Accessory Publication

Improved Synthesis of 14-Hydroxy Opioid Pharmaceuticals and Intermediates

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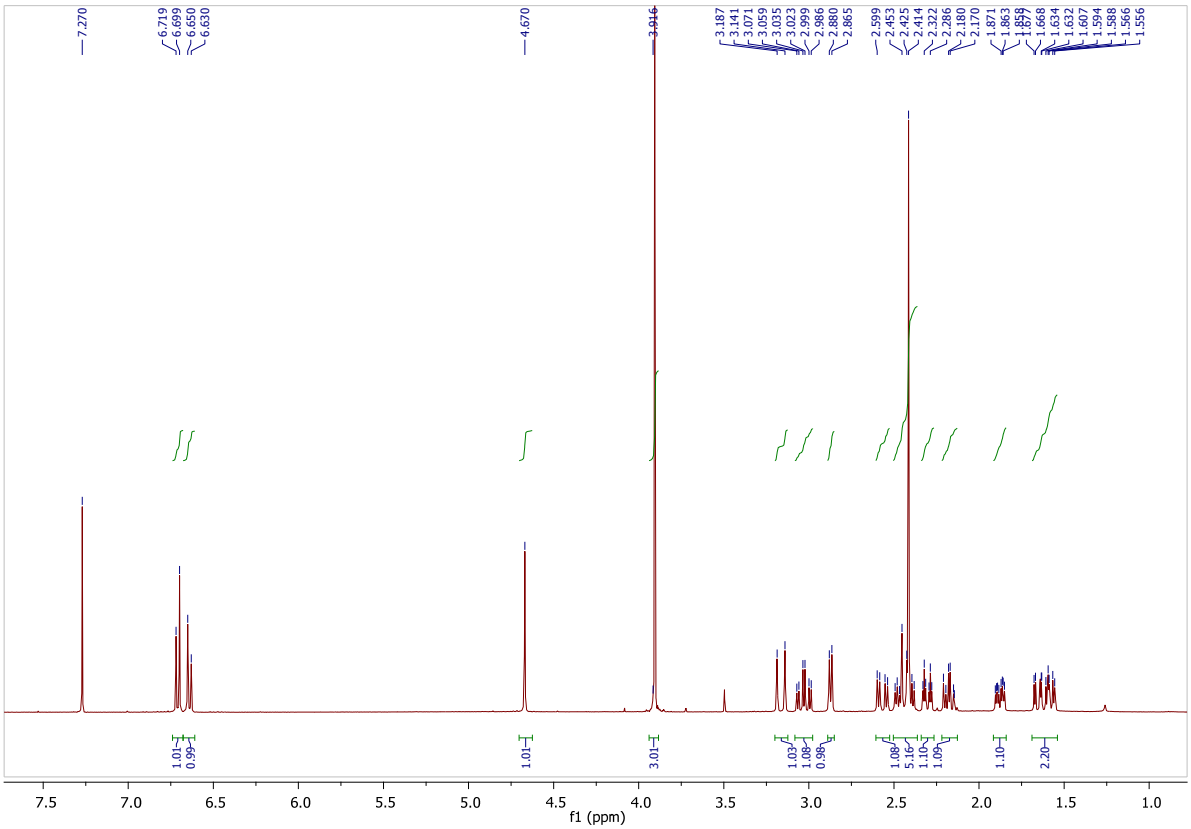
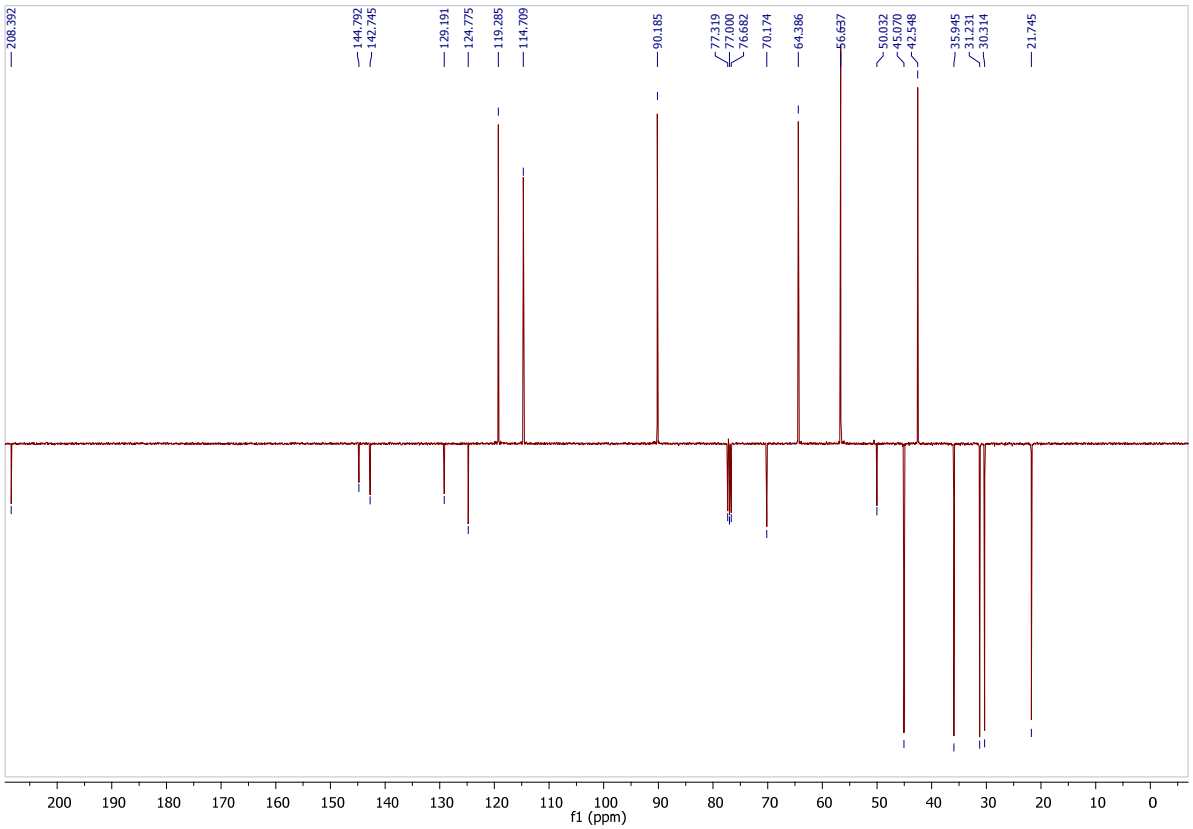
Figure 1. ^{1}H NMR of Crude Oxycodone (**1**) in $CDCl_3$ (sample from reduction of 14-hydroxycodeinone* over 5% $Pd/BaSO_4$ in MeOH)



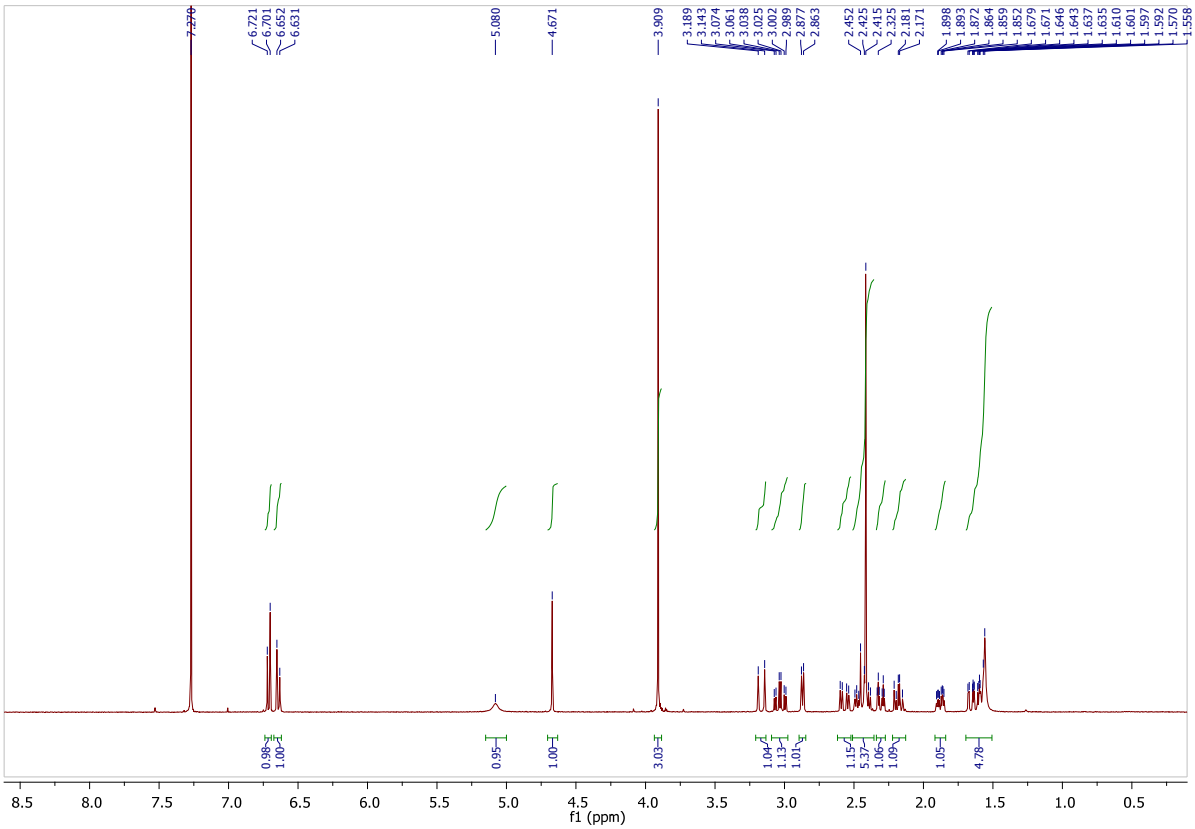
*Prepared via oxidation of thebaine in HOAc-TFA, according to reaction conditions reported in reference 1.

Figure 2. ^{13}C NMR of Crude Oxycodone (**1**) in $CDCl_3$ (sample from reduction of 14-hydroxycodeinone* over 5% $Pd/BaSO_4$ in MeOH)



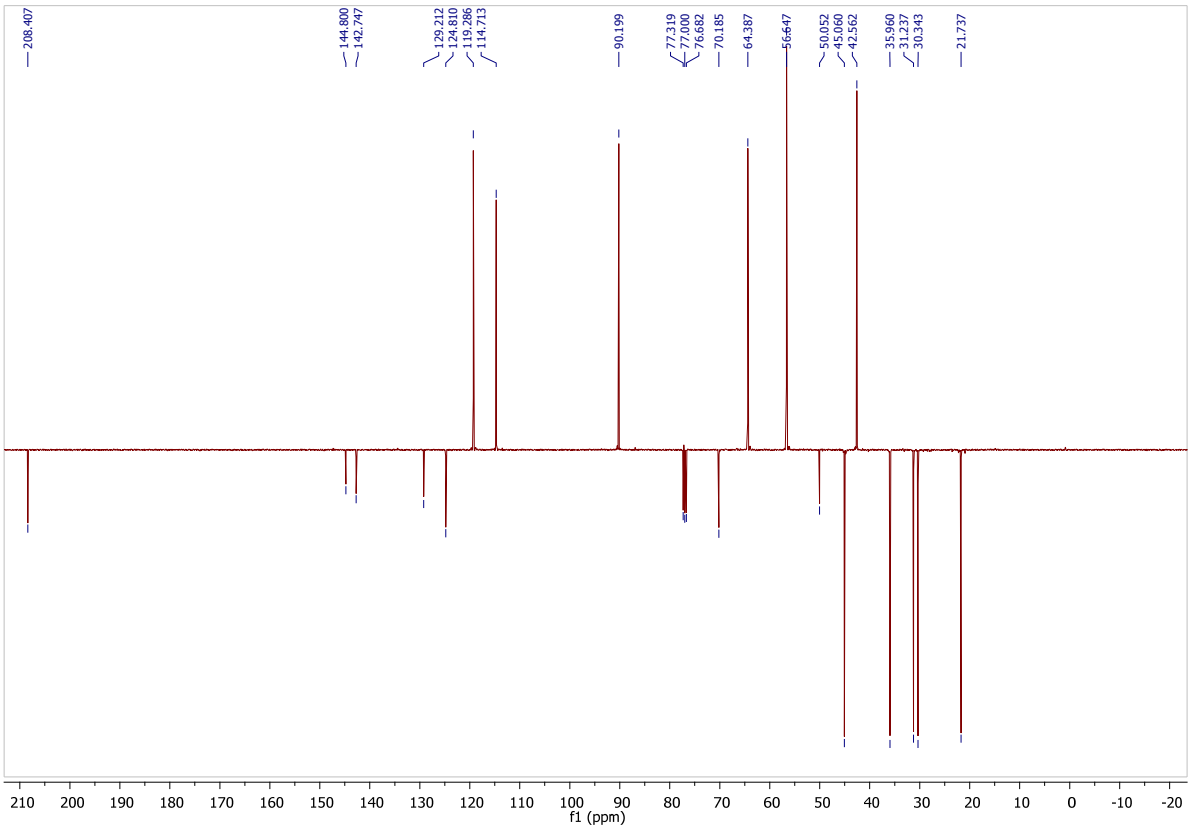
*Prepared according to conditions described in reference 1

Figure 3. ^{1}H NMR of Crude Oxycodone (**1**) in $CDCl_3$ (sample from reduction of 14-hydroxycodeinone hydrochloride* over 5% $Pd/BaSO_4$ in MeOH)



*Prepared via oxidation of thebaine hydrochloride with *m*-CPBA in 10% HOAc

Figure 4. ^{13}C NMR of Crude Oxycodone (**1**) in $CDCl_3$ (sample from reduction of 14-hydroxycodeinone hydrochloride* over 5% $Pd/BaSO_4$ in MeOH)



*Prepared via oxidation of thebaine hydrochloride with *m*-CPBA in 10% HOAc

Figure 5. Oxycodone (**1**) IR spectrum

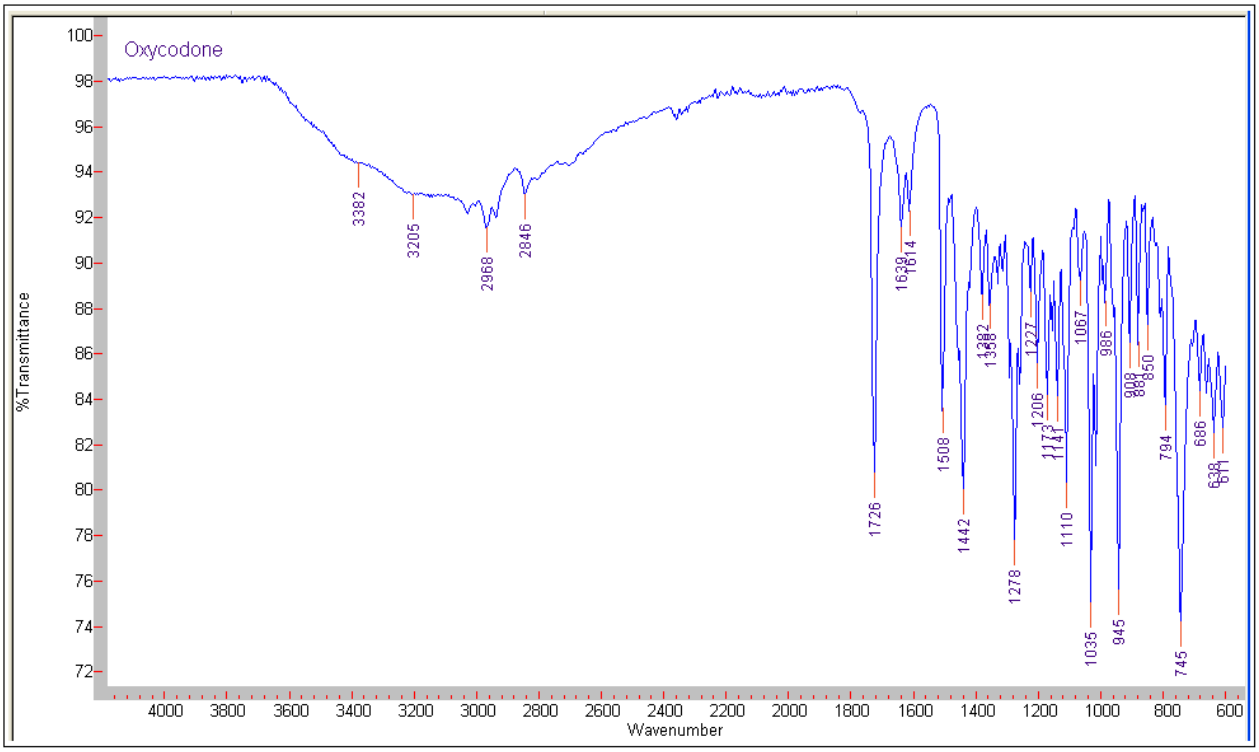
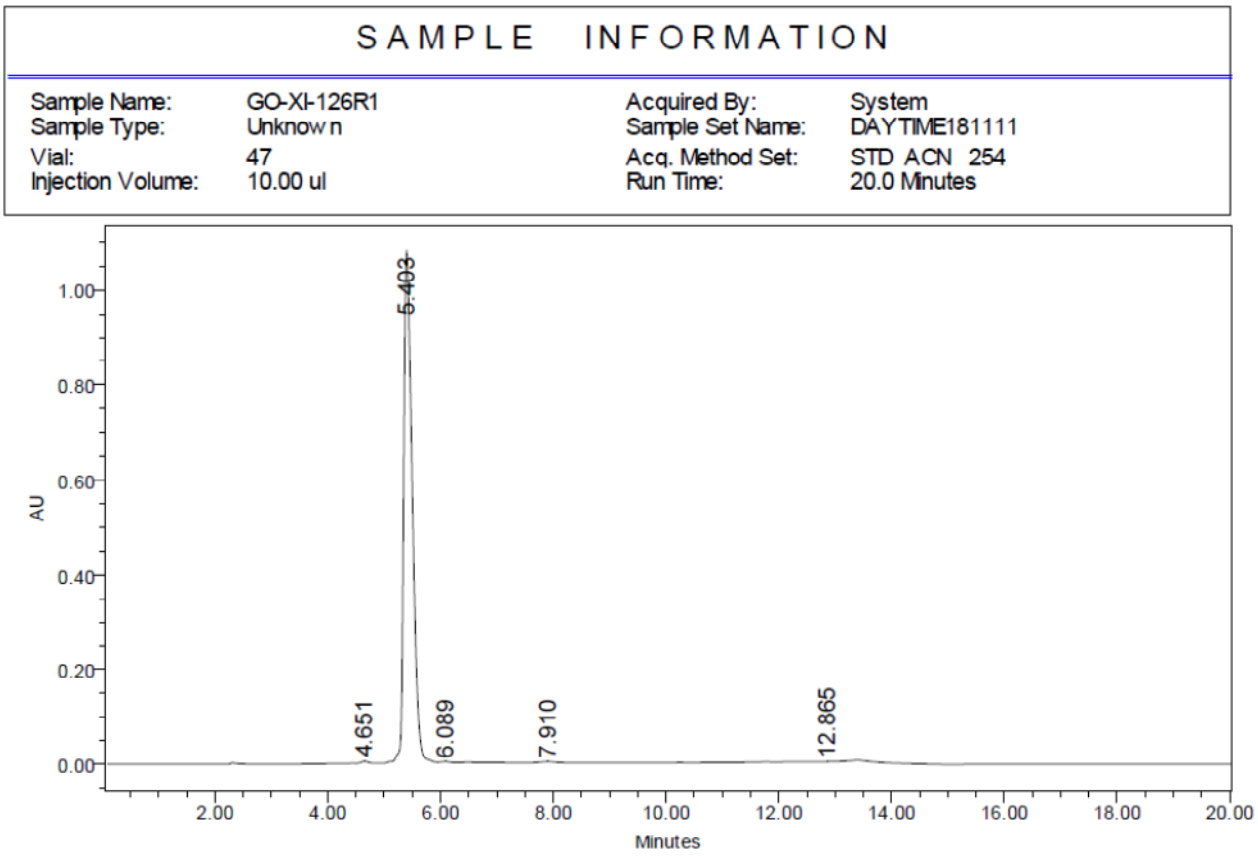


Figure 6. Oxycodone (**1**) HPLC

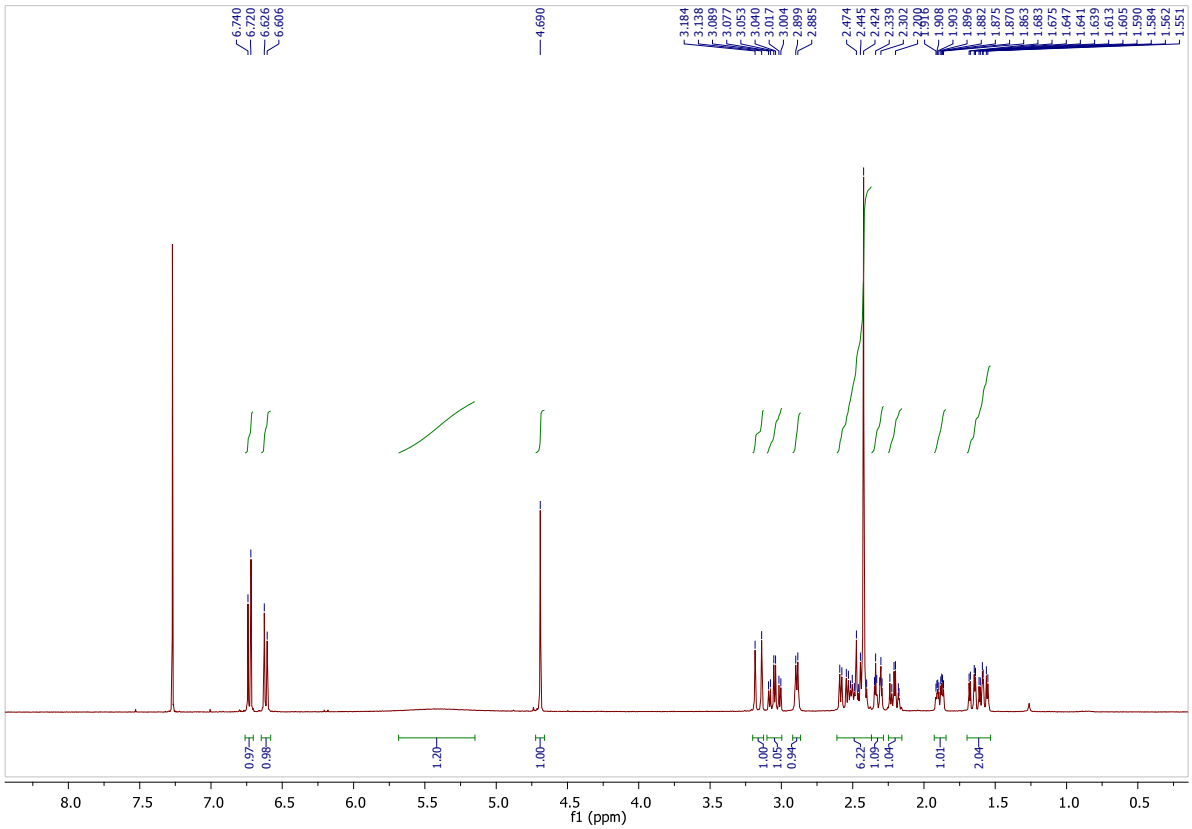


Peak Results

	Name	RT	Height	% Area	Area (µV*sec)
1		4.651	4440	0.37	40063
2		5.403	1064394	98.50	10710533
3		6.089	2061	0.14	15166
4		7.910	2335	0.35	37610
5		12.865	-1281	0.65	70289

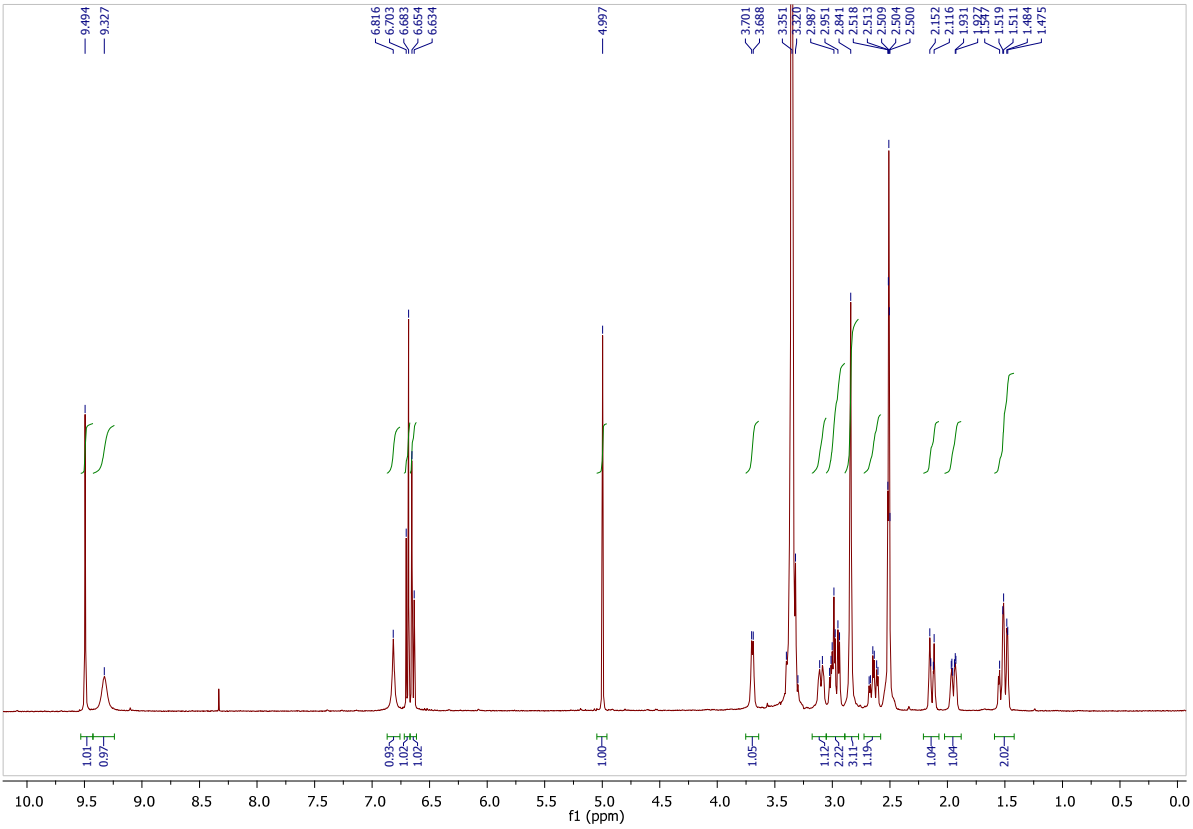
*Prepared via conditions in Table 1, Entry 8.

Figure 7. ^{1}H NMR of Crude Oxymorphone (**2**) in $CDCl_3$ (sample from reduction of 14-hydroxymorphinone Hydrochloride* over 5% $Pd/BaSO_4$ in MeOH)



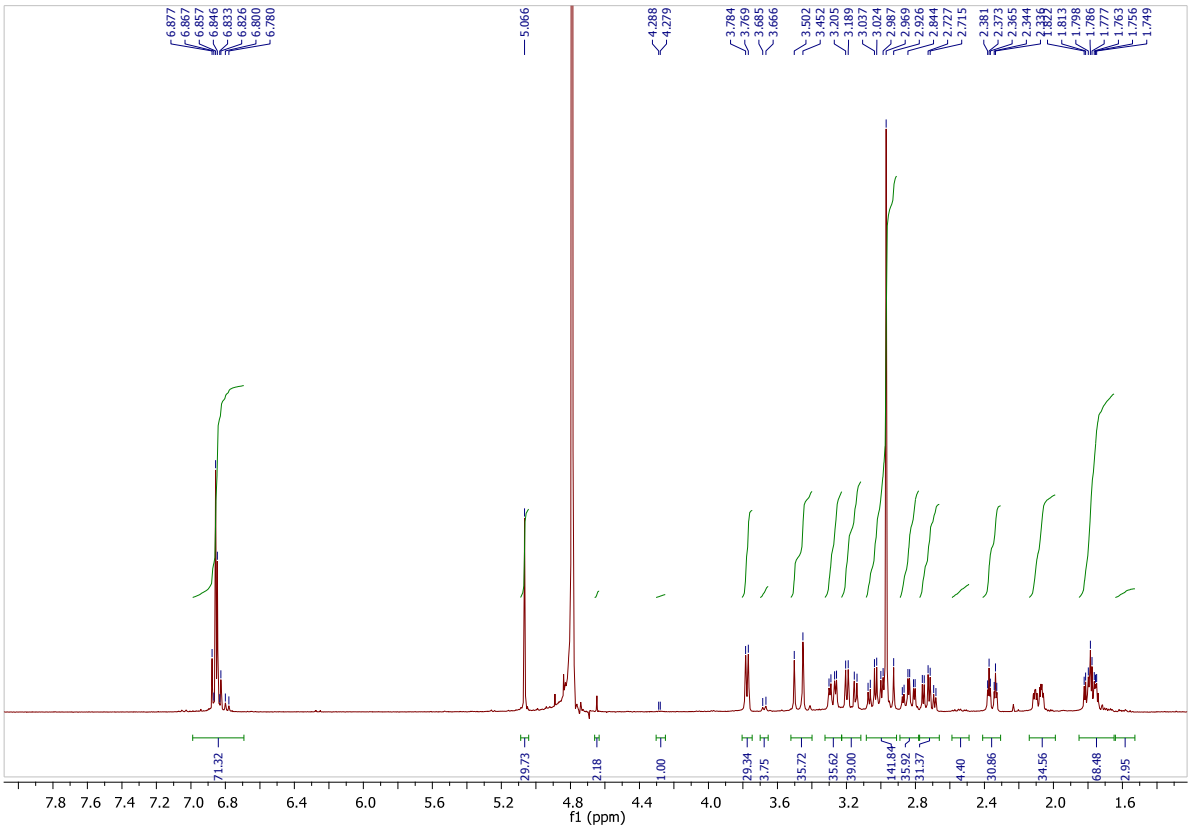
*Prepared via oxidation of oripavine hydrochloride with *m*-CPBA in 10% HOAc

Figure 8. ^{1}H NMR of Crude Oxymorphone Hydrochloride (**2·HCl**) in DMSO-d_6 (sample from reduction of 14-hydroxymorphinone Hydrochloride* over 5% Pd/$BaSO_4$ in MeOH)



*Prepared via oxidation of oripavine hydrochloride with *m*-CPBA in 10% HOAc

Figure 9. ^{1}H NMR of Crude Oxymorphone Hydrochloride (**2·HCl**) in D_2O*[1] (sample from reduction of 14-hydroxymorphinone Hydrochloride*[2] over 5% Pd/$BaSO_4$ in MeOH)



*[1]Oxymorphone hydrochloride forms a gem-diol, with a characteristic singlet at δ 4.65 ppm, in D_2O (Reference 2)
*[2]Prepared via oxidation of oripavine hydrochloride with *m*-CPBA in 10% HOAc

Figure 10. ^{13}C NMR of Crude Oxymorphone (**2**) in DMSO-d_6 (sample from reduction of 14-Hydroxymorphinone Hydrochloride over 5% Pd/$BaSO_4$ in MeOH)

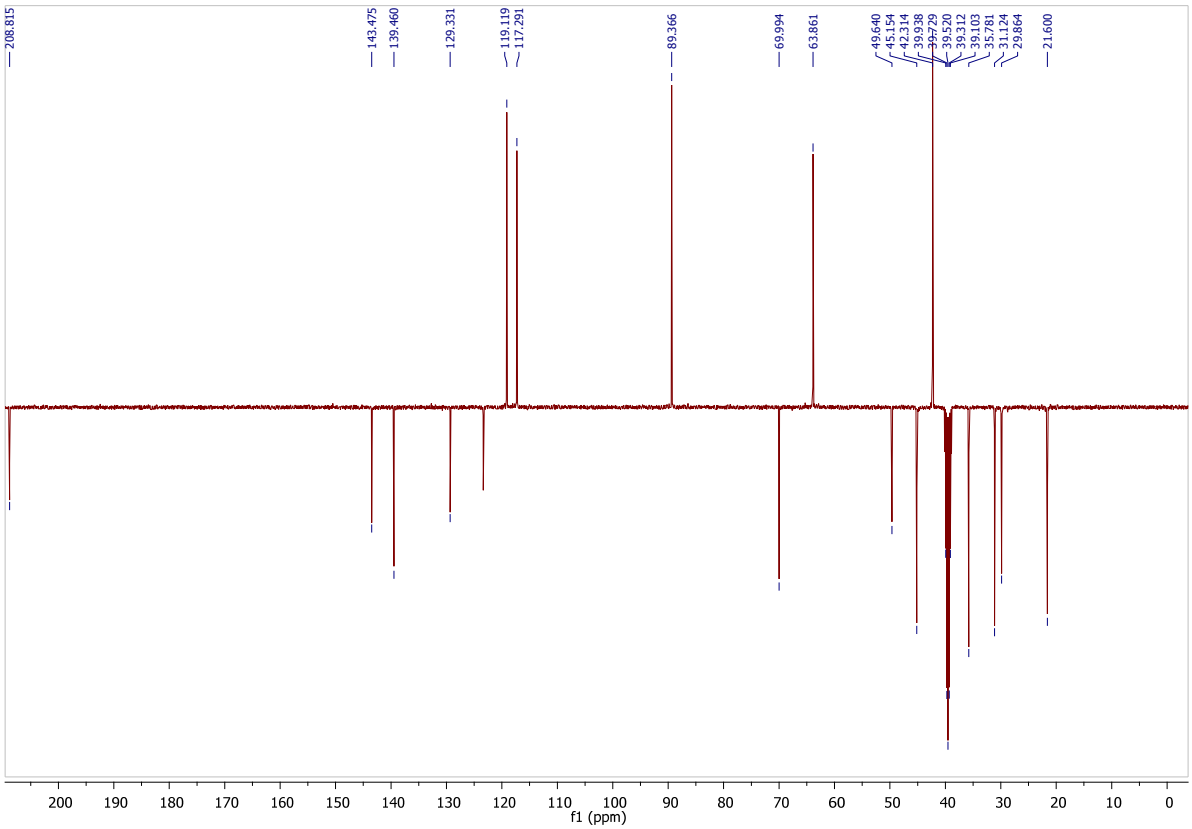


Figure 11. Oxymorphone (**2**) IR spectrum

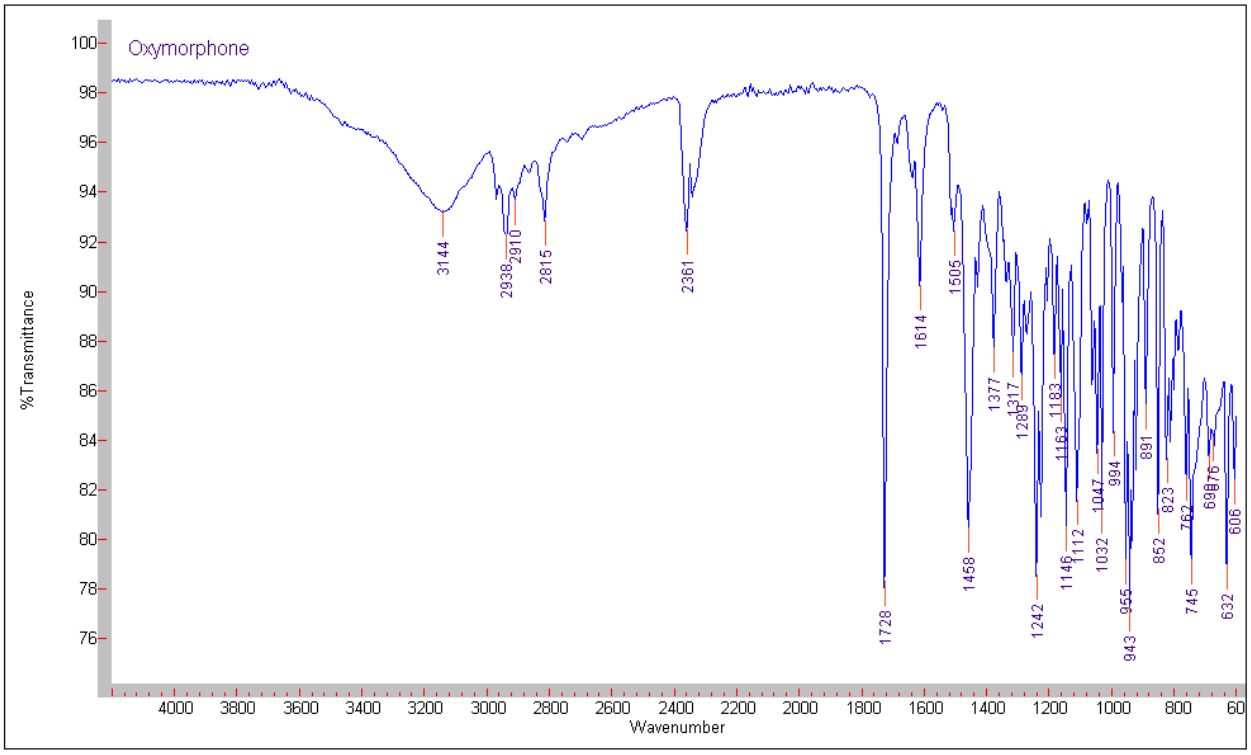
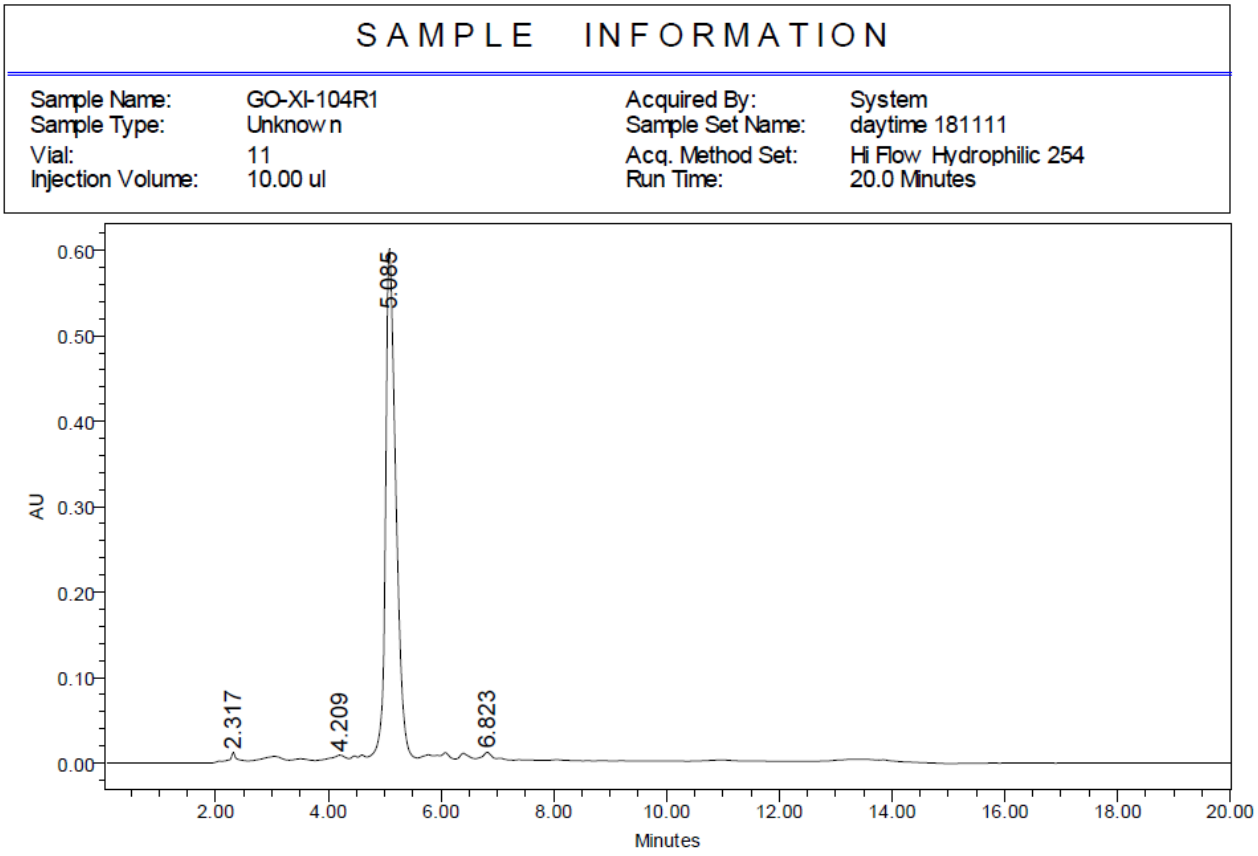


Figure 12. Oxymorphone (**2**) HPLC

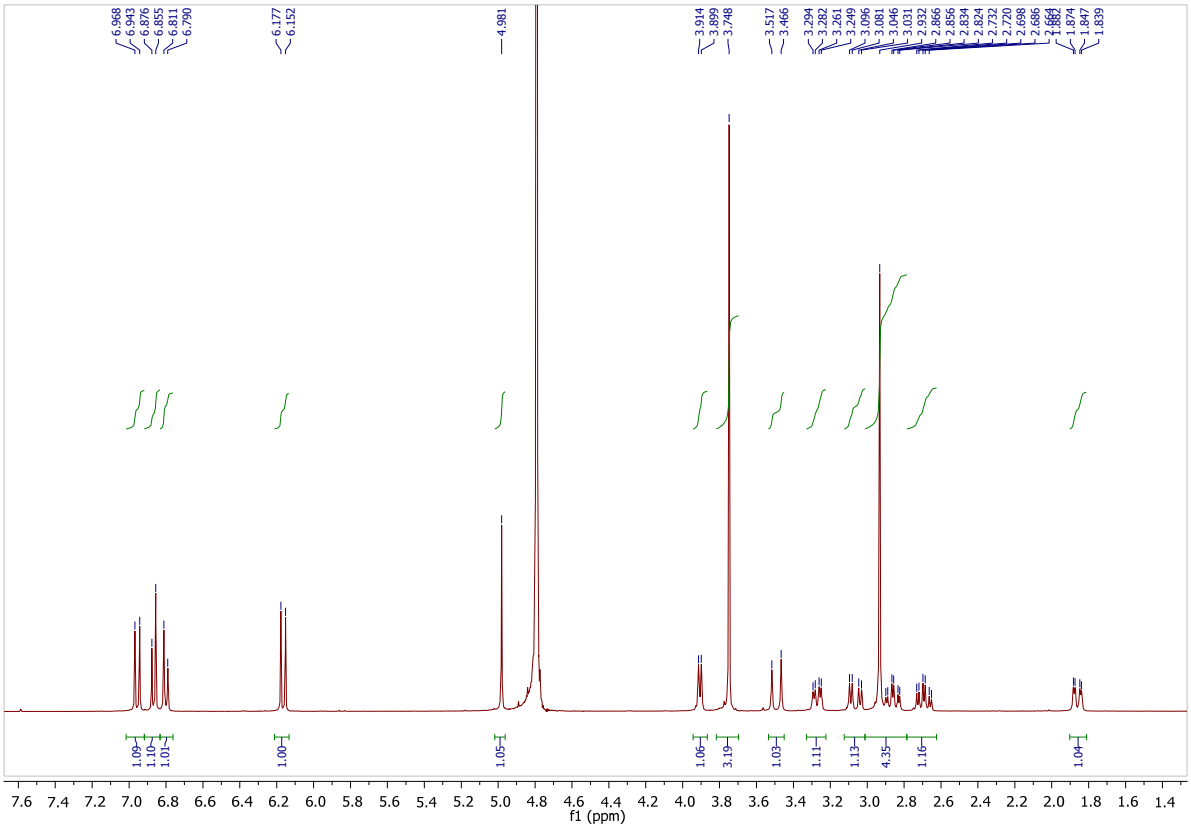


Peak Results

	Name	RT	Height	% Area	Area (µV*sec)
1		2.317	10836	2.65	195326
2		4.209	3717	0.80	59034
3		5.085	577565	94.50	6953258
4		6.823	7112	2.04	150357

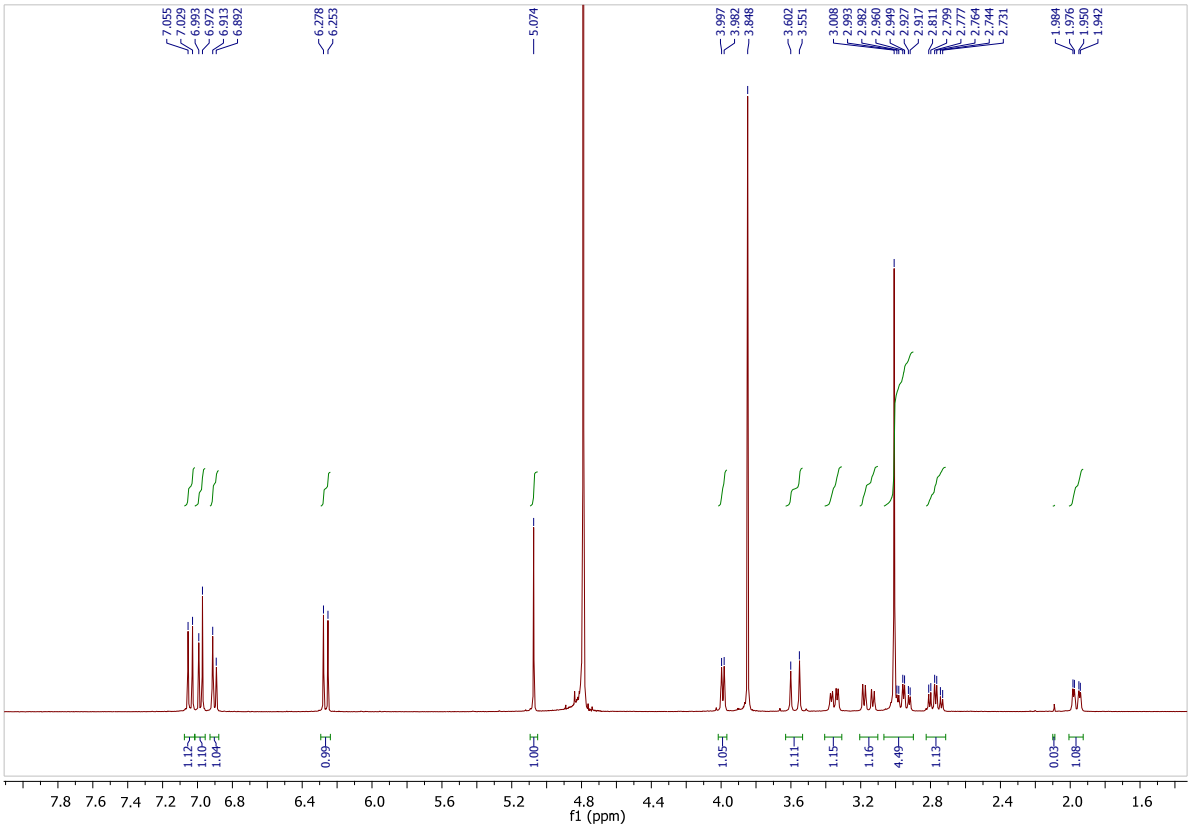
*Prepared via conditions in Table 1 Entry 11

Figure 13. ^{1}H NMR of 14-Hydroxycodeinone (**5**)* in D_2O + TFA



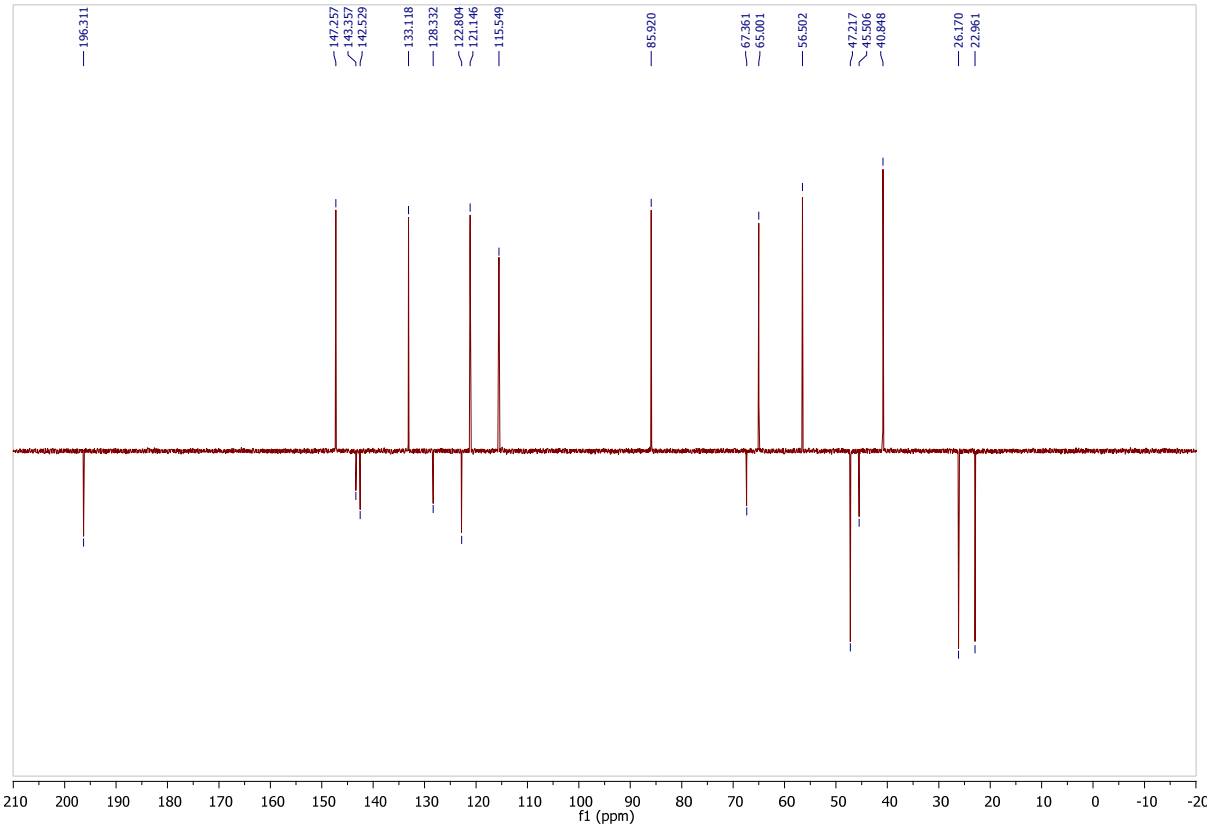
*Prepared via literature methods reported in reference 1

Figure 14. ^{1}H NMR of Crude 14-Hydroxycodeinone Hydrochloride (**5·HCl**)* in D_2O



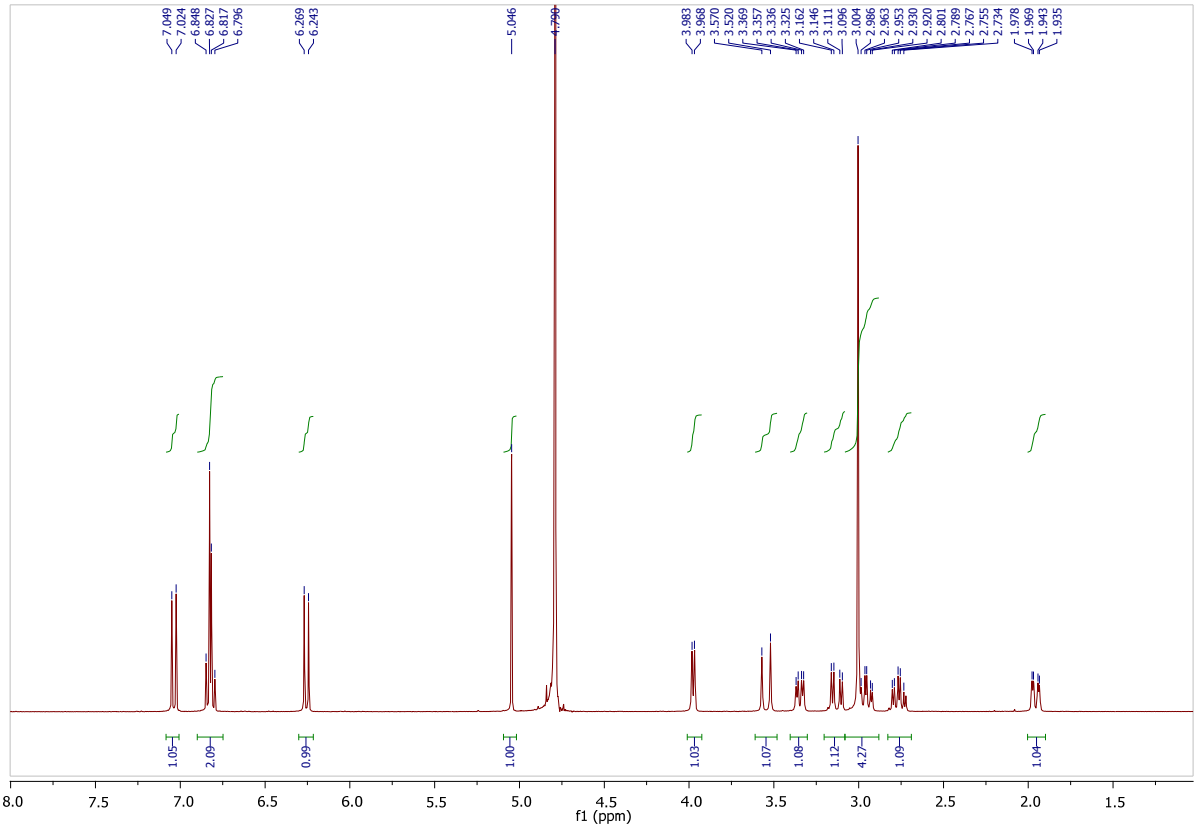
*Prepared via oxidation of thebaine hydrochloride with *m*-CPBA in 10% HOAc

Figure 15. ^{13}C NMR of Crude 14-Hydroxycodeinone Hydrochloride (**5·HCl**)* in D_2O



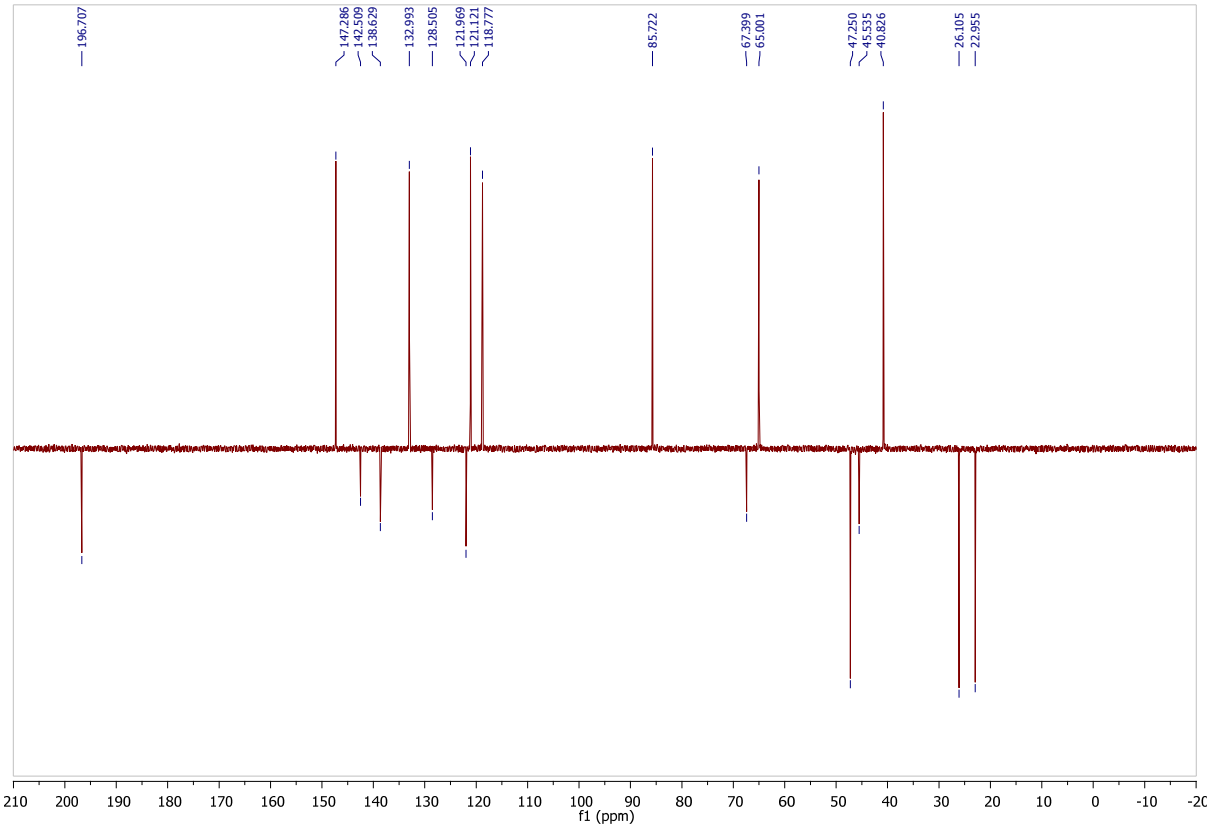
*Prepared via oxidation of thebaine hydrochloride with *m*-CPBA in 10% HOAc

Figure 16. ^{1}H NMR of Crude 14-Hydroxymorphinone Hydrochloride (**6·HCl**)* in D_2O



*Prepared via oxidation of oripavine hydrochloride with *m*-CPBA in 10% HOAc

Figure 17. ^{13}C NMR of Crude 14-Hydroxymorphinone Hydrochloride (**6·HCl**)* in D_2O



*Prepared via oxidation of oripavine hydrochloride with *m*-CPBA in 10% HOAc

Figure 18. ^{1}H NMR of Naltrexone (**7**) in $CDCl_3$

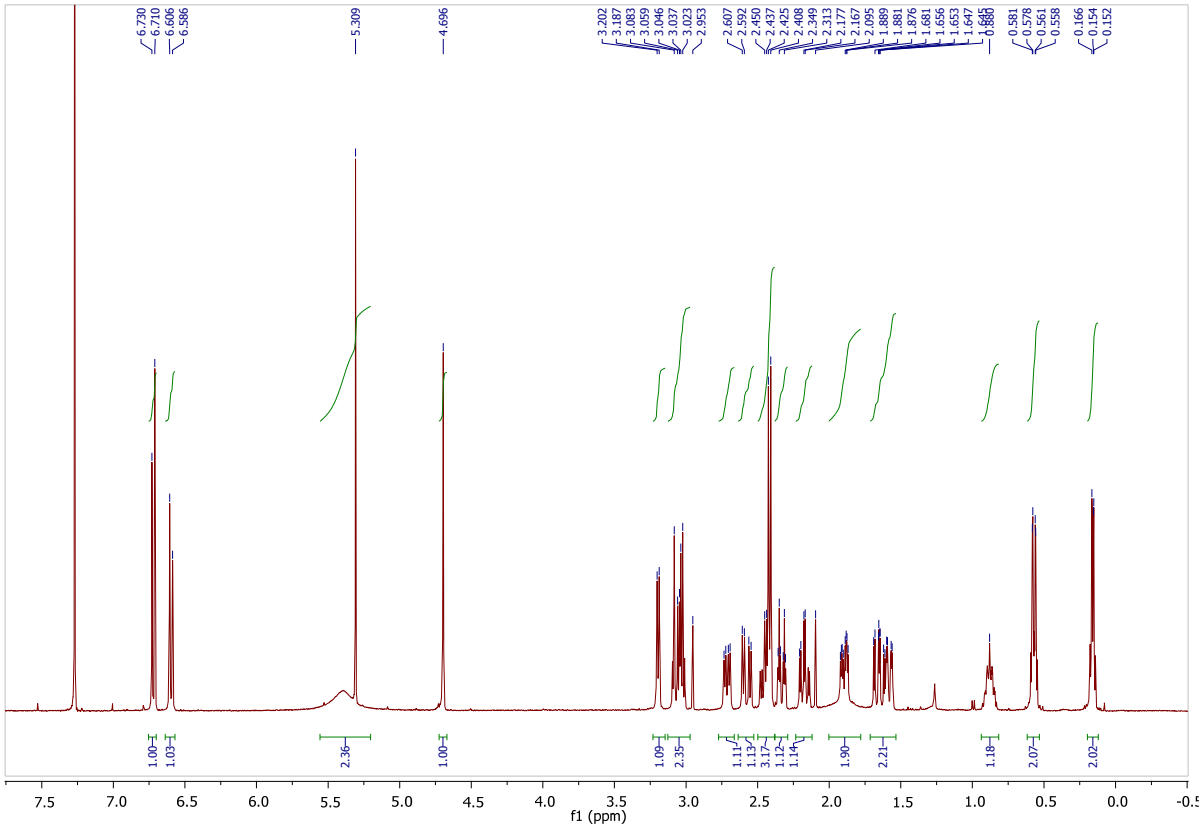


Figure 19. ^{13}C NMR of Naltrexone (**7**) in $CDCl_3$

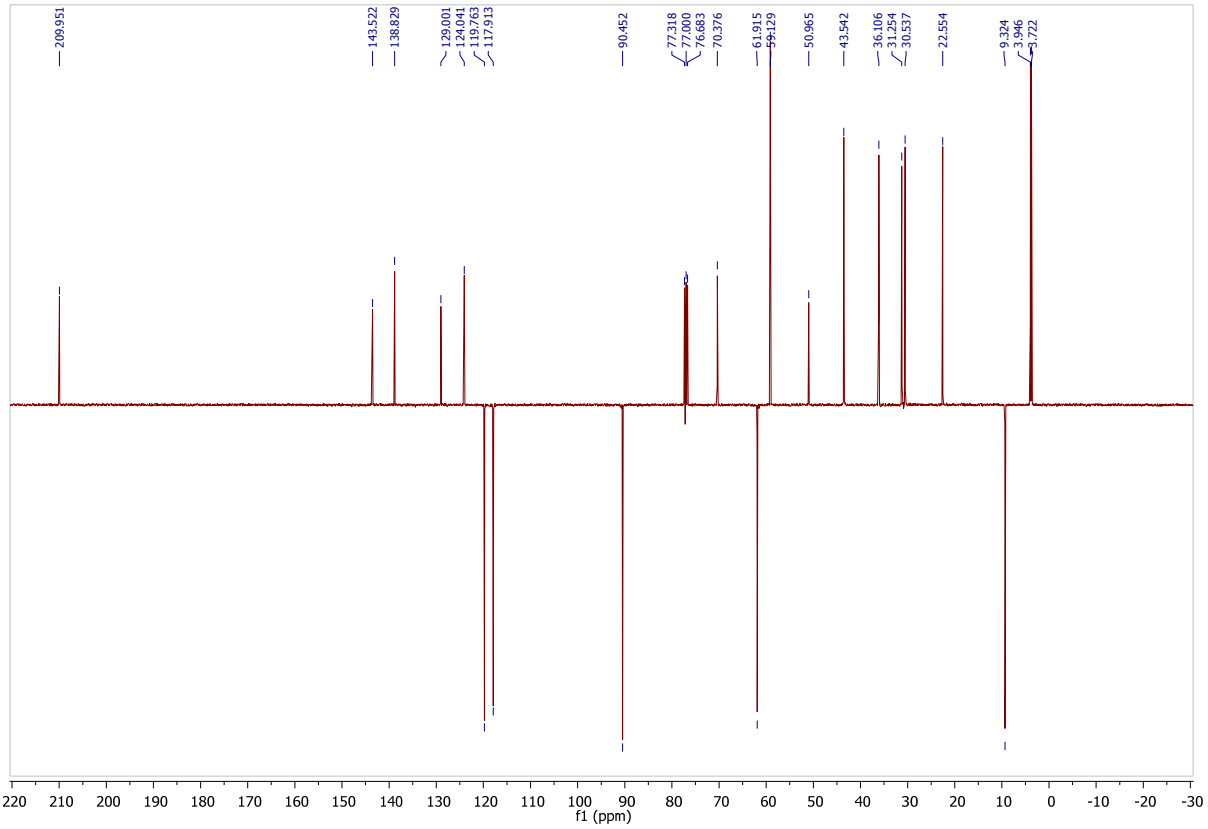


Figure 20. Naltrexone (**7**) IR spectrum

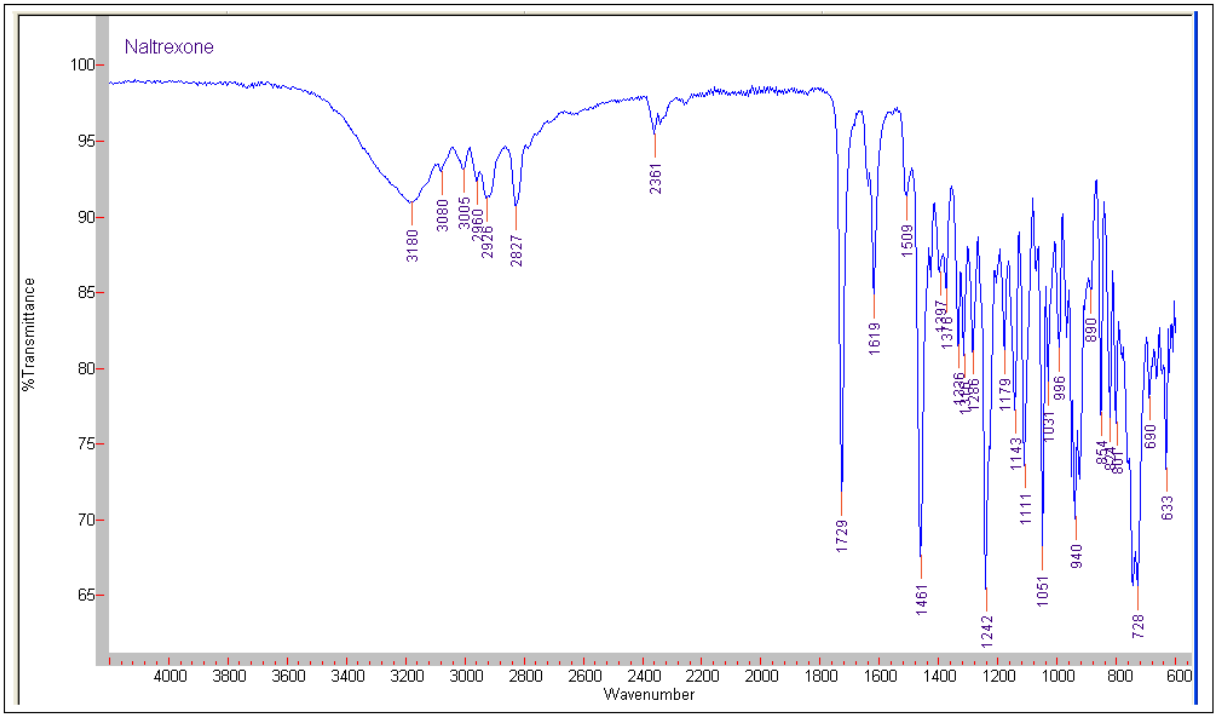
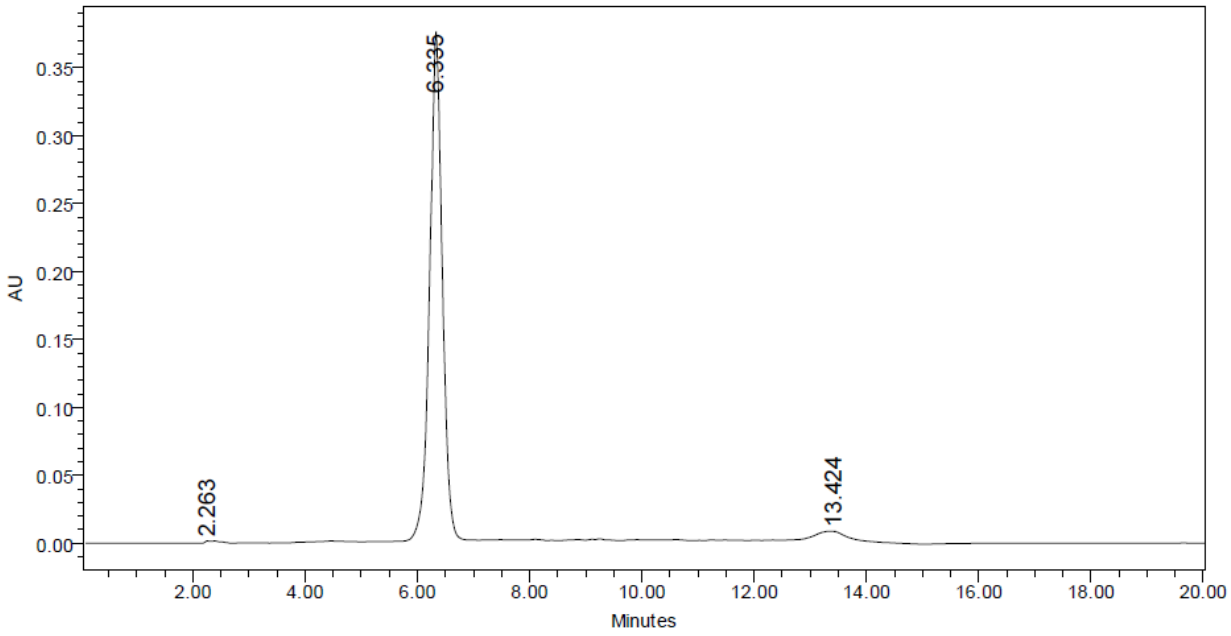


Figure 21. Naltrexone (**7**) HPLC

SAMPLE INFORMATION

Sample Name:	GO-Naltrexone-1	Acquired By:	System
Sample Type:	Unknown	Sample Set Name:	190912_Daytime
Vial:	91	Acq. Method Set:	Hi Flow Hydrophilic 254
Injection Volume:	20.00 ul	Run Time:	20.0 Minutes



Peak Results

	Name	RT	Height	% Area	Area (μV*sec)
1		2.263	1532	0.39	22953
2		6.335	373053	97.94	5791955
3		13.424	4277	1.67	98779

Figure 22. ^{1}H NMR of Crude *N*-Noroxymorphone Hydrochloride (**9·HCl**) in DMSO-d_6 (sample from reduction of 14-hydroxy-*N*-normorphinone Hydrochloride over 5% Pd/$BaSO_4$ in MeOH)

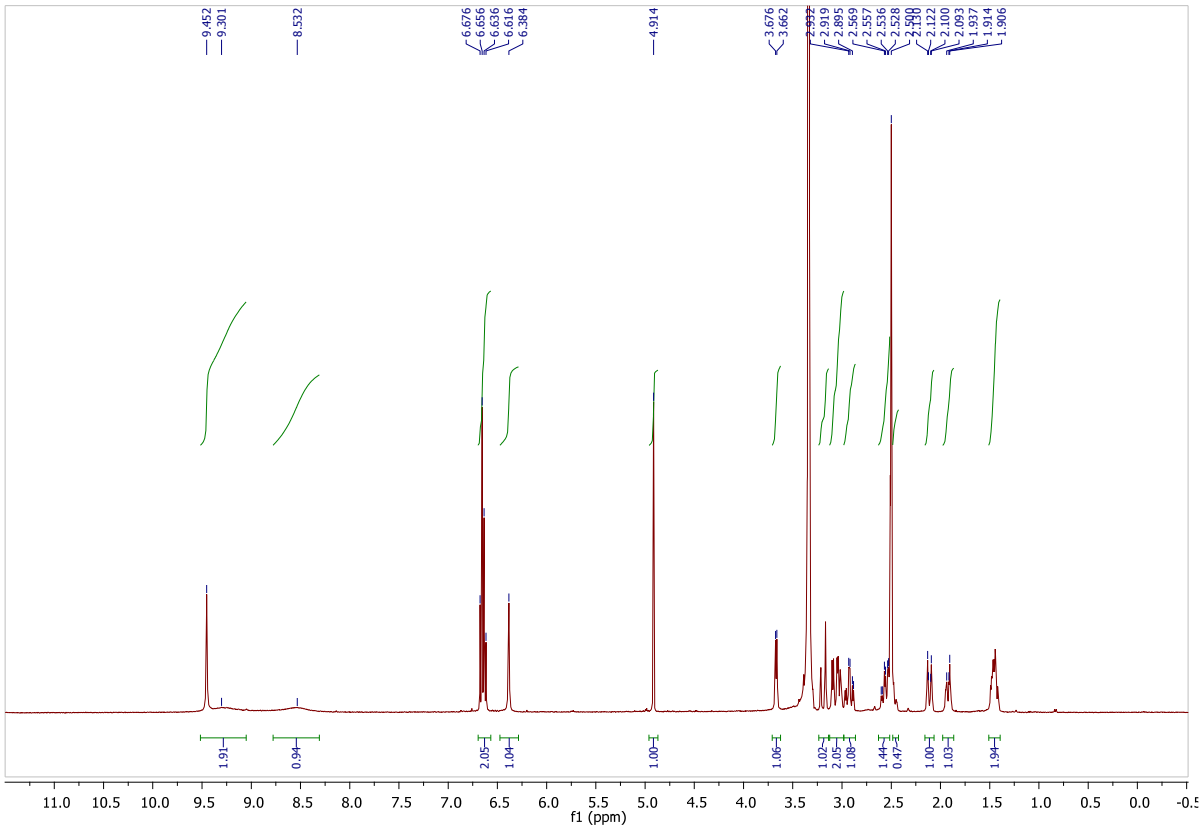
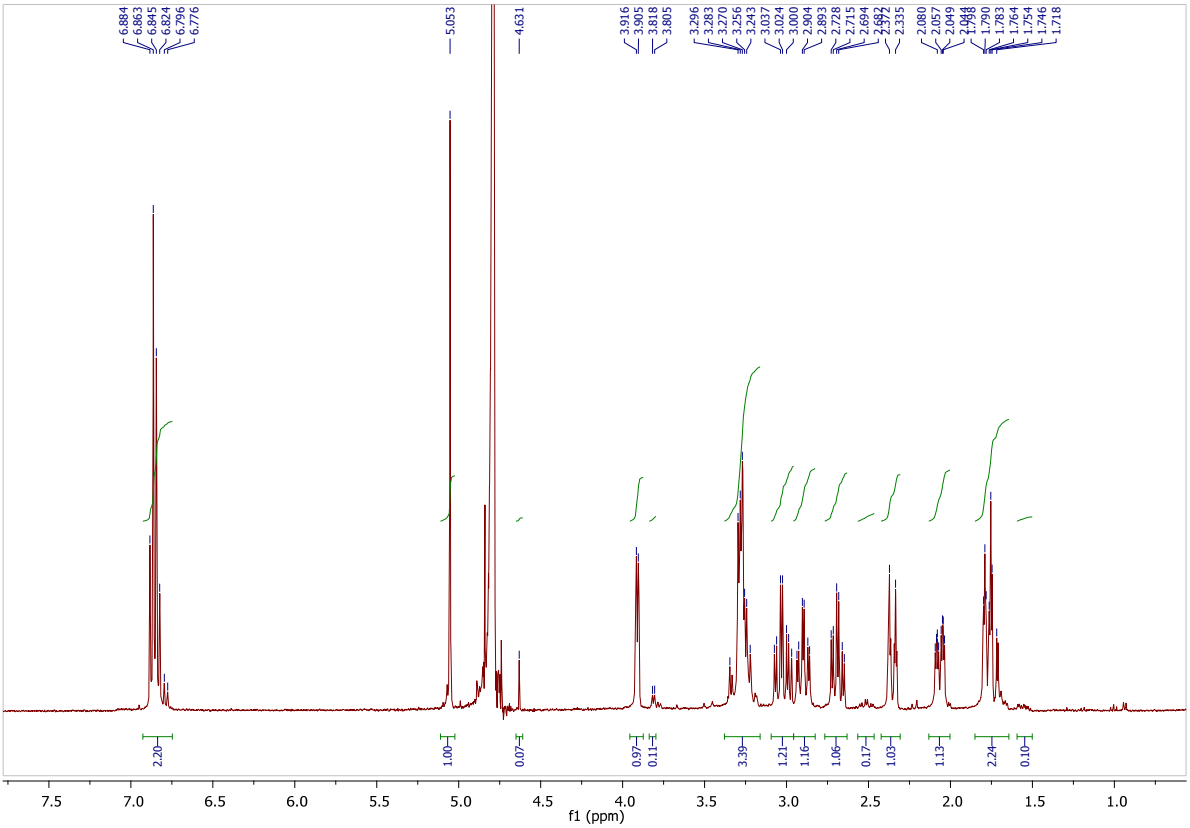


Figure 23. ^{1}H NMR of Crude *N*-Noroxymorphone Hydrochloride (**9·HCl**) in D_2O* (sample from reduction of 14-hydroxy-*N*-normorphinone Hydrochloride over 5% Pd/$BaSO_4$ in MeOH)



*The hydrochloride salt of 6-keto-morphinans such as oxycodone and oxymorphone are known to form gem-diols in D_2O (Reference 2); in the case of *N*-noroxymorphone, the singlet at δ 4.63 ppm is characteristic of the chemical shift due to H-6 of the gem-diol.

Figure 24. ^{13}C NMR of Crude *N*-Noroxymorphone (**9**) in DMSO-d_6 (sample from reduction of 14-Hydroxy-*N*-normorphinone Hydrochloride over 5% Pd/$BaSO_4$ in MeOH)

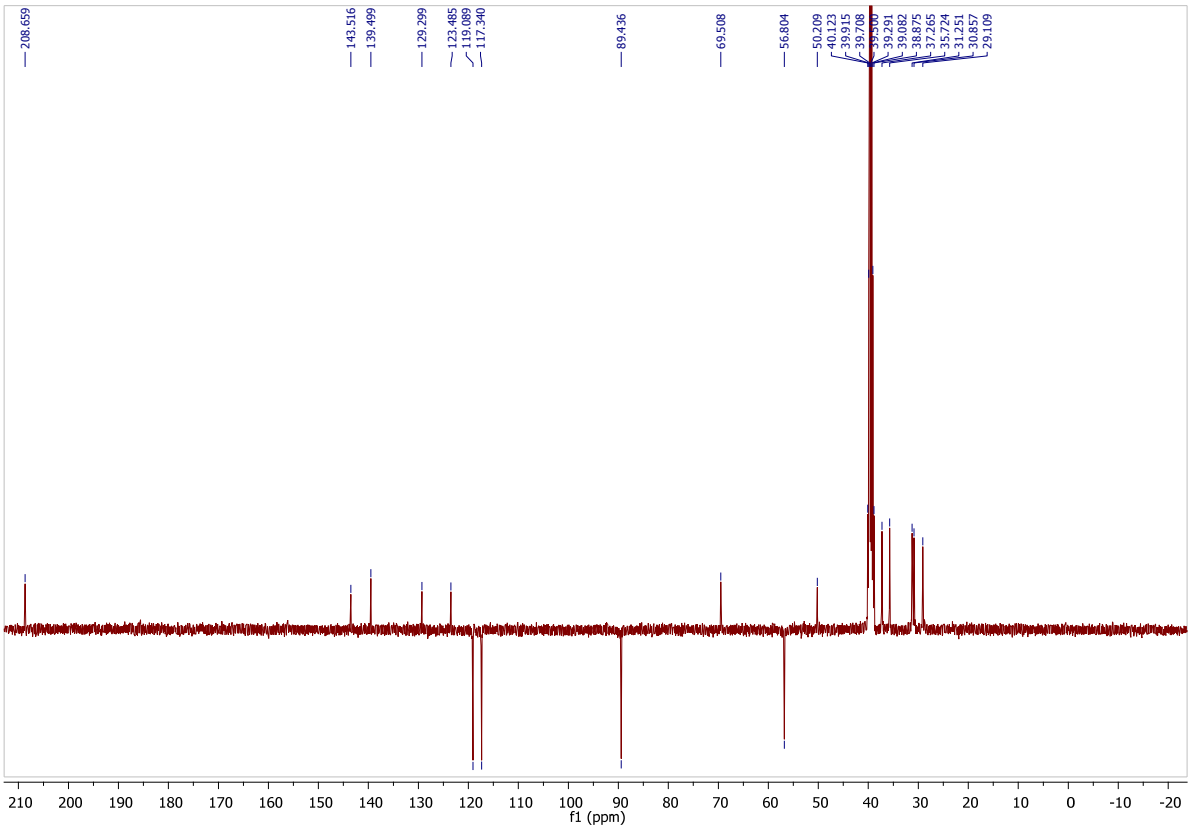


Figure 25. Noroxymorphone (**9**) IR spectrum

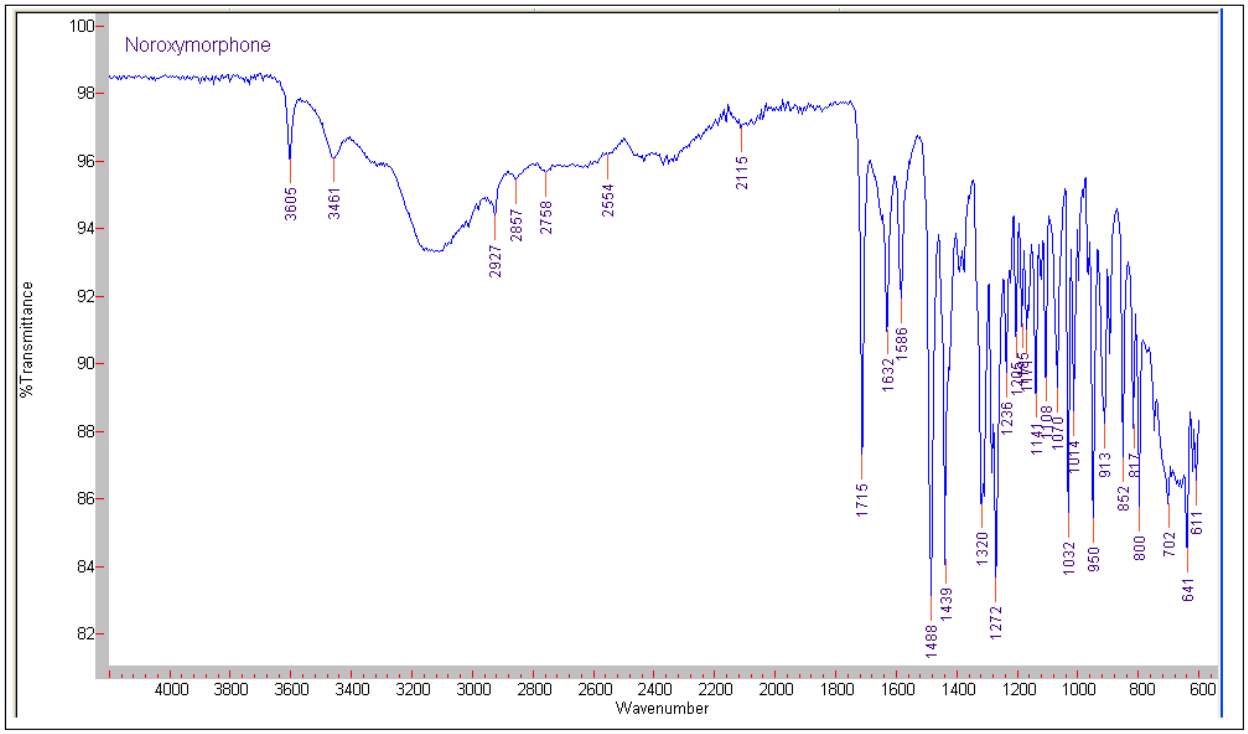
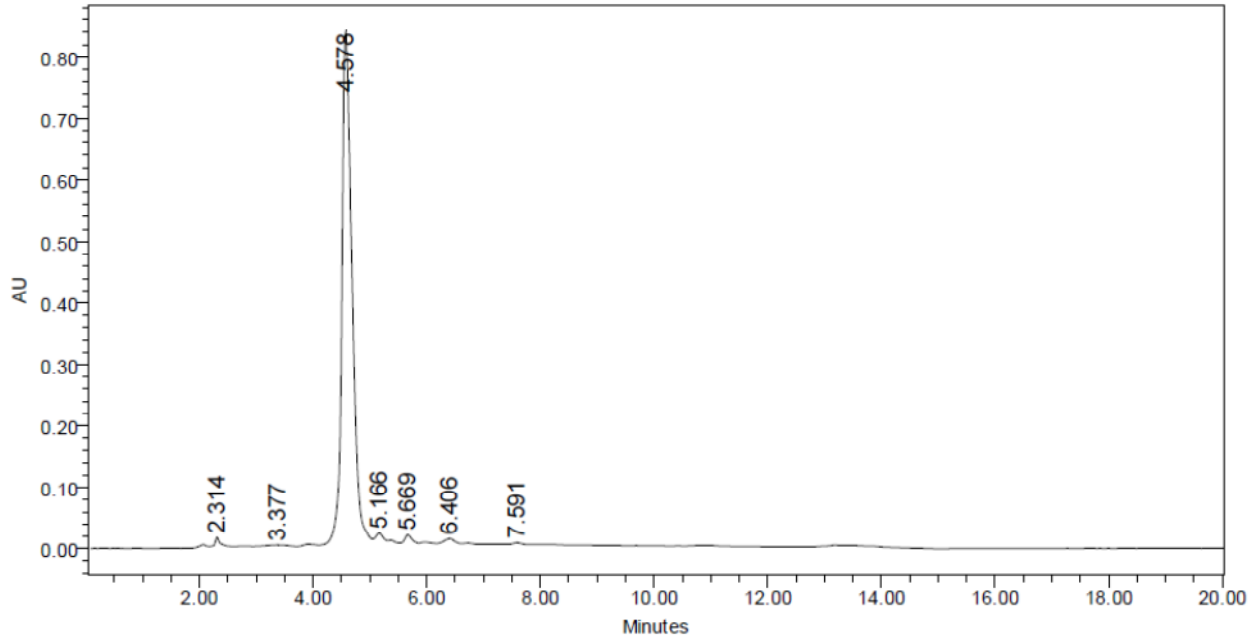


Figure 26. Noroxymorphone (**9**) HPLC

SAMPLE INFORMATION

Sample Name:	GO-XI-110R5	Acquired By:	System
Sample Type:	Unknown	Sample Set Name:	daytime 181111
Vial:	48	Acq. Method Set:	Hi Flow Hydrophilic 254
Injection Volume:	10.00 ul	Run Time:	20.0 Minutes

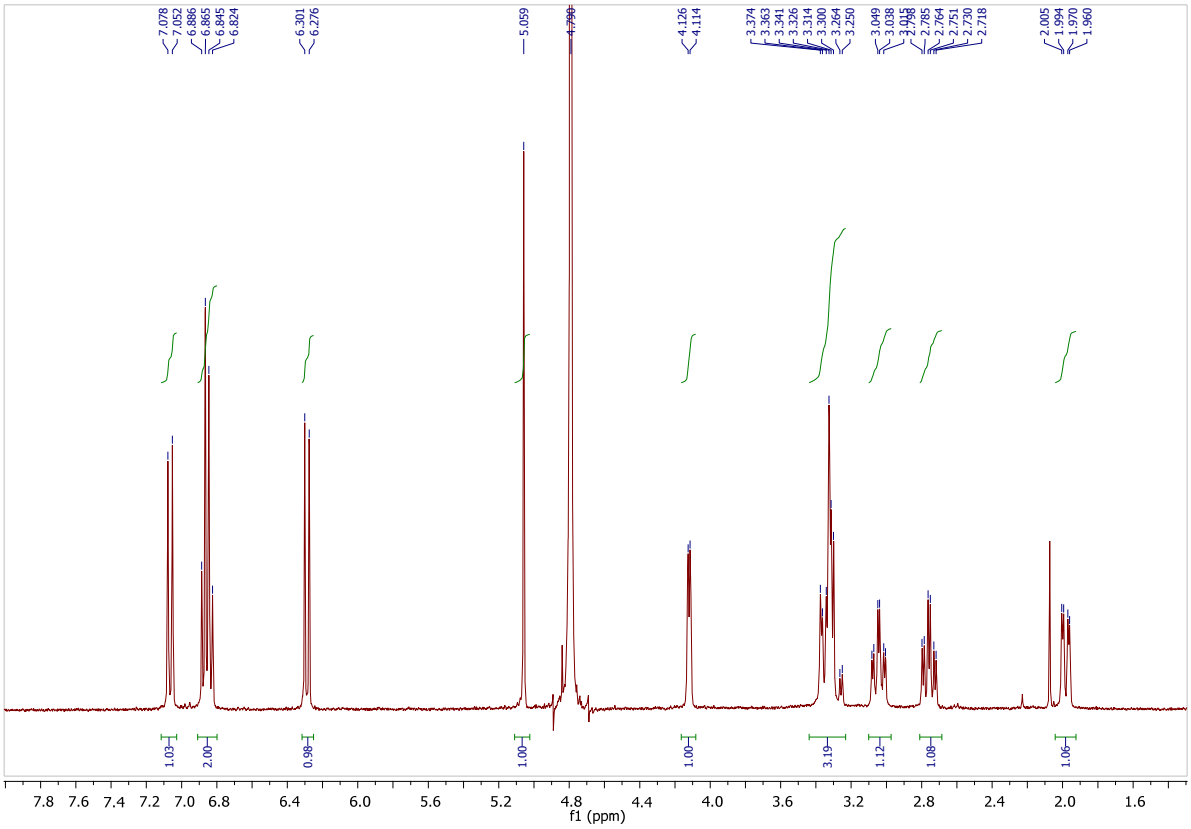


Peak Results

	Name	RT	Height	% Area	Area (µV*sec)
1		2.314	15411	1.43	146191
2		3.377	2275	0.51	52540
3		4.578	827675	95.66	9813537
4		5.166	10695	0.71	72964
5		5.669	8289	0.55	56334
6		6.406	7801	0.89	91420
7		7.591	2763	0.25	25512

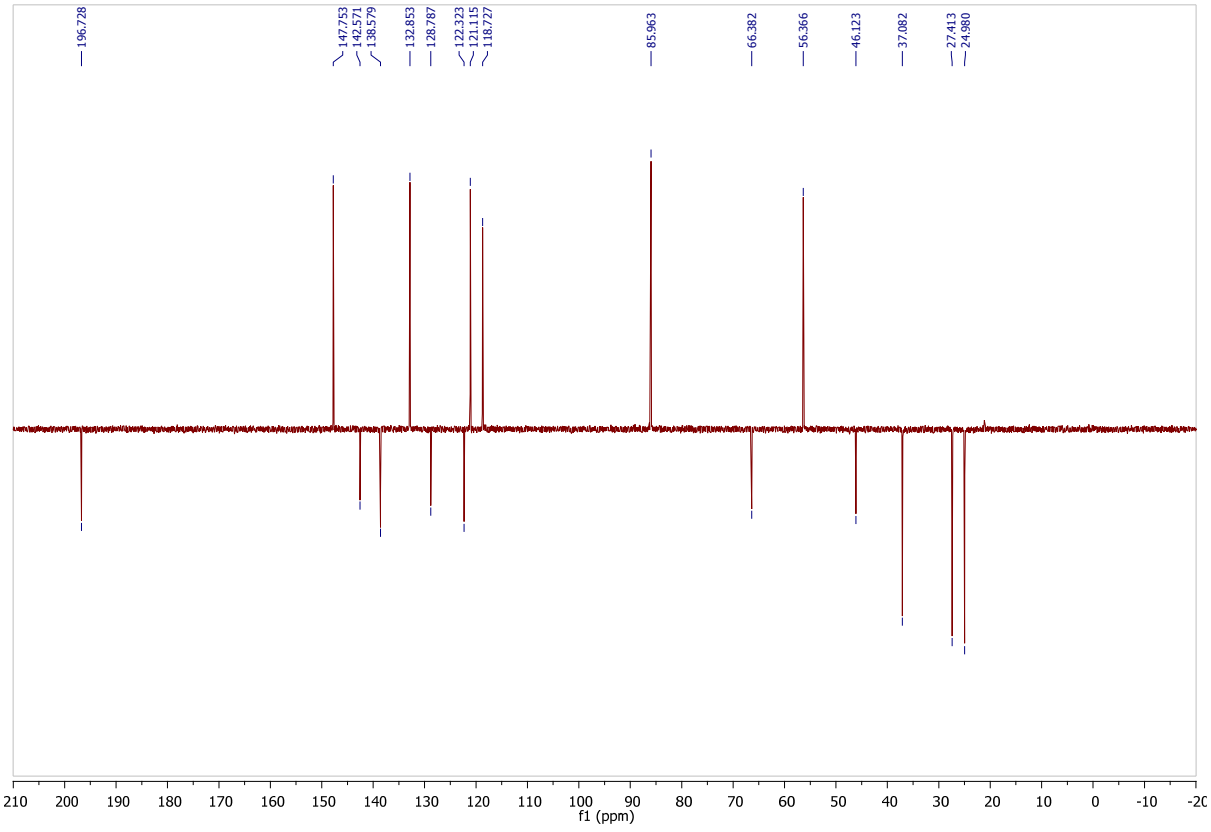
*Prepared via conditions in Table 2, Entry 3

Figure 27. ^{1}H NMR of Crude 14-Hydroxy-*N*-normorphinone Hydrochloride (**13·HCl**)* in D_2O



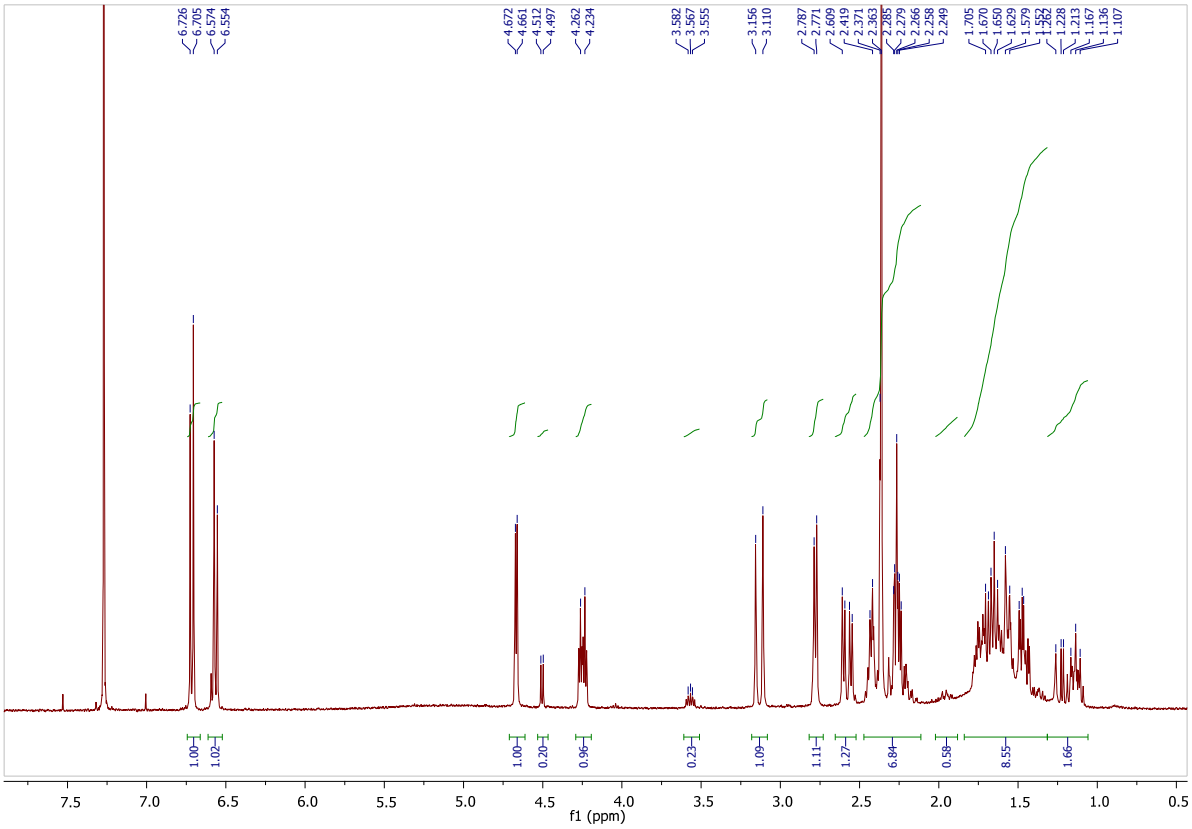
*Prepared via oxidation of *N*-nororipavine hydrochloride with *m*-CPBA in 10% HOAc

Figure 28. ^{13}C NMR of Crude 14-Hydroxy-*N*-normorphinone Hydrochloride (**13·HCl**)* in D_2O



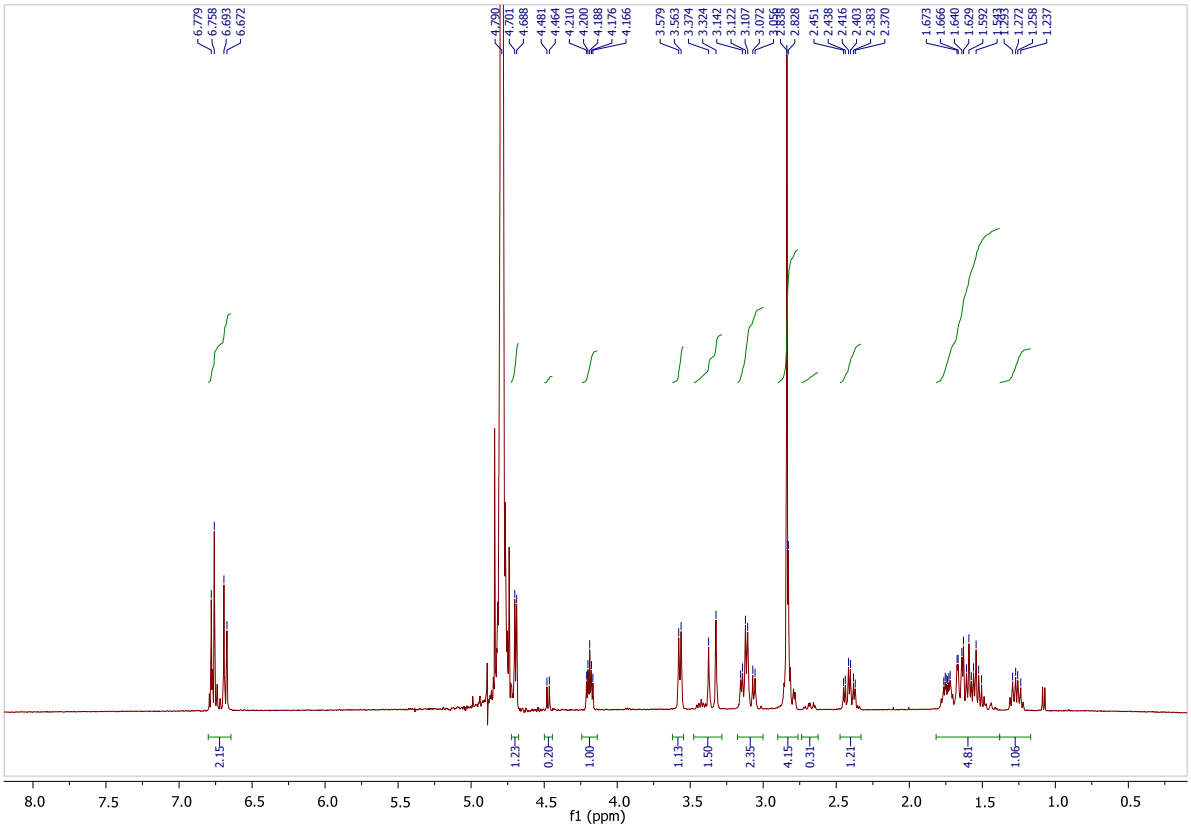
*Prepared via oxidation of *N*-nororipavine hydrochloride with *m*-CPBA in 10% HOAc

Figure 29. ^{1}H NMR of Crude Oxymorphol (**17**)* in $CDCl_3$



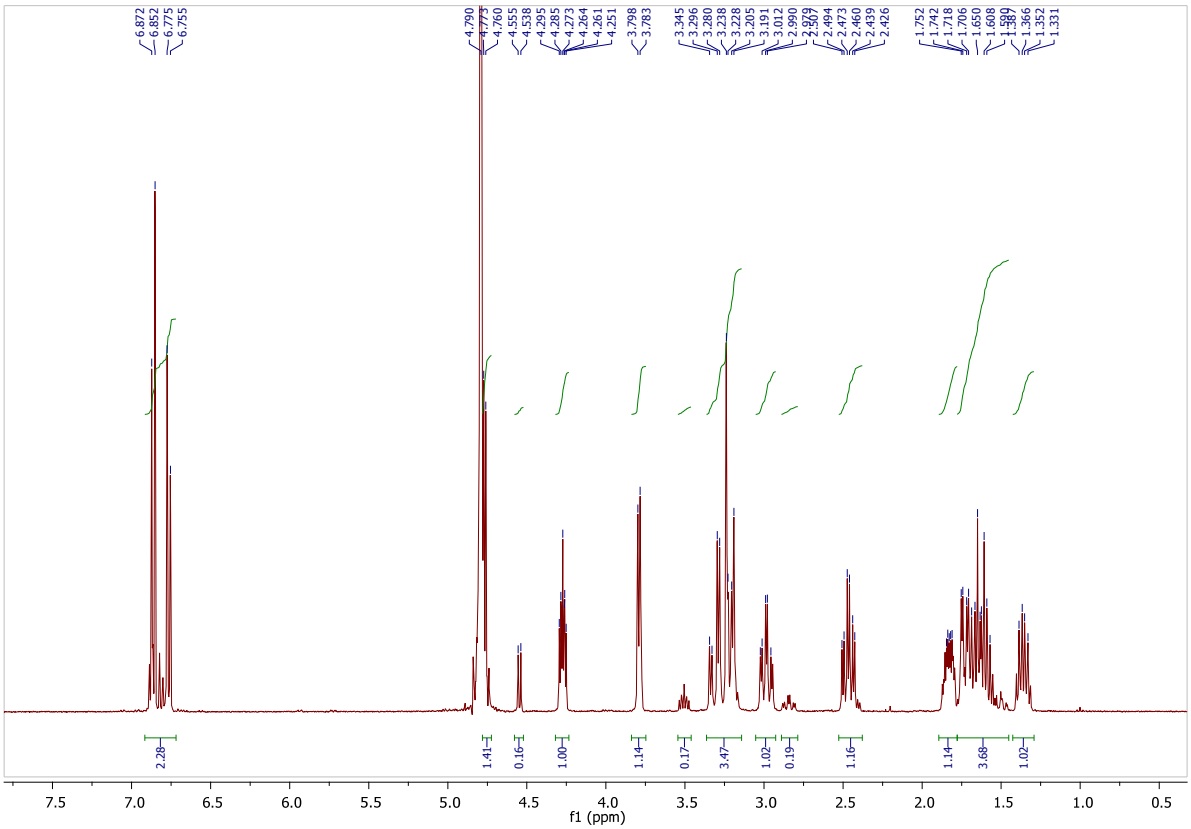
*Ratio of 6-epimers: α:ß ~ 5:1

Figure 30. ^{1}H NMR of Crude Oxymorphol (**17**)* in D_2O+HCl



*Ratio of 6-epimers: α:ß ~ 5:1

Figure 31. ^{1}H NMR of Crude *N*-Noroxymorphol Hydrochloride (**18**)* in D_2O



*Ratio of 6-epimers: α:ß ~ 14:1

References

[1] Hauser, F. M.; Chen, T.-K.; Carroll, F. I. *J. Med. Chem*. **1974**, *17*, 1117.

[2] Caldwell, G. W.; Gauthier, A. D.; Villani, F. J.; Maryanoff, C. A.; Leo, G. *Tetrahedron Lett*. **1991**, *32*, 3763.