An Enantioselective Approach Towards the Synthesis of 3-Aryl Substituted Piperidines: Application to (-)-Preclamol Synthesis

Thesis submitted in partial fulfilment of the requirements

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In

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Submitted By:

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Under the guidance of

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to the

School of Chemistry and Biochemistry

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INDIA

2017

Certificate

This is to certify that the project entitled "***An Enantioselective Approach Towards the Synthesis of 3-Aryl Substituted Piperidines: Application to (-)-Preclamol Synthesis***" being submitted by Ms. Pooja Sharma in the partial fulfilment of requirement for the award of the degree of Masters of Science in the School of Chemistry and Biochemistry, Thapar university, Patiala, is an original work carried under the supervision of Dr. Ranjana Prakash and Dr. Satyendra Kumar Pandey and no part of this project has been submitted for award of any other degree by me.

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Candidate's Declaration

I hereby declare that the work being presented in the dissertation entitled "***An Enantioselective Approach Towards the Synthesis of 3-Aryl Substituted Piperidines: Application to (-)-Preclamol Synthesis***" in partial fulfilment of the requirements for the award of the degree of Masters in Chemistry, School of Chemistry and Biochemistry, Thapar University, Patiala, is my own work during the period of January to July 2017, under the supervision of **Dr. Ranjana Prakash and Dr. Satyendra Kumar Pandey.** My thesis has not previously formed the basis for award of any degree, or other similar title or recognition.

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This is to certify that the above statement made by the candidate is correct and true to the best of our knowledge.

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Above all, I am grateful to God, Almighty who sustain this amazing world and without whose grace and blessings anybody can ever succeed.

Pooja Sharma

Pooja Sharma

LIST OF CONTENT

An Enantioselective Approach Towards the Synthesis of 3-Aryl Substituted Piperidines: Application to (-)-Preclamol Synthesis

1. Introduction

3-Aryl substituted piperidines and their derivatives (**1-4**) are among the most bioactive compounds in organic chemistry due to occurrence of these structural motifs either as itself or as a part of a more complex structural moiety in a large number of natural- and natural like bioactive molecules.[1-4] Among them, (-)-preclamol **1** structurally (-)-3-(3 hydroxyphenyl)-*N*-(*n*-propyl)-piperidine (3-PPP) is the advanced and novel selective D-2 like dopamine autoreceptor agonist, which has shown the central dopamine autoreceptor stimulating activity.[4a, 5-6] Additionally, (-)-preclamol **1** has been explored as a pharmacological tool for the study of dopaminergic mechanisms.[7-10] Furthermore, (-)-preclamol **1** has also been investigated as the antipsychotic potential for the determination of therapeutic effect in the treatment of Perkinson's, schizophrenia, depression and drug addiction diseases. [4a,11-12] In the total series, (-)-preclamol **1** seems to be the most interesting compound both from the therapeutical and the theoretical point of view, reducing dopamine autoreceptor function in two different possible ways by blocking post synaptic receptors and stimulating presynaptic receptors.[4b] (-)-Preclamol **1** has been selected for extended pharmacological studies as a potential antipsychotic drug.[13]

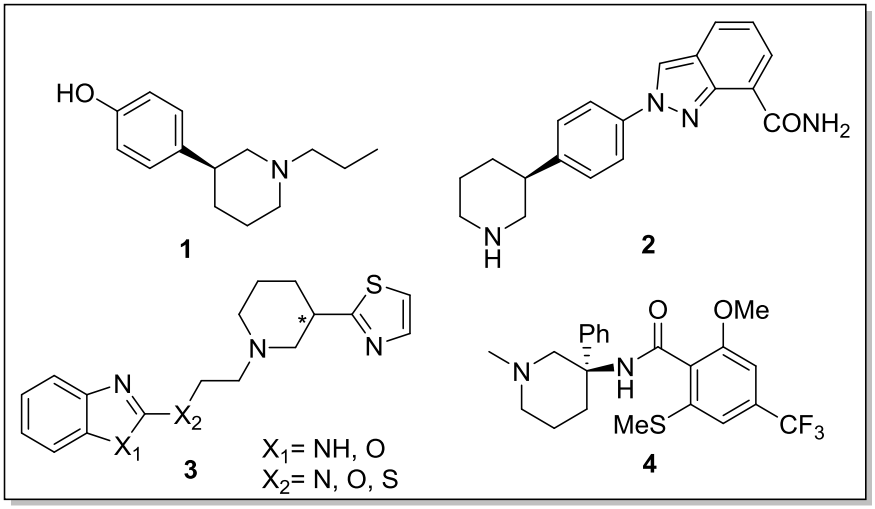


Figure 1. Structures of 3-aryl substituted piperidines (**1-4**)

1.1 Asymmetric organocatalyzed Michael addition reaction:

Michael addition reaction is the 1,4 -nucleophilic addition of nucleophile/carbanion to $\alpha.\beta$-unsarturated carbonyl compounds.[14] it is one of the most useful reaction for carbon-carbon bond formation catalyzed by organocatalysts. This reaction is one of the most significant reaction for the synthesis of nitro-alkanes, which are essential synthetic intermediates due to various possible transformations of nitro group and aldehyde to other functional groups. However, the requirement of a metal-free and environmental friendly reaction made the organocatalyst as an alternative option for Michael addition reaction of nitro-olefins to aldehyde.[15]

1.1.2 Organocatalzyed Michael addition reactions on conjugated nitro-olefins

Recently, Hayashi and co-workers defined an organocatalyzed asymmetric Michael reaction of nitro-alkenes **5** with α-substituted aldehydes **6** in the presence of catalytic amount of diphenylprolinol silyl ether to furnish α-substituted-δ-nitro aldehydes **7** in high diastereoselectivity (upto 97:3 *syn*:*anti*) , enantioselectivity (up to 99%*ee*) and with higher yield (up to 85%) (Figure 2).[15]

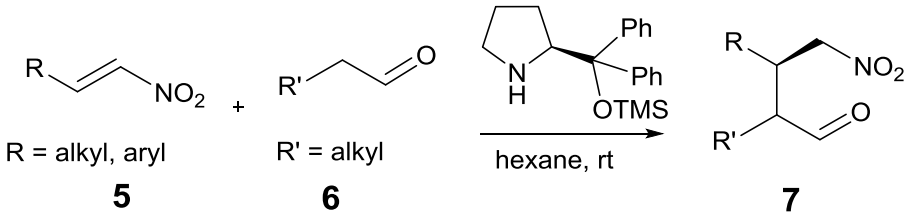


Figure 2. Organocatalyzed Michael addition reaction of aldehydes.

The parent diphenyl-2-pyrrolidinemethanol (diphenylprolinol) **8**, which is a commercially accessible amino alcohol as explained by Corey and co-workers, has proved to be a very helpful ligand for asymmetric synthesis. Not only the TMS-substituted compound **9**, additionally the TES and TBS derivatives of compound **9** are also found as excellent catalysts. However, the reaction becomes slower with the introduction of bulkier silyl groups.

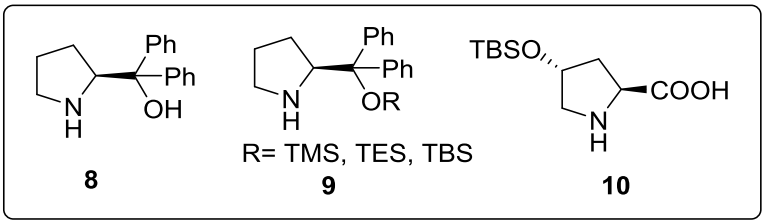


Figure 3: Some proline substituted organocatalysts.

More recently, Hayashi and co-workers defined the organocatalytic asymmetric Michael addition reaction of nitro-olefin **5** with acceptor acetaldehyde **11** in the presence of catalytic amount of diphenylprolinol silyl ether to afford the α-unsubstituted-δ-nitro aldehydes **12** in high yield (upto 77%) with a good enantioselectivity (up to 99%*ee*) Figure 4.[15]

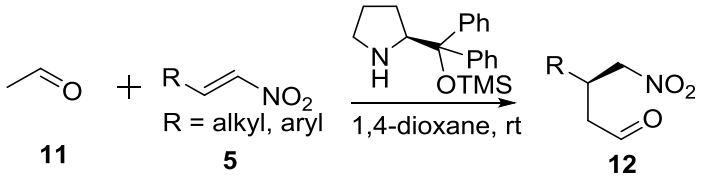


Figure 4. Organocatalyzed Michael addition reaction of acetaldehyde.

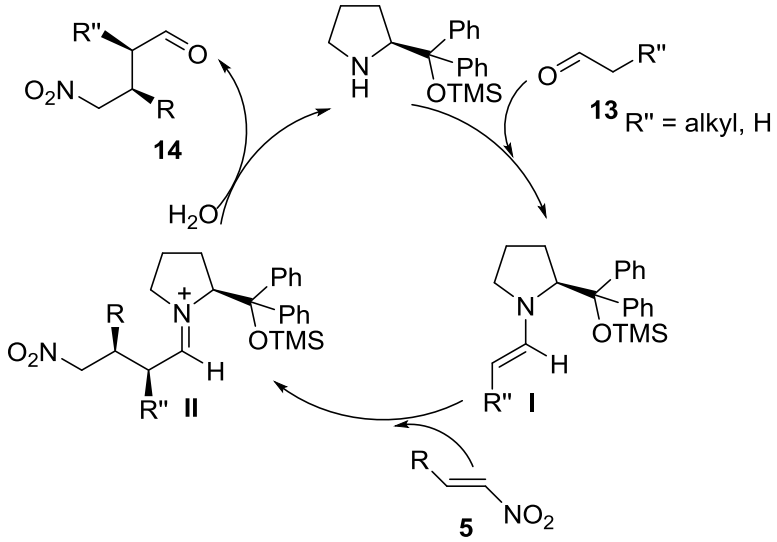


Figure 5. General mechanism for organocatalzyed Michael addition reaction.

A plausible mechanism for the organocatalzyed asymmetric Michael addition reaction of aldehyde to conjugated nitro-olefins is described in Figure **5**. Initially, on treatment with TMS-prolinol organocatalyst aldehyde **13** forms an enamine intermediate **I**, this intermediate on nucleophilic addition with nitro-olefin **5** produces imine intermediate **II**. Finally, the intermediate **II** on hydrolysis generates the nitro-aldehyde adduct **14** with simultaneous release of organocatalyst.

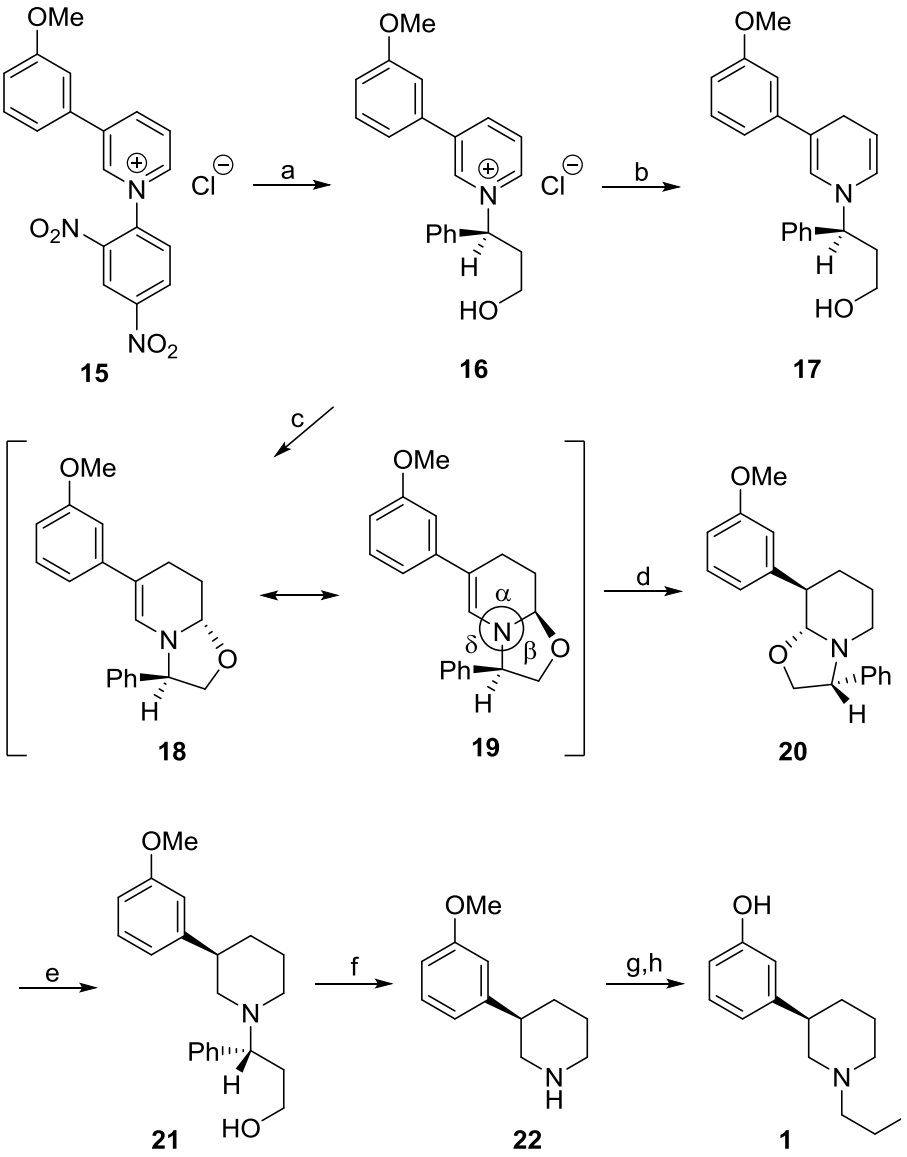
2. Review of Literature

Several synthesis of (-)-preclamol **1** has been reported in literature. Herein, we have described the latest approaches used to synthesize (-)-preclamol **1**.

Das, B. C. *et al*. (1997)[16]

Das, B.C. and co-workers reported the total synthesis (-)-preclamol **1** in seven steps with 26% overall yield. Salt **15** undergoes Zincke reaction to obtain salt **16** in high yield, followed by

reduction of **16** with sodium dithionite afforded a mixture of oxaazolidines **18** and **19**. The LAH reduction of this crude mixture of oxazolidines **18** and **19**, after hydrolysis furnished the

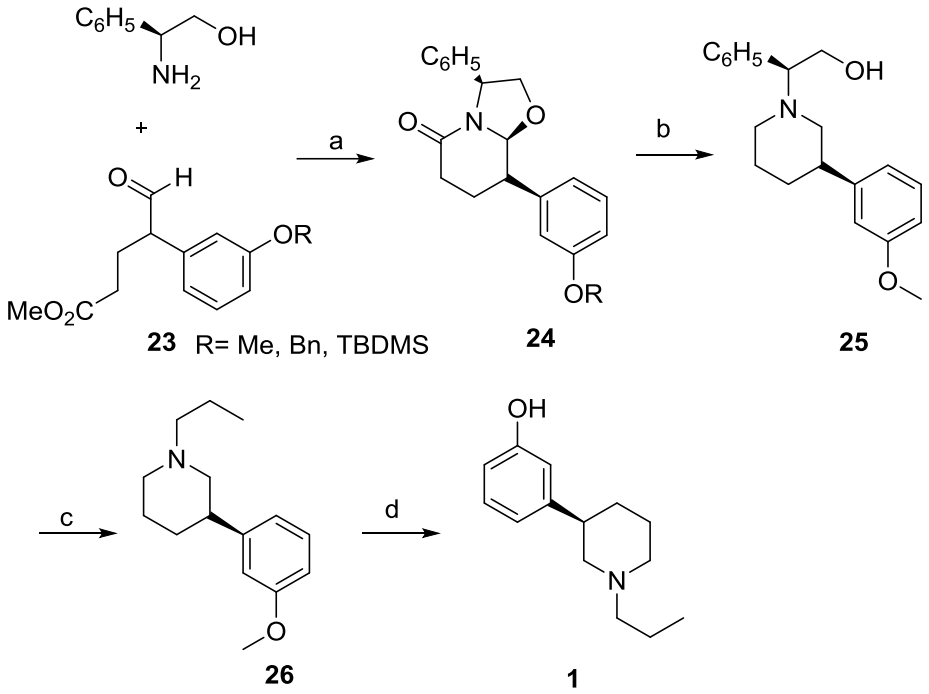


Scheme 1. *Reagents and conditions* **:** (a) (*R*)-(-)-phenylglycinol, *n*-butanol, reflux, 91%; (b) $Na_2S_2O_4$, K_2CO_3, H_2O, refluxing ether, 85%; (c) $Na_2S_2O_2$, K_2CO_2, H_2O, refluxing toluene, 81%; (d) $LiAlH_4$, THF, then H_2O, 74%; (e) $LiAlH_4$, THF, 91%; (f) H_2, Pd/C, HBF_4, 89%; (g) EtCOCl, then $LiAlH_4$, 80%; (h) HBr, reflux, 48%.

derivative **20**. Further reduction with LAH afforded 3-substituted piperidine derivative **21**, subsequently by hydrogenolysis afforded compound **22**. Then a two step propylation led to formation of (-)-preclamol **1**.

Bosch, J. *et al*. (2002)[17]

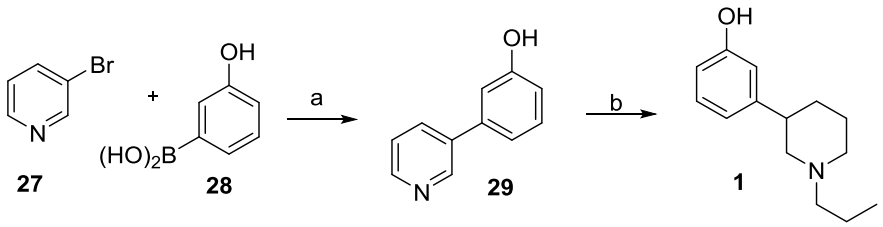
Bosch, J. and co-workers synthesised (-)-preclamol **1**, starting from heating a toluene solution of racemic oxoester **23** and (*S*)-Phenylglycinol to furnish lactam **24**, which on treatment with AlH_3 produced piperidine **25**. Catalytic hydrogenation of piperidine **25** in presence of propionaldehyde, subsequently by dimethylation of n alkyl piperidine **25** using HBr furnished the final compound (-)-preclamol **1**.



Scheme 2. *Reagents and conditions*: (a) toluene, reflux; (b) AlH_3; (c) H_2, $Pd(OH)_2/C$, CH_3CH_2CHO; (d) HBr.

Fernandes, R. A. *et al*. (2015)[18]

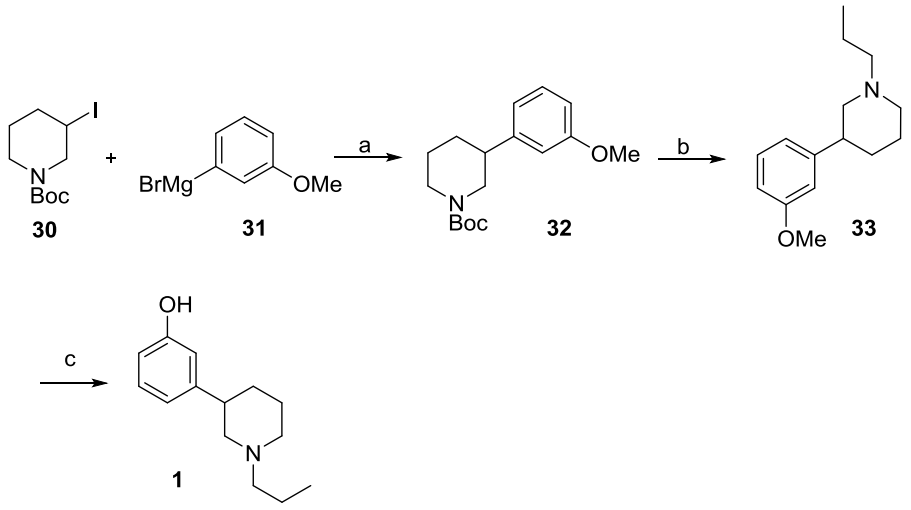
Fernandes, R. A. and co-workers synthesised (-)-preclamol **1** as depicited in Scheme 3. Coupling of pyridyl halides **27** with aryl boronic acid **28** under Suzuki Miyaura cross coupling conditions afforded coupled product **29**. Then compound **29** was then productively changed into (-)-preclamol **1** through *N*-quaternization followed by pyridyl ring hydrogenation.



Scheme 3. *Reagents and conditions* : (a) $Pd(OAc)_2$, ligand, K_2CO_3, EtOH:H_2O (4:1), rt, 1.5-2h; (b) i) C_3H_7Br, CH_3CN, 90 ^oC, 24 h, sealed tube ii) Pt-C, H_2, AcOH : MeOH (2:1), 50 ^oC, 24 h.

Cossy, J. *et al*. (2015)[19]

Cosy, J. and co-workers synthesised (-)-preclamol **1** in 3 steps with 32% overall yield. Coupling reaction of N-Boc 3- iodo piperidine **30** with 3-methoxyphenylmagnesium bromide **31** furnished the *N*-Boc protected piperidine **32** in 88% yield. Boc deprotection of compound **32** was carried out by using trifluoro acetic acid to afford the piperidine which on subsequent reductive amination with propanal furnished the compound **33** in 61% yield. Finally the cleavage of methoxy ether under presence of HBr furnished (-)-preclamol **1** in 63% yield.

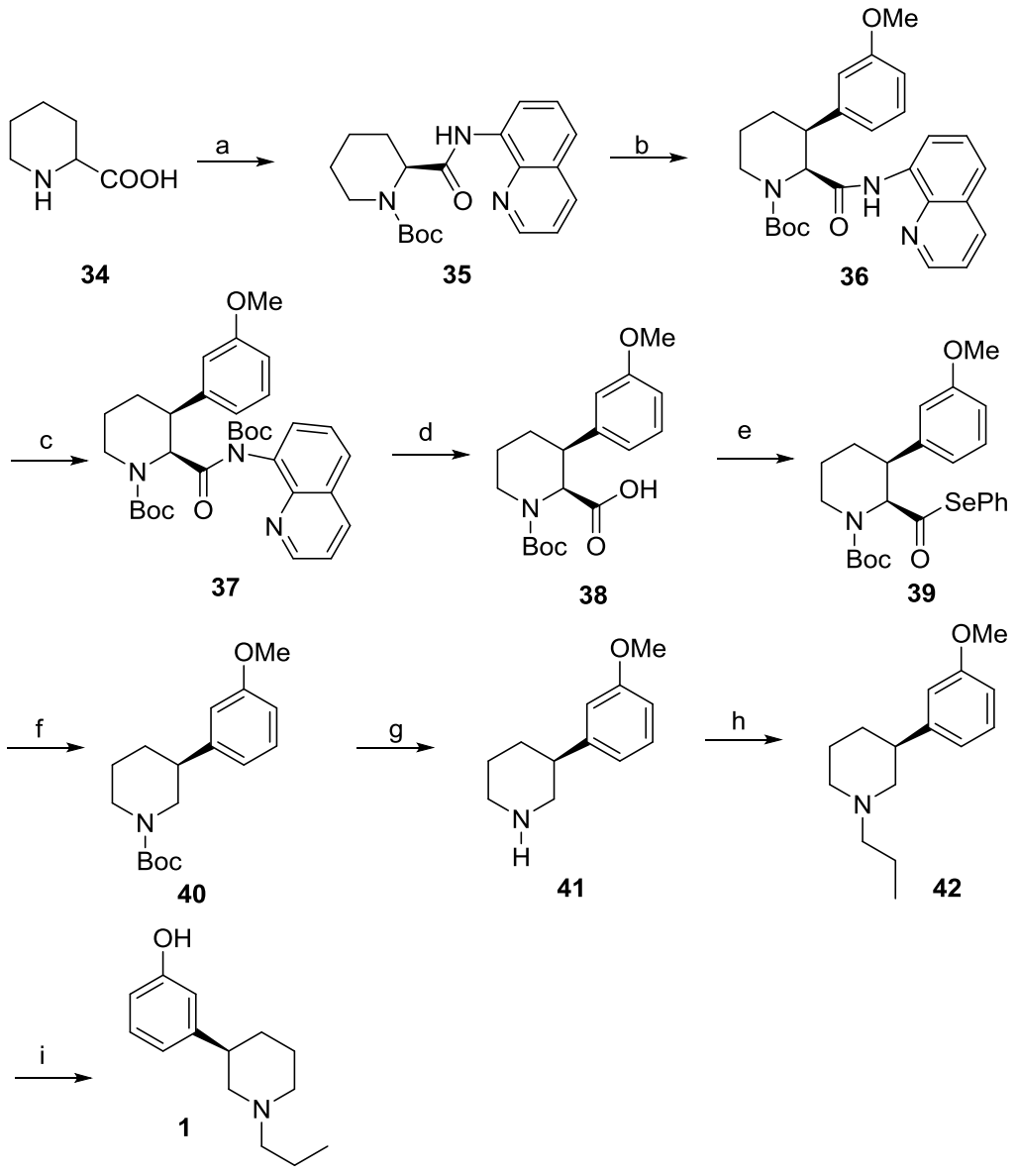


Scheme 4. *Reagents and conditions:* (a) $CoCl_2$, TMCD, -10 ^oC, THF, 88%; (b) i) TFA, rt, CH_2Cl_2 ii) Propanal, $NaBH_3CN$, AcOH, rt, MeOH, 61%; (c) aq. HBr, 100 ^oC, 63%.

Wu, B. *et al*. (2017)[20]

Wu, B**.** and co-workers reported the total synthesis of (-)-preclamol **1** from commercially available L-pipecolinic acid **34**. L-pipecolinic acid on treatment with Boc_2O/NaOH in

dioxane afforded the Boc protected piperidine which on subsequent coupling with 8-amino quninoline furnished the amide compound **35** in 72% yield over two steps. The compound **35** was further arylated through palladium catalyst with 3-iodo anisole to gave compound **36** in 77% yield. Further compound **36** was converted into acid **38** via two step reaction which involves Boc protection and removal of 8-amino quinoline moiety in 91% yield. Compound **38** on treatment with NaSePh, isobutyl chloroformate and *N*-methylmorpholine provided the compound **39** , which on radical decarboxylation furnished the compound **40** in good yield. Finally, Boc deprotection and S_N2-type reaction of compond **40** with 1-iodopropane delivered the compound **41**, which on demethylation with HBr afforded the target compound (-)-preclamol **1**.



Scheme 5. *Reagents and conditions*: (a) i) $(Boc)_2O$, NaOH, dioxane, ii) 8-amino-quinoline, EDCI, DMAP, CH_2Cl_2, 72% for 2 steps; (b) $Pd(OAc)_2$, 3-Iodoanisole, toluene, 100 ^oC, 12 h, AgOAc; (c) Boc_2O, DMAP, CH_3CN, 70 ^oC, 16 h, 83%; (d) LiOH, H_2O_2, 0 ^oC to rt, 91%; (e) *i*-BuOCOCl, N-Methylmorpholine, PhSeNa, THF, -10 ^oC to rt, 12 h, 78%; (f) AIBN, *n*-Bu_3SnH, toluene, N_2, 80 ^oC, 2 h (g) CF_3COOH, CH_2Cl_2, rt, 2 h, 79% for 2 steps; (h) K_2CO_3, *n*-C_3H_7Br, MeCN, 7 h, 75% (i) HBr, N_2, reflux, 120 ^oC, 2 h, 88%.

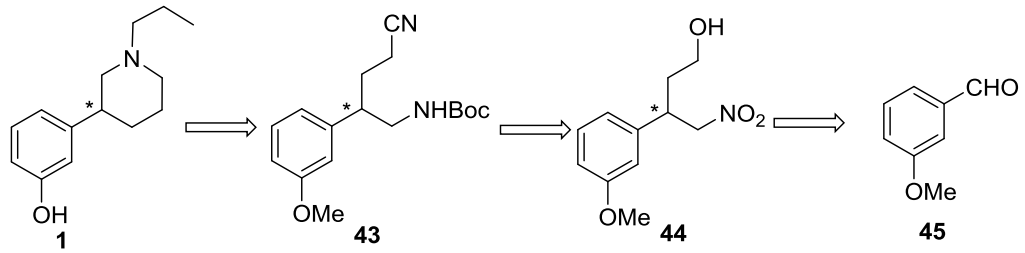
3. Present work:

3.1 Objective

Various synthetic routes for the synthesis of (-)- preclamol **1** have been reported in literature. Despite the existence of adequate synthetic routes, synthesis of (-)-preclamol **1** still requires reduction in total number of steps and strong stereochemical approach leading to high yields. Herein we wish to report a new synthetic approach for the synthesis of (-)-preclamol **1** using Henry reaction, Michael addition and DIBAL-H reduction as key steps.

3.2. Retrosynthetic approach

Our synthetic approach for the synthesis of (-)-3-(3 hydroxyphenyl)-N-(n-propyl)-piperidine [(-)-3PPP, preclamol] **1** was envisioned via the retrosynthetic route as shown in Scheme 6. The cyanide derivative **43** was visualised as a synthetic intermediate from which (-)-3-(3 hydroxyphenyl)-N-(n-propyl)-piperidine [(-)-3PPP, preclamol] **1** could be synthesised through DIBAL-H reduction followed by standard organic transformations. The derivative **43** in turn could be obtained from the nitro-alcohol derivative **44** by hydrogenation followed by base catalyzed nucleophilic substitution reaction. We envisaged that the nitro-alcohol **44** would serve as key intermediate in this approach and could be prepared by means of (*S*)-diphenyl prolinol silyl ether catalyzed Michael addition of acetaldehyde to nitro olefin derived from the aldehyde **45** via standard Henry reaction.

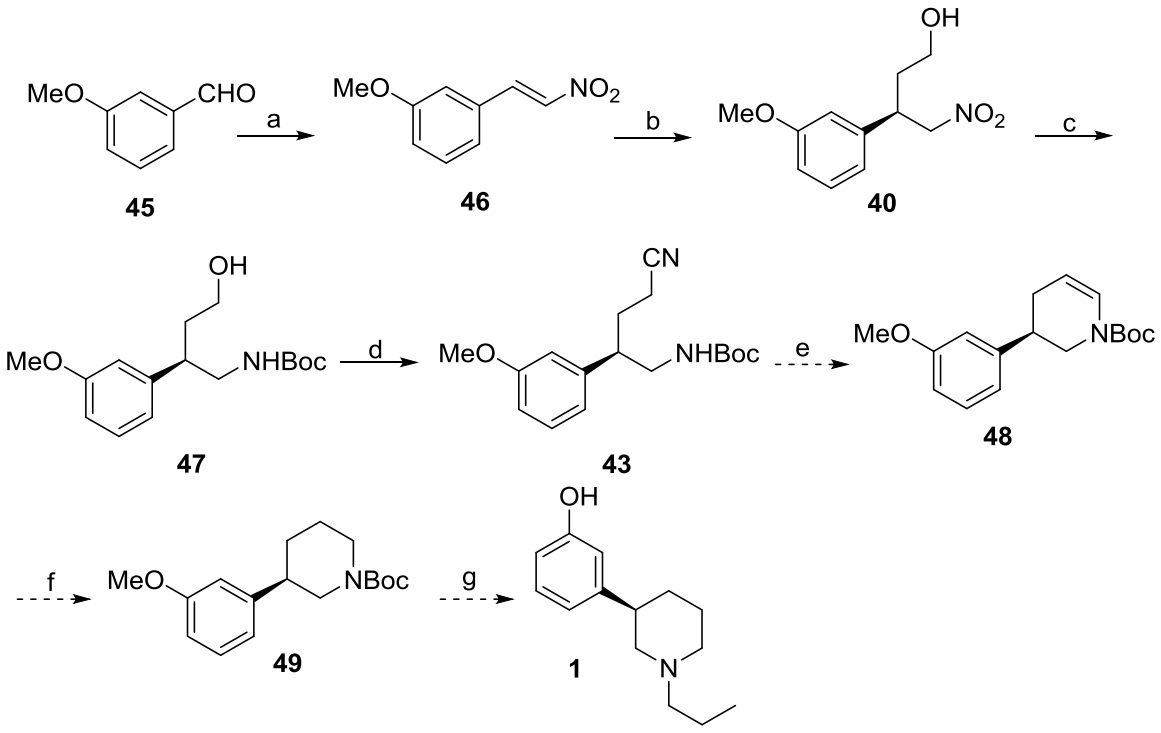


Scheme 6: Retrosynthetic approach for the synthesis of (-)-3-(3 hydroxyphenyl)-N-(*n*-propyl)-piperidine [(-)-3PPP, preclamol **1**].

4. Result and Discussion

As outlined in Scheme 7, the synthesis of (-)-(3 hydroxyphenyl)-N-(*n*-propyl)-piperidine[-(-)-3PPP, Preclamol] **1**, commenced with commercially available 3-methoxy benzldehyde **45.**

Compound **45** on treatment with nitromethane and ammonium acetate furnished nitrostyrene derivative **46** in 92% yield**.** With nitrostyrene derivative in hand, it was subjected to asymmeytic organocatalyzed Michael addition reaction in presence of catalytic amount of (*S*)-diphenyltrimethylsiloxymethyl pyrrolidine to give nitro-aldehyde, which on subsequent reduction with $NaBH_4$ in MeOH delivered nitro-alcohol derivative **40** in 83% yield**.** Nitro-alcohol derivative **40** was then subjected to hydrogenation in presence of catalytic amount of Pd/C and $(Boc)_2O$ to furnish Boc protected derivative **47** with 84% yield. The free hydroxyl group of compound **47** on *O*-mesylation and subsequent treatment with *tetra*-butyl ammonium cyanate in methyl *tert*-Butyl ether furnished cyanide derivative **43** in 96% yield.



Scheme 7. *Reagents and conditions* : (a) CH_3NO_2, NH_4OAc, Reflux, 80 ^oC, 24 h, 92% ; (b) acetaldehyde, TMS-prolinol, 1,4-dioxane, -4 ^oC, 18 h, 83%; (c)H_2, $Pd(OH)_2/C$, EtOAc, $(Boc)_2O$, 18 h, 84%; (d) i) MsCl, Et_3N, DCM, 0 ^oC, 30 min; ii) *n*-Bu_4NCN, MTBE, reflux, 50 ^oC, 3 h, 96%; (e) i) DIBAL-H, DCM; ii) $NaBH_3CN$; (f) H_2, Pd/C; (g) HBr.

In the ^1H NMR spectrum of **46**, aromatic protons were observed resonating at δ 7.99-7.95 (d, J = 8.0 Hz, 1H), 7.59-7.56 (d, J = 16.0 Hz, 1H), 7.39-7.34 (m, 1H), 7.15-7.13 (m, 1H), multiplet corresponding to olefinic protons was observed at δ 7.05-7.03 (m, 2H) and protons of methyl ether were observed at δ 3.85 (s, 3H). In the ^{13}C NMR, aromatic carbons were found resonating at δ 160.1, 131.3, 130.5, 121.8, 118.0, 114.0. The olefinic carbon were found resonating at δ 139.1, 137.4. The characteristic methyl carbon was observed at δ 55.5.

In the ^1H NMR spectrum of **40**, aromatic protons were observed resonating at δ 7.27-7.23 (m, 1H), 6.82-6.79 (m, 2H), 6.758-6.754 (m, 1H). A multiplet was observed at δ 4.66-4.56 (m, 1H) due to protons adjacent to nitro group, singlet corresponding to three methyl protons was observed at δ 3.79 (s, 3H), multiplet corresponding to protons adjacent to hydroxyl group were observed at δ 3.67-3.56 (m, 2H), protons adjacent to benzylic group were observed resonating at δ 3.50-3.44 (m, 1H). The characteristic hydroxyl protons appear as a broad singlet at δ 2.20 (brs, 1H). Methylene protons were found resonating at δ 1.95-1.87 (m, 2H). In the ^{13}C NMR, aromatic carbons were found resonating at δ 159.8, 140.4, 130.0, 119.1, 113.6, 112.6. Carbons adjacent to nitro group and hydroxyl group was observed resonating at δ 80.4, 60.4, respectively. The characteristic carbon of methyl ether was observed at δ 55.1. Two peaks at δ 40.9, 30.9 were observed due to methylene carbon and carbon adjacent to benzylic ring.

In the ^1H NMR spectrum of **47**, showed aromatic protons were observed resonating at δ 7.27-7.22 (m, 1H), 6.79-6.77 (m, 3H). A broad singlet corresponding to proton of hydroxyl was found at δ 4.52 (brs, 1H). A singlet corresponding to three protons of methyl ether were observed at δ 3.80 (s, 3H), protons adjacent to benzylic group and that to hydroxyl group were found resonating at δ 3.64-3.58 (m, 1H), 3.54-3.51 (m, 2H). The protons adjacent to Boc protected amine group were found resonating at δ 3.21-3.14 (m, 1H), 2.95-2.88 (m, 1H), methylene protons were observed at δ 1.97-1.88. A broad singlet due to free hydroxyl group was observed at δ 1.84-1.76 (s, 1H). The characteristic protons of *t*-butoxy group of Boc was observed at δ 1.38 (s, 9H). In the ^{13}C NMR, aromatic carbons were observed resonating at δ 159.7, 144.0, 129.7, 120.0, 113.6, 111.8. Carbons adjacent to hydroxyl group, Boc protected

amine group and benzylic group were observed resonating at δ 60.5, 45.8, and 36.1 respectively. Methylene carbon was observed at δ 42.2. Carbons of amine protected group were found resonating at δ 156.0 and 28.3

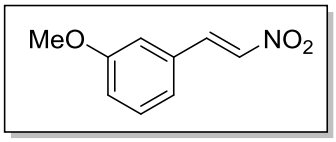
In the ^{1}H NMR spectrum of **43**, aromatic protons were observed resonating at δ 7.25-7.22 (m, 1H), 6.82-6.75 (m, 2H), 6.71 (brs, 1H). A broad singlet corresponding to amine group was found resonating at δ 4.46 (brs, 1H). A singlet corresponding to protons of methyl ether were observed at δ 3.79 (s, 3H). Protons adjacent to benzylic, amine protecting group and to that of cyano group were found resonating at δ 3.53-3.42 (m, 1H), 3.31-3.17 (m, 2H), 3.03-2.95 (m, 2H). The two methylene protons were observed at δ 2.16-2.08 (m, 1H) and 2.03-1.95 (m, 1H). The characteristic protons of *t*-butoxy group of amine protecting group were observed at δ 1.38 (s, 9H). In the ^{13}C NMR, aromatic carbon were found resonating at δ 159.8, 142.5, 129.8, 113.7 and 112.1.Carbons of amine protecting Boc group were observed at δ 155.8, 79.2 and 28.4, cyanide carbon was observed at δ 120.0. The characteristic carbon of methyl ether resonate at δ 55.1. Carbons adjacent to amine protecting group, benzylic and to cyano group resonate at δ 45.6, 43.3 and 36.1. Methylene carbon was found resonating at δ 42.5.

5. Conclusion

In conclusion, an enantioselective approach towards the development of a new synthetic route of (-)-preclamol from 3 methoxy benzaldehyde **45** has been attempted employing Henry reaction, asymmetric Michael addition showing the catalytic activity of TMS prolinol, DIBAL-H reduction as key steps. The merits of this approach is to provide a high yielding reaction steps. The protocol to synthesize the (-)-preclamol **1** is reached to synthesis of **39** and rest of work is in progress and will be reported in due course of time.

6. Experimental section

6.1. (*E*)-1-methoxy-3-(2-nitrovinyl)benzene, 46



To a solution 3-methoxy benzaldehyde **45** (2.0 g, 14.6 mmol) in nitomethane (46 mL) was added ammonium acetate (1.12 g, 14.6 mmol). The reaction mixture was refluxed for 24 h. After the completion of reaction, the reaction mixture was quenched with water, extracted

with ethyl acetae (3 x 30 mL). The combined organic layers were dried over anhydrous Na_2SO_4, concentrated in vacuo, purified by silica gel column chromatography (EtOAc/hexane 0.5:9.5) to afford the compound **46.**

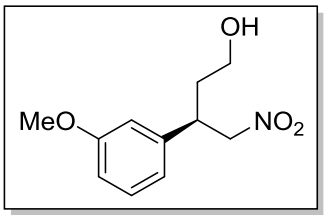
Yield: 2.4 g, 92%.

Molecular formula: $C_9H_9NO_3$

^{1}H NMR (400MHz, $CDCl_3$): δ 7.99-7.97 (d, J = 8Hz, 1H), 7.59-7.55 (d, 16Hz,1H), 7.39-7.34 (m, 1H), 7.15-7.13 (d, 1H), 7.05-7.03 (m, 2H).

^{13}C NMR (100MHz, $CDCl_3$): δ 160.2, 139.2, 137.4, 131.4, 130.5, 121.8, 118.0, 114.0, 114.0, 55.5.

6.2 (*R*)-3-(3-methoxyphenyl)-4-nitrobutan-1-ol, 40



To a 1, 4-dioxane Solution (2.8 mL) was added a mixture of (*S*)-diphenyltrimethylsiloxymethyl pyrrolidine (0.436 g, 1.34 mmol), nitrostyrene (2.4 g, 13.4 mmol) and acetaldehyde (5.90 g, 134.0 mmol) in a sealed tube at a temperature of -4 ^oC. The reaction mixture was stirred for 18 h and then quenched with 1N HCl, extracted with EtOAc (3 x 30 mL). The combined organic layers were dried over Na_2SO_4, concentrated in vacuo and is used as such for the next step without purification.

To the above crude product were added methanol (25 mL) and sodium borohydride (0.683 g, 20.1 mmol). The reaction mixture was allowed to stir at 0 ^oC for 30 minutes. After the completion of reaction, the reaction mixture was quenched with saturated NH_4Cl solution, extracted with EtOAc (3 x 30 mL), dried over anhydrous Na_2SO_4, concentrated in vacuo, purified by silica gel column chromatography (EtOAc/Hexane 3:7) to afford the compound **40**.

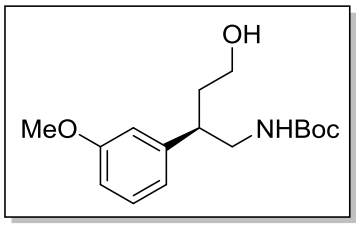
Yield: 2.5 g, 83%.

Molecular formula: $C_{11}H_{13}NO_4$

^{1}H NMR (400MHz, $CDCl_3$): δ 7.25-7.23 (m, 1H), 6.82-6.79 (m, 2H), 6.758-6.754 (m, 1H), 4.66-4.56 (m, 2H), 3.79 (s, 3H), 3.67-3.56 (m, 2H), 3.50-3.44 (m, 1H), 2.20 (brs, 1H), 1.95-1.87 (m, 1H)

^{13}C NMR (100MHz, $CDCl_3$): δ 159.8, 140.3, 130.0, 119.6, 113.6, 112.5, 80.4, 60.4, 59.6, 55.1, 40.9, 35.5.

6.3 *tert*-butyl (*R*)-(4-hydroxy-2-(3-methoxyphenyl)butyl)carbamate, 47



To a solution of **40** (2.5 g, 11.1 mmol) in EtOAc was added catalytic amount of $Pd(OH)_2/C$ and $(Boc)_2O$ (1.32 g, 11.2 mmol). The reaction mixture was subjected to hydrogenation for 24 h. After completion of reaction, reaction mixture was filtered through celite and was washed with 20% MeOH/DCM (50 mL) solution. The resulting solution was dried over Na_2SO_4, concentrated in vacuo, purified by silica gel column chromatography (EtOAc/hexane 3.5:6.5) to furnish compound **47**.

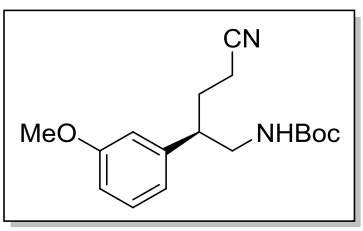
Yield: 2.7 g, 84%.

Molecular formula: $C_{16}H_{25}NO_4$

^{1}H NMR (400MHz, $CDCl_3$): δ 7.24-7.20 (m, 1H), 6.77-6.71 (m, 3H), 4.49 (brs, 1H), 3.78 (s, 3H), 3.61-3.56 (m, 1H), 3.52-3.45 (m, 1H), 3.18-3.11 (m, 1H), 2.93-2.85 (m, 1H), 1.94-1.86 (m, 1H), 1.94-1.86 (m, 2H), 1.82-1.73 (m, 1H), 1.38 (s, 9H)

^{13}C NMR (100MHz, $CDCl_3$): δ 159.7, 156.0, 144.0, 129.7, 120.0, 113.6, 111.8, 79.3, 60.5, 55.1, 45.8, 42.2, 36.1, 28.3.

6.4 tert-butyl (*R*)-(4-cyano-2-(3-methoxyphenyl)butyl)carbamate, 43



To a solution a alcohol **47** (2.7 g, 9.14 mmol) in DCM (30 mL) was treated with triethylamine (1.20 g, 11.8 mmol) followed by dropwise addition of methane sulphonyl chloride (1.1 g, 10.05 mmol). The reaction mixture was allowed to stir at a temperature of 0 ^{o}C for 30 minutes, quenched with saturated $NaHCO_3$ solution, extracted with DCM (3 x 30 mL). The combined organic layers were dried over anhydrous Na_2SO_4, concentrated in vacuo, which was immediately used in next reaction without purification.

The crude obtained from the above reaction was dissolved in t-butyl ether (30 mL) and then treated with tetrabutylammonium cyanide (4.8 g, 18.2 mmol). The reaction mixture was refluxed at a temperature of 50 ^{o}C for 3 h. The reaction mixture was quenched with saturated $NaHCO_3$ solution, extracted with EtOAc (3 x 30 mL). The organic phase was then dried over anhydrous Na_2SO_4, concentrated in vacuo, purified by silica gel column chromatography (EtOAc:hexane 1:9) to obtain compound **43**.

Yield: 2.6 g, 96%.

Molecular formula: $C_{17}H_{24}N_2O_3$

^{1}H NMR (400MHz, $CDCl_3$): δ 7.25-7.22 (m, 1H), 6.84-6.77 (m, 2H), 6.71 (brs, 1H), 4.44 (brs, 1H), 3.80 (s, 3H), 3.53-3.42 (m, 2H), 3.31-3.17 (m, 2H), 3.03-2.95 (m, 2H), 2.16-2.08 (m, 1H), 2.03-1.95 (m, 1H), 1.40 (s, 9H).

^{13}C NMR (100MHz, $CDCl_3$): δ 159.8, 155.8, 142.5, 129.8, 120.0, 113.7, 112.1, 79.2, 55.1, 45.6, 43.3, 42.599, 36.1, 28.5, 28.3.

References

1. (a) Kaellstroem, S.; Leino, R. *Bioorg*. *Med*. *Chem*. **2008**, *16*, 601-635; (b) Risi, D. C.; Fanton, G.; Pollini, G. P.; Trapella, C.; Valente, F.; Zanirato, V. *Tetrahedron Asymmetry* **2008**, *19*, 131-155; (c) Escolano, C.; Amat, M.; Bosch, J. *Chem*. *Eur*. *J*. **2006**, *12*, 8198-8200; (d) Cossy, J. *Chem*. *Rec*. **2005**, *5*, 70-80; (e) Puchot, K. C.; Comesse, S. *Amino Acids* **2005**, *29*, 101-130; (f) Fraser, H. L.; Floyd, M. B.; Sosa, A. C. B. *Prog*. *Heterocycl*. *Chem*. **2005**, *17*, 261-303; (g) Buffat, M. G. P. *Tetrahedron* **2004**, *60*, 1701-1729; (h) Laschat, S.; Dickner, T. *Synthesis* **2000**, 1781-1813; (i) Bailey, P. D.; Millwood, P. A.; Smith, P. D. *Chem*. *Commun*. **1998**, 633-640.
2. (a) Ahari, M.; Perez, A.; Menant, C.; Vasse, J. L.; Szymoniak, J. *Org*. *Lett*. **2008**, *10*, 2473-2476; (b) Alegret, C.; Ginesta, X.; Riera, A. *Eur*. *J*. *Org*. *Chem*. **2008**, 1789-1796; (c) Hooghe, M.; Dejaegher, Y.; Kimpe, D. N. *Tetrahedron* **2008**, *64*, 4575-4584; (d) Garrido, N. M.; Garcia, M.; Diez, D.; Sanchez, M. R.; Sanz, F.; Urones, J. G. *Org*. *Lett*. **2008**, *10*, 1687-1690; (e) Takahashi, M.; Micalizio, G. C. *J*. *Am*. *Chem*. *Soc*. **2007**, *129*, 7514-7516; (f) Kalamkar, N. B.; Kasture, V. M.; Dhavale, D. D. *J*. *Org*. *Chem*. **2008**, *73*, 3619-3622; (g) Davis, F. A.; Ramachandar, T. *Tetrahedron Lett*. **2008**, *49*, 870-872; (h) Pedersen, C. M.; Bols, M. *Tetrahedron* **2005**, *61*, 115-122; (i) Nencetti, S.; Demontis, G. C.; Mazzoni, M. R.; Betti, L.; Banti, I.; Rossello, A.; Lapucci, A. *J*. *Pharm*. *Pharmacol*. **2008**, *59*, 1439-1445; (j) Jin, J.; Wang, Y.; Wang, F.; Shi, D.; Erhard, K. F.; Wu, Z.; Guida, B. F.; Lawrence, S. K.; Behm, D. J.; Disa, J.; Vaidya, K. S.; Evans, C.; McMillan, L. J.; Rivero, R. A.; Neeb, M. J.; Douglas, S. A. *Bioorg*. *Med*. *Chem*. *Lett*. **2008**, *18*, 2860-2864; (k) Kokotos, C. G.; Aggarwal, V. K. *Chem*. *Commun*. **2006**, 2156-2158; (l) Liang, N.; Srinivas, P.; Datta, A. *Tetrahedron Lett*. **2005**, *46*, 7221-7223.
3. Gunasekara, N. S.; Noble, S.; Benfield, P. *Drugs* **1998**, *55*, 85-120; (b) Wagstaff, A. J.; Cheer, S. M.; Matheson, A. J.; Ormrod, D.; Goa, K. L. *Drugs* **2002**, *62*, 655-703.
4. (a) Pirtosek, Z.; Merello, M.; Carlsson, A.; Stern, G. *Adv*. *Neurol*. **1996**, *69*, 535-540; (b) Wikstroem, H.; Sanchez, D.; Lindberg, P.; Hacksell, V; Arvidsson, L. E.; Johansson, A. M.; Thorberg, S. O.; Nilsson, J. L. G.; Svensson, K.; *J*. *Med*. *Chem*.

1984, *27*, 1030-1036; (c) Tamminga, C. A.; Cascella, N. G; Lahti, R. A.; Lindberg, M.; Carlsson, A. J. *Neural Transm*. **1992**, *88*, 165-175; (d) Pirtosek, Z.; Merello, M.; Carlsson, A.; Stern, G. *Adv*. *Neurol*. **1996**, *69*, 535-540.

5. Liljefors, T.; Wikstrom, H. *J. Med Chem*. **1986**, *29*, 1896-1904.
6. (a) Astra, P. *Drugs Future* **1987**, *12*, 88-89; (b) Wikstrom, H.; Sanchez, D.; Lindberg, P.; Hacksell, U.; Arvidsson, L. E.; Johansson, A. M.; Thorberg, S. O.; Nilsson, J. L. G.; Svensson, K.; Hjorth, S.; Clark, D.; Carlsson, S. *J. Med. Chem*. **1984**, *27*, 1030-1036; (c) Liljefors, T.; Wikstrom, H. *J. Med. Chem*. **1986**, *29*, 1896-1904.
7. Heusler, P.; Newman, T. A.; Castro, F. A.; Cussac, D. *Neuropharmacology* **2007**, *52*, 1106-1113.
8. Jordan S.; Johnson J. L.; Regardie, K. *Prog Neuropsychopharmacol Biol Psychiatry* **2007**, *31*, 348-356.
9. Novi, F.; Millan, M. J.; Corsini, G. U.; Maggio, R. J. *Neurochem*. **2007**, *102*, 1410-1424.
10. Lane, J. R.; Powney, B.; Wise, A.; Rees, S.; Milligan, G. *Mol Pharmacol*. **2007**, *71*, 1349-1359.
11. Tamminga, C. A.; Cascella, N. G.; Lahti, R.A.; Lindberg, M.; Carlsson, A. *J. Neural Transm*. **1992**, *88*, 165-175.
12. Mailman, R. B.; Murthy, V. *Curr Pharm Des*. **2009**, *16*, 488-501.
13. Lahti, A. C.; Weiler, M. A.; Corey, P. K.; Lahti, R. A.; Carlsson, A.; Tamminga, C. *Biol Psychiatry*. **1998**, *4*, 2-11.
14. Little, R. D.; Masjedizadeh, M. R.; Wallquist, O.; McLoughlin, J. I. *J. Org. React*. **1995**, *47*, 315-552.
15. Hayashi, Y.; Gotoh, H.; Hayashi, T.; Shoji, M. *Angew. Chem. Int. Ed.* **2005**, *44*, 4212-4215.
16. Wong, S. W.; Marazano, C.; Gnecco, D.; Genisson, Y.; Chiaroni A.; Das, B. C. *J. Org. Chem*. **1997**, *62*, 729-733.
17. Amat, M.; Canto, M.; Llor, N.; Escolano, C.; Molins, E.; Espinosa, E.; Bosch, J. *J. Org. Chem*. **2002**, *67*, 5343-5351.
18. Nallasivam, J. L.; Fernandes, R. A. Eur. *J. Org. Chem*. **2015**, 3558-3567.
19. Gonnard, L.; Guerinot, A.; Cossy, J. *Chem. Eur. J*. **2015**, *21*, 12797-12803.
20. Zhang, S. J.; Sun, W. W.; Yu, Q. Y.; Cao, P.; Dong, X. P.; Wu, B. *Tetrahedron lett*. **2017**, *58*, 606-609.

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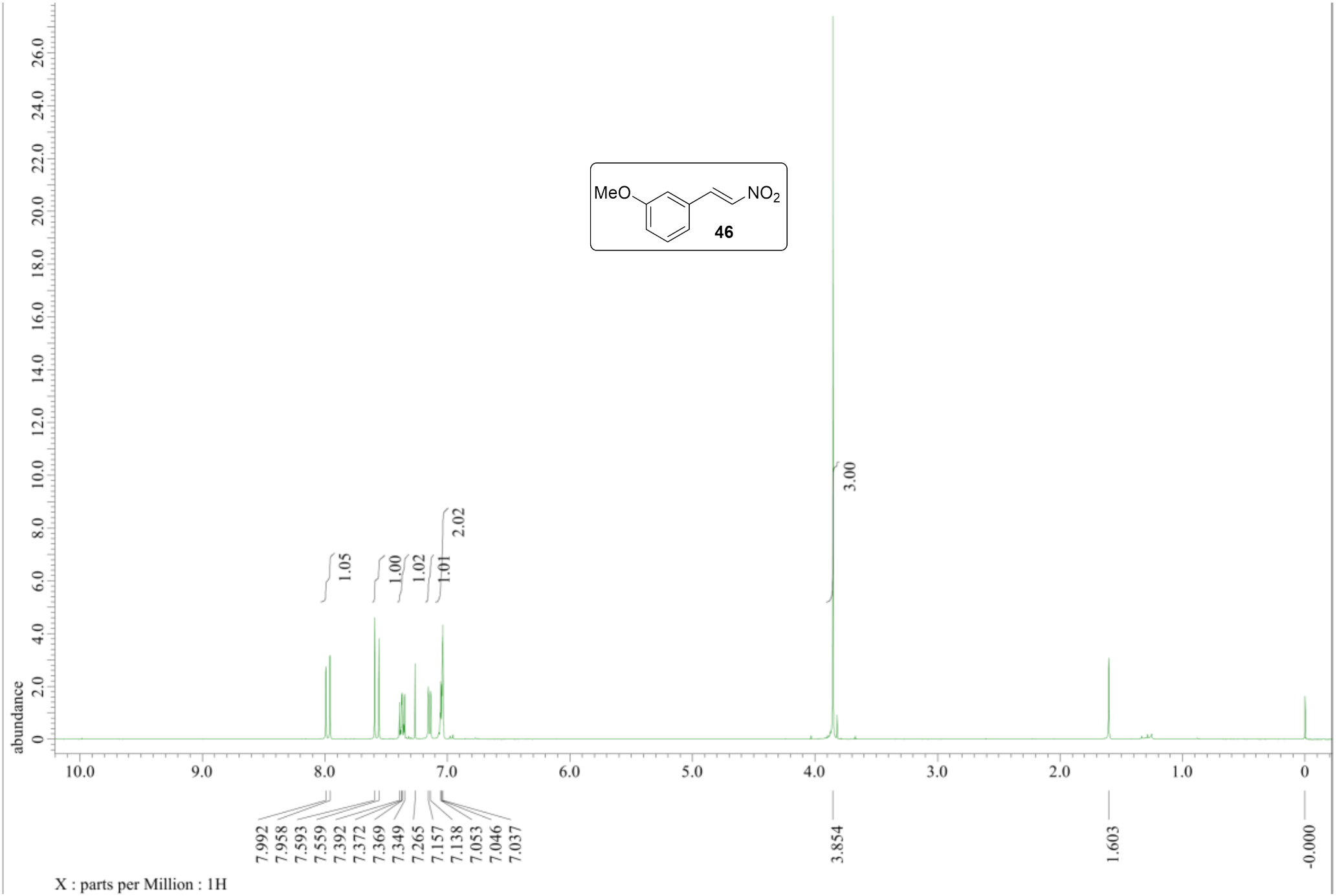

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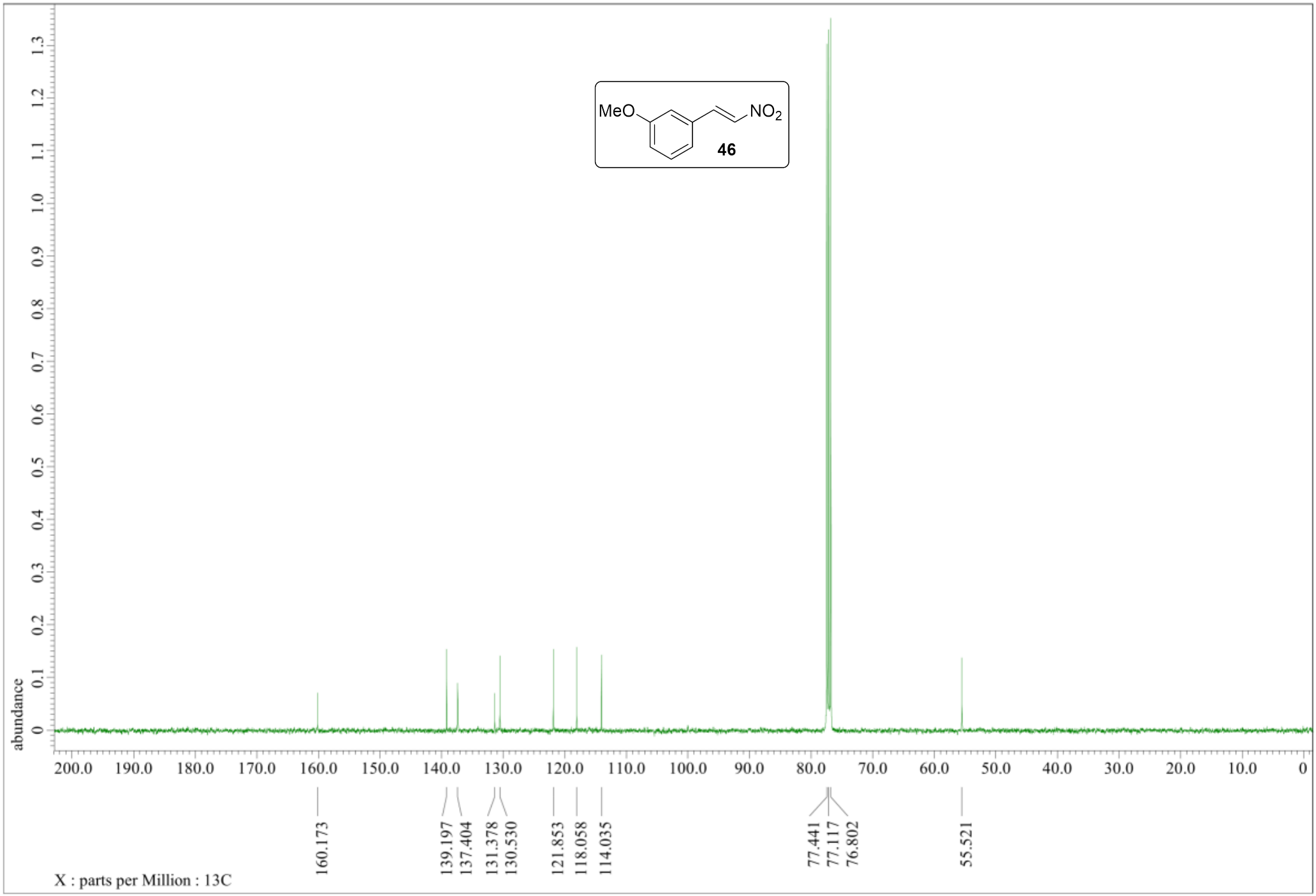

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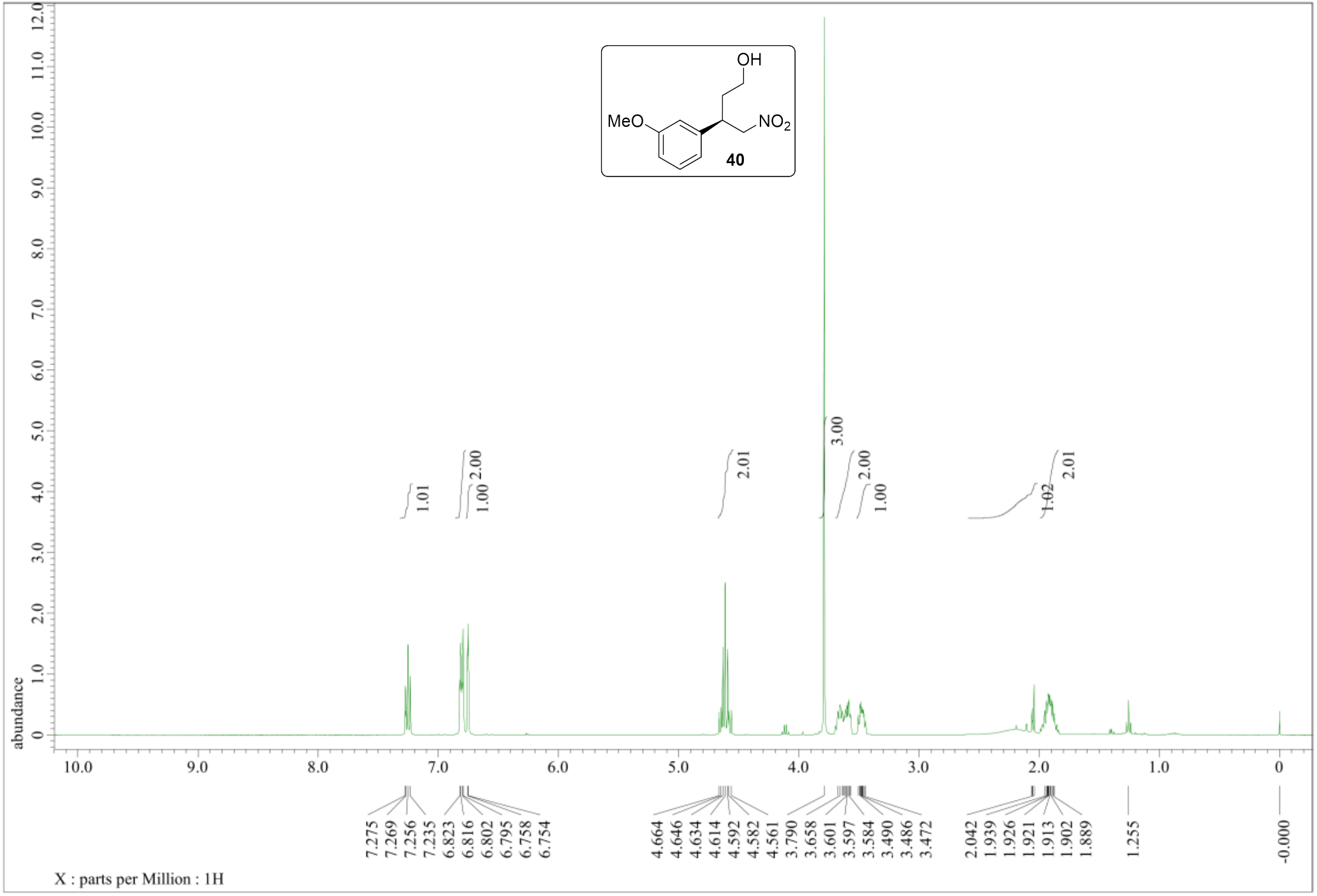

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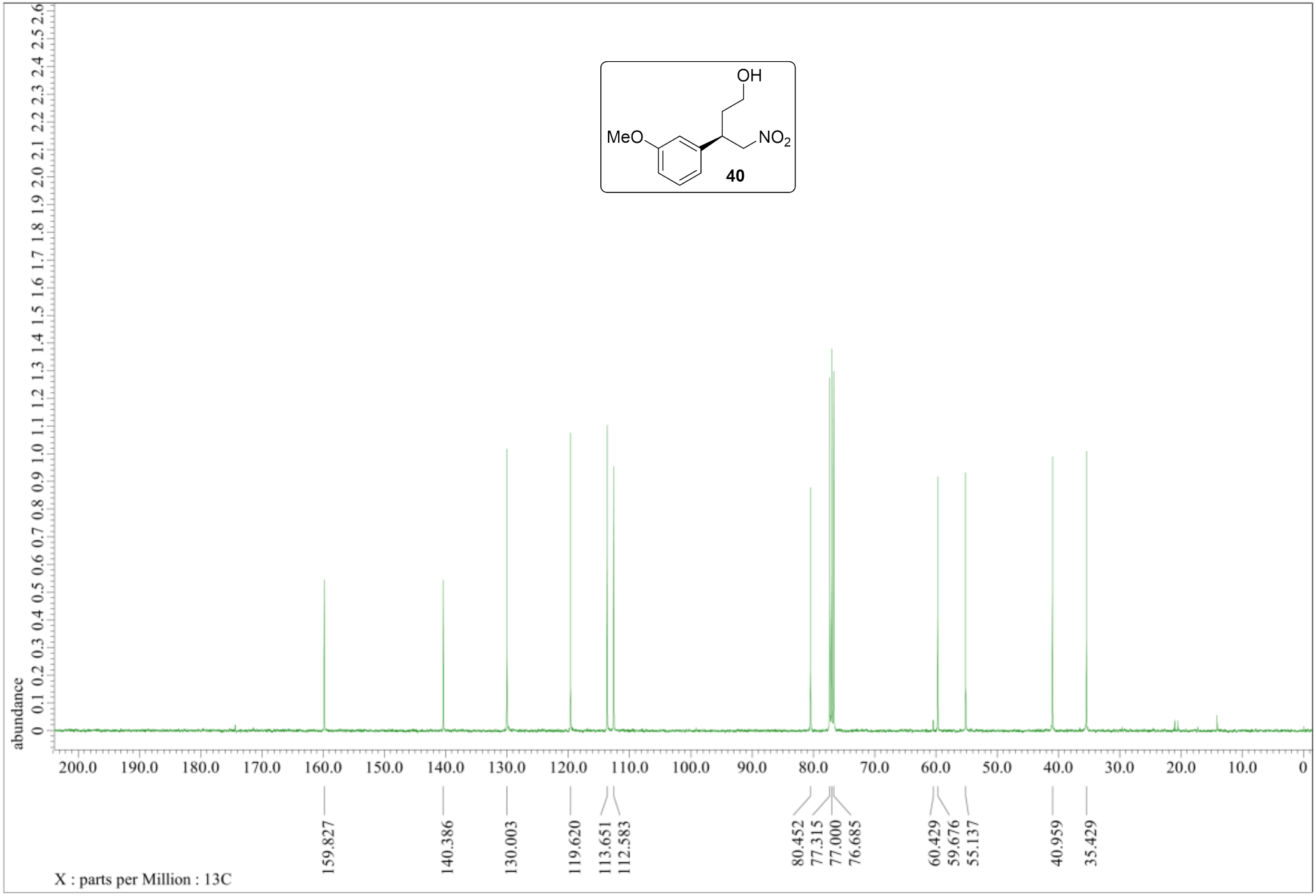

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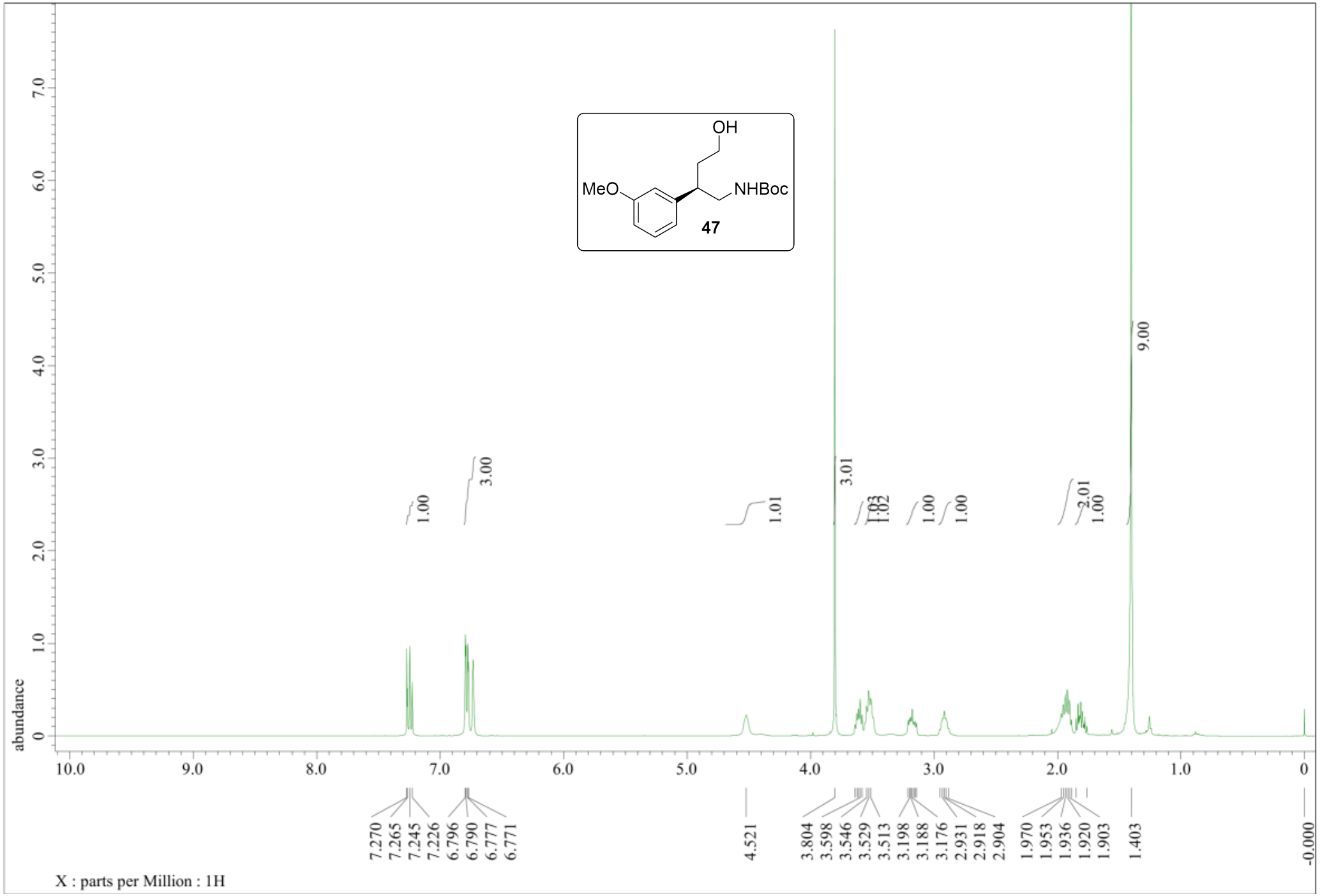

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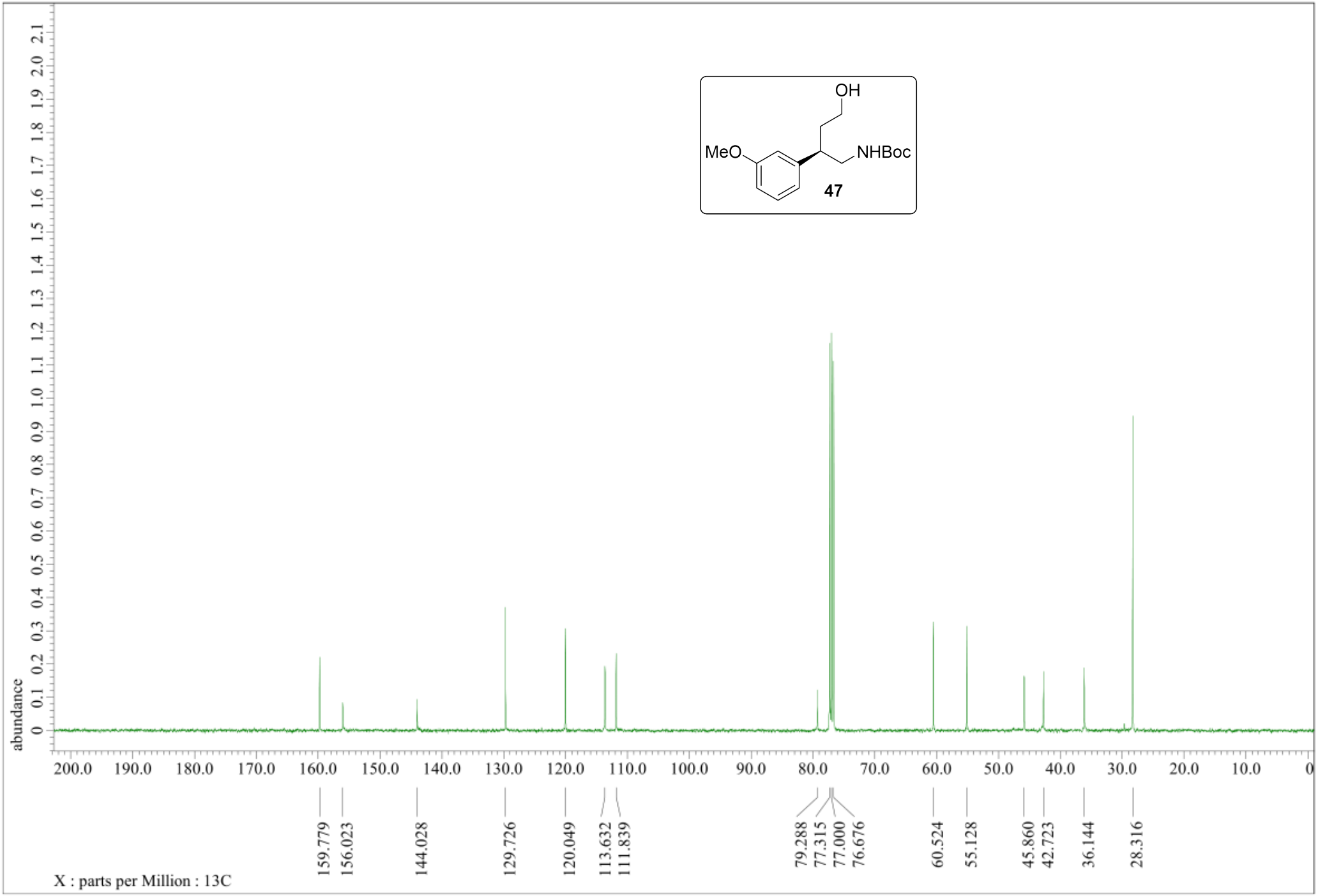

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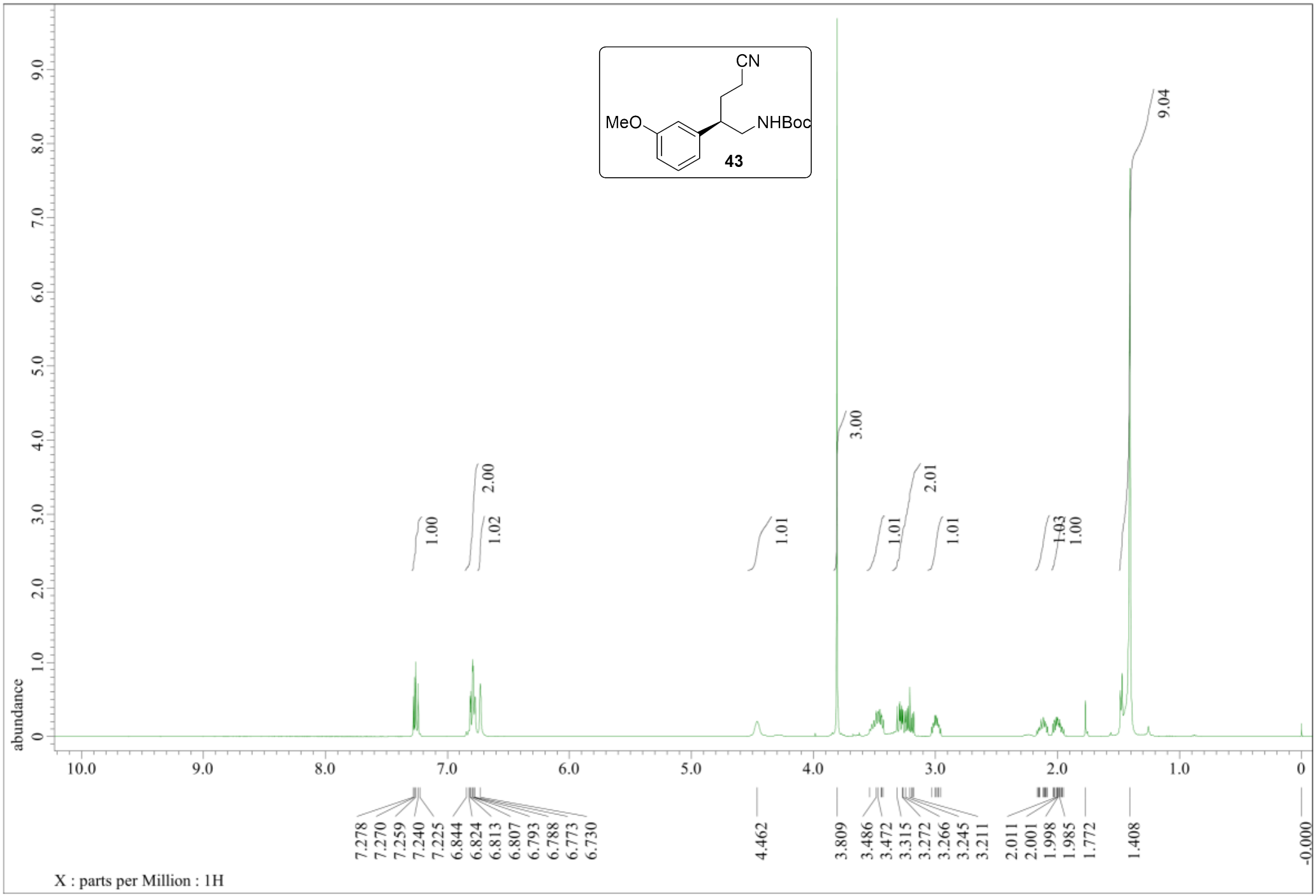

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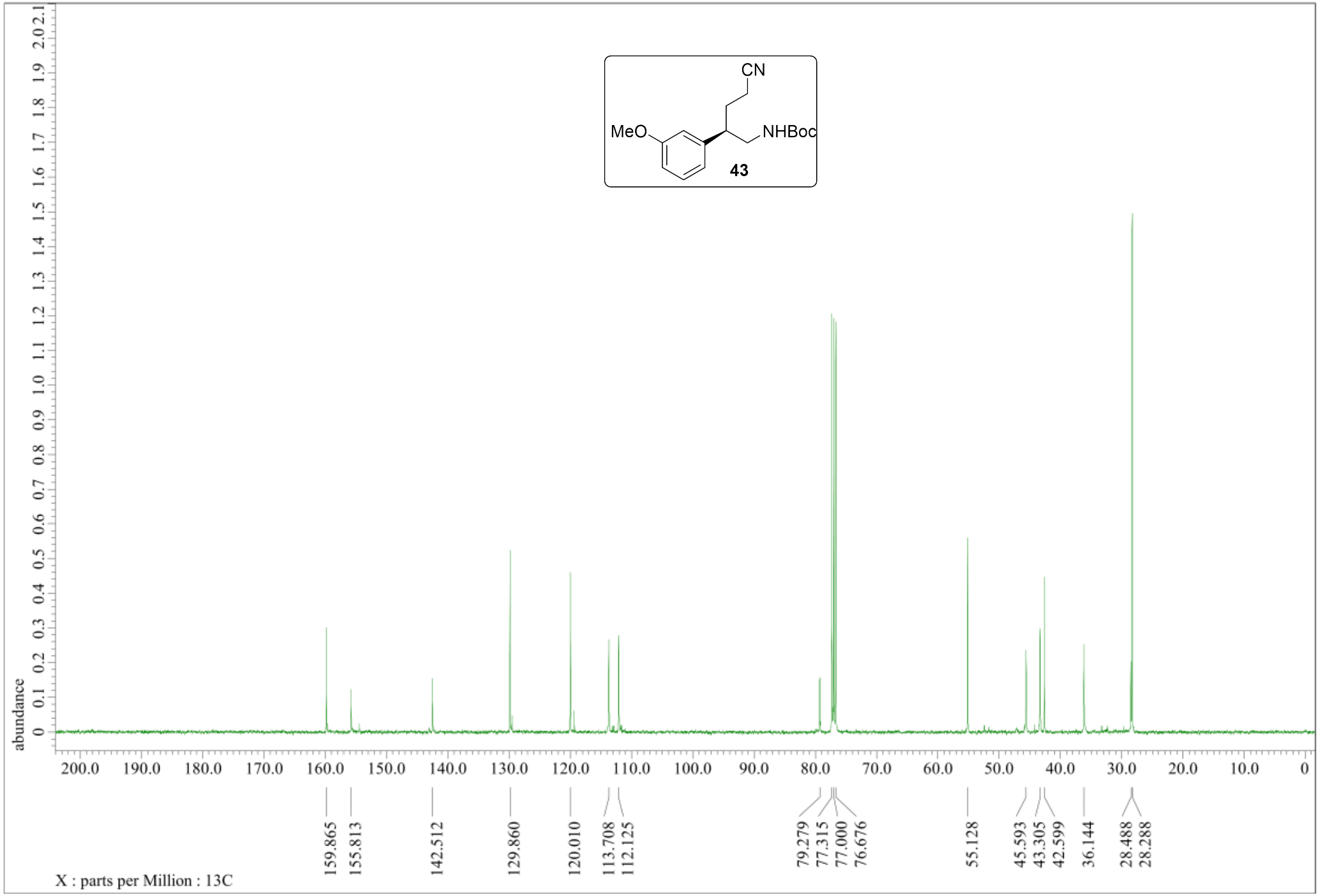

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Publication

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Chih-Chien Hsieh, Ping-Yee Law, Horace H. Loh, Chuan Shih, Yiu-Kay Lai, Shiu-Hwa Yeh, and Shau-Hua Ueng. "Discovery, structure-activity relationship studies, and anti-nociceptive effects of N-(1,2,3,4-tetrahydro-1-isoquinolinylmethyl)benzamides as novel opioid receptor agonists", European Journal of Medicinal Chemistry, 2017.
Publication

---

23 Buchner, I.K.. "A rapid and general access to 3-arylpiperidines", Tetrahedron Letters, 20010806 <%1
Publication

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