Electronic Supplementary Information

Catalyst- and excess reagent recycling in *aza*-Michael additions

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Contents

Supplementary data

Table S1 Leaching of the components of the *n*-Bu-TMG/imidazole/CO_2 mixture[a]

entry	imidazole (**2a**) (mmol)	*n*-Bu-TMG (mmol)	leaching	
			imidazole	*n*-Bu-TMG
1	0.5	0.5	yes	yes
2	0.5	0.75	no	yes
3	0.5	1	no	yes

[a] 4h, rt, CO_2 bubbling, then extraction with 1.2 ml ethyl acetate, leaching determined by GC-MS detection of the extract.

Table S2 Leaching of the components of the *n*-Bu-TMG/[bmim][BF_4] /CO_2 mixture[a]

entry	*n*-Bu-TMG (mmol)	[bmim][BF_4] (mmol)	leaching *n*-Bu-TMG
1	0.75	0.75	yes
2	0.75	1	no
3	0.75	1.5	no

[a] 4h, rt, CO_2 bubbling, then extraction with 1.2 ml ethyl acetate, leaching determined by GC-MS detection of the extract.

Table S3 Calculation of E-factors of the reaction of 16-DHP (**1**) and imidazole (**2a**)

	after run 1	after run 2	after run 3	after run 4	after run 5
steroid **1** (mg)[a]	31.4	62.8	94.2	125.6	157
imidazole **2a** (mg) [a]	34.04	40.848	47.656	54.464	61.272
[bmim][BF_4] (recycled) (mg) [a]	340	340	340	340	340
n-Bu-TMG (recycled) (mg) [a]	129	129	129	129	129
Σ starting material (mg) [a]	534.44	572.648	610.856	649.064	687.272
yield (%)	96	95	90	93	94
product **3a** (mg) [a]	36.68	72.98	107.37	142.90	178.82
solvent for extraction (mg) [a,b]	594.68	1189.35	1784.03	2378.70	2973.38
Σ (starting material and solvent[b]) (mg) [a]	1129.12	1762.00	2394.88	3027.76	3660.65
E-factor	29.78	23.14	21.31	20.19	19.47

[a] cumulative values, [b] assuming 85% recycle of the solvent

Table S4 *Aza*-Michael additions with other base catalysts

Entry	Nucleophile	Base	pKa[b] (nucleophile)	pKa[b] (base)	Product	Yield (%)[d]
1	imidazole (**2a**)	*n*-Bu-TMG	15.07		**3a**	96
2		*t*-Bu-TMG		(23.35)[c]		73
3		TBD		26.02		67
4		DABCO		18.29		traces
5	pyrazole (**2b**)	*n*-Bu-TMG	9.1		**3b**	76
6		*t*-Bu-TMG		(23.35)[c]		62
7		DABCO		18.29		22
8	1,2,4-triazole (**2c**)	*n*-Bu-TMG			**3c**	87
9		DABCO		18.29		65
10	indazole (**2f**)	*n*-Bu-TMG	7.61		**3f**	88
11		MTBD		25.47		79
12						75[d]
13	indole (**2g**)	*n*-Bu-TMG			**3g**	55
14		MTBD		25.47		55
15						51[d]
16	1,2,3-benzotriazole (**2h**)	*n*-Bu-TMG	6.89		**3i**	-
17		*t*-Bu-TMG		(23.35)[c]		-
18		DABCO		18.29		-

[a]Reaction conditions: 0.1 mmol of substrate (**1**) in 1.5 mmol [bmim][BF_4] and 0.75 mmol base , substrate (**1)** /nucleophile (**2**) = 1/5; 65°C, 8 h, Ar atmosphere; [b] basicity in MeCN [1]; [c] basicity of TMG, very similar basicities were reported for TMG (14.0) and *t*-Bu-TMG (13.3) in 50% aqueous ethanol [2];[d] 2nd run, conditions: 0.1 mmol of substrate (**1**) and 0.1 mmol nucleophile (added to the recycled mixture obtained via the removal of CO_2), 65°C, 8 h, Ar atmosphere.

Table S5 Acid-base properties of some *N*-heterocycles

N-heterocycle	pK_a (N-H)[a]	*N* parameter (nucleophilicity)[b]	*N* of the anion[b]
imidazole (**2a**)	18.3 (H_2O)	11.58 (DMSO) 11.47 (MeCN)	21.09 (DMSO)
benzimidazole (**2e**)	16.8 (H_2O)	10.50 (DMSO)	19.13 (DMSO)
1,2,3-benzotriazole (**2h**)	11.92 (H_2O)	7.69 (MeCN)	16.29 (DMSO)

[a] ref. [3], [b] ref. [4]

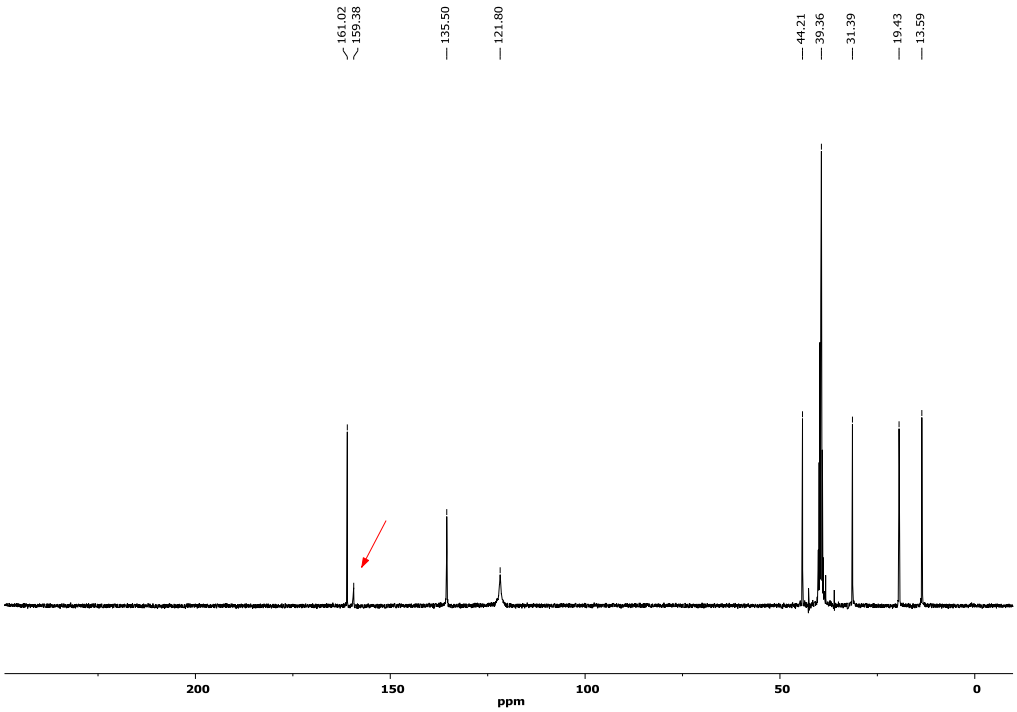


Figure S1. ^{13}C NMR spectrum of the *n*-Bu-TMG/imidazole (1/1) + CO_2 system in DMSO-d_6 (red arrow: signal of carbamate)

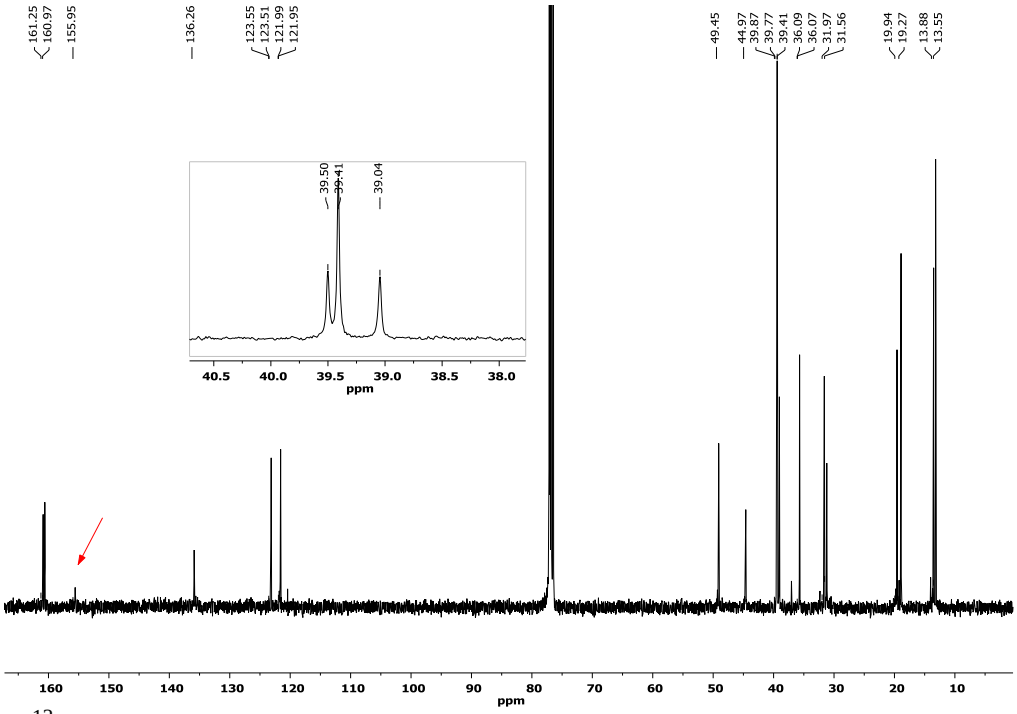


Figure S2. ^{13}C NMR spectrum of the *n*-Bu-TMG/[bmim][BF_4] (1/1) + CO_2 system in $CDCl_3$ (red arrow: signal of carboxylate)

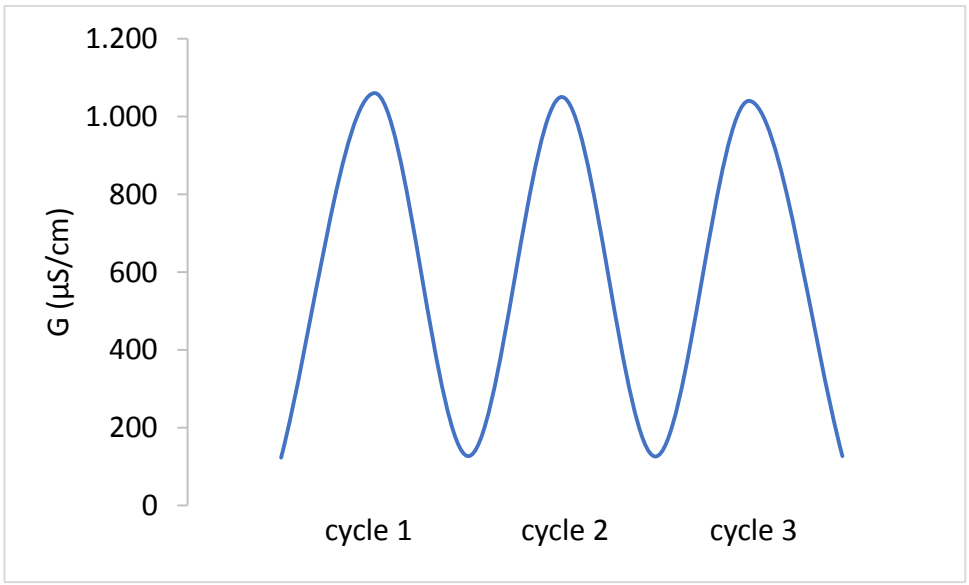


Figure S3. Monitoring the reversibility of the *n*-Bu-TMG /imidazole (**2a**) system by conductivity measurements

Characterisation of the products

16α-(1H-Imidazol-1-yl)-3β-hydroxy-pregn-5-ene-20-one (3a) [5]

Mp. 98-100°C; R_f= 0.29 (toluene/EtOAc, 1/1). $[\alpha]_D^{20}$= +12.4º (EtOH, c=0.5)

IR (KBr): ν=3460, 2924, 2849, 2359, 2342, 1701, 1541, 1232, 1049, 902 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ= 7.55 (s, 1 H, 2'-H), 7.03 (s, 1 H, 5'-H), 6.90 (s, 1 H, 4'-H), 5.31-5.37 (m, 1 H, 6-H), 5.25 (ddd, *J*=3.1 Hz, 8.1 Hz, 10.9 Hz, 1 H, 16-H), 3.49-3.59 (m, 1 H, 3-H), 2.77 (d, *J*=8.1 Hz, 1 H, 17-H), 1.04-2.59 (m, 18 H, ring protons, OH), 2.09 (s, 3 H, $COCH_3$), 1.02 (s, 3 H, 19-H_3), 0.72 (s, 3 H, 18-H_3).

^{13}C NMR (101 MHz, $CDCl_3$,): δ= 206.0, 141.2, 136.3, 129.6, 120.8, 116.9, 73.2, 71.6, 56.6, 55.8, 49.9, 45.31, 42.3, 38.8, 37.3, 36.6, 33.6, 31.8, 31.7, 31.6, 31.6, 20.9, 19.5, 14.1.

HRMS: m/z calcd for $C_{24}H_{35}N_2O_2$ $[M+H]^+$ 383.2699, found 383.2693.

16α-(1H-Pyrazol-1-yl)-3β-hydroxy-pregn-5-ene-20-one (3b)

Mp. 148-150°C; R_f= 0.50 (toluene/EtOAc, 1/1). $[\alpha]_D^{20}$= +8.4º (EtOH, c=0.5)

^{1}H NMR (400 MHz, $CDCl_3$): δ= 7.49 (d, *J*=1.1 Hz, 1 H, 5'-H), 7.38-7.42 (d, *J*=1.8 Hz, 1 H, 3'-H), 6.15 (d, *J*=1.1 Hz, 1.8 Hz, 1 H, 4'-H), 5.24-5.34 (m, 2 H, 6-H, 16-H), 3.48-3.59 (m, 1 H, 3-H), 3.25 (d, *J*=8.1 Hz, 1 H, 17-H), 1.05-2.34 (m, 18 H, ring protons, OH), 2.07 (s, 3 H, $COCH_3$), 1.00 (s, 3 H, 19-H_3), 0.71 (s, 3 H, 18-H_3).

^{13}C NMR (101 MHz, $CDCl_3$,): δ= 207.3, 140.8, 140.0, 130.0, 121.2, 104.8, 71.6, 70.7, 60.1, 55.3, 49.7, 45.0, 42.3, 38.4, 37.3, 36.6, 33.0, 31.7, 31.58, 31.56, 31.5, 20.9, 19.5, 14.2.

IR (KBr): ν= 3450, 2926, 2851, 2359, 2342, 1697, 1541, 1236, 1049, 962 cm^{-1}.

HRMS: m/z calcd for $C_{24}H_{34}N_2O_2Na$ $[M+Na]^+$ 405.2518, found 405.2515.

16α-(1H-1,2,4-Triazol-1-yl)-3β-hydroxy-pregn-5-ene-20-one (3c)

Mp. 97-100°C; R_f= 0.30 (toluene/MeOH, 1/1). $[\alpha]_D^{20}$= +2.4º (EtOH, c=0.3)

^{1}H NMR (400 MHz, $CDCl_3$): δ= 8.04 (s, 1 H, 5'-H), 7.89 (s, 1 H, 3'-H), 5.42 (ddd, *J*=2.7 Hz, 8.0 Hz, 9.7 Hz, 1 H, 16-H), 5.28-5.35 (m, 1 H, 6-H), 3.48-3.59 (m, 1 H, 3-H), 3.12 (d, *J*=8.0 Hz, 1 H, 17-H), 1.03-2.33 (m, 18 H, ring protons, OH), 2.09 (s, 3 H, $COCH_3$), 1.00 (s, 3 H, 19-H_3), 0.72 (s, 3 H, 18-H_3).

^{13}C NMR (101 MHz, $CDCl_{3,}$): δ= 206.5, 152.4, 143.3, 140.9, 121.1, 71.6, 70.7, 57.9, 55.4, 49.7, 45.1, 42.2, 38.4, 37.3, 36.6, 32.6, 31.63, 31.57, 31.5, 31.3, 20.9, 19.5, 14.1.

IR (KBr): ν= 3456, 2932, 2855, 2359, 2342, 1701, 1541, 1275, 1049, 910 cm^{-1}.

HRMS: m/z calcd for $C_{23}H_{33}N_3O_2Na$ $[M+Na]^+$ 406.2470, found 406.2470.

16α-(1H-1,2,3-Triazol-1-yl)-3β-hydroxy-pregn-5-ene-20-one (3d)

Mp. 144-146°C; R_f= 0.45 (toluene/MeOH, 3/1). $[\alpha]_D^{20}$= -13.9º (EtOH, c=0.5)

^{1}H NMR (400 MHz, $CDCl_3$): δ= 7.55 (brs, 2 H, 4'-H, 5'-H), 5.70 (ddd, J=2.6 Hz, 8.1 Hz, 10.2 Hz, 1 H, 16-H), 5.31-5.36 (m, 1 H, 6-H), 3.48-3.58 (m, 1 H, 3-H), 3.39 (d, *J*=8.1 Hz, 1 H, 17-H), 1.05-2.34 (m, 18 H, ring protons, OH), 2.15 (s, 3 H, $COCH_3$), 1.02 (s, 3 H, 19-H_3), 0.77 (s, 3 H, 18-H_3).

^{13}C NMR (101 MHz, $CDCl_{3,}$): δ= 206.4, 140.9, 134.1 (2C), 121.2, 71.7, 70.1, 63.8, 55.1, 49.9, 45.1, 42.3, 38.6, 37.3, 36.6, 33.1, 31.7, 31.62, 31.60 (2C), 20.9, 19.5, 14.3.

IR (KBr): ν= 3456, 2953, 2850, 2358, 2342, 1705, 1539, 1234, 1043, 962 cm^{-1}.

HRMS: m/z calcd for $C_{23}H_{33}N_3O_2Na$ $[M+Na]^+$ 406.2470, found . 406.2467

16α-(1H-Benzimidazol-1-yl)-3β-hydroxy-pregn-5-ene-20-one (3e)

Mp. 127-129°C; R_f= 0.45 (toluene/MeOH, 3/1). $[\alpha]_D^{20}$= +10.1º (EtOH, c=0.5)

^{1}H NMR (400 MHz, $CDCl_3$): δ= 8.06 (s, 1 H, 2'-H), 7.76-7.81 (m, 1 H, Ar-H), 7.48-7.54 (m, 1 H, Ar-H), 7.25-7.30 (m, 2 H, Ar-H), 5.58 (ddd, J=3.7 Hz, 8.6 Hz, 12.1 Hz, 1 H, 16-H), 5.32-

5.38 (m, 1 H, 6-H), 3.51-3.61 (m, 1 H, 3-H), 3.07 (d, *J*=8.6 Hz, 1 H, 17-H), 0.87-2.48 (m, 18 H, ring protons, OH), 2.06 (s, 3 H, $COCH_3$), 1.05 (s, 3 H, $H_3$19-H_3), 0.80 (s, 3 H, 18-H_3).

^{13}C NMR (101 MHz, $CDCl_3$,): δ= 206.2, 143.6, 142.1, 141.2, 132.9, 123.2, 122.5, 120.8, 120.4, 110.7, 71.7, 70.8, 56.8, 54.8, 49.9, 45.5, 42.3, 38.8, 37.3, 36.7, 32.3, 31.81, 31.77, 31.65 (2C), 20.9, 19.5, 14.0.

IR (KBr): ν= 3453, 2926, 2851, 2359, 2332, 1715, 1541, 1233, 1049, 800 cm^{-1}.

HRMS: m/z calcd for $C_{28}H_{37}N_2O_2$ $[M+H]^+$ 433.2855, found 433.2843 .

16α-(1H-Indazol-1-yl)-3β-hydroxy-pregn-5-ene-20-one (3f)

Mp. 201-203°C; R_f= 0.47 (toluene/EtOAc, 1:1). $[\alpha]_D^{20}$= +59.7º (EtOH, c=0.5)

^{1}H NMR (400 MHz, $CDCl_3$): δ= 8.00 (brs, 1 H, 3'-H), 7.65-7.67 (m, 1 H, Ar-H), 7.59-7.61 (m, 1 H, Ar-H), 7.33-7.39 (m, 1 H, Ar-H), 7.07-7.13 (m, 1 H, Ar-H), 5.75 (ddd, *J*=2.4 Hz, 7.9 Hz, 9.8 Hz, 1 H, 16-H), 5.31-5.37 (m, 1 H, 6-H), 3.50-3.61 (m, 1 H, 3-H), 3.43 (d, *J*=7.9 Hz, 1 H, 17-H), 0.86-2.40 (m, 18 H, ring protons, OH), 2.06 (s, 3 H, $COCH_3$), 1.04 (s, 3 H, 19-H_3), 0.82 (s, 3 H, 18-H_3).

^{13}C NMR (101 MHz, $CDCl_3$,): δ= 207.6, 140.8, 139.9, 133.7, 126.3, 123.8, 121.4, 120.8, 120.7, 109.9, 71.8, 70.6, 56.4, 55. 6, 49.8, 45.2, 42.4, 38.6, 37.4, 36.7, 33.3, 31.8, 31.70 (2C), 31.6, 21.0, 19.5, 14.4.

IR (KBr): ν= 3455, 2926, 2851, 2357, 2342, 1701, 1541, 1223, 1049, 906 cm^{-1}.

HRMS: m/z calcd for $C_{28}H_{36}N_2O_2Na$ $[M+Na]^+$ 455.2674, found . 455.2676

16α-(1H-Indol-1-yl)-3β-hydroxy-pregn-5-ene-20-one (3g)

Mp. 183-185°C; R_f= 0.51 (toluene/MeOH, 3/1).

^{1}H NMR (400 MHz, $CDCl_3$): δ= 7.57-7.59 (m, 1 H, Ar-H), 7.50-7.52 (m, 1 H, Ar-H), 7.17-7.21 (m, 1 H, Ar-H), 7.15-7.16 (m, 1 H, Ar-H), 7.05-7.09 (m, 1 H, Ar-H), 6.50-6.51 (m, 1 H,

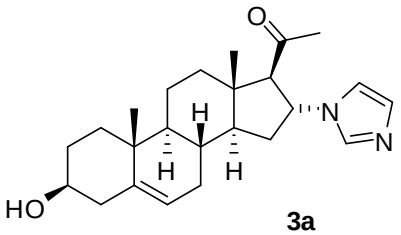
Ar-H), 5.60 (ddd, J=5.0 Hz, 8.2 Hz, 13.3 Hz, 1 H, 16-H), 5.34-5.40 (m, 1 H, 6-H), 3.51-3.61 (m, 1 H, 3-H), 3.01 (d, *J*=8.2 Hz, 1 H, 17-H), 1.09-2.39 (m, 18 H, ring protons, OH), 2.03 (s, 3 H, $COCH_3$), 1.05 (s, 3 H, 19-H_3), 0.81 (s, 3 H, 18-H_3).

^{13}C NMR (101 MHz, $CDCl_3$,): δ= 206.7, 140.8, 135.6, 128.3, 124.5, 121.4, 120.8, 120.6, 119.2, 110.1, 102.0, 71.5, 71.3, 56.4, 54.6, 49.7, 45.0, 42.0, 38.6, 37.0, 36.4, 33.0, 31.7, 31.6, 31.5, 31.4, 20.6, 19.2, 14.00.

IR (KBr): ν= 3461, 2912, 2852, 2359, 2342, 1691, 1541, 1229, 1060, 1010 cm^{-1}.

HRMS: m/z calcd for $C_{29}H_{37}NO_2Na$ $[M+Na]^+$ 454.2722, found 454.2719.

^{1}H- and ^{13}C NMR spectra of the products



3a

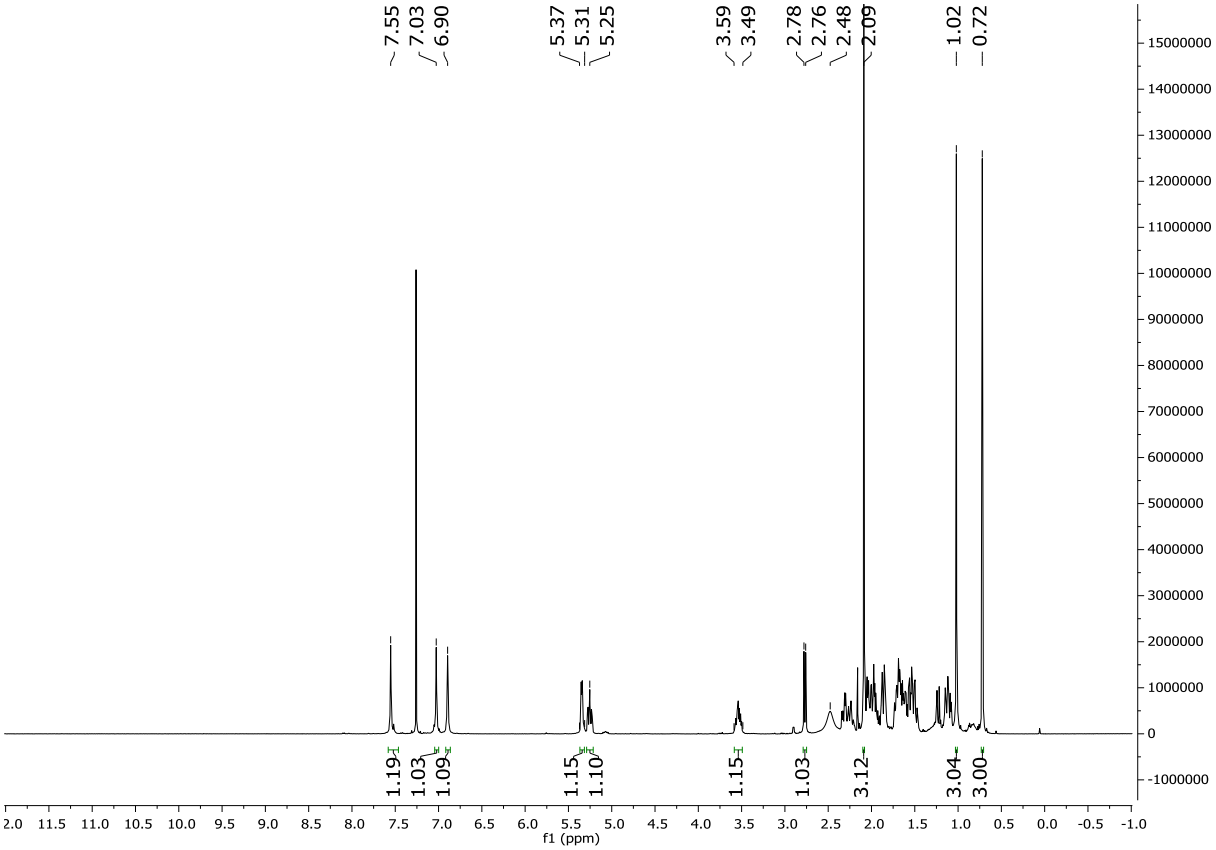


Figure S4 ^{1}H NMR spectrum of 16α-(1*H*-imidazol-1-yl)-3β-hydroxy-pregn-5-ene-20-one (**3a**) in $CDCl_3$

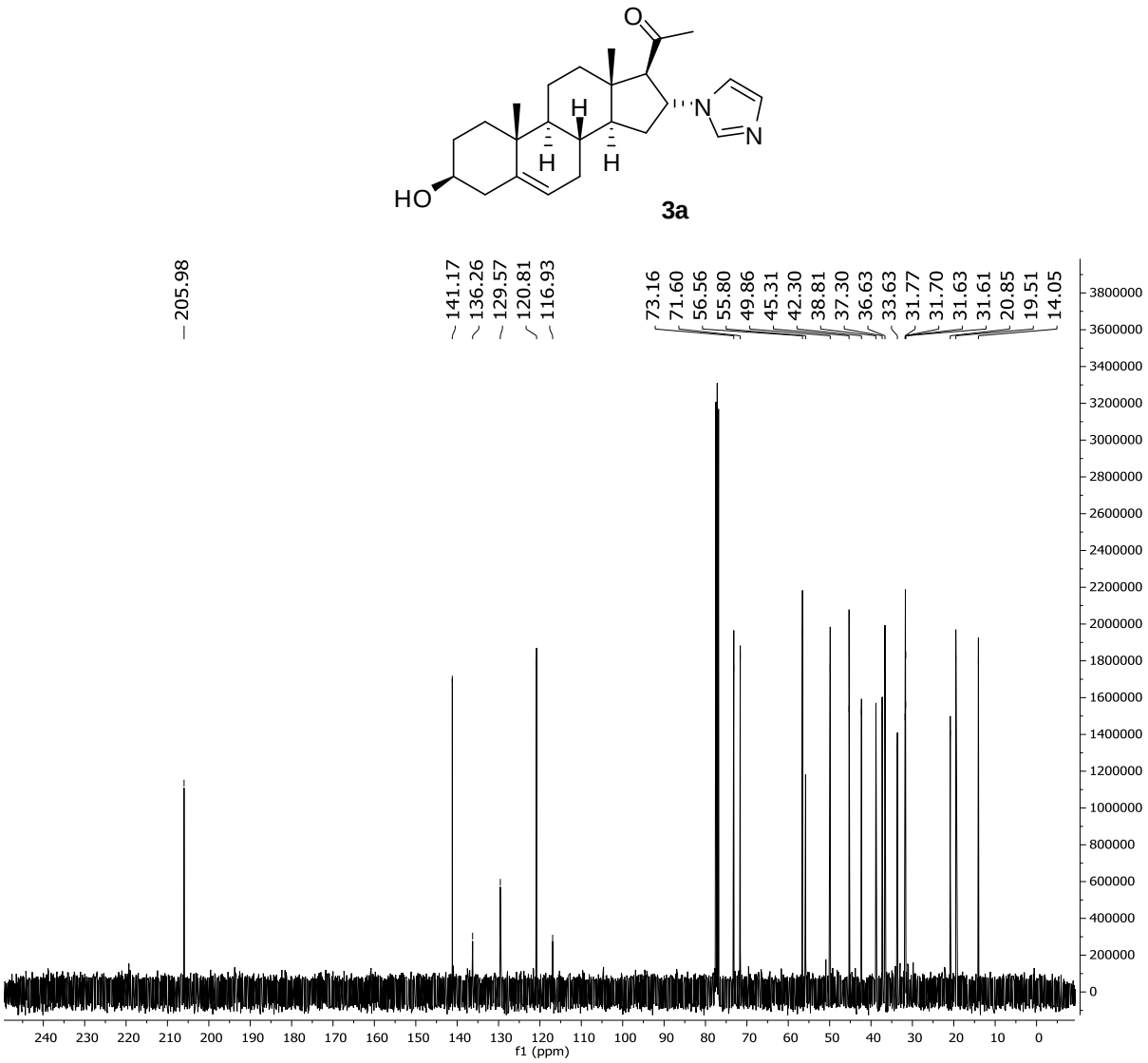


Figure S5 ^{13}C NMR spectrum of 16α-(1*H*-imidazol-1-yl)-3β-hydroxy-pregn-5-ene-20-one (**3a**) in $CDCl_3$

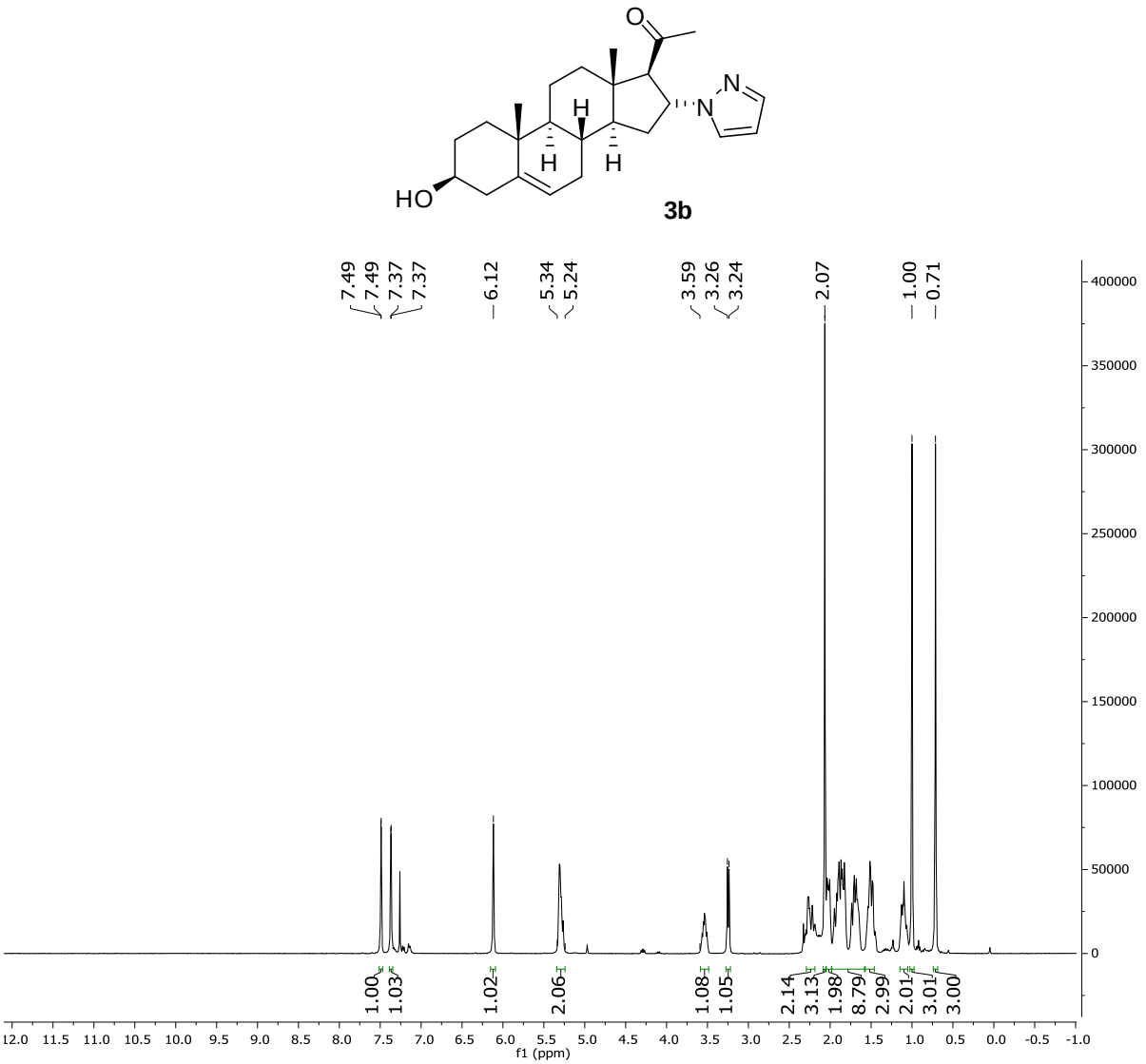


Figure S6 ^{1}H NMR spectrum of 16α-(1*H*-pyrazol-1-yl)-3β-hydroxy-pregn-5-ene-20-one (**3b**) in $CDCl_3$

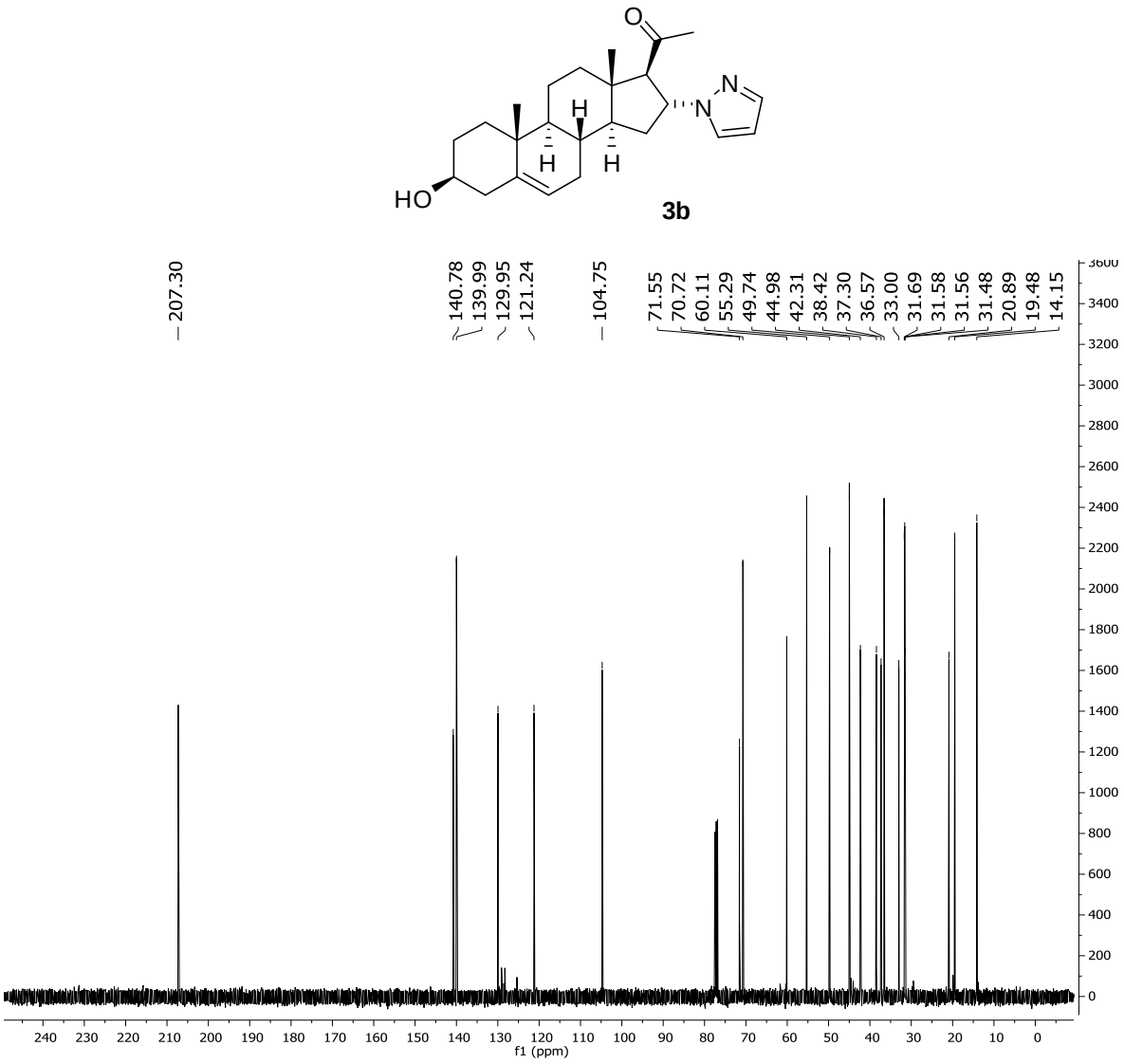


Figure S7 ^{13}C NMR spectrum of 16α-(1*H*-pyrazol-1-yl)-3β-hydroxy-pregn-5-ene-20-one (**3b**) in $CDCl_3$

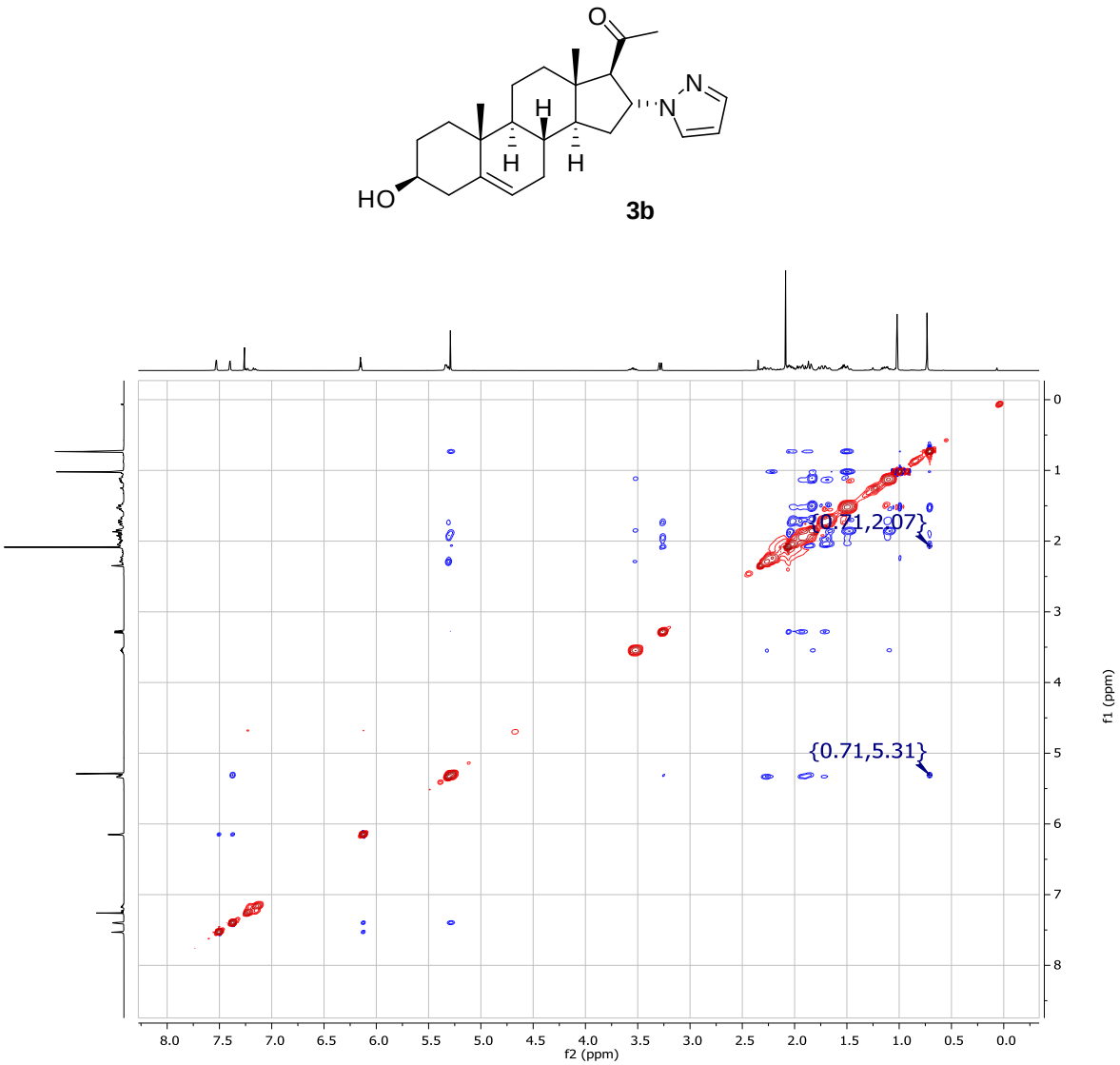


Figure S8 NOESY spectrum of 16α-(1*H*-pyrazol-1-yl)-3β-hydroxy-pregn-5-ene-20-one (**3b**) in $CDCl_3$

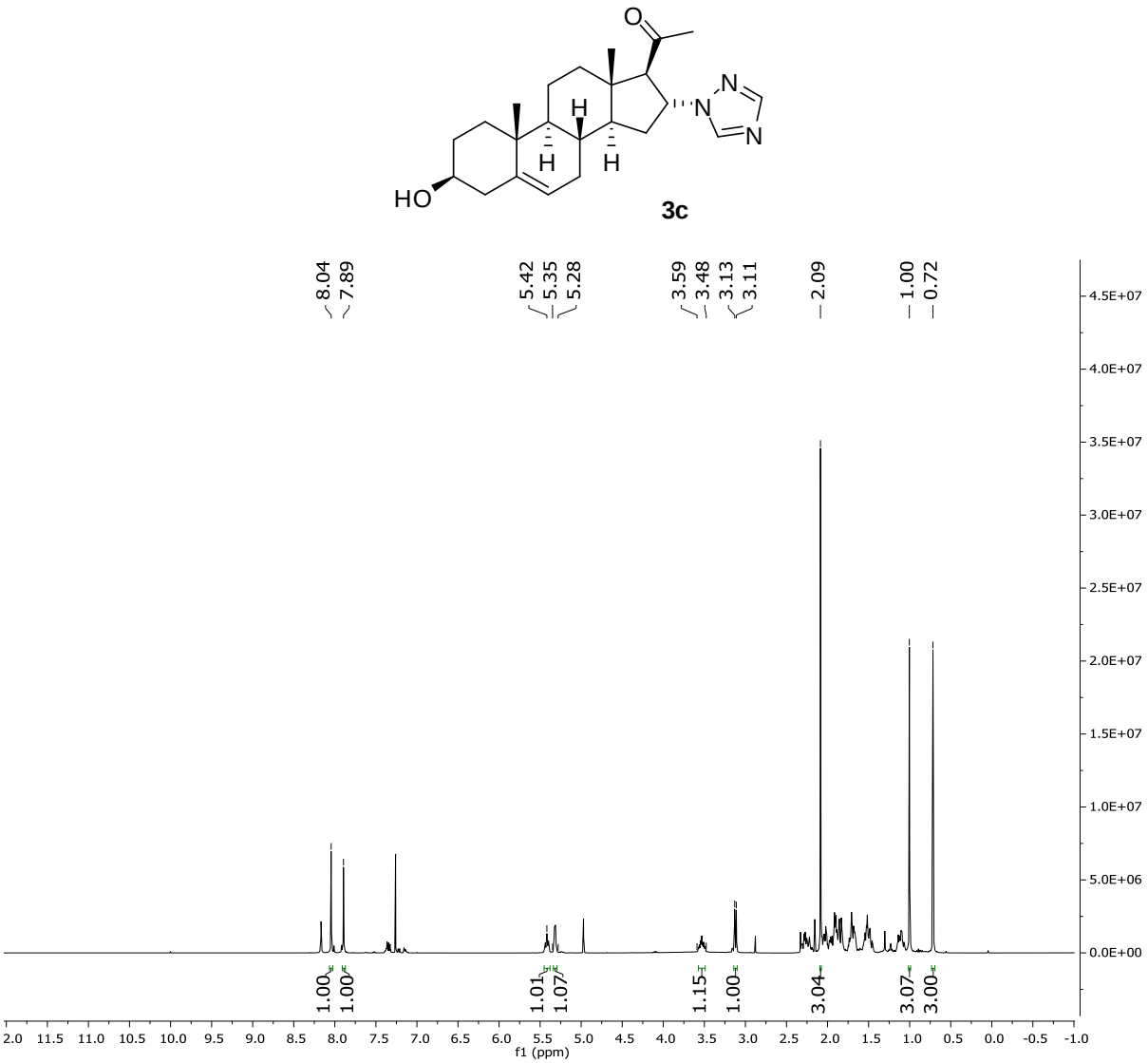


Figure S9 ^{1}H NMR spectrum of 16α-(1*H*-1,2,4-triazol-1-yl)-3β-hydroxy-pregn-5-ene-20-one (**3c**) in $CDCl_3$

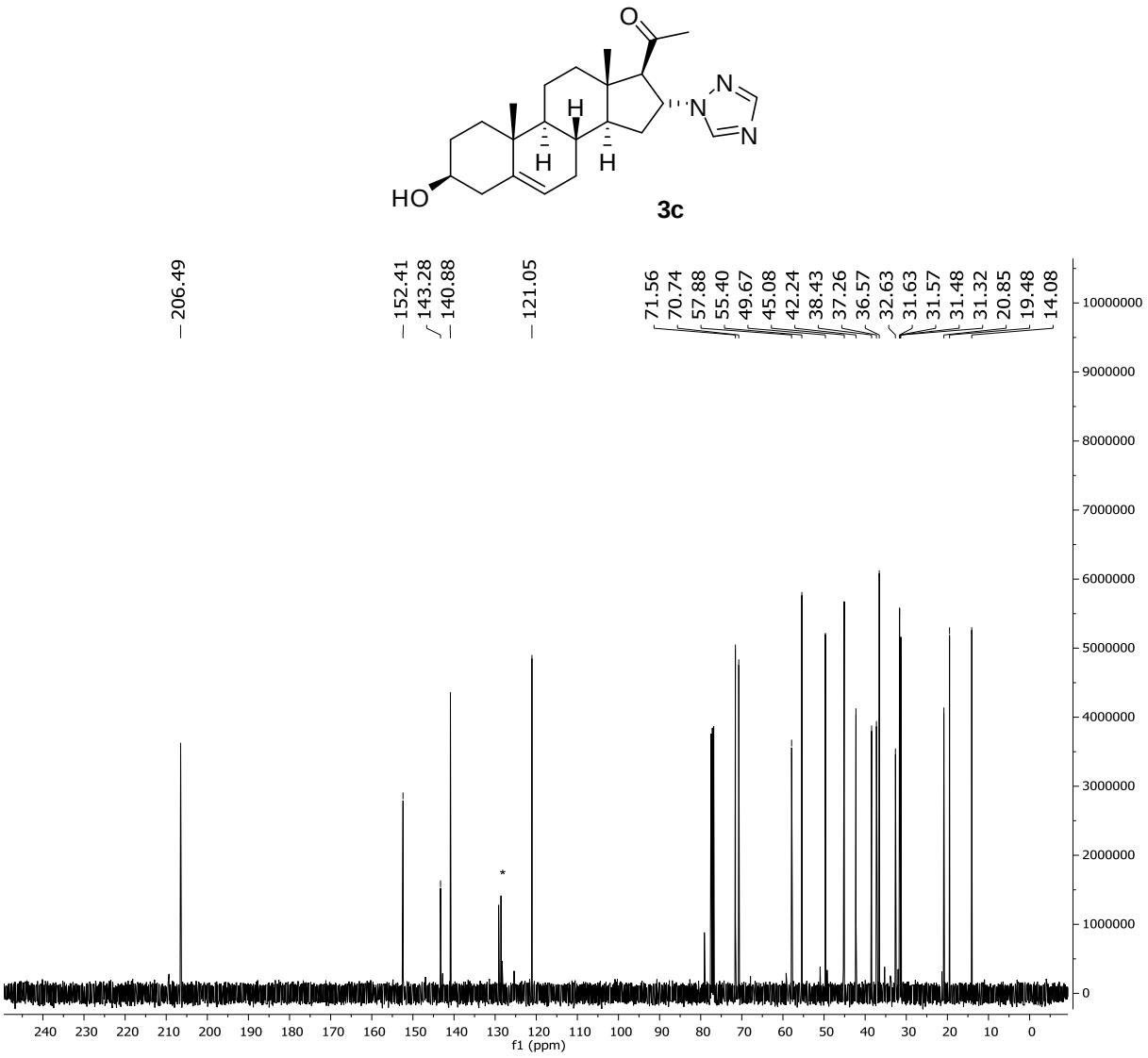


Figure S10 ^{13}C NMR spectrum of 16α-(1*H*-1,2,4-triazol-1-yl)-3β-hydroxy-pregn-5-ene-20-one (**3c**) in $CDCl_3$ (*: toluene)

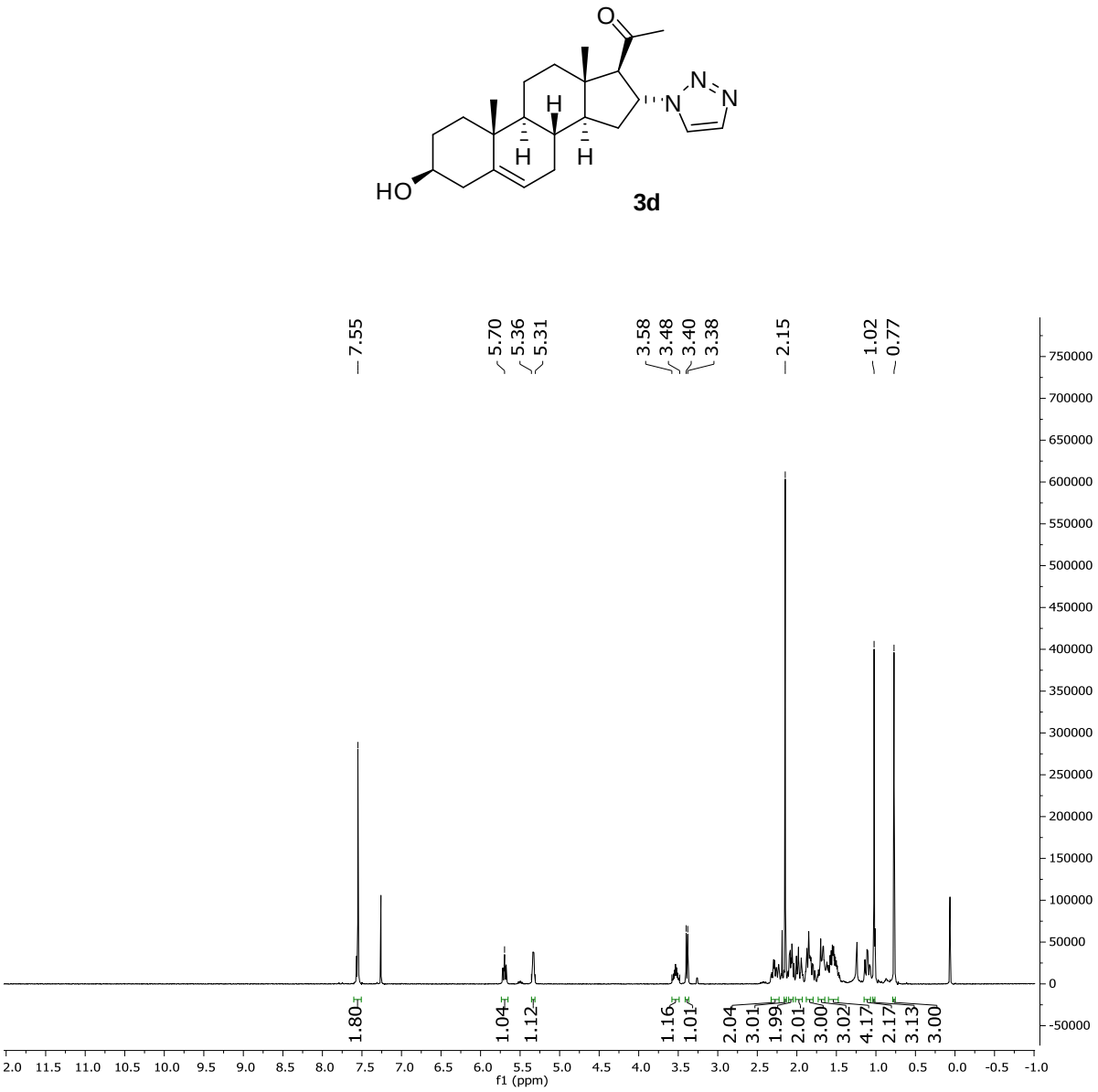


Figure S11 ^{1}H NMR spectrum of 16α-(1*H*-1,2,3-triazol-1-yl)-3β-hydroxy-pregn-5-ene-20-one (**3d**) in $CDCl_3$

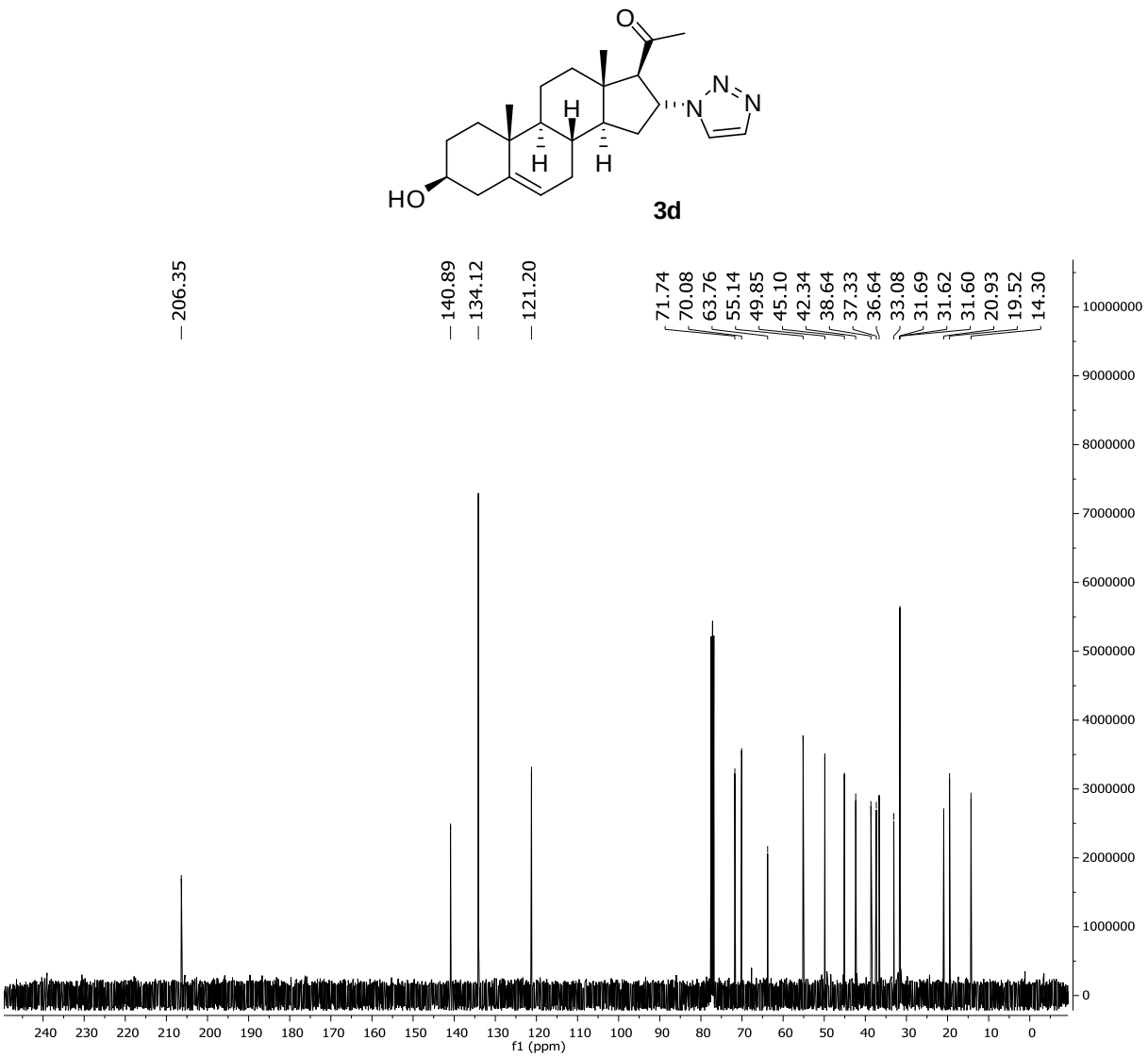


Figure S12 ^{13}C NMR spectrum of 16α-(1*H*-1,2,3-triazol-1-yl)-3β-hydroxy-pregn-5-ene-20-one (**3d**) in $CDCl_3$

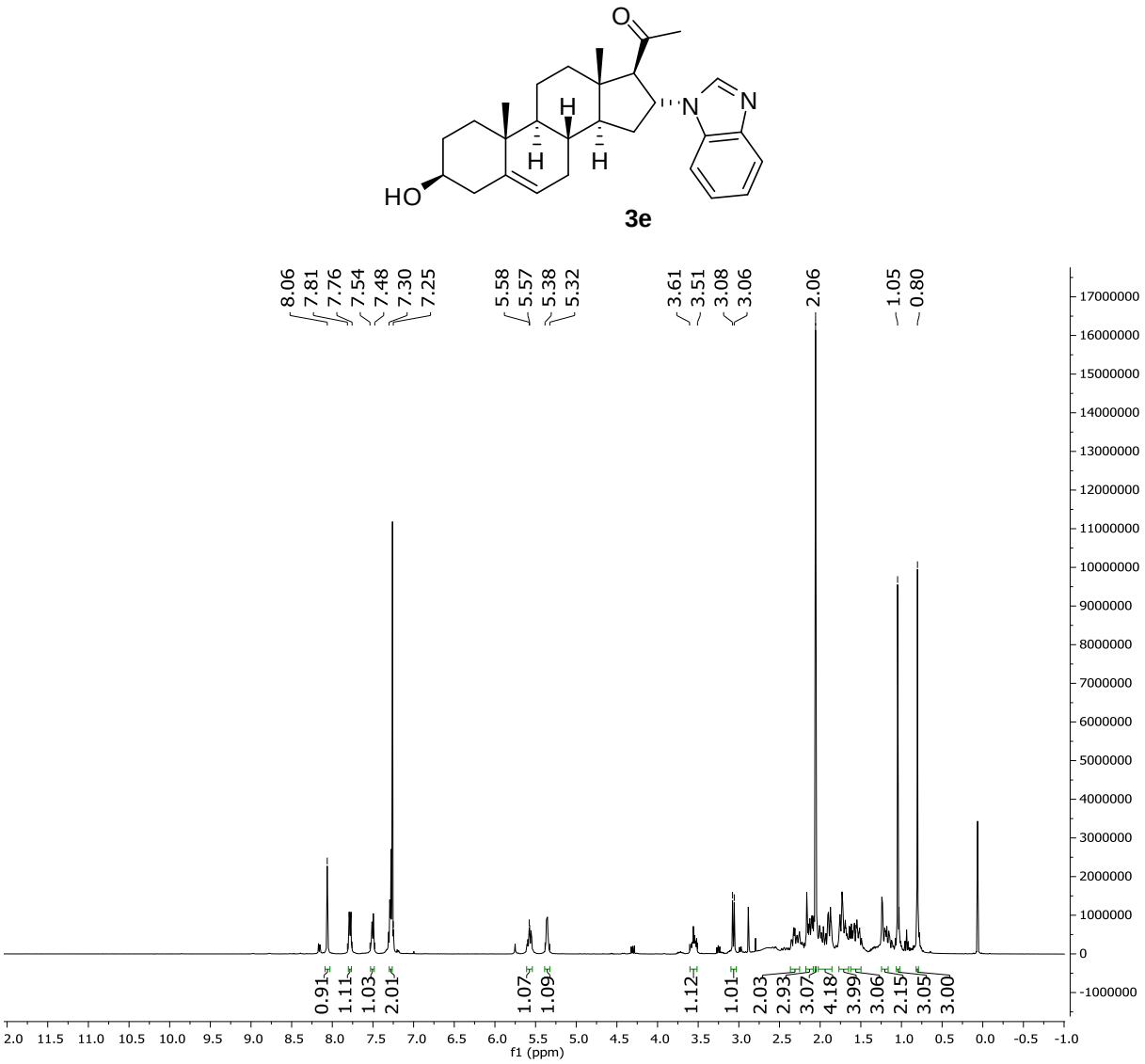


Figure S13 ^{1}H NMR spectrum of 16α-(1*H*-benzimidazol-1-yl)-3β-hydroxy-pregn-5-ene-20-one (**3e**) in $CDCl_3$

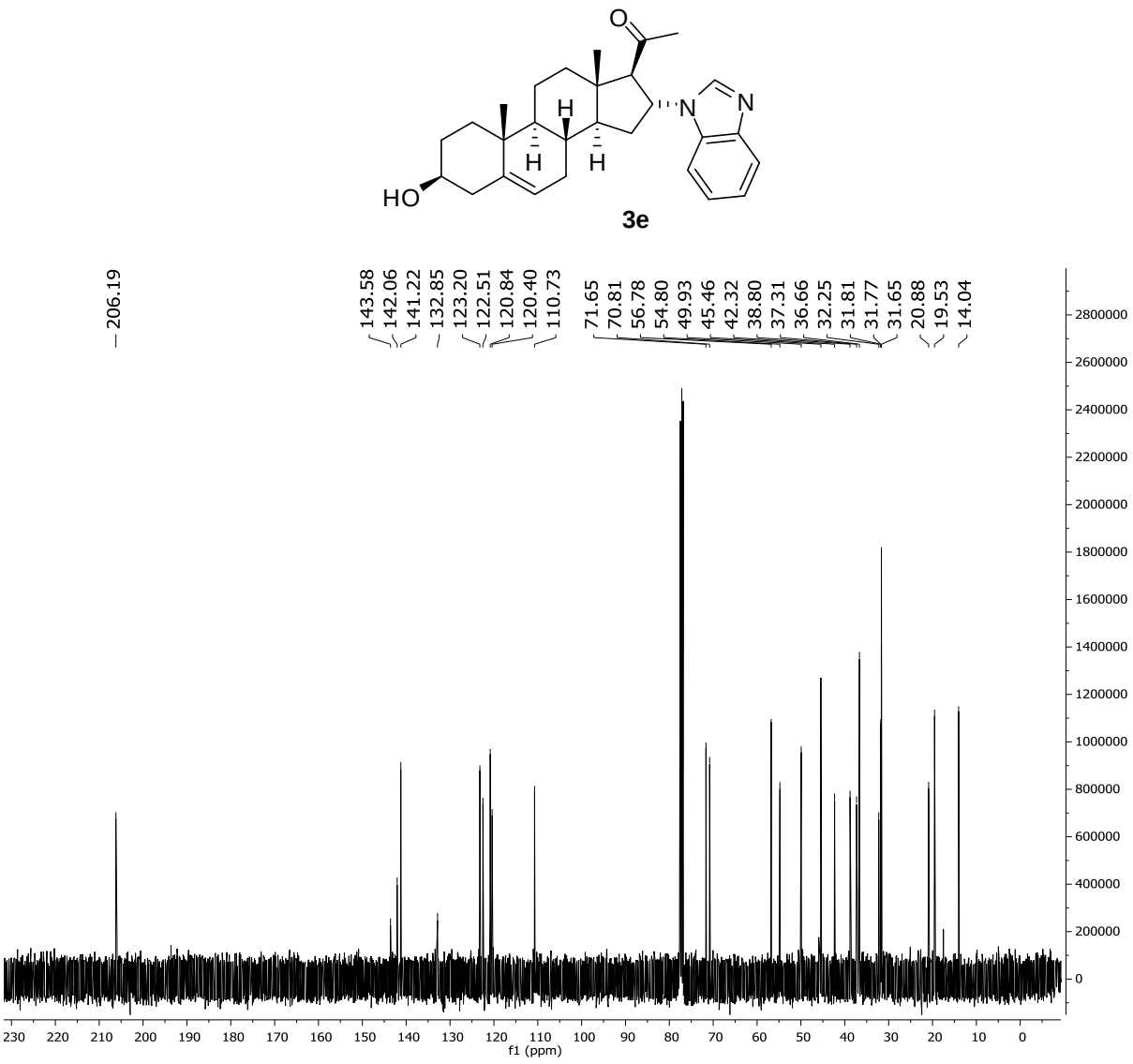


Figure S14 ^{13}C NMR spectrum of 16α-(1*H*-benzimidazol-1-yl)-3β-hydroxy-pregn-5-ene-20-one (**3e**) in $CDCl_3$

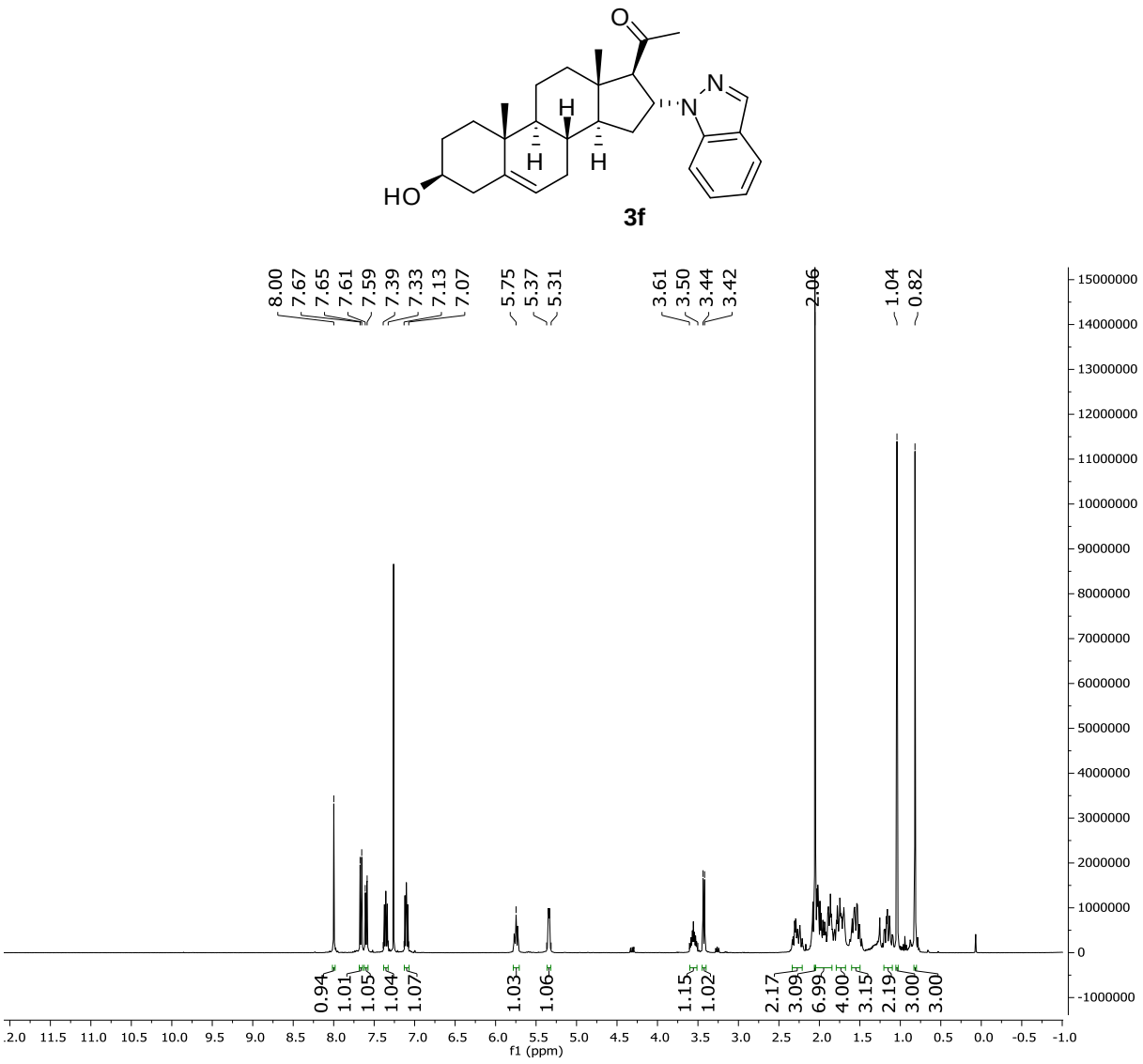


Figure S15 ^{1}H NMR spectrum of 16α-(1*H*-indazol-1-yl)-3β-hydroxy-pregn-5-ene-20-one (**3f**) in $CDCl_3$

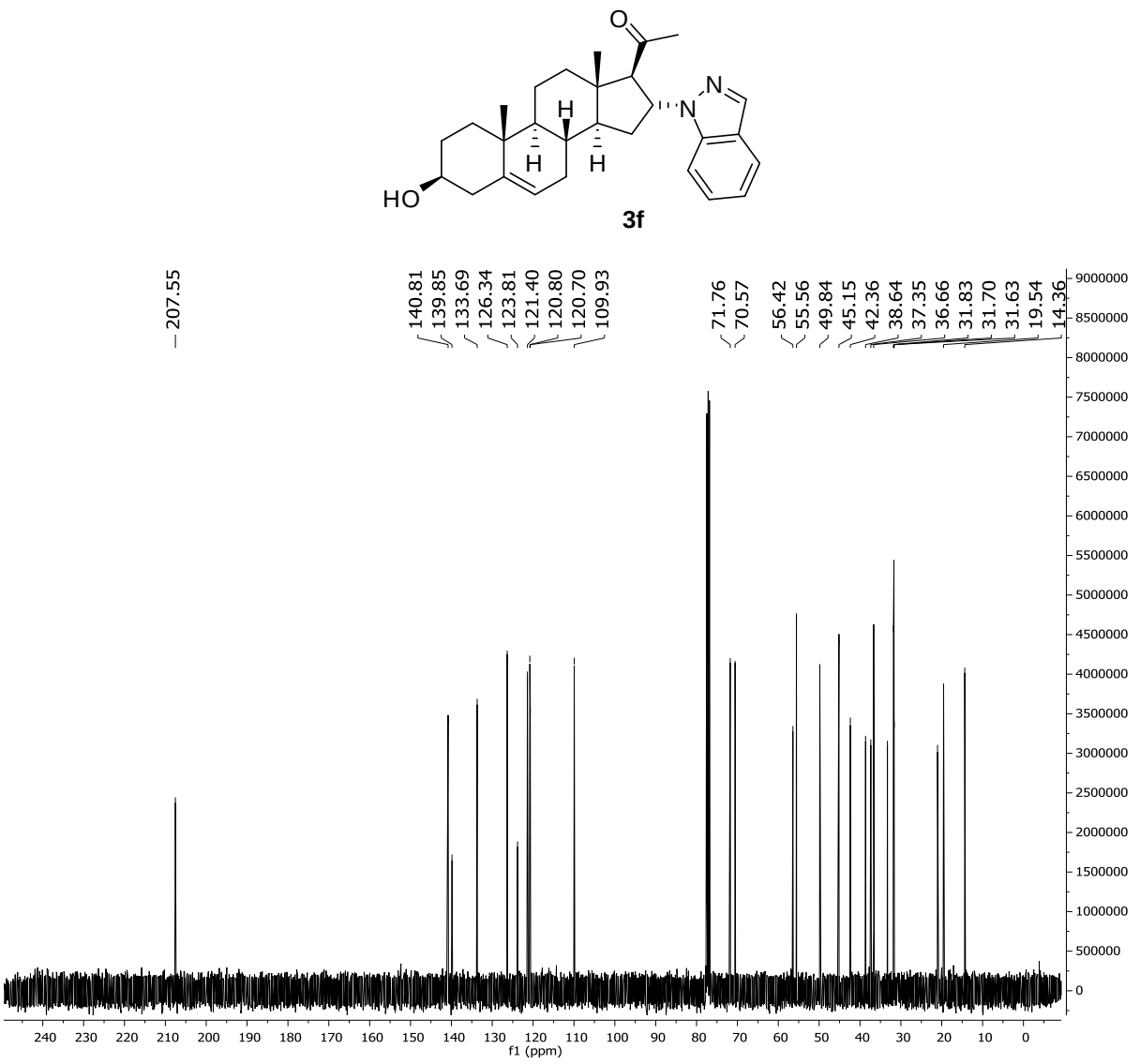


Figure S16 ^{13}C NMR spectrum of 16α-(1*H*-indazol-1-yl)-3β-hydroxy-pregn-5-ene-20-one (**3f**) in $CDCl_3$

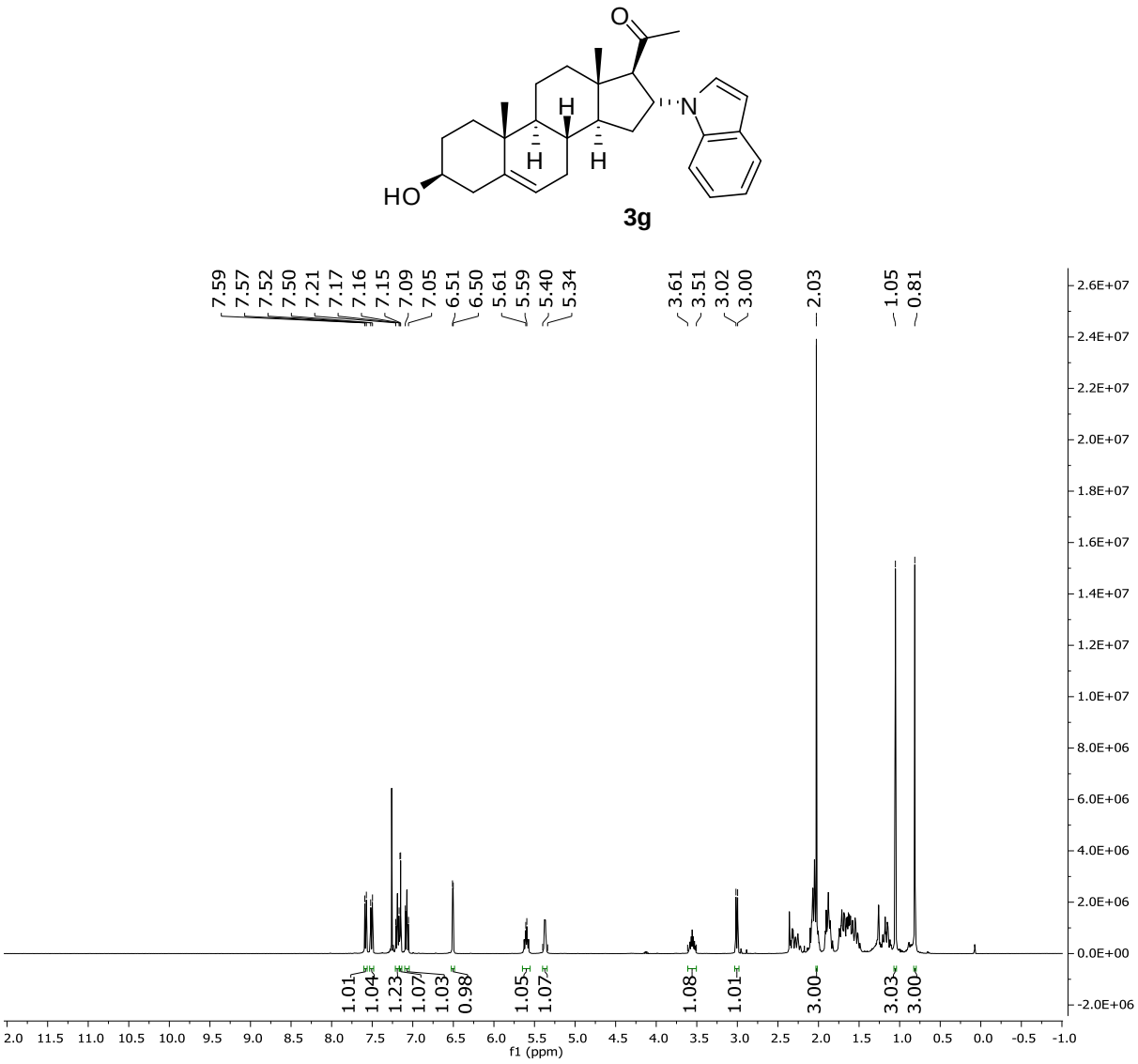


Figure S17 ^{1}H NMR spectrum of 16α-(1*H*-indol-1-yl)-3β-hydroxy-pregn-5-ene-20-one (**3g**) in $CDCl_3$

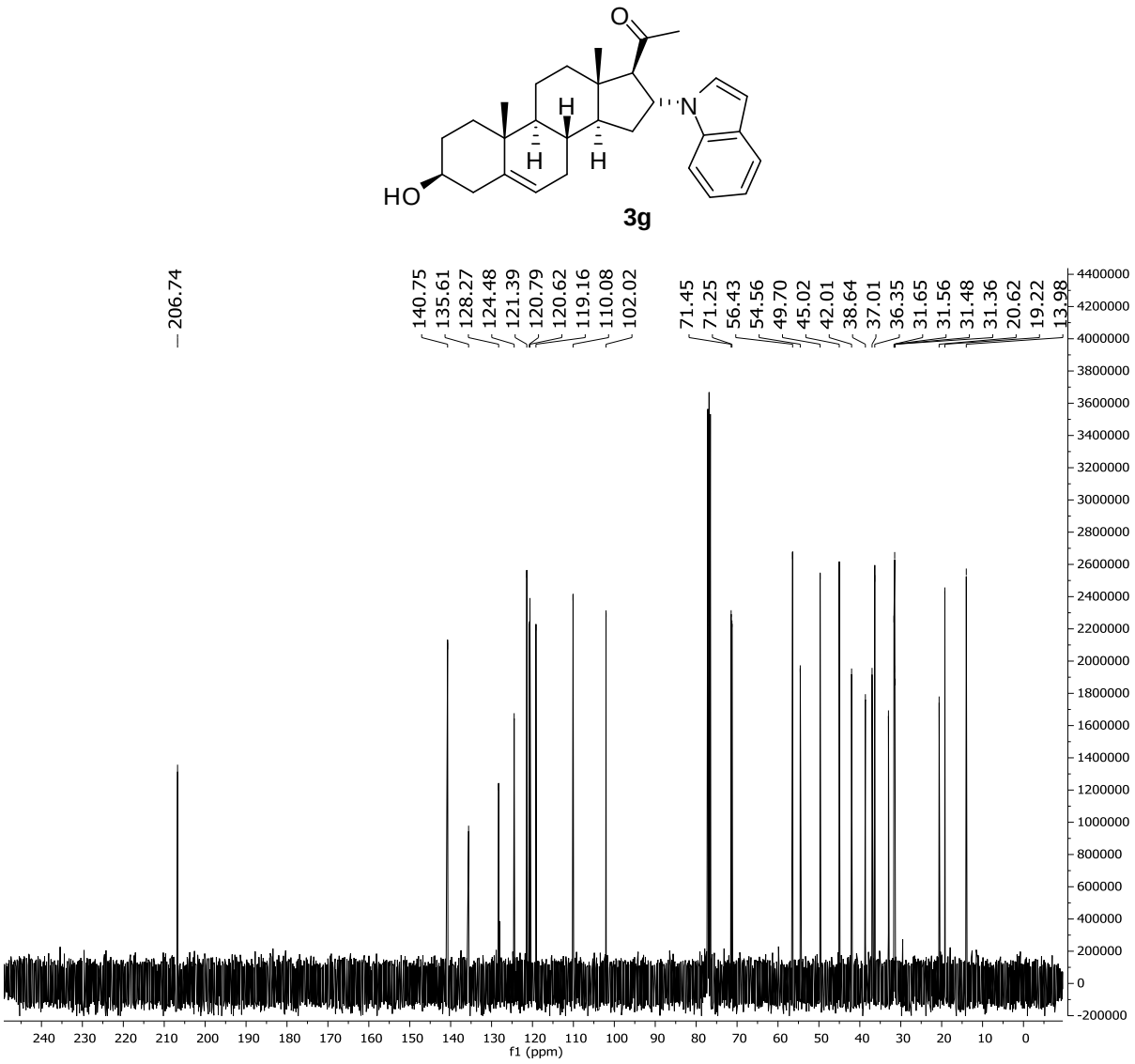


Figure S18 ^{13}C NMR spectrum of 16α-(1*H*-indol-1-yl)-3β-hydroxy-pregn-5-ene-20-one (**3g**) in $CDCl_3$

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