COUMARIN-FUSED AZADIENES: NEW DIENES FOR THE IEDDA REACTION

JAMIE KENDALL

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New Dienes for the IEDDA Reaction

by

Jamie Kendall

B. Sc. (2001), Dalhousie University, Halifax, Nova Scotia, Canada

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Abstract

Coumarin-fused 1-azadienes were prepared via a condensation between 3-formylcoumarin and a variety of amines. Coumarin-fused 2-azadienes were prepared via a condensation of 3-aminocoumarin and a variety of aldehydes. A new synthesis of 3-aminocoumarin was developed.

1,2-Imine addition products were observed when 1-azadiene **184** was reacted with enamine **134**. This reaction resulted in the formation of reduced aldol condensation product **242** (37%) and the desired Diels-Alder adduct **243** (1% yield). When 1-azadienes **186** and **187** were reacted with enamine **134**, aldol condensation product **250** was formed (53% yield with **186** and 77% yield with **187**). When 2-azadiene **222** was reacted with enamine **134**, compound **252** (95%), which is also the result of 1,2-addition, was formed.

Using modified Povarov reaction conditions with the 2-azadienes, cycloaddition products were isolated. Two procedures were employed. The first one involved the use of a preformed 2-azadiene, a catalytic amount of $Yb(OTf)_3$, a non-enamine dienophile in acetonitrile. The other procedure was a three-component (*in situ* generated diene) method that entailed the combination of 3-aminocoumarin **212**, a catalytic amount of $Yb(OTf)_3$, a non-enamine dienophile and an aldehyde. An *endo* and *exo* isomer was obtained in most cases with selectivity ranging from >95 : 5 in favor or *exo* to >95 : 5 in favor of *endo*. Two of the Povarov adducts were oxidized with bromine to produce pyrido[2,3-*c*]coumarins.

Acknowledgment

I would like to express my sincerest acknowledgment to my supervisor, Dr. G. J. Bodwell, for his stimulating supervision, continuous encouragement, excessive help and financial support throughout the course of this research. His assistance and patience in the preparation of this thesis are also greatly appreciated.

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To my dear parents, family and those who have given me a chance to prove myself in life

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Glossary of Abbreviations

Ac	acetyl
Abs.	absolute
Ar	aryl
Bp	boiling point
Bn	benzyl
Boc	*tert*-butoxycarbonyl
br	broad (IR spectra)
Bu	*n*-butyl
CMP	3-carbomethyoxypyrone
COSY	^{1}H-^{1}H correlation spectroscopy
d	doublet (^{1}H NMR)
D-A	Diels-Alder
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCM	dichloromethane
de	diastereomeric excess
DHF	dihydrofuran
DHP	2,3-dihydropyran
DMAP	4-dimethylaminopyridine
dr	diastereomeric ratio
DMF	*N*,*N*-dimethylformamide

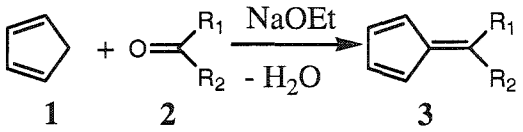
ee	enantiomeric excess
EDG	electron donating group
Eq.	equivalent
EWG	electron withdrawing group
Et	ethyl
gl.	Glacial
h	hours
hfc	3-(heptafluoropropylhydroxymethylene)-camphorato
HOMO	highest occupied molecular orbital
IED	inverse electron demand
IR	infrared spectroscopy
Kba	kilobars
KHMDS	potassium hexamethyldisilamide
LDA	lithium diisopropylamide
LUMO	lowest unoccupied molecular orbital
m	medium (IR spectra)
Me	methyl
Mp	melting point
MS	molecular sieve
NBS	*N*-bromosuccinimide
NOE	nuclear Overhauser effect

Ph	phenyl
q	quartet (^{1}H NMR)
Phth	phthalimido
s	strong (IR spectra)
t	triplet (^{1}H NMR)
TADDOL	α,α,α',α'-tetraaryl-1,3-dioxolan-4,5-dimethanol)
TBS	*tert*-butyldimethylsilyl
Tf	trifluoromethanesulfonyl
TFA	trifluoroacetic acid
THF	tetrahydrofuran
tlc	thin layer chromatography
TMS	trimethylsilyl
Tol	tolyl
Ts	tosyl
p-TSA	*para*-toluenesulfonic acid
vs	very strong (IR spectra)
w	weak (IR spectra)

Chapter 1: Introduction

1.1 The Early History of the Diels-Alder Reaction

A scientific discovery is both a finding and the recognition of that observation. When a researcher does not fulfill both criteria, this leaves the door open for someone else to "appropriate" the discovery at a later date. A perfect example of this can be found in the experience of Dr. Johannes Thiele, one of the most distinguished and well-rounded chemists of the late 1800s and early 1900s. Thiele was fully invested in the synthesis and study of fulvene chemistry. Fulvenes were known to be highly reactive and a new class of colored compounds, which could be used as synthetic building blocks in the preparation of new dyes. During that time, fulvenes were also being used to understand color and its relationship to chemical constitution. The most common approach at the time for the construction of fulvenes, **3**, was the condensation of cyclopentadiene with aldehydes or ketones, neat or in non-polar solvents (Scheme 1.1).[1]

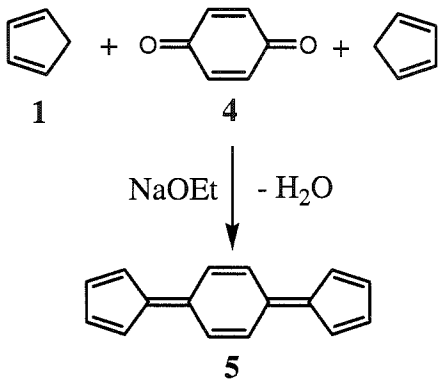


1 **2** **3**

Scheme 1.1

[1] Berson, J. A. *Tetrahedron* **1992,** *48*, 3-17.

It is conceivable, if not quite likely, that the synthesis of a "double fulvene" (e.g. **5**) by the condensation of two molecules of cyclopentadiene with a conjugated diketone, such as *p*-benzoquinone, would have been of significant interest to Thiele (Scheme 1.2). However, no publications containing this molecule, even a passing reference to, or any related molecule were ever published under his name.[1]



Scheme 1.2

In 1906, W. Albrecht, a former student of Thiele,[1] reported a thermal reaction between cyclopentadiene and *p*-benzoquinone that formed both a 1 : 1 adduct **6** and a 2 : 1 adduct **7**.[2] Albrecht was very definite about the structure he proposed for the products (vide infra) (Scheme 1.3). From the examination of the original paper, it can be seen that no reason is given as to why the reaction between cyclopentadiene and *p*-benzoquinone was studied in the first place. Even more interesting is that the paper itself does not reveal the date it was received or where the research was done, which was common practice at that time. Following Albrecht's original paper, no other papers were ever published with

his name again. Could it be that Thiele gave Albrecht a project that was aimed at the construction of the "double fulvene"? It is known that bases decompose quinones and it would not have been unreasonable for the cyclopentadiene and *p*-benzoquinone to be mixed before base was added, thus giving the mysterious products. In Albrecht's thesis, it is stated that only quinones do not eliminate water when combined with cyclopentadiene under the standard conditions of the fulvene synthesis.[3]

Though there is no evidence, Thiele most likely viewed Albrecht's work as disappointing and wanted nothing more to do with the project and hence gave permission for Albrecht to publish the facts, but without his name appearing on the paper. It is unclear whether or not Thiele and Albrecht realized the significance of this unprecedented observation, but their failure to study it further suggests they did not.

It was not until 1928 that a pair of researchers took a giant leap backwards and comprehended the findings of Thiele and Albrecht. This keen insight of Otto Diels and his student, Kurt Alder, led to the correct identification of the products arising from the reaction reported by Albrecht.[4] A key part of the structural determination was the demonstration that the 1 : 1 adduct **8** and 2 : 1 adduct **9** each had only two C=C, rather than three and four, respectively, as suggested by Albrecht (Scheme 1.3). This was demostrated by derivatization of the unknown products.

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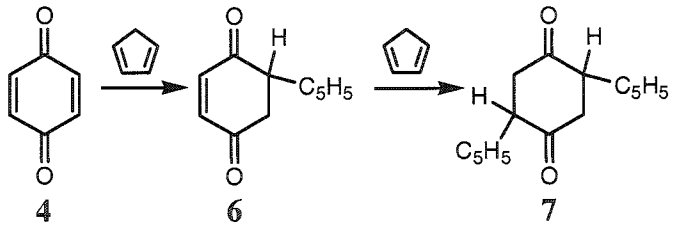
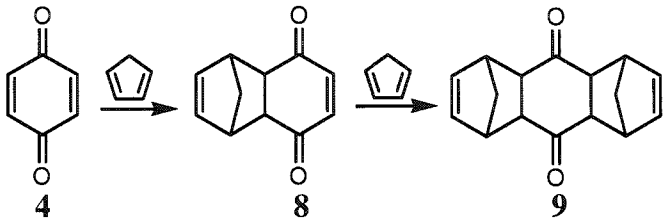
[2] Albrecht, W. *Justus Liebigs Ann. Chem.* **1906**, *348*, 31-49.
[3] Albrecht, W. Über Cyclopentadienchinone. 1902, Inaugural Dissertation, Munich.
[4] Diels, O.; Alder, K. *Justus Liebigs Ann. Chem.* **1928**, *460*, 98-122.



Albrecht's proposed reaction



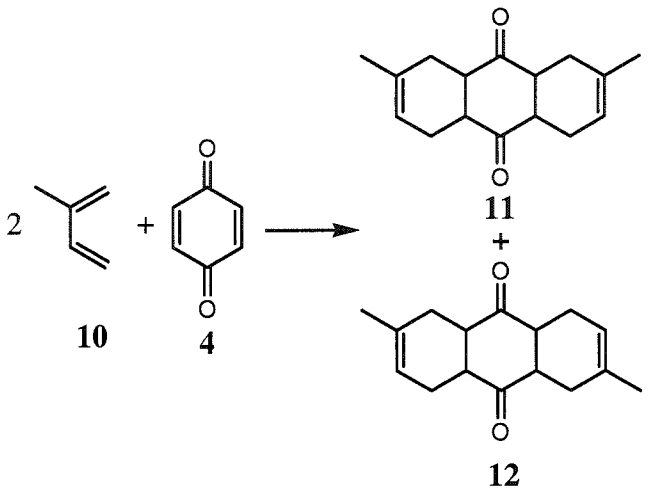
Diels' and Alder's proposed reaction

Scheme 1.3

Diels and Alder also referenced the work of von Euler and Josephson, who reported an unusual and unexpected reaction between *p*-benzoquinone and isoprene.[5] Von Euler and Josephson were unable to identify the products of this reaction, but were confident that the product was a 2 : 1 adduct of isoprene and *p*-benzoquinone (Scheme 1.4). The formation of a dioxime and a tetrabromide spoke convincingly for the 2 : 1 ratio. Full identification of the structure was not completed due to the fact that there was no straightforward way at the time to assign the proper relative regiochemistry. Von Euler and Josephson concluded their findings by saying that future work would be done to complete the identification and in the end it never materialized.[5] With the benefit of hindsight, it seems quite amazing that they did not pursue this work more vigorously. They not only had successfully reacted a diene with a dienophile (eight years before Diels

[5] Von Euler, H.; Josephson, K. O. *Ber. Dtsch. Chem. Ges.* **1920**, *53*, 822-826.

and Alder), but they also appeared to have had a sufficient understanding of what was occurring. The most likely explanation for von Euler not pursuing what would now be known as the "von Euler-Josephen (VEJ) reaction" was his groundbreaking research into fermentation, which ultimately earned him and A. Harden the Nobel Prize in 1929.



Scheme 1.4

Diels and Alder also cited Lebedev's work[6] for recognizing that 4-vinylcyclohexene was a dimer of butadiene, and Zincke's observation of the self-dimerization of tetrachlorocyclopentadienone.[7] Examining all of these experimental observations together revealed the characteristic pattern. Finally, the demonstration of the parent reaction, i.e. the formation of cyclohexene from butadiene and ethene by Joshel and Bunz in 1941

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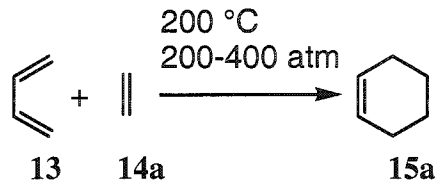
[6] a) Lebedev, S. V. *J. Russ. Phys. Chem. Soc.* **1910**, *42*, 949-952. b) Lebedev, S. V. *Chem. Abstr.* **1912**, *6*, 2009.

[7] a) Zincke, T.; Günther, H. *Justus Liebigs Ann. Chem.* **1892**, *272*, 243-270. b) Zincke, T.; Bergmann, F.; Francke, B.; Prenntzell, W. *Justus Liebigs Ann. Chem.* **1897**, *296*, 135-158. c) Zincke, T.; Meyer, K. H. *Justus Liebigs Ann. Chem.* **1909**, *367*, 1-13. d) Zincke, T. Pfaffendorf, W. *Justus Liebigs Ann. Chem.* **1909**, *394*, 3-22.

(Scheme 1.5),[8] solidified all of these reactions into one family of reactions, which is known commonly as the Diels-Alder reaction.



Scheme 1.5

Diels and Alder immediately recognized the potential significance of their work in total synthesis and other applications. Apparently they jealously guarded their new-found discovery, commanding all others not to pursue what they viewed as "their" work. They wrote in their paper, "We explicitly reserve for ourselves the application of the reaction discovered by us to the solution of problems."[4]

Fortunately, few heeded their warnings and cycloaddition experiments were used and studied without Diels' and Alder's blessing. Over the last eighty or so years, the Diels-Alder reaction, has become one of the most studied organic reactions of all time. There seems to be no end to the academic debate over the Diels-Alder reaction from its mechanism to its variants and to its application in total synthesis.

[8] a) Joshel, L. M.; Butz, L. W. *J. Am. Chem. Soc.* **1941**, *63*, 3350-3351. b) Houk, K. N.; Lin, Y. T.; Brown,

1.2 Mechanism and Theory of the Diels-Alder Reaction

The Diels-Alder reaction is far more than its end result of ring formation. The reaction is introduced as early as the introductory undergraduate level, which underscores its importance in the field of organic chemistry. Beyond the fundamental aspects of the reaction, there are many other facets, variants and nuances that are introduced at higher levels. A tremendous body of literature on the Diels-Alder reaction has been compiled. Only selected aspects of Diels-Alder chemistry that are relevant to this work will be discussed below. For more detailed discussion, the reader is referred to textbooks, monographs, etc in the vast literature on the Diels-Alder reaction.[9]

The Diels-Alder reaction (a [4π + 2π] cycloaddition) falls under the general heading of pericyclic reactions. It takes place between a 1,3-diene (the 4π component: the diene) and an alkene or alkyne (the 2π component: the dienophile) with simultaneous reaction at both ends of both components to afford a cyclohexene or 1,4-cyclohexadiene **15c** (Scheme 1.6). Each component undergoes reaction on only one face, which is formally described as the reaction being suprafacial in both components. This feature is

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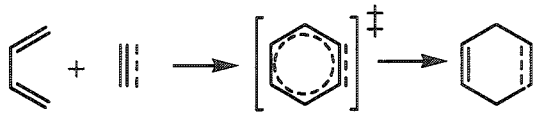
F. K. *J. Am. Chem. Soc.* **1986**, *108*, 554-556.

[9] For a small selection, see a) Norton, J. A. *Chem. Rev.* **1942**, *31*, 319-523. b) Martin, J. G.; Hill, R. K. *Chem. Rev.* **1961**, *61*, 537-562. c) Sauer, J. *Angew. Chem. Int. Ed. Engl.* **1966**, *5*, 211-230. d) Sauer, J. *Angew. Chem. Int. Ed. Engl.* **1967**, *6*, 16-33. e) Kwart, H.; King, K. *Chem. Rev.* **1968**, *68*, 415-477. f) Sauer, J.; Sustmann, R. *Angew. Chem. Int. Ed. Engl.* **1980**, *19*, 779-807. g) Pancír, J. *J. Am. Chem. Soc.* **1982**, *104*, 7424-7430. h) Gleiter, R.; Böhm, M. C. *Pure Appl. Chem.* **1983**, *55*, 237-244. i) Paquette, L. A.; In *Asymmetric Synthesis* Vol. 3, Morrison, J. D., Ed., Academic Press: New York, **1984**, Ch. 4. j) Desimoni, G.; Tacconi, G.; Bario, A.; Pollini, G. P. In *Natural Product Synthesis through Pericyclic Reactions.* ACS Monograph; American Chemical Society, Washington D. C. **1984**. Ch. 5. k) Helmchen, G.; Karge, R.; Weetman, J. In *Modern Synthetic Methods*. Scheffold. R., Ed., Springer Verlag: New York, **1986**, pp261. l) Francesco, F.; Taticchi, A. In *Dienes in the Diels-Alder Reaction* .Ed., Wiley: England, **2002**. m) Corey, E. J.; Nicolaou, K. C.; Synder, S. A.; Montagon, T.; Vassilikogiannakis, G. *Angew. Chem. Int. Ed. Engl.* **2002**, *41*, 1668-1698. n) Corey, E. J. *Angew. Chem. Int. Ed. Engl.* **2002**, *41*, 1650-1667.

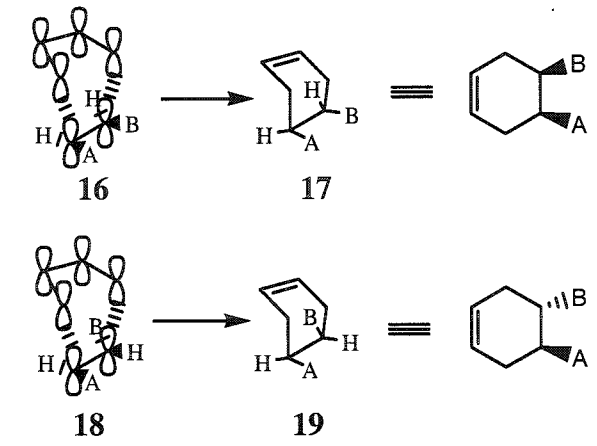
responsible for the stereospecificity of the reaction, whereby the relative stereochemistry within both the diene and the dienophile is preserved (Scheme 1.7).



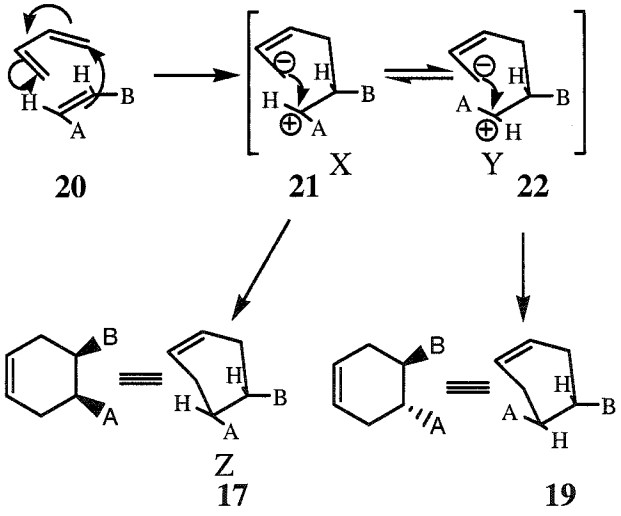
13 **14b** **15b** **15c**

Scheme 1.6

The Diels-Alder reaction is often described as being concerted, meaning that the two new sigma bonds are formed at the same time. In the case of the parent reaction (Scheme 1.5) and other reactions between two symmetrical components, the degree of bond formation of the two incipient bonds at the transition state should be equal. Such a reaction can be described as being concerted and synchronous. When the placement and/or nature of the substitutuents of either or both of the components lowers the symmetry of the transition state, differences in the electronic and steric effects associated with the two forming bonds will produce different degrees of bond formation at the transition state. Reactions of this type can be said to be concerted and asynchronous. When the two reaction components are strongly biased electronically, such that developing charges at the transition state can be stabilized, a stepwise mechanism can come into effect (Scheme 1.7). A consequence of this mechanism is the possibility of the loss of the stereospecificity alluded to earlier. This will take place when bond rotation (X $\rightarrow$ Y) occurs more quickly than (X $\rightarrow$ Z) (Scheme 1.8).



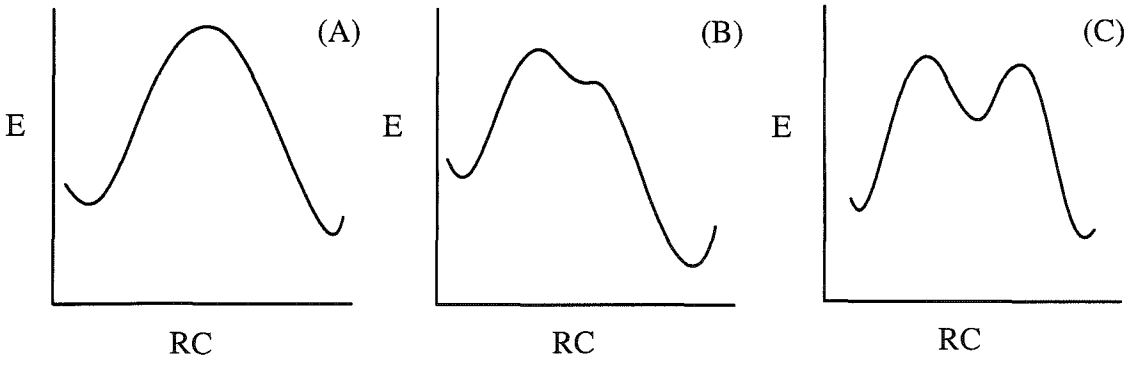
Scheme 1.7



Scheme 1.8

The three scenarios described above may be viewed as three regions on a continuum. Energy profiles corresponding to (A) a concerted synchronous, (B) a concerted asynchronous and (C) a stepwise Diels-Alder reaction are presented in Figure 1.1. As with any concerted reaction, there is no energy minimum between the reactants

and the product(s) in concerted synchronous and synchronous reactions. The same is true for the concerted asynchronous reaction, but as the degree of asynchronicity increases, a feature becomes increasingly prominent in the energy profile. Eventually this feature develops into an energy minimum that corresponds to a zwitterionic intermediate and the reaction is stepwise. A shallow energy well for this intermediate will corresponding to a short-lived intermediate, which may move on to product(s) before stereospecificity is lost. A deeper energy well will impart a longer lifetime to the intermediate, such that stereospecificity cannot be assured.



Concerted Synchronous

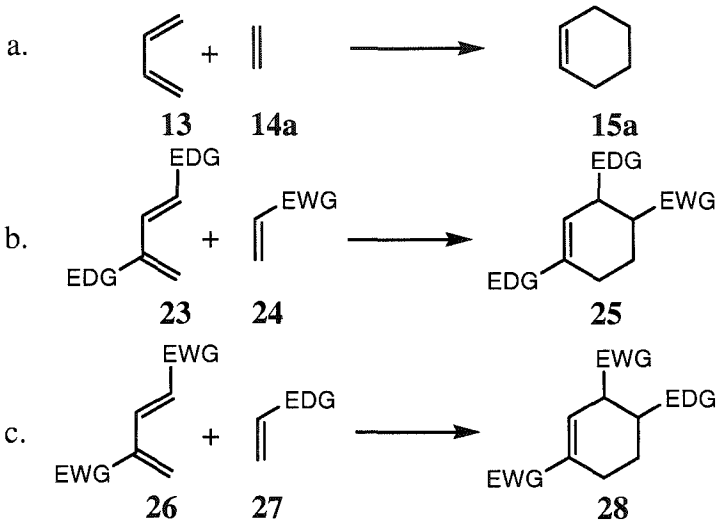
Limit of the Concerted Asynchronous

Non-Concerted (two-step)

Figure 1.1

The factors influencing the rate, stereoselectivity, regioselectivity, and enantioselectivity of the Diels-Alder reaction have been the subjects of extensive

study.[10, 11] Diels-Alder reactions can be classified into one of three processes: neutral, normal (electron demand), and inverse electron demand Diels-Alder reactions. The much more extensively studied normal Diels-Alder reaction involves electron rich dienes and electron deficient dienophiles, whereas the roles of the diene and the dienophile are reversed in inverse electron demand Diels-Alder (IEDDA) reactions (Scheme 1.9).



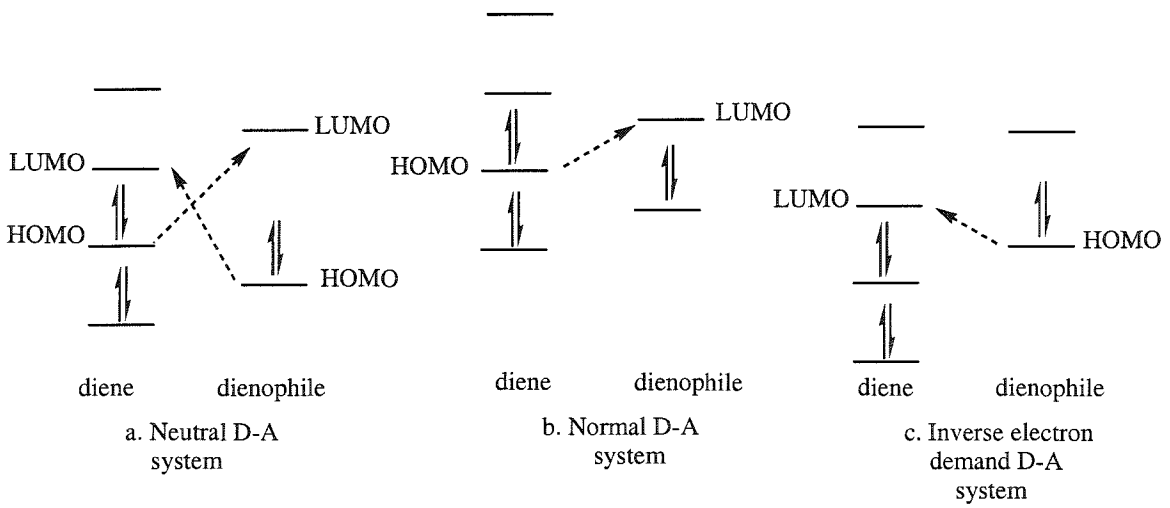
a = neutral Diels-Alder reaction
b = normal Diels-Alder reaction
c = inverse electron demand Diels-Alder reaction
EDG = electron donating group
EWG = electron withdrawing group

Scheme 1.9

[10] a) Woodward, R. B.; *The conversation of orbital symmetry*; Academic Press: New York, 1970. b) Horn, B.A.; Horek, S. L.; Zewail, A. H. *J. Am. Chem. Soc.* **1996**, *118*, 8755-8756. c) Houk, K. N.; Gonzalez, J. Et al. *Acc. Chem. Res.* **1995**, *28*, 81-90.

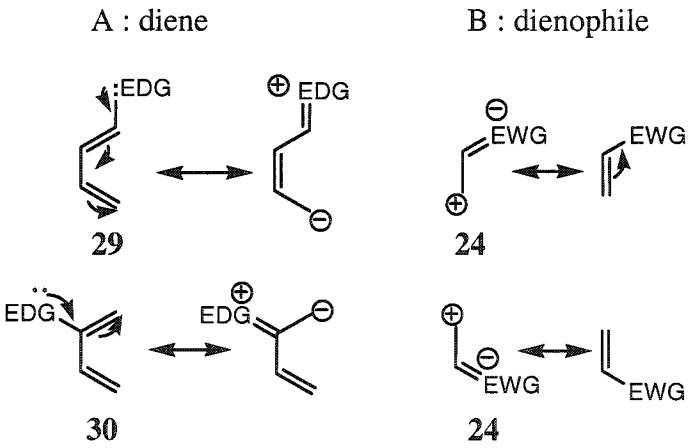
[11] a) Oppolzer, W. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 876-889. b) Sauer, J.; Sustmann, R. *Angew. Chem., Int. Ed. Engl.* **1980**, *19*, 779-807. c) Houk, K. N. *J. Am. Chem. Soc.* **1973**, *95*, 4092-4094. d) Burnier, J. S.; Jorgensen, W. L. *J. Org. Chem.* **1983**, *48*, 3923-3941.

According to the frontier molecular orbital (FMO) theory,[12] the rate of the Diels-Alder reaction is directly related to the magnitude of the smallest HOMO-LUMO energy separation (ΔE) of the reacting diene/ dienophile components: $HOMO_{diene}$-$LUMO_{dienophile}$ or $LUMO_{diene}$-$HOMO_{dienophile}$. For normal Diels-Alder reactions, the electron releasing groups on the diene unit raise the diene orbitals in energy relative to those of neutral systems. The addition of electron withdrawing groups on the dienophile lowers the energy of the dienophile orbitals (Scheme 1.10). Thus the key interaction for normal reactions is $HOMO_{diene}$-$LUMO_{dienophile}$. In inverse demand Diels-Alder reactions, the presence of electron donating groups on the dienophile and electron withdrawing groups on the diene cause the $HOMO_{dienophile}$-$LUMO_{diene}$ interaction to become more important (Scheme 1.10). In the neutral Diels-Alder reactions, both HOMO-LUMO interactions are possible, but the energy gaps are large compared to those of the normal and inverse electron demand versions. For this reason, require very forcing conditions.

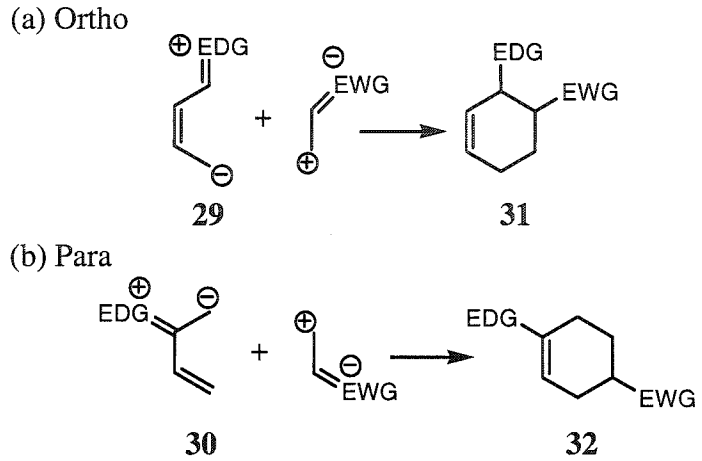


Scheme 1.10

One of the main reasons why the Diels-Alder reaction has such great utility is that the regio- and stereochemical outcome of the reaction can easily be predicted. When there is an electron-donating group in either the 1- or 2- position of the diene, this results in a polarization of the molecular orbitals. This electronic biasing of the diene can be explained in terms of orbital coefficient, but is perhaps more easily visualized using the simple valence bond description shown in Scheme 1.11. In any event, an electron donating substituent at the 1-position leads to a charge build-up at the 4-position and an electron donating substitutent at the 2-position leads to a charge build-up at the 1-position. Similar arguments can be used to explain the electronic bias of a dienophile bearing an electron-withdrawing group. Preferred interaction between the more charged ends of the two components then forms the basis for explanations of the observed regiochemical outcome, which is commonly known as the "ortho" and "para" rules (Scheme 1.12).



Scheme 1.11

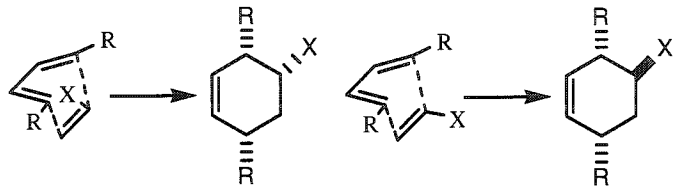


Scheme 1.12

Diels-Alder reactions can proceed via either an *endo* or *exo* transition state (Scheme 1.13). However, it was recognized early that most reactions prefer to proceed via an *endo* transition state and this is known as the Alder rule (Scheme 1.13).[12] As stated by Martin and Hill, "*Endo* addition involves the tendency for the dienophile substituents to be so oriented in the favored transition state that they lie directly above the residual unsaturation of the diene.... The transition state is best stabilized by spatial orbital overlap and simultaneously least destabilized by unfavorable steric repulsion has the lowest free energy of all possible transition states, and consequently predominates in the kinetically determined product".[13] Secondary orbital interactions have often been invoked to explain this phenomenon although there does not appear to be any strong evidence to

[12] Alder, K.; Stein, G. *Angew. Chem.* **1937**, *50*, 510-519.
[13] Martin, J. G.; Hill, R.K. *Chem. Rev.***1961**, *61*, 537-562

support it.[14] In fact, some researchers have concluded that this theory does not hold true.[15]



Scheme 1.13

Other theories regarding the source of the *endo* preference involve σ/ π orbital interactions in the ground state of an asymmetric diene,[16] as well as molecular orbital symmetry considerations.[17] As with most rules, they are made to be broken, and there are many cases where no selectivity, or even predominately the *exo* product, is seen.[18,19]

1.3 Inverse Electron Demand Diels-Alder (IEDDA) Reactions.

[14] Ginsburg, D. *Tetrahedron* **1983**, *39*, 2095-2135.
[15] a) Xidos, J. D.; Gosse, T. L.; Burke, D. E.; Poirier, R. A.; Burnell, D. J. *J. Am. Chem. Soc.***2001**, *123*, 5482-5488. b) Xidos, J. D.; Poirier, R. A.; Burnell, D. J. *J. Org. Chem.***1998**, *63*, 105-112.
[16] a) Paquette, L. A.; Schaefer, A. G.; Blount, J. F. *J. Am. Chem. Soc.* **1983**, *105*, 3642-3649. b) Gleiter, R.; Paquette, L. A. *Acc. Chem. Res.* **1983**, *16*, 328-334.
[17] Hoffmann, R.; Woodward, R. B. *J. Am. Chem. Soc.* **1965**, *87*, 4388-4389.
[18] a) Alder, K.; Günzl, W. *Chem. Ber.* **1960**, *93*, 809-825. b) Stockmann, H. *J. Org. Chem.***1961**, *26*, 2025-2029. c) Smith, J. R. L.; Norman, R. O. C.; Stillings, M. R. *Tetrahedron* **1978**, *34*, 1381-1383.
[19] a) Sodupe, M. *J. Am. Chem,. Soc.* **1997**, *119*, 4232-4238. b) Suarez, D.; Sordo, J. A. *Chem. Commun.* **1998**, 385-386. c) Oikawa, H.; Kobayashi, T.; Katayama, K.; Suzuki, Y.; Ichihara, A. *J. Org. Chem.* **1998**, *63*, 8748-8756.

IEDDA reactions require an electron deficient 1,3-diene. Dienes can be rendered electron deficient (i.e. the LUMO energy can be lowered) by the attachment of an electron-withdrawing group, by the replacement of one or more of the diene sp^2 carbon atoms by nitrogen or (at the termini) oxygen or both. In particularly electron deficient systems, the low-lying LUMO can cause the diene to be unstable. Embedding the diene in an aromatic system can counteract this. In such cases, the IEDDA reaction is generally followed by a retro Diels-Alder reaction, in which one or two of the original nitrogen atoms are expelled as RCN or N_2, respectively. A series of heteroaromatic dienes and their IEDDA behaviors are listed below (Figure 1.2).

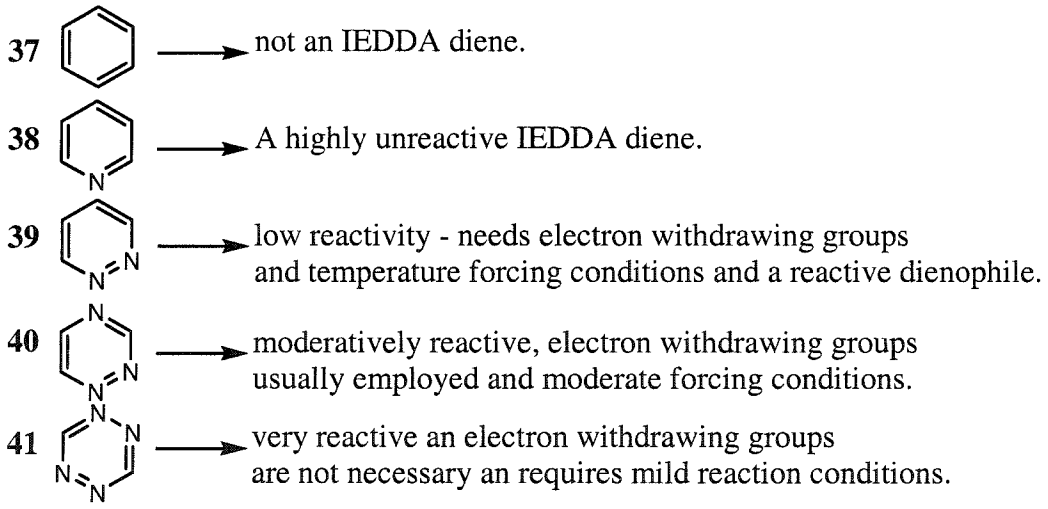


Figure 1.2

Since the initial discovery of the Diels-Alder reaction, the vast majority of study has been in the area of normal Diels-Alder reaction. Considerably less attention has been paid to the IEDDA reaction, although a substantial body of literature on the subject has

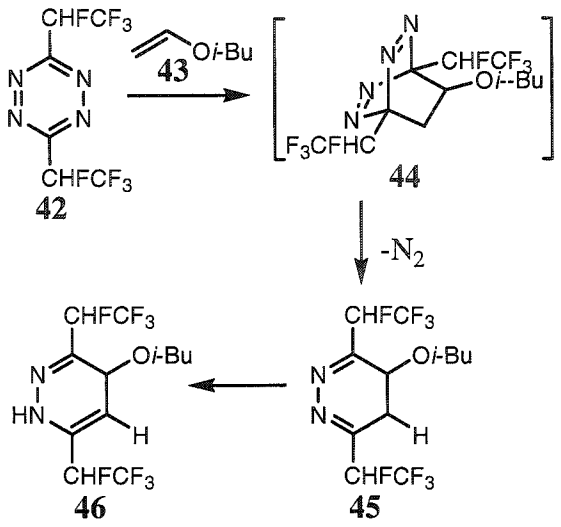
been complied. Perhaps the major reason for the comparatively small amount of IEDDA work on the reaction is the lack of ready access to a broad range of stable IEDDA-active electron deficient dienes. As alluded to above, this may well have its origin in the instability of many simple electron deficient dienes.

1.3.1 Heteroaromatic Azadienes Dienes

The first class of heteroaromatic azadienes to be used in the IEDDA reaction were tetrazines.[20] The heteroaromatic azadienes have since enjoyed widespread use and in the IEDDA reaction, they have found considerable application in the total synthesis of natural products.[21] 3,6-Bis(1,2,2,2-tetrafluoroethyl)-1,2,4,5-tetrazine (**42**) was the first system to be successfully applied in the IEDDA reaction (Scheme 1.14).[22] This and related azadienes undergo subsequent retro-Diels-Alder reactions, eliminating nitrogen, to afford dihydropyridazines or pyridazines.

---

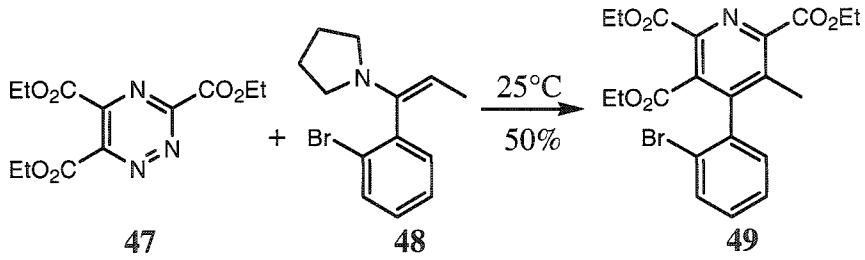
[20] a) Boger, D. L.; Weinreb, S. M. *Hetero Diels-Alder Methodolgy in Organic Synthesis;* Academic Press, Inc.: San Diego, **1987**. b) Fringuelli, F.; Taticchi, A. *Dienes In The Diels-Alder Reaction*; Wiley Interscience: New York, **1990**. c) Weinreb, S. M.; Staib, R. R. *Tetrahedron* **1982**, *38*, 3087-3128. d) Boger, D. L. *Tetrahedron* **1986**, *39*, 2869-2939.
[21] Boger, D. L. *Chem. Rev.* **1986**, *86*, 781-793.
[22] Carboni, R. A.; Lindsey, R. V., Jr. *J. Am. Chem. Soc.***1959**, *81*, 4342-4346.



Scheme 1.14

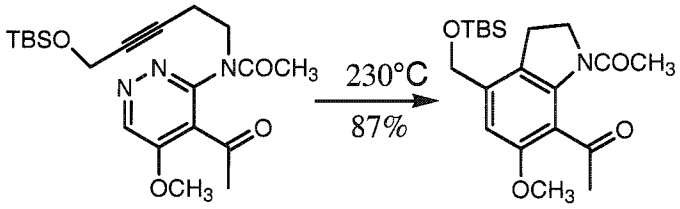
As expected, decreasing the number of nitrogen atoms in the heteroaromatic azadiene decreases the reactivity. 1,2,4-Triazines are typically less reactive than 1,2,4,5-tetrazines, but more reactive than 1,2-diazines (pyridazines). For example, 1,2,4-triazine **47** readily reacts in an intramolecular fashion at room temperature with enamine **48** to afford **49** (Scheme 1.15),[23] but 1,2-diazine **50** requires far more forcing conditions to react in an intramolecular fashion (Scheme 1.16).[24]

[23] Boger, D. L.; Panek, J. S. *Tetrahedron Lett.* **1984**, 25, 3175-3182.
[24] Boger, D. L.; Coleman, J. S. *J. Org. Chem.* **1984**, 49, 2240-2245.



47 48 49

Scheme 1.15

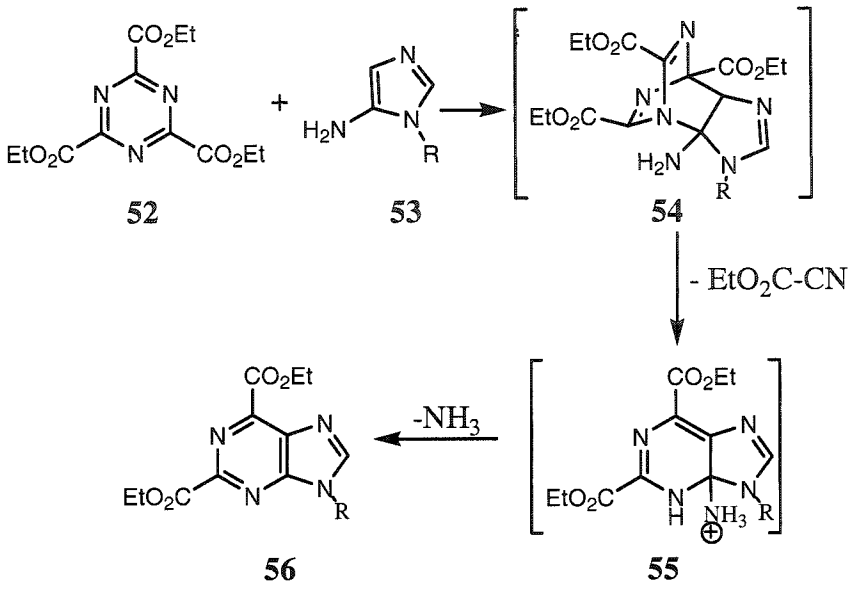


50 **51**

Scheme 1.16

More recently, 1,3,5-triazines have emerged as useful dienes. Like their 1,2,4-isomers, these aromatic systems have also been used in the total synthesis of natural products.[25] For example, the reaction of triester **52** with *N*-substituted 5-aminoimidazoles **53** (generated *in situ* by decarboxylation of 4-hydroxycarbonyl-5-aminoimidazole) gave purine derivatives **56**. The products presumably arose via an IEDDA reaction to give **54**, followed by the loss of ethyl cyanoformate to give **55** and then elimination of ammonia to give **56** (Scheme 1.17).

[25] Dang, Q.; Liu, Y.; Erion, M. D. *J. Am. Chem. Soc.* **1999**, *121*, 5833-5834.



R = Bn, β-*D*-ribofuranosyl, or 2,3,5-tri-*O*-acetyl- β-*D*-ribofuranosyl

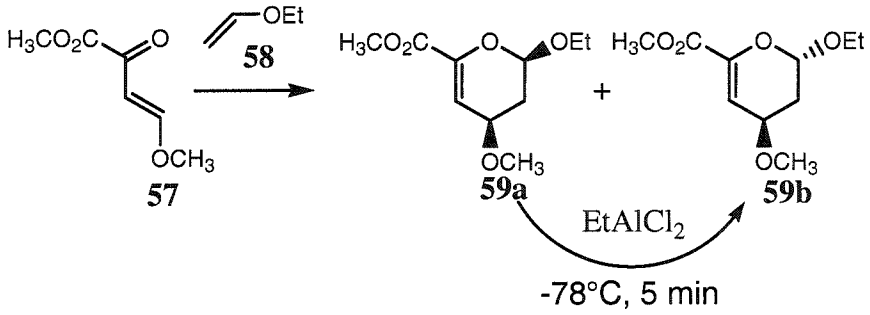
Scheme 1.17

1.3.2 α, β-Unsaturated Keto Esters]

α,β-Unsaturated carbonyl compounds (1-oxadienes) have also been found to participate in the IEDDA reaction.[26] The most common reactions are those with alkyl vinyl ethers, to afford 2-alkoxy-3,4-dihydro-2*H*-pyrans, which are important in carbohydrate synthesis.[27] An example of this type of reaction is the one between **57** with ethyl vinyl ether (Scheme 1.18).[28] This reaction produces a mixture of the *endo* adduct **59a** and the *exo* adduct **59b**. Enhanced yields and higher selectivity could be obtained by

[26] Desimoni, G.; Tacconi, G. *Chem. Rev.* **1975**, *75*, 651-692.
[27] a) Schmidt, R. R. *Pure Appl. Chem.* **1987**, *59*, 15-424. b) Schmidt, R. R.; Apparao, S.; Maier, M. E. *Synthesis* **1987**, *10*, 900-904. c) Maier, M. *Tetrahedron. Lett.* **1985**, *26*, 2065-2068. d) Tietze, L. F.; Voss, E. *Tetrahedron. Lett.* **1986**, *27*, 6181-6184.
[28] MacDonald, S. J. F.; Huizinga, W. B.; McKenzie, T. C. *J. Org. Chem.* **1988**, *53*, 3373-3377.

increasing the pressure and through the use of a Lewis acid (ethylaluminum dichloride). The two diastereomers could be isolated. It was also observed, using **59a**, when the temperature and amount of Lewis acid increased more *endo* adduct **59a** epimerized to the more stable *exo* adduct **59b**.



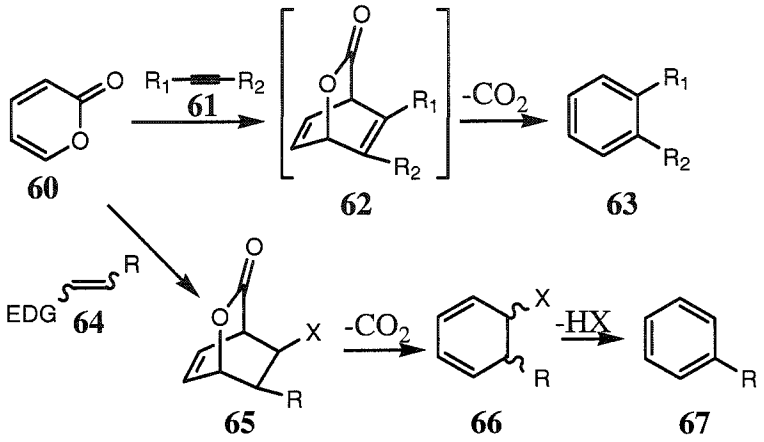
Conditions	Yields	A : B
a) neat, 13 kba, 24 °C, 65 h	82%	(5.7 : 1.0)
b) toulene, 110 °C, 29 h	48%	(1.8 : 1.0)
c) CH_2Cl_2, $EtAlCl_2$ (0.1 eq), -78 °C	75%	(0.8 : 1.0)

Scheme 1.18

1.3.3 2-Pyrone

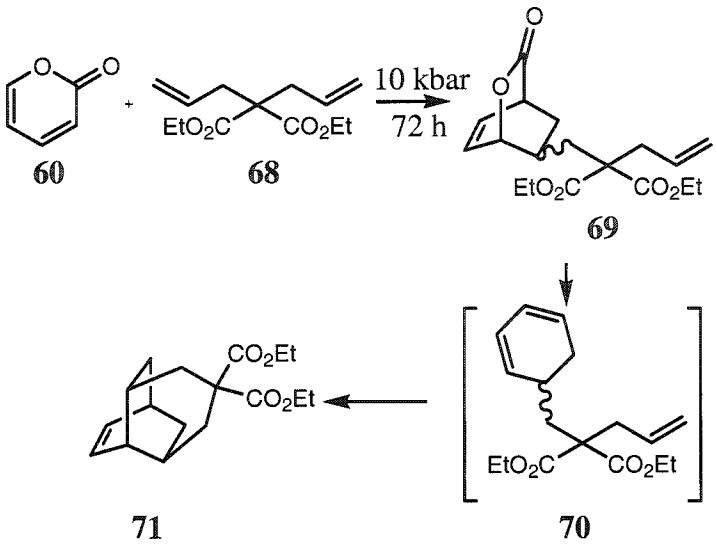
2-Pyrones undergo IEDDA reactions with a variety of electron rich dienophiles. For example, the reaction of the parent 2-pyrone with alkynes forms strained bicyclooctadienes that readily undergo extrusion of CO_2 (retro hetero Diels-Alder) to form aromatic products (Scheme 1.19). The uses of alkenes as dienophiles initially give rise to more stable and sometimes isolable bicyclooctenes. These can also give aromatic products upon heating via loss of CO_2 followed by elimination. However, these reactions

tend to require harsh conditions (up to 200 °C). As before, the substitution of the pyrone with an electron-withdrawing group (especially at the 3-position) renders the system more reactive.



Scheme 1.19

Since the dienophile in the first (intermolecular, IEDDA) cycloaddition is unactivated, the initial Diels-Alder reaction is slow to proceed and high pressure is required to induce the desired transformation. Adduct **69** is also isolable and required high temperatures (usually 200 – 220 °C) for the explusion of CO_2 and the subsequent intramolecular Diels-Alder cycloaddition (Scheme 1.20). The explusion of CO_2 from **65** affords a new diene **66**, which opens the door to the possibility of performing sequential Diels-Alder reactions. This has indeed been accomplished. Reaction of 2-pyrone **60** with α,ω-diene **68** gave rise to tricyclic compound **71** (Scheme 1.20).[29]

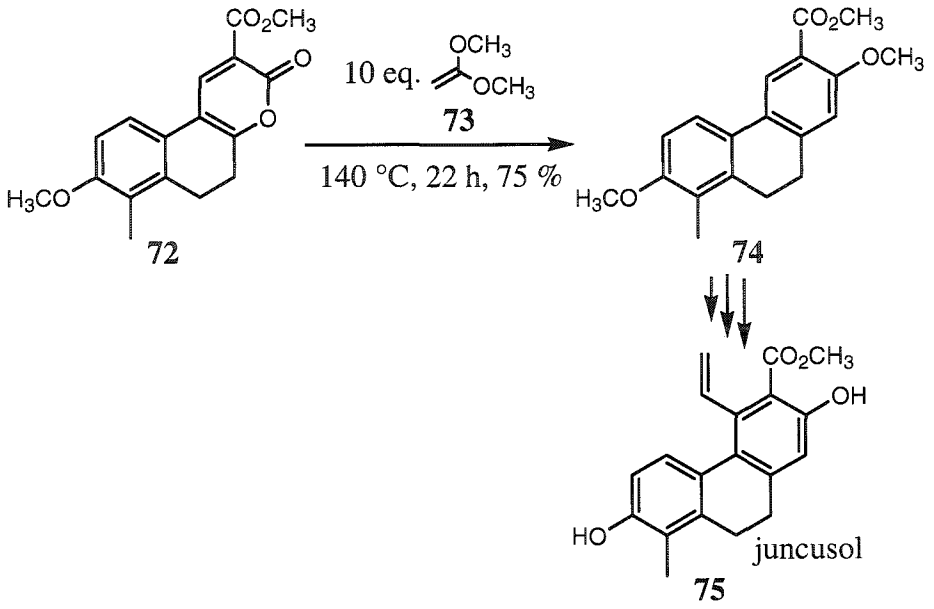


Scheme 1.20

The first natural product to be synthesized through the intermediacy of a 2-pyrone was juncusol, a marsh plant constituent that has potent antimicrobial and cytotoxic properties. The key step in this synthesis was the reaction of a multi-ringed 2-pyrone with 1,1-dimethoxyethylene at 140 °C, which formed the aromatized product in 75% yield. As before, the new aromatic ring is the result of a domino IEDDA (CO_2 extrusion) elimination sequence (Scheme 1.21).[30]

---

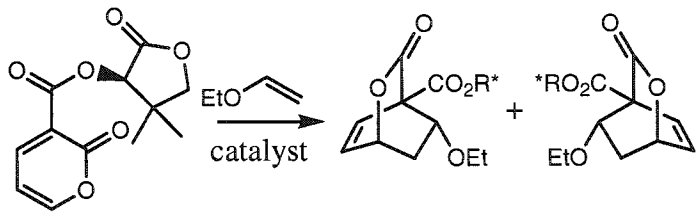
[29] Swarbrick, T. M.; Markó, I. E.; Kennard, L. *Tetrahedron. Lett.* **1991**, *32*, 2549-2552.
[30] a) Boger, D. L.; Mullican, M. D. *Tetrahedron. Lett.* **1982**, *23*, 4555-4558. b) Boger, D. L.; Mullican, M. D. *J. Org. Chem.* **1984**, *49*, 4045-4050.



Scheme 1.21

One of the more recent applications of 2-pyrones has been the recognition that the initially formed cycloadducts could be used as versatile precursors to a variety of multifunctional six-membered rings. The control of the relative stereochemistry that comes with the Diels-Alder reaction is one of the main advantages of this approach.[31] Two groups, those of Posner and Markó in particular, have contributed a significant amount to this area. They demonstrated separately that the 2-pyrone cycloaddition adducts formed can be turned into various enantiopure and biologically active compounds. This was accomplished by using chiral auxiliaries on either the diene or dienophile and through the use of chiral Lewis acids (Scheme 1.22).

[31] a) Afarinkia, K.; Vinader, V.; Nelson, T. D.; Posner, G. H. *Tetrahedron* **1992**, *48*, 9111-9171. b) Kalinin, V. N.; Shilova, O. S. *Russ. Chem. Rev.* **1994**, *63*, 661-666.



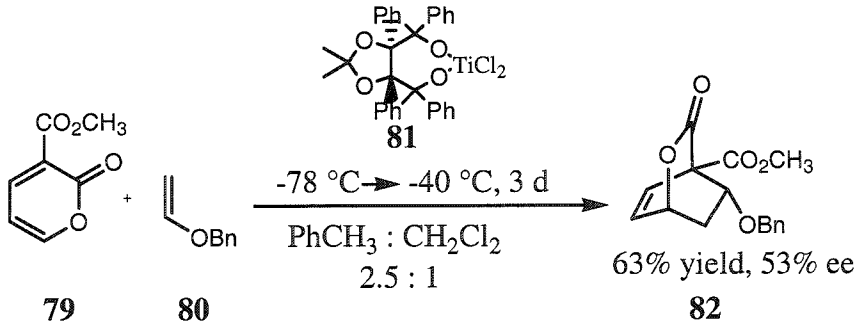
76 77 78

Entry	Catalyst	yield	de of **77**
1	(+)-Eu(hfc)$_3$	97%	>95%
2	Eu(fod)$_3$	94%	>95%
3	(-)-Eu(hfc)$_3$	91%	>95%

Scheme 1.22

Posner and coworkers found that a tartrate-derived TADDOL-complexed titanium (IV) (TADDOL is α,α,α',α'-tetraaryl-1,3-dioxolan-4,5-dimethanol) species catalyses the cycloaddition of 3-carbonmethoxypyrone (CMP) **79** with benzyl vinyl ether under very mild conditions to produce the *endo* bicycloadduct as a single diastereomer in 55% enantiomeric excess (Scheme 1.23).[32]

[32] Posner, G. H.; Carry, J. C.; Lee, J. K.; Bull, D. S.; Dai, H. *Tetrahedron. Lett.* **1994**, *35*, 1321-1324.



Scheme 1.23

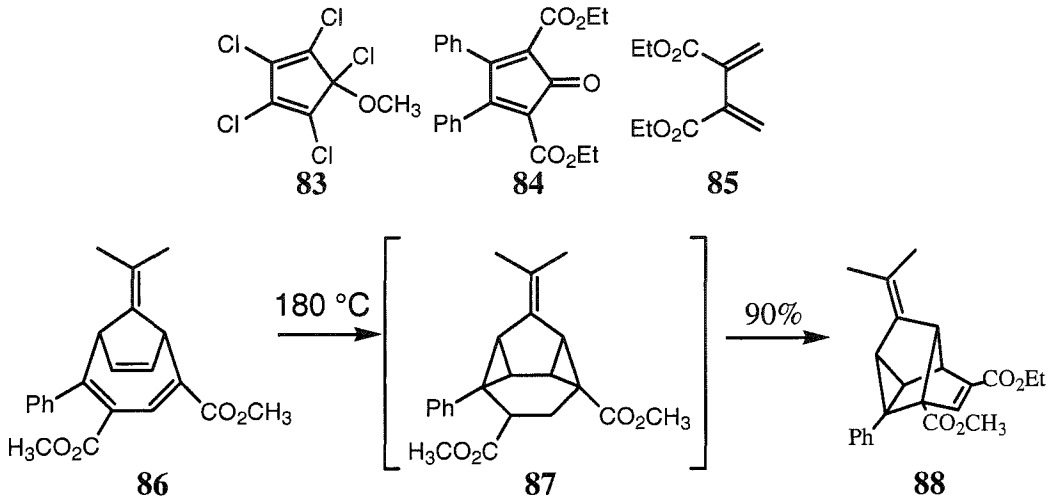
A more impressive result (86% yield, 95% ee) was obtained when a, (*R*)-(+)-binol-titanium Lewis acid complex was used to promote the cycloaddition of 3-CMP and benzyl vinyl ether.[33] The use of an ytterbium-based Lewis acid in combination with under high-pressure, has also been shown to afford high regioselectivity, and stereoselectivity.[34,35]

1.3.4 Other Electron Deficient Dienes

In the IEDDA literature, there are relatively few examples of all-carbon electron deficient dienes. Heterodienes have found much broader application than all-carbon electron deficient dienes as discussed above. Other than the 2-pyrones, all carbon dienes are not common. Other all-carbon systems that have found limited application include

[33] a) Posner, G. H.; Eydoux, F.; Lee, J. K.; Bull, D. S. *Tetrahedron. Lett.* **1994**,.*35*, 7541-7544. b) Posner, G. H.; Dai, H.; Lee, J. K.; Bull, D. S.; Eydoux, F.; Lee, J. K. *J. Org. Chem.* **1996**, *61*, 671-676.
[34] Posner, G. H.; Ishihara, Y. *Tetrahedron. Lett.* **1994**, *35*, 7545-7548.
[35] Markó, I. E.; Evans, G. R. *Tetrahedron. Lett.* **1994**, *35*, 2771-2774.

cyclopentadienes,[36] cyclopentadienones,[37] and thiophene-1,1-dioxides.[38] Other systems that have been used sporadically include systems such as 2,3-bis(ethoxycarbonyl)-1,3-butenediene, **85**[39,40] (Scheme 1.24).



Scheme 1.24

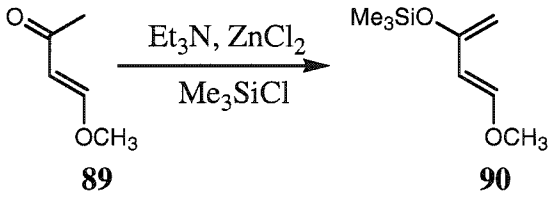
1.3.5 The Identification of a Potentially Useful Class of Electron Deficient Dienes and the Bodwell Group's Involvement in IEDDA Chemistry.

Danishefsky's diene (1-methoxy-3-trimethylsilyloxy-1,3-butadiene) was first reported in 1974 (Scheme 1.25). This is the parent compound of what has become one of the most widely used classes of dienes in the realm of the normal Diels-Alder reaction.

---

[36] Burry, L. C.; Bridson, J. N.; Burnell, D. J. *J. Org. Chem.* **1995**, *60*, 5931-5934.
[37] Harano, K.; Yasuda, M.; Kanematsu, K. *J. Org. Chem.* **1982**, *47*, 3736-3743.
[38] a) Bluestone, H.; Bimber, R.; Berkey, R.; Mandel, Z. *J. Org. Chem.* **1961**, *26*, 346-351. b) Raasch, M. S. *J. Org. Chem.* **1980**, *45*, 856-867.

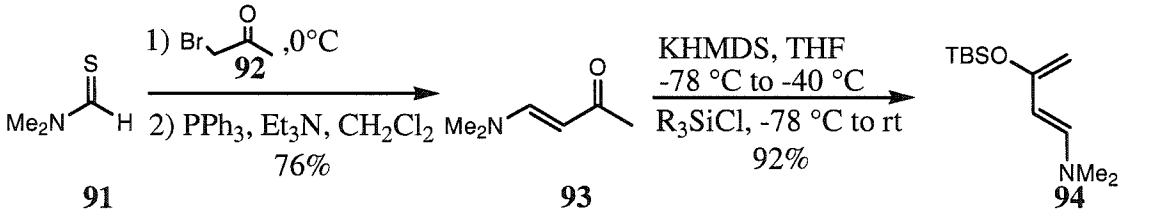
This popularity can be attributed to broad synthetic utility and ease of preparation.[41] As such, many dienes related to Danishefsky's diene have been prepared and applied to synthetic problems (Scheme 1.25). Rawal recently reported a similar diene **94**, but it has not yet been embraced by the synthetic community to the same extent as Danishefsky's diene (Scheme 1.26).[42]



89 **90**

Danishefsky's Diene

Scheme 1.25



91 **93** **94**

Rawal's Diene

Scheme 1.26

The electron-donating groups at the 1 and 3 positions of Danishefsky's and Rawal's dienes are responsible for their high reactivity towards a wide range of electron

---

[39] a) Grundke, C.; Hoffmann, H. M. R. *Chem. Ber.* **1987**, *120*, 1461-1462. b) Tarnchompoo, B.; Thebtaranonth, C.; Thebtaranonth, Y. *Tetrahedron. Lett.* **1987**, *28*, 6671-6674.
[40] Prinzbach, H.; Auge, W.; Basbudak, M. *Helv. Chim. Acta.* **1971**, *54*, 759-764.
[41] Danishefsky, S.; Kitahara, T. *J. Am. Chem. Soc.* **1974**, *96*, 7807-7808.

deficient dienophiles. In both dienes, the two electron-donating groups work together to electronically bias the two termini of the diene unit. This is directly translated into the high degree of predictable regiochemical control that is observed during reactions with electronically biased dienophiles. The functionality present in the resulting Diels-Alder adducts can be manipulated in a variety of different ways to build more complex systems. Rapid access to relatively complex systems is synonymous with potential application in synthesis, and this has indeed been realized on many occasions.[43]

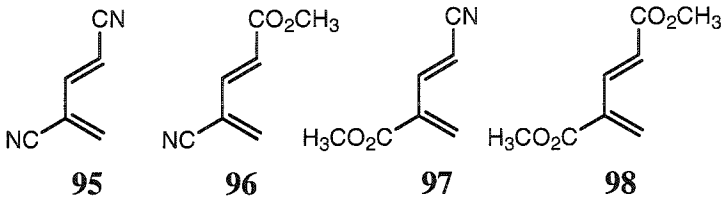
Using Danishefsky's and Rawal's dienes as models, and replacing the electron donating groups with electron withdrawing ones would conceivably give rise to a reactive electron deficient diene that exhibits high and predictable regioselectivity in IEDDA reactions with electron rich dienophiles. Provided that such dienes could be prepared easily and in quantity, such electron deficient dienes would have the potential to be as useful synthetically as Danishefsky's diene.

Early in the 1980s, Ahn and Hall[44] reported the synthesis of four acyclic electron deficient dienes (Figure 1.3). These dienes were prepared through Diels Alder reaction of cyclopentadiene with either methyl acrylate or acrylonitrile ether (Scheme 1.27). The resulting adducts **100** were then formylated and the resulting aldehydes **101** were then subjected to Wittig reactions to afford "protected" dienes **95-98**. Thermolysis (400-600 °C) induced retro-Diels-Alder reactions, which liberated the free dienes (Scheme 1.27).

---

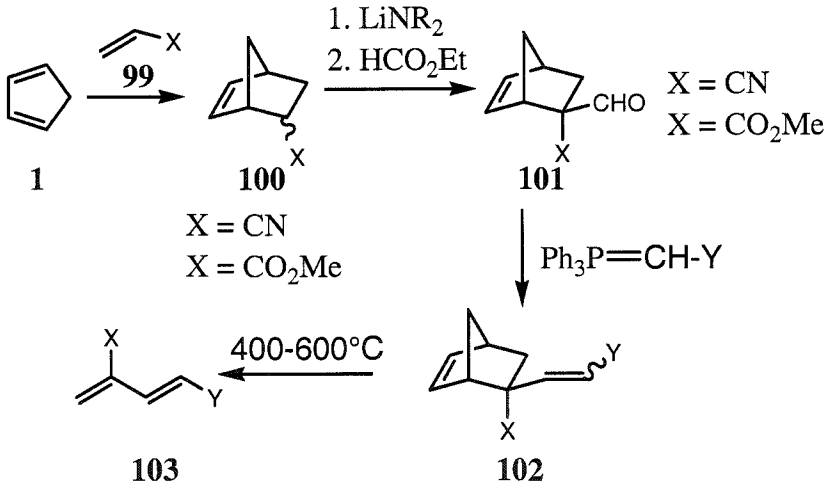
[42] Kozmin, S. A.; Janey, J. M.; Rawal, V. H. *J. Org. Chem.* **1999**, *64*, 3039-3052.
[43] Danishefsky, S. *Acc. Chem. Res.* **1981**, *14*, 400-406.
[44] Ahn, K. -D.; Hall, H. K. *J. Polym. Sci., Polym. Chem.*. **1981**, *19*, 629-644.

These dienes polymerized readily (as was the goal of this work) and their Diels-Alder chemistry was not investigated.



95 **96** **97** **98**

Figure 1.3



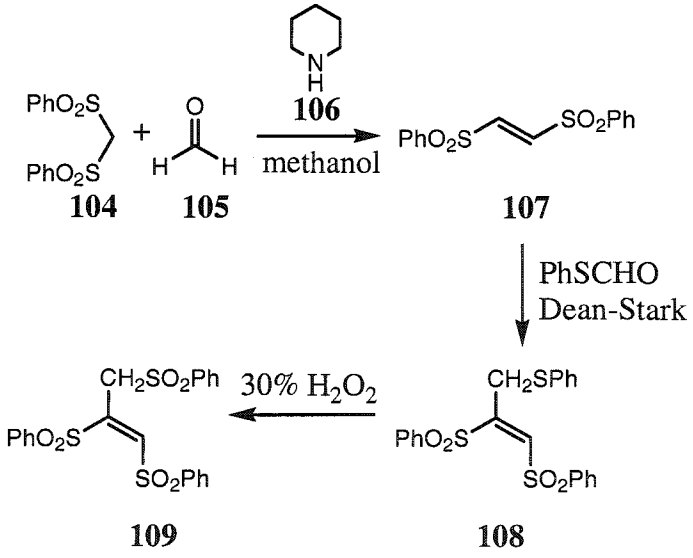
X = Y = CN
X = CN, Y = CO_2Me
X = CO_2Me, Y = CN
X = Y = CO_2Me

X = Y = CN
X = CN, Y = CO_2Me
X = CO_2Me, Y = CN
X = Y = CO_2Me

Scheme 1.27

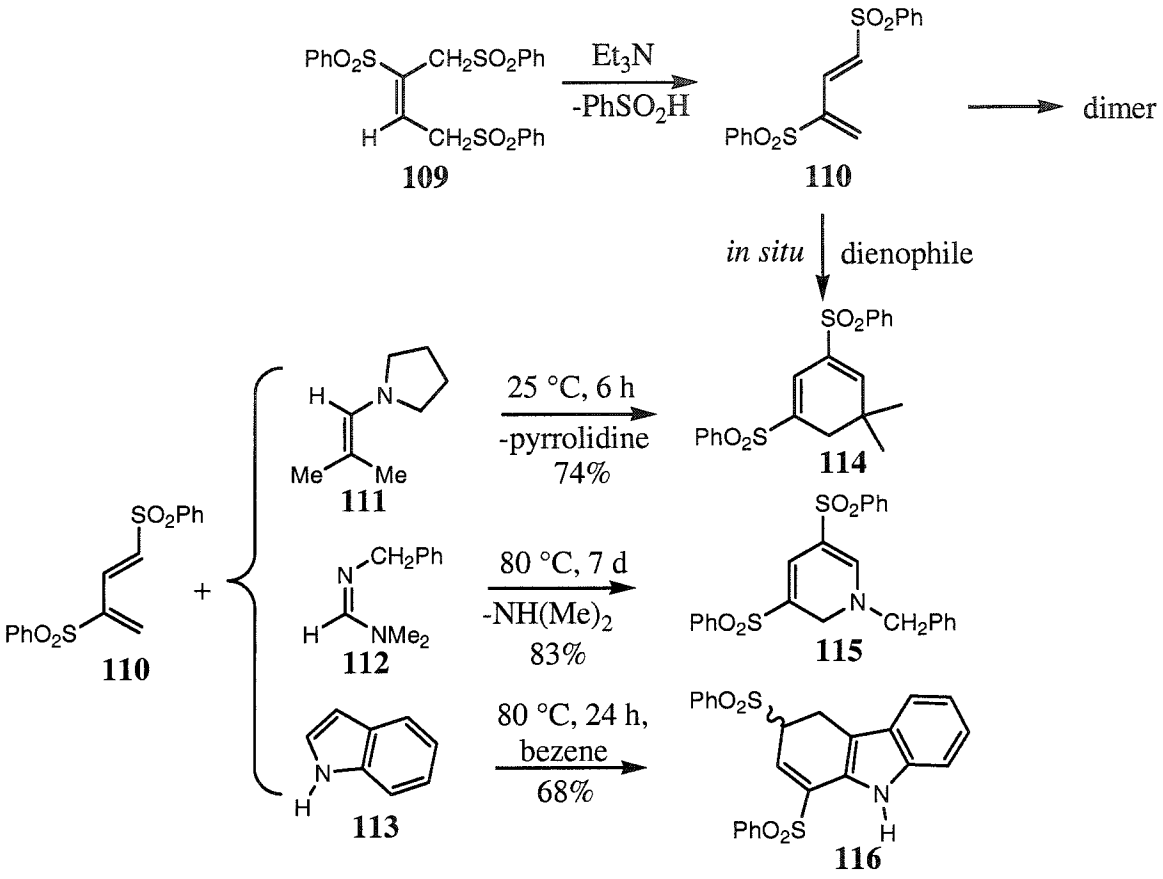
In the late 1980s and early 1990s, the Padwa group reported the synthesis of 1,3-bis(phenylsulfonyl)butadiene and its IEDDA reactions with several dienophiles (Scheme

1.28 & 1.29).[45] This work originated from the unexpected observation of the isomerization of 2,3-bis(phenylsulfonyl)butadiene, which was the original diene of interest (Scheme 1.28).[46] A targeted synthesis of **110** was then developed (Scheme 1.28).[47] The trisulfone **109** was prepared from a condensation of sulphone **104** with formaldehyde followed by a Knoevenagel-type condensation with the appropriate aldehyde (Scheme 1.28). Reaction of trisulfone **109** with triethyl amine resulted in the formation of **110**, which presumably arose from dimerization of diene **110**. Performing the reaction of **110**, in the presence of a selection of dienophiles **111-113** gave rise to products **114-116**. The initial IEDDA adducts were not observed or isolated, having apparently undergone (not surprisingly) further transformations, such as eliminations and isomerizations (Scheme 1.29).



[45] Padwa, A.; Gareau, Y.; Harrison, B.; Rodriguez, A. *J. Org. Chem.* **1992**, *57*, 3540-3545.
[46] a) Norman, B. H.; Gareau, Y.; Padwa, A. *J. Org. Chem.* **1991**, *56*, 2154-2161. b) Padwa, A.; Harrison, B.; Norman, B. H. *Tetrahedron. Lett.* **1989**, *30*, 3259-3262. c) Padwa, A.; Norman, B. H. *Tetrahedron. Lett.* **1988**, *29*, 2417-2420.

Scheme 1.28



Scheme 1.29

1.3.6 The Bodwell group's involvement in IEDDA chemistry.

The main focus of the Bodwell group has been the synthesis of cyclophanes, especially metacyclophanes, for which isophthalates are important precursors. Unfortunately, there does not appear to be a widely applicable method for their synthesis.

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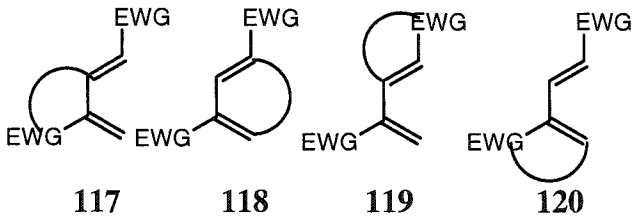
[47] Maskyama, Y.; Sato, H.; Kurusu, Y. *Tetrahedron Lett.* **1985**, *26*, 67-68.

Current methods rely on the elaboration of commercially available isophthalate systems, and/or aromatic substitution and functional group interconversions of various aromatic precursors. With this in mind, research in the Bodwell group aimed at using electron deficient 1,3-subsituted dienes as potentially general isophthalate progenitors was initiated. With the knowledge that known 1,3-disubstituted electron deficient dienes were not very stable (vide supra), annulated systems were targeted for initial study. It was envisaged that cycloalkane fusion, as in **117-120** (Figure 1.4), would provide some kinetic and thermodynamic stability, while still maintaining access to the reactive *s-cis* conformation.



117 **118** **119** **120**

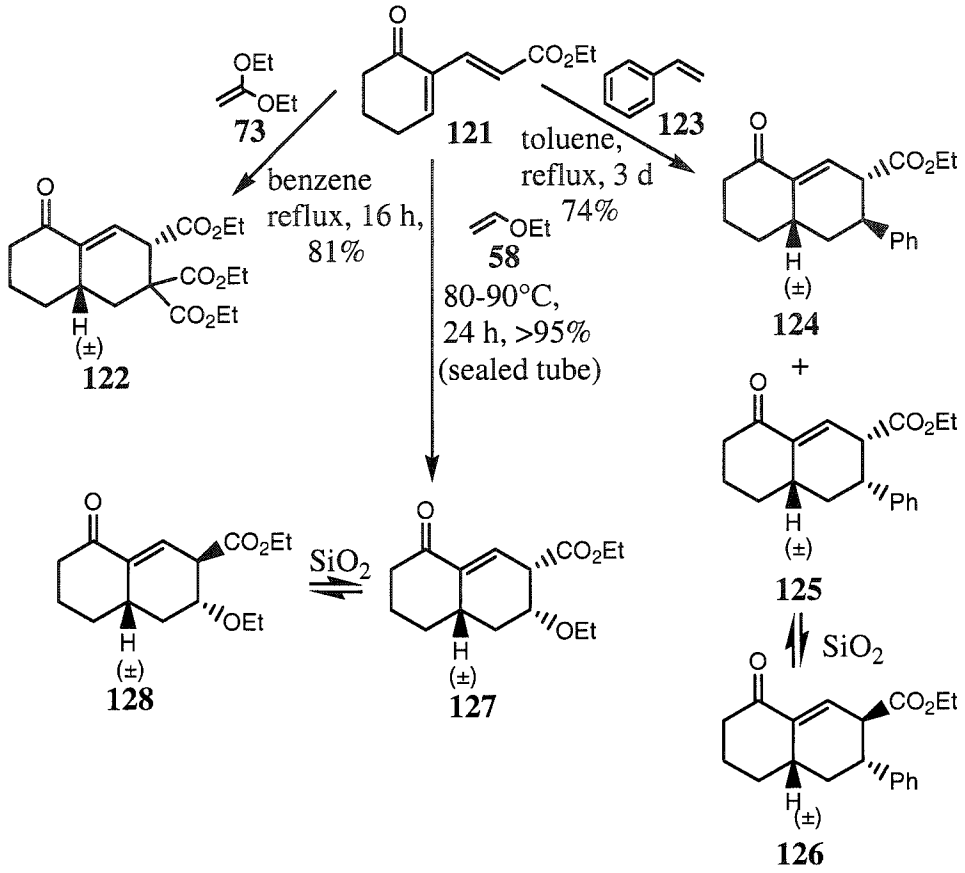
Figure 1.4

Based on synthetic considerations, diene **120** was the first choice for investigation. The preliminary system explored in the Bodwell group was **121** (Scheme 1.30). This was synthesized in 5 steps from 2-cyclohexene.[48]

The electron deficient diene **121** was stable at –20 °C for several weeks and readily reacted with 1,1-diethoxyethylene at reflux in benzene. The bicyclic product **122** was obtained in 81% yield. The presence of only one diastereomer is consistent with a

concerted process. Diene **121** underwent cycloaddition with a variety of other dienophiles, including styrene and ethyl vinyl ether. In the case of styrene, two diastereomers arising from *endo* and *exo* addition were obtained in a 78 : 22 ratio. The *endo* adduct **125** was observed to epimerize during flash chromatography. Epimerization during flash chromatography was also observed for the adduct **127** of diene **121** and ethyl vinyl ether. This reaction proceeded quantitatively and gave only one diastereomer (Scheme 1.30). The results described above were also consistent with a concerted IEDDA reaction. A series of other dienes **129-132** related to **121** have also been prepared and studied (Figure 1.5).[49]

[48] Bodwell, G. J.; Pi, Z. *Tetrahedron. Lett.* **1997**, *38*, 309-312.
[49] Results from Zulan Pi thesis, Memorial University Newfoundland, **1996**.



Scheme 1.30

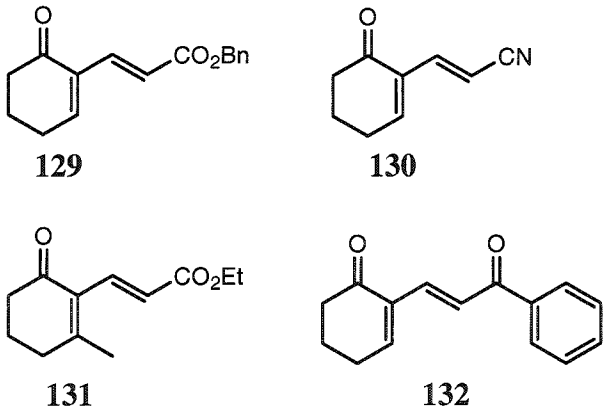


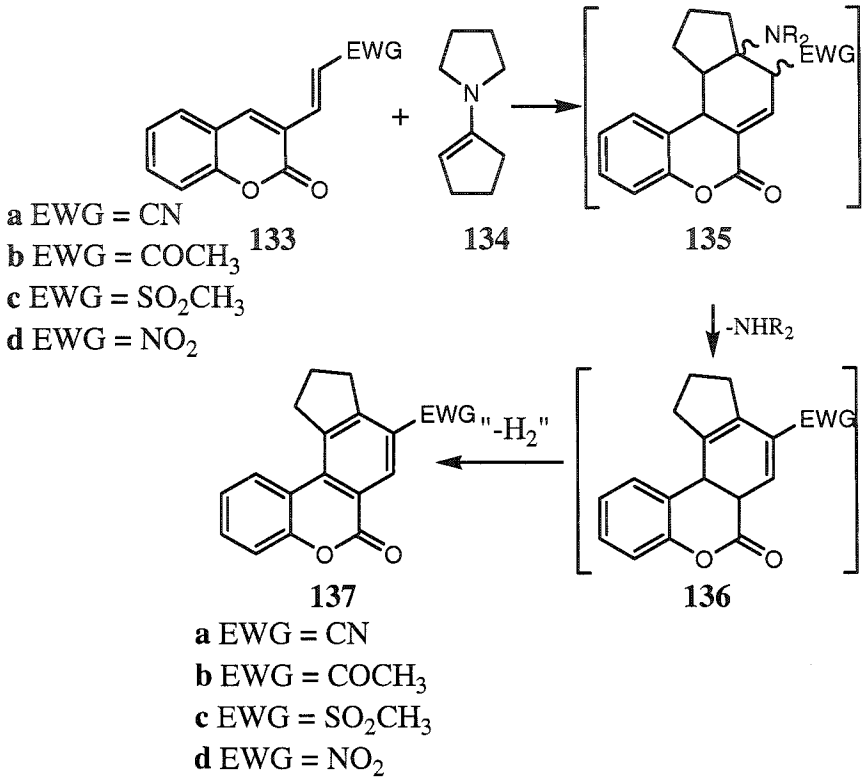
Figure 1.5

A coumarin-based system **133** was the next step in the evolution of electron deficient dienes in the Bodwell group (Scheme 1.31). The coumarin-based diene **133**, which was prepared in a single step and in high yield, was found to be much more stable than the cyclohexanone-based dienes, presumably due to the partial aromatic nature of the pyrone ring.

The increase in stability inevitably caused a decrease in the IEDDA reactivity. Some electron rich dienophiles that reacted with the diene **121**, e.g. ethyl vinyl ether, failed to react with diene **133**, even under more forcing conditions. Most of the work in this area was conducted using **133b**, but some other dienes (**133a**, **133c**, **133d**) were also prepared and found to exhibit a similar lack of reactivity to that of **133**.

When dienes **133a-133d** were reacted with enamines they gave rise to aromatic products. In no case was the initial Diels-Alder adducts observed. Thus no comment could be made regarding the mechanism (1 vs. 2 steps). An IEDDA-driven domino reaction was postulated to explain the formation of the observed products. Following an initial IEDDA reaction to give rise to adduct **135**, elimination of pyrolidine to give a new diene **136** can occur. Dehydrogenation of this diene then gives the observed aromatized product **137** (Scheme 1.31).[50] The mechanism of dehydrogenation has not been fully investigated and is not completely understood. Excess enamine appears to be at least partly responsible for accepting H_2.

[50] Bodwell, G. J.; Pi, Z. Pottie, I. R. *Synlett.* **1999**, *4*, 477-479.



Scheme 1.31

In work aimed at further exploiting the new IEDDA-driven domino reaction described above, a chromone-based system **140** was synthesized (Scheme 1.40). The goal of this research was to see if it was possible to provide access to functionalized xanthones. Xanthones are naturally occurring compounds that have shown great potential in treatments for various diseases, such as HIV[51] and cancer.[52]

[51] Groweiss, A.; Cardellina, J. H.; Boyd, M. R.; *J. Nat. Prod.* **2000**, *63*, 1537-1539.
[52] Decantini, M.; Bisi, A.; Cavalli, A.; Belluti, F.; Gobbi, S.; Rampa, A.; Valentia, P.; Palzer, M.; Palusczak, A.; Hartmann, R. W. *J. Med. Chem.* **2001**, *44*, 672-680.

Akiba *et al.* first reported a chromone-based diene similar to the coumarin **133**.[53] The synthesis of this diene was accomplished by with the reaction of 3-formylchromone with diethyl malonate, TBSOTf, and 2,6-lutidine, to give **139**. It was later discovered in the Bodwell group that using the Horner-Wadsworth-Emmons modification of the Wittig reaction could give the same product with similar yields (Scheme 1.32).[54] If reactions of this diene with enamines were to follow a mechanism analogous to that of the coumarin-based diene (Scheme 1.33), functionalized xanthones would result. However, this was not the case. Instead, 2-hydroxybenzophenones were the exclusive products. An intramolecular elimination apparently replaces the dehydrogenation step at the end of the domino sequence (Scheme 1.34).[55] Related dienes **140b** and **140c** bearing electron-withdrawing groups other then an ethyl ester have also been reported and these behave in a similar fashion to **139**. However, the key discovery was the demonstration that the 2-hydroxybenzophenones could be converted into isophthalates. Dakin reaction of **146** afforded isophthalate mono-ester **147**, which was esterified to afford diethyl isophthalate **148** (Scheme 1.34).[56]

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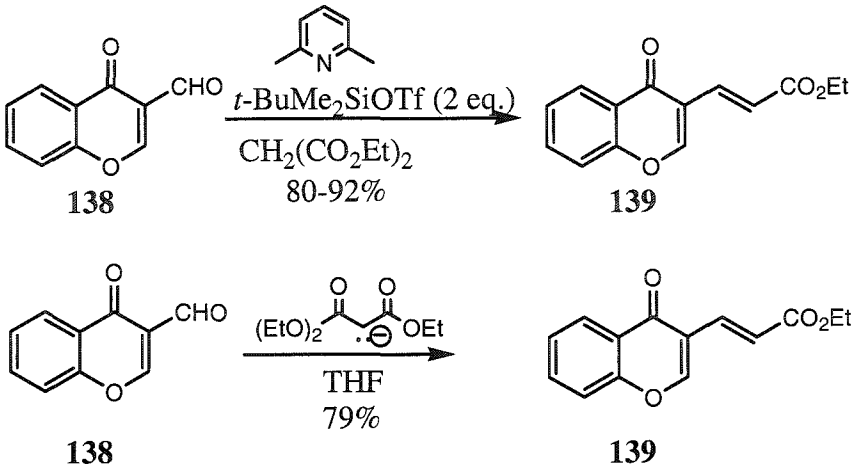
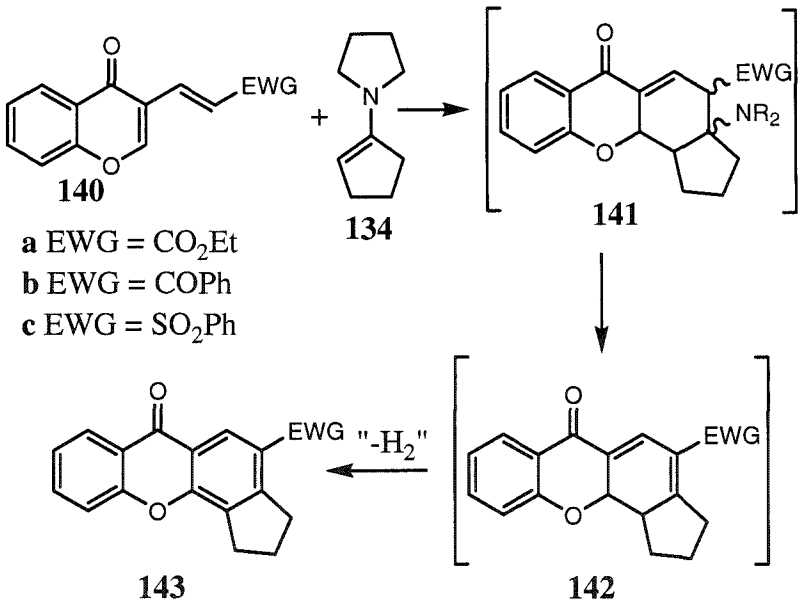
[53] Iwasaki, H.; Kum, T.; Yamaoto, Y.; Akiba, K. *Heterocycles* **1988**, *27*, 1599-1606.
[54] Bodwell, G. J.; Hawco, K. M.; da Silva, R. P. *Synlett.* **2003**, 179-182.
[55] Unpublished results, Krista Hawco.
[56] Bodwell, G. J.; Hawco, K. M.; Satou, T. *Synlett* **2003**, 879-881.



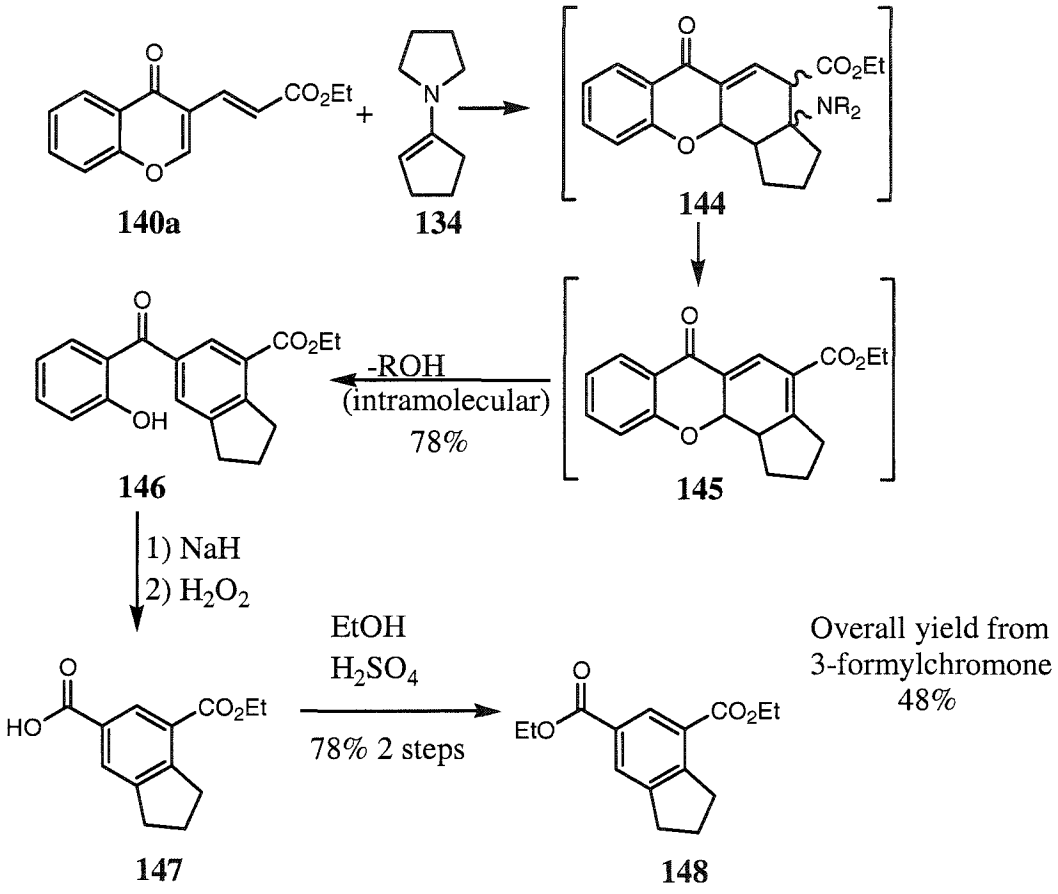
Scheme 1.32



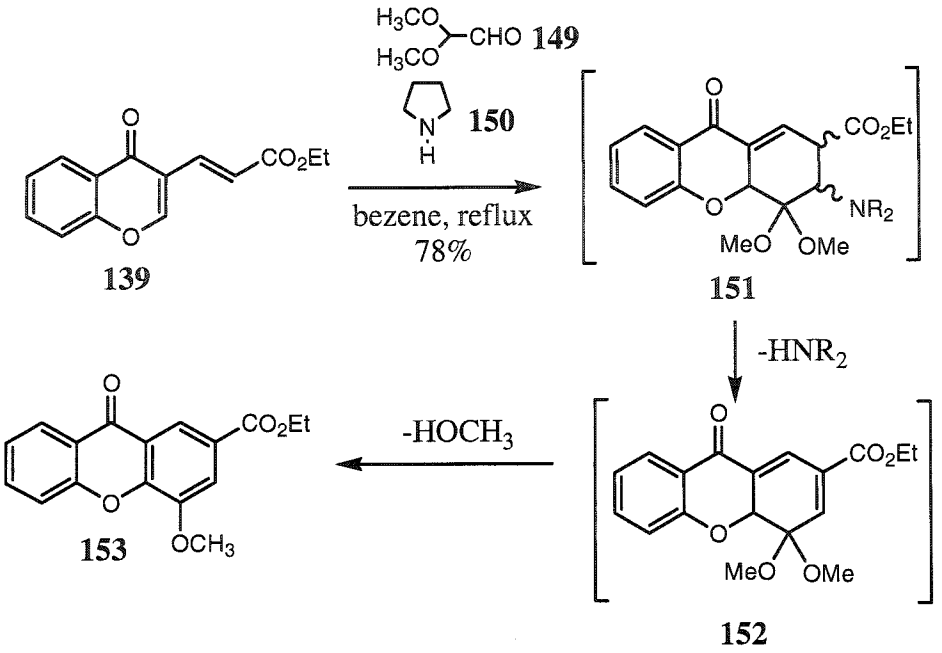
Scheme 1.33

The original goal of preparing xanthones could be achieved by using an appropriate dienophile (Scheme 1.35). This was accomplished by replacing the β-H required for the intramolecular elimination with an alkoxy group. Thus the use of the

enamine derived from dimethoxyacetaldehyde and pyrrolidine gave rise to xanthone **153** (82%) (Scheme 1.35).

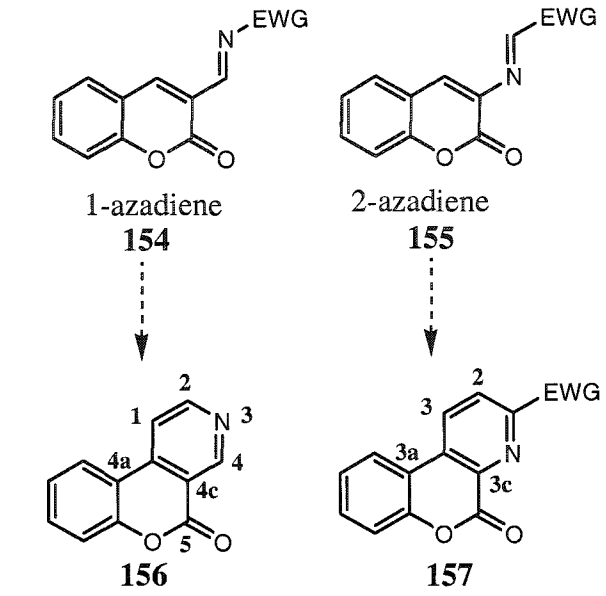


Scheme 1.34



Scheme 1.35

Although initially aimed solely at the synthesis and study of all-carbon dienes, an obvious extension of the IEDDA chemistry described above is the use of analogous heterodienes. Coumarin-based dienes **154** and **155** can therefore be identified as targets for synthesis and study (Scheme 1.36). The presence of the nitrogen atom would be expected to lower the LUMO energy (relative to coumarin-fused diene **133b**), thus rendering dienes **154** and **155** more reactive to electron rich dienophiles than **133b**, which was found to be unreactive towards ethyl vinyl ether. The decision to incorporate nitrogen only in the side chain is based on (perceived) synthetic considerations. If **154** and **155** undergo IEDDA-driven domino processes similar to those of **133b**, then the products obtained would be pyrido[3,4-*c*]coumarins **156** and pyrido[2,3-*c*]coumarins **157** (Scheme 1.36).



Scheme 1.36

Examples of pyrido[3,4-*c*]coumarins **157** are rare in the literature.[57] However, Boger has previously reported 1-azadiene precursors.[58] This particular diene readily participates in the IEDDA reaction, producing unaromatized products **159** and **160** (Scheme 1.37). These compounds were not aromatized, but, related compounds (also reported by Boger) were efficiently aromatized by double elimination (Scheme 1.38).[59] Furthermore coumarin-based azadiene **158** was used by Boger in the total synthesis of

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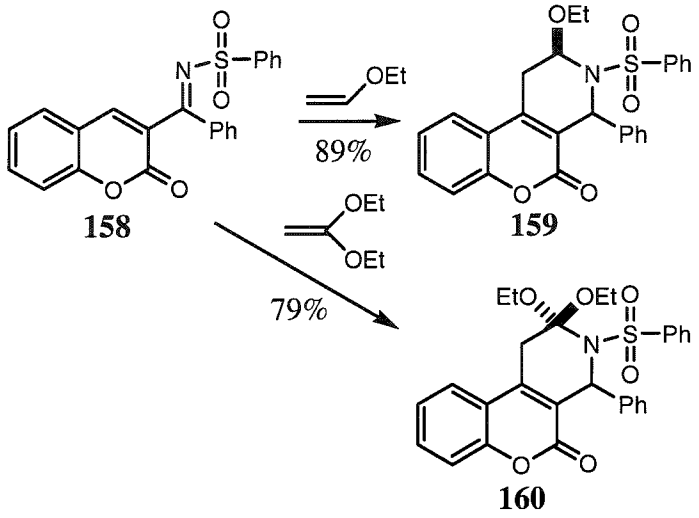
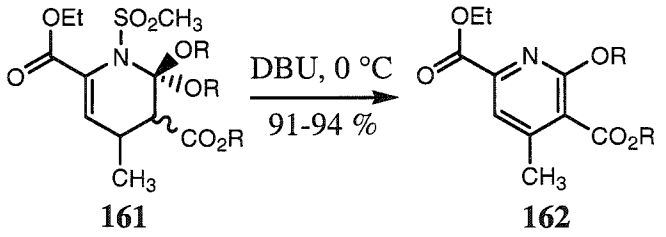
[57] a) Koelsch, C. F.; Sundet, S. A. *J. Am. Chem. Soc.* **1952**, *72*, 1681-. b) Courts, A.; Petrow, V. *J. Chem. Soc.* **1952**, 334-337. c) Reynolds, G.; VanAllan, J. A.; Petropolous *J. Heterocyclic Chem.* **1970**, *7*, 1061-1069. d) VanAllan, J. A.; Chang, S. C.; Reynolds *J. Heterocyclic Chem.* **1972**, *9*, 1245-1249. e) Reid, W.; Nyiondi-Bonguen *Justus Liebigs Ann. Der Chem.* **1973**, 1-4. f) Fujimoto, A.; Sakurai, A.; Midorikawa, H.; Iwase, E. *Nippon Kagaku Zasshi* **1974**, 1- g) Sakurai, A.; Midorikawa, H. *J. Chem. Soc., Perkin Trans.* **1975**, *1*, 2025-2028. h) Fujimoto, A.; Sakurai, A.; Iwase, E. *Bull. Chem. Soc. Japan* **1976**, *49*, 809-810.

[58] a) Boger, D. L.; Corbett, W. L.; Curran, T. T.; Kasper, A. M. *J. Am. Chem. Soc.* **1991**, *113*, 1713-1729. b) Boger, D. L.; Nakahara, S. *J. Org. Chem.* **1991**, *56*, 880-884.

Streptonigrone C.[60] Diels-Alder reaction with ketene acetal **164** gave adduct **165**, which was subsequently transformed into **166** and ultimately Streptonigrone C **167** (Scheme 1.39).

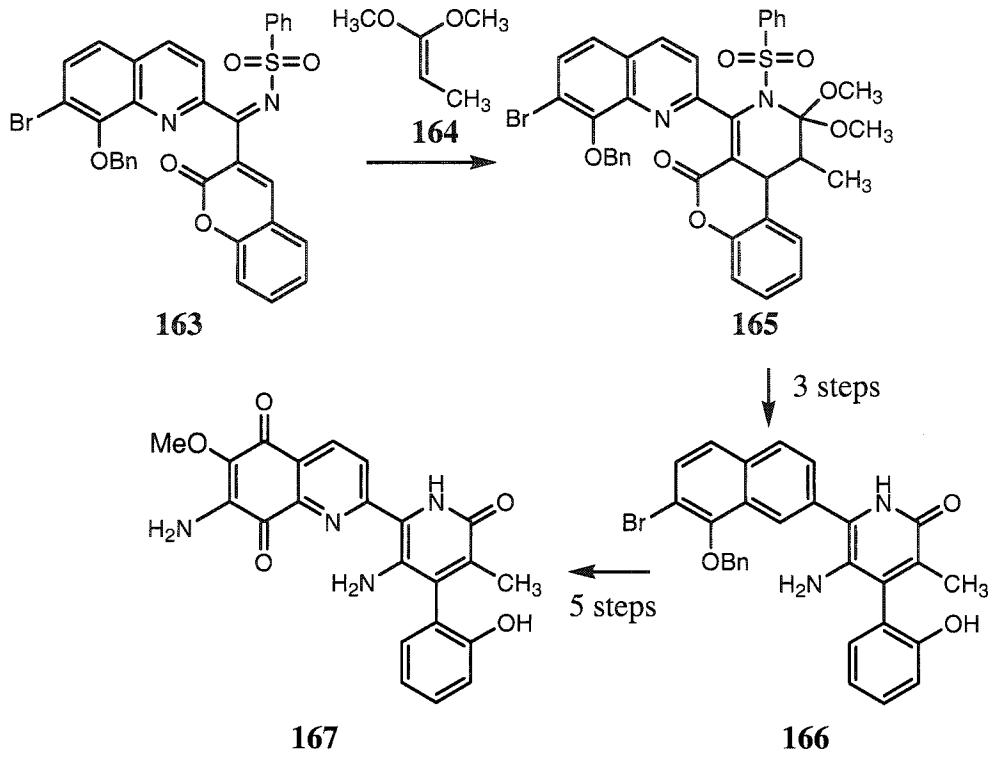


Scheme 1.37



Scheme 1.38

[59] Boger, D. L.; Zhang, M. *J. Org. Chem.* **1992**, *57*, 3974-3977.
[60] a) Boger, D. L.; Nakahara, S. *J. Org. Chem.***1991**, *56*, 880-884. b) Boger, D. L.; Cassidy, K. C.; Nakahara, S. *J. Am. Chem. Soc.* **1993**, *115*, 10733-10741.

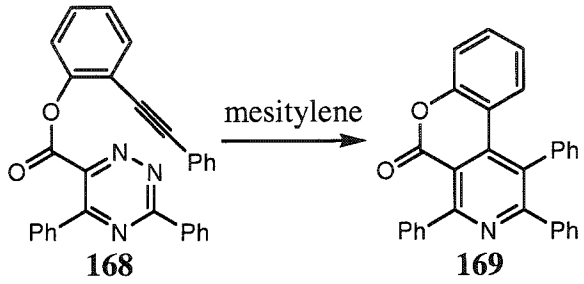


Scheme 1.39

In the literature, there are very few examples of pyrido[2,3-*c*]coumarins **157**.[61] The Yamanaka group prepared one example of this system using an intramolecular IEDDA reaction of a triazine with a pendent dienophile (Scheme 1.40).[56c] Recently, Guillaumet prepared a series of pyrido[2,3-*c*]coumarins by the condensation of 3-hydroxycoumarin **170** with various β-aminoketones **171**. This was then followed by an intramolecular cyclization (Scheme 1.41). This aromatic system has previously been found in the backbone of one natural product, Santiagonamine **174**. This is an alkaloid,

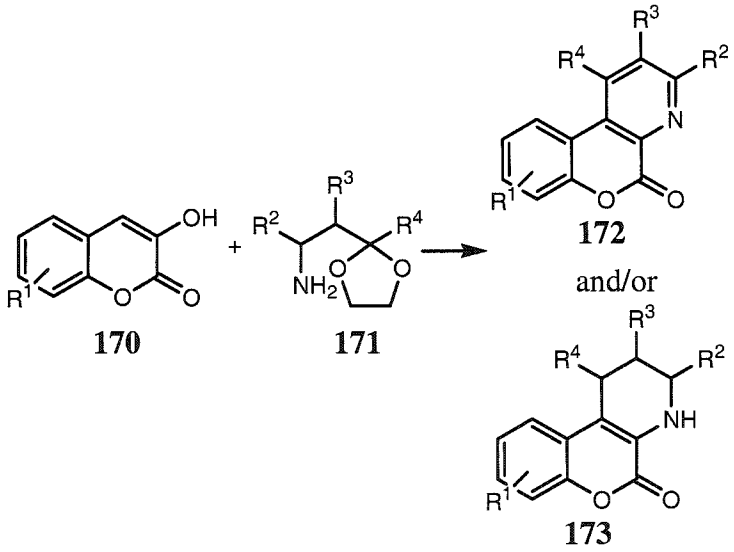
[61] a) Khan, M. A.; Gemal, A. L. *J. Heterocyclic. Chem.* **1977**, *14*, 1009- b) Tabakovic, K.; Tabakovic, I.; Juric, A. *J. Heterocycl. Chem.* **1980**, *17*, 801- c) Sagi, M.; Wada, K.; Konno, S.; Yamanaka, H. *Heterocylces* **1990**, *30*, 1009-1021.

which was isolated from Berberis Darwinii (*Berberidacea*), and has found to exhibit interesting wound healing properties (Figure 1.6).[62]



168 **169**

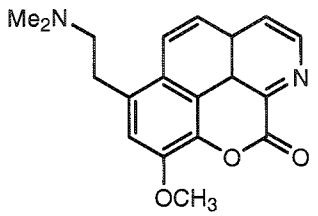
Scheme 1.40



170 **171** **172** **173**

Scheme 1.41

[62] a) Pavé, G.; Chalard, P.; Viaud-Massuard, M.; Troin, Y.; Guillaumet, G. *Synlett.* **2003**, 987-990. b) Lewis, W. H.; Stronard, R. J.; Porras-Reyes, B.; Mustoe, T. A.; Thomas, A. US Patent 5156847, **1992**.



174

Figure 1.6

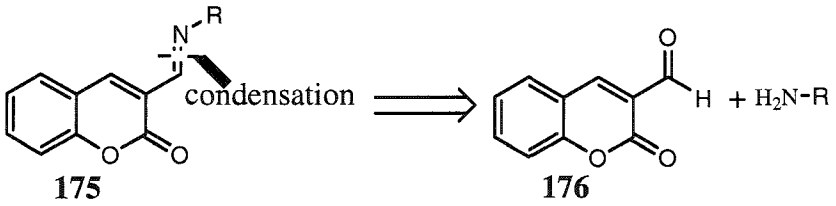
1.4 Goals of This Work

The goal of this work was to synthesize 1- and 2-azadienes corresponding to **154** and **155**, and to explore their behavior in IEDDA reactions, with an eye toward the synthesis of pyridocoumarins **156** and **157** (Scheme 1.36). It was also envisaged that the biological and physical properties of the azadienes and their aromatic counterparts could be investigated in collaboration with other groups.

Chapter 2: The Synthesis of the 1- and 2-Azadienes

2.1 Synthesis of 3-Formylcoumarin

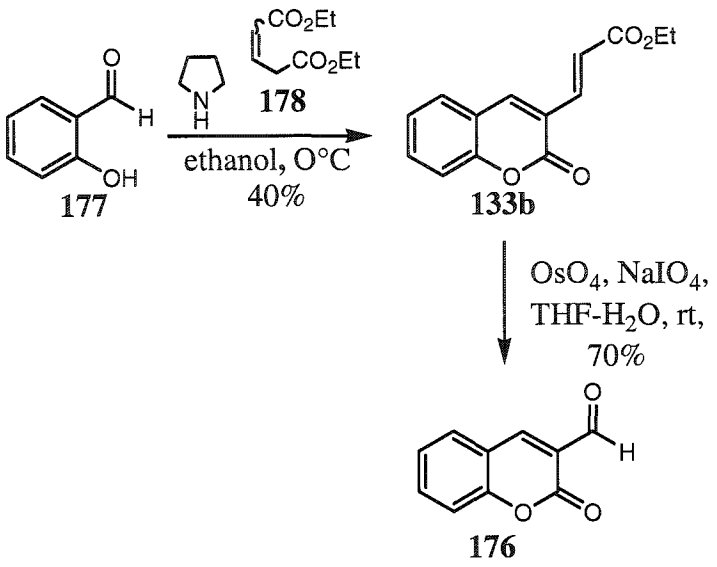
A retrosynthetic analysis of 1-azadienes reveals a simple retrosynthetic cut of the imine to produce 3-formylcoumarin **176** and an amine (Scheme 2.1). Very broad ranges of 1° amines are commercially available or can be prepared in short order. However, 3-formylcoumarin **176** is not commercially available. The Triggle group devised the first rational synthesis of 3-formylcoumarin **176**.[1] This was accomplished in two steps. Knoevenegal condensation,[2] which has been used in coumarin synthesis, between diethyl glutaconate and salicylaldehyde afforded **133b** in modest yield (40%). Oxidative cleavage of the exocyclic double bond afforded **176** (70%) (Scheme 2.2).



175 **176**

Scheme 2.1

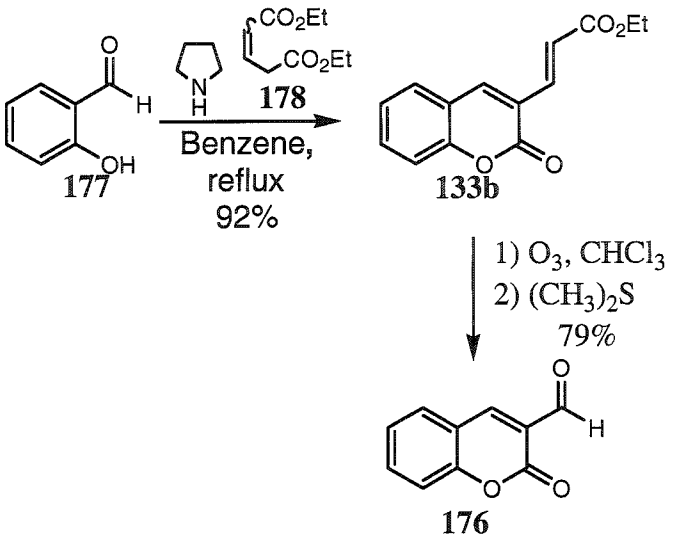
[1] Padmanabhan, S.; Peri, R.; Triggle, D. J. *Synth. Comm.* **1996**, *26*, 827-831.
[2] Jones, G. *The Knoevenegal Condensation. In Organic Recations*, John Wiley & Sons, Inc.: New York, 1967; *15*, 204-600.



Scheme 2.2

The Bodwell group developed a very similar synthesis of 3-formylcoumarin. The Triggle method involved the Knoevenegal condensation of salicyaldehyde with dimethyl glutaconate using benzene as the solvent to afford electron deficient **133b** in 92% yield. Selective oxidative cleavage of the exocyclic double bond by ozone to give 3-formylcoumarin **176** was accomplished in 79% yield.[3] This was then used as a common starting material for the synthesis of electron deficient dienes related to **133b**. Using the Bodwell synthesis, diene **133b** was routinely prepared on a 30 g scale and 3-formylcoumarin **176** was routinely prepared on a 5 g scale (Scheme 2.3).

[3] Pottie, I. *P.hD. Thesis*, **2002**, Memorial University of Newfoundland.

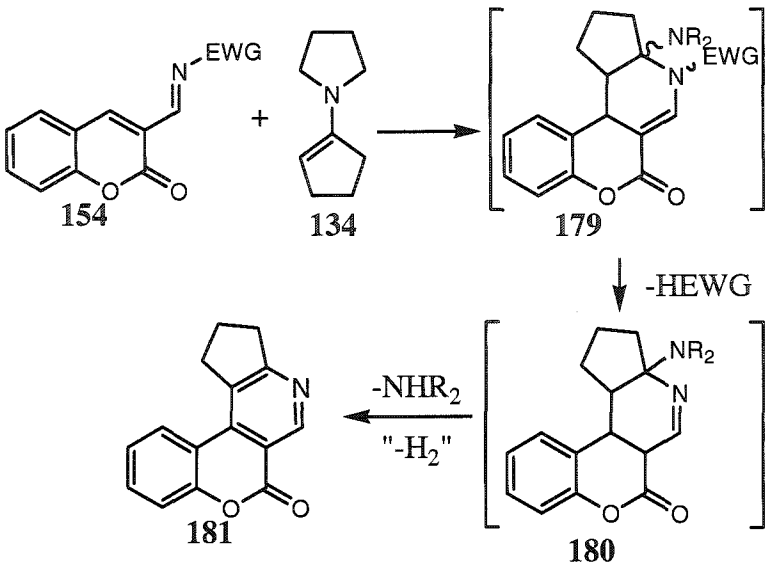


Scheme 2.3

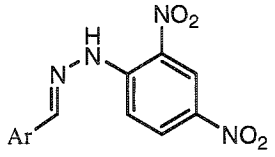
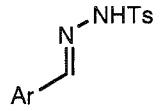
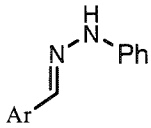
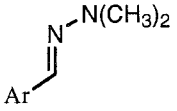
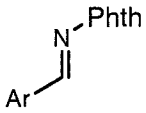
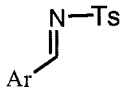
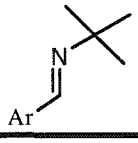
2.2 The Condensation of 3-Formylcoumarin with Amines.

To promote IEDDA behavior, it was envisaged that the 1-azadienes should contain electron-withdrawing groups. The carbonyl group of the coumarin will eventually manifest itself as an electron-withdrawing group at the 3-position (of the electron deficient diene unit), so other electron-withdrawing groups (and ideally also good leaving groups) may be installed at the 1-position by way of the primary amine (Scheme 2.4). A series of 1-azadienes was prepared by using two methods. The first method involved refluxing the amine and 3-formylcoumarin together in a non-polar solvent, such as benzene or toluene, using Dean-Stark conditions. The second method involved refluxing both the amine and 3-formylcoumarin together in toluene in the presence of anhydrous magnesium sulfate. Using these methods, seven 1-azadienes, shown in Table 2.1, were prepared. Yields ranged from 66-97% on a 1 g scale. The dienes prepared have a variety

of groups in the 1-position that could influence the Diels-Alder reaction. In 1-azadienes **182**, **183**, and **186**, the *N*-substituent is a nitrogen atom bonded to one or two electron withdrawing groups. As such these substituents are expected not to be strongly donating. At least for **183**, this is probably a reasonably assumption because the value of the substituent parameter σ_p° for the $-NHSO_2Me$ substituent is 0.03 and that of NHAc is 0.01. Thus the *N*-substituents of **182**, **183**, and **186** were not expected to strongly deactivate the azadiene towards IEDDA reaction. On the other hand, these groups are relatively good leaving groups, which may facilitate the planned post-IEDDA aromatizations. The *N*-substituents of **184** and **185** are both electron donating (*cf.* σ_p° = 0.73 for SO_2Me). This diene was expected to be the most reactive and have the additional benefit of the leaving group ability of $RSO_2^{\cdot}$. Diene **188** has an *N*-substituent that is electron donating and has very poor leaving group ability. However, *t*-butyl groups on nitrogen can be removed under acidic conditions. The bulky nature of the *t*-butyl group was also of interest for reasons that will be discussed in Chapter 3.


N
EWG
O
O
154
+
N
134
NR2
EWG
N
O
O
179
-HEWG
NR2
N
O
O
180
-NHR2
"-H2"
N
O
O
181

Scheme 2.4

Compound	1-azadiene	yield
182		76%
183		82%
184		66%
185		71%
186		87%
187		84%
188		97%

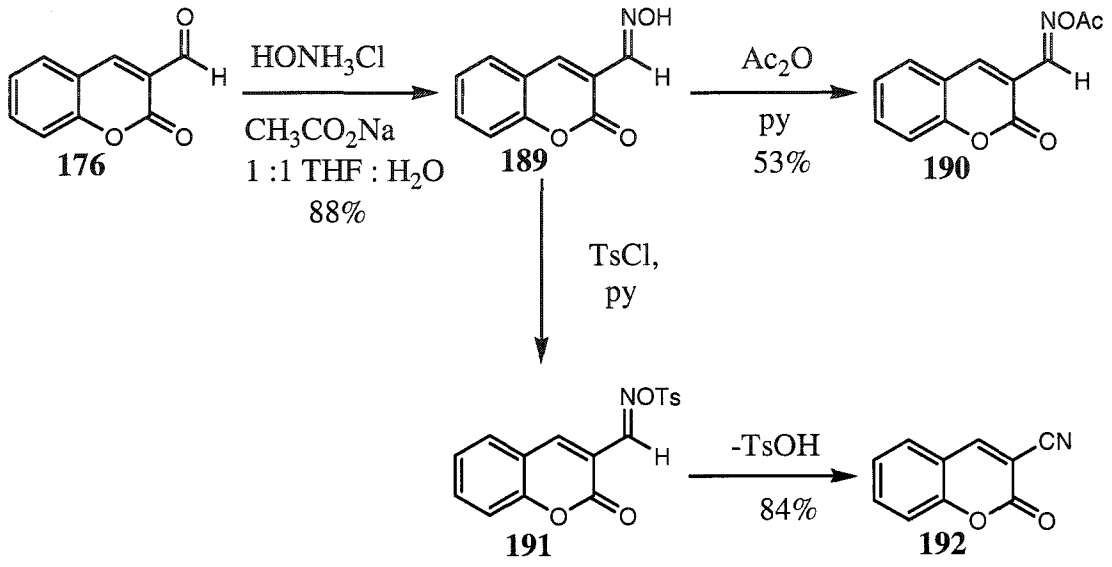
Ar = coumarin

Table 2.1 – 1-azadiene from 3-formylcoumarin and R-NH_2.

Oxime **189**, which was prepared in 88% yield by the reaction of 3-formylcoumarin **176** with hydroxylamine (Scheme 2.5), was envisioned as being a progenitor of several other 1-azadienes. Thus, acylation of oxime **189**, itself a 1-azadiene, gave rise to 1-azadiene **190**.[4] However, attempted tosylation of **189** resulted in the

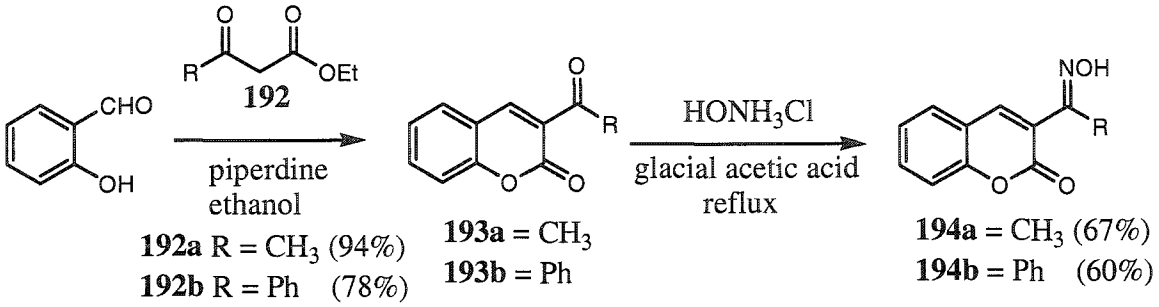
[4] Bashiardes, G.; Bodwell, G. J.; Davies, S. G. *J. Chem. Soc. Perkin Trans. 1* **1993**, 459-469.

formation of 3-cyanocoumarin **192**. Presumably tosylate **191** is formed, but undergoes elimination of tosic acid under the reaction conditions (Scheme 2.5).



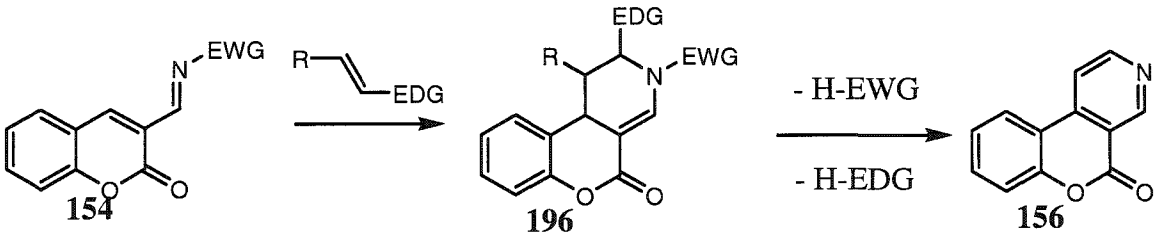
Scheme 2.5

To circumvent nitrile formation, 3-acetylcoumarin **193a** and 3-benzoylcoumarin **193b** were prepared (Scheme 2.6). This was accomplished by subjecting salicylaldehyde to the Knoevenagel reaction conditions in the presence of ethylacetoacetate (94% yield) and benzoylacetone (78% yield), respectively. These compounds proved to be unreactive towards hydroxylamine under the conditions used for the synthesis of **189**, but performing these reactions at reflux in glacial acetic acid led to the formation of **194a** (67%) and **194b** (60%). However, all attempts to prepare derivatives of **190** and **191** were unsuccessful, complex mixtures typically being produced.



Scheme 2.6

Implicit in the proposed conversion of 1-azadiene **154** to pyridocoumarins **156** is the removal of the EWG at some point. For several of the 1-azadienes described above, it is conceivable that the *N*-substituent could function not only as an electron withdrawing group to activate the diene towards the IEDDA reaction, but as a leaving group that could participate in an elimination reaction leading to an aromatic product **156** (Scheme 2.7).

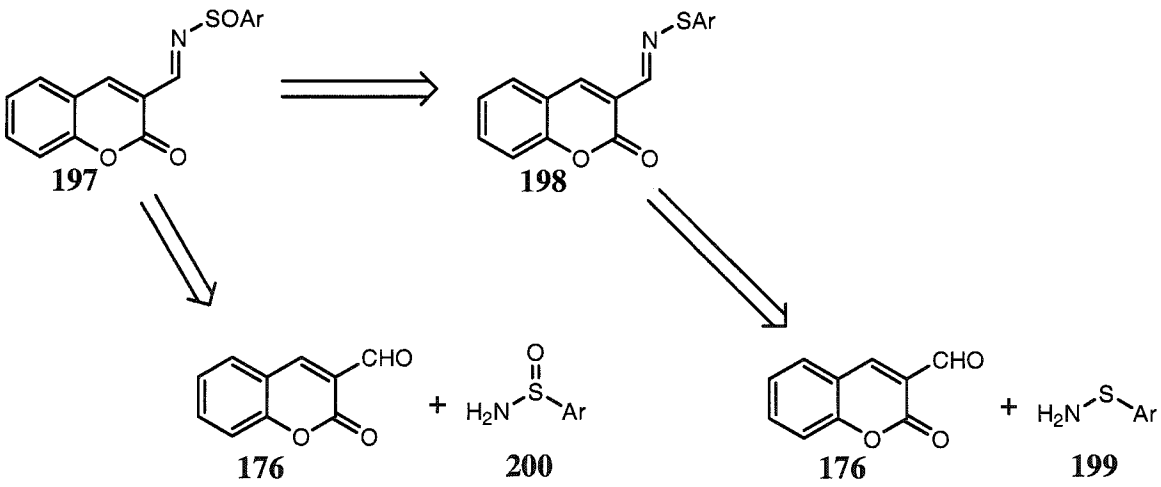


Scheme 2.7

Because a $-SO_2R$ group is both strongly electron withdrawing and can function as a leaving group, 1-azadiene **187** was deemed to be one of the most promising candidates. Since sulfoxides are known to undergo the aptly named sulfoxide elimination, diene **197**

was identified as an equally desirable diene. Furthermore, the chiral sulfur atom attached directly to the azadiene unit also opens the door to the possibility of performing asymmetric IEDDA reactions.

Since sulfoxides are generally not readily available, the syntheses are envisioned as proceeding through the condensation of 3-formylcoumarin **176** with sulfenamides **199** to afford 1-azadienes **198**, followed by oxidation (Scheme 2.8).[5] Sulfenamides **199** can be prepared from the reaction of ammonia and silver chloride with diaryl disulfides,[5b] and there is precedent for their oxidation to the corresponding sulfoxamides **200**.[5b]



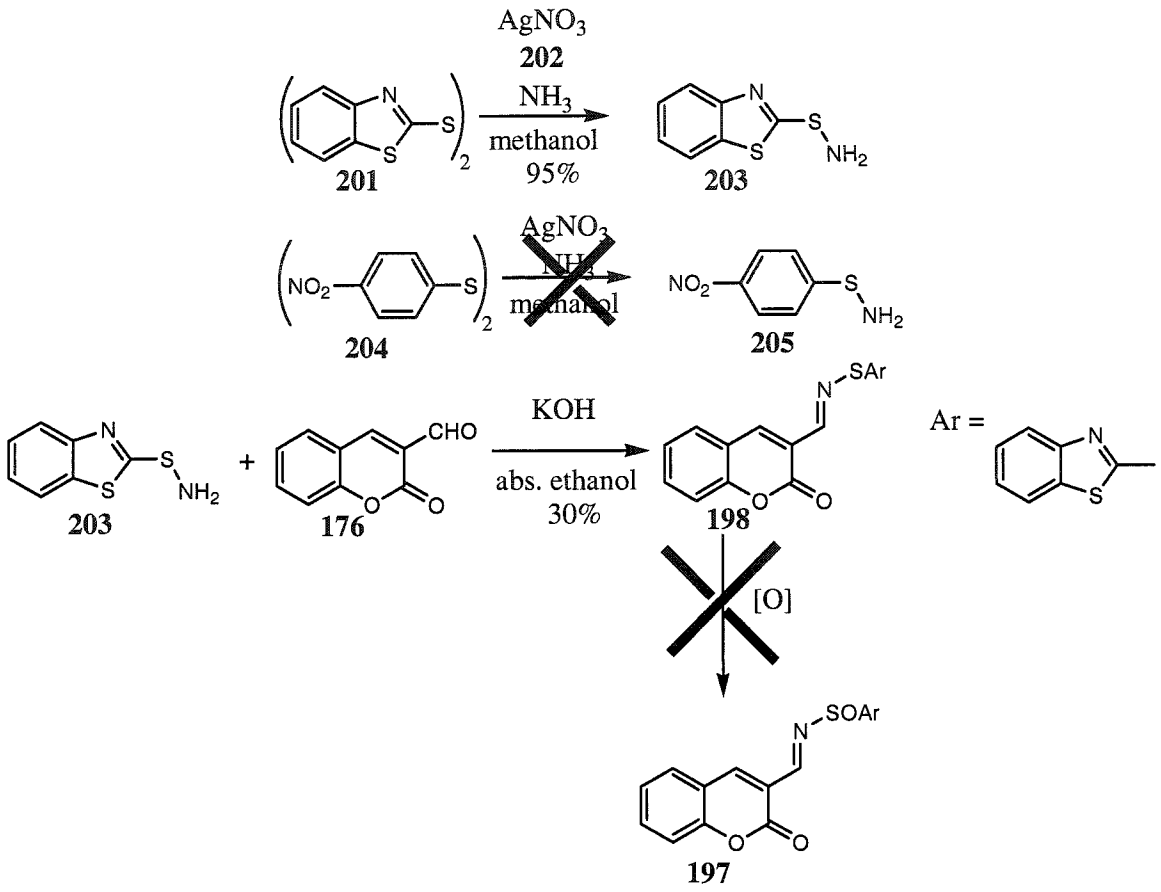
Scheme 2.8

[5] a) Davis, F. A.; Friedman, A. J.; Kluger, E. W. *J. Am. Chem. Soc.* **1974**, *96*, 5000-5001. b) Davis, F. A.; Slegeir, W. A.; Evans, S.; Schwartz, A.; Goff, D. L.; Palmer, R. *J. Org. Chem.* **1973**, *38*, 2809-2813. c) Davis, F. A.; Rajarathnam, E. R.; Szewczk, J. M.; Reddy, V.; Portonvo, P. S.; Zhang, H.; Fanelli, D.; Reddy, R. T.; Zhou, P.; Carroll, P.J. *J. Org. Chem.* **1997**, *62*, 2555-2563. d) Davis, F. A.; Lamendola, J. Jr.; Nadir, U.; Kluger, E. W.; Sedergran, T. C.; Panunto, T. W.; Billmers, R.; Jenkins, R. Jr.; Turchi, I. J.; Waston, W. H.; Chen, J. S.; Kimura, M. *J. Am. Chem. Soc.* **1980**, *102*, 2000-2005.

[5] Trost, B. M.; Curran, D. P. *Tetrahedron Lett.* **1981**, *22*, 1287-1290.

Reaction of disulfide **201** with ammonia afforded sulfenamide **203** in 95% yield. This sulfenamide was chosen since it was prepared in high yield in comparison to other sulfenamides and gave high yields when condensed with ketones and aldehydes. Attempts to prepare sulfenamides with electron withdrawing groups, using 4-nitrophenyldisulfide **204**, resulted in complex mixtures. The reaction of **203** with 3-formylcoumarin **176** gave rise to 1-azadiene **198**, but only in 30% yield, which is low in comparison with known reactions of other aldehydes and ketones. Attempts to oxidize this compound to the corresponding sulfoxamide **197** using either hydrogen peroxide[3d] or Oxone™ [6] resulted in the return of starting material or the formation of a complex mixture. In light of these difficulties, no further work was done in this area (Scheme 2.9).

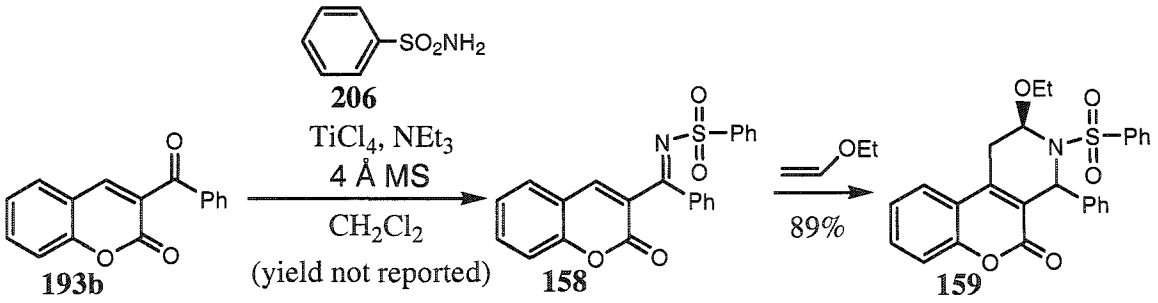
[6] Trost, B. M.; Curran, D. P. *Tetrahedron Lett.* **1981**, *22*, 1287-1290.



Scheme 2.9

Boger *et al.* previously demonstrated that sulfonylimine **158**, which was prepared by the $TiCl_4$-mediated condensation of 3-benzoylcoumarin **193b** and benzene/toluenesulfonamide, reacted with ethyl vinyl ether to afford IEDDA adduct **159** (89%) (Scheme 2.10).[7] However, no aromatized product was obtained.

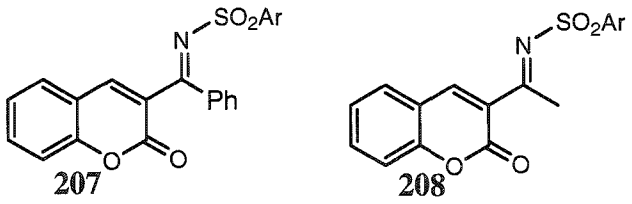
[7] a) Boger, D. L.; Corbett, W. L.; Curran, T. T.; Kasper, A. M. *J. Am. Chem. Soc.* **1991**, *113*, 1713-1729. b) Boger, D. L.; Nakahara, S. *J. Org. Chem.* **1991**, *56*, 880-884.



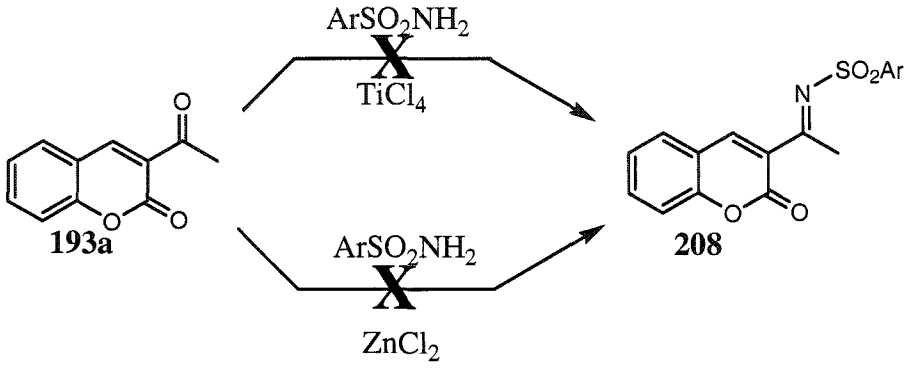
Scheme 2.10

Since 1,2-imine addition of enamines to the 1-azadiene emerged as a serious problem (see Chapter 3), the synthesis of substituted dienes such as **207** and **208** was investigated (Scheme 2.11). However, attempts to apply the $TiCl_4$-mediated condensation methodology to 3-formylcoumarin and 3-acetylcoumarin failed. 3-formylcoumarin was recovered when subjected to these reaction condensations and a complex mixture formed when used with 3-acetylcoumarin. When **193a** forms a complex mixture, this may be due to the preferential formation of titanium enolates[8] (Scheme 2.12). The use of a milder Lewis acid, $ZnCl_2$, also failed, possibly for the same reason (Scheme 2.12).[9] As an alternative, the tosylhydrazane **210** was prepared from with 3-acetylcoumarin using the same conditions as in the preparation of **183** (Scheme 2.13).

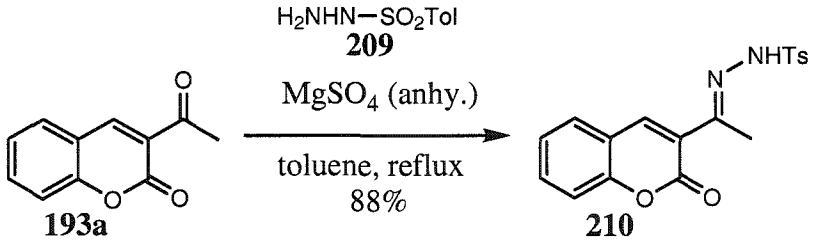
[8] Holba, A. G. and Premasager, V. *Tetrahedron Lett.* **1985**, 26, 571-574.
[9] Brake, G. M. and Matthews, R. S. *J. Fluorine Chem.* **1988**, 40, 109-117.



Scheme 2.11



Scheme 2.12



Scheme 2.13

2.3 The History of 3-Aminocoumarin

For the synthesis of the targeted 2-azadienes, 3-aminocoumarin **212** was required as a common starting material. It is a compound with a long history and has been reported to exhibit many interesting biological and photochemical properties.[10]

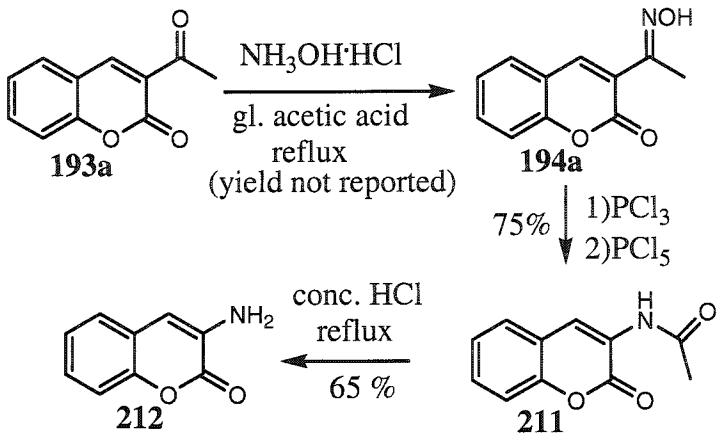
The first reported synthesis of 3-aminocoumarin was by Linch,[11] who prepared 3-aminocoumarin easily in three steps starting from 3-acetylcoumarin (Scheme 2.14). This involved conversion of 3-acetylcoumarin into its oxime **194a** (yield not reported), followed by Beckmann rearrangement[12] to give 3-acetamidocoumarin **211** (75%) and hydrolysis to afford 3-aminocoumarin (65%). It was said to be critical that the hydrolysis had to be performed under these conditions (refluxing **212** in concentrated hydrochloric acid and absolute ethanol). If this was not the case, significant amounts of 3-hydroxycoumarin were formed and the yield of **212** was affected dramatically and resulted in a poor yield. Due to the absence of spectroscopic methods at the time of Linch's experiments, only an elemental analysis and a melting point were reported for the putative 3-aminocoumarin **212**.

---

[10] a) Kokotos, G.; Tzougraki, C. *J. Heterocyclic Chem.* **1986**, *23*, 87-92 b) Kokotos, G.; Tzougraki C. *J. Chem. Soc. Perkin Trans. II* **1991**, *4*, 495-499.

[11] a) Linch, F. W. *Proc. Chem. Soc.* **1912**, 28, 144. b) Linch, F. W. *J. Chem. Soc.* **1912**, *101*, 1755-1759. c) Linch, F. W. *J. Chem. Soc.* **1912**, *101*, 1759-1765.

[12] a) Blatt, H. *Chem. Rev.* **1933**, *12*, 215-260. b) Jones, B. *Chem. Rev.* **1944**, *35*, 335-350.



Scheme 2.14

Attempts in the 1950s and 1960s by other investigators to repeat the reported hydrolysis of 3-acetamidocoumarin **211** and its derivatives resulted in the formation of 3-hydroxycoumarin and its derivatives.[13] This presumably occurs by a mechanism analogous to that of the hydrolysis of enamines.[14]

In the 1980s and 1990s, several groups successively repeated the synthesis of 3-aminocoumarin **212** using Linch's procedures.[11,15] During that time, other methods were explored for the expedient synthesis of 3-aminocoumarin, but these met with limited success.[16a] It was not until 1998 that Bonsignore's group reported a new and dramatically improved route to 3-aminocoumarin (Scheme 2.15).[16] The Boc-protected 3-aminocoumarin **215** was produced from commercially available coumarin-3-carboxylic

---

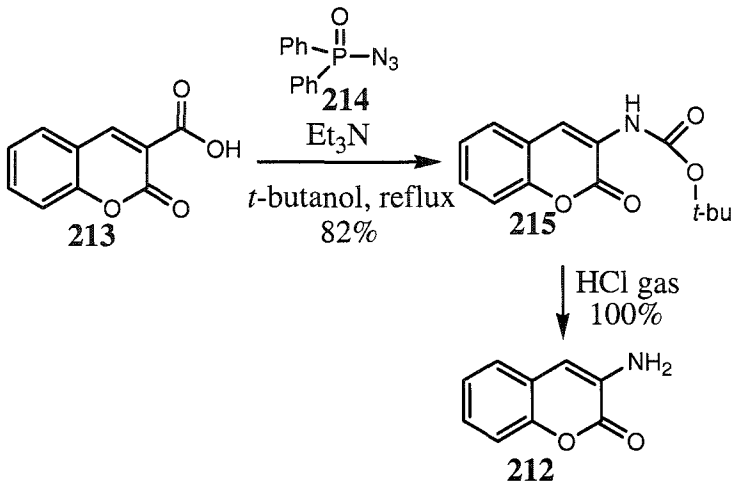
[13] a) Shaw, K. N. F.; McMillan, A.; Armstrong, M. D. *J. Org. Chem.* **1956**, *21*, 601-604. b) Trivedi, K. N.; Sethna, S. *J. Org. Chem.* **1960**, *25*, 1817-1819.

[14] In *The Chemistry of the Carbon-Nitrogen Double Bond.* Patai. S., Ed., Wiley: New York, **1970**, pp 465-504.

[15] a) Kokotos, G.; Tzougraki, C. *J. Heterocyclic Chem.* **1986**, *23*, 87-92. b) Kumar, P.; Mukerjee, A. K. *Indian J. Chem.* **1980**, *19B*, 704-707. c) Tripathy, P. K. and Mukerjee, A. K. *Indian J. Chem.* **1987**, *26B*, 61-62. d) Kulkarni, Y. D.; Srivastava, D.; Bishnoi, A.; Dua, P. R. *J. Indian Chem. Soc.* **1996**, *73*, 173-175.

[16] Bonsignore, L.; Loy, G. *J. Heterocyclic Chem.* **1998**, *35*, 117-119.

acid **213** using a method reported by the Yamada group.[17] This presumably proceeds via condenversion of the carboxylic acid to the corresponding acyl azide followed by Curtius rearrangement and trapping of the resulting isocyanate with *t*-BuOH. The Boc group was then removed upon treatment with gaseous hydrochloric acid.[18]



Scheme 2.15

2.4 A Straightforward and Efficient Synthesis of 3-Aminocoumarin.

The first attempts synthesize of 3-aminocoumarin **212** was preformed by following the work of Linch and others.[11, 13, 15] 3-Acetamidocoumarin **211** is commercially available and can be easily prepared in large quantities in one step by the reaction of salicylaldehyde and acetyl glycine (Scheme 2.16).[19] However, attempts to prepare 3-aminocoumarin by refluxing 3-acetamidocoumarin with conc. sulfuric acid in

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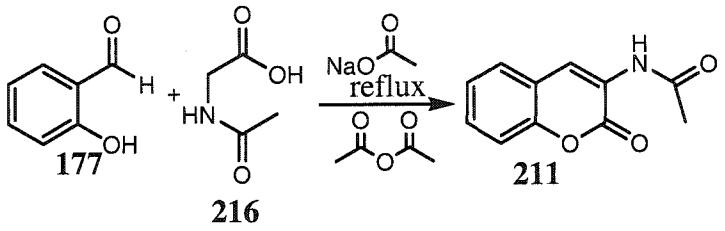
[17] Shioiri, T.; Ninomiya, K.; Yamada, S. *J. Am. Chem. Soc.* **1972**, *94*, 6203-6205.
[18] Stahl, G. L.; Walter, R.; Smith, C. W. *J. Org. Chem.* **1978**, *43*, 2285-2286.
[19] a) For the preparation of 3-acetylcoumarin. Herbst, R. M.; Shemin, D. *Org. Syn.* **1943**, Coll. Vol. 2, 11-12. b) Kenneth, N. F.; McMillan, A.; Armstrong, M. D. *J. Org. Chem.* **1956**, *21*, 601-604. c) Sethna, S.; Trivedi, K. N. *J. Org. Chem.* **1960**, *25*, 1807-1830.

ethanol failed and starting material was recovered. Several experiments were carried out with results consistent with those reported previously by others.[13] This route was consequently abandoned.

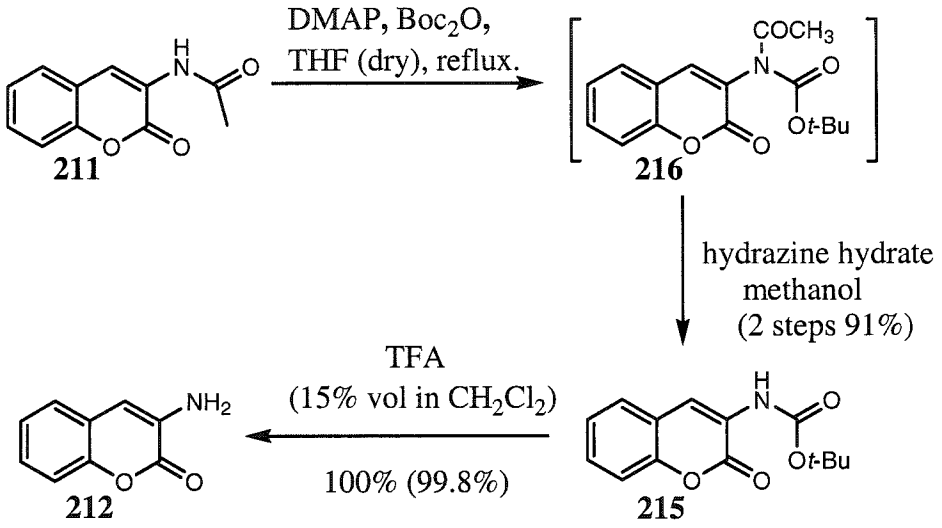


Scheme 2.16

The synthesis of 3-aminocoumarin **212** by Bosignore's route[16] was then attempted. Both the starting material, coumarin-3-carboxylic acid **213**, and the first reagent, diphenylphosphoroyl azide **214** (DPPA), are commercially available. However, due to Transport Canada regulations, DPPA could not be obtained commercially. Instead, it was easily prepared in multigram quantities by the reaction of diphenylphosphoroyl chloride and sodium azide.[20] Disappointingly, the reaction of DPPA with **213** in *t*-BuOH failed to afford **215**. No reaction was evident after 24 h. Longer reaction time led to the formation of coumarin-3-carboxylic acid *t*-butyl ester. Variations in the number of equivalents of DPPA and the mode of addition were fruitless. This route was also discarded.

The failure to reproduce the literature procedures led to the investigation of the following sequence, which takes advantage of chemistry developed by the groups of

Burk[21] and Bonsignore.[16] Burk developed a procedure in which an acetyl group on an amine can be converted into a Boc-protected secondary amine in one pot and in high yield. This involves an acylation-deacylation sequence. When this methodology was applied to 3-acetamidocoumarin, which was abundantly available (vide supra), this resulted in the production of the desired Boc protected compound in 91% yield (Scheme 2.17).



Scheme 2.17

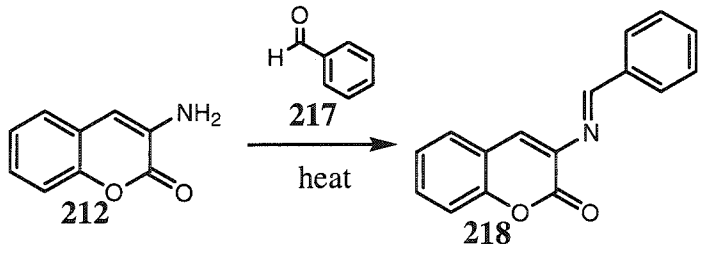
Following a procedure reported by Bonsignore,[16] exposure of **215** to anhydrous trifluoroacetic acid (15% by volume in anhydrous chloroform) led to the formation of 3-aminocoumarin in 99.8% yield after chromatography. From a practical perspective, 3-aminocoumarin can be used directly after the solvent is removed and, if desired, the slight discoloration of the crude product can be removed by crystallization from

[20] Boyer, J. H.; Mack, C. H.; Morgan, L. R. Jr. *J. Org. Chem.* **1958**, *28*, 1051-1053.

chloroform/hexane (Scheme 2.17). This synthetic route was used to prepare up to 5 g batches of 3-aminocoumarin in an overall yield of 91% in two steps from commercially available or easily prepared starting material. This may very well be the most convenient synthesis of 3-aminocoumarin.

2.5 The Synthesis of the 2-Azadienes.

Linch achieved the first synthesis of an electron deficient azadiene[11] a decade prior to the discovery of the Diels-Alder reaction. The most likely explanation for the preparation of this compound was to provide evidence for the proposed structure of 3-aminocoumarin by making a derivative. Linch carried out this synthesis by gently warming a 1 : 1 mixture of benzaldehyde and 3-aminocoumarin until a clear liquid was formed (Scheme 2.18). When the mixture cooled, a "white cake" was formed, which was then boiled several times in alcohol to remove any unreacted starting materials. **218** was then characterized by elemental analysis and melting point.

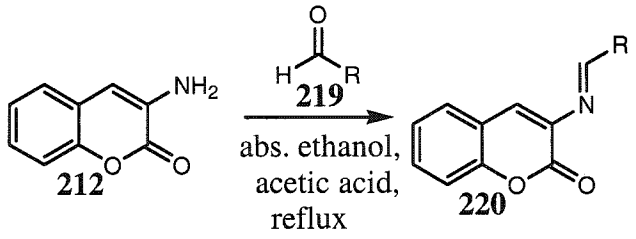


212 218

Scheme 2.18

[21] Burk, M. J.; Allen, J. G. *J. Org. Chem.* **1997**, *62*, 7054-7057.

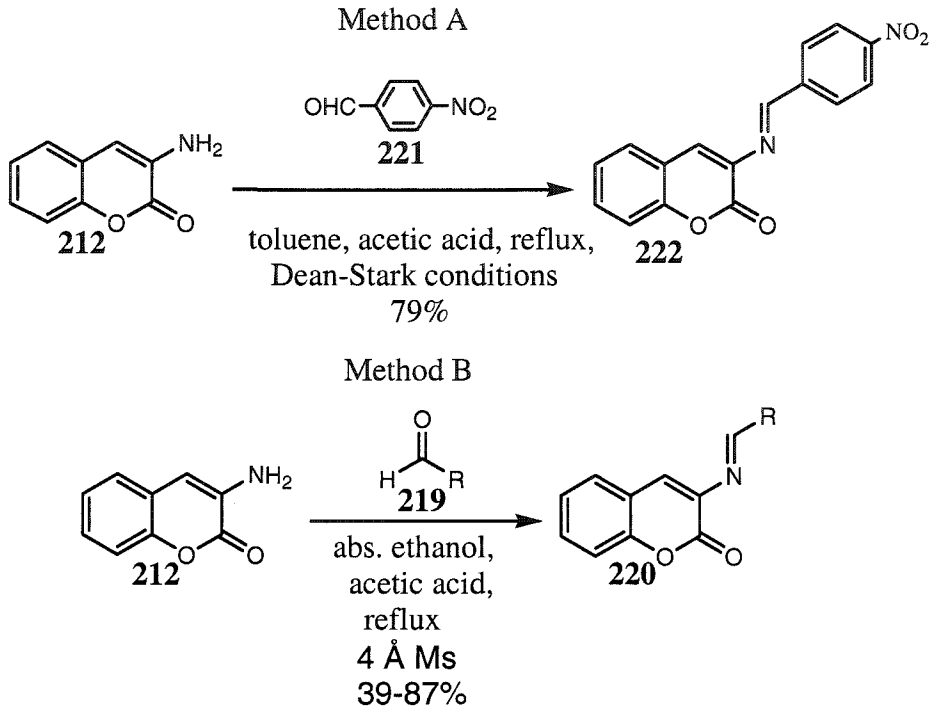
The only other reported condensations of 3-aminocoumarin with aldehydes were by Mukerjee and Bishnoi.[15b-d] These authors reported a series of condensations of 3-aminocoumarin with aromatic aldehydes in refluxing absolute alcohol containing traces of glacial acetic acid. The reported yields were 68-85 % (Scheme 2.19).



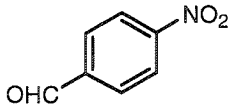
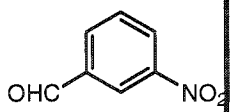
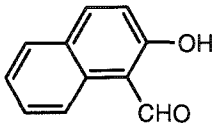
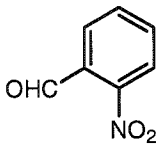
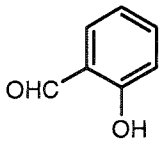
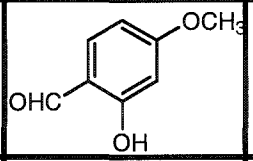
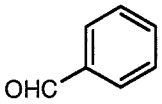
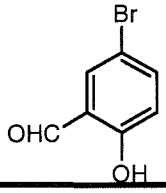
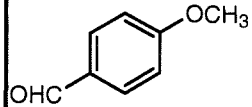
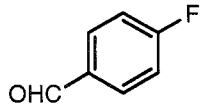
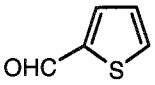
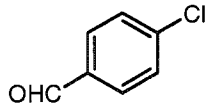
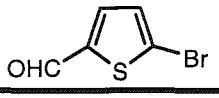
Scheme 2.19

The first attempt to synthesize a series of electron deficient dienes using Mukerjee and Bishnoi conditions[15b-d] resulted in formation of the desired diene and the recovery of significant amounts of starting material. Using Dean-Stark conditions, refluxing of 3-aminocoumarin and *p*-nitrobenzaldehyde in toluene containing traces of acetic acid produced a bright yellow solid, which was identified as the desired electron deficient diene **222** (Scheme 2.20). However, applying this method to other aldehydes resulted in the recovery of starting materials. Revisiting the Mukerjee's and Bishnoi's conditions, the simple addition of 4 Å molecular sieves produced the desired diene and traces of starting material, which could be removed by crystallization (Scheme 2.20). Attempts to purify the dienes by chromatography resulted in the hydrolysis and recovery of the initial

starting material. With this slightly modified procedure a series of 2-azadienes were produced (Table 2.2).



Scheme 2.20

Aldehyde	Rxn Time (hours)	proc. (A, B, C)	Yield (%)	Aldehyde	Rxn Time (hours)	proc. (A, B, C)	Yield (%)
	4	A	79 (**222**)		14	B	57 (**229**)
	16	B	39 (**223**)		14	B	62 (**230**)
	18	C	79 (**224**)		14	B	32 (**231**)
	14	B	65 (**225**)		14	B	64 (**232**)
	12	B	87 (**226**)		14	B	72 (**233**)
	14	B	83 (**227**)		14	B	72 (**234**)
	16	B	48 (**228**)				

a - using Dean stark conditions
b - using molecular sieves
c - condensation of salicylaldehyde and glycine

Table 2.2- 2-azadiene from 3-aminocoumarin and RCHO.

In summary, a formal synthesis of 3-aminocoumarin has been achieved. The route to 3-aminocoumarin is high yielding and easily reproducible. In addition, 3-

aminocoumarin has been more fully characterized. A simple and effective route to the 1- and 2-azadienes has been established and improved over previous syntheses. As a result, 23 new electron deficient azadienes have been prepared.

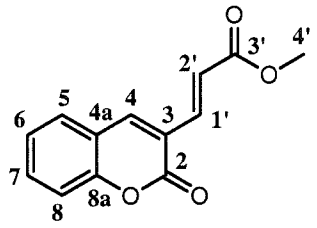
2.6 Experimental

General Procedure

All reactions were carried out without inert gas protection, unless otherwise noted. Tetrahydrofuran, THF, was distilled from Na/benzophenone. Dichloromethane was dried over $CaCl_2$ and distilled. All other commercially available chemicals, including solvents, were used as received without further purification. Thin layer chromatography (tlc) was performed on E. Merck 60 F_{254} precoated silica plates using UV visualization. Column chromatography was carried out on silica gel 60 (E. Merck, 230-400 mesh). Melting points were obtained either on a Thomas Hoover apparatus and/or Fisher-Johns apparatus and are uncorrected. Infrared spectra were obtained on a Mattson Polaris or a Bruker tensor 27 spectrometer using NaCl, KBr, or ZnSe plates with nujol unless otherwise noted. ^{1}H and ^{13}C nuclear magnetic resonance (NMR) spectra were recorded on a Bruker AVANCE spectrometer operating at 500.133 MHz and 125.770 MHz, respectively. NMR spectra were obtained using $CDCl_3$ solutions unless otherwise specified. Peaks reported are relative to internal standards: $(CH_3)_4Si$ (δ 0.00 ppm) for ^{1}H spectra and $CDCl_3$ (δ 77.23 ppm) for ^{13}C spectra. Assignments were made on the basis of 'H,'H-COSY, HMQC, HMBC, etc experiments. For carbon signals, the number of

attached protons, as determined by Dept and HMBC experiments, is indicated in brackets. Mass spectra were obtained using electron ionization at 70 electron volts, unless otherwise noted. Combustion analyses were carried out by the Microanalytical Services Laboratory, Department of Chemistry, University of Alberta, Edmonton, Alberta, Canada. High-resolution mass spectra were carried out by the Mass Spectrometry Center, Department of Chemistry, University of Ottawa, Ottawa, Ontario, Canada.

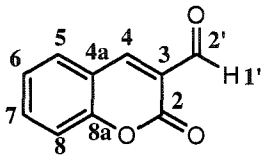
(*E*)-3-(2-Oxo-2*H*-chromen-3-yl)acrylic Acid Methyl Ester (133b)



To a room temperature solution of salicylaldehyde (17.5 mL, 20.0 g, 0.164 mol) and dimethyl glutaconate (23.0 mL, 25.9 g, 0.164 mol) in benzene (300 mL) was added dropwise piperidine (3.20 mL, 2.81 g, 33.0 mmol). The resulting mixture was stirred for 3 h under reflux using a Dean-Stark apparatus. The clear and colorless solution became a clear pale orange over the course of the reaction. The reaction mixture was cooled to room temperature and concentrated to approximately 40 mL under reduced pressure and a white precipitate formed. The resulting mixture was then suction filtered and the solids were washed with cold benzene to give **133b**, 22.7 g (98.6 mmol, 67%). The filtrate was then concentrated under reduced pressure to afford a brown oil. This was then subjected to flash chromatography (2% ethyl acetate/dichloromethane), which afforded **133b** (7.50 g, 32.6 mmol, 20%) as a white solid. Combined yield = 30.2 g (32.6 mmol, 80%).

R_f = 0.42 (2% ethyl acetate/dichloromethane). Mp 195-196 °C (chloroform/hexane) (Lit.[1] 115-117 °C). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.18 (s, 1H, H-4), 6.90-6.85 (m, 3H), 6.66 (d, 1H, *J* = 8.3 Hz), 6.63 (t, 1H, *J* = 7.5 Hz), 6.42 (d, 1H, *J* = 16.3 Hz), 3.12 (s, 3H, H-4'). ^{13}C NMR (126 MHz, $CDCl_3$): δ = 167.6 (0), 159.2 (0), 153.8 (0), 143.7 (1), 138.6 (1), 133.1 (1), 128.7 (1), 125.0 (1), 123.5 (1), 122.6 (0), 119.2 (0), 116.9 (d), 52.1 (3, C-4').

2-Oxo-2*H*-chromene-3-carbaldehyde (176)

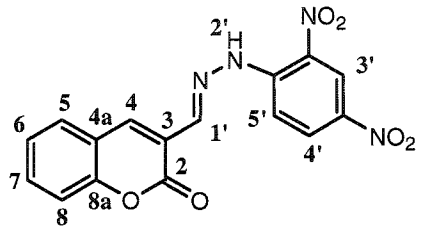


Ozone-rich air was bubbled through a magnetically stirred –55 °C solution of **133b** (5.00g, 21.7 mmol) in chloroform (300 mL) for 1 h, at which point the solution had become a deep blue. Nitrogen was then bubbled through the solution until the deep blue color disappeared and dimethyl sulfide (3.36 g, 54.2 mol, 4.00 mL) was added. The solution was then stirred overnight under nitrogen to afford a clear pale yellow solution. The solvent was removed under reduced pressure to give a pale yellow solid. This was subjected to flash chromatography (2% ethyl acetate/dichloromethane), which gave **176** (2.97 g, 17.1 mmol, 79%) as a pure white solid. R_f = 0.63 (2 % ethyl acetate/dichloromethane).

Mp = 131-132 °C (chloroform/hexane) (Lit.[1] 125-126 °C). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 10.26 (s, 1H, H-1'), 8.42 (s, 1H, H-4), 7.71-7.68 (m, 2H), 7.41-7.36 (m, 2H). ^{13}C

NMR (126 MHz, $CDCl_3$): δ = 188.0 (1, C-1'), 160.3 (0), 155.8 (0), 145.8 (1), 135.3 (1), 131.0 (1), 125.5 (1), 122.0 (0), 118.4 (0), 117.4 (1).

(*E*)-3-(2,4-Dinitrophenylhydrazonomethyl)-2*H*-chromen-2-one (182)



To a room temperature solution of deionized water (12 mL) and concentrated sulfuric acid (8 mL) was added 2,4-dinitrophenylhydrazine (1.60 g, 8.08 mmol). To a solution **176** (1.00 g, 5.74 mmol) in 95% ethanol (30 mL) the 2,4-dinitrophenylhydrazine solution, described above, was added dropwise. The clear colorless solution went to a dark orange solution containing a thick orange precipitate over the course of the reaction. After the addition was complete, the solution was allowed to react at room temperature for 2 h and the solution was then cooled to 6 °C. The solution was then suction filtered and the solid was washed with deionized water, absolute ethanol (50 mL) and diethyl ether (100 mL), which afforded **182** (1.54 g, 4.36 mmol, 76%) as a dark orange solid. Mp 300-301 °C (glacial acetic acid/concentrated sulfuric acid). ^{1}H NMR (500 MHz, D_2SO_4): δ = 8.79 (d, 1H, *J* = 2.0 Hz), 8.75 (s, 1H), 8.67 (s, 1H), 8.20 (dd, 1H, *J* = 9.8, 2.4 Hz), 7.74 (t, 1H, *J* = 7.9 Hz), 7.63 (d, 1H, *J* = 7.1 Hz), 7.30 (t, 1H, *J* = 8.2 Hz), 7.27 (d, 1H, *J* = 8.6 Hz), 7.01 (d, 1H, *J* = 9.1 Hz). IR (nujol, NaCl): υ_{max} = 3280 (w), 1725 (m), 1610 (m), 1518 (w), 763 (w) cm^{-1}; MS (EI) *m/z* (%) 354 (M^+, 68), 172 (60), 306 (39),

337 (37). Anal. Calcd for $C_{16}H_{10}N_4O_6$: C 54.24, H 2.84, N 15.81; found; C 53.76, H 2.82, N 15.76.

General Procedures for the Preparation for the 1-Azadienes

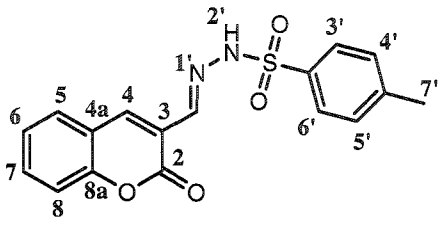
Procedure 1: Use of Dean-Stark conditions in the preparation of the 1-azadienes.

To a solution of **176** in dry benzene, was added the amine (3.0 equivalents). The mixture was reacted under reflux under nitrogen using a Dean-Stark apparatus. The reaction was monitored using TLC and worked up shortly after the aldehyde had been consumed. The reaction mixture was then cooled to 6 °C. The precipitate was collected by suction filtration and washed with cold benzene.

Procedure 2: Condensation of 3-formylcoumarin with amines using non-Dean-Stark conditions.

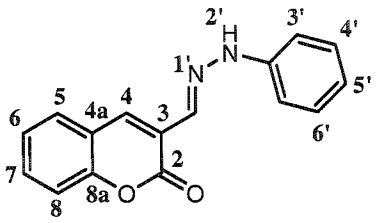
To a solution of **176** in dry toluene, amine (1.1 equivalents) and anhydrous $MgSO_4$ (2 g/mmol of aldehyde) were added. The solution was reacted under reflux conditions under N_2 overnight. The solution was then cooled to room temperature and filtered. The resulting cake was then washed with dichloromethane. The solvent was removed under reduced pressure and the resulting residue was then subjected to silica flash column chromatography. The product was crystallized from the appropriate solvent.

(*E*)-3-(Tosylhydrazonomethyl)-2*H*-chromen-2-one (183)



Using general procedure 1, **176** (1.00 g, 5.74 mmol) and *p*-toluenesulfonylhydrazine (3.21 g, 17.2 mmol) were reacted in benzene (50 mL) for 4 h. The clear colorless solution went to a thick cloudy yellow suspension over the course of the reaction. **183** (1.64 g, 4.79 mmol, 82%) was obtained as a pale yellow solid. Mp = 191-192 °C (chloroform/hexane). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.31 (s, 1H), 8.19 (s, 1H), 7.97 (s, 1H), 7.88 (d, 2H, J = 8.6 Hz), 7.61-7.56 (m, 2H), 7.35-7.33 (m, 4H), 2.43 (s, 3H, H-7'). ^{13}C NMR (126 MHz, $CDCl_3$): δ = 160.8 (0), 154.2 (0), 144.9 (0), 140.6 (1), 139.2 (1), 135.7 (0), 133.2 (1), 130.3 (1), 129.5 (1), 128.3 (1), 125.5 (1), 121.0 (0), 119.3 (0), 117.2 (1), 22.0 (3, C-7'). IR (nujol, NaCl) υ_{max} = 3260 (w), 1735 (s), 1690 (m), 1605 (m), 1565 (w), 1355 (w), 1170 (m), 1050 (w), 670 (w) cm^{-1}. MS (EI) *m/z* (%) = 342 (M^+, 1), 317 (38), 289 (10), 159 (100), 131 (20), 91 (38). Anal. Calcd for $C_{17}H_{14}N_2O_4S$: C 59.63, H 4.12, N 8.18; found; C 59.15, H 3.99, N 8.05.

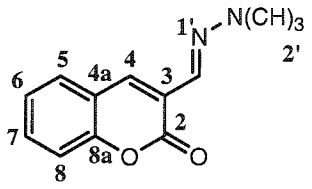
(*E*)-3-(Phenylhydrazonomethyl)-2*H*-chromen-2-one (184)



Using general procedure 1, **176** (0.75 g, 4.3 mmol), phenylhydrazine (1.72 g, 15.9 mmol) were reacted in benzene (100 mL) for 4 h. The clear colorless solution went to a thick dark orange suspension over the course of the reaction. **184** (0.75 g, 2.8 mmol, 66%) was obtained as an orange solid.

Mp 210-211 °C (ethyl acetate/hexane). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.30 (s, 1H), 8.33 (s, 1H, H-2'), 7.91 (s, 1H, H-4), 7.59 (dd, 1H, *J* = 7.7, 1.1 Hz), 7.51 (td, 1H, *J* = 7.6, 1.7 Hz), 7.37-7.30 (m, 5H), 7.17 (d, 1H, *J* = 8.0 Hz), 6.94 (t, 1H, *J* = 7.3 Hz). ^{13}C NMR (126 MHz, $CDCl_3$): δ = 161.2 (0), 153.5 (0), 144.1 (0), 134.7 (1), 131.4 (1), 130.2 (1), 129.6 (1), 128.4 (1), 125.0 (1), 122.8 (0), 121.2 (1), 120.0 (0), 116.8 (1), 113.2 (1). IR (nujol, NaCl): υ_{max} = 3287 (m), 1705 (s), 1600 (m), 1567 (w), 1538 (w), 1495 (w), 1258 (w), 1179 (w), 1062 (m), 926 (w), 759 (w), 688 (w) cm^{-1}. MS (EI) *m/z* (%) = 264 (M^+, 100), 219 (7), 172 (31), 130 (27), 77 (51), 65 (41). HRMS *m/z* [M^+] Calcd for $C_{16}H_{12}N_2O_2$ 264.0898, found 264.0899.

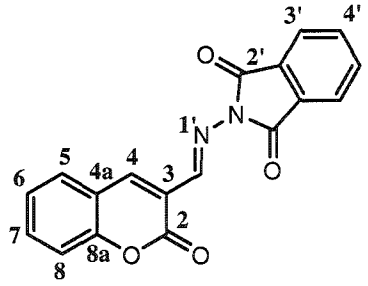
(*E*)-3-(*N*, *N*-Dimethylhydrazonomethyl)-2*H*-chromen-2-one (185)



Using general procedure 1, **176** (3.50 g, 20.1 mmol), 1,1-dimethylhydrazine (1.33 g, 22.1 mmol, 1.68 mL), and benzene (50 mL) were reacted for 4 h. The clear colorless solution went to a clear yellow over the course of the reaction. The solvent was removed under reduced pressure to give a dark yellow solid. The residue was then subjected to flash chromatography (dichloromethane), which afforded **185** (3.10 g, 14.3 mmol, 71%) as a yellow solid.

R_f = 0.71 (dichloromethane). Mp 118-119 °C (ethyl acetate/hexane). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.08 (s, 1H), 7.50 (d, 1H, *J* = 7.7 Hz), 7.43 (t, 1H, *J* = 8.0 Hz), 7.31 (d, 1H, *J* = 8.2 Hz), 7.27-7.23 (m, 1H), 3.08 (s, 6H, H-2'). ^{13}C NMR (126 MHz, $CDCl_3$): δ = 161.7 (0), 152.9 (0), 131.8 (1), 130.4 (1), 128.0 (1), 124.7 (1), 124.2 (0), 123.6 (1), 120.3 (0), 116.6 (1), 42.9 (3, C-2'). IR (nujol, NaCl) υ_{max} = 1709 (m), 1539 (w), 1051 (w) cm^{-1}. MS (EI) *m/z* (%) 216 (M^+, 60), 172 (52), 146 (17), 89 (22), 44 (100). Anal. Calcd for $C_{12}H_{12}N_2O_2$: C 66.65, H 5.59, N 12.95; found; C 66.71, H 5.57, N 12.91.

(*E*)-2-[(2-Oxo-2*H*-chromen-3-ylmethyl)amino]isoindole-1,3-dione (186)

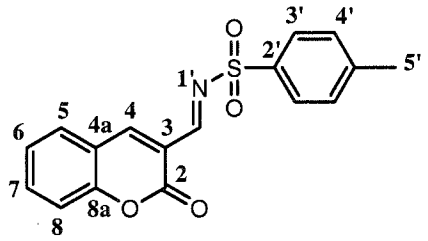


Using general procedure 1, **176** (2.00 g, 11.5 mmol), *N*-aminophthalimide (2.05 g, 12.6 mmol), and benzene (100 mL) were reacted for 4 h. The clear colorless solution

went to a thick yellow suspension over the course of the reaction. **186** (3.20 g, 10.1 mmol, 87%) was obtained as a yellow solid.

Mp 270-271 °C (glacial acetic acid). ^{1}H NMR (500 MHz, D_2SO_4): δ = 9.67 (s, 1H), 8.97 (s, 1H), 8.01-7.99 (m, 2H), 7.90-7.88 (m, 2H), 7.80 (t, 2H, J = 7.5 Hz), 7.52-7.46 (m, 2H). IR (nujol, NaCl): υ_{max} = 1727 (s), 1606 (w), 1560 (w), 1309 (m), 1286 (w), 1213 (w), 1178 (w), 1113 (m), 1084 (w), 1057 (w), 958 (m), 879 (w), 750 (m), 704 (m) cm^{-1}. MS (EI) *m/z* (%) = 318 (M^+, 9), 290 (4), 171 (100), 143 (25), 104 (58), 76 (52). Anal. Calcd for $C_{18}H_{10}N_2O_4$: C 67.92, H 3.17, N 8.80; found; C 67.77, H 3.26, N 8.73.

(*E*)-4-Methyl-*N*-(2-oxo-2*H*-chromen-3-ylmethylene)benzenesulfonamide (187)

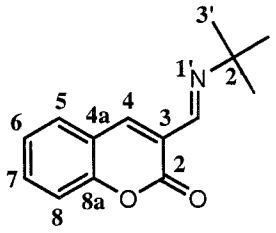


Using general procedure 2, **176** (2.00 g, 11.5 mmol), *p*-toulenesulfonamide (2.16 g, 12.6 mmol), anhydrous magnesium sulfate (25 g) were reacted in toluene (100 mL) for 24 h. The thick white suspension went to a thick pale yellow suspension over the course of the reaction. The pale yellow residue was then subjected to flash chromatography (2% ethyl acetate/dichloromethane), which afforded **187** (3.16 g, 9.66 mmol, 84%) as a pale yellow solid.

R_f = 0.72 (2% ethyl acetate/dichloromethane). Mp 196-197 °C (chloroform/hexane). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 9.20 (s, 1H, H-1'), 8.72 (s, 1H, H-4), 7.90 (d, 2H, J = 8.5

Hz), 7.70 (td, 1H, J = 8.0, 1.6 Hz), 7.64 (dd, 1H, J = 7.1, 1.4 Hz), 7.41-7.36 (m, 4H), 2.47 (s, 3H, H-5'). ^{13}C NMR (126 MHz, $CDCl_3$): δ = 164.5 (1, C-1'), 159.8 (0), 155.8 (0), 146.5 (1, H-4'), 145.4 (0), 135.6 (1), 134.3 (0), 130.7 (1), 130.2 (1, 2C), 128.7 (1, 2C), 125.7 (1), 120.0 (0), 118.5 (0), 117.4 (1), 21.9 (3, H-5'). IR (nujol, KBr): υ_{max} = 1725 (s), 1609 (m), 1318 (m), 1283 (m), 1152 (s), 1090 (w), 923 (w), 765 (m), 666 (m) cm^{-1}. MS (EI) *m/z* (%) = 327 (M^+, 1), 172 (96), 155 (24), 91 (100), 65 (19). HRMS *m/z* [M^+] Calcd for $C_{17}H_{13}NO_4S$ 327.0564, found 327.0562.

(*E*)-3-(*tert*-Butyliminomethyl)-2*H*-chromen-2-one (188)

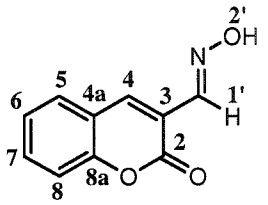


Using general procedure 1, **176** (1.00 g, 5.8 mmol), *tert*-butylamine (0.46 g, 6.4 mmol, 0.60 mL) were reacted in benzene (30 mL) for 4 h. The clear colorless solution went to a clear pale yellow solution over the course of the reaction. The solvent was removed under reduced pressure, which afforded **188** (1.29 g, 5.63 mmol, 97%) as a white solid.

Mp 106-107 °C (chloroform/hexane). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.50 (s, 1H), 8.44 (s, 1H), 7.61 (dd, 1H, J = 7.6, 1.4 Hz), 7.56 (td, 1H, J = 8.0, 1.6 Hz), 7.37 (d, 1H, J = 7.7 Hz), 7.31 (td, 1H, J = 7.4, 1.3 Hz), 1.33 (s, 9H, H-1'). ^{13}C NMR (126 MHz, $CDCl_3$): δ = 161.5 (0), 154.4 (0), 149.7 (1), 139.3 (1), 132.5 (1), 129.3 (1), 124.9 (1), 123.8 (0), 119.5

(0), 116.8 (1), 58.7 (0, C-2'), 29.8 (3, C-3'); IR (nujol, KBr): υ_{max} = 3076 (w), 1707 (s), 1646 (m), 1605 (s), 1596 (m), 1284 (m), 1217 (m), 1164 (s), 1120 (w), 1049 (m), 752 (s) cm^{-1}. MS (EI) *m/z* (%) = 229 (M^+, 24), 214 (41), 173 (100), 146 (88), 118 (m), 88 (18), 63 (12), 56 (18), 41 (49). HRMS *m/z* [M^+] Calcd for $C_{14}H_{15}NO_2$ 229.1101, found 229.1101.

3-(Hydroxyiminomethyl)-2*H*-chromen-2-one (189)

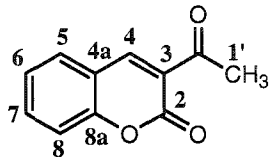


To a room temperature solution of **176** (2.00 g, 11.4 mmol) and hydroxylamine hydrochloride (1.34 g, 19.3 mmol) in 1:1 water/THF (150 mL), was added sodium acetate (1.36 g, 16.6 mmol). The solution was reacted at room temperature for 3 h. The clear colorless solution went to a thick white suspension over the course of the reaction. The mixture was suction filtered and washed the solid with deionized water, which afforded **189** (1.89 g, 9.78 mmol, 88%) as a white solid.

Mp 219-220 °C (95% ethanol). ^{1}H NMR (500 MHz, DMSO-d_6): δ = 11.79 (s, 1H, H-2'), 8.37 (s, 1H, H-4), 8.08 (s, 1H, H-1'), 7.84 (d, 1H, *J* = 7.7 Hz, H-5), 7.64 (t, 1H, *J* = 7.8 Hz), 7.43 (d, 1H, *J* = 8.2 Hz, H-8), 7.38 (t, 1H, *J* = 7.5 Hz, H-7). ^{13}C NMR (126 MHz, DMSO-d_6): δ = 159.2 (0), 153.1 (0), 142.3 (1, C-4), 137.6 (1, C-1'), 132.3 (1, C-6), 129.1 (1, C-5), 124.8 (1, C-7), 119.9 (0), 118.8 (0), 116.1 (1, C-8). IR (nujol, NaCl): υ_{max} = 3190 (m), 1725 (vs), 1606 (w), 1595 (w), 1295 (w), 970 (w), 955 (w), 745 (m). MS (EI)

m/z (%) = 189 (M^+, 96), 172 (54), 118 (90), 89 (100) cm^{-1}. Anal. Calcd for $C_{10}H_7NO_3$: C 63.49, H 3.73, N 7.40; found; C 63.07, H 3.86, N 7.30.

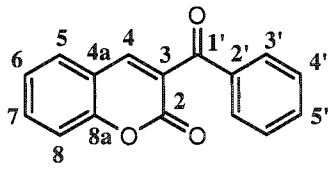
3-Acetyl-2*H*-chromen-2-one (193a)[22]



To a room temperature solution of salicyaldehyde (65.30 g, 0.535 mol, 56.0 mL), ethyl acetoacetate (73.00 g, 0.56 mol, 71.0 mL) in ethanol (700 mL) was added dropwise piperidine (4.55 g, 53.4 mmol, 5.0 mL). The resulting mixture was stirred at room temperature for 10 h. The clear colorless solution went to a clear thick bright yellow suspension over the course of the reaction. The solution was suction filtered and washed with pentane, which afforded **193a** (94.32 g, 0.501 mol, 94%) as a pale yellow solid. Mp 119-120 °C (95 % ethanol) (Lit.[22] 123 °C). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.52 (s, 1H, H-4), 7.68-7.65 (m, 2H), 7.39 (d, 1H, J = 9.4 Hz), 7.36 (t, 1H, J = 7.7 Hz), 2.74 (s, 3H, H-1'). ^{13}C NMR (126 MHz, $CDCl_3$): δ = 195.7 (0), 159.4 (0), 155.5 (0), 147.7 (1), 134.6 (1), 130.4 (1), 125.2 (1), 124.8 (0), 118.5 (0), 116.9 (1), 30.8 (3). IR (nujol, KBr) υ_{max} = 3029 (w), 1742 (s), 1678 (s), 1613 (w), 1558 (m), 1296 (w), 1211 (m), 1158 (w), 1123 (w), 978 (m), 922 (w), 759 (s), 639 (m), 552 (w), 457 (w) cm^{-1}. MS (EI) *m/z* (%) = 188 (M^+, 53), 173 (100), 145 (12), 101 (11), 63 (13), 43 (45).

[22] Pandya, K. R.; Pandya, K. C. *Arga. Uni. J. Res.* **1955**, *IV*, 305-315.

3-Benzoyl-2*H*-chromen-2-one (193b)[23]

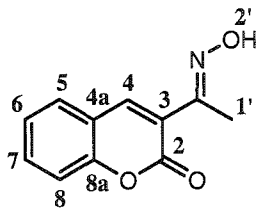


To a room temperature solution of salicyaldehyde (50.00 g, 0.409 mol, 44.0 mL), ethyl benzoylacetate (82.60 g, 0.430 mol, 75.0 mL) in 95 % ethanol (700 mL) was added dropwise piperidine (3.49 g, 41.0 mmol, 4.0 mL). The resulting mixture was reacted at room temperature for 7 h. The clear colorless solution went to a thick pale yellow suspension over the course of the reaction. The mixture was filtered and washed with pentane, which afforded **193b** (80.20 g, 0.321 mol, 78%) as a pale yellow solid.

Mp 133-134 °C (95 % ethanol) (Lit.[23] 130 °C). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.08 (s, 1H, H-4), 7.89 (d, 2H, J = 7.9 Hz), 7.67-7.60 (m, 3H), 7.49 (t, 2H, J = 7.6 Hz), 7.41 (d, 1H, J = 8.4 Hz), 7.36 (t, 1H, J = 8.3 Hz). ^{13}C NMR (126 MHz, $CDCl_3$): δ = 158.6 (0), 155.0 (0), 145.6 (1), 136.5 (0), 134.0 (1), 133.8 (1), 129.8 (1), 129.4 (1), 128.8 (1), 127.3 (0), 125.2 (1), 118.4 (0), 117.2 (1). IR (nujol, KBr): υ_{max} = 1718 (s), 1657 (w), 1609 (m), 1562 (m), 1241 (m), 1165 (w), 922 (w), 760 (m), 699 (w), 564 (w) cm^{-1}. MS (EI) *m/z* (%) = 250 (M^+, 30), 221 (19), 173 (10), 145 (4), 105 (90), 89 (17), 77 (100), 63 (16), 81 (39). HRMS *m/z* [M^+] Calcd for $C_{16}H_{10}O_3$ 250.0629, found 250.0617.

3-(Hydroxyiminoethyl)-2*H*-chromen-2-one (194a)[22]

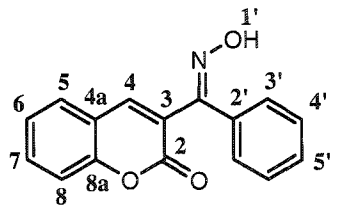
[23] Pandya, K. R.; Pandya, K. C. *Arga. Uni. J. Res.* **1955**, *IV*, 345-353.



To a room temperature solution of **193a** (3.00 g, 15.9 mmol) in glacial acetic acid (25 mL) was added hydroxylamine hydrochloride (1.66 g, 23.9 mmol). The mixture was reacted under reflux for 2.5 h. The clear colorless solution went to a clear brown over the course of the reaction. The solution was allowed to cool to room temperature and crystals formed. The solution was then suction filtered, which afforded **194a** as a white solid (2.16 g, 10.6 mmol, 67%).

Mp 201-202 °C (chloroform) (Lit.[22] 209 °C). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.88 (s, 1H, H-4), 7.84 (s, 1H, H-2'), 7.57-7.53 (m, 2H), 7.35 (d, 1H, J = 8.8 Hz), 7.30 (t, 1H, J = 7.6 Hz), 2.29 (s, 3H, H-1'). ^{13}C NMR (126 MHz, $CDCl_3$): δ = 159.6 (0), 154.9 (0), 154.2 (0), 141.3 (1, C-4), 132.5 (1), 128.7 (1), 125.2 (0), 124.9 (1), 119.1 (0), 116.8 (1), 13.5 (3, C-1'). IR (nujol, KBr): υ_{max} = 3300 (s), 3057 (w), 1720 (s), 1698 (m), 1610 (w), 1248 (w), 1136 (w), 914 (m), 757 (m), 632 (w) cm^{-1}. MS (EI) *m/z* (%) = 203 (M^+, 28), 186 (100), 159 (7), 115 (20), 102 (11), 63 (23). HRMS *m/z* [M^+] Calcd for $C_{11}H_9NO_3$ 203.0581, found 203.0559.

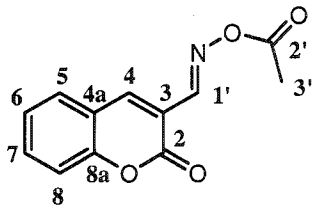
3-(Hydroxyiminophenylmethyl)-2*H*-chromen-2-one (194b)[23]



To a room temperature solution of **193b** (3.00 g, 12.0 mmol) in glacial acetic acid (25 mL) was added hydroxylamine hydrochloride (1.25 g, 18.0 mmol). The mixture was reacted under reflux for 7 h. The clear colorless solution went to a clear bright yellow over the course of the reaction. The solution was allowed to cool to room temperature and crystals formed. The mixture was suction filtered, which afforded **194b** (1.90 g, 7.17 mmol, 60%) as a pale yellow solid.

Mp 248-249°C (chloroform/hexane) (Lit.[23] 148-150 °C). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 10.84 (s, 1H, H-1'), 9.04 (s, 1H, H-4), 7.76 (d, 2H, *J* = 7.6 Hz), 7.72 (t, 1H, *J* = 7.9 Hz), 7.43-7.38 (m, 4H), 7.18 (t, 1H, *J* = 7.8 Hz). ^{13}C NMR (126 MHz, $CDCl_3$): δ = 162.0 (0), 159.5 (0), 154.8 (0), 149.1 (1), 137.9 (0), 134.6 (1), 130.2 (1), 129.3 (1, 2C), 125.7 (1), 125.0 (1), 120.81 (1), 120.80 (1), 118.9 (0), 116.9 (1). IR (nujol, KBr): υ_{max} = 3278 (m), 1712 (s), 1595 (s), 1551 (s), 1318 (w), 1250 (w), 1202 (m), 1032 (w), 971 (w), 791 (m), 741 (s), 688 (m), 535 (w) cm^{-1}. MS (EI) *m/z* (%) = 265 (M^+, 37), 173 (100), 120 (56), 105 (88), 43 (97). HRMS *m/z* [M^+] Calcd for $C_{16}H_{11}NO_3$ 265.0713, found 265.0720.

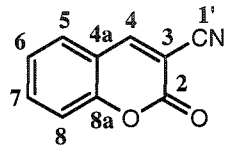
(*E*)-*O*-acetyl-3-(Hydroxyiminomethyl)-2*H*-chromen-2-one (190)



To a room temperature solution of **189** (0.50 g, 2.6 mmol), acetic anhydride (0.32 g, 3.1 mmol, 0.30 mL) in THF (25 mL) was added pyridine (0.22 g, 2.8 mmol, 0.23 mL). The mixture was reacted for 8 h. The clear colorless solution went to a pale clear yellow over the course of the reaction. The solvent was removed under reduced pressure to give a pale yellow solid and the residue was subjected to flash chromatography (5% ethyl acetate/dichloromethane), which afforded **190** (0.32 g, 1.3 mmol, 53%) as a pure white solid.

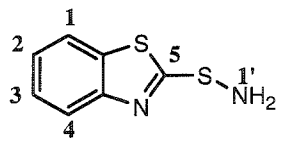
R_f = 0.61 (5% ethyl acetate/dichloromethane). Mp 116-117 °C (ethyl acetate/hexane). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.60 (s, 1H), 8.56 (s, 1H), 7.64-7.60 (m, 2H), 7.39-7.33 (m, 2H), 2.25 (s, 3H, H-3'). ^{13}C NMR (126 MHz, $CDCl_3$): δ = 168.2 (0), 159.8 (0), 154.7 (0), 150.4 (1), 141.6 (1), 133.8 (1), 129.6 (1), 125.4 (1), 118.7 (0), 118.1 (0), 117.2 (1), 19.6 (3, C-3'). IR (nujol, NaCl): υ_{max} = 1778 (m), 1727 (s), 1226 (m), 1190 (m), 917 (w), 764 (w) cm^{-1}. MS (EI) *m/z* (%) = 231 (M^+, 2), 189 (38), 171 (49), 143 (44), 115 (24), 89 (16), 43 (100). Anal. Calc. For $C_{12}H_9NO_4$: C 62.34, H 3.92, N 6.06; found; C 62.23, H 4.15, N 6.09.

3-Cyano-2*H*-chromen-2-one (192)



To a room temperature solution of **189** (1.00 g, 5.3 mmol) *p*-toluenesulfonyl chloride (3.02 g, 15.9 mmol) in dichloromethane (20 mL) was added dropwise triethylamine (1.71 g, 15.9 mmol) in dichloromethane (10 mL). The mixture was stirred for 3 h at 0 °C under nitrogen. The solution was allowed to warm to room temperature and allowed to react for an additional for 4 h. The solvent was removed under reduced pressure to give a thick pale yellow oil that was subjected to flash chromatography (dichloromethane), which afforded **192** (0.63 g, 4.5 mmol, 84%) as a white solid. R_f = 0.52 (dichloromethane). Mp 188-189 °C (ethyl acetate/hexane) (Lit.[24] 182 °C). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.30 (s, 1H, H-4), 7.74 (td, 1H, *J* = 7.2, 1.4 Hz), 7.64 (dd, 1H, *J* = 7.3, 1.5 Hz), 7.44-7.42 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$): δ = 156.6 (0), 154.8 (0), 152.0 (1), 135.8 (1), 129.5 (1), 125.9 (1), 117.6 (1), 117.3 (0), 113.7 (0), 103.6 (0). IR (nujol, NaCl): υ_{max} = 2942 (m), 2923 (m), 2212 (m), 1730 (s), 1601 (s), 1550 (w), 1450 (w) cm^{-1}. MS (EI) *m/z* (%) = 171 (M^+, 69), 143 (100), 115 (70), 89 (11), 63 (35), 39 (29).

2-Benzothiazolesulfenamide (203)[5b]

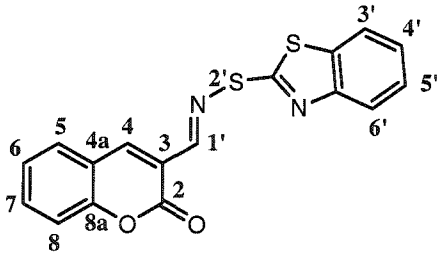


[24] Baker. W.; Howe, C. S. *J. Chem. Soc.* **1953**, 119-124.

Through a room temperature solution of 2,2'-dithiobis(benzothiazole) (5.00 g, 15.0 mmol) and silver nitrate (2.60 g, 15.3 mmol) in dry methanol (250 mL) was bubbled ammonia for 15 min. The clear colorless solution went to a thick yellow suspension during this time. The mixture was suction filtered and the solvent was removed under reduced pressure. The resulting white precipitate was then dissolved in diethyl ether (100 mL) and filtered. The solvent collected was removed under reduced pressure, which afforded **203** (2.61 g, 14.3 mmol, 95%) as a white solid.

Mp 122-123 °C (chloroform/hexane) (Lit.[5b] 123-124 °C). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.84 (d, 1H, *J* = 7.9 Hz), 7.82 (d, 1H, *J* = 8.5 Hz), 7.42 (td, 1H, *J* = 7.7, 1.2 Hz), 7.29 (t, 1H, *J* = 8.2 Hz), 3.28 (s, 2H). ^{13}C NMR (126 MHz, $CDCl_3$): δ = 178.6 (0), 154.8 (0), 135.2 (0), 126.2 (1), 123.9 (1), 121.7 (1), 121.3 (1). IR (nujol, NaCl): υ_{max} = 3323 (m), 3194 (w), 1431 (m), 1313 (w), 1088 (w), 1031 (m), 920 (m), 751 (m), 721 (w), 693 (w) cm^{-1}. MS (EI) *m/z* (%) = 182 (M^+, 100), 149 (48), 108 (30), 82 (9), 69 (19).

(*E*)-2-[(2-Oxo-2*H*-chromen-3-ylmethylidene)amino]benzothiazole (198)

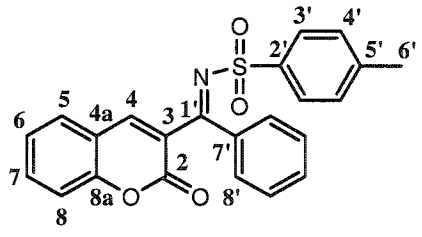


To a room temperature solution of **176** (2.00 g, 11.5 mmol), 2.14 g (11.7 mmol) of 2-benzothiazolesulfenamide in absolute ethanol (25 mL) was added potassium hydroxide (0.04 g, 0.7 mmol). The mixture was reacted at room temperature under

nitrogen for 18 h. The clear colorless solution went to a bright thick yellow suspension over the course of the reaction. The solvent removed under reduced pressure and the residue was subjected to flash chromatography (dichloromethane), which afforded **198** (1.36 g, 4.02 mmol, 35%) a bright yellow solid.

Mp 135-136 °C (chloroform/hexane). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.88 (s, 1H), 8.43 (s, 1H), 7.92 (d, 1H, *J* = 7.6 Hz), 7.88 (d, 1H, *J* = 8.2 Hz), 7.73 (dd, 1H, *J* = 7.7, 1.3 Hz), 7.63 (td, 1H, *J* = 8.0, 1.4 Hz), 7.46 (t, 1H, *J* = 7.6 Hz), 7.40-7.33 (m, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δ = 171.1 (0), 160.2 (0), 154.5 (0), 154.3 (0), 154.2 (1), 140.3 (1), 135.2 (0), 133.5 (1), 129.8 (1), 126.5 (1), 125.4 (1), 124.5 (1), 122.6 (0), 122.4 (1), 121.2 (1), 119.1 (0), 117.2 (1). IR (nujol, NaCl): υ_{max} = 1722 (s), 1597 (m), 1568 (w), 1178 (w), 112 (w), 1062 (w), 1029 (w), 1011 (w), 955 (w), 746 (w), 718 (w) cm^{-1}. MS (EI) *m/z* (%) = 338 (M^+, 7), 332 (13), 268 (3), 167 (100), 145 (4), 108 (15), 89 (11), 39 (7). HRMS *m/z* [M^+] Calcd for $C_{17}H_{10}N_2O_2S_2$ 338.0183, found 338.0224.

(*E*)-4-Methyl-*N*-[(2-oxo-2*H*-chromen-3-yl)phenylmethylene]benzenesulfonamide (207)

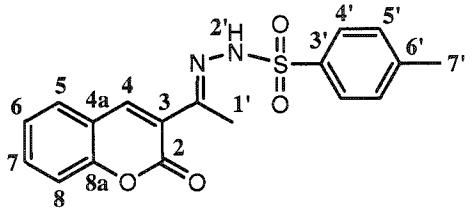


To a room temperature solution of **193b** (5.00 g, 20.0 mmol), *p*-toluenesulfonamide (4.10 g, 24.0 mmol), triethylamine (8.50 mL, 6.06 g, 60.0 mmol),

and 4Å molecular sieves (20 g) in dry dichloromethane (150 mL) was added dropwise titanium(IV) chloride (1.10 mL, 1.89 g, 10.0 mmol) over a 30 minute period at 0 °C, under nitrogen. The mixture was reacted for 3 h. The clear colorless solution went to a thick dark red suspension over the course of the reaction. The red precipitate redissolved back into the solution and the mixture was then filtered through Celite and the cake was washed with dichloromethane (50 mL). The solvent of the filtrate was removed under reduced pressure, which afforded an orange solid. The residue was then subjected to flash chromatography (2% ethyl acetate/dichloromethane), which afforded **207** (5.77 g, 14.3 mmol, 72%) as a white solid.

R_f = 0.83 (2% ethyl acetate/dichloromethane). Mp 190-191 °C (chloroform/hexane). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.93 (d, 2H, *J* = 8.1 Hz, H-4), 7.90 (s, 1H), 7.88 (d, 2H, *J* = 7.6 Hz), 7.66 (td, 1H, *J* = 7.6, 1.6 Hz), 7.63 (dd, 1H, *J* = 7.0, 1.5 Hz), 7.59 (t, 1H, *J* = 7.4 Hz), 7.46-7.42 (m, 2H), 7.38 (t, 1H, *J* = 7.8 Hz), 7.34 (d, 2H, *J* = 8.0 Hz), 2.46 (s, 3H, H-6'). ^{13}C NMR (126 MHz, $CDCl_3$): δ = 172.4 (0), 157.8 (0), 154.5 (0), 144.4 (0), 142.7 (1, C-4), 137.2 (0), 135.5 (0), 134.4 (1), 133.2 (1), 130.0 (2C, 1), 129.8 (1), 129.8 (1), 129.1 (2C, 1), 128.0 (1), 125.2 (1), 125.0 (0), 118.2 (0), 117.3 (1), 21.8 (3, C-6'). IR (nujol, KBr): υ_{max} = 3054 (w), 1726 (s), 1608 (w), 1558 (m), 1154 (m), 1088 (w), 803 (w), 752 (m), 689 (m) cm^{-1}. MS (EI) *m/z* (%) = 403 (M^+, 21), 248 (100), 236 (9), 194 (3), 155 (29), 91 (86), 77 (27). HRMS *m/z* [M^+] Calcd for $C_{23}H_{17}NO_4S$ 403.0877, found 403.0852.

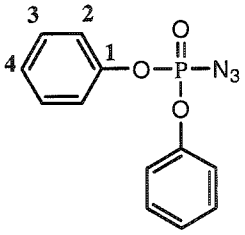
(*E*)-3-(Tosylhydrazono-1-ethyl)-2*H*-chromen-2-one (210)



Using general procedure 2, **193a** (2.00 g, 10.6 mmol), *p*-toluenesulfonamide (2.08 g, 11.2 mmol), and anhydrous magnesium sulfate (22.0 g) in toluene (100 mL) were reacted for 48 h. The clear colorless solution went to a bright yellow over the course of the reaction. The dichloromethane solution was then washed with 1 M HCl (50 mL) and was dried with anhydrous magnesium sulfate. The dichloromethane solution was gravity filtered and the solvent was removed under reduced pressure, which afforded **210** (3.34 g, 9.38 mmol, 88%) as a pale yellow solid.

Mp 157-158 °C (chloroform/hexane). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.96 (s, 1H, H-4), 7.86 (d, 2H, J = 8.6 Hz), 7.57-7.54 (m, 2H), 7.34-7.30 (m, 4H), 2.44 (s, 1H, H-2'), 2.42 (s, 3H, H-1'), 2.18 (s, 3H, H-7'). ^{13}C NMR (126 MHz, $CDCl_3$): δ = 160.0 (0), 154.3 (0), 150.3 (0), 144.6 (0), 142.2 (1), 135.5 (0), 132.7 (1), 129.9 (1), 129.0 (1), 128.2 (1), 126.1 (0), 125.6 (1), 119.1 (0), 116.7 (1), 21.8 (3), 15.3 (3). IR (nujol, KBr) υ_{max} = 3226 (m), 3021 (w), 1718 (m), 1607 (w), 1600 (w), 1342 (m), 1161 (s), 754 (m) cm^{-1}. MS (APCI) *m/z* (%) = 357 (M^+ +1). MS (EI) *m/z* (%) 200 (100), 172 (58), 144 (18), 115 (30), 91 (59), 89 (11). HRMS *m/z* [M^+] Calcd for $C_{18}H_{16}N_2O_4S$ 356.0829, found 356.0851.

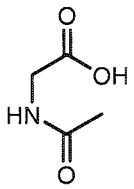
Diphenylphosphoryl azide[20] (214)



To a room temperature solution of diphenyl chlorophosphate (3.00 g, 11.2 mmol) in dry acetone (50 mL) was added sodium azide (0.76 g, 11.7 mmol). The mixture was reacted at room temperature for 3 h. The clear colorless solution went to a thick white suspension over the course of the reaction. The mixture was gravity filtered and the solvent removed under reduced pressure and the residue was then subjected to flash chromatography (dichloromethane), which afforded **214** (2.86 g, 10.4 mmol, 93%) as a thick clear colorless oil.

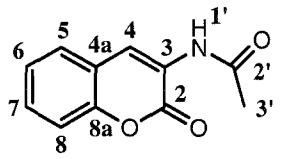
^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.42-7.37 (m, 5H), 7.32-7.18 (m, 5H). ^{13}C NMR (126 MHz, $CDCl_3$): δ = 150.1 (0, d, $J_{C\text{-}P}$ = 4.8 Hz), 150.0 (0, d, $J_{C\text{-}P}$ = 5.4 Hz), 130.3 (1), 126.6 (1), 126.3 (1), 120.6 (1, d, J = 4.8 Hz), 120.4 (1, d, J = 5.4 Hz). IR (nujol, NaCl): υ_{max} = 3432 (w), 3066 (m), 2522 (w), 2174 (vs), 1590 (s), 1489 (s), 1457 (m), 1300 (s), 1275 (s), 1202 (s), 1025 (m), 946 (s), 781 (s), 688 (m), 598 (w) cm^{-1}. MS (EI) *m/z* (%) = 275 (M^+, 100), 215 (11), 167 (73), 154 (31), 126 (26), 94 (28), 77 (77), 65 (55), 51 (36).

Acetylglycine (216)



To a room temperature solution of glycine (75.00 g, 1.00 mol) in deionized (300.0 mL) was added acetic anhydride (215.00 g, 2.1 mol, 198.7 mL). The mixture reacted at room temperature for 5 h. The clear colorless solution went to a thick white suspension over the course of the reaction. The solution was then cooled to 6 °C and the solution was then filtered and washed with cold deionized water (300 mL), which afforded **216** as a white solid (98.51 g, 0.64 mol, 85%).

3-Acetamido-2*H*-chromen-2-one (211)[21]

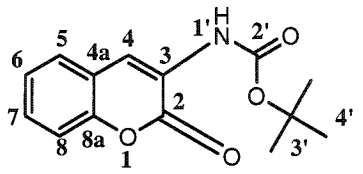


To a room temperature solution of salicylaldehyde (61.10 g, 0.50 mol), anhydrous sodium acetate (41.00g, 0.50 mol) in acetic anhydride (255.26 g, 2.50 mol, 250.0 ml) was added acetylglycine (58.6 g, 0.38 mol) and mixture was heated to 100 °C for 90 min. The clear colorless solution went to a dark clear red over the course of the reaction. The solution was cooled to room temperature and was diluted with ice water (300 mL) and cooled to 6 °C. The suspension produced was then filtered, which afforded **211** as a yellow solid (40.00 g, 0.20 mol). The solid was twice crystallized from ethanol, which afforded **211** (27.00 g, 0.13 mol, 27%) as a white solid.

Mp 195-196 °C (Lit.[21] 203-204 °C). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.69 (s, 1H, H-4), 8.10 (s, 1H, H-1'), 7.52 (dd, 1H, J = 7.4, 1.2 Hz), 7.46 (td, 1H, J = 7.9, 1.4 Hz), 7.34-7.30 (m, 2H), 2.26 (s, 3H, H-3'). ^{13}C NMR (126 MHz, $CDCl_3$): δ = 169.7 (0), 159.0 (0), 150.1

(0), 129.9 (1), 128.0 (1), 125.4 (1), 124.2 (0), 123.6 (1, C-4), 120.0 (0), 116.6 (1), 24.9 (3, C-3'). IR (nujol, NaCl): υ_{max} = 3331 (s), 1710 (s), 1683 (s), 1605 (m), 1530 (m), 1145 (m), 766 (w), 708 (w) cm^{-1}. MS (EI) *m/z* (%) = 203 (M^+, 18), 161 (100), 133 (37), 106 (8), 78 (10), 51 (9).

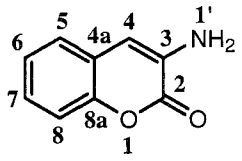
(2-Oxo-2*H*-chromen-3-yl)carbamic acid *tert*-butyl ester (215)



To a room temperature solution of **211** (5.00 g, 24.6 mmol), 4-(dimethylamino)pyridine (0.60 g, 49.1 mmol) in freshly distilled THF (120 mL) was added di-*tert*-butyl dicarbonate (22.48 g, 0.103 mol). The mixture was reacted under reflux for 4 h under nitrogen. The clear colorless solution went to a clear pale yellow over the course of the reaction. The solution was cooled to room temperature and was added hydrazine hydrate (3.94 g, 0.123 mol, 3.83 mL) and freshly distilled methanol (100 mL) in one portion. The solution was allowed to react at room temperature for an additional 4 h. The solution was then diluted with dichloromethane (200 mL) and was washed with 1 M HCl (aq.) (100 mL), 1 M $CuSO_4$ (aq.) (100 mL), and 1 M $NaHCO_3$ (aq.) (100 mL). The solution was then dried over anhydrous $MgSO_4$ filtered and the solvent was removed under reduced pressure to give a white solid. The residue was then subjected to silica flash column chromatography (dichloromethane), which afforded **215** (5.82 g, 22.3 mmol, 91%) as a white solid.

R_f = 0.86 (dichloromethane). Mp 85-86 °C (chloroform/hexane) (Lit.[16] 85-86 °C). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.29 (s, 1H, H-4), 7.47 (dd, 1H, *J* = 7.6, 1.0 Hz), 7.42 (td, 1H, *J* = 7.9, 1.8 Hz), 7.33-7.28 (m, 2H), 1.55 (s, 9H, H-4'). ^{13}C NMR (126 MHz, $CDCl_3$): δ = 158.8 (0), 152.7 (0), 149.7 (0), 129.2 (1), 127.5 (1), 125.2 (1), 124.8 (0), 120.6 (1, C-4), 120.3 (0), 116.5 (1), 81.9 (0, C-3'), 28.4 (3, C-4'). IR (nujol, NaCl): υ_{max} = 3322 (m), 1700 (s), 1304 (w), 1238 (m), 1159 (m), 1042 (w), 1013 (w), 904 (w), 692 (w) cm^{-1}. MS (EI) *m/z* (%) = 261 (M^+,10), 205 (8), 187 (100), 161 (75), 133 (24), 103 (44), 57 (65).

3-Amino-2*H*-chromen-2-one (212)



To a room temperature 15% TFA/chloroform solution by volume (50 mL), was added **215** (0.500 g, 19.1 mmol). The mixture was reacted at room temperature under nitrogen for 24 h. The solvent was removed under reduced pressure to produce a thick clear brown oil and the residue was subjected to flash chromatography (5 % ethyl acetate/ dichloromethane), which afforded **212** (0.307 g, 1.91 mmol, 99.7%) as a white solid. R_f = 0.61 (5 % ethyl acetate/ dichloromethane).

Mp 135-136 °C (chloroform/hexane) (Lit.[16] 132-135 °C). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.31-7.26 (m, 3H), 7.24-7.19 (m, 1H), 6.71 (s, 1H, H-4'), 4.15 (s, 1H, H-1'). ^{13}C NMR (126 MHz, $CDCl_3$): δ = 159.6 (0), 149.3 (0), 132.2 (0), 126.8 (1), 125.3 (1), 124.8 (1), 121.4 (0), 116.4 (1), 111.1 (1, C-4). IR (nujol, NaCl): υ_{max} = 3428 (w), 3324 (w), 1705

(s), 1647 (w), 1590 (w), 1227 (w), 1170 (w), 889 (w), 742 (m) cm^{-1}. MS (EI) *m/z* (%) = 161 (M^+, 100), 133 (49), 106 (21), 78 (35), 51 (13). HRMS *m/z* [M^+] Calcd for $C_9H_7NO_2$ 161.0463, found 161.0498.

General Procedure for the Preparation of the 2-Azadienes

Procedure 3: Use of Dean-Stark conditions in the preparation of the 2-azadienes.

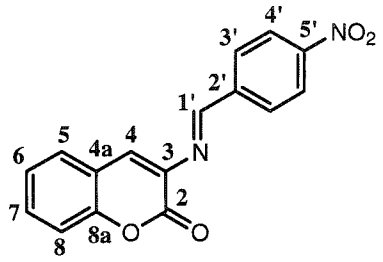
To a room temperature solution of **212** in toluene containing glacial acetic acid (0.10 mL), was added the aromatic aldehyde (1.05 equivalents) and the mixture was heated under reflux using a Dean-Stark apparatus under nitrogen. The reaction was monitored by TLC until 3-aminocoumarin was consumed. The solution was cooled to 6 °C and the resulting precipitate was then collected by suction filtration and washed with pentane. The product was crystallized from chloroform/hexane.

Procedure 4: Using non Dean-Stark conditions.

To a room temperature solution of **212** in absolute ethanol containing glacial acetic acid (0.10 mL) and 4 Å molecular sieves was added the aromatic aldehyde (1.05 equivalents) and the mixture was reacted overnight using reflux conditions under nitrogen. The solution was then cooled to room temperature and filtered. The solvent was

removed under reduced pressure and the residue was then crystallized from chloroform/hexane.

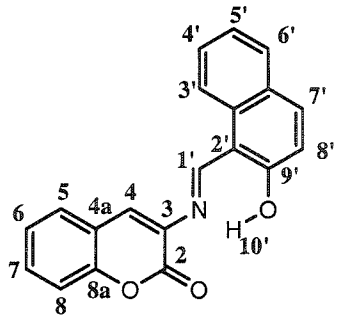
(*E*)-3-[(4-nitrobenzylidene)amino]-2*H*-chromen-2-one (222)



Using general procedure 3, **212** (1.00 g, 6.2 mmol), of 4-nitrobenzaldehyde (1.13 g, 7.47 mmol), 4 Å molecular sieves (~20 g), and absolute ethanol (25 mL) were reacted for 4 h. The pale yellow solution went to a thick yellow suspension over the course of the reaction. The solution was then filtered and washed with cold pentane (50.0 mL x 3), which afforded **222** (1.45 g, 4.93 mmol, 79%) as a yellow solid.

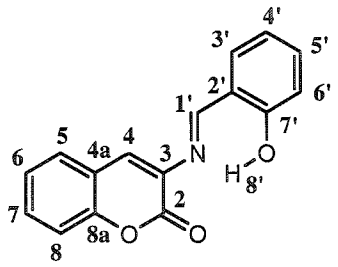
Mp 238-239 °C (chloroform/hexane). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 9.49 (s, 1H, H-1'), 8.33 (d, 2H, J = 9.3 Hz), 8.11 (d, 2H, J = 8.7 Hz), 7.83 (s, 1H, H-4), 7.60-7.55 (m, 2H), 7.39 (d, 1H, J = 8.3 Hz), 7.35 (t, 1H, J = 7.6 Hz). ^{13}C NMR (126 MHz, $CDCl_3$): δ = 161.7 (1, C-1'), 158.2 (0), 152.6 (0), 149.8 (0), 141.9 (0), 136.8 (1, C-4), 133.6 (0), 132.0 (1), 129.9 (1), 128.5 (1), 125.1 (1), 124.2 (1), 119.9 (0), 116.7 (1). IR (nujol, NaCl): υ_{max} = 1705 (s), 1618 (w), 1597 (w), 1520 (m), 1344 (m), 1288 (w), 1081 (m), 950 (w), 837 (w), 748 (w) cm^{-1}. MS (EI) *m/z* (%) = 294 (M^+, 77), 204 (5), 191 (7), 146 (100), 118 (35), 89 (13). HRMS *m/z* [M^+] Calcd for $C_{16}H_{10}N_2O_4$ 294.0639, found 294.0631.

(*E*)-3-[(2-Hydroxynaphthalen-1-ylmethylene)amino]-2*H*-chromen-2-one (223)



Using general procedure 4, **212** (0.80 g, 5.0 mmol), 2-hydroxy-1-naphthaldehyde (0.95 g, 5.2 mmol), 4 Å molecular sieves (~20 g), and absolute ethanol (25.0 mL) were reacted for 16 h. The yellow solution went to a thick dark orange suspension over the course of the reaction. The solvent was removed under reduced pressure and the residue was crystallized, which afforded **223** (0.61 g, 1.8 mmol, 39%) a dark orange solid. Mp 224-225 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 10.19 (s, 1H, H-2'), 8.19 (d, 1H, *J* = 7.8 Hz), 7.84 (d, 1H, *J* = 9.4 Hz), 7.73 (d, 1H, *J* = 7.1 Hz), 7.70 (s, 1H), 7.64-7.53 (m, 3H), 7.45-7.33 (m, 4H), 7.12 (d, 1H, *J* = 9.8 Hz). ^{13}C NMR (126 MHz, $CDCl_3$): δ = 167.8 (0), 159.6 (1), 158.1 (0), 152.1 (0), 137.1 (1), 133.4 (0), 131.4 (1), 131.3 (1), 131.0 (0), 129.5 (1), 128.5 (1), 128.0 (1), 127.9 (0), 125.2 (1), 124.2 (1), 121.2 (1), 119.9 (1), 119.8 (0), 116.7 (1), 110.1 (0). IR (nujol, KBr): υ_{max} = 1725 (s), 1619 (m), 1326 (m), 1289 (w), 1195 (w), 1063 (m), 1034 (w), 820 (m), 750 (s), 468 (w). MS (EI) *m/z* (%) = 315 (M^+, 100), 270 (5), 146 (27), 118 (22), 114 (5), 77 (10). M^+, found 315.0888, $C_{20}H_{13}NO_3$ requires M^+, 315.0894.

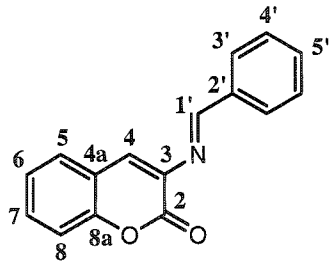
(*E*)-3-[(2-Hydroxybenzylidene)amino]-2*H*-chromen-2-one (224)[15a]



To a room temperature solution of glycine ethyl ester hydrochloride (8.35 g, 59.9 mmol), of triethylamine (9.0 mL, 6.53 g, 64.6 mmol) in deionized water (40.0 mL), was added salicylaldehyde (13.7 mL, 16.0 g, 131.0 mmol). The mixture was stirred vigorously for 18 h. The clear colorless solution went to a thick orange suspension over the course of the reaction. The solution was suction filtered, which afforded **224** (12.56 g, 47.3 mmol, 79%) as an orange solid.

Mp 177-178 °C (water/DMF) (Lit.[15a] 189-190 °C). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 12.93 (s, 1H, H-8'), 9.48 (s, 1H, H-1'), 7.71 (s, 1H, H-4), 7.67-7.61 (m, 2H), 7.46-7.28 (m, 4H), 7.03-6.85 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$): δ = 167.5 (1, C-1'), 161.7 (0), 158.1 (0), 152.4 (0), 134.4 (1, C-4), 134.2 (1), 133.5 (1), 132.0 (0), 131.7 (1), 128.3 (1), 125.1 (1), 119.8 (0), 119.6 (1), 119.5 (0), 117.6 (1), 116.7 (1). IR (nujol, KBr): υ_{max} = 3398 (w), 3038 (w), 1729 (s), 1611 (s), 1571 (m), 1294 (m), 1228 (w), 1147 (w), 1074 (m), 923 (w), 745 (s) cm^{-1}. MS (EI) *m/z* (%) = 265 (M^+, 83), 220 (7), 146 (100), 118 (33), 77 (24). HRMS *m/z* [M^+] Calcd for $C_{16}H_{11}NO_3$ 265.0738, found 265.0728.

(*E*)-3-(Benzylidene)amino-2*H*-chromen-2-one (225)

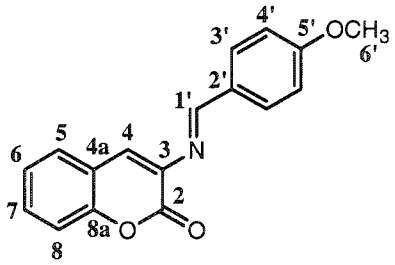


Using general procedure 4, **212** (0.65 g, 4.0 mmol), benzaldehyde (0.60 mL, 0.64 g, 6.0 mmol), 4 Å molecular sieves (~20 g), and absolute ethanol (20 mL) were reacted for 14 h. The clear colorless solution went to a clear pale yellow over the course of the reaction. The solvent was removed under reduced pressure, which afforded **225** (0.66 g, 2.7 mmol, 68%) as a pale yellow solid.

Mp 141-142 °C (Lit.[25] 140-150 °C). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 9.16 (s, 1H, H-1'), 7.95 (dd, 2H, *J* = 6.9, 2.2 Hz), 7.61 (s, 1H, H-4), 7.55-7.45 (m, 5H), 7.37 (d, 1H, *J* = 8.2 Hz), 7.27 (t, 1H, *J* = 7.4 Hz). ^{13}C NMR (126 MHz, $CDCl_3$): δ = 164.5 (1, C-1'), 158.6 (0), 152.4 (0), 136.3 (0), 135.9 (0), 132.31 (1), 132.28 (1), 131.0 (1), 129.4 (1), 129.0 (1), 128.0 (1), 124.7 (1), 120.2 (0), 116.6 (1). IR (nujol, KBr): υ_{max} = 3034 (w), 1715 (s), 1611 (m), 1574 (m), 1288 (m), 1218 (w), 1122 (w), 1061 (s), 998 (m), 915 (m), 750 (s), 693 (m) cm^{-1}. MS (EI) *m/z* (%) 249 (M^+, 22), 220 (4), 161 (100), 146 (31), 133 (34), 106 (14), 78 (26). HRMS *m/z* [M^+] Calcd for $C_{16}H_{11}NO_2$ 249.0789, found 249.0783.

(*E*)-3-[(4-Methoxybenzylidene)amino]-2*H*-chromen-2-one (226)

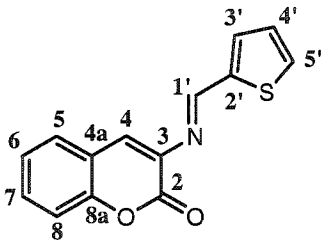
[25] Kulkarni, Y. D.; Srivastava, D. S.; Bishnoi, A.; Dva, P. R. *J. Indian Chem. Soc.* **1996**, *73*, 173-175.



Using general procedure 4, **212** (0.50 g, 3.1 mmol), *p*-anisaldehyde (0.40 mL, 0.43 g, 3.2 mmol), 4 Å molecular sieves (~20 g), and absolute ethanol (30 mL) were reacted for 12 h. The clear colorless solution went a clear pale yellow over the course of the reaction. The solvent was removed under reduced pressure, which afforded **226** (0.63 g, 2.3 mmol, 87%) as a pale yellow solid.

Mp 150-151 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 9.02 (s, 1H, H-1'), 7.89 (d, 2H, *J* = 9.0 Hz), 7.52-7.46 (m, 3H), 7.35 (d, 1H, *J* = 8.1 Hz), 7.28 (t, 1H, *J* = 8.1 Hz), 6.98 (d, 2H, *J* = 9.0 Hz), 3.88 (s, 3H, H-5'). ^{13}C NMR (126 MHz, $CDCl_3$): δ = 163.6 (1, C-1'), 163.2 (0), 158.9 (0), 152.3 (0), 136.5 (0), 131.3 (1), 131.1 (1), 130.6 (1), 129.2 (0), 127.8 (1), 124.8 (1), 120.4 (0), 116.5 (1), 114.5 (1), 55.6 (3, H-5'). IR (nujol, NaCl): υ_{max} = 1713 (s), 1604 (m), 1570 (m), 1300 (w), 1252 (s), 1170 (m), 1057 (m), 1020 (w), 835 (w), 751 (w) cm^{-1}. MS (EI) *m/z* (%) = 279 (M^+, 86), 236 (4), 207 (10), 146 (100), 77 (25), 69 (29). HRMS *m/z* [M^+] Calcd for $C_{17}H_{13}NO_3$ 279.0894, found 279.0885.

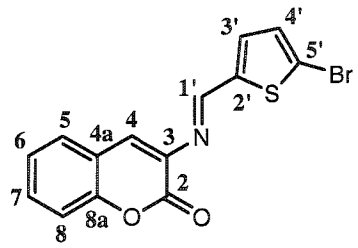
(*E*)-3-[(Thiophen-2-ylmethylene)amino]-2*H*-chromen-2-one (227)



Using general procedure 4, **212** (1.60 g, 3.1 mmol), 2-thiophenecarboxaldehyde (0.90 mL, 1.14 g, 10.1 mmol), 4 Å molecular sieves (~20 g), and absolute ethanol (30 mL) were reacted for 14 h. The clear colorless solution went to a clear pale yellow over the course of the reaction. The solvent was removed under reduced pressure, which afforded **227** (2.11 g, 8.27 mmol, 83%) as a pale yellow solid.

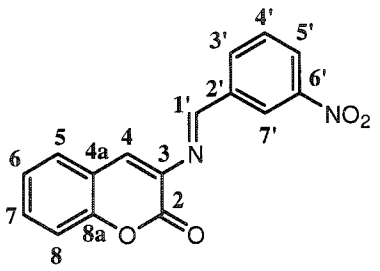
Mp 152-153 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 9.50 (s, 1H), 7.71 (s, 1H), 7.57-7.48 (m, 4H), 7.36 (d, 1H, *J* = 7.7 Hz), 7.30 (t, 1H, *J* = 7.4 Hz), 7.16 (t, 1H, *J* = 4.2 Hz). ^{13}C NMR (126 MHz, $CDCl_3$): δ = 158.6 (0), 157.4 (1), 152.2 (0), 143.5 (0), 134.7 (1, H-4), 134.0 (0), 133.8 (1), 131.6 (1), 131.1 (1), 128.3 (1), 128.0 (1), 124.9 (1), 120.3 (0), 116.5 (1). IR (nujol, NaCl): υ_{max} = 3099 (w), 3078 (w), 1720 (s), 1606 (m), 1591 (s), 1559 (w), 1290 (w), 1224 (w), 1078 (m), 912 (w), 754 (m), 726 (w) cm^{-1}. MS (EI) *m/z* (%) = 255 (M^+, 94), 226 (21), 146 (100), 118 (34), 96 (25), 51 (16). HRMS *m/z* [M^+] Calcd for $C_{14}H_9NO_2S$ 255.0353, found 255.0359.

(*E*)-3-[(5-Bromothiophen-2-ylmethylene)amino]-2*H*-chromen-2-one (228)



Using general procedure 4, **212** (0.60 g, 3.7 mmol), 5-bromo-2-thiophenecarboxaldehyde (0.50 mL, 0.75 g, 3.9 mmol), 4 Å molecular sieves (~20 g), and absolute ethanol (30 mL) were reacted for 16 h. The clear colorless solution went to a clear dark yellow over the course of the reaction. The solvent was removed under reduced pressure, which afforded **228** (0.60 g, 1.8 mmol, 48%) as a pale yellow solid. Mp 201-202 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 9.44 (s, 1H, H-1'), 7.72 (s, 1H, H-4'), 7.54-7.49 (m, 2H), 7.34 (d, 1H, J = 8.5 Hz), 7.30 (t, 1H, J = 8.2 Hz), 7.26 (d, 1H, J = 3.9 Hz), 7.11 (d, 1H, J = 3.8 Hz). ^{13}C NMR (126 MHz, $CDCl_3$): δ = 158.4 (0), 156.3 (1, C-1'), 152.2 (0), 145.2 (0), 135.9 (1, C-4), 133.7 (1), 133.2 (0), 131.3 (1), 128.2 (1), 125.0 (1), 120.211 (0), 120.207 (0), 116.5 (1). IR (neat, KBr): υ_{max} = 2945 (vw), 2923 (vw), 2866 (vw), 1959 (w), 1720 (vs), 1610 (m), 1578 (m), 1557 (w), 1453 (w), 1422 (s), 1284 (w), 1227 (w), 1059 (s), 968 (w), 920 (w), 803 (m), 749 (s), 460 (m). MS (EI) *m/z* (%) = 333 (M^+, 48), 304 (2), 226 (3), 189 (2), 146 (100), 118 (23), 95 (50), 45 (20). M^+, found 332.9469, $C_{14}H_8BrNO_2S$ requires M^+, 332.9458.

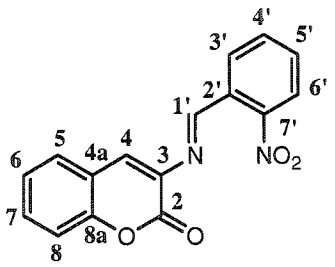
(*E*)-3-[(3-Nitrobenzylidene)amino]-2*H*-chromen-2-one (229)



Using general procedure 4, **212** (1.40 g, 8.7 mmol), 3-nitrobenzaldehyde (1.34 g, 8.9 mmol), 4 Å molecular sieves (~20 g), and absolute ethanol (30.0 mL) were reacted for 14 h. The clear colorless solution went to a clear dark yellow over the course of the reaction. The solvent was removed under reduced pressure, which afforded **229** (0.60 g, 1.8 mmol, 57%) as a dark yellow solid.

Mp 224-225 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 9.54 (s, 1H), 8.35 (dd, 1H, *J* = 8.5, 1.6 Hz), 8.24 (d, 1H, *J* = 7.7 Hz), 7.75 (t, 1H, *J* = 7.8 Hz), 7.60 (d, 1H, *J* = 7.7 Hz), 7.56 (td, 1H, *J* = 8.3, 1.9 Hz), 7.40 (d, 1H, *J* = 8.3 Hz), 7.34 (t, 1H, *J* = 7.4 Hz). ^{13}C NMR (126 MHz, $CDCl_3$): δ = 161.6 (1), 158.3 (0), 152.6 (0), 149.0 (0), 138.3 (0), 136.4 (1), 133.5 (0), 131.8 (1), 130.0 (1), 128.4 (1), 126.2 (1), 125.1 (1), 124.8 (1), 123.5 (1), 119.9 (0), 116.7 (1). IR (nujol, NaCl): υ_{max} = 1726 (s), 1619 (m), 1568 (w), 1522 (s), 1218 (w), 1155 (w), 1123 (w), 1083 (w), 1063 (m), 909 (w), 749 (m) cm^{-1}. MS (EI) *m/z* = (%) 294 (M^+, 13), 190.4 (4), 146 (100), 118 (3), 89 (21). HRMS *m/z* [M^+] Calcd for $C_{16}H_{10}N_2O_4$ 294.0646, found 294.0639.

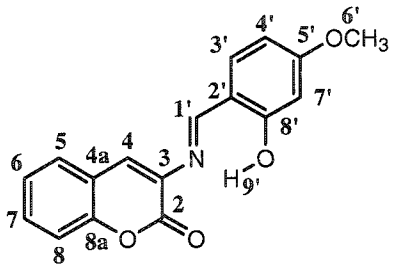
(*E*)-3-[(2-Nitrobenzylidene)amino]-2*H*-chromen-2-one (230)



Using general procedure 4, **212** (1.40 g, 8.7 mmol), 2-nitrobenzaldehyde (1.34 g, 8.9 mmol), 4 Å molecular sieves (~20 g), and absolute ethanol (30 mL) were reacted for 14 h. The clear colorless solution went to a clear dark yellow over the course of the reaction. The solvent was removed under reduced pressure, which afforded **230** (1.58 g, 5.37 mmol, 62%) as a dark yellow solid.

Mp 224-225 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 9.54 (s, 1H, H-1'), 8.29 (dd, 1H, *J* = 7.0, 1.3 Hz), 8.08 (dd, 1H, *J* = 7.8, 1.2 Hz), 7.75 (t, 1H, *J* = 7.5 Hz), 7.67-7.64 (m, 2H), 7.58-7.52 (m, 2H), 7.38 (d, 1H, *J* = 8.2 Hz), 7.32 (t, 1H, *J* = 8.0 Hz). ^{13}C NMR (126 MHz, $CDCl_3$): δ = 160.1 (1), 158.2 (0), 152.7 (0), 149.6 (0), 135.6 (0), 133.8 (1), 133.0 (1), 132.0 (1), 131.6 (1), 131.0 (0), 130.2 (1), 128.3 (1), 125.0 (1), 124.8 (1), 119.8 (0), 116.7 (1). IR (nujol, NaCl): υ_{max} = 1726 (s), 1619 (m), 1568 (w), 1522 (s), 1218 (w), 1155 (w), 1123 (w), 1083 (w), 1063 (m), 909 (w), 749 (m) cm^{-1}. MS (EI) *m/z* (%) = 294 (M^+, 8), 249 (11), 190 (7), 160 (65), 132 (100), 104 (36), 77 (24). HRMS *m/z* [M^+] Calcd for $C_{16}H_{10}N_2O_4$ 294.0639, found 294.0635.

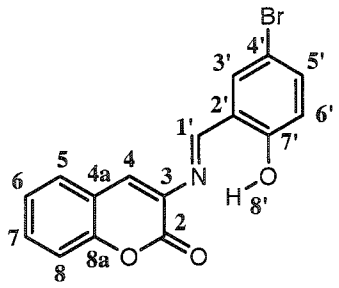
(*E*)-3-[(2-Hydroxy-4-methoxybenzylidene)amino]-2*H*-chromen-2-one (231)



Using general procedure 4, **212** (0.60 g, 3.7 mmol), 4-methoxysalicylaldehyde (0.59 g, 3.9 mmol), 4 Å molecular sieves (~20 g), and absolute ethanol (30 mL) were reacted for 14 h. The clear colorless solution went to a clear dark yellow over the course of the reaction. The solvent was removed under reduced pressure, which afforded **231** (0.35 g, 1.8 mmol, 32%) as a dark yellow solid.

Mp 195-196 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 13.40 (s, 1H, H-6'), 9.33 (s, 1H), 7.61 (s, 1H), 7.54-7.50 (m, 2H), 7.36 (d, 1H, *J* = 8.3 Hz), 7.33-7.29 (m, 2H), 6.52-6.48 (m, 2H), 3.85 (s, 3H, H-6'). ^{13}C NMR (126 MHz, $CDCl_3$): δ = 166.0 (1), 164.9 (0), 164.3 (0), 158.3 (0), 152.2 (0), 134.8 (1), 132.8 (1), 132.4 (0), 131.2 (1), 128.0 (1), 125.0 (1), 120.0 (0), 116.6 (1), 113.4 (0), 107.8 (1), 101.3 (1), 55.7 (3, C-6'). IR (nujol, NaCl): υ_{max} = 1716 (s), 1608 (m), 1554 (m), 1289 (w), 1221 (w), 1119 (m), 1074 (m), 1024 (w), 965 (w), 926 (w), 825 (w), 751 (m), 723 (w) cm^{-1}. MS (EI) *m/z* (%) = 295 (M^+, 100), 266 (4), 224 (3), 146 (58), 118 (20), 77 (7), 39 (7). HRMS *m/z* [M^+] Calcd for $C_{17}H_{13}NO_4$ 295.0843, found 295.0848.

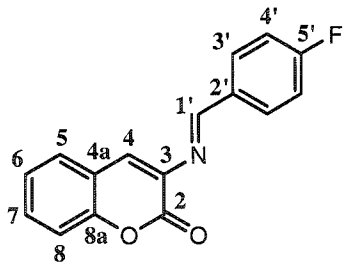
(*E*)-3-[(5-Bromo-2-hydroxybenzylidene)amino]-2*H*-chromen-2-one (232)



Using general procedure 4, **212** (0.50 g, 3.1 mmol), 5-bromo-salicylaldehyde (0.65 g, 3.3 mmol), 4 Å molecular sieves (~20 g), and absolute ethanol (30 mL) were reacted for 14 h. The clear colorless solution went to a clear bright yellow over the course of the reaction. The solvent was removed under reduced pressure, which afforded **232** (0.66 g, 1.9 mmol, 64%) as a bright yellow solid.

Mp 251-252 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 12.98 (s, 1H, H-8'), 9.47 (s, 1H, H-1'), 7.75 (s, 1H, H-4), 7.59-7.56 (m, 3H), 7.48 (dd, 1H, *J* = 8.6, 2.3 Hz), 7.40 (d, 1H, *J* = 8.8 Hz), 7.35 (td, 1H, *J* = 7.4, 1.4 Hz), 6.92 (d, 1H, *J* = 9.3 Hz). ^{13}C NMR (126 MHz, $CDCl_3$): δ = 166.1 (1), 160.6 (0), 157.9 (0), 152.5 (0), 136.7 (1), 135.5 (1), 135.4 (1), 132.1 (1), 131.3 (0), 128.4 (1), 125.2 (1), 120.9 (0), 119.6 (1), 116.7 (1), 111.0 (0), 96.3 (0). IR (nujol, KBr): υ_{max} = 3415 (w), 3154 (w), 1716 (s), 1614 (m), 1275 (s), 1170 (m), 1063 (w), 952 (w), 751 (w) cm^{-1}. MS (EI) *m/z* (%) = 343 (M^+, 50), 298 (3), 146 (100), 118 (33), 77 (16). HRMS *m/z* [M^+] Calcd for $C_{16}H_{10}BrNO_3$ 342.9843, found 342.9792.

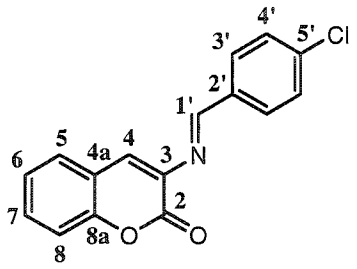
(*E*)-3-[(4-Fluorobenzylidene)amino]-2*H*-chromen-2-one (233)



Using general procedure 4, **212** (0.60 g, 3.7 mmol), 4-fluorobenzaldehyde (0.40 mL, 0.48 g, 3.3 mmol), 4 Å molecular sieves (~20 g), and absolute ethanol (30 mL) were reacted for 14 h. The clear colorless solution went to a clear pale yellow over the course of the reaction. The solvent was removed under reduced pressure, which afforded **233** (0.72 g, 1.9 mmol, 72%) as a pale yellow solid.

Mp 131-132 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 9.16 (s, 1H), 7.97-7.94 (m, 2H), 7.62 (s, 1H), 7.55-7.51 (m, 2H), 7.38 (d, 1H, J = 8.5 Hz), 7.33-7.29 (m, 2H), 7.18 (t, 1H, J = 8.3 Hz). ^{13}C NMR (126 MHz, $CDCl_3$): δ = 165.4 (0, d, $^{1}J_{C\text{-}F}$ = 253 Hz, C-5'), 162.9 (1), 158.6 (0), 152.3 (0), 135.4 (0), 132.8 (1), 132.7 (0, d, $^{4}J_{C\text{-}F}$ = 3 Hz, C-2'), 131.5 (1, d, $^{3}J_{C\text{-}F}$ = 9 Hz, C-3'), 131.1 (1), 128.0 (1), 124.9 (1), 120.2 (0), 116.6 (1), 116.2 (1, d, $^{2}J_{C\text{-}F}$ = 22 Hz). IR (nujol, KBr): υ_{max} = 1717 (s), 1210 (m), 1161 (w), 1101 (w), 1057 (m), 947 (w), 923 (w), 836 (w), 752 (s) cm^{-1}. MS (EI) *m/z* (%) = 267 (M^+, 70), 238 (14), 222 (3), 183 (7), 161 (64), 146 (100), 133 (36), 118 (28), 78 (26). HRMS *m/z* [M^+] Calcd for $C_{16}H_{10}FNO_2$ 267.0694, found 267.0701.

(*E*)-3-[(4-Chlorobenzylidene)amino]-2*H*-chromen-2-one (234)



Using general procedure 4, **212** (0.60 g, 3.7 mmol), 4-chlorobenzaldehyde (0.40 mL, 0.48 g, 3.3 mmol), 4 Å molecular sieves (~20 g), and absolute ethanol (25.0 mL) were reacted for 14 h. The clear colorless solution went to a clear pale yellow over the course of the reaction. The solvent was removed under reduced pressure, which afforded **234** (0.76 g, 1.9 mmol, 72%) as a pale yellow solid.

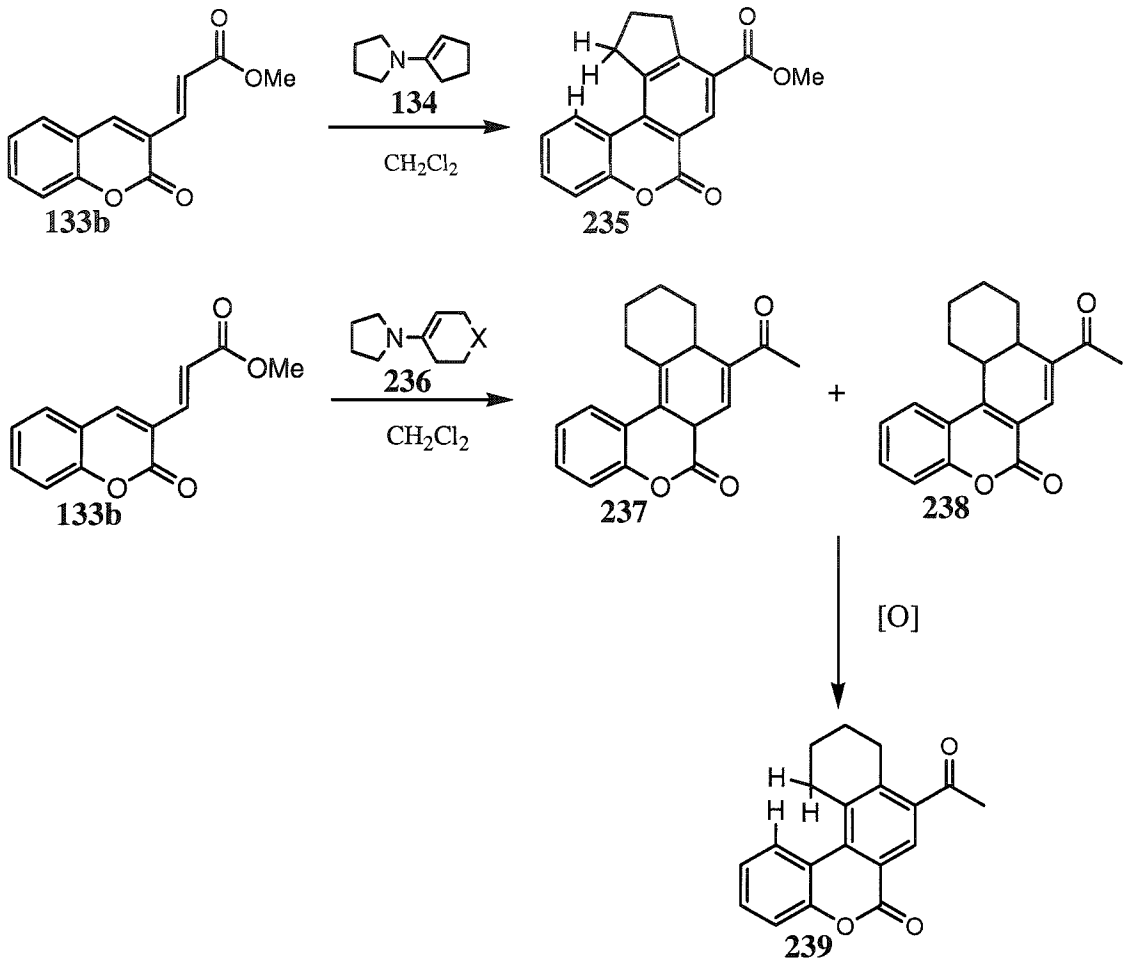
Mp 183-184 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 9.22 (s, 1H), 7.91 (d, 2H, J = 8.4 Hz), 7.67 (s, 1H), 7.58-7.53 (m, 2H), 7.49 (d, 2H, J = 9.0 Hz), 7.40 (d, 1H, J = 9.0 Hz), 7.34 (t, 1H, J = 7.0 Hz). ^{13}C NMR (126 MHz, $CDCl_3$): δ = 163.0 (1), 158.5 (0), 152.4 (0), 138.3 (0), 135.1 (0), 134.8 (0), 133.5 (1), 131.2 (1), 130.5 (1), 129.3 (1), 128.1 (1), 124.9 (1), 120.1 (0), 116.6 (1). IR (nujol, KBr): υ_{max} = 1725 (s), 1623 (m), 1586 (w), 1216 (w), 1151 (w), 1096 (m), 923 (w), 828 (w), 752 (m) cm^{-1}. MS (EI) *m/z* (%) = 283 (M^+, 43), 254 (6), 190 (2), 146 (100), 89 (38), 63 (16). HRMS *m/z* [M^+] Calcd for $C_{16}H_{10}ClNO_2$ 283.0399, found 283.0393.

Chapter 3: Results and Discussion

3.1 Attempted Inverse Electron Demand Diels-Alder Reactions of the 1-Azadienes.

Previous work in the Bodwell group resulted in the discovery that "all-carbon" diene **133b** underwent an IEDDA-driven domino reaction to give benzocoumarins. However, the use of enamines derived from six-membered ketones **236** gave a mixture of nonaromatized products **237** and **238**, which could be aromatized upon treatment with an oxidant such as DDQ. It was suggested that the reluctance of these systems to dehydrogenate resulted from more severe nonbonded interactions in **239** compared to **235** (Scheme 3.1).[1]

[1] Pottie, I. *Thesis,* The Memorial University of Newfoundland, **2002**.

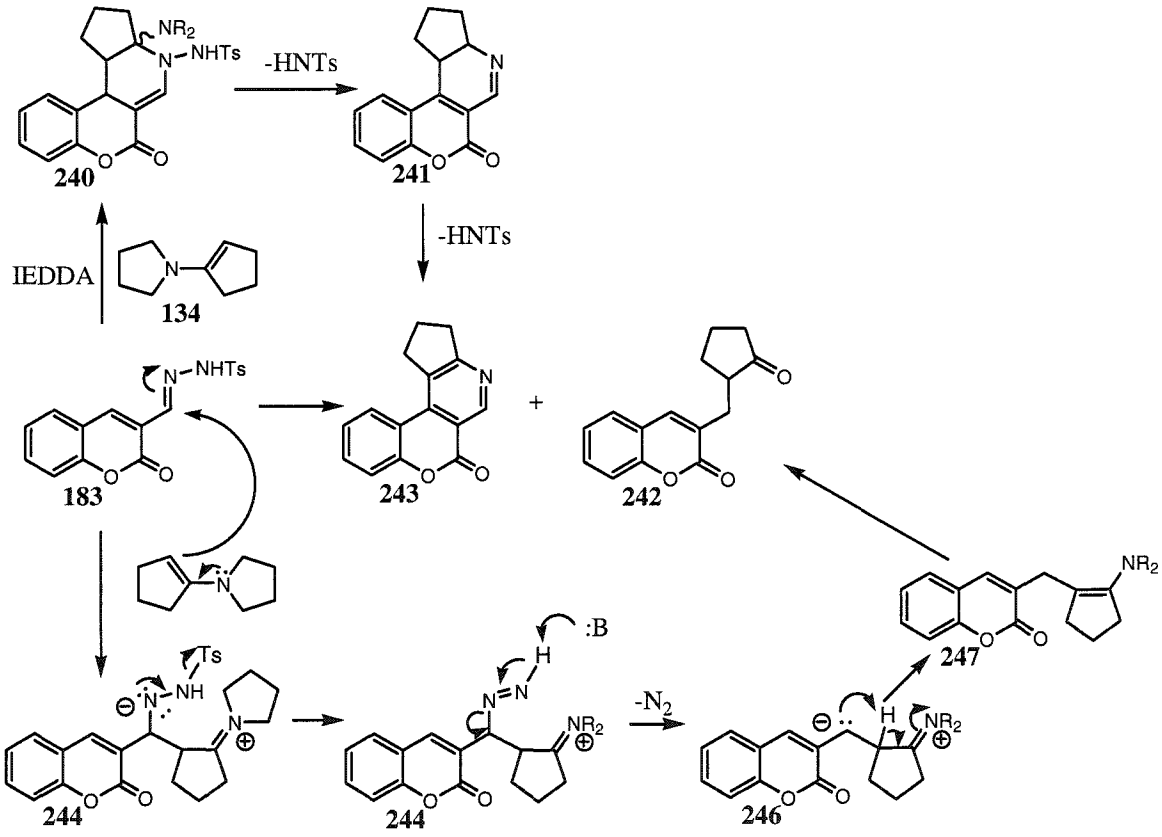


Scheme 3.1

The enamine derived from cyclopentanone and pyrrolidine was selected for initial studies of the IEDDA chemistry of the 1-azadienes. Not only is this enamine easily prepared and stable, but also it had been found to react reliably with other electron deficient dienes prepared previously in the Bodwell group.

Diene **183** reacted with enamine **134** to afford ketone **242** (37%), and the desired pyridocoumarin **243**, but only in 1% yield (Scheme 3.2). The formation of **243** can be explained by an IEDDA reaction between **183** and **134** to afford adduct **240**, followed by

successive elimination of *p*-toluenesulfonamide and pyrrolidine. It seems more likely that the elimination of *p*-toluenesulfonamide would occur first because it not only involves a more acidic proton and a better leaving group, but also leads to restoration of the partial aromaticity of the pyrene ring. Despite the very poor yield, the formation of **243** was an encouraging result (Scheme 3.2).

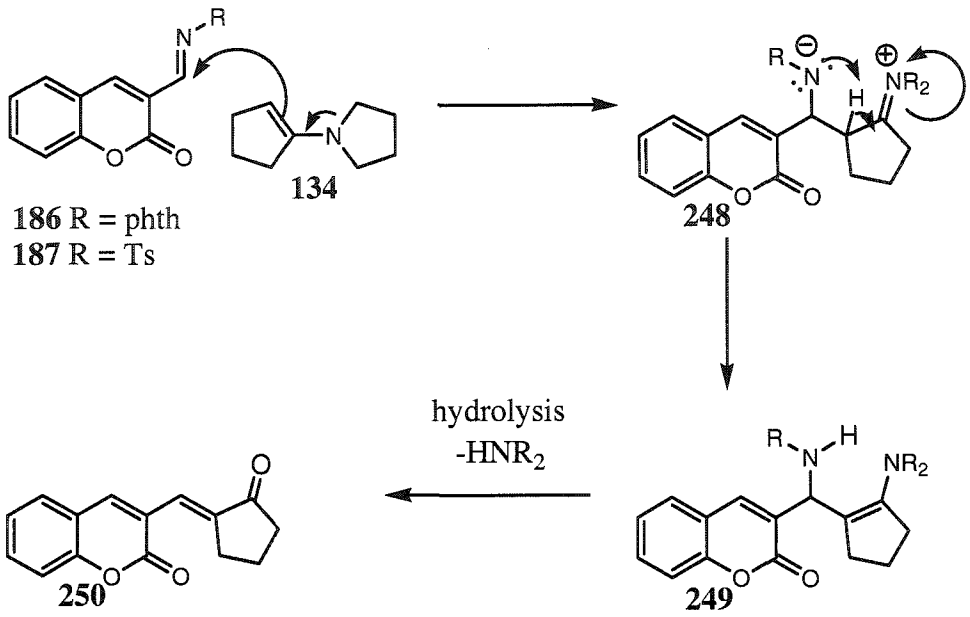


Scheme 3.2

The formation of **242** can be rationalized by an initial 1,2-addition of the enamine **134** to the imine unit of **183**. The resulting adduct **244** can expel the conjugate base of *p*-tolenesulfonamide to afford **245**, which can collapse to zwitterions **246** with the loss of

N_2. A 1,2 H-shift (or some other process) could then give **247**, hydrolysis of which provides the observed product **242**. Other plausible mechanisms to account for the formation of A can be postulated, but the lack of information about the nature of the intermediates renders this discussion academic. The key conclusion of this experiment is that the introduction of the nitrogen atom into the diene system has brought with it a 1,2-imine addition pathway that can compete with the desired cycloaddition (concerted) or stepwise (1,4-addition) pathway (Scheme 3.2).

An important feature of diene **183** is that the substituent on the diene nitrogen atom (NHTs) is not very electron withdrawing, if at all. This being the case, it was hoped that dienes **186** and **187**, which have electron-withdrawing N-substituents (phth and tosyl, respectively) would result in the formation of greater proportions of the pyridocouamrin product **243**. However, this was not the case. Both dienes reacted to afford α,β-unsaturated ketone **250** in moderate to good yield (Scheme 3.3). No trace of **243** was observed in either reaction. This product **250** also appears to be the end result of 1,2 addition to the imine moiety of **186** or **187**. Formation of this product can be explained via a intramolecular (or intermolecular) proton transfer in zwitterionic intermediate **246** affords enamine **247**. Hydrolysis and elimination of RNH_2 provide the observed product **250**. Interestingly, this is the product of an aldol condensation between cylcopentanone and 3-formylcoumarin, which are the direct precursors of **186** and **187**. The double bond geometry of **250** was established unambiguously by ^1H NOE experiments.

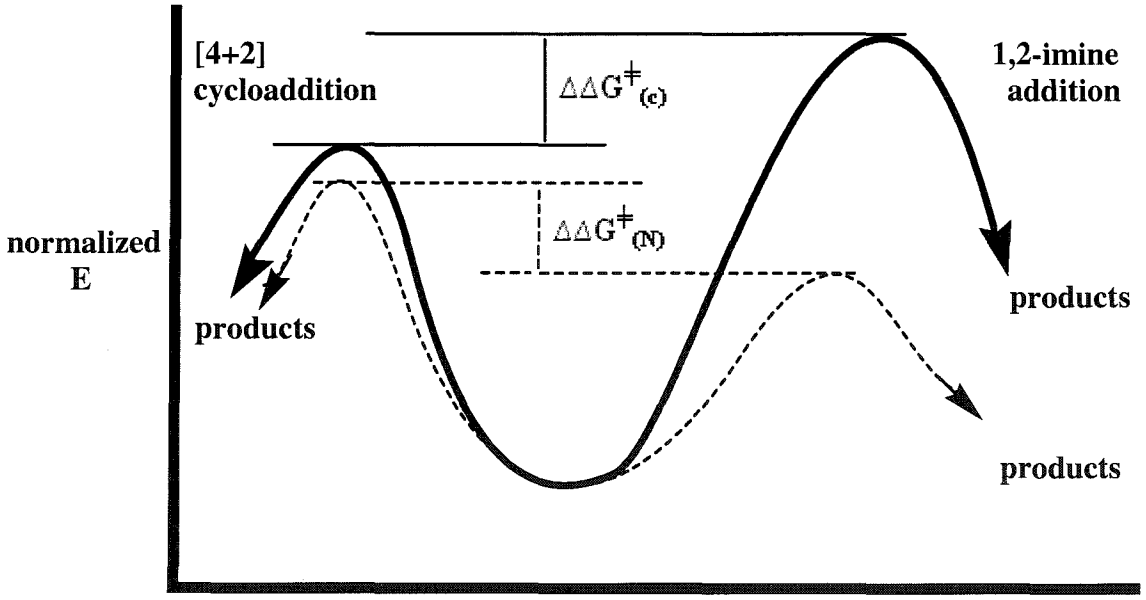


Scheme 3.3

The reactions of dienes **182**, **184**, **185**, **188**, **190**, **207**, **208**, and **210** with enamine **134** resulted in the complete consumption of the dienes, but no pure products could be isolated (except in the case of diene **185** where >95% of the diene was isolated). The low reactivity **185** is likely due to the dimethylamino group, which is very electron donating. The ^{1}H NMR spectra of the crude reaction mixtures indicated that complex mixtures had formed.

The observation that Ian Pottie's diene **133b** undergoes 1,4-addition, but the 1-azadienes described above undergo 1,2-addition can be explained using the energy profiles presented in Figure 3.1. Presumably, both systems can react either in a 1,2 or a 1,4 sense. In the case of all-carbon **133b**, its behavior suggests that $\Delta G^{\ddagger}$ for reaction in a 1,2-fashion is significantly higher than that for reaction in a 1,4-fashion. The replacement

of carbon with nitrogen at the 1-position would thus appear to have the effect of reversing the relative heights of the energy barriers for the two processes. The introduction of a nitrogen atom at the 1-position surely lowers the energy barrier to the desired 1,4-addition, but had the unforeseen effect of lowering the energy barrier to 1,2-addition to a much greater extent. The isolation of trace amount of desired product **243** supports the notion of such a competition. If only from an intuitive perspective, the presence of an electron deficient imine unit (as opposed to a Michael acceptor) in the side chain of the 1-azadiene also appears to be consistent with the above argument.



C = diene **133b**
N = 1-azadienes

Figure 3.1

In an attempt to block 1,2-addition of the dienophile to the imine unit in **207**, dienes **208** (which is known to react with ethyl vinyl ether and diethyl ketene acetal)[2] and **188** were reacted with enamine **134**. Disappointingly, these reactions also resulted in the formation of complex mixtures. In light of the very discouraging results with the 1-azadienes, work in this area was suspended.

The reason(s) why the 1-azadienes do not react in the desired fashion are not immediately obvious. Diels-Alder reactivity has been linked to the HOMO-LUMO gap between the reacting species, but this does not appear to be relevant here. Calculated (AM1) HOMO and LUMO energies of dienes **158**, **187**, **251**, **252** and dienophiles **58** and **134** are presented in Table 3.1 along with the respective HOMO-LUMO gaps. Looking at the HOMO-LUMO gaps there is little differences between the all-carbon and nitrogen containing 1-azadienes. This would seem to lend credence to the scenario proposed in Figure 3.1, in which the IEDDA reactions of **251** and **252** are shown to be nearly degenerate. However, this situation is severely more complicated than the simple HOMO-LUMO based argument would suggest. According to the calculated HOMO-LUMO gaps, **251** and **158** should be equally reactive towards ethyl vinyl ether. In fact **133b** (the methyl ester of **251**) was found to be unreactive toward ethyl vinyl ether at 140 °C, whereas **158** was reported to react with ethyl vinyl ether at in a sealed tube at 100 °C with the vinyl ether dissolved in dioxane under 12 kbar of pressure.[2]

---

[2] a) Boger, D. L.; Corbett, W. L.; Curran, T. T.; Kasper, A. M. *J. Am. Chem. Soc.* **1991**, *113*, 1713-1729. b) Boger, D. L.; Kasper, A. M. *J. Am. Chem. Soc.* **1989**, *111*, 1517-1519.

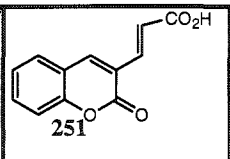
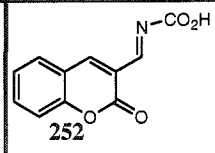
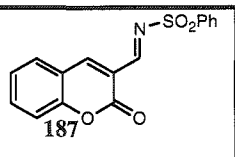
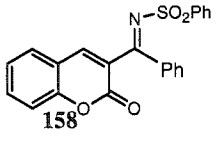
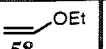
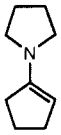
	 251 LUMO = -1.62 eV	 252 LUMO = -1.68 eV	 187 LUMO = -1.89 eV	 158 LUMO = -1.64 eV
 58 HOMO = -9.36 eV	7.74	7.68	7.47	7.72
 134 HOMO = -8.06 eV	6.44	6.38	6.17	6.42

Table 3.1 - Calculated HOMO-LUMO gaps (eV) for selected 1-azadienes and dienophiles 58 and 134.

Another consideration is the accessibility of the *s-cis* conformation of the 1-azadiene. Access to the *s-cis* conformation is requirement for the Diels-Alder reaction to occur. AM1 calculations indicates that the 1-azadiene is 3.3 kcal/mol higher in energy than the corresponding *s-trans* conformers, so the reactive *s-cis* conformer would be expected to predominate. By comparison, the *s-cis* and s-*trans* conformers of **251** were calculated to be roughly equal energy. An unfavorable dipole-dipole interaction in s-*trans* **252** can be used to explain why this conformer is disfavored. The large dihedral angle (45.1 ° compared to 0 ° for s-*cis*) is consistent with this explanation. (Table 3.2).

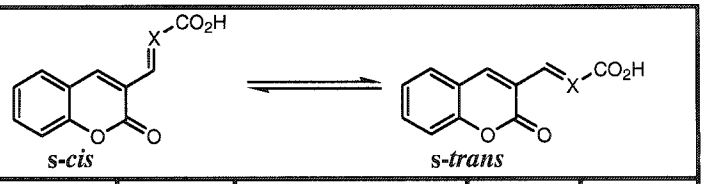
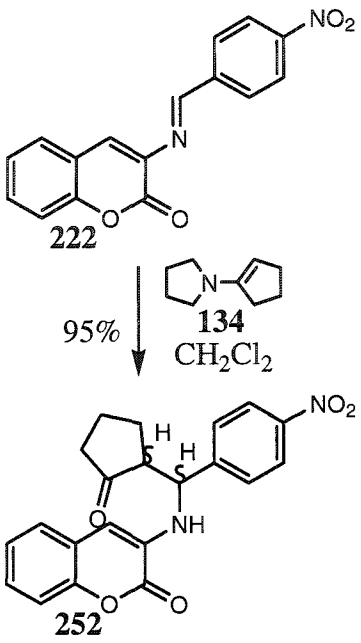
					
	s-*cis*			s-*trans*	
	X = N (251)	X = CH (251)		X = N (252)	X = CH (251)
ΔH_f° (kcal/mol)	-88.93	-105.8		-85.62	-105.7
dihedreal angle	-0.3	178.5		-45.1	178.9

Table 3.2 – Calculated heats of formation and dihedral angles for s-*cis* and s-*trans* conformers of selected dienes and 1-azadienes.

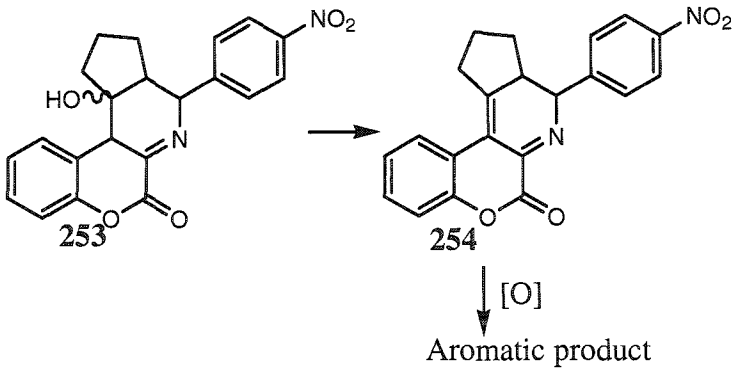
3.1 Attempted Inverse Electron Demand Diels-Alder Reactions Using the 2-Azadienes.

Subjection of 2-azadiene **222** to reaction with enamine **134** under the same conditions employed for the reactions with the 1-azadienes also resulted in 1,2-addition. In this case, however, ketone **252** was obtained in 95% yield as a 2 : 1 mixture of diastereomers (Scheme 3.4). No other products were isolated. The two diastereomers were not separable and no attempts were made to assign their relative stereochemistries. The apparent 1,2-addition can be explained in the same way as those to the 1-azadienes.



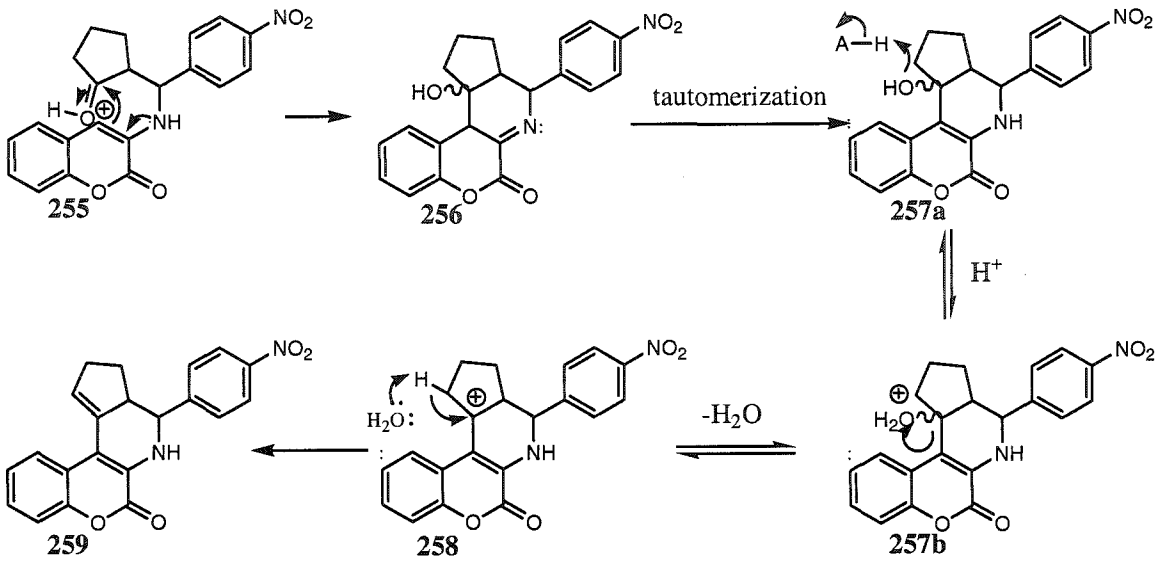
Scheme 3.4

Not only was the excellent yield of **252** encouraging, but there also appeared to be the possibility for a "plan B" ring closure. An enamine (nucleophilic, albeit tempered by the C=O group of the coumarin moiety) and a ketone (electrophilic) are present. C-C bond formation between these two functional groups would lead to the formation of a six-membered ring (i.e. **253**), which was, in a sense, the goal of the reaction. The tertiary alcohol in **253** looks to be a likely candidate for elimination, which would be a useful step in the direction of aromatization, which is another objective of the chemistry (Scheme 3.5).

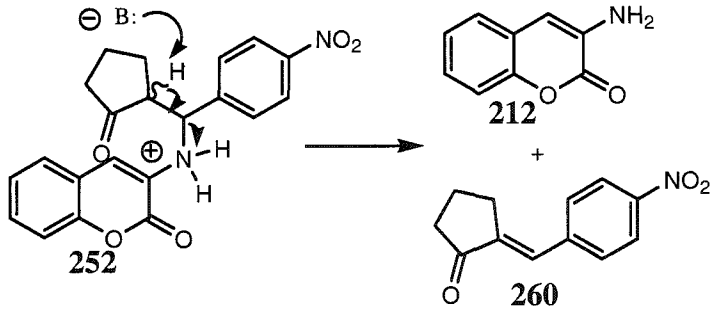


Scheme 3.5

Several attempts were made to induce **252** to undergo ring closure. The use of oxophilic Lewis acids (10 mol % $AlCl_3$, $BiCl_3$, and $Yb(OTf)_3$) resulted in no reaction either at room temperature or at reflux in tetralin. The use of the protic acid catalyst *p*-TsOH (10 mol %) at reflux in dichloromethane gave rise to the formation of three new products **259** (15%), **212** (56%), and **260** (85%) (Scheme 3.6 and Scheme 3.7). The most interesting product **259** was tentatively assigned on the basis of its mass spectrum, NOE and various 2-dimensional NMR experiments. Due to some ambiguity, a conclusive assignment could not be made. A proposed mechanism for the formation of **259** is given in Scheme 3.6. The other two products were 3-aminocoumarin **212** and α,β-unsaturated ketone **260**. An acid-catalyzed elimination mechanism can account for the formation of these products (Scheme 3.7 and Scheme 3.8).



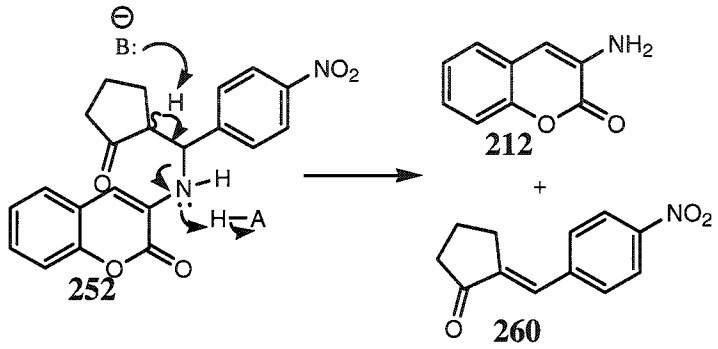
Scheme 3.6



Scheme 3.7

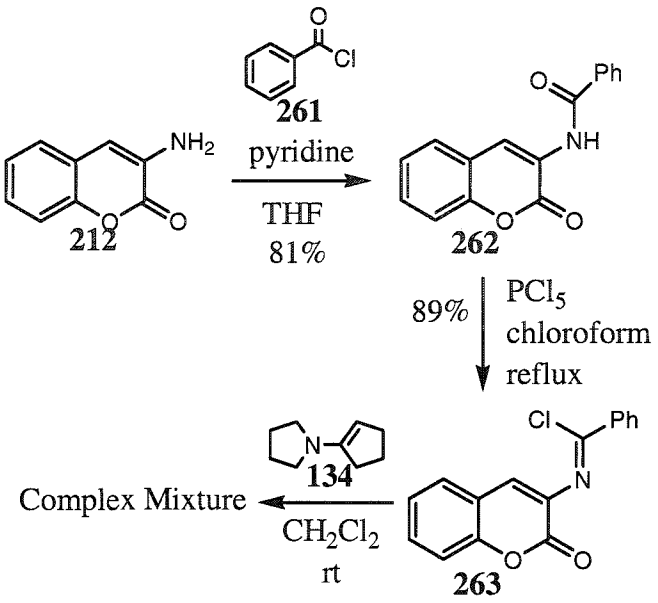
An attempt to bring about cyclization under basic conditions (NaH/THF) gave only 3-aminocoumarin **212** and elimination product **260** as observed from ^{1}H NMR. Simply heating **252** in toluene was also investigated, but, although this led to the

complete consumption of the starting material, 3-aminocoumarin **212** was the only product isolated. None of the elimination product **260** was observed.



Scheme 3.8

In an attempt to disfavor 1,2-addition, chloroimine **263** was synthesized from amide **262**, which was prepared from 3-aminocoumarin and benzoyl chloride followed by treatment with PCl_5 (84% 2 steps) (Scheme 3.9). However, reaction of **263** with enamine **134** led to the formation of a complex mixture.



Scheme 3.9

The situation for the 2-azadienes is similar to that of the 1-azadienes. As with the 1-azadienes, the calculated HOMO-LUMO gaps for the 2-azadienes show no clear trends. However, the s-*trans* conformer of **222** is now calculated to be lower in energy (by 3.2 kcal/mol) than the corresponding s-*cis* conformer. An unfavorable alignment of the dipoles in s-*cis* can be invoked to explain this preference.

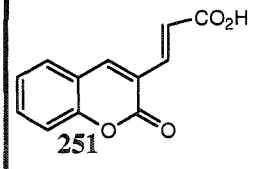
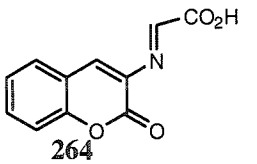
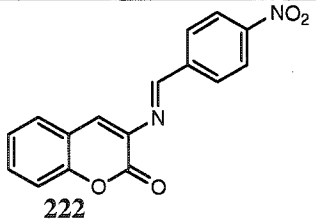
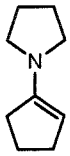
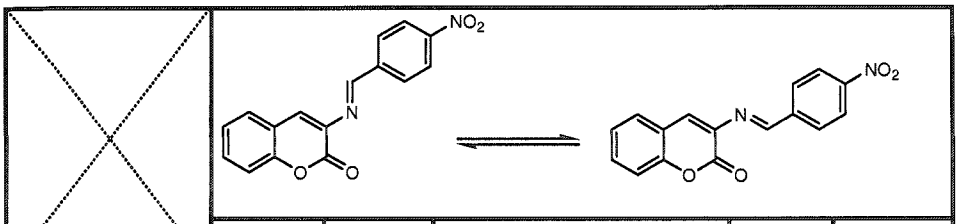
	 251 LUMO = -1.62 eV	 264 LUMO = -1.64 eV	 222 LUMO = -1.80 eV
 58 HOMO = -9.36 eV	7.74	7.72	7.56
 134 HOMO = -8.06 eV	6.44	6.42	6.26

Table 3.3 – Calculated HOMO-LUMO gaps (eV) for selected 2-azadienes and dienophiles 58 and 134.

Again, the other consideration is the accessibility of the *s-cis* conformation of the 2-azadiene. The s-*cis* conformation is an essential requirement for the Diels-Alder reaction to occur. AM1 calculations suggested that the 2-azadiene **222** is 3.2 kcal/mol more stable in the *s-trans* conformation than it is the desired *s-cis* conformation. However this energy difference is small enough for an appreciable proportion of the *s-cis* conformer to be present in solution. The *s-cis* confomer of all carbon diene **251** was calculated to be 0.4 kcal/mol lower in energy that the corresponding *s-trans* confomer. Evidently, the presence of the N atom serves to disfavor the *s-cis* conformation.



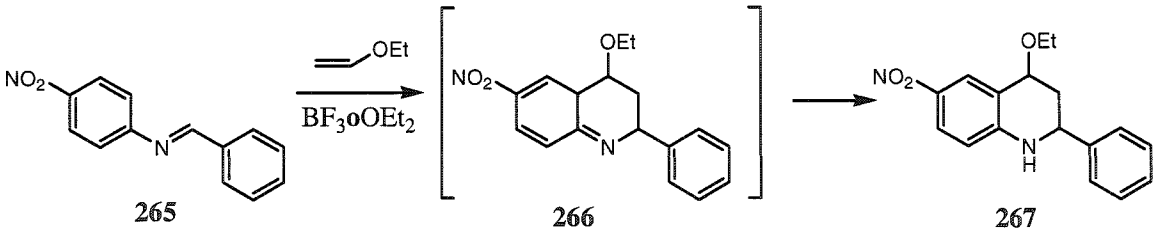
	X = N	X = CH		X = N	X = CH
ΔH_f° (kcal/mol)	-88.93	11.8		-85.62	12.2
dihedral angle	-0.3	178.5		-45.1	179

Table 3.4 – Calculated heats of formation and dihedral angles for s-*cis* and s-*trans* conformers of selected dienes and 2-azadienes.

3.2 The Povarov Reaction

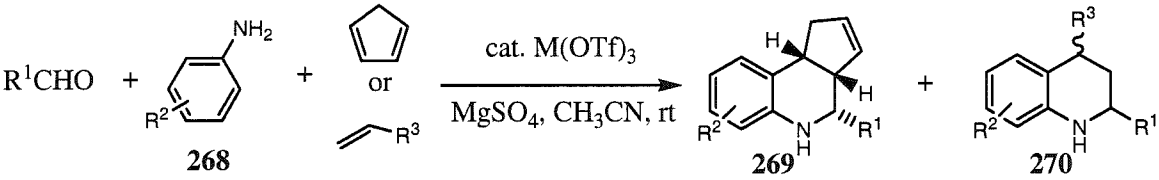
Benzannulated 2-azadienes are known to undergo Lewis acid-catalyzed IEDDA reactions to give reduced quinolines. In recognition of the pioneering work of Povarov in this area,[3] such reactions have been referred to as the Povarov reaction. A typical example is the reaction between imine **265**, which is the condensation product of aniline and 4-nitrobenzaldehyde, and ethyl vinyl ether in the presence of $BF_3{\cdot}OEt_2$ (Scheme 3.10). This presumably affords adduct **266**, tantomerism of which restores the aromaticity of an aromatic sextet and delivers the observed product **267**.

[3] Povarov, L. S. *Russ. Chem. Rev.* **1967**, *36*, 656-670.



Scheme 3.10

The Nagayama group demonstrated that other Lewis acids, e.g. $M(OTf)_3$, $Sc(OTf)_3$, and $Yb(OTf)_3$, effectively catalyzed the Povarov reaction and the azadiene (the imine) could be formed *in situ* (Scheme 3.11).[4] The latter development rendered the Povarov reaction a three-component reaction. A broad range of reduced quinolines has been prepared using the Povarov reaction.[5]



Scheme 3.11

Since reduced quinolines are present in a wide variety of natural products, the Povarov reaction seems well suited to natural product synthesis. One particular elegant

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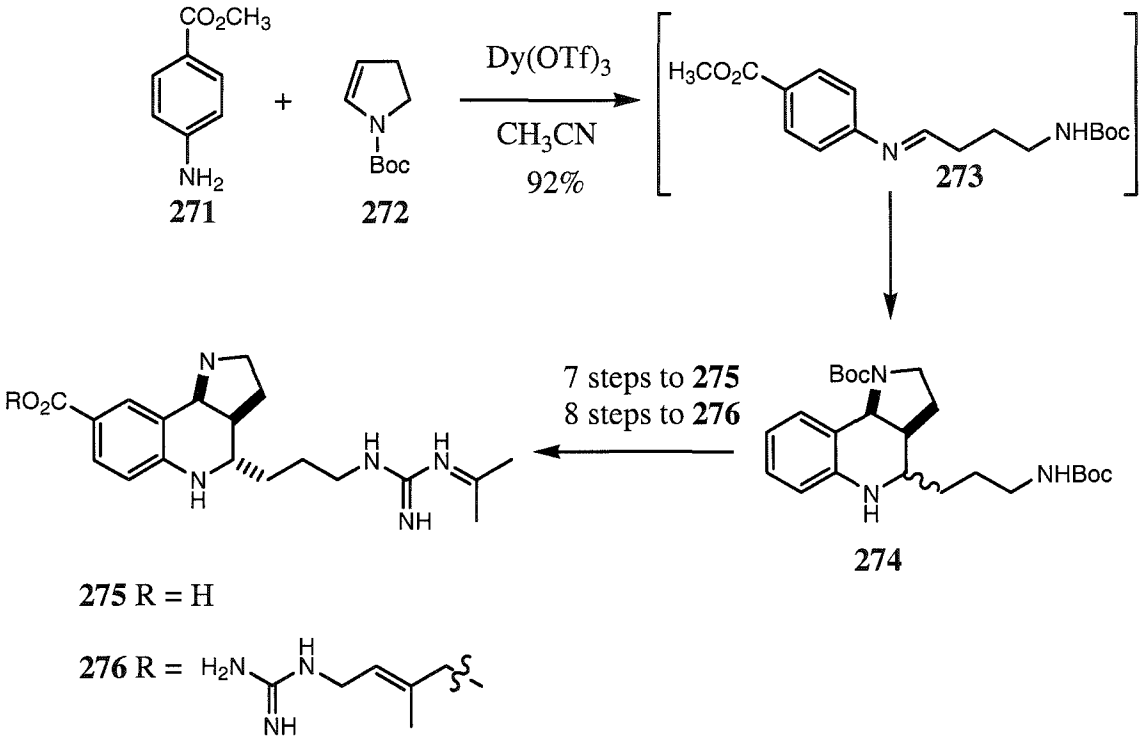
[4] a) Kobayashi, S.; Ishitani, H.; Nagayama, S. *Chem. Lett.* **1995**, 423-424. b) Kobayashi, S.; Ishitani, H.; Nagayama, S. *Synthesis* **1995**, 1195-1202. c) Kobayashi, S.; Nagayama, S. *J. Am. Chem. Soc.* **1996**, *118*, 8977-8978.

[5] Nomura, Y.; Kimura, M.; Takeuchi, Y. and Tomoda, S. *Chem. Lett.* **1978**, 267-270. b) Kametani, T.; Takeda, H.; Suzuki, Y.; Honda, T. *Syn. Commun.* **1985**, *15*, 499-505. c) Suzuki, Y.; Honda, T. *J. Heterocycloc Chem.* **1986**, *23*, 185-187. d) Lucchini, V.; Prato, M.; Scorrano, G.; Stivanello, M. *J. Chem. Soc. Prekin Trans 2* **1992**, 259-266.

example is Batey's syntheses of martinelline and martinellic acid (Scheme 3.12).[6] The key step of both syntheses was a $Dy(OTf)_3$-catalysed three-component Povarov reaction between aniline **271** and dihydropyrrole **272**, which functioned both as the aldehyde component and the dienophile (Scheme 3.12).

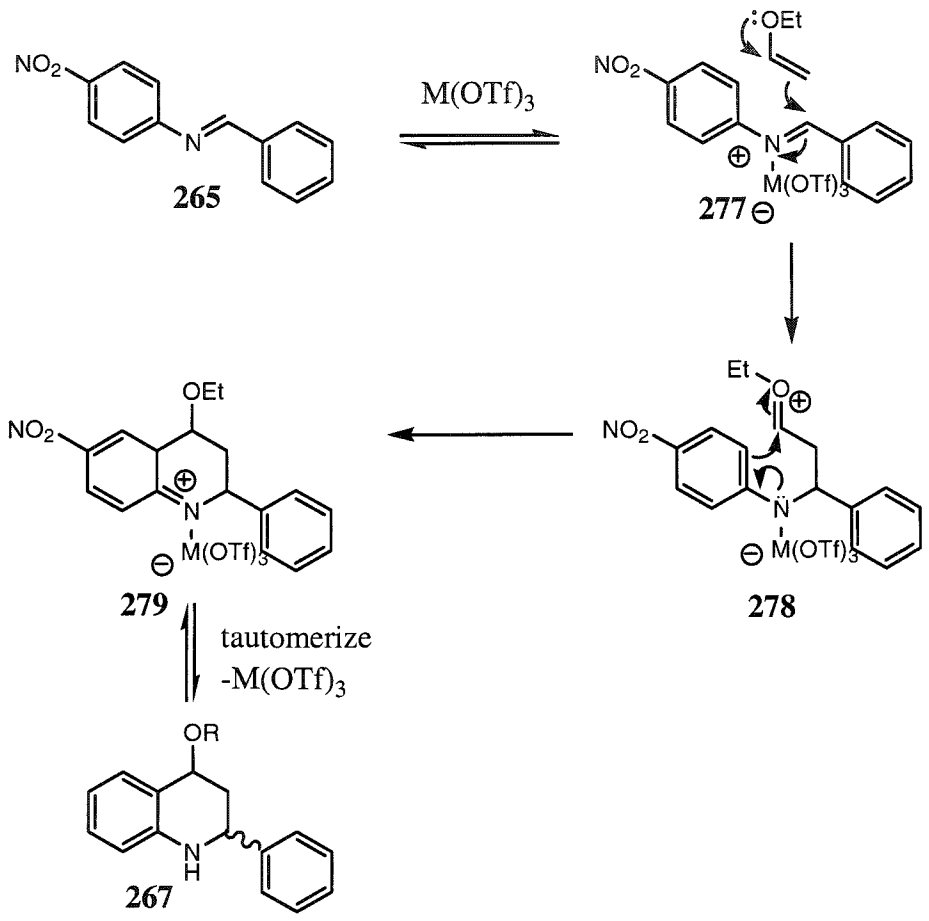


Scheme 3.12

Mechanistically, the Povarov reaction could proceed by a concerted asynchronous pathway, or by a two-step mechanism (See. Chapter.1 p. 10, Figure 1.1) (Scheme 3.13).

[6] a) Powell, D. A.; Batey, R. A. *Org. Lett.* **2002**, *4*, 2913-2916. b) Batey, R. A.; Simonic, P. D.; Lin, D.; Smyj, R. P. Lough, A. J. Chem. Comm. **1999**, 651-652.

There does not appear to be any conclusive evidence in the literature to support or refute either of these possible mechanisms.

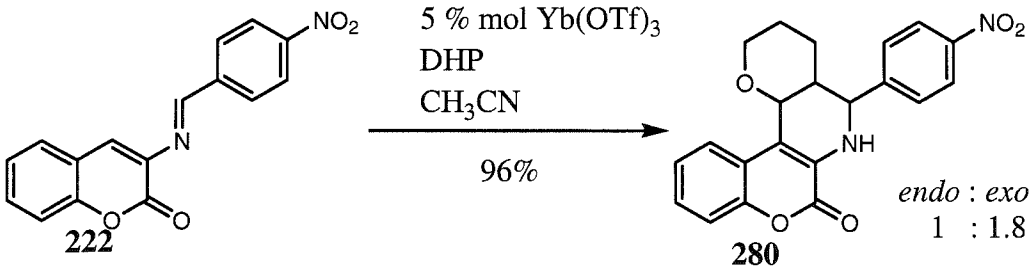


Scheme 3.13

3.3 Application of the Povarov reaction to 2-azadienes.

The similarity in structure between the 2-azadienes described in Chapter 2, e.g. **222**, and typical Povarov dienes, e.g. **265**, prompted the investigation of using Povarov

conditions to achieve cycloadditions of the 2-azadienes. $Yb(OTf)_3$ was chosen as the Lewis acid and general reaction conditions described by the Batey group[4b] were chosen for initial studies. Enamines are conspicuously absent as dienophile for the Povarov reaction, so 2,3-dihydo-2*H*-pyran (DHP) was chosen as the dienophile. Thus the reaction of diene **222** with DHP in the presence of $Yb(OTf)_3$ afforded adduct **280** as a mixture of two diastereomers in a ratio of 1 : 1.8. The combined yield was 96% (Scheme 3.14). Concerns that the partial aromaticity of the pyrone ring would not provide enough of an incentive for the tautomerization step were apparently unfounded.



Scheme 3.14

The two diastereomers were formally the products of *endo* and *exo* addition in an IEDDA reaction followed by migration of the double bond into the pyrone ring. This was determined using standard 1 and 2D NMR experiments as well as NOE experiments. The key indicators that were used to assign the relative stereochemistry of the *endo* **280a** and *exo* **280b** (and the other Povarov adducts stereochemistry below) were the magnitude of the coupling constant between H4a and H5 and the observation of an NOE between H12c and H5. In *endo* **280a** H4a and H5 are *cis* to one another and consequently will have an

approximate gauche relationship. The coupling constant is accordingly low (2.5 Hz in *endo* **280a**. Significant NOE effects (3.4% - 5.9%) were observed between each of H12c, H4a, and H5), which is consistent with an all-*cis* arrangement of these protons. The enhancement observed between H12c and H5 is only possible via a 1,3-diaxial interaction. In *exo* **280b** the coupling constant between H4a and H5 is 11.5 Hz, which is strongly indicative of a trans-diaxial arrangement. As expected, no NOE was observed between H12c and H5. However, an enhancement of 4.5% was observed between H12c and H4a (Figure 3.2). For both *endo* **280a** and *exo* **280b** (the major isomer) a small coupling constant was observed between H12c and H4a, which is consistent with a *cis* (gauche) arrangement. Although the NMR based assignments of the relative stereochemistry were quite compelling, attempts to grow crystals of both diastereomers of **280** were performed, but these did not provide crystals of sufficient quality for X-ray crystallography.

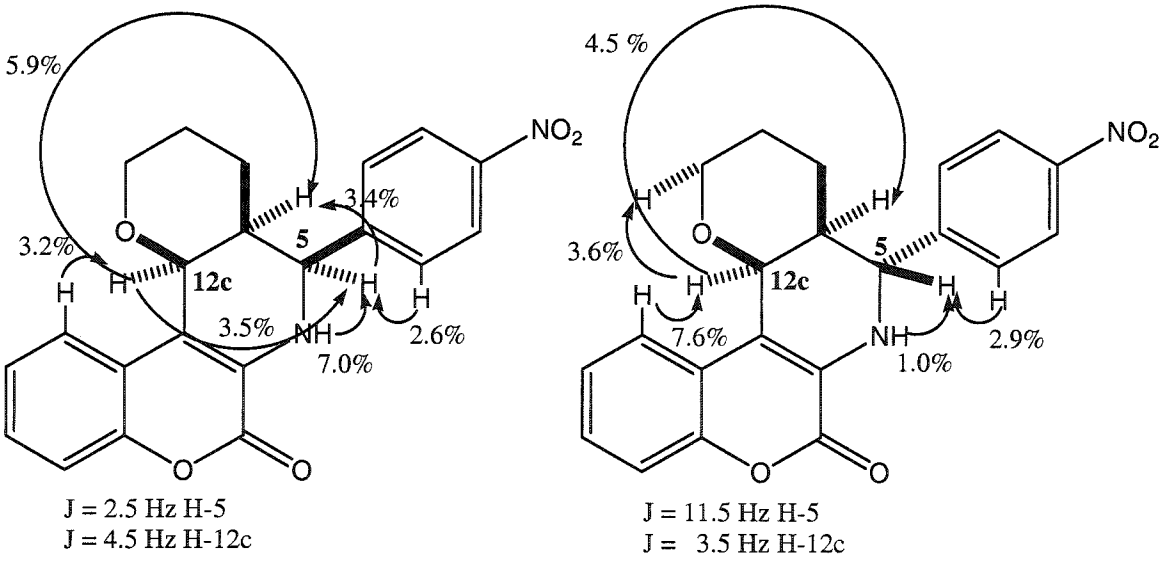


Figure 3.2

Following the successful reaction between diene **222** and DHP, a series of other dienophiles were reacted with **222** (Table 3.5). Reactions were run initially at room temperature and those that showed no signs of progress after several hours were heated at reflux. Those dienophiles that afforded Povarov adducts generally did so in good yield. The *exo*-adducts were generally preferred, with the exceptions of the reactions of indene, 4-bromostyrene, and acenaphthylene, which gave *endo* adducts with high selectivity (>95: 5). Assuming that the NMR-based assignments are correct, the anomalous selectivity of these reactions is surprising. No obvious explanation for the reversal in selectivity is apparent.

The identification of *endo* and *exo* diastereomers was accomplished using the NMR techniques described above. Some consistent chemical shift differences between *endo* and *exo* isomers were also observed, which on occasion also proved to be helpful in assigning the relative stereochemistry. Tabulated NMR data for all Povarov adducts are present in Appendix (Table A.1, Table A.2).

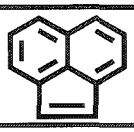
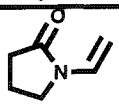
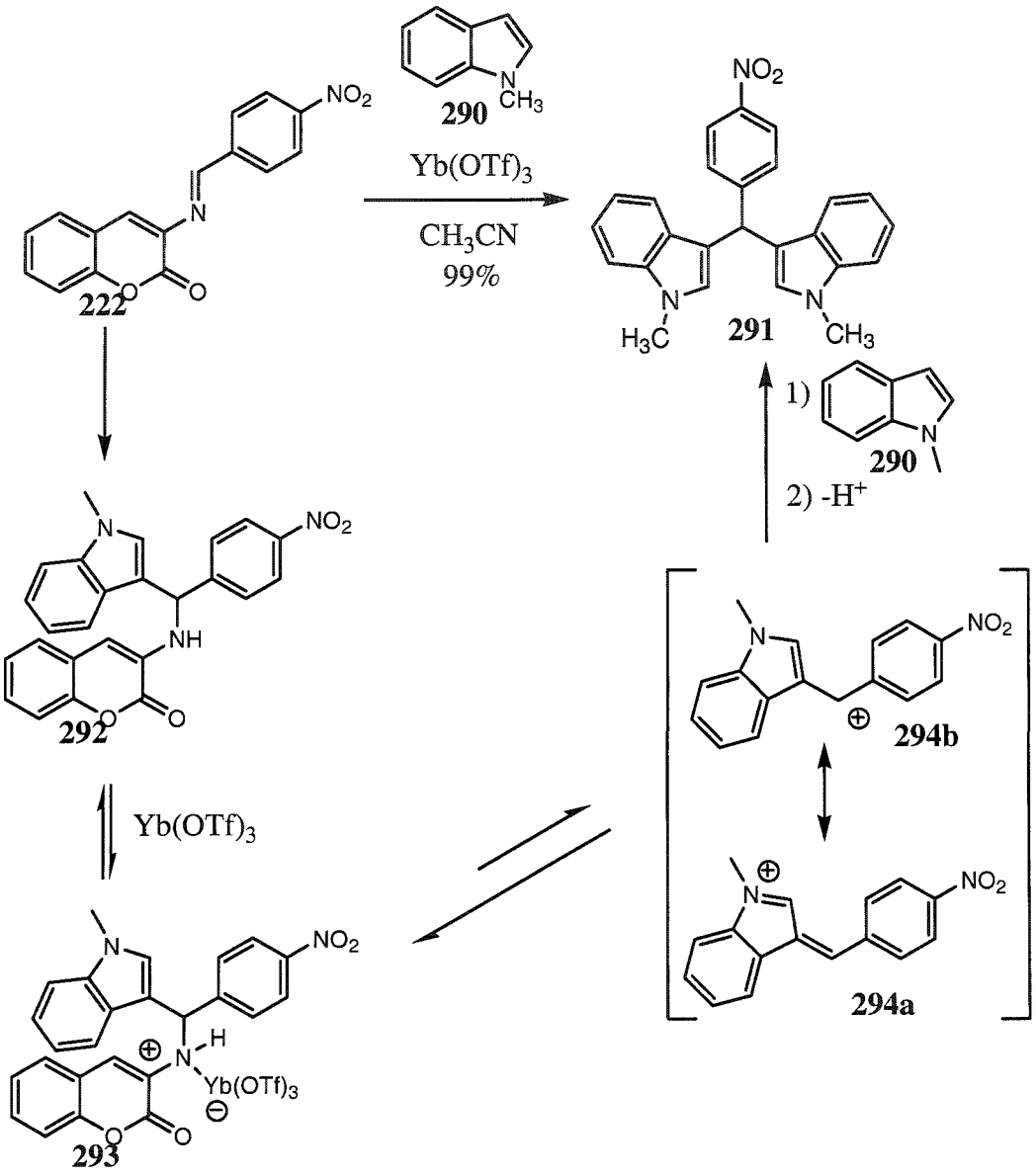
Dienophile	Rxn Time	Yield	*endo* : exo	Dienophile	Rxn Time	Yield	*endo* : exo
	20 min	90	1 : 1.8 (280a : 280b)		4.5 h	82	1 : 11.8 (285a : 285b)
	10 min	72	1 : 1.3 (281a : 281b)		18 h	61	>95 : 5 (286)
	8 h reflux	85	>95 : 5 (282)		5 min reflux	82	>95 : 5 (287)
	7 h reflux	61	1 : 3 (283a : 283b)		20 min	82	3 : 1 (288a : 288b)
	60 min	81	1.8 : 1 (284a : 284b)		25 min	76	1 : 1.7 (289a : 289b)

Table 3.5 – Dienophiles that reacted successfully with diene 222.

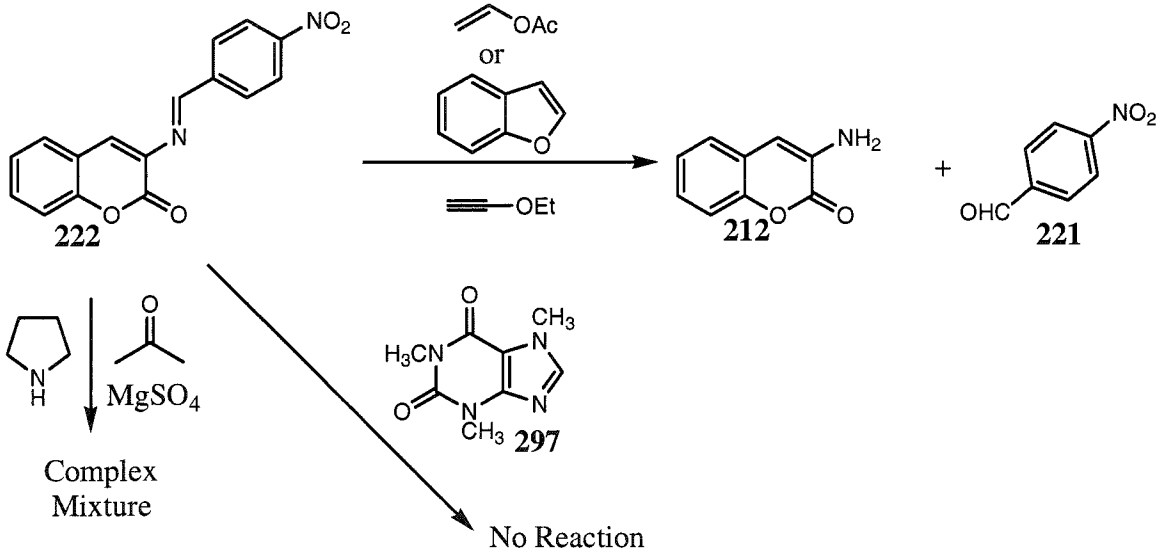
Several dienophiles that were reacted with **222** did not provide Povarov adducts. The reaction with 1-methylindole proceeded very quickly to afford **291** (99%), which consists of the aldehyde-desired portion of azadienes **222** and two units of the dienophile (Scheme 3.15). Surprisingly, the coumarin portion of **222** was not present in the product (1,2-addition of 1-methylindole to diene **222** would afford **292**). Lewis acid-catalyzed S_N1 reaction of **292** with another equivalent of 1-methylindole leads to the observed product **291** via **293** and donor/acceptor-stabilized diarylcation **294**.



Scheme 3.15

Curiously, the reactions between diene **222** and each of the dienophiles vinyl acetate, 2,3-benzofuran and ethyl ethynyl ether led to the formation of 3-aminocoumarin and 4-nitrobenzaldehyde, i.e. hydrolysis of azadiene **222** (Scheme 3.16). The reactions were monitored by tlc and ^{1}H NMR until the diene was consumed. The reason(s) why the

Povarov reaction does not occur and the mechanism by which hydrolyse take place are not immediately obvious. *In situ* generation of the dienophile 1-(2-propenyl)pyrrolidine from the reaction of acetone and pyrrolidine (a tactic that has been used successfully with diene **140**[7]) led to the formation of a complex mixture. Again, enamines appear to be unsuitable dienophiles for the azadienes of interest. Finally, the attempted reaction of diene **222** with caffeine did not proceed to any appreciable extent after 7 hours at reflux.

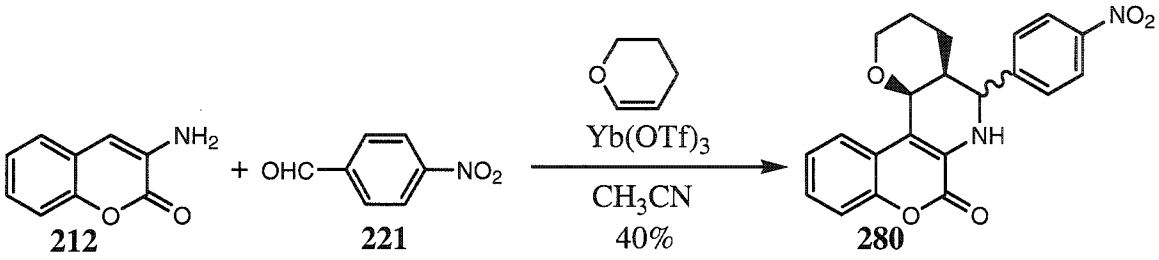


Scheme 3.16

The possibility of performing three-component Povarov reactions, i.e. generating the azadiene **222** *in situ*, was then investigated. Reaction of 3-aminocoumarin **212**, benzaldehyde **221** and DHP gave adduct **280** with a similar ratio to that observed in the

[7] Bodwell, G.; Hawco, K. The Memorial University of Newfoundland, *Unpublished Results*.

reaction of diene **222** with DHP (Scheme 3.17). However, the yield was only 40%, which compares quite unfavorable to the 90% yield obtained with the preformed diene **222**.



212 **221** **280**

Scheme 3.17

Variation of the aldehyde component was investigated (Table 3.6). The use of 4-acetoxybenzaldehyde proved to be successful in reactions with 3-aminocoumarin and both DHP and DHF. The yields for these reactions (55% and 30%, respectively) are comparable to those obtained using 4-nitrobenzaldehyde. Similar results were obtained using methyl 4-formylbenzoate and methyl glyoxalate.

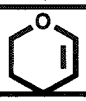
aldehyde	dienophile	endo : exo	rxn time	yield
		1 : 1.6 (280a : 280b)	24 h	40
		>95 : 5 (298)	2.5 d reflux	55
		1 : 1 (299a : 299b)	2.5 d reflux	15
		>95 : 5 (300)	7 d	31
		>95 : 5 (301)	2.5 d reflux	26

Table 3.6 – The use of different aldehydes in the three-component Povarov reaction.

Gratifyingly, X-ray quality crystals of the product that has been assigned as *exo* **299b** by NMR were obtained and its structure was determined crystallographically (Figure 3.3). This unambiguously confirmed the NMR-based assignments. The trans-diaxial relationship between H-11 and H-14 (crystallographic numbering) that was one of the key elements of the NMR-based assignments and can be seen clearly. Thus the NMR-based assignments can be viewed with a good level of confidence.

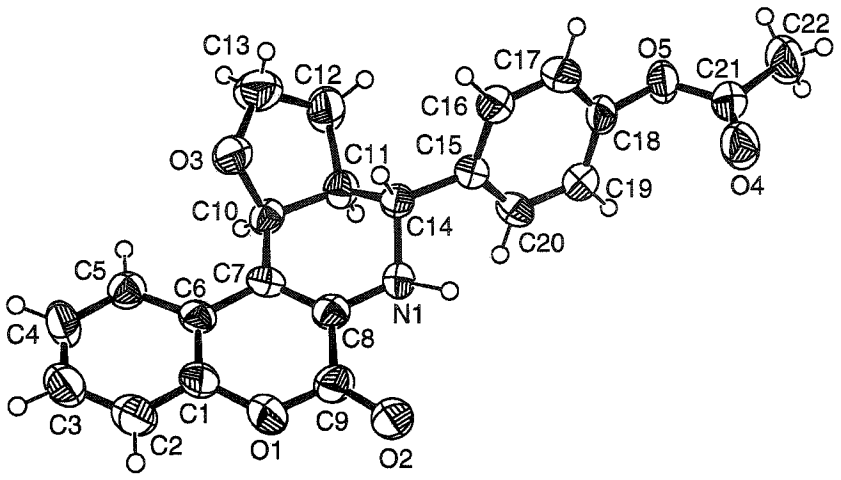
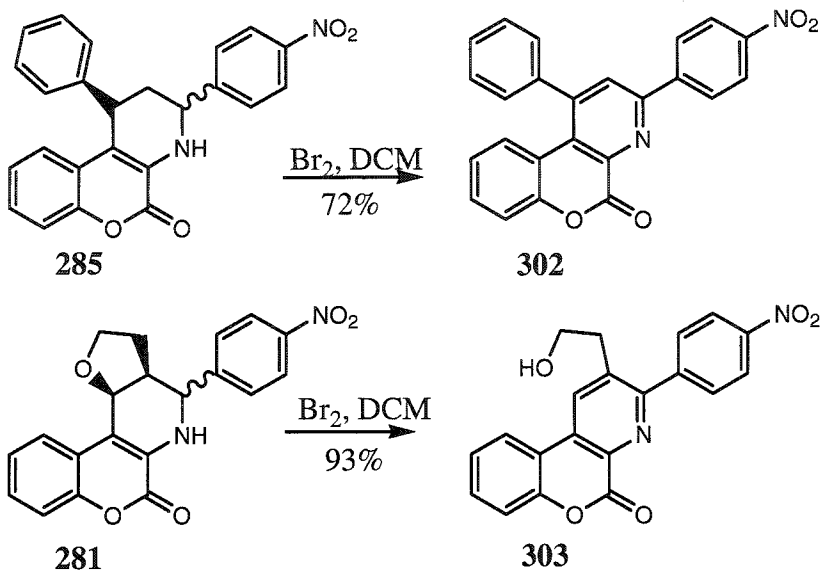
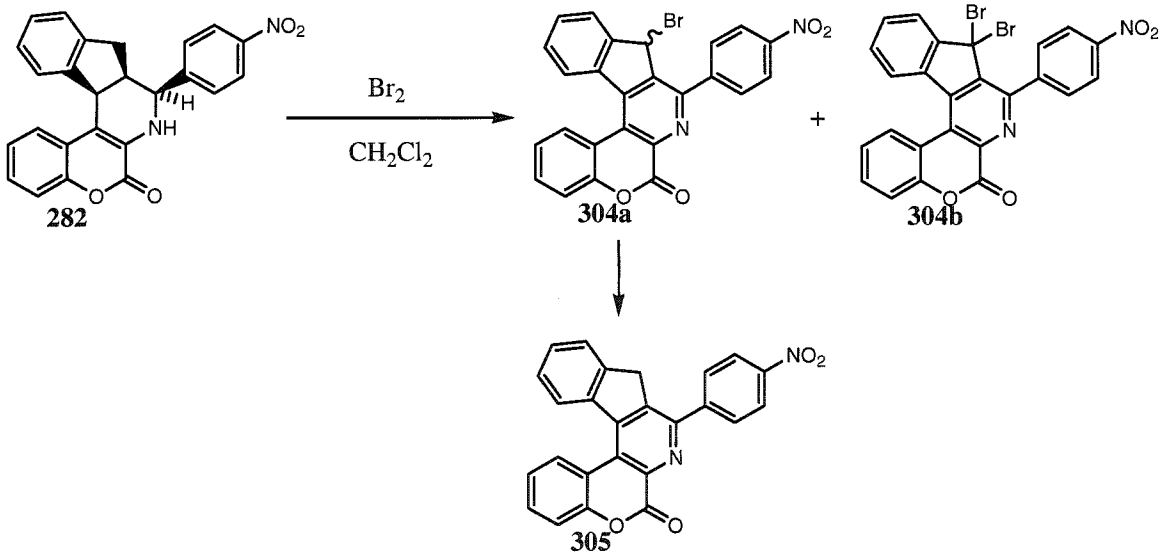


Figure 3.3 - Ortep representation of the *exo* adduct 299b. (The compound numbering is not the same as shown in the experimental section).

With the ultimate goal of this work being the generation of pyridocoumarins, attempts were made to aromatize some of the Povarov adducts. Treatment of adducts **285** and **281** produced pyridocoumarins **302** (72% yield) **303** (93% yield), respectively (Scheme 3.18). In the former case, a series of additions and eliminations reactions involving two equivalents of Br_2 leads to the observed product. In the case of **285**, the intramolecular elimination of the alcohol means that only one equivalent of Br_2 is required to bring about aromatization. Attempts to aromatize indene adduct **282** (Scheme 3.18) using Br_2 did not give the desired pyridocoumarin, but rather a mixture of several products. Attempted chromatographic separation of this mixture afforded what appears (by ^{1}H NMR) to be a mixture of brominated pyridocoumarins **304a** and **304b**. Clearly, other ways of aromatizing the Povarov adducts will have to be developed.



Scheme 3.18



Scheme 3.19

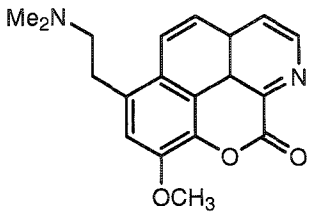
3.4 Summary and Outlook

A series of coumarin-fused 1- and 2-azadiene were prepared as substrates for IEDDA-driven domino reactions with enamines. However, their reactions with enamine **134** consistently failed to afford the desired products. 1,2-addition to the imine unit of the side chain emerged as the preferred mode of reaction. The use of $Yb(OTf)_3$ as a catalyst (Povarov reaction) and non-enamine dienophiles ultimately gave products consistent with the goals. Three-component Povarov reactions gave adducts in modest (<50%) yield, while the use of a preformed azadiene **222** typically gave yields in excess of 60%. Two adducts were successfully aromatized to give the desired pyridocoumarins.

There is much room for continuation of this work. Reasonable avenues of investigation include, but are not limited to

- careful optimization of both the two- and three- component Povarov reactions involving coumarin-fused azadienes.
- further investigation of the scope and limitations of the Povarov reactions
- the search for general and high-yielding methods for the aromatization of the Povarov adducts.

Accomplishment of these goals would provide the means for the expedient synthesis of a broad range of pyridocoumarins. The application of this methodology in the total synthesis of natural products, e.g. **174**, may also prove to be fruitful (Figure 3.4).



174

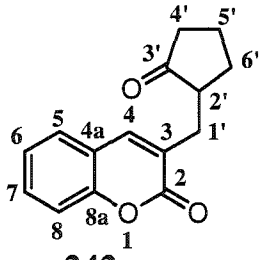
Figure 3.4

Experimental

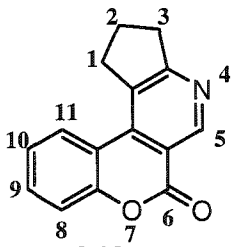
General Procedures

For general procedures refer to the corresponding section in Chapter 2.

3-(2-Oxocyclopentylmethyl)-2*H*-chromen-2-one (242) and 2,3-dihydro-7*H*-7-oxa-4-aza-cyclopenta[*c*]phenanthren-6-one (243)



242



243

To a solution of 3-(tosyl-hydrazonomethyl)-2*H*-chromen-2-one **183** (6.00 g, 17.5 mmol) in dry dichloromethane (20 mL) was added 1-(cyclopent-1-enyl)-pyrrolidine (7.21 g, 52.6 mmol, 7.67 mL) and the mixture was stirred under nitrogen at room temperature for 4 h. The initial pale yellow slurry went to a clear pale yellow solution and then to a

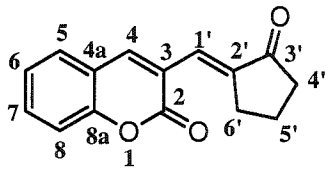
dark clear orange solution over the course of the reaction. The reaction was monitored by TLC and worked-up was initiated once the diene had been fully consumed. The solvent was removed under reduced pressure and the thick brown oily residue was subjected to flash chromatography (gradient: dichloromethane to 15% ethyl acetate/dichloromethane), which afforded **242** as a white solid (1.55 g, 6.54 mmol, 37%) and **243** as a white solid (0.05 g, 0.21 mmol, 1%).

242: R_f = 0.50 (dichloromethane). Mp = 73-74 °C (ethyl acetate/hexane). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.60 (s, 1H, H-4), 7.49 (t, 1H, *J* = 7.6 Hz), 7.46 (d, 1H, *J* = 8.2 Hz), 7.35 (d, 1H, *J* = 8.2 Hz), 7.27 (t, 1H, *J* = 7.4 Hz), 3.05 (dd, 1H, *J* = 13.3, 5.2 Hz), 2.62-2.51 (m, 2H), 2.39-2.34 (m, 1H), 2.25-2.11 (m, 2H), 2.06-2.00 (m, 1H), 1.85-1.75 (m, 1H), 1.63-1.55 (m, 1H). ^{13}C NMR (126 MHz, $CDCl_3$): δ = 219.8 (0, C-3'), 161.9 (0), 153.5 (0), 140.5 (1, C-4), 131.1 (1), 12.8 (0), 127.6 (1), 124.5 (1), 119.6 (0), 116.7 (1), 48.2 (2), 38.0 (2), 31.2 (1, C-2'), 29.8 (2), 20.7 (2). IR (nujol, NaCl): υ_{max} = 1721 (m), 1702 (s), 758 (2) cm^{-1}. MS (EI) *m/z* (%) = 242 (M^+, 35), 224 (10), 186 (73), 171 (17), 147 (100), 115 (41), 77 (31), 28 (60). Anal. Calc. For $C_{15}H_{14}O_3$: C 74.36, H 5.82; found; C 73.39, H 5.88.

243: R_f = 0.36 (15% ethyl acetate/dichloromethane). Mp = >208 °C (dec.) (ethyl acetate/hexane); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 9.41 (s, 1H), 8.15 (d, 1H, *J* = 8.1 Hz), 7.59 (t, 1H, *J* = 7.8 Hz), 7.42-7.37 (m, 2H), 3.51 (t, 2H, *J* = 7.2 Hz, H-3), 3.22 (t, 2H, *J* = 7.9 Hz, H-1), 2.35 (quint, 2H, *J* = 7.8 Hz, H-2). ^{13}C NMR (126 MHz, $CDCl_3$): δ = 173.1 (0), 160.8 (0), 153.0 (0), 152.2 (1, C-4), 138.1 (0), 132.2 (1), 130.6 (0), 127.3 (0), 124.8 (1), 118.3 (1), 117.9 (0), 115.0 (0), 34.8 (2, C-1), 33.2 (2, C-3), 22.8 (2, C-2). IR (nujol,

NaCl): υ_{max} = 1726 (s), 1605 (w), 1575 (w), 1546 (w), 1287 (w), 1105 (m), 1086 (m), 765 (m) cm^{-1}. MS (EI) *m/z* (%) = 237 (M^+, 106), 208 (30), 180 (10), 152 (8), 126 (4), 63 (8), 28 (80). HRMS *m/z* [M^+] calcd for $C_{15}H_{11}NO_2$ 237.0789, found 237.0785.

(*E*)-3-(2-Oxocyclopentylidenemethyl)-2*H*-chromen-2-one (250) (from diene 186)



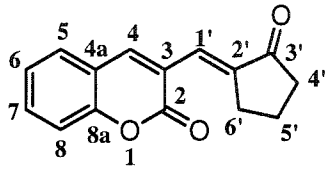
250

To a solution of **186** (1.50 g, 4.70 mmol) in dry THF (30 mL) was added 1-(cyclopent-1-enyl)-pyrrolidine **134** (2.06 mL, 14.1 mmol, 1.94 g) and the reaction mixture was stirred under nitrogen at room temperature for 3 h. The initial yellow slurry change to a bright clear orange solution over the course of the reaction. The reaction was monitored by TLC and was worked up once the diene had been fully consumed. The solvent was removed under reduced pressure and the dark clear brown oily residue was then subjected to flash chromatography (dichloromethane), which afforded **250** as a white solid (0.60 g, 2.5 mmol, 53%).

250: R_f = 0.91 (dichloromethane). Mp = 247-248 °C (chloroform/hexane). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.84 (s, 1H, H-4), 7.57-7.53 (m, 3H), 7.35 (d, 1H, *J* = 8.2 Hz), 7.32 (t, 1H, *J* = 7.7 Hz), 2.96 (td, 2H, *J* = 7.2, 2.7 Hz, H-1'), 2.44 (t, 2H, *J* = 7.4 Hz, H-6'), 2.07 (quint, 2H, *J* = 7.4 Hz, H-5'). NOE-D ($CDCl_3$): δ = 7.84 (7.57-7.53, 1.8 %; 2.96, 2.7 %), 2.96 (7.84, 1.5 %; 2.44, 1.2 %; 2.07, 0.6 %). ^{13}C NMR (126 MHz, $CDCl_3$): δ = 206.8 (0,

C-3'), 160.6 (0), 153.9 (0), 141.6 (1, C-4), 140.5 (0), 132.8 (1), 128.8 (1), 125.1 (1), 124.8 (1), 124.7 (0), 119.4 (0), 117.2 (1), 38.0 (2, C-4'), 30.3 (2, C-6'), 20.5 (2, C-5'). IR (nujol, NaCl): υ_{max} = 3070 (w), 1712 (s), 1633 (w), 1597 (m), 1563 (w), 1293 (w), 1076 (w), 768 (m) cm^{-1}. MS (EI) *m/z* 240 (M^+, 32), 211 (4), 197 (7), 184 (100), 115 (6), 77 (5). HRMS *m/z* [M^+] calcd for $C_{15}H_{12}O_3$ 240.0786, found 264.0777.

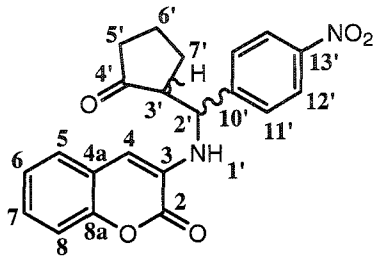
3-(2-Oxocyclopentylidenemethyl)-2*H*-chromen-2-one (250) (from diene 187)



250

To a solution of **187** (1.00 g, 3.10 mmol) in dry dichloromethane (30 mL) was added 1-(cyclopent-1-enyl)-pyrrolidine (1.34 mL, 9.20 mmol, 1.26 g) and the mixture was stirred under nitrogen at room temperature for 30 min. The clear colorless solution went to a bright clear orange solution over the course of the reaction. The reaction was monitored by TLC and work-up was initiated once the diene had been fully consumed. The solvent was removed under reduced pressure and the dark clear brown oily residue was then subjected to flash chromatography (dichloromethane), which afforded **250** as a white solid (0.56 g, 2.3 mmol, 77%). The product was crystallized from chloroform/hexane. See previous experiment for characterization data.

(2'R*,3'R*)-3-{[4-Nitrophenyl)(2-oxocyclopentyl)methyl]amino}-2*H*-chromen-2-one (252a) and (2'R*,3'S*)-3-{[4-Nitrophenyl)(2-oxocyclopentyl)methyl]amino}-2*H*-chromen-2-one (252b)



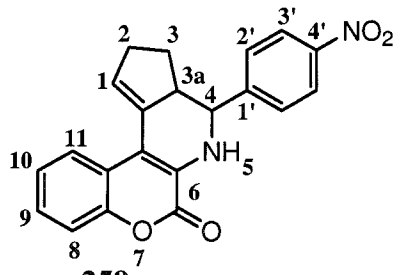
252

To a solution of **222** (0.50 g, 1.7 mmol) in dry dichloromethane (50 mL) was added 1-(cyclopent-1-enyl)pyrrolidine **134** (0.70 g, 5.1 mmol, 0.74 mL) and the mixture was stirred under nitrogen for 1 h. The pale clear orange solution change to a dark clear orange over the course of the reaction. The solvent was removed under reduced pressure and the resulting dark brown oil was subjected to flash chromatography (dichloromethane), which afforded **252a** and **252b** as a pale yellow solid (0.61 g, 1.6 mmol, 95%). The dr was determined to be 2 : 1.

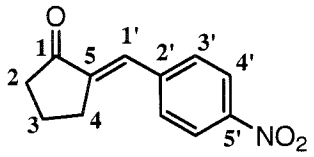
252a and **252b**: R_f = 0.50 (dichloromethane). Mp = 190-191 °C (chloroform/hexane). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.22 (t, 1.5H, *J* = 8.2 Hz), 7.54 (t, 1.5H, *J* = 8.2 Hz), 7.27-7.21 (m, 4.5H), 7.18-7.11 (m, 4.5H), 6.13 (s, 0.5H, H-4), 5.98 (s, 1H, H-4), 5.85 (d, 0.5H, *J* = 8.3 Hz), 5.82 (d, 1H, *J* = 5.5 Hz), 5.00 (q, 0.5H, *J* = 3.8 Hz), 4.96 (t, 1H, *J* = 5.0 Hz), 2.76-2.70 (m, 1.5H), 2.45-2.36 (m, 1.5H), 2.18-1.74 (m, 6H), 1.59-1.52 (m, 1H), 1.31-1.26 (m, 0.5H). ^{13}C NMR (126 MHz, $CDCl_3$): δ = 217.1 (0), 216.9 (0), 159.6 (0), 148.34 (0), 148.28 (0), 148.0 (0), 147.8 (0), 147.8 (0), 146.5 (0), 131.0 (0), 131.4 (0), 128.5 (0), 128.4 (1), 127.8 (1), 126.83 (1), 126.78 (1), 125.63 (1), 125.60 (1), 124.9 (1), 124.4 (1),

124.3 (1), 121.1 (0), 121.0 (0), 116.3 (1), 108.4 (1), 108.0 (1), 57.0 (1), 55.9 (1), 54.63 (1), 54.62 (1), 39.0 (2), 38.8 (2), 25.4 (2), 24.6 (2), 20.50 (2), 20.59 (2). IR (nujol, NaCl): υ_{max} = 3389 (m), 3061 (w), 1736 (m), 1695 (s), 1629 (m), 1602 (w), 1575 (w), 1509 (m), 1293 (w), 1216 (m), 1171 (m), 1109 (w), 1067 (w), 930 (w), 859 (w), 760 (m), 709 (w) cm^{-1}. MS (EI) *m/z* (%) = 379 (M^++1, 79), 359 (15), 295 (100), 218 (14), 162 (38). HRMS *m/z* [M^+] calcd for $C_{21}H_{18}N_2O_5$ 378.1214, found 378.1225.

4-(4-Nitrophenyl)-3,3a,4,5-tetrahydro-7*H*-7-oxa-5-azacyclopenta[*c*]phenanthren-6-one (259) and (*E*)-2-(4-nitrobenzylidene)cyclopentanone (260)



259



260

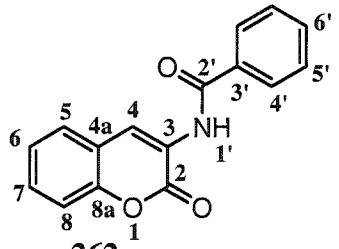
To a solution of **252** (0.50 g,1.3 mmol) in dry dichloromethane (30 mL) was added *p*-toluenesulfonic acid monohydrate (0.05 g, 0.26 mmol) and the mixture was heated reacted under reflux for 8 h. The initial clear faint yellow solution became a dark orange suspension over the course of the reaction. The solvent was removed under reduced pressure the orange residue was subjected to flash chromatography (dichloromethane), which afforded **259** as an orange solid (0.07 g, 0.19 mmol, 15%), **260** as a white solid (0.16 g, 0.75 mmol, 56%), and 3-amino-2*H*-chromen-2-one **212** as a white solid (0.18 g, 1.1 mmol, 85%).

259: R_f = 0.81 (dichloromethane). Mp = 211-212 °C (chloroform/hexane). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.25 (d, 2H, *J* = 8.3 Hz), 7.56 (d, 2H, *J* = 8.2 Hz), 7.48 (d, 1H, *J* = 8.3 Hz), 7.38 (d, 1H, *J* = 7.5 Hz), 7.34 (d, 2H, *J* = 3.7 Hz), 7.08 (s, 1H), 6.71 (s, 1H), 6.47 (s, 1H), 6.15 (s, 1H), 3.03-3.02 (m, 2H), 2.804-2.797 (m, 2H). NOE-D ($CDCl_3$): δ = 6.71 (6.15, 7.4%), 6.47 (7.56, 2.6%; 6.71, 5.7%), 6.15 (7.08, 3.5%; 2.804-2.797, 3.0%), 3.03-3.02 (7.56, 4.2%; 2.804-2.797, 3.0%), 2.804-2.797 (6.15, 2.3%; 3.03-3.02, 2.6%). ^{13}C NMR (126 MHz, $CDCl_3$): δ = 160.0 (0), 148.6 (0), 148.6 (0), 144.5 (0), 140.2 (0), 128.9 (1, 2C), 127.5 (1), 126.1 (1), 125.2 (1), 124.1 (1, 2C), 121.0 (0), 120.4 (1), 116.5 (1), 114.9 (1), 111.6 (1), 29.4 (2), 29.2 (2). IR (nujol, KBr): υ_{max} = 3370 (m), 1698 (s), 1633 (w), 1606 (w), 1581 (m), 1509 (s), 1343 (s), 1319 (w), 1156 (w), 1106 (w), 1064 (w), 874 (w), 848 (w), 776 (w), 756 (m), 508 (w) cm^{-1}. MS (EI) *m/z* (%) = 360 (M^+, 100), 343 (40), 313 (64), 285 (7), 224 (23), 152 (12). HRMS *m/z* [M^+] calcd for $C_{21}H_{16}N_2O_4$ 360.1109, found 360.1154.

260: R_f = 0.70 (dichloromethane). Mp = 239-240 °C (chloroform/hexane). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.27 (d, 2H, *J* = 9.5 Hz, H-4'), 7.68 (d, 2H, *J* = 8.6 Hz, H-3'), 7.40 (t, 1H, *J* = 2.7 Hz, H-1'), 3.02 (td, 2H, *J* = 7.4, 3.0 Hz, H-4), 2.47 (t, 2H, *J* = 7.7 Hz, H-2), 2.10 (quint, 2H, *J* = 7.5 Hz, H-3). NOE-D ($CDCl_3$): δ = 7.68 (8.27, 2.4%; 7.40, 1.6%; 3.02, 2.5%), 7.40 (7.69, 2.2%; 2.47, 0.6%), 3.02 (7.68, 2.7%; 2.47, 1.4%; 2.10, 2.1%), 2.47 (3.02, 1.8%; 2.10, 2.1%), 2.10 (3.02, 2.2%, 2.47, 2.4%). ^{13}C NMR (126 MHz, $CDCl_3$): δ = 207.5 (0, C-1), 147.8 (0), 142.2 (0), 140.1 (0), 131.0 (1, C-4'), 129.5 (1, C-1'), 124.1 (1, C-3'), 37.9 (2, C-2), 29.6 (2, C-4), 20.3 (2, C-3). IR (nujol, KBr) υ_{max} = 1710 (s), 1626 (m), 1594 (w), 1510 (s), 1340 (s), 1318 (w), 1221 (w), 1174 (m), 1107

(m), 911 (w), 860 (w), 842 (w), 810 (w), 748 (w), 689 (w) cm^{-1}. MS (EI) *m/z* (%) = 217 (M^+, 67), 206 (100), 170 (51), 161 (44), 158 (15), 142 (21), 128 (53), 115 (71), 77 (19), 39 (25). HRMS *m/z* [M^+] calcd for $C_{12}H_{11}NO_3$ 217.0738, found 217.0733.

_N_-(2-Oxo-2_H_-chromen-3-yl)benzamide (262)



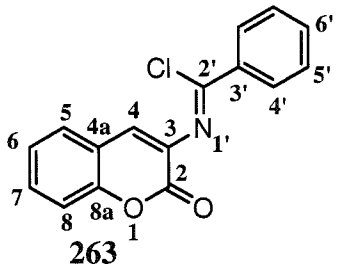
262

To a solution of 3-aminocoumarin **212** (1.40 g, 8.68 mmol) and benzoyl chloride (1.34 g, 9.53 mmol, 1.10 mL) in THF (50 mL) was added pyridine (0.72 g, 9.1 mmol, 0.75 mL) and the mixture was stirred at room temperature for 3 h. The clear colorless solution became a thick white suspension over the course of the reaction. The reaction was monitored by TLC and work-up was initiated once the diene had been fully consumed. The mixture was diluted with chloroform until the white precipitate had dissolved. The chloroform solution was then washed with aqueous 3 M HCl solution (50 mL) and then washed with 3 M NaOH solution (50 mL). The organic layer was dried with $MgSO_4$ and the solvent was removed under reduced pressure. The residue was then subjected to flash chromatography (dichloromethane), which afforded **262** as a white solid (1.85 g, 7.0 mmol, 81%).

262: R_f = 0.85 (dichloromethane). Mp = 174-175 °C (chloroform/hexane). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.86 (s, 1H, H-4), 8.84 (s, 1H, H-1'), 7.92 (d, 2H, *J* = 8.5 Hz), 7.61-

7.45 (m, 4H), 7.46 (t, 1H, J = 7.8 Hz), 7.36-7.31 (2H, m).^{13}C NMR (126 MHz, $CDCl_3$) δ 166.3 (0), 159.2 (0), 150.2 (0), 133.8 (0), 132.8 (1), 130.0 (1), 129.175 (1), 129.2 (1), 128.1 (1), 127.375 (1), 127.371 (1), 125.5 (1), 124.4 (0), 123.6 (1, C-4), 120.1 (0), 116.6 (1). IR (nujol, KBr): υ_{max} = 3367 (m), 3089 (w), 3069 (w), 1789 (s), 1716 (s), 1663 (s), 1601 (s), 1536 (m), 1255 (m), 1212 (s), 996 (m), 857 (w), 756 (s), 703 (s), 615 (s), 518 (w), 472 (w) cm^{-1}. MS (EI) *m/z* (%) = 265 (M^+, 20), 105 (100), 77 (48), 51 (13). HRMS *m/z* [M^+] calcd for $C_{16}H_{11}NO_3$ 265.0738, found 265.0757.

_N_-(2-Oxo-2_H_-chromen-3-yl)benzimidoyl chloride (263)



263

To a solution of **262** (0.40 g, 1.5 mmol) in dry chloroform (30 mL) was added phosphorus pentachloride (3.10 g, 14.9 mmol) and the mixture was stirred under reflux for 3 h. The clear colorless solution went to a clear pale yellow solution and a white gas was produced over the course of the reaction. When no more gas was observed, the reaction mixture was poured onto ice water. The resulting mixture was extracted with ether and the organic layer was washed with deionized water until it was pH neutral. The organic layer was dried with $MgSO_4$ and the solvent was removed under reduced pressure to afford **263** as a pale yellow solid (0.38 g, 1.3 mmol, 89%).

263: Mp = 144-145°C (chloroform/hexane). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.19 (d, 2H, J = 7.5 Hz), 7.58 (t, 1H, J = 7.4 Hz), 7.55-7.47 (m, 4H), 7.38 (d, 1H, J = 9.3 Hz), 7.31 (t, 1H, J = 7.7 Hz), 7.26 (s, 1H, H-4). ^{13}C NMR (126 MHz, $CDCl_3$): δ = 156.4 (0), 152.3 (0), 149.6 (0), 134.8 (0), 134.4 (0), 133.1 (1), 130.6 (1), 130.000 (1), 29.995 (1), 128.752 (1), 128.748 (1), 127.8 (1), 127.6 (1), 125.0 (1), 119.5 (0), 116.8 (1). IR (nujol, KBr): υ_{max} = 1711 (s), 1666 (m), 1534 (s), 1257 (w), 1176 (w), 1157 (w), 755 (m), 702 (m), 615 (w) cm^{-1}. MS (EI) *m/z* (%) = 283 (M^+ ^{35}Cl, 26), 248 (100), 220 (13), 190 (2), 145 (3), 105 (14), 89 (27), 77 (16), 63 (11). HRMS *m/z* [M^+] calcd for $C_{16}H_{10}ClNO_2$ 283.0399, found 283.0416.

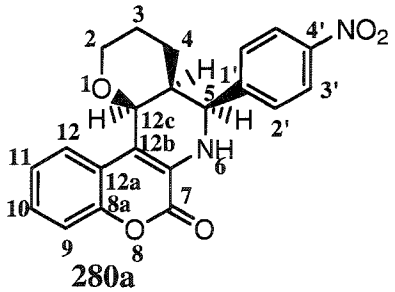
General Procedure 1: Preparation of Povarov adducts using the preformed diene.

To a solution of diene and $Yb(OTf)_3$ (5 mol %) in acetonitrile was added dienophile (3.0 equivalents). The reaction was monitored by TLC and work-up was initiated once the diene had been fully consumed. The solvent was removed under reduced pressure and the residue was subjected to flash chromatography. The isolated product(s) were then crystallized from the appropriate solvent(s). The dr was determined from ^{1}H NMR analysis of the crude reaction mixture.

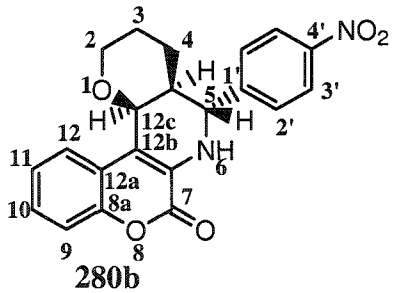
General Procedure 2: Preparation of Povarov adducts using the three-component reaction.

To a solution of 3-aminocoumarin **212**, the appropriate aldehyde (1.05 equivalents), and $Yb(OTf)_3$ (5 mol %) in acetonitrile was added dienophile (3.0 equivalents). The reaction was monitored by tlc and work-up was initiated once the **212** had been fully consumed. The solvent was removed under reduced pressure and the residue was subjected to flash chromatography. The isolated product was then crystallized from the appropriate solvent(s). The dr was determined from ^1H NMR analysis of crude reaction mixture.

(4a*S,5*R**,12a*R**)-5-(4-Nitrophenyl)-3,4,4a,5,6,12c-hexahydro-7*H*-1,8-dioxa-6-aza-2*H*-pyrano[5,6-*c*]phenanthren-7-one (280a) and (4a*S**,5*S**,12a*R**)-5-(4-nitrophenyl)-3,4,4a,5,6,12c-hexahydro-7*H*-1,8-dioxa-6-aza-2*H*-pyrano[5,6-*c*]phenanthren-7-one (280b)**



280a



280b

Using general procedure 1, **222** (0.50 g, 1.7 mmol), 3,4-dihydro-2*H*-pyran (0.50 mL, 5.1 mmol, 0.43 g), $Yb(OTf)_3$ (0.05 g) and acetonitrile (10 mL) were reacted for 20 min. The thick yellow suspension went to bright yellow suspension over the course of the reaction. A yellow residue was obtained and the dr was determined to be 1 : 1.8 in favor of **280b** by NMR. This residue was subjected to flash chromatography (dichloromethane), which afforded **280a** (0.15 g, 0.40 mmol, 25%), **280b** as a yellow solid (0.39 g, 1.1 mmol, 65%). Combined yield = 0.62 g, 1.6 mmol, 90%.

280a: R_f = 0.90 (dichloromethane). Mp = 228-229 °C (chloroform/hexane). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.27 (d, 2H, *J* = 9.1 Hz, H -3'), 8.21 (d, 1H, *J* = 7.6 Hz, H-12), 7.63 (d, 2H, *J* = 8.7 Hz, H-2'), 7.37-7.34 (m, 2H), 7.30-7.28 (m, 1H), 5.50 (d, 1H, J = 4.7 Hz, H-12c), 5.07 (s, 1H, H-6), 4.81 (d, 1H, *J* = 2.5 Hz, H-5), 3.65-3.64 (m, 1H, H-2α), 3.25 (td, 1H, *J* = 11.0, 1.2 Hz, H-2β), 2.38-2.35 (m, 1H, H-4a), 1.76-1.67 (m, 1H), 1.59-1.48 (m, 1H), 1.43-1.41 (m, 2H). NOE-D ($CDCl_3$): δ = 8.55 (7.63, 4.1%), 8.21 (5.50, 3.2%), 7.63 (8.55, 4.6%; 5.07, 2.2%; 4.81, 2.6 %), 5.50 (8.21, 3.5%; 4.81, 3.5%; 2.38-2.35, 5.9%), 5.07 (7.63, 4.2%; 4.81, 7.0%), 4.81 (7.63, 4.4%; 5.50, 3.0%; 5.07, 2.5%; 2.38-2.35, 3.4%), 3.65-3.64 (5.50, 3.7%; 3.25, 20.6%), 3.25 (3.65-3.64, 20.0%; 1.76-1.67, 5.7%; 1.59-1.48, 4.8%), 1.43-1.41 (7.63, 2.9%; 5.50, 5.0%; 4.81, 3.8%), 2.38-2.35 (1.76-1.67, 1.0%; 1.59-1.48, 2.0%;1.43-1.41, 2.8%). ^{13}C NMR (126 MHz, $CDCl_3$): δ = 158.5 (0), 148.5 (0), 147.9 (0), 147.2 (0), 130.7 (0), 128.0 (1, C-3'), 127.1 (1), 125.1 (1), 124.8 (1, C-12), 124.1 (1, C-2'), 120.3 (0), 116.7 (1), 116.6 (0), 71.8 (1, C-12c), 62.9 (2, C-2), 58.9 (1, C-5), 38.3 (1, C-4a), 24.3 (2), 19.7 (2); IR (neat, ZnSe): υ_{max} = 3340 (w),

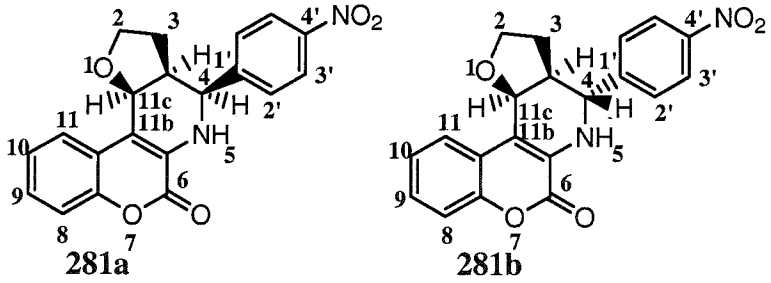
2854 (w), 1722 (s), 1618 (w), 1598 (w), 1516 (m), 1348 (s), 1181 (m), 1091 (s), 857 (m), 752 (s) cm^{-1}. HRMS *m/z* [M^+] calcd for $C_{21}H_{18}N_2O_5$ 378.1214, found 378.1225.

280b: R_f = 0.80 (dichloromethane). Mp = 263-264 °C (chloroform/hexane). ^1H NMR (500 MHz, $CDCl_3$): δ = 8.27 (d, 2H, *J* = 9.4 Hz, H-3'), 7.62 (d, 2H, *J* = 8.2 Hz, H-2'), 7.57-7.55 (m, 1H, H-12), 7.29-7.27 (m, 3H), 5.09 (s, 1H, H-6), 4.87 (d, 1H, *J* =11.4 Hz, H-5), 4.71 (d, 1H, *J* = 3.5 Hz, H-12c), 4.20-4.17 (m, 1H, H-2α), 3.82 (td, 1H, *J* = 11.6, 1.7 Hz, H-2β), 2.12-2.08 (m, 1H, H-4a), 1.94-1.78 (m, 2H), 1.48-1.46 (m, 2H). NOE-D ($CDCl_3$): δ = 8.27 (7.62, 5.6%), 7.62 (8.27, 3.6%; 5.09, 1.5%, 4.87, 2.9%; 2.12-2.08, 1.7%; 1.94-1.78, 1.6%; 1.48-1.46, 1.4%), 5.09 (7.62, 2.4%; 4.87, 1.0%); 4.87 (7.62, 5.2%; 5.09, 1.6%; 2.12-2.08, 1.0%; 1.94-1.78, 3.4%; 1.48-1.46, 1.3%), 4.71 (7.57-7.55, 7.6%; 3.82, 3.6%; 2.12-2.08, 4.5%; 1.94-1.78, 3.0%); 4.20-4.17 (3.82, 14.2%; 1.94-1.78, 4.2%; 1.48-1.46, 3.3%), 3.82 (4.71, 3.8%; 4.20-4.17, 14.8%; 1.94-1.78, 2.8%; 1.48-1.46, 3.5%), 2.12-2.08 (7.62, 3.9%; 5.09, 1.0%; 4.87, 1.6%; 4.71, 4.8%; 1.94-1.78, 2.6%; 1.48-1.46, 2.4%); ^{13}C NMR (126 MHz, $CDCl_3$): δ = 158.9 (0), 148.6 (0), 148.3 (0), 147.9 (0), 130.0 (0, C-2'), 129.0 (1), 126.8 (1), 125.1 (1), 124.3 (1, C-3'), 122.0 (1), 120.3 (0), 116.8 (1), 115.4 (0), 69.7 (1, C-12c), 69.3 (2, C-2), 54.2 (1, C-5), 38.9 (1, C-4a), 23.6 (2), 22.0 (2). IR (neat, ZnSe): υ_{max} = 3389 (w), 2946 (w), 1710 (s), 1633 (m), 1509 (s), 1341 (s), 1186 (m), 1090 (m), 752 (s) cm^{-1}. HRMS *m/z* [M^+] calcd for $C_{21}H_{18}N_2O_5$ 378.1214, found 378.1230.

Using general procedure 2, 3-aminocoumarin **212** (0.25 g, 1.6 mmol), 4-nitrobenzaldehyde (0.25 g, 1.6 mmol), and 3,4-dihydro-2*H*-pyran (0.42 mL, 4.6 mmol, 0.39 g), $Yb(OTf)_3$ (0.05 g), and acetonitrile (30 mL) were reacted for 24 h. The bright

yellow suspension went to a thick bright yellow suspension over the course of the reaction. A yellow residue was obtained and the dr was determined to be 1 : 1.6 in the favor of **280b** by NMR. The residue subjected to flash chromatography (dichloromethane), which afforded **280** as a yellow solid (0.23 g, 0.61 mmol, 40%). The final product was crystallized from chloroform/hexane.

(3a*S,4*R**,11c*S**)-4-(4-Nitrophenyl)-2,3,3a,4,5,11c-hexahydro-2*H*-1,7-dioxa-6-aza-6*H*-furano[4,5-*c*]phenanthren-6-one (281a) and (3a*S**, 4*S**, 11c*S**)-4-(4-nitrophenyl)-2,3,3a,4,5,11c-hexahydro-2*H*-1,7-dioxa-6-aza-6*H*-furano[4,5-*c*]phenanthren-6-one (281b)**



281a **281b**

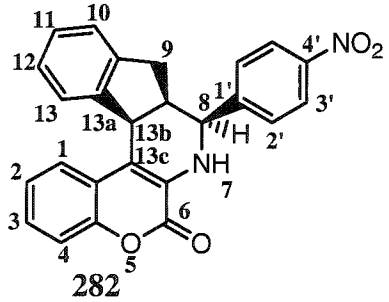
Using general procedure 1, **222** (0.50 g, 1.7 mmol), 3,4-dihydro-2*H*-furan (0.40 mL, 5.1 mmol, 0.36 g), $Yb(OTf)_3$ (0.05 g), and acetonitrile (10 mL) were reacted for 10 min. The bright yellow suspension went to a clear bright yellow over the course of the reaction. A yellow residue was obtained and the dr was determined to be 1 : 1.3, in favor of **281b** by NMR. The residue was subjected flash chromatography (dichloromethane), which afforded **281a** (0.11 g, 0.30 mmol, 18%) as a yellow solid, **281b** (0.21 g, 0.58 mmol, 34%) as a yellow solid, and mixed fraction (0.12 g, 0.33 mmol, 19%) as a yellow solid. Combined yield = 0.44 g, 1.2 mmol, 72%.

281a: R_f = 0.40 (dichloromethane). Mp = 251-252 °C (chloroform/hexane). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.31 (d, 2H, *J* = 7.9 Hz, H-3'), 7.85 (dd, 1H, *J* = 7.4, 1.5 Hz, H-11), 7.71 (d, 2H, *J* = 9.0 Hz, H-2'), 7.39-7.28 (m, 3H), 5.53 (d, 1H, *J* = 7.4 Hz, H-11c), 4.99 (s, 1H, H-5), 4.86 (d, 1H, *J* = 2.3 Hz, H-4), 3.92 (td, 1H, *J* = 8.3, 2.8 Hz, H-2), 3.82 (ddd, 1H, *J* = 9.3, 9.3, 6.7 Hz, H-2), 3.00-2.97 (m, 1H, H-3a), 2.20 (m, 1H, H-3β), 1.50-1.54 (m, 1H, H-3α). NOE-D ($CDCl_3$): δ = 8.31 (7.71, 4.4%), 7.85 (7.39-7.28, 5.1%; 5.53, 4.4%), 7.71 (8.31, 6.6%; 4.99, 2.4%; 4.86, 2.1%), 5.53 (7.85, 4.0%; 4.86, 2.0%; 3.00-2.97, 5.3%), 4.99 (7.71, 3.6%; 4.86, 1.0%), 4.86 (7.71, 4.6%; 5.53, 2.5%; 4.99, 2.5%; 3.00-2.97, 3.7%), 3.92 (3.82, 2.9%; 2.20, 2.8%; 1.60-.154, 1.2%), 3.82 (3.92, 9.5%; 2.20, 1.3%; 1.60-1.54, 1.3%); 3.00-2.97 (7.71, 2.6%; 5.53, 3.2%; 4.86, 3.6%; 1.60-1.54, 3.4%). ^{13}C NMR (126 MHz, $CDCl_3$): δ = 158.8 (0), 149.0 (0), 147.9 (0), 147.0 (0), 129.3 (0), 127.6 (1, C-2'), 127.5 (1), 125.0 (1), 124.6 (1, C-11), 124.4 (1, C-3'), 120.0 (0), 119.4 (0), 116.7 (1), 72.9 (1, C-2), 67.5 (2, C-2), 56.9 (1, C-4), 45.8 (1, C-3a), 25.2 (2, C-3). IR (neat, ZnSe): υ_{max} = 334 (w), 1714 (s), 1636 (m), 1594 (m), 1347 (s), 1322 (w), 1184 (s), 1048 (m), 763 (s) cm^{-1}. HRMS *m/z* [M^+] calcd for $C_{20}H_{16}N_2O_5$ 364.1058, found 364.0974.

281b: R_f = 0.25 (dichloromethane). Mp = 208-209 °C (chloroform/hexane). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.30 (d, *J* = 8.1 Hz, H-3'), 7.78-7.76 (m, 1H, H-11), 7.66 (d, 2H, *J* = 8.6 Hz, H-2'), 7.36-7.30 (m, 3H), 5.26 (s, 1H, H-5), 4.76 (d, 1H, *J* = 5.2 Hz, H-11c), 4.13 (ddd, 1H, *J* = 8.4, 8.4, 6.4 Hz, H-2α), 3.98 (ddd, 1H, *J* = 8.8, 8.8, 5.9 Hz, H-2β), 3.95 (d, 1H, *J* = 11.2 Hz, H-4), 2.55-2.49 (m, 1H, H-3a), 2.18-2.11 (m, 1H, H-3α), 1.79-1.73 (m, 1H, H-3β). NOE-D ($CDCl_3$): δ = 8.30 (7.66, 4.7%), 7.78-7.76 (7.36-7.30, 4.6%;

4.76, 5.7%), 7.66 (8.30, 4.9%; 5.26, 2.2%; 3.95, 3.5%; 2.55-2.49, 3.0%; 1.79-1.73, 1.7%), 5.26 (7.66, 2.1%; 3.95, 2.9%), 4.76 (7.78-7.76, 5.4%; 3.98, 2.9%; 2.55-2.49, 5.0%; 2.18-2.11, 2.4%); 4.13 (4.76, 0.5%; 3.98, 7.9%; 2.18-2.11, 2.8%; 1.79-1.73, 4.0%), 2.55-2.49 (7.66, 4.1%; 4.76, 5.6%; 2.18-2.11, 2.8%; 1.79-1.73, 1.9%), 2.18-2.11 (4.76, 1.7%; 4.13, 1.4%; 3.98, 3.8%; 2.55-2.49, 3.0%; 1.79-1.73, 11.0%), 1.79-1.73 (7.66, 1.7%; 4.13, 3.1%; 3.95, 4.3%; 2.55-2.49, 1.9%; 2.18-2.11, 12.3%). ^{13}C NMR (126 MHz, $CDCl_3$): δ = 158.8 (0), 148.6 (0), 148.4 (0), 147.4 (0), 130.5 (0), 129.4 (1, C-2'), 127.3 (1), 125.3 (1), 124.4 (1, C-3'), 123.3 (1, C-11), 120.8 (0), 116.8 (0), 116.7 (1), 72.7 (1, C-11c), 65.8 (2, C-2), 57.3 (1, C-4), 43.2 (1, C-3c), 28.4 (2, C-3). IR (neat, ZnSe): υ_{max} = 3397 (w), 1712 (s), 1653 (m), 1640 (m), 1516 (s), 1507 (s), 1388 (m), 1339 (s), 1189 (m), 1045 (m), 860 (w), 764 (s), 751 (m) cm^{-1}. HMRS *m/z* [M$^+$] calcd for $C_{20}H_{16}N_2O_5$ 364.1058, found 364.1086.

(8*S,8a*S**,13b*R**)-8-(4-Nitrophenyl)-8,8a,9,13b-tetrahydro-6*H*-5-oxa-7-aza-indeno[2,1-*c*]phenanthren-6-one (282)**



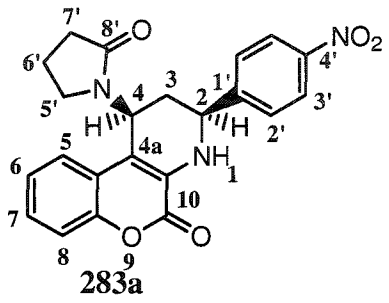
282

Using general procedure 1, **222** (0.50 g, 1.7 mmol), indene (0.60 mL, 5.1 mmol, 0.59 g), $Yb(OTf)_3$ (0.05 g), and acetonitrile (10 mL) and were reacted under reflux for 8

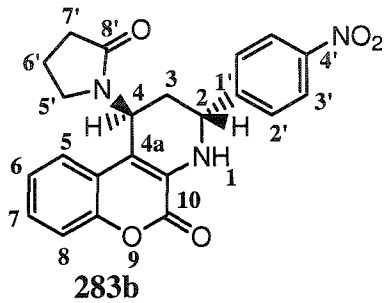
h. The bright yellow suspension went to a pale thick yellow suspension over the course of the reaction. The solution was then filtered and washed with pentane, which afforded **282** (0.59 g, 1.4 mmol, 85%) as a bright yellow solid. The dr ratio was determined to be greater than >95 : 5 in favor of the *endo* isomer.

282: Mp = 269-270 °C (chloroform/hexane). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.01 (d, 2H, *J* = 7.7 Hz, H-3'), 7.86-7.84 (m, 1H, H-1), 7.41-7.37 (m, 4H), 7.35 (d, 2H, *J* = 8.5 Hz, H-2'), 7.29 (d, 1H, *J* = 2.7 Hz), 6.99-6.95 (m, 2H), 6.83-6.82 (m, 1H), 5.21 (s, 1H, H-7), 4.91 (d, 1H, *J* = 7.8 Hz, H-13b), 4.72 (d, 1H, *J* = 4.4 Hz, H-8), 3.49-3.44 (m, 1H, H-8a), 3.18 (dd, 1H, *J* = 17.6, 5.4 Hz, H-9α), 2.87 (dd, 1H, *J* = 16.0, 7.9 Hz, H-9β). NOE-D ($CDCl_3$): δ = 8.01 (7.35, 3.7%), 7.86-7.84 (7.41-7.37, 4.1%, 5.0%; 4.91, 7.1%), 5.21 (7.35, 3.2%; 4.72, 3.6%), 4.91 (7.86-7.84, 6.6%; 7.29, 2.2%; 4.72, 1.1%, 3.49-3.44, 5.2%; 2.87, 1.6%), 4.72 (7.35, 5.1%; 5.21, 2.9%; 3.49-3.44, 4.3%; 3.18, 1.5%), 3.49-3.44 (7.35, 2.1%; 4.91, 5.0%; 4.72, 5.3%; 3.18, 1.2%; 2.87, 3.9%), 3.18 (7.35, 4.1%; 7.29, 1.9%; 5.21, 0.9%; 4.72, 1.7%; 3.49-3.44, 1.5%; 2.87, 18.2%). ^{13}C NMR (126 MHz, $CDCl_3$): δ = 158.8 (0), 148.7 (0), 148.4 (0), 147.3 (0), 142.8 (0), 142.4 (0), 1302. (0), 127.83 (1), 127.82 (1), 127.2 (1), 126.7 (1), 125.02 (1), 125.0 (1), 124.7 (1, C-1), 123.289 (1), 123.288 (1), 121.1 (0), 120.6 (0), 117.1 (1), 57.4 (1, C-8), 44.9 (1, C-8a), 42.8 (1, C-13b), 33.3 (2, C-9). IR (neat, ZnSe): υ_{max} = 3427 (w), 1702 (s), 1629 (m), 1504 (s), 1337 (s), 1207 (m), 1059 (w), 756 (s), 734 (s) cm^{-1}. HRMS *m/z* [M^+] calcd for $C_{25}H_{18}N_2O_4$ 410.1265, found 410.1276.

(2*R, 4*R**)-(2-(4-Nitrophenyl)-4-(2-oxopyrrolidin-1-yl)-1,2,3,4-tetrahydro-9-oxa-1-aza-10*H*-phenanthren-10-one (283a) and (2*S**, 4*R**)-(2-(4-nitrophenyl)-4-(2-oxopyrrolidin-1-yl)-1,2,3,4-tetrahydro-9-oxa-1-aza-10*H*-phenanthren-10-one (283b)**



283a



283b

Using general procedure 1, **222** (0.50 g, 1.7 mmol), 1-vinyl-2-pyrrolidinone (0.55 mL, 5.1 mmol, 0.57 g), $Yb(OTf)_3$ (0.05 g), and acetonitrile (10 mL) were reacted under reflux for 7 h. The bright yellow suspension went to a thick pale yellow suspension over the course of the reaction. The yellow precipitate produced was then filtered and washed with pentane to give **283b** (0.26 g, 0.64 mmol, 38%) as a pale yellow solid. The solvent of the mother liquor was evaporated, which afforded **283b** (0.16 g, 0.40 mmol, 23%) as a pale yellow solid. Combined yield = 0.42g, 1.0 mmol, 61%. The dr ratio was determined, from isolated material, to be 1: 3, in favor of the *exo* isomer **283b** by NMR.

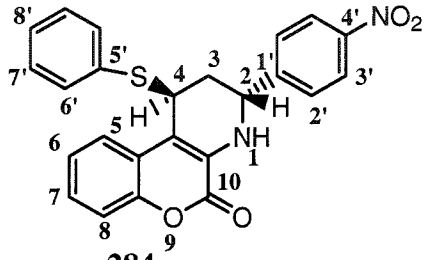
283a: Mp = 187-188 °C (chloroform/hexane). ^1H NMR (500 MHz, $CDCl_3$): δ = 8.27 (d, 2H, J = 9.4 Hz, H-3'), 7.64 (d, 2H, J = 8.9 Hz, H-2'), 7.36-7.32 (m, 2H), 5.77 (dd, 1H, J = 9.0, 7.8 Hz, H-4), 5.16 (s, 1H, H-1), 4.62 (dd, 1H, J = 10.8, 2.6 Hz, H-2), 3.13 (ddd, 1H, J = 14.2, 7.1, 7.1 Hz, H-5'β), 2.78 (ddd, 1H, J = 14.3, 7.2, 7.2 Hz, H-5'α), 2.50-2.46 (m, 1H, H-3α), 2.45-2.32 (m, 2H, H-7'), 2.23-2.16 (m, 1H, H-3β). NOE-D ($CDCl_3$): δ = 8.27 (7.64, 4.7%), 7.64 (8.27, 5.7%; 5.16, 2.7%; 4.62, 3.2%; 2.50-2.32, 1.7%; 2.23-2.16,

2.4%), 5.77 (7.36-7.32, 3.2%; 4.62, 0.9%; 2.50-2.32, 2.3%; 2.23-2.16, 0.6%), 5.16 (7.64, 4.0%; 4.62, 3.6%), 4.62 (7.64, 4.0%; 5.77, 1.8%; 5.16, 2.2%; 2.50-2.32, 3.0%; 2.23-2.16, 1.0%), 5.13 (2.78, 17.4%; 2.23-2.16, 5.0%; 1.80, 3.7%); 2.78 (7.36-7.32, 1.9%; 3.13, 17.9%; 1.80, 3.7%), 2.233-2.26 (7.64, 2.6%; 5.77, 1.6%; 4.62, 1.4%; 3.13, 4.7%; 2.50-2.32, 17.5%). ^{13}C NMR (126 MHz, $CDCl_3$): δ = 175.6 (0, C-8'), 158.4 (0), 148.2 (0), 148.0 (0), 132.6 (0), 127.5 (1,C-2'), 125.5 (1), 124.4 (1,C-3'), 122.1 (1), 119.5 (0), 117.1 (1), 115.6 (0), 55.0 (1, C-2), 45.2 (1, C-4), 42.8 (2, C-5'), 35.4 (2, C-3), 31.2 (2, C-7'), 18.2 (2,C-6'). IR (neat, ZnSe): υ_{max} = 3262 (w), 1704 (m), 1666 (s), 1623 (w), 1599 (w), 1507 (s), 1457 (m), 1344 (s), 1290 (m), 857 (s), 743 (s), 734 (s) cm^{-1}. HRMS *m/z* [M^+] calcd for $C_{25}H_{18}N_2O_4$ 405.1323, found 405.1331.

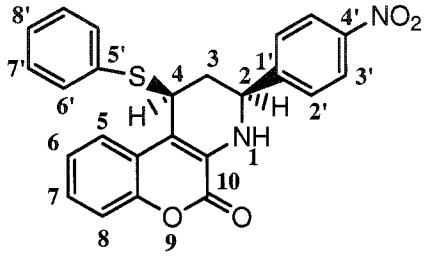
283b: Mp = 281-282 °C (chloroform/hexane). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.30 (d, 2H, *J* = 8.5 Hz, H-3'), 7.64 (d, 2H, *J* = 8.8 Hz, H-2'), 7.38-7.26 (m, 4H), 5.55 (dd, 1H, *J* = 5.0, 2.0 Hz, H-4), 5.33 (s, 1H, H-1), 4.65 (dd, 1H, *J* = 12.6, 3.4 Hz, H-2), 3.59 (ddd, 1H, *J* = 8.2, 8.2, 5.5 Hz, H-3β), 3.16 (ddd, 1H, *J* = 8.9, 8.9, 5.8 Hz, H-3α), 2.83-2.78 (m, 2H, H-7'), 2.42-2.39 (m, 1H, H-5'), 2.25-2.07 (m, 2H), 1.98-1.93 (m, 1H, H-5'). NOE-D ($CDCl_3$): δ = 8.30 (7.64, 12.5%), 5.55 (7.36-7.26, 7.1%; 2.42-2.39, 2.42%; 2.25-2.07, 5.1%), 5.33 (4.65, 1.3%), 4.05 (7.64, 4.9%; 5.33, 1.4%; 3.59, 5.0%; 2.42-2.39, 4.0%; 2.25-2.07, 2.4%), 3.59 (4.65, 6.8%; 3.16, 17.4%, 2.25-2.07, 3.7%), 3.16 (3.59, 13.2%; 2.42-2.39, 4.5%; 1.98-1.93, 2.8%). ^{13}C NMR (126 MHz, $CDCl_3$): δ = 175.0 (0, C-8'), 158.3 (), 148.6 (0), 148.2 (0), 148.0 (0), 130.8 (0), 127.7 (1, C-2'), 127.3 (1, C-3'), 125.7 (1), 124.5 (1), 121.6 (1), 120.0 (0), 117.0 (1), 112.1 (0), 52.8 (1, C-2), 47.0 (2, C-3), 43.1 (1, C-5c), 37.8 (2,C-7'), 31.3 (2, C-5'), 18.8 (2, C-6'). IR (neat, ZnSe): υ_{max} = 3389 (w),

1715 (s), 1663 (s), 1628 (m), 1600 (w), 1518 (s), 1507 (s), 1424 (m), 1347 (s), 1319 (m), 1292 (s), 1194 (s), 745 (s) cm^{-1}. HRMS *m/z* [M^+] calcd for $C_{25}H_{18}N_2O_4$ 405.1323, found 405.1334.

(2*S,4*R**)-(2-(4-Nitrophenyl)-4-(4-phenylsulfanyl)-1,2,3,4-tetrahydro-9-oxa-1-aza-10*H*-phenanthren-10-one (284a) and (2*R**,4*R**)-(2-(4-nitrophenyl)-4-(4-phenylsulfanyl)-1,2,3,4-tetrahydro-9-oxa-1-aza-10*H*-phenanthren-10-one (284b)**



284a



284b

Using general procedure 1, **222** (0.50 g, 1.7 mmol), phenyl vinyl sulfide (0.70 mL, 5.1 mmol, 0.69 g), $Yb(OTf)_3$ (0.05 g), and acetonitrile (20 mL) were reacted for 60 min. The bright yellow suspension went to a thick yellow suspension over the course of the reaction. A yellow residue was obtained and the dr ratio was determined to be 1.8 : 1, in favor of the *endo* isomer **284a** by NMR. The residue was then subjected to flash chromatography (dichloromethane), which afforded **284a** (0.14 g, 0.33 mmol, 19%) as a yellow solid, mixed fraction (0.08 g, 0.19 mmol, 11%) as a yellow solid, **284b** (0.36 g, 0.84 mmol, 49%) as a yellow solid. Combined yield = 0.58 g, 1.4 mmol, 81%.

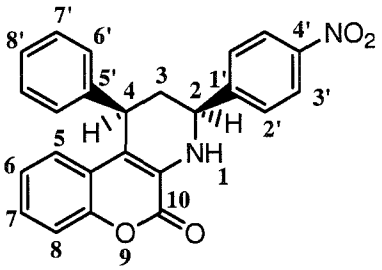
284a: R_f = 0.25 (dichloromethane). Mp = 225-226 °C (chloroform/hexane). ^1H NMR (500 MHz, $CDCl_3$): δ = 8.26 (d, 2H, *J* = 8.5 Hz, H-3'), 7.77-7.24 (m, 1H, H-5), 7.62 (d, 2H, *J* = 8.9 Hz, H-2'), 7.59-7.58 (d, 2H, *J* = 4.7 Hz, H-6'), 7.43-7.42 (t, 2H, *J* = 7.1 Hz),

7.38-7.32 (m, 4H), 5.26 (s, 1H, H-1), 5.11 (dd, 1H, J = 11.6, 3.3 Hz, H-2), 4.64 (dd, 1H, J = 3.4, 1.6 Hz, H-4), 2.34 (ddd, 1H, J = 13.4, 2.0, 2.0 Hz, H-3β), 2.20-2.12 (m, 1H, H-3α). NOE-D ($CDCl_3$): δ = 8.26 (7.62, 5.0%), 7.77-7.74 (7.43-7.42, 1.0%; 7.38-7.32; 4.0%; 4.64, 7.5%), 7.62 (8.26, 9.5%; 5.26, 1.3%; 5.11, 2.3%), 5.26 (7.2, 5.0%; 5.11, 2.5%), 5.11 (7.62, 4.6%; 5.11, 1.5%; 2.34, 3.4%), 4.64 (7.77-7.74, 8.2%; 7.62, 2.6%; 2.34, 3.4%; 2.15, 4.5%), 2.34 (7.62, 1.6%; 7.59-7.58, 1.6%; 5.11, 4.8%; 4.64, 4.3%; 2.15, 15.3%), 2.15 (7.62, 2.8%; 4.64, 4.8%; 2.34, 9.8%). ^{13}C NMR (126 MHz, $CDCl_3$): δ = 158.4 (0), 149.2 (0), 149.1 (0), 148.3 (0), 148.1 (0), 134.1 (0), 132.6 (1), 129.8 (1), 128.5 (1), 127.9 (1), 126.9 (1), 125.0 (1, C-2'), 124.4 (1, C-3'), 122.2 (1, C-5), 119.8 (0), 117.0 (1), 113.6 (0), 51.2 (1, C-2), 41.5 (1, C-4), 36.1 (2, C-3). IR (neat, ZnSe): υ_{max} = 3387 (w), 1719 (s), 1629 (m), 1599 (w), 1518 (m), 1504 (m), 1347 (m), 1328 (m), 1195 (m), 1069 (w), 782 (w), 692 (m) cm^{-1}. HRMS *m/z* [M^+] calcd for $C_{24}H_{18}N_2O_5S$ 430.0986, found 430.1015.

284b: R_f = 0.20 (dichloromethane). Mp = 200-201 °C (chloroform/hexane). ^1H NMR (500 MHz, $CDCl_3$): δ = 8.20 (d, 2H, J = 8.4 Hz, C-3'), 7.67 (dd, 1H, J = 7.6, 1.8 Hz, H-5), 7.48 (d, 2H, J = 9.4 Hz, H-2'), 7.37-7.27 (m, 6H), 7.16-7.08 (m, 2H), 5.59 (s, 1H, H-1), 4.92 (t, 1H, J = 4.6 Hz, H-2), 4.67 (t, 1H, J = 3.9 Hz, H-4), 2.71 (ddd, 1H, J = 14.4, 3.4, 3.4 Hz, H-3α), 2.60 (ddd, 1H, J = 14.6, 6.2, 6.2 Hz, H-3β). NOE-D ($CDCl_3$) δ = 8.20 (7.48, 4.1%), 7.67 (7.37-7.27, 4.5%; 7.16-7.08, 6.4%), 7.48 (8.20, 4.1%; 5.59, 1.4%; 4.92, 2.7%; 2.60, 1.8%), 5.59 (7.48, 5.3%; 4.92, 6.7%), 4.92 (7.48, 4.0%; 5.59, 2.4%; 4.07, 1.1%; 2.71, 1.9%, 2.60, 3.3%), 4.67 (7.67, 6.6%; 7.16-7.08, 2.3%; 4.92, 3.6%; 4.67, 4.0%, 2.60, 4.7%), 2.71 (7.48, 4.9%; 7.16-7.08, 2.3%, 4.92, 3.6%; 4.67, 4.0%; 2.60, 4.7%), 2.60 (4.92, 5.9%; 4.67, 6.4%; 2.71, 3.5%). ^{13}C NMR (126 MHz, $CDCl_3$): δ =

158.5 (0), 150.6 (0), 148.1 (0), 147.5 (0), 134.3 (0), 132.2 (1), 129.4 (1), 129.3 (0), 128.1 (1), 127.4 (1), 126.8 (1, C-2'), 124.9 (1), 123.9 (1, C-3'), 122.6 (1, C-5), 119.8 (0), 116.8 (1), 113.8 (0), 52.2 (1, C-2), 40.1 (1, C-4), 33.4 (2, C-3). IR (neat, ZnSe): υ_{max} = 3374 (w), 1701 (s), 1623 (m), 1516 (s), 1336 (m), 1314 (w), 1212 (m), 1073 (m), 850 (m), 741 (s), 694 (m) cm^{-1}. HRMS *m/z* [M^+] calcd for $C_{24}H_{18}N_2O_5S$ 430.0986, found 430.1001.

(2*R,4*R**)-2-(4-Nitrophenyl)-4-phenyl-1,2,3,4-tetrahydro-9-oxa-1-aza-10*H*-phenanthren-10-one (285b)**

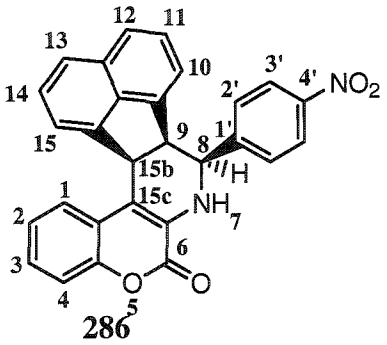


285b

Using general procedure 1, **222** (0.50 g, 1.7 mmol), styrene (0.60 mL, 5.1 mmol, 0.53 g), $Yb(OTf)_3$ (0.05 g), and acetonitrile (20 mL) were reacted for 25 min. The bright yellow suspension and went to a thick pale white suspension over the course of the reaction. A white residue was obtained and the dr ratio was determined to be 1 : 11.8, in favor of the *exo* isomer **285b** by NMR. The residue was then subjected to flash chromatography (50% dichloromethane/hexane), which afforded mixed fraction (0.32 g, 0.80 mmol, 47%) as a white solid, **285b** (0.23 g, 0.58 mmol, 34%) as a white solid. Combined yield = 0.56 g, 1.5 mmol, 82%. Not enough *endo* adduct was obtained pure enough for full characterization.

285b: R_f = 0.15 (50% dichloromethane/hexane). Mp = 249-250 °C (chloroform/hexane). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.10 (d, 2H, *J* = 8.9 Hz, H-3'), 7.50 (d, 2H, *J* = 7.1 Hz, H-2'), 7.30 (d, 1H, *J* = 7.0 Hz, H-8), 7.20 (td, 1H, *J* = 7.7, 1.3 Hz, H-7), 7.17 (m, 3H), 7.05-7.04 (m, 2H, H-6'), 7.00 (td, 1H, *J* = 7.8, 1.4 Hz, H-6), 6.93 (dd, 1H, *J* = 7.7, 1.6 Hz, H-5), 5.24 (s, 1H, H-1), 4.66 (d, 1H, *J* = 7.4 Hz, H-2), 4.44 (t, 1H, *J* = 7.6 Hz, H-4), 2.66-2.61 (dddd, 1H, *J* = 13.9, 7.0, 3.4, 1.7 Hz, H-3α), 2.33 (ddd, 1H, *J* = 17.4, 8.6, 8.6 Hz, H-3β). NOE-D ($CDCl_3$): δ = 8.10 (7.50, 4.1%), 7.50 (8.1, 6.3%; 5.24, 3.3%; 4.66, 4.4%; 2.33, 2.8%), 7.30 (7.20, 2.1%; 7.05-7.04, 0.6%), 7.20 (7.30, 1.9%; 7.05-7.04, 1.6%), 7.05-7.04 (7.50, 0.5%; 7.17-7.09, 1.1%; 4.44, 2.1%), 7.24 (7.50, 4.3%; 4.66, 4.6%), 4.66 (7.50, 4.9%; 5.24, 3.5%; 4.44, 2.4%; 2.66-2.61, 3.9%; 2.33, 2.5%), 4.44 (7.17-7.09, 3.2%; 7.05-7.04, 3.8%; 4.66, 1.3%; 2.66-2.61, 4.1%; 2.33, 1.7%), 2.66-2.61 (7.50, 1.7%; 717-7.09, 2.1%; 4.66, 4.4%; 4.44, 6.5%; 2.33, 16.9%), 2.33 (7.50, 3.5%; 7.05-7.04, 3.6%; 4.66, 1.9%; 4.44, 1.9%; 2.66-2.61, 16.7%). ^{13}C NMR (126 MHz, $CDCl_3$): δ = 158.0 (0), 149.4 (0), 148.6 (0), 147.6 (0), 142.9 (0), 131.2 (0), 129.1 (1), 127.60 (1), 127.58 (1), 127.5 (1), 127.1 (1), 126.7 (1), 124.4 (1), 124.3 (1), 124.0 (1, C-3'), 120.4 (0), 119.5 (0), 116.7 (1), 54.8 (1, C-2), 41.8 (2, C-3), 40.2 (1, C-4). IR (neat, ZnSe) υ_{max} = 3326 (w), 1696 (s), 1685 (s), 1620 (m), 1515 (s), 1497 (w), 1191 (m), 1183 (m), 746 (s), 703 (s) cm^{-1}. HRMS *m/z* [M^+] calcd for $C_{20}H_{18}N_2O_5$ 398.1265, found 398.1271.

(8*S,9*S**,15b*R**)-8-(4-Nitrophenyl)-8,8a,13a-tetrahydro-6*H*-5-oxa-7-aza-acenaphthene[2,1-*c*]phenanthren-6-one (286)**



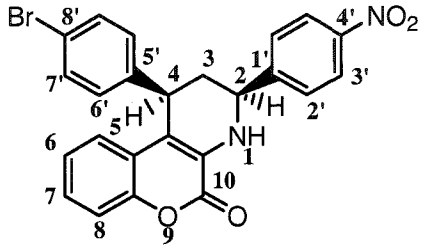
286

Using general procedure 1, **222** (0.50 g, 1.7 mmol), acenaphthylene (0.78 g, 5.1 mmol), $Yb(OTf)_3$ (0.05 g), and acetonitrile (20 mL) were reacted for 16 h. The bright yellow suspension went to a thick pale yellow suspension over the course of the reaction. The solution was then filtered and washed with pentane, which afforded **286** (0.18 g, 0.40 mmol, 24%) as a pale white solid. The mother liquor was concentrated under reduced pressure and residue was then crystallized from chloroform/hexane, which afforded **286** (0.12 g, 0.27 mmol, 16%) as a white solid. Combined yield = 0.30 g, 0.67 mmol, 40%. The dr ratio was determined to be greater than >95 : 5 in favor of the *endo* isomer by NMR.

286: Mp = >300 °C (chloroform/hexane). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.16 (d, 2H, *J* = 8.8 Hz, H-3'), 8.01-7.99 (m, 1H, H1), 7.58 (d, 2H, *J* = 8.0 Hz), 7.50-7.41 (m, 4H), 7.29 (t, 1H, *J* = 7.6 Hz), 7.24-7.20 (m, 2H), 6.07 (d, 1H, *J* = 7.2 Hz, H-10), 5.44 (d, 1H, *J* = 8.5 Hz, H-15b), 4.93-4.90 (m, 2H, H-7, H-8), 4.74 (t, 1H, *J* = 7.0 Hz, H-9). NOE-D ($CDCl_3$): δ = 8.16 (7.50-7.41, 1.2%), 8.01-7.99 (5.44, 4.3%), 7.58 (7.24-7.20, 0.5%), 4.44 (8.01-7.99, 6.1%; 4.74, 3.4%), 4.74 (5.44, 7.2%; 4.93-4.90, 1.2%). ^{13}C NMR (126 MHz, $CDCl_3$): δ = 158.7 (0), 149.6 (0), 147.7 (0), 143.3 (0), 141.0 (0), 140.2 (0), 139.7 (0), 132.0 (0), 131.5 (0), 128.6 (1), 128.14 (1), 128.11 (1), 127.5 (1), 125.5 (0), 125.0 (1),

124.4 (1), 124.2 (1), 123.6 (1, C-3'), 123.4 (1, H-1), 122.2 (1), 120.0 (1), 117.4 (1), 61.3 (1, C-7, C-8), 52.6 (1, C-9), 42.2 (1, C-15b). IR (neat, ZnSe): υ_{max} = 3304 (w), 1706 (s), 1634 (w), 1602 (w), 1521 (m), 1346 (s), 1179 (s), 794 (s) cm^{-1}. HRMS *m/z* [M^+] calcd for $C_{28}H_{18}N_2O_4$ 446.1265, found 446.1285.

(2*S, 4*S**)-(2-(4-Nitrophenyl)-4-(4-bromophenyl)-1,2,3,4-tetrahydro-9-oxa-1-aza-10*H*-phenanthren-10-one (287)**



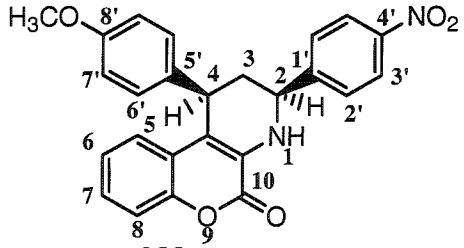
287

Using general procedure 1, **222** (0.50 g, 1.7 mmol), 4-bromostyrene (0.60 mL, 5.1 mmol, 0.59 g), $Yb(OTf)_3$ (0.05 g), and acetonitrile (20 mL) were reacted under reflux conditions for 5 min. The bright yellow suspension went to a thick pale yellow suspension over the course of the reaction. The yellow residue produced was then subjected to flash chromatography (dichloromethane), which afforded **287** as a pale yellow solid (0.57 g, 1.4 mmol, 82%). The dr ratio was determined to be greater than 95 % in favor of the *endo* isomer by NMR.

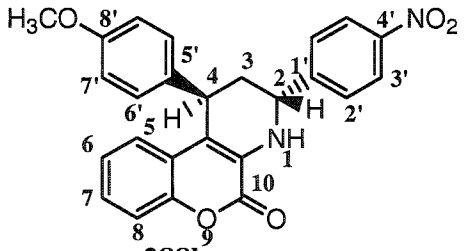
287: R_f = 0.30 (dichloromethane). Mp = 246-247 °C (chloroform/hexane). ^1H NMR (500 MHz, $CDCl_3$): δ = 8.14 (d, 2H, *J* = 10.3 Hz, H-3'), 7.50 (d, 2H, *J* = 8.8 Hz, H-2'), 7.34-7.29 (m, 3H), 7.22 (td, 1H, *J* = 7.6, 1.6 Hz), 7.01 (td, 1H, *J* = 7.3, 1.2 Hz), 6.94 (d, 2H, *J* = 8.4 Hz), 6.88 (dd, 1H, *J* = 8.4, 1.3 Hz), 5.26 (s, 1H, H-1), 4.66 (d, 1H, *J* = 8.6 Hz, H-2),

4.42 (t, 1H, J = 7.8 Hz, H-4), 2.64-2.60 (m, 1H, H-3α), 2.30-2.23 (ddd, 1H, J = 18.0, 9.0, 9.0 Hz, H-3β). NOE-D ($CDCl_3$): δ = 8.14 (7.50, 4.35%), 7.50 (8.14, 10.61%; 5.26, 5.69%; 4.66, 2.30%; 2.30-2.23, 1.52%), 6.94 (7.34-7.29, 5.61%; 5.26, 1.32%; 4.42, 3.06%, 2.30-2.23, 2.01%), 6.88 (7.01, 4.24%; 6.94, 1.29%; 4.42, 4.01%), 5.26 (7.50, 2.62%; 4.66, 3.09%), 4.66 (7.50, 4.38%; 5.26, 3.22%; 4.42, 1.44% ; 2.64-2.60, 3.00%), 2.64-2.60 (7.50, 1.02%; 4.66, 4.27%, 6.94, 1.84%; 4.42, 5.53%; 2.30-2.23, 20.3%), 2.30-2.23 (7.50, 4.27%; 6.94, 3.25%; 2.64-2.60, 18.6%). ^{13}C NMR (126 MHz, $CDCl_3$): δ = 159.0 (0), 149.3 (0), 148.8 (0), 147.9 (0), 142.2 (0), 132.5 (1), 131.6 (0), 129.5 (1, C-6'), 127.8 (1, C-2'), 127.1 (1), 124.8 (1), 124.3 (1, C-3'), 121.0 (0), 120.3 (0), 118.9 (0), 117.1 (1), 55.0 (1, C-2), 42.6 (2, C-3), 40.0 (1, C-4). IR (neat, ZnSe): υ_{max} = 3391 (w), 3386 (w), 1724 (s), 1716 (s), 1623 (w), 1510 (s), 1340 (s), 1337 (s), 1296 (m), 1094 (m), 754 (s), 752 (s) cm^{-1}. HRMS *m/z* [M^+] calcd for $C_{24}H_{17}BrN_2O_4$ 410.0195, found 476.0370.

(2*S,4*R**)-(2-(4-Nitrophenyl)-4-(4-methoxyphenyl)-1,2,3,4-tetrahydro-9-oxa-1-aza-10*H*-phenanthren-10-one (288a) and (2*R**,4*R**)-(2-(4-nitrophenyl)-4-(4-methoxyphenyl)-1,2,3,4-tetrahydro-9-oxa-1-aza-10*H*-phenanthren-10-one (288b)**



288a



288b

Using general procedure 1, **222** (0.50 g, 1.7 mmol), 4-methoxystyrene (0.70 mL, 5.1 mmol, 0.70 g), $Yb(OTf)_3$ (0.05 g), and acetonitrile (20 mL) were reacted for 20 min.

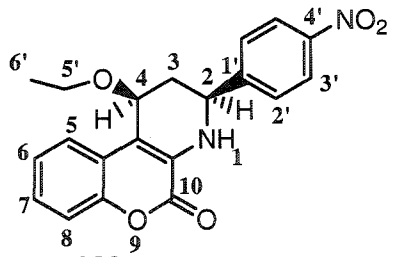
The bright yellow suspension went to a thick white suspension over the course of the reaction. A yellow residue was obtained and dr was determined to be 3 : 1, in favor of the *endo* isomer **288a** by NMR. The residue was then subjected to flash chromatography (dichloromethane), which afforded **288a** (0.19 g, 0.44 mmol, 33%) as a white solid, mixed fraction (0.21 g, 0.49 mmol, 36%) as a white solid, and **288b** as a white solid (0.18g, 0.42 mmol, 31%). Combined yield = 0.58 g, 1.4 mmol, 82%.

288a: R_f = 0.30 (dichloromethane). Mp = 123-125 °C (chloroform/hexane). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.11 (d, 2H, *J* = 8.9 Hz, H-3'), 7.49 (d, 2H, *J* = 9.1 Hz, H-2'), 7.32 (d, 1H, *J* = 8.0 Hz), 7.24-7.20 (m, 1H), 7.0-6.97 (m, 2H), 6.95 (d, 2H, *J* = 9.2 Hz, H-6'), 6.69 (d, 2H, *J* = 9.0 Hz, H-7'), 5.25 (s, 1H, H-1), 4.67 (d, 1H, *J* = 7.5 Hz, H-2), 4.40 (t, 1H, *J* = 7.3 Hz, H-4), 3.71 (s, 3H, H-9'), 2.64-2.60 (m, 1H, H-3α), 2.32 (ddd, 1H, *J* = 17.0, 8.3, 8.3 Hz, H-3β). NOE-D ($CDCl_3$): δ = 8.11 (7.49, 4.4%), 7.49 (8.11, 5.3%; 6.95, 1.9%; 5.25, 2.5%; 4.67, 3.7%), 7.32 (7.24-7.20, 1.0%; 7.01-6.97, 0.7%), 5.25 (7.49, 3.4%; 4.67, 3.6%), 4.67 (7.49, 4.3%; 5.25; 3.4%; 4.40, 1.8%; 2.64-2.60, 3.2%; 2.32, 1.9%), 4.40 (7.01-6.97 & 6.95, 8.3%; 4.67, 1.7%; 2.64-2.60, 4.2%; 2.32, 2.0%), 3.71 (6.69, 2.5%), 2.64-2.60 (7.49, 1.6%; 6.95, 1.6%; 4.67, 4.2%; 4.40, 5.3%; 2.32, 21.0%), 2.32 (7.49, 4.0%; 6.95, 3.6%; 2.64-2.60, 19.5%); ^{13}C NMR (126 MHz, $CDCl_3$): δ = 159.0 (0), 158.5 (0), 149.6 (0), 148.6 (0), 148.5 (0), 147.5 (0), 134.6 (0), 131.0 (0), 128.6 (1), 127.5 (1), 126.6 (1, C-6'), 124.5 (1, C-2'), 124.3 (1), 123.9 (1, H-3'), 120.5 (0), 119.8 (0), 116.7 (1), 114.5 (1, C-7'), 55.4 (3, C-9'), 54.8 (1, C-2), 42.3 (2, C-3), 39.3 (1, C-4). IR (neat, ZnSe): υ_{max} = 3356 (m), 2925 (w), 1702 (s), 1635 (m), 1622 (m), 1507 (s), 1341

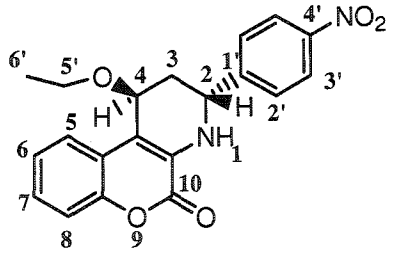
(s), 1246 (s), 1178 (m), 835 (m), 835 (m), 748 (s) cm^{-1}. HRMS *m/z* [M^+] calcd for $C_{25}H_{20}N_2O_5$ 410.1371, found 410.1345.

288b: R_f = 0.25 (dichloromethane). Mp = 123-125 °C (chloroform/hexane). ^1H NMR (500 MHz, $CDCl_3$): δ = 8.21 (d, 2H, *J* = 8.5 Hz, H-3'), 7.52 (d, 2H, *J* = 9.5 Hz, H-2'), 7.33 (d, 1H, *J* = 8.3 Hz, H-5), 7.24 (td, 1H, *J* = 7.8, 1.1 Hz), 7.19-7.15 (m, 3H), 7.10 (td, 1H, *J* = 7.7, 1.4 Hz, H-6), 6.90 (d, 2H, *J* = 8.9 Hz, H-7'), 5.15 (s, 1H, H-1), 4.44 (dd, 1H, *J* = 11.5, 3.4 Hz, H-2), 4.39 (dd, 1H, *J* = 5.2, 1.4 Hz, H-4), 3.81 (s, 3H, H-9'), 2.28-2.25 (m, 1H), 2.21-2.18 (m, 1H). NOE-D ($CDCl_3$): δ = 8.21 (7.52, 5.9%), 7.52 (8.21, 4.0%; 5.15, 2.0%; 4.44, 3.0%), 7.33 (7.19-7.15, 1.2%; 7.10, 0.9%), 6.90 (7.19-7.15, 4.0%; 3.81, 3.2%), 5.15 (7.52, 4.2%; 4.44, 4.5%), 4.39 (7.19-7.15; 9.6%; 2.28-2.25 & 2.21-2.18, 5.9%), 3.81 (6.90, 2.5%); ^{13}C NMR (126 MHz, $CDCl_3$): δ = 159.1 (0), 158.8 (0), 149.7 (0), 148.5 (0), 147.9 (0), 136.0 (0), 129.6 (0), 129.2 (1), 127.9 (1), 126.6 (1), 124.5 (1), 124.0 (1, C-3'), 122.7 (1), 120.8 (0), 117.2 (0), 116.8 (1), 114.6 (1,H-7'), 55.5 (3, C-9'), 50.8 (1, C-2), 39.7 (2, C-3). IR (neat, ZnSe): υ_{max} = 3356 (m), 2925 (w), 1702 (s), 1635 (m), 1622 (m), 1507 (s), 1341 (s), 1246 (s), 1178 (m), 835 (m), 835 (m), 748 (s) cm^{-1}. HRMS *m/z* [M^+] calcd for $C_{25}H_{20}N_2O_5$ 410.1371, found 410.1352.

(2*R, 4R*)-4-Ethoxy-2-(4-nitrophenyl)-1,2,3,4-tetrahydro-9-oxa-1-aza-10*H*-phenanthren-10-one (289a) and (2*S**, 4R*)-4-ethoxy-2-(4-nitrophenyl)-1,2,3,4-tetrahydro-9-oxa-1-aza-10*H*-phenanthren-10-one (289b)**



289a



289b

Using general procedure 1, **222** (0.50 g, 1.7 mmol), ethyl vinyl ether (0.80 mL, 8.5 mmol, 0.61 g), $Yb(OTf)_3$ (0.05 g), and acetonitrile (10 mL) were reacted for 25 min. The bright yellow suspension remained a clear bright yellow over the course of the reaction. A yellow residue was obtained and the dr was determined to be 1 : 1.7, in favor of the *exo* isomer **289b** by NMR. The residue was then subjected to flash chromatography (90% dichloromethane/hexane), which afforded **289a** (0.18 g, 0.51 mmol, 30%) as a pale yellow solid, mixed fraction (0.10 g, 0.28 mmol, 17%) as a pale yellow solid, **289b** (0.17 g, 0.48 mmol, 29%) as a pale yellow solid. Combined yield = 0.45 g, 1.2 mmol, 76%.

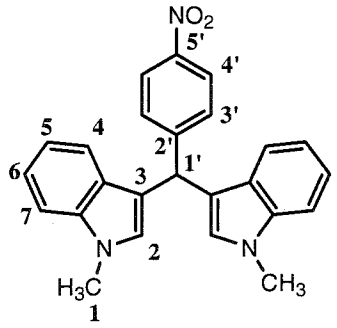
289a: R_f = 0.31 (90% dichloromethane/hexane). Mp = 156-157 °C (chloroform/hexane). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.18 (d, 2H, *J* = 9.1 Hz, H-3'), 7.53 (d, 2H, *J* = 8.3 Hz, H-2'), 7.45 (dd, 1H, *J* = 9.1, 1.8 Hz, H-5), 7.33 (td, 1H, *J* = 7.6, 1.6 Hz), 7.30-7.24 (m, 2H), 5.50 (s, 1H, H-1), 4.91 (dd, 1H, *J* = 8.1, 4.4 Hz, H-2), 4.80 (t, 1H, *J* = 3.8 Hz, H-4), 3.41 (m, 1H, H-5'), 3.33 (m, 1H, H-5'), 2.75 (dt, 1H, *J* = 14.4, 4.2 Hz, H-3β), 2.33 (dt, 1H, *J* = 14.6, 4.9 Hz, H-3α), 0.81 (t, 2H, *J* = 6.6 Hz). NOE-D ($CDCl_3$): δ = 8.19 (7.53, 3.6%), 7.53 (8.19, 4.9%; 5.50, 2.7%; 4.91, 3.2%; 2.75, 3.2%), 7.45 (0.81, 4.1%), 5.50 (7.53, 3.5%; 4.91, 3.4%; 3.41, 2.4%; 0.81, 1.6%), 4.91 (7.53, 3.5%; 5.50, 3.2%; 2.75, 2.0%, 2.33, 3.6%), 4.80 (7.45, 5.0%; 3.41, 3.2%; 3.33, 4.8%; 0.81, 2.7%), 3.33 (4.80,

1.2%; 3.41, 2.6%; 2.75, 2.4%; 0.81, 2.7%), 2.75 (7.53, 3.5%; 4.91, 2.0%; 4.80; 2.2%; 3.41, 1.0%; 3.33, 3.8%; 2.33, 16.8%), 2.33 (4.91, 3.5%; 4.80, 3.5%; 2.75, 17.3%); 0.81 (2.75, 2.1%; 2.33, 2.0%). ^{13}C NMR (126 MHz, $CDCl_3$): δ = 158.0 (0), 150.6 (0), 148.3 (0), 147.2 (0), 129.2 (0), 126.9 (1, C-2'), 126.7 (1), 125.1 (1), 124.0 (1, C-3'), 122.3 (1, C-5), 120.4 (0), 116.8 (1), 115.4 (0), 68.2 (1, C-4), 63.4 (2, C-5'), 52.0 (1, C-2), 32.1 (2, C-3), 15.2 (3, C-6'). IR (neat, ZnSe): υ_{max} = 3376 (m), 2957 (w), 1701 (s), 1626 (w), 1596 (w), 1574 (w), 1513 (s), 1338 (s), 1200 (s), 1081 (s), 931 (w), 760 (s), 738 (s) cm^{-1}. HRMS *m/z* [M^+] calcd for $C_{20}H_{18}N_2O_5$ 366.1214, found 366.1195.

289b: R_f = 0.25 (90% dichloromethane/hexane). Mp = 168-169 °C (chloroform/hexane). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.30 (d, 2H, *J* = 9.2 Hz, H-3'), 7.68 (d, 2H, *J* = 7.9 Hz, H-2'), 7.53-7.50 (m, 1H, H-5), 7.35-7.31 (m, 3H), 6.25 (s, 1H, H-1), 4.71-4.68 (m, 2H, H-2, H-4), 3.98-3.92 (m, 1H), 3.77-3.71 (m, 1H), 2.49-2.45 (m, 1H), 1.88-1.82 (m, 1H), 1.37 (t, 2H, *J* = 6.6 Hz). ^{1}H NMR (500 MHz, benzene-*d*6): δ = 7.82 (d, 2H, J = 9.1 Hz, H-3'), 7.32 (dd, 1H, J = 7.5, 1.0 Hz, H-2'), 7.12 (dd, 1H, J = 8.4, 1.4 Hz, H-8), 7.03 (td, 1H, J = 7.7, 1.2 Hz, H-6), 6.92 (td, 1H, J = 7.6, 1.6 Hz, H-7), 6.74 (d, 2H, J = 7.8 Hz, H-2'), 4.84 (s, 1H, H-1), 4.08-4.06 (m, 2H, H-3), 3.39-3.36 (m,1H, H-5'), 3.22-3.18 (m, 1H, H-5'), 1.80-1.77 (m, 1H, H-6'). NOE-D (benzene-*d*6): δ = 7.82 (6.74, 5.7%), 7.32 (7.03, 2.6%; 4.08-4.06, 6.1%), 7.03 (7.32, 6.8%), 6.92 (7.12, 1.8%; 7.03, 1.0%), 6.74 (7.82, 5.8%; 4.84, 3.3%; 4.08-4.06, 4.4%), 4.84 (6.74, 4.2%; 4.08-4.06, 4.4%), 4.08-4.06 (7.32, 5.1%; 6.74, 5.9%; 4.84, 3.6%; 3.39-3.36, 4.5%; 3.22-3.18, 3.5%; 1.80-1.77, 5.0%), 3.39-3.36 (4.84, 1.0%; 3.22-3.18, 2.9%; 1.12-1.06, 1.7%), 3.22-3.18 (4.08-4.06, 1.0%; 3.39-3.36, 4.5%; 1.12-1.06, 6.1%), 1.80-1.77 (6.74, 1.2%; 4.08-4.06, 5.7%; 3.39-3.36, 3.7%;

1.12-1.06, 15.5%), 1.12-1.06 (4.08-4.06, 2.1%; 1.80-1.77, 6.1%). ^{13}C NMR (126 MHz, $CDCl_3$): δ = 158.0 (0), 149.3 (0), 148.5 (0), 148.1 (0), 130.1 (0), 128.1 (1, C-2'), 126.8 (1), 125.1 (1), 124.4 (1, C-3'), 121.8 (1, C-5), 120.6 (0), 117.0 (0), 115.3 (0), 68.3 (1,), 64.5 (2, C-5'), 51.4 (1), 35.3 (2, C-3), 16.1 (3, C-6'). IR (neat, ZnSe): υ_{max} = 3393 (w), 3363 (w), 2952 (w), 1715 (s), 1631 (w), 1600 (w), 1518 (m), 1506 (m), 1348 (m), 1335 (m), 1194 (s), 1076 (s), 761 (s), 750 (m) cm^{-1}. HRMS *m/z* [M^+] calcd for $C_{20}H_{18}N_2O_5$ 366.1214, found 366.1103.

(±)-3-[(4-Nitrophenyl)methyl]-1-methyl-1*H*-indole (291)

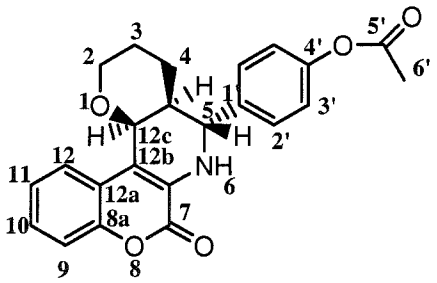


Using general procedure 1, **222** (0.50 g, 1.7 mmol), 4-bromostyrene (0.70 mL, 5.1 mmol, 0.67 g), $Yb(OTf)_3$ (0.05 g), and acetonitrile (10 mL) were reacted for 5 min. The yellow suspension went to a clear bright orange solution over the course of the reaction. The orange residue produced was then subjected to flash chromatography (50% dichloromethane/hexane), which afforded **291** as a bright orange solid (0.67 g, 1.5 mmol, 99%).

291: R_f = 0.54 (50% dichloromethane/hexane). Mp = 209-210 °C (chloroform/hexane). ^1H NMR (500 MHz, $CDCl_3$): δ = 8.12 (d, 2H, *J* = 9.2 Hz, H-4'), 7.49 (d, 2H, *J* = 8.4 Hz,

H-3'), 7.33 (d, 2H, J = 4.1 Hz), 7.31 (d, 2H, J = 4.3 Hz), 7.25 (m, 2H), 7.01 (t, 2H, J = 7.8 Hz), 6.53 (s, 2H, H-2), 5.97 (s, 1H, H-1'), 3.70 (s, 6H, H-1). ^{13}C NMR (126 MHz, $CDCl_3$): δ = 152.5 (0), 146.7 (0), 137.7 (0), 129.7 (1), 128.5 (1, C-2), 127.3 (0), 123.8 (1), 122.0 (1), 119.9 (1), 119.3 (1), 116.9 (0), 109.5 (1), 40.3 (1, C-1'), 33.0 (3, C-1). IR (neat, ZnSe): υ_{max} = 2952 (w), 1592 (w), 1510 (m), 1472 (m), 1339 (s), 1010 (w), 732 (s) cm^{-1}. HRMS *m/z* [M$^+$] calcd for $C_{25}H_{20}N_3O_2$ 395.1623, found 395.1632.

5-(4-Acetoxyphenyl)-3,4,4a,5,6,12c-hexahydro-7*H*-1,8-dioxa-6-aza-2*H*-pyrano[5,6-*c*]phenanthren-7-one (298)



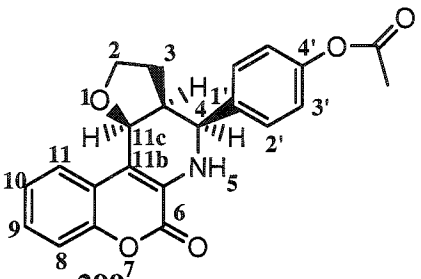
298

Using general procedure 2, **222** (0.30 g, 1.9 mmol), 4-acetoxybenzaldehyde (0.30 mL, 1.9 mmol, 0.32 g), 3,4-dihydro-2*H*-pyran (0.50 mL, 5.6 mmol, 0.39 g), $Yb(OTf)_3$ (0.05 g), and acetonitrile (30 mL) were reacted at reflux for 2.5 d. The bright yellow suspension turned paler over the course of the reaction. The yellow residue produced was subjected to flash chromatography (dichloromethane), which afforded **298** as a white solid (0.40 g, 1.0 mmol, 55%). The dr was determined to be greater than >95 : 5 in favor of the *exo* isomer by NMR.

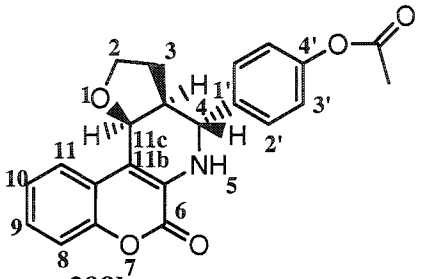
298: R_f = 0.40 (dichloromethane). Mp = 230-231 °C (chloroform/hexane). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.57-756 (m, 1H, H-12), 7.45 (d, 2H, *J* = 8.5 Hz, H-2'), 7.30-7.25 (m, 3H), 7.15 (d, 2H, *J* = 8.3 Hz, H-3'), 5.09 (s, 1H, H-6), 4.78 (d, 1H, *J* = 11.5 Hz, H-5), 4.71 (d, 1H, *J* = 2.8 Hz, H-12c), 4.20-4.16 (m, 1H, H-2β), 3.81 (td, 1H, *J* = 11.5, 2.2 Hz, H-2α), 2.33 (s, 3H, H-6'), 2.09-2.06 (m, 1H, H-4a), 1.92-1.88 (m, 1H), 1.81-176 (m, 1H), 1.62-1.60 (m, 1H, H-3α), 1.45-1.42 (m, 1H, H-3β). NOE-D ($CDCl_3$): δ = 7.57-7.56 (7.30-7.25, 4.5%; 4.71, 8.0%; 3.81, 1.4%), 7.45 (7.15, 4.0%; 5.09, 1.9%; 4.78, 3.9%; 2.09-2.06, 3.0%), 7.15 (7.45, 4.1%; 2.33, 1.9%), 5.09 (7.45, 3.8%; 4.78, 8.0%), 4.78 (7.45, 6.2%; 5.09, 2.4%; 2.09-2.06, 1.7%, 1.92-1.88, 3.6%), 4.71 (7.57-7.56, 9.4%; 3.81, 5.1%; 2.33, 1.6%; 2.09-2.06, 5.9%; 1.92-1.88, 3.2%), 4.20-4.26 (3.81, 16.6%; 2.33, 1.4%; 1.92-1.88, 5.6%; 1.45-1.42, 3.8%), 3.81 (7.57-7.56, 1.3%; 4.71, 4.8%; 4.20-4.16, 17.4%; 2.33, 1.2%; 1.87-1.76, 3.6%; 1.62-1.60, 4.1%), 2.09-2.06 (7.45, 4.2%; 5.09, 1.2%; 4.78, 1.0%; 4.71, 4.3%; 1.92-1.88, 2.0%; 1.62-1.60, 2.0%). ^{13}C NMR (126 MHz, $CDCl_3$): δ = 169.5 (0), 158.0 (0), 150.9 (0), 148.4 (0), 137.9 (0), 130.3 (0), 129.1 (1, C-3'), 126.3 (1), 125.0 (1), 122.2 (1, C-2'), 121.9 (1, C-12), 120.7 (0), 116.7 (1), 114.5 (0), 70.1 (1, C-12c), 69.4 (2, C-2), 54.0 (1, C-5), 38.7 (1, C-4a), 24.4 (2), 22.8 (2), 21.4 (3, C-6'). IR (neat, ZnSe): υ_{max} = 3411 (w), 2937 (w), 2852 (w), 1717 (s), 1635 (m), 1507 (m), 1184 (s), 1061 (s), 1043 (s), 791 (s) cm^{-1}. HRMS *m/z* [M^+] calcd for $C_{23}H_{21}NO_5$ 391.1418, found 391.1406.

(3a*S, 4*R**, 11c*S**)-4-(4-Acetoxyphenyl)-2,3,3a,4,5,11c-hexahydro-2*H*-1,7-dioxa-6-aza-6*H*-furano[4,5-*c*]phenanthren-6-one (299a) and (3a*S**, 4*S**, 11c*S**)-4-(4-**

acetoxyphenyl)-2,3,3a,4,5,11c-hexahydro-2*H*-1,7-dioxa-6-aza-6*H*-furano[4,5-*c*]phenanthren-6-one (299a)



299a



299b

Using general procedure 2, **212** (0.30 g, 1.9 mmol), 4-acetoxybenzaldehyde (0.30 mL, 1.9 mmol, 0.32 g), 3,4-dihydrofuran (0.42 mL, 5.6 mmol, 0.39 g), $Yb(OTf)_3$ (0.05 g), and acetonitrile (30 mL) were reacted at reflux for 2.5 d. The bright yellow suspension went to a thick pale yellow suspension over the course of the reaction. A yellow residue was obtained and dr ratio was determined to be 1 : 1 by NMR. The residue was subjected to flash chromatography (dichloromethane), which afforded **299a** (0.08g, 0.21 mmol, 11%) as a white solid, mixed fraction (0.01g, 0.03mmol, 1%) as a white solid, **299b** (0.01g 0.03 mmol, 1%) as a white solid. Combined yield = 0.21 g, 0.56 mmol, 15%.

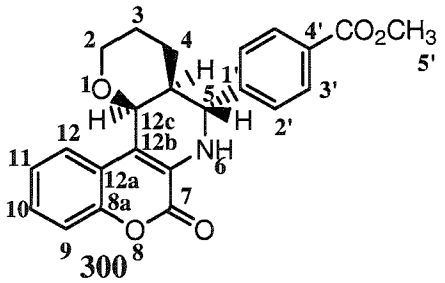
299a: R_f = 0.60 (dichloromethane). Mp = 183-184 °C (chloroform/hexane). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.83-7.81 (m, 1H, H-11), 7.52-7.50 (m, 2H, H-2'), 7.33-7.27 (m, 3H), 7.16-7.14 (m, 2H, H-3'), 5.49 (d, 2H, *J* = 7.4 Hz, H-11c), 4.94 (s, 1H, H-5), 4.72 (d, 1H, *J* = 2.8 Hz, H-4), 3.91 (td, 1H, *J* = 8.6, 2.7 Hz, H-2α), 3.81-3.76 (m, 1H, H-2β), 2.95-2.92 (m, 1H, H-3a), 2.23-2.16 (m, 1H, H-3α), 1.68-1.62 (m 1H, H-3β). NOE-D ($CDCl_3$): δ = 7.83-7.81 (7.33-7.27, 4.9%; 5.49, 5.1%), 7.52-7.50 (7.16-7.14, 4.3%; 4.94, 3.1%; 4.72, 3.9%; 2.95-2.92, 2.6%; 2.33-2.16, 3.2%; 1.68-1.61, 1.6%), 7.16-7.11 (7.52-7.50;

4.4%), 5.49 (7.52-7.50, 5.6%; 4.72, 2.2%; 2.95-2.92, 6.1%), 4.74 (7.52-7.50, 3.8%; 4.72, 3.1%), 4.72 (7.52-7.50, 5.2%; 5.49, 1.8%; 4.74, 2.3%; 2.95-2.92, 3.9%), 3.91 (3.79, 6.7%; 2.33-2.16, 3.5%; 1.68-1.62, 2.1%), 3.79 (5.49, 1.0%; 3.91, 6.8%; 2.23-2.16, 3.5%; 1.68-1.62, 2.1%), 2.95-2.92 (7.52-7.50, 3.4%; 5.49, 6.0%; 4.72, 4.3%; 3.79, 2.1%; 2.23-2.16, 1.7%; 1.68-1.62, 4.5%), 2.23-2.16 (3.91, 3.7%; 2.95-2.92, 0.9%; 1.68-1.62, 14.5%), 1.68-1.62 (7.52, 1.8%; 3.91, 1.4%; 3.79, 3.7%; 2.95-2.92, 4.9%; 2.23-2.16, 16.4%). ^{13}C NMR (126 MHz, $CDCl_3$): δ = 169.0 (0, C-5'), 158.9 (0), 150.6 (0), 148.9 (0), 138.1 (0), 129.8 (0), 127.8 (1, C-2'), 127.1 (1), 124.8 (1), 124.5 (1, C-11), 122.2 (1, C-3'), 120.3 (0), 118.8 (0), 116.6 (1), 73.0 (1, C-11c), 67.7 (2, C-2), 57.6 (1, C-4), 47.0 (1, C-3c), 25.9 (2, C-3), 22.1 (3, C-6'). IR (neat, ZnSe): υ_{max} = 3371 (w), 2869 (w), 1709 (s), 1631 (w), 1502 (m), 1204 (s), 1186 (vs), 1050 (m), 778 (s) cm^{-1}. HRMS *m/z* [M^+] calcd for $C_{22}H_{19}NO_5$ 377.1262, found 377.1258.

299b: R_f = 0.40 (dichloromethane). Mp = 158-159 °C (chloroform/hexane). ^1H NMR (500 MHz, $CDCl_3$): δ = 7.78-7.75 (m, 1H, H-11), 7.46 (d, 2H, *J* = 9.1 Hz, H-2'), 7.32-7.30 (m, 3H), 7.16 (m, 2H, *J* = 8.3, H-3'), 5.25 (s, 1H, H-5), 4.75 (d, 1H, *J* = 5.1 Hz, H-11c), 4.10 (ddd, 1H, *J* = 8.2, 6.4 Hz, H-2β), 3.97 (ddd, 1H, *J* = 9.0, 5.4 Hz, H-2α), 3.84 (d, 1H, *J* = 11.1 Hz, H-4), 2.52-2.47 (m, 1H, H-3a), 2.18-2.12 (m, 1H, H-3β), 1.84-1.78 (m, 1H, H-3α). NOE-D ($CDCl_3$): δ = 7.78-7.75 (7.32-7.30, 4.8%; 4.75, 6.2%), 7.48-7.45 (7.18-7.15, 5.0%; 5.25, 2.8%; 3.84, 5.7%; 2.57-2.47, 3.2%; 1.84-1.78, 2.5%), 7.48-7.45 (7.18-7.15, 4.7%), 5.25 (7.48-7.45, 3.9%; 3.84, 5.3%; 2.34, 3.7%), 5.25 (7.48-7.45, 3.9%; 3.84, 5.3%; 2.34, 3.7%), 4.75 (7.78, 6.2%; 3.97, 2.3%; 2.52-2.47, 5.7%; 2.18-2.12, 1.8%), 4.10 (3.97, 9.0%; 3.84, 1.5%; 2.18-2.12, 1.5%; 1.84-1.78, 3.4%), 3.97 (4.75,

1.5%, 4.10, 7.6%; 2.18-2.12, 3.6%; 1.84-1.78, 1.3%), 3.84 (7.48, 7.0%; 5.25, 3.2%; 4.10, 1.2%; 2.52-2.47, 1.3%; 1.84-1.78, 3.8%), 2.52-2.47 (7.48, 4.3%; 4.75, 6.7%; 3.84, 2.6%; 2.18-2.12, 2.9%; 1.84-1.78, 2.0%), 2.18-2.12 (4.75, 1.7%, 4.10, 1.4%; 3.97, 4.1%; 2.52-2.47, 3.6%; 1.84-1.78, 12.5%), 1.84-1.78 (7.48, 2.2%; 4.1 , 3.3%; 3.97, 1.6%; 3.84, 3.1%; 2.52-2.47, 2.5%; 2.18-2.12, 13.4%). ^{13}C NMR (126 MHz, $CDCl_3$): δ = 169.6 (0, C-5'), 158.8 (0), 151. (0), 148.4 (0), 137.6 (0), 130.8 (0), 129.5 (1, C-2'), 126.8 (1), 12.51 91), 123.2 (1, C-11), 122.3 (1, C-3'), 121.2 (0), 116.6 (1), 116.0 (0), 72.9 (1, C-11c), 65.9 (2, C-2), 57.1 (1, C-4), 43.1 (1, C-3a), 28.6 (2, C-3), 21.3 (3, C-6'). IR (neat, ZnSe): υ_{max} = 3305 (m), 1744 (s), 1730 (s), 105 (m), 1242 (s), 1176 (s), 1046 (m), 787 (s) cm^{-1}. HRMS *m/z* [M^+] calcd for $C_{22}H_{19}NO_5$ 377.1262, found 377.1280.

(4a*S, 5*S**,12c*R**)-4-(7-Oxo-2,3,4,4a,5,6,7,12c-octahydro-1,8-dioxa-6-aza-benzo[*c*]phenanthren-5-yl)benzoic acid methyl ester (300)**



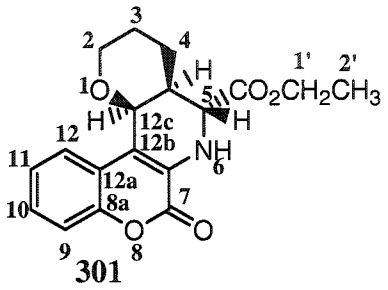
300

Using general procedure 2, **212** (0.30 g, 1.9 mmol), methyl 4-formylbenzoate (0.32 g, 1.9 mmol), dihydropyran (0.50 mL, 0.47 g, 5.6 mmol), $Yb(OTf)_3$ (0.05 g), and acetonitrile (40 mL) were reacted for 7 d. The thick yellow suspension went to a thick pale white suspension over the course of the reaction. A white residue was obtained and the dr ratio was determined to be 95 : 5 in favor of the *exo* isomer by NMR. The residue

produced was then subjected to flash chromatography (dichloromethane), which afforded **300** as a white solid (0.22 g, 0.56 mmol, 31%).

300: R_f = 0.30 (dichloromethane). Mp = 206-207 °C (chloroform/hexane). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.08 (d, 2H, *J* = 7.6 Hz, H-3'), 7.57-7.55 (m, 1H, H-12), 7.56 (d, 2H, *J* = 7.3 Hz, H-2'), 7.30-7.25 (m, 3H), 5.11 (s, 1H, H-6), 4.82 (d, 1H, *J* = 11.5 Hz, H-5), 4.70 (d, 1H, *J* = 3.4 Hz, H-12c), 4.19-4.16 (m, 1H, H-2β), 3.94 (s, 3H, H-5'), 3.81 (td, 1H, *J* = 11.9, 2.1 Hz, H-2α), 2.11-2.08 (m, 1H, H-4a), 1.93-1.87 (m, 1H, H-4β), 1.82-1.75 (m, 1H), 1.62-1.60 (m, 1H), 1.50 (d, 1H, *J* = 14.1 Hz), 1.44 (d, 1H, *J* = 12.1 Hz). NOE-D ($CDCl_3$): δ = 8.08 (7.50, 3.9%; 3.94, 2.6%), 7.57-7.55 (7.30-7.25, 5.6%; 4.70, 7.6%), 7.50 (8.08, 5.2%; 5.11, 1.4%; 4.82, 3.3%; 2.11-2.08, 1.8%; 1.93-1.87, 1.6%; 1.50, 1.0%), 5.11 (7.50, 3.8%; 4.82, 3.5%; 3.94, 2.9%), 4.82 (7.50, 7.2%; 5.11, 3.1%; 2.11-2.08, 2.0%; 1.93-1.87, 3.8%; 1.50, 1.8%), 4.70 (7.57-7.55, 8.6%; 3.81, 3.8%; 2.11-2.08, 5.3%; 1.82-1.75, 2.6%), 4.19-4.16 (3.81, 18.0%; 1.93-1.87, 4.5%; 1.44, 3.2%), 3.81 (7.57-7.55, 1.7%; 4.70, 4.4%; 1.82-1.75, 3.8%; 1.44, 4.7%), 2.11-2.08 (7.50, 4.3%; 4.70, 4.5%; 1.82-1.75, 2.6%; 1.50, 2.3%), 1.93-1.87 (7.50, 3.0%; 4.82, 4.6%; 4.19-4.16, 4.6%; 3.81, 1.7%; 1.62-1.60, 4.7%, 1.50, 16.9%), 1.82-1.75 (4.70, 2.8%; 3.81, 3.3%; 2.11-2.08, 3.7%; 1.93-1.87, 12.8%; 1.50, 18.3%; 1.44, 4.3%). ^{13}C NMR (126 MHz, $CDCl_3$): δ = 166.8 (0), 159.0 (0), 148.4 (0), 145.6 (0), 130.6 (0), 130.6 (0), 130.38 (0), 130.35 (0), 130.2 (1, C-3'), 126.4 (1, H-12), 125.0 (1), 120.6 (1, H-2'), 116.7 (1), 114.8 (1), 69.9 (1, C-12c), 69.3 (2, C-2), 54.43 (1, C-5), 54.35 (3, C-5'), 38.7 (2), 23.7 (2), 22.0 (2). IR (neat, ZnSe) υ_{max} = 3400 (w), 2844 (w), 1714 (s), 1704 (s), 1506 (w), 1279 (m), 1058 (m), 783 (s) cm^{-1}. HRMS *m/z* [M^+] calcd for $C_{23}H_{21}NO_5$ 391.1418, found 391.1424.

(4a*S,5*R**,12c*S**)-4-(7-Oxo-2,3,4,4a,5,6,7,12c-octahydro-1,8-dioxa-6-aza-benzo[*c*]phenanthren-5-carboxylic acid ethyl ester)benzoic acid methyl ester (301)**



301

Using general procedure 2, **212** (0.30 g , 1.9 mmol), ethyl glyoxalate solution in toluene (0.65 mL, 0.67 g, 5.6 mmol), dihydropyran (0.50 mL, 0.47 g, 5.6 mmol), $Yb(OTf)_3$ (0.05 g), and acetonitrile (40 mL) were reacted under reflux for 2.5 d. The thick yellow suspension and went to a thick pale white suspension over the course of the reaction. A white residue was obtained and the dr ratio was determined to be >95 : 5 in favor for the *exo* isomer. The residue produced was then subjected to flash chromatography (dichloromethane), which afforded **301** as a white solid (0.15 g, 0.45 mmol, 26%).

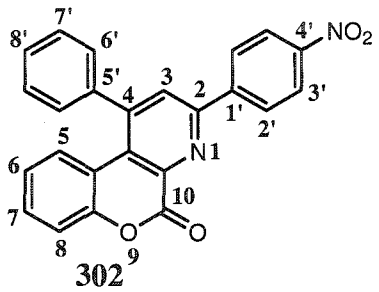
301: R_f = 0.20 (dichloromethane). Mp = 102-103 °C (chloroform/hexane). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.60-7.58 (m, 1H, H-12), 7.28-7.22 (m, 3H), 5.26 (s, 1H, H-6), 4.69 (d, 1H, *J* = 3.4 Hz, H-12c), 4.39 (d, 1H, *J* = 10.2 Hz, H-5), 4.30 (q, 2H, *J* = 7.2 Hz, H-1'), 4.03-4.01 (m, 1H, H-2β), 3.80 (td, 1H, *J* = 10.2, 2.8 Hz, H-2α), 2.18-2.15 (m, 1H, H-4a), 2.12-2.10 (m, 1H), 2.01-1.91 (m, 2H), 1.58-1.54 (m, 1H), 1.34 (t, 3H, *J* = 6.9 Hz, H-2'). NOE-D ($CDCl_3$): δ = 7.60-7.58 (7.28-7.22, 3.2%; 4.69, 5.6%), 5.26 (4.39, 3.4%), 4.69 (7.60-7.58, 5.8%; 3.80, 3.5%; 2.18-2.15, 4.5%; 2.12-2.10, 2.8%), 4.39 (5.26, 3.0%; 2.18-

2.15, 3.1%; 2.12-2.10, 3.6%), 4.03-4.01 (3.80, 11.4%; 2.12-2.10, 4.0%; 1.58-1.54, 3.2%), 3.80 (4.69, 3.7%; 4.03-4.01, 10.4%; 2.01-1.91, 3.3%; 1.58-1.54, 3.5%). ^{13}C NMR (126 MHz, $CDCl_3$): δ = 171.5 (0), 158.6 (0), 148.4 (0), 128.9 (0), 126.5 (1), 125.0 (1), 122.1 (1), 120.4 (0), 116.7 (1, C-12), 114.4 (0), 69.9 (1, C-12c), 68.4 (2, C-2), 62.0 (2, C-1'), 53.5 (1, C-5), 35.1 (1, C-4a), 24.4 (2), 22.2 (2), 14.4 (3, C-2'). IR (neat, ZnSe) υ_{max} = 3418 (w), 2938 (w), 2872 (w), 1737 (s), 1706 (s), 1616 (w), 1500 (m), 1260 (m), 1198 (s), 1190 (s), 1088 (m), 784 (s), 779 (s) cm^{-1}. HRMS *m/z* [M^+] calcd for $C_{18}H_{19}NO_5$ 329.1262, found 329.1284.

General Procedure 3: Aromatization of Diels-Alder adducts.

To a solution of Diels-Alder adduct in dichloromethane was added dropwise bromine (1M solution in dichloromethane, 2.1 equivalents) in the dark over a 15 to 30 min period. The resulting mixture was stirred at room temperature overnight. Solid sodium hydrogen sulfate was added to the reaction and the mixture was diluted with ethyl acetate. The solution was then washed with 1 M aqueous sodium carbonate solution and dried ($MgSO_4$). The solvent was removed under reduced pressure and the residue was crystallized from chloroform/hexane.

2-(4-Nitrophenyl)-4-phenyl-9-oxa-1-aza-phenanthren-10-one (302)

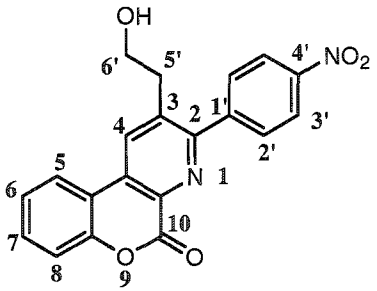


302

Using general procedure 3, **285** (0.24 g, 0.66 mmol), dichloromethane (20 mL), and bromine solution (1.80 mL, 1.8 mmol, 0.28 g) were reacted. The clear brown solution went to a thick bright yellow suspension over the course of the reaction, $NaHSO_4$ (0.20 g) was added to the reaction mixture and the solution was diluted ethyl acetate (30 mL). Crystallization afforded **302** (0.17 g, 0.43 mmol, 71%) as a white solid.

304: Mp = >300 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.42 (d, 2H, J = 7.0 Hz, H-3'), 8.37 (d, 2H, J = 8.9 Hz, H-2'), 8.04 (s, 1H, H-3), 7.61-7.58 (m, 3H), 7.48-7.44 (m, 2H), 7.43-7.40 (m, 2H), 7.10 (d, 1H, J = 7.2 Hz), 6.94-6.90 (m, 1H). ^{13}C NMR (126 MHz, $CDCl_3$): δ = 158.9 (0), 155.0 (0), 151.4 (0), 151.3 (0), 149.8 (0), 149.1 (0), 143.1 (0), 139.9 (0), 139.5 (0), 131.3 (1), 129.9 (1), 129.7 (1), 128.5 (1, C-3'), 128.3 (1, H-3), 128.2 (1), 128.1 (1), 124.4 (1, H-2'), 124.2 (1), 118.2 (1), 117.0 (0). IR (neat, ZnSe): υ_{max} = 1783 (s), 1652 (w), 1558 (m), 1458 (w), 1339 (s), 1160 (m), 862 (m), 757 (s), 703 (m) cm^{-1}. HRMS *m/z* [M^+] calcd for $C_{24}H_{14}N_2O_4$ 394.0952, found 394.0955.

3-(2-Hydroxyethyl)-2-(4-nitrophenyl)-9-oxa-1-aza-phenanthren-10-one (303)



303

Using general procedure 3, **281** (0.13 g, 0.36 mmol), dichloromethane (20 mL) and bromine solution (0.75 mL, 0.75 mmol, 0.12 g) were reacted. The clear colorless solution went to a thick bright yellow suspension over the course of the reaction. $NaHSO_4$ (0.20 g) was added to the reaction mixture and the solution was diluted with ethyl acetate (30.0 mL). Crystallization afforded **305** as a white solid (0.12 g, 0.33 mmol, 93%). Mp = 160-161 °C. ^{1}H NMR (500 MHz, DMSO-d6): δ = 8.95 (s, 1H, H-4), 8.45 (dd, 1H, J = 8.0 Hz, 0.9 Hz), 8.40 (d, 2H, J = 12.5 Hz), 8.31 (s, 1H), 7.94-7.91 (m, 2H), 7.65 (td, 1H, J = 7.8, 1.4 Hz), 7.48 (d, 2H, J = 7.3 Hz), 3.72 (t, 2H, J = 6.3 Hz), 3.01 (t, 2H, J = 6.4 Hz). ^{13}C NMR (126 MHz, DMSO-*d*6): δ = 158.3 (0), 157.8 (0), 150.8 (0), 147.4 (0), 145.4 (0), 139.7 (0), 135.3 (0), 133.0 (0), 131.5 (1), 130.7 (1), 124.8 (1), 124.4 (1), 123.4 (1), 117.2 (1), 116.6 (0), 60.6 (2), 35.4 (2). IR (neat, ZnSe): υ_{max} = 3454 (vs), 1740 (s), 1602 (m), 1517 (s), 1431 (w), 1343 (s), 1176 (s), 1026 (s), 553 (m), 759 (m) cm^{-1}. HRMS *m/z* [M^+] calcd for $C_{24}H_{14}N_2O_4$ 362.1130, found 361.0814.

Chapter 4: Compounds for Collaborative Studies

4.1 – Introduction

The recognition that 2-azadienes of the general structure **306** were bichromophoric systems piqued the interest of Dr. D. W. Thompson (Memorial University of Newfoundland), who is very interested in studying electron transfer. Samples of all of the dienes that were prepared in this work were given to Dr. Thompson and initial studies of their photophysical properties led to the observation of some very unusual behavior. Of particular interest were compounds **223** and **224** (Figure 4.1). To further probe this unusual behavior, some related compounds were identified as subjects for further study, i.e. **307** - **310** (Figure 4.1) syntheses of these compounds are described below. Details of the work regarding the photochemistry of these compounds are beyond the scope of this thesis and will be discussed in detail in forthcoming theses and publications from the Thompson group.

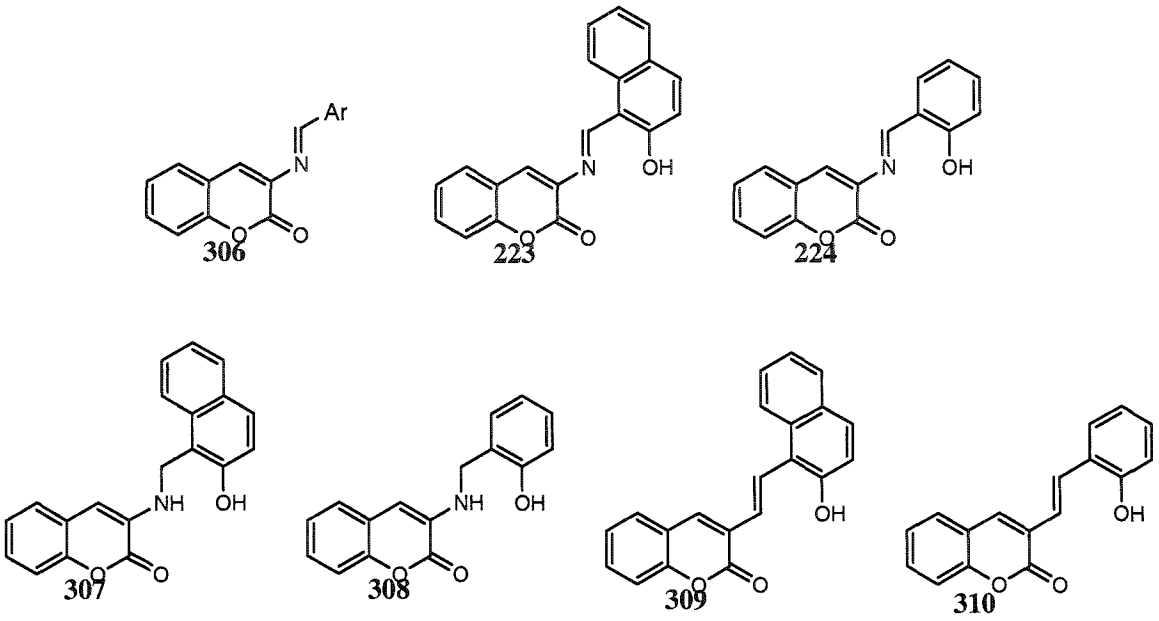
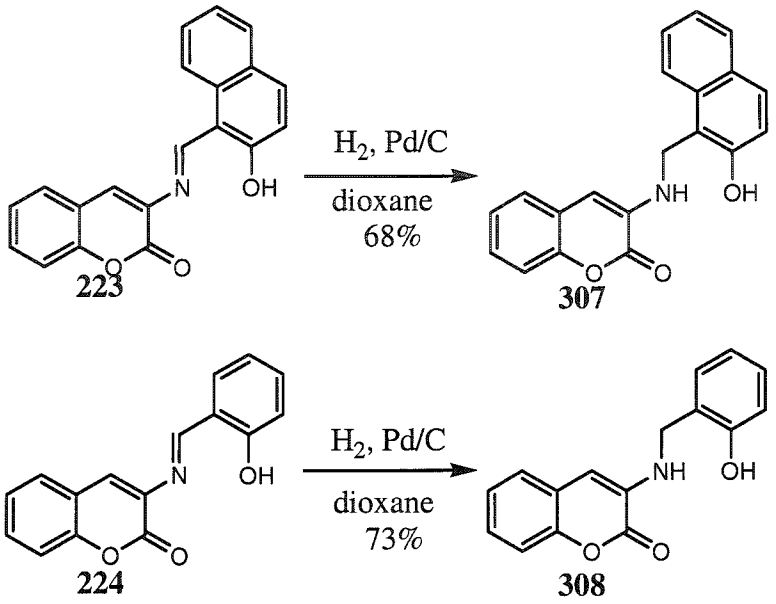


Figure 4.1

Imines can be reduced to secondary amines using palladium-catalyzed hydrogenation.[1] This methodology was applied to dienes **223** and **224** to produce **307** and **308**, albeit in only fair yield (Scheme 4.1).

[1] Kokotos, G.; Tzougraki, C. *J. Heterocyclic Chem.* **1986**, *23*, 87-92.

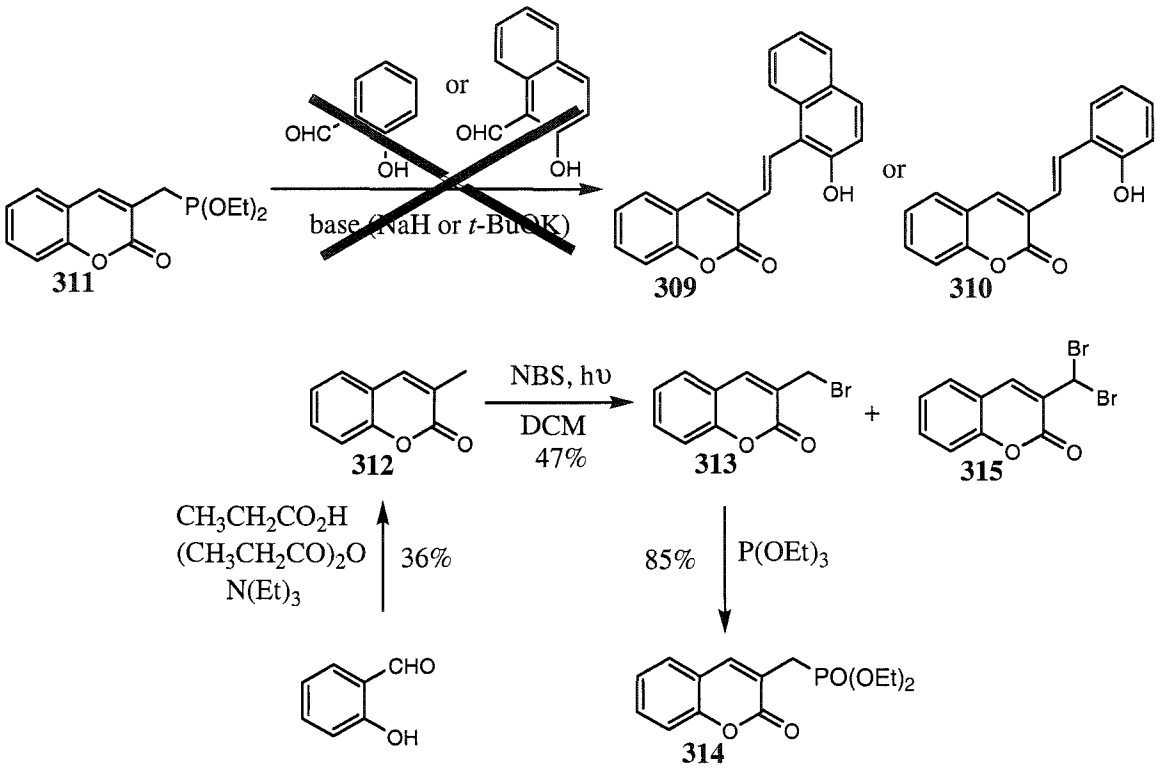


Scheme 4.1

An attempt to synthesize alkenes **309** and **310** using the Horner-Wadsworth-Emmons reaction with phosphonate **311** was then initiated (Scheme 4.2). Phosphonate **311** was prepared in four steps from salicylaldehyde (Scheme 4.2). 3-Methylcoumarin was produced from a Knoevenegal condensation and the methyl group was then radically brominated using light and NBS (47%).[2] Reaction of the resulting benzylic bromide with triethyl phosphite then afforded the desired phophonate **311** (85%) (Scheme 4.2).[3] Unfortunately, attempts to prepare **309** and **310** using the Horner-Wadsworth-Emmons reaction resulted in the formation of complex mixtures. No further attempts were made to produce **309** and **310**. Protection of the relatively acidic phenol protons may eventually facilitate these reactions.

[2] Incremona, J. H.; Martin, J. C. *J. Am. Chem.* **1970**, *92*, 627-634.
[3] Nagata, W.; Wakabayashi, T.; Hayase, Y. *Org. Synth.Coll. Vol. 6*, 448.

It was also desired to synthesize 1-azadiene **316**. This compound was produced using general procedure in Chapter 2 (Figure 4.2).



Scheme 4.2

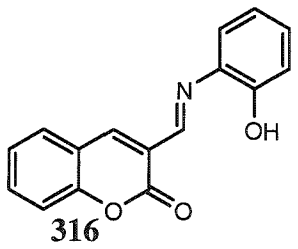


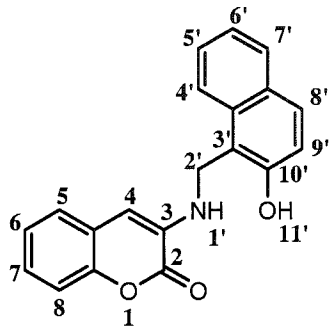
Figure 4.2

4.2 Experimental

General Procedures

For general procedures please refer to the section in Chapter 2.

3-[(2-Hydroxynaphthalen-1-ylmethyl)amino]-2*H*-chromen-2-one (307)

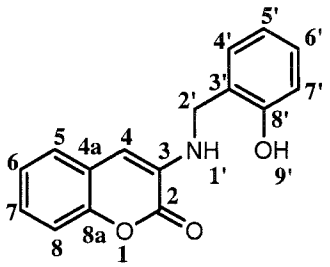


To a solution of **223** (0.73 g, 2.3 mmol) in dioxane (50 mL), was added Pd/C (0.03 g, 5% wt. Pd) and the mixture was stirred under a slight positive pressure of hydrogen for 24 h. The mixture remained bright orange over the course of the reaction. The catalyst was removed by suction filtration and the solvent was removed under reduced pressure to give a pale brown oil (0.83 g). The oil was then subjected to flash chromatography (5% ethyl acetate/dichloromethane), which afforded **307** as an orange solid (0.50 g, 1.6 mmol, 68%).

R_f = 0.40 (5% ethyl acetate/dichloromethane). Mp 178-179 °C (chloroform/hexane). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.93 (d, 1H, J = 8.8 Hz), 7.84 (d, 1H, J = 8.0 Hz), 7.78 (d, 1H, J = 9.2 Hz), 7.54 (m, 1H), 7.40 (t, 1H, J = 7.1 Hz), 7.34 (d, 1H, J = 8.4 Hz), 7.30-7.29 (m, 2H), 7.24-7.21 (m, 1H), 7.12 (d, 1H, J = 8.7 Hz), 6.72 (s, 1H, H-4), 6.56 (s, 1H),

5.69 (s, 1H), 4.83 (d, 2H, J = 4.0 Hz). ^{13}C NMR (126 MHz, $CDCl_3$): δ = 159.6 (0), 153.2 (0), 148.7 (0), 133.4 (0), 132.9 (0), 130.5 (1), 129.5 (0), 129.1 (1), 127.5 (1), 126.9 (1), 125.8 (1), 125.0 (1), 123.8 (1), 122.2 (1), 121.4 (0), 118.5 (1), 116.4 (1), 113.4 (0), 108.9 (1, C-4), 40.4 (2). IR (neat, ZnSe): υ_{max} = 3405 (m), 3276 (s), 1682 (s), 1620 (m), 1514 (w), 1497 (m), 1352 (m), 1177 (m), 858 (m), 738 (s) cm^{-1}. HRMS *m/z* [M^+] Calcd. for $C_{20}H_{15}NO_3$ 317.1051, found 317.1054.

3-(2-Hydroxybenzylamino)-2*H*-chromen-2-one[1] (308)



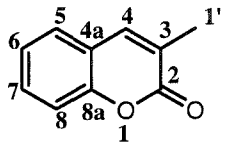
To a solution of **224** (3.00 g, 11.3 mmol) in dioxane (50 mL), was added Pd/C (0.03 g, 5% wt. Pd) and the mixture was stirred at room temperature under a slight positive pressure of hydrogen for 24 h. The supernatant changed from bright orange to colorless during the course of the reaction. The mixture was filtered and the solvent was removed under reduced pressure to give **309** as a pale yellow oil (3.01 g), which was then crystallized from chloroform/hexane to afford a pale yellow solid (2.21 g, 8.27 mmol, 73%).

Mp 158-159 °C (chloroform/hexane) (Lit.[4] 169-170 °C). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.31-7.18 (m, 6H), 6.92 (t, 1H, J = 7.9 Hz), 6.86 (d, 1H, J = 7.5 Hz), 6.55 (s, 1H, H-4),

[4] Kokotos, G.; Tzougraki, C. *J. Heterocyclic Chem.* **1986**, *23*, 87-92.

5.89 (s, 1H), 5.24 (s, 1H), 4.42 (s, 2H, H-1'). ^{13}C NMR (126 MHz, $CDCl_3$): δ = 159.8 (0), 155.1 (0), 148.6 (0), 133.2 (0), 129.6 (1), 129.4 (1), 126.8 (1), 125.8 (1), 124.9 (1), 122.8 (0), 121.3 (0), 121.1 (1), 116.41 (1), 116.38 (1), 109.0 (1, H-4), 45.0 (2, C-2'). IR (neat, ZnSe): υ_{max} = 3426 (s), 1694 (s), 1625 (m), 1502 (m), 998 (w), 836 (m), 754 (s) cm^{-1}. MS (EI) *m/z* (%) = 267 (M^+, 26), 174 (11), 161 (100), 133 (35), 107 (59), 83 (21), 51 (34). HRMS *m/z* [M^+] Calcd. for $C_{16}H_{13}NO_3$ 267.0895, found 267.0905.

3-Methyl-2*H*-chromen-2-one



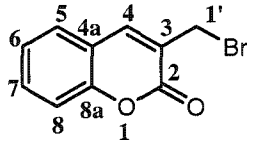
To a solution of salicyaldehyde (105.0 mL, 120.3 g, 0.985 mol) and propionic acid (75.0 mL, 74.48 g, 1.00 mol) in propionic anhydride (260.0 mL, 263.9 g, 2.00 mol), was added triethylamine (150.0 mL, 115.8 g, 1.10 mol) and the mixture was heated under reflux for 8 h. The clear colorless solution became clear brown over the course of the reaction. The reaction was cooled to room temperature and a white precipitate formed. The solution was filtered and washed with hexane, which afforded **312** as an off white solid (56.71 g, 0.35 mol, 36%).

Mp 82-83 °C (chloroform/hexane) (Lit.[5] 90-92 °C). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.52 (s, 1H, H-4), 7.46 (td, 1H, *J* = 7.8, 1.3 Hz), 7.42 (dd, 1H, *J* = 7.7, 1.4 Hz), 7.31 (d, 1H, *J* = 7.7 Hz), 7.25 (td, 1H, *J* = 7.8, 1.4 Hz), 2.23 (s, 3H, H-1'). ^{13}C NMR (126 MHz, $CDCl_3$): δ = 162.4 (0), 153.4 (0), 139.4 (1, C-4), 130.6 (1), 127.1 (1), 126.0 (0), 124.4 (1),

119.8 (0), 116.6 (1), 17.4 (3, H-1'). IR (neat, ZnSe): υ_{max} = 3042 (w), 2988 (w), 2951 (w), 1701 (s), 1608 (m), 1193 (m), 1074 (m), 1002 (m), 752 (s) cm^{-1}. MS (EI) *m/z* (%) = 160 (M^+, 66), 131 (100), 103 (17), 77 (24), 51 (31).

3-Bromomethyl-2*H*-chromen-2-one (313) and 3-dibromomethyl-2*H*-chromen-2-one (315)

To a solution of 3-methyl-2*H*-chromen-2-one (7.00 g, 43.7 mmol) in dichloromethane (100 mL) was added *N*-bromosuccinimide (8.20 g, 45.9 mmol). The solution was stirred at 0 °C with irradiation by a Watt floodlight for 12 h. The clear colorless solution went to clear orange over the course of the reaction. The solution was washed with 1 M HCl (50 mL) and 1 M K_2CO_3 (50 mL) and the organic layer was dried with $MgSO_4$. The solvent was removed under reduced pressure and the residue was the subjected to flash chromatography (30% dichloromethane/hexane), which afforded **313** as a white solid (0.43 g, 1.3 mmol, 3%) and **315** (4.92 g, 20.6 mmol, 47%) as a white solid.

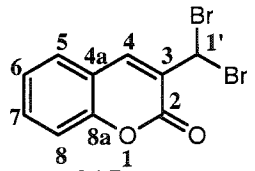


313

313: R_f = 0.65 (30% dichloromethane/hexane). Mp 118-119 °C (chloroform/hexane). ^1H NMR (500 MHz, $CDCl_3$): δ = 7.86 (s, 1H, H-4), 7.55 (td, 1H, J = 7.8, 1.4 Hz), 7.51 (dd, 1H, J = 7.6, 2.0 Hz), 7.36 (d, 1H, J = 8.2 Hz), 7.31 (td, 1H, J = 7.4, 1.3 Hz), 4.44 (s, 2H,

[5] Singer, L. A.; Kong, N. P. *J. Am. Chem. Soc.* **1966**, *88*, 5213-5219.

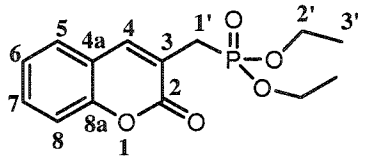
H-1'). ^{13}C NMR (126 MHz, $CDCl_3$): δ = 160.1 (0), 154.0 (0), 142.1 (1, C-4), 132.4 (1), 128.3 (1), 125.8 (0), 124.9 (1), 119.1 (0), 117.0 (1), 27.7 (2, C-1'). IR (neat, ZnSe): υ_{max} = 3043 (w), 1707 (s), 1608 (m), 1208 (m), 1191 (m), 1068 (m), 759 (s) cm^{-1}. MS (EI) *m/z* (%) = 238 (M^+, 9), 182 (5), 159 (100), 131 (26), 115 (35), 77 (25), 51 (27). HRMS *m/z* [M^+] calcd for $C_{10}H_7BrO_2$ 237.9629, found 237.9636.



315

315: R_f = 0.90 (30% dichloromethane/hexane). Mp 209-216 °C (chloroform/hexane). ^1H NMR (500 MHz, $CDCl_3$): δ = 8.34 (s, 1H, H-4), 7.62-7.60 (m, 2H), 7.40-7.35 (m, 2H), 6.84 (s, 1H, H-1'). ^{13}C NMR (126 MHz, $CDCl_3$): δ = 157.7 (0), 153.9 (0), 143.1 (1, C-4), 133.3 (1), 129.2 (0), 129.0 (1), 125.3 (1), 118.8 (0), 117.0 (1), 33.8 (1, H-1'). IR (neat, ZnSe): υ_{max} = 3067 (w), 3041 (w), 3008 (w), 1719 (s), 1605 (m), 1198 (m), 1067 (m), 782 (m), 755 (s) cm^{-1}. MS (EI) *m/z* (%) = 318 (M^+, 7), 239 (100), 193 (4), 159 (9), 130 (71), 102 (35), 51 (24). M^+, found 315.8711, $C_{10}H_7Br_2O_2$ requires M^+, 315.8733.

(2-Oxo-2*H*-chromen-3-ylmethyl)phosphonic acid diethyl ester (314)

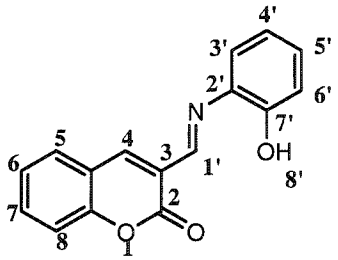


A mixture of triethylphosphite (9.00 mL, 8.69 g, 52.3 mmol), and **313** (2.50 g, 10.5 mmol) was reacted under reflux conditions for 4 h. The clear colorless solution

became a clear pale clear yellow over the course of the reaction. The solvent was removed under vacuum, which produced a yellow oil. The residue was subjected to silica flash column chromatography (50% ethyl acetate/dichloromethane), which afforded **314** as a pale yellow oil (2.63 g, 8.88 mmol, 85%).

R_f = 0.25 (50% ethyl acetate/dichloromethane). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.74 (d, 1H, J = 4.1 Hz), 7.54-7.48 (m, 2H), 7.35-7.27 (m, 2H), 4.19-4.07 (m, 4H), 3.20 (d, 2H, *J* = 22.5 Hz, H-1'), 1.33 (t, 6H, *J* = 7.0 Hz). ^{13}C NMR (126 MHz, $CDCl_3$): δ = 161.4 (0), 153.4 (0), 141.9 (1, d, $J_{P\text{-}C}$ = 8.0 Hz, C-4), 131.5 (1), 127.9 (1), 124.7 (1), 120.4 (0, d, $J_{P\text{-}C}$ = 10.2 Hz), 119.4 (0, d, $J_{P\text{-}C}$ = 3.1 Hz), 116.7 (1), 62.6 (d, 2H, $J_{C\text{-}P}$ = 6.3 Hz, C-2'), 27.0 (d, 2H, $J_{P\text{-}C}$ = 140.2 Hz, C-1'), 16.5 (d, 3H, $J_{P\text{-}C}$ = 6.3 Hz, C-3'). IR (neat, ZnSe): υ_{max} = 3469 (br), 2982 (w), 2908 (w), 1719 (s), 1609 (m), 1292 (m), 1019 (vs), 957 (s), 758 (s) cm^{-1}. MS (EI) *m/z* (%) = 296 (M^+, 60), 251 (9), 212 (35), 160 (100), 131 (66), 77 (69). HRMS *m/z* [M^+] Calcd. for $C_{14}H_{17}O_5P$ 296.0812, found 296.0804.

3-[(2-Hydroxyphenylimino)methylene]-2*H*-chromen-2-one (316)

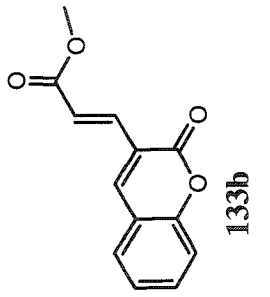


Using general procedure 1 (Chapter 2), **176** (0.70 g, 4.0 mmol) and 2-aminophenol (0.50 g, 4.6 mmol), were reacted in toluene (50 mL) for 24 h. The pale yellow solution became a thick bright yellow suspension over the course of the reaction.

The mixture was cooled to 6 °C and then filtered, which afforded **316** as a bright yellow solid (0.85 g, 3.2 mmol, 80%).

Mp 249-250 °C (chloroform/hexane). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 9.00 (s, 1H, H-1'), 8.62 (s, 1H, H-4), 7.70 (d, 1H, *J* = 8.6 Hz), 7.64 (t, 1H, *J* = 7.8 Hz), 7.43-7.38 (m, 3H), 7.26-7.25 (s, 2H), 7.04 (d, 1H, *J* = 7.6 Hz), 6.94 (t, 1H, *J* = 7.1 Hz). ^{1}H NMR (500 MHz, DMSO-d6): δ = 9.21 (s, 1H), 9.02 (s, 1H), 8.78 (s, 1H), 7.90 (d, 1H, *J* = 7.5 Hz), 7.71 (t, 1H, *J* = 7.8 Hz), 7.49 (d, 1H, *J* = 8.5 Hz), 7.44 (t, 1H, *J* = 7.8 Hz), 7.26 (d, 1H, *J* = 8.5 Hz), 7.13 (t, 1H, *J* = 7.8 Hz), 6.93 (d, 1H, *J* = 8.5 Hz), 6.86 (t, 1H, *J* = 7.5 Hz). ^{13}C NMR (126 MHz, $CDCl_3$): δ = 161.3 (0), 154.9 (0), 153.2 (0), 150.4 (1, C-1'), 140.6 (1, C-4), 135.2 (0), 133.7 (1), 130.6 (1), 129.9 (1), 125.6 (1), 123.3 (0), 120.8 (1), 119.4 (0), 117.3 (1), 116.7 (1), 115.2 (1). ^{13}C NMR (126 MHz, DMSO-d6): δ = 160.2 (0), 153.8 (0), 151.7 (1), 151.6 (0), 140.9 (1), 133.2 (1), 129.9 (1), 128.4 (1), 125.0 (1), 122.6 (0), 119.6 (1), 119.5 (1), 119.0 (0), 116.3 (1), 116.2 (1). IR (nujol, KBr): υ_{max} = 3392 (w), 1704 (s), 1606 (w), 1586 (w), 1143 (m), 751 (m) cm^{-1}. MS (EI) *m/z* (%) = 265 (M^+, 100), 236 (9), 220 (34), 120 (69), 118 (20), 89 (12). HRMS *m/z* [M^+] Calcd. for $C_{16}H_{11}NO_3$ 265.0738, found 265.0728.

Appendix



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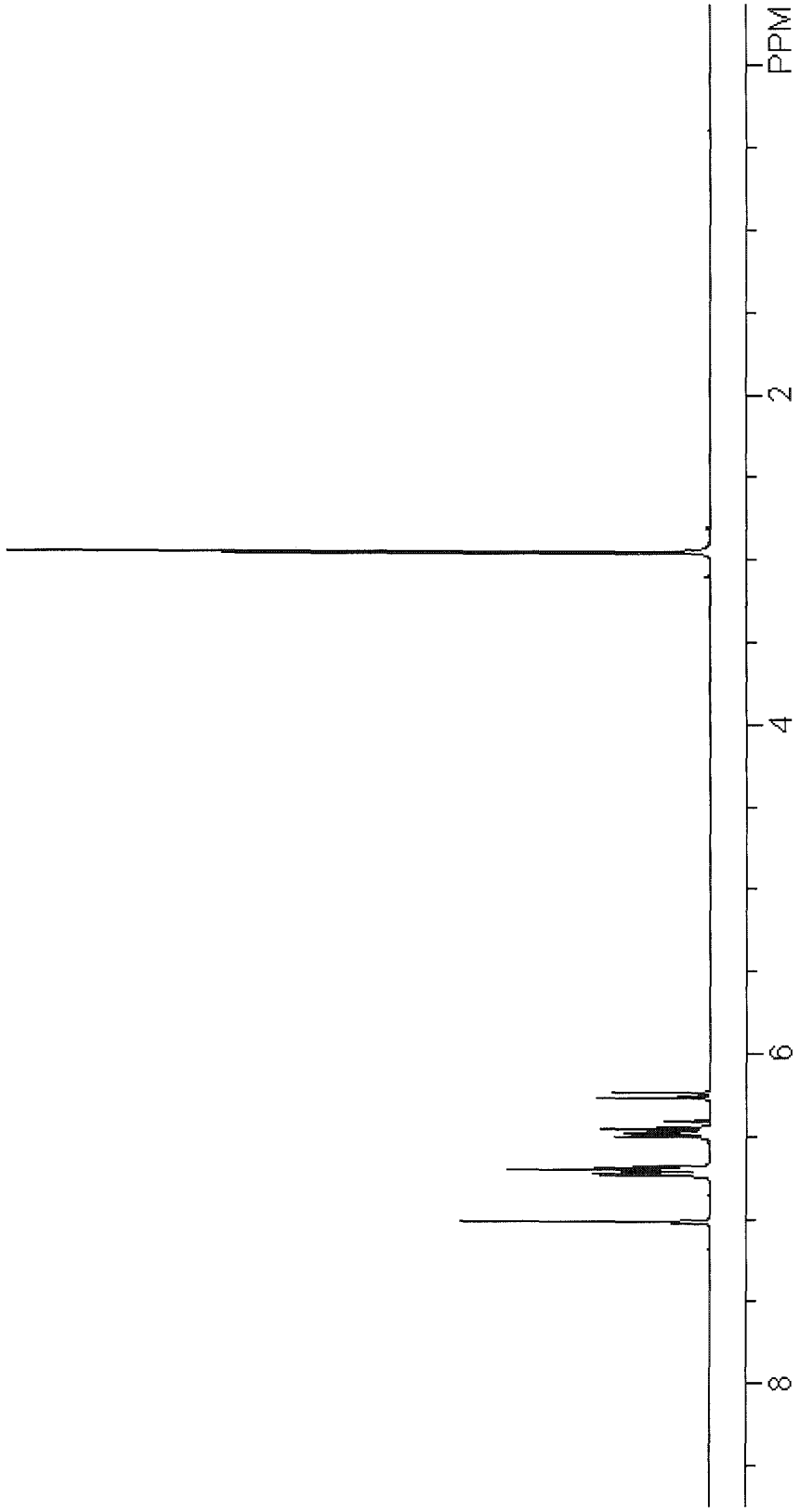

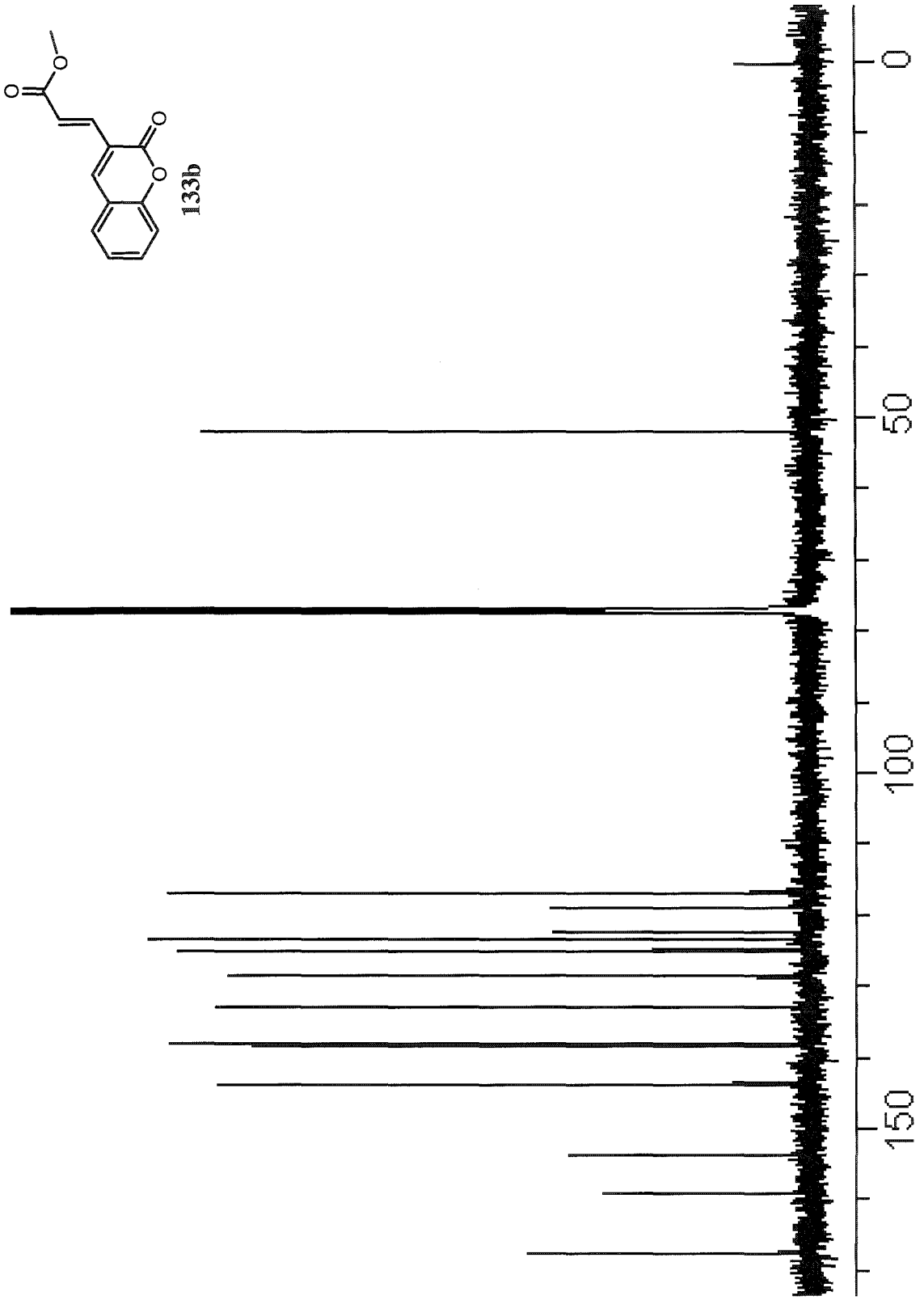
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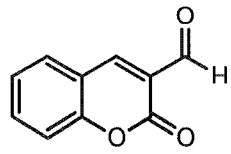

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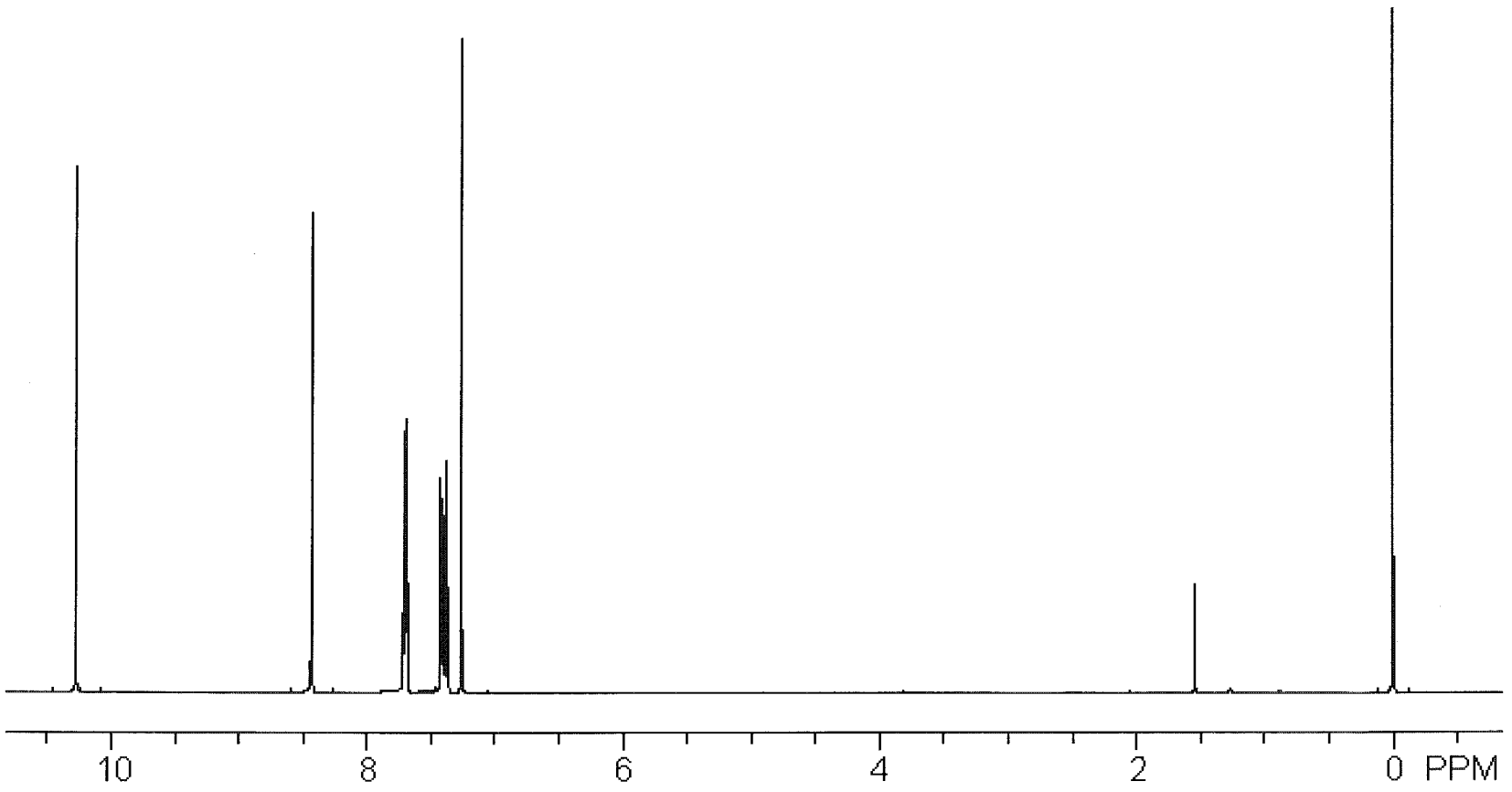

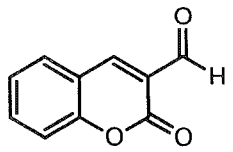

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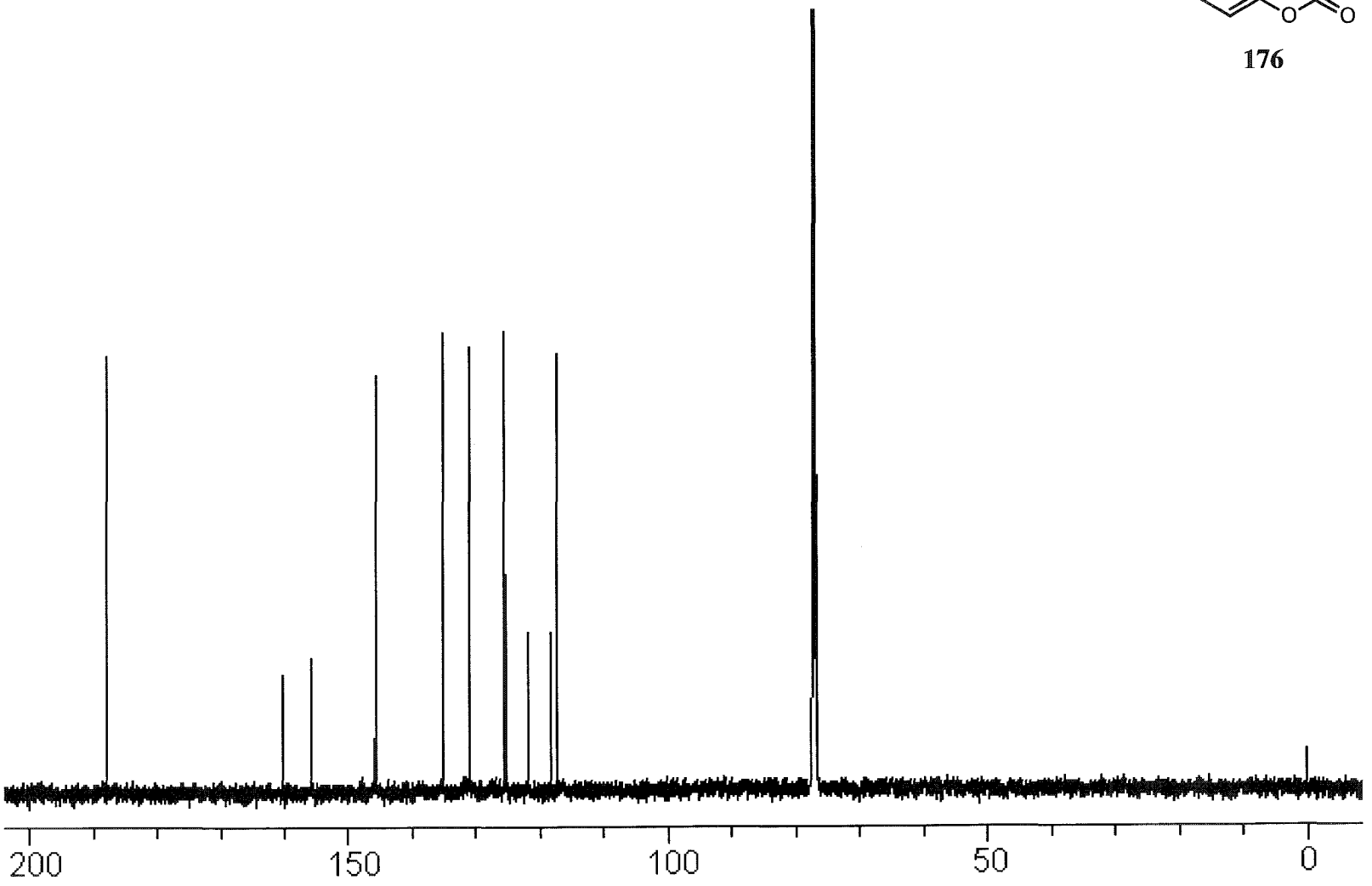

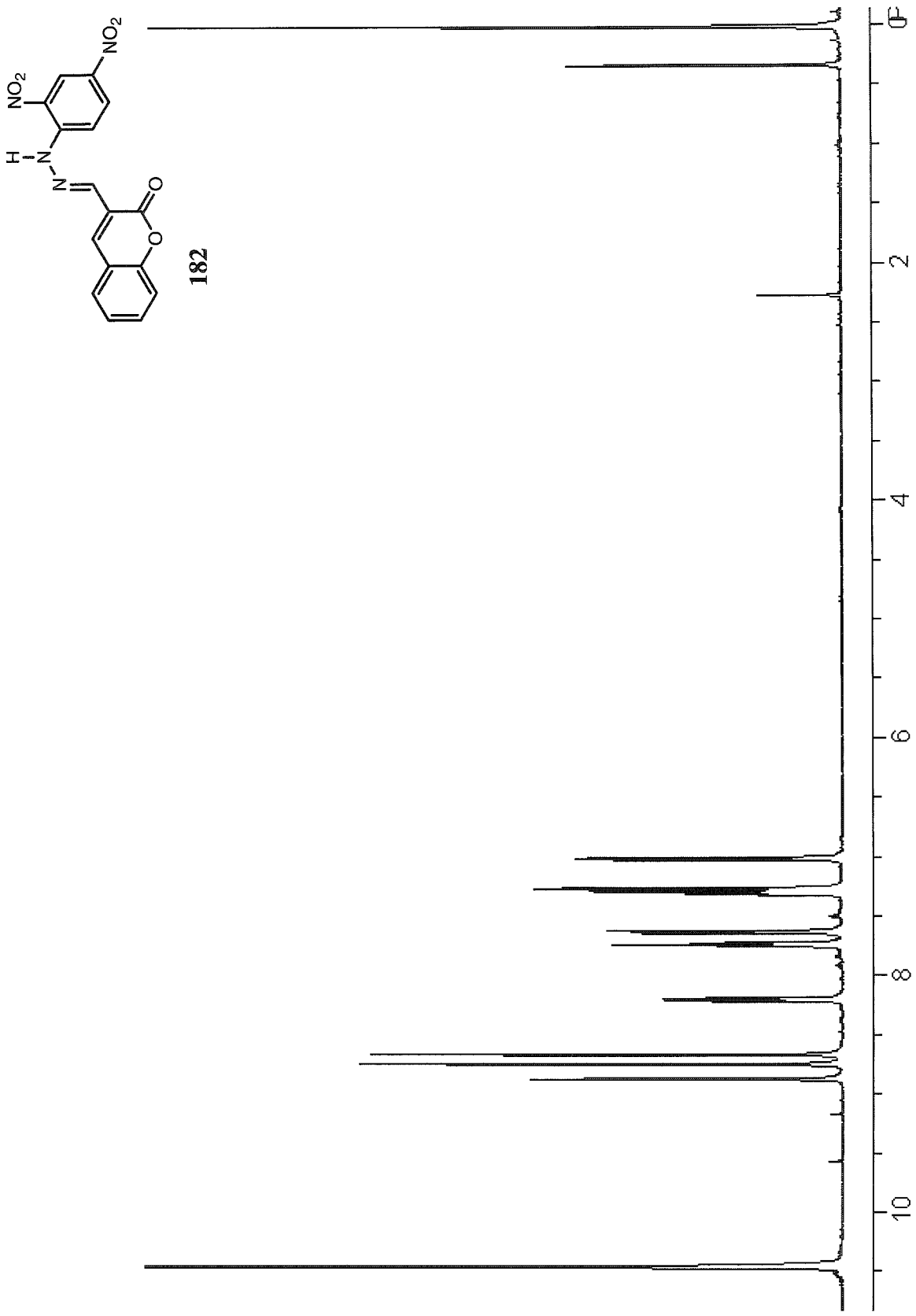
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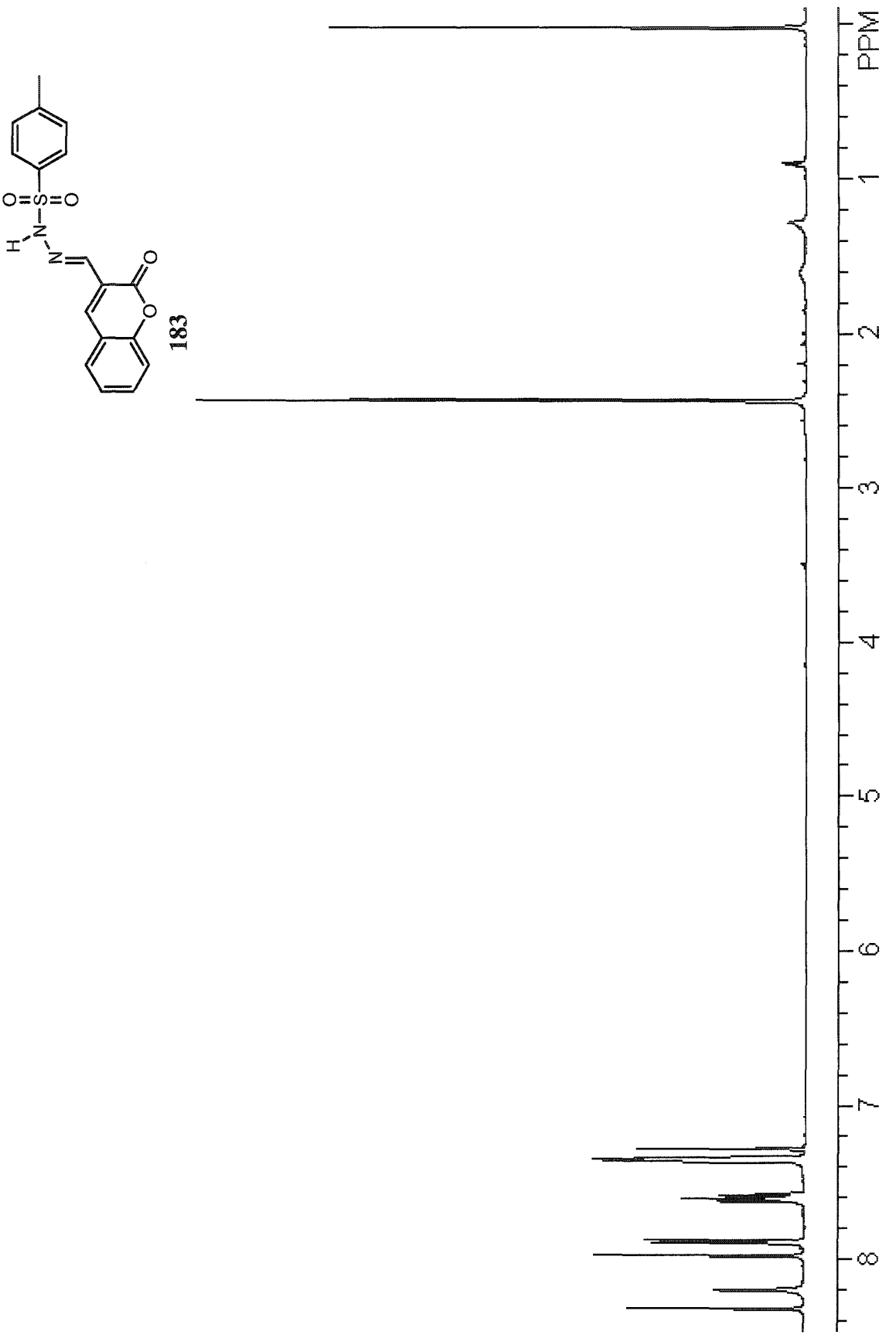
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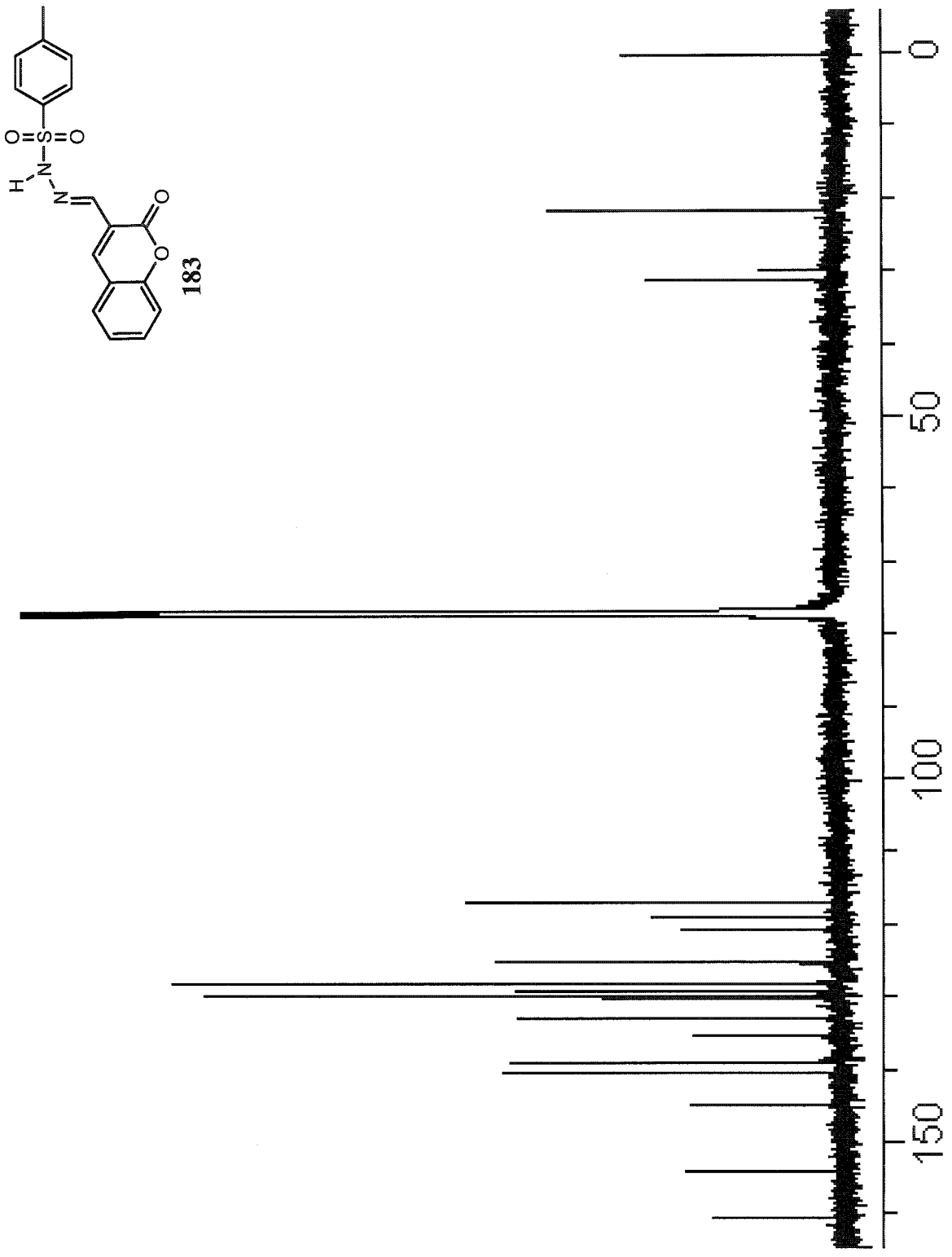
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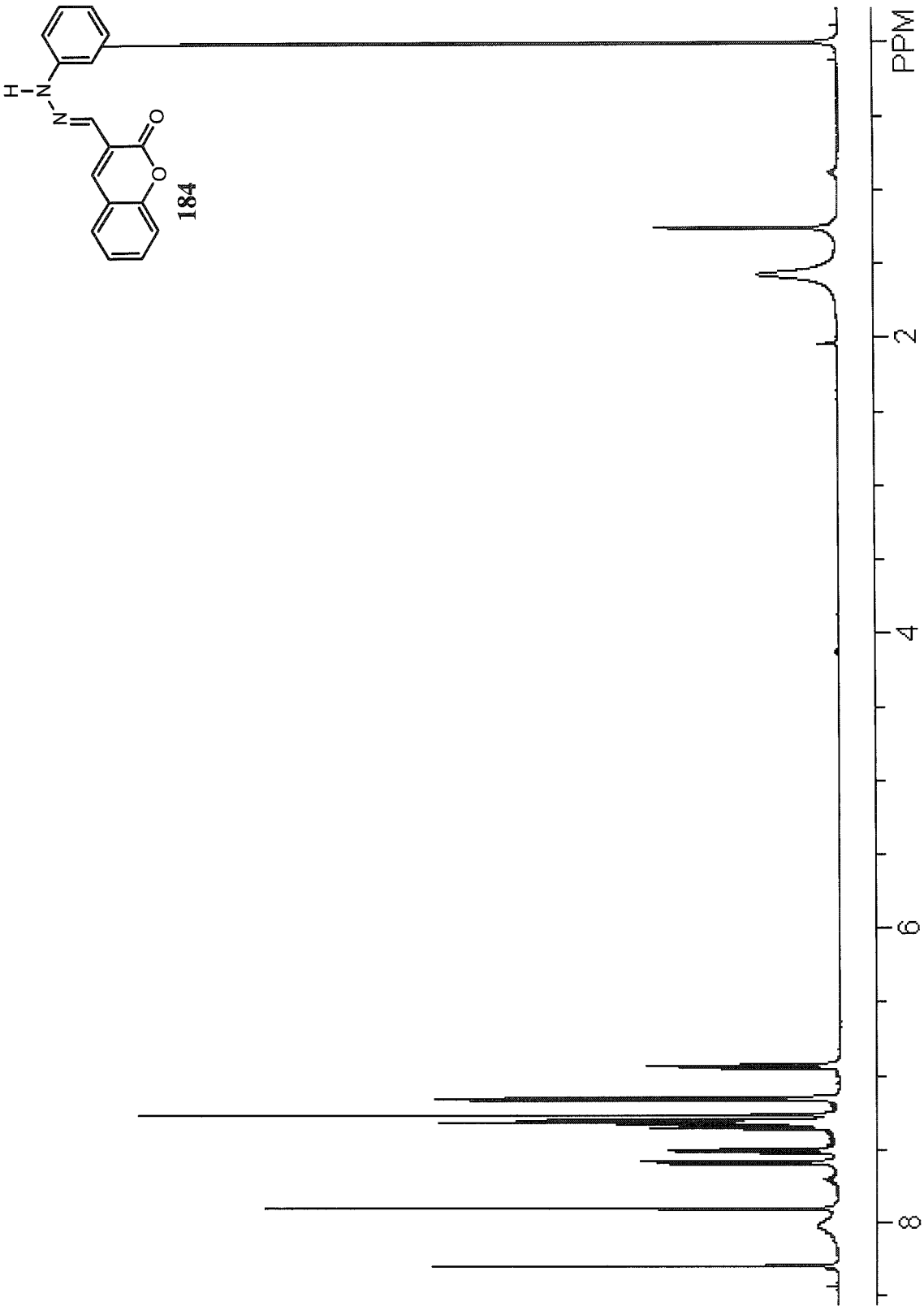
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PPM
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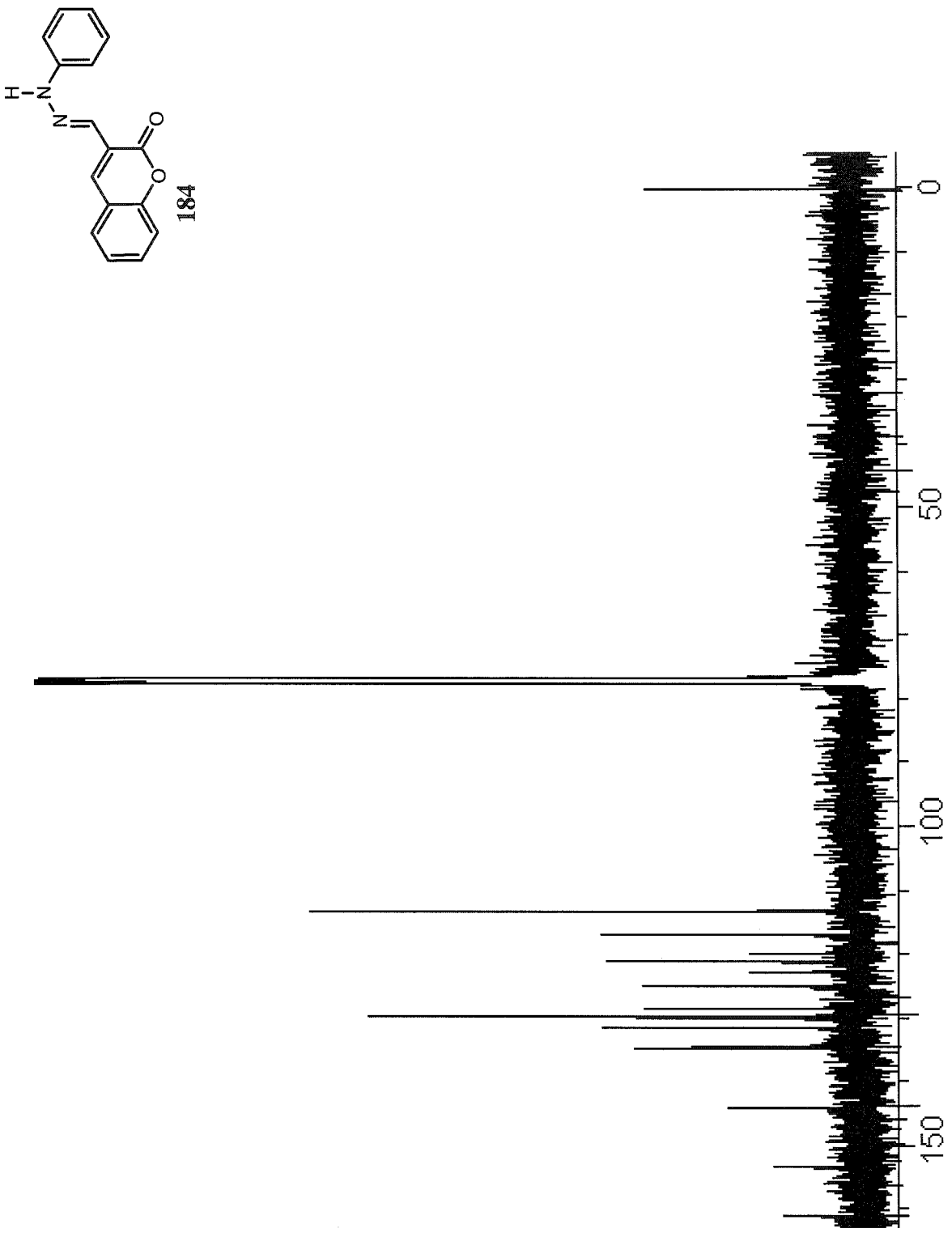
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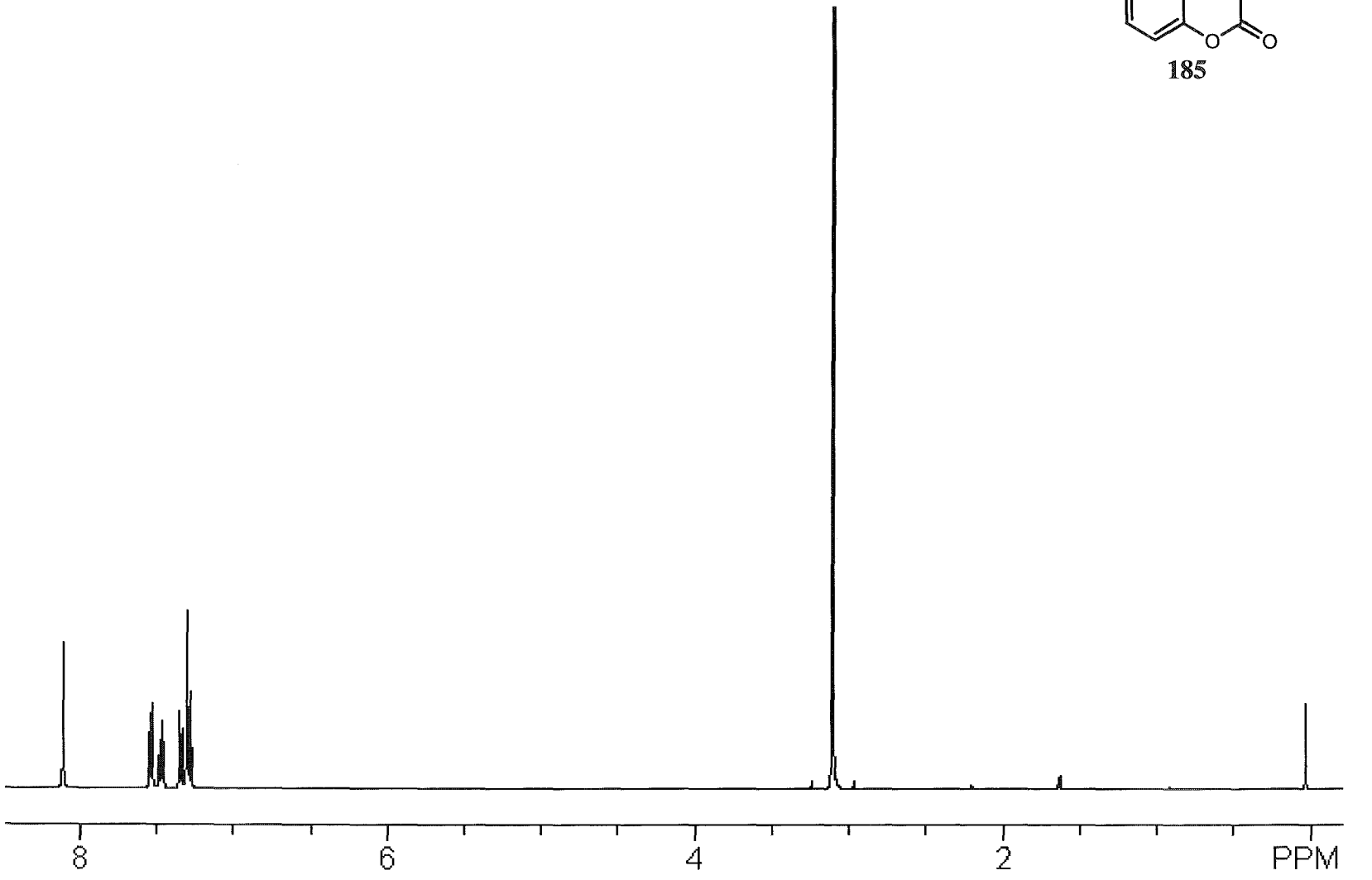

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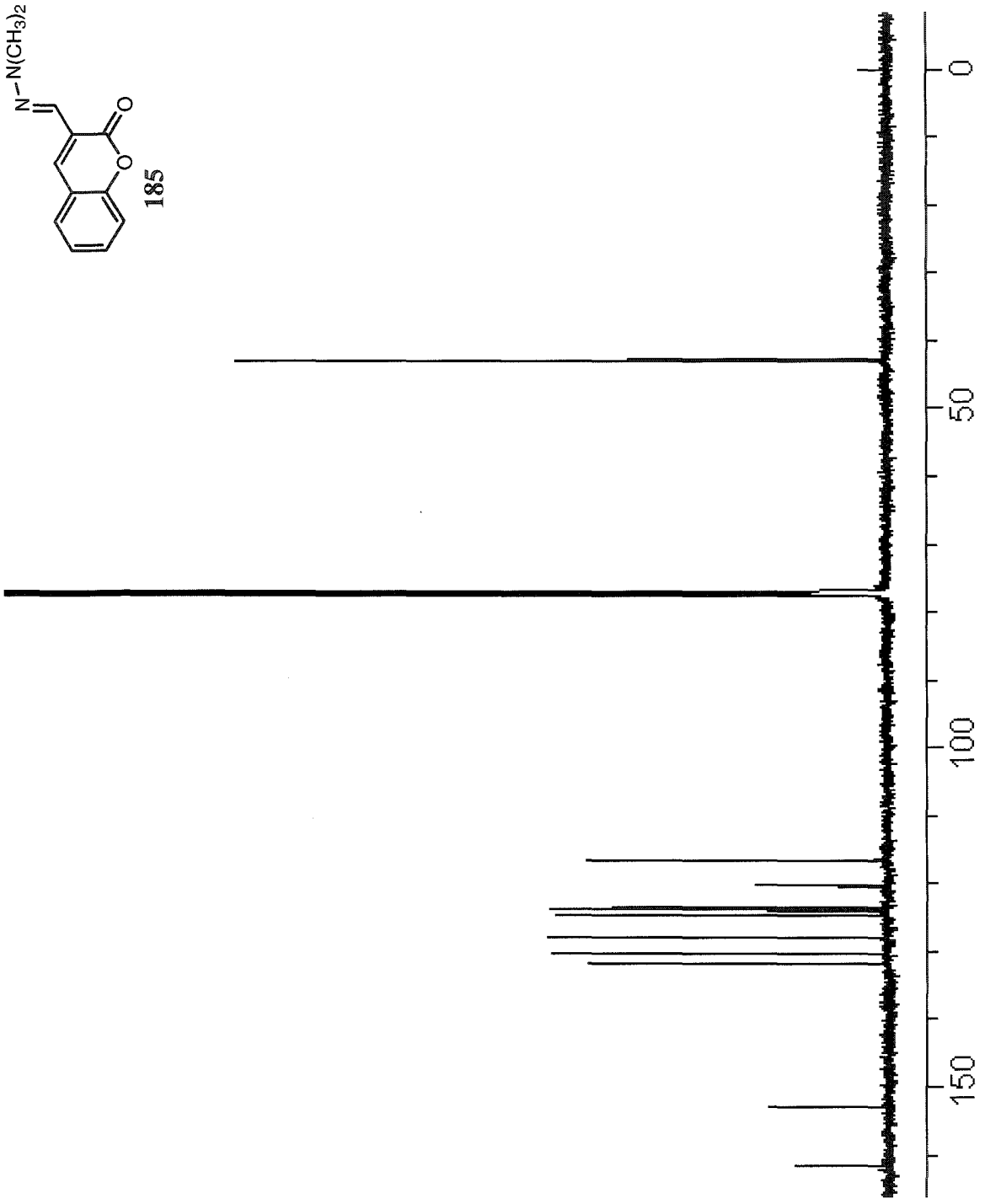
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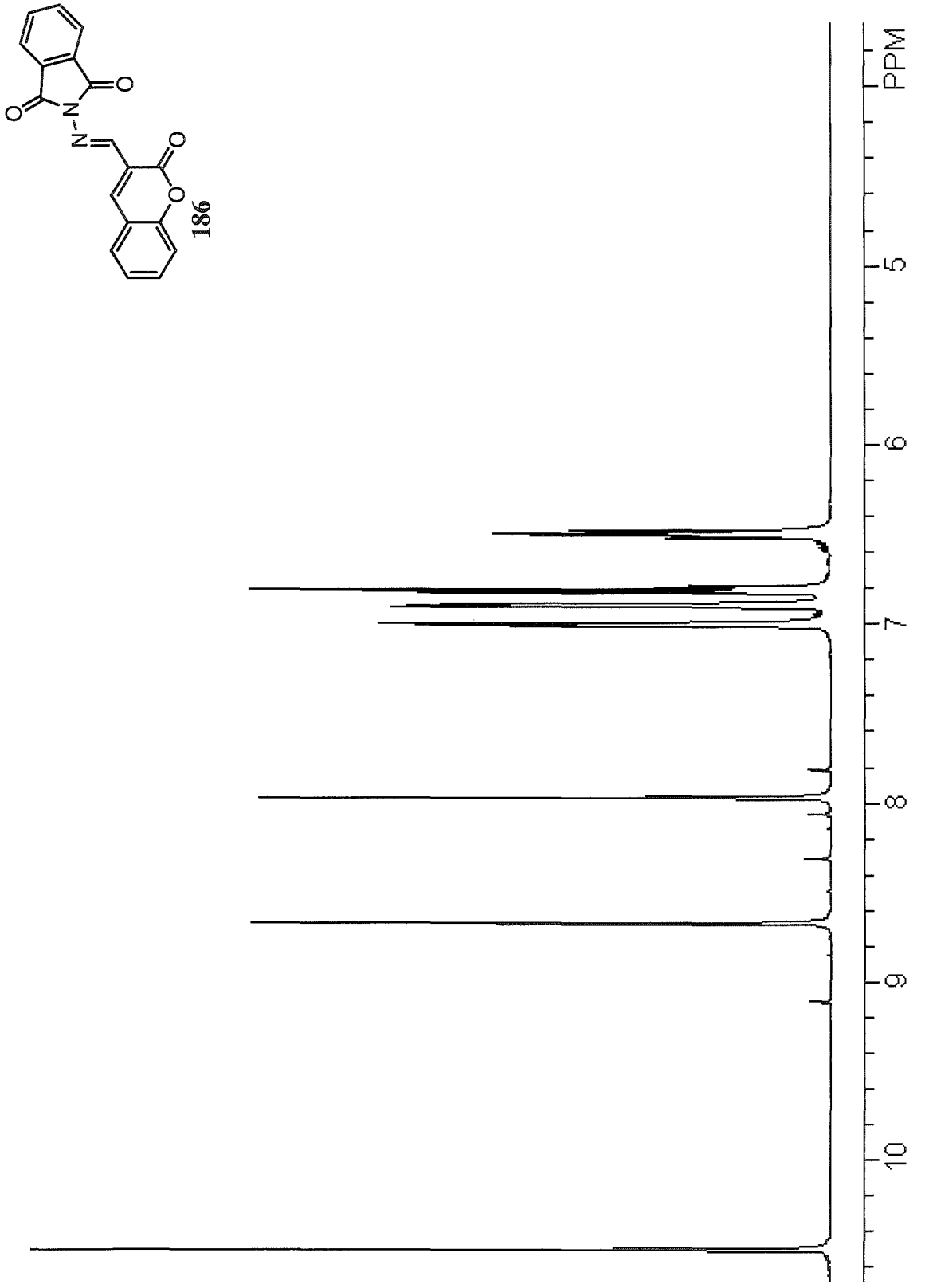
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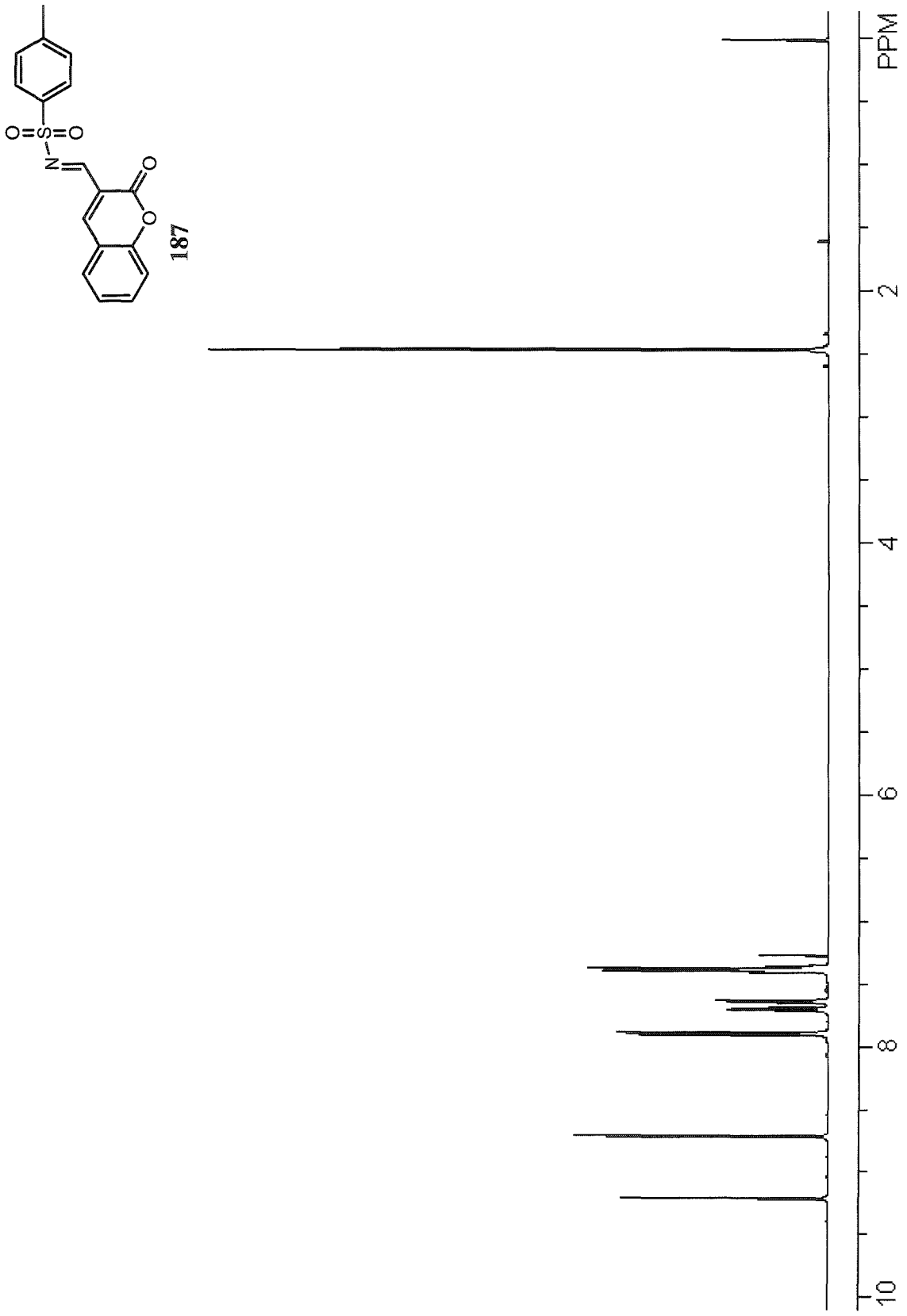
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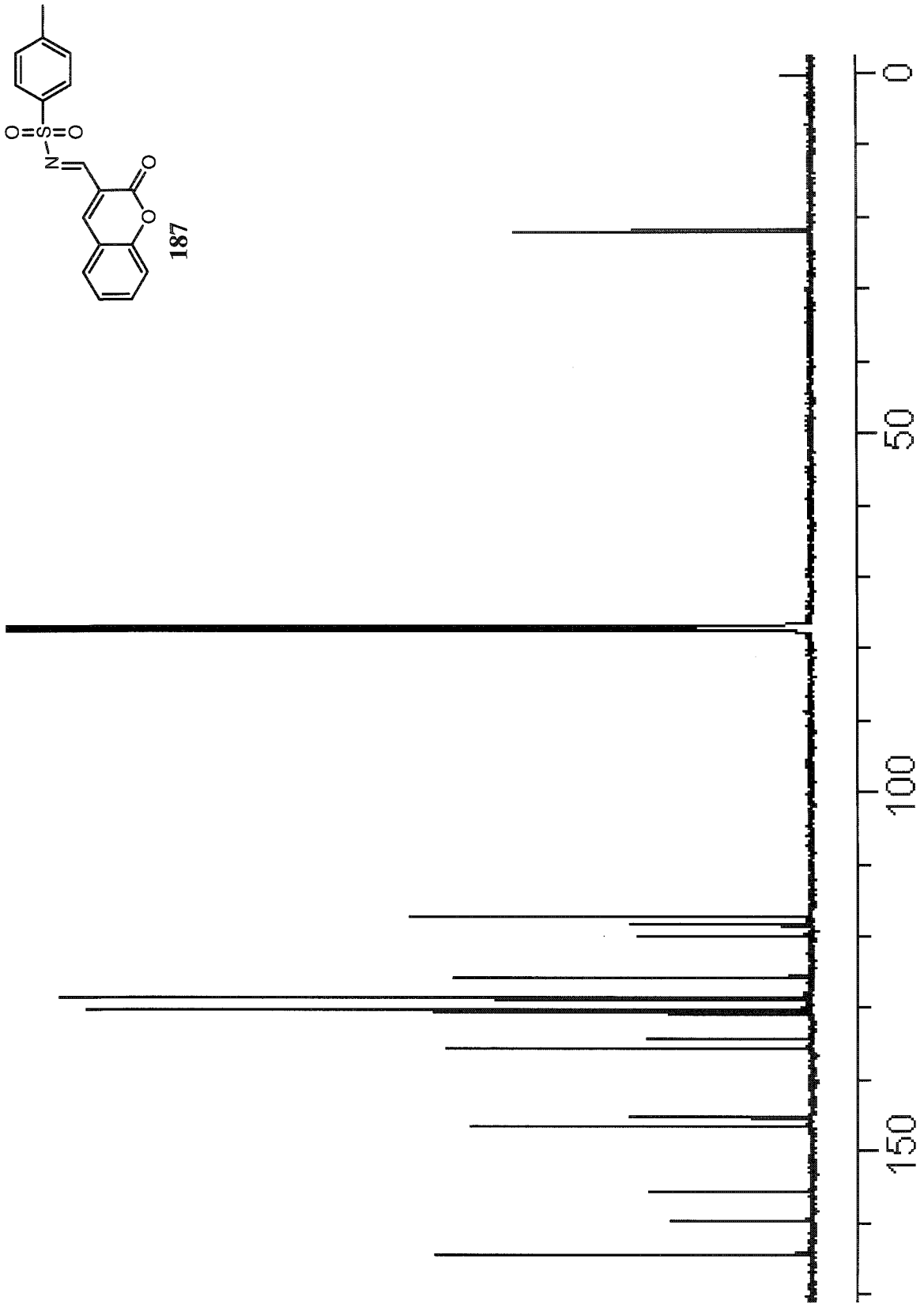
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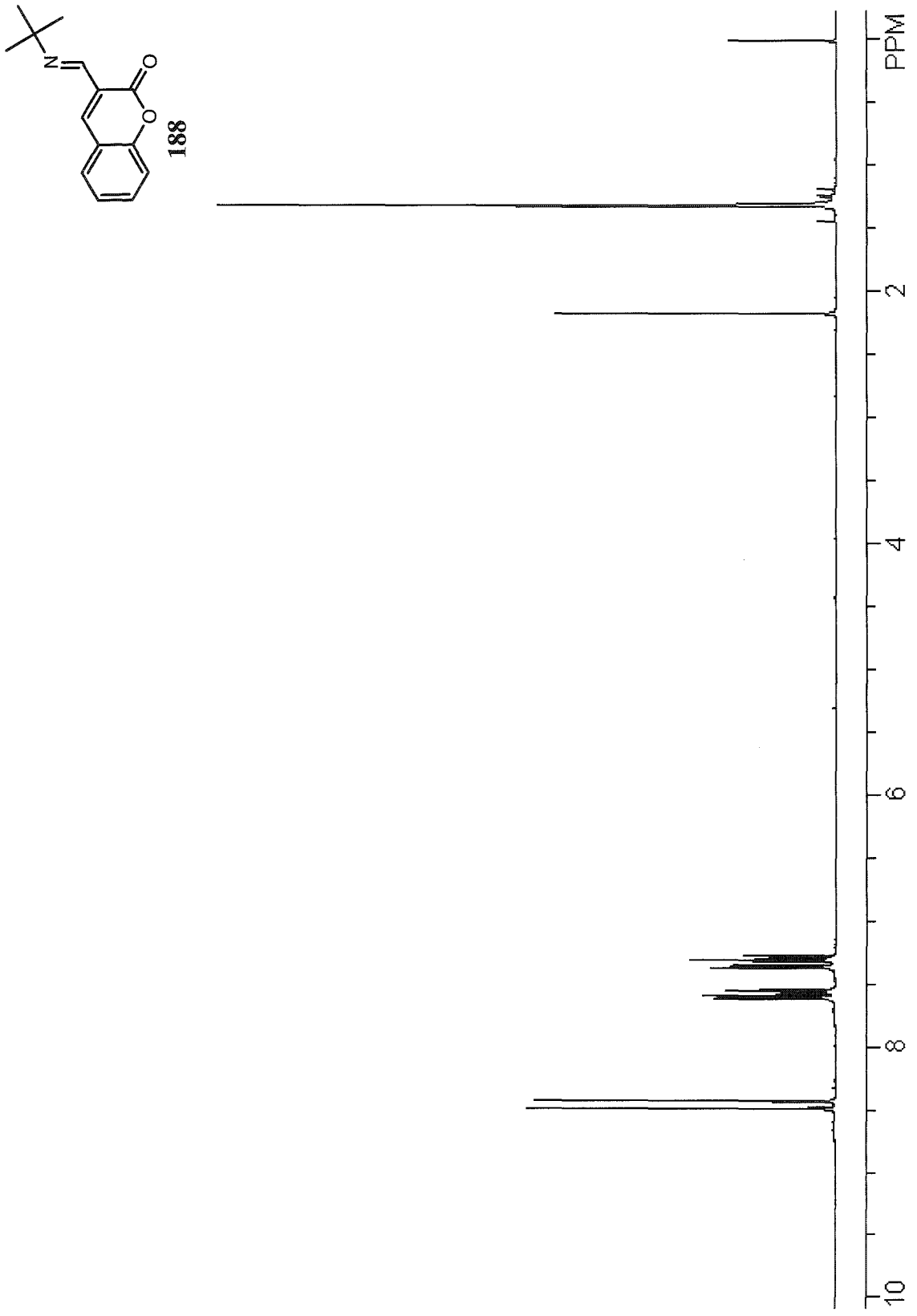
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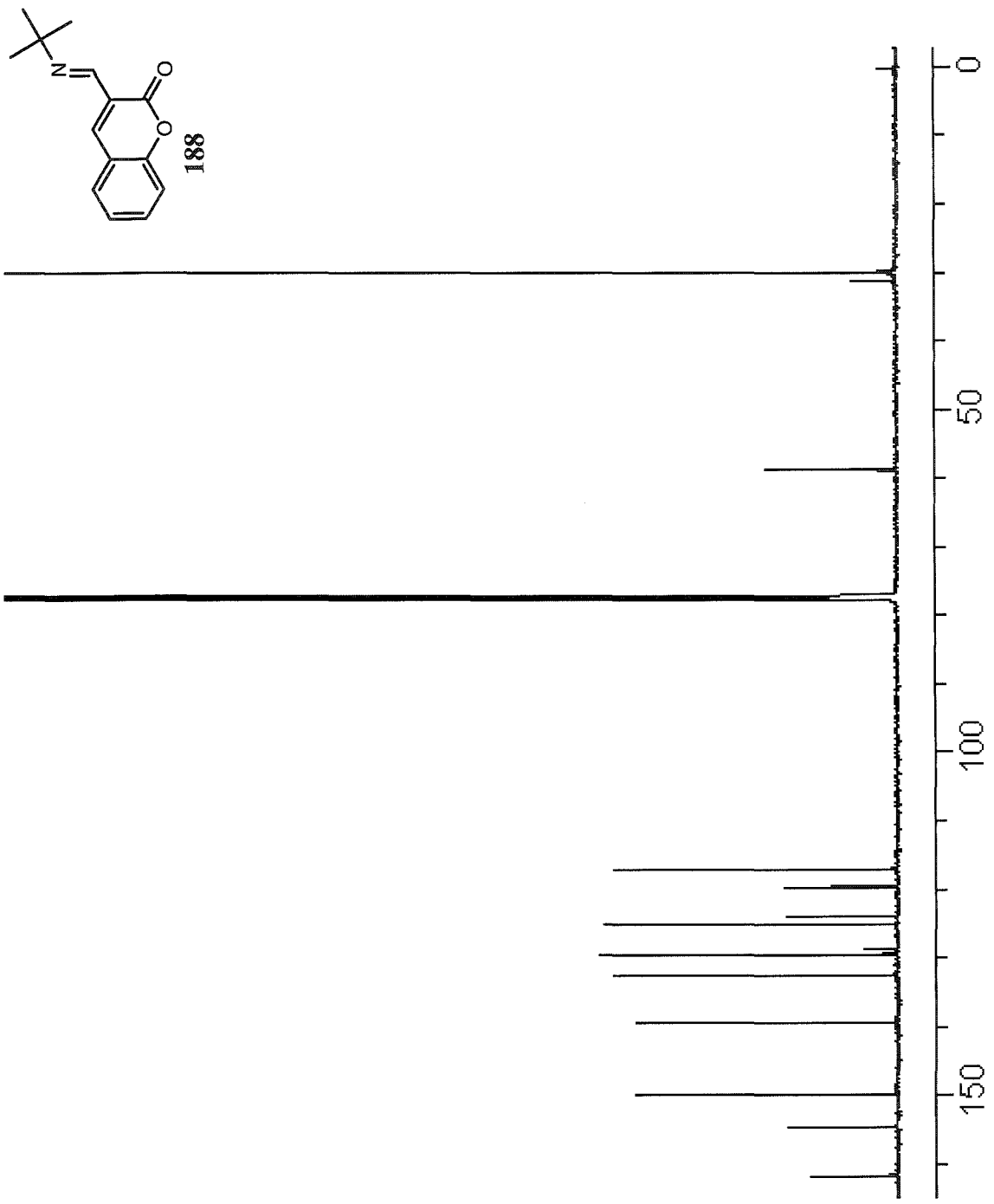
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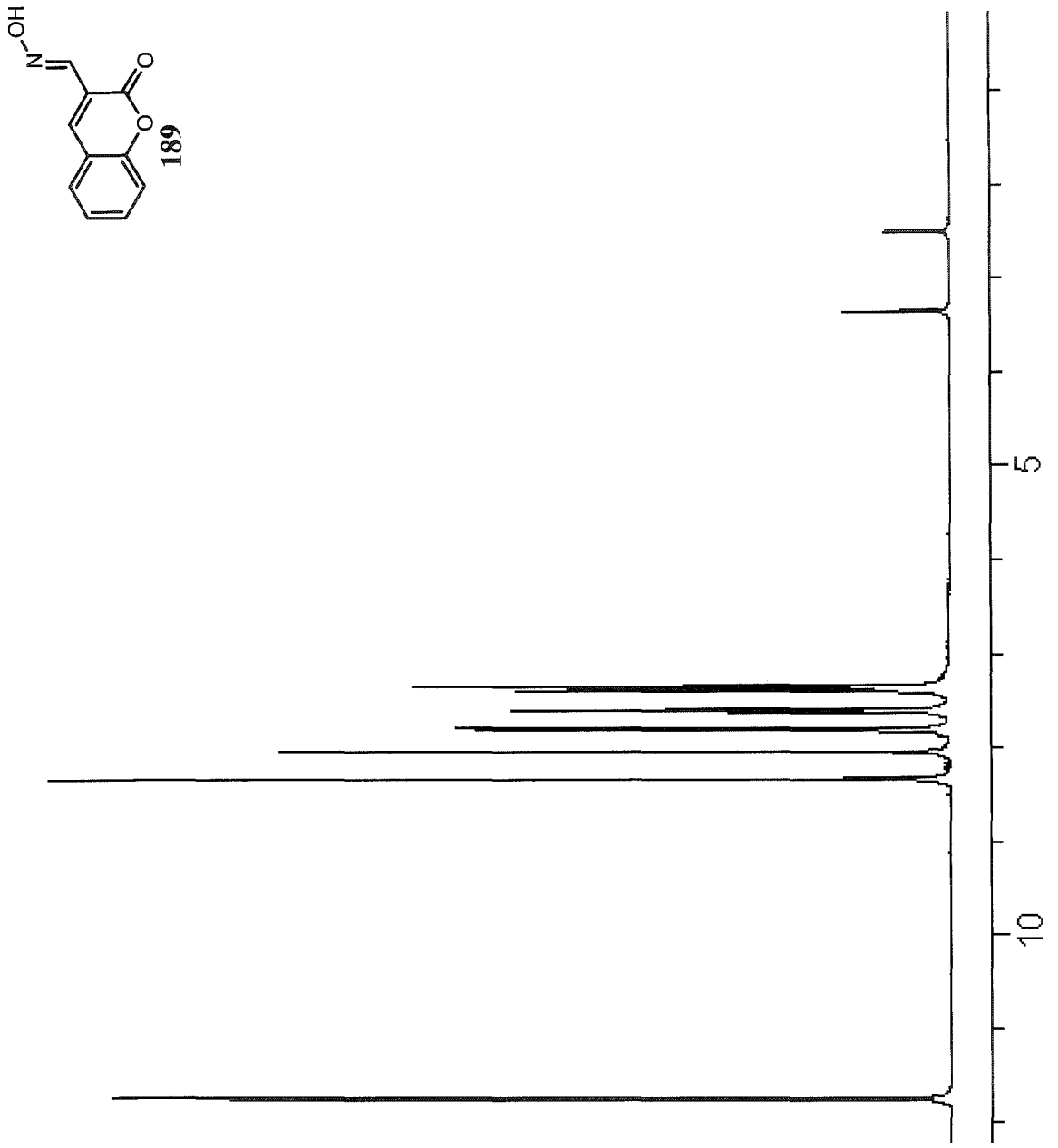
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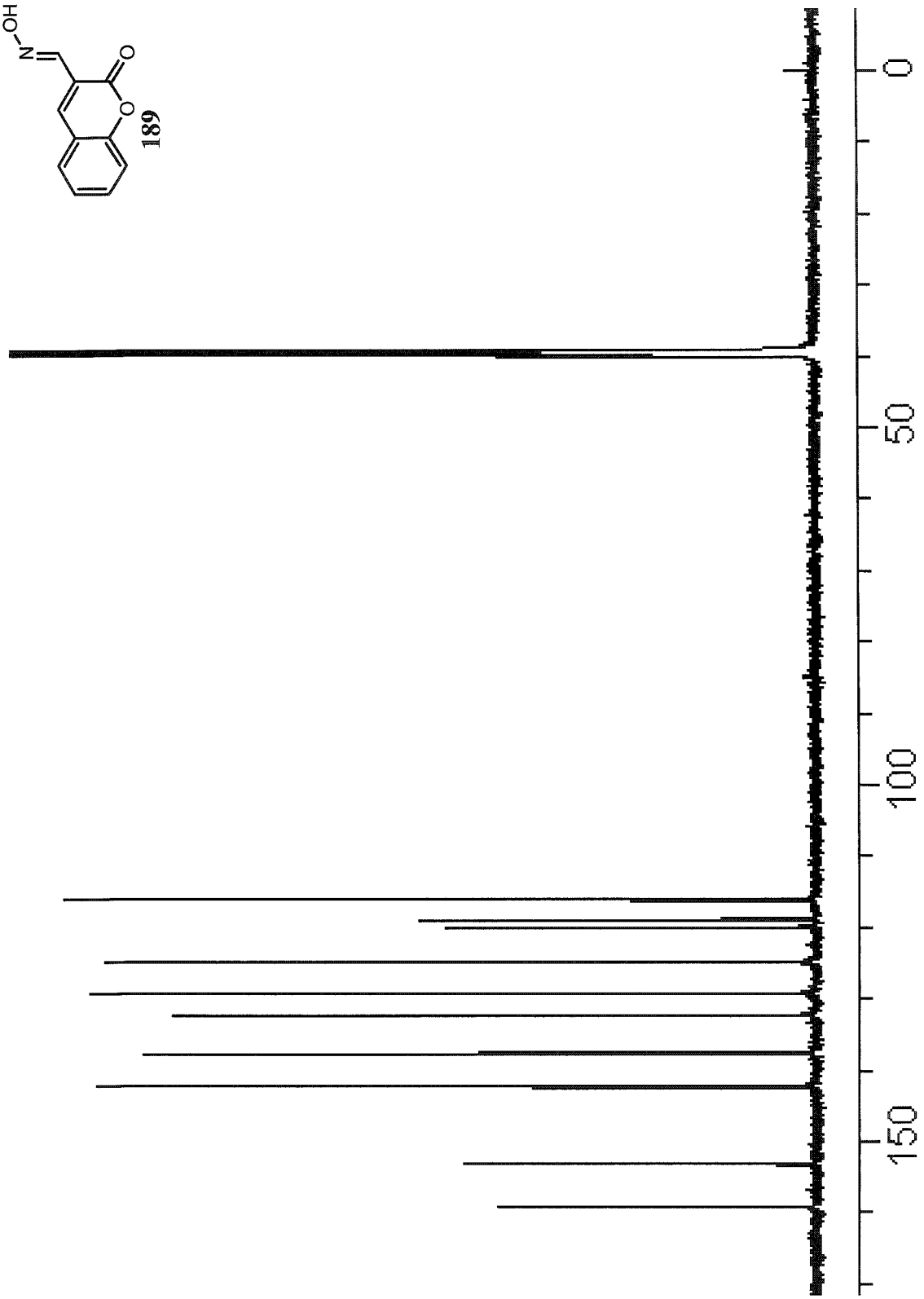
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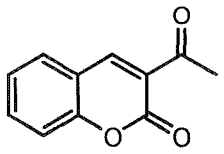

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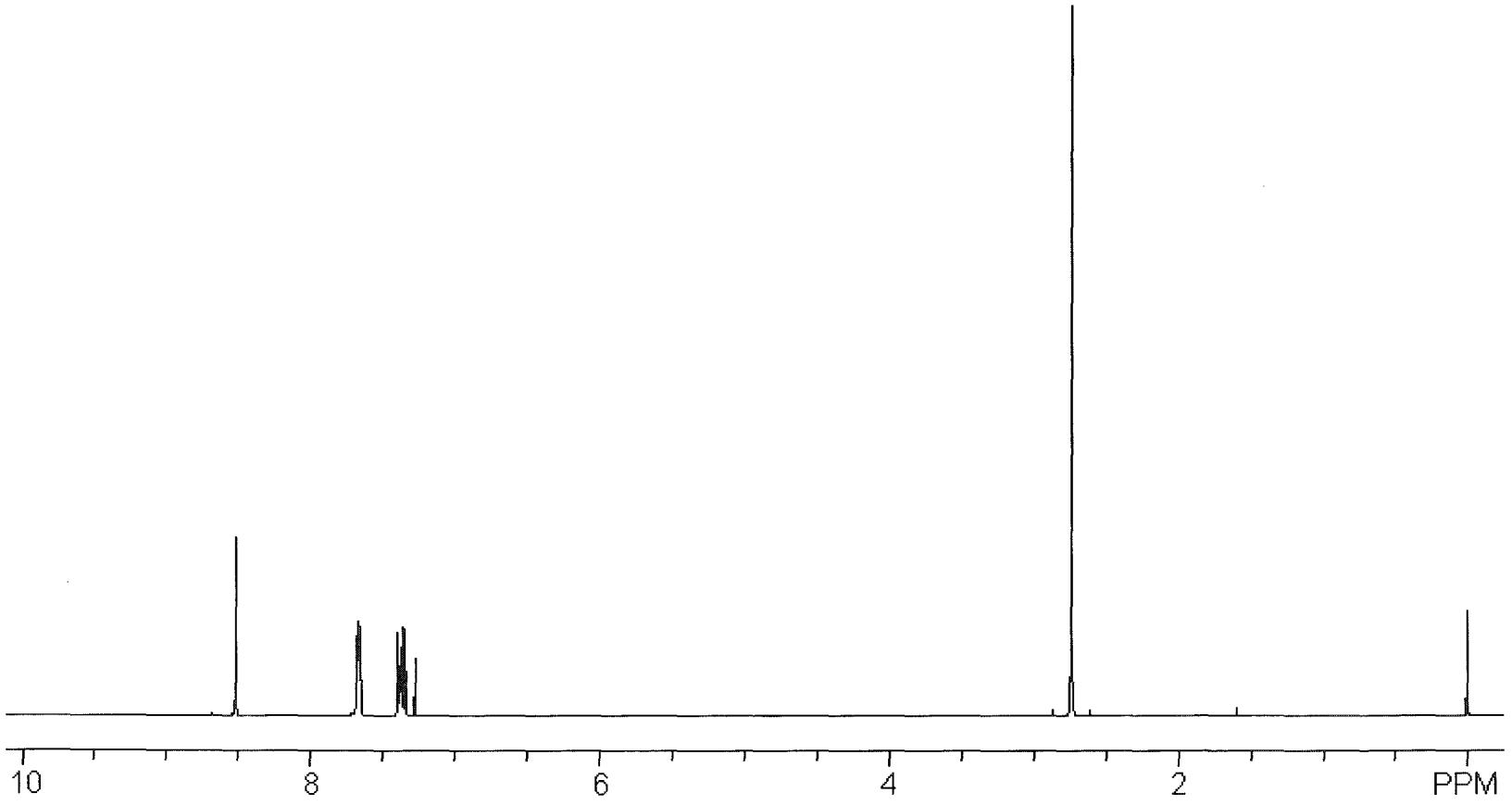

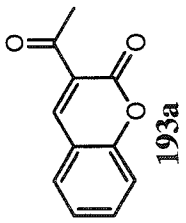

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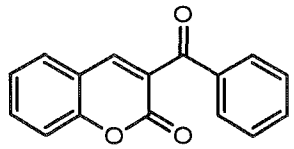

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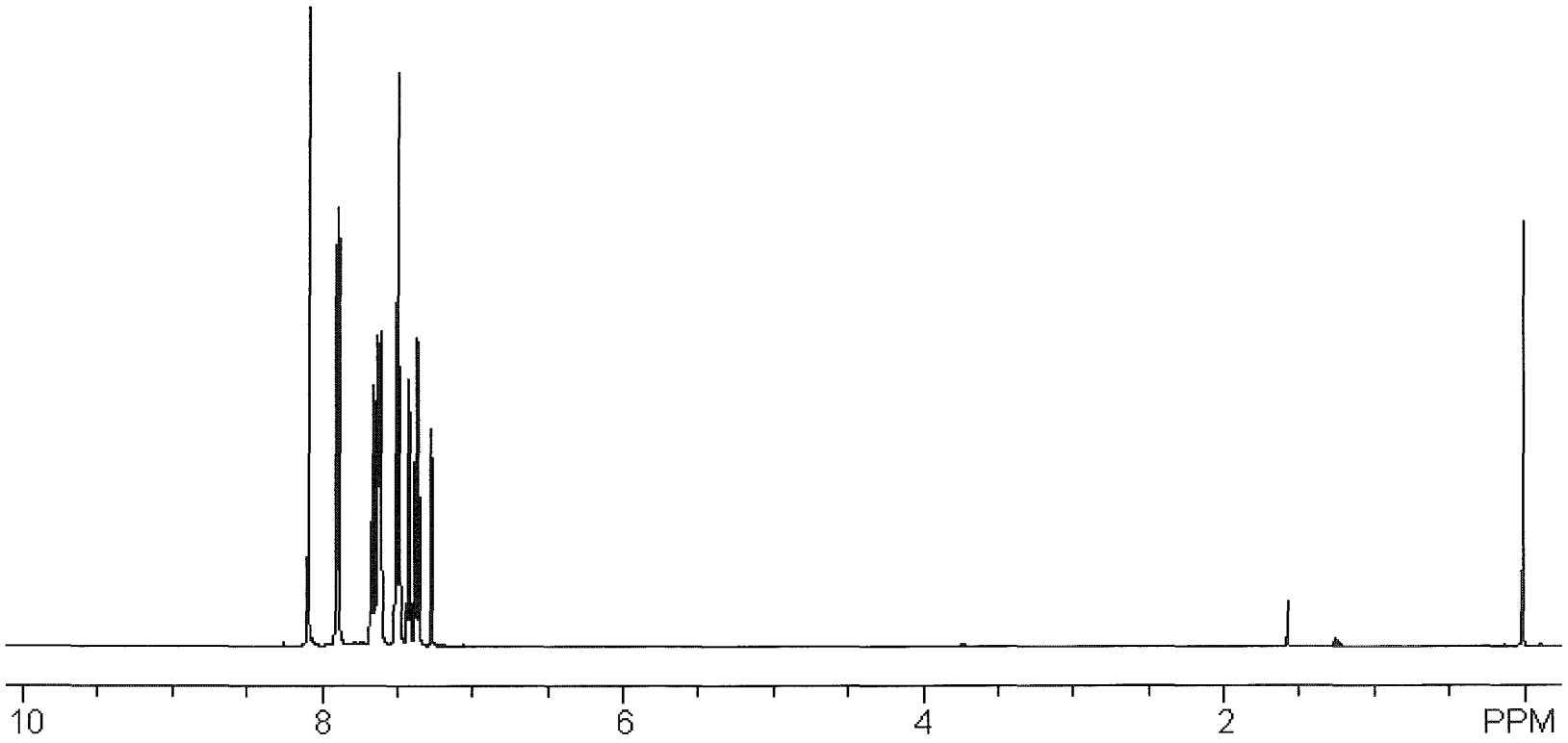

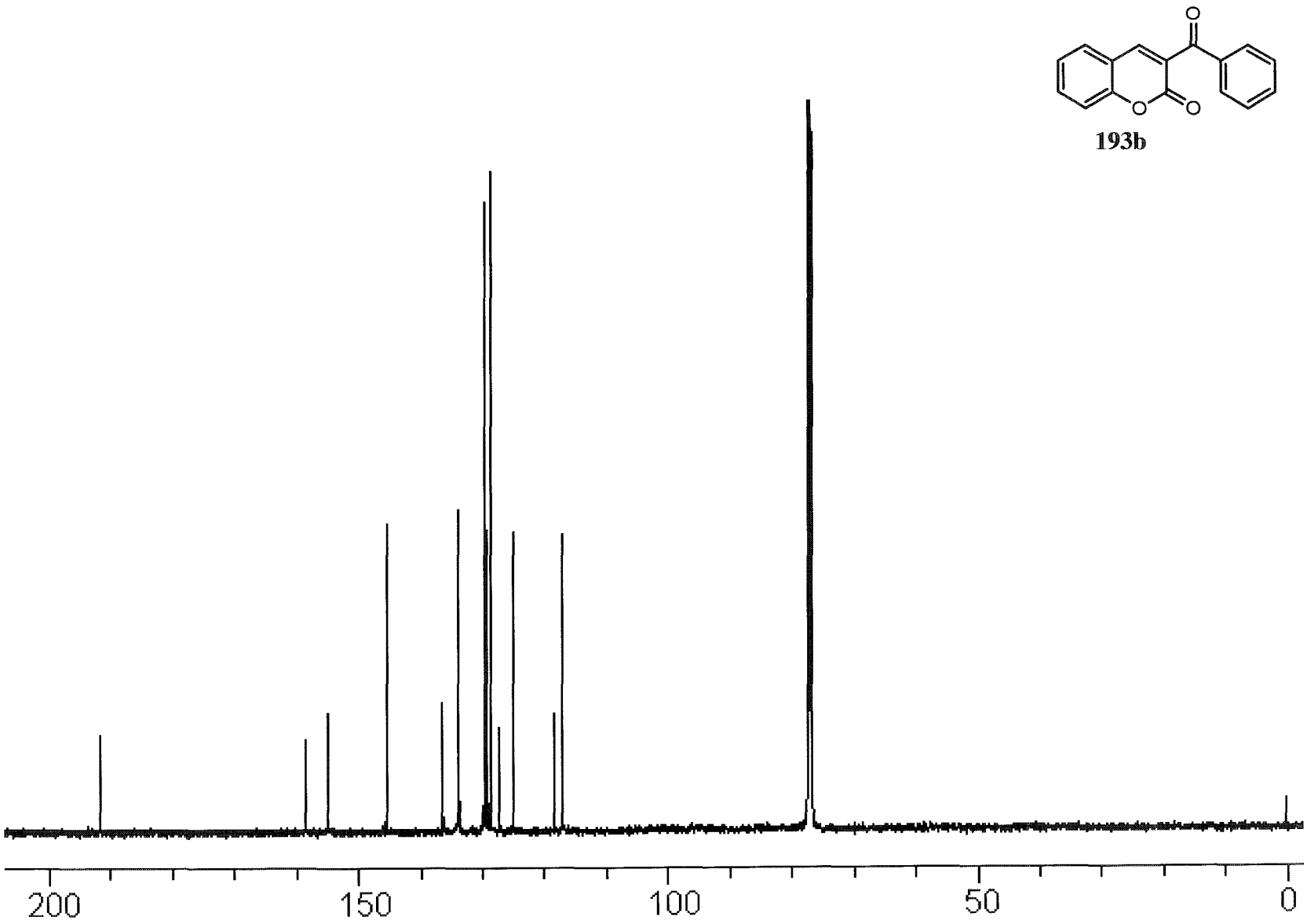

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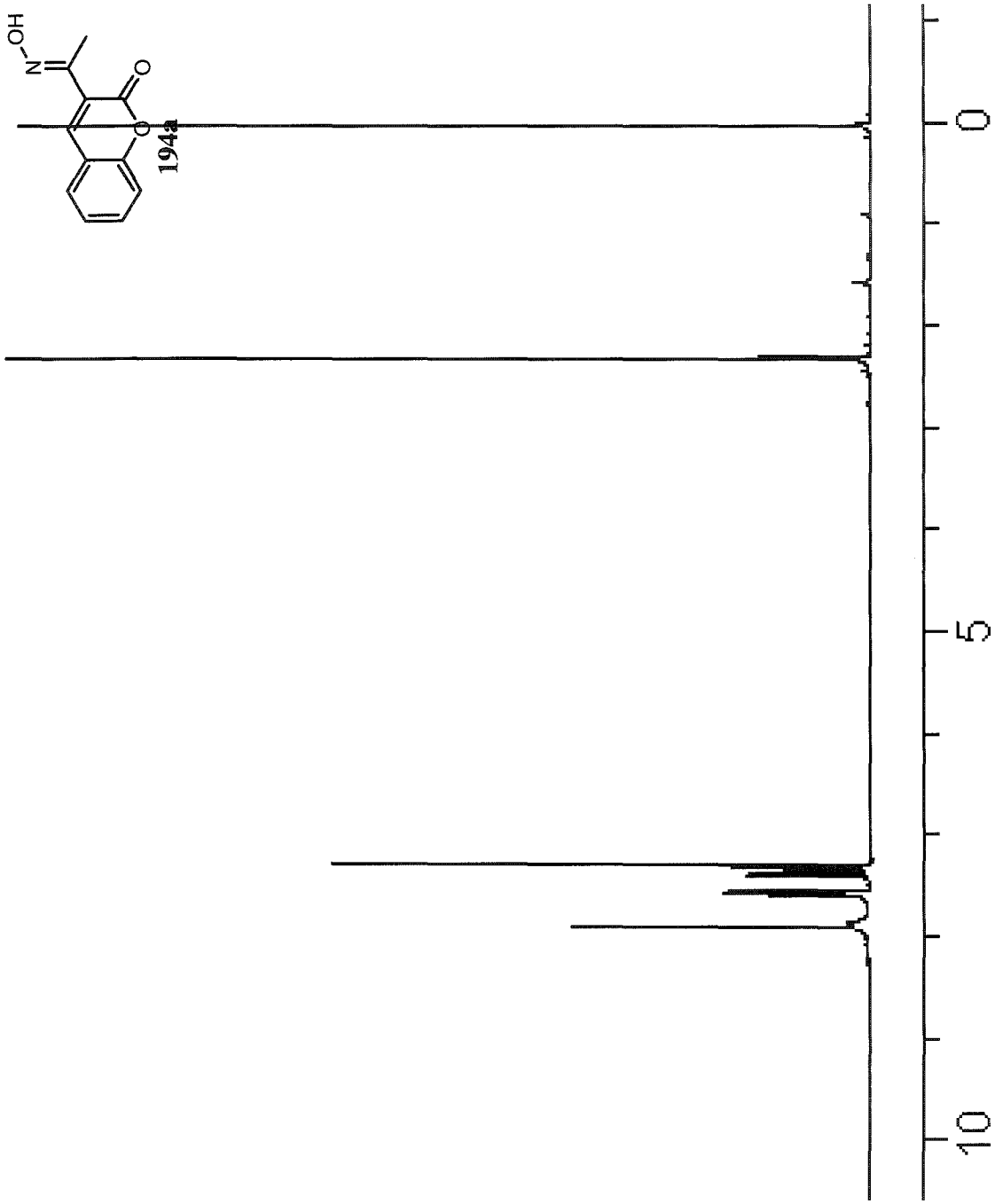
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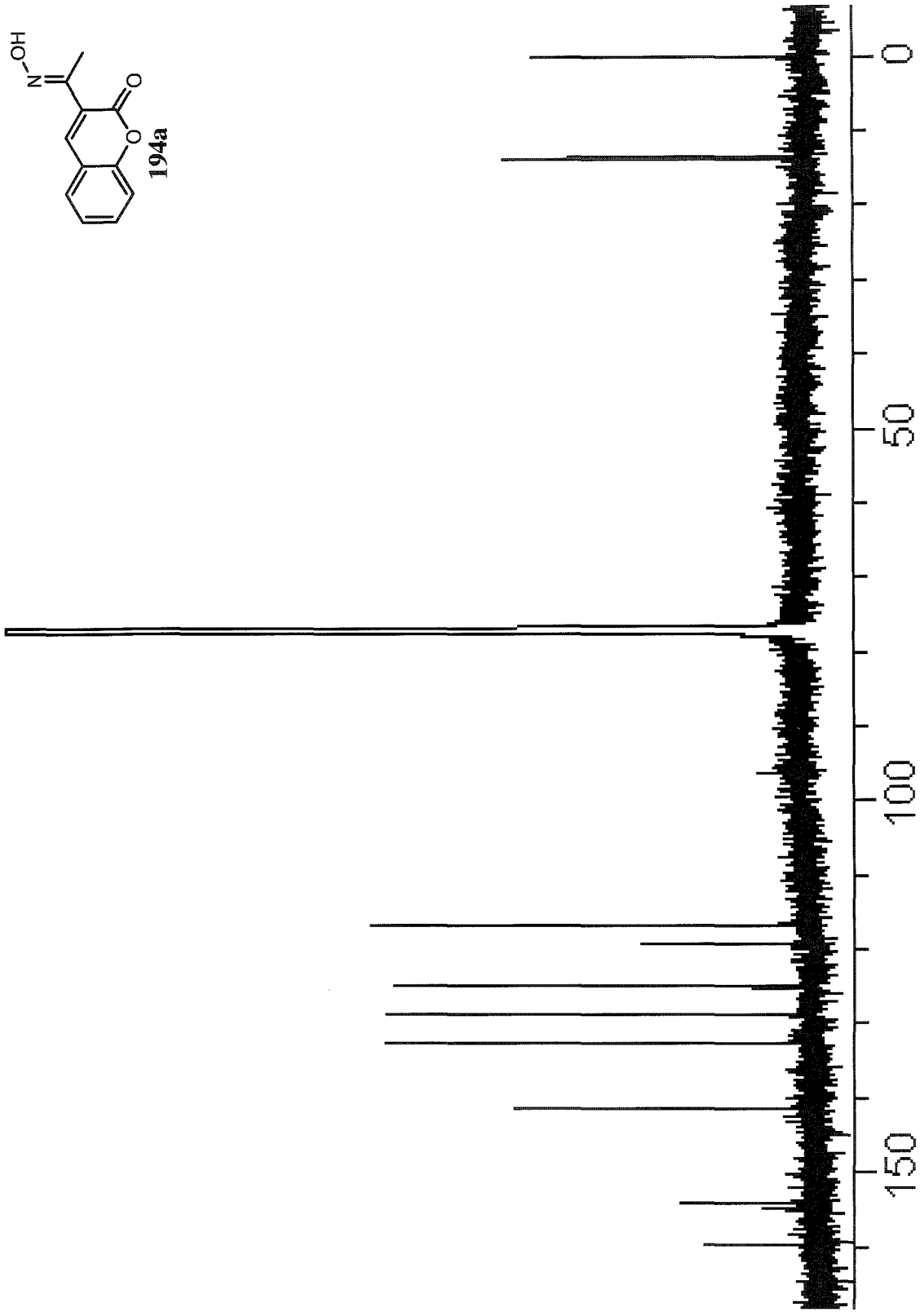
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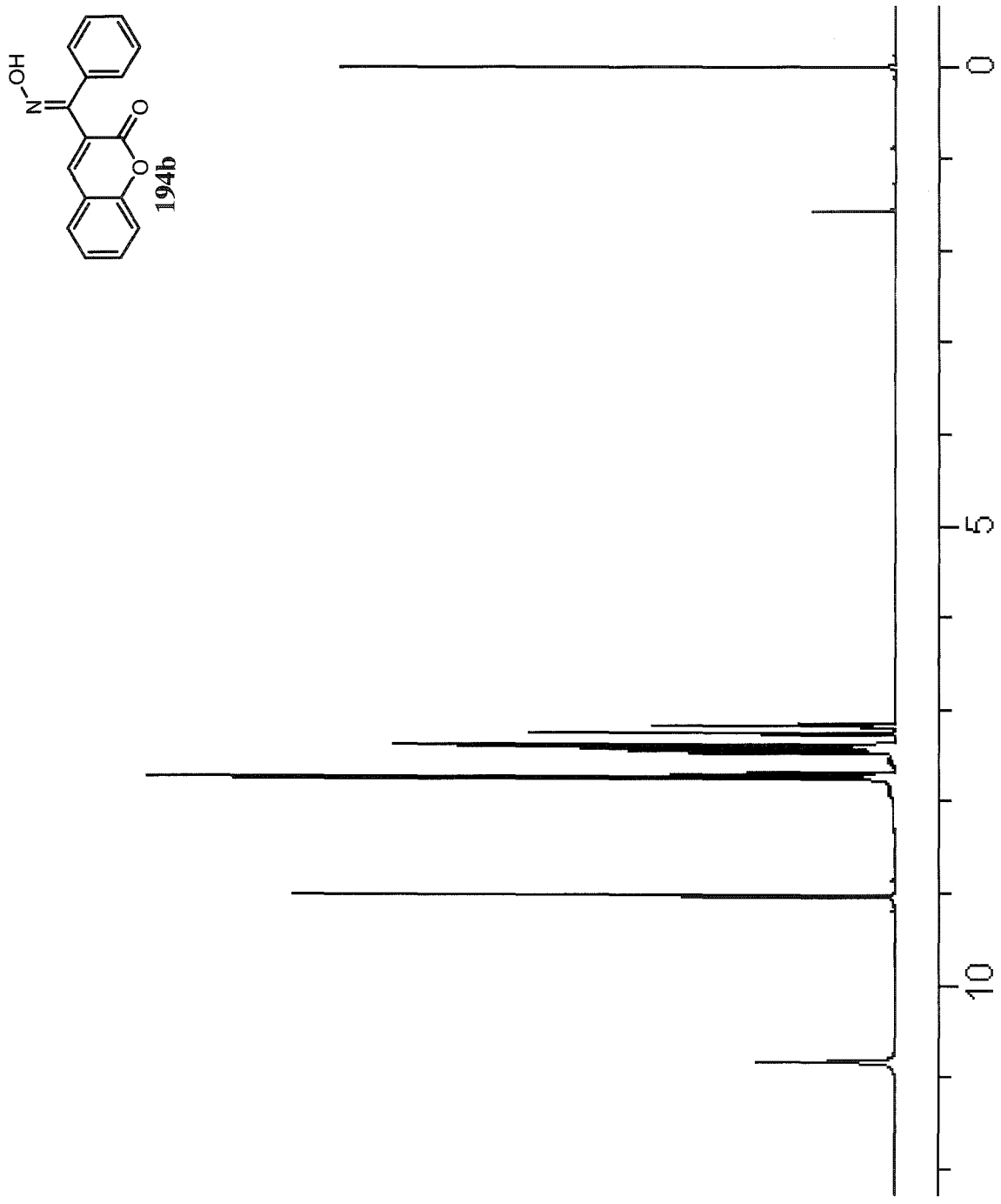
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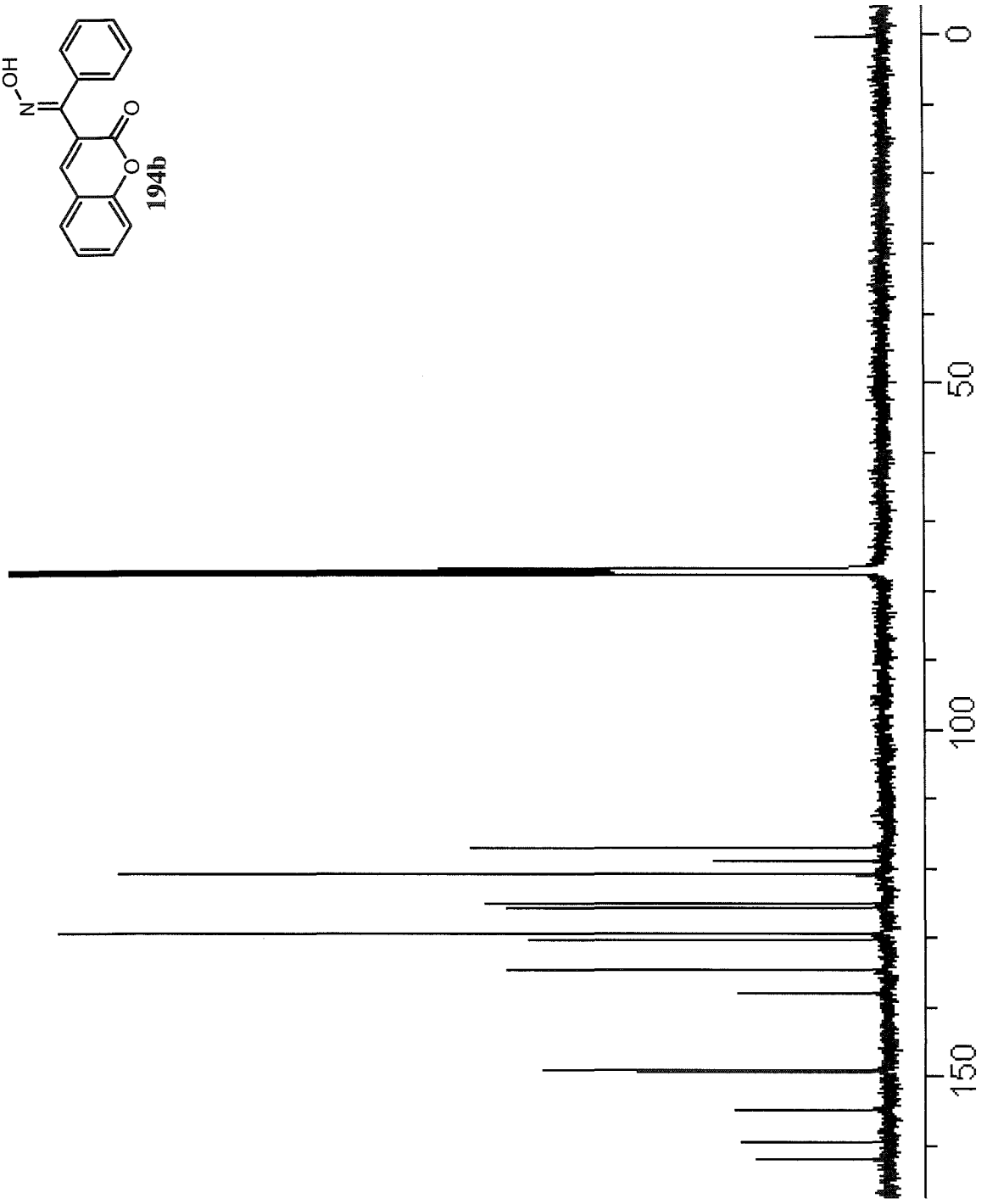
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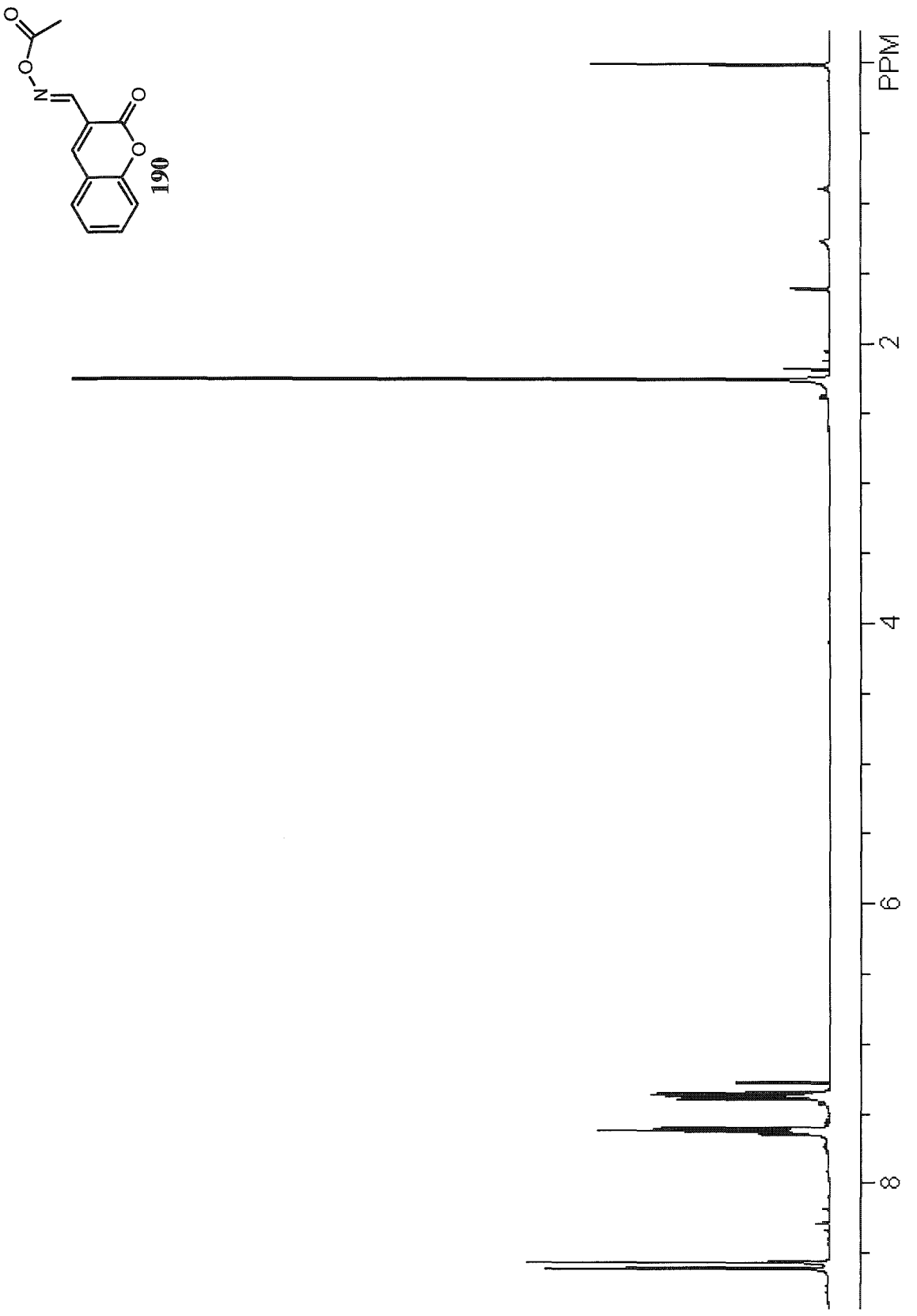
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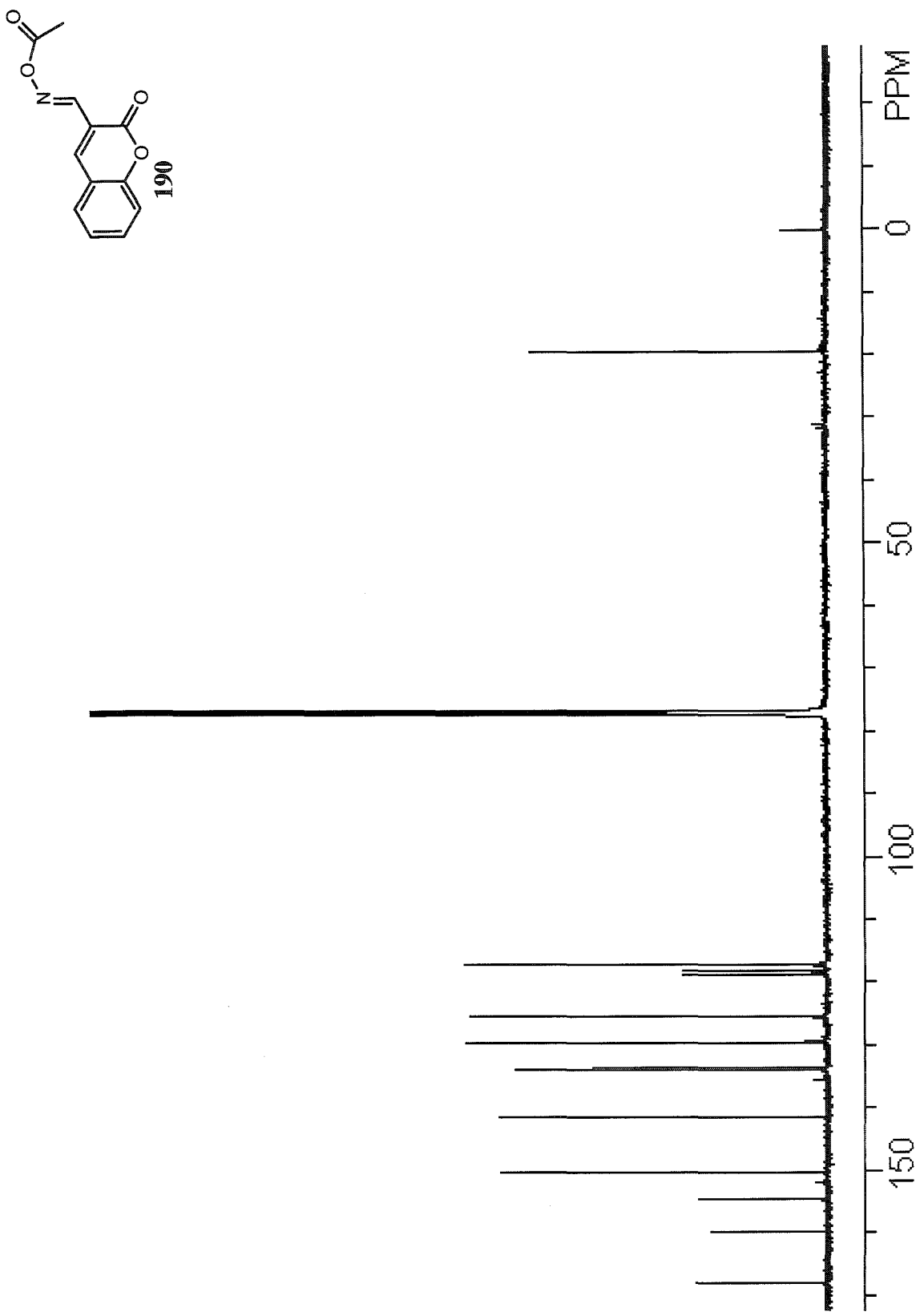
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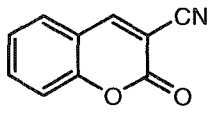

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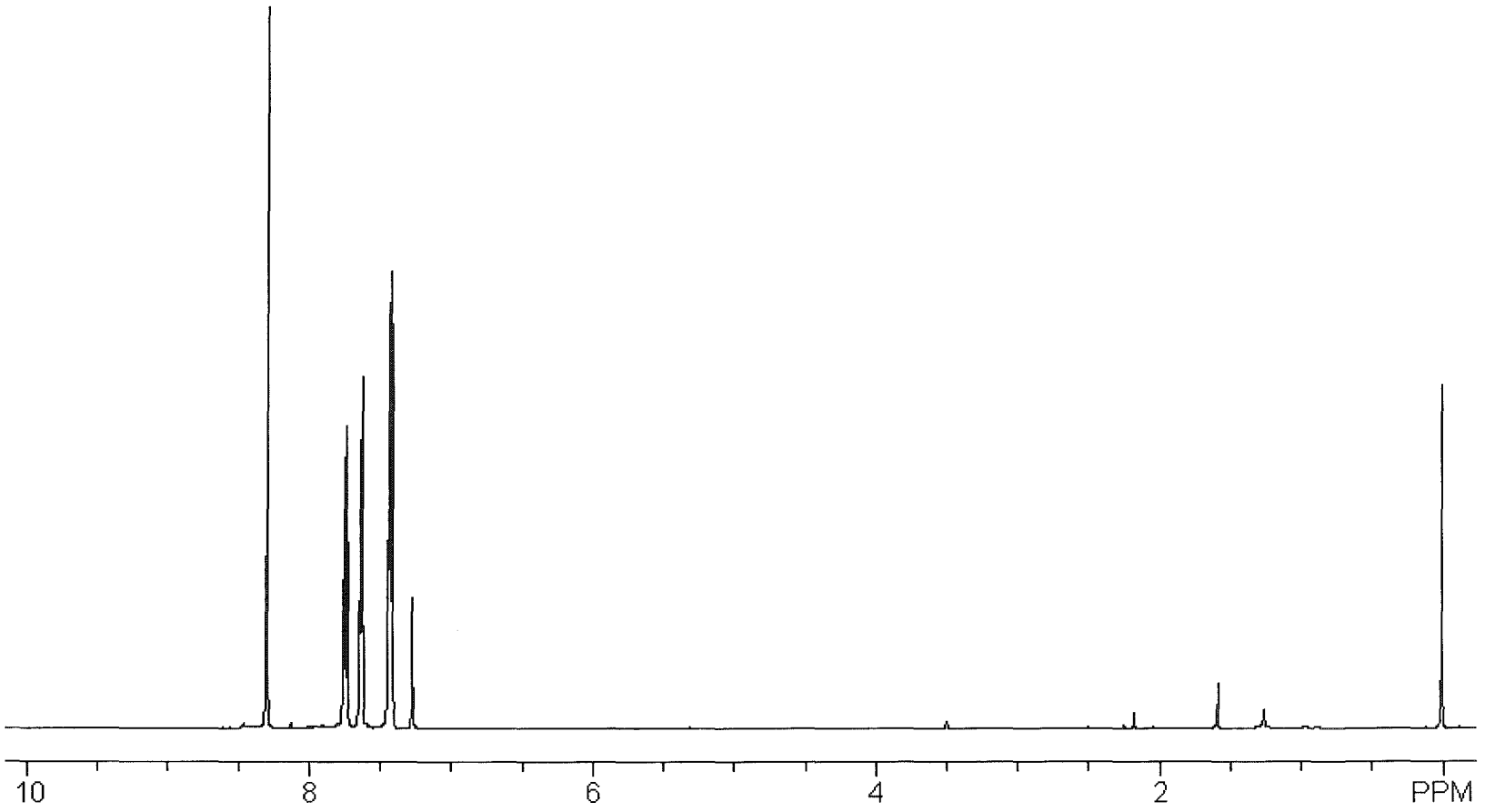

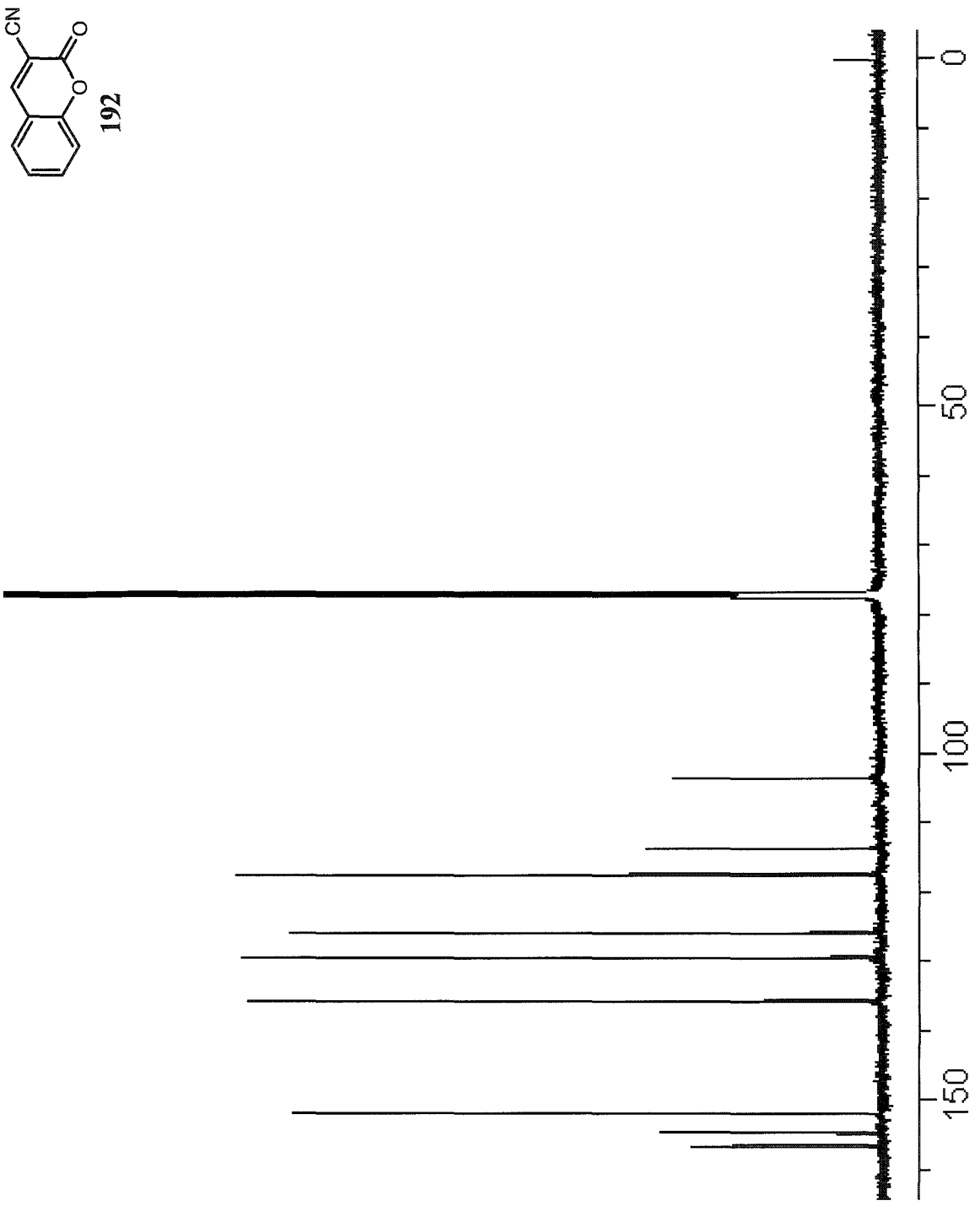
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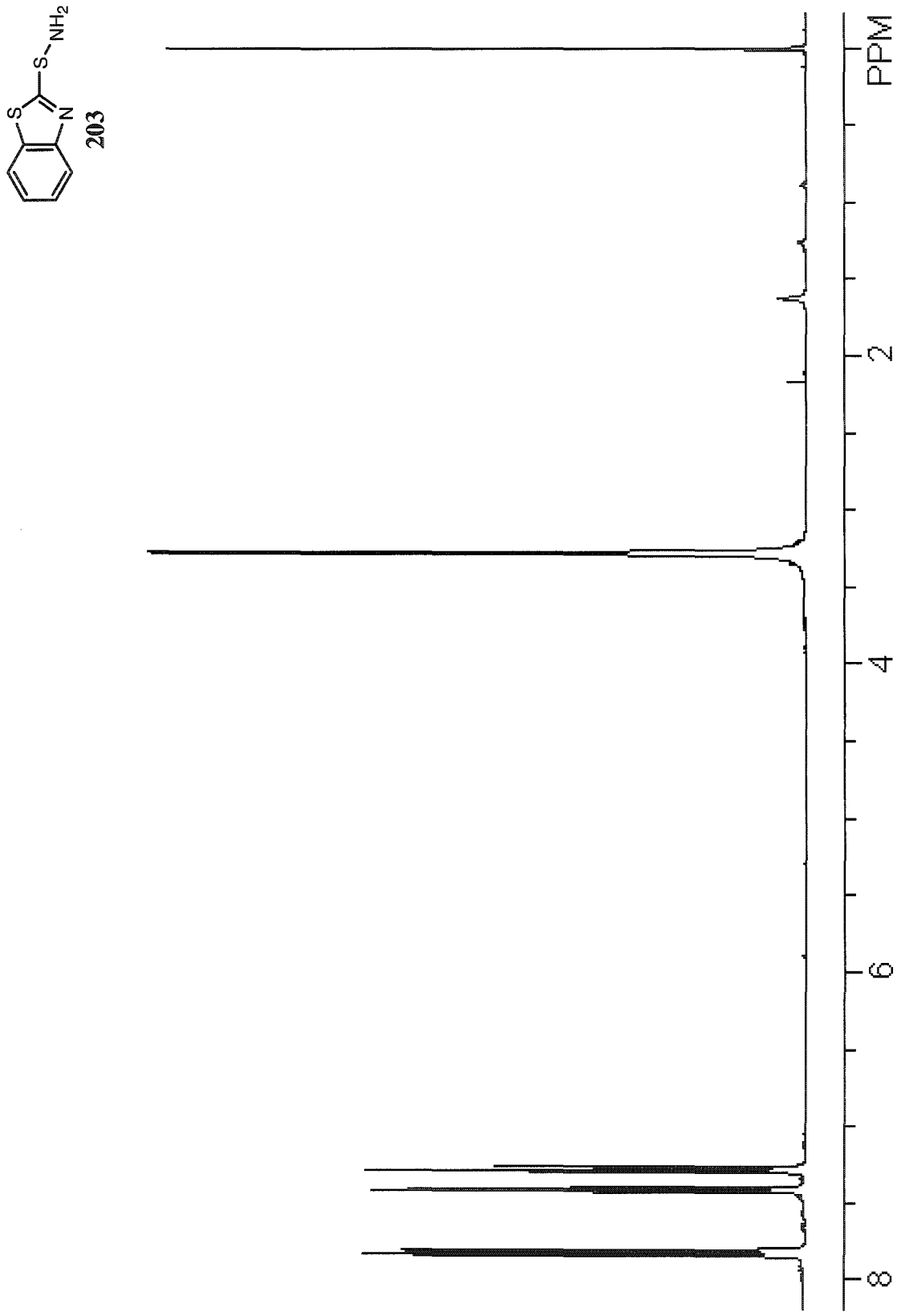
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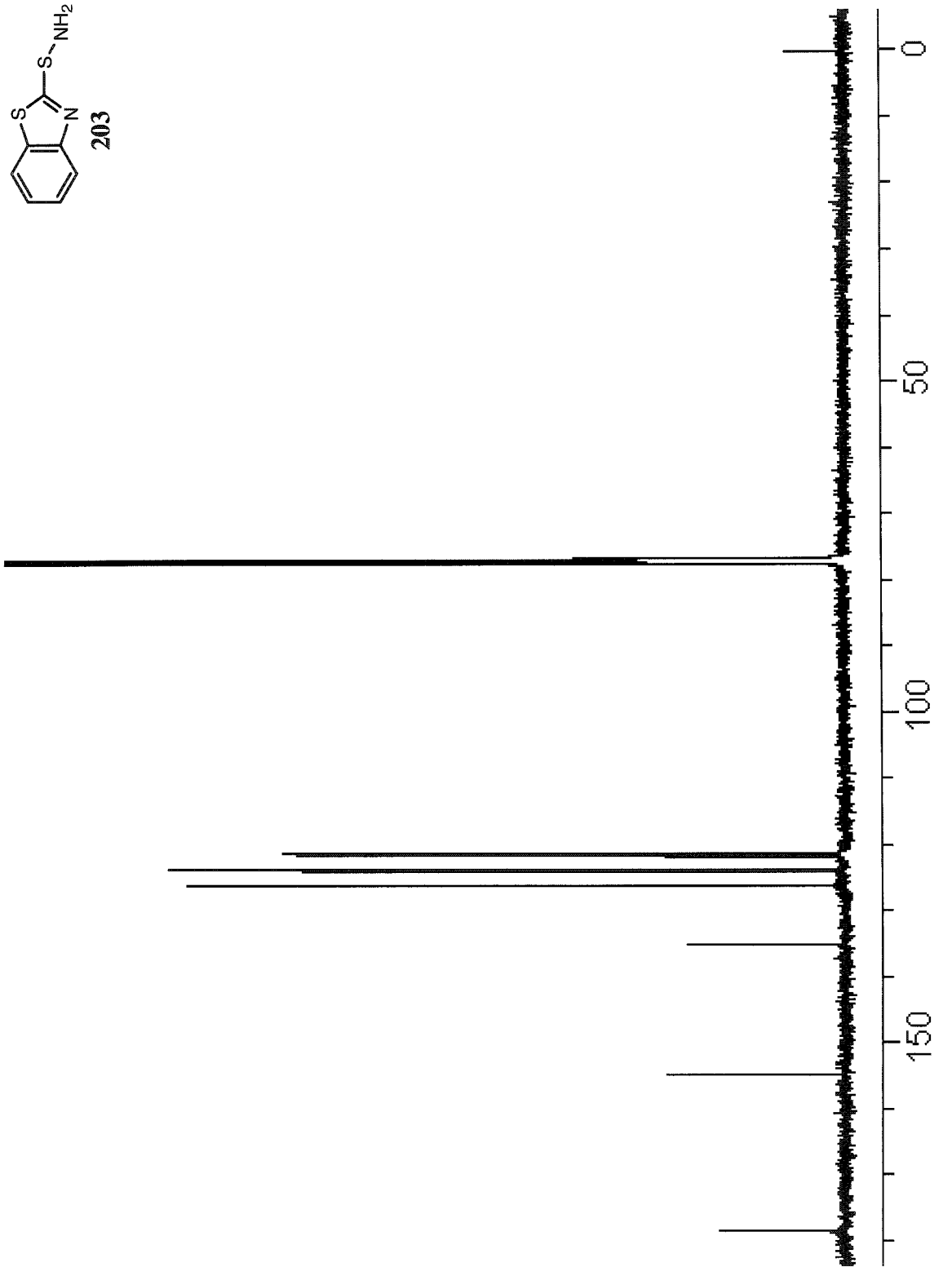
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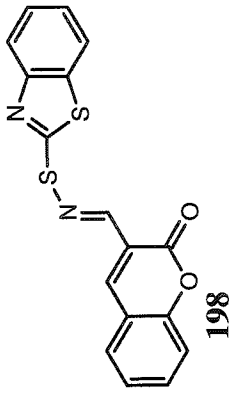

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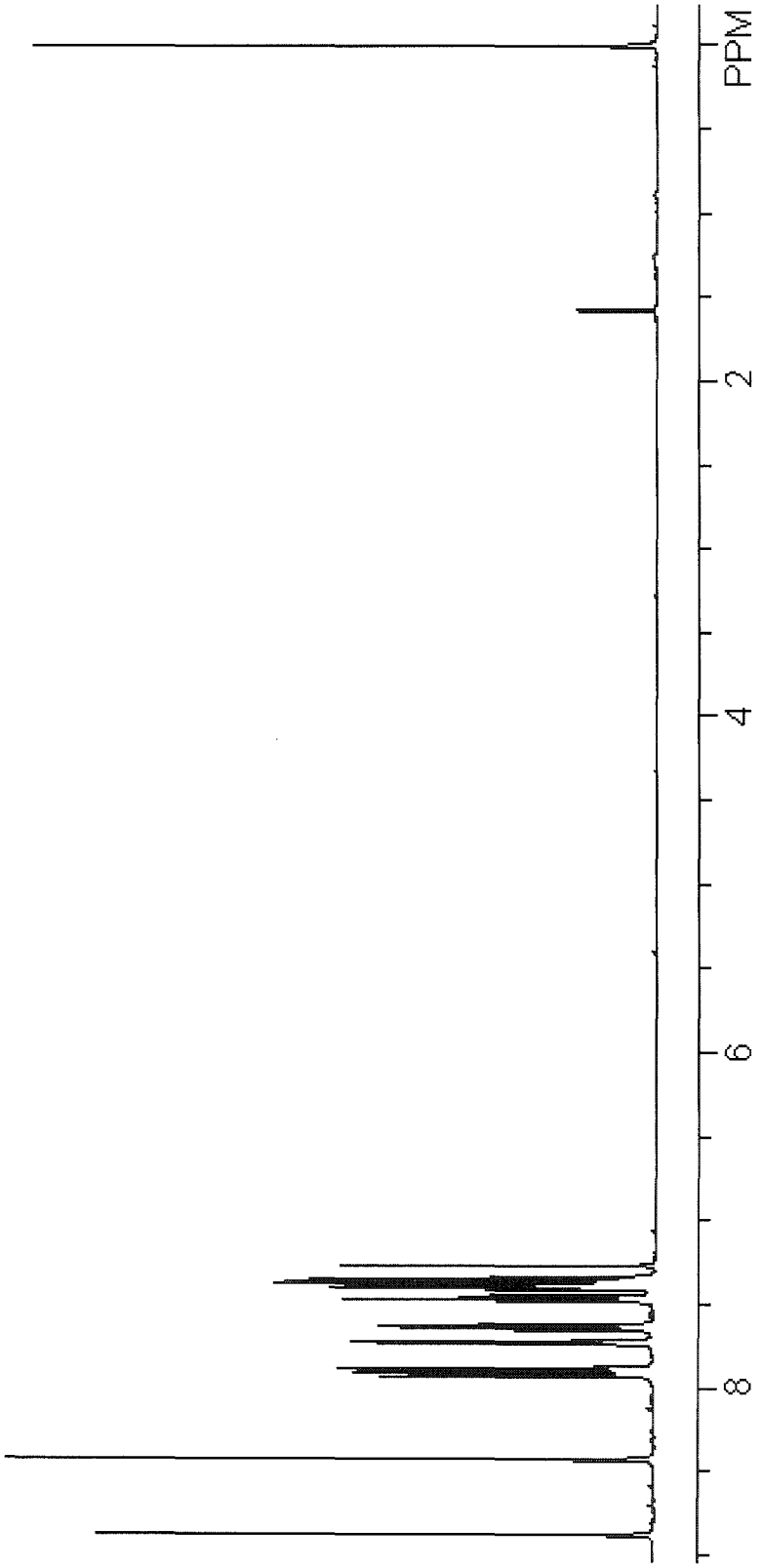

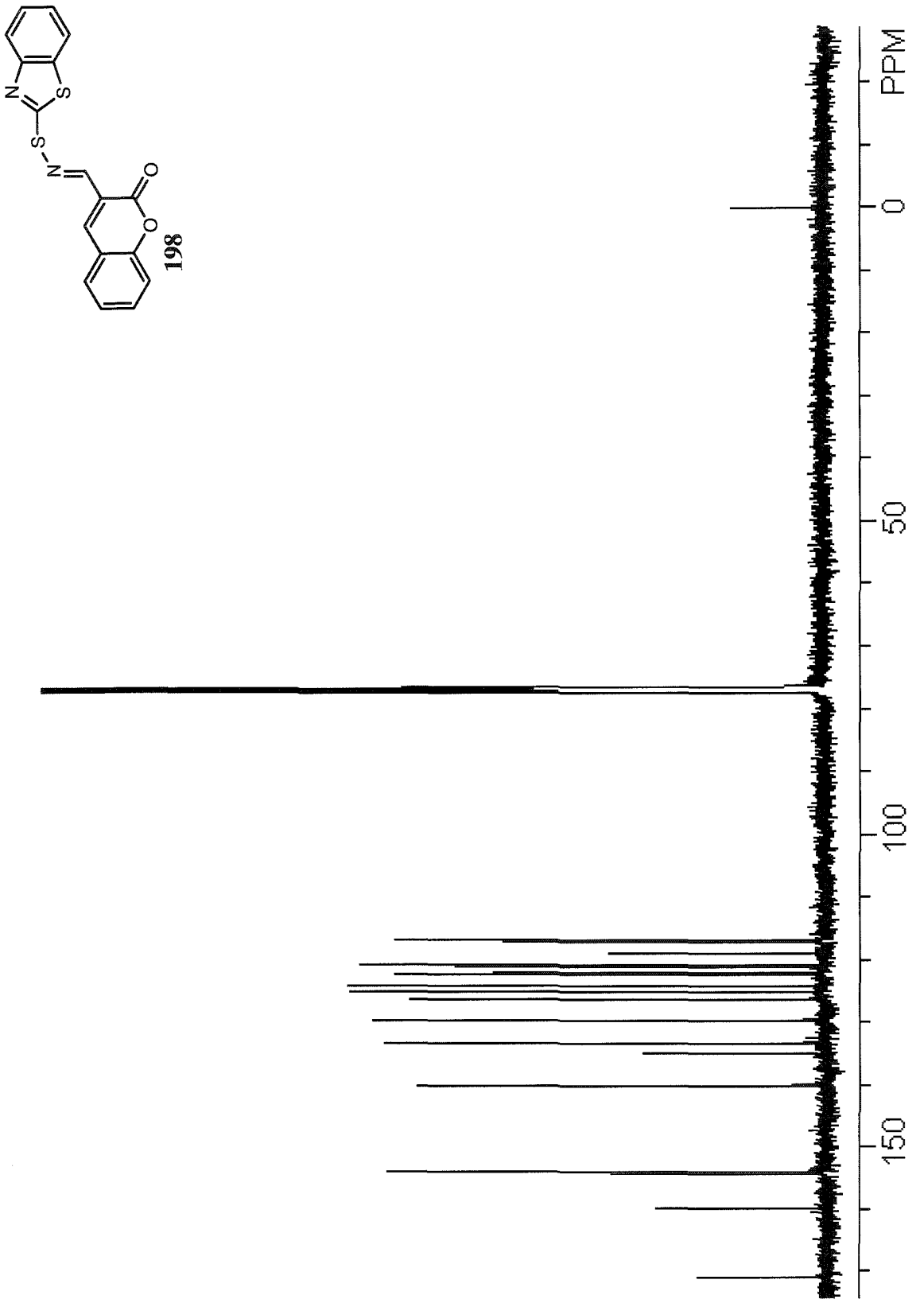
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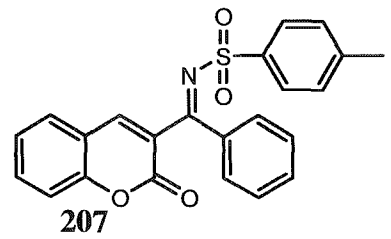

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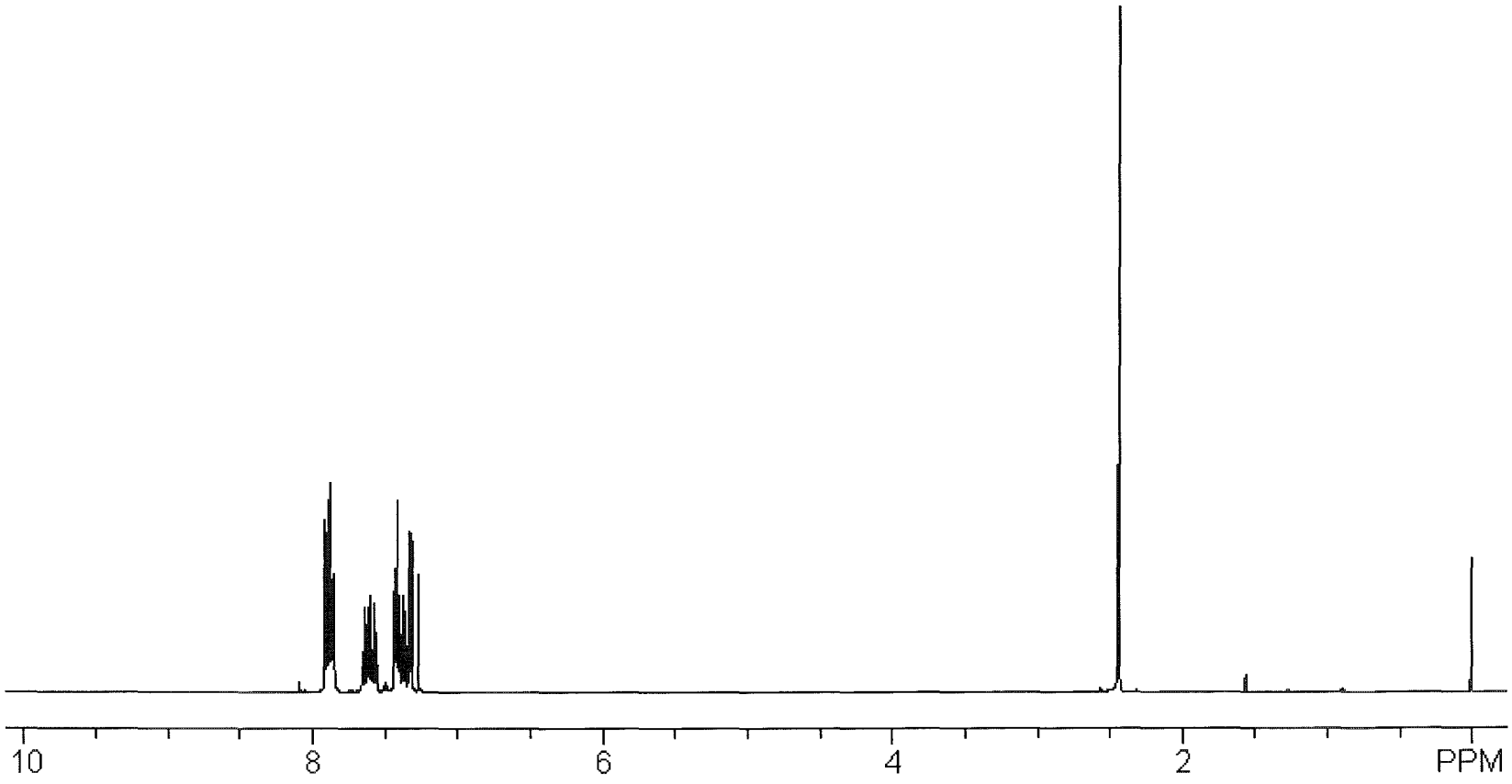

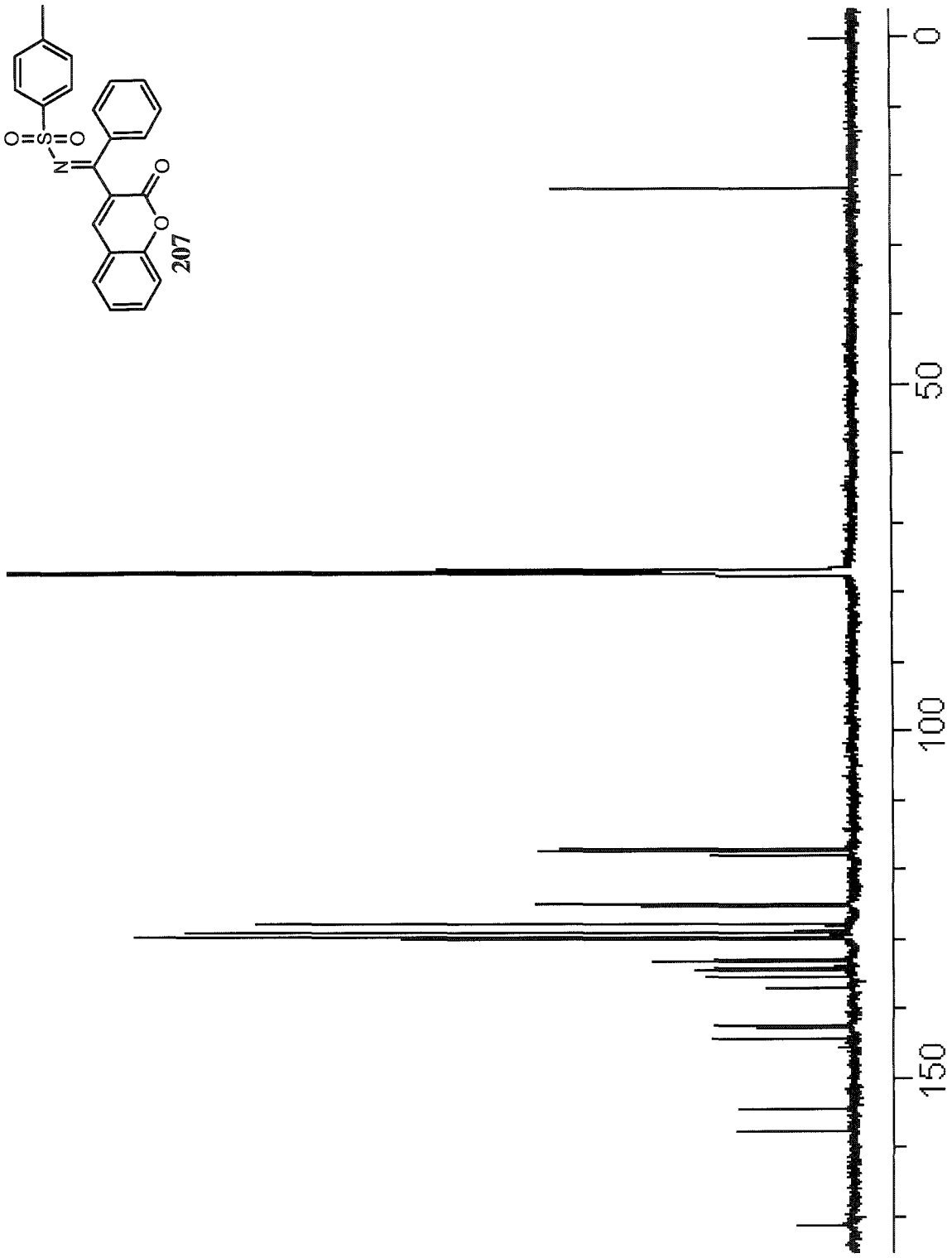
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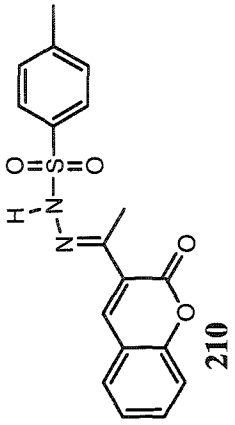

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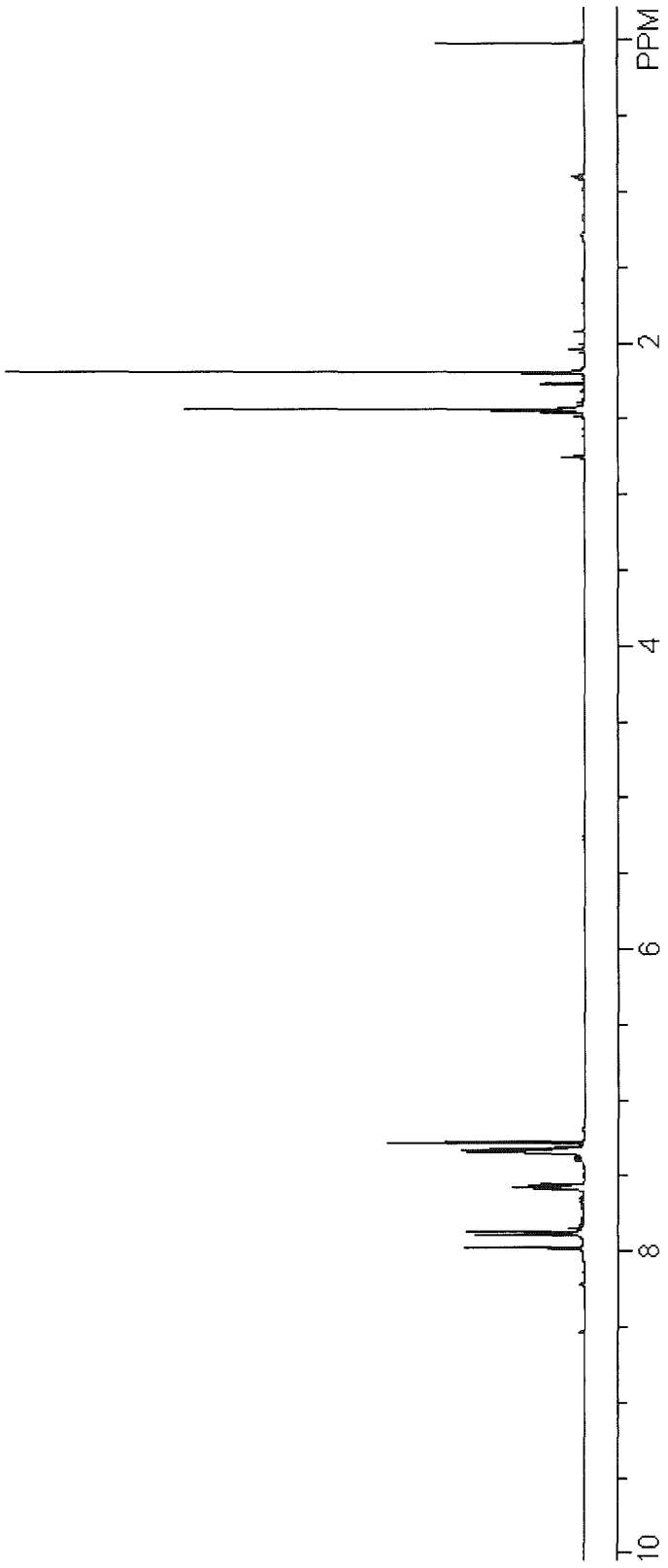

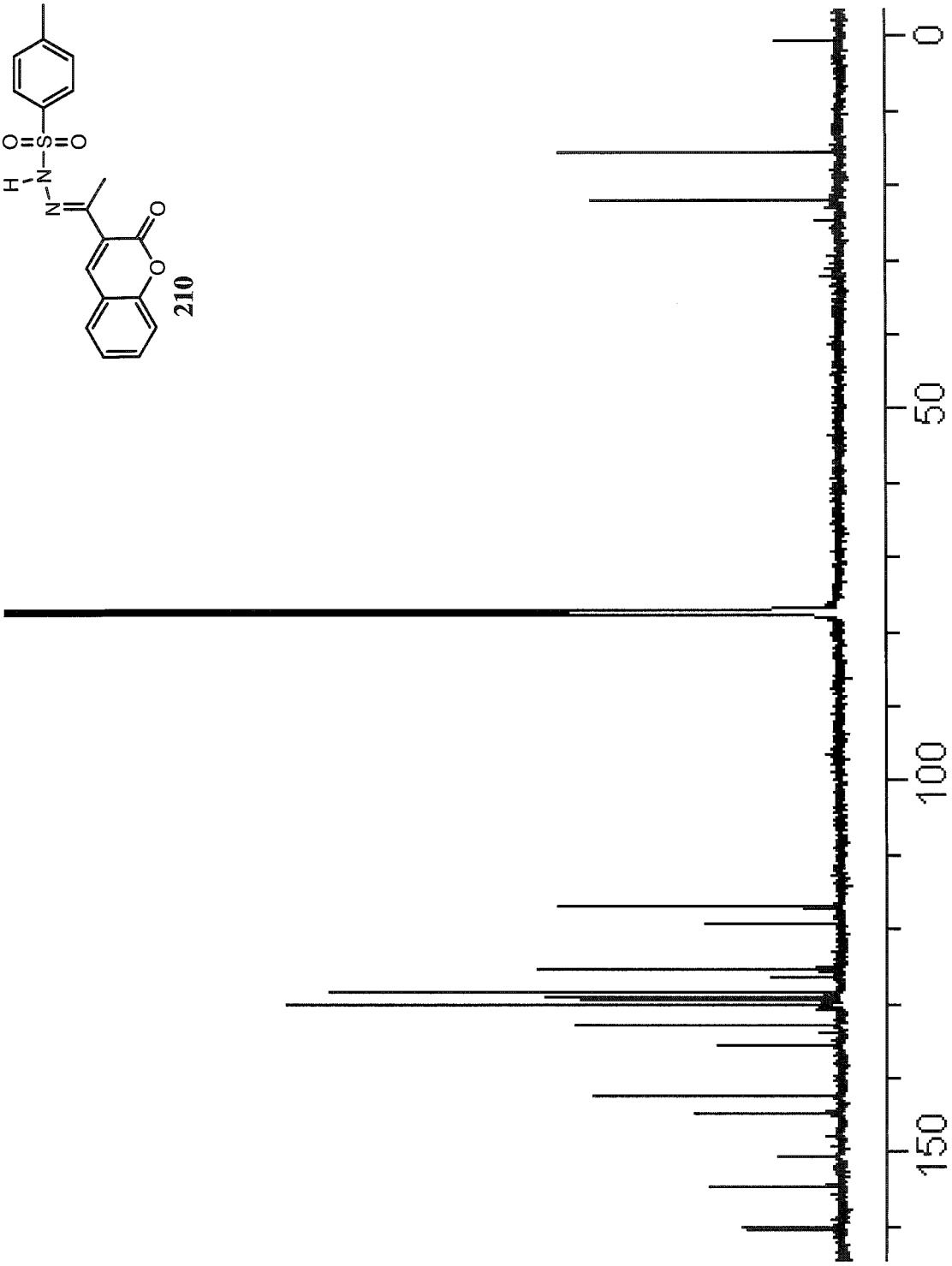
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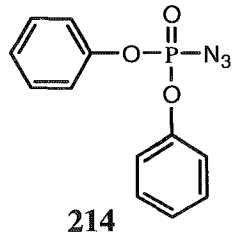

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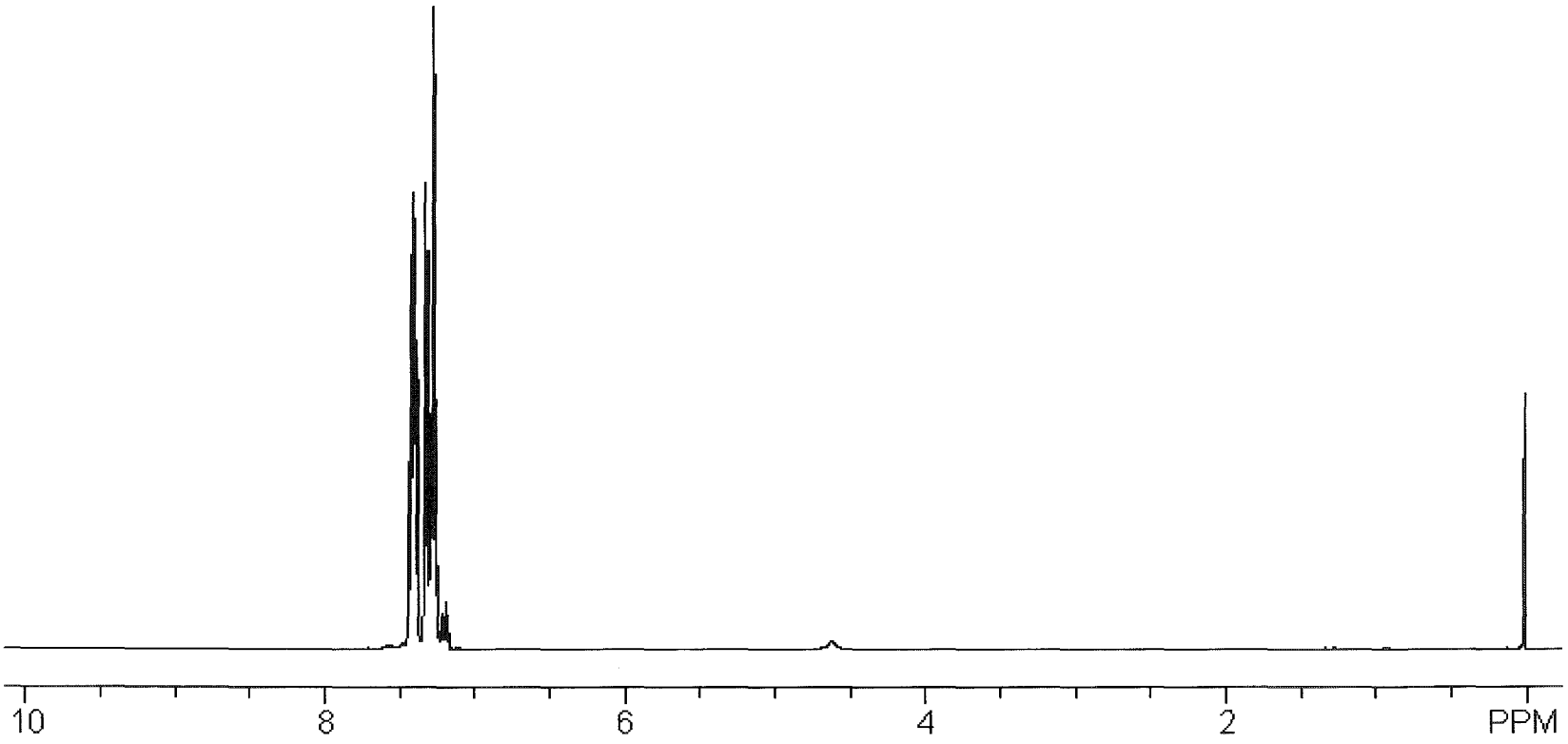

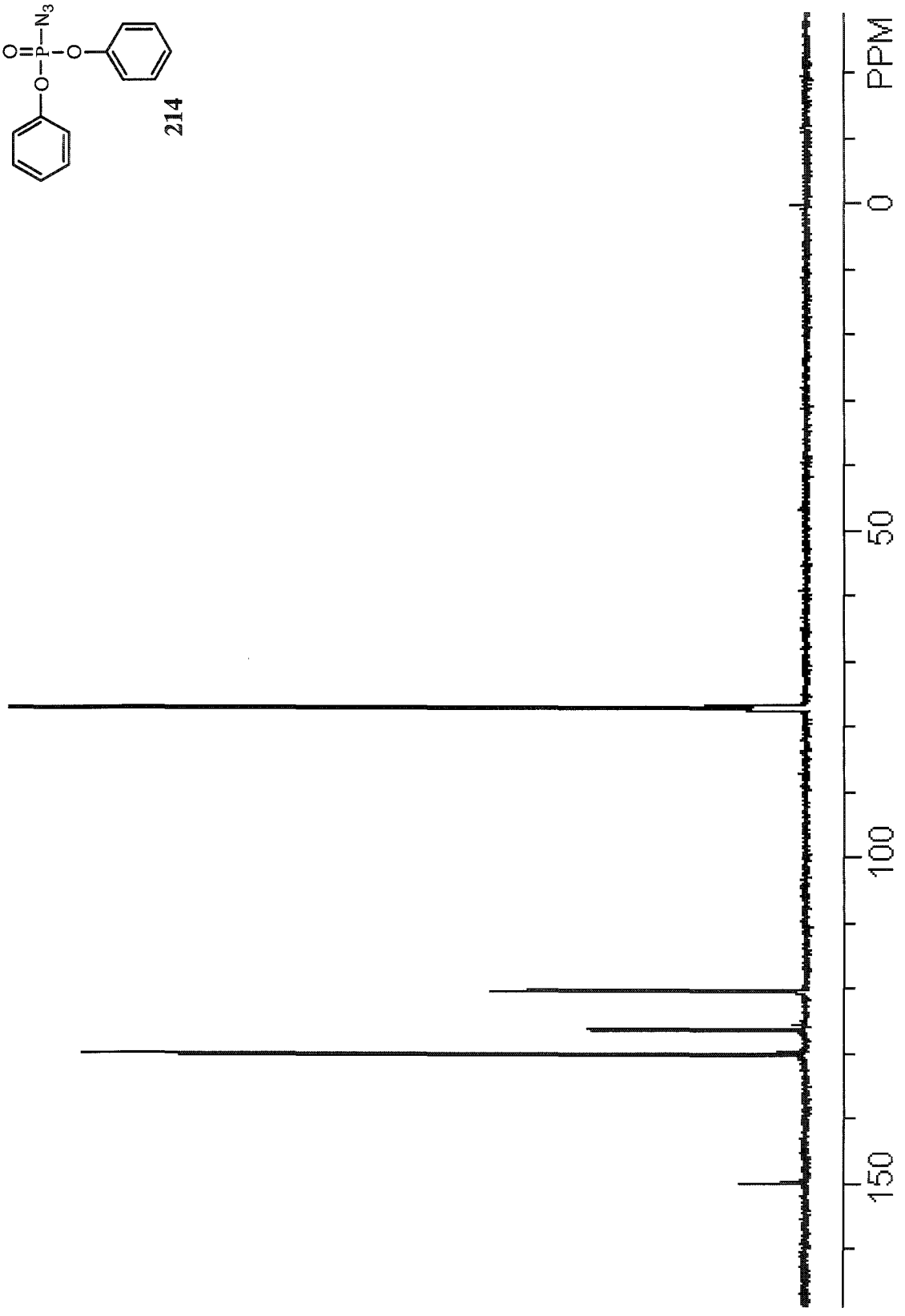
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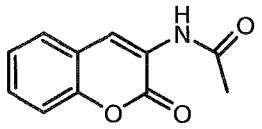

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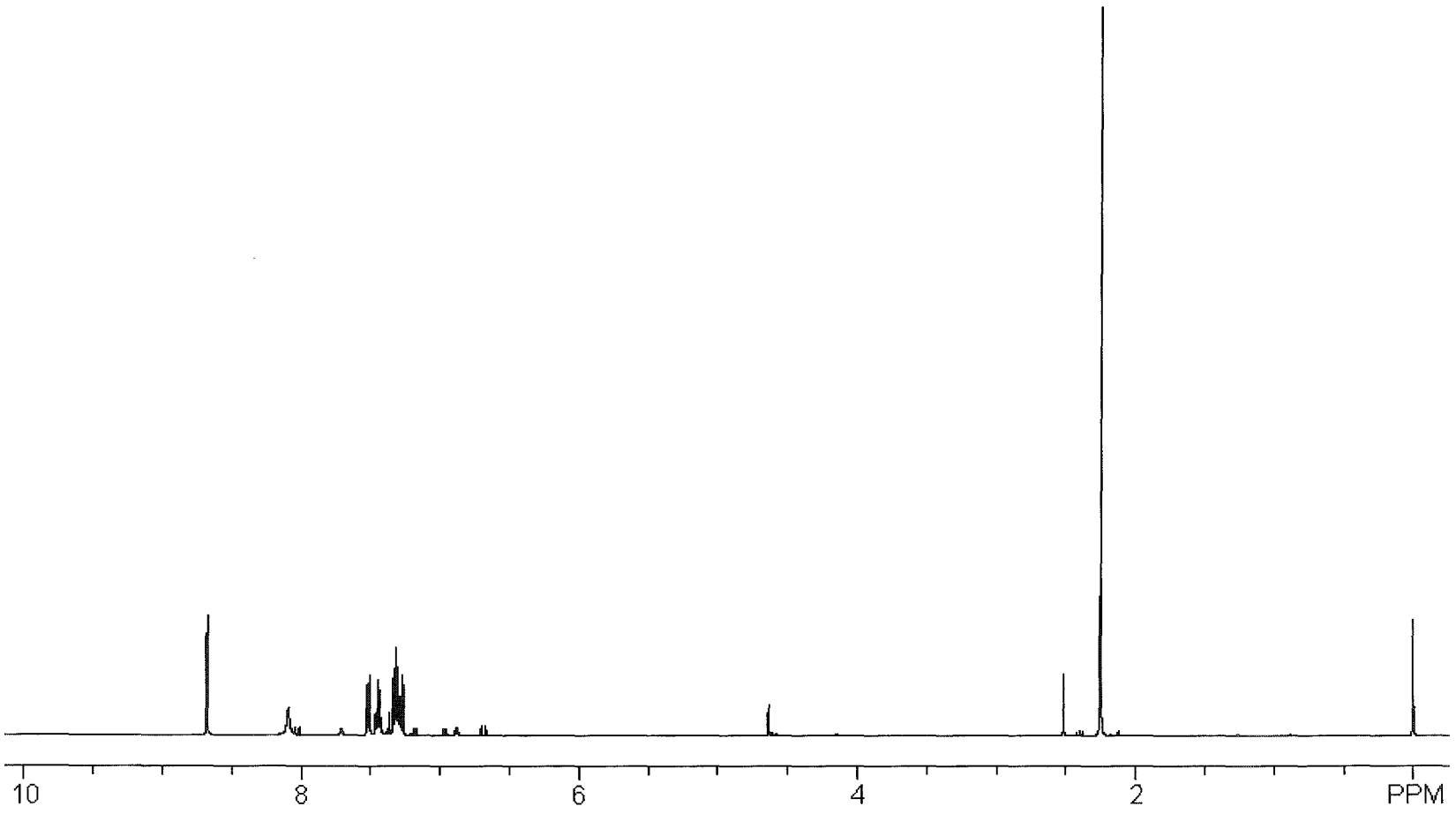

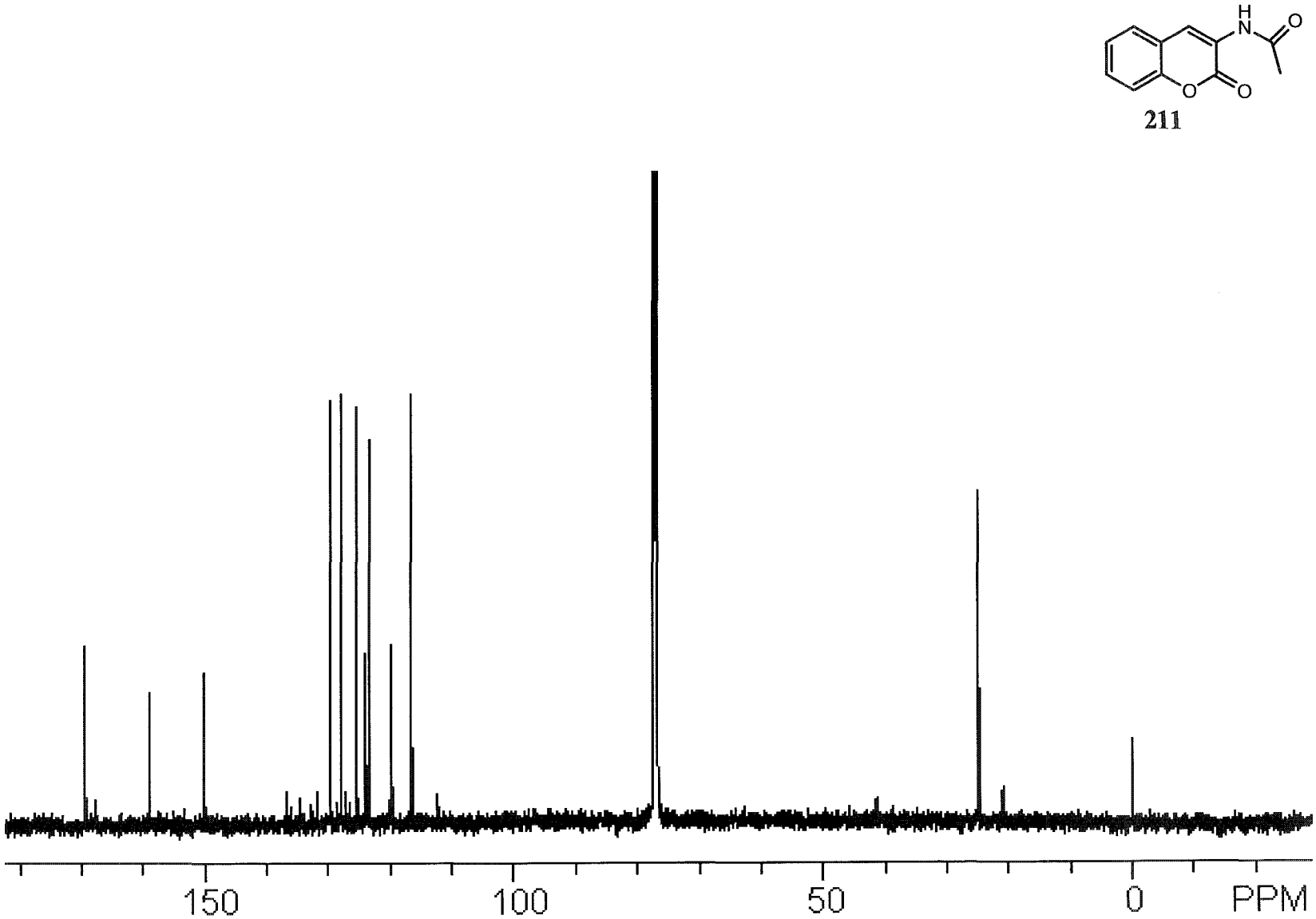

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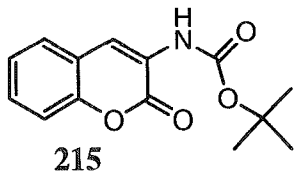

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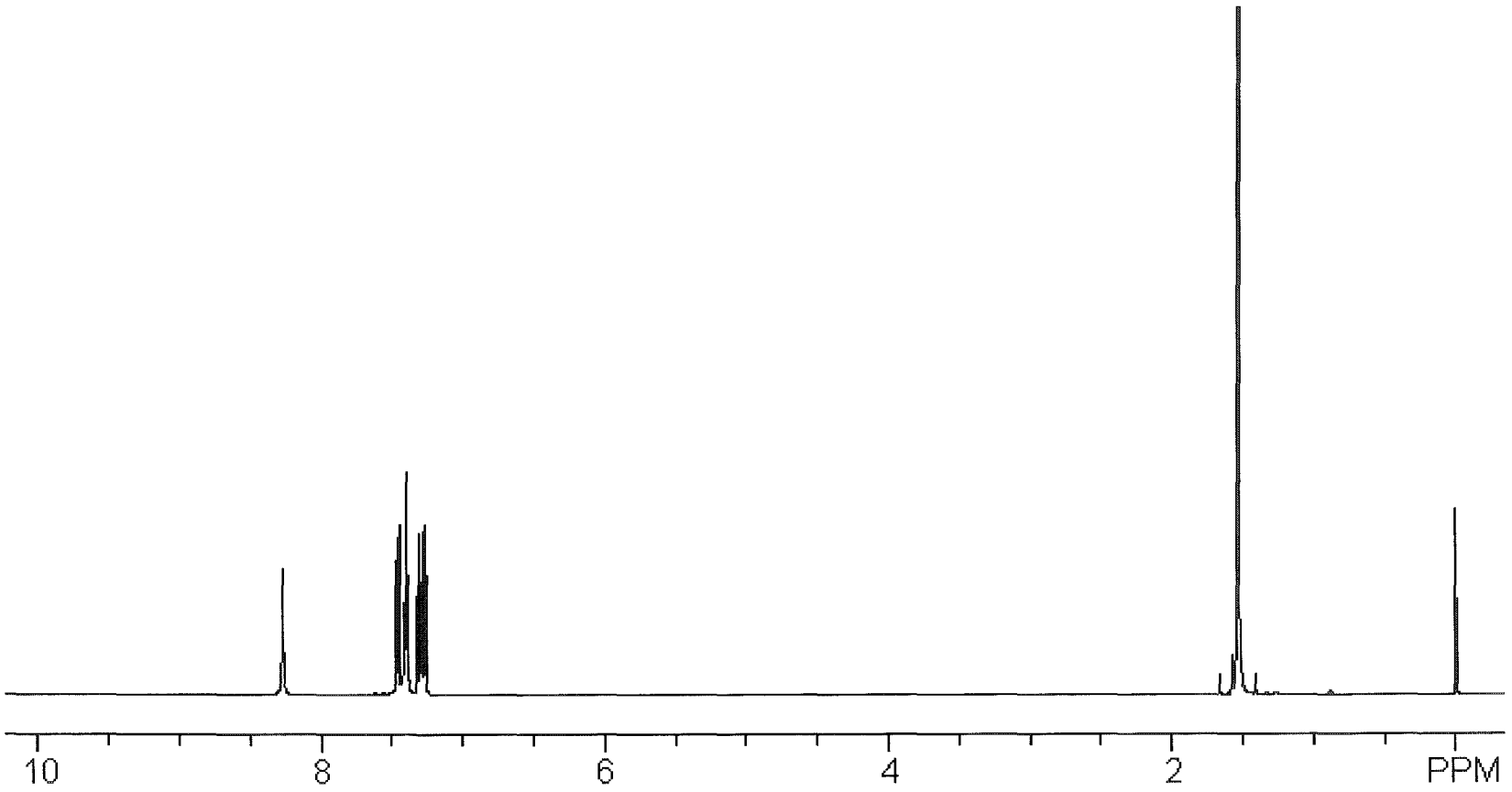

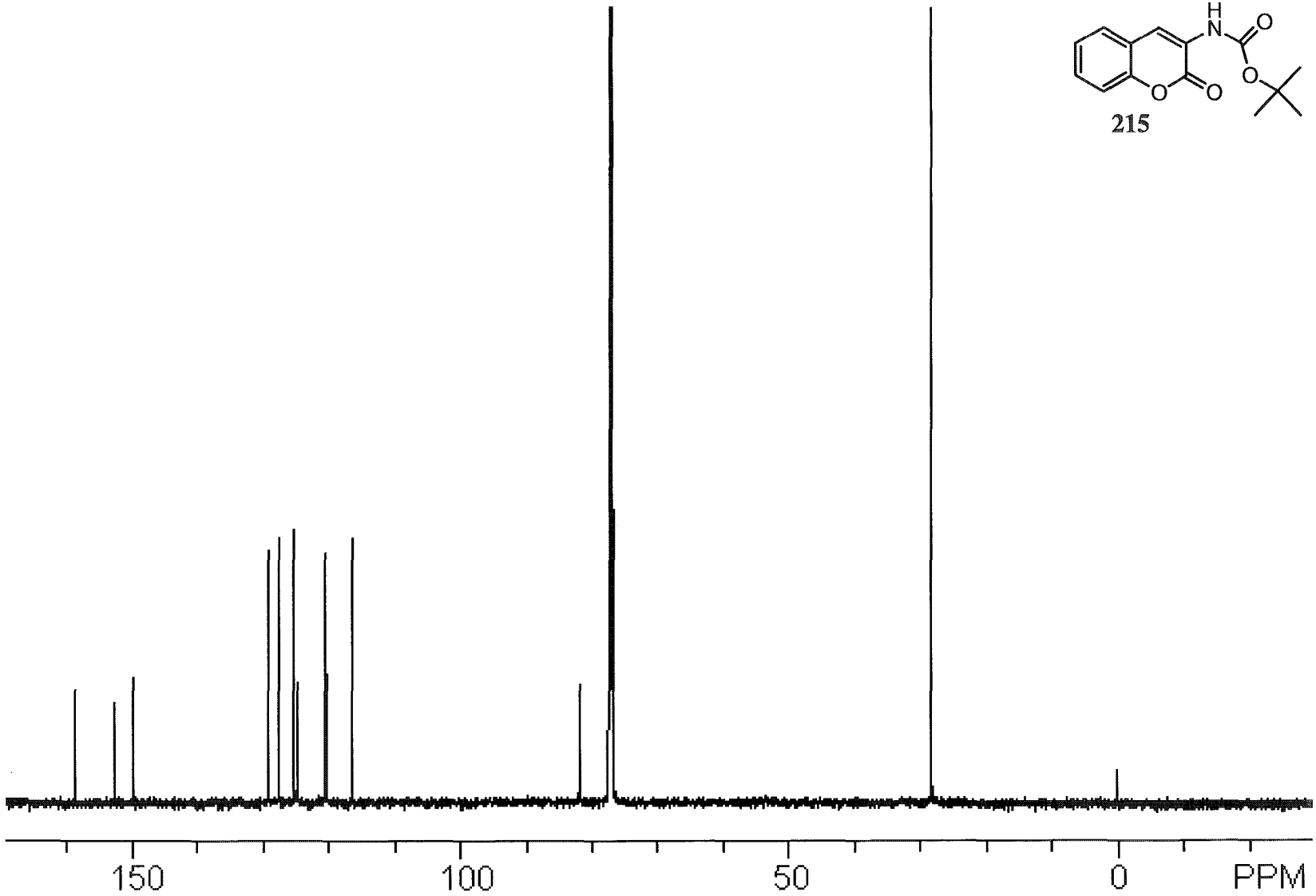

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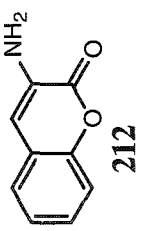

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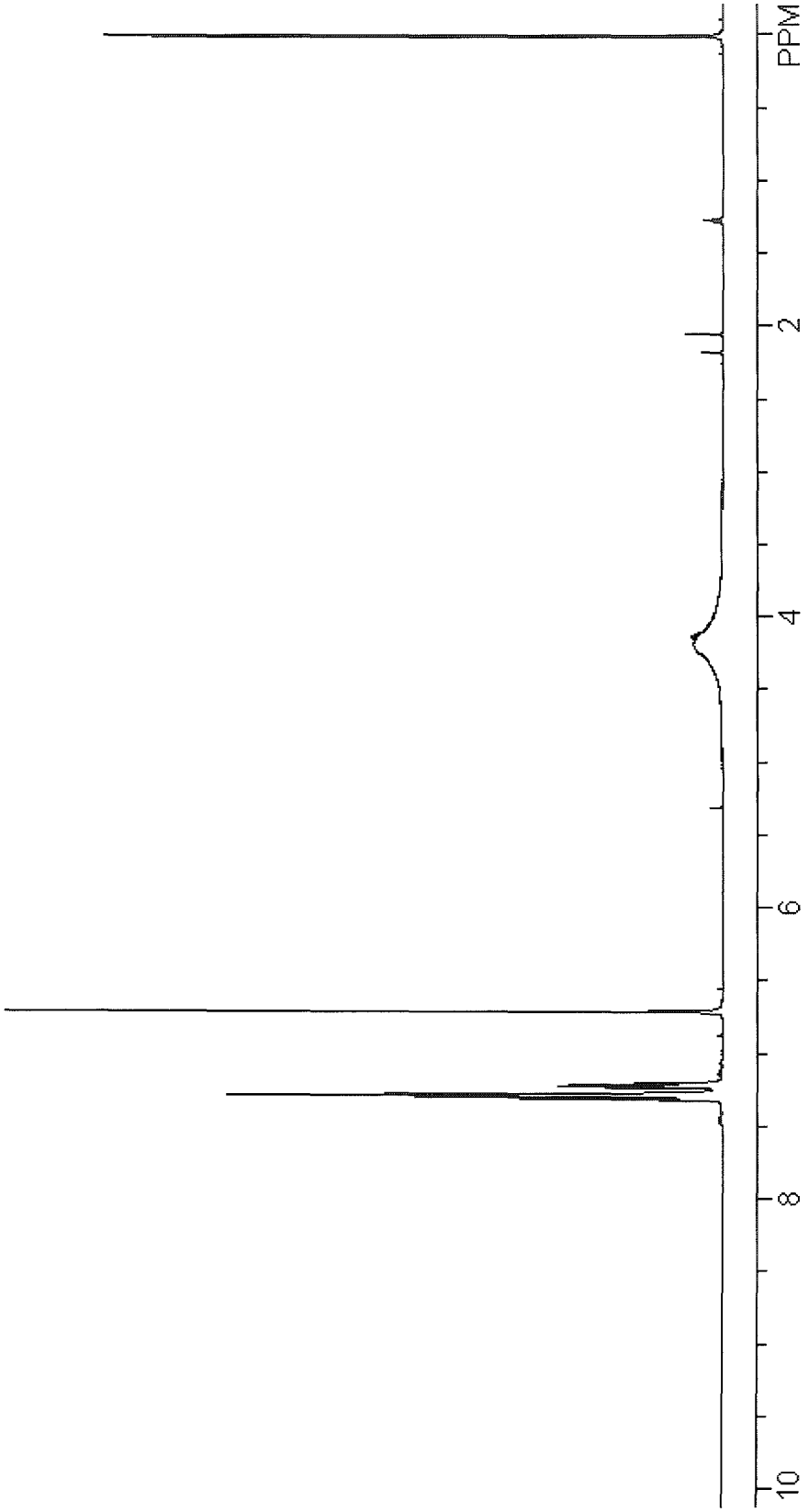

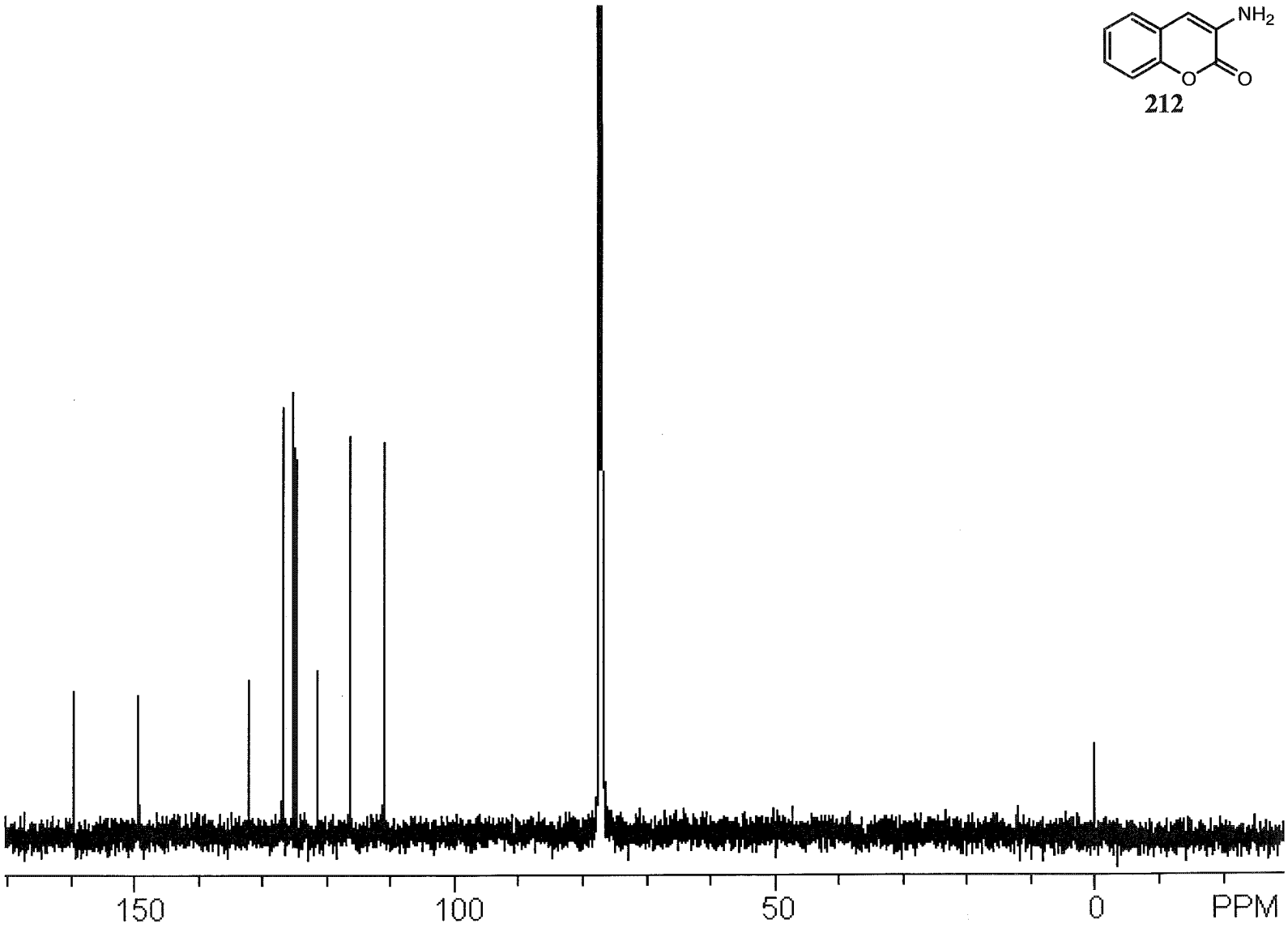
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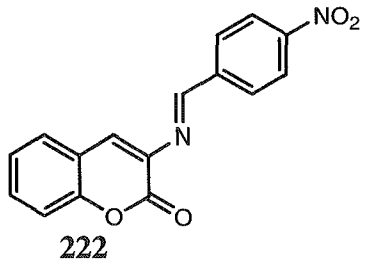

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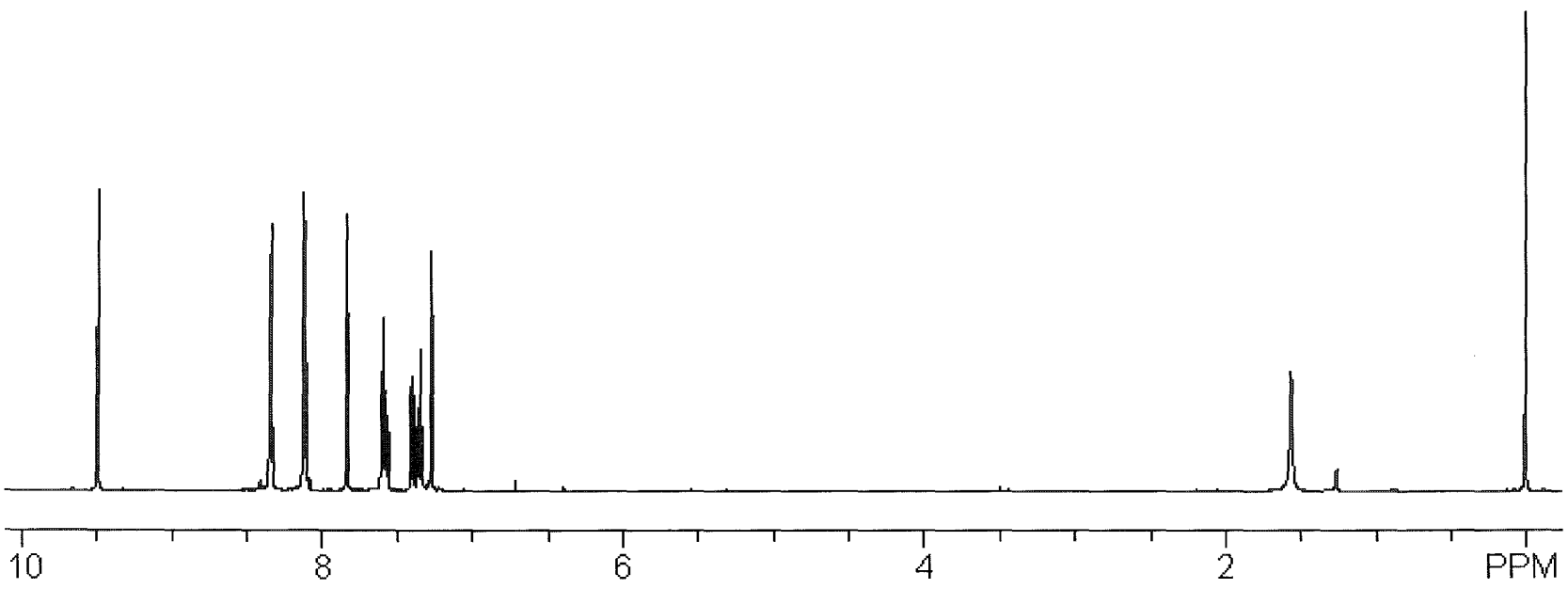

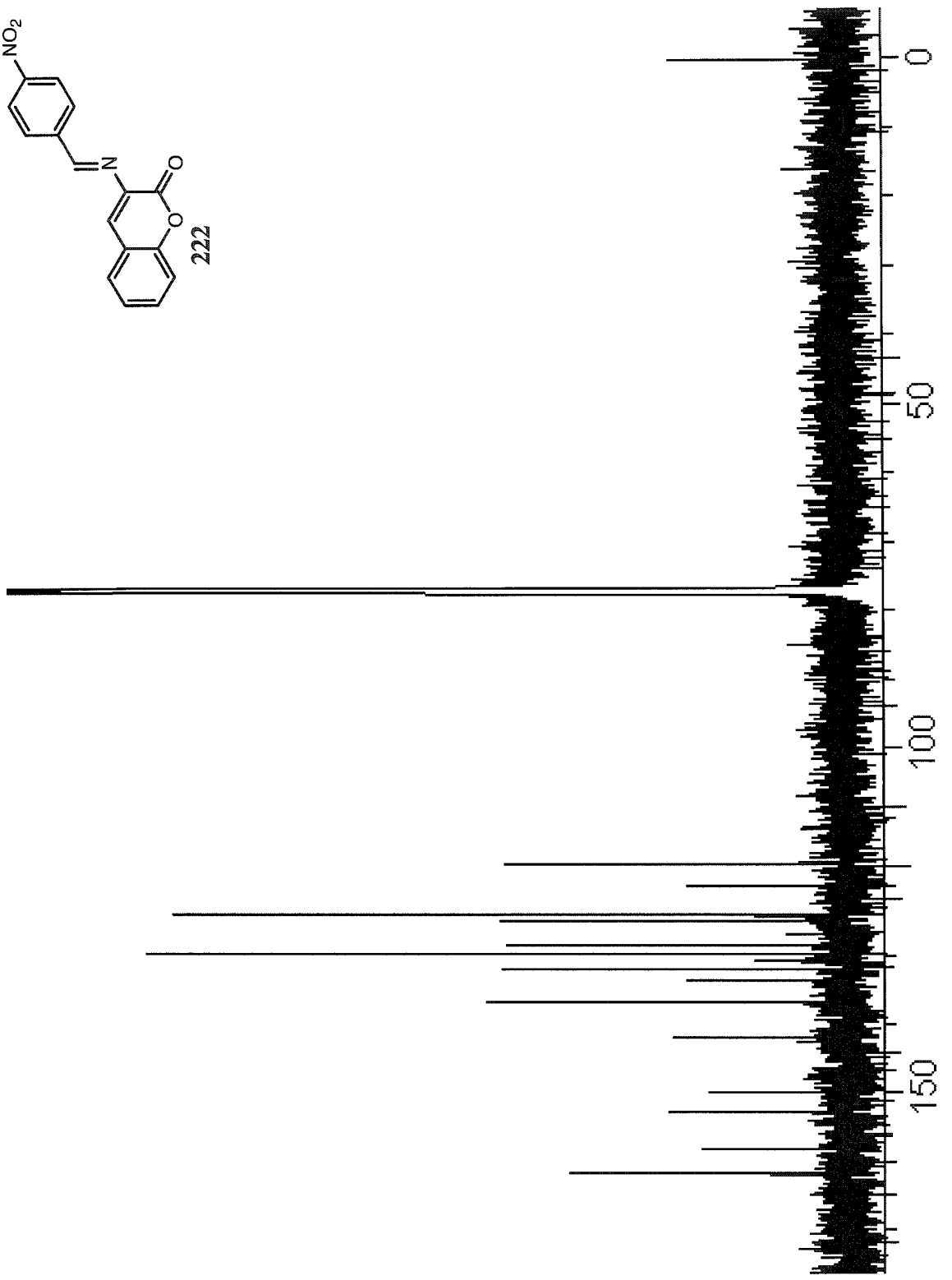
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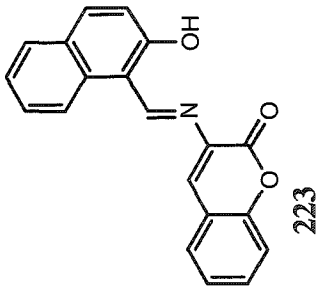

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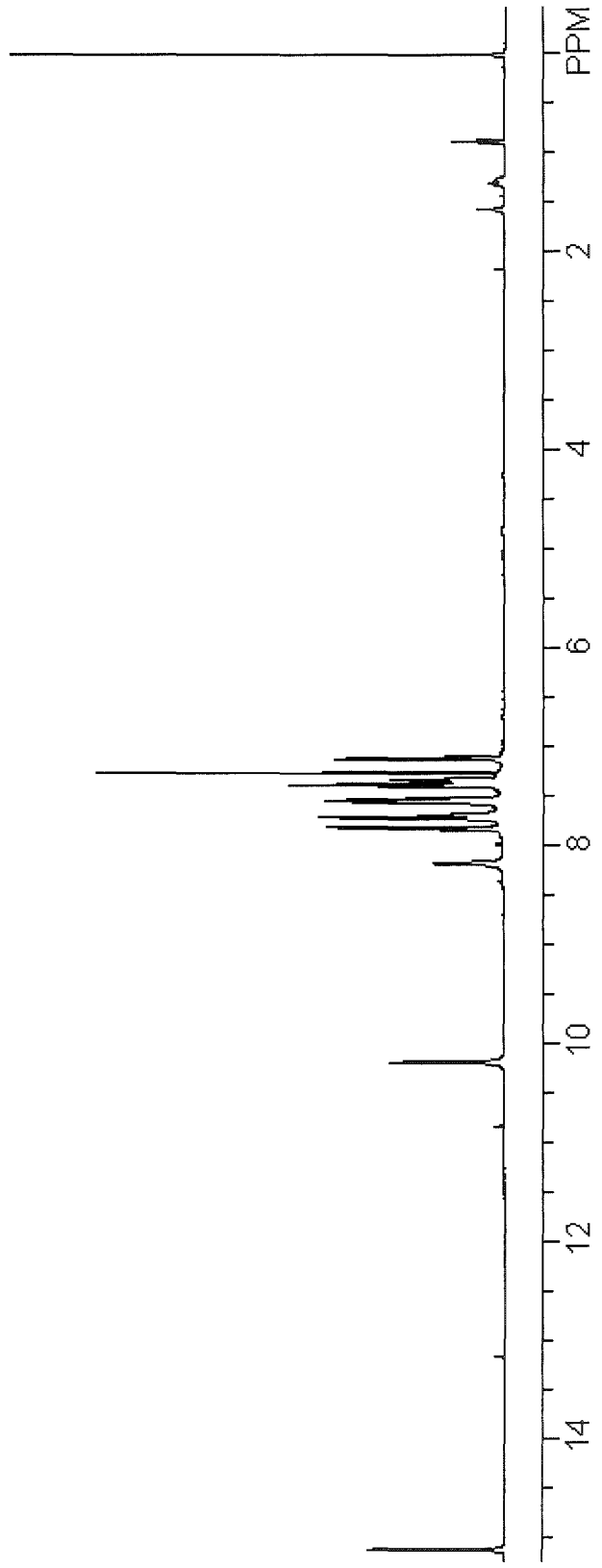

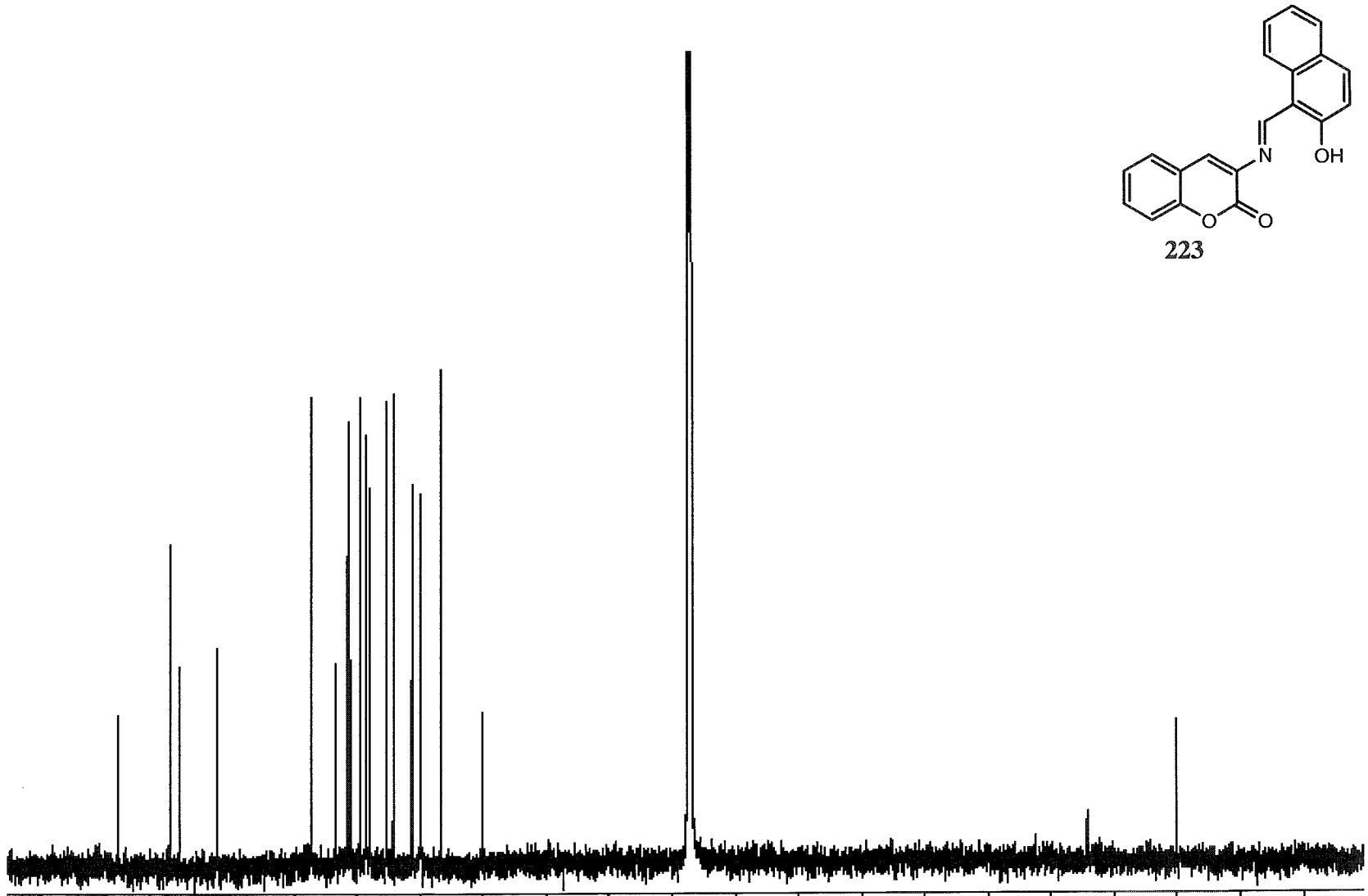

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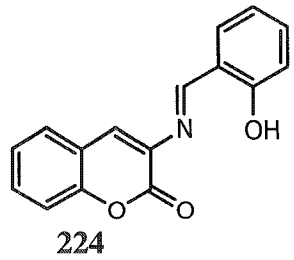

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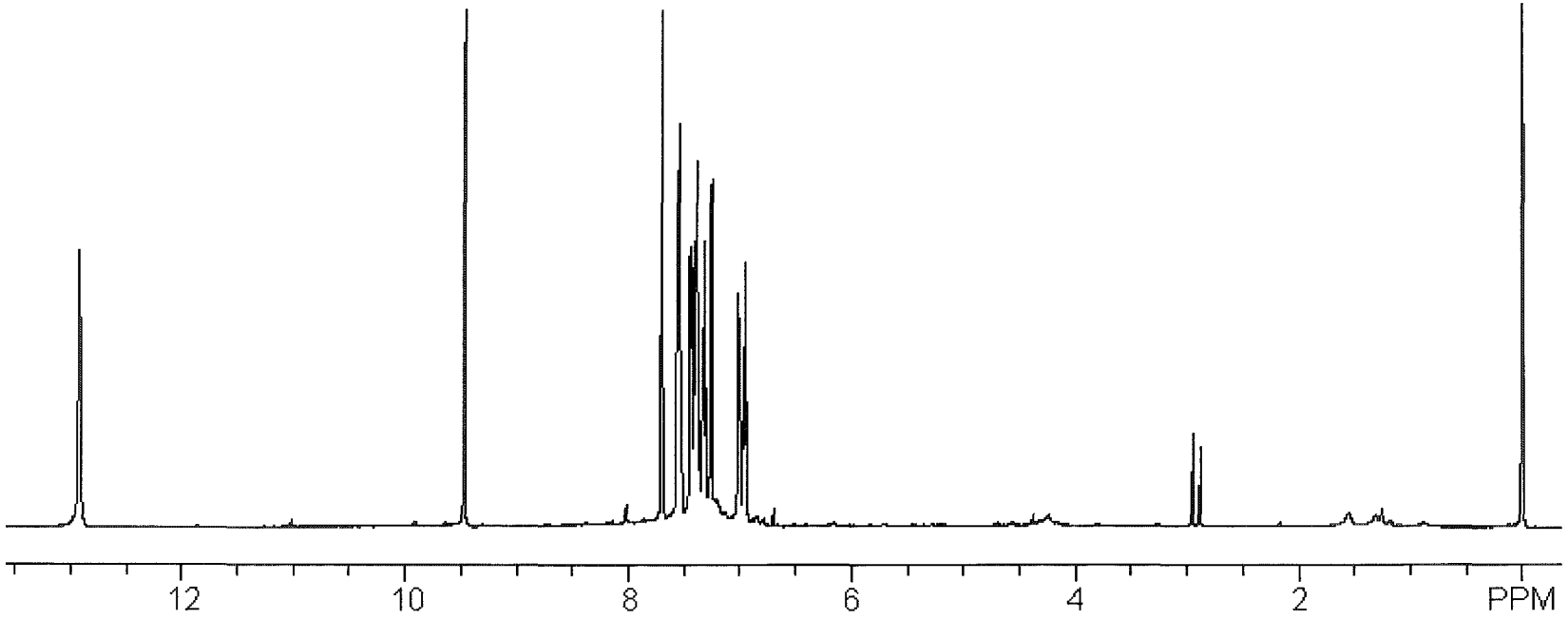

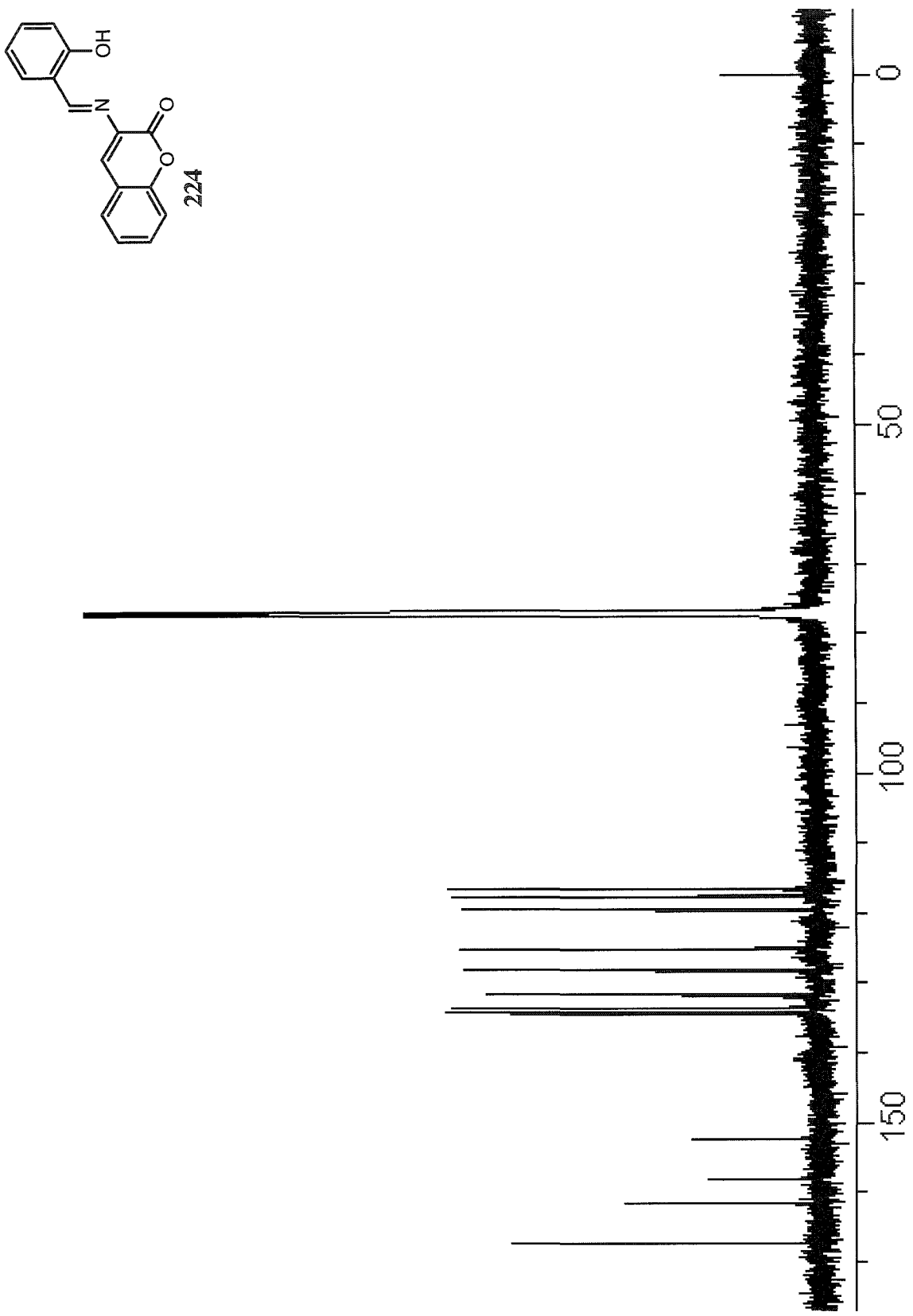
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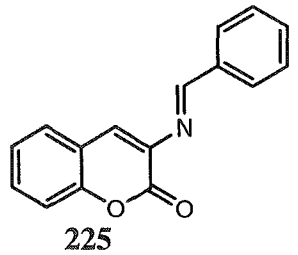

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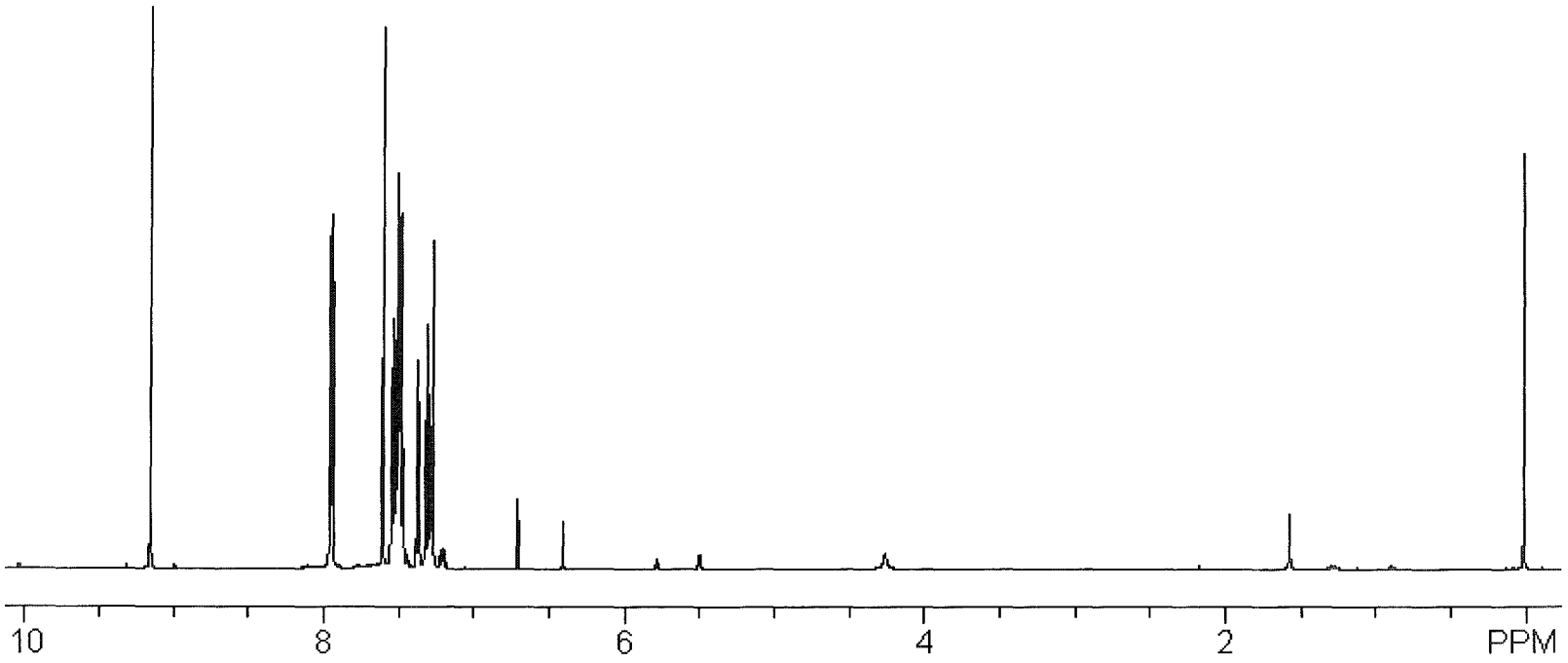

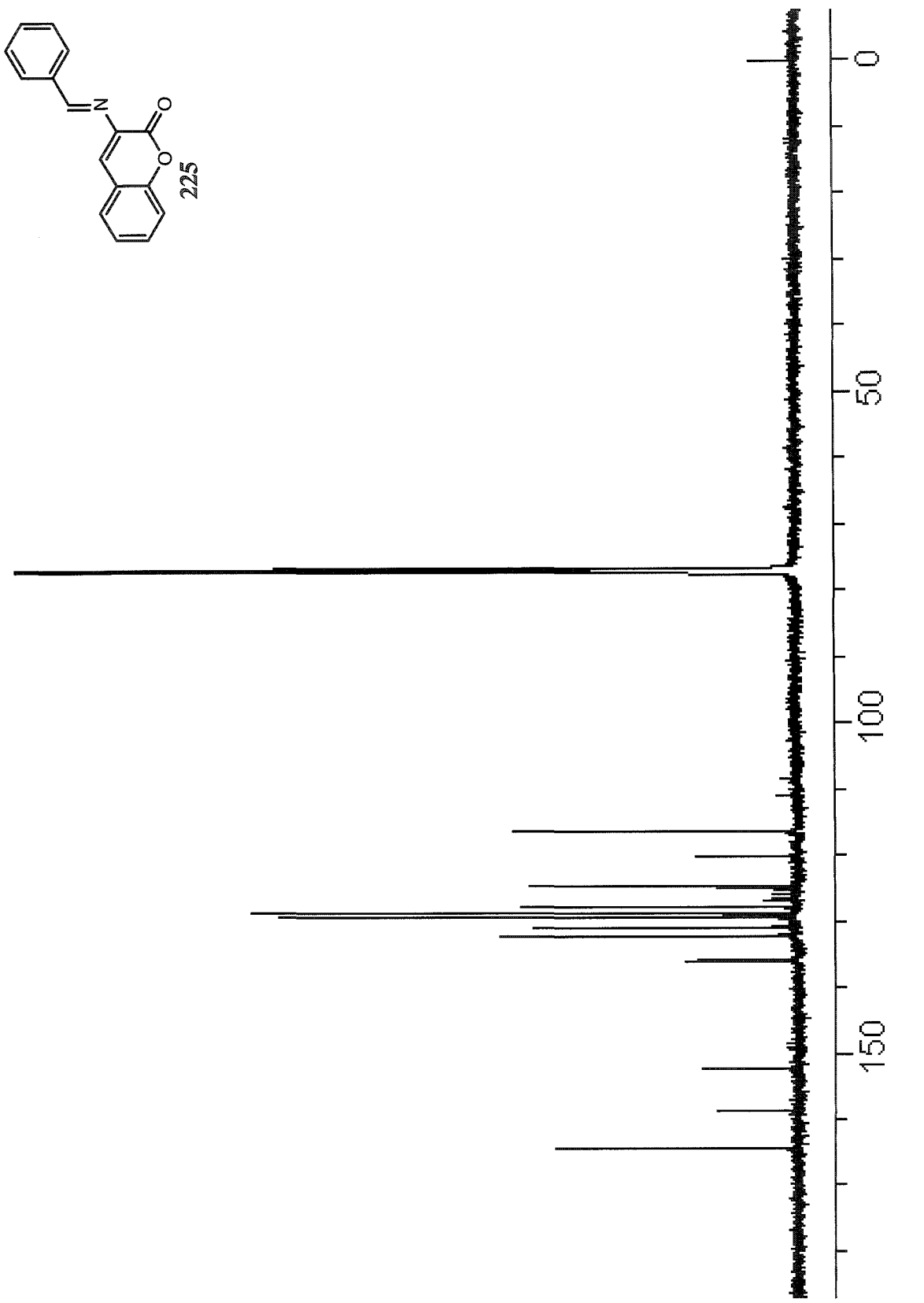
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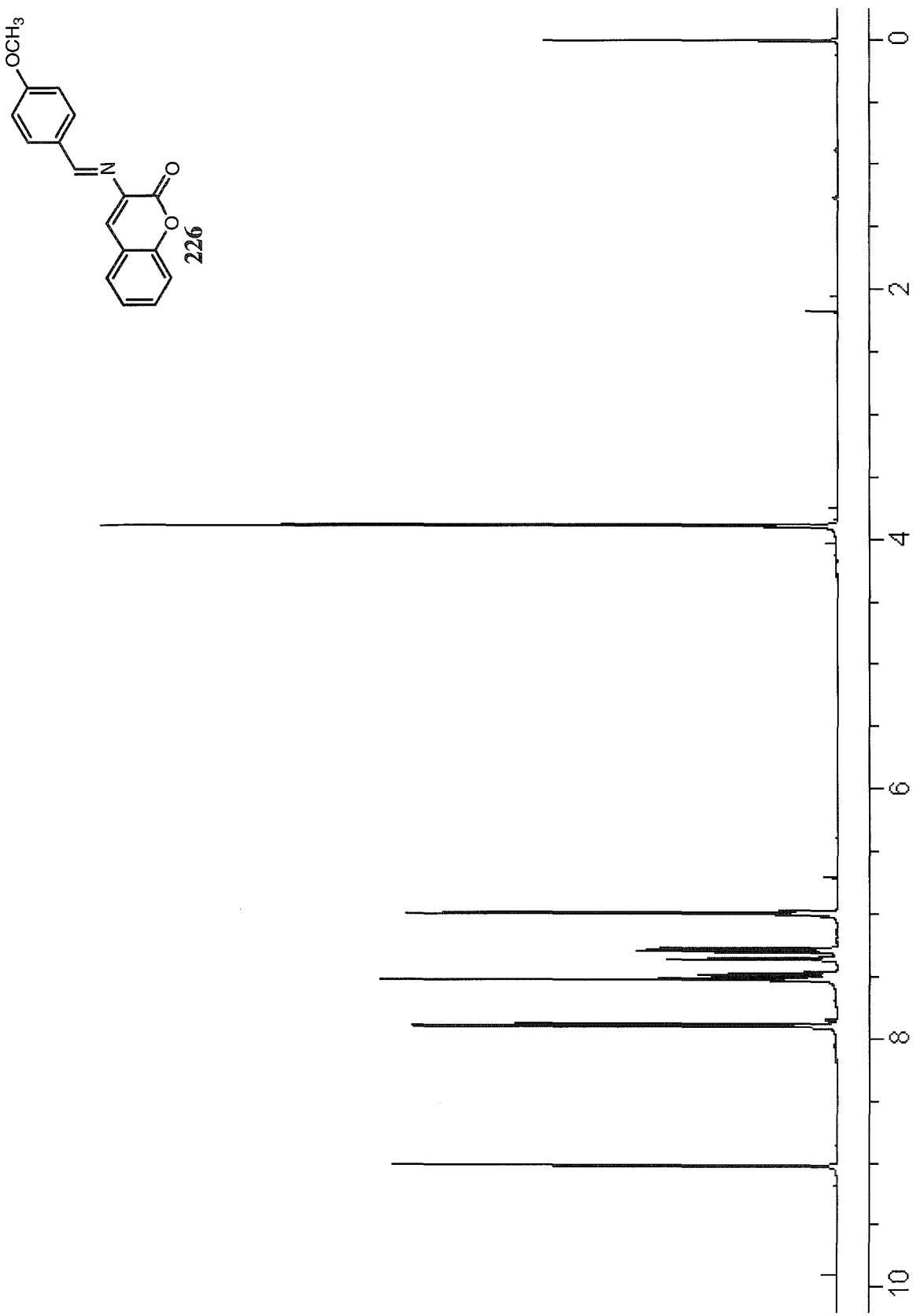
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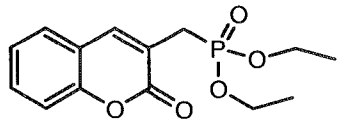

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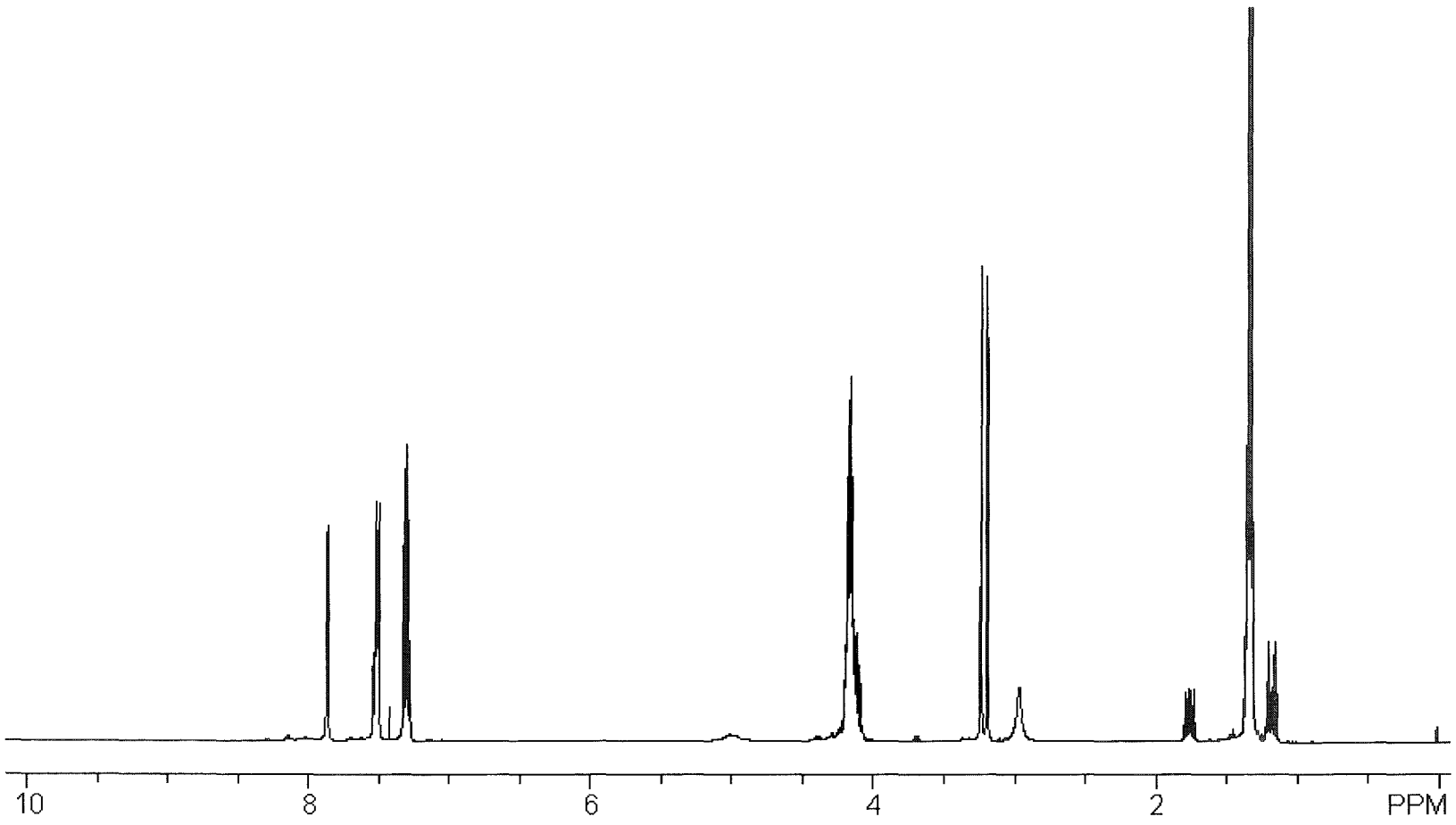
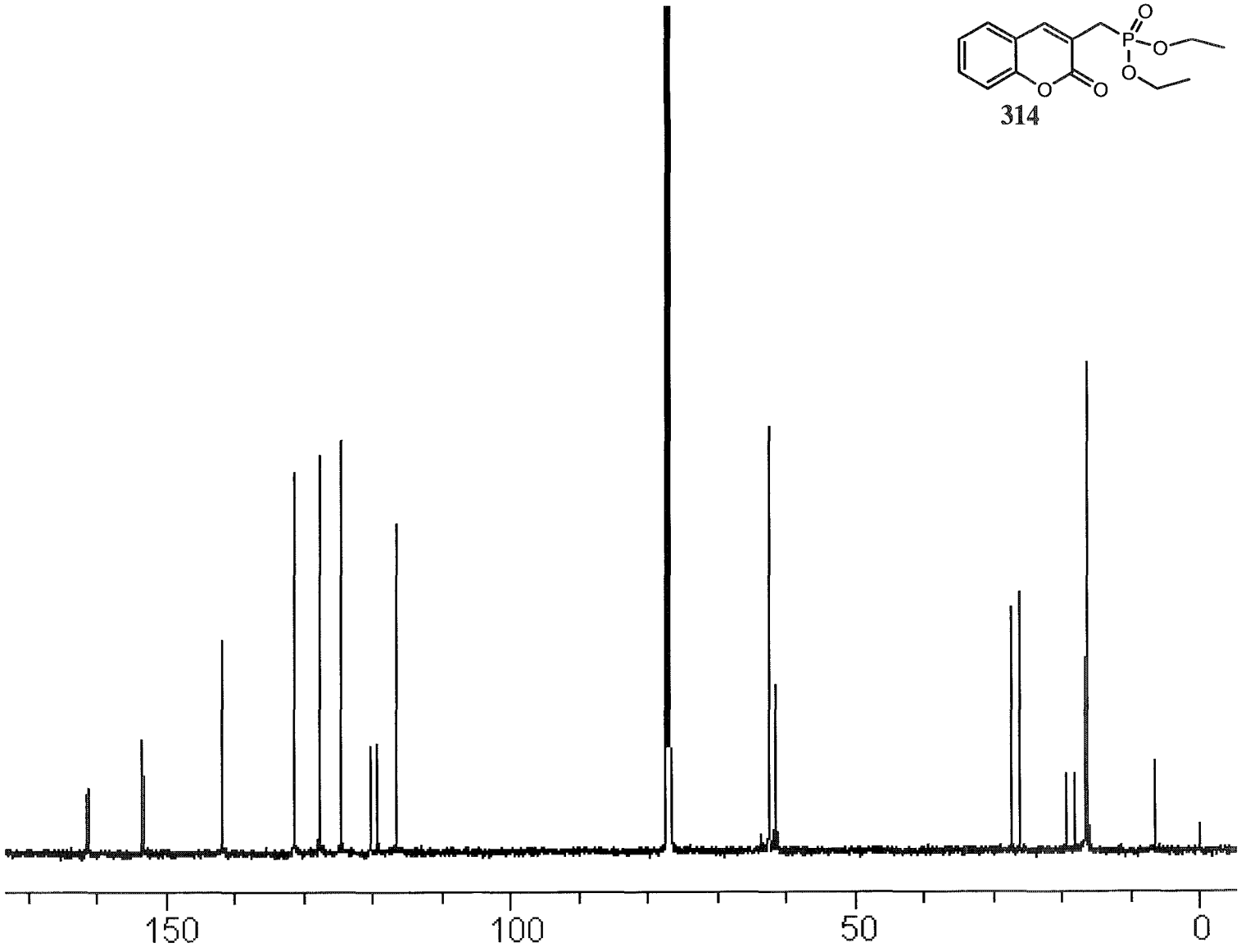


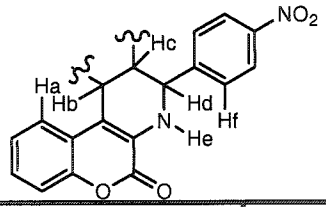


314

Chemical Shift NMR Tables

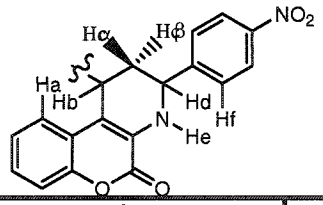
for the

Povarov Adducts

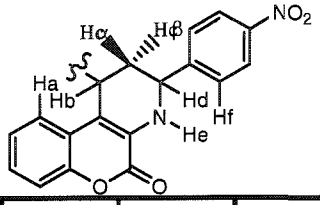


Compound	proton	endo			exo			$\delta_{endo} - \delta_{exo}$
		δ	multi	J (Hz)	δ	multi	J (Hz)	
280	Ha	8.21	m		7.56	m		0.65
	Hb	5.50	d	4.7	4.71	d	3.5	0.79
	Hc	2.36	m		2.10	m		0.26
	Hd	4.81	d	2.5	4.87	d	11.4	-0.06
	He	5.07	s		5.09	s		-0.02
	Hf	7.63	d	8.7	7.62	d	8.2	0.01
281	Ha	7.85	dd	7.4, 1.5	7.76	m		0.09
	Hb	5.53	d	7.4	4.76	d	5.2	0.77
	Hc	2.98	m		2.52	m		0.46
	Hd	4.86	d	2.3	3.95	d	11.2	0.91
	He	4.99	s		5.26	s		-0.27
	Hf	7.71	d	9	7.66	d	8.6	0.05
282	Ha	7.85	m					
	Hb	4.91	d	7.8				
	Hc	3.46	m					
	Hd	4.72	d	4.4				
	He	5.21	s					
	Hf	7.35	d	8.5				
286a	Ha	8.00	m					
	Hb	5.44	d	8.5				
	Hc	4.74	t	7				
	Hd	4.92	m					
	He	4.92	m					
	Hf							
298	Ha				7.60	m		
	Hb				4.71	d	2.8	
	Hc				2.08	m		
	Hd				4.78	d	11.5	
	He				5.09	s		
	Hf				7.45	d	8.5	
299	Ha	7.82	m		7.76	m		0.06
	Hb	5.49	d	7.4	4.75	d	5.1	0.74
	Hc	2.94	m		2.50	m		0.44
	Hd	4.72	d	2.8	3.84	d	11.1	0.88
	He	4.94	s		5.25	s		-0.31
	Hf	7.51	m		7.46	d	9.1	0.05

Table A.1 – NMR shift values for bridgehead containing Povarov adducts.



Compound	proton	endo			exo			$\delta_{endo} - \delta_{exo}$
		δ	multi	J (Hz)	δ	multi	J (Hz)	
284	Ha							
	Hb	5.77	dd	9.0, 7.8	5.55	dd	5.0, 2.0	0.22
	Hcα	2.48	m		3.16	ddd	8.9, 8.9, 5.8	-0.68
	Hcβ	2.20	m		3.59	ddd	8.2, 8.2, 5.5	-1.39
	Hd	4.62	dd	10.8, 6.2	4.65	dd	12.6, 3.4	-0.03
	He	5.16	s		5.33	s		-0.17
	Hf	7.64	d	8.9	7.64	d	8.8	0
287	Ha							
	Hb	4.42	t	7.8				
	Hcα	2.62	m					
	Hcβ	2.26	m					
	Hd	4.66	d	8.6				
	He	5.26	s					
	Hf	7.50	d	8.8				
288	Ha				7.33	d	8.3	
	Hb	4.40	t	7.3	4.39	dd	5.2, 1.4	0.01
	Hcα	2.62	m					
	Hcβ	2.32	ddd	17.0, 8.3, 8.3				
	Hd	4.67	d	7.5	4.44	dd	11.5, 3.4	0.23
	He	5.25	s		5.15	s		0.1
	Hf	7.49	d	9.1	7.52	d	9.5	-0.03



284	Ha	7.76	dd	7.6, 1.8	7.50	m		0.26
	Hb	4.67	t	3.9	4.64	d	3.4, 1.6	0.03
	Hcα	2.71	ddd	14.4, 3.4, 3.4	2.15	m		0.56
	Hcβ	2.60	ddd	14.6, 6.2, 6.2	2.34	ddd	13.4, 2.0, 2.0	0.26
	Hd	4.92	d	4.6	5.11	dd	11.6, 3.3	-0.19
	He	5.59	s		5.26	s		0.33
	Hf	7.48	d	9.4	7.62	d	8.9	-0.14
289	Ha	7.45	dd	9.1, 1.8	7.52	m		-0.07
	Hb	4.80	t	3.8	4.70	m		1
	Hcα	2.33	dt	14.6, 4.9				
	Hcβ	2.75	dt	14.4, 4.2				
	Hd	4.91	dd	8.1, 4.4	4.70	m		0.21
	He	5.50	s		6.25	s		-0.75
	Hf	7.53	d	8.3	7.68	d	7.9	-0.15
285	Ha	6.93	dd	7.7, 1.6				
	Hb	4.44	t	7.6				
	Hcα	2.63	dddd	13.9, 7.0, 3.4, 1.7				
	Hcβ	2.33	ddd	17.4, 8.6, 8.6				
	Hd	4.66	d	7.4				
	He	5.24	s					
	Hf	7.50	d	7.1				

Table A.2 - NMR shift values for Povarov adducts without a bridgehead.

X-ray Analysis for

299b

Experimental

Data Collection

A colorless prism crystal of $H_{19}NO_5C_{22}$ having approximate dimensions of 0.64 x 0.10 x 0.08 mm was mounted on a glass fiber. All measurements were made on a Bruker P4/CCD system with graphite monochromated Mo-Kα radiation and a sealed tube generator.

Cell constants and an orientation matrix for data collection corresponded to a primitive monoclinic cell with dimensions:

a = 19.587(2) Å

b = 5.0527(4) Å β = 100.997(2)°

c = 18.853(2) Å

V = 1831.6(2) $Å^3$

For Z = 4 and F.W. = 377.40, the calculated density is 1.37 g/cm^3. The systematic absences of:

h0l: $l \pm 2n$

0k0: $k \pm 2n$

uniquely determine the space group to be:

$P2_1/c$ (#14)

The data were collected at a temperature of -80 $\pm$ 1^{o}C.. The full hemisphere of data was collected with 30 sec., 0.3 deg. frames to a maximum 2θ value of 52.8^{o}.

Data Reduction

Of the 12732 reflections which were collected, 3760 were unique (R_{int} = 0.044 the linear absorption coefficient, μ, for Mo-Kα radiation is 1.0 cm^{-1}. The Siemens area detector absorption routine (SADABS) was used to correct the data with maximum and minimum effective transmissions of 0.9922 to 0.9402 respectively. The data were corrected for Lorentz and polarization effects.

Structure Solution and Refinement

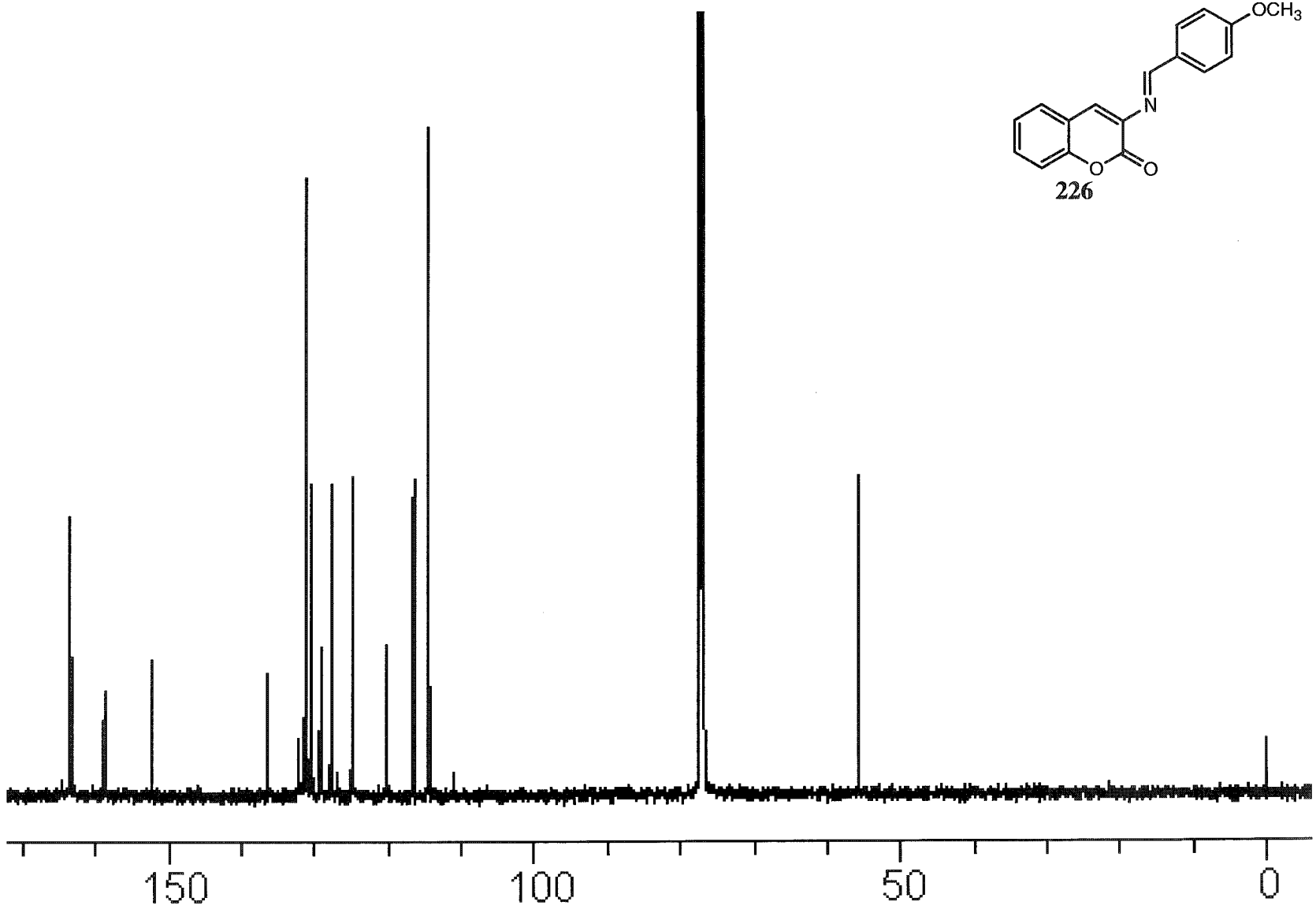
The structure was solved by direct methods[2] and expanded using Fourier techniques[3]. The non-hydrogen atoms were refined anisotropically. Hydrogen atoms were included but not refined. The final cycle of full-matrix least-squares refinement[4] on F^2 was based on 3760 observed reflections and 253 variable parameters and converged (largest parameter shift was 0.00 times its esd) with unweighted and weighted agreement factors of:

$$R1 = \Sigma \, ||Fo| - |Fc|| \, / \, \Sigma \, |Fo| = 0.052$$

$$wR2 = [\Sigma (w (Fo^2 - Fc^2)^2) / \Sigma \, w(Fo^2)^2]^{1/2} = 0.142$$

The standard deviation of an observation of unit weight[5] was 1.03. The weighting scheme was based on counting statistics. The maximum and minimum peaks on the final difference Fourier map corresponded to 0.38 and -0.37 $e^-/Å^3$, respectively.

Neutral atom scattering factors were taken from Cromer and Waber[6]. Anomalous dispersion effects were included in Fcalc[7]; the values for $\Delta f'$ and $\Delta f''$ were those of Creagh and McAuley[8]. The values for the mass attenuation coefficients are those of Creagh and Hubbell[9]. All calculations were performed using the teXsan[10] crystallographic software package of Molecular Structure Corporation except for refinement, which was performed using SHELXL-97[11].



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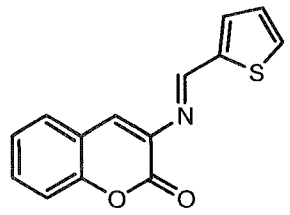

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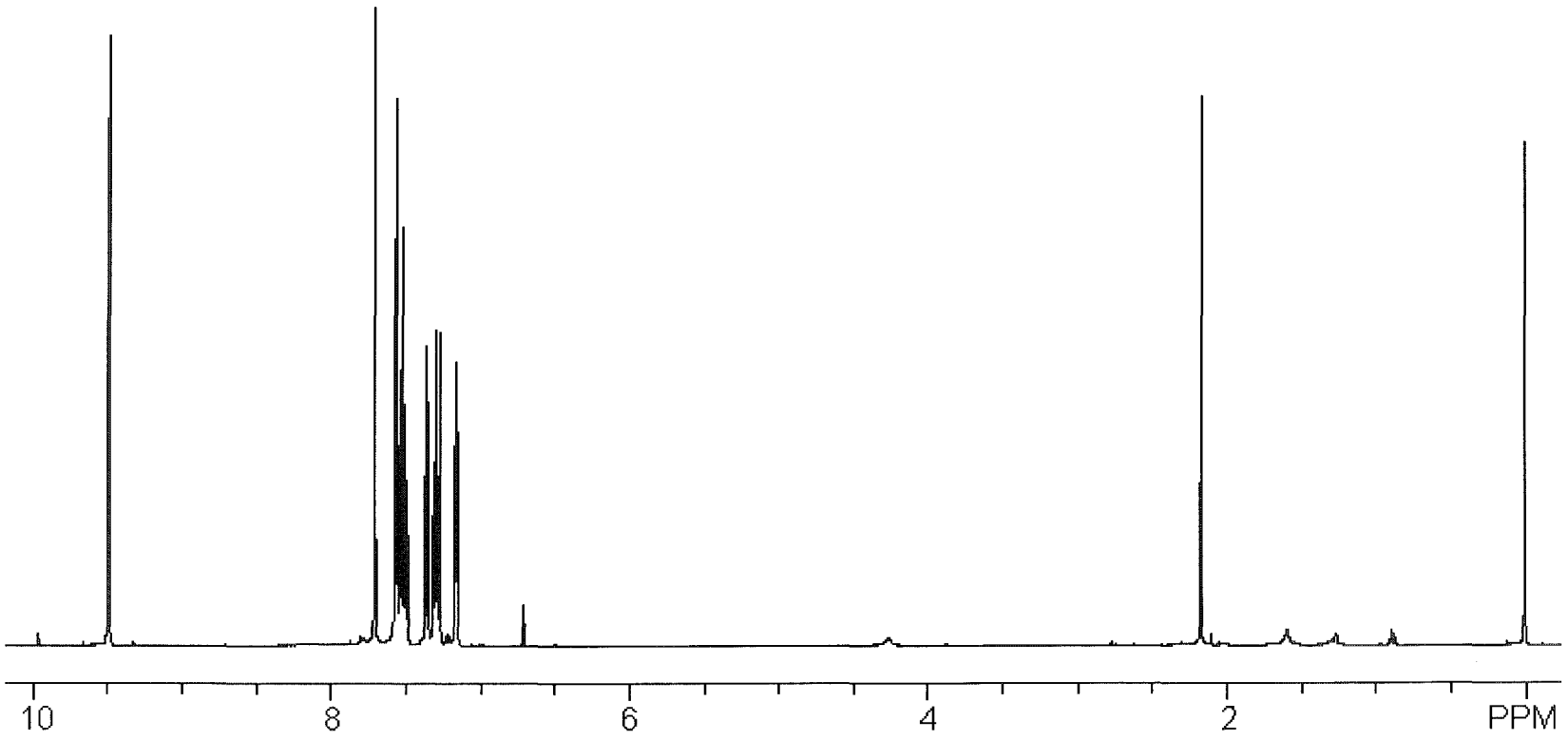

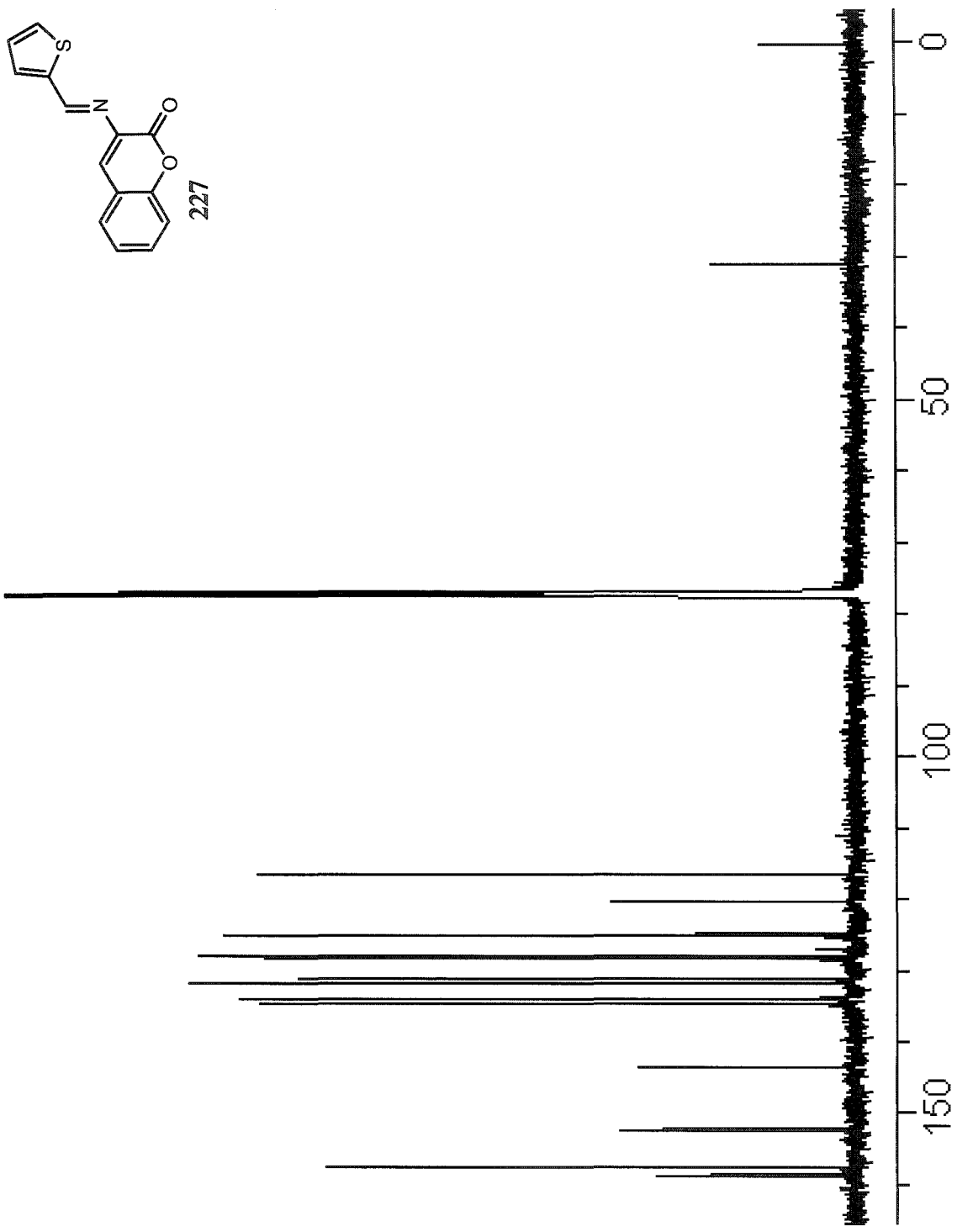
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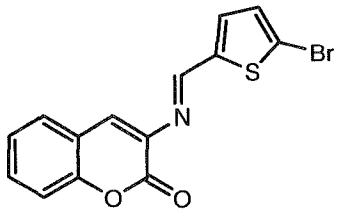

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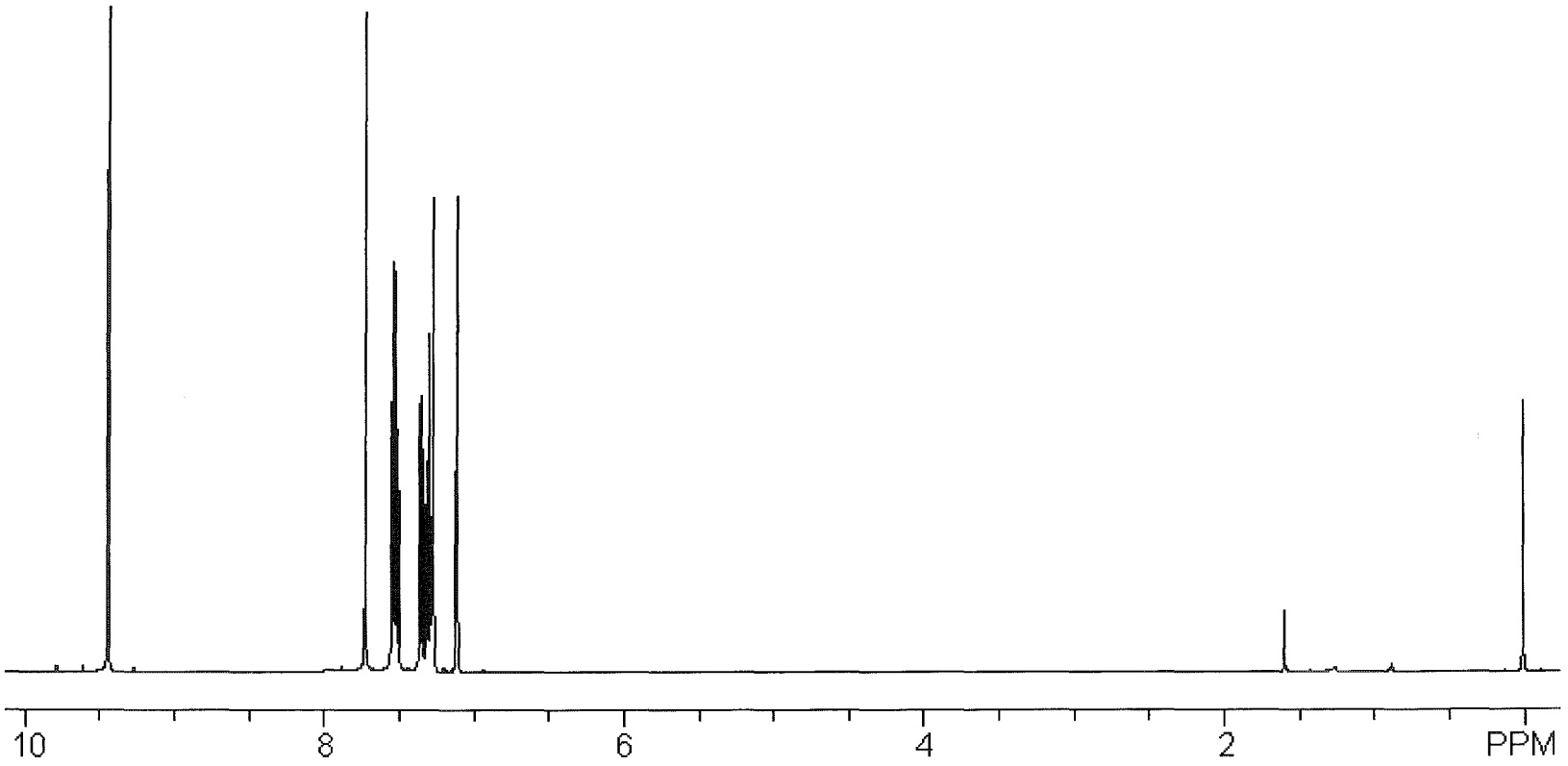

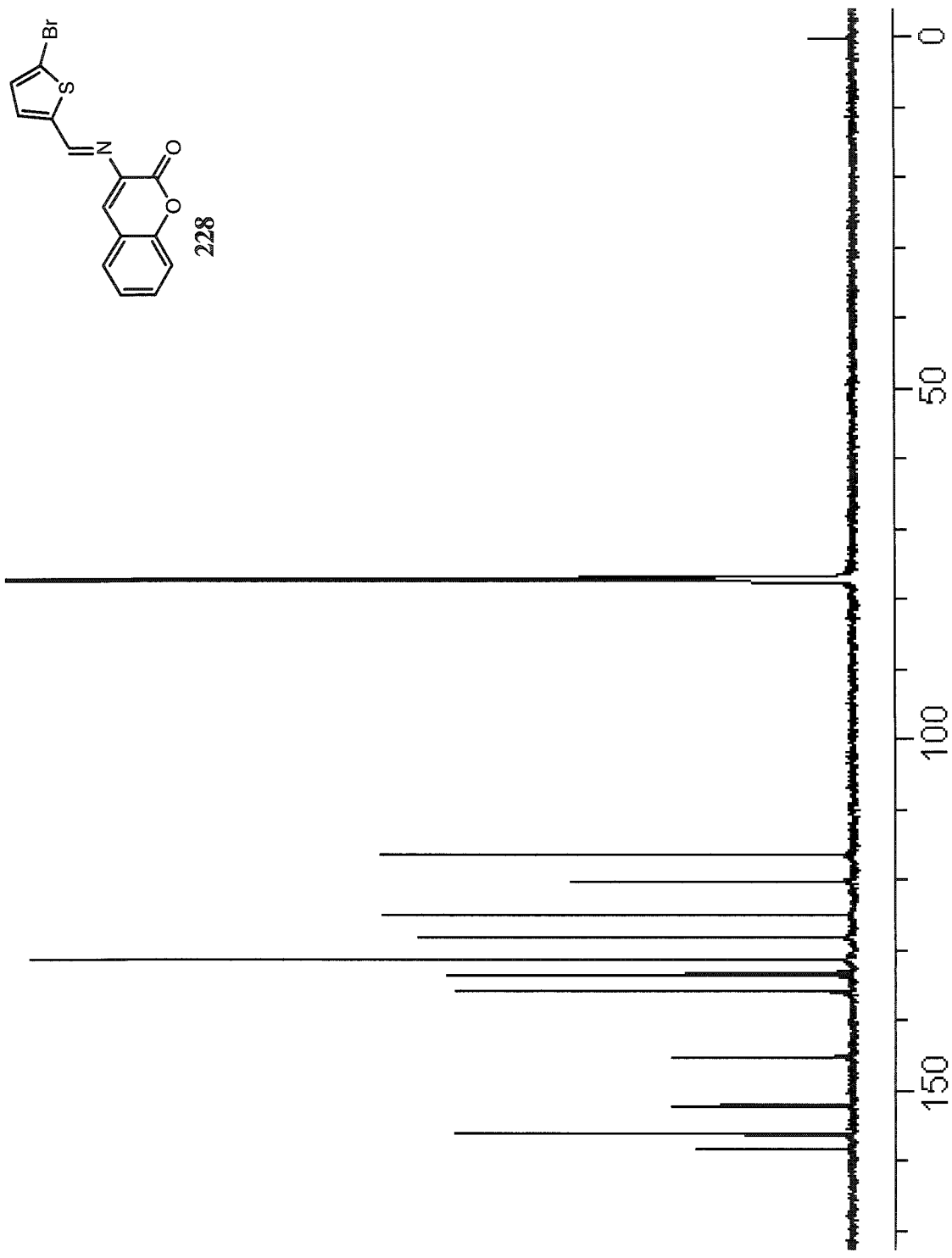
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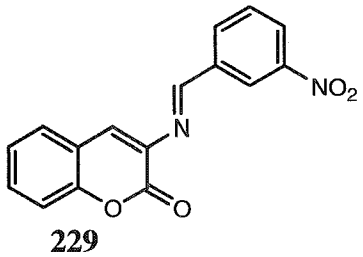

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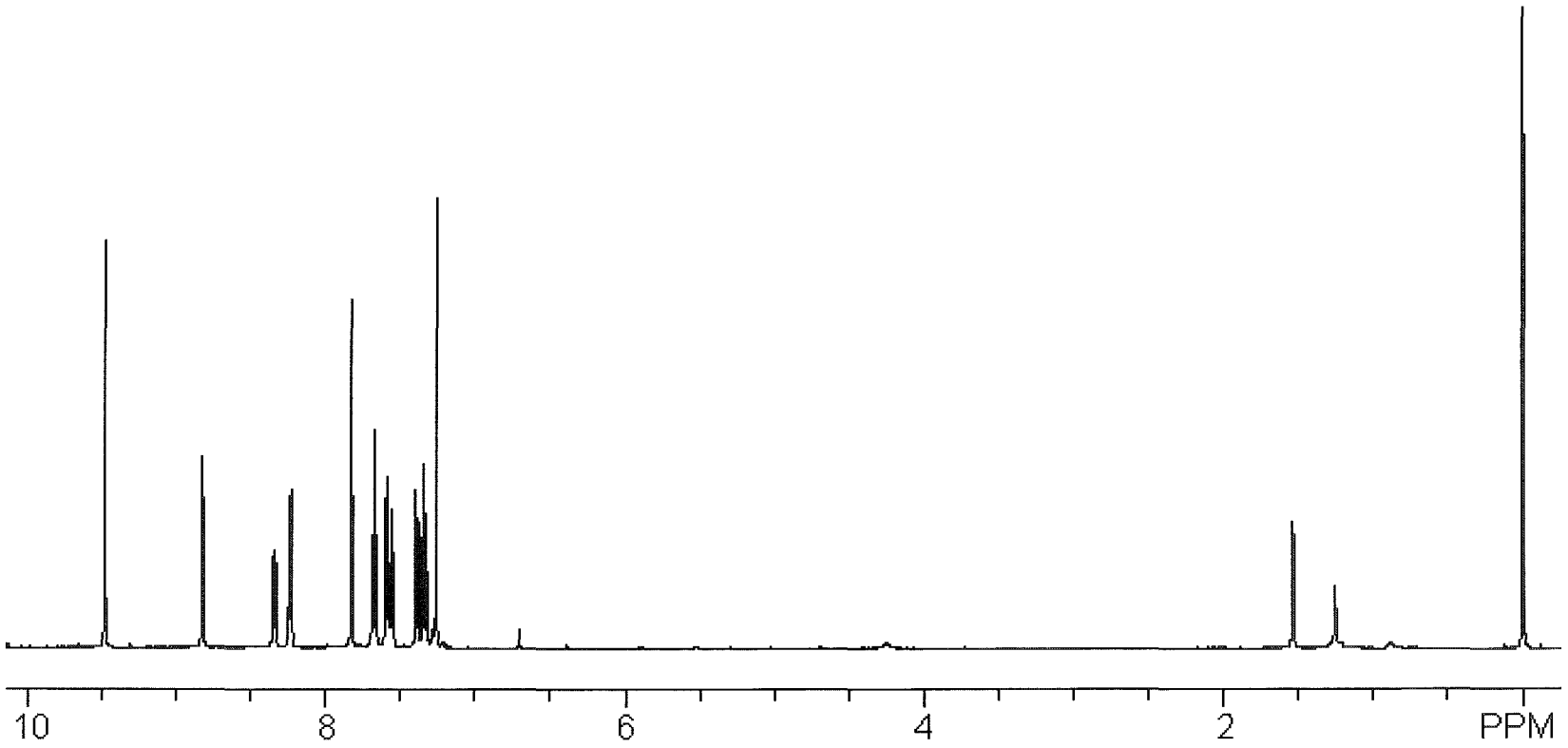

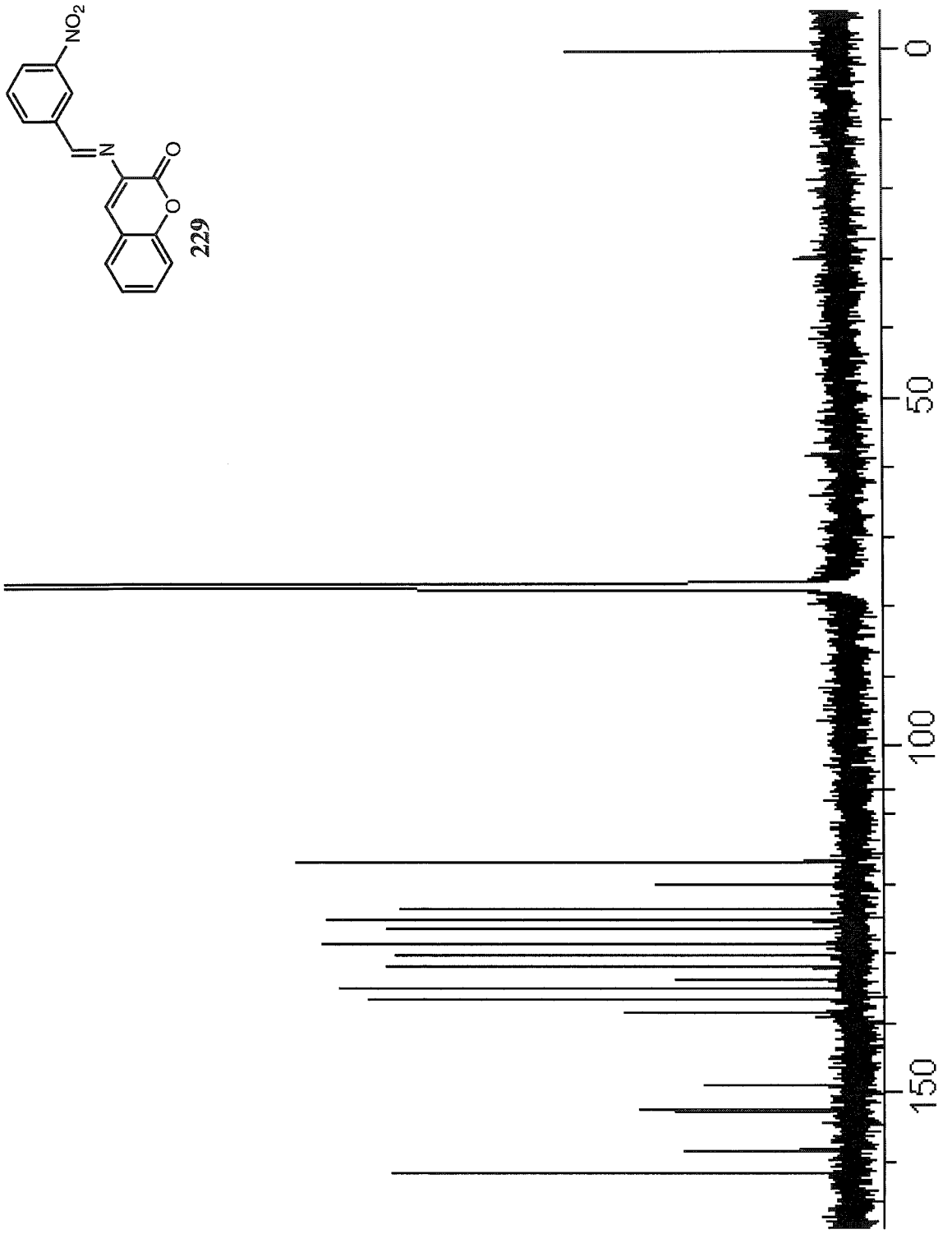
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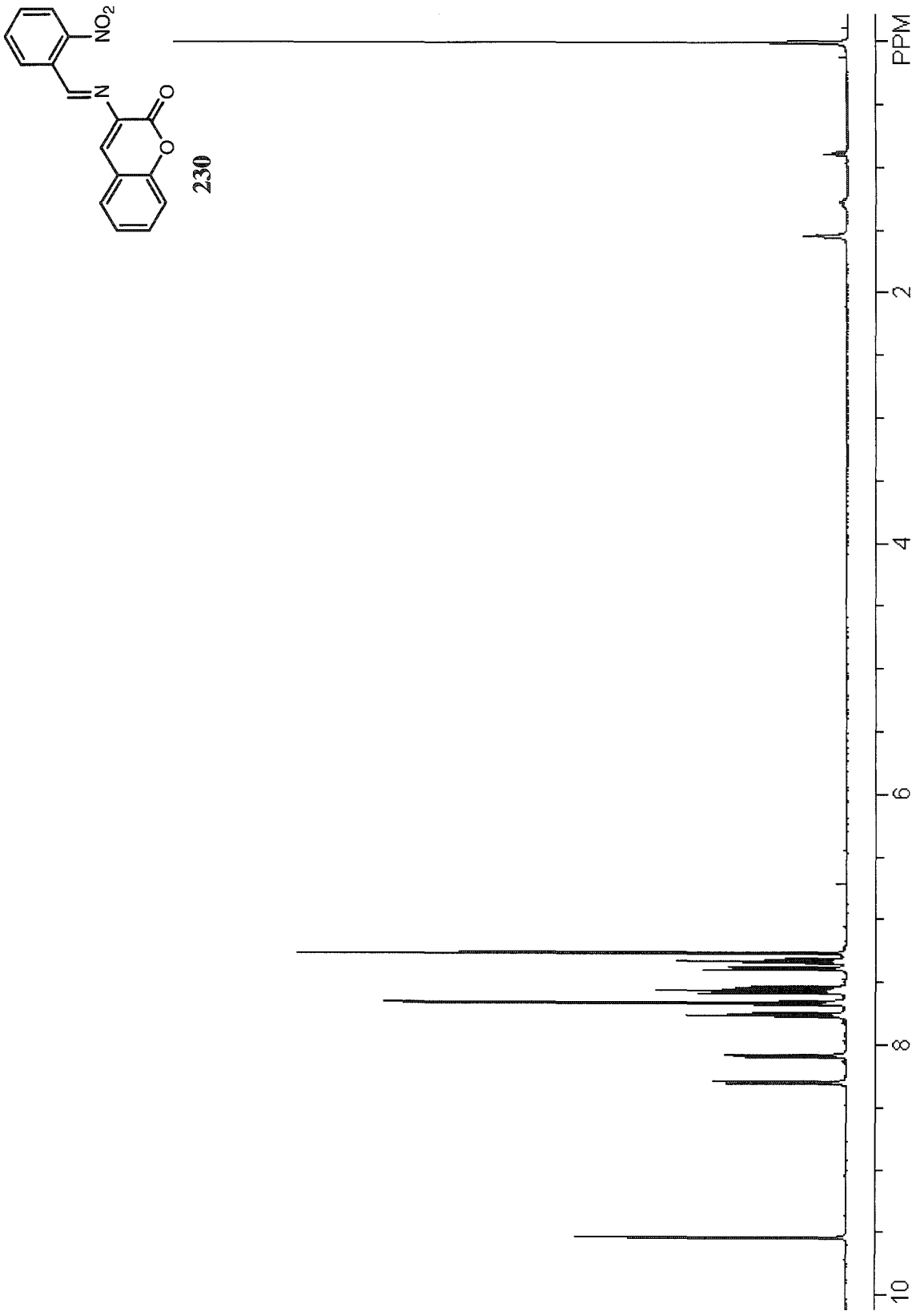
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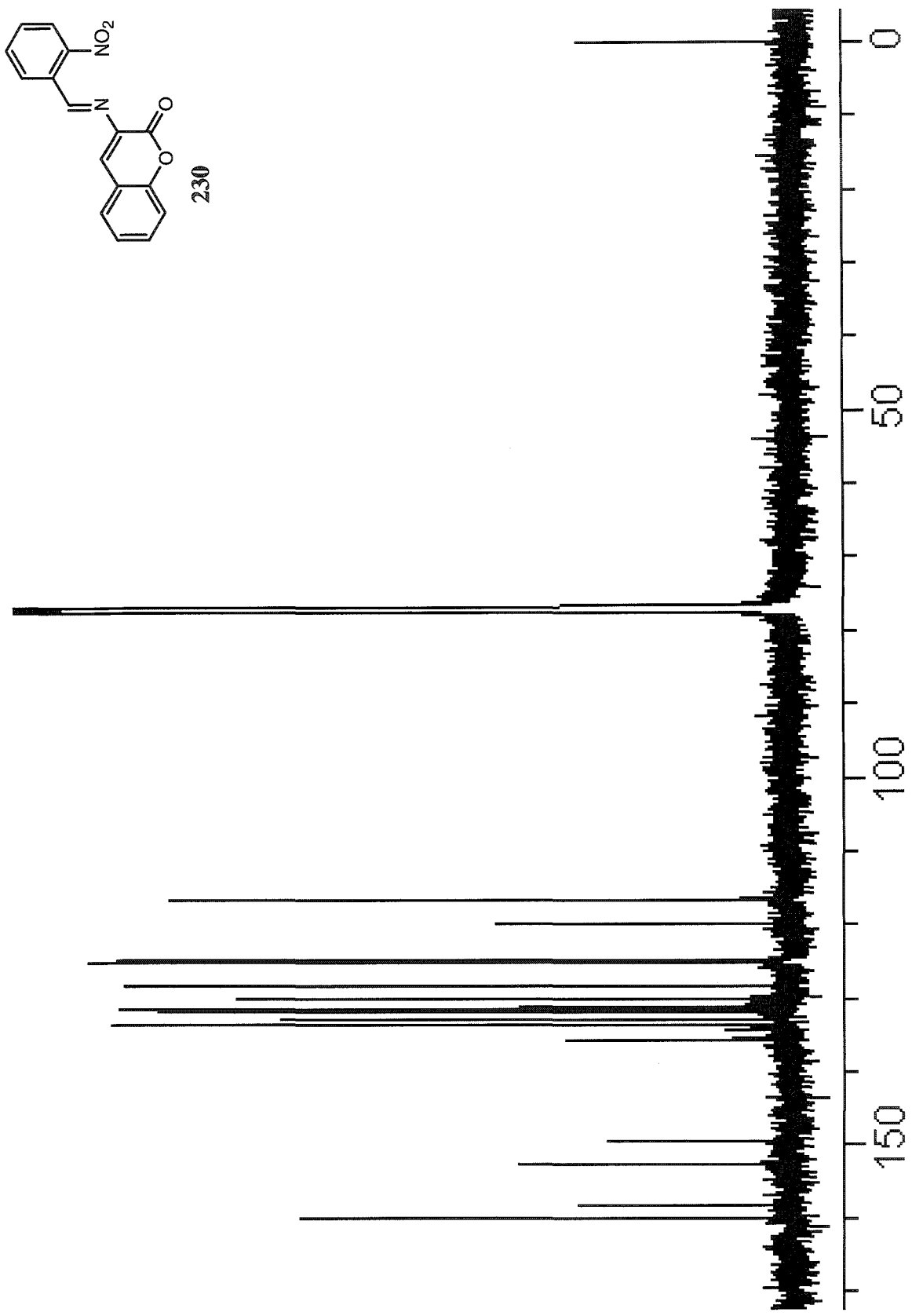
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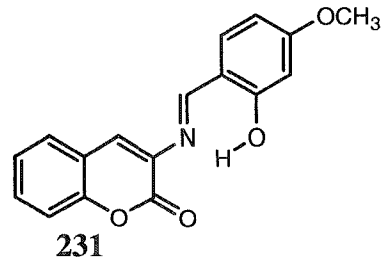

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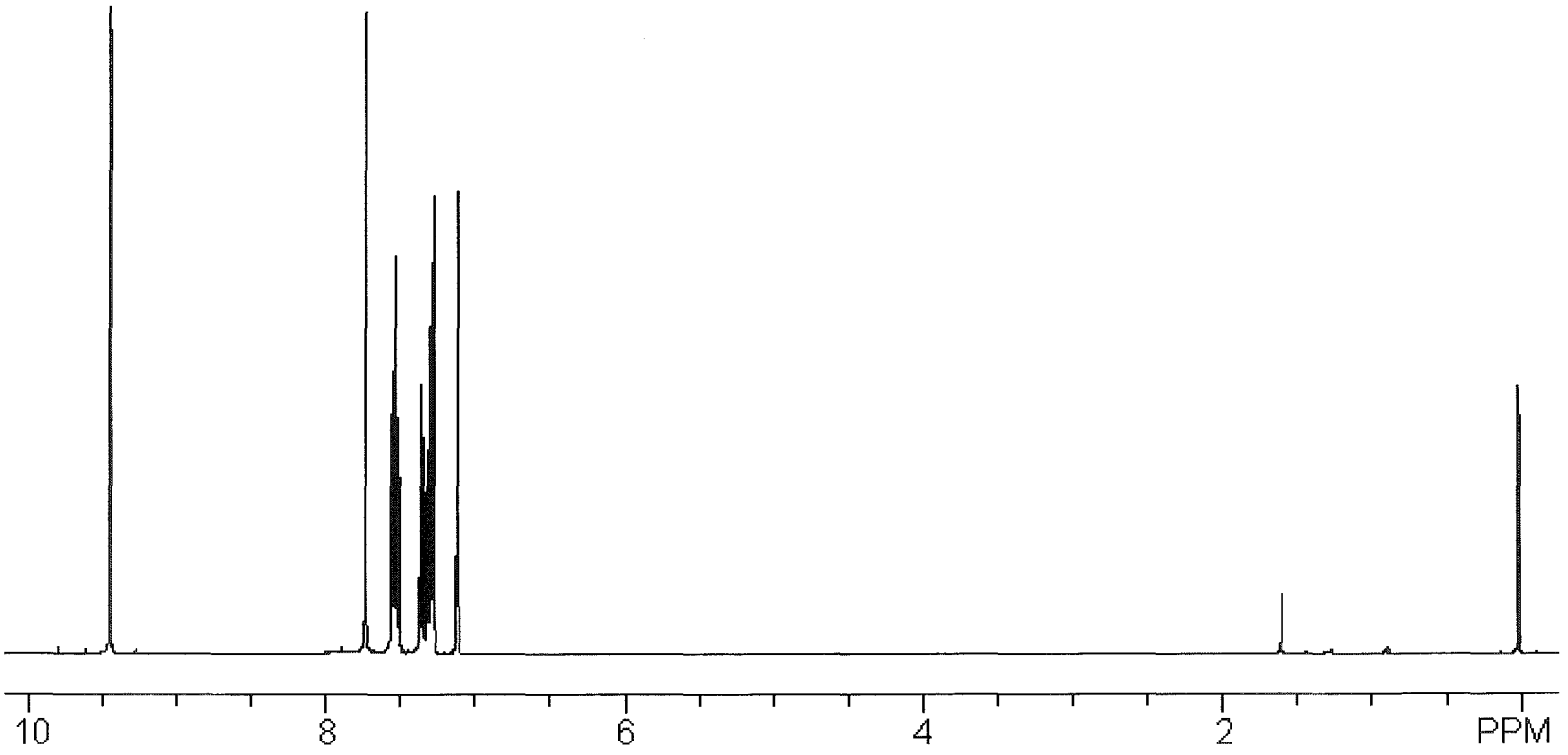

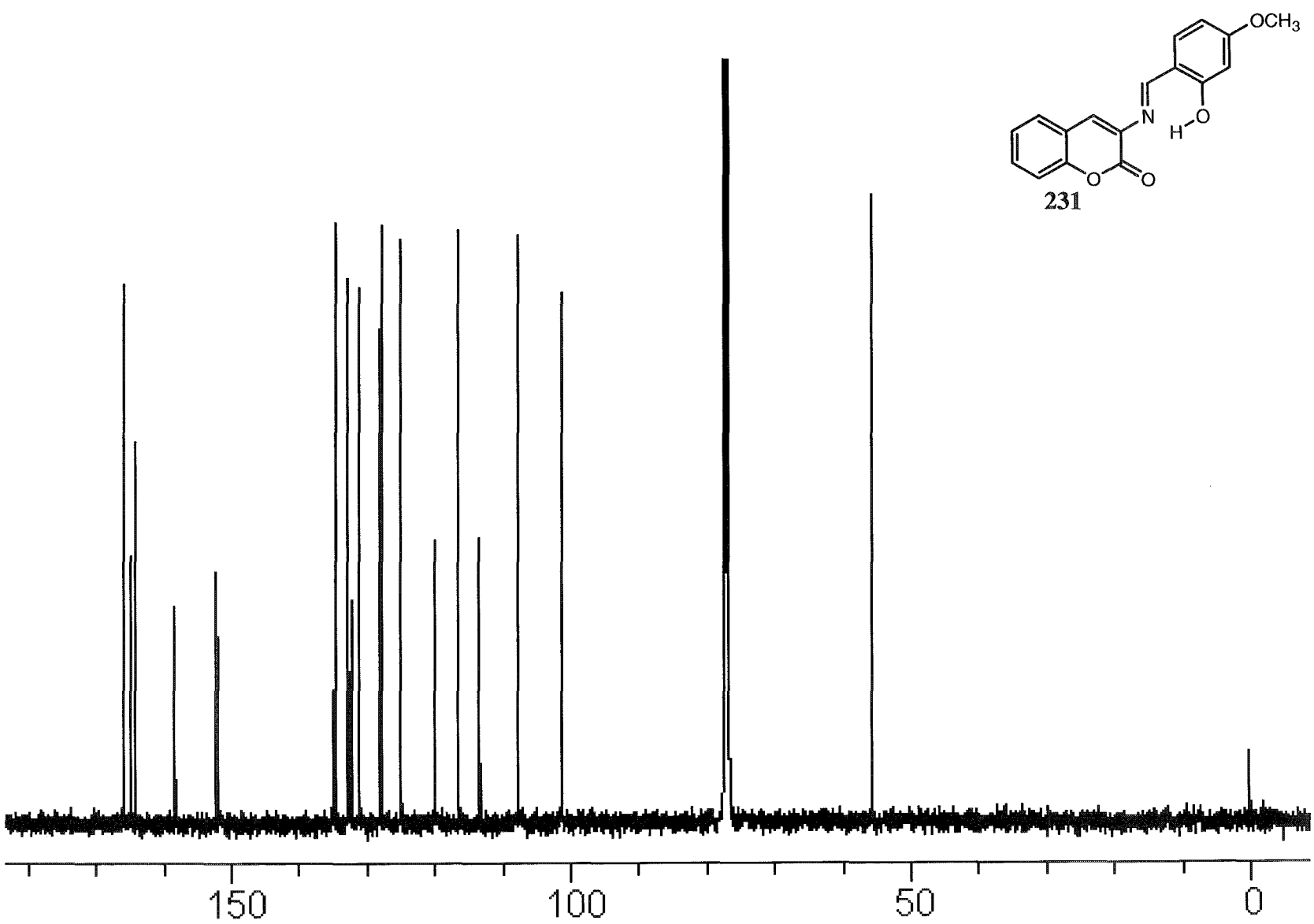
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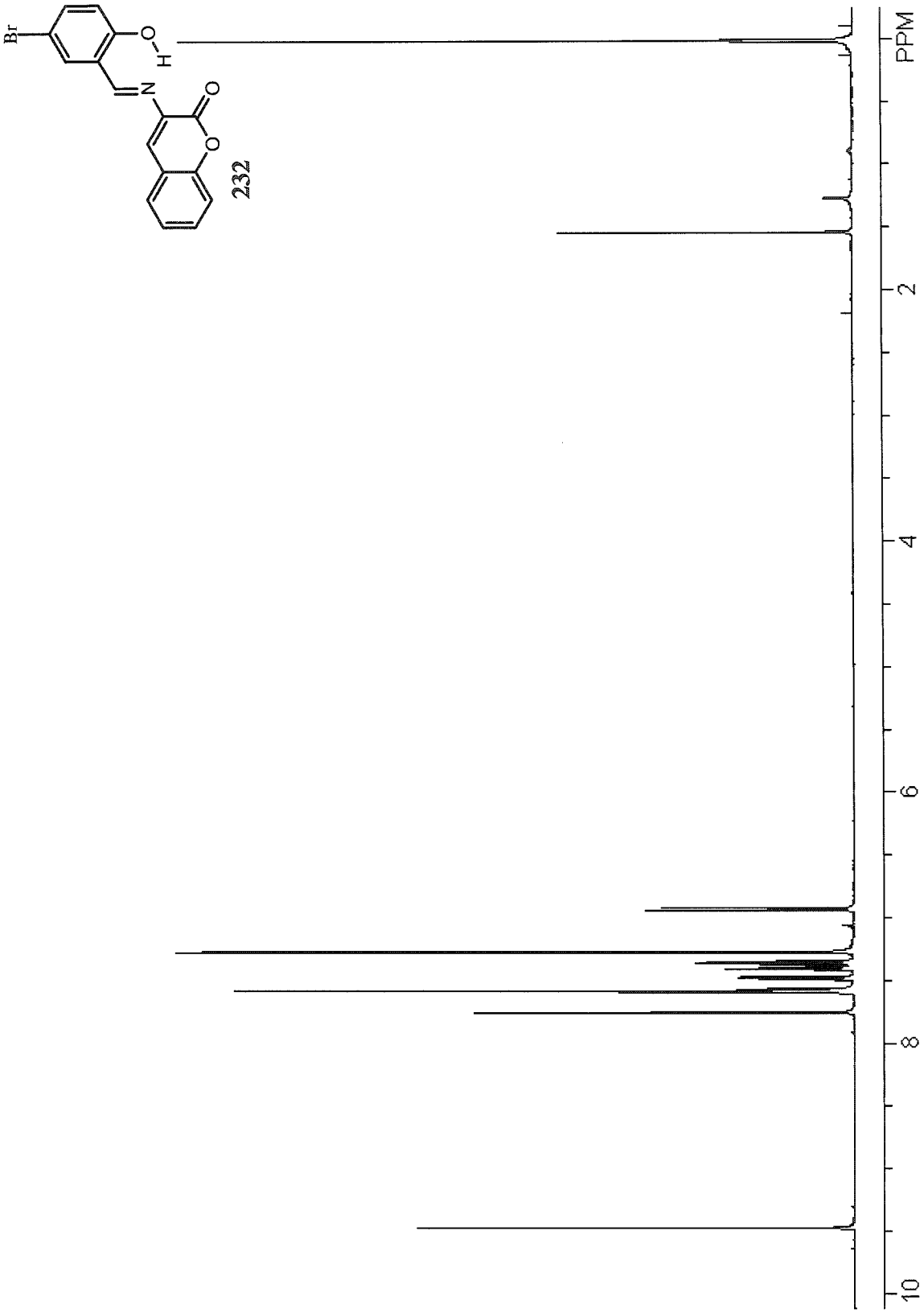
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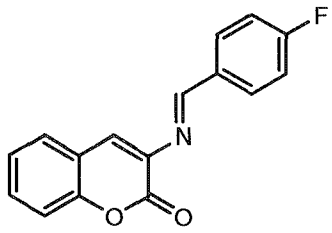

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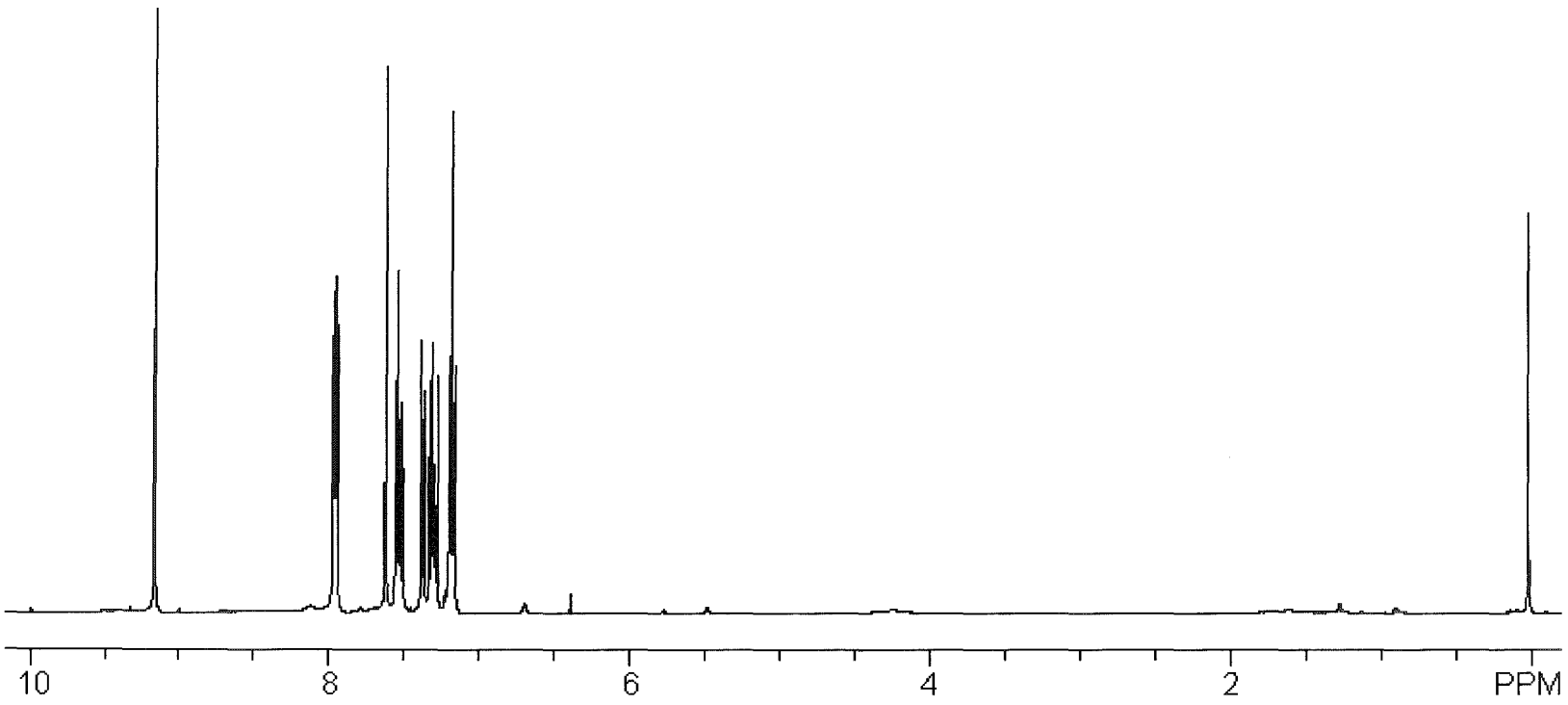

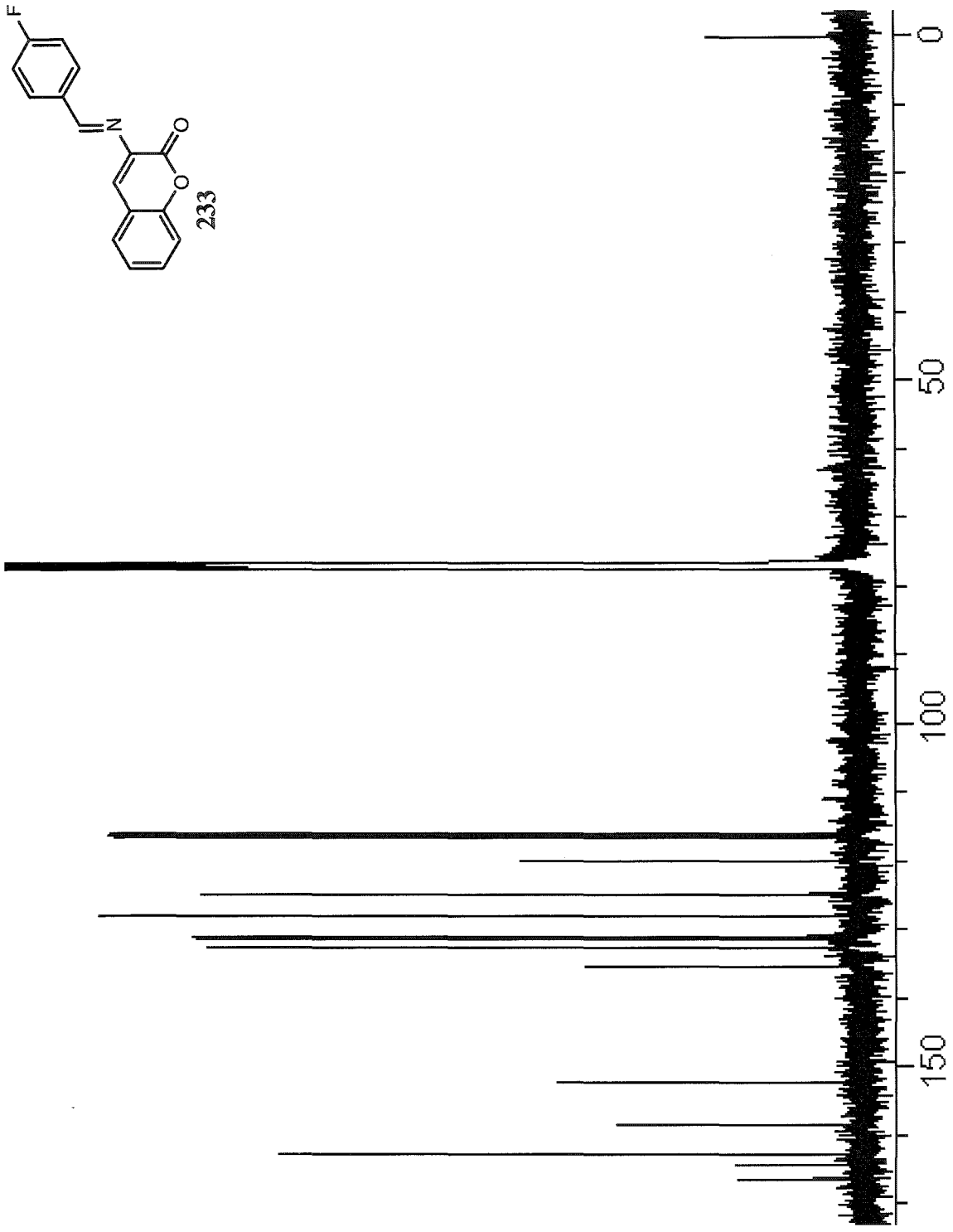
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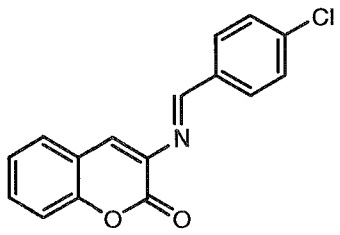

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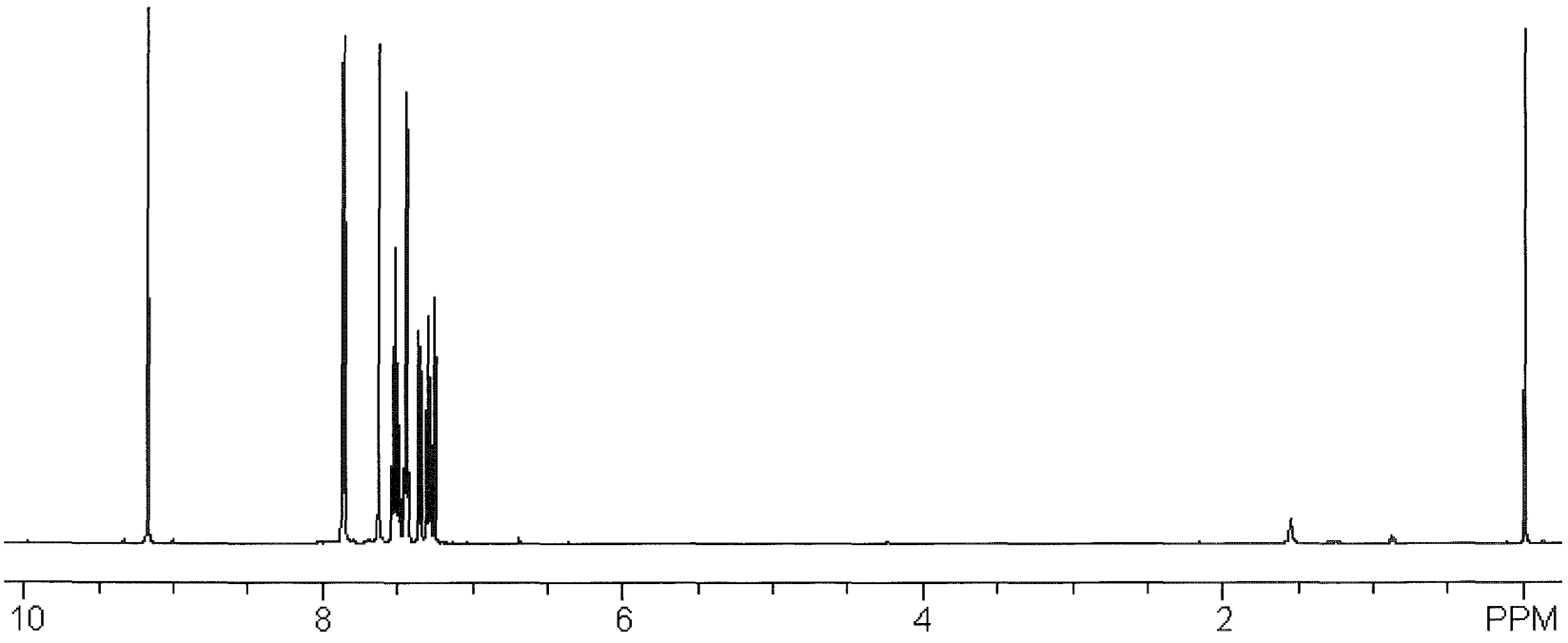

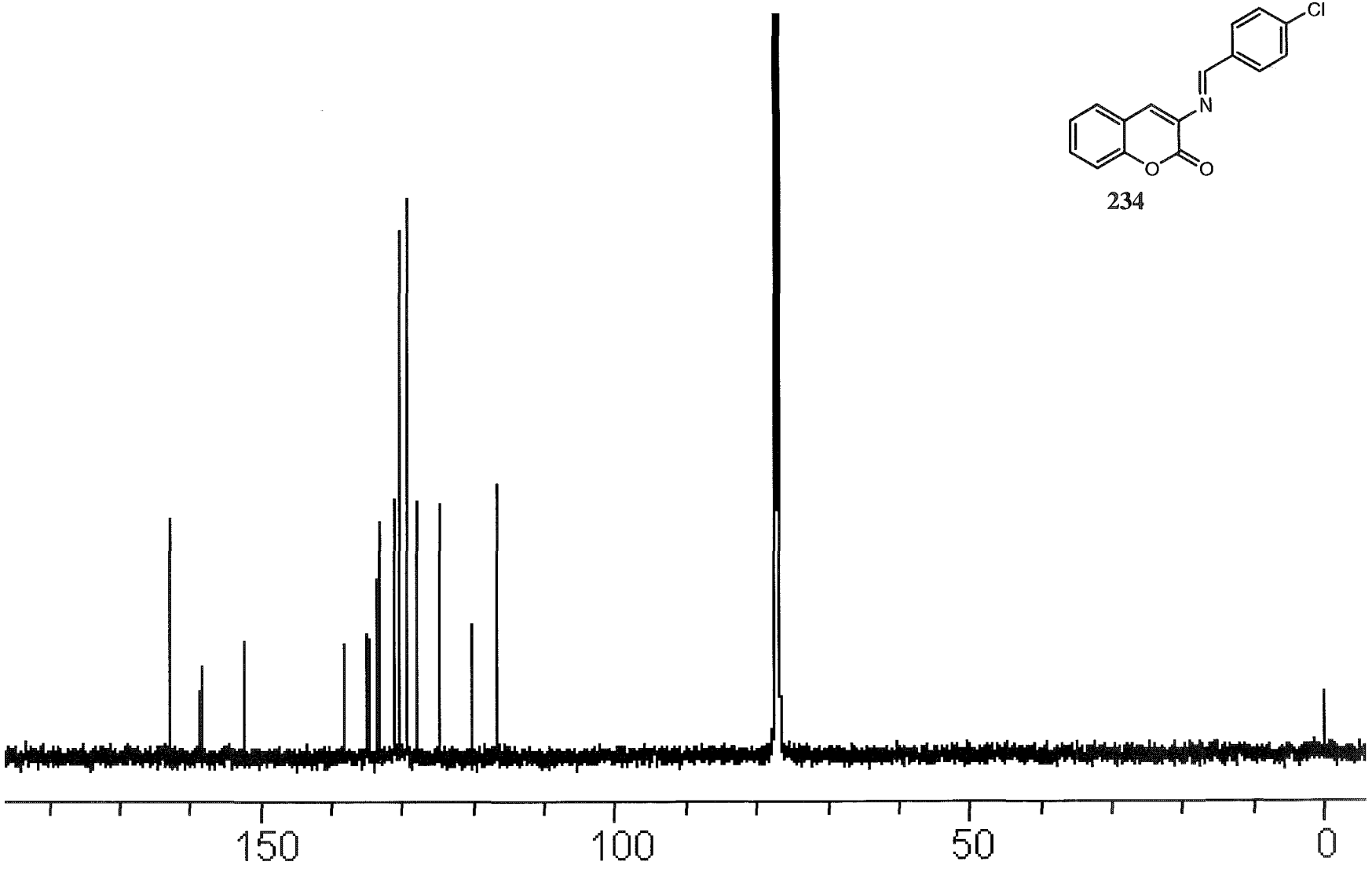

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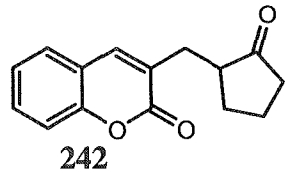

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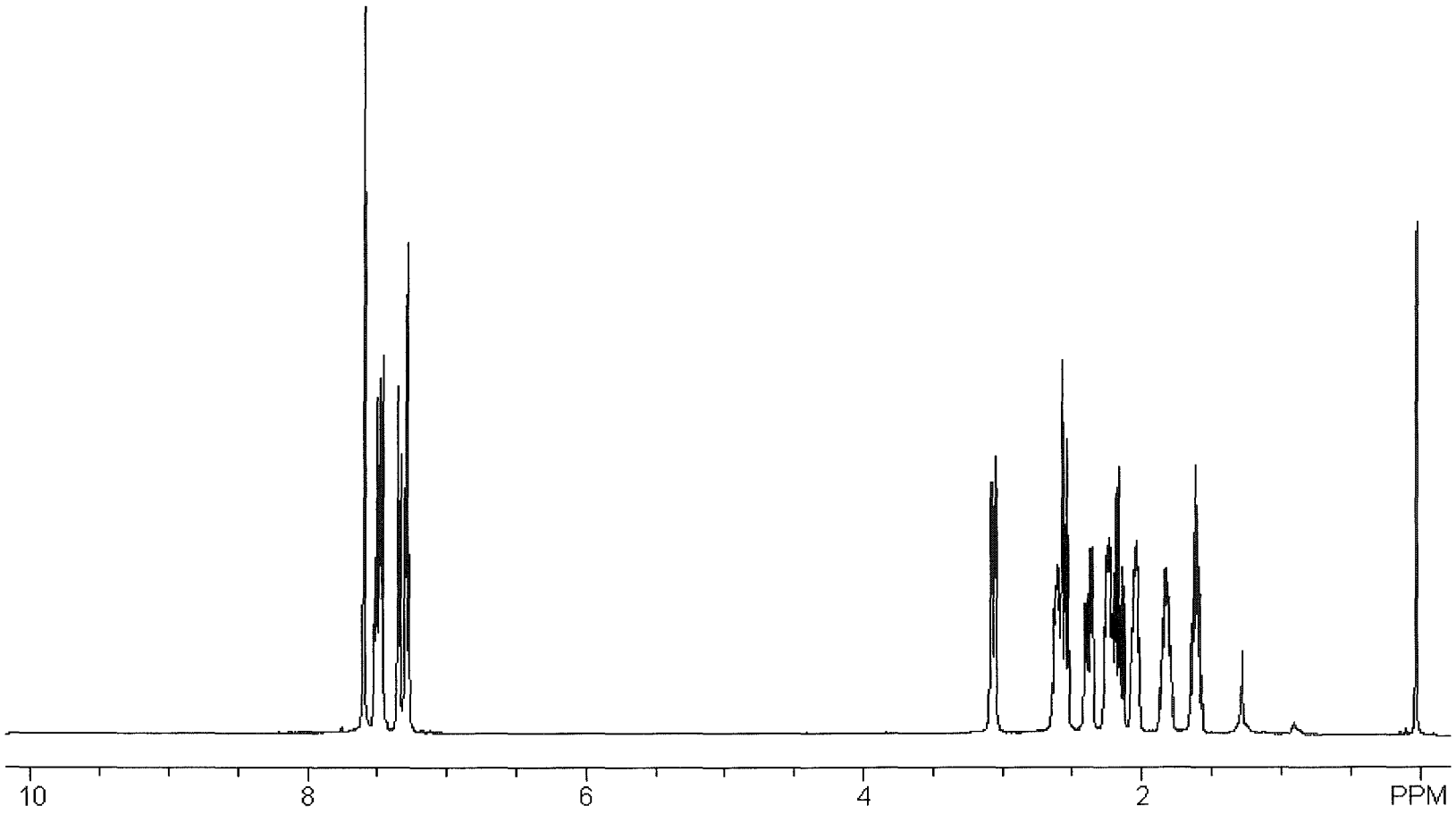

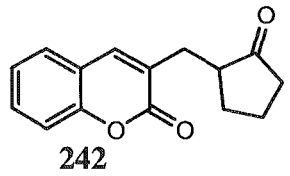

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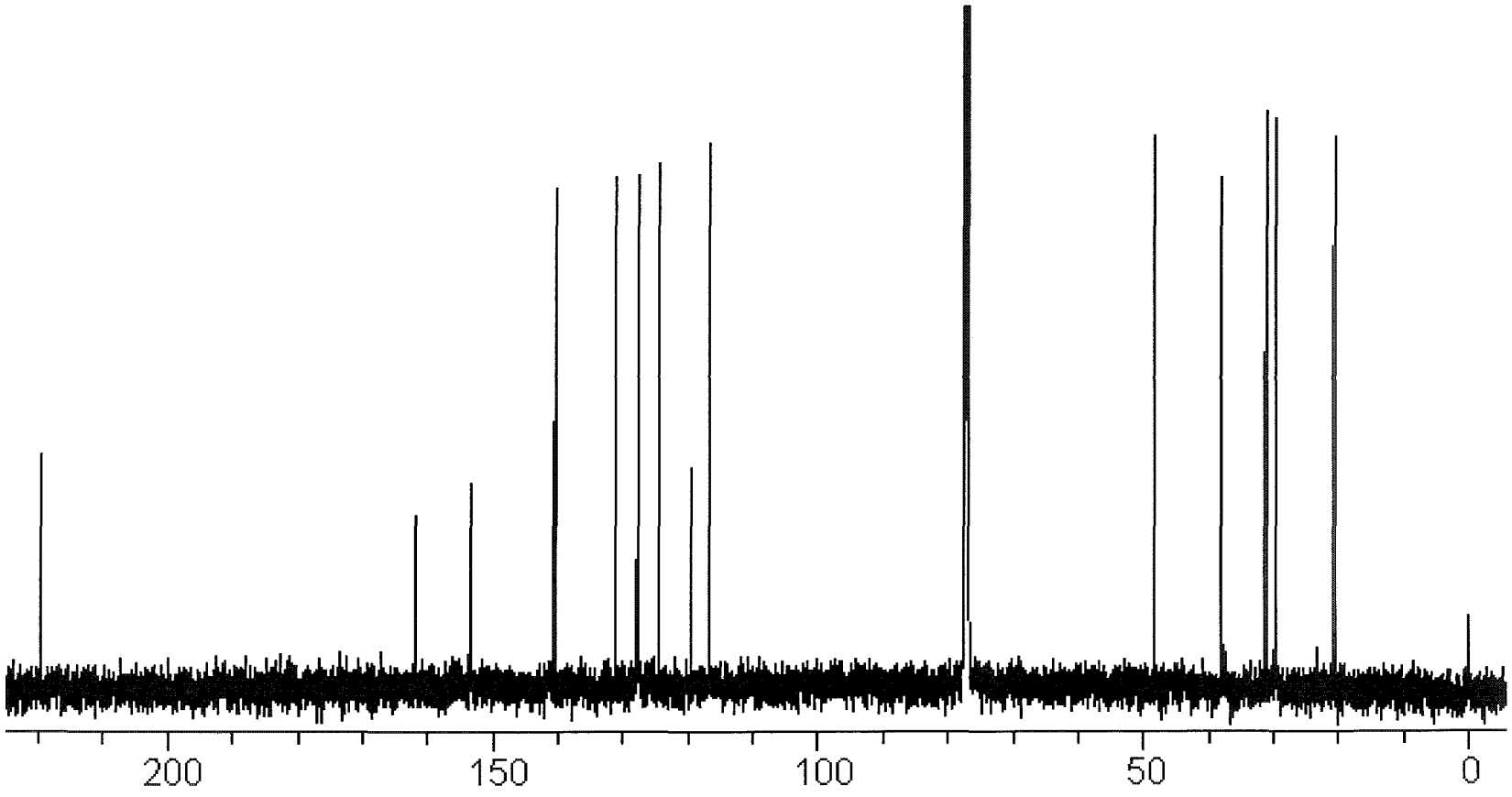

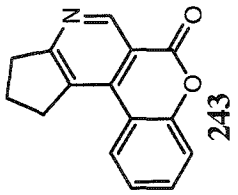

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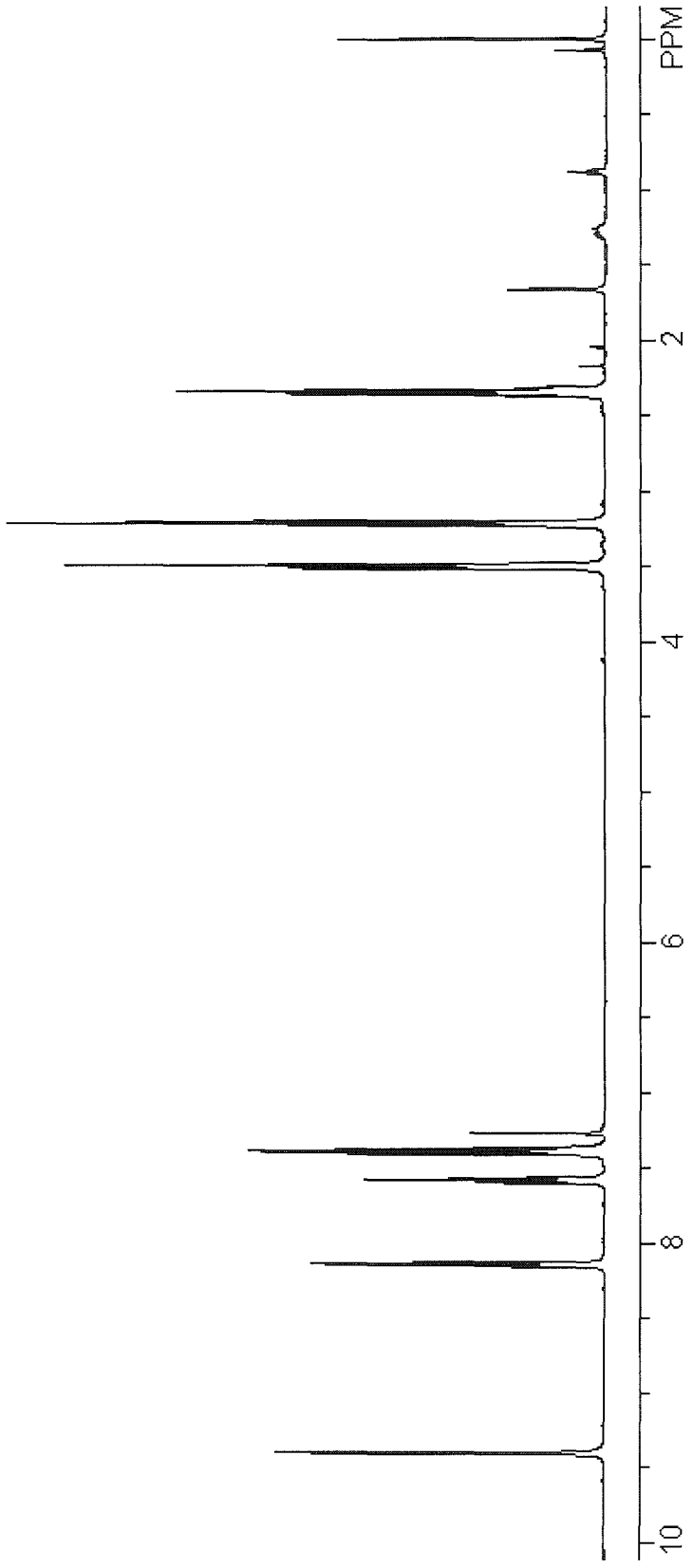

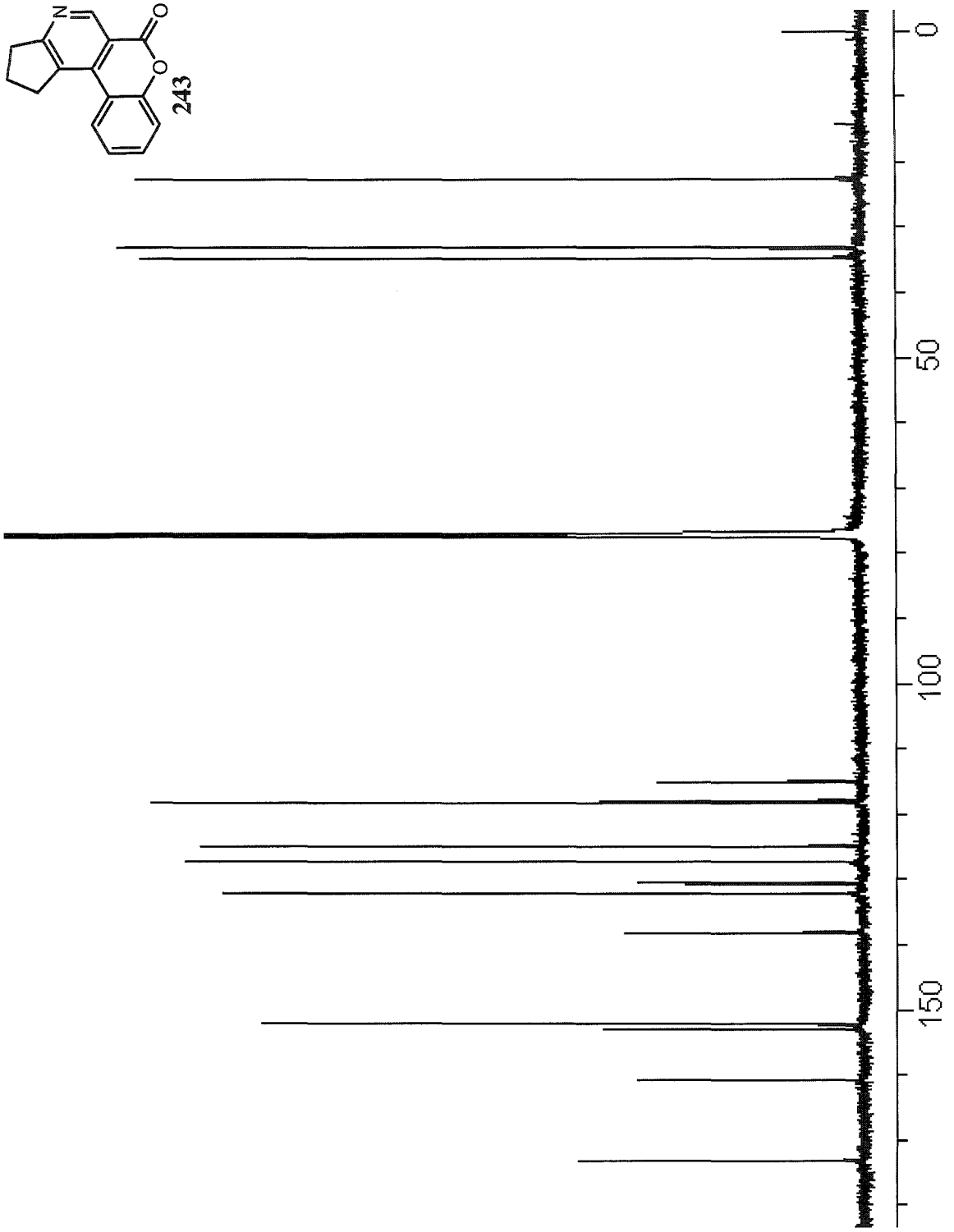
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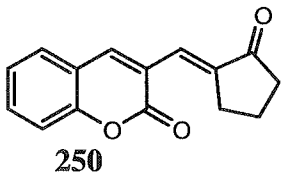

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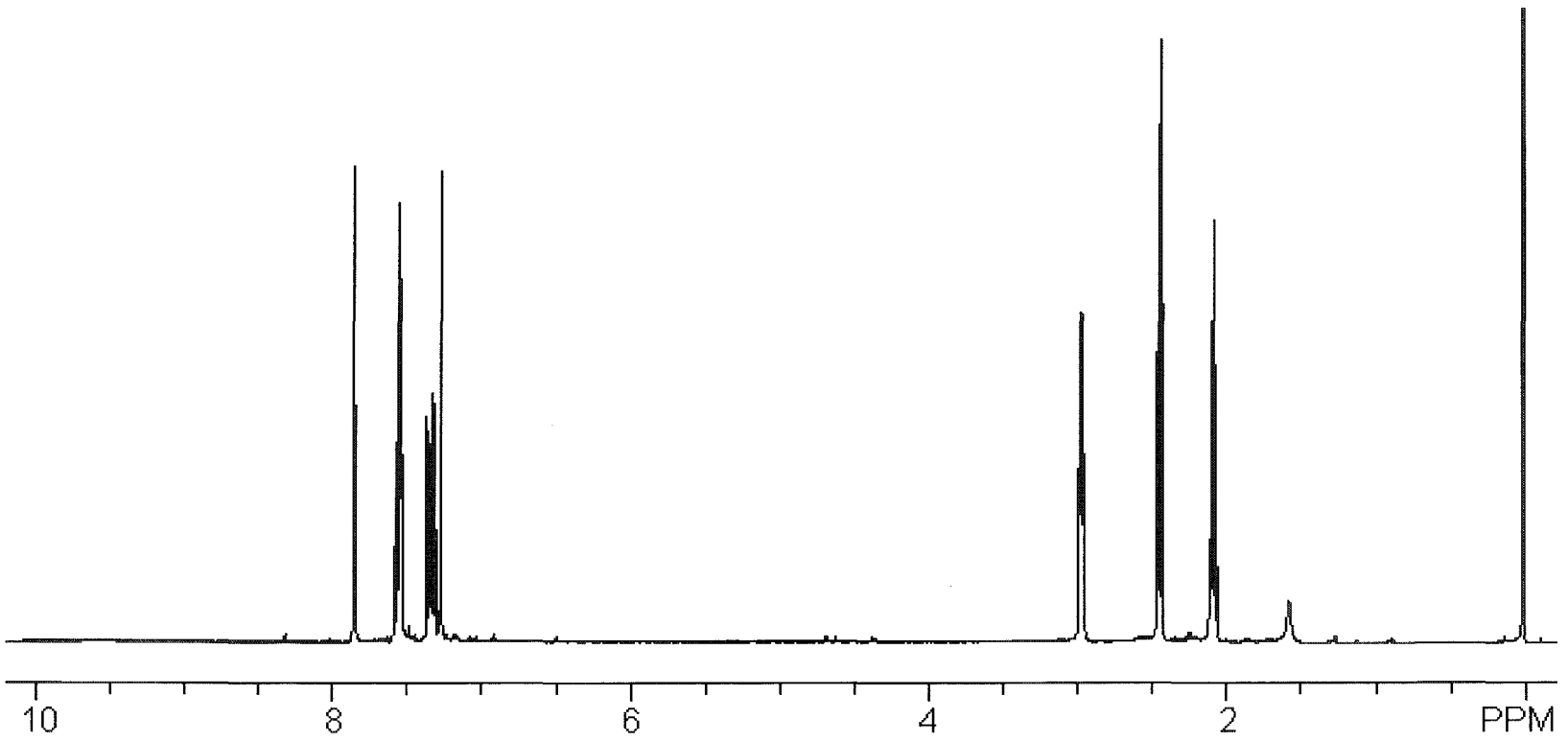

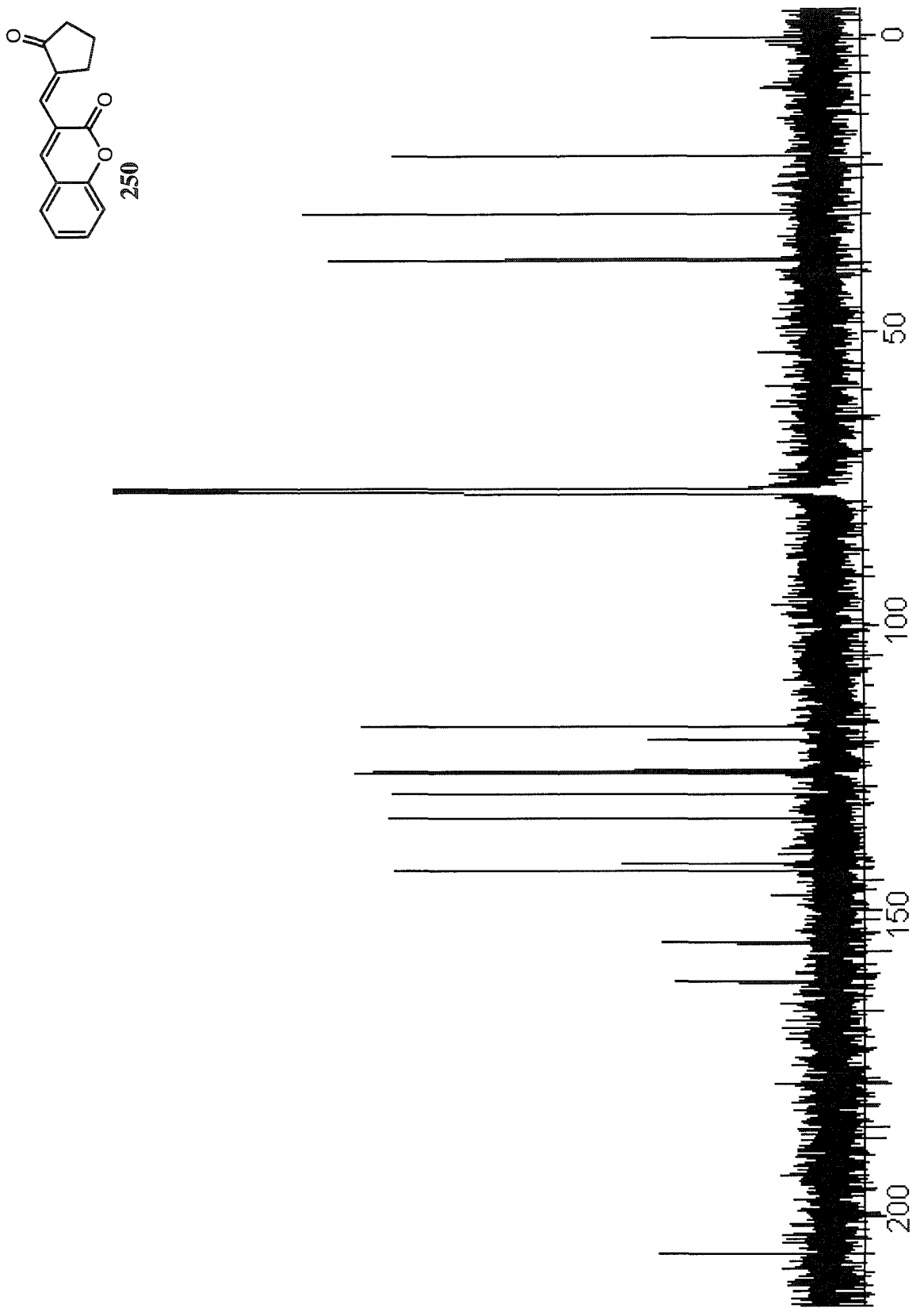
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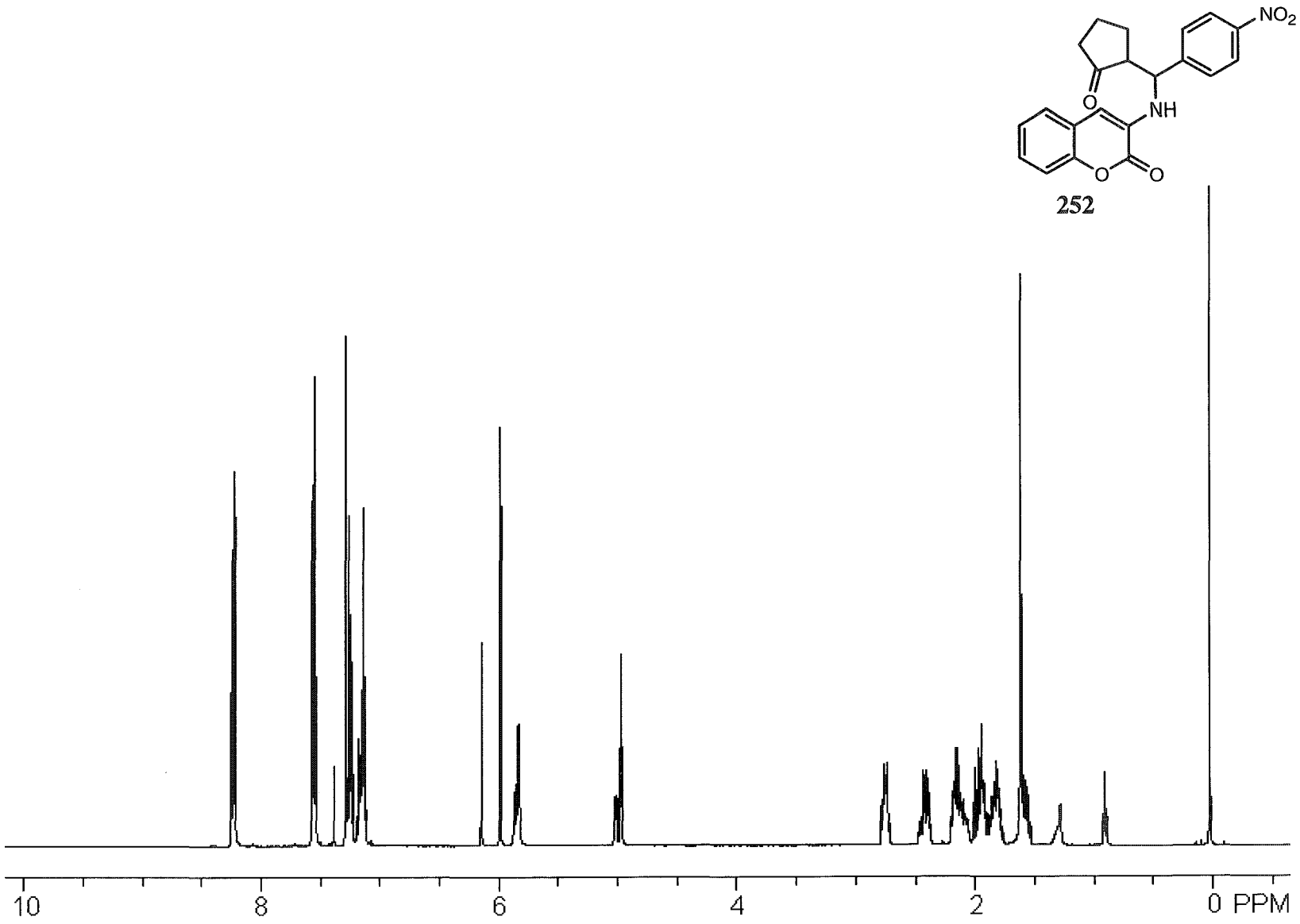
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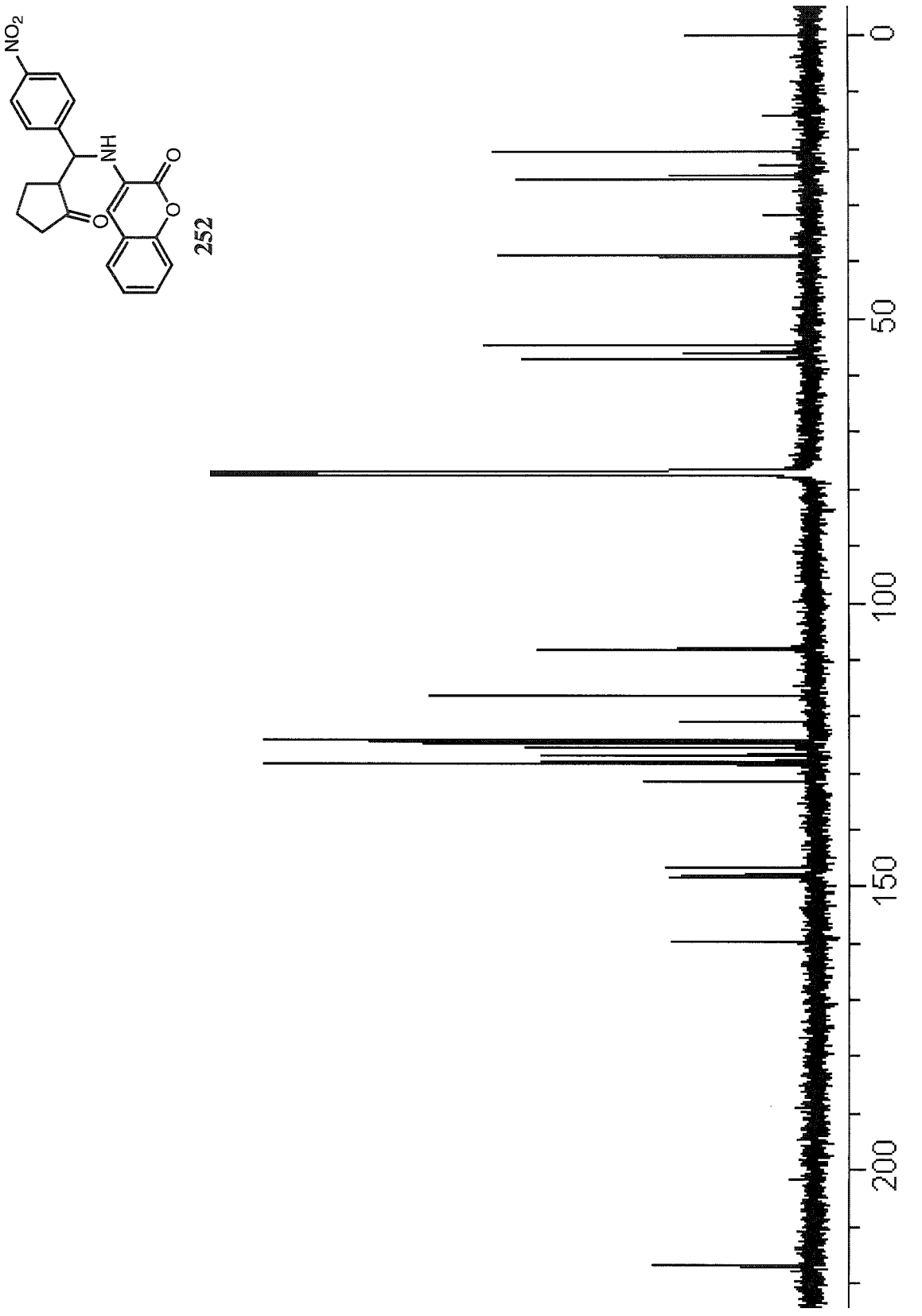
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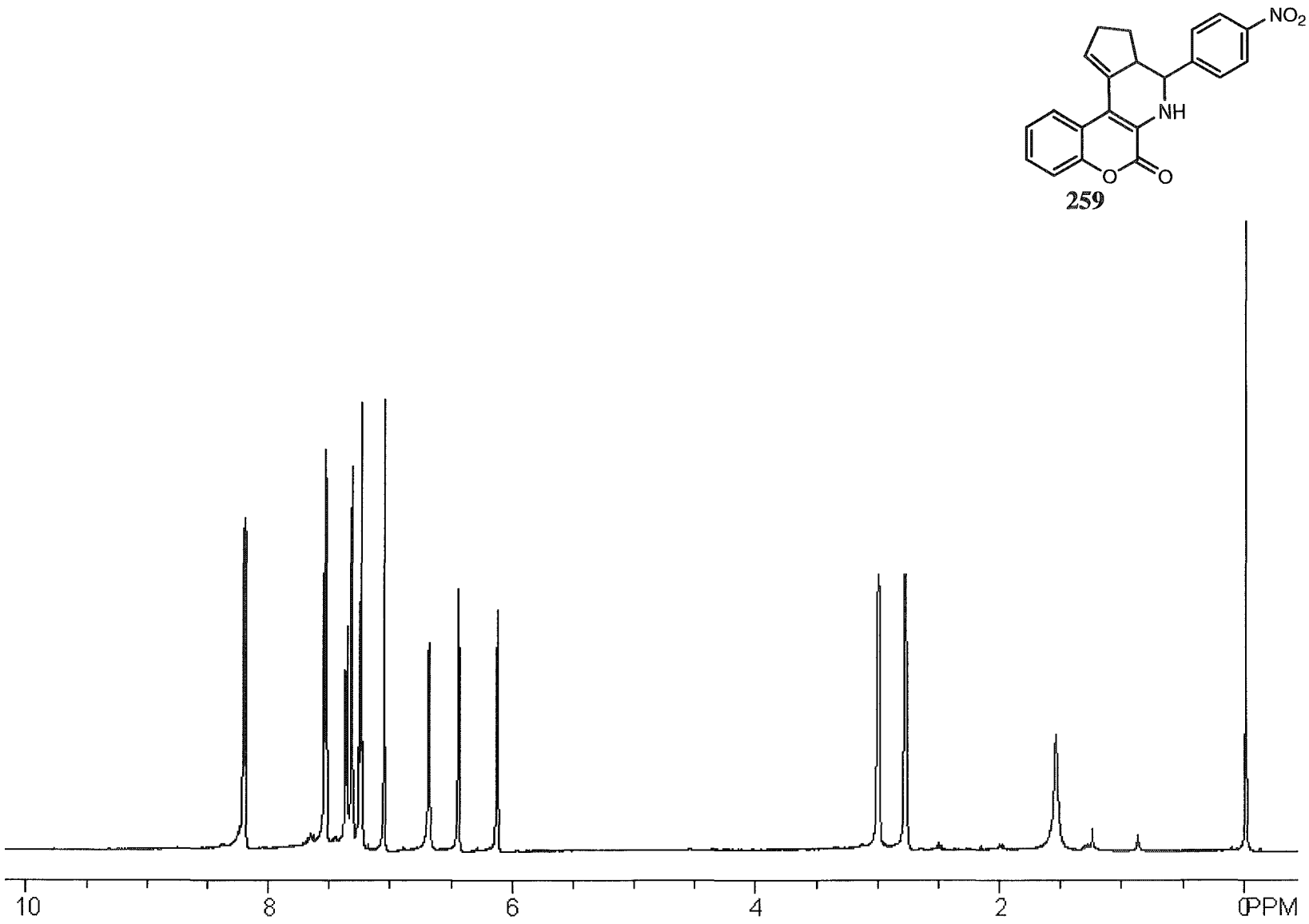
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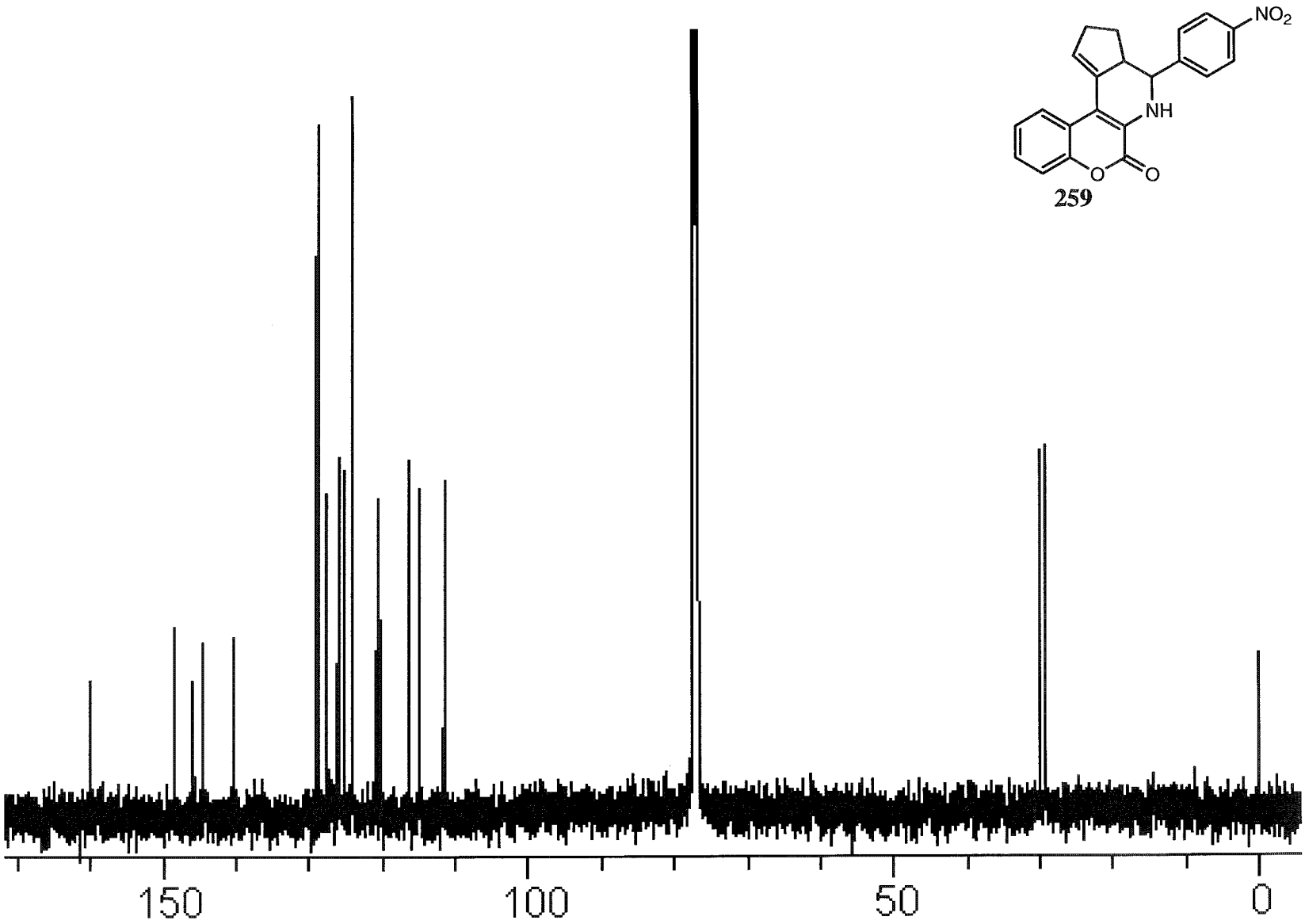
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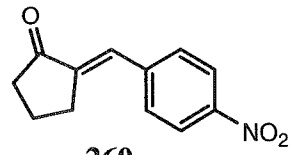

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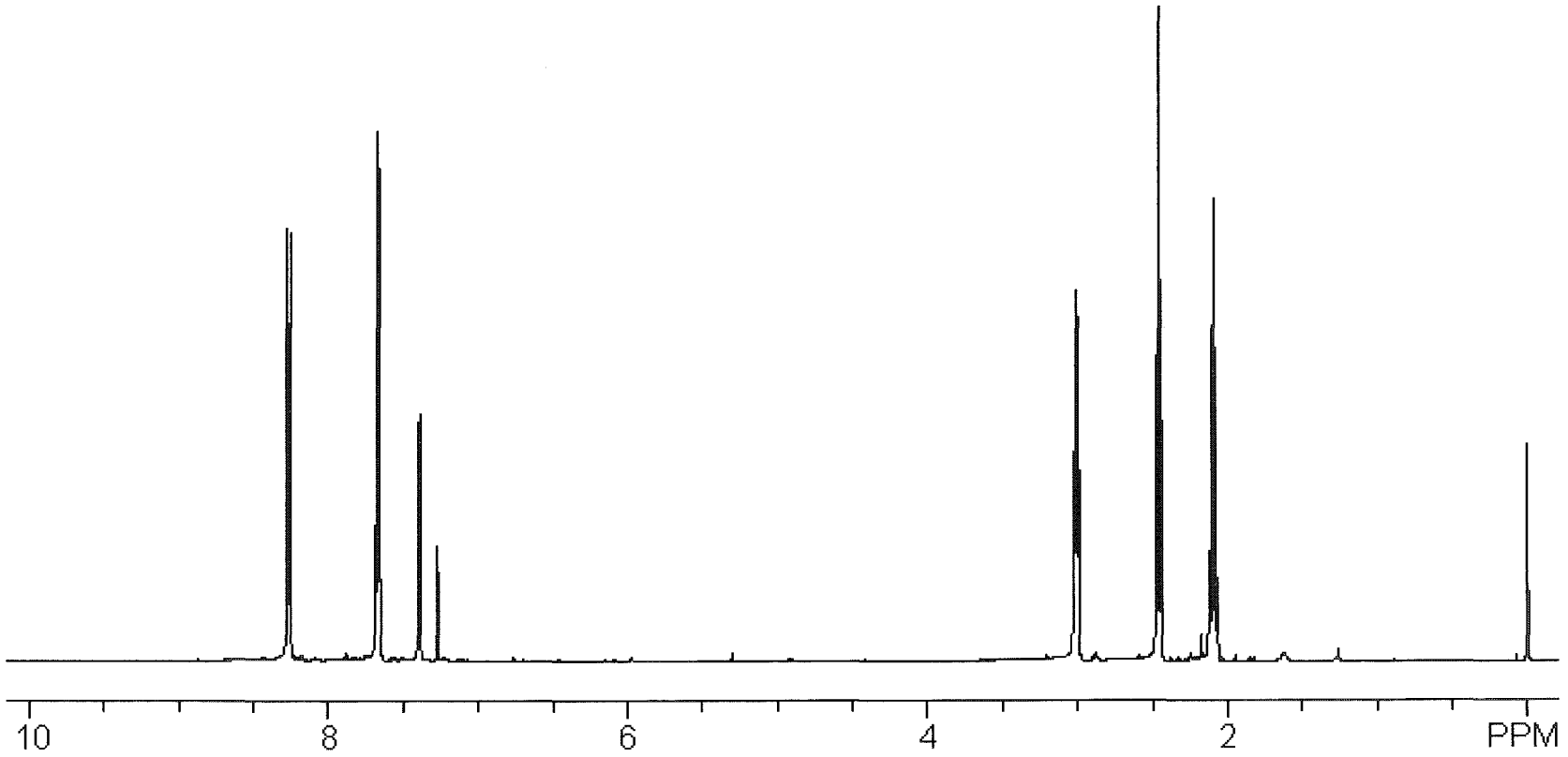

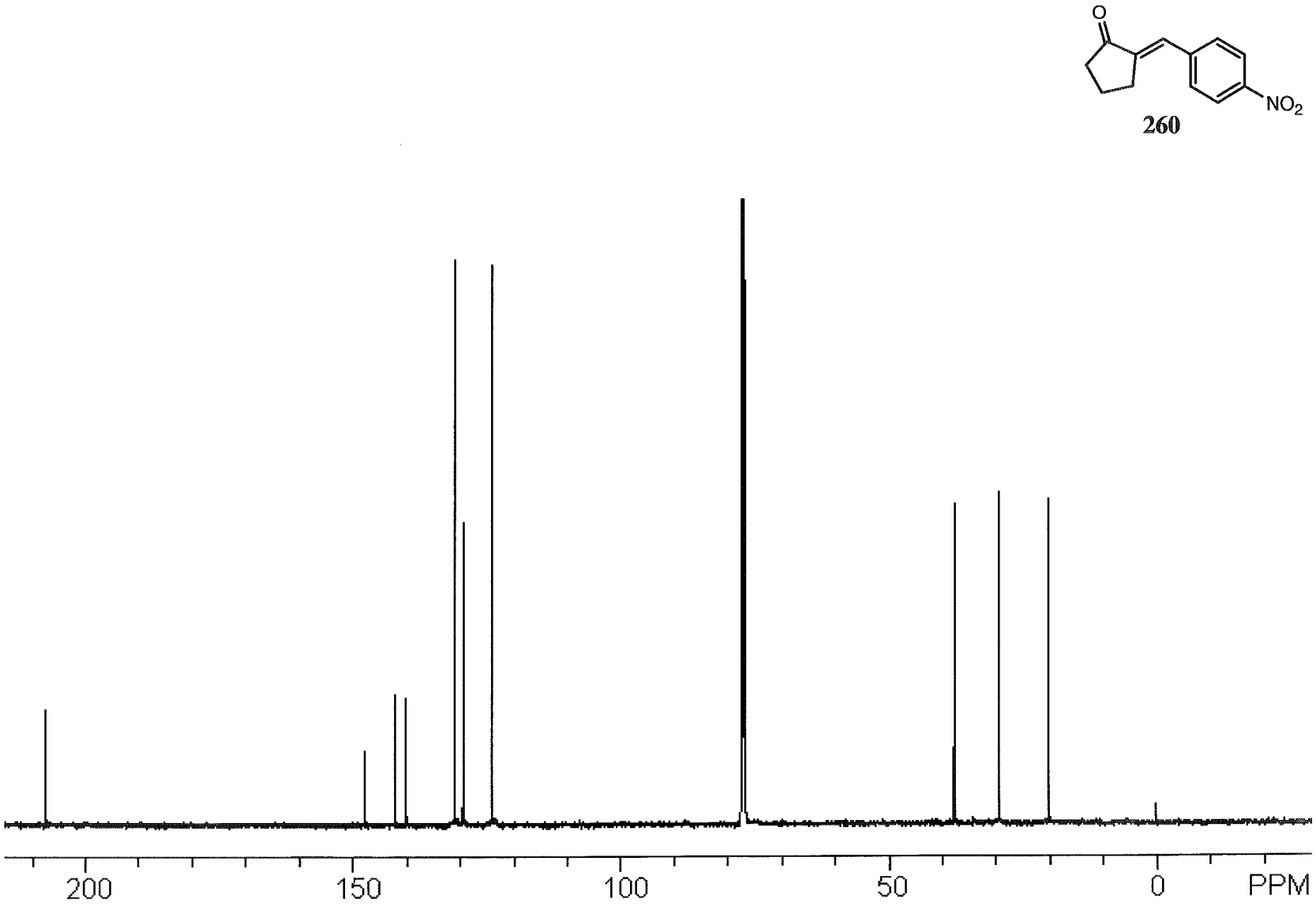
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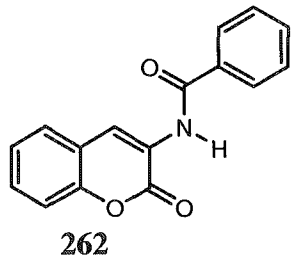

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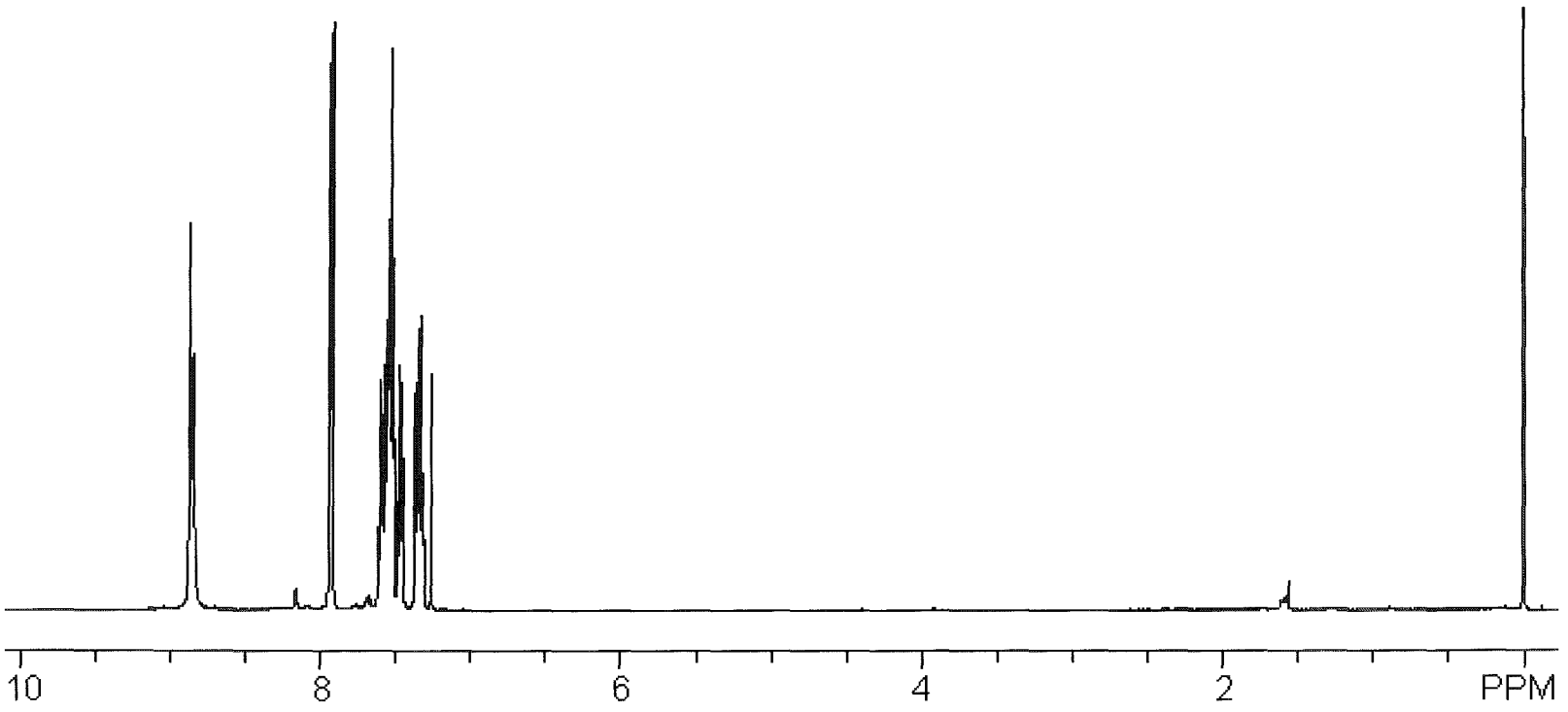

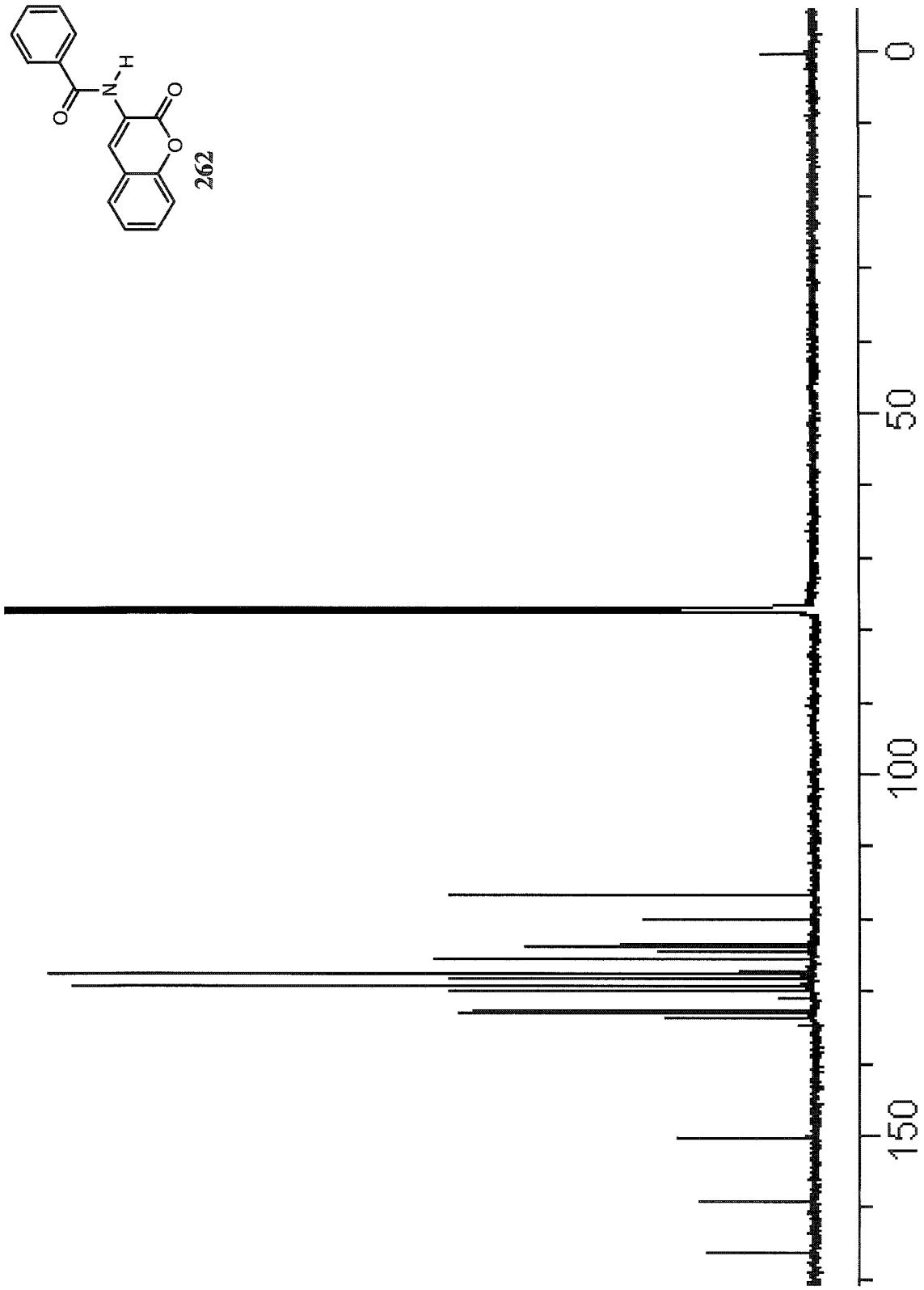
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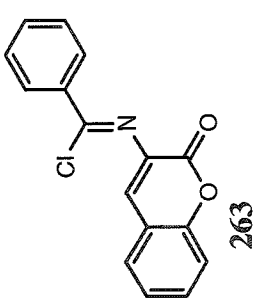

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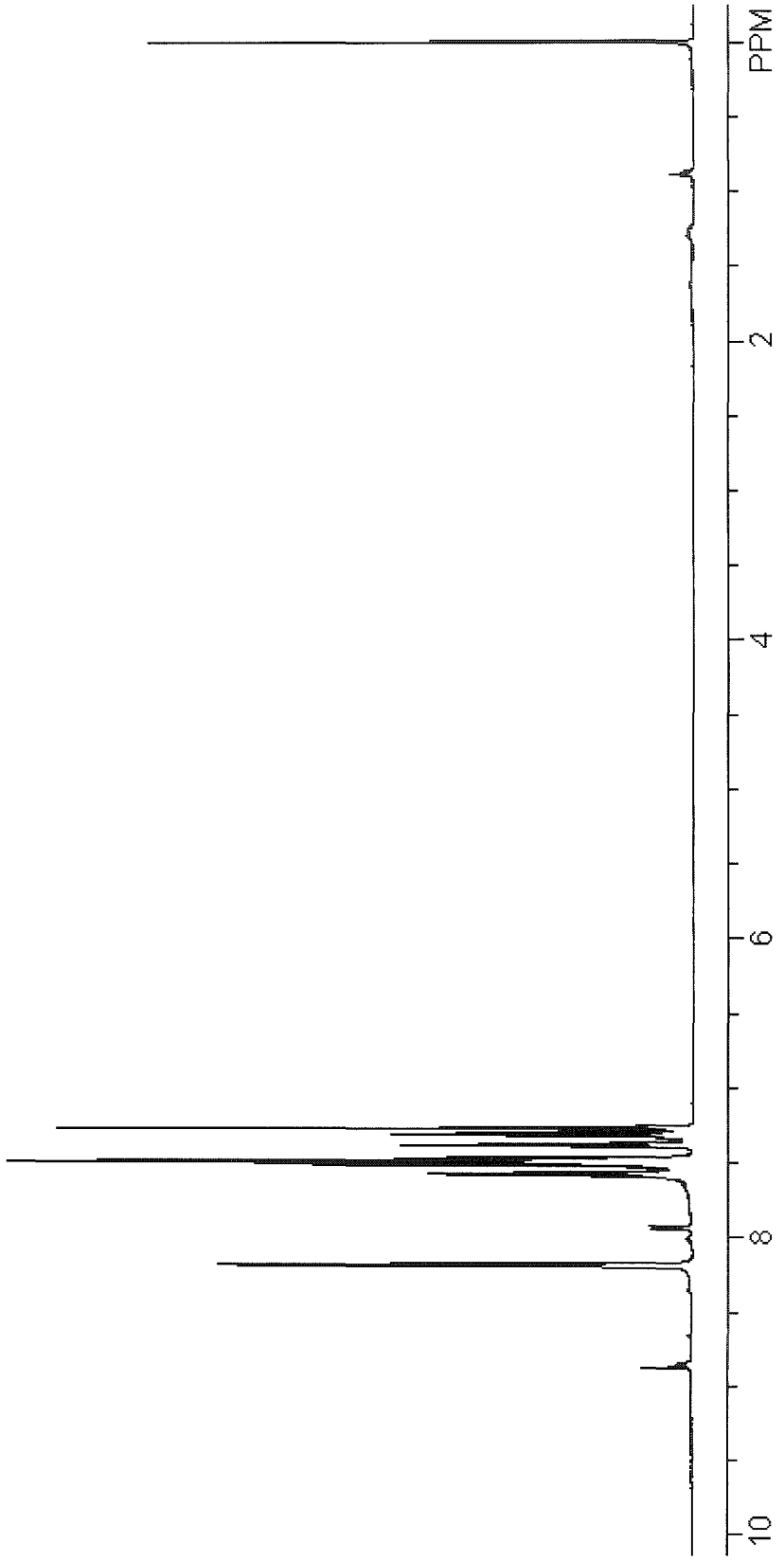

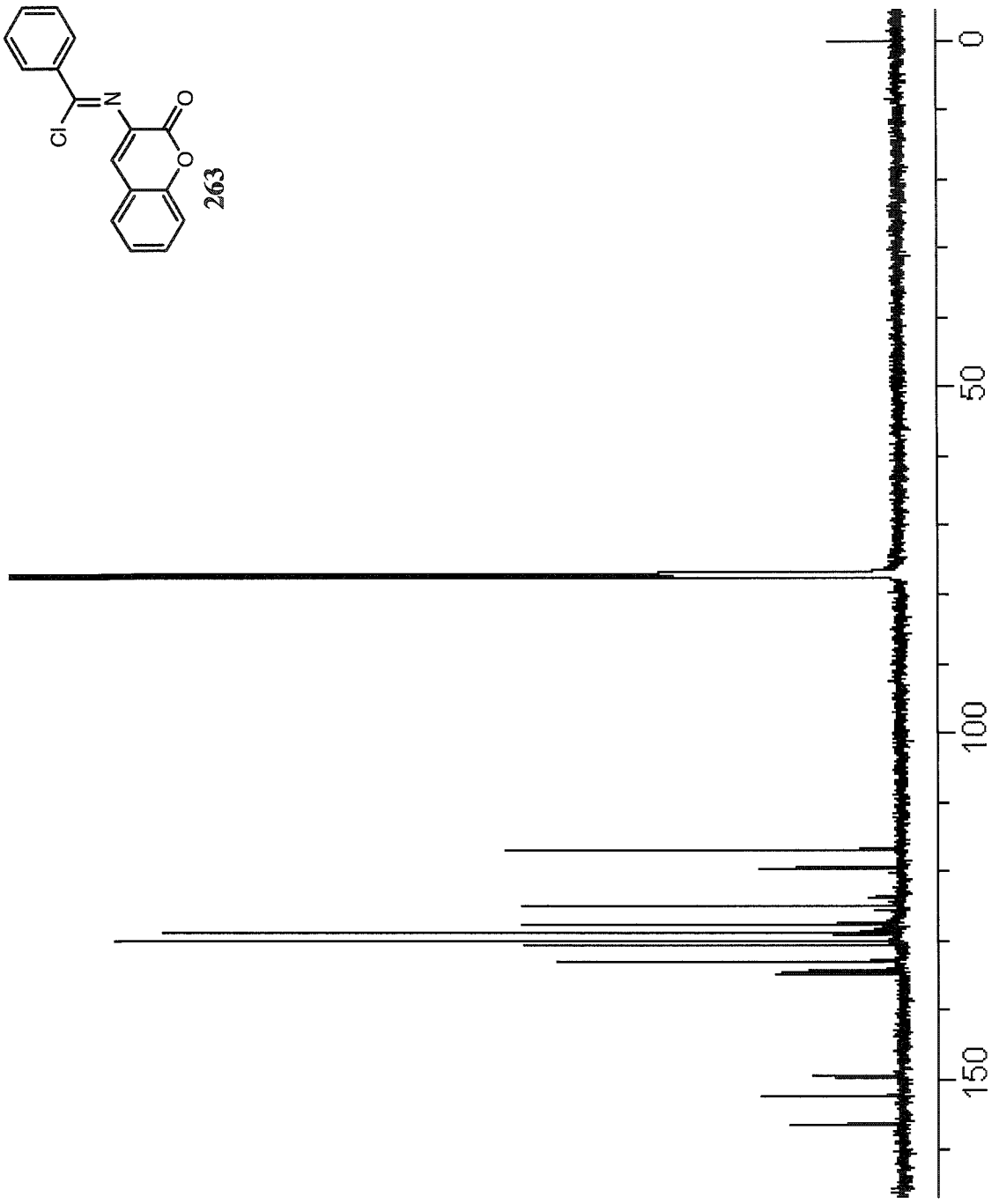
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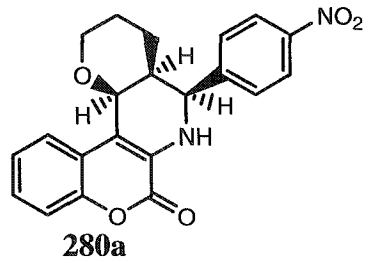

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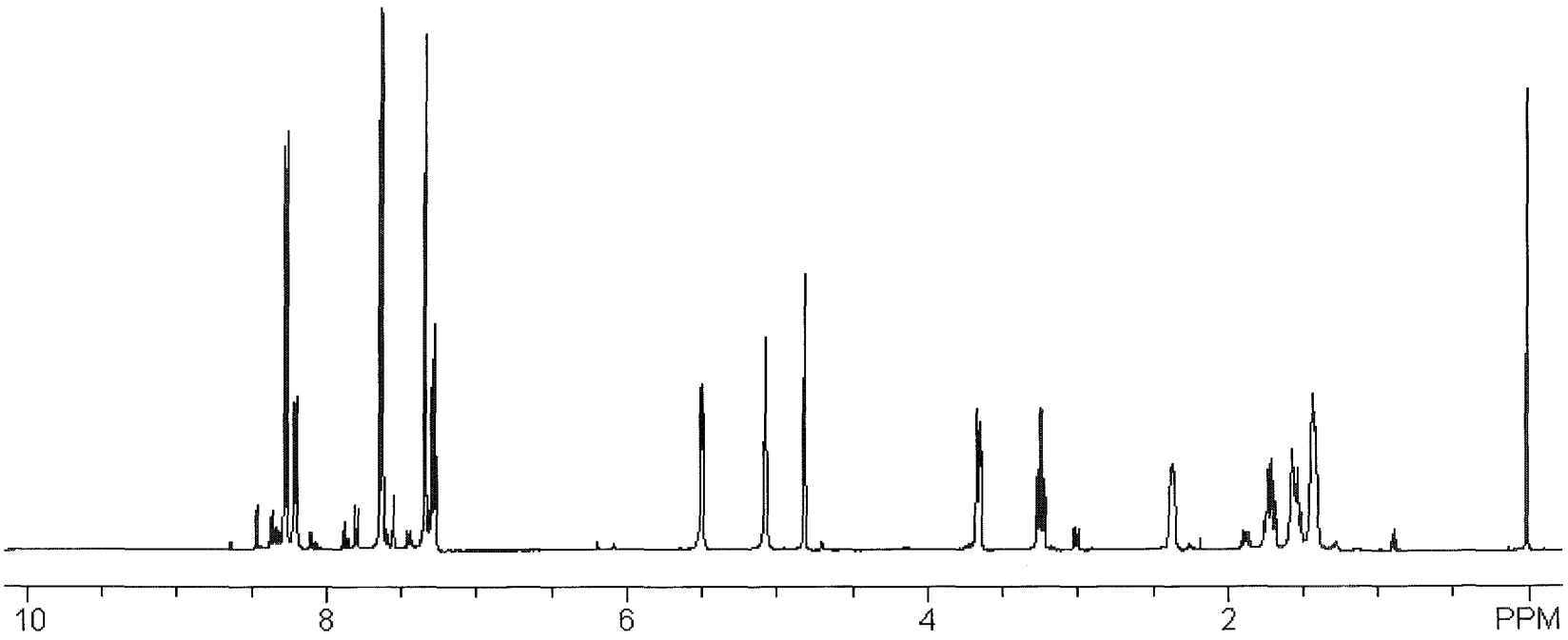

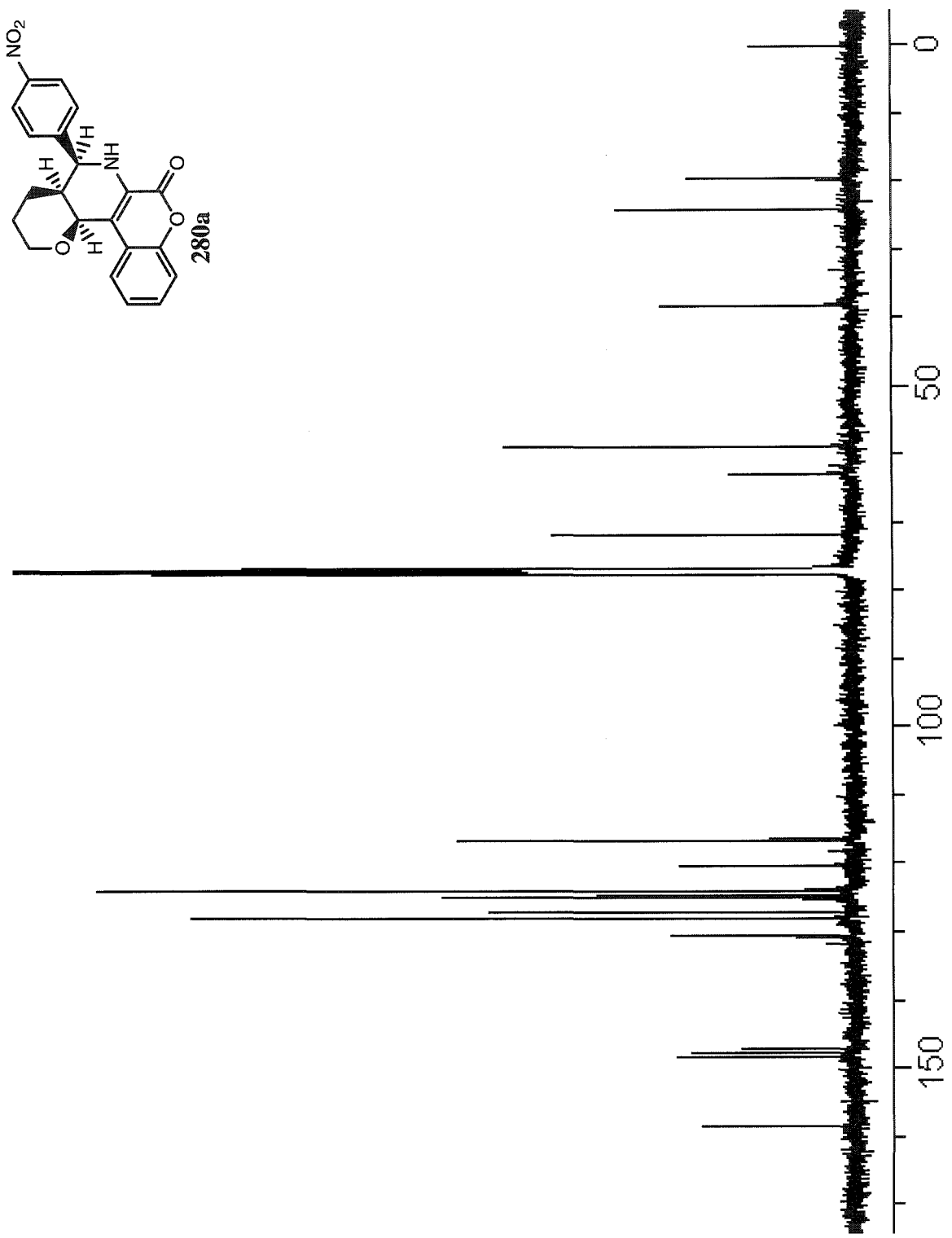
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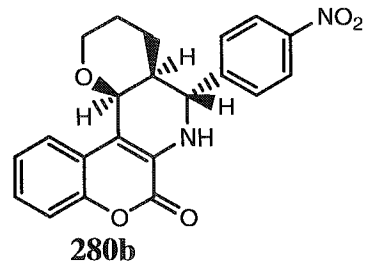

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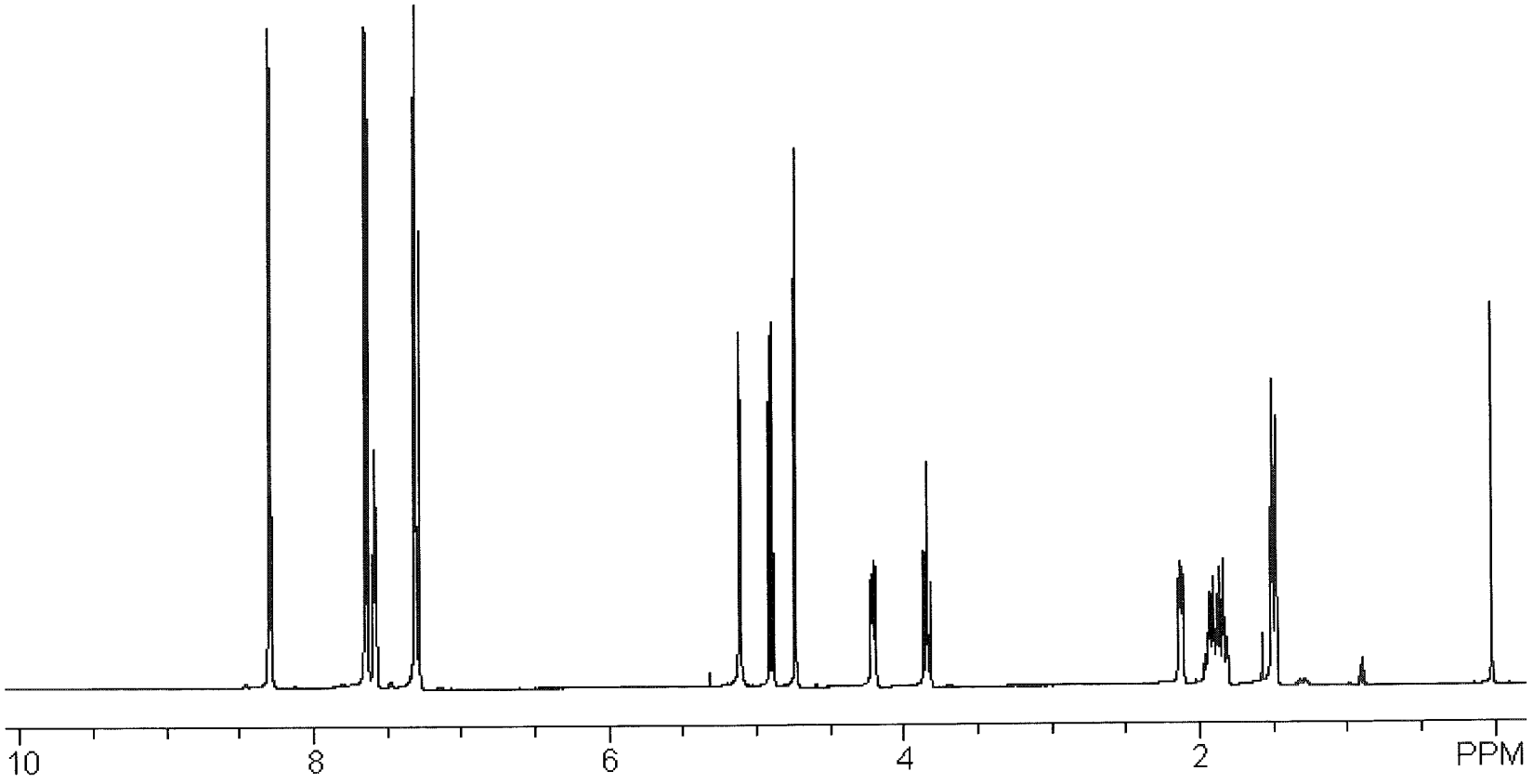

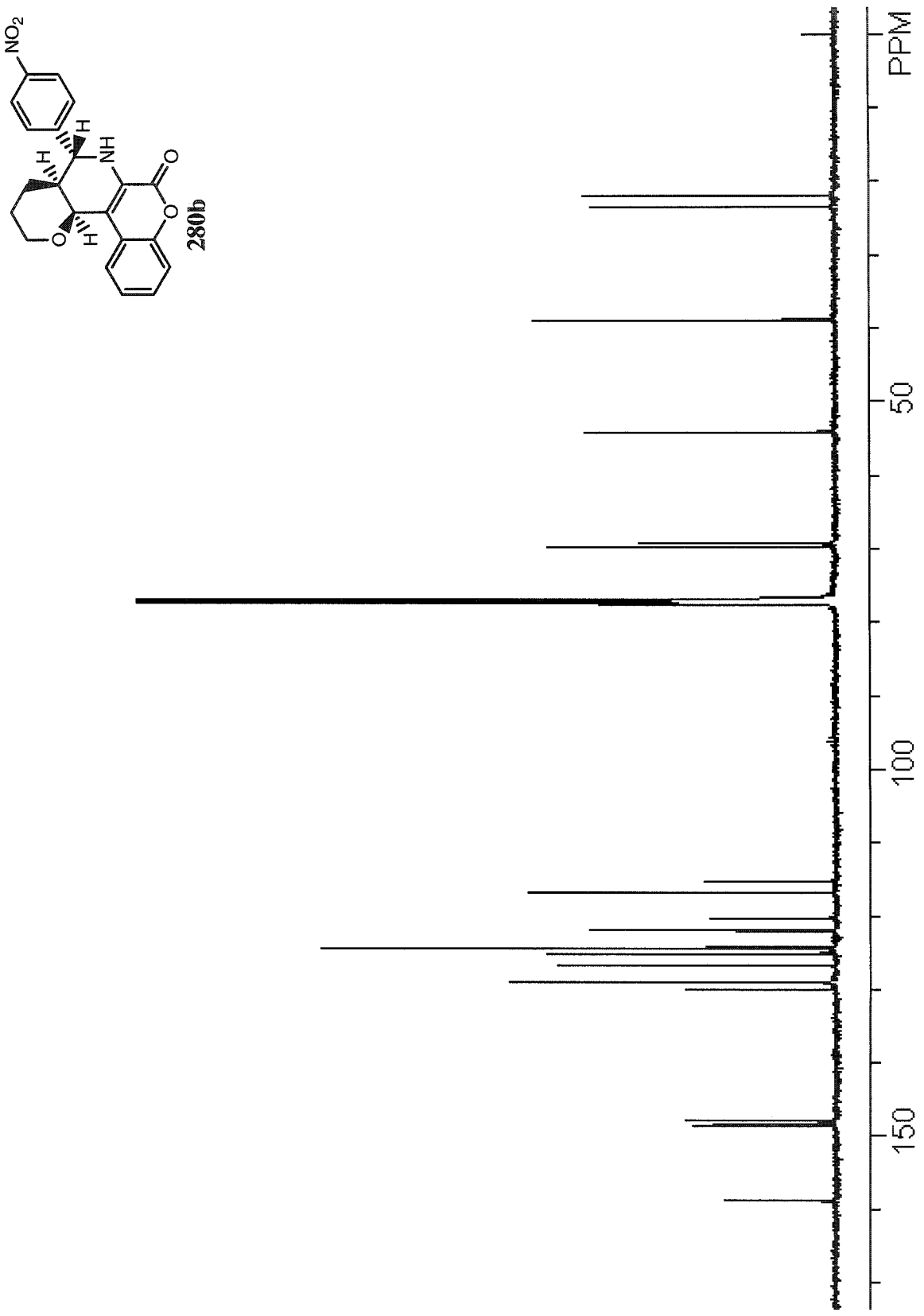
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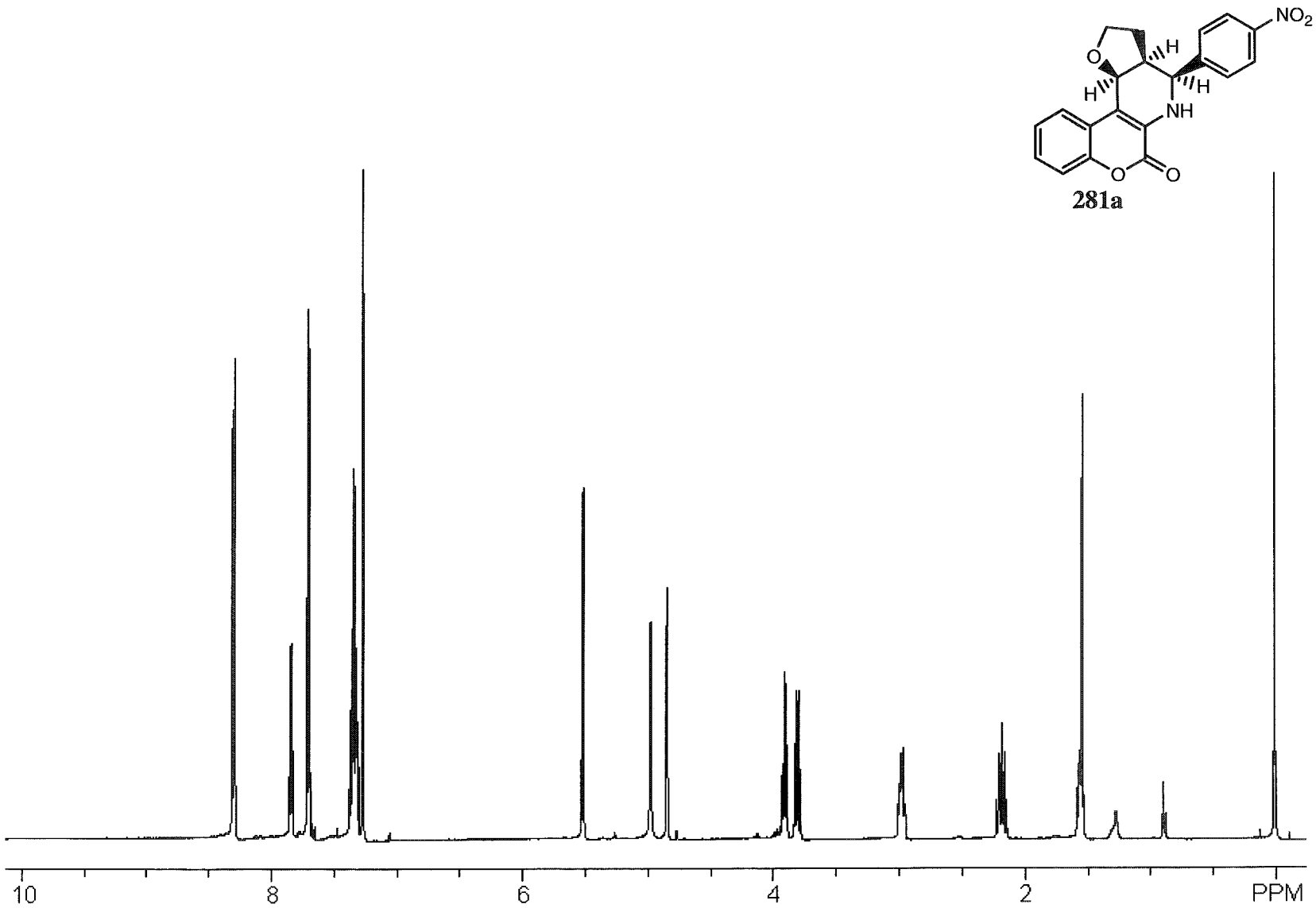

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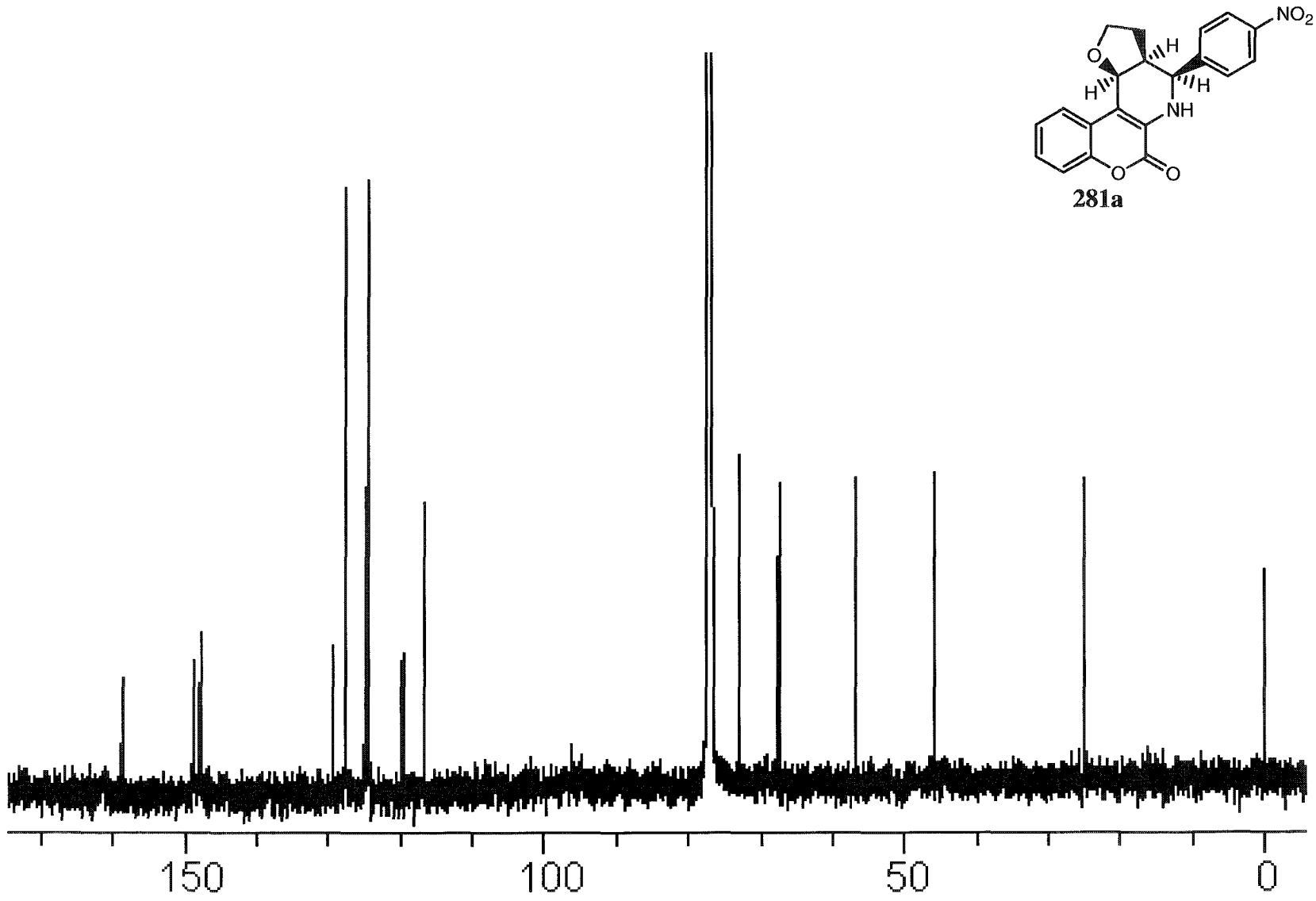

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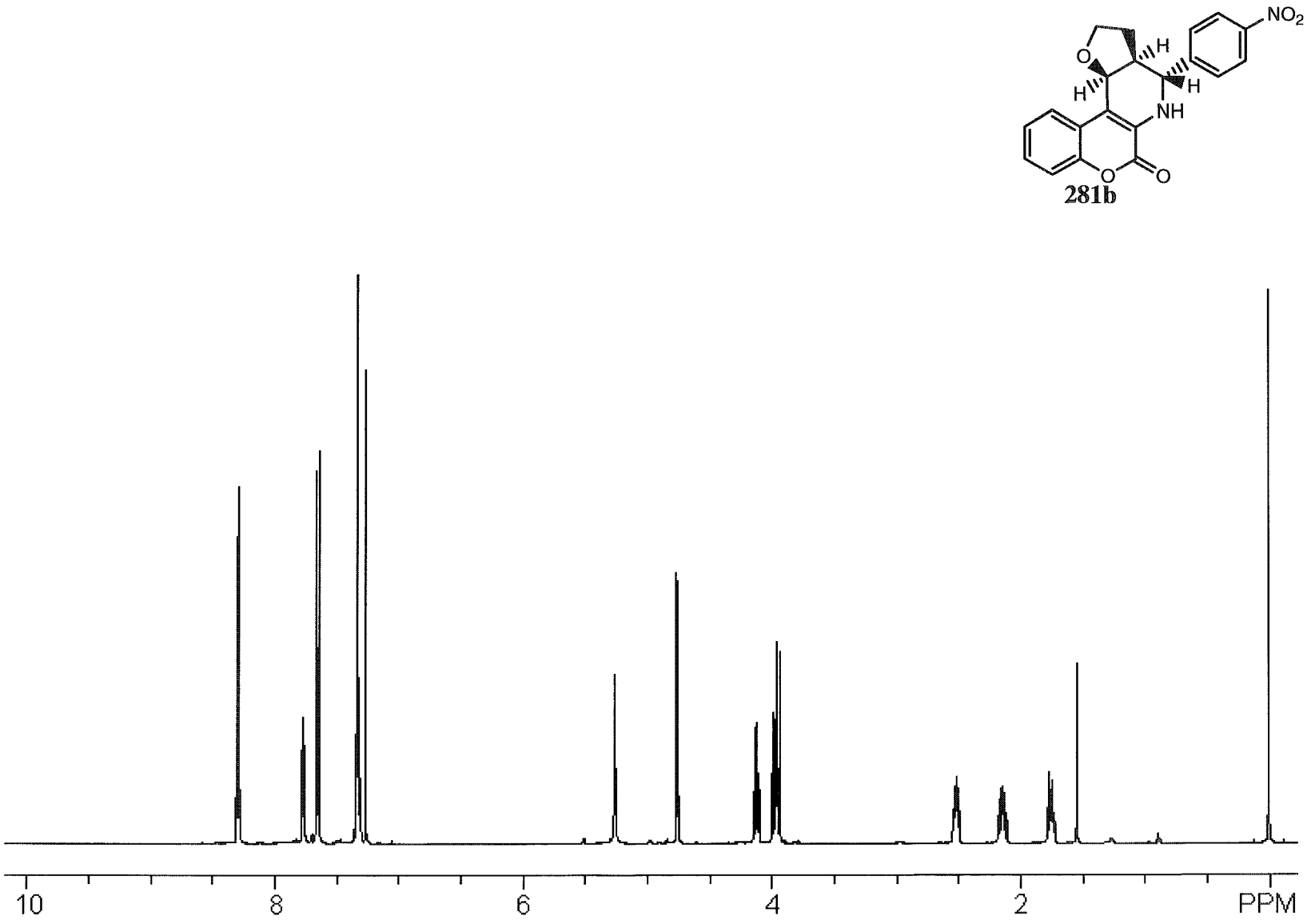
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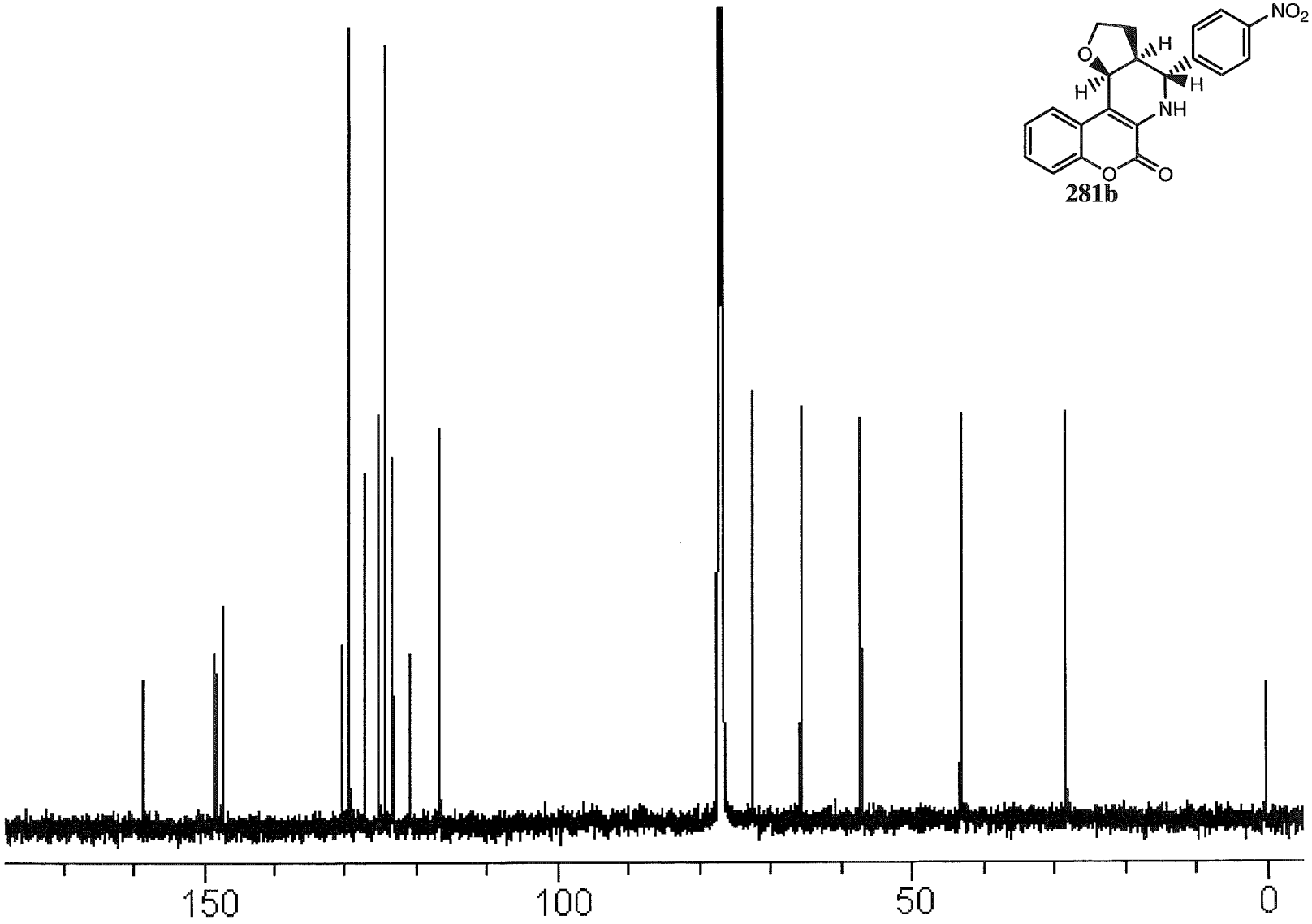
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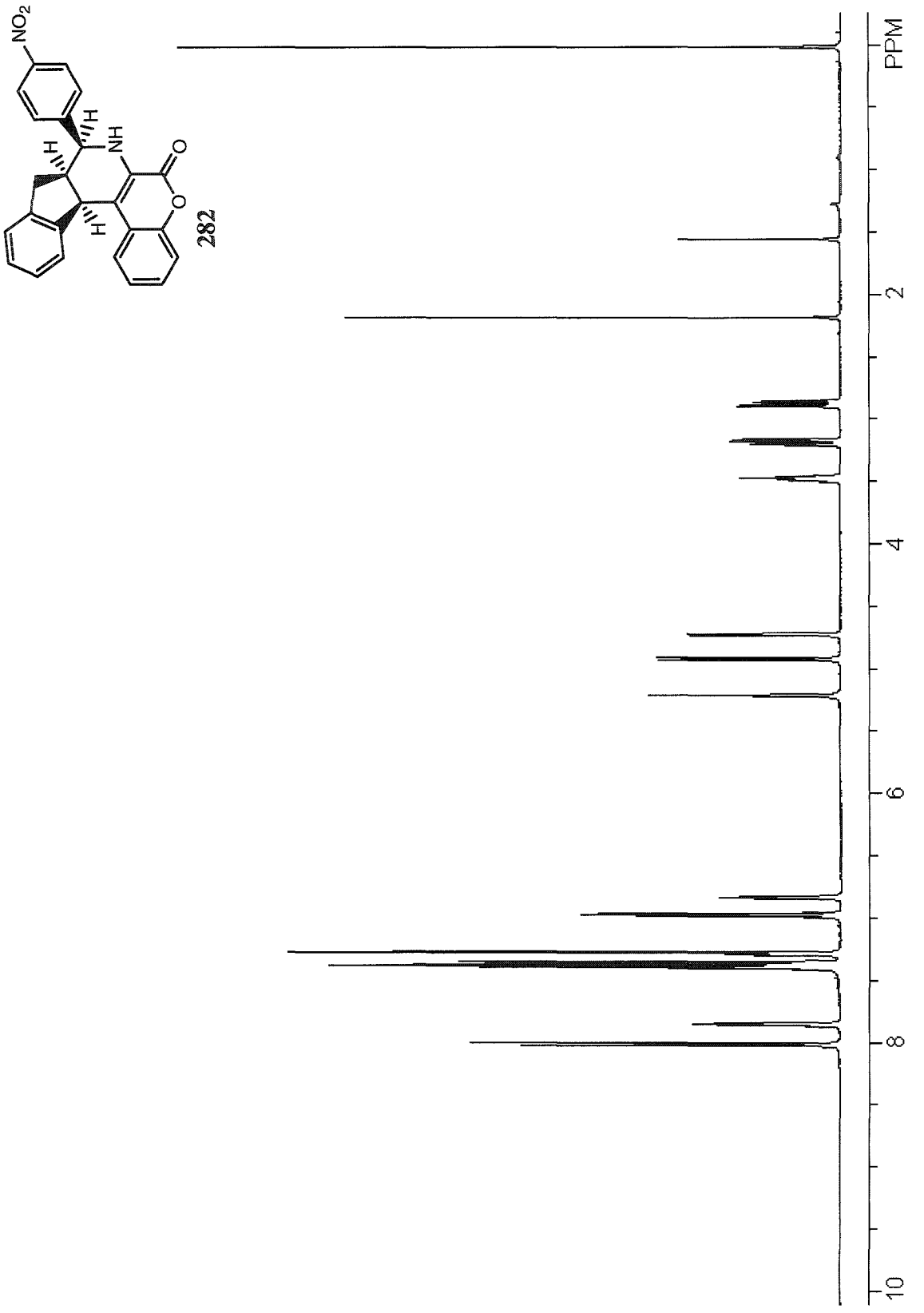
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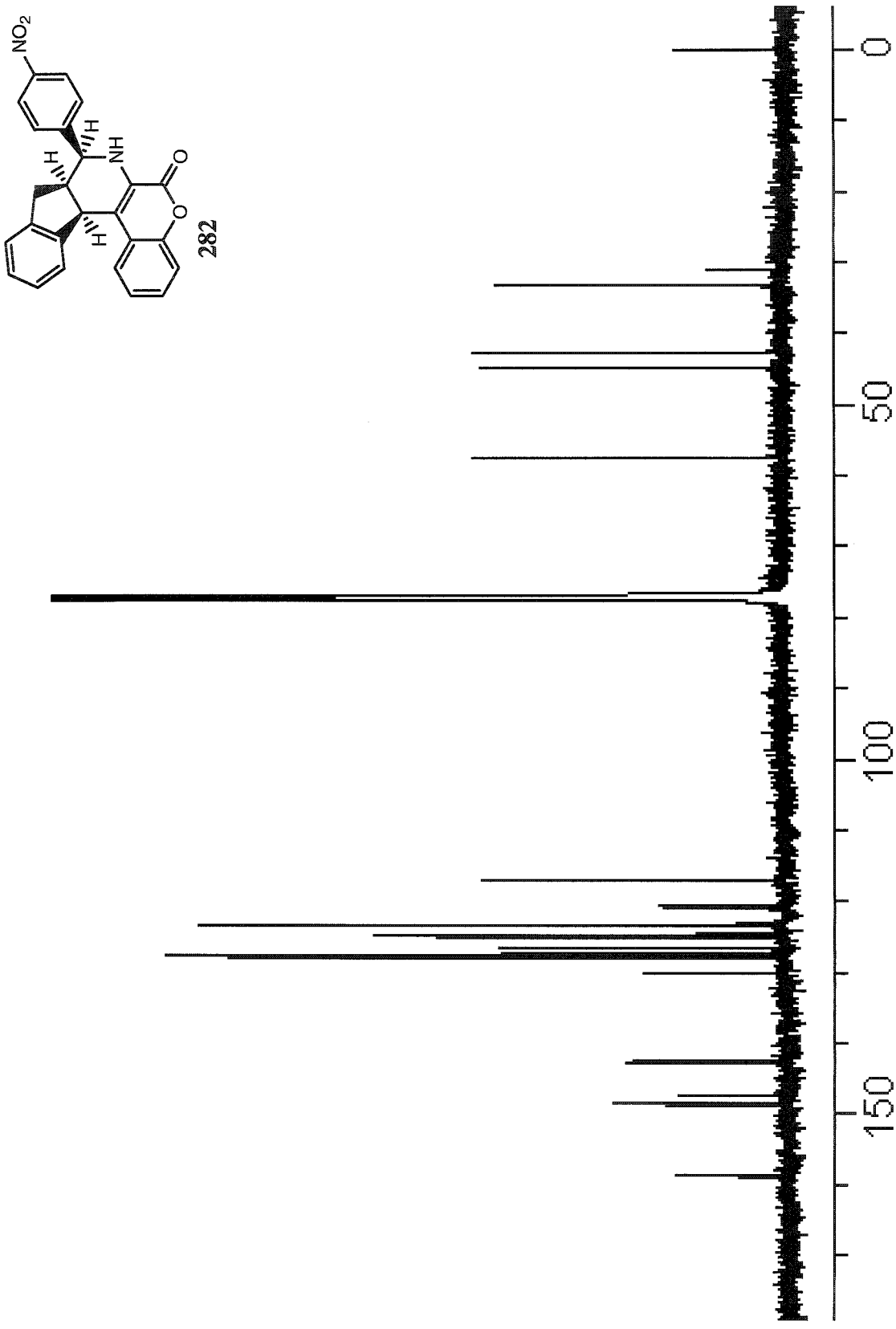
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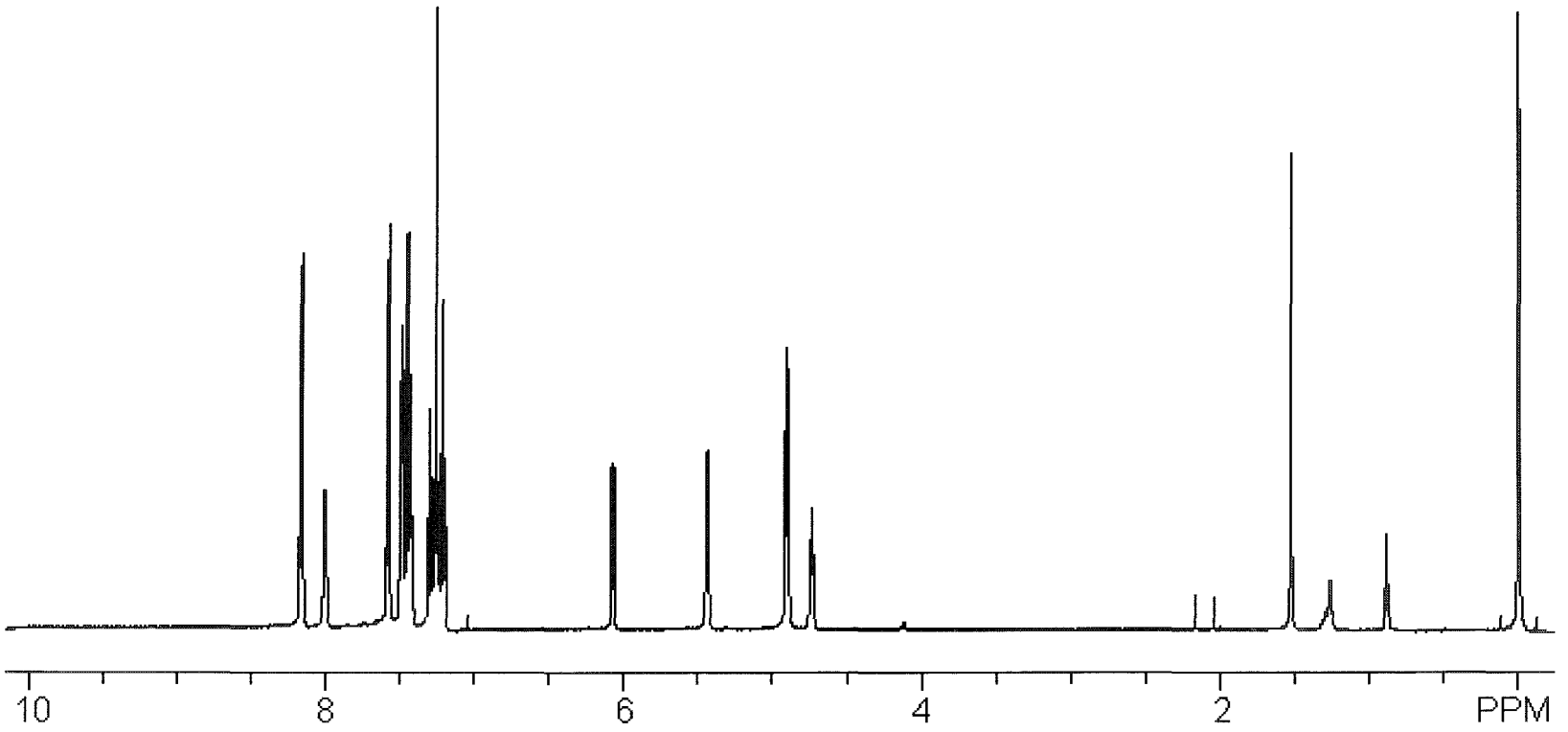

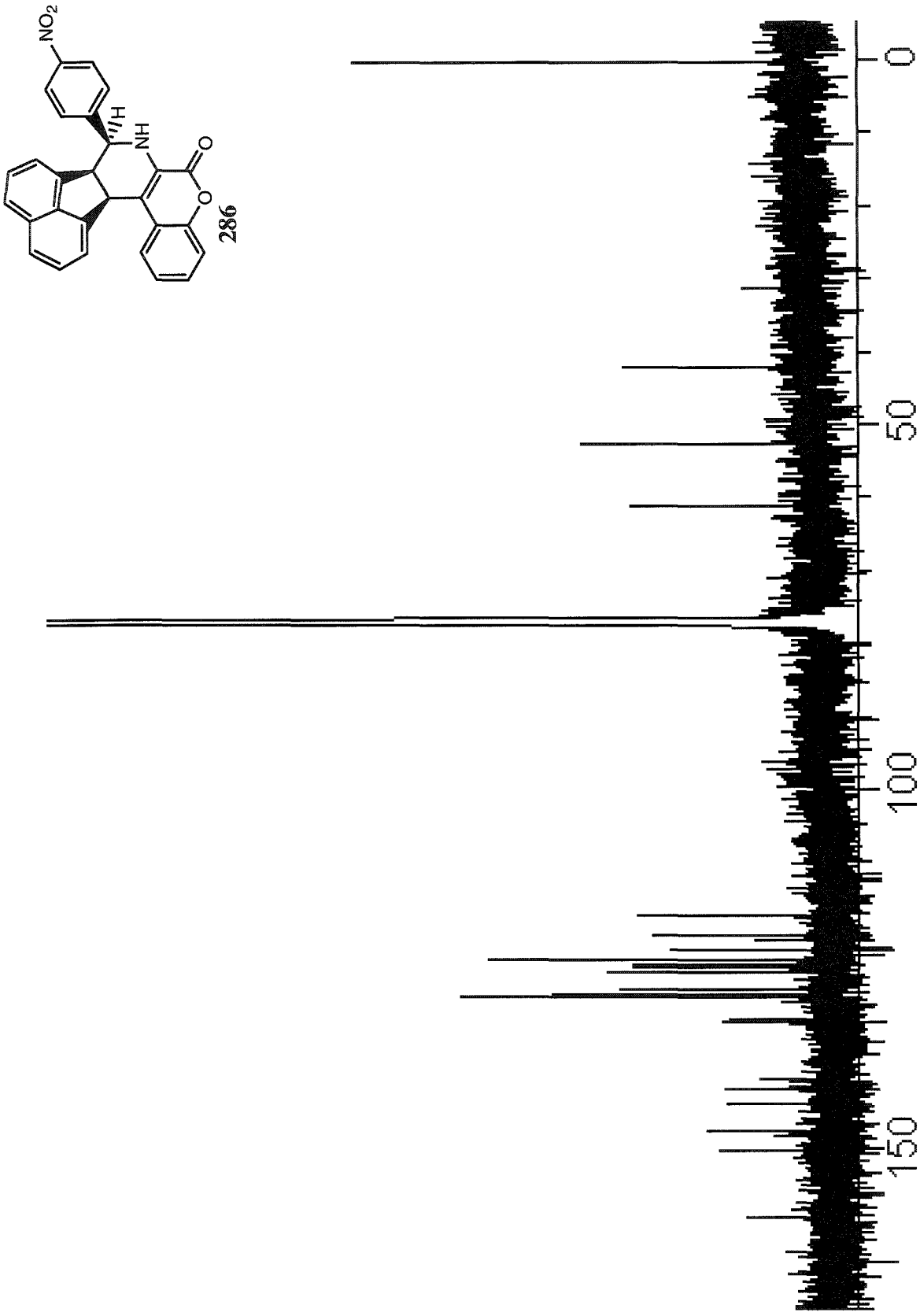
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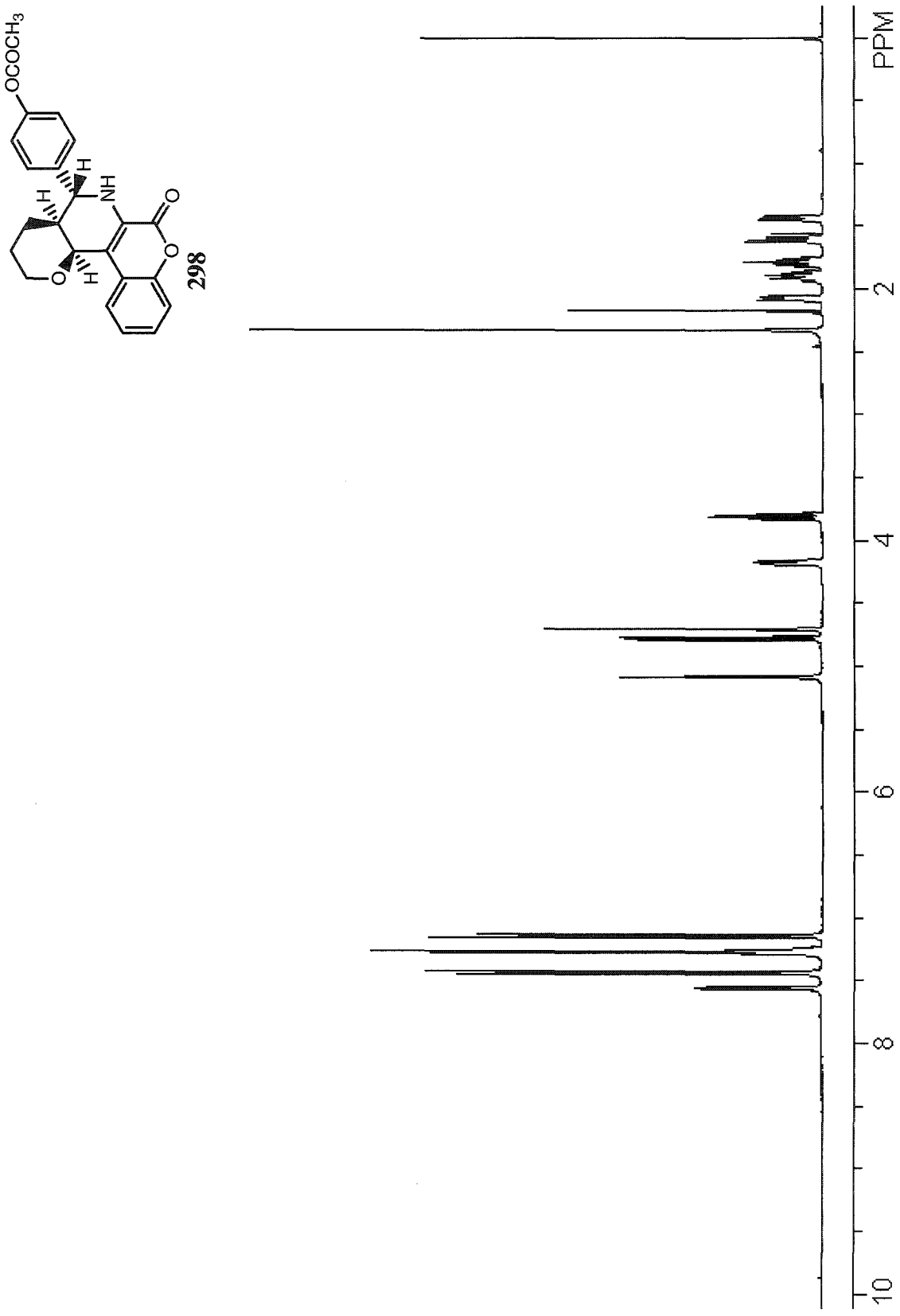
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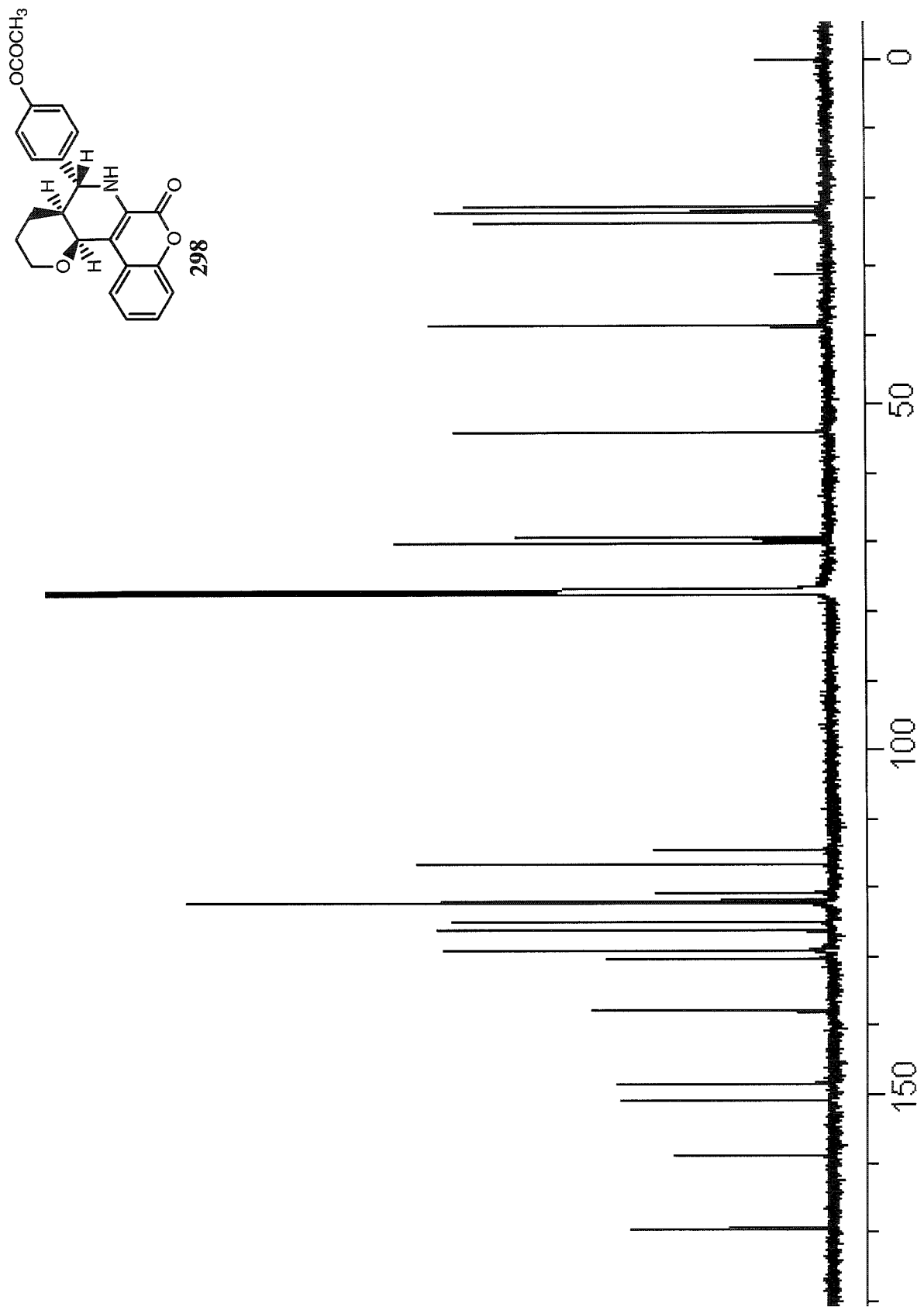
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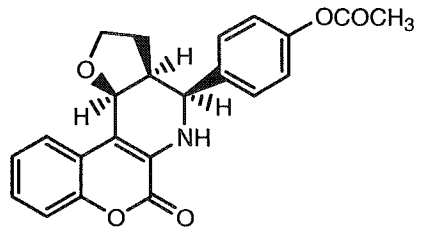

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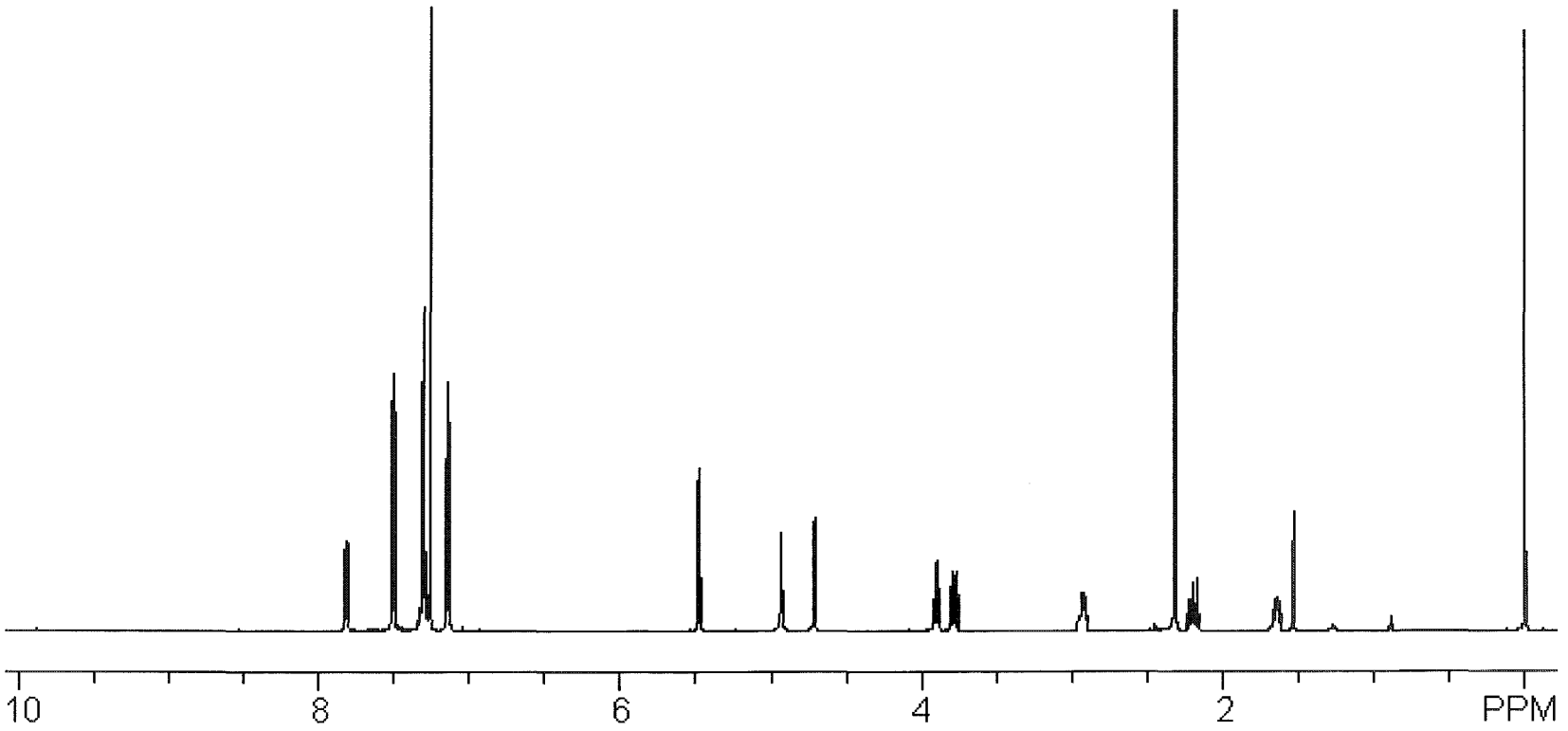

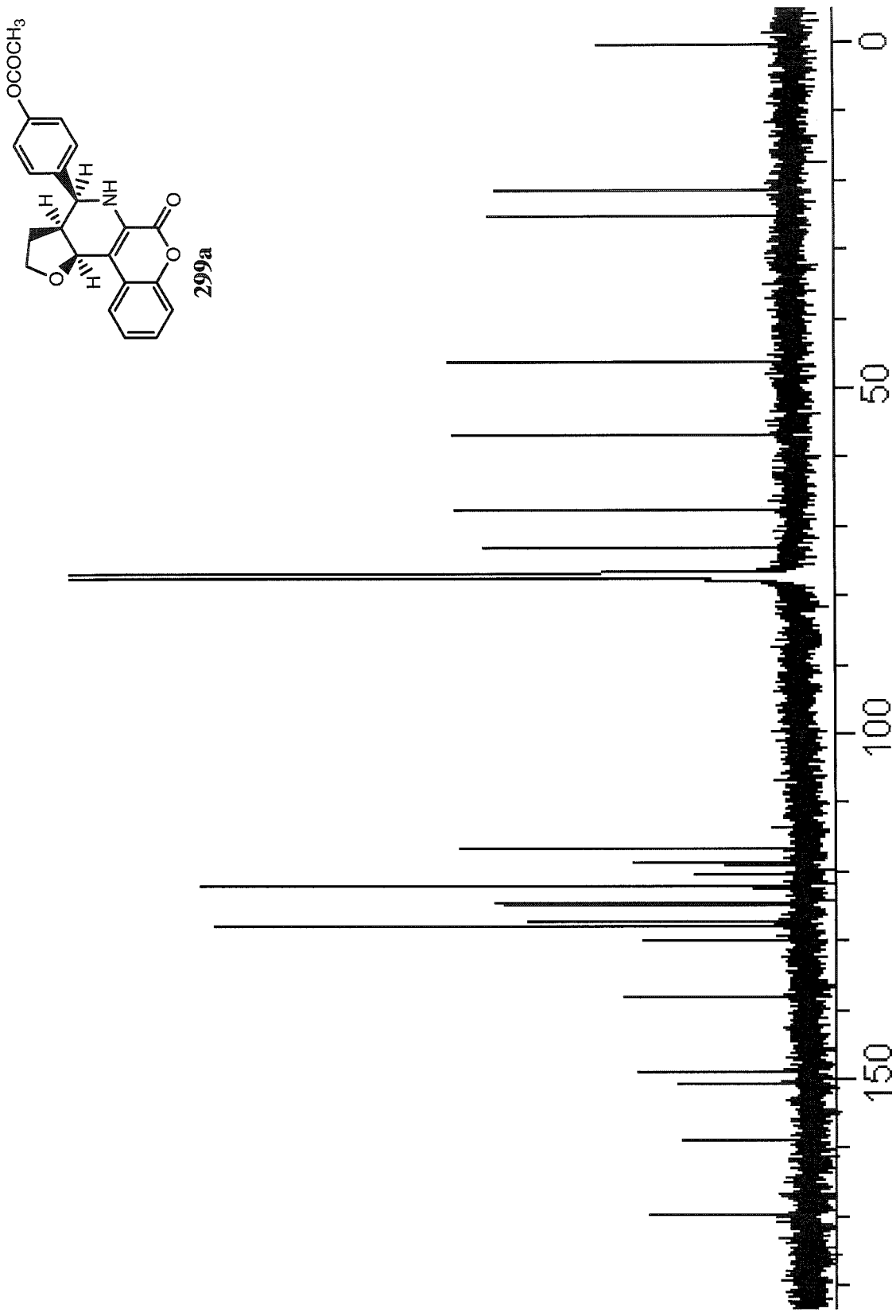
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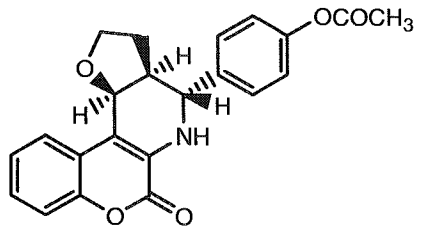

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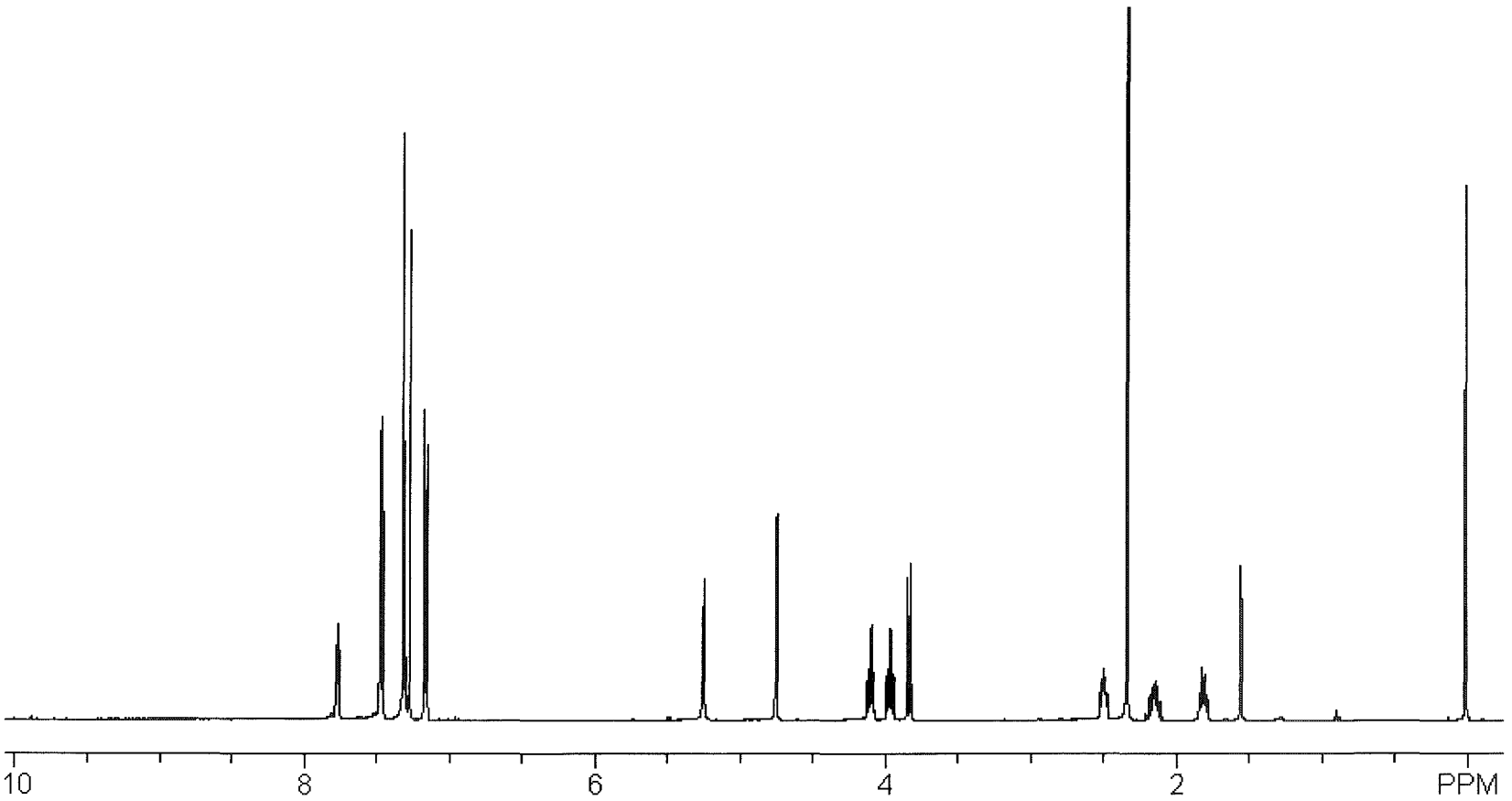

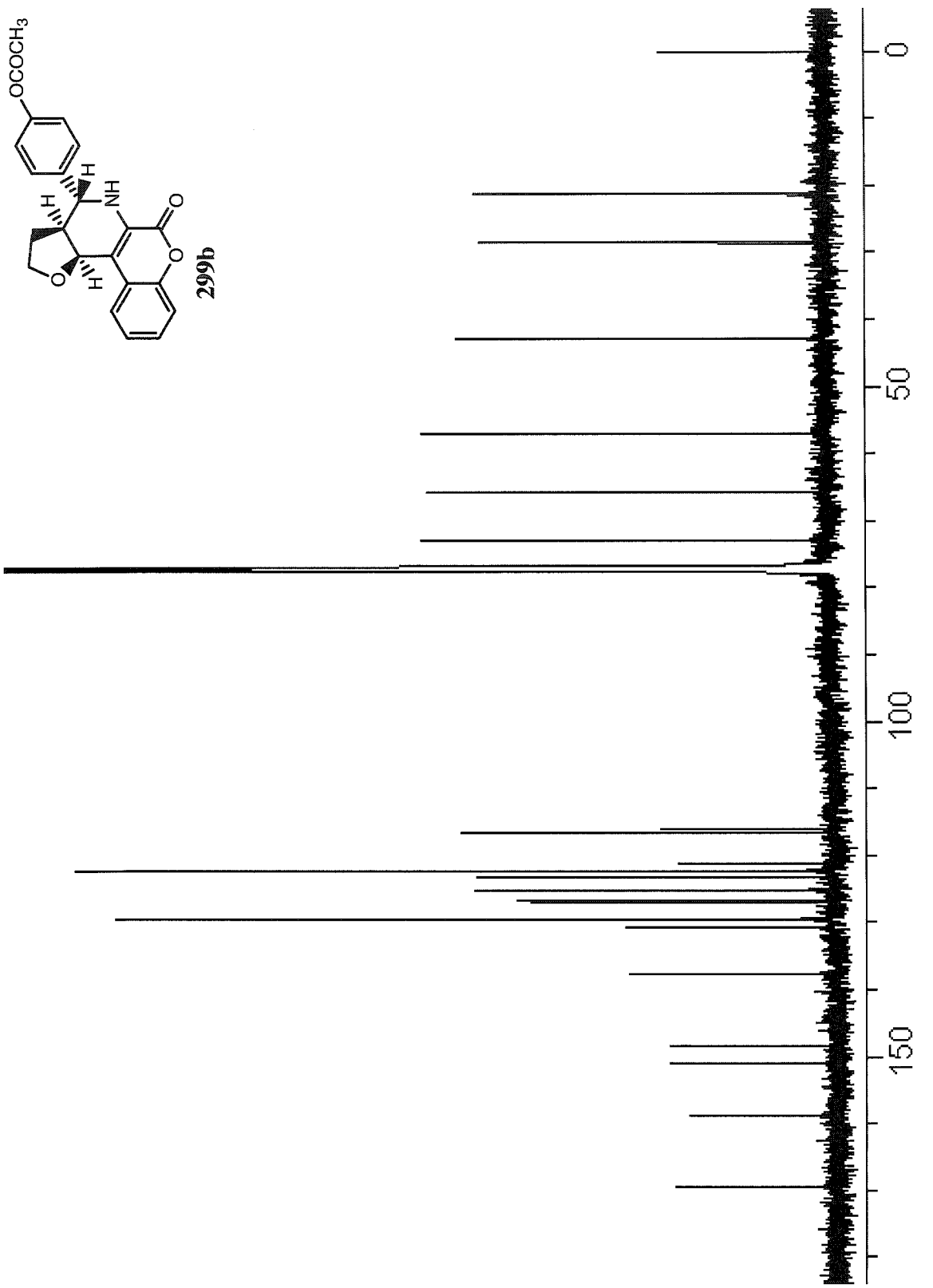
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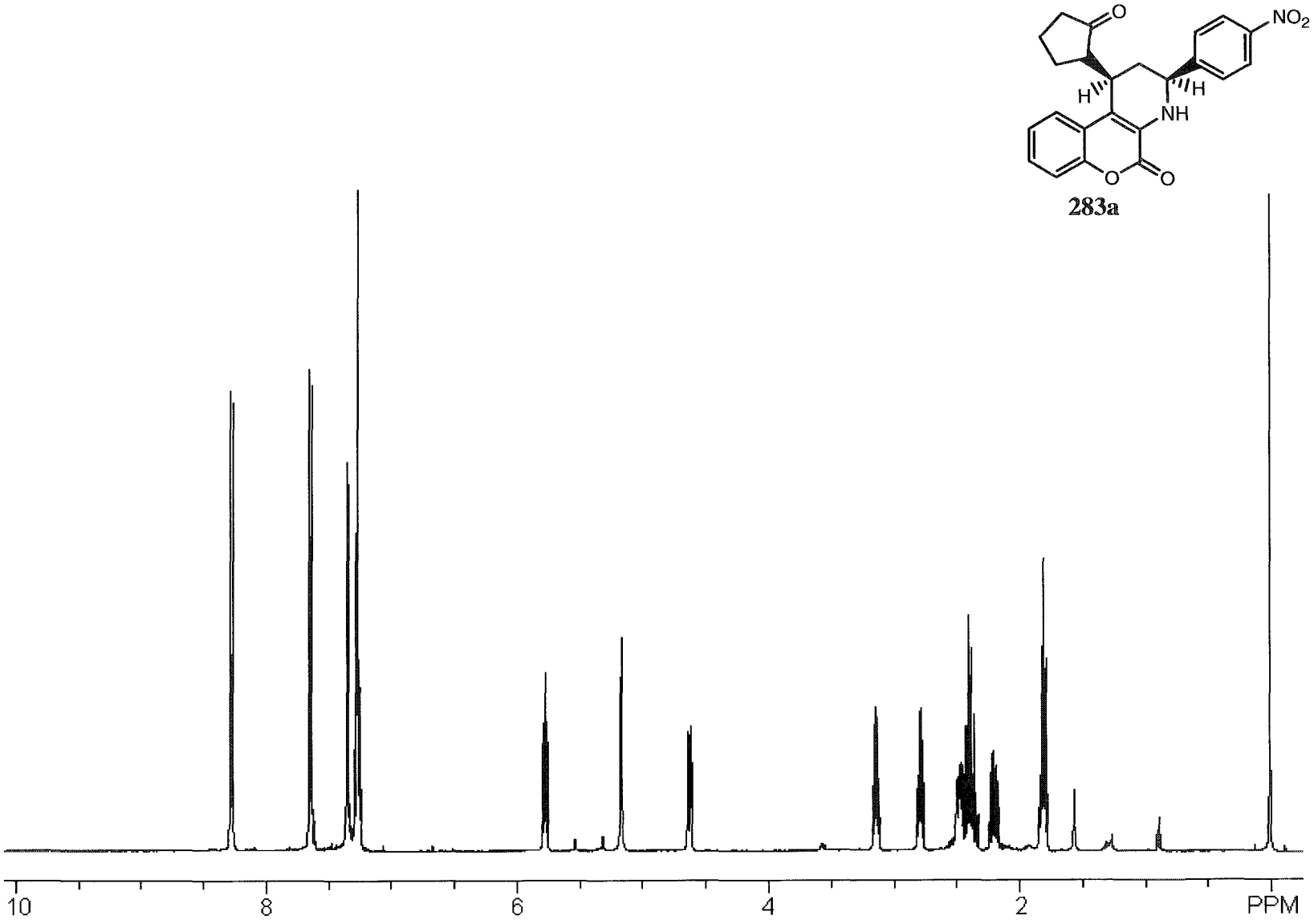
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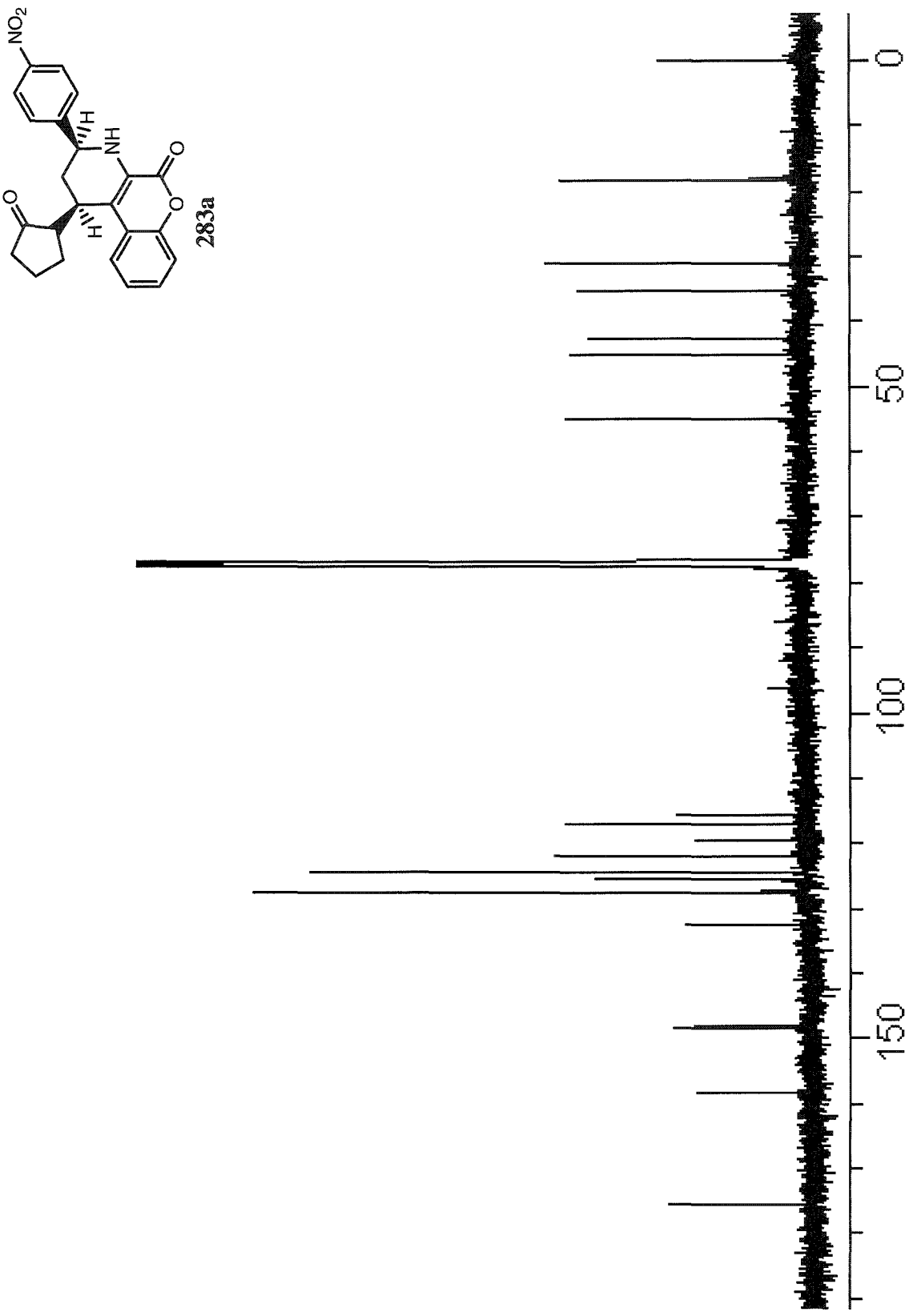
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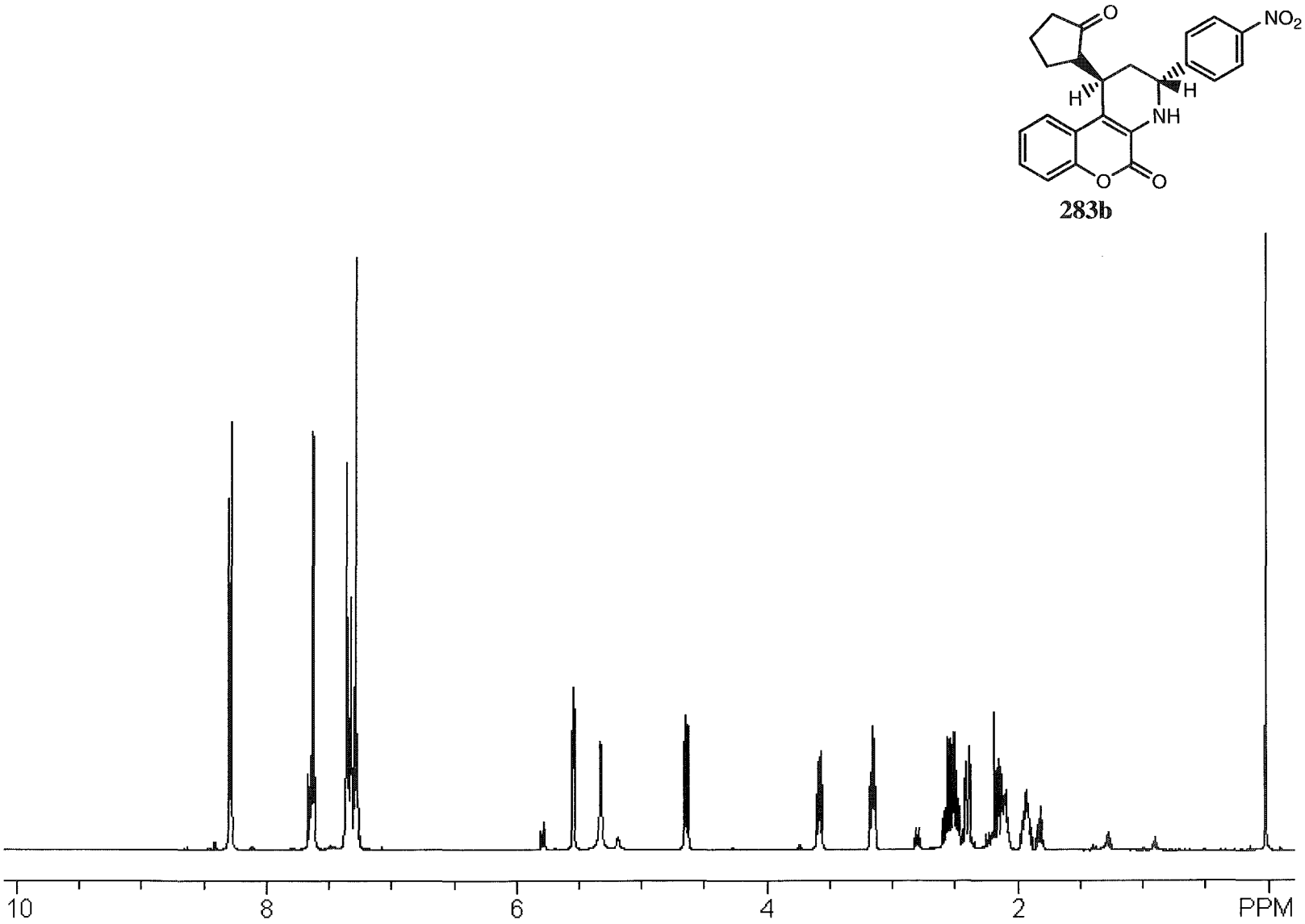
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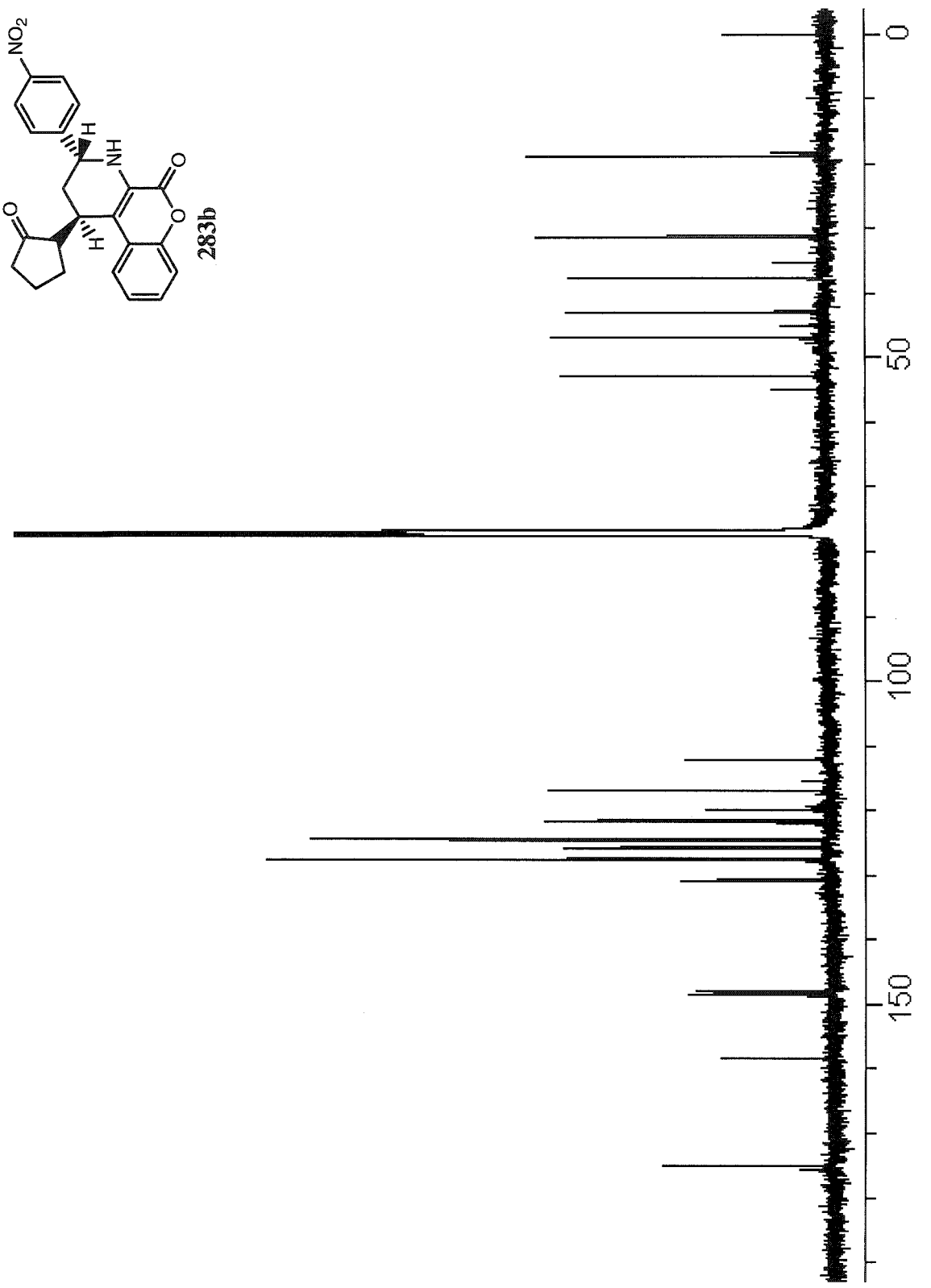
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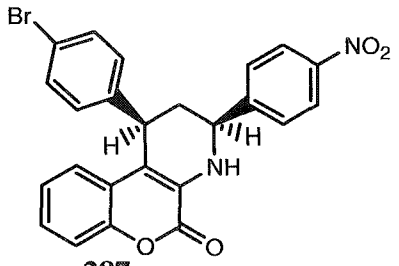

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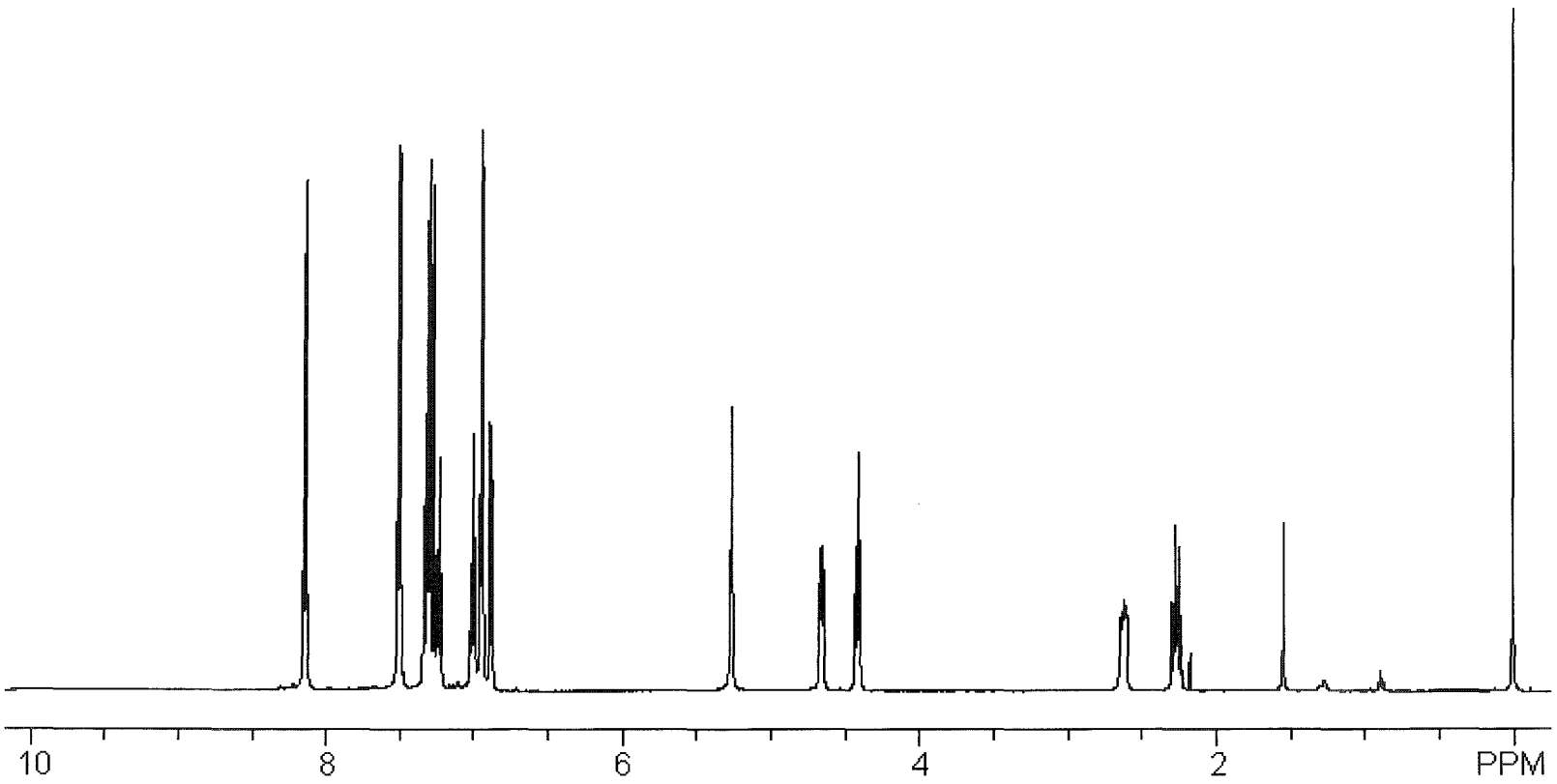

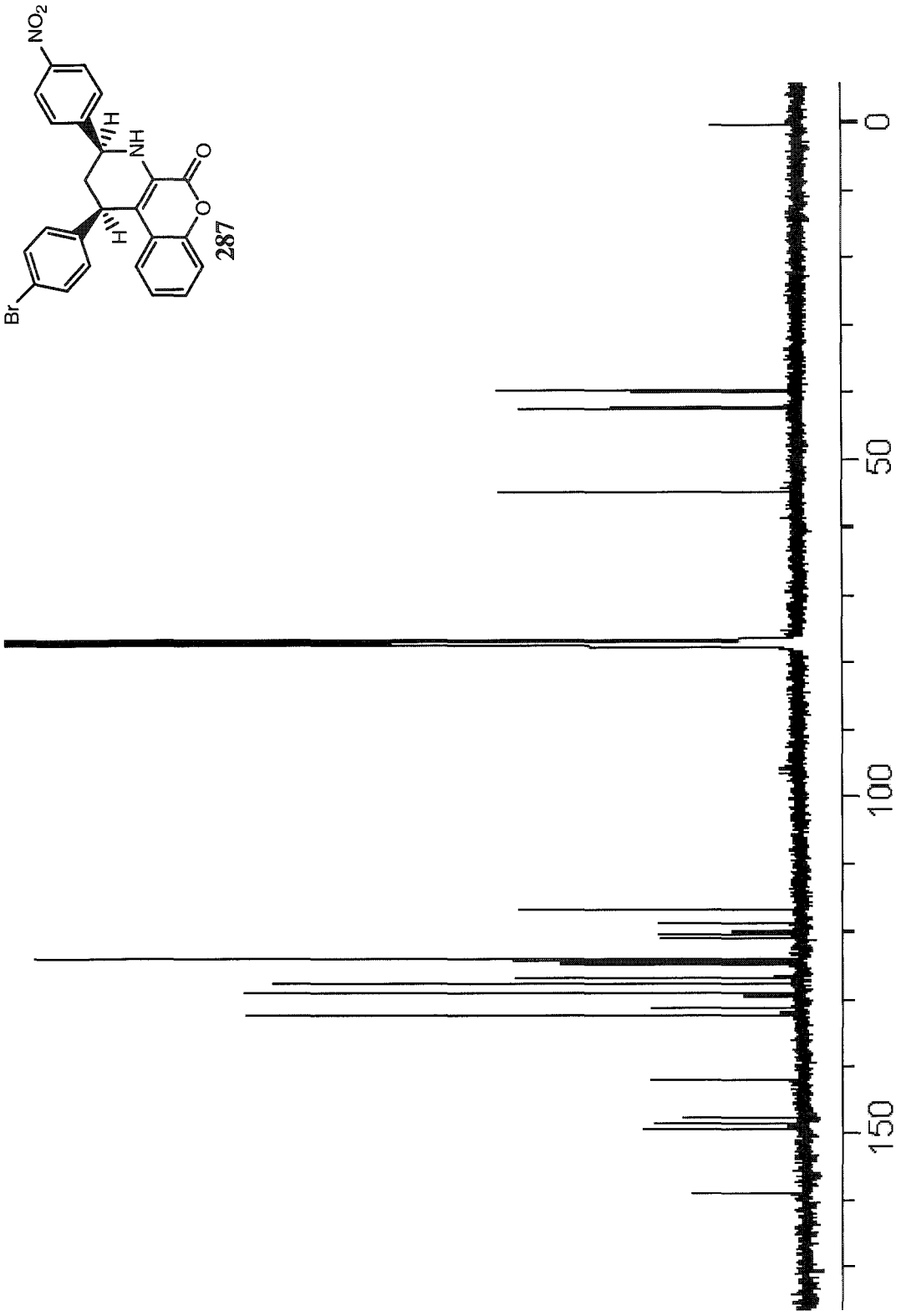
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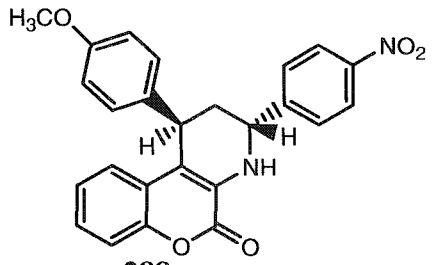

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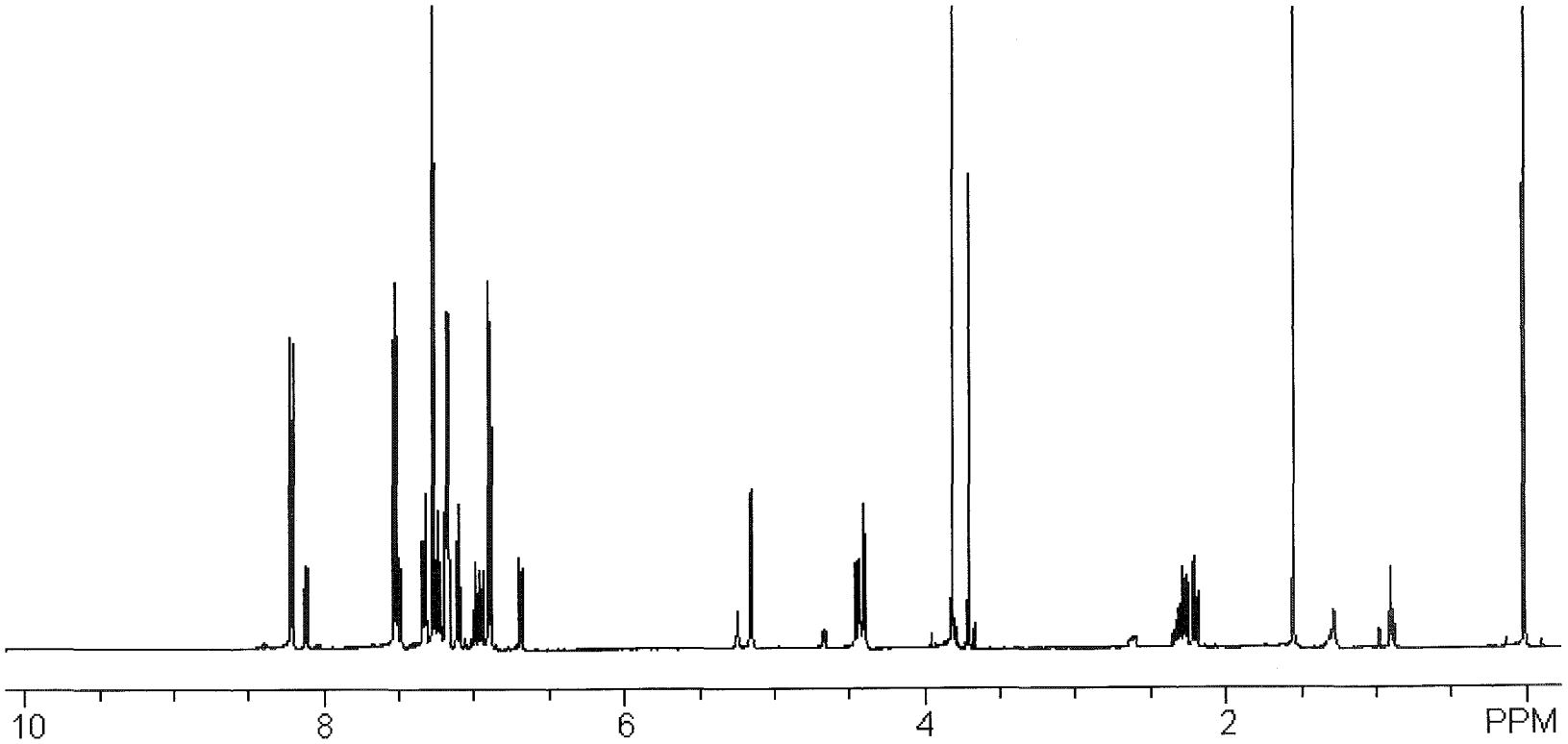

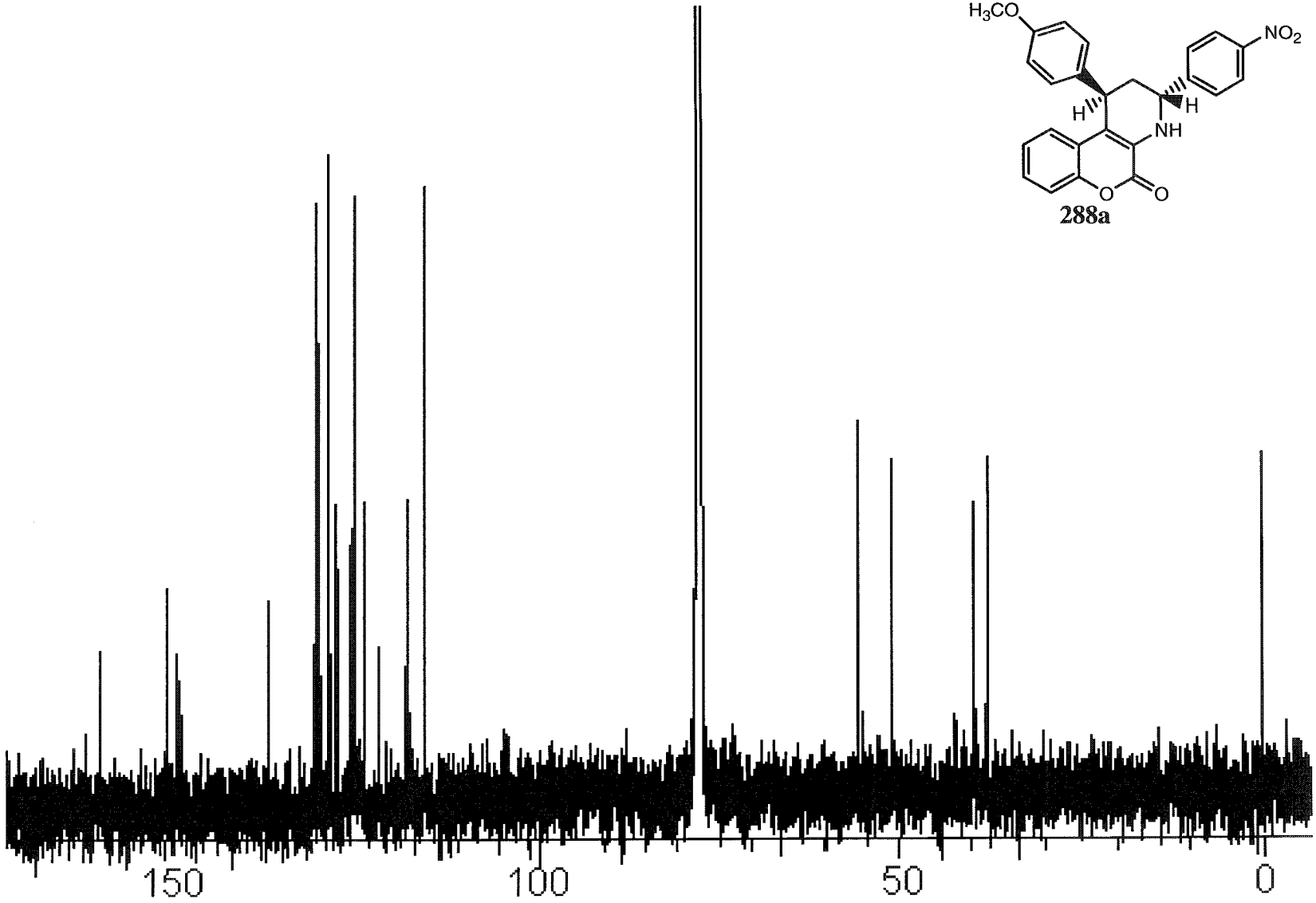

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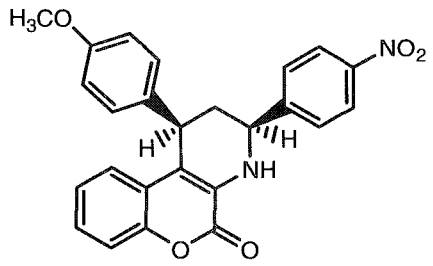

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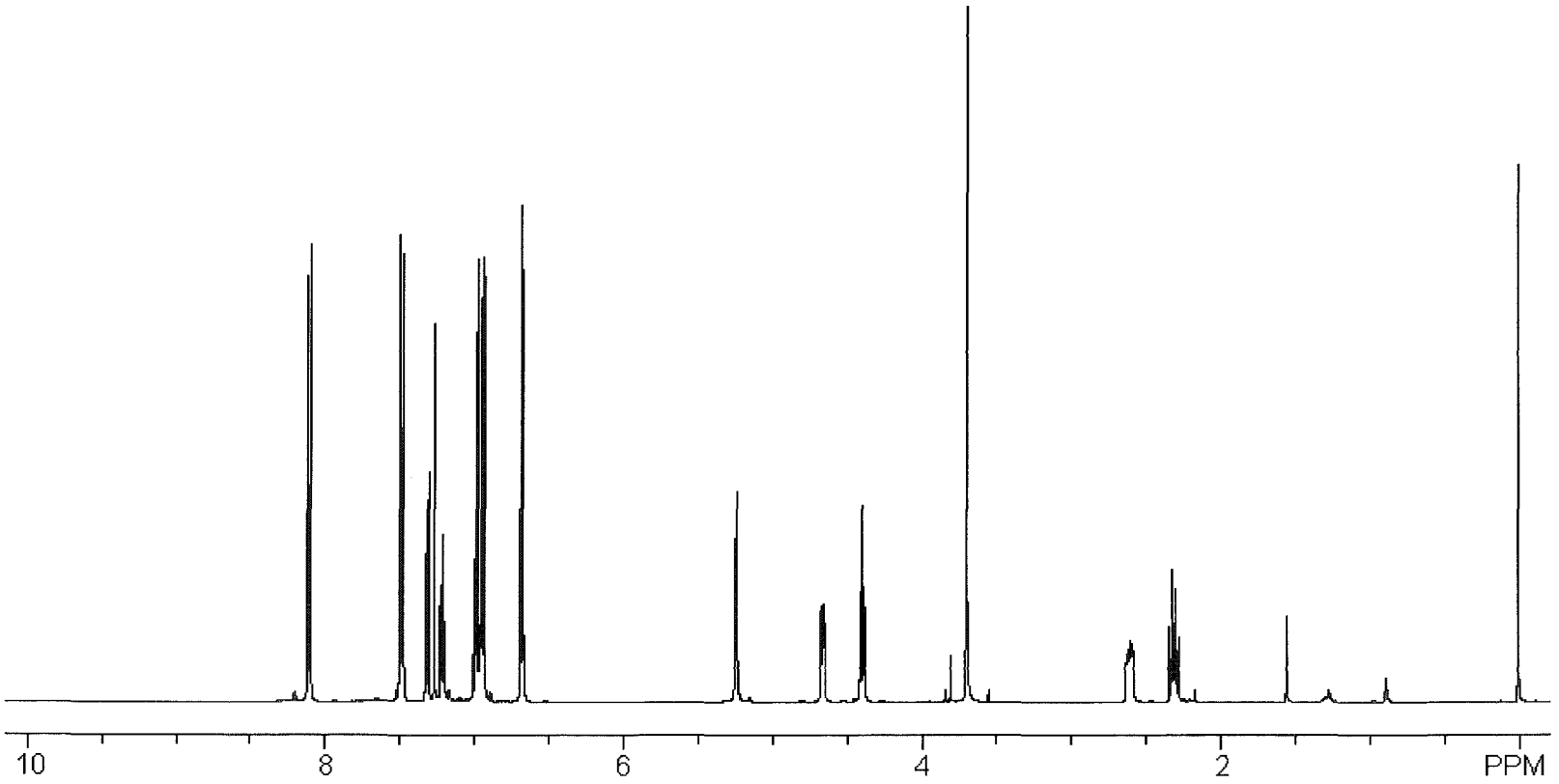

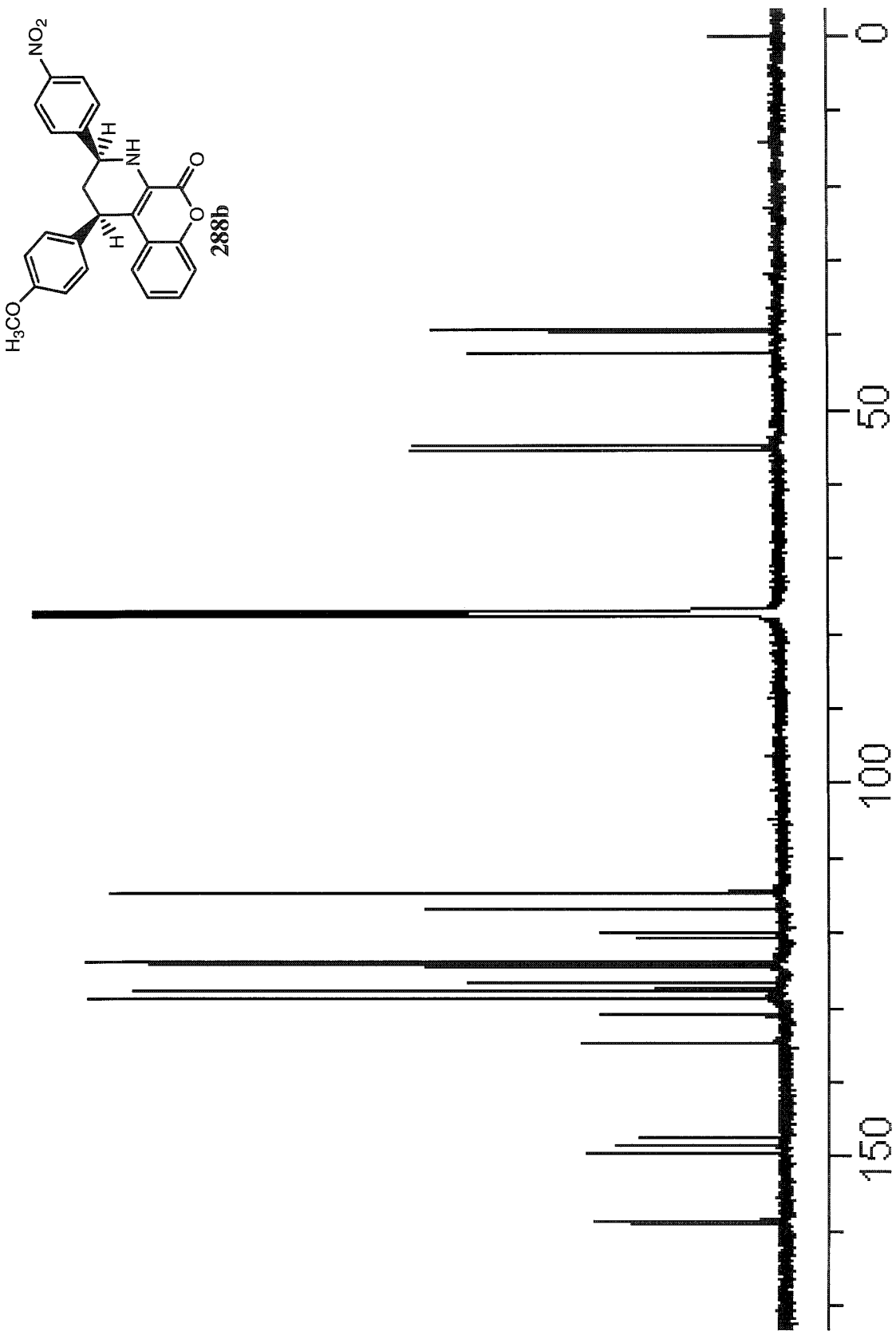
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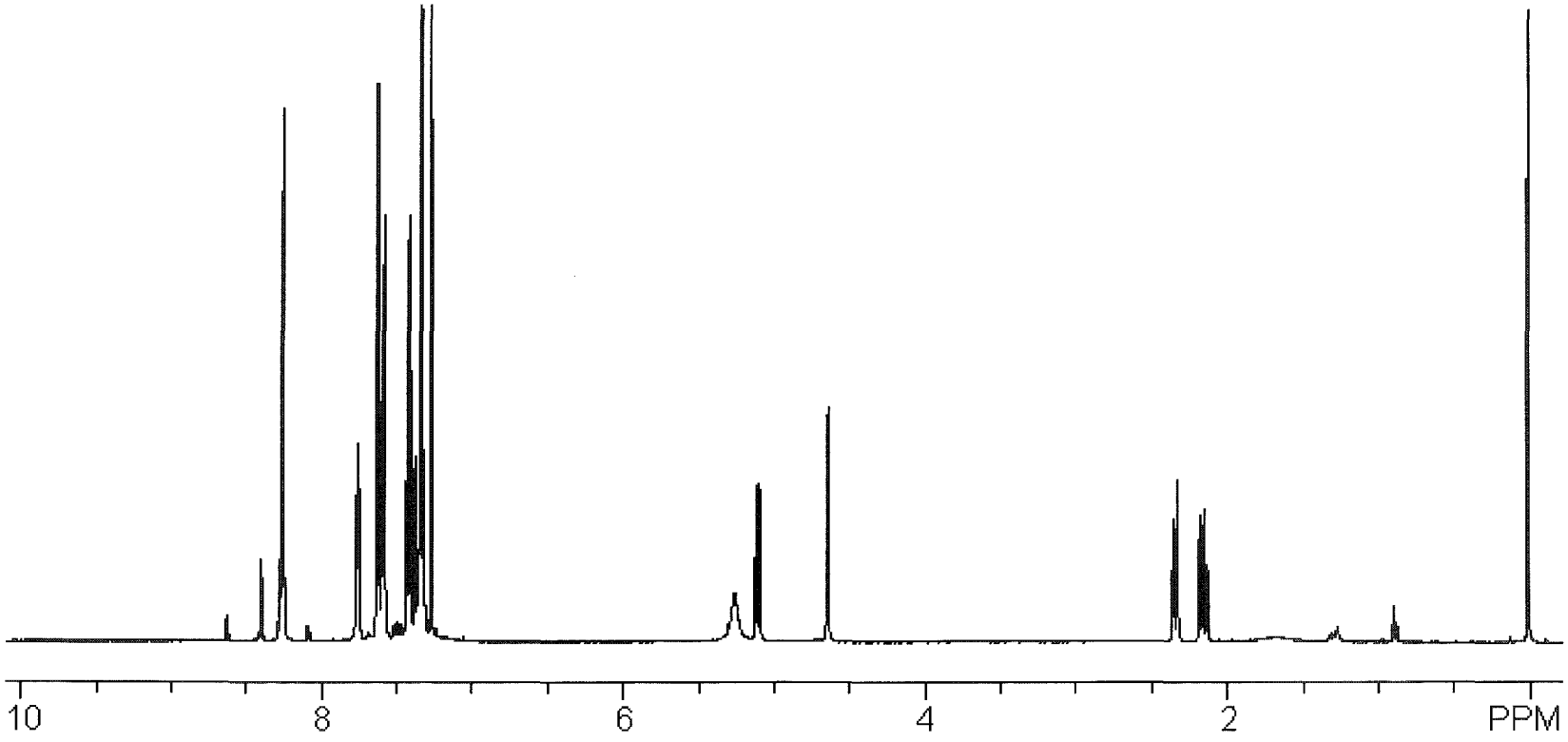

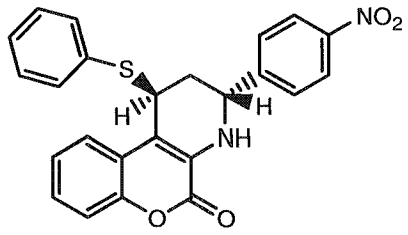

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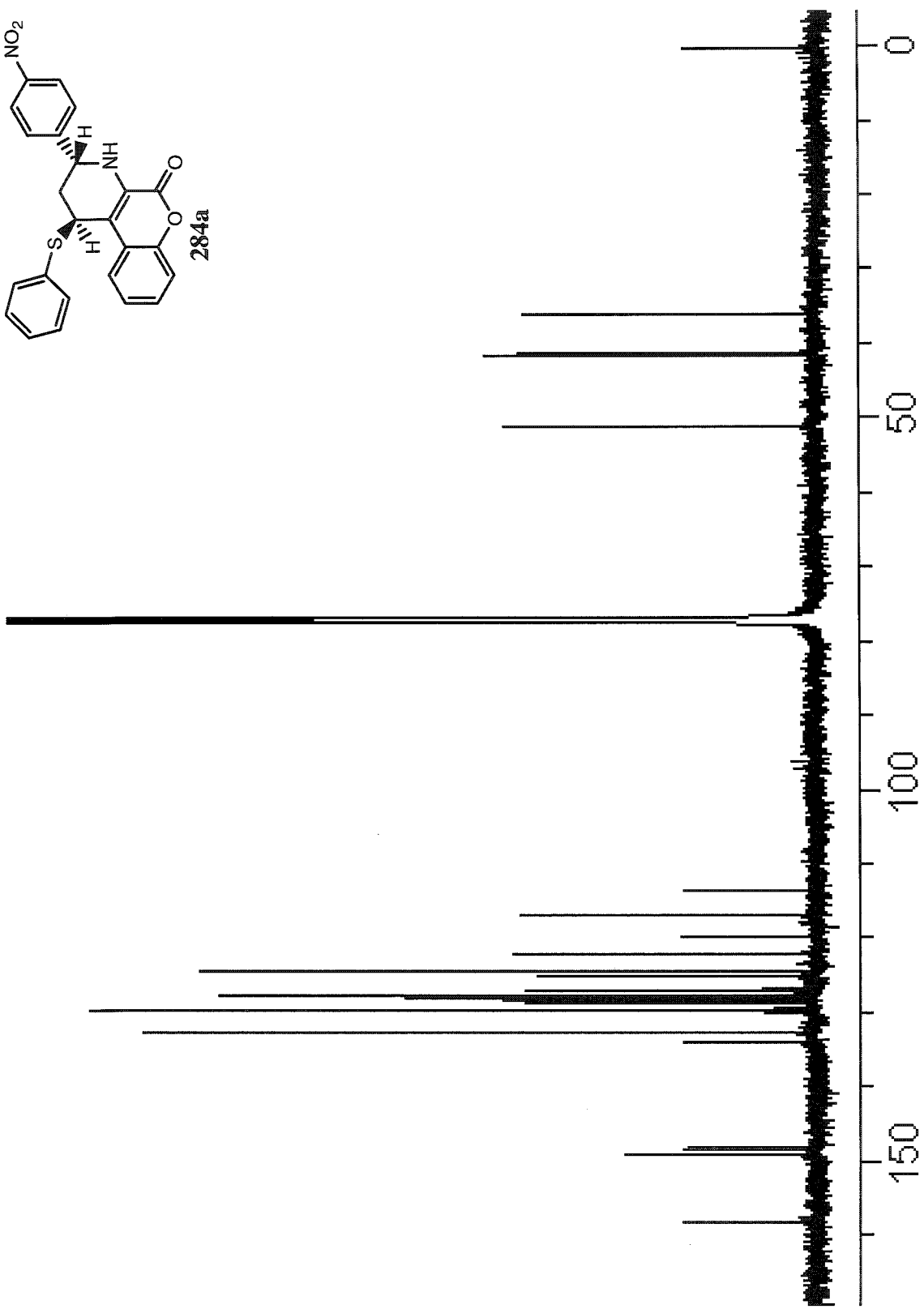
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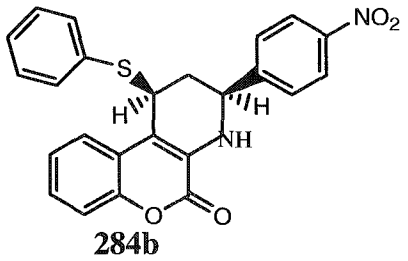

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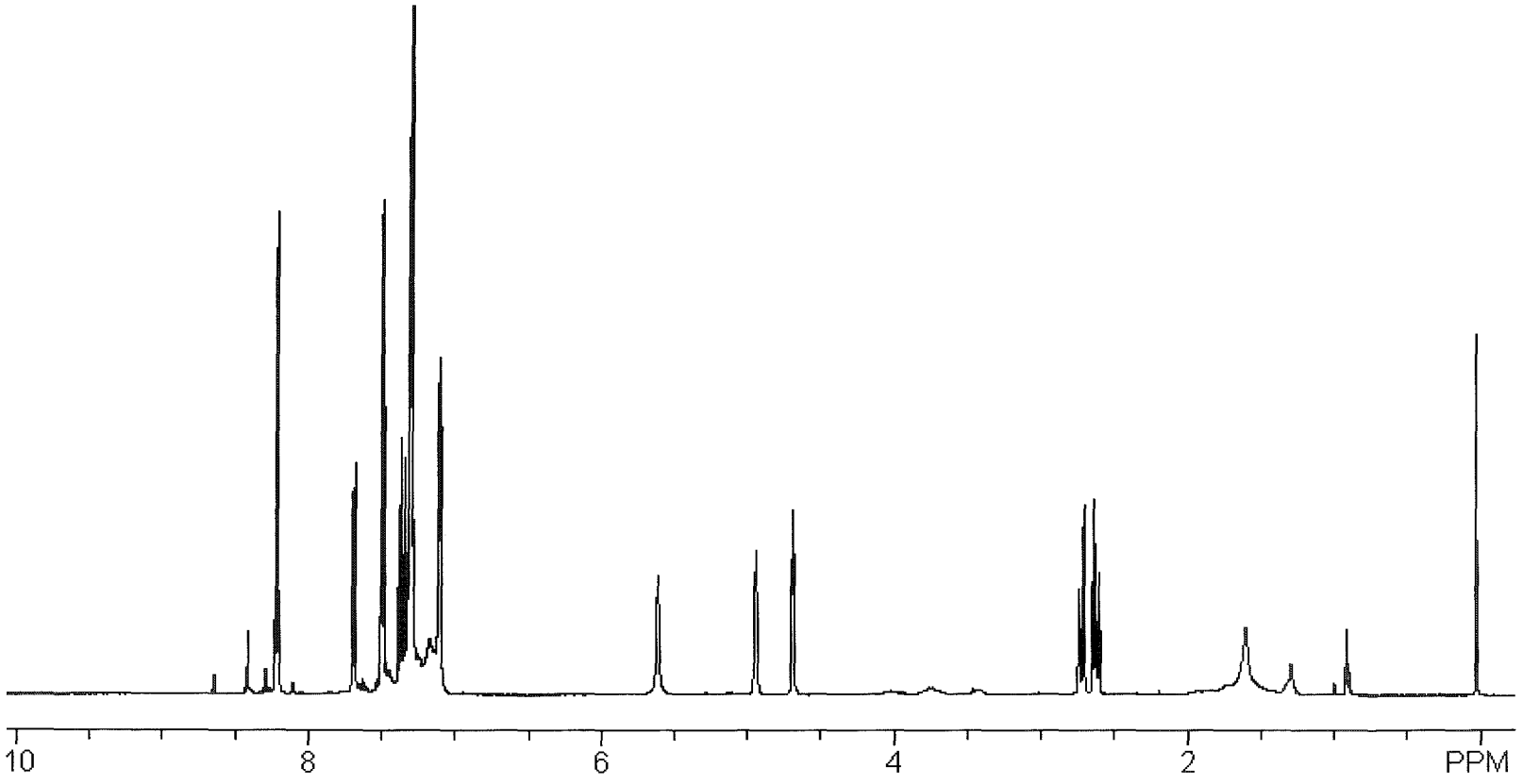

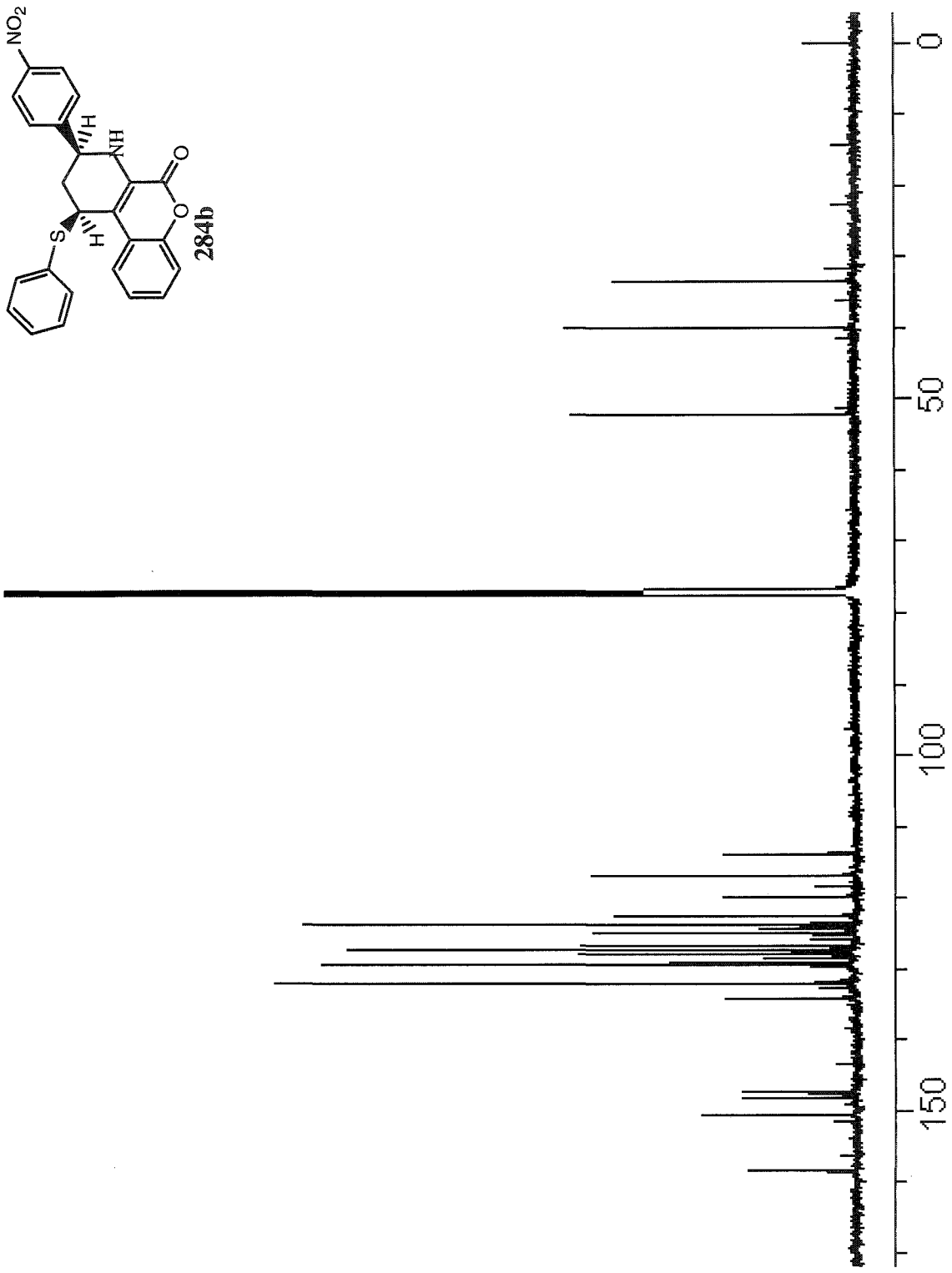
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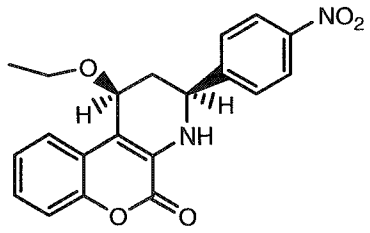

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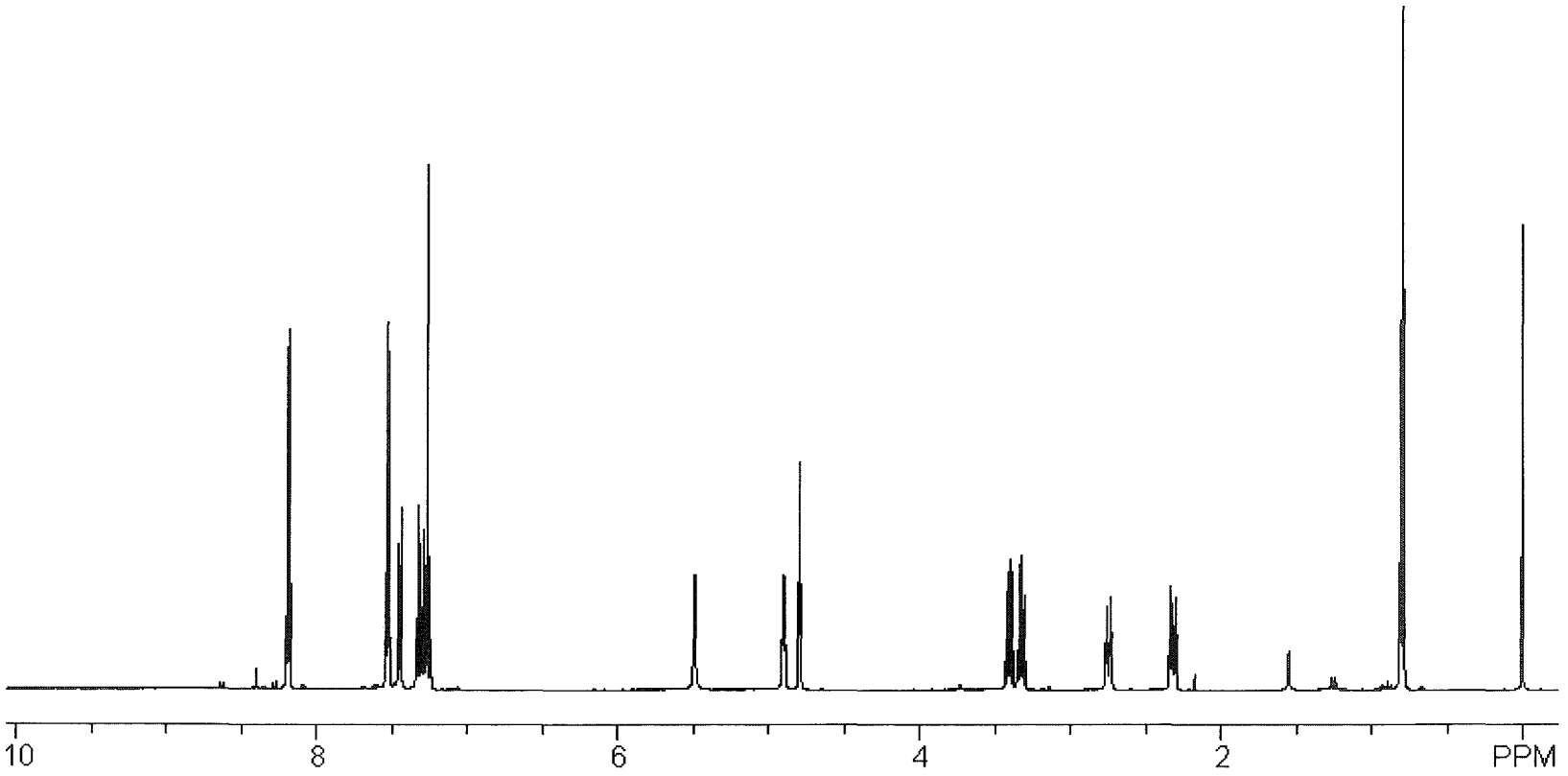

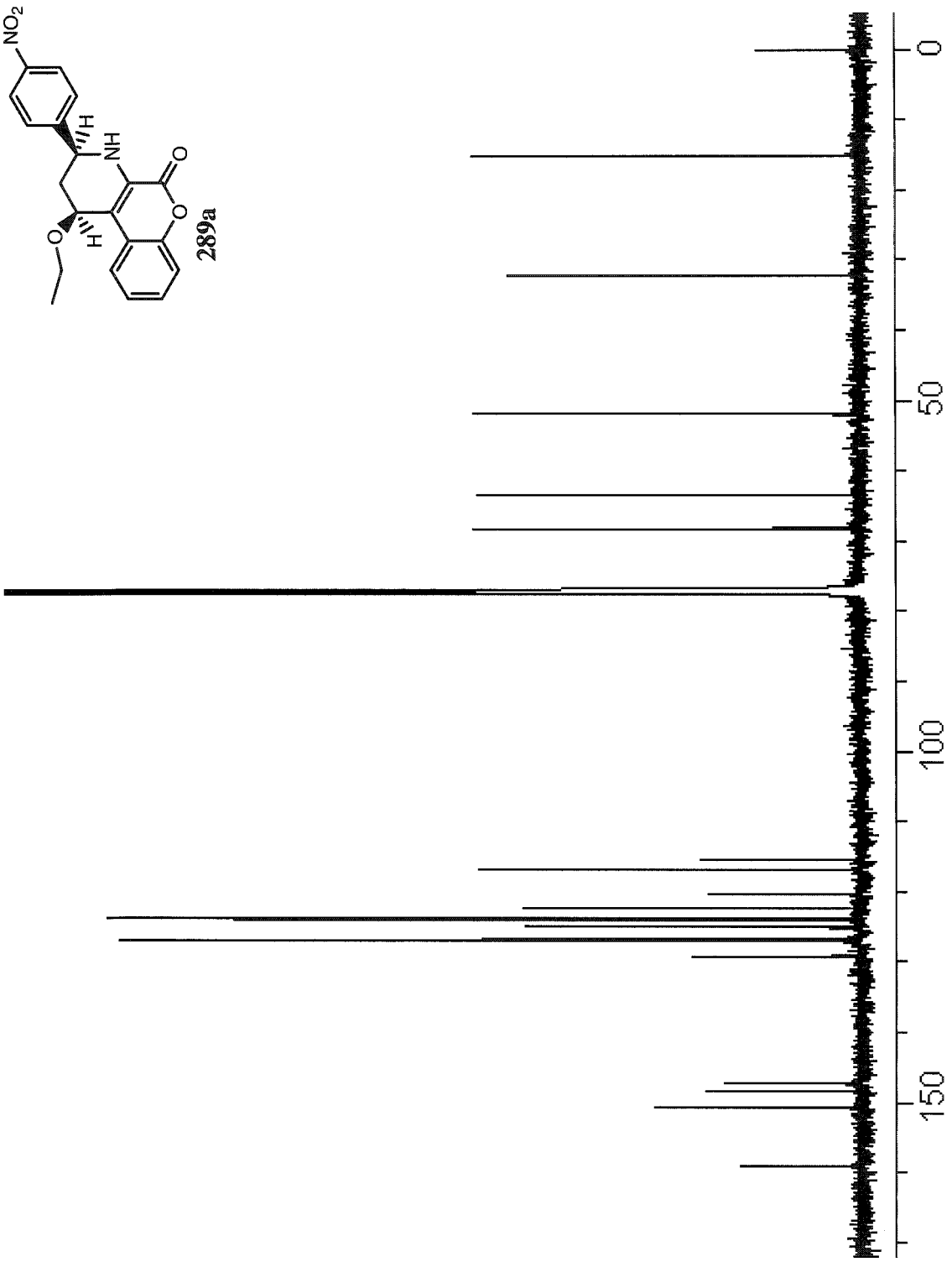
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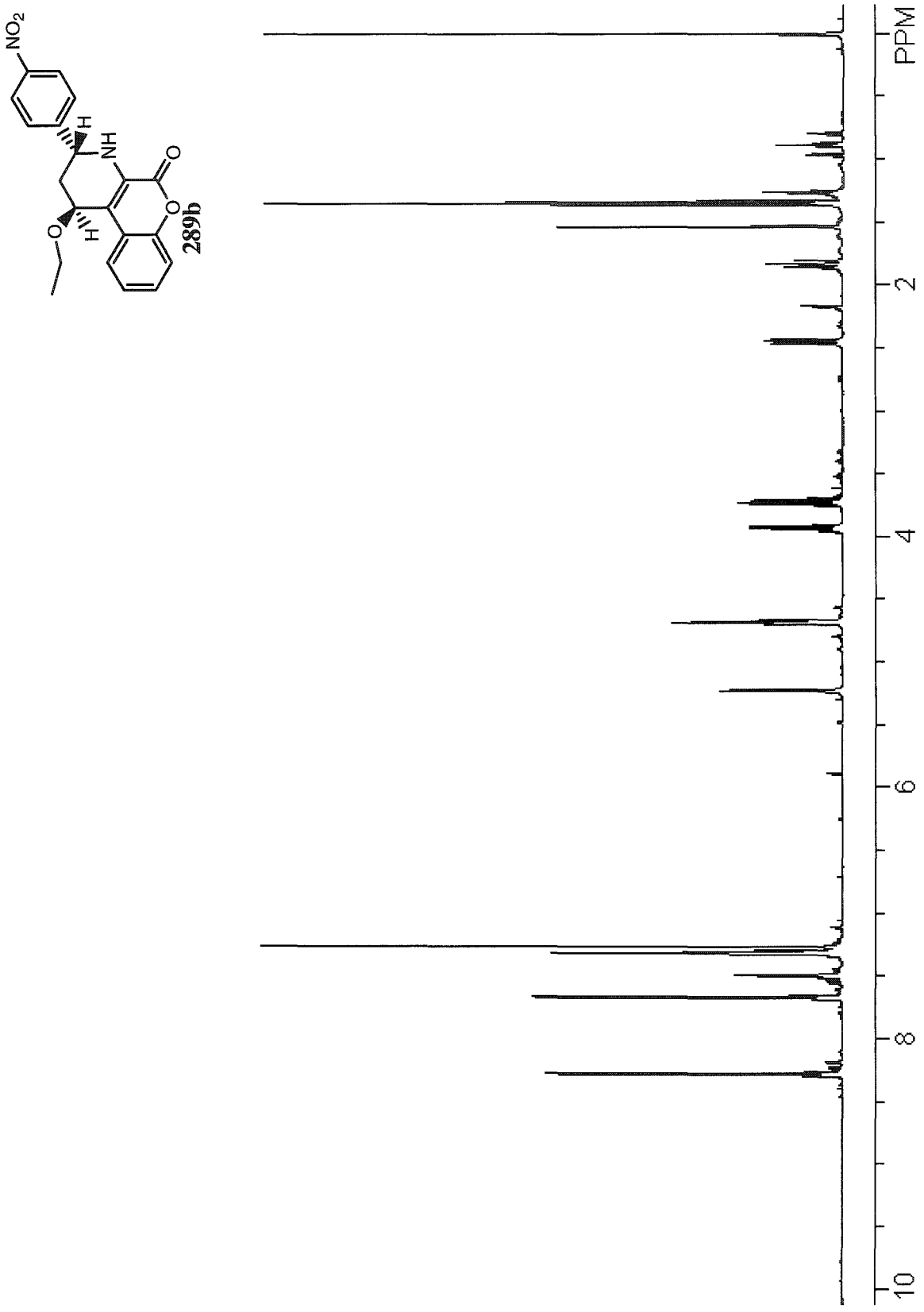
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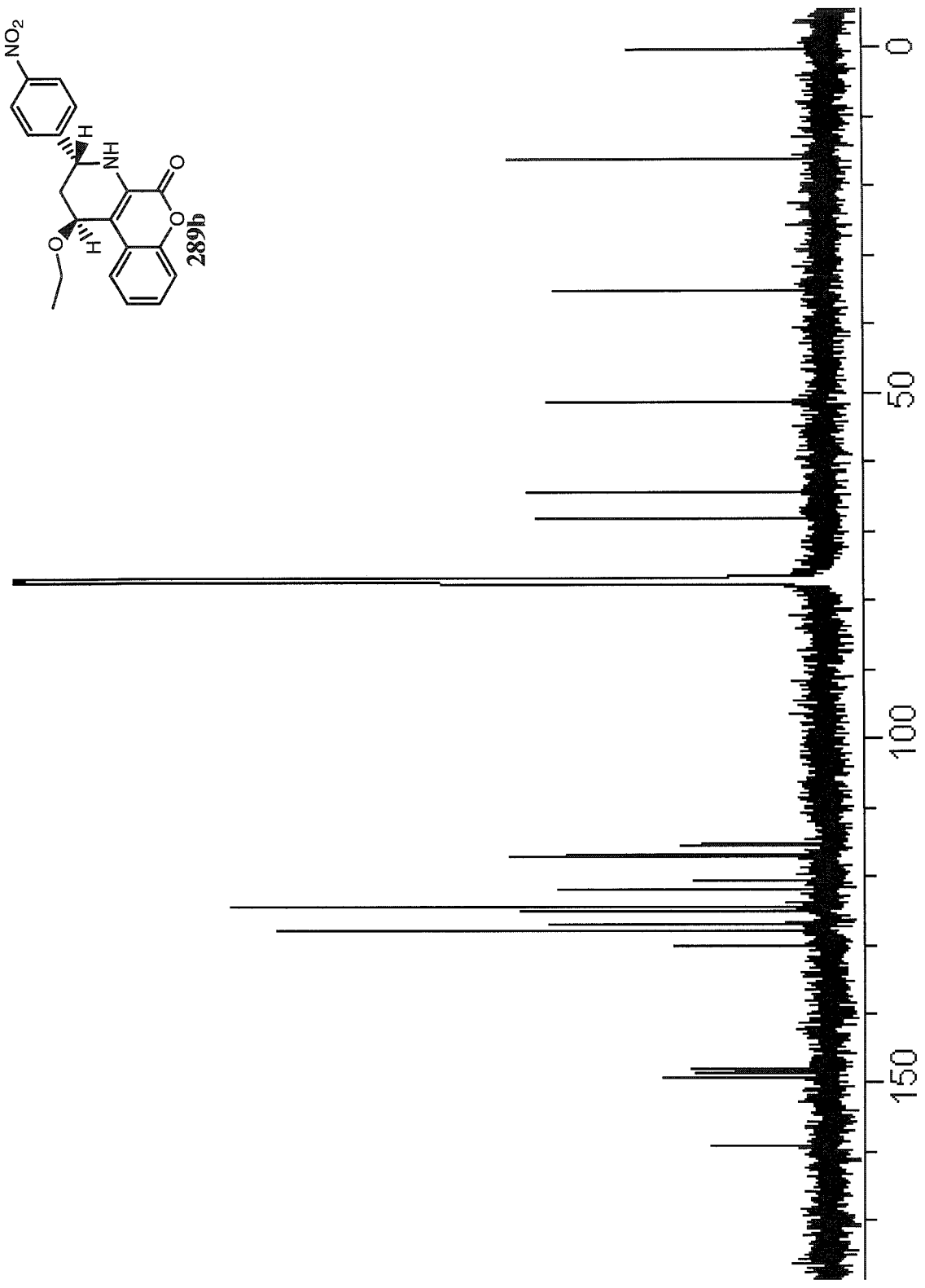
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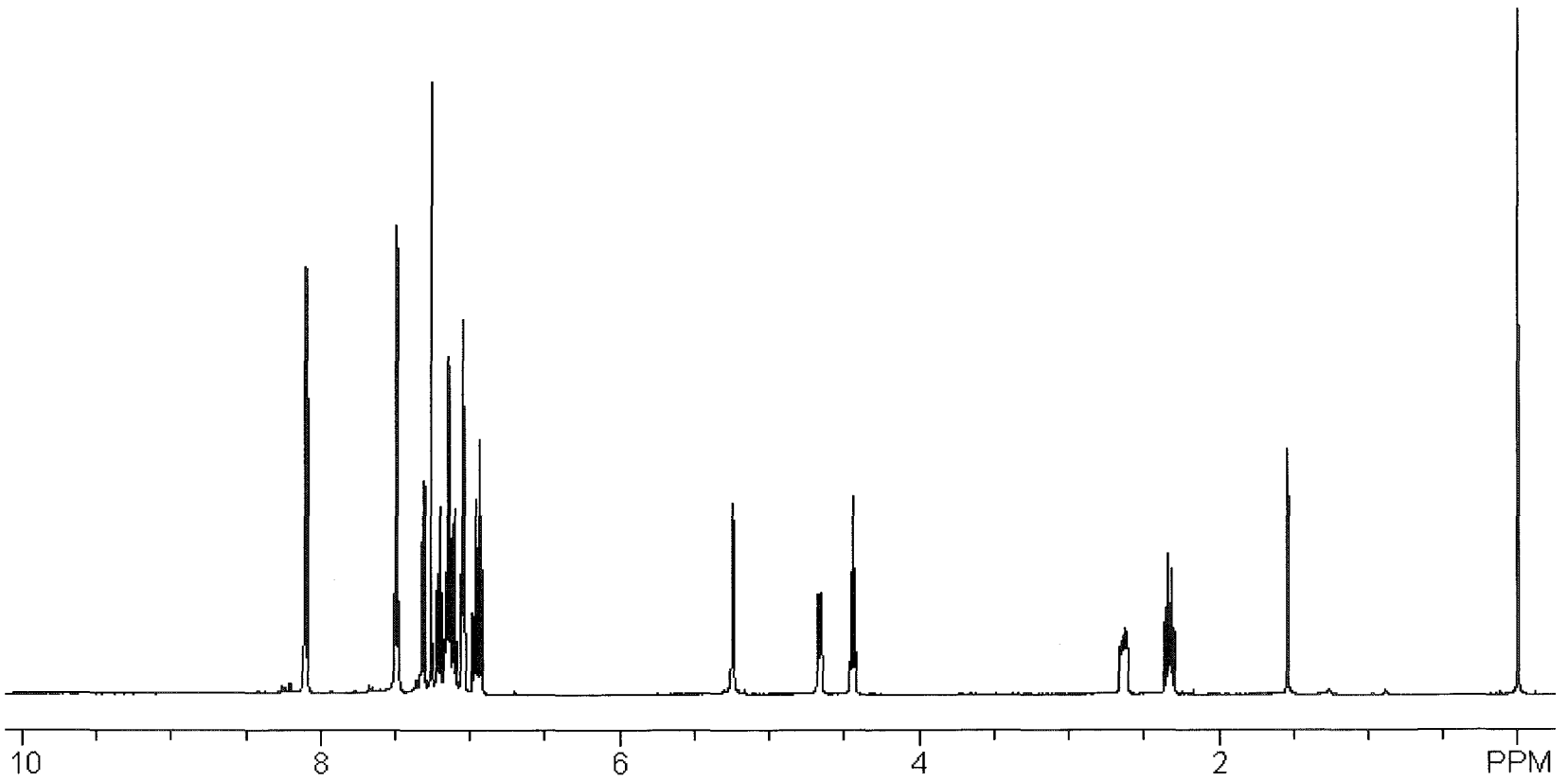

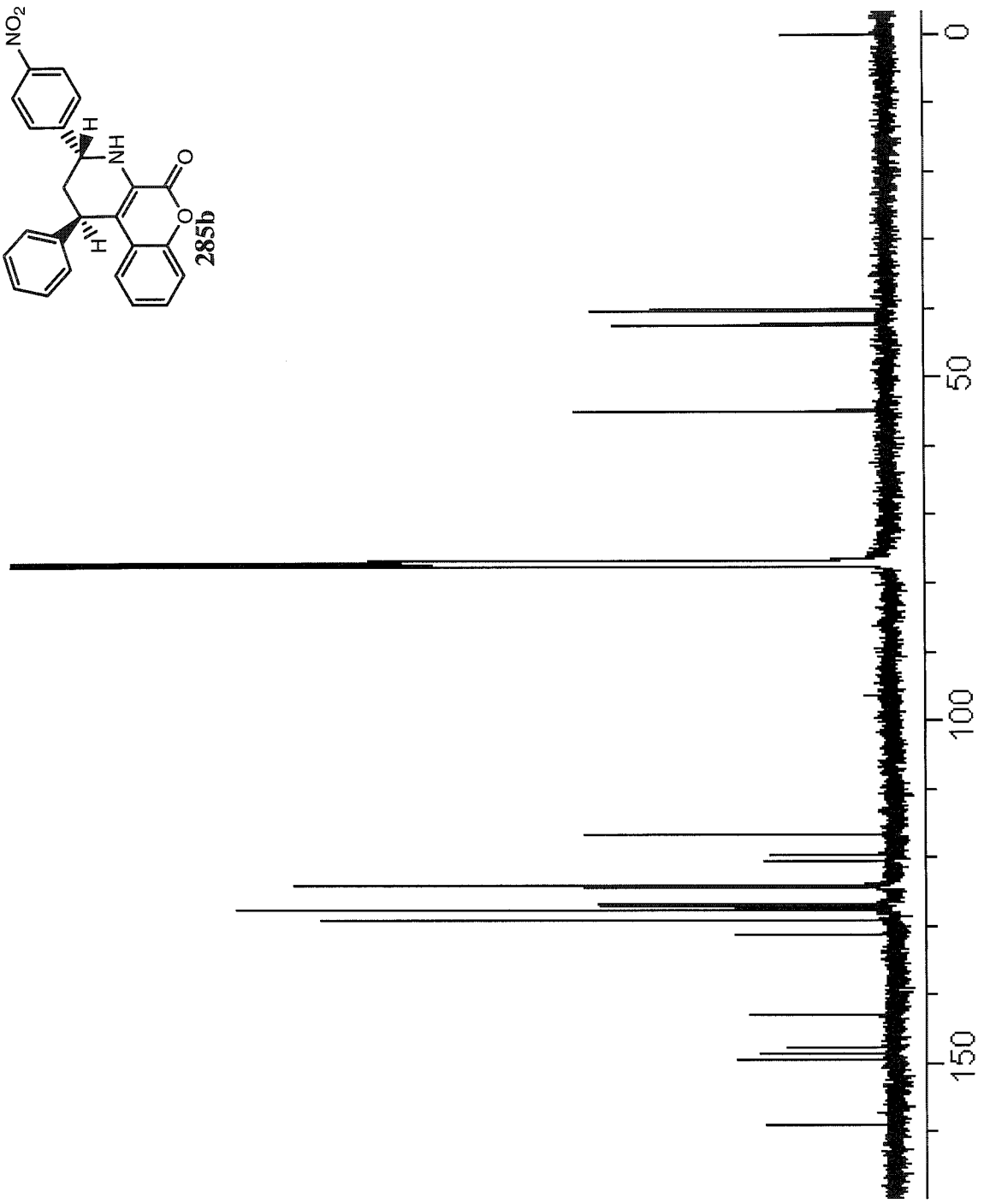
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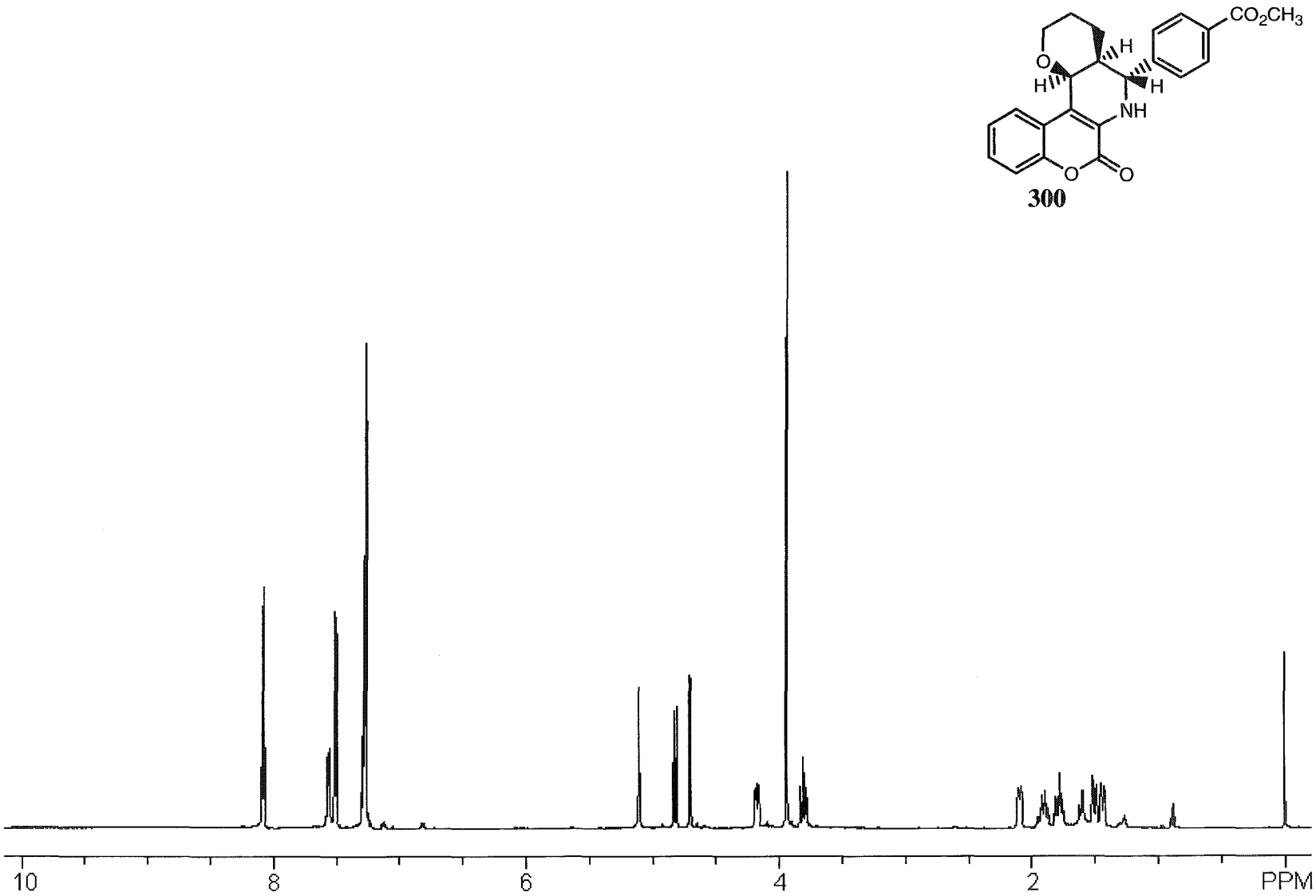
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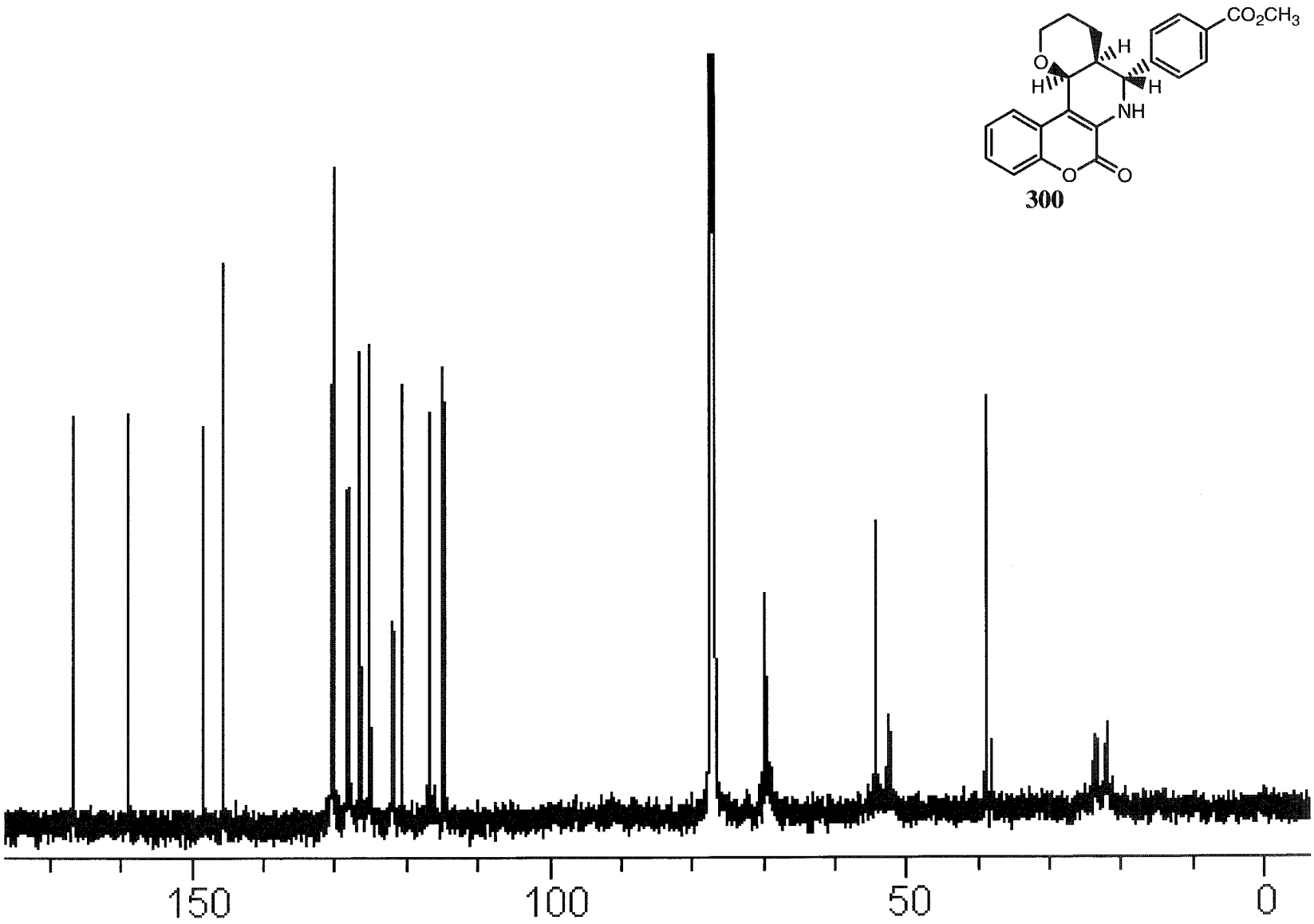
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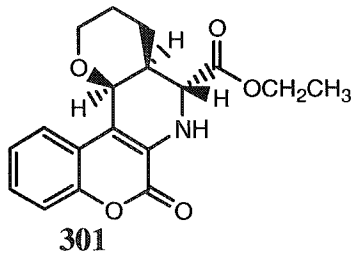

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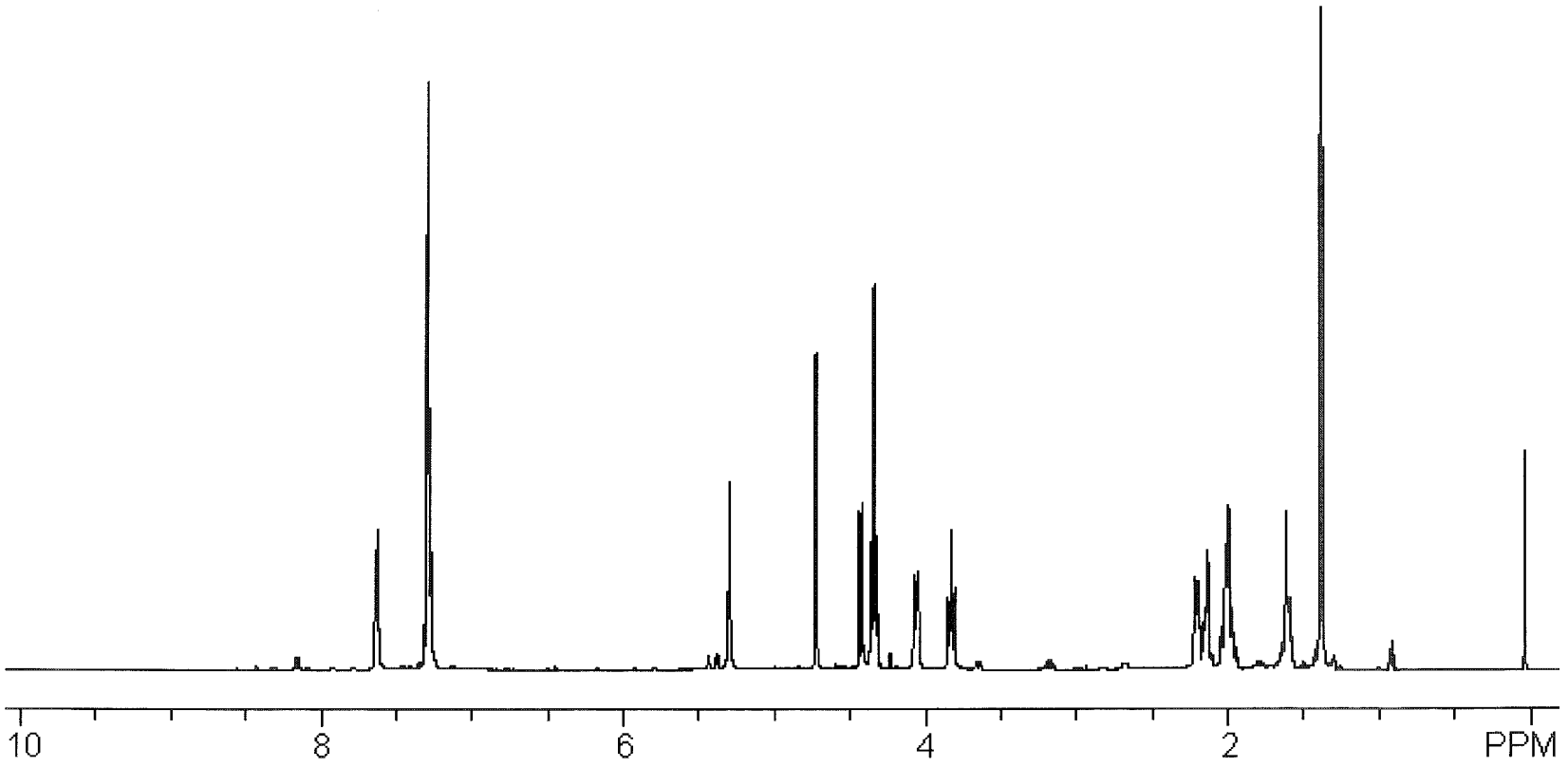

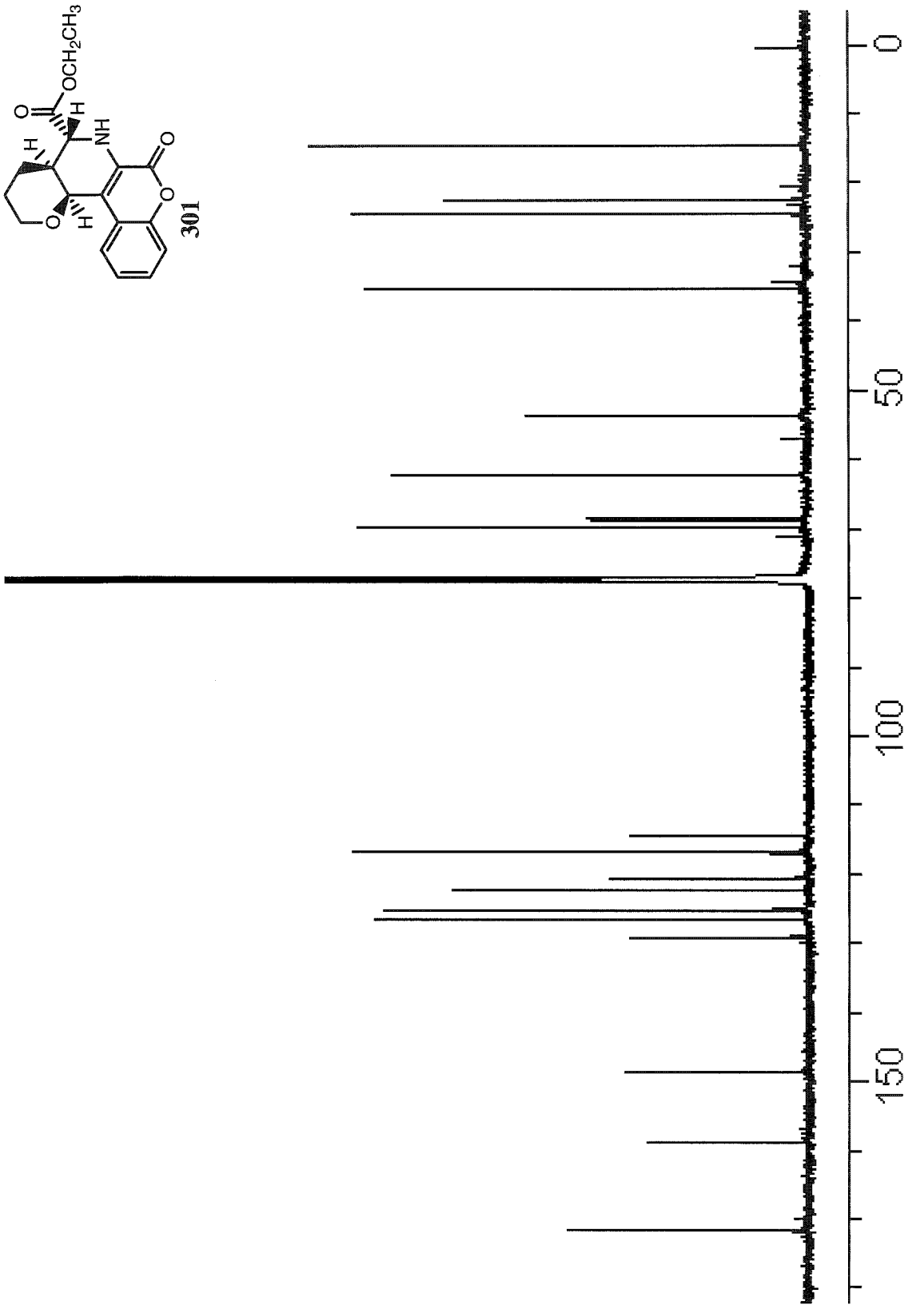
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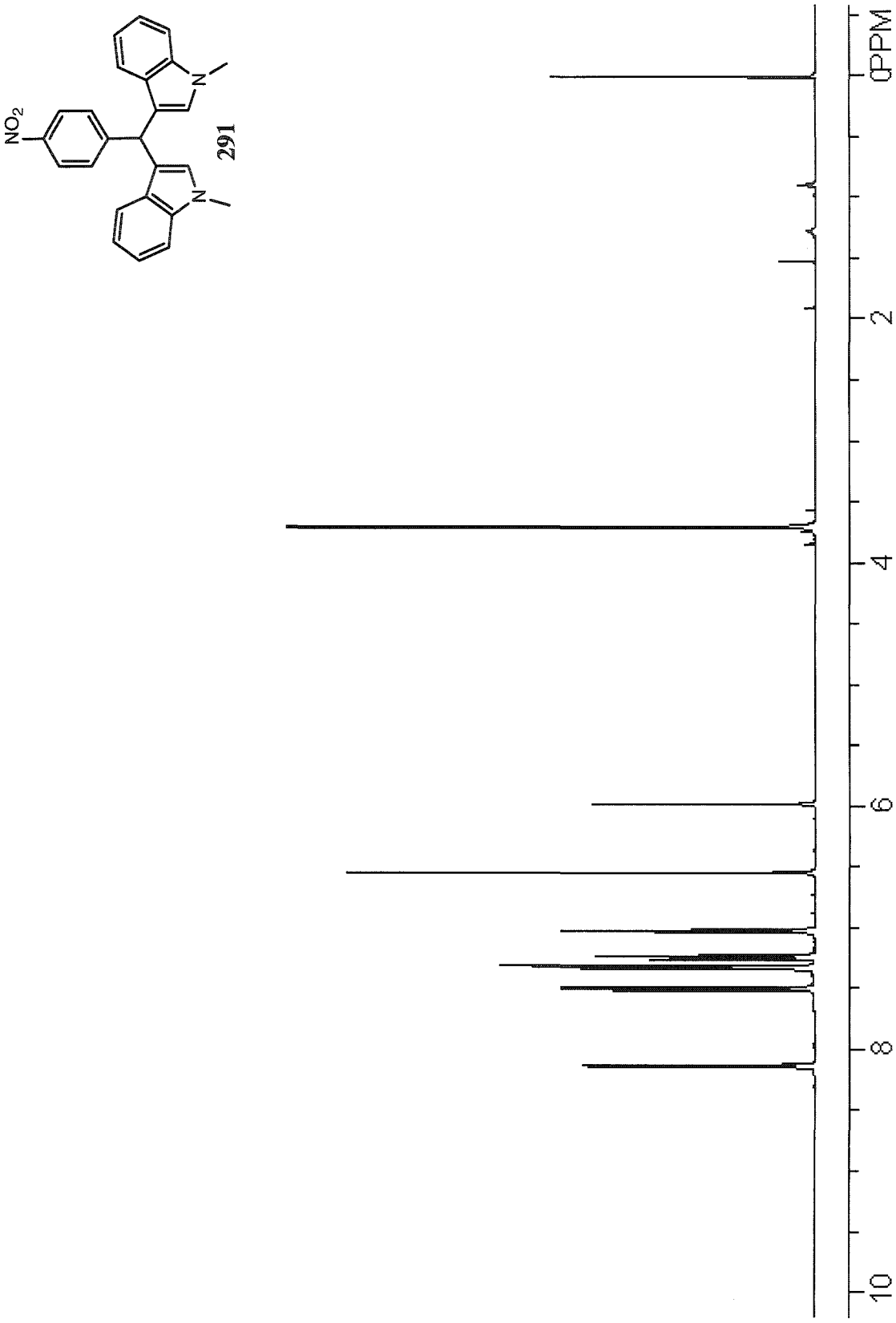
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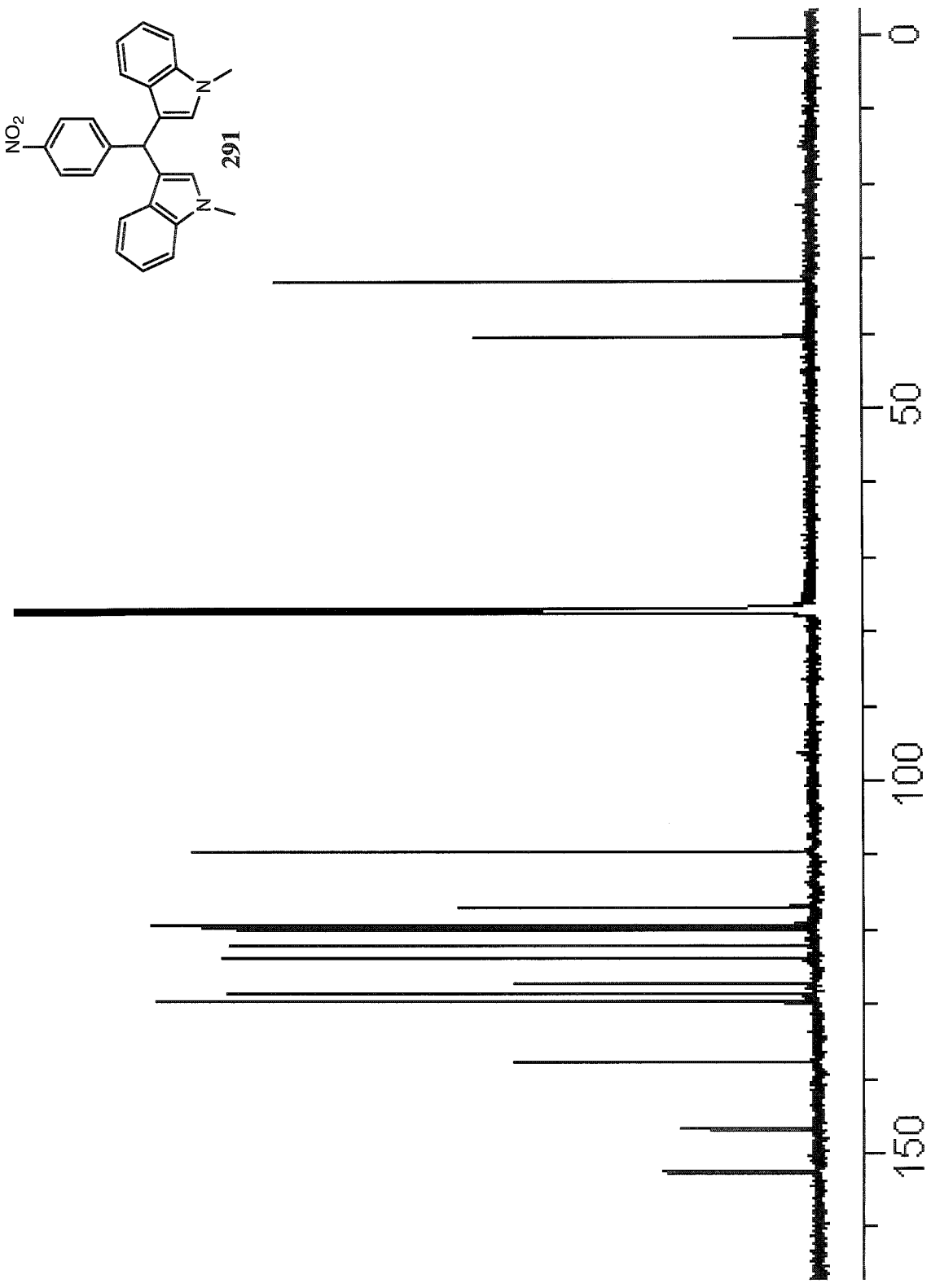
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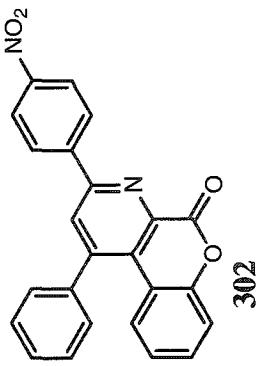

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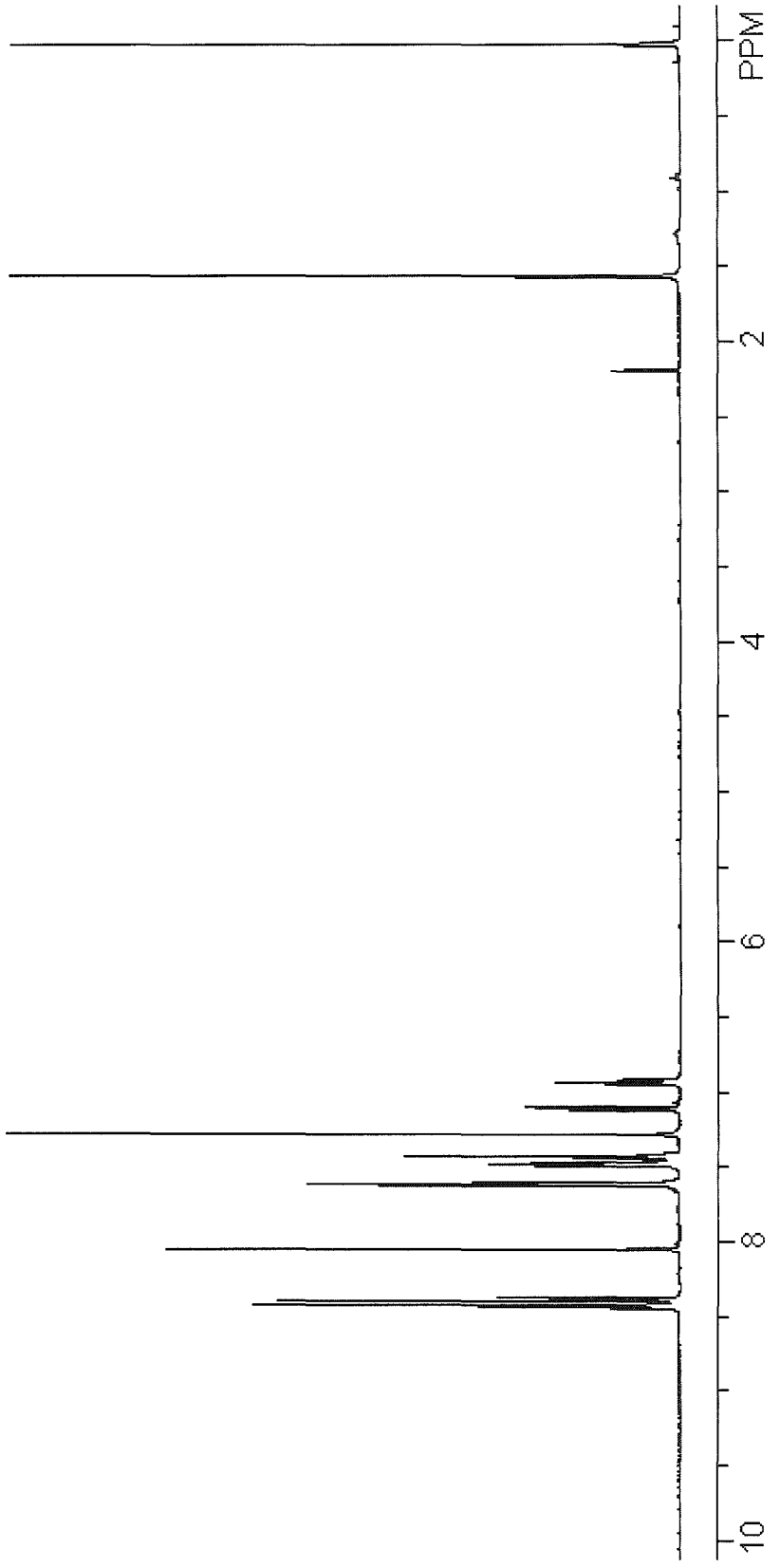

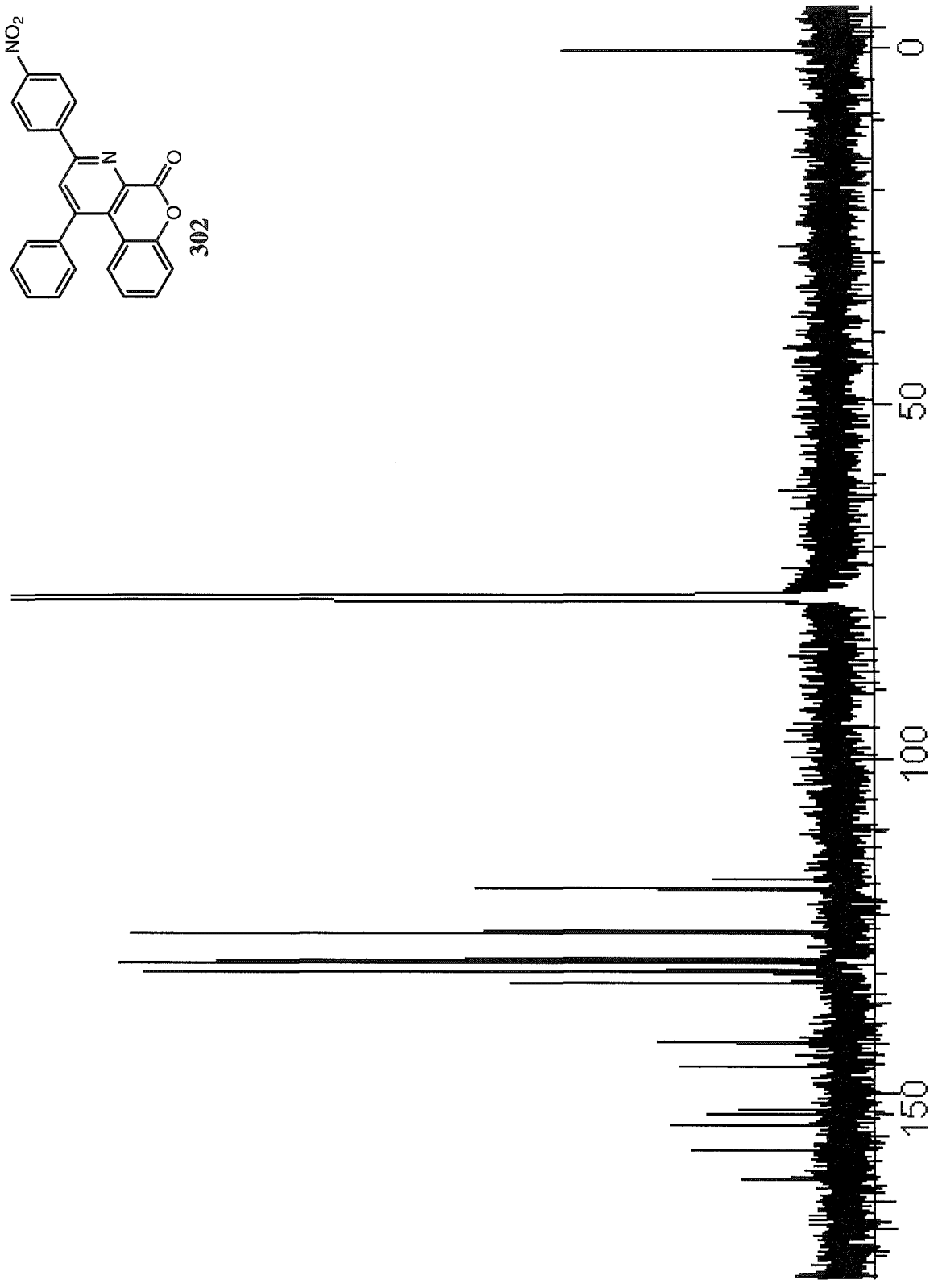
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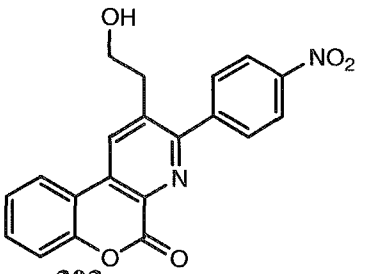

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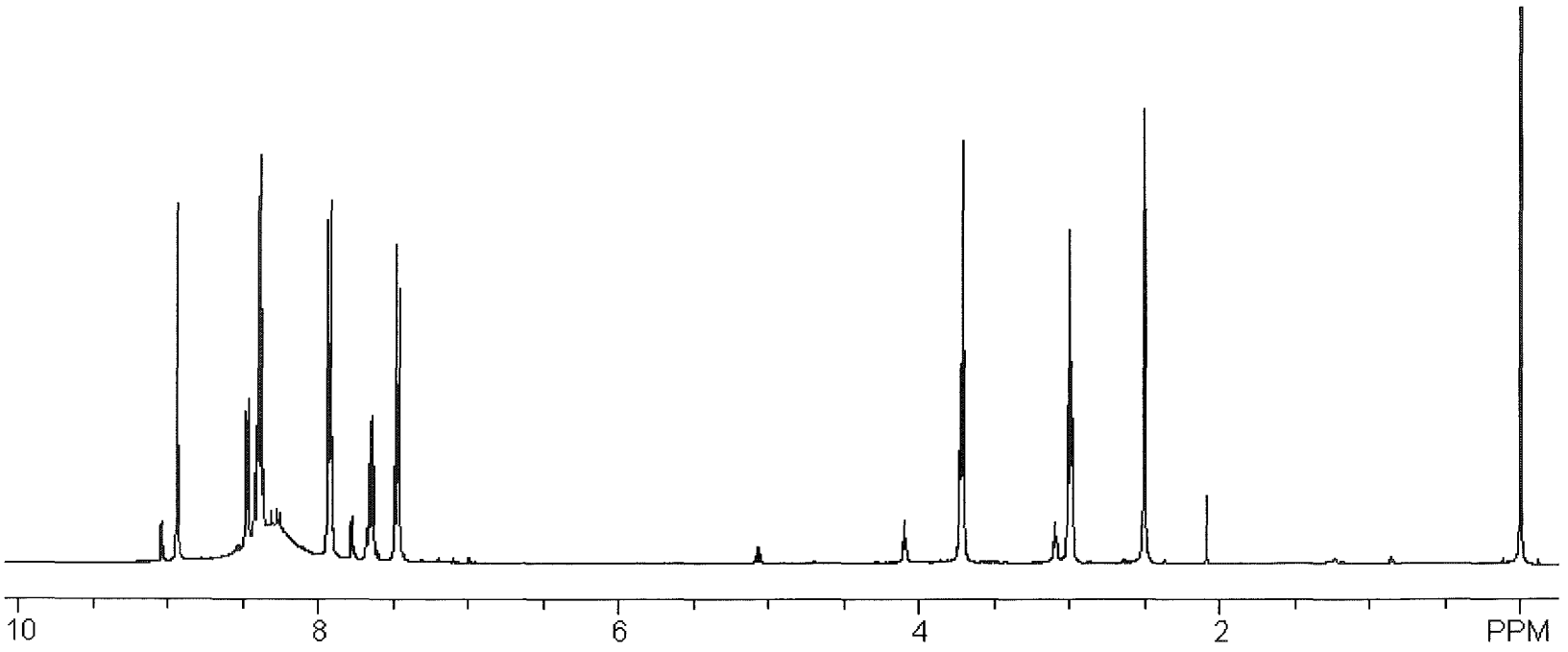

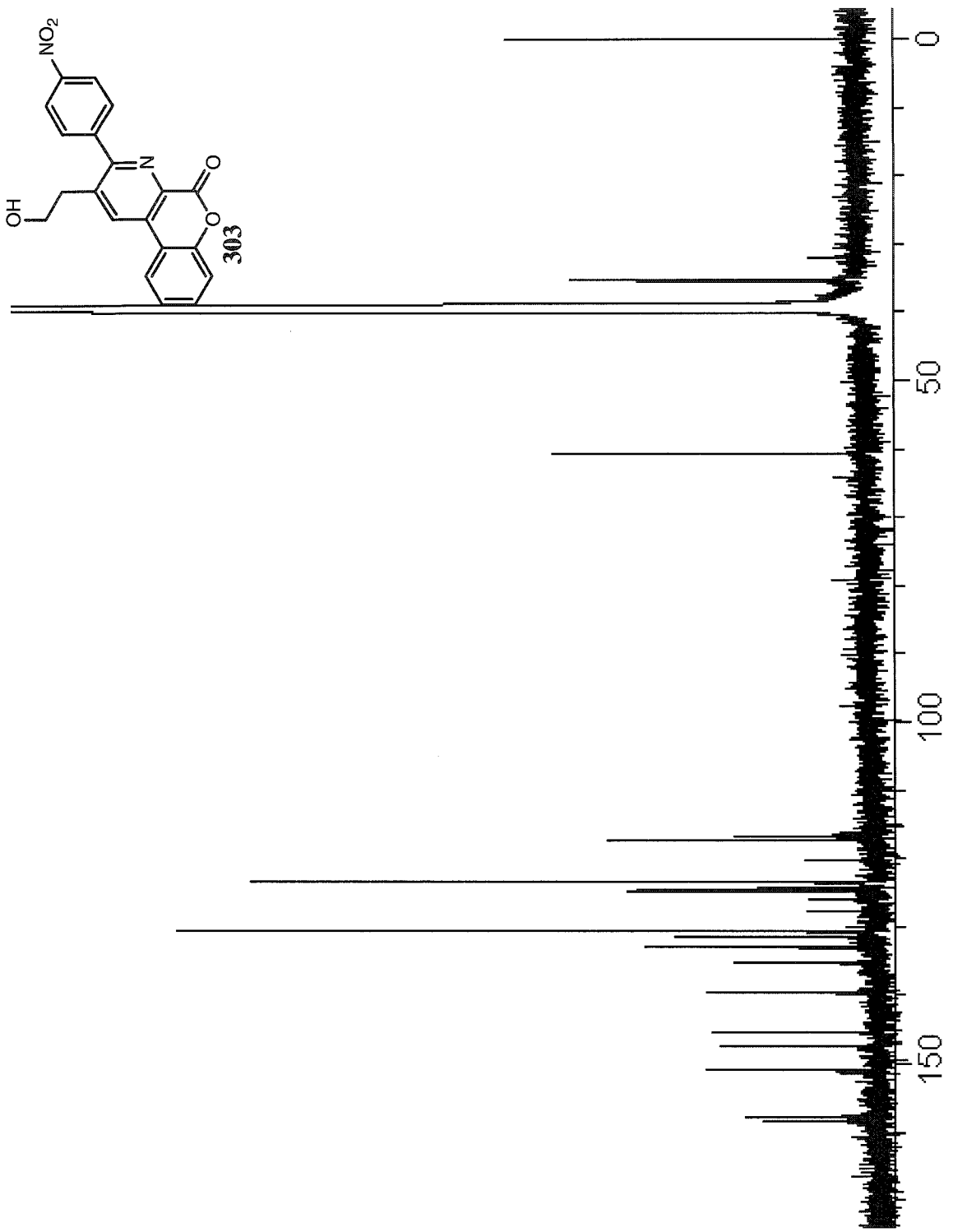
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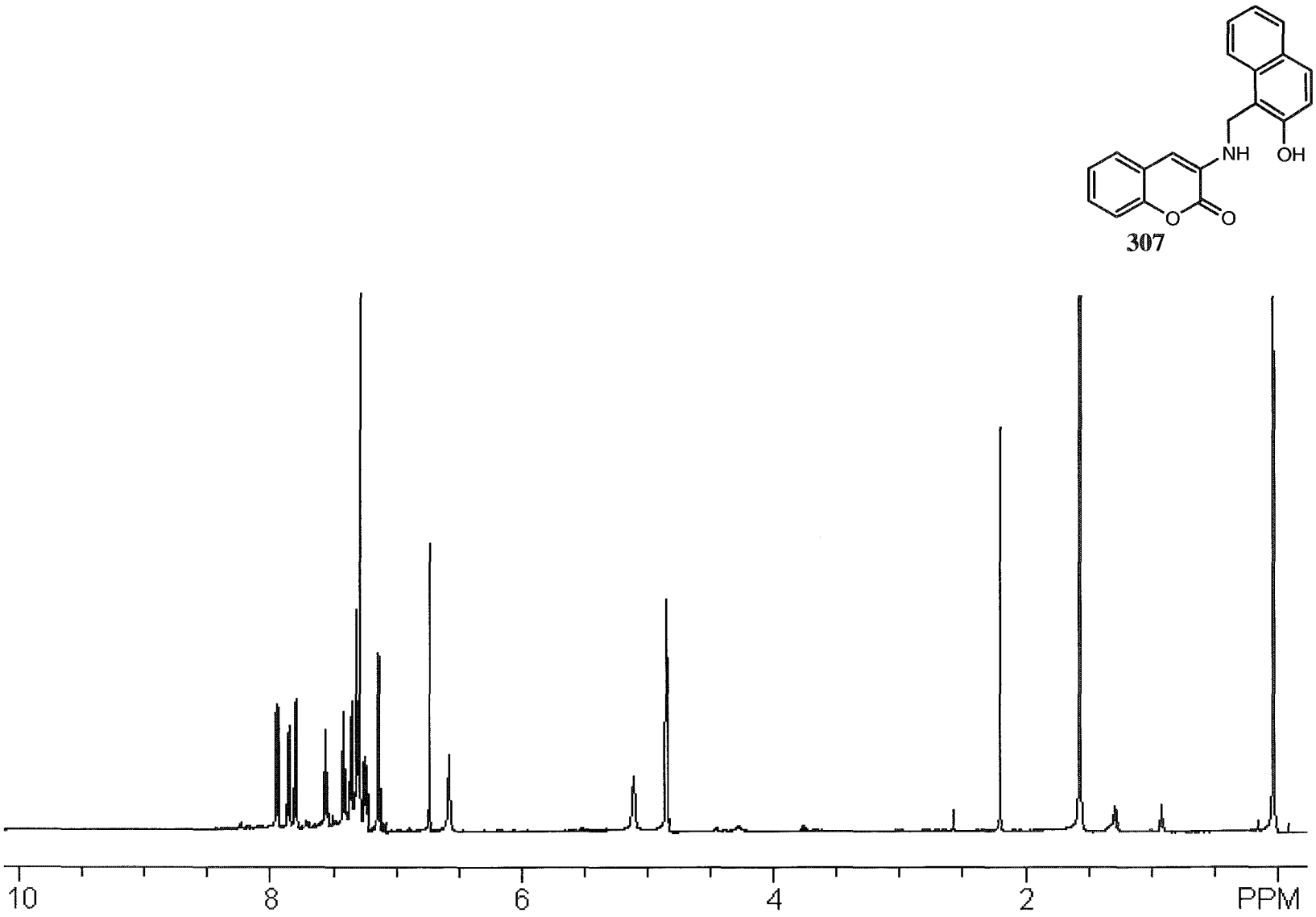

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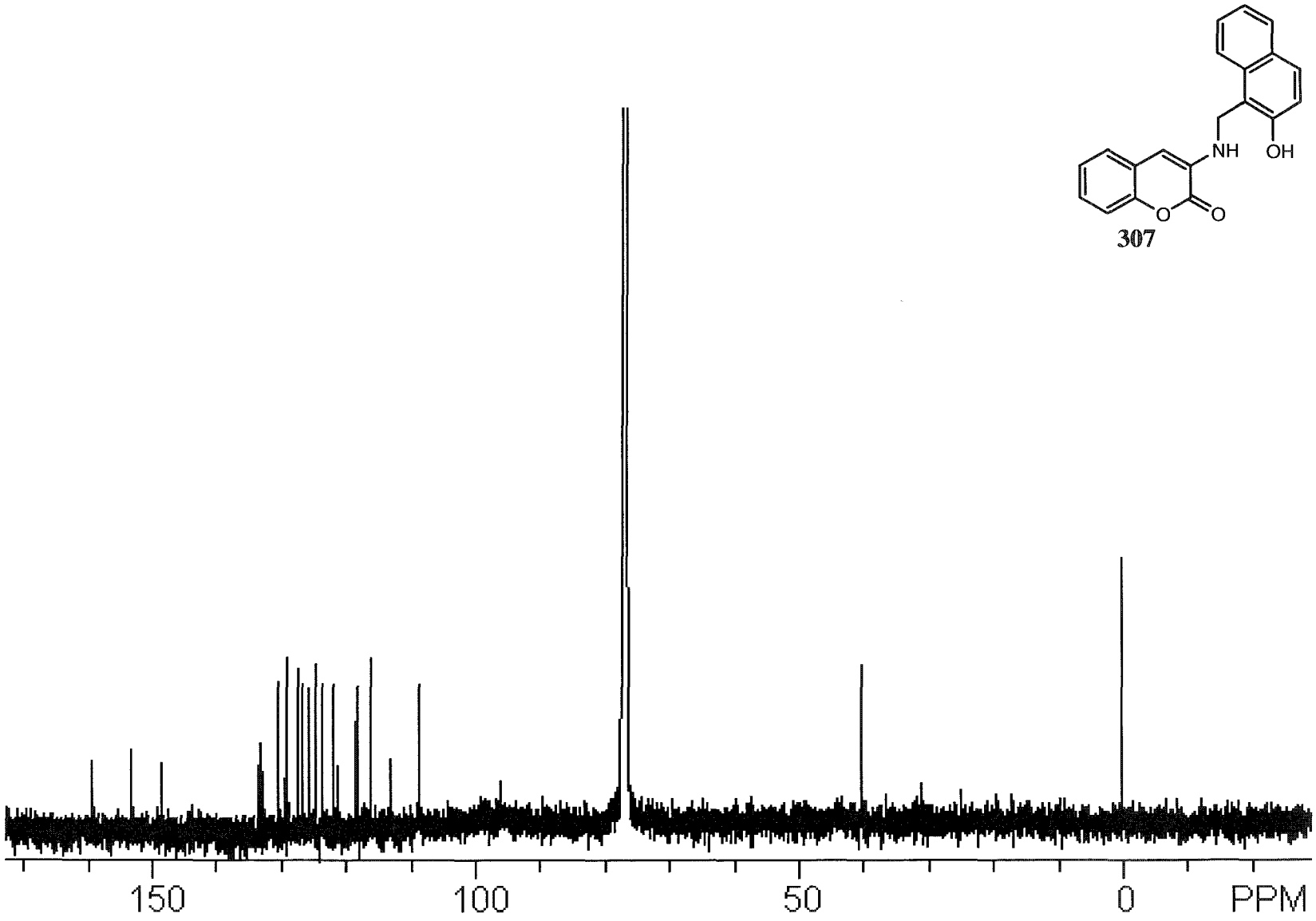

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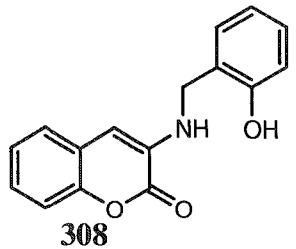

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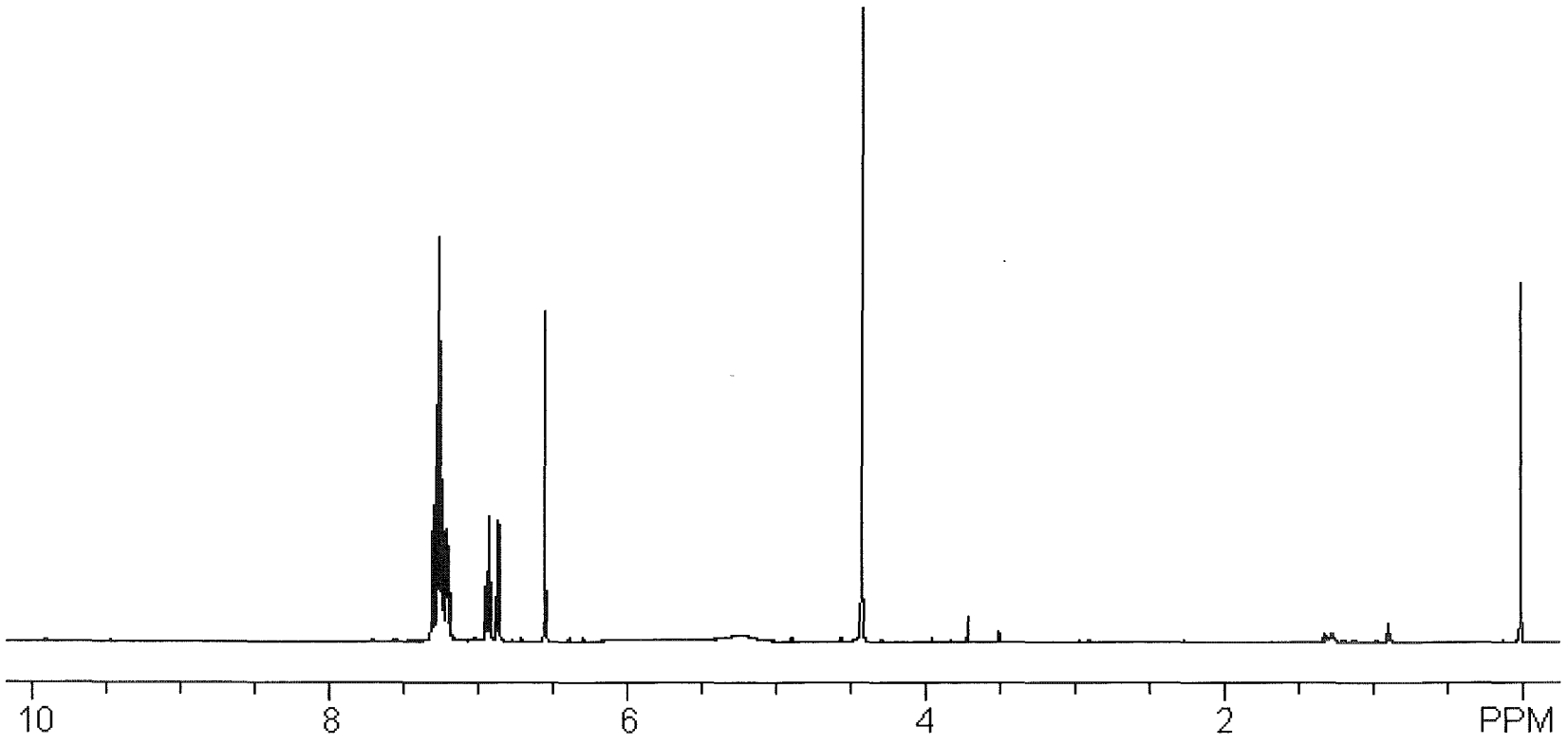

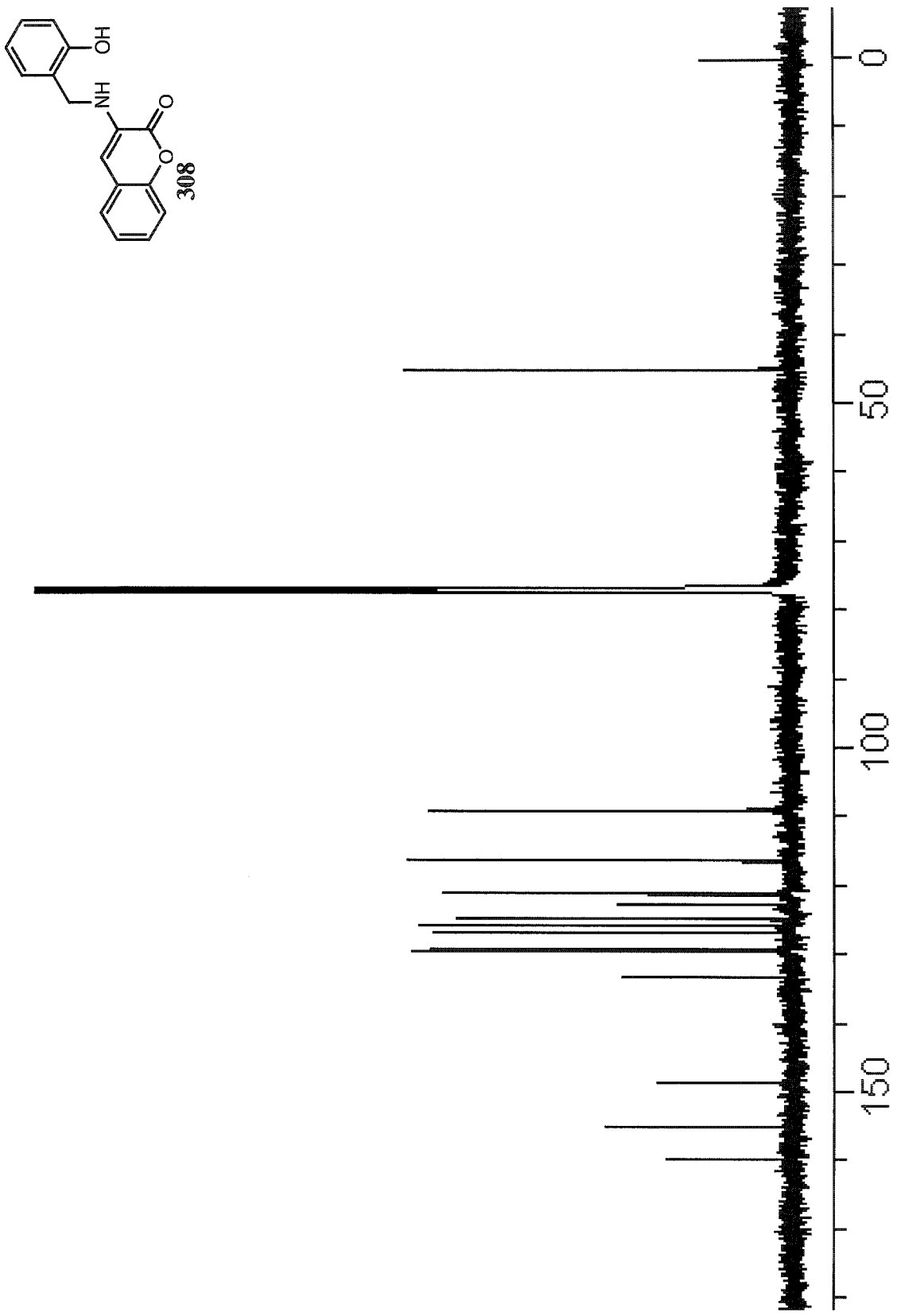
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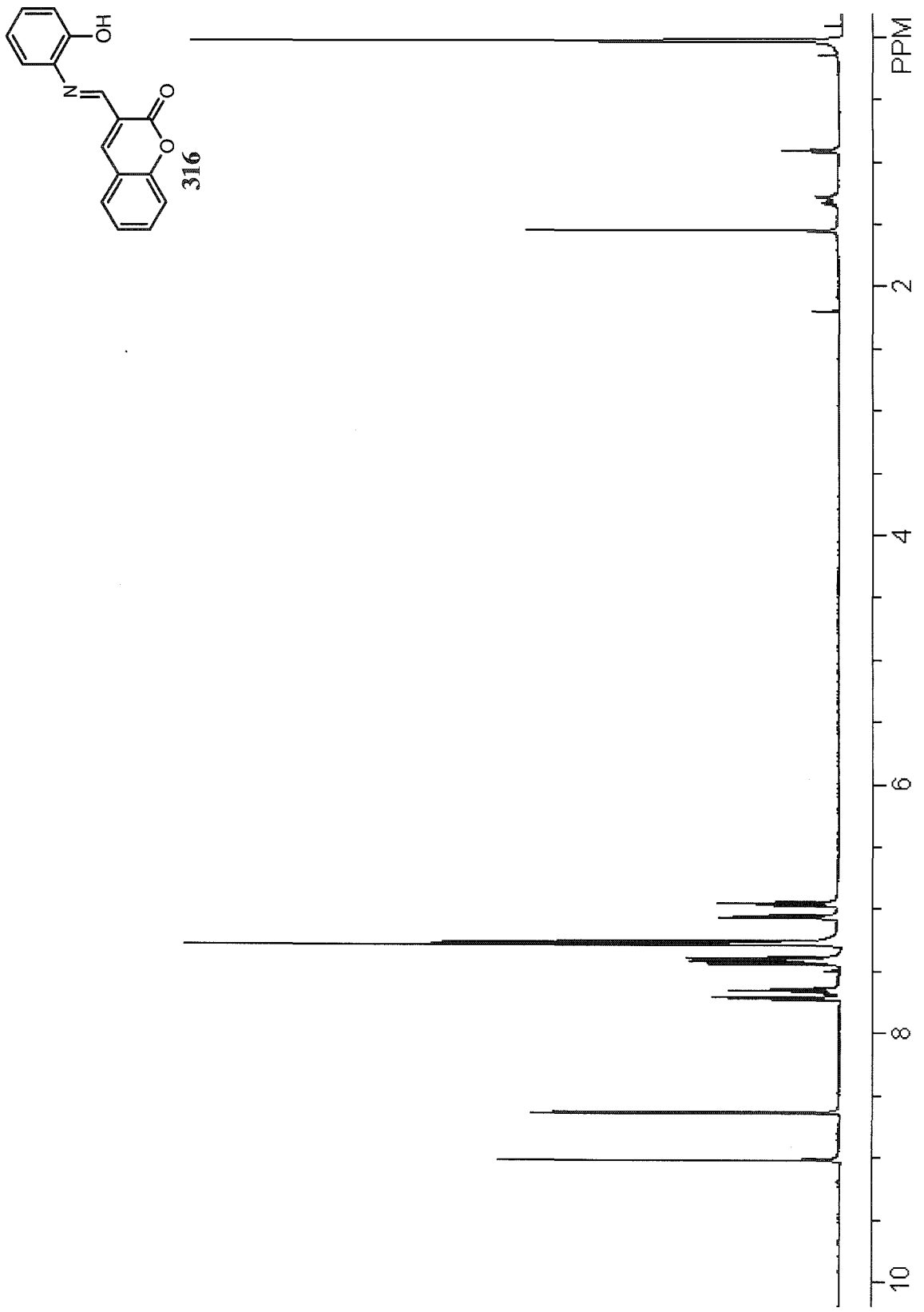
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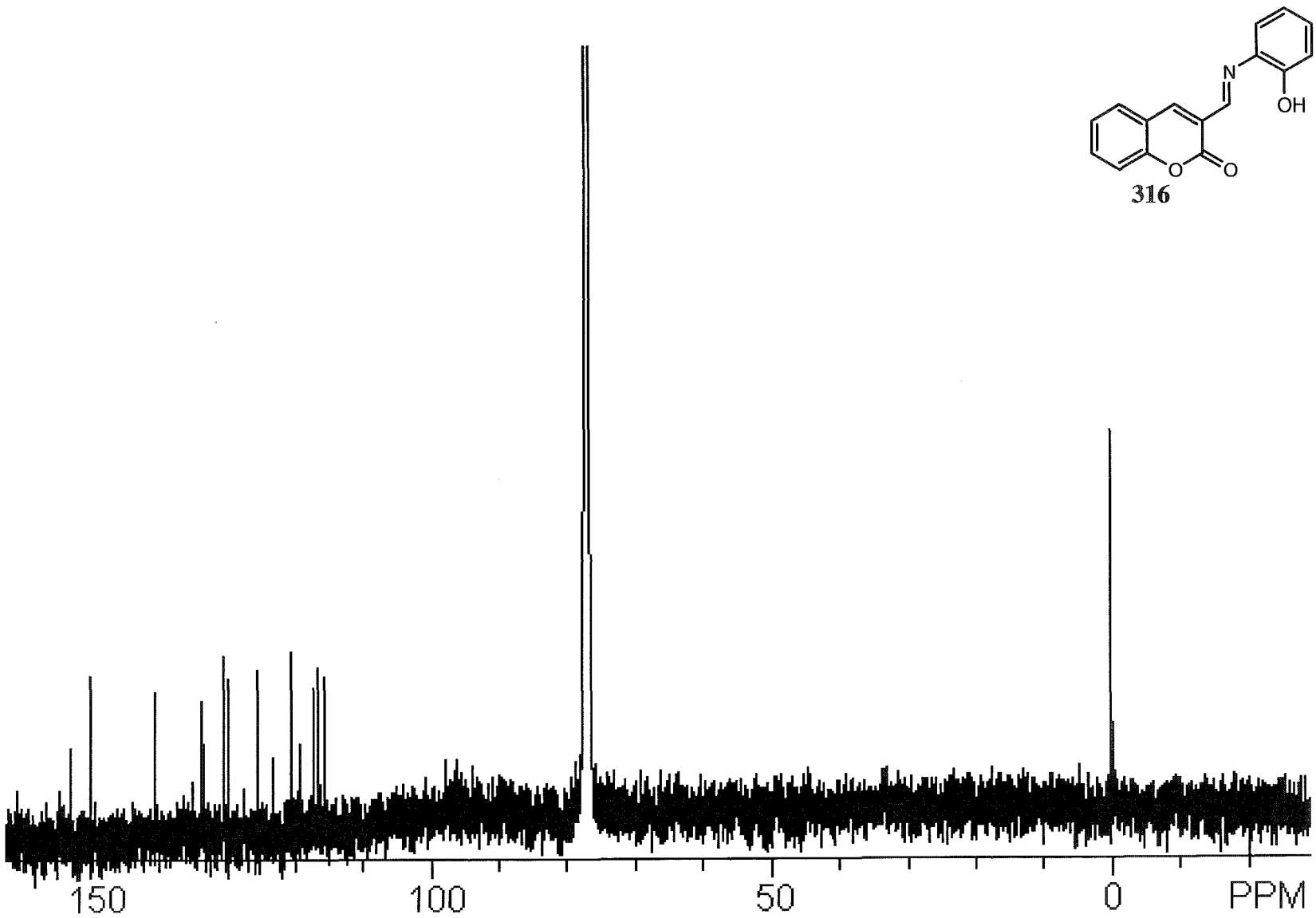
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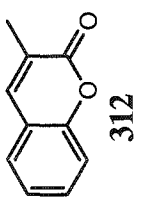

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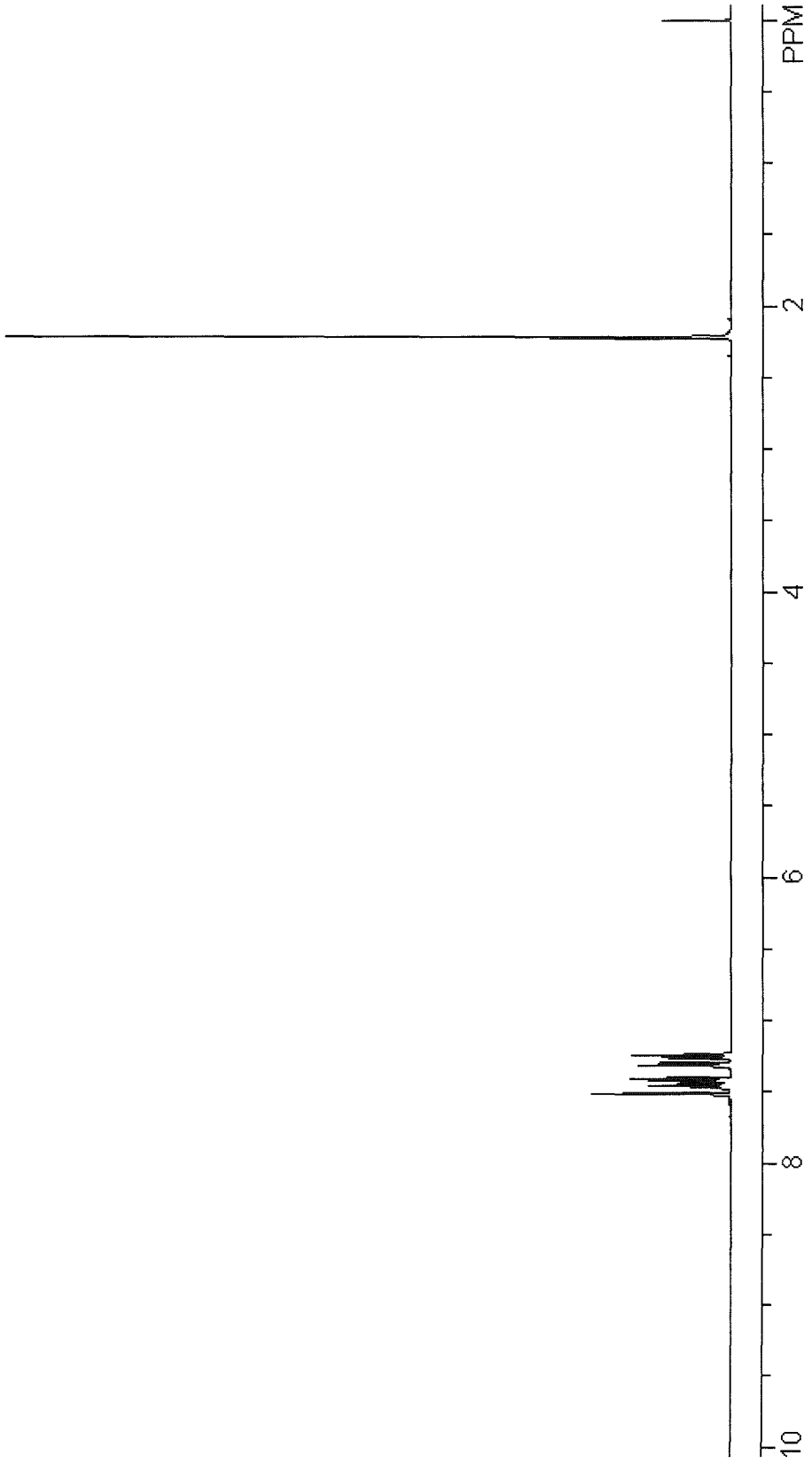

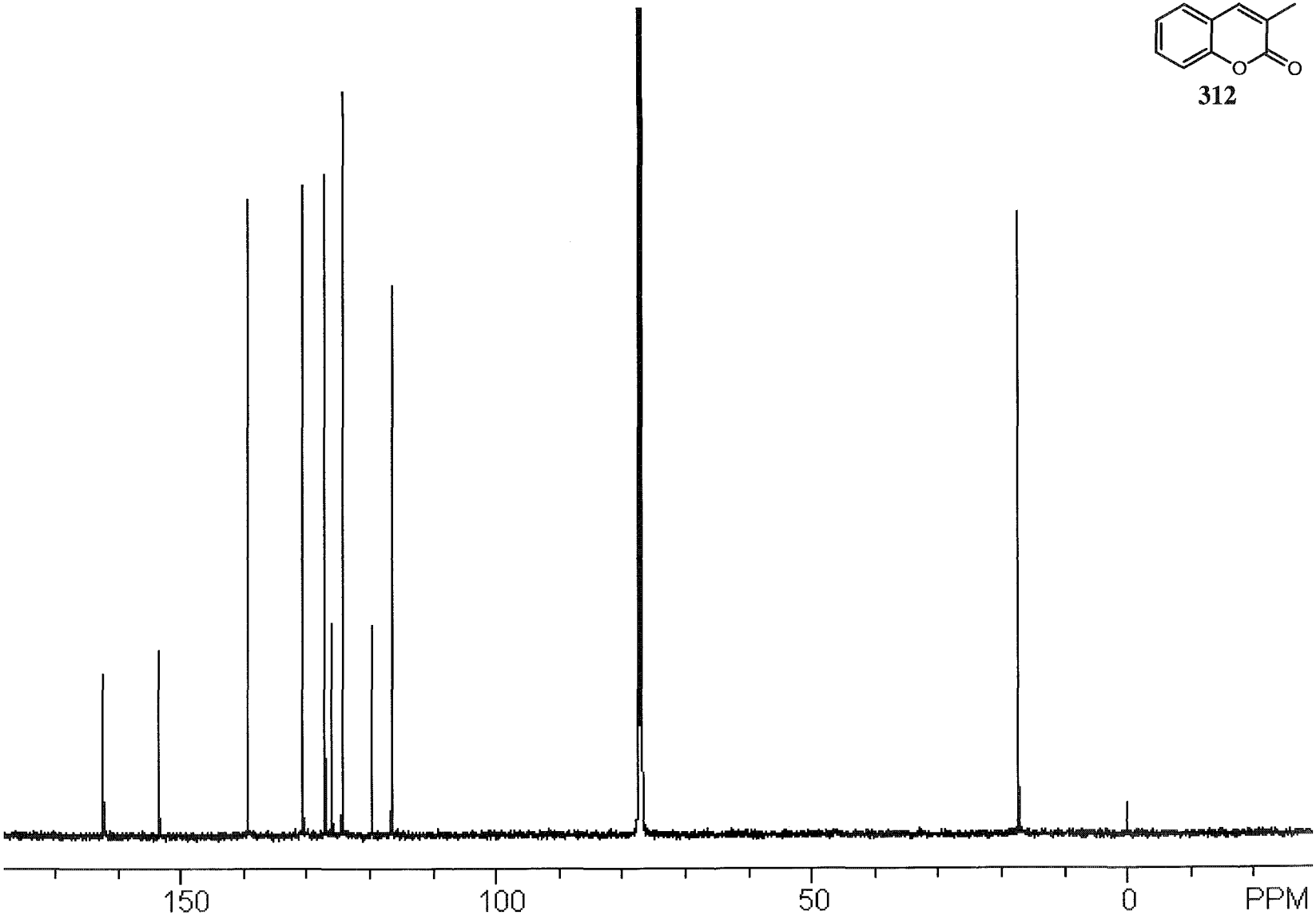
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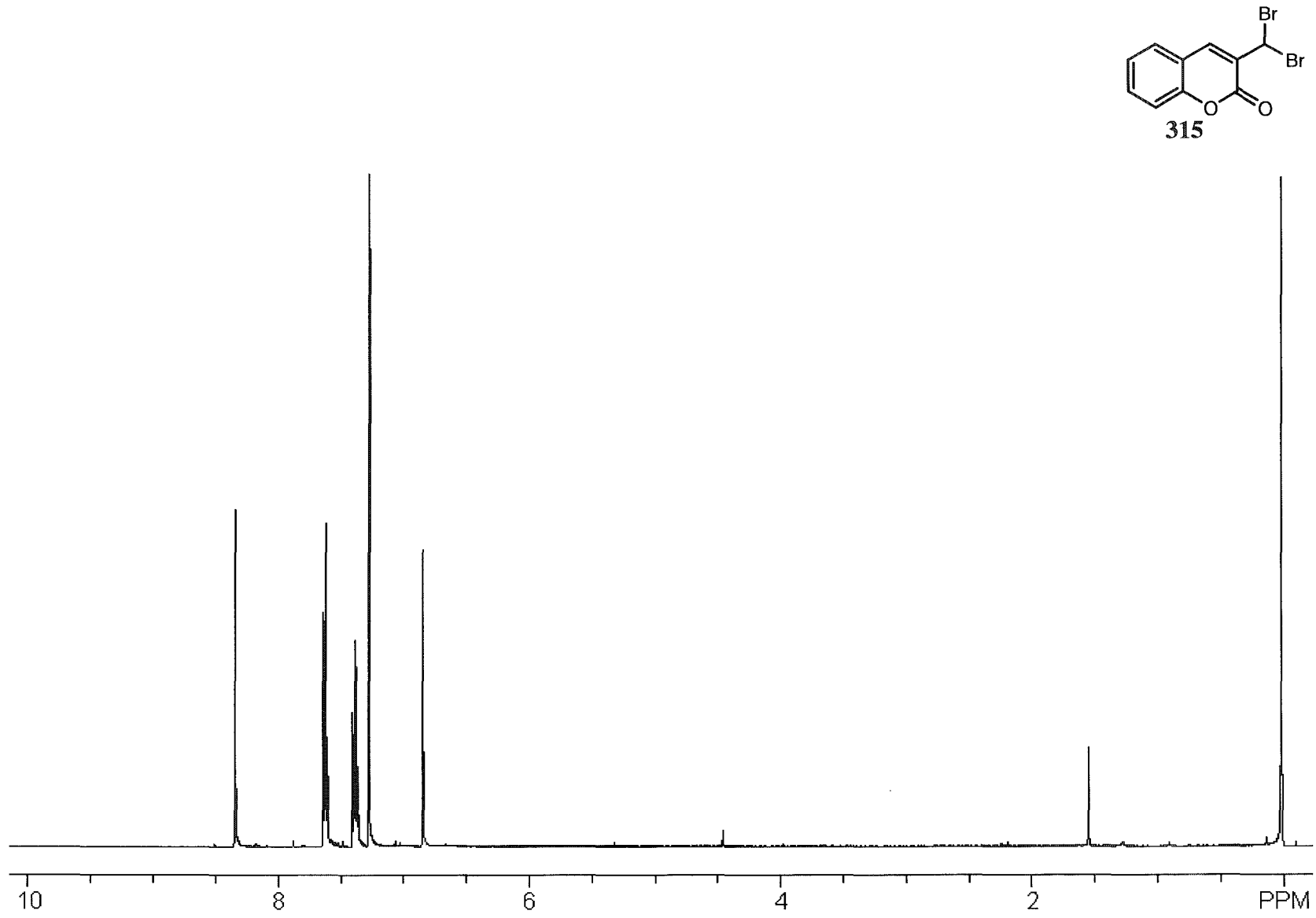
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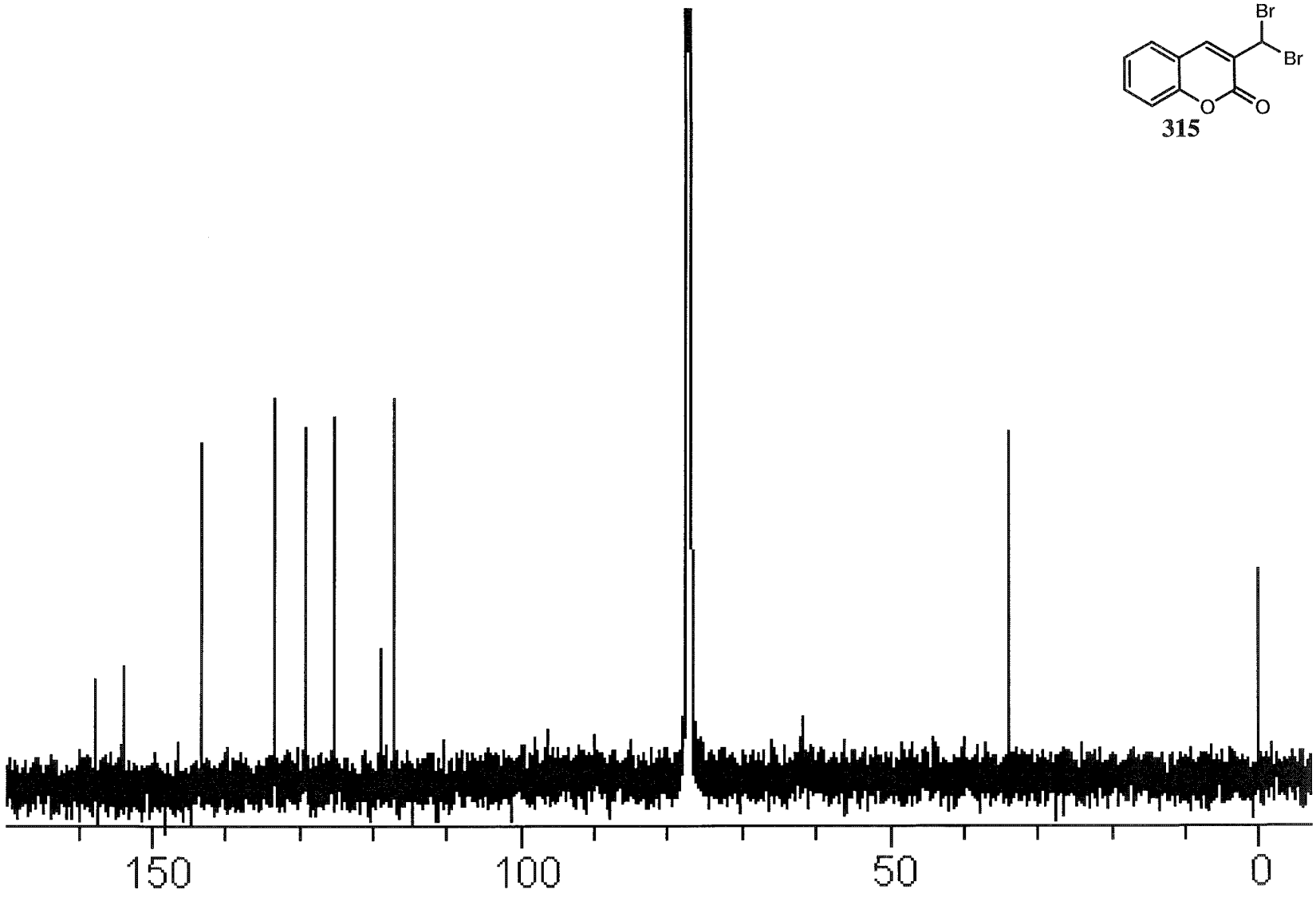
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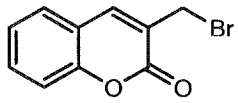

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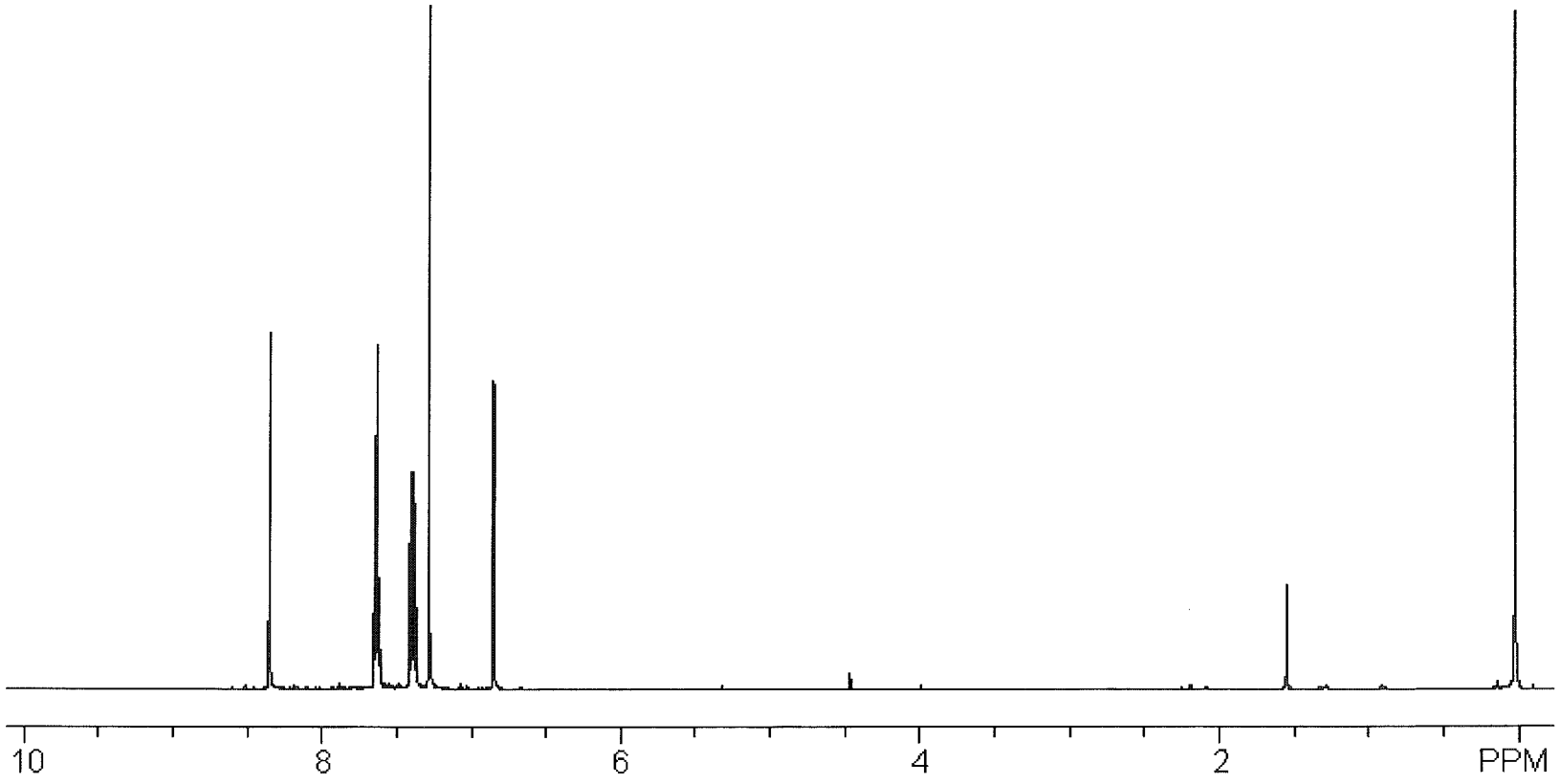

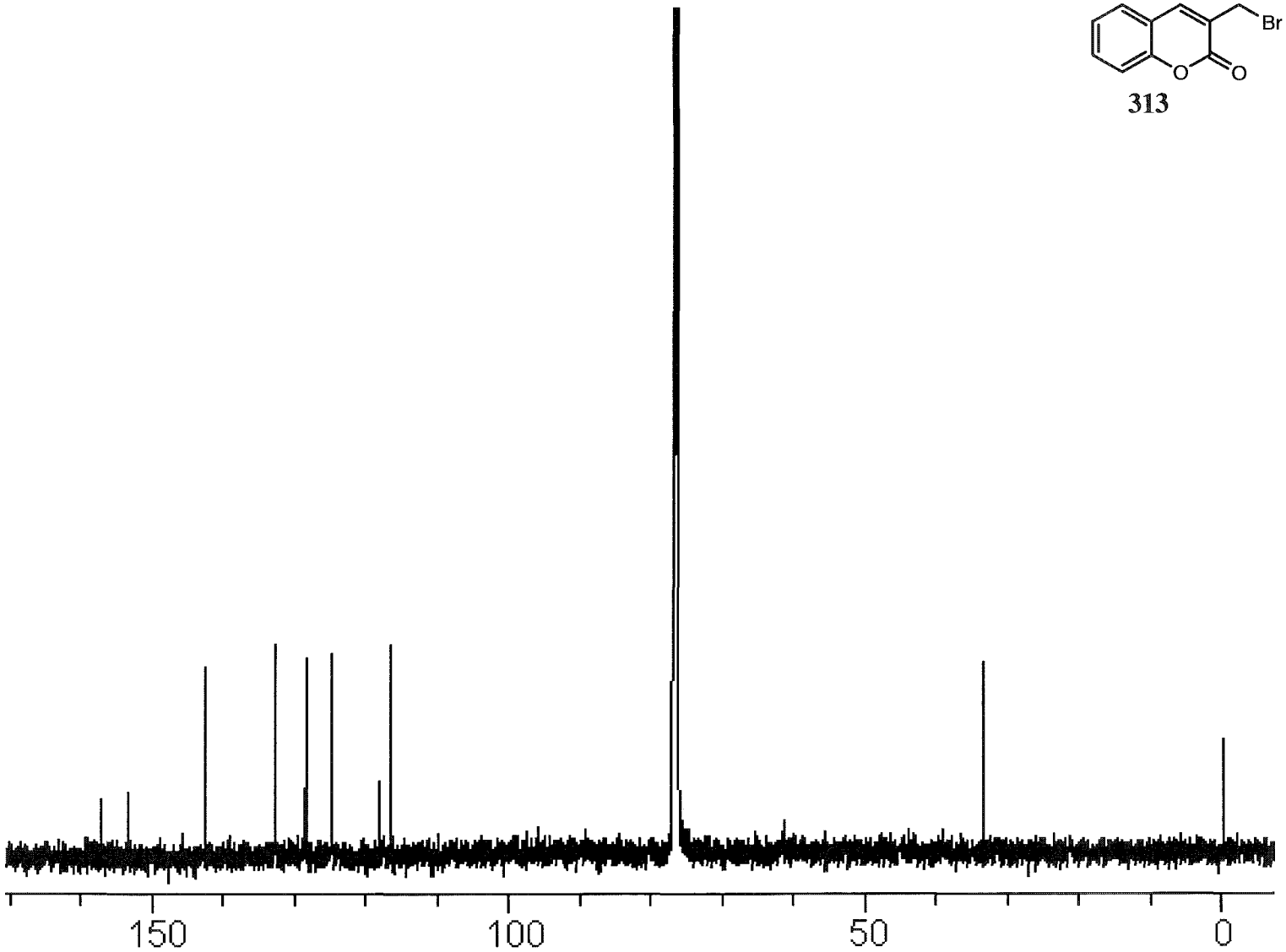
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References

(1) CrystalClear: Rigaku Corporation, 1999.

(2) SHELX97: Sheldrick, G.M. (1997).

(3) DIRDIF94: Beurskens, P.T., Admiraal, G., Beurskens, G., Bosman, W.P., de Gelder, R., Israel, R. and Smits, J.M.M.(1994). The DIRDIF-94 program system, Technical Report of the Crystallography Laboratory, University of Nijmegen, The Netherlands.

(4) Least Squares function minimized: (SHELXL97)

$\Sigma w(F_o^2-F_c^2)^2$ where

$w = 1/ [\sigma^2(Fo^2) + (0.0583 \cdot P)^2 + 1.0972 \cdot P]$

$P = (Max(Fo^2,0) + 2Fc^2)/3$

(5) Standard deviation of an observation of unit weight:

$[\Sigma w(F_o^2-F_c^2)^2/(N_o-N_v)]^{1/2}$

where: N_o = number of observations

N_v = number of variables

(6) Cromer, D. T. & Waber, J. T.; "International Tables for X-ray Crystallography", Vol. IV, The Kynoch Press, Birmingham, England, Table 2.2 A (1974).

(7) Ibers, J. A. & Hamilton, W. C.; Acta Crystallogr., 17, 781 (1964).

(8) Creagh, D. C. & McAuley, W.J .; "International Tables for Crystallography", Vol C, (A.J.C. Wilson, ed.), Kluwer Academic Publishers, Boston, Table 4.2.6.8, pages 219-222 (1992).

(9) Creagh, D. C. & Hubbell, J.H..; "International Tables for Crystallography", Vol C, (A.J.C. Wilson, ed.), Kluwer Academic Publishers, Boston, Table 4.2.4.3, pages 200-206 (1992).

(10) teXsan for Windows version 1.06: Crystal Structure Analysis Package, Molecular Structure Corporation (1997-9).

(11) SHELX97: Sheldrick, G.M. (1997).

EXPERIMENTAL DETAILS

A. Crystal Data

Empirical Formula	$H_{19}NO_5C_{22}$
Formula Weight	377.40
Crystal Color, Habit	colorless, prism
Crystal Dimensions	0.64 X 0.10 X 0.08 mm
Crystal System	monoclinic
Lattice Type	Primitive
Lattice Parameters	a = 19.587(2) Å
	b = 5.0527(4) Å
	c = 18.853(2) Å
	β = 100.997(2) ^{o}
	V = 1831.6(2) $Å^3$
Space Group	$P2_1/c$ (#14)
Z value	4
D_{calc}	1.368 g/cm^3
F_{000}	792.00
μ(MoKα)	0.97 cm^{-1}

B. Intensity Measurements

Diffractometer	Bruker P4/ CCD
Radiation	MoKα (λ = 0.71073 Å)
	graphite monochromated
Temperature	-80 ± 1°C
Scan Rate	30s, 0.3 deg frames
$2\theta_{max}$	52.8°
No. of Reflections Measured	Total: 12732
	Unique: 3760 (R_{int} = 0.044)
Corrections	Lorentz-polarization
	SADABS correction
	(Trans factors 0.9922 - 0.9402)

C. Structure Solution and Refinement

Structure Solution	Direct Methods (SHELX97)
Refinement	Full-matrix least-squares on F^2
Function Minimized	$\Sigma\, w\, (Fo^2 - Fc^2)^2$
Least Squares Weights	$w = 1/ [\, \sigma^2(Fo^2) + (0.0583 \cdot P)^2 + 1.0972 \cdot P\,]$ where $P = (Max(Fo^2,0) + 2Fc^2)/3$
Anomalous Dispersion	All non-hydrogen atoms
No. Observations ($I>2.00\sigma(I)$)	2611
No. Variables	253
Reflection/Parameter Ratio	10.32
Residuals: R1; wR2	0.052 ; 0.142
Goodness of Fit Indicator	1.03
Max Shift/Error in Final Cycle	0.00
Maximum peak in Final Diff. Map	0.38 $e^-/Å^3$
Minimum peak in Final Diff. Map	-0.37 $e^-/Å^3$