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Supporting information

Quality by Design Driven Improved Process of Abiraterone Acetate

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1. **Experimental section and instrumental details:** The syntheses of all intermediates and final API were carried out at the Research and Development Center, IPDO, Dr. Reddy's Laboratories Ltd., Telangana., India. All experiments were performed under an inert atmosphere (nitrogen or argon) using commercially available or laboratory reagent-grade chemicals and solvents and maintained anhydrous conditions. Reactions were carried out in a reaction vessel or cylindrical vessel with a mechanical stirrer. Purified water used in the workup process was collected from a Millipore Water purified system. Distillation operations were carried out in a Buchi rotary evaporator system under vacuum, Filtration operations were performed in a Buchner funnel and dried under vacuum in a calibrated vacuum tray dryer. Yields calculated based on the input and

output weights for every intermediate and final product were calculated on dry weight. All materials were stored with proper labels with suitable storage conditions. HPLC-grade acetonitrile and methanol, orthophosphoric acid, potassium dihydrogen phosphate, tetrabutylammonium hydrogen sulphate, and trifluoroacetic acid were procured from Merck Life Science. Chromatographic purification of products was carried out by flash column Chromatography on silica gel (60-120 mesh) for purification of compounds using Reveleris® X2 Flash Chromatography System from Buchi. Materials. Starting materials DHEA 7 (purity >95%) and BET 5 (purity >95%) were obtained from external sources and were used for the synthesis of intermediates and API at Dr. Reddy's Laboratories. Commercial grade reagents, aqueous hydrochloric acid (HCl) from Spectrochem Pvt. Ltd. (Hyderabad, India), 30% hydrogen peroxide (H_2O_2) and sodium hydroxide (NaOH) from Sigma-Aldrich (Hyderabad, India), NMR solvent $CDCl_3$ was purchased from Sigma-Aldrich and ^{1}H and ^{13}C NMR experiments for intermediate or impurities, and API were recorded on a Bruker Avance 500, 600 MHz and 125, 150 MHz NMR spectrometer respectively in $CDCl_3$ solvent. The instrument was equipped with a cryogenic probe to regulate the sample temperature at 25 °C. 1D data i.e., ^{1}H and ^{13}C chemical shift values were reported with reference to the $CDCl_3$ solvent peak at 7.25 ppm and 77 ppm. Mass spectra were recorded using electrospray (ESI) techniques. Low and High-resolution mass spectra were measured with a Finnigan TSQ70 and VG, analytical ZAB2-E instruments, respectively. The FT-IR spectra were recorded on the Perkin-Elmer model spectrum series FT-IR as a KBR pellet.

2. Synthesis and Characterization of the Intermediate and API

(A) Synthesis of Hydroxy Hydrazone 8 Intermediate

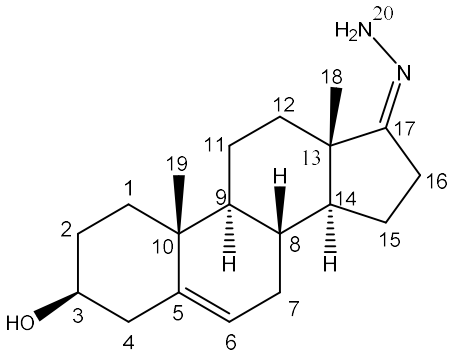


Figure S1. Chemical Structure of Hydrazone Intermediate **8**.

Add Dehydroepiandrosterone (DHEA) **7** (10 kg, 34.7 mol), methanol (60 L), and hydrazine hydrate (8.67 kg, 173 mol) to the reaction vessel at room temperature. Heat the reaction mixture to 35±5 °C and stir at 40 RPM for 12-14 h. Distil off 50% of the solvent at 40 °C under vacuum (680 mmHg). Add water (60 L) to the reaction mixture. Stir the mixture at 25-35 °C for 1-2 h at 40 RPM. Filter the solid product and wash with water (40 L). Dry the wet cake under vacuum (680 mmHg) at 60-65 °C for 6 h to obtain the final product **8** (10.3 kg, yield 98%, HPLC purity 99%); HRMS analysis: *m/z* calcd for $C_{19}H_{30}N_2O+H^+$: 303.46 $[M+H]^+$; found: 303.2419; IR (KBr cm^{-1}): 3435.46, 2927.34, 2927.34, 1655.22, 1628.53, 1604.37, 1475.12, 1389.05, 1376.23, 1299.76, 1248.98, 1208.80, 1185.43, 1104.93, 1048.28, 1022.10.

Table S1. Chemical Shift Assignments of Hydroxy Hydrazone Intermediate **8**

Position No	Proton	^{1}H (δ ppm)	Multiplicity, *J* in Hz	^{13}C (δ ppm)	DEPT-135
1	H1	1.09	m	37.24	CH_2
	H1’	1.85	m		

2	H2	1.50	m	31.62	CH_2
	H2’	1.84	m		
3	H3	3.52	m	71.56	CH
4	H4	2.30	m	42.25	CH_2
	H4’	2.25	m		
5	-	-	-	141.14	C
6	H6	5.37	m	121.05	CH
7	H7	1.60	m	31.32	CH_2
	H7’	2.06	m		
8	H8	1.60	m	31.31	CH
9	H9	1.02	m	50.46	CH
10	-	-	-	36.65	C
11	H11	1.60	m	20.68	CH_2
	H11’	1.51	m		
12	H12	1.92	m	34.11	CH_2
	H12’	1.37	m		
13	-	-	-	43.81	C
14	H14	1.13	m	53.98	CH
15	H15	1.88	m	23.41	CH_2
	H15’	1.43	m		
16	H16	2.19	m	24.42	CH_2
	H16’	2.28	m		
17	-	-	-	166.20	C
18	H18	0.87	s	16.79	CH_3
19	H19	1.03	s	19.42	CH_3
20	H20	4.76	bs	-	-
s = singlet, bs = broad signal, m = multiplet					

(B) Synthesis of Vinyl Iodide Intermediate 9

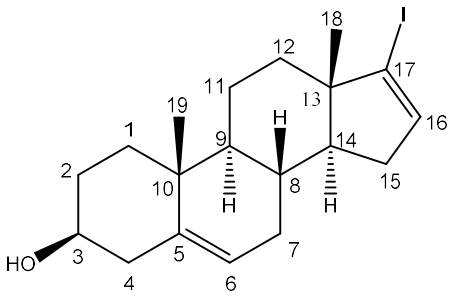


Figure S2. Chemical Structure of Vinyl Iodide Intermediate **9**.

Add Hydroxy Hydrazone **8** (10 kg, 33 mol), methanol (70 L), and dichloromethane (7.5 L) to the reaction vessel. Stir at 40 RPM and check for dissolution at 0-10 °C. In a separate reaction vessel, add methanol (2.5 L), dichloromethane (47.5 L), and iodine (16.8 kg, 66.2 mol). Cool the mixture to -10 to 0 °C. Add tetramethyl guanidine (26.65 kg, 231.7 mol) to the iodine solution at -10 to 0 °C, over 30 - 45 min. Slowly add the Hydroxy Hydrazone **8** solution to the iodine solution over 3 h at -10 to 0 °C. Maintain the temperature for an additional 2-3 h. Heat the reaction mixture to 0-10 °C and maintain for 1-2 h. Distil off the reaction mixture under vacuum (680 mmHg) below 40 °C. Add water (100 L) to the residue and stir at 40 RPM for 1-2 h at 25-35 °C. Filter the compound and wash it with water (20 L). After drying, add dichloromethane (50 L) and stir at 40 RPM for 10-15 min to obtain a clear solution. Add 0.1 N HCl solution (20 L) to the reaction mixture and ensure the pH is acidic. Separate the layers. Wash the organic layer with sodium thiosulfate solution (3 kg in 20 L water) followed by 5% sodium chloride solution (1.5 kg NaCl in 20 L water). Distil off the organic layer under vacuum (680 mmHg) below 40 °C until 2-3 vol remains. Add methanol (10 L) and distill off below 60 °C under vacuum (680 mmHg) until 5-6 vol remains. Cool the reaction mixture to 0-5 °C and stir at 40 RPM for 60-90 min. Filter the solid and wash

with methanol (10 L). Dry the material at 50-55 °C under vacuum (680 mmHg) for 5-6 h to obtain compound **9** (11.1 kg, yield 84%, purity 99%). HRMS analysis: *m/z* calcd for $C_{19}H_{27}IO$-H_2O + H^+: 381.11 $[M+H-H_2O]^+$; found: 381.1058; IR (KBr cm^{-1}): 3638.07, 3309.50, 2968.35, 2929.93, 2902.38, 2834.30, 1458.76, 1450.62, 1437.47, 1367.71, 1246.23, 1062.08, 1043.71, 1018.21, 1007.26, 993.60, 952.01, 833.13, 744.21, 635.74.

Table S2. Chemical Shift Assignments of Vinyl Iodide Intermediate **9**

Position No	Proton	^{1}H (δ ppm)	Multiplicity, *J* in Hz	^{13}C (δ ppm)	DEPT-135
1	H1	1.09	m	37.13	CH_2
	H1’	1.84	m		
2	H2	1.51	m	31.57	CH_2
	H2’	1.85	m		
3	H3	3.53	m	71.66	CH
4	H4	2.31	m	42.19	CH_2
	H4’	2.25	m		
5	-	-	-	141.18	C
6	H6	5.36	m	121.13	CH
7	H7	1.61	m	31.19	CH_2
	H7’	2.02	m		
8	H8	1.69	m	31.00	CH
9	H9	1.02	m	50.46	CH
10	-	-	-	36.72	C
11	H11	1.67	m	20.79	CH_2
	H11’	1.53	m		
12	H12	1.64	m	36.14	CH_2
	H12’	1.23	m		
13	-	-	-	49.91	C
14	H14	1.48	m	54.78	CH
15	H15	1.96	m	33.74	CH_2

	H15’	2.15	m		
16	H16	6.14	dd, J = 1.71, 3.18	137.48	CH
17	-	-	-	112.66	C
18	H18	0.76	s	15.10	CH_3
19	H19	1.05	s	19.30	CH_3
s = singlet, d = doublet, dd = doublet of doublet, dt = doublet of triplet, m = multiplet					

(C) Synthesis of Abiraterone Acetate 1

Add Vinyl iodide intermediate **9** (25 kg, 28.69 mol), isopropanol (150 L), diethyl (3-pyridyl) borane **5** (8.95 kg, 27.84 mol), and bis(triphenylphosphine) palladium (II) dichloride (0.197 kg, 0.13 mol) to the reaction vessel. Stir the mixture at 40 RPM for 10-15 min. Add sodium carbonate solution (46.5 kg, 202.72 mol in 100 L water) to the reaction mixture and stir for 10 min. Heat the reaction mixture to 78-82 °C and stir at 40 RPM for 2-3 h. Cool the reaction mixture to 25 -30 °C and extract with toluene (75 L). Transfer the toluene layer to a reaction vessel, add methanol (100 L) and water (100 L), and heat to 50-60 °C. Adjust the pH to 0.5-1.0 using diluted HCl solution (7.5 L HCl in 7.5 L water). Separate the layers and wash the aqueous layer with toluene (50 L). Add thiosilica (1.0 kg, 4% w/w) to the organic layer and stir at 40 RPM for 20-30 min at 65-70 °C. Cool the mixture to 50-55 °C. Add sodium hydroxide solution (5.4 kg, 136 mol in 25 L water) and stir at 50-55 °C for 5 h. Separate the aqueous and organic layers at 50-55 °C. Add thiosilica (4 kg) to the organic layer and stir at 65-70 °C for 30 min. Filter the thiosilica on a Celite bed. Distil off toluene below 50 °C under vacuum (680 mmHg) until the reaction mass is 3.0-3.5 times the batch size. Cool the reaction mass to 5-10 °C and stir at 40 RPM for 60 min. Filter the compound. Dry the material under vacuum (680 mmHg) at 65-70 °C for 5-6 h (dry weight: 23 kg). Add acetone (125 L), triethylamine (14.9 kg, 147 mol), and 4-(dimethylamino) pyridine (0.72 kg, 5.89 mol) to the dried compound at 25-35 °C under a nitrogen atmosphere. Heat the reaction mass to 38-42 °C.

Slowly add acetic anhydride (12 kg, 117 mol) and stir the reaction mass at 40 RPM for 3-4 h at 38-42 °C. Add Ultra DX carbon (2.5 kg, 10% w/w) and thiosilica (0.5 kg, 2% w/w) to the reaction mass and stir for 20-30 min. Filter the reaction mass through a Celite bed followed by a 0.2-micron filter and wash the bed with acetone (25 L). Transfer the filtrate to a reaction vessel, slowly add water (75 L), and stir for 1-2 h at 25-30 °C. Filter the solid and wash with water (50 L). Dry the compound under vacuum (680 mmHg) at 40-45 °C for 5-6 h to obtain the title compound **1** (19.2 kg, yield:78%, purity: 99.7%). The ESI *+ve* ionization mass displayed protonated molecular ion at *m/z* = 392.3 matching with the corresponding formula $C_{26}H_{33}NO_2$; IR (KBr cm^{-1}): 3439.34, 3047.06, 2936.97, 2891.55, 2854.99, 1735.17, 1667.84, 1602.31, 1559.28, 1374.26, 1244.99, 1138.44, 1244.99, 1034.85.

Table S3. Chemical Shift Assignments of Abiraterone Acetate **1**

Position No	Proton	^{1}H (δ ppm)	Multiplicity, *J* in Hz	^{13}C (δ ppm)	DEPT-135
1	H1	1.15	m	36.87	CH_2
	H1’	1.86	m		
2	H2	1.60	m	27.69	CH_2
	H2’	1.87	m		
3	H3	4.61	m	73.80	CH
4	H4	2.34	m	38.09	CH_2
5	H5	-	-	139.98	C
6	H6	5.41	m	122.24	CH
7	H7	1.68	m	31.46	CH_2
	H7’	2.06	m		
8	H8	1.76	dd, *J* = 4.6,10.6,15.8	30.36	CH
9	H9	1.08	m	50.21	CH
10	-	-	-	36.74	C
11	H11	1.60	m	20.77	CH_2

	H11’	1.66	m		
12	H12	1.49	m	35.16	CH_2
	H12’	2.04	m		
13	-	-	-	47.28	C
14	H14	1.59	m	57.42	CH
15	H15	2.26	m	31.74	CH_2
	H15’	2.05	m		
16	H16	5.99	dd, J = 1.8, 3.4	129.15	CH
17	H17	-	-	151.63	C
18	H18	1.05	s	16.53	CH_3
19	H19	1.07	s	19.21	CH_3
20	H20	-	-	132.89	C
21	H21	7.64	td, J = 1.8, 7.9	133.61	CH
22	H22	7.21	dd, J = 4.7, 7.9	122.95	CH
23	H23	8.45	dd, J = 1.4, 4.7	147.85	CH
25	H25	8.62	d, J = 2.1	147.91	CH
26	-	-	-	170.47	C
27	H26	2.03	s	21.39	CH_3
s = singlet, d = doublet, dd = doublet of doublet, td = triplet of doublet, m = multiplet					

3. DoE Statistical Analysis

A) Hydroxy Hydrazone Intermediate 8

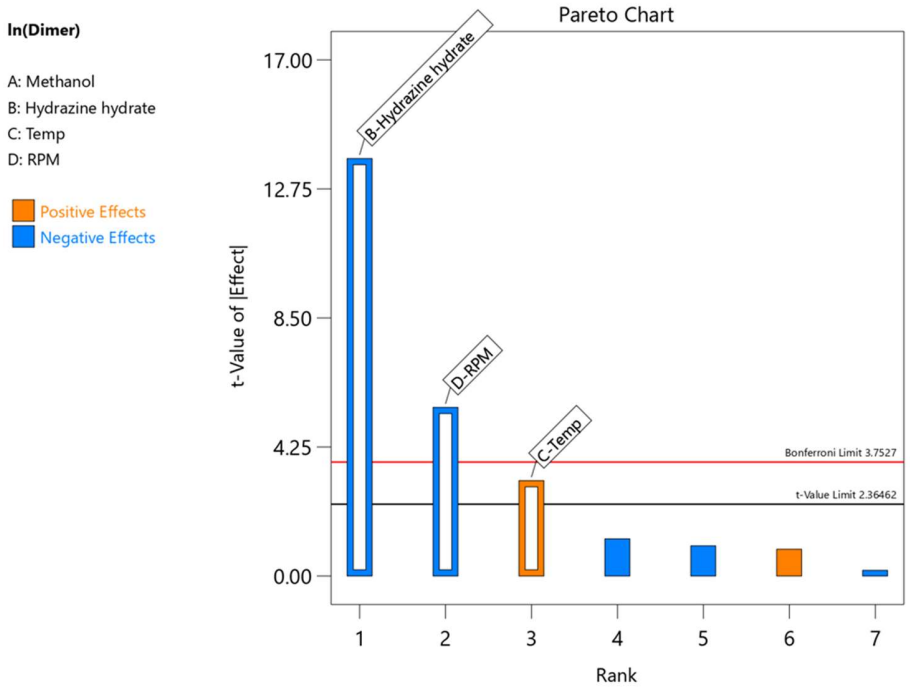


Figure S3. Pareto Chart of Dimer **11**.

Table S4. ANOVA Table of DIMER **11**

Source	Sum of Squares	*df*	Mean Square	*F*-value	*p*-value	
Model	1.89	3	0.6309	76.59	< 0.0001	significant
B-Hydrazine hydrate	1.56	1	1.56	189.09	< 0.0001	
C-Temp	0.0811	1	0.0811	9.85	0.0201	
D-RPM	0.2538	1	0.2538	30.81	0.0014	
Curvature	0.5833	1	0.5833	70.81	0.0002	
Residual	0.0494	6	0.0082			
Lack of Fit	0.0271	4	0.0068	0.6058	0.6999	not significant
Pure Error	0.0223	2	0.0112			
Cor Total	2.53	10				

Table S5. Fit Statistics of DIMER **11**

Std. Dev.	**0.0908**	**R²**	**0.9745**
Mean	-1.29	Adjusted R²	0.9618
C.V.%	7.04	Predicted R²	0.9183
		Adeq Precision	23.5356

B) Vinyl Iodide Intermediate 9

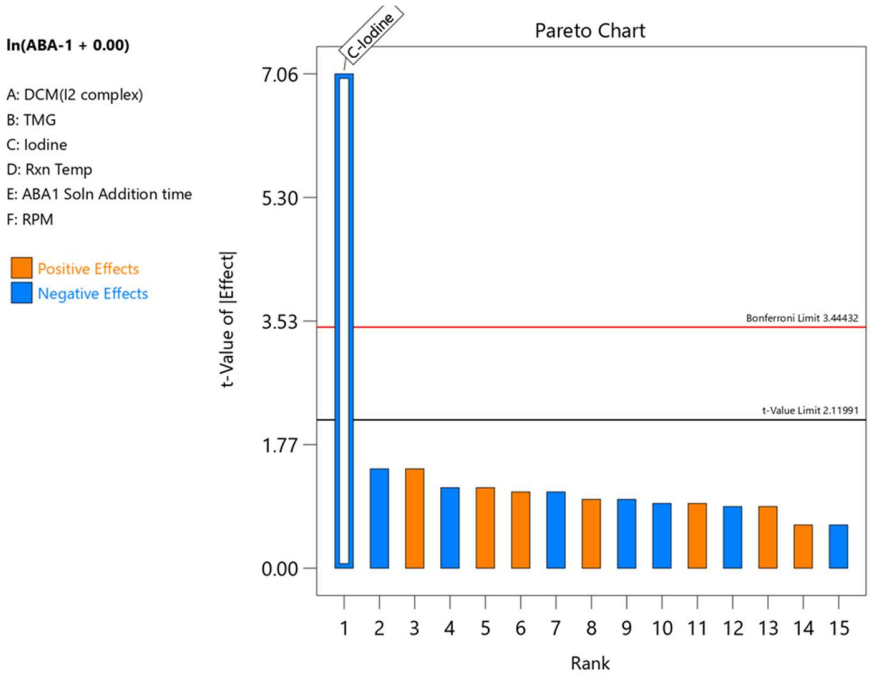


Figure S4. Pareto Chart of Unreacted Hydroxy Hydrazone **8**.

Table S6. ANOVA Table of Unreacted Hydroxy Hydrazone **8**

Source	Sum of Squares	*df*	Mean Square	*F*-value	*p*-value	
Model	224.91	1	224.91	38.86	< 0.0001	significant
C-Iodine	224.91	1	224.91	38.86	< 0.0001	
Residual	92.60	16	5.79			
Lack of Fit	92.60	15	6.17			
Pure Error	0.0000	1	0.0000			
Cor Total	317.51	17				

Table S7. Fit Statistics of Unreacted Hydroxy Hydrazone **8**

Std. Dev.	**2.41**	**R^2**	**0.7084**
Mean	-3.58	Adjusted R^2	0.6901
C.V.%	67.29	Predicted R^2	0.6366
		Adeq Precision	9.3507

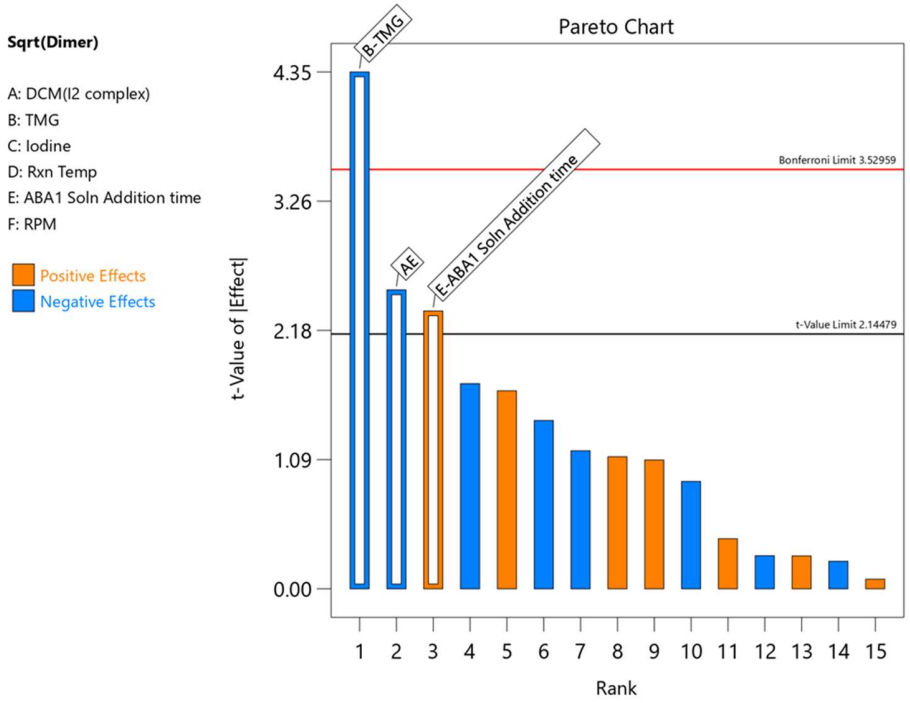


Figure S5. Pareto Chart of Dimer **11**.

Table S8. ANOVA Table of Dimer **11**

Source	Sum of Squares	*df*	Mean Square	*F*-value	*p*-value	
Model	9.76	3	3.25	10.07	0.0009	significant
B-TMG	6.01	1	6.01	18.61	0.0007	
E-ABA1 Sol Addition time	1.74	1	1.74	5.38	0.0360	
AE	2.01	1	2.01	6.22	0.0257	

Residual	4.52	14	0.3231			
Lack of Fit	4.44	13	0.3413	3.96	0.3762	not significant
Pure Error	0.0862	1	0.0862			
Cor Total	14.28	17				

Table S9. Fit Statistics of Dimer **11**

Std. Dev.	**0.5684**	**R^2**	**0.6834**
Mean	1.39	Adjusted R^2	0.6155
C.V.%	40.79	Predicted R^2	0.4664
		Adeq Precision	9.6817

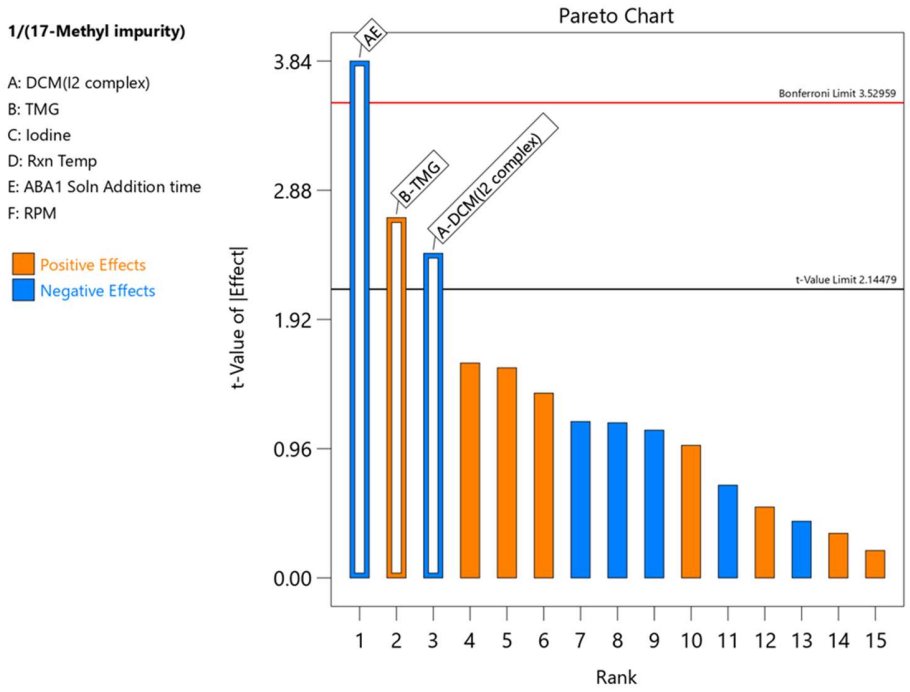


Figure S6. Pareto Chart of 17-Methyl Impurity **12**.

Table S10. ANOVA Table of 17-Methyl Impurity **12**

Source	Sum of Squares	*df*	Mean Square	*F*-value	*p*-value	

Model	0.0188	3	0.0063	9.21	0.0013	significant
A-DCM (I_2 complex)	0.0039	1	0.0039	5.79	0.0305	
B-TMG	0.0049	1	0.0049	7.14	0.0182	
AE	0.0100	1	0.0100	14.70	0.0018	
Residual	0.0095	14	0.0007			
Lack of Fit	0.0094	13	0.0007	4.96	0.3392	not significant
Pure Error	0.0001	1	0.0001			
Cor Total	0.0283	17				

Table S11. Fit Statistics of 17-Methyl Impurity **12**

Std. Dev.	**0.0261**	**R^2**	**0.6637**
Mean	0.1143	Adjusted R^2	0.5916
C.V.%	22.81	Predicted R^2	0.4300
		Adeq Precision	9.4531

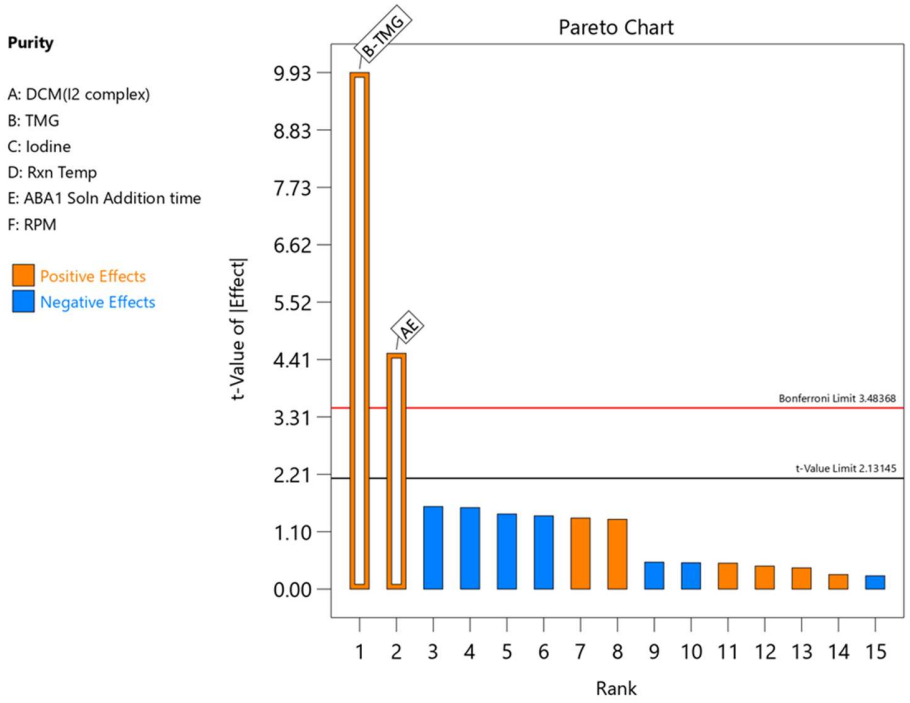


Figure S7. Pareto Chart of Purity **9**.

Table S12. ANOVA Table of Purity **9**

Source	Sum of Squares	*df*	Mean Square	*F*-value	*p*-value	
Model	1119.66	2	559.83	59.60	< 0.0001	significant
B-TMG	926.59	1	926.59	98.65	< 0.0001	
AE	193.07	1	193.07	20.55	0.0005	
Curvature	180.81	1	180.81	19.25	0.0006	
Residual	131.50	14	9.39			
Lack of Fit	131.11	13	10.09	26.05	0.1523	not significant
Pure Error	0.3872	1	0.3872			
Cor Total	1431.98	17				

Table S13. Fit Statistics of Purity **9**

Std. Dev.	**3.06**	**R^2**	**0.8949**
Mean	75.20	Adjusted R^2	0.8799
C.V.%	4.08	Predicted R^2	0.8400
		Adeq Precision	15.3434

C) Suzuki Coupling Abiraterone 1a Synthesis

Table S14. ANOVA for Vinyl Iodide **9** Content

Source	Sum of Squares	*df*	Mean Square	*F*-value	*p*-value	
Model	1266.53	5	253.31	72.17	< 0.0001	significant
A-Total vol	117.38	1	117.38	33.45	0.0004	
C-Na2CO3	119.47	1	119.47	34.04	0.0004	
E-Water%	61.14	1	61.14	17.42	0.0031	
CE	106.01	1	106.01	30.20	0.0006	
E^2	727.87	1	727.87	207.39	< 0.0001	
Residual	28.08	8	3.51			
Lack of Fit	27.82	7	3.97	15.33	0.1942	not significant

Pure Error	0.2592	1	0.2592			
Cor Total	1294.61	13				

Table S15. Fit Statistics for Vinyl Iodide **9** Content

Std. Dev.	**1.87**	**R^2**	**0.9783**
Mean	10.12	Adjusted R^2	0.9648
C.V.%	18.52	Predicted R^2	0.9384
		Adeq Precision	26.7422

Table S16. ANOVA Table of Abiraterone **1a**

Source	Sum of Squares	*df*	Mean Square	*F*-value	*p*-value	
Model	32.39	5	6.48	17.95	0.0004	significant
A-Total vol	1.94	1	1.94	5.37	0.0491	
C-Na2CO3	3.43	1	3.43	9.52	0.0150	
E-Water%	2.69	1	2.69	7.47	0.0257	
CE	3.77	1	3.77	10.46	0.0120	
E^2	16.90	1	16.90	46.82	0.0001	
Residual	2.89	8	0.3609			
Lack of Fit	2.88	7	0.4115	62.90	0.0968	not significant
Pure Error	0.0065	1	0.0065			
Cor Total	35.28	13				

Table S17. Fit Statistics of Abiraterone **1a**

Std. Dev.	**0.6008**	**R^2**	**0.9182**
Mean	0.6347	Adjusted R^2	0.8670
C.V.%	94.66	Predicted R^2	0.6185
		Adeq Precision	13.6178

4. ^{1}H and ^{13}C NMR Data

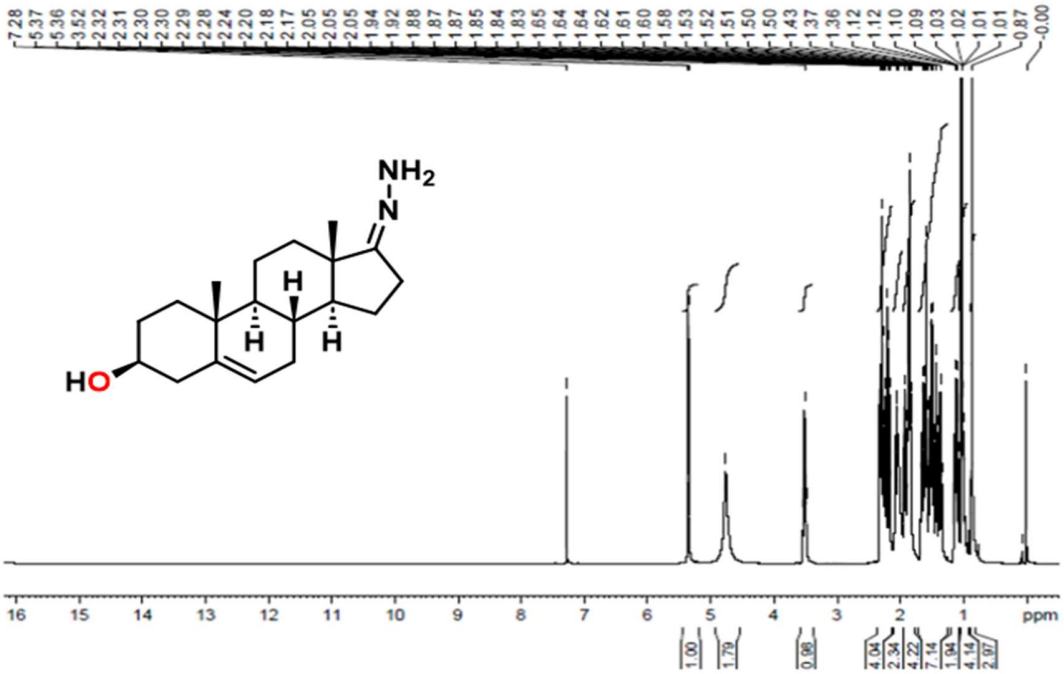


Figure S8. ^{1}H NMR Spectrum of Hydrazone Intermediate **8**.

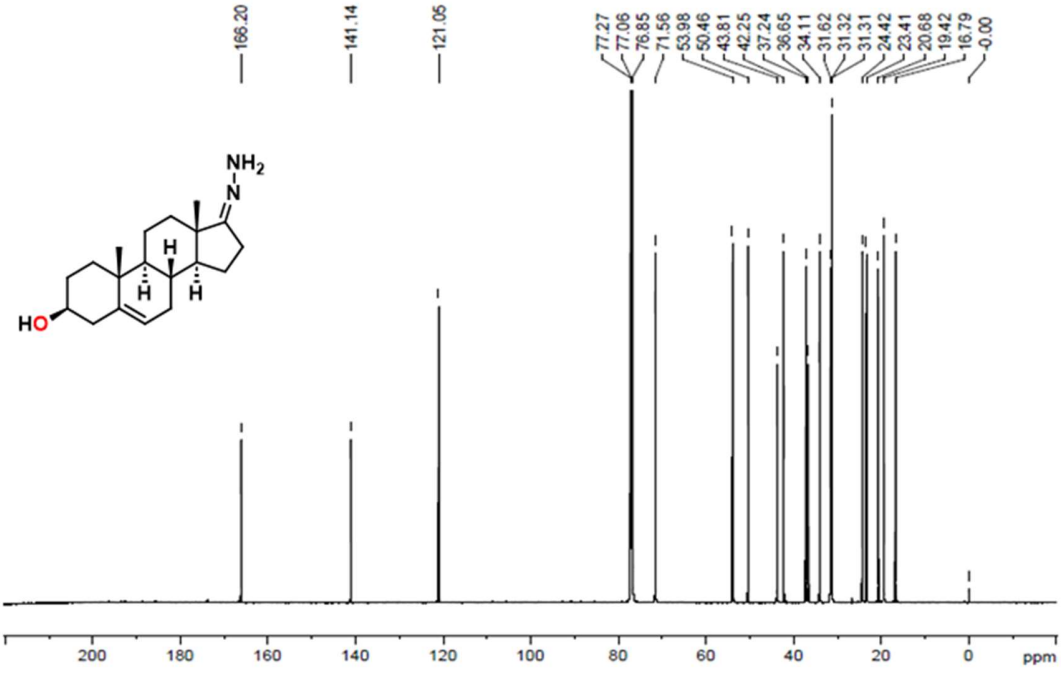


Figure S9. ^{13}C NMR Spectrum of Hydrazone Intermediate **8**.

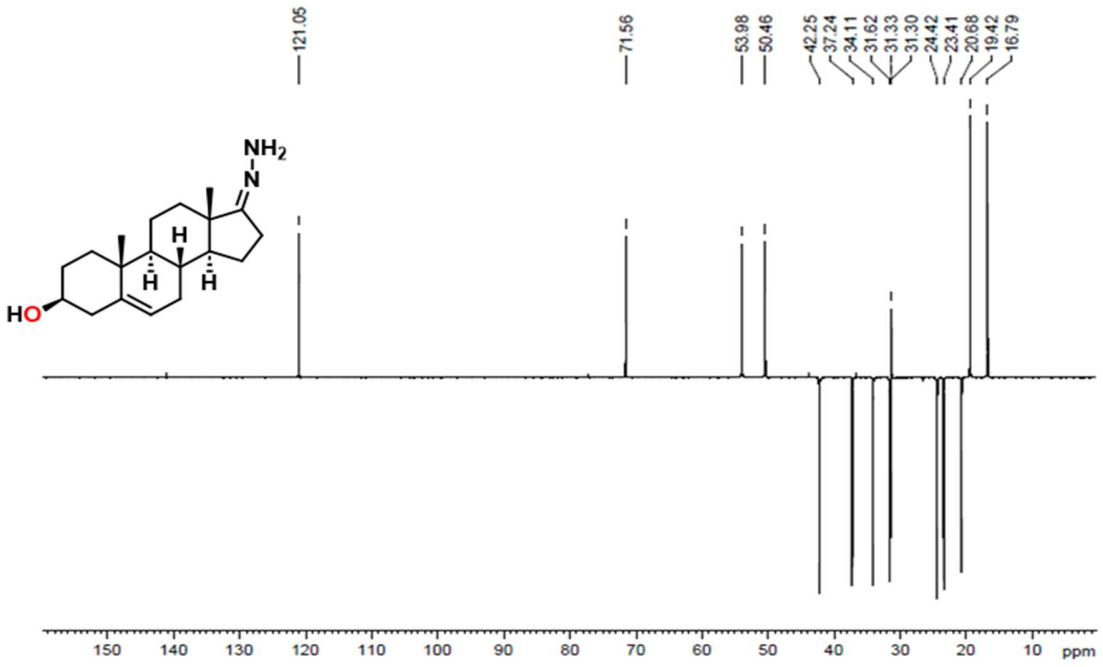


Figure S10. DEPT-135 NMR Spectrum of Hydrazone Intermediate **8**.

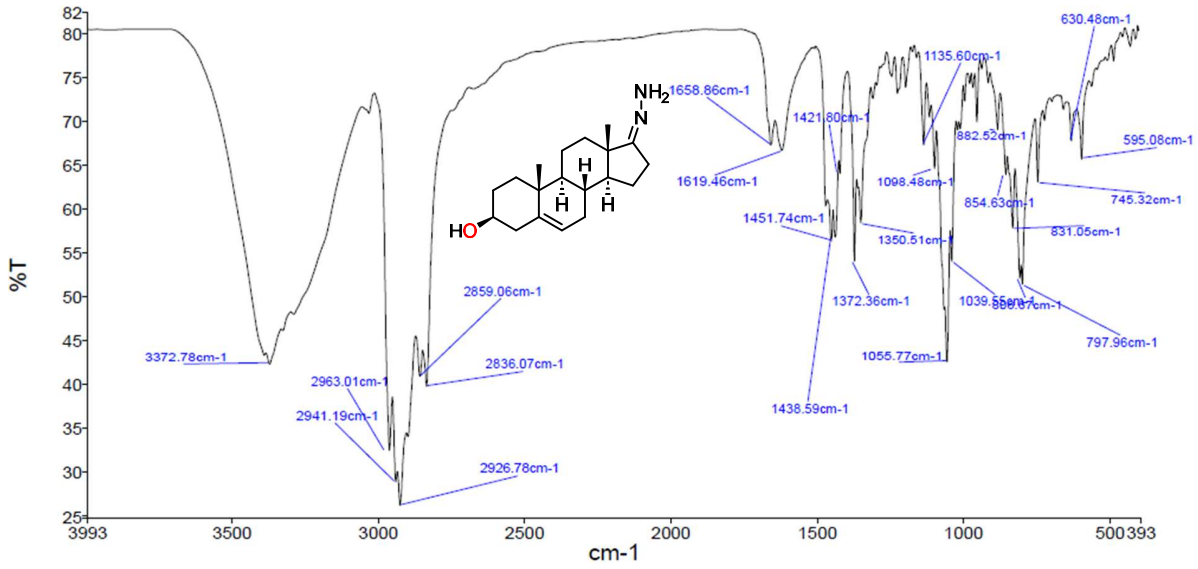


Figure S11. FT-IR Spectrum of Hydrazone Intermediate **8**.

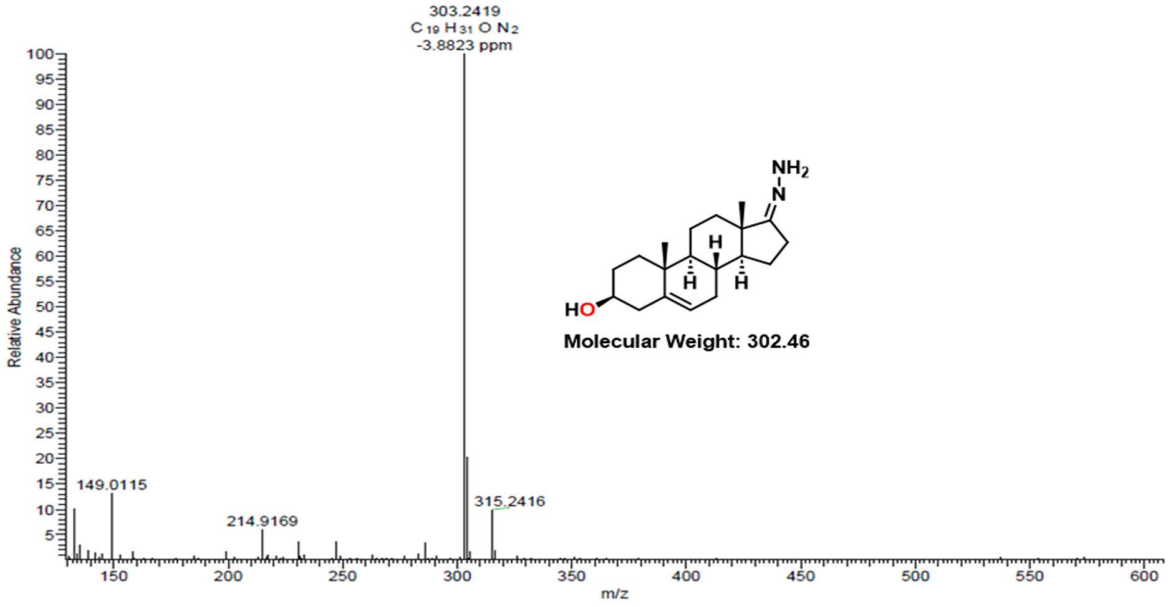


Figure S12. Mass Spectrum of Hydrazone Intermediate **8**.

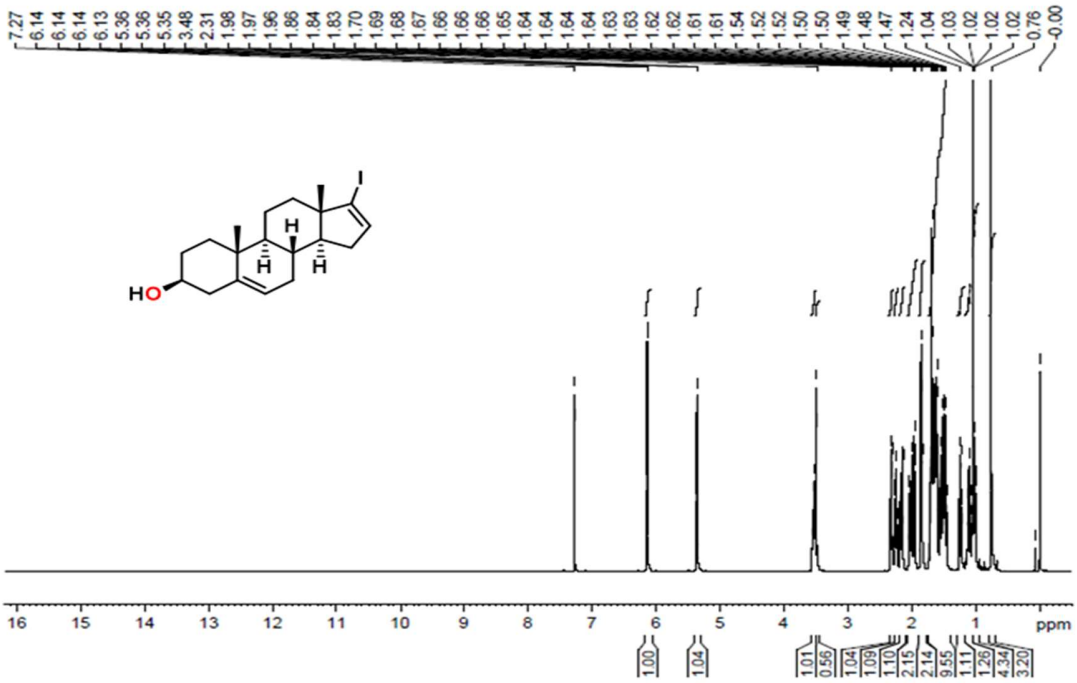


Figure S13. ^{1}H NMR Spectrum of Vinyl Iodide Intermediate **9**.

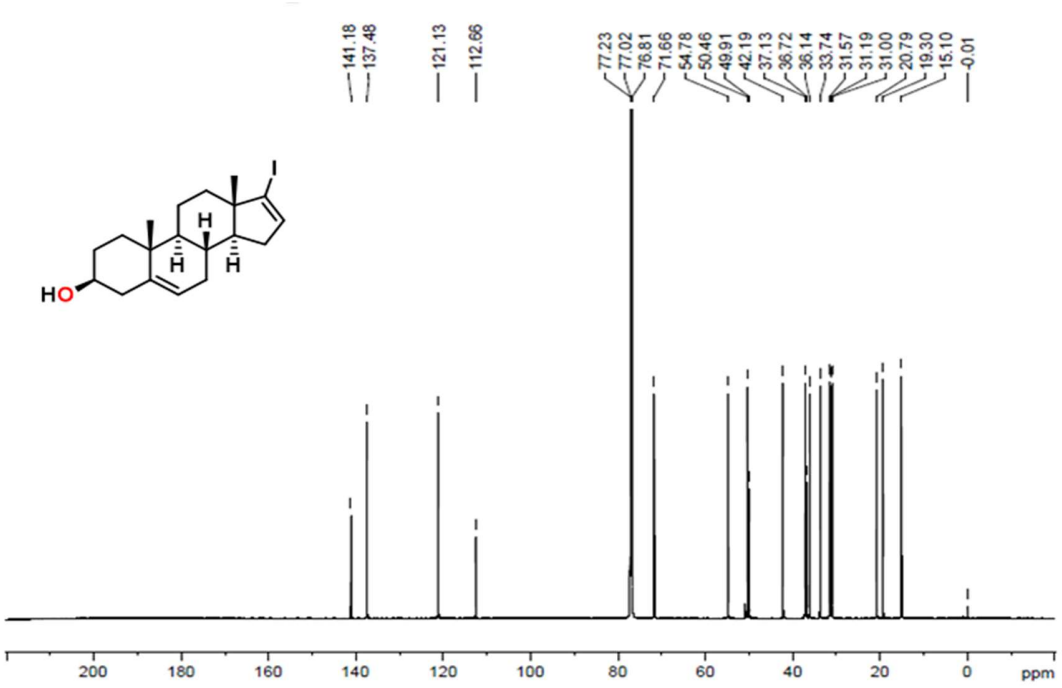


Figure S14. ^{13}C NMR Spectrum of Vinyl Iodide Intermediate **9**.

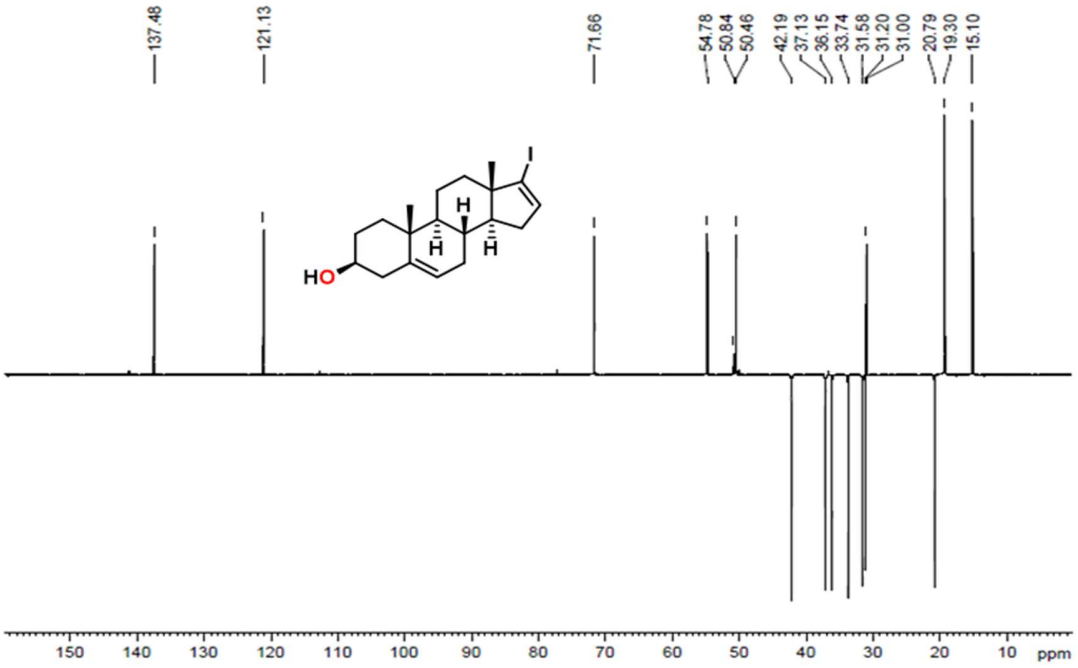


Figure S15. DEPT-135 NMR Spectrum of Vinyl Iodide Intermediate **9**.

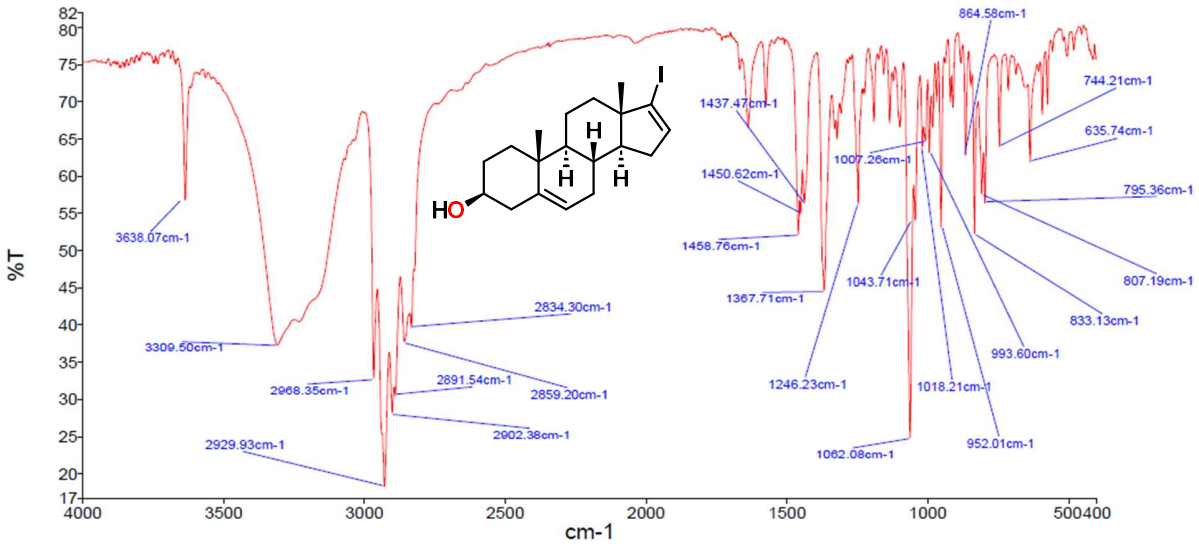


Figure S16. FT-IR Spectrum of Vinyl Iodide Intermediate **9**.

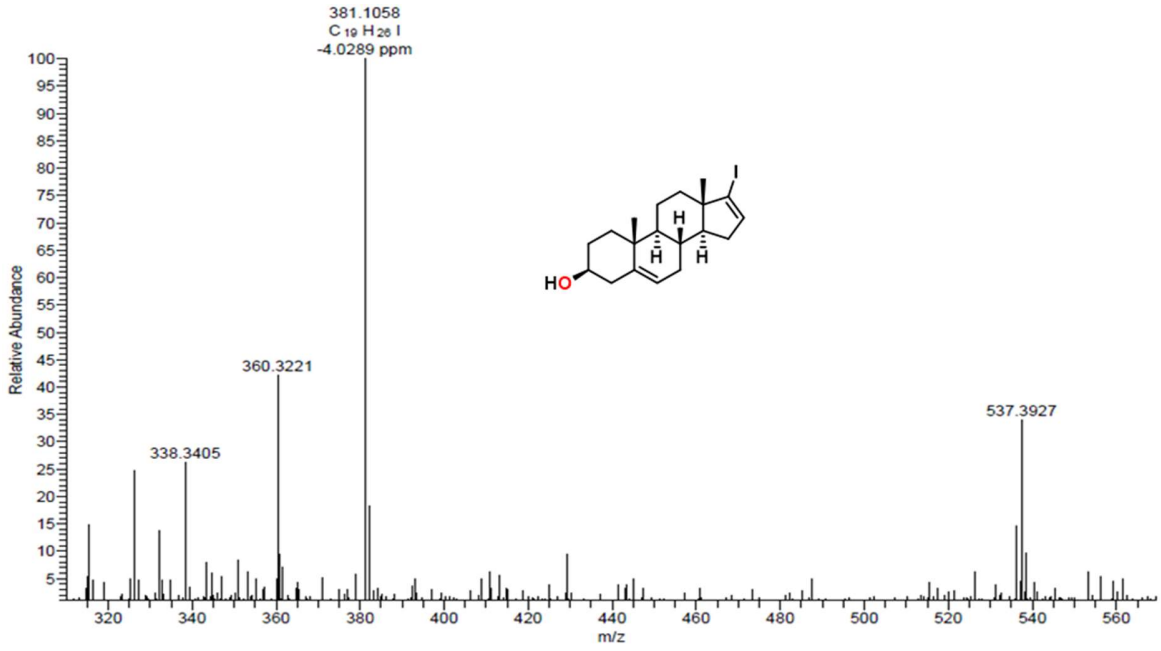


Figure S17. Mass Spectrum of Vinyl Iodide Intermediate **9**.

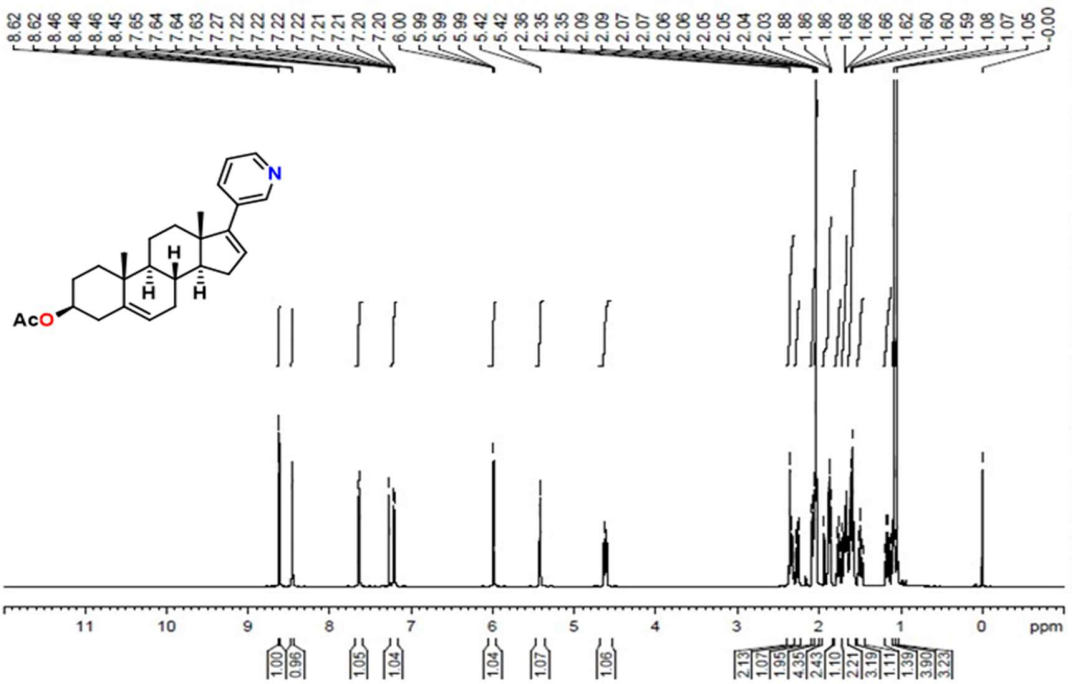


Figure S18. [1]H NMR Spectrum of Abiraterone Acetate **1**.

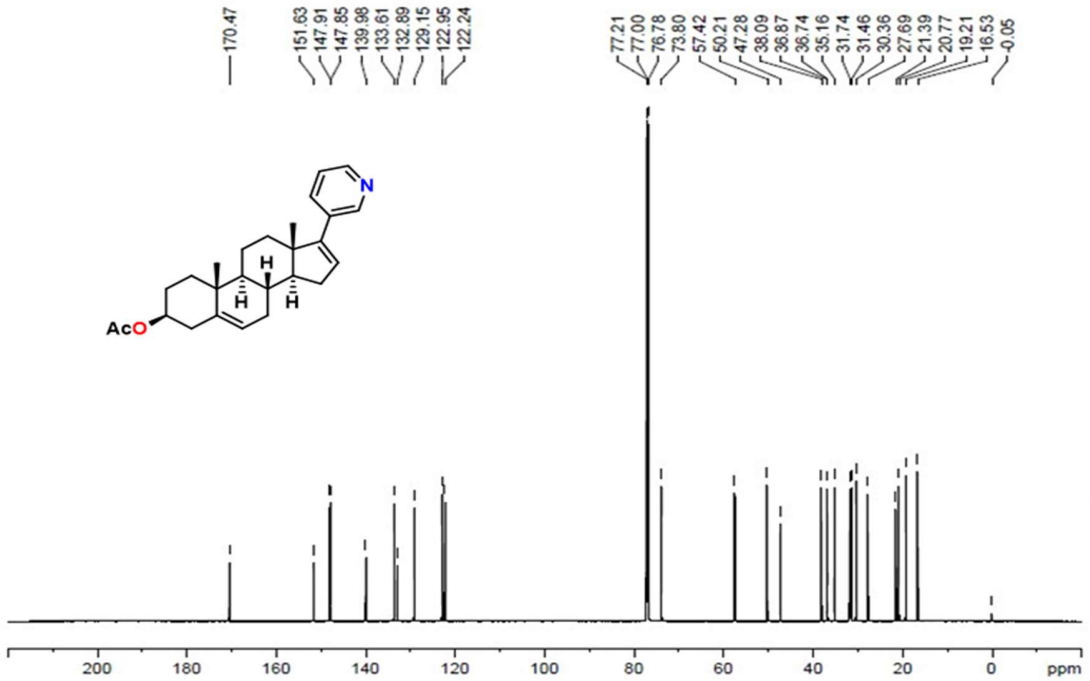


Figure S19. [13]C NMR Spectrum of Abiraterone Acetate **1**.

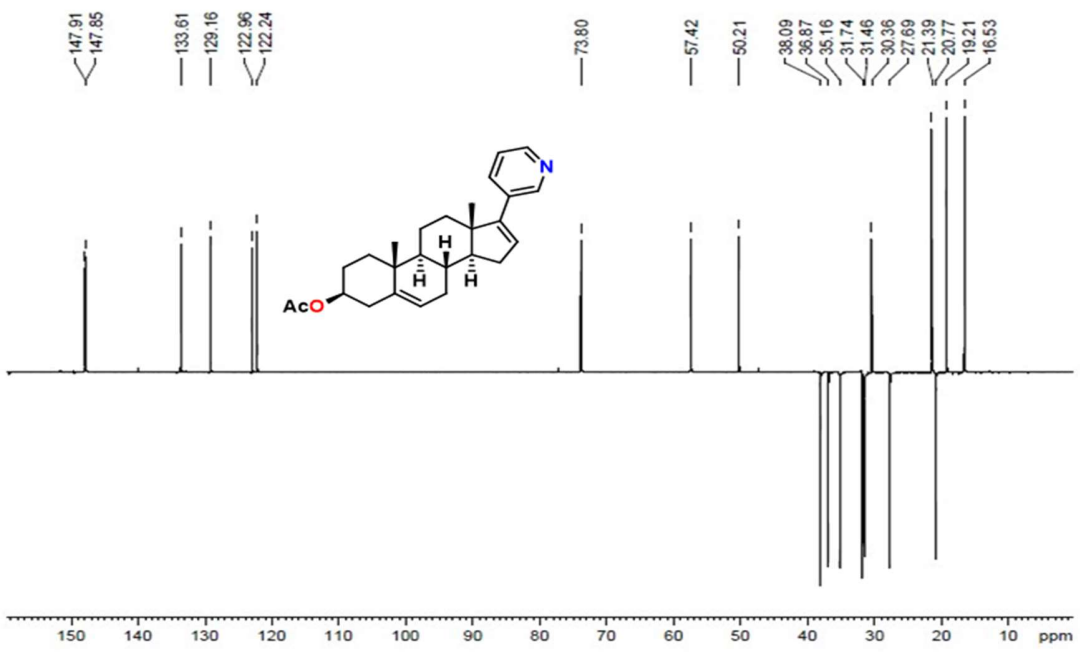


Figure S20. DEPT-135 NMR Spectrum of Abiraterone Acetate **1**.

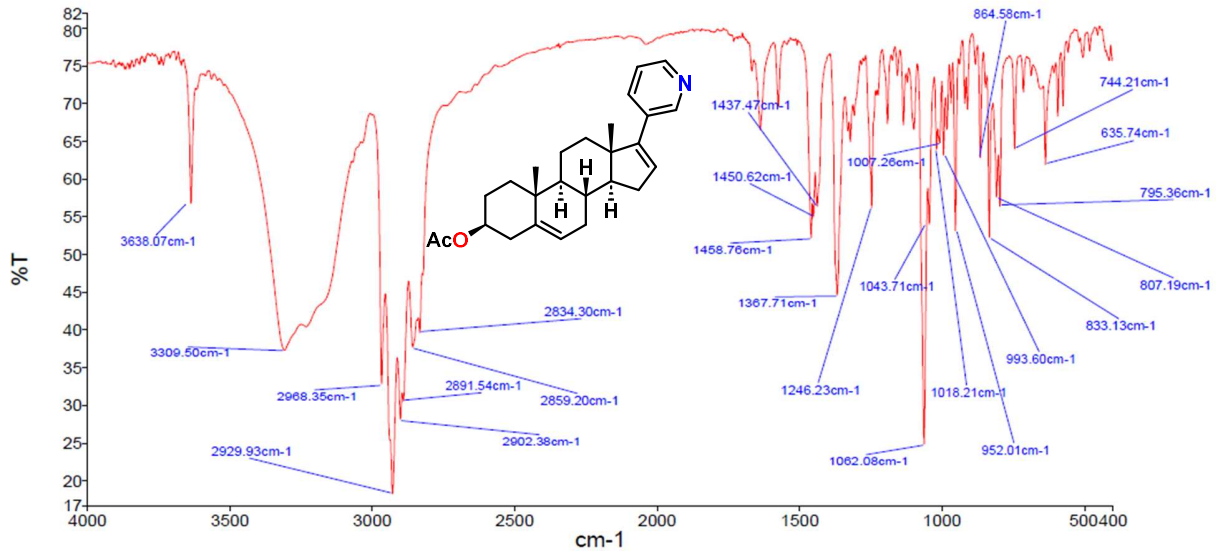


Figure S21. FT-IR Spectrum of Abiraterone Acetate **1**.

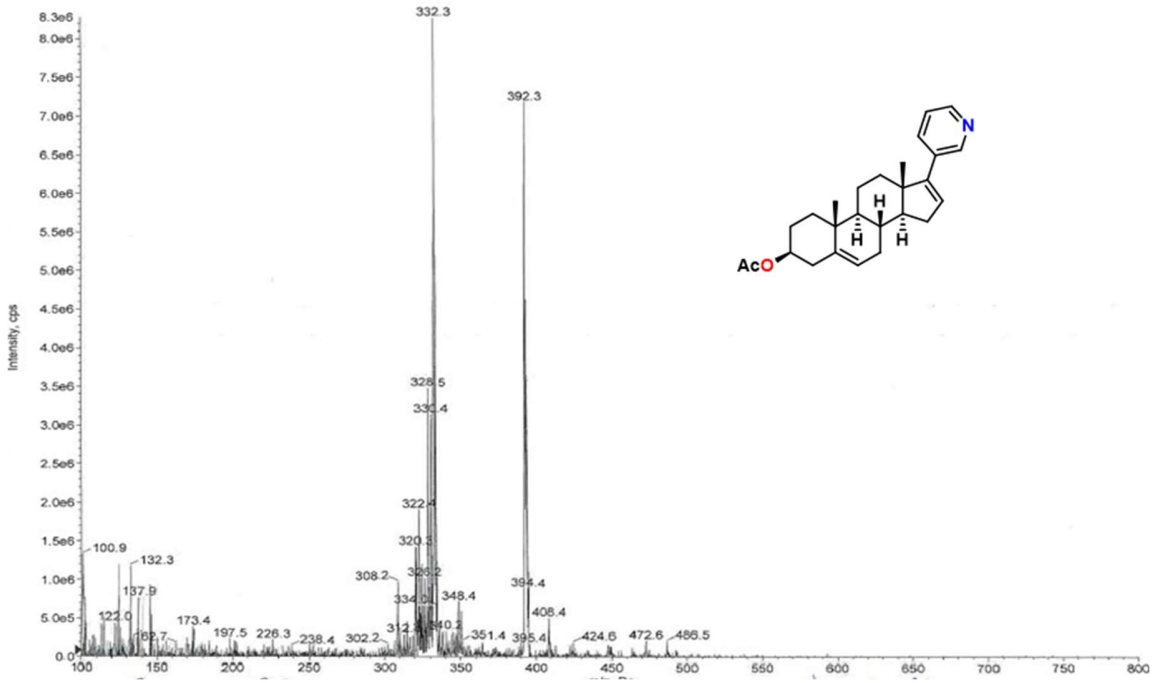
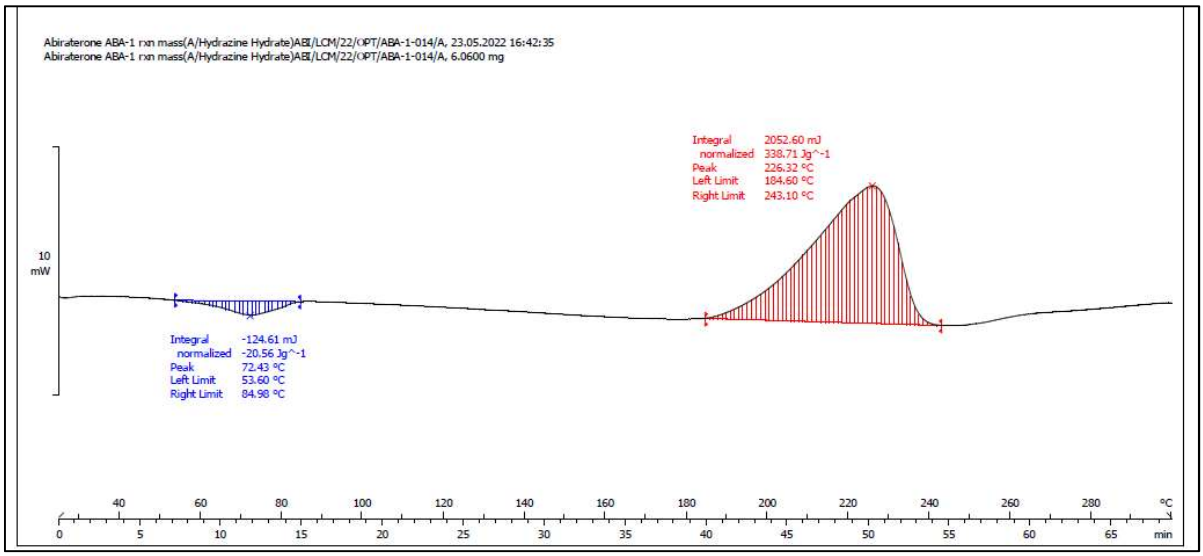


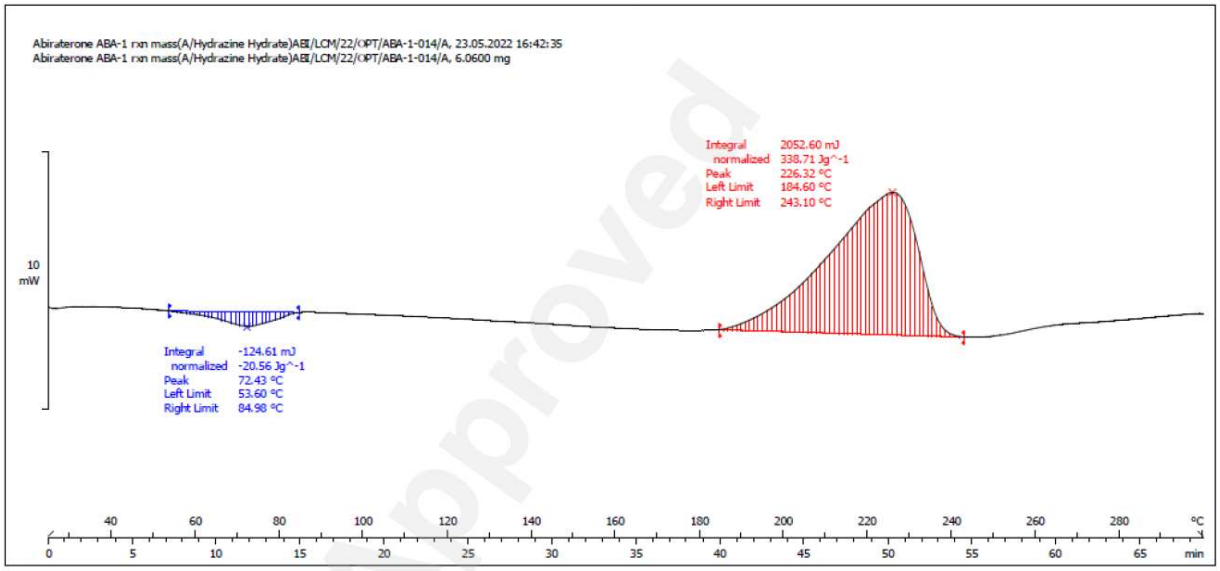
Figure S22. Mass Spectrum of Abiraterone Acetate **1**.

5. Safety and Hazard Evaluation

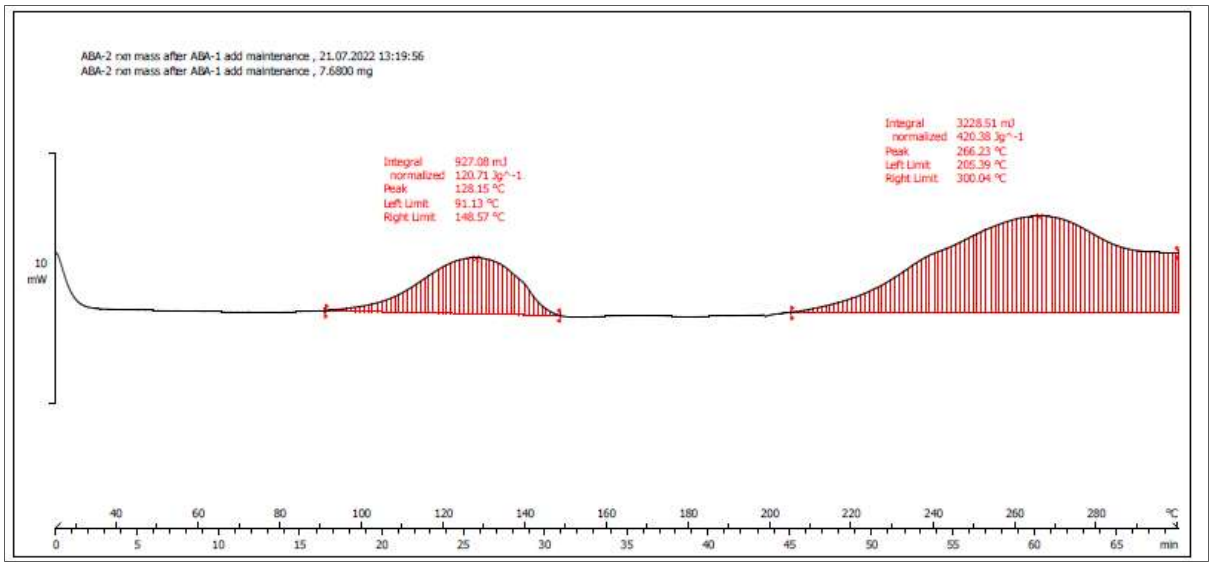
Safety and hazard evaluations have been conducted for all three chemical conversions. As part of the study, thermal stability data have been established using the DSC (Differential Scanning Calorimetry) technique. During Step 1, the formation of the hydrazone intermediate (8) revealed an exothermic event at 185 °C. However, the optimized process conditions are maintained below 65 °C. In Step 2, the formation of the vinyl iodide intermediate (9) showed an exothermic event at 91 °C during the reaction mass DSC. Consequently, the process was optimized with the slow addition of starting materials and reagents at temperatures below 10 °C. In Stage 3, the Suzuki coupling reaction showed no exothermic events. Furthermore, safe operating and handling procedures for reagents, raw materials, and solvents were established based on the safety and hazard assessment.

a) DSC graph of Hydrazone (8) reaction mass





b) DSC graph of Vinyl iodide (9) reaction mass



c) DSC graph of Suzuki coupling reaction mass

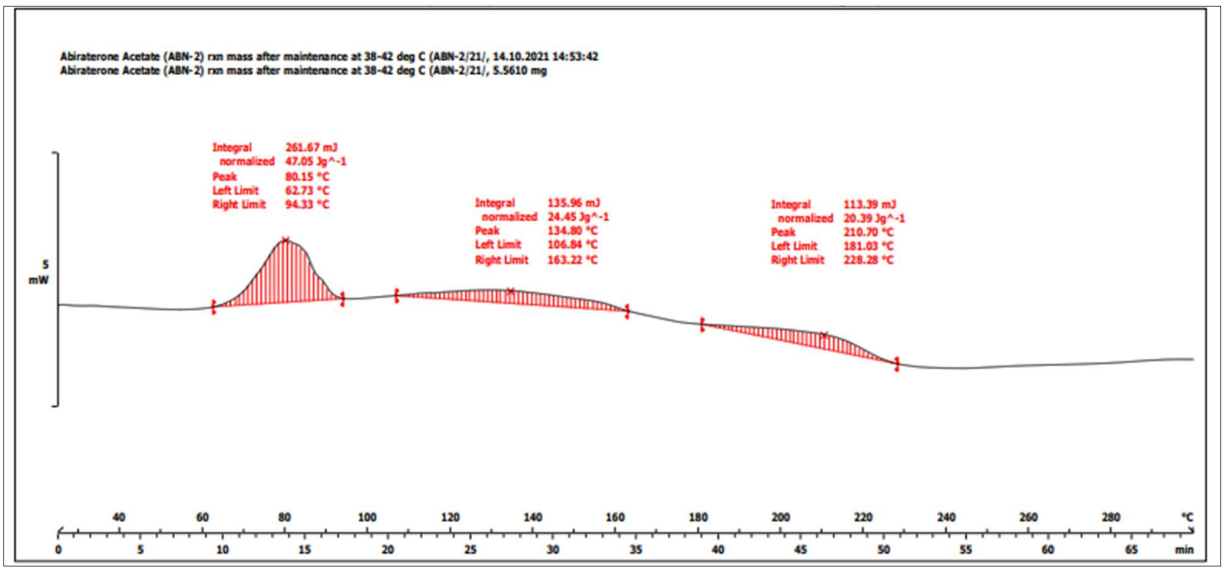


Figure 23. DSC thermograms of a) Step 1, b) Step 2, and c) Step 3.