10.1071/CH15527_AC

©The Authors 2016

Australian Journal of Chemistry 2016, 69(6), 662-671

Supplementary Material

Synthesis and Biological Screening of Silicon-Containing Ibuprofen Derivatives: A Study of Their NF-κβ Inhibitory Activity, Cytotoxicity, and Their Ability to Bind IKKβ

Synthesis of SCIDs and Their Biological Screening

David J. Pérez,[A,B] *Uzma I. Zakai,*[B,E] *Song Guo,*[C] *Ilia A. Guzei,*[D] *Zeferino Gómez-Sandoval,*[A] *Rodrigo Said Razo-Hernández,*[A] *Robert West,*[B] *and Ángel Ramos-Organillo*[A,E]

[A]Facultad de Ciencias Químicas, Universidad de Colima, km 9 carretera Colima-Coquimatlán, Coquimatlán, Colima. CP 28400, México.

[B]The Organosilicon Research Center, Department of Chemistry, 1101 University Avenue, Madison, WI 53706, USA.

[C]Carbone Cancer Center, Wisconsin Institutes for Medical Research, 1111 Highland Avenue, Madison, WI 53705, USA.

[D]Molecular Structure Laboratory Department of Chemistry, 1101 University Avenue, Madison, WI 53706, USA.

[E]Corresponding authors. Email: aaramos@ucol.mx; zakaiu@yahoo.com

EXPERIMENTAL SECTION

Crystallographic experimental section (data collection)

A colorless crystal with approximate dimensions 0.68 x 0.19 x 0.11 mm^3 was selected under oil under ambient conditions and attached to the tip of a MiTeGen MicroMount©. The crystal was mounted in a stream of cold nitrogen at 100 (1) K and centered in the X-ray beam by using a video camera. The crystal evaluation and data collection were performed on a Bruker Quazar SMART APEXII diffractometer with Mo Kα (λ = 0.71073 Å) radiation and the diffractometer to crystal distance of 4.96 cm. The initial cell constants were obtained from three series of ω scans at different starting angles. Each series consisted of 12 frames collected at intervals of 0.5º in a 6º range about ω with the exposure time of 10 seconds per frame. The reflections were successfully indexed by an automated indexing routine built in the APEXII program suite. The final cell constants were calculated from a set of strong reflections from the actual data collection. The data were collected by using the full sphere data collection routine to survey the reciprocal space to the extent of a full sphere to a resolution of 0.70 Å. A total of 24278 data were harvested by collecting 6 sets of frames with 0.5º scans in ω and φ with exposure times of 10 sec per frame. These highly redundant datasets were corrected for Lorentz and polarization effects. The absorption correction was based on fitting a function to the empirical transmission surface as sampled by multiple equivalent measurements.[1]

Structure Solution and Refinement

The systematic absences in the diffraction data and the *E*-statistics were uniquely consistent for the space group *Cc* (Table S1) that yielded chemically reasonable and computationally stable results of refinement.[2-4]

A successful solution using direct methods provided most non-hydrogen atoms from the *E*-map. The remaining non-hydrogen atoms were located in an alternating series of least-squares cycles and difference Fourier maps. All non-hydrogen atoms were refined with anisotropic displacement coefficients. All hydrogen atoms (except for the amide H atom, located in the Fourier difference map) were included in the structure factor calculation at idealized positions and were allowed to ride on the neighboring atoms with relative isotropic displacement coefficients. The absolute configuration at C18 is *S*. The final least-squares refinement of 294

parameters against 6457 data resulted in residuals *R* (based on F^2 for $I \geq 2\sigma$) and *wR* (based on F^2 for all data) of 0.0315 and 0.0820, respectively. The final difference Fourier map was featureless. The molecular diagram is drawn with 50% probability ellipsoids (Figure S1).

Crystallographic Results

Crystal 10e. The crystal structure of compound **10e** was determined; complete data are presented in (Table S2 and S3). Typical angles and lengths for all the functional groups present in **10e** are observed. The Si–C bonds lengths and angles fit well with the average values and are typical for the tetrahedral substituted silicon. The solid state structure of **10e** reveals a packing of two molecules per unit cell, and the formation of classical and non-classical intermolecular interactions. A hydrogen bond between the carbonyl oxygen and amide proton [N(1)---H(1)---O(1)] see data in Table S4. Also the O(1)-C(7) (carbonyl group) participates in short contact interactions, working as a trifurcated acceptor facilitating the interactions with H(18) and H(14). Additionally, a short contact interaction between C(19) and H(15) is also observed. Non-classical intermolecular interactions of the type π---H are also seen between C(12)---H(24) and C(13)---H(12), with a distance of 2.873 Å and 2.777 Å, and angles of 169.73° and 140.21° respectively.

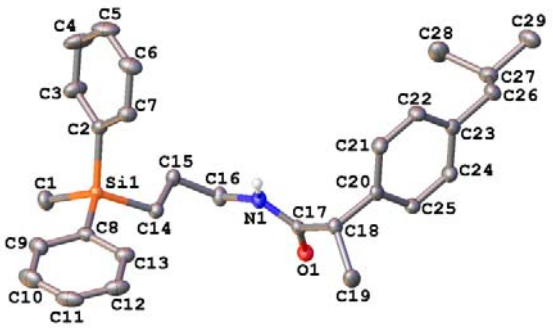


Figure S1. X- ray structure of **10e,** hydrogen atoms are omitted except for the N-H

Table S1. Summarized data for the crystal **10e**

Summarized data for the crystal **10e** (CCDC 1417632)	
Identification code	west201
Chemical Formula	C_{29} H_{37} N O Si

MW	443.69
Crystal system	Monoclinic
Space group	Cc
Crystal Color	Colorless
Crystal dimensions	0.68 x 0.19 x 0.11 mm^3
Volume	2621(3) Å3
T, K	100(1) K
Unit cell parameters	
a, Å	9.860(8)
b, Å	32.27(2)
c, Å	8.903(7)
α, deg	90°.
β, deg	112.260(12)°
γ, deg	90°
Absorption coefficient	0.110 mm^{-1}
Max. and min. transmission	0.9876 and 0.9295
θ range, for data collection	2.32 to 28.67°.
δ, calc. mg m^{-3}	1.124 mg m^{-3}
Z	4
Reflections collected	24278
Independent reflections	6457 [R(int) = 0.0241]
GOF, F^2	1.022
Final R indices [I>2sigma(I)]	R1 = 0.0315, wR2 = 0.0810
R indices (all data)	R1 = 0.0325, wR2 = 0.0820

Table S2. Bonds lengths for **10e**

Bond	Lenght	Bond	Lenght
Si(1)-C(1)	1.8641(17)	C(14)-H(14B)	0.99
Si(1)-C(14)	1.8705(15)	C(15)-C(16)	1.5274(18)
Si(1)-C(2)	1.8775(16)	C(15)-H(15A)	0.99
Si(1)-C(8)	1.8814(16)	C(15)-H(15B)	0.99
O(1)-C(17)	1.2356(18)	C(16)-H(16A)	0.99
N(1)-C(17)	1.3348(17)	C(16)-H(16B)	0.99
N(1)-C(16)	1.4587(18)	C(17)-C(18)	1.5337(19)
N(1)-H(1)	0.88	C(18)-C(20)	1.5234(19)
C(1)-H(1A)	0.98	C(18)-C(19)	1.531(2)
C(1)-H(1B)	0.98	C(18)-H(18)	1
C(1)-H(1C)	0.98	C(19)-H(19A)	0.98
C(2)-C(7)	1.396(2)	C(19)-H(19B)	0.98
C(2)-C(3)	1.400(2)	C(19)-H(19C)	0.98
C(3)-C(4)	1.392(2)	C(20)-C(21)	1.3898(19)
C(3)-H(3)	0.95	C(20)-C(25)	1.3943(18)
C(4)-C(5)	1.381(3)	C(21)-C(22)	1.395(2)
C(4)-H(4)	0.95	C(21)-H(21)	0.95
C(5)-C(6)	1.387(3)	C(22)-C(23)	1.3934(19)
C(5)-H(5)	0.95	C(22)-H(22)	0.95
C(6)-C(7)	1.394(2)	C(23)-C(24)	1.3928(19)
C(6)-H(6)	0.95	C(23)-C(26)	1.510(2)
C(7)-H(7)	0.95	C(24)-C(25)	1.390(2)
C(8)-C(13)	1.395(2)	C(24)-H(24)	0.95
C(8)-C(9)	1.402(2)	C(25)-H(25)	0.95
C(9)-C(10)	1.394(2)	C(26)-C(27)	1.540(2)
C(9)-H(9)	0.95	C(26)-H(26A)	0.99
C(10)-C(11)	1.377(3)	C(26)-H(26B)	0.99
C(10)-H(10)	0.95	C(27)-C(28)	1.522(2)
C(11)-C(12)	1.385(3)	C(27)-C(29)	1.531(2)
C(11)-H(11)	0.95	C(27)-H(27)	1
C(12)-C(13)	1.397(2)	C(28)-H(28A)	0.98
C(12)-H(12)	0.95	C(28)-H(28B)	0.98
C(13)-H(13)	0.95	C(28)-H(28C)	0.98
C(14)-C(15)	1.5332(18)	C(29)-H(29A)	0.98
C(14)-H(14A)	0.99	C(29)-H(29B)	0.98
		C(29)-H(29C)	0.98

Table S3. Bond angles for **10e**

Bond	Angle	Bond	Angle
C(1)-Si(1)-C(14)	110.38(7)	N(1)-C(16)-C(15)	110.01(11)
C(1)-Si(1)-C(2)	109.81(8)	N(1)-C(16)-H(16A)	109.7
C(14)-Si(1)-C(2)	109.53(7)	C(15)-C(16)-H(16A)	109.7
C(1)-Si(1)-C(8)	109.63(7)	N(1)-C(16)-H(16B)	109.7
C(14)-Si(1)-C(8)	107.13(8)	C(15)-C(16)-H(16B)	109.7
C(2)-Si(1)-C(8)	110.33(7)	H(16A)-C(16)-H(16B)	108.2
C(17)-N(1)-C(16)	122.69(12)	O(1)-C(17)-N(1)	123.40(12)
C(17)-N(1)-H(1)	118.7	O(1)-C(17)-C(18)	121.62(12)
C(16)-N(1)-H(1)	118.7	N(1)-C(17)-C(18)	114.98(12)
Si(1)-C(1)-H(1A)	109.5	C(20)-C(18)-C(19)	113.46(10)
Si(1)-C(1)-H(1B)	109.5	C(20)-C(18)-C(17)	108.69(10)
H(1A)-C(1)-H(1B)	109.5	C(19)-C(18)-C(17)	109.97(12)
Si(1)-C(1)-H(1C)	109.5	C(20)-C(18)-H(18)	108.2
H(1A)-C(1)-H(1C)	109.5	C(19)-C(18)-H(18)	108.2
H(1B)-C(1)-H(1C)	109.5	C(17)-C(18)-H(18)	108.2
C(7)-C(2)-C(3)	117.92(12)	C(18)-C(19)-H(19A)	109.5
C(7)-C(2)-Si(1)	120.33(11)	C(18)-C(19)-H(19B)	109.5
C(3)-C(2)-Si(1)	121.74(11)	H(19A)-C(19)-H(19B)	109.5
C(4)-C(3)-C(2)	120.75(15)	C(18)-C(19)-H(19C)	109.5
C(4)-C(3)-H(3)	119.6	H(19A)-C(19)-H(19C)	109.5
C(2)-C(3)-H(3)	119.6	H(19B)-C(19)-H(19C)	109.5
C(5)-C(4)-C(3)	120.43(16)	C(21)-C(20)-C(25)	118.11(12)
C(5)-C(4)-H(4)	119.8	C(21)-C(20)-C(18)	119.97(11)
C(3)-C(4)-H(4)	119.8	C(25)-C(20)-C(18)	121.88(12)
C(4)-C(5)-C(6)	119.88(15)	C(20)-C(21)-C(22)	120.87(11)
C(4)-C(5)-H(5)	120.1	C(20)-C(21)-H(21)	119.6
C(6)-C(5)-H(5)	120.1	C(22)-C(21)-H(21)	119.6
C(5)-C(6)-C(7)	119.63(15)	C(23)-C(22)-C(21)	121.22(13)
C(5)-C(6)-H(6)	120.2	C(23)-C(22)-H(22)	119.4
C(7)-C(6)-H(6)	120.2	C(21)-C(22)-H(22)	119.4
C(6)-C(7)-C(2)	121.39(14)	C(24)-C(23)-C(22)	117.56(12)
C(6)-C(7)-H(7)	119.3	C(24)-C(23)-C(26)	121.03(11)
C(2)-C(7)-H(7)	119.3	C(22)-C(23)-C(26)	121.38(12)
C(13)-C(8)-C(9)	117.57(12)	C(25)-C(24)-C(23)	121.43(12)
C(13)-C(8)-Si(1)	121.59(10)	C(25)-C(24)-H(24)	119.3
C(9)-C(8)-Si(1)	120.81(11)	C(23)-C(24)-H(24)	119.3
C(10)-C(9)-C(8)	121.06(15)	C(24)-C(25)-C(20)	120.81(13)
C(10)-C(9)-H(9)	119.5	C(24)-C(25)-H(25)	119.6
C(8)-C(9)-H(9)	119.5	C(20)-C(25)-H(25)	119.6
C(11)-C(10)-C(9)	120.28(15)	C(23)-C(26)-C(27)	113.62(11)

C(11)-C(10)-H(10)	119.9	C(23)-C(26)-H(26A)	108.8
C(9)-C(10)-H(10)	119.9	C(27)-C(26)-H(26A)	108.8
C(10)-C(11)-C(12)	119.92(13)	C(23)-C(26)-H(26B)	108.8
C(10)-C(11)-H(11)	120	C(27)-C(26)-H(26B)	108.8
C(12)-C(11)-H(11)	120	H(26A)-C(26)-H(26B)	107.7
C(11)-C(12)-C(13)	119.82(15)	C(28)-C(27)-C(29)	110.73(12)
C(11)-C(12)-H(12)	120.1	C(28)-C(27)-C(26)	110.80(13)
C(13)-C(12)-H(12)	120.1	C(29)-C(27)-C(26)	110.06(12)
C(8)-C(13)-C(12)	121.35(14)	C(28)-C(27)-H(27)	108.4
C(8)-C(13)-H(13)	119.3	C(29)-C(27)-H(27)	108.4
C(12)-C(13)-H(13)	119.3	C(26)-C(27)-H(27)	108.4
C(15)-C(14)-Si(1)	115.07(10)	C(27)-C(28)-H(28A)	109.5
C(15)-C(14)-H(14A)	108.5	C(27)-C(28)-H(28B)	109.5
Si(1)-C(14)-H(14A)	108.5	H(28A)-C(28)-H(28B)	109.5
C(15)-C(14)-H(14B)	108.5	C(27)-C(28)-H(28C)	109.5
Si(1)-C(14)-H(14B)	108.5	H(28A)-C(28)-H(28C)	109.5
H(14A)-C(14)-H(14B)	107.5	H(28B)-C(28)-H(28C)	109.5
C(16)-C(15)-C(14)	112.89(11)	C(27)-C(29)-H(29A)	109.5
C(16)-C(15)-H(15A)	109	C(27)-C(29)-H(29B)	109.5
C(14)-C(15)-H(15A)	109	H(29A)-C(29)-H(29B)	109.5
C(16)-C(15)-H(15B)	109	C(27)-C(29)-H(29C)	109.5
C(14)-C(15)-H(15B)	109	H(29A)-C(29)-H(29C)	109.5
H(15A)-C(15)-H(15B)	107.8	H(29B)-C(29)-H(29C)	109.5

Table S4 Hydrogen bonds for west201 [Å and °].

D-H...A	d(D-H), (Å)	d(H...A), (Å)	d(D...A), (Å)	<(DHA)
N(1)-H(1)...O(1)#1	0.845(19)	2.08(2)	2.904(2)	166.7° (18)

Table S5. Summarized data for NF-κβ Inhibition (**10a** and **10b)**

	10a	**10b**
[μM][A]	% Inhibition	
100.00	67.61	61.94
100.00	61.09	53.38
100.00	76.83	63.13
100.00	78.04	58.08

50.00	49.41	31.56
50.00	48.82	23.86
50.00	54.70	30.07
50.00	59.22	23.77
25.00	28.52	19.67
25.00	11.08	8.48
25.00	37.83	17.88
25.00	37.40	27.72
12.50	28.93	5.50
12.50	33.12	0.78
12.50	30.41	-0.41
12.5	30.32204	24.54251
6.25	14.1593	-3.9508
6.25	-7.77954	15.73955
6.25	7.505032	9.826942
6.25	9.20574	-9.20033
3.125	-6.53082	-14.3088
3.125	-9.69592	-12.5014
3.125	-6.07023	-10.5534
3.125	-11.0651	-0.44384
1.5625	-13.1931	-13.0566
1.5625	-13.3669	12.3129
1.5625	8.196214	-11.0003
1.5625	-0.41917	28.45614
0.78125	-15.6653	-23.188
0.78125	-37.0202	-6.73789
0.78125	-9.38331	2.796396

0.78125	-15.9556	0.267418

[A] Represents the [μM] tested for each compound

Table S6. Summarized data for NF-κβ Inhibition (**10c**-**10e**)

Compound	**10c**	**10d**	**10e**
[μM][A]	% Inhibition		
100.00	66.251	65.021	-12.479
100.00	62.445	54.540	-21.365
50.00	59.486	41.412	-9.618
50.00	62.445	33.023	-16.988
25.00	17.771	26.661	-7.630
25.00	14.124	1.718	-17.881
12.50	0.287	12.119	-7.112
12.50	-2.273	-12.638	-15.103
6.25	-0.706	6.929	1.295
6.25	-10.746	-12.284	-18.423
3.125	1.530	11.256	4.694
3.125	-5.935	-18.178	-14.996
1.563	-2.649	7.004	-0.844
1.563	-9.290	-11.035	-19.422
0.781	-4.987	5.313	-5.339
0.781	-6.948	-13.700	-11.011

[A] Represents the [μM] tested for each compound

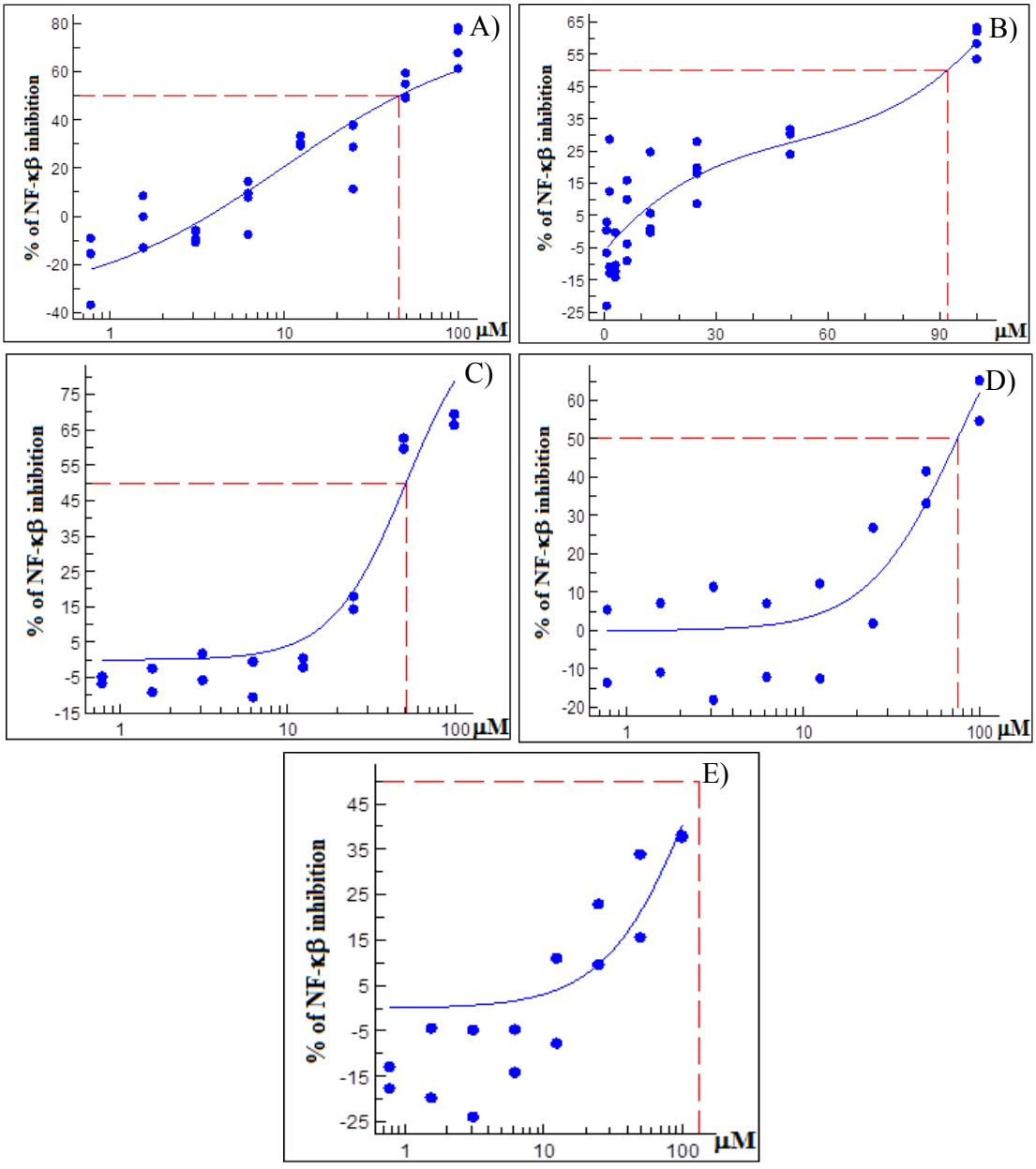


Figure S2. **Dose response curves.** The dose response curves for the compounds **10a** (A), **10b** (B), **10c** (C) and **10d** (D) and ibuprofen (E) that reached significant inhibition values with respect to that of ibuprofen.

Cytotoxicity. The raw data for the cytotoxicity screening are shown in Table S7 (**4a**-**4e**) and for the amides (**10a**-**10e**) in Table S8.

Table S7. Summarized data for SCIDs ester (**4a**-**4e**)

Compound	**4a**	**4b**	**4c**	**4d**	**4e**
[μM][A]			%Inhibition		
100.00	-1.34	-17.55	27.51	6.46	-71.55
100.00	-44.37	-28.59	-9.01	1.74	-12.00
100.00	-47.72	1.10	6.05	-0.72	-49.12
100.00	-11.46	-1.56	37.93	-2.78	-7.81
50.00	6.21	-44.08	-11.75	10.02	-41.55
50.00	37.06	-10.92	24.97	-4.16	-21.32
50.00	-23.08	-20.14	17.73	-12.67	-28.90
50.00	-1.65	-23.61	-12.20	-24.71	-22.11
25.00	-26.24	0.20	1.58	4.44	2.60
25.00	-0.41	-11.64	-0.41	-2.24	-52.80
25.00	-18.77	-12.89	-14.56	-9.35	-34.58
25.00	-30.45	-19.11	-10.90	-26.20	-16.14
12.50	3.01	15.69	5.61	-9.32	-21.30
12.50	-18.71	-36.82	18.07	-17.97	14.03
12.50	10.00	34.12	29.33	2.50	4.18
12.50	22.52	4.71	7.01	-63.20	-19.65
6.25	-32.50	16.83	-11.18	-11.24	-16.09
6.25	9.94	-7.15	-7.49	-9.67	12.98
6.25	-54.10	39.39	11.73	-12.02	-16.77
6.25	37.21	7.22	5.53	-1.18	28.48
3.13	-12.67	9.45	-18.30	18.36	4.09
3.13	-35.49	3.01	-18.30	9.62	17.06

3.13	10.60	-30.14	27.42	-19.54	-7.26
3.13	7.24	7.55	-8.08	-19.90	32.49
1.56	0.50	6.12	-16.63	-4.49	-12.42
1.56	5.87	-21.70	-14.51	21.65	-2.40
1.56	-0.04	13.70	-22.47	7.34	-30.83
1.56	16.96	8.97	6.45	-11.34	6.23
0.78	-33.87	-16.85	-22.27	9.11	-36.70
0.78	-6.35	-3.44	-16.28	5.29	-10.92
0.78	8.79	-14.56	-10.86	-23.63	6.40
0.78	29.53	-11.06	2.23	-8.12	-1.81

[A] Represents the [μM] tested for each compound

Table S8. Summarized data for the SCIDs amide (**10a-10e**)

Compound	**10a**	**10b**	**10c**	**10d**	**10e**
[μM][A]			%Inhibition		
100.00	48.57	56.29	78.83	6.32	-12.16
100.00	52.71	59.61	82.00	21.23	20.97
100.00	56.37	46.00	75.16	-9.98	-12.51
100.00	52.73	55.71	80.76	18.20	16.06
50.00	46.88	38.95	-2.88	-19.44	0.95
50.00	44.98	42.09	10.67	-7.48	11.47
50.00	49.23	37.59	16.58	-7.14	-11.87
50.00	42.45	43.08	-1.39	-67.00	-10.64
25.00	-48.00	16.03	-24.80	-16.13	3.68
25.00	-49.61	24.51	-45.46	11.17	-3.01
25.00	3.98	-0.23	5.60	-9.52	0.18
25.00	-9.01	14.43	-19.74	-43.66	-25.60

12.50	-36.54	-29.57	-4.45	40.19	-12.33
12.50	16.51	1.14	3.96	-33.82	-4.74
12.50	-7.15	12.31	5.00	-40.86	17.42
12.50	-26.64	37.80	-13.32	-45.03	6.71
6.25	-10.20	-16.75	-16.05	-6.40	-2.87
6.25	4.53	-8.40	-9.88	-5.27	-27.19
6.25	-16.84	-28.10	9.08	-12.65	-57.83
6.25	-15.56	7.80	7.55	-1.07	-57.83
3.13	-7.71	7.52	18.44	-11.72	-5.31
3.13	-14.36	11.43	-2.59	22.89	26.01
3.13	0.79	-38.62	0.19	-11.56	-11.16
3.13	-24.68	-7.29	-45.26	7.18	-13.71
1.56	-30.31	6.14	-1.50	-38.67	15.01
1.56	7.80	-8.27	-29.77	-41.50	-0.44
1.56	-13.17	-13.28	-31.94	-6.32	20.13
1.56	15.23	-8.81	-10.33	5.70	29.14
0.78	-7.02	-36.71	20.19	7.52	-5.37
0.78	23.05	-13.97	8.81	8.62	9.00
0.78	-2.97	-5.42	-22.31	1.16	26.40
0.78	-27.53	14.48	-7.15	5.45	30.60

[A] Represents the [μM] tested for each compound

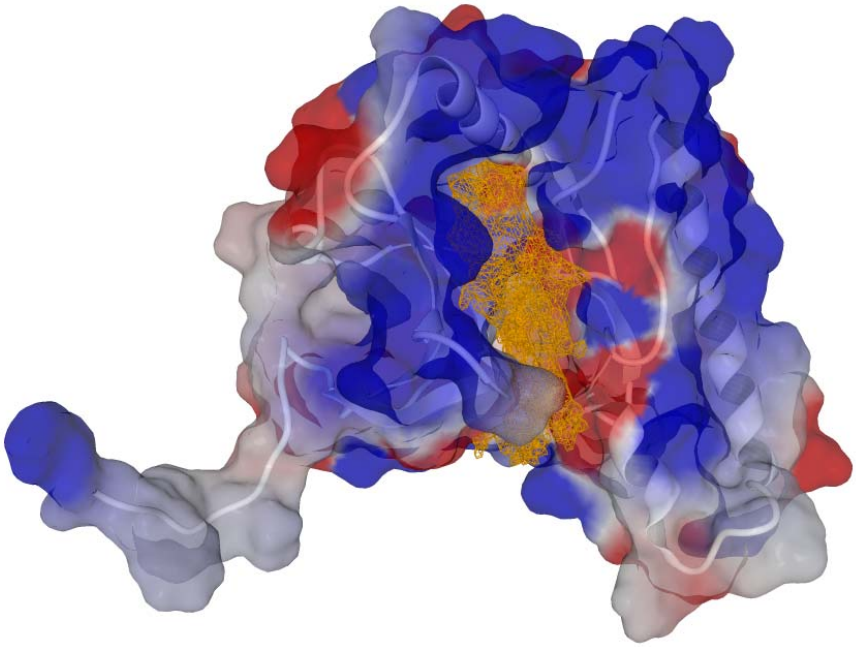


Figure S3. Depiction of the secondary structure of IKKβ. The ATP-BS cavity is represented in orange; the blue and red contour depicts the electrostatic surface of IKKβ.

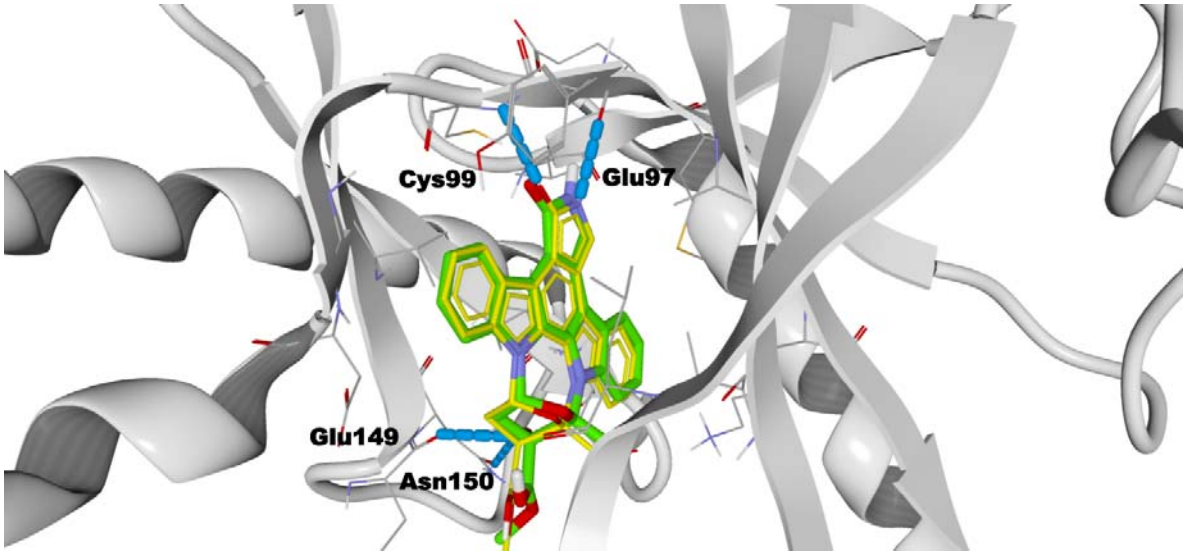


Figure S4. Validation of the molecular docking calculation. The experimental binding mode of the reference ligand was reproduced with a Root Media Square Deviation (RMSD) of 0.41. Experimental binding mode is presented as the yellow colored sticks and the calculated pose in green (thicker sticks). The blue dashed lines are the calculated hydrogen bonds which corresponded well with those observed in experimental binding. The ligand was bound into the ATP-BS cavity.

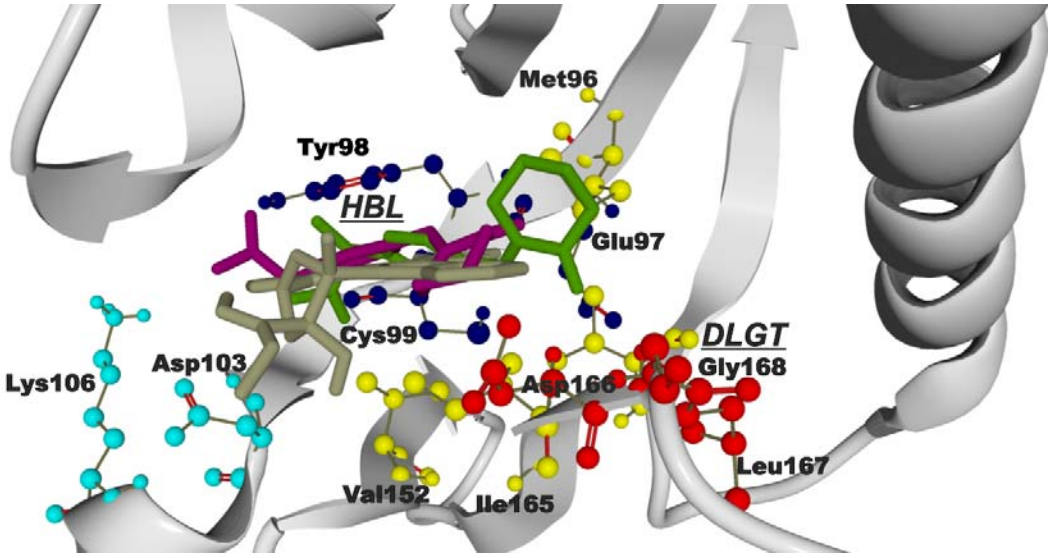


Figure S5. Depiction of the calculated binding into the ATP-BS of model IKKβ inhibitors: KSA700 (gray), pelubiprofen *R* (green), pelubiprofen *S* (purple). The Hydrogen Bond Loop (HLB) residues are displayed in blue, the catalytic triad: Asp166, Leu167 and Gly168 (DLGT) in red, some of the residues of the lipophilic pocket in yellow and Lys106 & Asp103 in cyan.

Docking results presented in Table S9 indicate that **10b**, **10c** and **10d** (*R*&*S*) can interact more favorably with Asp103 (interactions ranging from -4.9 to -19.7 kcal/mol) than ibuprofen *R* (-5.0 kcal/mol), and *S* which shows an unfavorable interaction of +0.31 kcal/mol (Table S7). Asp103 is only present in IKK subunits,[5] hence interacting with it could be related to a higher selectivity for the SCIDs to bind IKKβ.

Table S9. Data for key interactions expressed in kcal/mol formed by the SCIDs amides with the key residues that form the ATP binding site of IKKβ enzyme.

	10a		**10b**		**10c**		**10d**	
Residues	*R*	*S*	*R*	*S*	*R*	*S*	*R*	*S*
Asn150	-0.5	-0.4	-1.4	-2.2	-4.4	----	-10.2	-1.3
Asp103	-16.0	-13.3	-16.1	-19.7	-8.6	-4.9	-9.1	-6.2
Asp166	-0.9	-0.5	-3.5	-2.8	-12.5	-4.1	-9.0	-8.8
Cys99	-12.9	-9.3	-9.6	-8.4	----	-4.3	----	-2.3
Glu97	-2.9	-2.9	-1.0	-1.5	----	-3.4	----	-2.9

Glu149	1.2	-11.0	-13.3	-9.1	-15.2	----	-23.8	-2.7
Gly102	-8.7	-8.6	-5.8	-7.9	-0.7	-3.4	----	-14.7
Ile165	-7.4	-3.9	-8.3	-8.8	-10.8	-6.7	-7.8	-10.0
Leu21	----	-19.4	-14.6	-22.7	-8.8	-12.1	-7.8	----
Lys44	----	----	-0.4	----	-5.7	-8.2	-3.1	-9.2
Lys106	-5.7	-7.0	-3.0	----	----	----	----	----
Met96	-2.8	-3.5	-3.2	----	-1.7	-7.3	-0.3	-9.9
Thr23	-0.4	-5.8	-4.3	-3.3	-7.9	----	-10.4	----
Tyr98	-14.7	-17.9	-12.1	-13.0	----	-10.3	----	-1.8
Val29	-6.3	-2.5	-6.1	-6.7	----	-3.4	-4.4	-12.5
Val152	-1.1	-9.8	-11.3	-9.5	-0.7	-8.7	-4.1	-5.6

Table S10. Data for important interactions expressed in kcal/mol with the key residues of the ATP binding site for the IKKβ inhibitors and ATP.

	Pelubiprofen		Ibuprofen		KSA700	ATP
Residues	R	S	R	S	PDB: 4KIK	
Asn150	-0.4	-0.7	----	-5.5	-3.2	----
Asp103	-1.8	----	-5.0	0.3	-10.1	0.9
Asp166	-4.4	----	----	-14.0	-8.9	-8.3
Cys99	-2.9	-5.5	-7.2	----	-12.3	---
Glu97	-1.7	-2.9	-1.9	0.8	-6.0	0.7
Glu149	----	----	----	-2.3	-13.2	----
Gly102	-2.4	-3.9	-7.1	----	-5.2	----

Gly168	----	----	----	----	----	-2.1
Ile165	-11.3	-8.6	-8.9	-10.6	-21.9	----
Leu21	-17.0	-7.8	-17.8	----	-28.3	----
Leu167	----	----	----	----	----	-0.7
Lys44	-4.8	-7.9	-0.3	-17.0	-5.1	-30.6
Lys106	----	-3.7	----	-0.5	----	-0.7
Met96	-2.8	-10.7	-4.7	-8.0	-7.1	----
Tyr98	-17.7	-13.4	-17.8	----	-12.8	----
Val29	-8.7	-3.3	-0.7	-10.3	-14.9	----
Val152	-7.6	-8.4	-5.6	----	-11.3	----

Table S11. Data for key interactions expressed in kcal/mol for the Carbon Analogues (CAs) of the amides with the key residues that form the ATP binding site of IKKβ enzyme.

	10aCA		10bCA		10cCA		10dCA	
Residues	*R*	*S*	*R*	*S*	*R*	*S*	*R*	*S*
Asn150	----	-0.3	----	-8.7	-0.7	-0.9	-3.1	-5.3
Asp103	----	-14.8	----	----	-9.4	-10.3	-5.5	-2.5
Asp166	-4.7	-0.70	-6.66	-1.5	-9.4	----	-10.5	-16.3
Cys99	----	-11.5	----	-11.7	-1.4	-5.5	-4.5	----
Glu97	----	-2.2	----	-2.9	----	-1.9	-0.6	----
Glu149	----	-5.8	----	-2.7	-1.0	-0.5	-3.1	-1.2
Gly102	----	-6.2	----	-6.6	-2.2	----	-3.1	----
Ile165	----	-5.7	----	-7.9	-7.8	-18.4	-12.0	-8.9
Leu21	----	-27.10	----	-29.0	-15.6	-5.8	-16.1	----
Lys44	----	----	-4.2	-0.7	-13.5	-12.5	-12.9	-20.0

Lys106	----	----	----	-2.7	-1.9	----	-0.7	----
Met96	----	-4.10	----	0.8	-13.5	-14.4	-5.9	-2.2
Thr23	----	-1.23	----	----	----	----	----	----
Tyr98	----	-18.97	----	-21.2	-5.6	-5.0	-4.6	----
Val29	----	-6.68	-0.7	-6.5	-9.5	-7.1	-9.7	-12.1
Val152	----	-9.72	----	-11.2	-6.5	-4.0	-4.8	-0.9

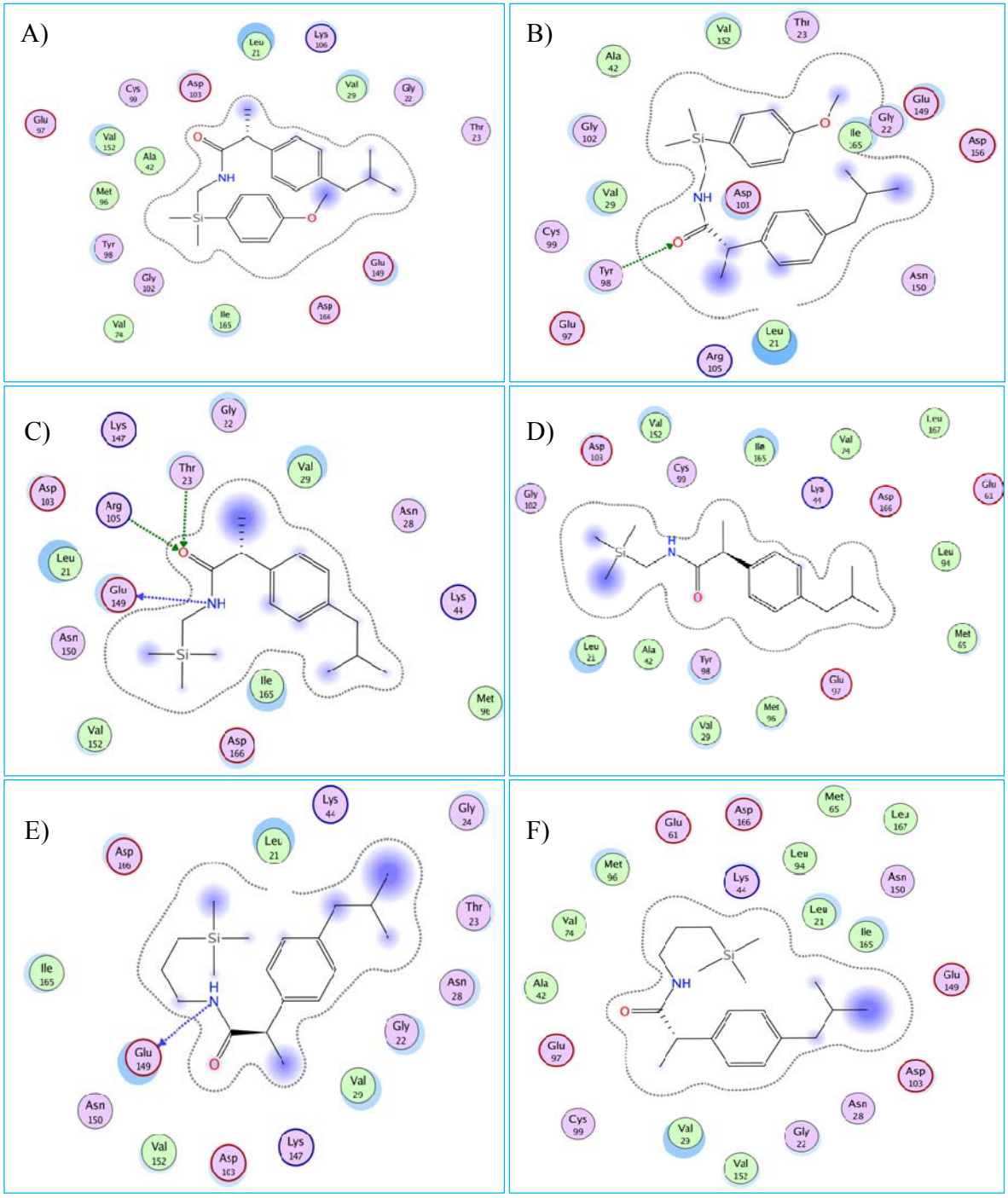
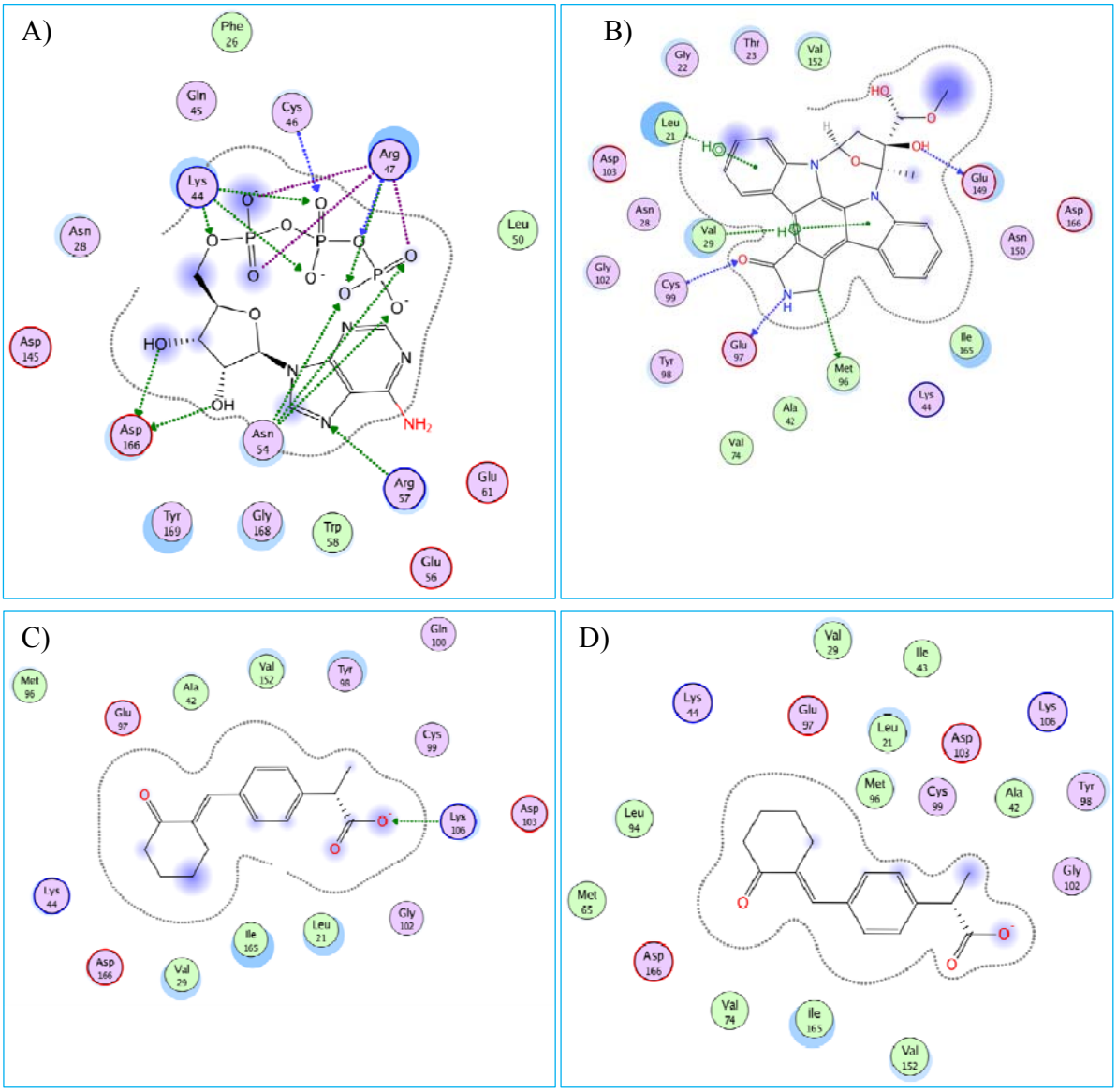


Figure S6. Interactions with the residues into the ATP-BS found for the SCID´s with IKKβ enzyme. Depicted residues are those found to interact strongly with ligand. (Legend: Green spheres represent lipophilic residues and pink spheres electrophilic. Blue and red circled spheres are basic and acidic residues respectively. Hydrogen bond is depicted as a green line (when formed to an acidic residue) or as a blue dashed one when formed to a basic residue. Blue smudged marks represent solvent exposure. Gray dashed lines represent the contour of the binding cavity. A) **10b**(*R)* B) **10b**(*S)* C) **10c**(*R)* D) **10c**(*S)* E) **10d**(*R)*. F) **10d**(*S)*


A)
Phe 26
Gln 45
Cys 46
Arg 47
Lys 44
Asn 28
Leu 50
Asp 145
HO
OH
Asp 166
Asn 54
NH2
Arg 57
Glu 61
Tyr 169
Gly 168
Trp 58
Glu 56
B)
Gly 22
Thr 23
Val 152
Leu 21
Asp 103
Glu 149
Asn 28
Asp 166
Val 29
Asn 150
Gly 102
Cys 99
Glu 97
Met 96
Ile 165
Tyr 98
Lys 44
Ala 42
Val 74
C)
Gln 100
Met 96
Ala 42
Val 152
Tyr 98
Glu 97
Cys 99
Lys 106
Asp 103
Lys 44
Gly 102
Ile 165
Leu 21
Asp 166
Val 29
D)
Val 29
Ile 43
Lys 44
Glu 97
Lys 106
Leu 21
Asp 103
Met 96
Cys 99
Ala 42
Tyr 98
Leu 94
Gly 102
Met 65
Asp 166
Val 74
Ile 165
Val 152

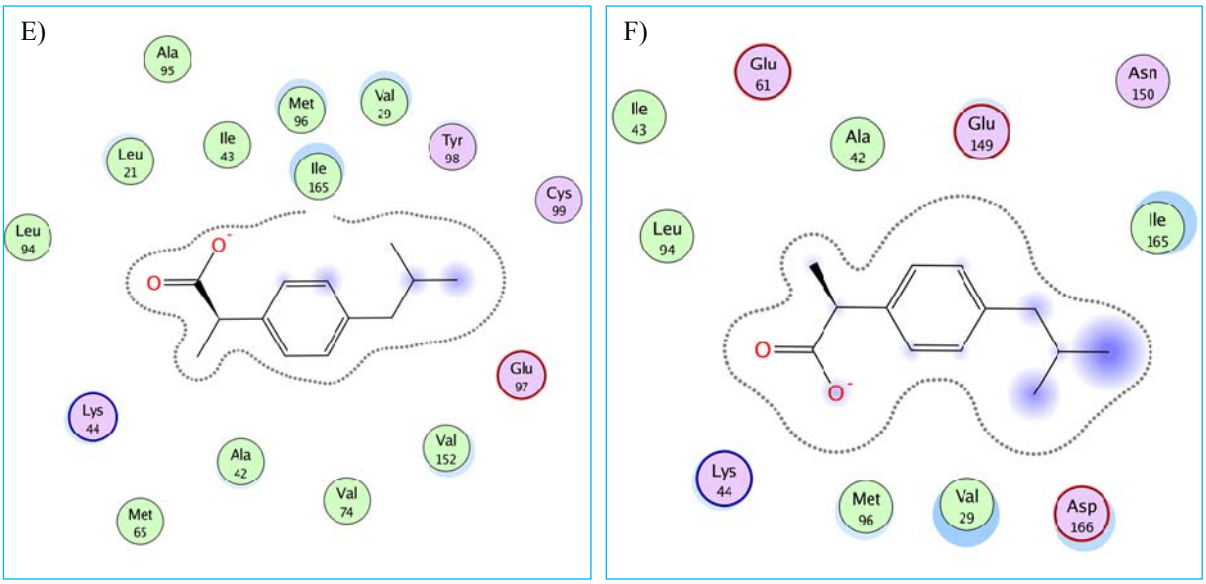


Figure S7. Interactions with the residues into the ATP-BS found for IKKβ inhibitors. Legends are same as Figure S6. A) ATP B) KSA_700 (ligand bound to the enzyme in the crystal C) Pelubiprofen(*R)* D) Pelubiprofen(*S)* E) Ibuprofen (*R*) and F) Ibuprofen (*S*).

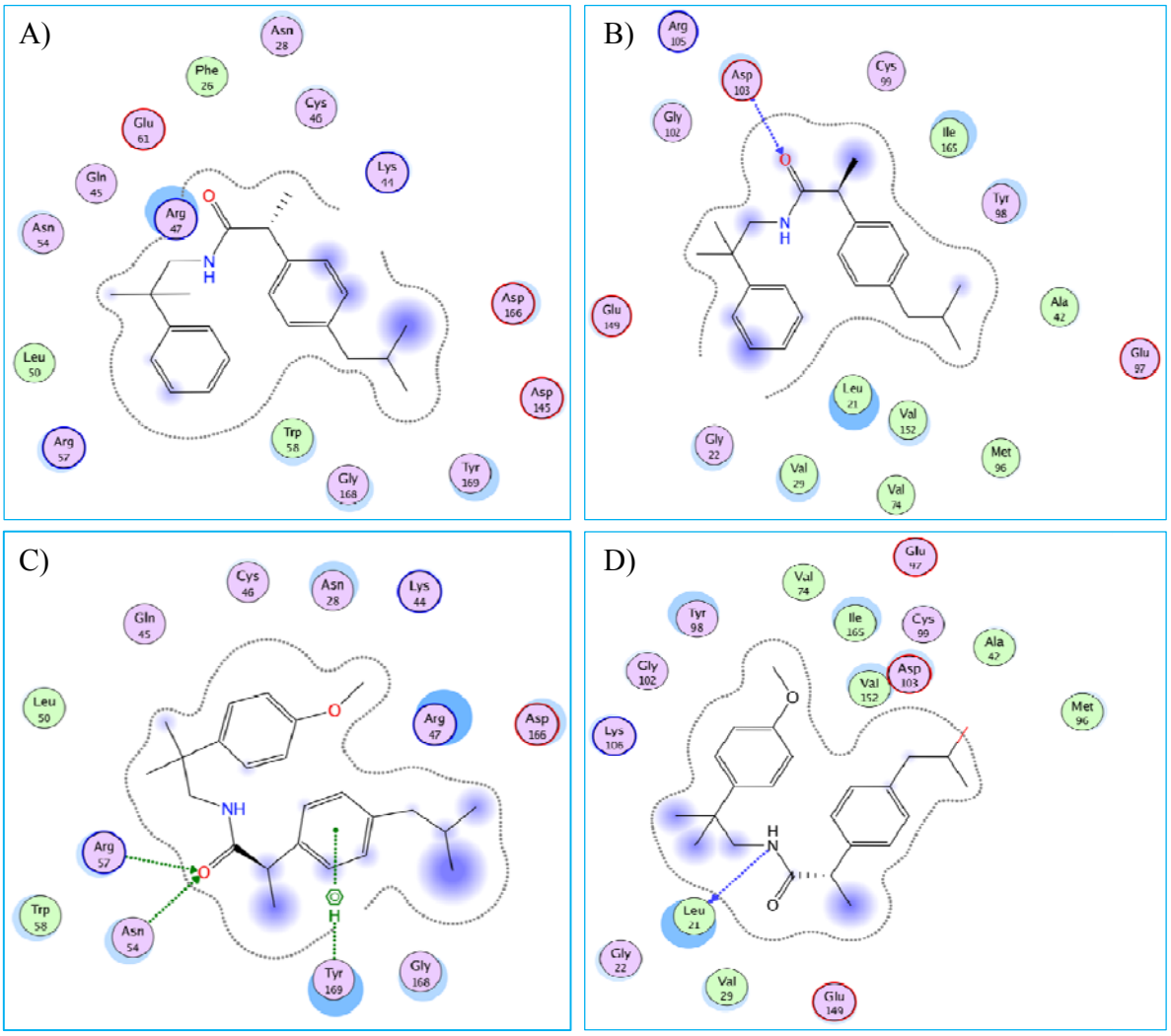


Figure S8. Interactions with the residues into the ATP-BS found for the CA with IKKβ enzyme, depicted residues are those found to interact strongly with ligand. Legends are same as Figure S6 A) **10a**CA(*R)*, B) **10a**CA(*S)*, C)**10b**CA(*R)*, D)**10b**CA(*S)*.

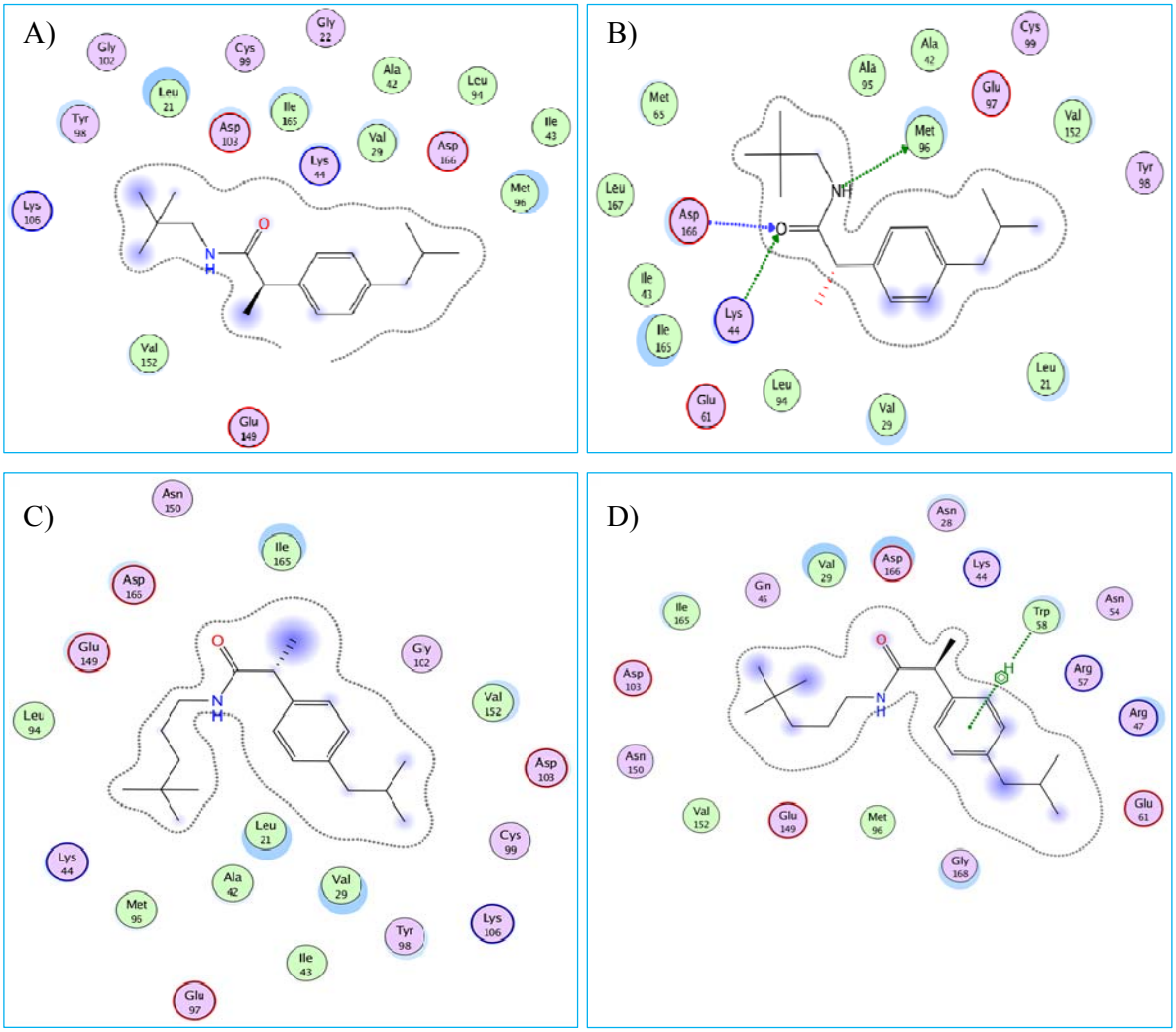


Figure S9. Interactions with the residues into the ATP-BS found for the CA with IKKβ enzyme, depicted residues are those found to interact strongly with ligand. Legends are same as Figure S6. A) **10c**CA(*R)*, B) **10d**CA(*S)*, C) **10d**CA(*R)*, D)**10d**CA(*S)*.

Table S12. Calculated molecular volumes for the amides Carbon Analogues

Carbon Analogue (CA)	**MV ($Å^3$)**
10aCA	394.84
10bCA	421.78
10cCA	330.38
10dCA	367.42

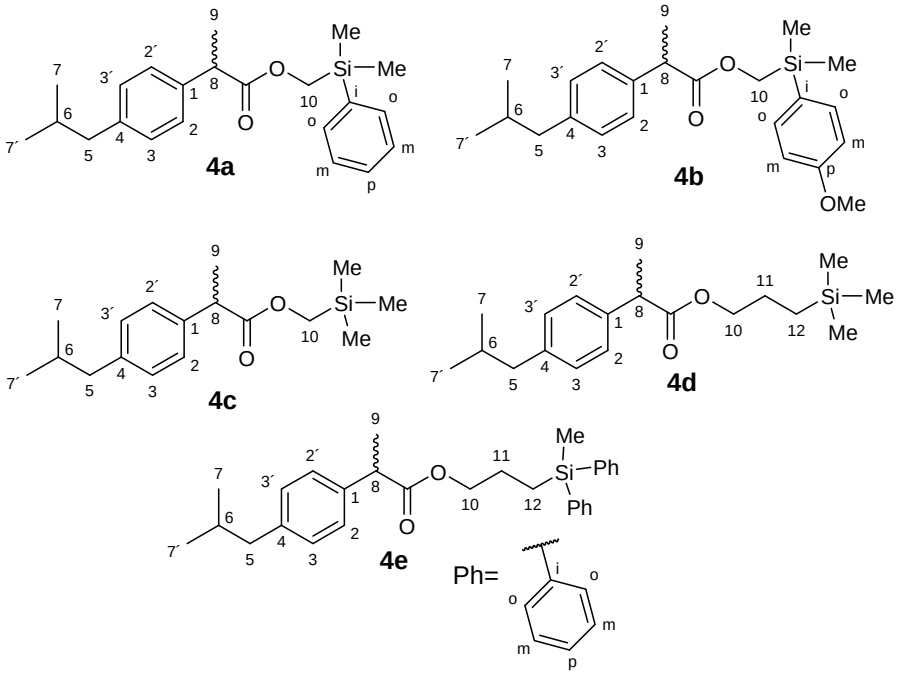


Figure S10. Signal assignments for ^{13}C and ^{1}H NMR (SCIDs ester).

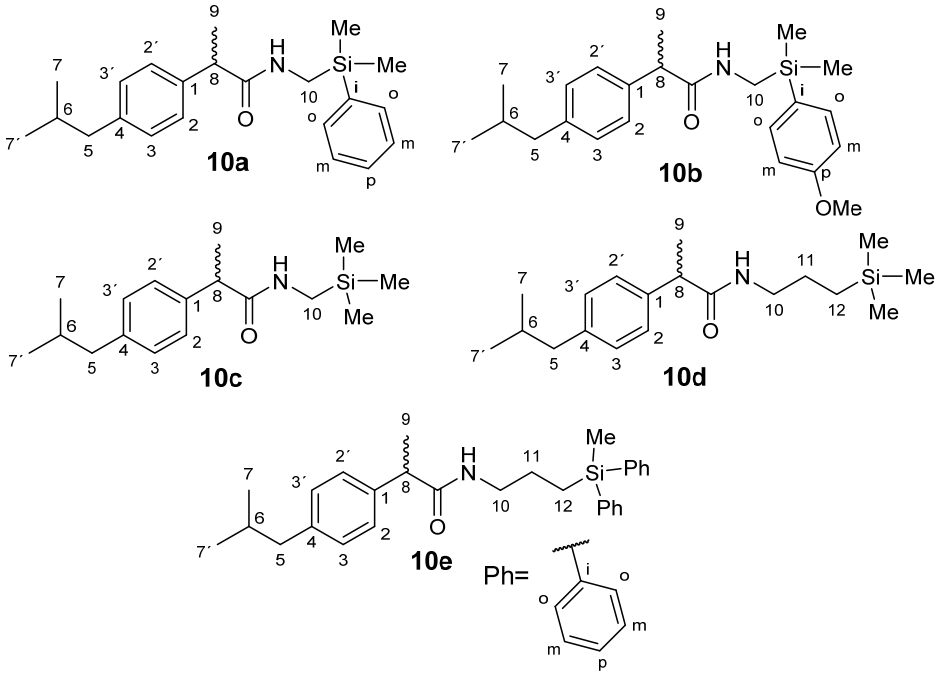


Figure S11. Signal assignments for ^{13}C and ^{1}H NMR (SCIDs amide)

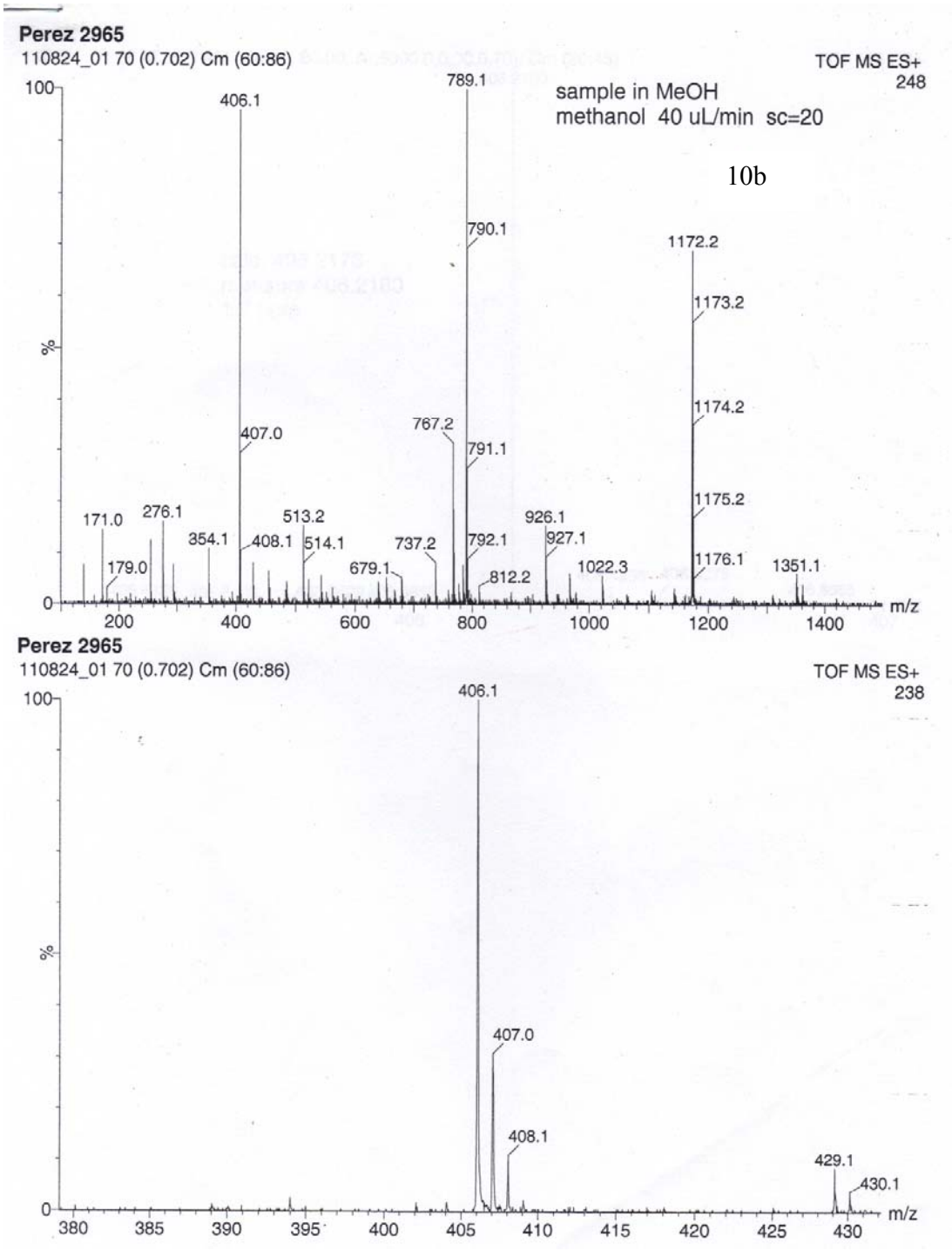


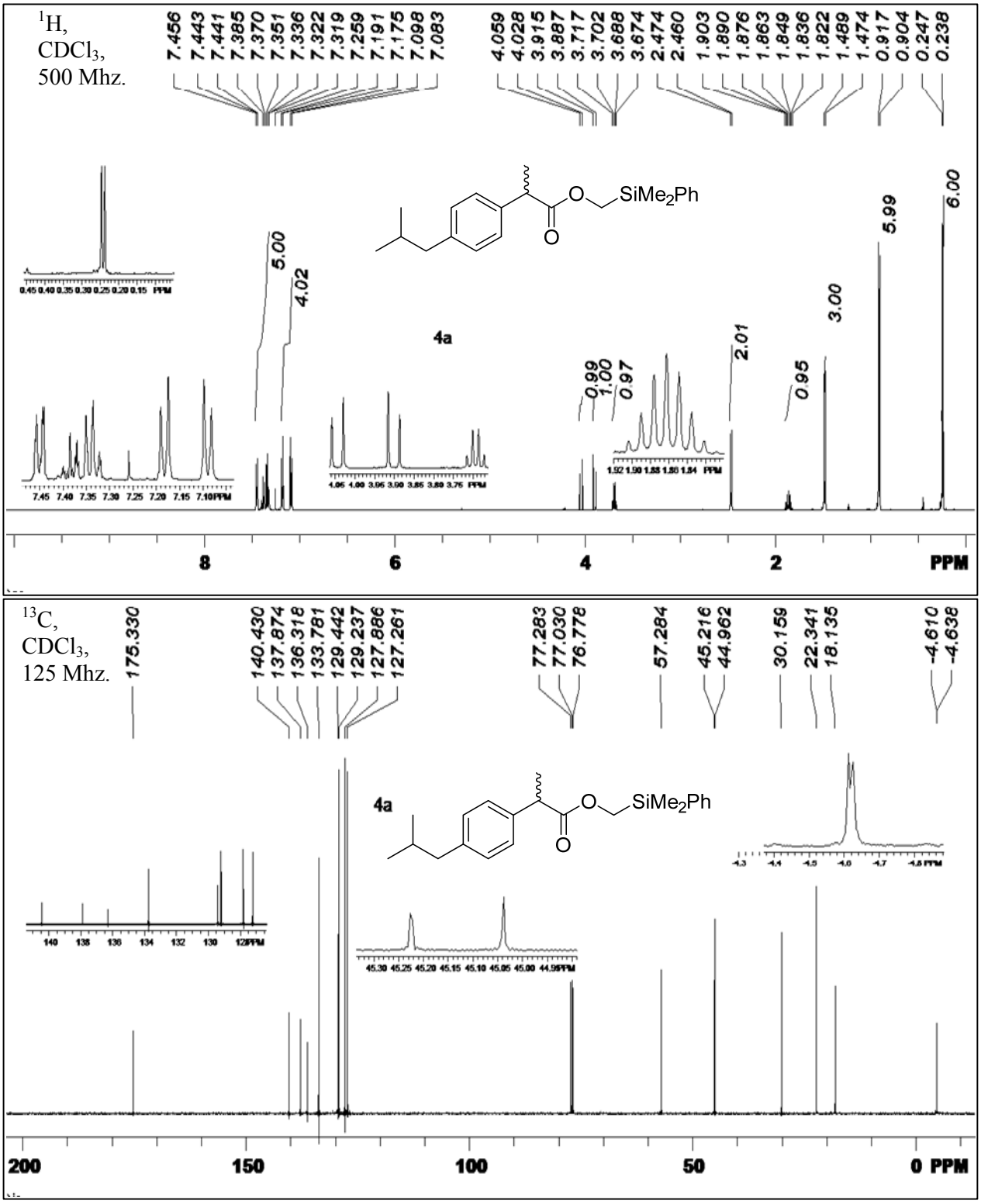
Figure S12. Low Resolution Mass Spectra of compound **10b**. Assignment of the most intense peaks, (m/z, % of intensity): 406.1 ($[M^{*}+Na]^{+}$, 95), 767.2 ($[2M+H]^{+}$, 30), 789.1 ($[2M+Na]^{+}$,100), 1172.2 ($[3M+Na]^{+}$,70). $^{*}[M]^{+}$ represents the molecular ion.

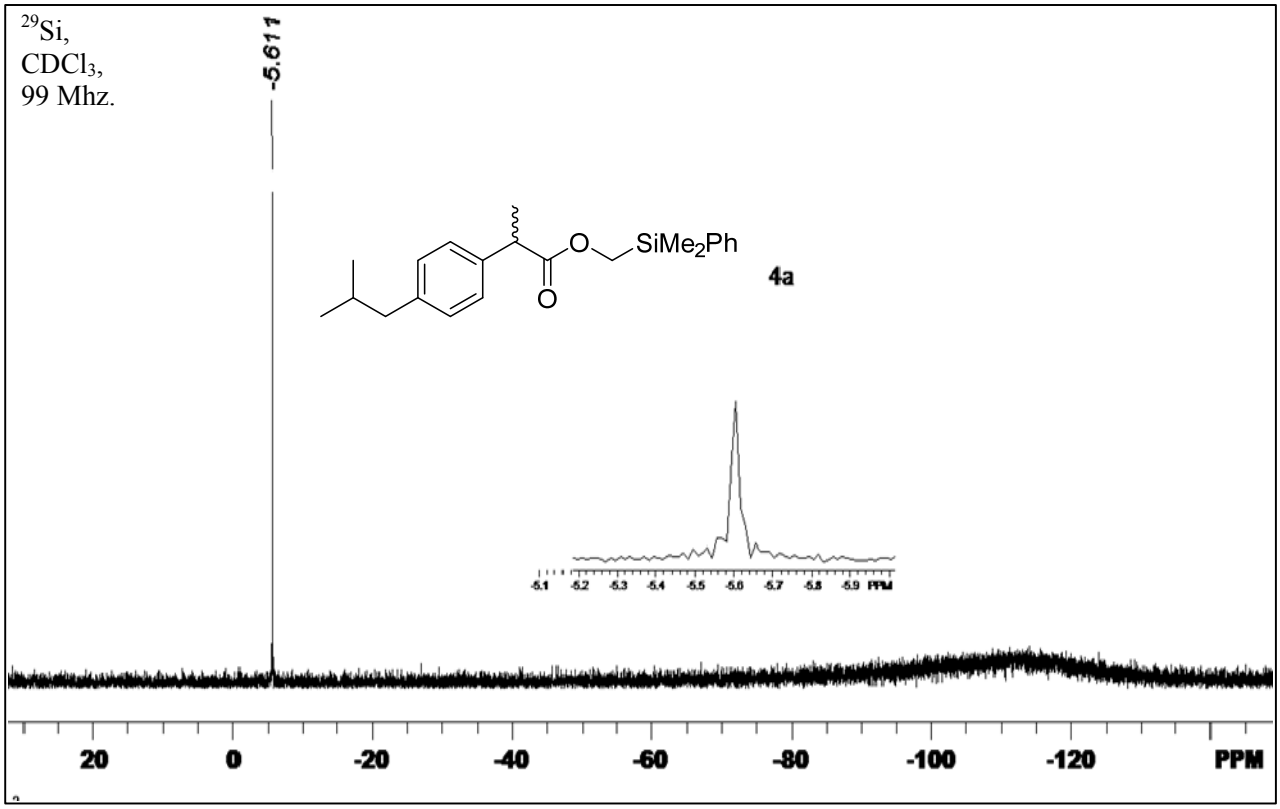
Table S13. Equivalency of the assignments of compound **10e** in solid state and in solution.

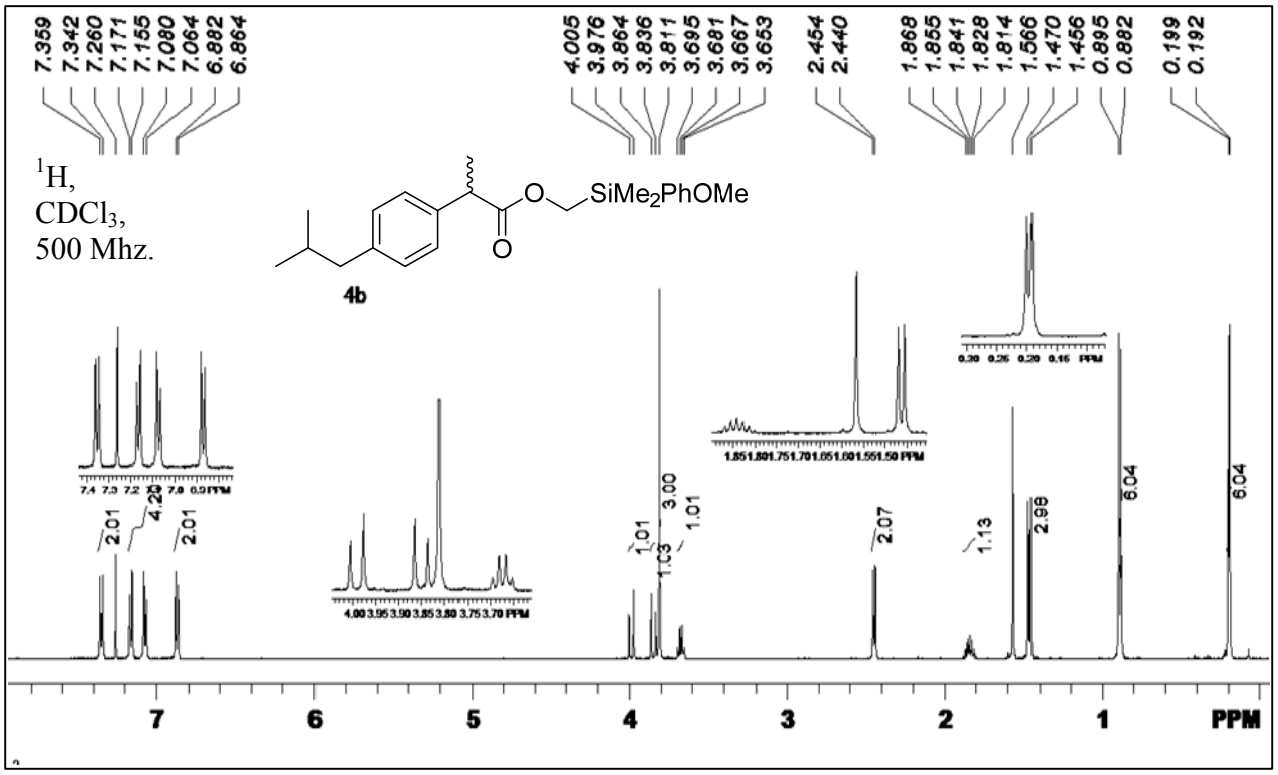
Atom in solid state [A]		Atom in solution [B]	
C	*H*	*C*	*H*
C1	H1	-Si*C*H$_3$	-SiC*H*$_3$
C2	---	C*i*	---
C3	H3	C*o*	H*o*
C4	H4	C*m*	H*m*
C5	H5	C*p*	H*p*
C6	H6	C*m*	H*m*
C7	H7	C*o*	H*o*
C8	---	C*i*	---
C9	H9	C*o*	H*o*
C10	H10	C*m*	H*m*
C11	H11	C*p*	H*p*
C12	H12	C*m*	H*m*
C13	H13	Co	Ho
C14	H14	C12	H12
C15	H15	C11	H11
C16	H16	C10	H10
C17	---	*C*=O	---
C18	---	C8	---
C19	H19	C9	H9
C20	---	C1	---
C21	H21	C3′	H3′
C22	H22	C2′	H2′
C23	---	C4	---
C24	H24	C3	H3
C25	H25	C2	C2
C26	H26	C5	C5
C27	H27	C6	C6
C28	H28	C7	C7
C29	H29	C7′	C7′
O1	---	C=*O*	---
N1	NH1	H*N*-C=O	N-*H*

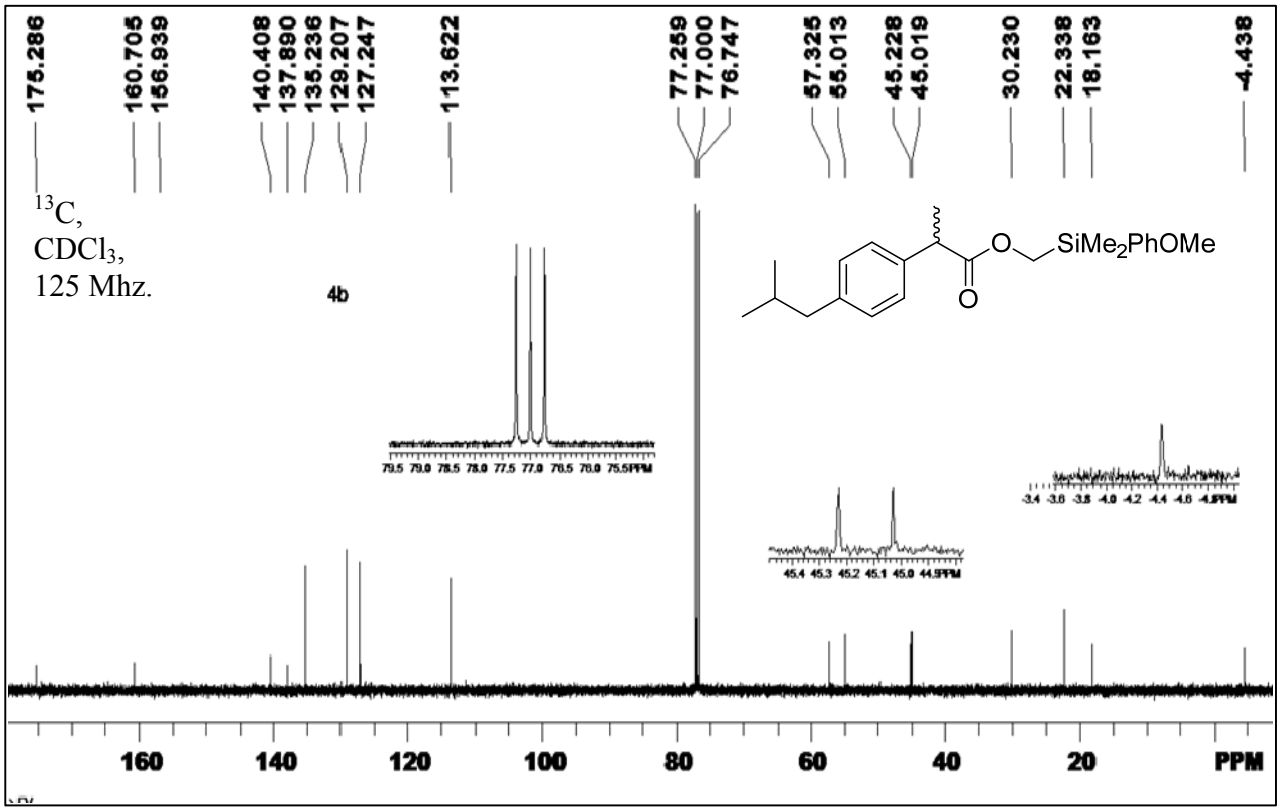
[A] Refers to the crystal state. Numbering of the carbon, hydrogen, oxygen and silicon atoms of compound **10e** is presented in the ORTEP diagram (Figure S1). [B] Refers to the solution of compound **10e** in $CDCl_3$. The assignment of the atoms is presented in Figure S11.

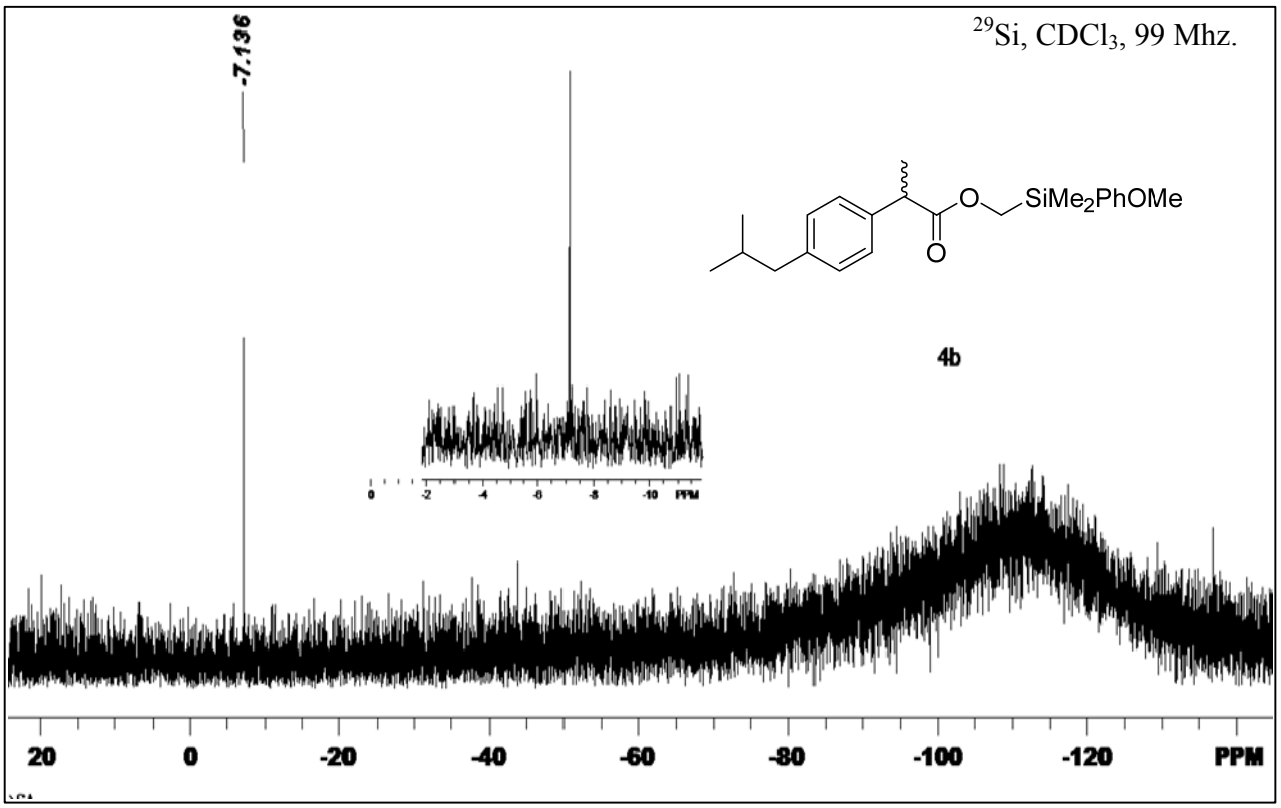
NMR spectra data

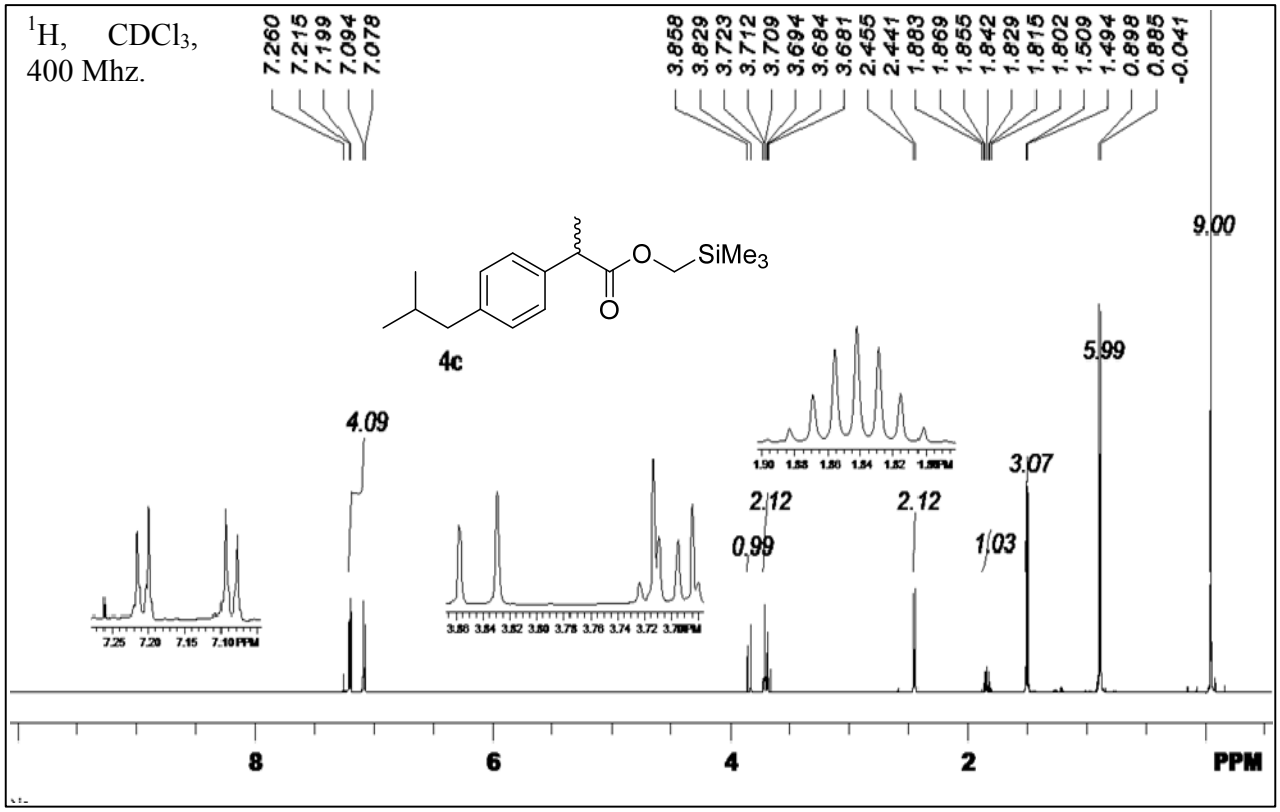


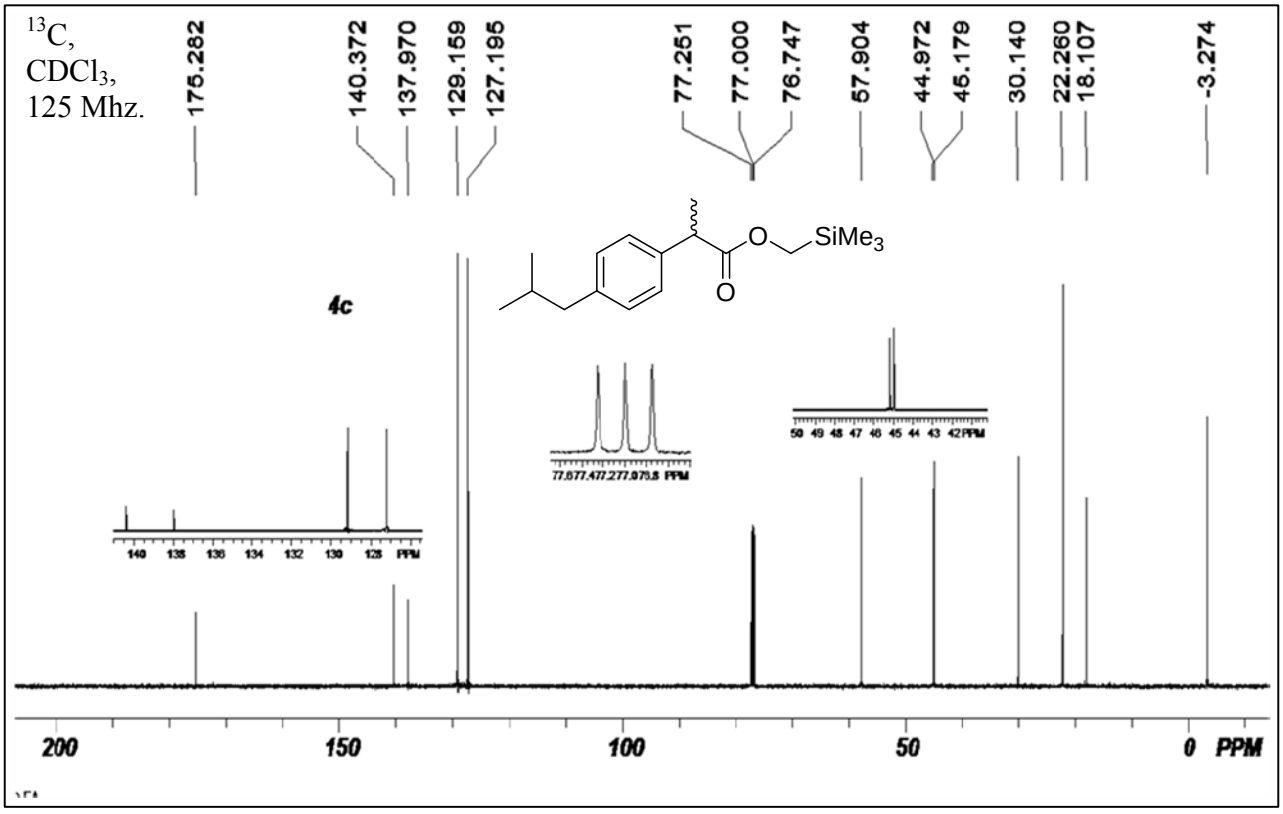

^{29}Si,
$CDCl_3$,
99 Mhz.
-5.611
O
SiMe$_2$Ph
O
4a
20
0
-20
-40
-60
-80
-100
-120
PPM

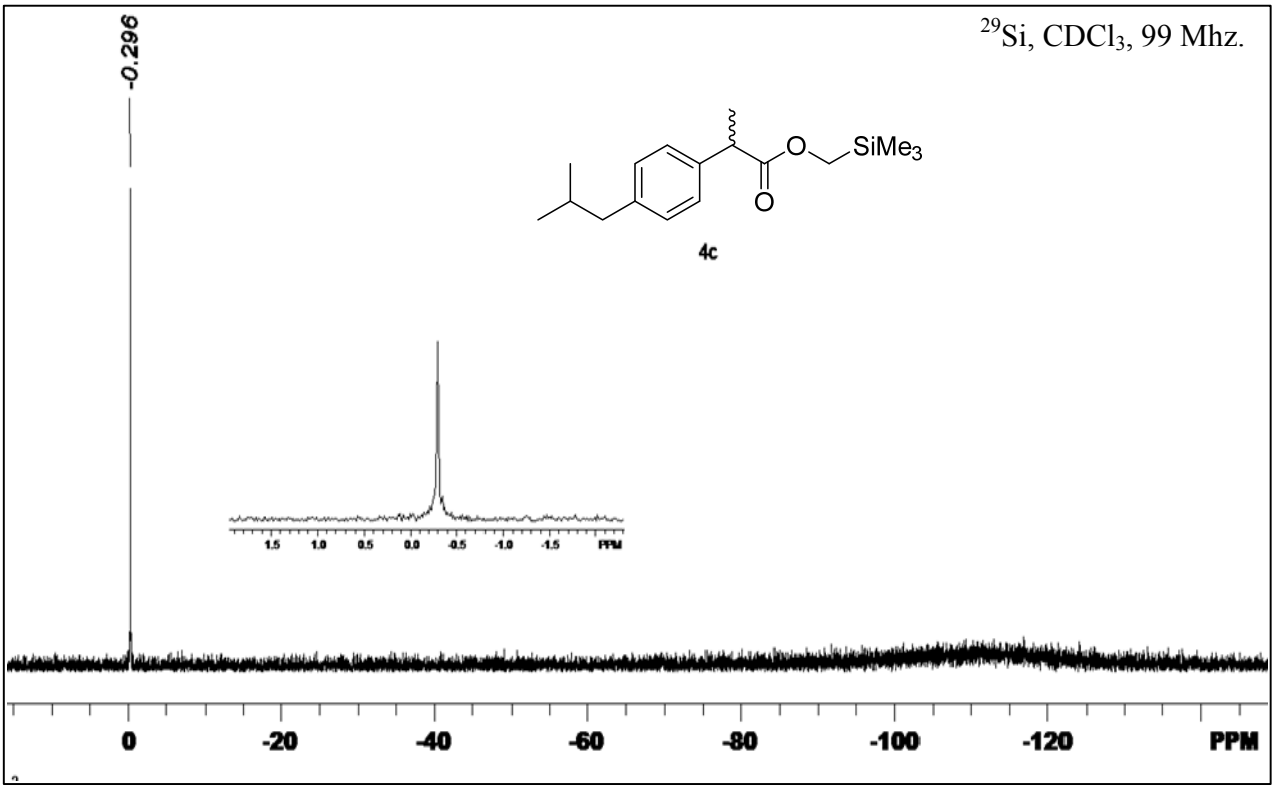

7.359
7.342
7.260
7.171
7.155
7.080
7.064
6.882
6.864
4.005
3.976
3.864
3.836
3.811
3.695
3.681
3.667
3.653
2.454
2.440
1.868
1.855
1.841
1.828
1.814
1.566
1.470
1.456
0.895
0.882
0.199
0.192
^{1}H,
$CDCl_3$,
500 Mhz.
O
SiMe$_2$PhOMe
O
4b
2.01
4.20
2.01
1.01
3.00
1.01
1.03
2.07
1.13
2.98
6.04
6.04
7
6
5
4
3
2
1
PPM

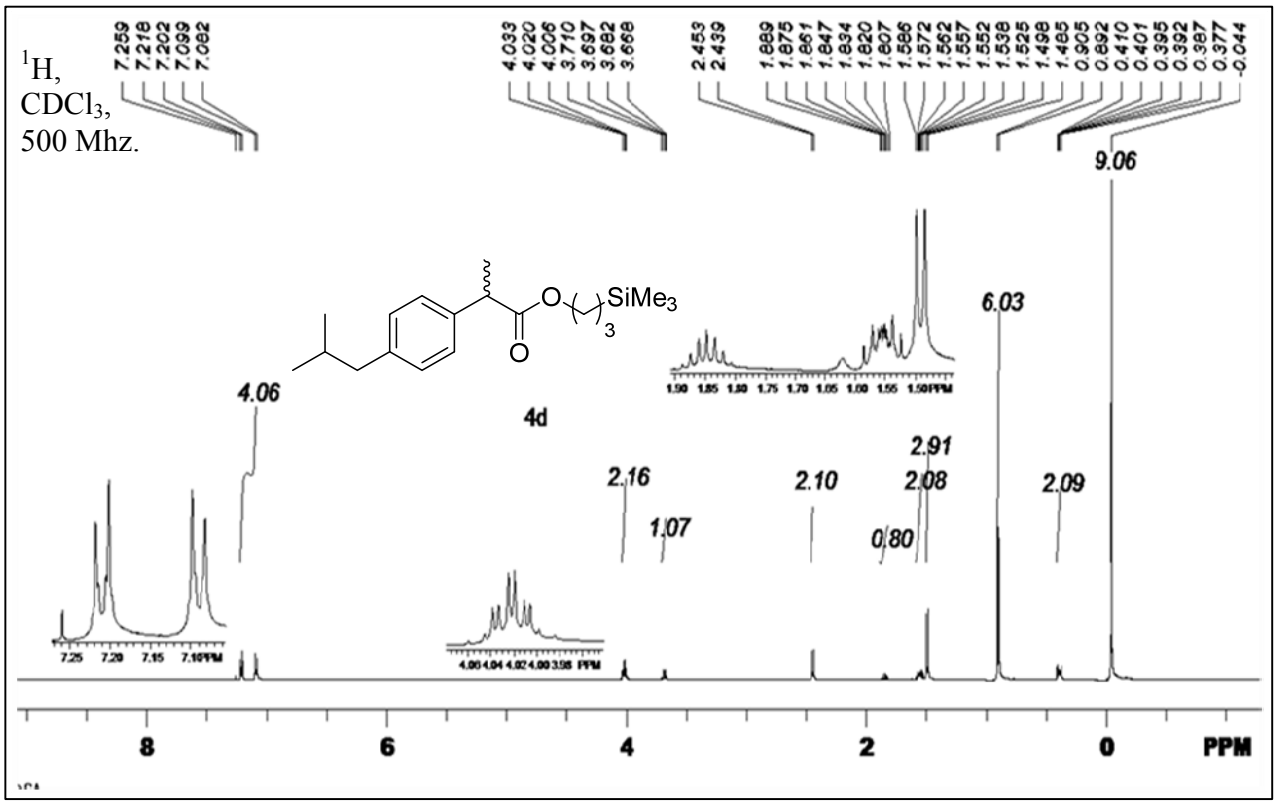

175.286
160.705
156.939
140.408
137.890
135.236
129.207
127.247
113.622
77.259
77.000
76.747
57.325
55.013
45.228
45.019
30.230
22.338
18.163
-4.438
13C,
CDCl3,
125 Mhz.
4b
O
SiMe2PhOMe
O
160
140
120
100
80
60
40
20
PPM

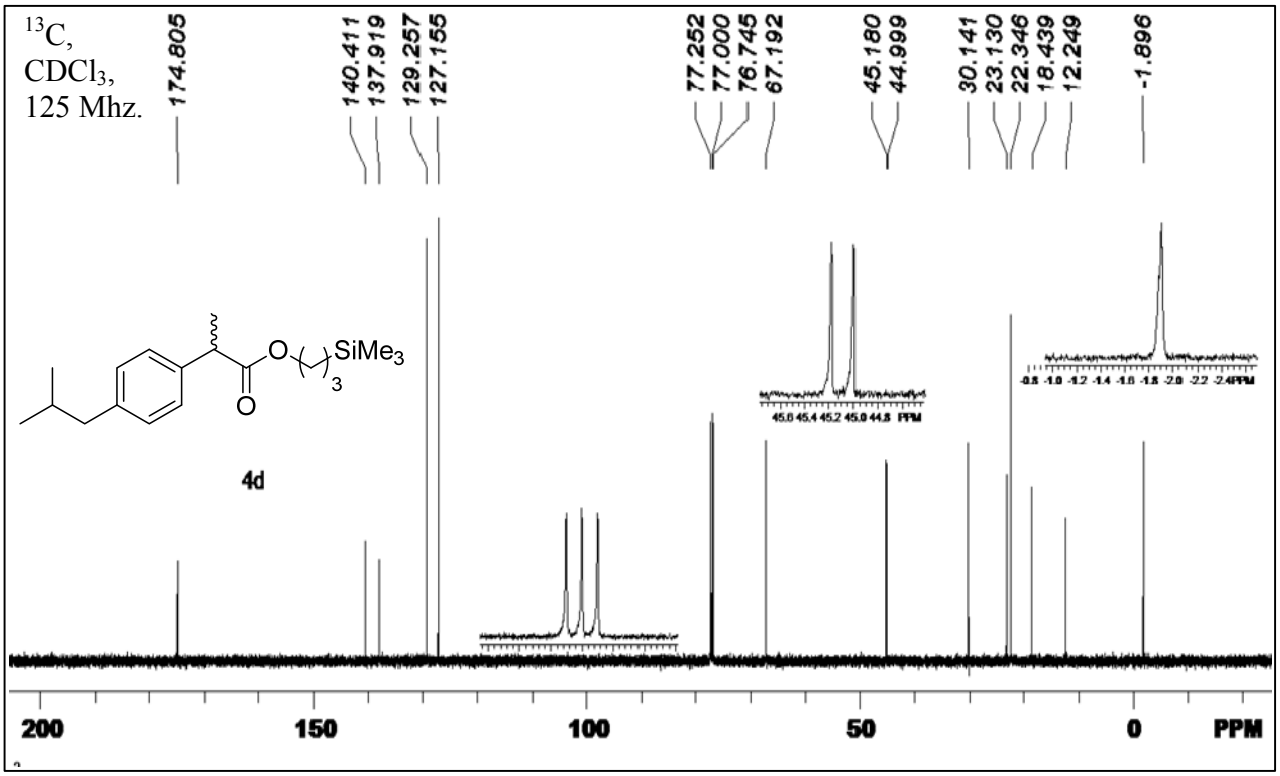

29Si, CDCl3, 99 Mhz.
-7.136
O
SiMe2PhOMe
O
4b
20
0
-20
-40
-60
-80
-100
-120
PPM

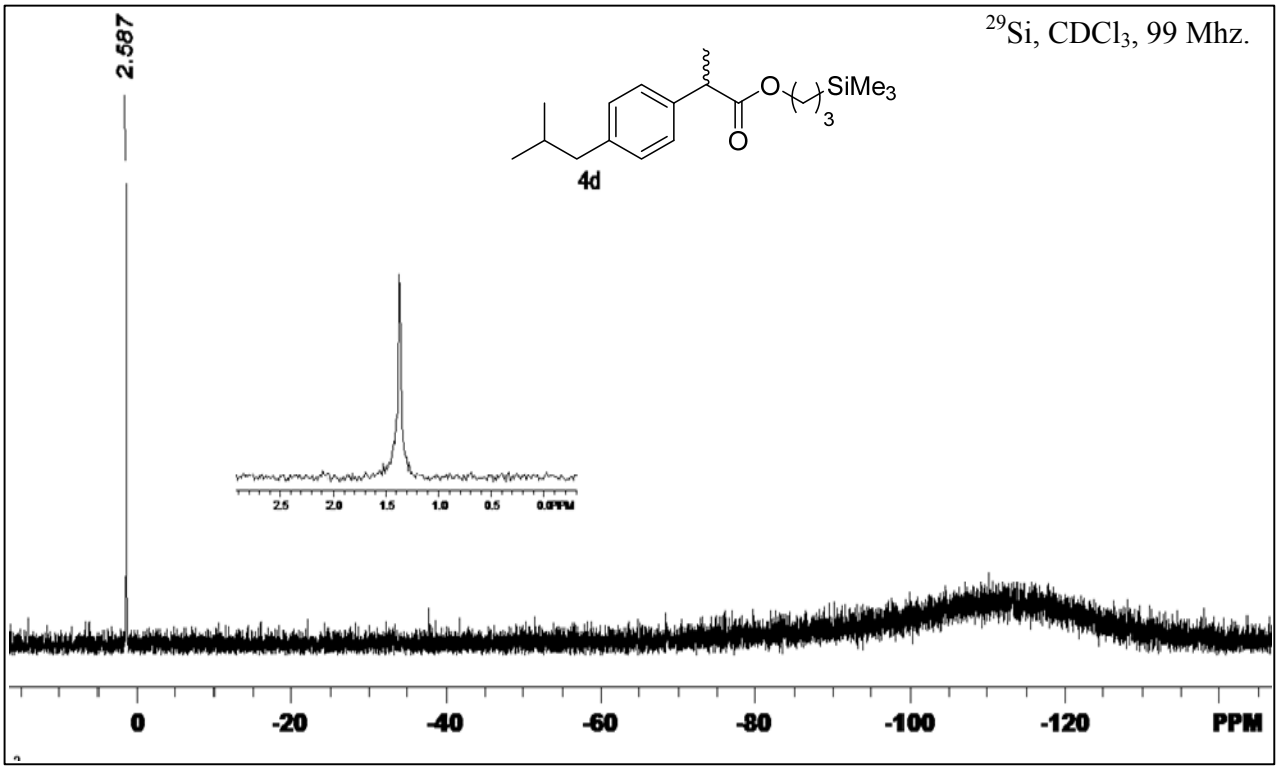

^{1}H, CDCl$_3$, 400 Mhz.
7.260
7.215
7.199
7.094
7.078
3.858
3.829
3.723
3.712
3.709
3.694
3.684
3.681
2.455
2.441
1.883
1.869
1.855
1.842
1.829
1.815
1.802
1.509
1.494
0.898
0.885
-0.041
SiMe3
O
O
4c
9.00
5.99
4.09
3.07
2.12
2.12
0.99
1.03
8
6
4
2
PPM

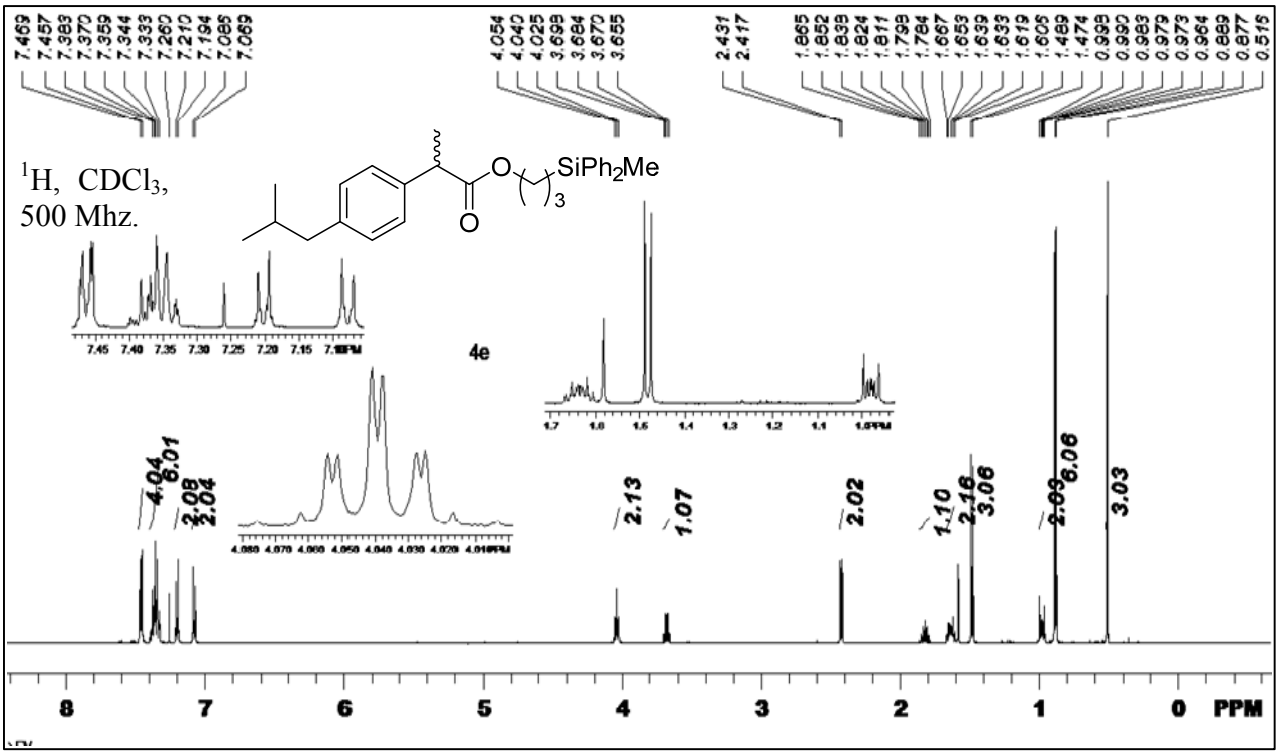

^{13}C, CDCl$_3$, 125 Mhz.
175.282
140.372
137.970
129.159
127.195
77.251
77.000
76.747
57.904
44.972
45.179
30.140
22.260
18.107
-3.274
SiMe3
O
O
4c
200
150
100
50
0
PPM

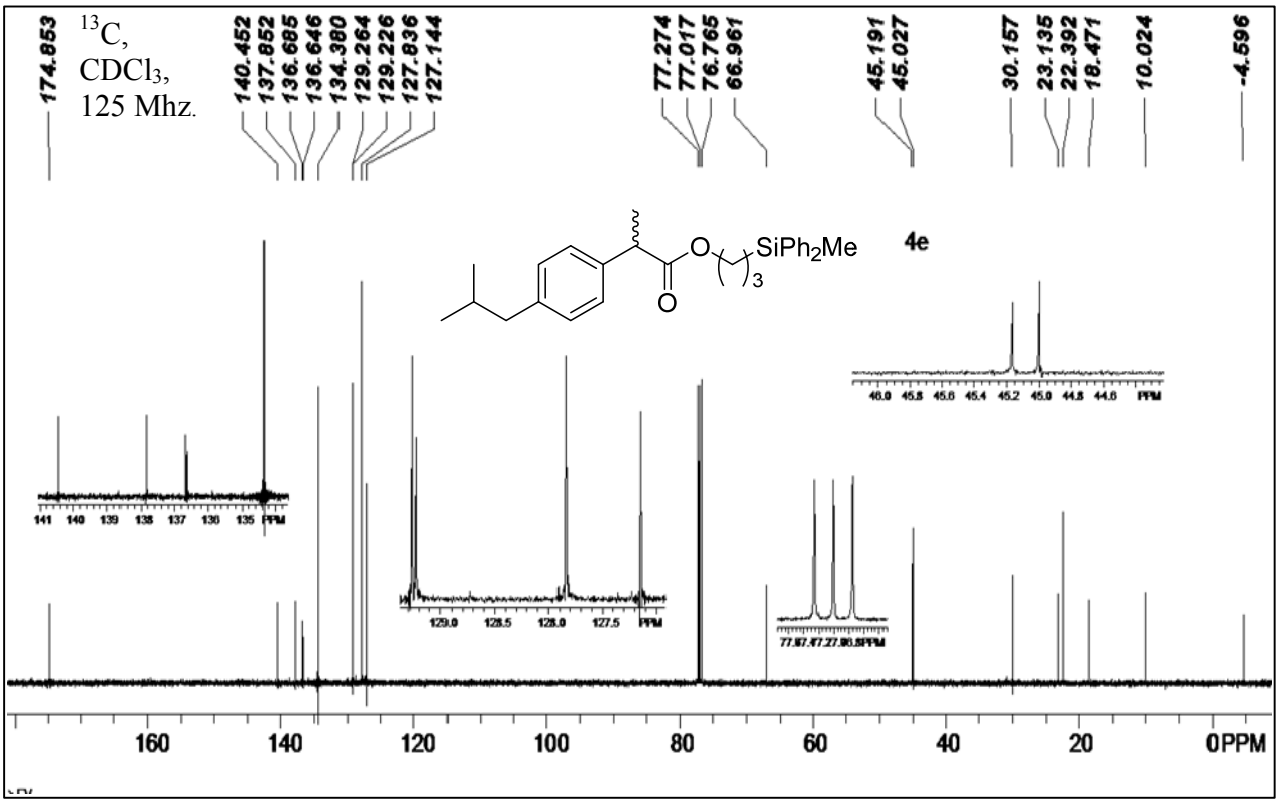

^{29}Si, $CDCl_3$, 99 Mhz.
-0.296
O
O
SiMe3
4c
0
-20
-40
-60
-80
-100
-120
PPM

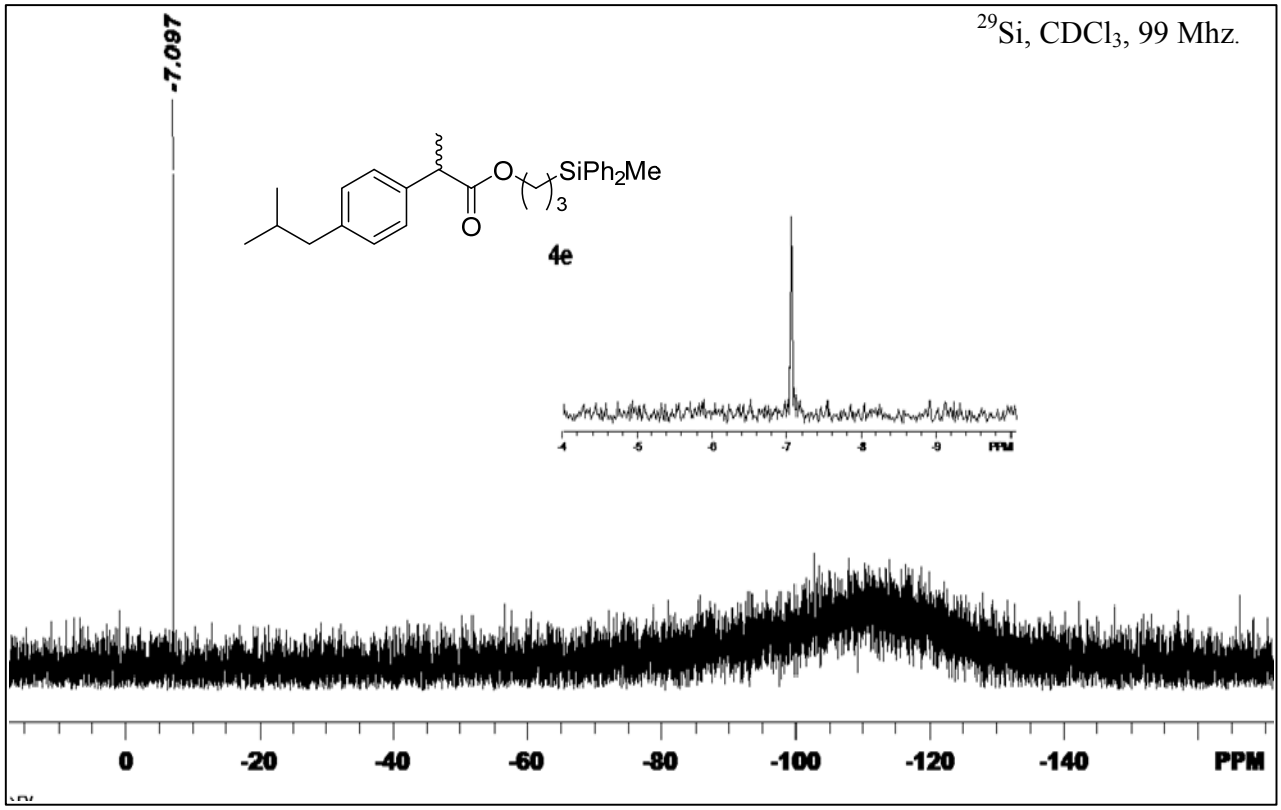

^{1}H,
$CDCl_3$,
500 Mhz.
7.259
7.218
7.202
7.099
7.082
4.033
4.020
4.006
3.710
3.697
3.682
3.668
2.453
2.439
1.889
1.875
1.861
1.847
1.834
1.820
1.807
1.586
1.572
1.562
1.557
1.552
1.538
1.525
1.498
1.485
0.905
0.892
0.410
0.401
0.395
0.392
0.387
0.377
-0.044
9.06
6.03
4.06
2.91
2.16
2.10
2.08
2.09
1.07
0.80
O
O
SiMe3
3
4d
8
6
4
2
0
PPM


^{13}C,
$CDCl_3$,
125 Mhz.
174.805
140.411
137.919
129.257
127.155
77.252
77.000
76.745
67.192
45.180
44.999
30.141
23.130
22.346
18.439
12.249
-1.896
SiMe3
4d
200
150
100
50
0
PPM

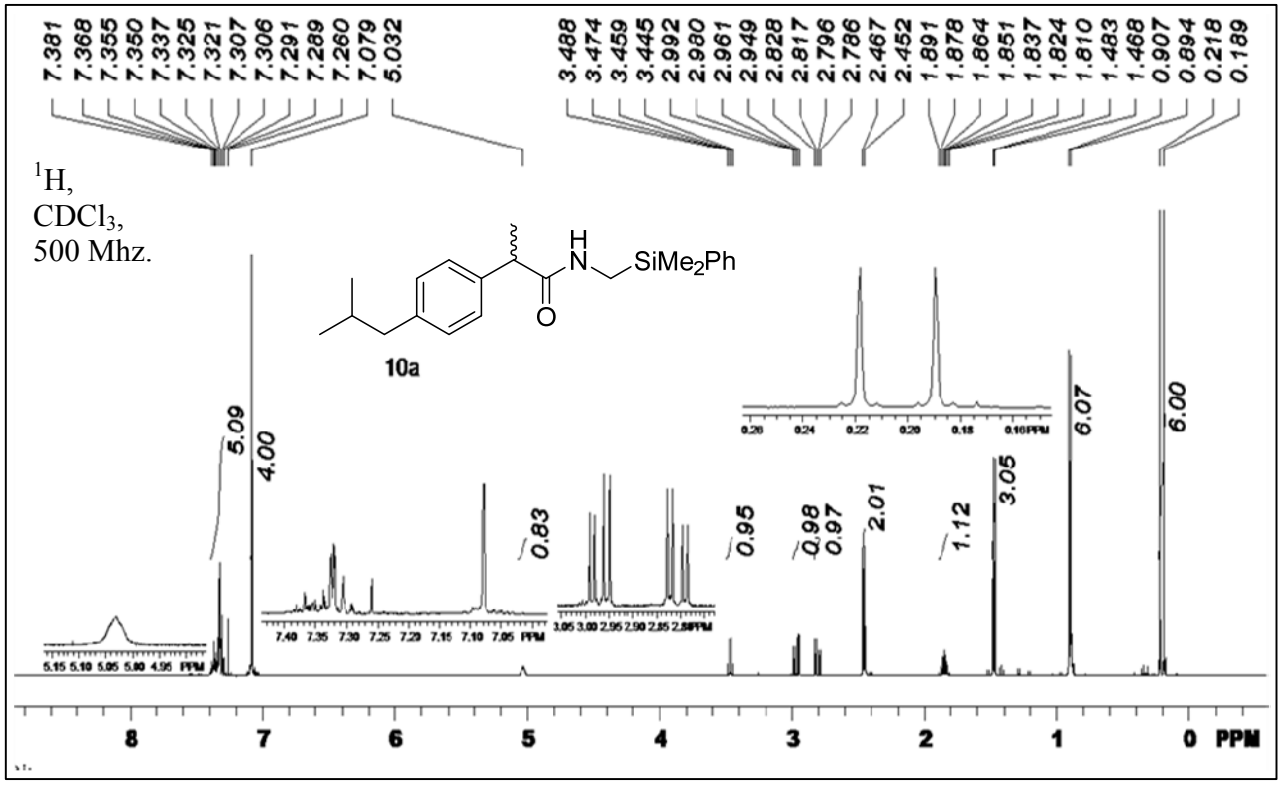

^{29}Si, $CDCl_3$, 99 Mhz.
2.587
SiMe3
4d
0
-20
-40
-60
-80
-100
-120
PPM


7.469
7.457
7.383
7.370
7.359
7.344
7.333
7.260
7.210
7.194
7.085
7.069
4.054
4.040
4.025
3.699
3.684
3.670
3.655
2.431
2.417
1.865
1.852
1.839
1.824
1.811
1.798
1.784
1.667
1.653
1.639
1.633
1.619
1.605
1.489
1.474
0.998
0.990
0.983
0.979
0.973
0.964
0.889
0.877
0.515
1H, CDCl3,
500 Mhz.
SiPh2Me
O
3
4e
4.04
6.01
2.08
2.04
2.13
1.07
2.02
1.10
2.16
3.06
2.09
6.06
3.03
8
7
6
5
4
3
2
1
0
PPM

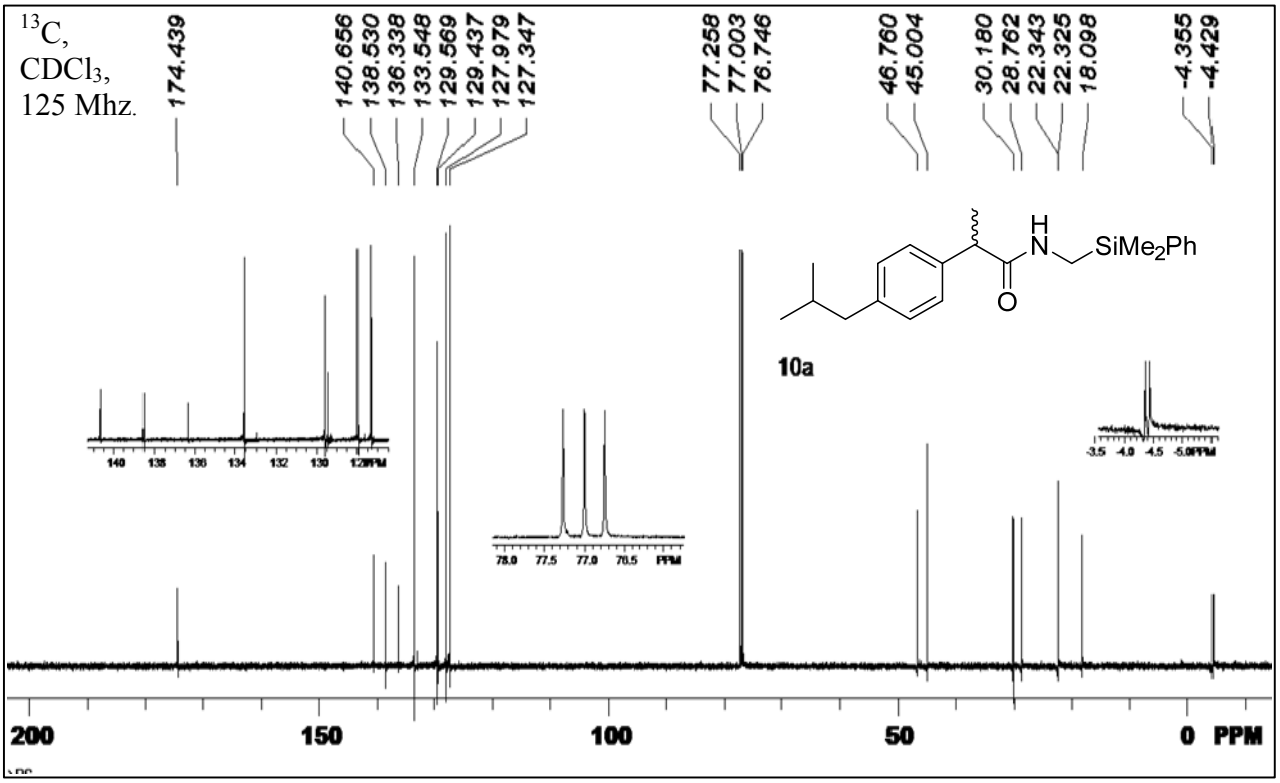

174.853
13C,
CDCl3,
125 Mhz.
140.452
137.852
136.685
136.646
134.380
129.264
129.226
127.836
127.144
77.274
77.017
76.765
66.961
45.191
45.027
30.157
23.135
22.392
18.471
10.024
-4.596
SiPh2Me
O
3
4e
160
140
120
100
80
60
40
20
0PPM

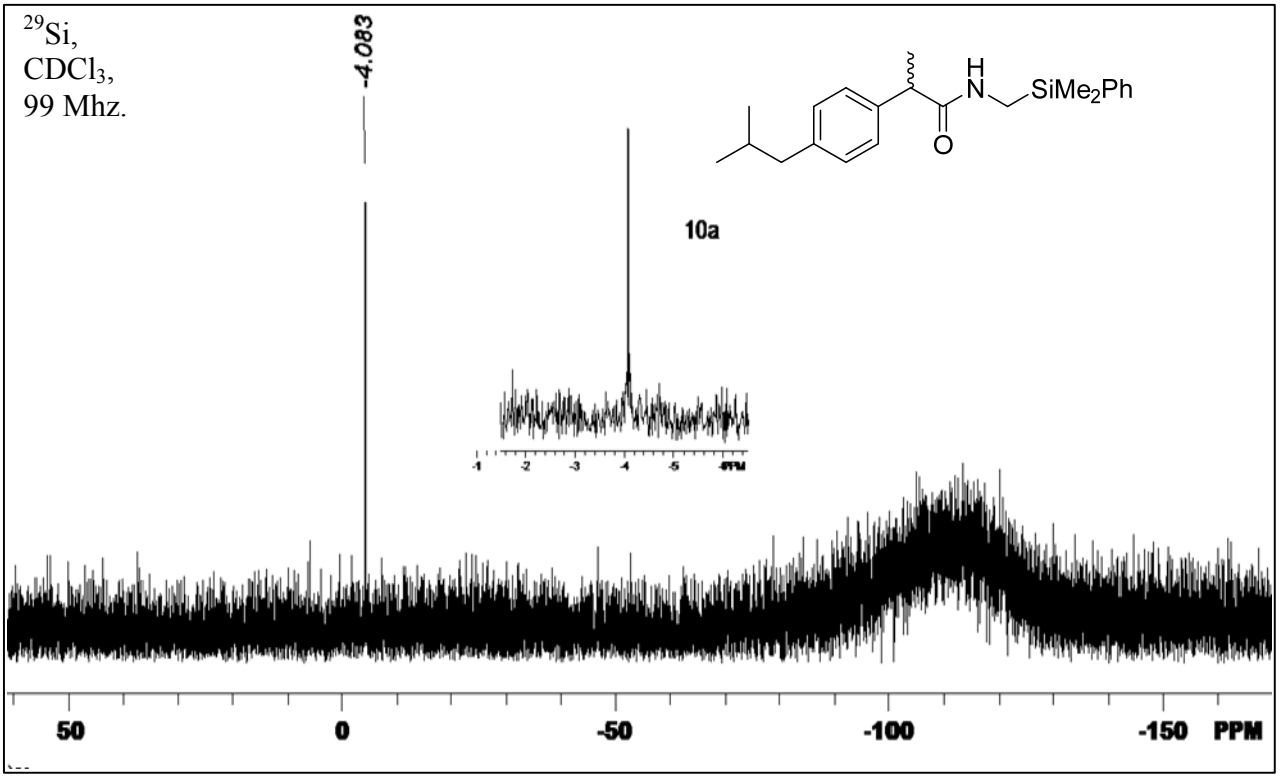


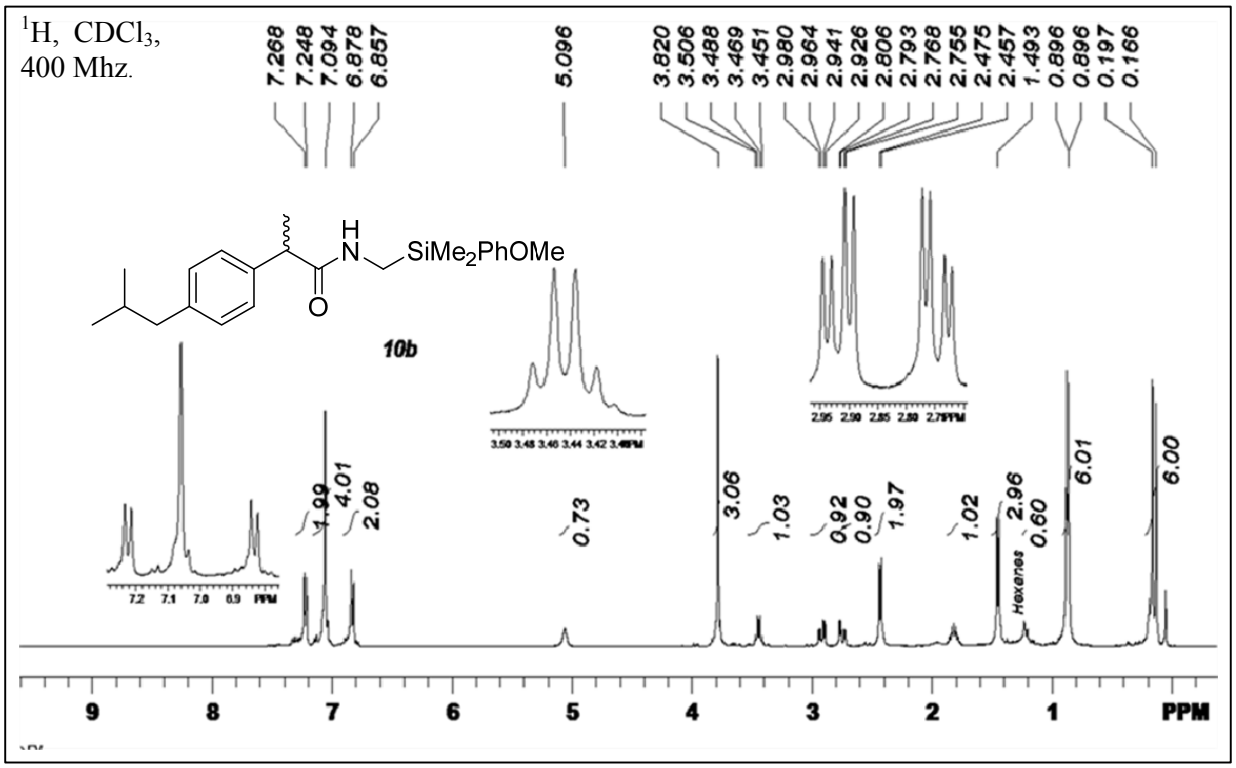
^{29}Si, $CDCl_3$, 99 Mhz.

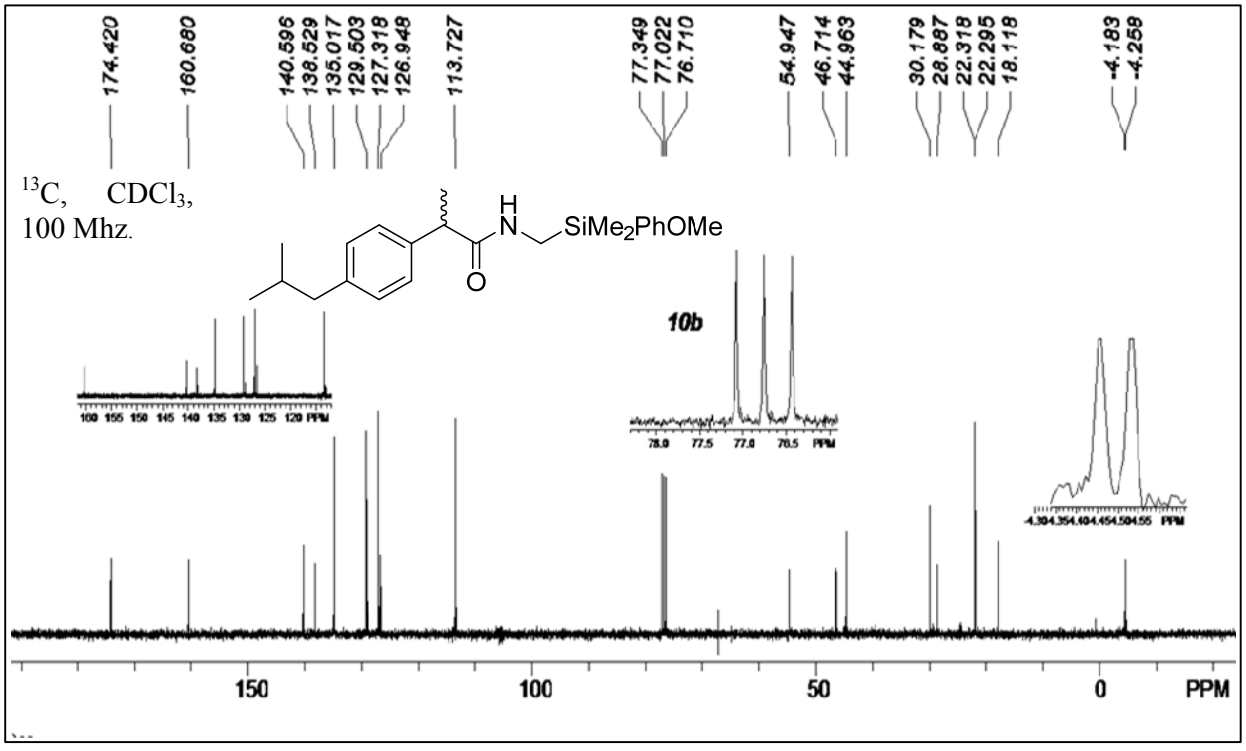


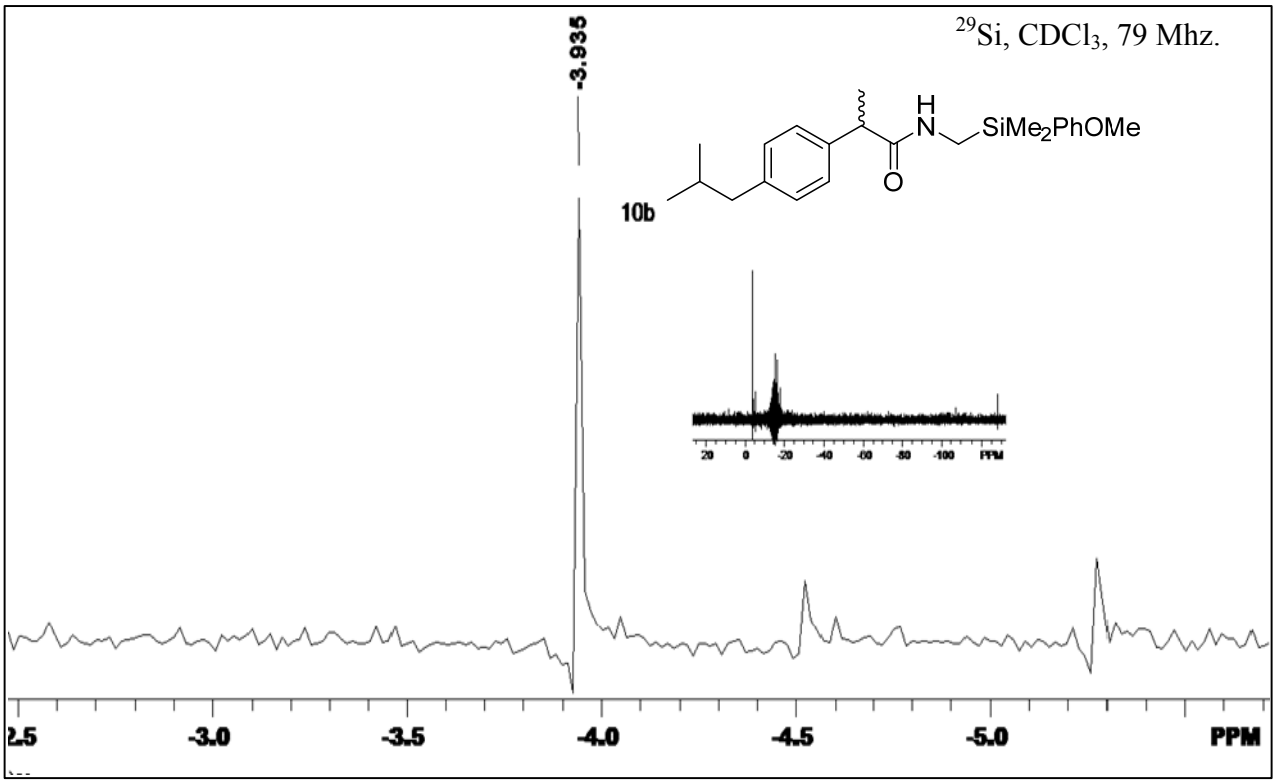
^{1}H,
$CDCl_3$,
500 Mhz.

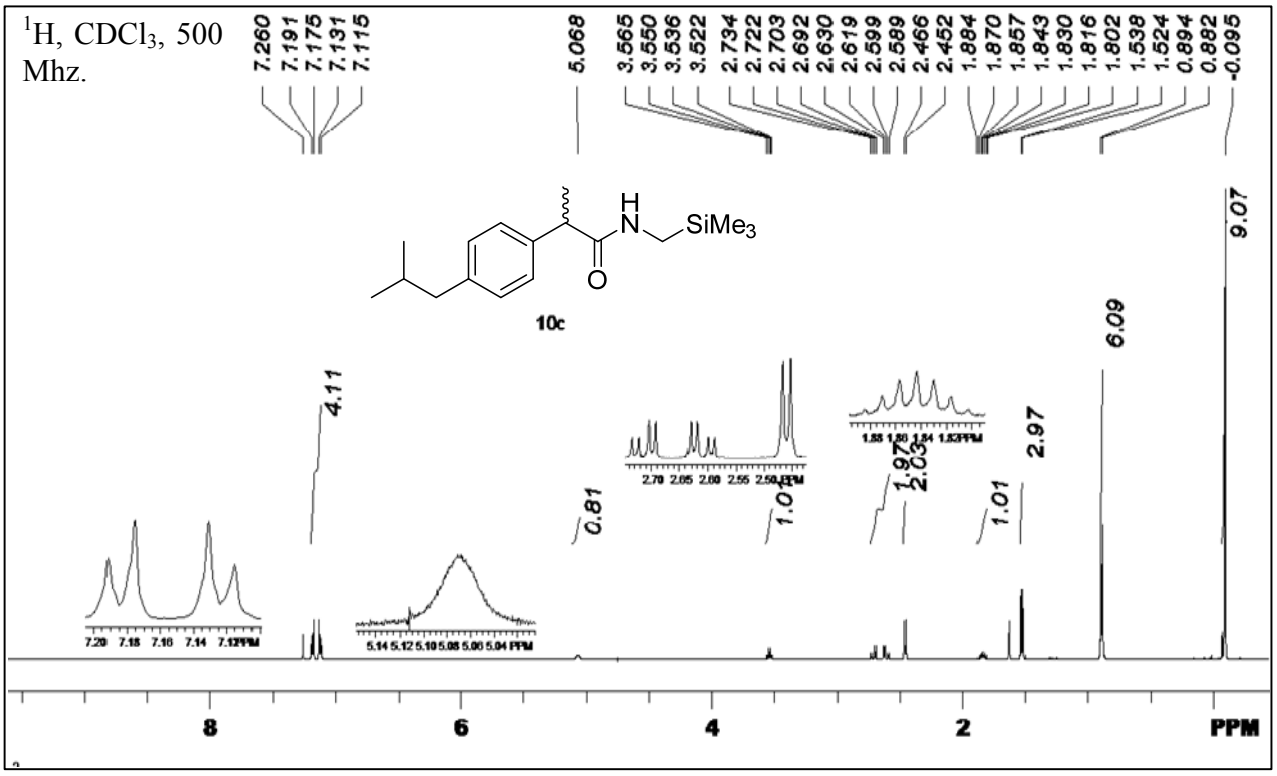

13C,
CDCl3,
125 Mhz.
174.439
140.656
138.530
136.338
133.548
129.569
129.437
127.979
127.347
77.258
77.003
76.746
46.760
45.004
30.180
28.762
22.343
22.325
18.098
-4.355
-4.429
H
N
SiMe2Ph
O
10a
200
150
100
50
0 PPM

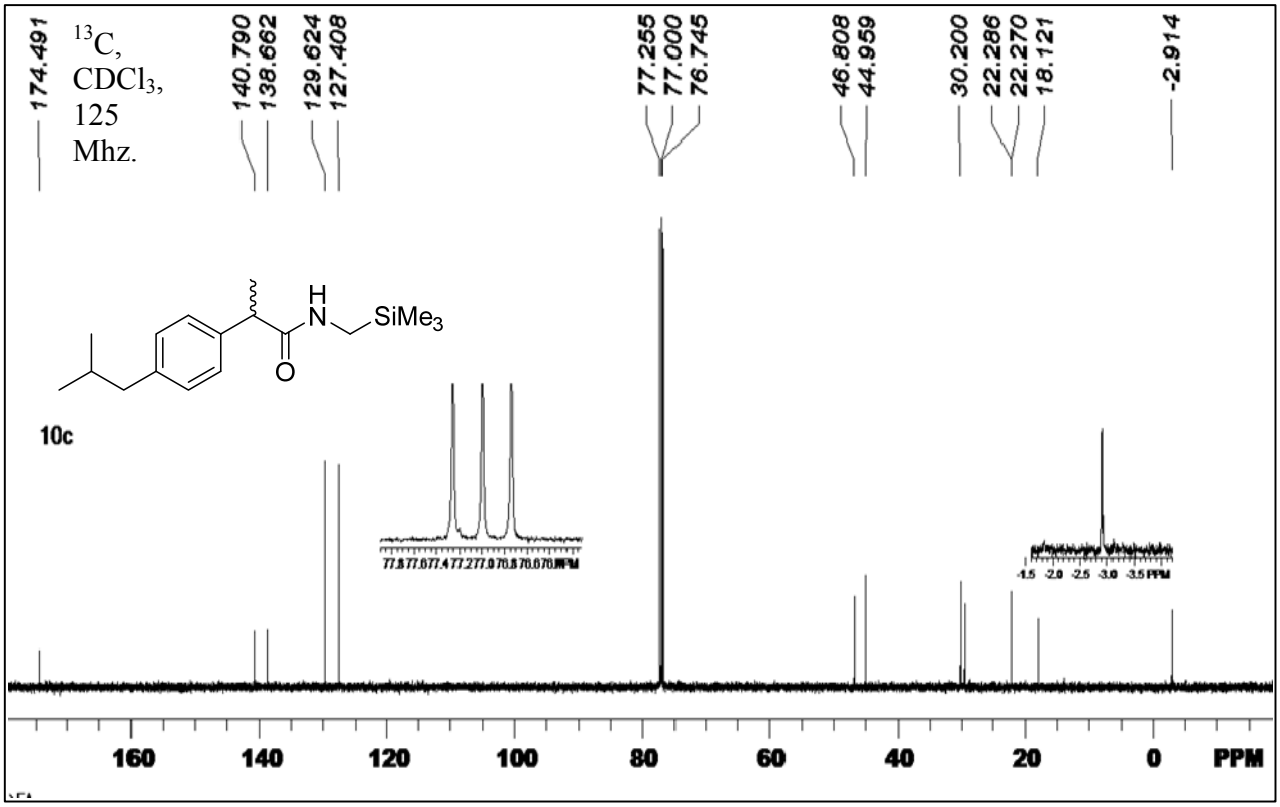

29Si,
CDCl3,
99 Mhz.
-4.083
H
N
SiMe2Ph
O
10a
50
0
-50
-100
-150 PPM


^{1}H, CDCl$_3$,
400 Mhz.
7.268
7.248
7.094
6.878
6.857
5.096
3.820
3.506
3.488
3.469
3.451
2.980
2.964
2.941
2.926
2.806
2.793
2.768
2.755
2.475
2.457
1.493
0.896
0.896
0.197
0.166
SiMe2PhOMe
10b
1.99
4.01
2.08
0.73
3.06
1.03
0.92
0.90
1.97
1.02
2.96
0.60
Hexanes
6.01
6.00
9
8
7
6
5
4
3
2
1
PPM

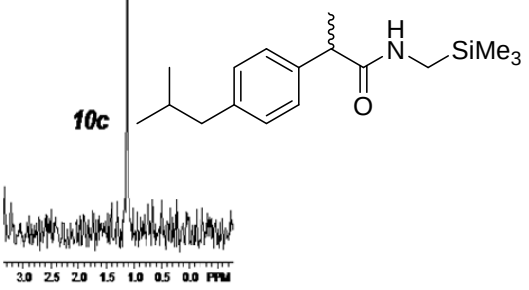

174.420
160.680
140.596
138.529
135.017
129.503
127.318
126.948
113.727
77.349
77.022
76.710
54.947
46.714
44.963
30.179
28.887
22.318
22.295
18.118
-4.183
-4.259
^{13}C, CDCl$_3$,
100 Mhz.
SiMe2PhOMe
10b
150
100
50
0
PPM


^{29}Si, $CDCl_3$, 79 Mhz.
-3.935
SiMe2PhOMe
10b
2.5
-3.0
-3.5
-4.0
-4.5
-5.0
PPM


^{1}H, $CDCl_3$, 500 Mhz.
7.260
7.191
7.175
7.131
7.115
5.068
3.565
3.550
3.536
3.522
2.734
2.722
2.703
2.692
2.630
2.619
2.599
2.589
2.466
2.452
1.884
1.870
1.857
1.843
1.830
1.816
1.802
1.538
1.524
0.894
0.882
-0.095
SiMe3
10c
9.07
6.09
4.11
2.97
2.03
1.97
1.01
1.01
0.81
8
6
4
2
PPM



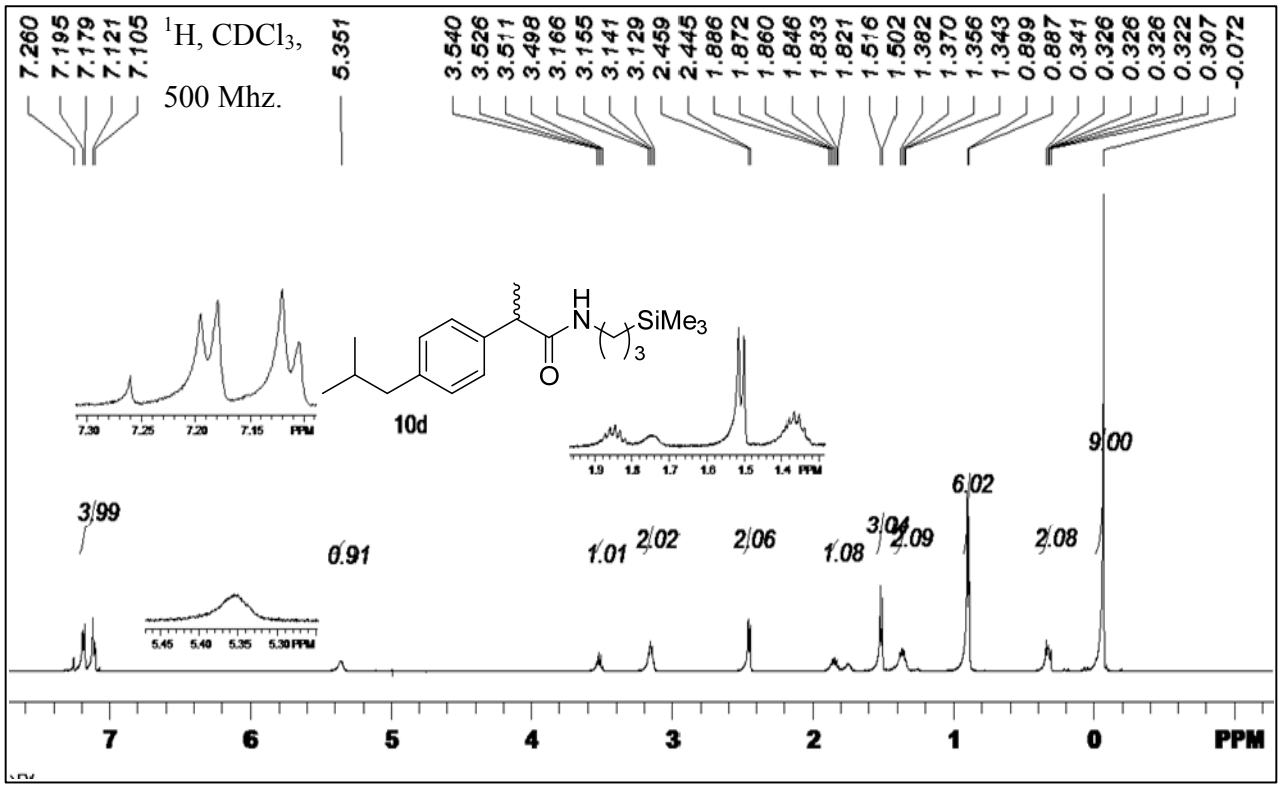
^{13}C, $CDCl_3$, 125 Mhz.

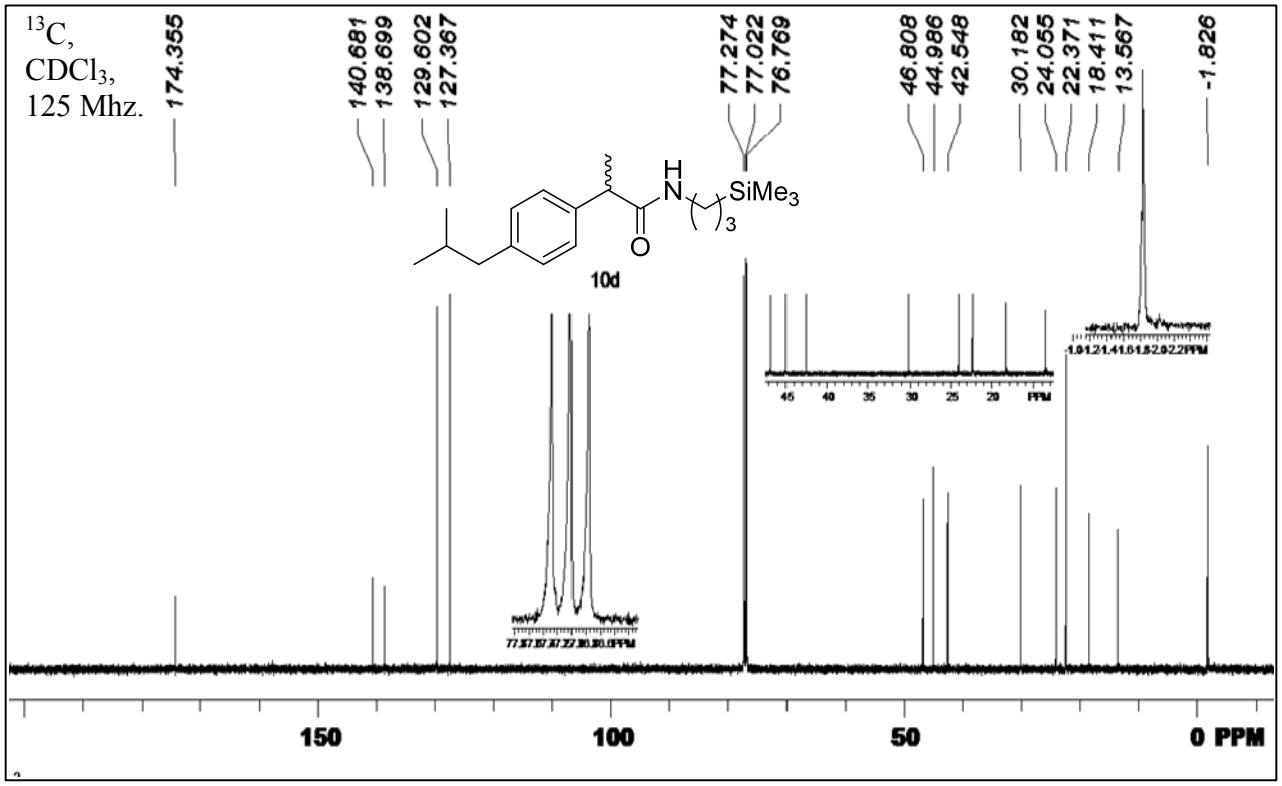


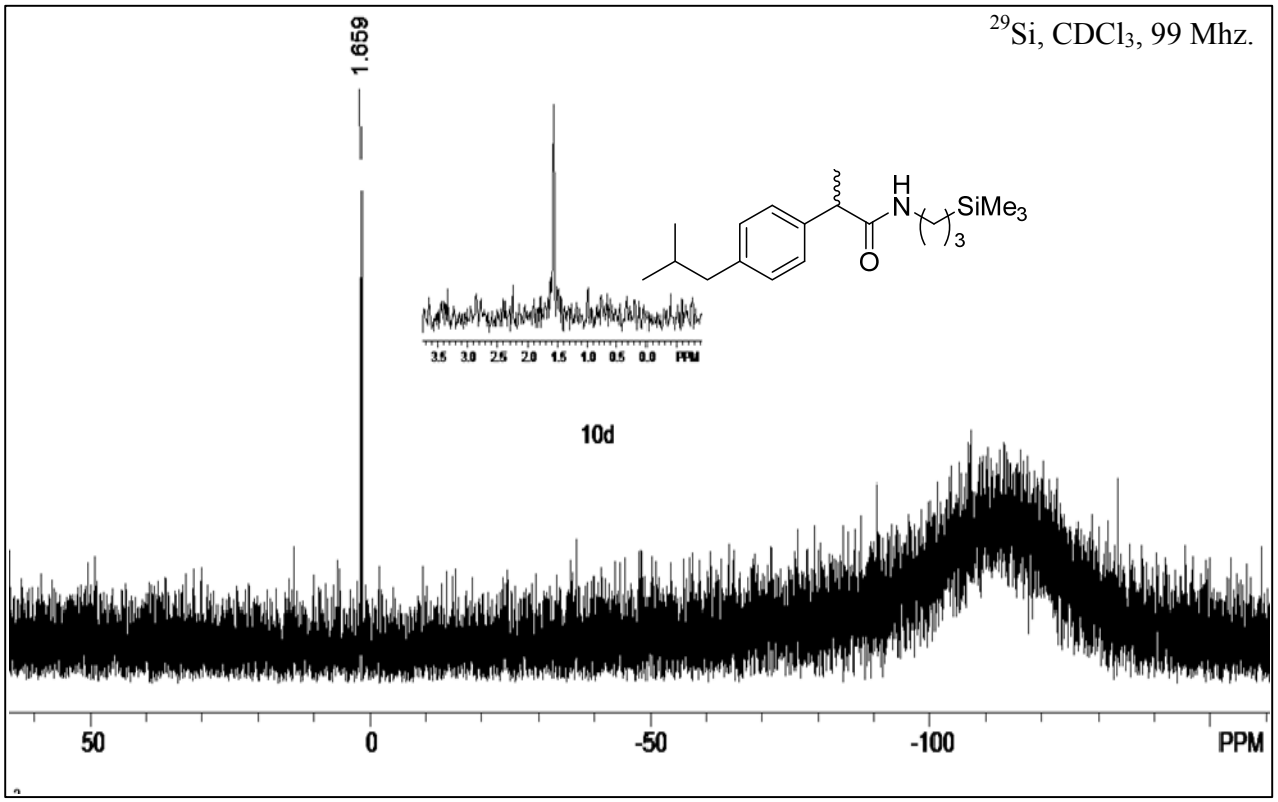
10c

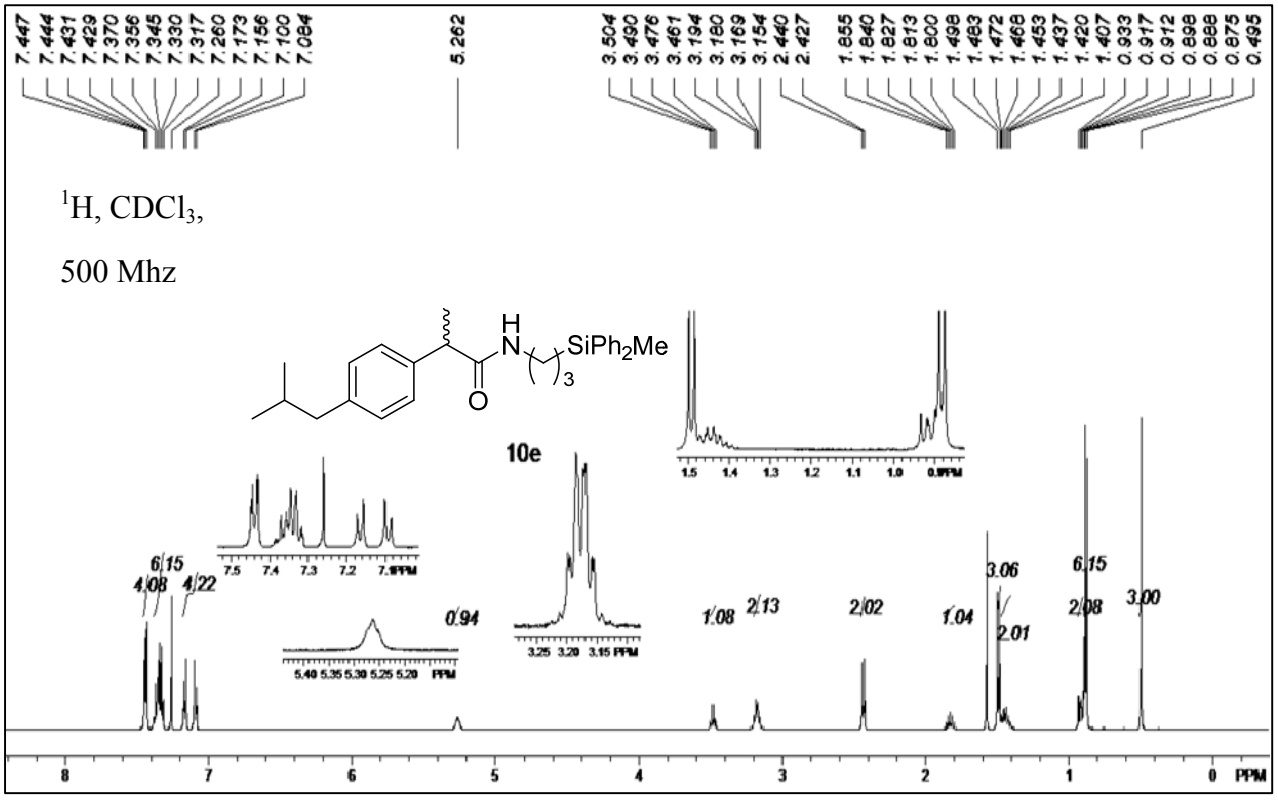
^{29}Si, $CDCl_3$, 99 Mhz.

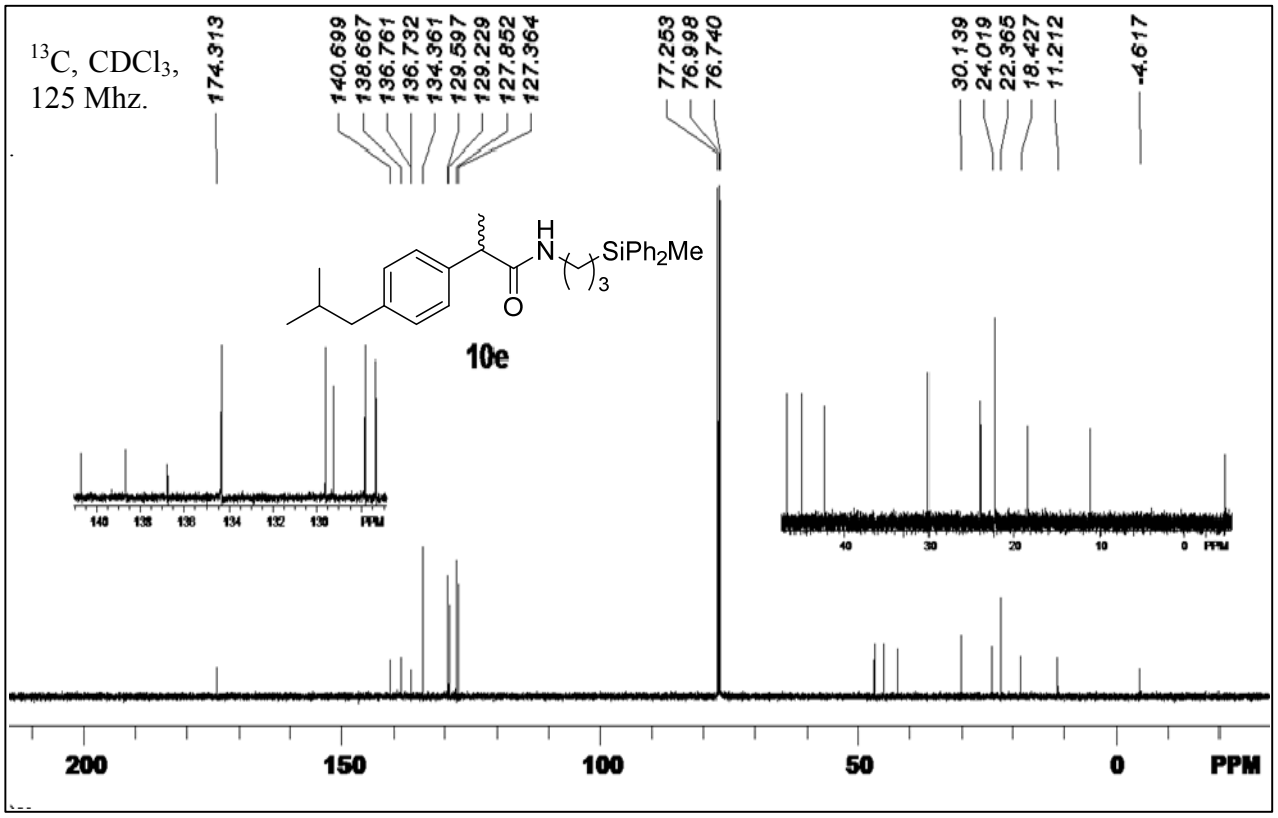
10c

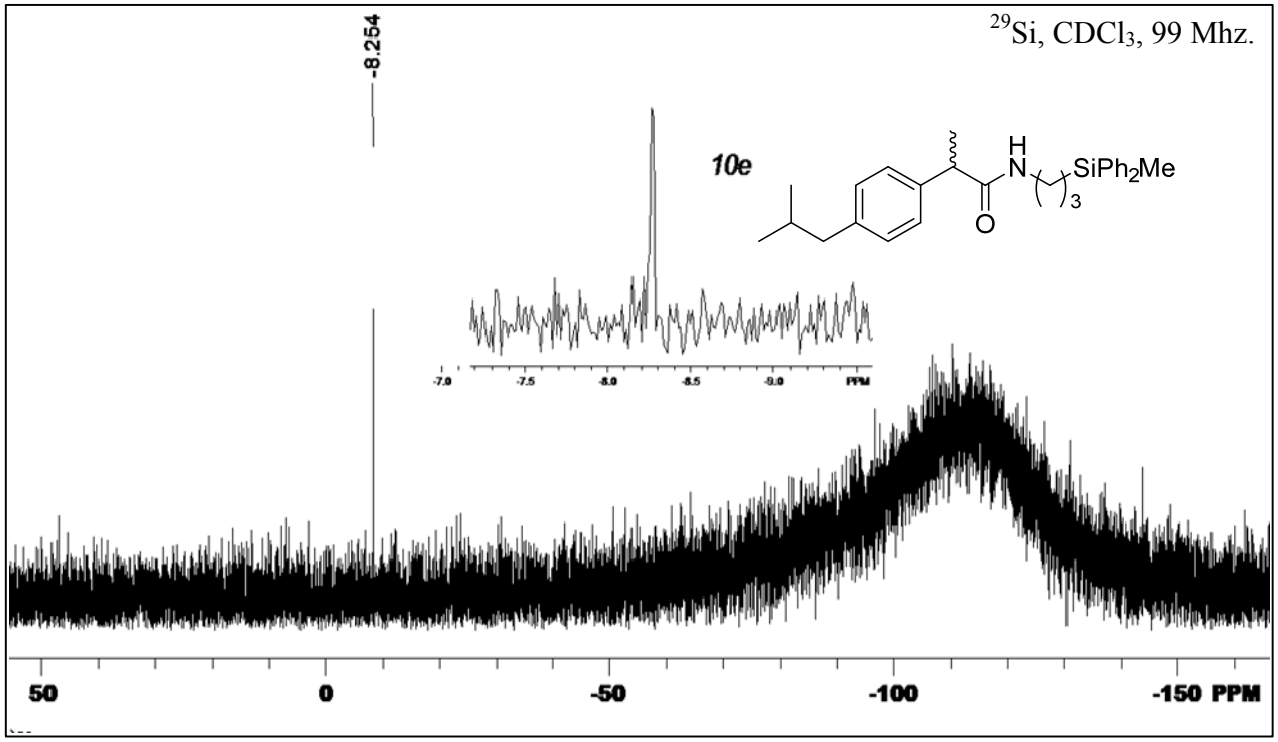

^{1}H, CDCl$_3$,
500 Mhz.
7.260
7.195
7.179
7.121
7.105
5.351
3.540
3.526
3.511
3.498
3.166
3.155
3.141
3.129
2.459
2.445
1.886
1.872
1.860
1.846
1.833
1.821
1.516
1.502
1.382
1.370
1.356
1.343
0.899
0.887
0.341
0.326
0.326
0.326
0.322
0.307
-0.072
10d
3.99
0.91
1.01
2.02
2.06
1.08
3.04
2.09
6.02
2.08
9.00
7
6
5
4
3
2
1
0
PPM


^{13}C,
CDCl$_3$,
125 Mhz.
174.355
140.681
138.699
129.602
127.367
77.274
77.022
76.769
46.808
44.986
42.548
30.182
24.055
22.371
18.411
13.567
-1.826
10d
150
100
50
0 PPM


^{29}Si, CDCl$_3$, 99 Mhz.
1.659
10d
50
0
-50
-100
PPM


^{1}H, CDCl$_3$,
500 Mhz
10e
6.15
4.08
4.22
0.94
1.08
2.13
2.02
1.04
3.06
2.01
6.15
2.08
3.00
PPM


^{13}C, CDCl$_3$,
125 Mhz.
174.313
140.699
138.667
136.761
136.732
134.361
129.597
129.229
127.852
127.364
77.253
76.998
76.740
30.139
24.019
22.365
18.427
11.212
-4.617
SiPh$_2$Me
10e
200
150
100
50
0
PPM


^{29}Si, CDCl$_3$, 99 Mhz.
-8.254
10e
SiPh$_2$Me
50
0
-50
-100
-150 PPM

References

[1] Bruker, **2009**, Madison, Wisconsin, USA.
[2] O. V. Dolomanov, L. J. Bourhis, R. J. Gildea, J. A. K. Howard, H. Puschmann, *J. Appl. Cryst.*, **2009**, *42*, 339.
[3] I. A. Guzei, **2006-2008**,
[4] G. Sheldrick, *Acta Cryst. A* **2008**, *64*, 112.
[5] S. Nagarajan, M. R. Doddareddy, H. Choo, Y. S. Cho, K.-S. Oh, B. H. Lee, A. N. Pae, *Bioorg. Med. Chem.*, **2009**, *17*, 2759.