Supporting Information

Development of a Scalable Synthesis of a GPR40 Receptor Agonist

Shawn D. Walker, Christopher J. Borths, Evan DiVirgilio, Liang Huang, Pingli Liu, Henry Morrison, Kiyoshi Sugi, Masahide Tanaka, Jacqueline C. S. Woo and Margaret M. Faul*

Chemical Process Research and Development, Amgen Inc., Thousand Oaks, California 91320, U.S.A.

Table of Contents:

Proton (^{1}H) and Carbon-13 (^{13}C) NMR Spectra of AMG 837 Sodium Salt

^{1}H and ^{13}C NMR analysis of AMG 837 sodium salt was carried out to confirm its structure. The spectra were recorded in deuterated DMSO (DMSO-D6) at 27 °C (300 K) in a 3 mm NMR tube. ^{1}H and ^{13}C NMR spectra (Figures 1 and 2) were acquired at 400.13 and 100.62 MHz respectively on a Bruker DPX 400 spectrometer. Chemical shifts are reported in the δ scale (ppm) by assigning the residual solvent peak to 2.50 ppm for CD_2HSOCD_3 for ^{1}H and 39.51 ppm for the methyl group of DMSO for ^{13}C.

Assignments were made on the basis of chemical shifts and proton-proton coupling constants together with COSY and NOESY spectra (Figures 3 and 4) for proton; and carbon chemical shifts together with HMQC and HMBC spectra (Figures 5 and 6) for carbon (Table 1). ^{1}H NMR spectrum provided evidence for two AA'BB' spin systems (δ 6.93 and 7.26 ppm; δ 7.82 and 7.90 ppm); two p-disubstituted benzene rings (A and B rings); a 1,3-disubstituted benzene ring (δ 7.52, 7.53, 7.69 and 7.81 ppm); a down-field methylene group (δ 5.15 ppm); and a 3-substituted hex-4-ynoic acid sodium salt. 2D ^{1}H-^{1}H NOESY spectrum showed NOE correlations between the down-field methylene proton H-13 with the aromatic protons H-8 and H-10 of the 1,3-disubstituted benzene ring, and with the aromatic protons H-16 and H-20 of the p-disubstituted ring B, indicating that the down-field methylene H-13 is attached to C-9 of the 1,3-disubstituted benzene ring and to the oxygen bonded to C-15 of the p-disubstituted ring B. 2D ^{1}H-^{1}H NOESY spectrum showed NOE correlations between the aromatic protons H-8 and 12 of the 1,3-disubstituted benzene ring with the aromatic protons H-2 and 6 of the p-disubstituted ring A, indicating that these two ring are connected through carbons C-7 and C-1.

1D ^{13}C NMR spectrum showed the presence of all the carbons of the molecule (Figure 2). 2D ^{1}H-^{13}C HMQC spectrum showed the one-bond C-H correlations. 2D ^{1}H-^{13}C HMBC showed C-H correlations through two and three bonds. 1D ^{13}C NMR spectrum shows four carbons coupled with ^{19}F, C-29 as a quartet through one C-F bond correlation (δ 127.0, 1JC-F=271.9Hz), C-4 as a quartet through C-C-F bond correlations (δ 127.9, 2JC-F=31.7Hz), and C-3, 5 as a quartet through C-C-C-F bond correlations (δ 125.8, 3JC-F=3.8Hz). 2D ^{1}H-^{13}C HMBC showed a number structurally informative C-H correlations for the 3-substituted hex-4-ynoic moiety such as C-18, 21, 22, 23, 25, 26/H-27, C-18, 21, 23, 25/H-22 and C-17, 18, 19, 22, 23, 25, 26/H-21 indicating that the 3-substituted hex-4-ynoic moiety is attached to position C-18 of a p-disubstituted benzene ring. ^{1}H-^{13}C HMBC showed C-H correlations for the down-field methylene group at position 13 such as C-8, 9, 10, 15/H-13 and C-13/H-8, 10 indicating that this group is attached to the p-disubstituted benzene ring B at C-15 through an oxygen and to carbon C-9 of the 1,3-disubstituted benzene ring. ^{1}H-^{13}C HMBC showed C-H correlations for the 1,3-disubstituted benzene ring such as C-7/H-2, 6 and C-1/H-8, 12 indicating that the 1,3-disubstituted benzene ring and p-disubstituted benzene ring A are connected through the carbons C-7 and C-1 respectively.

The NMR spectroscopy evidence supports the structure of AMG 837 sodium salt as sodium 3-(4-{[4'-(trifluoromethyl)biphenyl-3-yl]methoxy}phenyl)hex-4-ynoate depicted below:

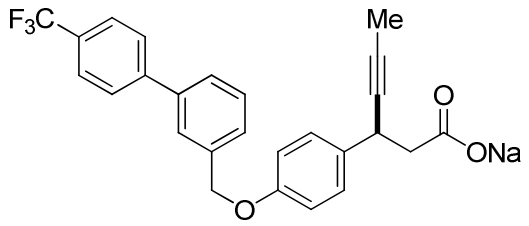


Figure 1 ^{1}H NMR Spectrum of AMG 837 sodium salt in DMSO-D6

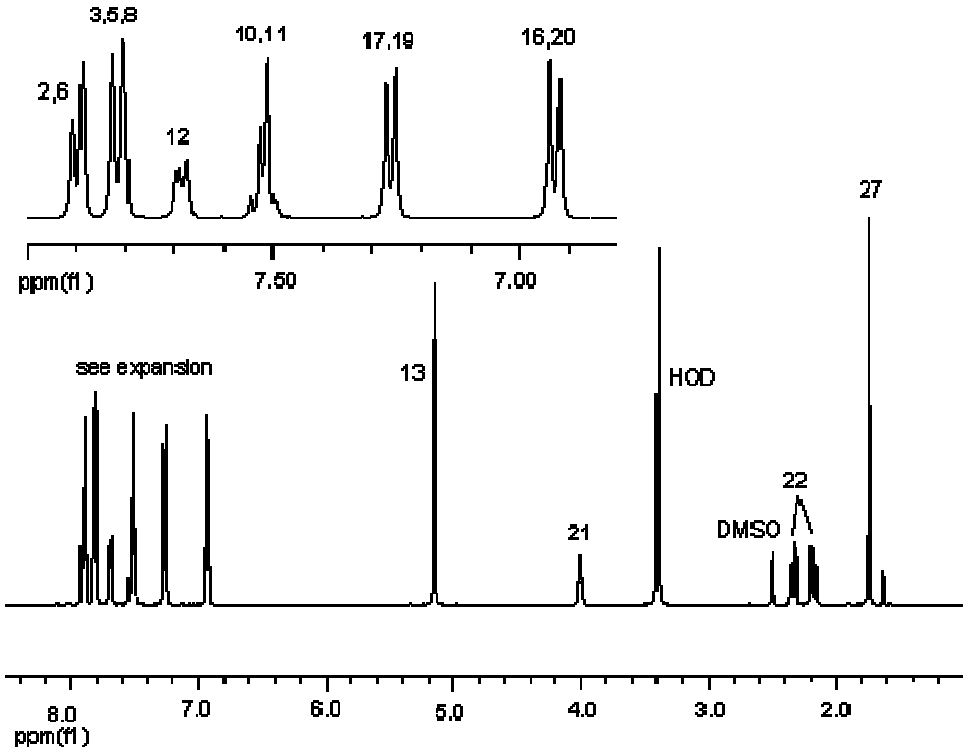


Figure 2 ^{13}C NMR Spectrum of AMG 837 sodium salt in DMSO-D6

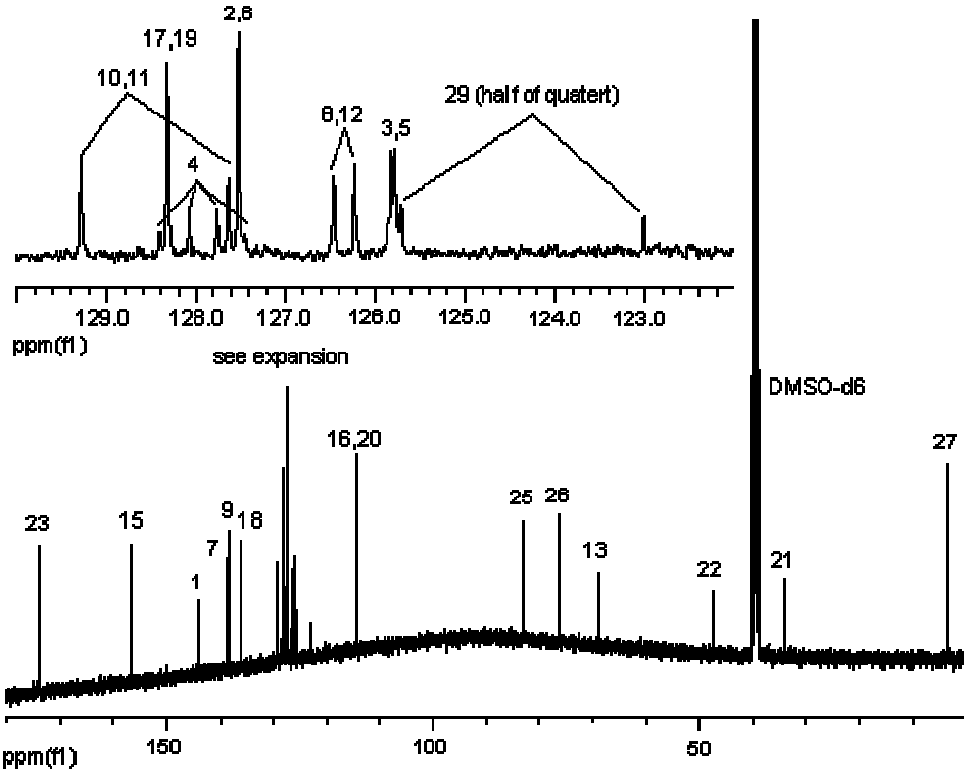


Figure 3 2D ^{1}H-^{1}H COSY of AMG 837 sodium salt in DMSO-D6

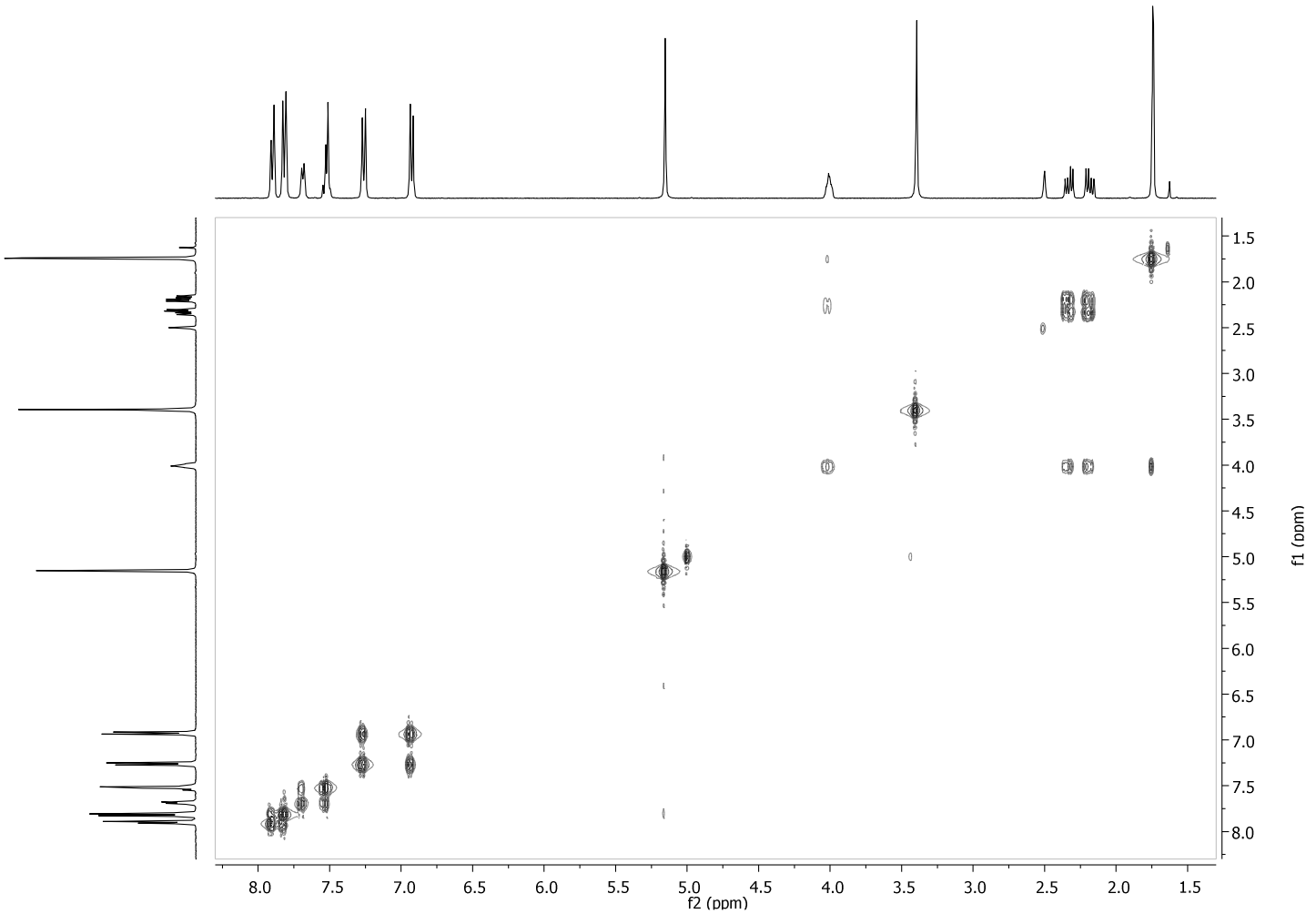


Figure 4 2D ^{1}H-^{1}H NOESY of AMG 837 sodium salt in DMSO-D6

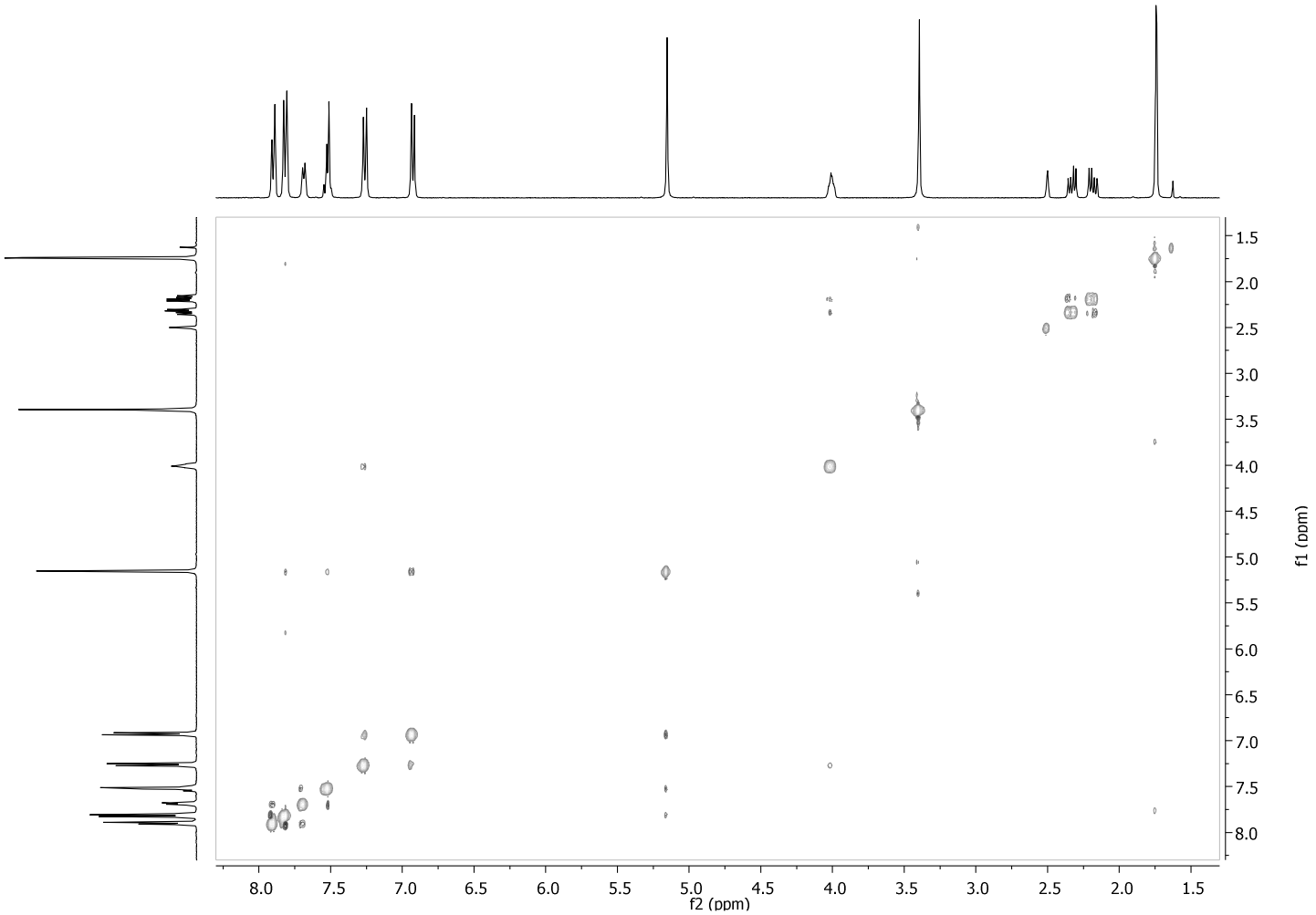


Figure 5 2D ^{1}H-^{13}C HMQC of AMG 837 sodium salt in DMSO-D6

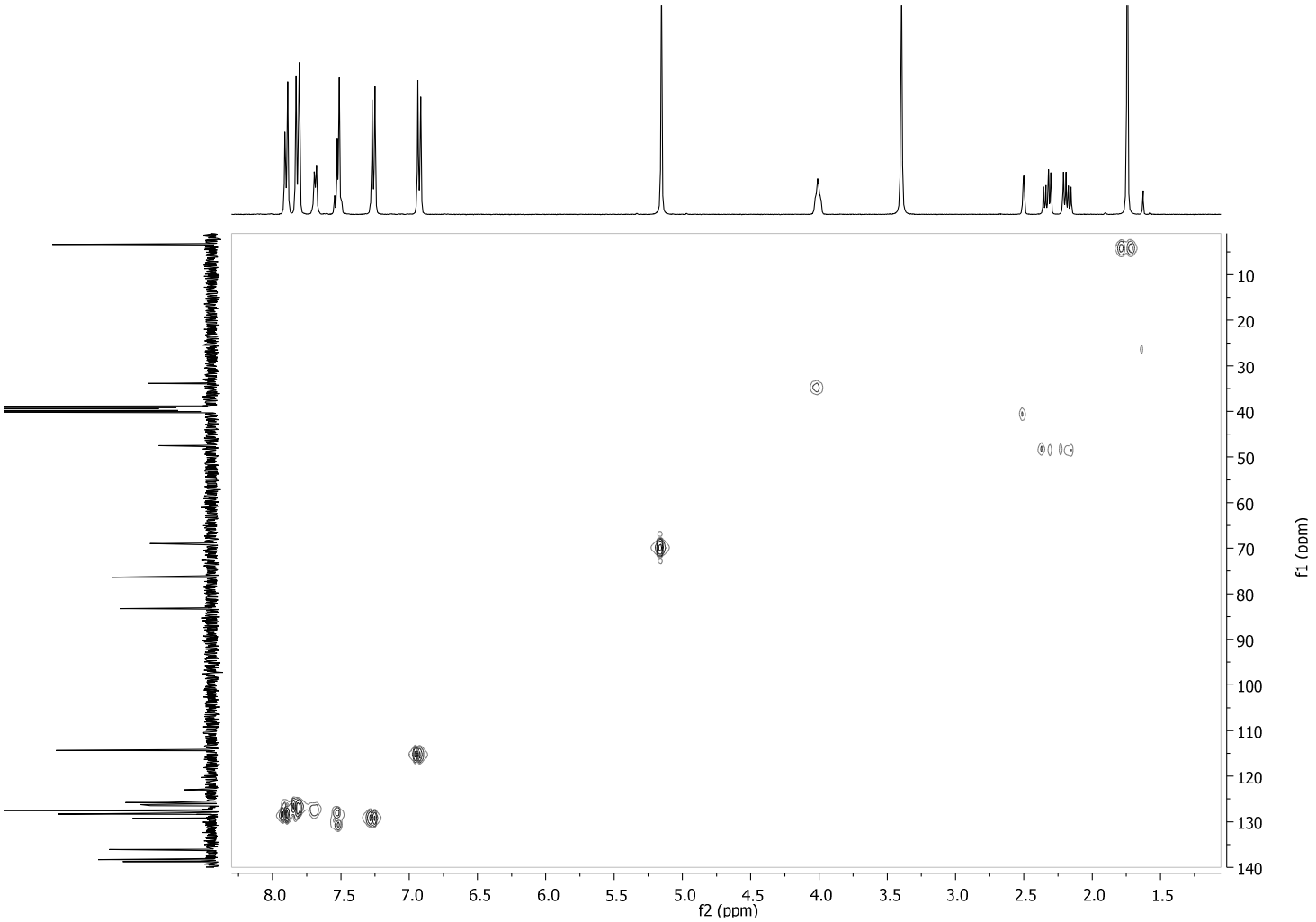


Figure 6 2D ^{1}H-^{13}C HMBC of AMG 837 sodium salt in DMSO-D6

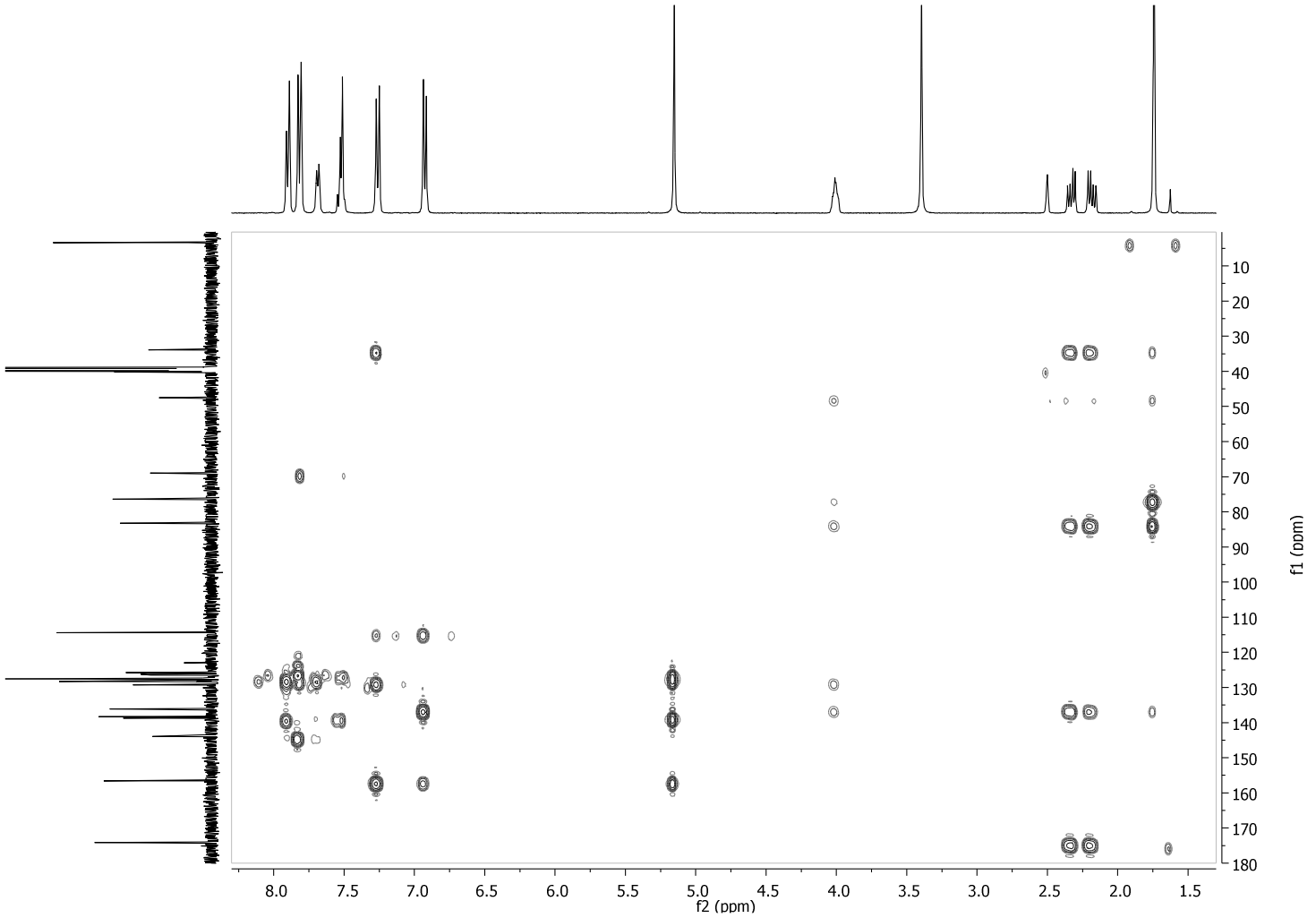
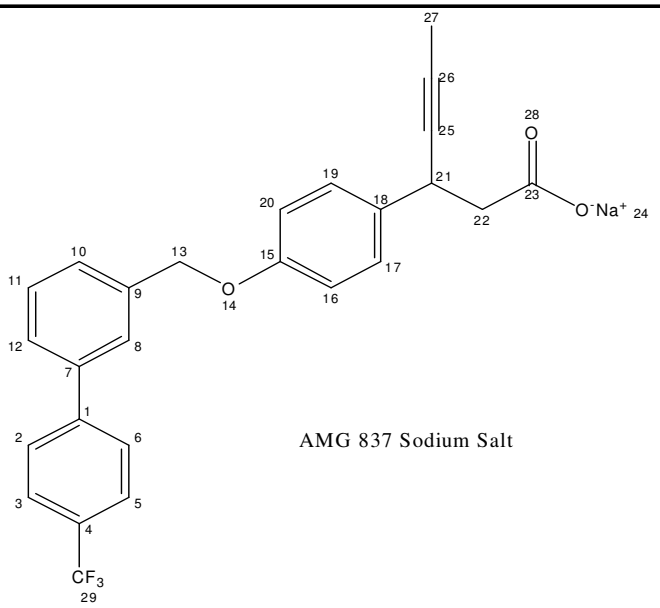

8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
f2 (ppm)
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
f1 (ppm)

Table 1. Interpretation of the ^{1}H and ^{13}C NMR Spectra of AMG 837 sodium salt



position	^{1}H (δ/ppm, J/Hz)[a]	^{13}C (δ/ppm)[a]
1		143.9
2,6	7.90 (d, 2H, J=8.2Hz)	127.5
3,5	7.82 (d, 2H, J=8.2Hz)[b]	125.8 (q, $^{3}J_{C-F}$=3.8Hz)
4		127.9 (q, $^{2}J_{C-F}$=31.7Hz)
7		138.7
8	7.81 (bs, 1H)	126.5[c]
9		138.3
10	7.52 (bd, 2H, J=6.3Hz)[b]	127.6[d]
11	7.53 (t, 1H, J=6.3Hz)	129.3[d]
12	7.69 (dt, 1H, J=1.9,6.3Hz)	126.2[c]
13	5.15 (s, 2H)	69.0
14		
15		156.6
16,20	6.93 (d, 2H, J=8.6Hz)	114.4
17,19	7.26 (d, 2H, J=8.6Hz)	128.3
18		136.1
21	4.01 (m, 1H)	33.9
22	2.33 (dd, 1H, J=6.9,14.7Hz) 2.18 (dd, 1H, J=7.3,14.7Hz)	47.5
23		174.2
24		
25		83.3
26		76.4
27	1.74 (d, 3H, J=2.3Hz)	3.3
28		
29		127.0 (q, $^{1}J_{C-F}$=271.9Hz)

[a] Signal splitting patterns: s=singlet, d=doublet, bd=broad doublet, dd=doublet of doublets, dt=doublet of triplets, m=multiplet, q=quartet; [b] overlapping; [c,d] interchangeable

Mass Spectrum

The electrospray ionization (ESI) analysis mass spectrum with exact mass measurement (Figure 7) exhibits a protonated molecular ion, (MH^+), at the m/z value of 461.1326, which is in agreement with the molecular weight of the assigned structure. The theoretical molecular weight for the protonated ion of AMG 837 sodium salt 461.1335 u. The close agreement between the two values confirms the molecular formula for the compound as $C_{26}H_{20}NaF_3O_3$. Furthermore, the MS/MS (Figure 8) spectrum of the protonated molecular ion reflects a fragmentation pattern consistent with the assigned structure.

Figure 7 Electrospray Ionization (ESI) Mass Spectrum of AMG 837 Na Salt

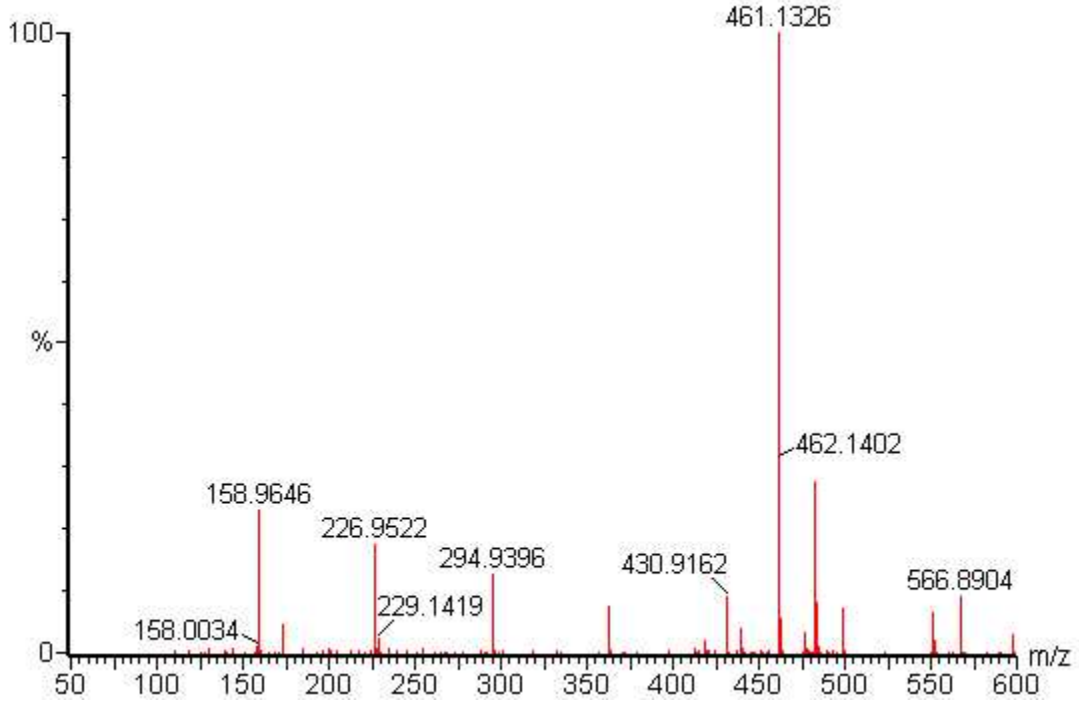
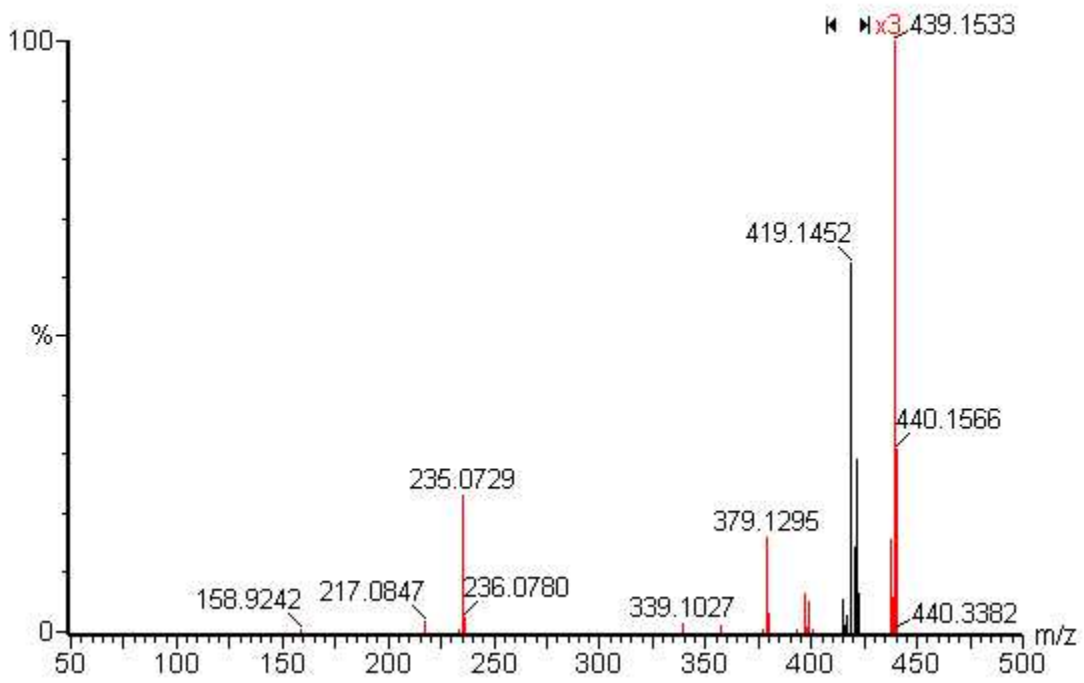


Figure 8 MS/MS Spectrum of AMG 837 Na Salt



Infrared Spectrum

Figure 9 shows the Fourier transform infrared (FTIR) spectrum of AMG 837 sodium salt. Assignments of all the major bands observed in the spectrum were established in terms of the molecular structure of AMG 837 sodium salt (Table 2). The band at 3590 cm^{-1} can be assigned to the OH stretch of the carboxyl group. The observed broad band centered at 3395 cm^{-1} can be assigned to hydrogen bonding. The OH stretch modes and the hydrogen bonding are observed due to the presence of water. The observed broad overlapped bands in the region of 3064-2865 cm^{-1} are assigned to CH_3 antisymmetric and symmetric stretches, CH_2 antisymmetric and symmetric stretches and CH stretches of the aromatic rings. The band corresponding to acetylene carbon-carbon stretch is not observed due to the weak dipole moment of the carbon-carbon triple bond. The expected frequency of the acetylene carbon-carbon stretch is about 2200 cm^{-1}. The C=C stretch of the aromatic rings are observed in the region of 1640-1500 cm^{-1}. The modes of the carboxylate species CO_2^- antisymmetric and symmetric stretches are observed at 1582 and 1413 cm^{-1}. The C-O-C stretch modes associated with the oxygen

atom that connects benzene and methylbenzene are observed at 1328 cm^{-1}. The CF_3 antisymmetric and symmetric stretches are observed at 1124 and 1112 cm^{-1}, respectively. The medium frequency region is mainly predominant with C-C stretch modes of the aromatic rings and C-H bending modes. The region between a 1000 to 700 cm^{-1} is also predominant with the C-H bending modes. The region between a 700 to 400 cm^{-1} is mainly predominant with the skeletal modes of the compound.

Figure 9 Infrared Spectrum of a KBr Pellet of AMG 837 Na Salt

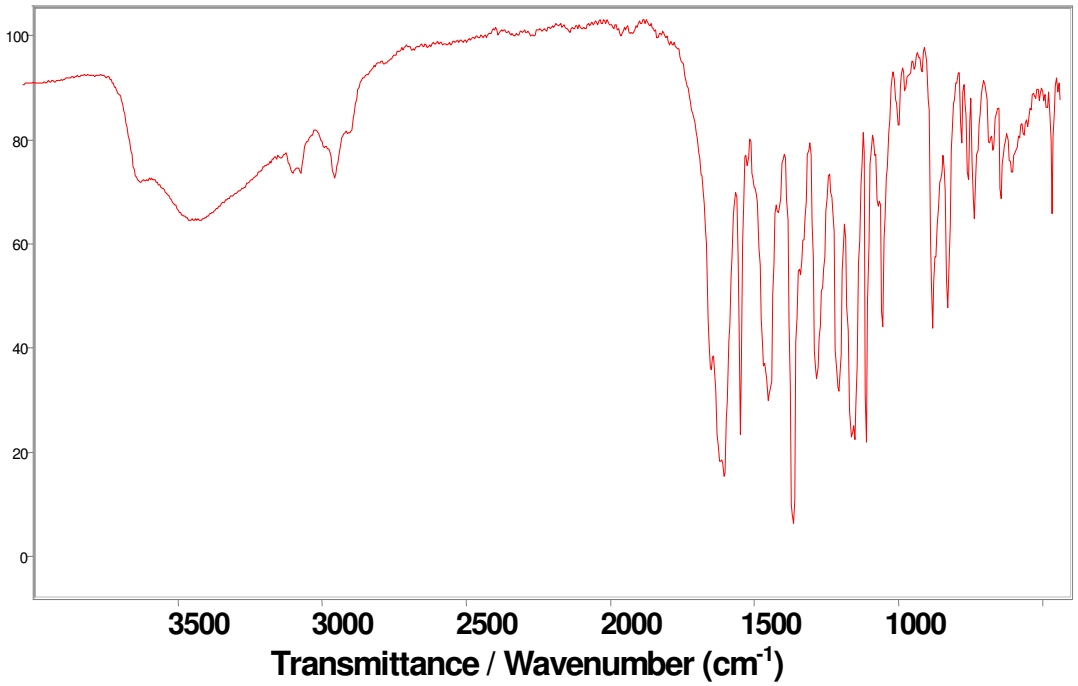


Table 2 Interpretation of the Infrared Spectrum of AMG 837 Na Salt

Wavenumbers (cm^{-1})	Rel. Int.	Approximate Assignments
3590	m sh	O-H stretch
3395 ctr	w v bd	Hydrogen bonding
3064 3035 2949 2919 2865	w w w w w	CH_3 antisymmetric/ CH_3 symmetric stretch/ CH_2 antisymmetric stretch/ CH_2 symmetric stretch/ CH stretch (aromatic)
1640-1500	s	C=C stretch (aromatic)/ CO_2^- antisymmetric stretch
1429 1413 1404	s sh s s sh	CO_2^- symmetric stretch/ CH_3 antisymmetric deformation/ CH_3 symmetric deformation/ CH_2 deformation
1328 1302 1288	vs w sh w sh	C-O stretch/ CH2 wag/ CH2 twist
1246 1223	m w sh	CH3 symmetric deformation
1168	m	C-C stretch/ C-H bend
1124 1112	s s	CF3 antisymmetric stretch/ CF3 symmetric stretch
1071	s	C-H bend
1030 1016	w sh m	C-H bend
961 843 832 815 789 743 720 699 647 633 606 568 428	w m m sh w sh m w w m w w w w bd w	Low frequency CH bending modes/ CF3 antisymmetric deformation/ CF3 symmetric deformation/ skeletal deformation modes
Abbreviations used: Rel. Int.; relative intensities; ctr, center of the peak; s, strong; m, moderate; w, weak; v, very; sh, shoulder; bd, broad.		

Proton (^{1}H) and Carbon-13 (^{13}C) NMR Spectra of AMG 837 Hemi-Calcium Salt

The NMR spectroscopy evidence (Figures 10 and 11) supports the structure of AMG 837 hemi-calcium salt dihydrate as depicted below:

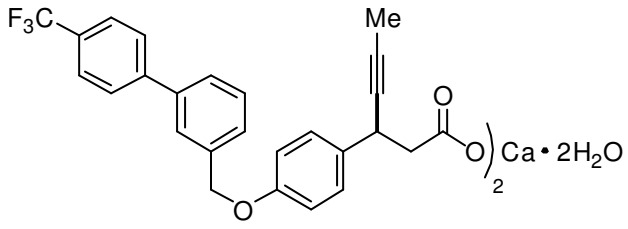


Figure 10 ^{1}H NMR Spectrum of AMG 837 hemi-calcium salt in DMSO-D6

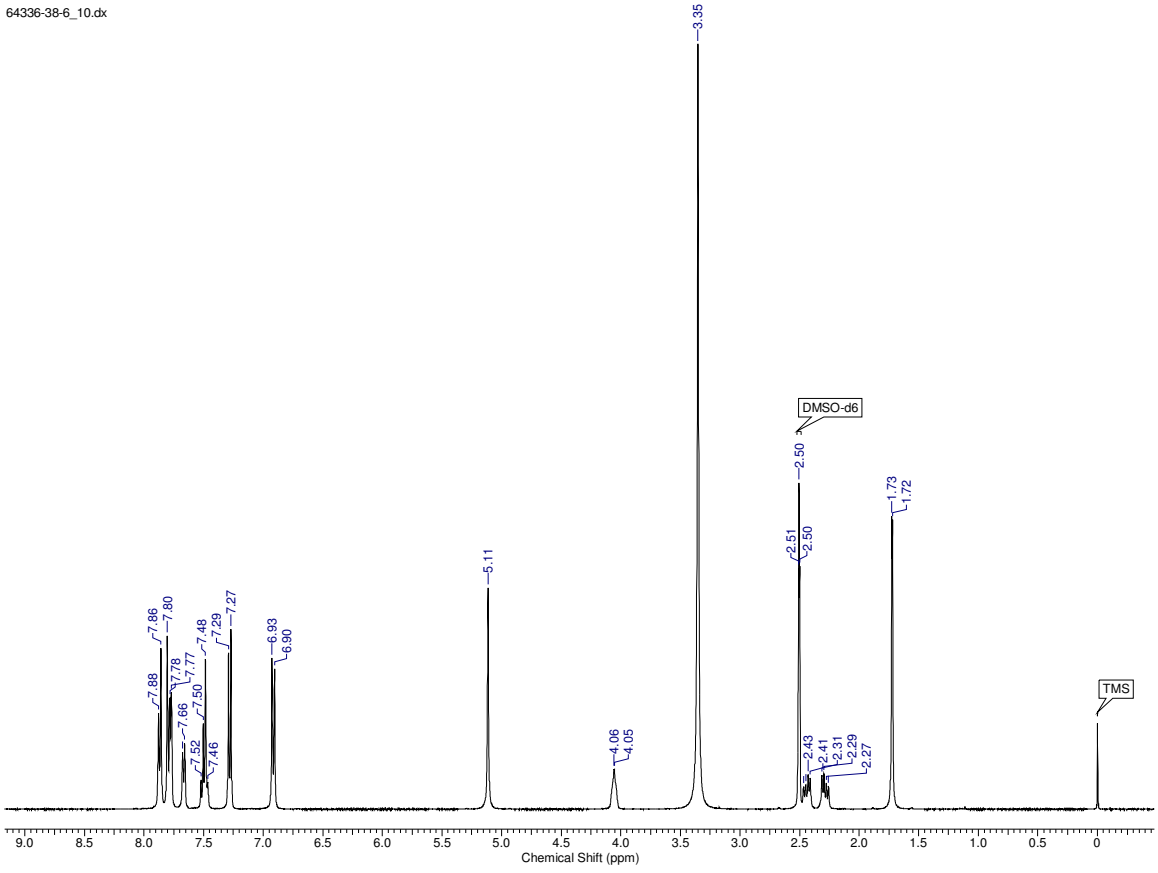


Figure 11 **^{13}C NMR Spectrum of AMG 837 hemi-calcium salt in DMSO-D6**