

Synthesis of Chalcone with Mannich Side Chain. part iv

Abstract :

The compound 3-Hydroxy-4'-methoxychalcone was prepared by reacting 3-hydroxybenzaldehyde with 4-methoxyacetophenone. The aminomethylation of this chalcone was accomplished by reaction with formaldehyde and suitable amine in acetonitrile to obtain 4-hydroxy-4'-methoxy-3,5-bis-dimethylaminomethylchalcone(2) 4-hydroxy-4'-methoxy-3,5-bis-pyrrolidinomethylchalcone(3) and 4-hydroxy-4'-methoxy-3,5-bis-piperidinomethylchalcone(4). The products were purified by column and thin layer chromatography and were identified along with their intermediates by spectroscopic methods: UV, IR, and NMR and mass spectrometry.

Key Words: chalcones, Mannich bases.

Introduction

The Mannich reaction is a three-component single pot reaction in which a secondary amine reacts with an aldehyde and an active hydrogen compound to afford compounds known as

Mannich bases. Sometimes the secondary amine is replaced by a primary amine or ammonia.

Studies on the chemistry of Mannich bases are of interest in various areas of applications. A large number of aminoalkyl derivatives have been synthesized in order to correlate their structure and reactivity with their pharmacological potential. Also Mannich bases represent easily obtainable intermediates for the synthesis of other compounds such as heterocycles, aminoalcohols ...*etc.*

Mannich bases are known for their biological potential. Some Mannich bases possess anticonvulsant activity^{1,2}, others exhibit analgesic potency³, some Mannich bases were reported¹³ as potential chemo preventive agents. Mannich bases with putative cytotoxic activity were reported^{4,5,6}. Stephen *et.al.*⁷ claimed antimalarial activity for some aminomethylated phenols. Tomas *et.al.*⁸ described the antibacterial potential of some fused Mannich ketones. Afaf *et.al.*⁹. Reported some aminomethylated benzimidazoles with potent antimicrobial activity. The anticancer potential of some Mannich bases was outlined^{10,11}.

Chalcones are valuable intermediates in organic synthesis because of their ability to act as activated unsaturated systems in addition reactions of carbanions. They react with active methylene compounds of some phytochemicals to offered synthetics of pharmacy potential^{12,13,14,15}.

Chalcones exhibits diverse pharmacological activities, including antileishmania¹⁷, anti-inflammatory¹⁶, antimetotic¹⁷, antiinvasive¹⁸, antituberculosis¹⁹, antifungal²⁰, antimalarial²¹, antiplasmodial²¹, antitumor²², antioxidant²³, immunosuppressive²⁴, and cytotoxic²⁵ properties.

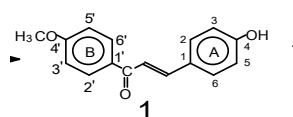
Bearing such interesting properties of Mannich bases and chalcones in mind it, was decided to join Mannich bases and chalcones in one molecule probably which potential

pharmacological activities. The target molecule is approached via effective and facile strategy involving synthesis of chalcones and subsequent aminomethylation.

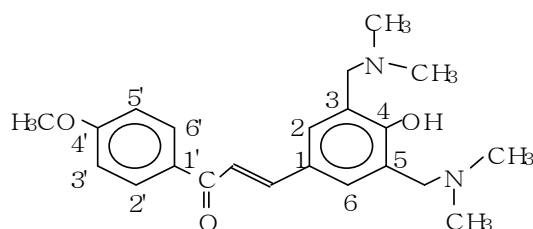
Materials and methods :

Synthesis of 3-hydroxy-4'-methoxychalcone (1):

Ten ml of 10% sodium hydroxide solution were added to a solution of the 4-methoxyacetophenone (0.02 mol) and 3-hydroxybenzaldehyde (0.02 mol) in ethanol (6 ml). The mixture was stirred at room temperature for 24 h and poured into water (100 ml). After neutralization with 10% hydrochloric acid a yellow solid was obtained. m.p 150-153 °C (yield 80%).

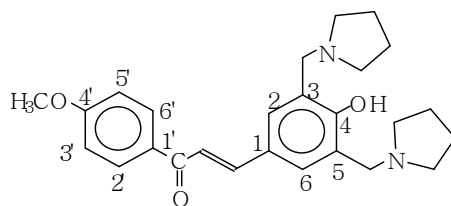


Synthesis of 4-hydroxy-4'-methoxy-3,5-bis-dimethylaminomethylchalcone(2):



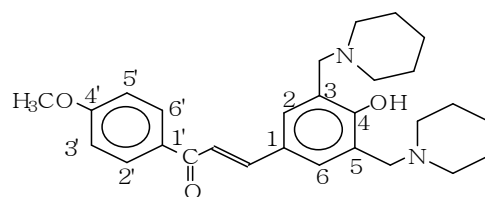
A mixture of 4-hydroxy-4'-methoxychalcone (**1**) (0.005 mol), formalin (0.01 mol) and dimethylamine (0.01 mol) were reacted in refluxing acetonitrile (50 ml) for 36 h. On cooling the precipitate was formed. This crude product was fractionated on silica gel G using the solvent (hexane/ethylacetate/methanol/isopropylamine 7.5:1:1:0.5), 4-hydroxy-4'-methoxy-3,5-bis-dimethylaminomethylchalcone (**2**) was obtained as pale yellow crystals, m.p 112-116 °C (yield 41%)

Synthesis of 4-hydroxy-4'-methoxy-3,5-bis-pyrrolidinomethylchalcone (3):



A mixture of 4-hydroxy-4'-methoxychalcone (**1**) (0.005 mol), formalin (0.01 mol) and pyrrolidine (0.01 mol) were reacted in refluxing acetonitrile (50 ml) for 36 h. On cooling the precipitate was formed. This crude product was fractionated on silica gel G using the solvent (hexane/ethylacetate/methanol/isopropylamine 7.5:1:1:0.5), 4-hydroxy-4'-methoxy-3,5-bis-dimethylaminomethylchalcone (**2**) was obtained as pale yellow crystals, m.p 122-124 °C (yield 50%)

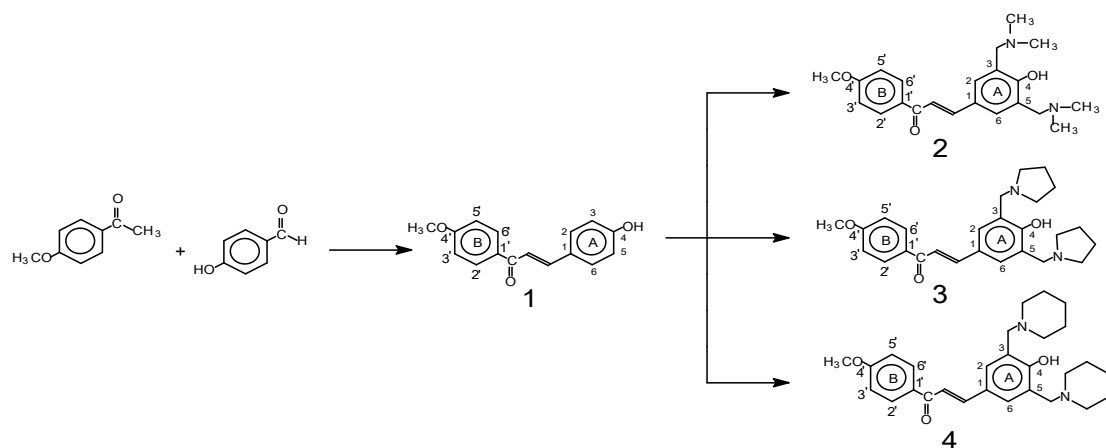
Synthesis of 4-hydroxy-4'-methoxy-3,5-bis-piperidinomethylchalcone (**4**):



A mixture of 3-hydroxy-4'-methoxychalcone (**1**) (0.005 mol), formalin (0.01 mol) and piperidine (0.01 mol) were reacted in refluxing acetonitrile (50 ml) for 36 h. On cooling the precipitate was formed. This crude product was fractionated on silica gel G using the solvent system: hexane / ethyl acetate/ isopropyl amine (6:3:1) where 3-hydroxy-4'-methoxy-4-piperidinochalcone (**4**) was obtained as pale yellow crystals, m.p 124-125 °C (yield 42%).

Results and discussion

Three chalcones with Mannich side chain (**2**), (**3**) and (**4**) were prepared together with their intermediate.



4-Hydroxy-4'-methoxychalcone was obtained by reaction of 4-methoxyacetophenone and 4-hydroxybenzaldehyde in alkaline ethanol solution m.p 152-154 °C (yield 85%) The UV_{λ} spectrum $\lambda_{\max}$ (ethanol), 250, 316 and 324 and 372 nm due to the benzoyl and cinnamoyl chromophores. The IR spectrum showed $\nu(KBr)$ 829 (C-H, Ar, bending), 1226.6 (C-O), 1554, 1581, 1600 (C=C, Ar, st,vib), 1643 (C=O. st, vib), 3000 and 2800 and 3080 (C-H Ar) and 3182 cm^{-1} (OH). The ^1H -NMR spectrum showed signal at δ 3.95 (s, 3H) assigned for methoxyl group. The α and β protons resonate at δ 7.58 (d, J = 15.1 Hz, 1H) and δ 7.7 (d, J = 15.1 Hz, 1H). The signal at 7.71 (d, J = 9.0 Hz, 2H) was assigned for C_3 and C_5 -H, while the signal at δ 7.06 (d, J = 9.0 Hz, 2H) is due to C_2 , and C_6 -H of ring B. The doublet at δ 8.33 (J = 8.5 Hz, 2H) was assigned for $C_{3'}$ and C_5' -H, while the signal at δ 7.70 (d, J = 8.5 Hz, 2H), is characteristic of $C_{2',6'}$ -H of ring A. ^1H - ^1H cosy NMR demonstrated a diagonal relationship between α - and β -H of the chalcone moiety. Also coupling between C_3 and C_5 -H C_2 , of ring B and C_6 -H of ring A. The ^{13}C NMR spectrum showed a pattern characteristic of a C_{16} system. Apt experiments

showed 11 carbons in positive mode (one $-\text{OCH}_3$, one Me, nine $=\text{CH}-$), and five types are in negative mode (quaternary carbons).

When 4-hydroxy-4'-methoxychalcone (**1**) was reacted with dimethylamine and formalin in dry acetonitrile under reflux the 4-hydroxy-4'-methoxy-3,5-bis-dimethylaminomethylchalcone (**2**) was obtained. m.p 112-116 (yield 41%) The ^1H -NMR spectrum showed a singlet at δ 2.40 (12H) assigned for four methyl groups. The signal at δ 3.70 (s, 2H), is characteristic of $\text{N}-\text{CH}_2$. The methoxy groups. The resonance at δ 7.73 (d, 1H, $J = 15.5$) is characteristic of β -H, while the singlet at δ 7.45 (2H) was assigned C_2 and C_6 -H. The signal at δ 6.98 (J 8.2 Hz, 2H) was assigned for C_3 - and C_5 -H, while the signal at δ 8.07 (d, J 8.2 Hz, 2H) is characteristic of C_2 and C_6 -H. ^{13}C NMR spectrum showed a pattern characteristic of a C_{22} system. Apt experiments showed 13 carbons in negative mode (one $-\text{OCH}_3$, four Me, eight $=\text{CH}-$), and 9 carbons in positive (two CH_2 -, and seven quaternary carbons). The mass spectrum gave m/z 369.2 (42%) for the molecular ion. Other fragment at m/z 324.2 (100%) (base peak) is due to loss of amino group.

When 4-hydroxy-4'-methoxychalcone (**1**) was reacted with pyrrolidine and formalin in dry acetonitrile under reflux the 4-hydroxy-4'-methoxy-3,5-bis-pyrrolidinomethylchalcone (**2**) was obtained. m.p 122-124, (yield 50%) In the IR showed $\nu(\text{KBr})$ 808 (C-H, Ar, bending), 1022 (C-N), 1163, 1253 (C-O), 1586 (C=C, Ar, st, vib), 1652 (C=O. st, vib), 2830 (C-H, aliphatic) 2930 (C-H

and 2962 (OH) cm^{-1} . The ^1H -NMR spectrum showed a multiplet at δ 1.82-1.88 (8H) characteristic of the four methylene groups of $\begin{smallmatrix} \text{CH}_2- \\ | \\ \text{CH}_2- \end{smallmatrix}$ moiety. The resonance centered at δ 2.05-3.25 (8H) was assigned for four methylenes of $\begin{smallmatrix} -\text{CH}_2 \\ | \\ -\text{CH}_2 \end{smallmatrix} \text{N}-$ of the pyrrolidine ring. signal at δ 3.98 (s, 4H), is characteristic of two methylenes $\text{N}-\text{CH}_2-$ in the Mannich side chain. The methoxy groups were observed as a singlet at δ 3.78. The resonance at δ 7.43 (s, 1 H) was assigned for β -H while the signal at δ 7.73 (d, 1H, $J = 15.5$ Hz) was assigned for α -H. The singlet at δ 7.40 (2H) was assigned C_2 -H and C_6 -H. The signal at δ 6.06 (J 9.0 Hz, 2H) was assigned for C_3 - and C_5 -H, while the signal δ 8.05 (d, J 9.0 Hz, 2H) assigned for C_2 - and C_6 -H. ^1H - ^1H cosy NMR demonstrated a diagonal relationship between 8 protons of $\begin{smallmatrix} \text{CH}_2- \\ | \\ \text{CH}_2- \end{smallmatrix}$ (δ 1.82-1.88) and 8 protons of $\begin{smallmatrix} -\text{CH}_2 \\ | \\ -\text{CH}_2 \end{smallmatrix} \text{N}-$ (δ 2.05-3.25). The ^{13}C NMR spectrum showed a pattern characteristic of a C_{25} system. Apt experiments showed 9 carbons in negative mode (one $-\text{OCH}_3$, eight $=\text{CH}-$), and 17 carbons in positive (ten CH_2 -, and seven quaternary carbons). The noesy experiments showed long range coupling between C_2 -H and C_6 -H. The mass spectrum gave m/z 350 (100%) (base peak) for the molecular ion. Other fragment at m/z 279 (99%) are due to loss of amino group.

When 4-hydroxy-4-methylchalcone was reacted with piperidine and formaldehyde in dry acetonitrile under reflux. The 4-hydroxy-4'-methoxy-

3,5-bis-piperlidinomethylchalcone (**4**) was obtained, m.p 124-125 °C (42%). The UV spectrum gave λ_{max} (ethanol) 252, and 354 nm due to the benzoyl and cinnamoyl chromophores. The IR showed $\nu(\text{KBr})$ 829 (C-H, Ar, bending), 1149 (C-N), 1255 (C-O), 1471 and 1598 (C=C, Ar, st,vib), 1652 (C=O. st, vib), , 2796 (C-H, aliphatic) 2848 (C-H Ar) and 3933 (OH) cm^{-1} . The ^1H -NMR spectrum showed a multiplet at δ 2.40-2.60 (2H) characteristic of $\text{—}\overline{\text{CH}_2}\text{—}$ of the piperidine moiety, while the multiplet at δ 1.70-1.90 (4H) was assigned for the $\text{<}\begin{smallmatrix} \text{CH}_2\text{—} \\ \text{CH}_2\text{—} \end{smallmatrix}\text{—}$ protons .The resonance at δ 1.53-1.73 (4H) was assigned for $\text{—}\begin{smallmatrix} \text{CH}_2\text{—} \\ \text{CH}_2\text{—} \end{smallmatrix}\text{>N—}$ of the piperidine ring. The methoxyl protons resonate at δ 3.90 (s, 3H). The signal at δ 3.64 (s, 2H), is characteristic of $\text{>N—CH}_2\text{—}$. The resonance at δ 7.40 (s, 2H) was assigned for $\beta\text{—H}$ and the signal at δ 7.74 (d, 1H, $J=15.5$ Hz) was assigned for $\alpha\text{—H}$ The singlet at δ 7.39 (2H) was assigned $\text{C}_2\text{—}$ and $\text{C}_6\text{—H}$. The signal at δ 6.98 (J 9.0 Hz, 2H) is characteristic of $\text{C}_3\text{—}$ and $\text{C}_5\text{—H}$, while the signal δ 8.05 (d, J 9.0 Hz, 2H) was assigned for $\text{C}_2\text{—}$ and $\text{C}_6\text{—H}$. ^1H - ^1H cosy NMR demonstrated a diagonal relationship between the α and β protons of the chalcone moiety which resonate at δ 7.74 and δ 7.40 respectively, also demonstrated a diagonal relationship between all protons at piperidine moiety. The ^{13}C NMR spectrum showed a pattern characteristic of a C_{28} system. Apt experiments showed 9 carbons in negative mode (one —OCH_3 , eight =CH—), and 19 in positive mode (twelve $\text{CH}_2\text{—}$, and seven quaternary carbons). The mass spectrum gave m/z 449.5 (3%) for the molecular ion. The

most important fragments are at m/z 364.4 (100%) (base peak) due to loss of amino group, and m/z . 279.3 (80%) due to lost of two amino groups.

References

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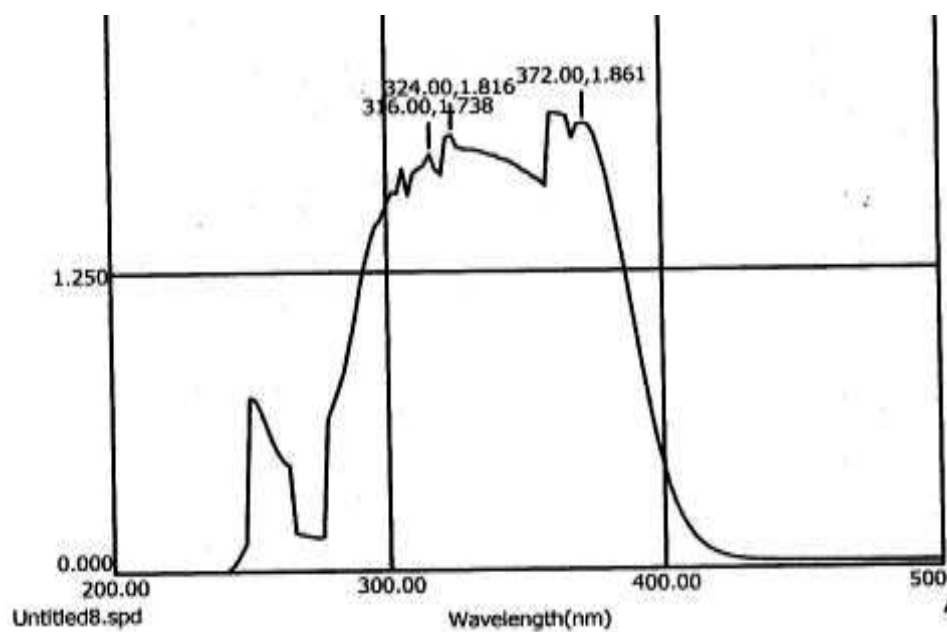


Fig UV spectrum of 4-hydroxy-4'-methoxychalcone (1)

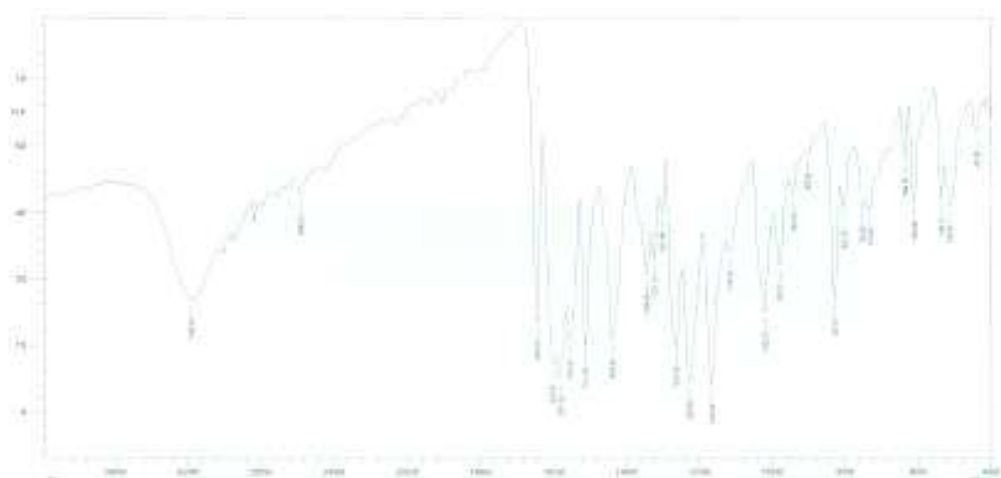


Fig IR spectrum of 4-hydroxy-4'-methoxychalcone (1)

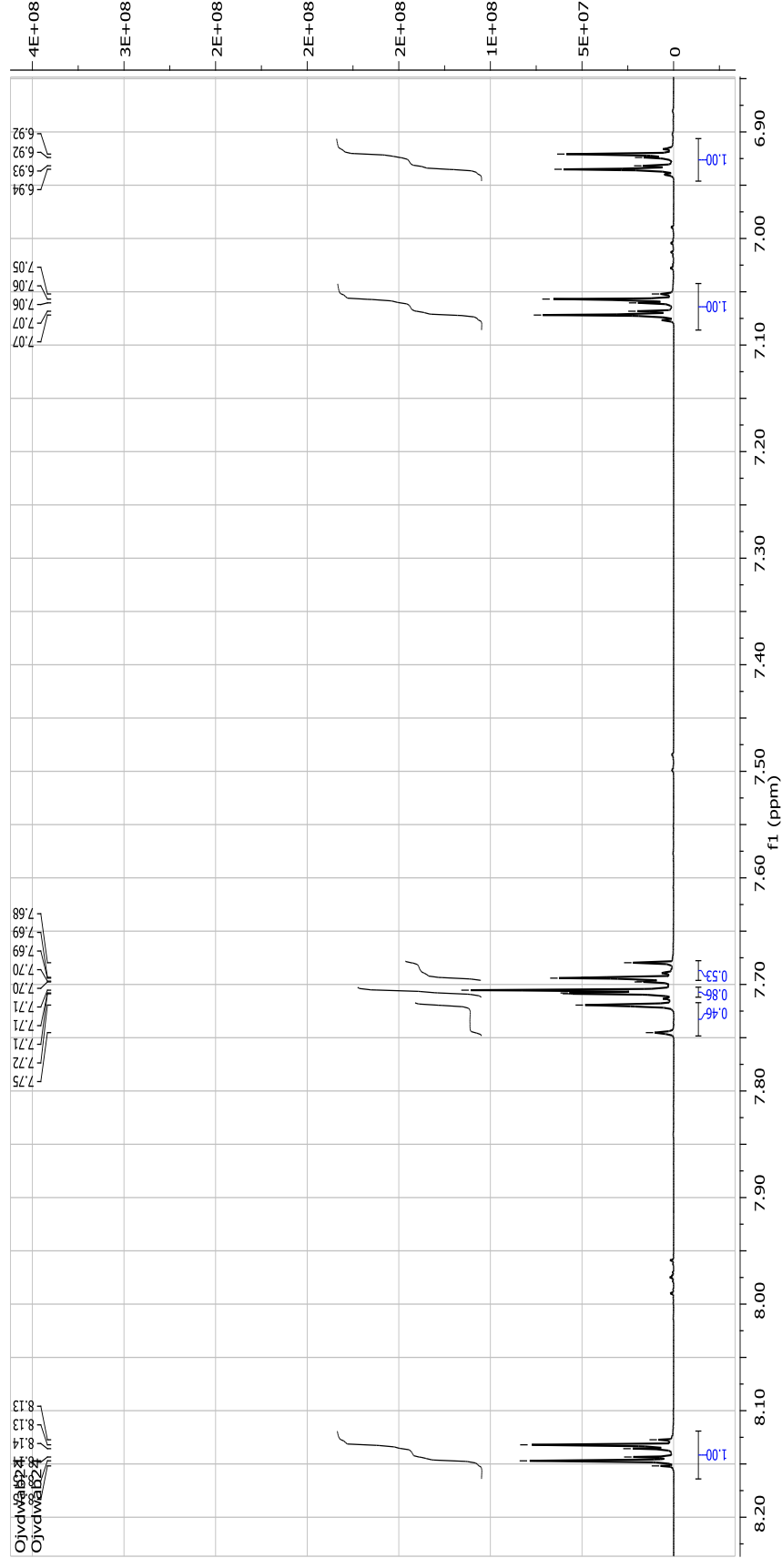


Fig ¹H NMR spectrum of 4-hydroxy-4'-methoxychalcone (1)

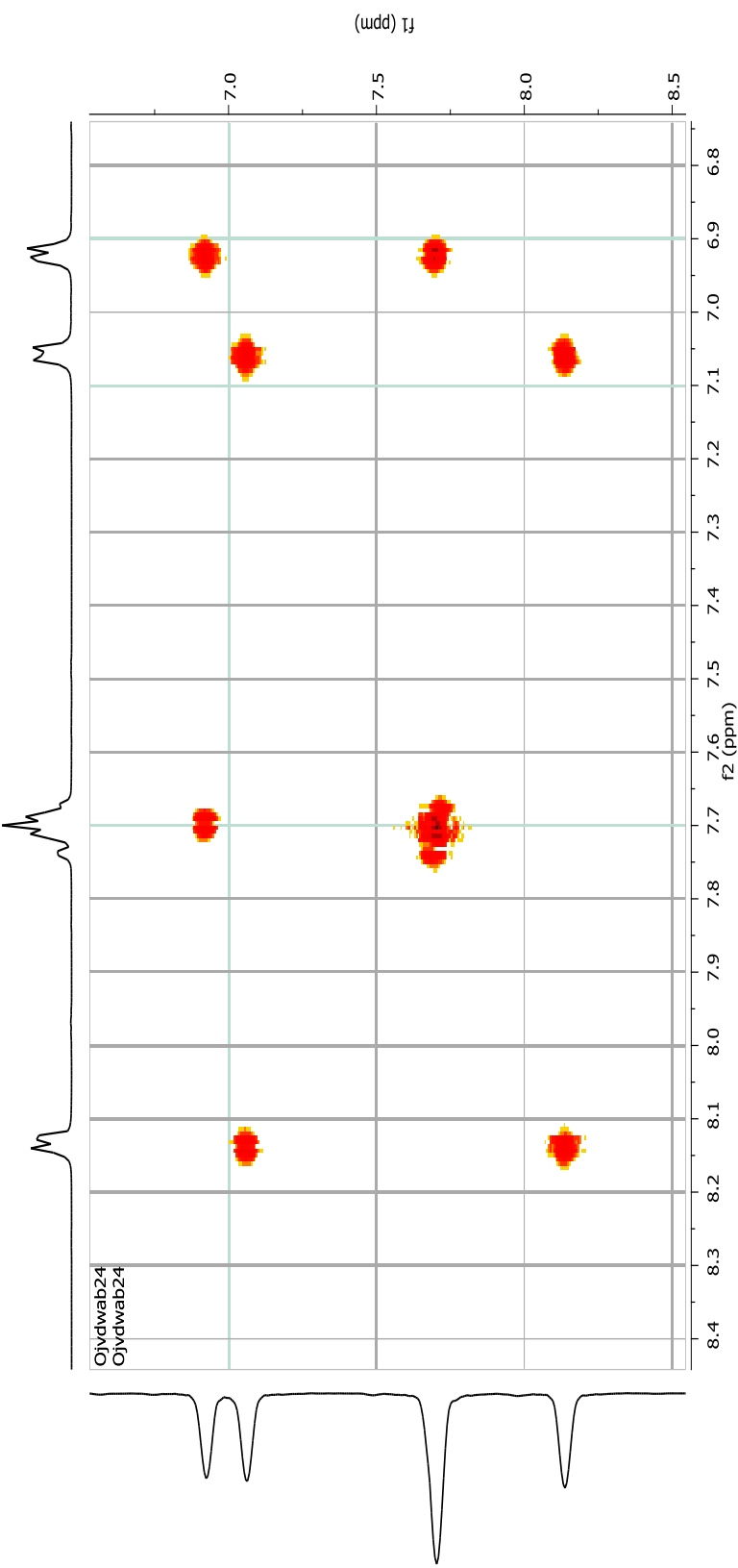


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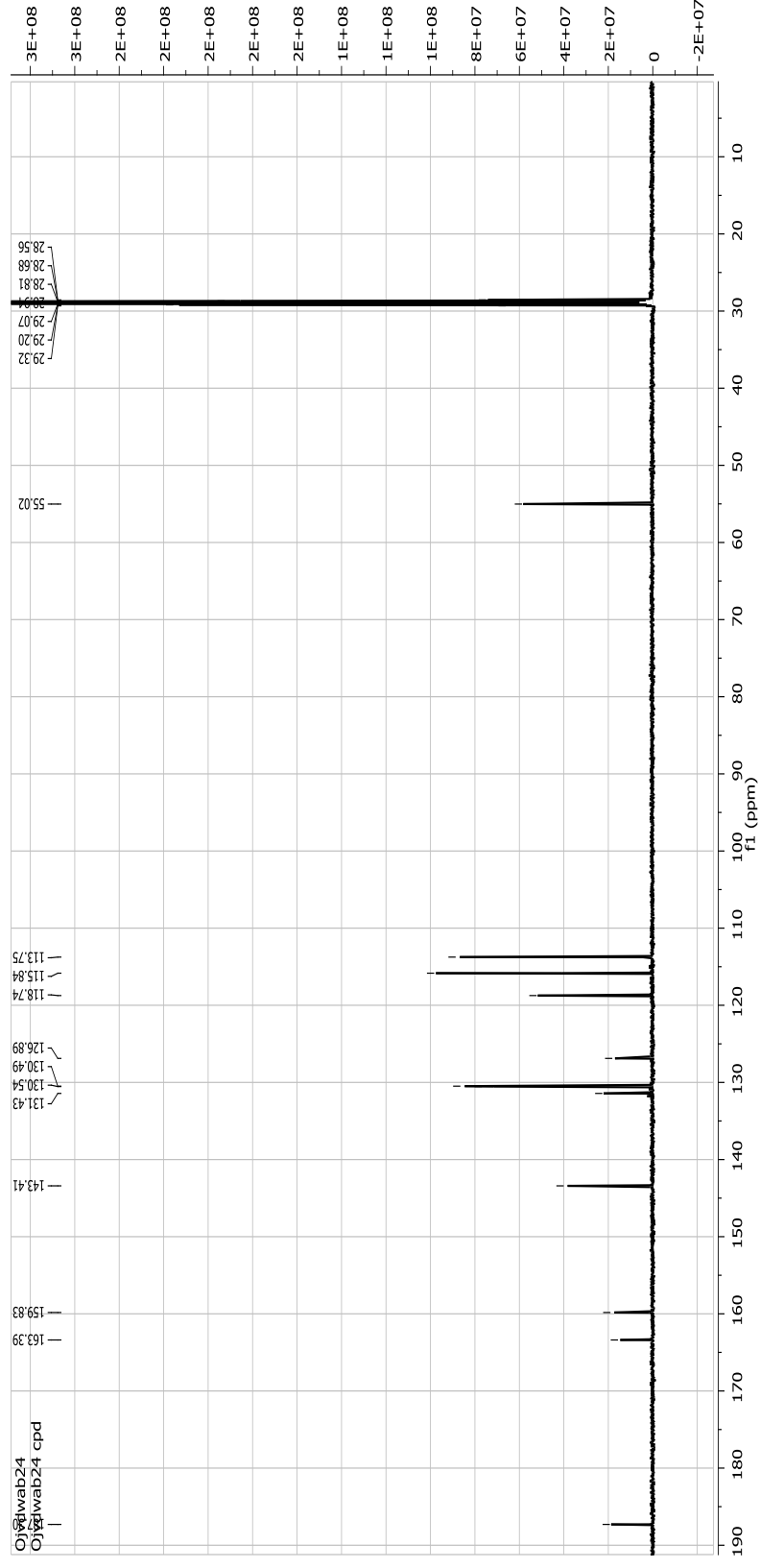


Fig ¹³C NMR spectrum of 4-hydroxy-4'-methoxychalcone (1)

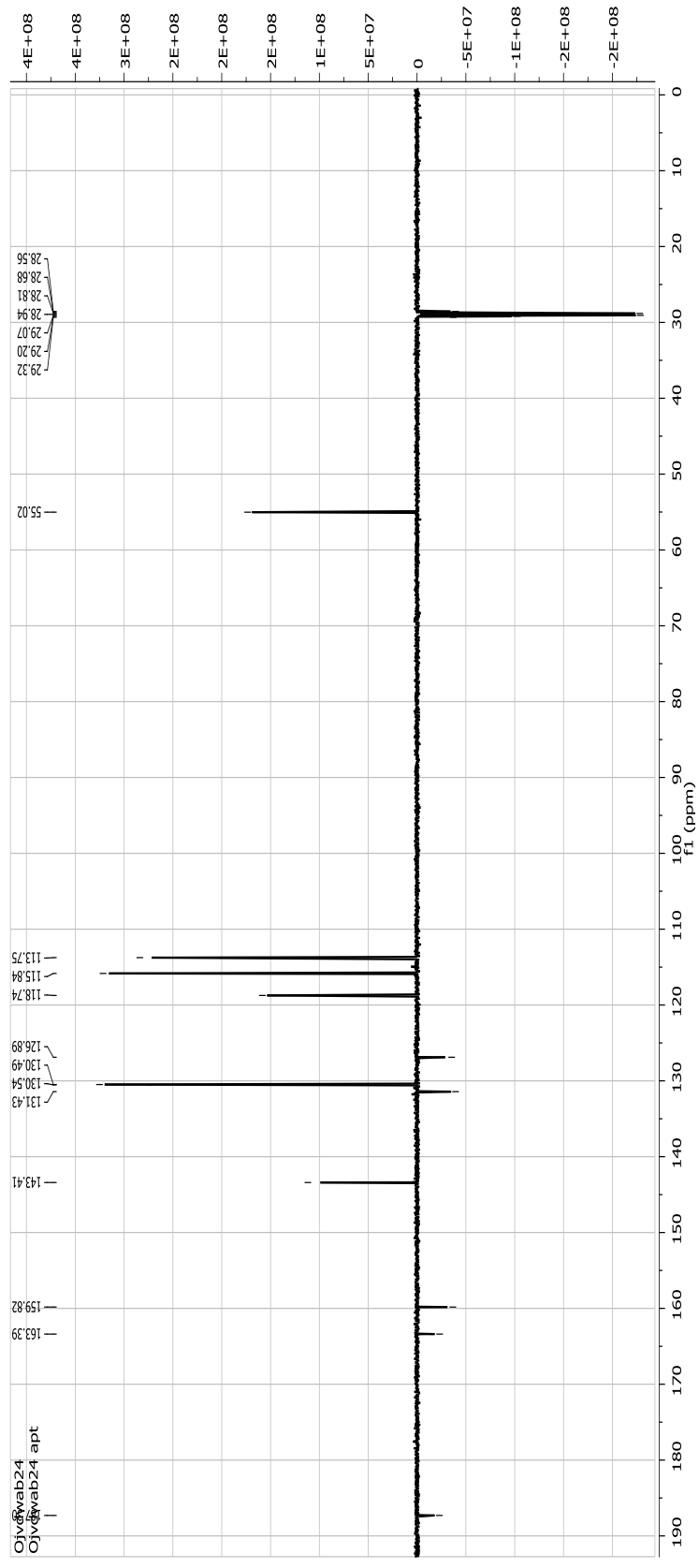


Fig Apt experiments of 4-hydroxy-4'-methoxychalcone (1)

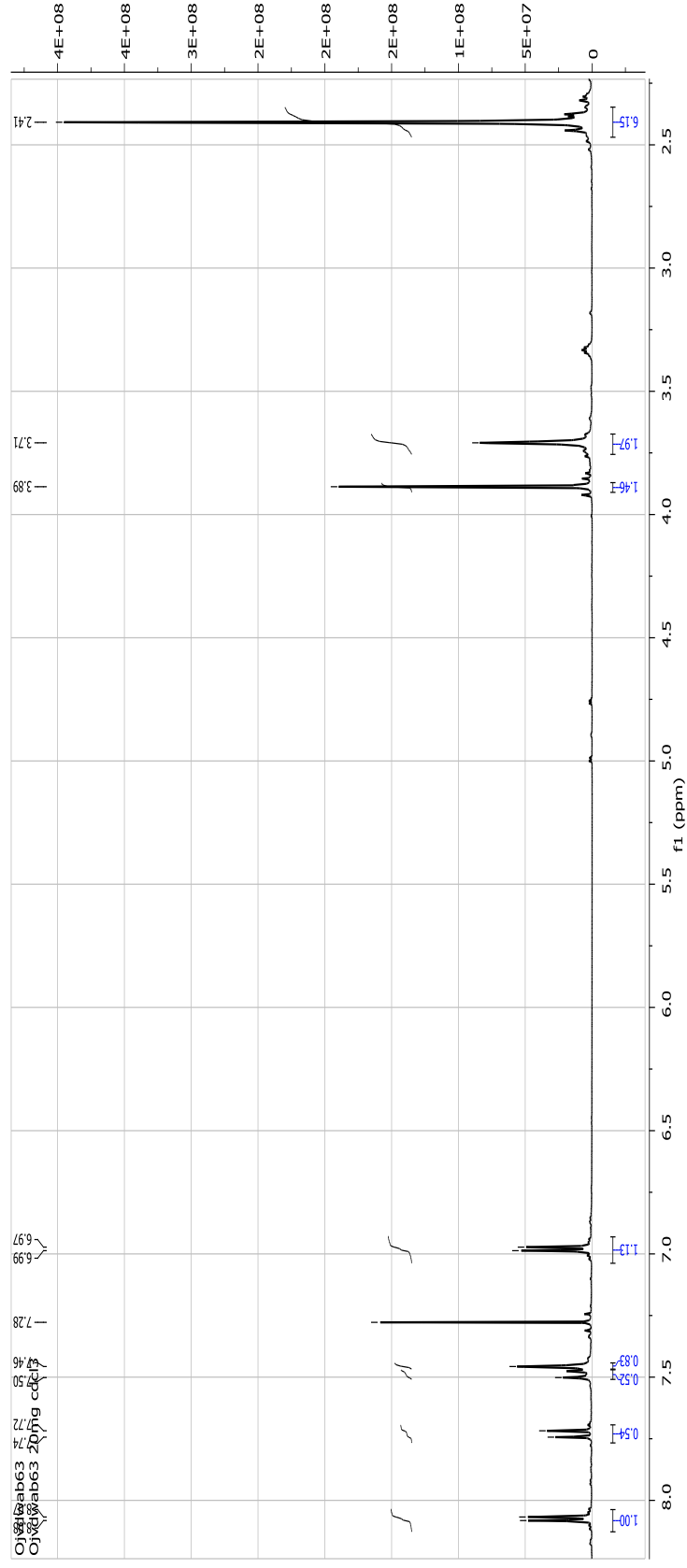


Fig ¹H-NMR spectrum of 4-hydroxy-4'-methoxy-3,5-bis-dimethylaminomethylchalcone (2)

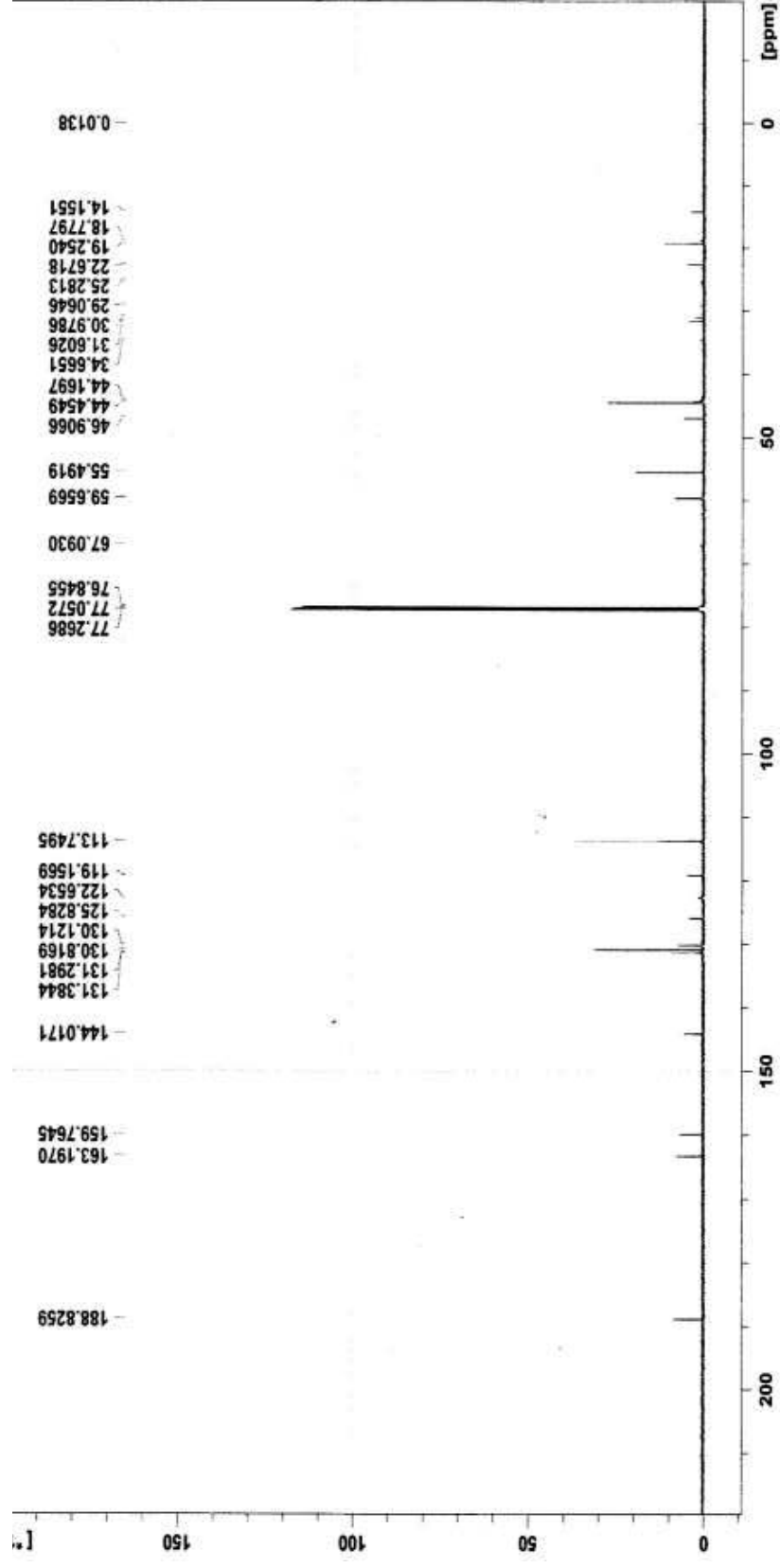


Fig ^{13}C NMR spectrum of 4-hydroxy-4'-methoxy-3,5-bis-dimethylaminomethylchalcone (2)

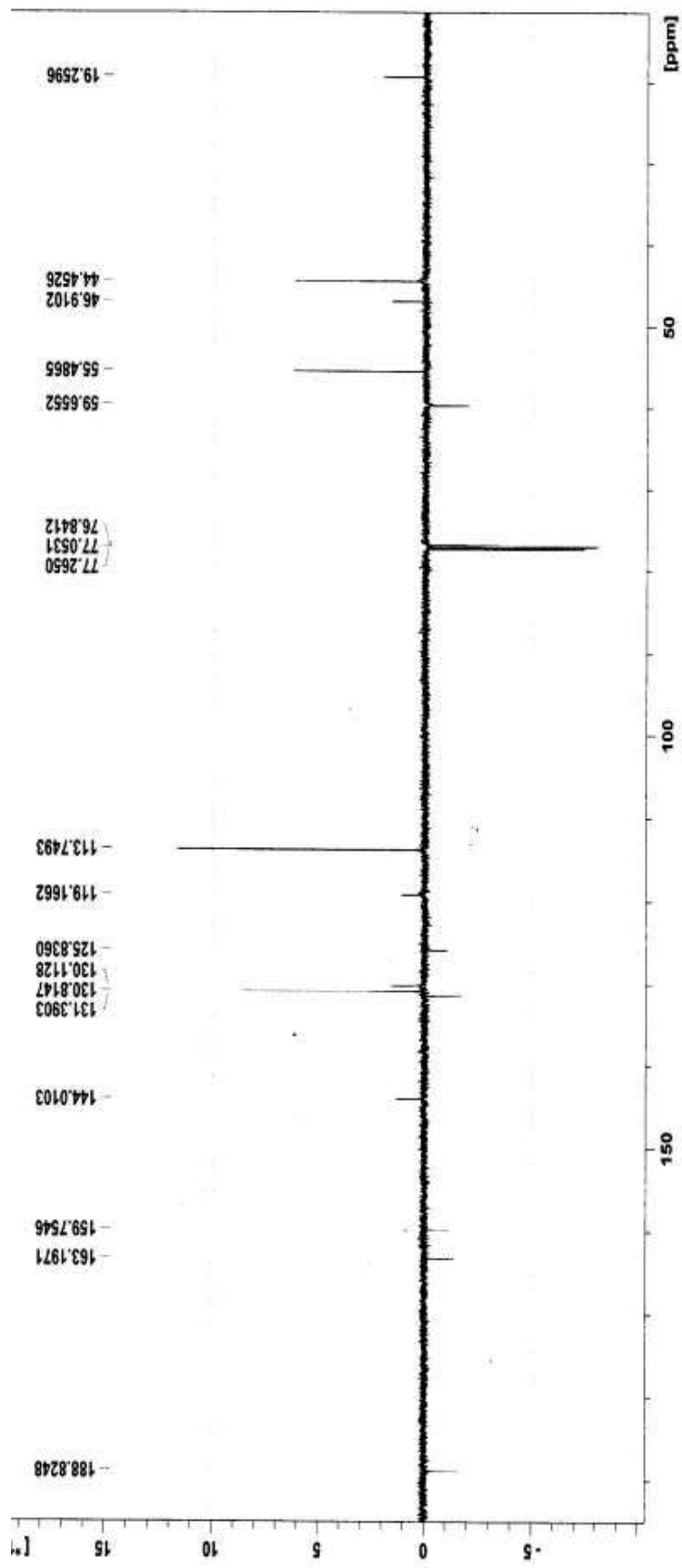


Fig Apt experiments of 4-hydroxy-4'-methoxy-3,5-bis-dimethylmethylchalcone (2)

Fig Mass spectrum of 4-hydroxy-4'-methoxy-3,5-bis-dimethylmethylchalcone (2)

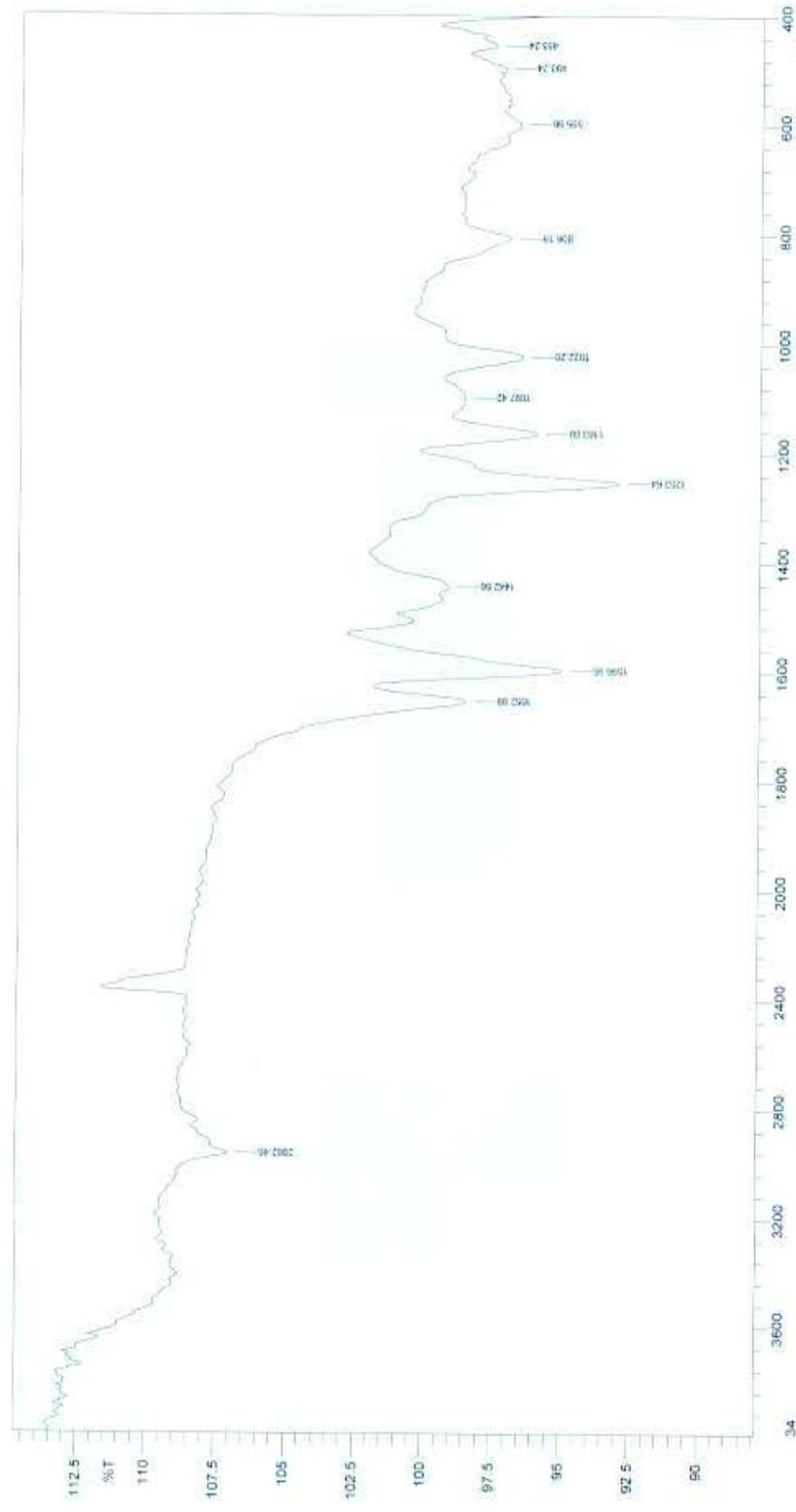


Fig IR spectrum of 4-hydroxy-4'-methoxy-3,5-bis-pyrrolidinomethylchalcone (3)

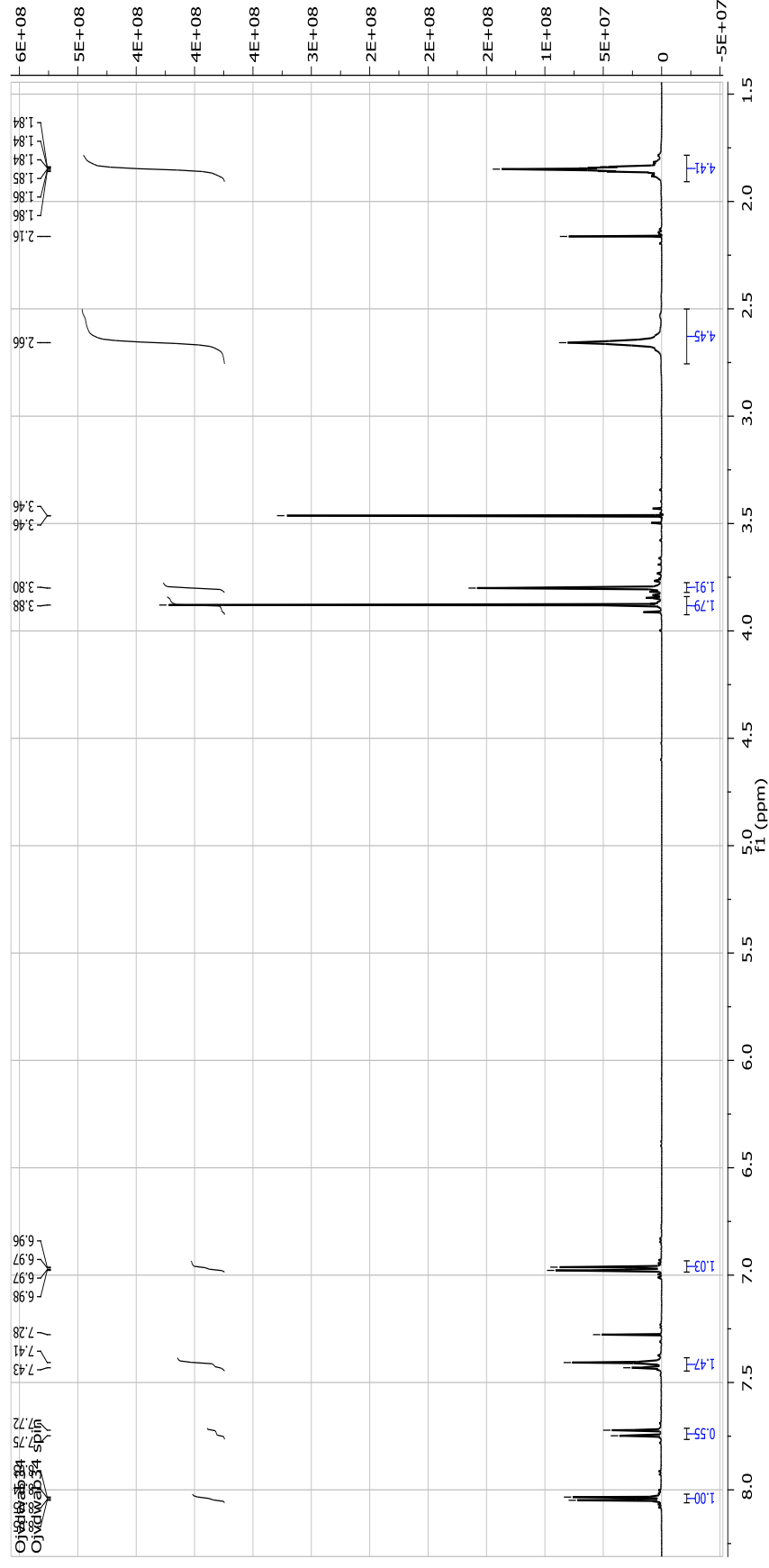


Fig ¹H-NMR spectrum of 4-hydroxy-4'-methoxy-3,5-bis-pyrrolidinomethylchalcone (3)

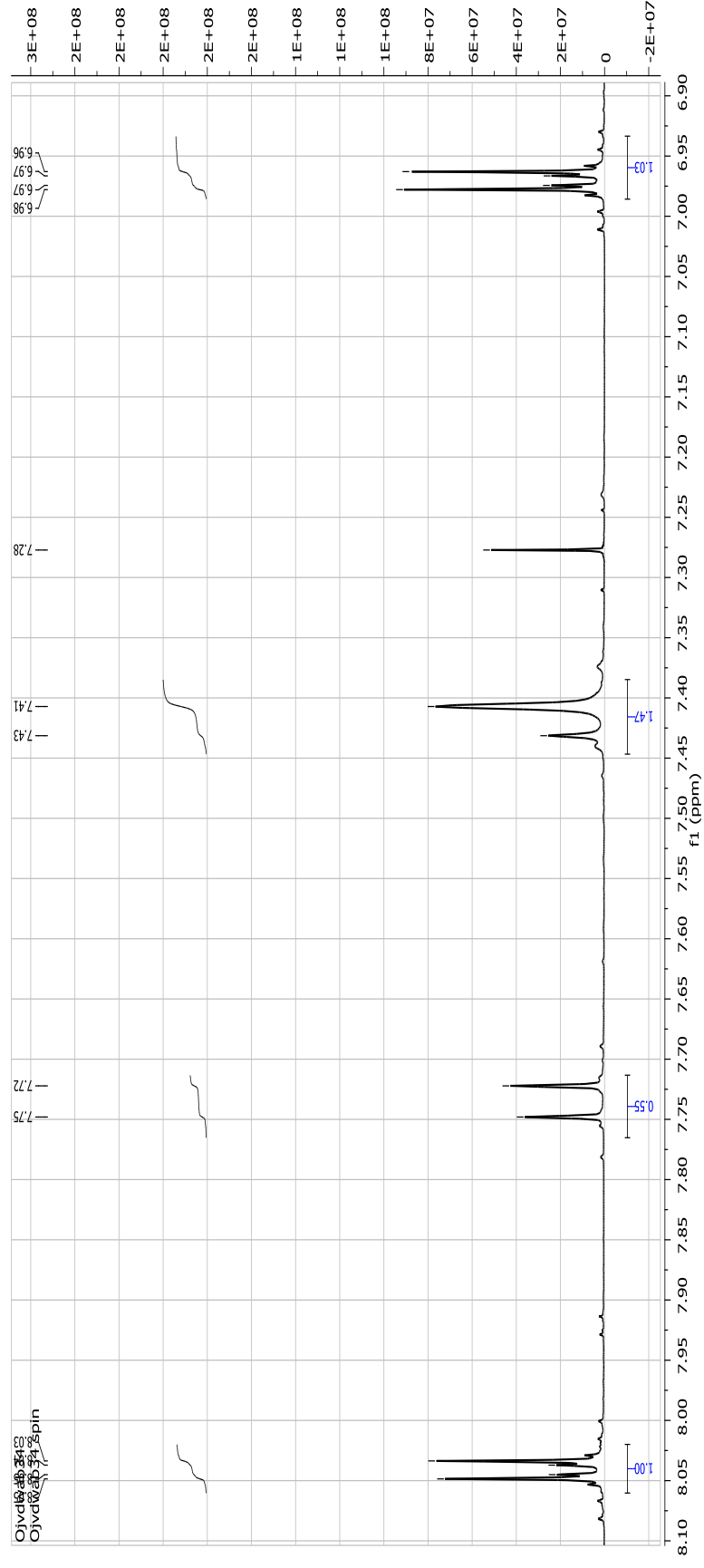


Fig ^1H -NMR spectrum of 4-hydroxy-4'-methoxy-3,5-bis-pyrrolidinomethylchalcone (3)

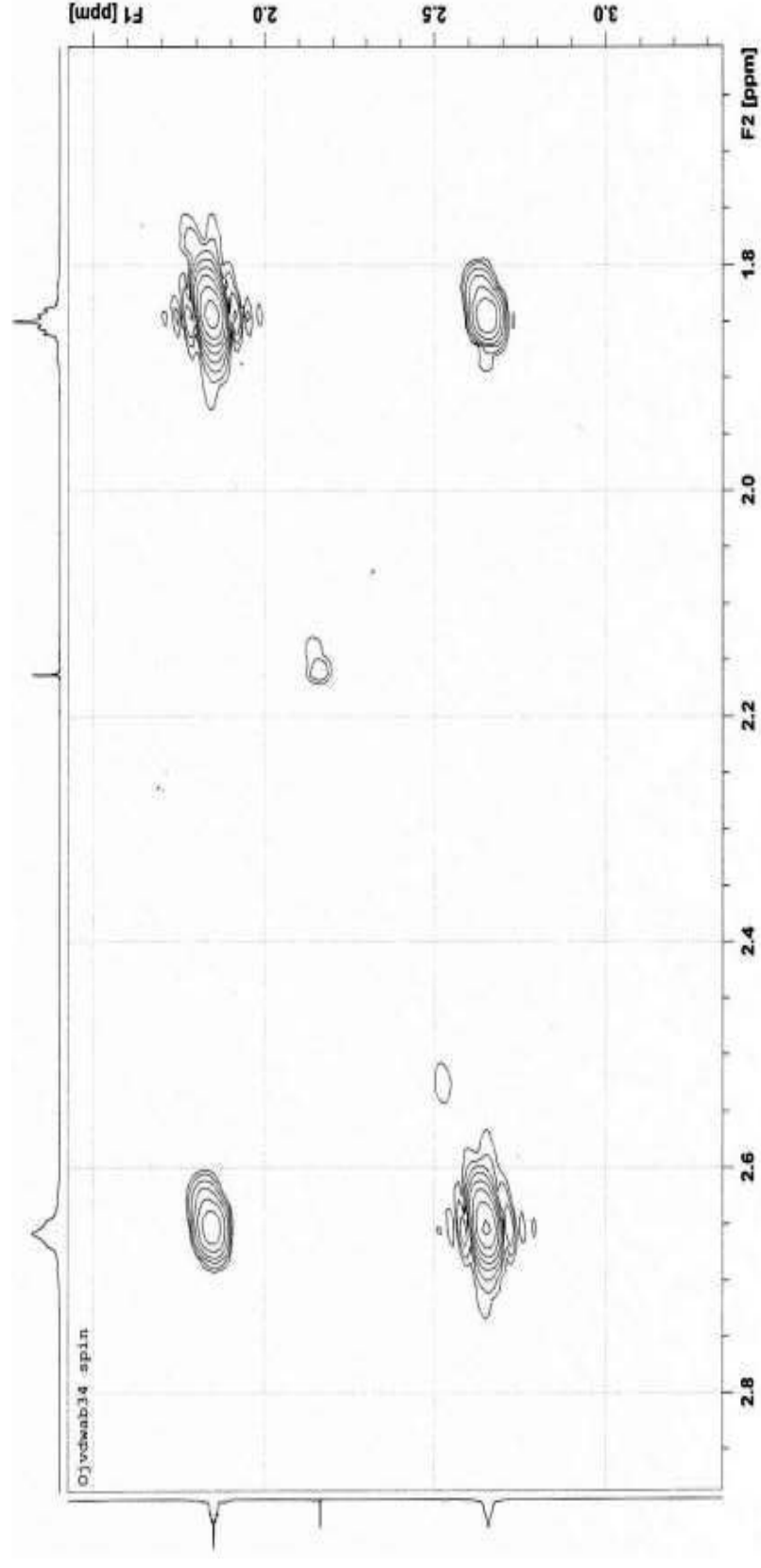


Fig ^1H - ^1H cosy NMR of 4-hydroxy-4'-methoxy-3,5-bis-pyrrolidinomethylchalcone (3)

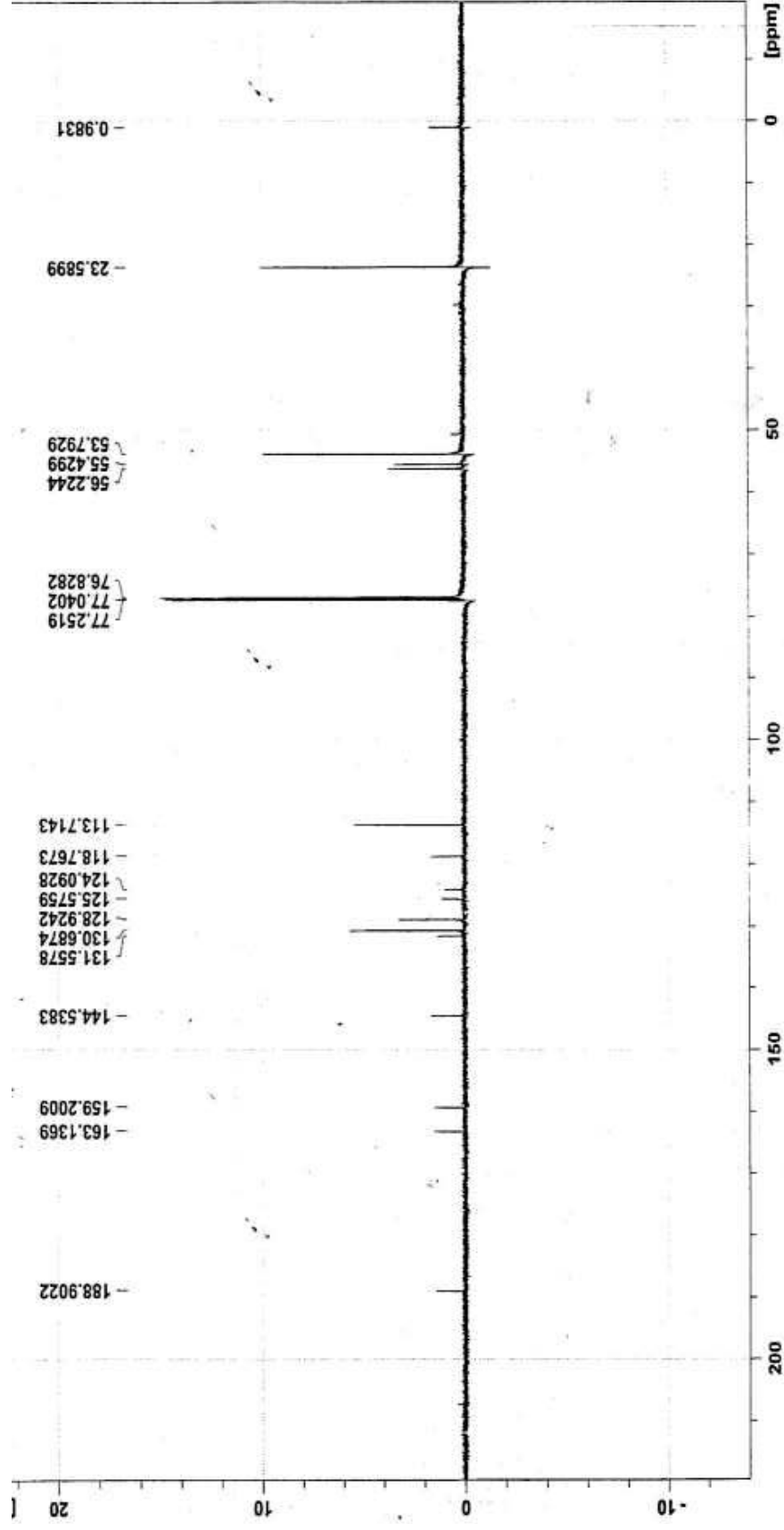


Fig ^{13}C -NMR spectrum of 4-hydroxy-4'-methoxy-3,5-bis-pyrrolidinomethylchalcone (3)

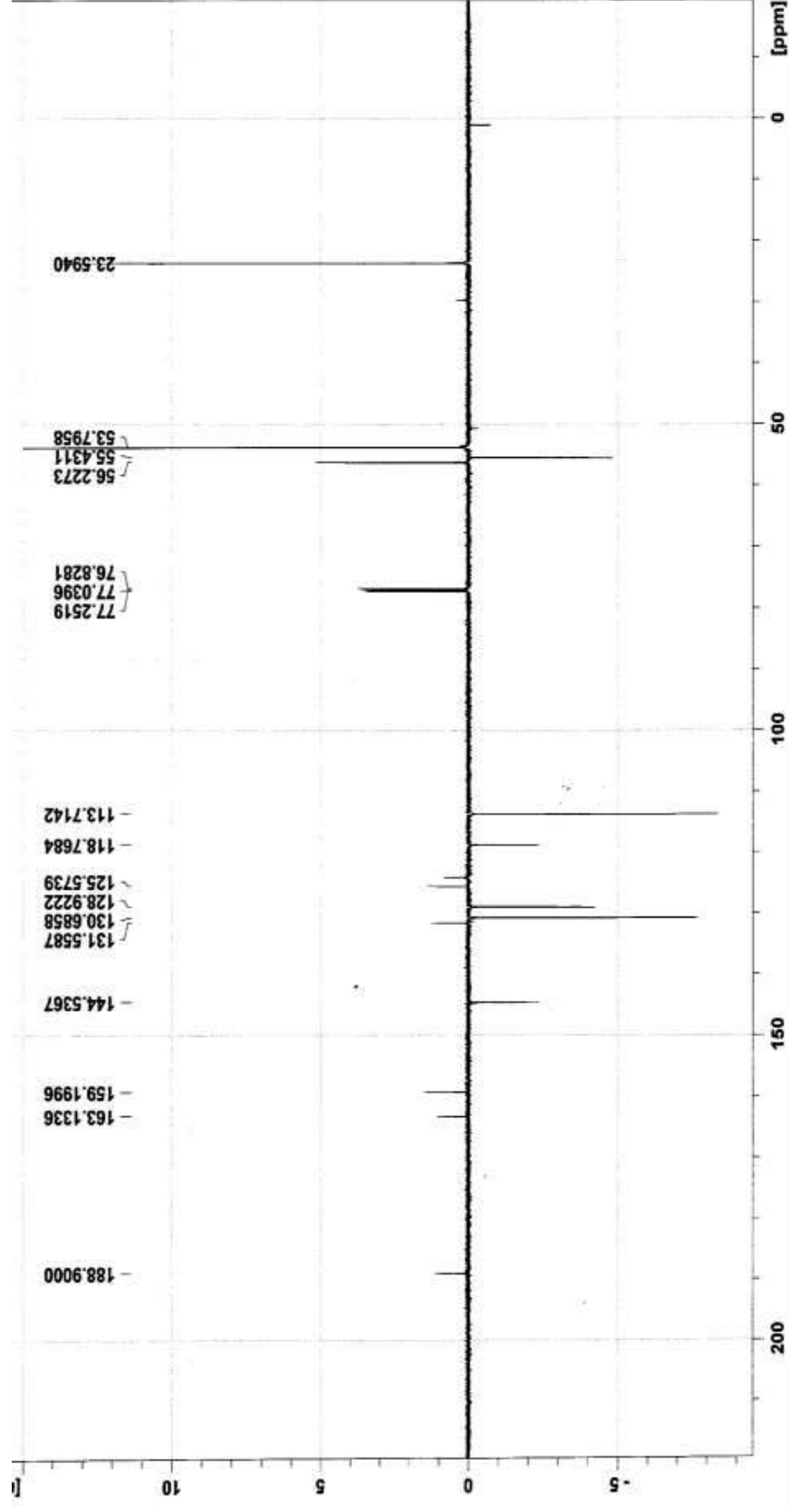


Fig Apt experiments of 4-hydroxy-4'-methoxy-3,5-bis-pyrrolidinomethylchalcone (3)

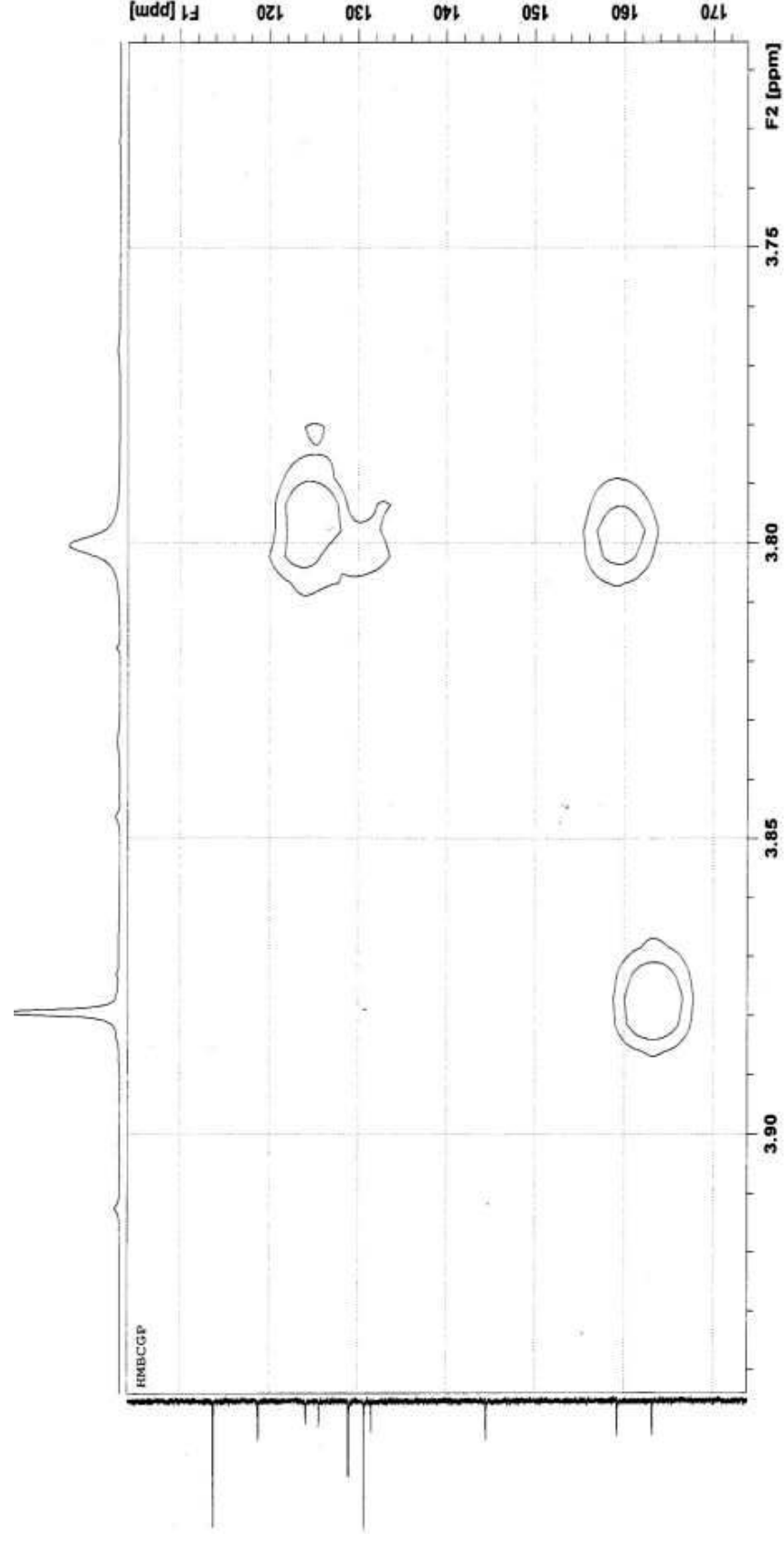


Fig nousey experiment of 4-hydroxy-4'-methoxy-3,5-bis-pyrrolidinomethylchalcone (3)

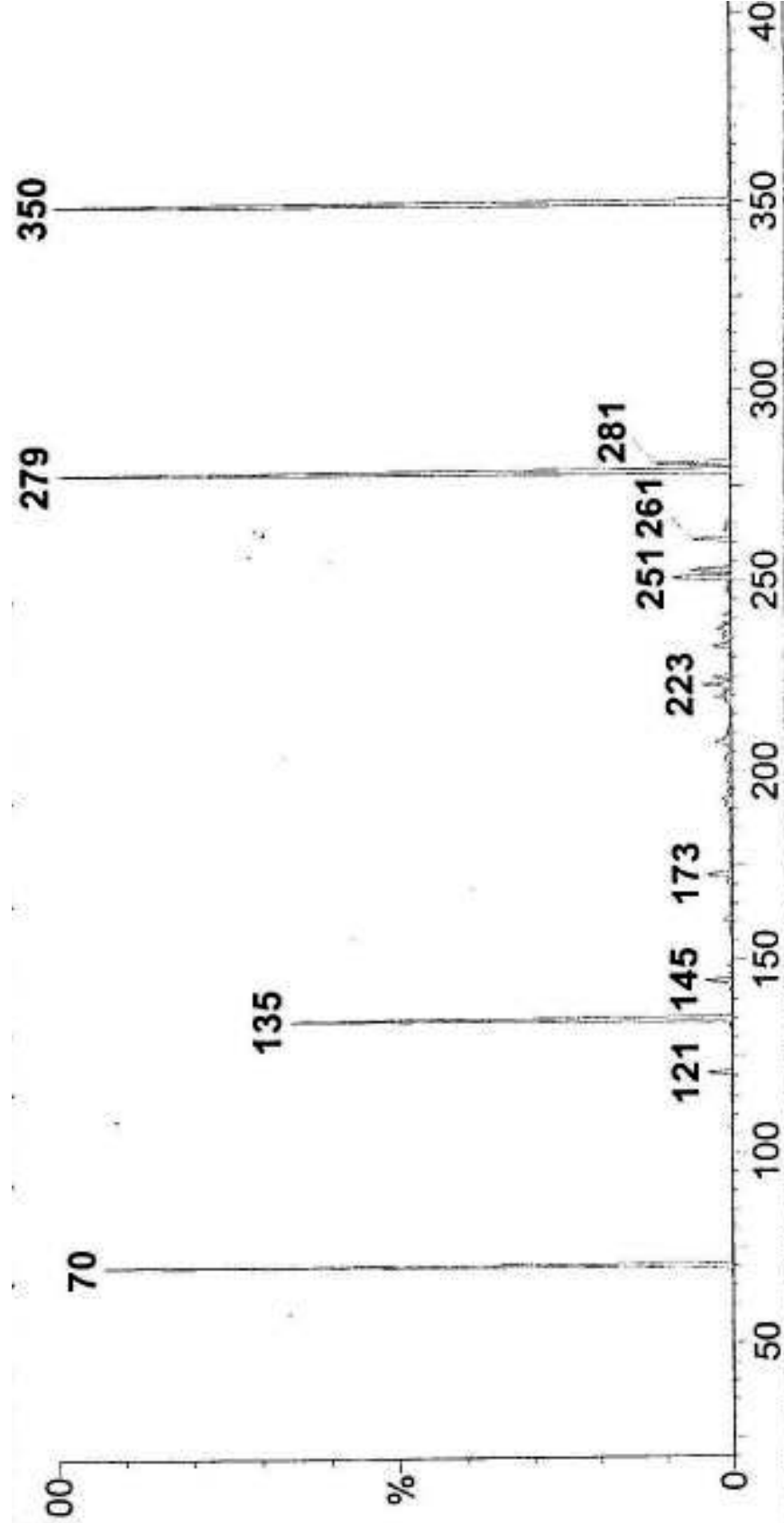


Fig Mass spectrum of 4-hydroxy-4'-methoxy-3,5-bis-pyrrolidinomethylchalcone (3)

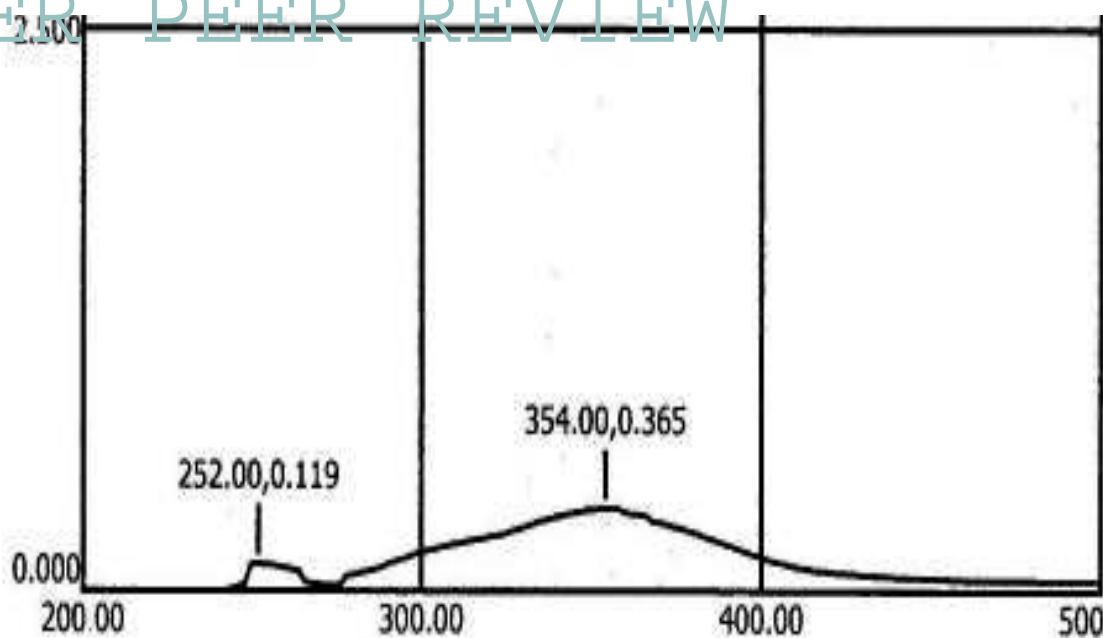


Fig UV spectrum of 4-hydroxy-4'-methoxy-3,5-bis-piperlidinomethylchalcone (4)



Fig IR spectrum of 4-hydroxy-4'-methoxy-3,5-bis-piperlidinomethylchalcone (4)

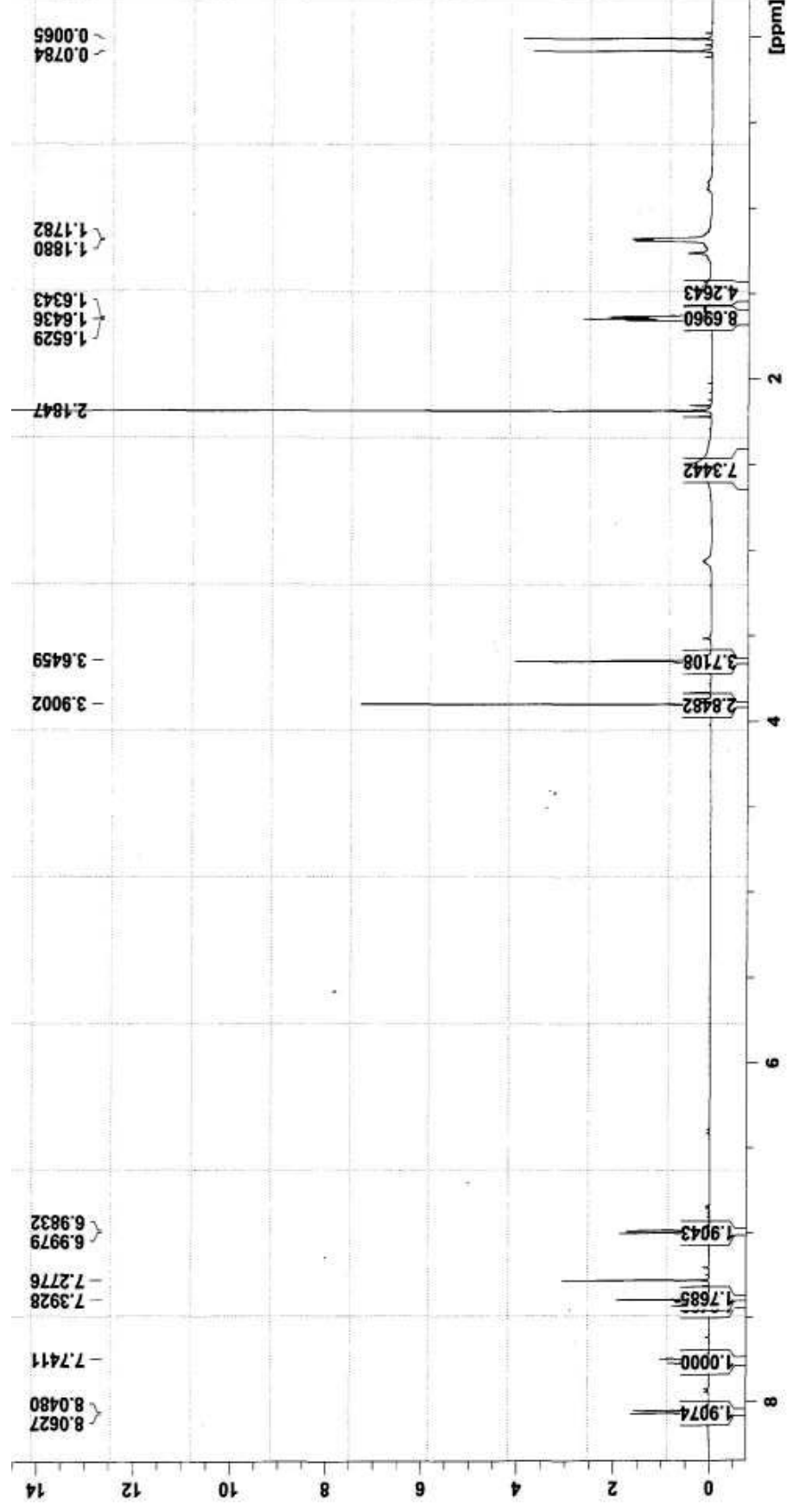


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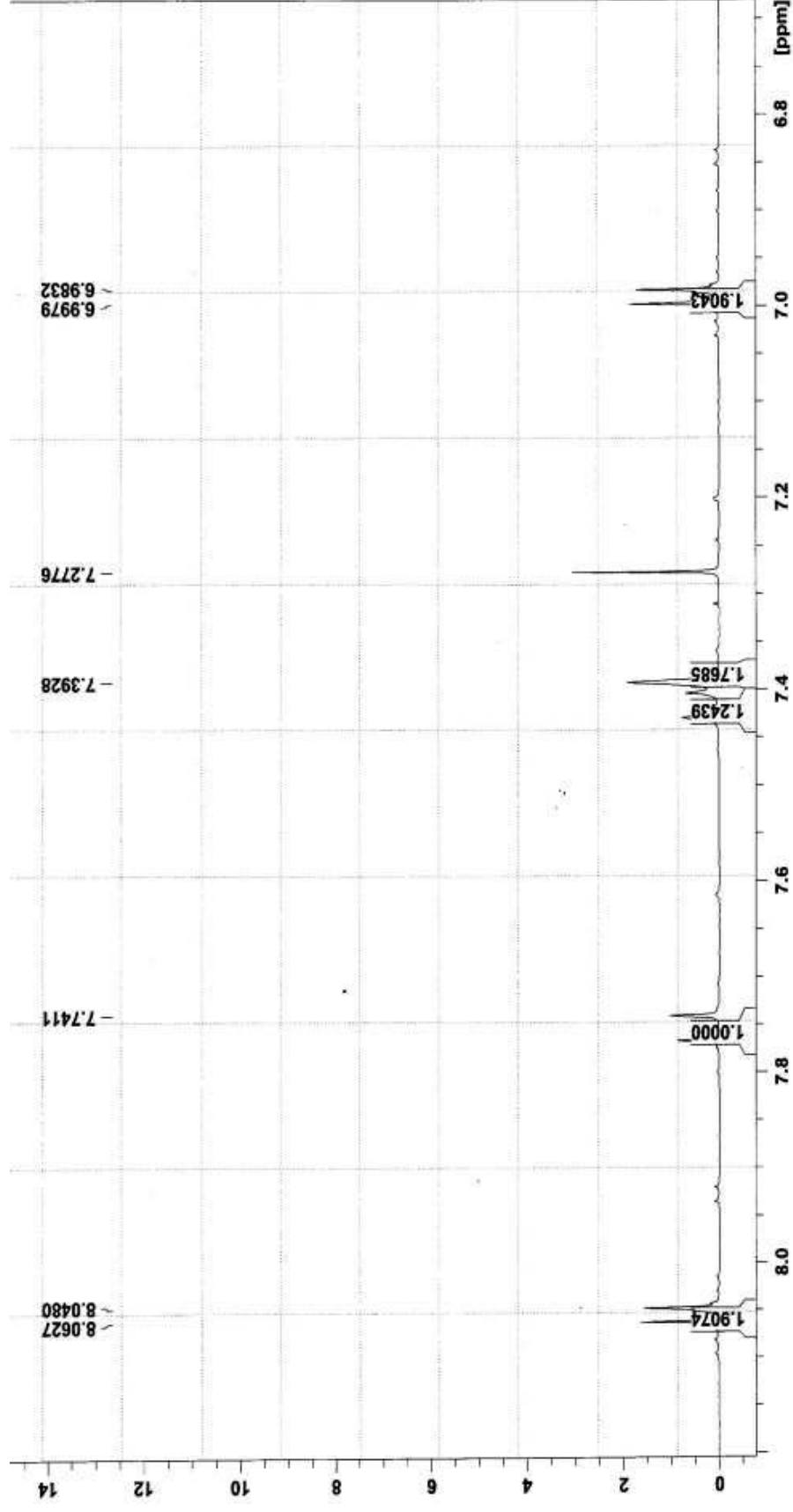


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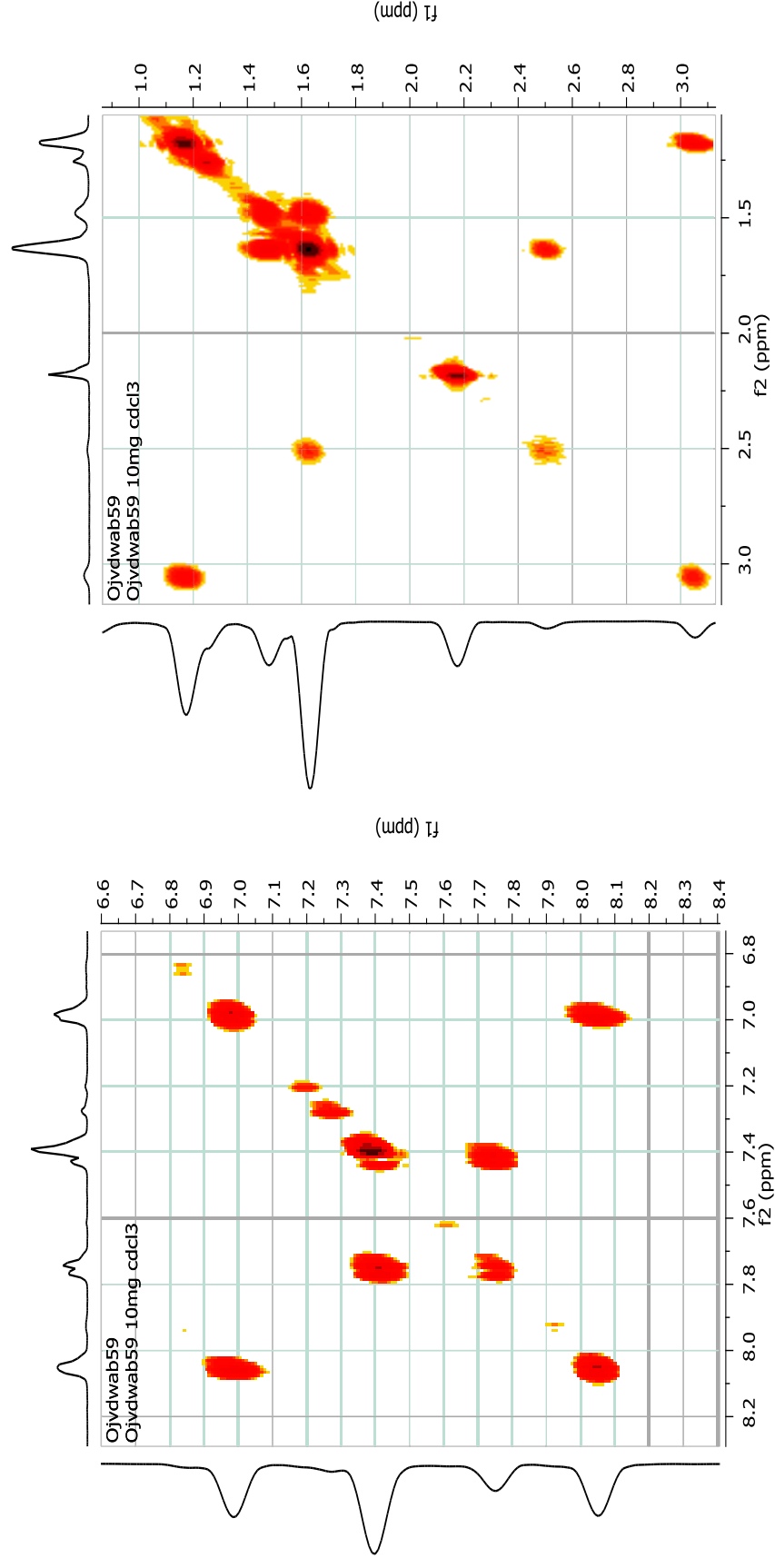


Fig of 4-hydroxy-4'-methoxy-3,5-bis-piperidinomethylchalcone (4)

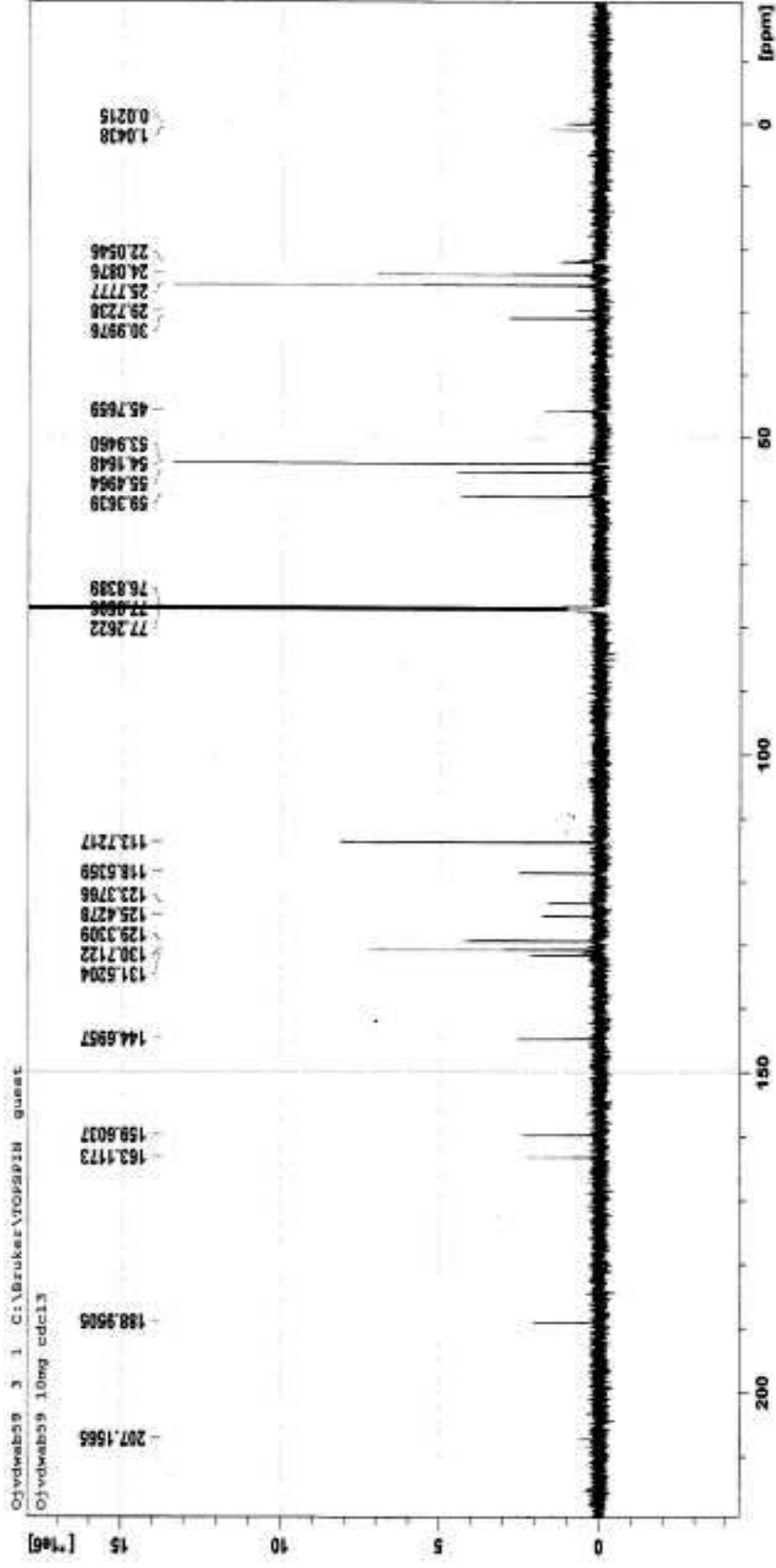


Fig ¹³C NMR of 4-hydroxy-4'-methoxy-3,5-bis-piperidinomethylchalcone (4)

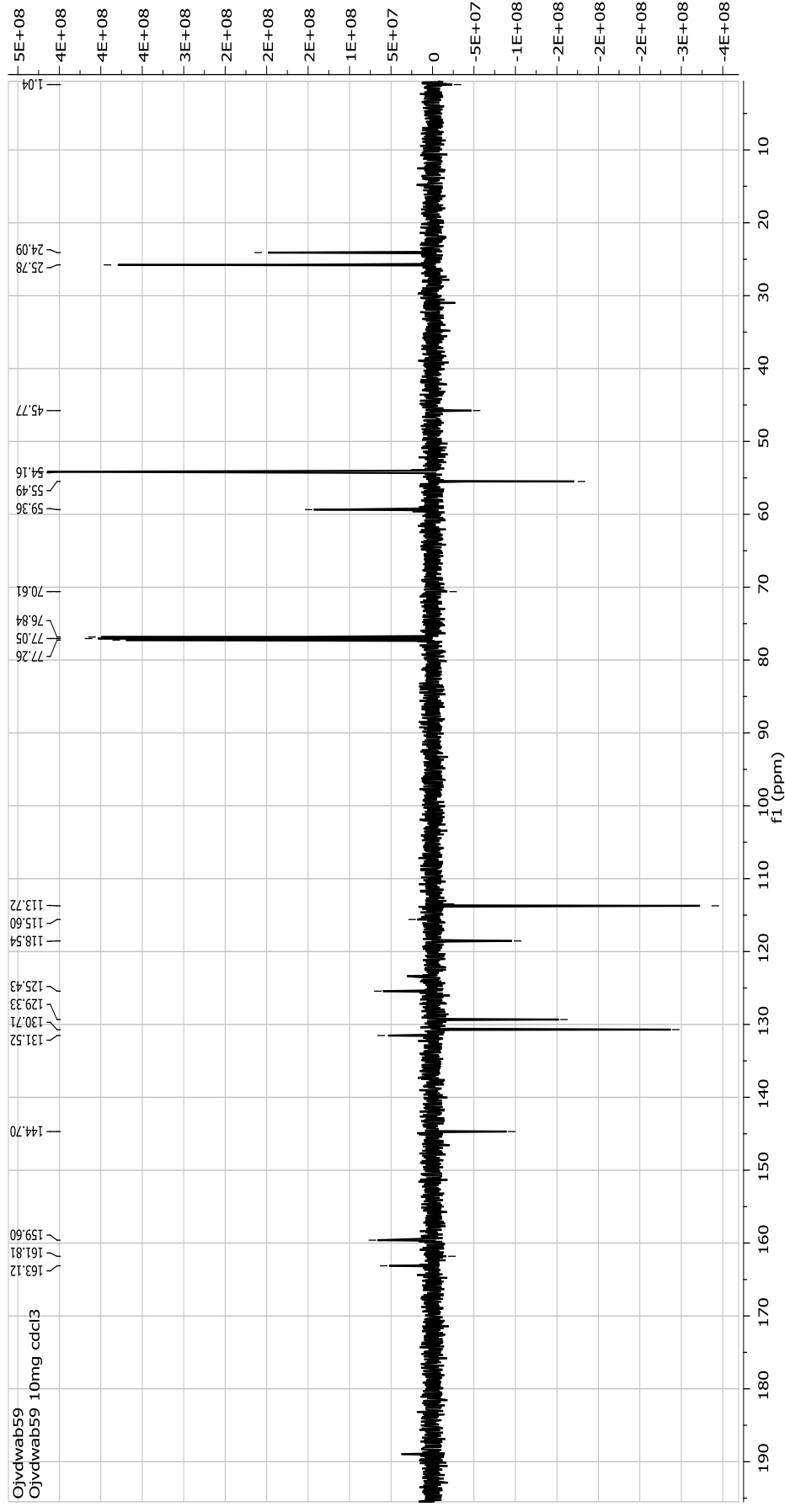


Fig Apt experiments of 4-hydroxy-4'-methoxy-3,5-bis-piperidinomethylchalcone (4)

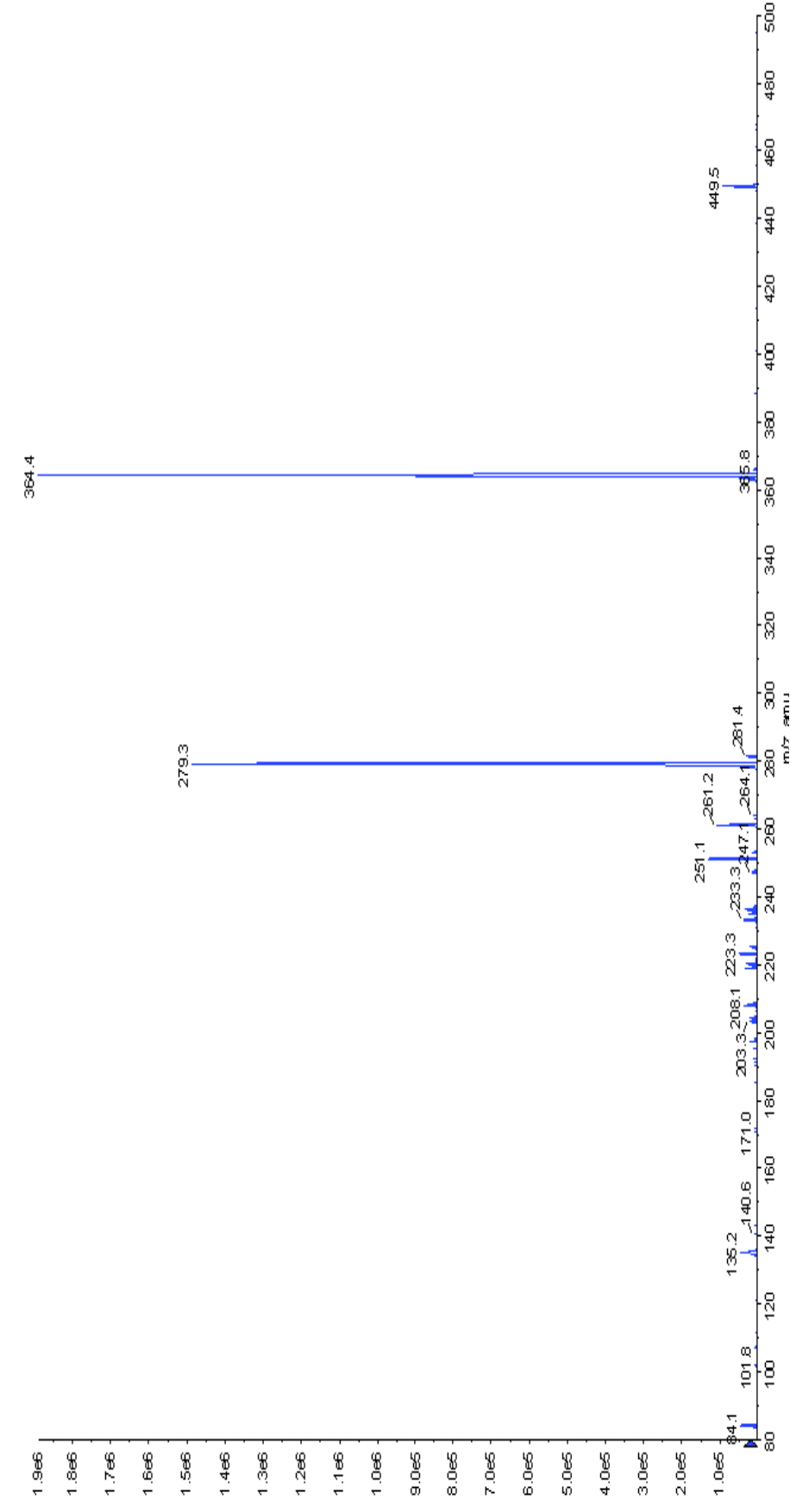


Fig Mass spectrum of 4-hydroxy-4'-methoxy-3,5-bis-piperlidinomethylchalcone (4)

