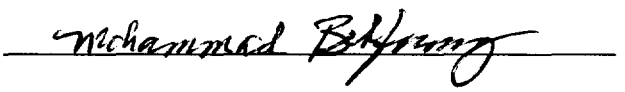
Total Synthesis of 7-*N*-Acetyldemethyllavendamycin Piperazine amide

An Honors 499 Thesis

by

Jeremy S. York

Thesis Advisor
Dr. Mohammad Behforouz



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Abstract

This thesis is part of ongoing research in the structure-activity relationship studies of various lavendamycin analogs as possible chemotherapeutic agents. Lavendamycin and its analogs have proven to be active anti-tumor and anti-cancer compounds in preliminary studies. The specific work contained in this thesis focuses on the synthesis of a new analog of the lavendamycin molecule. This analog was synthesized in hopes of gaining a better understanding of the effects of structure on the activity of the compound and on the solubility of the compound. This in turn will lead to analogs of lavendamycin that have a high selective toxicity and a high level of solubility in physiological solvents.

Acknowledgements

I would like to first and foremost thank Dr. Mohammad Behforouz who has been my mentor throughout this project. He has enabled me to take the knowledge I have gained in the classroom and apply it in the laboratory. He has given me the guidance to make this project a wonderful learning experience that has given me skills which will be of great use in my future endeavors.

I would also like to thank Ms. Wen Cai who has given me guidance on a daily basis throughout this research project. She was always willing to help with any aspect of my project and the time she gave me helped immensely with my research. I would also like to thank a former graduate student, Ms. Jayana Lineswala, whose M.S. thesis provided a wonderful reference source as the compound that I made was very similar to several compounds that she had made.

I am also grateful for the funding that made this research project possible. Without the help of outside sources such as the National Institute of Health, the American Cancer Society, and Eli Lilly and Company none of this would have been possible.

I would finally like to thank the Ball State Chemistry Department for the opportunities it provided to me as a student. The faculty is wonderful and all the knowledge I have gained couldn't have been accomplished without them. The undergraduate research program that exists here is one of the best in my mind and the department should be commended for it.

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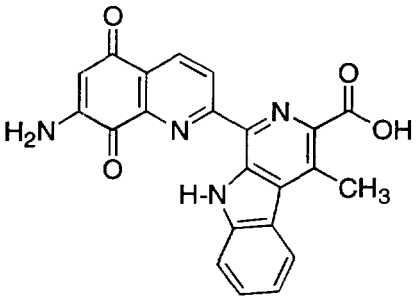
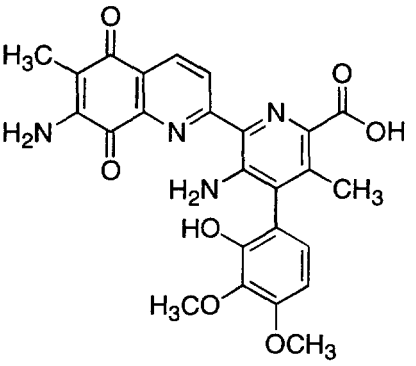
III. Background Information



A



B

Lavendamycin (**A**) was first isolated from a *Streptomyces Lavendulae* bacteria fermentation broth by researchers at Bristol Laboratories in 1981.[7] Lavendamycin was a red solid that had limited solubility in most organic solvents. The structure was eventually determined by NMR Spectroscopy, Mass Spectrometry, and IR Spectroscopy. The structure of lavendamycin was very similar to the previously discovered compound, Streptonigrin (**B**), and thus their biological activities are also very similar.[7] Both compounds have been shown to exhibit potent antitumor activity[11], but have been unusable thus far because of their high degree of cytoxicity. Lavendamycin also exhibits low water solubility, which makes it even less suitable for clinical applications.

The relationship between streptonigrin and lavendamycin caused a number of scientists to begin research into lavendamycin and its analogs. The first group to publish a total synthesis of the lavendamycin methyl ester was Kende and his associates. In order to make the quinoline moiety he used a procedure known as the Friedlander condensation. This condensation formed the A-B ring portion and

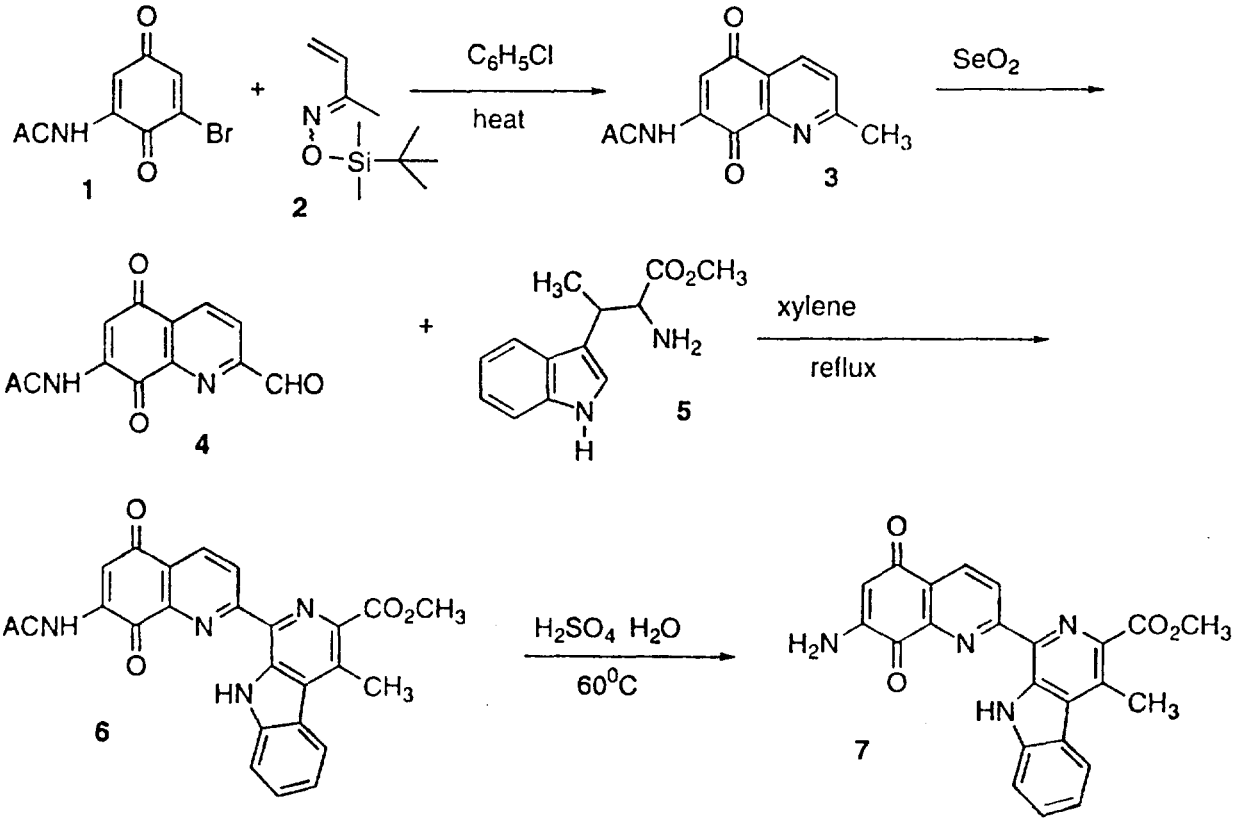
was followed by a Bischler-Napieralski cyclodehydration with β-methyl tryptophan methyl ester to complete the pentacyclic product.[9] Hibino and Rao have also reported a formal synthesis of lavendamycin. Their method involved a Pictet-Spengler condensation reaction in order to join the β-methyl tryptophan methyl ester and a quinoline analog to form the pentacyclic product.[8,10]

Behforouz and his coworkers at Ball State University reported a short practical synthesis of lavendamycin methyl ester using the Pictet-Spengler condensation reaction in 1993.[3] Using a novel azadiene Diels-Alder reaction, they were able to form the quinoline analog before the condensation reaction. Therefore no further transformations were required to form the complete pentacyclic ring. This synthesis was completed in five steps with an overall yield of 33%.

This synthetic route has been a part of ongoing structure-activity relationship studies for Behforouz's research group. Using this synthetic route many analogs of the lavendamycin antitumor agent have been made in the hopes of finding a relationship between the structure of the compound and the biological activity of the compound.

IV. Synthesis of Analogs of Lavendamycin

In 1993 Behforouz's research group published an article entitled "A Highly Concise Synthesis of Lavendamycin Methyl Ester" in *The Journal of Organic Chemistry* which improved upon the previous methods of synthesis by raising the overall yield, limiting the number of intermediates, and working with stable intermediates.[3] A very distinct difference between this synthesis and previous ones was the construction of the quinolinedione AB-ring system prior to the CDE-ring formation. This approach is what helped in improving the stability of the intermediates involved and giving overall yields which were much higher than those previously reported.[3]



The procedure involved five steps with an overall yield of 33%. A Diels-Alder condensation of bromoquinone (**1**) and a 1-azadiene (**2**) formed the AB ring system of the compound (**3**). The methyl group of the quinolinedione was then oxidized to an aldehyde (**4**), which was used in the Pictet-Spengler condensation with β-methyl tryptophan (**5**) to synthesize the 7-*N*-acetyldemethyllavendamycin methyl ester (**6**). This compound was then hydrolyzed to produce the desired final compound (**7**).

There have been additional improvements to this method which were reported by Behforouz in 1996.[2] In this method the overall yield of the synthesis of lavendamycin methyl ester was improved to 40%. This method uses 8-hydroxyquinoline as the starting material for the synthesis of the quinolinedione which serves as the AB-ring portion of the lavendamycin. The details of this procedure will be covered later as it was the method implemented in the synthesis of the analog in this thesis.

V. Biological Activity

Behforouz's group at Ball State University have been focusing on structure-activity relationship studies for lavendamycin and its analogs for several years now. Many analogs have been synthesized and tested due to the efficient procedure which was described previously. Many of these derivatives of lavendamycin have been tested and found to be biologically active against different types of tumor cells. This testing has been made possible by the collaborators of Dr. Behforouz's research group which include the National Institute of Health, National Cancer Institute, and Eli Lilly and Company.

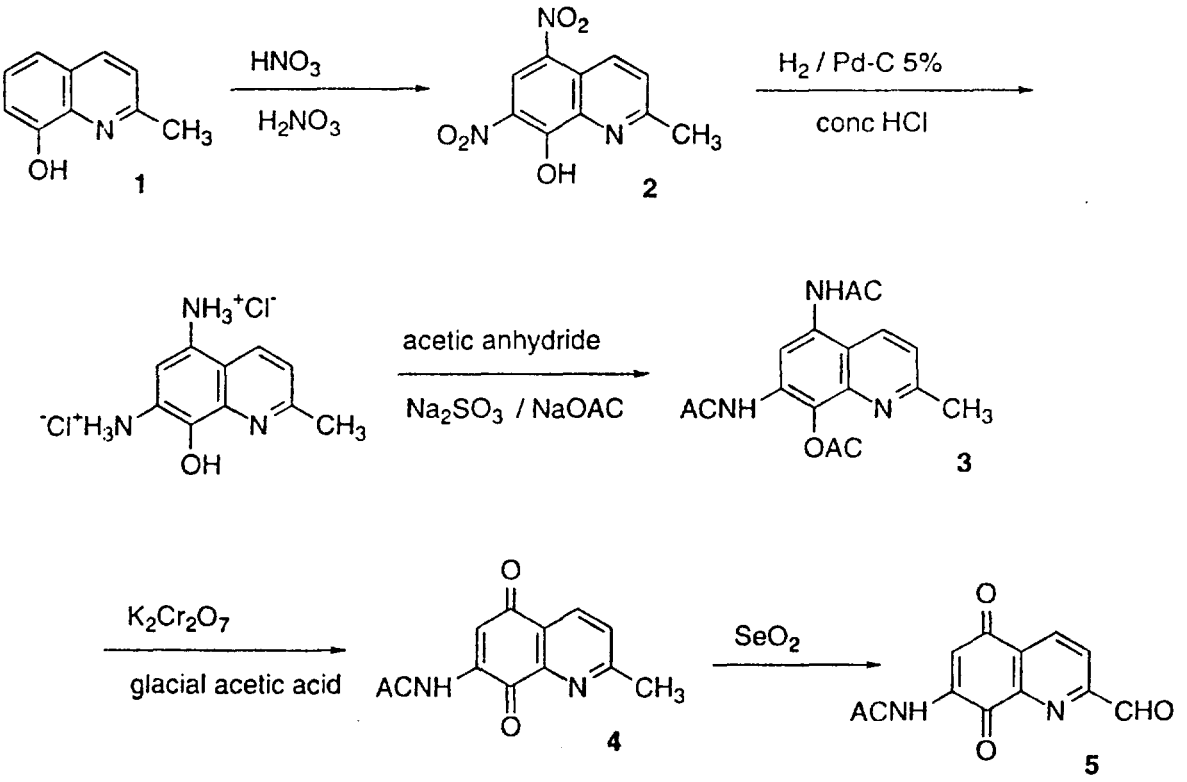
The testing which these outside sources have preformed have given the research group results which show that placing an acetamido group at the C-7 position of the lavendamycin is necessary to retain selective toxicity for the compound. In conjunction with that it has been shown that an ester or amide functional group at the C-2' position has improved the biological activity of the compound along with the fact that these groups also tend to increase the solubility of a compound.

With this in mind my thesis project was focused around the synthesis of an analog with a C-7 acetamido group and a C-2' amide group. By synthesizing this analog it will be possible to further deduce the role of the amide functional group at the C-2' position and to use the free nitrogen of the piperazine to form a salt of the lavendamycin. This salt will then hopefully increase the solubility of the compound in physiological solvents.

VI. Total Synthesis of 7-*N*-Acetyldemethyllavendamycin Piperazine amide

The final lavendamycin analog is the result of a Pictet-Spengler condensation of a quinolinedione aldehyde and a tryptophan amide. Both of these compounds are completely functionalized prior to the condensation reaction. The reactants and the solvents used in the condensation reaction were carefully purified and dried prior to use in the reaction. This ensured that the reaction would proceed properly and give the highest yield and purest product.

Scheme 1[2,3]



The quinolinedione was prepared according to Scheme 1. The starting material, 8-hydroxy-2-methylquinoline (**1**), was available commercially from the Aldrich Company. Nitration of 8-hydroxy-2-methylquinoline with a 70:30 (by

volume) mixture of HNO_3:H_2SO_4 in an ice bath to control the exothermic reaction afforded the known dinitro compound **2** in 73% yield. This compound (**2**) was reduced with hydrogen in the presence of 5% Pd/C in a 10% HCl solution at room temperature for 15 hr using a Parr hydrogenator at 40 psi. The catalyst was filtered off and the red ammonium salt solution was treated with an excess amount of acetic anhydride in the presence of large amounts of sodium acetate and sodium sulfite. The yellowish-white solid that was obtained was 5,7-diacetamido-8-acetoxy-2-methylquinoline. This compound was treated with MeOH:H_2O under reflux to hydrolyze the acyl group and produce the pure sample of 5,7-diacetamido-8-hydroxy-2-methylquinoline (**3**).[2]

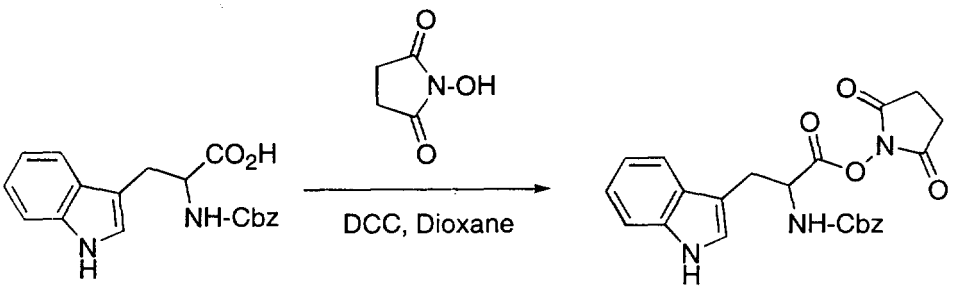
The diacetamido compound **3** was then oxidized by treating with potassium dichromate in a solution of H_2O:glacial acetic acid at room temperature to give the (acylamino)quinone (**4**) in 85% yield.[2]

7-Acetamido-2-methylquinoline-5,8-dione (**4**) was oxidized by selenium dioxide in a wet dioxane solution. The selenium dioxide and water react to form a reactive oxide of selenium which serves to oxidize the methyl group of the dione to the aldehyde. The resulting product, 7-Acetamido-2-formylquinoline-5,8-dione (**5**), was used in the synthesis of this lavendamycin analog.[3]

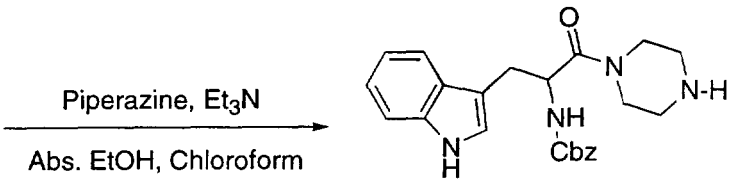
The tryptophan amide was prepared according to Scheme 2. The starting material, *N*-Cbz tryptophan (**6**), was also commercially available from the Aldrich company. Reaction of *N*-Cbz tryptophan with *N*-hydroxysuccinimide in the presence of dicyclohexylcarbodiimide afforded the Cbz-tryptopahn succinimide ester (7) in 6 hr.[4]

This compound (7) was then treated with piperazine to replace the ester bond with an amide.[4] This reaction afforded the Cbz-tryptophan piperazine amide (**8**). The Cbz protecting group was then cleaved off using ammonium formate in the presence of 10% palladium on charcoal in dry methanol. This reaction then afforded the final tryptophan piperazine amide (**9**).[4]

Scheme 2[4]



6 **7**



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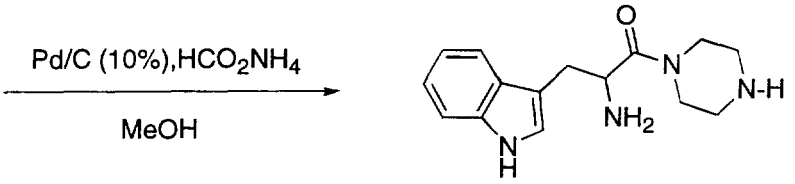


9

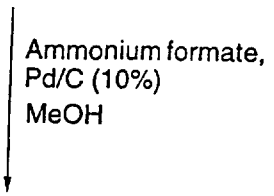
Compound (**9**) was then used along with the quinolinedione (**5**) in the Pictet-Spengler condensation reaction to afford 7-*N*-acetyldemethyllavendamycin amide of piperazine (**10**). **10** has not been isolated as a pure product yet due to its

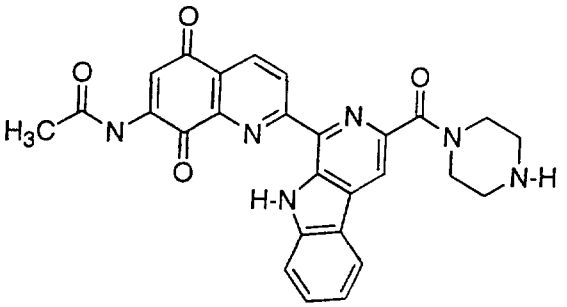
low solubility in most solvents which has made the most common methods of purification extremely difficult. Steps will be taken to obtain a pure product of this compound for future biological testing.

Scheme 3[4]

5

9





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VII. Experimental

A. General Information

Reagents: 8-hydroxy-2-methylquinoline, selenium dioxide, *N*-carbobenzyloxytryptophan, *N*-hydroxysuccinimide, *N*-dicyclohexylcarbodiimide, and Piperazine were purchased from the Aldrich Chemical Company.

Solvents: All solvents used were purchased reagent grade (except for anisole which was purchased dry), and then were dried and distilled in the laboratory.

Melting Points: All melting points were determined using a Thomas-Hoover capillary melting point apparatus and are uncorrected.

NMR Spectra: ^{1}H NMR Spectra were obtained using a JEOL 400 Mhz spectrometer in either $CDCL_3$ or DMSO solvents using the residual chloroform (7.24 ppm) or DMSO (2.50 ppm) as the internal standards.

Low Resolution and High Resolution Mass Spectra:

EI and HR Mass Spectra were obtained by the Chemistry Department at the University of Illinois.

Thin-Layer Chromatography: Baker silica gel strips with fluorescent indicator were used to determine purity for all products.

B. Solvent Purification

It was necessary to dry and distill 1,4 dioxane prior to its use in several of the above reactions due to its tendency to polymerize. The solvent was purified by refluxing it with an excess of potassium hydroxide for about an hour. The solvent was then decanted into another container and dried by refluxing with sodium spheres for 1-2 hr, and then placing benzophenone in the reflux mixture as

an indicator. Once the reflux mixture turned a dark blue color it was dry, and then the solvent was distilled into a dry container.

Methanol, absolute ethanol, chloroform, and triethylamine were also dried prior to use according to known procedures of drying solvents which usually just required refluxing with sodium hydride or calcium hydride for an hour and then distilling. This was done in order to ensure that no unnecessary moisture was introduced into any reaction.

C. Experimental Procedures

Synthesis of 8-hydroxy-2-methyl-5,7-dinitroquinoline (2)[2]

In a solution of 70:30 (v:v) HNO_3:H_2SO_4 that was cooled in an ice bath, 8-hydroxy-2-methylquinoline (**1**, 40.10 g, 0.25 mol) was added portionwise. The mixture continued to stir for 2 hr and then it was poured into a 2 L beaker that contained 1 L of an ice:water (1:1) mixture. This mixture was stirred vigorously until a yellow precipitate formed. This bright yellow precipitate was filtered and washed with ice:water, and then it was washed with diethyl ether. The yellow crystals were then dried on a vacuum pump to afford 39.82 g (63%) of **2**: mp 297 °C. The structure of **2** was confirmed by ^{1}H NMR.

Synthesis of 5,7-Diacetamido-8-hydroxy-2-methylquinoline (3)[2]

In a suspension of 8-hydroxy-2-methyl-5,7-dinitroquinoline (**2**, 6.05 g, 24 mmol) and 10% hydrochloric acid solution (10 mL conc HCl in 90 mL H_2O) in a hydrogenation bottle was added 2.0 g of 5% Pd-C. The mixture was hydrogenated under 30 psi for 18 h. The reaction mixture was then filtered and

the filter cake was washed with water. The filtrate which contained the ammonium salt was then used for the preparation of **3**. The ammonium salt solution was treated with 20 g of sodium acetate and 10 g of sodium sulfite. This red solution was then stirred and 67 mL of acetic anhydride was added dropwise over 1 h. The mixture was allowed to stir for an additional hour and then another 30 min in an ice bath. The yellow product was filtered and washed with cold water while the filtrate was concentrated down to about ¼ of its original volume. Then with stirring additional acetic anhydride (13 mL) was added and the mixture was stirred for an additional 15 min at room temperature and then 15 min in an ice bath. The solid was filtered off and washed with cold water to remove any inorganic salt. The two product samples were dried and combined to yield 6.38 g (85%) of the 5,7-diacetamido-8-acetoxy-2-methylquinoline. This product was then treated with 400 mL MeOH:H_2O (10:1) under reflux for 30 min and then evaporation of the solution afforded 5.60 g (100%) of 5,7-diacetamido-8-hydroxy-2-methylquinoline (**3**) as a white solid: mp. 229 °C. The structure of **3** was confirmed by ^{1}H NMR.

Synthesis of 7-Acetamido-2-methylquinoline-5,8-dione (4)[2]

In a stirred suspension of 5,7-diacetamido-8-hydroxy-2-methylquinoline (**3**, 6.60 g, 24 mmol) in glacial acetic acid (244 mL) was added a solution of potassium dichromate (17.45 g) in water (230 mL). The resulting solution was allowed to stir for 15 h and then was extracted with CH_2Cl_2. The combined organic extracts were washed with a 5% sodium bicarbonate solution and the aqueous layer was extracted with CH_2Cl_2. The combined organic extracts were

dried over $MgSO_4$ and the solvent was removed under vacuum to afford 2.70 g (67 %) of an orange yellow solid (**4**): mp 215 °C. The structure of **4** was confirmed by ^1H NMR and ^{13}C NMR.

Synthesis of 7-Acetamido-2-formylquinoline-5,8-dione (5)[3]

A solution of 7-Acetamido-2-methylquinoline-5,8-dione (**4**, 0.69 g, 3.0 mmol) in 45 mL of 1,4 dioxane with a small amount of water (0.4 mL) was treated with selenium dioxide (0.542 g, 4.8 mmol). The solution was allowed to reflux under argon for 23 h. The solution was filtered and washed with CH_2Cl_2, and the filtrate was evaporated dry to afford an orange brown solid. The solid was purified by dissolving in chloroform and filtered to afford 0.065 g (70%) of an orange solid (**5**): mp 225 °C. The structure of **5** was confirmed by ^1H NMR and ^{13}C NMR.

Synthesis of Benzyloxycarbonyltryptophansuccinimide ester (7)[4]

A solution of *N*-carbobenzyloxytryptophan (**6**, 0.338 g, 1 mmol) in 50 mL of dry 1,4-dioxane was treated with *N*-hydroxysuccinimide (0.115 g, 1mmol). The reaction mixture was stirred until it was clear while the flask was cooled to about 12 °C. *N*-dicyclohexylcarbodiimide was then added and a white precipitate immediately formed. The reaction mixture was then stirred for an additional 2 h in the ice bath, and another 2 h at room temperature. The reaction was then filtered and rinsed with dioxane. The filtrate was evaporated to afford a thick colorless liquid that upon drying under vacuum afforded 3.95 g (90%) of **7** as a white solid: mp 87 °C dec, ^{1}HNMR ($CDCl_3$) δ 2.73 (s, 4H), 3.42-3.50 (m, 2H),

5.07-5.17 (m, 3H), 7.07-7.17 (m, 3H), 7.33 (s, 5H), 7.54 (d, 1H, J = 7.41 Hz), 8.27 (s, 1H)..

Synthesis of Benzyloxycarbonyltryptophan amide of piperazine (8)[4]

A solution of benzyloxycarbonyltryptophan succinimide ester (7, 4.22 g, 9.69 mmol) in 48 mL of absolute ethanol and 52 mL of chloroform was treated with triethylamine (0.98 g, 9.69 mmol) and piperazine (0.82 g, 9.69 mmol). The reaction mixture stirred at room temperature for about 6 h until complete. The reaction mixture was evaporated to dry and dissolved into ethyl acetate. The solution was washed with water and then a 10% citric acid solution was added dropwise until the pH was <7.0 then the mixture was brought back to a basic pH by adding a 5% sodium bicarbonate solution dropwise. The solution was then washed a final time with water and dried over sodium sulfate. The solvent was removed under vacuum to afford 3.9 g (80%) of **8** as a colorless solid: mp 98 °C dec; ^{1}H NMR ($CDCl_3$) δ 3.09-3.22 (m, 8H), 4.91 (t, 1H, J = 7.24 Hz), 5.12 (d, 2H, 7.45 Hz), 5.90 (d, 1H, J = 8.40 Hz), 6.93 (s, 1H), 7.21-7.38 (m, 8H), 7.64 (d, 1H, J = 7.32 Hz), 8.13 (s, 1H).

Synthesis of Tryptophan amide of Piperazine (9)[4]

A solution of benzyloxycarbonyltryptophan amide of piperazine (**8**, 2.0 g, 4.92 mmol) in 50 mL of dry methanol was treated with ammonium formate (0.62 g) and 10% Pd-C (1.74 g). The reaction was stirred at room temperature for 4 h until complete. The reaction mixture was filtered and the Pd-C was rinsed with methanol. The filtrate was evaporated to afford a thick colorless liquid that was dried on a vacuum pump until 1.15 g (68%) of a white solid, **9**, was obtained: mp

94 °C dec; ^{1}H NMR ($CDCl_3$) δ 2.08 (m, 1H), 2.75 (m, 1H), 2.96 (m, 2H), 3.08 (m, 3H), 3.25 (m, 1H), 3.42 (m, 1H), 3.62 (m, 1H), 4.04 (t, 2H, J = 8.0 Hz), 7.05 (s, 1H), 7.11 (t, 1H, J = 7.35 Hz), 7.18 (t, 1H, J = 7.35 Hz), 7.33 (d, 1H, J = 8.1 Hz), 7.56 (d, 1H, J = 8.1 Hz), 8.19 (br s, 1H); EIMS, *m/e* (rel inten) 272 (M^+, 3), 255 (37), 159 (33), 143 (65), 142 (13), 132 (11), 131 (33), 130 (100), 87 (55), 85 (28), 77 (11), 56 (13).

Synthesis of 7-*N*-Acetyldemethyllavendamycin amide of piperazine (10)[4]

A suspension of 7-acetamido-2-formylquinoline-5,8-dione (**5**, 48.8 mg, 0.2 mmol) in 120 mL of anisole was heated to 70 °C. A solution of tryptophan amide of piperazine (**9**, 54 mg, 0.2 mmol) dissolved in 4 mL of pyridine was prepared. The solution was added to the reaction mixture and the reaction was slowly heated to 120 °C over two hours. The reaction was then heated to 165 °C over the next 1 h. This heat was maintained for 24 h. The reaction mixture was then hot filtered and the precipitates were washed with ethyl acetate and acetone to afford 41 mg (40%) of **10** as a dark yellow solid: mp >300 °C dec; EIMS, *m/e* (rel inten) 495 (10), 460 (37), 307 (71), 289 (62), 155 (100), 136 (100). HRMS calcd for $C_{27}H_{22}N_6O_4$ 495.1781, found 495.1779.

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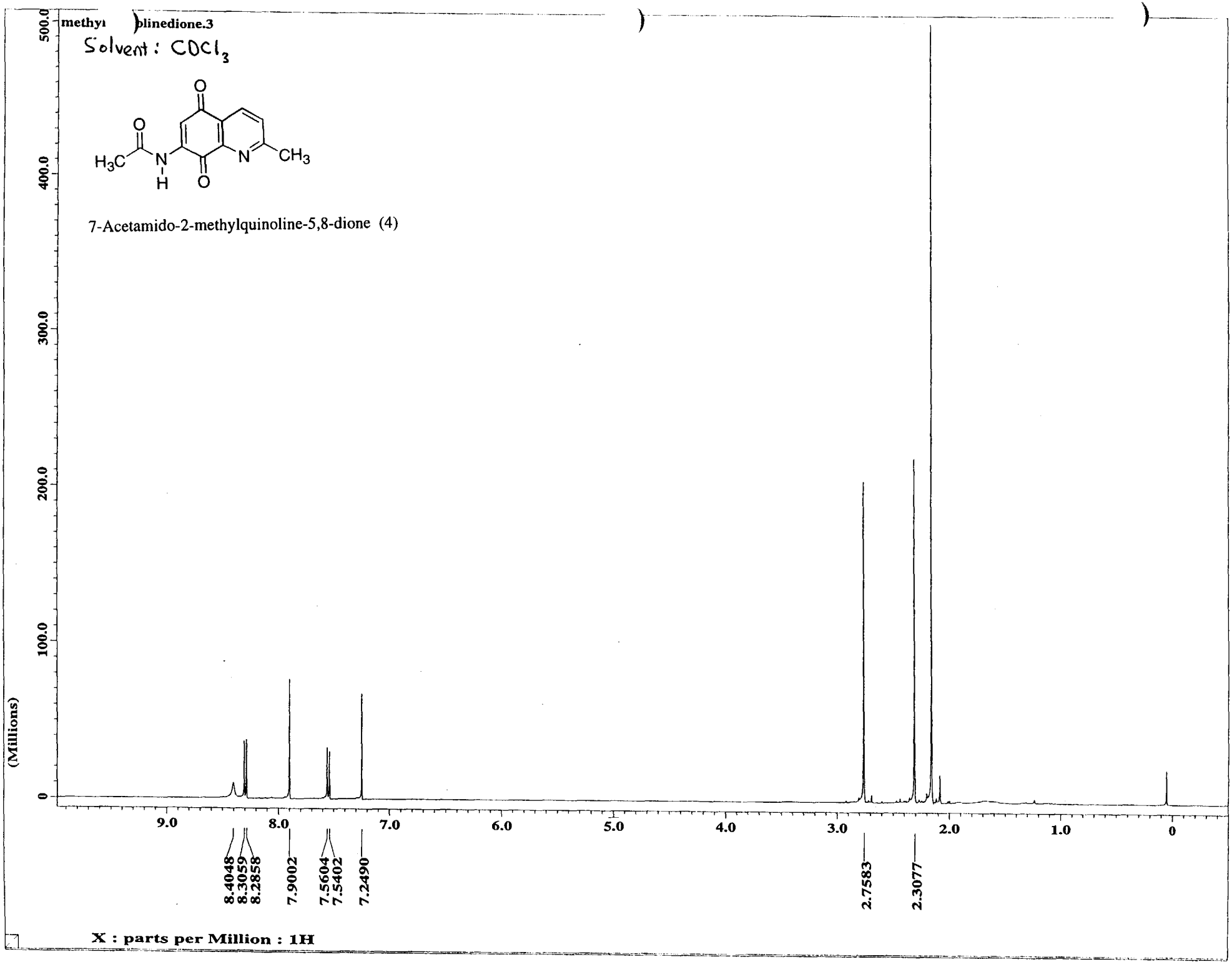
IX. NMR and MS Spectral Data

1. ^{1}H NMR of 7-Acetamido-2-methylquinoline-5,8-dione
2. ^{13}C NMR of 7-Acetamido-2-methylquinoline-5,8-dione
3. ^{1}H NMR of 7-Acetamido-2-formylquinoline-5,8-dione
4. ^{13}C NMR of 7-Acetamido-2-formylquinoline-5,8-dione
5. ^{1}H NMR of Benzyoxycarbonyltryptophan succinimide ester
6. ^{1}H NMR of Benzyloxycarbonyltryptophan amide of piperazine
7. ^{1}H NMR of Tryptophan amide of piperazine
8. EIMS of Tryptophan amide of piperazine
9. ^{1}H NMR of 7-*N*-Acetyldemethyllavendamycin amide of piperazine
10. EIMS of 7-*N*-Acetyldemethyllavendamycin amide of piperazine
11. HRMS of 7-*N*-Acetyldemethyllavendamycin amide of piperazine


methyl plinedione.3
Solvent : CDCl3
O
O
H3C
N
H
O
N
CH3
7-Acetamido-2-methylquinoline-5,8-dione (4)
500.0
400.0
300.0
200.0
100.0
0
(Millions)
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0
8.4048
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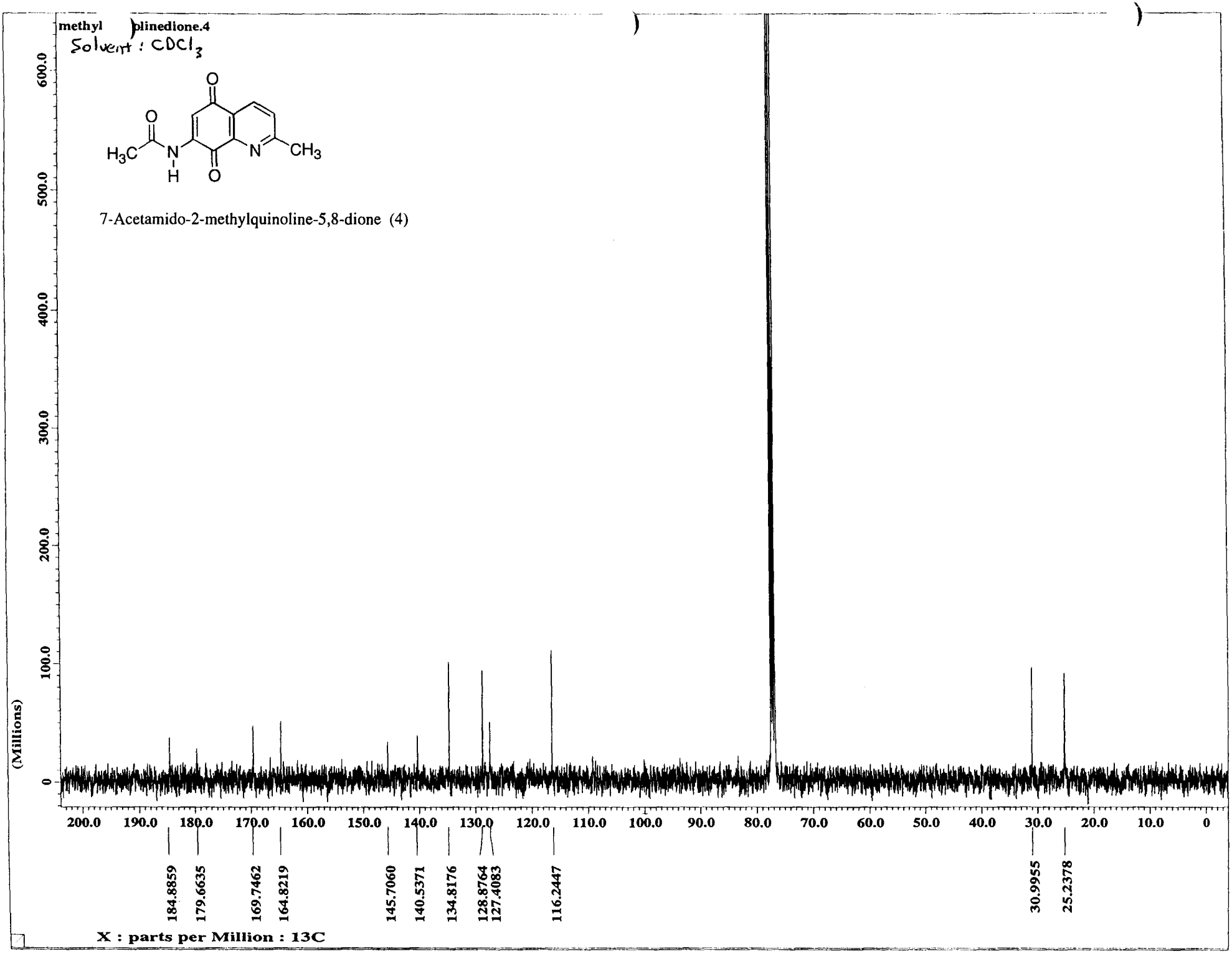
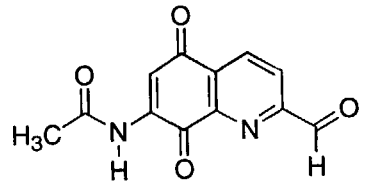
2.3077
X : parts per Million : 1H


methyl plinedione.4
Solvent : CDCl3
7-Acetamido-2-methylquinoline-5,8-dione (4)
(Millions)
600.0
500.0
400.0
300.0
200.0
100.0
0
200.0 190.0 180.0 170.0 160.0 150.0 140.0 130.0 120.0 110.0 100.0 90.0 80.0 70.0 60.0 50.0 40.0 30.0 20.0 10.0 0
184.8859
179.6635
169.7462
164.8219
145.7060
140.5371
134.8176
128.8764
127.4083
116.2447
30.9955
25.2378
X : parts per Million : 13C

formy olinedione.3

Solvent: $CDCl_3$



7-Acetamido-2-formylquinoline-5,8-dione (5)

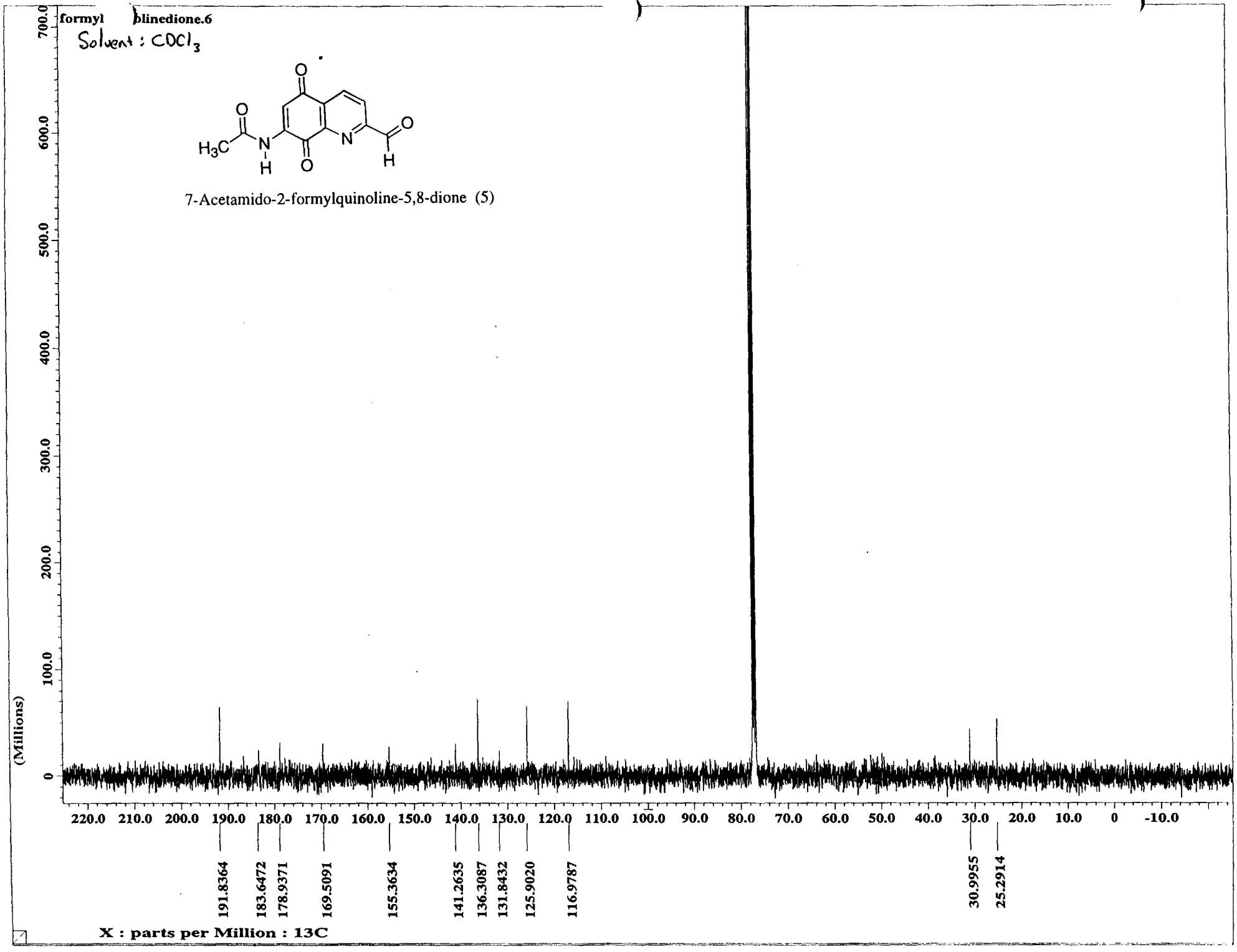
(Millions)

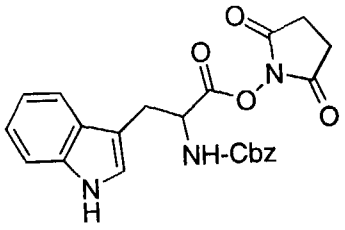
10.2907

8.6292
8.6091
8.4415
8.3306
8.3114
8.0486

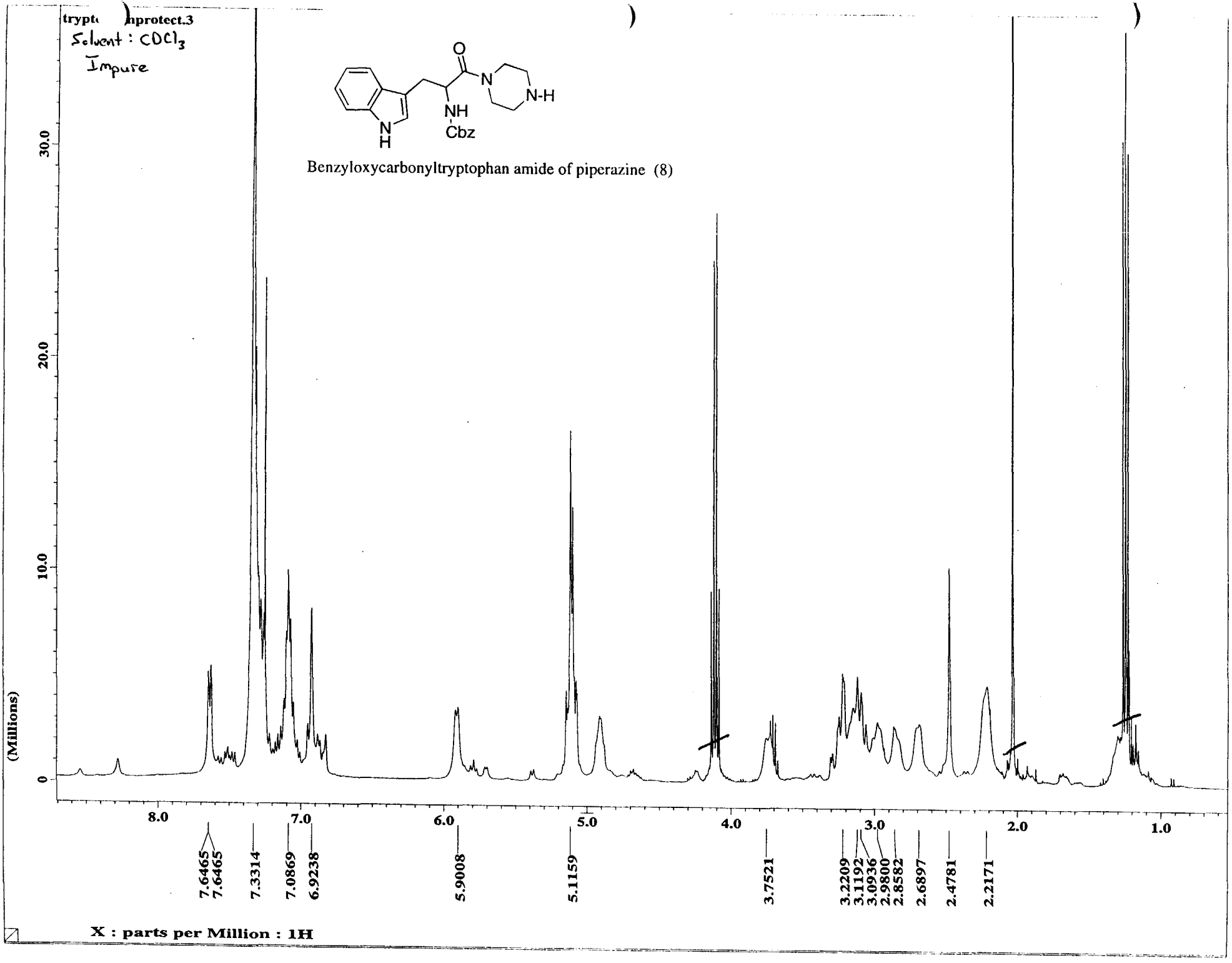
2.3453

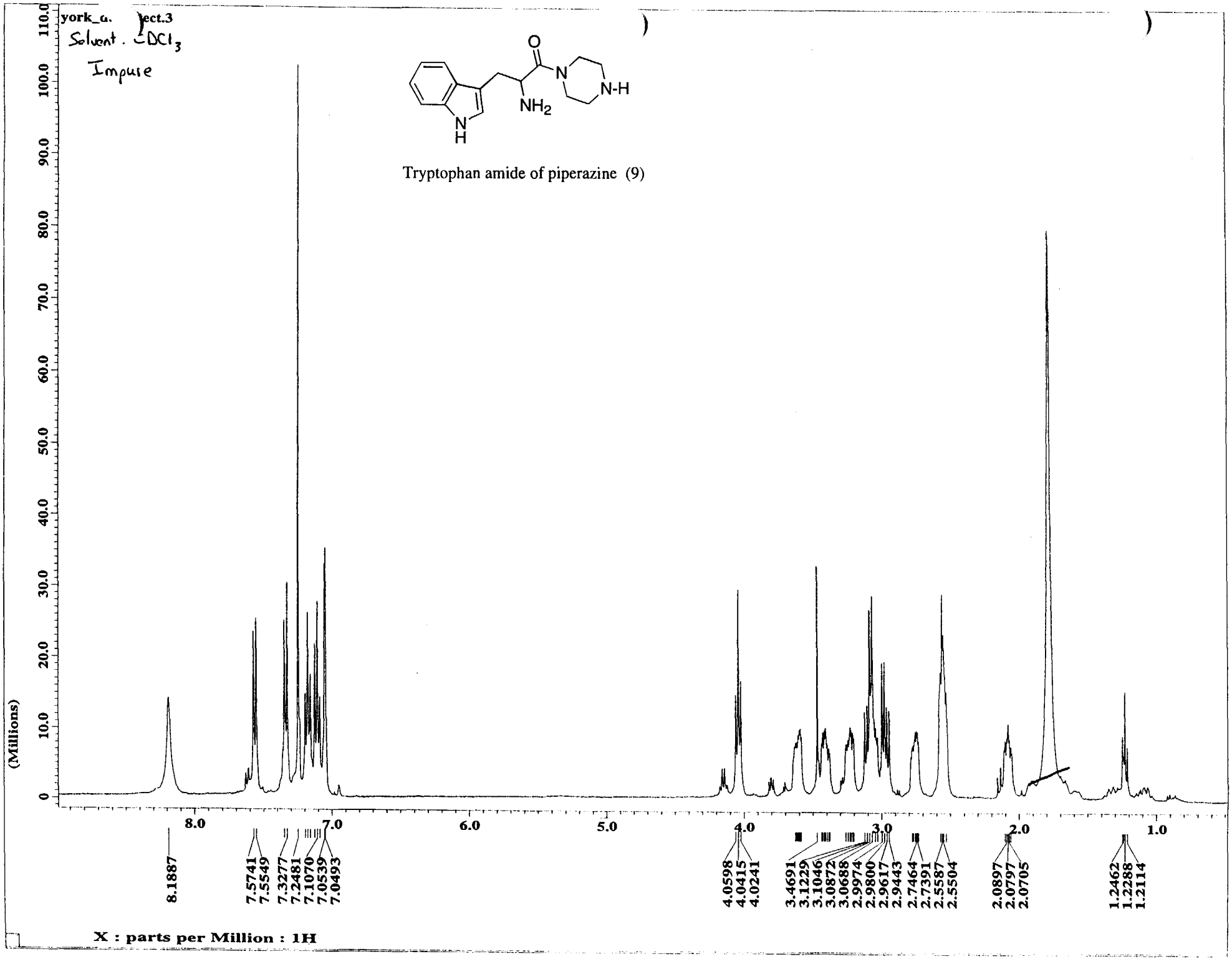
X : parts per Million : 1H

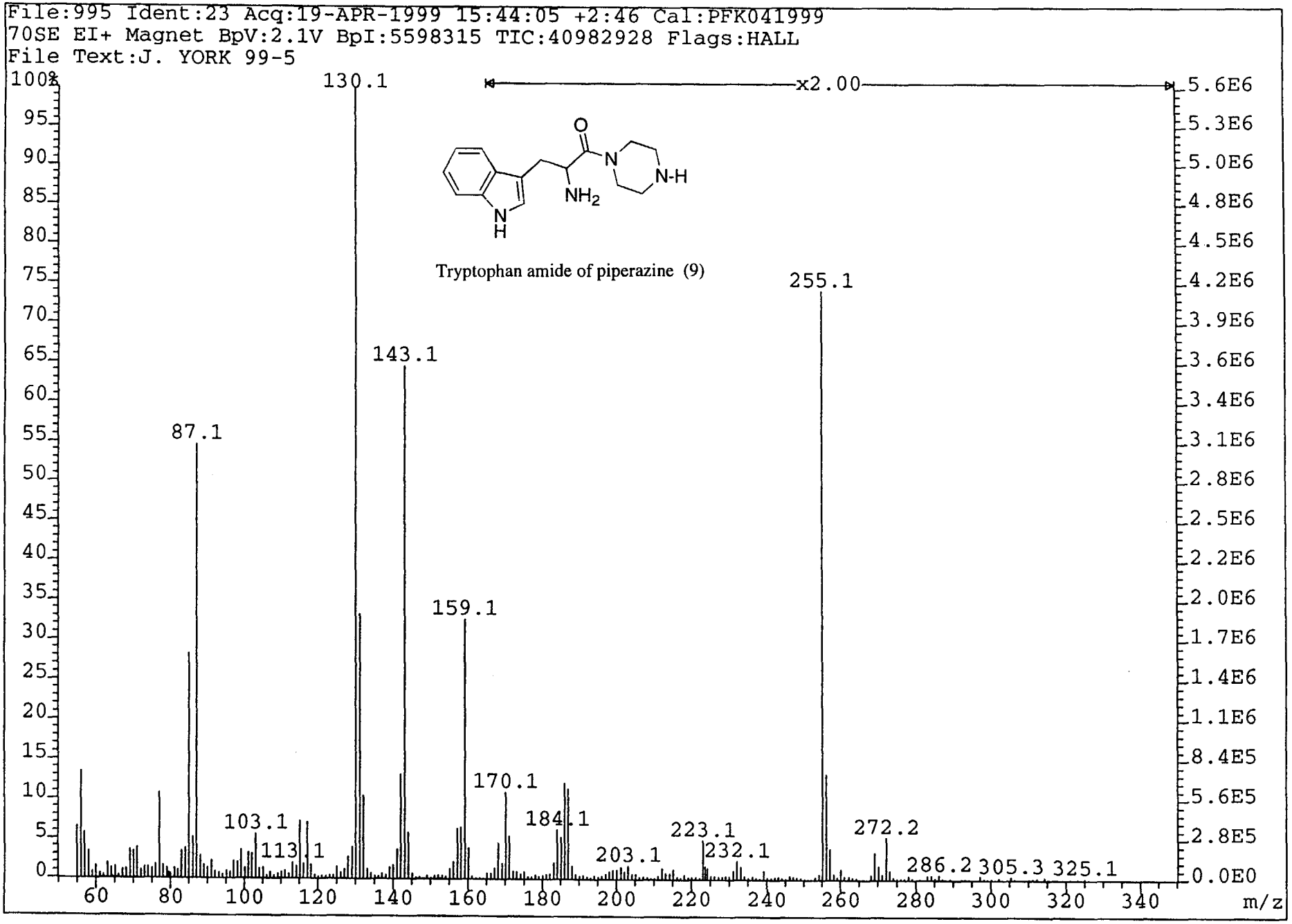

formyl blinedione.6
Solvent : $CDCl_3$
7-Acetamido-2-formylquinoline-5,8-dione (5)
(Millions)
700.0
600.0
500.0
400.0
300.0
200.0
100.0
0
220.0 210.0 200.0 190.0 180.0 170.0 160.0 150.0 140.0 130.0 120.0 110.0 100.0 90.0 80.0 70.0 60.0 50.0 40.0 30.0 20.0 10.0 0 -10.0
191.8364
183.6472
178.9371
169.5091
155.3634
141.2635
136.3087
131.8432
125.9020
116.9787
30.9955
25.2914
X : parts per Million : 13C



Benzyloxycarbonyltryptophan succinimide ester (7)


trypt hprotect.3
Solvent : CDCl3
Impure
O
N
N-H
NH
Cbz
N
H
Benzyloxycarbonyltryptophan amide of piperazine (8)
30.0
20.0
10.0
0
(Millions)
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
7.6465
7.6465
7.3314
7.0869
6.9238
5.9008
5.1159
3.7521
3.2209
3.1192
3.0936
2.9800
2.8582
2.6897
2.4781
2.2171
X : parts per Million : 1H


york_a. ect.3
Solvent. CDCl3
Impure
O
N
N-H
NH2
N
H
Tryptophan amide of piperazine (9)
(Millions)
110.0
100.0
90.0
80.0
70.0
60.0
50.0
40.0
30.0
20.0
10.0
0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
8.1887
7.5741
7.5549
7.3277
7.2481
7.1070
7.0539
7.0493
4.0598
4.0415
4.0241
3.4691
3.1229
3.1046
3.0872
3.0688
2.9974
2.9800
2.9617
2.9443
2.7464
2.7391
2.5587
2.5504
2.0897
2.0797
2.0705
1.2462
1.2288
1.2114
X : parts per Million : 1H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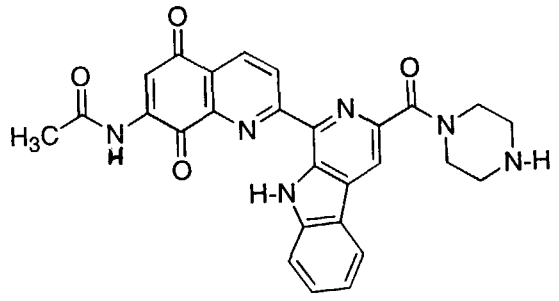
70SE EI+ Magnet BpV:2.1V BpI:5598315 TIC:40982928 Flags:HALL
File Text:J. YORK 99-5
x2.00
Tryptophan amide of piperazine (9)
130.1
255.1
143.1
87.1
159.1
170.1
103.1
113.1
184.1
223.1
232.1
203.1
272.2
286.2
305.3
325.1
m/z

1d_sp m.102

Solvent: DMSO

Impure



7-*N*-Acetyldemethyllavendamycin amide of piperazine (10)

(Millions)

400.0

300.0

200.0

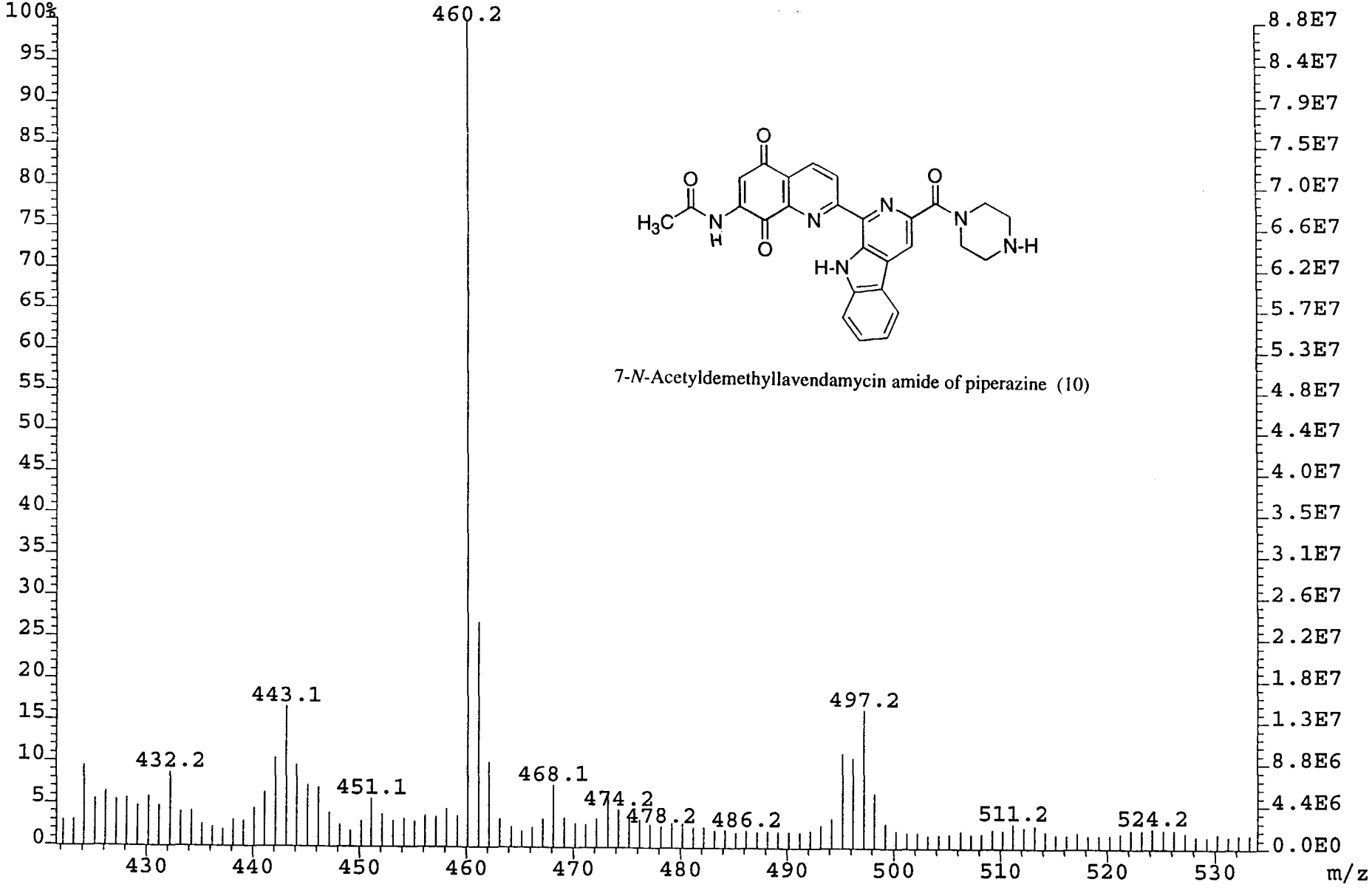
100.0

0

12.0 11.0 10.0 9.0 8.0 7.0 6.0 5.0 4.0 3.0 2.0 1.0 0

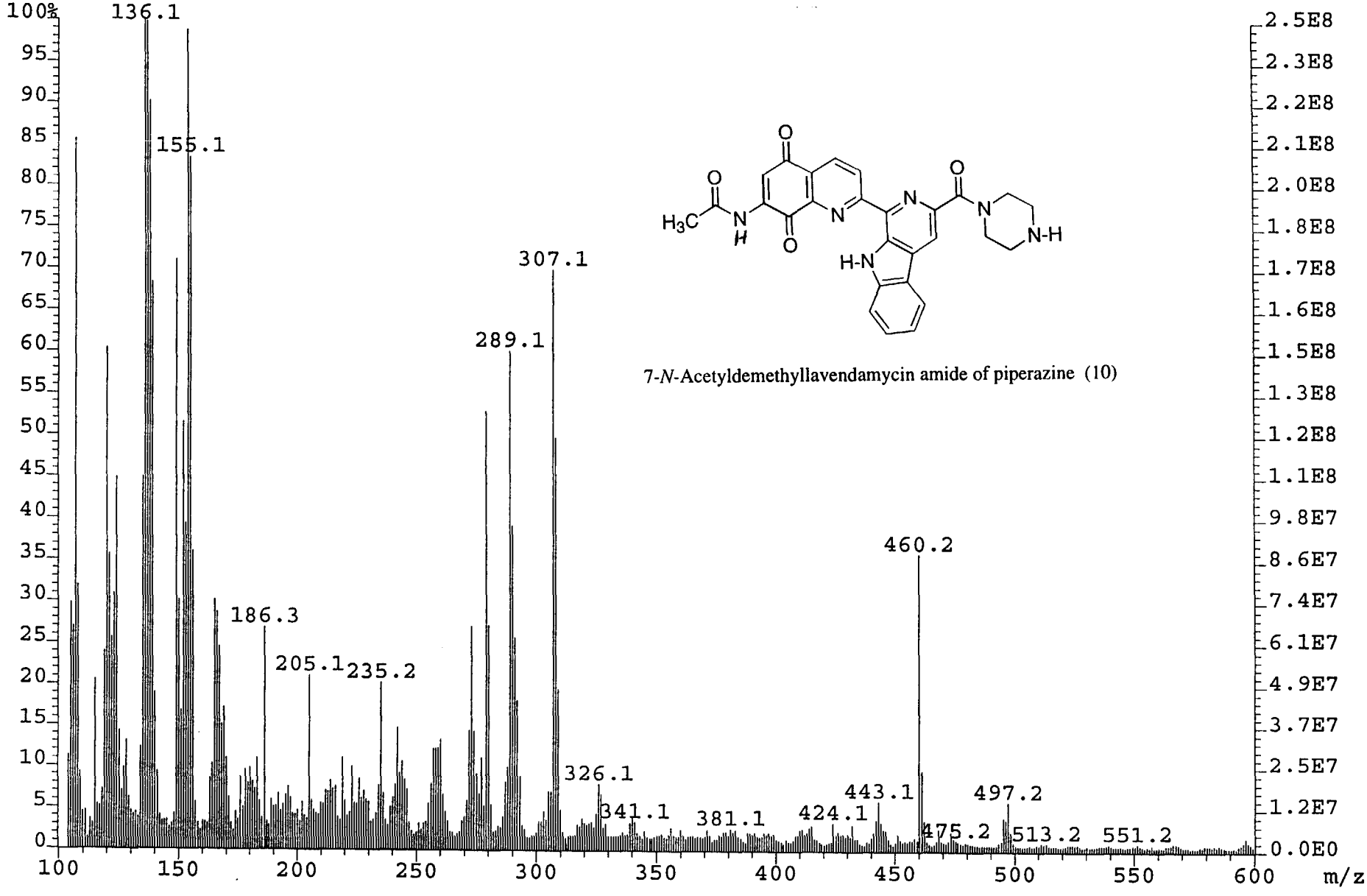
X : parts per Million : 1H

File:9912 Ident:2 Acq:19-APR-1999 16:06:41 +1:02 Cal:CSI041999
ZAB-SE FAB+ Magnet BpV:30.6V TIC:8266320384 Flags:HALL
File Text:J. YORK 99-12 IN 3NBA



7-*N*-Acetyldemethyllavendamycin amide of piperazine (10)

File:9912 Ident:2 Acq:19-APR-1999 16:06:41 +1:02 Cal:CSI041999
ZAB-SE FAB+ Magnet BpV:30.6V TIC:8266320384 Flags:HALL
File Text:J. YORK 99-12 IN 3NBA



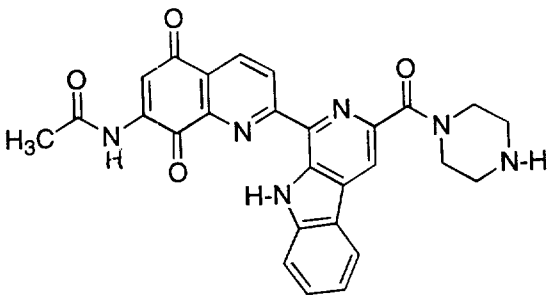
7-*N*-Acetyldemethyllavendamycin amide of piperazine (10)

Elemental Composition Date : 22-APR-1999

Heteroatom Max: 40 Ion: Both Even and Odd
limits:

				-0.5	0	10	5	3
495.177900		10.0		50.0	80	100	7	5

Mass	PPM	mDa	Calc. Mass	DBE	C	H	N	O
495.177900	0.4	0.2	495.178079	19.5	27	23	6	4



7-*N*-Acetyldemethyllavendamycin amide of piperazine (10)