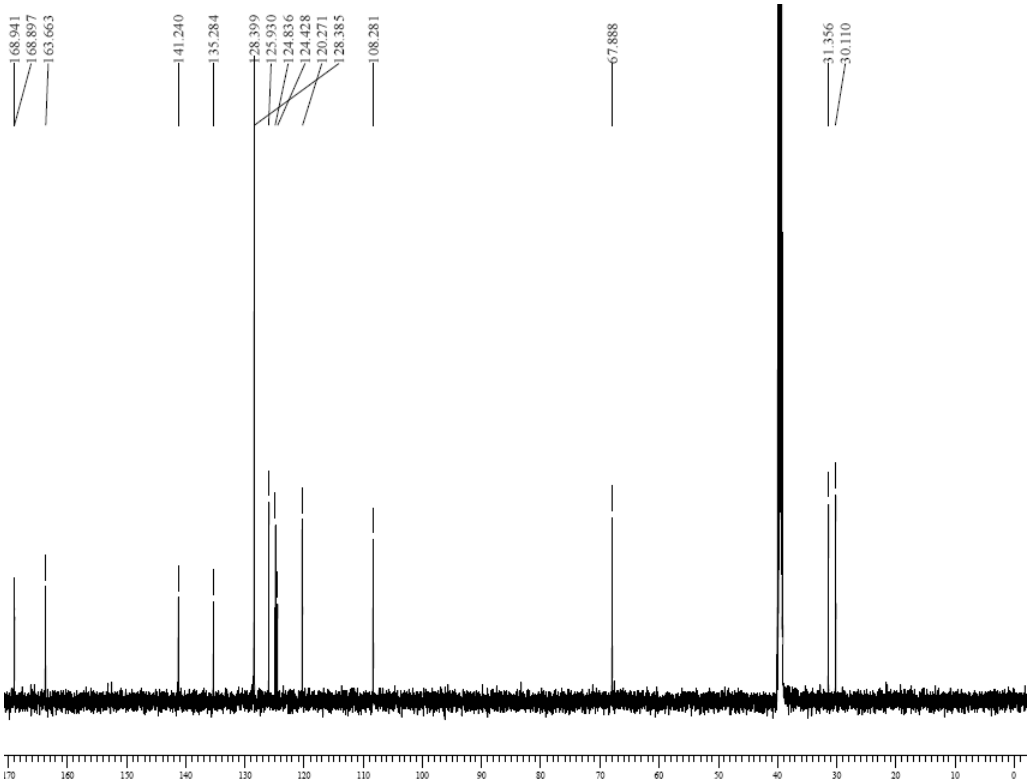
5-(2-Phenylethoxy)phthalimide (5c)



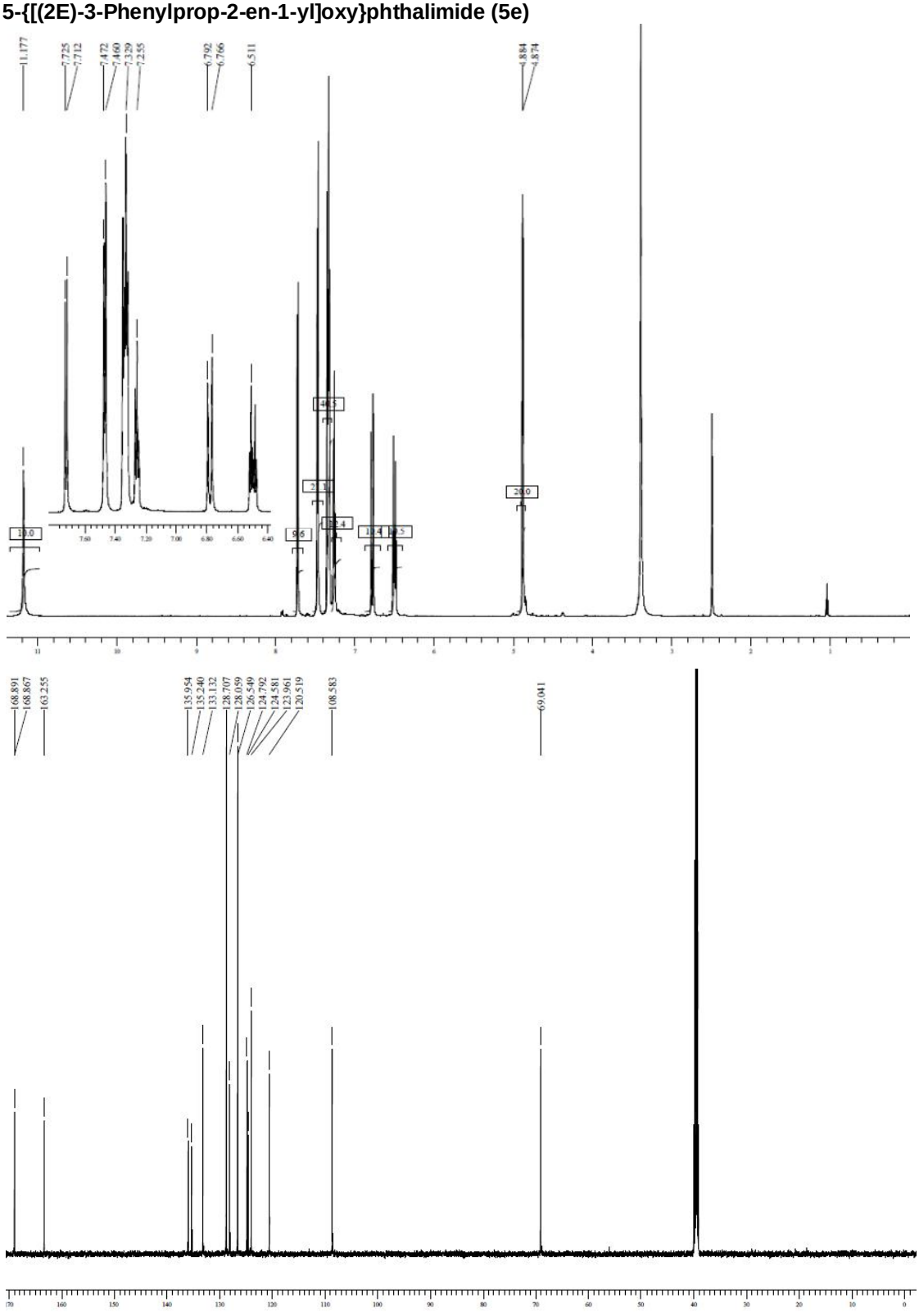


5-(3-Phenylpropoxy)phthalimide (5d)

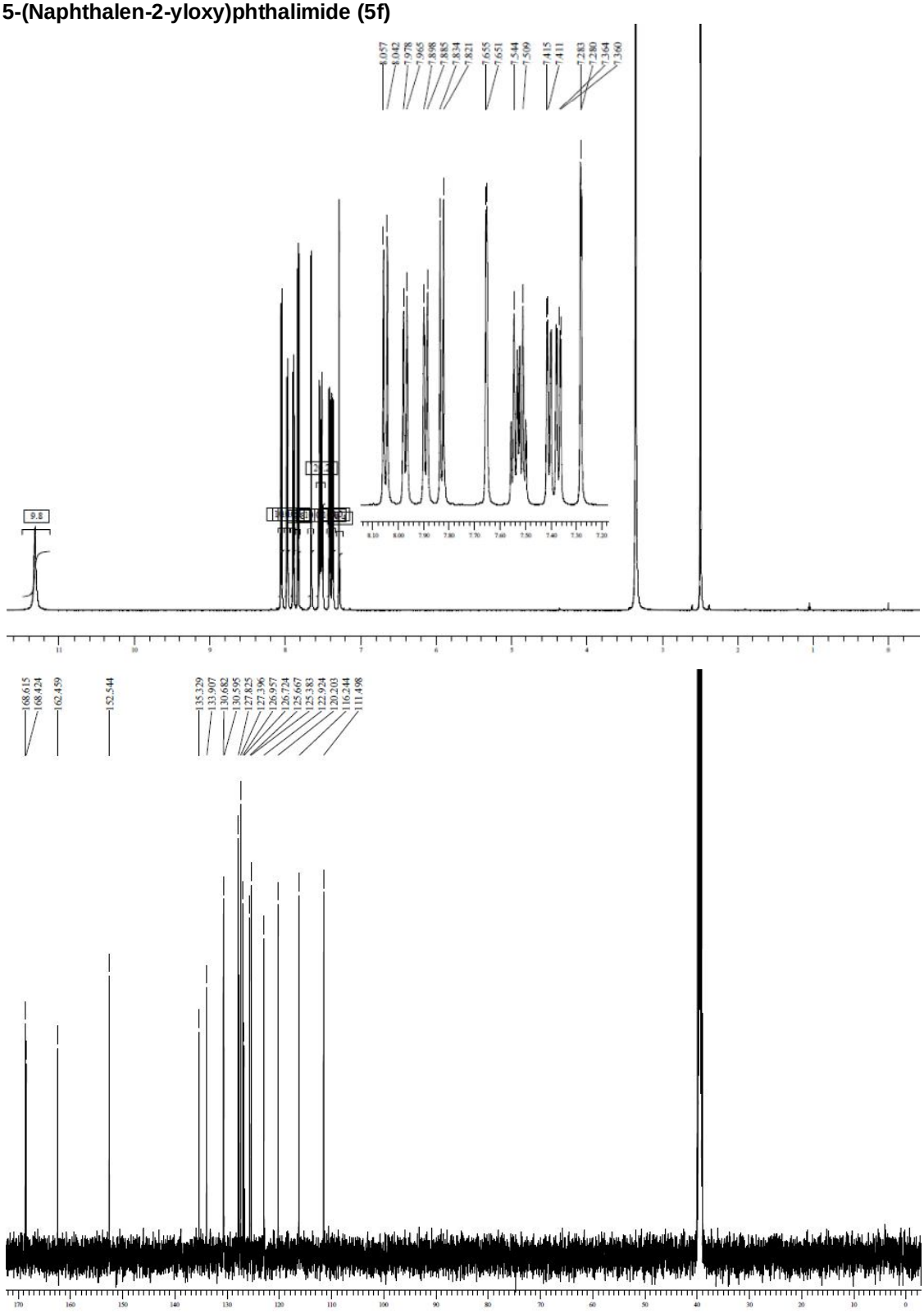




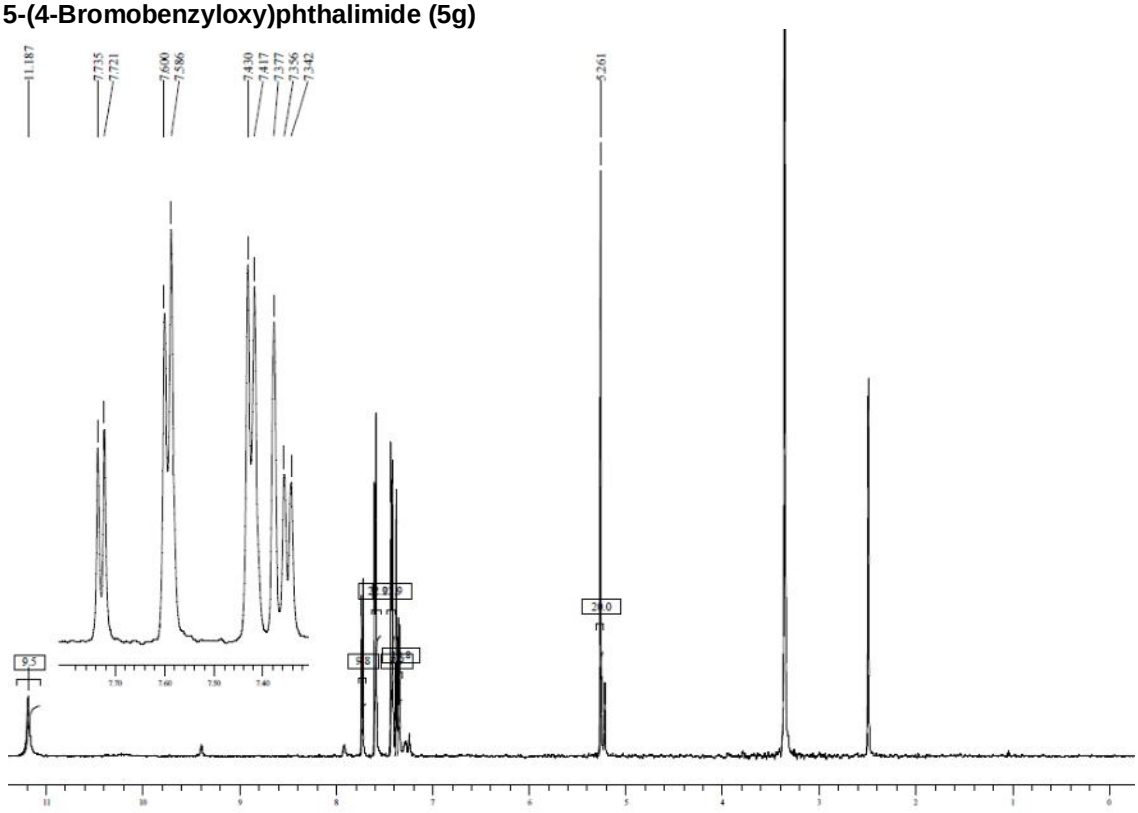
5-{[(2E)-3-Phenylprop-2-en-1-yl]oxy}phthalimide (5e)

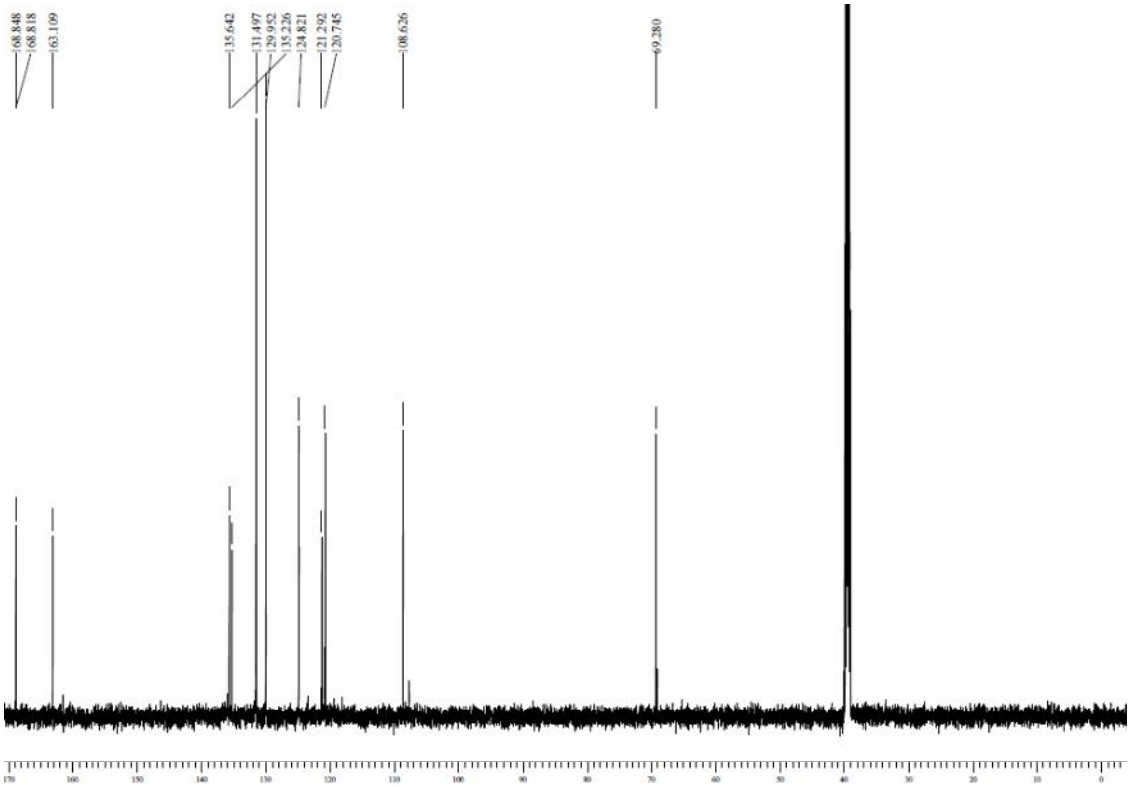


5-(Naphthalen-2-yloxy)phthalimide (5f)

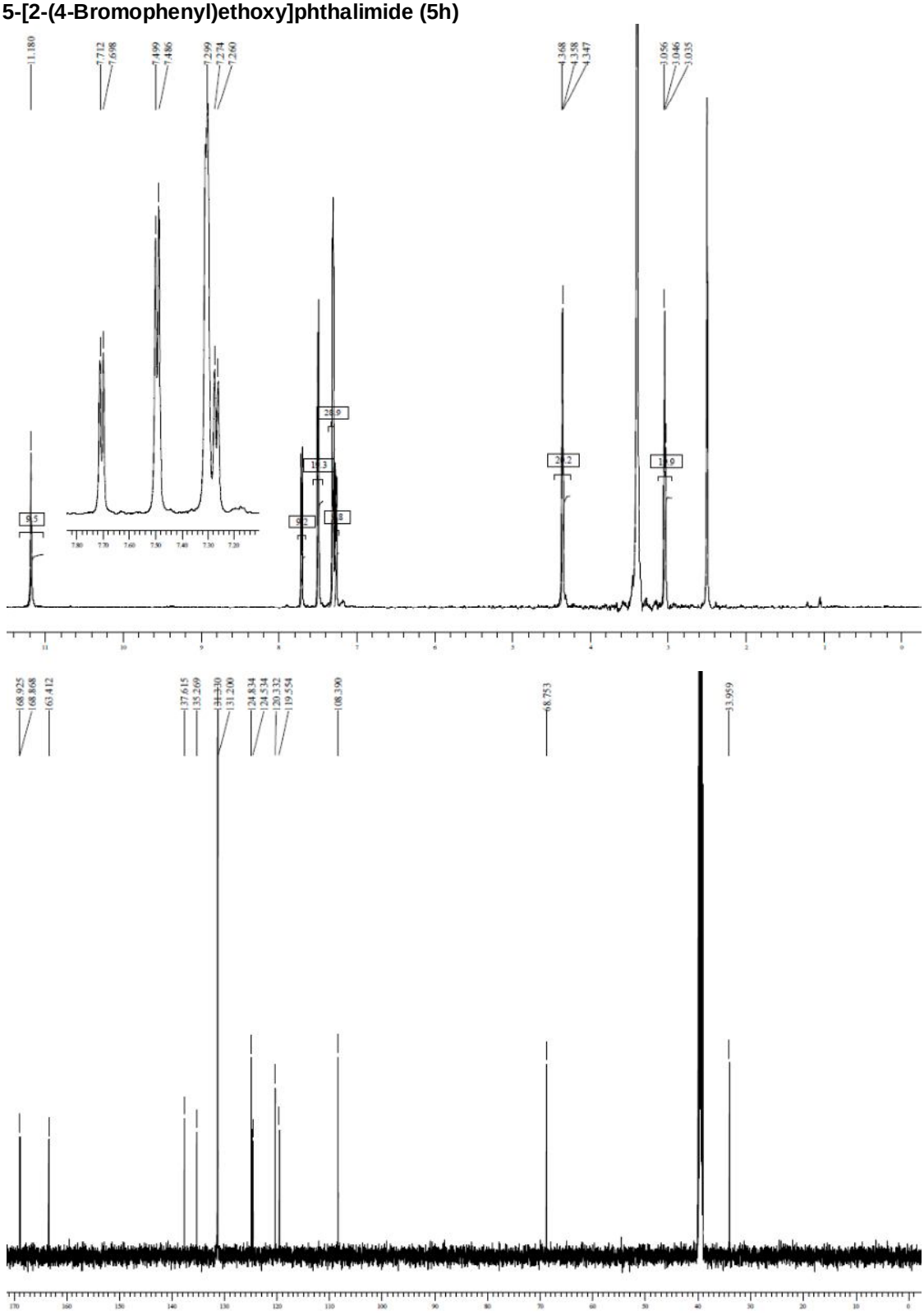


5-(4-Bromobenzyloxy)phthalimide (5g)

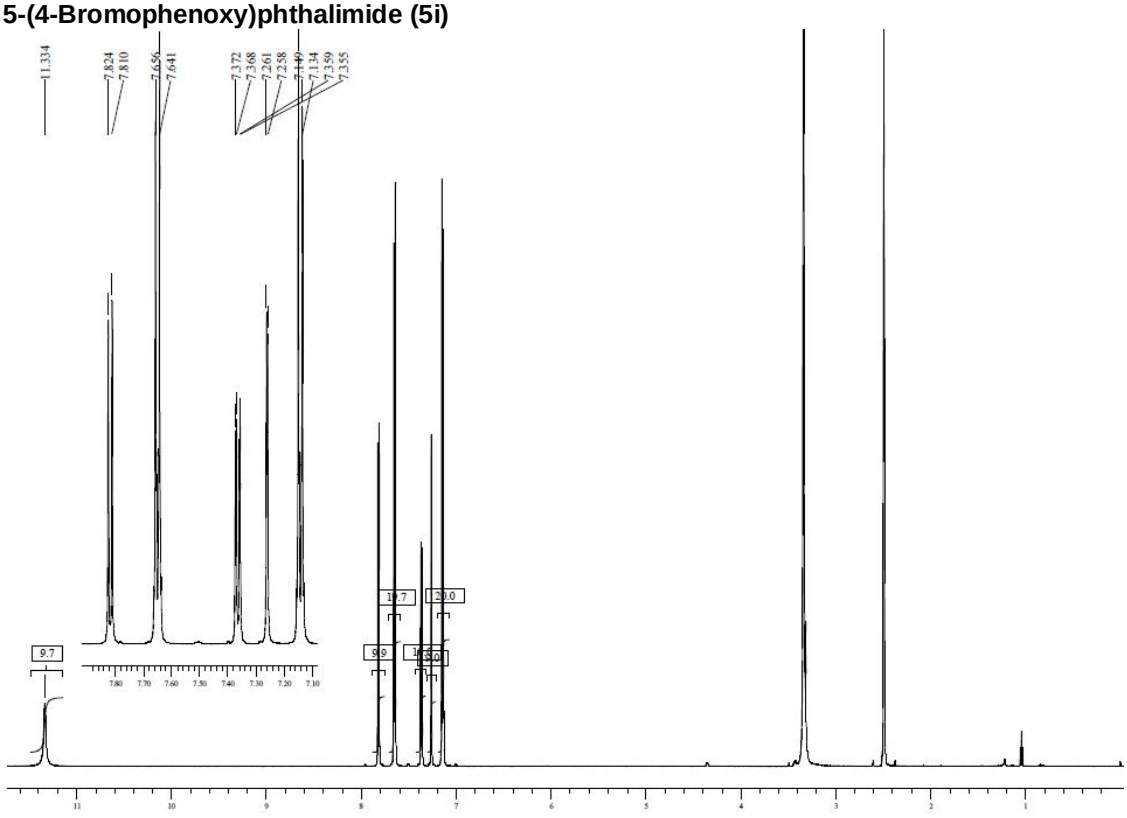


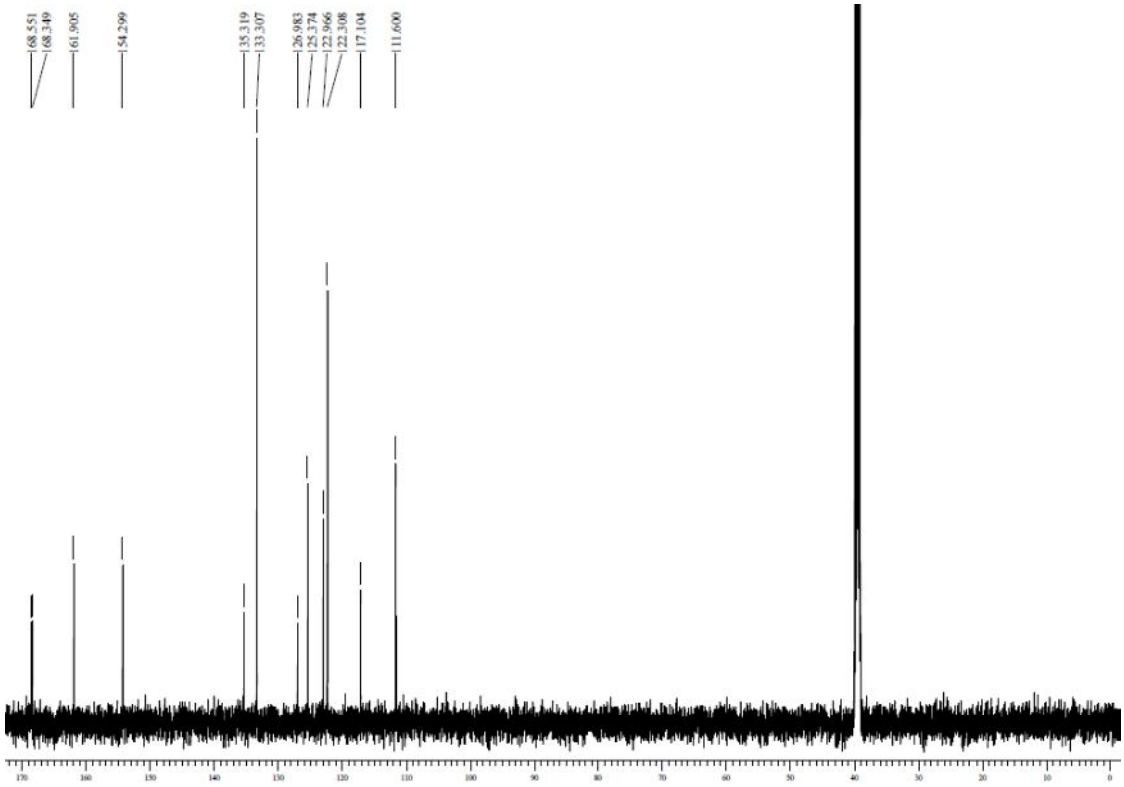


5-[2-(4-Bromophenyl)ethoxy]phthalimide (5h)



5-(4-Bromophenoxy)phthalimide (5i)





ANNEXURE C

Supplementary Information

MONOAMINE OXIDASE INHIBITION BY C-4 SUBSTITUTED PHTHALONITRILES

Supplementary Information

Chromatograms of the HPLC analyses of the synthesized compounds

Chromatograms are indicated at 210, 254 and 300 nm respectively.

Monoamine oxidase inhibition by C4-substituted phthalonitriles

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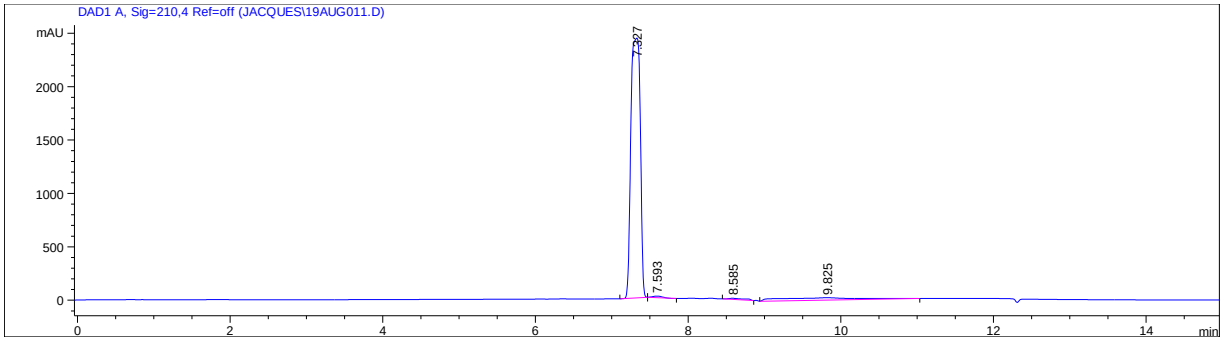
Pharmaceutical Chemistry, School of Pharmacy, North-West University, Private Bag X6001, Potchefstroom, 2520, South Africa

S1: HPLC traces of the following new/unknown compounds

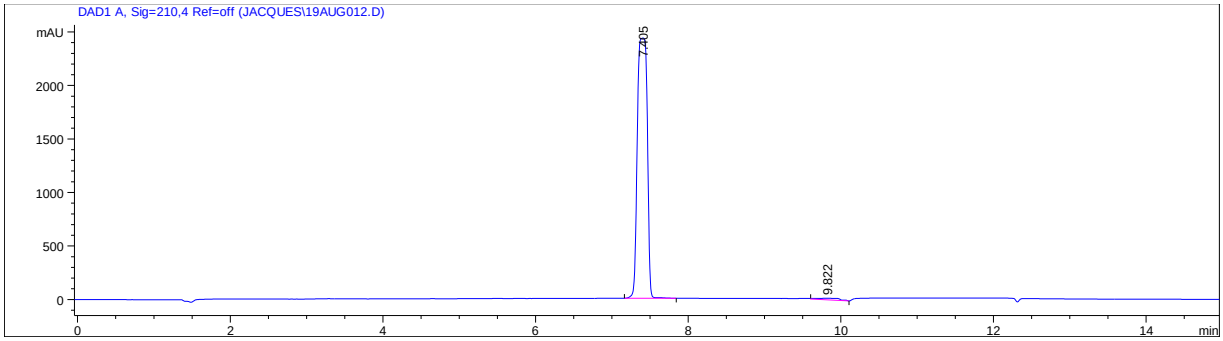
- 4-Phenoxyphthalonitrile (**4a**)
- 4-Benzyloxyphthalonitrile (**4b**)
- 4-(2-Phenylethoxy)phthalonitrile (**4c**)
- 4-(3-Phenylpropoxy)phthalonitrile (**4d**)
- 4-{[(2E)-3-Phenylprop-2-en-1-yl]oxy}phthalonitrile (**4e**)
- 4-(Naphthalen-2-yloxy)phthalonitrile (**4f**)
- 4-(4-Bromophenoxy)phthalonitrile (**4g**)
- 4-(4-Bromobenzyloxy)phthalonitrile (**4h**)
- 4-[2-(4-Bromophenyl)ethoxy]phthalonitrile (**4i**)
- 4-(Benzyloxy)benzonitrile (**5a**)
- 3-(Benzyloxy)benzonitrile (**5b**)
- 4-{[(2E)-3-Phenylprop-2-en-1-yl]oxy}benzonitrile (**5c**)
- 3-{[(2E)-3-Phenylprop-2-en-1-yl]oxy}benzonitrile (**5d**)
- 4-(4-Bromobenzyloxy)benzonitrile (**5e**)
- 3-(4-Bromobenzyloxy)benzonitrile (**5f**)
- 4-[2-(4-bromophenyl)ethoxy]benzonitrile (**5g**)
- 4-[2-(Benzyloxy)ethoxy]benzonitrile (**5h**)
- {[(2E)-3-phenylprop-2-en-1-yl]oxy}benzene **(6b**)
- 1-Bromo-4-(phenoxymethyl)benzene (**6c**)
- 1-Bromo-4-(2-phenoxyethyl)benzene (**6d**)

Method: To determine the purity of the previously unreported compounds, HPLC analyses were carried out. HPLC analyses were performed with an Agilent 1100 HPLC system equipped with a quaternary pump and an Agilent 1100 series diode array detector. A Venusil XBP C18 column (4.60 × 150 mm, 5 µm) was used and the mobile phase consisted initially of 30% acetonitrile and 70% MilliQ water at a flow rate of 1 mL/min. At the start of each HPLC run a solvent gradient program was initiated by linearly increasing the composition of the acetonitrile in the mobile phase to 85% acetonitrile over a period of 5 min. Each HPLC run lasted 15 min and a time period of 5 min was allowed for equilibration between runs. A volume of 20 µL of solutions of the test compounds in acetonitrile (1 mM) was injected into the HPLC system and the eluent was monitored at wavelengths of 210, 254 and 300 nm.

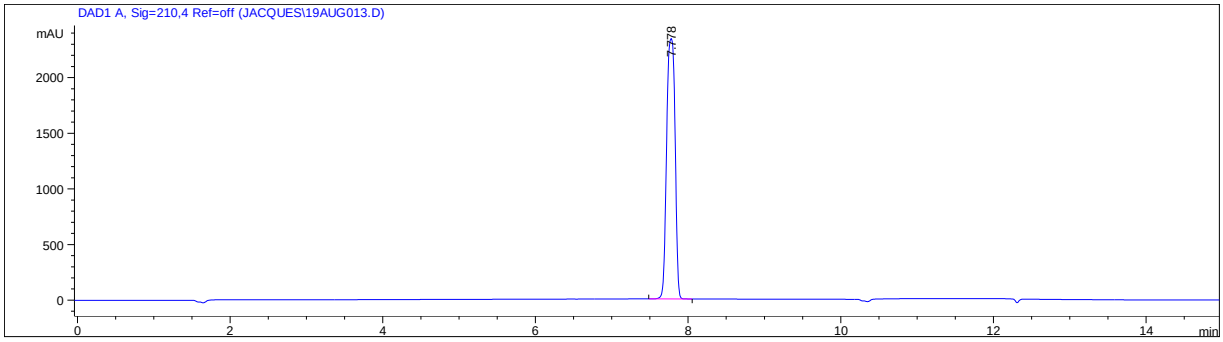
4-Phenoxyphthalonitrile (4a)



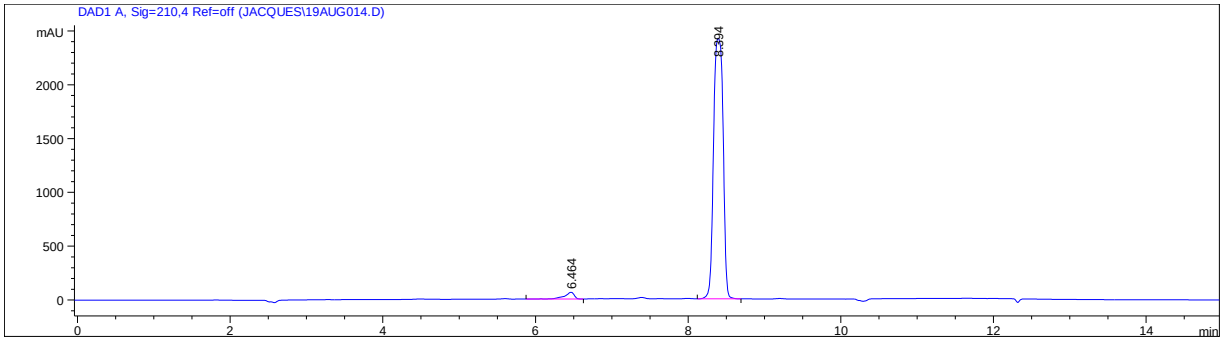
4-Benzyloxyphthalonitrile (4b)



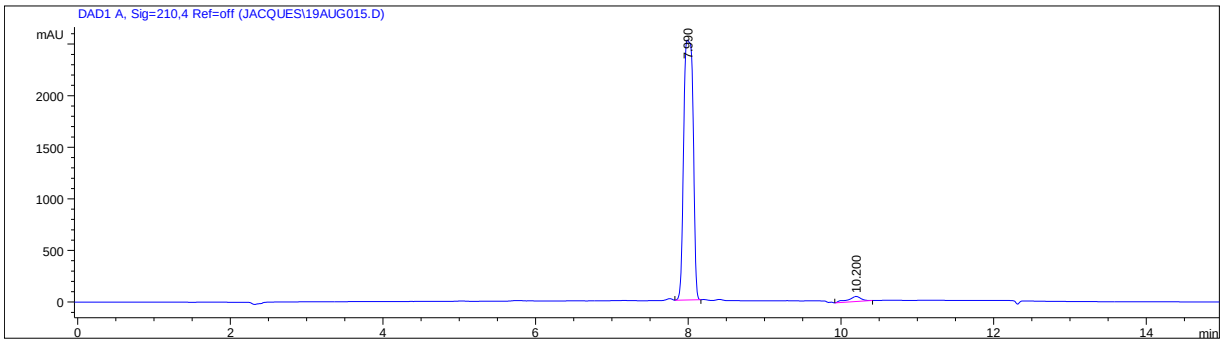
4-(2-Phenylethoxy)phthalonitrile (4c)



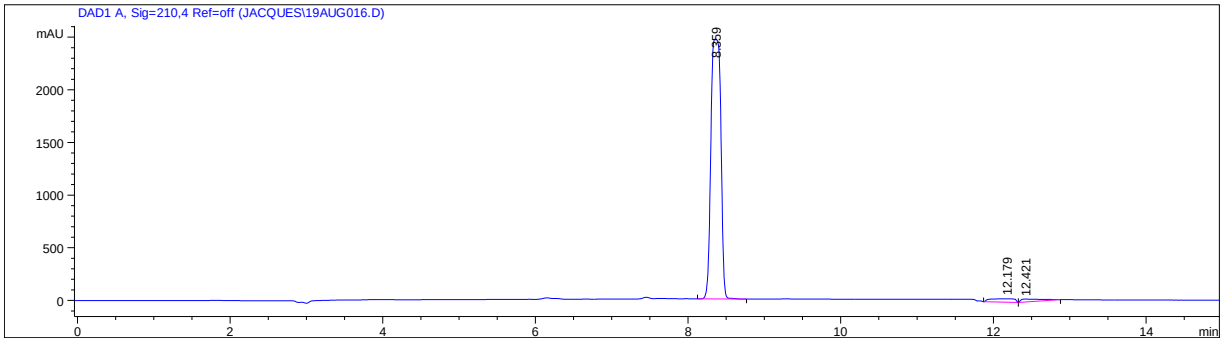
4-(3-Phenylpropoxy)phthalonitrile (4d)



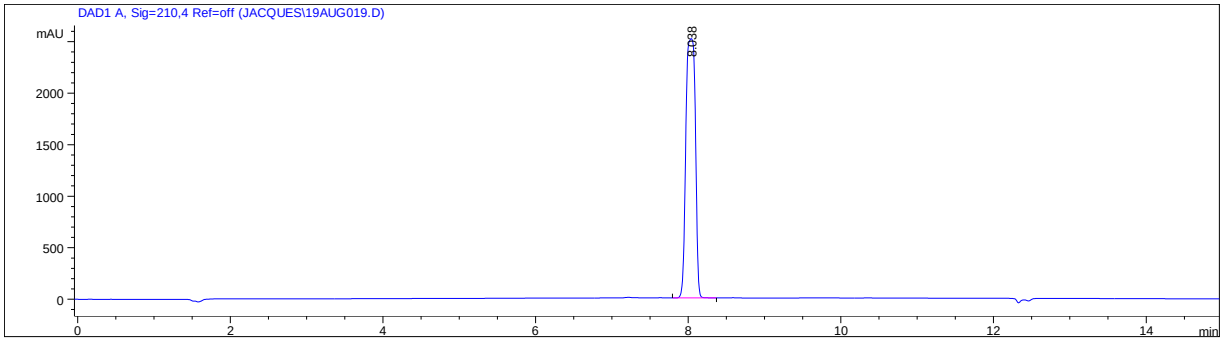
4-{[(2E)-3-Phenylprop-2-en-1-yl]oxy}phthalonitrile (4e)



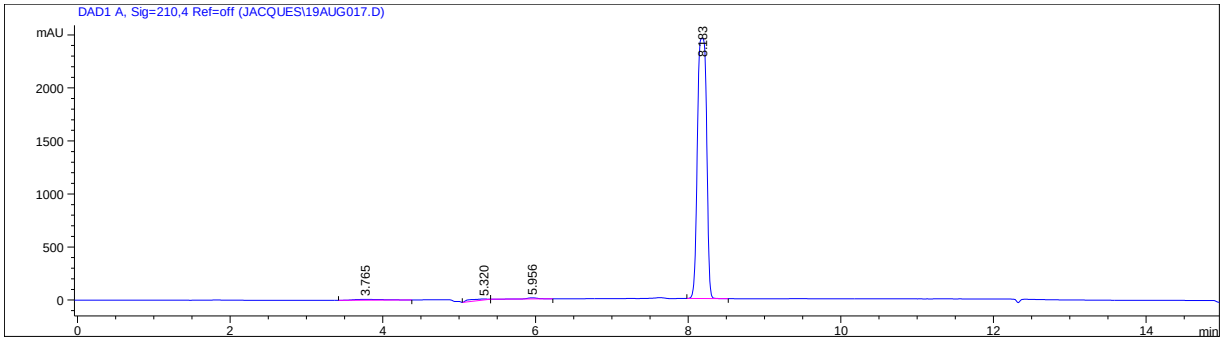
4-(Naphthalen-2-yloxy)phthalonitrile (4f)



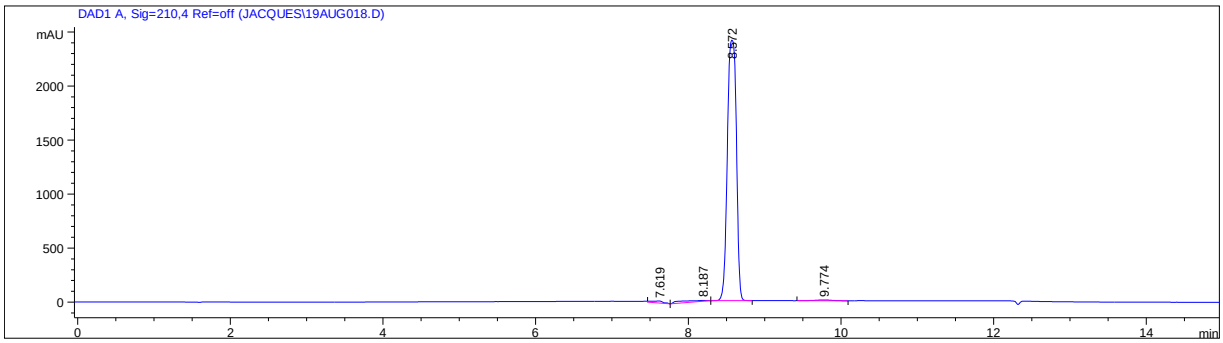
4-(4-Bromophenoxy)phthalonitrile (4g)



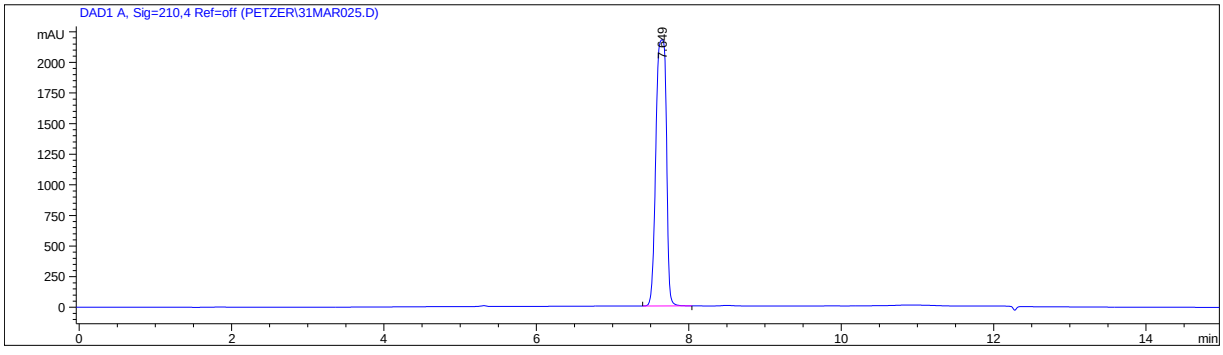
4-(4-Bromobenzyloxy)phthalonitrile (4h)



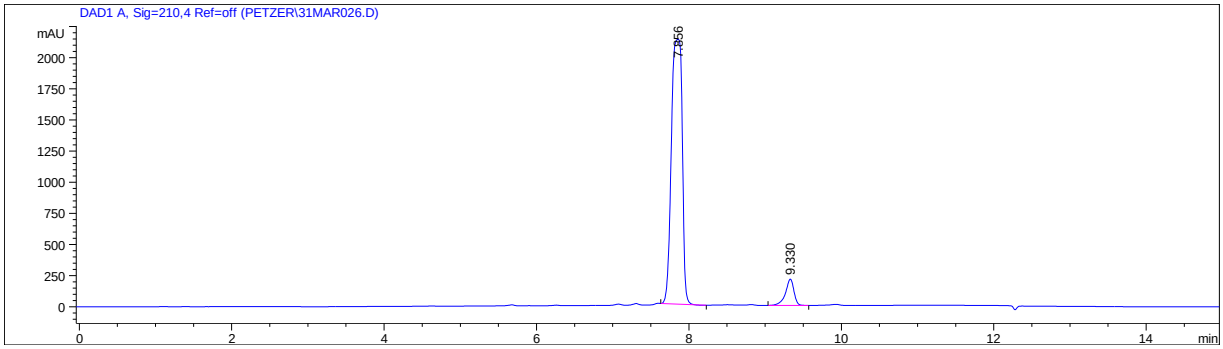
4-[2-(4-Bromophenyl)ethoxy]phthalonitrile (4i)



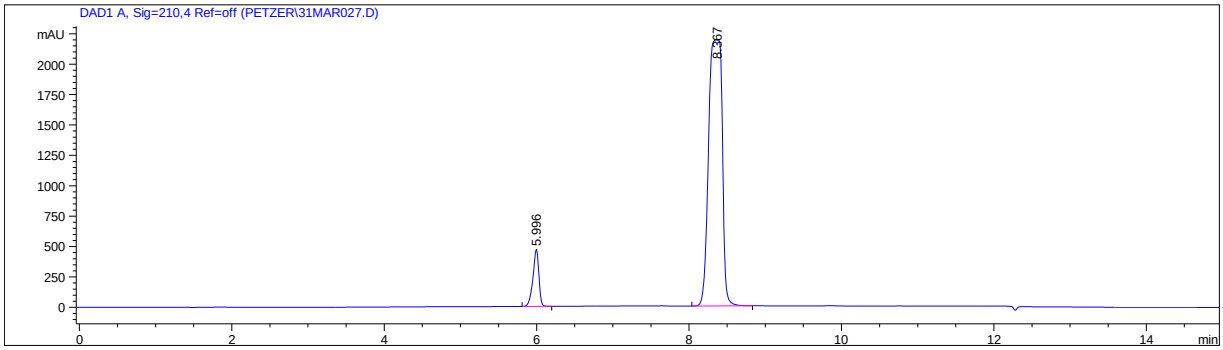
4-(Benzyloxy)benzonitrile (5a)



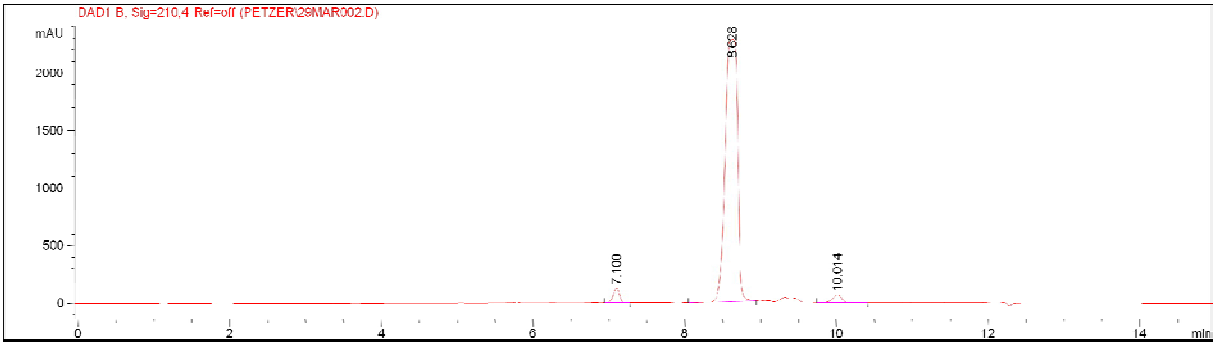
3-(Benzyloxy)benzonitrile (5b)



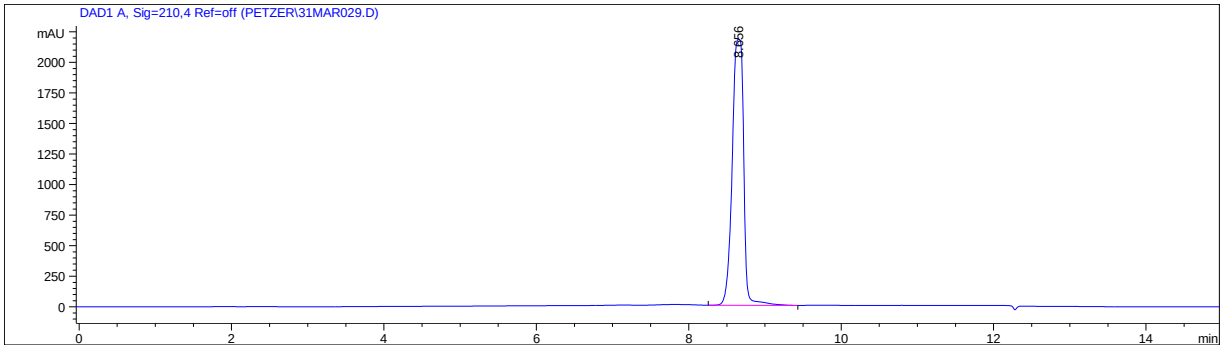
4-{[(2E)-3-Phenylprop-2-en-1-yl]oxy}benzonitrile (5c)



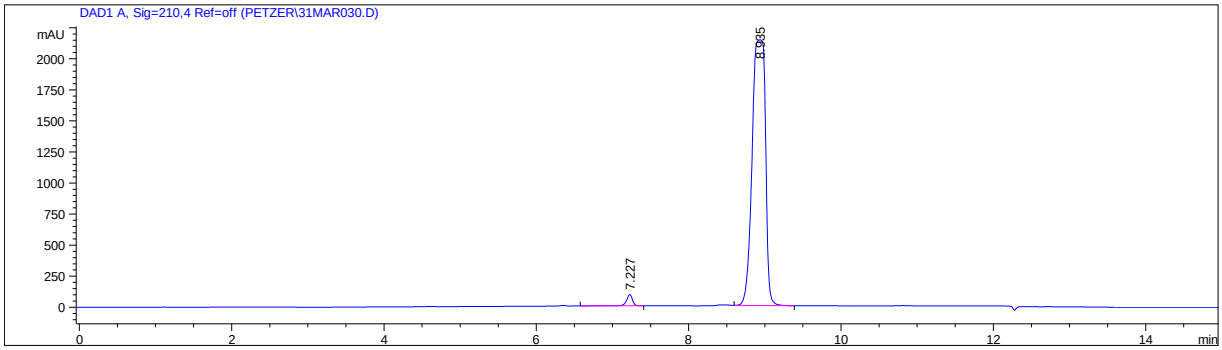
3-{[(2E)-3-Phenylprop-2-en-1-yl]oxy}benzonitrile (5d)



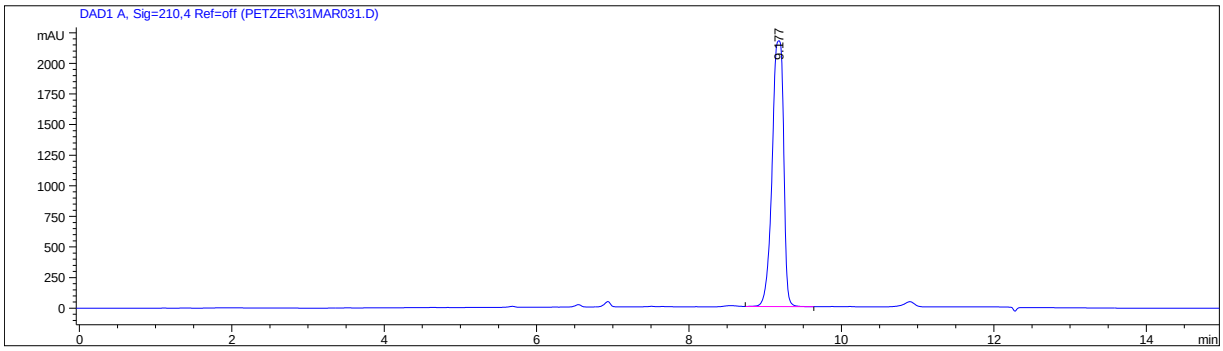
4-(4-Bromobenzyloxy)benzonitrile (5e)



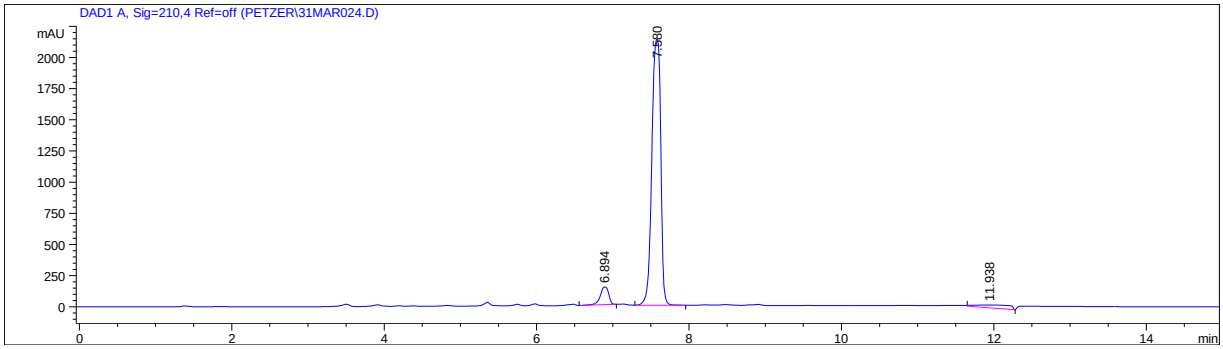
3-(4-Bromobenzyloxy)benzonitrile (5f)



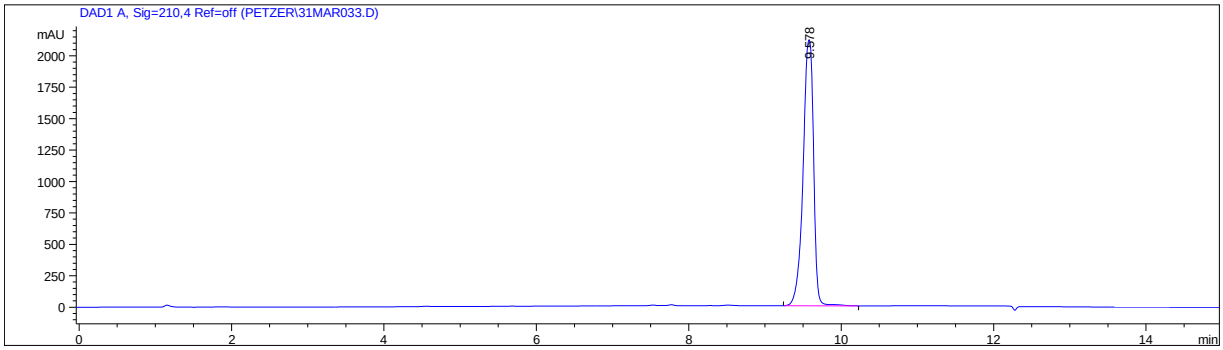
4-[2-(4-Bromophenyl)ethoxy]benzonitrile (5g)



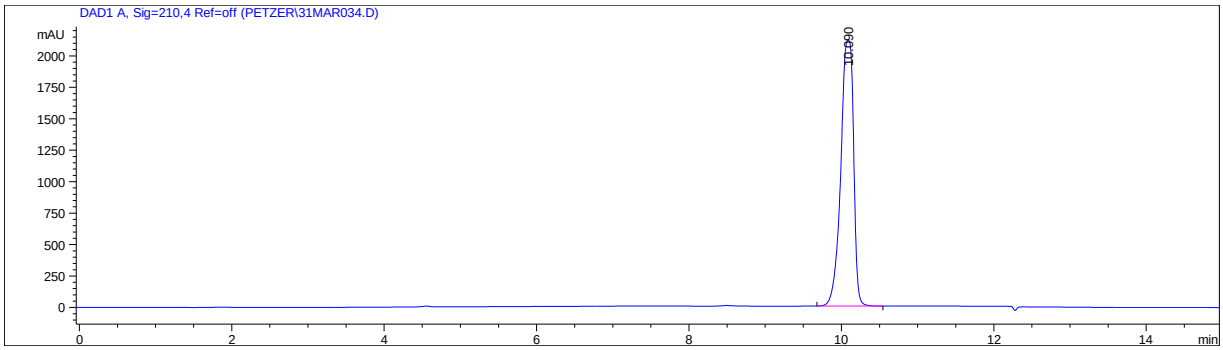
4-[2-(Benzyloxy)ethoxy]benzonitrile (5h)



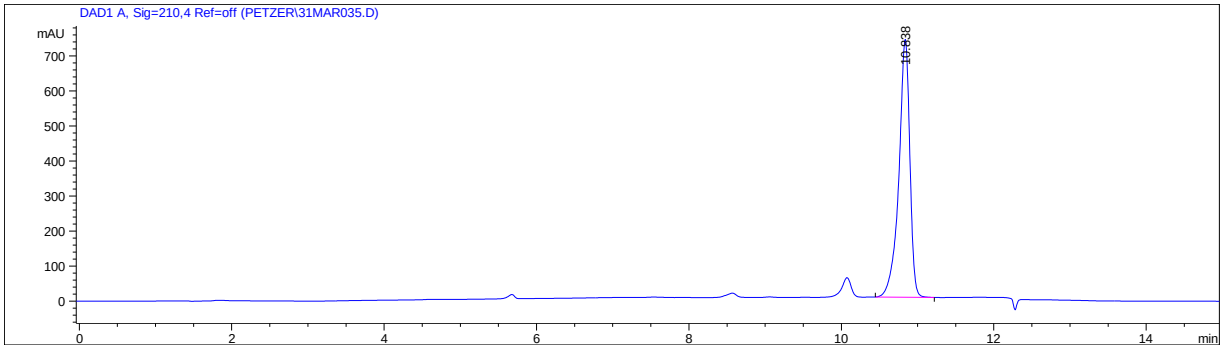
{[(2E)-3-phenylprop-2-en-1-yl]oxy}benzene (6b)



1-Bromo-4-(phenoxymethyl)benzene (6c)



1-Bromo-4-(2-phenoxyethyl)benzene (6d)

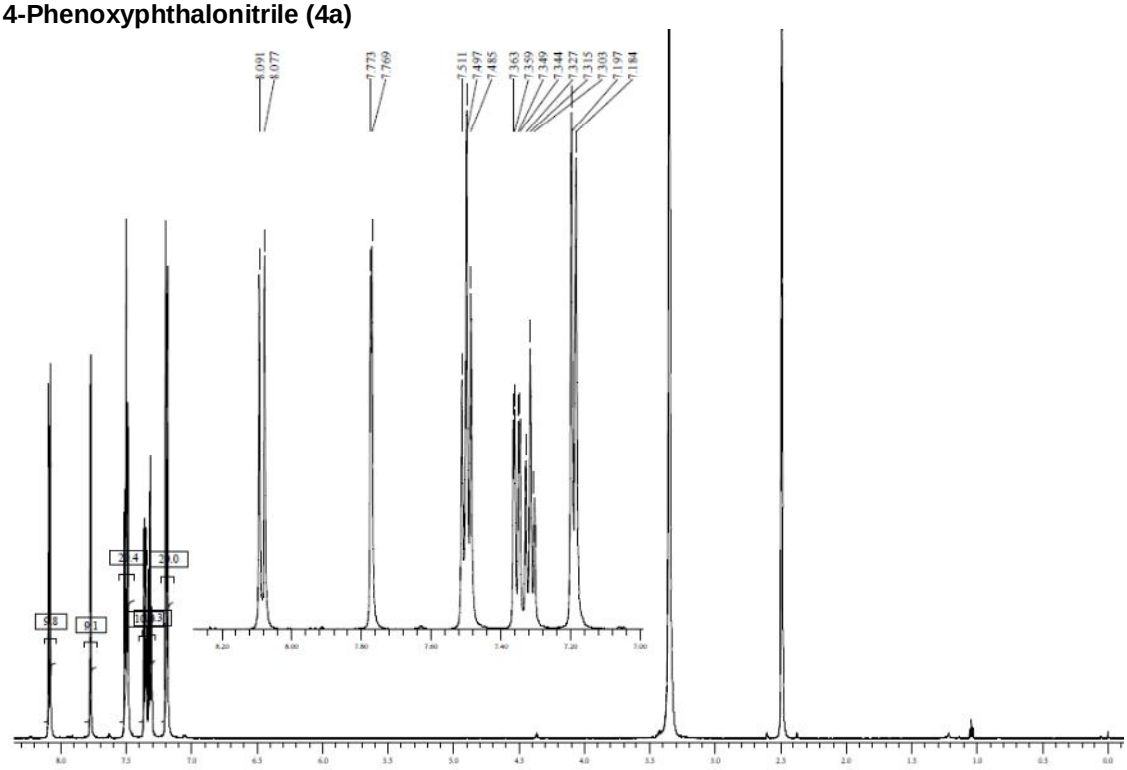


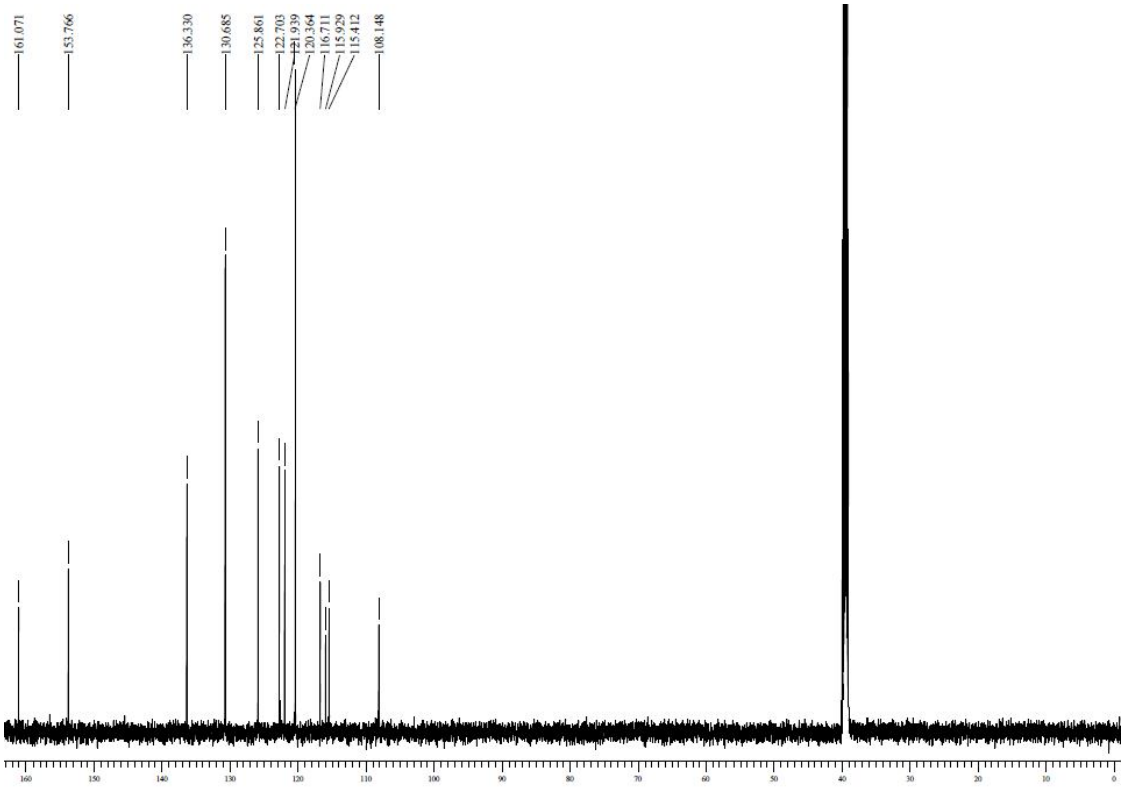
S2: ^{1}H NMR spectra of the following new/unknown compounds

- 4-Phenoxyphthalonitrile (**4a**)
- 4-Benzyloxyphthalonitrile (**4b**)
- 4-(2-Phenylethoxy)phthalonitrile (**4c**)
- 4-(3-Phenylpropoxy)phthalonitrile (**4d**)
- 4-{[(2E)-3-Phenylprop-2-en-1-yl]oxy}phthalonitrile (**4e**)
- 4-(Naphthalen-2-yloxy)phthalonitrile (**4f**)
- 4-(4-Bromophenoxy)phthalonitrile (**4g**)
- 4-(4-Bromobenzyloxy)phthalonitrile (**4h**)
- 4-[2-(4-Bromophenyl)ethoxy]phthalonitrile (**4i**)
- 4-(Benzyloxy)benzonitrile (**5a**)
- 3-(Benzyloxy)benzonitrile (**5b**)
- 4-{[(2E)-3-Phenylprop-2-en-1-yl]oxy}benzonitrile (**5c**)
- 3-{[(2E)-3-Phenylprop-2-en-1-yl]oxy}benzonitrile (**5d**)
- 4-(4-Bromobenzyloxy)benzonitrile (**5e**)
- 3-(4-Bromobenzyloxy)benzonitrile (**5f**)
- 4-[2-(4-bromophenyl)ethoxy]benzonitrile (**5g**)
- 4-[2-(Benzyloxy)ethoxy]benzonitrile (**5h**)
- {[(2E)-3-phenylprop-2-en-1-yl]oxy}benzene **(6b**)
- 1-Bromo-4-(phenoxymethyl)benzene (**6c**)
- 1-Bromo-4-(2-phenoxyethyl)benzene (**6d**)

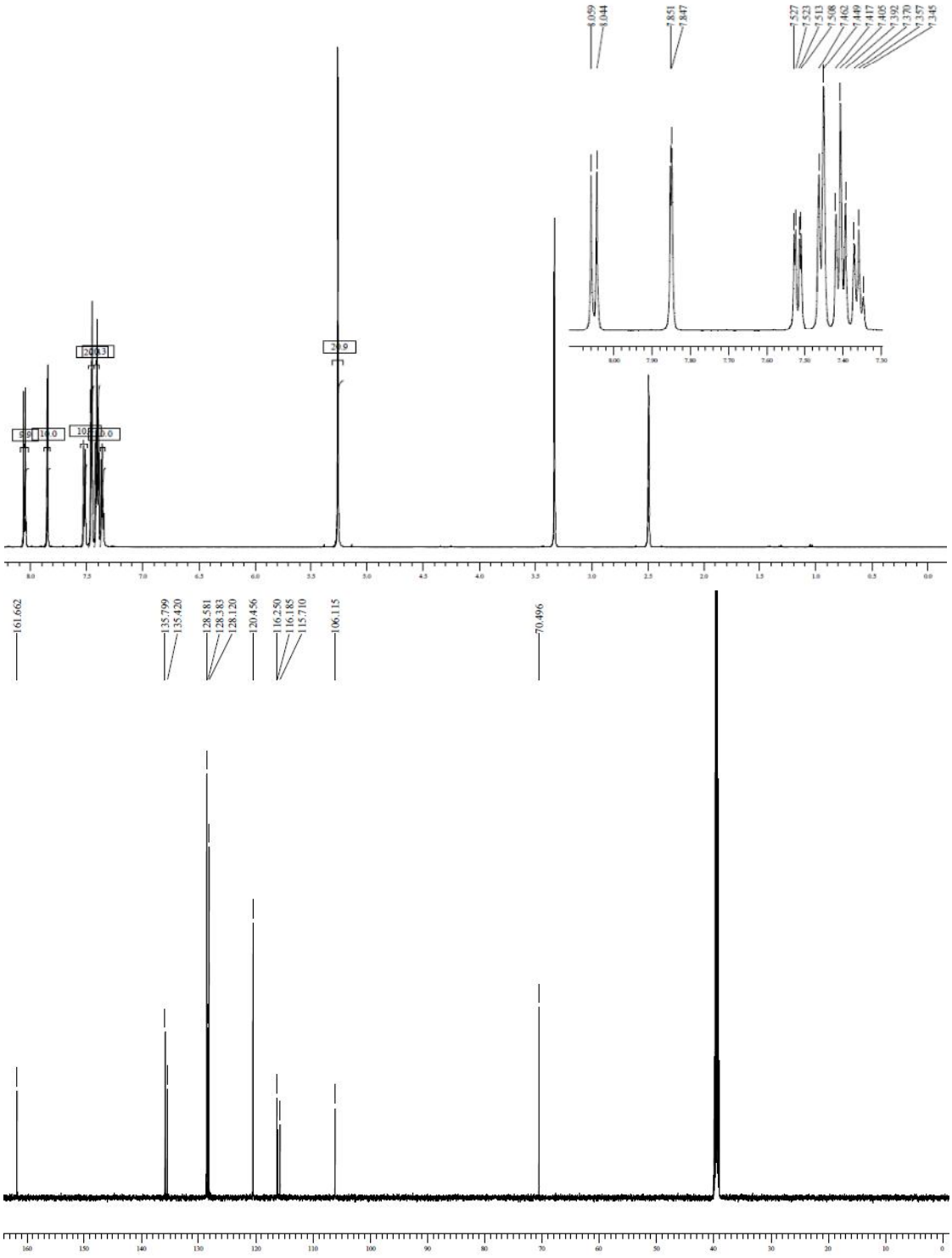
Proton (^{1}H) and carbon (^{13}C) NMR spectra were recorded on a Bruker Avance III 600 spectrometer at frequencies of 600 MHz and 150 MHz, respectively. All NMR measurements were conducted in DMSO-d*6*.

4-Phenoxyphthalonitrile (4a)

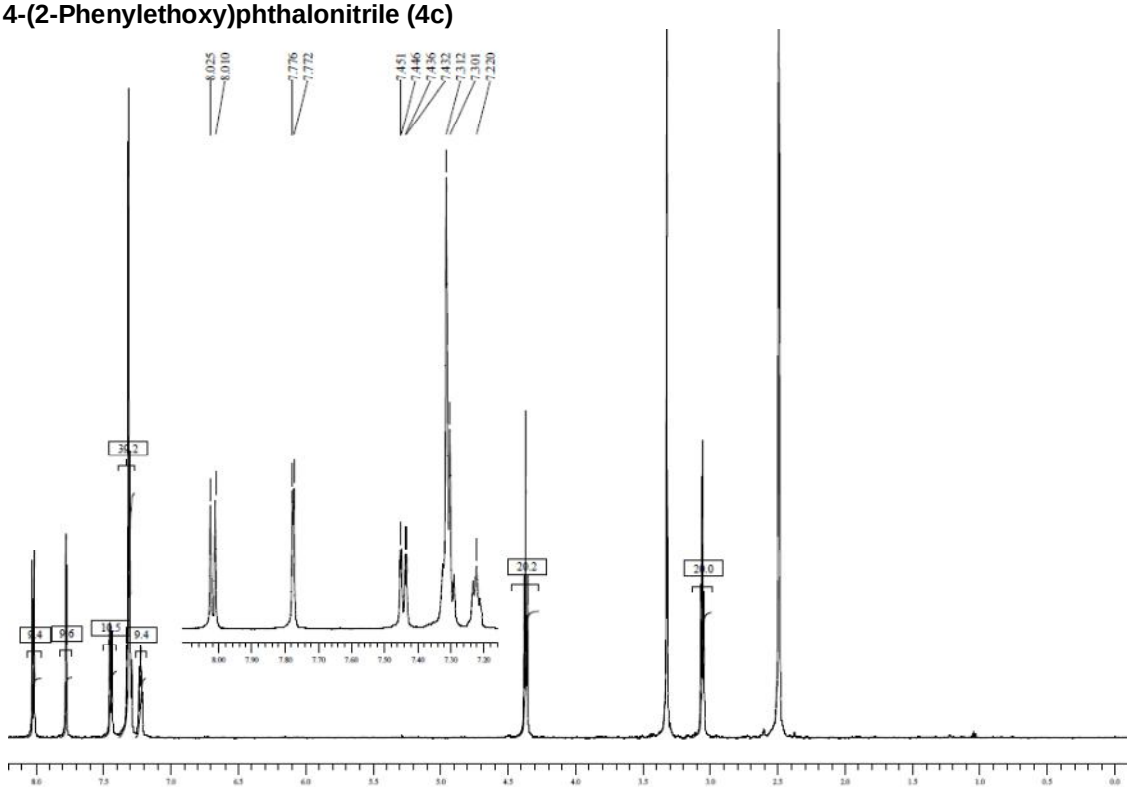


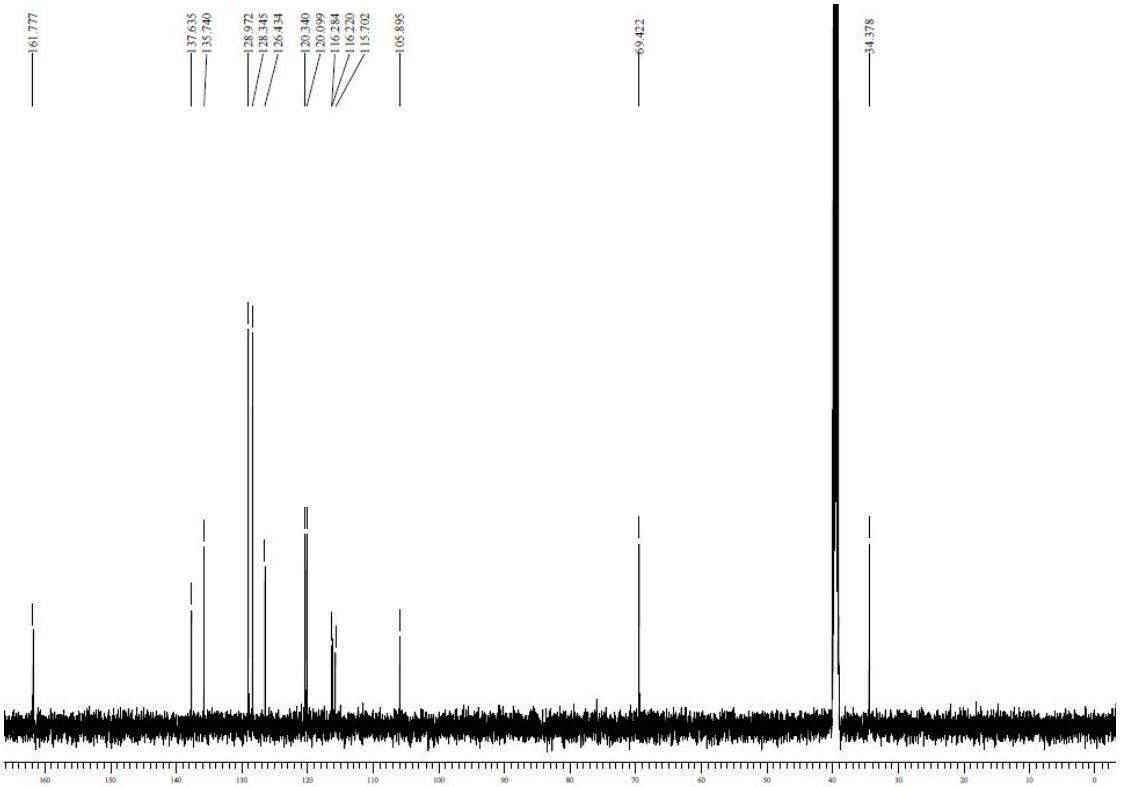


4-Benzyloxyphthalonitrile (4b)

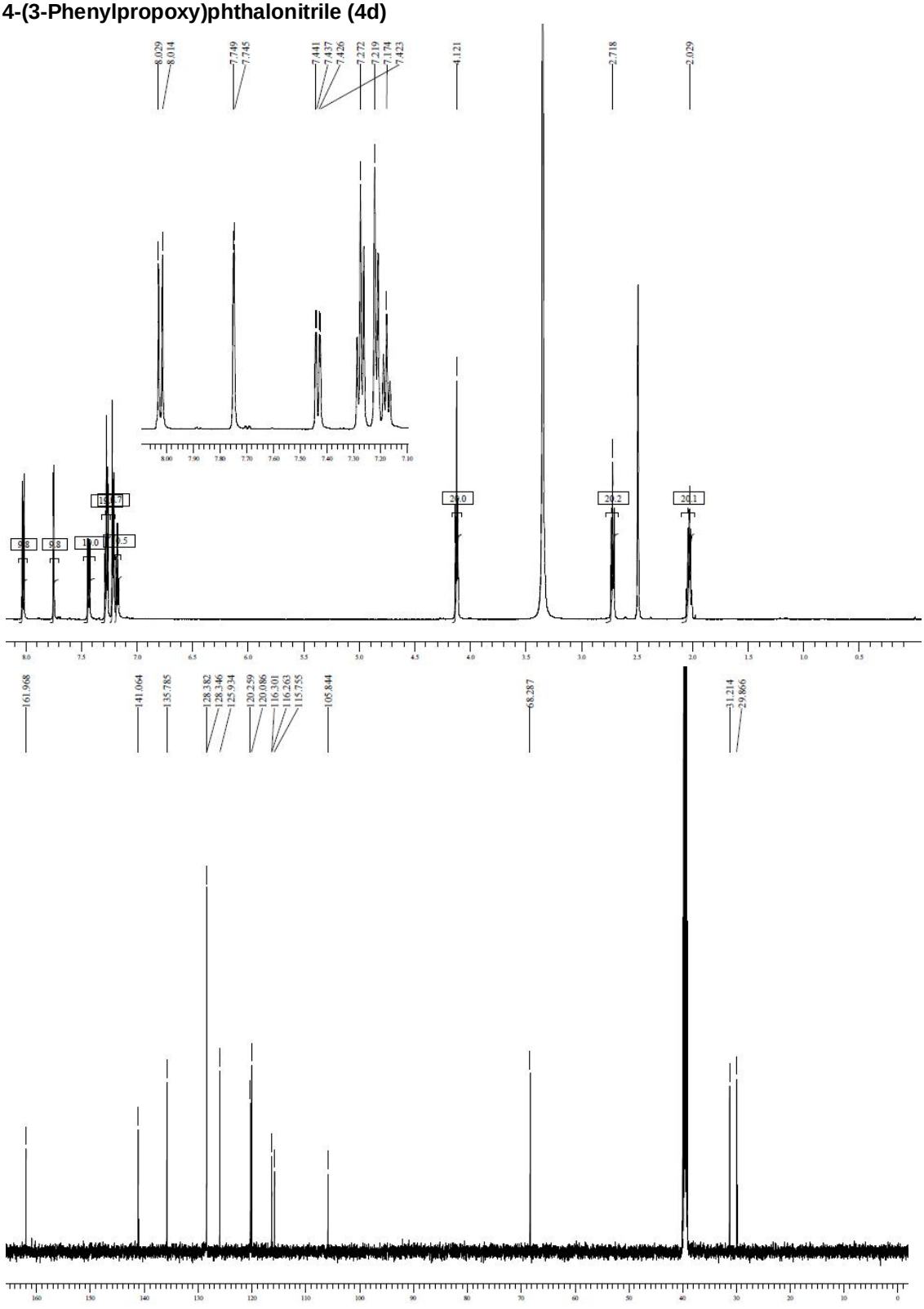


4-(2-Phenylethoxy)phthalonitrile (4c)

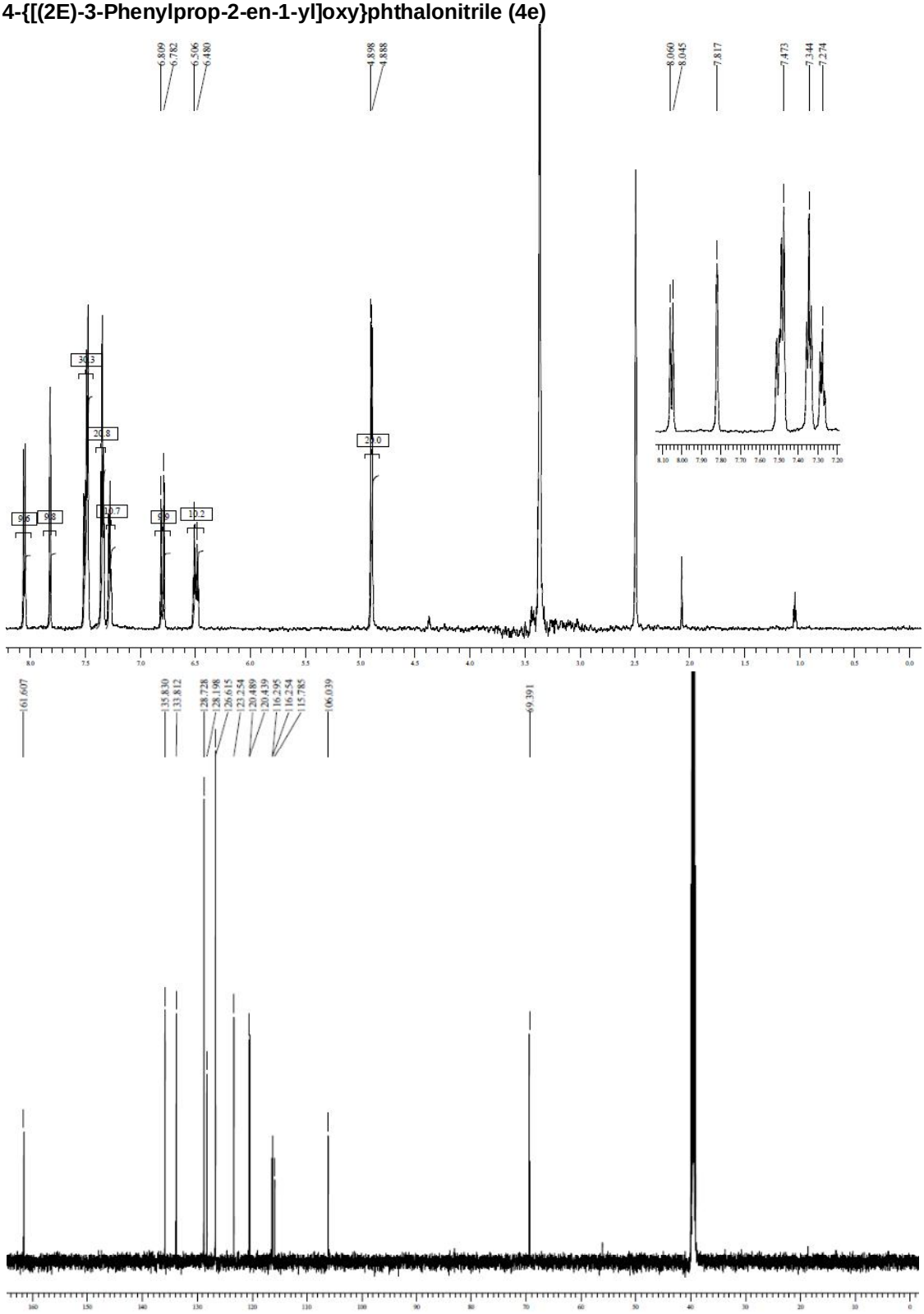




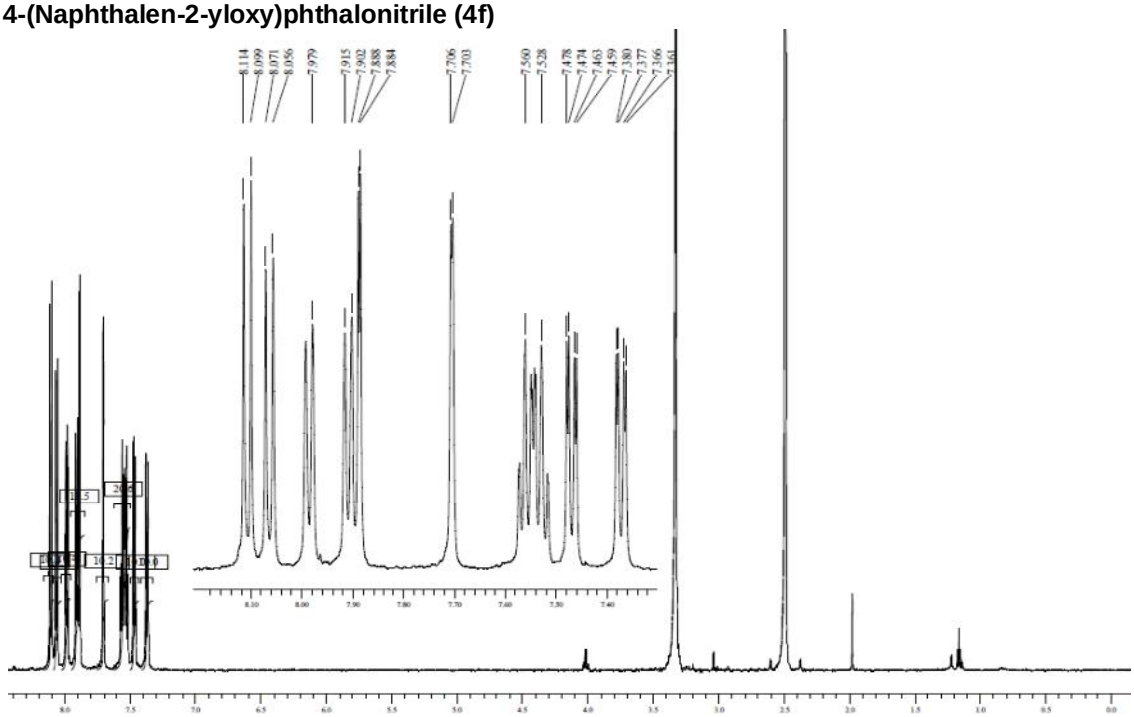
4-(3-Phenylpropoxy)phthalonitrile (4d)

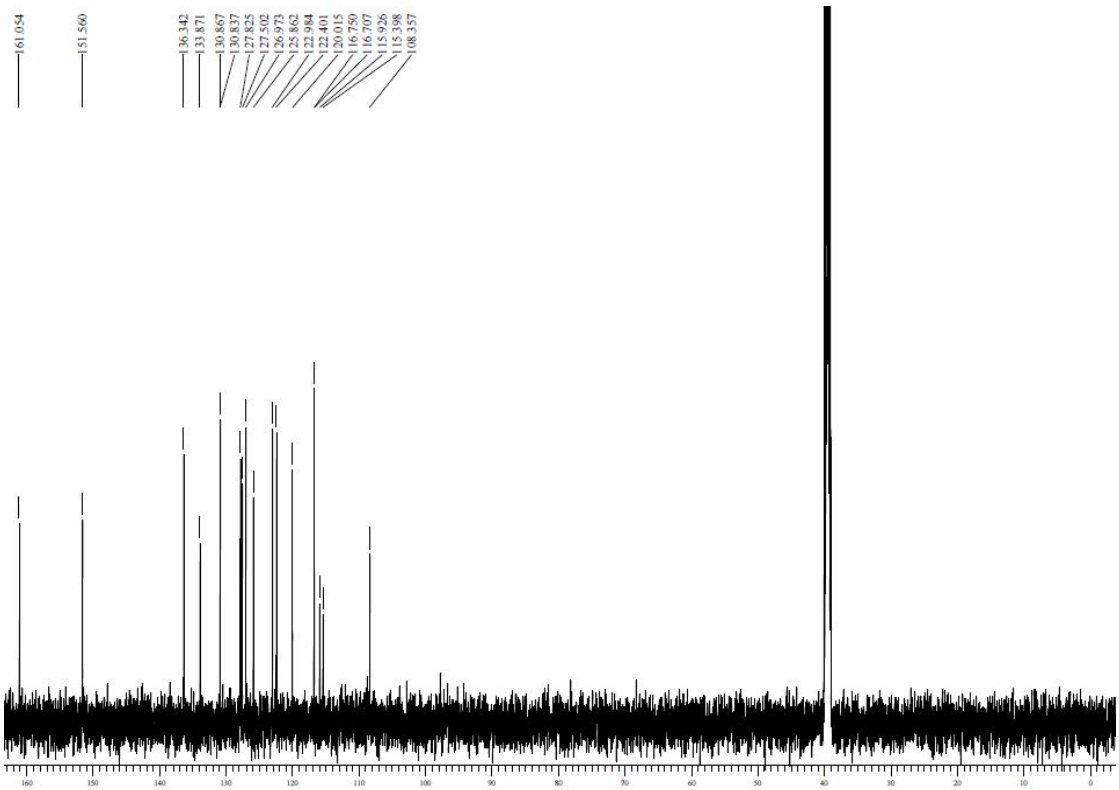


4-{[(2E)-3-Phenylprop-2-en-1-yl]oxy}phthalonitrile (4e)

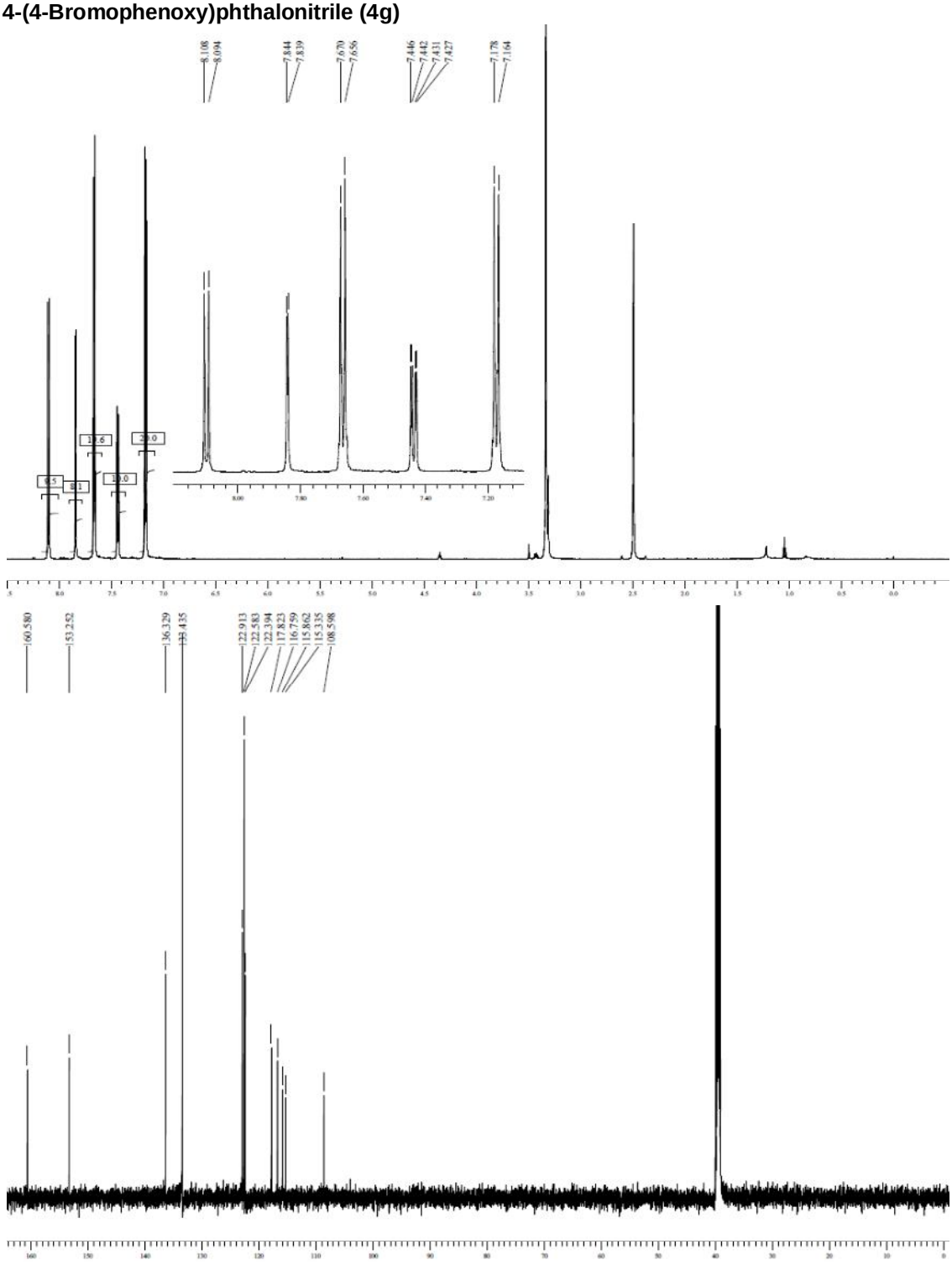


4-(Naphthalen-2-yloxy)phthalonitrile (4f)

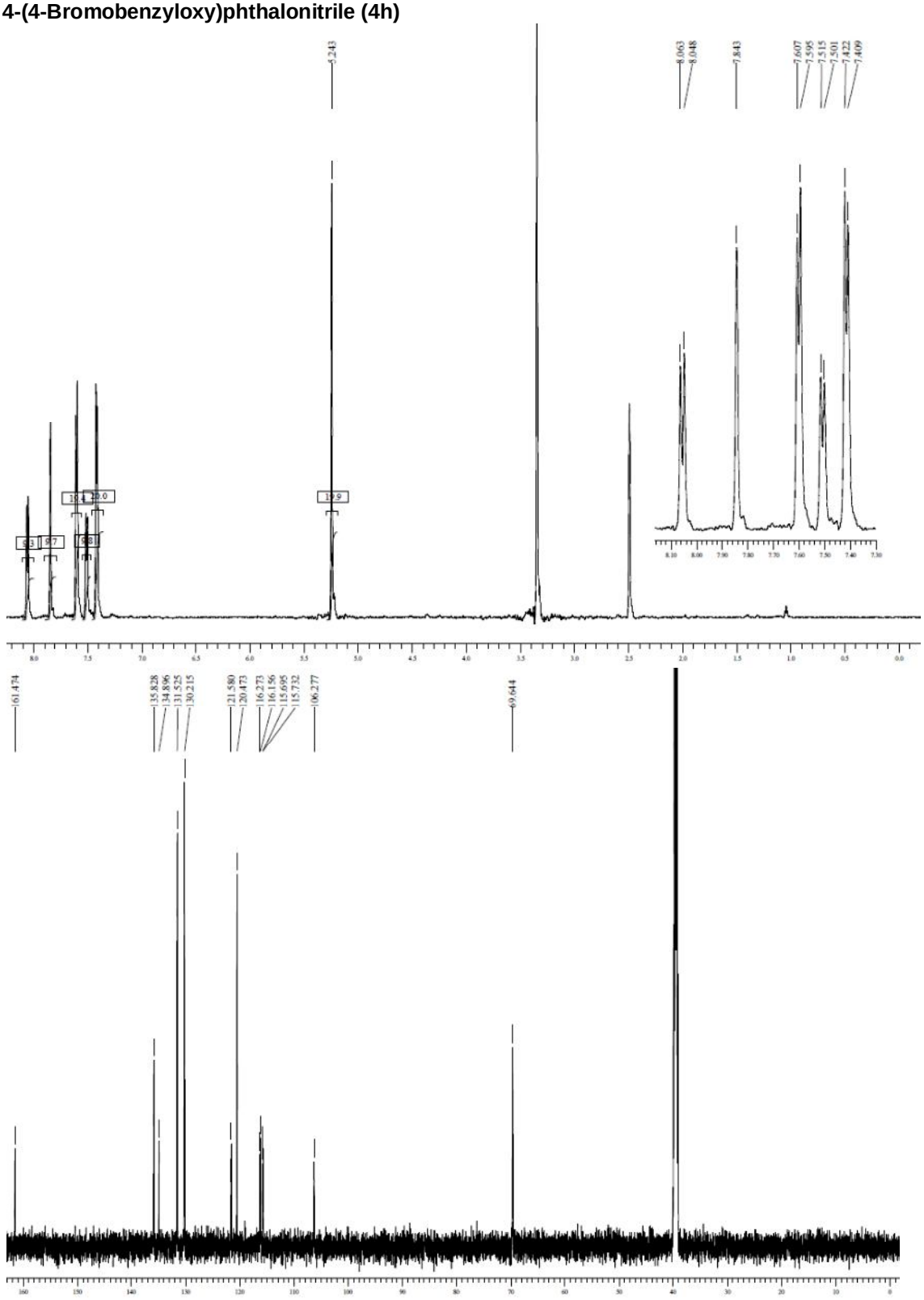




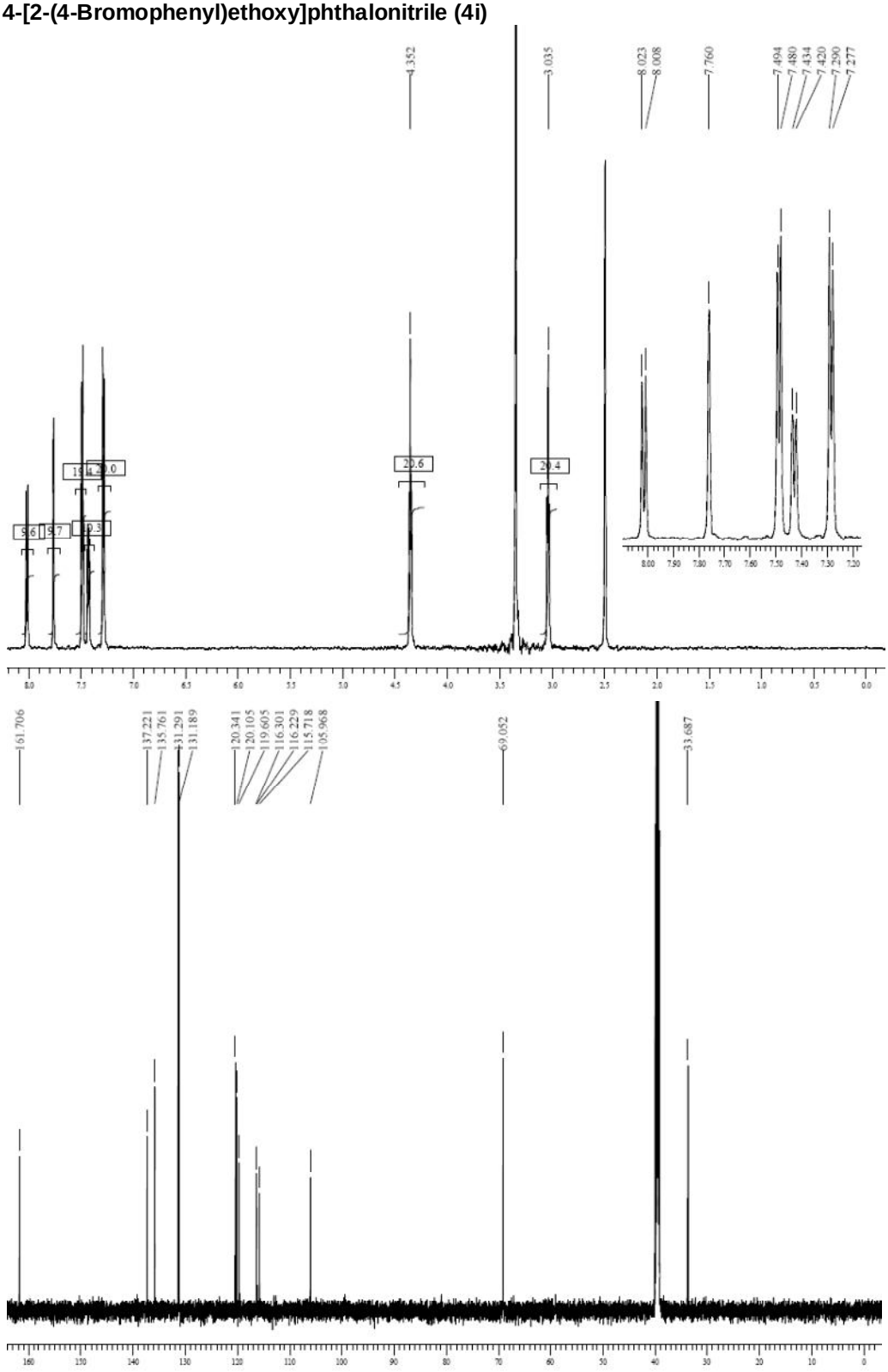
4-(4-Bromophenoxy)phthalonitrile (4g)



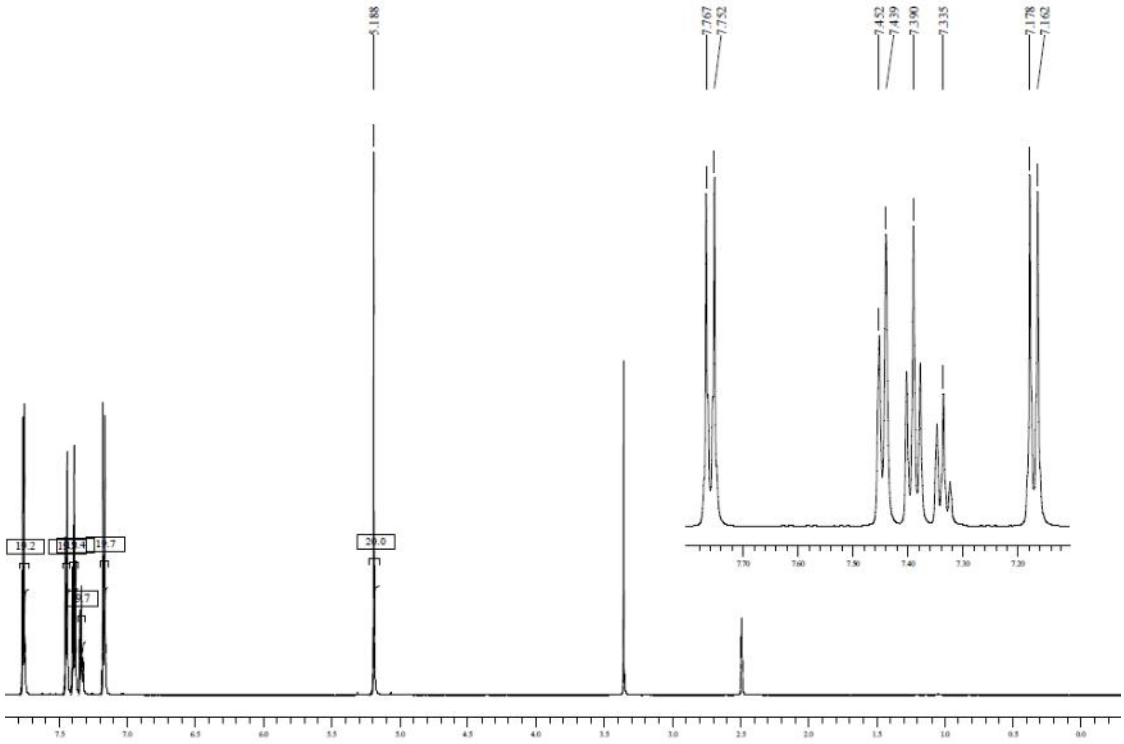
4-(4-Bromobenzyloxy)phthalonitrile (4h)

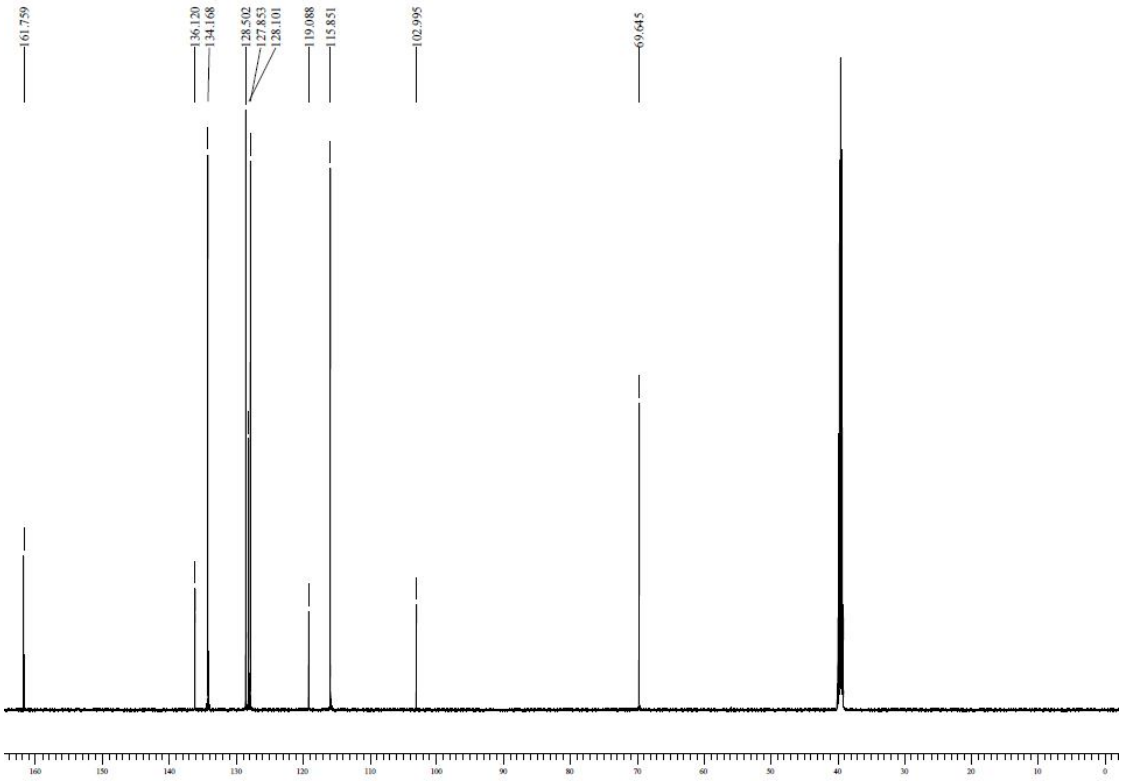


4-[2-(4-Bromophenyl)ethoxy]phthalonitrile (4i)

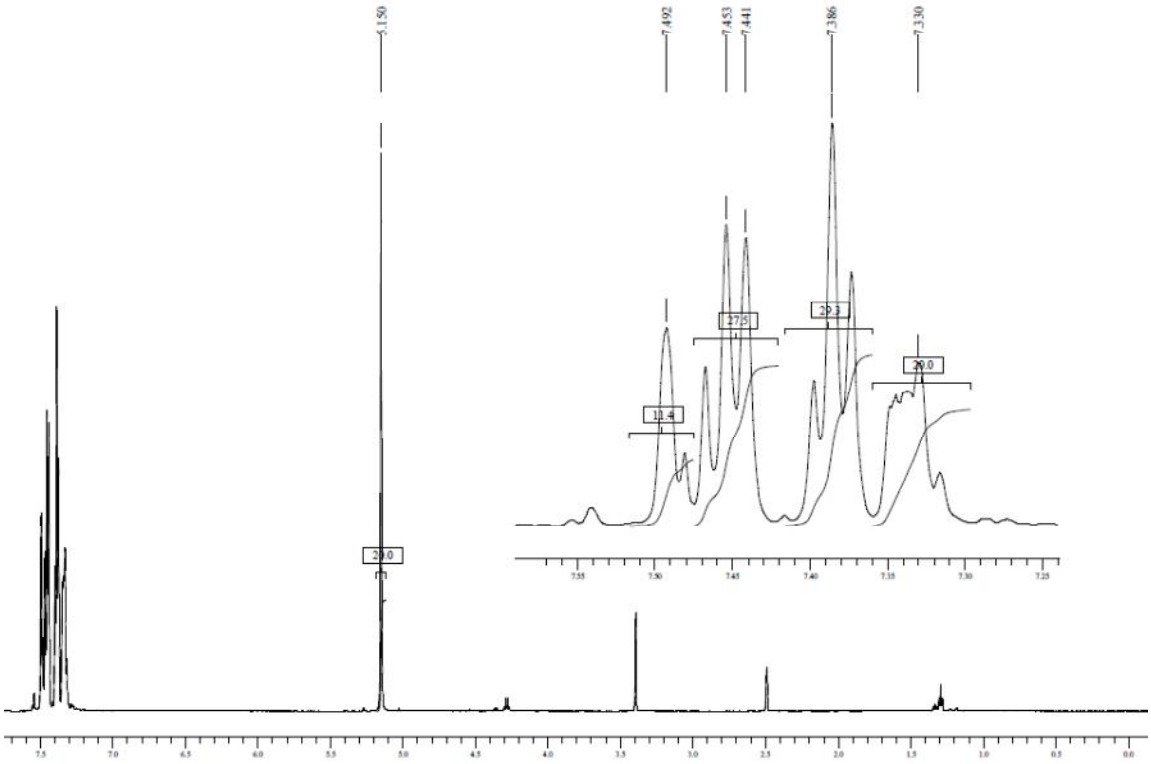


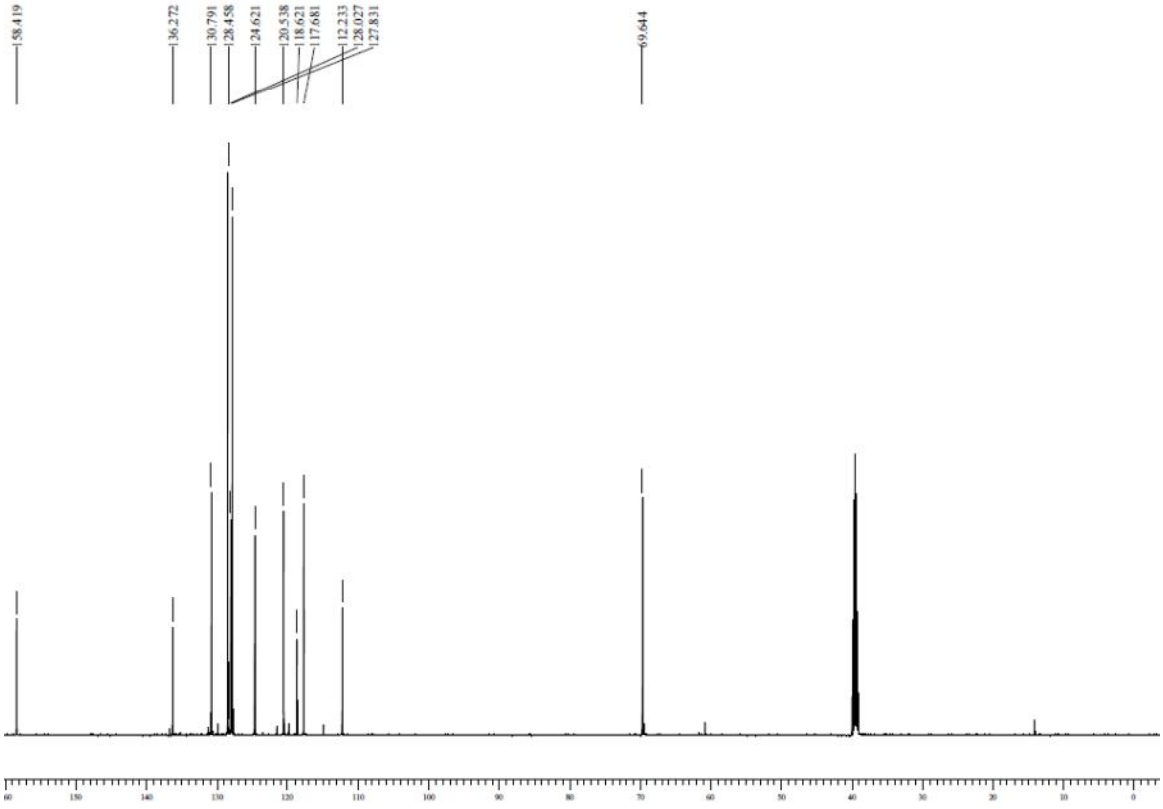
4-(Benzyloxy)benzonitrile (5a)



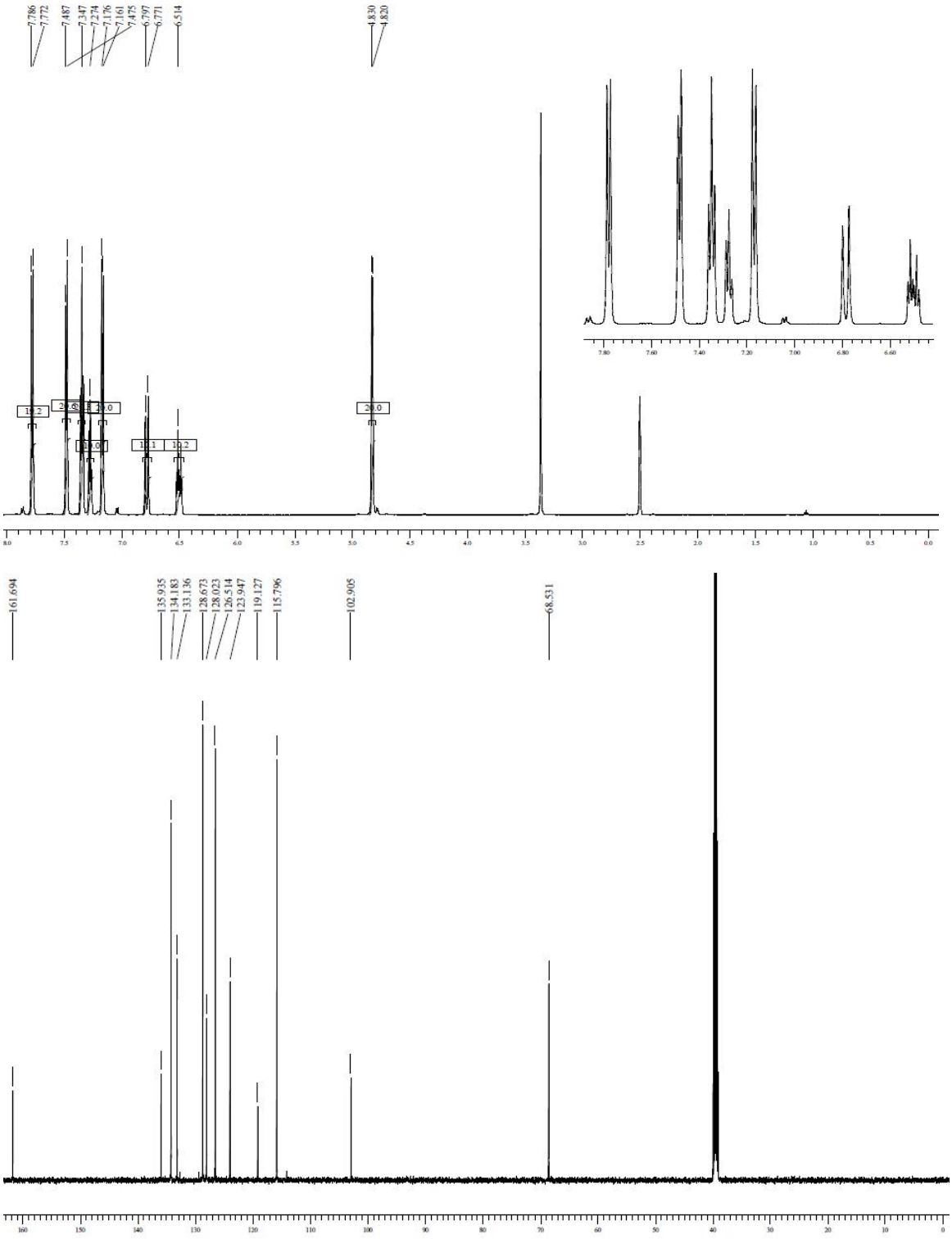


3-(Benzyloxy)benzonitrile (5b)

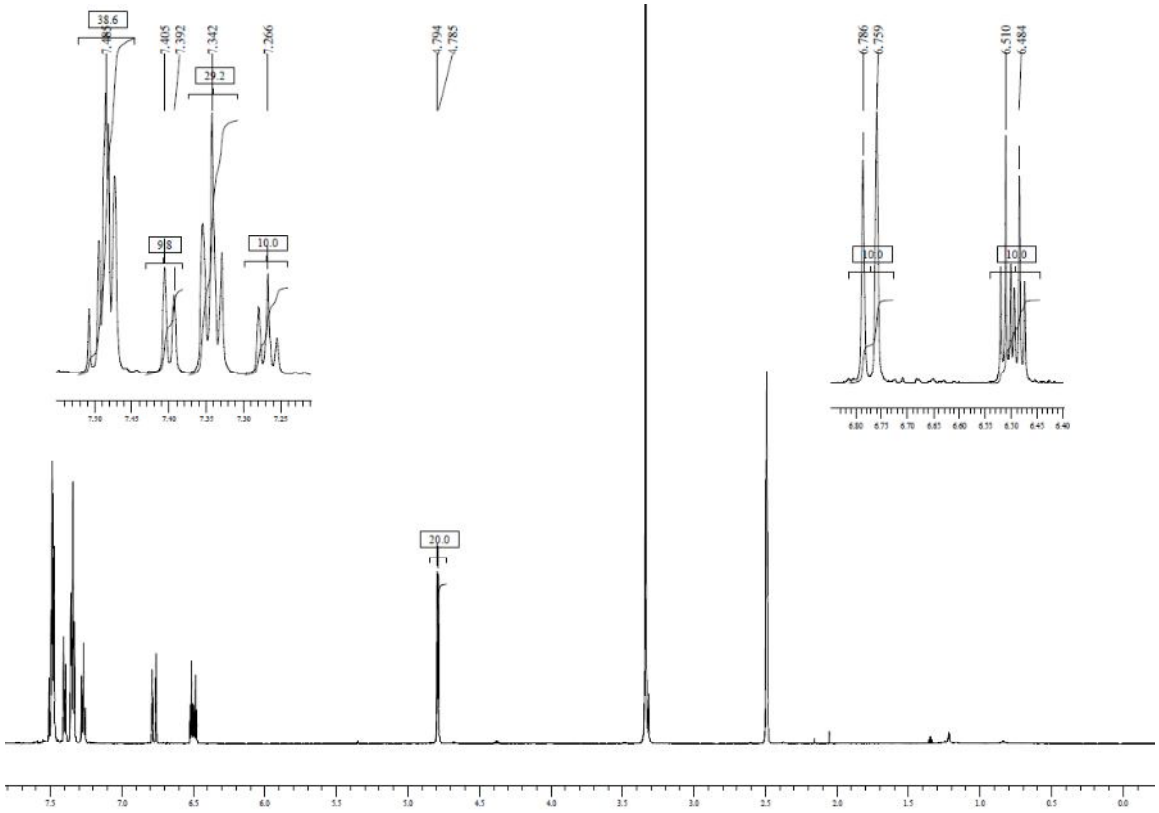


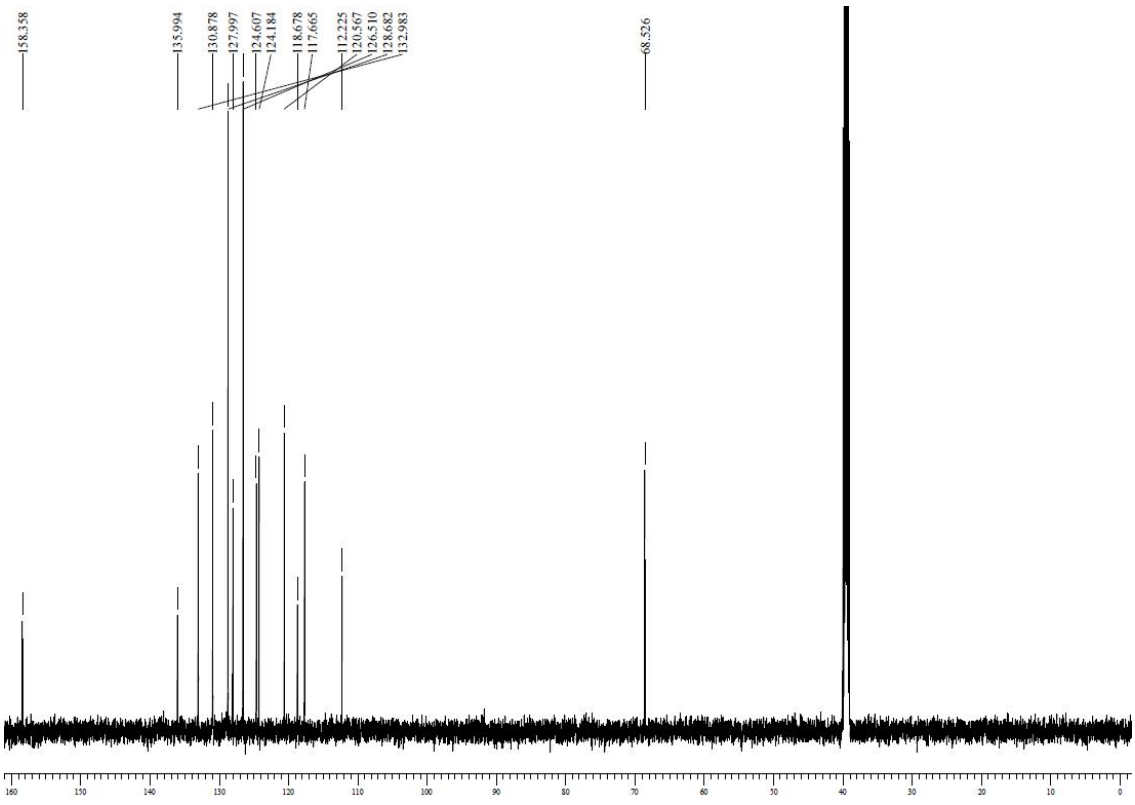


4-{[(2E)-3-Phenylprop-2-en-1-yl]oxy}benzonitrile (5c)

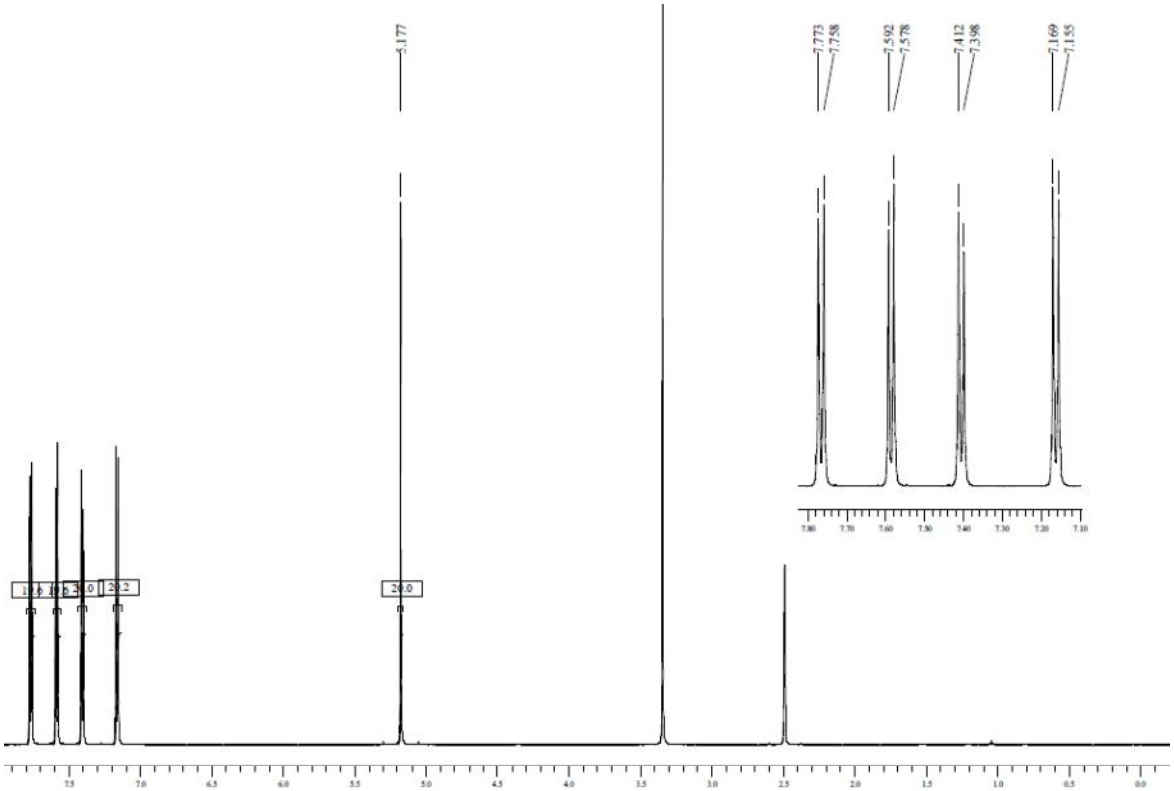


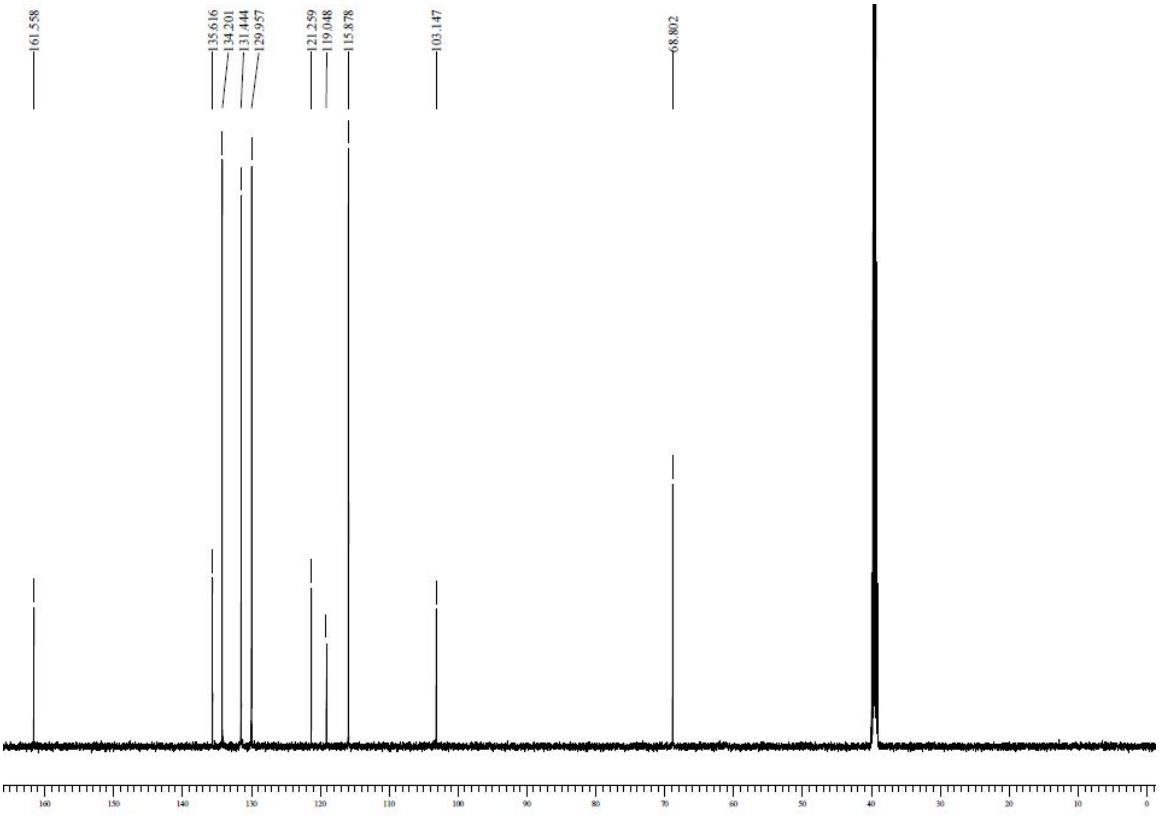
3-{[(2E)-3-Phenylprop-2-en-1-yl]oxy}benzonitrile (5d)



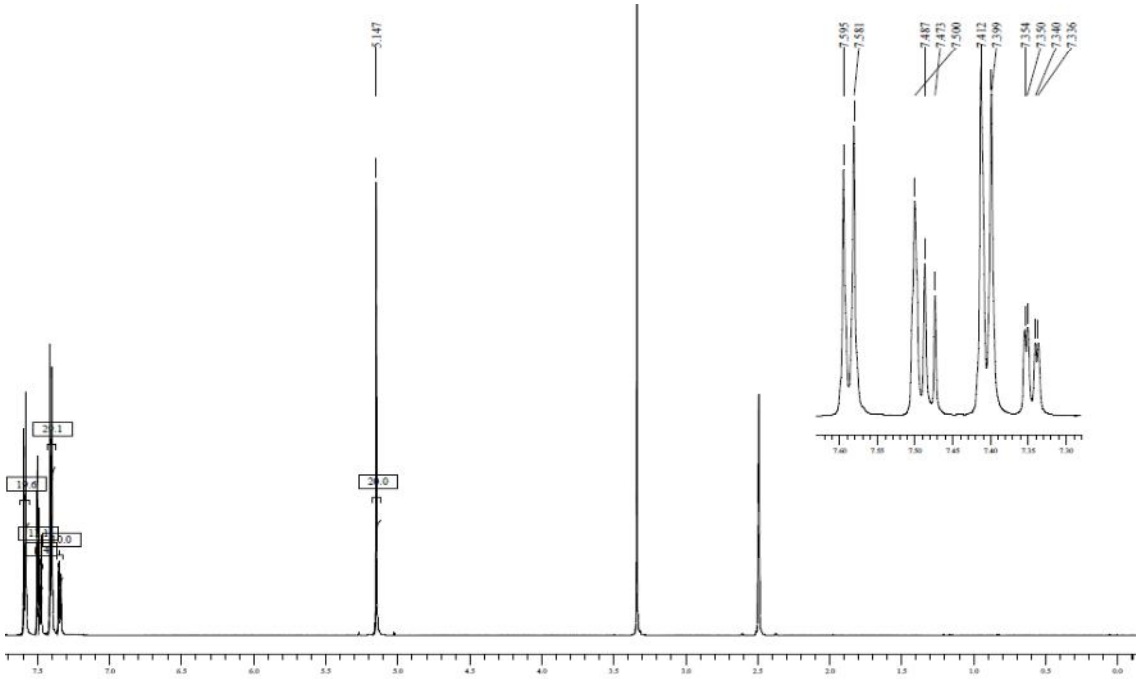


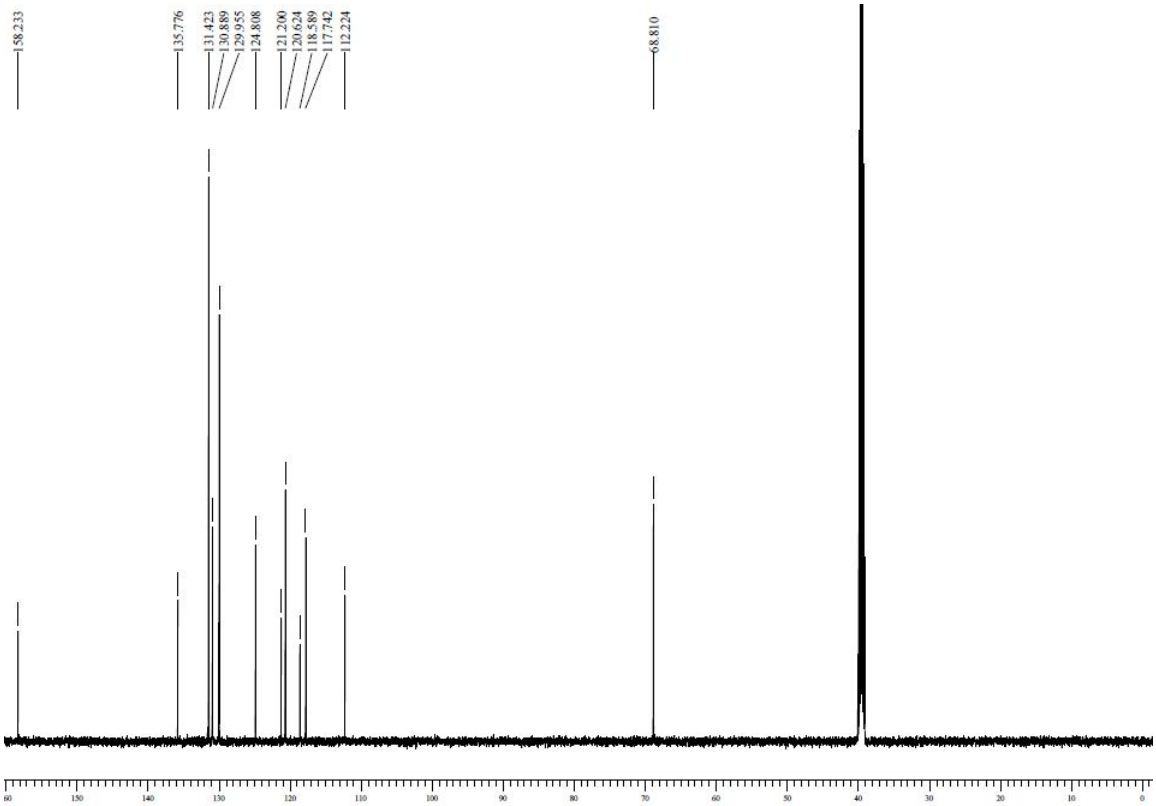
4-(4-Bromobenzyloxy)benzonitrile (5e)



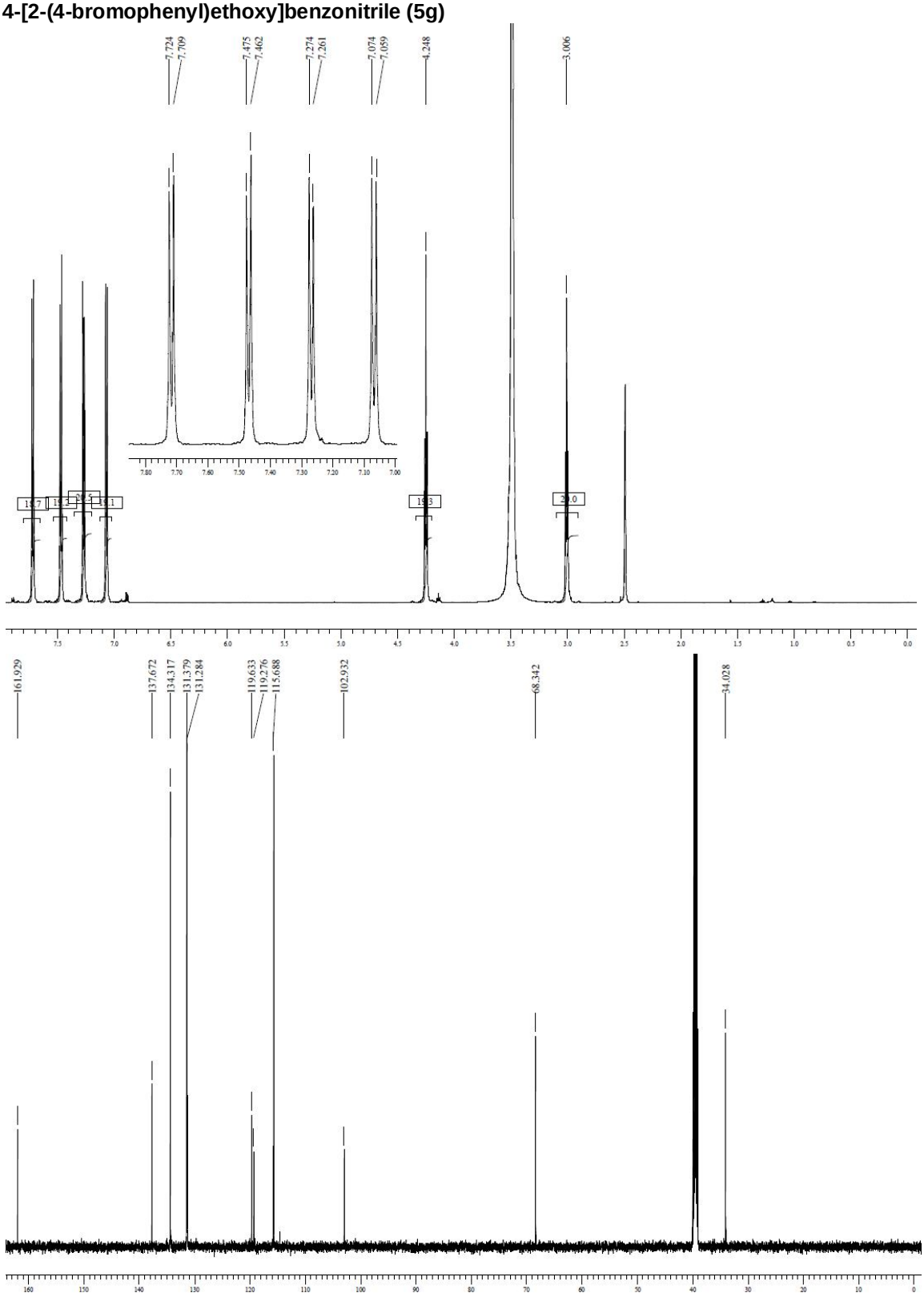


3-(4-Bromobenzyloxy)benzonitrile (5f)

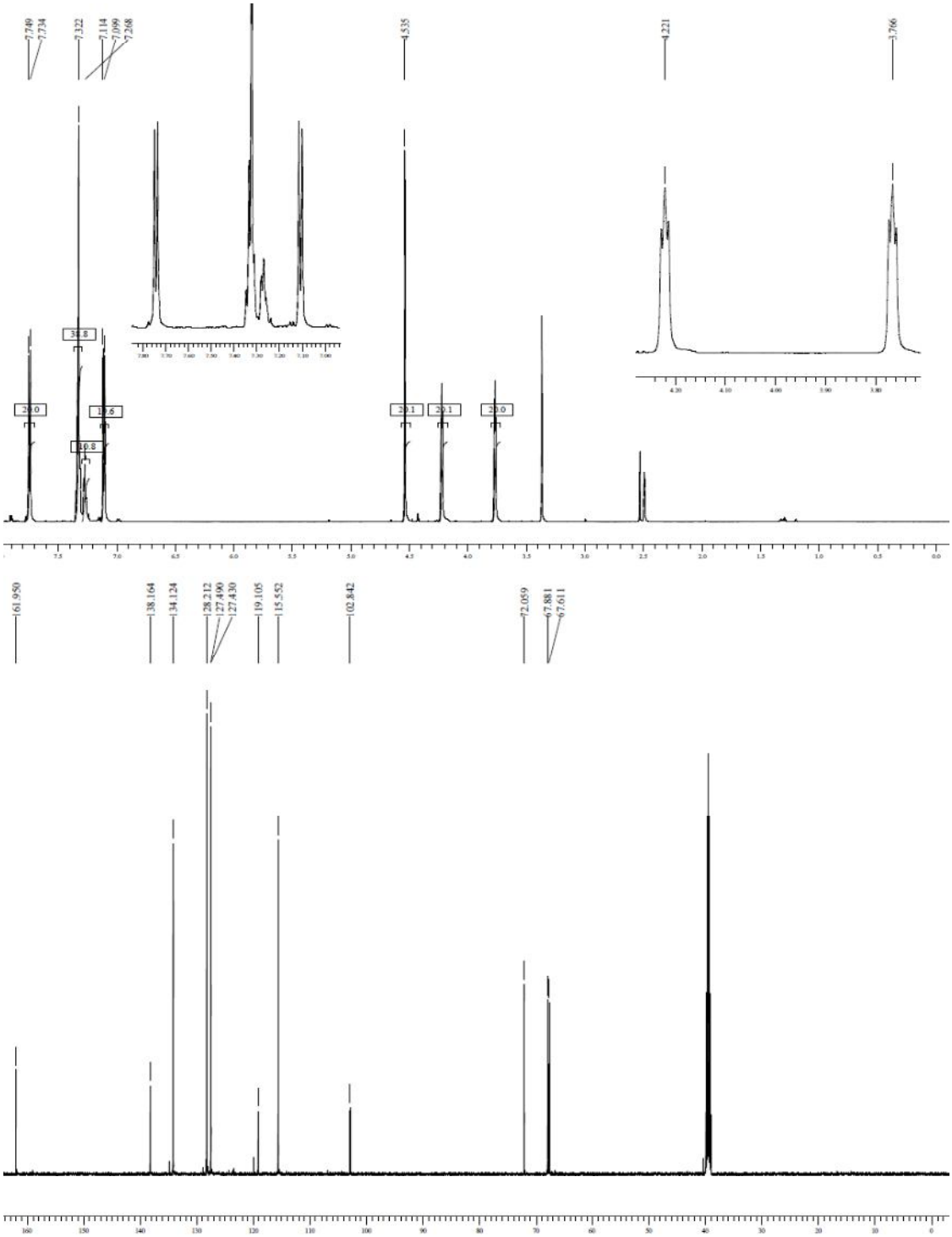




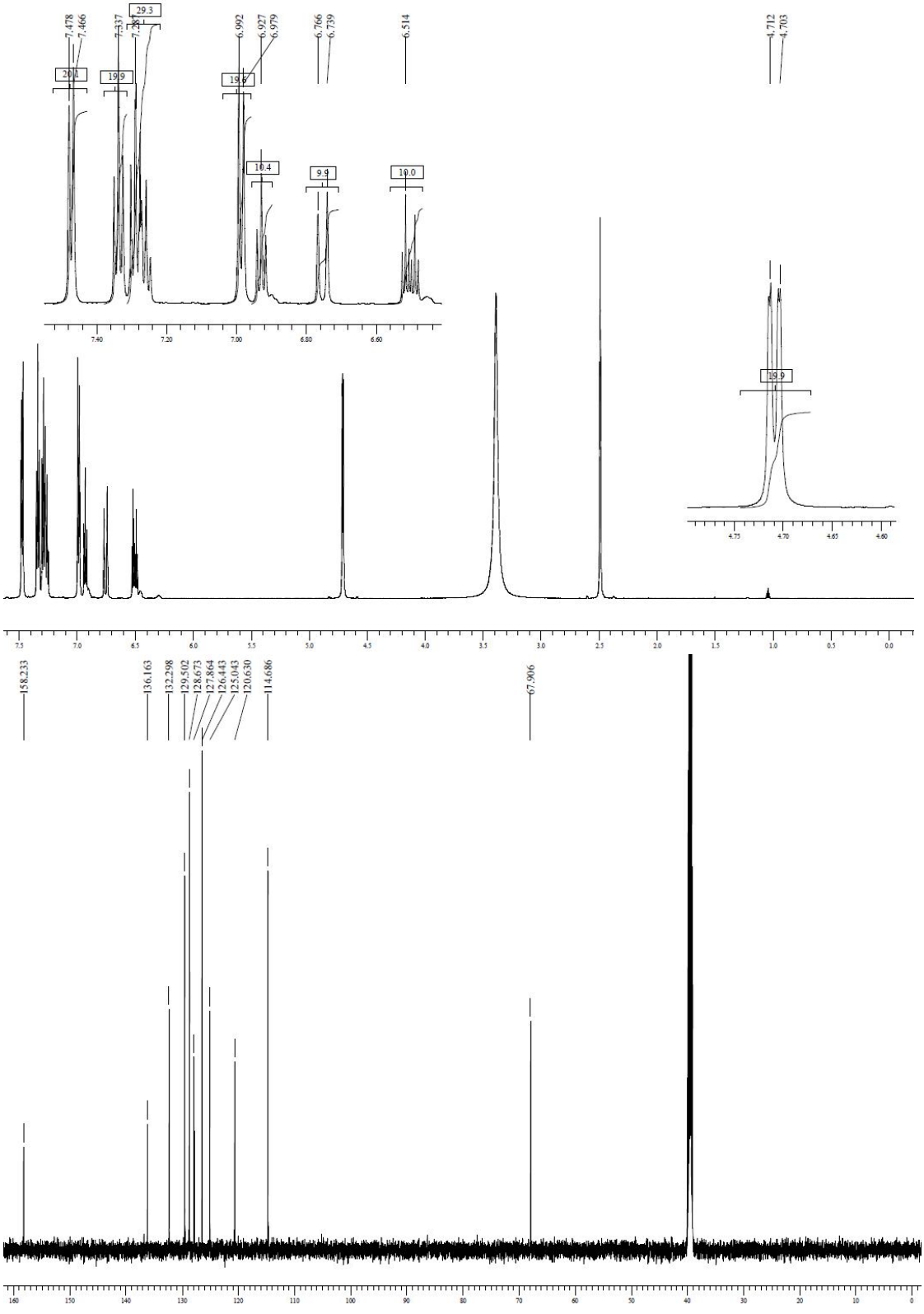
4-[2-(4-bromophenyl)ethoxy]benzonitrile (5g)



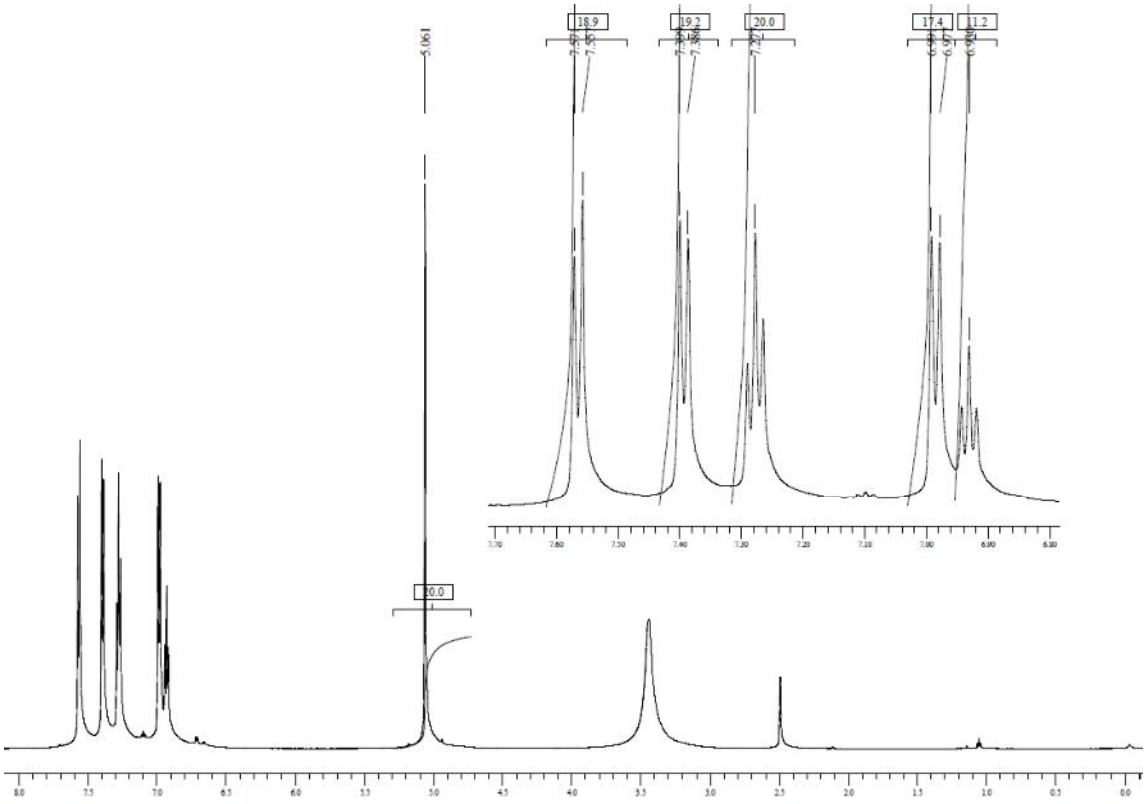
4-[2-(Benzyloxy)ethoxy]benzonitrile (5h)

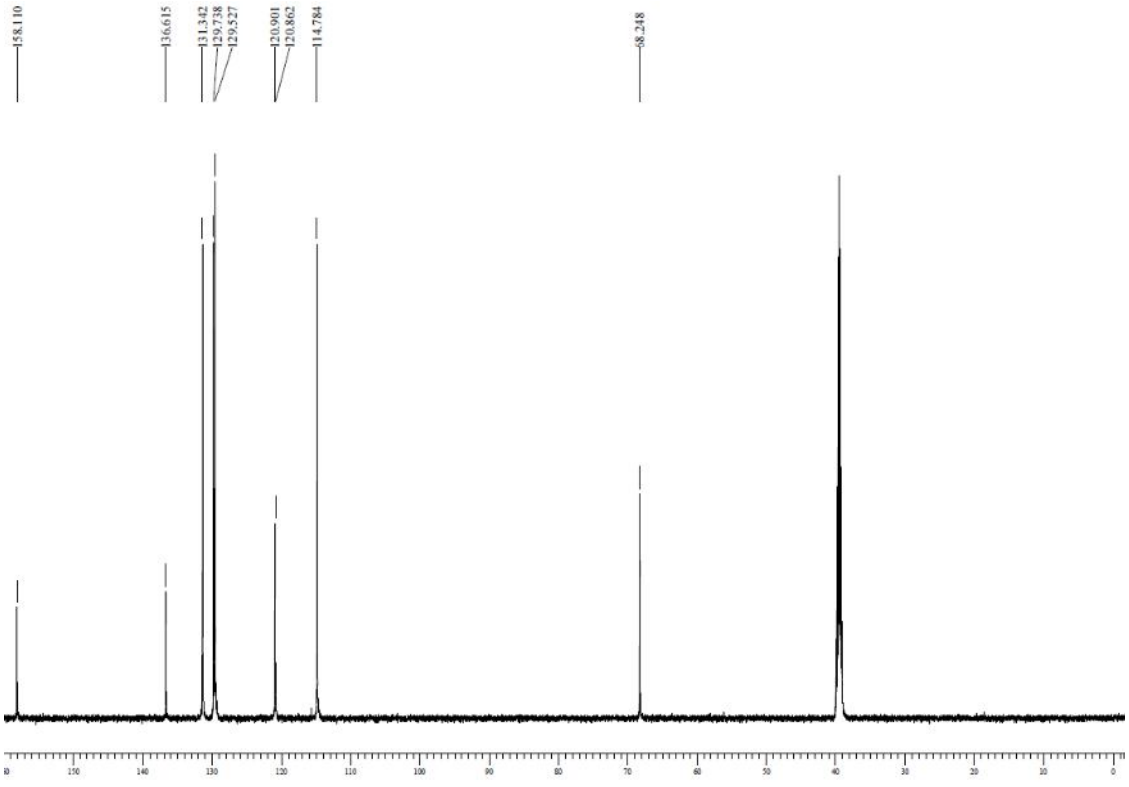


{[(2E)-3-phenylprop-2-en-1-yl]oxy}benzene (6b)



4.5.2. 1-Bromo-4-(phenoxymethyl)benzene (6c)





4.5.3. 1-Bromo-4-(2-phenoxyethyl)benzene (6d)