Identification and control of critical process impurities: An improved process for the preparation of dolutegravir sodium

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SUPPORTING INFORMATION

Figure-S1: FTIR spectrum of intermediate-**3**

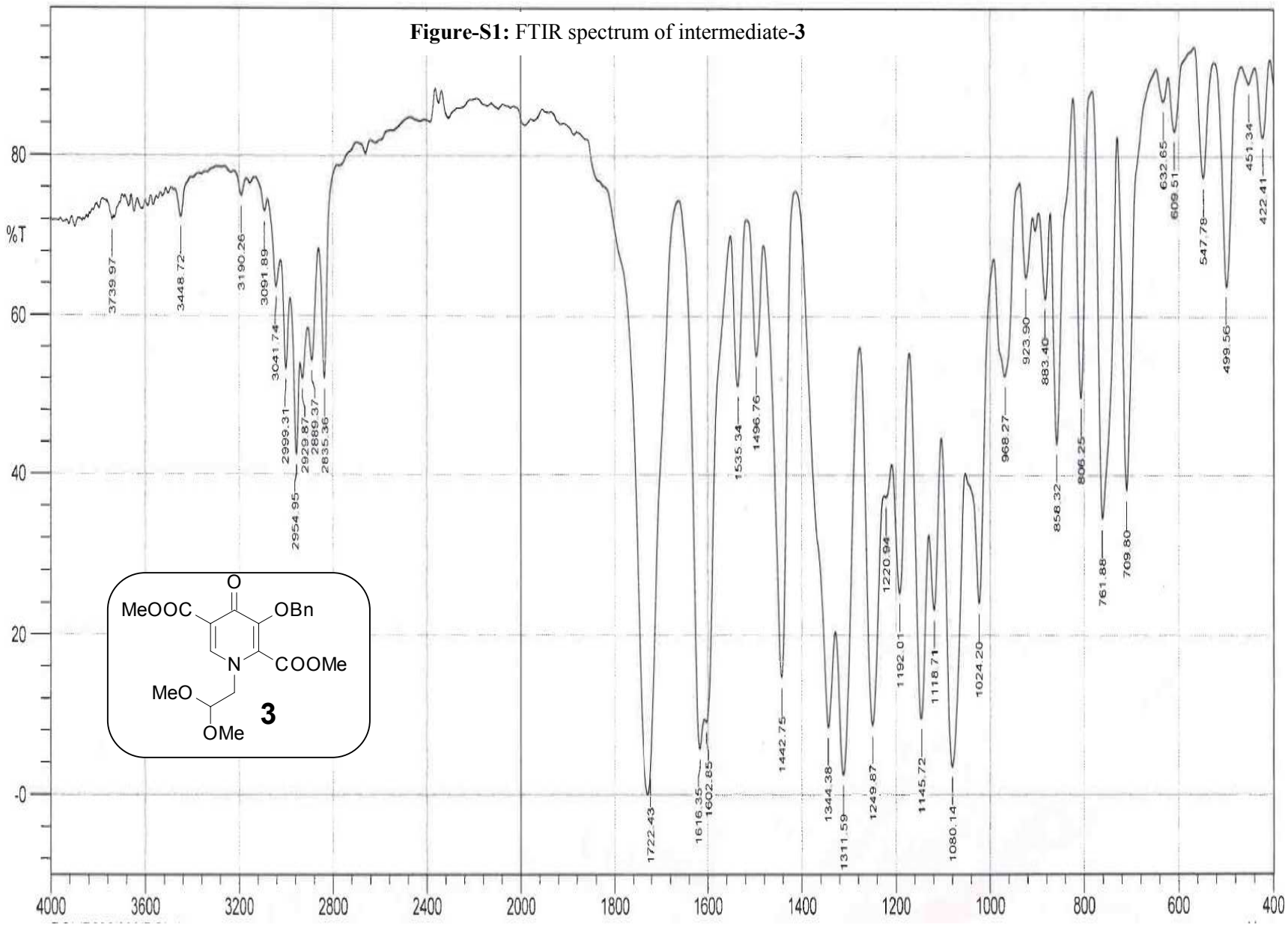


Figure-S2: H-NMR spectrum of intermediate-**3**

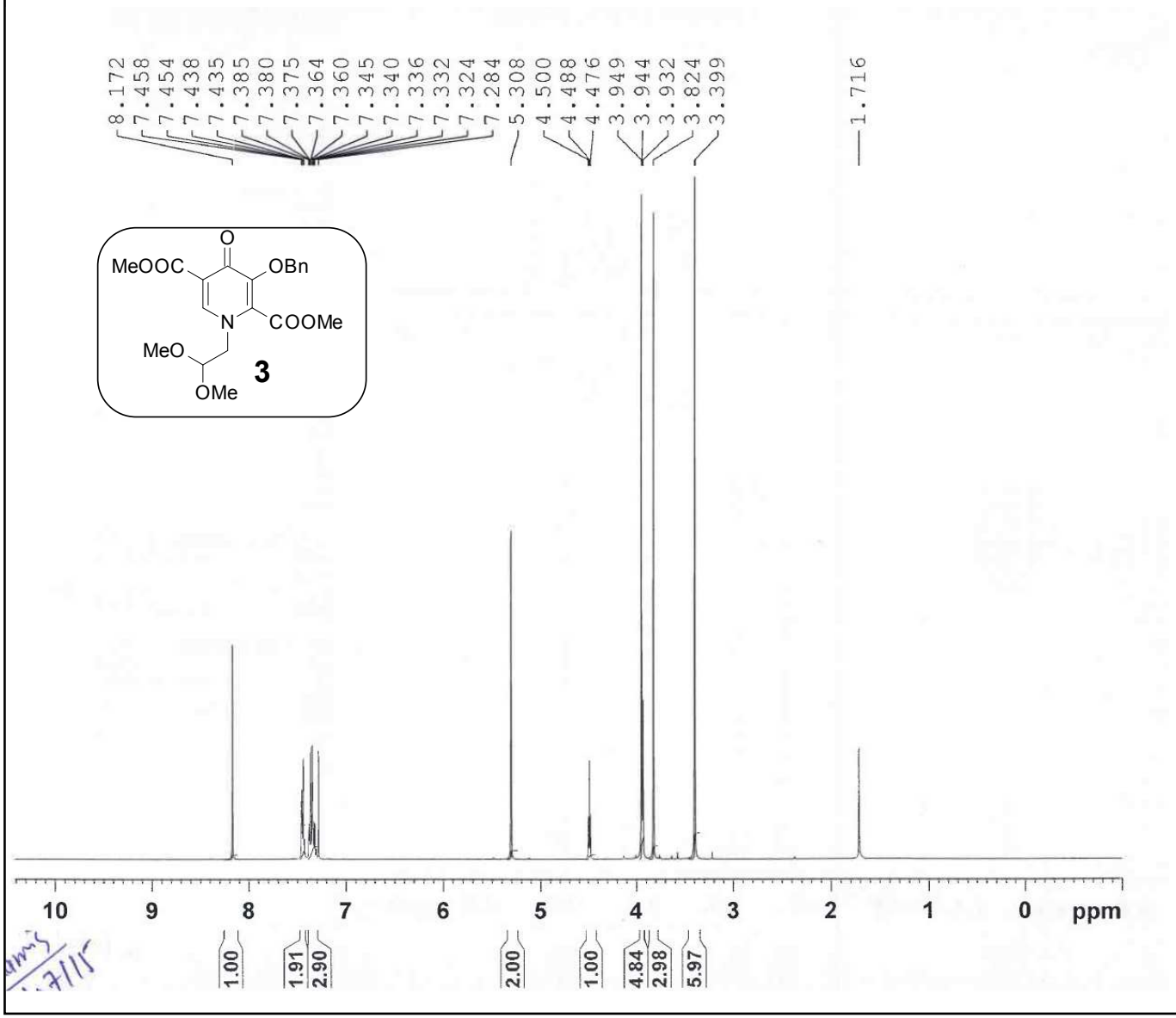


Figure-S3: C-NMR spectrum of intermediate-**3**

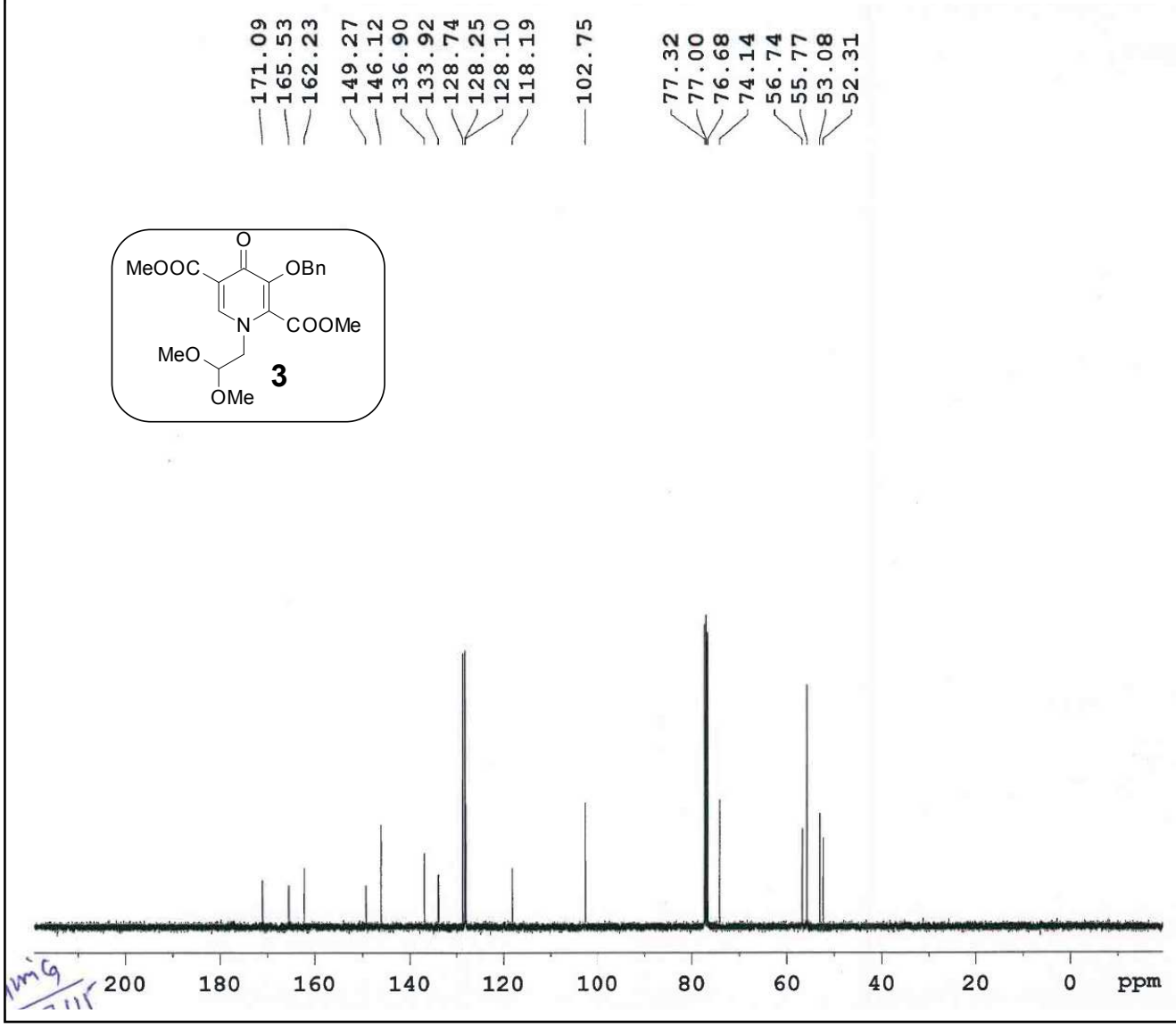


Figure-S4: ESI-MS spectrum of intermediate-**3**

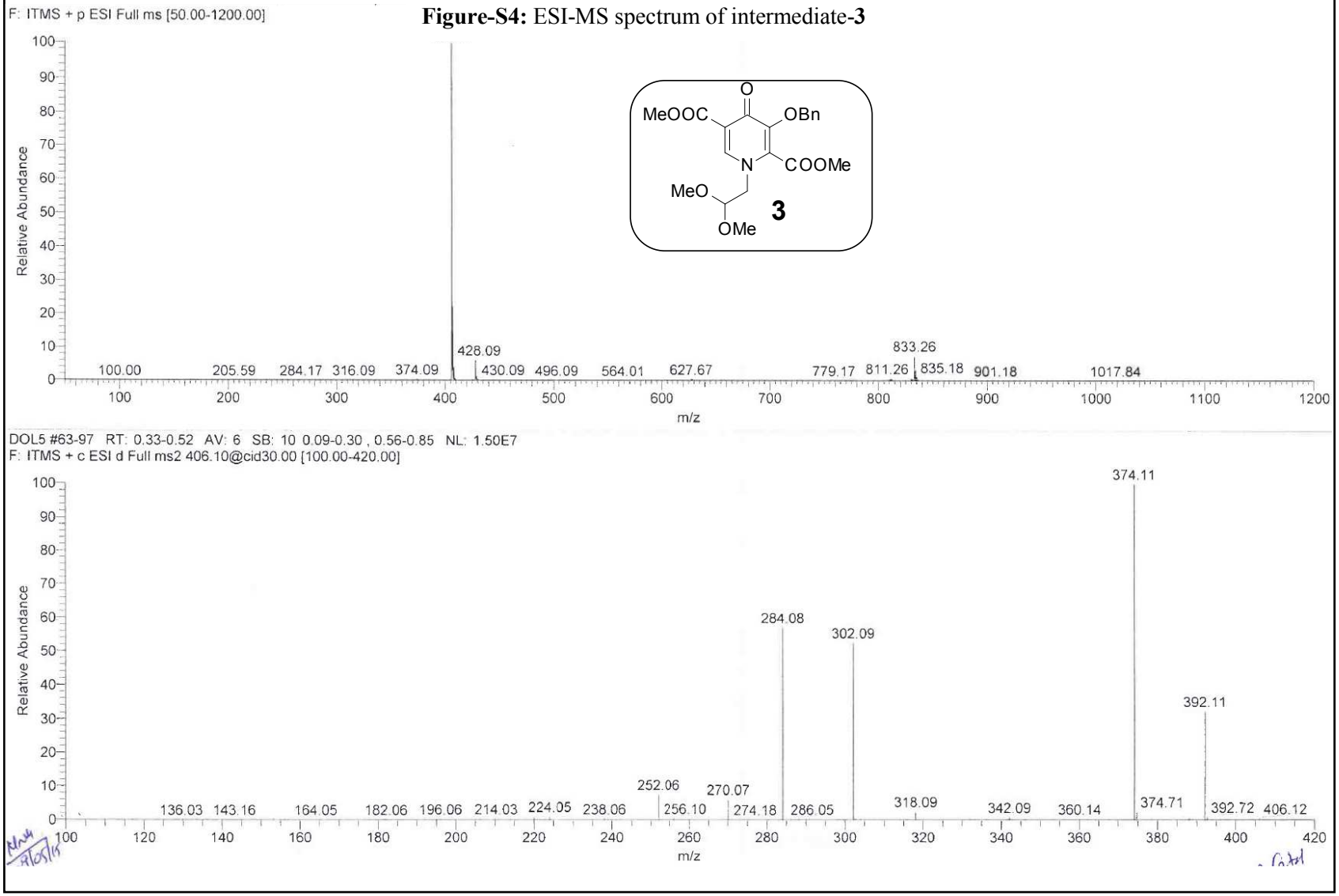
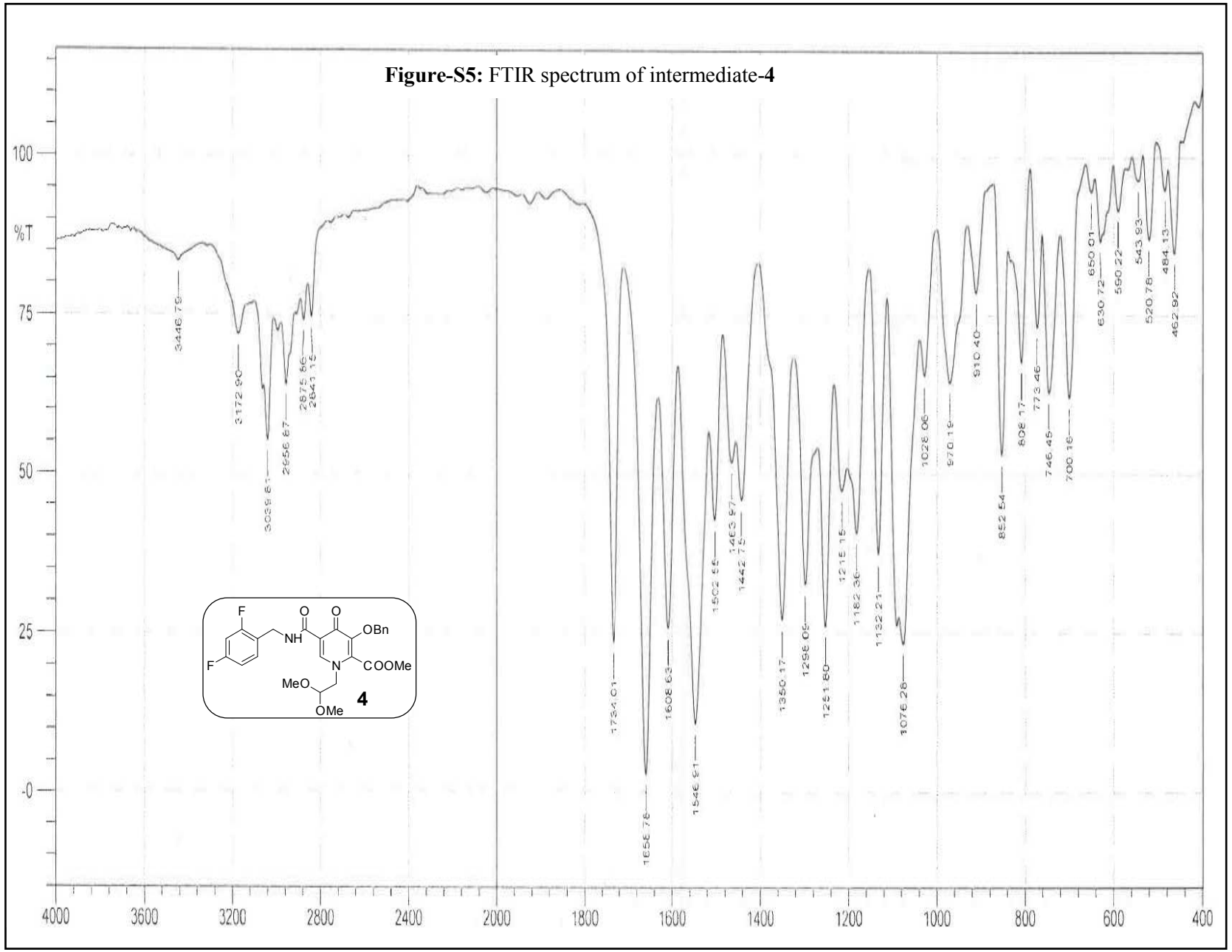


Figure-S5: FTIR spectrum of intermediate-**4**



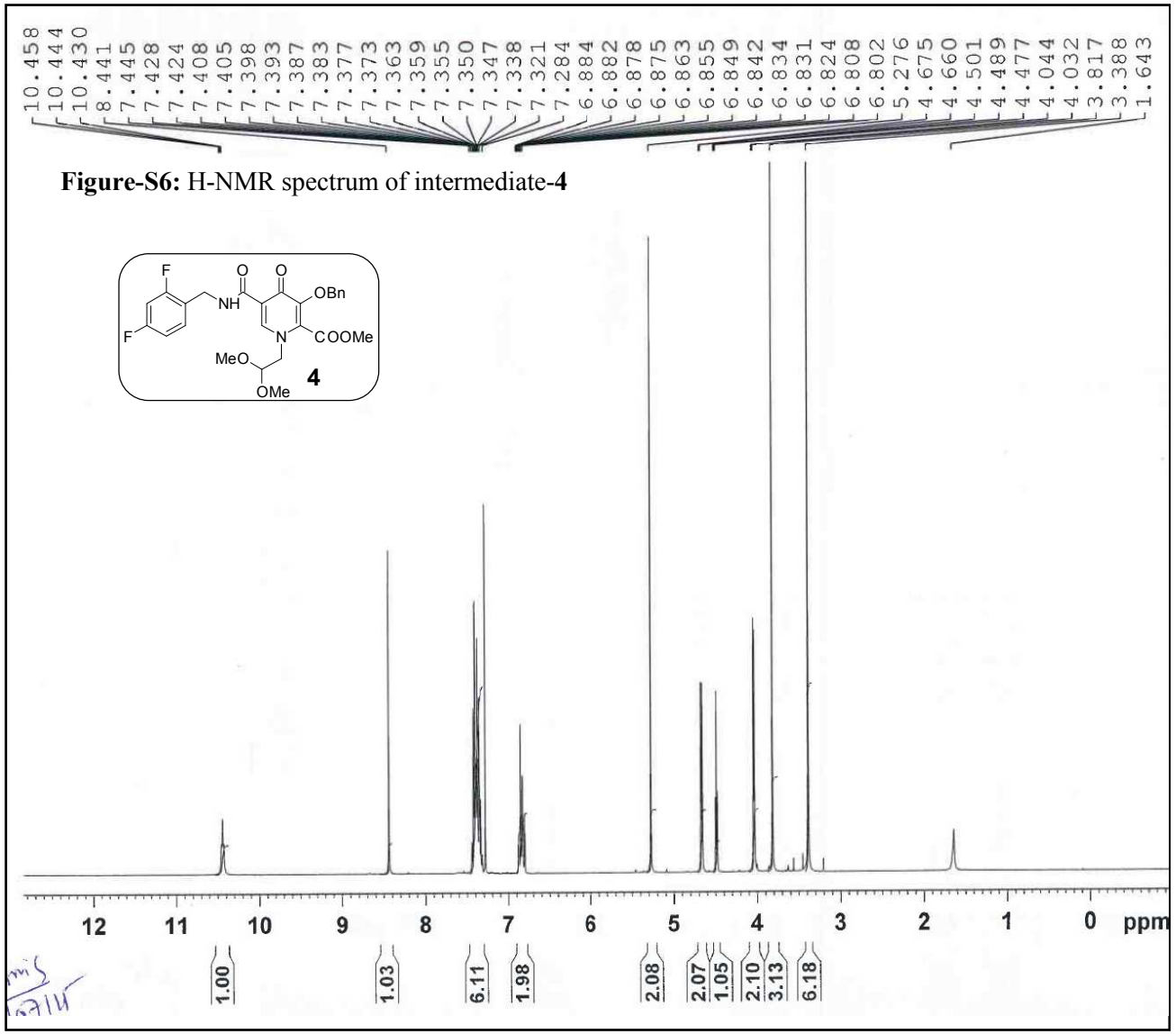


Figure-S6: H-NMR spectrum of intermediate-**4**

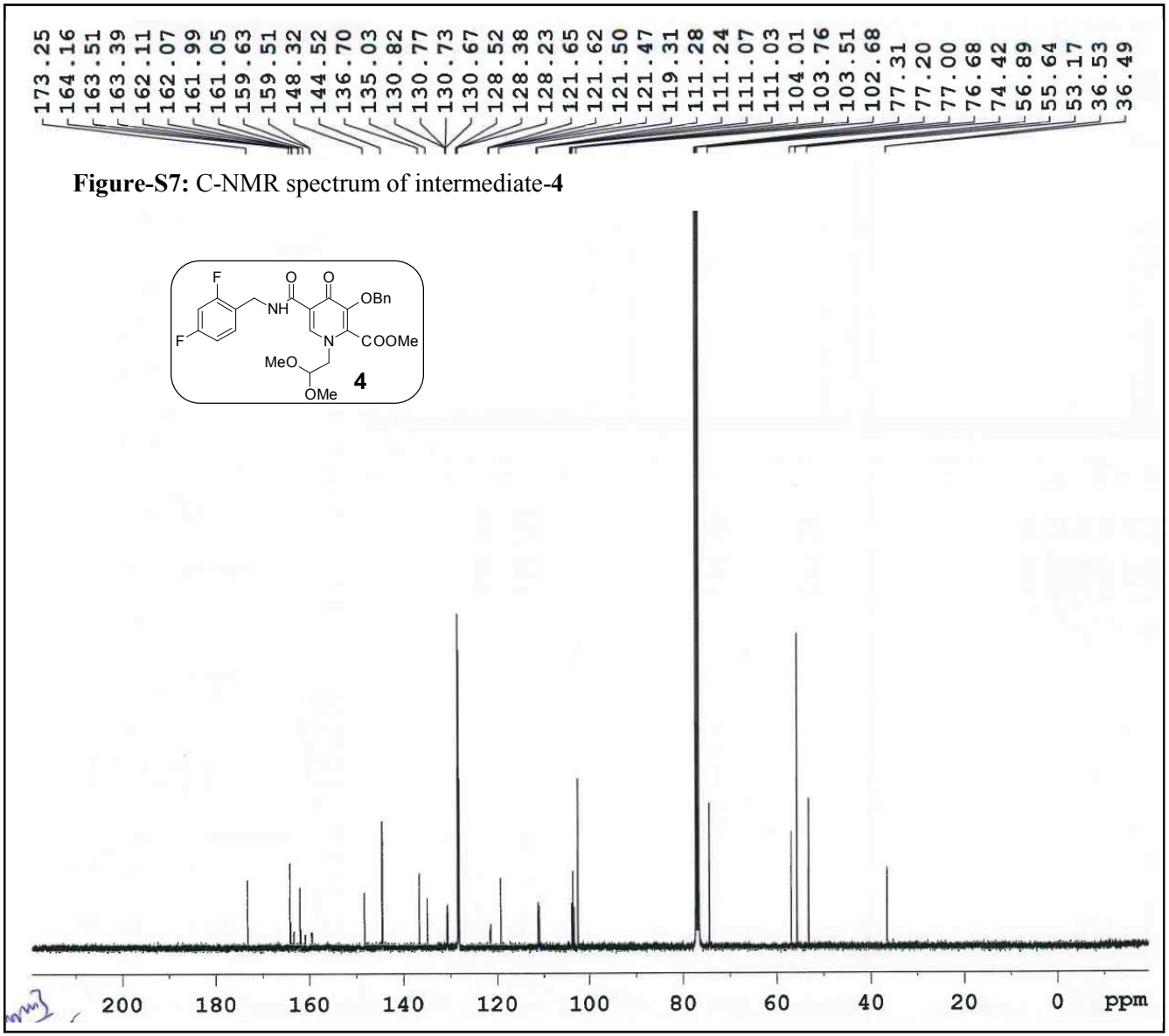


Figure-S7: C-NMR spectrum of intermediate-**4**

Figure-S8: ESI-MS spectrum of intermediate-**4**

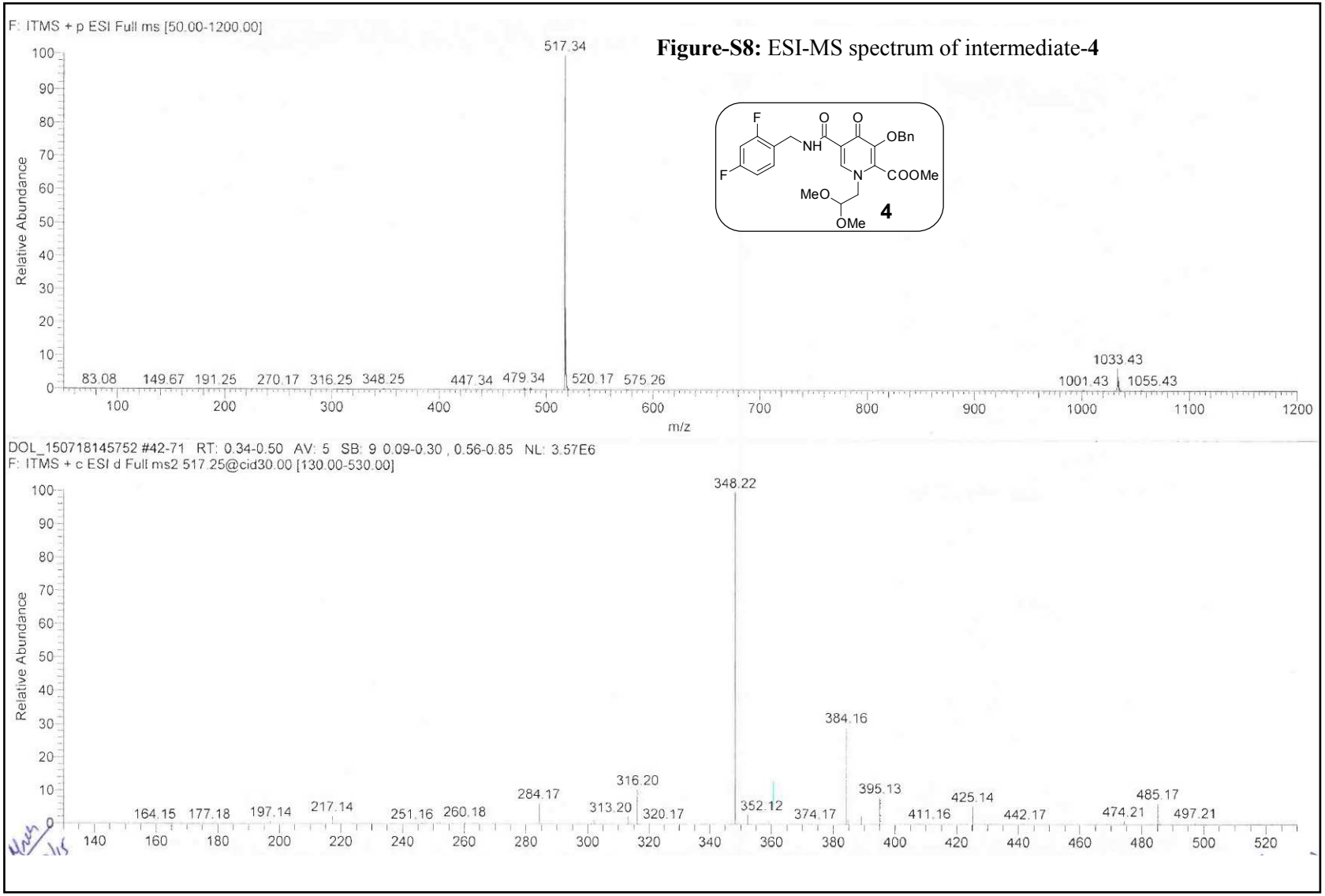
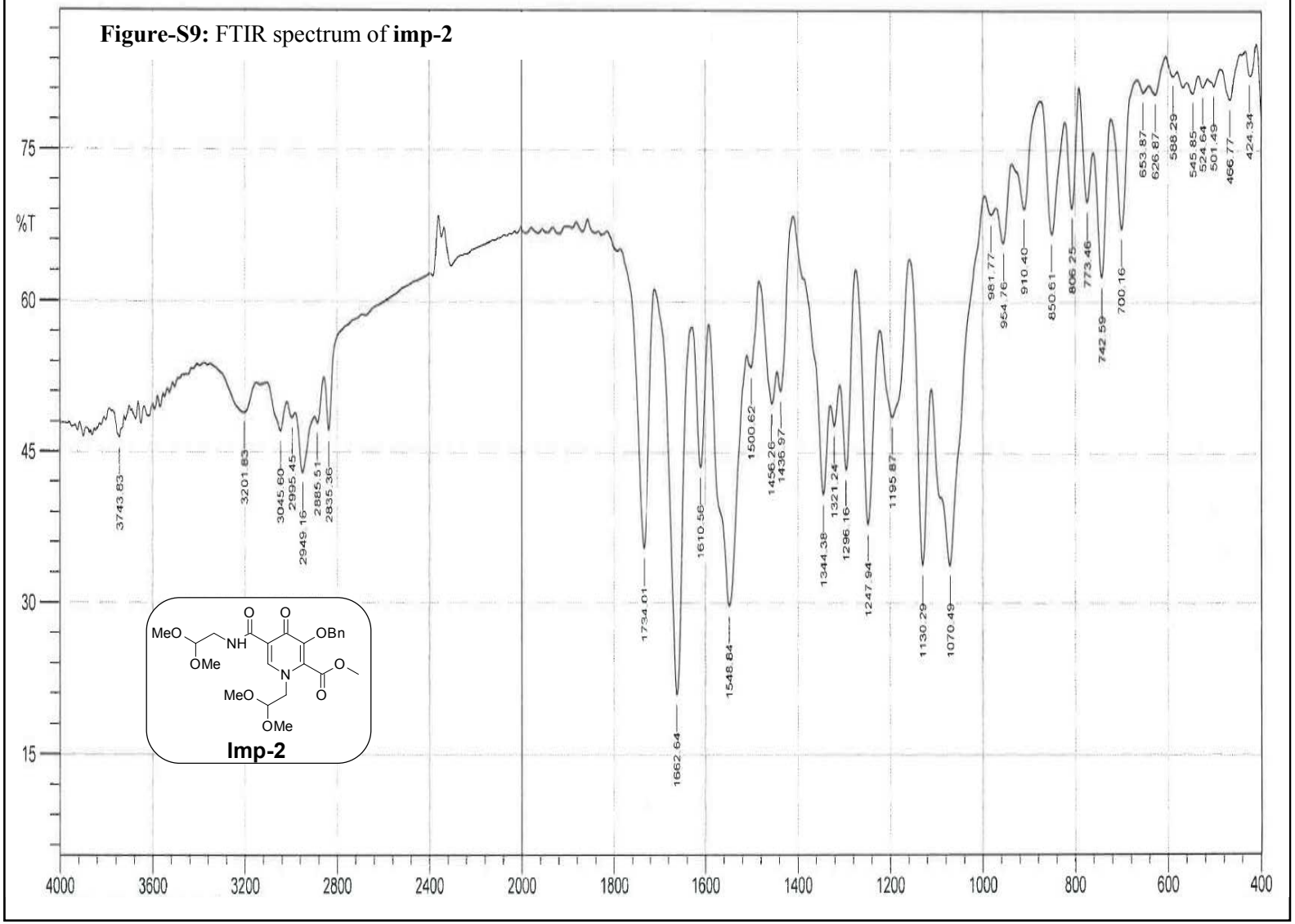


Figure-S9: FTIR spectrum of **imp-2**



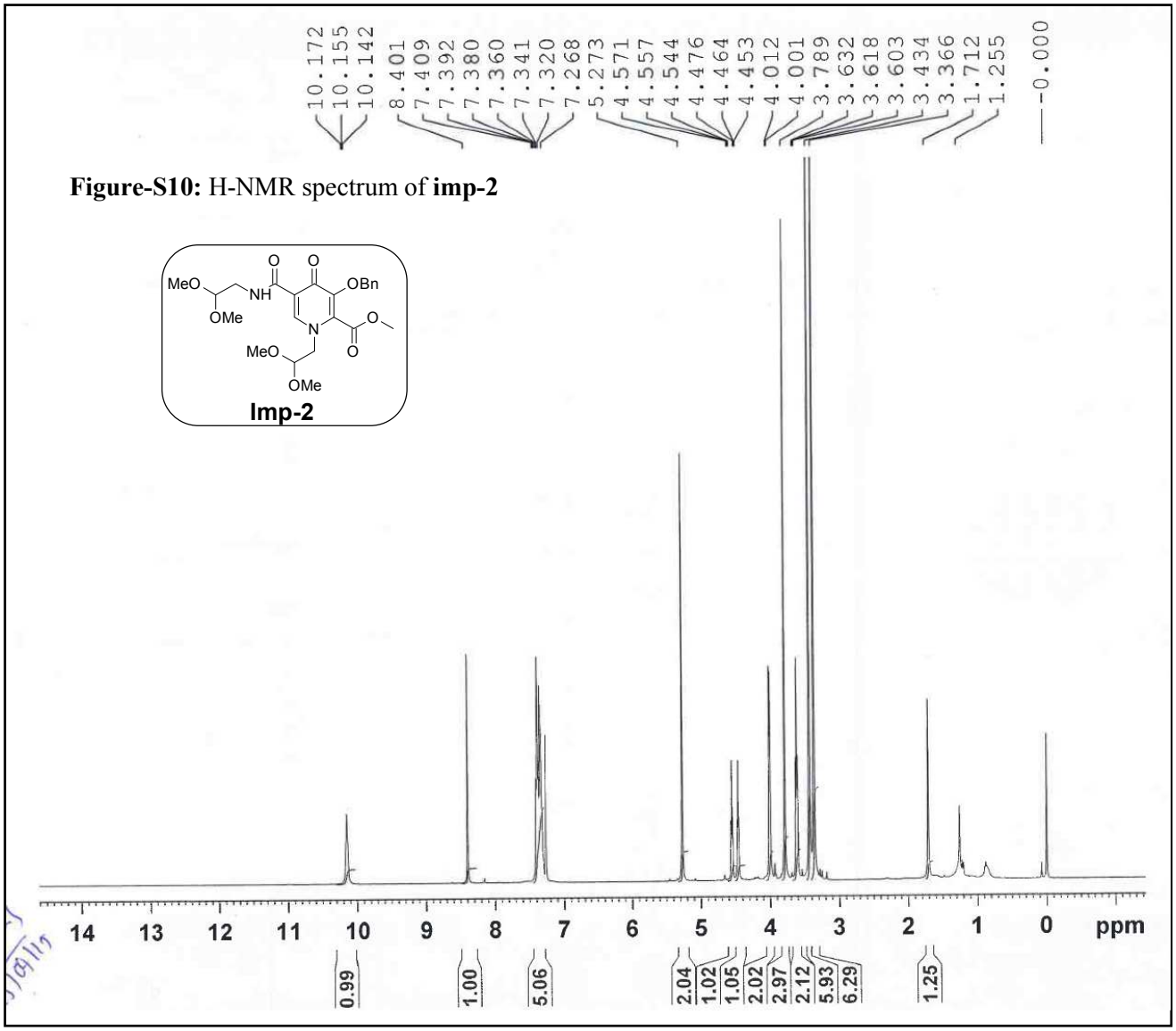


Figure-S10: H-NMR spectrum of **imp-2**

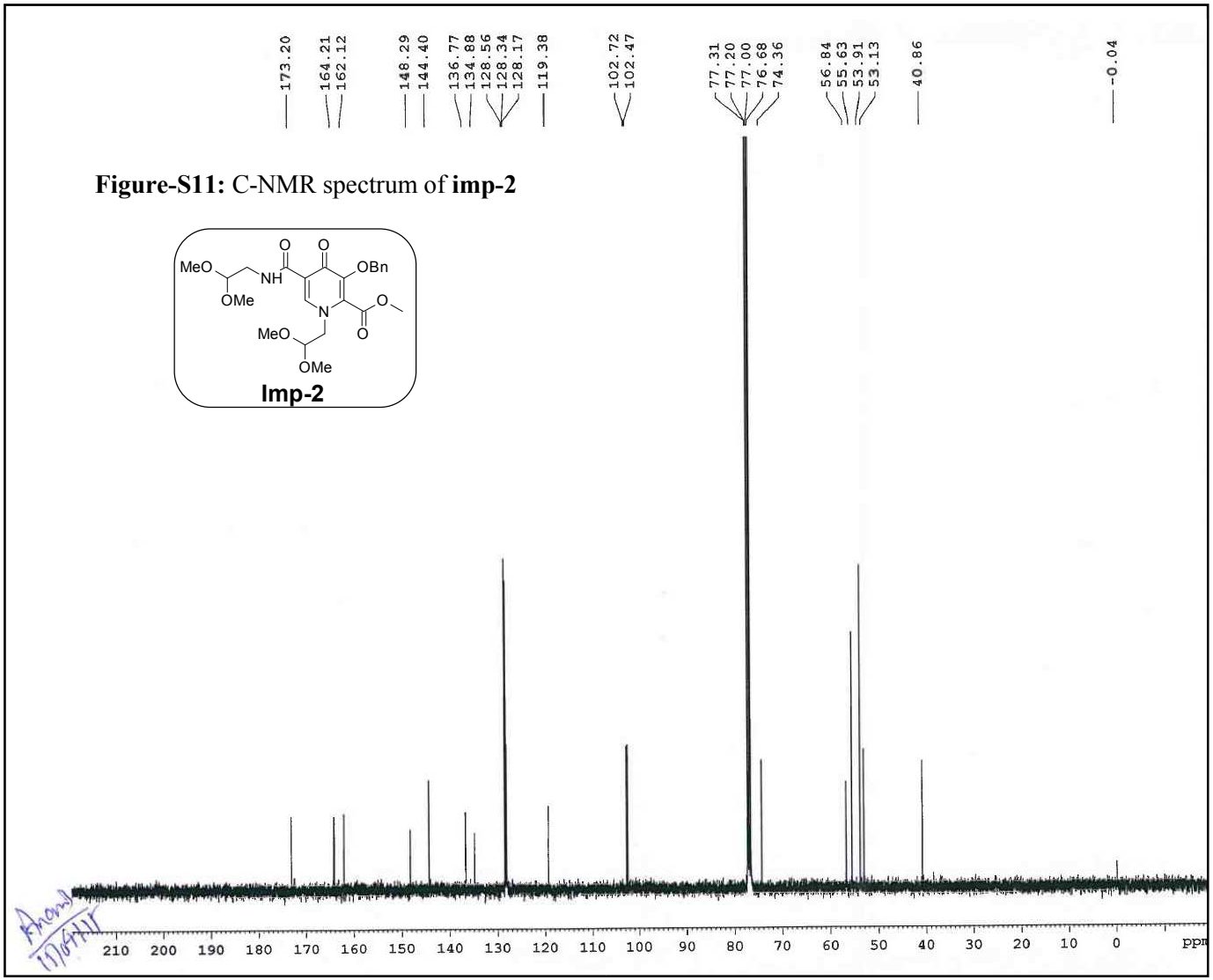


Figure-S11: C-NMR spectrum of **imp-2**

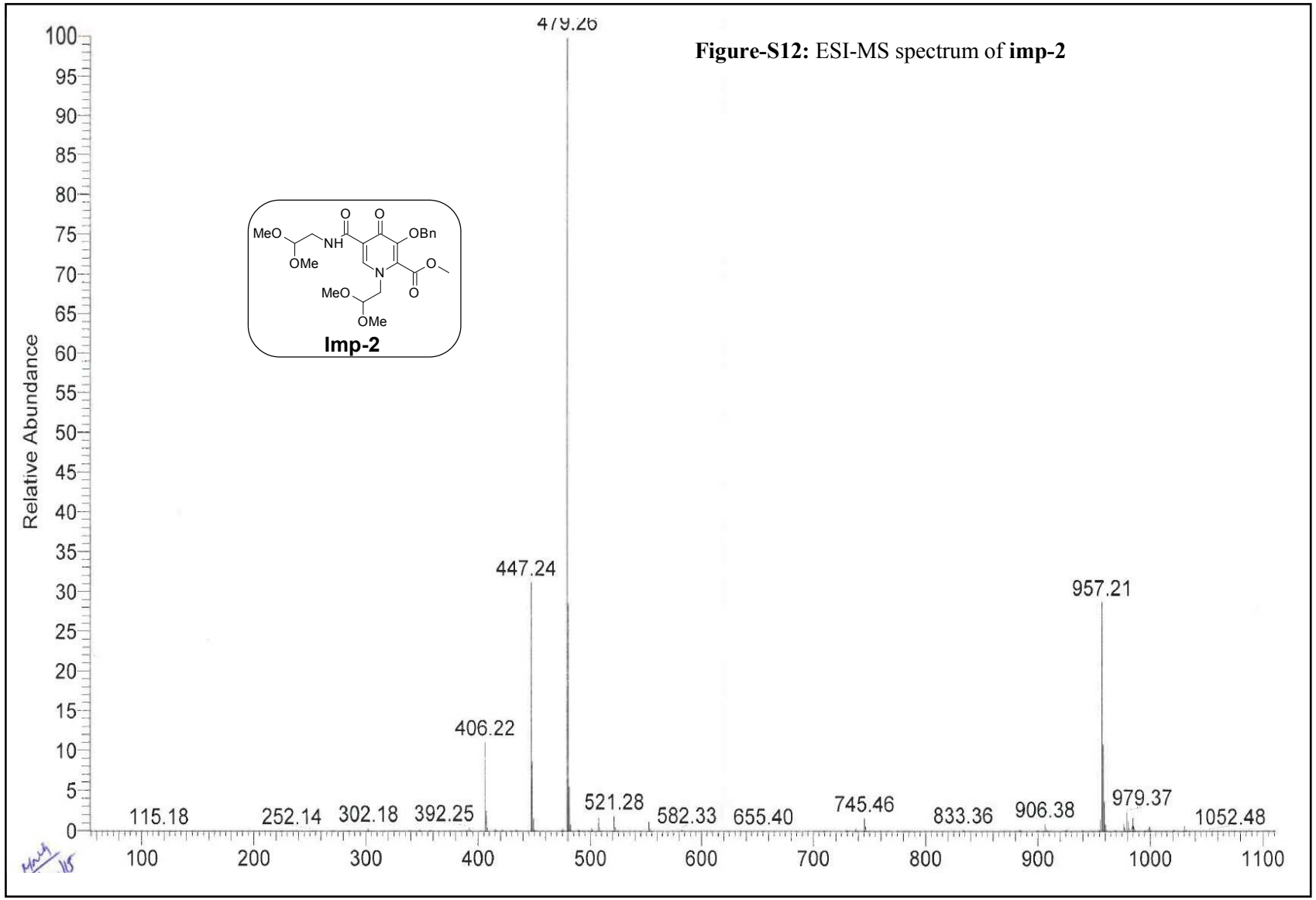


Figure-S12: ESI-MS spectrum of **imp-2**

Figure-S13: FTIR spectrum of **imp-1**

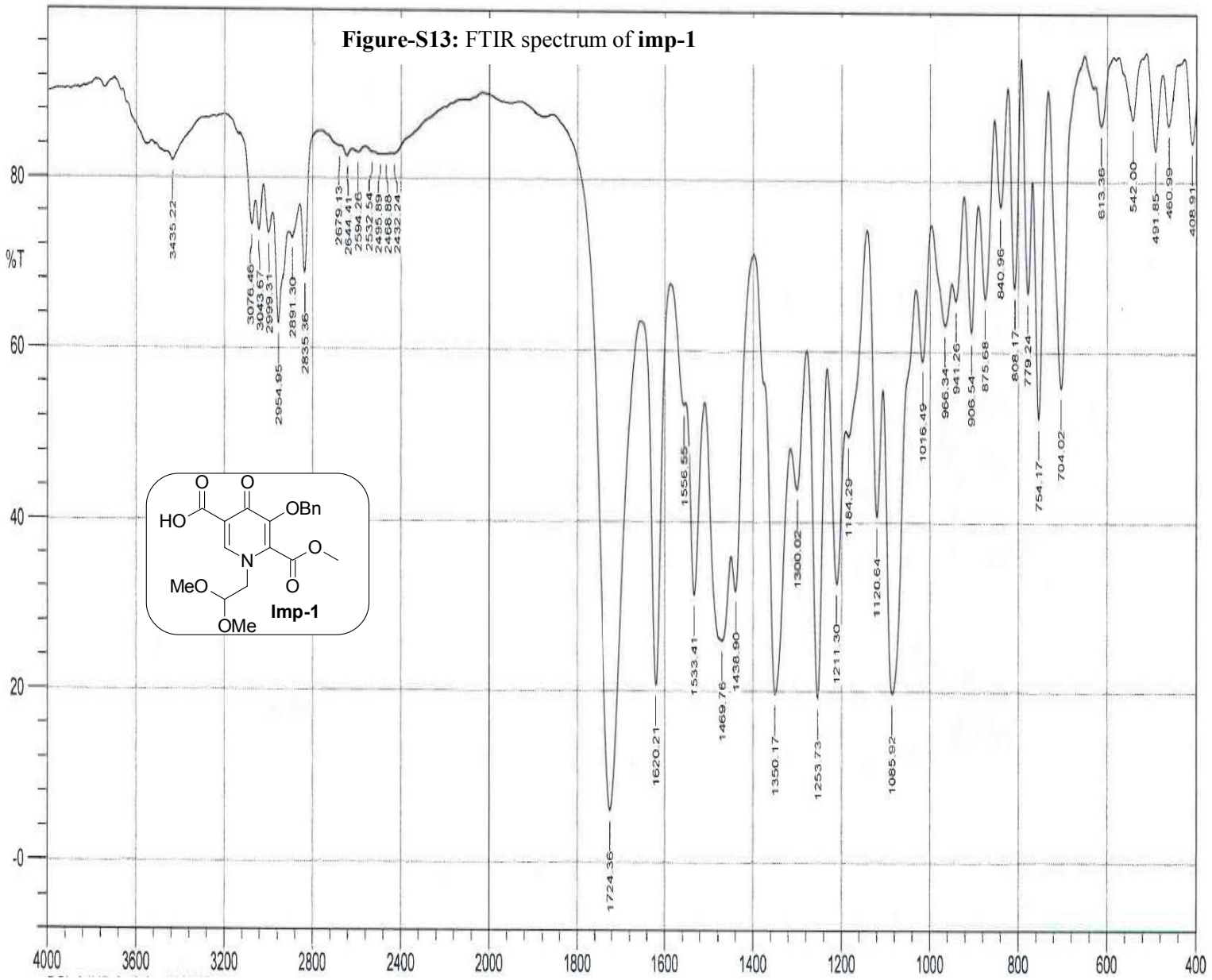
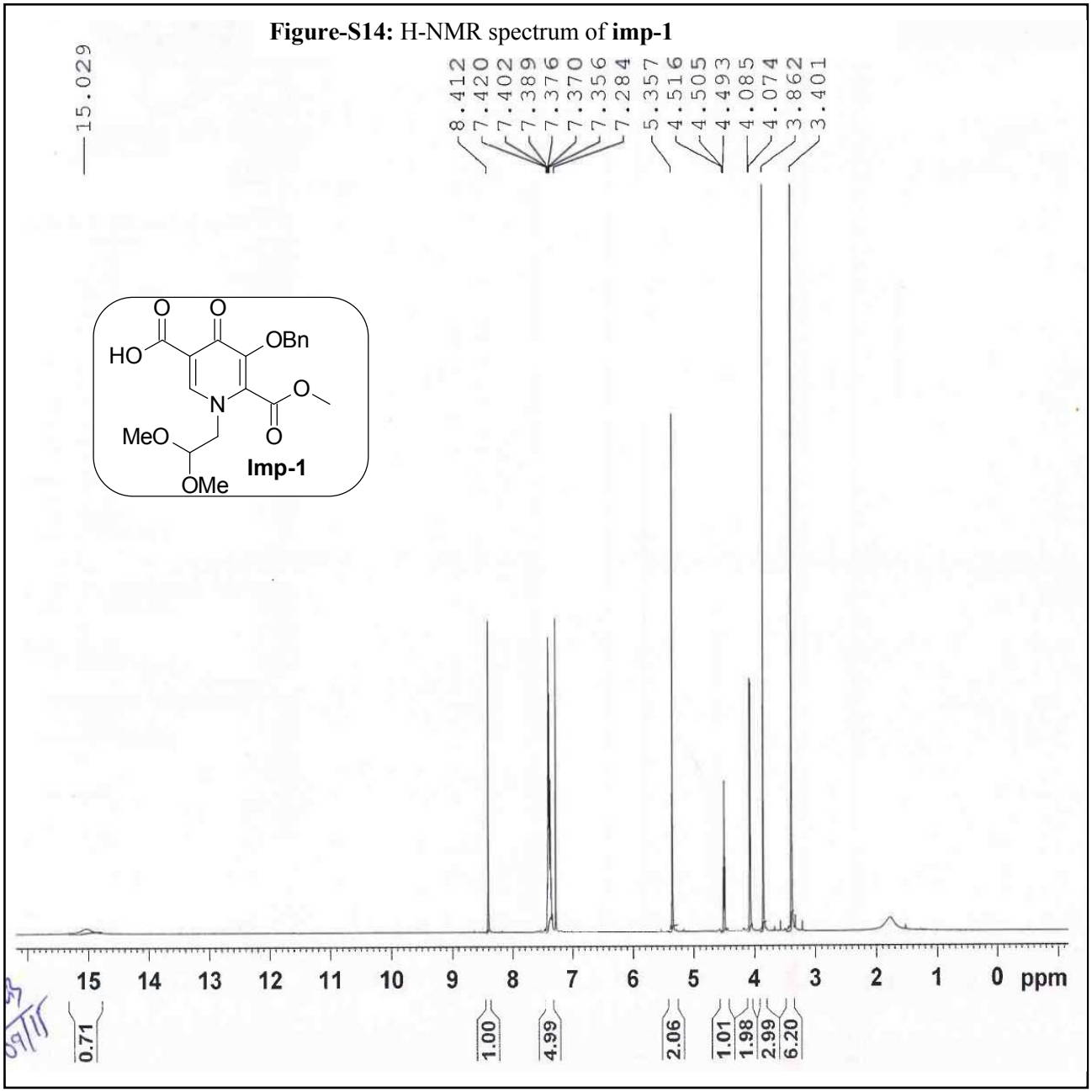


Figure-S14: H-NMR spectrum of **imp-1**



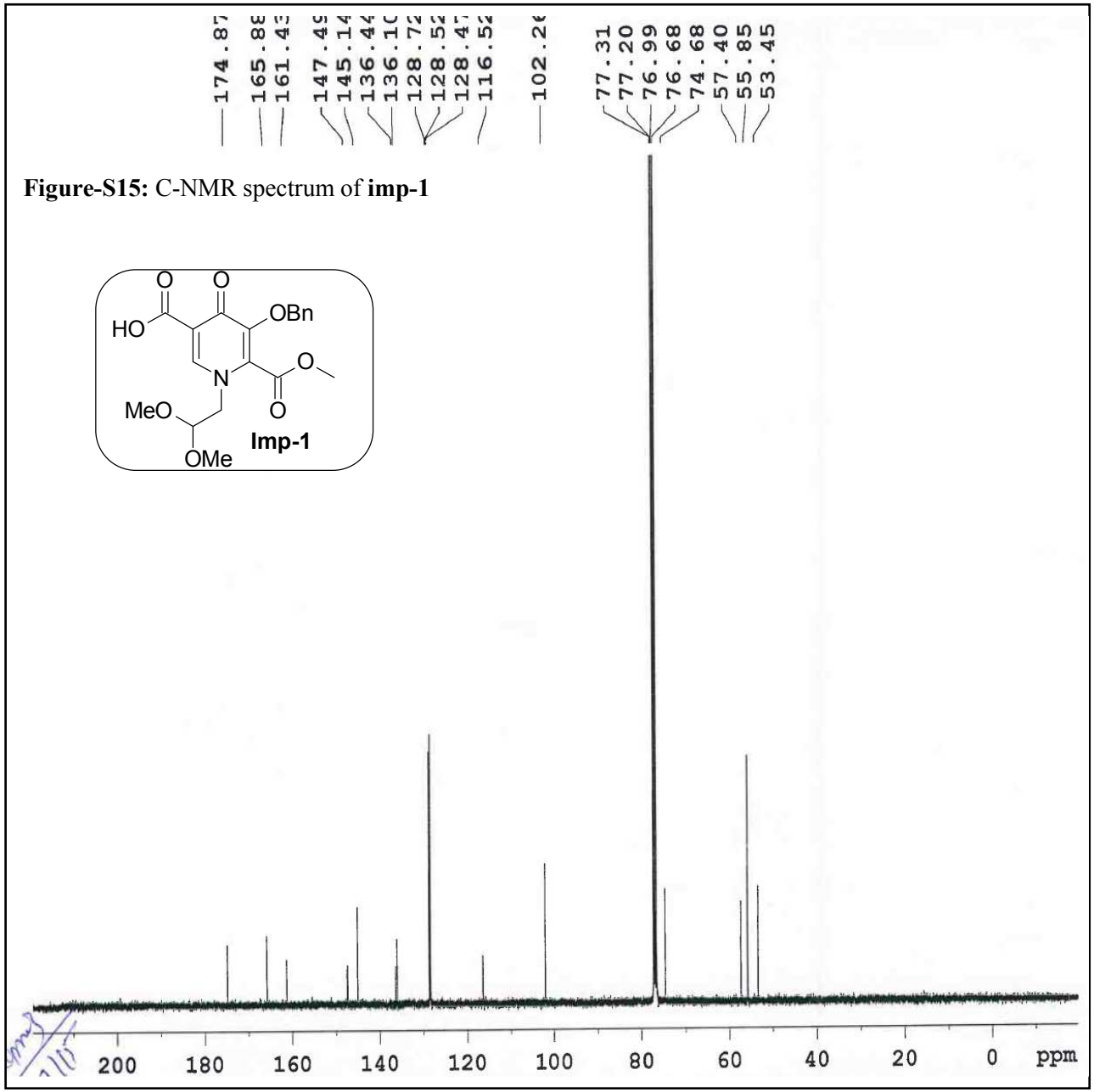


Figure-S15: C-NMR spectrum of **imp-1**

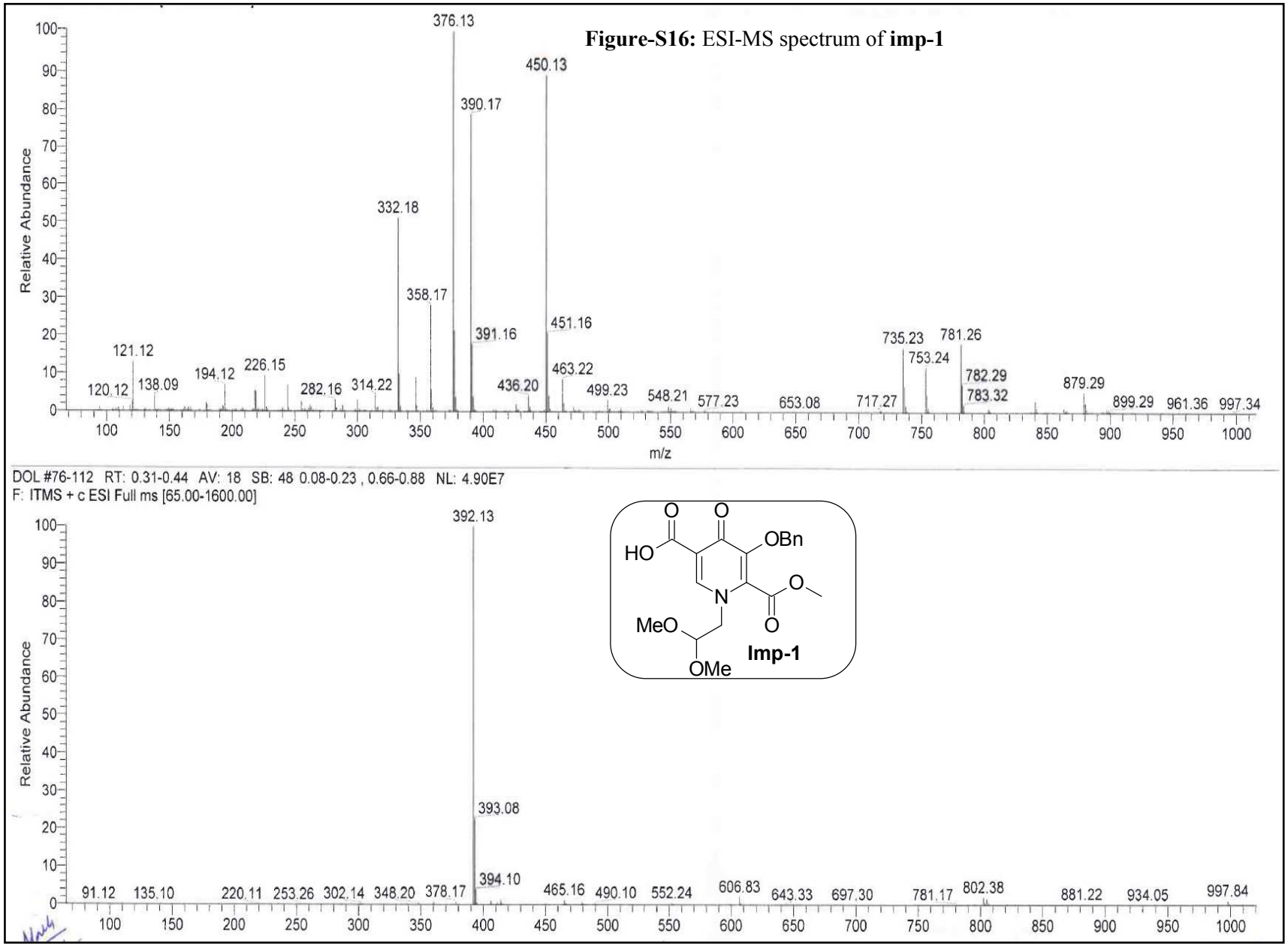


Figure-S16: ESI-MS spectrum of **imp-1**

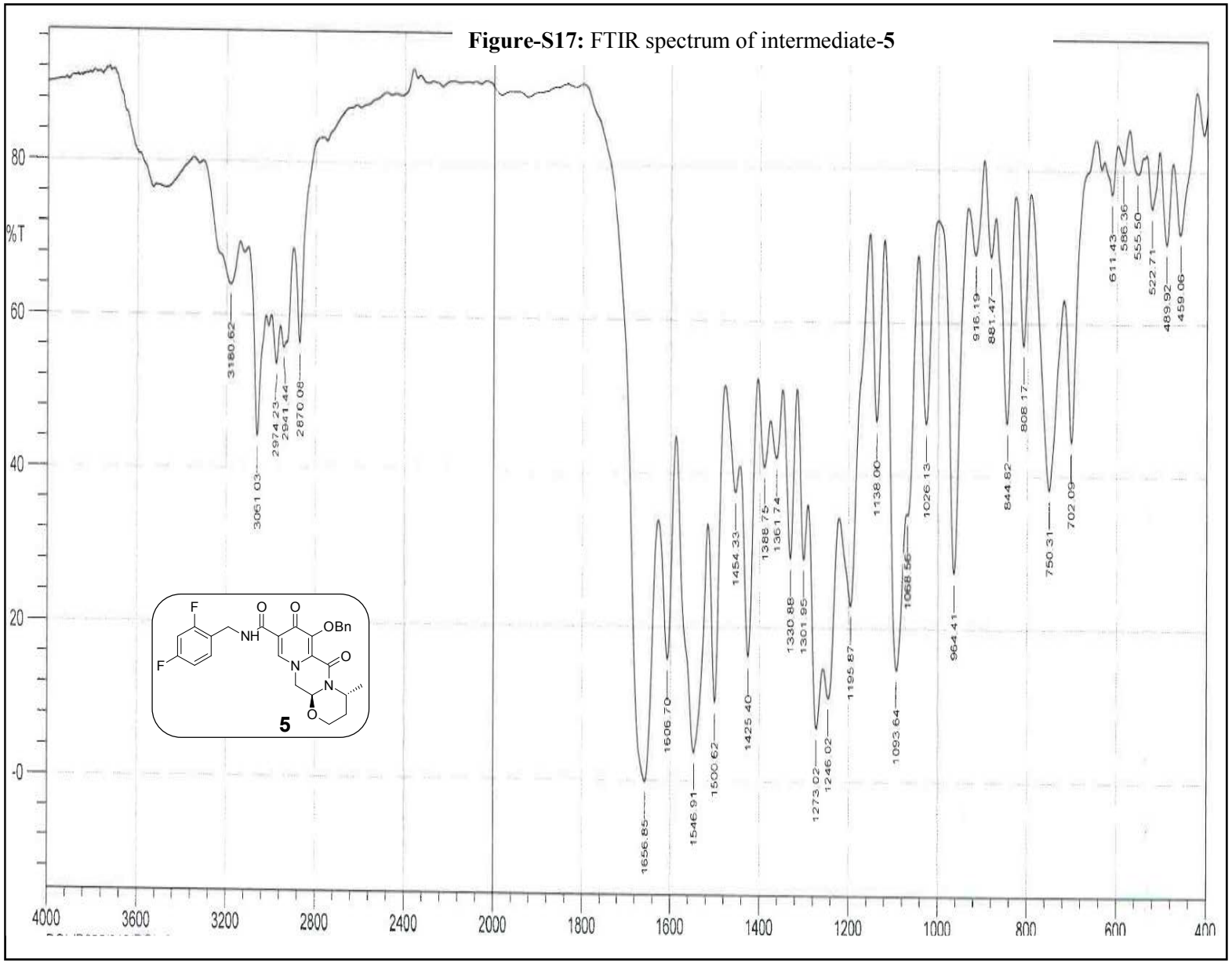


Figure-S17: FTIR spectrum of intermediate-**5**

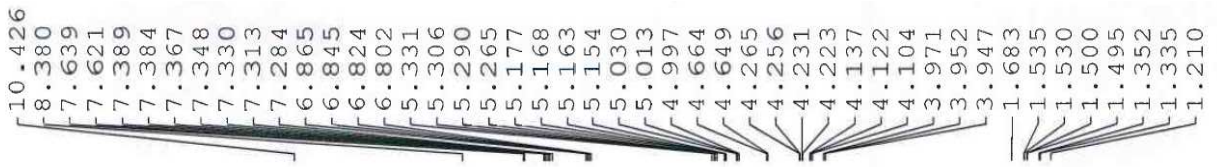
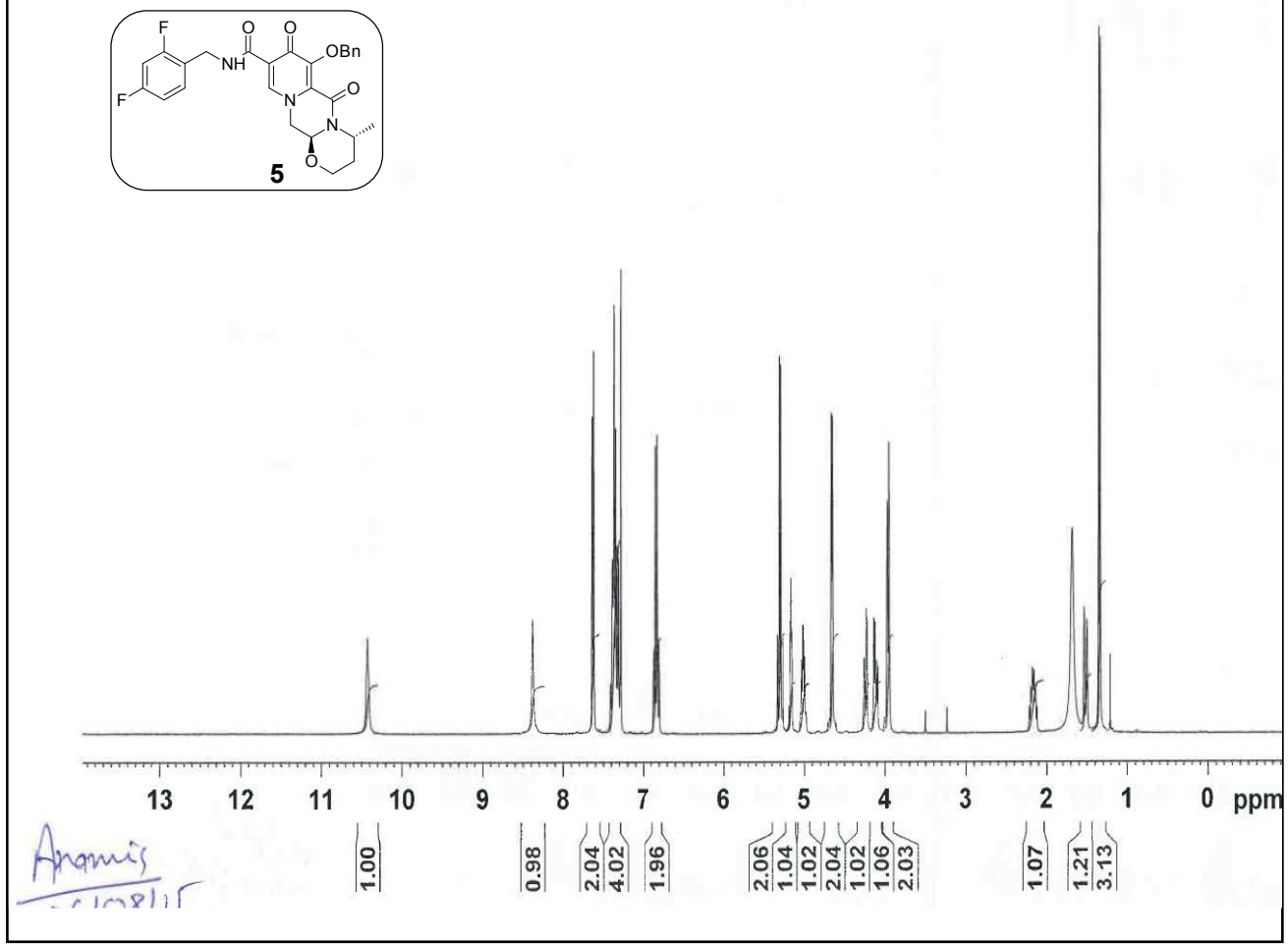


Figure-S18: H-NMR spectrum of intermediate-**5**



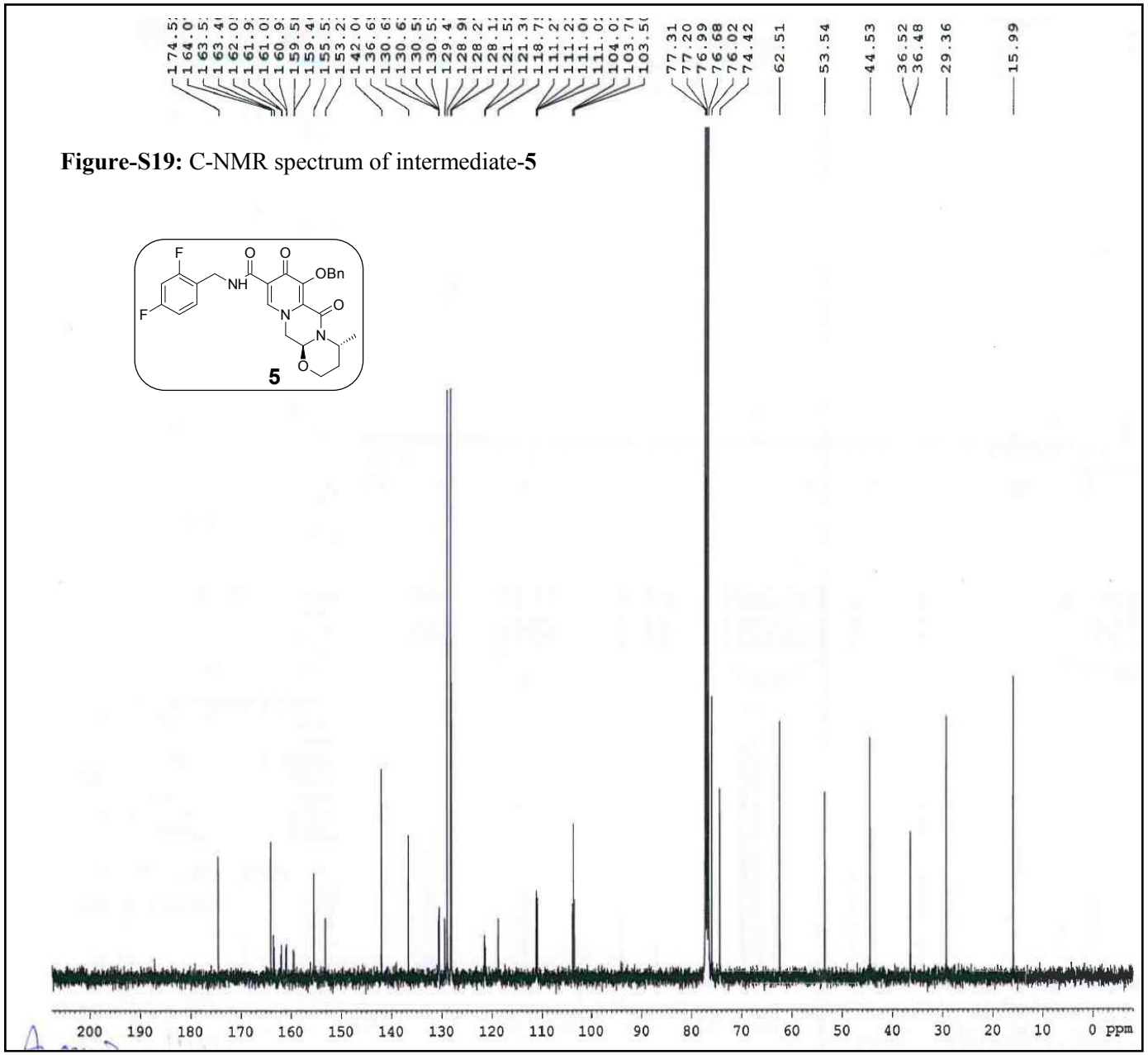


Figure-S19: C-NMR spectrum of intermediate-**5**

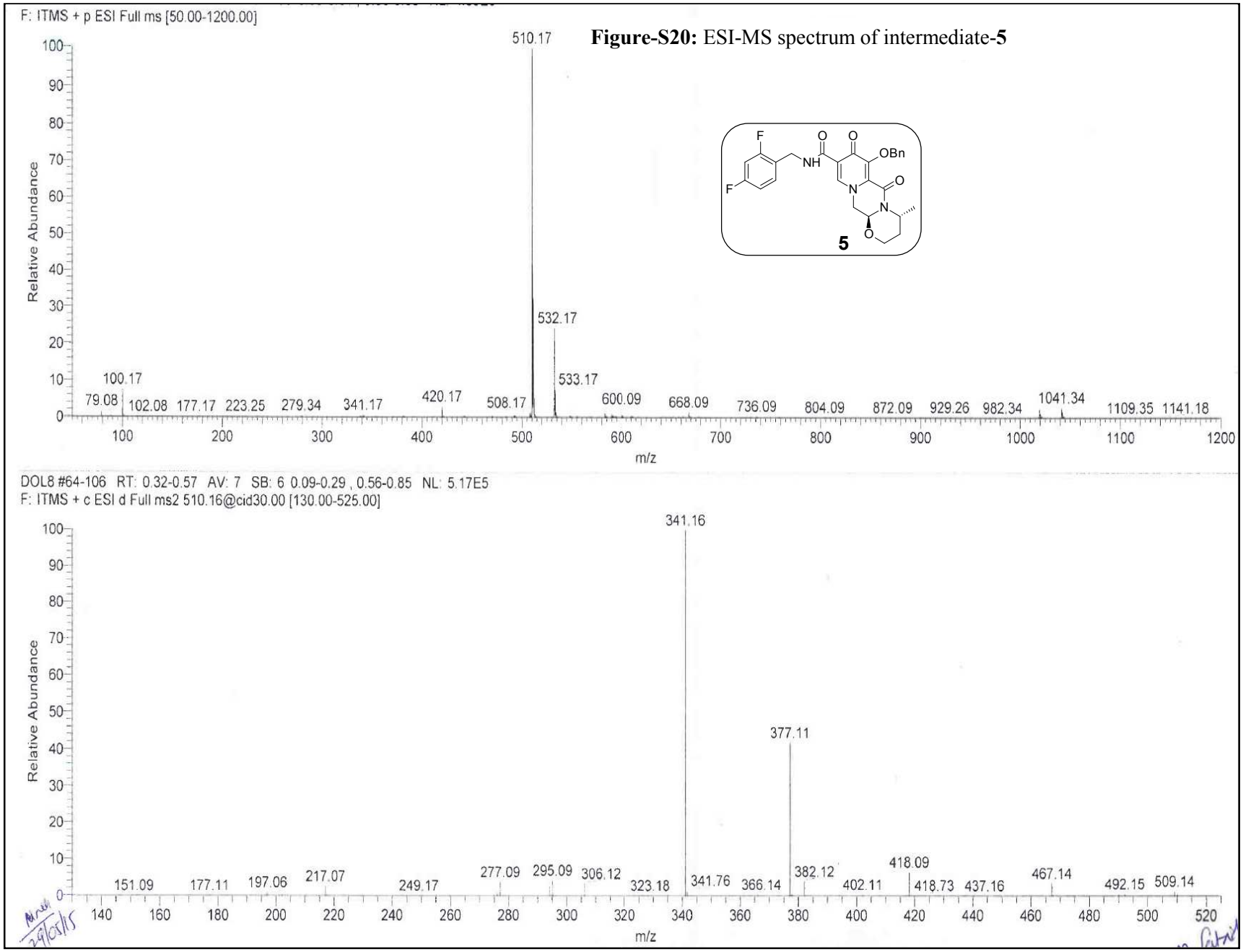
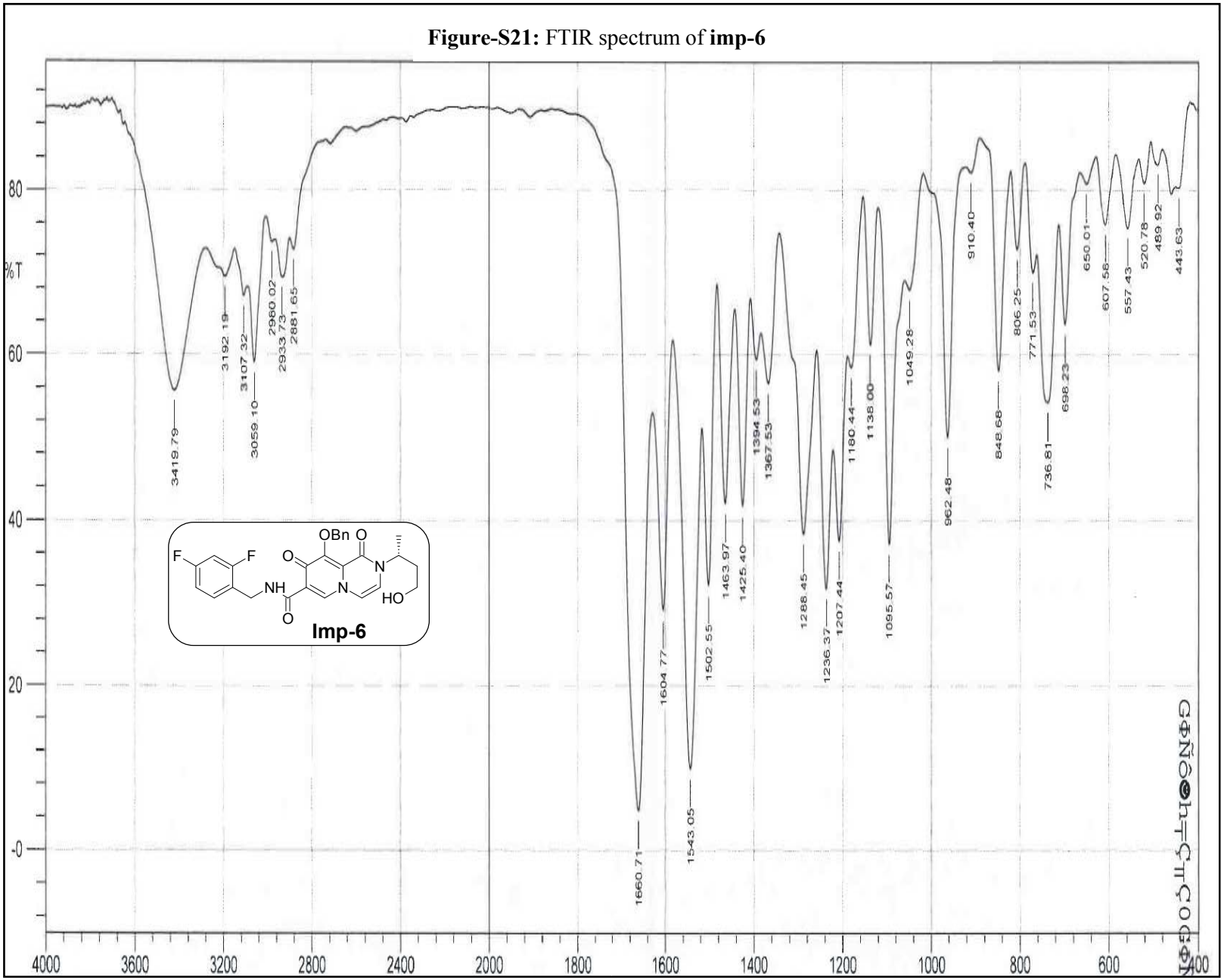


Figure-S20: ESI-MS spectrum of intermediate-**5**

Figure-S21: FTIR spectrum of **imp-6**



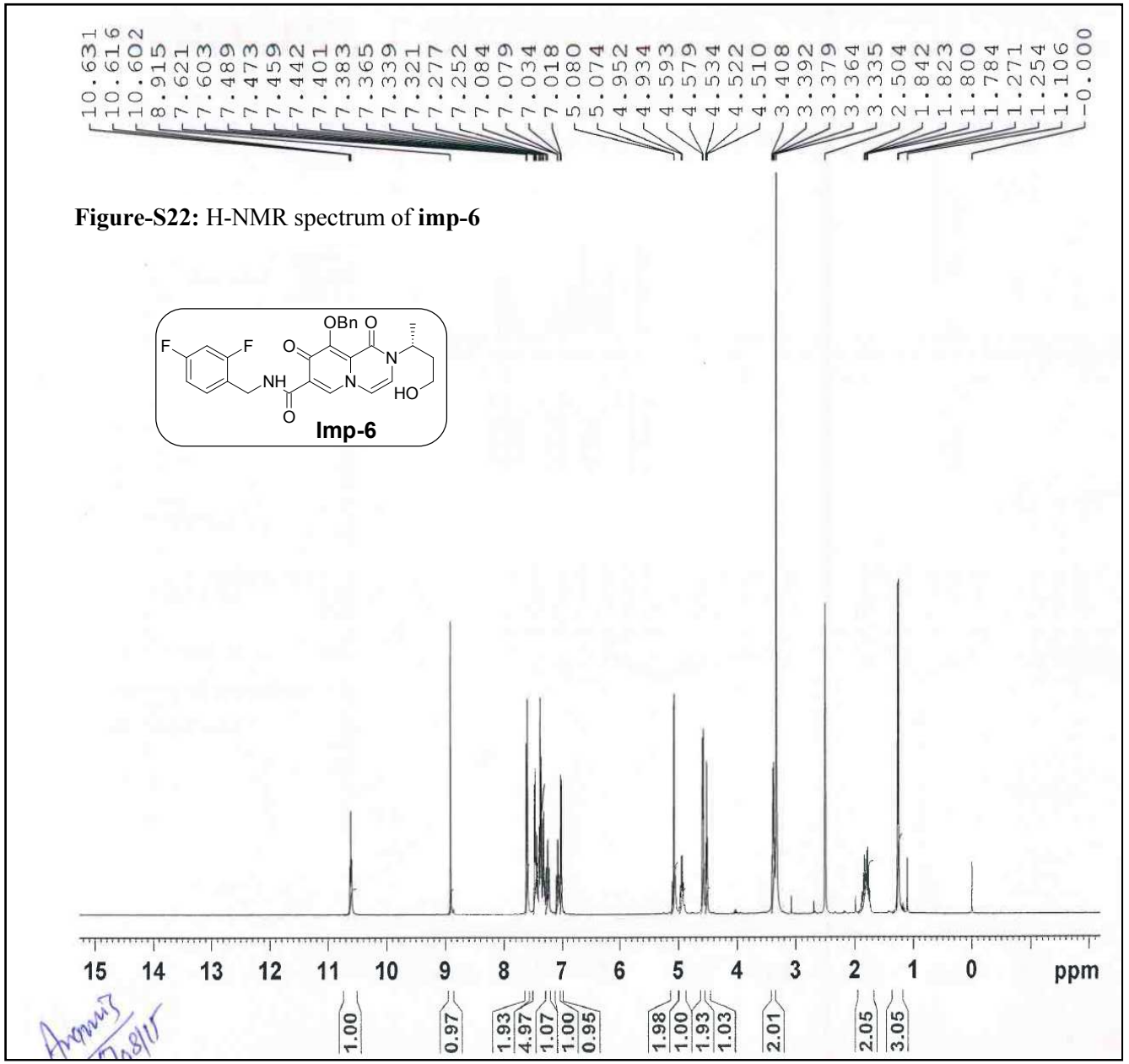


Figure-S22: H-NMR spectrum of **imp-6**

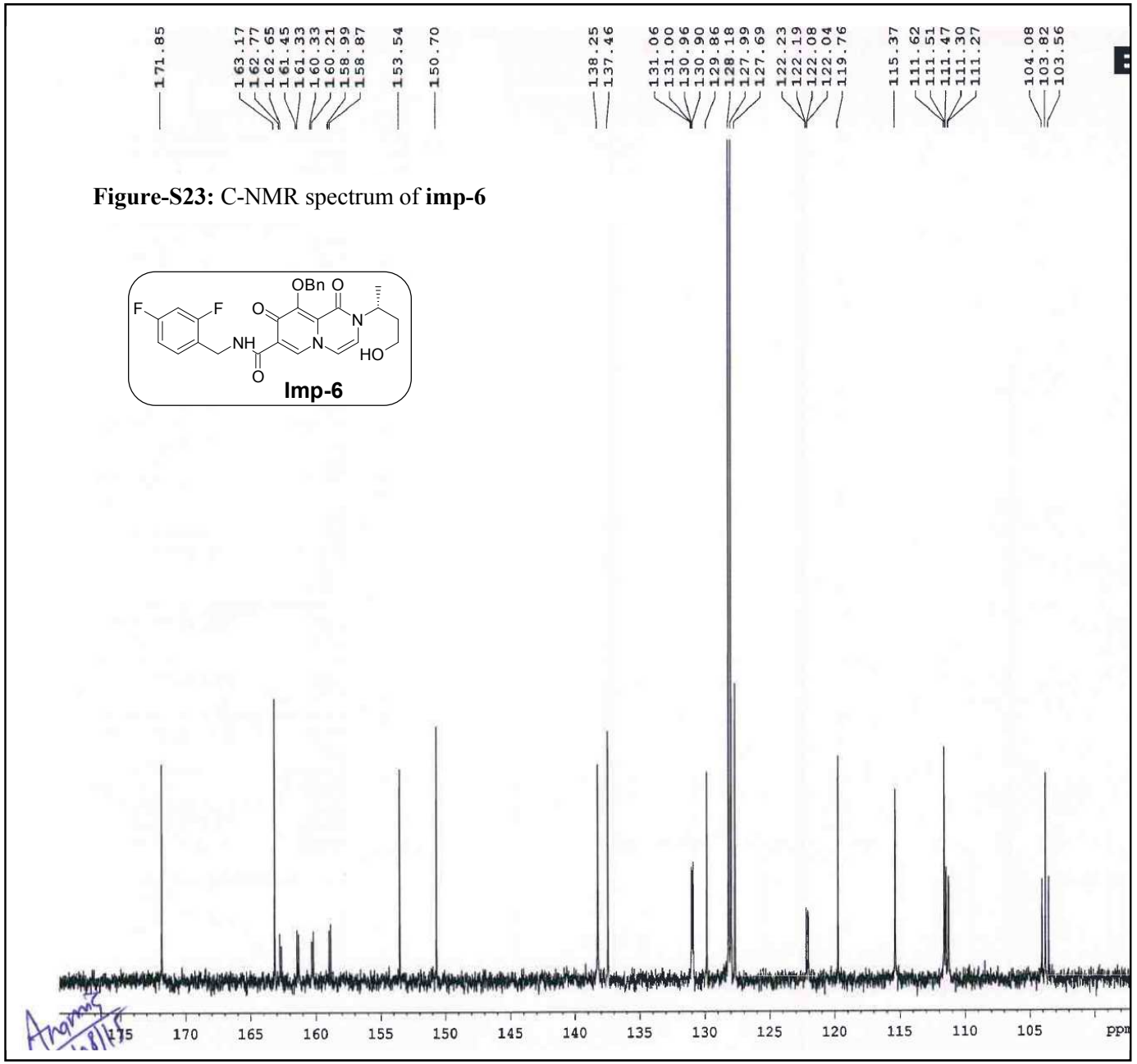


Figure-S23: C-NMR spectrum of **imp-6**

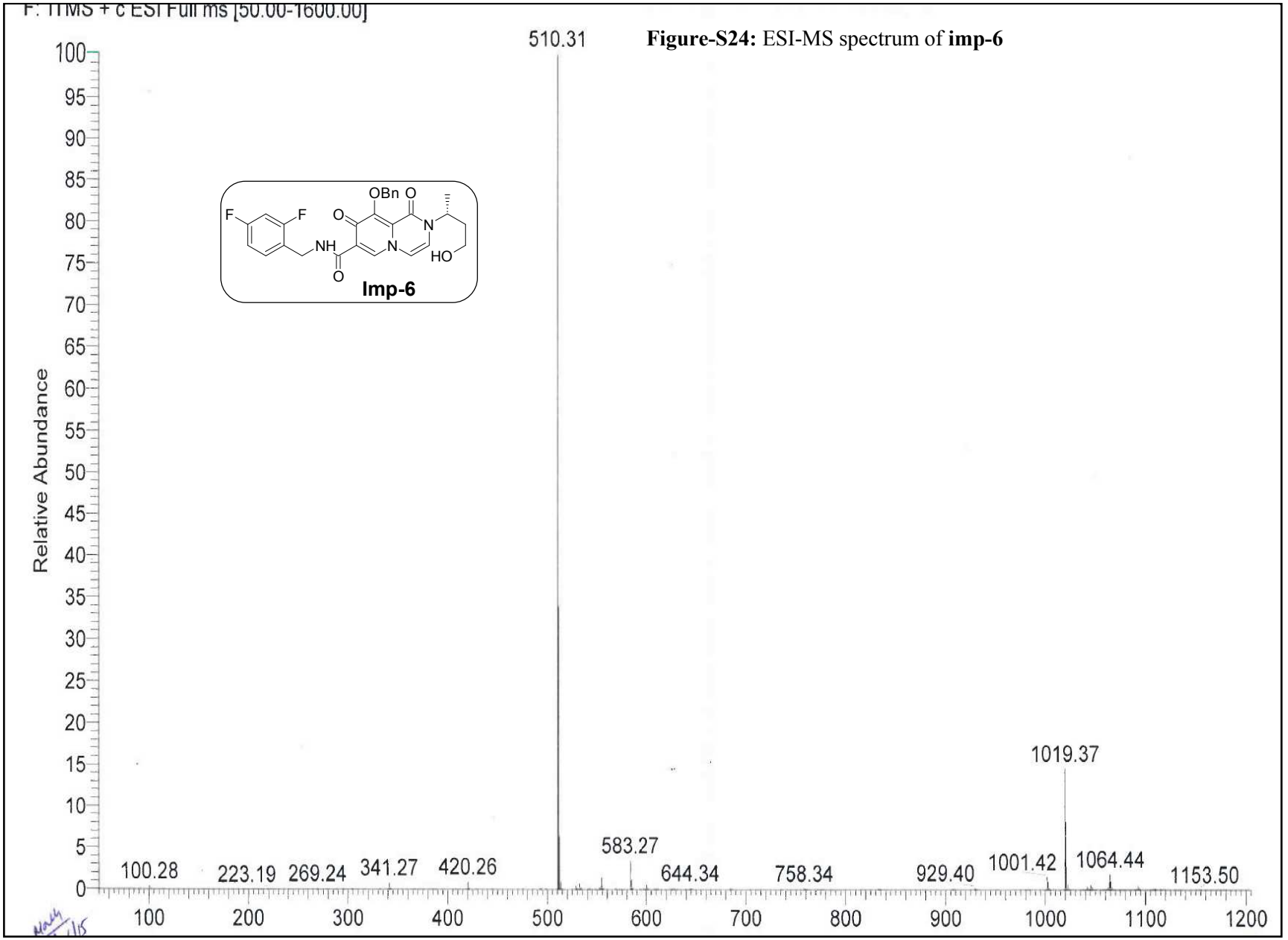
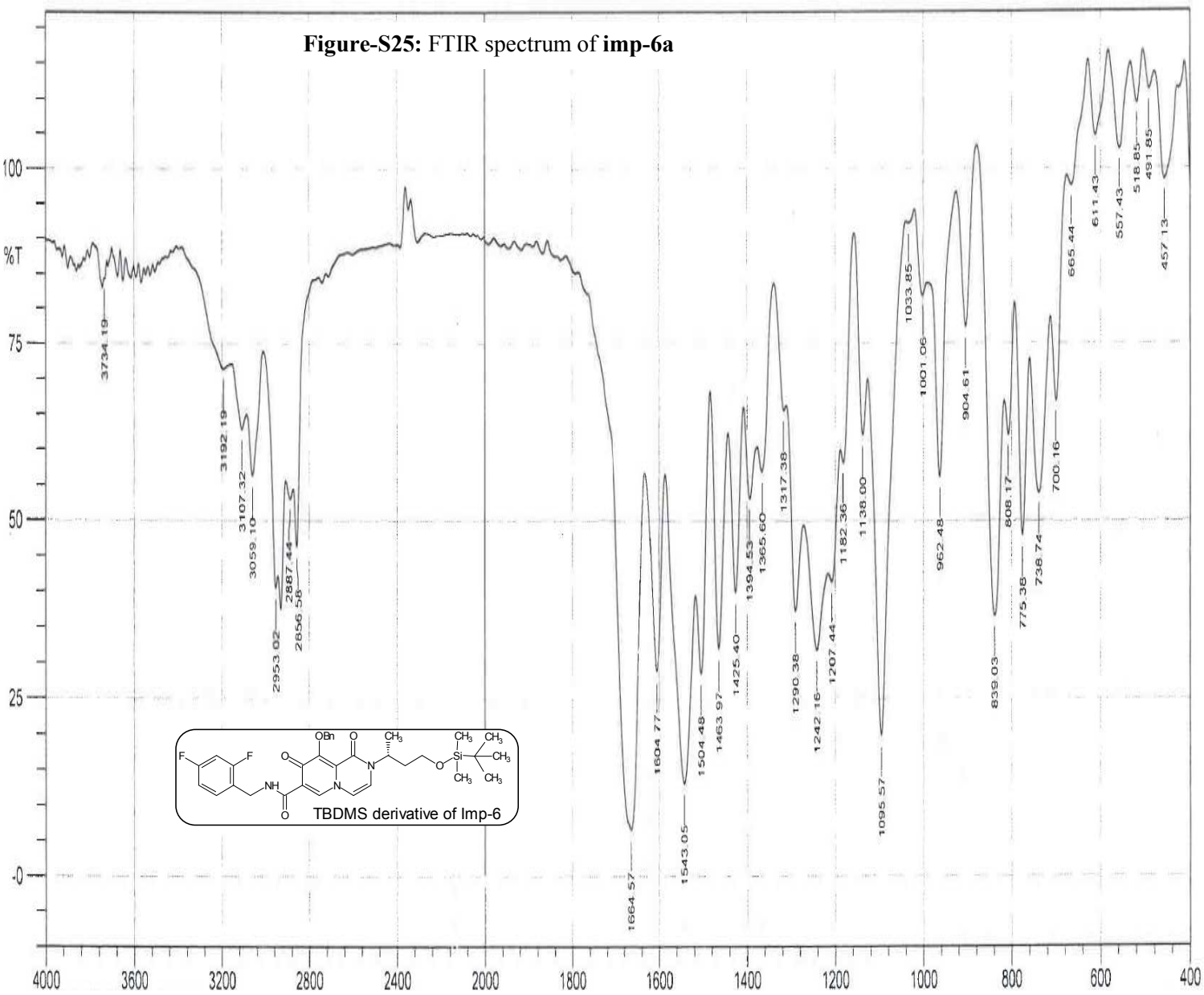


Figure-S24: ESI-MS spectrum of **imp-6**

Figure-S25: FTIR spectrum of **imp-6a**



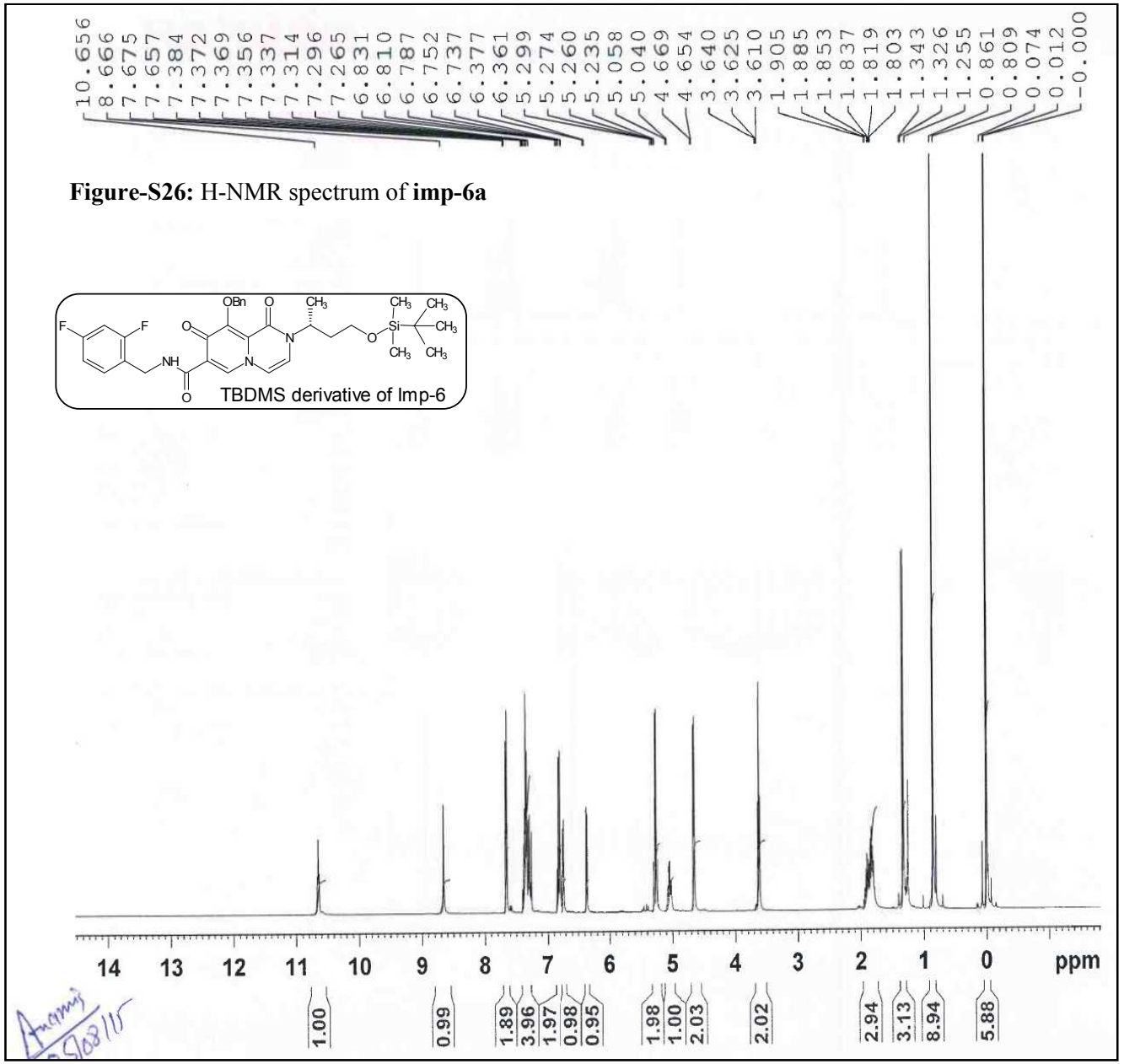


Figure-S26: H-NMR spectrum of **imp-6a**

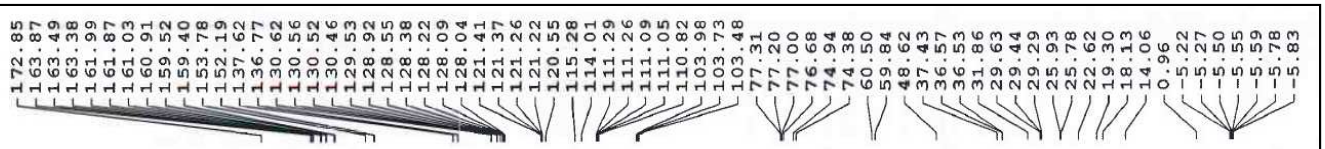
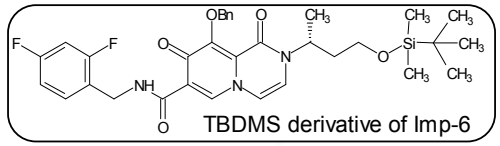


Figure-S27: C-NMR spectrum of **imp-6a**



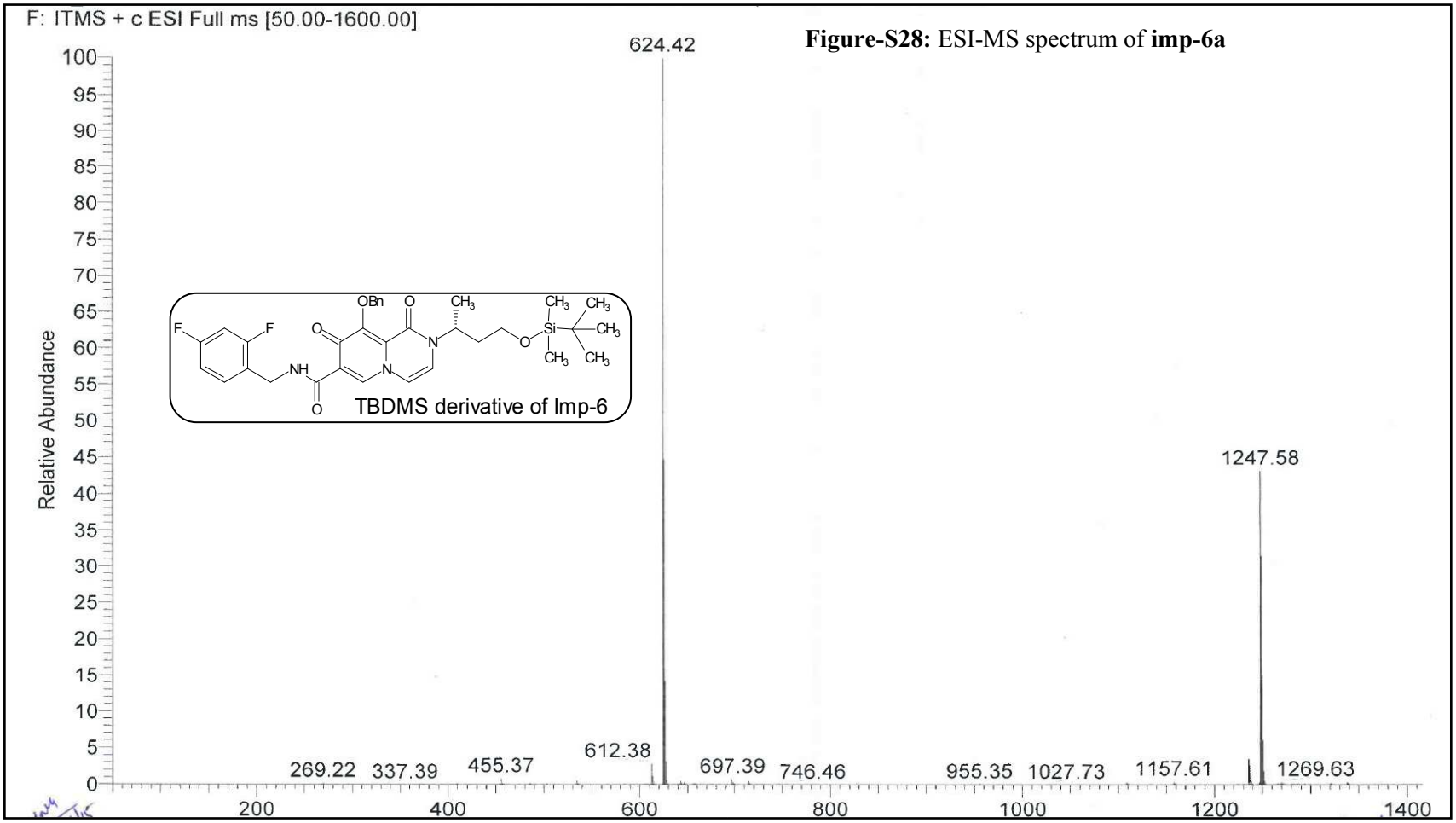


Figure-S28: ESI-MS spectrum of **imp-6a**

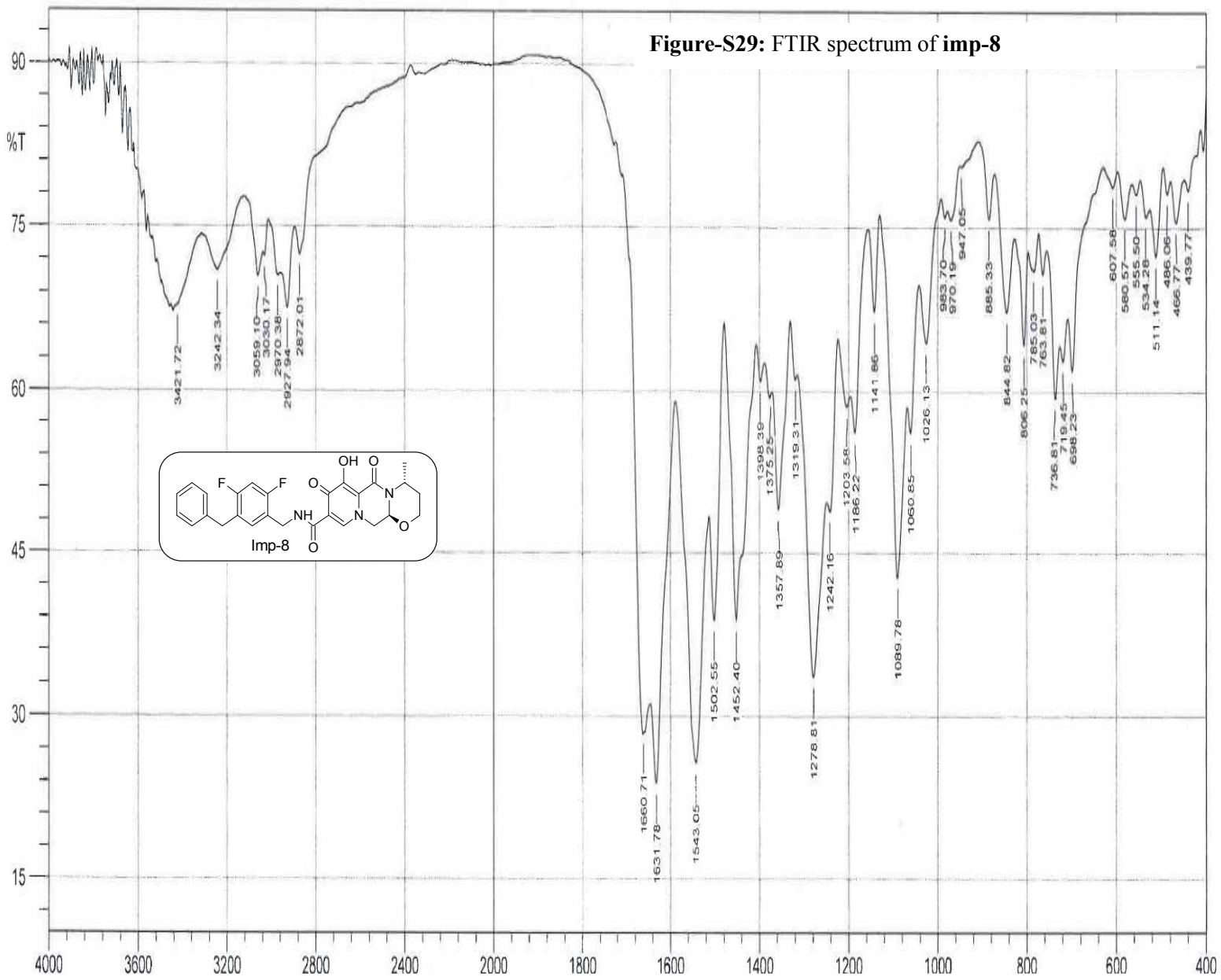


Figure-S29: FTIR spectrum of **imp-8**

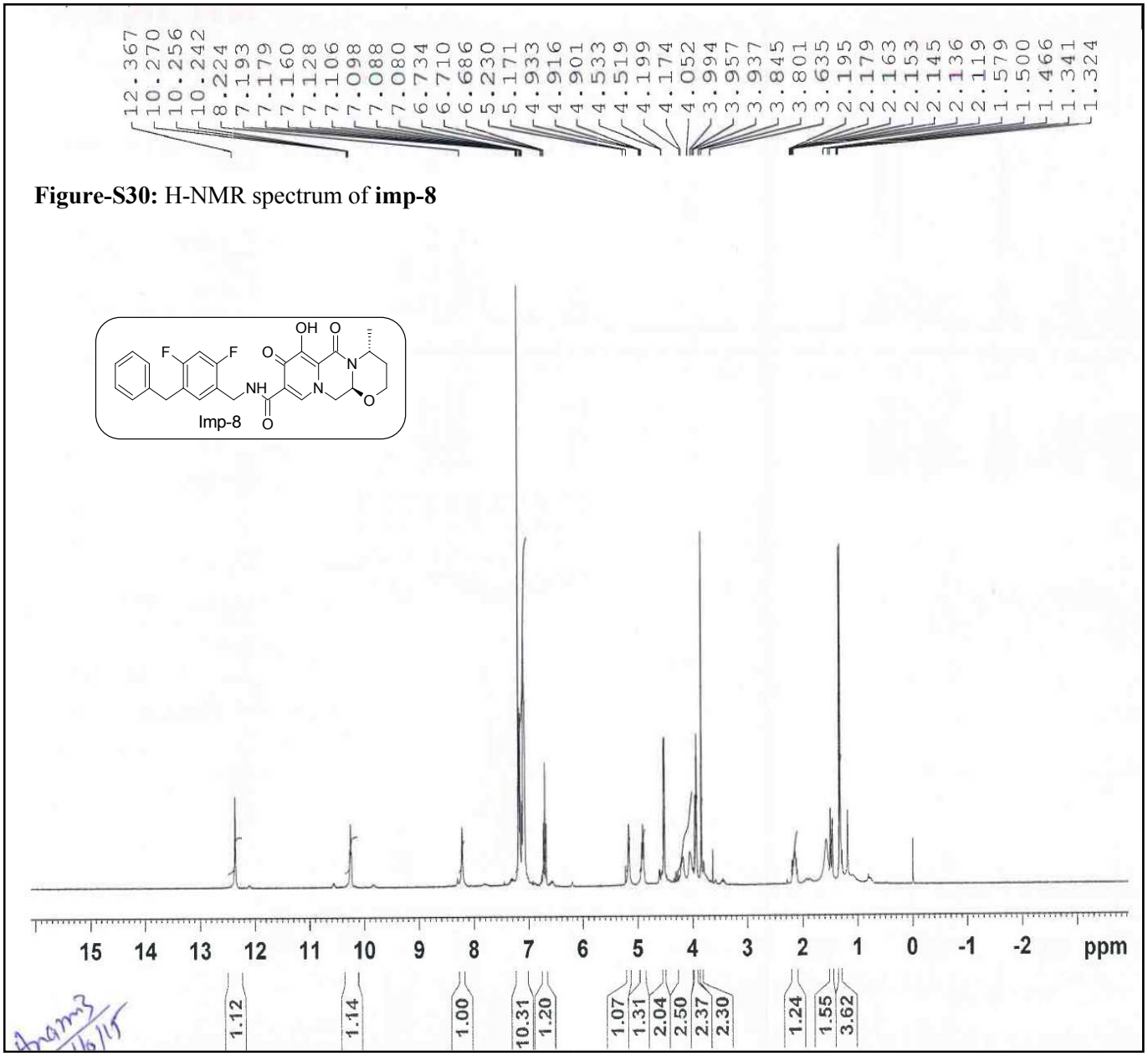
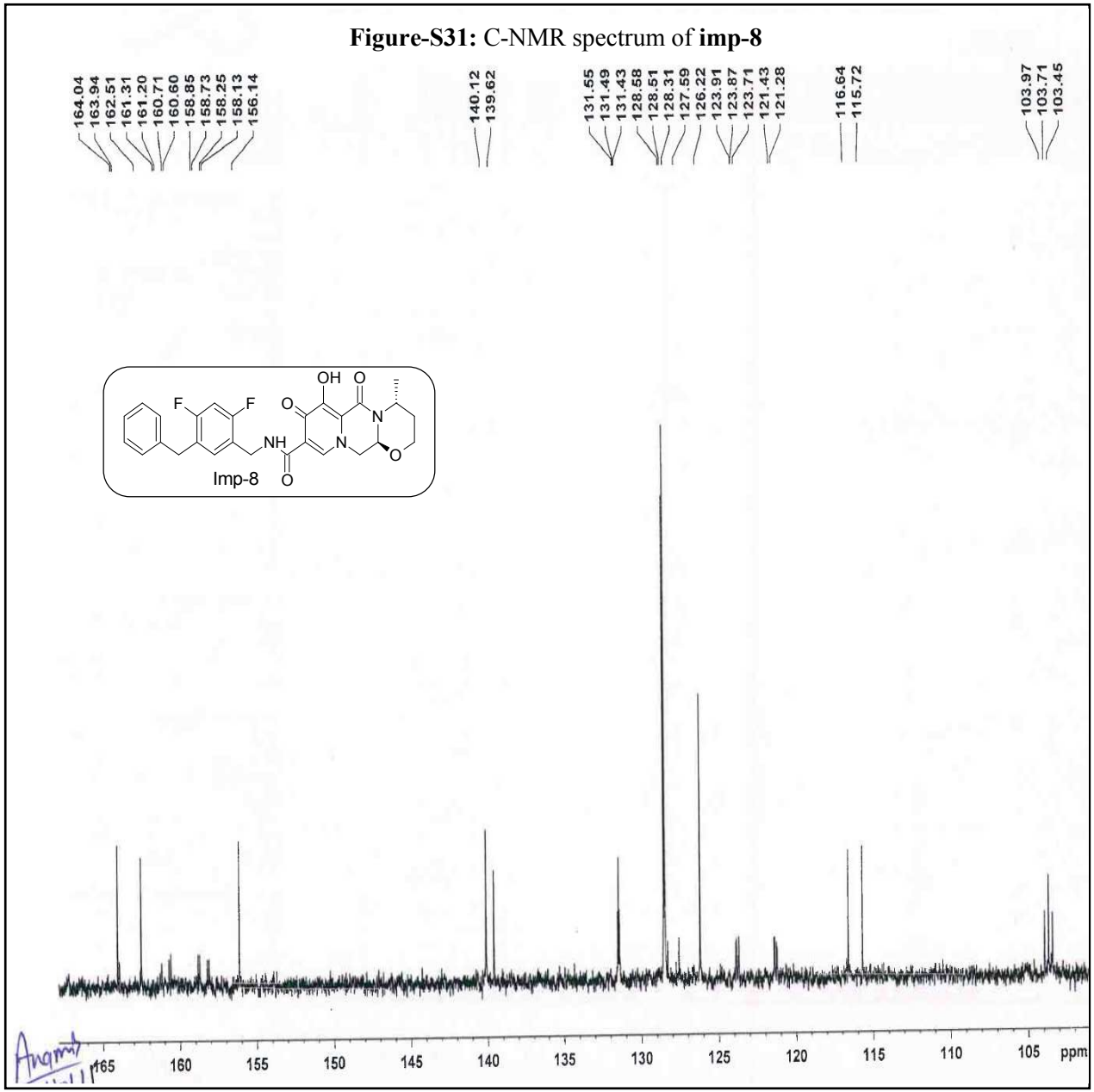


Figure-S30: H-NMR spectrum of **imp-8**

Figure-S31: C-NMR spectrum of **imp-8**



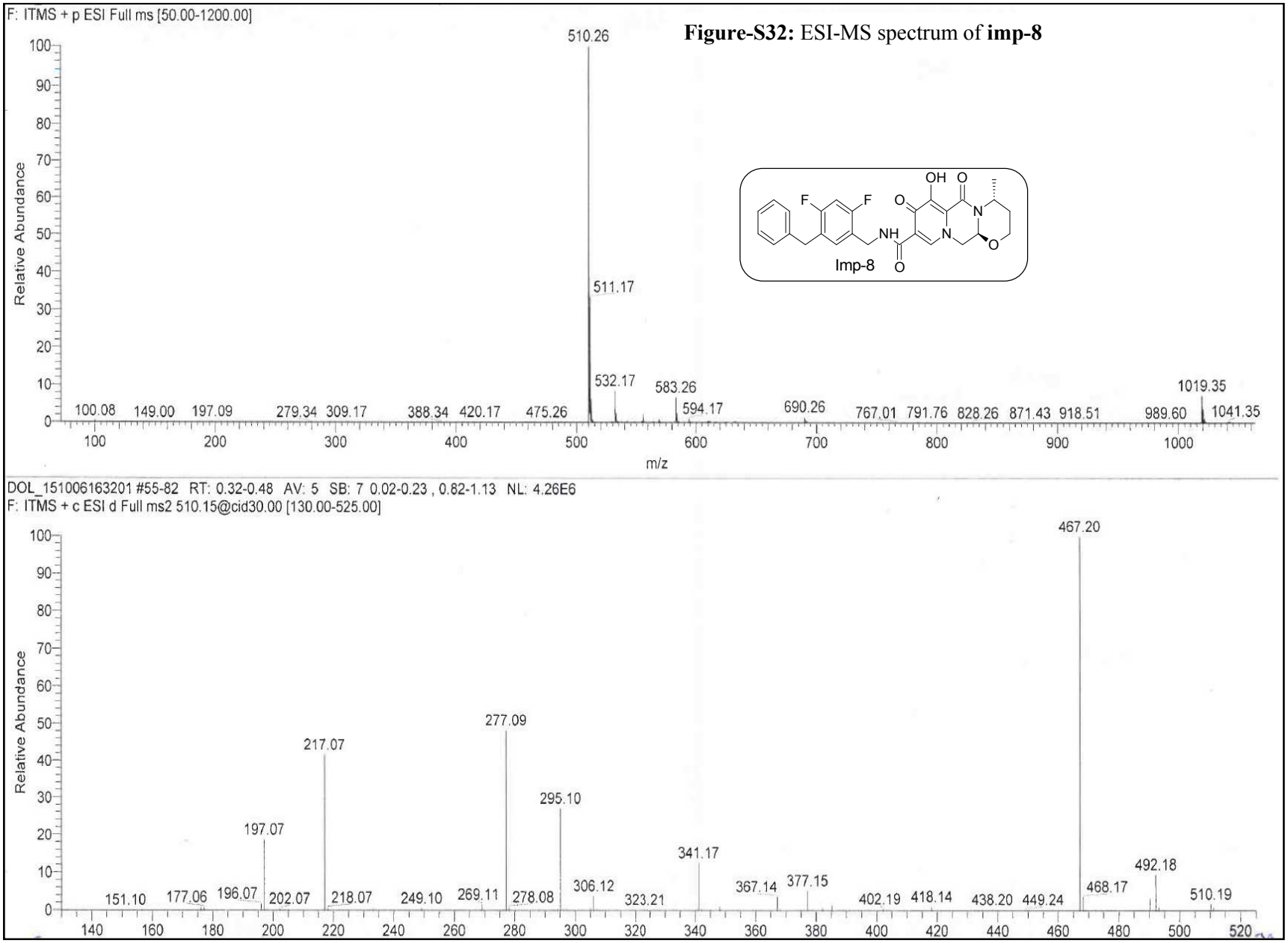
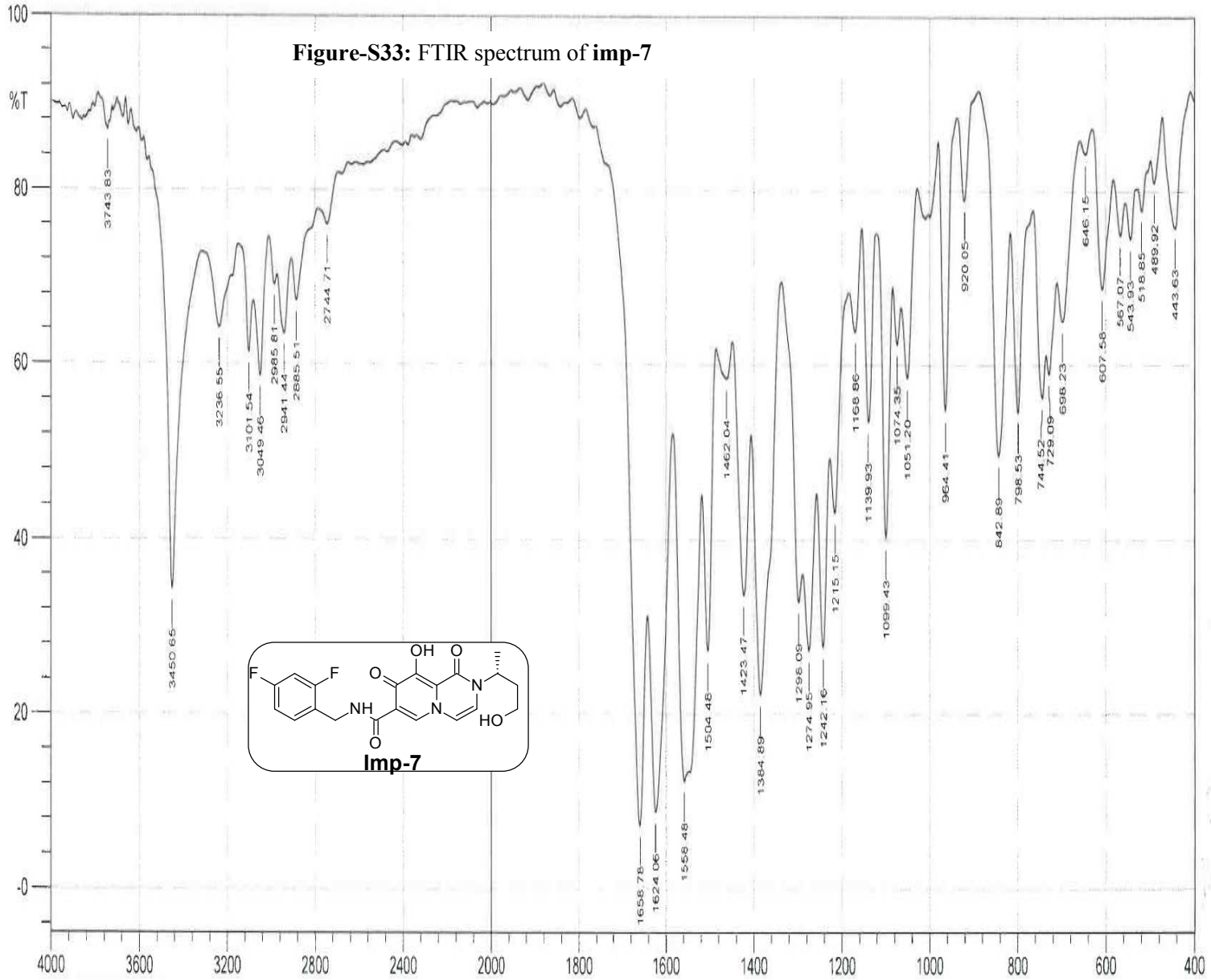


Figure-S32: ESI-MS spectrum of **imp-8**

Figure-S33: FTIR spectrum of **imp-7**



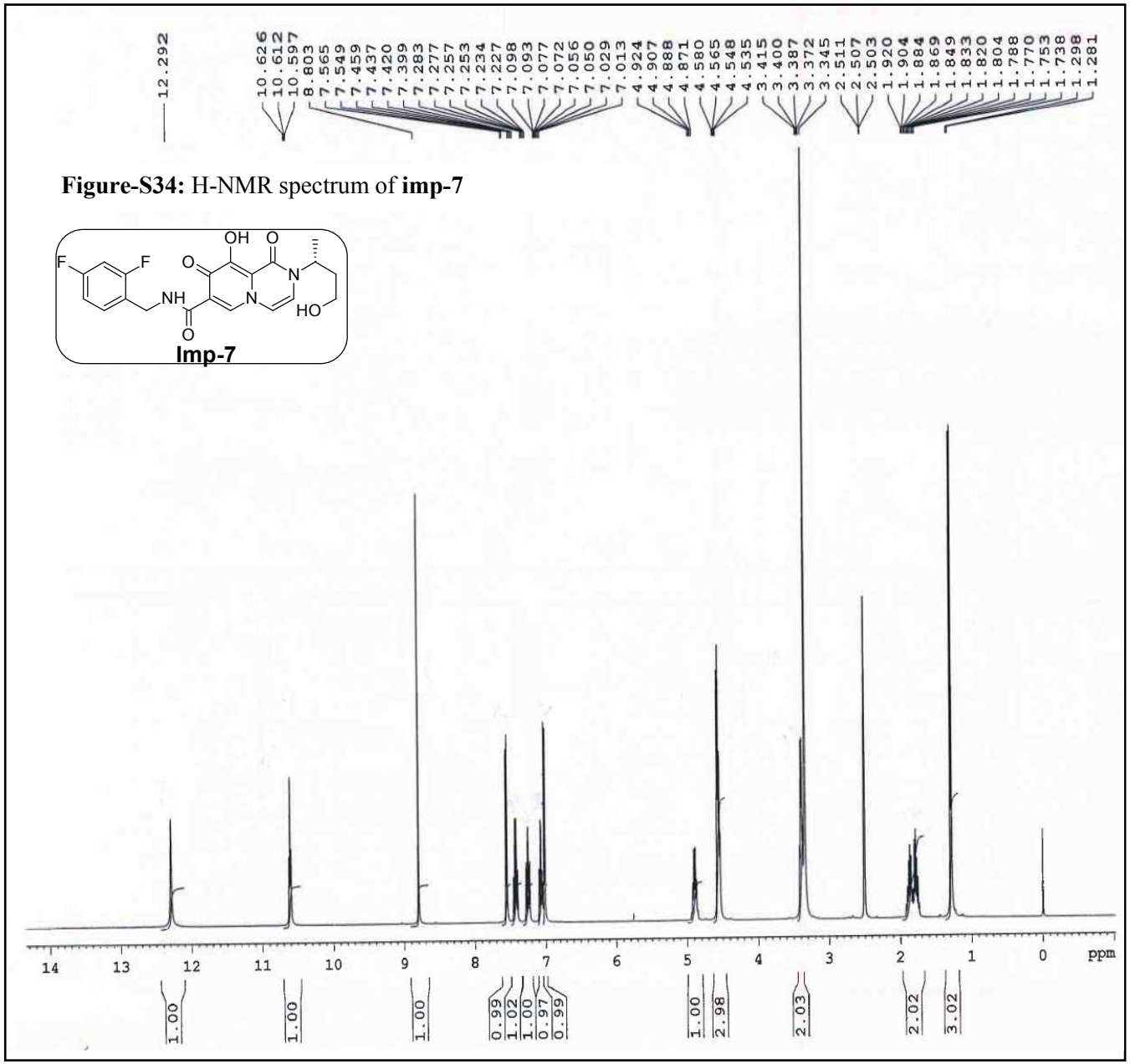


Figure-S34: H-NMR spectrum of **imp-7**

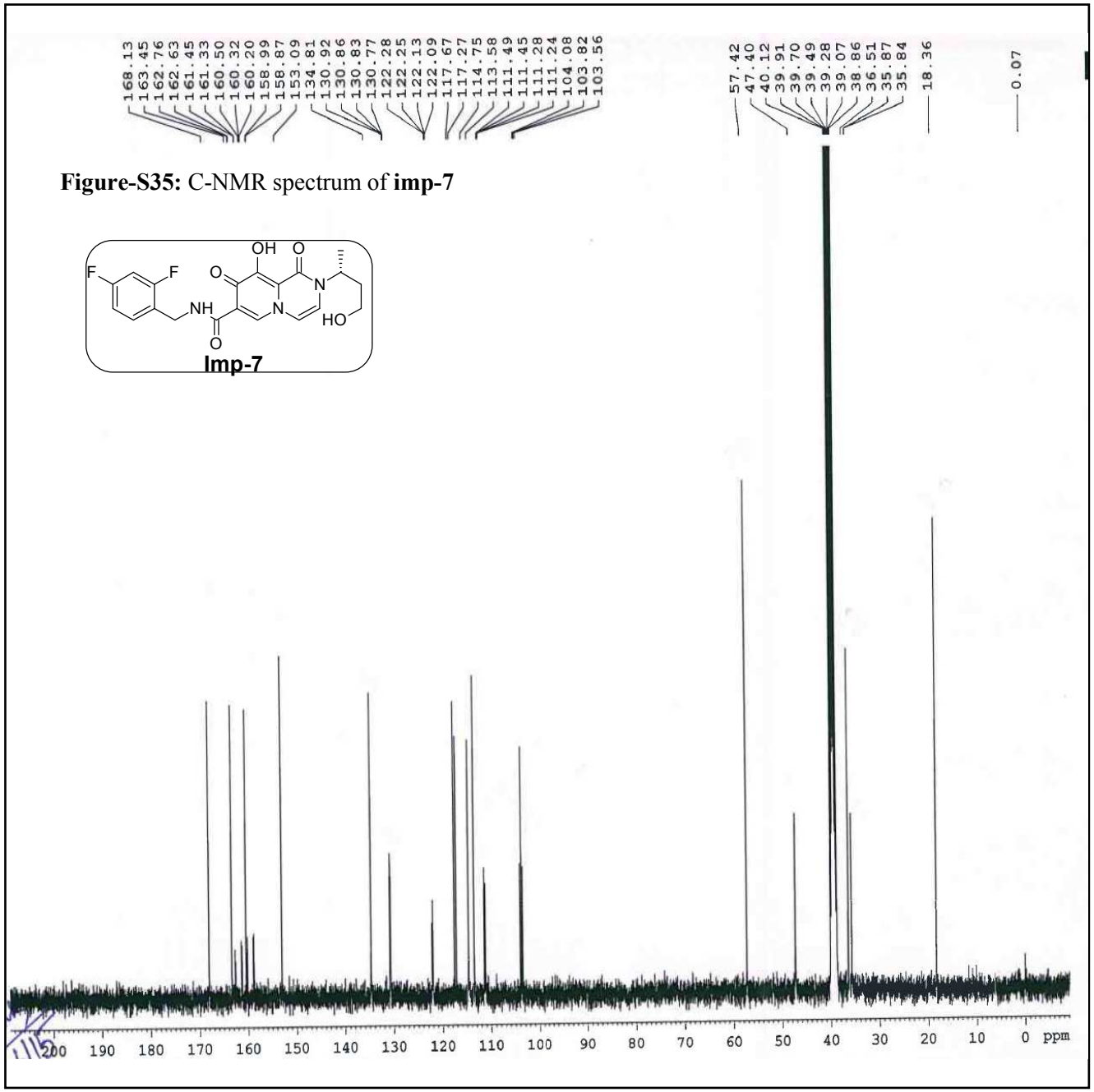
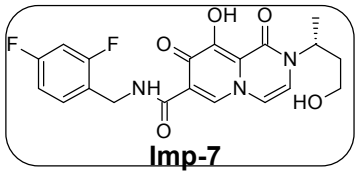


Figure-S35: C-NMR spectrum of **imp-7**

Figure-S36: ESI-MS spectrum of **imp-7**



Imp-7

Figure-S37: FT-IR spectrum of API-**1**

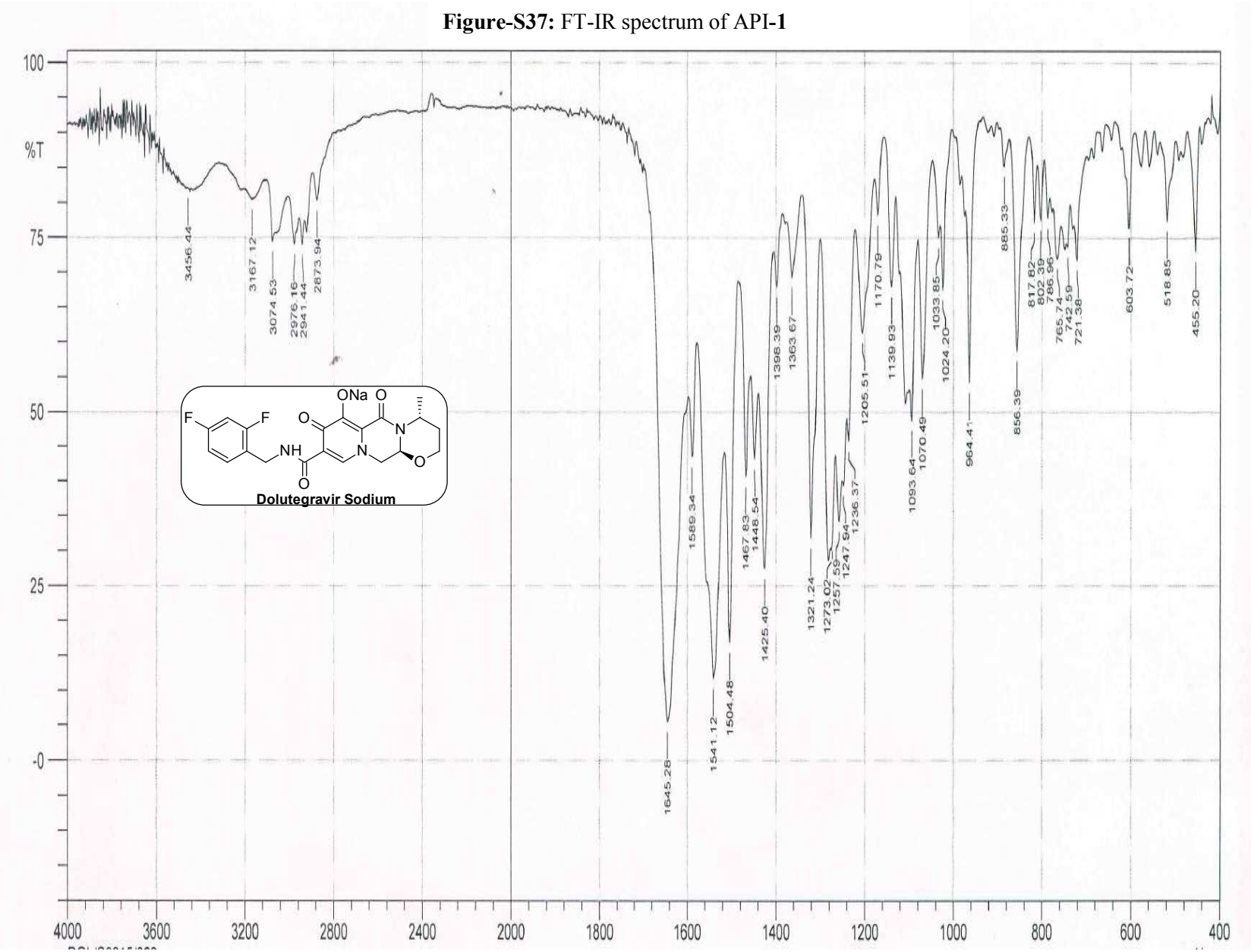


Figure-S38: H-NMR spectrum of API-**1**

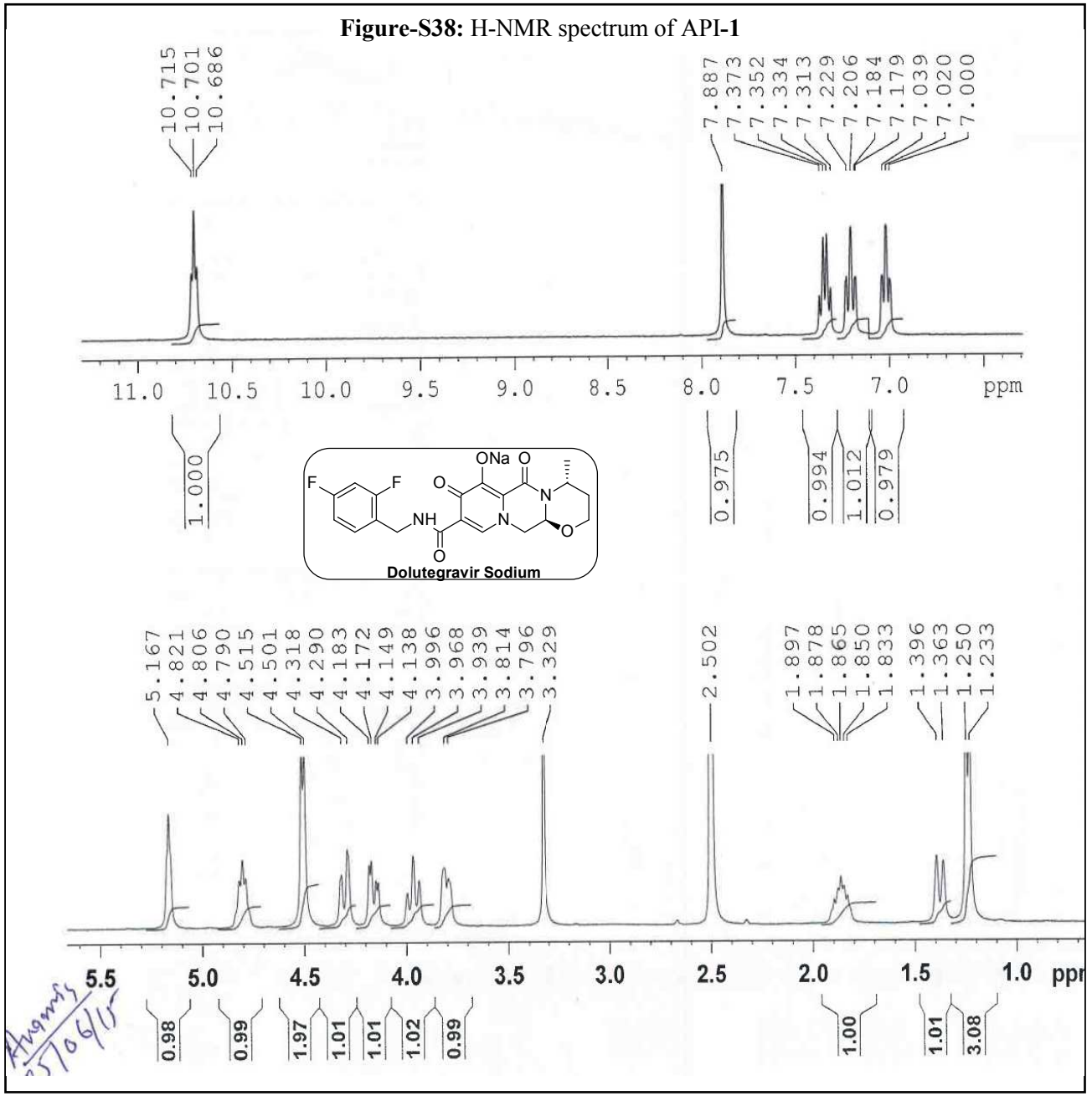


Figure-S39: C-NMR spectrum of API-**1**

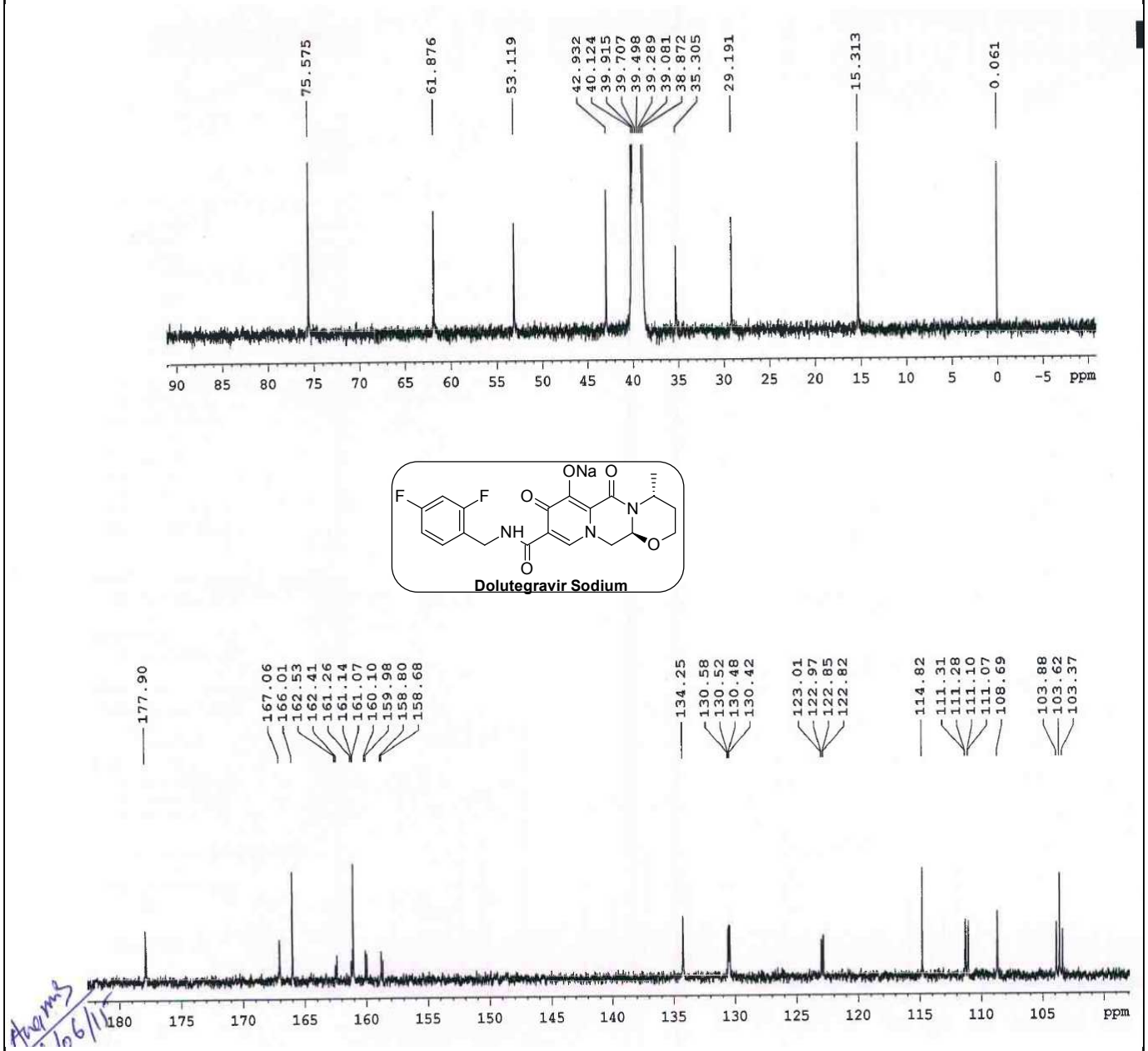


Figure-S40: ESI-MS spectrum of API-**1**

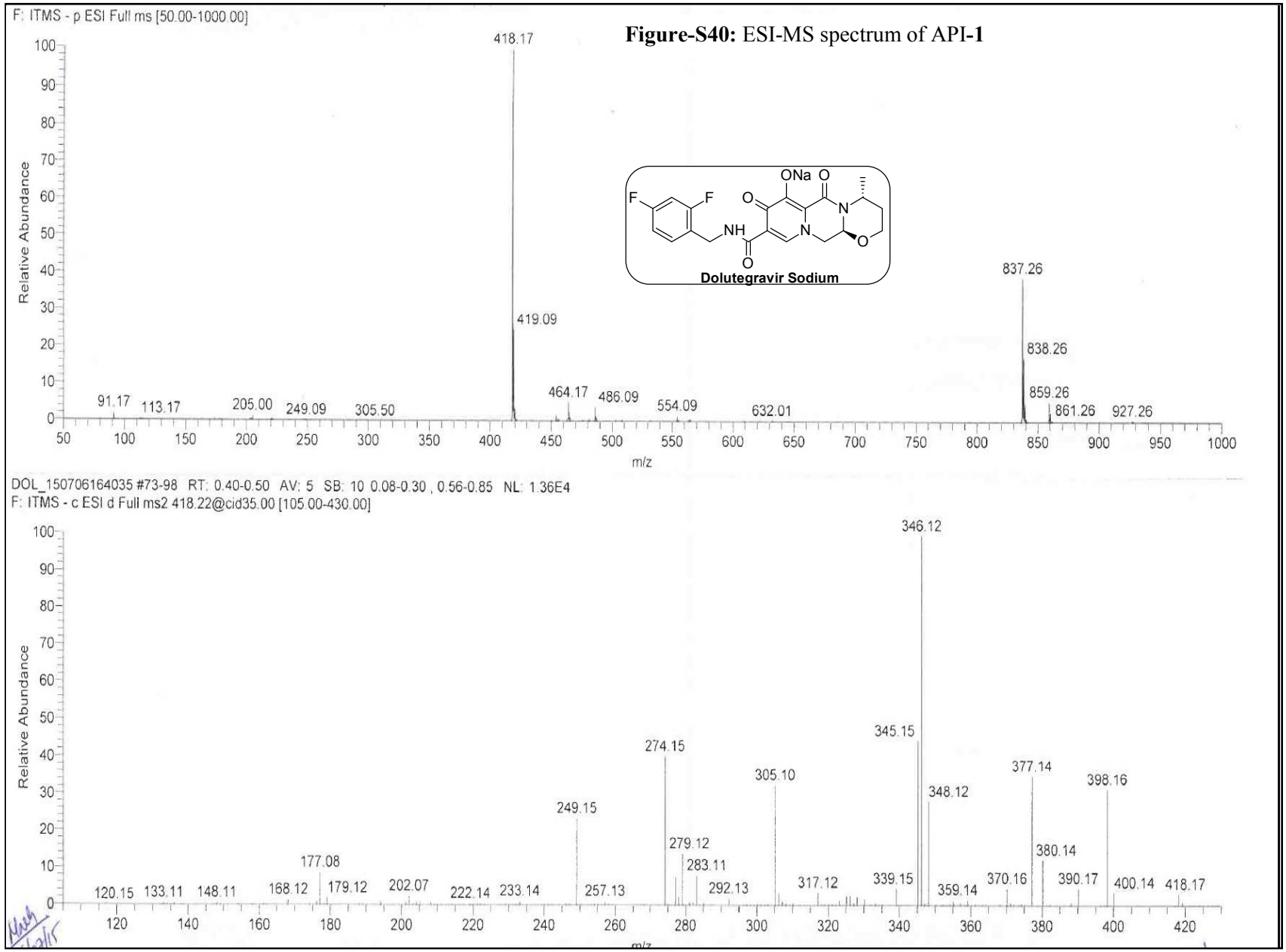
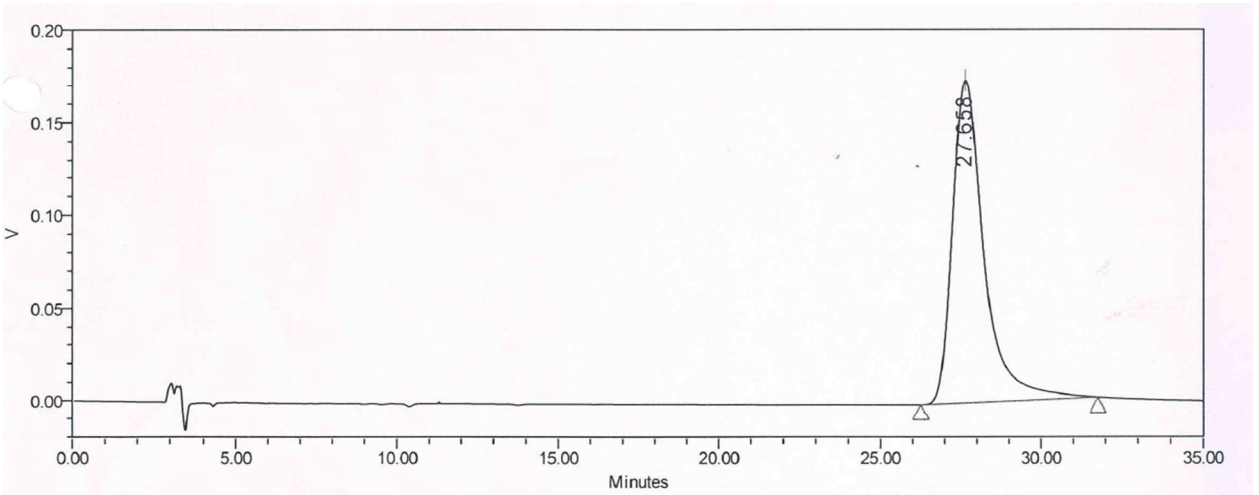
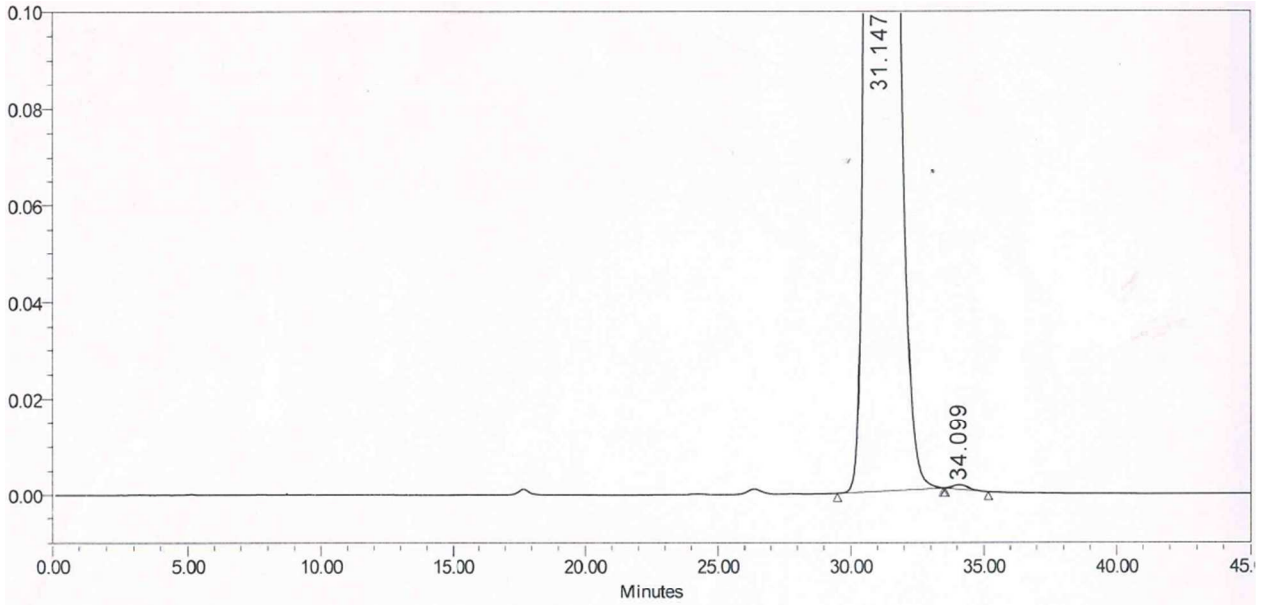


Figure-S41: HPLC chromatogram of enantiomer purity of API-**1**



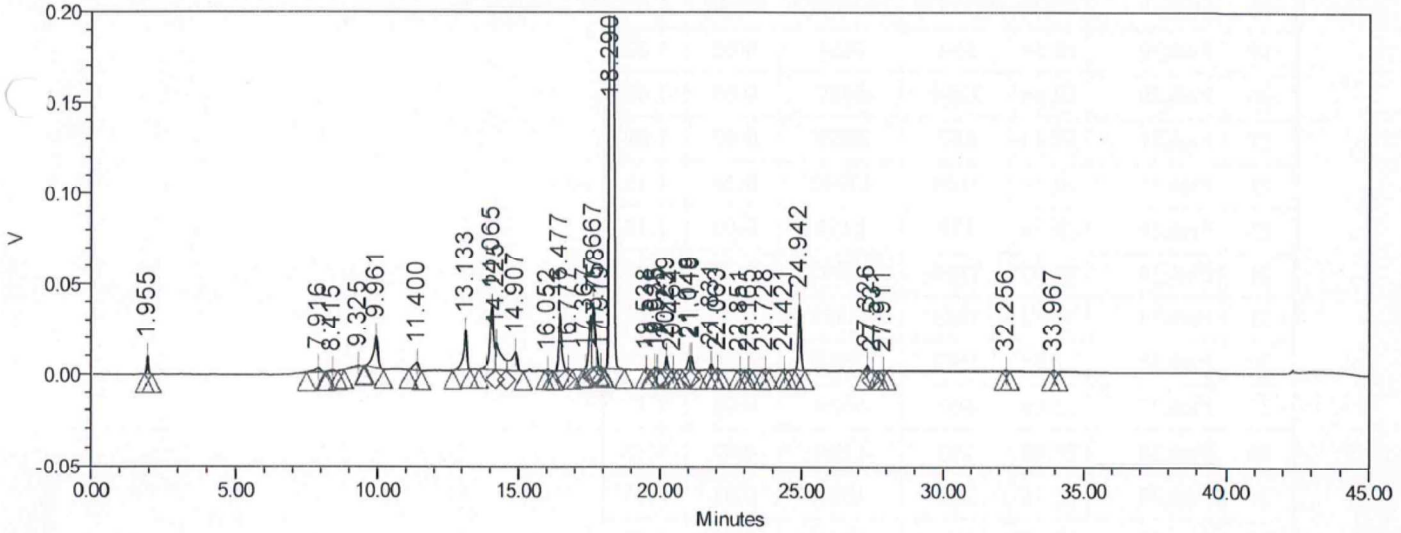
	Peak Name	RT	Height (µV)	Area	% Area
1	DOL-Na	27.66	174018	11915041	100.00
Sum				11915041	

Figure-S42: HPLC chromatogram of diastereomer purity of API-**1**



	Peak Name	RT	Height (µV)	Area	% Area	RT Ratio
1	DOL-Na	31.15	1228667	54797736	99.94	1.00
2	Impurity-B	34.10	861	34442	0.06	1.09
um				0.0		

Figure-S43: HPLC chromatogram for the conversion (reaction monitoring) of **2** to **3** spiked with 5% w/w water



Sample Name DOL RM-1; Injection 1; Date Acquired 8/1/2015 3:30:53 AM IST; Date Processed 8/1/2015 11:28:17 AM IST

	Peak Name	RT	Height (µV)	Area	% Area	RT Ratio
1	Peak1	1.96	9540	38205	0.22	0.11
2	Peak2	7.92	2109	34304	0.20	0.43
3	Peak3	8.41	571	7419	0.04	0.46
4	Peak4	9.33	703	13493	0.08	0.51
5	Peak5	9.96	17734	195016	1.13	0.54
6	Peak6	11.40	4409	49140	0.29	0.62
7	Peak7	13.13	21145	173494	1.01	0.72
8	Peak8	14.06	34860	310335	1.80	0.77

→ Imp-1

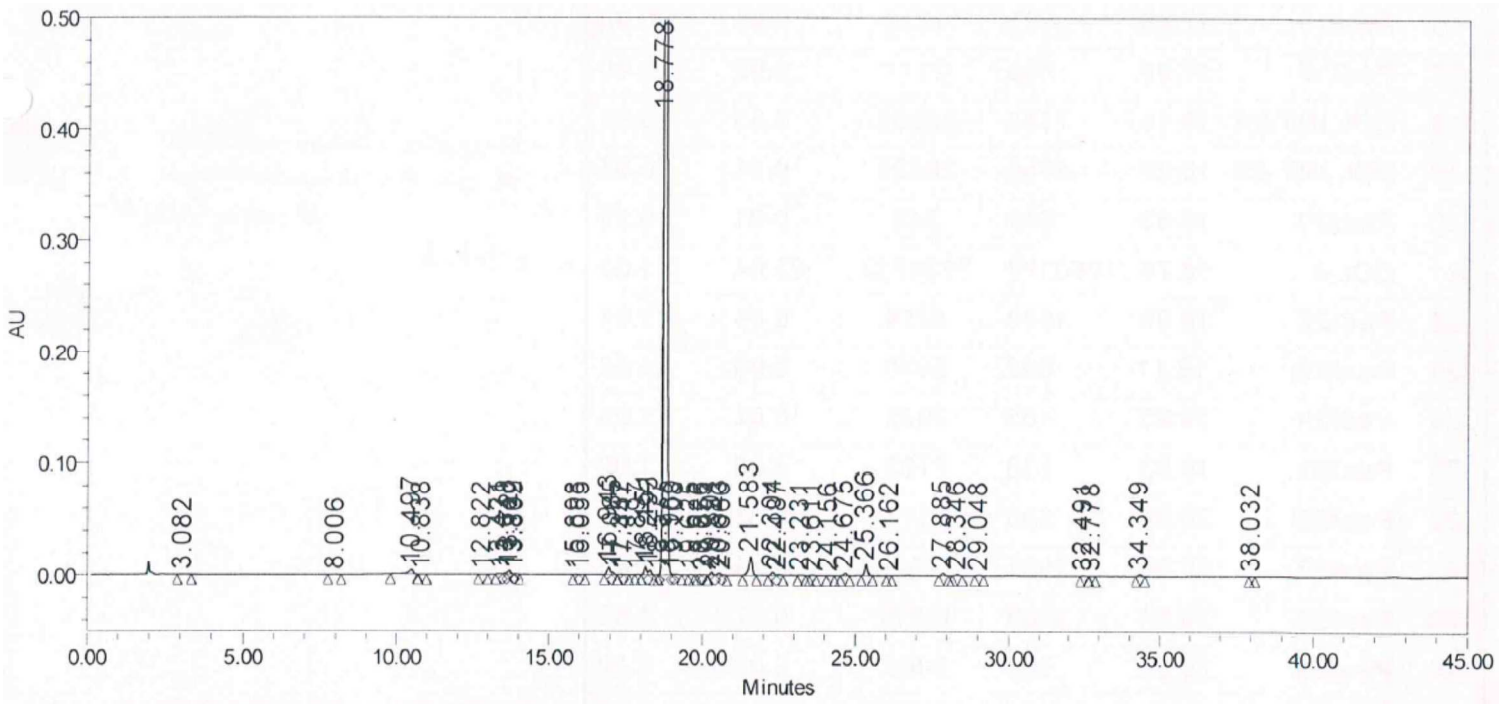
Compound 3 Rxn mass (Reaction spiked with 5% w/w water)

	Peak Name	RT	Height (µV)	Area	% Area	RT Ratio
9	Peak9	14.22	14667	226118	1.31	0.78
10	Peak10	14.91	10188	174949	1.02	0.82
11	Peak11	16.05	697	3554	0.02	0.88
12	Peak12	16.48	31862	230298	1.34	0.90
13	Peak13	16.78	1040	6818	0.04	0.92
14	Peak14	17.37	261	906	0.01	0.95
15	Peak15	17.67	35434	227871	1.32	0.97
16	Peak16	17.76	10477	33800	0.20	0.97
17	Peak17	17.92	337	1568	0.01	0.98
18	DOL-1	18.29	2431378	15050854	87.46	1.00
19	Peak19	19.54	534	3054	0.02	1.07
20	Peak20	19.84	1254	8089	0.05	1.08
21	Peak21	19.93	807	2869	0.02	1.09
22	Peak22	20.24	7109	43902	0.26	1.11
23	Peak23	20.46	279	1453	0.01	1.12
24	Peak24	21.05	7160	47997	0.28	1.15
25	Peak25	21.12	7433	45458	0.26	1.15
26	Peak26	21.83	3141	17905	0.10	1.19
27	Peak27	22.06	800	4659	0.03	1.21
28	Peak28	22.85	153	1100	0.01	1.25
29	Peak29	23.16	275	1601	0.01	1.27
30	Peak30	23.73	500	3203	0.02	1.30
31	Peak31	24.42	446	2362	0.01	1.34
32	Peak32	24.94	35677	217959	1.27	1.36
33	Peak33	27.33	2853	19244	0.11	1.49
34	Peak34	27.53	147	1013	0.01	1.51
35	Peak35	27.91	157	1106	0.01	1.53
36	Peak36	32.26	481	3040	0.02	1.76
37	Peak37	33.97	666	4585	0.03	1.86
Sum				17208741		

— Cpd 3

— Imp-2

Figure-S44: Representative HPLC chromatogram for the conversion (reaction monitoring) of **2** to **3**



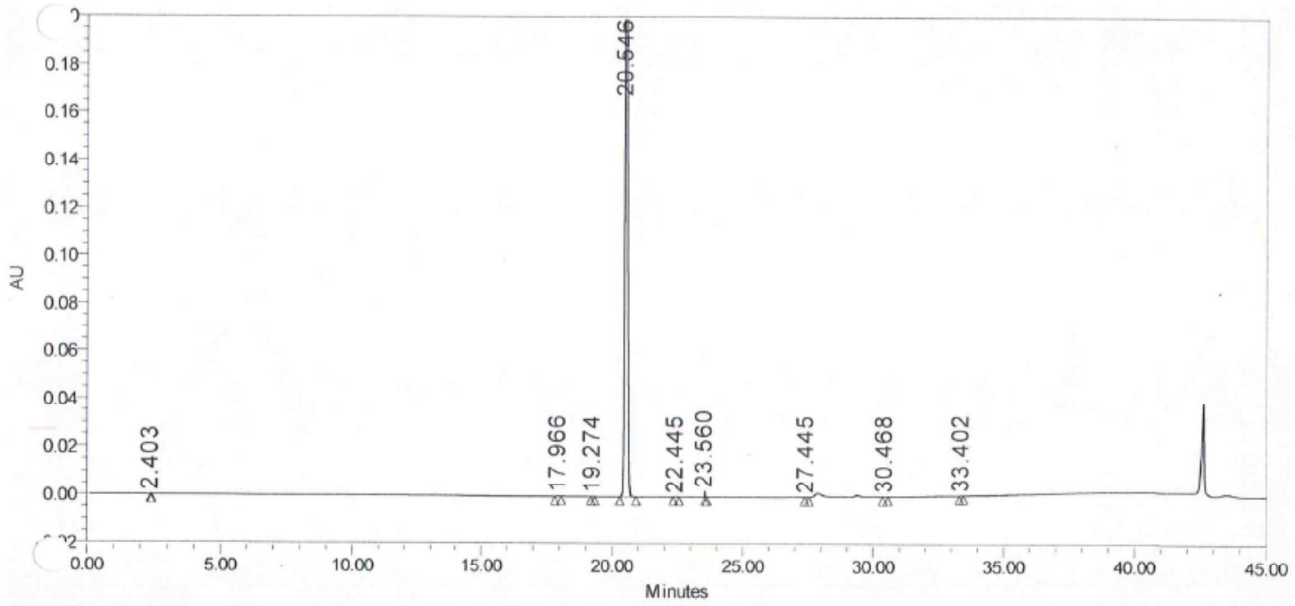
	Peak Name	RT	Height (µV)	Area	% Area	RT Ratio
1	Peak1	3.08	131	1927	0.02	0.16
2	Peak2	8.01	159	2239	0.03	0.43
3	Peak3	10.50	4589	56469	0.66	0.56
4	Peak4	10.84	129	1160	0.01	0.58
5	Peak5	12.82	105	639	0.01	0.68
6	Peak6	13.42	417	3599	0.04	0.71

Cpd 3 Reaction mass
(Regular process)

→ Imp-1

	Peak Name	RT	Height (µV)	Area	% Area	RT Ratio	
7	Peak7	13.62	1420	7136	0.08	0.73	
8	Peak8	13.72	3764	25124	0.29	0.73	
9	Peak9	13.86	413	940	0.01	0.74	
10	Peak10	13.90	484	1829	0.02	0.74	
11	Peak11	15.90	279	1813	0.02	0.85	
12	Peak12	16.06	187	1106	0.01	0.86	
13	DOL INT-1A	16.94	6826	46274	0.54	0.90	} - Acyclic intermediates of 2 + amino acetaldehyde dimethyl acetal
14	DOL INT-1B	17.08	2321	12545	0.15	0.91	
15	Peak15	17.36	351	2365	0.03	0.92	
16	Peak16	17.45	223	1213	0.01	0.93	
17	Peak17	17.90	409	2117	0.02	0.95	
18	DOL INT-2A	18.15	7355	45306	0.53	0.97	} - Acyclic intermediates of 2+ amino acetaldehyde dimethyl acetal
19	DOL INT-2B	18.29	4754	26828	0.31	0.97	
20	Peak20	18.58	619	842	0.01	0.99	
21	DOL-1	18.78	1260177	7934737	93.04	1.00	— CPd 3
22	Peak22	18.98	1602	4714	0.06	1.01	
23	Peak23	19.11	652	5033	0.06	1.02	
24	Peak24	19.63	405	2032	0.02	1.05	
25	Peak25	19.93	539	2792	0.03	1.06	
26	Peak26	20.06	390	2174	0.03	1.07	
27	Peak27	20.30	2951	17625	0.21	1.08	
28	Peak28	20.54	2063	14687	0.17	1.09	
29	Peak29	20.67	597	2485	0.03	1.10	
30	Peak30	21.58	17340	137954	1.62	1.15	
31	Peak31	22.30	2833	19279	0.23	1.19	
32	Peak32	22.49	882	6632	0.08	1.20	
33	Peak33	23.23	297	2149	0.03	1.24	
34	Peak34	23.61	501	3215	0.04	1.26	
35	Peak35	24.16	88	531	0.01	1.29	
36	Peak36	24.68	2338	14993	0.18	1.31	
37	Peak37	25.37	10199	65915	0.77	1.35	— Imp-2
38	Peak38	26.16	144	693	0.01	1.39	
39	Peak39	27.88	2422	17425	0.20	1.48	
40	Peak40	28.35	1236	9368	0.11	1.51	
41	Peak41	29.05	597	4075	0.05	1.55	
42	Peak42	32.49	483	3511	0.04	1.73	
43	Peak43	32.78	171	1002	0.01	1.75	
44	Peak44	34.35	1844	12969	0.15	1.83	
45	Peak45	38.03	141	737	0.01	2.03	
Sum				8528199.1			

Figure-S45: HPLC chromatogram of intermediate **3**



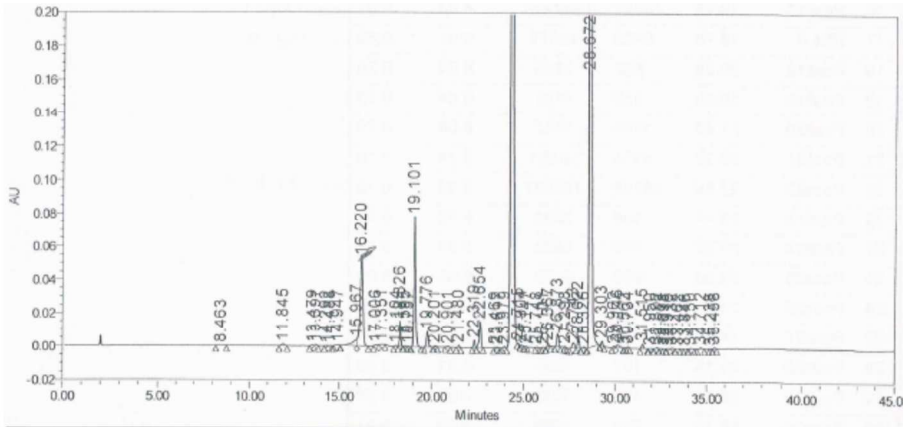
	Peak Name	RT	Height (µV)	Area	% Area	RT Ratio
1	Peak1	2.40	169	154	0.01	0.12
2	Peak2	17.97	88	712	0.03	0.87
3	Peak3	19.27	31	134	0.01	0.94
4	DOL-1	20.55	322847	2143743	99.75	1.00
5	Peak5	22.45	121	815	0.04	1.09
6	Peak6	23.56	2304	2396	0.11	1.15
7	Peak7	27.44	107	572	0.03	1.34
8	Peak8	30.47	57	351	0.02	1.48
9	Peak9	33.40	51	243	0.01	1.63
Sum				2149120.8		

Compound 3 (optimized)

— Cpd 3

— Imp-2

Figure-S46: HPLC chromatogram of crude intermediate **4** (before IPA isolation)



	Peak Name	RT	Height (µV)	Area	% Area	RT Ratio	
1	Peak1	8.46	179	3012	0.03	0.30	
2	Peak2	11.84	1033	10638	0.10	0.41	
3	Peak3	13.48	531	4690	0.04	0.47	
4	Peak4	13.70	884	8792	0.08	0.48	
5	Peak5	14.29	157	1038	0.01	0.50	
6	Peak6	14.49	105	616	0.01	0.51	
7	Peak7	14.95	450	4528	0.04	0.52	
8	Peak8	15.97	3941	67496	0.62	0.56	
9	Peak9	16.22	52900	580559	5.37	0.57	
10	Peak10	17.01	433	4934	0.05	0.59	
11	Peak11	17.35	399	5305	0.05	0.61	
12	Peak12	18.10	418	2844	0.03	0.63	
13	Peak13	18.33	14672	70064	0.65	0.64	
14	Peak14	18.59	312	1480	0.01	0.65	
15	Peak15	18.76	258	1113	0.01	0.65	
16	Peak16	19.10	78637	500160	4.63	0.67	— Imp-1
17	DOL-1	19.78	9493	65673	0.61	0.69	— Cpd 3
18	Peak18	20.20	682	3786	0.04	0.70	
19	Peak19	20.90	556	4162	0.04	0.73	
20	Peak20	21.48	1399	6867	0.06	0.75	

Compound 4
(crude mass
before IPA isolation)

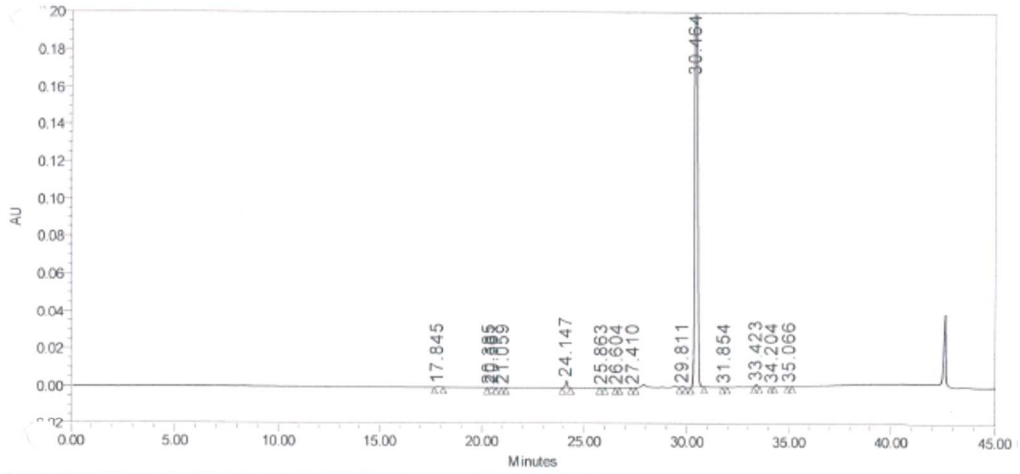
21	Peak21	22.32	4374	25461	0.24	0.78
22	Peak22	22.65	15748	106087	0.98	0.79
23	Peak23	23.47	606	3388	0.03	0.82
24	Peak24	23.62	479	2626	0.02	0.82
25	Peak25	23.98	886	6429	0.06	0.84
26	Peak26	24.72	551	2478	0.02	0.86
27	Peak27	24.90	453	2342	0.02	0.87
28	Peak28	25.15	197	928	0.01	0.88
29	Peak29	25.75	497	3038	0.03	0.90
30	Peak30	26.10	269	1799	0.02	0.91
31	Peak31	26.37	2190	13377	0.12	0.92
32	Peak32	26.87	7755	53746	0.50	0.94
33	Peak33	27.30	686	3427	0.03	0.95
34	Peak34	27.74	3130	26144	0.24	0.97
35	Peak35	28.02	6920	41983	0.39	0.98
36	Peak36	28.33	1056	6774	0.06	0.99
37	DOL-2	28.67	1434084	9068029	83.89	1.00

— Imp-2

38	Peak38	29.30	2779	15567	0.14	1.02
39	Peak39	29.96	791	5348	0.05	1.05
40	Peak40	30.15	1694	20134	0.19	1.05
41	Peak41	30.56	211	919	0.01	1.07
42	Peak42	30.73	555	3236	0.03	1.07
43	Peak43	31.52	2776	18616	0.17	1.10
44	Peak44	31.95	234	1383	0.01	1.11
45	Peak45	32.30	728	4303	0.04	1.13
46	Peak46	32.51	207	1184	0.01	1.13
47	Peak47	32.69	117	556	0.01	1.14
48	Peak48	32.92	193	1658	0.02	1.15
49	Peak49	33.13	453	4120	0.04	1.16
50	Peak50	33.46	72	734	0.01	1.17
51	Peak51	33.85	99	566	0.01	1.18
52	Peak52	34.15	427	2879	0.03	1.19
53	Peak53	34.71	846	6487	0.06	1.21
54	Peak54	35.24	187	991	0.01	1.23
55	Peak55	35.46	601	4394	0.04	1.24
Sum				10808890.5		

— Imp-3

Figure-S47: HPLC chromatogram of isolated intermediate **4** (after IPA isolation)



	Peak Name	RT	Height (µV)	Area	% Area	RT Ratio	
1	Peak1	17.84	327	3586	0.11	0.59	
2	Peak2	20.39	89	565	0.02	0.67	
3	Peak3	20.56	214	1377	0.04	0.67	— Imp-1
4	Peak4	21.06	82	490	0.01	0.69	
5	Peak5	24.15	3968	27949	0.83	0.79	— Imp-2
6	Peak6	25.86	115	748	0.02	0.85	
7	Peak7	26.60	39	233	0.01	0.87	
8	Peak8	27.41	40	274	0.01	0.90	
9	Peak9	29.81	589	4528	0.13	0.98	
10	DOL-2	30.46	448516	3334145	98.49	1.00	
11	Peak11	31.85	122	840	0.02	1.05	
12	Peak12	33.42	1231	8717	0.26	1.10	— Imp- 3
13	Peak13	34.20	41	225	0.01	1.12	
14	Peak14	35.07	254	1723	0.05	1.15	
Sum				3385399.7			

Compound 4 (isolated)

Figure-S48: LC-MS of **6** showing *m/z* 509 for peaks due to **5** and **imp-8**

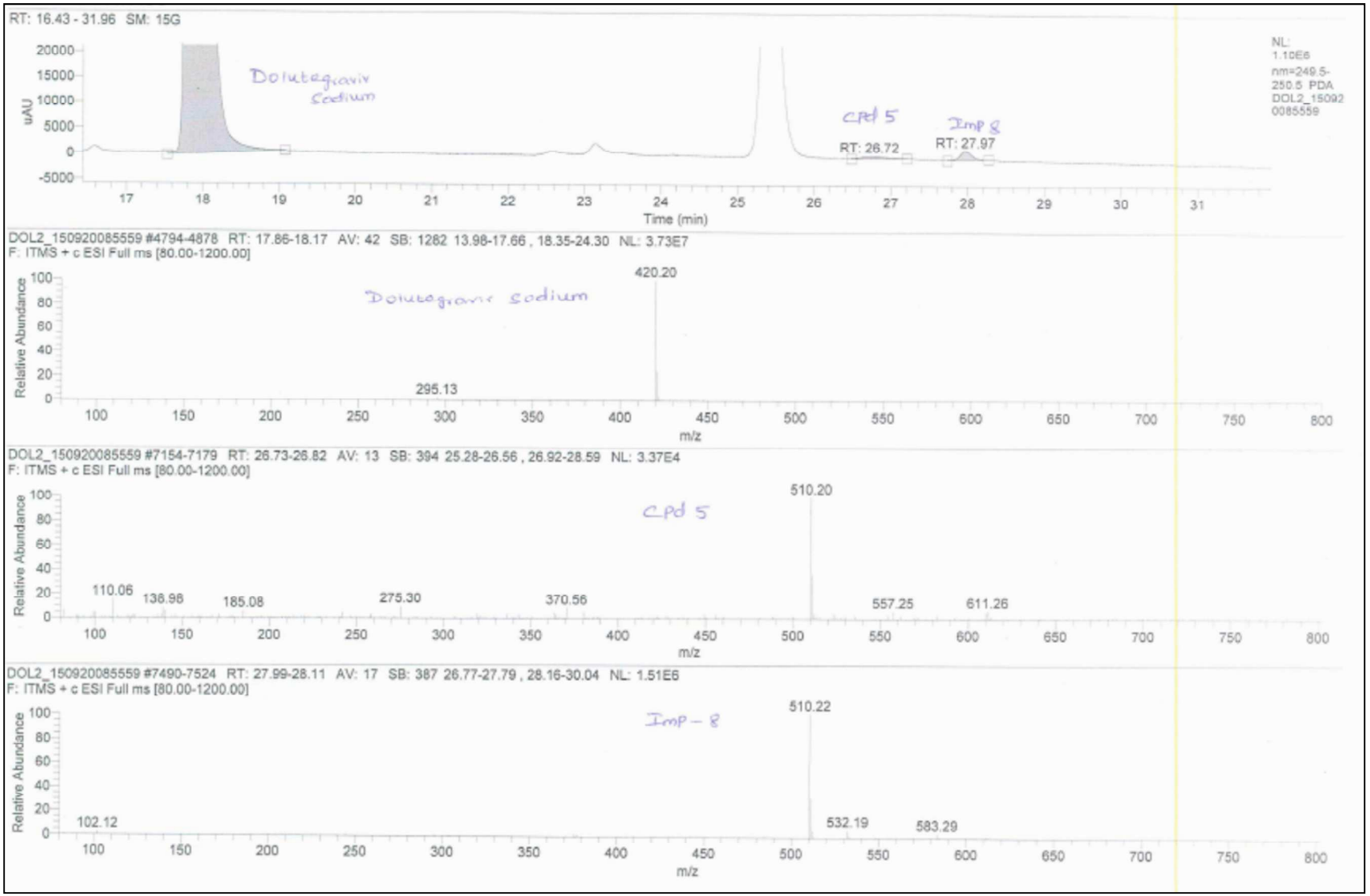


Figure-S49: Expanded H-NMR of aromatic region of **imp-8**

Results of optimization studies of Dolutegravir sodium (1)

Table-S1: Selective hydrolysis of diester **2**

S.No	Reagent (Base)	Reaction condition	Remarks
1	LiOH; 3.5 eq	**Batch size**: 1g; Complete conversion in methanol	Yield:
2	LiOH; 3.5 eq	**Batch size**: 10 g; 5h for reaction completion in methanol. Solid formed by pH adjustment.	Yield: 69.3%
3	LiOH; 5.0 eq	**Batch size**: 10 g; 4h for reaction completion in methanol. Solid formed by seeding the pH adjusted mass.	Yield: 65%
4	NaOH; 1.0 eq	More impurities observed as compared to LiOH in methanol as solvent.	--

Issues encountered with half-ester route:

1. On bigger scale, reaction completion was not consistent and due to different impurity profiles, product isolation by pH adjustment was also inconsistent.

2. Addition of solid LiOH to reaction mass was exothermic. Similarly slow addition is desirable for minimum impurity formation. Due to poor solubility of LiOH in methanol, the above condition was not achievable.

Table-S2: Solvent screening for the conversion of **2** to **3**

S. No.	Solvent	Reaction Condition	Remarks
1	Methanol	Reactants **2** and **2b** were taken in methanol and refluxed (60^oC)	Reaction did not go for completion. Conversion ~70%
2	Acetonitrile	Reactants **2** and **2b** were taken in acetonitrile and refluxed (80^oC)	Reaction did not go for completion. Conversion ~70%
3	Methanol and Toluene	Reactants **2** and **2b** were taken in methanol and refluxed (60^oC). Distilled and exchanged with toluene for azeotropic distillation.	57% of **3** formed.
4	Isopropyl alcohol	Reactants **2** and **2b** were taken in methanol and refluxed (80^oC)	Reaction did not go for completion. Conversion ~80%
5	Toluene	Reactants **2** and **2b** were taken in methanol and refluxed (110^oC)	80% of **3** formed. Impurities observed on TLC.

6	Methanol	Reactants **2** and **2b** were taken in methanol and refluxed (60^oC) followed by azeotropic distillation.	Reaction completed but material is impure on TLC.
7	n-Butanol	Reactants **2** and **2b** were taken in methanol and refluxed (117^oC)	Reaction did not go for completion. Conversion ~40%
8	n-Propanol	Reactants **2** and **2b** were taken in methanol and refluxed (97^oC)	Reaction did not go for completion. Not clean conversion. Conversion ~40%
9	*Tert*-Butanol	Reactants **2** and **2b** were taken in methanol and refluxed (85^oC)	Reaction completed but material is impure on TLC.

Table-S3: Screening of reaction conditions for the conversion of **2** to **3**[*]

S. No.	Additive	Yield (%)	Remarks
1	Acetic acid	95 (cpd **4**)	Reaction was slow. Work-up generated impurities.
2	Potassium carbonate	84 (cpd **3**)	Product isolated using cyclohexane
3	Sodium bicarbonate	87 (cpd **3**)	Yellow solid of **3** formed
4	Powdered sodium bicarbonate	81 (cpd **3**)	White solid of **3** formed
5	Mixture of powdered sodium bicarbonate and sodium sulphate	69 (cpd **4**)	Faster reaction but yield was low.
6	Diisopropylethylamine and sodium sulphate	84.3 (cpd **4**)	Minimum impurity profile observed.
7	Diisopropylethylamine	87 (cpd **4**)	Due to anhydrous nature of base, reaction generated lesser impurities even in the absence of sodium sulphate.
8	Water spiked	--	Conversion was 87%, lower than the regular trend.

[*] Reactions are performed in methanol

Table-S4: Screening of reaction conditions for the conversion of **3** to **4**

S. No.	Reaction condition	Yield (%)	Purity (%)	Remarks
Solvent Screen				
1	**Solvent**: Toluene **Additive**: Acetic acid **Reaction temperature**: 90^0C	87	98	Reaction completed with clean conversion.92-93%
2	**Solvent**: Toluene **Additive**: Citric acid **Reaction temperature**: 90^0C	--	--	No reaction.
3	**Solvent**: Acetonitrile **Additive**: Acetic acid **Reaction temperature**: 80^0C	--	--	Reaction did not go for completion. Conversion ~50%
4	**Solvent**: Isopropyl alcohol **Additive**: Acetic acid **Reaction temperature**: 90^0C	--	--	Very little conversion observed.
Screening of reaction condition for complete conversion of 3 to 4				
5	**2,4-Difluorobenzylamine** **Lot-1:** 0.7 mol eq. **Lot-2:** 0.2 mol eq. **Lot-3:** 0.2 mol eq. **Lot-4:** 0.2 mol eq. **Lot-5:** 0.1 mol eq.	90	(91) *In situ*	Reaction completed. *Total reagent*: 1.4 mol eq. *Total Lots*: 5 lots
6	**2,4-Difluorobenzylamine** **Lot-1:** 1.0 mol eq. **Lot-2:** 0.1 mol eq. **Lot-3:** 0.1 mol eq.	87	98%	Reaction completed. *Total reagent*: 1.2 mol eq. *Total Lots*: 3 lots
Solvent screening for crystallization				
7	Hexane	91.9	NA	Crude solid with Pale-yellow color description
8	Methanol	71	98.9	White solid but yield is low
9	IPA (3.0 V)	85	97.5	Lower crystallization temperature.
10	IPA (2.0 V)	87	97.7	Higher crystallization and higher yield.

Table-S5: Solvent screening for the conversion of **4** to **4a**

S. No.	Catalyst	Solvent	Remarks
1	Methanesulphonic acid and acetic acid	Toluene	Reaction did not go for completion.
2	Methanesulphonic acid and acetic acid	Methanol	Reaction not initiated
3	Methanesulphonic acid (mol 0.4 eq) and acetic acid (mol 6.0 eq) at 80^{o}C	Acetonitrile	Yield: 57%
4	Methanesulphonic acid (mol 0.3 eq) and acetic acid (mol 6.0 eq) at 65^{o}C	Acetonitrile	Yield: 77%
5	Formic acid, Sulphuric acid	Formic acid (10V)	Yield: 58%
6	Formic acid, Sulphuric acid	Toluene	Upon holding the reaction mass, complete degradation observed.
7	Formic acid, Sulphuric acid	Ethyl acetate	Upon holding the reaction mass, complete degradation observed.
8	Phosphomolybdic acid (PMA)	Acetonitrile	30%
9	Formic acid, phosphomolybdic acid	Ethyl acetate	Reaction did not go for completion.
10	Acetic acid and Pyridinium *p*-toluenesulphonate (PPTS)	Acetonitrile	Reaction not initiated
11	PPTS	Isopropyl alcohol	Reaction not initiated
12	PPTS	Acetonitrile	Reaction not initiated

Table-S6: Screening of reaction conditions for the control of diastereomer and olefin impurity during conversion **4** to **5**

S. No.	Reaction condition	Diastereomer (%)	Imp-6 (%)
1	DIPEA (0.4 eq) added to reaction mass before the addition of (3*R*)-aminobutan-1-ol	0.66	0.46
2	Sodium acetate (1.0 eq) added to reaction mass before the addition of (3*R*)-aminobutan-1-ol	0.66	0.47
3	Pyridine (0.5 eq) added to reaction mass before the addition of (3*R*)-aminobutan-1-ol	0.71	0.76
4	Magnesium methanesulphonate used as additive	0.54	0.78
5	Reaction mass containing **4a** added reverse manner to (3*R*)-aminobutan-1-ol	0.74	0.42
6	(3*R*)-Aminobutan-1-ol added to reaction mass at low temperature	0.68	NA

Table-S7: Screening of reagents for the conversion of **5** to **6**

S. No.	Solvent	Reaction Condition	Remarks
1	Pd/C, Ammonium formate	Transfer hydrogenation in methanol	No reaction
2	Lithium bromide	Reaction mass was refluxed (80^{o}C) in acetonitrile **HPLC: NA**	Reaction completed. But yield is low due to formation of more impurities.
3	Lithium bromide	Reaction mass was stirred at room temperature in acetonitrile **HPLC: 88.47**	Reaction completed. But still more side products observed.
4	Lithium chloride	Reaction mass was stirred at room temperature in acetonitrile **HPLC: 91.72**	Reaction was slower and completed after adding excess of reagent and heating the reaction mass.
5	Lithium methanesulfonate	Reaction mass was stirred at room temperature in acetonitrile **HPLC: NA**	Starting material consumed but desired product was not formed.
6	Sodium chloride	Reaction mass was refluxed (80^{o}C) in acetonitrile	No reaction
7	Potassium bromated-sodium dithionite	Reaction mass was stirred in ethyl acetate water biphasic system.	Lot of impurities observed.
8	PPTS	Reaction mass was refluxed (80^{o}C) in acetonitrile	No reaction
9	*p*TSA	Reaction mass was refluxed (38^{o}C) in dichloromethane.	Reaction did not go for completion.
10	Sodium hydride	Reaction mass was stirred at room temperature in tetrahydrofuran **HPLC: 94.80**	Reaction completed and dolutegravir sodium is formed. But more of desfluoro impurity was also formed.
11	Trifluoroacetic acid	Reaction mass was refluxed (38^{o}C) in dichloromethane **HPLC: 98.82**	Clean conversion observed
12	Trifluoroacetic acid	Reaction mass was stirred at 50^{o}C in ethyl acetate.	Reaction did not go for completion
13	Trifluoroacetic acid	Reaction mass was stirred at 50^{o}C in acetonitrile. **HPLC: 97.47**	Reaction was slower than in DCM solvent.
14	Trifluoroacetic acid (1.0 eq) and acetic acid (5.0 eq)	Reaction mass was refluxed (38^{o}C) in dichloromethane	No reaction.

Table-S8: Purity of **6** performed at different scales

Peak id	RT	RRT	Lab development batch	Lab assurance batch	Kilo lab batch	Pilot plant batch
Batch Size			**25 g**	**135 g**	**1.0 Kg**	**5.0 Kg**
Unknown	13.48	0.74	..	..	..	0.01%
Imp-7	14.58	0.80	0.07%	0.04%	0.05%	0.05%
Unknown	16.12	0.88	0.01%	..	0.01%	..
2-Desfluoro**	16.90	0.93	0.08%	0.02%	0.06%	0.02%
4-Desfluoro**	17.37	0.95	0.01%	0.09%	0.14%	0.07%
Dolutegravir	18.27	1.00	99.74%	99.76%	99.65%	99.74%
Hydrated imp-7	24.66	1.35	..	0.02%	..	0.02%
Bis-olefin	25.84	1.41	..	0.02%	..	0.02%
Unknown	26.23	1.44	0.01%	..	..	..
Hydrated Bis-olefin	27.25	1.49	0.01%	0.01%	0.01%	..
Imp-8	28.55	1.56	0.07%	0.06%	0.06%	0.06%

** 2-Desfluoro impurity and 4-desfluoro impurity are carried forward from 2,4-difluorobenzylamine raw material.

Table-S9: Comparison of representative lab and plant batch data of all the intermediates and final API

Compound 3			**Compound 5**			**Compound 6**			**Compound 1 (API)**		
Y:	86%	86%	**Y:**	70%	66%	**Y:**	84%	80%	**Y:**	95%	92%
RRT	**Lab**	**Pilot plant**	**RRT**	**Lab**	**Pilot plant**	**RRT**	**Lab**	**Pilot plant**	**RRT**	**Lab**	**Pilot plant**
0.49	0.03	0.04	0.53	0.01	0.04	0.69	..	0.01	0.74	..	0.01
0.52	0.02	0.01	0.54	0.01	0.01	0.70	..	0.01	0.80	0.04	0.05
0.70	1.09	0.92	0.57	0.01	0.02	0.74	..	..	0.93	0.02	0.02
0.78	0.04	0.03	0.59	..	0.01	0.80	0.06	0.08	0.95	0.09	0.07
0.81	0.01	..	0.61	0.18	0.17	0.93	0.08	0.02	**1.0**	**99.76**	**99.74**
0.88	0.02	0.02	0.66	0.02	0.01	0.95	0.02	0.09	1.35	0.02	0.02
0.97	0.16	0.22	0.77	0.01	0.02	**1.0**	**99.72**	**99.66**	1.41	0.02	0.02
1.0	**97.80**	**98.3**	0.87	0.01	0.01	1.35	0.02	0.02	1.49	0.01	..
1.02	..	..	0.90	0.76	0.75	1.41	0.02	0.02	1.57	0.06	0.06
1.04	0.01	0.01	0.92	0.05	0.14	1.49	0.01	..	..	..	...
1.06	0.03	0.01	**1.0**	**98.28**	**98.74**	1.57	0.06	0.06	..	..	..
1.15	0.20	0.13	1.77	0.01	0.01	1.72	..	0.01	..	..	..
1.19	0.02	..	1.79	0.08	0.01	..	..	..	..	..	..
1.23	0.04	0.04	1.88	0.07	0.06	..	..	..	..	..	..
1.26	0.01	0.02	..	..	..	..	..	..	..	..	..

Note: Y: Yield (%)