



KJE-3900

Master thesis in organic chemistry

Ring closing reactions of barbituric acid derivatives

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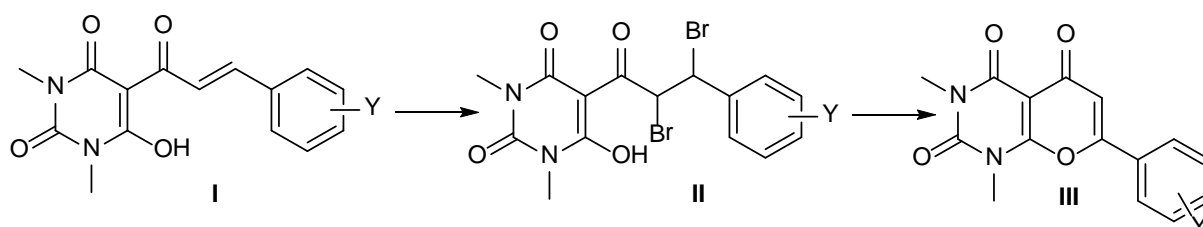
Last, but not the least, I would like to thank my family members, who supported me by listening for my chemistry stories, encouraged and believed in me.

Symbols and abbreviations

°C	degrees Celsius
DCM	dichloromethane
TEA	triethylamine
THF	tetrahydrofuran
EWG	electron withdrawing group
EDG	electron donating group
EtOH	ethanol
mg	milligram
gHMBC	gradient Heteronuclear Multiple Bond Correlation
Temp	temperature
m.p.	melting point
d.p.	decomposition point
g	gram
mol	mole
mmol	milli mole
MS	mass spectrometry
IR	infrared spectroscopy
NMR	nuclear magnetic resonance spectroscopy
ppm	part per million
s	singlet
d	doublet
dd	double doublet
t	triplet
m	multiplet
UV	ultraviolet
MHz	mega Hertz

Summary

The aim for this project was to cyclize the chalcones derivatives in order to produce flavonoids. The starting materials were synthesized according to the procedure that was earlier discovered by members of the group.



Scheme 1. Synthetic rout for target flavonoids.

This was achieved via halogenation of double bond and ring closing based on nucleophilic substitution. By changing the substituents Y on an aromatic ring of the starting material, the effect on bromination of the double bond and a formation of five or six member rings was studied. The reaction with chalcones without any substituent on the aromatic ring led to a formation of six member ring, meanwhile the chalcones with an electron withdrawing group led to a mixture of five and six member rings.

However, during this project we faced with some difficulties in synthesizing particular five or six member rings. The results showed mostly the mixtures of them.

1. Background

1.1. Barbituric acid

First barbituric acid (2,4,6-trioxohexahydropyrimidine) (Figure 1) was synthesized in 1864 by German chemist Adolf von Baeyer (1835-1975)^[1].

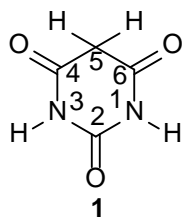


Figure 1. The structure of barbituric acid.

For almost a half of the century many derivatives were synthesized, but only early in the 20th century it was discovered that some barbituric acid derivatives have an effect on the central nervous system. During that period many derivatives of barbituric acid were used as drugs side-effects.

One of the ways of making potentially biologically active compounds is modification on C-5 of barbituric acid (Figure 1). Combination of barbituric acid moiety with other pharmacophoric groups gives possibility to synthesized numerous derivatives with potential biological effect.

Figure 2 displays barbituric acid derivatives which were tested for biological activity could demonstrate anti-cancer or metal sequestering properties^[2, 3].

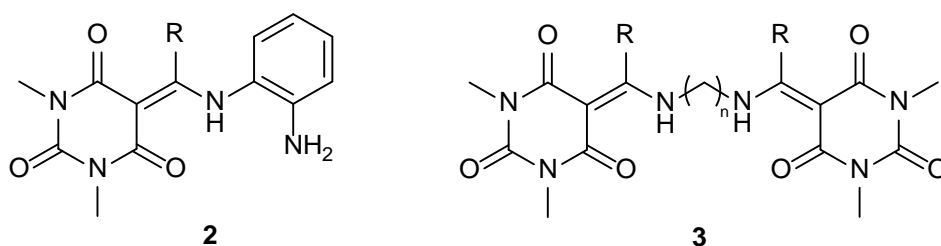


Figure 2. Barbituric acid derivatives.

1.2. Chalcones

Chalcones are the products of the condensation of a simple or substituted aromatic moiety with a simple or substituted acetophenone in presence of base. This group of compounds is widely used in anticancer research, as an antimicrobial or an antitubercular ^[4, 5].

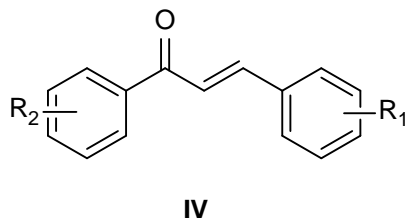


Figure 3. Structure of chalcones.

Gorovoy^[6], Guyader^[7], reported a large number of chalconoids with different substituents, which were synthesized by using barbituric acid as starting compound (Figure 4). Some of these were exhibiting biological activity.

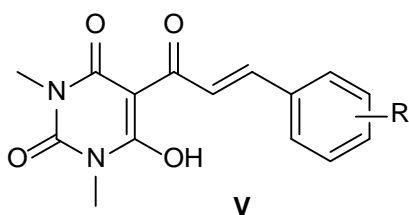


Figure 4 Structure of chalcone with barbituric acid moiety.

Guyader^[7], have been synthesized 5-, 6- and 7-member ring heterocyclic compounds (Figure 5).

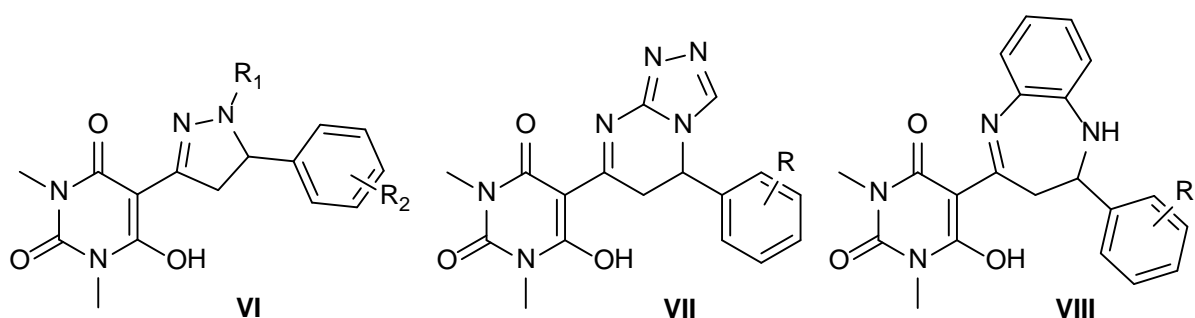


Figure 5. Chemical structures of 5-, 6- and 7- member ring heterocyclic compounds.

These compounds were tested for kinase activities and results showed that some of them are slightly active, though have low water solubility.

Another biologically important class is flavonoids. Flavonoids can be synthesized by cyclisation of chalcones, making use of the reactivity of the α,β -unsaturated carbonyl group (Figure 6).

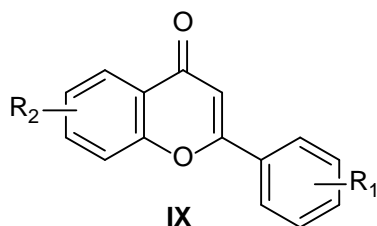


Figure 6. Structure of flavonoid.

1.3. Flavonoids

Flavonoids are commonly found in fruits, vegetables, nuts, seeds, stems, flowers, tea, wine, propolis and honey and very often used for medical reason to treat human diseases. There are 14 classes of flavonoids, which differ by the pattern of substitution of the B ring and the oxidation level. Though the compounds of the same group also differ by substitution of the A and C rings^[8] as shown in a Figure 7.

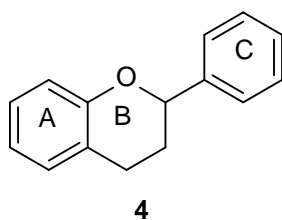


Figure. 7 Basic structure of flavonoid.

Flavonoids are compounds, that consist of 15 carbons atoms in three a simple or substituted rings ($C_6-C_3-C_6$) or ($C_6-C_2-C_6$) and carbonyl function on it. They can be subdivided in to several classes: flavones **5**, flavanone **6**, isoflavone **7**, isoflavanone **8** and to five member ring isomers auronones with (*E*)- **9** and (*Z*)- **10** configurations. (Figure 8)

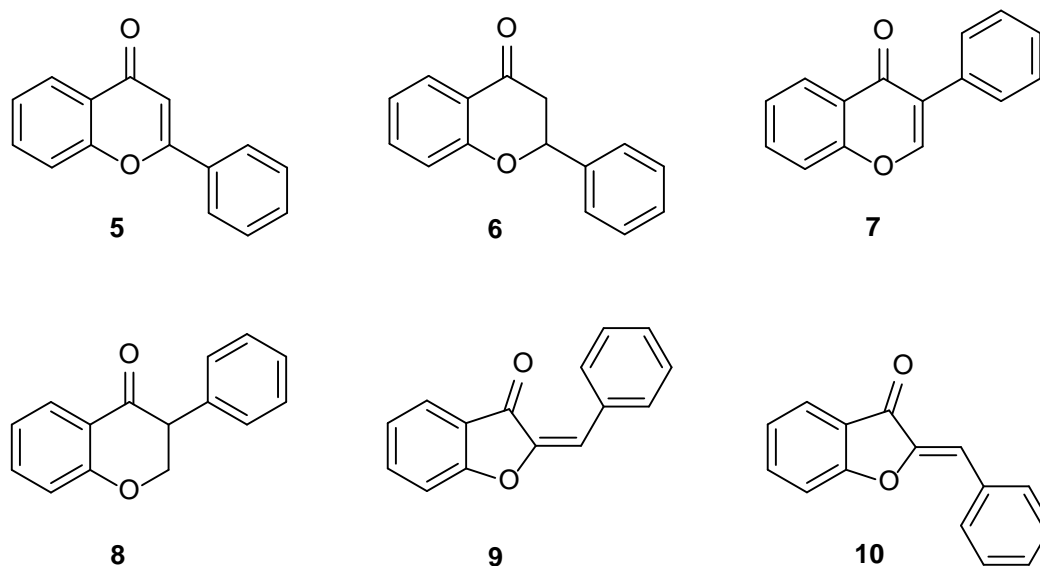


Figure 8. Flavonoids.

In nature more often 6-member ring instead 5-member ring flavonoids can be found. But aurones are well studied too and some of them are potential inhibitors of Hepatitis C virus^[9].

In addition to the flavonoids that were displayed in a Figure 8, there are also polymeric derivatives, called tannins, which are divided into two groups depending on their structure, *i.e.* condensed and hydrolysable. As it can be seen from a Figure 9, condensed tannins are the polymers of flavonoids and hydrolysable tannins that contain gallic acid.

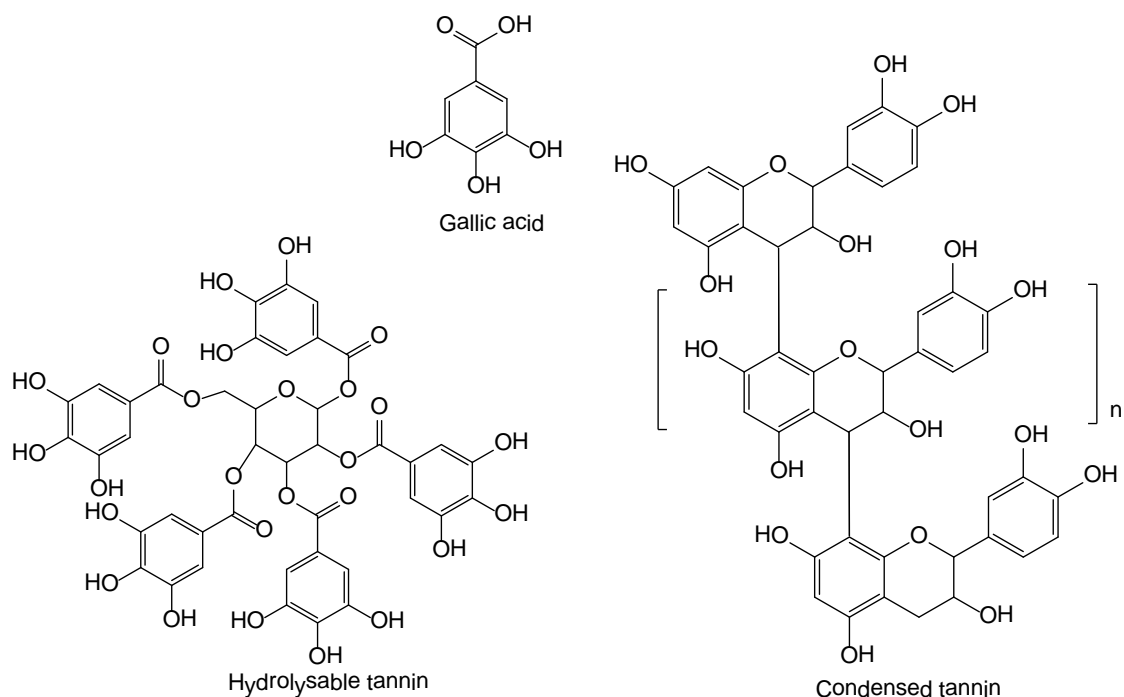


Figure 9. Chemical structure of gallic acid, hydrolysable tannin and condensed tannin.

An interest in flavonoids is increasing with every day when they are being discovered to be more and more significant for medical reasons. Many of isolated flavone possesses antifungal, antiviral and antibacterial, anticancer^[10], cytotoxicity, anti – inflammatory^[11, 12] and antitumor activities. Moreover, they have been used for chemotherapy treatments. They also showed the possibility to protect the human body from free radicals and act like an antioxidants^[13]. Figure 9 introduce to the most widely used flavonoids, which can be divided into groups of flavonoids, like flavones (luteolin)^[14], flavonol (quercetin)^[15], flavanone (naringenin)^[16], isoflavone (genistein)^[17] and flavan – 3 – ol (catechin)^[18]. (Figure 10)

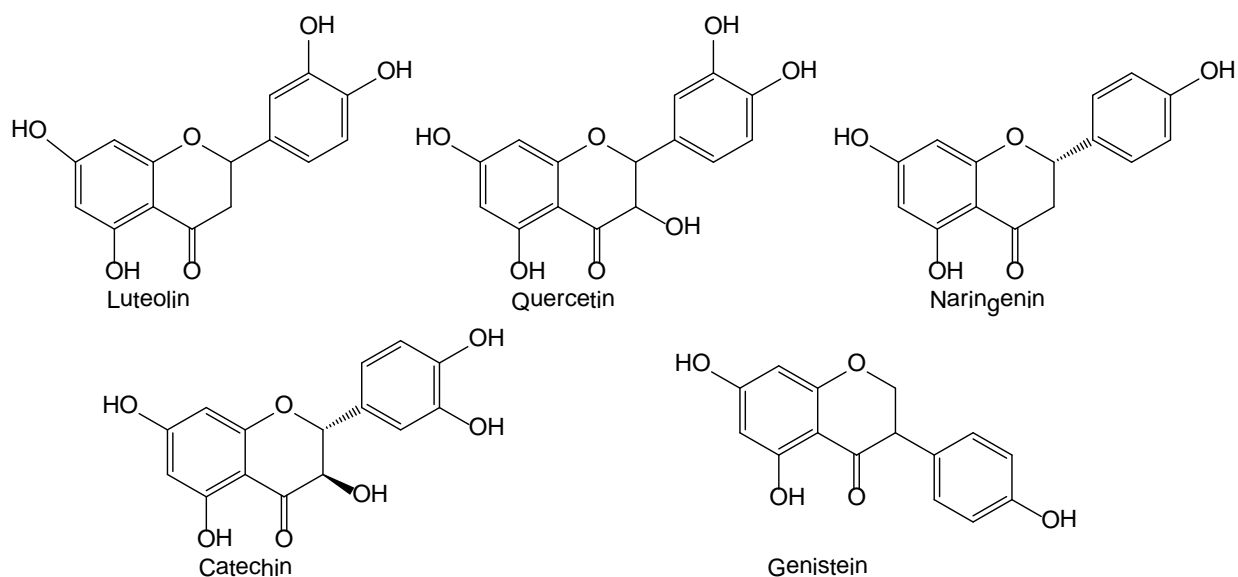


Figure 10. Chemical structures of most widely used flavonoids.

1.3.1. Antimicrobial activity

The fact that pathogens are becoming more resistant to the antimicrobial agents leads to a need for development of new therapeutic agents. Therefore flavonoids are becoming a very important subject of medical research. Already in ancient times they have been used for treatment of human diseases, for example *Tagetes minuta* plant^[19] was used for infectious disease treatment according to argentinean medicine. Flavonoids have been widely investigated and known for their antibacterial, antifungal and antiviral activities.

1.3.2. Antibacterial activity

Flavonoids exhibit direct and synergistic antibacterial activity and suppression of bacterial virulence factors, including enzymes, toxins and signal receptors^[20]. Antibacterial activity can be displayed by six main classes of flavonoids, which are flavones, flavonols, chalcones, flavan-3-ols and flavolans.

1.3.3. Antifungal activity

Most of the flavonoids that exhibit antifungal activity are found in plants as isoflavonoids, flavans or flavanones. Having an ability to inhibit spore germination of plant pathogens they can be used in a human body too^[21]. For the first time there was used chlorine containing flavonoid chlorflavonin which was specific for antifungal features and was found in *Aspergillus candidus*^[22].

1.3.4. Antiviral activity

There have been reported flavonoids that possess antiviral activity against 11 types of viruses^[23]. It is known that flavones can act against Herpes simplex virus type 1^[24]. Moreover flavonoids are widely investigated against human immunodeficiency virus (HIV), which is causative agent of AIDS. It have been tested that flavans are more active than flavones and flavonones in the inhibition of immunodeficiency viruses^[25].

1.3.5. Antioxidant activity

One of the most attractive features of flavonoids is the possibility to act as an antioxidant. During the metabolism processes in our body there are produced free radicals and reactive oxygen species (ROS), which continuously make damage for our organism. This oxidative damage can be a cause of some diseases as cataracts, cognitive dysfunction, cancer or heart disease^[8]. Some of the flavonoids, like quercetin, kaempferol, morin, myricetin and rutin act as antioxidants and protect the body against ROS^[26], by suppressing the formation of reactive oxygen species, by scavenging reactive oxygen species or by upregulating antioxidant defenses.

1.3.6. Other biological activities

In addition to the mentioned before flavonoids contain a large number of compounds which expose more than 30 types of biological and chemical activities. They are known for their antiulcer activity^[27], hepatoprotective activity^[28], anti – inflammatory^[29], antidiabetic effects^[30], effects on cardiovascular system^[31], antiatherosclerotic^[32], antithrombogenic^[33], cardioprotective^[34], antineoplastic activity^[35], effects of nervous systems^[36] and many others. So, it suggests that the new ways for the synthesis of the flavonoids need to be discovered and investigated.

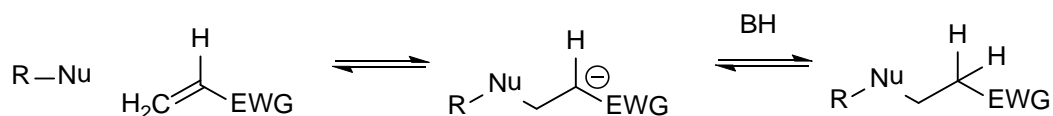
There are many ways for synthesis of new useful flavonoids. One of the possibility for flavonoids synthesis from chalconoids can be 1, 4-addition.

1.4. Cyclisation by 1, 4-addition

“1, 4 - addition” is known as the Michael reaction. This is conjugated addition to a α , β -unsaturated carbonyl compounds.

Like in intermolecular, the intramolecular Michael reaction involves the addition of a nucleophile, also called a ‘Michael donor’, to an acceptor the ‘Michael acceptor’, usually of

electron poor olefins which contain one or more functional groups that are able to stabilize a carbanion. (Scheme2).



Scheme 2. Scheme for Michael reaction.

The intramolecular Michael reaction most often leads to the formation of a ring, either carbo- or heterocyclic.

There are basically two ways to promote the reactivity.

One way is to make nucleophile more negative. It can be done by using base as a catalyst, like tertiary amines or hydroxides. But strong base can lead an unwanted result, like destruction of molecule.

Another way is to increase electrophility of β -unsaturated carbon. For that reason it can be used Lewis-acid^[37] such as boron trifluoride, aluminum trichloride or zinc chloride. In this case Lewis acid coordinates to the carbonyl of the acrylate to activate an olefin. To activate an olefin there can be also used Cupper (II), Iron (III) or In(III) complexes as catalyst.

2. The Aim

The aim of the project was the cyclization of chalcones derivatives that were based on barbituric acid compounds, which have been mentioned before (Scheme 1).

The cyclisation product is a compound that contains aromatic heterocyclic skeleton (Figure 11).

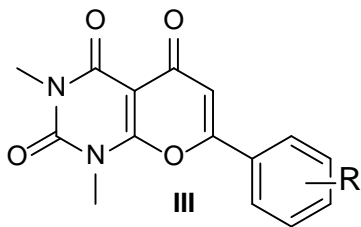


Figure. 11 Structure of flavone.

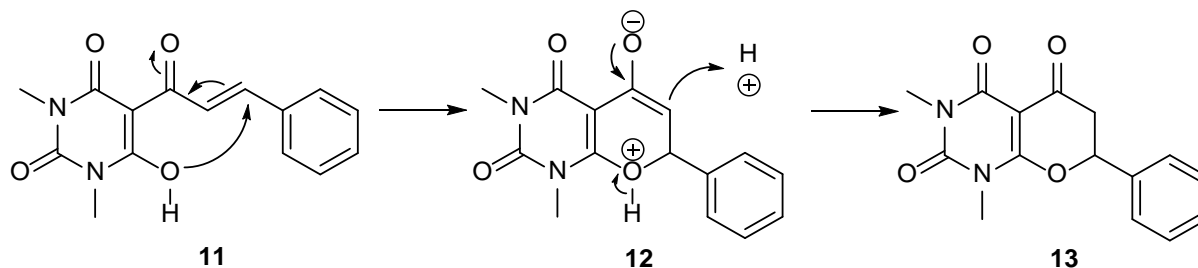
Compounds were to be tested for kinase activity.

3 Results and discussion

3.1 Intramolecular cyclisation by conjugate addition of chalcones 1

3.1.1. Thermal ring closing

Intramolecular ring closing of compound **11** should be possible to make by using: microwave irradiation, ultrasound or heating^[38]. The proposed mechanism for the synthesis is shown in Scheme 3.



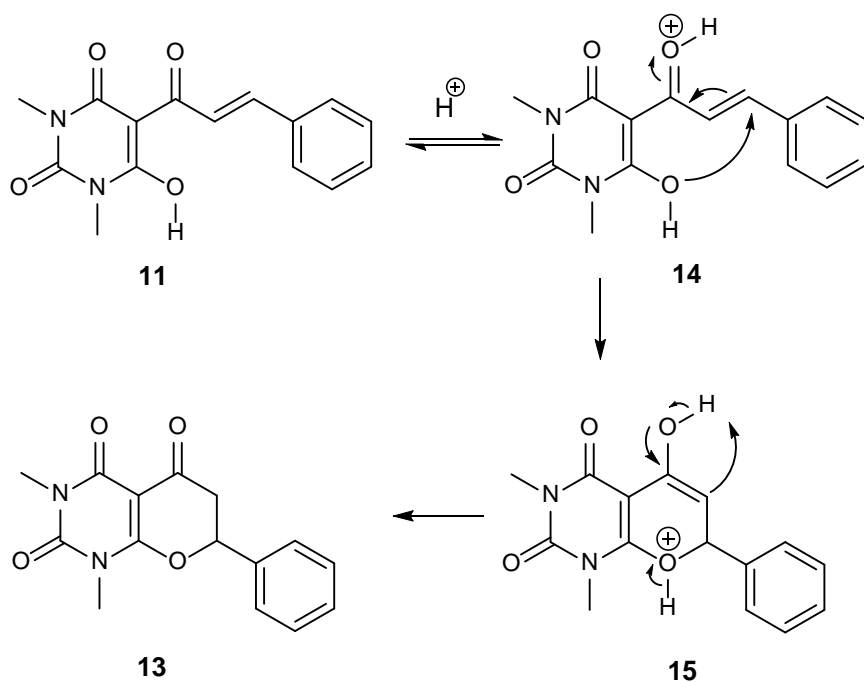
Scheme 3. Proposed mechanism for thermal ring closing .

Compound **11** was dissolved in DCM (dichloromethane) and heated by microwave irradiation from five minutes till one hour in temperature range between 25-35 °C. Temperature depended on the solvent boiling point, i.e. benzene 80 °C, tetrahydrofuran 66 °C. Using microwave irradiation or ultrasound cyclization did not give successful result.

Solid compound **11** decomposed when it was heated to 50-60 °C above the melting point.

3.1.2. Acid or base catalysed ring closing

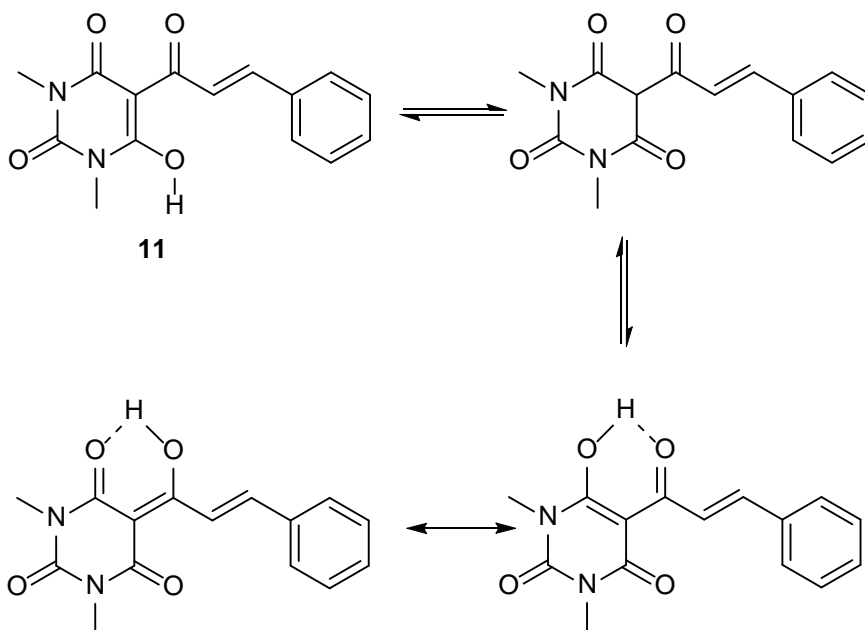
In order to ring close compound **11** conjugate addition catalyzed by acid or base as described in literature^[37, 39] was also studied. Suggested mechanism for acid as catalyst ring closing is shown in Scheme 4.



Scheme 4. Acid catalysed ring closing.

We used a wide range of acids like H₂SO₄, HCl, Dowex50, AcOH the reaction did not work. Microwave irradiation or heating with strong acid under reflux caused destruction of compound **11**.

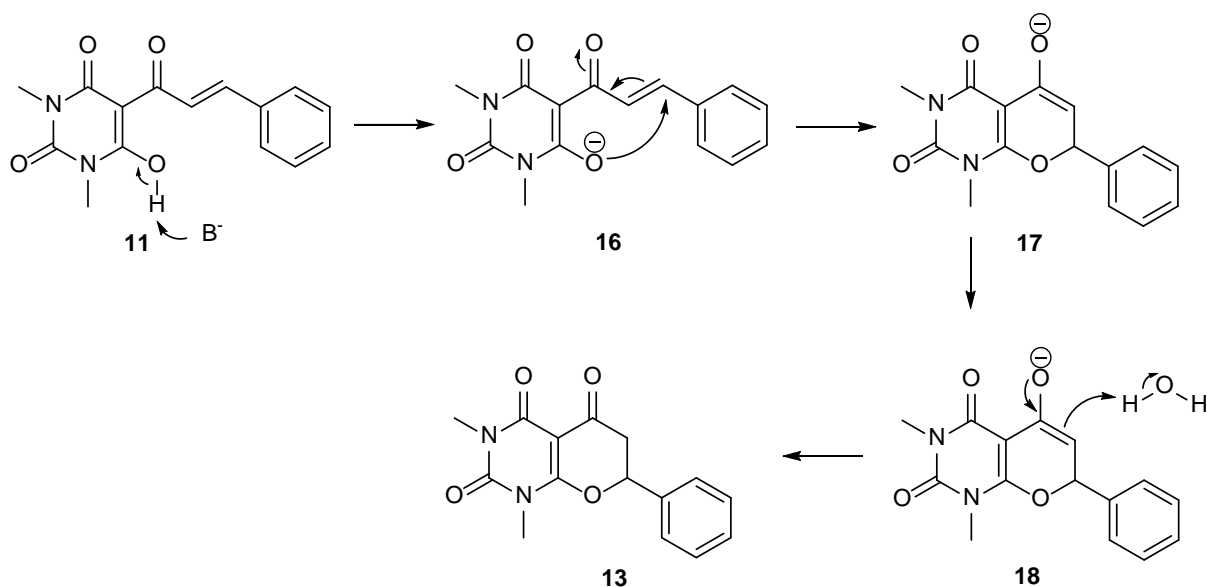
A possible explanation for the difficulties with acid catalysed ring closing is that the keto-enol equilibrium of α,β -unsaturated ketones favors the keto structure, which is then less likely to cyclize (Scheme 5). Another explanation that arises, is that tautomers can be the reason for non-ring closing since hydrogen bonding stabilizes the structures^[40].



Scheme 5. Keto-enol equilibrium of α,β -unsaturated ketones.

Reaction with TEA (triethylamine), pyridine or piperidine as base did not give the wanted result.

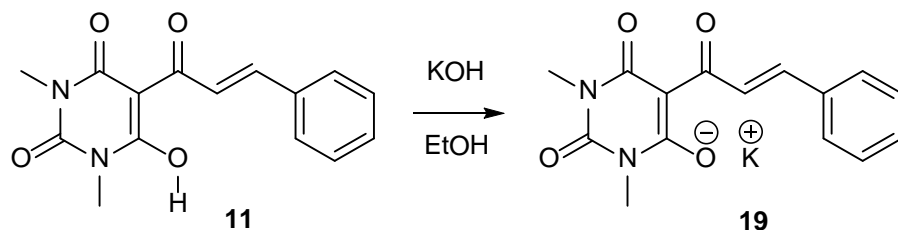
Theoretical mechanism for base catalyzed ring closing is shown in Scheme 6.



Scheme 6. Base catalyzed ring closing.

Problems with base catalyzed ring closing can be explained with not good enough electrophile side in the intermediate compound **16**.

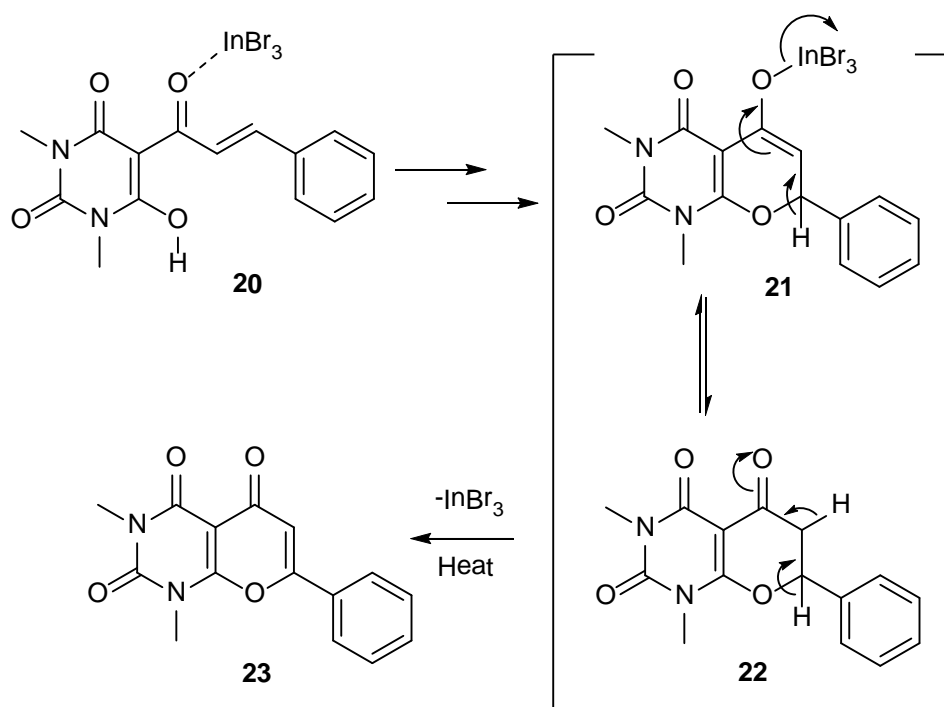
In the reaction with KOH as base in EtOH under reflux, instead of ring closing, precipitate of salt was obtained in a yield >90 % (Scheme 7). Using H₂O instead of EtOH, resulted in decomposition of compound **11**.



Scheme 7. Reaction in ethanol.

3.1.3. Lewis acid catalysed ring closing

An interesting method for the synthesis of flavones, which was carried out under solvent free condition with silica gel supported InBr₃^[41]. The mechanism is shown in Scheme 8, but ring closing did not appear for the barbituric acid based compound.



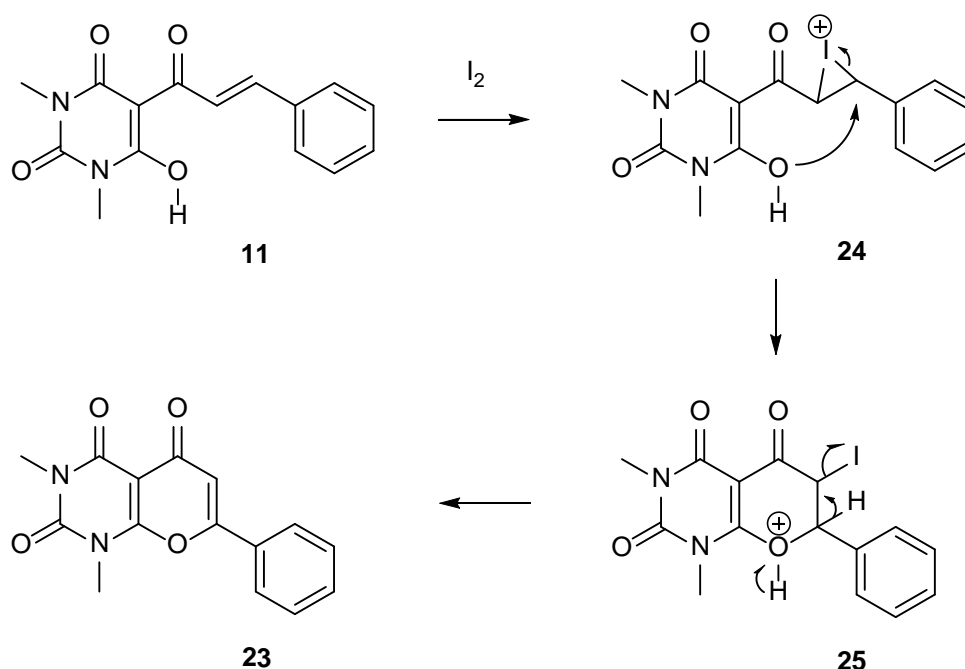
Scheme 8. Synthesis of flavones under solvent free conditions with InBr₃ supported by silica gel.

Using other Lewis acids such as CuCl_2 ^[42] or FeCl_3 as catalyst for ring closing in THF (tetrahydrofuran) or DCM in room temperature or under reflux did not give wanted result.

3.2 Intramolecular cyclisation by nucleophilic substitution

3.2.1. I_2 catalysed ring closing

The first flavonoid that was successfully made from compound **11** was obtained using I_2 as catalyst^[38, 43]. A possible mechanism for the reaction is shown in Scheme 9.



Scheme 9. Iodide catalysed ring closing.

From compound **11** in DCM and catalytic amount of I_2 under reflux for 17 hours compound **23** was obtained, unfortunately compound **23** was just a byproduct of the reaction. By changing time, temperature or solvent or amount of I_2 only 1-8% yield was reached.

Poor yield can be explainable by as described in Scheme 5.

3.2.2. Halogenation of the double bond and ring closing

In order to investigate the reactivity of the double bond of compound **11** bromination of the double bond was made.

Reaction of the double bond was fast at room temperature in DCM and gave more than 96% yield.

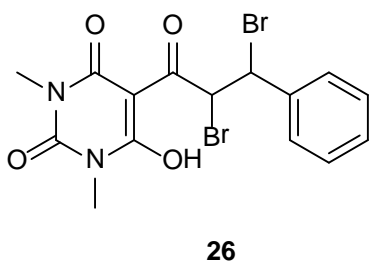
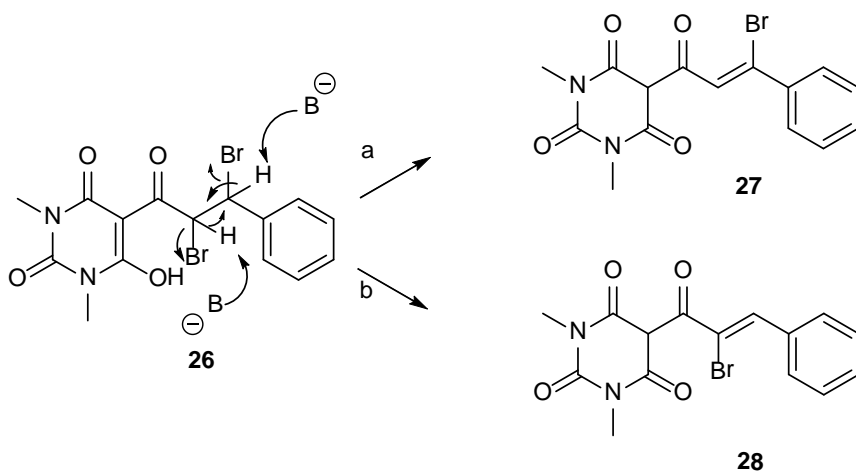


Figure 12. Compound 26.

Because of success cyclisation by using I_2 , it was decided to cyclize compound **26** via nucleophilic substitution^[44].

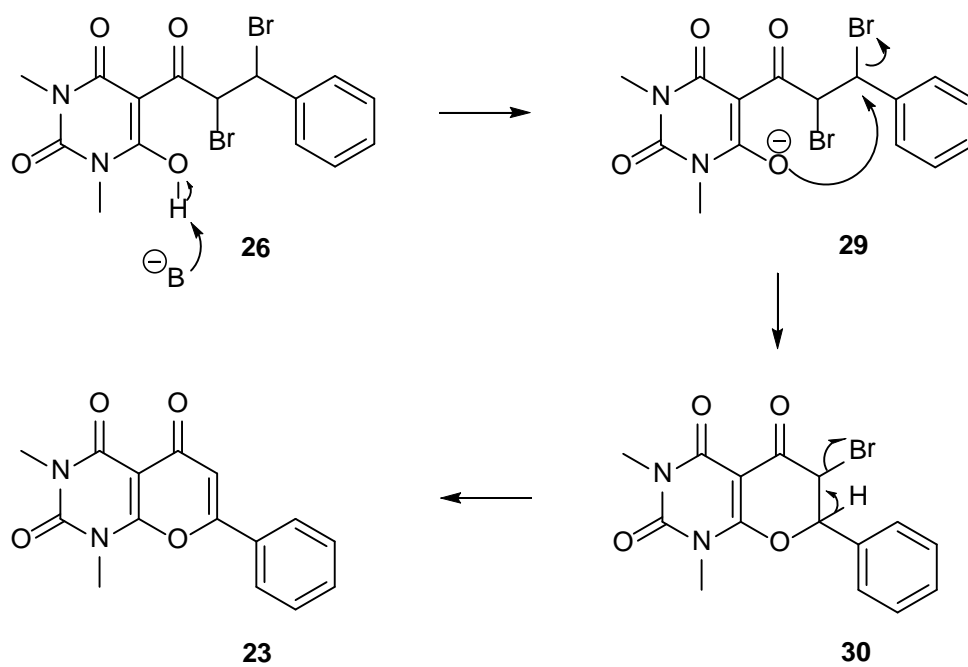
In order to cyclize compound **26** it was heated to the melting point, at these conditions or refluxing in THF compound **26** lost both bromines and gave the unsaturated compound. Heat is not a common way for dehalogenation. Dehalogenation is usually done using Zn dust or NaI.

Using slightly milder conditions, benzene and pyridine under reflux, a mixture of compounds **27** or **28** were obtained. The explanation for dehalogenation can be a very acidic proton on one of carbons that are situated close to Br.



Scheme 10. Mechanism for dehydrohalogenation.

Cyclisation of a compound **26** works well under reflux with TEA. From 1H NMR it was found out that the cyclized product contained TEA, which was not possible to remove by washing or heating. Proposed mechanism for cyclization is in Scheme 11.



Scheme 11. Cyclisation with triethylamine.

3.3. Cyclisation of compound 31

The new starting material (compound **31**) with electron donating group on aromatic ring was chosen in order to investigate how it can effect bromination of the double bond and ring closing.

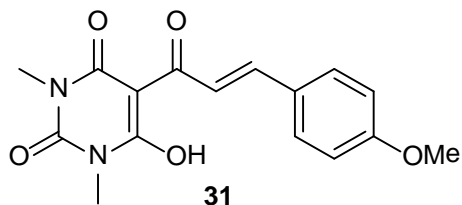


Figure 13. Compound 31.

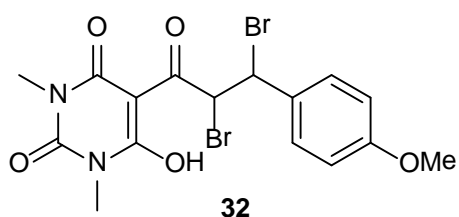


Figure 14. Compound 32.

Bromination of a double bond went very fast at room temperature in DCM or chloroform giving over 96% yield, but when it was left in chloroform under reflux for 18 hours, cyclisation product (Figure 15) with three bromines on it was produced.

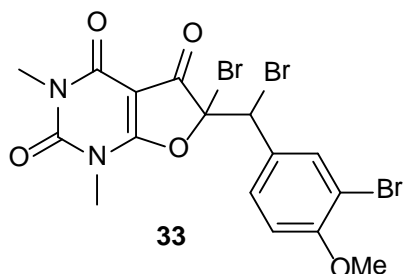


Figure 15. Compound 33

To further investigate this reaction, *p*-methoxycinnamic acid (Figure 16) was reacted under the same conditions. This compound was chosen since it is the simplest commercial available compound that contains similar functional groups as compound **31**.

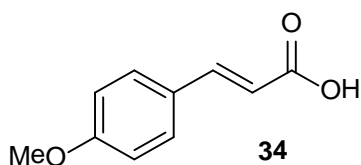


Figure16. *p*-methoxycinnamic acid.

From the ^1H NMR spectrum (Figure 17) can be seen, that the major compound after reaction is the tribromo compound. Doublet at 7.92 ppm, double doublet at 7.64 ppm and doublet at 7.09 ppm are protons from the aromatic ring on carbons 3, 4 and 6 of brominated compound. Two doublets from p-methoxycinnamic acid double bond moved from 7.75 ppm, 6.33 ppm to 5.56 ppm and 5.37 ppm. This proves that it is possible to make bromination of double bond and electrophilic aromatic substitution under these conditions.

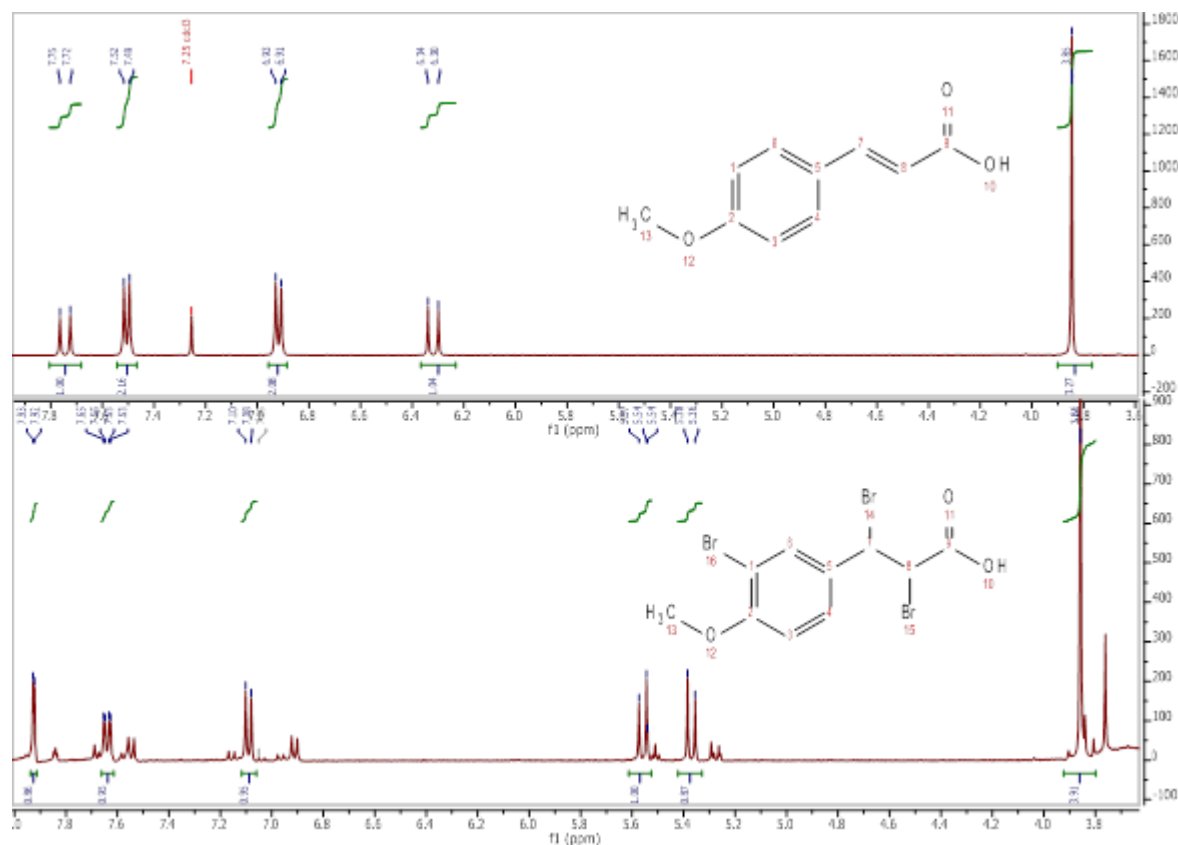


Figure 17. ^1H NMR spectrum.

There are two possible mechanisms for obtaining the final product. The first possible mechanism can be explained as bromination of the double bond on compound **31**. The second step can be spontaneous cyclisation that forms flavonoid **35**. The final step could be bromination of double bond on compound **35** or **36** and addition of bromine on the aromatic ring. Final product can be the compound **37** or **38**. This method is less likely because of the compound **35** or **36** bromination of double bonds in a separate step did not occur.

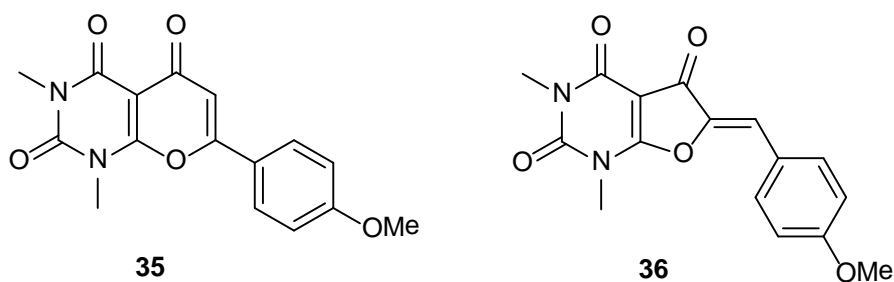


Figure 18. Compounds 35 and 36.

The second possible mechanism for this reaction could be explained as bromination of a double bond **31** and cyclization followed by substitution of bromine on an aromatic ring. The second mechanism is more likely, because in separate steps it is possible to produce only bromination of double bond, but not substitution on aromatic ring. Non cyclized tri bromo compound was not obtained.

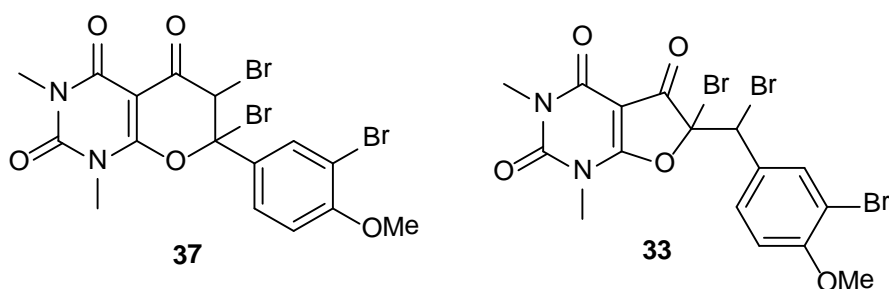


Figure 19. Compounds 37 and 38.

New compounds could be a five **38** or six **37** membered ring flavonoid. Because of the same molecular weight and similar ^1H NMR or ^{13}C NMR shifts it is difficult to tell which isomer is formed. To find out which ring had formed there was a need to run a gHMBC. This experiment allowed us to identify coupling between proton nuclei with carbon nuclei that are separated by more than one bond. From Figure 20 it can be seen that there is a correlation between a proton peak 6.2 ppm and carbon 68 ppm, 126 ppm, 131 ppm, 134 ppm, 168 ppm and 175 ppm peaks.

Because of correlation between proton 6.2 ppm and two carbons that are two or three bonds away can be assumed that the new compound is five membered ring compounds.

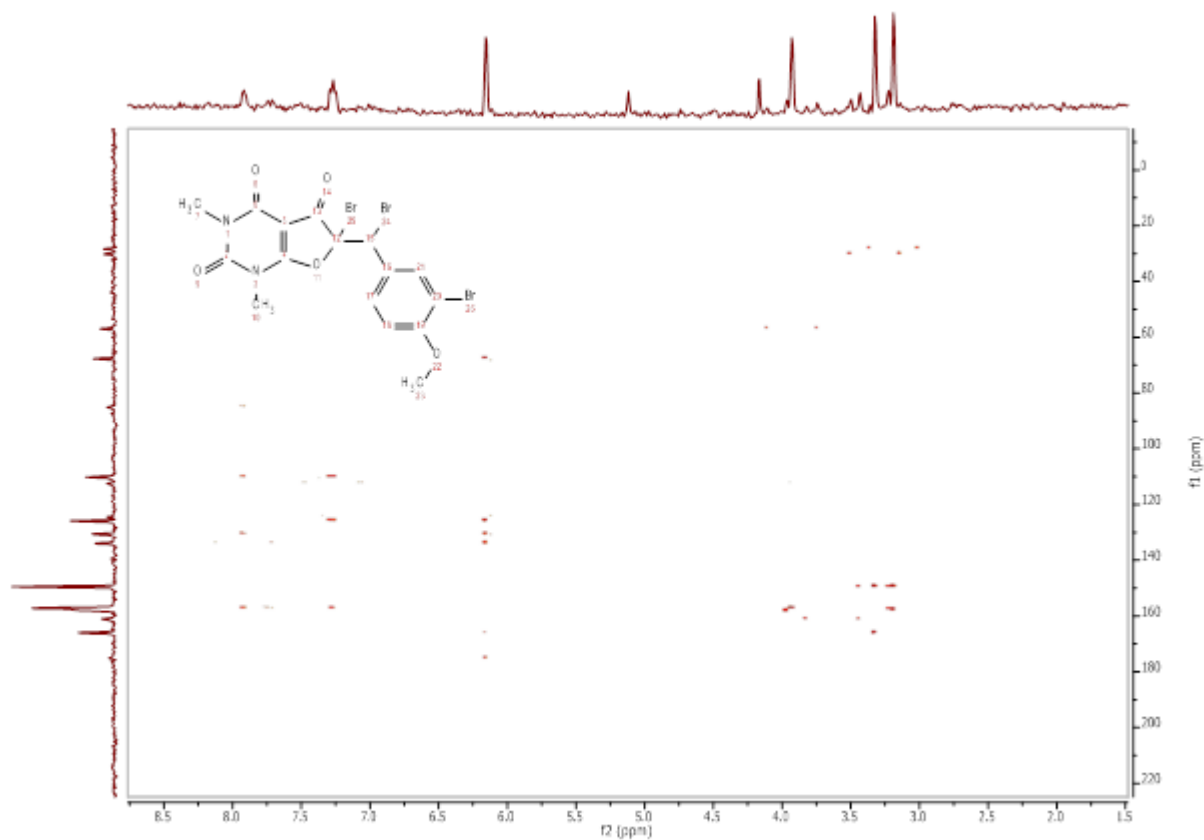
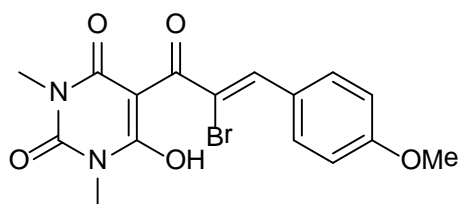


Figure 20 gHMBC correlations between proton and carbon

Compound **31** behaved the same way as compound **11** under the same conditions using pyridine or TEA as base. The loss of one bromine appeared (Figure 21).



39

Figure 21. Compound **39**.

3.4. Cyclisation of the compound 40

Because of unexpected results with electron donating group on aromatic ring, it was decided to make a bromination of double bond and cyclization using compound **40** with electron withdrawing group on an aromatic ring as starting material.

Bromination of the double bond of compound **40** did not take a place in DCM at room temperature or under reflux. It was possible only in chloroform under reflux for 17-18 hours. Yield of bromination was 65-75%.

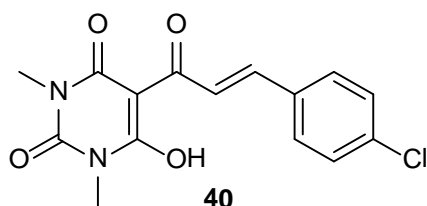
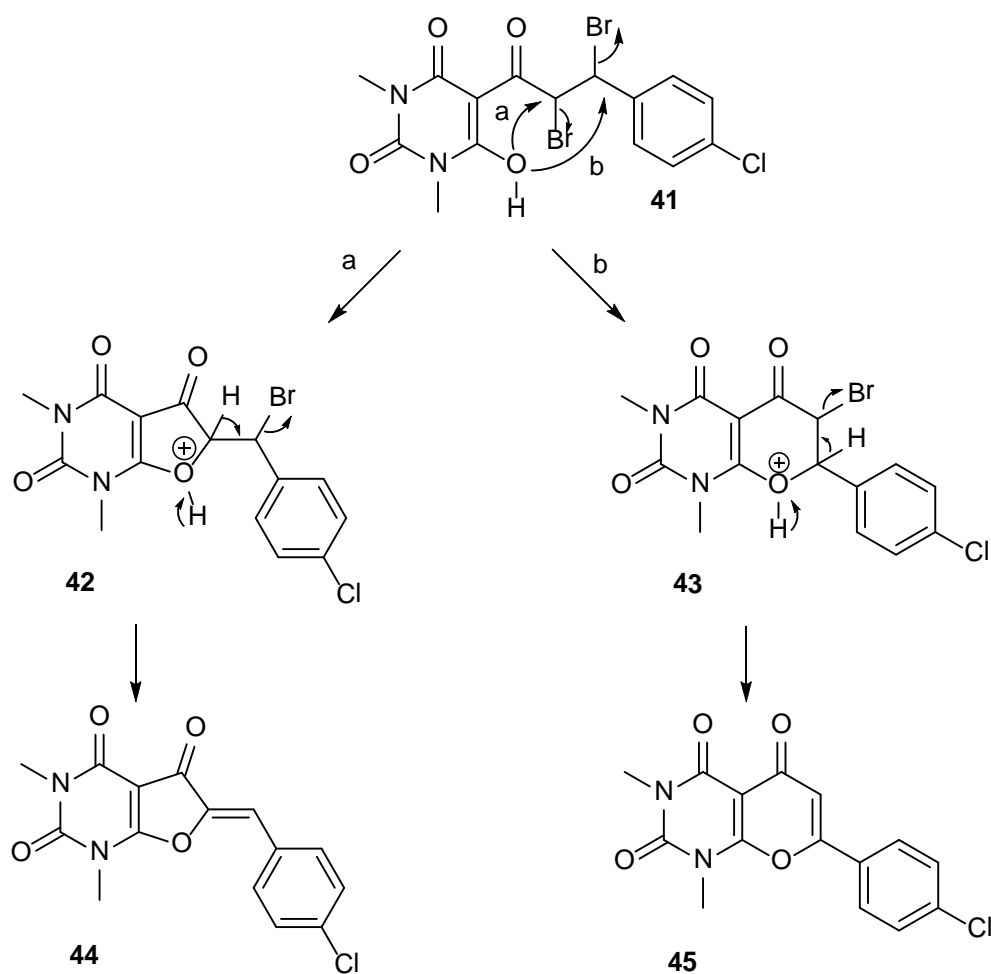


Figure 22. Compound 40.

Cyclisation (Scheme 12) was possible in benzene by using TEA as base, but after cyclisation it still contained TEA, which was not possible to remove by washing or heating. Ring closing with even better yield, up to 75%, was obtained by changing TEA to pyridine. Pyridine was successfully removed by heating to 110 °C.



Scheme 12. Mechanism for ring closing compound 41.

From Scheme 12 it can be seen, that there is a possibility to form two isomers and ^1H NMR experiment confirmed this theory. From Figure 23 can be seen two pairs of doublets. One pair of doublet 7.99 ppm and 7.64 ppm belongs to the aromatic ring of one of the isomers and 7.58 ppm and 7.92 ppm to another isomer. Amount of formed isomers are not equal, but it is difficult to say which isomer is favored.

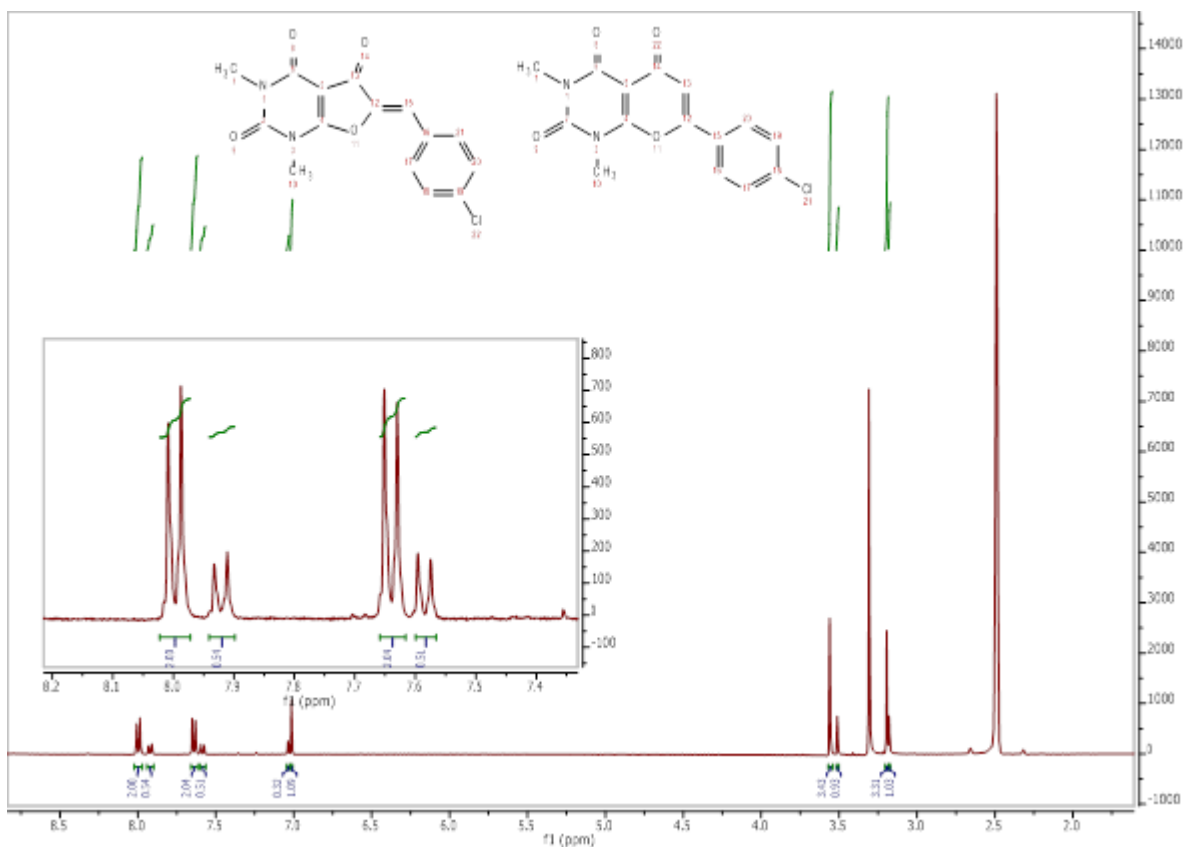


Figure 23. ^1H NMR spectra of isomers 37 and 39.

From the gHMBC NMR spectra (Figure 24) can be seen which the major isomer of the reaction was. The proton at 7.01 ppm which could be the proton on the double bond has a correlation with carbons at 98 ppm, 129 ppm, 168 ppm, 171 ppm. Correlation between a proton of a double bond with only one carbon atom of an aromatic ring suggests that the major isomer may be a six member ring compound.

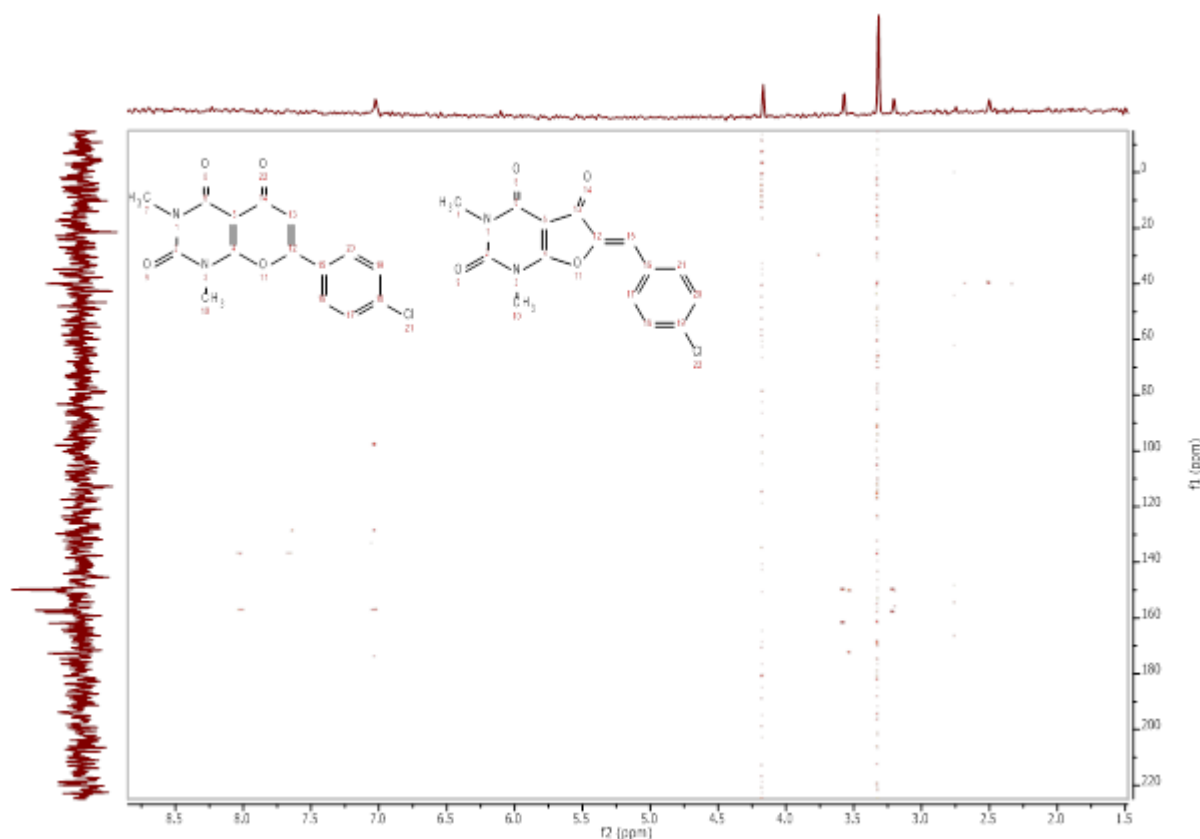


Figure 24. gHMBC NMR spectrum.

Because of bad solubility it was difficult to obtain good spectra, so these two structural isomers were difficult to distinguish.

The control of five or six membered ring formation was not successful. Changing solvent or temperature mostly affected the yield, but not which compound was formed.

3.5. Cyclisation of compound 46

In order to investigate all main substitution variations the last compound that was chosen for testing was with strong electron withdrawing group (Figure 25).

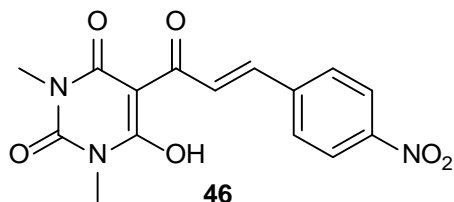


Figure 25. Compound 46.

Bromination was possible only in chloroform under reflux for 17-18 hours and the yield of brominated compound was 75-85%.

Cyclisation resulted in a mixture of compounds **47** and **48** (Figure 26) with yield 71-80%

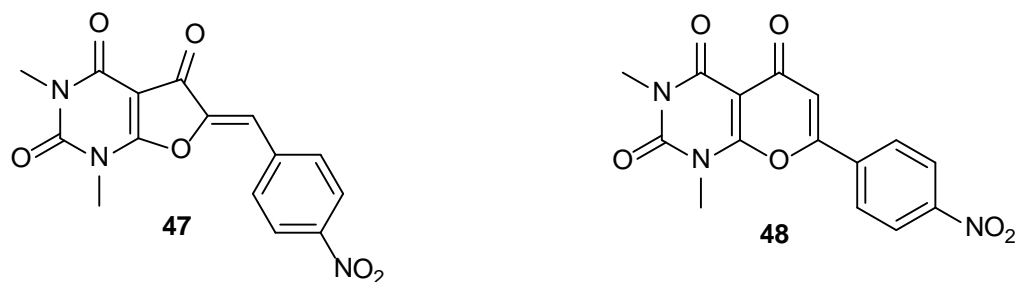


Figure 26. Target compounds **47** and **48**.

^1H NMR spectrum (Figure 27) of target compounds **47** and **48** showed that the isomers exist in a ratio about 1:1. It means that nucleophilic substitution occurs almost equally on both electrophilic sides.

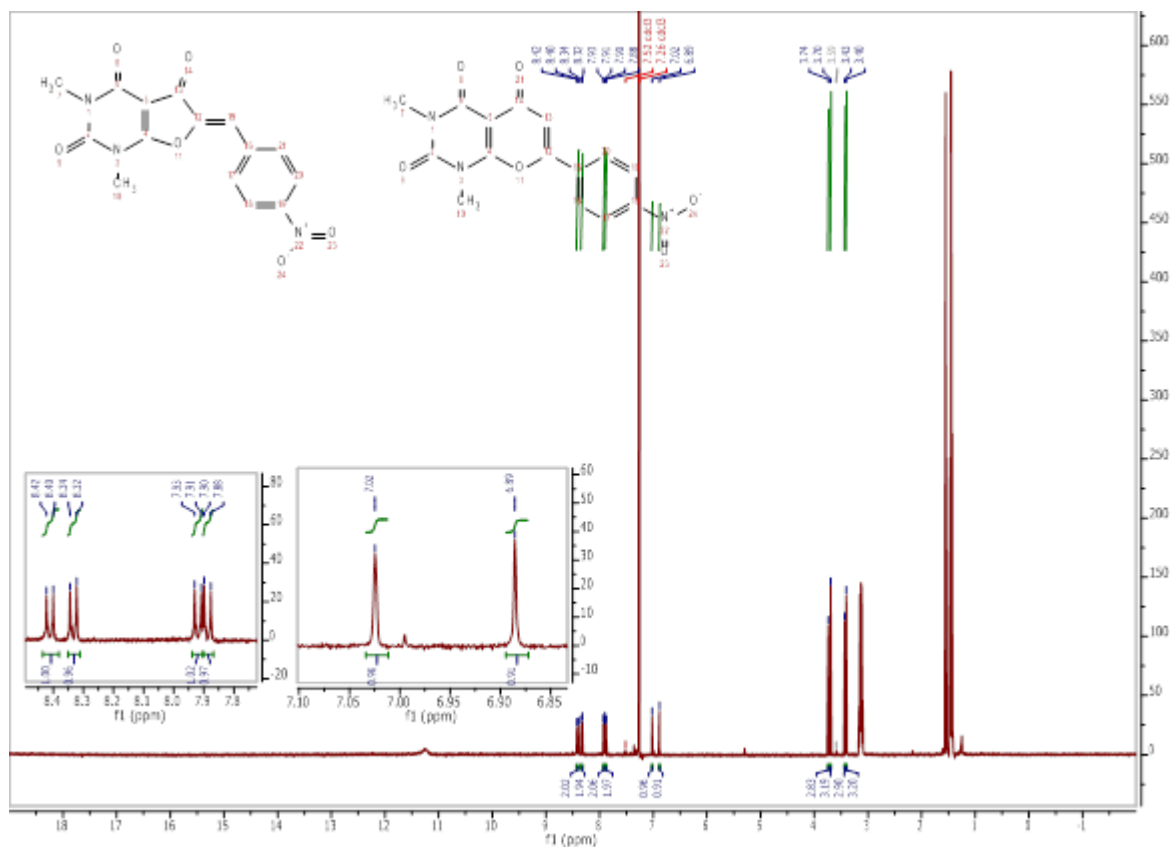


Figure 27. ^1H NMR spectra of **47** and **48** isomers.

Attempts to regulate the electrophilicity by changing temperature, base or solvents was not successful.

In general for all chalcones, which were tried to cyclize **11**, **31**, **40**, **46**, the substituent on the aromatic ring had greatest effect for double bond halogenation. Electron density was

changing in all conjugated chains, depending what kind of substituent Y (EWG or EDG) was on the aromatic ring (Figure 28).

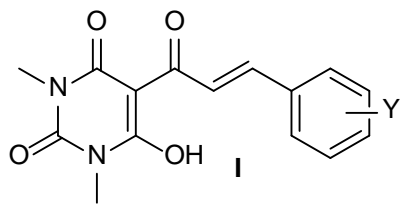


Figure 28. Chemical structure of starting chalcones.

From data in a Table 1 can be seen how substituent on the aromatic ring affect the yield of bromination of double bond. The results vary from very fast bromination at room temperature or even ring closing at high temperature of compounds with an electron donating group to a very slow and only in high temperature bromination of the compounds with an electron withdrawing group (Figure 29).

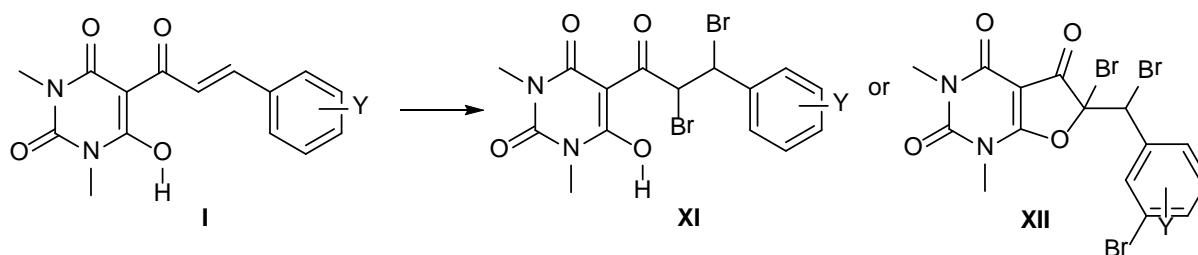
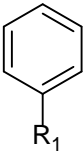
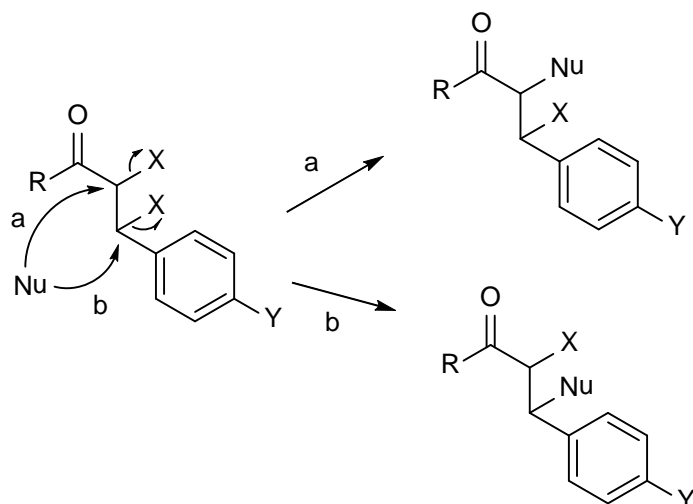


Figure 29. Compound 3 bromination products.

Table 1. Results of bromination of double bond with different substituent on aromatic ring.

	Solvent							
	CCl ₂ H ₂				CCl ₃ H			
	Room temp.		Reflux		Room temp.		Reflux	
	Product	Yield	Product	Yield	Product	Yield	Product	Yield
-H	XII	>96%	XII	>96%	XII	>96%	XII	>96%
-OMe	XII	>96%	XI	84%	XII	>96%	XI	89%
	No		No		No			
-Cl	reaction	-	reaction	-	reaction	-	XII	75%
	No		No		No			
-NO ₂	reaction	-	reaction	-	reaction	-	XII	81%

Depending on substituent (EWG or EDG) nucleophilic substitution can occur by pathway **a** or **b**. (Scheme 13) If the reaction goes according to pathway **a**, it forms a five membered ring, if by pathway **b**, six membered ring. That suggests that substituent **Y** on the aromatic ring has an influence on the electrophilicity of a compound and it has an also effect on the yield of the reaction.



Scheme 13. Principal scheme of nucleophile attack place.

As it can be seen from Table 2, it is hard or even impossible to make cyclization with electron donating group and the yields are higher it using an electron withdrawing groups as a **Y** substituent.

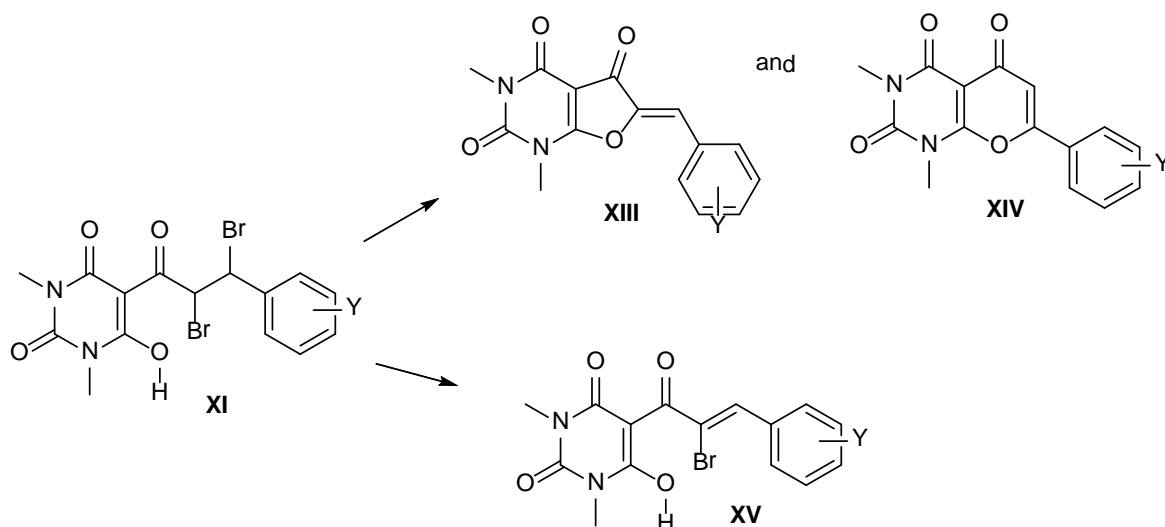
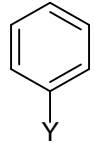


Figure 30. Cyclization products.

Table 2. Results for the ring closing synthesis.

	Base			
	Et ₃ N		Pyridine	
	Product	Yield	Product	Yield
-H	XI	40%	XII	65-75%
-OMe	XII	30%	XII	60-71%
-Cl	X and XI	45-70%	X and XI	75%
-NO ₂	X and XI	45-70%	X and XI	70-81%

From Table 3 can be seen how substituents on the aromatic ring affect five or six membered ring formation. Reactions with unsubstituted aromatic ring led to six membered ring formation. With strong electron withdrawing group more five membered ring was formed. Five membered ring formation with electron donating group was an exception, because ring closing was following a different mechanism and under different conditions.

Table 3. Ratio of 5/6 membered ring formation.

	Substitution on the aromatic ring			
	-OMe	-H	-Cl	-NO ₂
5 membered ring	100%	-	20%	50%
6 membered ring	-	100%	80%	50%

4. Conclusions and future outlook

Reactivity of double bond of chalconoids was investigated in bromination on double bond with different substituents on aromatic ring. In addition to that, the conditions for cyclisation for chalconoids were examined by changing the substituents on the aromatic ring of chalconoids.

Fourteen new compounds were synthesized from chalcones and seven of them are flavonoids derivatives.

These methods for flavonoids synthesis offer several advantages including good yield, simple workup procedure, cheap chemicals and fast result. Only few steps were needed for the synthesis of new flavonoids. The reaction condition did not require any sophisticated equipment.

Main disadvantage of this method was that it was difficult to control five or six member ring formation and in most of the cases, the result was a mixture of two isomers.

Because of bad solubility these structural isomers were almost impossible to distinguish by NMR. It was also difficult to separate compounds.

One of the opportunities to control five or six member ring formation can be different mechanism or conditions for ring closing.

It would be interesting to make triple bond from double bond. For the future outlook one of the attempts could be gold catalysis^[45, 46] for making electrophilic part more efficient.

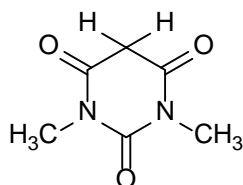
5. Experimental section

Solvent and reagents were purchased from Sigma-Aldrich, Fluka, Acros, Kenetics, SAFC and Merck. All reagents and solvents were used without further purification. Reactions were monitored by ^1H NMR spectra or silica gel plate 60 F₂₅₄.

All new compounds were identified by: ^1H NMR and ^{13}C NMR spectra were recorded by a Varian Mercury400 plus (399.65/100.54 Mhz) at room temperature. Noteworthy data was reported in chemical shifts (δ) in part per million (ppm), relative to TMS ($\delta = 0.000$ ppm) as an internal standard. Coupling constant (J) was measured Hertz (Hz). Multiplicity was reported in following order: s, singlet, d, doublet; dd, double doublet; t, triplet; m, multiplet). IR spectra were recorded on a Varian 7000e FT-IR spectrometer. Mass spectra were recorded on a Thermo electron LTQ Orbital positive and negative Electron Ion Source.

5.1. Synthesis of starting materials

Synthesis of 1,3-dimethylbarbituric acid

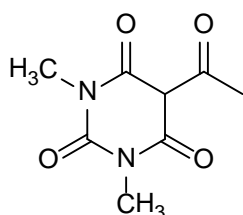


49

Figure 31. Compound 49.

Dimethylurea (7,5 g, 85 mmol; 1 eq) and malonic acid (9,7 g, 93 mmol; 1,1 eq) were mixed in an flask and acetic anhydride (16 ml) was added. The mixture slowly heated to 90 °C. When the exothermic reaction starts heating was stopped immediately, reaction temperature raised 130°C. The solution was heated to 130°C one more time and cooled to room temperature. Isopropanol was added to the solution causing a white precipitate to appear. The white precipitate was filtered and dried at room temperature.

Synthesis of 5-acetyl-1,3-dimethylbarbituric acid



50

Figure 32. Compound 50.

Compound 49 (15,25 g; 100 mmol; 1 eq) was suspended in a small amount of water and NaHCO₃ (8,2 g; 100 mmol; 1 eq) was added as a concentrated water solution. The insoluble part was filtered off and acetic anhydride (18,48 ml; 200 mmol; 2 eq) was added to the stirred solution. The reaction mixture stirred was overnight and a white precipitate formed. Precipitate was filtered, washed with H₂O and dissolved in 10% NH₄OH. 3M HCl was added

to the solution until pH 7. The white precipitate was filtered off and washed with H₂O and dried at room temperature.

General procedure for synthesis of chalconoids

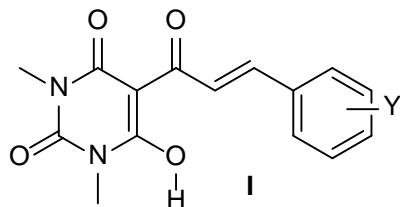


Figure 33. Chalconoids.

5-acetyl-1,3-dimethylbarbituric acid 1 eq. was mixed with 2 eq. of chosen benzaldehyde. The mixture was heated in an oil bath for two minutes kept at 170°C. A catalytic amount of piperidine was added and the mixture was allowed to cool to room temperature. Ethanol was added to the solution and heated to boiling temperature. The solution was allowed to cool to room temperature. Precipitate filtered off and dried at room temperature.

5.2. Bromination of chalcones

Synthesis of 5-(2,3-dibromo-3-phenylpropanoyl)-6-hydroxy-1,3-dimethylpyrimidine-2,4(1H,3H)-dione **26**

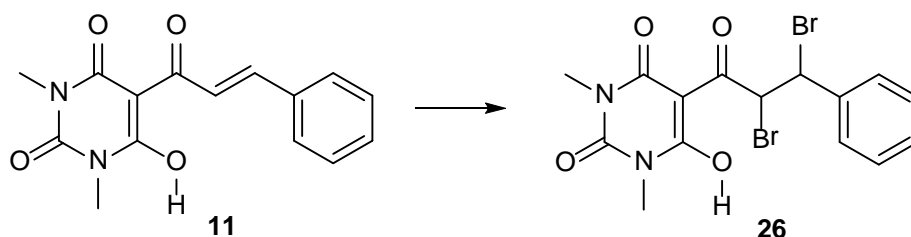


Figure 34. Bromination of double bond of compound 11.

Compound **11** (286 mg; 100 mmol, 1 eq) was dissolved in 4ml of dichloromethane. Bromine (103 mg; 200 mmol; 2 eq) was added to the solution. The mixture was stirred at room temperature for 20 minutes and the solvent was evaporated.

High-resolution mass spectroscopy (ESI): (M)⁻ calculated 445,0907 for C₁₅H₁₃Br₂N₂O₄ found 445,000.

^1H NMR (400 MHz, Chloroform- d) δ 18.15 (s, 1H), 7.52 (dd, J = 8.0, 1.6 Hz, 2H), 7.46 – 7.35 (m, 3H), 7.21 (d, J = 11.7 Hz, 1H), 5.53 (d, J = 11.7 Hz, 1H), 3.45 (s, 3H), 3.42 (s, 3H).
 ^{13}C NMR (101 MHz, Chloroform- d) δ 190.31, 170.19, 160.35, 149.68, 137.76, 129.44, 128.92, 128.26, 94.28, 49.38, 46.45, 28.37.
 IR: 3048, 1728, 1659, 1505, 1451, 1367, 1335, 1277, 1222, 1145, 1058, 1007, 905, 843, 800, 795, 639 cm^{-1} .

Synthesis of 5-(2,3-dibromo-3-(4-methoxyphenyl)propanoyl)-6-hydroxy-1,3-dimethylpyrimidine-2,4(1H,3H)-dione **32**

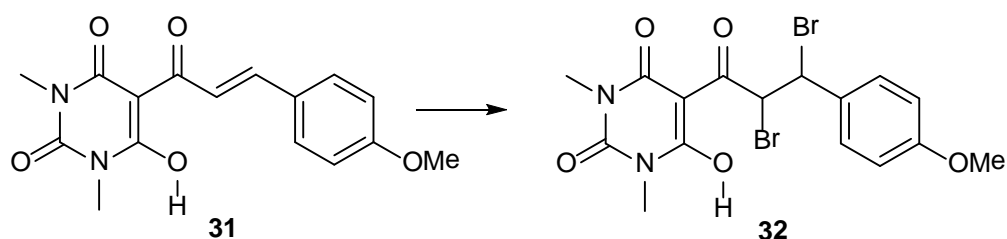


Figure 35. Bromination of double bond of compound **31**.

Compound **31** (316 mg; 100 mmol, 1 eq) was dissolved in dichloromethane 6 ml. Bromine (103 mg; 200 mmol; 2 eq) was added to the solution. The mixture was stirred at room temperature for 20 minutes and the solvent was evaporated.

High-resolution mass spectroscopy (ESI): $(\text{M}+\text{H})^+$ calculated 474.9426 for $\text{C}_{16}\text{H}_{17}\text{Br}_2\text{N}_2\text{O}_4$ found 474.9327 (80%).

^1H NMR (400 MHz, Chloroform- d) δ 18.12 (s, 1H), 7.44 (d, J = 8.7 Hz, 3H), 7.19 (dd, J = 11.8, 1.0 Hz, 2H), 6.92 (d, J = 8.8 Hz, 3H), 5.54 (d, J = 11.7 Hz, 2H), 3.83 (s, 6H), 3.44 (s, 6H), 3.41 (s, 6H).

^{13}C NMR (101 MHz, Chloroform- d) δ 190.38, 170.18, 160.32, 149.69, 129.67, 129.02, 114.28, 94.24, 55.34, 49.83, 46.73, 28.32.

IR: 3043, 2443, 2286, 1728, 1660, 1608, 1557, 1501, 1450, 1367, 1308, 1255, 1220, 1178, 1142, 1061, 1033, 955, 907, 834, 802, 754, 730, 644 cm^{-1} .

Synthesis of 5-(2,3-dibromo-3-(4-chlorophenyl)propanoyl)-6-hydroxy-1,3-dimethylpyrimidine-2,4(1H,3H)-dione **41**

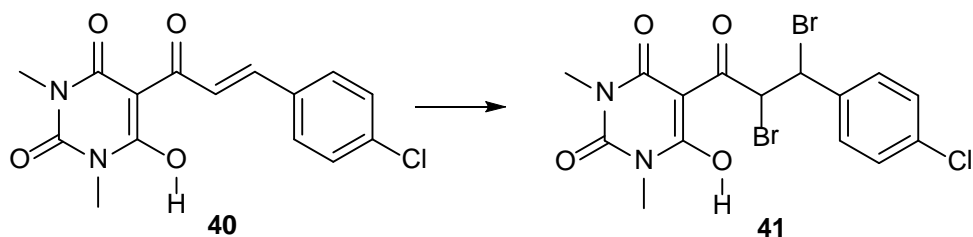


Figure 36. Bromination of double bond of compound **40**.

Compound **40** (320 mg; 100 mmol, 1 eq) was dissolved in dichloromethane (4 ml). Bromine (103 mg; 200 mmol; 2 eq) was added to the solution. The mixture was heated under reflux for 17 hours and the solvent was evaporated. The solid product was purified by silica gel column chromatography (dichloromethane / EtOAc 5:1).

High-resolution mass spectroscopy (ESI): $(M+H)^+$ calculated 478.8931 for $C_{15}H_{13}Br_2ClN_2O_4$ found 478.8824 (100%),

1H NMR (400 MHz, Chloroform- d) δ 18.13 (s, 1H), 7.44 (dd, $J = 8.6, 1.8$ Hz, 2H), 7.38 (dd, $J = 8.6, 1.8$ Hz, 2H), 7.14 (dd, $J = 11.7, 1.7$ Hz, 1H), 5.49 (d, $J = 11.7, 1.9$ Hz, 1H), 3.44 (d, $J = 1.7$ Hz, 3H), 3.41 (d, $J = 1.6$ Hz, 3H).

^{13}C NMR (101 MHz, Chloroform- d) δ 190.04, 170.18, 160.34, 149.61, 136.37, 135.28, 130.61, 129.59, 129.17, 128.51, 94.25, 48.27, 46.23, 28.37.

IR: 2677, 2362, 2337, 2157, 2172, 1974, 1728, 1662, 1506, 1364, 1219, 1093, 1016, 800, 755, 679 cm^{-1} .

Synthesis of 5-(2,3-dibromo-3-(4-nitrophenyl)propanoyl)-6-hydroxy-1,3-dimethylpyrimidine-2,4(1H,3H)-dione **51**

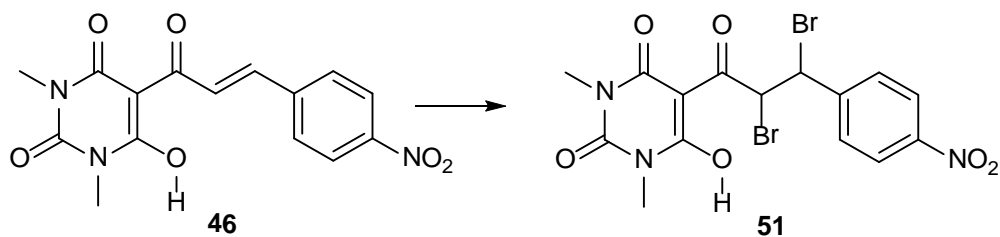


Figure 37. Bromination of double bond of compound **46**.

Compound **46** (331 mg; 100 μ mol, 1 eq) was dissolved in dichloromethane (7 ml). Bromine (103 mg; 200 μ mol; 2 eq) was added to the solution. The mixture was under reflux for 17 hours. The reaction was monitored by TLC and $^1\text{H NMR}$. The solvent was evaporated.

High-resolution mass spectroscopy (ESI): $(\text{M}+\text{Na})^+$ Calculated for $\text{C}_{15}\text{H}_{13}\text{Br}_2\text{N}_3\text{O}_6$ 513,9982, found 513,8912 (100%).

$^1\text{H NMR}$ (400 MHz, Chloroform- d) δ 18.16 (s, 1H), 8.27 (dd, $J = 8.8, 2.2$ Hz, 2H), 7.68 (dd, $J = 8.9, 2.2$ Hz, 2H), 7.26 (d, $J = 2.3$ Hz, 0H), 7.16 (dd, $J = 11.7, 2.3$ Hz, 1H), 5.56 (dd, $J = 11.8, 2.2$ Hz, 1H), 3.45 (d, $J = 2.2$ Hz, 3H), 3.41 (d, $J = 2.3$ Hz, 3H).

$^{13}\text{C NMR}$ (101 MHz, Chloroform- d) δ 189.59, 179.45, 179.08, 170.20, 160.32, 149.5, 148.20, 144.71, 129.34, 124.17, 94.28, 76.68, 46.79, 45.63, 28.42.

IR: 3040, 2454, 2286, 1728, 1659, 1567, 1523, 1444, 1375, 1200, 1198, 1654, 1005, 908, 860, 830, 800, 756, 717, 695, 641 cm^{-1} .

5.3. Synthesis of mono bromo compounds chalconoids

Synthesis of (Z)-5-(3-bromo-3-(4-methoxyphenyl)acryloyl)-1,3-dimethylpyrimidine-2,4,6(1H,3H,5H)-trione **39**

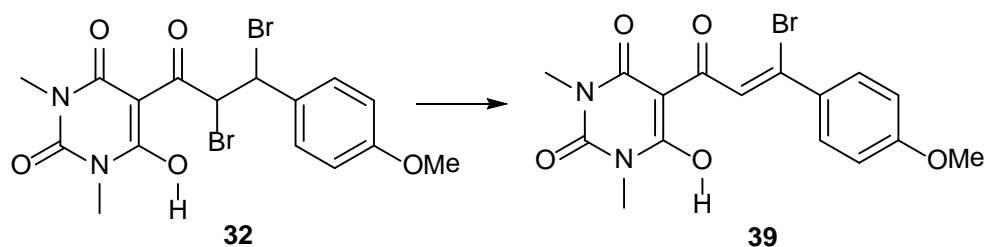


Figure 38. Compounds **32** and **39**.

Compound **32** (236mg, 1 eq, 0.5 mmol) was dissolved in benzene (5 ml). Pyridine (40 mg, 1 eq, 0.5mmol) was added to solution and left for one hour under reflux. Precipitate was filtered off and washed with benzene. The solid product **39** was left for drying at room temperature.

High-resolution mass spectroscopy (ESI): $(\text{M}+\text{H})^+$ Calculated for $\text{C}_{16}\text{H}_{15}\text{BrN}_2\text{O}_5$ 395.0164, found 395.0236 (45%). $(\text{M}+\text{Na})^+$ calculated 417,0651 for $\text{C}_{15}\text{H}_{13}\text{Br}_2\text{ClN}_2\text{O}_4$ found 417.0052 (100%).

^1H NMR (400 MHz, Chloroform- d) δ 7.41 (d, J = 8.6 Hz, 2H), 7.04 – 6.94 (m, 2H), 5.91 (s, 1H), 4.47 (s, 1H), 3.85 (s, 3H), 3.56 (s, 3H), 3.36 (s, 3H)..

^{13}C NMR (101 MHz, cdCl_3) δ 172.73, 145.90, 141.04, 128.31, 127.44, 127.06, 114.21, 97.01, 82.23, 77.31, 77.00, 76.68, 55.38, 50.72, 29.80, 28.14.

IR: 3082, 1732, 1680, 1624, 1603, 1485, 1430, 1365, 1310, 1252, 1182, 1129, 1050, 1024, 911, 840, 791, 748, 660 cm^{-1} .

5.4 Synthesis of flavonoids

Synthesis of 6-bromo-6-(bromo(3-bromo-4-methoxyphenyl)methyl)-1,3-dimethylfuro[2,3- d]pyrimidine-2,4,5(1H,3H,6H)-trione **33**.

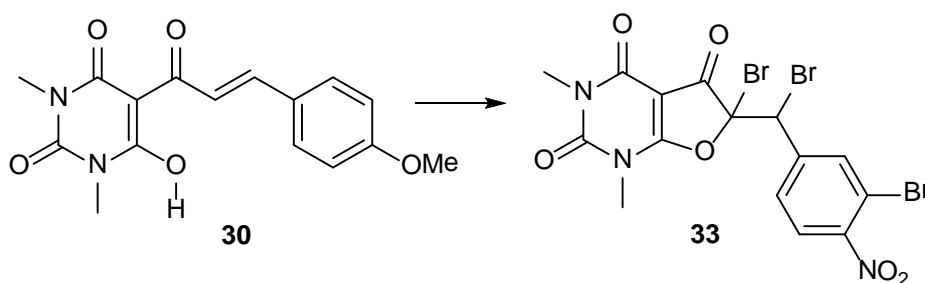


Figure 39. Ring closing of compound **30**.

Compound **30** (316mg; 100mmol, 1eq) was dissolved in chloroform (4ml). Bromine (103 mg; 200mmol; 2eq) was added to the solution and left for 17 hours under reflux. Precipitate was filtered and washed with chloroform and dried in room temperature.

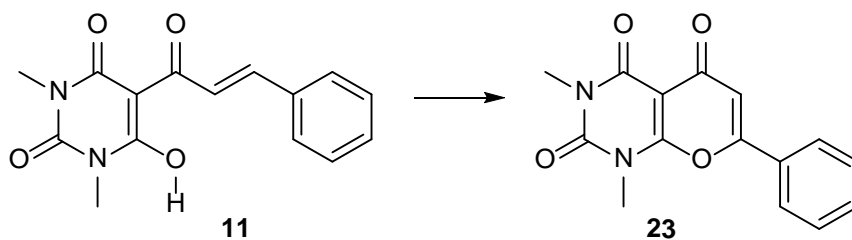
High-resolution mass spectroscopy (ESI): $(\text{M}+\text{Na})^+$ calculated 572,8319 for $\text{C}_{16}\text{H}_{13}\text{Br}_3\text{ClN}_2\text{O}_5$ found 572.8274 (50%).

^1H NMR (400 MHz, DMSO- d_6) δ 7.91 (d, J = 2.2 Hz, 1H), 7.73 (dd, J = 8.6, 2.2 Hz, 1H), 7.26 (d, J = 8.7 Hz, 1H), 6.14 (s, 1H), 3.92 (s, 3H), 3.31 (d, J = 2.9 Hz, 3H), 3.18 (s, 3H).

^{13}C NMR (101 MHz, Chloroform- d) δ 172.73, 145.90, 141.04, 128.31, 127.44, 127.06, 114.21, 82.23, 76.68, 55.37, 50.72, 29.80, 28.14.

IR: 3070, 2952, 2394, 2285, 1735, 1688, 1646, 1583, 1480, 1432, 1402, 1367, 1266, 1196, 1057, 1009, 985, 916, 887, 841, 805, 773, 754, 722, 676, 643 cm^{-1} .

Cyclization of 23. (Z)-1,3-dimethyl-6-(4-nitrobenzylidene)furo[2,3-d]pyrimidine-2,4,5(1H,3H,6H)-trione



Compound **11** (284 mg; 100 mmol, 1 eq) was dissolved in 4ml of DCM. A catalytic amount of iodide (10 mg) was added to the solution and left for 17 hours under reflux and concentrated in vacuo. The solid product was purified by silica gel column chromatography (dichloromethane/ EtOAc 5:1)

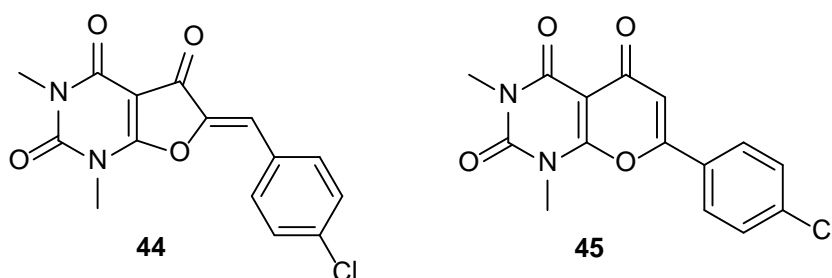
High-resolution mass spectroscopy (ESI): (M+H)⁺ calculated 285.0797 for C₁₅H₁₂N₂O₄ found 258.0875 (100%). (M+Na)⁺ calculated 307.0689, found 307.0695 (9%).

¹H NMR (400 MHz, Chloroform-d) δ 7.72 (dd, *J* = 7.4, 2.3 Hz, 2H), 7.47 (dd, *J* = 5.2, 2.1 Hz, 3H), 6.98 (s, 1H), 3.67 (s, 3H), 3.37 (s, 3H).

¹³C NMR (101 MHz, cdcl₃) δ 170.86, 133.48, 130.10, 130.00, 129.76, 128.49, 128.27, 40.63, 40.40, 24.94.

IR: 3086, 2924, 2737, 2675, 2432, 2260, 1720, 1675, 1618, 1582, 1530, 1485, 1459, 1429, 1363, 1252, 1191, 1160, 1126, 1066, 1011, 950, 886, 787, 747, 694 cm⁻¹.

Synthesis of (Z)-1,3-dimethyl-6-(4-nitrobenzylidene)furo[2,3-d]pyrimidine-2,4,5(1H,3H,6H)-trione and 1,3-dimethyl-7-(4-nitrophenyl)-1H-pyrano[2,3-d]pyrimidine-2,4,5(3H)-trione (44** and **45**).**



Compound **41** (318mg; 100mmol, 1eq) was dissolved in benzene (4ml). Pyridine (96mg; 120mmol; 1,2eq) was added to the solution and left for 17 hours under reflux. Precipitate was filtered and washed with benzene and dried at room temperature. The solid product was heated for 15 minutes at 110°C.

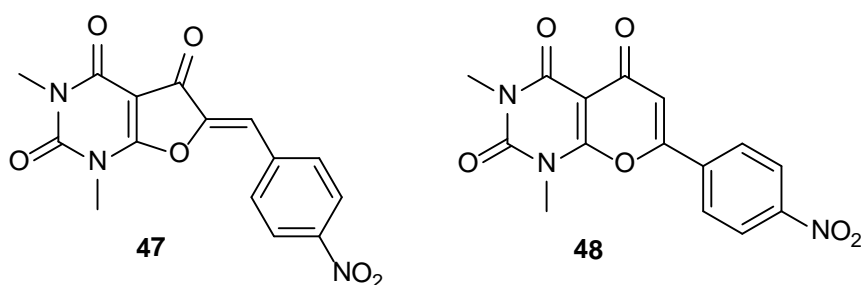
High-resolution mass spectroscopy (ESI): (M+H)⁺ calculated 319.7189 for C₁₅H₁₁ClN₂O₄ found 319.0486 (20%). (M+Na)⁺ calculated 341.7087, found 341.0301 (30%), (M+K)⁺ calculated 357,8169, found 357.0040 (5%).

¹H NMR (400 MHz, DMSO-d₆) δ 8.00 (7.94 – 7.88 (m, 2H), 7.64 (d, *J* = 8.6 Hz, 2H), 7.59 (d, *J* = 8.6 Hz, 1H), 7.04 (s, 1H), 7.01 (s, 2H), 3.56 (s, 3H), 3.51 (s, 1H), 3.19 (s, 3H), 3.18 (s, 1H).

¹³C NMR (101 MHz, dms) δ 174.57, 173.98, 161.86, 157.99, 149.76, 137.03, 133.44, 129.79, 128.87, 128.22, 111.59, 104.99, 97.99, 30.03, 28.15.

IR: 1677, 1619, 1422, 1375, 1289, 1237, 1184, 1114, 1031, 949, 901, 851, 786, 747, 688, 636 cm⁻¹.

Synthesis of 1,3-dimethyl-7-(4-nitrophenyl)-1H-pyrano[2,3-d]pyrimidine-2,4,5(3H)-trione and (Z)-1,3-dimethyl-6-(4-nitrobenzylidene)furo[2,3-d]pyrimidine-2,4,5(1H,3H,6H)-trione (47 and 48).



Compound **51** (329 mg; 100 mmol, 1 eq) was dissolved in benzene (5 ml). Pyridine (96 mg; 120 mmol; 1,2 eq) was added to the solution and left for 17 hours under reflux. Precipitate was filtered and washed with benzene and dried at room temperature. The solid product was heated for 15 minutes at 110°C.

High-resolution mass spectroscopy (ESI): (M+H)⁺ calculated 330.0773 for C₁₅H₁₁N₄O₅ found 330.0719 (45%). (M+Na)⁺ calculated 351.9762, found 352.0534 (100%).

^1H NMR (400 MHz, Chloroform- d) δ 8.41 (d, $J = 8.9$ Hz, 2H), 8.33 (d, $J = 8.9$ Hz, 2H), 7.92 (d, $J = 8.9$ Hz, 2H), 7.89 (d, $J = 8.9$ Hz, 2H), 7.02 (s, 1H), 6.89 (s, 1H), 3.74 (s, 3H), 3.70 (s, 3H), 3.43 (s, 3H), 3.40 (s, 3H).

^{13}C NMR (101 MHz, cdCl_3) δ 131.67, 126.56, 124.67, 124.31, 111.49, 104.98, 76.44, 45.99, 8.59.

IR: 3744, 2422, 2254, 1717, 1676, 1622, 1586, 1497, 1430, 1407, 1302, 1194, 1129, 1091, 1006, 885, 848, 787, 750 cm^{-1} .

6. Reference

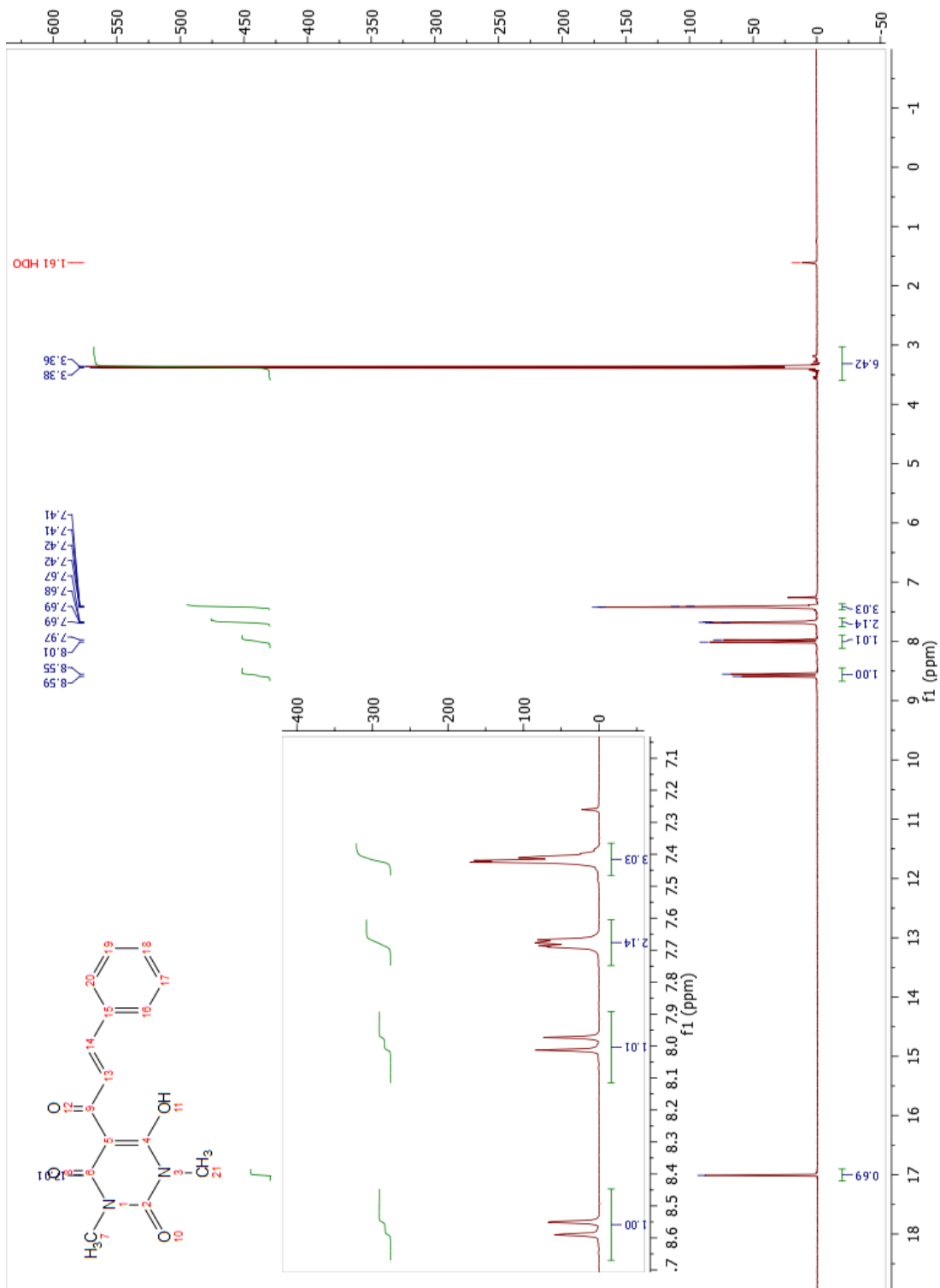
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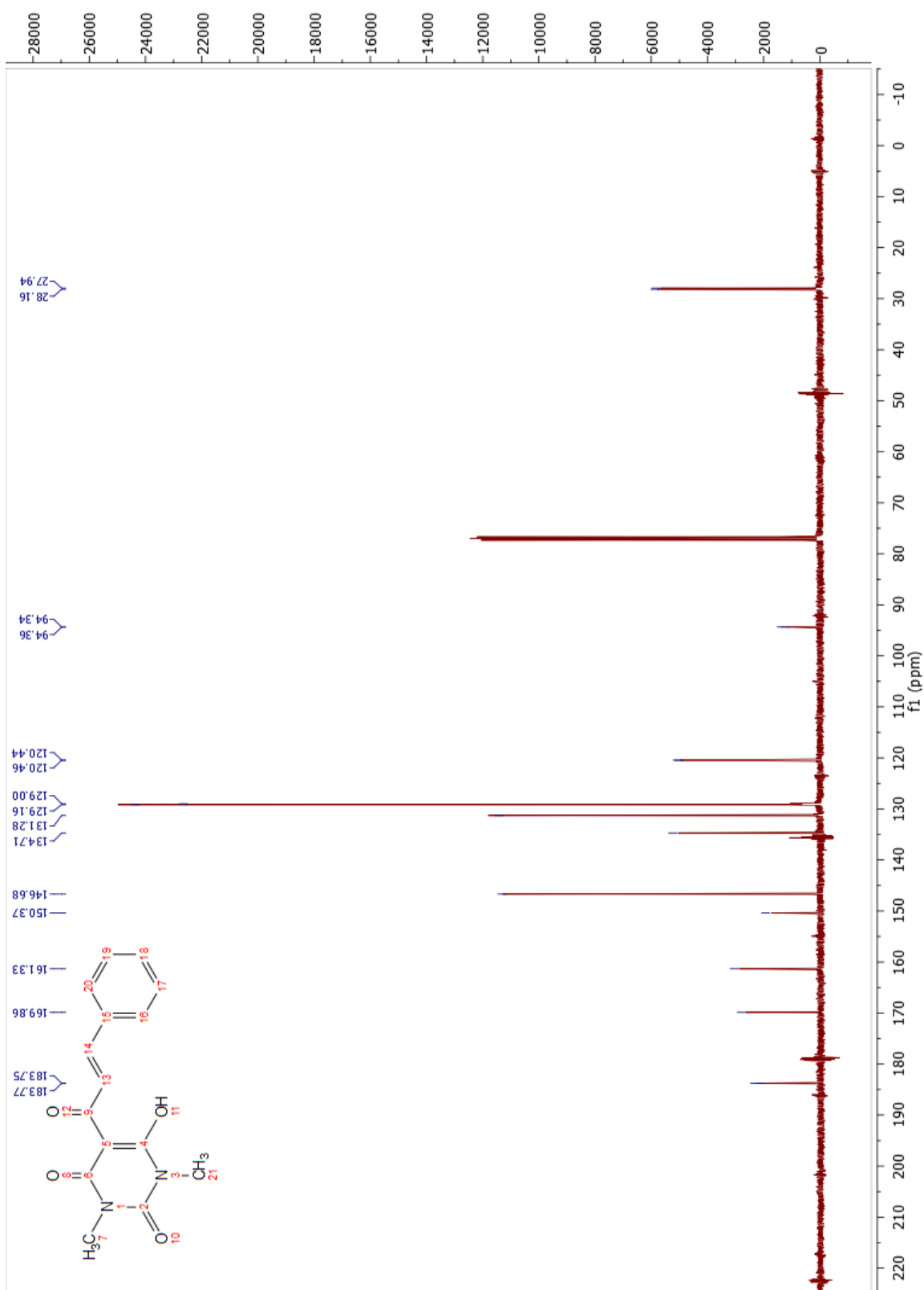
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7. Appendix

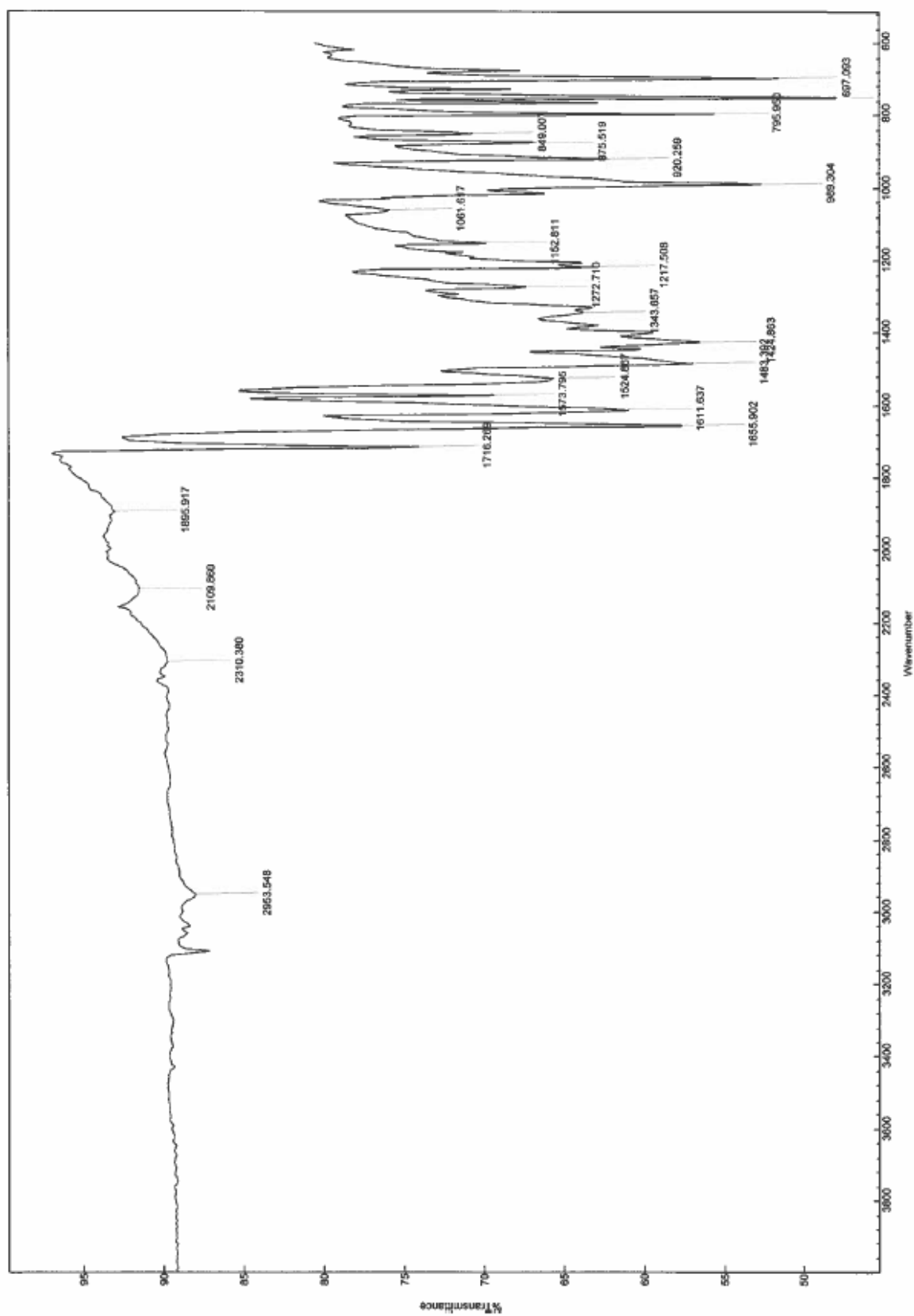
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¹³C NMR 5-cinnamoyl-6-hydroxy-1,3-dimethylpyrimidine-2,4(1H,3H)-dione



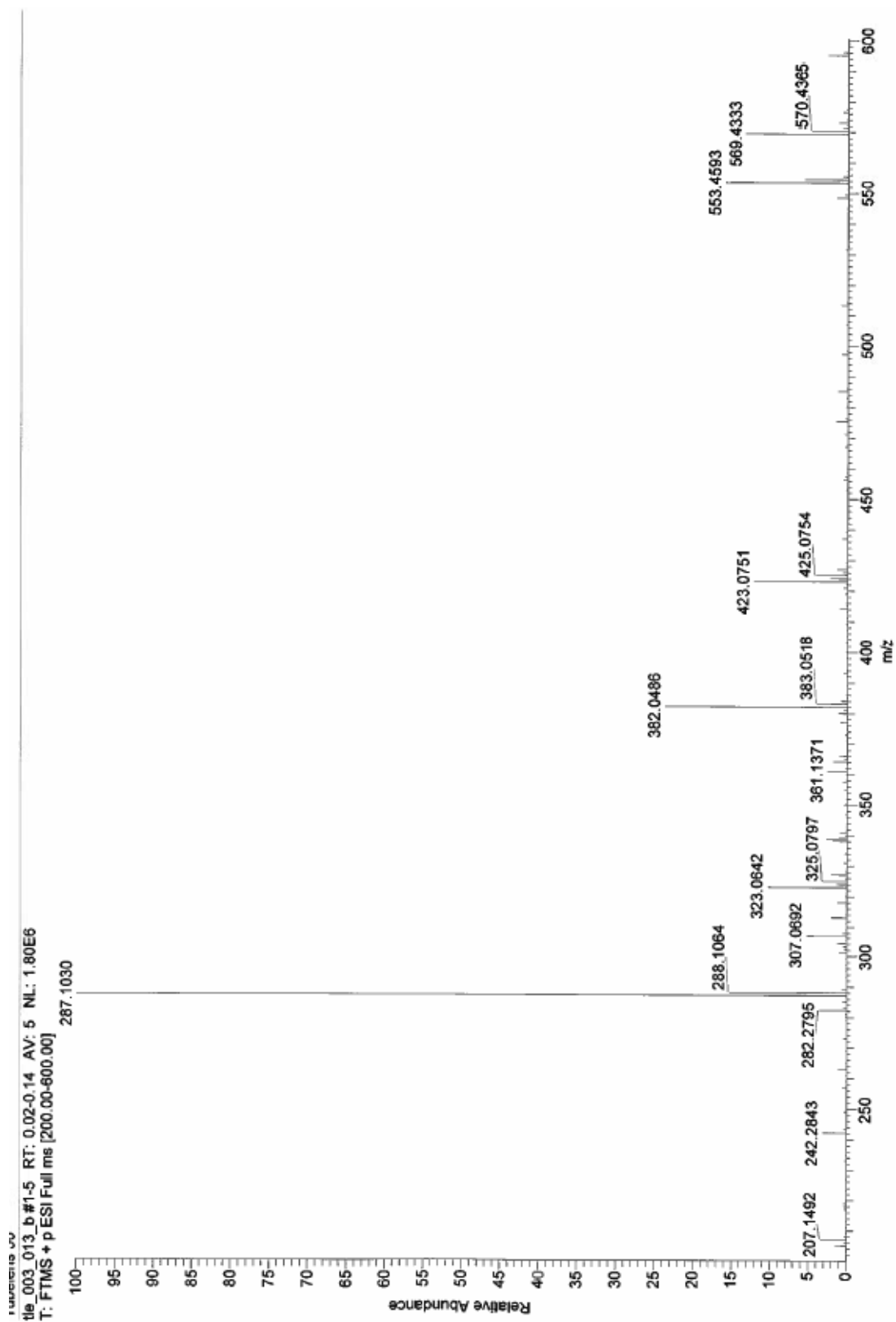
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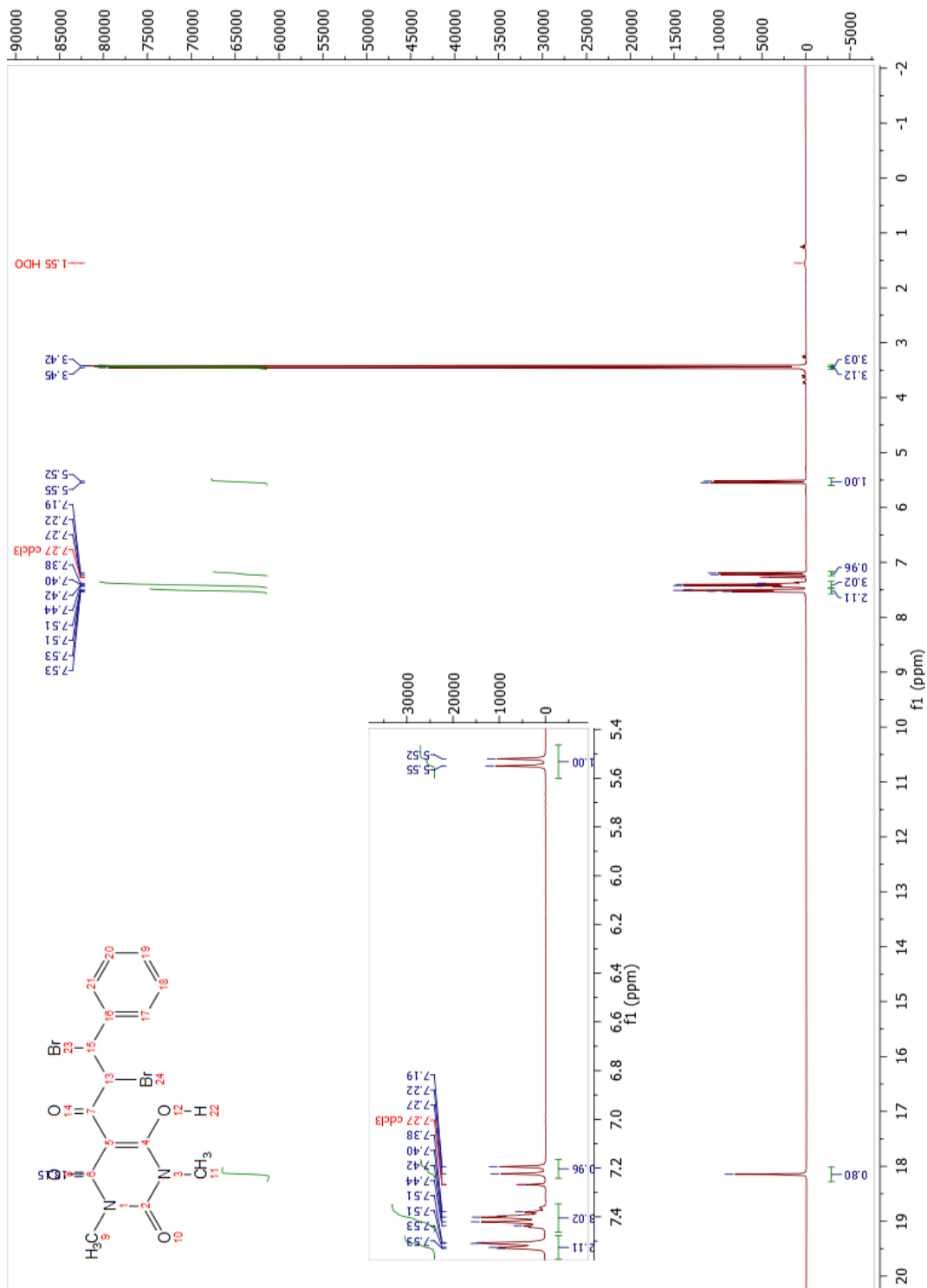
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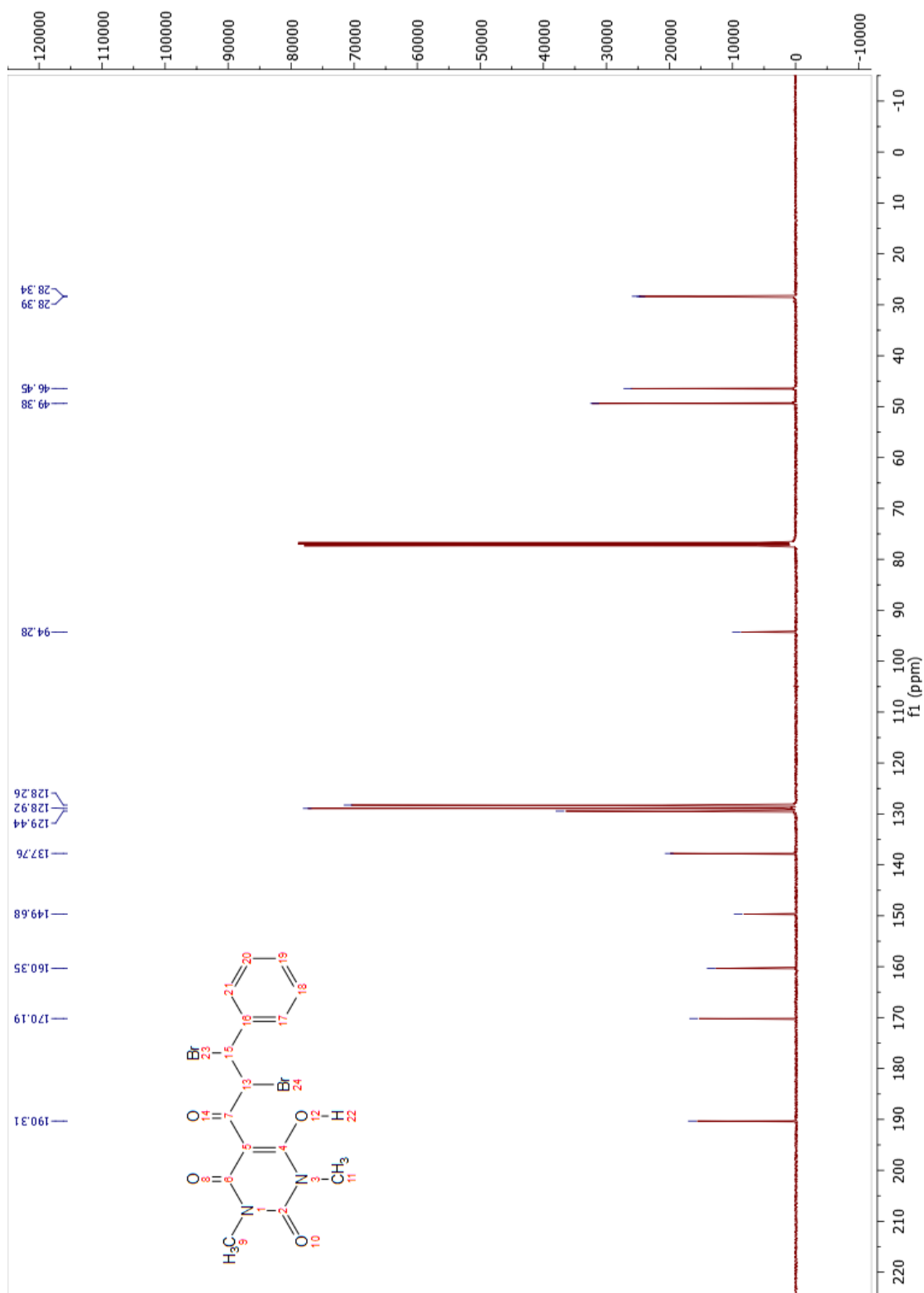
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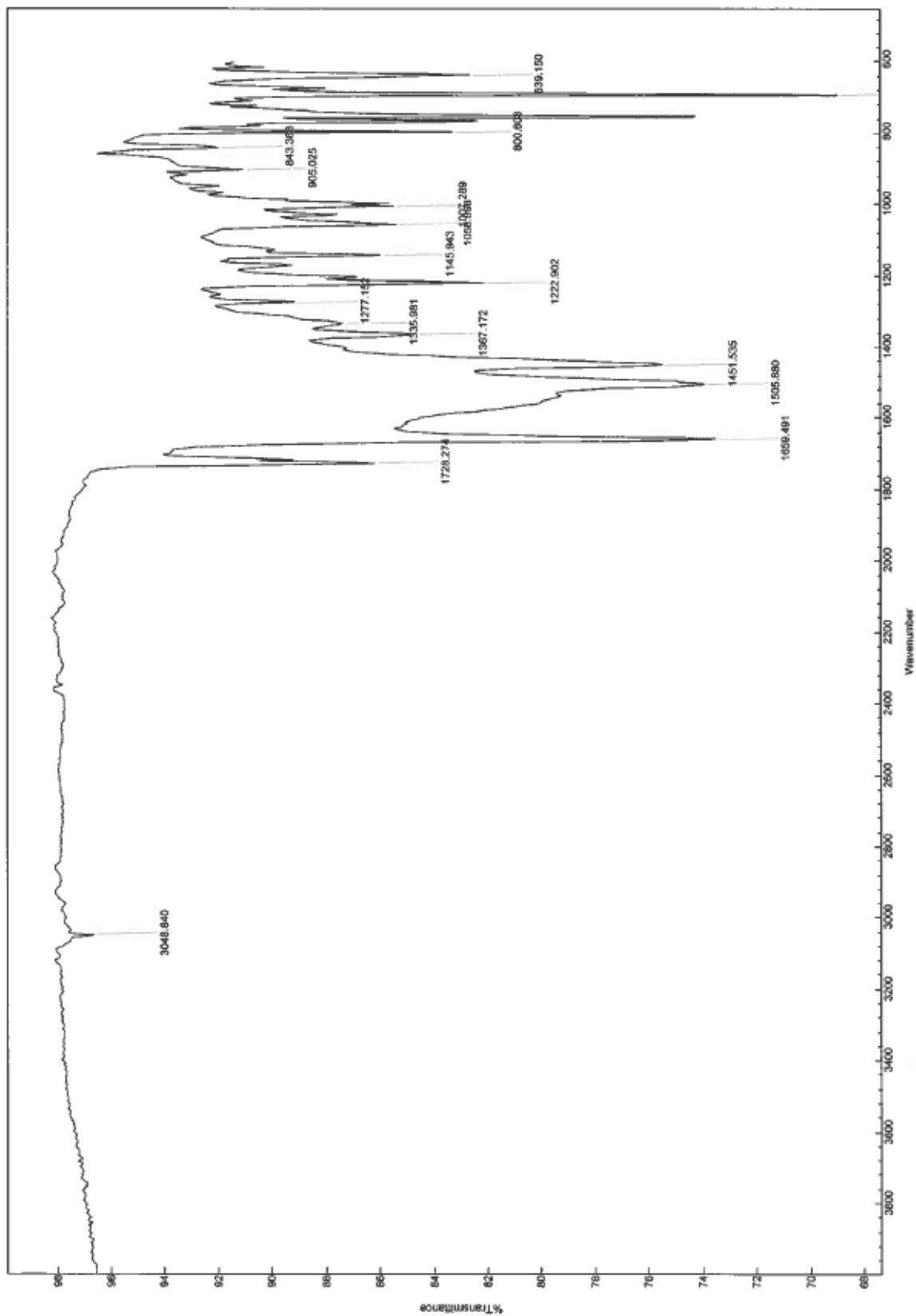
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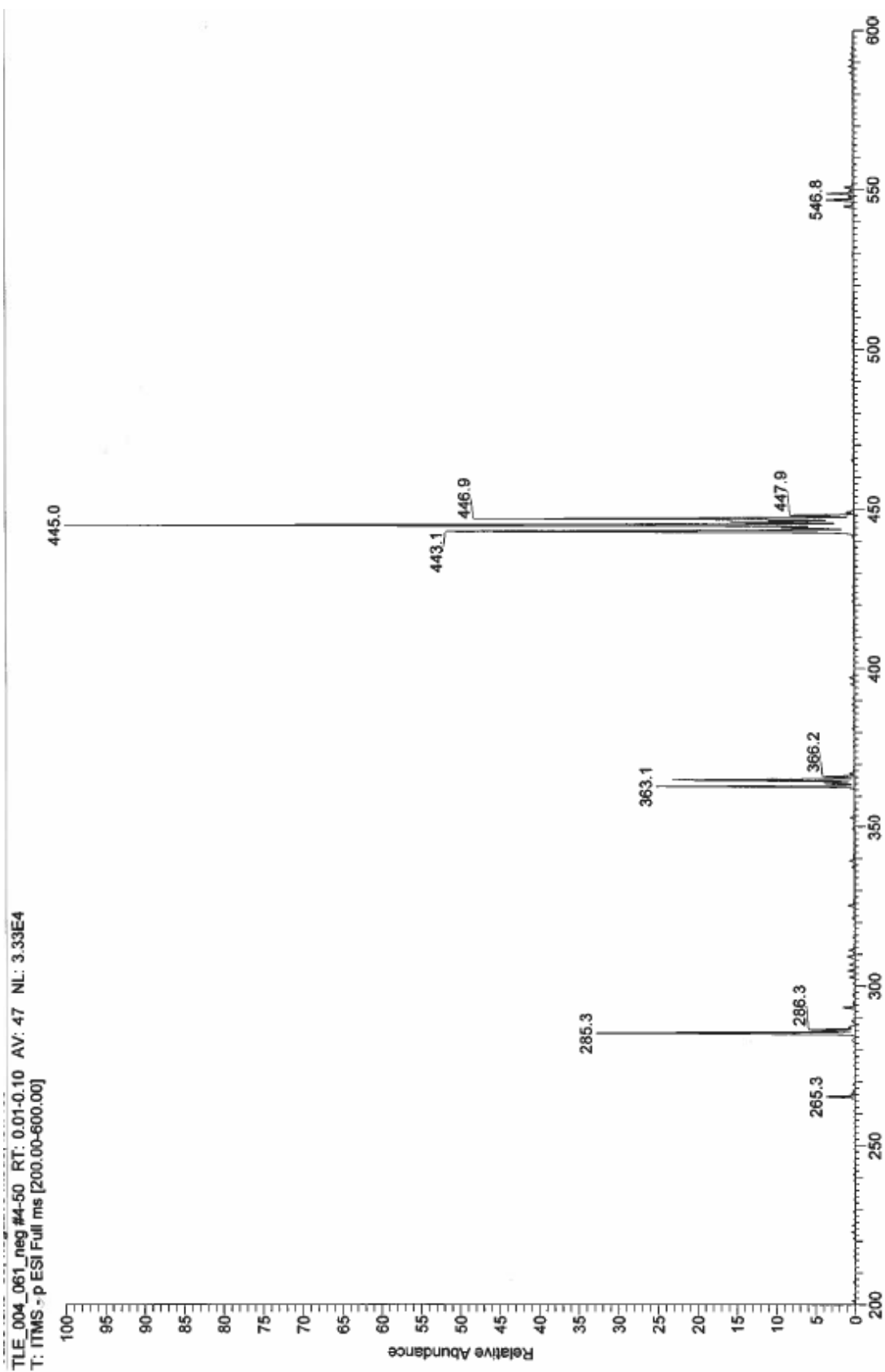
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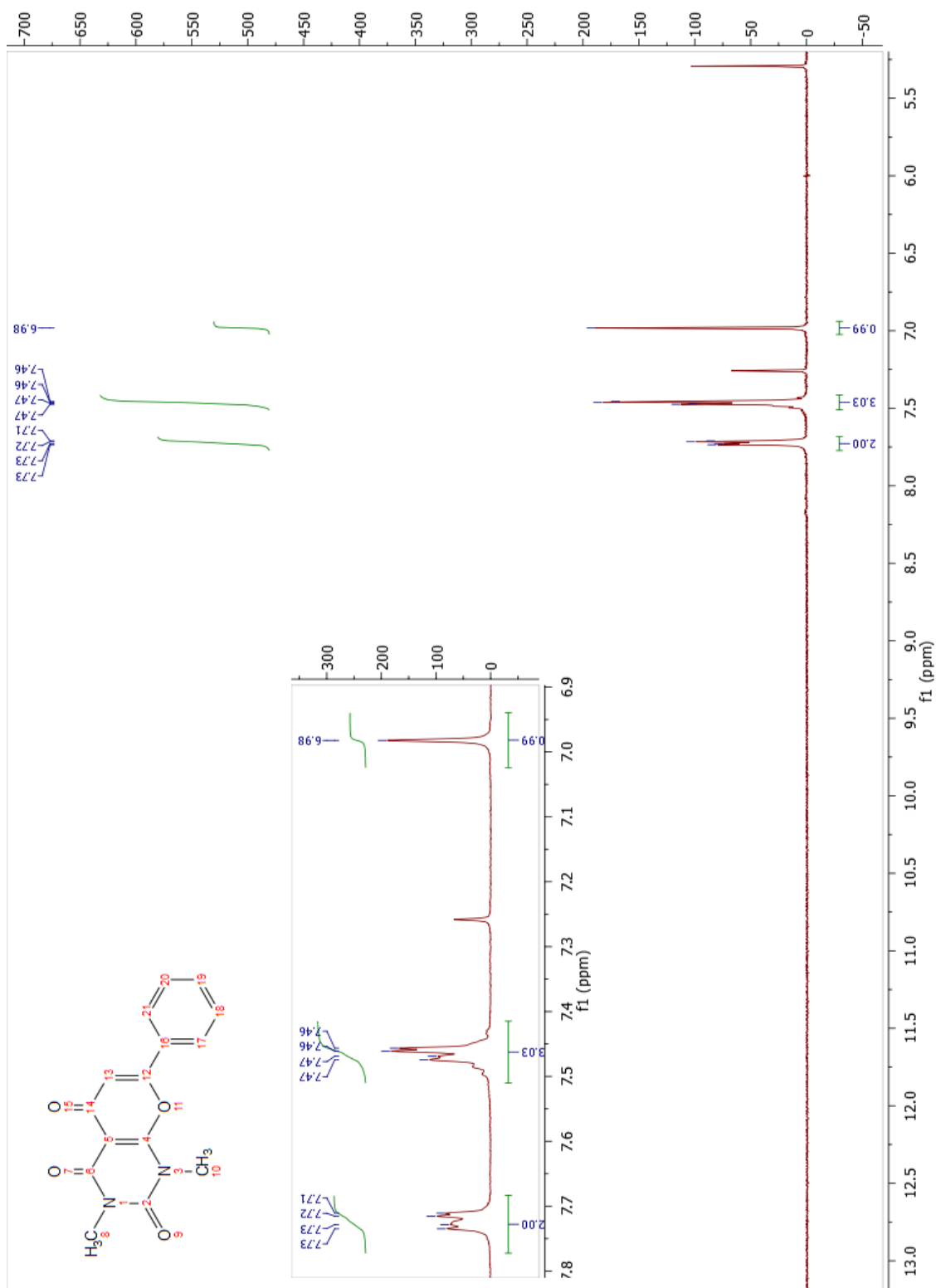
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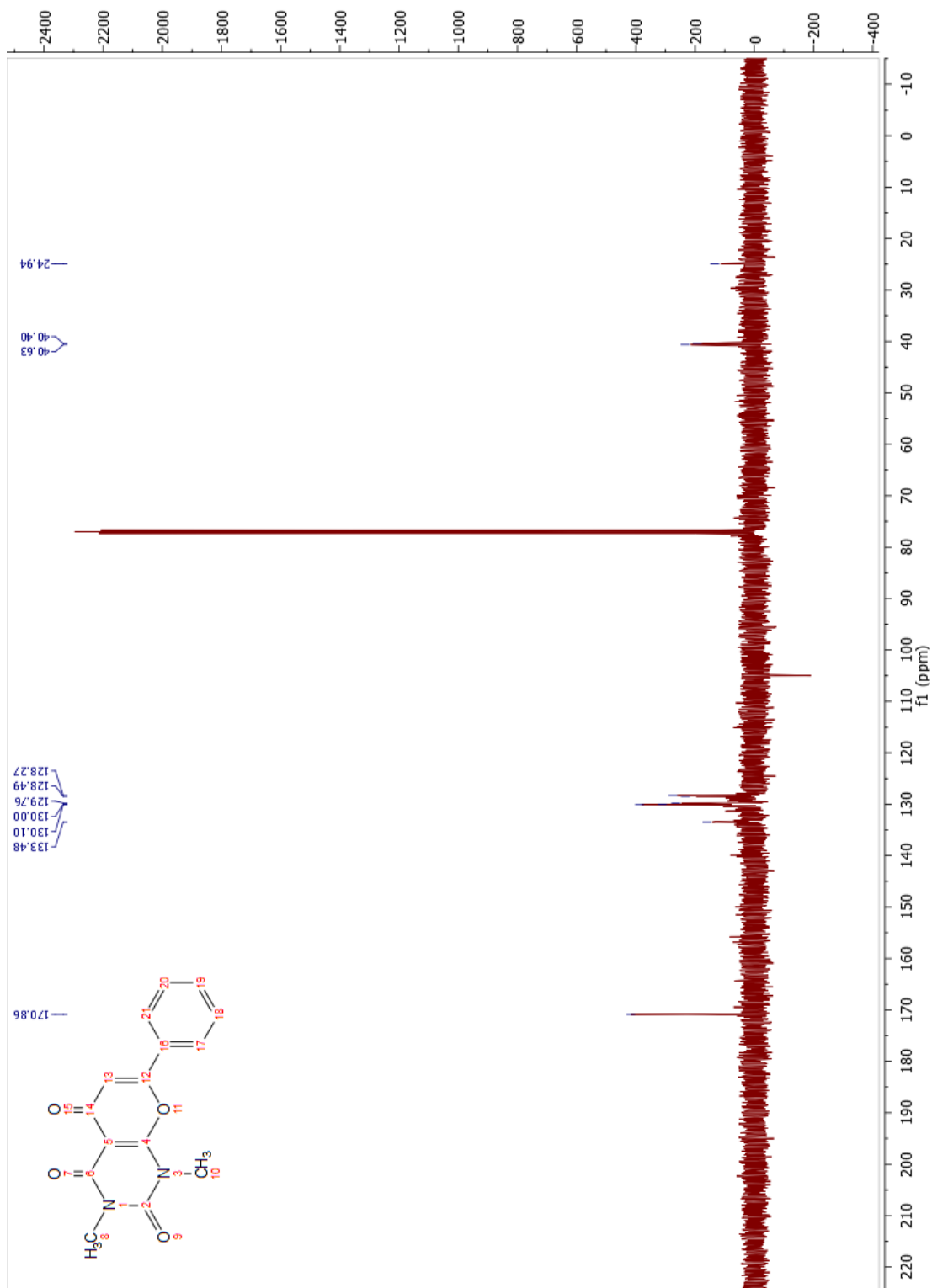
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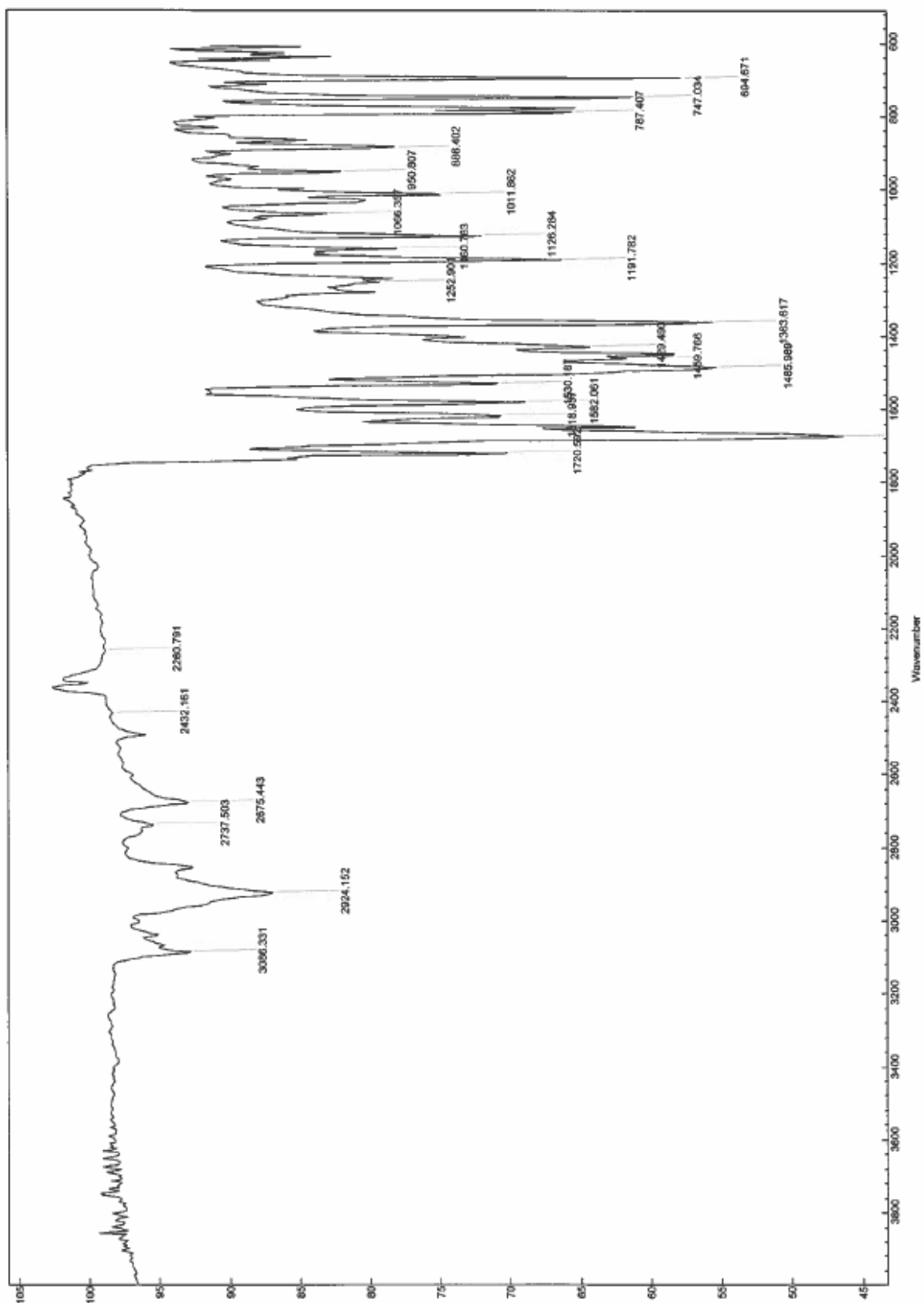
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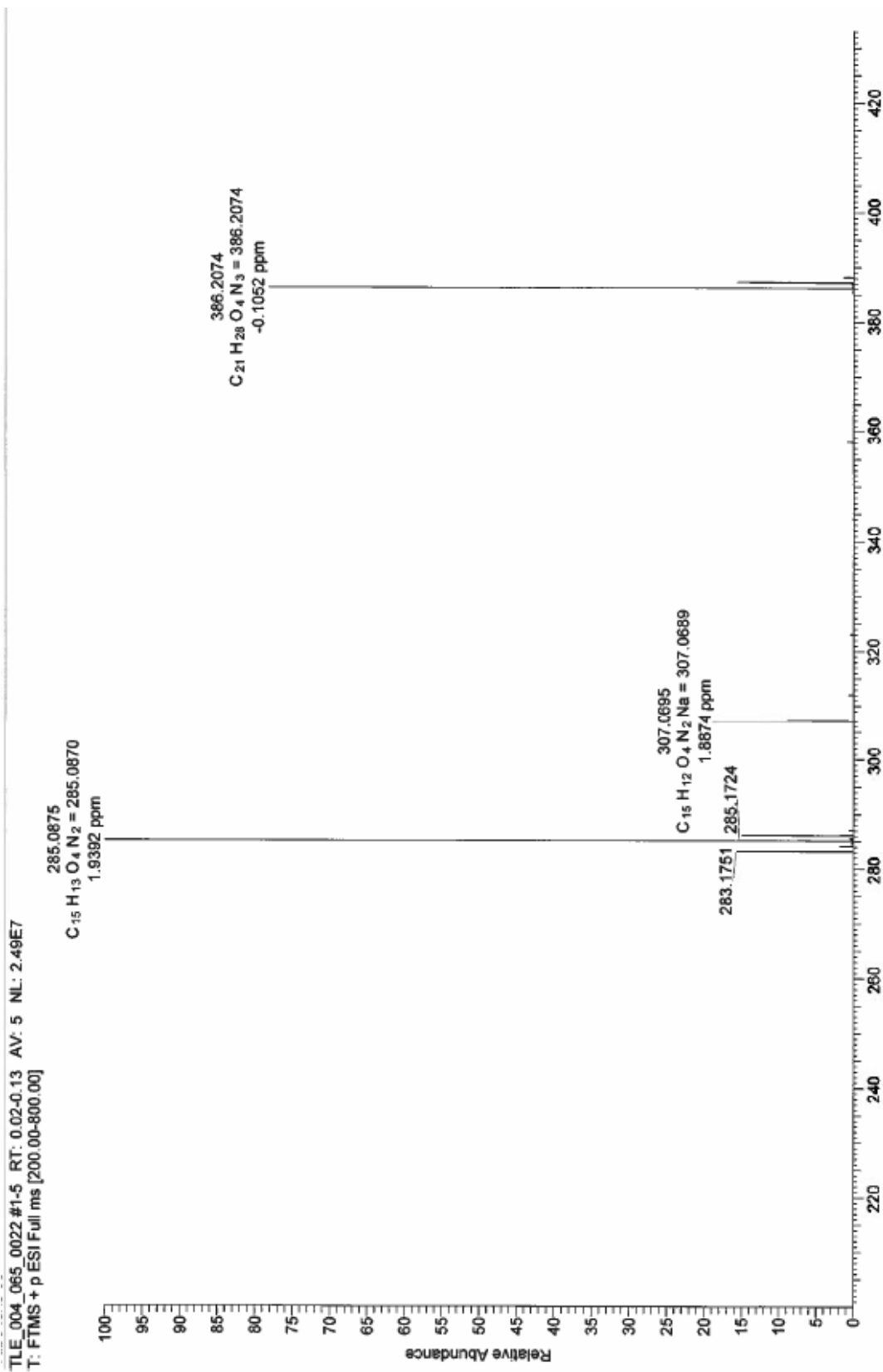
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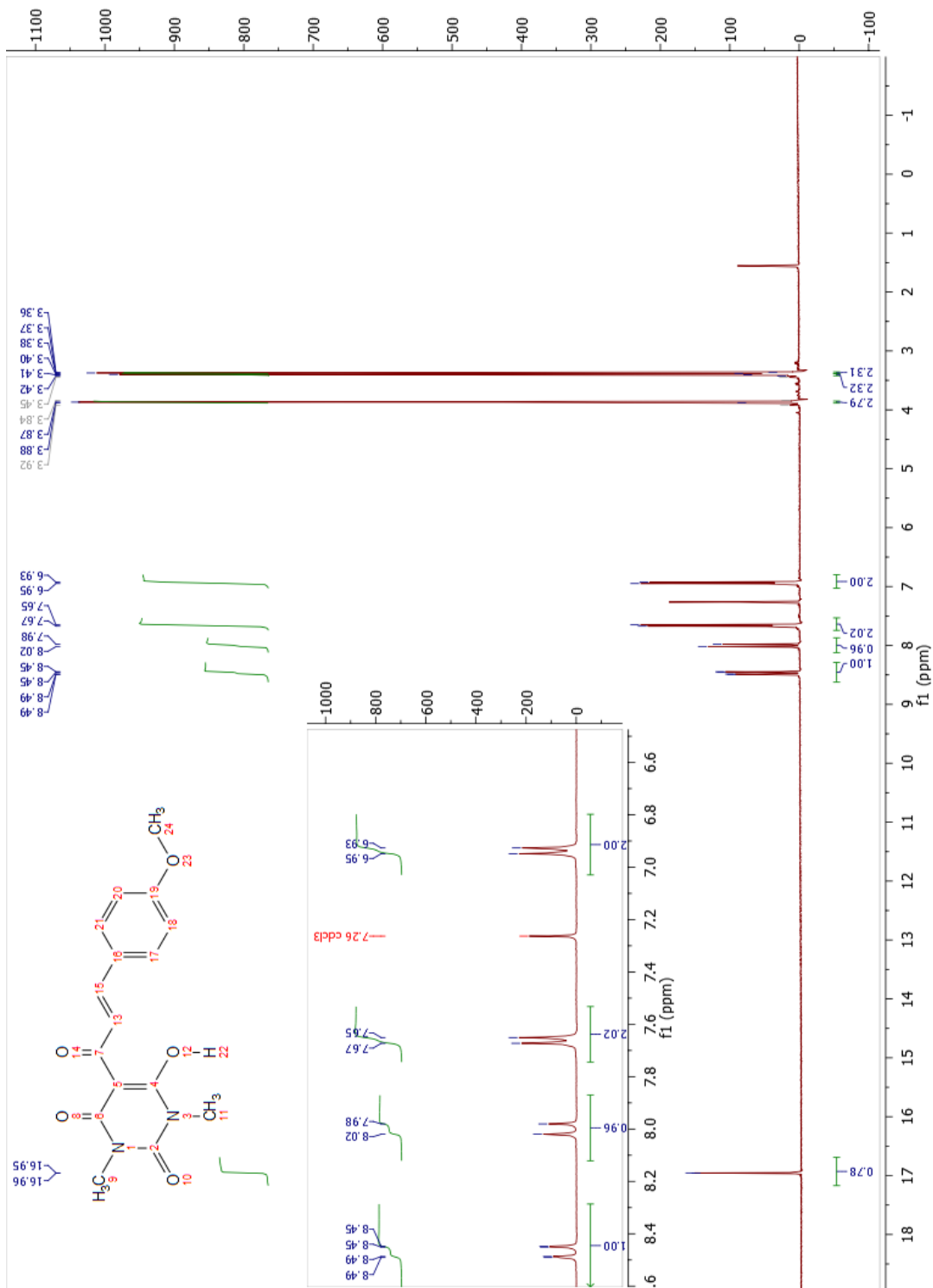
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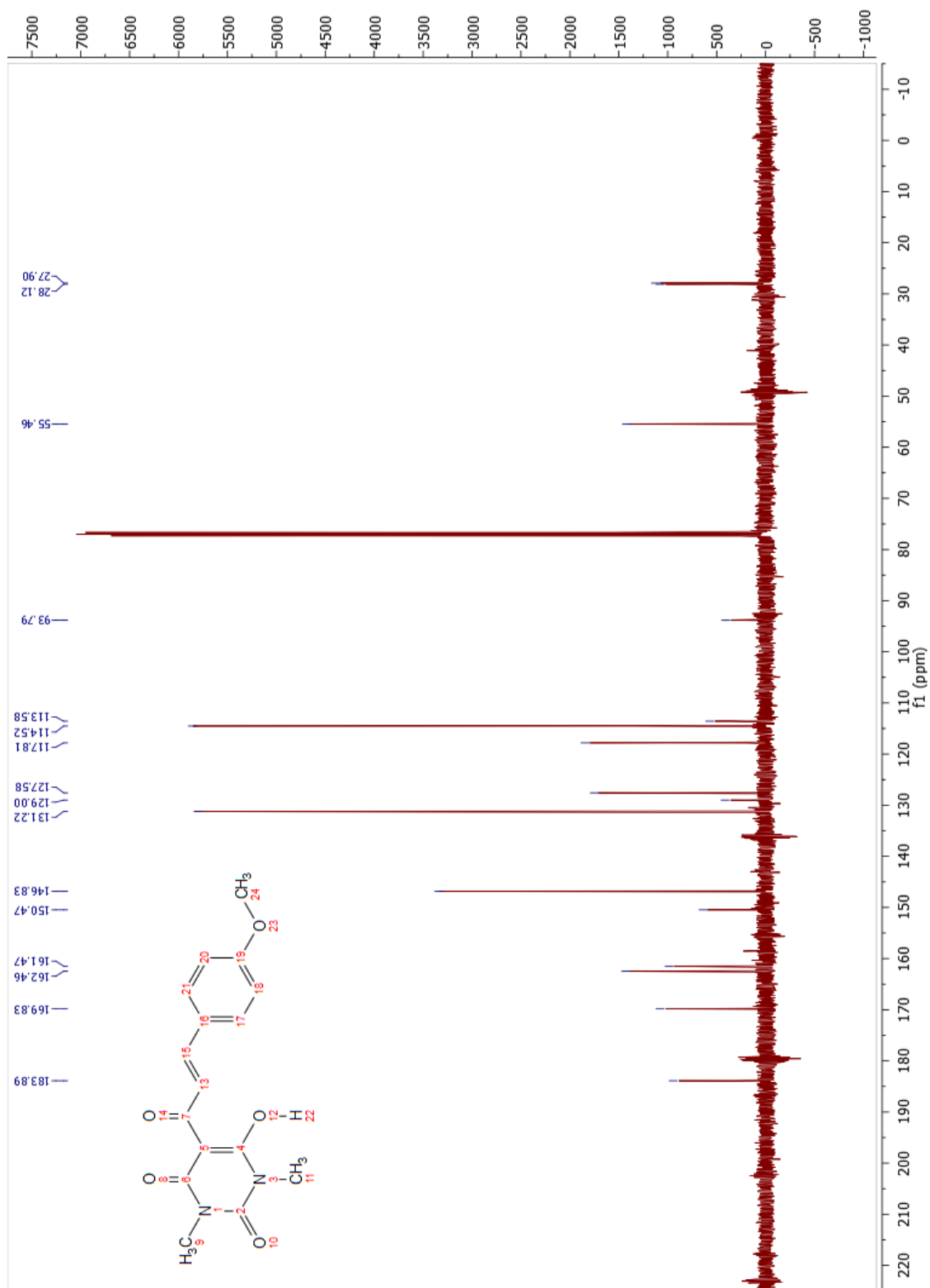
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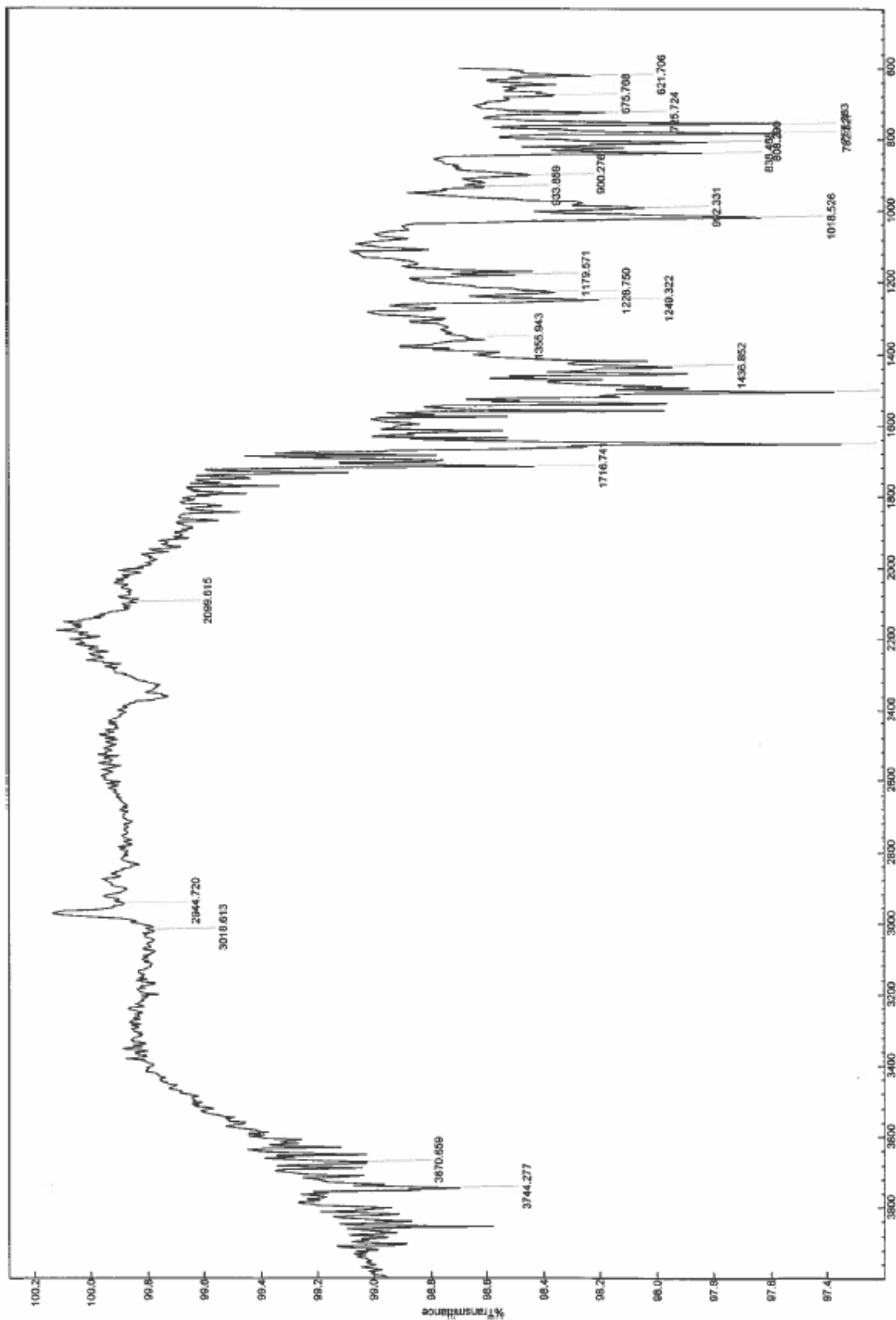
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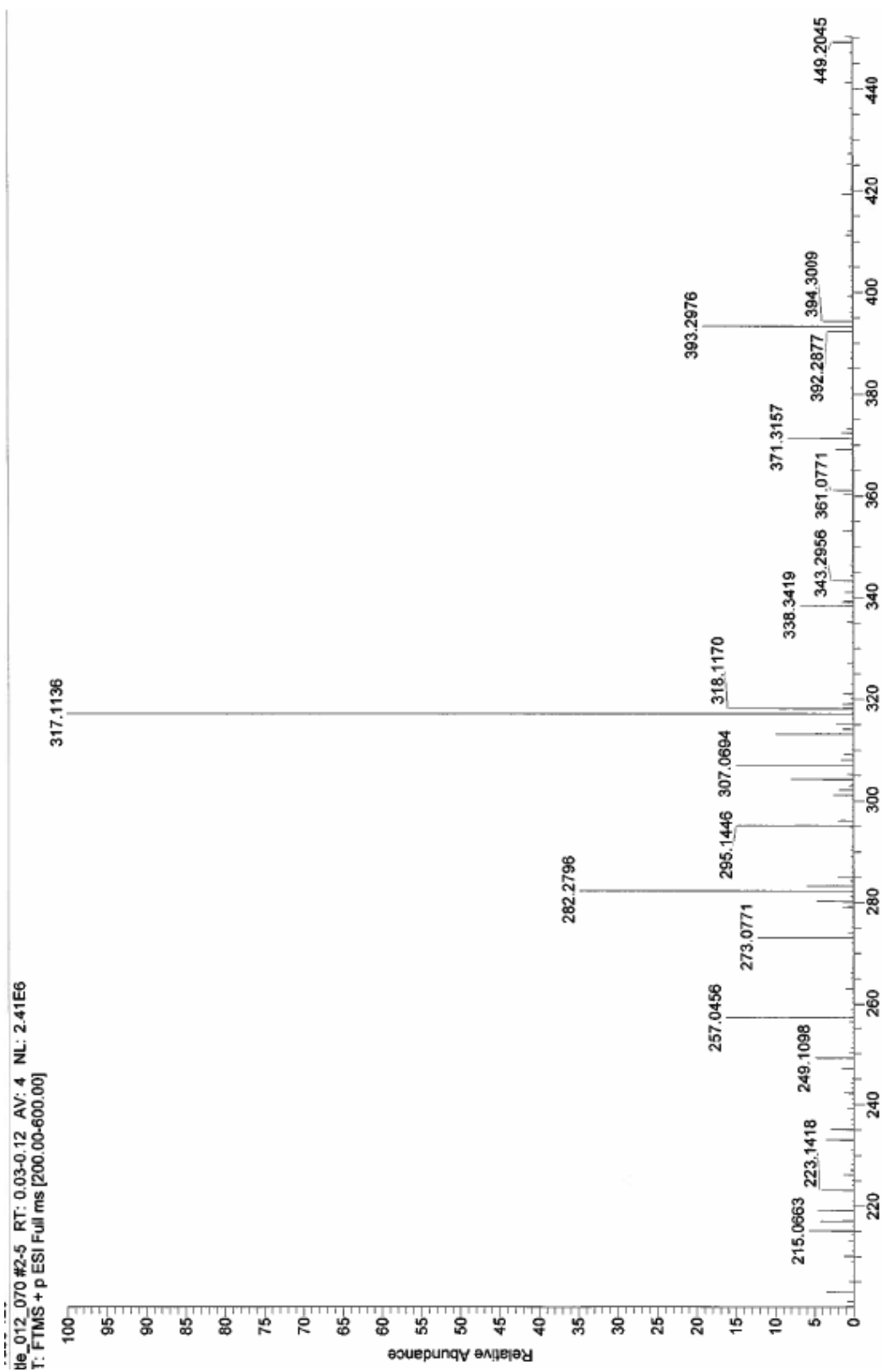
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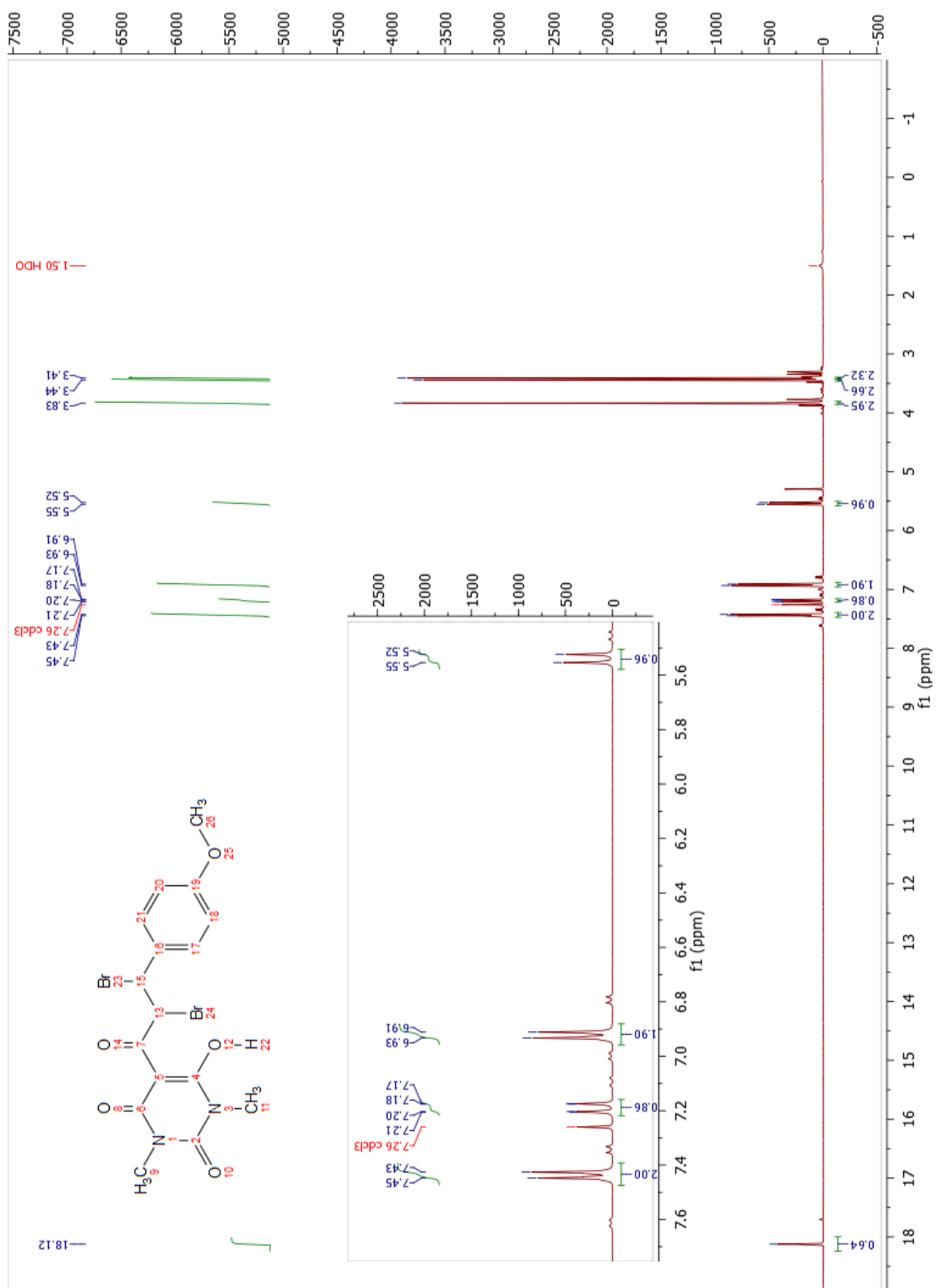
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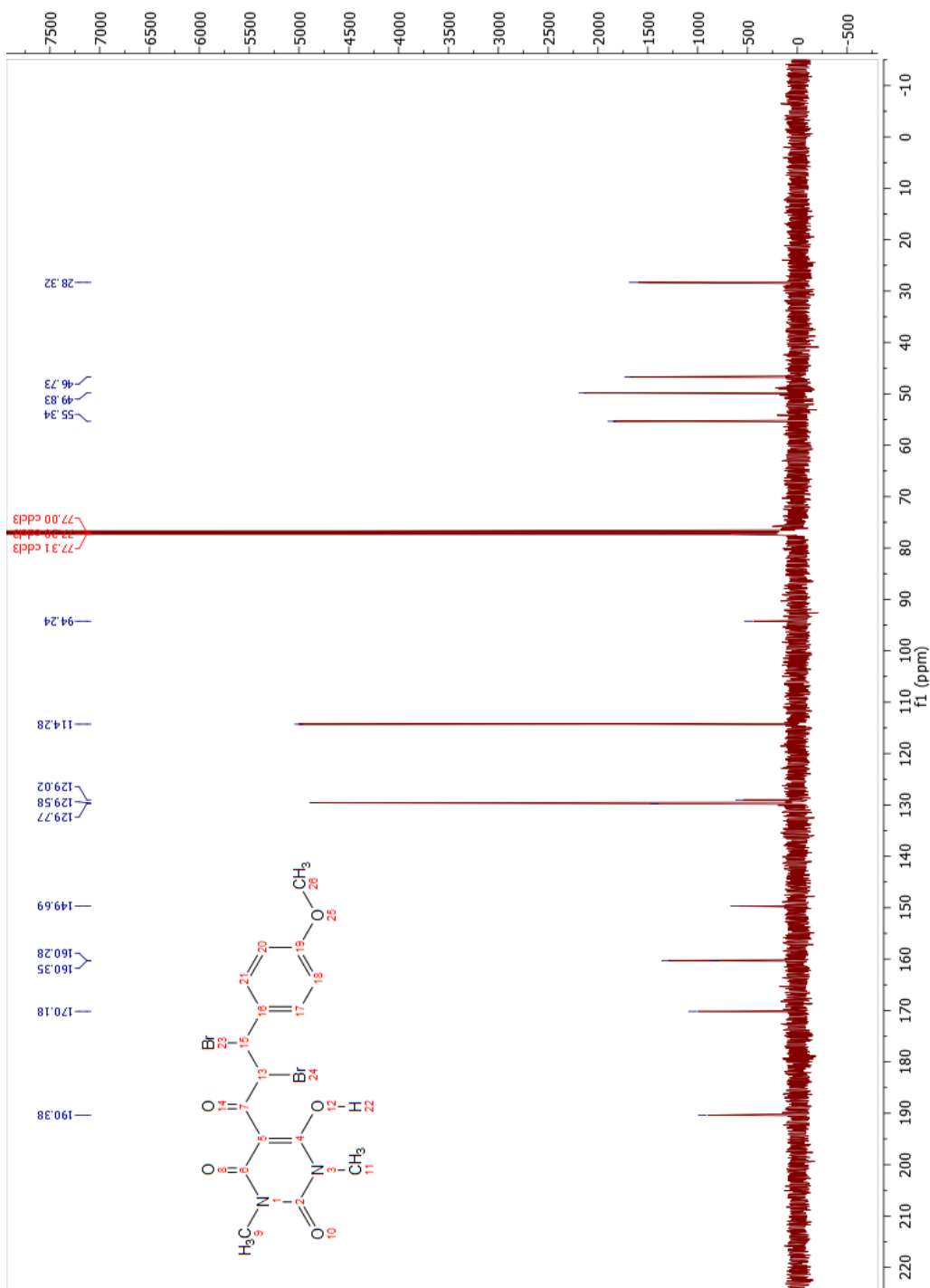
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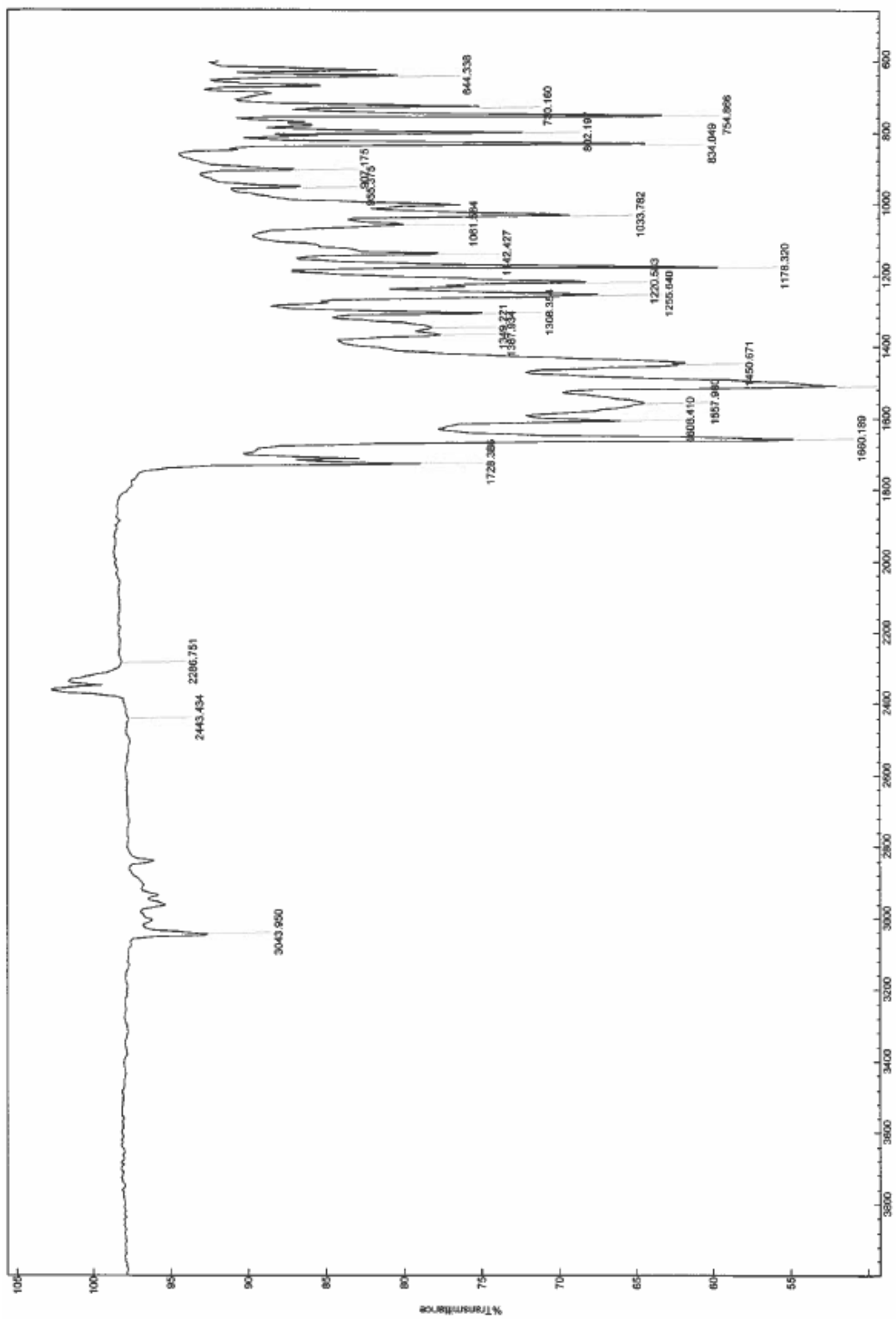
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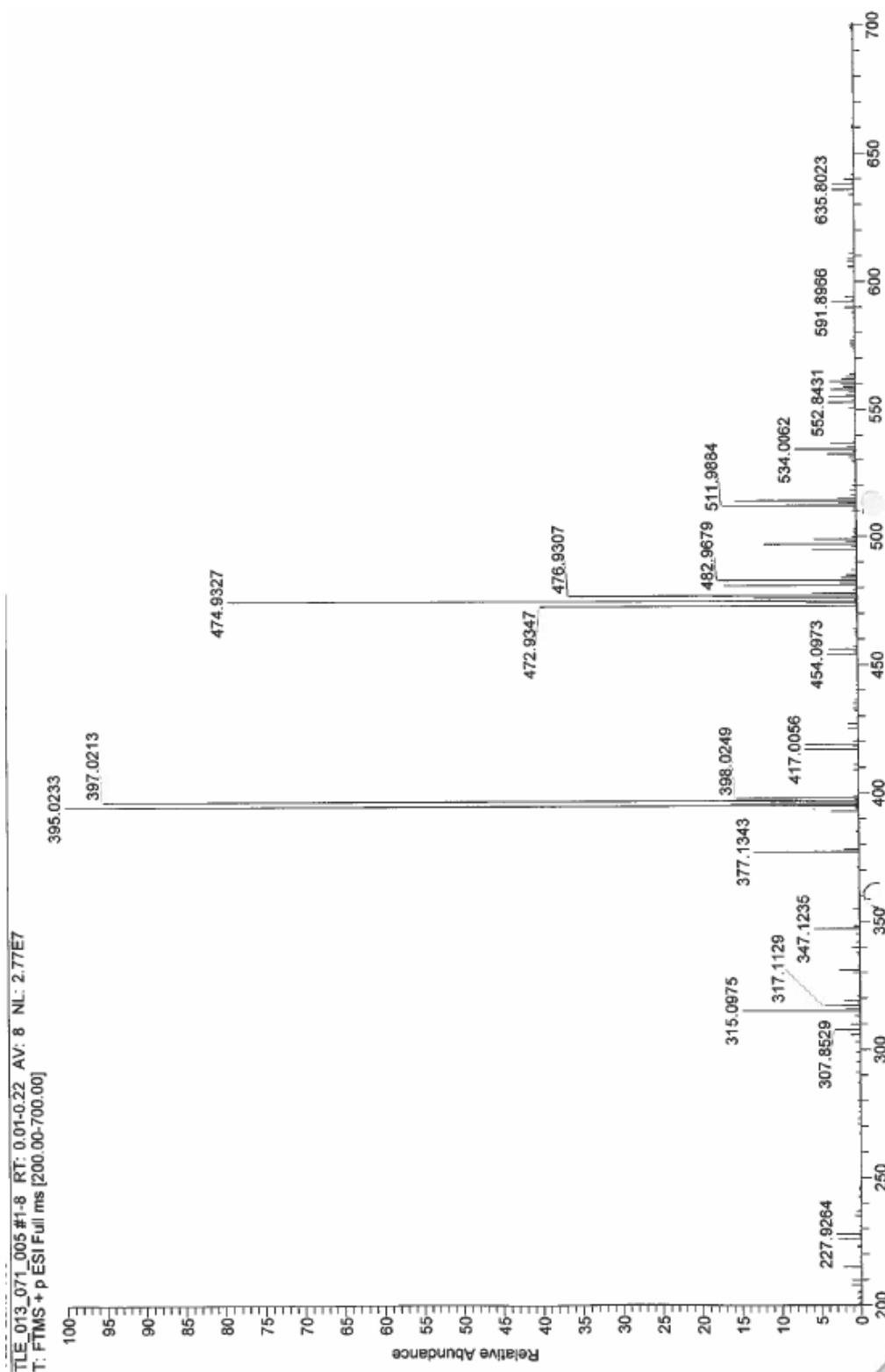
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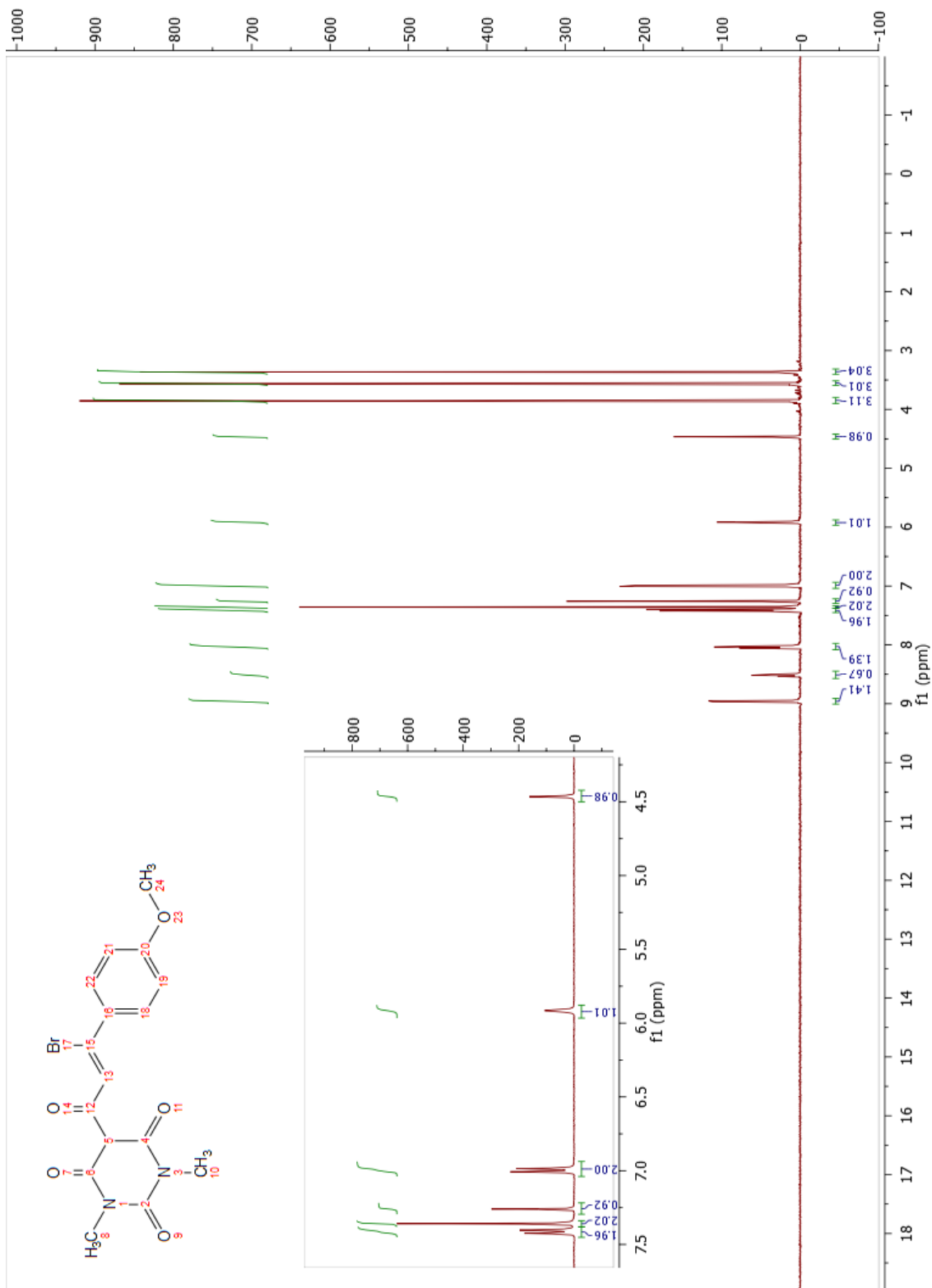
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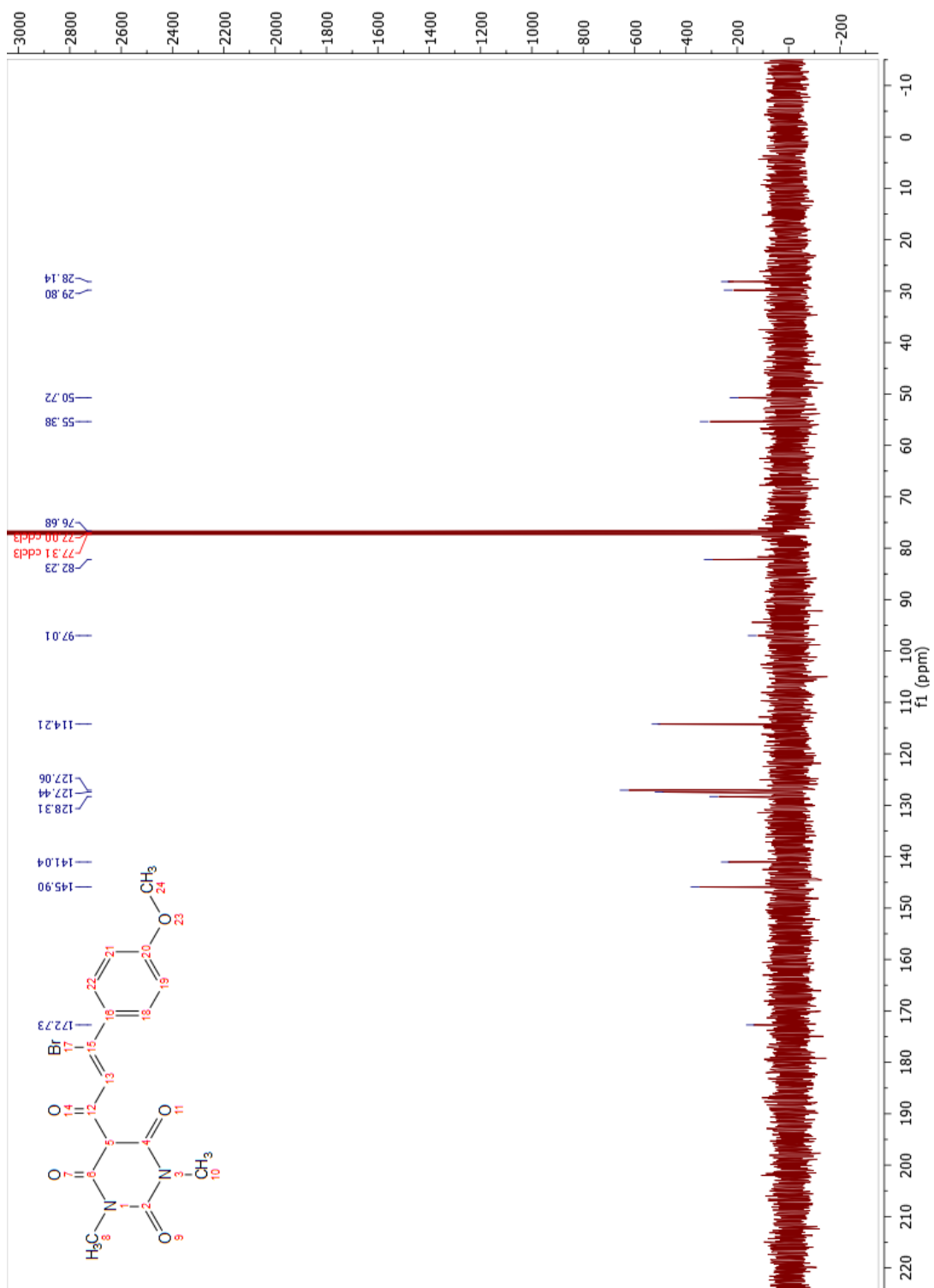
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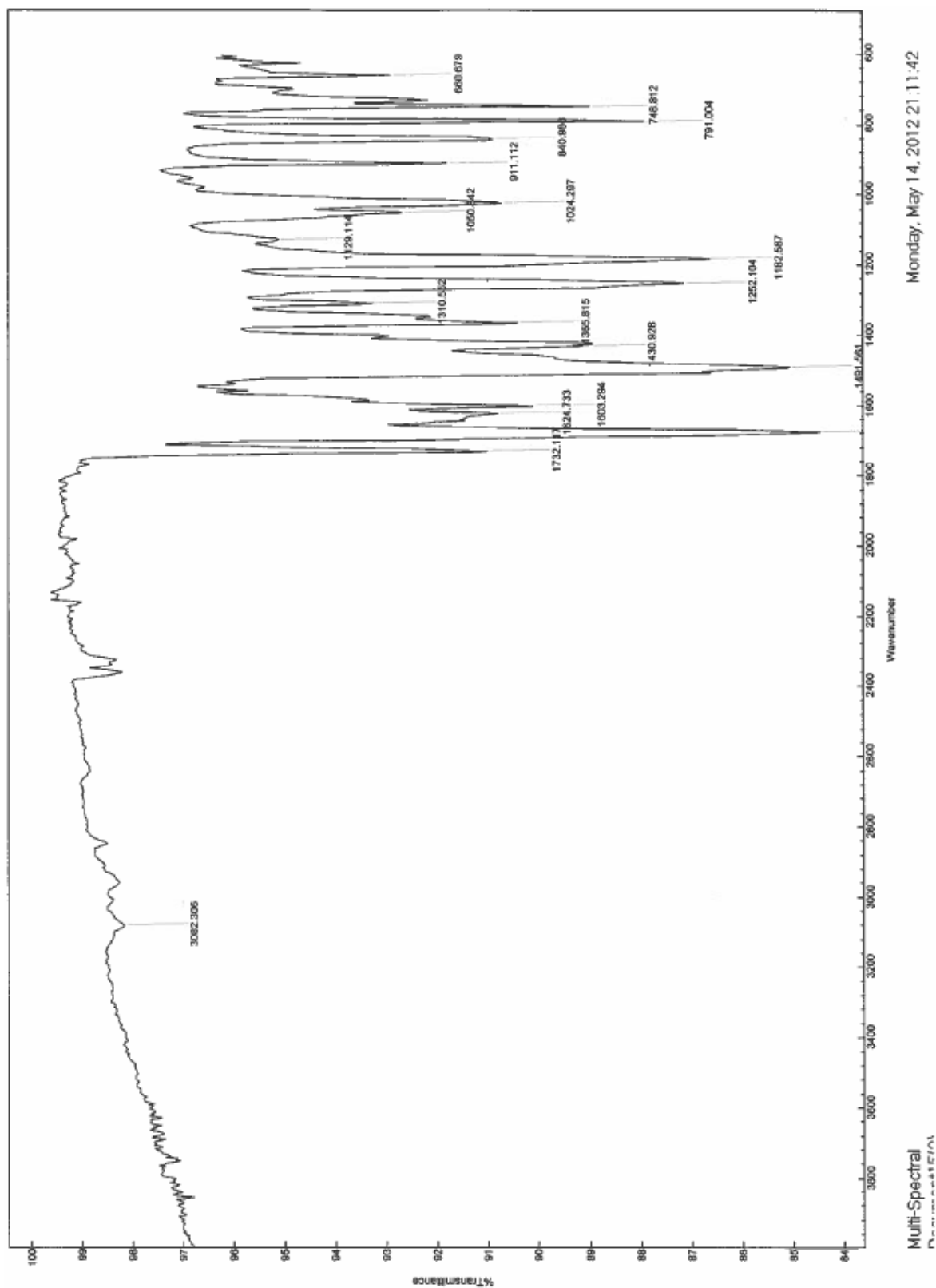
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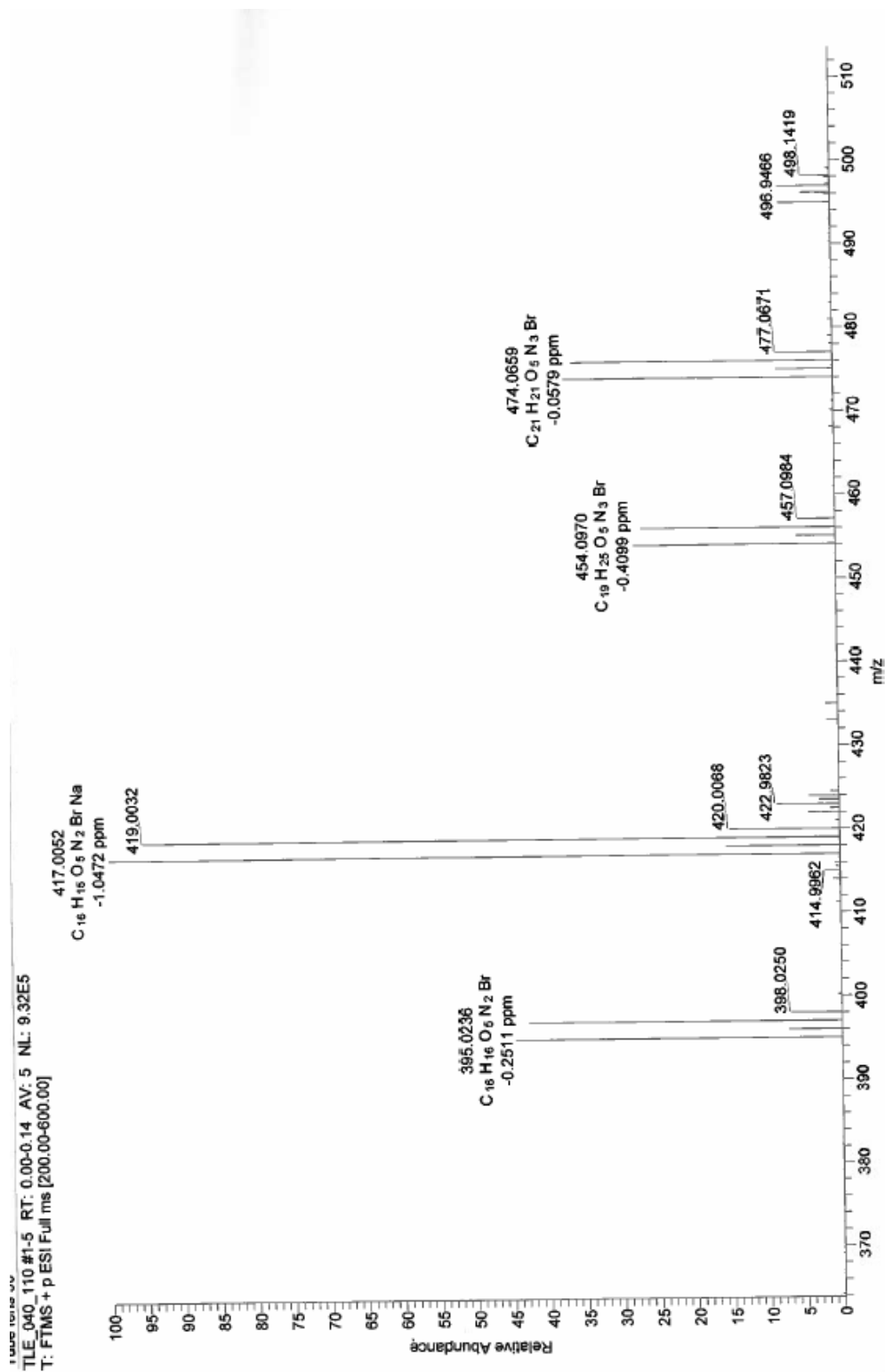
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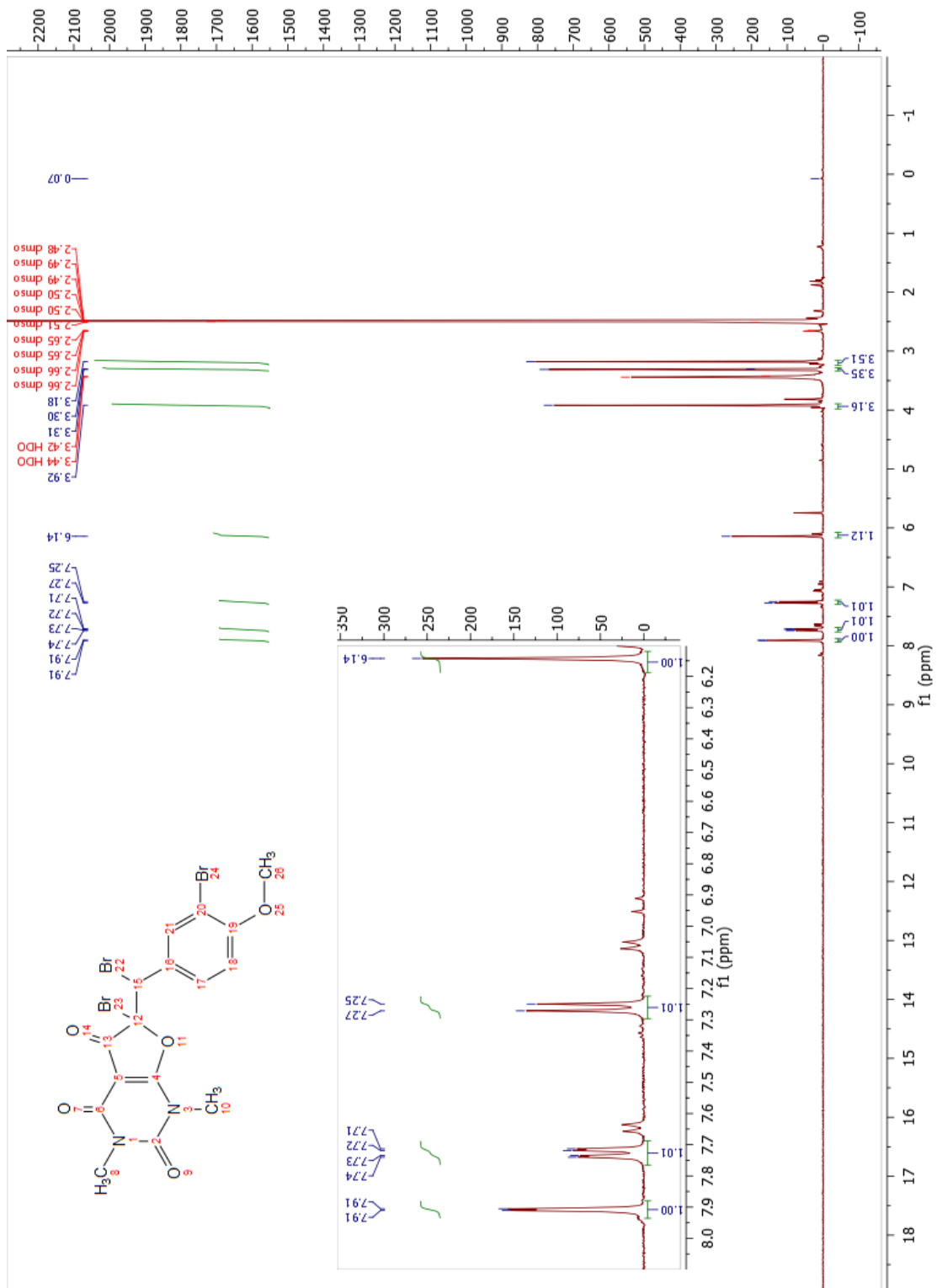
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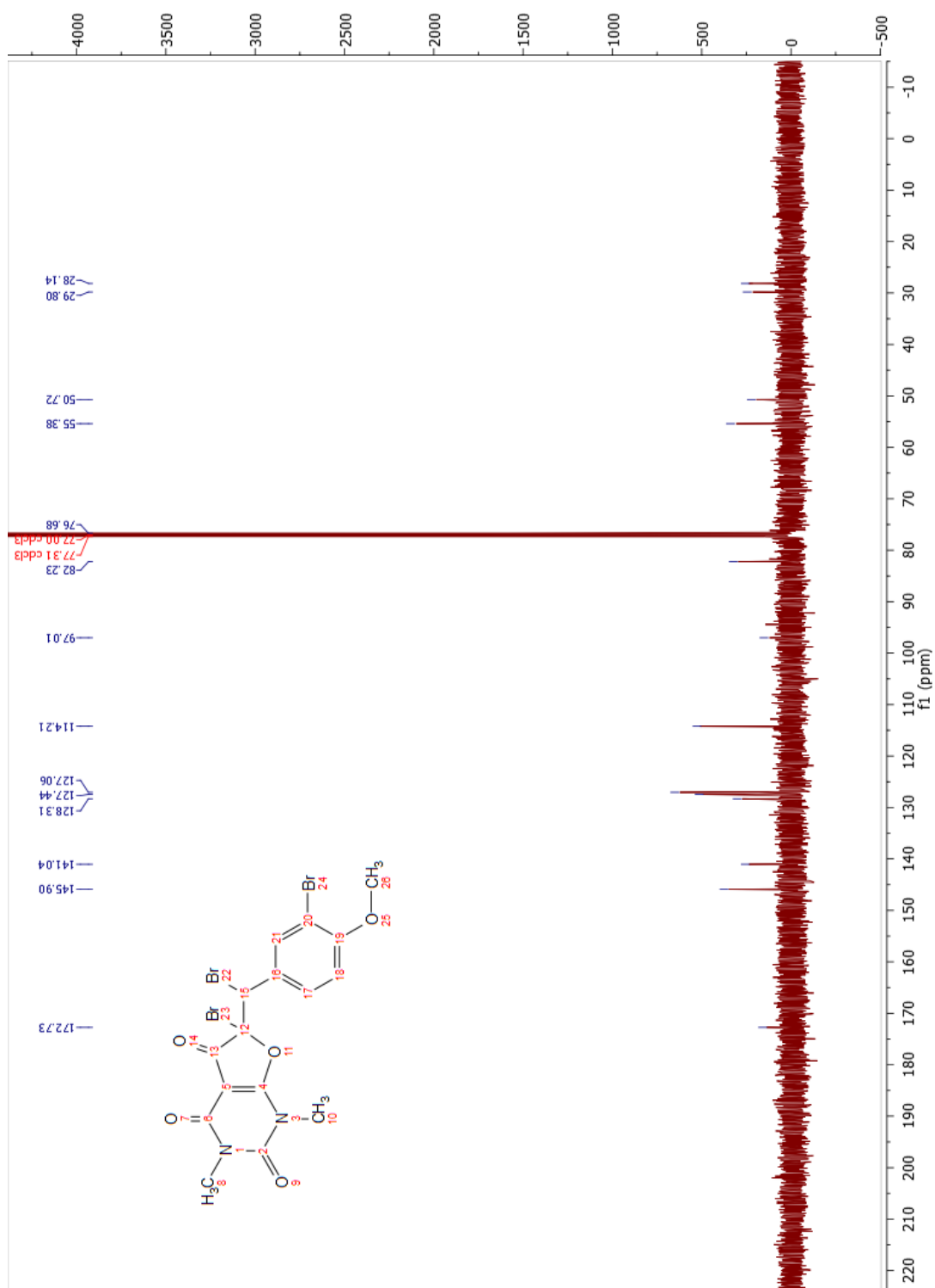
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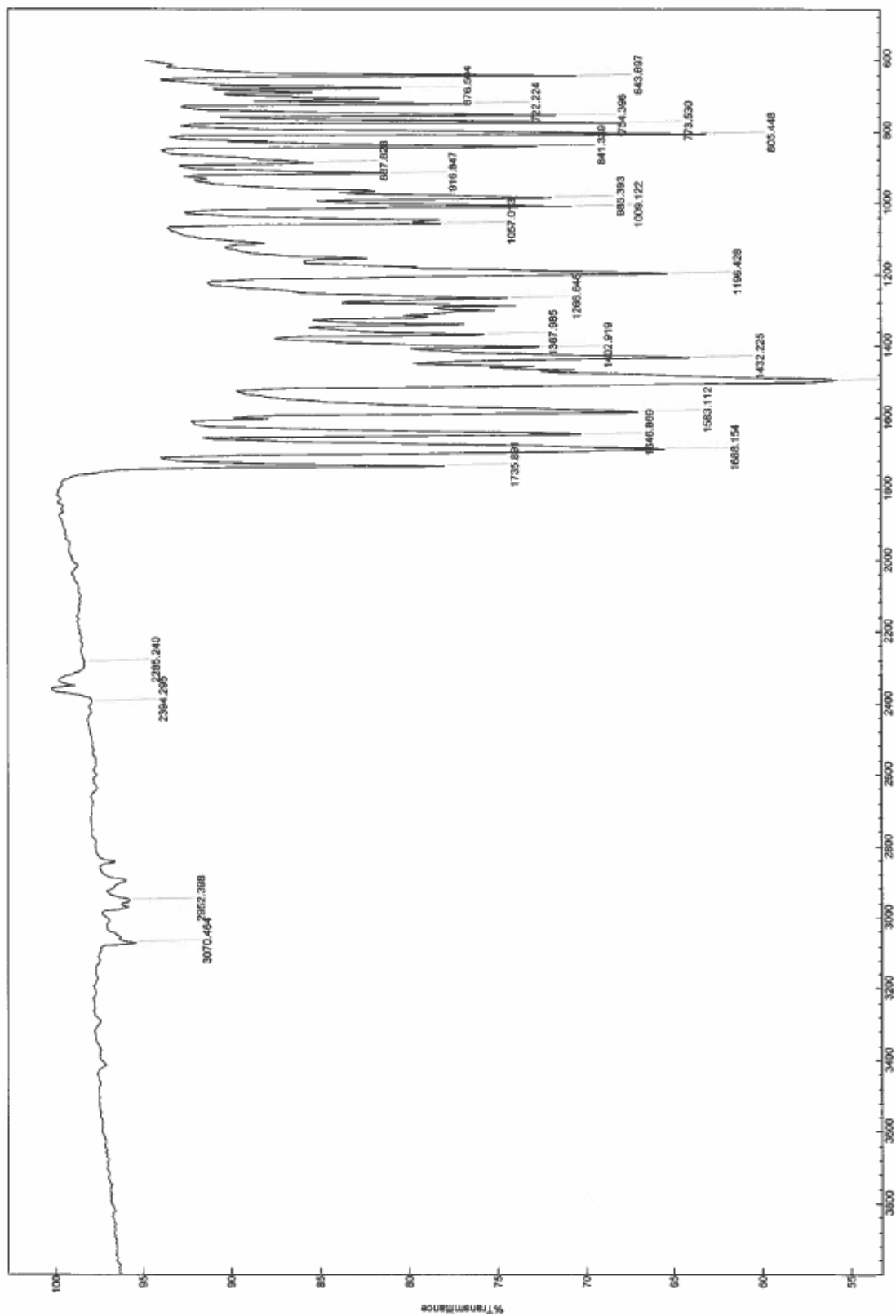
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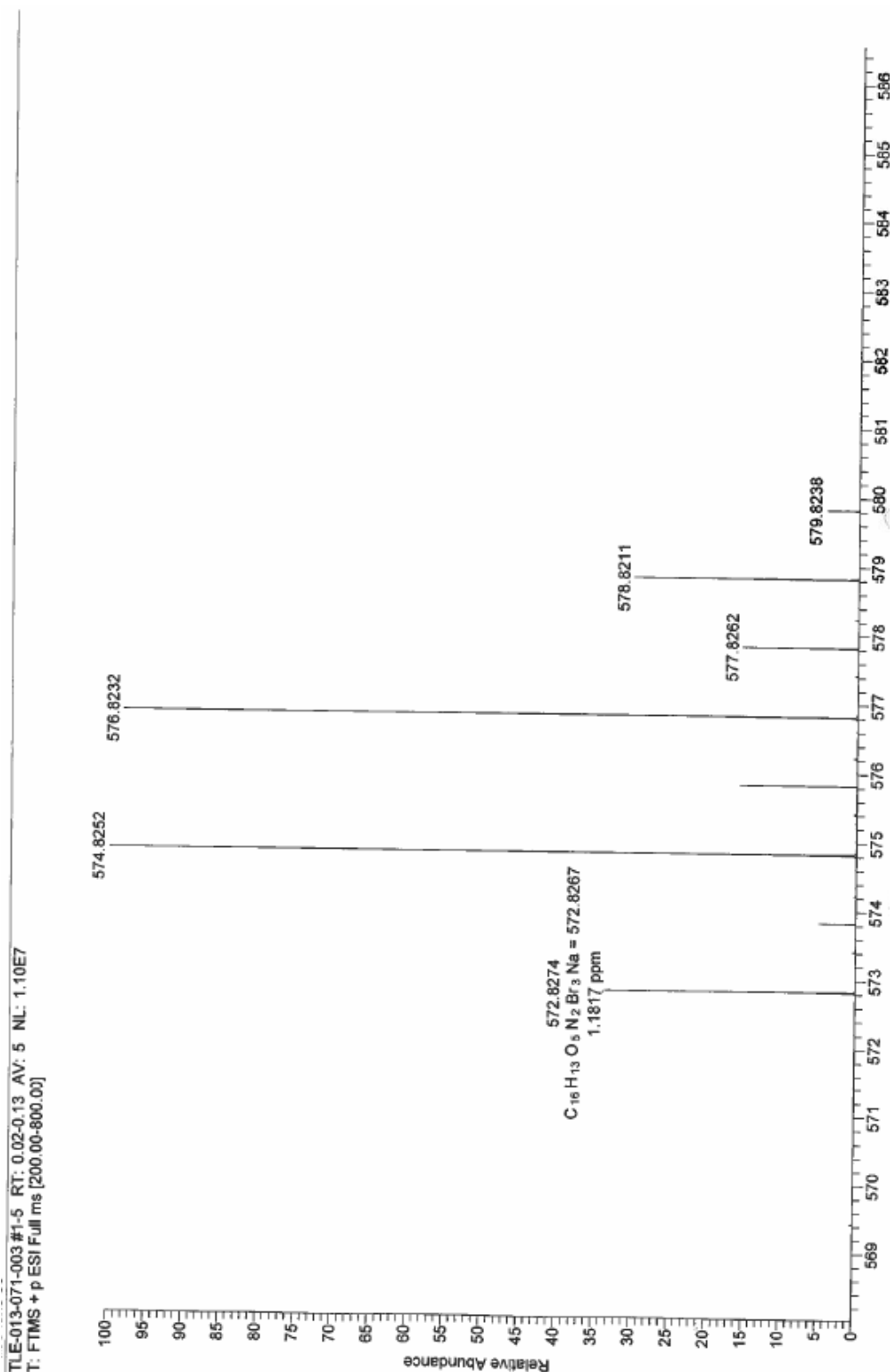
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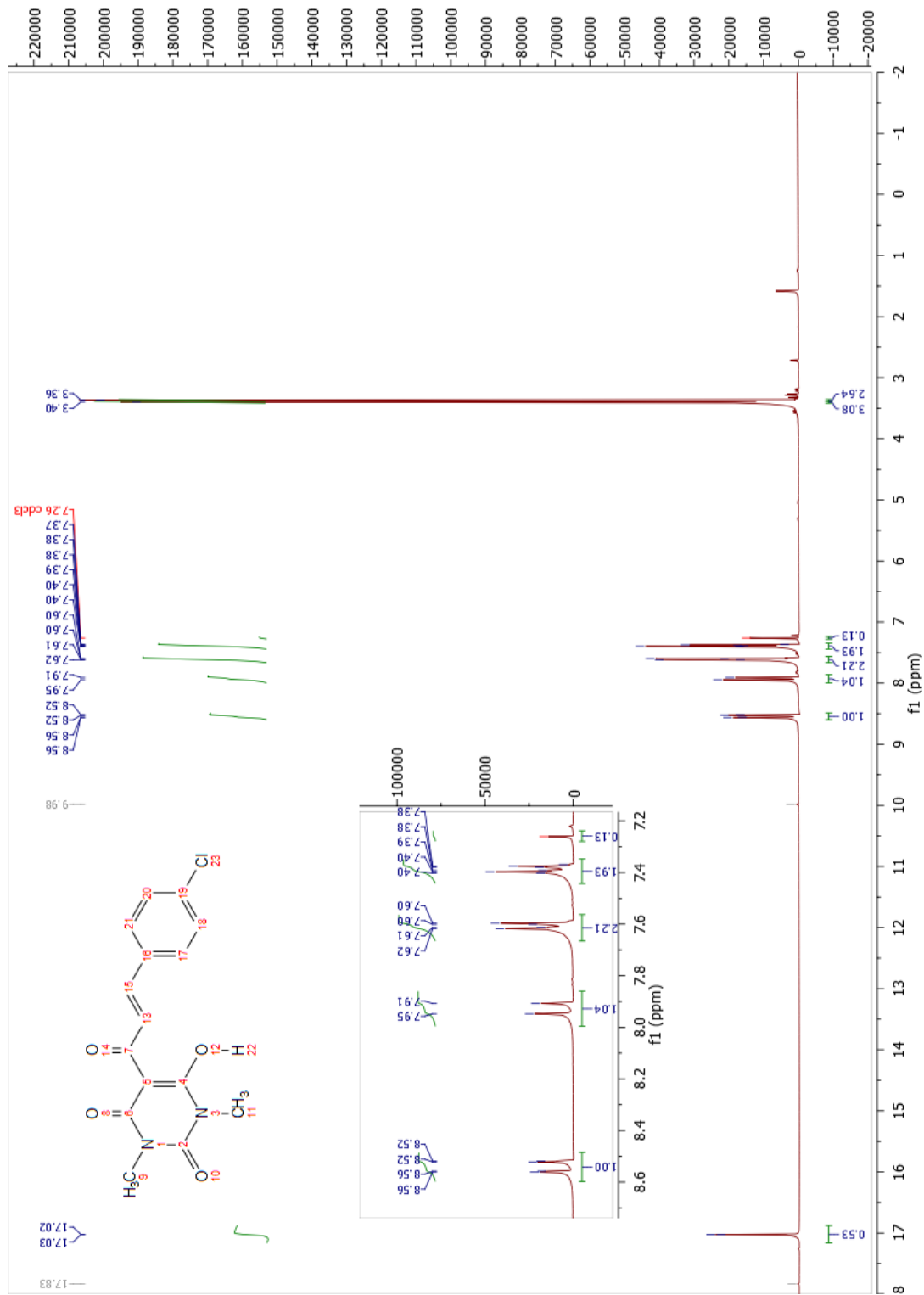
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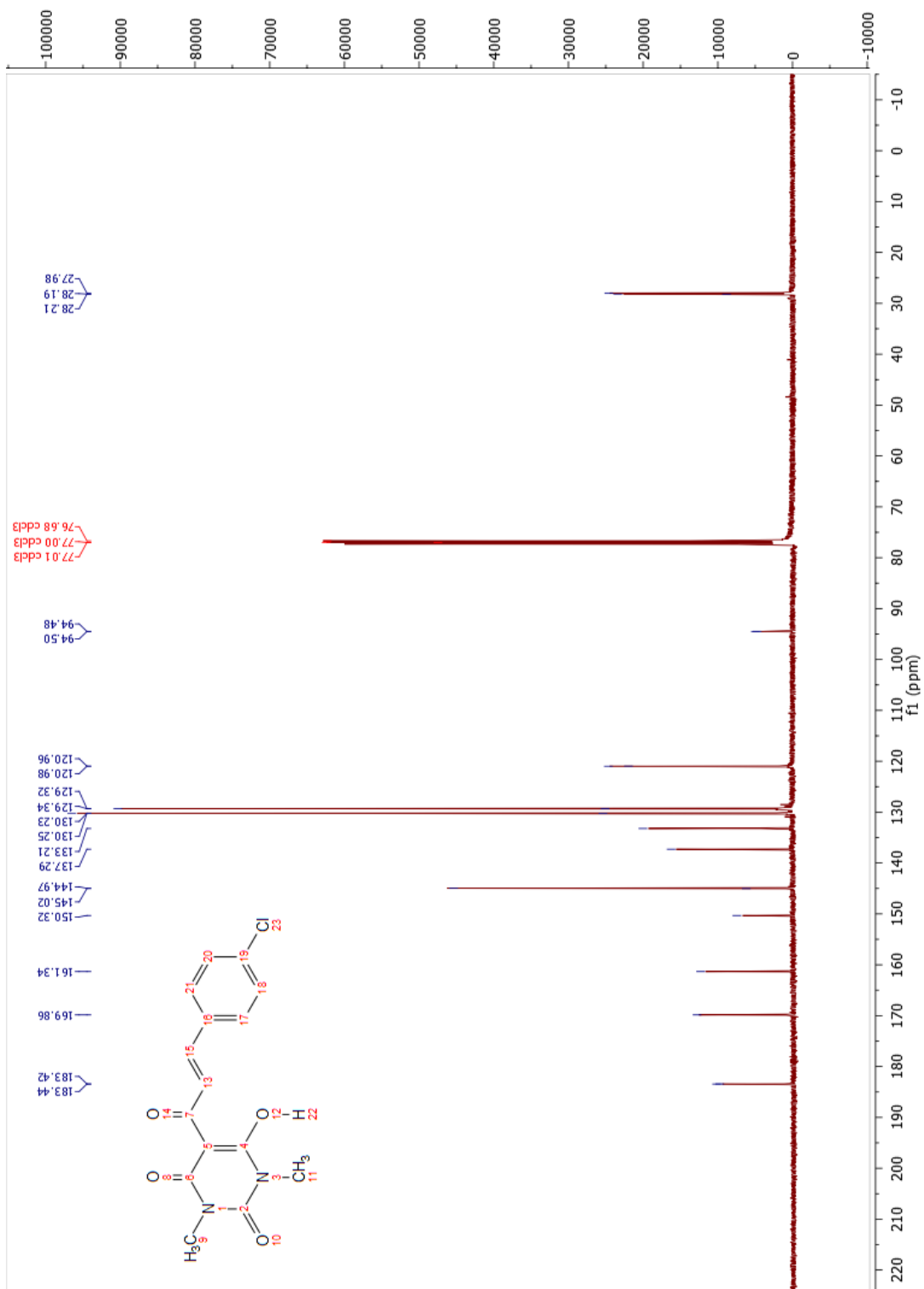
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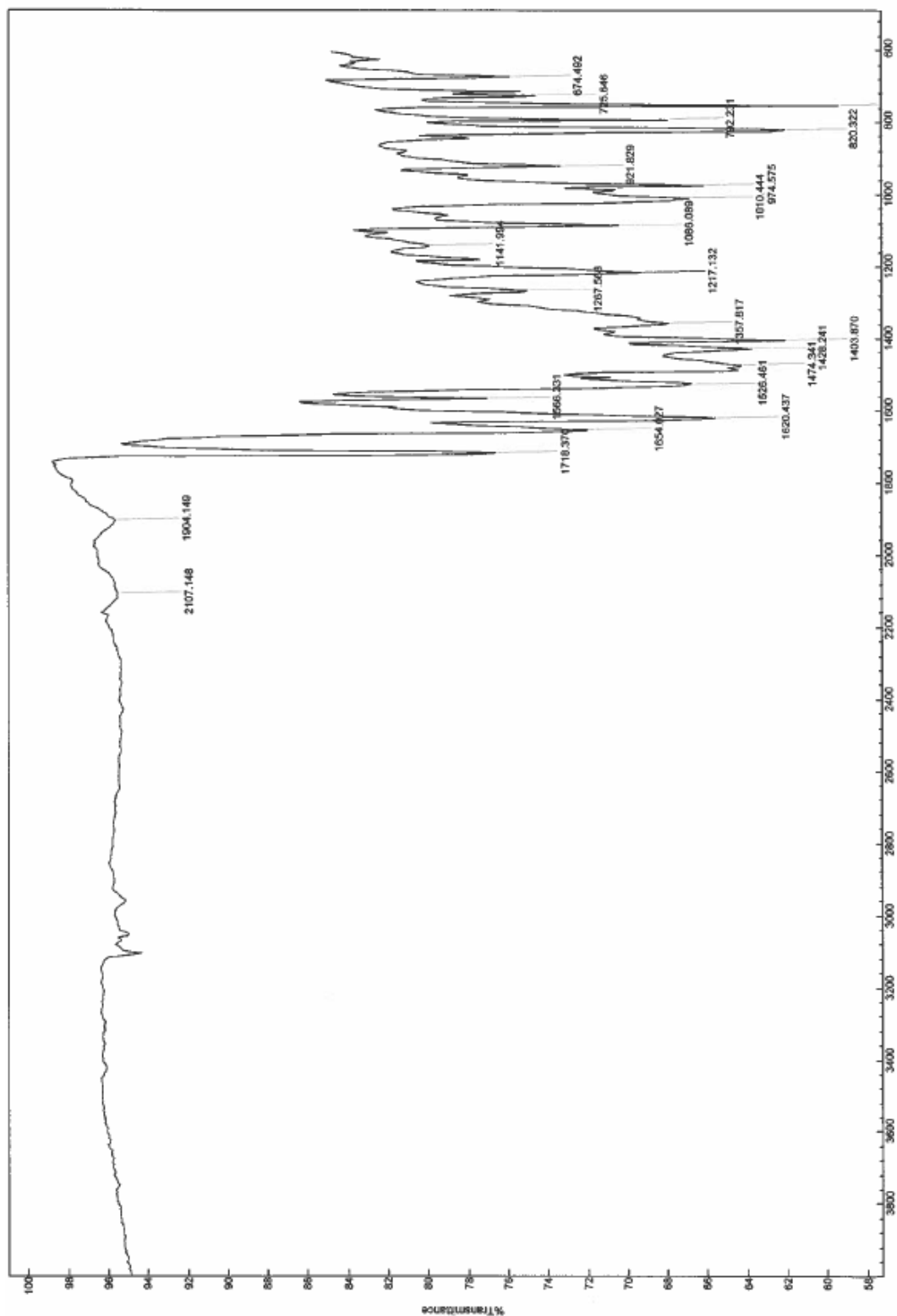
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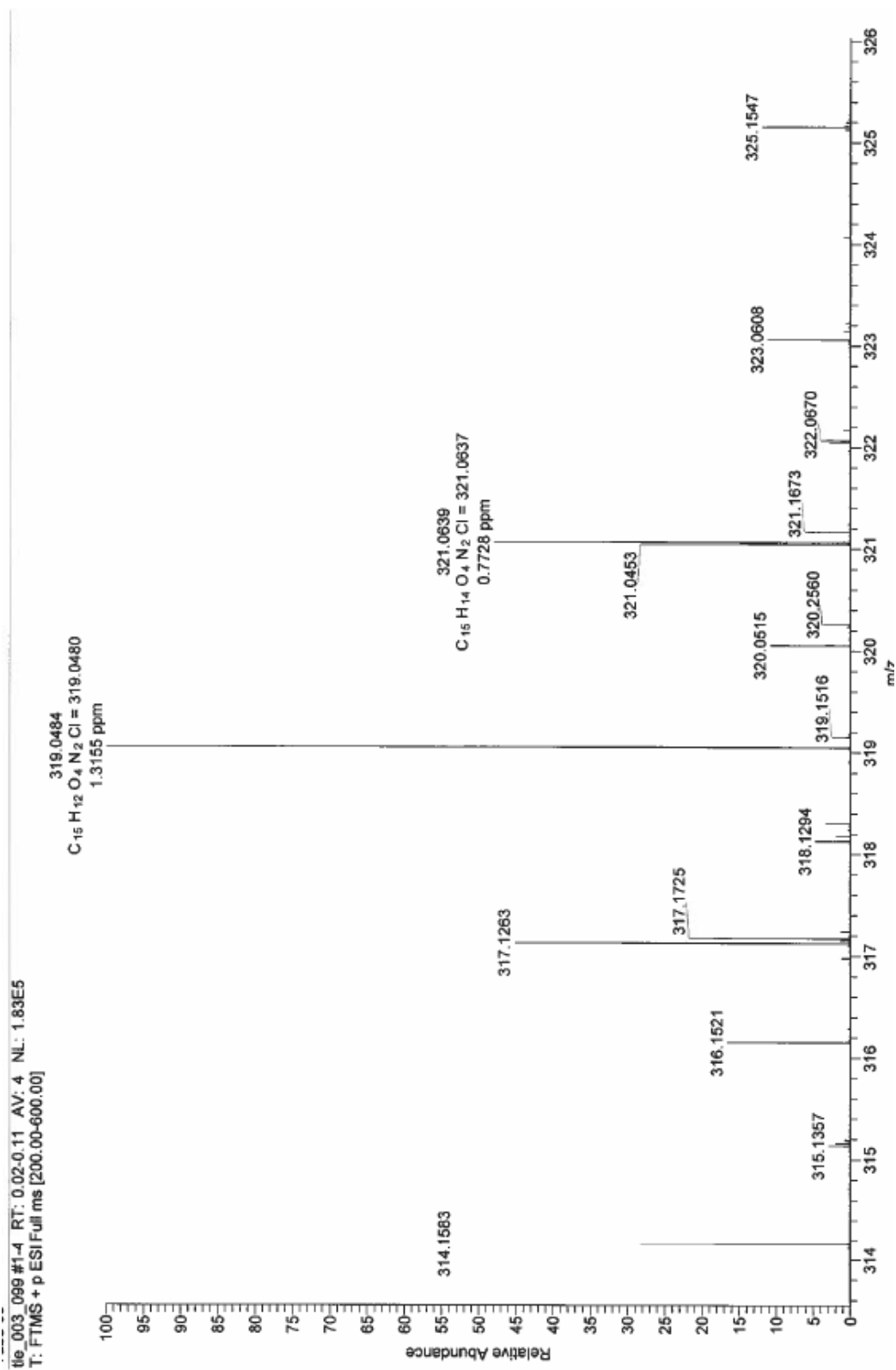
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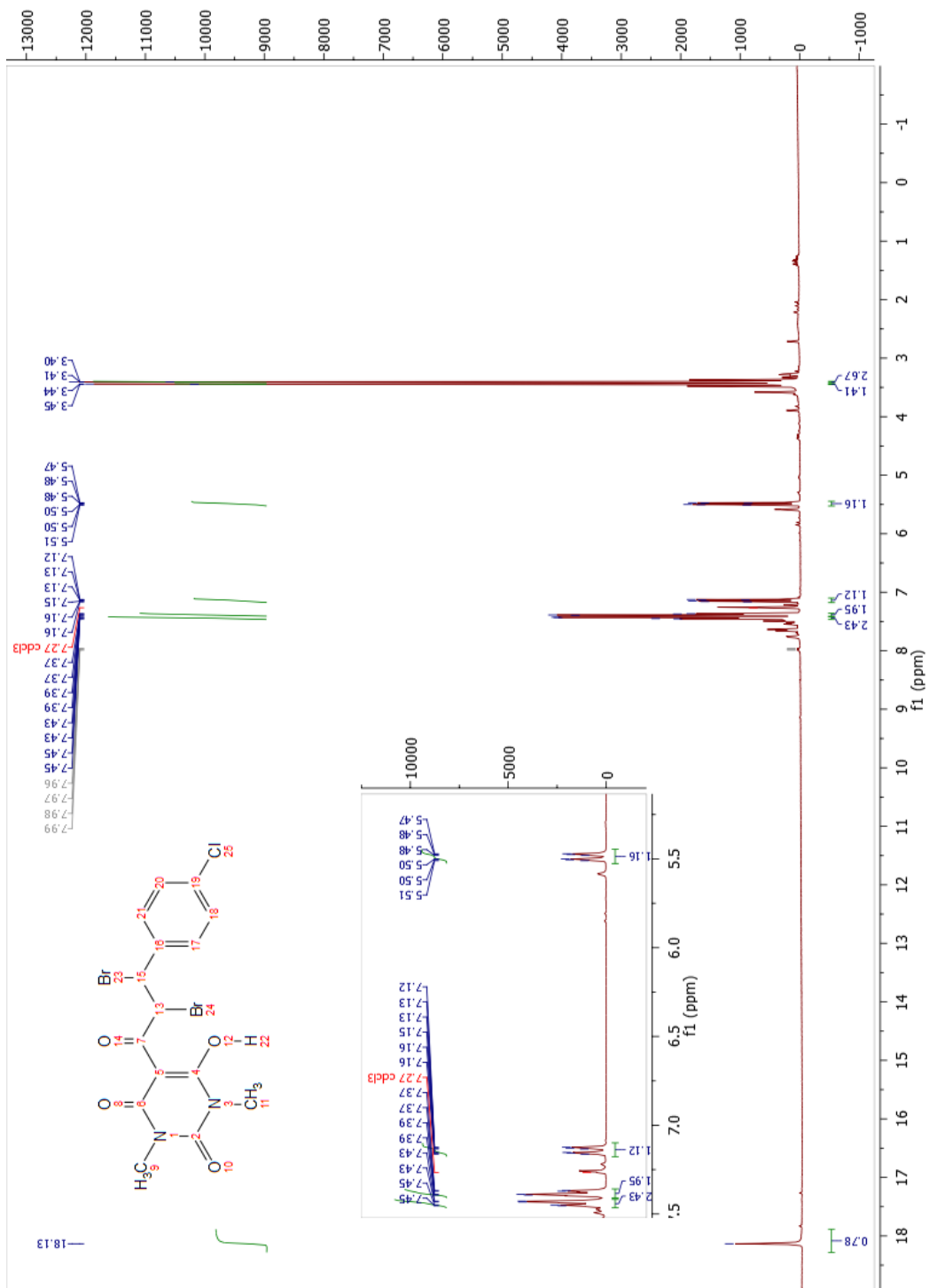
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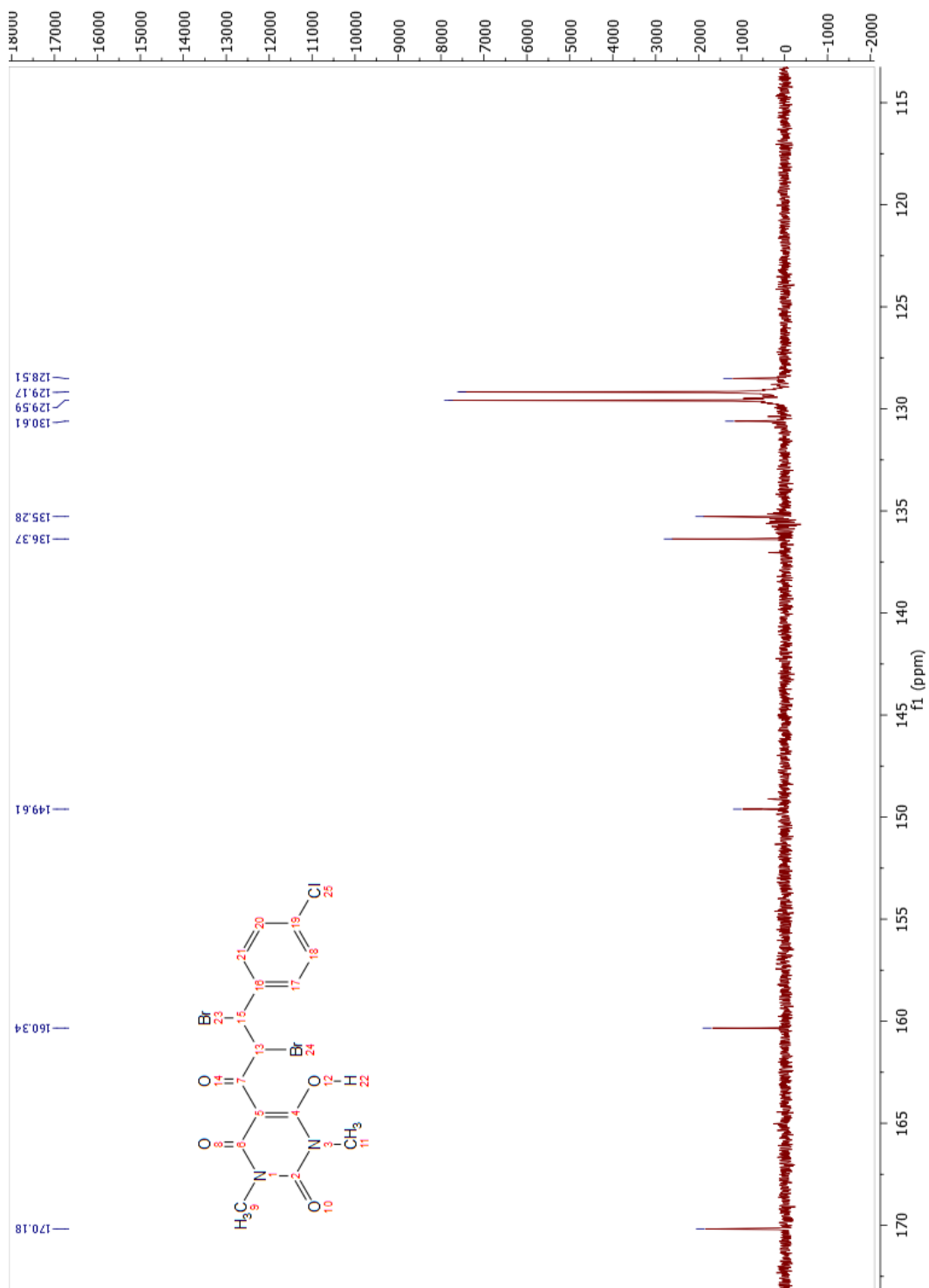
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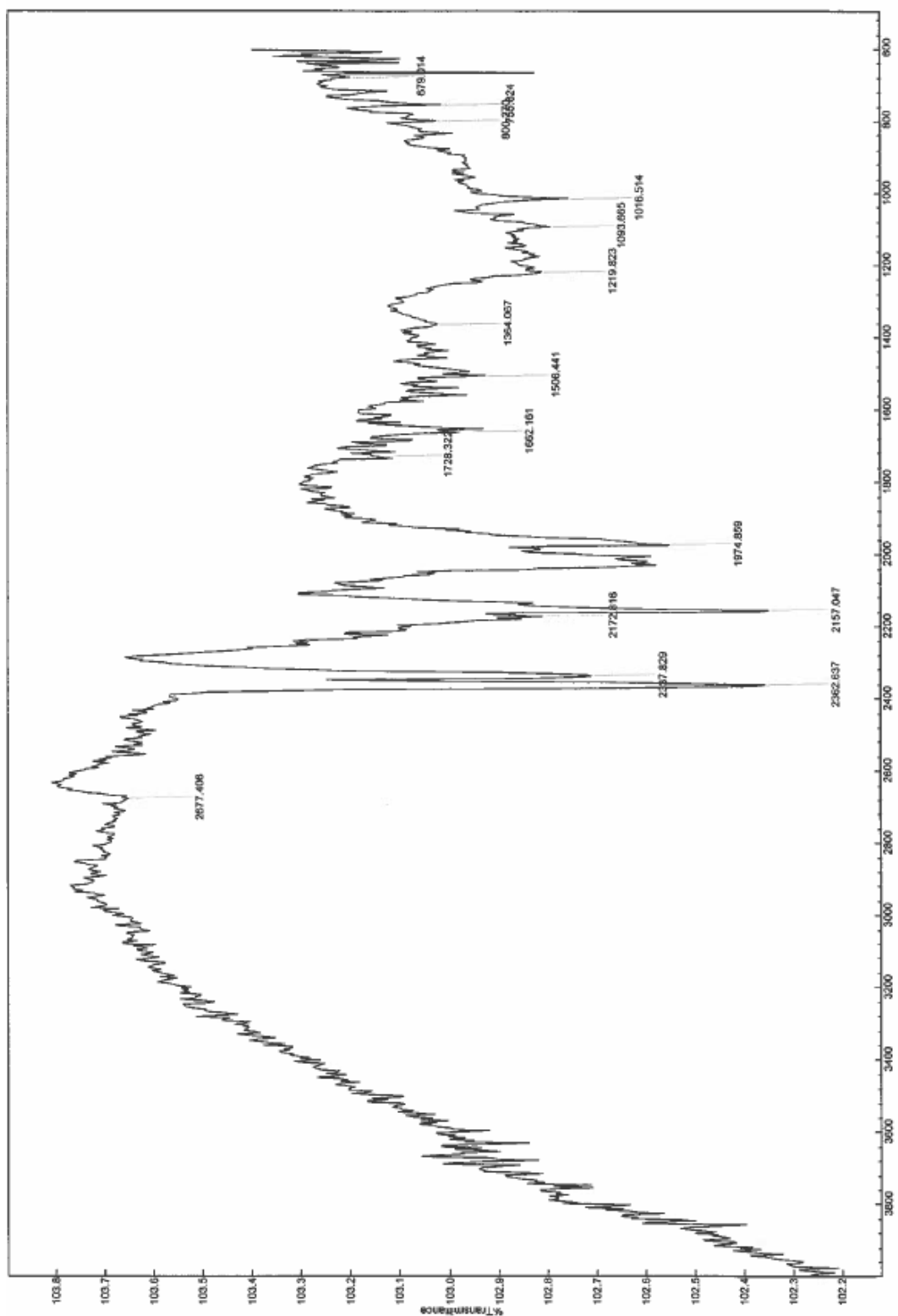
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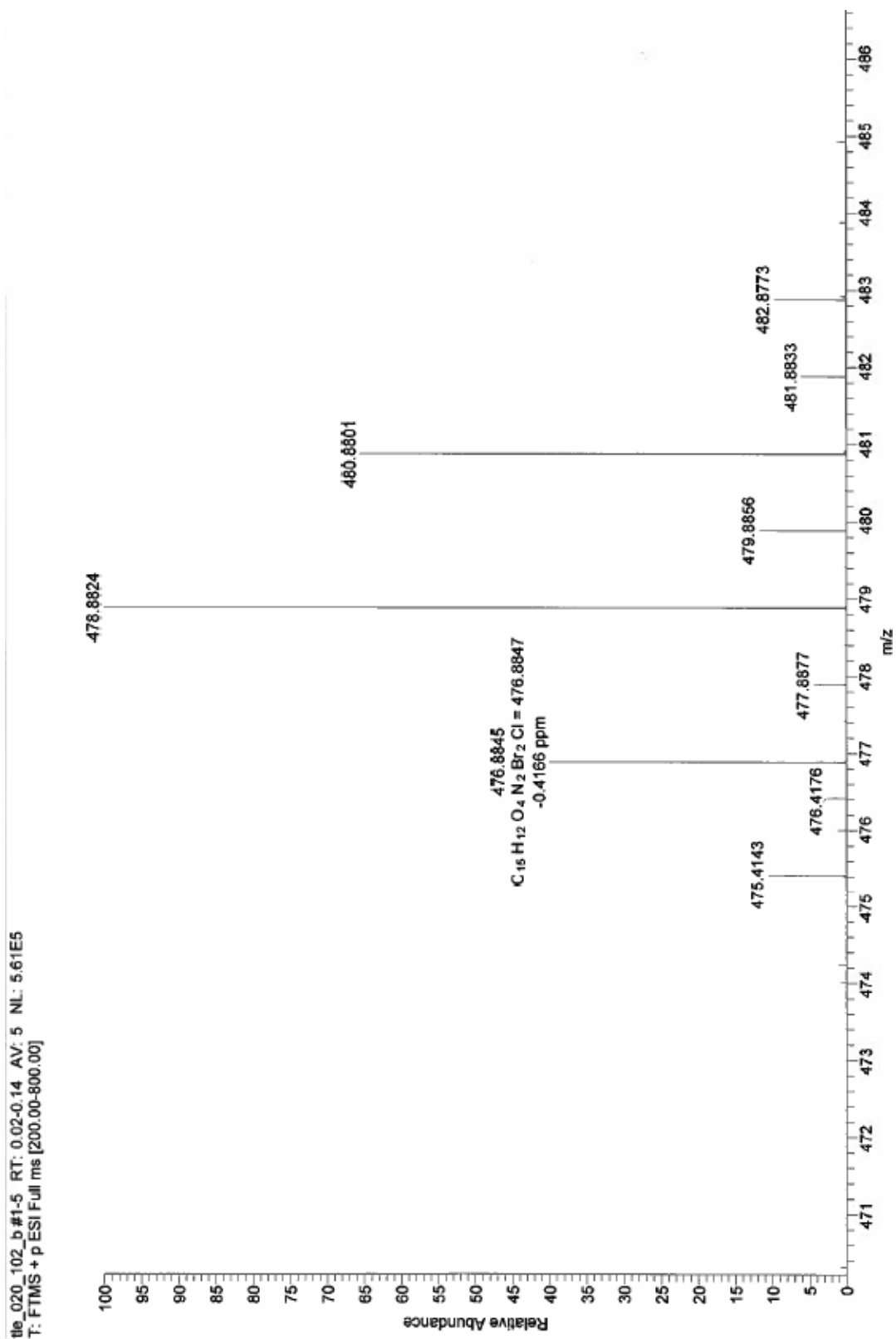
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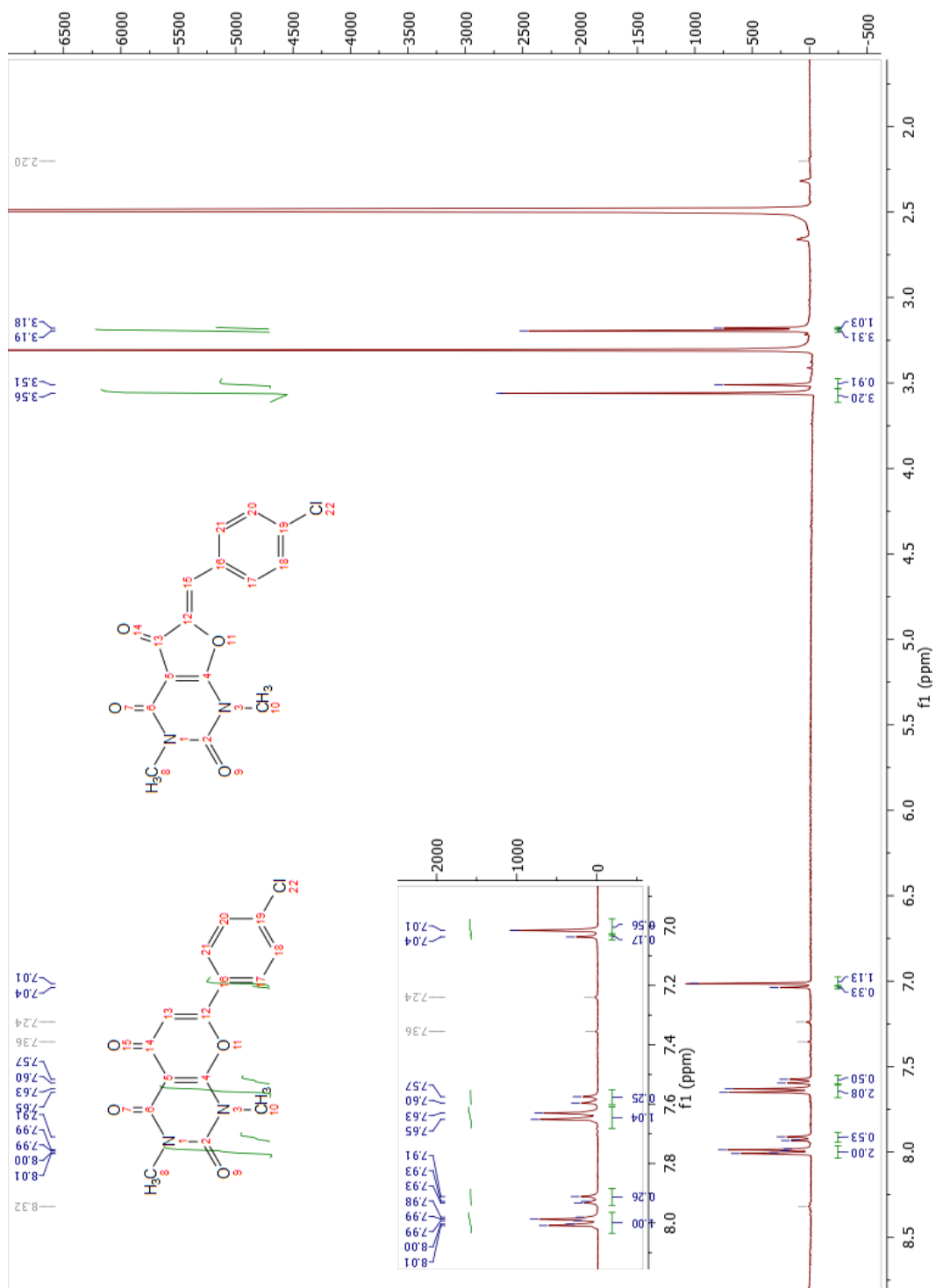
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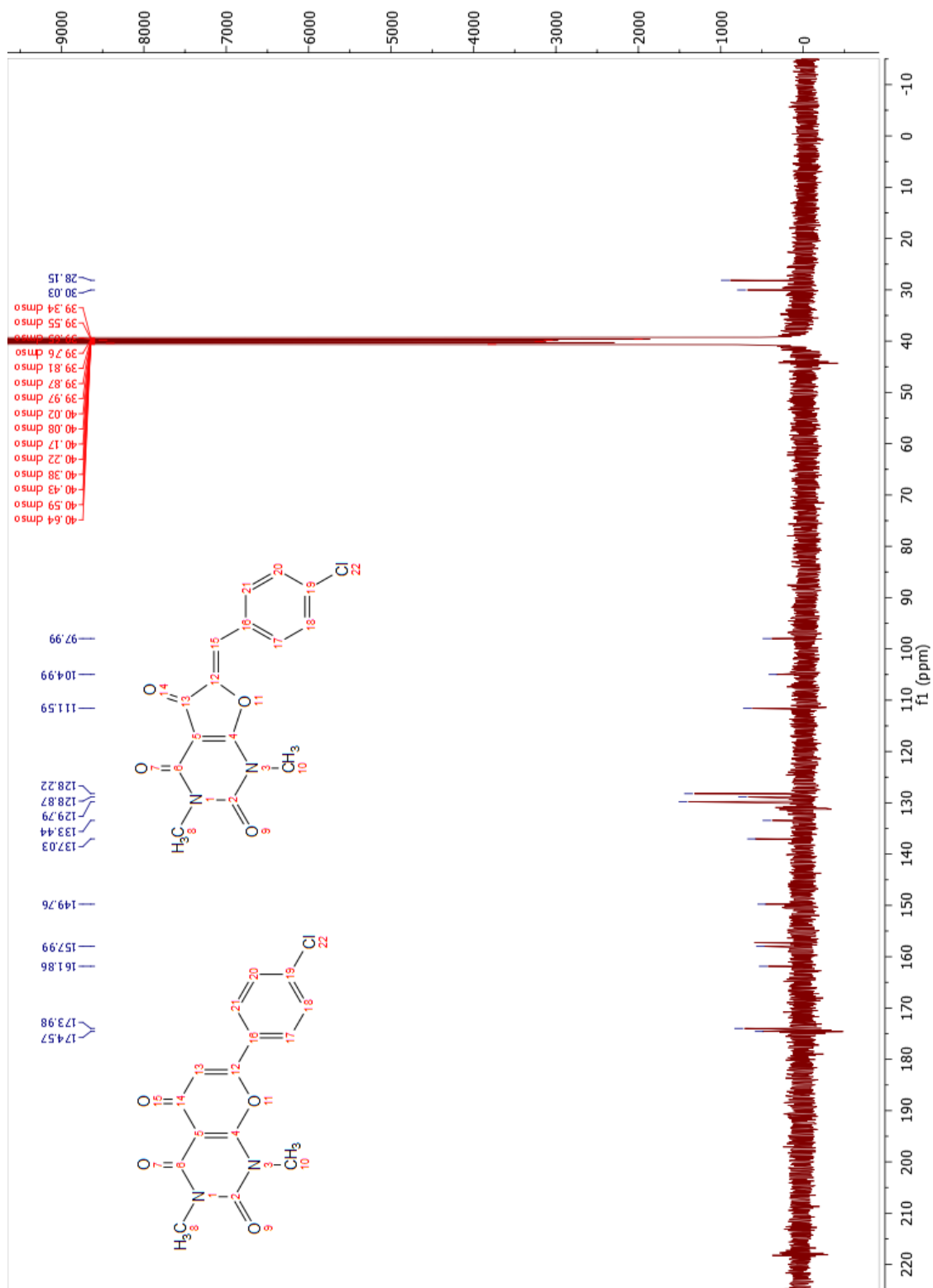
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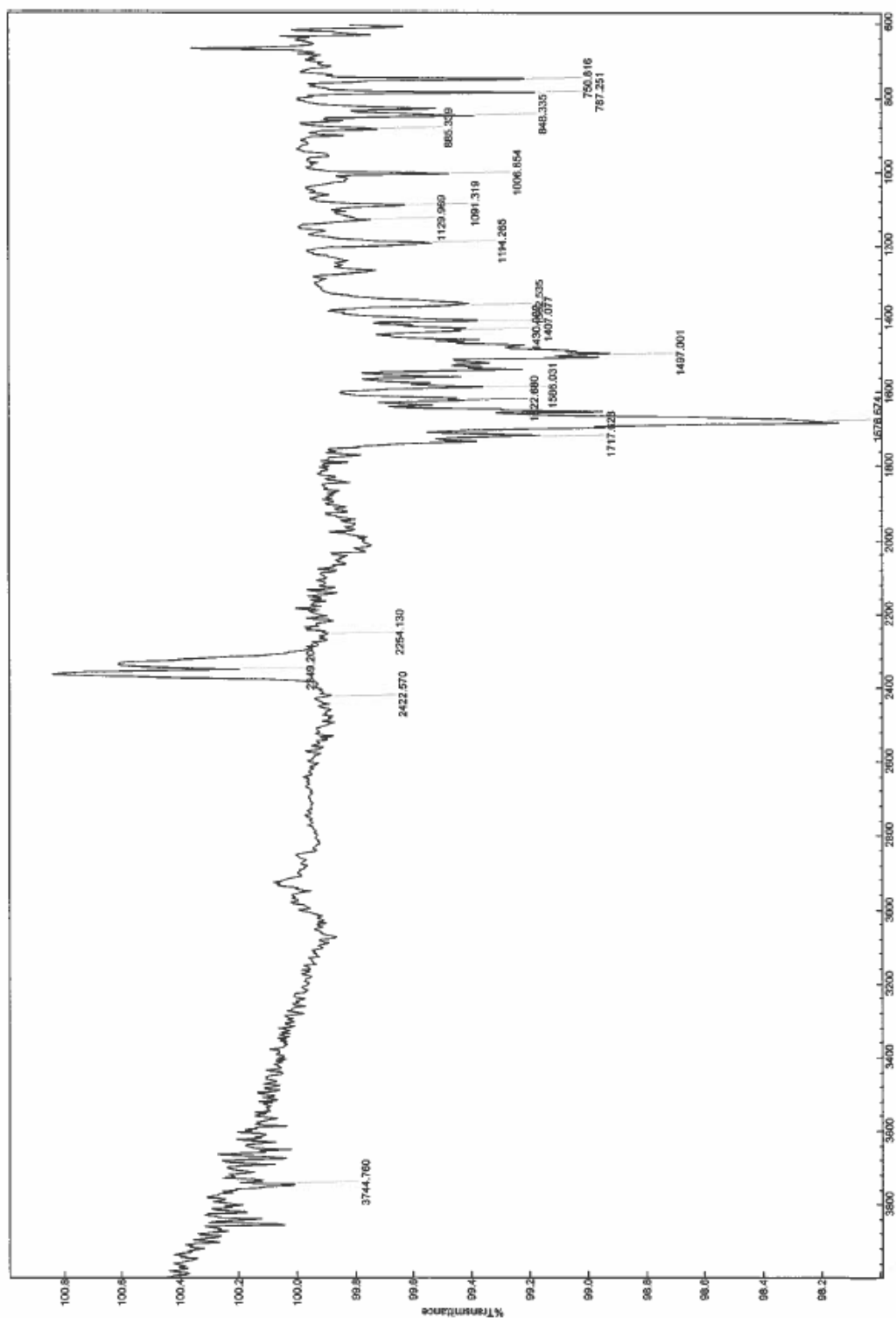
¹H NMR of (Z)-6-(4-chlorobenzylidene)-1,3-dimethylfuro[2,3-d]pyrimidine-2,4,5(1H,3H,6H)-trione and 7-(4-chlorophenyl)-1,3-dimethyl-1H-pyrano[2,3-d]pyrimidine-2,4,5(3H)-trione



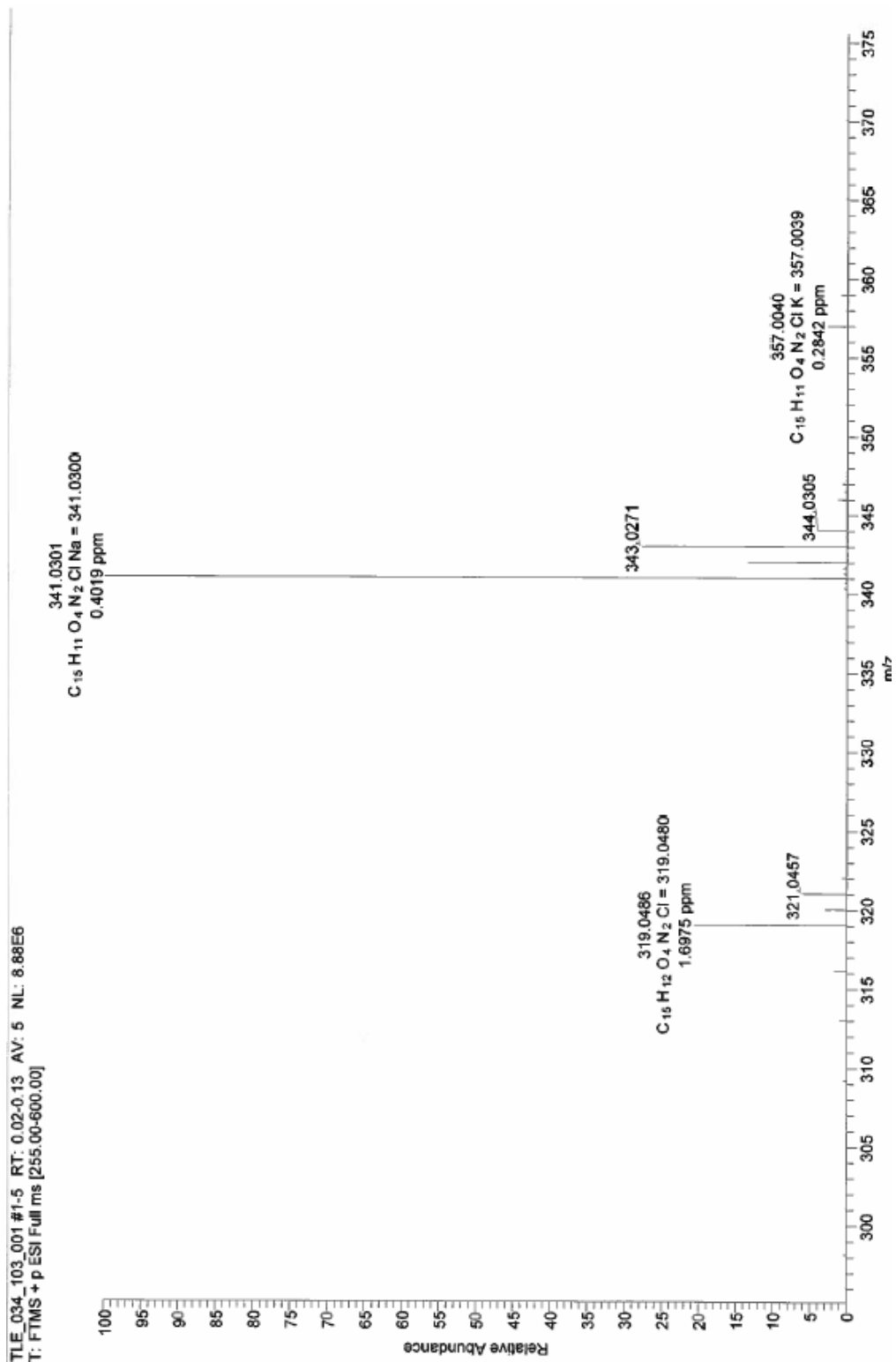
¹³C NMR of (Z)-6-(4-chlorobenzylidene)-1,3-dimethylfuro[2,3-d]pyrimidine-2,4,5(1H,3H,6H)-trione and 7-(4-chlorophenyl)-1,3-dimethyl-1H-pyrano[2,3-d]pyrimidine-2,4,5(3H)-trione



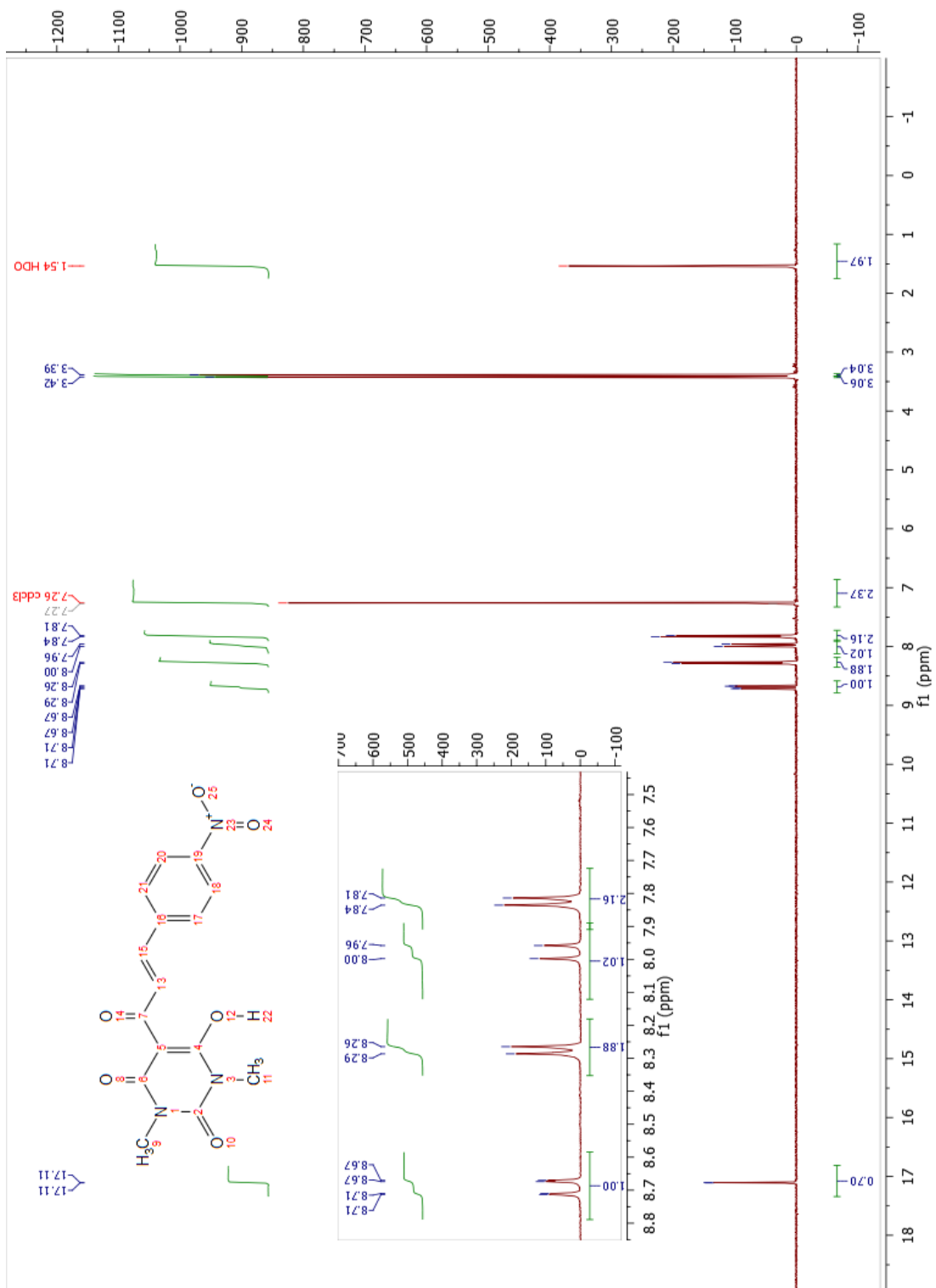
IR of Z)-6-(4-chlorobenzylidene)-1,3-dimethylfuro[2,3-d]pyrimidine-2,4,5(1H,3H,6H)-trione and 7-(4-chlorophenyl)-1,3-dimethyl-1H-pyrano[2,3-d]pyrimidine-2,4,5(3H)-trione



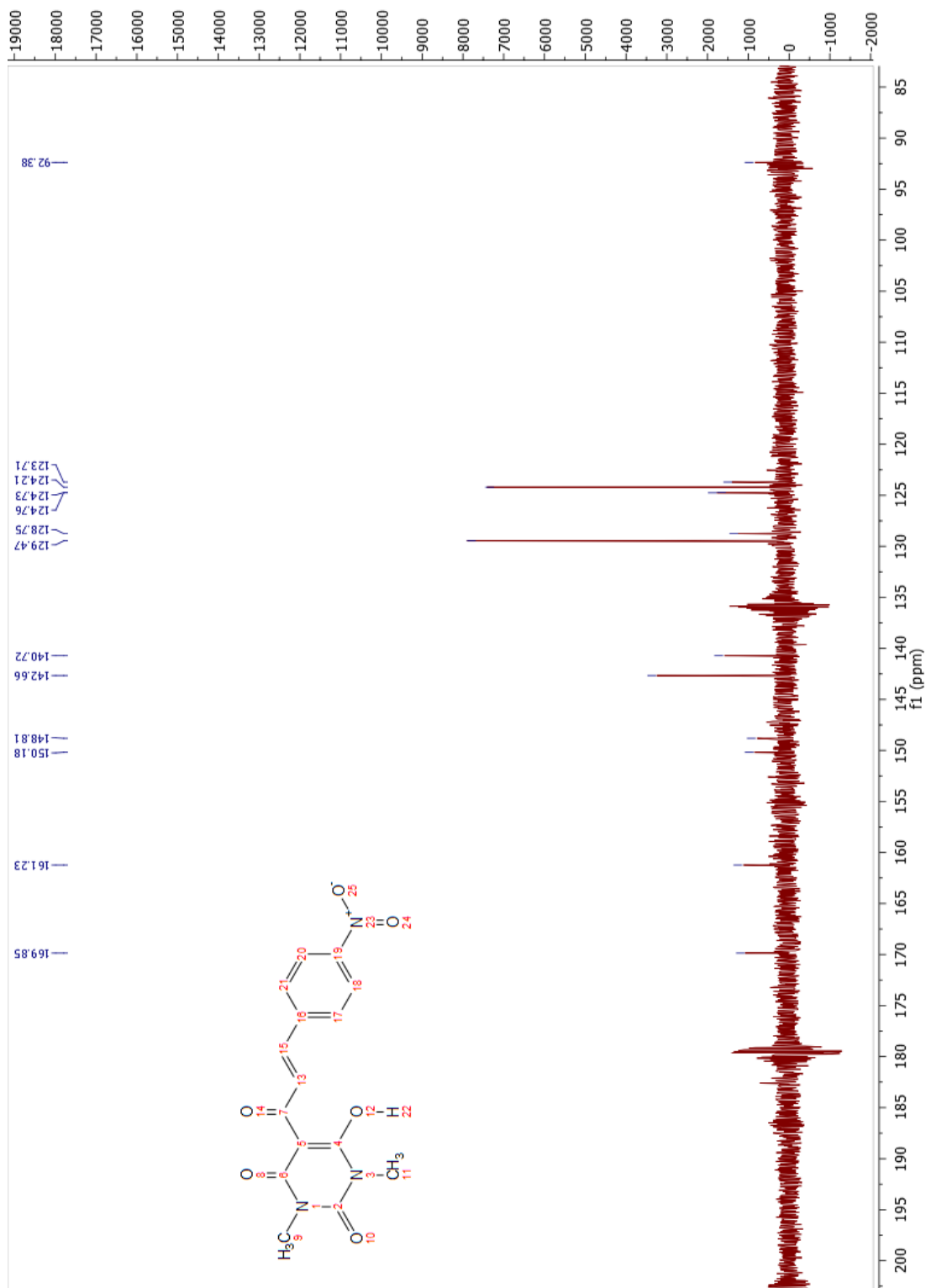
MS of *Z*-6-(4-chlorobenzylidene)-1,3-dimethylfuro[2,3-d]pyrimidine-2,4,5(1H,3H,6H)-trione and 7-(4-chlorophenyl)-1,3-dimethyl-1H-pyrano[2,3-d]pyrimidine-2,4,5(3H)-trione



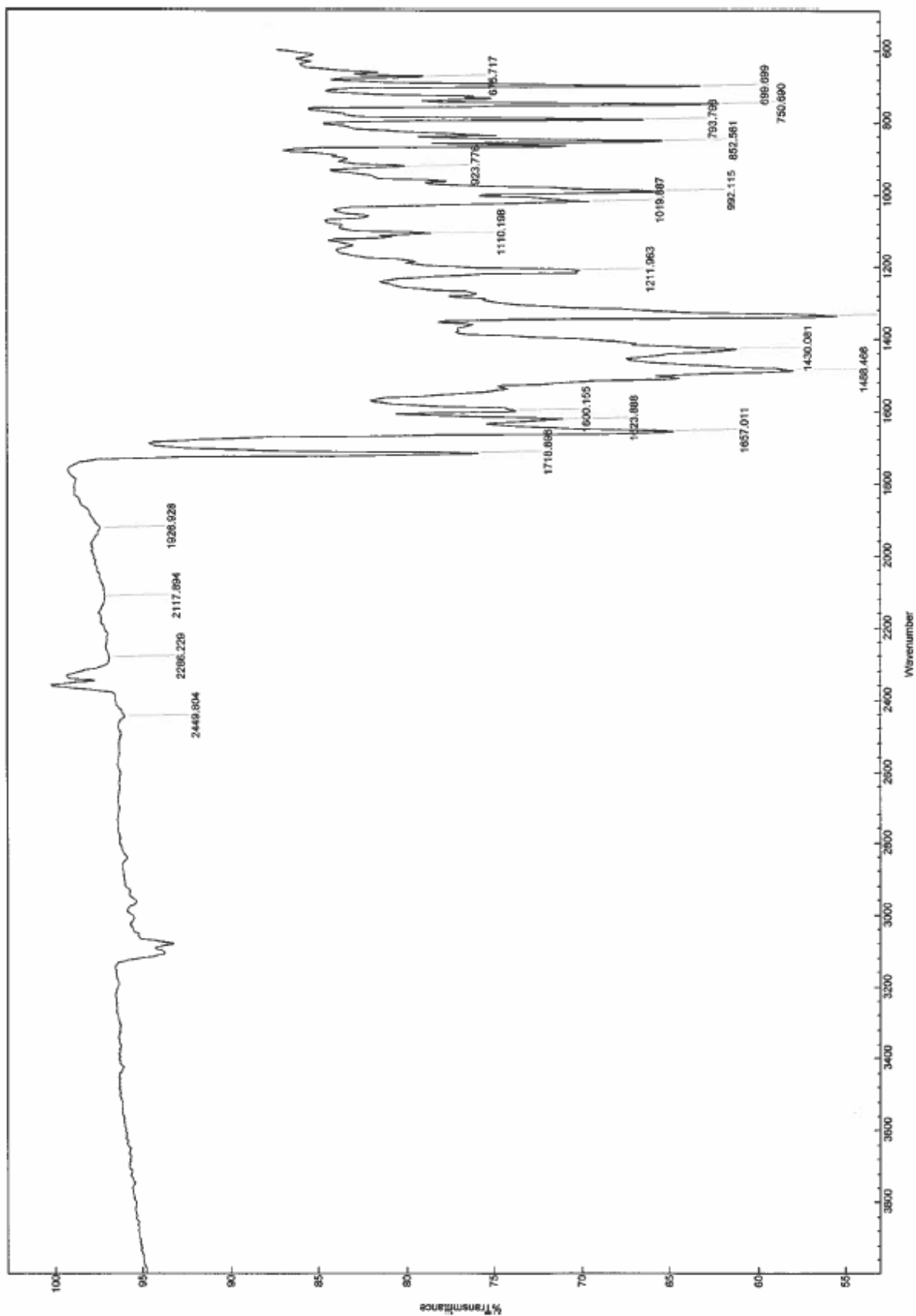
¹H NMR of (E)-6-hydroxy-1,3-dimethyl-5-(3-(4-nitrophenyl)acryloyl)pyrimidine-2,4(1H,3H)-dione



¹³C NMR of (E)-6-hydroxy-1,3-dimethyl-5-(3-(4-nitrophenyl)acryloyl)pyrimidine-2,4(1H,3H)-dione



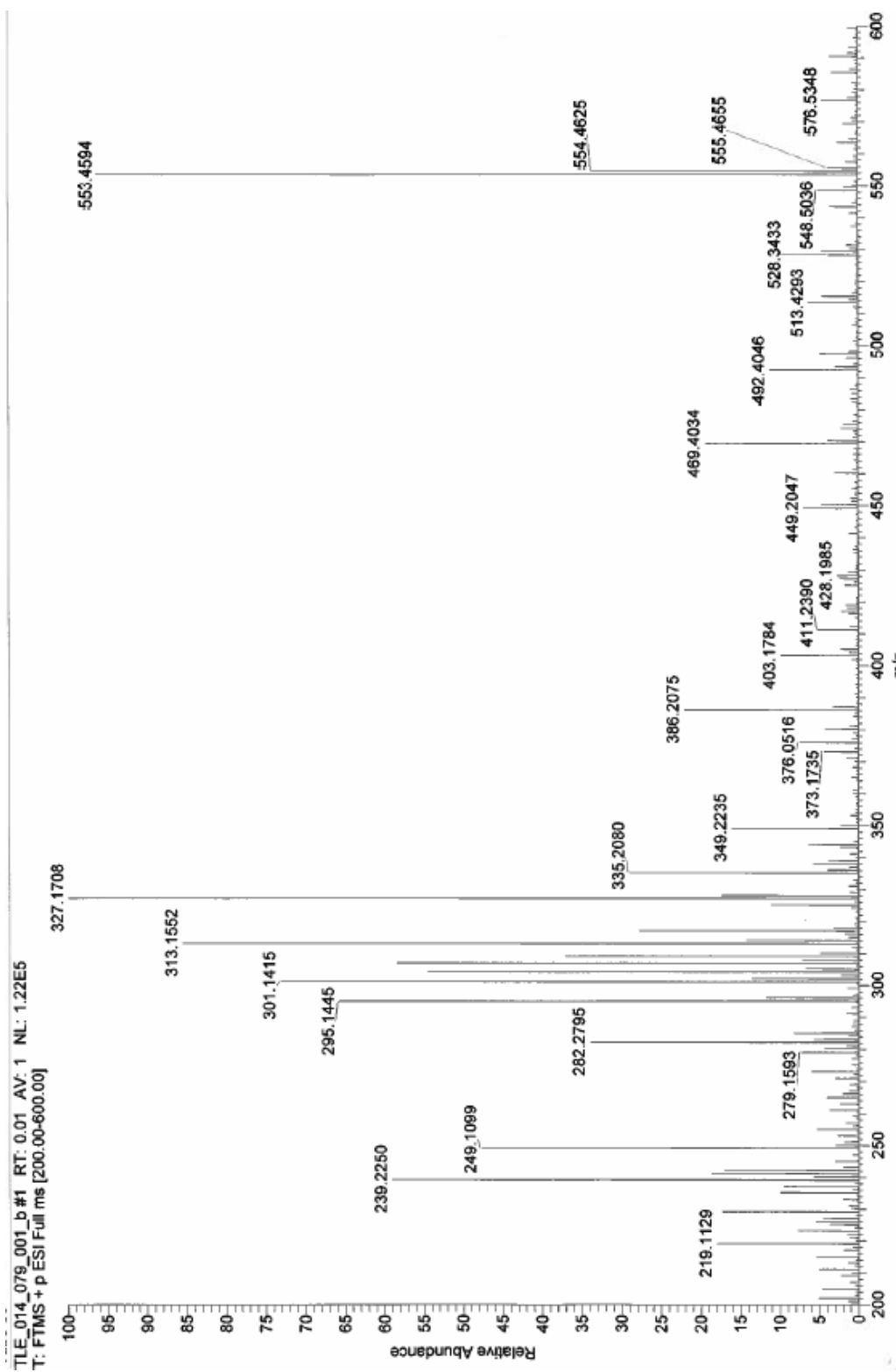
IR of (E)-6-hydroxy-1,3-dimethyl-5-(3-(4-nitrophenyl)acryloyl)pyrimidine-2,4(1H,3H)-dione



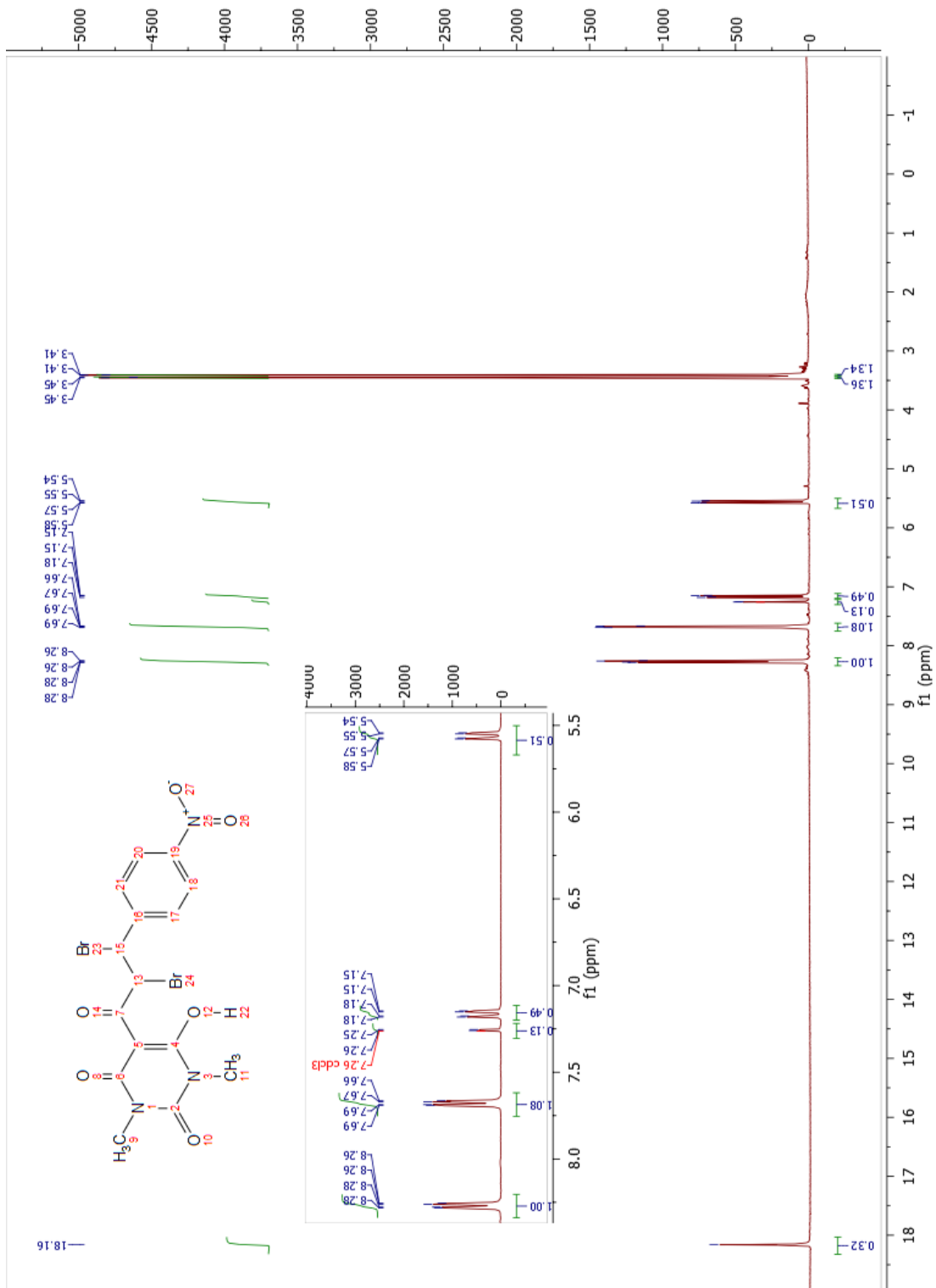
Monday, May 14, 2012 20:33:52

Multi-Spectral
NIR-FTIR

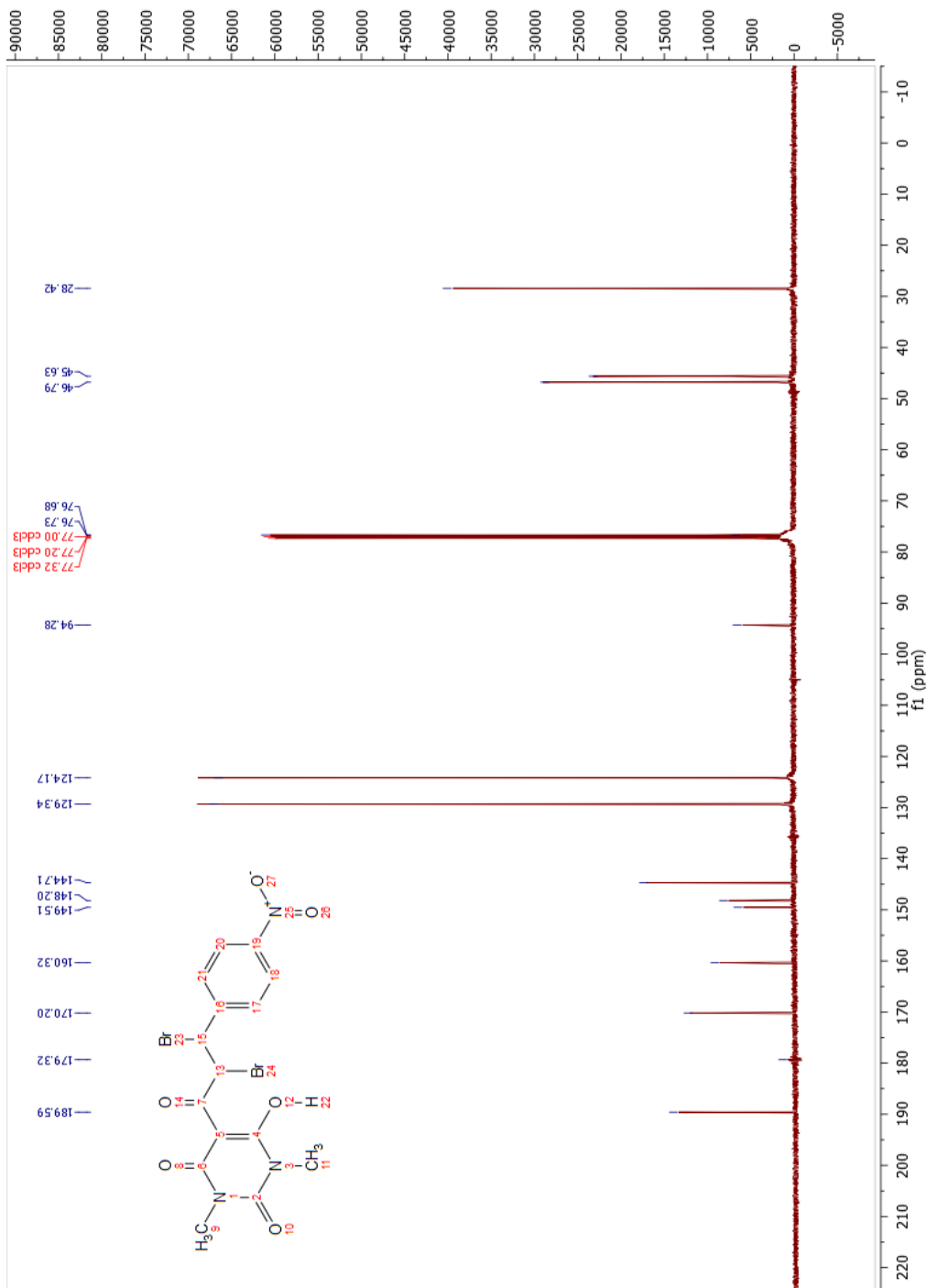
MS of (E)-6-hydroxy-1,3-dimethyl-5-(3-(4-nitrophenyl)acryloyl)pyrimidine-2,4(1H,3H)-dione



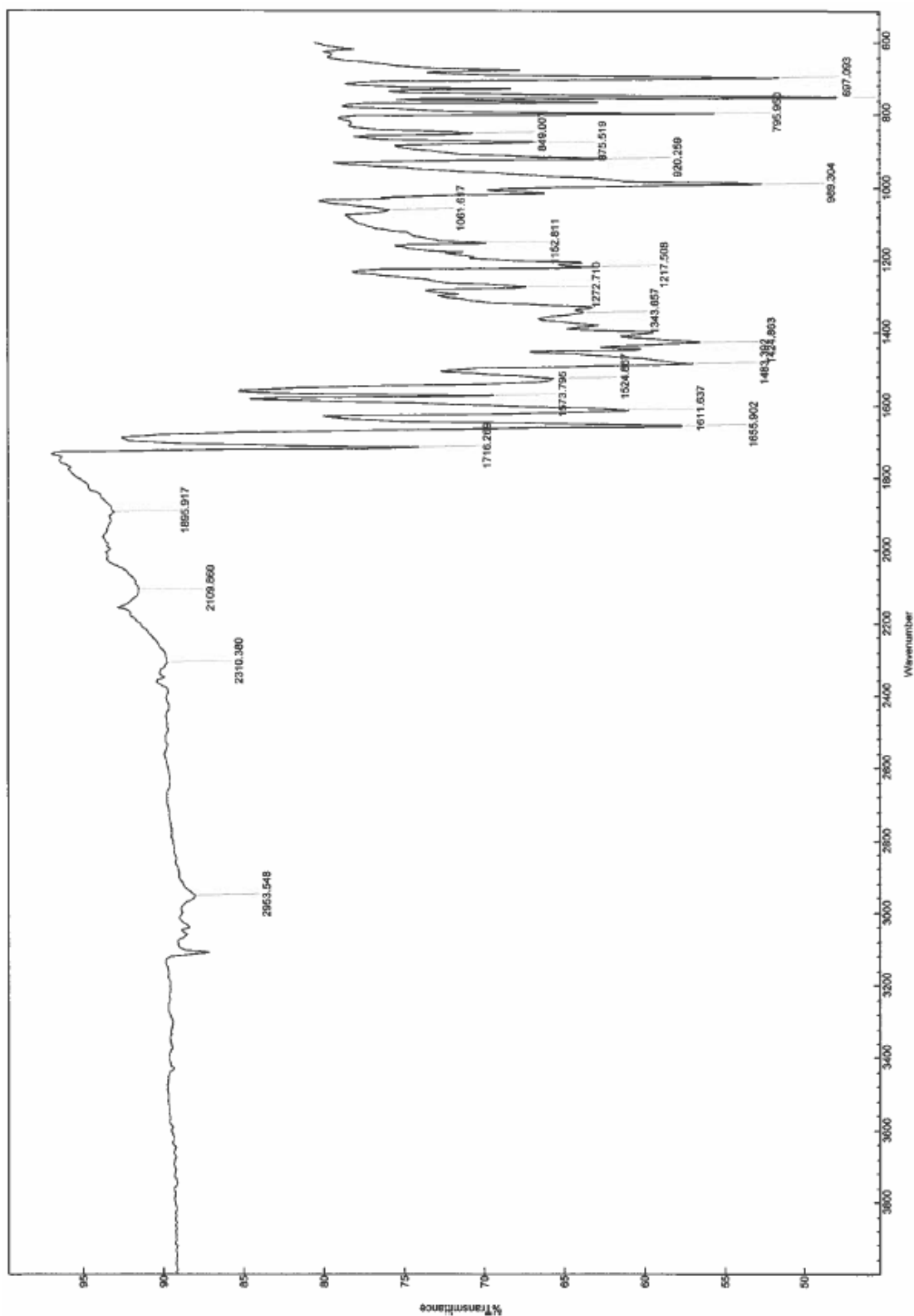
¹H NMR of 5-(2,3-dibromo-3-(4-nitrophenyl)propanoyl)-6-hydroxy-1,3-dimethylpyrimidine-2,4(1H,3H)-dione



¹³C NMR of 5-(2,3-dibromo-3-(4-nitrophenyl)propanoyl)-6-hydroxy-1,3-dimethylpyrimidine-2,4(1H,3H)-dione



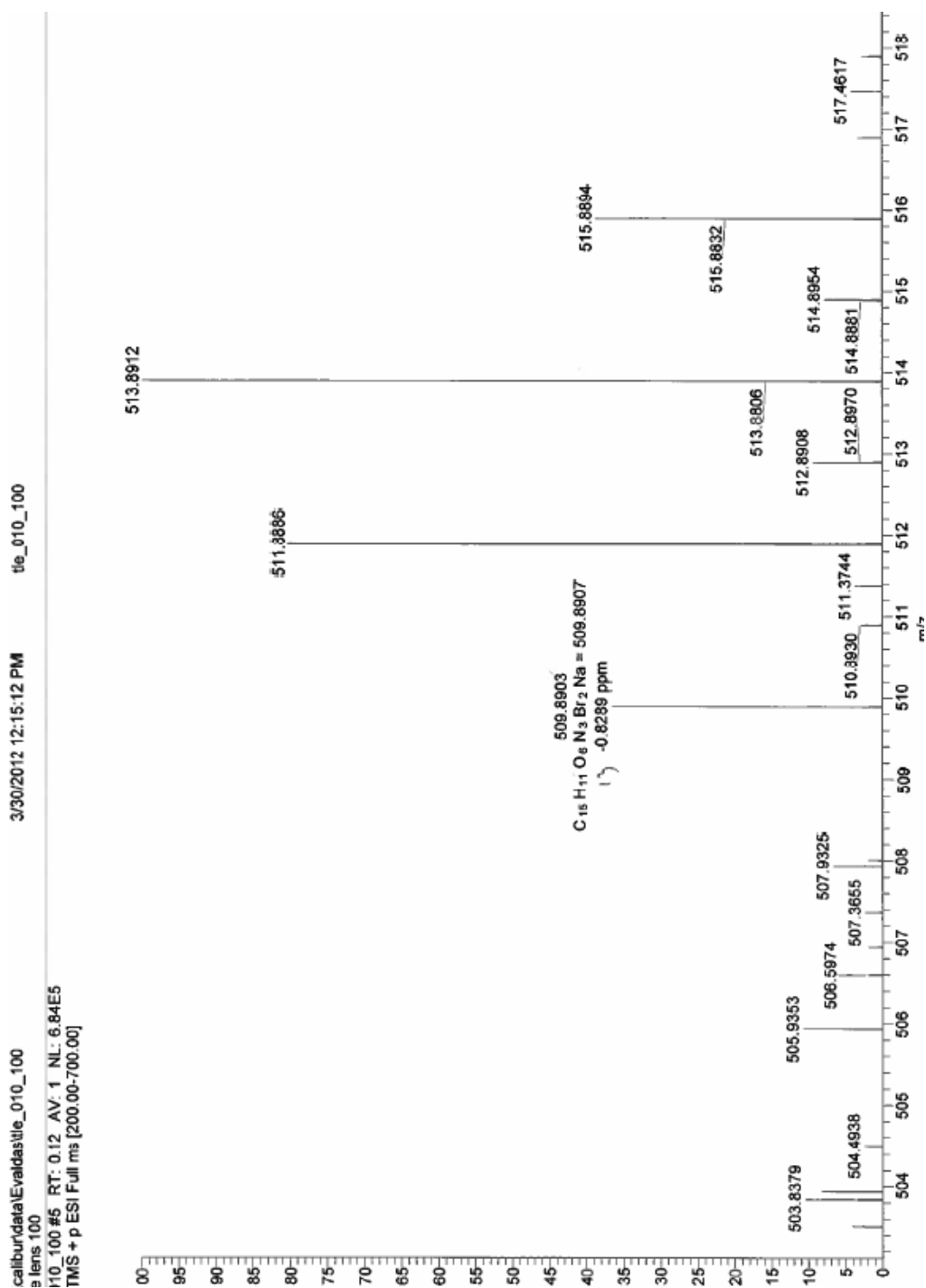
IR of 5-(2,3-dibromo-3-(4-nitrophenyl)propanoyl)-6-hydroxy-1,3-dimethylpyrimidine-2,4(1H,3H)-dione



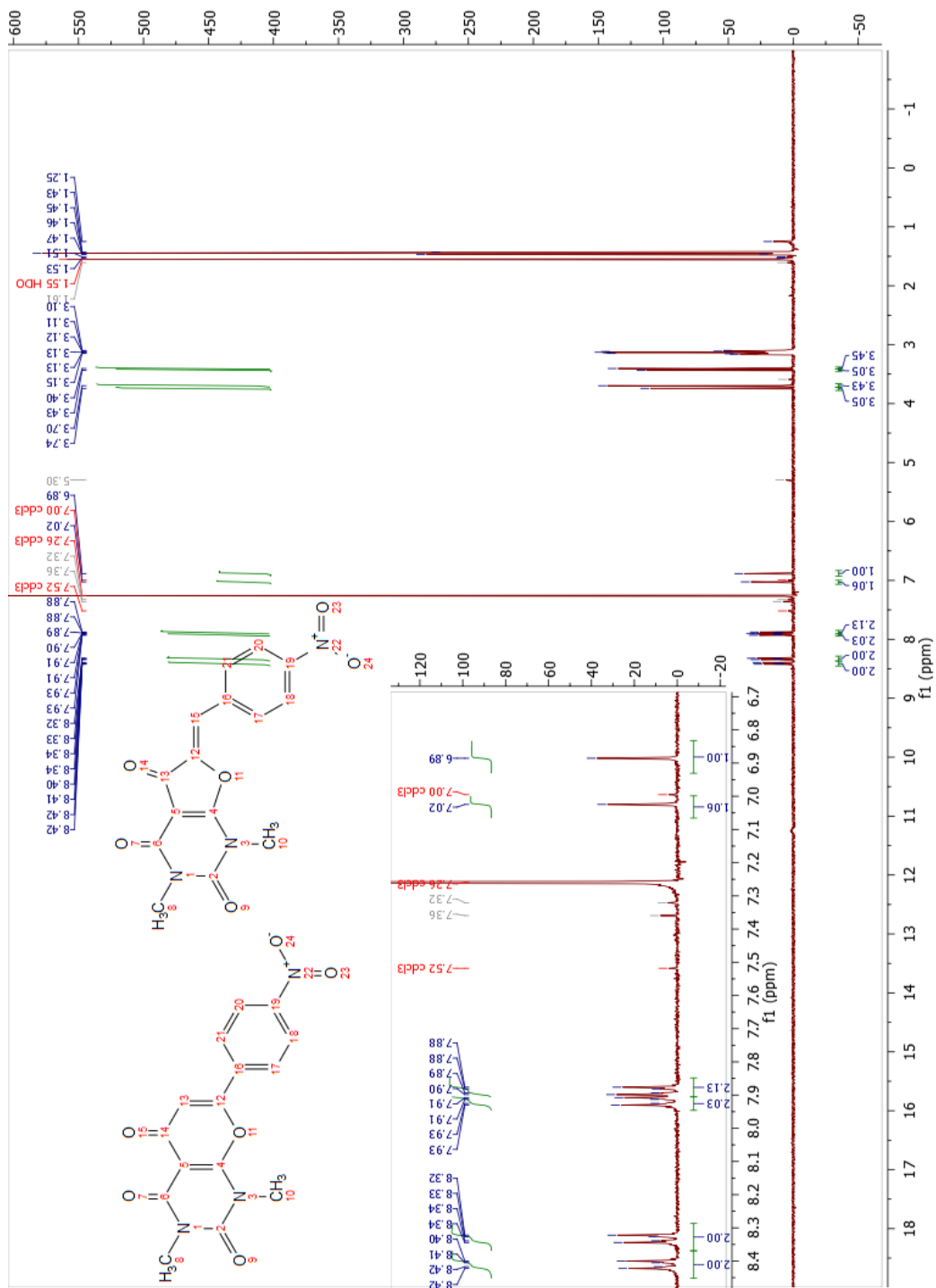
Monday, May 14, 2012 20:50:05

Multi-Spectral
Data Collection

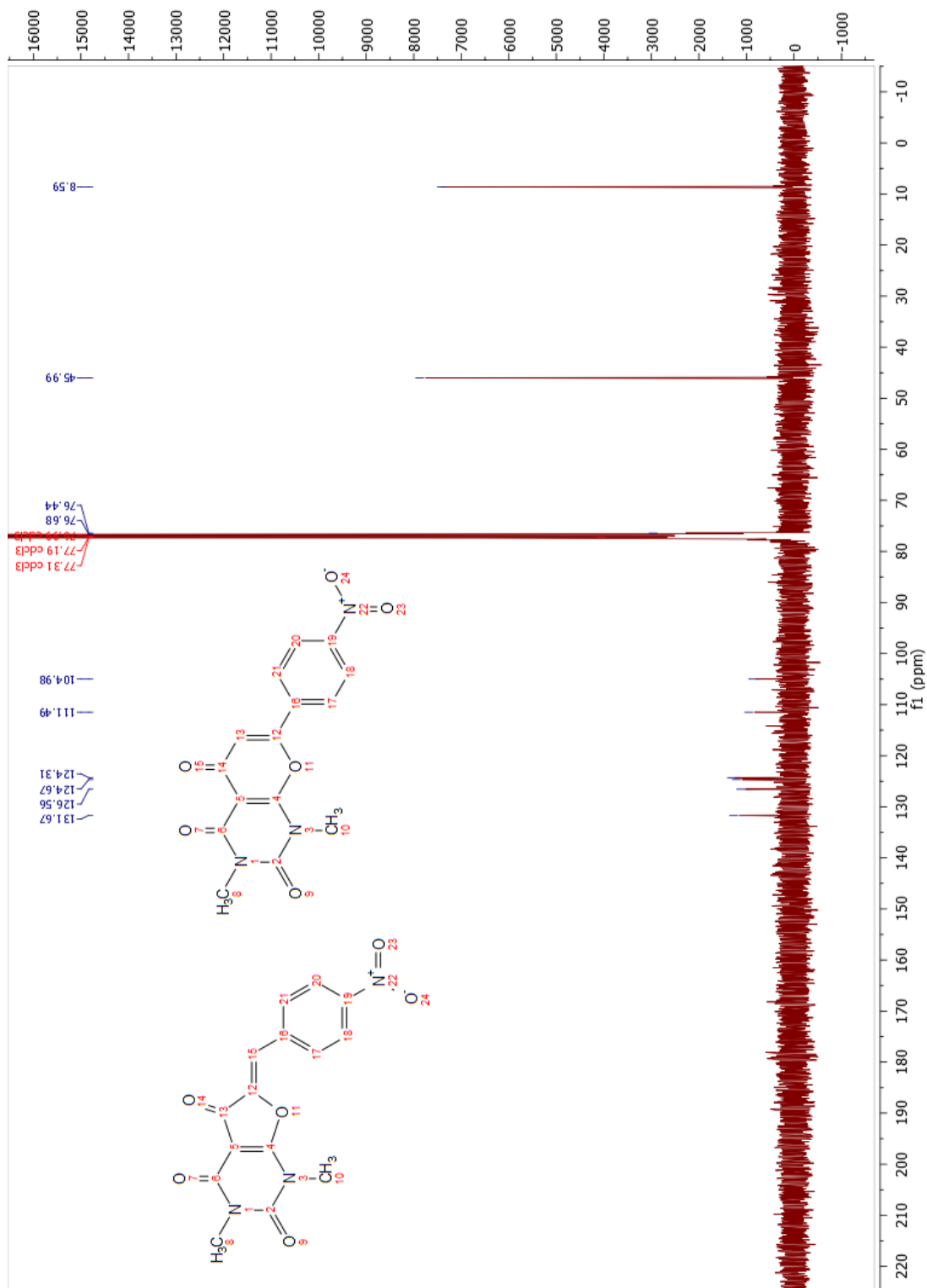
MS of 5-(2,3-dibromo-3-(4-nitrophenyl)propanoyl)-6-hydroxy-1,3-dimethylpyrimidine-2,4(1H,3H)-dione



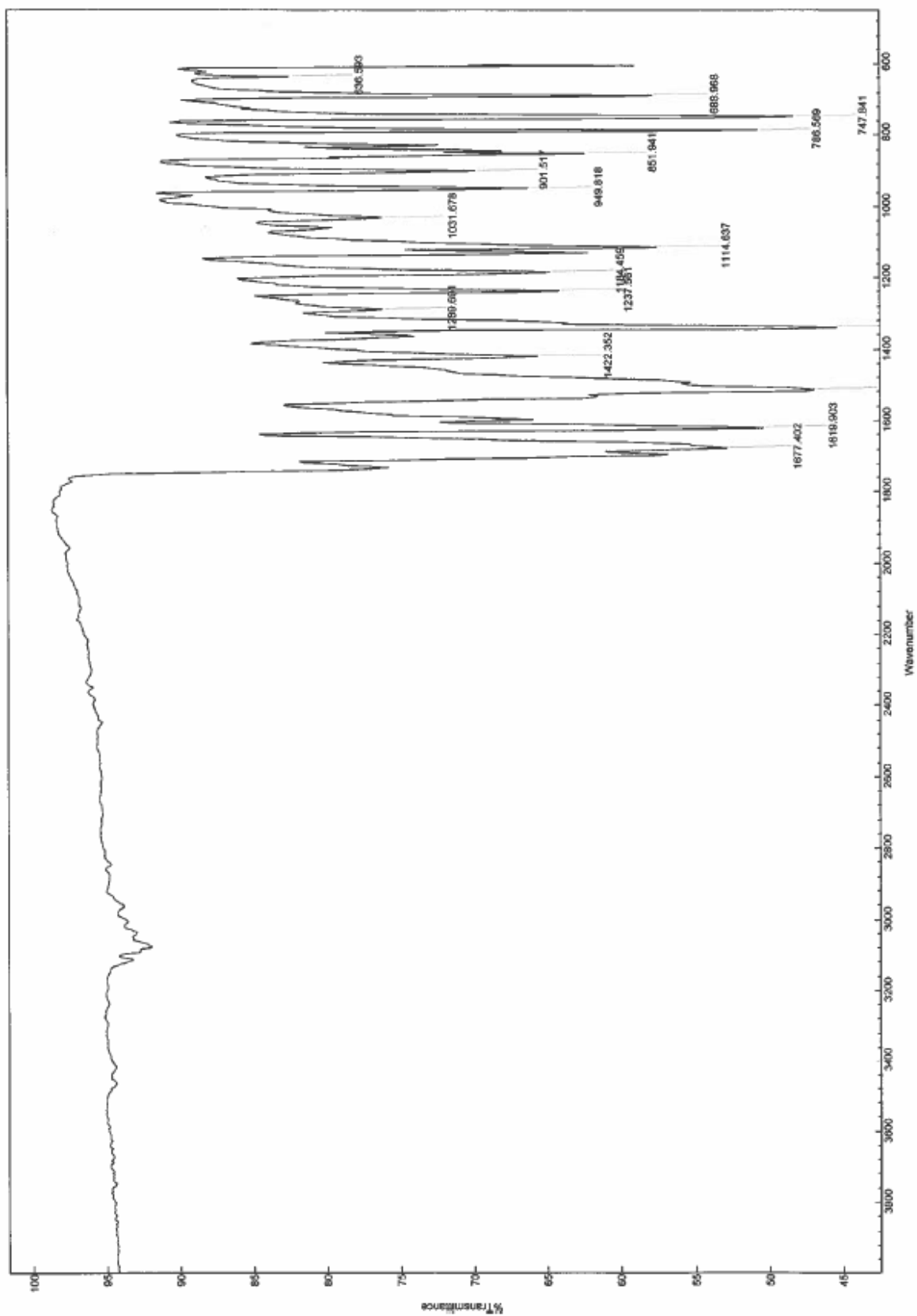
¹H NMR of 1,3-dimethyl-7-(4-nitrophenyl)-1H-pyrano[2,3-d]pyrimidine-2,4,5(3H)-trione and (Z)-1,3-dimethyl-6-(4-nitrobenzylidene)furo[2,3-d]pyrimidine-2,4,5(1H,3H,6H)-trione



^{13}C NMR of 1,3-dimethyl-7-(4-nitrophenyl)-1H-pyrano[2,3-d]pyrimidine-2,4,5(3H)-trione and (Z)-1,3-dimethyl-6-(4-nitrobenzylidene)furo[2,3-d]pyrimidine-2,4,5(1H,3H,6H)-trione



IR of 1,3-dimethyl-7-(4-nitrophenyl)-1H-pyrano[2,3-d]pyrimidine-2,4,5(3H)-trione and (Z)-1,3-dimethyl-6-(4-nitrobenzylidene)furo[2,3-d]pyrimidine-2,4,5(1H,3H,6H)-trione



Monday, May 14, 2012 20:38:54

Multi-Spectral
P... ..

MS of 1,3-dimethyl-7-(4-nitrophenyl)-1H-pyrano[2,3-d]pyrimidine-2,4,5(3H)-trione and (Z)-1,3-dimethyl-6-(4-nitrobenzylidene)furo[2,3-d]pyrimidine-2,4,5(1H,3H,6H)-trione

