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L-Proline Nitrate: A Recyclable and Green Catalyst for the Synthesis of Highly Functionalized Piperidines

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Electronic Supplementary Information

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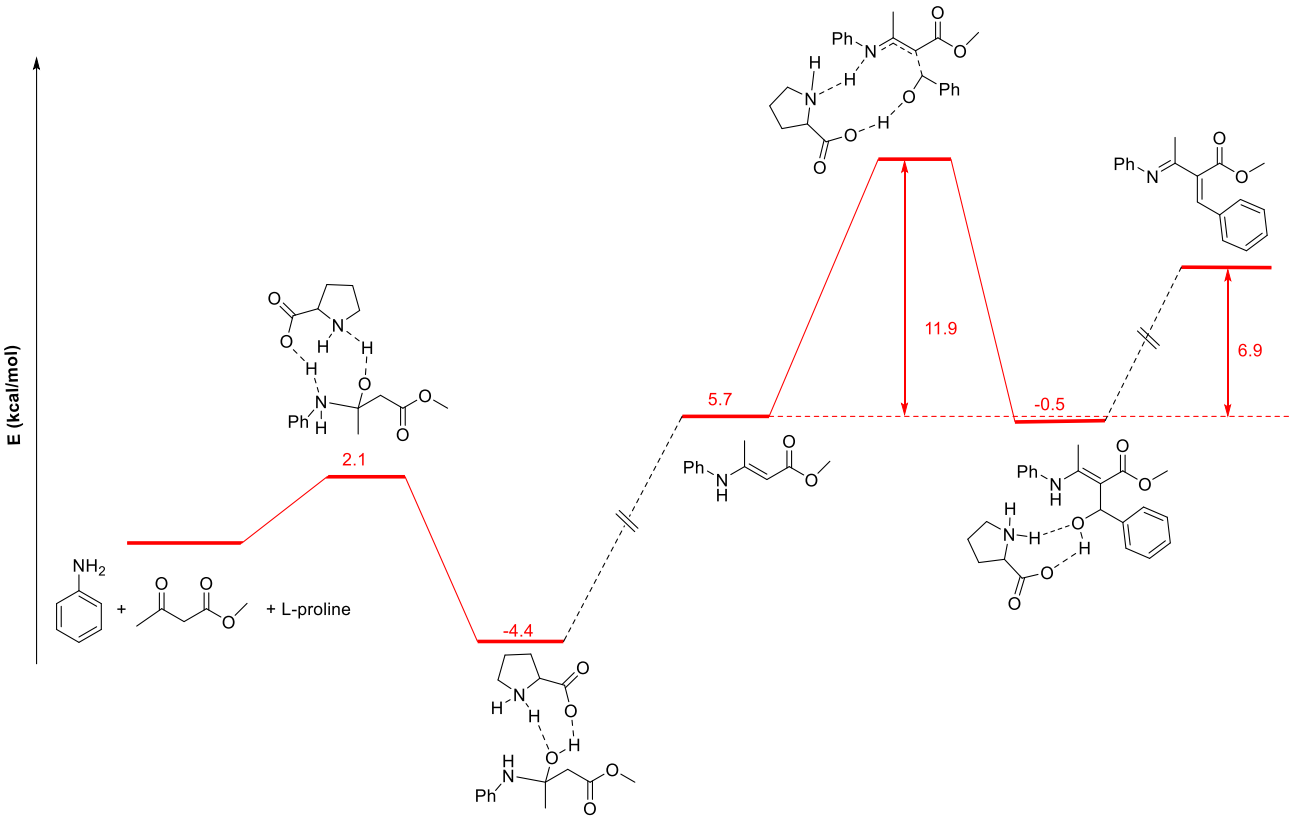


Figure S1. Energetics of the reaction via L-proline mediated aniline enamine pathway

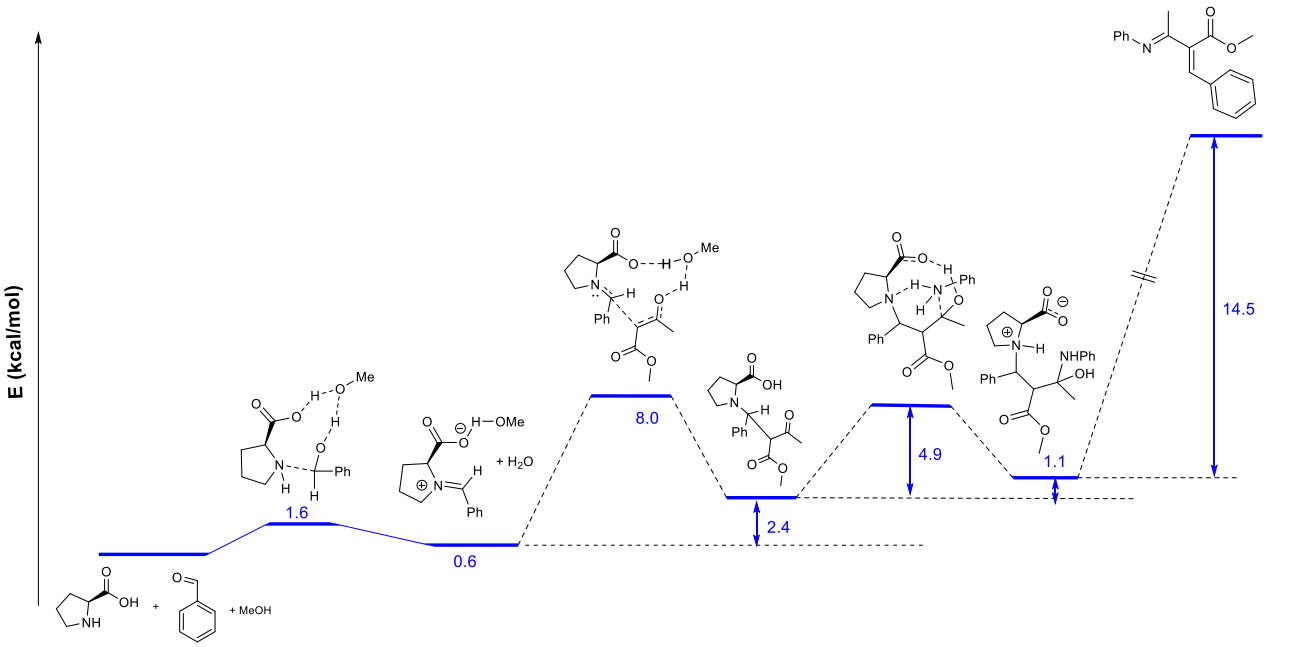
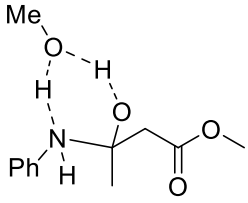
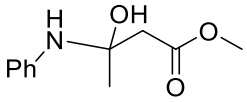
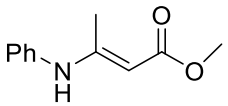
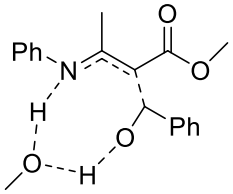
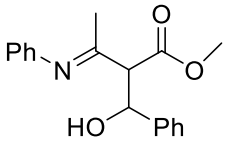
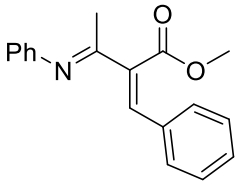
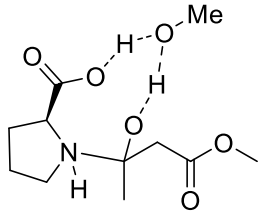
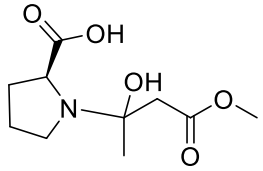
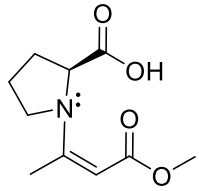
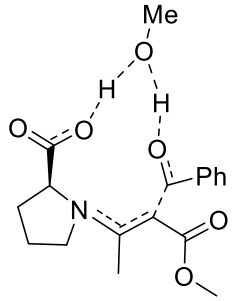
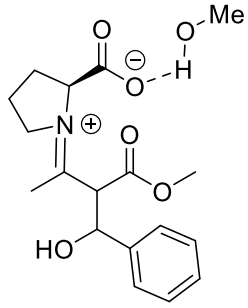
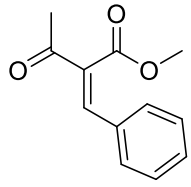
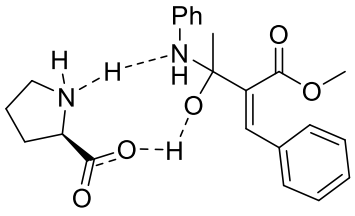
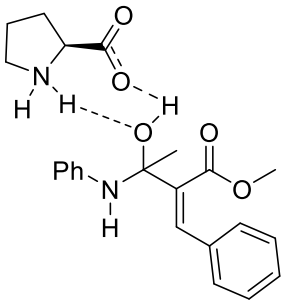
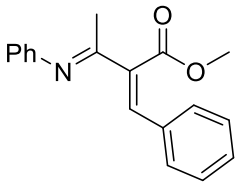
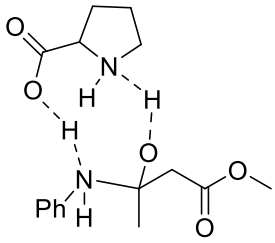
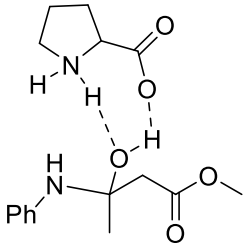
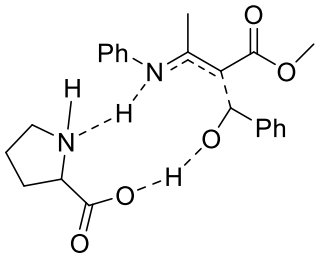


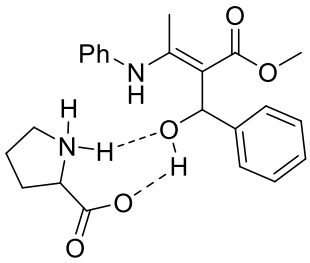
Figure S2. Energetics of the reaction via L-proline mediated iminium activation of the aldehydes

Table S1. Absolute energies of reactants, intermediates and transition states at B3LYP/6-31G(d)

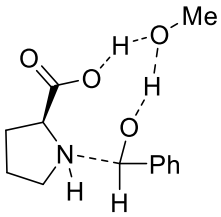
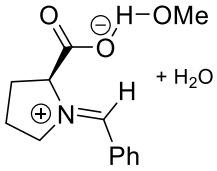
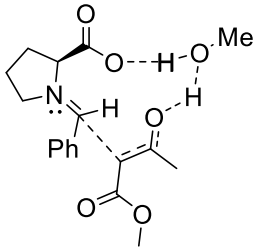
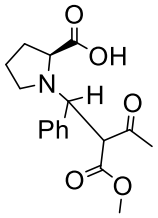
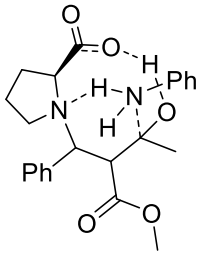
	Absolute Energy [a]	**Absolute Energy (PCM)[b]**	**ZPVE (kcal mol^{-1})**
Aniline	-287.6017597	-287.6083904	73.67215
Methyl Acetoacetate	-421.025418	-421.0334358	80.61808
Methyl Acetoacetate-enol	-421.0205123	-421.0274342	81.27901
MeOH	-115.7144051	-115.7192461	32.30035
Proline	-401.037168	-401.1567542	91.22973
Benzaldehyde	-345.573442	-345.579287	69.16718
Enamine	-632.2083078	-632.2153068	140.14109
Water	-76.4089533	-76.4160764	-76.41607
TS and Intermediates of pathway a			
 Aniline+Acetoacetate+MeOH TS	-824.3259904	-824.3411007	187.43726
 Aniline+Acetoacetate Product	-708.629732	-708.6406468	157.14814
 Aniline Enamine	-632.2083078	-632.2153068	140.14109
 AnilineEnamine+Benzaldehyde+MeOH TS	-1093.460188	-1093.478482	241.11673
 AnilineEnamine+Benzaldehyde Product	-977.7693597	-977.7814592	211.06697
 AnilineEnamine+Benzaldehyde-H2O Product	-901.3354226	-901.3466171	193.3764

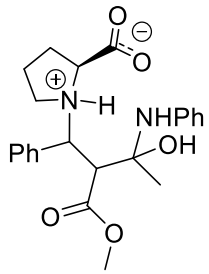
TS and Intermediates of pathway b			
 Acetoacetate+Proline+MeOH TS	-937.8823602	-937.901659	205.50227
 Acetoacetate+Prolineadduct	-822.181354	-822.1936773	174.38638
 Proline enamine product	-745.7507395	-745.7632826	157.16132
 ProlineEnamine+Benzaldehyde+MeOH TS	-1207.033019	-1207.05127	260.90579
 ProlineEnamine+Benzaldehyde+MeOH Product	-1207.042528	-1207.065895	262.80969
 BenzelideneAcetoacetate Product	-690.1651566	-690.1739074	135.05945

 BenzylideneAcetoacetate+Aniline+Proline TS	-1378.899603	-1378.928762	301.50421
 BenzelydeneAcetoacetate+Aniline+Proline Product	-1378.915744	-1378.946544	304.06227
 AnilineEnamine+Benzaldehyde-H2O Product	-901.3354226	-901.3466171	193.3764
TS and Intermediates of L-proline mediated aniline enamine pathway			
 Acetoacetate+Aniline+Proline TS	-1109.771264	-1109.799322	248.09215
 Acetoacetate+Aniline+Proline Product	-1109.783283	-1109.812718	249.99701
 AnilineEnamine+Aldehyde+Proline TS	-1378.918221	-1378.935127	302.22473

 AnilineEnamine+Aldehyde+Proline Product	-1378.934508	-1378.958308	304.40079

TS and Intermediates of L-proline mediated iminium activation of aldehyde

 Aldehyde + Proline+ MeOH TS	-862.4388175	-862.454731	193.95554
 Benzaldehyde+Proline+MeOH iminium	-786.0109137	-786.0375646	178.97453
 Iminium +acetoacetate+MeOH TS	-1207.0370152	-1207.0540376	261.40103
 Iminium +acetoacetate product	-1091.3290846	-1091.3425379	228.35161
 Iminium +acetoacetate+Aniline TS	-1378.9097971	-1378.9444223	302.81736



Iminium +acetoacetate+Aniline product

-1378.9229 -1378.9553161 305.92218

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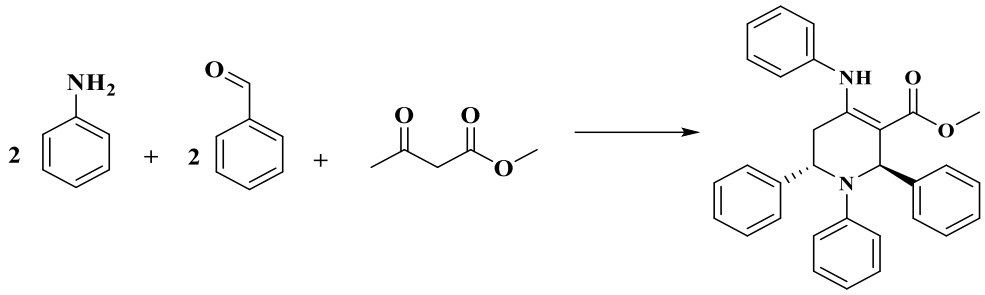
[a] All energies are givenin Hartrees except ZPVE.

[b] Energies are calculated by single-point calculation on gas phase optimized geometries for methanol as a solvent with the Polarized Continuum Model (PCM) at the same level of theory.

Calculation of green chemistry metrics [1]



F Wt.	**93.12 gmol^{-1}**	**106.12 gmol^{-1}**	**116.11 gmol^{-1}**	**460.57 gmol^{-1}**
	(3.5 mmol)	**(3.5 mmol)**	**1.75 mmol**	
Weight	**0.331 g**	**0.371 g**	**0.203 g**	**0.721 g**

1. **E factor**: The E factor of organic conversion can be calculated as mass of waste i.e. the total mass of raw materials minus the total mass of product, all divided by the total mass of product. The ideal value for E factor should be zero.[2]

E-factor = [mass of waste]/ mass of product

Where mass of waste = total mass of raw materials minus the total mass of product

= [0.331 g (aniline) + 0.371 g (benzaldehyde) + 0.203 g (methyl acetoacetate) + 0.0312g (proline nitrate) + 0.395 g (methanol)- 0.721 g (product)]

Mass of waste = 0.6107 g

E-factor = 0.6107/0.721

E-factor = 0.8469 (including mass of methanol and proline nitrate)

As methanol and proline nitrate can be recycled, E-factor excluding mass of methanol and proline nitrate is

Mass of waste = [0.331 g (aniline) + 0.371 g (benzaldehyde) + 0.203 g (methyl acetoacetate) - 0.721 g (product)] = 0.184 g

E-factor = 0.184/0.721= 0.255 (excluding the mass of methanol)

2. **Atom economy (AE):** AE serves to determine the efficiency of a chemical reaction with regard to how many atoms from the starting materials reside within the product. The ideal value for AE should be 100%.[3]

AE = MW of product ÷ ∑(MW of stoichiometric reactants) × 100

AE = 460.57 (**product**) ÷ [2(93.12) (**aniline**) + 2(106.12) (**benzaldehyde**) + 116.11(**MAA**)] × 100

AE = 89.50%

3. **Process mass intensity (PMI)**: PMI is defined as the total mass used in a process divided by the mass of product. The ideal value for PMI should be 1.[4]

PMI = ∑(mass of stoichiometic reactants + solvents used in the process) / mass of product

= [0.331 g (aniline) + 0.371 g (benzaldehyde) + 0.203 g (methyl acetoacetate) + 0.0312g (proline nitrate) + 0.395 g (methanol + 1 g (water) + 0.0867 g (toluene)] / 0.721 g (**product**)

PMI = 3.354

4. **Reaction mass efficiency (RME)**: Reaction mass efficiency is defined as the mass of product divided by the sum of total mass of stoichiometic reactants. The ideal value for RME should be 100%.[4]

RME = mass of product /∑(mass of stoichiometic reactants) × 100

= 0.721 g (**product**)/ [0.331 g (aniline) + 0.371 g (benzaldehyde) + 0.203 g (methyl acetoacetate)] × 100

= 0.721/ 0.905* 100

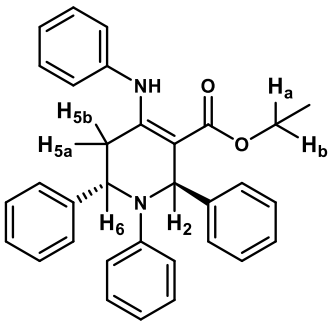
RME = 79.66%

General experimental details

All solvents and chemicals were obtained commercially and were used as received. Melting points were determined in an open capillary and are uncorrected. IR spectra were recorded using a Spectrum-60 spectrometer instrument. NMR spectra were taken with a Bruker Avance II at 400 MHz / Bruker DMX spectrometer at 500 MHz (1H) and 125 MHz (13C) using CDCl3 or DMSO-d6 as the solvent with TMS as internal standard. The crystal data were collected with SuperNova, X-ray diffractometer using graphite monochromated Mo-Kα radiation (λ = 0.71073 Å) at 100 K. The structure was solved by direct methods using using SHELXS97 software. All of the non-hydrogen atoms were refined anisotropically by full-matrix least-squares on F^2 using SHELXL97. All H atoms were allowed to ride on the parent atom in the model during refinement.

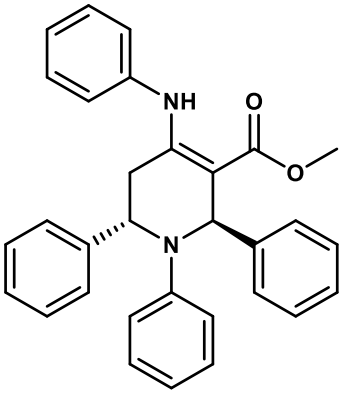
General procedure for the preparation of functionalized piperidines:

A mixture of 1,3-dicarbonyl (1.75 mmol), amine (3. 5 mmol), aldehyde (3.5 mmol) and L-proline nitrate (31.2 mg, 0.175 mmol) in MeOH (0.5 mL) was stirred at room temperature for an appropriate time (Table 2). After completion of the reaction, as indicated by TLC, solid obtained was filtered under suction to get product of sufficient purity. To recover the catalyst, initially methanol from the filtrate was removed under reduced pressure and residue was washed with a little quantity of water to get an aqueous solution of the catalyst as a filtrate. Water from the filtrate was removed under reduced pressure and the last traces of water were removed by forming azeotrope with a very little amount of toluene to get the catalyst which was then available for the next run.



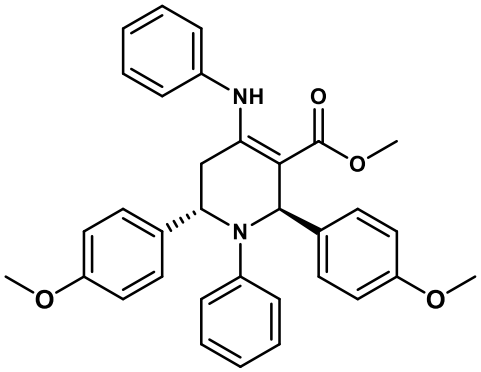
Scheme S1: Functionalised piperidine depicting different types of hydrogen

Methyl 1,2,6-triphenyl-4-(phenylamino)-1,2,5,6-tetrahydropyridine-3-carboxylate (4a)[5]



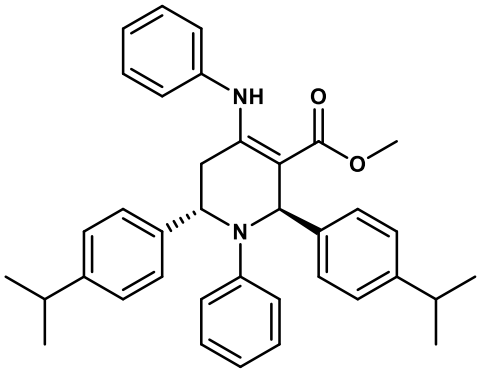
White solid; (Yield 0.721g; 90%); mp: 165-167 °C; IR (cm^{-1}): 3258, 1660, 1586, 1504, 1251, 1078; ^1H NMR (500 MHz, $CDCl_3$) δ 2.78-2.85 (m, 2H, H_{5a} H_{5b}), 3.93 (s, 3H, OCH_3), 5.14 (brs,1H, H_6), 6.28-7.31 (m, 21H, H_2+Ar-H), 10.25 (s, 1H, NH); HRMS (ESI): m/z $[M+Na]^+$ calc. for $C_{31}H_{28}N_2NaO_2$ 483.2048, found 483.2036.

Methyl 2,6-bis(4-methoxyphenyl)-1-phenyl-4-(phenylamino)-1,2,5,6-tetrahydropyridine-3-carboxylate (4b)[5]



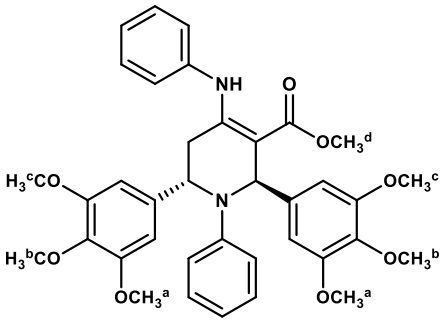
White solid; (Yield 0.737g; 81%); mp 174-176 °C; IR (cm^{-1}): 3058, 1651, 1592, 1245, 1189, 1070 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ ppm: 2.77-2.83 (m, 2H, H_{5a} H_{5b}), 3.78 (m, 6H, OCH_3), 3.92 (s, 3H, OCH_3), 5.0 (brs, 1H, H_6), 6.36-7.26 (m, 19H, H_2+Ar-H), 10.26 (s, 1H, NH); HRMS (ESI): m/z $[M+Na]^+$ calc. for $C_{33}H_{32}N_2NaO_4$ 543.2260, found 543.1450.

Methyl 2,6-bis(4-isopropylphenyl)-1-phenyl-4-(phenylamino)-1,2,5,6-tetrahydropyridine-3-carboxylate (4e)



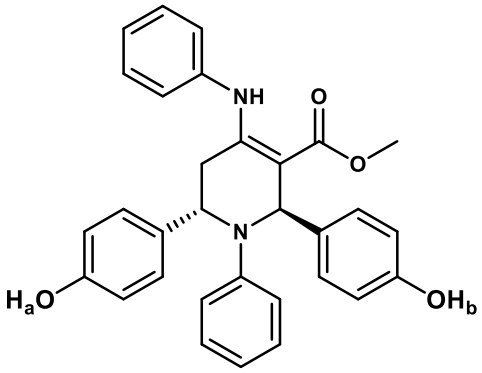
White solid; (Yield 0.753g; 79%); mp 160-162 °C; IR (cm^{-1}): 3231, 1654, 1589, 1501, 1261, 1074 cm^{-1}, ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm (syn:anti = 10:90):, 1.20-1.22 (m, 1.2H, CH (C**H**$_3$)$_2$), 1.27-1.35 (m, 10.8H, CH (C**H**$_3$)$_2$), 2.72-2.83 (m, 0.46H, [C**H** (CH_3)$_2$], 2.86-2.98 (m, 1.54H, [C**H** (CH_3)$_2$], 3.77(s, 0.44H, OCH_3),3.97(s, 2.56H, OCH_3), 5.15 (br s, 1H, H_6), 6.22-7.61 (m, 19.7H, H_2+Ar-H), 10.29 (s, 0.9H, NH); 10.7 (s, 0.1H, NH); ^{13}C NMR (100 MHz,$CDCl_3$): 23.91, 24.03, 24.07, 24.20, 33.63, 33.75, 33.84, 50.99, 54.80, 98.00, 112.90, 115.20, 115.93, 123.88, 125.78, 126.11, 126.26, 126.57, 126.70, 126.90, 128.76, 128.87, 129.30, 137.91, 140.38, 141.09, 146.68, 147.11, 147.85, 156.53,168.70; HRMS (ESI): m/z $[M+Na]^+$ calc. for $C_{37}H_{40}N_2NaO_2$ 567.2987, found 567.2107.

Methyl 1-phenyl-4-(phenylamino)-2,6-bis(3,4,5-trimethoxyphenyl)-1,2,5,6-tetrahydropyridine-3-carboxylate (4f)[6]



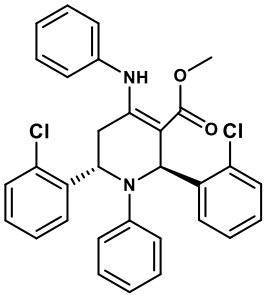
White solid (Yield 0.863g; 77%); mp 145-147 °C; IR (cm^{-1}): 3241, 2996, 2938, 2835, 1656, 1592, 1502, 1461, 1416, 1323, 1256, 1126, 1006 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm: 2.77-3.00 (m, 2H, H_{5a} +H_{5b}), 3.69-3.73 (m, 12H, OCH_3^a, OCH_3^c), 3.83-3.84 (m, 9H, OCH_3^b+ OCH_3^d), 5.06 (brs, 1H, H_6), 6.34-7.15 (m, 15H, H_2+ArH), 10.25 (s, 1H, NH); HRMS (ESI): m/z $[M+Na]^+$ calc. for $C_{37}H_{40}N_2NaO_8$ 663.2682, found 662.9989.

Methyl 26-bis(4-hydroxyphenyl)-1-phenyl-4-(phenylamino)-1,2,5,6-tetrahydropyridine-3-carboxylate (4h)



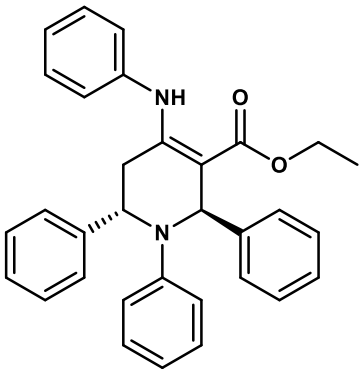
White solid; (Yield 0.673g; 78%); mp 170-172 °C; IR (cm^{-1}): 3290, 1594, 1319, 1247, 1074 cm^{-1}; ^1H NMR (500 MHz, DMSO- d_6) δ ppm: 2.74-2.86 (m, 2H, H_{5a}+ H_{5b}), 3.84 (s, 3H, OCH_3), 5.19 (br s, 1H, H_6), 6.17 (s, 1H, H_2), 6.65-7.17 (m, 18H, Ar-H), 9.24(s, 1H, OH_a), 9.28 (s, 1H, OH_b), 10.17 (s, 1H, NH); ^{13}C NMR (125 MHz, DMSO- d_6): 33.20, 51.01, 54.05, 56.12, 98.02, 115.14, 124.62, 127.08, 127.17, 128.97, 134.03, 137.62, 154.69, 156.23, 167.52; HRMS (ESI): m/z $[M+Na]^+$ calc. for $C_{31}H_{28}N_2NaO_4$ 515.1174, found 515.1947.

Methyl 2,6-bis(2-chlorophenyl)-1-phenyl-4-(phenylamino)-1,2,5,6-tetrahydropyridine-3-carboxylate (4i)



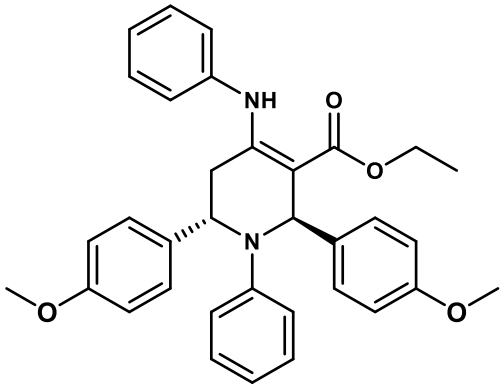
White solid; (Yield 0.722g; 78%); mp 166-168 °C; IR (cm^{-1}): 3249, 1660, 1595, 1327, 1246, 1046 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ ppm: (syn:anti 13:87) 2.8 (dd, J=16.06, 8.04 Hz, 1H, H_{5a}), 3.06 (dd, J= 16.04, 8 Hz, 1H, H_{5b}), 3.73 (s, 0.4H, OCH_3), 3.89 (s, 2.6H, OCH_3), 5.46 (brs, 0.87H, H_6), 5.46 (brs, 0.13H, H_6), 6.508 (s, 1H, H_2), 6.40-7.45 (m, 19H, H_2+Ar-H), 10.10 (s, 0.87H, NH), 10.77 (s, 0.13H, NH); ^{13}C NMR (100 MHz,$CDCl_3$): 29.55, 34.42, 50.80, 51.11, 99.20, 114.25, 117.65, 122.00, 124.78, 125.92, 126.11, 127.16, 128.03, 128.52, 128.72, 128.98, 129.01, 129.18, 129.28, 129.32, 129.65, 131.11, 132.39, 133.37, 137.88, 138.72, 140.09, 146.32, 155.54, 168.87; HRMS (ESI): m/z $[M+Na]^+$ calc. for $C_{31}H_{26}Cl_2N_2NaO_2$ 551.1269, found 551.0179.

Ethyl 1,2,6-triphenyl-4-(phenylamino)-1,2,5,6-tetrahydropyridine-3-carboxylate (4j)[7]



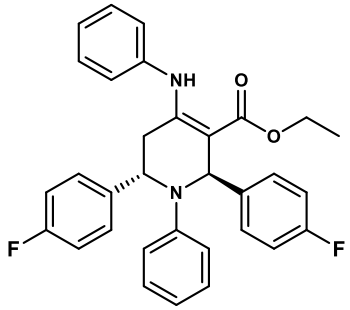
White solid; (Yield 0.664g; 80%); mp 171-172 °C; IR (cm^{-1}): 3059, 3018, 2980, 2872, 1651, 1504, 1454, 1371, 1255, 1070 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ ppm: 1.47 (t, 3H, $OCH_2C\mathbf{H_3}$), 2.78-2.86 (m, 2H, H_{5a}+ H_{5b}), 4.33-4.44 (m, 2H, $OC\mathbf{H_2}CH_3$), 5.14 (brs, 1H, H_6), 6.27-7.33 (m 21H, H_2+Ar-H), 10.29 (s, 1H, NH); HRMS (ESI): m/z $[M-H]^+$ calc. for $C_{32}H_{29}N_2O_2$ 473.2229, found 473.2400.

Ethyl 2,6-bis(4-methoxyphenyl)-1-phenyl-4-(phenylamino)-1,2,5,6-tetrahydropyridine-3-carboxylate (4k)[8]



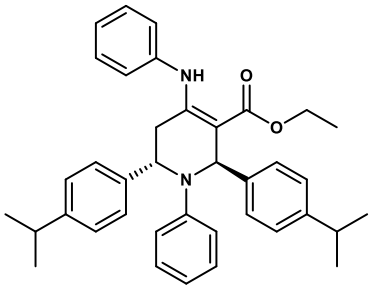
White solid; (Yield 0.645g, 69%); mp 165-167°C; IR (cm^{-1}): 3750, 2988, 2902, 2819, 2029, 1974, 1496, 1417, 1240, 687, 667 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ ppm: 1.46 (t, J=6.88 Hz, 3H, OCH_2CH_3), 2.77- 2.84 (m,2H, H_{5a}, H_{5b}), 3.78 (s, 3H, OCH_3), 3.79 (s, 3H, OCH_3), 4.33-4.45 (m, 2H, $OCH_{2(a+b)}CH_3$), 5.09 (brs, 1H, H_6), 6.37-7.09 (m, 19H, H_2+ Ar-H) 10.31 (s, 1H, NH); HRMS (ESI): m/z $[M-H]^+$ calc. for $C_{32}H_{29}N_2O_2$ 533.2440, found 533.1925.

Ethyl 2,6-bis(4-fluorophenyl)-1-phenyl-4-(phenylamino)-1,2,5,6-tetrahydropyridine-3-carboxylate (4m)



White solid; (Yield 0.643g; 72%); mp 204-205 °C; IR (cm^{-1}): 3671, 2996, 2981, 2815, 2187, 2053, 1970, 1648, 1607, 1499, 1251, 751 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ ppm: 1.44-1.46 (t, 3H, J= 7.0 Hz, OCH_2CH_3), 2.72-2.85 (dd, 2H, J= 15.1, 7.52 Hz, H_{5a}+H_{5b}), 4.30 (m, 1H, OCH_aCH_3), 4.33 (m, 1H, OCH_bCH_3), 5.10 (d, 1H, H_6), 6.38-7.31 (m, 19H, H_2+ Ar-H), 10.31 (s, 1H, NH); ^{13}C NMR (100 MHz,$CDCl_3$): 14.83, 33.82, 54.63, 59.85, 98.06, 113.03, 114.94, 115.15, 115.39, 115.61,116.60, 125.68, 125.90, 127.89, 127.97, 128.11, 128.19, 128.88, 129.0, 129.04, 129.39,137.77, 138.11, 138.14,139.51,139.52, 146.65, 155.93, 160.32, 160.78, 162.75, 163.22, 168.09; HRMS (ESI): m/z $[M+Na]^+$ calc. for $C_{32}H_{28}F_2N_2NaO_2$ 533.2017, found 533.1345.

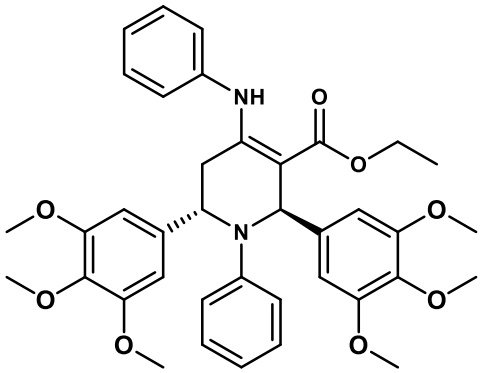
Ethyl 2,6-bis(4-isopropylphenyl)-1-phenyl-4-(phenylamino)-1,2,5,6-tetrahydropyridine-3-carboxylate (4n)



White solid; (Yield 0.782g; 80%); mp 169-170 °C; IR (cm^{-1}): 3230. 1653, 1577, 1261, 1190, 1076 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ ppm (syn:anti = 09:91): 1.20-1.22 (m, 1.1H, CH ($C\mathbf{H_3}$)$_2$), 1.27-1.35 (m, 10.9H, CH ($C\mathbf{H}_3$)$_2$), 1.50-1.53 (t, 3H, J= 7.12 Hz, $OCH_2C\mathbf{H_3}$), 2.72 -2.76 (m, 0.47H, H_{5a}+H_{5b}), 2.86 -2.97 (m, 1.53H, H_{5a}+H_{5b}), 2.86-3.00 (m, 2H, $CH(CH_3)_2$, $CH(CH_3)_2$), 4.34-4.54 (m, 2H, $O\mathbf{CH_2}CH_3$), 5.16 (brs, 1H, H_6), 6.22-7.32 (m, 19H, H_2+Ar-H), 10.34 (s, 0.91H, NH), 10.7 (s, 0.09H, NH); ^{13}C NMR (100 MHz,$CDCl_3$): 14.85, 23.91, 24.06, 24.20, 24.29, 33.63, 33.74, 33.84, 54.77, 59.20, 98.29, 112.92, 115.27, 115.90, 123.80, 125.68, 126.05, 126.27, 126.45, 126.58, 126.70, 126.94,

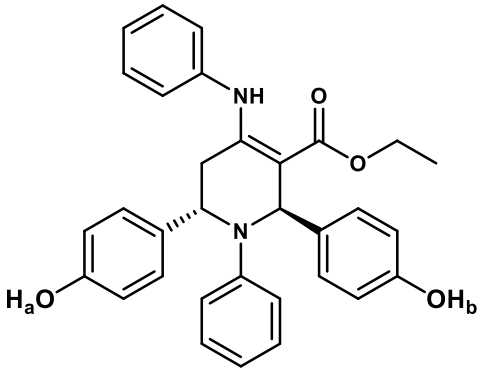
128.74, 128.88, 129.28, 137.99, 140.43, 141.21, 146.63, 147.15, 147.84, 156.34,168.39; HRMS (ESI): m/z $[M+Na]^+$ calc. for $C_{38}H_{42}N_2NaO_2$ 581.3144, found 581.2186.

Ethyl 1-phenyl-4-(phenylamino)-2,6-bis(3,4,5-trimethoxyphenyl)-1,2,5,6-tetrahydropyridine-3-carboxylate (4o)



White solid; (Yield 0.824g; 72%); mp 175-176 °C; IR (cm^{-1}): 3401, 2971, 2942, 2194, 1954, 1648, 1508, 1247, 1106, 718 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ ppm: 1.43-1.47 (t, 3H, OCH_2CH_3), 2.77-2.80 (dd, J= 14.9, 7.4 Hz, 1H, H_{5a}), 2.95-3.00 (dd, J= 14.9, 7.4 Hz, 1H, H_{5b}), 3.70-3.75 (m, 12H, OCH_3), 3.86-3.88 (m, 6H, OCH_3), 4.29-4.50 (m, 2H, O**CH_2**CH_3), 5.06 (brs, 1H, H_6), 6.39-7.28 (m, 13H, H_2+ Ar-H), 10.34 (s, 1H, NH); ^{13}C NMR (100 MHz,$CDCl_3$): 15.05, 33.70, 55.43 55.97, 56.02, 56.46, 58.42, 59.56, 60.88, 60.94, 97.50, 103.12, 103.83, 113.02, 116.49, 125.99, 126.17, 128.82, 128.97, 129.40, 136.44, 136.97, 137.84, 138.53, 139.72, 146.94, 152.99,153.37, 156.76, 168.09; HRMS (ESI): m/z $[M+Na]^+$ calc. for $C_{37}H_{40}N_2NaO_7$ 677.2839, found 677.1614.

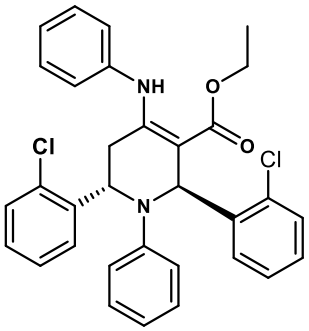
Ethyl 2,6-bis(4-hydroxyphenyl)-1-phenyl-4-(phenylamino)-1,2,5,6-tetrahydropyridine-3-carboxylate (4q)



White solid; (Yield 0.78g; 88%); mp 175-177 °C; IR (cm^{-1}): 3012, 2868, 2673, 1578, 1288, 1164 cm^{-1}; ^1H NMR (500 MHz, DMSO- d_6) δ ppm: 1.37 (t, 3H, J= 7.0 Hz, OCH_2CH_3), 2.73-2.89 (m, 2H, H_{5a}+

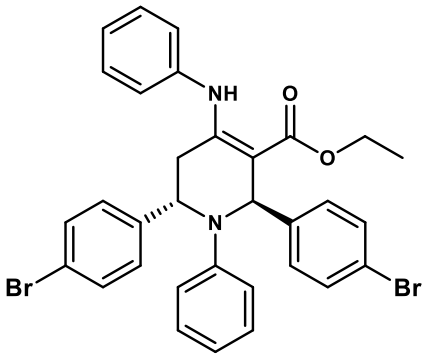
H_{5b}), 4.27- 4.37 (m, 2H, OC**H₂**CH_3), 5.20 (brs, 1H, H_6), 6.17 (s, 1H, H_2), 6.64-7.17 (m, 18H, Ar-H), 9.24(s, 1H, OH_a), 9.28 (s, 1H, OH_b), 10.25 (s, 1H, NH); ^{13}C NMR (120 MHz, DMSO- d_6): 14.59, 33.61, 54.24, 59.33, 98.44, 115.13, 124.45, 127.09, 129.00, 134.16, 137.77, 154.73, 156.23, 167.20; HRMS (ESI): m/z $[M+Na]^+$ calc. for $C_{32}H_{30}N_2NaO_4$ 529.2103, found 529.1274.

Ethyl 2,6-bis(2-chlorophenyl)-1-phenyl-4-(phenylamino)-1,2,5,6-tetrahydropyridine-3-carboxylate (4r)



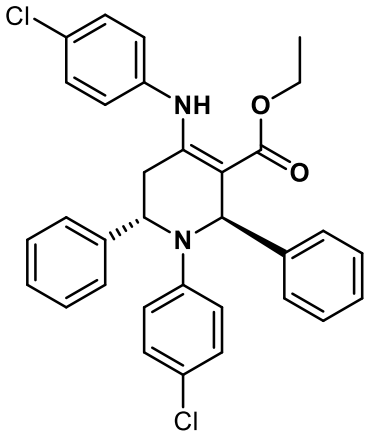
White solid; (Yield 0.618g; 65%); mp 158-160 °C; IR (cm-1): 3509, 2926, 2859, 2111, 1962, 1751, 1619, 1255, 1173, 743 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm: 1.36 (t, J= 6.88 Hz, 3H, OCH_2CH_3), 2.88-3.0 (m, 2H, H_{5a} +H_{5b}), 4.29-4.32 (m, 2H, OC**H₂**CH_3), 5.41 (brs, 1H, H_6), 6.41-7.22 (m, 19H, H_2+Ar-H), 10.12 (s, 1H, NH); HRMS (ESI): m/z $[M+H]^+$ calc. for $C_{32}H_{29}Cl_2N_2O_2$ 543.1606, found 543.0548.

Ethyl 2,6-bis(4-bromophenyl)-1-phenyl-4-(phenylamino)-1,2,5,6-tetrahydropyridine-3-carboxylate (4t)[9]



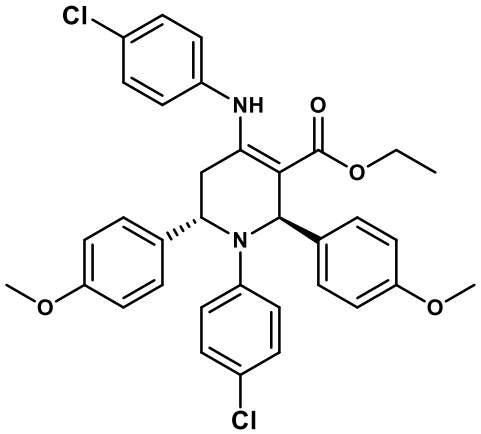
White solid; (Yield 0.962g; 87%); mp 221-222 °C; IR (cm^{-1}): 3034, 1650, 1594, 1499, 1250, 1178, 1065 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm: 1.45 (t, J=5.52Hz, 3H, OCH_2CH_3), 2.75-2.81 (m, 2H, H_{5a}+H_{5b}), 4.32-4.44 (m, 2H, OC**H₂**CH_b), 5.07 (brs , 1H, H_6) 6.34 (s. 1H, H_2), 6.41-7.40 (m, 18H, Ar-H), 10.28 (s, 1H, NH)

Ethyl 1-(4-chlorophenyl)-4-(4-chlorophenylamino)-2,6-diphenyl-1,2,5,6-tetrahydropyridine-3-carboxylate (4u)



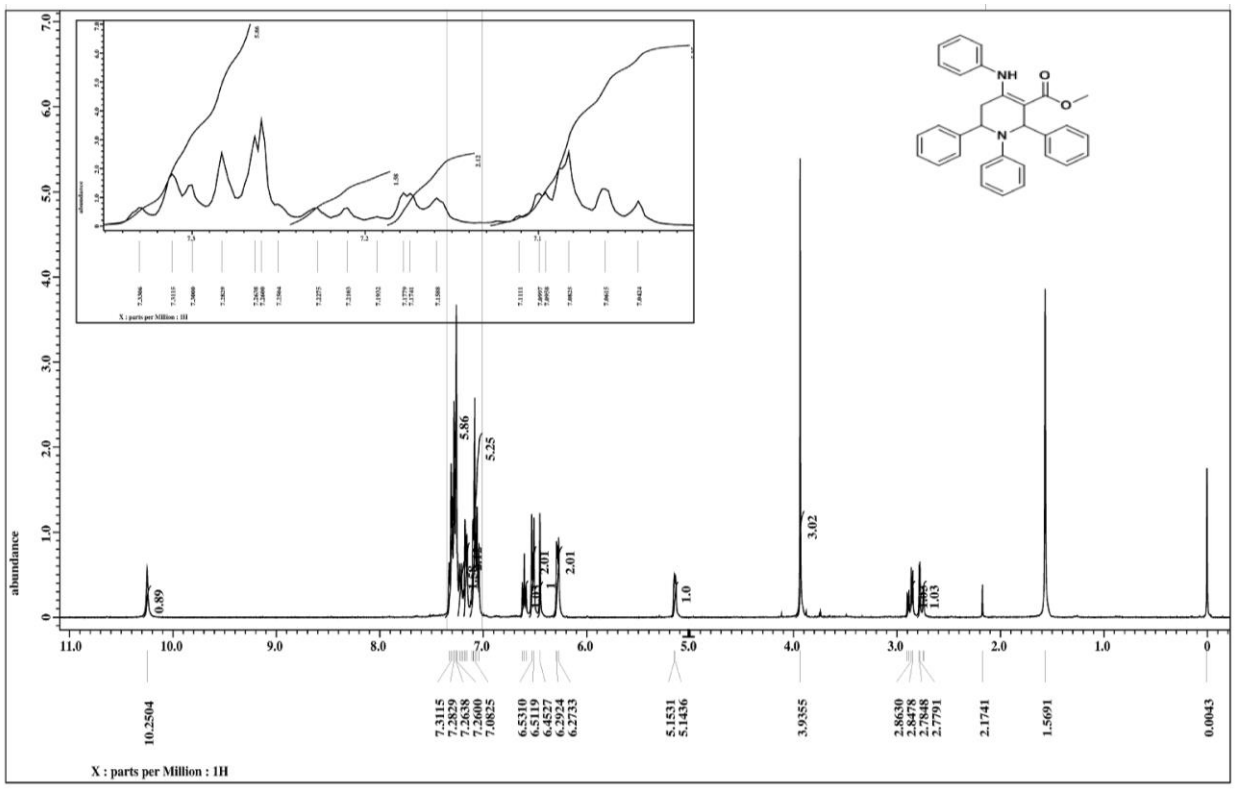
White solid; (Yield 0.599g, 63%); mp 204-206 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 1.47 (t, J= 7.64 Hz, 3H, OCH_2CH_3), 2.71-2.84 (m, 2H, H_{5a} +H_{5b}), 4.34-4.37 (m, 2H, OC**H$_2$**CH_3), 5.11 (brs, 1H, H_6), 6.16-7.30 (m, 19H, H_2+Ar-H), 10.24 (s, 1H, NH); HRMS (ESI): m/z $[M+Na]^+$ calc. for $C_{32}H_{28}Cl_2N_2NaO_2$ 565.1426, found 565.0034.

Ethyl 1-(4-chlorophenyl)-4-(4-chlorophenylamino)-2,6-bis(4-methoxyphenyl)-1,2,5,6-tetrahydropyridine-3-carboxylate (4v)[5]

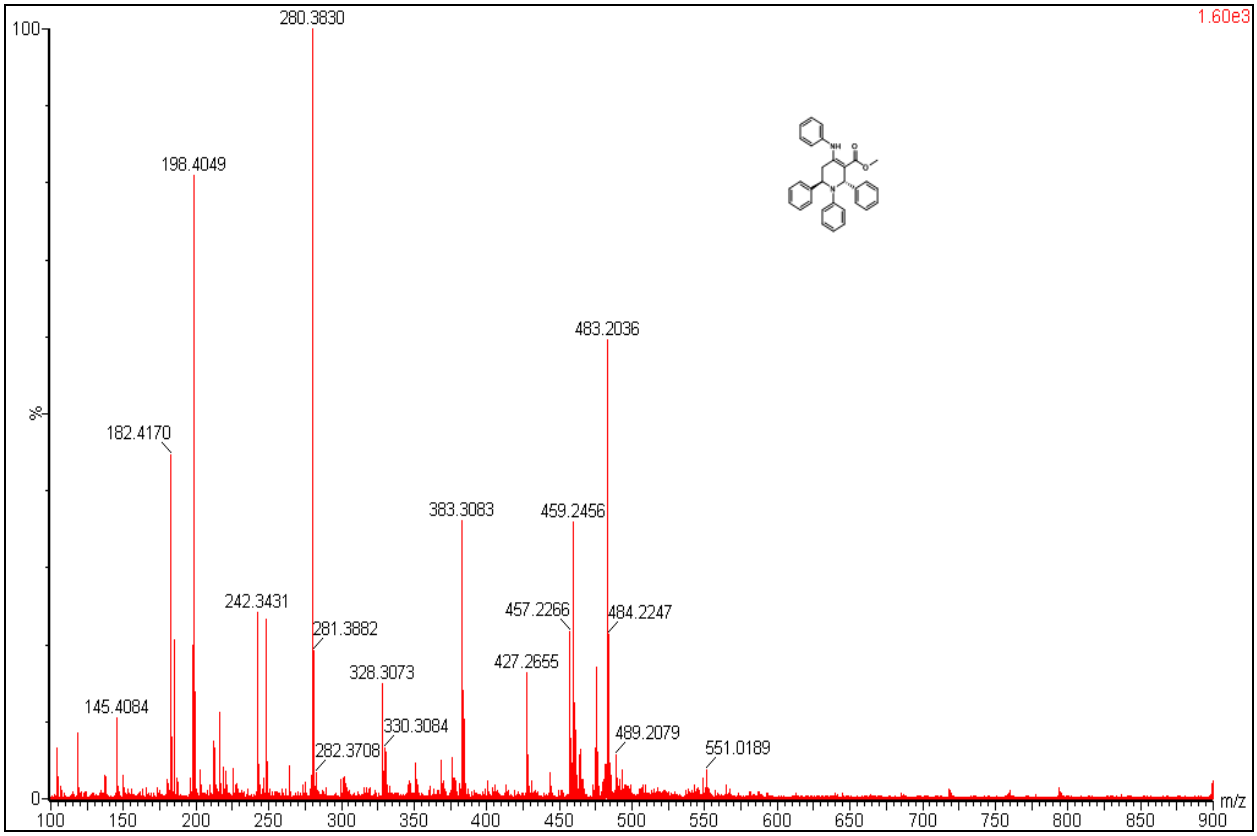


White solid; (Yield 0.802g; 76%); mp 179-181 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm: 1.46 (t, 3H, OCH_2CH_3), 2.67-2.82 (m, 2H, H_{5a} +H_{5b}), 3.75-3.80 (m, 6H, OCH_3), 4.33-4.45 (m, 2H, OC**H$_2$**CH_3), 5.05 (brs, 1H, H_6), 6.25- 7.07 (m, 17H, H_2+Ar-H) 10.26 (s, 1H, NH); HRMS (ESI): m/z $[M+Na]^+$ calc. for $C_{34}H_{32}Cl_2N_2NaO_4$ 625.1637, found 624.9412.

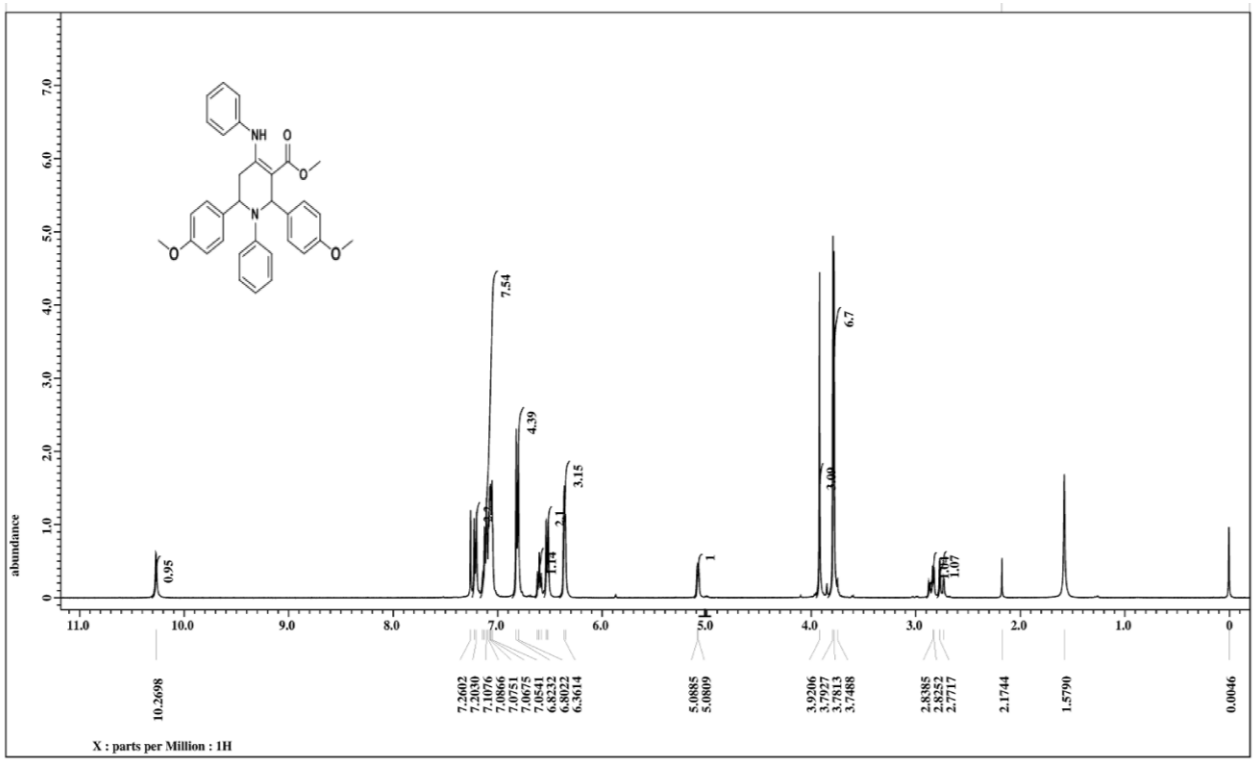
^{1}H Spectrum of 4a



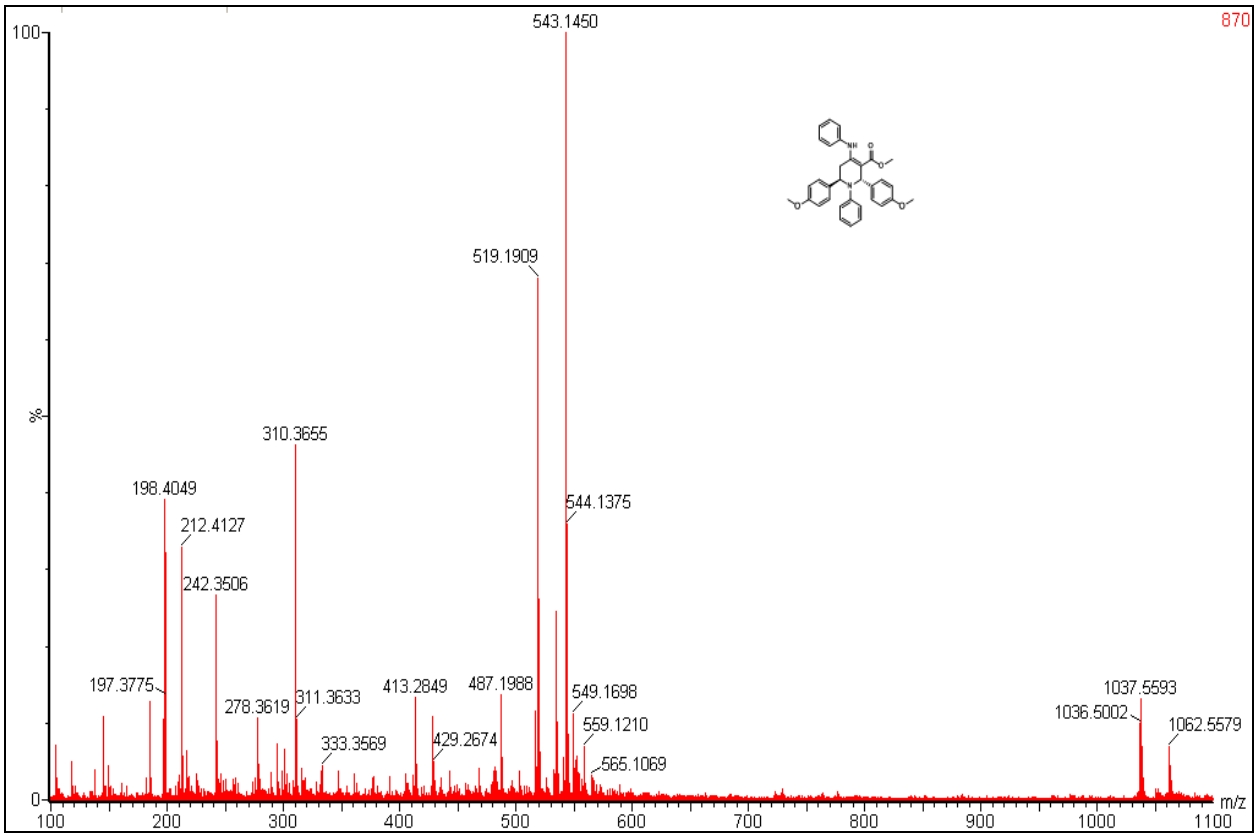
Mass Spectrum of 4a



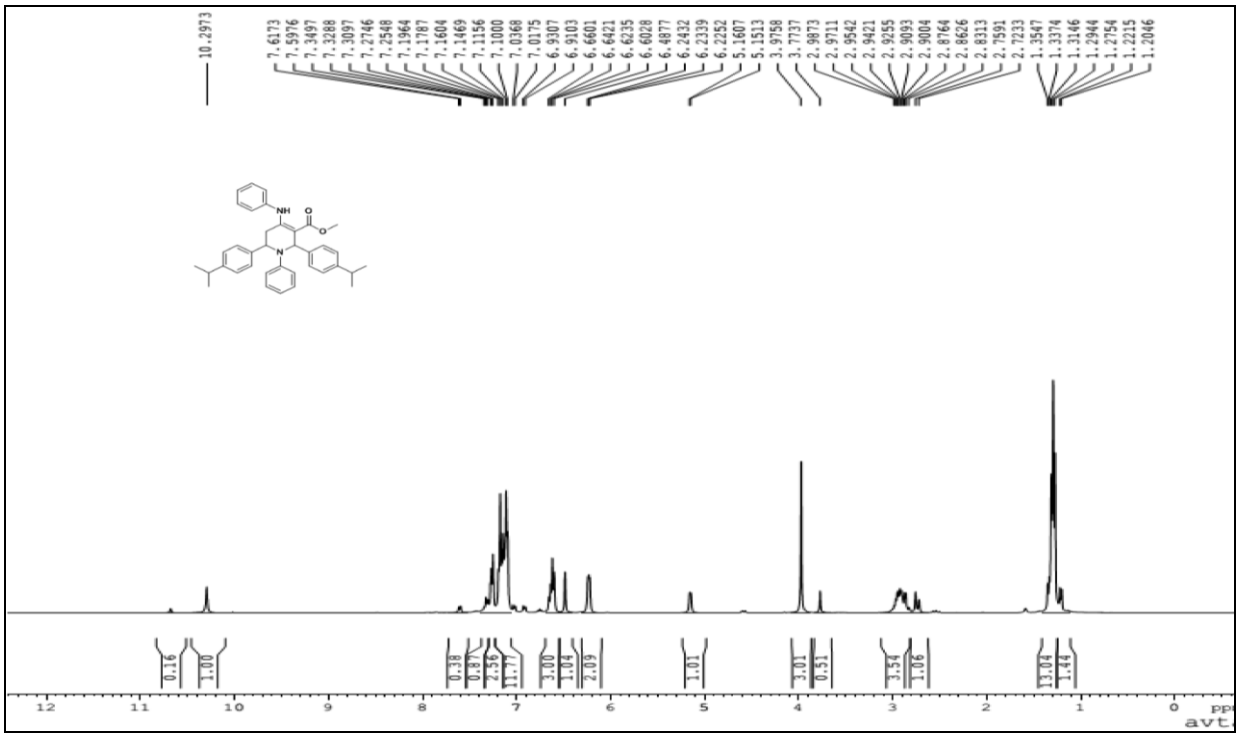
^{1}H Spectrum of 4b



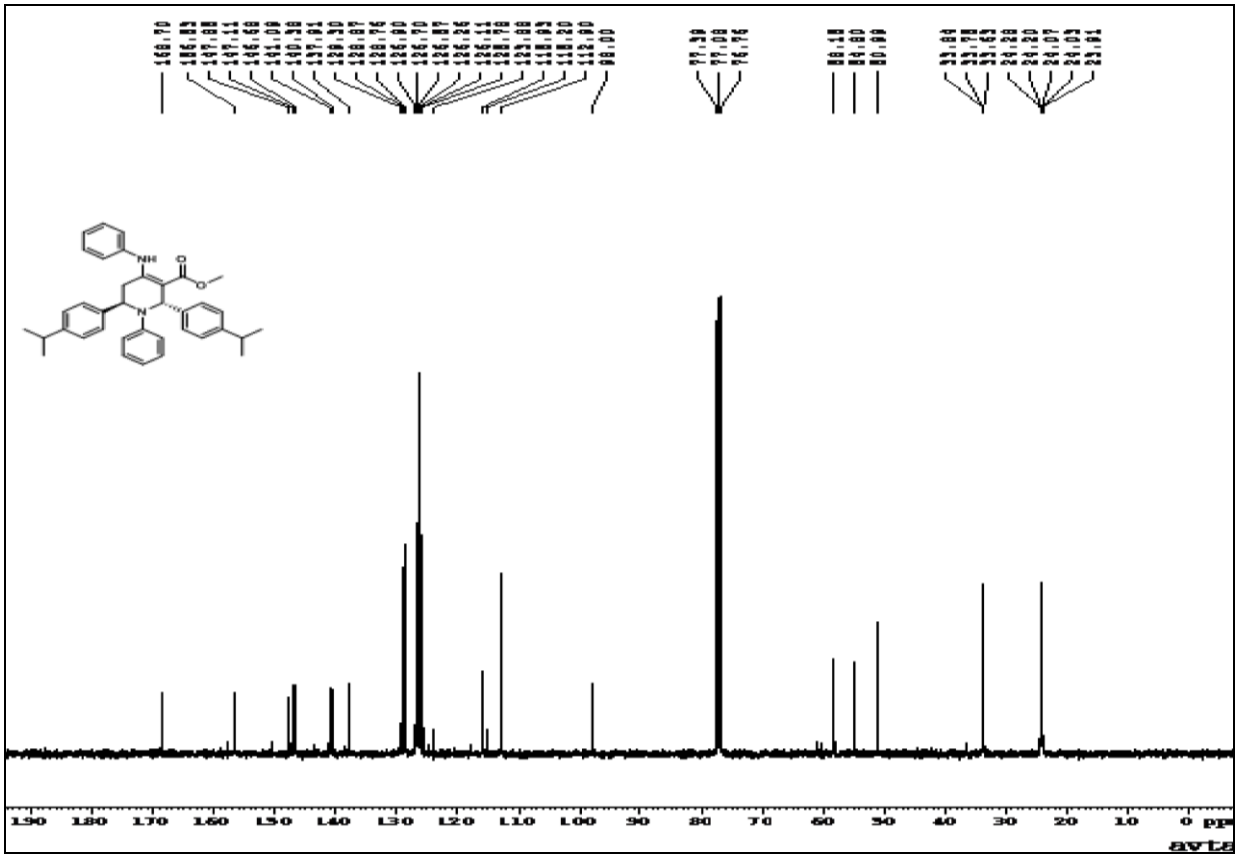
Mass Spectrum of 4b



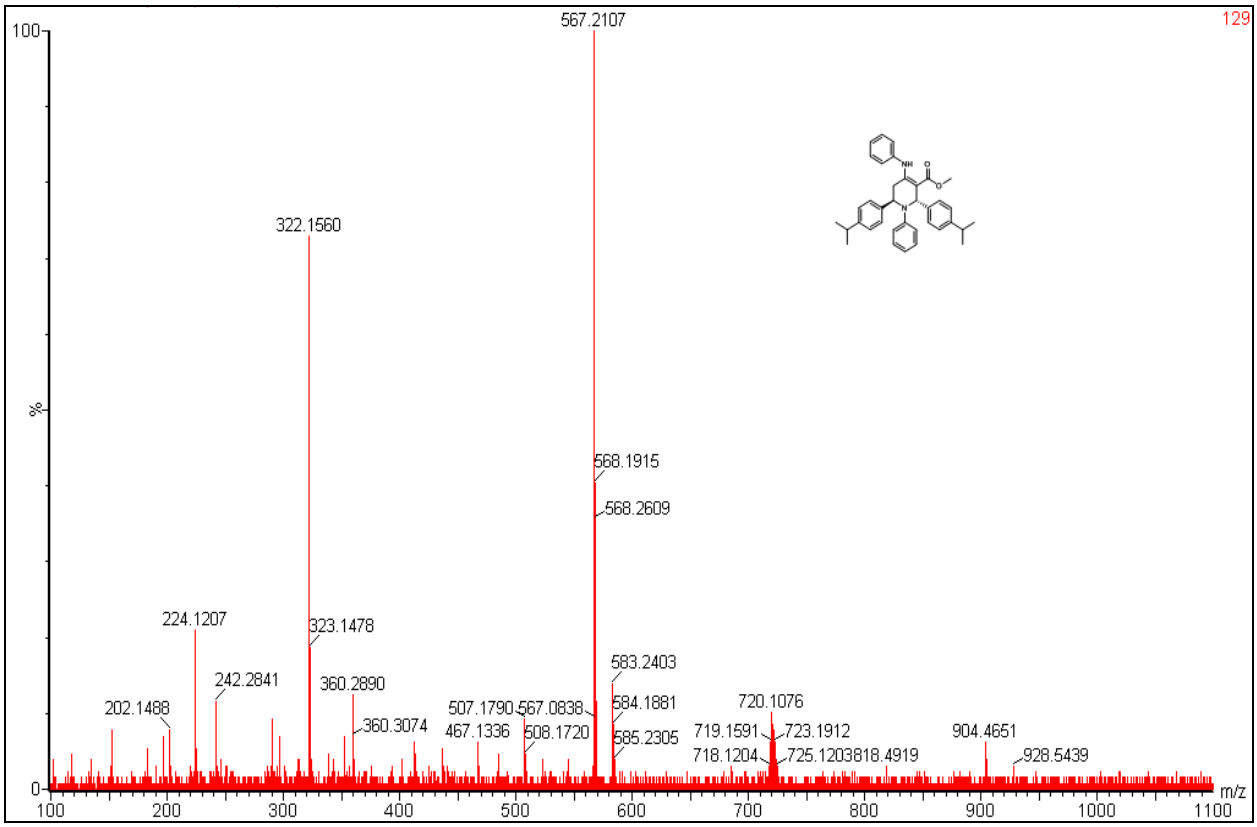
^{1}H Spectrum of 4e (Diasterotropic ratio syn:anti = 10:90)



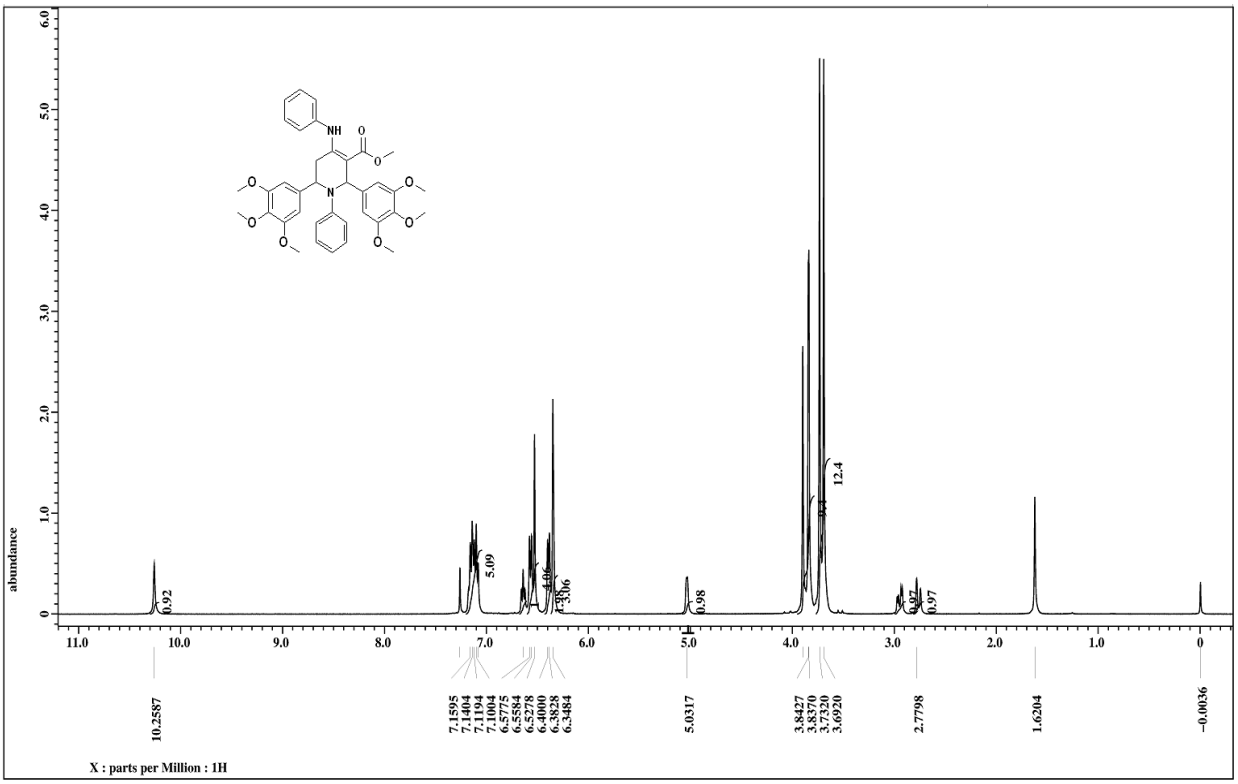
^{13}C Spectrum of 4e



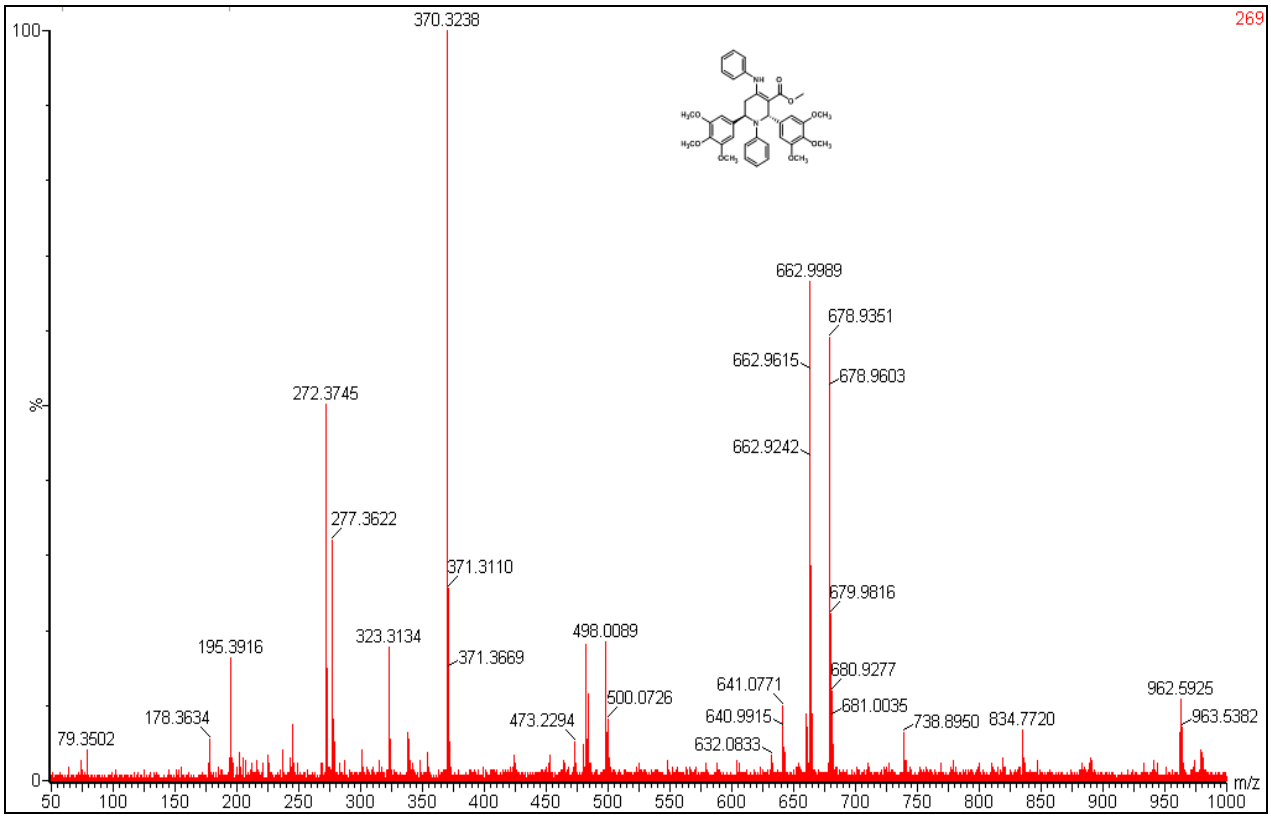
Mass Spectrum of 4e



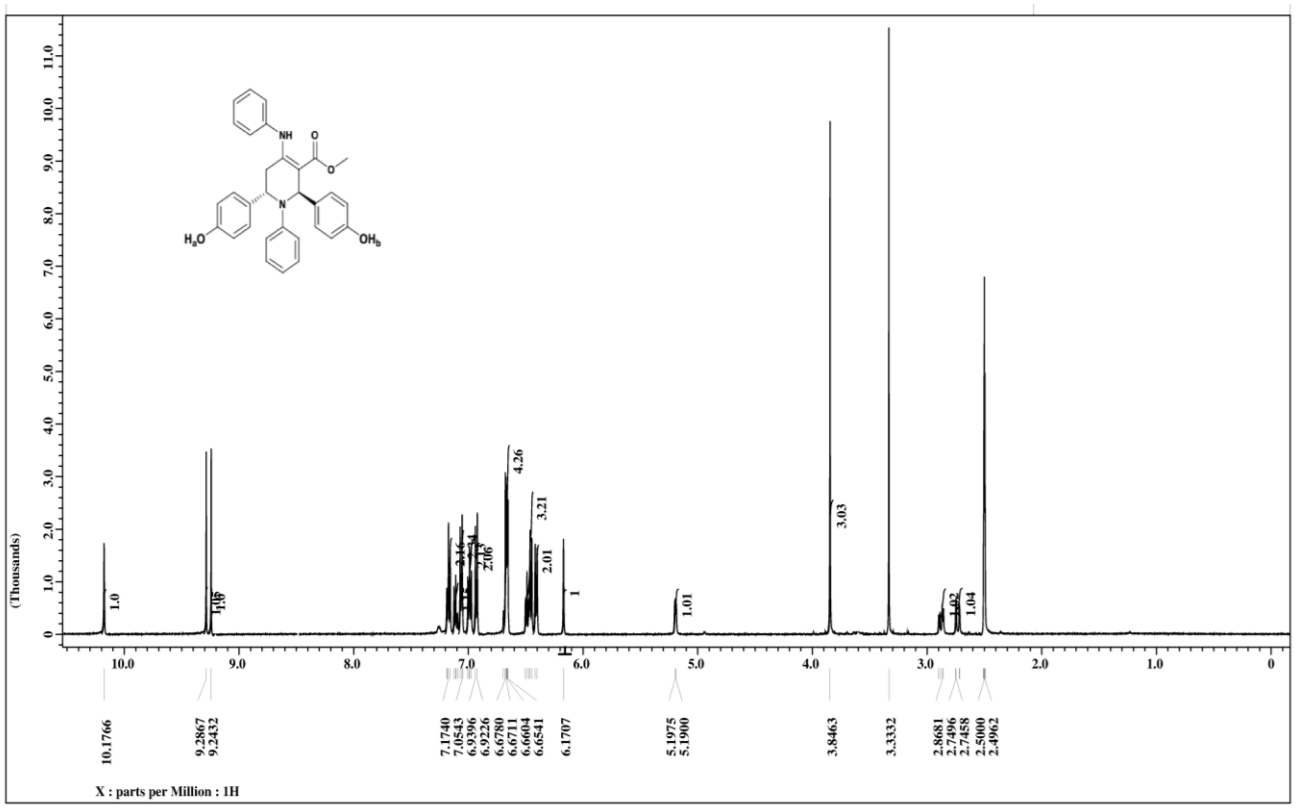
^{1}H Spectrum of 4f



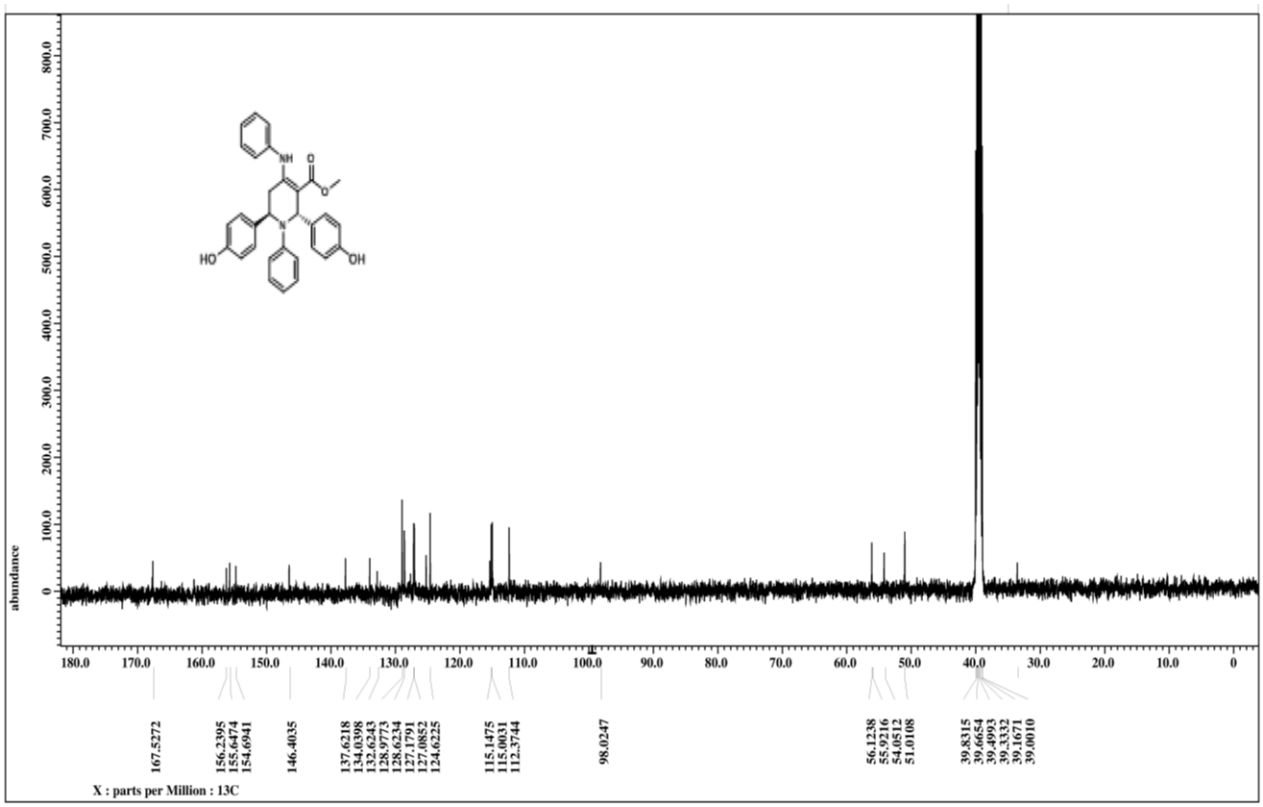
Mass Spectrum of 4f



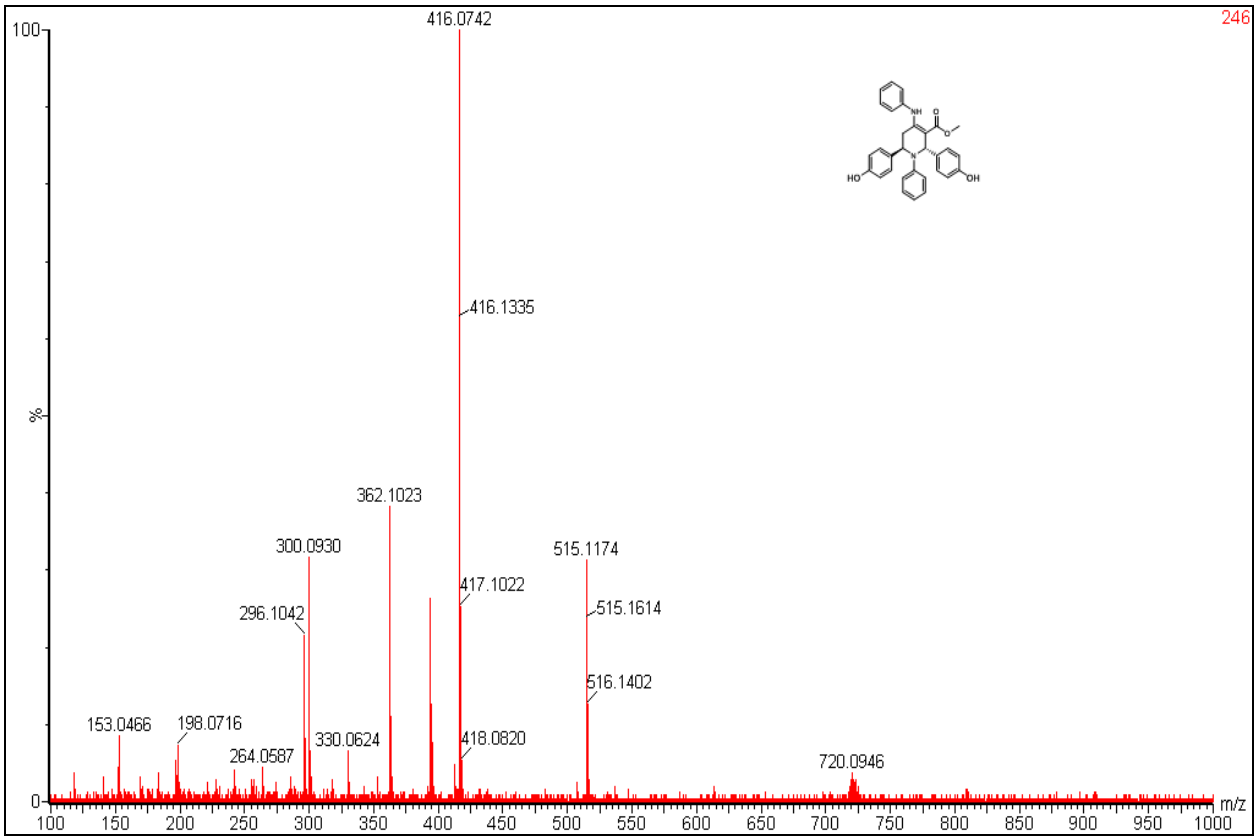
^{1}H Spectrum of 4h



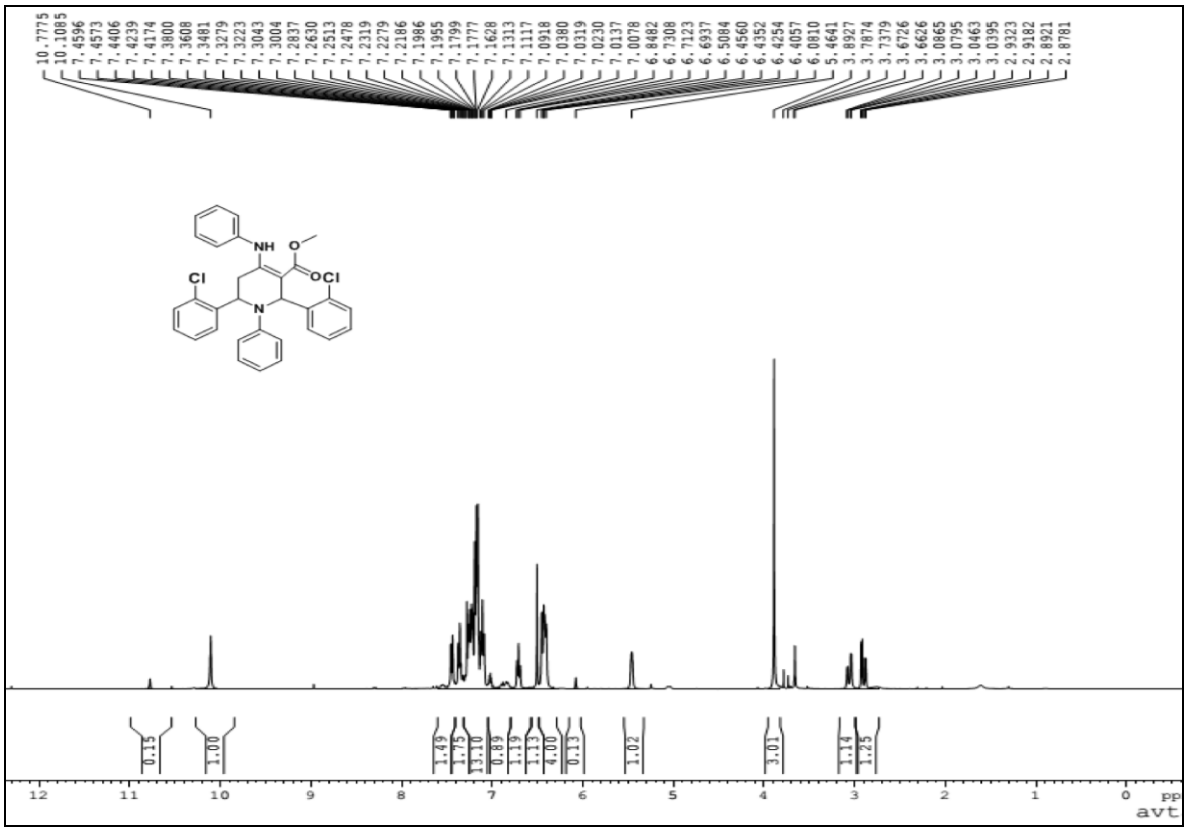
^{13}C Spectrum of 4h



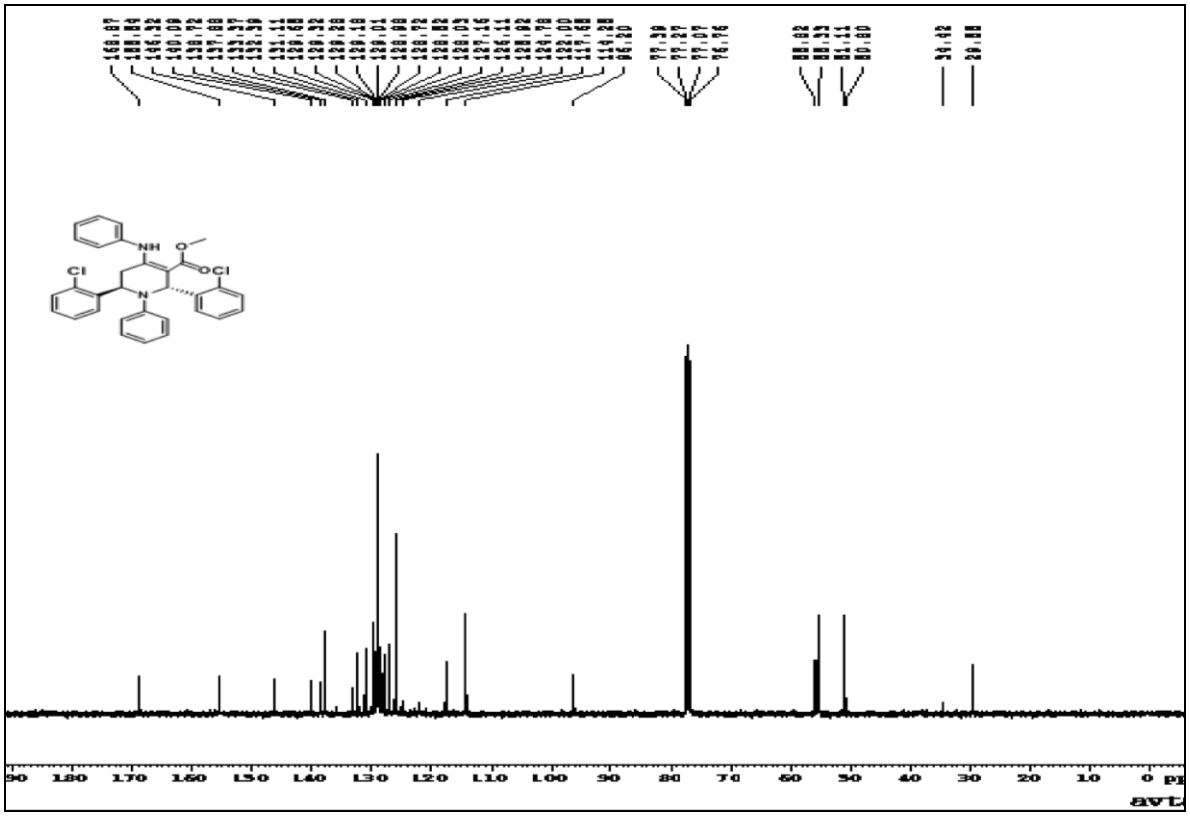
Mass Spectrum of 4h



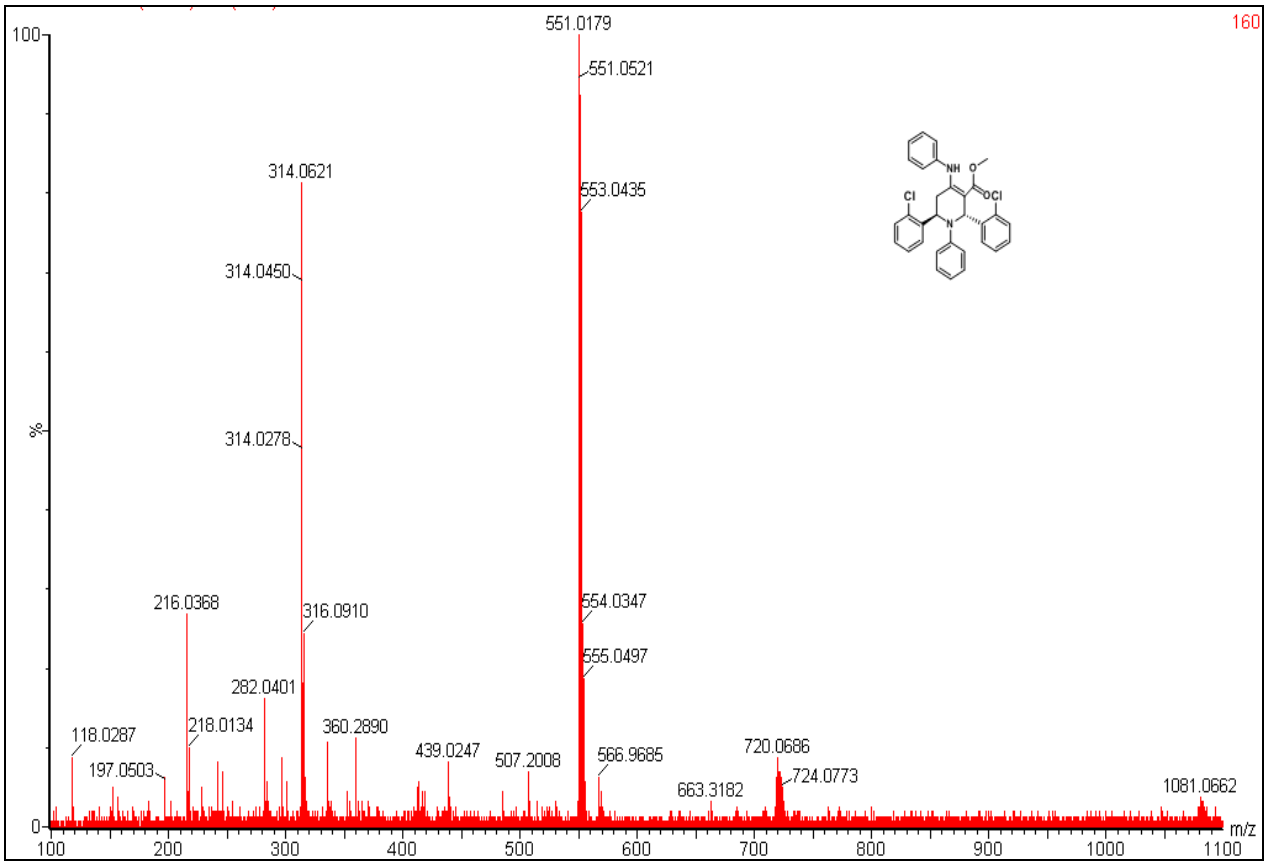
^{1}H Spectrum of 4i (Diasterotropic ratio syn:anti = 13:87)



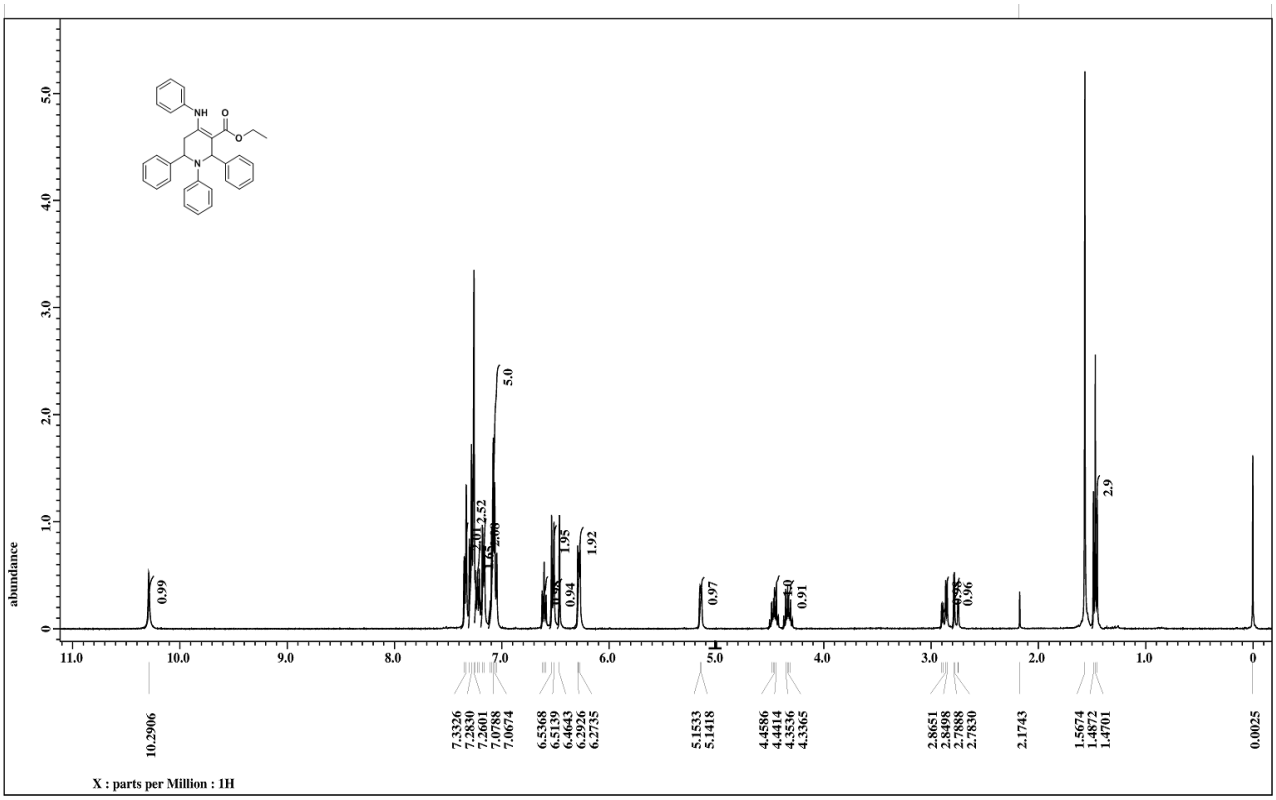
^{13}C Spectrum of 4i



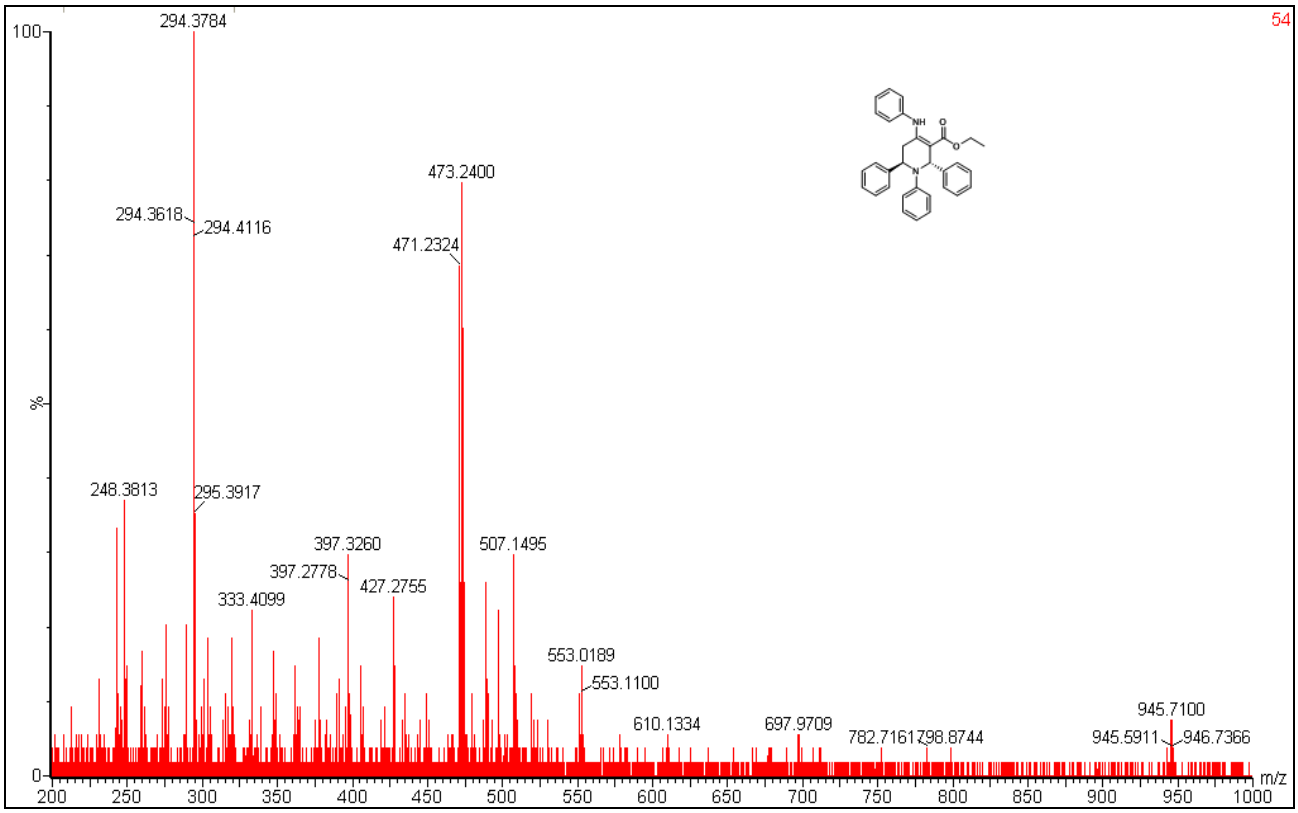
Mass Spectrum of 4i



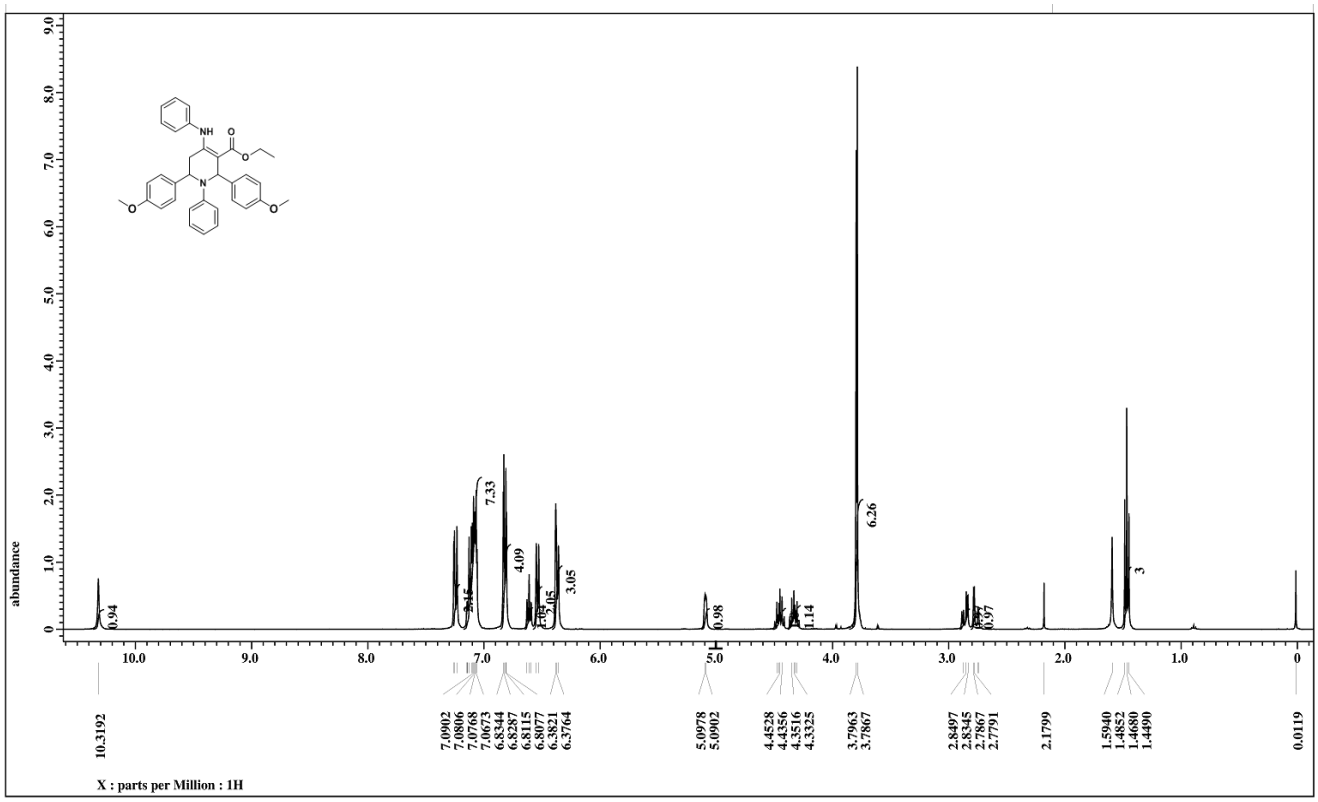
^{1}H Spectrum of 4j



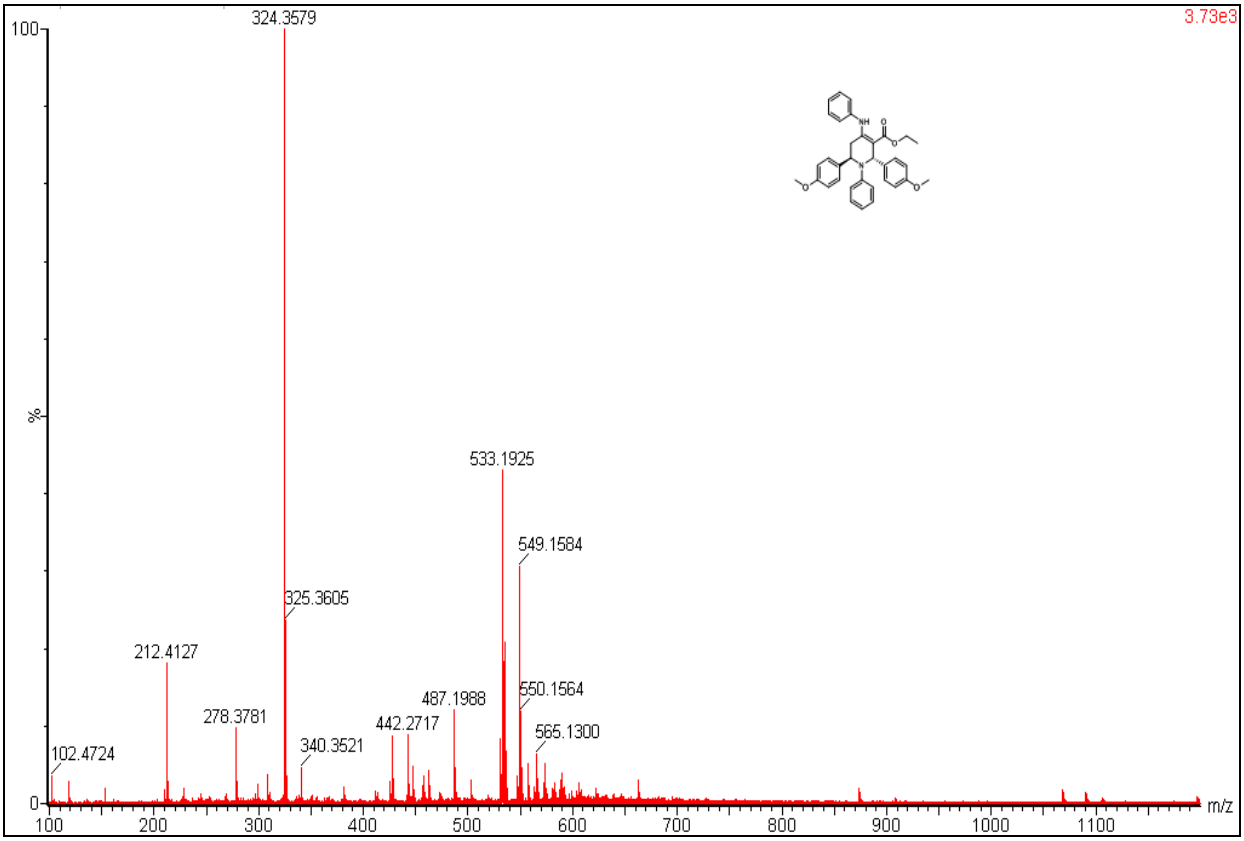
Mass Spectrum of 4j



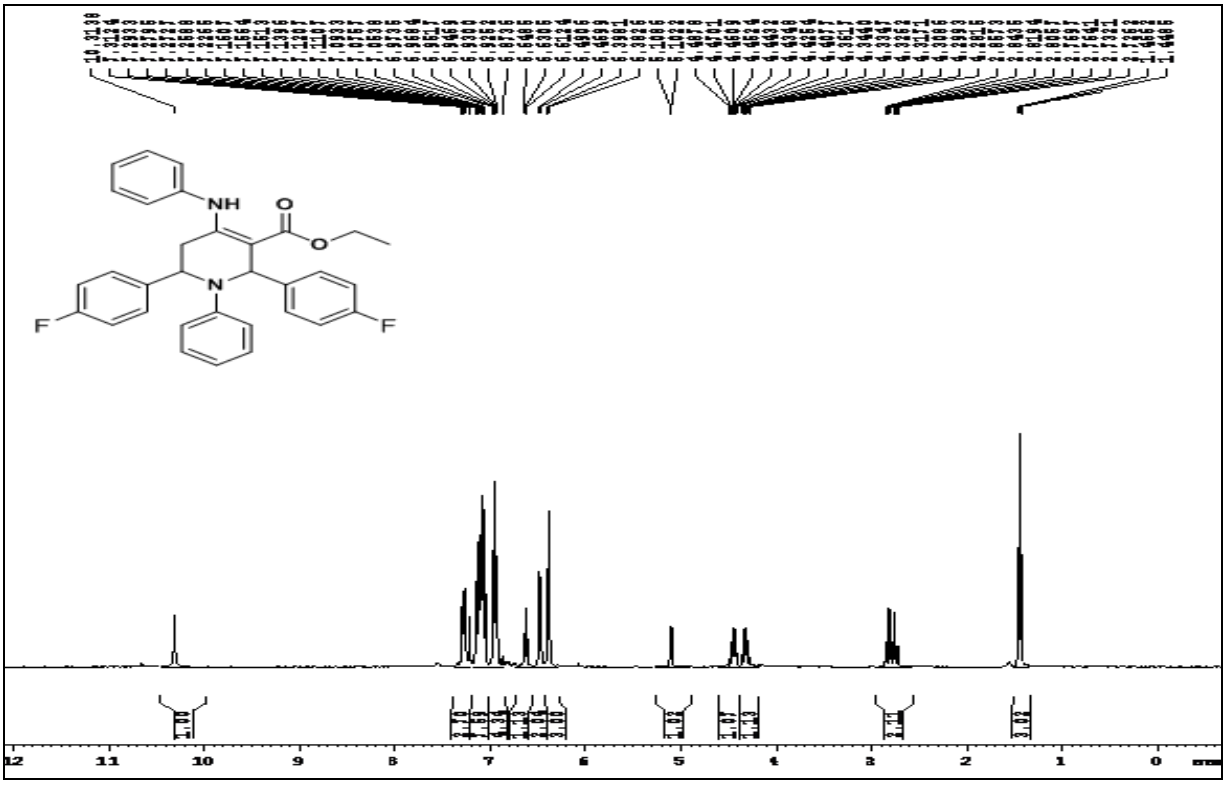
^{1}H Spectrum of 4k



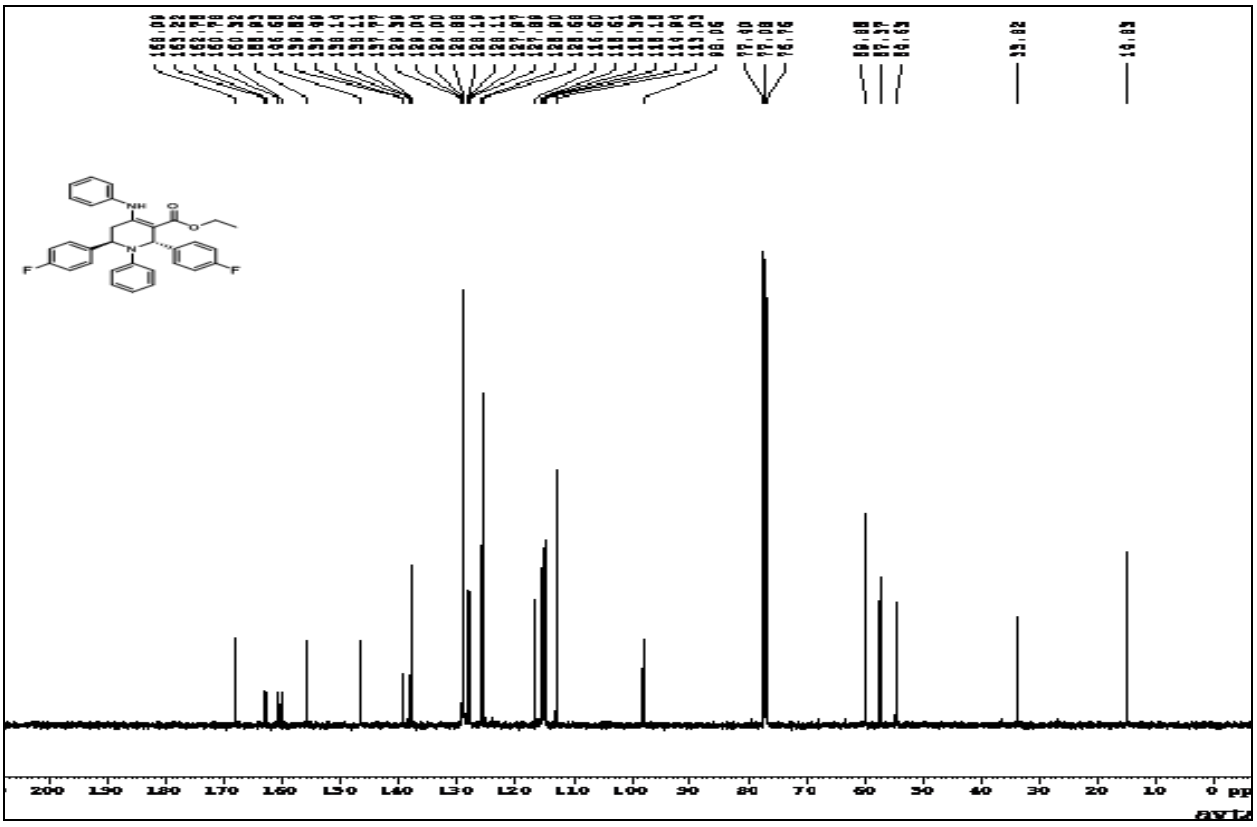
Mass Spectrum of 4k



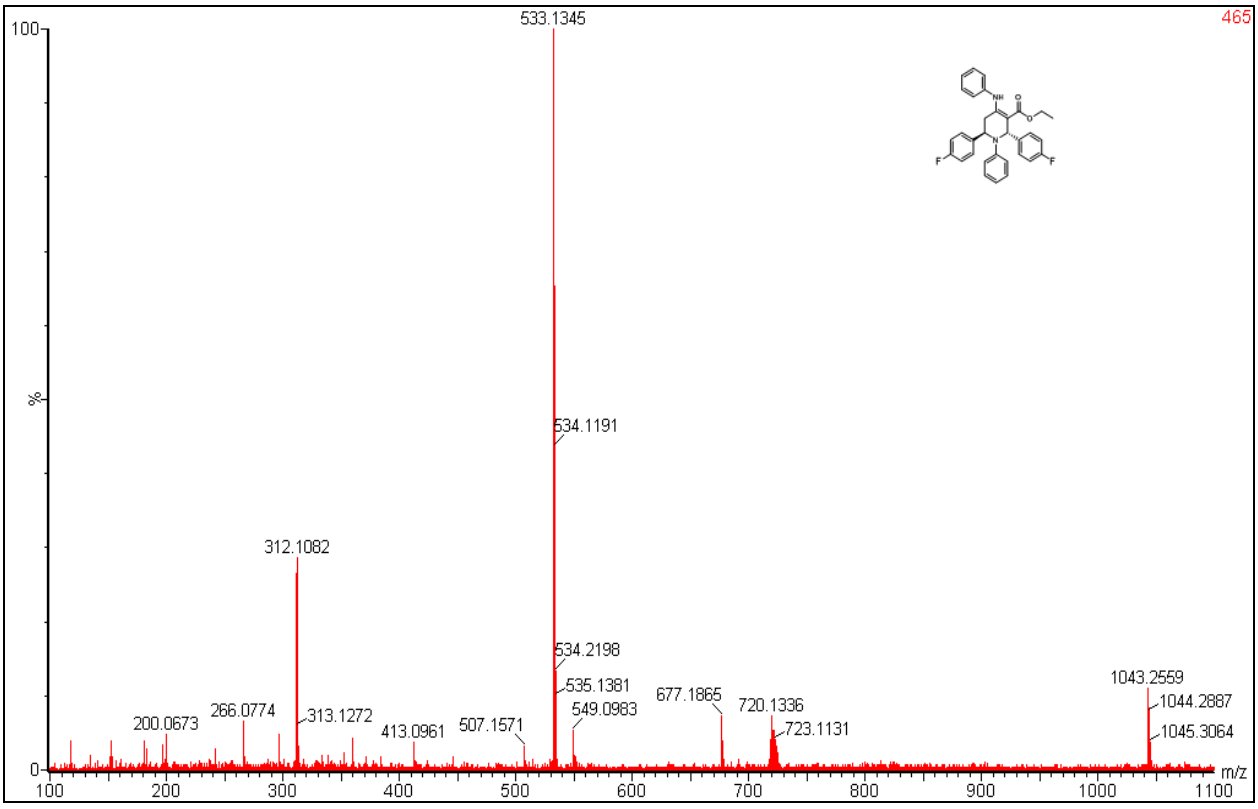
^{1}H Spectrum of 4m



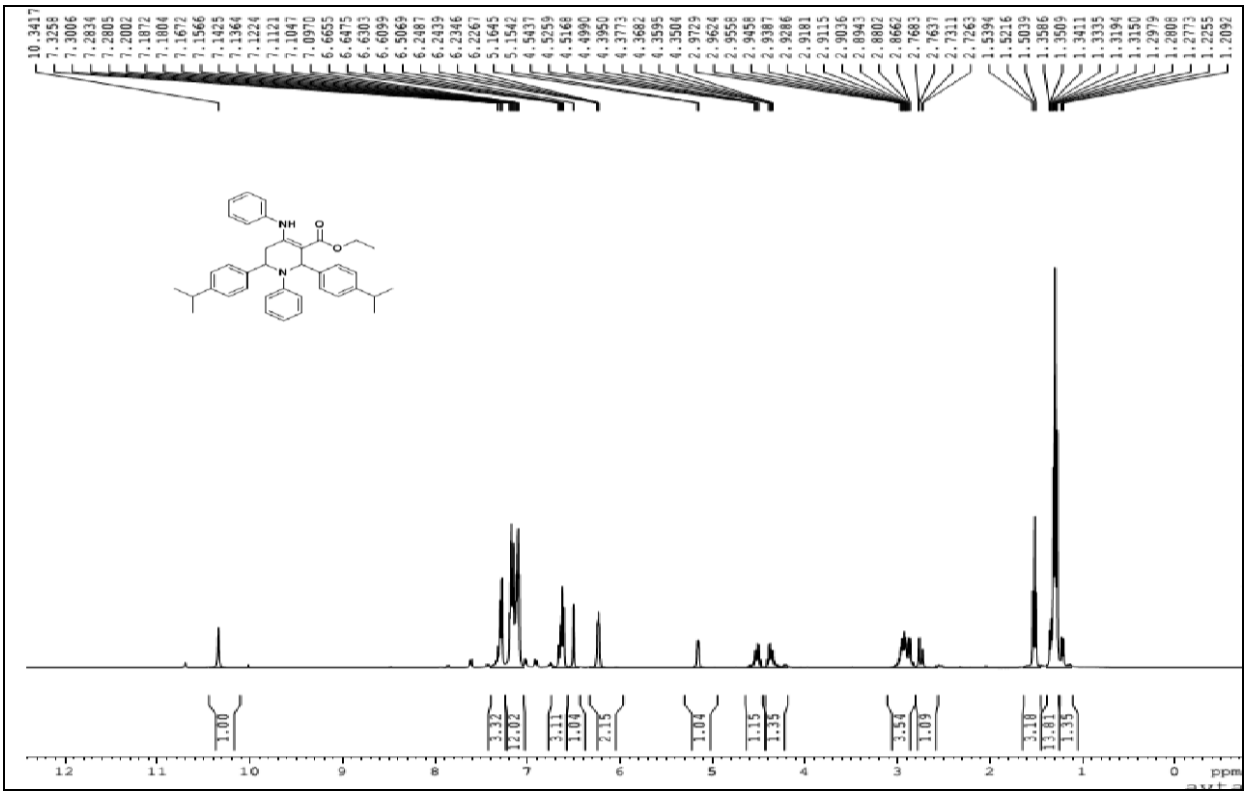
^{13}C Spectrum of 4m



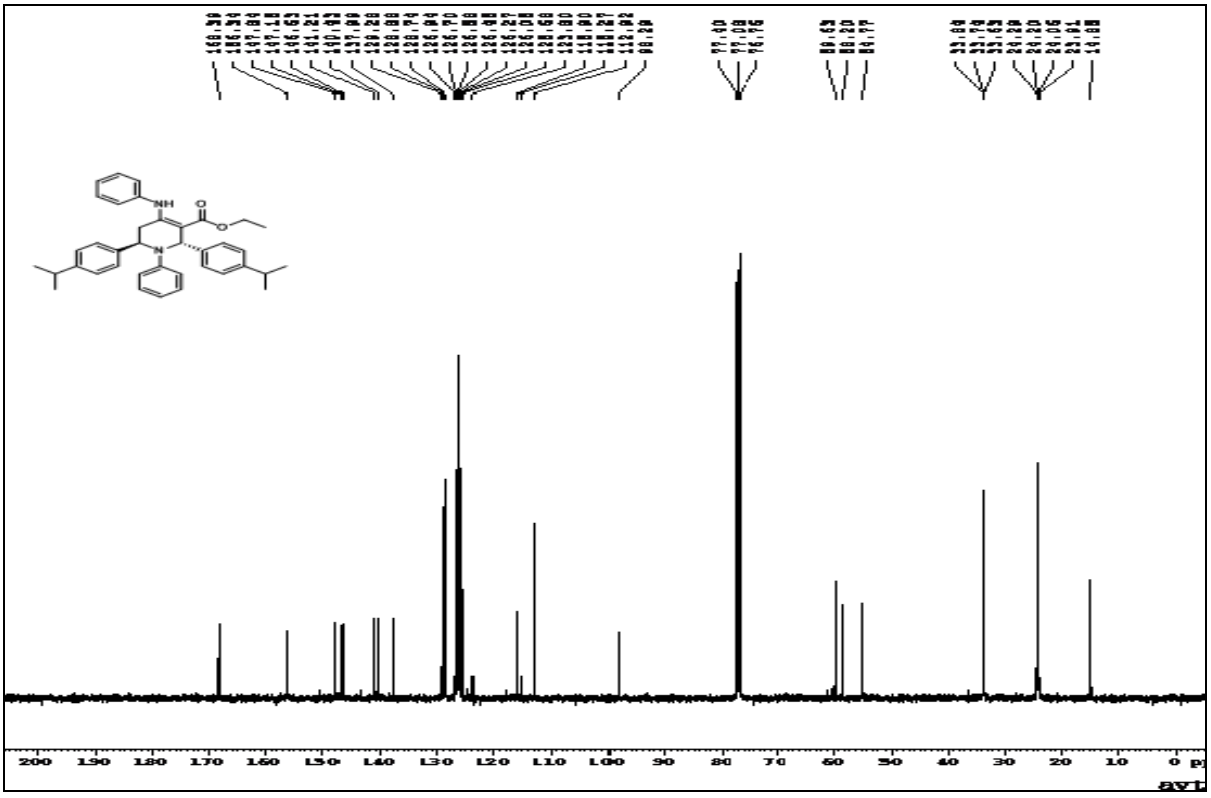
Mass Spectrum of 4m



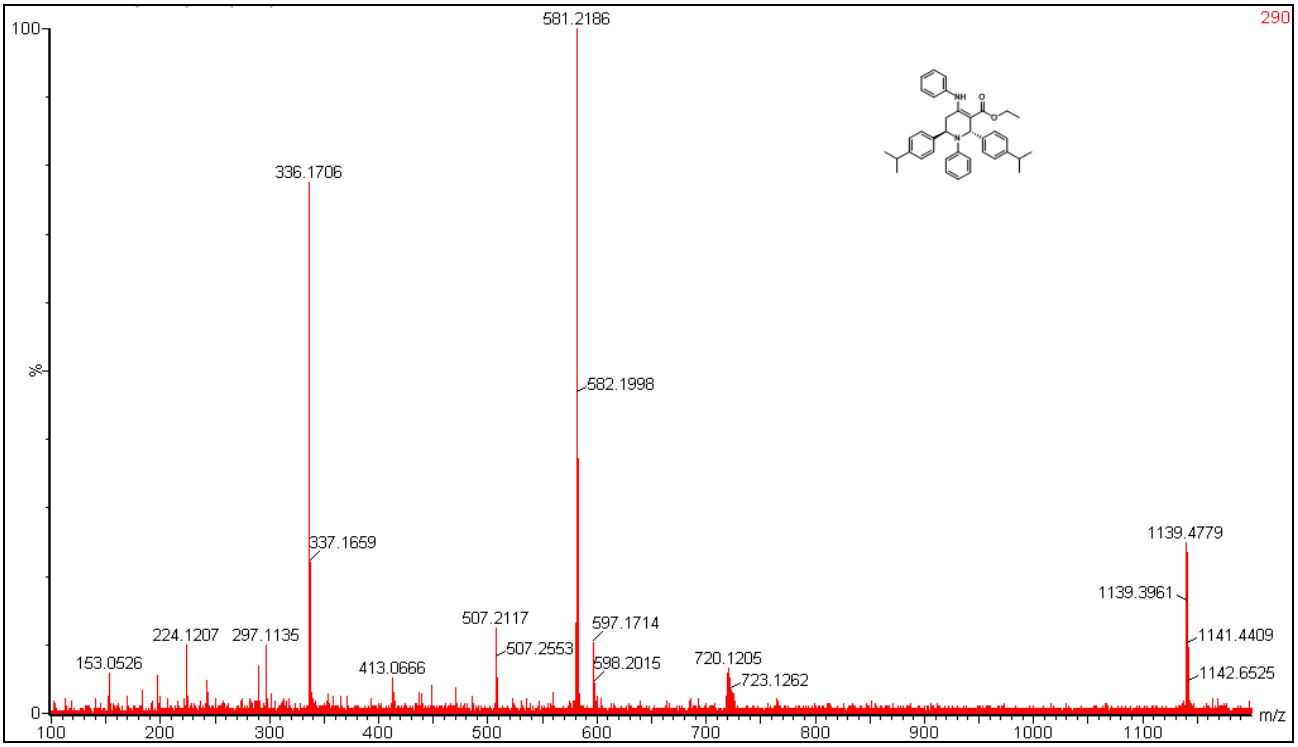
^{1}H Spectrum of 4n (Diasterotropic ratio syn:anti = 09:91)



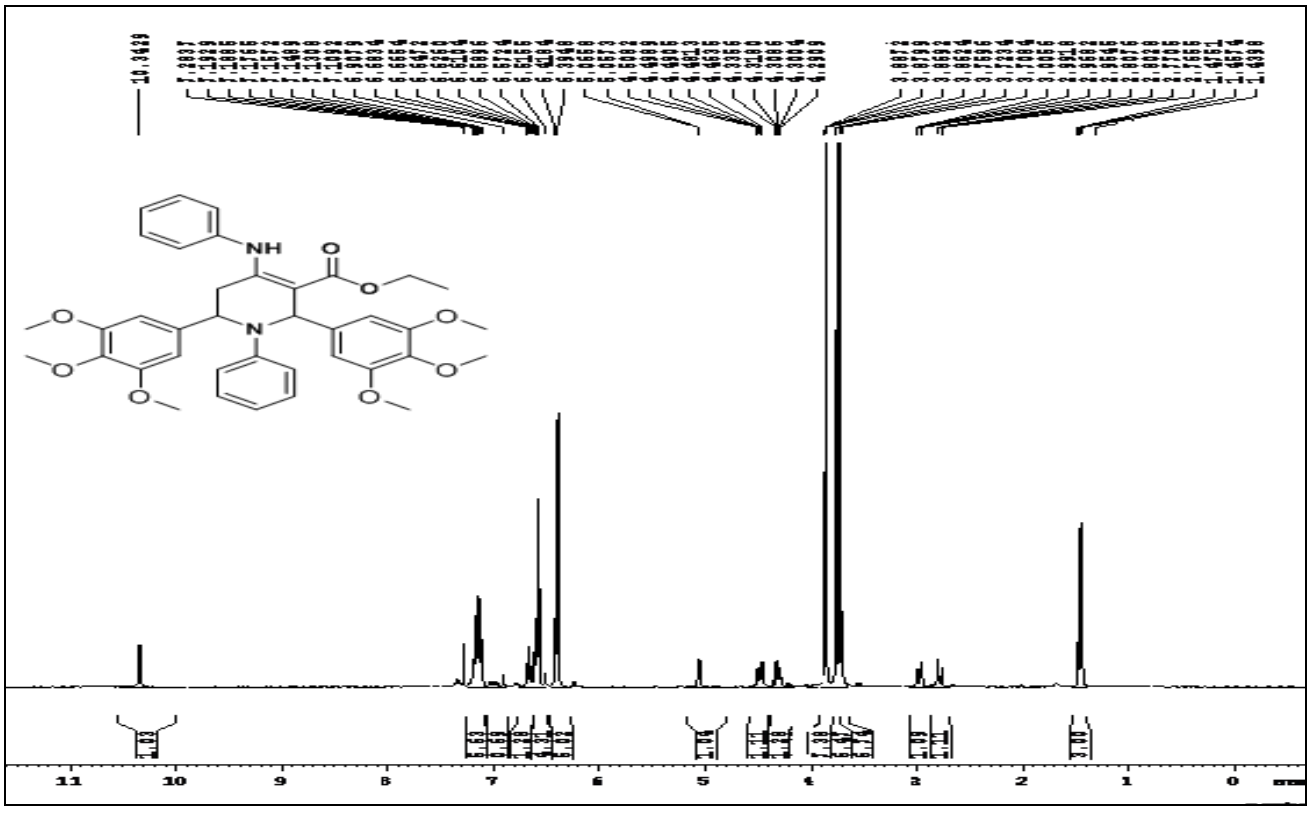
^{13}C Spectrum of 4n



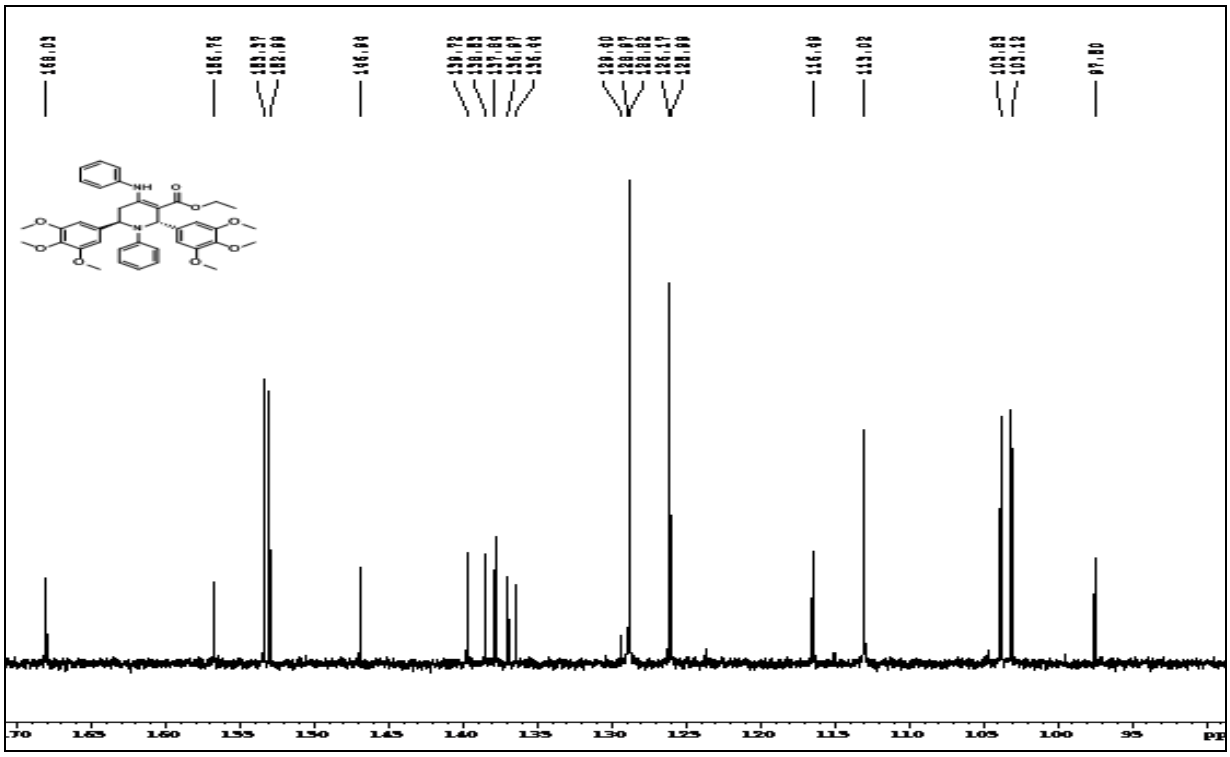
Mass Spectrum of 4n



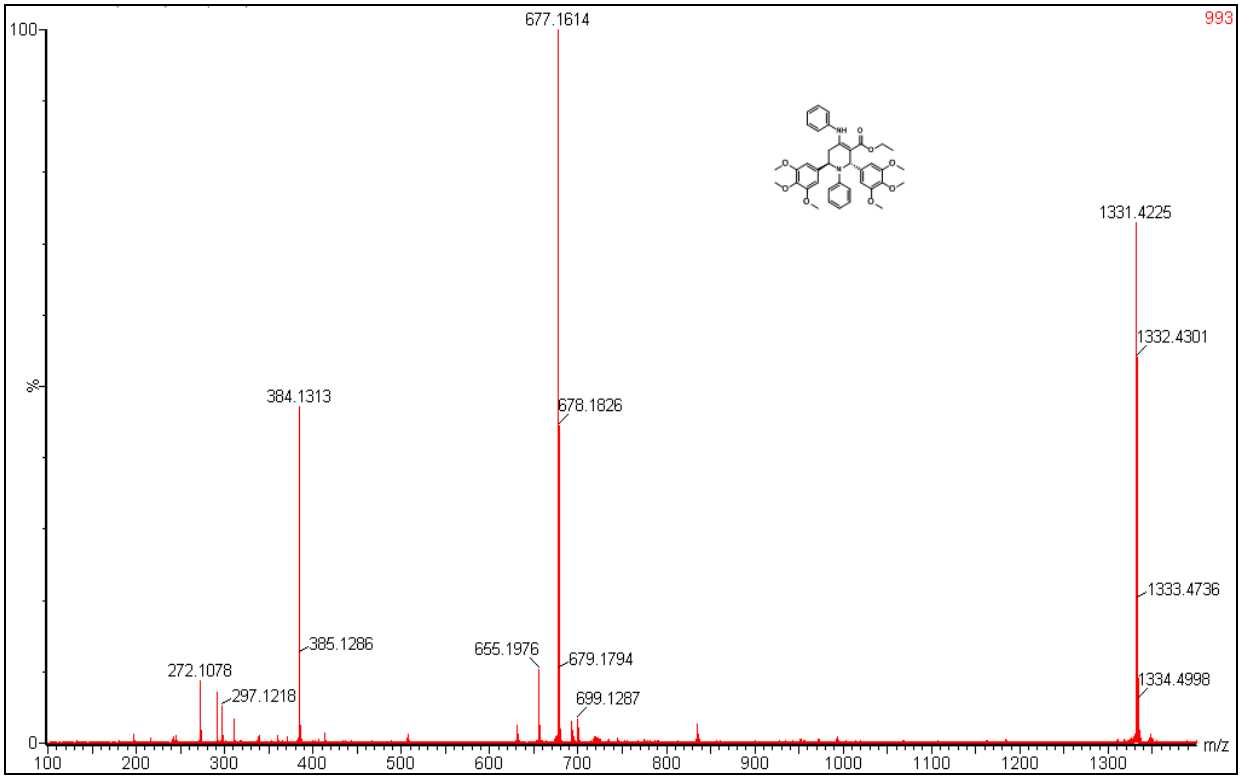
[1]H Spectrum of 4o



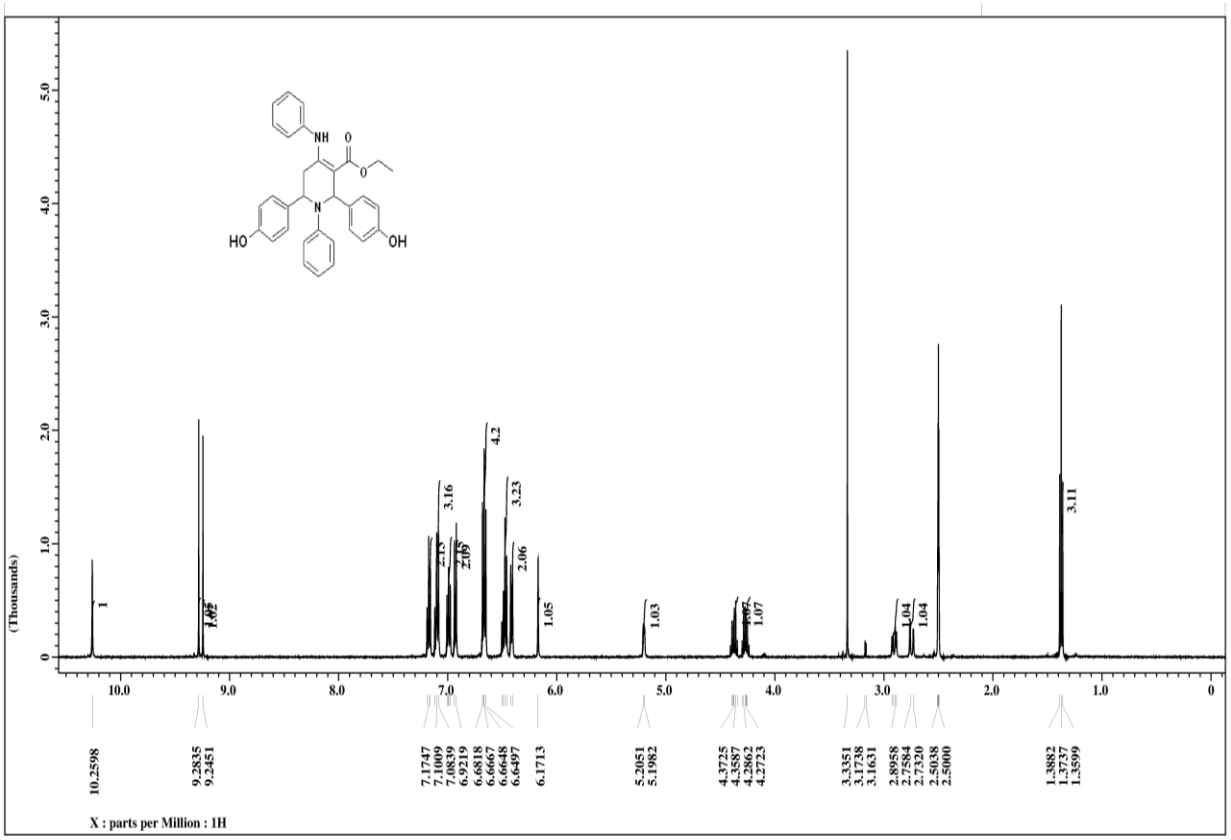
^{13}C Spectrum of 4o



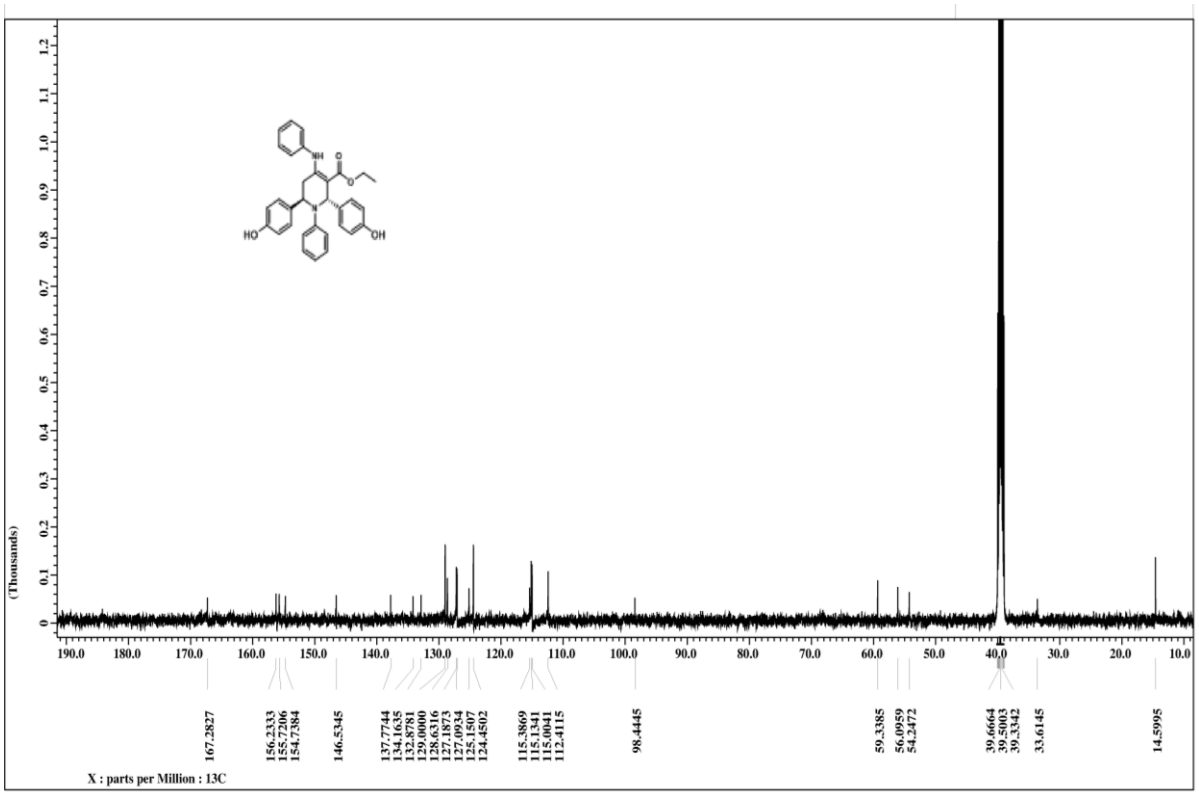
Mass Spectrum of 4o



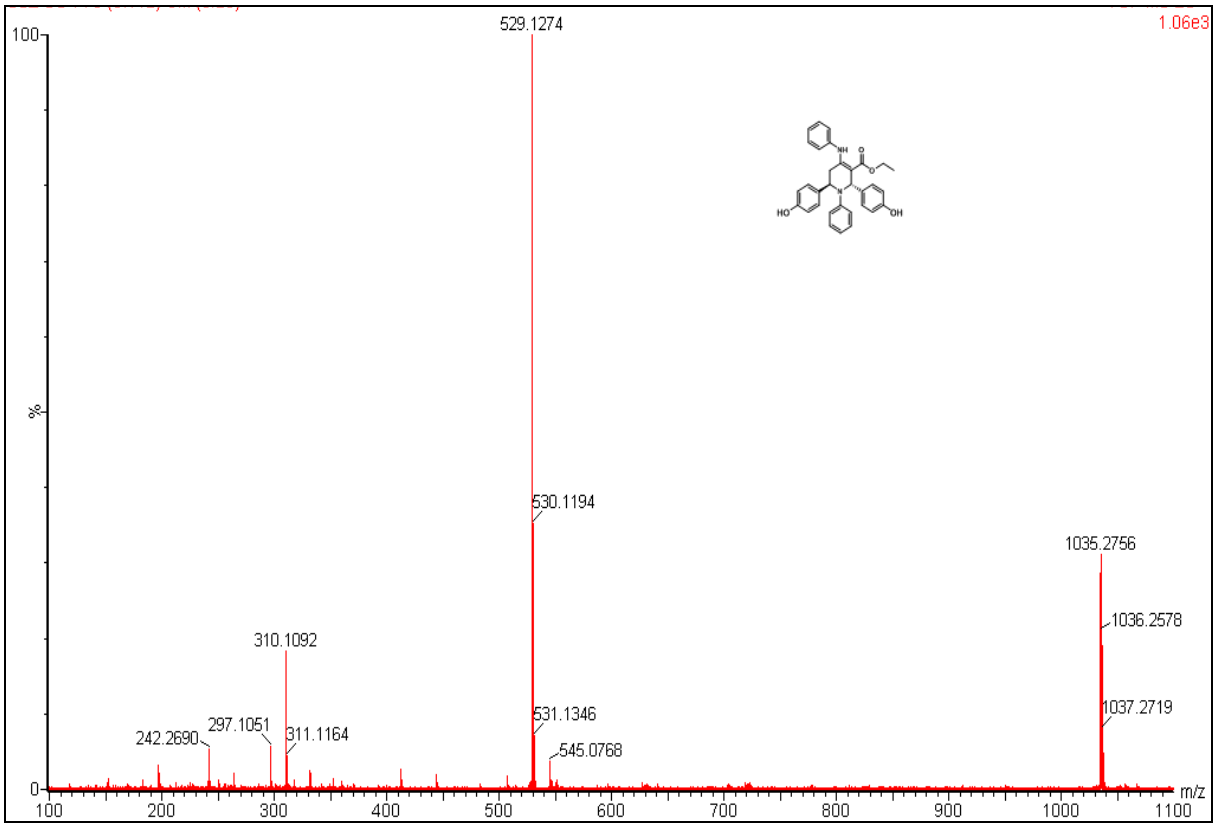
^{1}H Spectrum of 4q



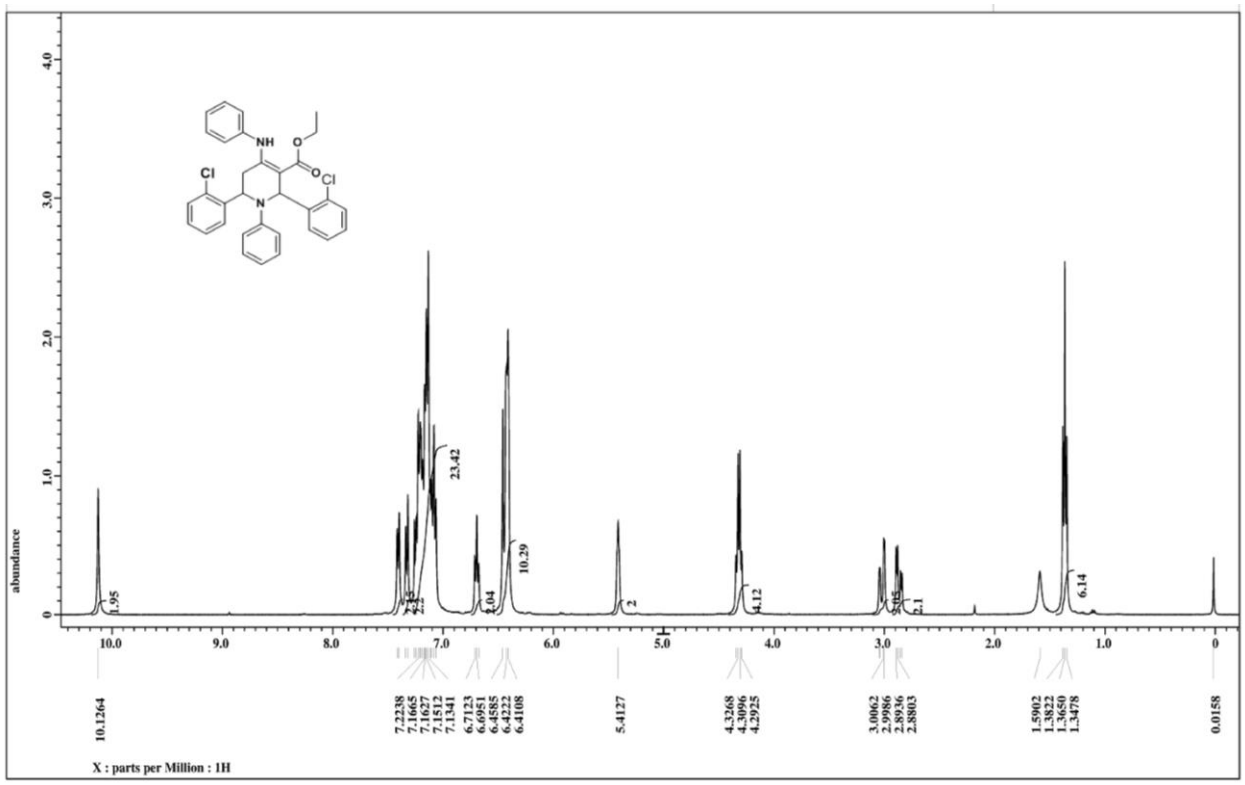
^{13}C Spectrum of 4q



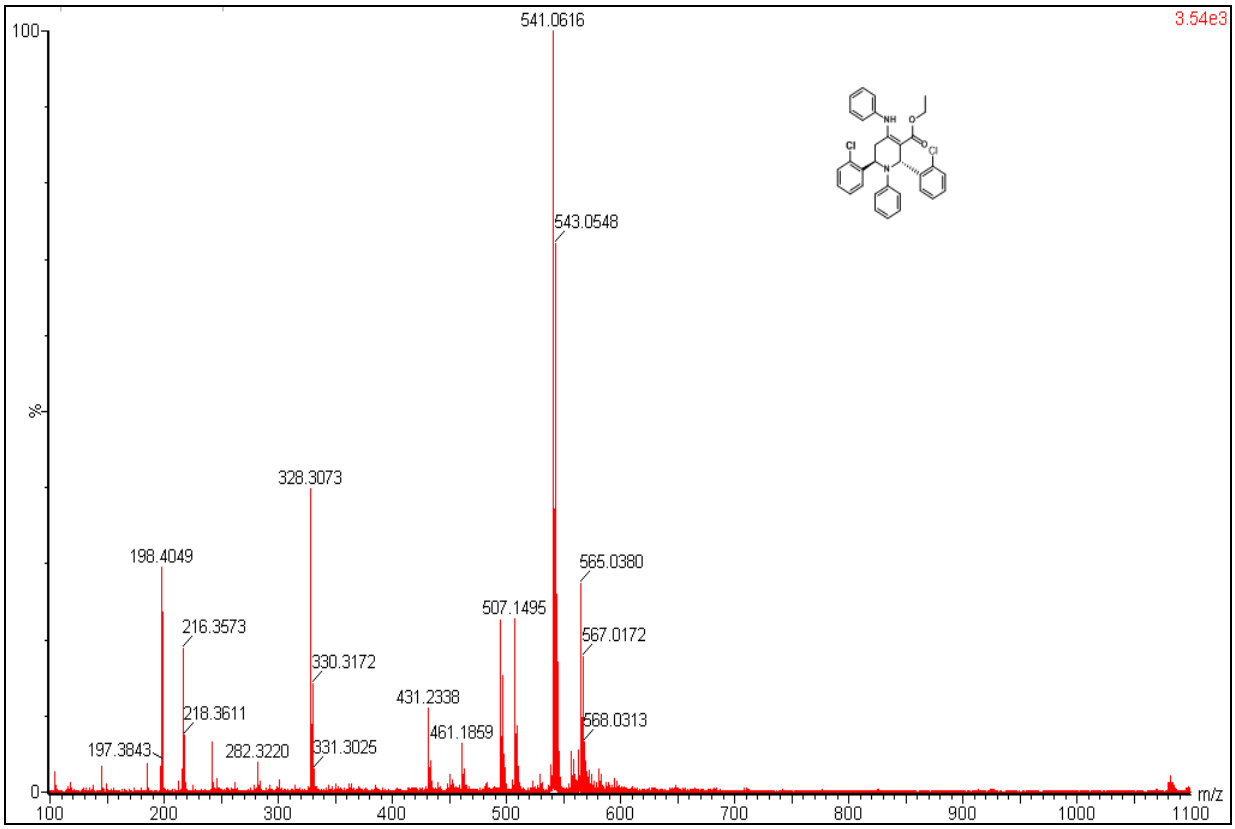
Mass Spectrum of 4q



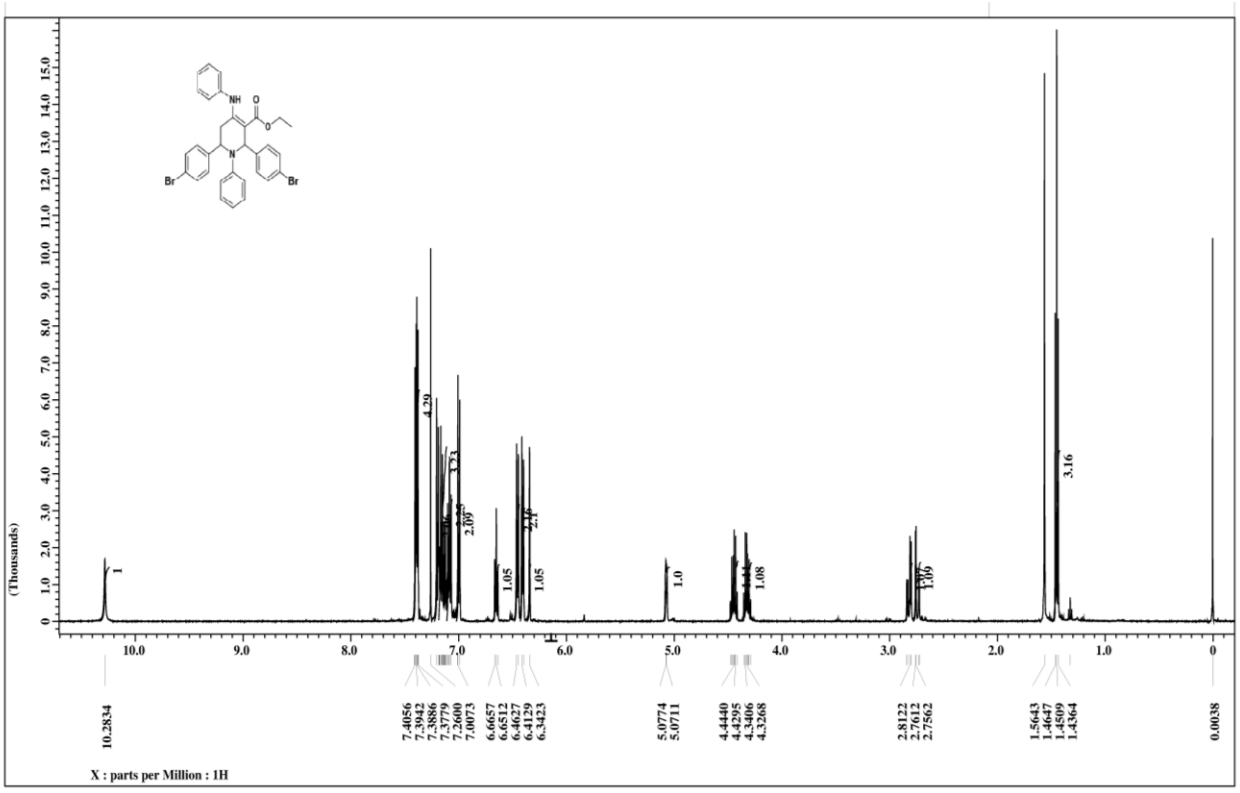
^{1}H Spectrum of 4r



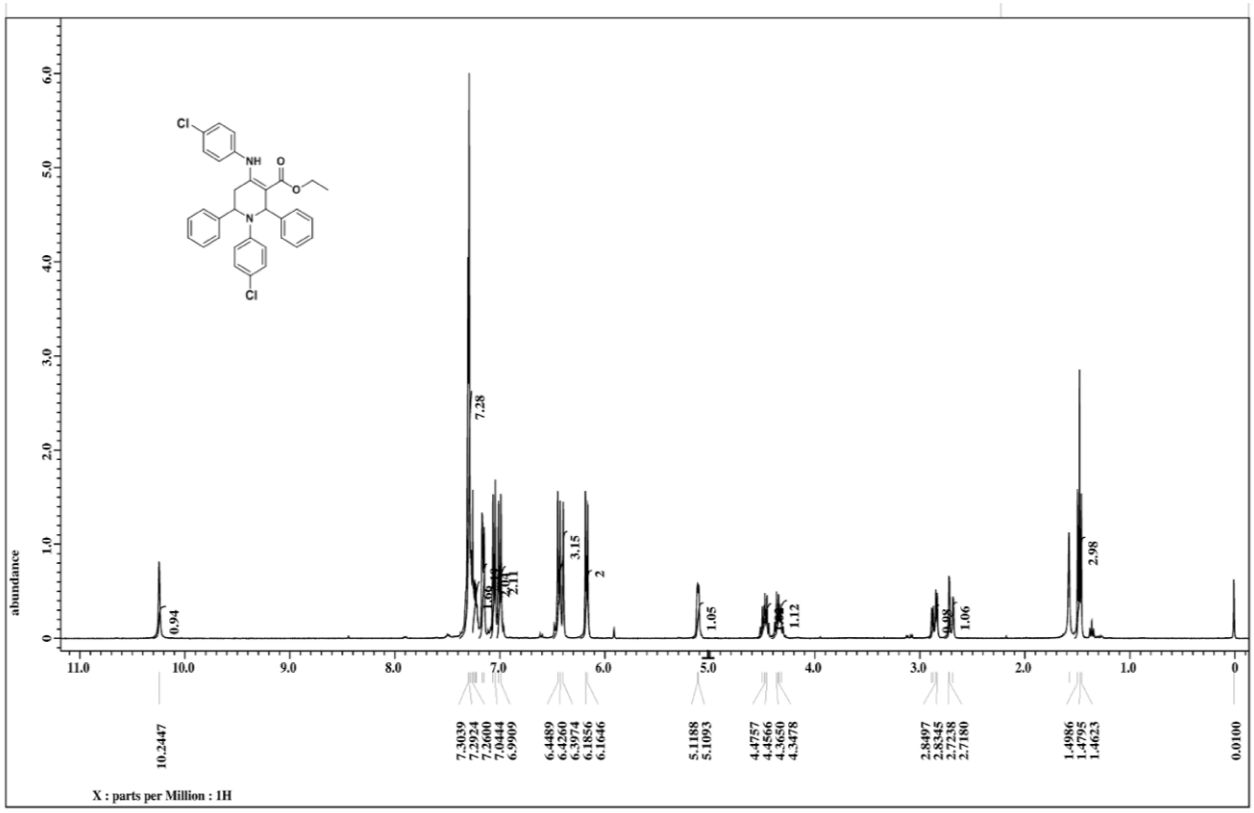
Mass Spectrum of 4r



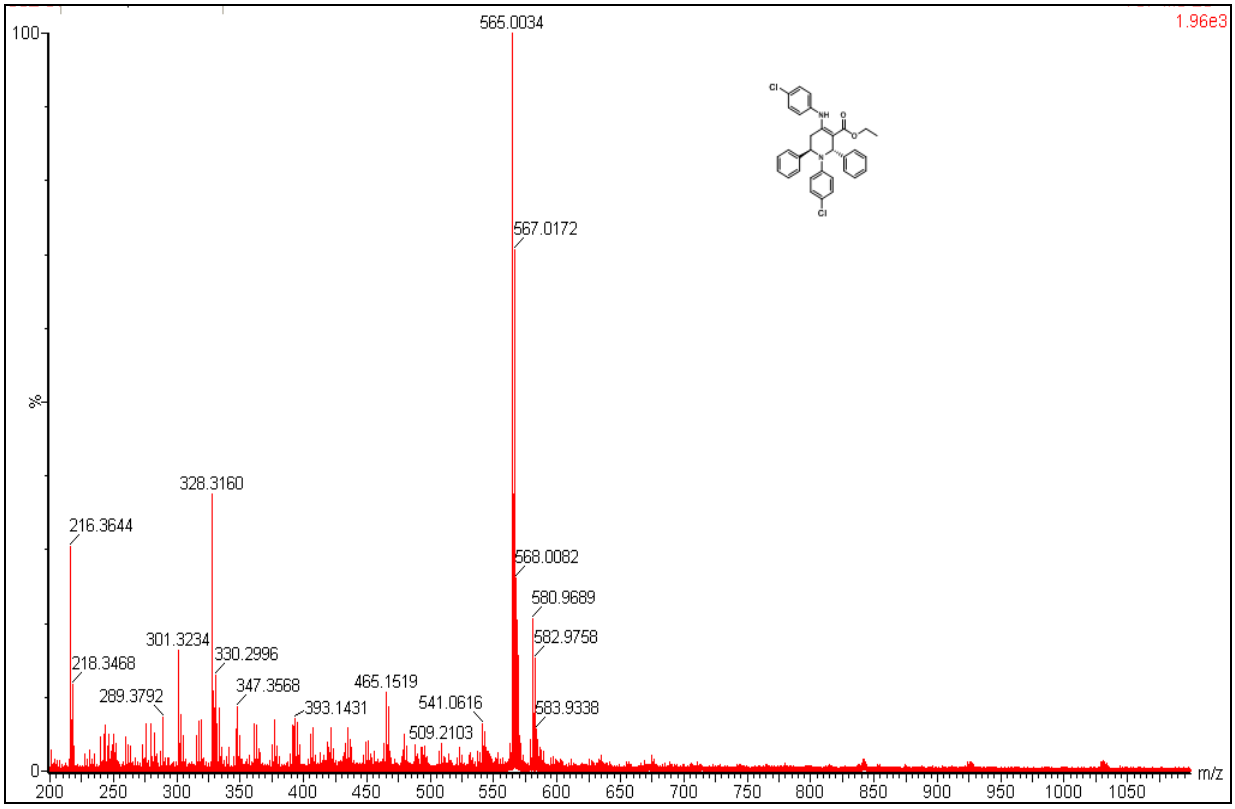
^{1}H Spectrum of 4t



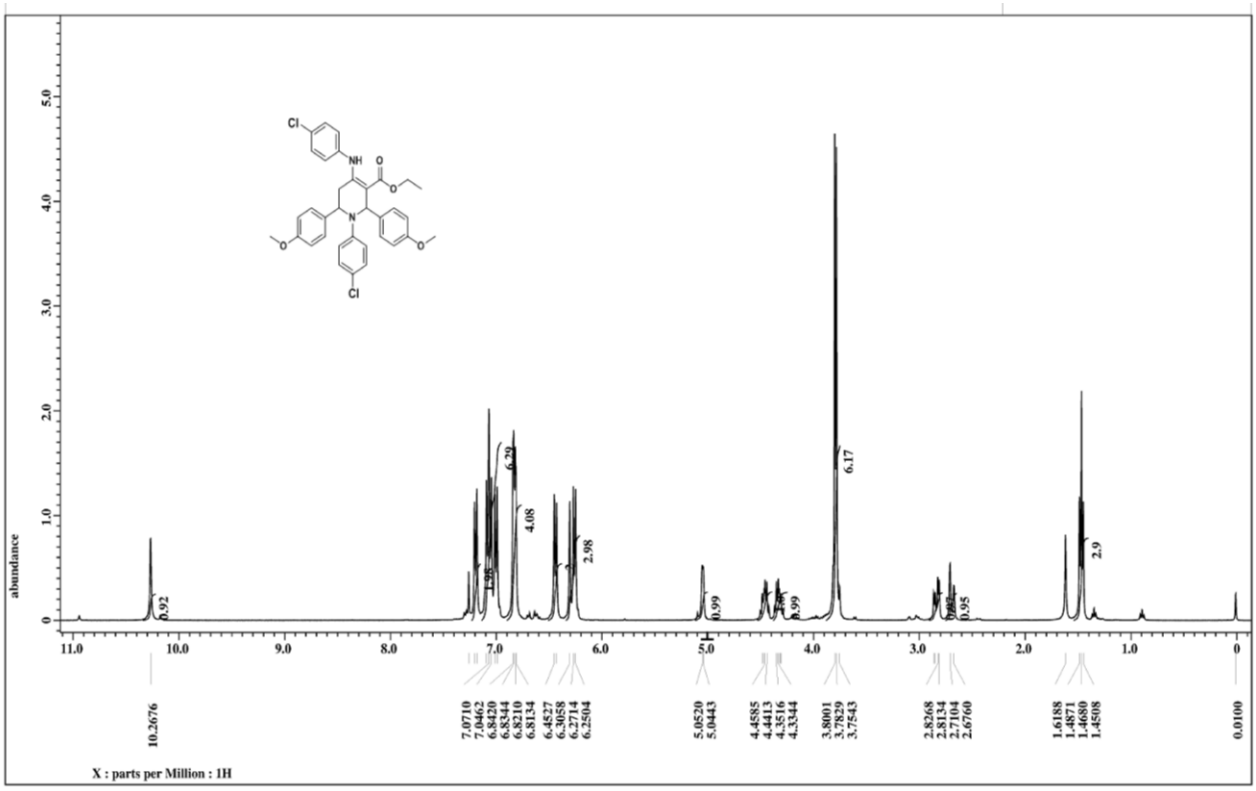
^{1}H Spectrum of 4u



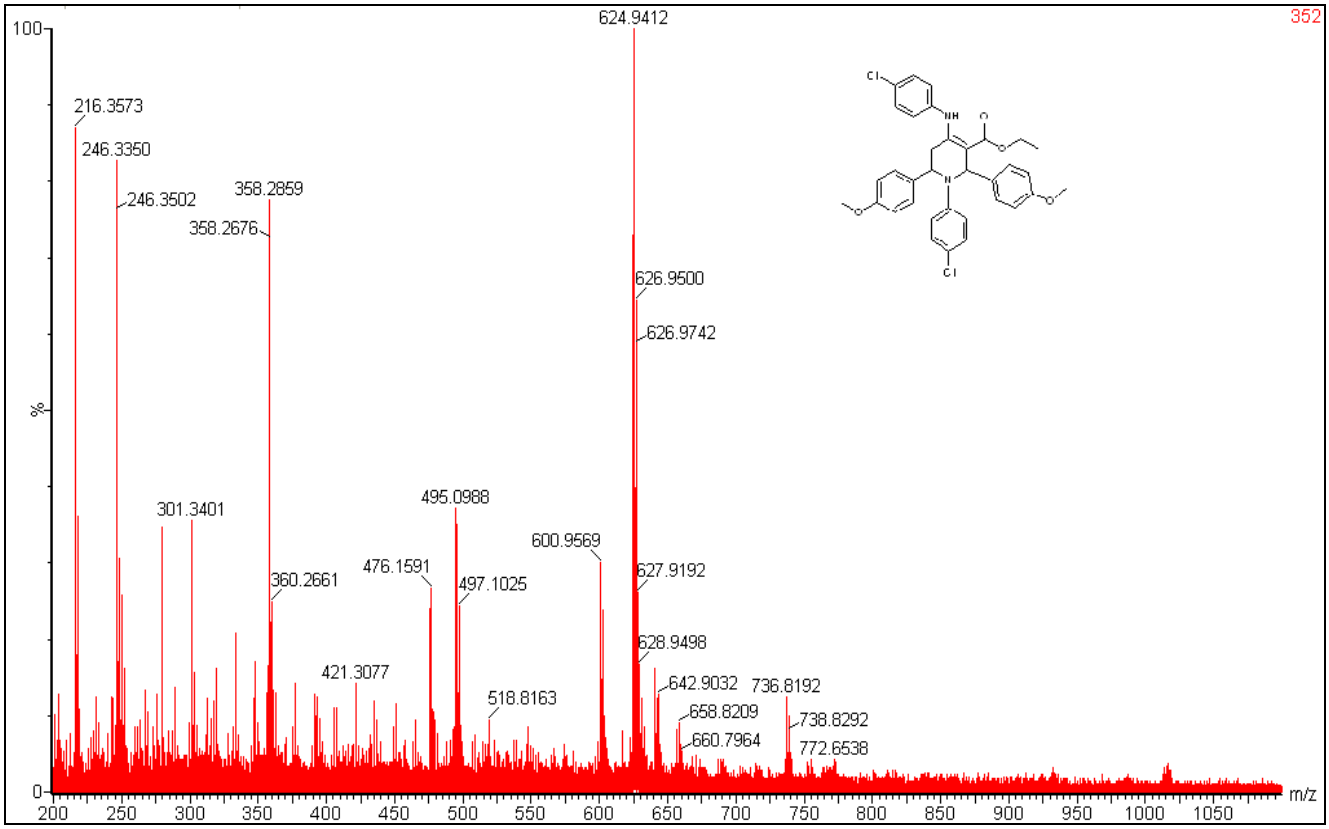
Mass Spectrum of 4u



^{1}H Spectrum of 4v



Mass Spectrum of 4v



X-Ray Structure of 4o (CCDC 1047298)

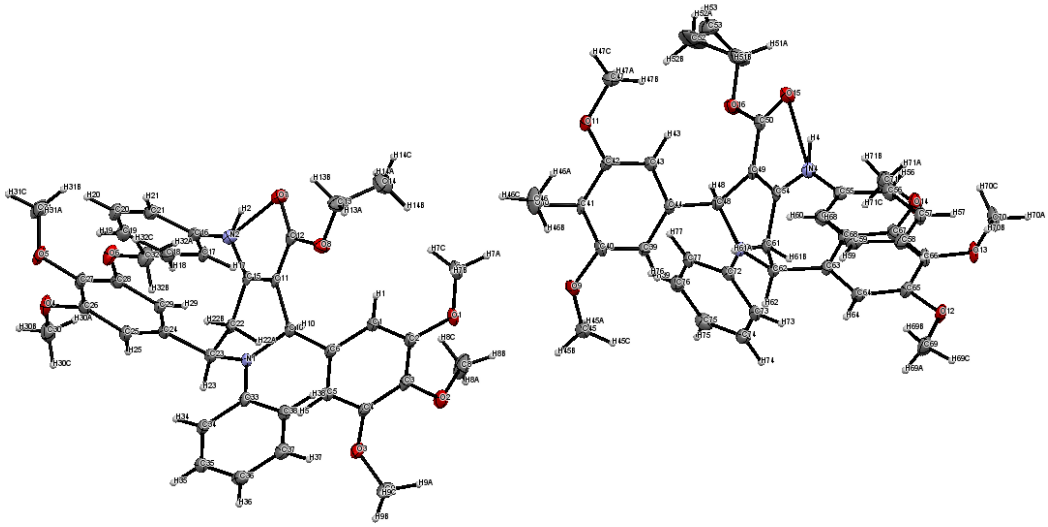


Figure S3. Twin molecules in the unit cell of **4o**

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