An Efficient Approach Towards Total Synthesis of Retinoid Compounds

Thesis submitted in partial fulfilment of the requirements

For the award of the degree of

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In

Chemistry

Submitted By:

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Under the guidance of

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to the

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INDIA

2017

Candidate's Declaration

I hereby declare that the work being presented in the dissertation entitled. "***An Efficient Approach Towards Total Synthesis of Retanoid Compounds***" 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. Satyendra Kumar Pandey.** My thesis has not previously formed the basis for award of any degree, or other similar title or recognition.

Bimal Kumar

Patiala **Bimal Kumar**

Date: 3 July, 2017

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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Certificate

This is to certify that the project entitled "***An Efficient Approach Towards Total Synthesis of Retinoid Compounds***" being submitted by Mr. Bimal Kumar, Roll No: 301502008 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 a bonafide work carried under the supervision of Dr. Satyendra Kumar Pandey and no part of this project has been submitted for award of any other degree in this or any other university.

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LIST OF CONTENTS

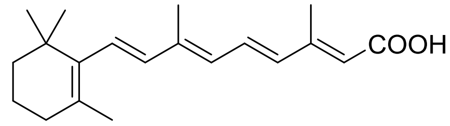
CONTENTS **PAGE NO.**

1. INTRODUCTION 1-3
2. REVIEW OF LITERATURE 3-4
3. PRESENT WORK
    3.1 OBJECTIVES 5
    3.2 RETROSYNTHETIC APPROACH 5-6
4. RESULT AND DISCUSSION 6-9
5. CONCLUSION 9-10
6. EXPERIMENTAL SECTION 10-13
7. REFERENCES 14-16
8. SPECTRA 16-28

An Efficient Approach Towards Total Synthesis of Retinoid Compounds

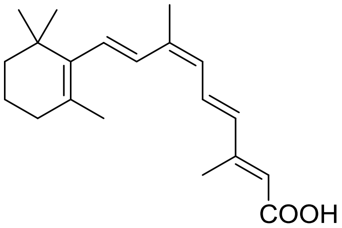
1. Introduction

Retinoids exist as natural and synthetic analogues of Vitamin A, retinol and all-*trans*-retinoic acid (ATRA) **1**. These small hormones are important biologically active molecules that have essential functions in cell growth, proliferation, modulation, differentiation and various physiological processes such as vision[1]. Naturally occurring retinoids are responsible for the health of central nervous system (CNS)[2] and the embryonic development in vertebrates[3]. In adult brain ATRA has got a very important place as it is the reason for growth and survival of neurons, development of neural connections etc. Also ATRA is found in that hippocampus area of the brain which involves major neural processes such as long term depression and learning memory.[4, 5]



1

Due to binding and activating the nuclear receptors undergo conformational changes and the retinoids regulate the gene transcription.[6, 7] There are two families of the retinoid receptors which belong to the superfamily of intramolecular receptors (IRs) as retinoid x receptors (RXR)[8] and retinoid acid receptors (RARs)[9] both having three distinct subfamilies as RXRα,β,γ and RARα,β,γ.[10] ATRA is the physiological ligand that makes the RAR-RXR heterodimers to activate the RAR hormonal pathway.[11] However the 9-*cis*-retinoic acid (9-*cis*-RA)[12] **2** makes RAR-RAR homodimers to activate the RAR hormonal pathway.[13] The RXRs form heterodimers with the thyroid hormone receptor (TR) and peroxisome proliferator- activated receptors (PPAR).[14,15]



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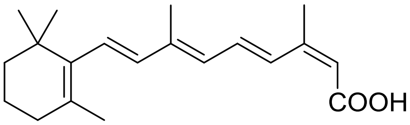

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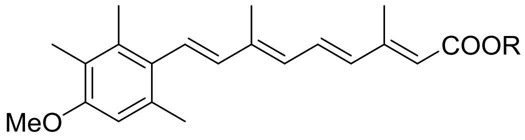
The classification of these receptors is established on the different ways they respond to synthetic and natural ligands, their ability to modulate a wide variety of genes. The ligands binding and reacting with these receptors make structurally very diverse molecules.[16, 17]



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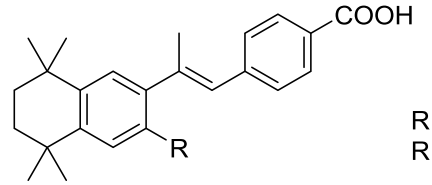
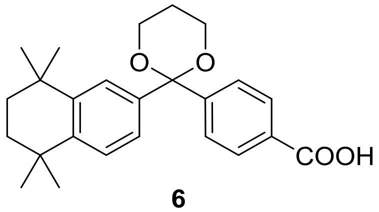


R: H in TTNPB
R: CH_3 in 3-methyl TTNPB

5

These include the molecules like ATRA **1**, 9-*cis*-RA **2**, 13-*cis*-RA **3** and synthetic derivative such as etretinate **4** which contain a tetraene moiety, the molecules like TTNPB **5** and 3-methyl-TTNPB[18] **5** which are based on stilbene while compounds like SR11237[1] **6** and LGD1069[20] **7** which are based upon benzophenone carboxylic acid.



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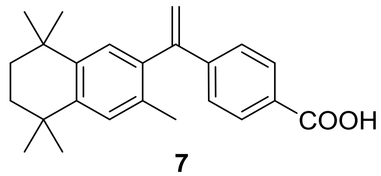

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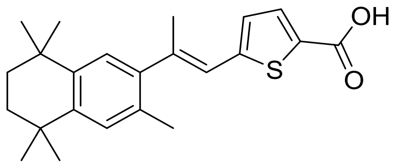
The retinoids **6** and **7** are selective activators of the RXRs with little or no activation of the RARs.[18, 19] These compounds are important analyses to study the means of action of retinoid X receptors. The ability of retinoids to regulate proliferation and differentiation of cells *in vivo* and *in vitro* has significant applications in the treatment of dermatological diseases[21] for example the naturally occurring retinoids as ATRA **1** and 13-*cis*-retinoic acid **3** have been used to treat skin diseases as acne[22], psoriasis[23]. Also ATRA **1** and 13-*cis*-retinoic acid **3** are known to be used a chemo-therapeutic[24-27] and cancer chemoprevention due to the ability of retinoids to modulate the *in vivo* cell processes like proliferation, modulation of apoptosis known as programmed cell death.[28, 29] However, there are some severe concerns regarding the dangerous side effects and toxicity associated with high levels of retinoids which is a serious block for the treatment of even less severe diseases.[30]

Some synthetic retinoids such as etretinate **4** is currently used for the treatment of dermatological diseases including acute promyelocytic leukemia, epithelial cancers and several are being experimentally evaluated for oncological applications.[21] However, widespread use of these agents has been pretty less than expected because of the observation of a number of undesirable side effects like night blindness, dry eye, bone toxicity, skin irritation and teratogenicity etc. due to short and long term use.[29, 30] Such side effects of retinoids may arise because of their ability to activate multiple retinoid receptors in a wide range of target tissues. Similarly unselective modulation of ATRA and its signalling pathways can cause some major neurological dysfunctions.[31-34] Thus it gives us an opportunity to find new retinoids with selective biological profiles and identification and development of novel, receptor-selective retinoids are critical to further use and control of side effects and toxicity which can lead to greater therapeutic targets and significant advantages in the field of medicine.[21, 29]

The thiophene analogues of **5** like (*E*)-5-(2-(3,5,5,8,8-pentamethyl-5,6,7,8-tetrahydronaphthalen-2-yl)prop-1-en-1-yl)thiophene-2-carboxylic acid **8**, (*E*)-5-(2-(3,5,5,8,8-pentamethyl-5,6,7,8-tetrahydronaphthalen-2-yl)prop-1-en-1-yl)thiophene-3-carboxylic acid **9** and (*E*)-4-(2-(3,5,5,8,8-pentamethyl-5,6,7,8-tetrahydronaphthalen-2-yl)prop-1-en-1-yl)thiophene-2-carboxylic acid **10** are RXR agonists[35] which induce the transglutaminase (Tgase) activity in leukemia cell.[36]



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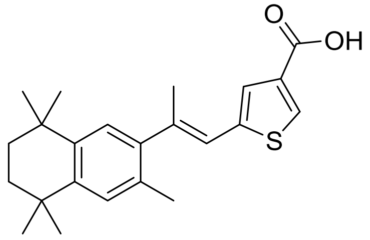

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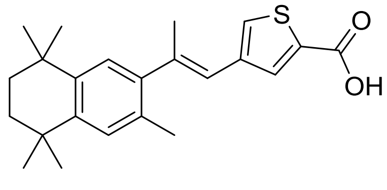


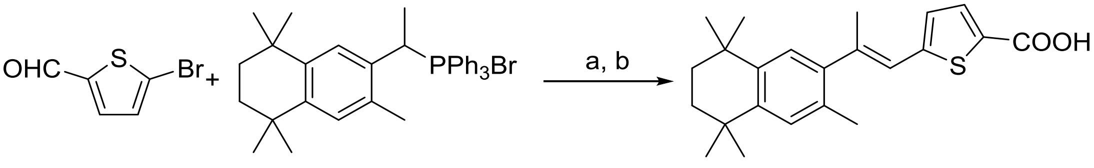
10

In present text we are concerned with compound **8**, an analogue of 3-methyl-TTNPB **5** which shows the transcriptional activity of RARβ, RARγ and RXRα for EC_{50} at concentration of 23 nM, 37 nM, and 11 nM respectively. For the purpose of detailed activity studies and biological evaluation, a straightforward and reliable method for the synthesis of (*E*)-5-(2-(3,5,5,8,8-pentamethyl-5,6,7,8-tetrahydronaphthalen-2-yl)prop-1-en-1-yl)thiophene-2-carboxylic acid **8** is of great utility and interest.

2. Review of literature

Beard *et al.* (1995)[36]

Beard and co-workers reported the synthesis of (*E*)-5-(2-(3,5,5,8,8-pentamethyl-5,6,7,8-tetrahydronaphthalen-2-yl)prop-1-en-1-yl)thiophene-2-carboxylic acid **8** and its retinoid analogues as described in Scheme 1. The phosphonium salt **12** and thiophene aldehyde **11** on treatment with *n*-BuLi in dry THF yielded the bromo intermediate, which on further treatment *n*-BuLi in dry THF at -78 °C furnished the target compound **8**.

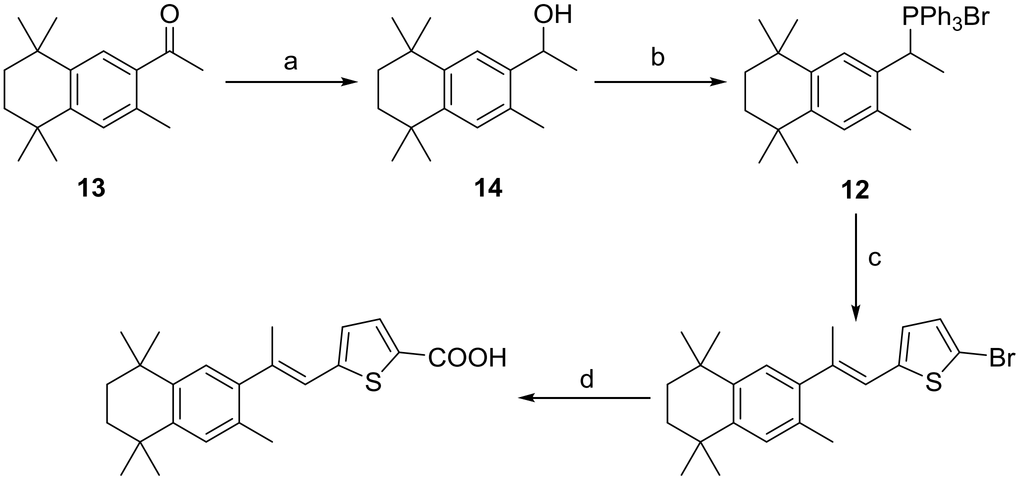


11 **12** **8**

Scheme 1: *Reagents and conditions:* (a) *n*-BuLi, THF, 0 °C to rt 72 h; (b) *n*-BuLi, THF, -78 °C to 0 °C, CO_2, H^+.

Chandraratna, R. A. S. e*t al.* (1994)[37]

Rosshantha A. S. Chandraratna and co-workers synthesized compound **8** (Scheme 2) using easily accessible ketone **13** as starting material. The compound **14** was obtained from ketone **13** on reduction with $NaBH_4$. Further, alcohol **14** was readily converted into its phosphonium salt **12** on treatment with PBr_3 and PPh_3 which on Wittig olefination reaction with 5-bromothiophene-2-carbaldehyde **11** in diethyl ether furnished **15** with bromo group at second position of thiophene moiety. The olefinic compound **15** on purging carbon dioxide in the presence *tert*- butyl lithium furnished target molecule **8** in reasonable yields.



13 **14** **12**

8 **15**

Scheme 2: *Reagents and conditions:* (a) $NaBH_4$, CH_3OH, 1 h; (b) PBr_3, PPh_3, Benzene, 6 h; (c) 5-bromothiophene-2-carbaldehyde, *n*-BuLi, Et_2O, 12 h; (d) *t*-BuLi, CO_2, Et_2O, 4 h.

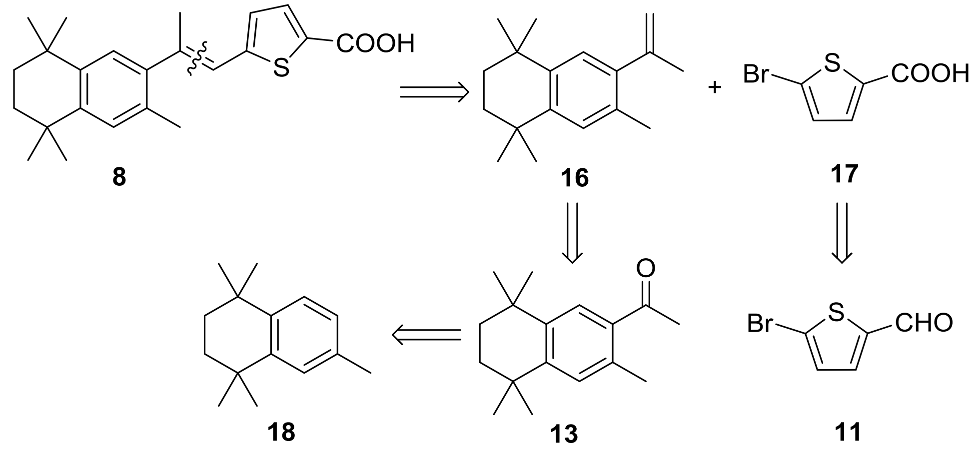
3. Present work

3.1 Objective:

Various methods for the synthesis of Methyl (*E*)-5-(2-(3,5,5,8,8-pentamethyl-5,6,7,8-tetrahydronaphthalen-2-yl)prop-1-en-1-yl)thiophene-2-carboxylate **8** have been well-documented in the literature. Despite the presence of efficient chemistry routes, synthesis of **8** still require reduction in total steps leading to high yields. Herein, we wish to report a new synthetic approach for target compound **8** using $AlCl_3$ mediated Friedel-Crafts acylation, two carbon Wittig homologation and Heck coupling reaction as key steps.

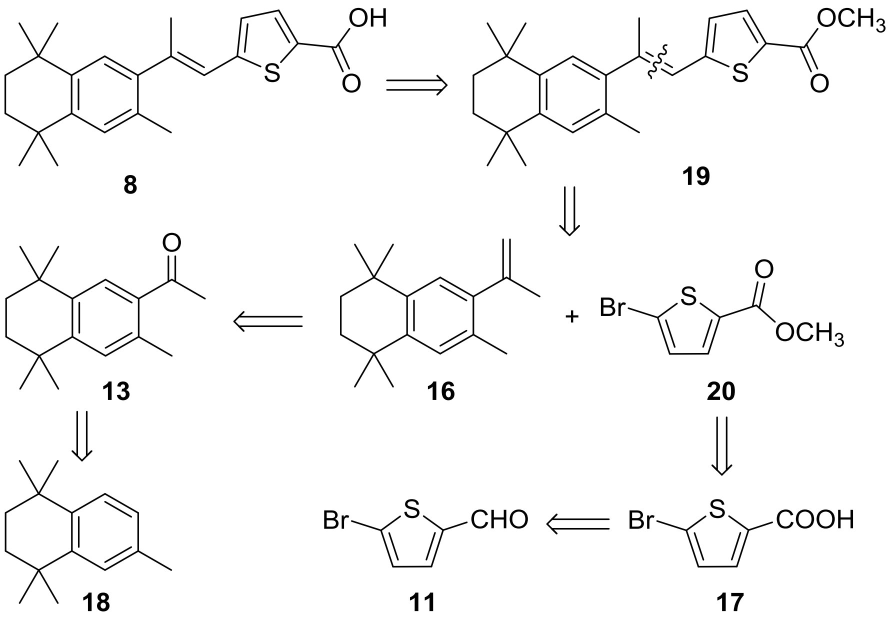
3.2. Retrosynthetic approach:

The retrosynthetic approach for the synthesis of compound **8** is described in Scheme 3. The retinoid derivative **8** could be accessed from alkene **16** and thiophene acid **17** under Heck coupling conditions. The alkene **16** could be obtained from the ketone **13** via one carbon Wittig homologation which in turn could be accessible from commercially available compound **18** using Fridel-Craft acylation. Further, acid derivative **17** could be obtained from the oxidation of commercially available aldehyde **11**.



Scheme 3: Retrosynthetic analysis of compound **8**

Alternatively, compound **8** could be synthesized from ester **19** by hydrolysis. The ester derivative **19** could be assimilated from alkene **16** and thiophene ester **20** under Heck coupling conditions as depicted in Scheme 4. The ester derivative needed for coupling could be prepared from esterification of thiophene acid **17** using a standard organic procedure.

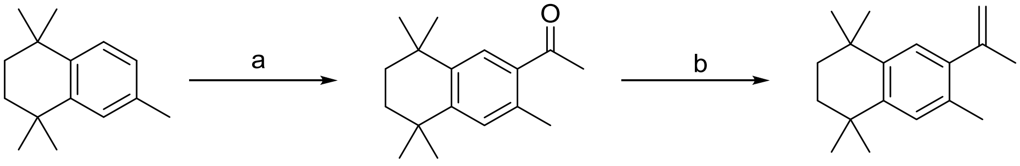


Scheme 4: Alternative retrosynthetic approach

4. Results and discussion

The synthetic sequence for compound **8** commenced using commercially available tetrahydronaphthalene derivative **18** as shown in the Scheme 5. The compound **18** on treatment with acyl chloride and $AlCl_3$ in DCM furnished ketone **13** with 88% yield. In the ^1H NMR spectrum of **13** aromatic protons gave signals at δ 7.66 (s, 1H) and 7.14 (s, 1H) respectively. The acyl protons and benzylic methyl protons gave two peaks at δ 2.57 (s, 3H) and 2.49 (s, 3H) respectively, while a singlet due to four protons cyclohexane moiety were observed at δ 1.69. An intense singlet due to 12 protons of four methyl groups attached to the cyclohexane moiety were found resonating at δ 1.29 (d, J = 6.8 Hz). In the ^{13}C-NMR spectrum, the characteristic carbonyl carbon gave a signal at δ 201.39 while the aromatic carbons were observed resonating at their respective positions. The signals observed at δ 34.82, 34.32 and 33.89 corresponds to the carbons of the cyclohexane moiety and the four methyl carbons were found resonating at δ 31.51. The methyl carbon of acyl group and the one attached to benzene moiety gave signals at δ 29.34 and

21.51 respectively. The IR spectra of **13** showed stretching of CH_3 groups at 2927 cm^{-1} and 2867 cm^{-1}, C=O stretching at 1675 cm^{-1}, α-CH_3 bending at 1359 cm^{-1} and C-H bending at 886 cm^{-1} and 992 cm^{-1}.

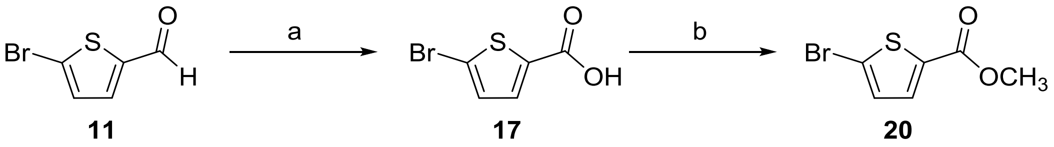


18 **13** **16**

Scheme 5: *Reagents and conditions*: (a) CH_3COCl, $AlCl_3$, DCM, 0 °C to rt, 10 h, 88 %; (b) CH_3PPh_3Br, *n*-BuLi, rt to 0 °C, 6 h, 92%.

Further ketone derivative **13** on one carbon Wittig homologation using methyl triphenyl phosphonium bromide yielded the alkene **16** with 92 % yield. In the ^1H NMR spectrum of **16** aromatic protons were observed at δ 7.08 (s, 1H) and 7.05 (s, 1H), while characteristic alkene protons were found resonating at δ 5.15 (s, 1H) and 4.85 (s, 1H) respectively confirming the formation of the product **16**. The signals received at δ 2.26 (s, 3H) and 2.04 (s, 3H) were for the two methyl groups attached to benzene moiety at side alkene group and at benzylic position respectively. A singlet for four protons of the cyclohexane moiety is found at δ 1.67 (s, 4H), while a doublet at δ 1.27 for J = 4.8 Hz corresponds to the four methyl groups attached to the cyclohexane moiety. In the ^{13}C NMR spectrum of **16** aromatic carbons appear resonating at their corresponding positions while, aliphatic carbons of cyclohexane moiety found resonating at δ 35.19, 33.87 and 31.88. The methyl group adjacent to alkene and the one to benzene appear at δ 24.50 and 19.71 respectively. IR peaks of alkene **16** showed stretching of CH_3 groups at 2964, 2927 and 2866 cm^{-1} while a strong signal at 894 cm^{-1} verified the $=CH_2$ bending.

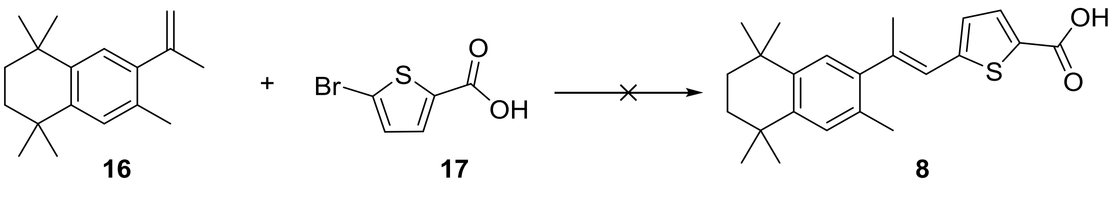
In Scheme 6, the synthesis of second key fragment thiophene acid **17** and ester **20** is described. The commercially available thiophene aldehyde **11** on treatment with BAIB and TEMPO in DCM-H_2O (2:1) gave corresponding carboxylic acid **17** at the aldehyde position with 93% yield. In the ^1H NMR spectrum of **17**, thiophene protons were found resonating at δ 7.64 (d, J = 4.0 Hz, 1H), 7.11 (d, J = 4.4 Hz, 1H). In the ^{13}C-NMR spectrum the characteristic carbonyl carbon was found resonation at δ 166.34 which confirms the formation of acid group, while remaining aromatic carbons were observed at their respective positions. IR peaks of acid **17** at broad region 2600-3200 cm^{-1} were found due to O-H stretching, also C=O stretching at 1657 cm^{-1} and C-O stretching at 1272 cm^{-1}.



Scheme 6: *Reagents and conditions:* (a) BAIB, TEMPO, DCM-H_2O (2:1), rt, 12 h, 93%; (b) CH_3OH, H_2SO_4, 65 °C, 30 h, 90%.

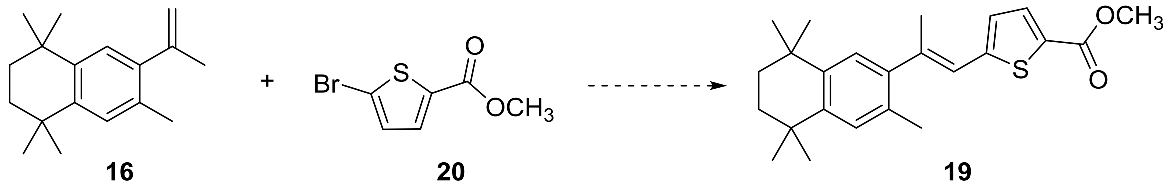
The pure carboxylic acid derivative **17** was further converted into its methyl ester **20** on refluxing with excess methanol in the presence of conc. H_2SO_4 with yield of 90%. In the ^{1}H NMR spectrum of **20**, a singlet corresponding to the methyl protons at δ 3.87 (s, 3H) was observed indicating formation of methyl ester **20** while the remaining thiophene protons were found at δ 7.55 (d, J = 4.0 Hz, 1H) and 7.07 (d, J = 3.6 Hz, 1H). In the ^{13}C-NMR spectrum, the carbonyl carbon and methyl group were observed resonating at δ 161.55 and δ 52.32 respectively, while aromatic carbons furnished peaks at δ 134.58, 133.69, 130.88, and 120.24. IR peaks at 1709 cm^{-1} and 1252 cm^{-1} showed the C=O stretching and C-O stretching respectively.

After successful construction of the alkene **16** and acid fragment **17** we tried to accomplish the synthesis of final compound **8** as described in Scheme **7**. Firstly, coupling of alkene **16** and acid **17** was tried under Heck coupling conditions as described in Table 1, but the results were not fruitful. From this we deduce that the acid functionality on **17** might be acting as a hindrance for the coupling with alkene **16**.



Scheme 7: Heck Coupling conditions: Table 1

Further, to obtain an access to the target compound **8**, another route using methyl ester derivative **20** instead of acid **17** was tried for coupling as depicted in Scheme 8. Therefore, for this, alkene **16** and ester **20** fragments were subjected to the Heck coupling conditions for obtaining the target compound **8** in good yield. A number of coupling conditions by varying palladium catalyst, solvents and reaction time period were tried as depicted in Table 1, but the results were not satisfactory. Further, work is still in progress for achieving the target compound **8**.



Scheme 8: Heck Coupling conditions: Table 1

Table 1: Various Reaction Conditions Used for Heck Coupling[38]

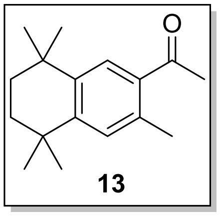
S. No.	Reagents used	Solvent	Temperature	Time
1.	$Pd(OAc)_2$, Tri-*o*-tolyl phosphine, Et_3N	CH_3CN	100 °C	8 h
2.	K_2CO_3, Bu_4NBr, TPP, $Pd(OAc)_2$	$DMF:H_2O$ (9:1)	50 °C	2h
3.	$PdCl_2(MeCN)_2$, Et_3N, HCOOH	CH_3CN	20 °C	1.5 h
4.	$Pd(OAc)_2$, PPh_3, Ag_2CO_3	DMF	rt	12 h
5.	$Pd(dba)_3$, Et_3N	$CH_3CH(OH)CH_3$ (IPA)	78 °C	18 h
6.	$Pd(OAc)_2$, PPh_3, Ag_2CO_3	CH_3CN	80 °C	10 h

5. Conclusion

In conclusion, we worked on a concise and highly efficient synthetic approach for synthesis of target compound retinoid **8** that utilizes the Heck coupling reaction as key step. The development of an effective Friedel–Crafts acylation on naphthalene derivative further allows rapid access to an alkene precursor that could be utilize for facile coupling with thiophene acid or ester derivative to afford the target compound. A key advantage of our strategy is to provide a high yielding method. The protocol to synthesize the target compound is reached to the synthesis of **16** and **20** and rest of the work is in progress and will be reported in due course of time.

6. Experimental Section:

6.1. 1-(3,5,5,8,8-pentamethyl-5,6,7,8-tetrahydronaphthalen-2-yl)ethan-1-one, 13



13

To a suspension of $AlCl_3$ (1.58 g, 11.88 mmol) in DCM (10 mL) at 0 °C was added a solution of acyl chloride (0.84 mL, 12.87 mmol) and **18** (2.0 g, 9.9 mmol) in DCM (10 mL) drop wise. The resulting mixture was allowed to warm to room temperature and was stirred for 10 hours. After completion the reaction mixture was cooled to 0 °C and quenched with 1N HCl (5 mL). The aqueous layer was extracted with EtOAc. The extract was dried over Na_2SO_4 and concentrated in vacuum to give a yellowish solid which was purified by silica gel column chromatography with hexane-EtOAc (9.9:0.1) to obtain **13**.

Yield: 2.1 g, 88%

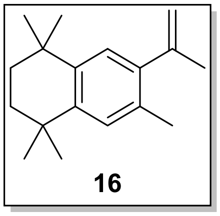
Molecular Formula: $C_{17}H_{24}O$

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.66 (s, 1H), 7.14 (s, 1H), 2.57 (s, 3H), 2.49 (s, 3H), 1.69 (s, 4H), 1.29 (d, J= 6.8 Hz, 12H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 210.39, 149.03, 142.29, 135.34, 135.08, 130.12, 128.19, 34.85, 34.81, 34.32, 33.89, 31.80, 31.51, 29.33, 21.51.

IR (CH_2Cl_2) ν: 2927, 2867, 1675, 1359, 886, 992 cm^{-1}.

6.2. 1,1,4,4,6-pentamethyl-7-(prop-1-en-2-yl)-1,2,3,4-tetrahydronaphthalene, 16



16

To a solution of methyl triphenyl phosphonium bromide (14.64 g, 41.0 mmol) in THF (120 mL) was added *n*-BuLi (16.4 mL, 41.0 mmol, 2.5M in n-hexane) at -78 °C and the reaction mixture was stirred for 3 hours and then cooled to 0 °C. To the above reaction mixture, a solution of **13** (2 g, 8.2 mmol) in THF (20 mL) was added drop wise at 0 ºC and was stirred for 3 hours at room temperature. After completion the reaction mixture was quenched with cold water and was allowed to warm to room temperature. The aqueous layer was extracted with EtOAc, dried over Na_2SO_4 and concentrated in vacuum, purified by silica gel column chromatography with hexane-EtOAc (10:0), furnished **16** as white solid.

Yield: 1.73 g, 92%

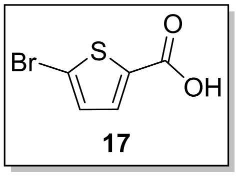
Molecular Formula: $C_{18}H_{26}$

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.08 (s, 1H), 7.05 (s, 1H), 5.15 (s, 1H), 4.85 (s, 1H), 2.26 (s, 3H), 2.04 (s, 3H), 1.67 (s, 4H), 1.27 (d, J = 4.8 Hz, 12H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 146.05, 143.25, 141.97, 140.96, 131.45, 127.96, 125.85, 114.51, 35.19, 33.87, 31.88, 24.50, 19.71.

IR (CH_2Cl_2) ν: 2964, 2927, 2866, 894 cm^{-1}.

6.3. 5-bromothiophene-2-carboxylic acid, 17



17

To a stirred solution of **11** in DCM-H_2O (2:1, 15 mL) was added BAIB (3.70 g, 11.50 mmol) and TEMPO (163 mg, 1.05 mmol) and the reaction mixture was stirred for 12 hours at room temperature. After completion the reaction mixture was quenched with saturated NH_4Cl solution and extracted with DCM. The extract was dried over Na_2SO_4, concentrated under reduced pressure, purified by silica gel column chromatography with hexane-EtOAc (3:7) to obtain **17** as white solid.

Yield: 1.0 g, 93%

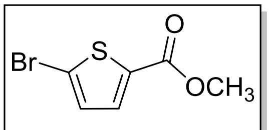
Molecular Formula: $C_5H_3BrO_2S$

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.64 (d, J = 4.0 Hz, 1H), 7.11 (d, J = 4.4 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 166.34, 135.33, 133.79, 131.29, 122.24

IR (CH_2Cl_2) ν: 3100, 2978, 2796, 2646, 2577, 2352, 1657, 1272 cm^{-1}.

6.4. Methyl 5-bromothiophene-2-carboxylate, 20



20

To a solution of **17** (1 g, 4.83 mmol) in excess methanol (40 mL) was added concentrated H_2SO_4 (1 mL) and the resulting mixture was refluxed for 30 hours. After completion the reaction mixture was quenched with water and extracted with EtOAc. The extract was dried over Na_2SO_4, concentrated under vacuum and purified by column chromatography over silica gel with hexane-EtOAc (9:1) to furnish **20** as yellow solid.

Yield: 0.96 g, 90%

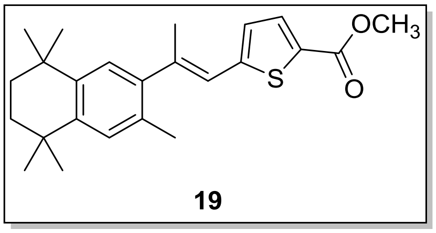
Molecular Formula: $C_6H_5BrO_2S$

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.55 (d, J = 4.0 Hz, 1H), 7.07 (d, J = 3.6 Hz, 1H), 3.87 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 161.55, 134.58, 133.69, 130.88, 120.24, 52.32

IR (CH_2Cl_2) ν: 1709, 1252, 812 cm^{-1}.

6.5. Methyl (*E*)-5-(2-(3,5,5,8,8-pentamethyl-5,6,7,8-tetrahydronaphthalen-2-yl)prop-1-en-1-yl)thiophene-2-carboxylate, 19



19

General Experimental Procedure for Heck Reaction:

A mixture of bromo ester **20** (100 mg, 0.412 mmol) and alkene **16** (91 mg, 0.412 mmol), varied amounts of Pd (II) salt, ligand (tri-*o*-tolyl phosphine) and base such as Et_3N or Ag_2CO_3 in solvent such as DMF, CH_3CN or IPA etc.(different conditions as specified in Table 1)[38] was allowed to stir at different temperatures (ranging from rt to 100 °C) for different amounts of time.[38] After completion the reaction mixture was cooled to 0 °C and quenched with water. The aqueous layer was extracted with EtOAc. The extract was dried over Na_2SO_4 and concentrated in vacuum for further analysis.

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8. Spectra:

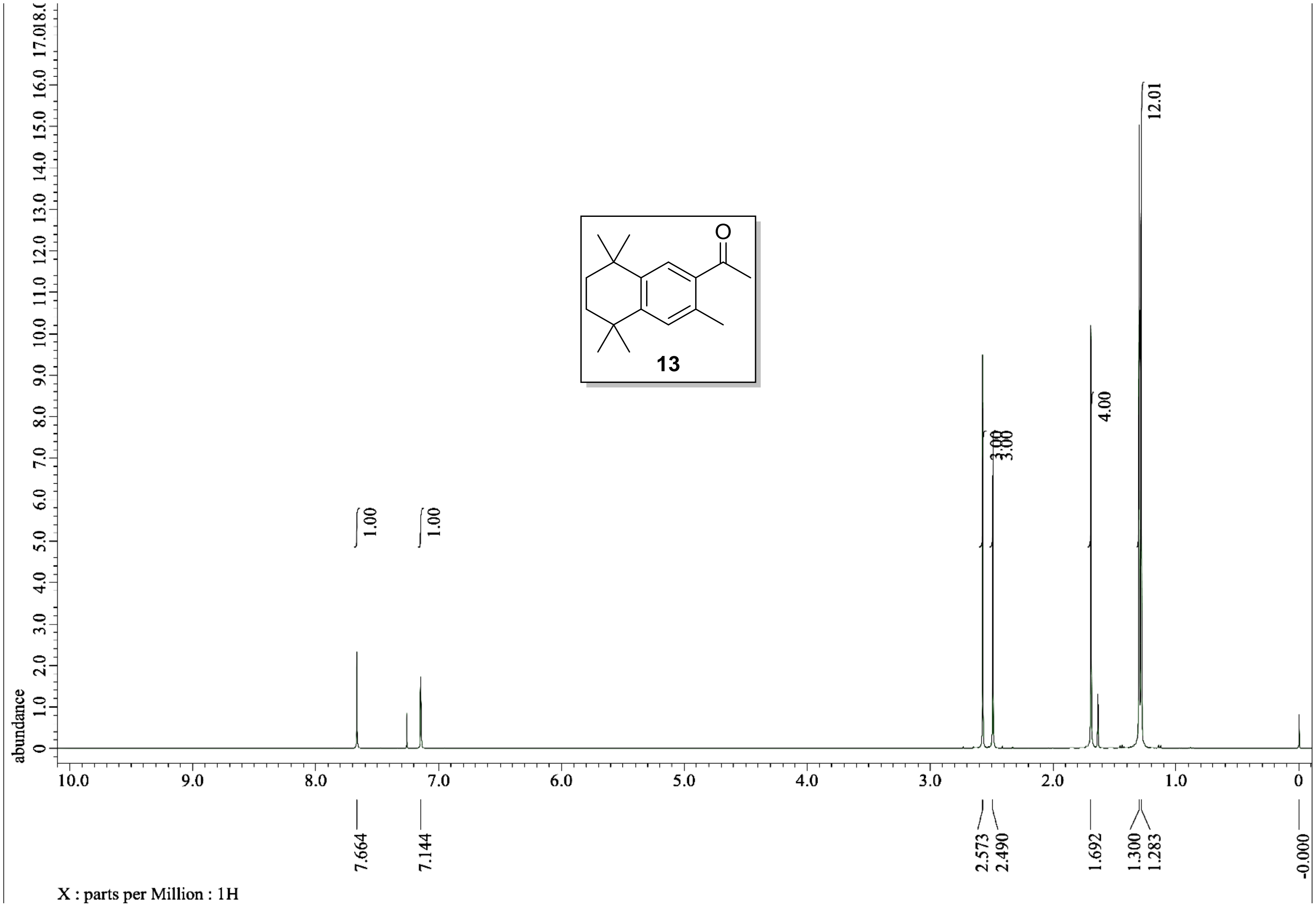
1. ^{1}H, ^{13}C NMR and IR Spectra of **13**

2. ^{1}H, ^{13}C NMR and IR Spectra of **16**

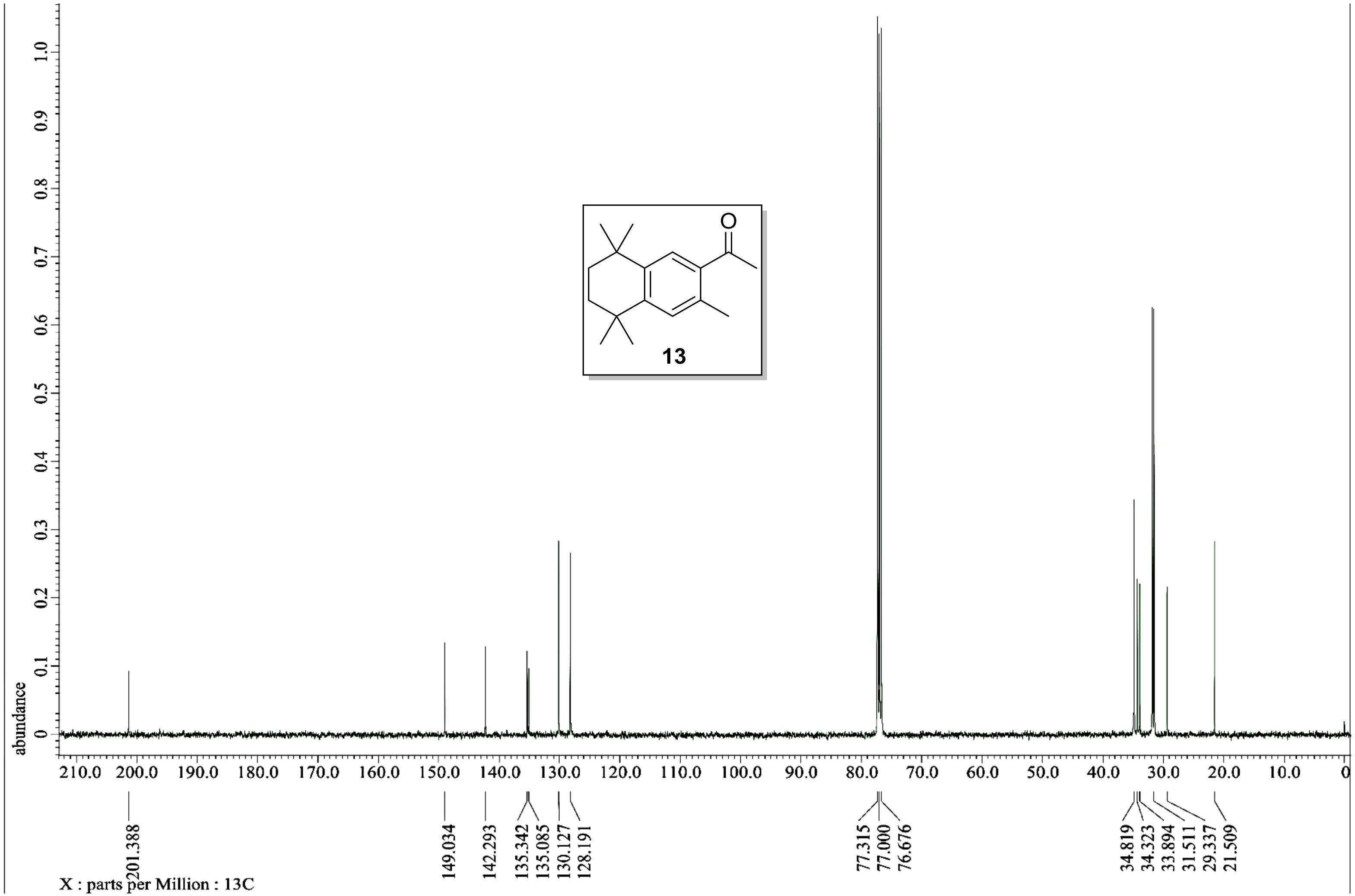
3. ^{1}H, ^{13}C NMR and IR Spectra of **17**

4. ^{1}H, ^{13}C NMR and IR Spectra of **20**

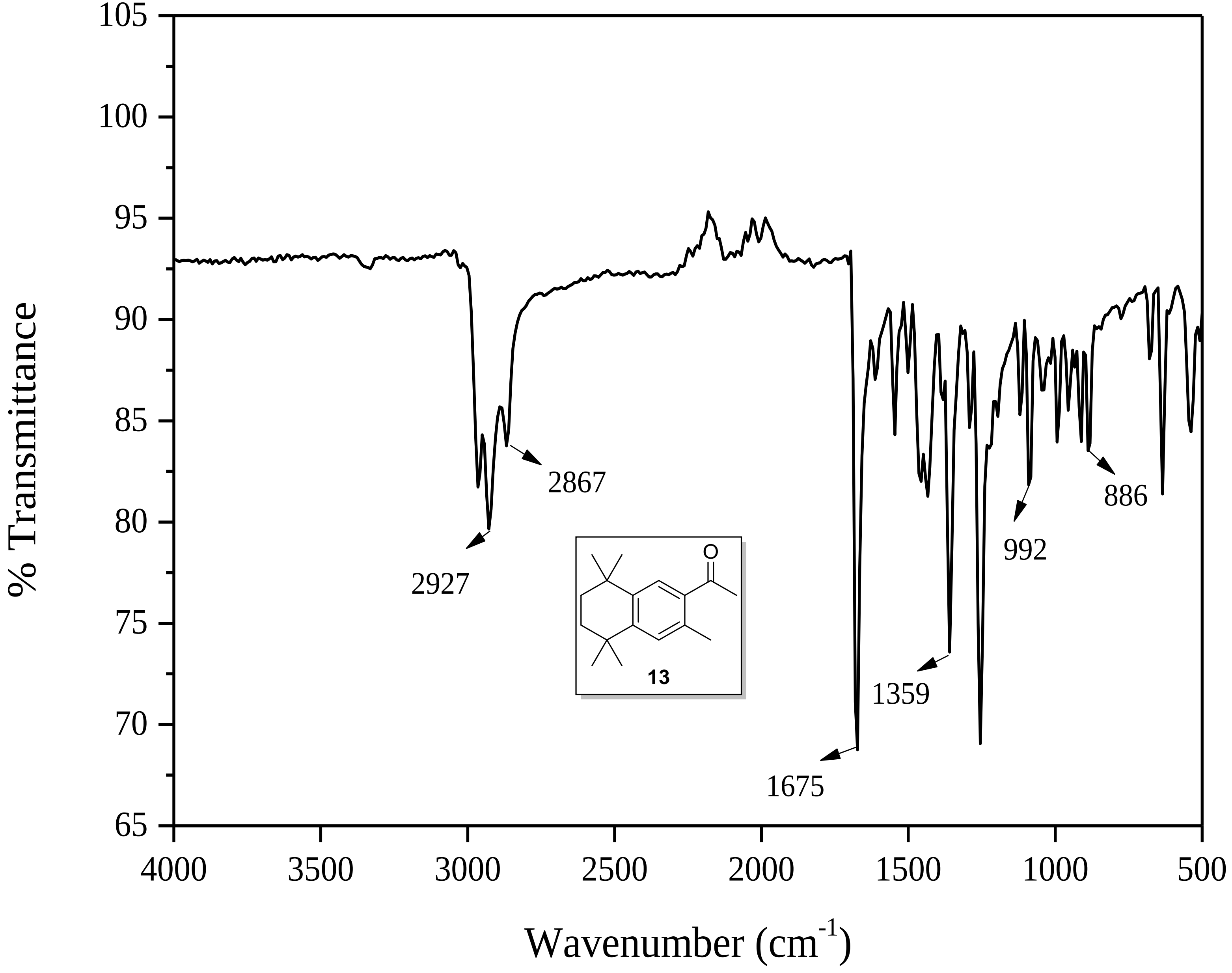
^{1}H-NMR spectrum of 13



^{13}C-NMR spectrum of 13



IR spectrum of 13



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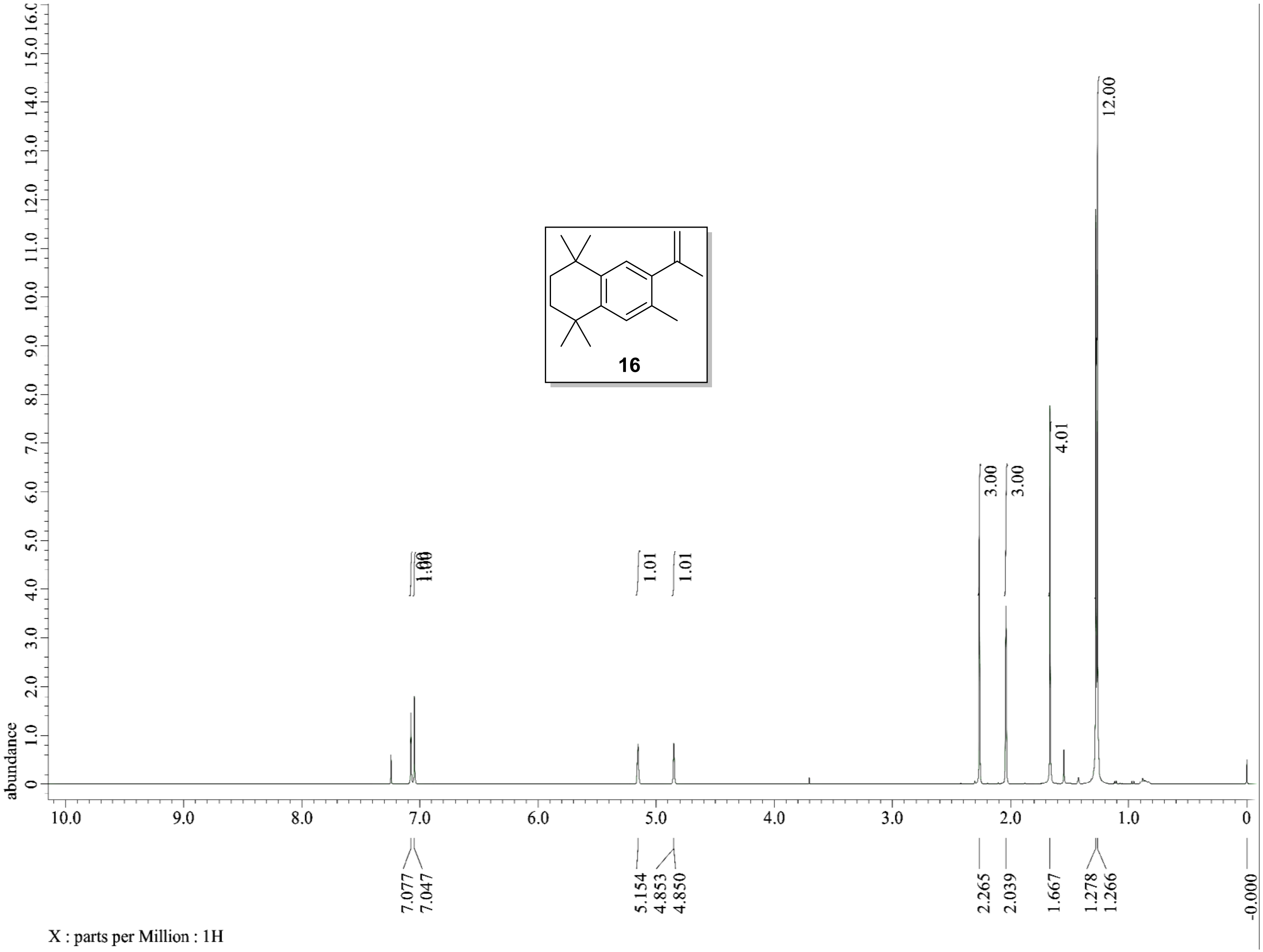

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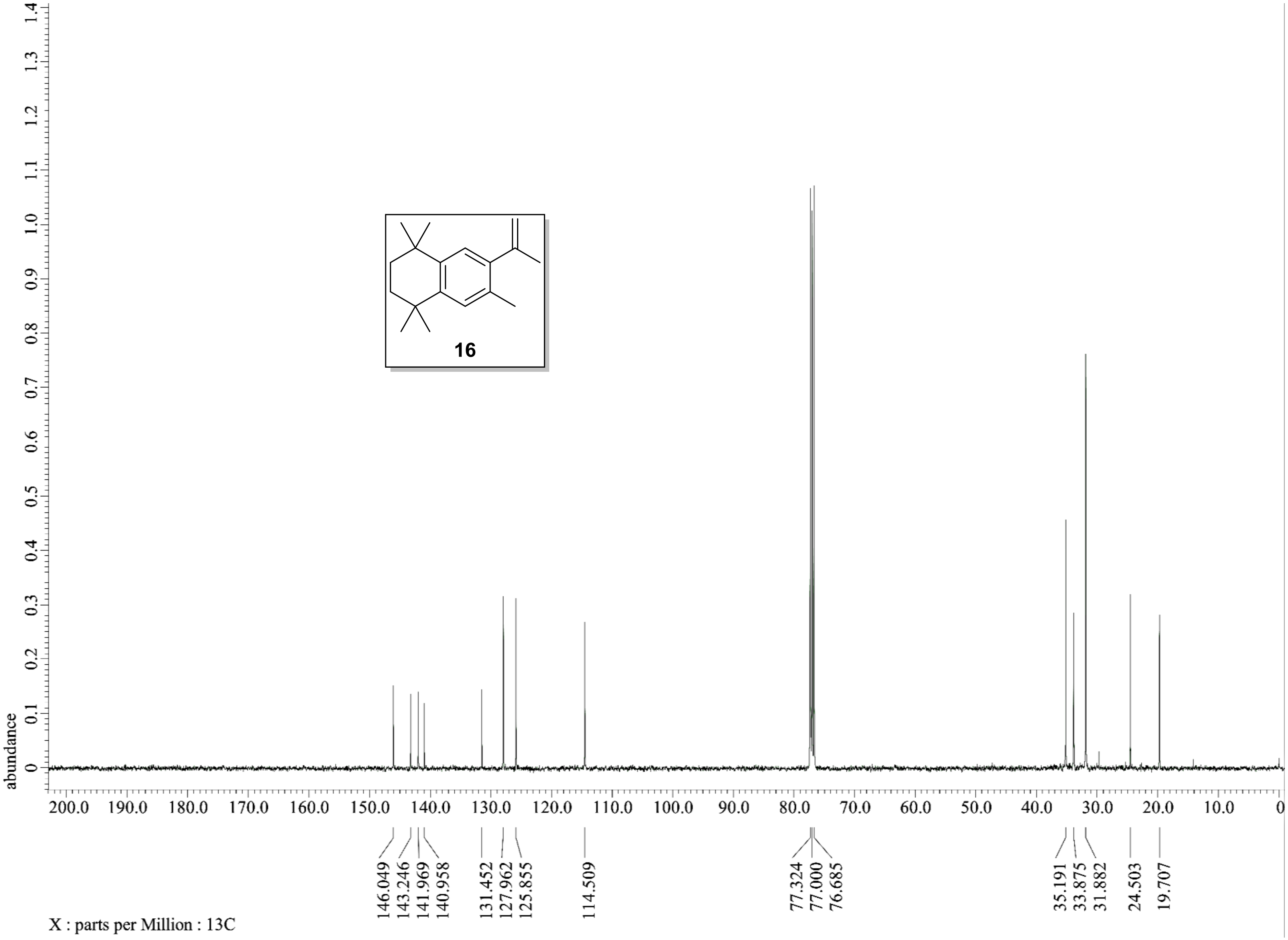

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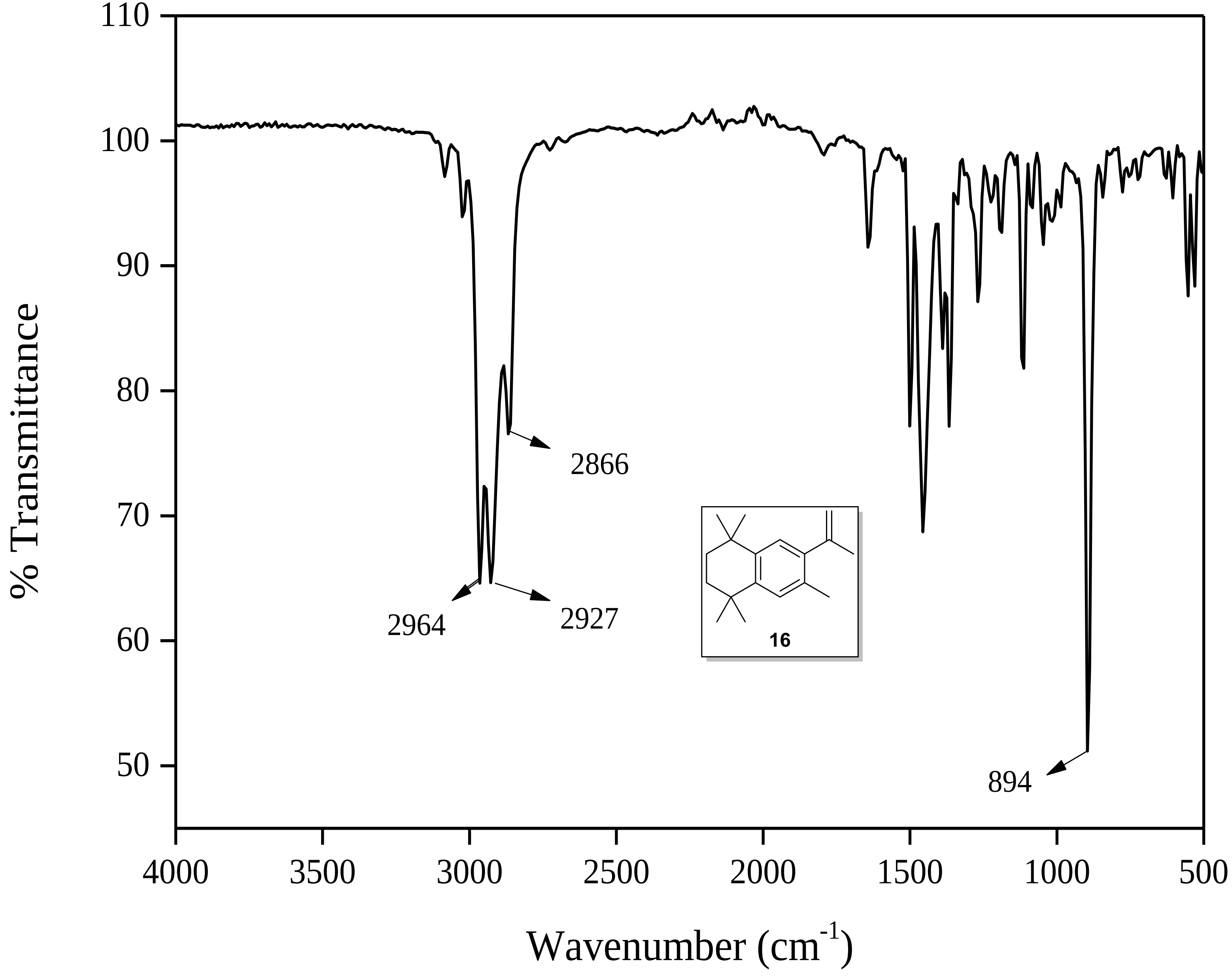

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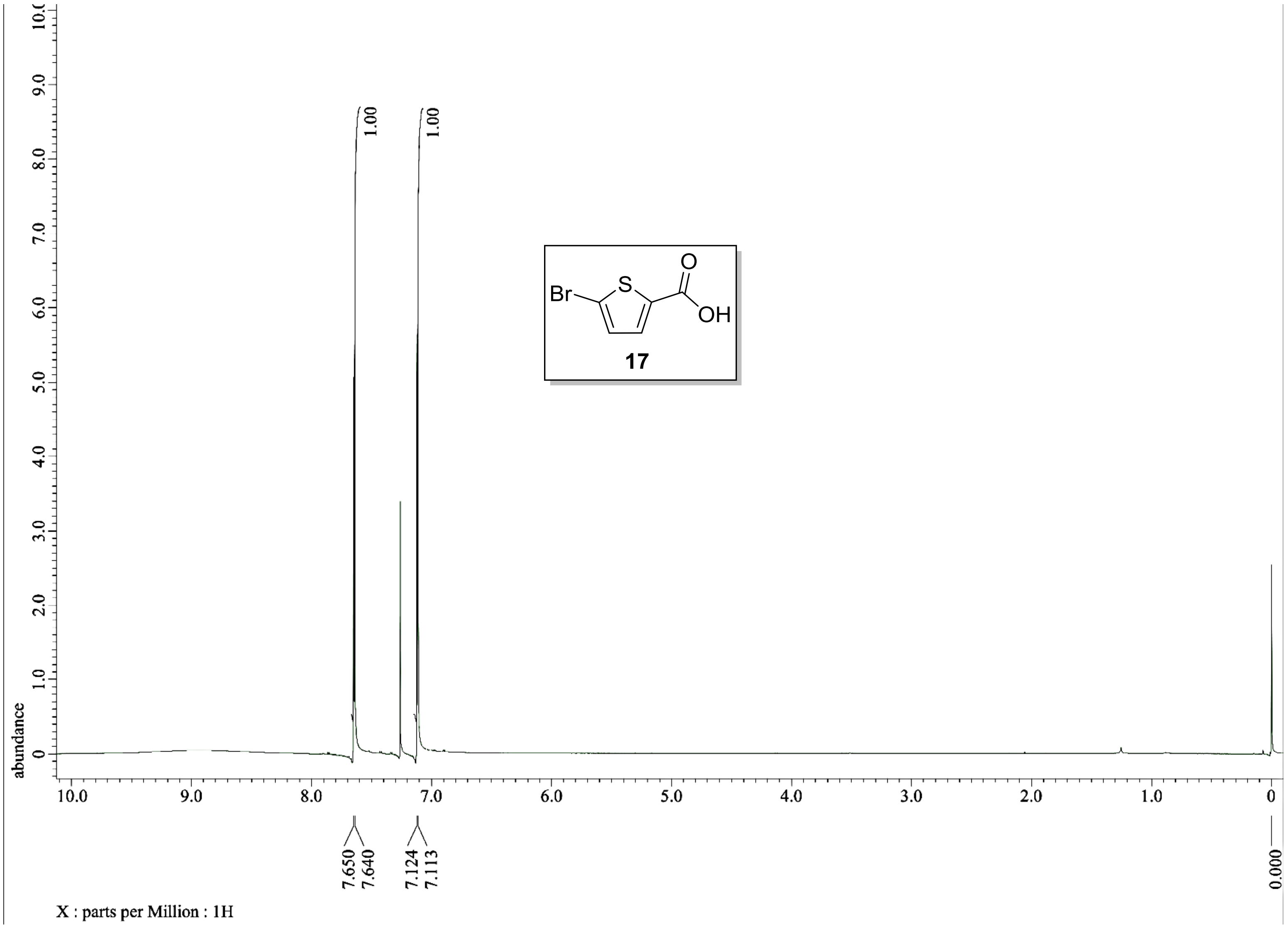

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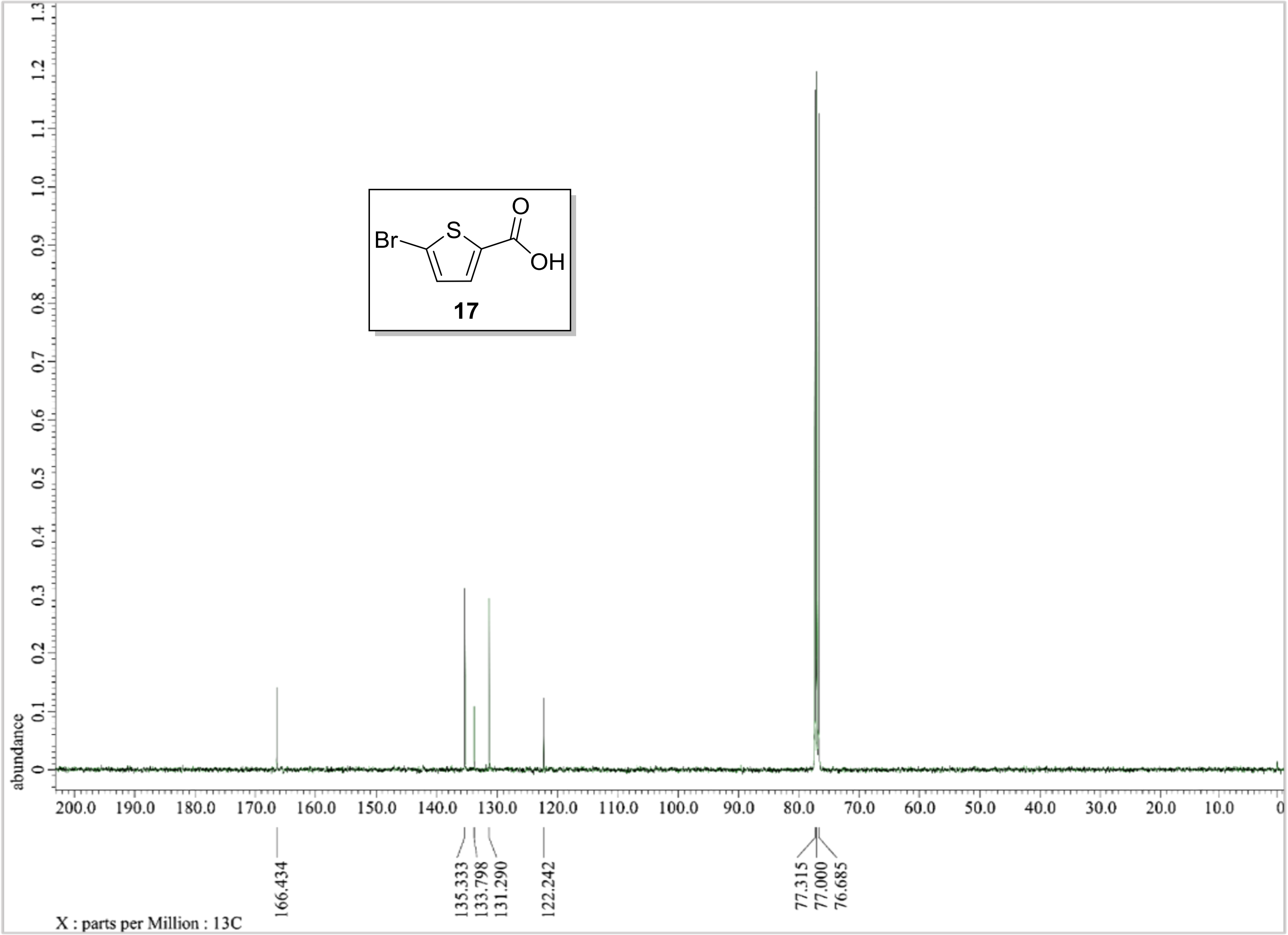
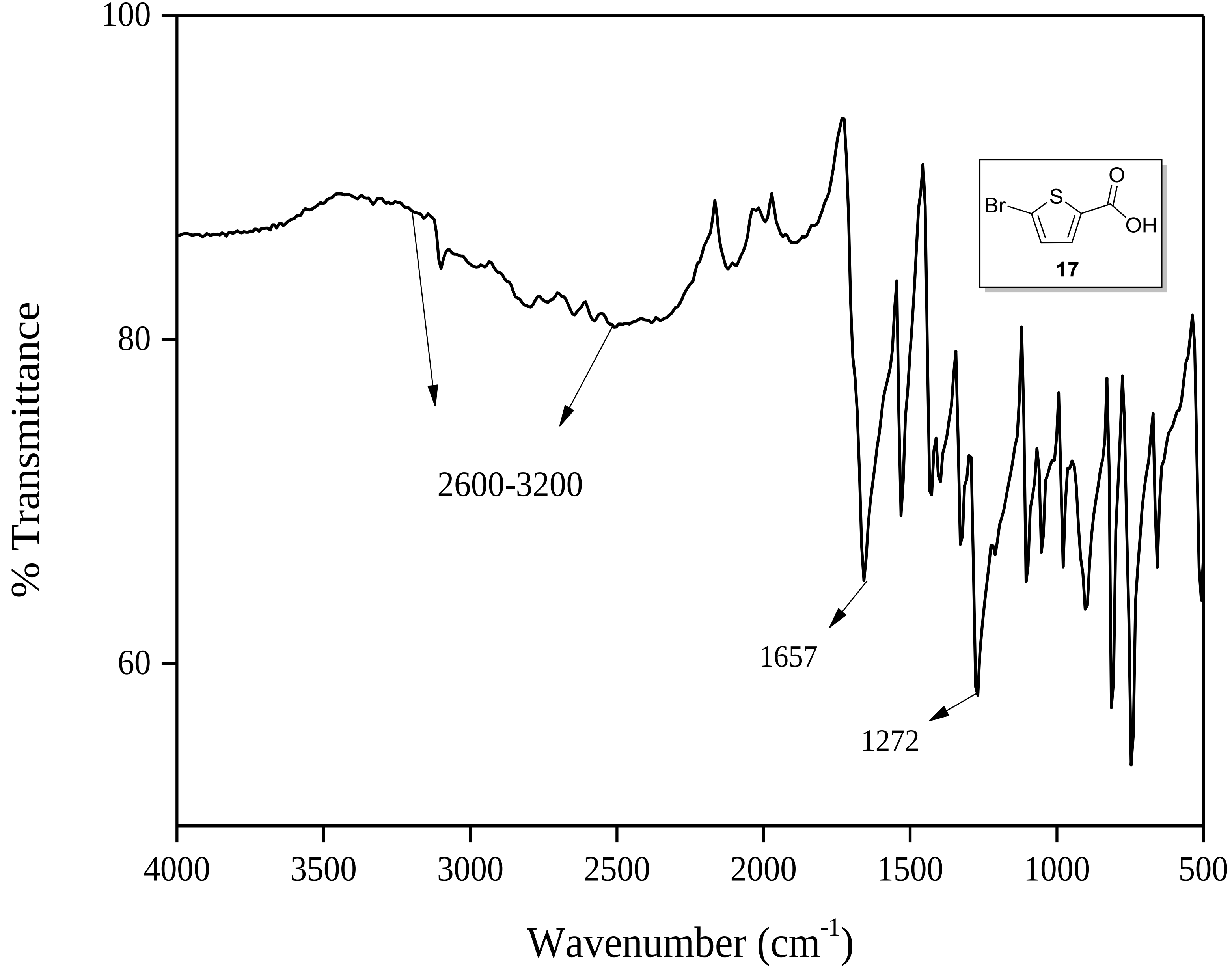
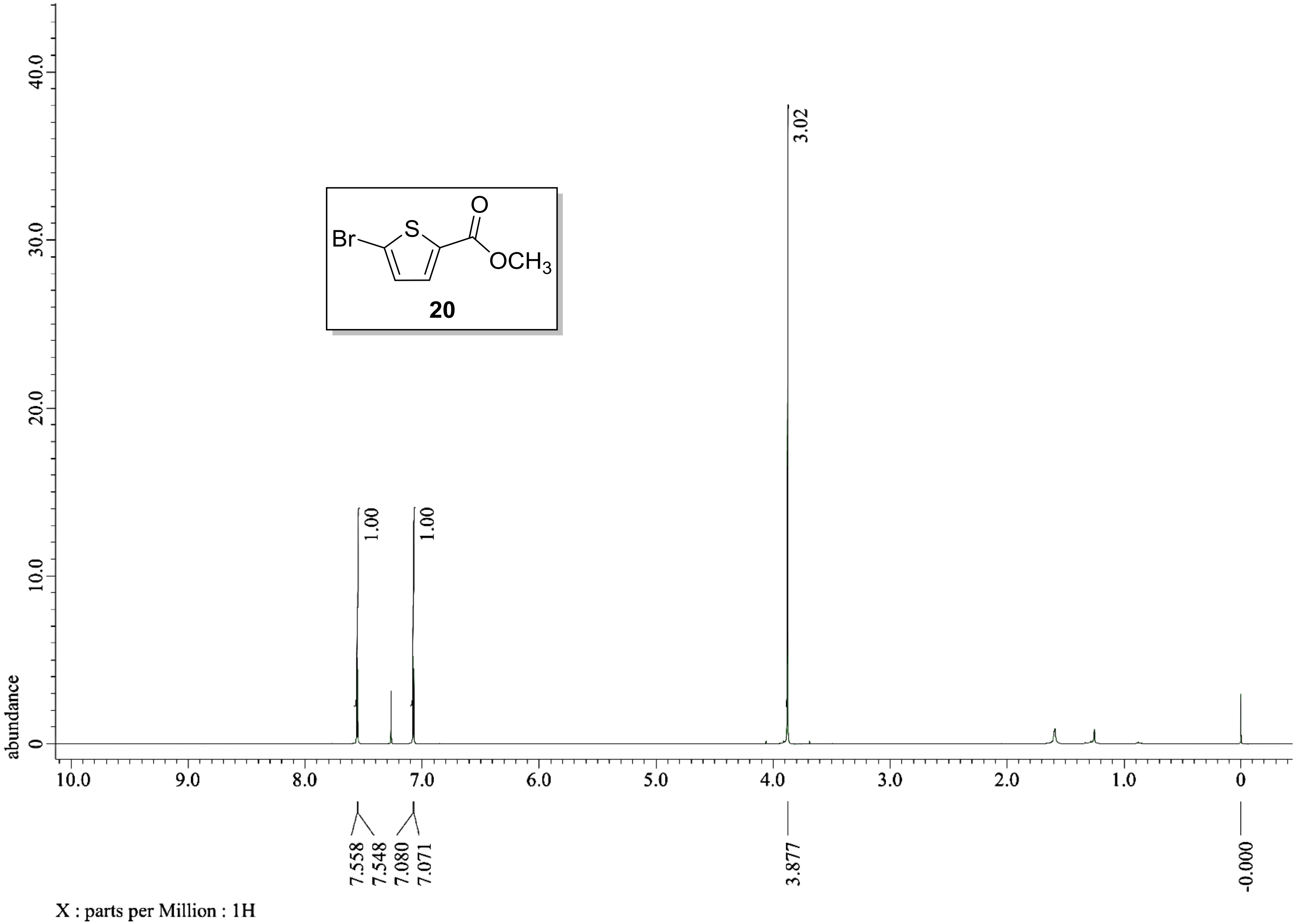




IR spectrum of 17

^{1}H-NMR spectrum of 20



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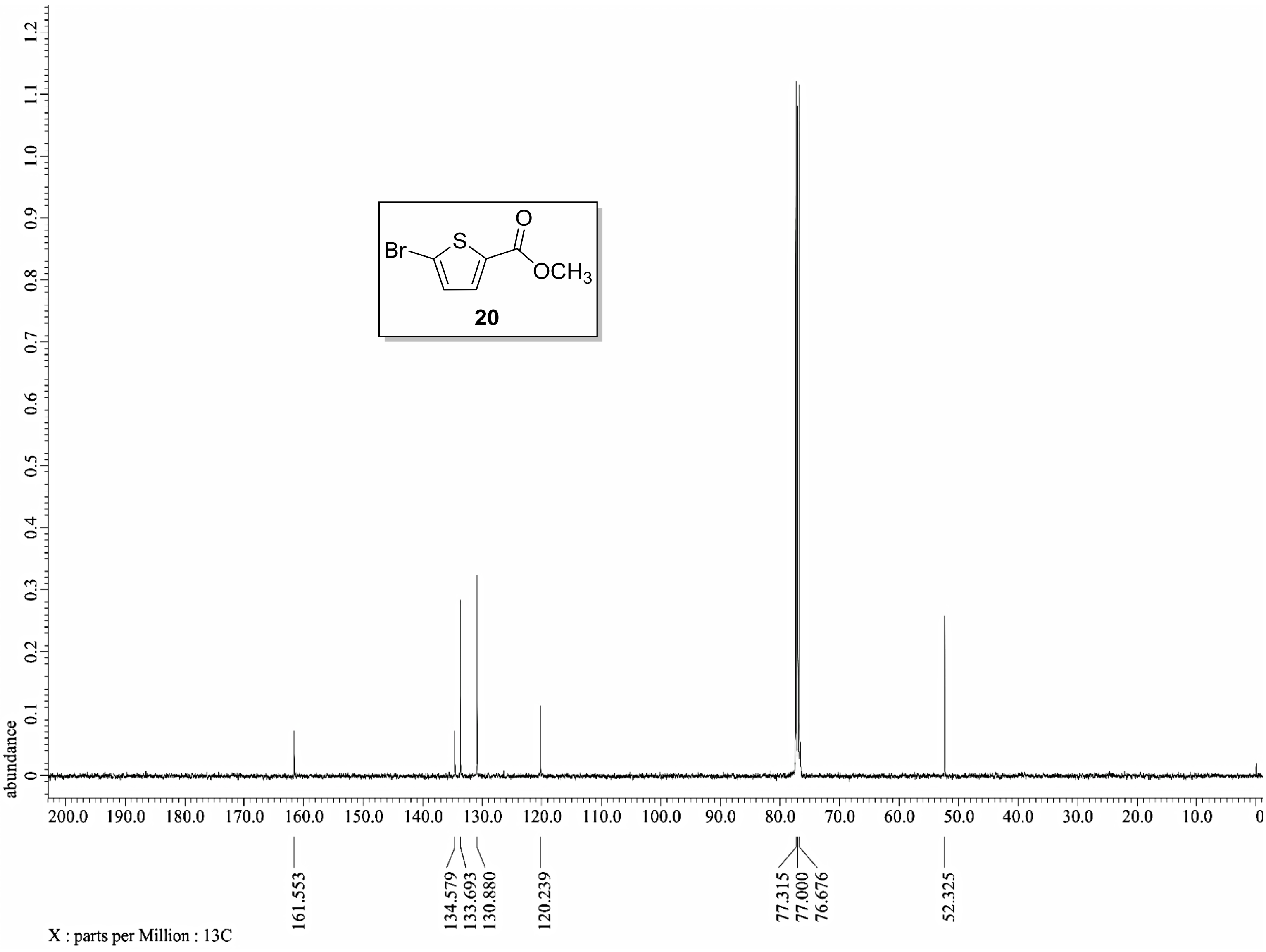

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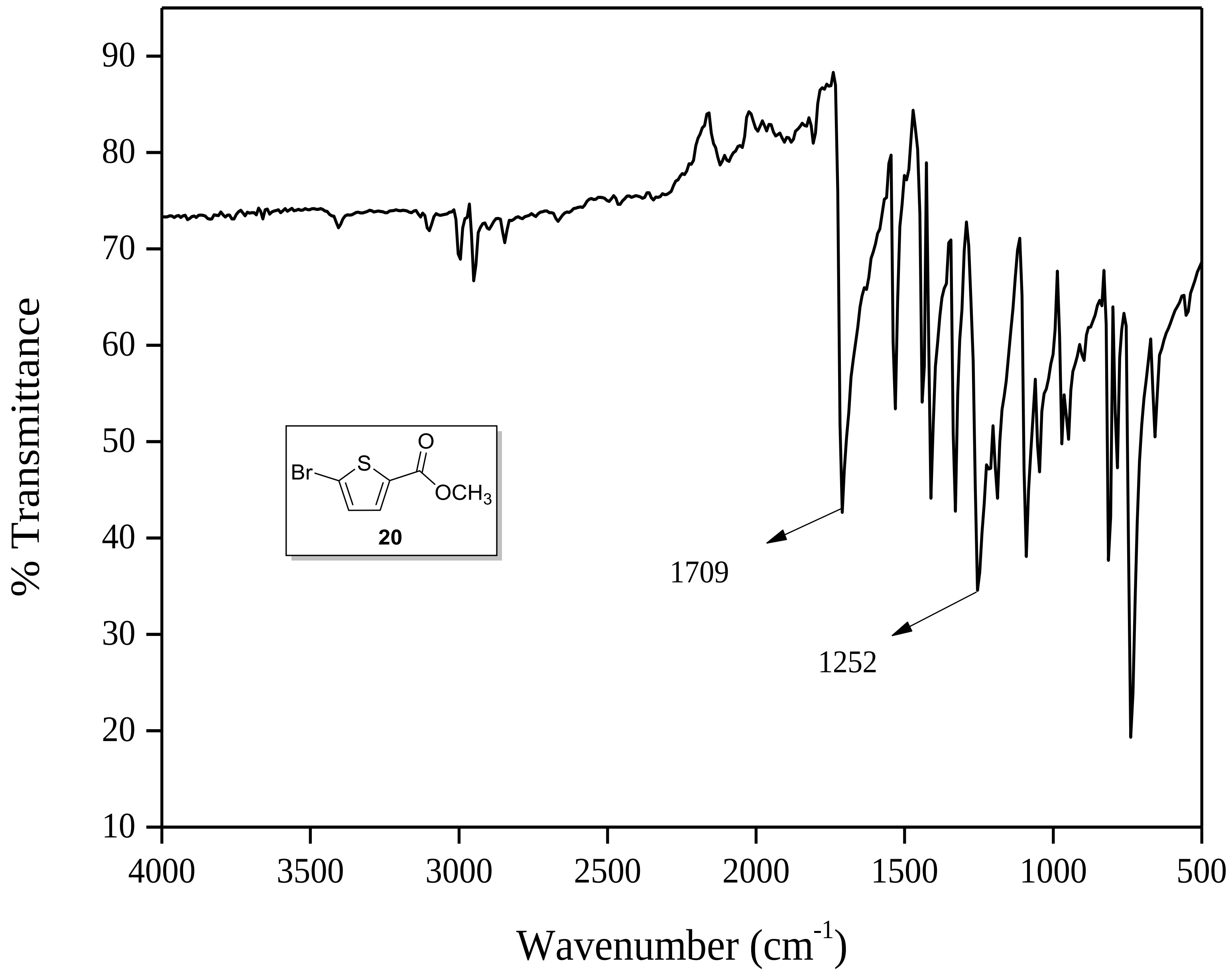

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