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Benzamides 之合成及其生物活性探討

Synthesis of Benzamides and Their Biological Activity

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口試委員會審定書

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本論文係陳宗熙君（學號 R01423023）在國立臺灣大學藥學所完成之碩（博）士學位論文，於民國 103 年 7 月 29 日承下列考試委員審查通過及口試及格，特此證明

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謝珮文

系主任、所長 （簽名）

誌謝

感謝我的指導教授沈雅敬的細心指導，每當實驗遇到瓶頸時總是細心的與我討論，並鼓勵我對於難題堅持下去，因此才能有最後的成果，對於 benzamide 化合物做一個初步完整的 SAR 探討，讓我碩班的生涯獲得滿滿的收穫；同時也感謝老師對於日常生活的慰問及關心，讓在台北的生活多了一些溫暖。同時在此感謝謝珮文老師和郭曜豪老師以及沈雅敬老師來參與我的口試,給予我許多寶貴的經驗和指導。

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生命總是有許多打擊，感謝那些挫折，讓我變得更加堅強!

中文摘要

根據 Jay P. Powers 等人所發表三環之 benzamides 發現具有對 HSDs 具有抑制的活性, 由於當免疫失調時, glucocorticoids 會對多重器官組織造成負面影響, 而 HSDs inhibitor 可以改善 cortisol 造成的生理代謝失控的情況, 也能對於免疫系統做出適當的調整; 而 Nanthan 合成了一系列 benzamides 化合物來對運送會造成 Alzheimer's 的 Aβ 的運送蛋白 RAGE 來做 binding 的競爭,發現化合物 **45** 具有良好活性, 參考 Jay 和 Nathan 所合成的結構, 我們先設計出 *N*-(cyclohex-2-enyl)-*N*-phenalkylbenzamide 進行不同碳鏈長度之改變, 意外發現碳鏈長度 n = 1 的分子 *N*-benzyl-*N*-(cyclohex-2-enyl)benzamide 具有優異的抗發炎反應, 因此本人接續進行對 benzyl group 進行不同的官能基取代修飾, 並改變合成路徑以及提升產率之工作。

以未取代和 12 種取代之 benzylamine 做為起始物, 先後進行 N-alkylation 以及 benzoylation , 得到終產物 benzamides; 抗發炎活性測試發現以 *ortho*-位置以 fluorine 原子取代之化合物 **5** 活性最高, 次之為無取代之化合物 **2** 具有顯著抗發炎活性, 並以此二終產物進行下一階段的動物活性測試。

為了討論 cyclohexene 的雙鍵對分子之抗發炎活性的影響, 因此合成無雙鍵之 benzamides, 來做抗發炎活性之測試; 首先根據之前所發表之相似結構的合成方法嘗試以未取代和不同取代之 12 種 benzylamines 與 cyclohxeanone 進行 imination 和 reduction, 得到中間產物後, 繼以 benzoylation 來得到終產物; 但由於總產率過低, 且反應耗時過長, 遂進行合成路徑之重新設計, 改以直接由含雙鍵之 benzamides 直接進行氫化反應, 將雙鍵直接還原, 得到無雙鍵之 benzamides, 而產率由原本小 1 %提升至 48-99 %不等, 且無伴隨副產物之生成, 為此類 benzamides 化合物提供一個因六圓環所造成立體障礙過大而無法進行 S_N2 反應的替代路徑。

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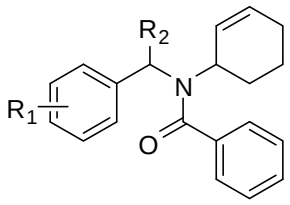
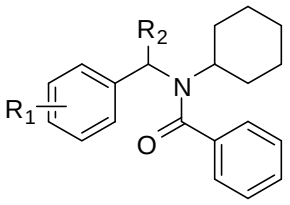
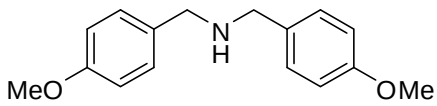


2: R_1 = H
5: R_1 = *o*-F
8: R_1 = *m*-F
11: R_1 = *p*-F
14: R_1 = *p*-Cl
17: R_1 = *p*-CH_3
20: R_1 = *o*-CF_3
23: R_1 = *p*-CF_3
26: R_1 = *p*-OMe
29: R_1 = *o*, *p*-OMe
32: R_1 = *m*,*p*-OMe
35: R_1 = *o*, *m*, *p*-OMe
38: R_1 = H, R_2 = CH_3



3: R_1 = H
6: R_1 = *o*-F
9: R_1 = *m*-F
12: R_1 = *p*-F
15: R_1 = *p*-Cl
18: R_1 = *p*-CH_3
21: R_1 = *o*-CF_3
24: R_1 = *p*-CF_3
27: R_1 = *p*-OMe
30: R_1 = *o*, *p*-OMe
33: R_1 = *m*,*p*-OMe
36: R_1 = *o*, *m*, *p*-OMe
39: R_1 = H, R_2 = CH_3



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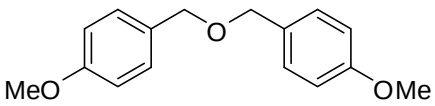

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Abstract

A patent published by Jay P. Powers and his team suggested that the benzamides comprised of three rings may have activity to inhibit HSDs. When the immune system of human body loses its balance, secreted glucocorticoids might have the deleterious impacts to organs or tissues which can be tuned by the application of HSDs inhibitors. HSDs inhibitors may recover the unleashed status of physical metabolism caused by cortisol, and mediate an appropriate adjustment among the immune system.

A series of benzamides designed by Nathan may compete the binding between the RAGE protein and Aβ which contribute to the occur of Alzheimer's. And they found compound **45** would have the best activity to impede the binding of RAGE to Aβ among the compounds they synthesized.

On the basis of the structures created by Jay and Nathan, the different number of carbons of N-benzyl group in *N*-(cyclohex-2-enyl)-*N*-phenalkylbenzamide suggested by our lab showed that one carbon unit might have the excellent activity against inflammation surprisingly. Herein I continued to do modification on the benzyl group, and discover new pathway to elevate the yield.

The scheme started from 13 kinds of benzylamines underwent N-alkylation and benzoylation in succession to generate the final compounds. Compound **5** with *ortho*-F in its benzyl group has the most potent activity in anti-inflammation assay, the second one with the best potency would be compound **2**. As the result, compounds **2** and **5** exhibited the most potent activity in anti- inflammmatory assay. Both compounds were sent for further *In vivo* animal study.

In order to investigate the influence of the double bond in cyclohex-2-enyl group on anti-inflammatory activities, a series of compounds without double bond have been synthesized. According to methods claimed by the previous papers with similar

structure to construct, we synthesized 13 kinds of benzylamines to undergo imination and reduction with cyclohexanone to obtain intermediates, then followed by the benzoylation to funish final products. However the devastating demerit of the scheme as we mentioned was time-consuming and quite low yield. Thus we re-designed the scheme by directly hydrogenation of the double bond to synthesize the final compounds. The new pathway we offered without side products elevated the yield from less than one percntage to more than forty-eight to ninty-nine percentage. The finding indicated the new pathway for synthesizing the compounds with similar structures that might have too large steric hindrance to proceed the S_N2 reaction. In the anti-inflammatory assay, benzamides without double bond revealed the tendency of decline of anti-inflammatory activity except compound **30**. However, the *ortho*-position remains imperative to the activity of inhibition of release of superoxide anion from neutrophils.

目錄

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縮寫表

Ac	Acetyl
Å	Anstron
Cald.	Calculated
DCM	Dichromethane
DMAP	4-Dimethylaminopyridine
DMF	Dimethylforamide
d	Doublet
dd	Doublet of doublet
EAE	Experimental autoimmune enxephalomyelitis
EAN	Experimental allergic neutritis
ESI	Electron spray ionization
Et	Ethyl
Hex	Hexane
Hz	Hertz
IR	Infrared radiation
J	Coupling constant
KBr	Potassium Bromide
KI	Potassium Iodide
Me	Methyl
MeOH	Methanol
ml	Mini liter
mmol	Mini molar
µl	Micro liter

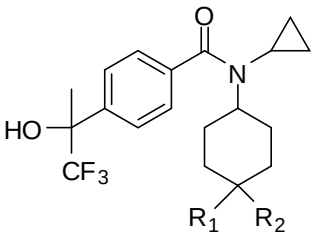
$NaBH_4$	Sodium borohydride
Na_2CO_3	Sodium bicarbonate
NMR	Nuclear Magnetic Resonance
$MgSO_4$	Magnesium sulfate
ph	Phenyl
Pd/C	Palladium on activated carbon
p-TSA	*p*-Toluenesulfonic acid
R.T.	Room temperature
S_N2	Substituted nucleophilic reaction
THF	Tetrahydrofuran
TLC	Thin layer chromatography

一、研究背景

1.1 Benzamides 作為 HSDs inhibotor 效用之研究

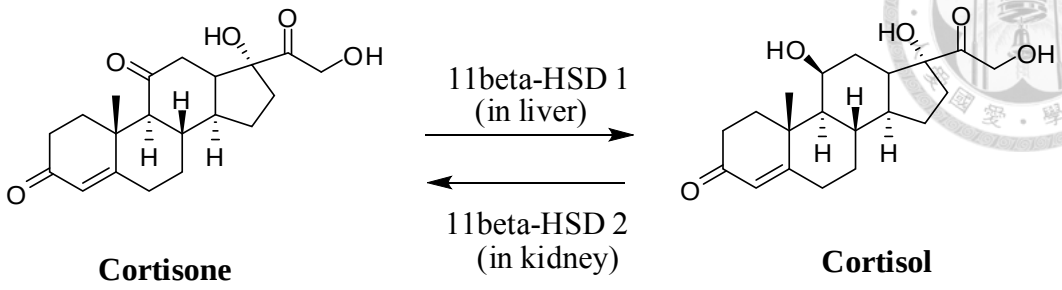
在 2009 年由 Jay P. Powers, Michael Degraffenreid, Xiao He, Lisa Julian, Dustin L. McMinn, Daqing Sun, Yosup Rew, Xuelei Yan 等人共同發表之專利中，針對 hydroxysteroid dehydrigenases (HSDs), 包含 11β-hydroxysteroid dehydrogenase, 17β-hydroxysteroid dehydrogenase, 20α-hydroxysteroid dehydrogenase 和 3α- steroid dehydrogenase 活性調控設計一系列的 benzamides 分子來進行 SAR 和活性探討[1]。

圖一、Jay P. Powers 等人所發表之部分 benzamides 之主要結構



Jay P. Powers 作者等人設計的 benzamide derivatives 所針對的酵素 11β-steroid dehydrogenase 具有 2 種 isoforms, 互為相反的作用；在肝臟中，11β-steroid dehydrogenase type 1 (11β-HSD 1) 將像是 cortisone 的 11-keto glucocorticoids 轉換成如 cortisol 的 11-hydroxy glucocorticoids ；而在 *In vitro* 中，cortisol 對於 mineralocorticoid receptor (MR)是強力的 agonist，但在腎臟組織中，cortisol 對 MRs 的功能被 11β-hydroxysteroid dehydrogenase type 2 將 cortisol 轉換成不活化的 cortisone 的功能所破壞，如圖二所示，此平衡機制確保人體內 cortisol 的量維持在生理水準, 而不對 MRs 作用，但高濃度的 cortisol 依然可以壓制 11β-HSD 2 的活性，而致活 MRs。

圖二、11β-Hydroxysteroid dehydrogenase 之功能



Cortisone **Cortisol**

HSDs 在許多疾病上扮演重要的調節角色，像是 diabetes, 過去研究發現在 11β-HSD 1 gene knockout mice 中發現在使用 11β-HSD 1 inhibitor 後，對於肝醣生成的最重要兩種酵素：phosphoenopyruvate carboxylase (PEPCK) 以及 glucose-6-phosphate (G6Pase) 的 mRNA 的量以及活性都有明顯的下降, 卻不會造成 hypoglycemia[2]; 相關研究也指出對 murine 使用 11β-HSD 1 inhibitor, 使得胰島細胞的 β cell 的 insulin 分泌量上升[3],而 glucocorticoids 則會使胰島素的分泌量下降[4]; 而與 diabetes 高度相關的 obesity 也有相關研究指出抑制 pre-adipocytes (stromal cell) 的 11β-HSD 1 會減少分化的速率，進而可以推測 omental fat depot 的擴張程度減少因而減少中心部位肥胖[5]。

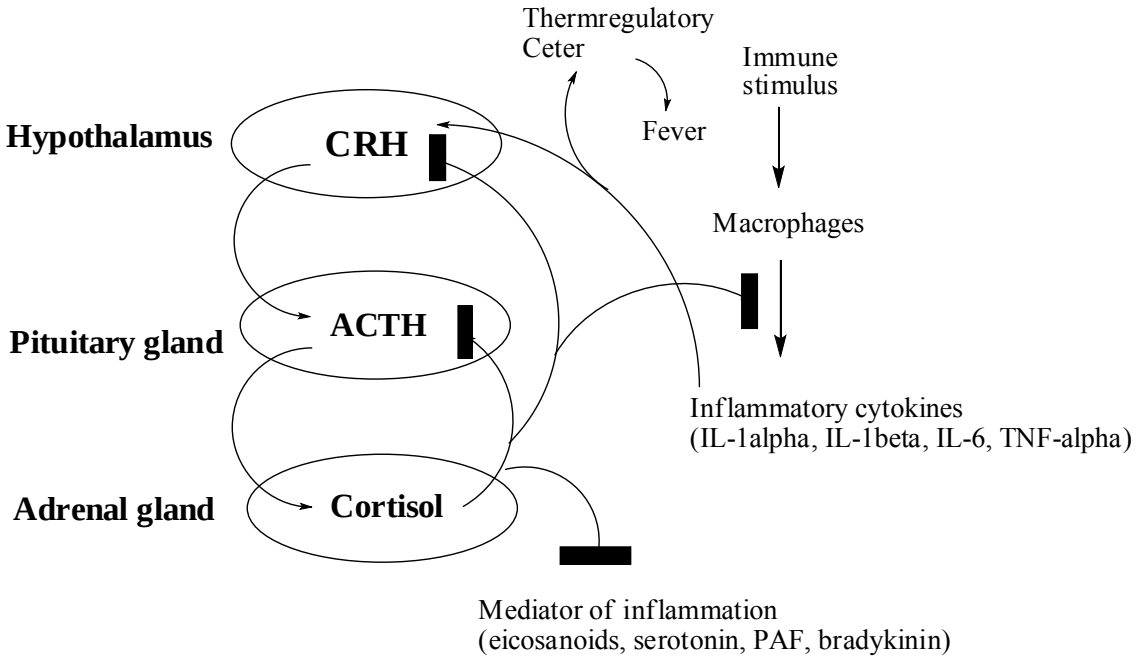
11β-HSD 1 與 osteoporosis 也有相當關聯，研究發現 glucocorticoids 會引起 osteoblast 的分化和軟骨組織的發育受到抑制[6], 而當使用 non-specific 11β-HSD 1 inhibitor, 如 carbenoxolone 的使用會使得此現象減緩[7]; 另有研究也顯示 glucocorticoid 會使得 osteoclast 對骨質中鈣的再吸收有增強的趨勢[8], 因此推論對 11β-HSD 1 進行抑制將會對 osteoporosis 將有良好的改善。

而 11β-HSD 1 與大腦的情緒表相也有相當程度的關聯, 壓力和 glucocorticoid 被研究指出會影響大腦認知的運作[9], 使用 11β-HSD 1 inhibitor 對於焦慮等情緒障礙的改善有顯著的進步[10]; 此外 11β-HSD 會在海馬迴細胞中重新活化 11-DHC, 將

之轉變成 corticosterone, 進而強化 kinase 的神經毒性, 導致與年紀相關的學習障礙的發生[11], 因此 11β-HSD 1 inhibitor 被認為可以對抗 glucocorticoids 所造成的神經傷害。

此外, 11β-HSD 1 與身體的免疫反應也有相當程度的關聯, 因 cortisol 人體內扮演多重抗發炎的角色, cortisol 藉由抑制 NF-κB 來對細胞免疫系統所分泌的 cytokines, 而此反應會限制之後延伸的免疫反應,而這些 cytokines 包括 IL-1, IL-2, IL-6, 和 TNF-α 會刺激下視丘分泌 CRH (corticotropin-release hormone), CRH 再刺激腦下垂體分泌 ACTH 以及 cortisol, 這些刺激與抑制的反應形成一個負回饋的系統, 又稱為 HPA (hypothalamic-pituitary-adrenal) axis, 如圖三。

圖三、HPA (hypothalamic-pituitary-adrenal) axis 之示意圖



在已知 glucocorticoidsc 會抑制免疫系統下, 11β-HSD 扮演平衡調節的角色在動態的 HPA axis 和免疫系統之間(balance between cell-mediated and humoral responses), 在動物實驗中, 壓力下會導致 glucocorticoids 的分泌量增加, 使得免疫平衡偏向 humoral reaction, 像是 leshimaniasis、tuberculosis 以及 leprosy 等疾病都是免疫系統偏向 humoral reaction, 而此時 cell-mediated reaction 才是人體所需, 因此使用 11β-HSD inhibitors 可以將平衡導向 cell-mediated reaction, 因此 11β-HSD inhibitors 可以當作暫時使身體獲得所需正確免疫反應得一種藥品[1, 13]。(簡單而言 humoral reaction 為辨識外界抗原例如病菌, 並由分化的 B cell 製造抗體來做初步對抗外界侵入的物質;相反而言,cellular response 為可以辨認抗原的 T cell 對受到感染病毒的細胞進行辨認然後活化和增生並釋出 perforins 以及 granzymes 來溶解破壞受到感染的細胞。)

圖四、壓力強度與所引起之免疫反應的種類[12]

Low stress response	High stress response
Cell-mediated immunity is more vigorous than humoral immunity.	Humoral immunity is more vigorous than cell-mediated immunity.(High IgE level possible)
Susceptible to cell-mediated autoimmune diseases, for example: EAE, EAN and athrititis.	Resistant to autoimmune disease.
Resistant to pathogenic organism requiring cell-mediated immunity for their control, for example: leshimaniasis、tuberculosis and leprosy.	Susceptible to pathogenic organisms requiring cell-mediated immunity for control, such as pathogen-susceptible human population.

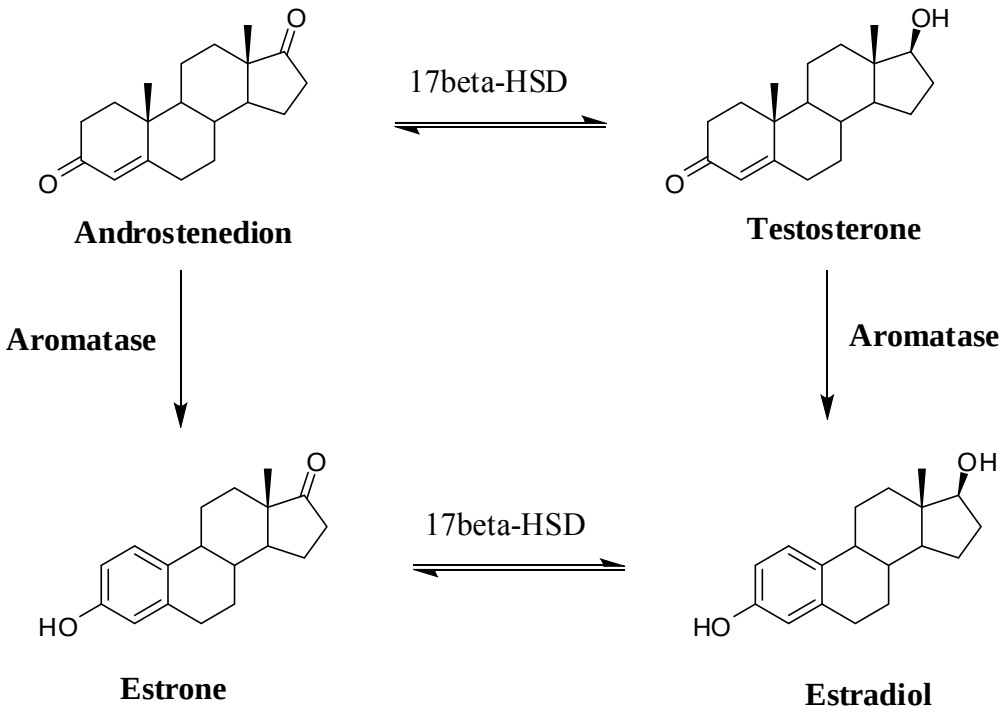
之前所發表的研究指出在缺乏 11β-HSD 1 的 mice 對於 experimental athritis 的 phagocytosis by macrophage 需求有時間延遲的現象以及血液中的 apoptotic neutrophils 的數目增加，顯示缺乏 11β-HSD 1 的 mice 對於發炎反應有 delayed resolution 的現象發生, 代表 11β-HSD 1 與促使下游發炎反應的初始時期有很大的關聯[12]。

此外, 在其他研究中也發現 11β-HSD 1 對於青光眼也有相當程度的關聯, 與 aqueous humor 的製造有關[1]。

11β-HSD 2 如之前所提及, 會遮蔽 glucocorticoid 對於 MR 強力的 agonist 作用, 若使用 11β-HSD 2 inhibitor 則會 cortisol/cortisone 的平衡偏向 cortisol 的方向，而 glucocorticoid 會增加血管壁對 Angiotensin II 的敏感度, 進而導致 salt-sensitive hypertension, 根據研究顯示若減少 11β-HSD 2 在肝臟的活性, 則可以使 cortisol/cortisone 的平衡往 cortisone 的方向移動, 有利於高血壓的治療[14]。

17β-hydroxy steroid dehydrogenases (17β-HSDs) 與 estrogen 以及 androgen receptor 結合, 並催化 estradiol/estrogen、testosterone/androstenedione 之間的轉換, 如圖四; androgens 與 estrogens 當在 17 號位置為 β configuration 為活化態, 而 keto form 則為不活化態, 因無法與 receptor 相結合, 不同的 17-HSDs isozymes 與 cervical cancer, malignant breast cancer 等不同的 androgen- and estrogen-related disorders 有關[1]。

圖五、estradiol/estrogen、testosterone/androstenedione 轉換示意圖



圖六、Glucocorticoids 在各系統、器官及組織所引起之症狀

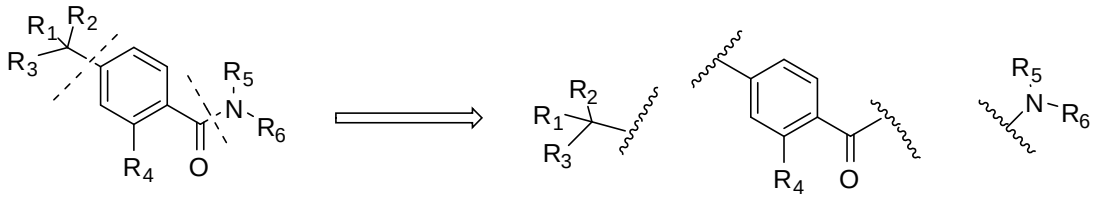
System /Organs / Tissues	Disorders / Symptoms
Brain / CNS	**Depression / Psychosis**
Eyes	**Glaucoma**
Endocrine system	**↓ LH, RSH release, ↓ TSH release**
GI tract	**Peptic ulcerations**
Carbohydrate / lipid metabolism	**↑ Hepatic glycogen deposition** **↑ Peripheral insulin resistance** **↑ Gluconeogenesis**
Adipose tissue	**Promote visceral obesity**
Cardiovascular / Renal	**Salt and Water retention** **Hypertension**

Skin / muscle / connective tissue	**Protein catabolism/collagen breakdown / Skin thinning / Muscular atrophy**
Bone and calcium metabolism	**↓ bone formation** **↓ bone mass and osteoporosis**
Growth and development	**↓Linear growth**
Immune system	**Anti-inflammation/Immunosupression**

1.2 Jay. P. Powers 所提出之 benzamides 合成路徑

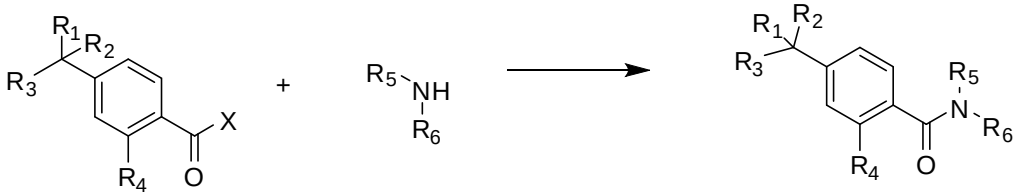
Jay 團隊對於骨架 A 拆成 a、b 和 c 三個部分來排列組合提出三個合成路徑(圖六、圖七所示), equition.1 提供了一個形成 amide bond 的方法, X 可以為 F、Cl、OH 等可以活化 carbonyl 的原子, 而—$CR_1R_2R_3$ group 必須在主要的 coupling reaction 發生前先接上;所採用的 coupling reagent 可以為有機或無機的 base, 像是 HBTU, 而輔助催化的試劑為 DMAP 或 HOBT。

圖七、Benzamide 骨架 A 拆解及 eq.1 骨架 A 合成 scheme



A **a** **b** **c**

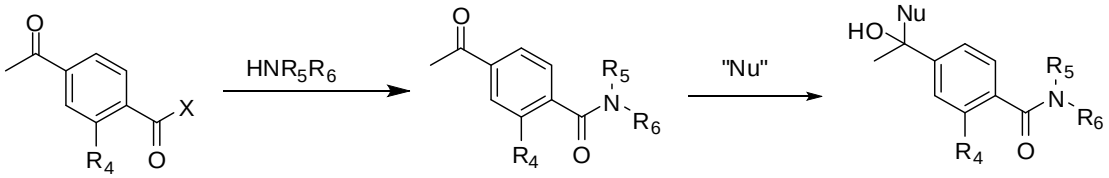
eq.1



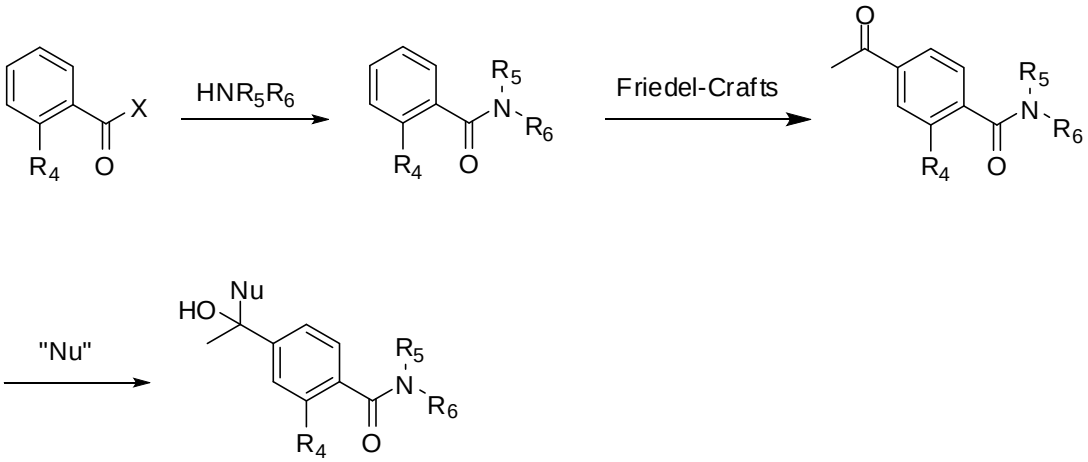
骨架 A 的—$CR_1R_2R_3$ group 也可以在 coupling reaction 後再進行合成，所採用的 nucleophile 分別來自於 CF_3TMS、MeLi 或 MeMgBr 的 CF_3^- or CH_3^-, 如圖七的 eq. 2；另一個將—$CR_1R_2R_3$ group 接上的方法如圖七 eq.3 所示，可以利用 Freidel-Craft 將 keto group 接上，再進行 nucleophile attack,如同 eq. 2 所採用的方法。

圖八、骨架 A 合成 scheme 之 eq. 2, eq.3

eq. 2



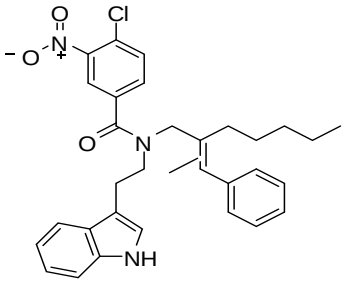
eq. 3



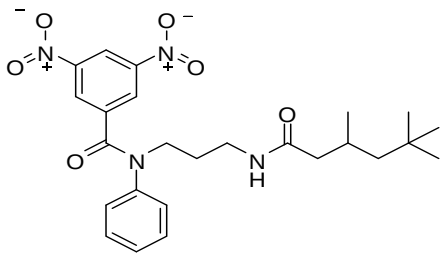
1.3 Benzamides 作為 anti-Alzheimer's drug

阿茲海默症被認為是 amyloid-β 在腦部堆積所造成的慢性腦部退化疾病, 過去研究採用針對 β-secretase[15] 和 γ-secretase[16] 的抑制來當作 Aβ-targeted immunotherapy. 而 Nathan T. Ross 等作者以 Advanced Glycation Endoproduct (RAGE)為 target, RAGE 為一種 immunoglobumin, 可利用它自身的 extracellular V domain 與多種廣泛的 ligands 做結合[17, 18], RAGE 可以穿透血腦障壁來運送 Aβ, 使得 Alzheimer 的病情加重, 而作者透過 High-throughput screen 找出三個化合物 **42-44** 作為 RAGE-Aβ binding inhibitor 的 hit compounds[21], 再經過分析這三個 compound 的結構後,再以一般的 pharmacophore hypothesis 來進行修飾, 而找到化合物 **45**, 在 *In vitro* 實驗中有可抑制 RAGE-Aβ binding, 而在具有阿茲海默的 mice model 中可以大幅減少 Aβ 在腦部的累積。

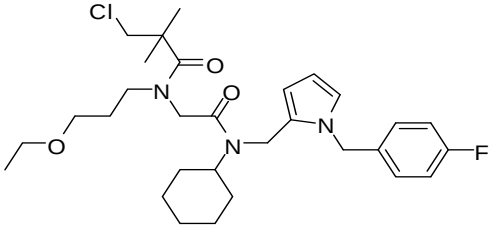
圖九、由 High-Throughput screen 所篩選出來當作 RAGE-Aβ modulators



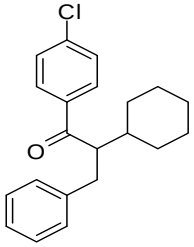
42



43



44

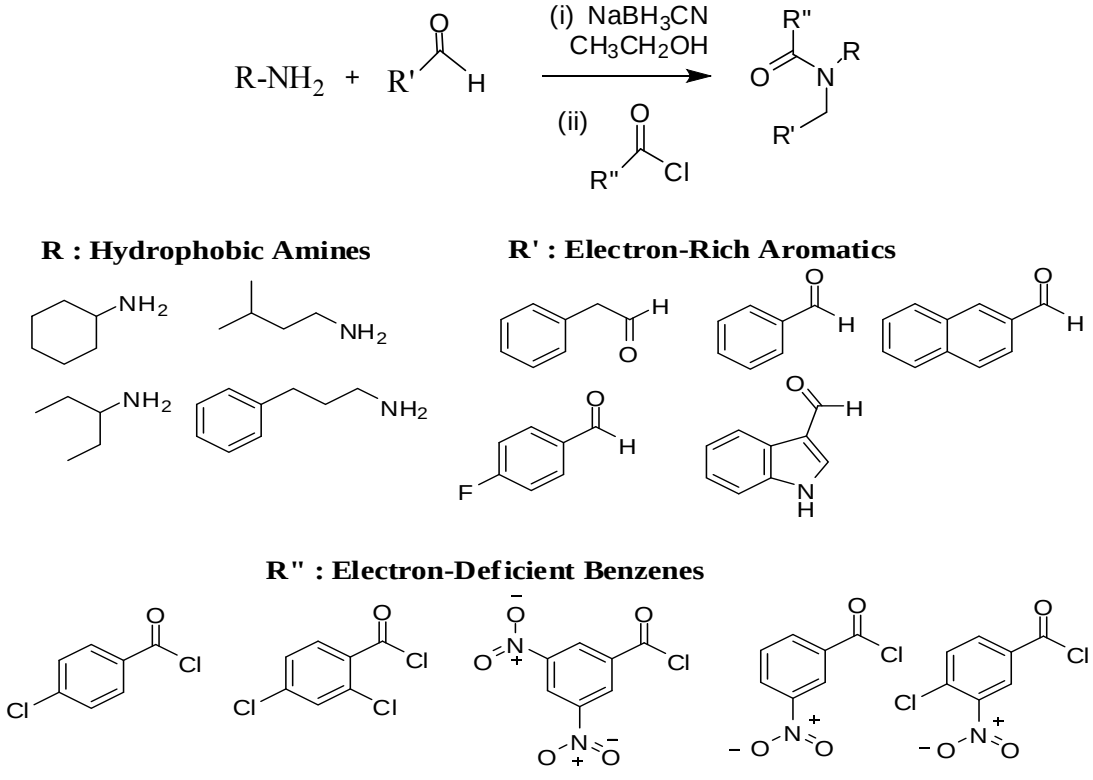


45

1.4 Nathan T.Ross 的 benzamides 合成策略

Nathan 將欲合成的 target compounds 分成 3 個部分, 分別為 hydrophobic amines、electron-rich aromatics 以及 electron-deficient benzenes, 如圖;而合成方法以化合物 45 作為範例, 以 1 當量的 cyclohexylamine 和 1 當量的 benzaldehyde 溶於 methanol 中,在 60℃下加熱攪拌 3 小時, 然後再冷卻置室溫, 之後將 1 當量溶於 ethanol 中的 cyanoborohydride 分 2 次加入, 每次加入後在室溫下攪拌 30 分鐘, 之後再加熱到 64℃攪拌 6 小時, 最後用水終止反應, 用 DCM 萃取濃縮, 再將中間產物溶於 dry 的 DCM 中,先後加入 0.1 當量的 DMAP 以及 1.1 當量的 diisopropylethylamine 在室溫下反應 overnight,最後以逆向的 isocratic HPLC 純化 (ACN/H_2O = 3/1)得到終產物, 但最後無標明產率。

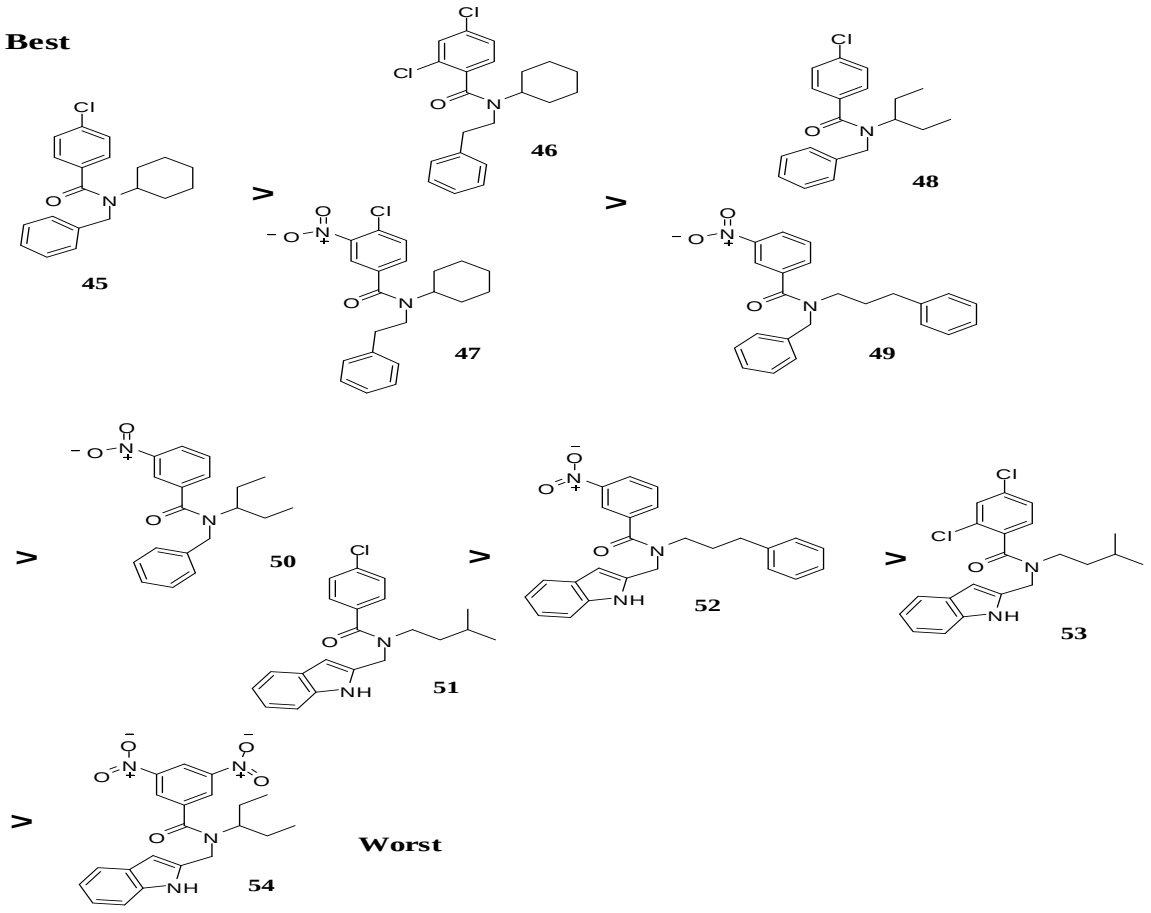
圖十、由資料庫所篩選出的 building blocks



1. 5 Nathan T. Ross 合成之 benzamides 抑制 RAGE-Aβ binding 之活性比較

在使用 ^{125}I-Aβ 40 binding assay 分析所有 building blocks 所組成之 benzamides 化合物後比較發現 化合物內具有 indole-或 nitro-substituted 的 electro-deficient benzene ring 表現最差，而 phenyl electron-rich aromatics 以及 chloro-substituted 的 electron deficient benzene ring 則表現較佳，而化合物 **45** 在 *In vivo* 中具有最佳表現及較好的 bioviability。

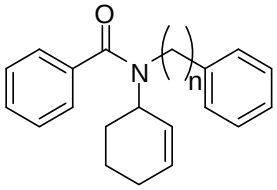
圖十一、以結構相似度大於 85%的各分類中的代表性 compounds 對於 RAGE binding affinity 之活性比較



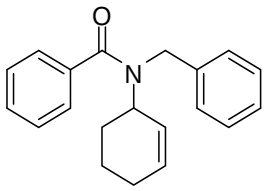
1.6 研究目的

根據 Jay P. Powers 等人在 2009 之前所發表之結構, 可以歸納出具三環之 Benzamide 應該是 HSDs inhibitor 的基本活性骨架, 而 *N*-cyclopropyllbenzamides 系列已被大量發表,且以專利保護起來, 因此在考慮到化合物 **55** 以及 Nathan 所發表之化合物 **45** 之下, 我們將 cyclopropyl group 換成六圓環, 且考慮到立體障礙可能過大, 會對於整體結構活性, 因此我們在 *N*-cyclohexyl group 的 2 號位置加上雙鍵, 來固定六圓環的部分結構, 以減少六圓環在空間上所造成過大的立體障礙而影響活性; 而回顧 Jay 和 Nathan 所發表過的 benzamides, 發現在 *N*-alkylbenzylamine 的苯環上並未做太多取代基的討論(Jay 所發表含 *N*-alkylbenzylamine 的三環 benzamide 只有化合物 **55**, **56**, **58-61**), 因此本實驗室決定先以不同碳鏈長度的 *N*-alkylbenzlamine 來做活性的探討,如圖 11; 最後意外發現 n = 1 的化合物 **2** 具有強烈的抗發炎能力, 因此我們再 benzylamine 的苯環上接上不同的取代基,以期許是否有更好的表現,而為了確立 *N*- cyclohex-2-enyl group 的雙鍵對於抗發炎的重要性, 我們將換成 *N*-cyclohexyl group 來觀察立體障礙對於整體活性的影響。

圖十二、*N*-alkylbenzyl-*N*-(cyclohex-2-enyl)benzamide 結構



圖十三、Jay P. Power (**55**, **56**, **58-61**)、Nathan(**45**)及本實驗室所設計之結構(**2**)



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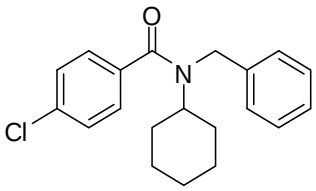

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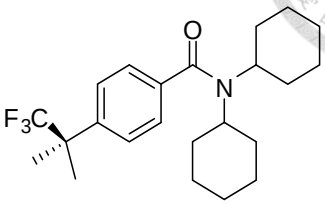
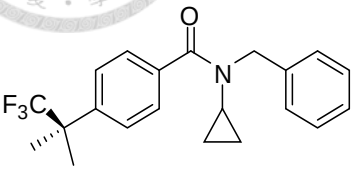
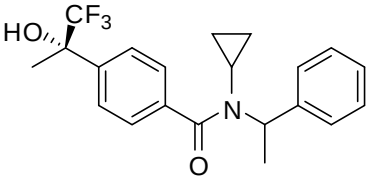


55



56



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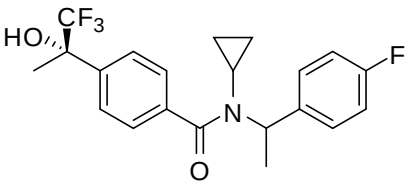

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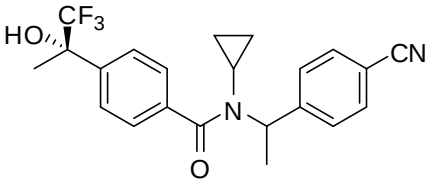

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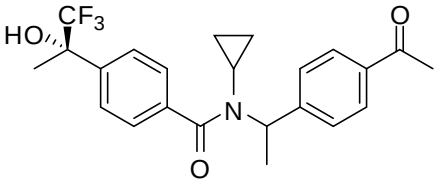


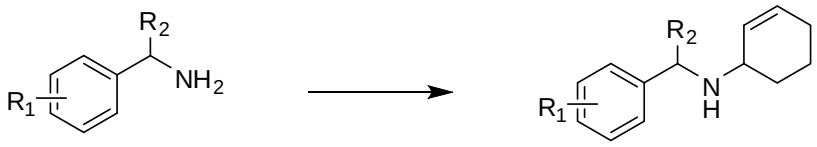
61

二 、 結果與討論

2.1 化學合成方法

2.1.1 *N*-benzylcyclohexy-2-enamine (1)之製備

以直觀的方法,在冰浴下先使用三當量的三己基胺將 benzylamine 去質子化，作為 nucleophile 對 3-bromocyclohexene 的 allyl carbon 做 S_N2 的反應，為了避免 benzylamine 一次接上 2 個 cyclohexene，將 1.1 當量的 3-bromocyclohexene 分成 0.5，0.3，0.3 當量於每隔一小時滴入，之後於室溫下反應 16 小時，點片確認反應結束後以一次水終止反應，並以乙酸乙酯萃取後再用飽和食鹽水除去三已基胺，將有機層減壓濃縮後得到的粗產物以 flash column 純化得到純的中間產物 *N*-benzylcyclohexy-2-enamine (**1**)。



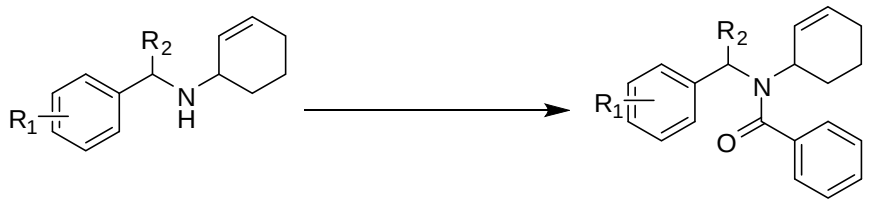
		yield
R_1 = H, R_2 = H	**1** : R_1= H, R_2 = H	44%
R_1 = *o*-F, R_2 = H	**4** : R_1= *o*-F, R_2 = H	42%
R_1 = *m*-F, R_2 = H	**7** : R_1= *m*-F, R_2 = H	47%
R_1 = *p*-F, R_2 = H	**10**: R_1= *p*-F, R_2 = H	51%
R_1 = *p*-Cl, R_2 = H	**13**: R_1 = *p*-Cl, R_2 = H	44%
R_1 = *p*-CH_3, R_2 = H	**16**: R_1 = *p*-CH_3, R_2 = H	50%
R_1 = *o*-CF_3, R_2 = H	**19**: R_1 = *o*-CF_3, R_2 = H	51%
R_1 = *p*-CF_3, R_2 = H	**22**: R_1 = *p*-CF_3, R_2 = H	41%
R_1 = *p*- OMe, R_2 = H	**25**: R_1 = *p*- OMe, R_2 = H	49%
R_1 = *o*, p-OCH_3, R_2 = H	**28**: R_1 = *o*, *p*-OCH_3, R_2 = H	45%
R_1 = *m*, *p*-OCH_3, R_2 = H	**31**: R_1 = *m*, *p*-OCH_3, R_2 = H	29%
R_1 = *o*, *m*, *p*-OCH_3, R_2 = H	**34**: R_1 = *o*, *m*, *p*-OCH_3, R_2 = H	54%
R_1 = H, R_2 = CH_3	**37**: R_1 = H, R_2 = CH_3	43%

Reagents and conditions : Et_3N, Dry DCM, 3-bromocyclohexene, 0℃→ R.T..

路徑一、 化合物 1, 4, 7, 10, 13, 16, 19, 22, 25, 28, 31, 34, 37 的合成路徑

2.1.2 *N*-benzyl-*N*-(cyclo-2-enyl)benzamide (2) 之製備

為了使 *N*-benzylcyclohexy-2-enamine **1** 順利接上 benzoyl group, 選用 benzoyl bromide 來進行 benzoylation; 與上步驟相似地先將中間產物 enamine 溶於 dry DCM, 接著在冰浴下攪拌時緩慢的滴入三當量的三已基胺, 經過二十分鐘的去質子化過程後,再緩慢滴入兩當量的 benzoyl chloride, 使之在室溫下反應 16 小時, 得到單一終產物 *N*-benzyl-*N*-(cyclo-2-enyl)benzamide (**2**)。



		yield
1 : R_1 = H, R_2 = H	**2** : R_1 = H, R_2 = H	86%
4 : R_1 = *o*-F, R_2 = H	**5** : R_1 = *o*-F, R_2 = H	42%
7 : R_1 = *m*-F, R_2 = H	**8** : R_1 = *m*-F, R_2 = H	66%
10: R_1 = *p*-F, R_2 = H	**11**: R_1 = *p*-F, R_2 = H	61%
13: R_1 = *p*-Cl, R_2 = H	**14**: R_1 = *p*-Cl, R_2 = H	34%
16: R_1 = *p*-CH_3, R_2 = H	**17**: R_1 = *p*-CH_3, R_2 = H	53%
19: R_1 = *o*-CF_3, R_2 = H	**20**: R_1 = *o*-CF_3, R_2 = H	46%
22: R_1 = *p*-CF_3, R_2 = H	**23**: R_1 = *p*-CF_3, R_2 = H	44%
25: R_1 = *p*- OMe, R_2 = H	**26**: R_1 = *p*- OMe, R_2 = H	73%
28: R_1 = *o*, p-OCH_3, R_2 = H	**29**: R_1 = 2, 4-OCH_3, R_2 = H	67%
31: R_1 = *m*, *p*-OCH_3, R_2 = H	**32**: R_1 = 3, 4-OCH_3, R_2 = H	71%
34: R_1 = *o*, *m*, *p*-OCH_3, R_2 = H	**35**: R_1 = 3, 4, 5-OCH_3, R_2 = H	30%
37: R_1 = H, R_2 = CH_3	**38**: R_1 = H, R_2 = CH_3	82%

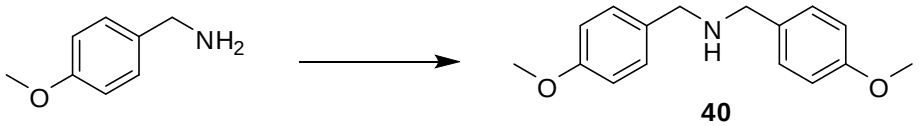
Reagents and conditions : Et_3N, Dry DCM, Benzoyl chloride, 0℃→ R.T..

路徑二. 化合物 2, 5, 8, 11, 14, 17, 20, 23, 26, 29, 32, 35, 38 的合成路徑

2.1.3 化合物 40、41 之合成

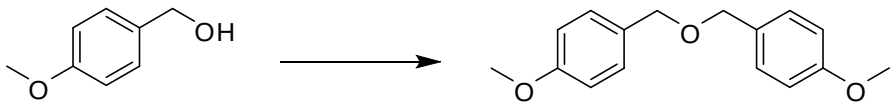
同樣以直觀的方法先將 1 當量 4-methoxybenzylamine 以及 1 當量的 (4-methoxyphenyl)methanol 分別溶於 5 ml 的 DCM 至於雙頸瓶內, 在冰浴下分別加入 3 當量和 6 當量的三己胺後攪拌 20 分鐘來將 amine group 和 hydroxyl group 來去質子化, 再分別加入 1.1 和 1.2 當量的 4-methoxybenzylchloride, 而為了避免 amine group 一次接上 2 個 4-methoxybenzyl group, 將 1.2 當量 4-methoxybenzylchloride 分成 3 次加入, 每次間隔時間 1 小時; 之後再分別加入 0.1 當量的 potassium iodide, 將 4-methoxybenzylchloride 的 Cl 置換成 I, 因 iodide 為比 chloride 為更好的 leaving group; 在室溫下反應 6 小時後,分別得到化合物 **40** 和 **41**, 如路徑三。

(1)



40

(2)



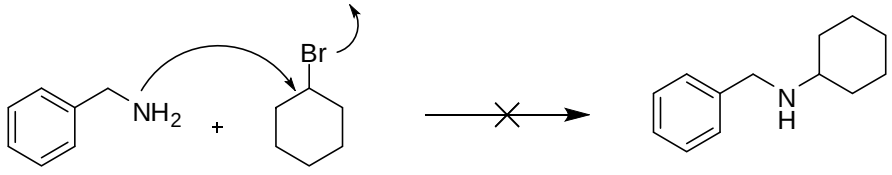
41

Reagents and conditions : (1) 4-methoxybenzylchloride, Et_3N, KI, DCM, 0℃→R.T., 23% . (2) 4-methoxybenzylchloride, Et_3N, KI, DCM, 0℃→R.T., 43%

路徑三、化合物 40、41 之合成方法

2.1.4 *N*-benzylcyclohexanamine 之製備

為了討論 benzamide 的雙鍵對分子活性的影響, 所以合成一系列無雙鍵的 *N*-benzyl-*N*-cyclohexylbenzamide 及衍生物; 分析 *N*-benzyl-*N*-cyclohexylbenzamide 的逆合成路徑,必須先合成 *N*-benzylcyclohexanamine,於是先嘗試使用直觀的方法將 benzylamine 去質子化,然後在不同的反應條件下嘗試對 cyclohexylbromide 進行 N-alkylation, 發現產率都極低,可能原因為 deprotonated 的 amide 要攻擊 cyclohexylbromide 上的二級碳因立體障礙比起部分結構呈現平面的 3-bromocyclohexene 來的大,所以鍵型成的機率大幅降低, 而 3-bromocyclohexene 的 Br 原子位於 allyl carbon 的位子,使得此分子的 Br 為比在 secondary carbon 上的 Br 為更好的 leaving group ; 因此利用 S_N2 的方法來合成 *N*-benzylcyclohexanamine 不是理想的方法!

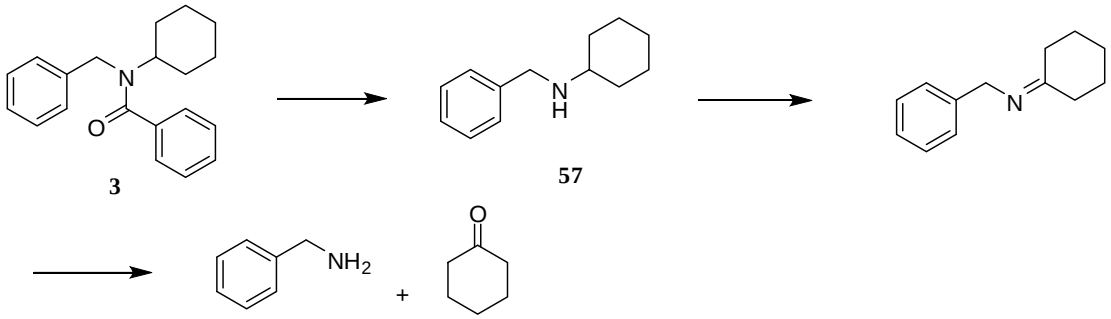


Reagents and conditions : Entry 1. : Et_3N, KI, dry DCM, 0℃→R. T., No reaction. Entry 2. : Et3N, KI, LC grade ACN, 0℃→60℃, < 1%

路徑四、benzylamine 無法對 cyclohexylbromide 進行 N-alkylation

於是我們利用逆合成的路徑推導, 發現 benzamide 可以由 benzylamine 和 cyclohexanone 進行 imination 後,再進行 reduction 將雙鍵還原得到,如路徑四所示; 根據之前的研究 [1, 2],對於 imination 進行一系列的反應嘗試,如表一, 可以得知 Toluene 為比 DCM 為更好的溶劑來進行 imination, 而 cyclohexanone 的當量、溫

度以及反應的時間的增加對於產率的提升呈現正相關，而分子篩體積的使用量的提升對於相對產率提升之助益可說明無水環境對於 imination 的重要性,因此根據表一可以得到 imination 的最佳條件；反應中加入 p-TSA,作為酸催化作用，p-TSA 在溶劑終能釋出質子使 cyclohexanone 的 carbonyl group 帶正電,增加酮基碳上的部分正電,進而吸引 benzylamine 的 lone pair electrons 攻擊,如反應機構一所示。

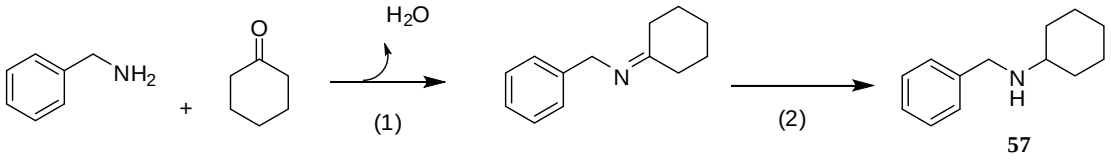


路徑五、 *N*-benzyl-*N*-cyclohexylbenzamide 的逆合成路徑

Entry	Cyclohexanone equivalance	Solvent	Temperature	Reaction Time	Molecular Sieves vol.	Yield
1.	1.2	DCM	R.T.	1 day	2 ml	0%
2.	1.2	Toluene	60℃	1 day	2 ml	10%
3.	2	Toluene	60℃	1 day	2 ml	17%
4.	2	Toluene	60℃	1 day	4 ml	22%
5.	2	Toluene	60℃	3 days	4 ml	68%

表一、 Imination 反應之條件嘗試

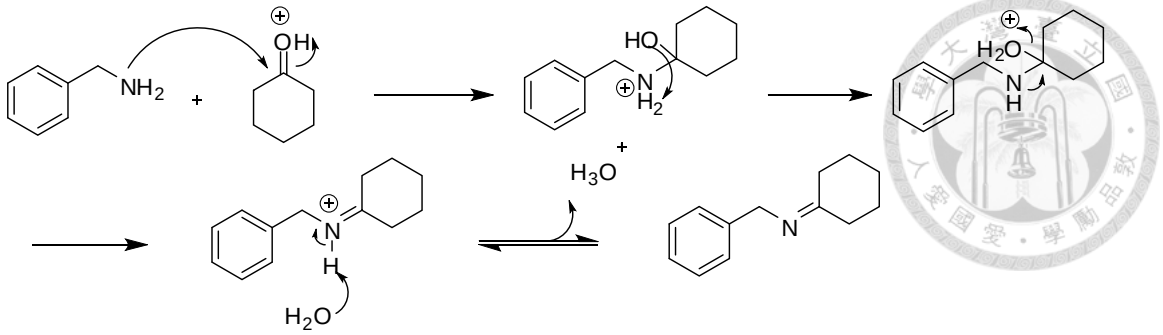
接著將 imination 的中間產物溶於 MeOH,在冰浴下攪拌,然後緩慢的加入 $NaBH_4$, $NaBH_4$ 能將醛、酮等活性較大的雙鍵還原,而一般碳-碳雙鍵則不行,如反應機構二所示;$NaBH_4$ 反應 20 分鐘後,觀察氫氣是否不再產生後, 將 crude 直接減壓濃縮抽乾,再用 $NaHCO_{3(aq)}$ 中和 crude, 以 EtOAc 萃取後, 用 $MgSO_4$ 除水後減壓濃縮有基層, 再過 flash column 純化得到 *N*-benzylcyclohexanamine 。



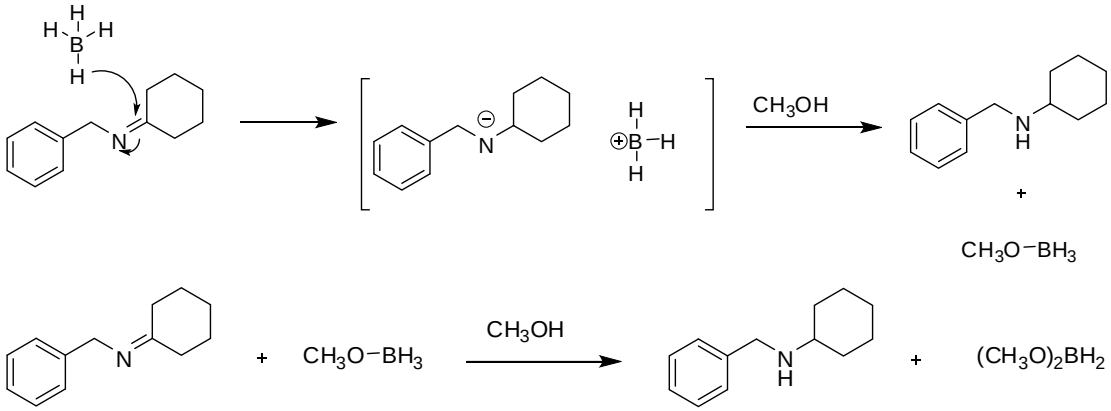
57

Reagents and conditions : (1) Toluene, 4Å molecular sieves, *p*-TSA, 60℃, 3 days; (2) $NaBH_4$, MeOH, 0℃, 20 mins; 68% for two steps.

路徑六、 *N*-benzylcyclohexanamine 之合成路徑

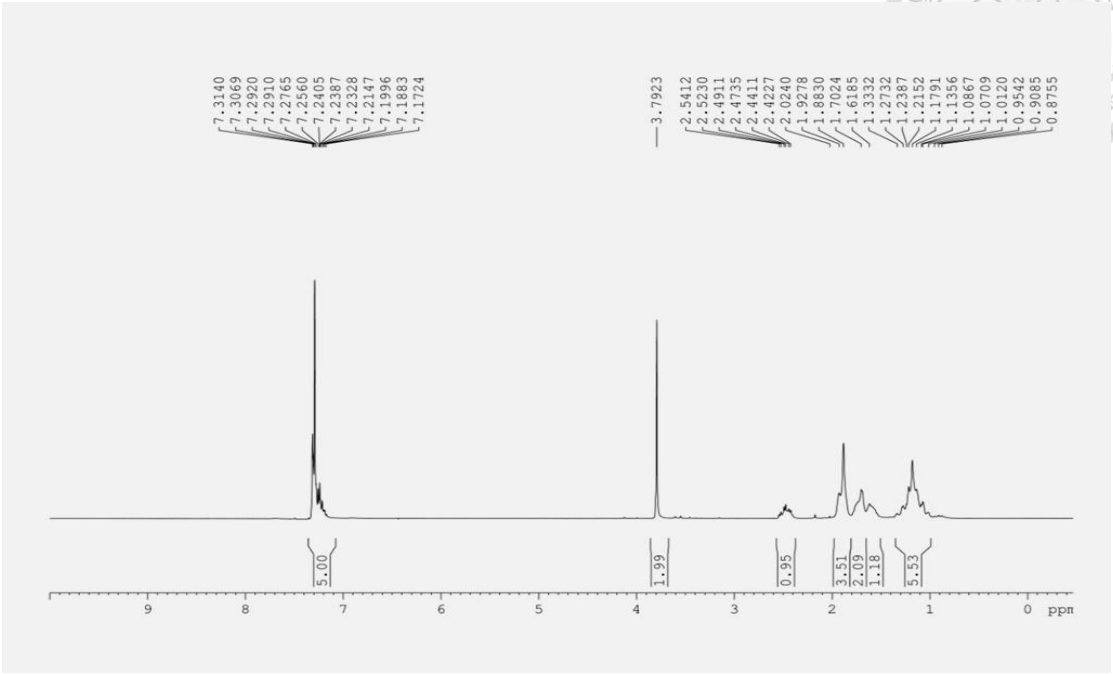


反應機構一、Imination 之酸催化反應

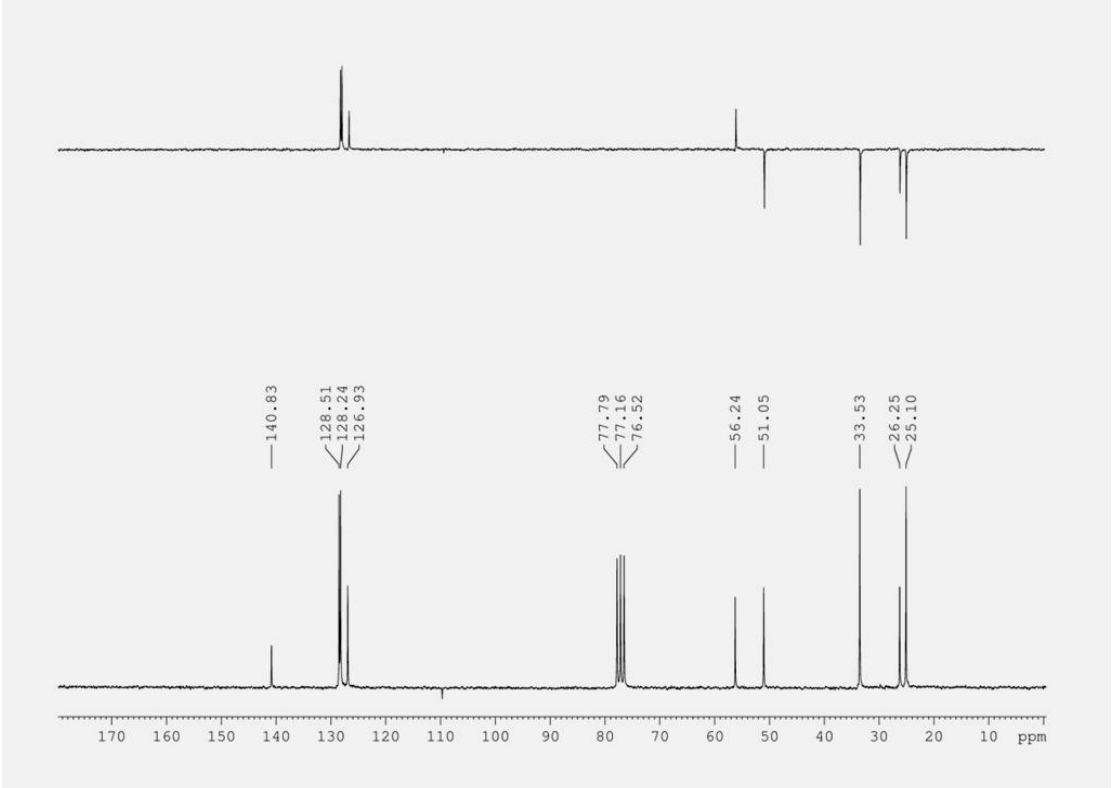


反應機構二、 Sodium borohydride 還原 imine 雙鍵之反應

圖十三、化合物 **57** 之氫核磁共振圖譜($CDCl_3$, 200 MHz)



圖十四、化合物 **57** 之 ^{13}C 與 DEPT135 核磁共振

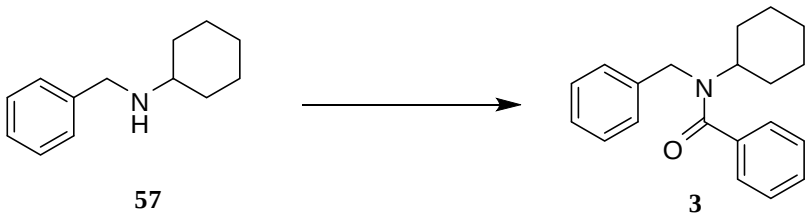


2.1.5 *N*-benzyl-*N*-cyclohexylbenzamide (3) 之製備

以合成出的 *N*-benzylcyclohexanamide 接續下一步的 benzoylation,嘗試以 *N*-benzyl-*N*-(cyclo-2-enyl)benzamide (**2**)的合成方法以及之前所發表相似產物的合成條件,來進行測試, 發現因六圓環所造成的立體障礙以及二級胺的質子不易解離的情況下,在 mild base 和室溫之下的溫和反應條件,是無法使得二級胺去質子化,必須採用較強的鹼以及較高的反應溫度才能勉強進行 benzoylation; 並加入 0.1eq KI, 其在溶液中解離出的 iodide 來置換 benzoyl chloride 形成 benzoyl iodide, iodide 為比 bromide 更好的 leaving group, 如表二; 以 Entry 5 條件反應一天後, 用 MeOH 終止未反應的 sodium hydride ,再直接減壓濃縮抽乾,之後用 $NaHCO_3$ 中和 crude,接著以 DCM 萃取濃縮後以逆向的 HPLC 分離 (mobile phase : ACN/H_2O = 3/1)得到純的化合物。

Entry	Solvent	Base	Equivalence	Time	Temp.	Yield
1.	DCM	Et_3N	3	1 day	R.T.	N.R.
2.	DCM	Et_3N/pyr.	1/0.1	1 day	R.T.	N.R.
3.	DCM	Et_3N/DMAP	1/0.1	1 day	R.T.	N.R.
4.	THF	NaH	1.1	1 day	R.T.	N.R.
5.	DMF	NaH	1.5	1 day	60℃	6%

表二、*N*-benzylcyclohexanamide 進行 benzoylation 之條件嘗試

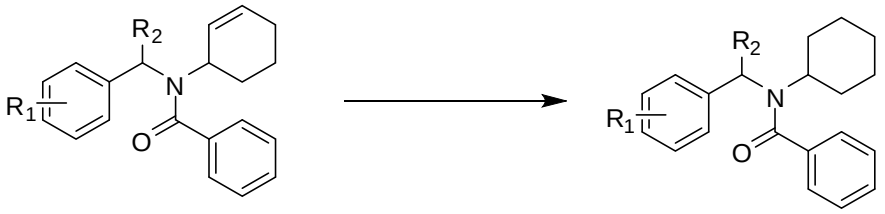


57 **3**

Reagents and conditions : benzoyl chloride, sodium hydride, KI, DMF, 60℃, 1day, 6% for one step.

路徑七、 *N*-benzyl-*N*-cyclohexylbenzamide (**3**)之合成路徑之一

由於以 S_N2 的方法進行 benzoylation 所花費時間太長，且產率不高,所以重新更改設計合成路徑,以原本的 *N*-benzyl-*N*-(cyclo-2-enyl)benzamide (**2**)做為起始物，用 palladium on activated carbon 當非勻相催化劑對雙鍵做直接的氫化還原,以 RP-TLC (mobile phase：ACN/H_2O = 1/2) 確認反應是否結束之後，用 celite 除去 Pd/C，以 Methanol 沖洗後減壓濃縮，再用 flash column 以 EtOAc/ Hexane 系統純化得到純的 *N*-benzyl-*N*-cyclohexylbenzamide (**3**)；由於此方法可以避免六圓環所造成的立障過大而無法使 secondary amine 去質子化的問題，因此可以大幅提升產率，且反應時間約莫 3 到 4 小時即可完全反應，並且副產物極少，可直接用 flash column 純化，節省 5 到 6 小時 HPLC 的使用時間，比起之前研究所發表相似物的合成方法，產率大幅提升，如路徑七。



		Yield
2 : R_1 = H, R_2 = H	**3** : R_1= H, R_2 = H	33%
5 : R_1 = *o*-F, R_2 = H	**6** : R_1= *o*-F, R_2 = H	69%
8 : R_1 = *m*-F, R_2 = H	**9** : R_1= *m*-F, R_2 = H	99%
11: R_1 = *p*-F, R_2 = H	**12**: R_1= *p*-F, R_2 = H	77%
14: R_1 = *p*-Cl , R_2 = H	**15**: R_1 = *p*-Cl, R_2 = H	69%
17: R_1 = *p*-CH_3, R_2 = H	**18**: R_1 = *p*-CH_3, R_2 = H	95%
20: R_1 = *o*-CF_3, R_2 = H	**21**: R_1 = *o*-CF_3, R_2 = H	48%
23: R_1 = *p*-CF_3, R_2 = H	**24**: R_1 = *p*-CF_3, R_2 = H	78%
26: R_1 = *p*- OMe, R_2 = H	**27**: R_1 = *p*- OMe, R_2 = H	42%
29: R_1 = *o*, p-OCH_3, R_2 = H	**30**: R_1 = *o*, *p*-OCH_3, R_2 = H	65%
32: R_1 = *m*, *p*-OCH_3, R_2 = H	**33**: R_1 = *m*, *p*-OCH_3, R_2 = H	69%
35: R_1 = *o*, *m*, *p*-OCH_3, R_2 = H	**36**: R_1 = *o*, *m*, *p*-OCH_3, R_2 = H	65%
38: R_1 = H, R_2 = CH_3	**39**: R_1 = H, R_2 = CH_3	53%

Reagents and conditions : Palladium on activated carbon, Methanol, hydrogen gas (1 atm).

路徑八、 *N*-benzyl-*N*-cyclohexylbenzamide (**3**)之合成路徑之二

2.2 生物活性探討

2.2.1 抗發炎活性及 SAR 探討

本實驗室委託長庚大學天然物研究所黃聰龍教授實驗室代為測定化合物之抗發炎活性, 結果顯示化合物 5 對於人類嗜中性白血球產生 superoxide anion 的 IC_{50} 之表現最為優異, IC_{50} 為 0.11±0.05 μg/ml 。而抑制 Elastase release 表現最佳者為化合物 **23** , IC_{50} = 1.09±0.20 μg/ml; 實驗數據如下:

Compound	Superoxide anion		Elastase release	
	IC_{50} (μg/ml)[a]	Inh%	IC_{50} (μg/ml)[a]	Inh%
2	0.17±0.03	86.18±5. 75	3.42±1.69	76.54±2.26
3	0.67±0.12		7.01±0.06	
5	0.11±0.05	84.35±3.84	5.98±1.79	54.99±6.90
6	0.19±0.03		4.09±0.18	
8.	0.62±0.16	77.33±3.46	5.42±1.91	60.43±7.50
9	0.92±0.21		5.50±0.20	
11	0.21±0.03	83.70±4.15	5.40±1.03	65.21±3.86
12	1.00±0.28		5.50±0.67	
14	0.20±0.04	65.19±3.64	3.65±1.14	72.88±6.63
15	0.73±0.61		3.85±061	
17	0.24±0.06	90.06±2.91	4.47±1.12	83.17±5.70
18	0.69±0.10		4.07±0.33	
20	＞10	24.20±7.48	＞10	47.97±5.81
21	＞10		7.40±1.55	
23	1.17±0.39	59.28±7.21	1.09±0.20	88.69±7.43
24	2.38±0.53		7.11±0.53	
26	1.11±0.37	82.67±4.45	＞10	44.77±5.87
27	2.05±0.40		＞10	
29	7.84±0.37	70.20±4.17	7.79±0.43	71.49±7.74
30	2.72±0.56		5.24±0.15	
32	4.24±1.32	72.97±8.02	7.65±1.01	58.51±4.18
33	5.00±0.98		8.44±0.97	
35	＞10	14.05±7.12	＞10	3.38±3.79
36	＞10		＞10	

38	6.07±0.40	6.20±0.80
39	＞10	＞10
40	8.84±0.50	＞10
41	4.18±0.85	＞10

表三、化合物 **2**, **3, 5**, **6**, **8**, **9**, **11**, **12**, **14**, **15**, **17**, **18, 20**, **21**, **23**, **24**, **26**, **27**, , **29**, **30**, **32**, **33**, **35, 36, 38, 39, 40, 41** 之抗發炎活性 IC_{50}

Percentage of inhibition (Inh%) at 10 μg/ml concentration. Results are presented as mean ± S.E.M.(n=3 or 4). [a]Concentration necessary for 50% inhibition (IC_{50})

由表三我們可以歸納出下列四點:

1. Benzyl group 的苯環上 *o*-, *m*-, *p*-位子對抗發炎活性的影響: 以 benzyl group 上無取代的化合物 **2** 標準(IC_{50}= 0.17±0. 03 μg/ml), 若為 *o*-F, 則活性提升為 IC_{50}= 0.11±0.05 μg/ml, 而改以 *m*-F 或 *p*-F, 則發現 *p*-F 對抗發炎活性只略微下降為 IC_{50}= 0.21±0.03 μg/ml,影響不大, 但 *m*-F 則下降 5.6 倍, IC_{50}= 0.62±0.16 μg/ml,可得到結論為 *meta* 位置最好不要有取代基, 否則會使得活性下降。
2. Benzyl group 的苯環上 *para* 位置之取代基大小對抗氧化活性的影響: *p*ara 位接 F, Cl, 或 CH_3 的 IC_{50} 大約都落在 0.2 μg/ml 左右,無明顯變化; 若稍微增加取代基的長度,以 *p*-CF_3 為例, IC_{50} = 1.17±0.39 μg/ml, 活性約莫才減少 5 倍, 但相較於 *o*-CF_3 (IC_{50} ＞10 μg/ml) 對比 *o*-F 之活性則相差 100 以上; 綜合第一點推論 benzyl group 的 *para* 位置比起 *ortho* 位置的影響力遠遠較低, 且 *ortho* 位置不宜接過大的取代基, 否則活性則會迅速下降, 而 *para* 位置上取代基的大小則無明顯過大的波動影響。
3. Benzyl group 的苯環上 *ortho*-, *meta*-位置之重要性比較: *p*-OMe 的 IC_{50} = 1.11±0.37 μg/ml, 而 *m*, *p*-OMe 的 IC_{50} = 4.24±1.32 μg/ml , 抗發炎活性下降約剩 1/4, 但若是 *o*, *p*-OMe, IC_{50} = 7.84±0.37 μg/ml, 活性下降程度約為 *m*,

p-OMe 的 2 倍，因此結合第 1, 2 點做出歸納出 benzyl group 上的取代位置對抗發炎活性的影響程度為 *ortho*＞*meta*＞*para*。

4. 除了化合物 **29**、**30** 呈現在雙鍵消失後，抗發炎活性上升外，其餘化合物都呈現活性下降的趨勢；值得注意的是化合物 **6** 對比化合物 **5** 的抗發炎活性雖略微下降，但對照其他化合物，也表現出優異的抗發炎活性(IC_{50} = 0.19±0.03 μg/ml)，顯示出 *ortho*-position 的重要性。

2.2.2 抗癌細胞活性

本實驗室委託國立中國醫藥研究所郭曜豪教授實驗室代為測定化合物對於喉癌(HEp-2)、肝癌(Hep-G2)、肺癌(A549)與乳腺癌(MCF-7)之抗腫瘤活性，發現化合物 **21** 在 28 個化合物中對於喉癌的表現最佳(ED_{50} 為 5.82±0.51 μg/ml)；化合物 **20** 在肺癌和乳腺癌的抗腫瘤活性在 12 個化合物中表現最佳(ED_{50} 分別為 10.31±0.13 以及 10.02±0.06 μg/ml)；而在肝癌項目中則為化合物 **11** (ED_{50} = 10.37±0.55 μg/ml)表現最好，化合物 **20** (ED_{50} = 10.46±0.0.16 μg/ml)緊追在後,實驗數據如下:

Compound	ED_{50} (μg/ml)			
	HEp-2	Hep G2	MCF-7	A549
2.	23.40±0.15	11.43±0.51	15.05±0.69	17.91±0.27
3	13.89±0.17		20.19±0.90	
5	23.31±0.05	17.42±0.92	16.43±0.40	17.63±0.13
6	15.20±0.14		21.26±0.49	
8	22.34±0.31	14.89±0.58	(－)	12.52±0.52
9	16.50±0.59		22.23±0.38	
11	20.67±0.26	10.37±0.55	16.68±0.49	18.67±0.22
12	31.30±0.94		(－)	
14	23.47±0.14	10.63±0.28	19.09±0.80	20.51±0.17
15	11.24±0.40		12.48±0.40	
17	22.61±0.31	14.82±0.98	17.31±0.70	20.57±0.35
18	10.39±0.70		12.17±0.35	
20	10.01±0.18	10.46±0.16	10.02±0.06	10.31±0.13
21	5.82±0.51		13.09±0.24	
23	23.02±0.15	10.70±0.24	11.16±0.51	16.45±0.33
24	6.78±0.38		11.38±0.44	
26	27.42±0.89	20.52±0.18	18.99±0.53	24.53±0.50
27	14.06±0.14		20.71±0.81	
29	25.03±0.12	18.50±0.43	20.22±0.14	22.66±0.05
30	8.59±0.18		11.56±0.14	
32	(－)	(－)	(－)	(－)

33	23.15±0.66		(－)	
35	(－)	(－)	(－)	(－)
36	(－)		(－)	
38	12.74±0.40		13.98±0.41	
39	13.13±0.28		13.67±0.55	
40	31.36±0.40		(－)	
41	(－)		(－)	

(－): ED_{50} ＞40μg/40ml

Cell line:

HEp-2: Human laryngeal carcinoma

Hep G2: Human heptocellular carcinoma

MCF-7: Human breast adenocarcinoma

A549: Human lung carcinoma

表四、化合物 2, 3, 5, 6, 8, 9, 11, 12, 14,15, 17, 18, 20, 21, 23, 24, 26, 27 29, 30, 32, 33, 35, 36, 38, 39, 40, 41 之抗癌活性

兩組化合物比較之下，在 HEp-2 的項目中,雙鍵的存在對於活性產生明顯的差異，例如化合物 **3** 對 **2**、化合物 **6** 對 **5**、化合物 **9** 對 **8**、化合物 **15** 對 **14**、化合物 **18** 對 **17**、化合物 **21** 對 **20** 以及化合物 **27** 對 **26** 之抗喉癌活性都有明顯的提升約 2 倍左右，而化合物 **24** 對 **23**、化合物 **30** 對 **29** 之活性更是提高約 4 倍，而化合物 **21** (ED_{50} = 5.82±0.51 μg/ml)表現最為優異，其次依序為化合物 **24** (ED_{50} = 6.78± 0.38 μg/ml)和化合物 **30** (ED_{50} = 8.59±0.18 μg/ml)，依此可推測在 benzyl group 的 *ortho* 位置有-O-X (X = CH_3, CF_3) group 取代可以大幅提升 bindfing affinity，而若只有單原子取代則效果提升則不那麼明顯如化合物 **6** (ED_{50} = 15.20± 0.14 μg/ml) 之 benzyl group 的 *ortho* group 以 fluorine 取代；因此可以在

N-cyclohexylbenzamides 系列的 benzyl group 的 *ortho* 位置再進行不同的 funtion group 做修飾, 同時以化合物 **21**、**24** 和 **30** 的 cyclohexyl group 以及 benzoyl group 做取代修飾, 期待是否對於抗喉癌活性是否能再進一步提升。

而在 MCF-7, 雙鍵所造成之影響則無太大差異, 除了化合物 **30** (ED_{50} =11.56±0.14 μg/ml)對化合物 **29** (ED_{50} = 20.22±0.14 μg/ml)提升將近 2 倍的活性外, 其餘都在相近範圍之間, 可以嘗試在六圓環或是 benzoyl group 上以不同取代基來嘗試開發。

三、結論

我們利用化學方法合成出 *N*-benzyl-*N*-(cyclo-2-enyl)benzamide (**2**)及一系列 12 個衍生物, 其中化合物 **5** 具有卓越的抗發炎效果 (IC_{50}= 0.11±0.05 μg/ml),而根據抗發炎活性(表三), 可以做出以下三點結論: (1) 化合物 **2** 的 benzyl group 之 *meta* 位置最好不要有取代基, 否則會使得活性下降。(2) 化合物 **2** 的 benzyl group 之 *para* 位置上的取代基之大小變化在一定範圍內時對整體活性的影響不大, 反觀 benzyl group 之 *ortho* 位置上的取代基之大小對於抗發炎活性之表現的浮動程度甚鉅。(3) 化合物 **2** 的 benzyl group 之苯環上三個位置對整體抗發炎活性的影響力為 *ortho*＞*meta*＞*para*。而未來可以嘗試在化合物 **2** 的 benzyl group 的 *ortho* 位置嘗試接上 Cl, Br, I 等不同原子的取代基來觀察是否有更優異的抗發炎表現。

為了討論化合物 **5** 的 cyclohexene 的雙鍵對於抗發炎活性的影響,我們合成 *N*-benzyl-*N*-cyclohexylbenzamide (**3**)以及其它 12 個衍生物; 根據過去所發表類似化合物 **3** 的化合物的方法來合成化合物 **3** 及其衍生物, 發現產率低落,且耗時長久, 顯示要對 *N*-benzylcyclohexanamide 進行去質子化來進行 benzoylation 會遇到 cyclohexyl group 所造成的立體障礙過大的問題; 因此我們開發出了另一條路徑, 使用原本已合成出的 *N*-benzyl-*N*-(cyclo-2-enyl)benzamide (**2**)及一系列衍生物來對其 cyclohexene group 做直接的氫化反應來合成 *N*-benzyl-*N*-cyclohexylbenzamide (**3**) 及其它 12 個衍生物, 結果發現反應時間大幅縮短為 3 小時左右, 且反應條件不需過於劇烈, 並大幅減少耗材成本, 為此類似骨架之化合物提供一個簡便的合成途徑。最後在抗發炎的實驗中顯示出, 除了化合物 **30** 為呈現在雙鍵消失後, 抗發炎活性上升外, 其餘化合物都呈現活性下降的趨勢, 但 *ortho* 位置依然對嗜中性白血球釋出 superoxide anion 的抑制活性上扮演關鍵的角色。

N-benzyl-*N*-(cyclo-2-enyl)benzamide(**2**)及一系列 12 個衍生物在抗癌細胞活性中, 以化合物 **20** 在喉癌、肺癌和乳腺癌測試項目中表現最佳, ED_{50} 分別為

10.01±0.18μl/ml、10.31±0.13μl/ml 以及 10.02±0.06 μl/ml; 而在而在肝癌項目中則為化合物 **11** (ED_{50} = 10.37 ± 0.55 μl/ml) 表現最好；而與 *N*-benzyl-*N*-cyclohexylbenzamide 及其它 12 個無雙鍵之 benzamides 相比，在 HEp-2 的項目中，無雙鍵的 N-cyclohexylbenzamides 的抗喉癌活性明顯提升許多，尤其是 benzyl group 的 *ortho*- position 以-O-X (X = CH_3, CF_3) group 取代可以大幅提升抗癌活性，例如活性最佳的化合物 **21** (ED_{50} =5.82±0.51 μl/ml) 和次之的化合物 **24** (ED_{50} =6.78±0.38 μl/ml) 和化合物 **30** (ED_{50} = 8.59±0.18 μl/ml)。

藉由合成這 26 個化合物，我們對化合物 **3** 完成部分結構 SAR 的探討,以做為更進一步 SAR 的設計及修飾來提供一個大致的方向，希望未來能夠開發出更具潛力的 benzamide 抗發炎藥物。

四、實驗部分

4.1. 一般實驗方法

1. 所有無水反應進行時所用到的玻璃雙頸瓶及攪拌石皆先置於真空下用吹風機加熱乾燥,冷卻後再灌入氮氣使用 。
2. 所有無水反應之起始物皆於反應前使用真空系統移除溶劑。
3. 所有無水反應所使用之溶劑皆為 LC 級溶劑,加入分子篩並充氮氣保存。

4.2. 實驗試劑及儀器來源

4.2.1. 試劑

實驗使用之試劑皆由藥品供應商購入 ， 使用前皆無經過處理而直接使用。

Acros:

Benzylamine, (Trifluoromethyl)amine, 4-methylbenzylamine, 2-fluorobenzylamine, 3-fluorobenzylamine, 4-fluorobenzylamine, 4-chlorobenzylamine, 2-(Trifluoromethyl)benzylamine, 4-methoxybenzylamine, 2,4-dimethoxybenzylamine, 3,4-dimethoxybenzylamine, 3,4,5-trimethoxybenzyamne, DL-alpha-methylbenzylamine benzoylchloride, cyclohexylbromide, KBr, KI, Toluene, *p*-TSA, Et_3N

Sigma-Aldrich:

N,N-dimethylforamide, Pd/C, $NaHCO_3$, 4-(Dimethylamino)pyridine, 4-methoxybenzyl chloride

Alfa Aeser:

NaH, cyclohexanone

Lancaster:

$NaBH_4$

Merck:

Methanol (LC grade), Acetonitrile (LC grade), pyridine, $CDCl_3$

Fisher Chemical:

$MgSO_4$ (Dried)

Macron Chemical:

DCM (ACS grade)

Echo Chemical:

EtOAc (ACS grade), n-Hexane (ACS grade), methanol (ACS grade), acetone (ACS grade）

Germany:

Merck Silica gel 60 (0.063-0.200 mm)

4.2.2. 薄層分析法（Thin layer chromatography, TLC）

使用 Merck Kiesegel 60 F254 之矽膠(silica gel)薄層層析片, 利用流動相(mobile phase)展開後 ， 用紫外燈(254nm)照射 ， 或以顯色劑 anisaldehyde 以及碘粉染

片後加熱觀察。

4.2.3. 核磁共振光譜

使用 Bruker-400(400MHz), DPX-200(200MHz),AVIII-600 (600MHz)，以 $CDCl_3$ 配置樣品, 以 ppm 為化學位移之單位，校正標準為 $CDCl_3$ (^1H: 7.24 ppm, ^{13}C: 77.16 ppm)。^1H-NMR 分裂型式定義如下: s, 單峰 (Singlet) ; d, 雙分裂 (Doublet) ; t,三分裂 (Triplet) ; q, 四分裂 (Quartet) ; dd, 雙重雙分裂 (Doublet of doublets) ; m, 多分裂 (Multiplet)。偶和常數 (Coupling constant) 以 *J* 表示，單位為 Hz。

4.2.4. 高效能液相層析儀（High-Performance Liquid Chromatography, HPLC)

（1）幫浦（Pump）: HITACHI L-7100 Pump (Japan)

（2）偵測器（Detector）: HITACHI L-4000H UV Detector (Japan)

（3）積分儀（Integrator）: HITACHI D-2500 Chromato-Integrator (Japan)

（4）層析管柱（Column）: LiChrosper® Si 60 (5 μm, 250mm × 10 mm) (Merck, KGaA, Darmstadt, Germany)

LiChrosper® ^{100} RP-18e (5 μm, 250mm × 10 mm) (Merck, KGaA, Darmstadt, Germany)

4.2.5. 質譜儀 (Mass Spectrometer）

(1) Bruker Esquire 2000 Mass Spectrophotometer (Low-Resolution) (Germany)

(2) FINNIGAN MAT 95S Mass Spectrometer (High-Resolution) (U.S.A.)

國立台灣大學理學院化學系貴重儀器中心

4.2.6 減壓濃縮機（Rotavapor）

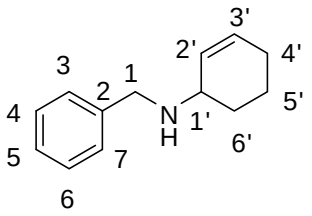
（1）EYELA Rotary Vacuum Evaporator N-N Series (Japan)

(2) EYELA Waterbath SB-450 (Japan)

(3) TAKA Vacuum Pump VP series (Japan)

(4) PANCHUM Vacuum VP series (Taiwan)

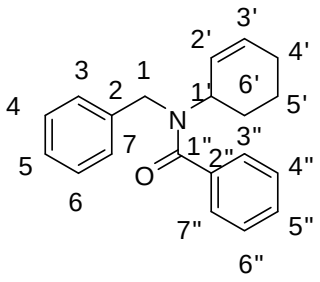
4.3 合成步驟與數據



Chemical Formula: $C_{13}H_{17}N$
Exact Mass: 187.1361

N-benzylcyclohexy-2-enamine (**1**)

To a stirring of benzylamine (400 mg, 3.73 mmol) in dichloromethane was added triethylamine (1.13 g, 11.19 mmol) dropwisely, the mixture was stirred in the ice-bath for 10 minutes , then the reaction was returned to the room temperature, followed by addition of 3-bromocyclohexene (300 mg, 1.86 mmol). The mixture reacted for an hour, then 3-bromocyclohexene (113 mg, 1.12 mmol) was added. The mixture was stirred overnight after the above step was repeated after an hour. The reaction was quenched with 15 ml H_2O, extracted by 75ml ethyl acetate, washed with brine, and then dried by $MgSO_4$. The organic layers were collected, concentrated, and then purified by column chromatography (silica gel; EtOAc/Hexane = 1/30, 200 ml; EtOAc/Hexane=1/20, 400 ml) to give the 276 mg compound (1.47 mmol, 44%) . ^{1}H NMR (200 MHz, $CDCl_3$) δ7.38-7.19 (m, H-3, H-4, H-5, H-6, H-7), 5.84-5.71 (d, *J* = 4 Hz, 2H, H-2', H-3'), 3.92-3.78 (dd, *J* = 12 Hz, 1.64, 2H, H-1), 3.22 (s, 1H, H-1'), 1.90-1.30 (m,7H, NH, H-4', H-5', H-6', NH); ^{13}C NMR (50 MHz, $CDCl_3$) δ 140.6 (C-2), 129.8 (C-3'), 128.7 (C-2'), 128.2 (C-4, C-6), 128.0 (C-3, C-7), 126.7 (C-5), 52.2 (C-1'), 50.8 (C-1), 29.3 (C-6'), 25.2 (C-4'), 20.1(C-5'). IR (thin film from KBr): 3021, 2922, 2853, 2831, 1581, 1584, 1497, 1450, 728, 694 cm^{-1}; HRMS (ESI) calc. For $C_{13}H_{17}N + H$ $[M+H]^+$:188.1439, found: 188.1319

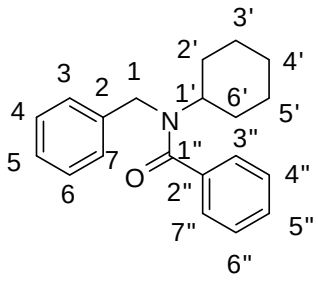


Chemical Formula: $C_{20}H_{21}NO$
Exact Mass: 291.1623

N-benzyl-*N*-(cyclohex-2-enyl)benzamide (2)

To a stirring of *N*-benzylcyclohex-2-enamine (259 mg, 1.37 mmol) in 3 ml dichloromethane was added triethylamine (415 mg, 4.11 mmol) dropwisely, the mixture was stirred in the ice-bath for 10 minutes , then the reaction was returned to the room temperature, followed by addition of benzoyl chloride (230 mg, 3.01 mmol) drop by drop. The mixture was stirred overnight with the color change from transparence to white color. The reaction was quenched with 50 ml H_2O, extracted by 210 ml hexane, washed with brine, and then dried by $MgSO_4$. The organic layers were collected, concentrated, and then purified by column chromatography (silica gel; EtOAC/Hexane = 1/30, 500 ml) to give the 214 mg compound (0.34 mmol, 86%) . ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.40-7.24 (m, 10H, H-3, H-4, H-5, H-6, H-7, H-3", H-4", H-5", H-6", H-7"), 5.88-5.82 (m, 1H, H-3'), 5.52-5.48 (d, *J* = 15.5 Hz, 1H, H-2'), 4.89-4.82 (d, *J* = 15.5 Hz, 1H, H-1'), 4.46-4.39 (d, *J* = 15.6 Hz, 2H, H-1), 2.20-1.38 (m, 7H, H-4', H-5', H-6', NH) ; ^{13}C NMR (50 MHz, $CDCl_3$) δ 172.2 (C-1"), 139.0 (C-2), 136.6 (C-2"), 131.8 (C-3'), 129.1 (C-2'), 128.2 (C-5"), 128.0 (C-4", C-6"), 127.7 (C-4, C-6), 126.7 (C-3, C-7), 126.3 (C-3", C-7"), 126.0 (C-5), ^{13}C NMR (50 MHz, CDCl3) δ 55.66 (C-1'), 44.97 (C-1), 28.47 (C-6'), 23.98 (C-4'), 21.10 (C-5')

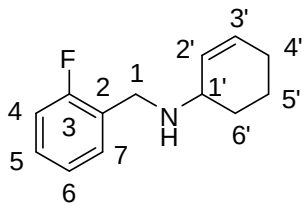
IR (thin film from KBr): 3060, 3026, 2930, 2858, 1633, 1601, 1494, 784, 727, 696 cm^{-1}; HRMS (ESI) calc. For $C_{20}H_{21}N$ + H $[M+H]^+$:292.1701, found: 292.1695.



Chemical Formula: $C_{20}H_{23}NO$
Exact Mass: 293.1780

N-benzyl-*N*-cyclohexylbenzamide (3)

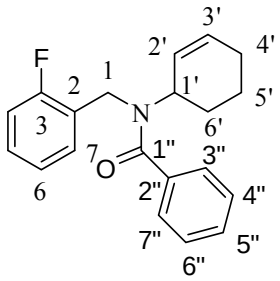
The double neck bottle which contained 40 mg Pd/C was vacuumed at first, and then the solution of *N*-cyclohexyl-*N*-benzylbenzamide (100 mg, 0.34 mmol) in 3 ml MeOH was injected into the vacuumed system and stirred in the room temperature. The following reaction was capped, purged with hydrogen gas for 3 hours. After the reaction is completed and checked by TLC film (mobile phase : ACN/H_2O = 3/1) ,the Pd/C in the mixture was removed by celite, washed with 200 ml MeOH and the filtered solution was collected and concentrated. The crude was purified by column chromatography (silica gel; EtOAc/Hexane = 1/10, 400 ml) to give 33 mg compound (0.11 mmol , 33%). ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.39-7.20 (m, 10H, H-3, H-4, H-5, H-6, H-7, H-3", H-4", H-5", H-6", H-7"), 4.68 (s, 2H, H-1), 3.61 (s, 1H, H-1'), 1.65-0.98 (m, 10H, H-2', H-3', H-4', H-5', H-6') ; ^{13}C NMR (50 MHz, CDCl3) δ 172.5 (C-1"), 139.5 (C-2), 137.4 (C-2"), 129.3 (C-5"), 128.6 (C-4, C-6, C-4", C-6"), 128.5 (C-3, C-7), 127.0 (C-3", C-7"), 126.3 (C-5), 59.4 (C-1'), 44.6 (C-1), 32.1 (C-2', C-6'), 25.8 (C-5'), 25.3 (C-3', C-7'); IR (thin film from KBr): 3063, 3027, 2929, 1633, 1576, 732, 699 cm^{-1}; HRMS (ESI) calc. For $C_{20}H_{23}N$ + H $[M+H]^+$: 294.1858, found: 294.1913.



Chemical Formula: $C_{13}H_{16}FN$
Exact Mass: 205.1267

N-(2-fluorobenzyl)cyclohex-2-enamine (4)

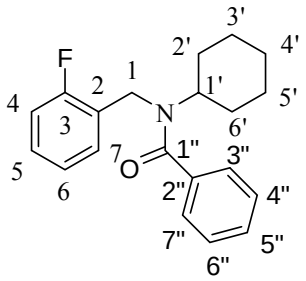
To a stirring of 2-fluorobenzylamine (400 mg, 3.19 mmol) in 5 ml dichloromethane was added triethylamine (0.97 g, 9.6 mmol) drop by drop, the mixture was stirred in the ice-bath for 10 minutes , then the reaction was returned to the room temperature, followed by addition of 3-bromocyclohexene (256 mg, 1.60 mmol). The mixture reacted for an hour, then 3-bromocyclohexene (154 mg, 0.96 mmol) was added. The mixture was stirred overnight after the above step was repeated after an hour. The reaction was quenched with 30 ml H_2O, extracted by 180 ml ethyl acetate, washed with brine, and then dried by $MgSO_4$. The organic layers were collected, concentrated, and then purified by column chromatography (silica gel; EtOAc/Hexane = 1/10, 200 ml; EtOAc/Hexane = 1/4, 250 ml) to give the 276 mg compound (1.35 mmol, 42%) . ^{1}H NMR (200 MHz,$CDCl_3$) δ 7.30-7.23 (m, 1H, H-5), 7.11-6.84 (m, 3H, H-4, H-6, H-7), 5.69-5.57 (m ,2H, H-3', H-4'), 3.84-3.70 (dd, *J* = 13.7, 2.1 Hz, 2H, H-1), 3.10-3.09 (d, *J* = 3.7 Hz, 1H, H-1'), 1.91-1.35 (m, 7H, NH, H-4', H-5', H-6') ; ^{13}C NMR (50 MHz, $CDCl_3$) δ 161.5-158.6 (C-3, *J* = 243.5 Hz), 130.2-130.1 (C-7, *J* = 50 Hz), 129.66 (C-3'), 129.0 (C-2'), 128.5-128.3 (C-5, J = 6.5 Hz), 127.7-127.4 (C-2, *J* = 15.5Hz), 124.0-123.9 (C-6, *J* = 3.0 Hz),115.3-114.9 (C-4, *J* = 22.0 Hz), 52.3 (C-1'), 44.2 (C-1), 29.3 (C-6'), 25.2 (C-4'), 20.1 (C-5'). IR (thin film from KBr): 3020, 2928, 2857, 2836, 1615, 1589, 1551, 1486, 1449, 783, 723 cm^{-1}. HRMS (ESI) calc. For $C_{13}H_{16}FN + H$ $[M+H]^+$: 206.1345, found: 206.1436.



Chemical Formula: $C_{20}H_{20}FNO$
Exact Mass: 309.1529

N-(cyclohex-2-enyl)-*N*-(2-fluorobenzyl)benzamide (5)

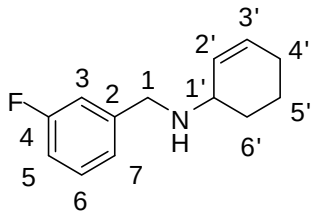
To a stirring of *N*-(2-fluorobenzyl)cyclohex-2-enamine (250 mg, 1.25 mmol) in 3 ml dichloromethane was added triethylamine (379 mg, 3.15 mmol) dropwisely, the mixture was stirred in the ice-bath for 10 minutes, then the reaction was returned to the room temperature, followed by the addition of benzoyl chloride (386 mg, 2.95 mmol) drop by drop. The mixture was stirred overnight with the color change from transparence to white color. The reaction was quenched with 50 ml H_2O, extracted by 210 ml hexane, washed with brine, and then dried by $MgSO_4$. The organic layers were collected, concentrated, and then purified by column chromatography (silica gel; EtOAC/Hexane = 1/10, 400 ml) to give the 214 mg compound (0.69 mmol, 55%) . ^{1}H NMR (200MHz,$CDCl_3$) δ 7.41-6.98 (m, 9H, H-4, H-5, H-6, H-7, H-3", H-4", H-5", H-6", H-7"), 5.87-5.80 (M, 1H, H-3'), 5.49-5.44 (d, *J* = 9.9 Hz, 1H, H-2'), 4.85-4.68 (t, *J* = 17.5 Hz, 1H, H-1'), 4.57-4.50 (d, *J* = 15.8 Hz, 2H, H-1), 1.91-1.39 (m, 7H, NH, H-4', H-5', H-6') ; ^{13}C NMR (50 MHz, $CDCl_3$) δ 172.8 (C-1"), 162.6-157.7 (C-3, *J* = 243.5 Hz), 136.8 (C-2"), 132.6 (C-3'), 129.6 (C-2'), 128.6-128.5 (C-7, *J* = 3.5 Hz), 128.2 (C-5"), 127.7 (C-5, C-4",C-6"), 126.5 (C-3",C-7"), 126.1 (C-2), 124.1 (C-6), 115.1-114.9 (C-4, *J* = 21.5 Hz), 57.0 (C-1'), 38.8 (C-1), 28.5 (C-6'), 24.4 (C-4'), 21.5 (C-5'). IR (thin film from KBr): 3025, 2934, 2863, 2843, 1638, 1586, 1487, 1095, 899, 756, 700 cm^{-1}; HRMS (ESI) calc. For $C_{20}H_{20}FN\,O$ + H $[M+H]^+$: 310.1607, found: 310.1604.



Chemical Formula: $C_{20}H_{22}FNO$
Exact Mass: 311.1685

N-cyclohexyl-*N*-(2-fluorobenzyl)benzamide (6)

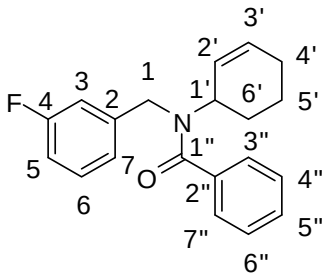
The double neck bottle which contained 40 mg Pd/C was vacuumed at first, and then the solution of *N*-cyclohexyl-*N*-(2-fluororbenzyl)benzamide (100 mg, 0.32 mmol) in 3 ml MeOH was injected into the vacuumed system and stirred in the room temperature. The following reaction was capped, purged with hydrogen gas for 3 hours. After the reaction is completed and checked by TLC film (mobile phase : ACN/H_2O = 5/1), the Pd/C in the mixture was removed by celite, washed with 200 ml MeOH and the filtered solution was collected and concentrated. The crude was purified by column chromatography (silica gel; EtOAc/Hexane = 1/10, 400 ml) to give 69 mg compound (0.22 mmol, 69%). ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.39-6.98 (m, 9H, H-4, H-5, H-6, H-7, H-3", H-4", H-5", H-6", H-7"), 4.73 (s, 2H, H-1), 3.61 (s, 1H, H-1'), 1.65-0.99 (m, 10H, H-3', H-4', H-5', H-6', H-7'); ^{13}C NMR (50 MHz, CDCl3) δ 172.6 (C-1"), 162.5-157.6 (C-3, *J* = 243.5 Hz), 137.2 (C-2"), 129.4 (C-7), 128.8 (C-5"), 128.6 (C-5, C-4", C-6"), 126.4 (C-3", C-7"), 126.2 (C-2), 124.2 (C-6), 115.2 -115.0 (C-4, *J* = 21.5 Hz), 59.3(C-1'), 37.7 (C-1), 31.6 (C-2', C-6'), 25.2 (C-4', C-5'). IR (thin film from KBr): 3063, 2931, 2855, 1637, 1586, 1488, 755, 699 cm^{-1}. HRMS (ESI) calc. For $C_{20}H_{22}FN\,O$ + H $[M+H]^+$:312.1763, found:312.1848.



Chemical Formula: $C_{13}H_{16}FN$
Exact Mass: 205.1267

N-(3-fluorobenzyl)cyclohex-2-enamine (7)

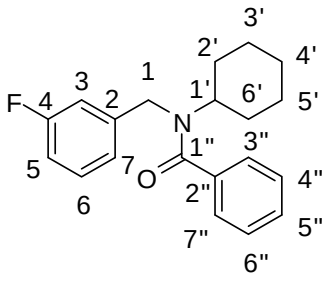
To a stirring of 3-fluorobenzylamine (400 mg, 3.19 mmol) in 5 ml dichloromethane was added triethylamine (0.97 g, 9.6 mmol) drop by drop, the mixture was stirred in the ice-bath for 10 minutes , then the reaction was returned to the room temperature, followed by addition of 3-bromocyclohexene (256 mg, 1.60 mmol). The mixture reacted for an hour, then 3-bromocyclohexene (154 mg, 0.96 mmol) was added. The mixture was stirred overnight after the above step was repeated after an hour. The reaction was quenched with 30 ml H_2O, extracted by 180 ml ethyl acetate, washed with brine, and then dried by $MgSO_4$. The organic layers were collected, concentrated, and then purified by column chromatography (silica gel; EtOAc/Hexane = 1/10, 150ml; EtOAc/Hexane = 1/4, 100 ml) to give the 305 mg compound (1.49 mmol, 47%) . ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.18-6.81 (m, 4H, H-3, H-5, H-6, H-7), 5.67-5.63 (m, 2H, H-2', H-3'), 3.74 (2H, H-1), 1.92-1.39 (m, 7H, H-4', H-5', H-6', NH) ; ^{13}C NMR (50 MHz, $CDCl_3$) δ 165.5, 160.6, 143.6, 143.5, 130.4, 130.3, 129.9, 129.7, 129.3, 123.7, 123.6, 122.6, 118.9, 118.5, 115.2, 114.9, 114.7, 114.5, 114.3, 113.9, 113.5, 52.4 (C-1'), 50.4 (C-1), 29.5 (C-6), 26.4 (C-4), 20.2 (C-5). IR (thin film from KBr): 3021, 2927, 2856, 1736, 1615, 1589, 1486, 1449, 783, 685 cm^{-1}; HRMS (ESI) calc. For $C_{13}H_{16}FN + H$ $[M+H]^+$: 206.1345, found: 206.1267.



Chemical Formula: $C_{20}H_{20}FNO$
Exact Mass: 309.1529

N-(cyclohex-2-enyl)-*N*-(3-fluorobenzyl)benzamide (8)

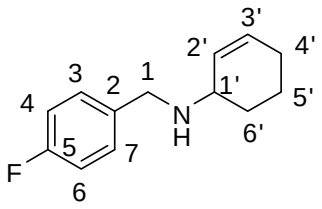
To a stirring of *N*-(3-fluorobenzyl)cyclohex-2-enamine (285 mg, 1.35 mmol) in 3 ml dichloromethane was added triethylamine (422 mg, 4.17 mmol) dropwisely, the mixture was stirred in the ice-bath for 10 minutes, then the reaction was returned to the room temperature, followed by addition of benzoyl chloride (430 mg, 3.06 mmol) drop by drop. The mixture was stirred overnight with the color change from transparence to white color. The reaction was quenched with 50 ml H_2O, extracted by 210 ml hexane, wash with brine, and then dried by $MgSO_4$. The organic layers were collected, concentrated, and then purified by column chromatography (silica gel; EtOAC/Hexane = 1/10, 400 ml) to give the 277 mg compound (0.90 mmol, 66%) . ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.31-6.76 (m, 9H, H-3, H-5, H-6, H-7, H-3", H-4", H-5", H-6", H-7"), 5.80-5.74 (m, 1H, H-3'), 5.43-5.38 (d, *J* = 9.8 Hz, 1H, H-2') , 4.76-4.69 (d, *J* = 15.5 Hz, 1H, H-1'), 4.37-4.29 (d, *J* = 15.8 Hz, 2H, H-1), 1.81-1.27 (m, 6H, H-4', H-5', H-6') ; ^{13}C NMR (50 MHz, $CDCl_3$) δ 172.5 (C-1"), 165.3-160.4 (C-4, *J* = 244 Hz), 142.1-141.9 (C-2, *J* = 7 Hz), 136.6 (C-2"), 132.4 (C-3'), 129.8-129.4 (C-6, *J* = 8.5, 11.5 Hz), 128.5 (C-4", C-6"), 127.7 (C-2'), 126.3 (C-7, C-3", C-7"), 122.5 (C-3), 114.0-113.3 (C-5, *J* = 17.5, 20.5 Hz), 56.9 (C-1'), 44.9 (C-1), 28.7 (C-6'), 24.2 (C-4'), 21.3 (C-5'). IR (thin film from KBr): 3063, 3024, 2935, 2863, 2833, 1636, 1589, 781, 700 cm^{-1}. HRMS (ESI) calc. For $C_{20}H_{20}FN\,O$ + H $[M+H]^+$: 310.1607, found: 310.1608.



Chemical Formula: $C_{20}H_{22}FNO$
Exact Mass: 311.1685

N-cyclohexyl-*N*-(3-fluorobenzyl)benzamide (**9**)

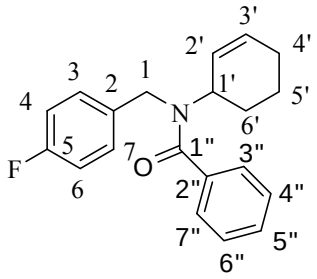
The double neck bottle which contained 40 mg Pd/C was vacuumed at first, and then the solution of *N*-cyclohexyl-*N*-(3-fluororbenzyl)benzamide (100 mg, 0.32 mmol) in 3 ml MeOH was injected into the vacuumed system and stirred in the room temperature. The following reaction was capped, purged with hydrogen gas for 3 hours. After the reaction is completed and checked by TLC film (mobile phase : ACN/H_2O = 5/1) ,the Pd/C in the mixture was removed by celite, washed with 200 ml MeOH and the filtered solution was collected and concentrated. The crude was purified by column chromatography (silica gel; EtOAc/Hexane = 1/10, 400ml) to give 69 mg compound (0.22 mmol , 69%). ^{1}H NMR (200MHz,$CDCl_3$) δ 7.39-6.98 (m, 9H, H-3, H-5, H-6, H-7, H-3", H-4", H-5", H-6", H-7"), 4.73 (s, 2H, H-1), 3.61 (s, 1H, H-1'), 1.65-0.99 (m, 10H, H-2', H-3', H-4', H-5', H-6', H-7') ; ^{13}C NMR (50 MHz, CDCl3) δ 172.5 (C-1"), 165.4-160.5 (C-4, *J* = 244 Hz), 142.2-142.1 (C-2, *J* = 6.5 Hz) 137.1 (C-2"), 130.0-128.8 (C-6, *J* = 8.5 Hz), 129.4 (C-5") , 128.6 (C-4", C-6"), 126.2 (C-7, C-3", C-7"), 122.6 (C-3), 114.1-113.5 (C-5, *J* = 9.0, 9.5, 12.0 Hz), 59.3(C-1'), 44.2 (C-1), 32.0 (C-2, C-6), 25.7 (C-3, C-7), 25.2 (C-5). IR (thin film from KBr): 3059, 2930, 2855, 1633, 1590, 1487, 700, 687 cm^{-1}. HRMS (ESI) calc. For $C_{20}H_{22}FN$ O + H $[M+H]^+$:312.1763, found: 312.1830.



Chemical Formula: $C_{13}H_{16}FN$
Exact Mass: 205.1267

N-(4-fluorobenzyl)cyclohex-2-enamine (**10**)

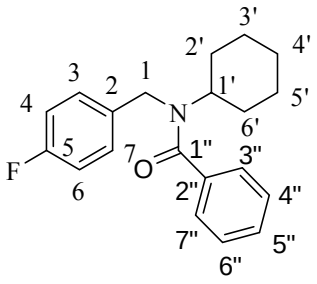
To a stirring of 4-fluorobenzylamine (400 mg, 3.19 mmol) in 5 ml dichloromethane was added triethylamine (0.97 g, 9.6 mmol) drop by drop, the mixture was stirred in the ice-bath for 10 minutes , then the reaction was returned to the room temperature, followed by the addition of 3-bromocyclohexene (256 mg, 1.60 mmol). The mixture reacted for an hour, then 3-bromocyclohexene (154 mg, 0.96 mmol) was added. The mixture was stirred overnight after the above step was repeated after an hour. The reaction was quenched with 30 ml H_2O, extracted by 180 ml ethyl acetate, washed with brine, and then dried by $MgSO_4$. The organic layers were collected, concentrated, and then purified by column chromatography (silica gel; EtOAc/Hexane = 1/10, 150 ml; EtOAc/Hexane = 1/4, 250 ml) to give the 336 mg compound (1.63 mmol, 51%) . ^{1}H NMR (200 MHz,$CDCl_3$) δ 7.22-7.15 (m, 2H, H-3, H-7), 6.90-6.82 (t, *J* = 8.7 Hz, 2H, H-4, H-6), 5.69-5.56 (m, 2H, H-2', H-3'), 3.74-3.61 (m, 2H, H-1), 3.06 (s, 1H, H-1'), 1.87-1.29 (m, 7H, NH, H-4', H-5', H-6') ; ^{13}C NMR (50 MHz, $CDCl_3$) δ164.2-159.4 (C-5, *J* = 243 Hz), 136.5-136.4 (C-2, *J* = 22.5 Hz), 129.8-129.6 (C-3, C-7, *J* = 6.0 Hz), 129.5 (C-3'), 128.9 (C-2'), 115.2-114.8 (C-4, C-6, *J* = 21 Hz), 52.3 (C-1'), 50.1 (C-1), 29.4 (C-6'), 25.2 (C-4'), 20.1 (C-5'). IR (thin film from KBr): 3021, 2927, 2856, 2836, 1602, 1448, 825, 770, 723 cm^{-1}. HRMS (ESI) calc. For $C_{13}H_{16}FN$+ H $[M+H]^+$: 206.1345, found: 206.1398.



Chemical Formula: $C_{20}H_{20}FNO$
Exact Mass: 309.1529

N-(cyclohex-2-enyl)-*N*-(4-fluorobenzyl)benzamide (**11**)

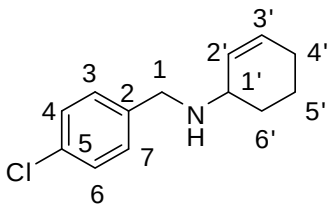
To a stirring of *N*-(4-fluorobenzyl)cyclohex-2-enamine (316 mg, 1.54 mmol) in 3 ml dichloromethane was added triethylamine (467 mg, 4.62 mmol) dropwisely, the mixture was stirred in the ice-bath for 10 minutes, then the reaction was returned to the room temperature, followed by the addition of benzoyl chloride (476 mg, 3.39 mmol) drop by drop. The mixture was stirred overnight with the color change from transparence to white color. The reaction was quenched with 50 ml H_2O, extracted by 210 ml hexane, wash with brine, and then dried by $MgSO_4$. The organic layers were collected, concentrated, and then purified by column chromatography (silica gel; EtOAc/Hexane = 1/30, 400 ml; EtOAc/Hexane = 1/10, 200 ml) to give the 290 mg compound (0.94 mmol, 61%) . ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.30-7.17 (m, 7H, H-3, H-7, H-3", H-4", H-5", H-6", H-7"), 6.92-6.83 (t, *J* = 8.2 Hz, 2H, H-4, H-7), 4.71-4.63 (d, *J* = 15.2 Hz, 1H, H-1'), 4.36-4.28 (d, *J* = 15.3 Hz, 2H, H-1), 1.81-1.37 (m, 6H, H-3", H-4", H-5", H-6", H-7"); ^{13}C NMR (50 MHz, $CDCl_3$) δ 172.6 (C-1"), 164.1-159.2 (C-5, *J* = 243 Hz), 136.7 (C-2'), 135.1 (C-2),132.2 (C-2', C-3'), 129.4 (C-5"), 128.7-128.5 (C-3, C-7, *J* = 9 Hz), 127.9 (C-4", C-6"), 126.3 (C-3", C-7") 115.3-114.9 (C-4, C-6, *J* = 21 Hz), 57.0 (C-1'), 44.7 (C-1), 28.7 (C-6'), 24.3 (C-4'), 21.4 (C-5'). IR (thin film from KBr):3066, 3026, 2935, 2863, 2843, 1710, 1645, 1567, 1432, 849, 696 cm^{-1}. HRMS (ESI) calc. For $C_{20}H_{20}FNO$ + H $[M+H]^+$: 310.1607, found : 310.1610.



Chemical Formula: $C_{20}H_{22}FNO$
Exact Mass: 311.1685

N-cyclohexyl-*N*-(4-fluorobenzyl)benzamide (12)

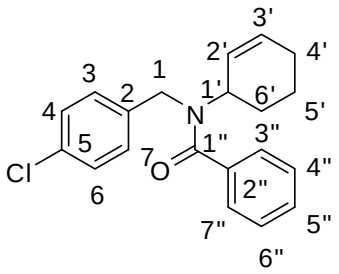
The double neck bottle which contained 40 mg Pd/C was vacuumed at first, and then the solution of *N*-cyclohexyl-*N*-(4-fluororbenzyl)benzamide (100mg, 0.32 mmol) in 3 ml MeOH was injected into the vacuumed system and stirred in the room temperature. The following reaction was capped, purged with hydrogen gas for 3 hours. After the reaction is completed and checked by TLC film (mobile phase : ACN/H_2O = 5/1) ,the Pd/C in the mixture was removed by celite, washed with 200 ml MeOH and the filtered solution was collected, concentrated. The crude was purified by column chromatography (silica gel; EtOAc/Hexane = 1/10, 400ml) to give 77 mg compound (0.25 mmol , 77%). ^{1}H NMR (200 MHz,$CDCl_3$) δ 7.36-6.92 (m, 9H, H-3, H-4, H-6, H-7, H-3", H-4", H-5", H-6", H-7"), 4.62 (s, 2H, H-1), 3.59 (s, 2H, H-1'), 1.64-0.96 (m, 10H, H-2", H-3", H-4", H-5", H-6"); ^{13}C NMR (50 MHz, CDCl3) δ 172.4 (C-1"), 164.2-159.4 (C-5, *J* = 243Hz), 137.2 (C-2'), 135.2 (C-2), 129.3 (C-3, C-7, C-5"), 128.6 (C-4", C-6"), 126.2 (C-3", C-7"), 115.4-115.0 (C-4, C-6), 59.3 (C-1'), 44.0 (C-1), 32.1 (C-2, C-6), 25.7 (C-3, C-5), 25.2 (C-4) . IR (thin film from KBr): 3063, 2957, 2926, 2842, 1618, 1597, 1437, 849, 698 cm^{-1}. HRMS (ESI) calc. For $C_{20}H_{22}FNO$ + H $[M+H]^+$:312.1763, found: 312.1829.



Chemical Formula: $C_{13}H_{16}ClN$
Exact Mass: 221.0971

N-(4-clorobenzyl)cyclohex-2-enamine (13)

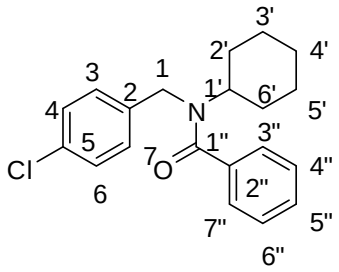
To a stirring of 4-clorobenzylamine (400 mg, 2.84 mmol) in 5 ml dichloro-methane was added triethylamine (0.86 g, 8.5 mmol) dropwisely, the mixture was stirred in the ice-bath for 10 minutes, then the reaction was returned to the room temperature, followed by the addition of 3-bromocyclohexene (228 mg, 1.42 mmol). The mixture reacted for an hour, then 3-bromocyclohexene (137 mg, 0.85 mmol) was added. The mixture was stirred overnight after the above step was repeated after an hour. The reaction was quenched with 50 ml H_2O, extracted by 180 ml ethyl acetate, washed with brine, and then dried by $MgSO_4$. The organic layers were collected, concentrated, and then purified by column chromatography (silica gel; EtOAc/Hexane = 1/10, 250 ml; EtOAc/Hexane = 1/4, 200 ml) to give the 275 mg compound (1.24 mmol, 44%) . ^{1}H NMR (200 MHz,$CDCl_3$) δ 7.16 (s, 4H, H-3, H-4, H-6, H-7), 5.70-5.63 (m, 4H, H-2', H-3'), 3.75-3.61 (dd, *J* = 13.4 Hz, *J* = 1.0 Hz, 2H, H-1), 3.08-3.06 (d, *J* = 4 Hz, 1H, H-1'), 1.88-1.29 (m, 7H, NH, H-4', H-5', H-6') ; ^{13}C NMR (50 MHz, $CDCl_3$) δ 139.3 (C-2), 132.4 (C-5), 129.7 (C-3'), 129.4 (C-3, C-7), 129.0 (C-2'), 128.4 (C-4, C-6), 52.3 (C-1'), 50.1 (C-1), 29.4 (C-6), 25.3 (C-4), 20.1 (C-5). IR (thin film from KBr): 3063, 3024, 2931, 2860, 1635, 1577, 1490, 794, 700 cm^{-1}. HRMS (ESI) calc. For $C_{13}H_{16}ClN$ + H $[M+H]^+$: 222.1049, found: 222.1116.



Chemical Formula: $C_{20}H_{20}ClNO$
Exact Mass: 325.1233

N-(cyclohex-2-enyl)-*N*-(4-chlorobenzyl)benzamide (14)

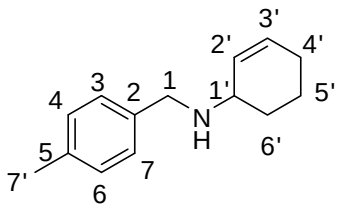
To a stirring of *N*-(4-chlorobenzyl)cyclohex-2-enamine (215 mg, 0.97mmol) in 3 ml dichloromethane was added triethylamine (294 mg, 2.91 mmol) dropwisely, the mixture was stirred in the ice-bath for 10 minutes, then the reaction was returned to the room temperature, followed by the addition of benzoyl chloride (299 mg, 2.13 mmol) drop by drop. The mixture was stirred overnight with the color change from transparence to white color. The reaction was quenched with 50 ml H_2O, extracted by 210 ml hexane, wash with brine, and then dried by $MgSO_4$. The organic layers were collected, concentrated, and then purified by column chromatography (silica gel; EtOAc/Hexane = 1/10, 150 ml; EtOAc/Hexane = 1/4, 200 ml) to give the 200 mg compound (0.62 mmol, 63%) . ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.32-7.20 (m, 9H, H-3, H-4, H-6, H-7, H-3', H-4', H-5', H-6', H-7'), 5.77 (s, 1H, H-3'), 5.43 (s, 1H, H-2'), 4.73-4.65 (d, *J* = 14.9 Hz, 1H, H-1'), 4.37-4.29 (d, *J* = 15.5 Hz, 2H, H-1), 1.84-1.18 (m, 7H, NH, H-4', H-5', H-6') ; ^{13}C NMR (50 MHz, $CDCl_3$) δ 172.7 (C-1"), 137.9 (C-2, C-2"), 136.7 (C-5), 132.4 (C-3, C-7), 139.6 (C-4, C-6), 128.6 (C-4", C-6"), 128.5 (C-3'), 127.9 (C-2'), 126.4 (C-3", C-7"), 57.0 (C-1'), 44.8 (C-1), 28.9 (C-6), 24.4 (C-4), 21.4 (C-5); IR (thin film from KBr): 3063, 3024, 2931, 2860, 1635, 1577, 1490, 794, 700cm^{-1}; HRMS (ESI) calc. For $C_{20}H_{20}ClNO$ + H $[M+H]^+$: 326.1331, found :326.1301.



Chemical Formula: $C_{20}H_{22}ClNO$
Exact Mass: 327.1390

N-cyclohexyl-*N*-(4-chlorobenzyl)benzamide (15)

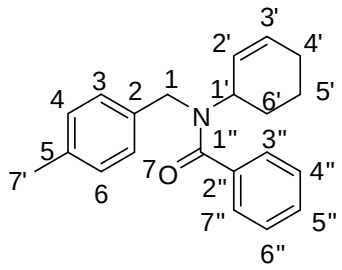
The double neck bottle which contained 40 mg Pd/C was vacuumed at first, and then the solution of *N*-cyclohexyl-*N*-(4-chlororbenzyl)benzamide (100 mg, 0.31 mmol) in 3 ml MeOH was injected into the vacuumed system and stirred in the room temperature. The following reaction was capped, purged with hydrogen gas for 3 hours. After the reaction is completed and checked by TLC film (mobile phase : ACN/H_2O = 2/1) ,the Pd/C in the mixture was removed by celite, washed with 200 ml MeOH and the filtered solution was collected, concentrated. The crude was purified by column chromatography (silica gel; EtOAc/Hexane = 1/10, 400 ml) to give 70 mg compound (0.21 mmol , 69%). ^{1}H NMR (200 MHz,$CDCl_3$) δ 7.38-7.24 (m, 9H, H-3, H-4, H-6, H-7), 4.62 (s, 2H, H-1), 3.60 (s, 1H, H-1'), 1.65-0.98 (m, 10H, H-3', H-4', H-5', H-6', H-7') ; ^{13}C NMR (50 MHz, $CDCl_3$) δ 172.5 (C-1"), 138.0 (C-2"), 137.1 (C-2), 132.5 (C-5), 129.4 (C-3, C-7), 128.6 (C-4, C-6, C-4", C-6"), 127.0 (C-5"), 126.2 (C-3", C-7"),59.4 (C-1'), 44.1 (C-1), 32.1 (C-2', C-6'), 25.7 (C-3', C-5'), 25.2 (C-4'). IR (thin film from KBr): 3063,3024, 2930, 2855, 1633, 1576, 1491, 699 cm^{-1}. HRMS (ESI) calc. For $C_{20}H_{22}ClNO$ + H $[M+H]^+$: 328.1468, found: 328.1501.



Chemical Formula: $C_{14}H_{19}N$
Exact Mass: 201.1517

N-(4-methylbenzyl)cyclohex-2-enamine (16)

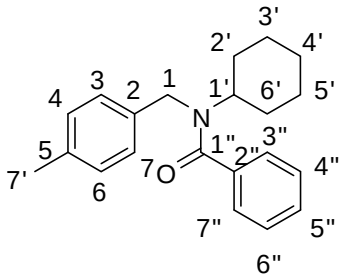
To a stirring of 4-methylbenzylamine (400 mg, 3.30 mmol) in 5 ml dichloro -methane was added triethylamine (1.00 g, 9.9 mmol) dropwisely, the mixture was stirred in the ice-bath for 10 minutes , then the reaction was returned to the room temperature, followed by the addition of 3-bromocyclohexene (321 mg, 1.99 mmol). The mixture reacted for an hour, then 3-bromocyclohexene (192 mg, 1.20 mmol) was added. The mixture was stirred overnight after the above step was repeated after an hour. The reaction was quenched with 50 ml H_2O, extracted by 180 ml ethyl acetate, washed with brine, and then dried by $MgSO_4$. The organic layers were collected, concentrated, and then purified by column chromatography (silica gel; EtOAc/Hexane = 1/10, 400 ml) to give the 356 mg compound (1.64 mmol, 50%) . ^{1}H NMR (200 MHz, $CDCl_3$) δ7.09 (d, 2H, *J* = 8.0 Hz, H-3, H-7), 6.97 (d, 2H, *J* = 8.0 Hz, H-4, H-6) 5.67-5.56 (t, *J* = 11.2 Hz, 2H, H-2', H-3'), 3.73-3.59 (t, *J* = 13.7 Hz, H-1), 3.06 (s, 1H, H-1'), 2.19 (s, 3H, H-7'), 2.19-1.32 (m, 7H, NH, H-4', H-5', H-6') ; ^{13}C NMR (50 MHz, $CDCl_3$) δ 137.5 (C-2), 136.0 (C-5), 129.8 (C-3'), 128.8 (C-4, C-6), 128.6 (C-2'), 127.9 (C-3, C-7), 52.1 (C-1'), 50.5 (C-1), 29.3 (C-6'), 25.2 (C-4'), 20.9 (C-7'), 20.1 (C-5'). IR (thin film from KBr): 3019, 2924, 2856, 2836, 1514, 1447, 805, 723 cm^{-1}. HRMS (ESI) calc. For $C_{14}H_{19}N + H$ $[M+H]^+$: 202.1595, found: 202.1578.



Chemical Formula: $C_{21}H_{23}NO$
Exact Mass: 305.1780

N-(cyclohex-2-enyl)-*N*-(4-methylbenzyl)benzamide (17)

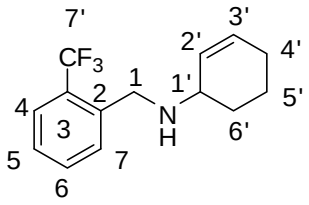
To a stirring of *N*-(4-methylbenzyl)cyclohex-2-enamine (336 mg, 1.56 mmol) in 3 ml dichloromethane was added triethylamine (473 mg, 4.68 mmol) dropwisely, the mixture was stirred in the ice-bath for 10 minutes, then the reaction was returned to the room temperature, followed by addition of benzoyl chloride (482 mg, 3.43 mmol) drop by drop. The mixture was stirred overnight with the color change from transparence to white color. The reaction was quenched with 50 ml H_2O, extracted by 210 ml hexane, wash with brine, and then dried by $MgSO_4$. The organic layers were collected, concentrated, and then purified by column chromatography (silica gel; EtOAc/Hexane = 1/10, 300 ml) to give the 252 mg compound (0.83 mmol, 53%) . ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.31-7.00 (m, 9H, H-3, H-4, H-6, H-7, H-8), 5.78-5.74 (m, 1H, H-3'), 5.44-4.39 (d, *J* = 9.9 Hz, 1H, H-2'), 4.63-4.69 (d, *J* = 15 Hz, 1H, H-1'), 4.34-4.27 (d, *J* = 15.5 Hz, 2H, H-1), 2.22 (s, 3H, H-7'), 1.82-1.26 (m, 6H, H-4', H-5', H-6') ; ^{13}C NMR (50MHz, CDCl3) δ 172.5 (C-1"), 137.0 (C-5), 136.3 (C-2, C-2"), 132.1 (C-1), 129.3 (C-3'), 129.0 (C-2'), 128.5 (C-3, C-7), 128.1 (C-4, C-6), 127.0 (C-4", C-6"), 126.4 (C-3",C-7"), 57.0 (C-1'), 45.0 (C-1), 28.8 (C-6'), 24.4 (C-4'), 21.5 (C-7), 21.0 (C-5'). IR (thin film from KBr): 3059, 3023, 2928, 2859, 1649, 1577, 1493, 700 cm^{-1}. HRMS (ESI) calc. For $C_{21}H_{23}N$ + H $[M+H]^+$: 306.1858, found: 306.1852.



Chemical Formula: $C_{21}H_{25}NO$
Exact Mass: 307.1936

N-cyclohexyl-*N*-(4-methylbenzyl)benzamide (**18**)

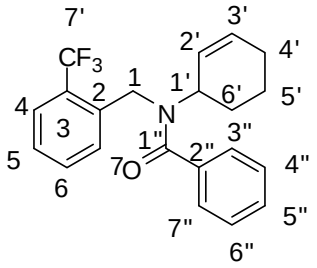
The double neck bottle which contained 40 mg Pd/C was vacuumed at first, and then the solution of *N*-cyclohexyl-*N*-(4-methylbenzyl)benzamide (100 mg, 0.33 mmol) in 3 ml MeOH was injected into the vacuumed system and stirred in the room temperature. The following reaction was capped, purged with hydrogen gas for 3 hours. After the reaction is completed and checked by TLC film (mobile phase : ACN/H_2O = 5/1) ,the Pd/C in the mixture was removed by celite, washed with 200 ml MeOH and the filtered solution was collected, concentrated. The crude was purified by column chromatography (silica gel; EtOAc/Hexane = 1/10, 400ml) to give 95 mg compound (0.31 mmol , 95%). ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.39-7.08 (m, 9H, H-3, H-4, H-6, H-7, H-3", H-4", H-5", H-6", H-7"), 4.66 (s, 2H, H-1), 3.60 (s, 1H, H-1'), 2.31 (s, 3H, H-7'), 1.65-0.84 (m, 10H, H-2', H-3', H-4', H-5', H-6'); ^{13}C NMR (50 MHz, $CDCl_3$) δ 172.4 (C-1"), 137.5 (C-5), 136.3 (C-2, C-2"), 129.1 (C-3, C-7), 128.5 (C-4, C-6), 127.0 (C-4", C-6"), 126.2 (C-3", C-7"), 59.3 (C-1'), 44.3 (C-1), 32.0 (C-2', C-6'), 25.8 (C-3', C-5'), 25.2 (C-4'), 21.1 (C-7). IR (thin film from KBr): 3061, 3021, 2929, 2854, 1635, 1576, 1514, 1450, 1410, 849, 704 cm^{-1}. HRMS (ESI) calc. For $C_{21}H_{25}N$ + H $[M+H]^+$: 308.2014, found: 308.2074.



Chemical Formula: $C_{14}H_{16}NF_3$
Exact Mass: 255.1235

N-(2-trifluoromethyl)benzyl)cyclohex-2-enamine (19)

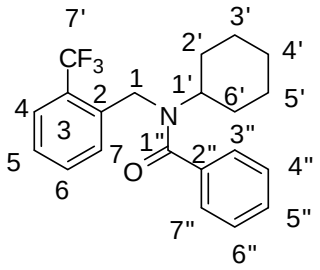
To a stirring of 2-(trifluoromethyl)benzylamine (400 mg, 2.30 mmol) in 5 ml dichloromethane was added triethylamine (0.70 g, 6.9 mmol) drop by drop, the mixture was stirred in the ice-bath for 10 minutes, then the reaction was returned to the room temperature, followed by addition of 3-bromocyclohexene (185 mg, 1.15 mmol). The mixture reacted for an hour, then 3-bromocyclohexene (111 mg, 0.69 mmol) was added. The mixture was stirred overnight after the above step was repeated after an hour. The reaction was quenched with 30 ml H_2O, extracted by 180 ml ethyl acetate, washed with brine, and then dried by $MgSO_4$. The organic layers were collected, concentrated, and then purified by column chromatography (silica gel; EtOAc/Hexane = 1/30, 200ml; EtOAc/Hexane = 1/20, 200ml; EtOAc/Hexane = 1/10, 200ml) to give the 228 mg compound (0.95 mmol, 41%) . ^{1}H NMR (200 MHz,$CDCl_3$) δ 7.62-7.15 (m, 3H, H-4, H-6, H-7), 5.64 (s, 2H, H-2', H-3'), 3.88 (s, 2H, H-1), 3.11 (s, 1H, H-1'), 1.91-1.37 (NH, H-4', H-5', H-6') ; ^{13}C NMR (50 MHz, CDCl3) δ 139.6 (C-2), 131.9 (C-6), 130.5 (C-2), 129.8 (C-3'), 129.2 (C-2'), 128.5, 127.9, 127.4 (C-7'), 126.7 (C-5), 125.8 (C-7), 125.7 (C-4), 122.0 (C-3). IR (thin film from KBr): 3063, 3027, 2933, 2862, 1643, 1579, 1494, 860, 700 cm^{-1}. HRMS (ESI) calc. For $C_{14}H_{16}FN$ + H $[M+H]^+$: 256.1313, found: 256.1230.



Chemical Formula: $C_{21}H_{20}F_3NO$
Exact Mass: 359.1497

N-(cyclohex-2-enyl)-*N*-(2-(trifluoromethyl)benzyl)benzamide (20)

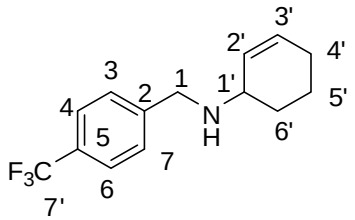
To a stirring of *N*-(2-trifluoromethyl)benzyl)cyclohex-2-enamine (208 mg, 0.86 mmol) in 3 ml dichloromethane was added triethylamine (261 mg, 2.59 mmol) dropwisely, the mixture was stirred in the ice-bath for 10 minutes, then the reaction was returned to the room temperature, followed by the addition of benzoyl chloride (266 mg, 1.90 mmol) drop by drop. The mixture was stirred overnight with the color change from transparence to white color. The reaction was quenched with 50 ml H_2O, extracted by 210 ml hexane, wash with brine, and then dried by $MgSO_4$. The organic layers were collected, concentrated, and then purified by column chromatography (silica gel; EtOAC/Hexane = 1/30, 400 ml) to give the 164 mg compound (0.45 mmol, 46%) . ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.58-7.18 (m, 9H, H-4, H-5, H-6, H-3', H-4', H-5', H-6', H-7'), 5.83-5.77 (m, 1H, H-3'), 5.41-5.36 (d, *J* = 10 Hz, 1H, H-2'), 5.03-4.95 (d, *J* = 16.8 Hz, 1H, H-1'), 4.62-4.48 (m, 3H, H-1), 1.96-1.26 (m, 7H, NH, H-4', H-5' H-6') ; ^{13}C NMR (50 MHz, $CDCl_3$) δ 172.9 (C-1"), 137.8 (C-2"), 136.6 (C-2), 133.1 (C-6), 132.0 (C-5"), 129.7 (C-3'), 128.8 (C-2'), 127.3 (C-4", C-6"), 126.6 (C-5), 126.5 (C-3", C-7"), 126.0 (C-7), 125.9 (C-3, C-4), 121.9 (C-7'), 57.1 (C-1'), 41.8 (C-8), 28.7 (C-6'), 24.3 (C-4'), 21.4 (C-5'). IR (thin film from KBr): 3063, 3027, 2933, 2862, 1649, 1579, 1494, 1409, 766, 700 cm^{-1}. HRMS (ESI) calc. For $C_{21}H_{20}FNO + H$ $[M+H]^+$: 360.1575, found : 360.1570.



Chemical Formula: $C_{21}H_{22}F_3NO$
Exact Mass: 361.1653

N-cyclohexyl-*N*-(2-(trifluorormethyl)benzyl)benzamide (21)

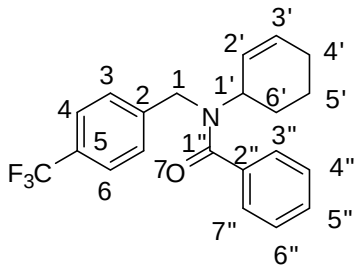
The double neck bottle which contained 40 mg Pd/C was vacuumed at first, and then the solution of *N*-(cyclohex-2-enyl)-*N*-(2-(trifluoromethyl)benzyl)benzamide (100mg, 0.28 mmol) in 3 ml MeOH was injected into the vacuumed system and stirred in the room temperature. The following reaction was capped, purged with hydrogen gas for 3 hours. After the reaction is completed and checked by TLC film (mobile phase : ACN/H_2O = 2/1) ,the Pd/C in the mixture was removed by celite, washed with 200 ml MeOH and the filtered solution was collected, concentrated. The crude was purified by column chromatography (silica gel; EtOAc/Hexane = 1/10, 400ml) to give 48 mg compound (0.13 mmol , 48%). ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.41-7.26 (m, 9H, H-4, H-5, H-6, H-7, H-3", H-4", H-5", H-6", H-7"), 4.71 (s, 2H, H-1), 3.65 (s, 1H, H-1'), 1.71-1.02 (m, 10H, H-2', H-3', H-4', H-5', H-6', H-7') ; ^{13}C NMR (50MHz, $CDCl_3$) δ 172.7 (C-1"), 137.4 (C-2"), 137.0 (C-2), 131.9 (C-6), 129.6 (C-5"), 128.7 (C-4", C-6"), 127.6 (C-3), 126.7 (C-5), 126.2 (C-3", C-7"), 126.0 (C-7), 125.9 (C-4), 121.9 (C-7'), 59.4 (C-1'), 40.9 (C-1), 31.7 (C-2'), 30.7 (C-6'), 29.8 (C-5), 25.7 (C-3'), 25.1 (C-5'). IR (thin film from KBr): 3063, 3031, 2932, 2856, 1640, 1578, 1439, 767 cm^{-1}. HRMS (ESI) calc. For $C_{21}H_{22}FNO$ + H $[M+H]^+$:362.1731, found: 362.1795.



Chemical Formula: $C_{14}H_{16}NF_3$
Exact Mass: 255.1235

N-(4-trifluoromethyl)benzyl)cyclohex-2-enamine (22)

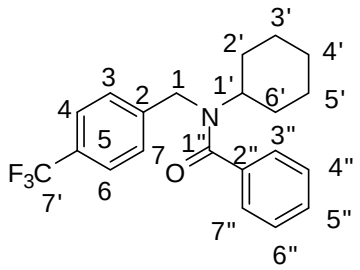
To a stirring of 4-(trifluoromethyl)benzylamine (200 mg, 1.14 mmol) in 5 ml dichloromethane was added triethylamine (0.34 g, 3.42 mmol) drop by drop, the mixture was stirred in the ice-bath for 10 minutes , then the reaction was returned to the room temperature, followed by addition of 3-bromocyclohexene (91 mg, 0.45 mmol). The mixture reacted for an hour, then 3-bromocyclohexene (54 mg, 0.27 mmol) was added. The mixture was stirred overnight after the above step was repeated after an hour. The reaction was quenched with 30 ml H_2O, extracted by 180 ml ethyl acetate, washed with brine, and then dried by $MgSO_4$. The organic layers were collected, concentrated, and then purified by column chromatography (silica gel; EtOAc/Hexane = 1/20, 600ml) to give the 140 mg compound (0.58 mmol, 51%) . ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.48-7.34 (dd, *J* = 8.4, 20.2 Hz, 4H, H-3, H-4, H-6, H-7), 5.73-5.58 (m, 2H, H-3', H-2'), 3.86-3.72 (t, *J* = 14.2 Hz, 2H, H-1), 3.11-3.09 (d, *J* = 1.7 Hz, 1H, H-1'), 1.94-1.46 (m, 7H, H-4', H-5', H-6', NH) ; ^{13}C NMR (50 MHz, $CDCl_3$) δ 145.1 (C-2), 129.7 (C-3'), 129.5 (C-2'), 129.3 (C-3, C-7), 128.4 (C-5), 125.3 (C-4, C-6), 125.2 (C-7'), 52.5 (C-1'), 50.4 (C-1), 29.4 (C-6), 25.3 (C-4), 20.2 (C-5).HRMS (ESI) calc. For $C_{14}H_{16}FN$ + H $[M+H]^+$: 256.1313, found: 256.1240.



Chemical Formula: $C_{21}H_{20}F_3NO$
Exact Mass: 359.1497

N-(cyclohex-2-enyl)-*N*-(4-(trifluoromethyl)benzyl)benzamide (23)

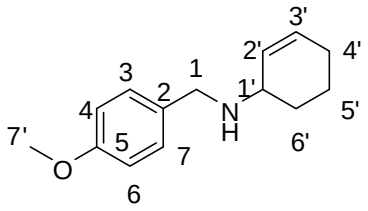
To a stirring of *N*-(4-trifluoromethyl)benzyl)cyclohex-2-enamine (120 mg, 0.50 mmol) in 3 ml dichloromethane was added triethylamine (151 mg, 1.50 mmol) dropwisely, the mixture was stirred in the ice-bath for 10 minutes, then the reaction was returned to the room temperature, followed by the addition of benzoyl chloride (84 mg, 0.50 mmol) drop by drop. The mixture was stirred overnight with the color change from transparence to white color. The reaction was quenched with 15 ml H_2O, extracted by 75 ml ethyl acetate, wash with brine, and then dried by $MgSO_4$. The organic layers were collected, concentrated, and then purified by column chromatography (silica gel; EtOAC/Hexane = 1/30, 200 ml, EtOAC/Hexane = 1/20, 200 ml) to give the 70 mg compound (0.22 mmol, 44%) . ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.76-7.24 (m, 9H, H-3, H-4, H-6, H-7, H-3", H-4", H-5", H-6", H-7"), 5.91-5.85 (m, 1H, H-3'), 5.50-5.45 (d, *J* = 10.0 Hz, 1H, H-2') , 4.87-4.79 (d, *J* = 15.4 Hz, 1H, H-1'), 4.50-4.42 (d, *J* = 16 Hz, 2H, H-1), 2.03-1.40 (m, 6H, H-4', H-5', H-6'). IR (thin film from KBr): 3063, 3027, 2926, 2853, 2850, 1621, 1432, 1409, 809, 699 cm^{-1}. HRMS (ESI) calc. For $C_{21}H_{20}FNO + H$ $[M+H]^+$: 360.1575, found : 360.1568.



Chemical Formula: $C_{21}H_{22}F_3NO$
Exact Mass: 361.1653

N-cyclohexyl-*N*-(4-(trifluorormethyl)benzyl)benzamide (24)

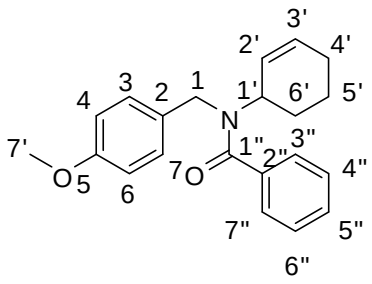
The double neck bottle which contained 40 mg Pd/C was vacuumed at first, and then the solution of *N*-(cyclohex-2-enyl)-*N*-(4-(trifluoromethyl)benzyl)benzamide (45 mg, 0.13 mmol) in 3 ml MeOH was injected into the vacuumed system and stirred in the room temperature. The following reaction was capped, purged with hydrogen gas for 3 hours. After the reaction was completed and checked by TLC film (mobile phase : ACN/H_2O = 2/1) ,the Pd/C in the mixture was removed by celite, washed with 200 ml MeOH and the filtered solution was collected, concentrated. The crude was purified by column chromatography (silica gel; EtOAc/Hexane = 1/10, 400 ml) to give 33 mg compound (0.10 mmol , 73%). ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.58-7.10 (H-3, H-4, H-6, H-7, H-3", H-4", H-5", H-6", H-7"), 4.72 (s, 2H, H-1), 3.66 (s, 1H, H-1'), 3.00 (s, 1H), 2.34 (s, 2H), 1.16-1.33 (m, 5H), 1.10-0.87 (m, 2H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 172.8 (C-1"), 143.4 (C-2), 138.0 (C-2"), 136.7 (C-5), 129.2-128.7 (*J* = 21.0, 19.5 Hz, C-3, C-7), 127.3 (C-4", C-6"), 126.3 (C-3", C-7"), 125.6 (C-4, C-6), 125.4 (C-7'); IR (thin film from KBr): 2932, 2856, 1636, 1578, 1411, 822, 700 cm^{-1}. HRMS (ESI) calc. For $C_{21}H_{22}FNO$ + H $[M+H]^+$:362.1731, found: 362.1791.



Chemical Formula: $C_{14}H_{19}NO$
Exact Mass: 217.1467

N-(4-methoxybenzyl)cyclohex-2-enamine (25)

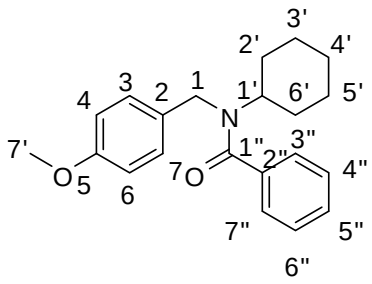
To a stirring of 4-methoxybenzylamine (400 mg, 2.92 mmol) in 5 ml dichloro-methane was added triethylamine (0.89 g, 8.8 mmol) drop by drop, the mixture was stirred in the ice-bath for 10 minutes , then the reaction was returned to the room temperature, followed by addition of 3-bromocyclohexene (235 mg, 1.46 mmol). The mixture reacted for an hour, then 3-bromocyclohexene (141 mg, 0.88 mmol) was added. The mixture was stirred overnight after the above step was repeated after an hour. The reaction was quenched with 50 ml H_2O, extracted by 180 ml ethyl acetate, washed with brine, and then dried by $MgSO_4$. The organic layers were collected, concentrated, and then purified by column chromatography (silica gel; EtOAc/Hexane = 1/30, 200 ml; EtOAc/Hexane = 1/10, 400 ml) to give the 232 mg compound (1.24 mmol, 49%) . ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.24-7.16 (dd, *J* = 8.6, 8.6, 2.0 Hz, 1H, H-3, H-7), 6.82-6.75 (dd, *J* = 8.6, 2.0 Hz, 2H, H-4, H-6), 5.74-5.62 (t, *J* = 11.8 Hz, 2H, H-1), 3.78-3.60 (overlapped, 5H, H-1, H-7'), 3.16-3.13 (d, *J* = 5.1 Hz, 1H, H-1'), 1.93-1.40 (m, 7H, H-4', H-5', H-6') ; ^{13}C NMR (50 MHz, $CDCl_3$) δ 158.4 (C-5), 132.6 (C-2), 129.8 (C-3'), 129.2 (C-3, C-7), 128.7 (C-2'), 113.6 (C-4, C-6), 55.0 (C-7'), 52.1 (C-1'), 50.2 (C-1), 29.3 (C-6'), 25.2 (C-4'), 20.1 (C-5'). IR (thin film from KBr): 2929, 2833, 1611, 1584, 1511, 1462, 1443, 824, 724 cm^{-1}. HRMS (ESI) calc. For $C_{14}H_{19}NO$+ H $[M+H]^+$: 218.1545, found: 218.1539.



Chemical Formula: $C_{21}H_{23}NO_2$
Exact Mass: 321.1729

N-(cyclohex-2-enyl)-*N*-(4-methoxybenzyl)benzamide (26)

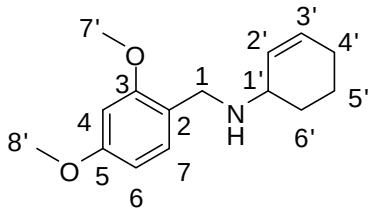
To a stirring of *N*-(4-methoxybenzyl)cyclohex-2-enamine (210 mg, 0.97mmol) in 3 ml dichloromethane was added triethylamine (294 mg, 2.91 mmol) dropwisely, the mixture was stirred in the ice-bath for 10 minutes , then the reaction was returned to the room temperature, followed by the addition of benzoyl chloride (300 mg, 2.13 mmol) drop by drop. The mixture was stirred overnight with the color change from transparence to white color. The reaction was quenched with 50 ml H_2O, extracted by 210 ml hexane, wash with brine, and then dried by $MgSO_4$. The organic layers were collected, concentrated, and then purified by column chromatography (silica gel; EtOAc/Hexane = 1/30, 200 ml; EtOAc/Hexane = 1/10, 300 ml) to give the 226 mg compound (0.70 mmol, 73%) . ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.32-7.19 (m, 7H, H-3, H-7, H-3", H-4", H-5", H-6", H-7"), 6.75-6.74 (d, *J* = 2.6 Hz, 2H, H-4, H-6), 5.75-5.73 (d, *J* = 4.2 Hz, 1H, H-3'), 5.41 (s, 1H, H-2'), 4.70-4.66 (d, *J* = 7.3 Hz, H-1'), 4.32-4.28 (d, *J* = 7.5 Hz, 2H, H-1), 3.65 (s, 3H, H-7'), 1.80-1.34 (m, 6H, H-4', H-5', H-6') ; ^{13}C NMR (50 MHz, CDCl3) δ 172.4 (C-1"), 158.3 (C-5), 136.9 (C-2"), 131.9 (C-3"), 131.4 (C-2), 129.2 (C-2'), 128.4 (C-5"), 128.0 (C-4", C-6"), 126.2 (C-3", C-7"), 113.6 (C-4, C-6), 56.9 (C-7), 55.1 (C-1'), 44.6 (C-1), 28.7 (C-6'), 24.2 (C-4'), 21.4 (C-5'). IR (thin film from KBr): 3068, 2933, 2857, 1635, 1583, 1411, 758, 700 cm^{-1}. HRMS (ESI) calc. For $C_{21}H_{23}NO_2$+ H $[M+H]^+$: 322.1807, found: 322.1810.



Chemical Formula: $C_{21}H_{25}NO_2$
Exact Mass: 323.1885

N-cyclohexyl-*N*-(4-methoxybenzyl)benzamide (27)

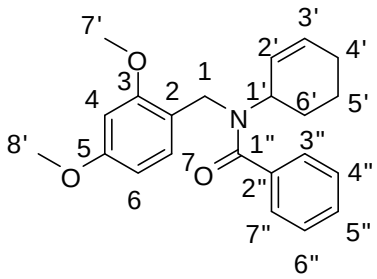
The double neck bottle which contained 40 mg Pd/C was vacuumed at first, and then the solution of *N*-cyclohexyl-*N*-(4-methylbenzyl)benzamide (100mg, 0.31 mmol) in 3 ml MeOH was injected into the vacuumed system and stirred in the room temperature. The following reaction was capped, purged with hydrogen gas for 3 hours. After the reaction is completed and checked by TLC film (mobile phase : ACN/H_2O = 4/1) ,the Pd/C in the mixture was removed by celite, washed with 200 ml MeOH and the filtered solution was collected, concentrated. The crude was purified by column chromatography (silica gel; EtOAc/Hexane = 1/10, 400ml) to give 42 mg compound (0.13 mmol , 42%). ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.37 (s, 7H, H-3, H-7, H-3", H-4", H-5", H-6", H-7"), 6.84-6.80 (dd, *J* = 8.5 Hz , 2H, H-4, H-6), 4.61 (s, 2H, H-1), 3.76 (s, 3H, H-1), 3.57 (s, 1H, H-1'), 1.65-0.97 (m, 10H, H-2', H-3', H-4', H-5' H-6') ; ^{13}C NMR (50 MHz, $CDCl_3$) δ 172.4 (C-1"), 158.5 (C-5), 137.5 (C-2"),131.6 (C-5), 129.2 (C-3, C-7), 128.5 (C-4", C-6"), 126.2 (C-3", C-7"), 113.8 (C-4, C-6), 59.4 (C-1'), 55.3 (C-7'), 44.0 (C-1), 32.1 (C-2, C-6), 29.8 (C-4), 25.3 (C-3, C-5). IR (thin film from KBr): 3063, 2932, 2854, 1629, 1512, 1413, 698 cm^{-1}. HRMS (ESI) calc. For $C_{21}H_{25}NO_2$+ H $[M+H]^+$: 324.1963, found: 324.2047.



Chemical Formula: $C_{15}H_{21}NO_2$
Exact Mass: 247.1572

N-(2,4-dimethoxybenzyl)cyclohex-2-enamine (28)

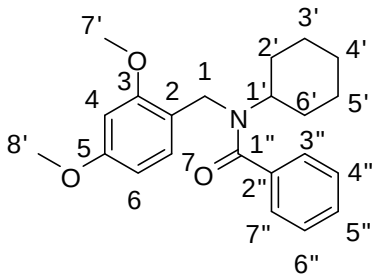
To a stirring of 2,4-dimethoxybenzylamine (400mg, 2.40mmol) in 5 ml dichloromethane was added triethylamine (0.73g, 7.2mmol) drop by drop, the mixture was stirred in the ice-bath for 10 minutes , then the reaction was returned to the room temperature, followed by addition of 3-bromocyclohexene (193mg, 1.20mmol). The mixture reacted for an hour, then 3-bromocyclohexene (115mg, 0.72mmol) was added. The mixture was stirred overnight after the above step was repeated after an hour. The reaction was quenched with 30 ml H_2O, extracted by 150 ml ethyl acetate, washed with brine, and then dried by $MgSO_4$. The organic layers were collected, concentrated, and then purified by column chromatography (silica gel; EtOAc/Hexane = 1/30, 200ml; EtOAc/Hexane = 1/20, 200ml; EtOAc/Hexane = 1/10, 200 ml) to give the 267 mg compound (1.08 mmol, 45%) . ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.15-7.14 (d, 1H, H-7), 6.43 (s, 1H, H-4), 6.40 (s, 1H, H-6), 5.75-5.68 (m, 2H, H-1), 3.73 (s, 3H, H-8'), 3.73 (s, 3H, H-7'), 3.73-3.70 (overlapped, 2H, H-1), 3.16 (s, 1H, H-1'), 1.99-1.44 (m, 5H, H-4', H-5', H-6', NH); ^{13}C NMR (50 MHz, CDCl3) δ 160.0 (C-5), 158.6 (C-3), 130.4 (C-3'), 130.2 (C-2'), 128.7 (C-7), 121.3 (C-2), 103.8 (C-6), 98.6 (C-4), 55.4 (C-8'), 55.3 (C-7'), 52.3 (C-2), 46.0 (C-1), 29.5 (C-6'), 25.4 (C-4'), 20.3 (C-5'). IR (thin film from KBr): 3017, 2999, 2933, 2858, 2834, 1613, 1588, 1505, 1463, 833, 723 cm^{-1}. HRMS (ESI) calc. For $C_{15}H_{21}NO_2$+ H $[M+H]^+$: 248.1650, found: 248.1717.



Molecular Formula: $C_{22}H_{25}NO_3$
Exact Mass: 351.1834

N-(cyclohex-2-enyl)-*N*-(2,4-dimethoxybenzyl)benzamide (29)

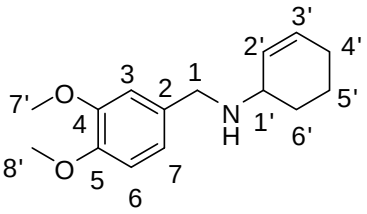
To a stirring of *N*-(2,4-dimethoxybenzyl)cyclohex-2-enamine (150 mg, 0.61 mmol) in 3 ml dichloromethane was added triethylamine (294 mg, 2.91 mmol) dropwisely, the mixture was stirred in the ice-bath for 10 minutes, then the reaction was returned to the room temperature, followed by the addition of benzoyl chloride (300 mg, 2.36 mmol) drop by drop. The mixture was stirred overnight with the color change from transparence to white color. The reaction was quenched with 50 ml H_2O, extracted by 210 ml EtOAc, wash with brine, and then dried by $MgSO_4$. The organic layers were collected, concentrated, and then purified by column chromatography (silica gel; EtOAc/Hexane = 1/4, 400ml) to give the 229mg compound (0.65mmol, 67%) . ^{1}H NMR (200 MHz,$CDCl_3$) δ 7.30-7.08 (m, 6H, H-7, H-3", H-4", H-5", H-6", H-7"), 6.38-6.34 (s, 1H, H-2'), 6.34 (s, 1H, H-3'), 5.73-5.67 (m, 1H, H-3'), 5.42 (s, 1H, H-2'), 4.67 (d, *J* = 15.9 Hz, 1H, H-1'), 4.37-4.30 (d, *J* = 14.1 Hz, 2H, H-1), 3.69 (s, 3H, H-8'), 3.66 (s, 3H, H-7'), 1.80-1.21 (m, 6H, H-4', H-5', H-6'); ^{13}C NMR (50 MHz, $CDCl_3$) δ 172.4 (C-1"), 159.5 (C-5), 157.2 (C-3), 137.2 (C-2"), 131.8 (C-3'), 129.1 (C-2'), 128.4 (C-5"), 128.0 (C-7), 127.4 (C-4", C-6"), 126.3 (C-3", C-7"), 119.3 (C-2), 103.9 (C-6), 98.1 (C-4), 56.8 (C-1'), 55.2 (C-8'), 55.1 (C-7'), 39.5 (C-1), 28.3 (C-6'), 24.3 (C-4'), 21.4 (C-5') . IR (thin film from KBr): 3057, 3023, 3001, 2935, 2860, 2835, 1633, 1586, 1454, 833, 780, 700cm^{-1}. HRMS (ESI) calc. For $C_{22}H_{24}NO_3$ + H $[M+H]^+$: 352.1912, found : 352.1914.



Molecular Formula: $C_{22}H_{27}NO_3$
Exact Mass: 353.1991

N-cyclohexyl-*N*-(2,4-dimethoxybenzyl)benzamide (30)

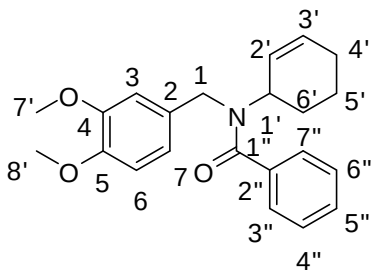
The double neck bottle which contained 40 mg Pd/C was vacuumed at first, and then the solution of *N*-(cyclohex-2-enyl)-*N*-(3,4-dimethoxybenzyl)benzamide (100mg, 0.28 mmol) in 3 ml MeOH was injected into the vacuumed system and stirred in the room temperature. The following reaction was capped, purged with hydrogen gas for 3 hours. After the reaction is completed and checked by TLC film (mobile phase : ACN/H_2O = 2/1) ,the Pd/C in the mixture was removed by celite, washed with 200 ml MeOH and the filtered solution was collected, concentrated. The crude was purified by column chromatography (silica gel; EtOAc/Hexane = 1/10, 400ml) to give 65 mg compound (0.18 mmol , 65%). ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.38-7.14 (m, 6H, H-7, H-3", H-4", H-5", H-6", H-7"), 6.47-6.46 (d, *J* = 2.4 Hz, 1H, H-4), 6.43-6.42 (d, *J* = 1 Hz, 1H, H-6), 4.62-4.36 (m, 2H, H-1), 3.81 (s, 3H, H-8'), 3.77 (s, 3H, H-7'), 2.73 (s, 1H, H-1'), 1.65-0.85 (m, 10H, H-3", H-4", H-5", H-6", H-7"); ^{13}C NMR (50 MHz, $CDCl_3$) δ172.4 (C-1'), 159.7 (C-5), 157.4 (C-3), 137.6 (C-2"), 129.1 (C-7), 128.5 (C-5"), 128.3 (C-4", C-6"), 126.2 (C-3", C-7"), 119.5 (C-2), 104.0 (C-6), 98.3 (C-4), 59.3 (C-1'), 55.8 (C-8'), 55.4 (C-7'), 44.9 (C-1), 31.5 (C-2'), 30.5 (C-6'), 29.8 (C-4'), 25.8 (C-3'), 25.2(C-5'). IR (thin film from KBr): 3056, 2996, 2931, 2854, 1632, 1586, 1505, 1452, 1413, 833, 781, 700 cm^{-1}. HRMS (ESI) calc. For $C_{22}H_{27}NO_3$ + H $[M+H]^+$: 354.2069, found: 354.2140.



Chemical Formula: $C_{15}H_{21}NO_2$
Exact Mass: 247.1572

N-(3,4-dimethoxybenzyl)cyclohex-2-enamine (31)

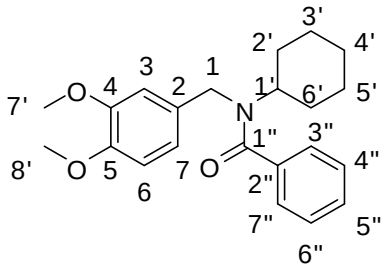
To a stirring of 3,4-dimethoxybenzylamine (400mg, 2.40mmol) in 5 ml dichloromethane was added triethylamine (0.73g, 7.2mmol) drop by drop, the mixture was stirred in the ice-bath for 10 minutes , then the reaction was returned to the room temperature, followed by addition of 3-bromocyclohexene (193mg, 1.20mmol). The mixture reacted for an hour, then 3-bromocyclohexene (115mg, 0.72mmol) was added. The mixture was stirred overnight after the above step was repeated after an hour. The reaction was quenched with 30 ml H_2O, extracted by 150 ml ethyl acetate, washed with brine, and then dried by $MgSO_4$. The organic layers were collected, concentrated, and then purified by column chromatography (silica gel; EtOAc/Hexane = 1/30, 200ml; EtOAc/Hexane = 1/20, 200 ml; EtOAc/Hexane = 1/10 =200 ml) to give the 171mg compound (0.69mmol, 29%) . ^{1}H NMR (200 MHz, $CDCl_3$) δ6.83-6.68 (m, 3H, H-3, H-6, H-7), 5.71-5.59 (m, 2H, H-2', H-3'), 3.78 (s, 3H, H-7'), 3.75 (s, 3H, H-8'), 3.68-3.67 (d, J = 1.2, 2H, H-1), 3.13-3.10 (m ,1H, H-1'), 1.93-1.40 (m, 7H, NH, H-4', H-5', H-6') ; ^{13}C NMR (50MHz, $CDCl_3$) δ148.7 (C-8'), 147.7 (C-7'), 133.1 (C-1), 129.7 (C-3'), 128.7 (C-2'), 120.0 (C-6), 111.3 (C-5), 110.8 (C-3), 55.7 (C-7'), 55.6 (C-8'), 52.2 (C-1'), 50.6 (C-1), 29.3 (C-6'), 25.1 (C-4'), 20.1 (C-5'). IR (thin film from KBr): 3016, 2932, 2861, 2833, 1608, 1590, 1514, 1463, 1416, 806, 764, 723 cm^{-1}. HRMS (ESI) calc. For $C_{15}H_{21}NO_2$+ H $[M+H]^+$: 248.1650, found: 248.1679.



Molecular Formula: $C_{22}H_{25}NO_3$
Exact Mass: 351.1834

N-(cyclohex-2-enyl)-*N*-(3,4-dimethoxybenzyl)benzamide (32)

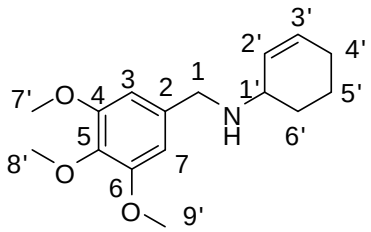
To a stirring of *N*-(3,4-dimethoxybenzyl)cyclohex-2-enamine (150 mg, 0.61 mmol) in 3 ml dichloromethane was added triethylamine (185 mg, 1.83 mmol) dropwisely, the mixture was stirred in the ice-bath for 10 minutes, then the reaction was returned to the room temperature, followed by the addition of benzoyl chloride (188 mg, 1.33 mmol) drop by drop. The mixture was stirred overnight with the color change from transparence to white color. The reaction was quenched with 30 ml H_2O, extracted by 150 ml EtOAc, wash with brine, and then dried by $MgSO_4$. The organic layers were collected, concentrated, and then purified by column chromatography (silica gel; EtOAc/Hexane = 1/10, 200 ml; EtOAc, 200 ml) to give the 151 mg compound (0.43 mmol, 71%) . ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.31 (m, 5H, H-3", H-4", H-5", H-6", H-7"), 6.90-6.71 (m, 3H, H-3, H-6, H-7), 5.78-5.67 (1H, *J* = 3.98, H-2'), 5.43-5.41 (1H, *J* = 3.88, H-3'), 4.71-4.68 (1H, *J* = 7.36, H-1'), 4.33-4.29 (2H, *J* = 7.48, H-1), 3.78 (s, 3H, H-7'), 3.75 (s, 3H, H-8'), 1.86-1.35 (m, 6H, H-4", H-5", H-6"); ^{13}C NMR (50 MHz, $CDCl_3$) δ 172 (C-1"), 148.9 (C-4), 147.7 (C-5), 137.1 (C-2"), 132.1 (C-3'), 131.9 (C-2'), 129.5 (C-2), 128.7 (C-4", C-6"), 128.3 (C-3", C-7"), 126.4 (C-7), 119.5 (C-6), 111.0 (C-3), 57.2 (C-1'), 56.0 (C-7', C-8'), 45.1 (C-1) 28.6 (C-6'), 24.3(C-4'), 20.8(C-5'). IR (thin film from KBr): 3061, 3029, 3001, 2933, 2856, 2834, 1632, 1515, 1446, 1409, 894, 785, 701 cm^{-1}. HRMS (ESI) calc. For $C_{22}H_{24}NO_3$ + H $[M+H]^+$: 352.1912, found : 352.1915.



Molecular Formula : $C_{22}H_{27}NO_3$
Exact Mass : 353.1991

N-cyclohexyl-*N*-(3,4-dimethoxybenzyl)benzamide (33)

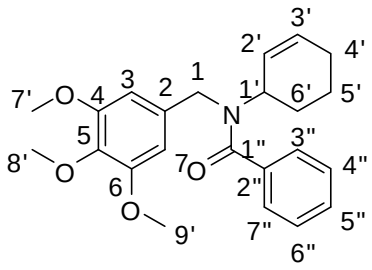
The double neck bottle which contained 40 mg Pd/C was vacuumed at first, and then the solution of *N*-(cyclohex-2-enyl)-*N*-(3,4-dimethoxybenzyl)benzamide (100 mg, 0.28 mmol) in 3 ml MeOH was injected into the vacuumed system and stirred in the room temperature. The following reaction was capped, purged with hydrogen gas for 3 hours. After the reaction is completed and checked by TLC film (mobile phase : ACN/H_2O = 2/1) ,the Pd/C in the mixture was removed by celite, washed with 200 ml MeOH and the filtered solution was collected, concentrated. The crude was purified by column chromatography (silica gel; EtOAc/Hexane = 1/10, 400ml) to give 69 mg compound (0.20 mmol , 69%). ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.35-7.23 (m, 5H, H-2", H-3", H-4", H-5", H-6"), 6.93-6.44 (m, 3H, H-3, H-6, H-7), 4.61 (s , 2H, H-1), 3.82 (s, 6H, H-7', H-8'), 3.56 (s, 1H, H-1'), 1.68-0.92 (m, 10H, H-2', H-3', H-4', H-5', H-6') ; ^{13}C NMR (50MHz, $CDCl_3$) δ 172.4 (C-1"), 148.9 (C-4), 147.9 (C-5), 137.5 (C-2"), 132.2 (C-2), 129.3 (C-5"), 128.6 (C-4", C-6"), 126.1 (C-3", C-7"), 119.2 (C-7), 111.0 (C-6), 110.74 (C-3), 59.4 (C-1'), 55.9 (C-7', C-8'), 44.3 (C-1), 32.0 (C-2'), 30.9 (C-6'), 29.7 (C-5), 25.8 (C-3'), 25.2 (C-5'). IR (thin film from KBr): 3059, 2931, 2854, 1632, 1515, 1413, 701 cm^{-1}. HRMS (ESI) calc. For $C_{22}H_{27}NO_3$ + H $[M+H]^+$: 354.2069, found: 354.2157.



Chemical Formula: $C_{16}H_{23}NO_3$
Exact Mass: 277.1678

N-(3,4,5-trimethoxybenzyl)cyclohex-2-enamine (34)

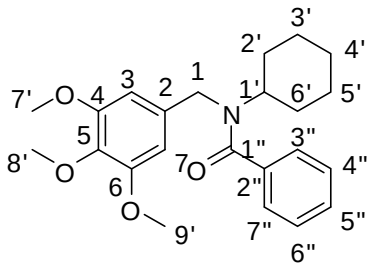
To a stirring of 3,4,5-dimethoxybenzylamine (400 mg, 2.03 mmol) in 5 ml dichloromethane was added triethylamine (0.62 g, 6.10 mmol) drop by drop, the mixture was stirred in the ice-bath for 10 minutes , then the reaction was returned to the room temperature, followed by addition of 3-bromocyclohexene (168 mg, 1.01 mmol). The mixture reacted for an hour, then 3-bromocyclohexene (100 mg, 0.60 mmol) was added. The mixture was stirred overnight after the above step was repeated after an hour. The reaction was quenched with 30 ml H_2O, extracted by 150 ml ethyl acetate, washed with brine, and then dried by $MgSO_4$. The organic layers were collected, concentrated, and then purified by column chromatography (silica gel; EtOAc/Hexane = 1/4, 200 ml; EtOAc/Hexane = 1/1, 200 ml) to give the 249 mg compound (1.10 mmol, 91%) . ^{1}H NMR (200 MHz, $CDCl_3$) δ 6.51 (s, 2H, H-3, H-7), 5.67-5.64 (d, *J* = 5.8 Hz, 2H, H-2', H-3'), 3.95 (s, 6H, H-7', H-9'), 3.78 (s, 3H, H-8'), 3.74-3.67 (dd, *J* = 7.3、1.7 Hz, 2H, H-1), 2.07-1.38 (m, 7H, NH, H-4', H-5', H-6') ; ^{13}C NMR (50 MHz, $CDCl_3$) δ 153.0 (C-4, C-6), 136.4 (C-5), 129.7 (C-3'), 128.8 (C-2'), 104.7 (C-3, C-7), 60.6 (C-8'), 55.9 (C-7', C-9'), 52.4 (C-1'), 51.1 (C-1), 29.3 (C-6'), 25.2 (C-4'), 20.1 (C-5'). IR (thin film from KBr): 3021, 2996, 2933, 2861, 2835, 1519, 1505, 1455, 1419, 829, 783, 755, 724 cm^{-1}. HRMS (ESI) calc. For $C_{16}H_{23}NO_3$+ H $[M+H]^+$: 278.1756, found: 278.1801.



Chemical Formula: $C_{23}H_{27}NO_4$
Exact Mass: 381.1940

N-(cyclohex-2-enyl)-*N*-(3,4,5-dimethoxybenzyl)benzamide (35)

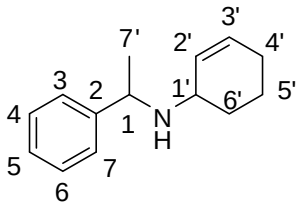
To a stirring of *N*-(3,4,5-trimethoxybenzyl)cyclohex-2-enamine (229 mg, 0.84 mmol) in 3 ml dichloromethane was added triethylamine (255 mg, 2.52 mmol) dropwisely, the mixture was stirred in the ice-bath for 10 minutes, then the reaction was returned to the room temperature, followed by the addition of benzoyl chloride (260 mg, 1.85 mmol) drop by drop. The mixture was stirred overnight with the color change from transparence to white color. The reaction was quenched with 30 ml H_2O, extracted by 150 ml EtOAc, wash with brine, and then dried by $MgSO_4$. The organic layers were collected, concentrated, and then purified by column chromatography (silica gel; EtOAc/Hexane = 1/4, 200 ml; EtOAc/Hexane = 1/1, 200 ml) to give the 95 mg compound (0.24 mmol, 30%) . ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.34 (s, 5H, H-3", H-4", H-5", H-6", H-7"), 6.53 (s, 2H, H-3, H-7), 5.83-5.79 (t, *J* = 3.8 Hz, 1H, H-3'), 5.47-5.42 (d, *J* = 9.6 Hz, 1H, H-2'), 4.74-4.66 (d, *J* = 15.4 Hz, 1H, H-1'), 4.35-4.28 (d, *J* = 15.3 Hz, 1H, H-1), 3.77 (s, 6H, H-7', H-9'), 3.75 (s, 3H, H-8'), 1.87-1.25 (m, 6H, H-4", H-5", H-6"); ^{13}C NMR (50MHz, $CDCl_3$) δ 172.7 (C-1"), 153.1 (C-4, C-6), 135.9 (C-5), 136.7 (C-2"), 135.1 (C-2), 132.2 (C-3'), 129.5 (C-2'), 128.7 (C-5"), 128.0 (C-4", C-6"), 126.3 (C-3", C-7"), 60.8 (C-8'), 57.1 (C-1'), 56.1 (C-7', C-9'), 45.4 (C-1), 28.8 (C-6'), 24.4 (C-4'), 21.5 (C-5'). IR (thin film from KBr): 3063, 3024, 2930, 2853, 2838, 1737, 1634, 1591,1501, 1455, 1407, 898, 701 cm^{-1}. HRMS (ESI) calc. For $C_{23}H_{27}NO_4$ + H $[M+H]^+$: 382.2018, found : 382.2028.



Chemical Formula: $C_{23}H_{29}NO_4$
Exact Mass: 383.2097

N-cyclohexyl-*N*-(3,4, 5-trimethoxybenzyl)benzamide (36)

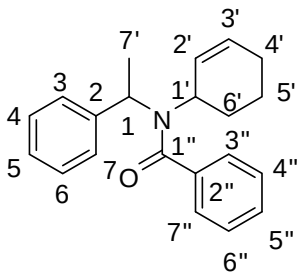
The double neck bottle which contained 40 mg Pd/C was vacuumed at first, and then the solution of *N*-(cyclohex-2-enyl)-*N*-(3,4,5-trimethoxybenzyl)benzamide (80 mg, 0.21 mmol) in 3 ml MeOH was injected into the vacuumed system and stirred in the room temperature. The following reaction was capped, purged with hydrogen gas for 3 hours. After the reaction is completed and checked by TLC film (mobile phase : ACN/H_2O = 2/1) ,the Pd/C in the mixture was removed by celite, washed with 200 ml MeOH and the filtered solution was collected, concentrated. The crude was purified by column chromatography (silica gel; EtOAc/Hexane = 1/10, 400 ml) to give 53 mg compound (0.14 mmol , 65%). ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.37 -7.24 (m, 5H, H-3", H-4", H-5", H-6", H-7"), 6.55-6.31 (s, 2H, H-3, H-7), 4.60 (s, 2H, H-1), 3.82-3.79 (overlapped, 9H, H-7', H-8', H-9'), 3.59 (s, 1H, H-1'), 1.66-0.99 (m, 10H, H-2', H-3', H-4', H-5', H-6', H-7') ; ^{13}C NMR (50 MHz, $CDCl_3$) δ 172.5 (C-1"), 153.2 (C-7, C-9), 137.3 (C-5), 136.7 (C-2"), 135.2 (C-2), 129.4 (C-5"), 128.7 (C-4", C-6"), 123.1 (C-3",C-7"), 61.0 (C-8'), 59.4 (C-1'), 56.1 (C-7', C-9'), 44.7 (C-1), 32.0 (C-2', C-6'), 30.9 (C-4'), 25.8 (C-3'), 25.2 (C-5'). IR (thin film from KBr): 2931, 2854, 1633, 1590, 1506, 1456, 1416, 780, 700 cm^{-1}. HRMS (ESI) calc. For $C_{23}H_{29}NO_4$ + H $[M+H]^+$: 384.2175, found: 384.2247.



Chemical Formula: $C_{14}H_{19}N$
Exact Mass: 201.1517

N-(1-phenylethyl)cyclohex-2-enamine (37)

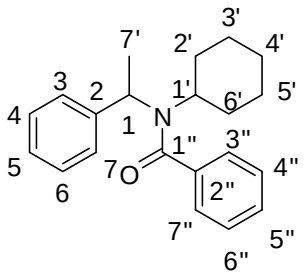
To a stirring of DL-alpha-methylbenzylamine (400 mg, 3.31 mmol) in 5 ml dichloro -methane was added triethylamine (1.11 g, 10.9 mmol) drop by drop, the mixture was stirred in the ice-bath for 10 minutes , then the reaction was returned to the room temperature, followed by the addition of 3-bromocyclohexene (266 mg, 1.65 mmol). The mixture reacted for an hour, then 3-bromocyclohexene (160 mg, 0.99 mmol) was added. The mixture was stirred overnight after the above step was repeated after an hour. The reaction was quenched with 50 ml H_2O, extracted by 180 ml ethyl acetate, washed with brine, and then dried by $MgSO_4$. The organic layers were collected, concentrated, and then purified by column chromatography (silica gel; EtOAc/Hexane = 1/10, 150 ml; EtOAc/Hexane = 1/4, 100 ml) to give the 287 mg compound (1.45 mmol, 43%) . ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.20-7.07 (m, 4H, H-3, H-4, H-5, H-6, H-7), 5.68-5.46 (m, 2H, H-2', H-3'), 3.90-3.83 (t, J = 6.7 Hz, 1H, H-1), 2.84 (m, 1H, H-1'), 1.78-1.18 (m, 10H, NH, H-4', H-5', H-6', H-7'); ^{13}C NMR (50 MHz, $CDCl_3$) δ 146.0 (C-2), 130.7 (C-3'), 129.5 (C-2'), 128.2 (C-4, C-5), 126.6 (C-3), 126.5 (C-6), 54.8-54.5 (C-1), 50.0-49.6 (C-1'), 30.5-28.8 (C-6'), 25.1-25.7 (C-4'), 25.1 (C-7'), 20.3-19.8 (C-5'). IR (thin film from KBr): 3022, 2957, 2925, 2858, 2831, 1600, 1583, 1492, 1450, 761, 700 cm^{-1}. HRMS (ESI) calc. For $C_{14}H_{19}N$+ H $[M+H]^+$: 202.1595, found: 202.1589.



Chemical Formula: $C_{21}H_{23}NO$
Exact Mass: 305.1780

N-(cyclohex-2-enyl)-*N*-(phenylethyl)benzamide (38)

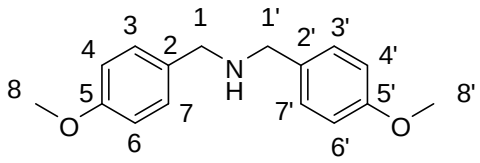
To a stirring of *N*-(1-phenylethyl)cyclohex-2-enamine (336 mg, 1.56 mmol) in 3 ml dichloromethane was added triethylamine (406 mg, 4.02 mmol) drop by drop, the mixture was stirred in the ice-bath for 10 minutes , then the reaction was returned to the room temperature, followed by the addition of benzoyl chloride (414 mg, 2.94 mmol) drop by drop. The mixture was stirred overnight with the color change from transparence to white color. The reaction was quenched with 50 ml H_2O, extracted by 210 ml hexane, wash with brine, and then dried by $MgSO_4$. The organic layers were collected, concentrated, and then purified by column chromatography (silica gel; EtOAc/Hexane = 1/10, 200 ml; EtOAc/Hexane = 1/4, 100 ml) to give the 334 mg compound (1.10 mmol, 82%) . ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.45-7.16 (m, 10H, H-3, H-4, H-5, H-6, H-7, H-3", H-4", H-5", H-6", H-7"), 5.74-5.37 (m, 2H, H-2', H-3'), 4.80 (s, 1H, H-1), 1.94-1.18 (m, 10H, H-1', H-4', H-5', H-6', H-7') ; ^{13}C NMR (50 MHz, $CDCl_3$) δ 171.5 (C-1"), 138.3 (C-2), 138.2 (C-2"), 129.1 (C-3'), 129.0 (C-2'), 128.6 (C-5"), 128.3 (C-4", C-6"), 127.2 (C-4, C-6), 127.0 (C-3, C-7), 126.2 (C-5), 126.1 (C-3", C-7"), 55.6 (C-1), 30.1 (C-1'), 28.5 (C-6'), 24.7 (C-4'), 22.7 (C-5'), 19.0 (C-7'). IR (thin film from KBr): 3058, 3025, 2935, 2861, 2831, 1638, 1577, 1494, 1428, 757, 699 cm^{-1}. HRMS (ESI) calc. For $C_{21}H_{23}NO$+ H $[M+H]^+$: 306.1858, found: 306.1830.



Chemical Formula: $C_{21}H_{25}NO$
Exact Mass: 307.1936

N-cyclohexyl-*N*-(1-phenylethyl)benzamide (39)

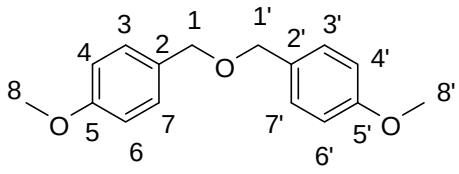
The double neck bottle which contained 40 mg Pd/C was vacuumed at first, and then the solution of The double neck bottle which contained 40 mg Pd/C was vacuumed at first, and then the solution of *N*-(cyclohex-2-enyl)-*N*-(phenylethyl)benzamide (100mg, 0.33 mmol) in 3 ml MeOH was injected into the vacuumed system and stirred in the room temperature. The following reaction was capped, purged with hydrogen gas for 3 hours. After the reaction is completed and checked by TLC film (mobile phase : ACN/H_2O = 2/1) ,the Pd/C in the mixture was removed by celite, washed with 200 ml MeOH and the filtered solution was collected, concentrated. The crude was purified by column chromatography (silica gel; EtOAc/Hexane = 1/10, 400ml) to give 53 mg compound (0.17 mmol , 53%). ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.42-7.18 (m, 10H, H-3, H-4, H-5, H-6, H-7, H-3', H-4', H-5', H-6', H-7'), 4.88-4.85 (d, *J* = 6.4 Hz, 1H, H-1), 3.01 (s, 1H, H-1'), 1.77-0.86 (m, 13H, H-2', H-3', H-4', H-5', H-6', H-7') ; ^{13}C NMR (50 MHz, $CDCl_3$) δ 171.5 (C-1"), 140.8 (C-2), 138.8 (C-2"), 128.9 (C-3'), 128.7 (C-2'), 128.3 (C-5"), 127.2 (C-4, C-6, C-4", C-6"), 126.4 (C-3, C-7), 125.9 (C-5, C-3", C-7"), 59.3 (C-1), 44.3 (C-1'), 32.0 (C-2', C-6'), 25.8 (C-3', C-5'), 25.2 (C-7') . IR (thin film from KBr): 3066, 3031, 2929, 2855, 1633, 1508, 1457, 1410, 700 cm^{-1}. HRMS (ESI) calc. For $C_{21}H_{25}NO$+ H $[M+H]^+$: 308.2014, found: 308.2073.



Chemical Formula: $C_{16}H_{19}NO_2$
Exact Mass: 257.1416

Bis(4-methoxybenzyl)amine (40)

To a stirring of 4-methoxybenzylamine (400 mg, 2.92 mmol) in 5 ml dichloromethane was added triethylamine (0.89 g, 8.76 mmol) drop by drop, the mixture was stirred in the ice-bath for 10 minutes , then the reaction was returned to the room temperature, followed by the addition of 4-methoxybenzylchloride (228 mg, 1.46 mmol). The mixture reacted for an hour, then 4-methoxybenzylchloride (137 mg, 0.88 mmol) was added. The above step was repeated after an hour with addition of 5mg potassium chloride. The mixture was stirred overnight. After the reaction checked by TLC film, it was quenched with 40 ml H_2O, extracted by 180 ml ethyl acetate, washed with brine, and then dried by $MgSO_4$. The organic layers were collected, concentrated, and then purified by column chromatography (silica gel; EtOAc/Hexane = 1/20, 200ml) to give the 248 mg compound **40 (**0.66 mmol, 23%).^{1}H NMR (200 MHz, $CDCl_3$) δ 7.28-7.25 (d, *J* = 4.0 Hz, 4H, H-3, H-7, H-3', H-7'), 6.90-6.85 (d, *J* = 4.0 Hz, 4H, H-4, H-6, H-4', H-6'), 3.78 (s, 6H, H-8, H-8'), 3.73 (s, 4H, H-1, H-1'), 1.86 (s, 1H, NH) ; ^{13}C NMR (50 MHz, $CDCl_3$) δ 158.6 (C-5, C-5'), 132.4 (C-2, C-2'), 129.3 (C-3, C-7, C-3', C-7'), 113.7 (C-4, C-6, C-4', C-6'), 55.2 (C-8, C-8'), 52.4 (C-1, C-1'). IR (thin film from KBr): 3034, 2977, 2933, 2833, 1611, 1584, 1511, 1463, 1440, 821 cm^{-1}. HRMS (ESI) calc. For $C_{16}H_{19}NO_2$+ H $[M+H]^+$: 258.1494, found: 258.1572.



Chemical Formula: $C_{16}H_{18}O_3$
Exact mass: 258.1256

4,4'-oxybis(methylene)bis(methoxybenzene) (**41**)

To a stirring of (4-methoxyphenyl)methanol (400 mg, 2.90 mmol) in 5 ml dichloromethane was added triethylamine (880 mg, 8.70 mmol) drop by drop, the mixture was stirred in the ice-bath for 10 minutes , then the reaction was returned to room temperature, followed by addition of 4-methoxybenzylchloride (543 mg, 3.48 mmol) drop by drop. Then 5 mg potassium iodide was also added into the reaction mixture. After 16 hours the reaction was quenched with 50 ml H_2O, extracted by 180 ml EtOAc, washed with brine, and then dried by $MgSO_4$. The organic layers were collected, concentrated, and then purified by column chromatography (silica gel; EtOAC/Hexane = 1/10, 400 ml) to give the 321 mg compound **41** (1.24mmol, 43%). ^{1}H NMR (200MHz,$CDCl_3$) δ 7.13-7.05 (m, 4H, H-3, H-7, H-3', H-7'), 6.77-6.82 (m, 4H, H-4, H-6, H-4', H-6'), 4.36 (s, 4H, H-1, H-1'), 3.62 (s, 6H, H-8, H-8') ; ^{13}C NMR (50 MHz, CDCl3) δ 158.9 (C-5, C-5'), 133.2 (C-2, C-2'), 128.5 (C-3, C-7, C-3', C-7'), 118.5 (C-4, C-6, C-4', C-6'), 64.4 (C-1, C-1'), 55.1 (C-8, C-8'). IR (thin film from KBr): 3009, 2959, 2932, 2903, 2836, 1611, 1585, 1515, 1463, 1407, 818 cm^{-1}. HRMS (ESI) calc. For $C_{16}H_{18}O_3$+ H $[M+H]^+$: 259.1334, found: 259.1424.

五、參考文獻：

1. Jay P. Powers, Michael Degraffenreid, Xiao He, Lisa Julian, Dustin L. McMinn, DaqingSun, YosupRew, XueleiYan.N-Benzyl-N-methyl-4-(1,1,1-triflu oro -2-hydroxypropan-2-yl)benzamide; modulating activity of hydroxysteroid dehydrogenases (HSDs), 11 beta-hydroxysteroid dehydrogenases,(also; 17 beta-, 20 alpha-, and 3 alpha-); antidiabetic agents;, obesity, glaucoma, osteoporosis, cognitive disorders; immunotherapy; *US7205289 B2,* **2007**
2. Yuri Kotelevtsev , Megan C. Holmes, Ann Burchell, Pamela M. Houston, Dieter Schmoll, Pauline Jamieson, Ruth Best, Roger Brown, Christopher R. W. Edwards, Jonathan R. Seckl and John J. Mullins. 11β-hydroxysteroid dehydroxysteroid dehydrogenase type1 knockout mice show attenuated glucocorticoid-inducible responses and resist hyperglycemia on obesity or stress. Proc. *Natl. Acad. Sci.* USA **1997**, *94*: 14924-14929.
3. Behrous Davani, Akhtar Khan, Malin Hult, Eva Mårtensson, Sam Okret,Suad Efendic, Hans Jörnvall, and Udo C. T. Oppermann. Type 1 11β-Hydroxysteroid Dehydrogenase Mediates Glucocorticoid Activation and Insulin Release in Pancreatic Islets, *J. Biol. Chem.* **2000,** *275*:34841-34844.
4. B. Billaudel , B.Ch. J. Sutter. Direct effect of corticosterone upon insuline secretion studied by three different techniques. *Horm. Metab. Res.* **1979**, *11*:555-560.
5. J Bujalska, L L Gathercole, J W Tomlinson, C Darimont, J Ermolieff, A N Fanjul, P A Rejto, and P M Stewart. A novel selective 11β-hydroxysteroid dehydrogenase type 1 inhibitor prevents human adipogenesis, *Lancet.* **1997**, *349*:1210-1213.

6. C-H Kim, S-L Cheng and G S Kim . Effects of dexamethasone on proliferation, activity, and cytokine secretion of normal human bone marrow stromal cells: possible mechanisms of glucocorticoid-induced bone loss, *J. Endocrinol.* **1999**, *162*:371 379.
7. C. G. Bellows, A. Ciaccia, J. N. M. Heersche. Osteoprogenitor cells in cell populations derived from mouse and rat calvaria differ in their response to corticosterone, cortisol, and cortisone, *Bone* **1998**, *23*:119-125.
8. M.S Cooper, E.A Walker, R Bland, W.D Fraser, M Hewison,P.M Stewart. Expression and functional consequences of 11β-hydroxysteroid dehydrogenase activity in human bone, *Bone* **2000**, *27*:375-381.
9. Dominique J.-F. de Quervain, Benno Roozendaal3, Roger M. Nitsch, James L. McGaugh and Christoph Hock. Acute cortisone administration impairs retrieval of long-term declarative memory in humans, *Nature* **1998**, *394*:787-790.
10. François Tronche, Christoph Kellendonk, Oliver Kretz, Peter Gass, Katrin Anlag, Paul C. Orban, Rudolf Bock, Rüdiger Klein and Günther Schütz . Disruption of the glucocorticoid receptor gene in the nervous system results in reduced anxiety, *Nature Genetics* **1999**, *23*:99-103.
11. Yau JL, Noble J, Kenyon CJ, Hibberd C, Kotelevtsev Y, Mullins JJ, Seckl JR. Lack of tissue glucocorticoid reactivation in 11beta-hydroxysteroid dehydrogenase type 1 knockout mice ameliorates age-related learning impairments. *Proc Natl. Acad. Sci*. USA **2001**, *98*:4716-4721.
12. Don Mason, Genetic variation in the stress response: Susceptibility to the experimental allergic encephalomyelitis and the implications for human inflammatary disease, *Immunology Today* **1991**, *12*:57-60

13. Chester Chenguang, Yuan, Nianhe Han, Qmgyian Luo, Dustin McMinn, N-cyclohexylbenzamides and benzenacetamides as inhibitor of 11beta -hydroxysteroid dehydrogenase . *United States Patent*, US 7,932,421 B2; April. 26, 2011.

14. Schimit, M.W, Baldridge. K. K, Boatz. J. A, Elbert. S. T, Gordon, M. S., Jesen, J. H.; Koseki, S., Matsunaga, N., Nguyen, K. A.; S., Windus, T. L., Dupuiss, M., Montgomery. J. A. General atomic and molecular electronic structure system. J. *Comput. Chem.* **1993**, *14*, 1347-1363.

15. Bode, B. M., Gordon, M .S. Macmolplt. A graphical user interface for GAMESS *J. Mol. Graphics Modeling* **1998**, *16*, 133-138.

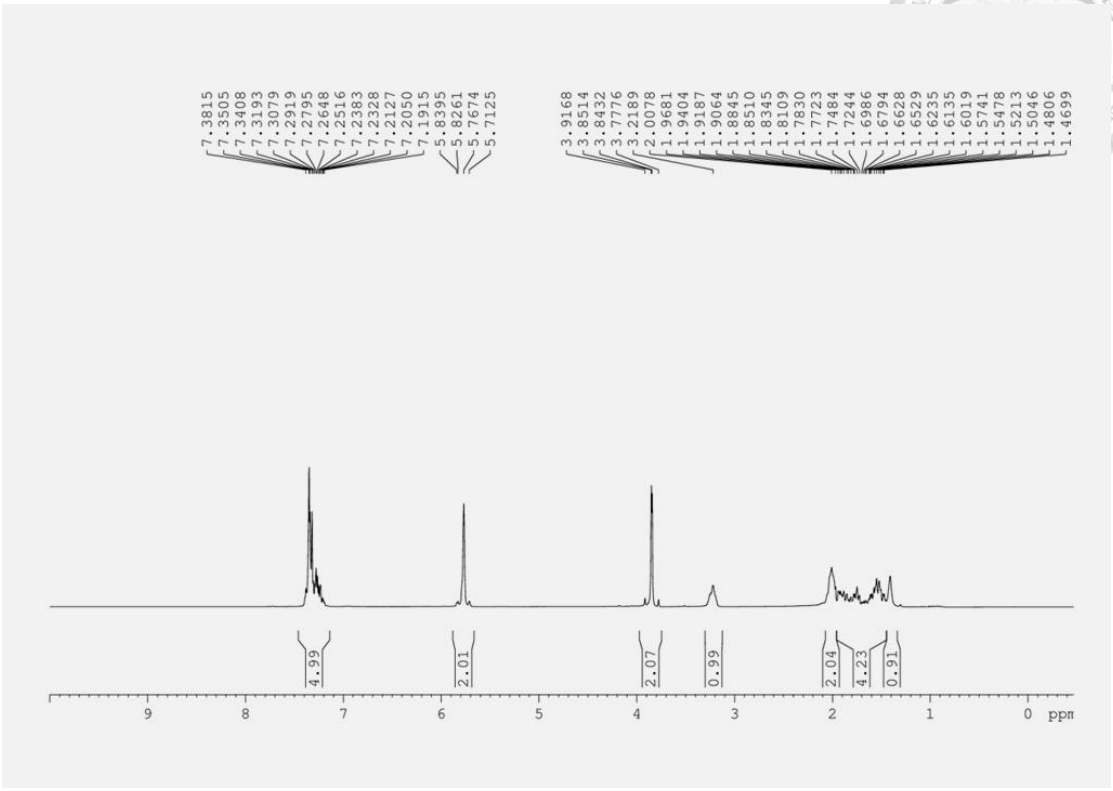
16. Neeper. M. ; Schimit, A. M.; Brett, J.; Yan, S. D., Wang, F.; Pan, Y. C.; Eliiston, K. Stern, D. Shaw, A. Cloning and Expression of a Cell Surface Receptor for Advanced Glycosylation End Products of Protein. *J. Biol. Chem*. **1992**, *267*, 14998-15004.

17. Nathan T. Ross, Rashid Deane, Sheldon Perry, Benjamin L. Miller. Structure-activity relationships of small molecule inhibitors of RAGE-Aβ binding. *Tetrahedron*. **2013**, *69*, 7653-7658.

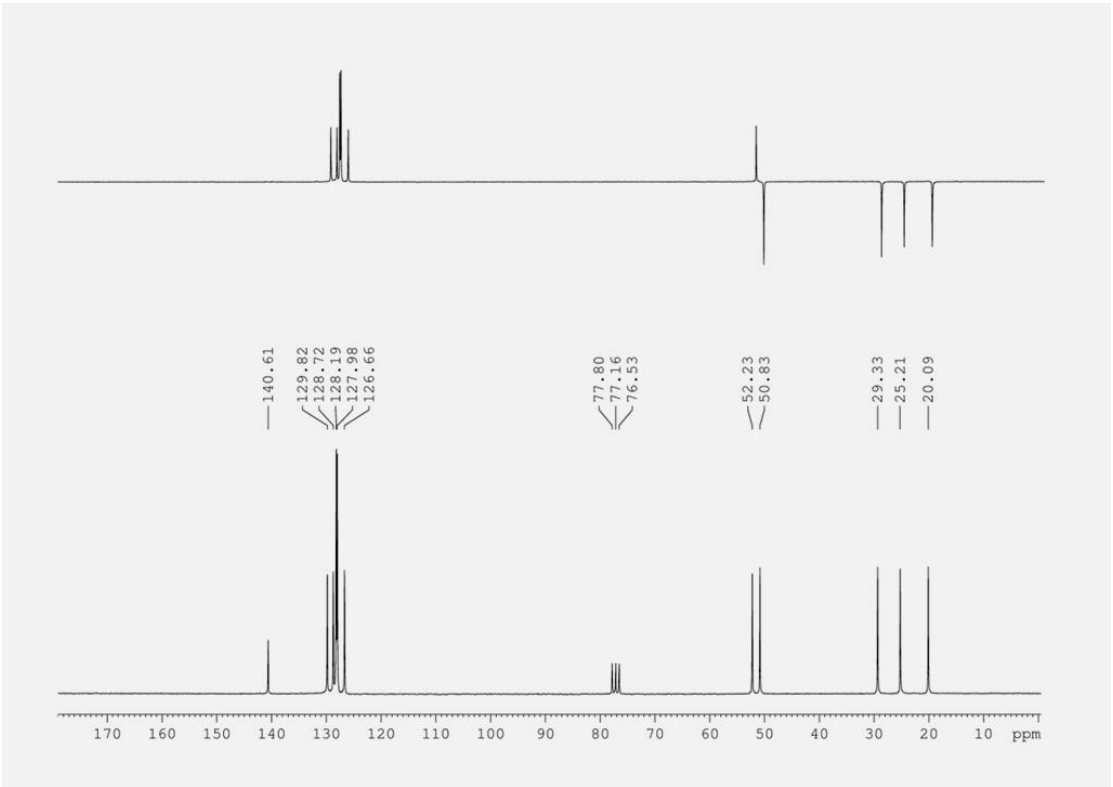
18. Deane, R., Singh, I,, Sagare, A. P.; Bell, R. D., Ross, N. T., LaRue, B., Love, R., Perry S., Paquette, N., Deane, R. J.; Thiyagarajan, M.; Zarcone, T.; Fritz, G.; Freidman, A. E.; Miller, B. L..; Zlolovic, B. V. A multimodal of RAGE-specific inhibitor reduced amyloid beta-mediated brain disorder in a mouse model of Alzheimer disease. *J. Clin.Imvest.* **2012**, *122*, 1377-1392

六、附圖

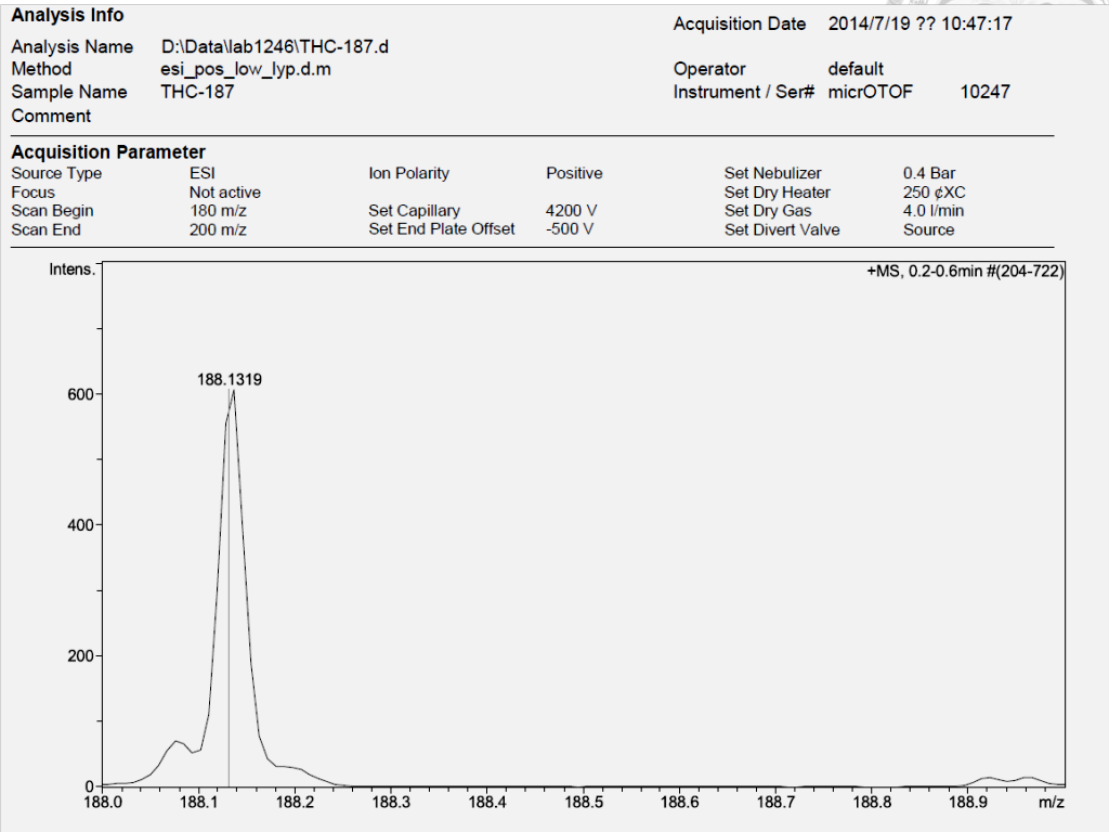
附圖一、化合物 1 之氫核磁共振圖譜($CDCl_3$, 200 MHz)



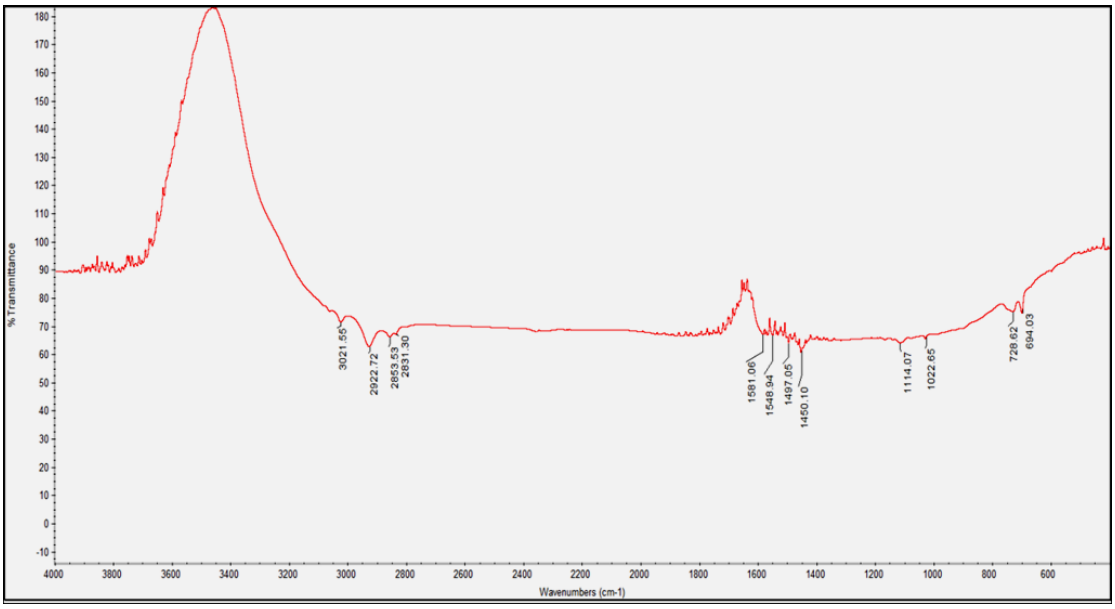
附圖二、化合物 1 之 ^{13}C 與 DEPT135 核磁共振圖譜



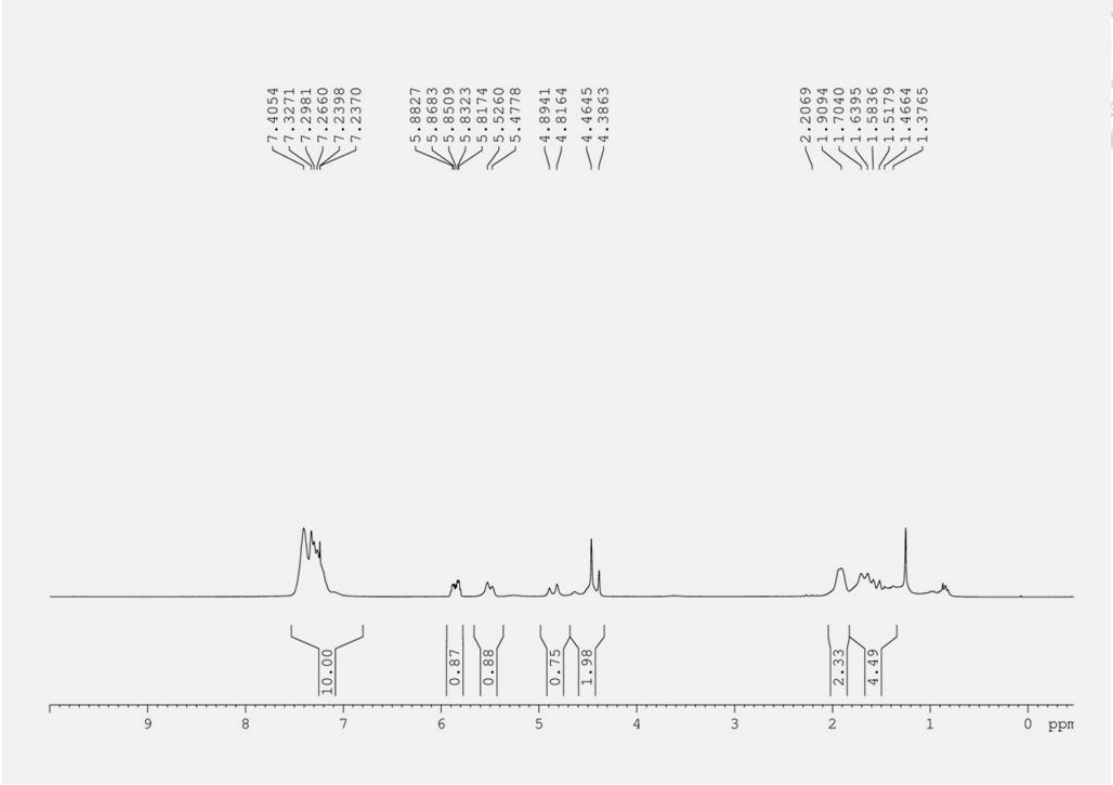
附圖三、化合物 1 之 HRESIMS 圖譜



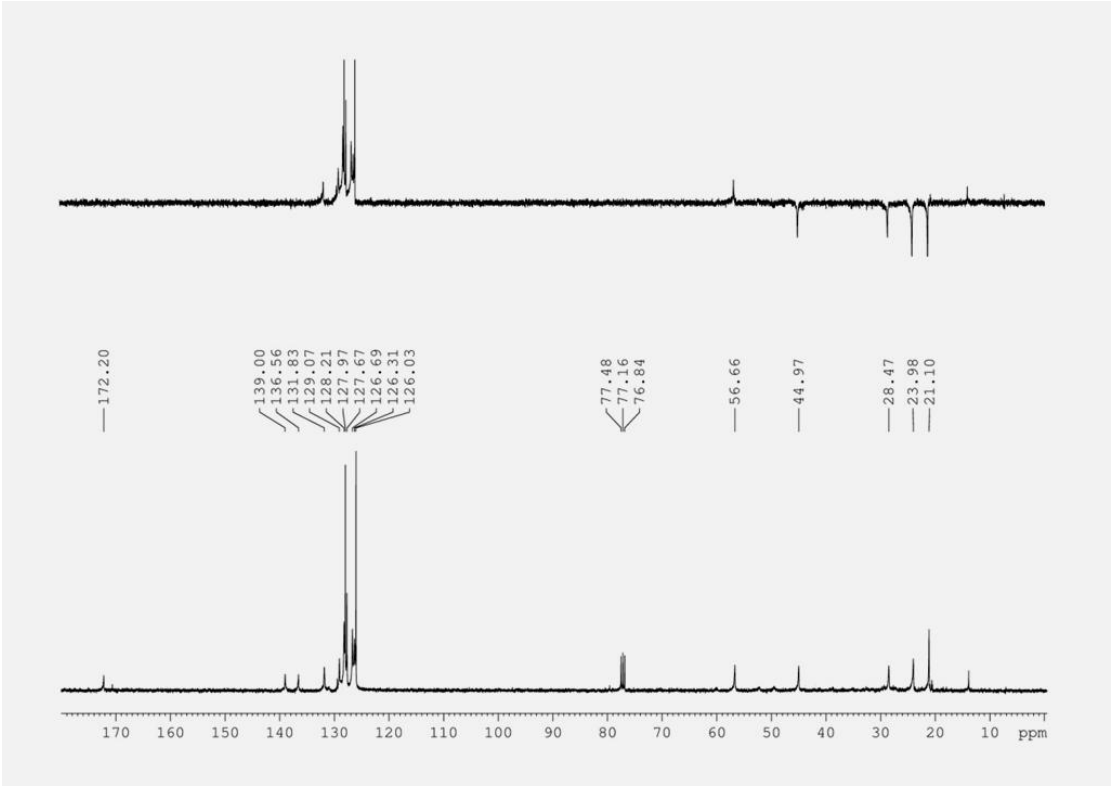
附圖四、化合物 1 之 IR 圖譜



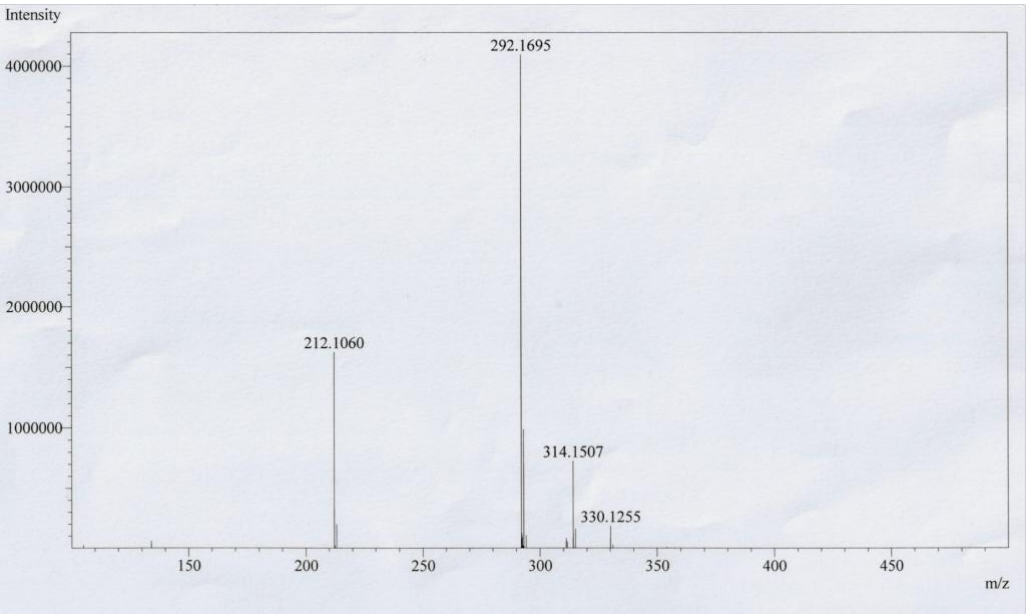
附圖五、化合物 2 之氫核磁共振圖譜($CDCl_3$, 200 MHz)



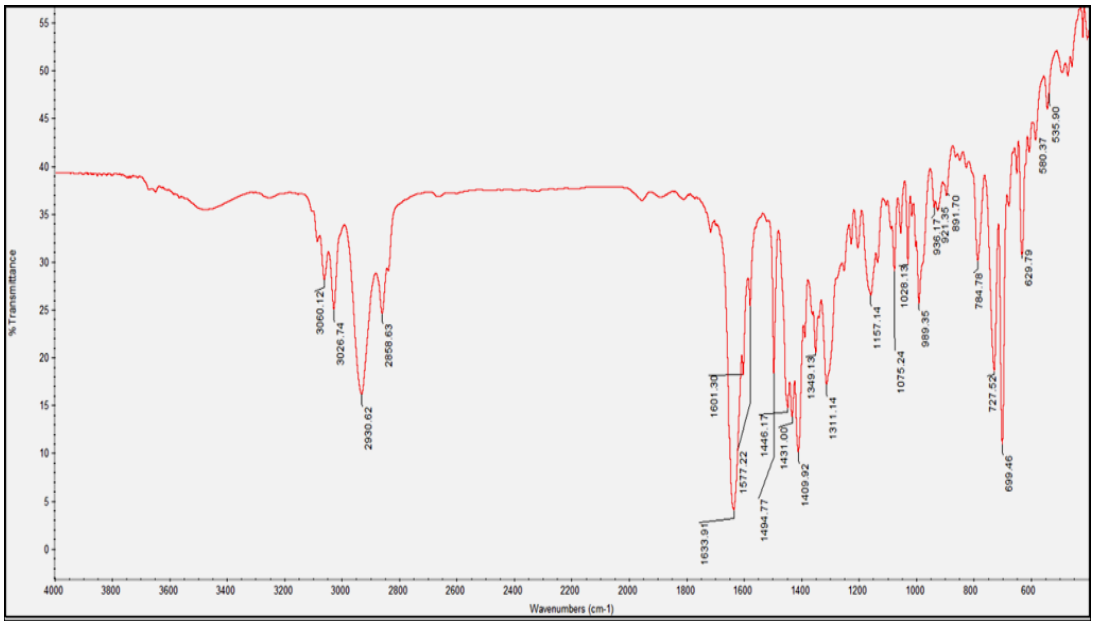
附圖六、化合物 2 之 ^{13}C 與 DEPT 135 核磁共振圖譜



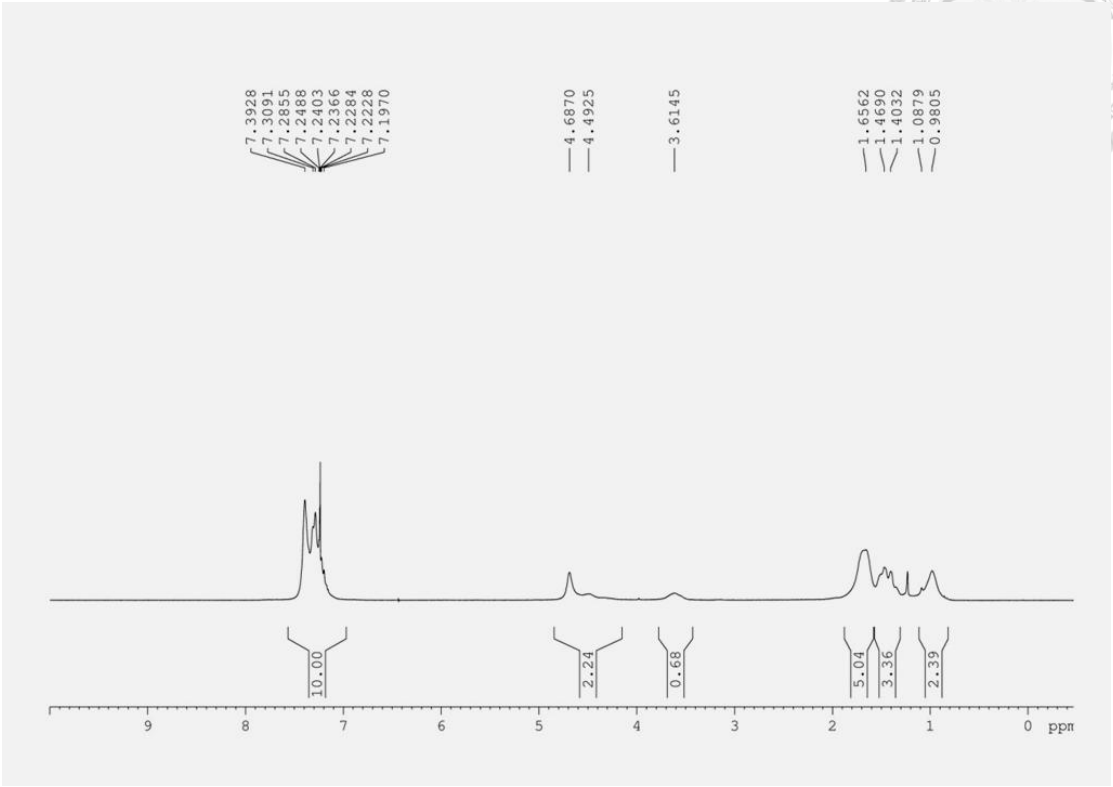
附圖七、化合物 2 之 HRESIMS 圖譜



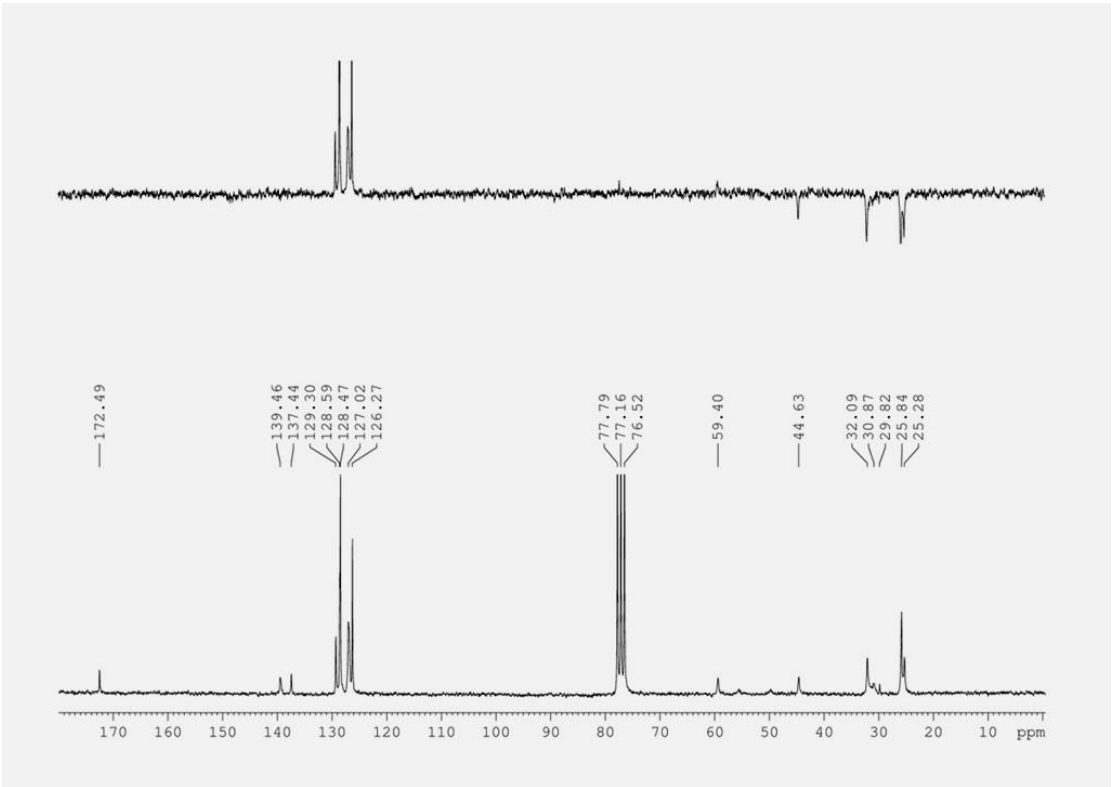
附圖八、化合物 2 之 IR 圖譜



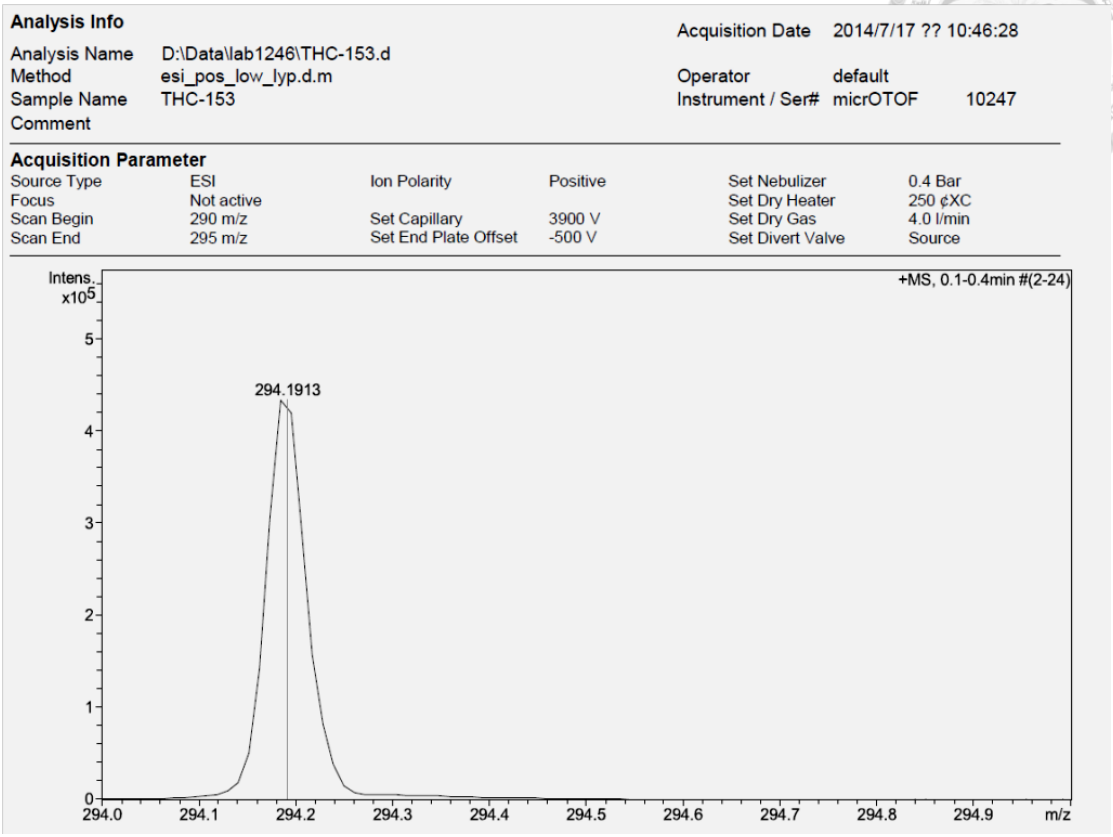
附圖九、化合物 3 之氫核磁共振圖譜($CDCl_3$, 200 MHz)



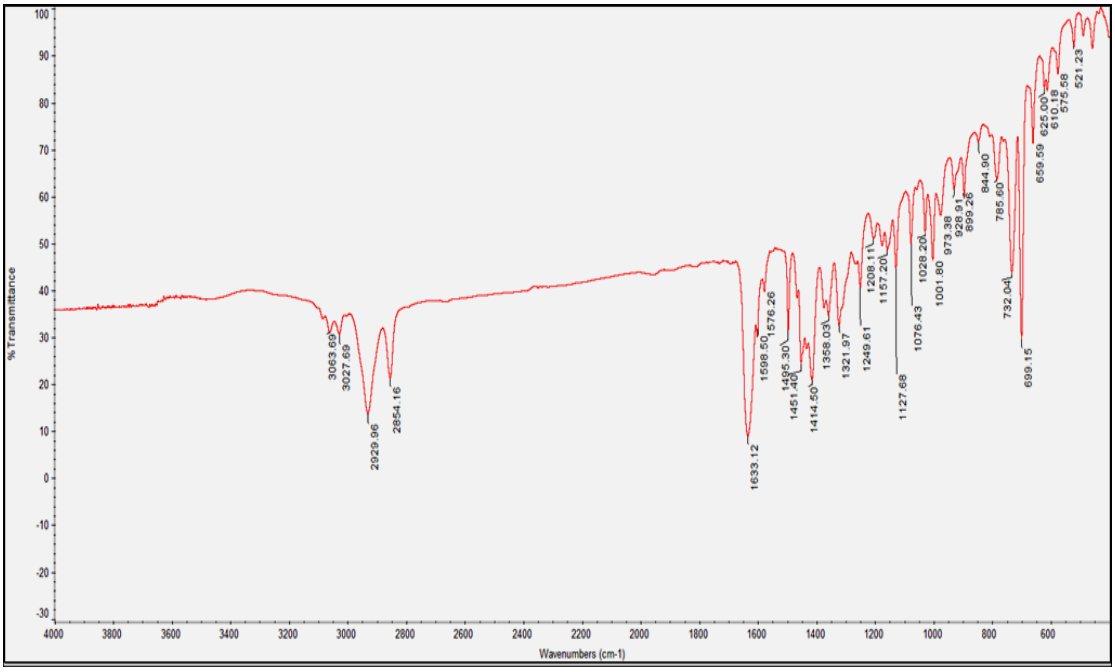
附圖十、化合物 3 之 ^{13}C 與 DEPT135 核磁共振圖譜



附圖十一、化合物 3 之 HRESIMS 圖譜



附圖十二、化合物 3 之 IR 圖譜



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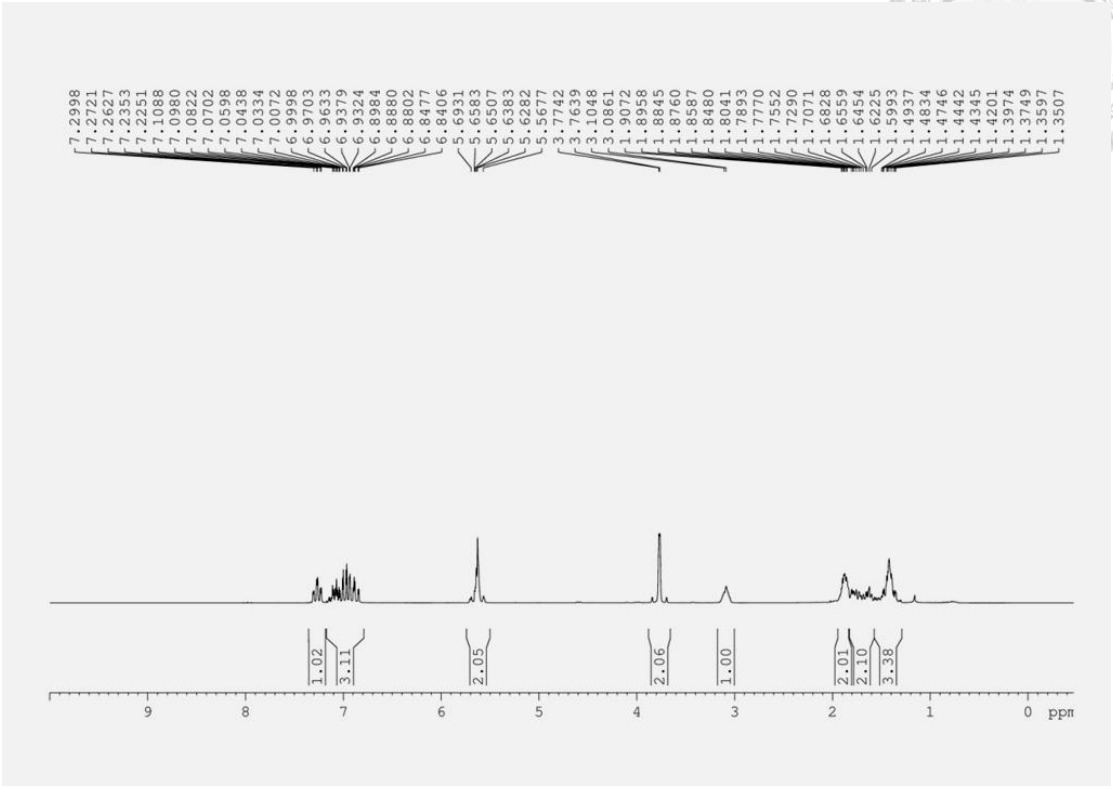
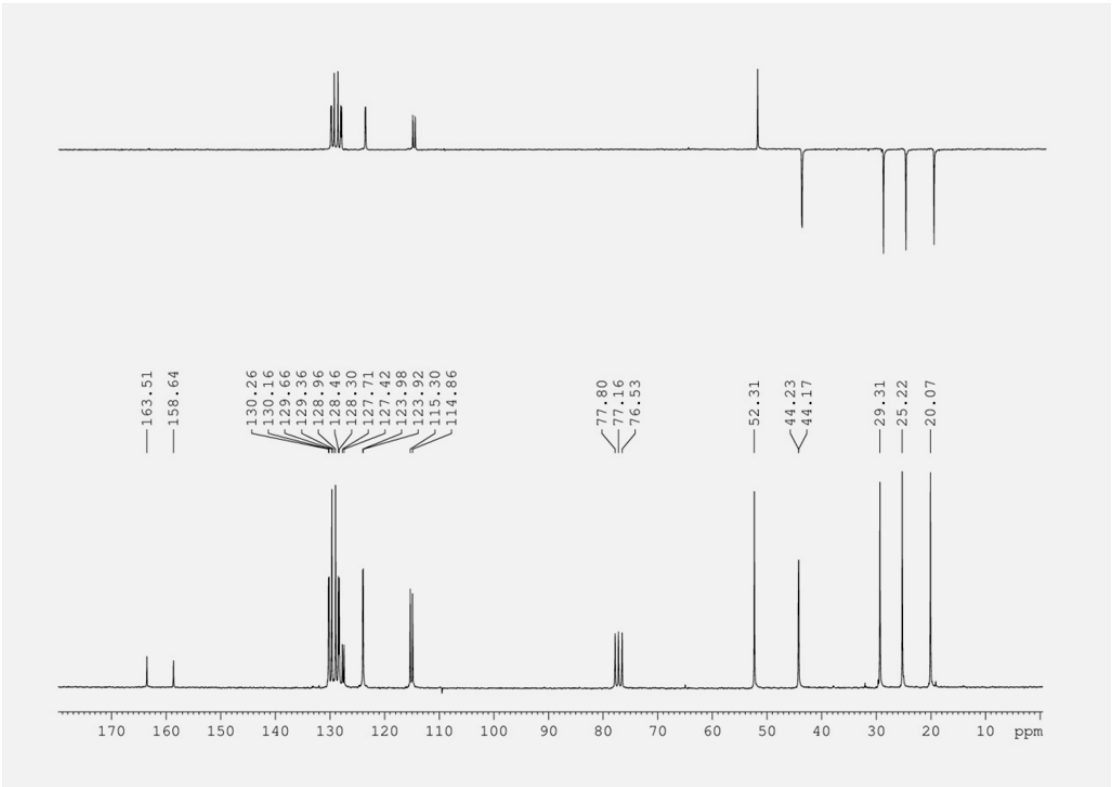
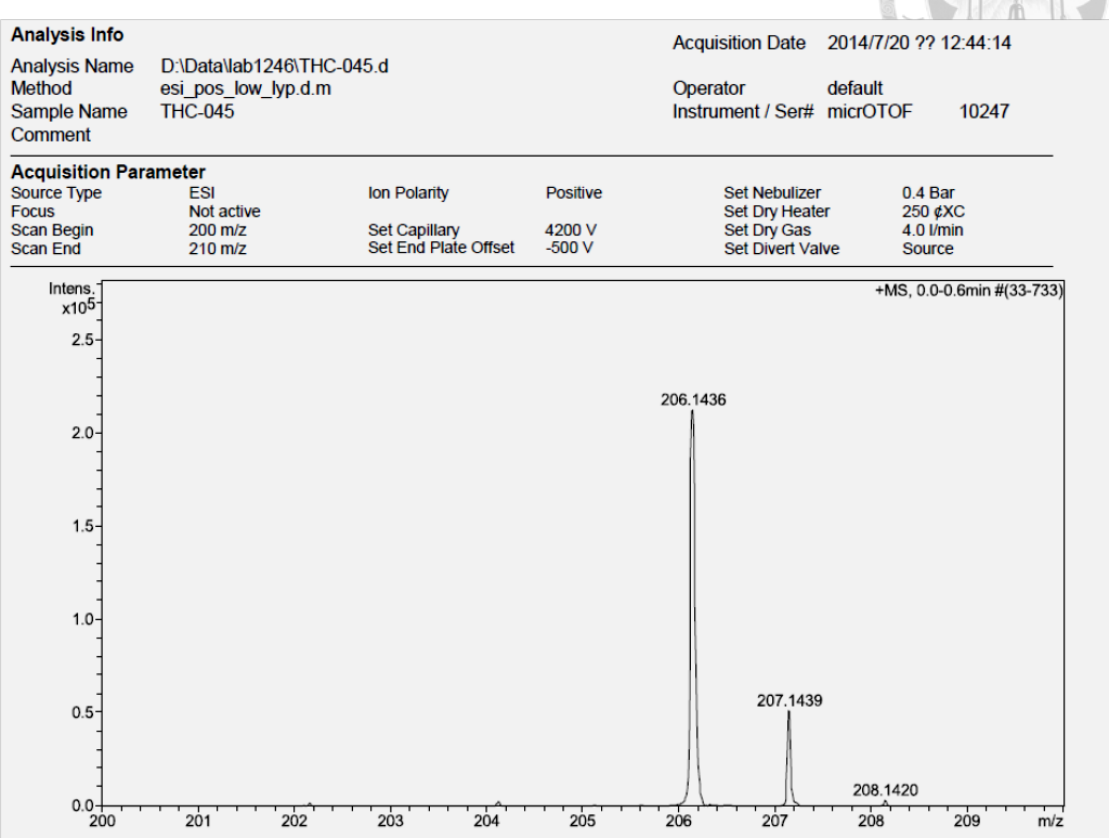


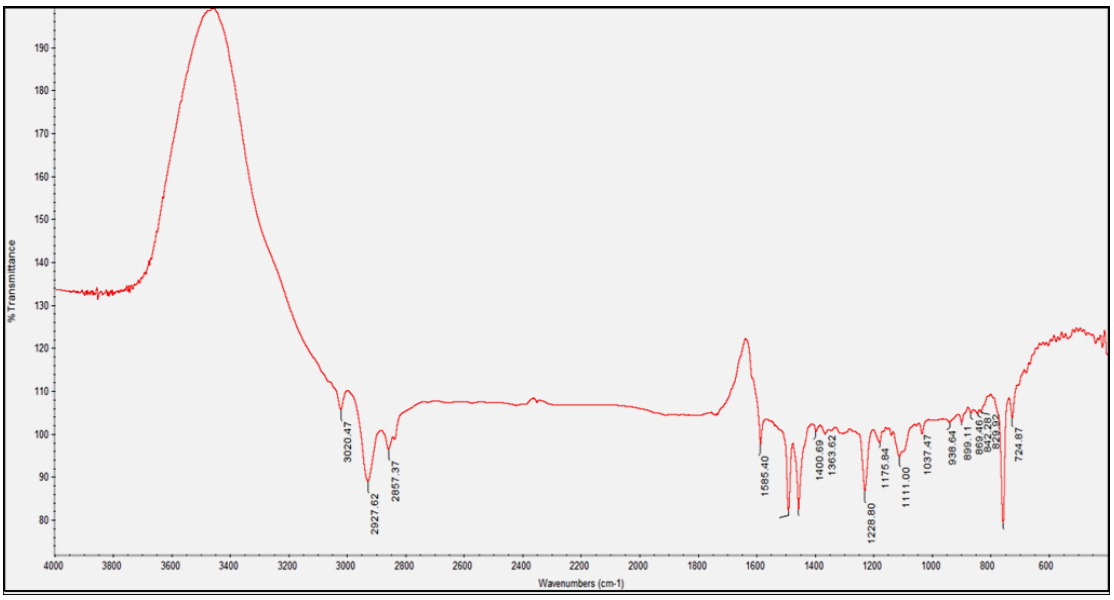
附圖十四、化合物 **4** 之 ^{13}C 與 DEPT135 核磁共振圖譜



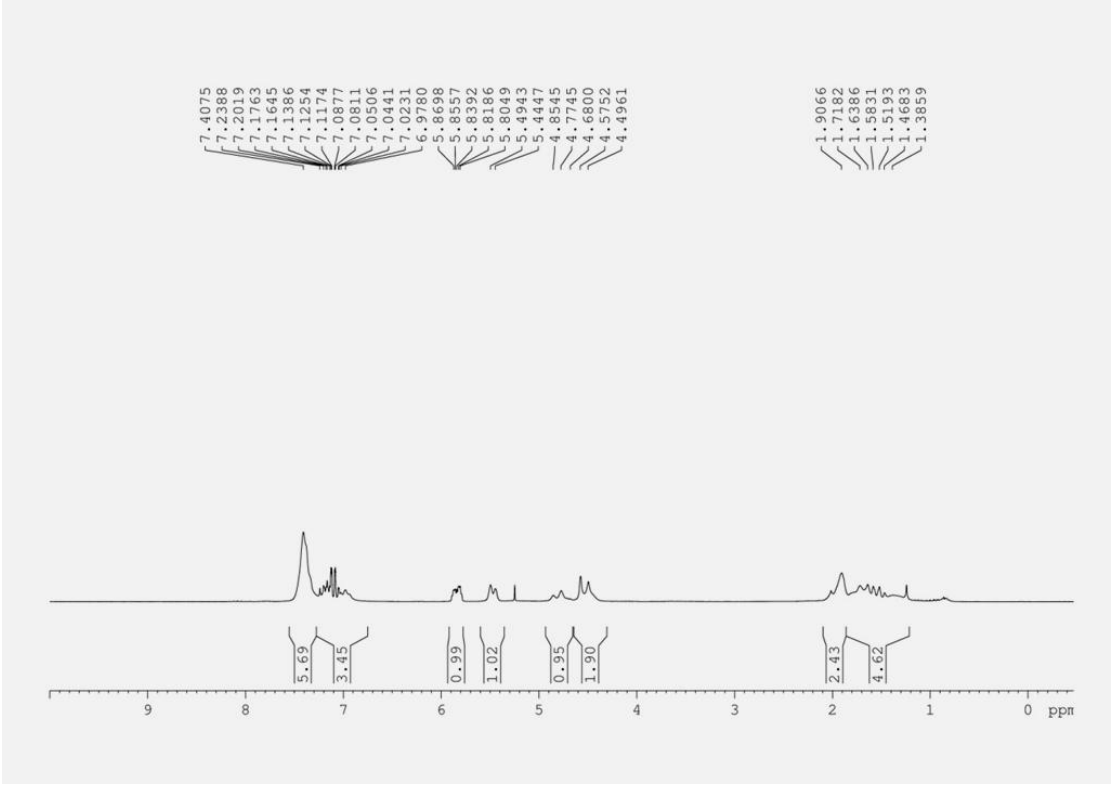
附圖十五、化合物 **4** 之 HRESIMS 圖譜



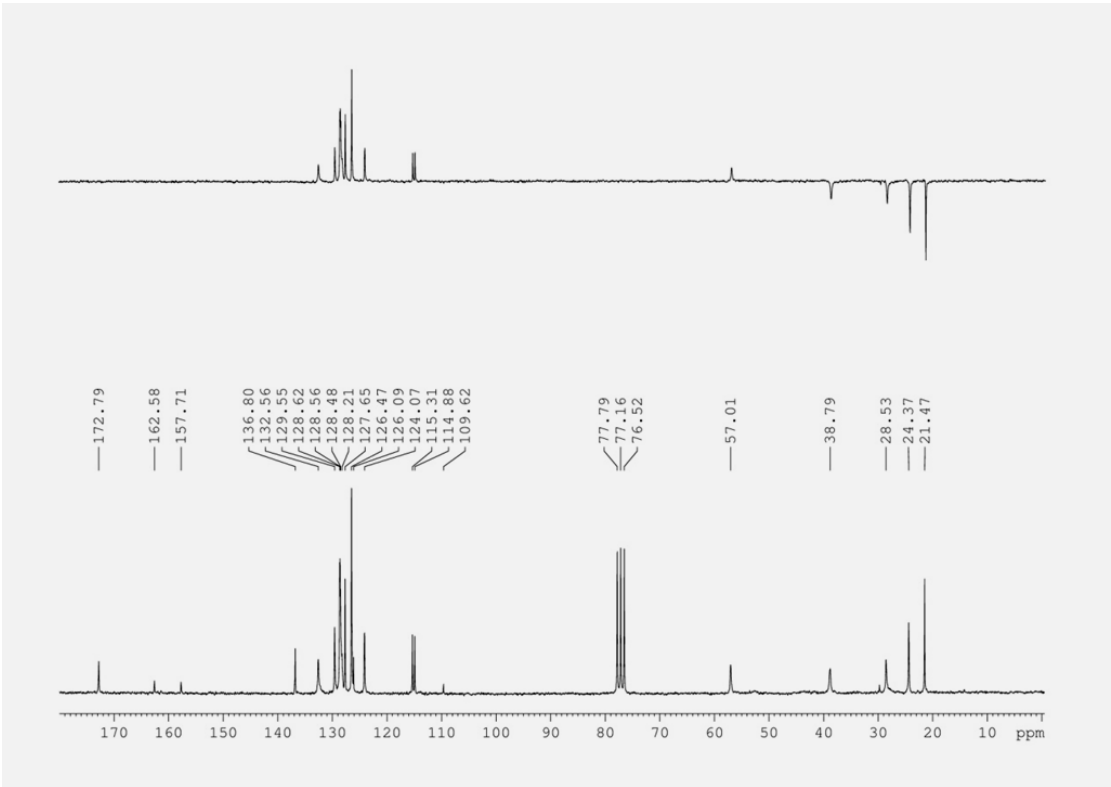
附圖十五、化合物 **4** 之 IR 圖譜



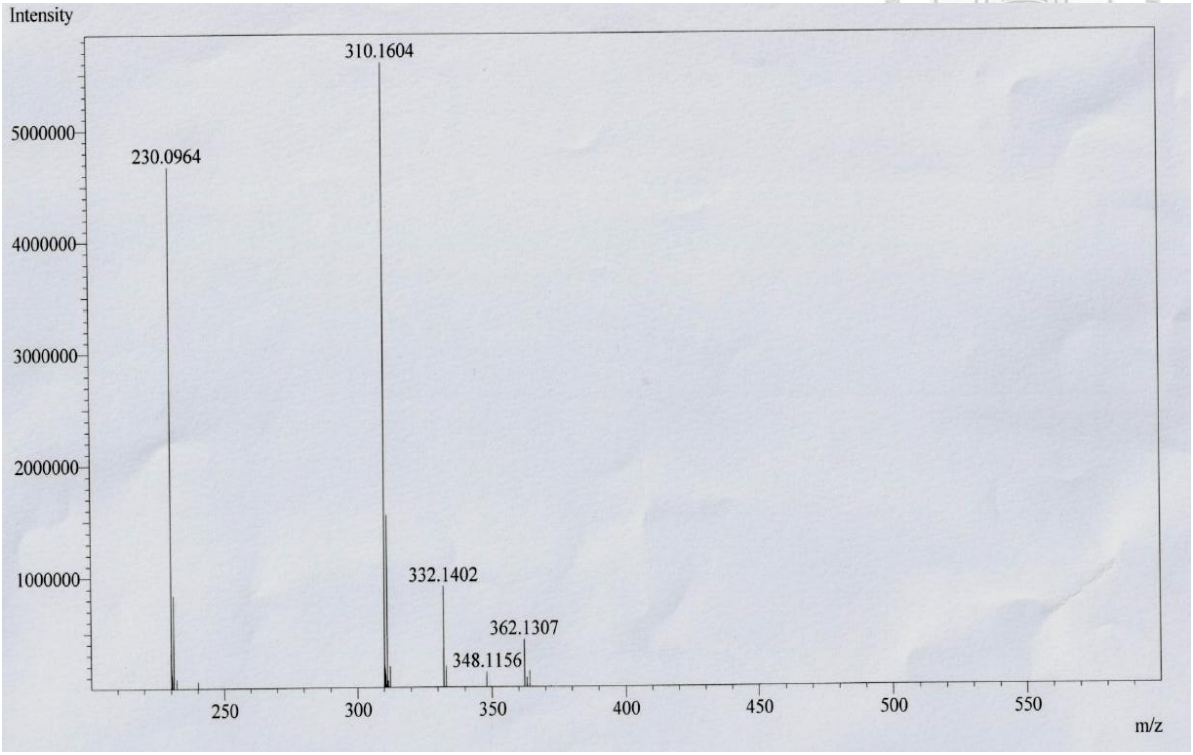
附圖十七、化合物 5 之氫核磁共振圖譜($CDCl_3$, 200MHz)



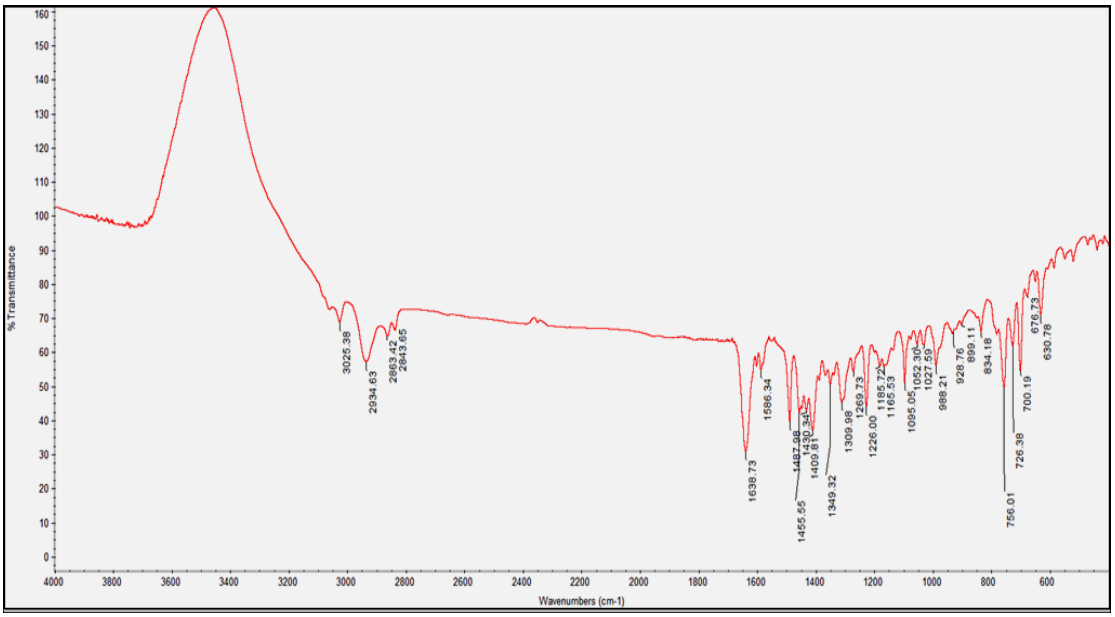
附圖十八、化合物 5 之 ^{13}C 與 DEPT135 核磁共振圖譜



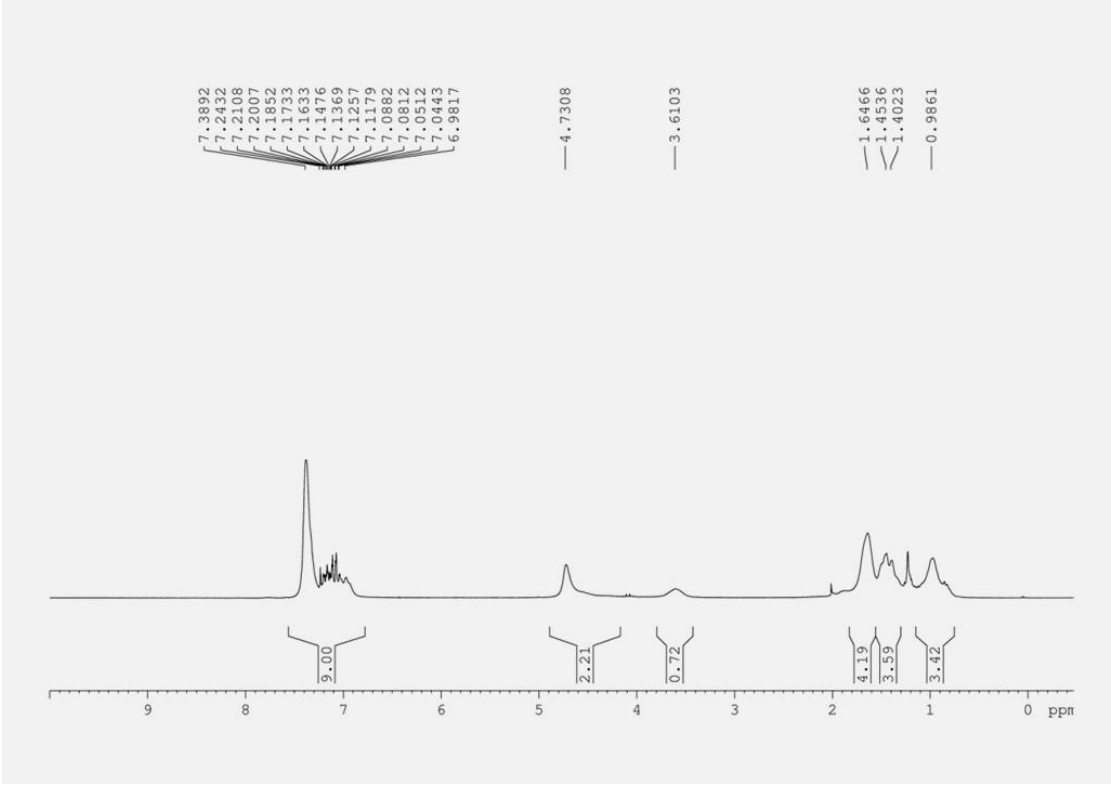
附圖十九、化合物 5 之 HRESIMS 圖譜



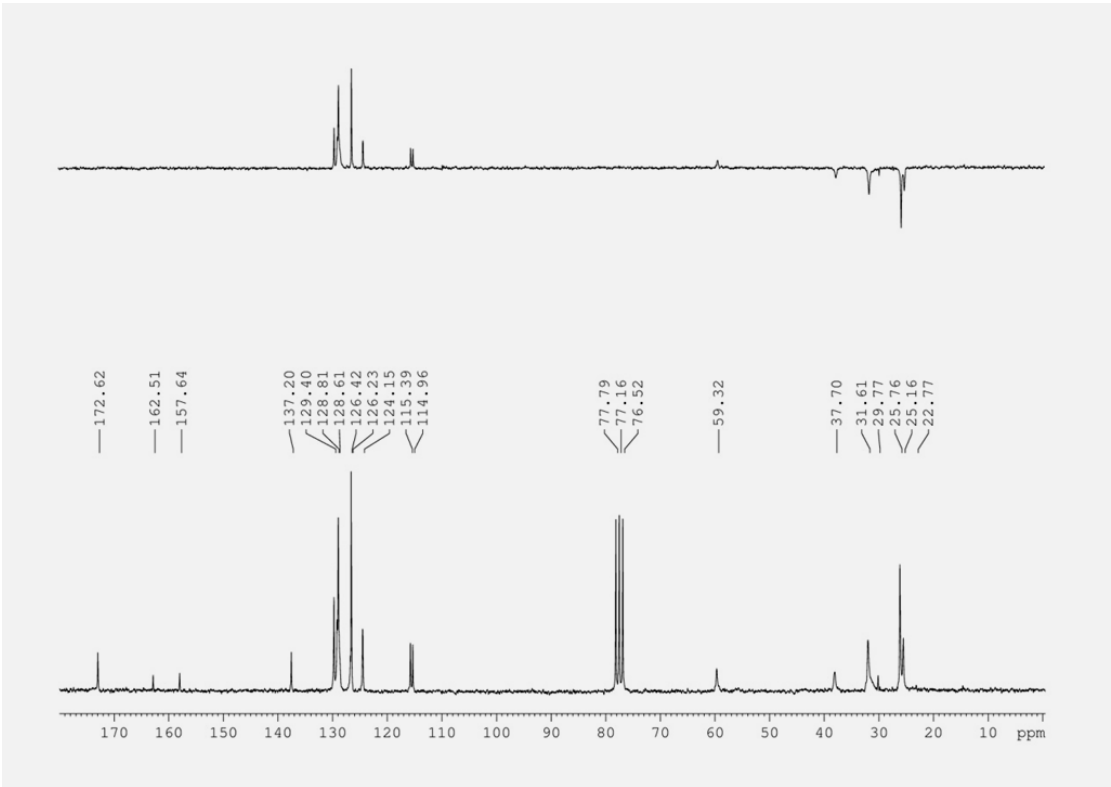
附圖二十、化合物 5 之 IR 圖譜



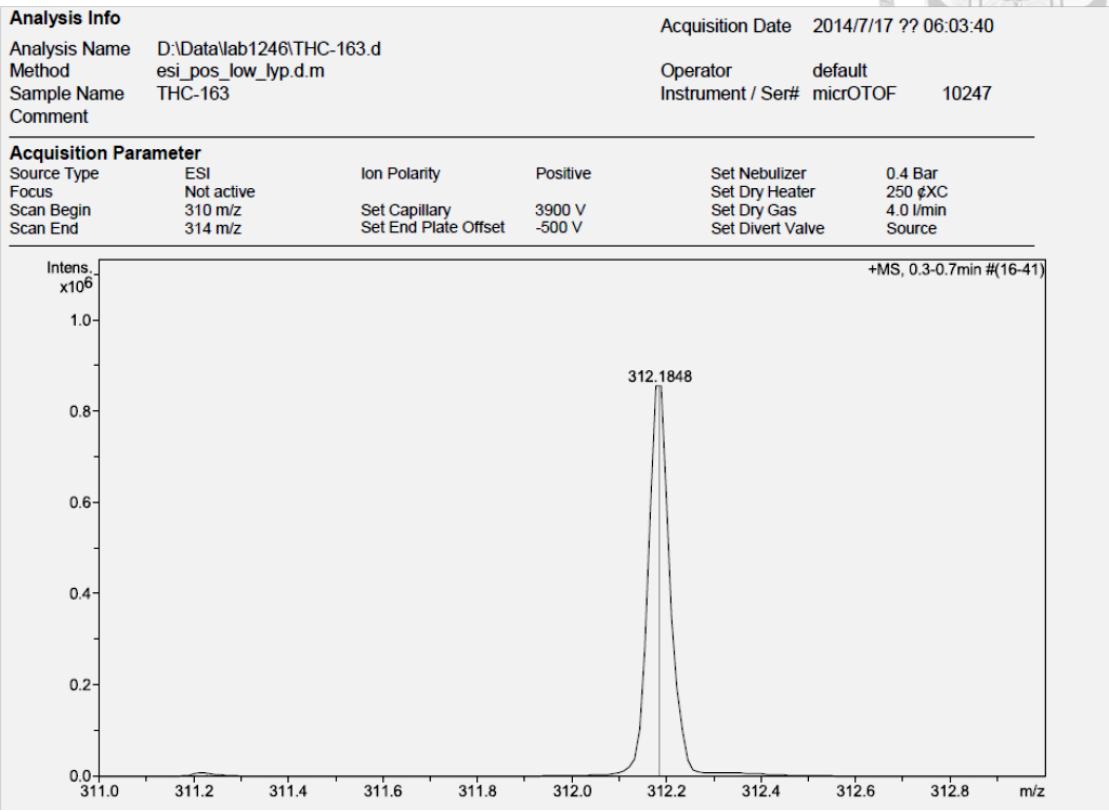
附圖二十一、化合物 **6** 之氫核磁共振圖譜($CDCl_3$, 200MHz)



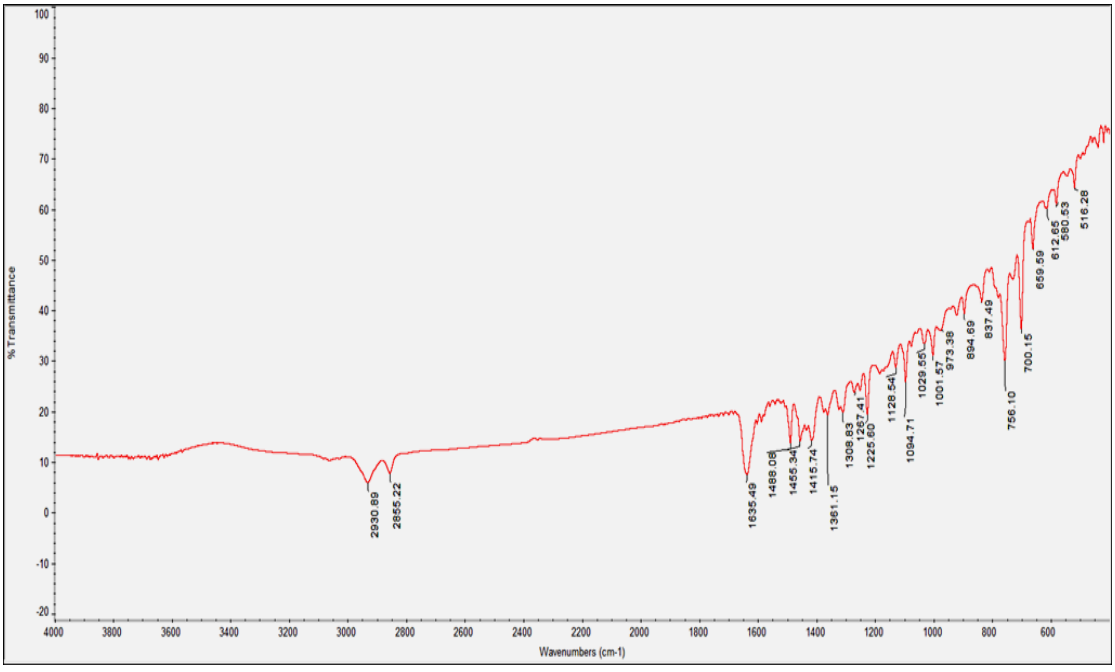
附圖二十二、化合物 **6** 之 ^{13}C 與 DEPT135 核磁共振圖譜



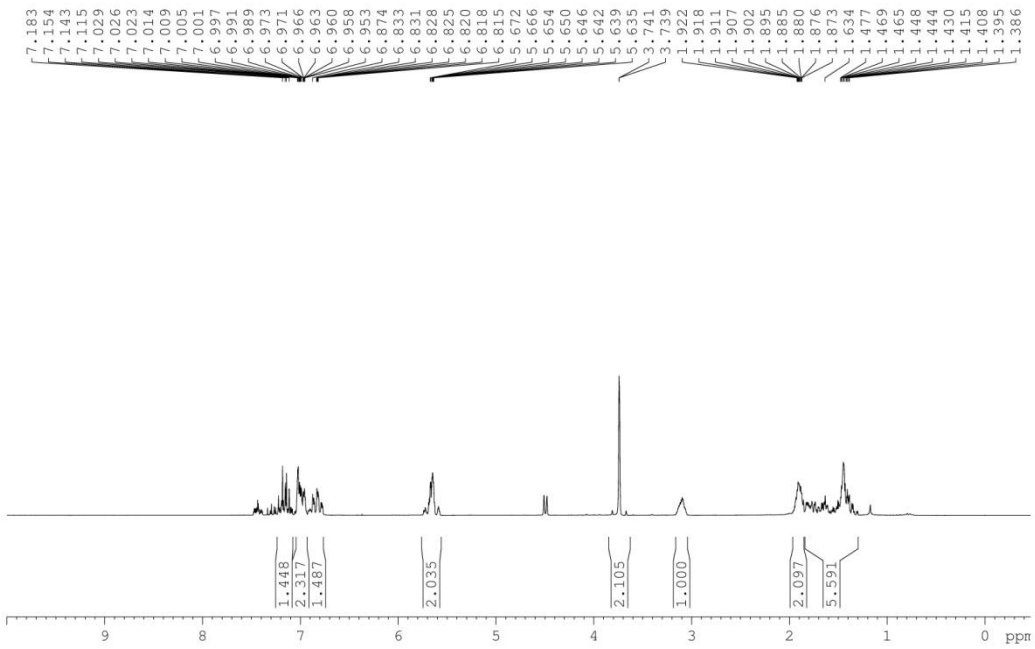
附圖二十三、化合物 6 之 HRESIMS 圖譜



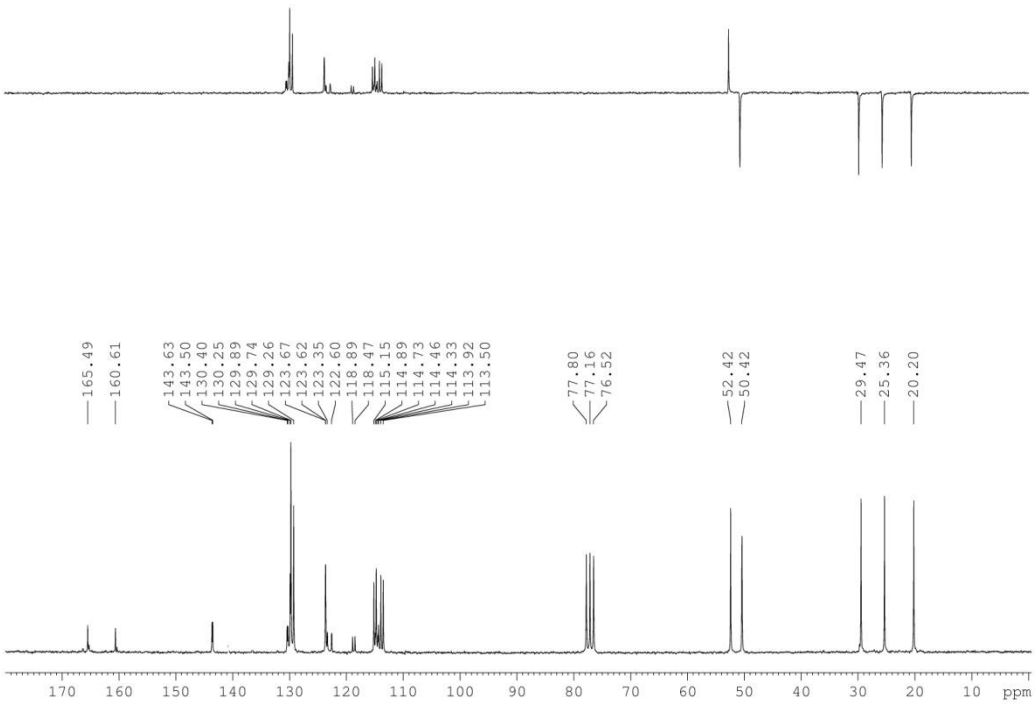
附圖二十四、化合物 6 之 IR 圖譜



附圖二十五、化合物 7 之氫核磁共振圖譜($CDCl_3$, 200MHz)



附圖二十六、化合物 7 之 ^{13}C 與 DEPT135 核磁共振圖譜



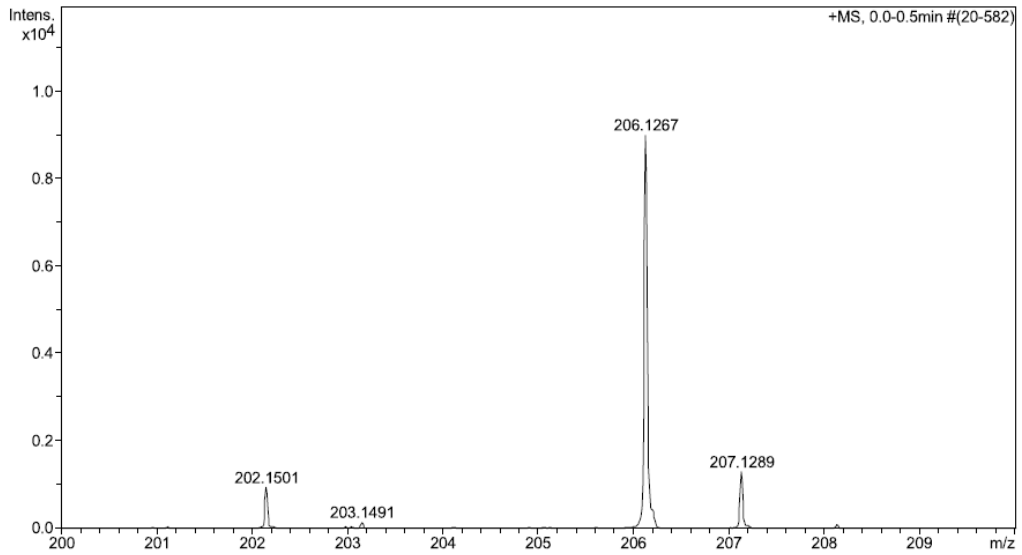
附圖二十七、化合物 7 之 HRESIMS 圖譜

Analysis Info

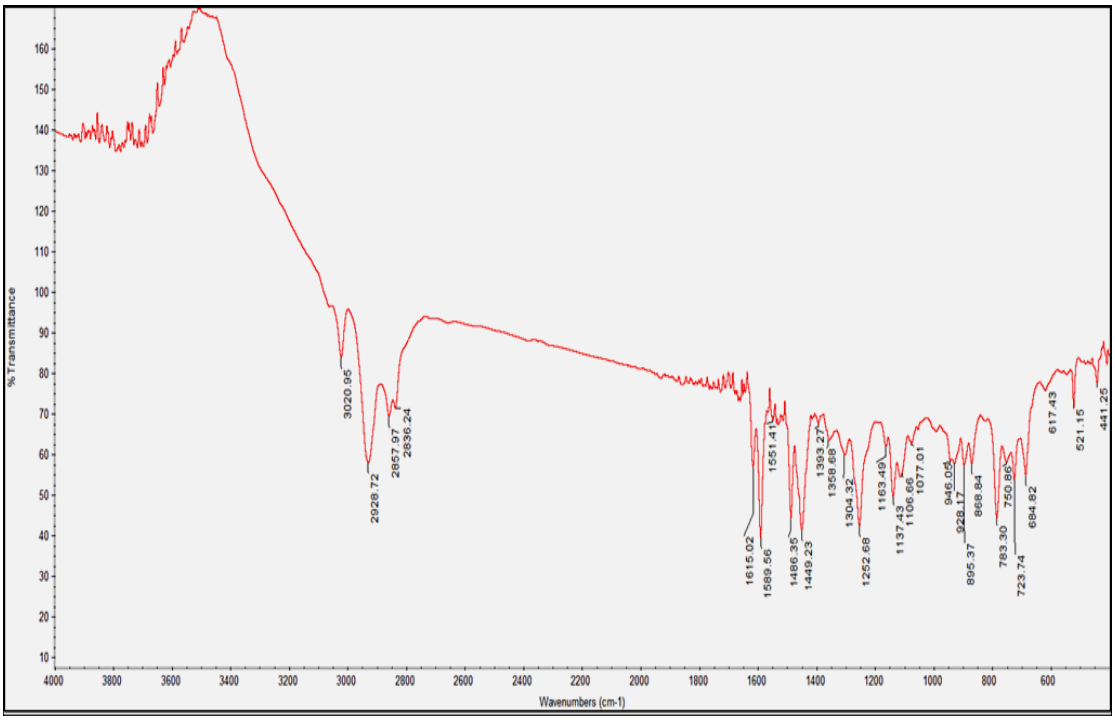
Analysis Name	D:\Data\lab1246\THC-041-02.d	Acquisition Date	2014/7/19 ?? 10:39:33
Method	esi_pos_low_lyp.d.m	Operator	default
Sample Name	THC-041-02	Instrument / Ser#	micrOTOF 10247
Comment			

Acquisition Parameter

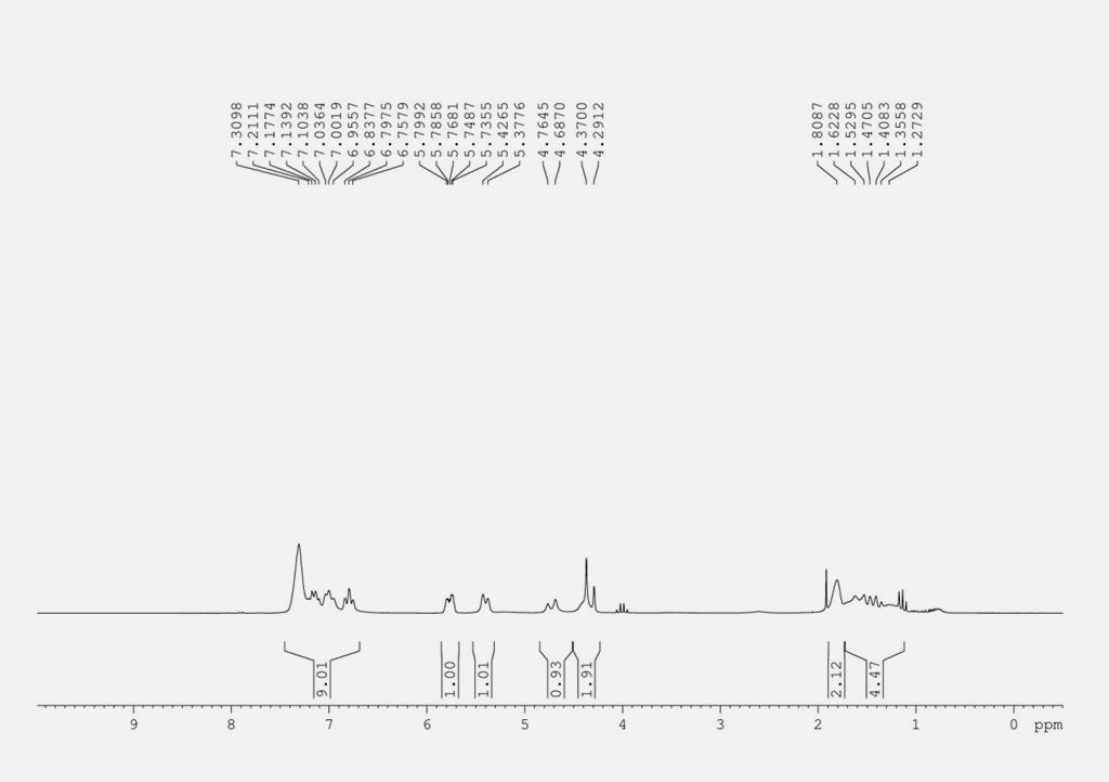
Source Type	ESI	Ion Polarity	Positive	Set Nebulizer	0.4 Bar
Focus	Not active			Set Dry Heater	250 ¢XC
Scan Begin	200 m/z	Set Capillary	4200 V	Set Dry Gas	4.0 l/min
Scan End	210 m/z	Set End Plate Offset	-500 V	Set Divert Valve	Source



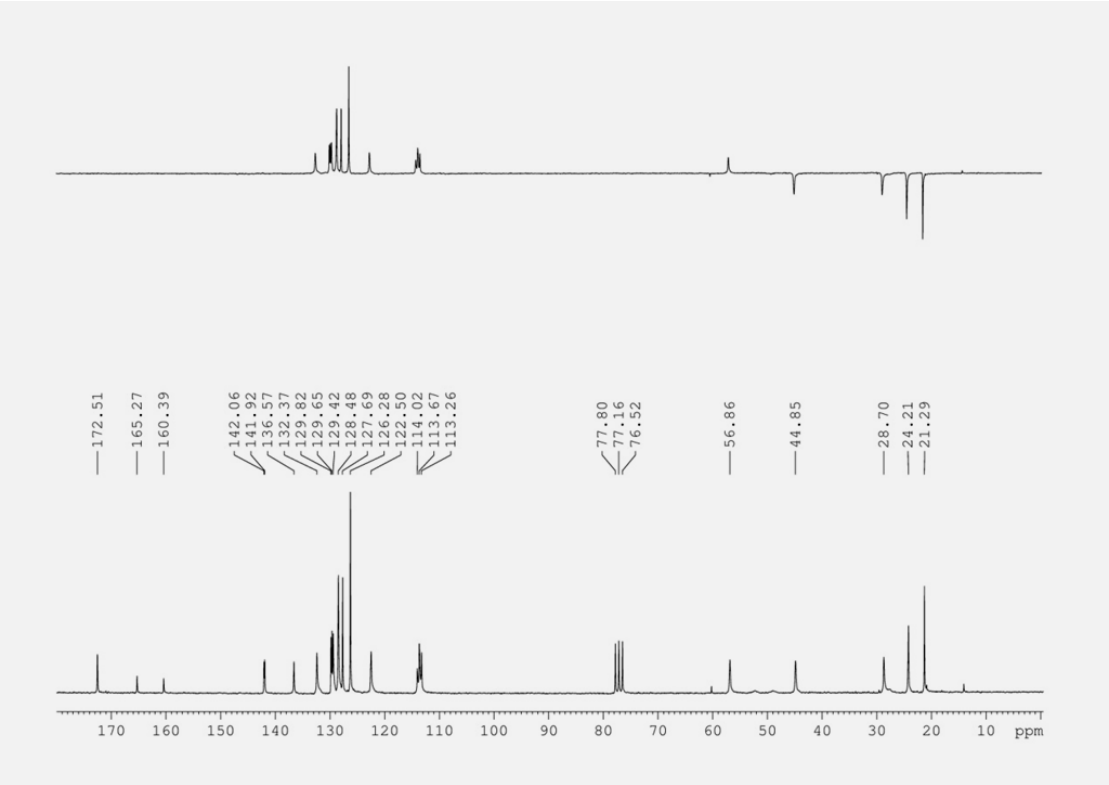
附圖二十八、化合物 7 之 IR 圖譜



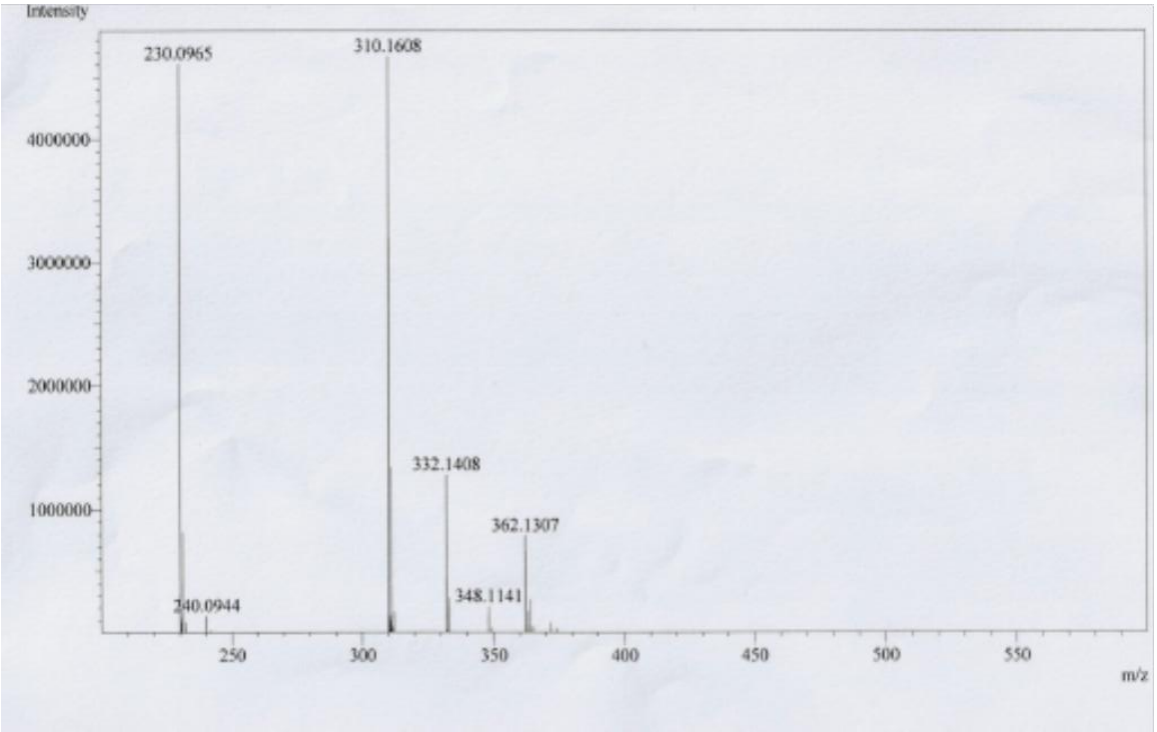
附圖二十九、化合物 **8** 之氫核磁共振圖譜($CDCl_3$, 200 MHz)



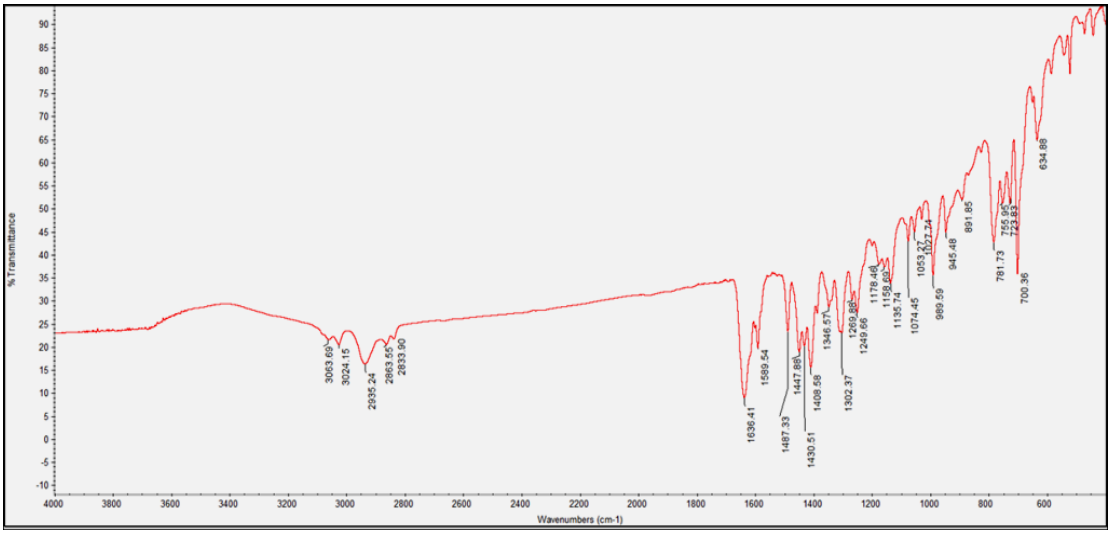
附圖三十、化合物 8 之 ^{13}C 與 DEPT135 核磁共振圖譜



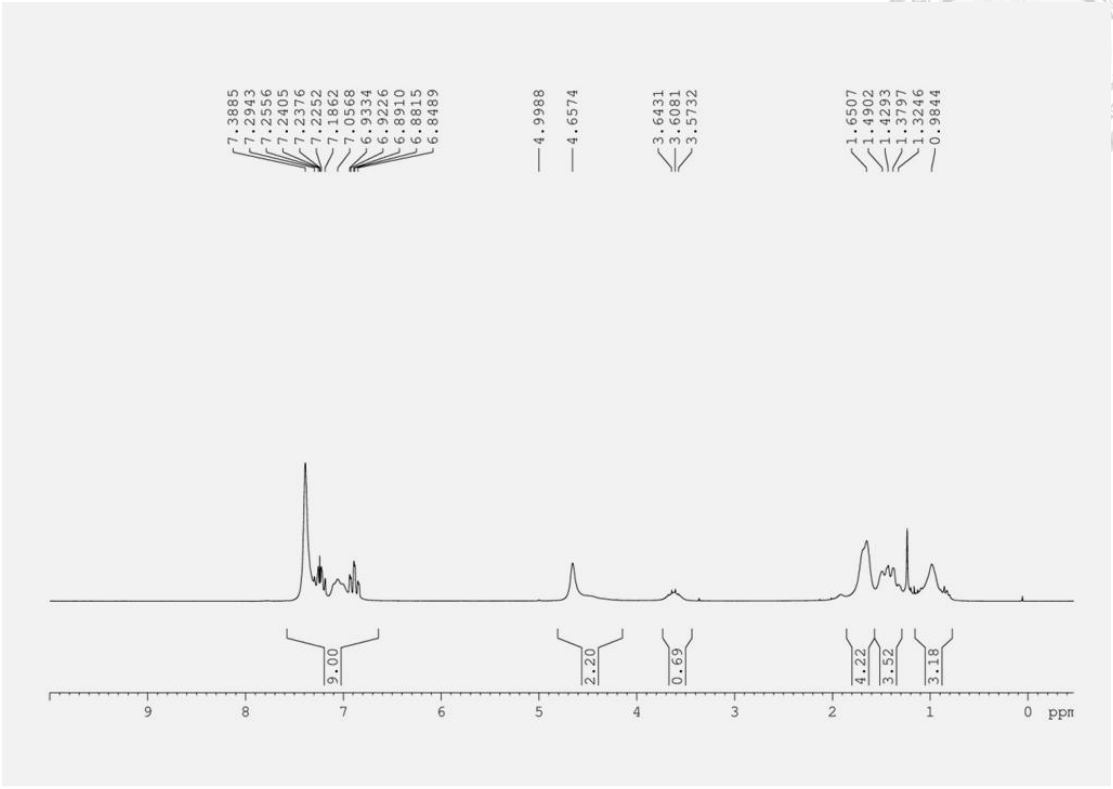
附圖三十一、化合物 8 之 HRESIMS 圖譜



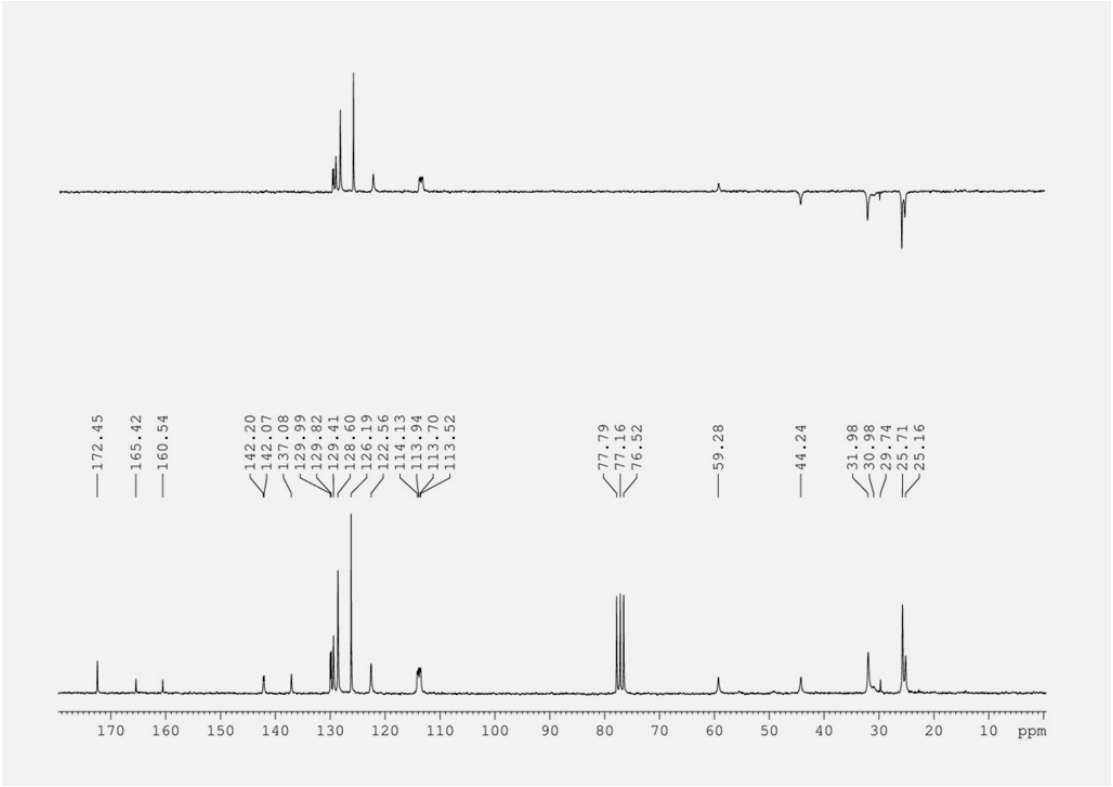
附圖三十二、化合物 8 之圖譜



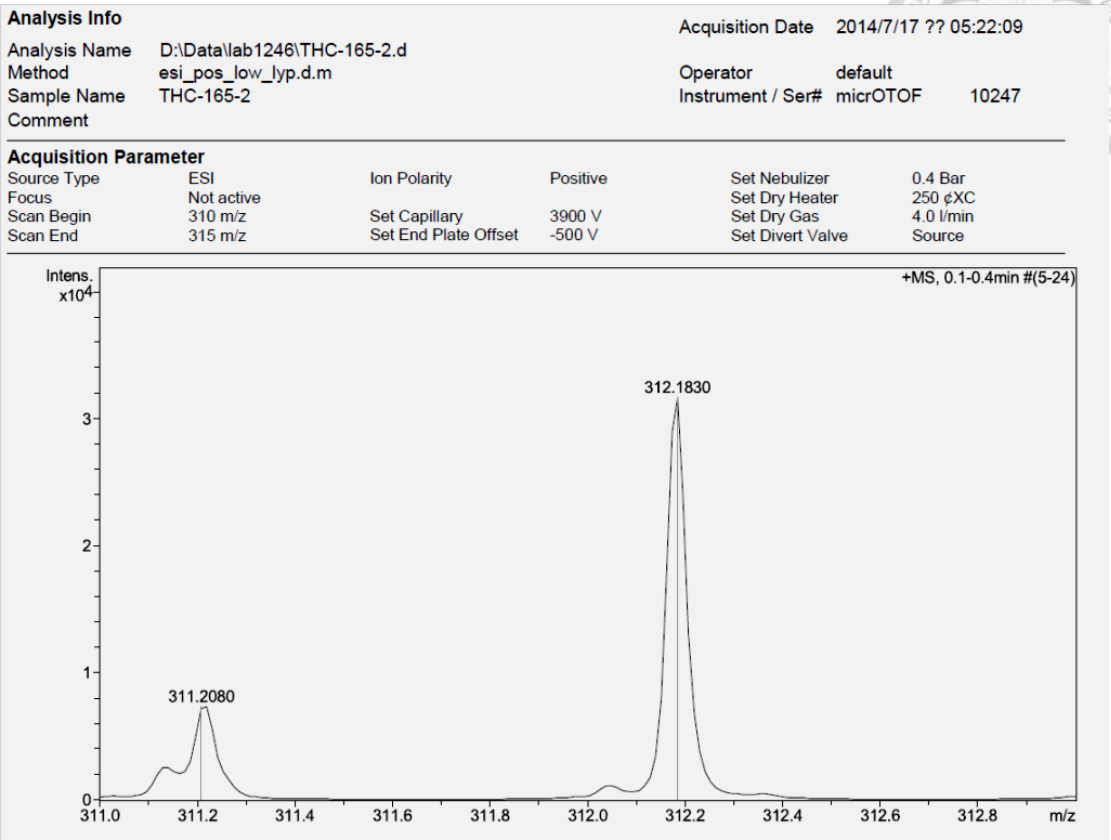
附圖三十三、化合物 **9** 之氫核磁共振圖譜($CDCl_3$, 200 MHz)



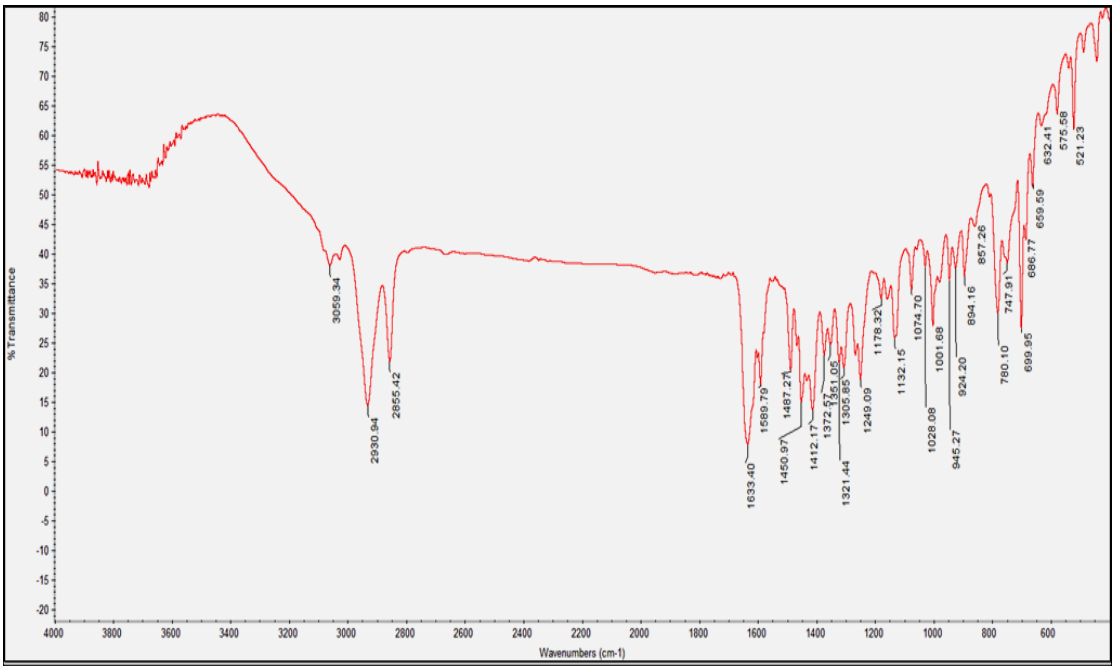
附圖三十四、化合物 **9** 之 ^{13}C 與 DEPT135 核磁共振圖譜



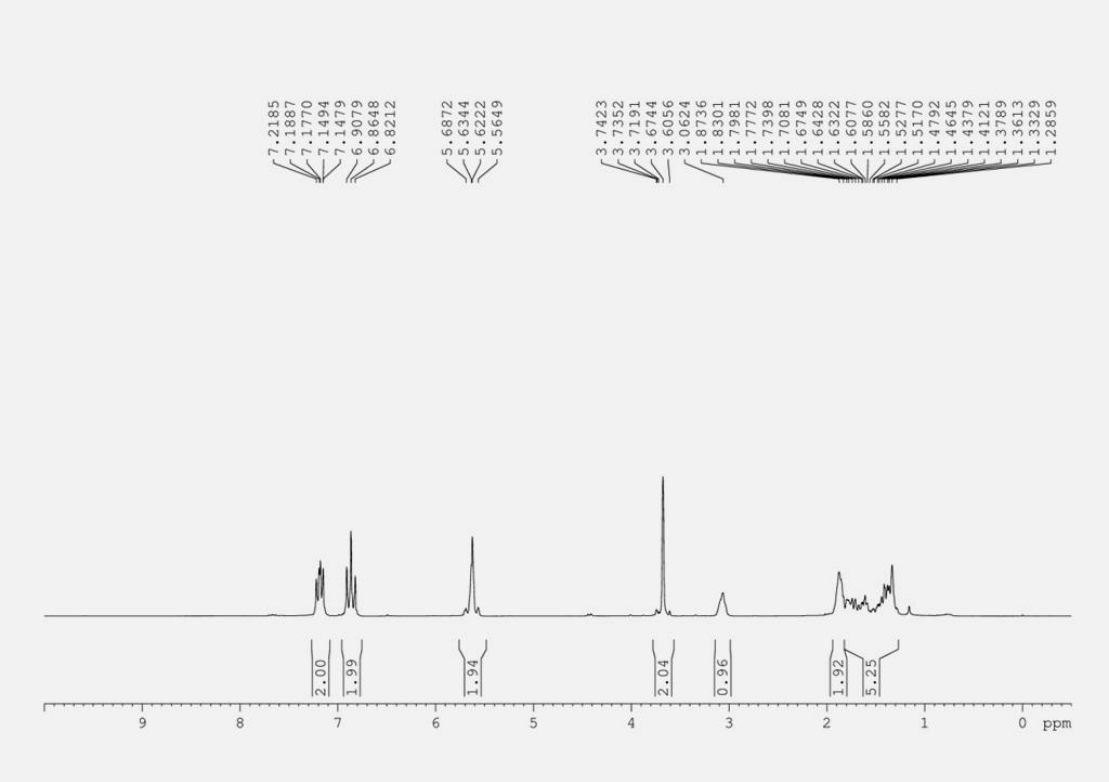
附圖三十五、化合物 9 之 HRESIMS 圖譜



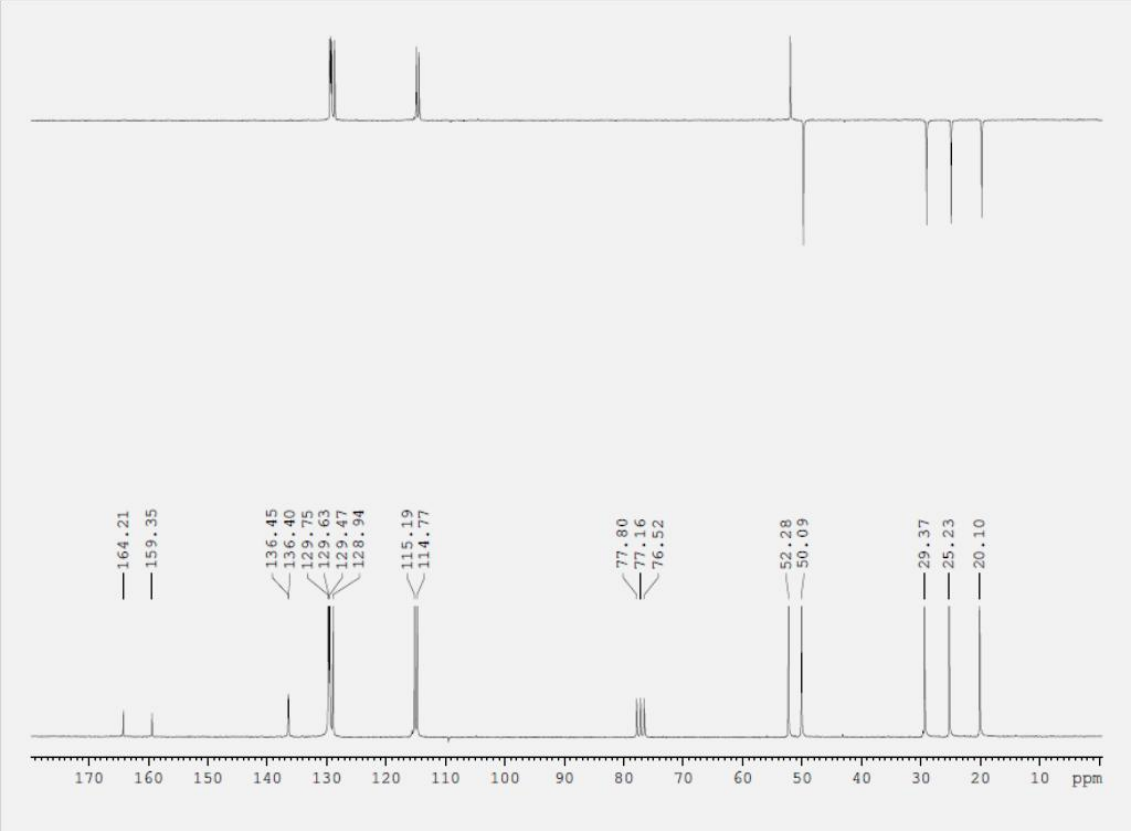
附圖三十五、化合物 9 之 IR 圖譜



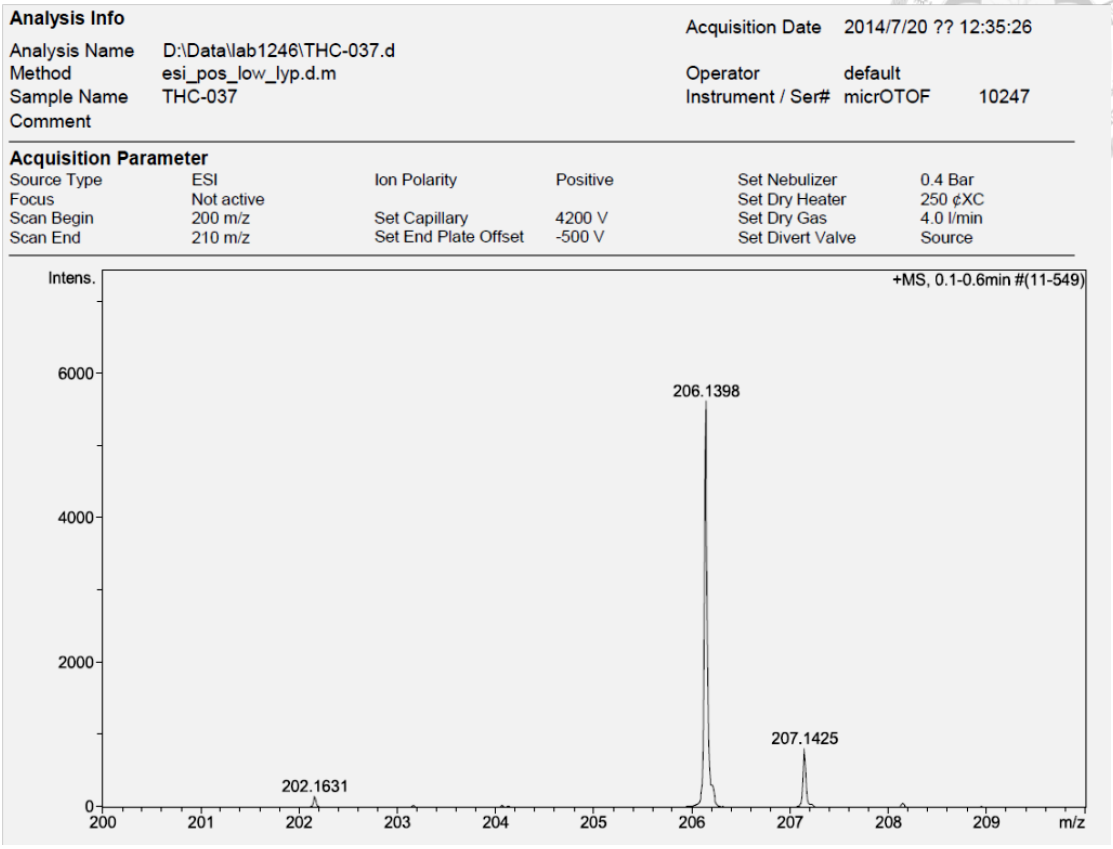
附圖三十七、化合物 10 氫核磁共振圖譜($CDCl_3$, 200 MHz)



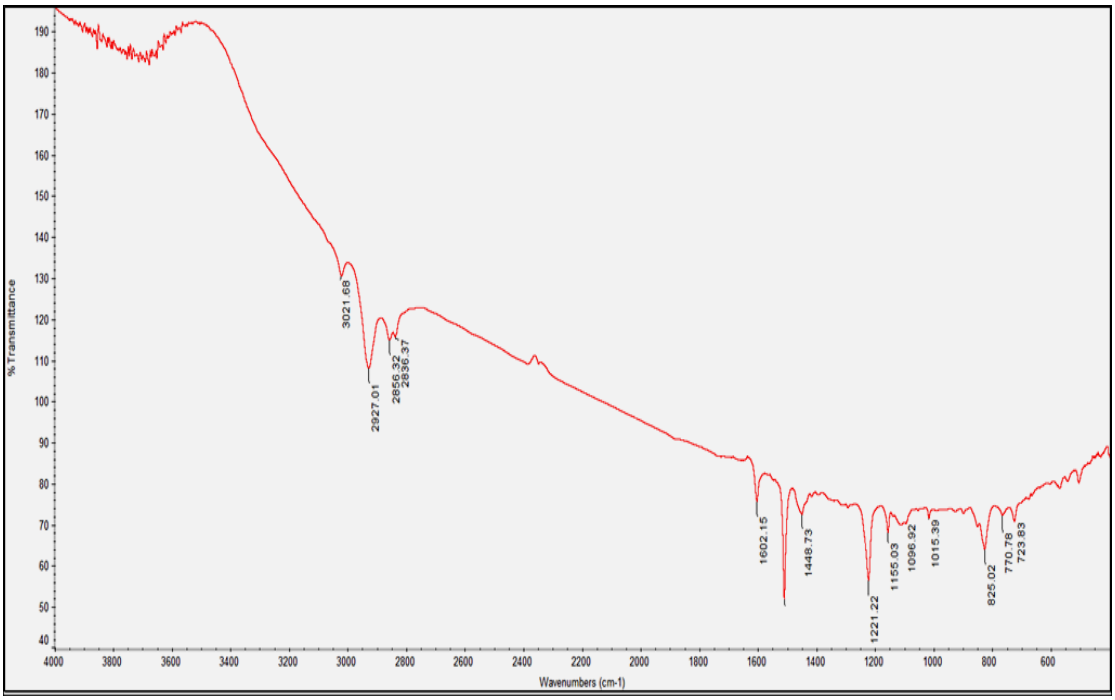
附圖三十八、化合物 10 之 ^{13}C 與 DEPT135 核磁共振圖譜



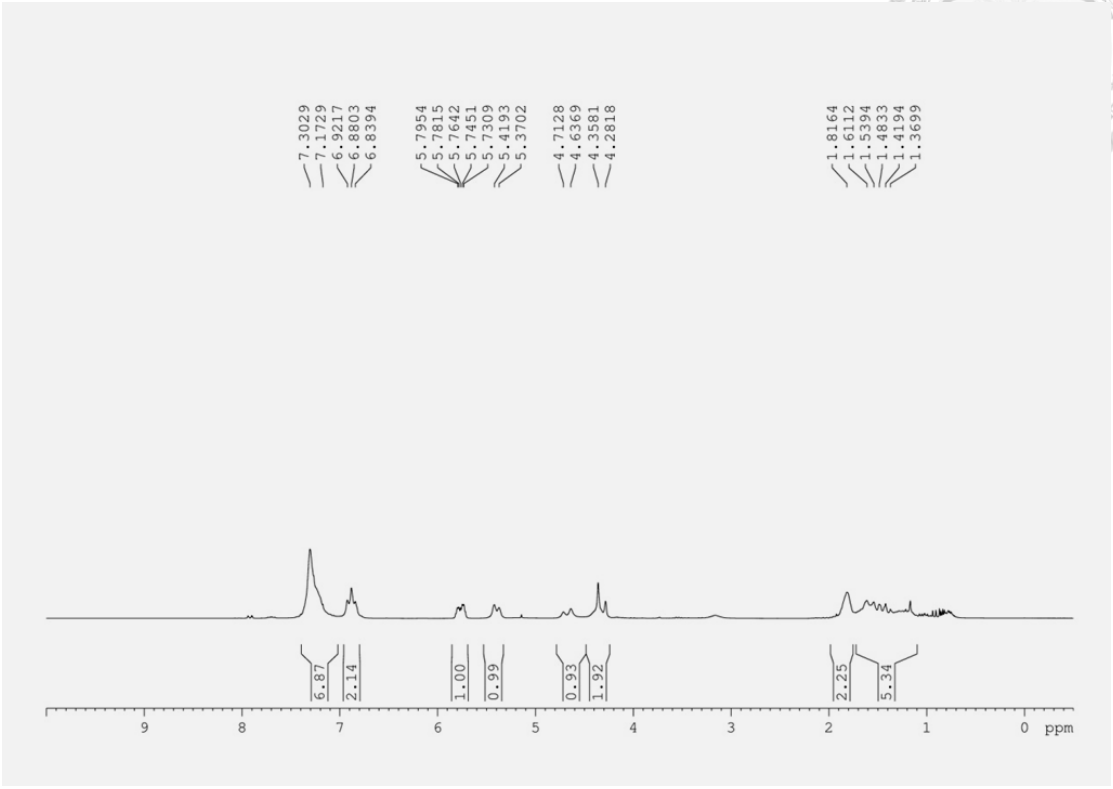
附圖三十九、化合物 10 之 HRESIMS 圖譜



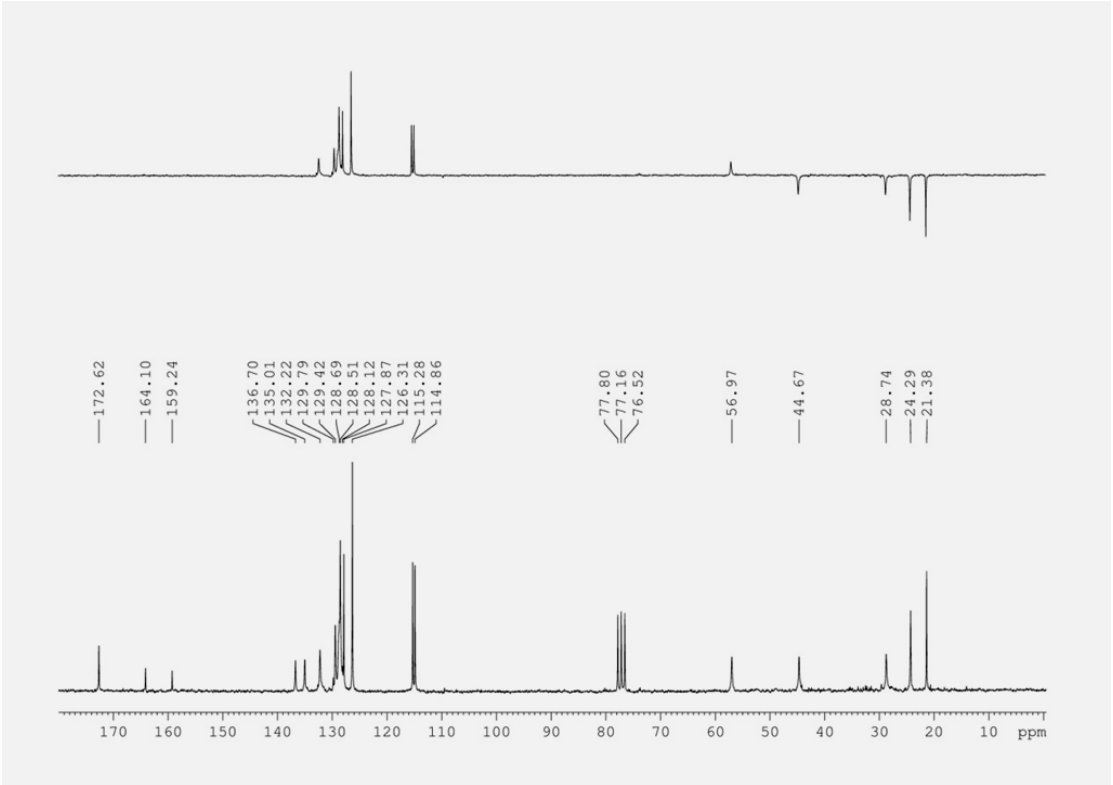
附圖四十、化合物 10 之 IR 圖譜



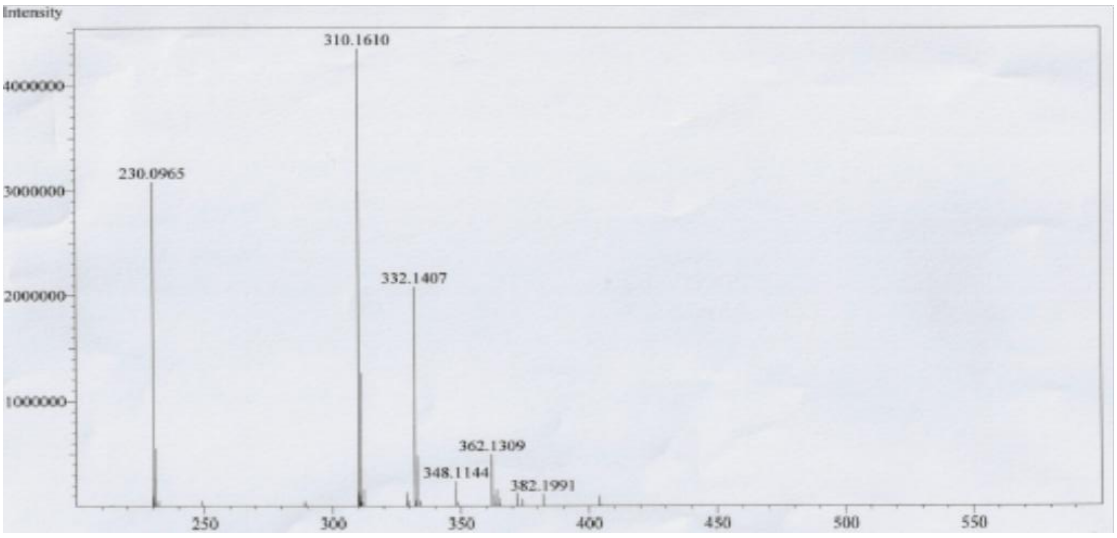
附圖四十一、化合物 11 之氫核磁共振圖譜($CDCl_3$, 200 MHz)



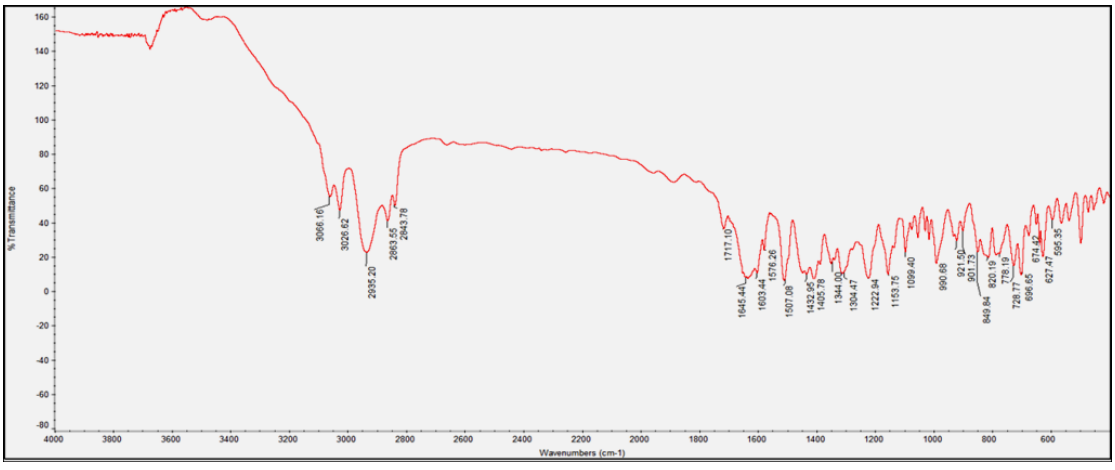
附圖四十二、化合物 11 之 ^{13}C 與 DEPT135 核磁共振圖譜



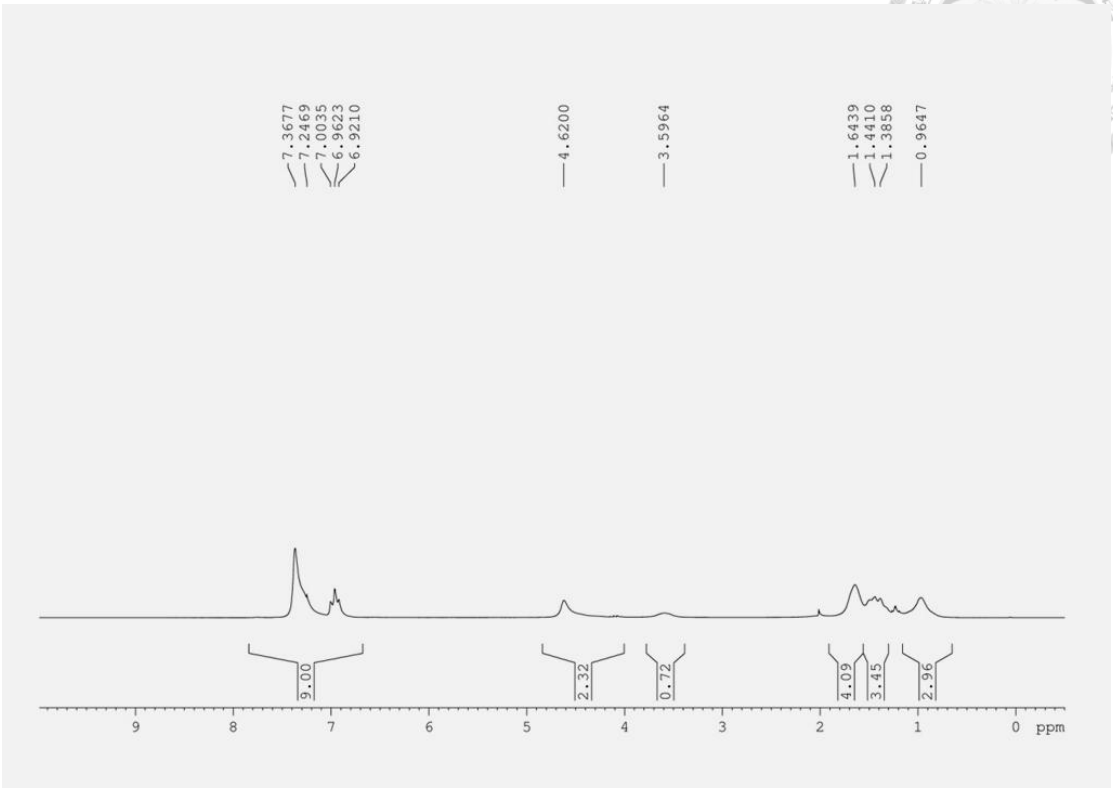
附圖四十三、化合物 11 之 HRESIMS 圖譜



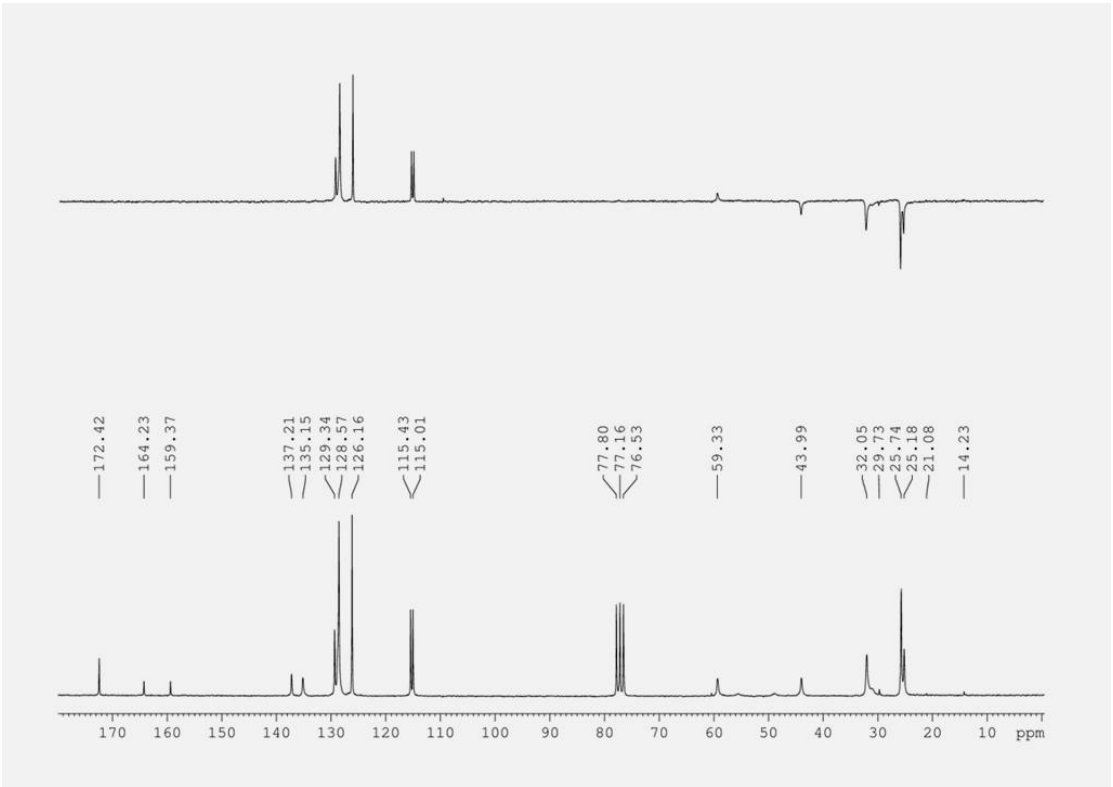
附圖四十四、化合物 11 之 IR 圖譜



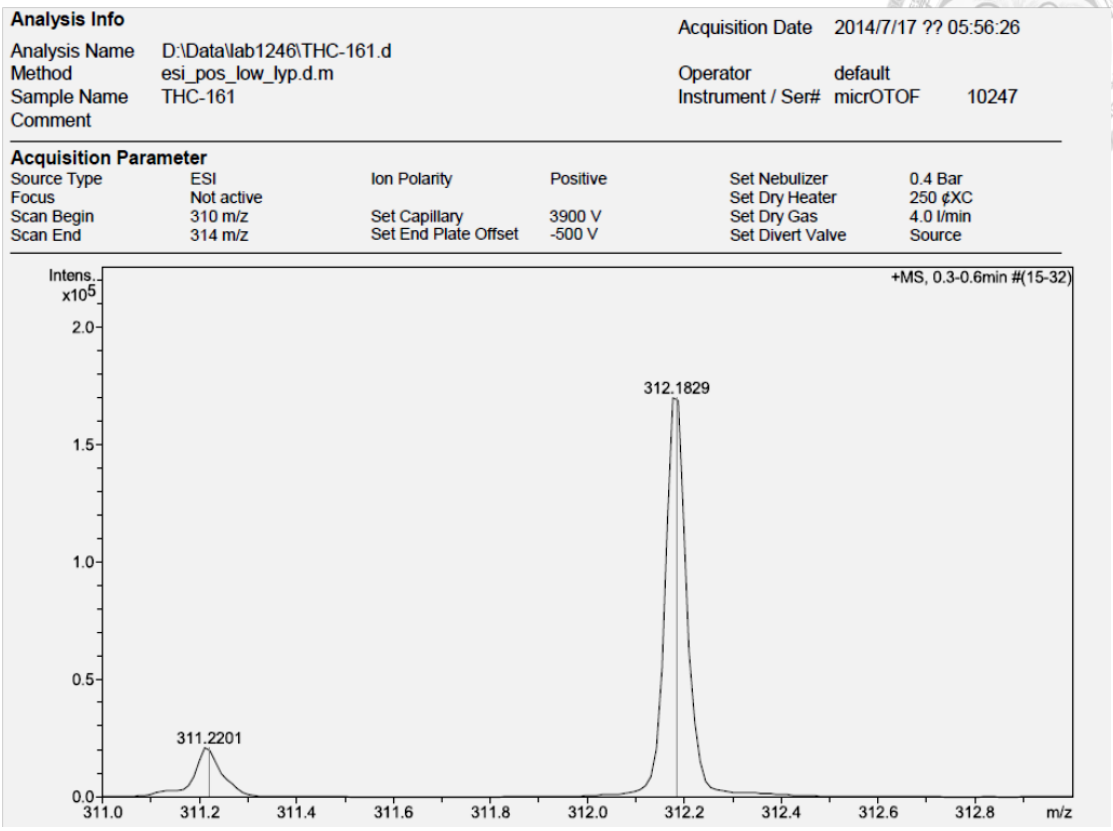
附圖四十五、化合物 12 之氫核磁共振圖譜($CDCl_3$, 200 MHz)



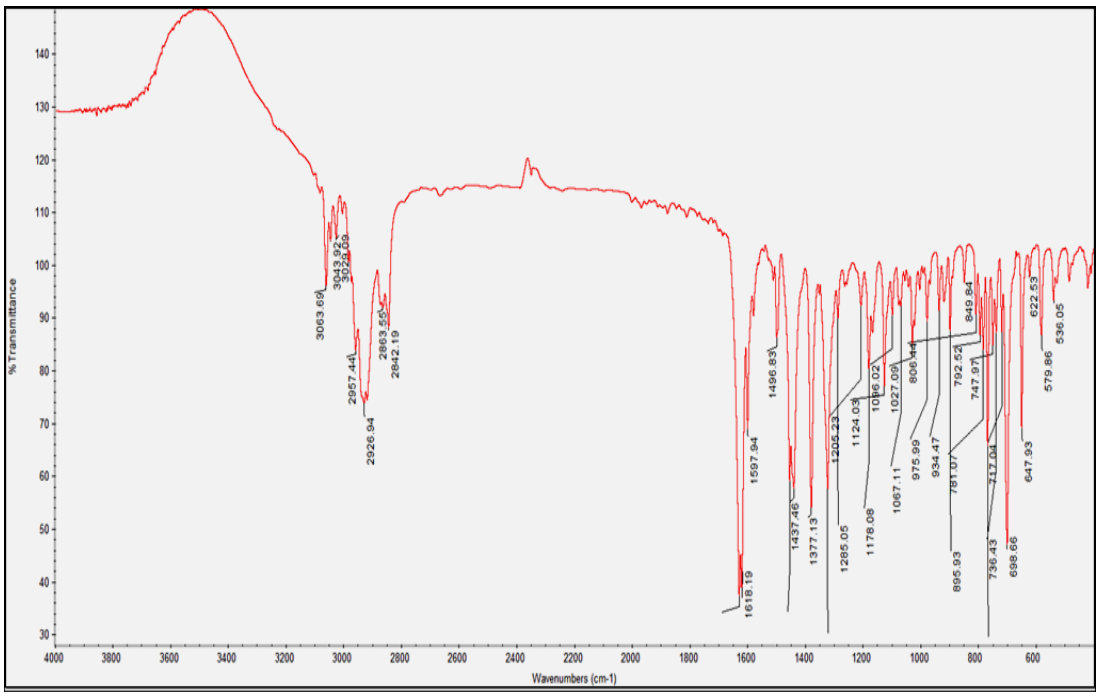
附圖四十六、化合物 12 之 ^{13}C 與 DEPT135 核磁共振圖譜



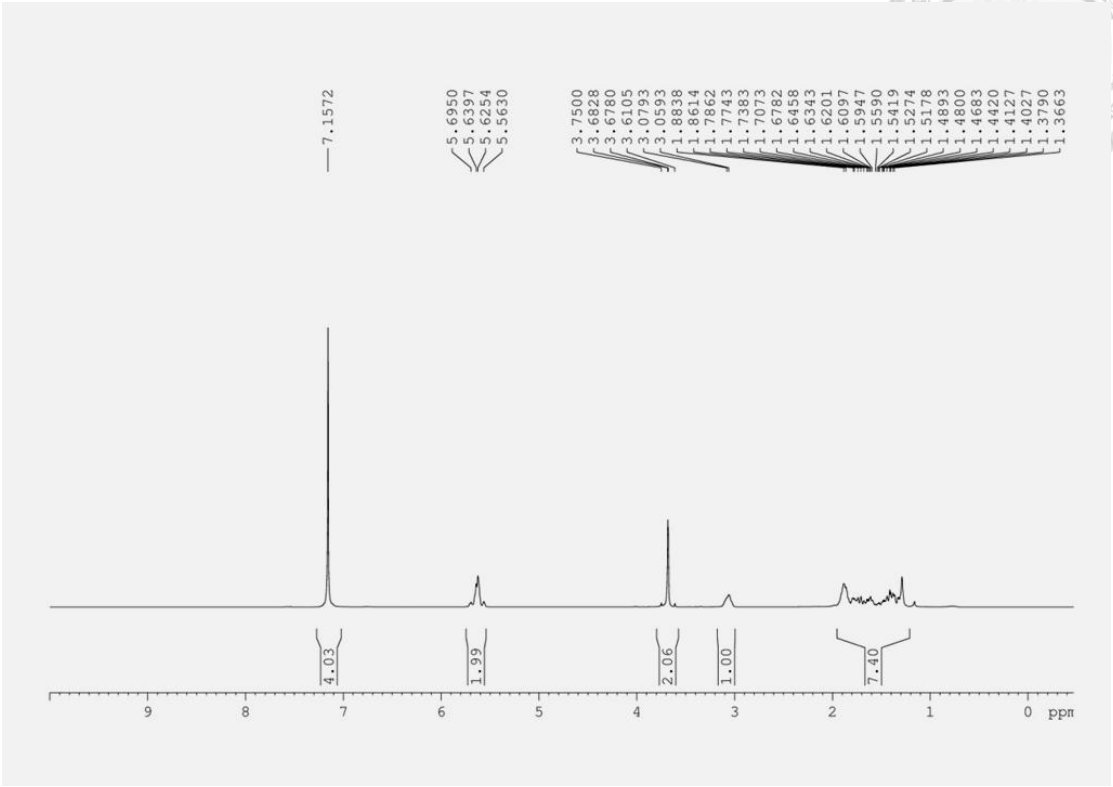
附圖四十七、化合物 12 之 HRESIMS 圖譜



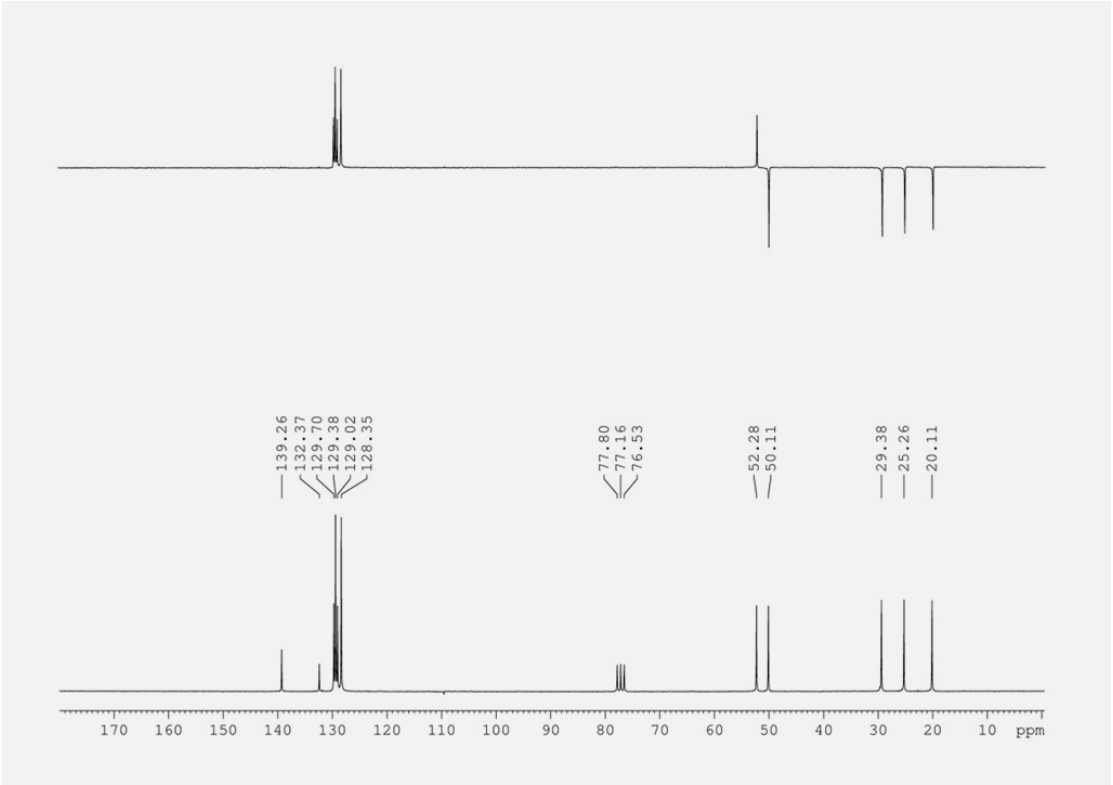
附圖四十八、化合物 12 之 IR 圖譜



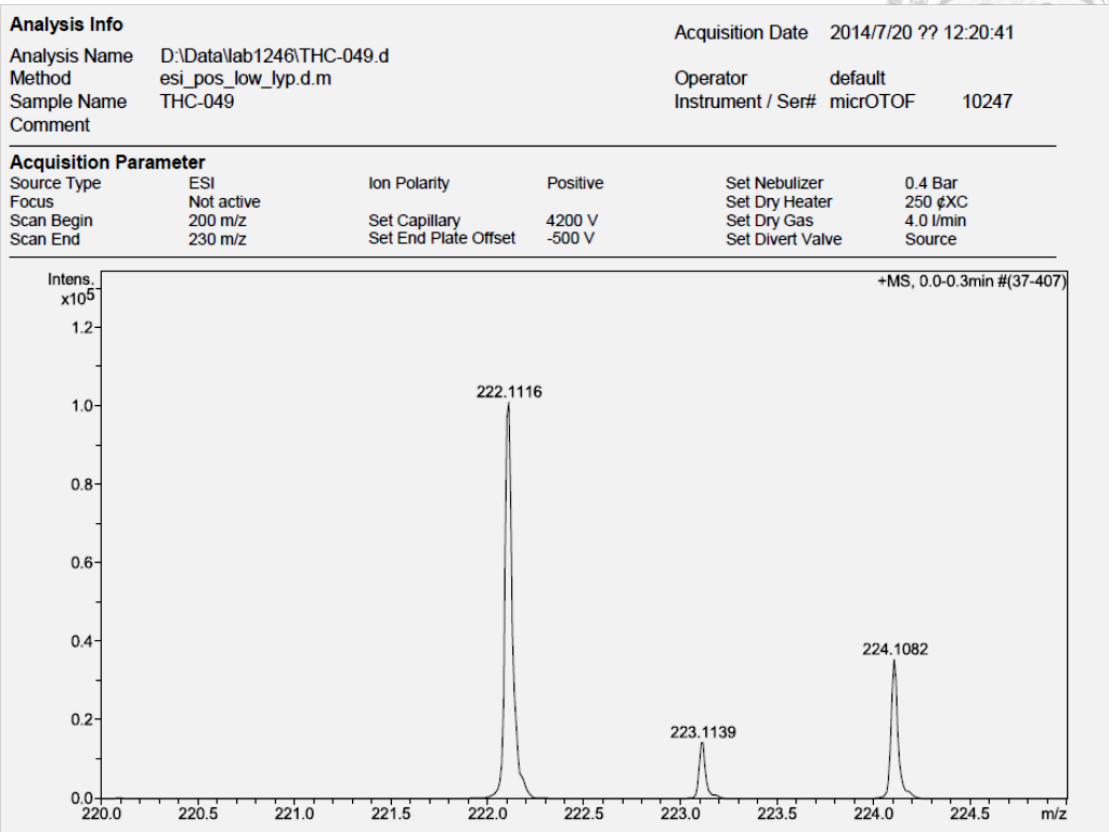
附圖四十九、化合物 13 之氫核磁共振圖譜($CDCl_3$, 200 MHz)



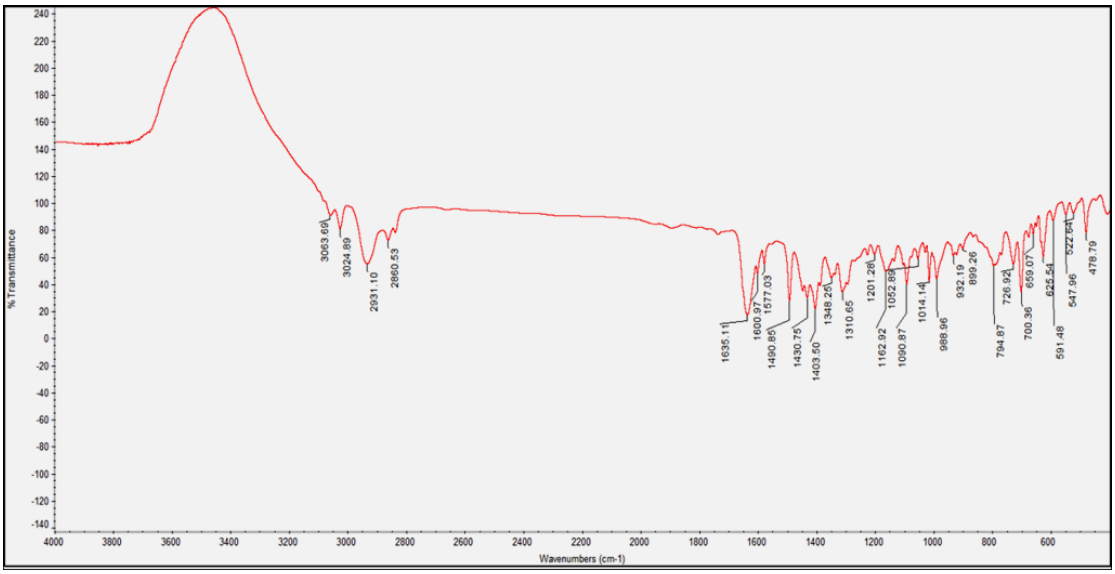
附圖五十、化合物 13 之 ^{13}C 與 DEPT135 核磁共振圖譜



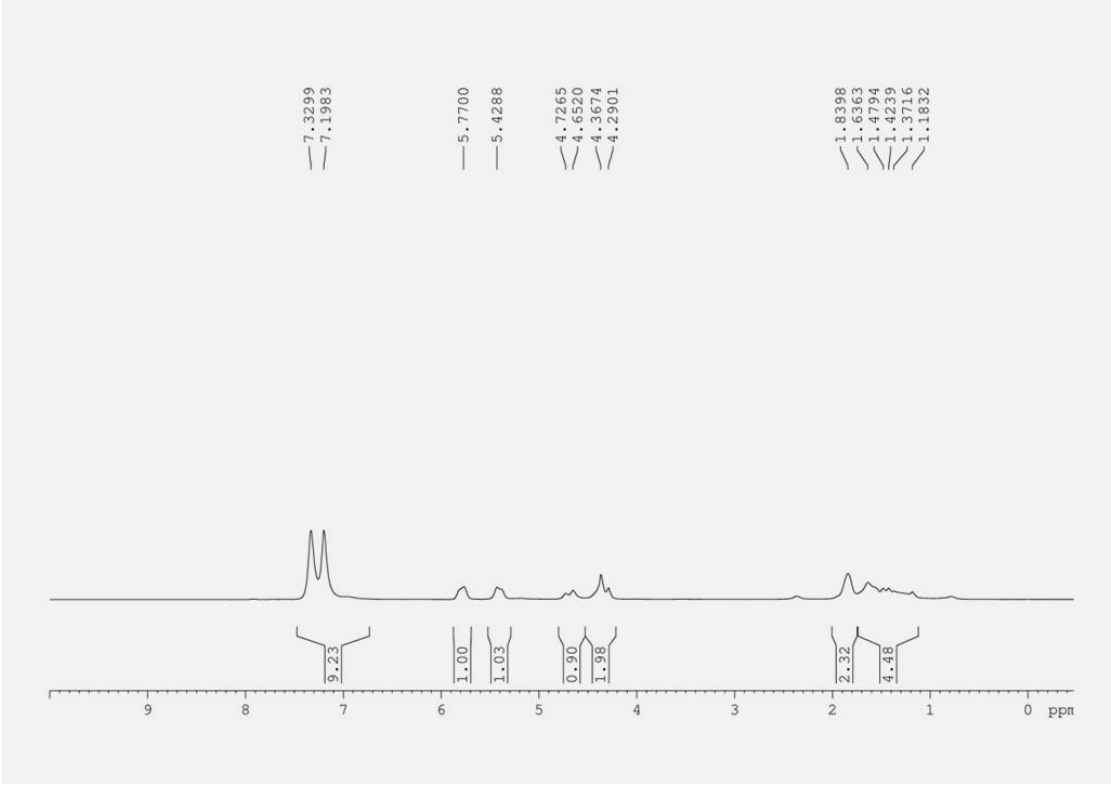
附圖五十一、化合物 13 之 HRESIMS 圖譜



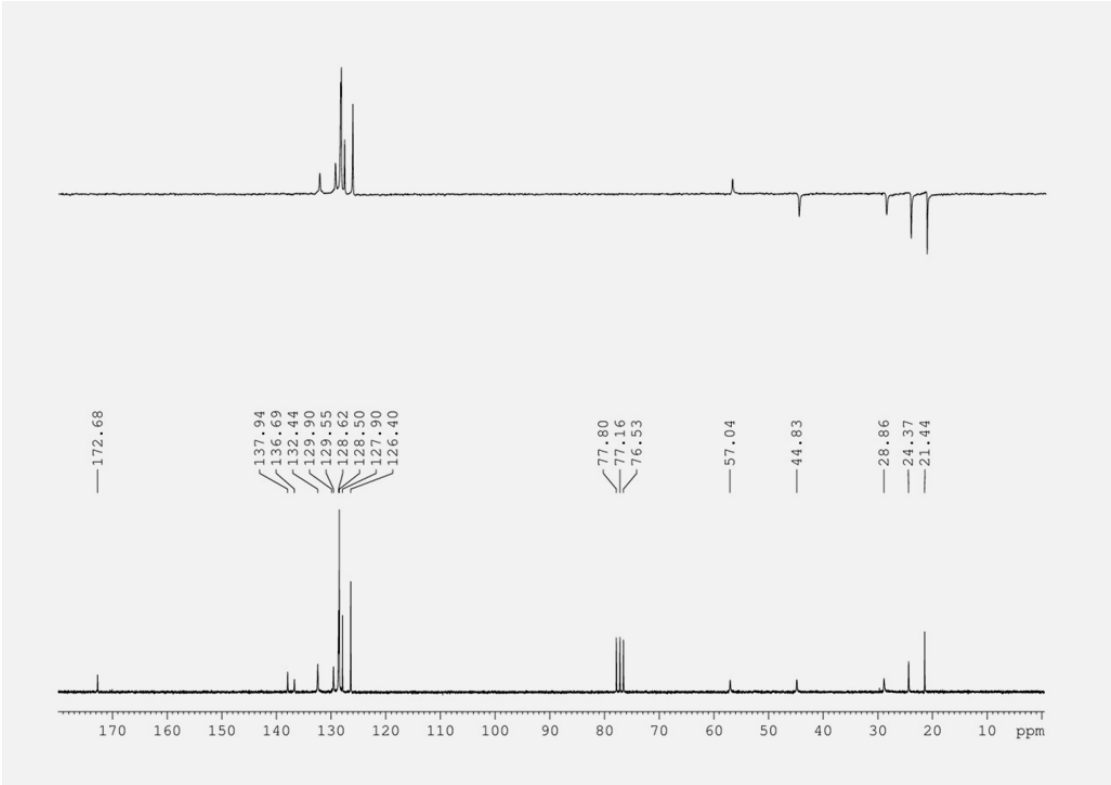
附圖五十二、化合物 13 之 IR 圖譜



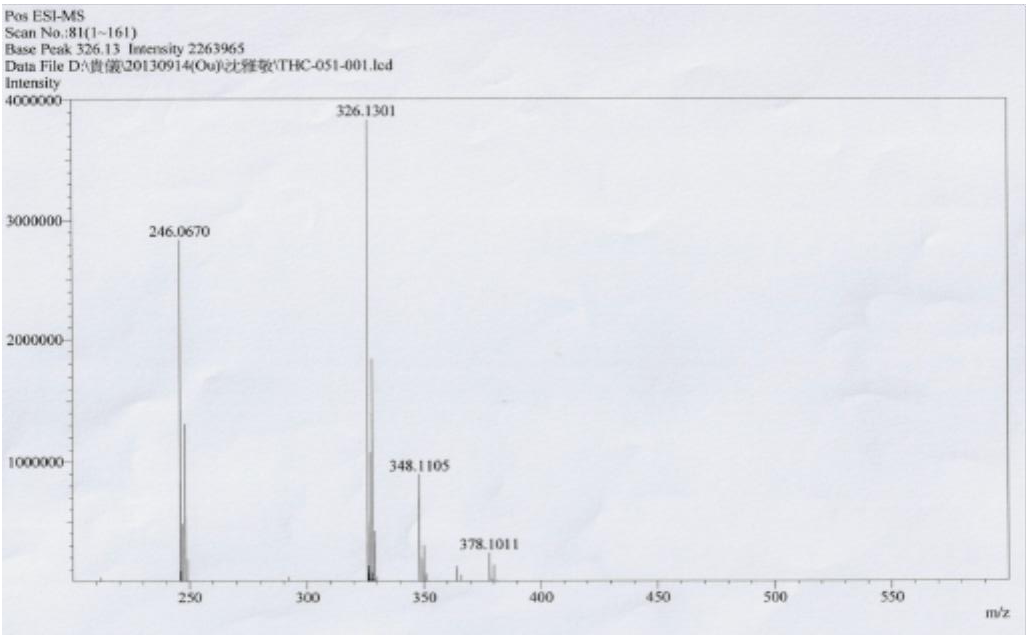
附圖五十三、化合物 **14** 之氫核磁共振圖譜($CDCl_3$, 200 MHz)



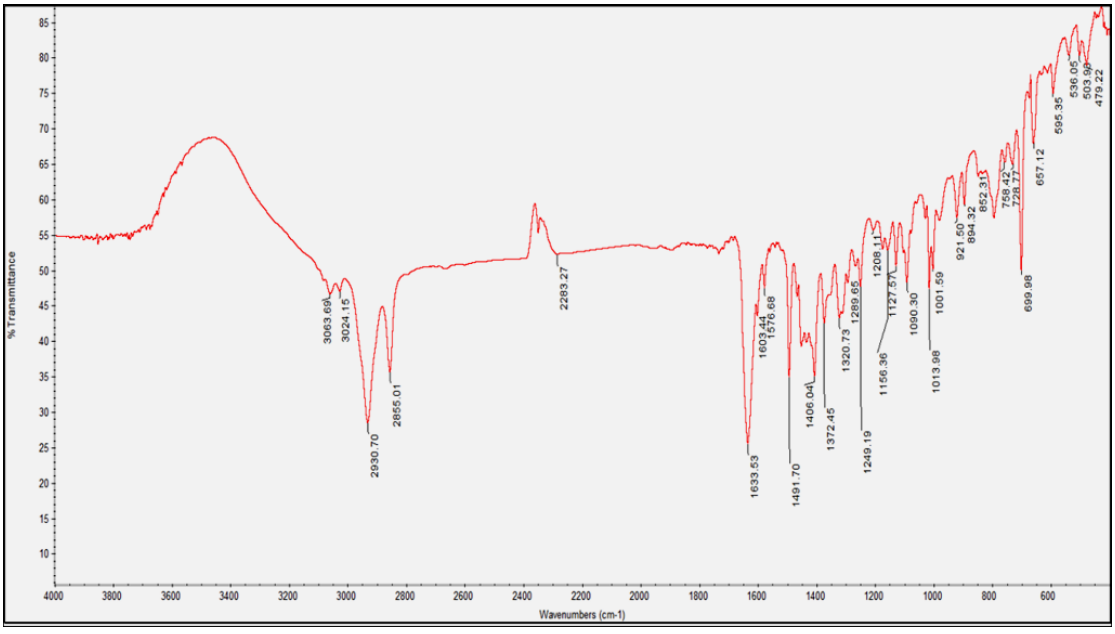
附圖五十四、化合物 **14** 之 ^{13}C 與 DEPT135 核磁共振圖譜



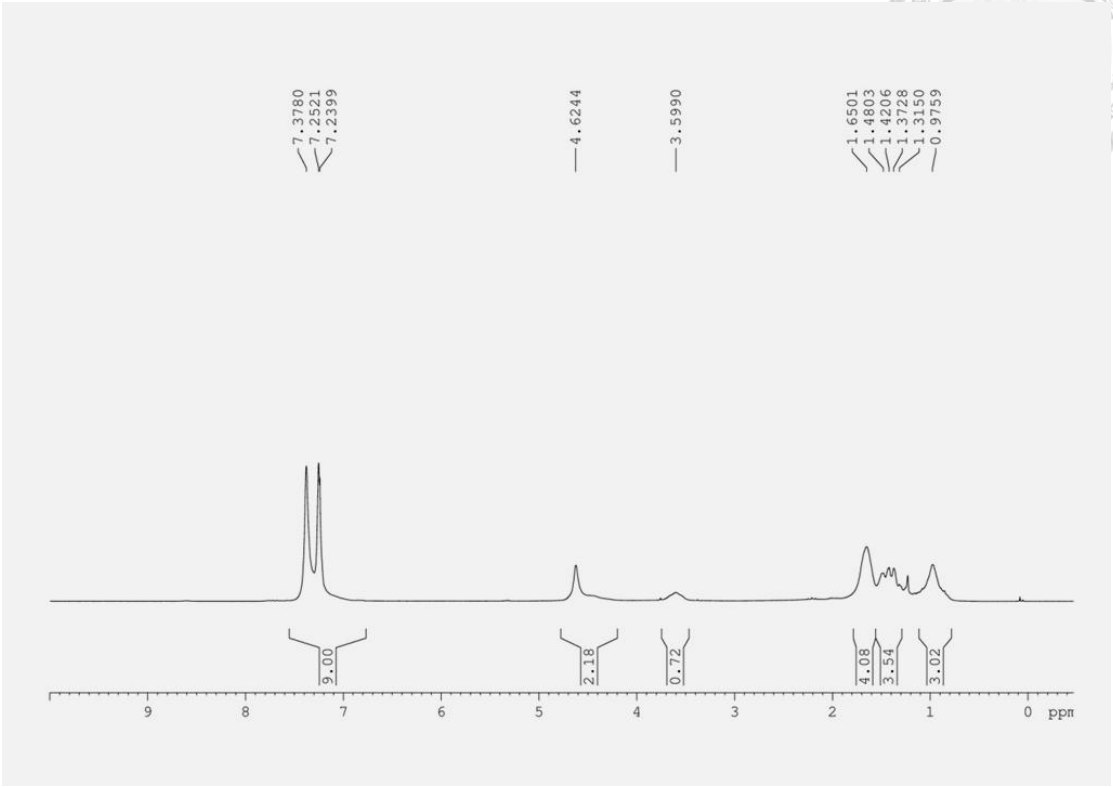
附圖五十五、化合物 14 之 HRESIMS 圖譜



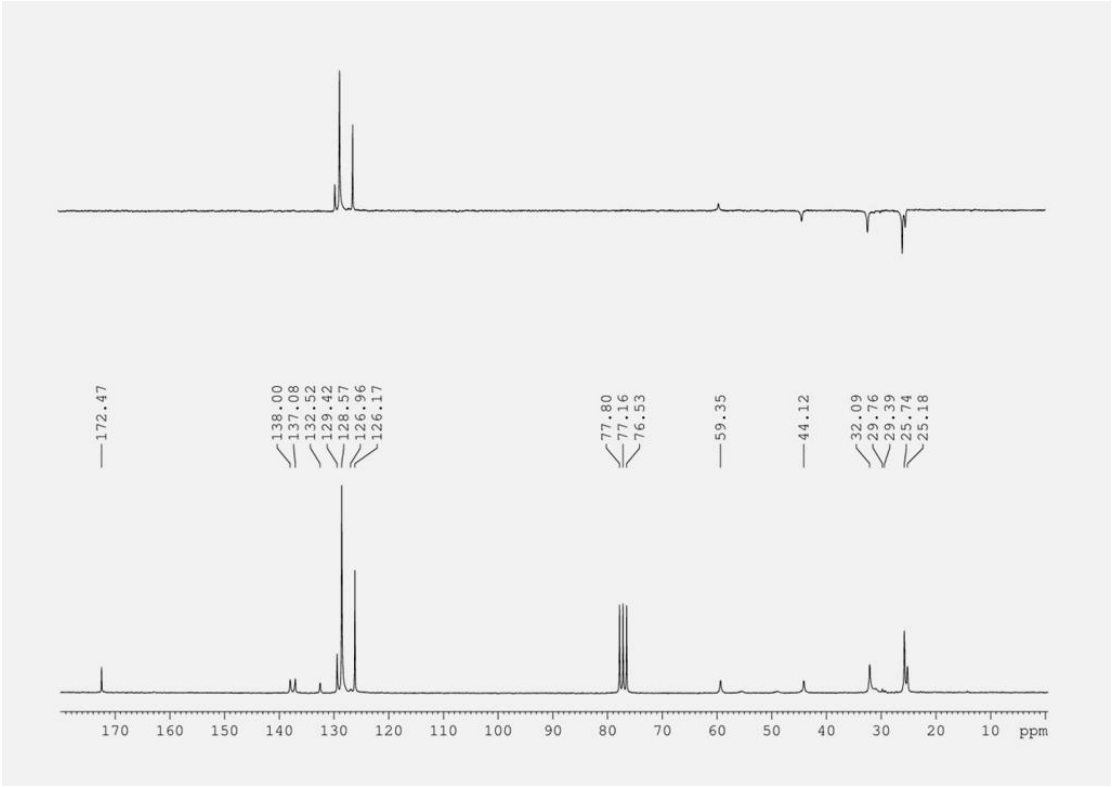
附圖五十六、化合物 14 之 IR 圖譜



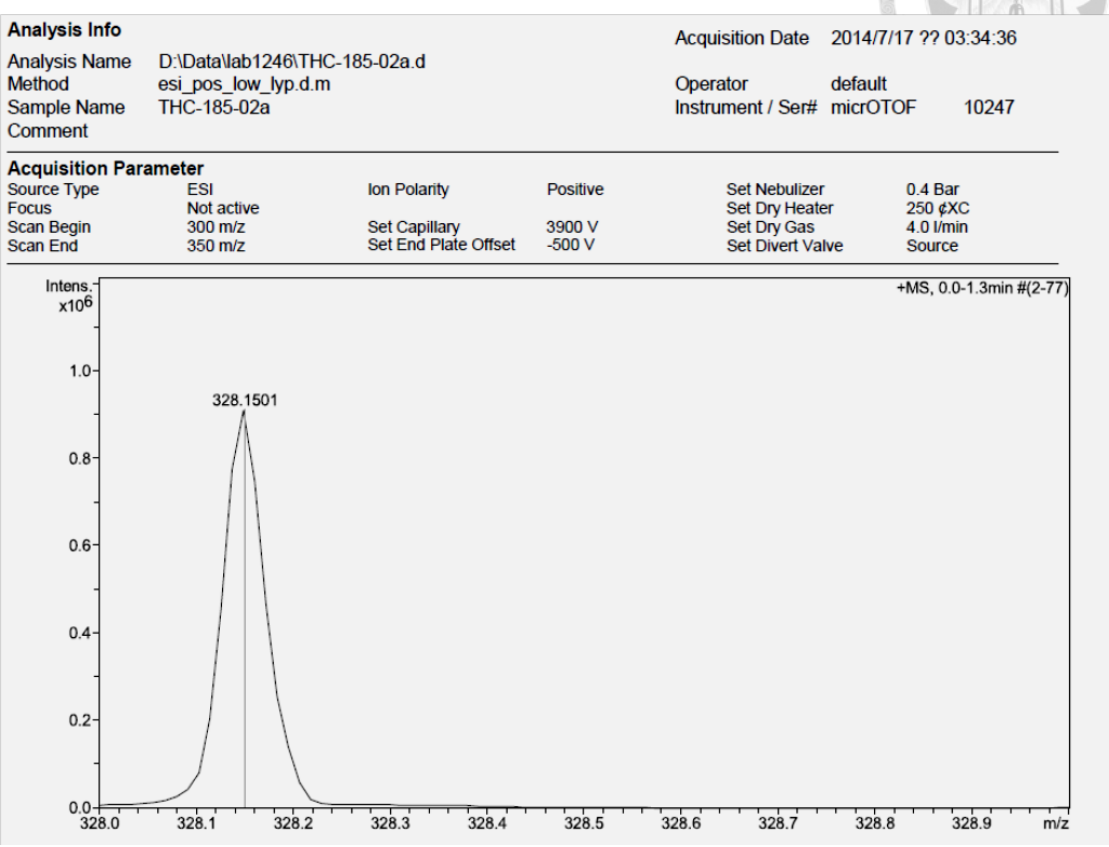
附圖五十七、化合物 15 之氫核磁共振圖譜($CDCl_3$, 200 MHz)



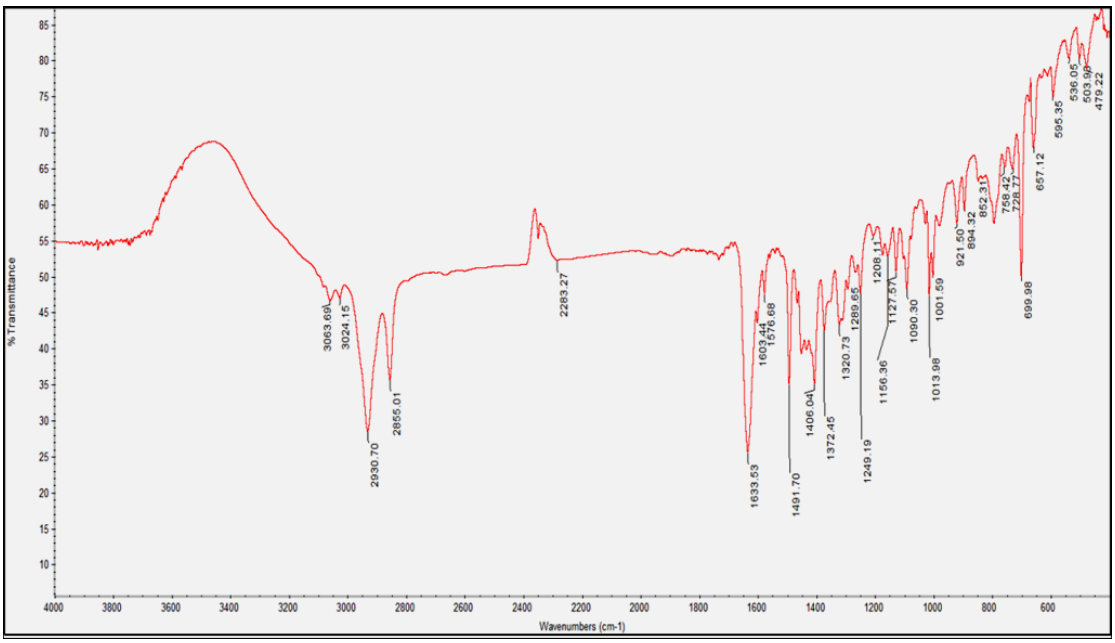
附圖五十八、化合物 15 之 ^{13}C 與 DEPT135 核磁共振圖譜



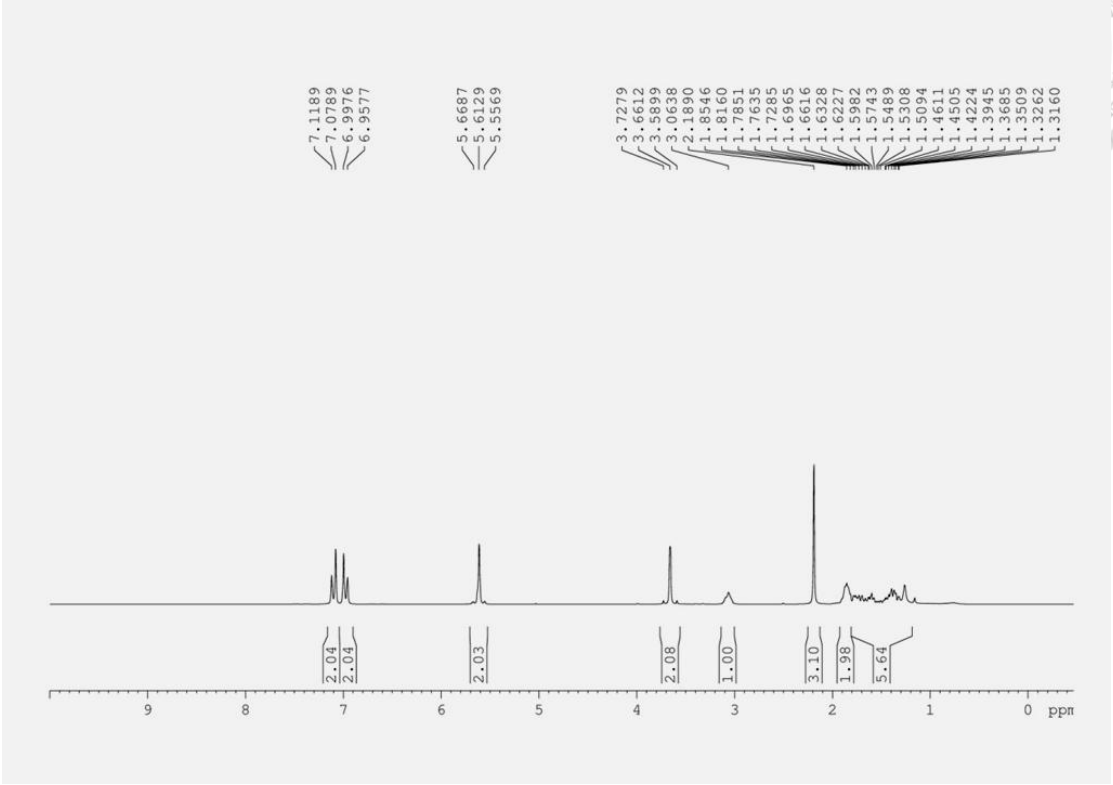
附圖五十九、化合物 15 之 HRESIMS 圖譜



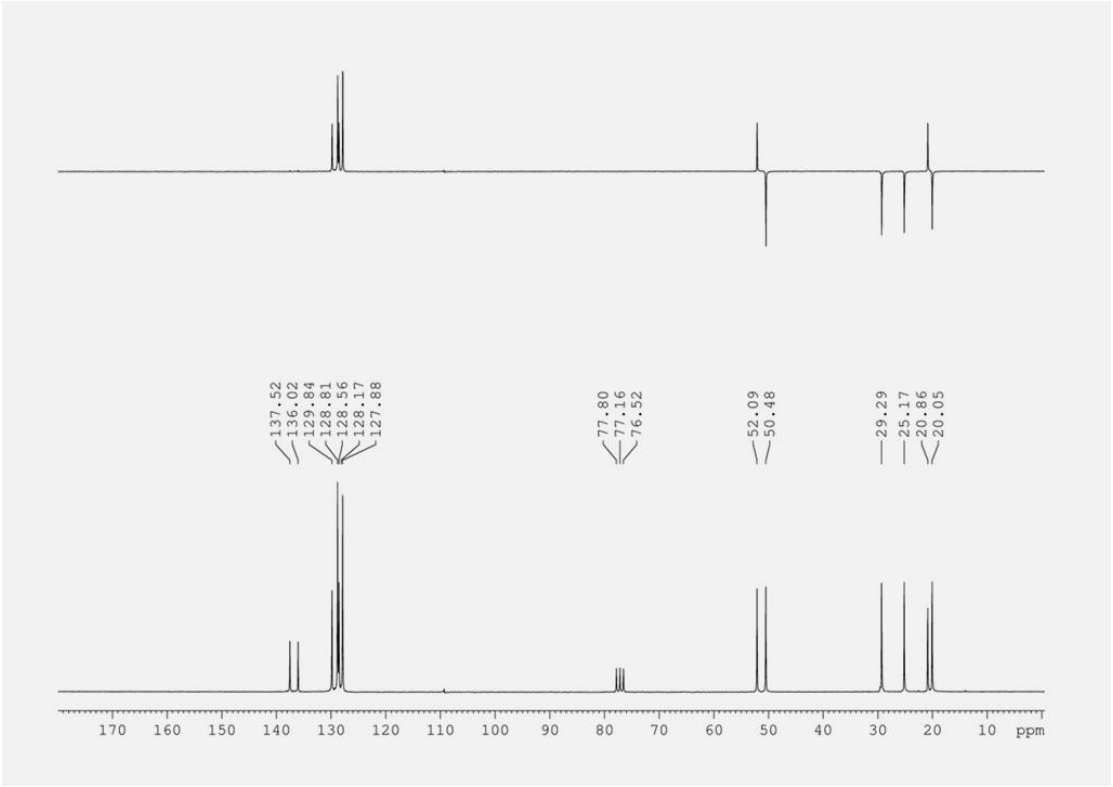
附圖六十、化合物 15 之 IR 圖譜



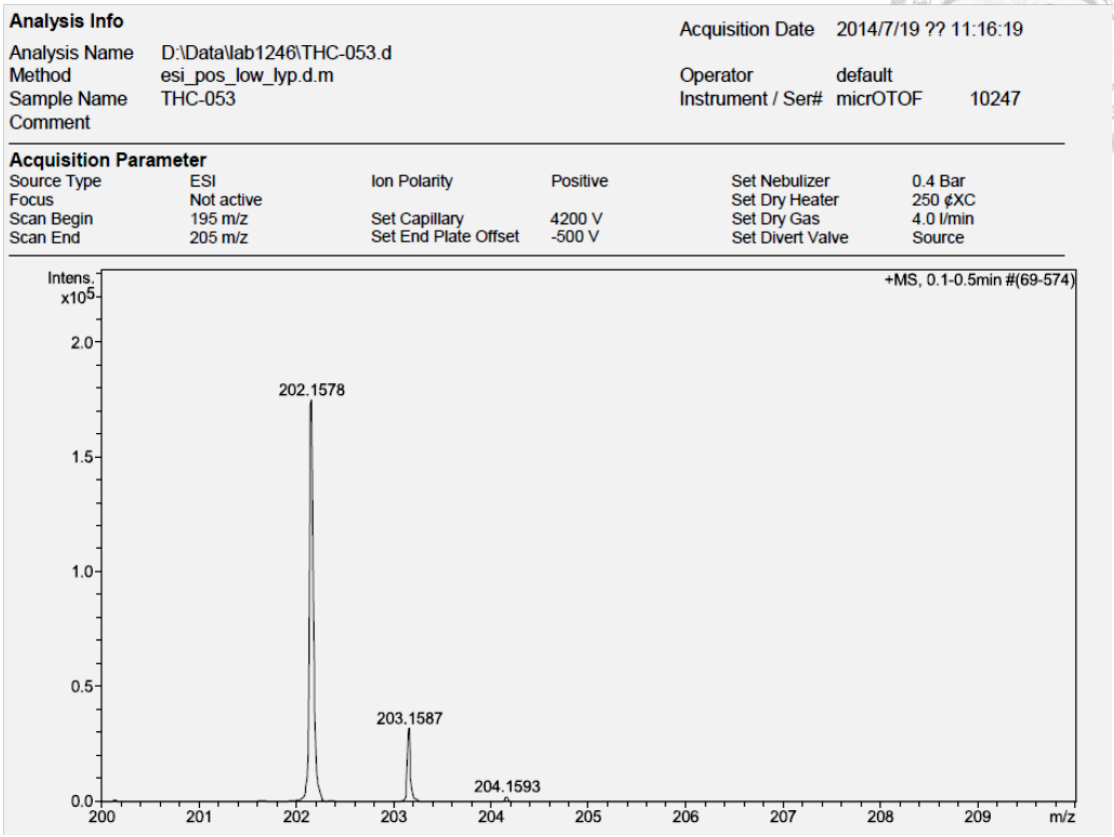
附圖六十一、化合物 16 之氫核磁共振圖譜($CDCl_3$, 200 MHz)



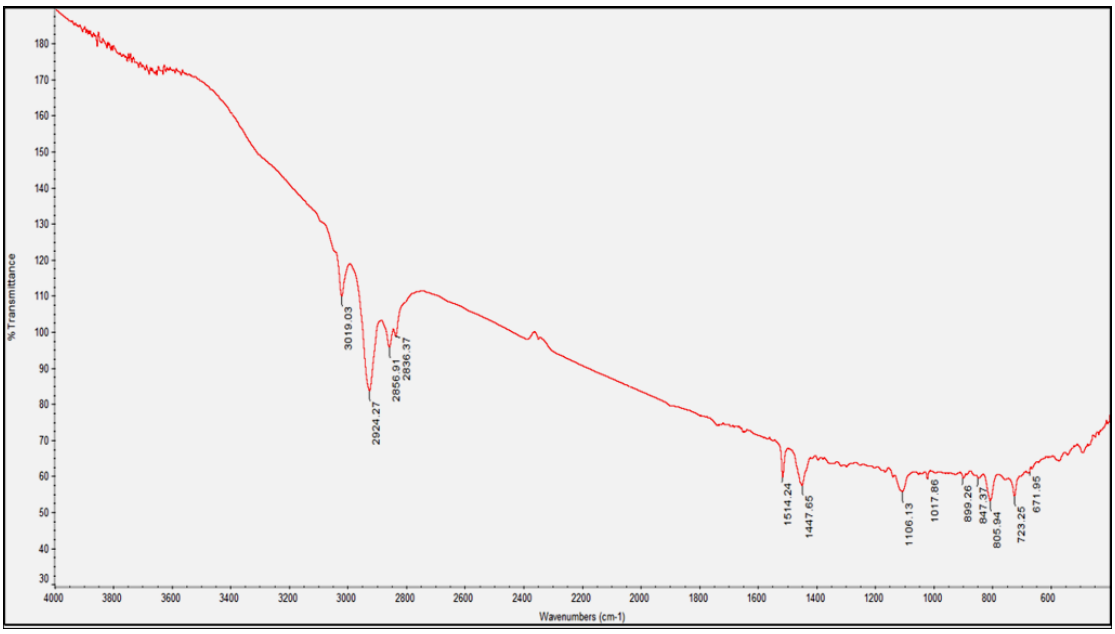
附圖六十二、化合物 16 之 ^{13}C 與 DEPT135 核磁共振圖譜



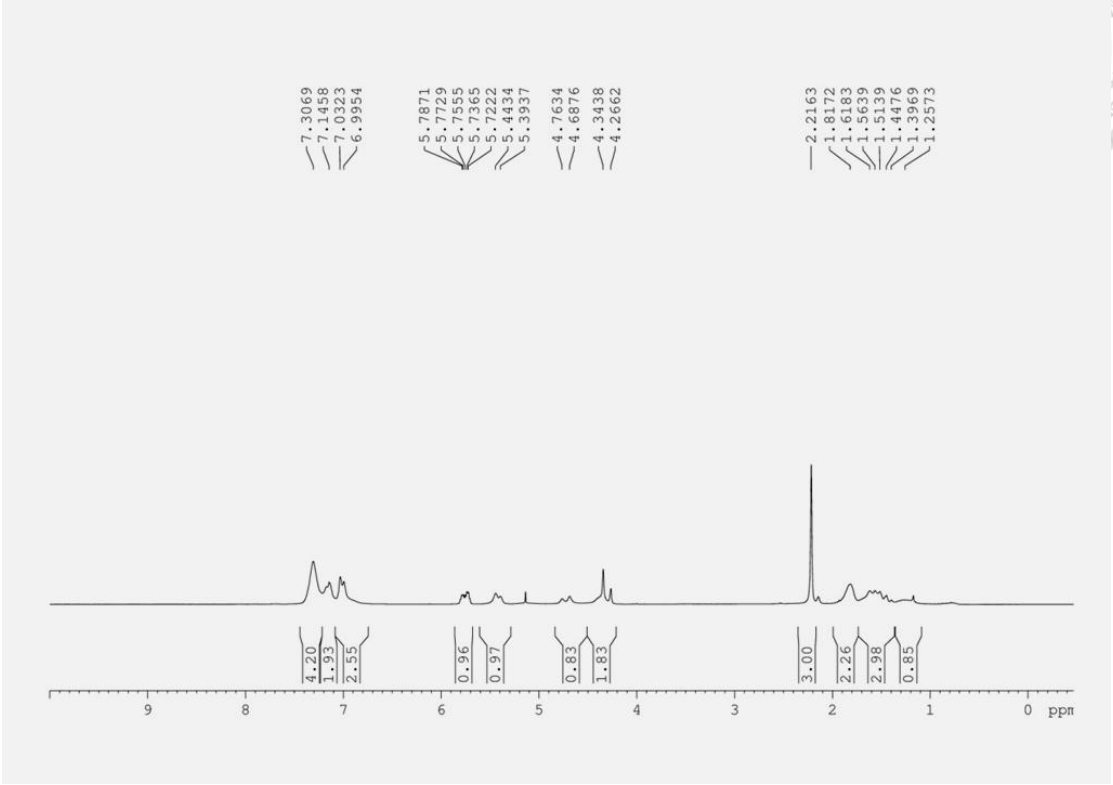
附圖六十三、化合物 16 之 HRESIMS 圖譜



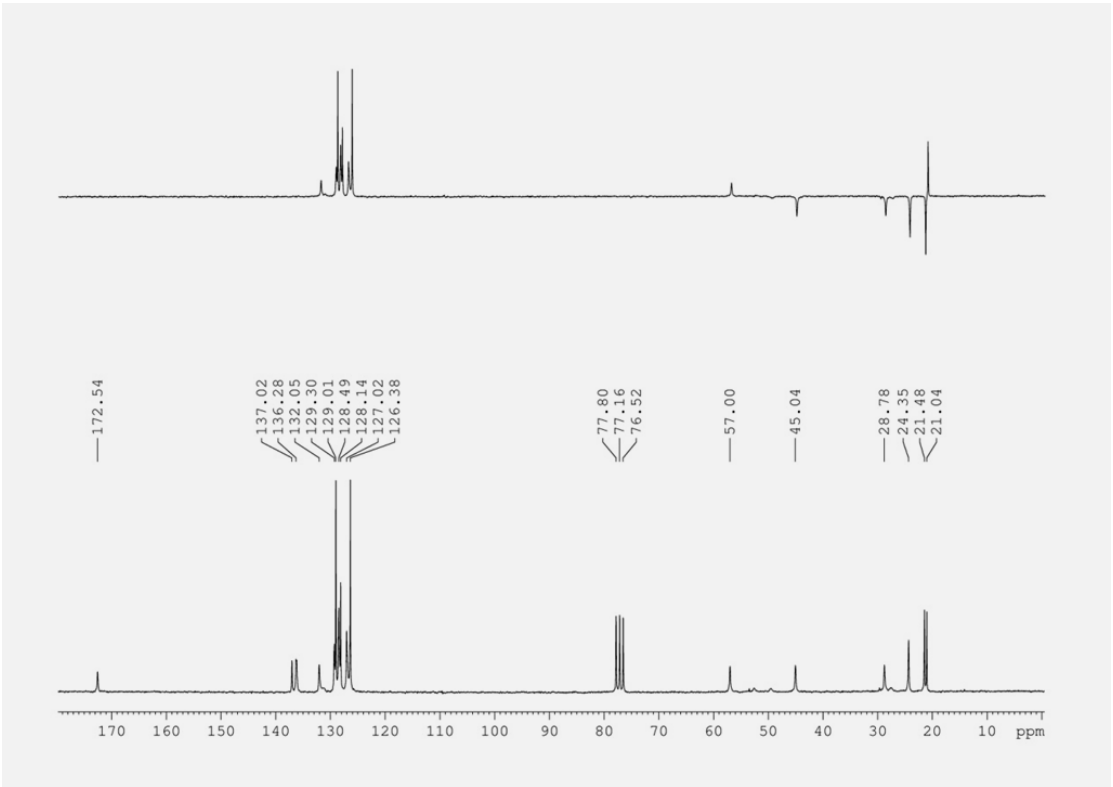
附圖六十四、化合物 16 之 IR 圖譜



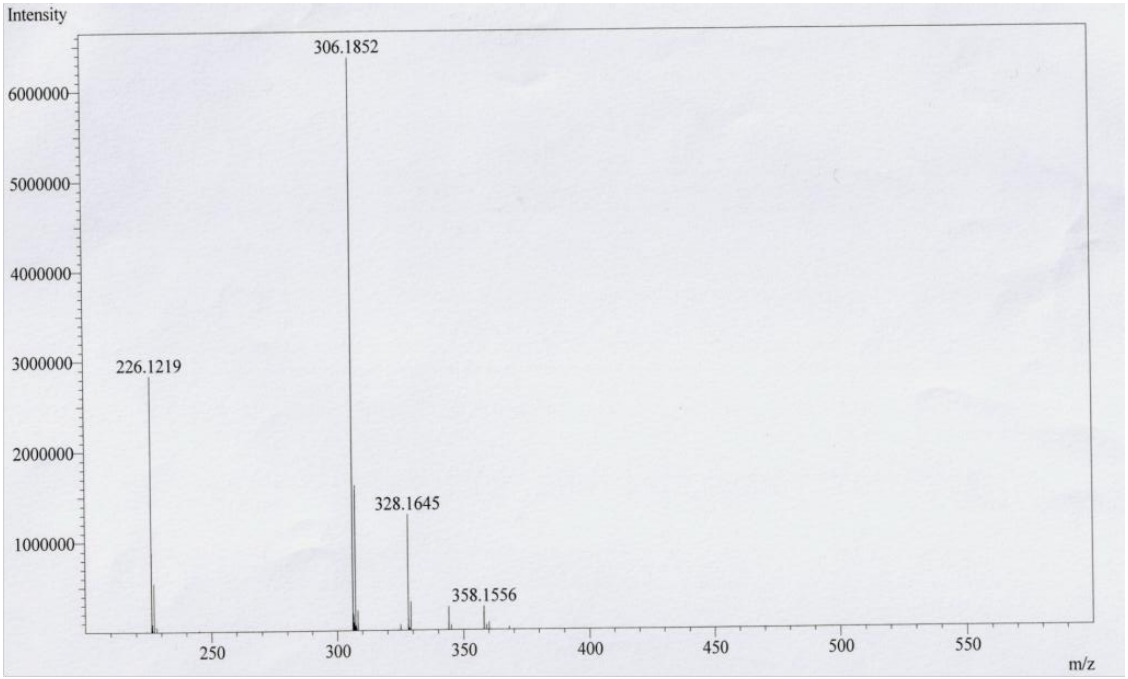
附圖六十五、化合物 17 之氫核磁共振圖譜($CDCl_3$, 200 MHz)



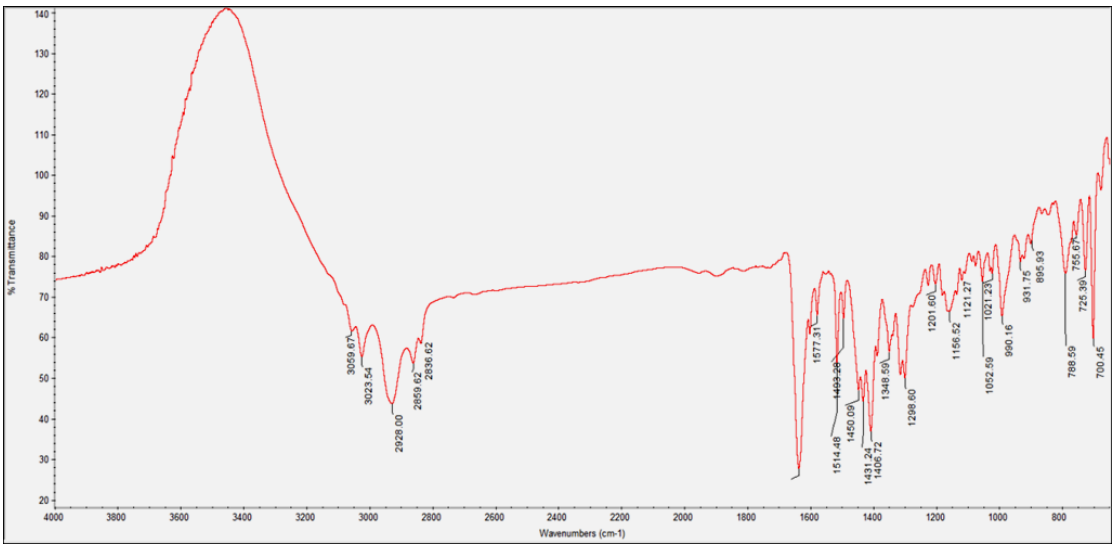
附圖六十六、化合物 17 之 ^{13}C 與 DEPT135 核磁共振圖譜



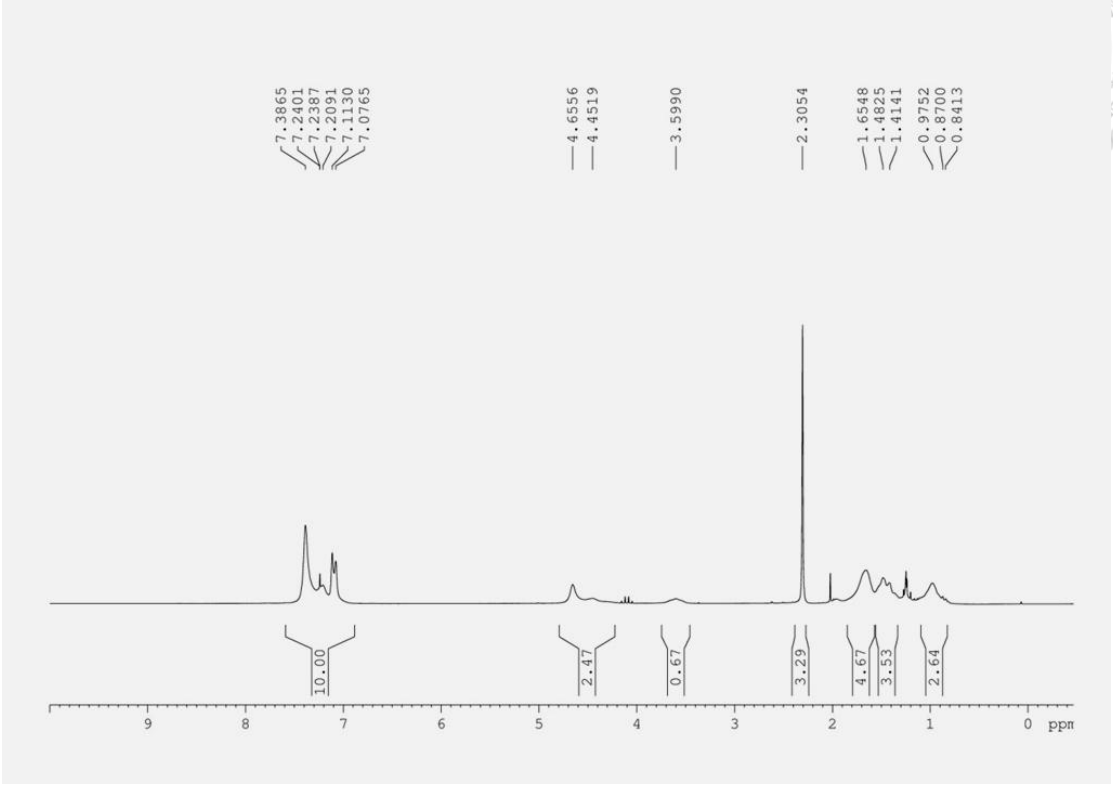
附圖六十七、化合物 17 之 HRESIMS 圖譜



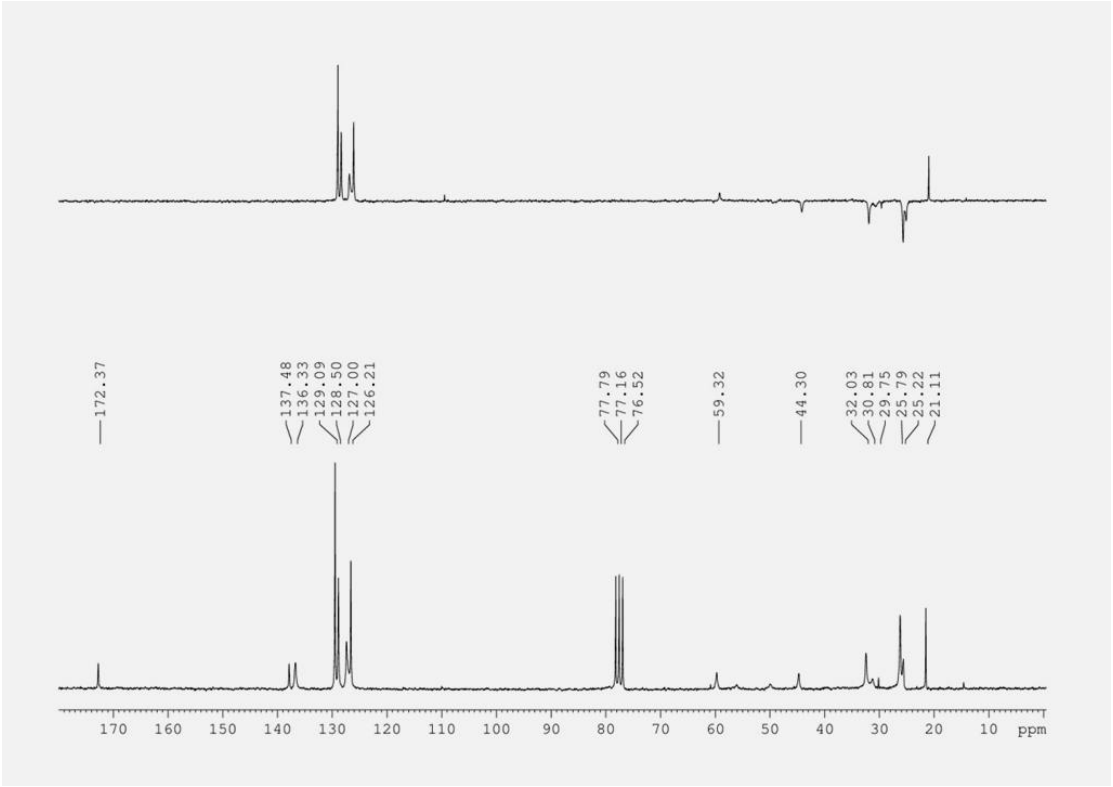
附圖六十八、化合物 17 之 IR 圖譜



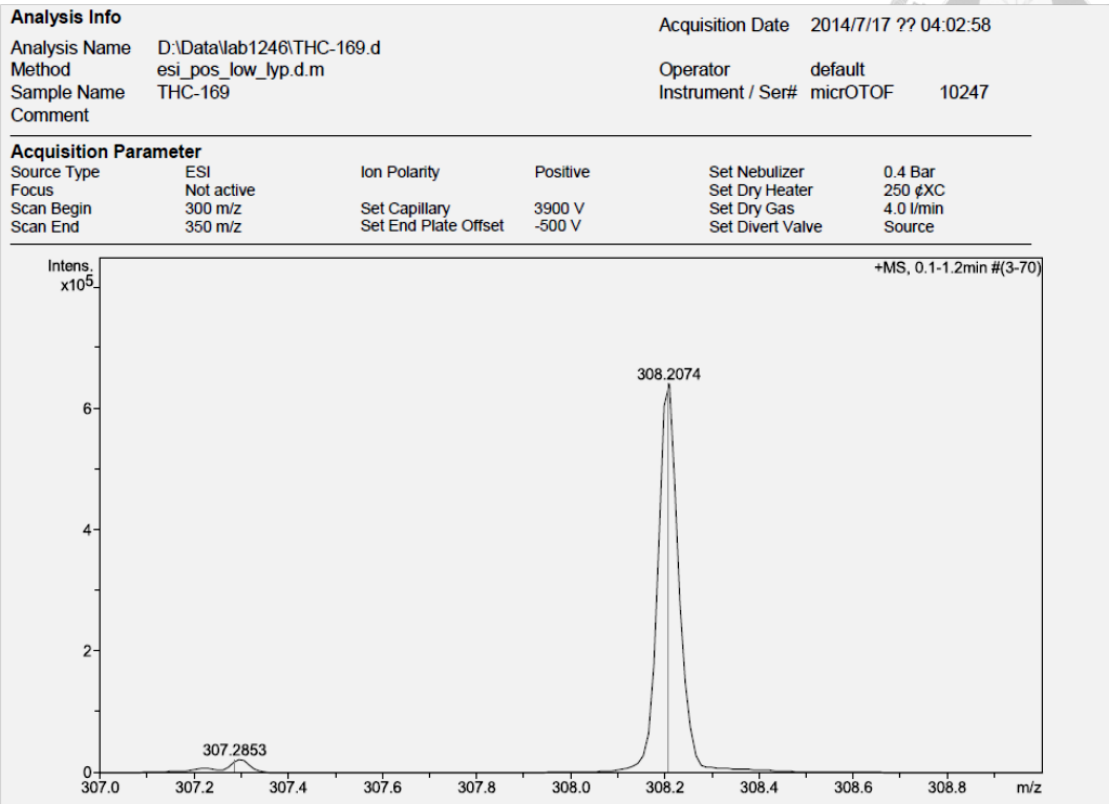
附圖六十九、化合物 18 之氫核磁共振圖譜($CDCl_3$, 200 MHz)



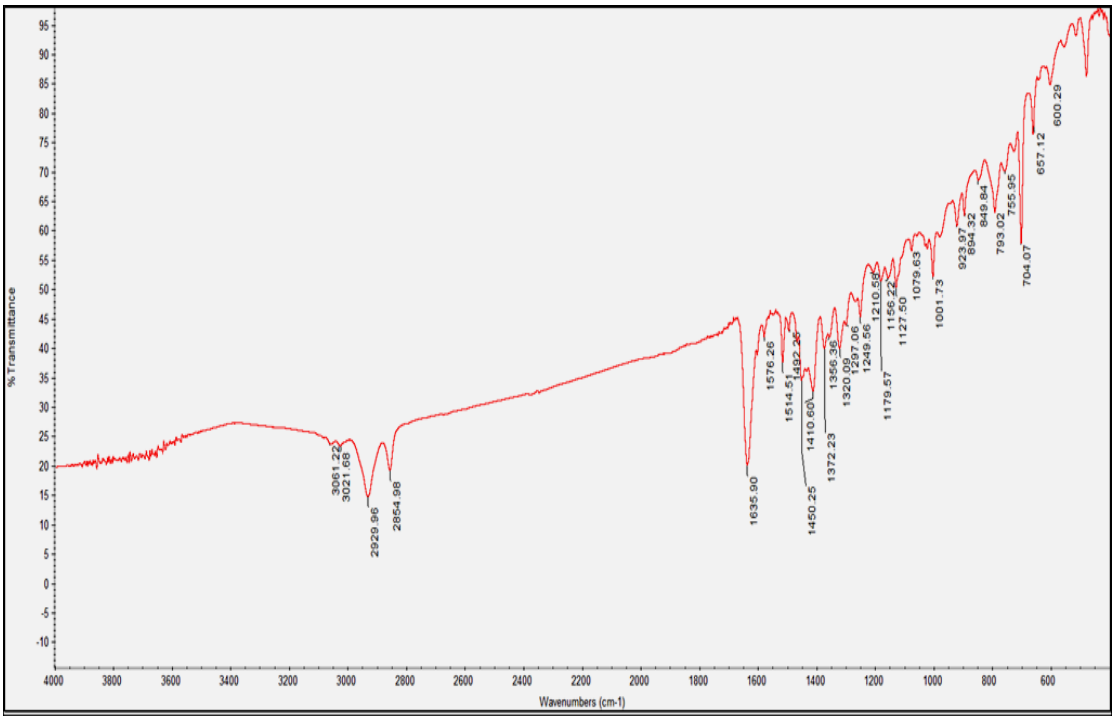
附圖七十、化合物 18 之 ^{13}C 與 DEPT135 核磁共振圖譜



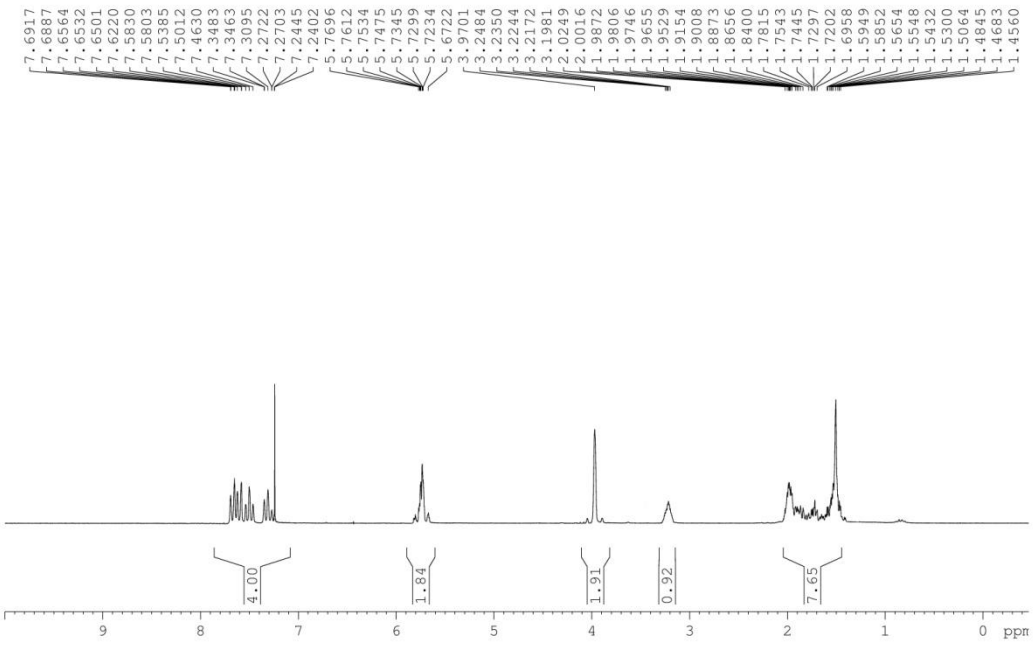
附圖七十一、化合物 18 之 HRESIMS 圖譜



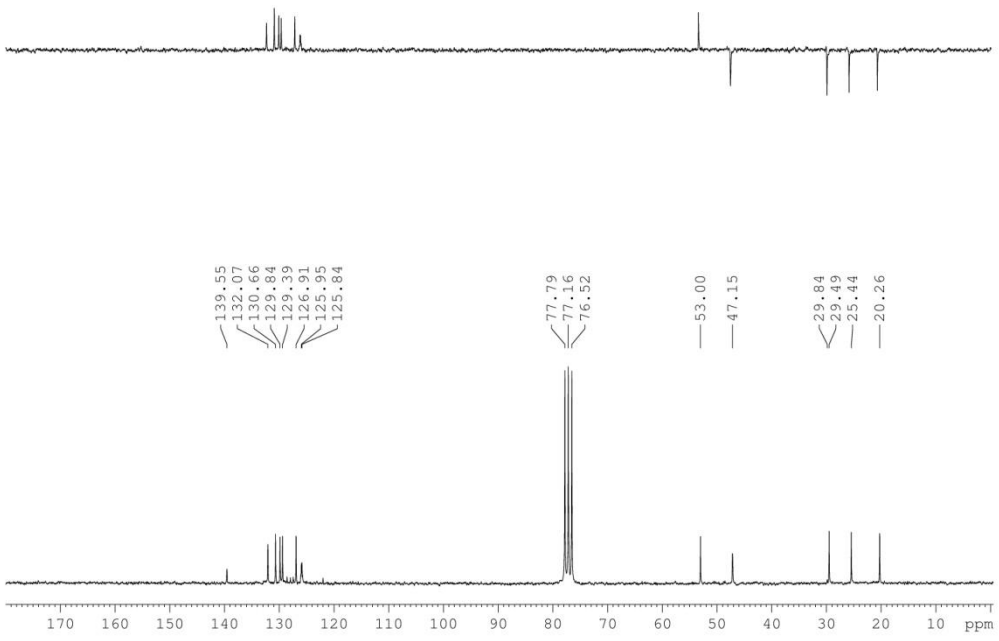
附圖七十二、化合物 18 之 IR 圖譜



附圖七十三、化合物 19 之氫核磁共振圖譜(CDCl$_3$, 200 MHz)



附圖七十四、化合物 19 之 ^{13}C 與 DEPT135 核磁共振圖譜



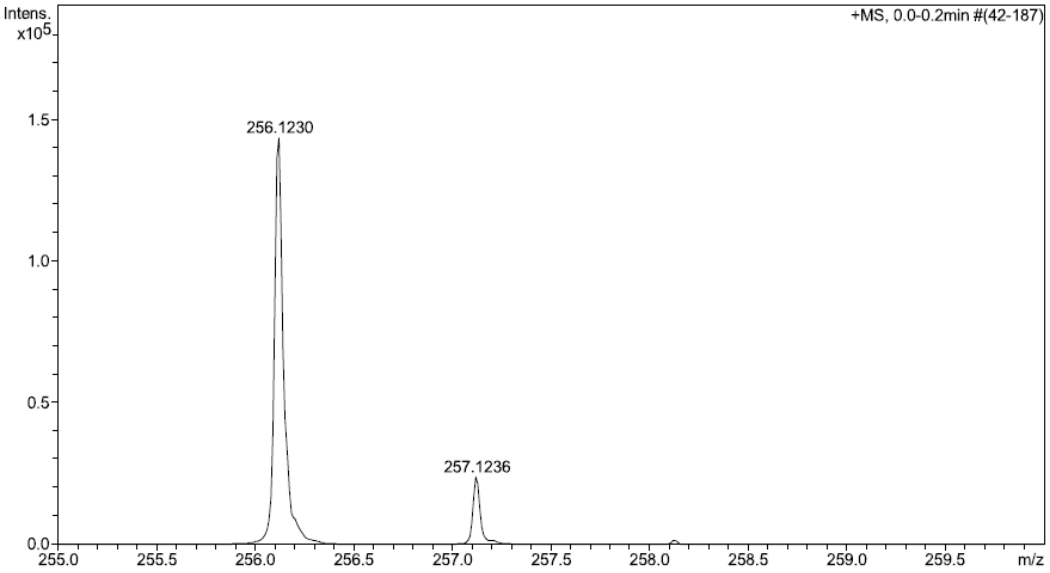
附圖七十五、化合物 19 之 HRESIMS 圖譜

Analysis Info

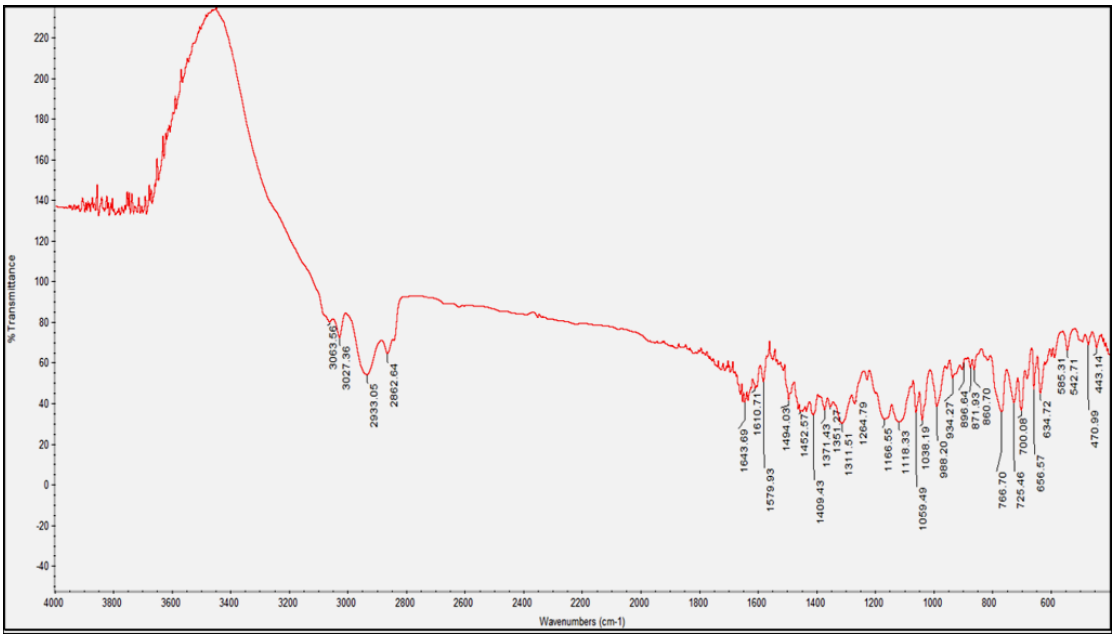
Analysis Name	D:\Data\lab1246\THC-017-02.d	Acquisition Date	2014/7/19 ?? 10:56:53
Method	esi_pos_low_lyp.d.m	Operator	default
Sample Name	THC-017-02	Instrument / Ser#	micrOTOF 10247
Comment			

Acquisition Parameter

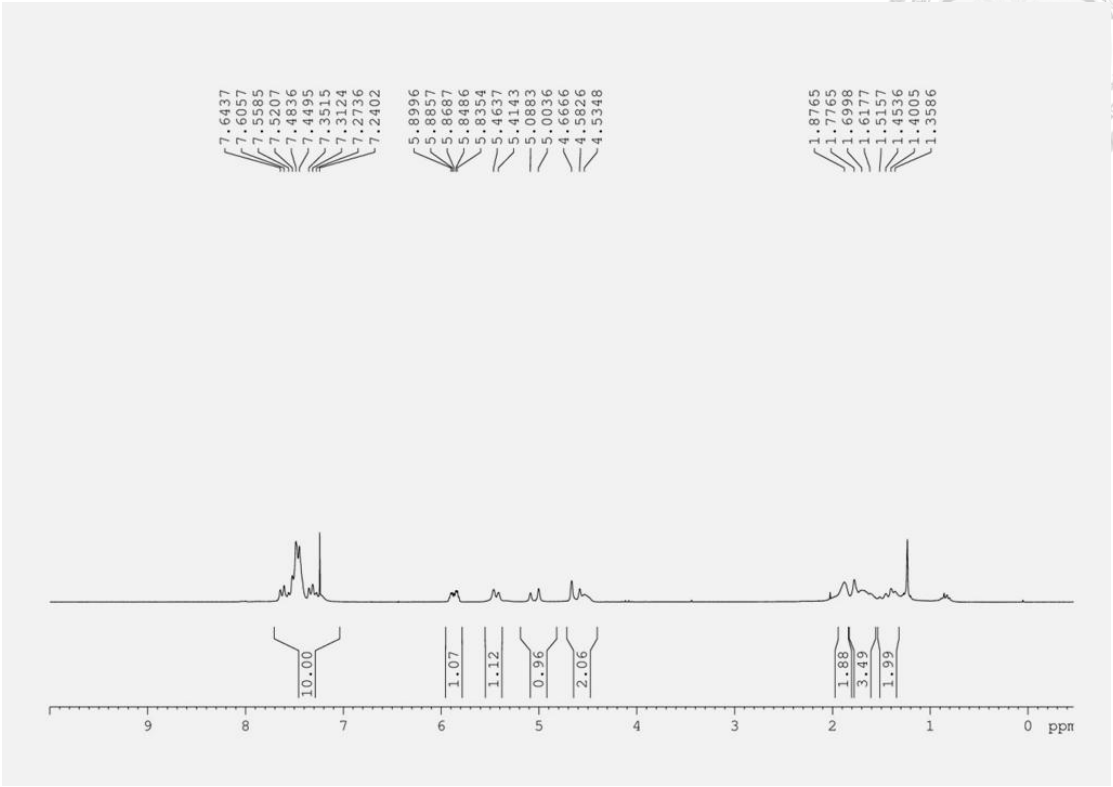
Source Type	ESI	Ion Polarity	Positive	Set Nebulizer	0.4 Bar
Focus	Not active			Set Dry Heater	250 ¢XC
Scan Begin	250 m/z	Set Capillary	4200 V	Set Dry Gas	4.0 l/min
Scan End	260 m/z	Set End Plate Offset	-500 V	Set Divert Valve	Source



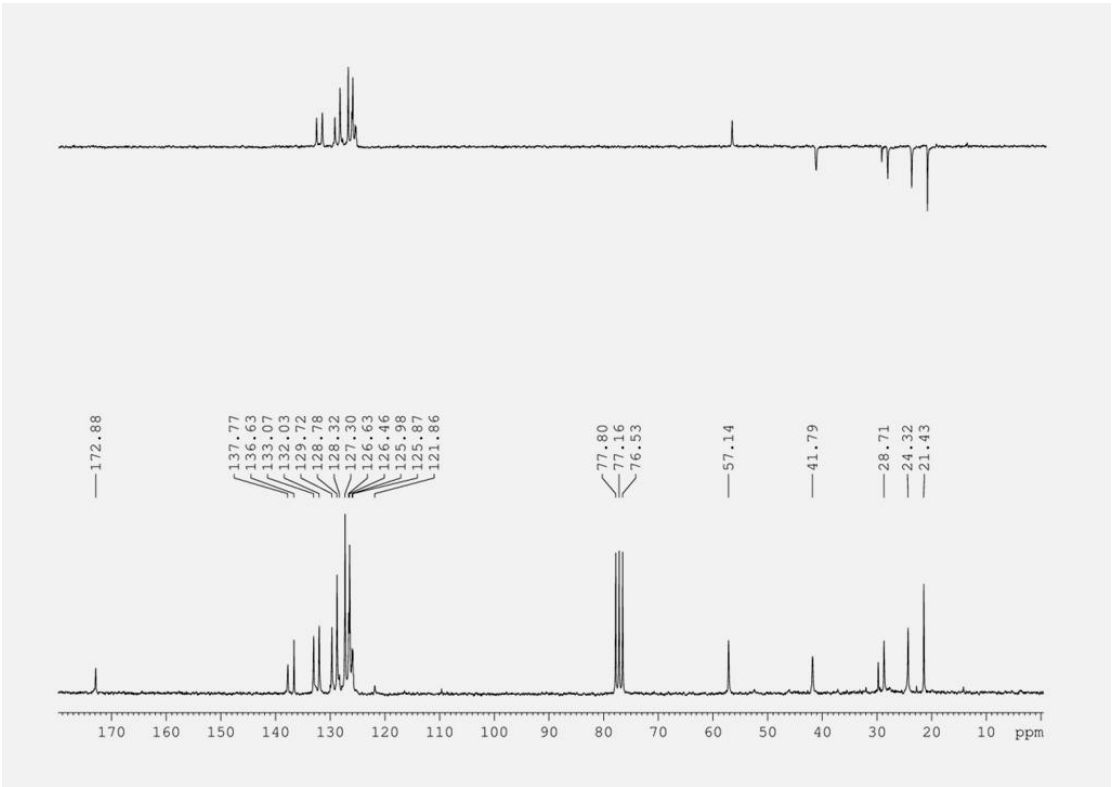
附圖七十六、化合物 19 之 IR 圖譜



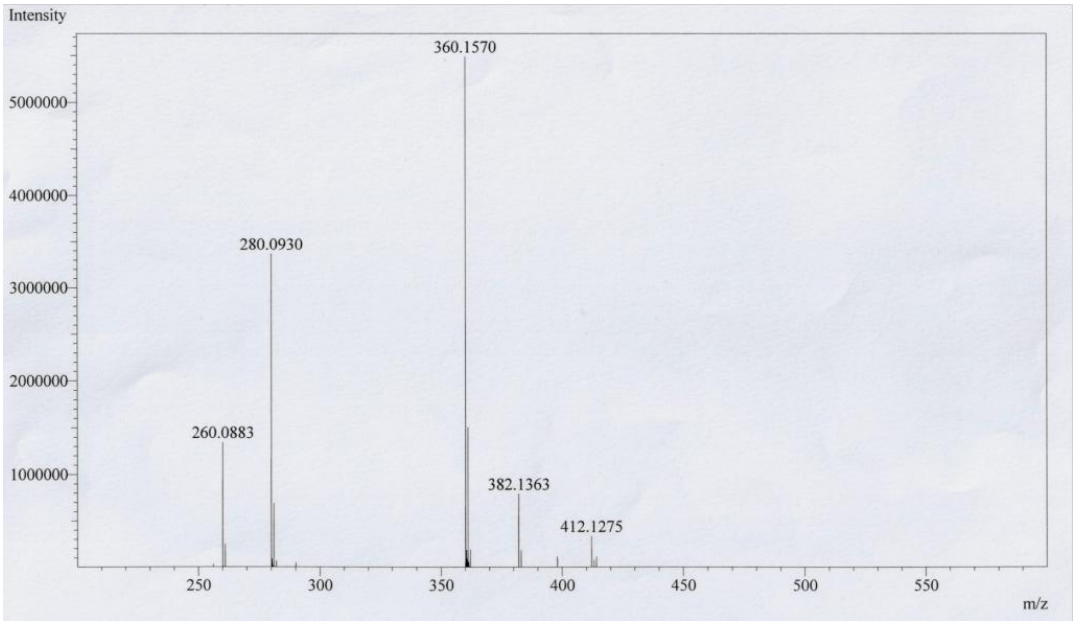
附圖七十七、化合物 20 之氫核磁共振圖譜($CDCl_3$, 200 MHz)



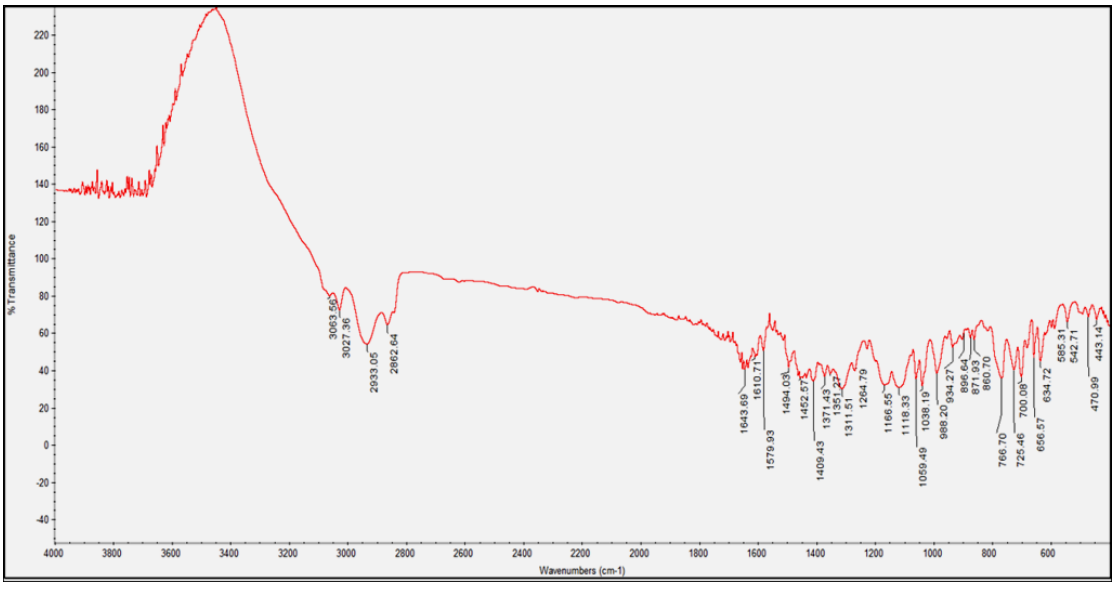
附圖七十八、化合物 20 之 ^{13}C 與 DEPT135 核磁共振圖譜



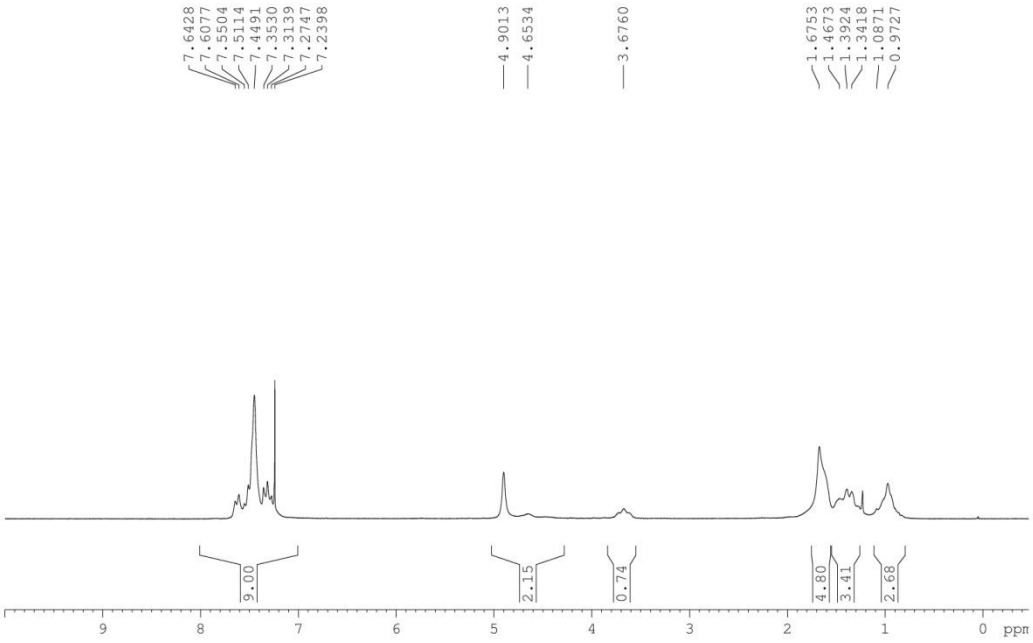
附圖七十九、化合物 20 之 HRESIMS 圖譜



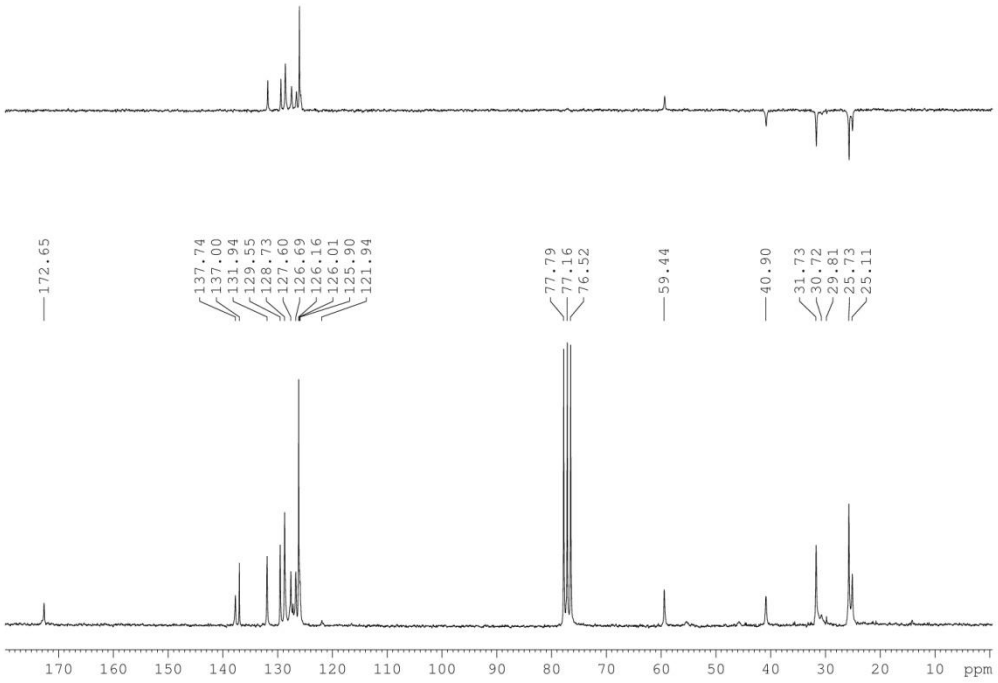
附圖八十、化合物 20 之 IR 圖譜



附圖八十一、化合物 21 之氫核磁共振圖譜($CDCl_3$, 200 MHz)



附圖八十二、化合物 21 之 ^{13}C 與 DEPT135 核磁共振圖譜



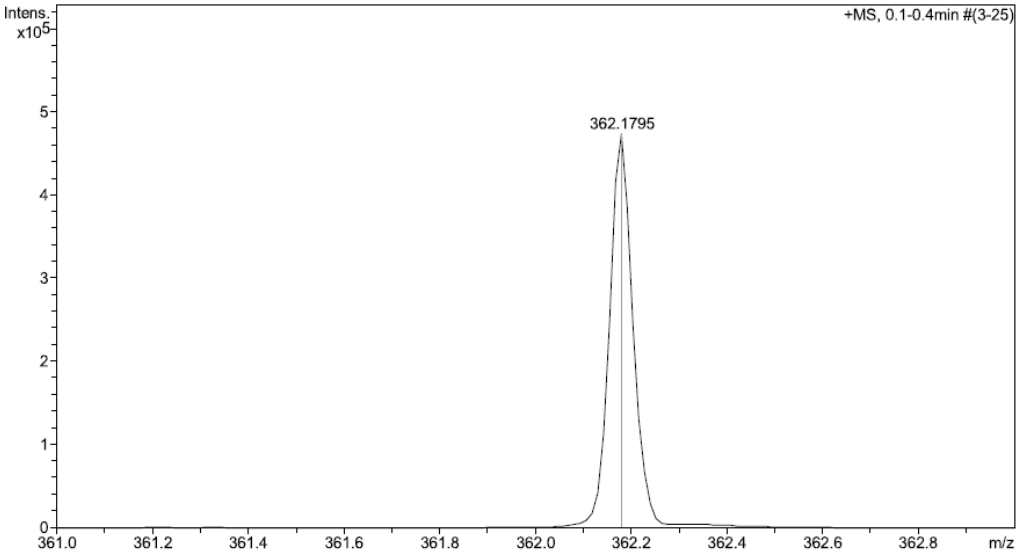
附圖八十三、化合物 21 之 HRESIMS 圖譜

Analysis Info

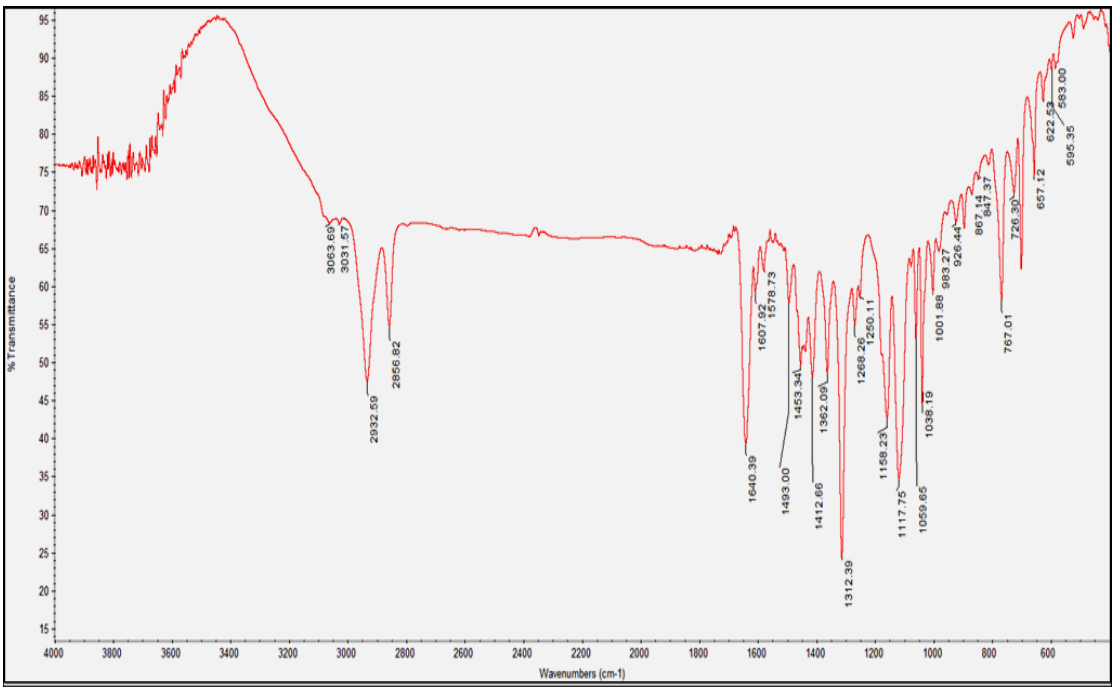
Analysis Name	D:\Data\lab1246\THC-155-02.d	Acquisition Date	2014/7/17 ?? 10:32:15
Method	esi_pos_low_lyp.d.m	Operator	default
Sample Name	THC-155-02	Instrument / Ser#	micrOTOF 10247
Comment			

Acquisition Parameter

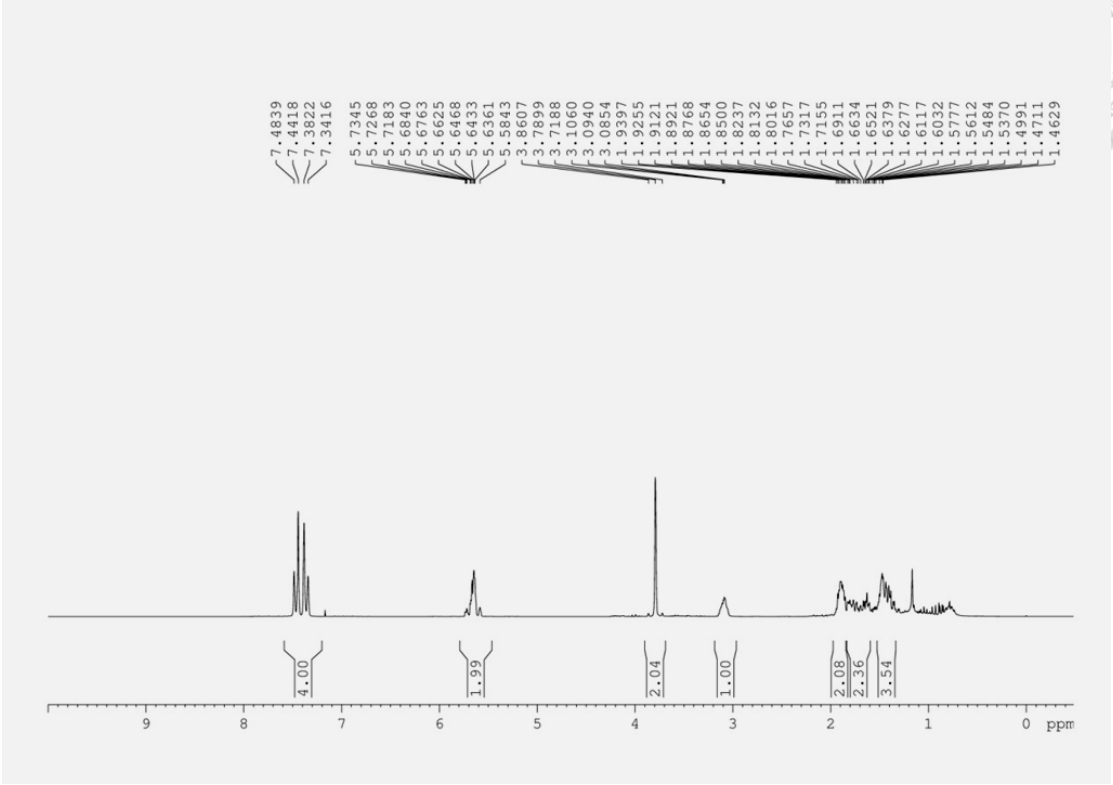
Source Type	ESI	Ion Polarity	Positive	Set Nebulizer	0.4 Bar
Focus	Not active			Set Dry Heater	250 ¢XC
Scan Begin	360 m/z	Set Capillary	3900 V	Set Dry Gas	4.0 l/min
Scan End	365 m/z	Set End Plate Offset	-500 V	Set Divert Valve	Source



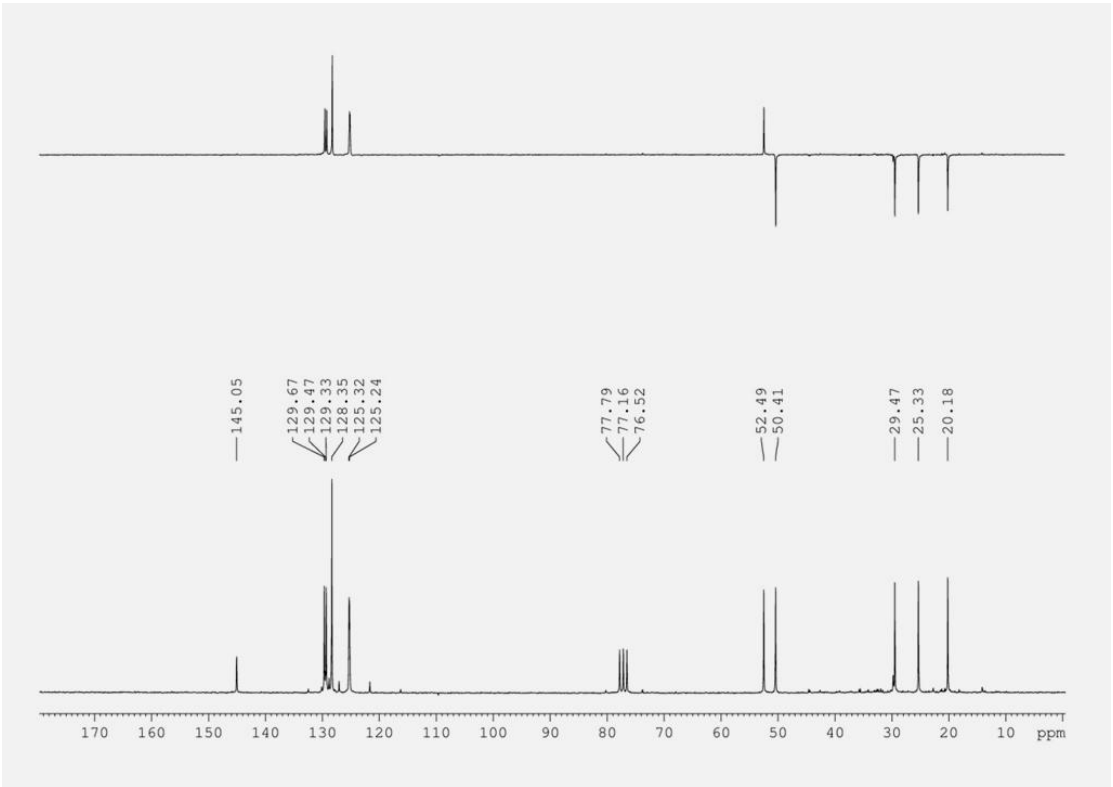
附圖八十四、化合物 21 之 IR 圖譜



附圖八十五、化合物 22 之氫核磁共振圖譜($CDCl_3$, 200 MHz)



附圖八十六、化合物 22 之 ^{13}C 與 DEPT135 核磁共振圖譜



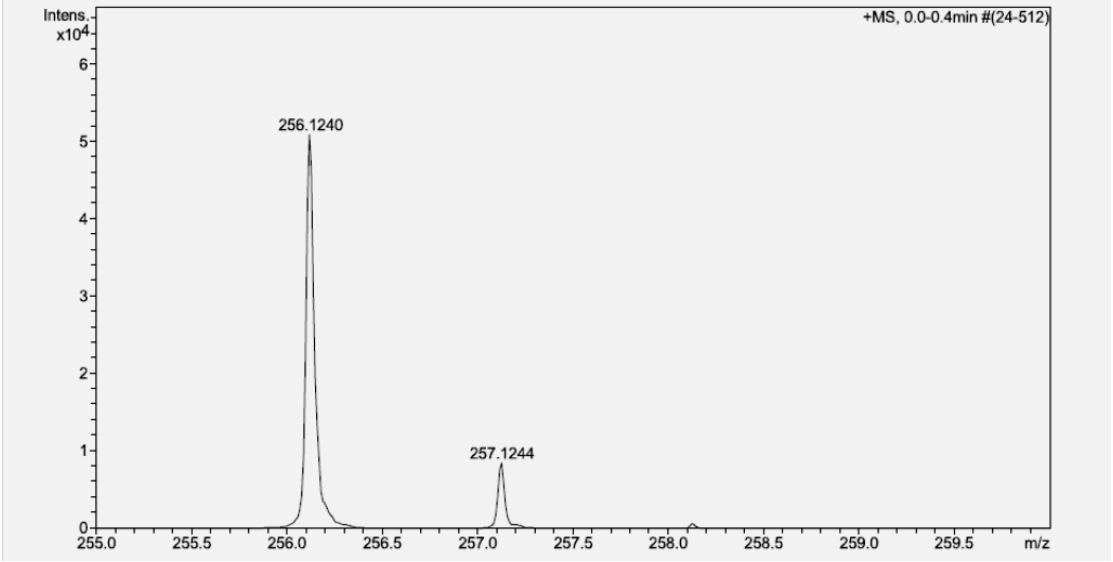
附圖八十七、化合物 22 之 HRESIMS 圖譜

Analysis Info

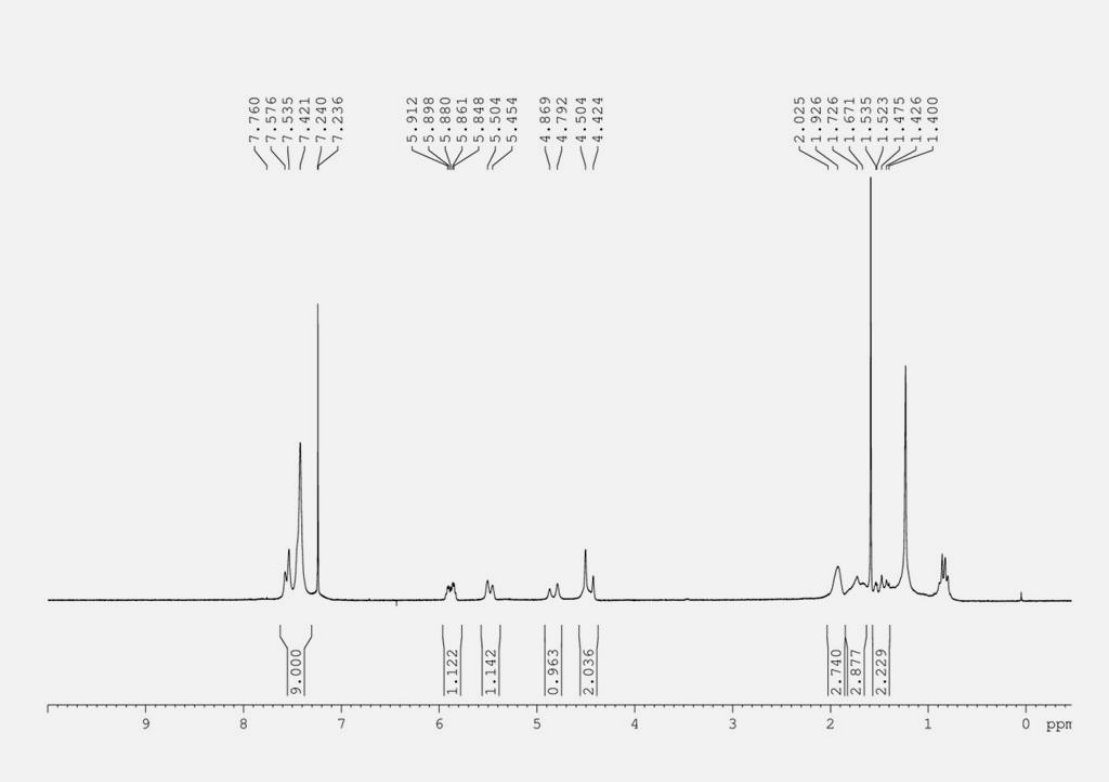
Analysis Name	D:\Data\lab1246\THC-007-02.d	Acquisition Date	2014/7/19 ?? 11:03:44
Method	esi_pos_low_lyp.d.m	Operator	default
Sample Name	THC-007-02	Instrument / Ser#	micrOTOF 10247
Comment			

Acquisition Parameter

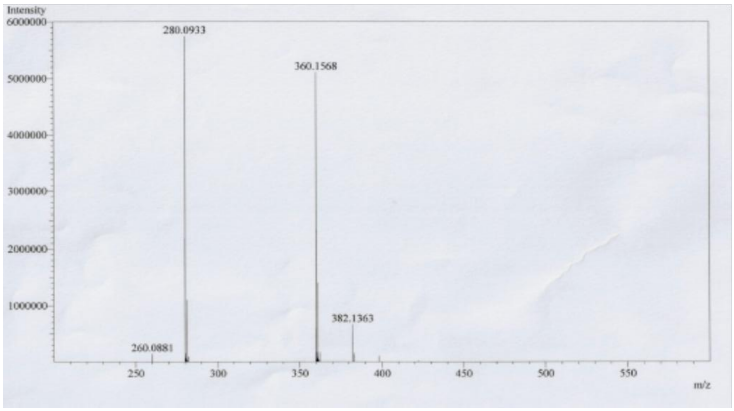
Source Type	ESI	Ion Polarity	Positive	Set Nebulizer	0.4 Bar
Focus	Not active			Set Dry Heater	250 ¢XC
Scan Begin	250 m/z	Set Capillary	4200 V	Set Dry Gas	4.0 l/min
Scan End	260 m/z	Set End Plate Offset	-500 V	Set Divert Valve	Source



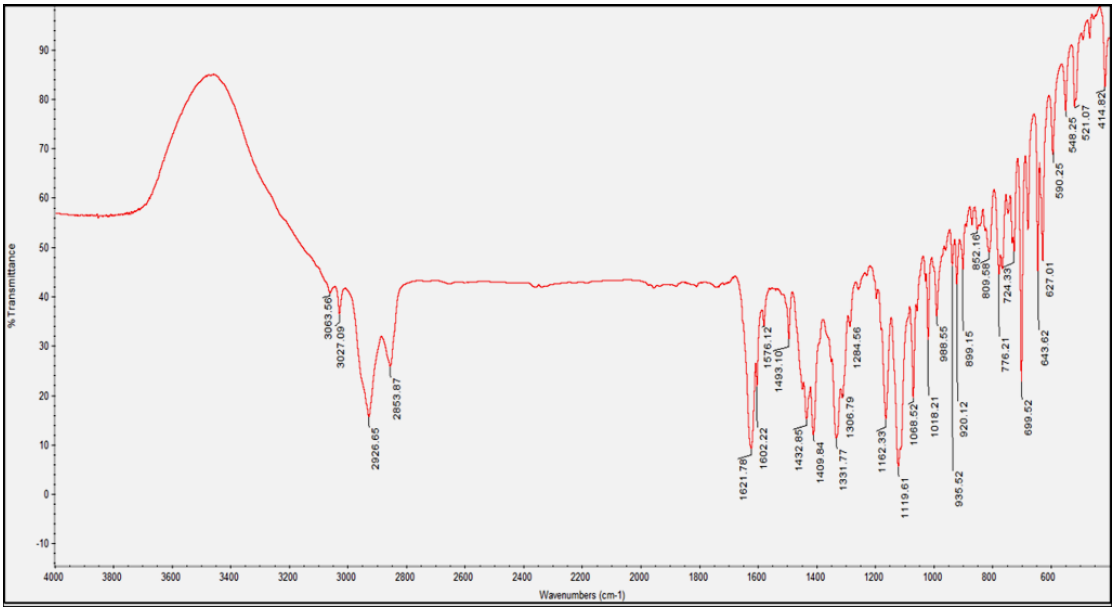
附圖八十九、化合物 23 之氫核磁共振圖譜($CDCl_3$, 200 MHz)



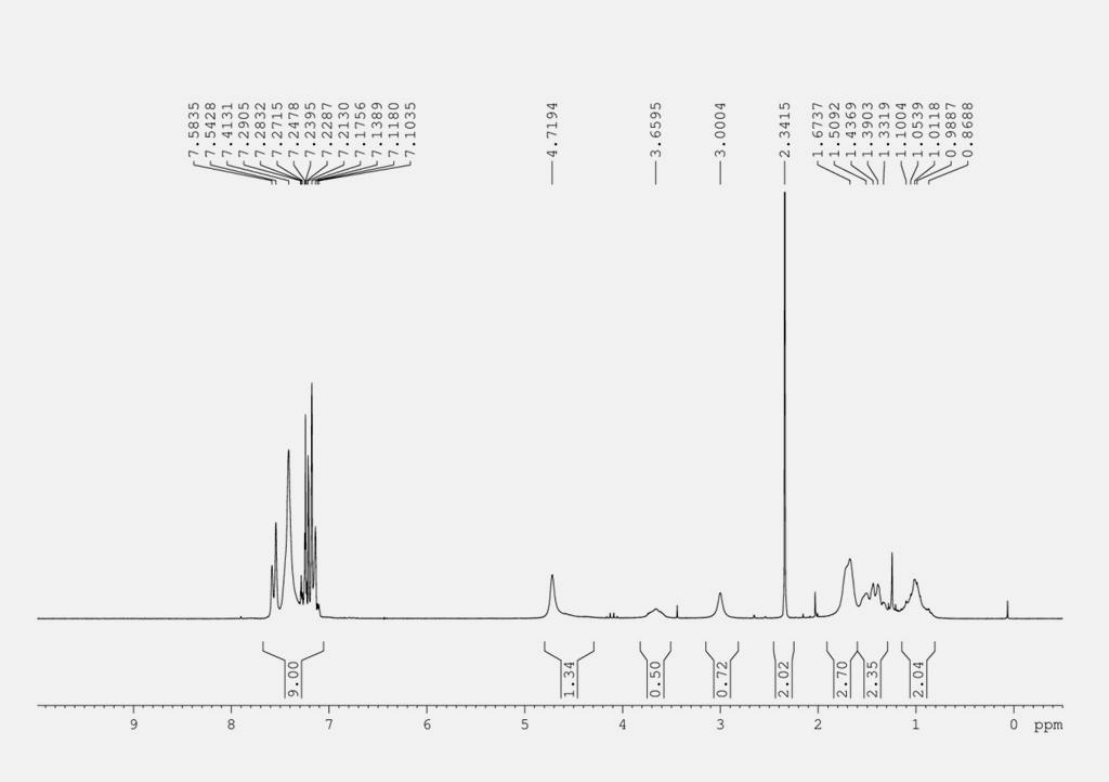
附圖九十一、化合物 23 之 HRESIMS 圖譜



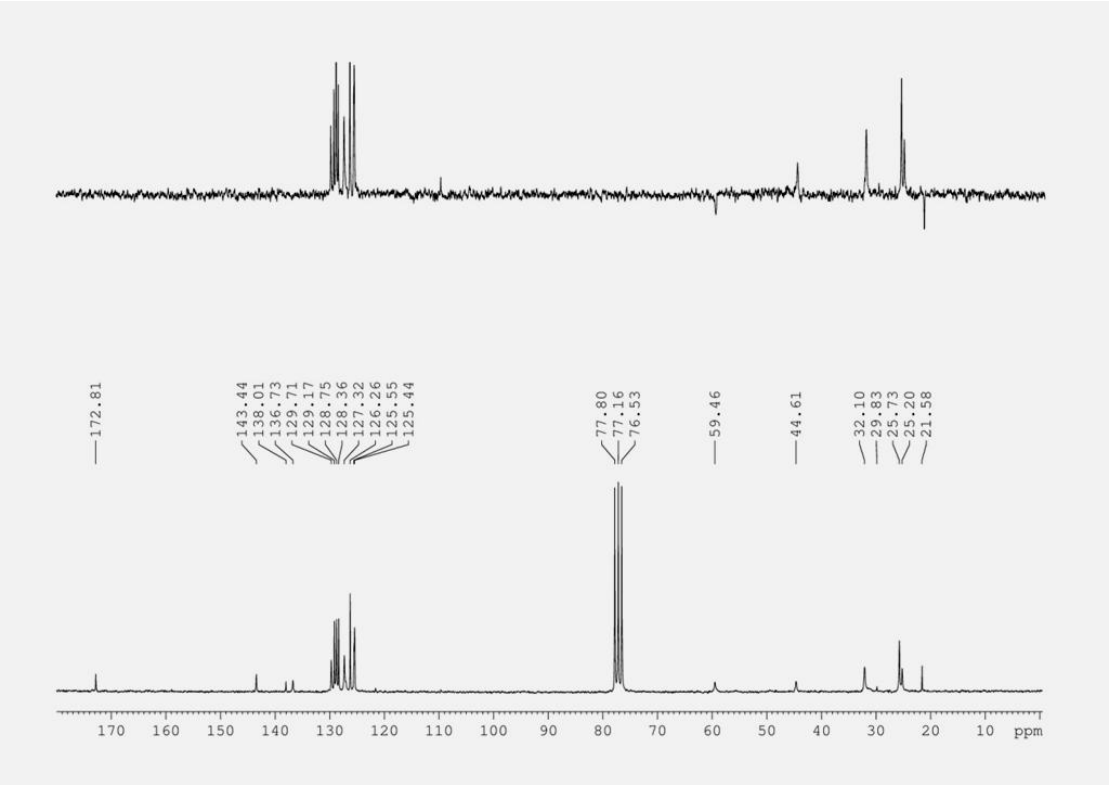
附圖九十二、化合物 23 之 IR 圖譜



附圖九十三、化合物 24 之氫核磁共振圖譜($CDCl_3$, 200 MHz)



附圖九十四、化合物 24 之 ^{13}C 與 DEPT135 核磁共振圖譜



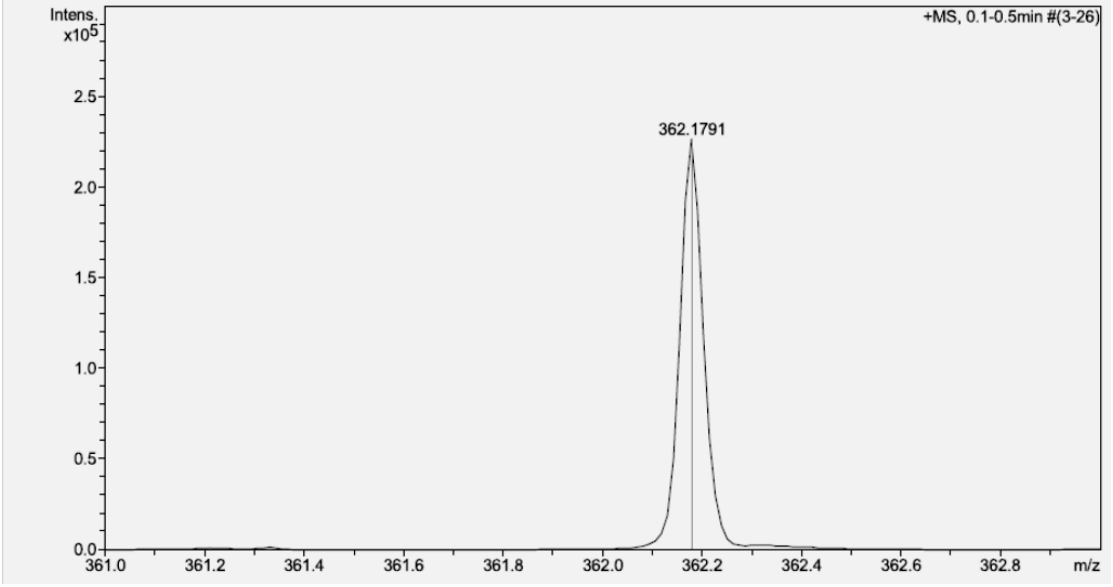
附圖九十五、化合物 24 之 HRESIMS 圖譜

Analysis Info

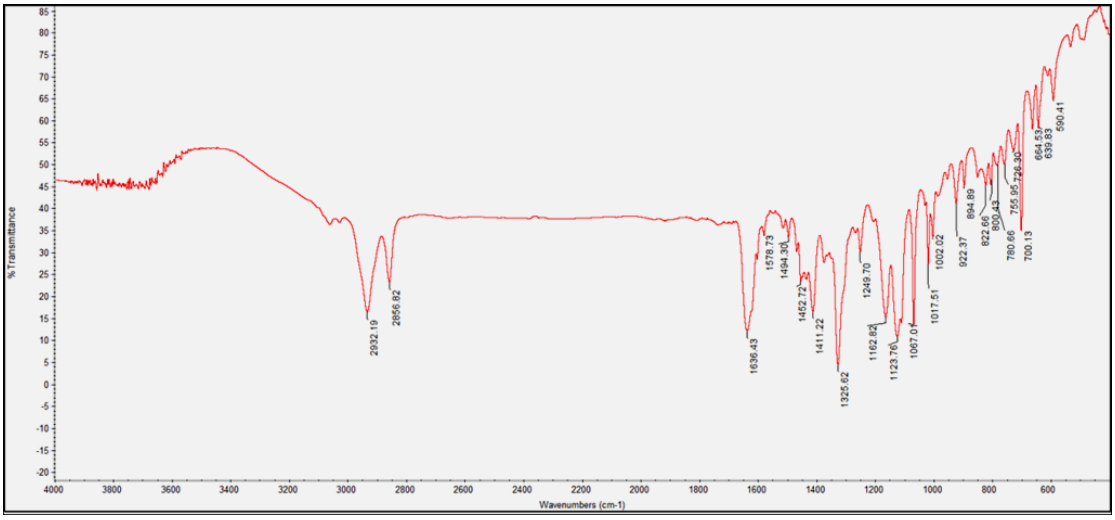
Analysis Name	D:\Data\lab1246\THC-157-02.d	Acquisition Date	2014/7/17 ?? 10:39:36
Method	esi_pos_low_lyp.d.m	Operator	default
Sample Name	THC-157-02	Instrument / Ser#	micrOTOF 10247
Comment			

Acquisition Parameter

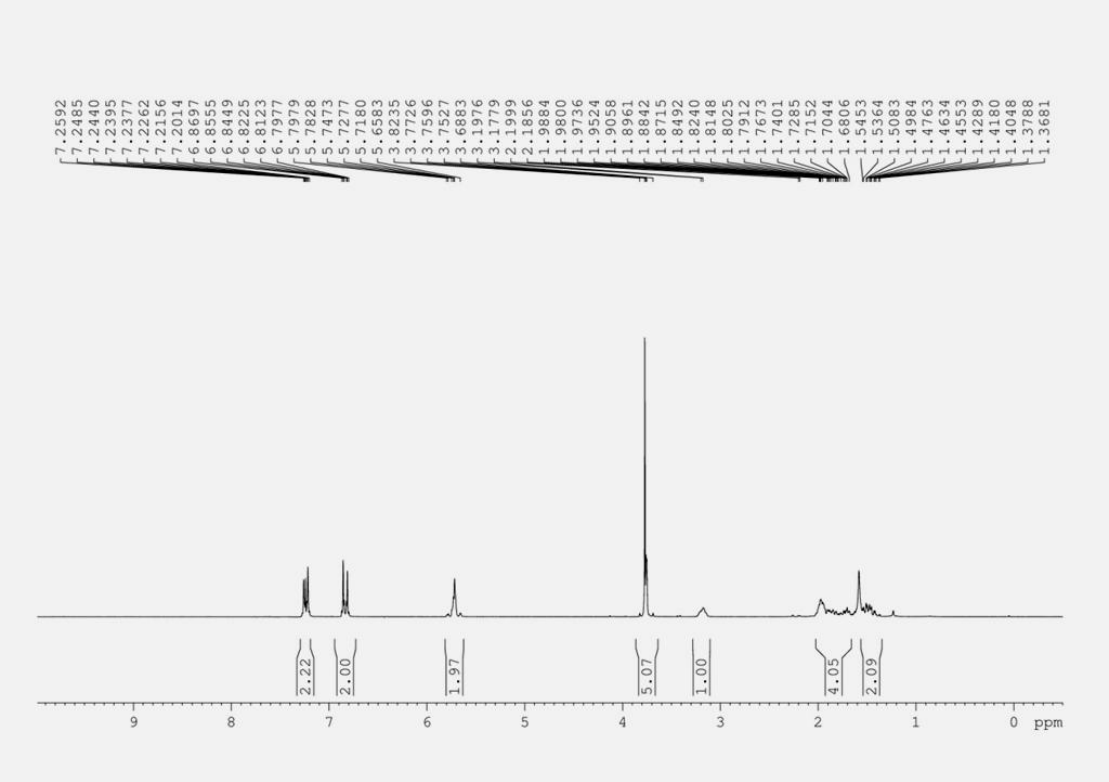
Source Type	ESI	Ion Polarity	Positive	Set Nebulizer	0.4 Bar
Focus	Not active			Set Dry Heater	250 ¢XC
Scan Begin	360 m/z	Set Capillary	3900 V	Set Dry Gas	4.0 l/min
Scan End	365 m/z	Set End Plate Offset	-500 V	Set Divert Valve	Source



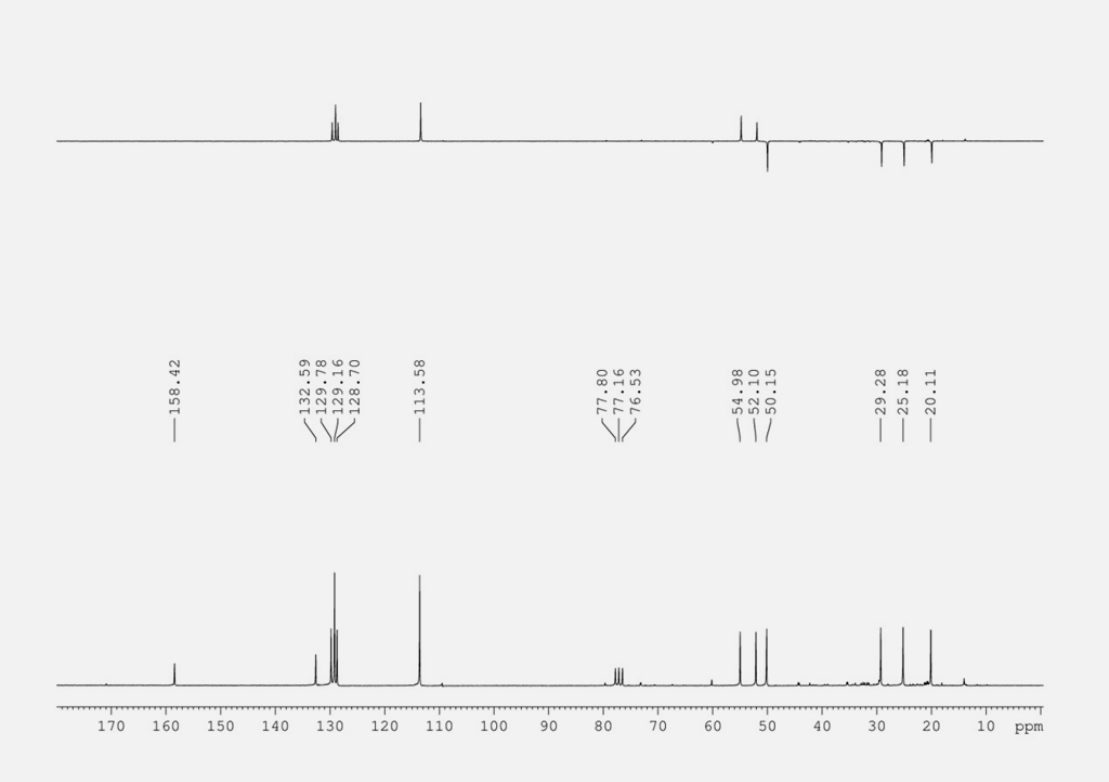
附圖九十六、化合物 24 之 IR 圖譜



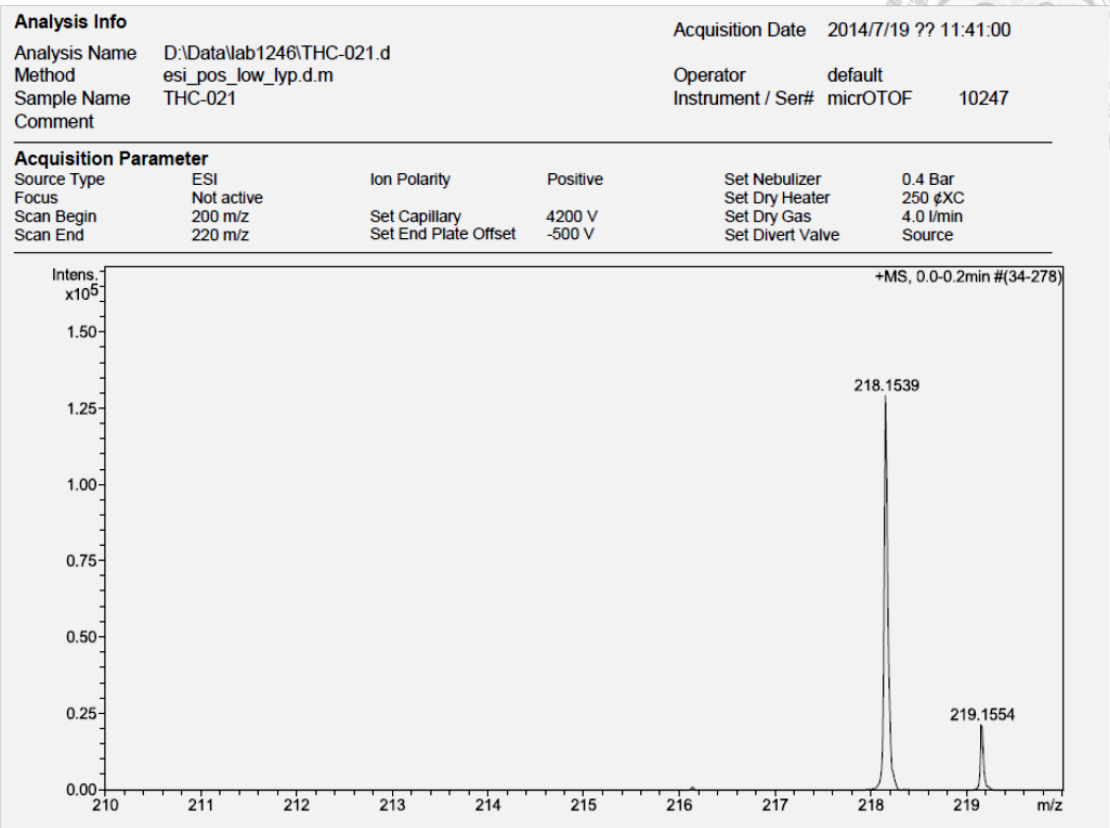
附圖九十七、化合物 25 之氫核磁共振圖譜($CDCl_3$, 200 MHz)



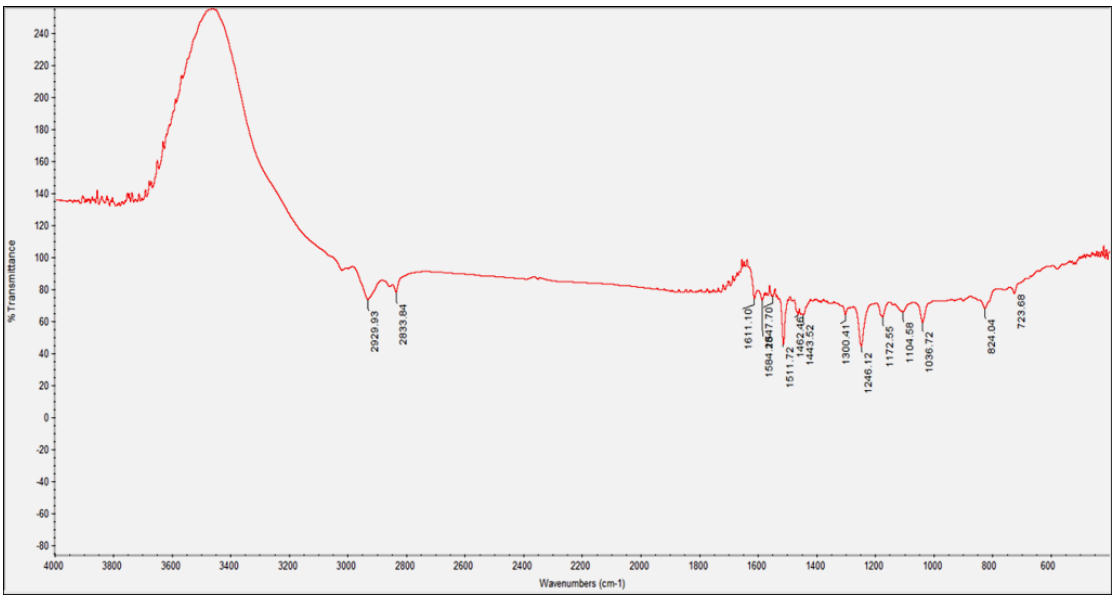
附圖九十八、化合物 25 之 ^{13}C 與 DEPT135 核磁共振圖譜



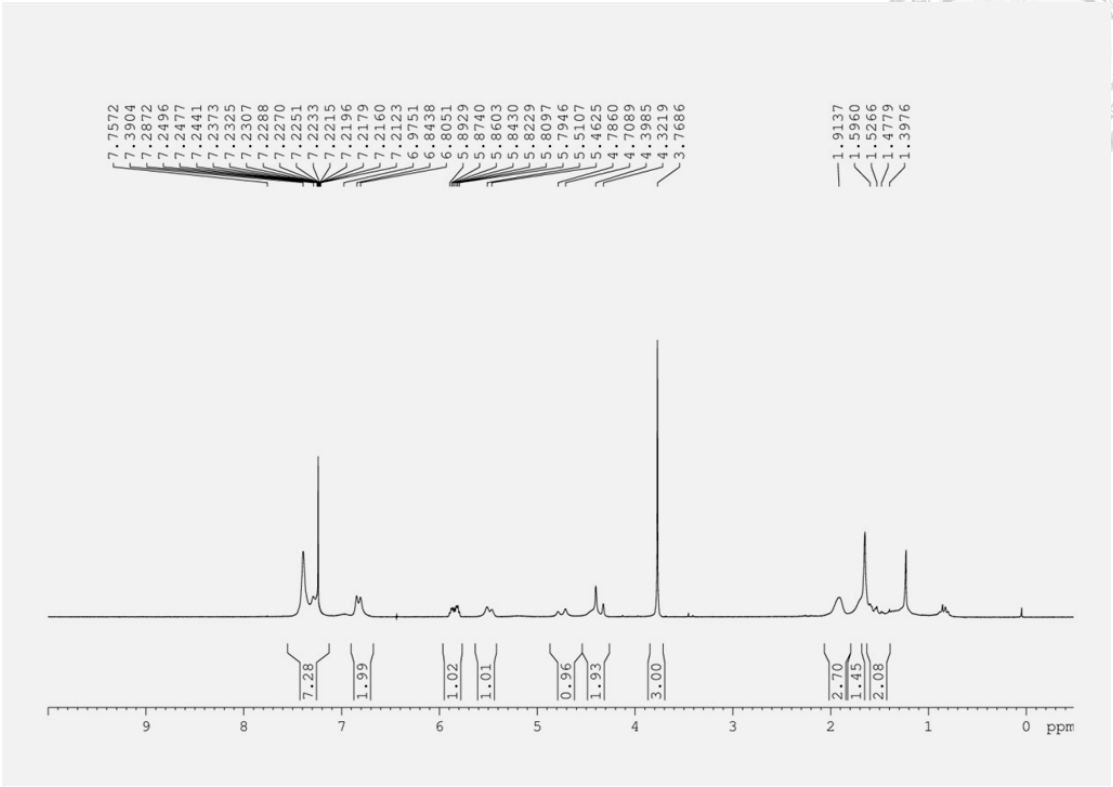
附圖九十九、化合物 25 之 HRESIMS 圖譜



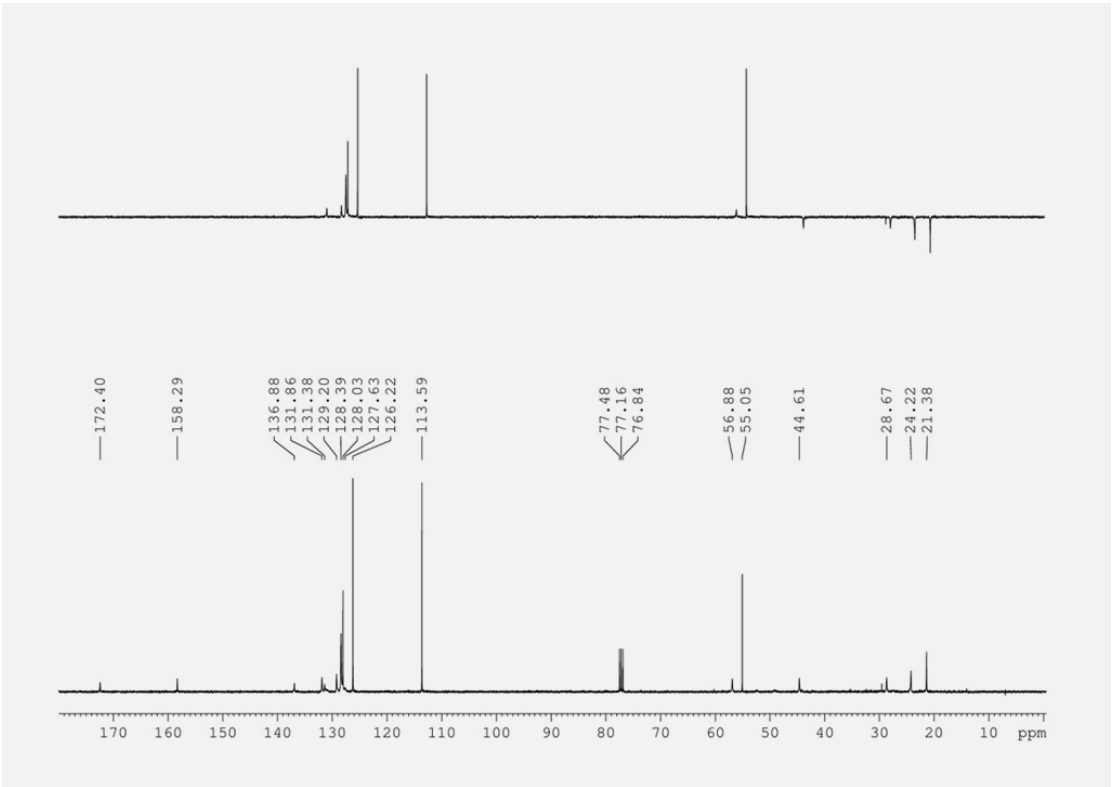
附圖一百、化合物 25 之 IR 圖譜



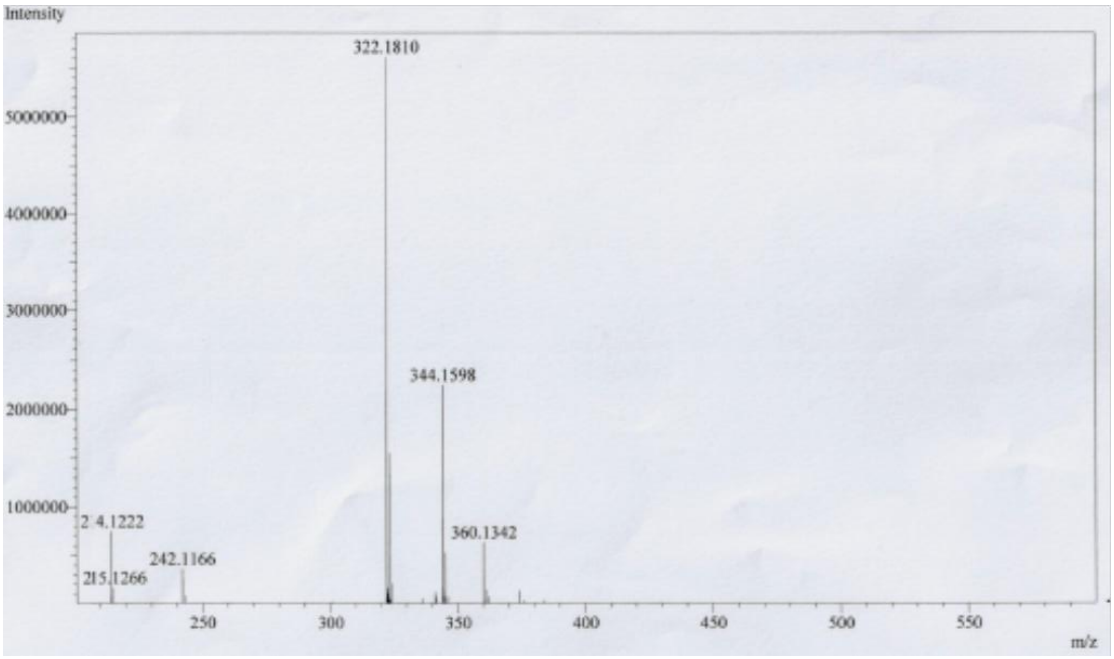
附圖一百零一、化合物 26 之氫核磁共振圖譜($CDCl_3$, 200 MHz)



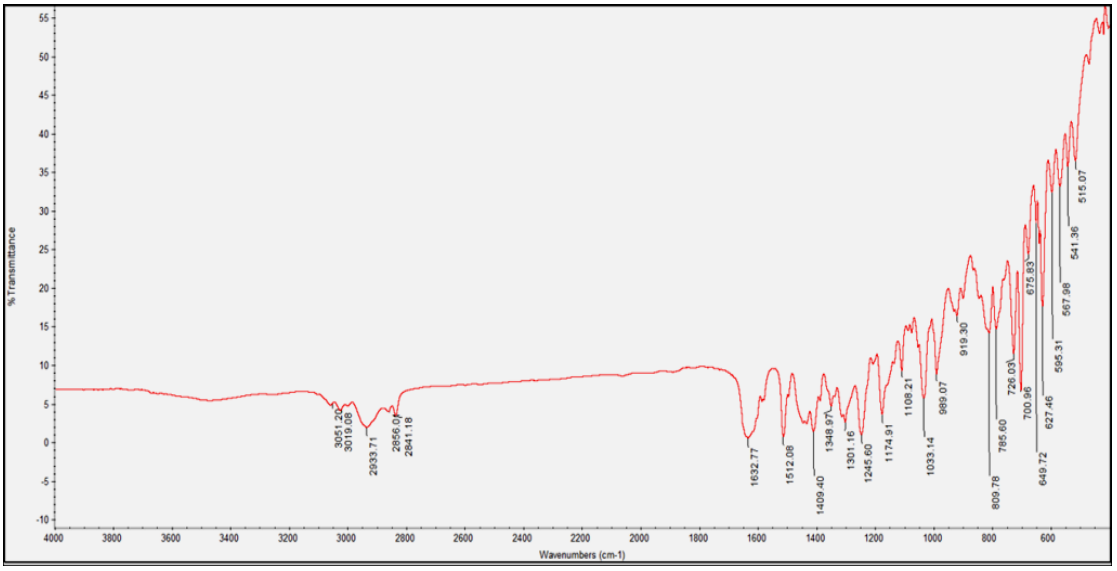
附圖一百零二、化合物 26 之 ^{13}C 與 DEPT135 核磁共振圖譜



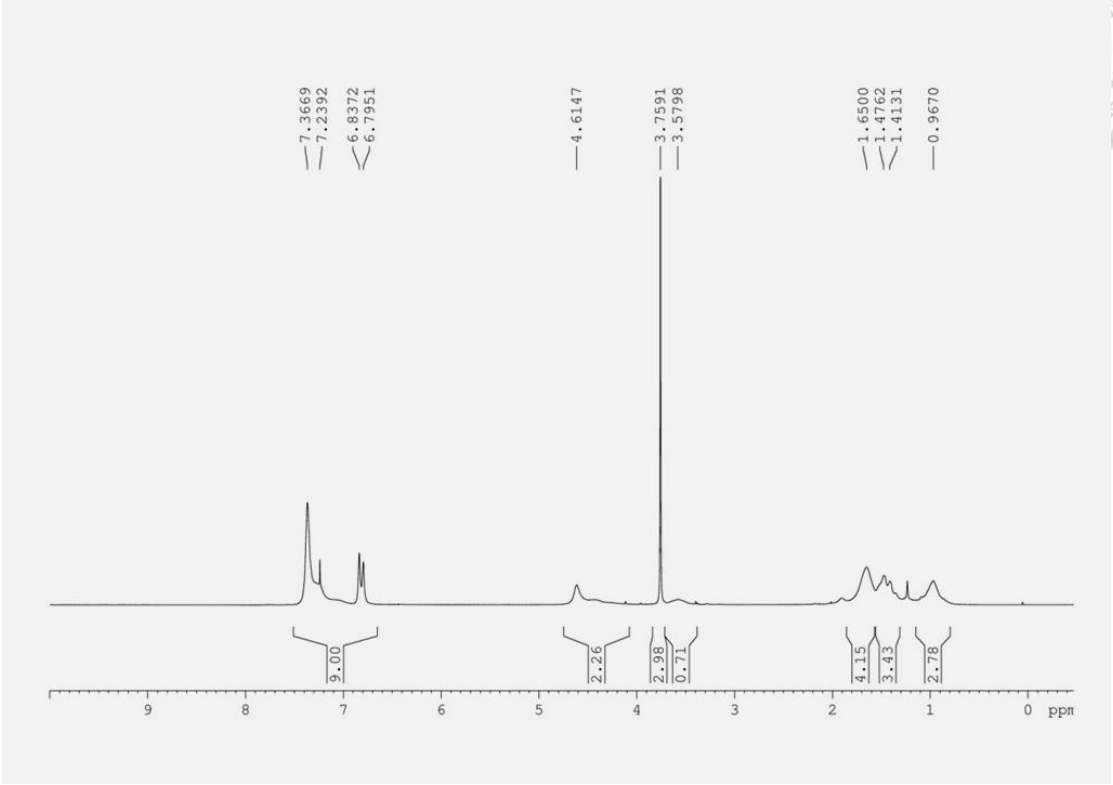
附圖一百零三、化合物 26 之 HRESIMS 圖譜



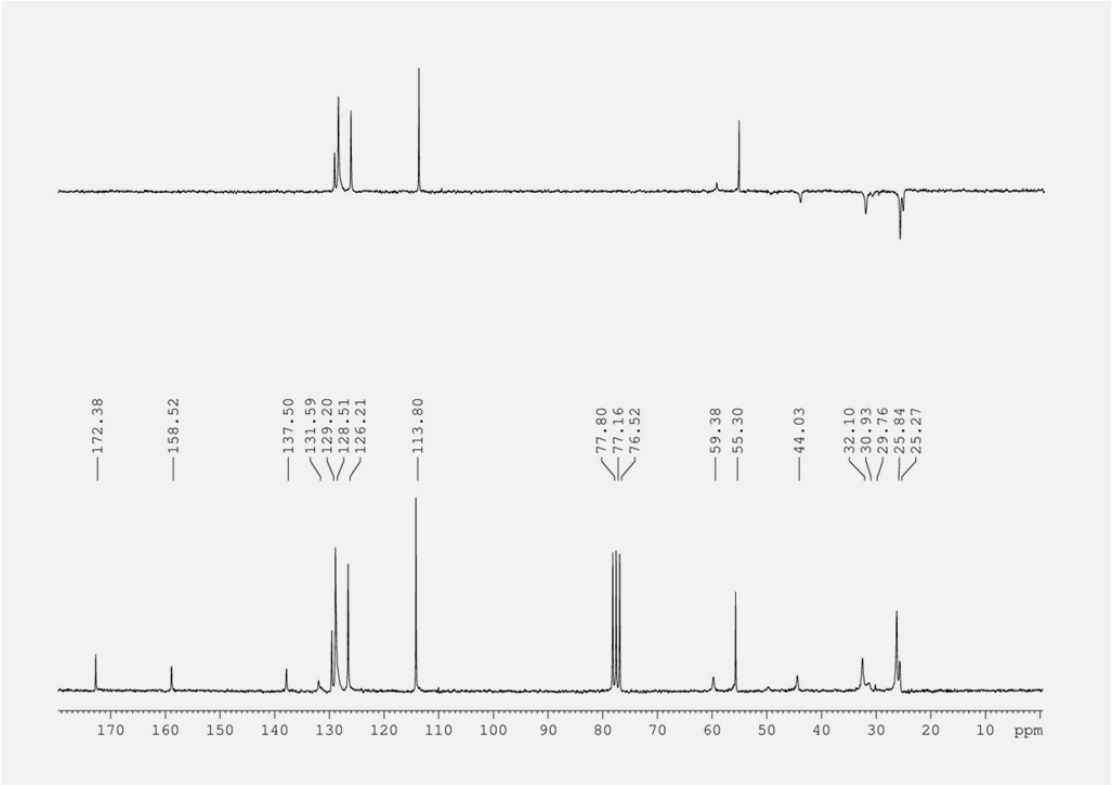
附圖一百零四、化合物 26 之 IR 圖譜



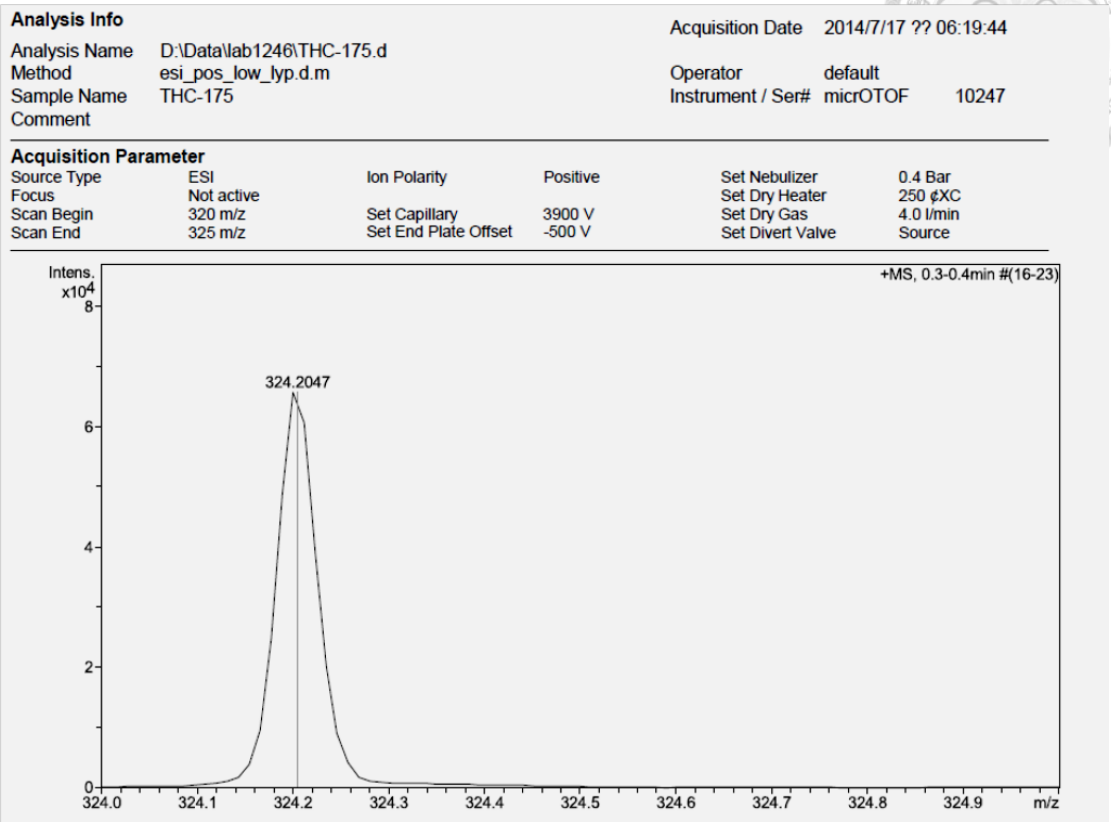
附圖一百零五、化合物 27 之氫核磁共振圖譜($CDCl_3$, 200 MHz)



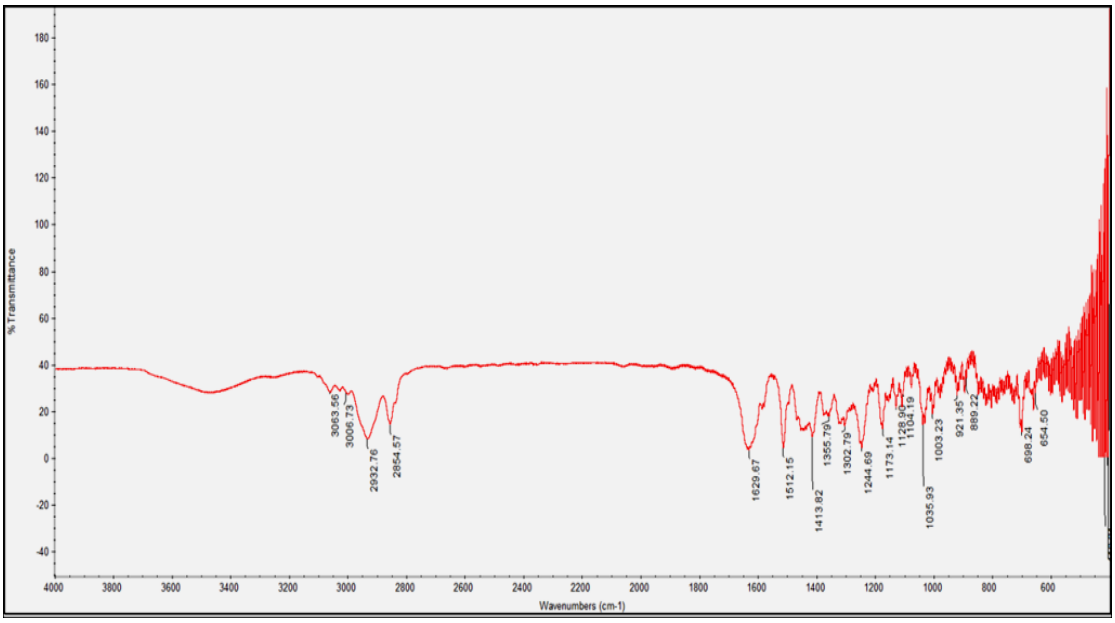
附圖一百零六、化合物 27 之 ^{13}C 與 DEPT135 核磁共振圖譜



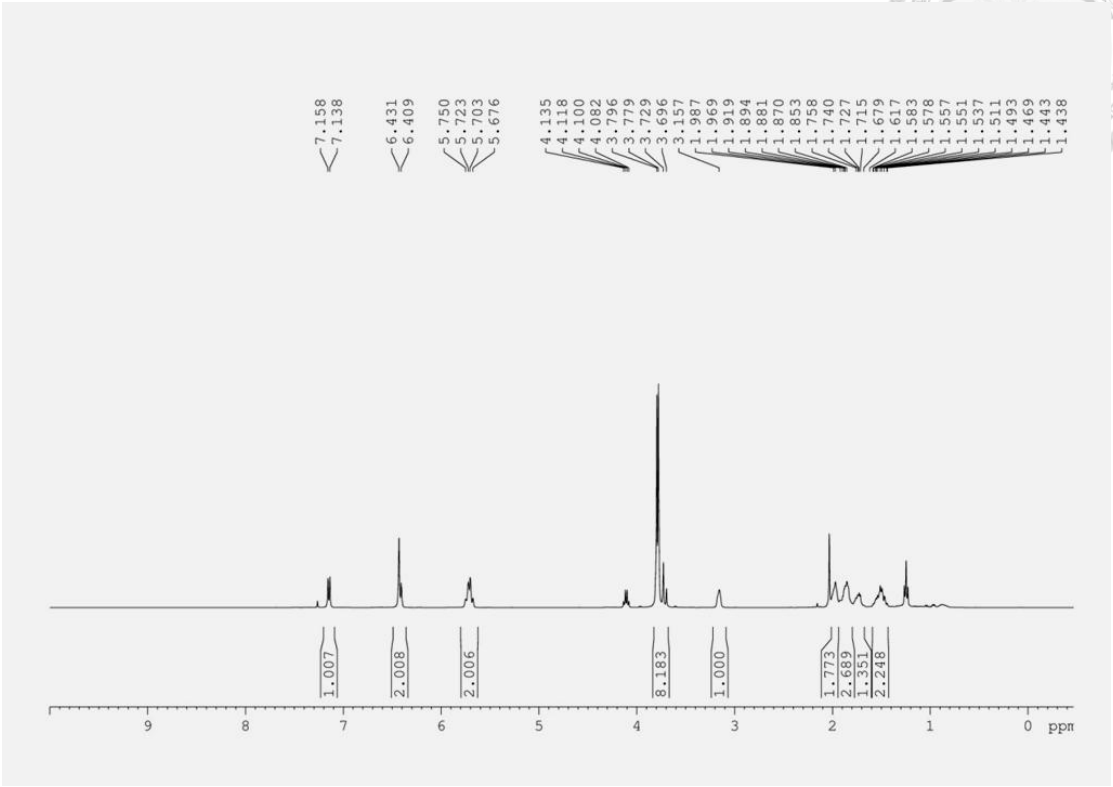
附圖一百零七、化合物 27 之 HRESIMS 圖譜



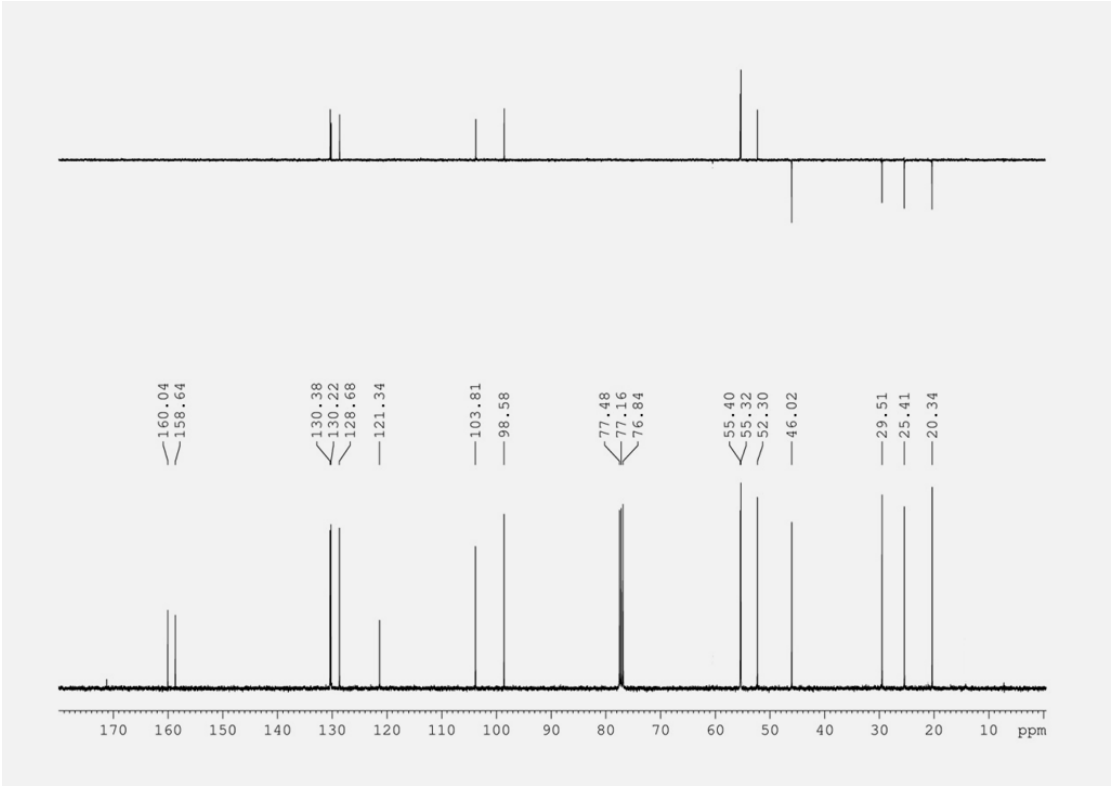
附圖一百零八、化合物 27 之 IR 圖譜



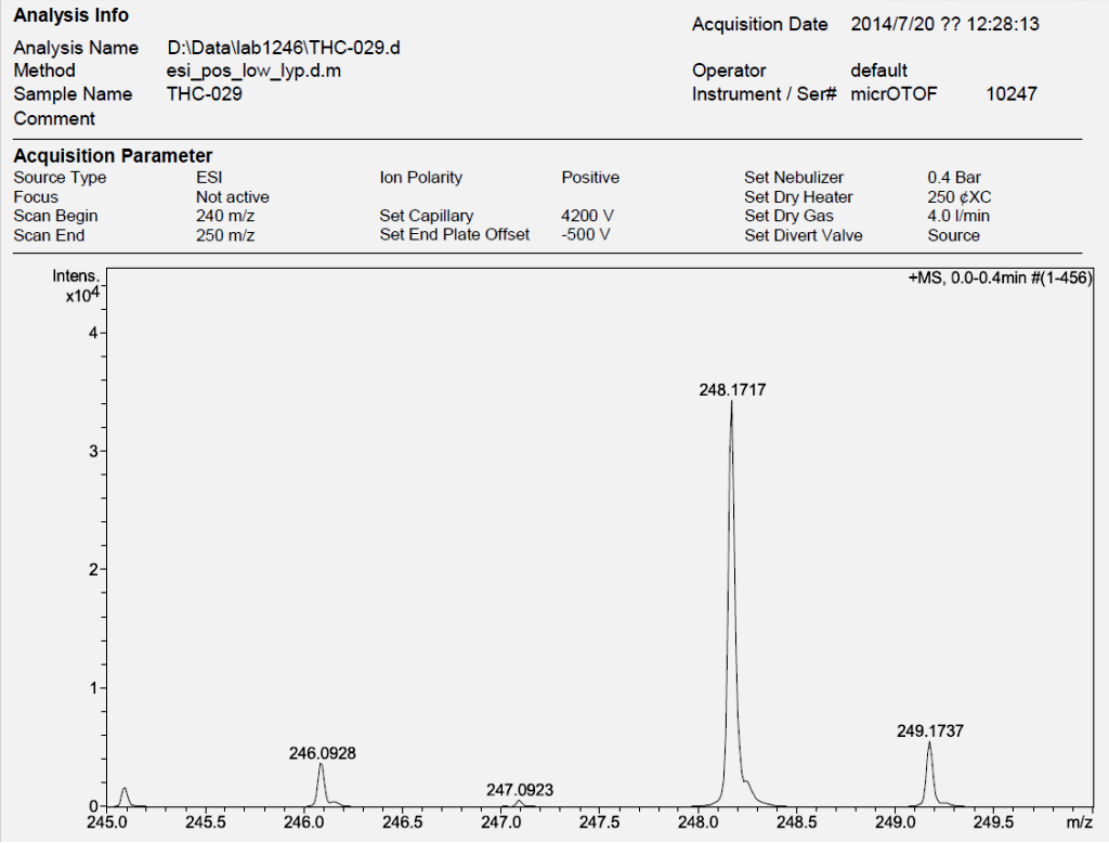
附圖一百零九、化合物 28 之氫核磁共振圖譜($CDCl_3$, 200 MHz)



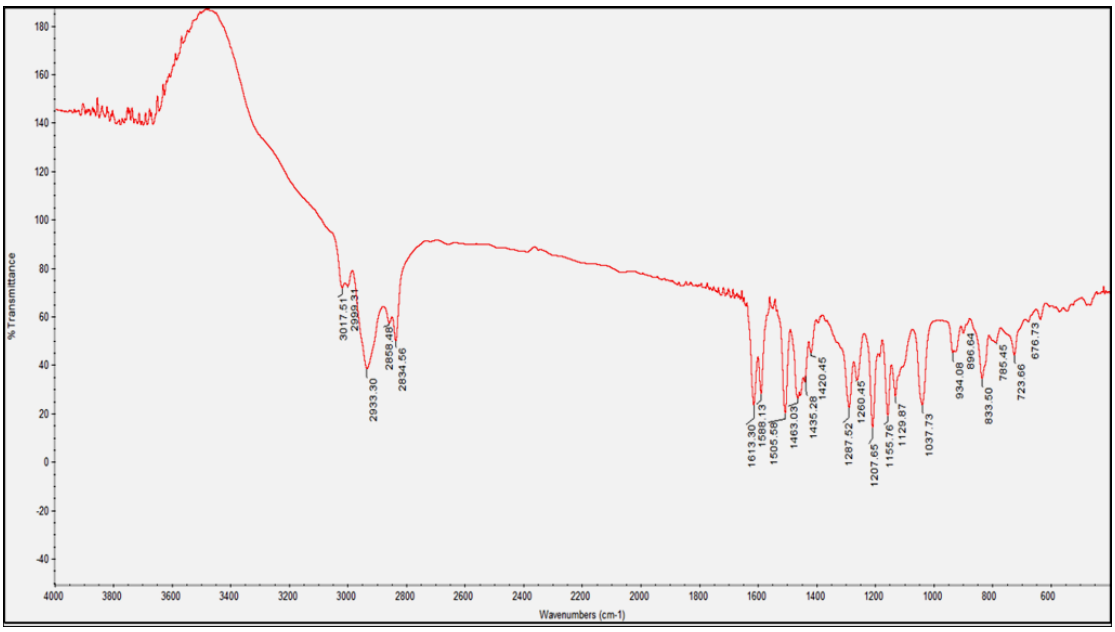
附圖一百一十、化合物 28 之 ^{13}C 與 DEPT135 核磁共振圖譜



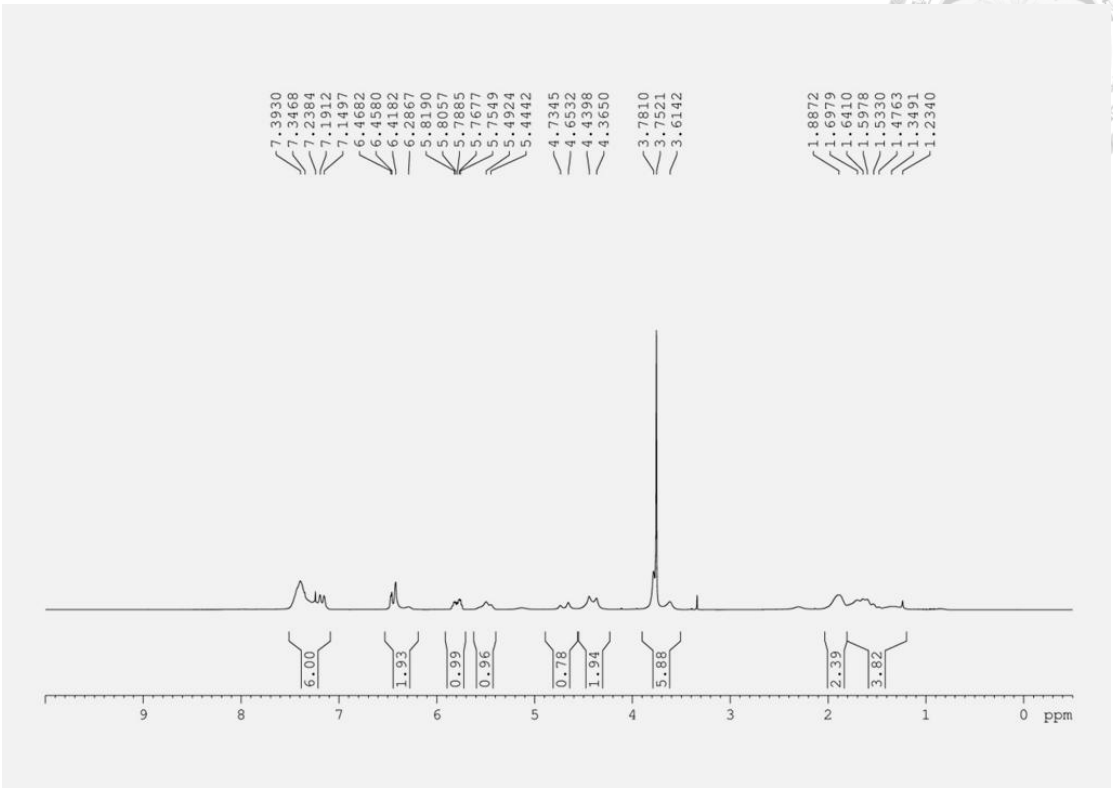
附圖一百一十一、化合物 28 之 HRESIMS 圖譜



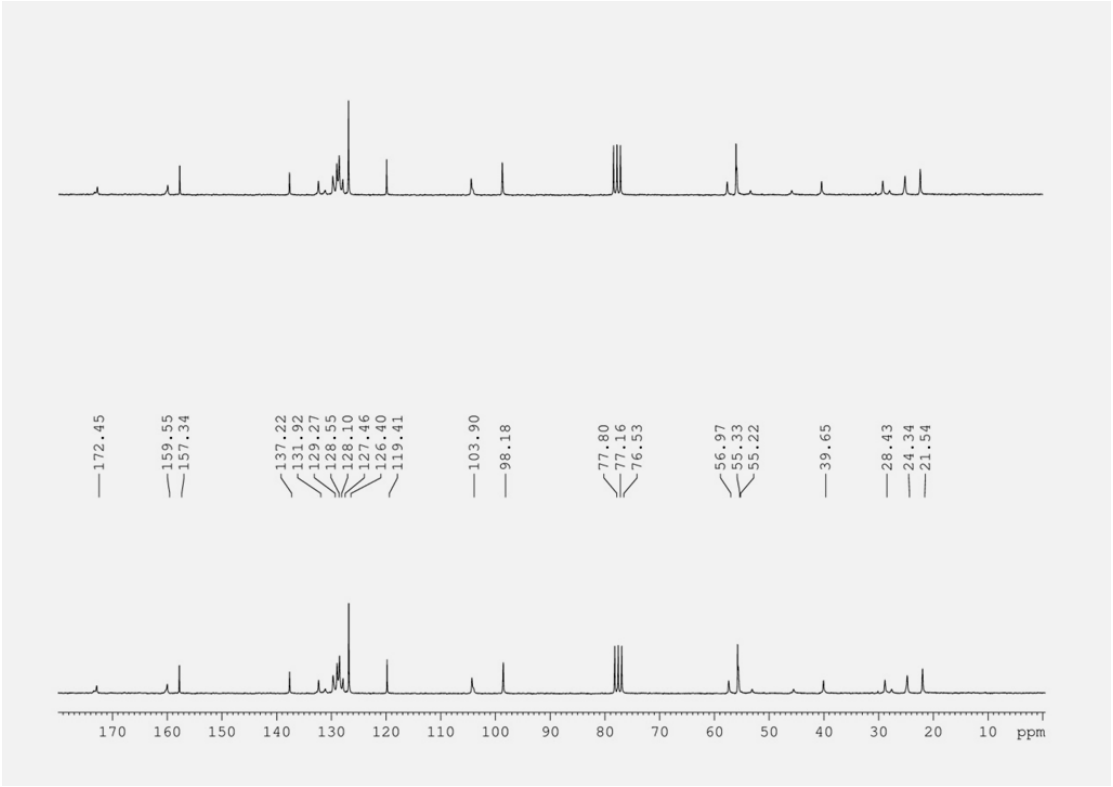
附圖一百一十二、化合物 28 之 IR 圖譜



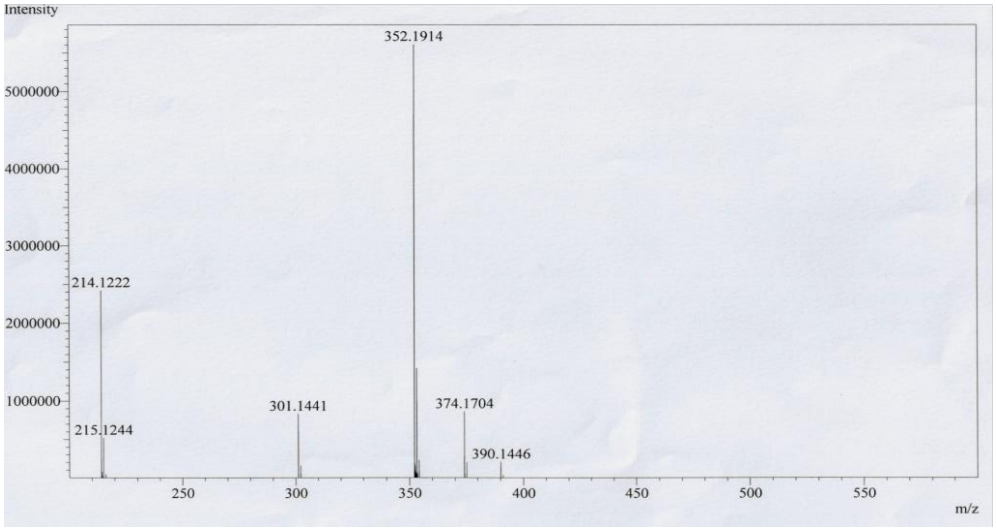
附圖一百一十三、化合物 29 之氫核磁共振圖譜($CDCl_3$, 200 MHz)



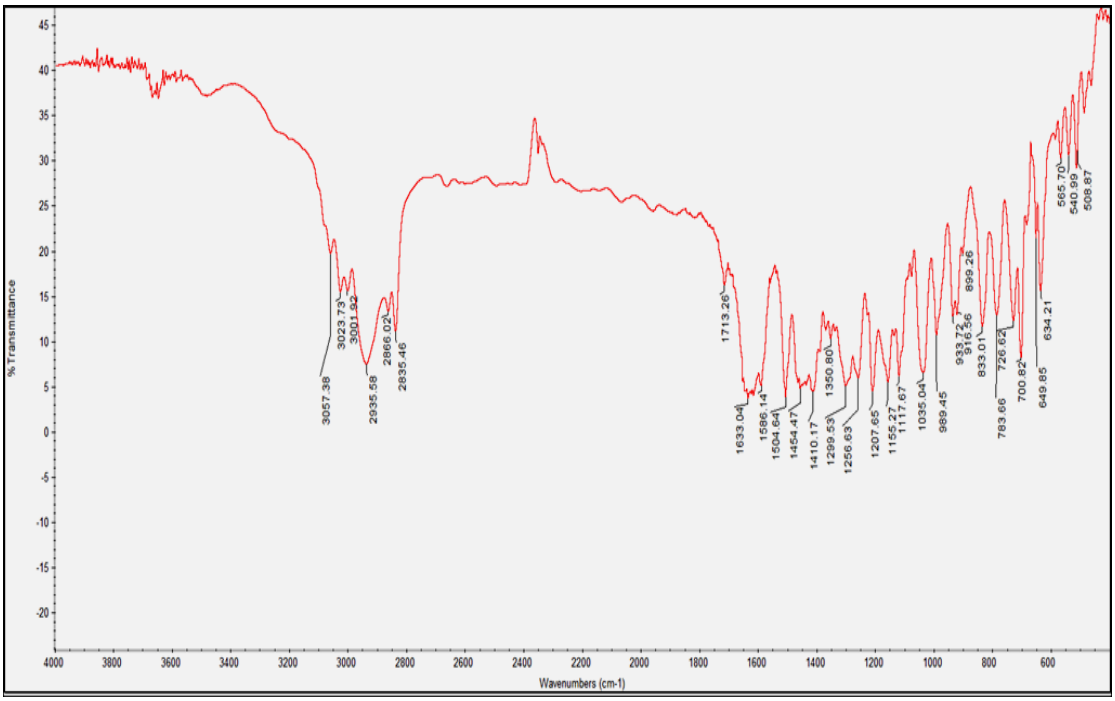
附圖一百一十四、化合物 29 之 ^{13}C 與 DEPT135 核磁共振圖譜



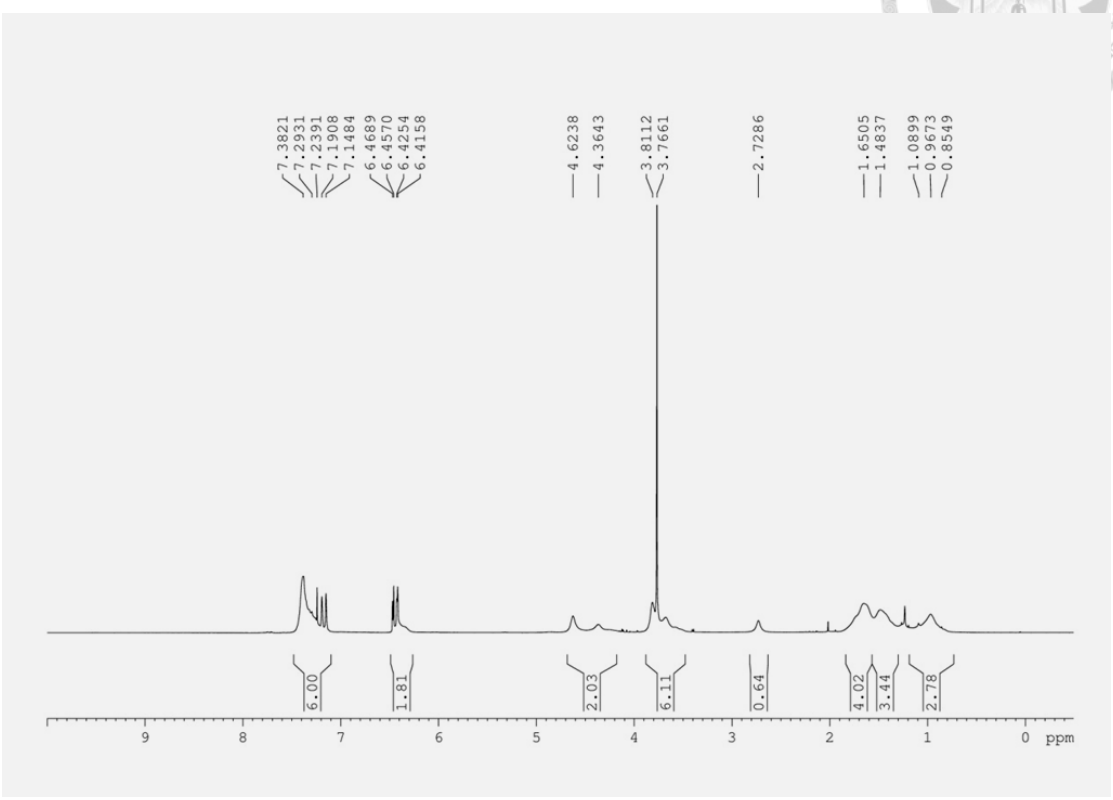
附圖一百一十五、化合物 29 之 HRESIMS 圖譜



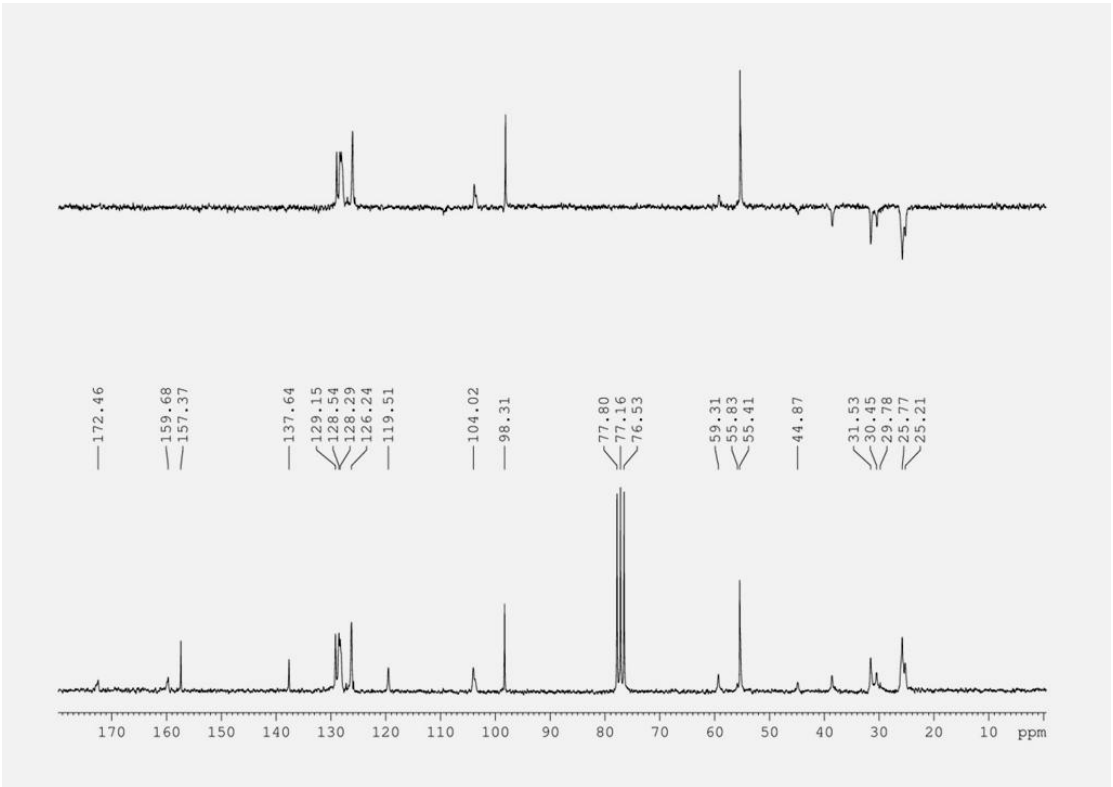
附圖一百一十六、化合物 29 之 IR 圖譜



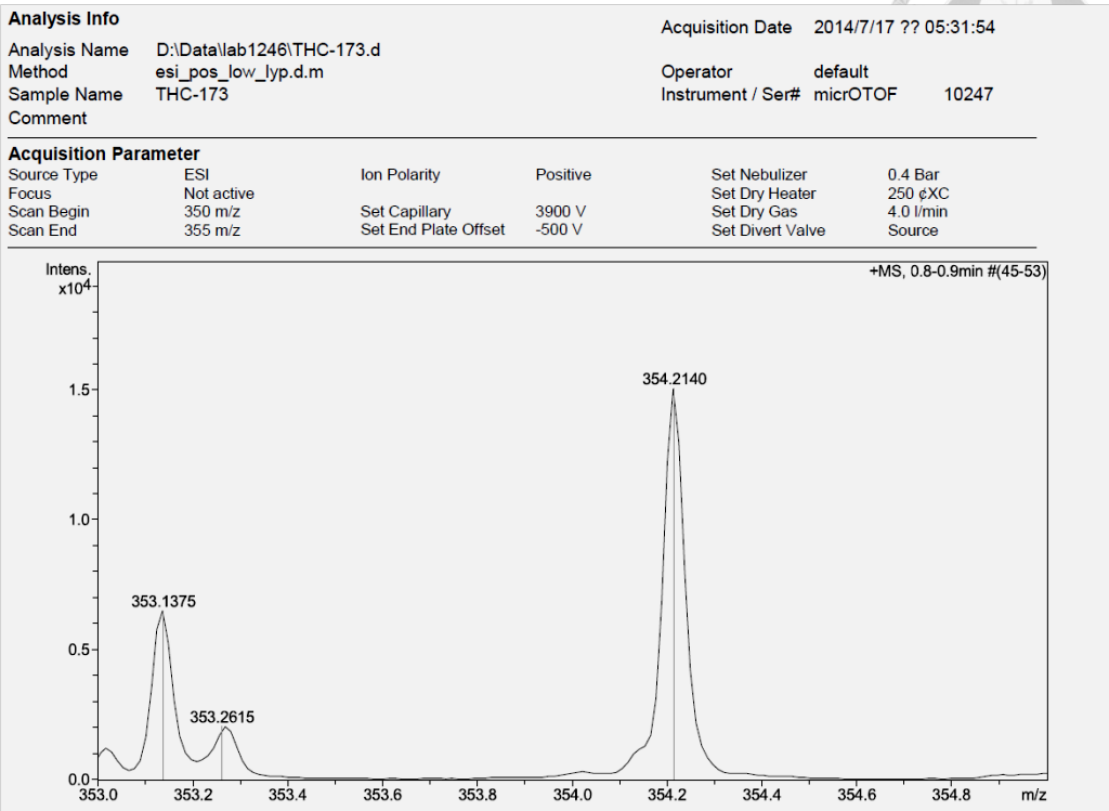
附圖一百一十七、化合物 30 之氫核磁共振圖譜($CDCl_3$, 200 MHz)



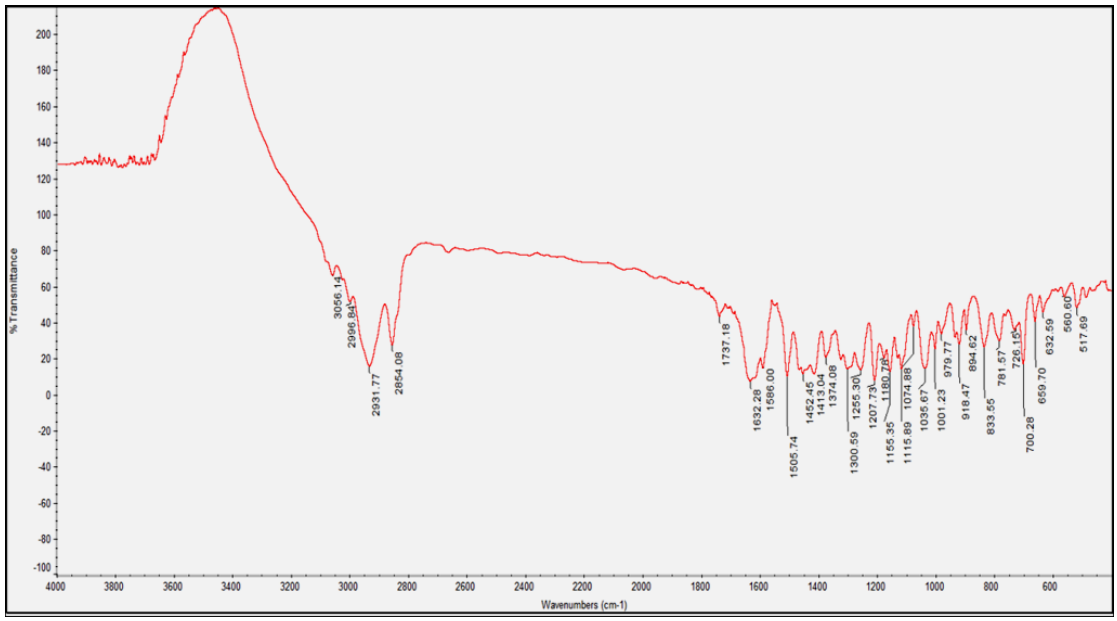
附圖一百一十八、化合物 30 之 ^{13}C 與 DEPT135 核磁共振圖譜



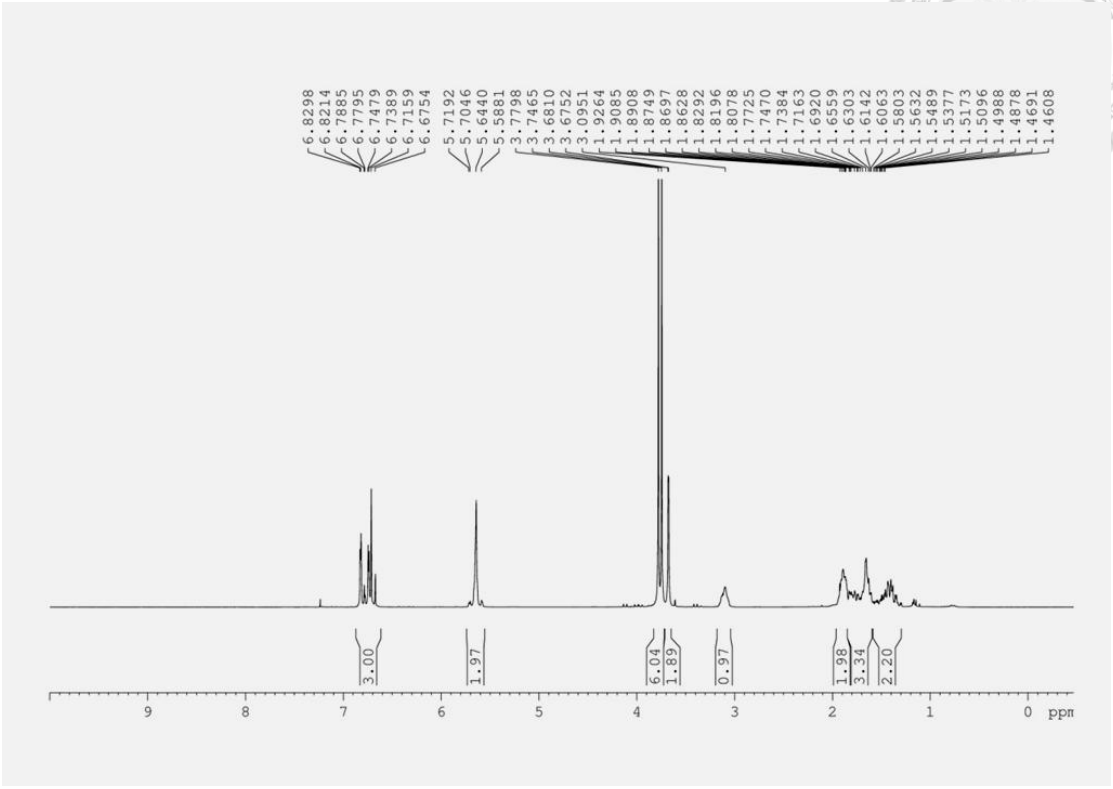
附圖一百一十九、化合物 30 之 HRESIMS 圖譜



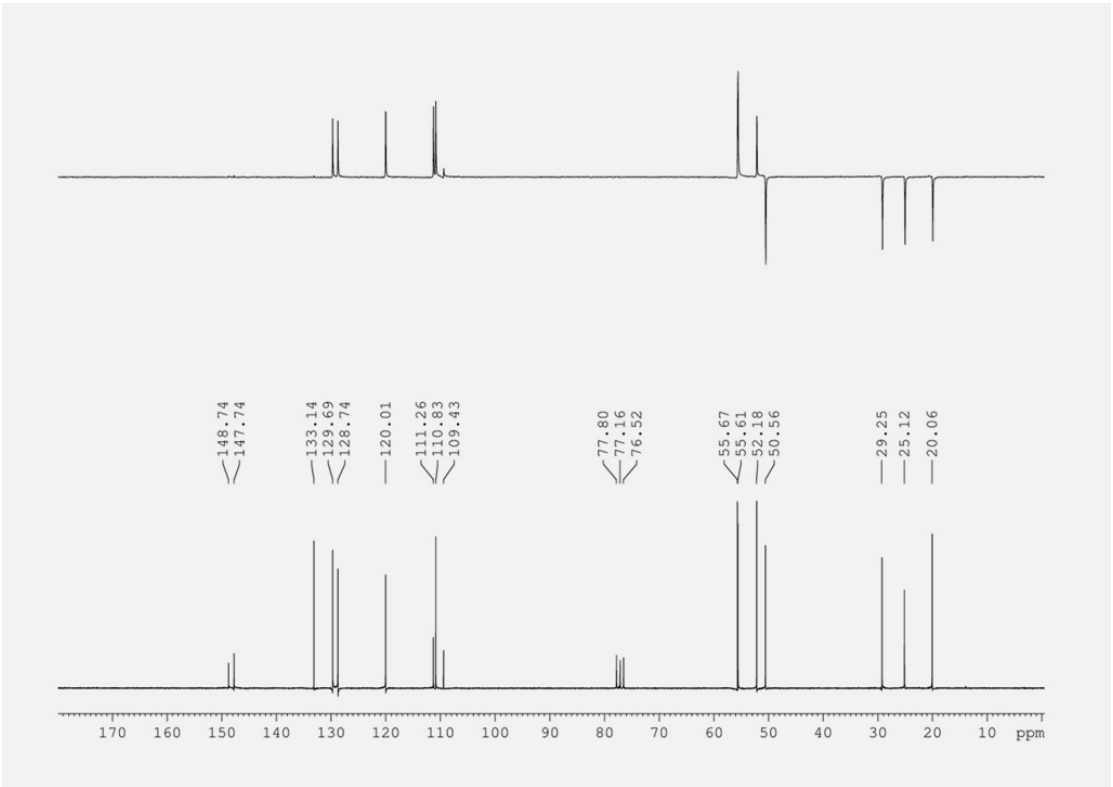
附圖一百二十、化合物 30 之 IR 圖譜



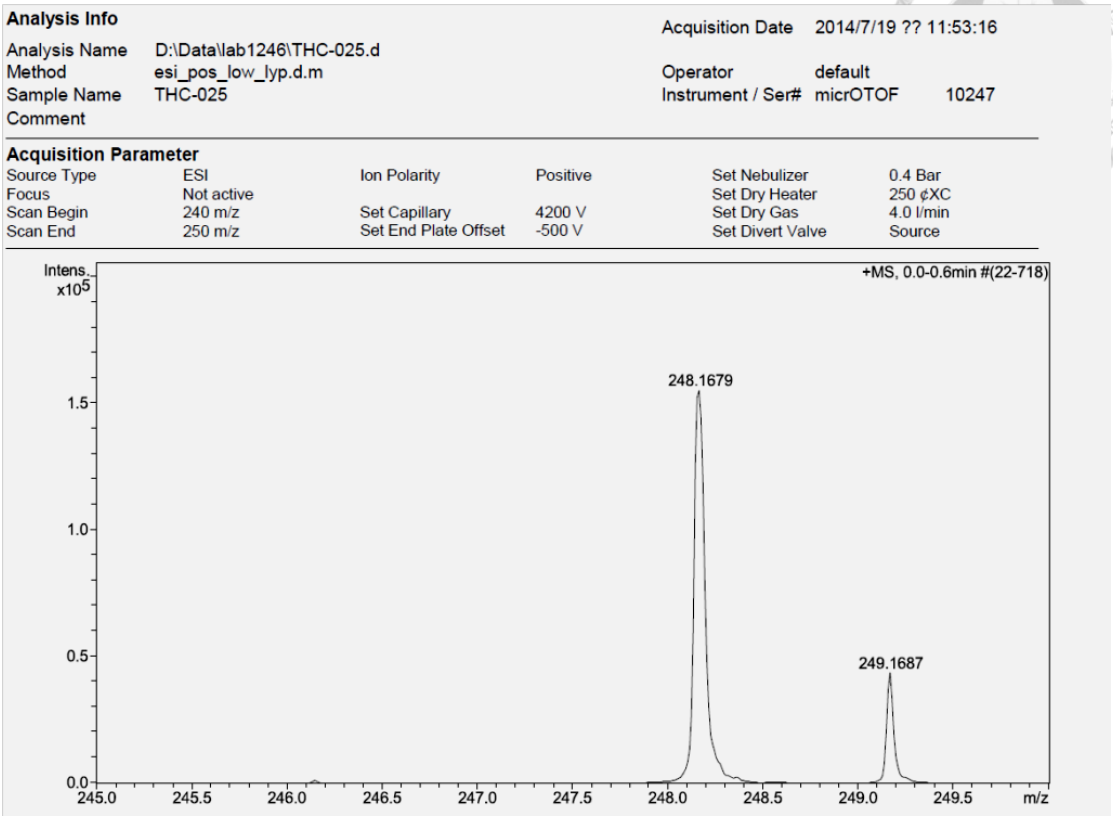
附圖一百二十一、化合物 31 之氫核磁共振圖譜($CDCl_3$, 200 MHz)



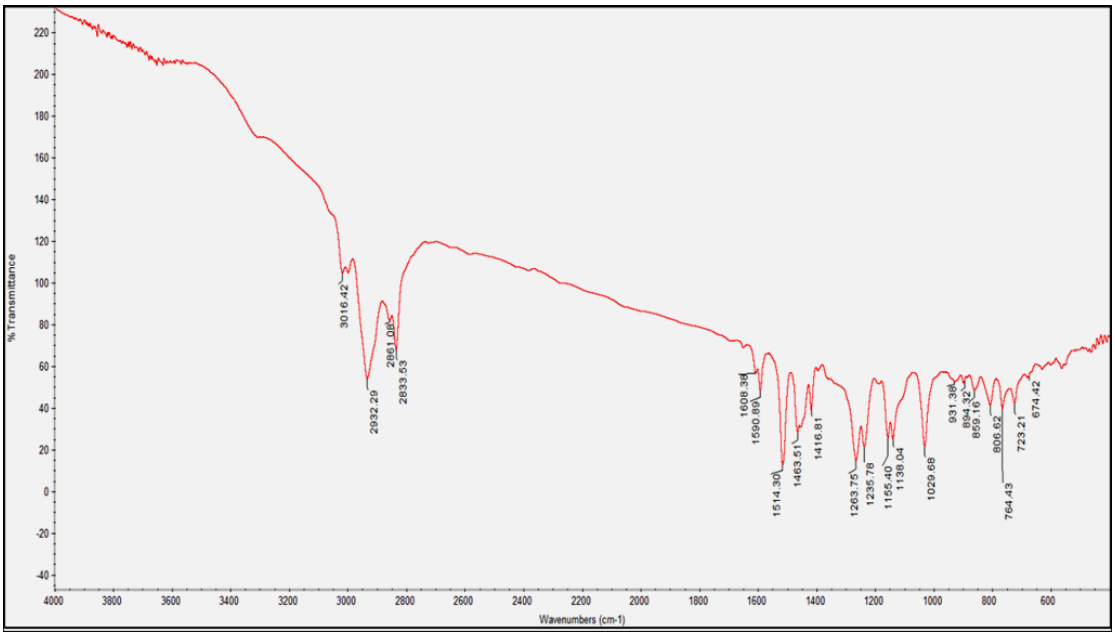
附圖一百二十二、化合物 31 之 ^{13}C 與 DEPT135 核磁共振圖譜



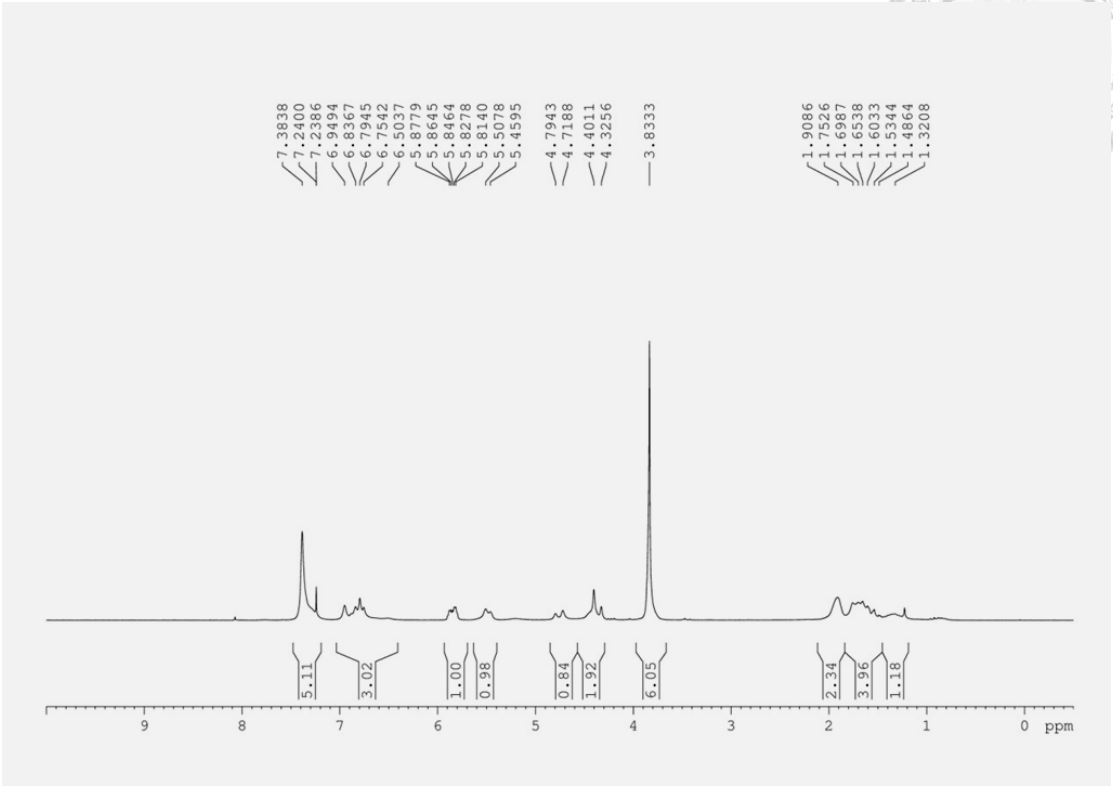
附圖一百二十三、化合物 31 之 HRESIMS 圖譜



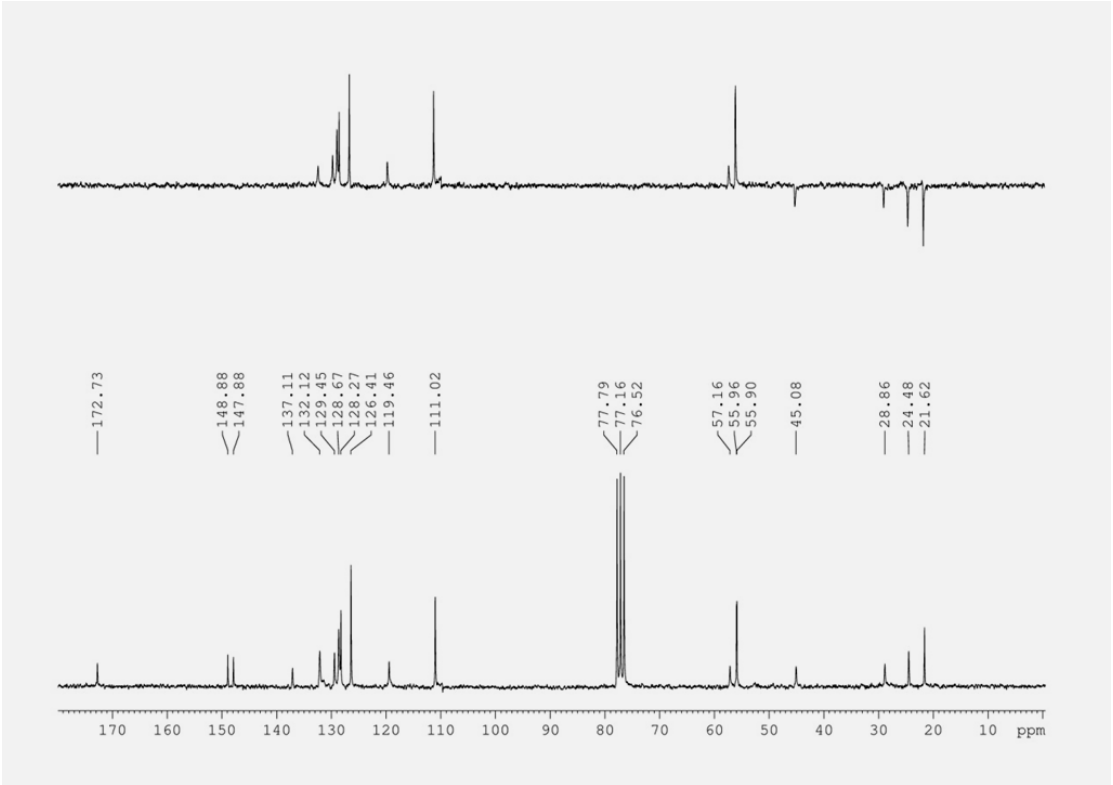
附圖一百二十四、化合物 31 之 IR 圖譜



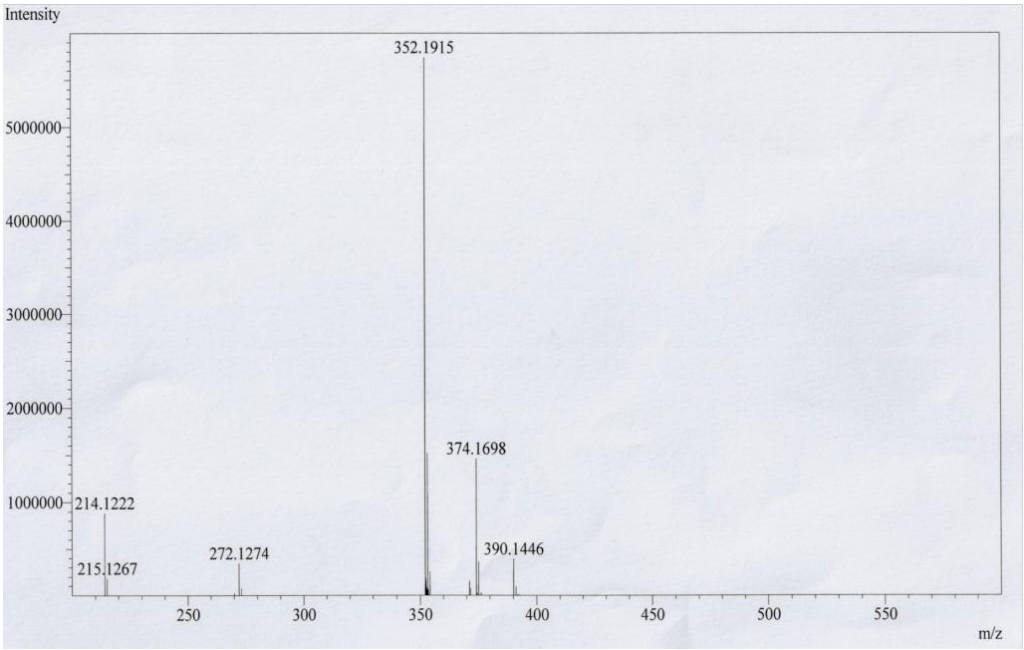
附圖一百二十五、化合物 32 之氫核磁共振圖譜($CDCl_3$, 200 MHz)



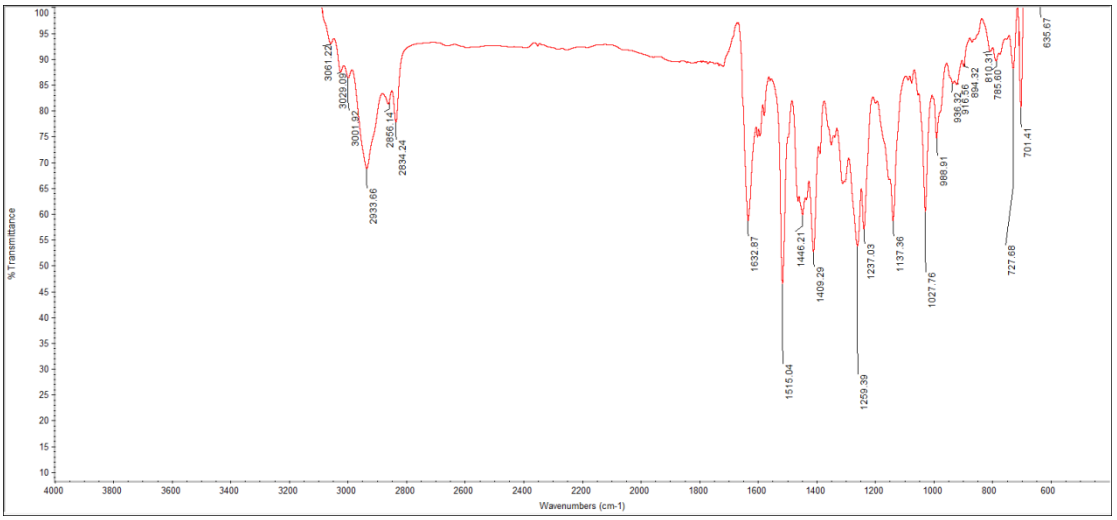
附圖一百二十六、化合物 32 之 ^{13}C 與 DEPT135 核磁共振圖譜



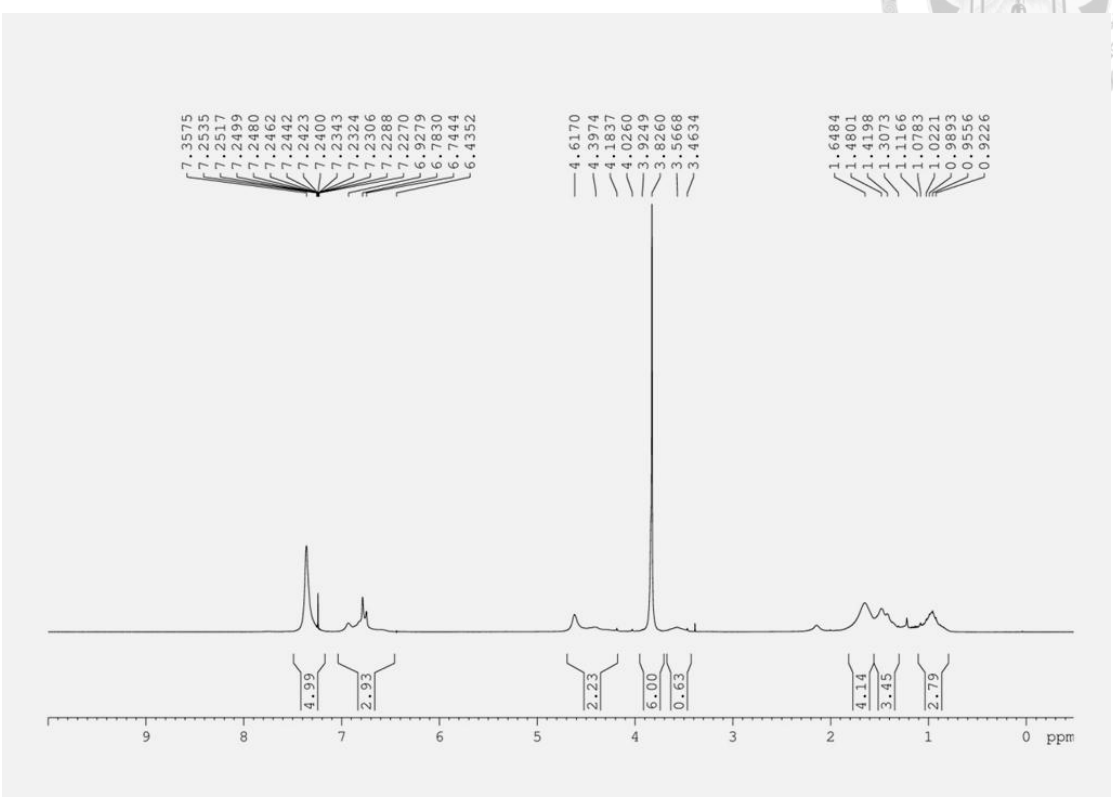
附圖一百二十七、化合物 32 之 HRESIMS 圖譜



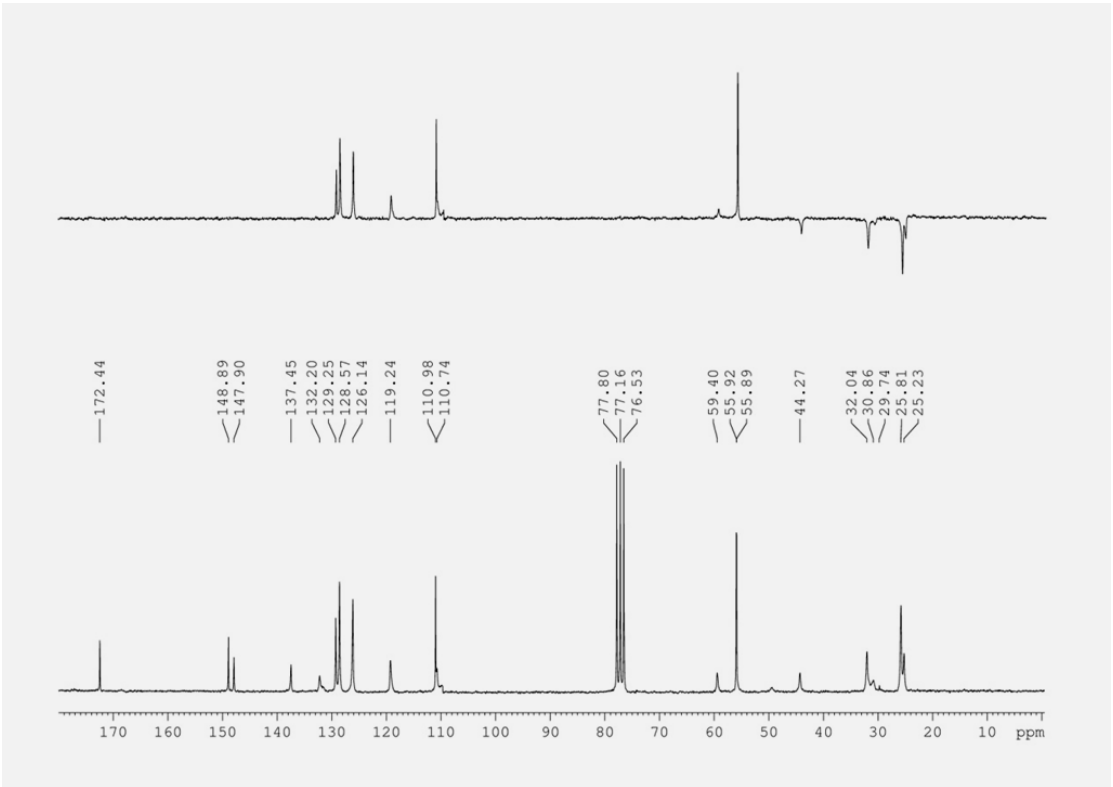
附圖一百二十八、化合物 32 之 IR 圖譜



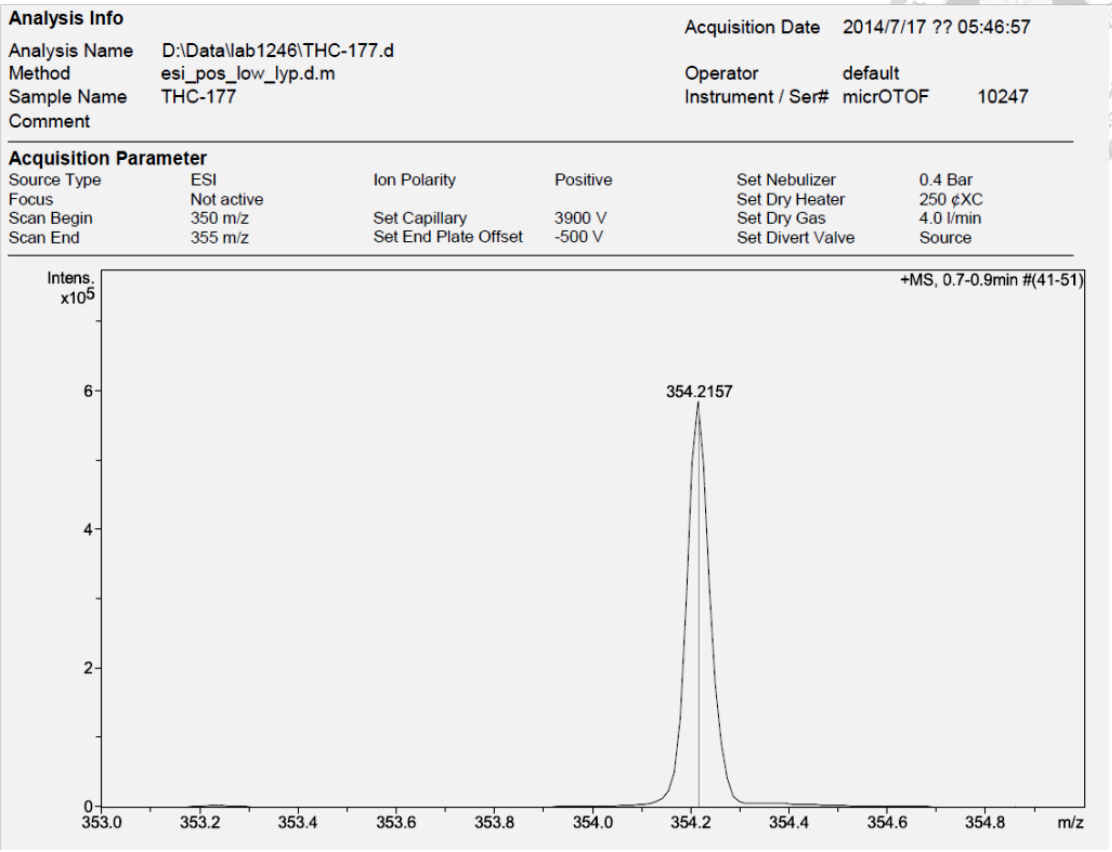
附圖一百二十九、化合物 33 之氫核磁共振圖譜($CDCl_3$, 200 MHz)



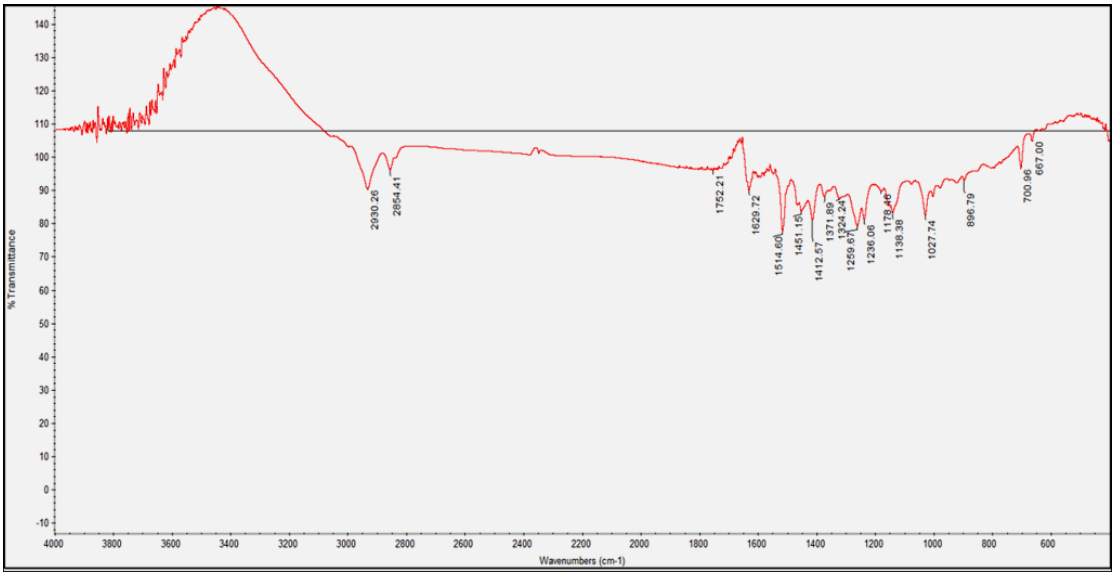
附圖一百三十、化合物 33 之 ^{13}C 與 DEPT135 核磁共振圖譜



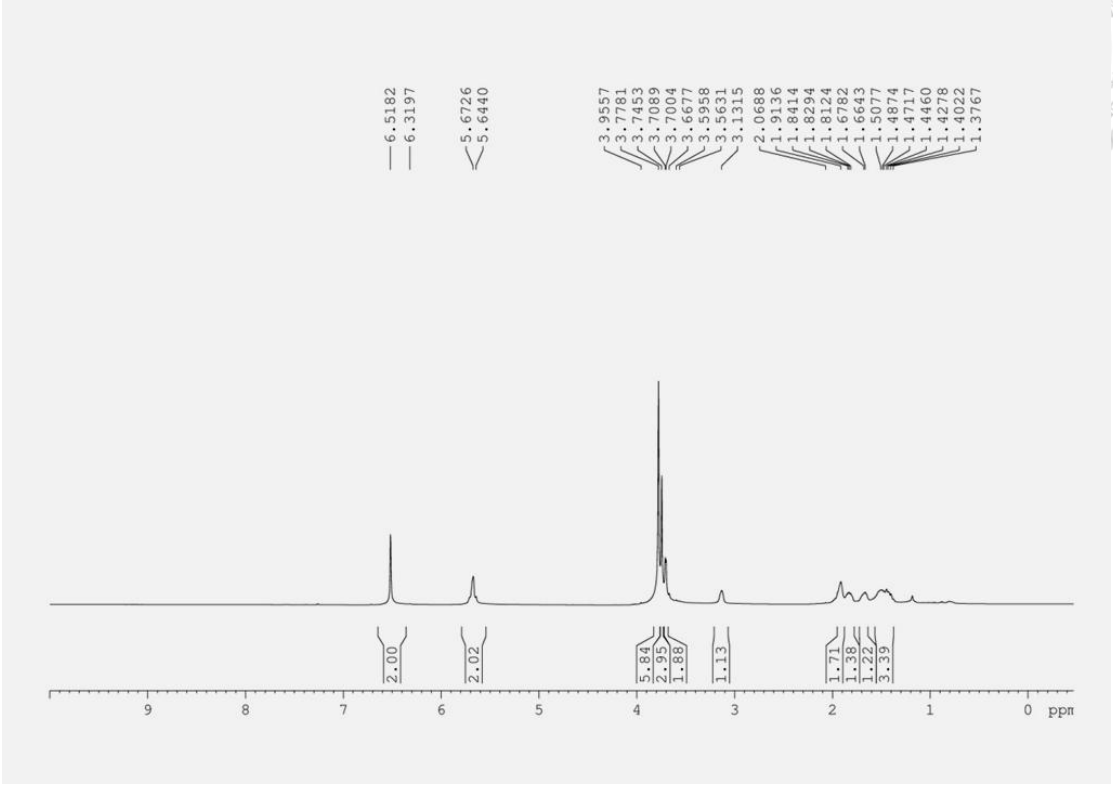
附圖一百三十一、化合物 33 之 HRESIMS 圖譜



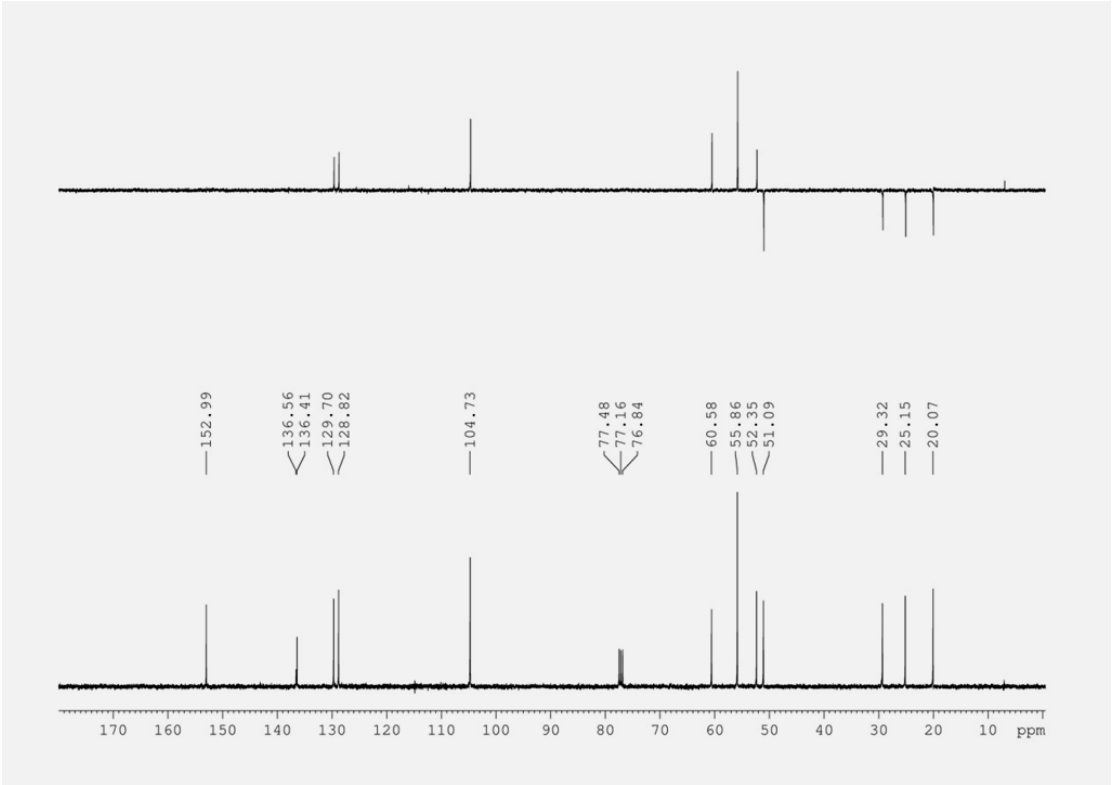
附圖一百三十二、化合物 33 之 IR 圖譜



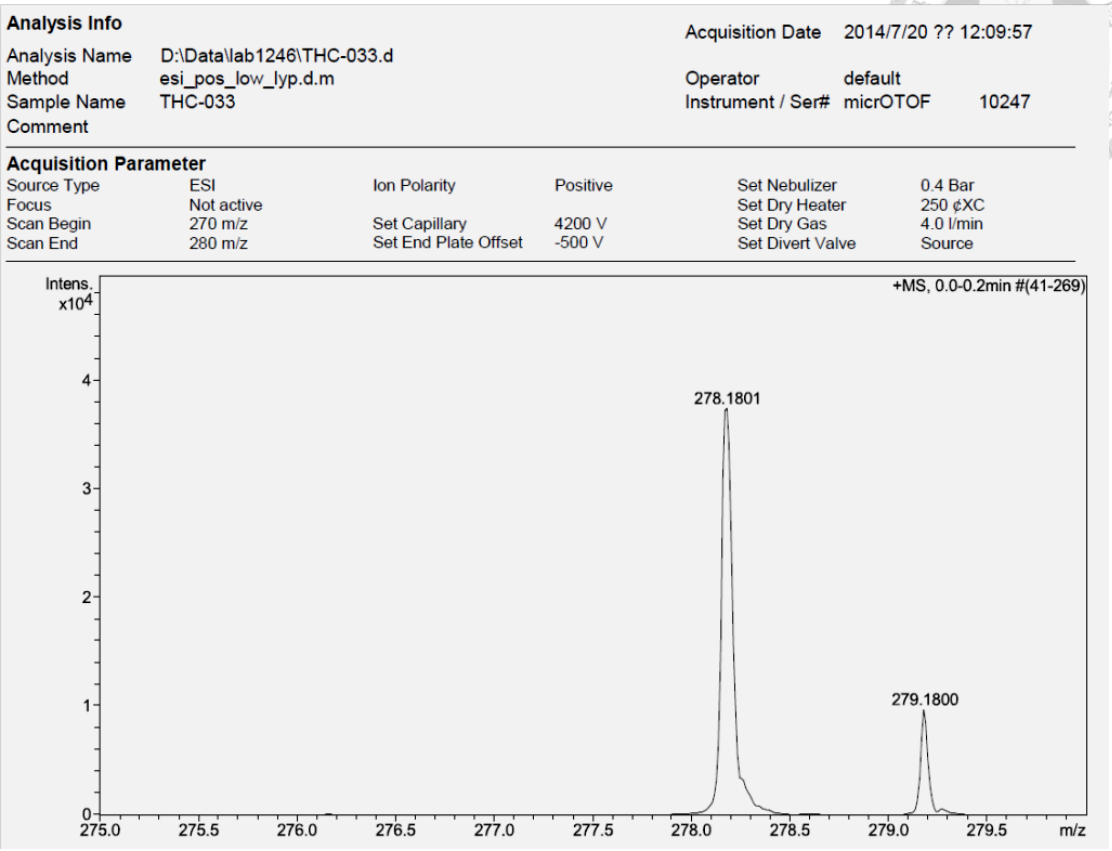
附圖一百三十三、化合物 **34** 之氫核磁共振圖譜($CDCl_3$, 200 MHz)



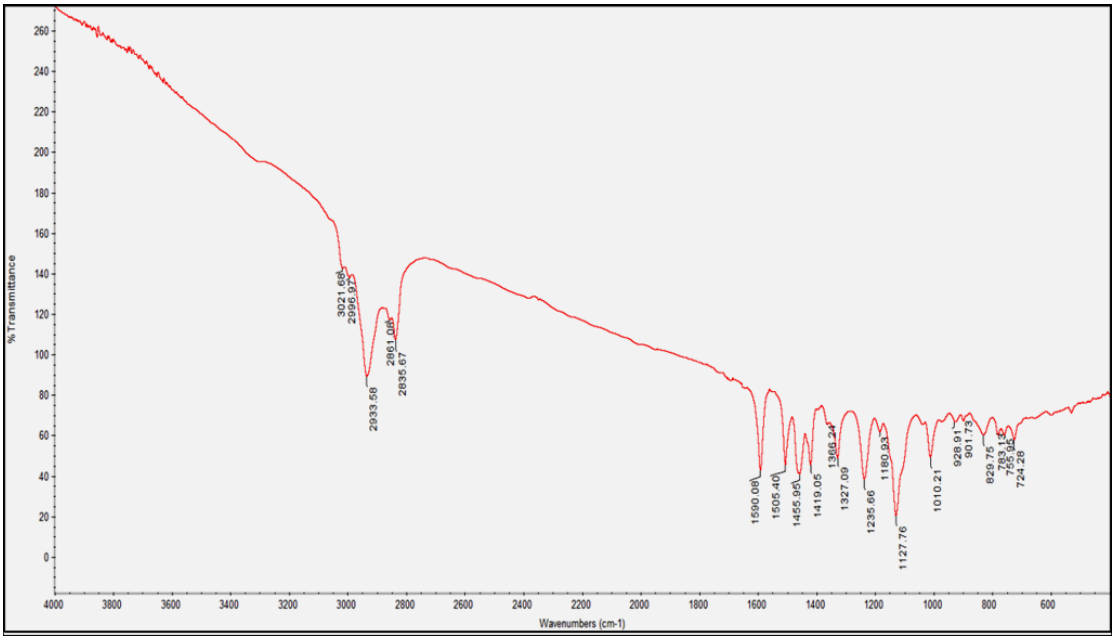
附圖一百三十四、化合物 **34** 之 ^{13}C 與 DEPT135 核磁共振圖譜



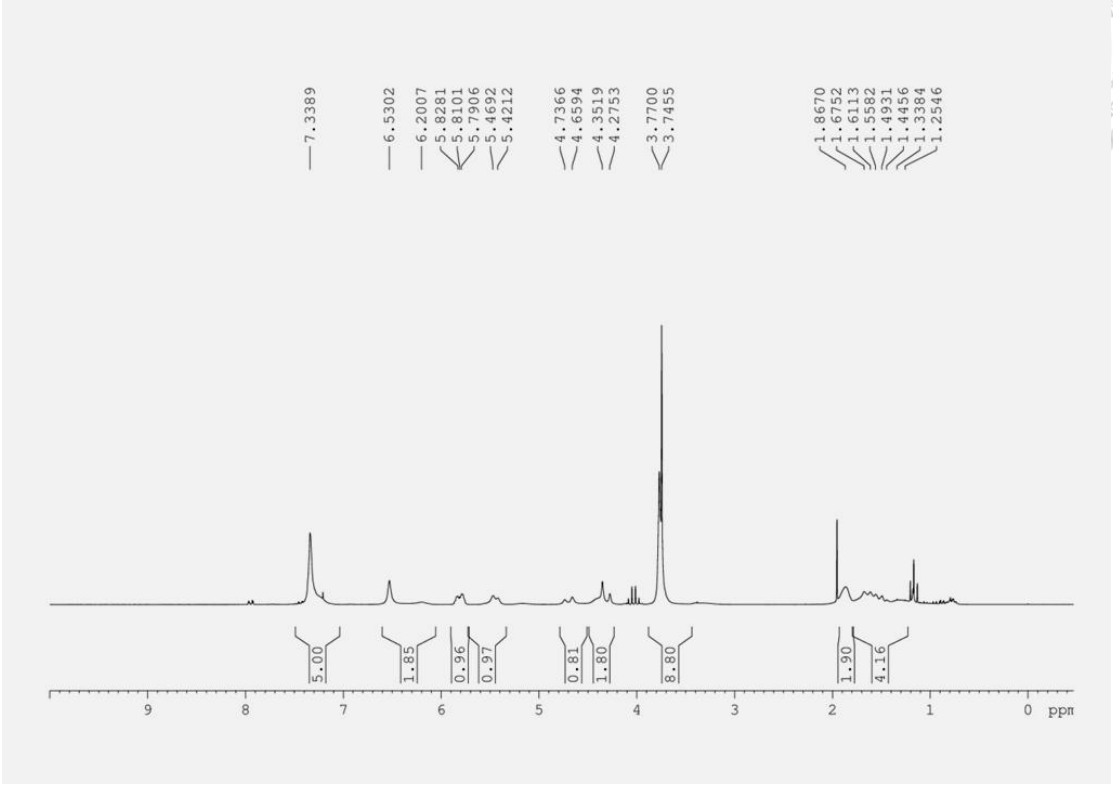
附圖一百三十五、化合物 34 之 HRESIMS 圖譜



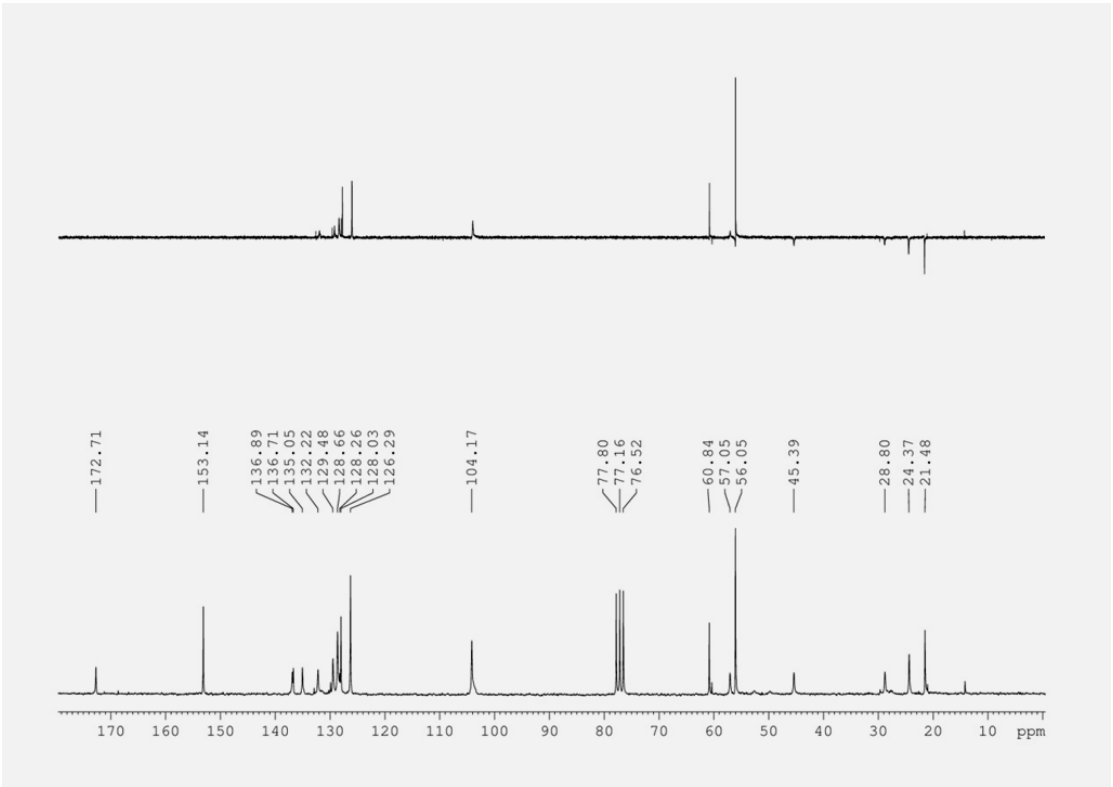
附圖一百三十六、化合物 34 之 IR 圖譜



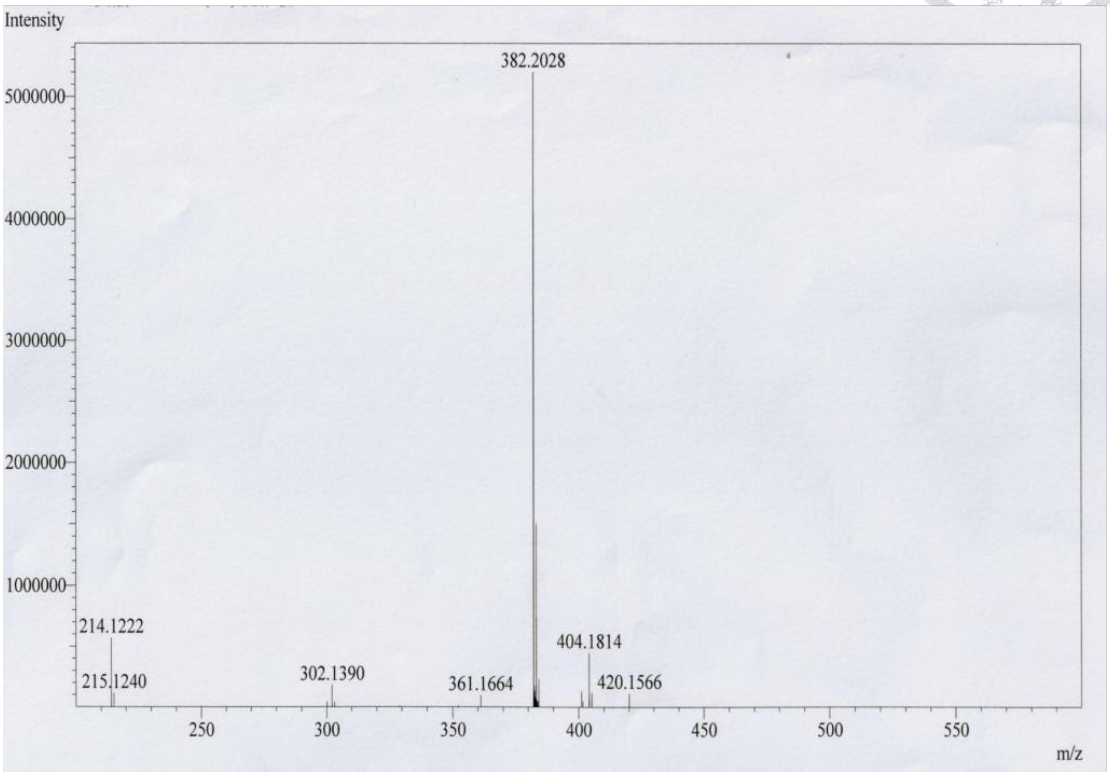
附圖一百三十七、化合物 35 之氫核磁共振圖譜($CDCl_3$, 200 MHz)



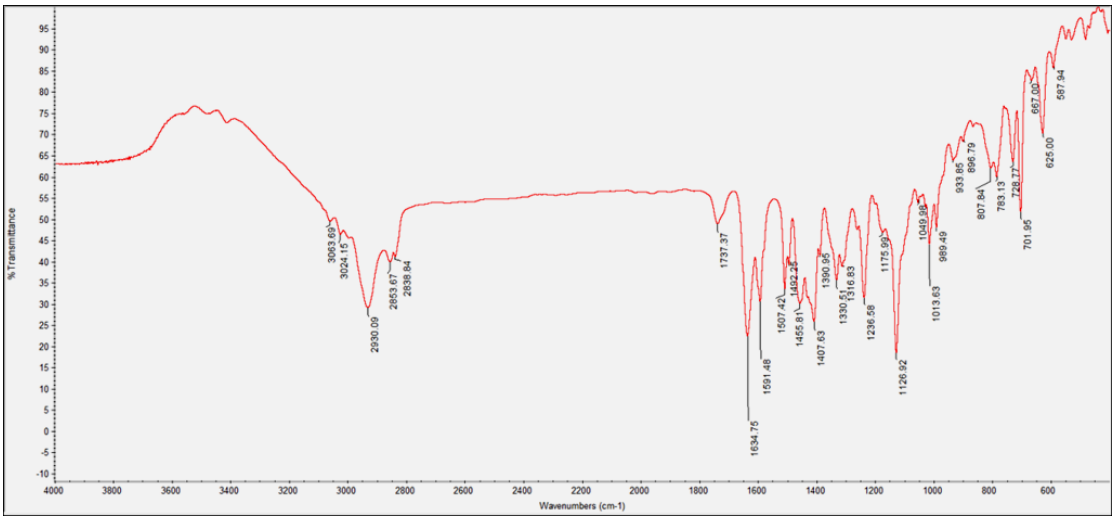
附圖一百三十八、化合物 35 之 ^{13}C 與 DEPT135 核磁共振圖譜



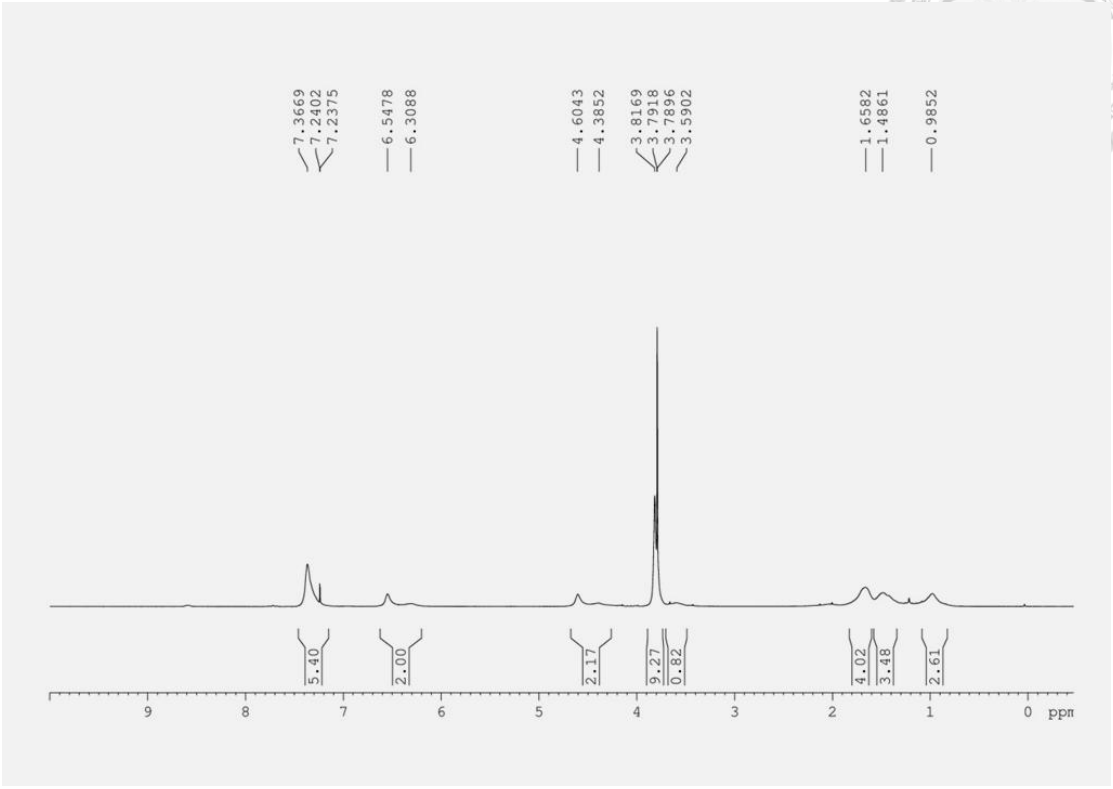
附圖一百三十九、化合物 35 之 HRESIMS 圖譜



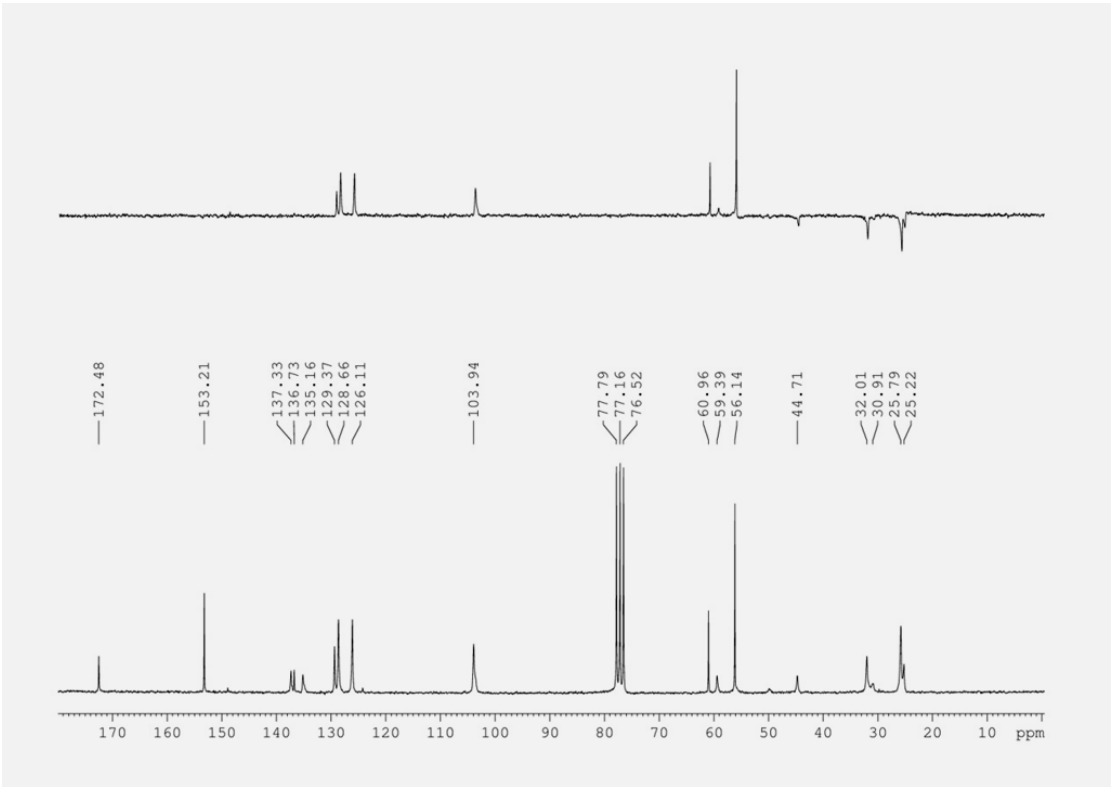
附圖一百四十、化合物 35 之 IR 圖譜



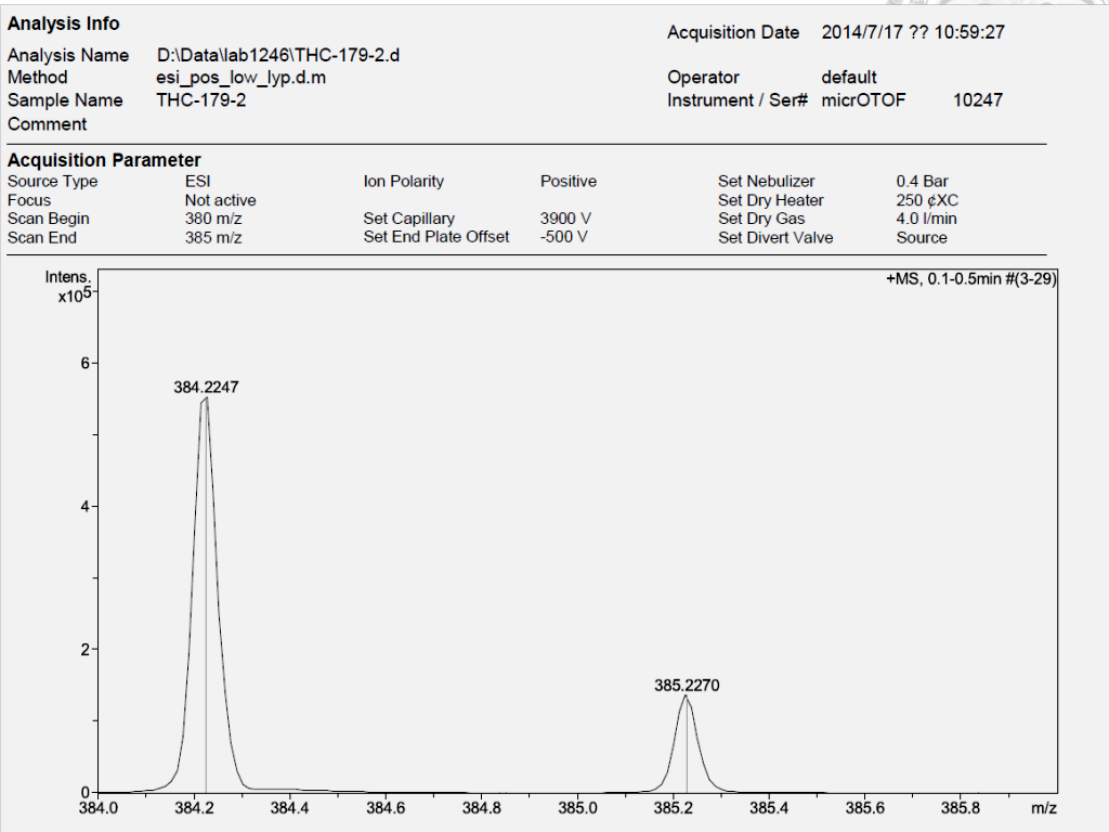
附圖一百四十一、化合物 36 之氫核磁共振圖譜($CDCl_3$, 200 MHz)



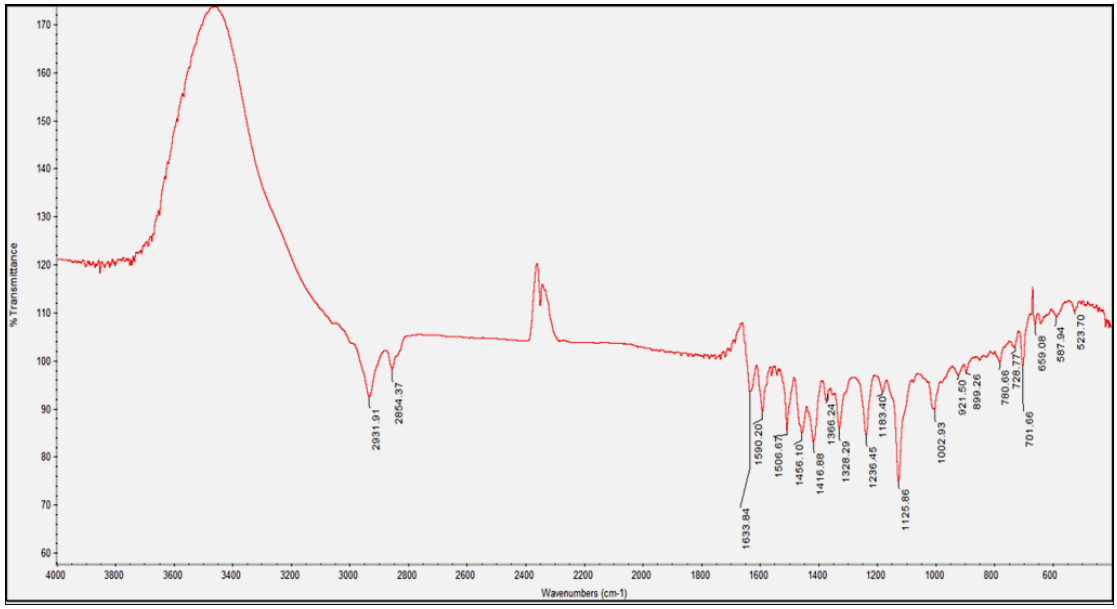
附圖一百四十二、化合物 36 之 ^{13}C 與 DEPT135 核磁共振圖譜



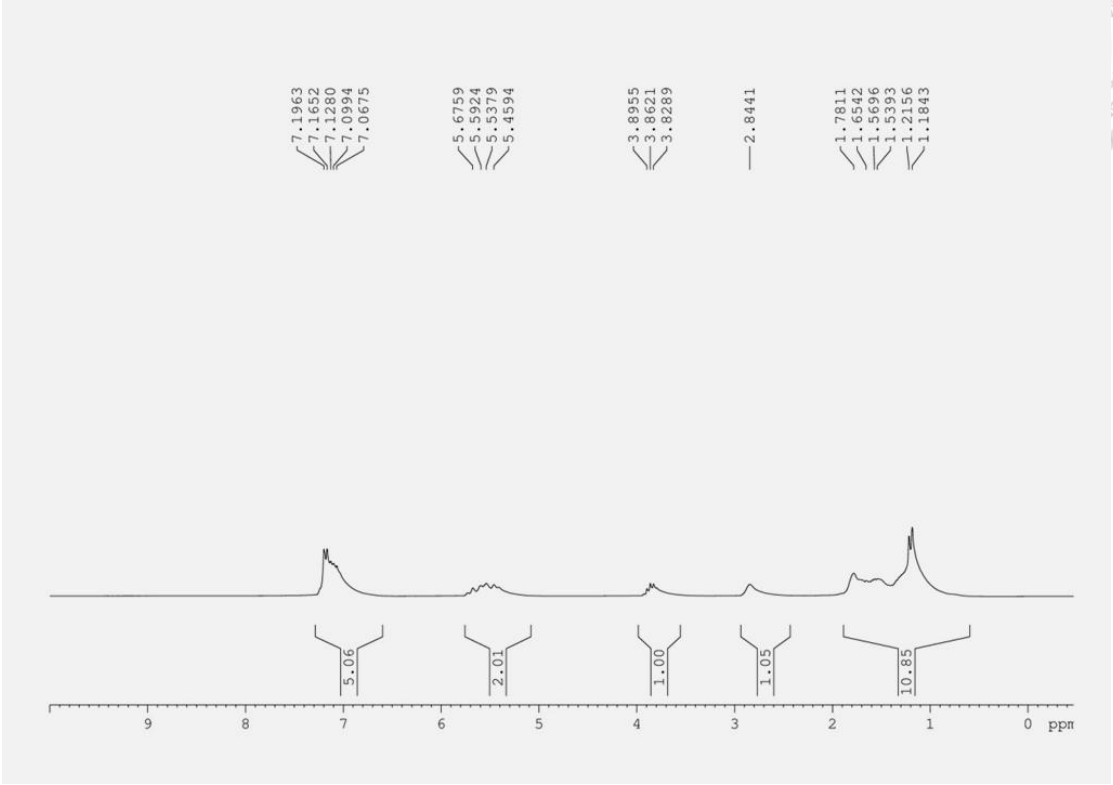
附圖一百四十三、化合物 36 之 HRESIMS 圖譜



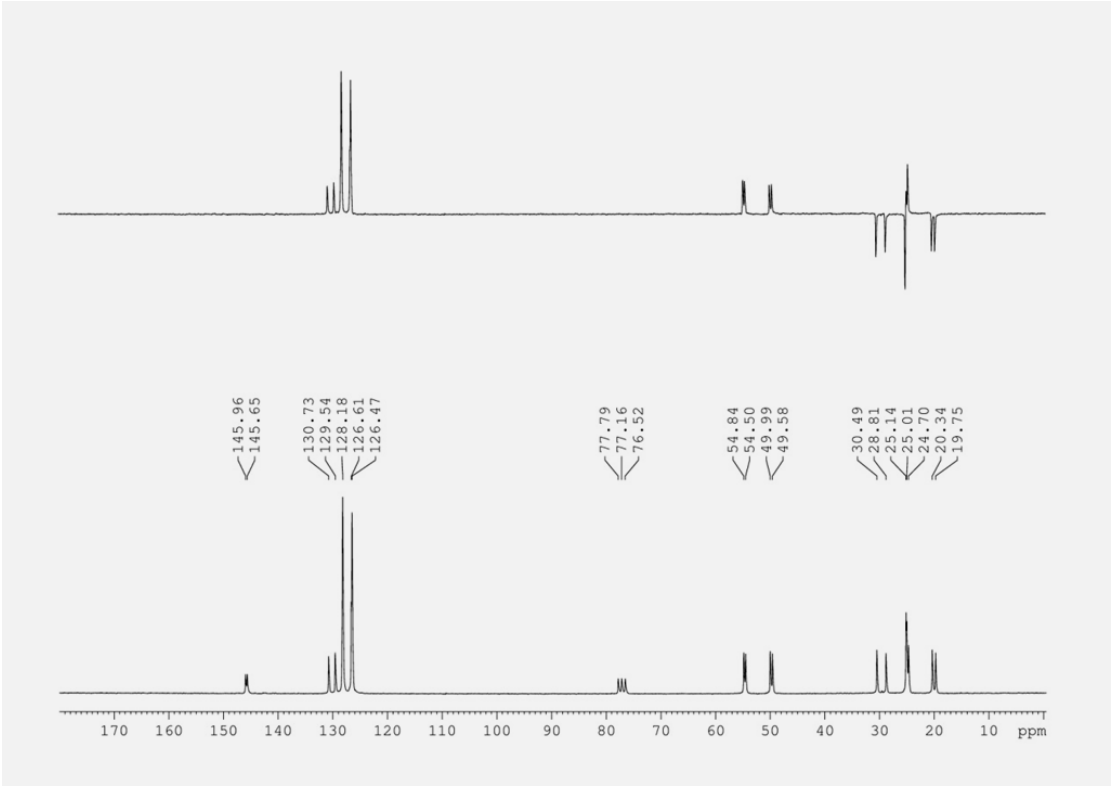
附圖一百四十四、化合物 36 之 IR 圖譜



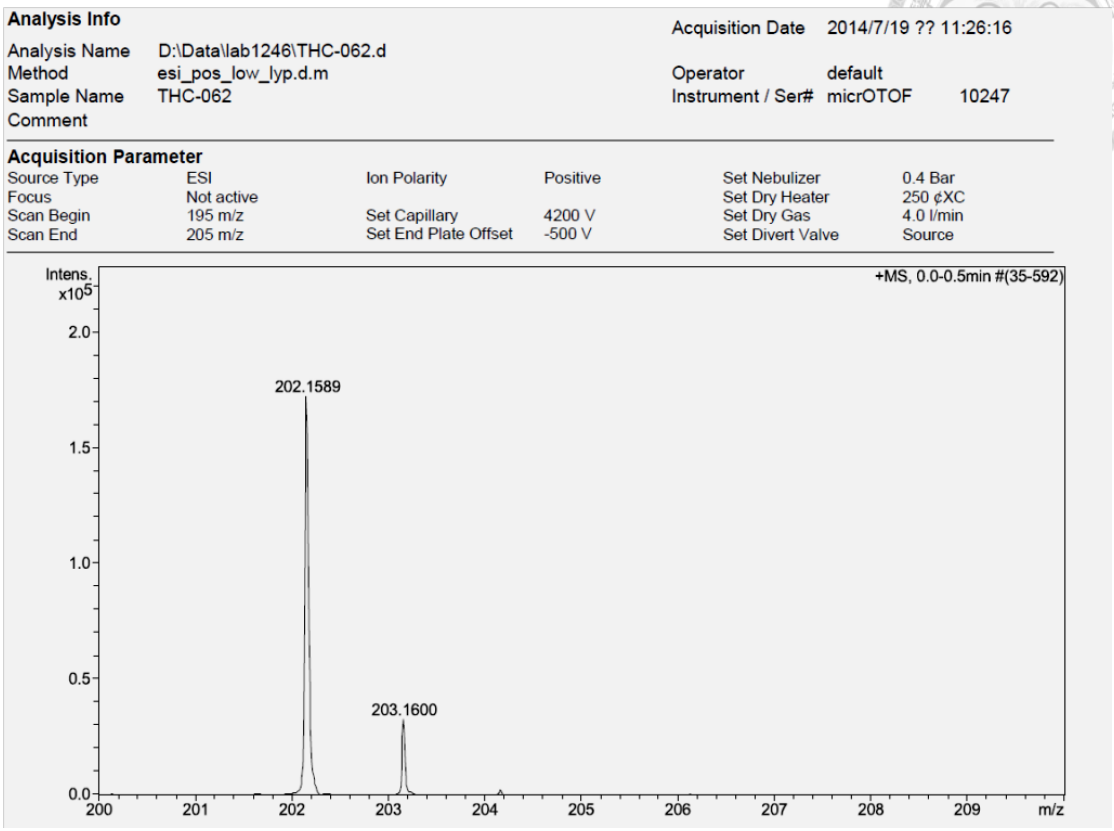
附圖一百四十五、化合物 37 之氫核磁共振圖譜($CDCl_3$, 200 MHz)



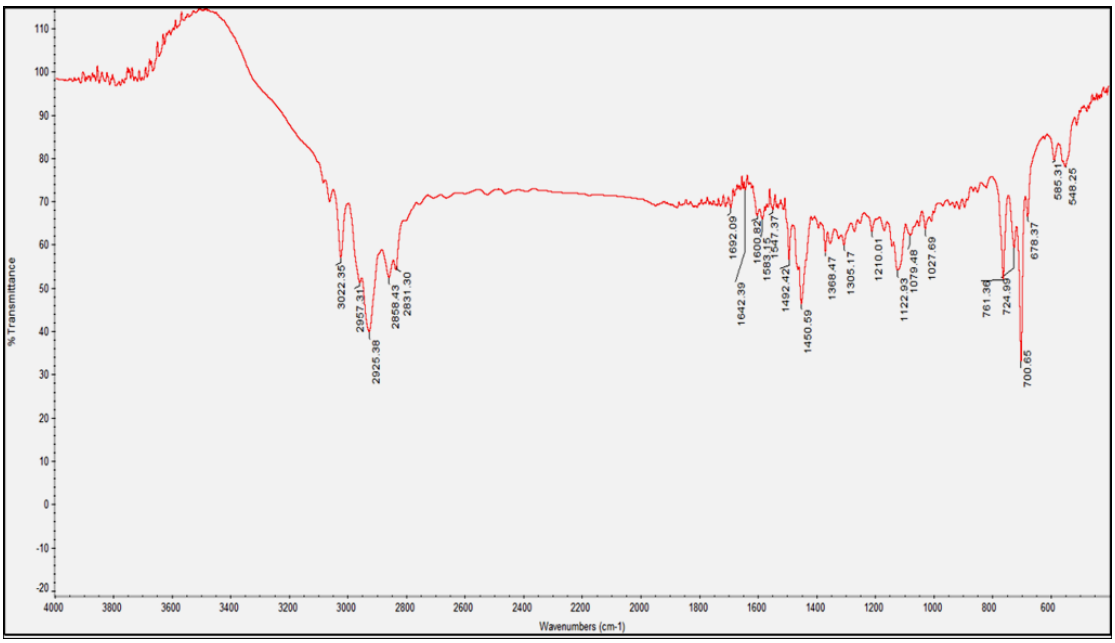
附圖一百四十六、化合物 37 之 ^{13}C 與 DEPT135 核磁共振圖譜



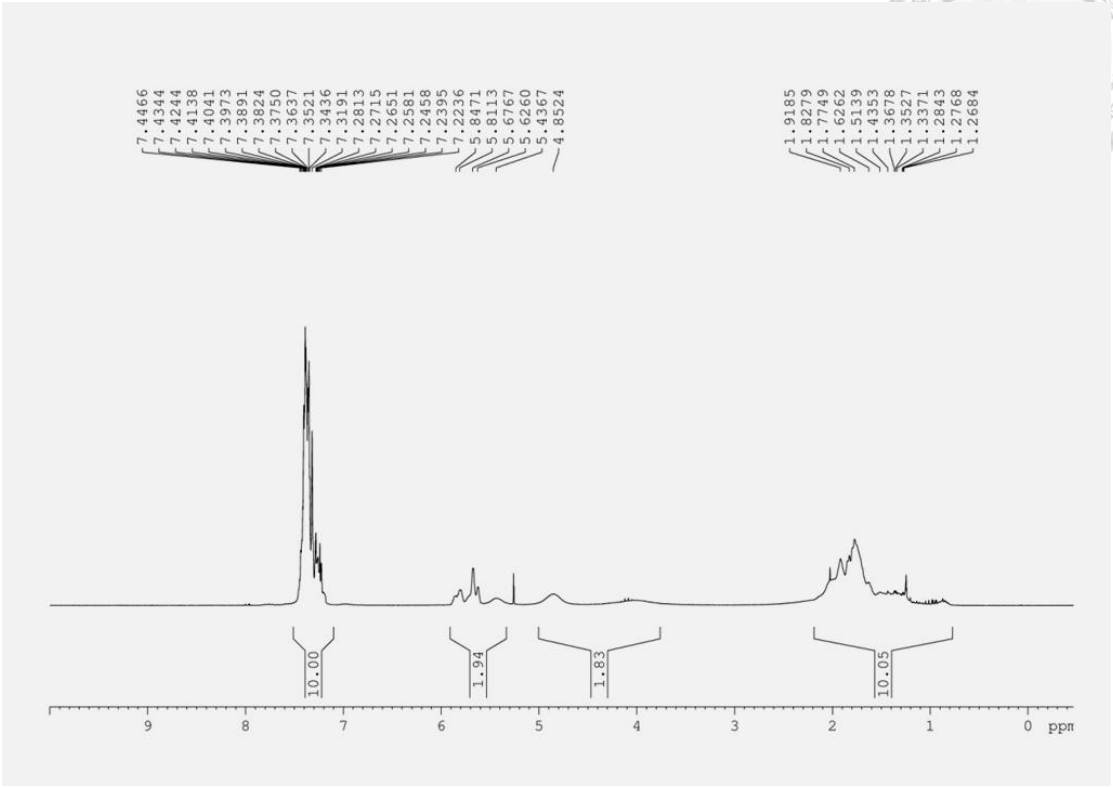
附圖一百四十七、化合物 37 之 HRESIMS 圖譜



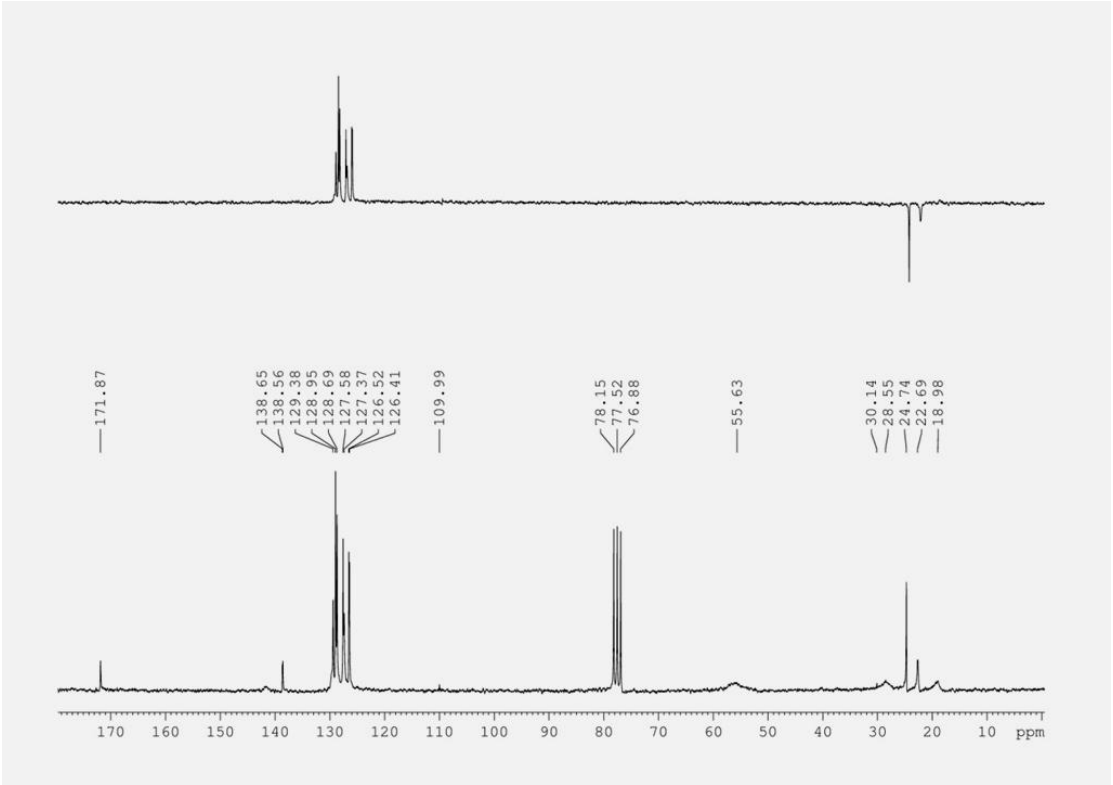
附圖一百四十八、化合物 37 之 IR 圖譜



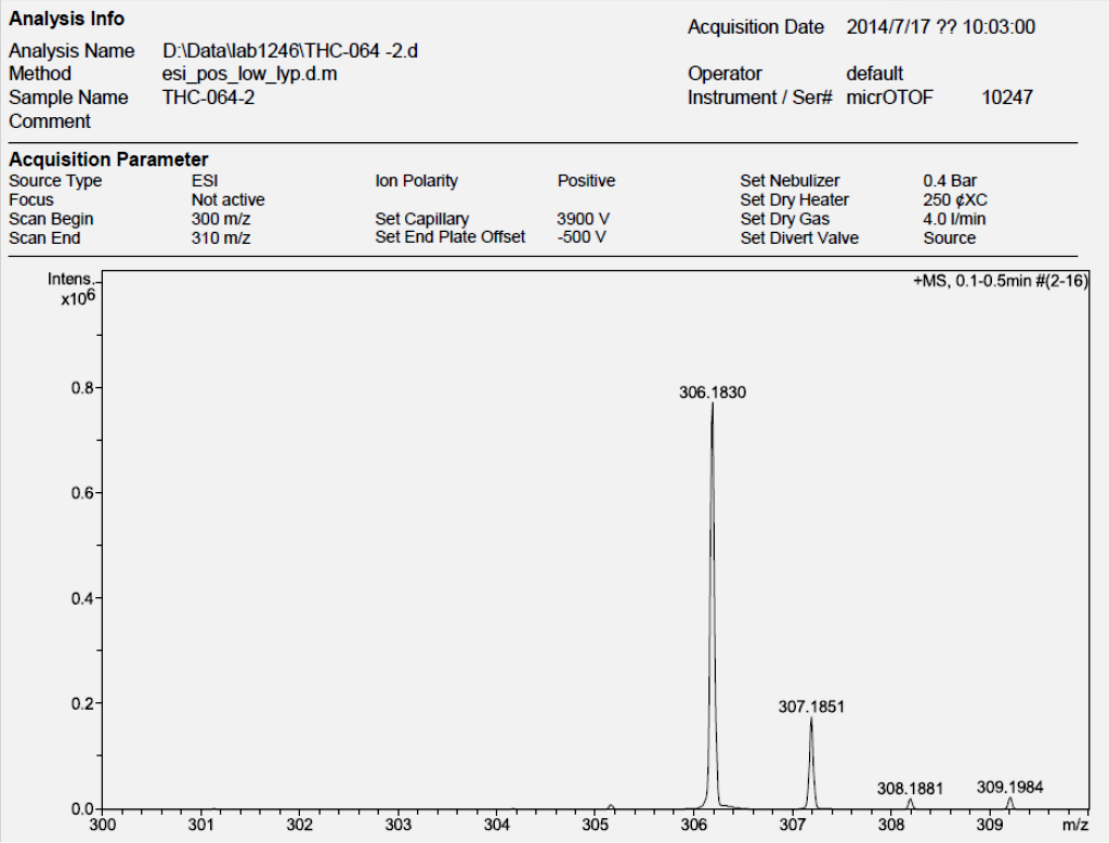
附圖一百四十九、化合物 38 之氫核磁共振圖譜($CDCl_3$, 200 MHz)



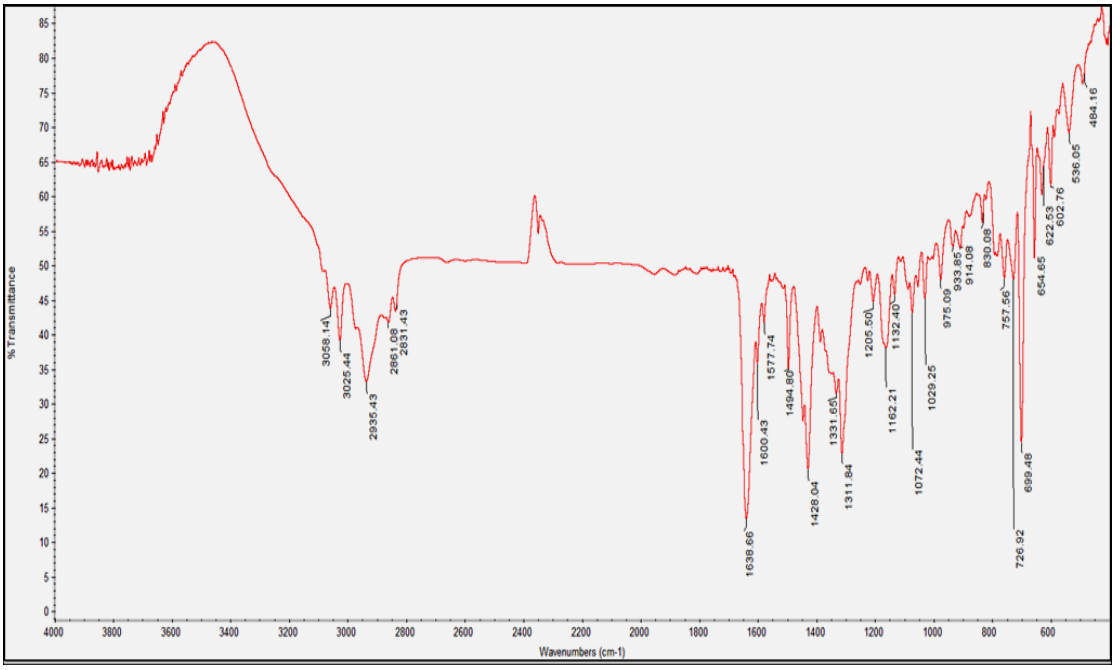
附圖一百五十、化合物 38 之 ^{13}C 與 DEPT135 核磁共振圖譜



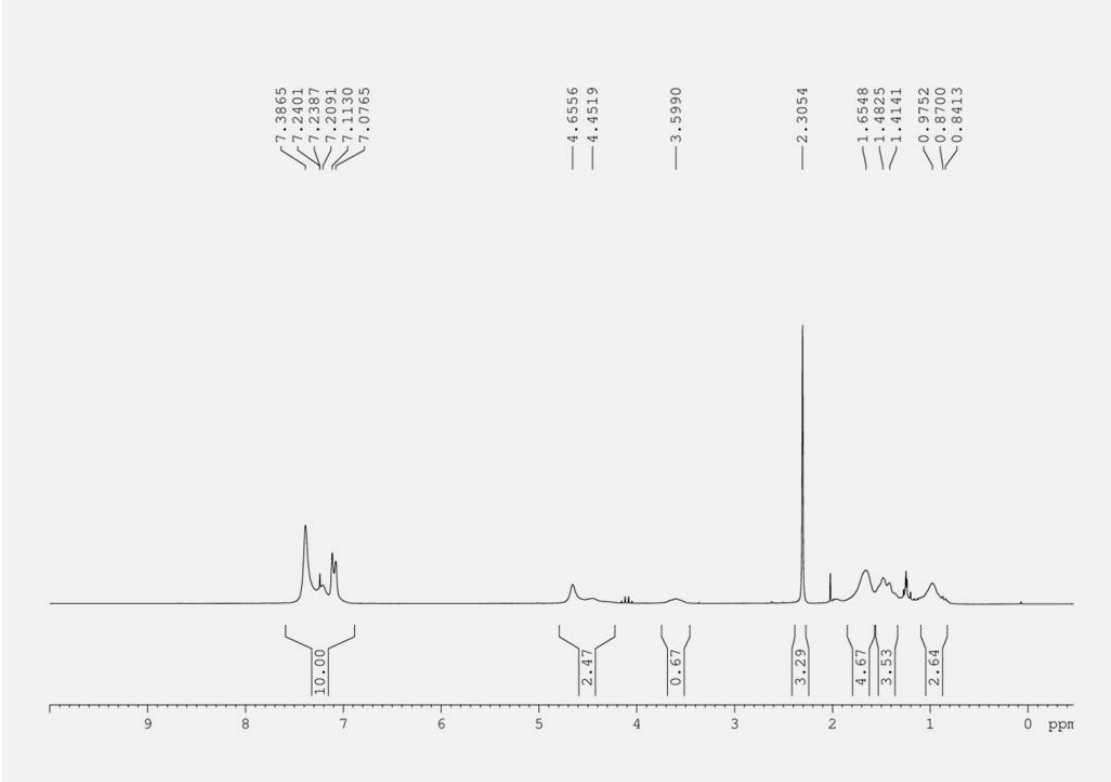
附圖一百五十一、化合物 38 之 HRESIMS 圖譜



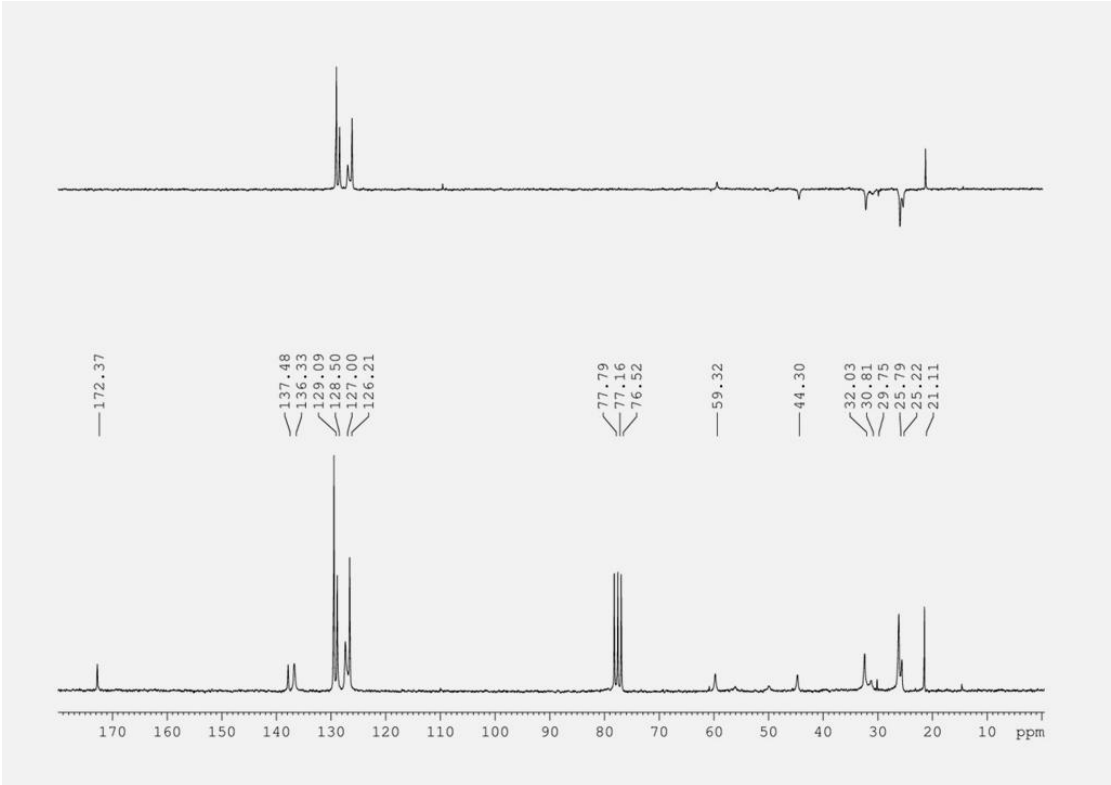
附圖一百五十二、化合物 38 之 IR 圖譜



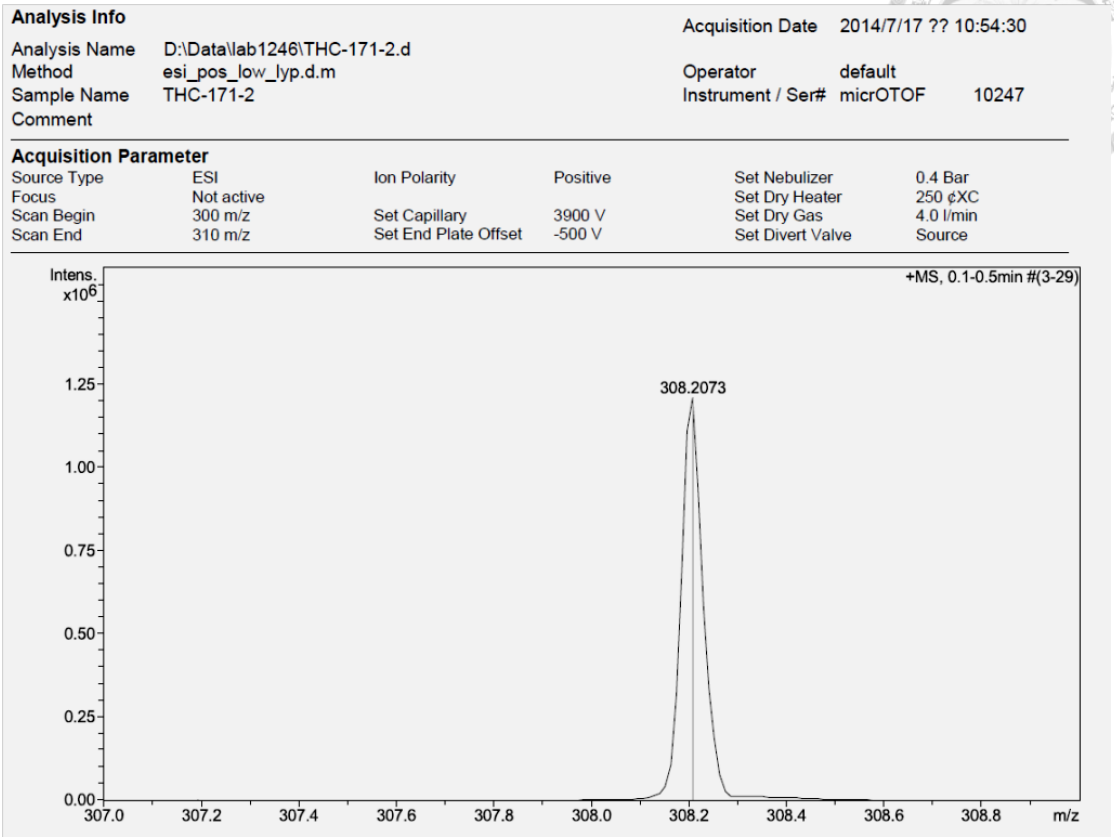
附圖一百五十三、化合物 39 之氫核磁共振圖譜($CDCl_3$, 200 MHz)



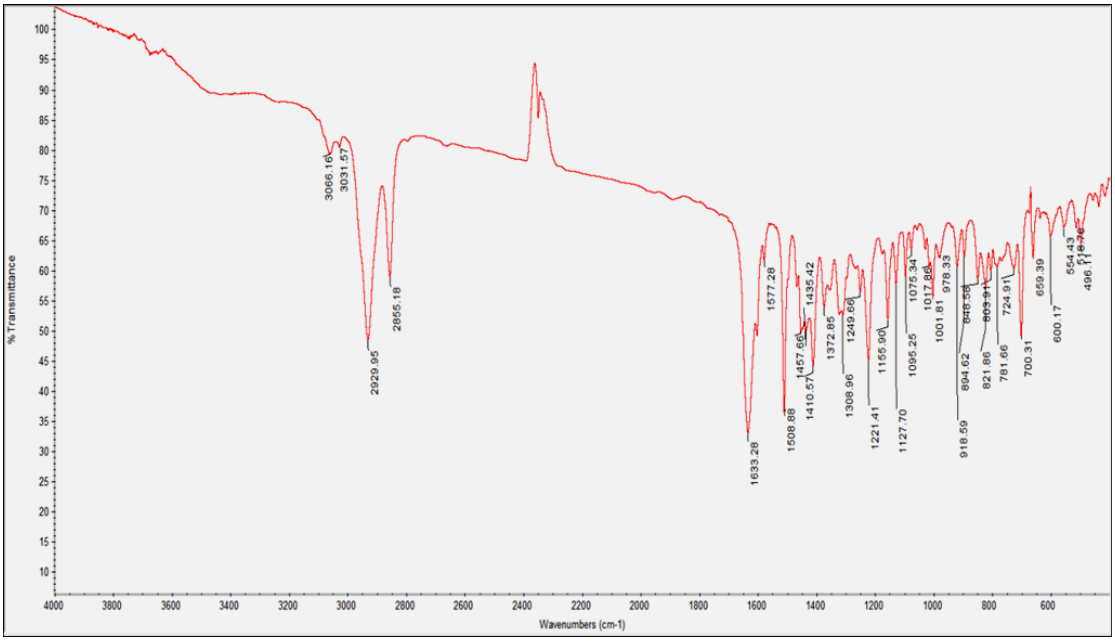
附圖一百五十四、化合物 39 之 ^{13}C 與 DEPT135 核磁共振圖譜



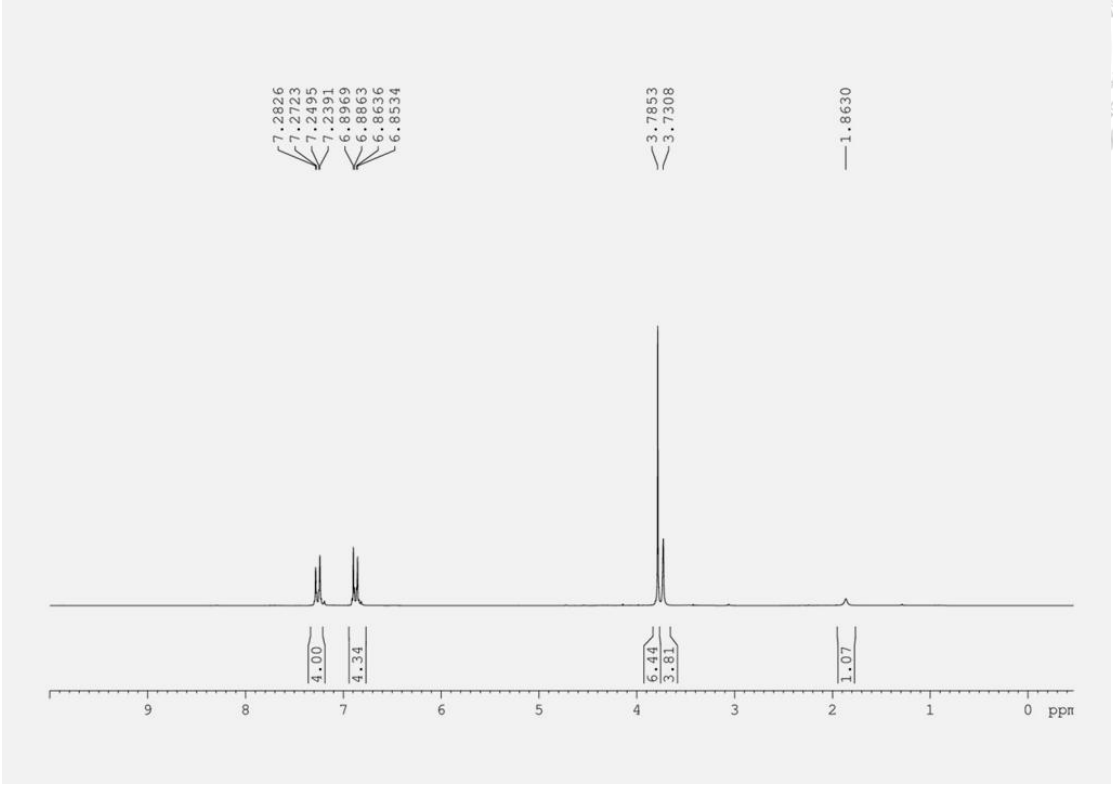
附圖一百五十五、化合物 39 之 HRESIMS 圖譜



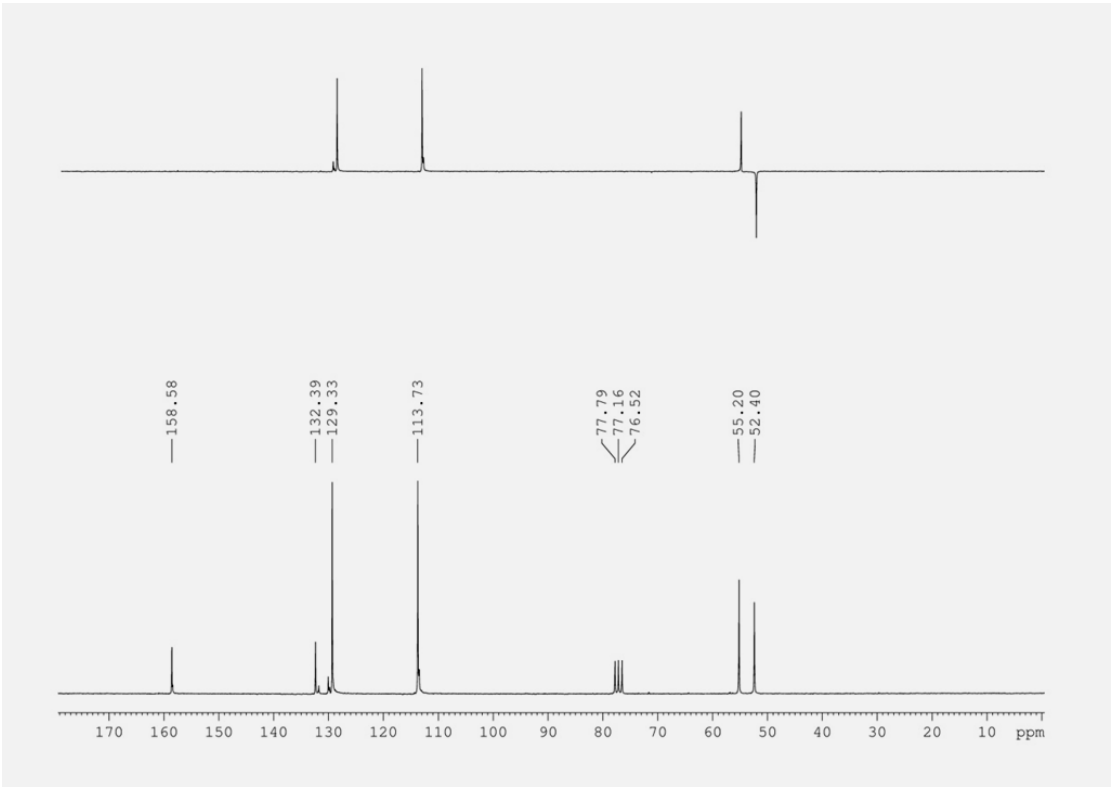
附圖一百五十六、化合物 39 之 IR 圖譜



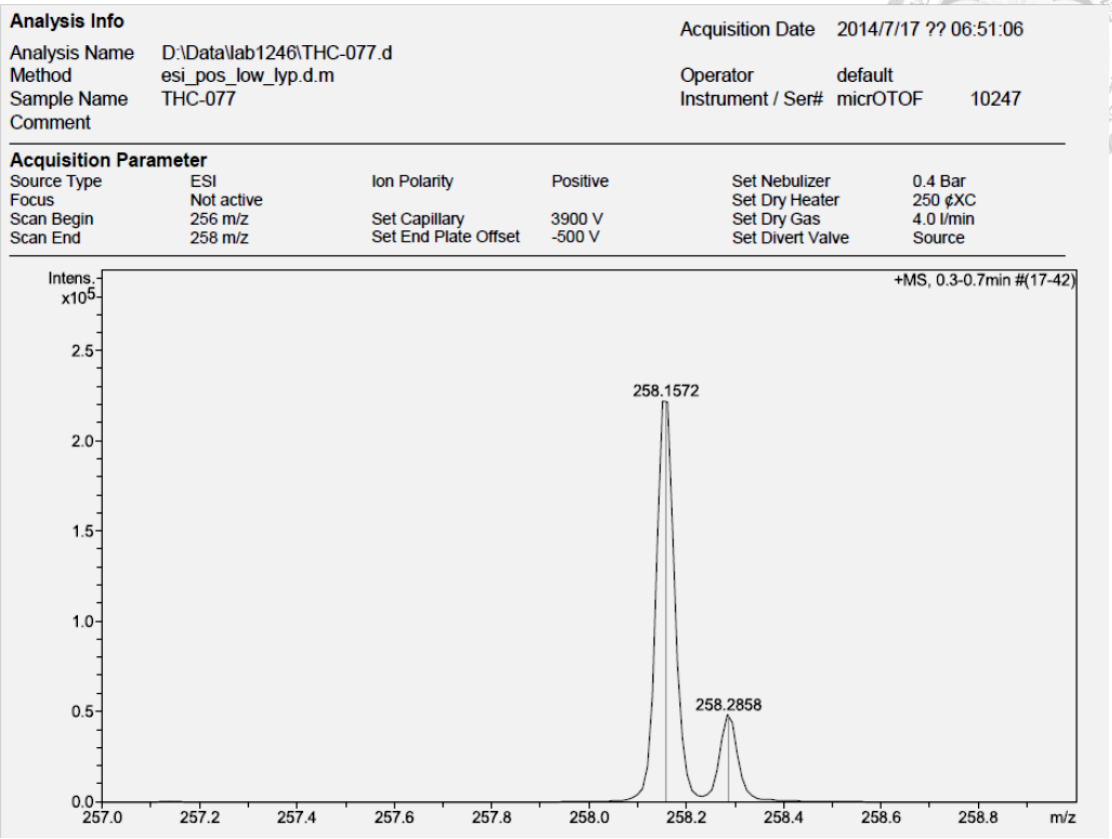
附圖一百五十七、化合物 40 之氫核磁共振圖譜($CDCl_3$, 200 MHz)



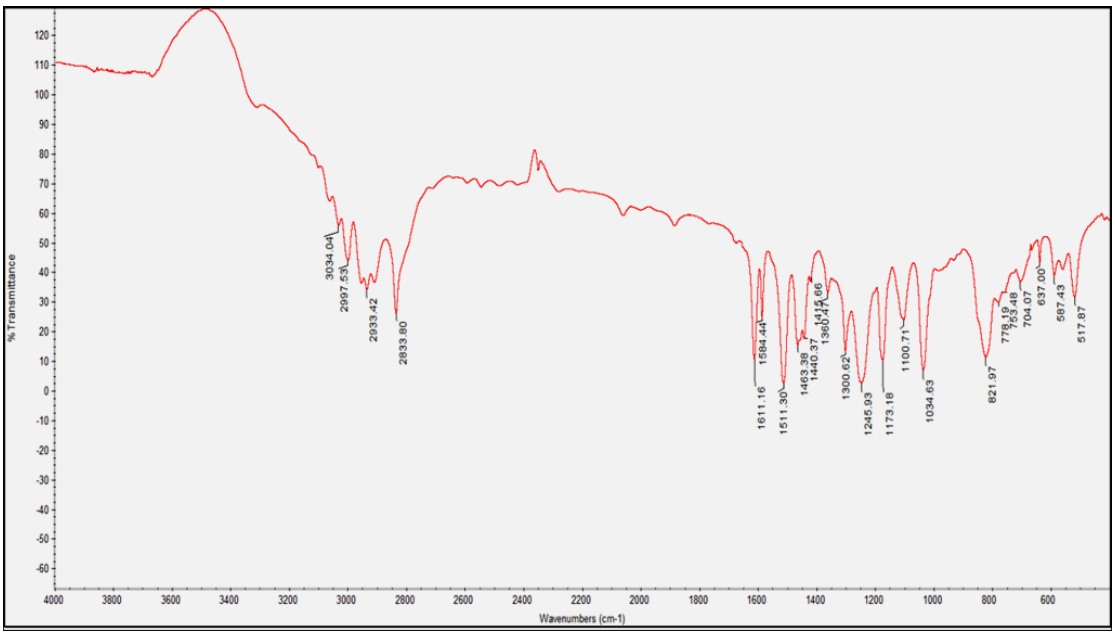
附圖一百五十八、化合物 40 之 ^{13}C 與 DEPT135 核磁共振圖譜



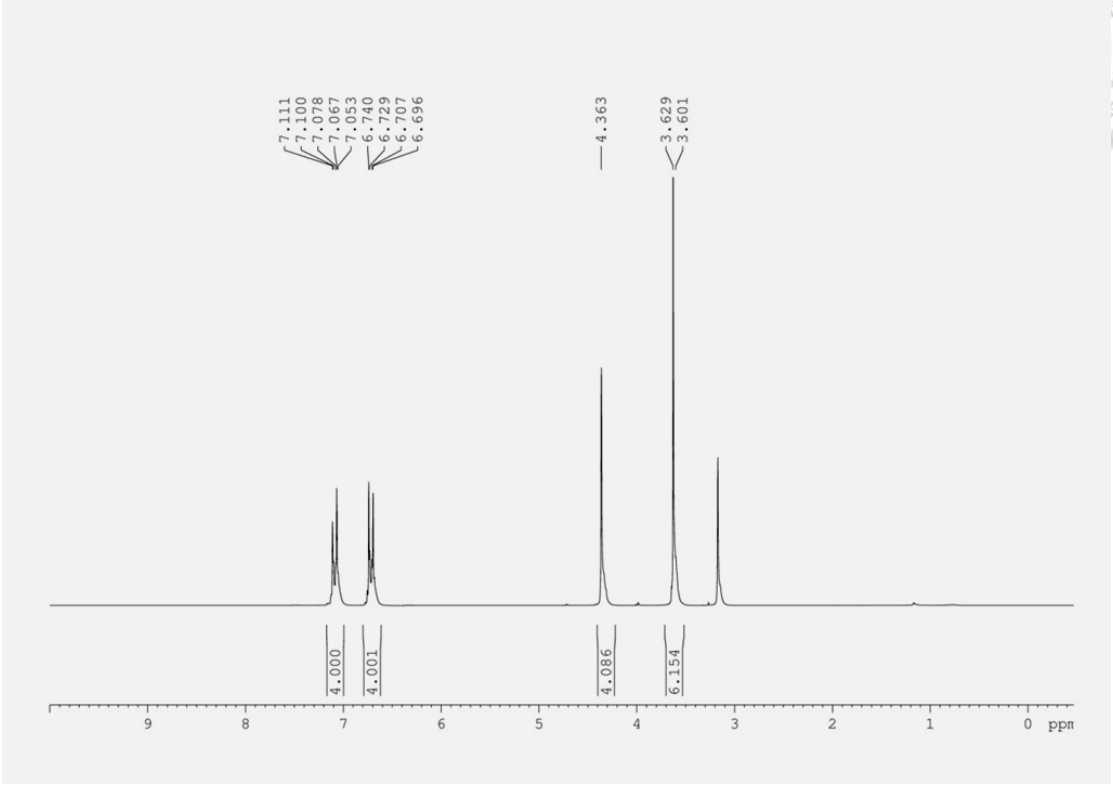
附圖一百五十九、化合物 40 之 HRESIMS 圖譜



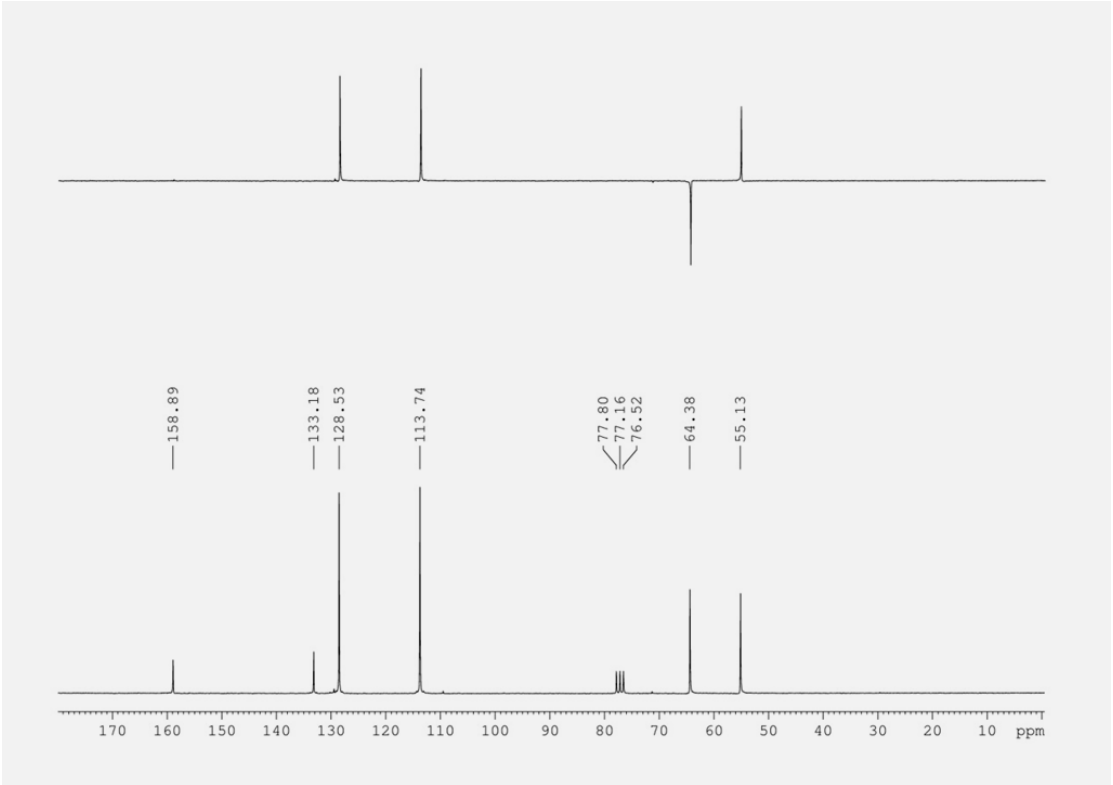
附圖一百六十、化合物 40 之 IR 圖譜



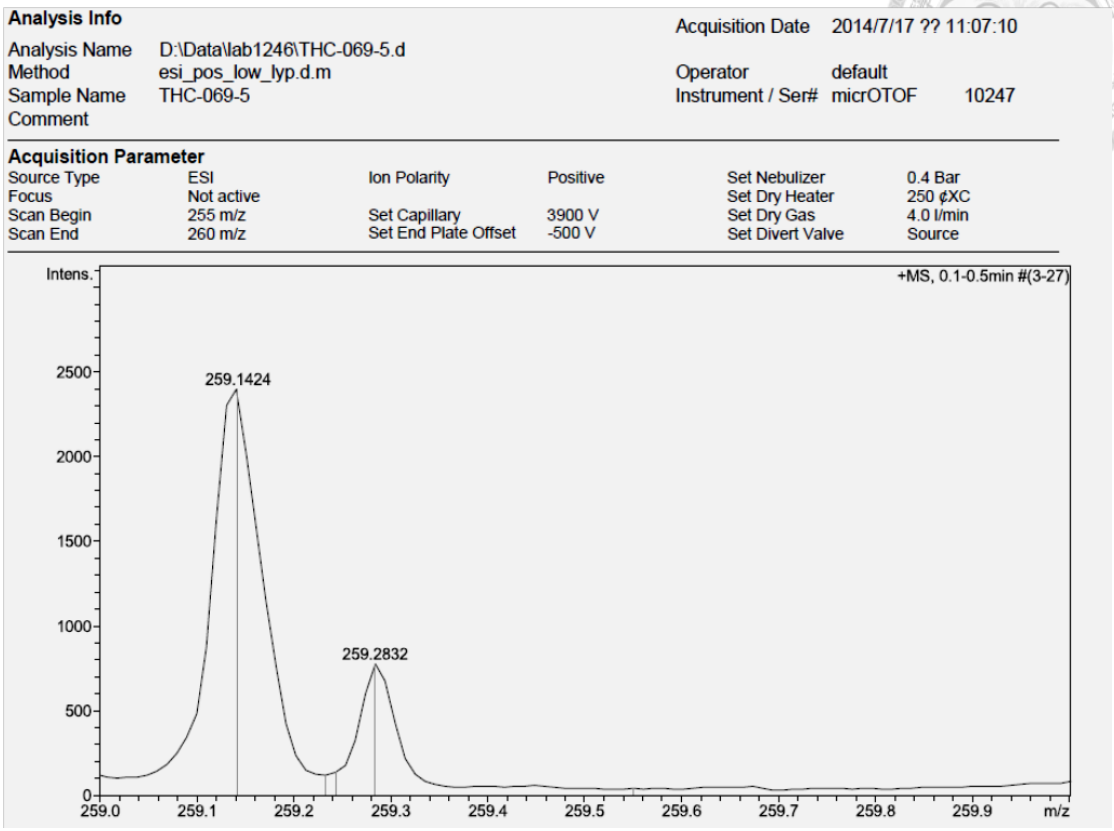
附圖一百六十一、化合物 **41** 之氫核磁共振圖譜($CDCl_3$, 200 MHz)



附圖一百六十二、化合物 **41** 之 ^{13}C 與 DEPT135 核磁共振圖譜



附圖一百六十三、化合物 41 之 HRESIMS 圖譜



附圖一百六十四、化合物 41 之 IR 圖譜