

**Discovery of new nicotinamides as apoptotic VEGFR-2 inhibitors: virtual screening, synthesis, anti-proliferative, immunomodulatory, ADMET, toxicity, and molecular dynamic simulation studies**

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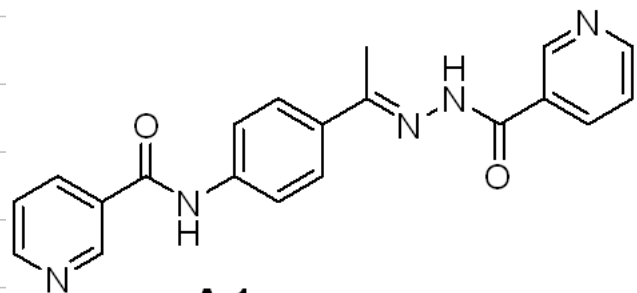
**\*Corresponding authors:**

**Ibrahim H. Eissa**

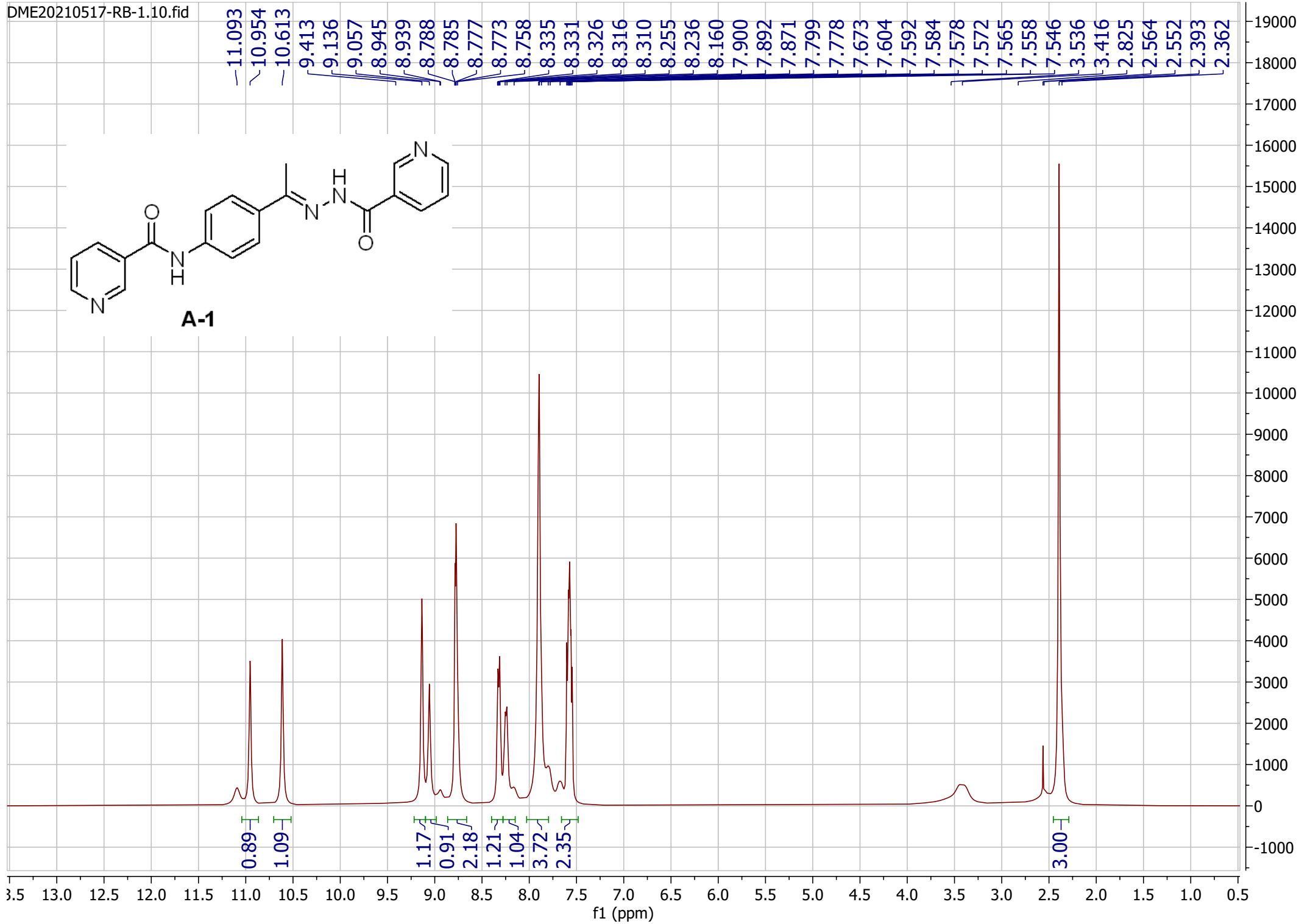
Medicinal Chemistry Department, Faculty of Pharmacy (Boys), Al-Azhar University, Cairo 11884, Egypt. **Email:** [Ibrahimeissa@azhar.edu.eg](mailto:Ibrahimeissa@azhar.edu.eg)

**Ahmed M. Metwaly**

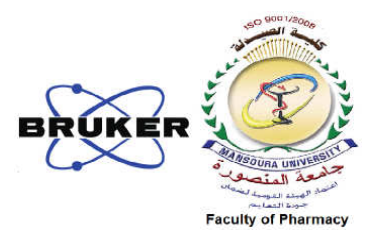
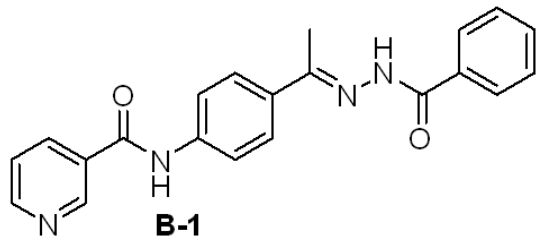
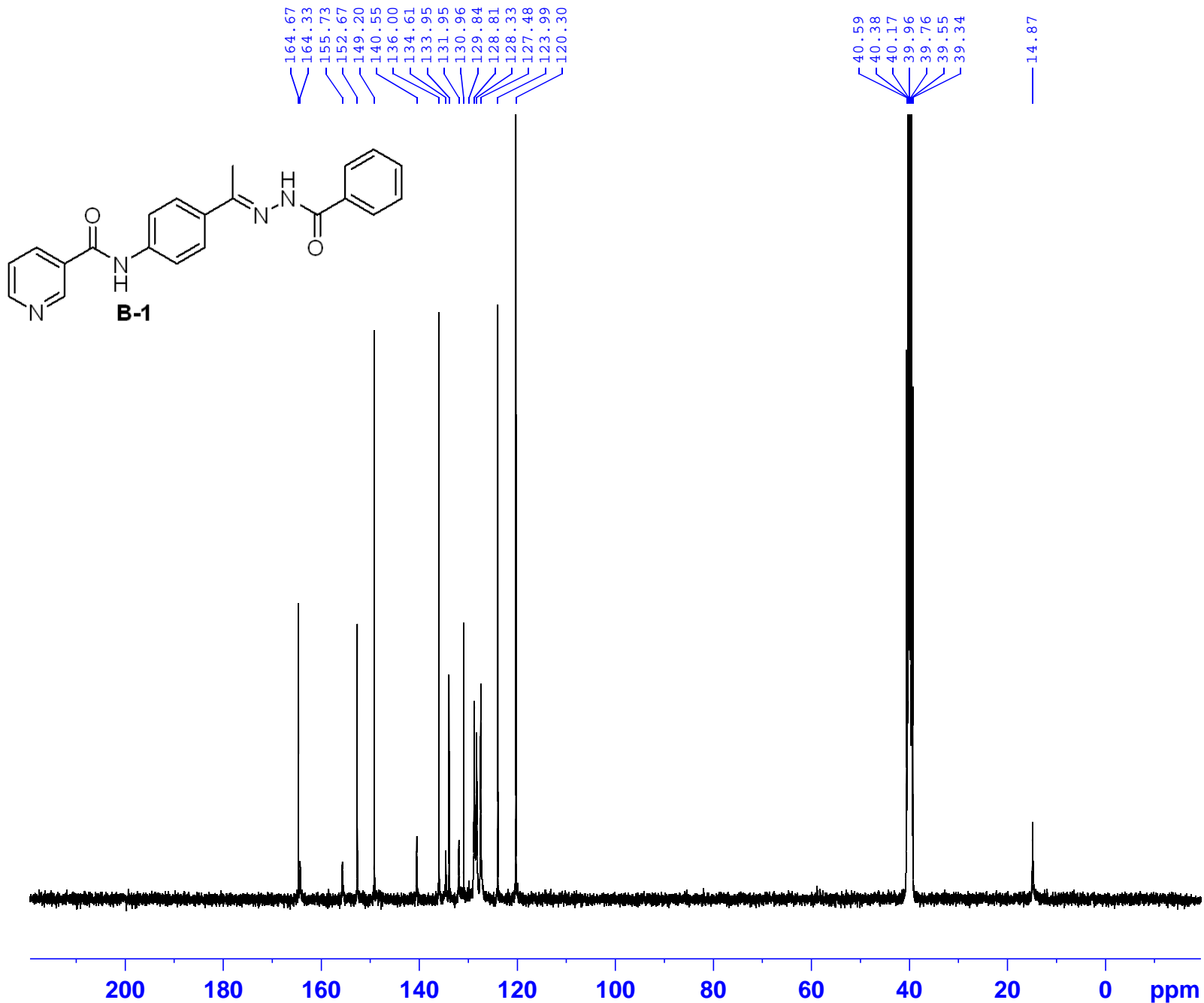
Pharmacognosy and Medicinal Plants Department, Faculty of Pharmacy (Boys), Al-Azhar University, Cairo 11884, Egypt. **Email:** [ametwaly@azhar.edu.eg](mailto:ametwaly@azhar.edu.eg)



A-1



Wagdy eldehna -RB4-carbon-Es

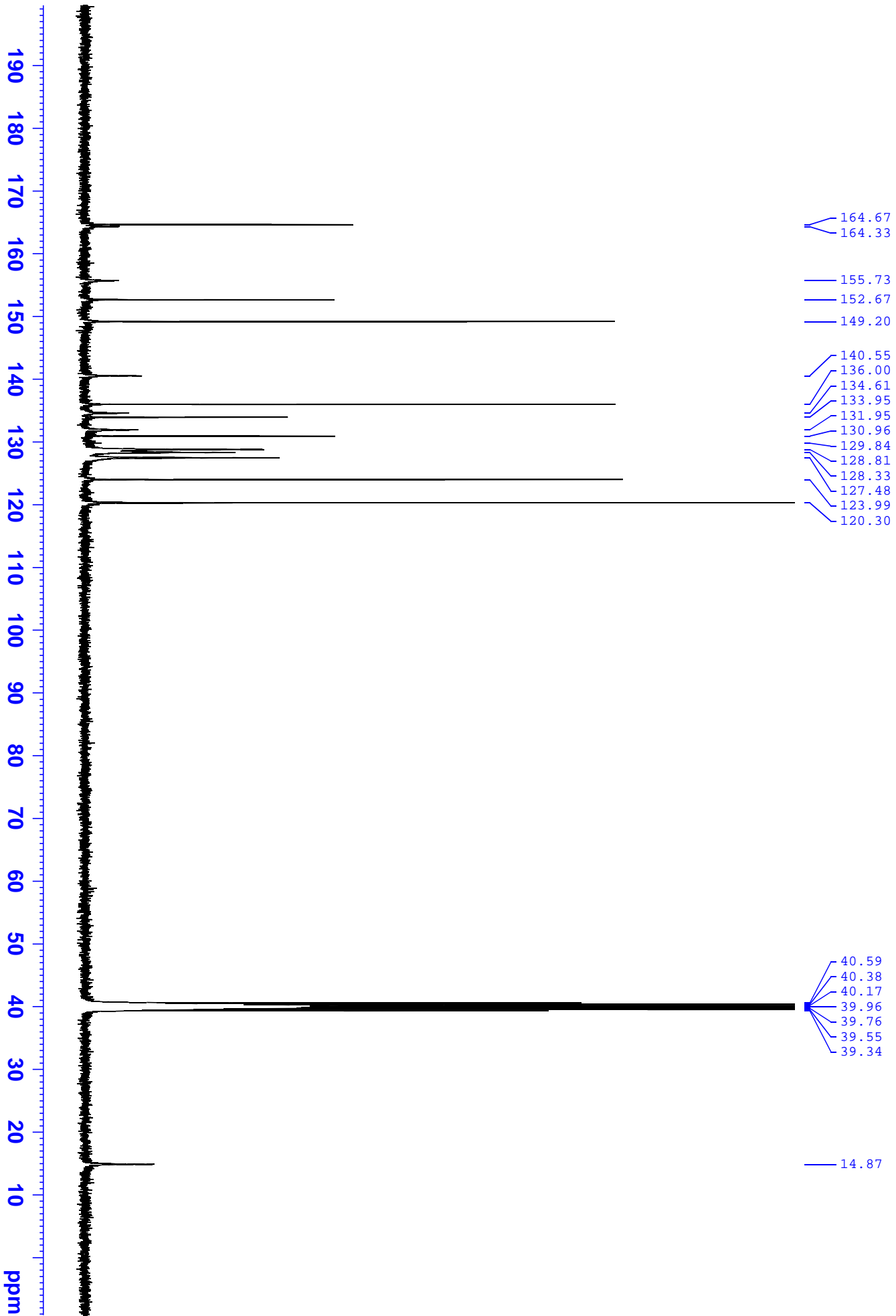


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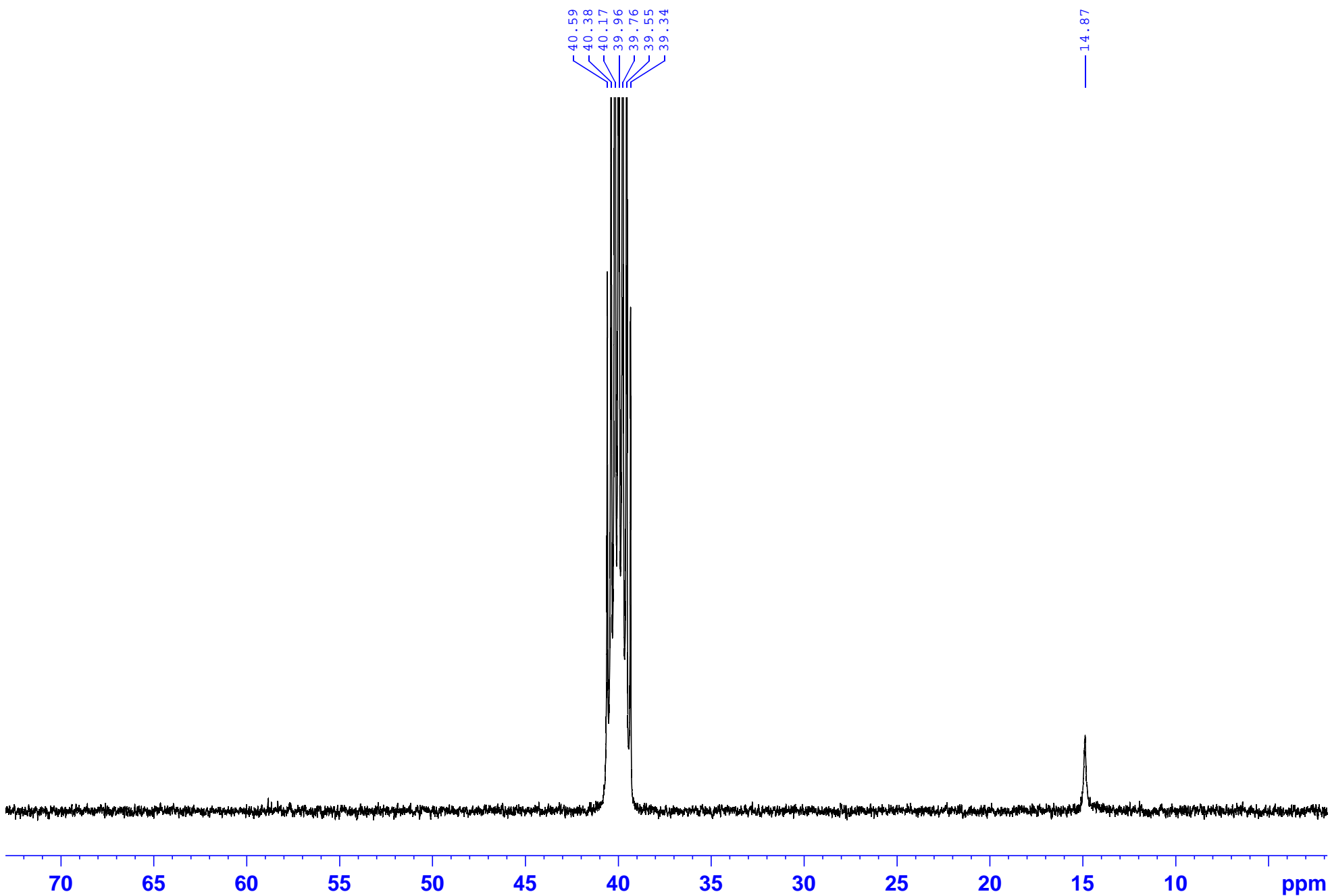
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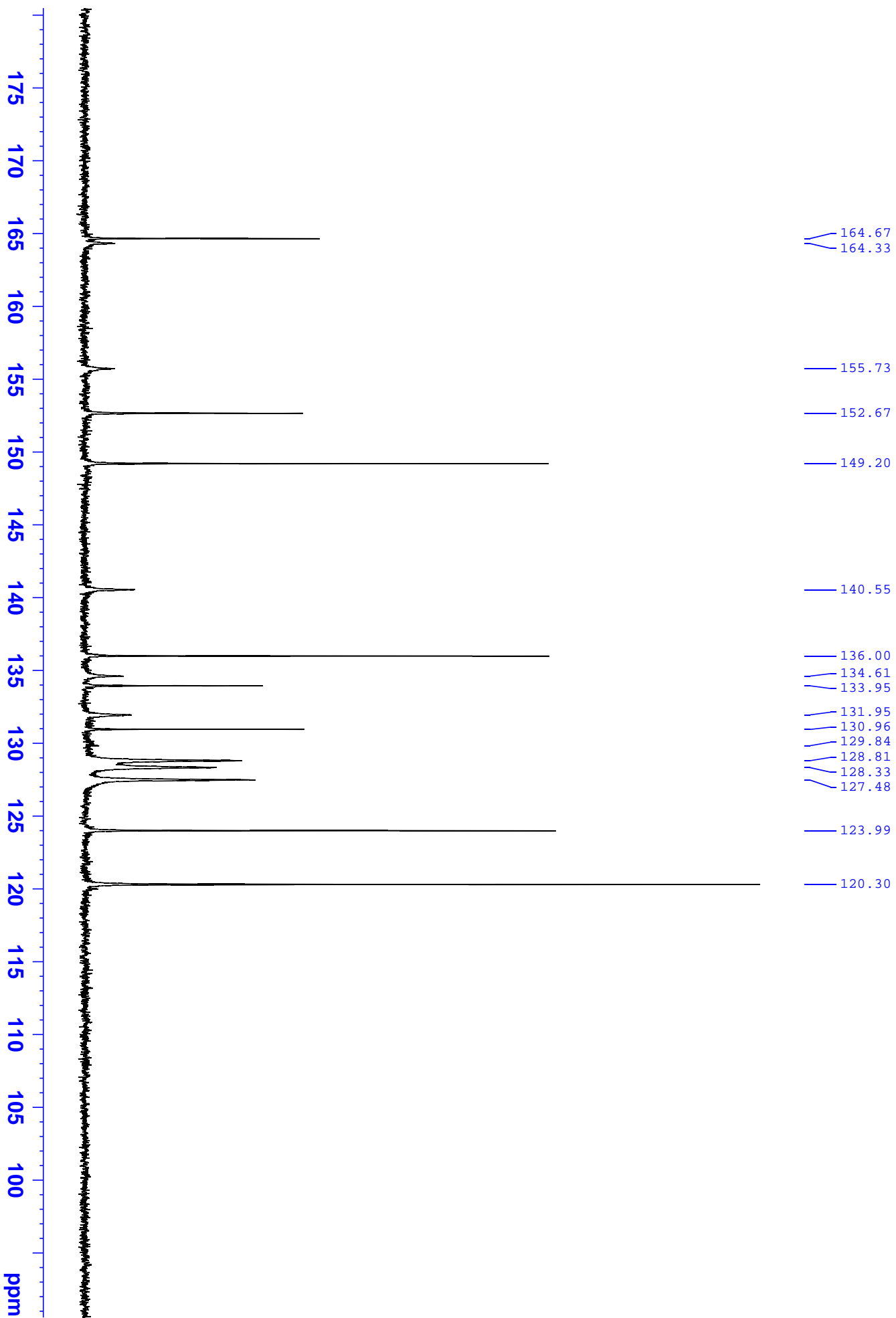
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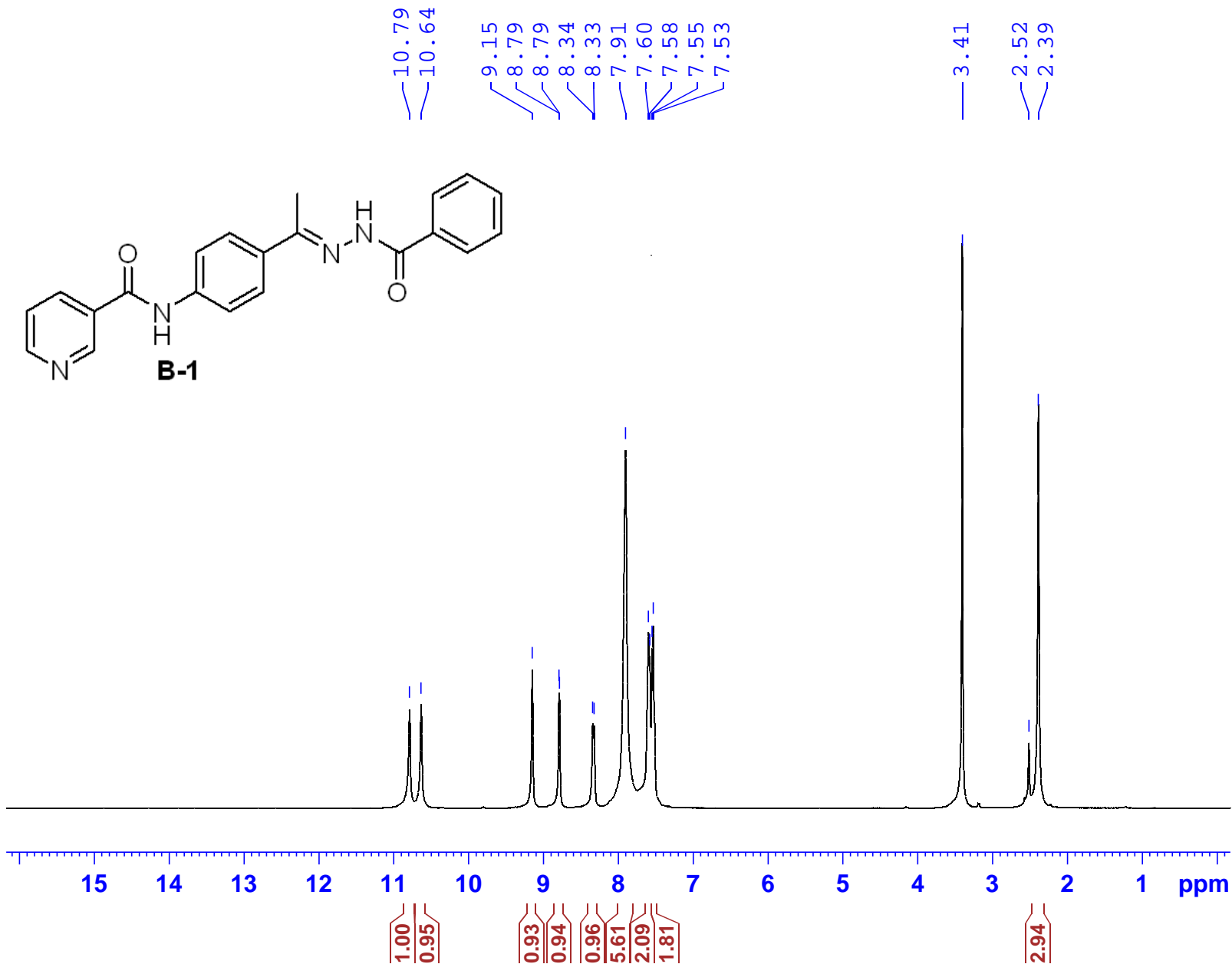
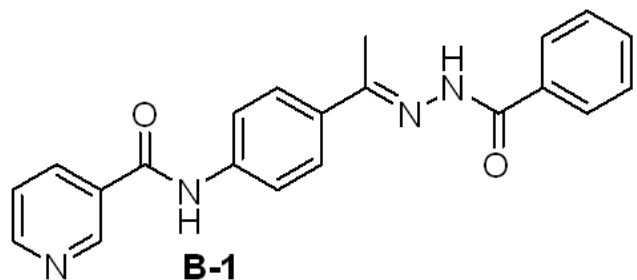
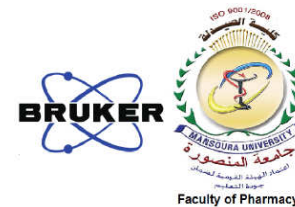
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Wagdy eldehna -RB4-carbon-Es



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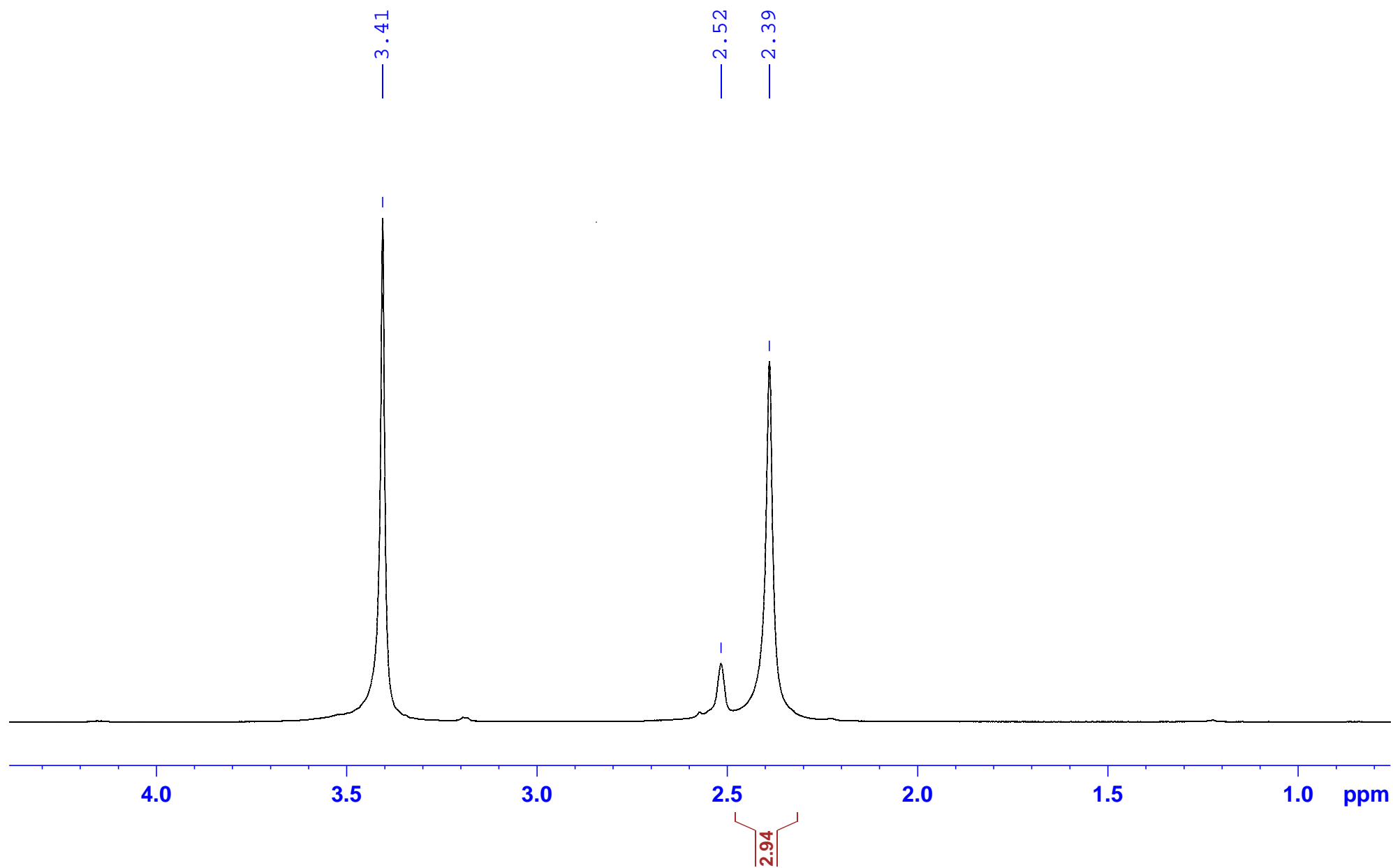


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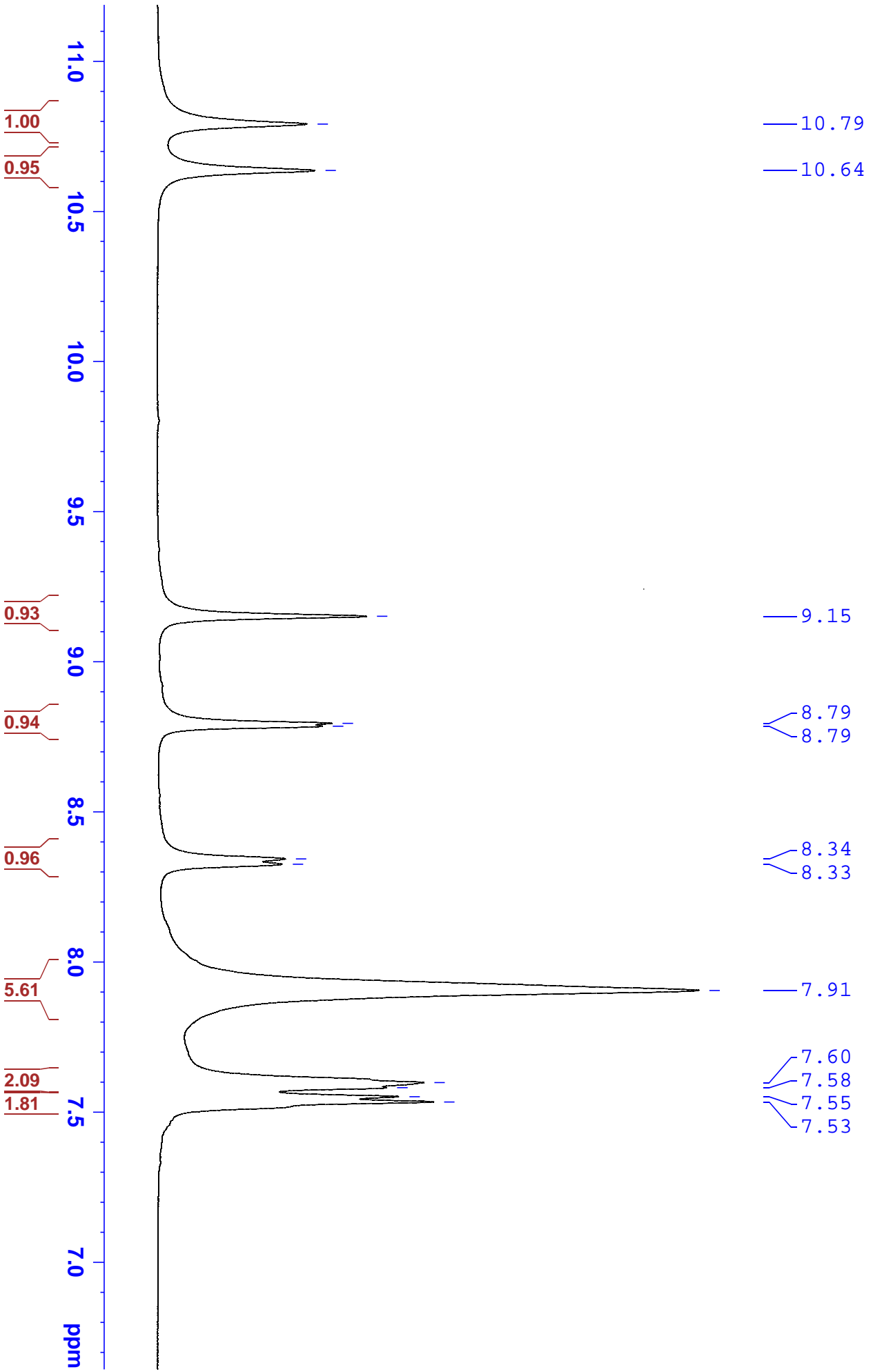
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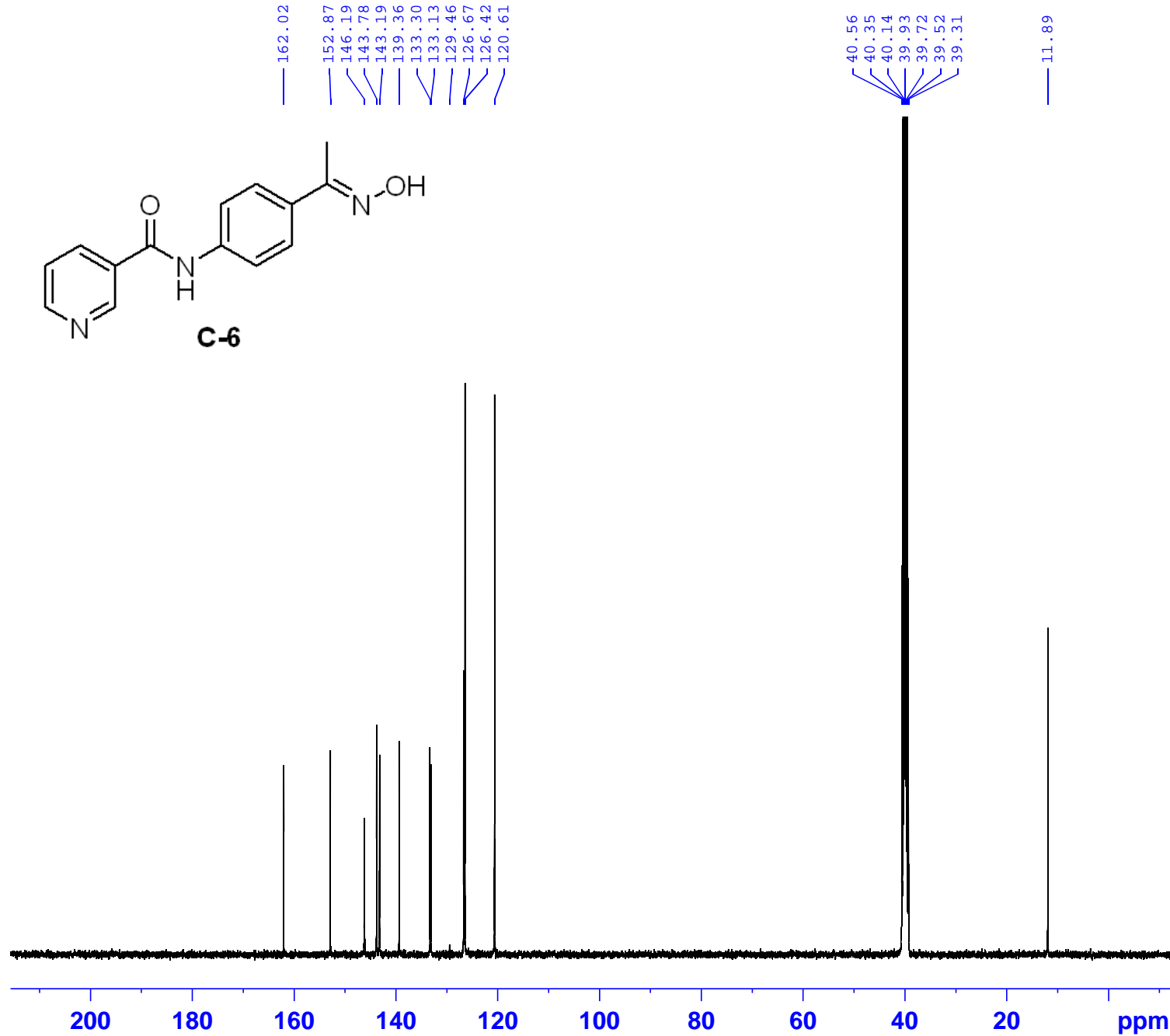
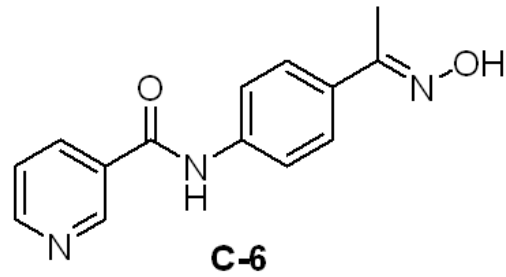
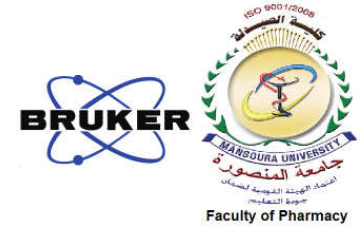
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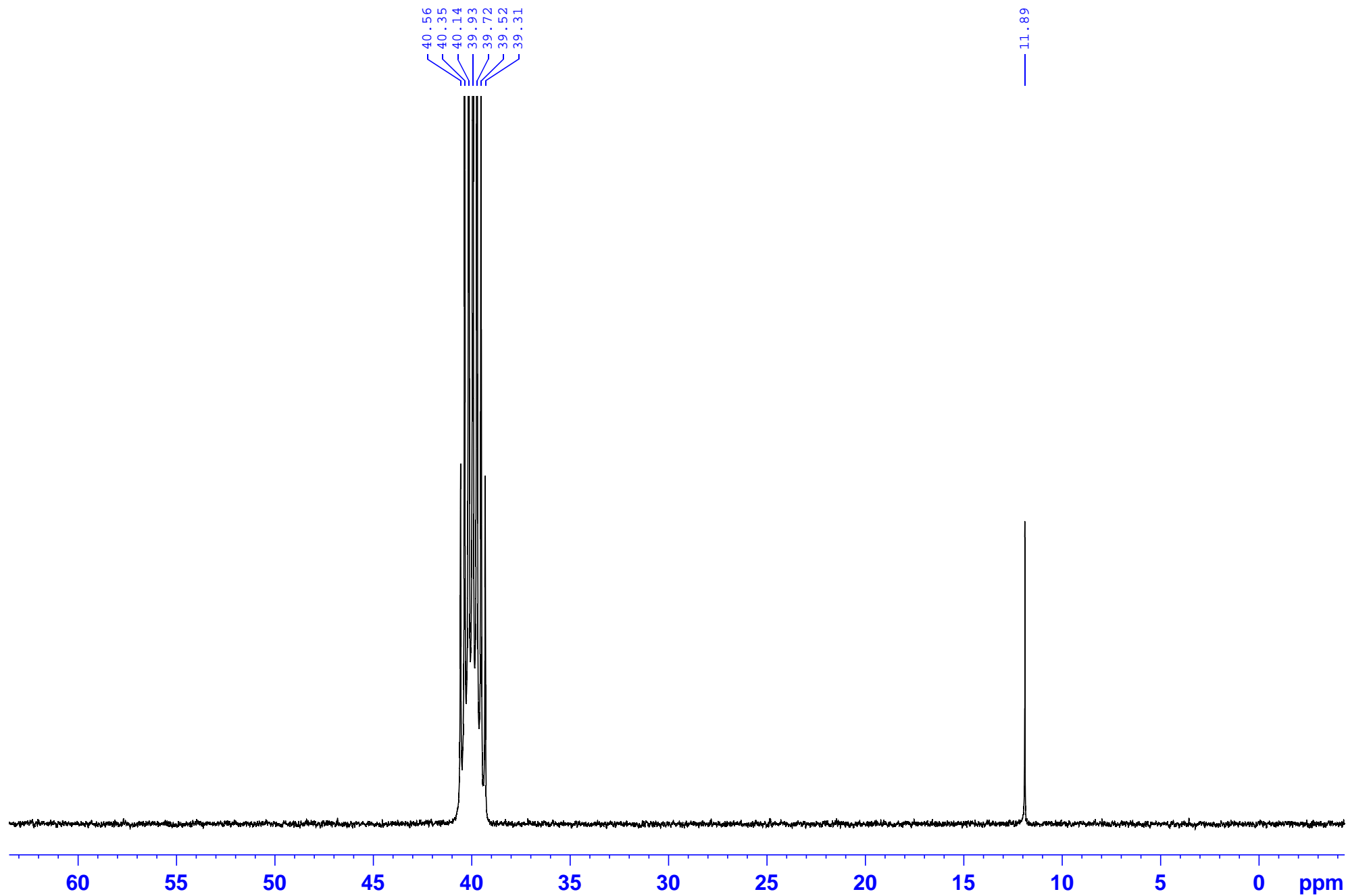


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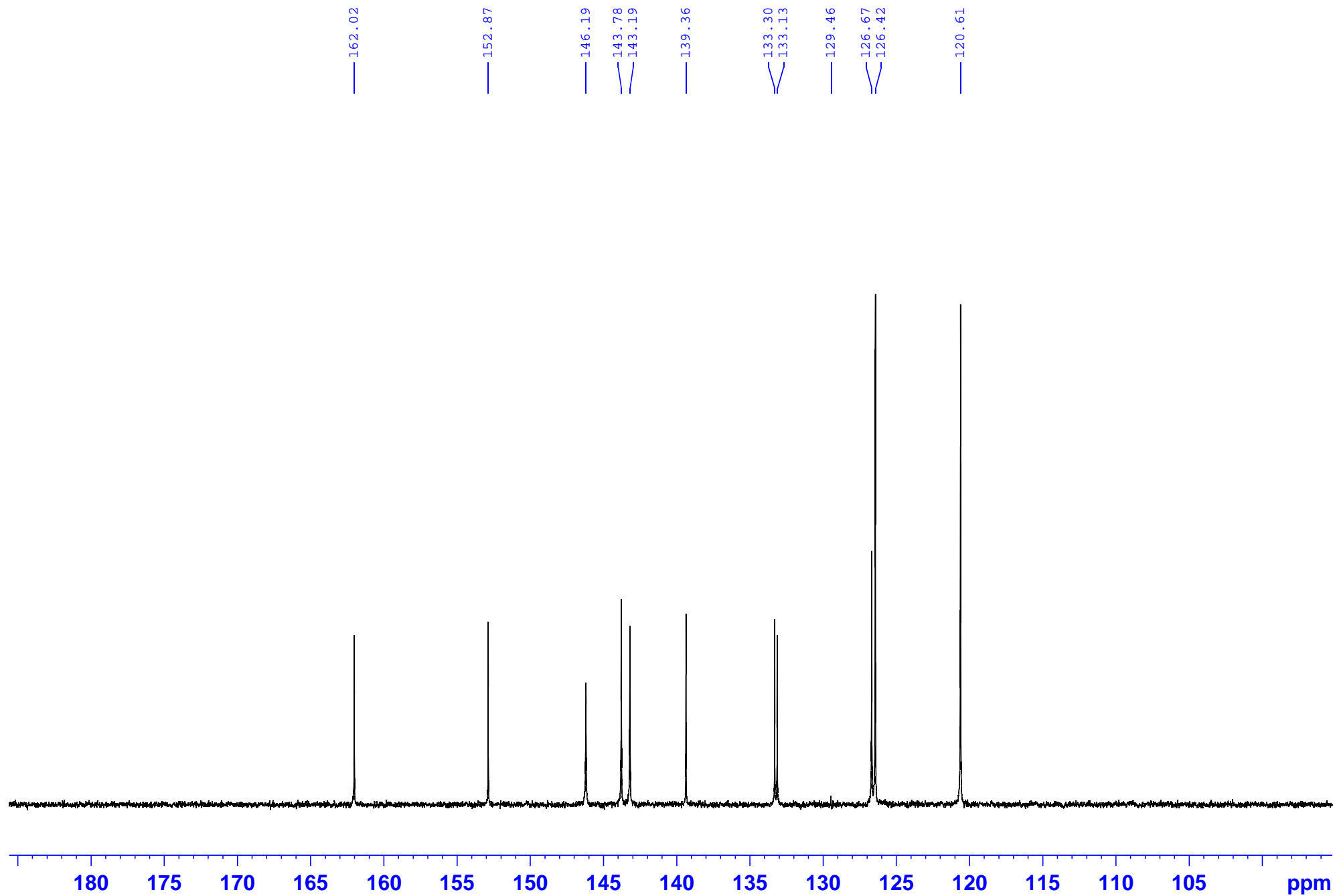
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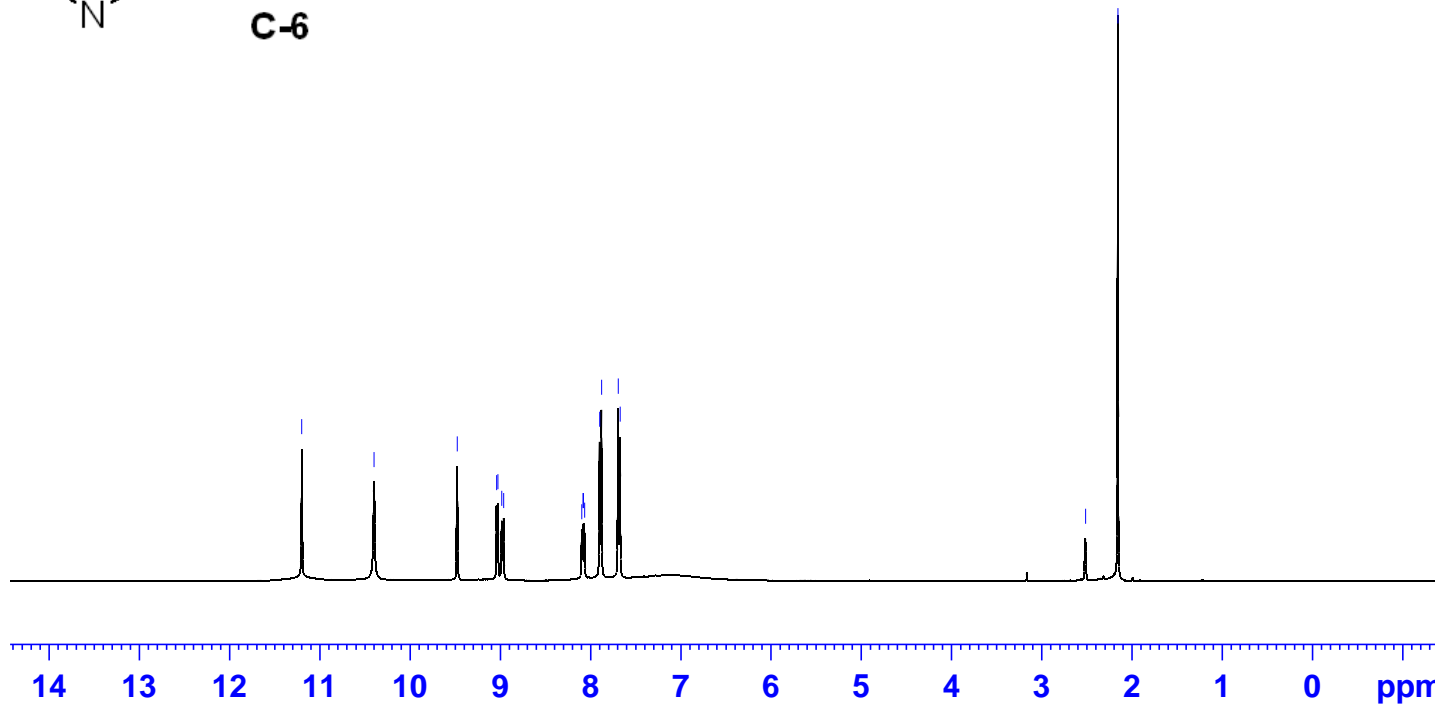
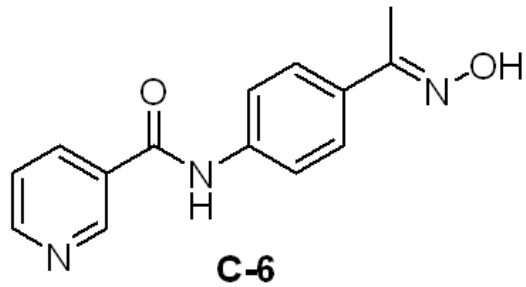
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Wagdy El Dahna-RB 5-DMSO-Hnmr-A

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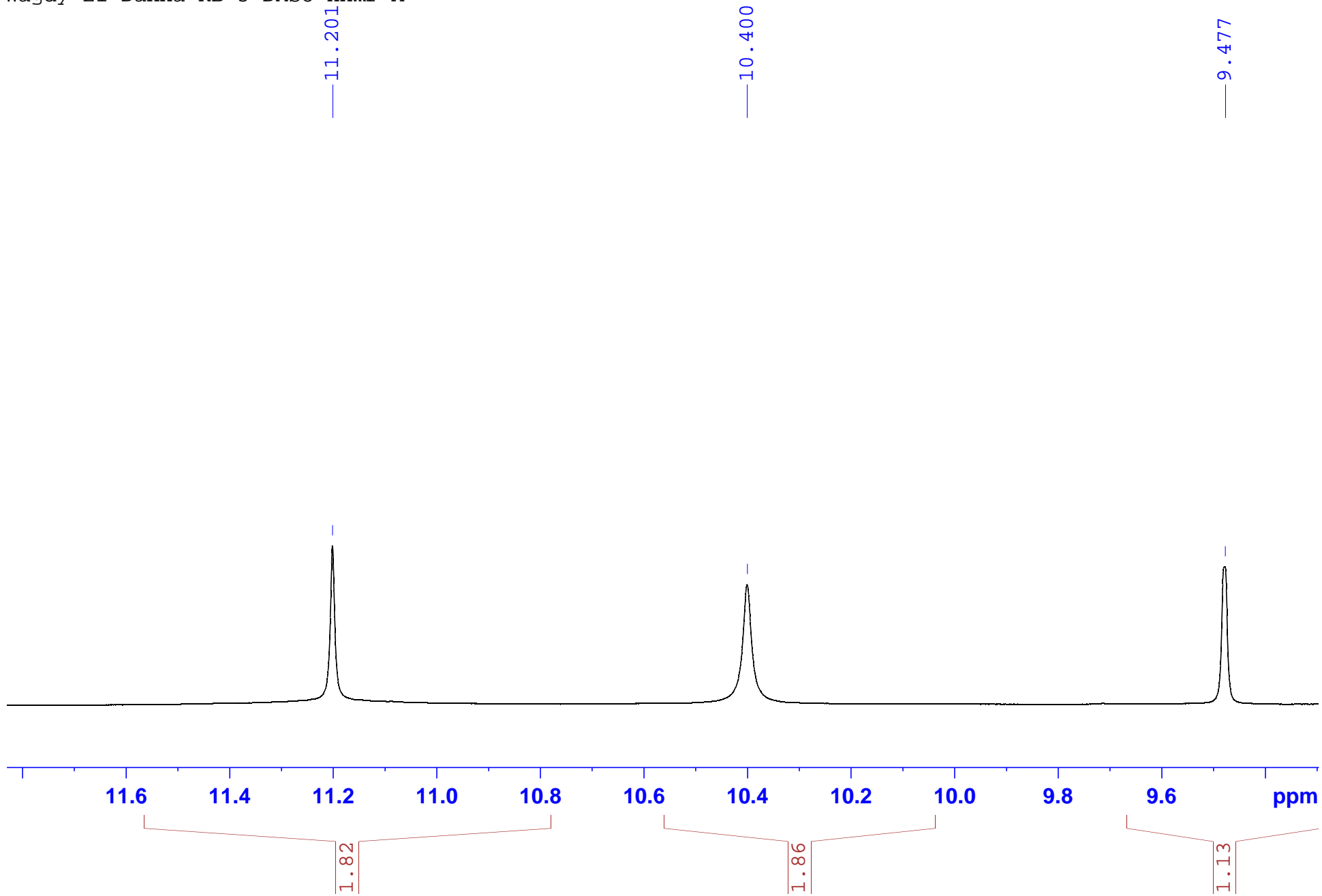


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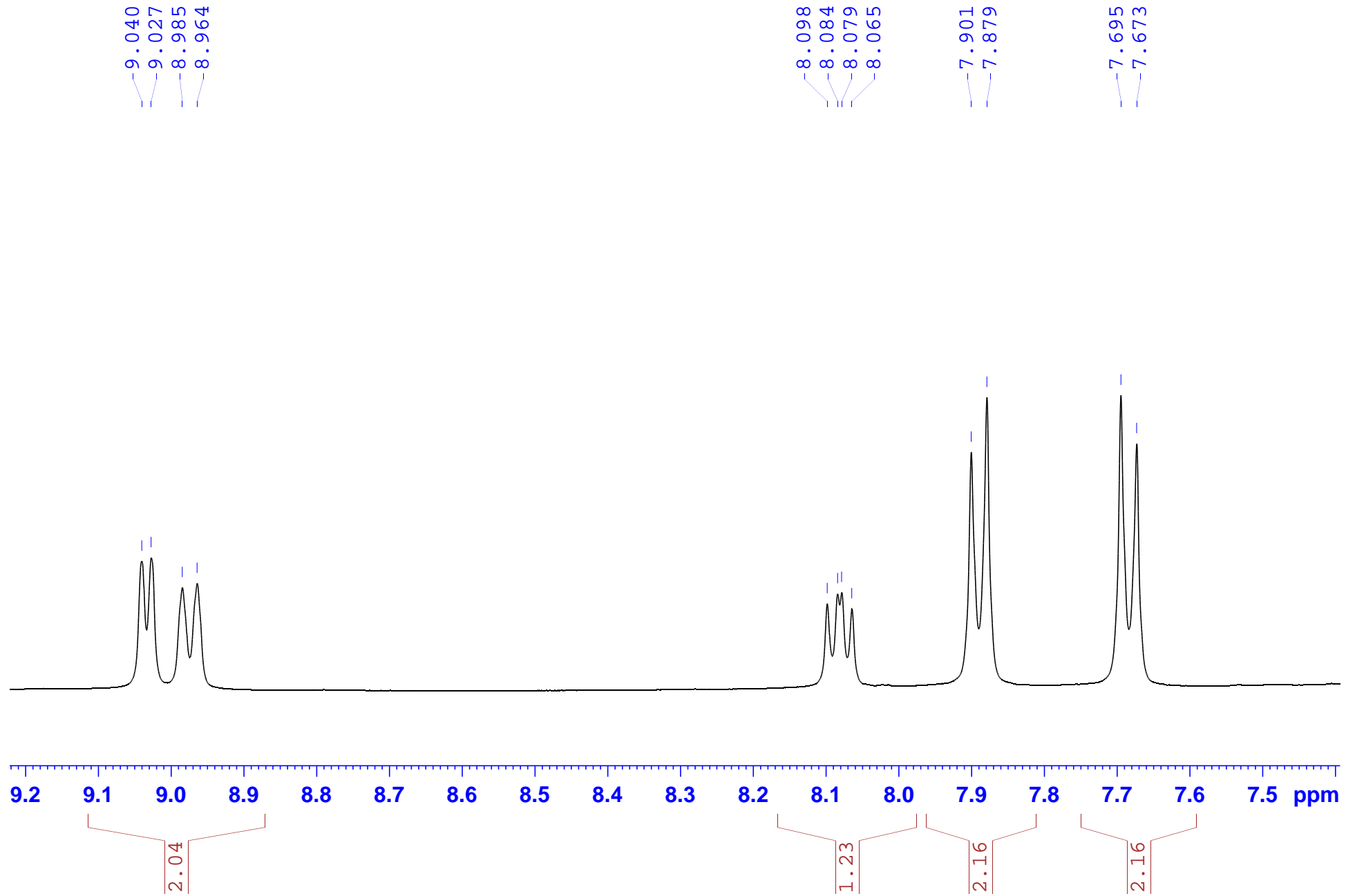
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Wagdy El Dahna-RB 5-DMSO-Hnmr-A



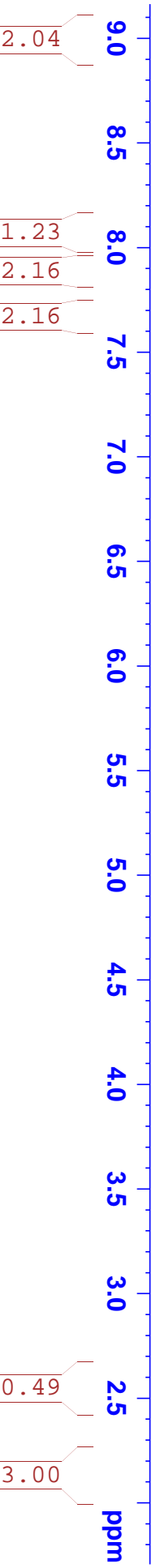
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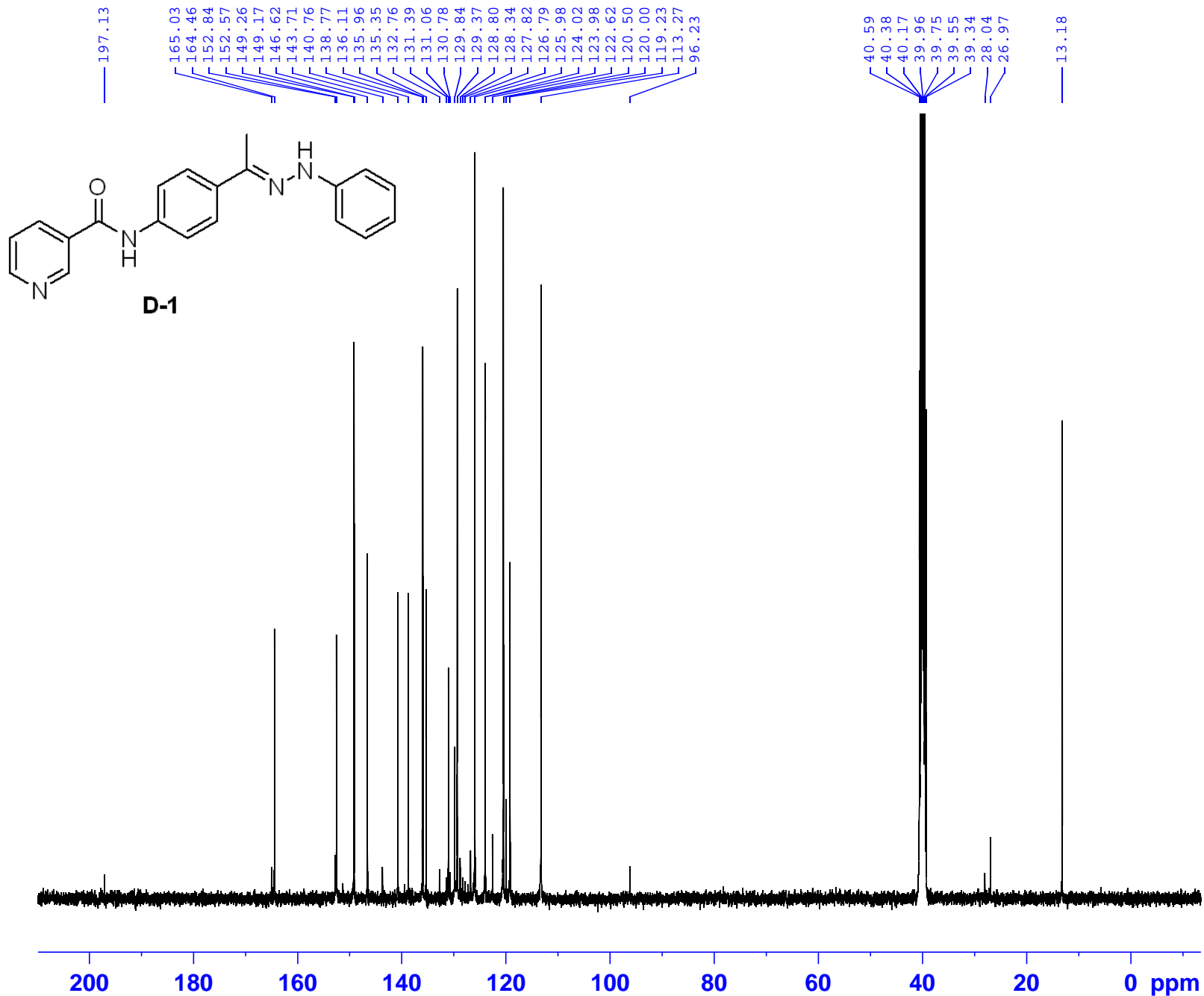
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2.515  
2.156





Wagdy eldehna -RB8-carbon-Es

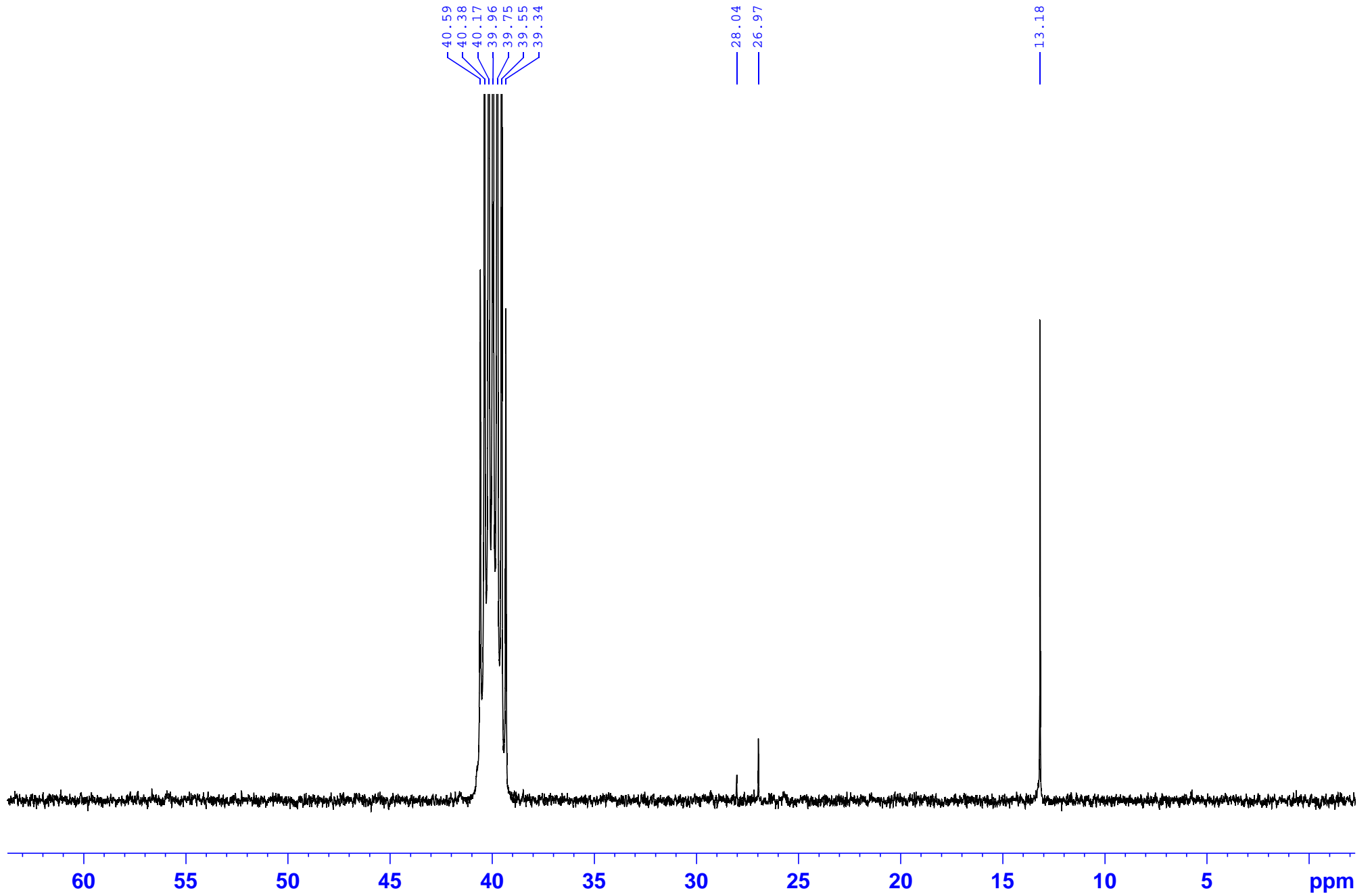


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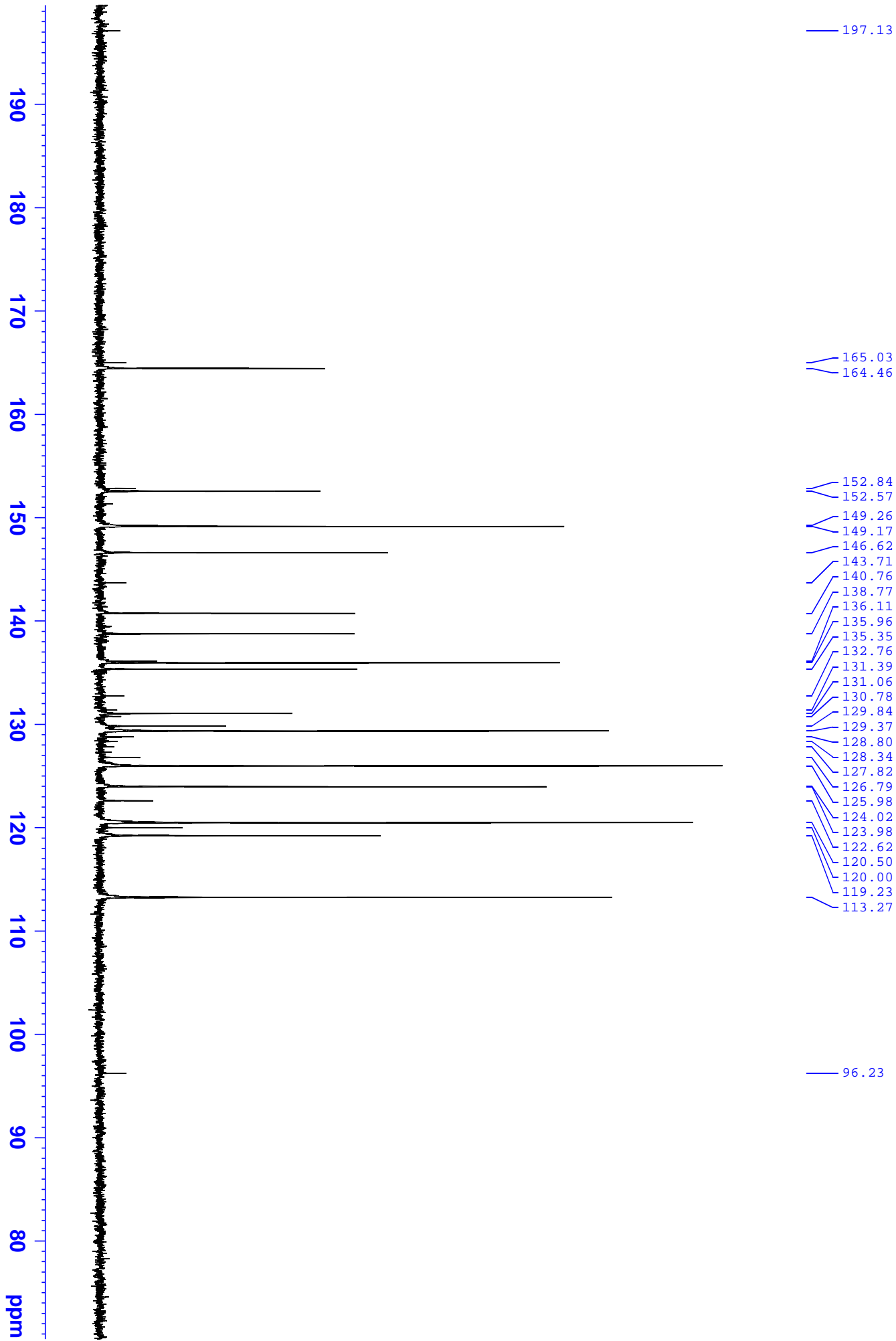
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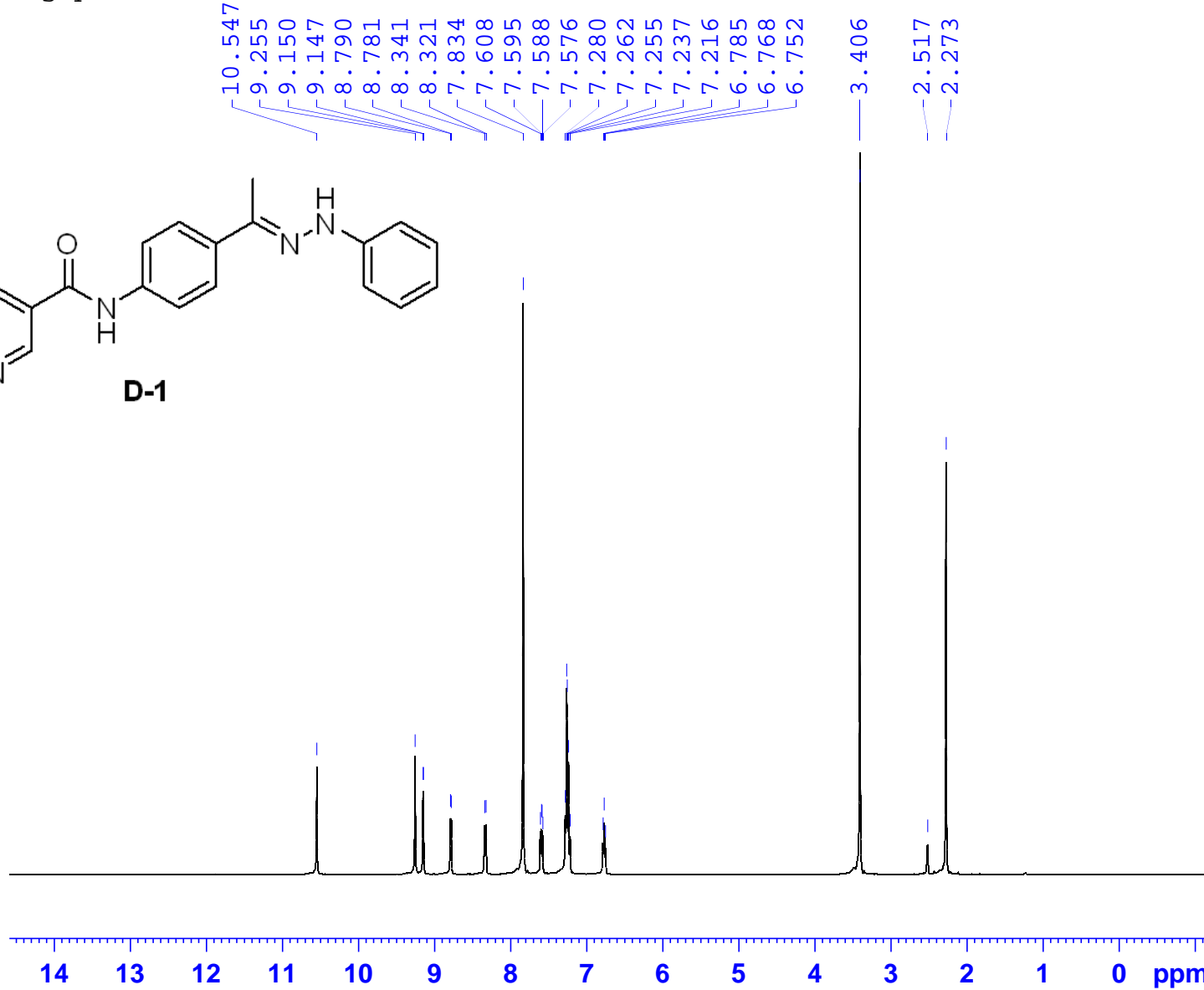
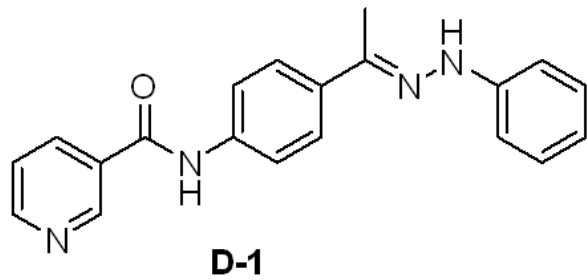
Wagdy eldehna -RB8-carbon-Es



Wagdy eldehna -RB8-carbon-Es



Wagdy El Dahna-RB 8-DMSO-Hnmr-A

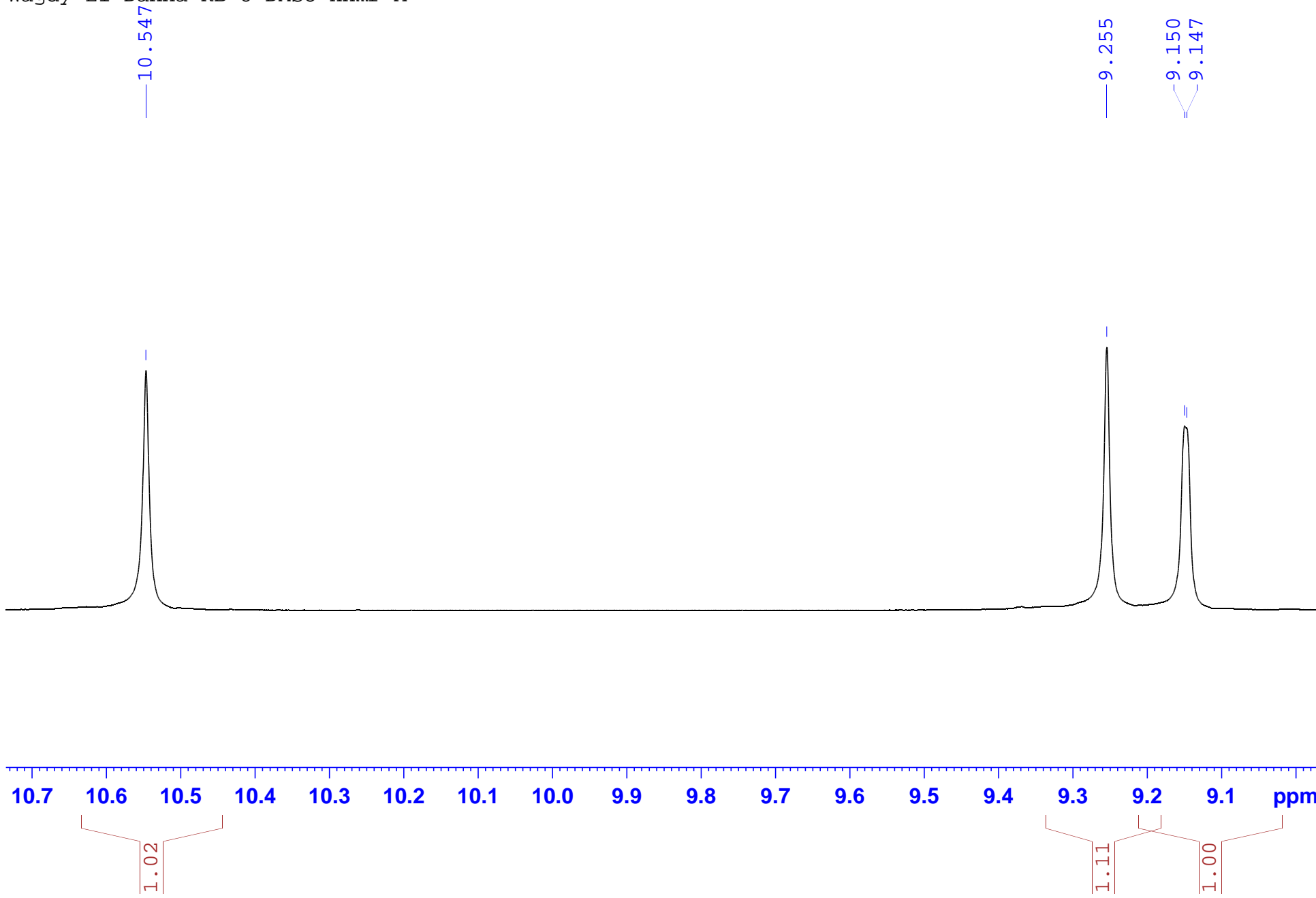


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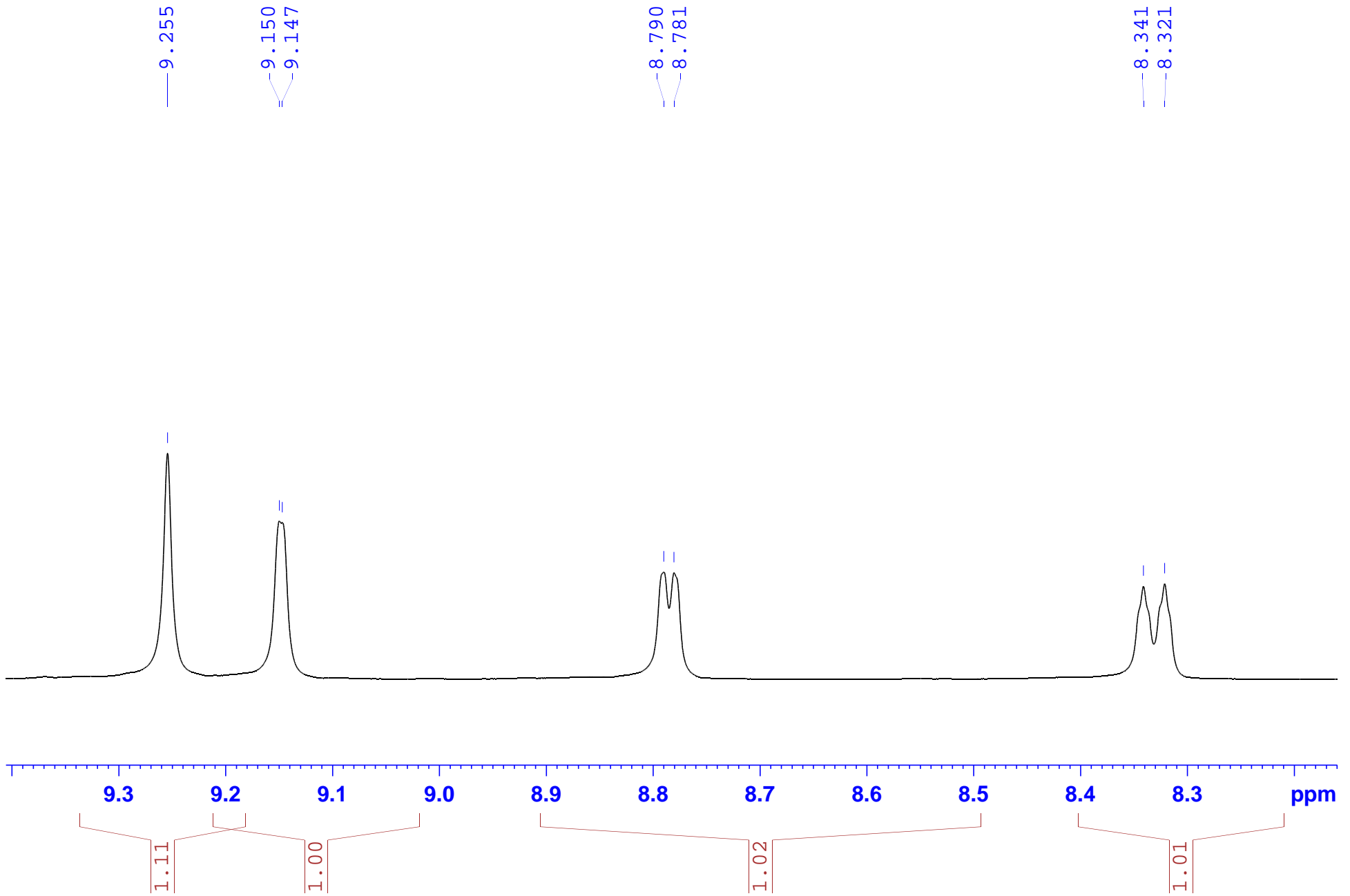
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FIDRES 0.244532 Hz  
AQ 4.0894465 sec  
RG 99.3  
DW 62.400 usec  
DE 6.50 usec  
TE 294.4 K  
D1 1.00000000 sec  
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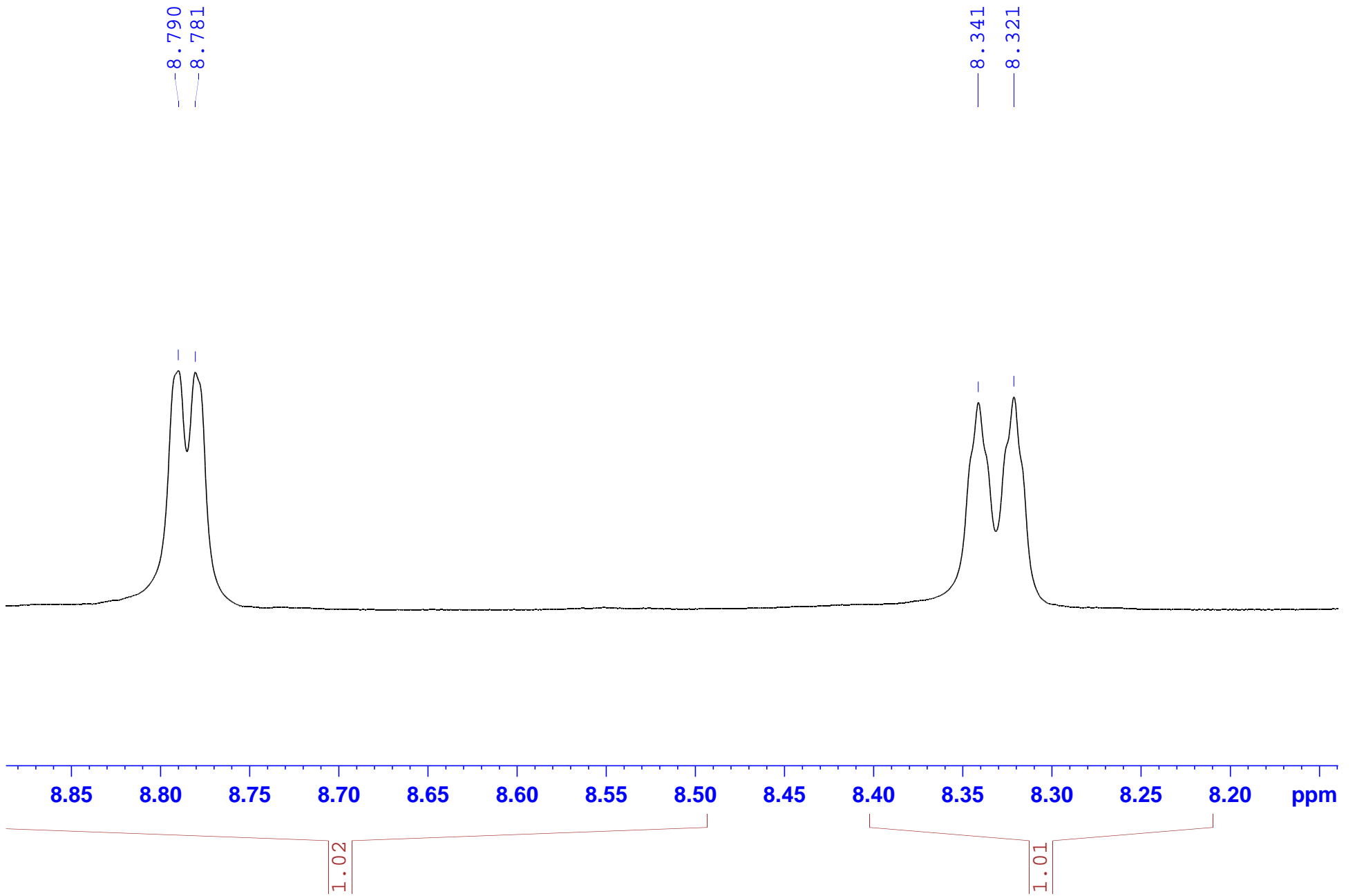
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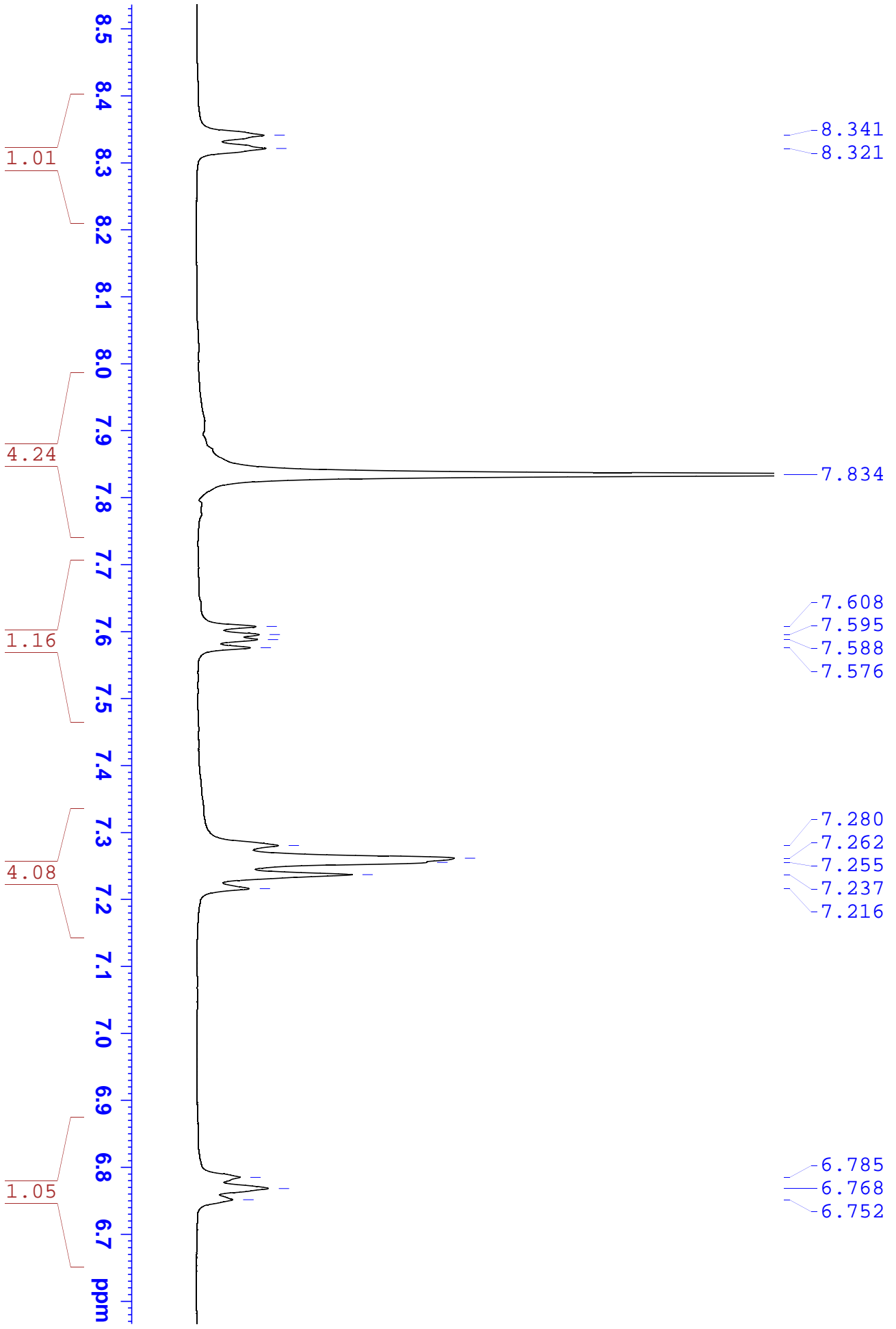
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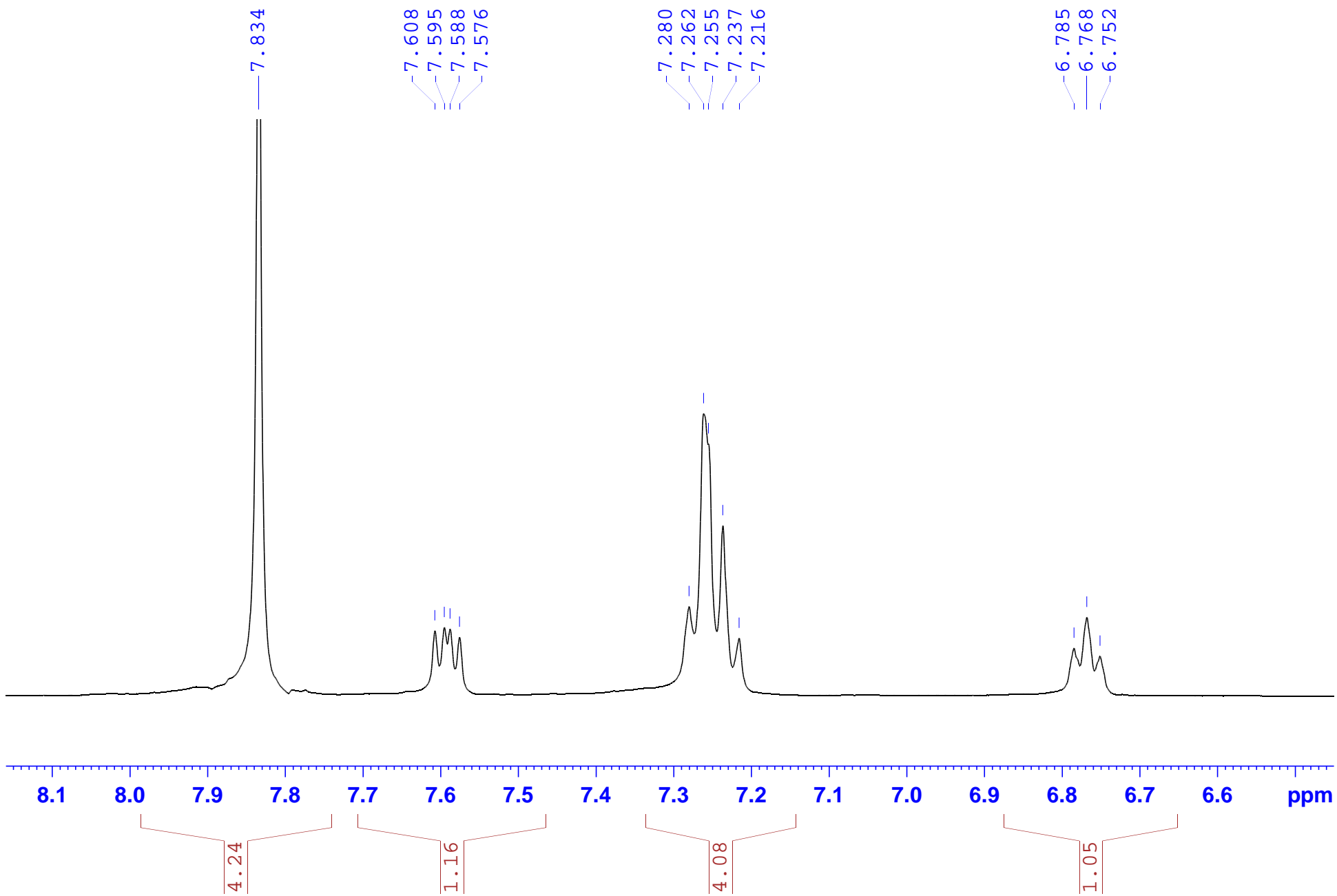


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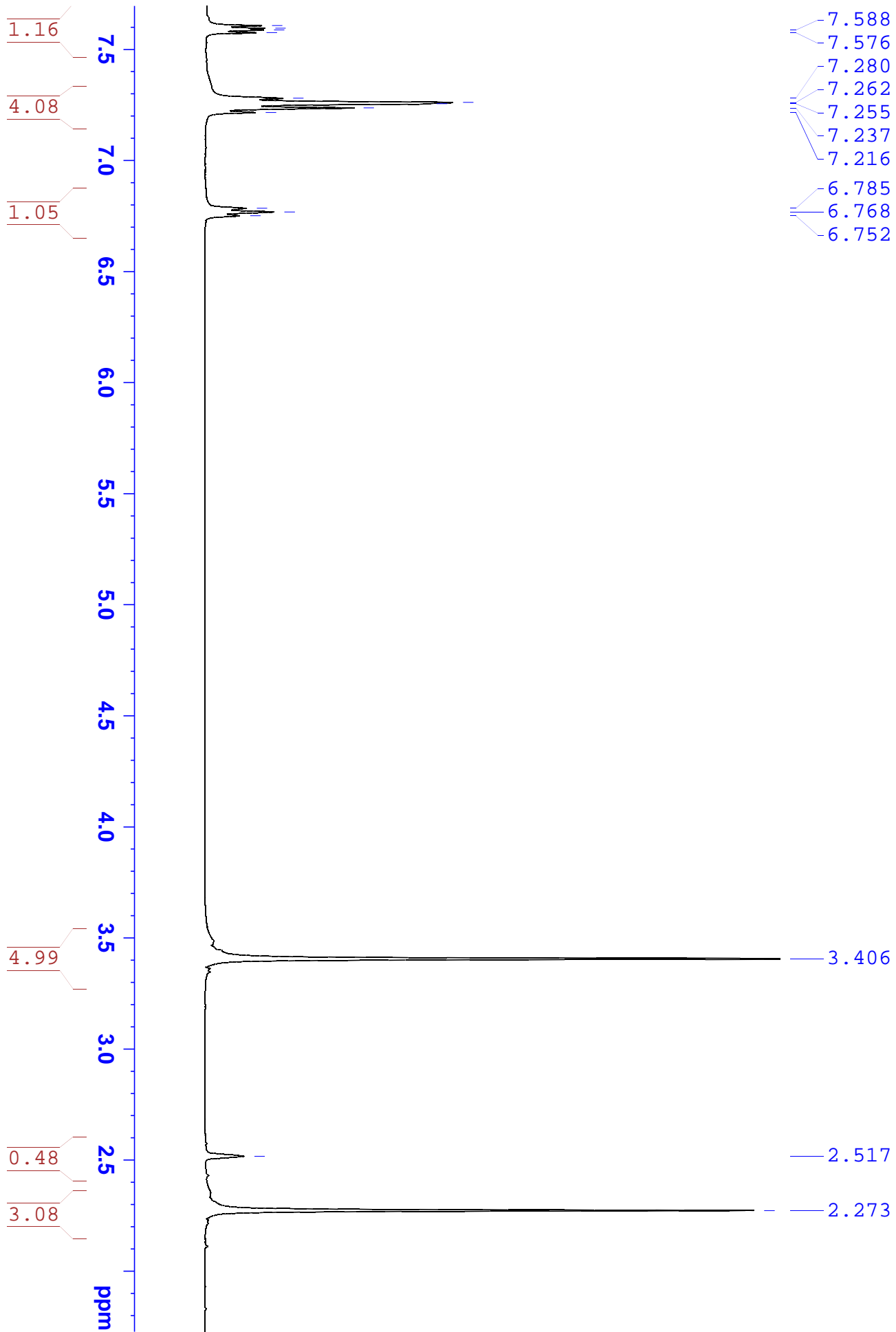


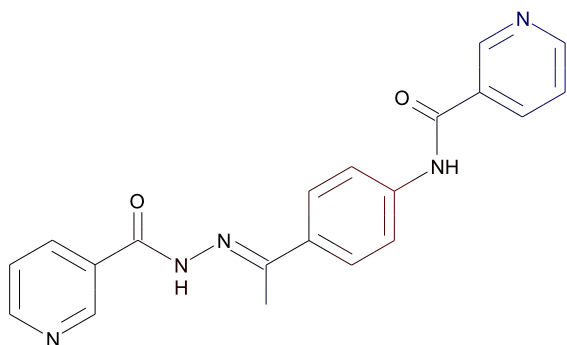


Wagdy El Dahna-RB 8-DMSO-Hnmr-A



Wagdy El Dahna-RB 8-DMSO-Hnmr-A





$C_{20}H_{17}N_5O_2$

Molecular Weight: 359.38128

ALogP: 1.147

Rotatable Bonds: 5

Acceptors: 5

Donors: 2

## Model Prediction

Prediction: Non-Mutagen

Probability: 0.716

Enrichment: 1.28

Bayesian Score: -1.11

Mahalanobis Distance: 7.98

Mahalanobis Distance p-value: 0.993

Prediction: Positive if the Bayesian score is above the estimated best cutoff value from minimizing the false positive and false negative rate.

Probability: The estimated probability that the sample is in the positive category. This assumes that the Bayesian score follows a normal distribution and is different from the prediction using a cutoff.

Enrichment: An estimate of enrichment, that is, the increased likelihood (versus random) of this sample being in the category.

Bayesian Score: The standard Laplacian-modified Bayesian score.

Mahalanobis Distance: The Mahalanobis distance (MD) is the distance to the center of the training data. The larger the MD, the less trustworthy the prediction.

Mahalanobis Distance p-value: The p-value gives the fraction of training data with an MD greater than or equal to the one for the given sample, assuming normally distributed data. The smaller the p-value, the less trustworthy the prediction. For highly non-normal X properties (e.g., fingerprints), the MD p-value is wildly inaccurate.

## Structural Similar Compounds

Name	77-46-3	79455-30-4	PENICILLIN G POTASSIUM
Structure			
Actual Endpoint	Non-Mutagen	Non-Mutagen	Non-Mutagen
Predicted Endpoint	Non-Mutagen	Non-Mutagen	Non-Mutagen
Distance	0.549	0.570	0.581
Reference	Kazius et. al., J. Med. Chem. (2005) 48, 312-320	Kazius et. al., J. Med. Chem. (2005) 48, 312-320	EMIC

## Model Applicability

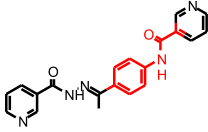
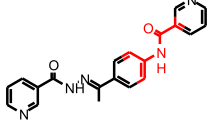
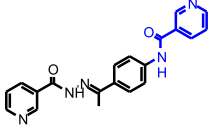
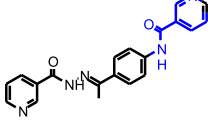
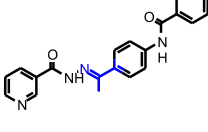
Unknown features are fingerprint features in the query molecule, but not found or appearing too infrequently in the training set.

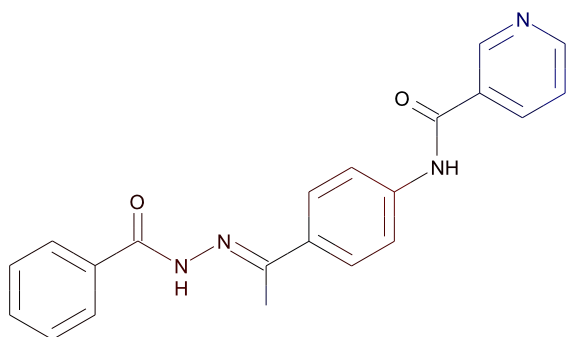
1. All properties and OPS components are within expected ranges.

## Feature Contribution

### Top features for positive contribution

Fingerprint	Bit/Smiles	Feature Structure	Score	Mutagen in training set
SCFP_12	555539852	 [*]:[cH]:[c](:[cH]:[*] )C(=O)N[c]1:[cH]:[c H]:[*]:[cH]:[cH]:1	0.447	22 out of 24

SCFP_12	818445224	 [*][c]1:[cH]:[cH]:[c] (NC(=O)[c](:[*]):[*] ):[cH]:[cH]:1	0.434	12 out of 13
SCFP_12	2096901122	 [*]:[cH]:[c](NC(=O)[c] ):[*]:[*]:[cH]:[*] ]	0.429	33 out of 37
<b>Top Features for negative contribution</b>				
<b>Fingerprint</b>	<b>Bit/Smiles</b>	<b>Feature Structure</b>	<b>Score</b>	<b>Mutagen in training set</b>
SCFP_12	1165971455	 [*]NC(=O)[c]1:[cH]:[c H]:[cH]:n:[cH]:1	-0.762	0 out of 2
SCFP_12	903335088	 [*]NC(=O)[c]1:[cH]:[c H]:[*]:n:[cH]:1	-0.762	0 out of 2
SCFP_12	-331724199	 [*]N=C(/C)[c](:[*] ):[*]	-0.762	0 out of 2



$C_{21}H_{18}N_4O_2$   
 Molecular Weight: 358.39322  
 ALogP: 2.297  
 Rotatable Bonds: 5  
 Acceptors: 4  
 Donors: 2

### Model Prediction

Prediction: Non-Mutagen

Probability: 0.724

Enrichment: 1.3

Bayesian Score: -0.747

Mahalanobis Distance: 7.86

Mahalanobis Distance p-value: 0.996

Prediction: Positive if the Bayesian score is above the estimated best cutoff value from minimizing the false positive and false negative rate.

Probability: The estimated probability that the sample is in the positive category. This assumes that the Bayesian score follows a normal distribution and is different from the prediction using a cutoff.

Enrichment: An estimate of enrichment, that is, the increased likelihood (versus random) of this sample being in the category.  
 Bayesian Score: The standard Laplacian-modified Bayesian score.

Mahalanobis Distance: The Mahalanobis distance (MD) is the distance to the center of the training data. The larger the MD, the less trustworthy the prediction.

Mahalanobis Distance p-value: The p-value gives the fraction of training data with an MD greater than or equal to the one for the given sample, assuming normally distributed data. The smaller the p-value, the less trustworthy the prediction. For highly non-normal X properties (e.g., fingerprints), the MD p-value is wildly inaccurate.

### Structural Similar Compounds

Name	34433-31-3	89459-43-8	89784-39-4
Structure			
Actual Endpoint	Non-Mutagen	Mutagen	Mutagen
Predicted Endpoint	Non-Mutagen	Mutagen	Mutagen
Distance	0.499	0.548	0.562
Reference	Kazius et. al., J. Med. Chem. (2005) 48, 312-320	Kazius et. al., J. Med. Chem. (2005) 48, 312-320	Kazius et. al., J. Med. Chem. (2005) 48, 312-320

### Model Applicability

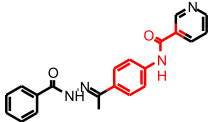
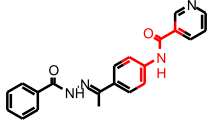
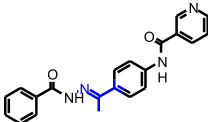
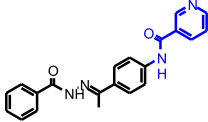
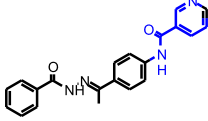
Unknown features are fingerprint features in the query molecule, but not found or appearing too infrequently in the training set.

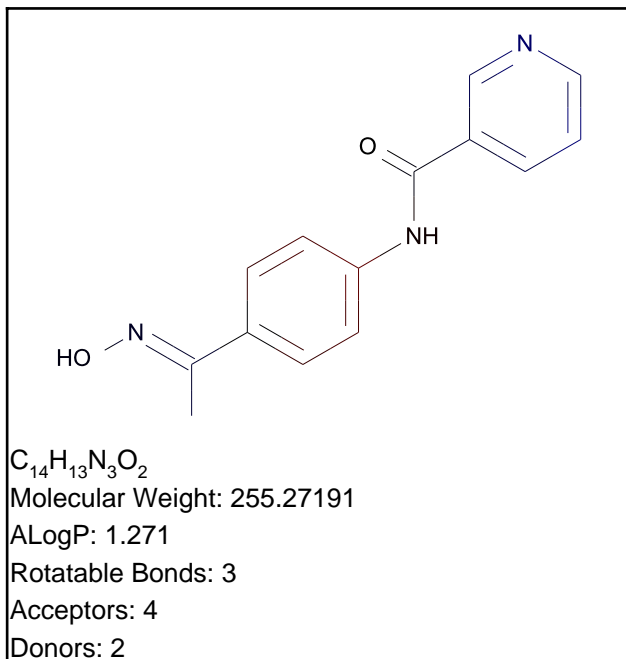
- All properties and OPS components are within expected ranges.

### Feature Contribution

#### Top features for positive contribution

Fingerprint	Bit/Smiles	Feature Structure	Score	Mutagen in training set
SCFP_12	555539852	 <chem>[*]:[cH]:[c](:[cH]:[*])C(=O)N[c]1:[cH]:[cH]:[*]:[cH]:[cH]:1</chem>	0.447	22 out of 24

SCFP_12	818445224	 [*][c]1:[cH]:[cH]:[c] (NC(=O)[c](:[*]):[*] ):[cH]:[cH]:1	0.434	12 out of 13
SCFP_12	2096901122	 [*]:[cH]:[c](NC(=O)[c ](:[*]):[*]):[cH]:[* ]	0.429	33 out of 37
<b>Top Features for negative contribution</b>				
<b>Fingerprint</b>	<b>Bit/Smiles</b>	<b>Feature Structure</b>	<b>Score</b>	<b>Mutagen in training set</b>
SCFP_12	-331724199	 [*]N=C(/C)[c](:[*]) :[*]	-0.762	0 out of 2
SCFP_12	1165971455	 [*]NC(=O)[c]1:[cH]:[c H]:[cH]:n:[cH]:1	-0.762	0 out of 2
SCFP_12	903335088	 [*]NC(=O)[c]1:[cH]:[c H]:[*]:n:[cH]:1	-0.762	0 out of 2



### Model Prediction

Prediction: Non-Mutagen

Probability: 0.718

Enrichment: 1.29

Bayesian Score: -1.02

Mahalanobis Distance: 7.73

Mahalanobis Distance p-value: 0.998

Prediction: Positive if the Bayesian score is above the estimated best cutoff value from minimizing the false positive and false negative rate.

Probability: The estimated probability that the sample is in the positive category. This assumes that the Bayesian score follows a normal distribution and is different from the prediction using a cutoff.

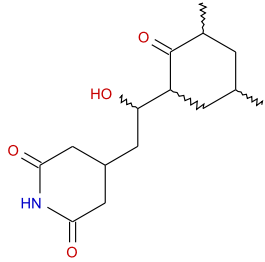
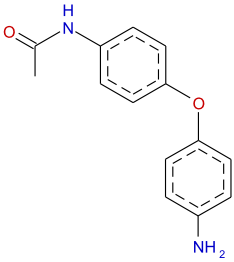
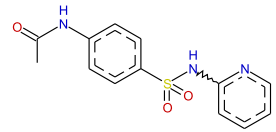
Enrichment: An estimate of enrichment, that is, the increased likelihood (versus random) of this sample being in the category.

Bayesian Score: The standard Laplacian-modified Bayesian score.

Mahalanobis Distance: The Mahalanobis distance (MD) is the distance to the center of the training data. The larger the MD, the less trustworthy the prediction.

Mahalanobis Distance p-value: The p-value gives the fraction of training data with an MD greater than or equal to the one for the given sample, assuming normally distributed data. The smaller the p-value, the less trustworthy the prediction. For highly non-normal X properties (e.g., fingerprints), the MD p-value is wildly inaccurate.

### Structural Similar Compounds

Name	Cycloheximide	2687-41-4	19077-98-6
Structure			
Actual Endpoint	Non-Mutagen	Mutagen	Non-Mutagen
Predicted Endpoint	Non-Mutagen	Mutagen	Non-Mutagen
Distance	0.518	0.518	0.526
Reference	Environ. Mol. Mut. 19(21):1992	Kazius et. al., J. Med. Chem. (2005) 48, 312-320	Kazius et. al., J. Med. Chem. (2005) 48, 312-320

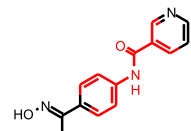
### Model Applicability

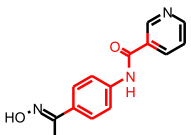
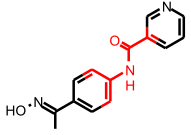
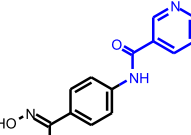
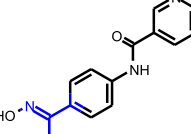
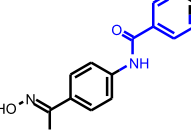
Unknown features are fingerprint features in the query molecule, but not found or appearing too infrequently in the training set.

1. All properties and OPS components are within expected ranges.

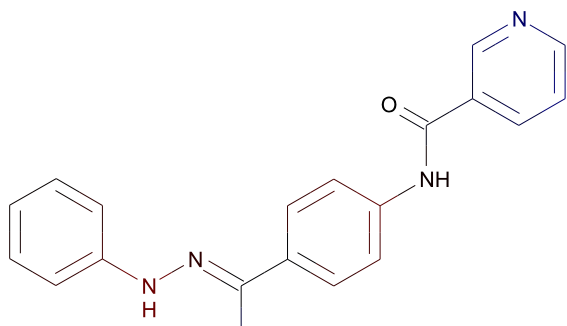
### Feature Contribution

#### Top features for positive contribution

Fingerprint	Bit/Smiles	Feature Structure	Score	Mutagen in training set
SCFP_12	555539852	 <chem>[*]:[cH]:[c](:[cH]:[*])C(=O)N[c]1:[cH]:[cH]:[*]:[cH]:[cH]:1</chem>	0.447	22 out of 24

SCFP_12	818445224	 <chem>[*][c]1:[cH]:[cH]:[c](NC(=O)[c](:[*]):[*])[cH]:[cH]:1</chem>	0.434	12 out of 13
SCFP_12	2096901122	 <chem>[*]:[cH]:[c](NC(=O)[c](:[*]):[*])[cH]:[*]</chem>	0.429	33 out of 37
<b>Top Features for negative contribution</b>				
<b>Fingerprint</b>	<b>Bit/Smiles</b>	<b>Feature Structure</b>	<b>Score</b>	<b>Mutagen in training set</b>
SCFP_12	1165971455	 <chem>[*]NC(=O)[c]1:[cH]:[cH]:[cH]:[cH]:n:[cH]:1</chem>	-0.762	0 out of 2
SCFP_12	-331724199	 <chem>[*]N=C(/C)[c](:[*]):[*]</chem>	-0.762	0 out of 2
SCFP_12	903335088	 <chem>[*]NC(=O)[c]1:[cH]:[cH]:[cH]:[cH]:n:[cH]:1</chem>	-0.762	0 out of 2





$C_{20}H_{18}N_4O$

Molecular Weight: 330.38312

ALogP: 3.063

Rotatable Bonds: 5

Acceptors: 4

Donors: 2

## Model Prediction

**Prediction: Mutagen**

Probability: 0.75

Enrichment: 1.34

Bayesian Score: 0.586

Mahalanobis Distance: 8.09

Mahalanobis Distance p-value: 0.989

Prediction: Positive if the Bayesian score is above the estimated best cutoff value from minimizing the false positive and false negative rate.

Probability: The estimated probability that the sample is in the positive category. This assumes that the Bayesian score follows a normal distribution and is different from the prediction using a cutoff.

Enrichment: An estimate of enrichment, that is, the increased likelihood (versus random) of this sample being in the category.

Bayesian Score: The standard Laplacian-modified Bayesian score.

Mahalanobis Distance: The Mahalanobis distance (MD) is the distance to the center of the training data. The larger the MD, the less trustworthy the prediction.

Mahalanobis Distance p-value: The p-value gives the fraction of training data with an MD greater than or equal to the one for the given sample, assuming normally distributed data. The smaller the p-value, the less trustworthy the prediction. For highly non-normal X properties (e.g., fingerprints), the MD p-value is wildly inaccurate.

## Structural Similar Compounds

Name	4394-00-7	Phenmedipham	112022-13-6
Structure			
Actual Endpoint	Non-Mutagen	Mutagen	Mutagen
Predicted Endpoint	Non-Mutagen	Mutagen	Mutagen
Distance	0.528	0.535	0.538
Reference	Kazius et. al., J. Med. Chem. (2005) 48, 312-320	Environ. Mol. Mut. 19(21):1992	Kazius et. al., J. Med. Chem. (2005) 48, 312-320

## Model Applicability

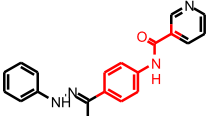
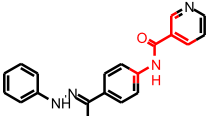
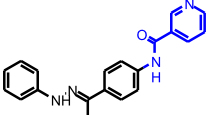
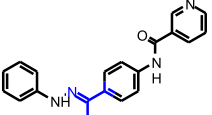
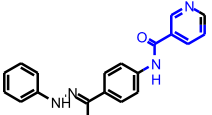
Unknown features are fingerprint features in the query molecule, but not found or appearing too infrequently in the training set.

1. All properties and OPS components are within expected ranges.

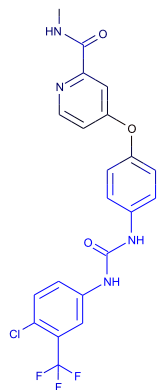
## Feature Contribution

### Top features for positive contribution

Fingerprint	Bit/Smiles	Feature Structure	Score	Mutagen in training set
SCFP_12	555539852	 [*]:[cH]:[c]:[cH]:[*] ])C(=O)N[c]1:[cH]:[cH]:[*]:[cH]:[cH]:1	0.447	22 out of 24

SCFP_12	818445224	 <chem>[*][c]1:[cH]:[cH]:[c](NC(=O)[c](:[*]):[*])[cH]:[cH]:1</chem>	0.434	12 out of 13
SCFP_12	124026986	 <chem>[*]:[cH]:[c](:[cH]:[*])C(=O)N[c](:[*]):[*]</chem>	0.429	33 out of 37
<b>Top Features for negative contribution</b>				
<b>Fingerprint</b>	<b>Bit/Smiles</b>	<b>Feature Structure</b>	<b>Score</b>	<b>Mutagen in training set</b>
SCFP_12	1165971455	 <chem>[*]NC(=O)[c]1:[cH]:[cH]:[cH]:[cH]:n:[cH]:1</chem>	-0.762	0 out of 2
SCFP_12	-331724199	 <chem>[*]N=C(/C)[c](:[*]):[*]</chem>	-0.762	0 out of 2
SCFP_12	903335088	 <chem>[*]NC(=O)[c]1:[cH]:[cH]:[cH]:[cH]:n:[cH]:1</chem>	-0.762	0 out of 2

# Sorafenib



$C_{21}H_{16}ClF_3N_4O_3$   
 Molecular Weight: 464.82494  
 ALogP: 4.175  
 Rotatable Bonds: 6  
 Acceptors: 4  
 Donors: 3

## Model Prediction

Prediction: Non-Mutagen

Probability: 0.0531

Enrichment: 0.0951

Bayesian Score: -19.7

Mahalanobis Distance: 13.1

Mahalanobis Distance p-value: 2.73e-006

Prediction: Positive if the Bayesian score is above the estimated best cutoff value from minimizing the false positive and false negative rate.

Probability: The estimated probability that the sample is in the positive category. This assumes that the Bayesian score follows a normal distribution and is different from the prediction using a cutoff.

Enrichment: An estimate of enrichment, that is, the increased likelihood (versus random) of this sample being in the category.

Bayesian Score: The standard Laplacian-modified Bayesian score.

Mahalanobis Distance: The Mahalanobis distance (MD) is the distance to the center of the training data. The larger the MD, the less trustworthy the prediction.

Mahalanobis Distance p-value: The p-value gives the fraction of training data with an MD greater than or equal to the one for the given sample, assuming normally distributed data. The smaller the p-value, the less trustworthy the prediction. For highly non-normal X properties (e.g., fingerprints), the MD p-value is wildly inaccurate.

# TOPKAT\_Ames\_Mutagenicity

## Structural Similar Compounds

Name	GLYBURIDE	38914-96-4	93957-54-1
Structure			
Actual Endpoint	Non-Mutagen	Mutagen	Non-Mutagen
Predicted Endpoint	Non-Mutagen	Mutagen	Non-Mutagen
Distance	0.590	0.592	0.600
Reference	PDR 1994	Kazius et. al., J. Med. Chem. (2005) 48, 312-320	US Environmental Protection Agency at <a href="http://www.epa.gov/NCCT/dsstox/sdf_isscan_external.html">http://www.epa.gov/NCCT/dsstox/sdf_isscan_external.html</a>

## Model Applicability

Unknown features are fingerprint features in the query molecule, but not found or appearing too infrequently in the training set.

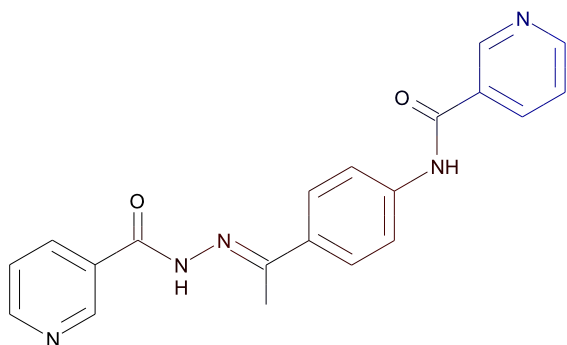
- All properties and OPS components are within expected ranges.

## Feature Contribution

### Top features for positive contribution

Fingerprint	Bit/Smiles	Feature Structure	Score	Mutagen in training set
SCFP_12	347281112	 <chem>[*]N[c]1:[cH]:[*]:[c]([*]):[c](:[cH]:1)C([*])([*])[*]</chem>	0.337	18 out of 22





$C_{20}H_{17}N_5O_2$

Molecular Weight: 359.38128

ALogP: 1.147

Rotatable Bonds: 5

Acceptors: 5

Donors: 2

## Model Prediction

Prediction: Non-Carcinogen

Probability: 0.242

Enrichment: 0.755

Bayesian Score: -1.2

Mahalanobis Distance: 11

Mahalanobis Distance p-value: 0.0949

Prediction: Positive if the Bayesian score is above the estimated best cutoff value from minimizing the false positive and false negative rate.

Probability: The estimated probability that the sample is in the positive category. This assumes that the Bayesian score follows a normal distribution and is different from the prediction using a cutoff.

Enrichment: An estimate of enrichment, that is, the increased likelihood (versus random) of this sample being in the category.

Bayesian Score: The standard Laplacian-modified Bayesian score.

Mahalanobis Distance: The Mahalanobis distance (MD) is the distance to the center of the training data. The larger the MD, the less trustworthy the prediction.

Mahalanobis Distance p-value: The p-value gives the fraction of training data with an MD greater than or equal to the one for the given sample, assuming normally distributed data. The smaller the p-value, the less trustworthy the prediction. For highly non-normal X properties (e.g., fingerprints), the MD p-value is wildly inaccurate.

## Structural Similar Compounds

Name	Acetohexamide	Alizapride	Penicillin
Structure			
Actual Endpoint	Non-Carcinogen	Carcinogen	Non-Carcinogen
Predicted Endpoint	Non-Carcinogen	Carcinogen	Non-Carcinogen
Distance	0.578	0.581	0.603
Reference	US FDA (Centre for Drug Eval.& Res./Off. Testing & Res.) Sept. 1997	US FDA (Centre for Drug Eval.& Res./Off. Testing & Res.) Sept. 1997	US FDA (Centre for Drug Eval.& Res./Off. Testing & Res.) Sept. 1997

## Model Applicability

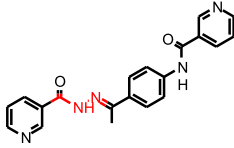
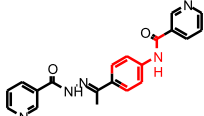
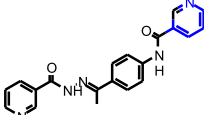
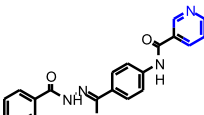
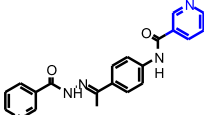
Unknown features are fingerprint features in the query molecule, but not found or appearing too infrequently in the training set.

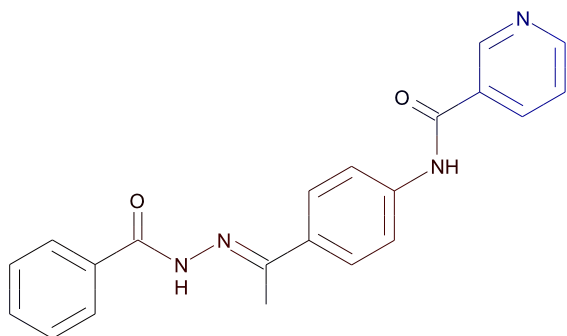
1. All properties and OPS components are within expected ranges.
2. Unknown ECFP\_2 feature: 128986386: [\*]N=C(/C)\[c](:[\*]):[\*]
3. Unknown ECFP\_2 feature: 560380707: [\*]NN=C([\*])[\*]

## Feature Contribution

### Top features for positive contribution

Fingerprint	Bit/Smiles	Feature Structure	Score	Carcinogen in training set
ECFP_6	1087070950	 [*]N=[*]	0.724	10 out of 14

ECFP_6	544048674	 <chem>[*]C(=[*])NN=[*]</chem>	0.617	2 out of 2
ECFP_6	738938915	 <chem>[*]C(=[*])N[c]1:[cH]:[cH]:[*]:[cH]:[cH]:1</chem>	0.617	2 out of 2
<b>Top Features for negative contribution</b>				
<b>Fingerprint</b>	<b>Bit/Smiles</b>	<b>Feature Structure</b>	<b>Score</b>	<b>Carcinogen in training set</b>
ECFP_6	2013347047	 <chem>[*][c]1:[*]:n:[cH]:[cH]:[cH]:1</chem>	-0.805	0 out of 4
ECFP_6	764951226	 <chem>[*]1:[cH]:[cH]:[cH]:n:[cH]:1</chem>	-0.482	0 out of 2
ECFP_6	-1818873508	 <chem>[*][c]1:[cH]:[cH]:[cH]:n:[cH]:1</chem>	-0.482	0 out of 2



$C_{21}H_{18}N_4O_2$

Molecular Weight: 358.39322

ALogP: 2.297

Rotatable Bonds: 5

Acceptors: 4

Donors: 2

## Model Prediction

Prediction: Non-Carcinogen

Probability: 0.231

Enrichment: 0.721

Bayesian Score: -1.96

Mahalanobis Distance: 11.7

Mahalanobis Distance p-value: 0.0236

Prediction: Positive if the Bayesian score is above the estimated best cutoff value from minimizing the false positive and false negative rate.

Probability: The estimated probability that the sample is in the positive category. This assumes that the Bayesian score follows a normal distribution and is different from the prediction using a cutoff.

Enrichment: An estimate of enrichment, that is, the increased likelihood (versus random) of this sample being in the category.

Bayesian Score: The standard Laplacian-modified Bayesian score.

Mahalanobis Distance: The Mahalanobis distance (MD) is the distance to the center of the training data. The larger the MD, the less trustworthy the prediction.

Mahalanobis Distance p-value: The p-value gives the fraction of training data with an MD greater than or equal to the one for the given sample, assuming normally distributed data. The smaller the p-value, the less trustworthy the prediction. For highly non-normal X properties (e.g., fingerprints), the MD p-value is wildly inaccurate.

## Structural Similar Compounds

Name	Mebendazole	Alizapride	Indapamide
Structure			
Actual Endpoint	Non-Carcinogen	Carcinogen	Non-Carcinogen
Predicted Endpoint	Non-Carcinogen	Carcinogen	Non-Carcinogen
Distance	0.570	0.601	0.601
Reference	US FDA (Centre for Drug Eval.& Res./Off. Testing & Res.) Sept. 1997	US FDA (Centre for Drug Eval.& Res./Off. Testing & Res.) Sept. 1997	US FDA (Centre for Drug Eval.& Res./Off. Testing & Res.) Sept. 1997

## Model Applicability

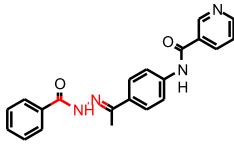
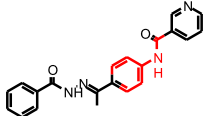
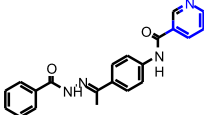
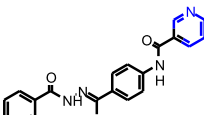
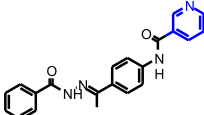
Unknown features are fingerprint features in the query molecule, but not found or appearing too infrequently in the training set.

1. All properties and OPS components are within expected ranges.
2. Unknown ECFP\_2 feature: 128986386: [\*]N=C(/C)\[c](:[\*]):[\*]
3. Unknown ECFP\_2 feature: 560380707: [\*]NN=C([\*])[\*]

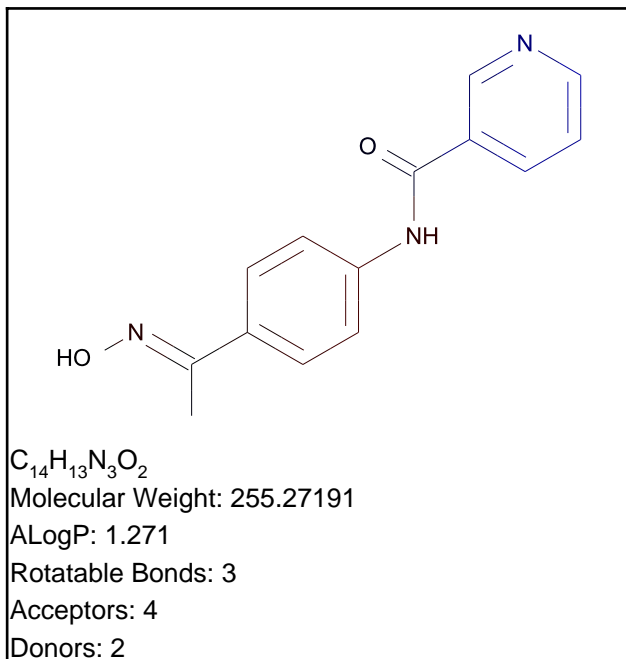
## Feature Contribution

### Top features for positive contribution

Fingerprint	Bit/Smiles	Feature Structure	Score	Carcinogen in training set
ECFP_6	1087070950	 [*]N=[*]	0.724	10 out of 14

ECFP_6	544048674	 <chem>[*]C(=[*])NN=[*]</chem>	0.617	2 out of 2
ECFP_6	738938915	 <chem>[*]C(=[*])N[c]1:[cH]:[cH]:[*]:[cH]:[cH]:[cH]:1</chem>	0.617	2 out of 2
<b>Top Features for negative contribution</b>				
<b>Fingerprint</b>	<b>Bit/Smiles</b>	<b>Feature Structure</b>	<b>Score</b>	<b>Carcinogen in training set</b>
ECFP_6	2013347047	 <chem>[*][c]1:[*]:n:[cH]:[cH]:[cH]:[cH]:1</chem>	-0.805	0 out of 4
ECFP_6	764951226	 <chem>[*]1:[cH]:[cH]:[cH]:n:[cH]:1</chem>	-0.482	0 out of 2
ECFP_6	-1818873508	 <chem>[*][c]1:[cH]:[cH]:[cH]:[cH]:n:[cH]:1</chem>	-0.482	0 out of 2





### Model Prediction

Prediction: Non-Carcinogen

Probability: 0.233

Enrichment: 0.726

Bayesian Score: -1.83

Mahalanobis Distance: 10.9

Mahalanobis Distance p-value: 0.121

Prediction: Positive if the Bayesian score is above the estimated best cutoff value from minimizing the false positive and false negative rate.

Probability: The estimated probability that the sample is in the positive category. This assumes that the Bayesian score follows a normal distribution and is different from the prediction using a cutoff.

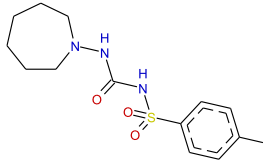
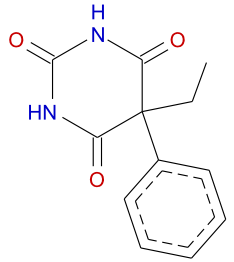
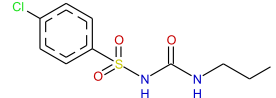
Enrichment: An estimate of enrichment, that is, the increased likelihood (versus random) of this sample being in the category.

Bayesian Score: The standard Laplacian-modified Bayesian score.

Mahalanobis Distance: The Mahalanobis distance (MD) is the distance to the center of the training data. The larger the MD, the less trustworthy the prediction.

Mahalanobis Distance p-value: The p-value gives the fraction of training data with an MD greater than or equal to the one for the given sample, assuming normally distributed data. The smaller the p-value, the less trustworthy the prediction. For highly non-normal X properties (e.g., fingerprints), the MD p-value is wildly inaccurate.

### Structural Similar Compounds

Name	Tolazamide	Phenobarbital	Chlorpropamide
Structure			
Actual Endpoint	Non-Carcinogen	Carcinogen	Non-Carcinogen
Predicted Endpoint	Non-Carcinogen	Carcinogen	Non-Carcinogen
Distance	0.576	0.586	0.591
Reference	US FDA (Centre for Drug Eval.& Res./Off. Testing & Res.) Sept. 1997	US FDA (Centre for Drug Eval.& Res./Off. Testing & Res.) Sept. 1997	US FDA (Centre for Drug Eval.& Res./Off. Testing & Res.) Sept. 1997

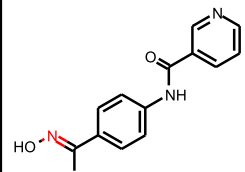
### Model Applicability

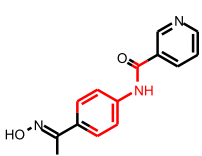
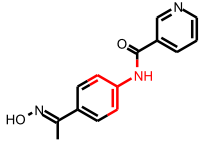
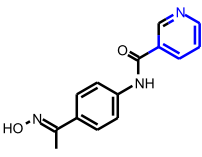
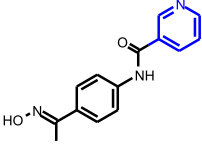
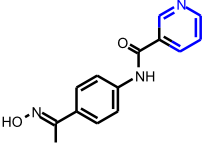
Unknown features are fingerprint features in the query molecule, but not found or appearing too infrequently in the training set.

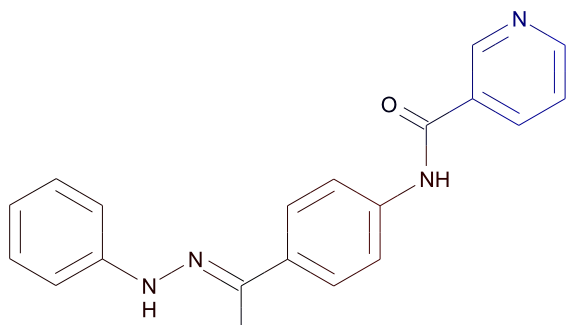
1. All properties and OPS components are within expected ranges.
2. Unknown ECFP\_2 feature: 128986386: [\*]N=C(/C)\[c](:[\*]):[\*]
3. Unknown ECFP\_2 feature: 559672449: [\*]C(=NO)[\*]
4. Unknown ECFP\_2 feature: 2025254696: [\*]=NO

### Feature Contribution

#### Top features for positive contribution

Fingerprint	Bit/Smiles	Feature Structure	Score	Carcinogen in training set
ECFP_6	-1087070950	 [*]N=[*]	0.724	10 out of 14

ECFP_6	738938915	 <chem>[*]C(=*)N[c]1:[cH]:[cH]:[*]:[cH]:[cH]:[cH]:1</chem>	0.617	2 out of 2
ECFP_6	-177077903	 <chem>[*]N[c](:[cH]:[*]):[cH]:[*]</chem>	0.279	4 out of 9
<b>Top Features for negative contribution</b>				
<b>Fingerprint</b>	<b>Bit/Smiles</b>	<b>Feature Structure</b>	<b>Score</b>	<b>Carcinogen in training set</b>
ECFP_6	2013347047	 <chem>[*][c]1:[*]:n:[cH]:[cH]:[cH]:1</chem>	-0.805	0 out of 4
ECFP_6	-1818873508	 <chem>[*][c]1:[cH]:[cH]:[cH]:n:[cH]:1</chem>	-0.482	0 out of 2
ECFP_6	764951226	 <chem>[*]1:[cH]:[cH]:[cH]:n:[cH]:1</chem>	-0.482	0 out of 2



$C_{20}H_{18}N_4O$

Molecular Weight: 330.38312

ALogP: 3.063

Rotatable Bonds: 5

Acceptors: 4

Donors: 2

## Model Prediction

Prediction: Non-Carcinogen

Probability: 0.234

Enrichment: 0.729

Bayesian Score: -1.77

Mahalanobis Distance: 11.7

Mahalanobis Distance p-value: 0.0253

Prediction: Positive if the Bayesian score is above the estimated best cutoff value from minimizing the false positive and false negative rate.

Probability: The estimated probability that the sample is in the positive category. This assumes that the Bayesian score follows a normal distribution and is different from the prediction using a cutoff.

Enrichment: An estimate of enrichment, that is, the increased likelihood (versus random) of this sample being in the category.

Bayesian Score: The standard Laplacian-modified Bayesian score.

Mahalanobis Distance: The Mahalanobis distance (MD) is the distance to the center of the training data. The larger the MD, the less trustworthy the prediction.

Mahalanobis Distance p-value: The p-value gives the fraction of training data with an MD greater than or equal to the one for the given sample, assuming normally distributed data. The smaller the p-value, the less trustworthy the prediction. For highly non-normal X properties (e.g., fingerprints), the MD p-value is wildly inaccurate.

## Structural Similar Compounds

Name	Mebendazole	Bunolol	Etodolac
Structure			
Actual Endpoint	Non-Carcinogen	Carcinogen	Non-Carcinogen
Predicted Endpoint	Non-Carcinogen	Carcinogen	Non-Carcinogen
Distance	0.559	0.582	0.606
Reference	US FDA (Centre for Drug Eval.& Res./Off. Testing & Res.) Sept. 1997	US FDA (Centre for Drug Eval.& Res./Off. Testing & Res.) Sept. 1997	US FDA (Centre for Drug Eval.& Res./Off. Testing & Res.) Sept. 1997

## Model Applicability

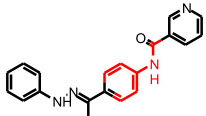
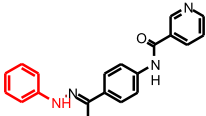
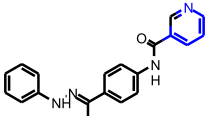
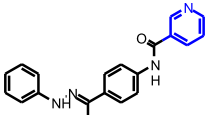
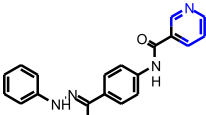
Unknown features are fingerprint features in the query molecule, but not found or appearing too infrequently in the training set.

1. All properties and OPS components are within expected ranges.
2. Unknown ECFP\_2 feature: 128986386: [\*]N=C(/C)\[c](:[\*]):[\*]
3. Unknown ECFP\_2 feature: 560380707: [\*]NN=C([\*])[\*]
4. Unknown ECFP\_2 feature: -1236714312: [\*]=NN[c](:[\*]):[\*]

## Feature Contribution

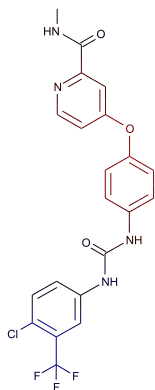
### Top features for positive contribution

Fingerprint	Bit/Smiles	Feature Structure	Score	Carcinogen in training set
ECFP_6	-1087070950	 [*]N=[*]	0.724	10 out of 14

ECFP_6	738938915	 <chem>[*]C(=*)N[c]1:[cH]:[cH]:[cH]:[*]:[cH]:[cH]:[cH]:1</chem>	0.617	2 out of 2
ECFP_6	547788473	 <chem>[*]N[c]1:[cH]:[cH]:[cH]:[cH]:[cH]:[cH]:1</chem>	0.424	1 out of 1
<b>Top Features for negative contribution</b>				
Fingerprint	Bit/Smiles	Feature Structure	Score	Carcinogen in training set
ECFP_6	2013347047	 <chem>[*][c]1:[*]:n:[cH]:[cH]:[cH]:[cH]:1</chem>	-0.805	0 out of 4
ECFP_6	-1818873508	 <chem>[*][c]1:[cH]:[cH]:[cH]:[cH]:n:[cH]:1</chem>	-0.482	0 out of 2
ECFP_6	764951226	 <chem>[*]1:[cH]:[cH]:[cH]:n:[cH]:1</chem>	-0.482	0 out of 2

# Sorafenib

# TOPKAT\_Mouse\_Female\_FDA\_None\_vs\_Carcinogen



$C_{21}H_{16}ClF_3N_4O_3$

Molecular Weight: 464.82494

ALogP: 4.175

Rotatable Bonds: 6

Acceptors: 4

Donors: 3

## Model Prediction

**Prediction: Carcinogen**

Probability: 0.257

Enrichment: 0.801

Bayesian Score: -0.321

Mahalanobis Distance: 14.9

Mahalanobis Distance p-value: 4.21e-007

Prediction: Positive if the Bayesian score is above the estimated best cutoff value from minimizing the false positive and false negative rate.

Probability: The estimated probability that the sample is in the positive category. This assumes that the Bayesian score follows a normal distribution and is different from the prediction using a cutoff.

Enrichment: An estimate of enrichment, that is, the increased likelihood (versus random) of this sample being in the category.

Bayesian Score: The standard Laplacian-modified Bayesian score.

Mahalanobis Distance: The Mahalanobis distance (MD) is the distance to the center of the training data. The larger the MD, the less trustworthy the prediction.

Mahalanobis Distance p-value: The p-value gives the fraction of training data with an MD greater than or equal to the one for the given sample, assuming normally distributed data. The smaller the p-value, the less trustworthy the prediction. For highly non-normal X properties (e.g., fingerprints), the MD p-value is wildly inaccurate.

## Structural Similar Compounds

Name	Glimepiride	Glyburide	Fluvastatin
Structure			
Actual Endpoint	Carcinogen	Non-Carcinogen	Non-Carcinogen
Predicted Endpoint	Carcinogen	Non-Carcinogen	Non-Carcinogen
Distance	0.605	0.615	0.625
Reference	US FDA (Centre for Drug Eval.& Res./Off. Testing & Res.) Sept. 1997	US FDA (Centre for Drug Eval.& Res./Off. Testing & Res.) Sept. 1997	US FDA (Centre for Drug Eval.& Res./Off. Testing & Res.) Sept. 1997

## Model Applicability

Unknown features are fingerprint features in the query molecule, but not found or appearing too infrequently in the training set.

- OPS PC20 out of range. Value: -3.3309. Training min, max, SD, explained variance: -3.1862, 4.4571, 1.28, 0.0167.

## Feature Contribution

### Top features for positive contribution

Fingerprint	Bit/Smiles	Feature Structure	Score	Carcinogen in training set
ECFP_6	738938915	 [*]C(=[*])N(c1cc(F)c(Cl)cc1)N(c2cc(F)cc2)N(c3cc(F)cc3)N(c4cc(F)cc4)N(c5cc(F)cc5)N(c6cc(F)cc6)N(c7cc(F)cc7)N(c8cc(F)cc8)N(c9cc(F)cc9)N(c10cc(F)cc10)N(c11cc(F)cc11)N(c12cc(F)cc12)N(c13cc(F)cc13)N(c14cc(F)cc14)N(c15cc(F)cc15)N(c16cc(F)cc16)N(c17cc(F)cc17)N(c18cc(F)cc18)N(c19cc(F)cc19)N(c20cc(F)cc20)N(c21cc(F)cc21)N(c22cc(F)cc22)N(c23cc(F)cc23)N(c24cc(F)cc24)N(c25cc(F)cc25)N(c26cc(F)cc26)N(c27cc(F)cc27)N(c28cc(F)cc28)N(c29cc(F)cc29)N(c30cc(F)cc30)N(c31cc(F)cc31)N(c32cc(F)cc32)N(c33cc(F)cc33)N(c34cc(F)cc34)N(c35cc(F)cc35)N(c36cc(F)cc36)N(c37cc(F)cc37)N(c38cc(F)cc38)N(c39cc(F)cc39)N(c40cc(F)cc40)N(c41cc(F)cc41)N(c42cc(F)cc42)N(c43cc(F)cc43)N(c44cc(F)cc44)N(c45cc(F)cc45)N(c46cc(F)cc46)N(c47cc(F)cc47)N(c48cc(F)cc48)N(c49cc(F)cc49)N(c50cc(F)cc50)N(c51cc(F)cc51)N(c52cc(F)cc52)N(c53cc(F)cc53)N(c54cc(F)cc54)N(c55cc(F)cc55)N(c56cc(F)cc56)N(c57cc(F)cc57)N(c58cc(F)cc58)N(c59cc(F)cc59)N(c60cc(F)cc60)N(c61cc(F)cc61)N(c62cc(F)cc62)N(c63cc(F)cc63)N(c64cc(F)cc64)N(c65cc(F)cc65)N(c66cc(F)cc66)N(c67cc(F)cc67)N(c68cc(F)cc68)N(c69cc(F)cc69)N(c70cc(F)cc70)N(c71cc(F)cc71)N(c72cc(F)cc72)N(c73cc(F)cc73)N(c74cc(F)cc74)N(c75cc(F)cc75)N(c76cc(F)cc76)N(c77cc(F)cc77)N(c78cc(F)cc78)N(c79cc(F)cc79)N(c80cc(F)cc80)N(c81cc(F)cc81)N(c82cc(F)cc82)N(c83cc(F)cc83)N(c84cc(F)cc84)N(c85cc(F)cc85)N(c86cc(F)cc86)N(c87cc(F)cc87)N(c88cc(F)cc88)N(c89cc(F)cc89)N(c90cc(F)cc90)N(c91cc(F)cc91)N(c92cc(F)cc92)N(c93cc(F)cc93)N(c94cc(F)cc94)N(c95cc(F)cc95)N(c96cc(F)cc96)N(c97cc(F)cc97)N(c98cc(F)cc98)N(c99cc(F)cc99)N(c100cc(F)cc100)N(c101cc(F)cc101)N(c102cc(F)cc102)N(c103cc(F)cc103)N(c104cc(F)cc104)N(c105cc(F)cc105)N(c106cc(F)cc106)N(c107cc(F)cc107)N(c108cc(F)cc108)N(c109cc(F)cc109)N(c110cc(F)cc110)N(c111cc(F)cc111)N(c112cc(F)cc112)N(c113cc(F)cc113)N(c114cc(F)cc114)N(c115cc(F)cc115)N(c116cc(F)cc116)N(c117cc(F)cc117)N(c118cc(F)cc118)N(c119cc(F)cc119)N(c120cc(F)cc120)N(c121cc(F)cc121)N(c122cc(F)cc122)N(c123cc(F)cc123)N(c124cc(F)cc124)N(c125cc(F)cc125)N(c126cc(F)cc126)N(c127cc(F)cc127)N(c128cc(F)cc128)N(c129cc(F)cc129)N(c130cc(F)cc130)N(c131cc(F)cc131)N(c132cc(F)cc132)N(c133cc(F)cc133)N(c134cc(F)cc134)N(c135cc(F)cc135)N(c136cc(F)cc136)N(c137cc(F)cc137)N(c138cc(F)cc138)N(c139cc(F)cc139)N(c140cc(F)cc140)N(c141cc(F)cc141)N(c142cc(F)cc142)N(c143cc(F)cc143)N(c144cc(F)cc144)N(c145cc(F)cc145)N(c146cc(F)cc146)N(c147cc(F)cc147)N(c148cc(F)cc148)N(c149cc(F)cc149)N(c150cc(F)cc150)N(c151cc(F)cc151)N(c152cc(F)cc152)N(c153cc(F)cc153)N(c154cc(F)cc154)N(c155cc(F)cc155)N(c156cc(F)cc156)N(c157cc(F)cc157)N(c158cc(F)cc158)N(c159cc(F)cc159)N(c160cc(F)cc160)N(c161cc(F)cc161)N(c162cc(F)cc162)N(c163cc(F)cc163)N(c164cc(F)cc164)N(c165cc(F)cc165)N(c166cc(F)cc166)N(c167cc(F)cc167)N(c168cc(F)cc168)N(c169cc(F)cc169)N(c170cc(F)cc170)N(c171cc(F)cc171)N(c172cc(F)cc172)N(c173cc(F)cc173)N(c174cc(F)cc174)N(c175cc(F)cc175)N(c176cc(F)cc176)N(c177cc(F)cc177)N(c178cc(F)cc178)N(c179cc(F)cc179)N(c180cc(F)cc180)N(c181cc(F)cc181)N(c182cc(F)cc182)N(c183cc(F)cc183)N(c184cc(F)cc184)N(c185cc(F)cc185)N(c186cc(F)cc186)N(c187cc(F)cc187)N(c188cc(F)cc188)N(c189cc(F)cc189)N(c190cc(F)cc190)N(c191cc(F)cc191)N(c192cc(F)cc192)N(c193cc(F)cc193)N(c194cc(F)cc194)N(c195cc(F)cc195)N(c196cc(F)cc196)N(c197cc(F)cc197)N(c198cc(F)cc198)N(c199cc(F)cc199)N(c200cc(F)cc200)N(c201cc(F)cc201)N(c202cc(F)cc202)N(c203cc(F)cc203)N(c204cc(F)cc204)N(c205cc(F)cc205)N(c206cc(F)cc206)N(c207cc(F)cc207)N(c208cc(F)cc208)N(c209cc(F)cc209)N(c210cc(F)cc210)N(c211cc(F)cc211)N(c212cc(F)cc212)N(c213cc(F)cc213)N(c214cc(F)cc214)N(c215cc(F)cc215)N(c216cc(F)cc216)N(c217cc(F)cc217)N(c218cc(F)cc218)N(c219cc(F)cc219)N(c220cc(F)cc220)N(c221cc(F)cc221)N(c222cc(F)cc222)N(c223cc(F)cc223)N(c224cc(F)cc224)N(c225cc(F)cc225)N(c226cc(F)cc226)N(c227cc(F)cc227)N(c228cc(F)cc228)N(c229cc(F)cc229)N(c230cc(F)cc230)N(c231cc(F)cc231)N(c232cc(F)cc232)N(c233cc(F)cc233)N(c234cc(F)cc234)N(c235cc(F)cc235)N(c236cc(F)cc236)N(c237cc(F)cc237)N(c238cc(F)cc238)N(c239cc(F)cc239)N(c240cc(F)cc240)N(c241cc(F)cc241)N(c242cc(F)cc242)N(c243cc(F)cc243)N(c244cc(F)cc244)N(c245cc(F)cc245)N(c246cc(F)cc246)N(c247cc(F)cc247)N(c248cc(F)cc248)N(c249cc(F)cc249)N(c250cc(F)cc250)N(c251cc(F)cc251)N(c252cc(F)cc252)N(c253cc(F)cc253)N(c254cc(F)cc254)N(c255cc(F)cc255)N(c256cc(F)cc256)N(c257cc(F)cc257)N(c258cc(F)cc258)N(c259cc(F)cc259)N(c260cc(F)cc260)N(c261cc(F)cc261)N(c262cc(F)cc262)N(c263cc(F)cc263)N(c264cc(F)cc264)N(c265cc(F)cc265)N(c266cc(F)cc266)N(c267cc(F)cc267)N(c268cc(F)cc268)N(c269cc(F)cc269)N(c270cc(F)cc270)N(c271cc(F)cc271)N(c272cc(F)cc272)N(c273cc(F)cc273)N(c274cc(F)cc274)N(c275cc(F)cc275)N(c276cc(F)cc276)N(c277cc(F)cc277)N(c278cc(F)cc278)N(c279cc(F)cc279)N(c280cc(F)cc280)N(c281cc(F)cc281)N(c282cc(F)cc282)N(c283cc(F)cc283)N(c284cc(F)cc284)N(c285cc(F)cc285)N(c286cc(F)cc286)N(c287cc(F)cc287)N(c288cc(F)cc288)N(c289cc(F)cc289)N(c290cc(F)cc290)N(c291cc(F)cc291)N(c292cc(F)cc292)N(c293cc(F)cc293)N(c294cc(F)cc294)N(c295cc(F)cc295)N(c296cc(F)cc296)N(c297cc(F)cc297)N(c298cc(F)cc298)N(c299cc(F)cc299)N(c300cc(F)cc300)N(c301cc(F)cc301)N(c302cc(F)cc302)N(c303cc(F)cc303)N(c304cc(F)cc304)N(c305cc(F)cc305)N(c306cc(F)cc306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