Electronic Supplementary Material (ESI) for Organic & Biomolecular Chemistry

Electronic Supplementary Information for

Discovery of New Heterocycles with Activity against Human Neutrophile Elastase Based On A Boron Promoted One-Pot Assembly Reaction.

Francesco Montalbano,[a] Pedro M. S. D. Cal,[a] Marta A. B. R. Carvalho,[a] Lídia M. Gonçalves,[a] Susana D. Lucas,[a] Rita C. Guedes,[a] Luís F. Veiros,[b] Rui Moreira,[a] Pedro M. P. Gois[a]*

[a] *Research Institute for Medicines and Pharmaceutical Sciences (iMed.UL), Faculty of Pharmacy, University of Lisbon, Av.Prof. Gama Pinto, 1649-003 Lisbon, Portugal.* pedrogois@ff.ul.pt.

[b] *Centro de Química Estrutural, Departamento de Engenharia Química, Instituto Superior Técnico, Universidade Técnica de Lisboa, 1049-001 Lisboa, Portugal.*

Table of Contents

General Remarks

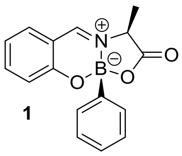
Tetrahydrofuran (THF) was distilled over calcium hydride/benzophenone immediately prior to use and ethyl acetate was distilled over potassium carbonate. All reactions were performed in oven-dried glassware under argon. Methanol and ethanol used as reaction solvents were distilled. The aldehydes, boronic acids and amino acids were purchased from Aldrich and used without further purification. Reaction mixtures were analysed by TLC using F_{254} from Merck (Ref. 105554, silica gel 60), and visualisation of TLC spots was effected using UV and phosphomolybdic acid solution. Proton and carbon nuclear magnetic resonance spectra (^{1}H/^{13}C NMR) were recorded on Bruker AMX 400, spectrophotometer with $CDCl_3$ as solvent, ^{11}boron nuclear magnetic resonance (^{11}B NMR) were recorded on Bruker AMX 300, spectrophotometer with $CDCl_3$ as solvent. Chemical shifts for ^{1}H NMR spectra are reported as δ in units of parts per million (ppm) downfield from $SiMe_4$ (δ 0.0) and relative to the signal of chloroform (δ 7.26, singlet). Multiplicities are given as: s (singlet), d (doublet), t (triplet), q (quartet), dd (double of doublet), td (triplet of doublets) or m (multiplets). The number of protons (n) for a given resonance is indicated by nH. Coupling constants are reported as a *J* value in Hertz. Carbon nuclear magnetic resonance spectra (^{13}C NMR) are reported as δ in units of parts per million (ppm) downfield from $SiMe_4$ (δ 0.0) and relative to the signal of chloroform (δ 77.16, triplet). The *dr*s were determined based on the ^{1}H, ^{13}C and NOESY NMR spectroscopy and by comparison with the x-rays obtained for compounds: **3**, **5** and **6** (Gois et al *Tetrahedron* **2010**, *66*, 2736–2745).

General procedure for preparation of boron heterocycles using water as solvent

A round bottom flask equipped with a magnetic stirrer was charged with amino acid (2.0 equiv.), aldehyde (1.5 equiv.) and distilled water (2.0 mL). This suspension was stirred at 90ºC for 1 h after which the boronic acid (0.41 mmol) was added, the mixture was then stirred at 90ºC for 20 h. The reaction mixture, which appears as a biphasic composition of precipitate and a supernatant liquid, was filtered and the solid retained in the filter was then washed with water followed by hexane. The desired compound was recovered with dichloromethane, which was subsequently removed under reduced pressure.

Compounds characterization

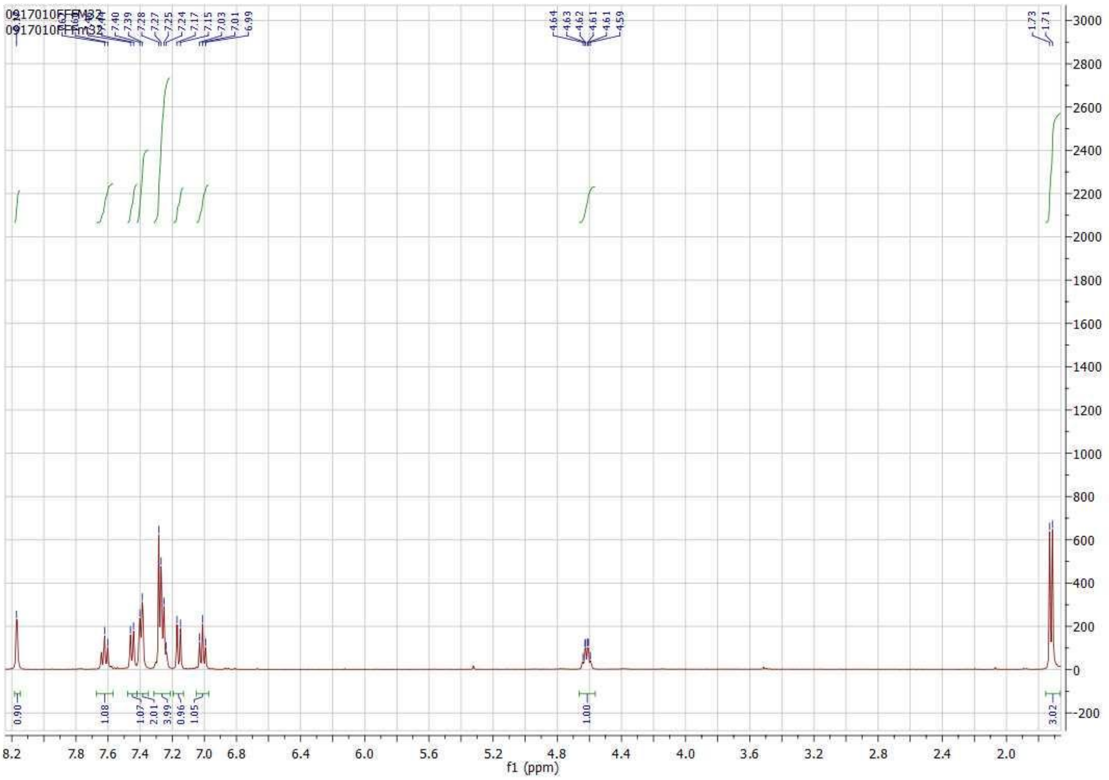
Compound 1

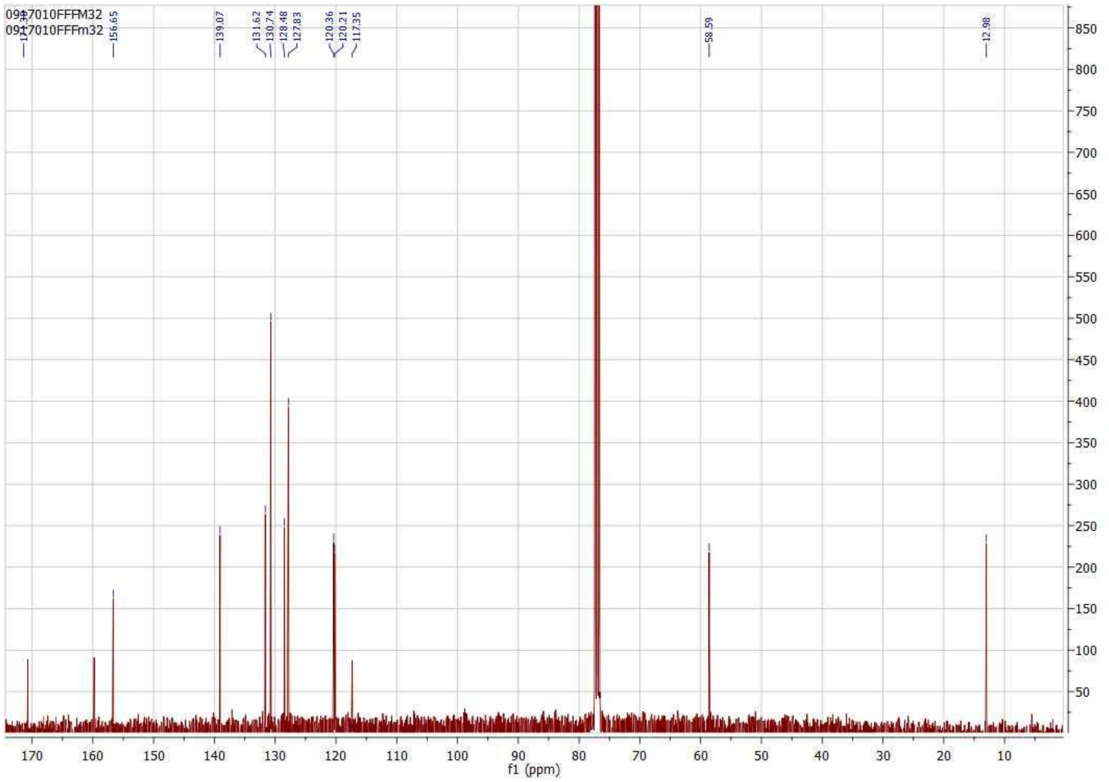


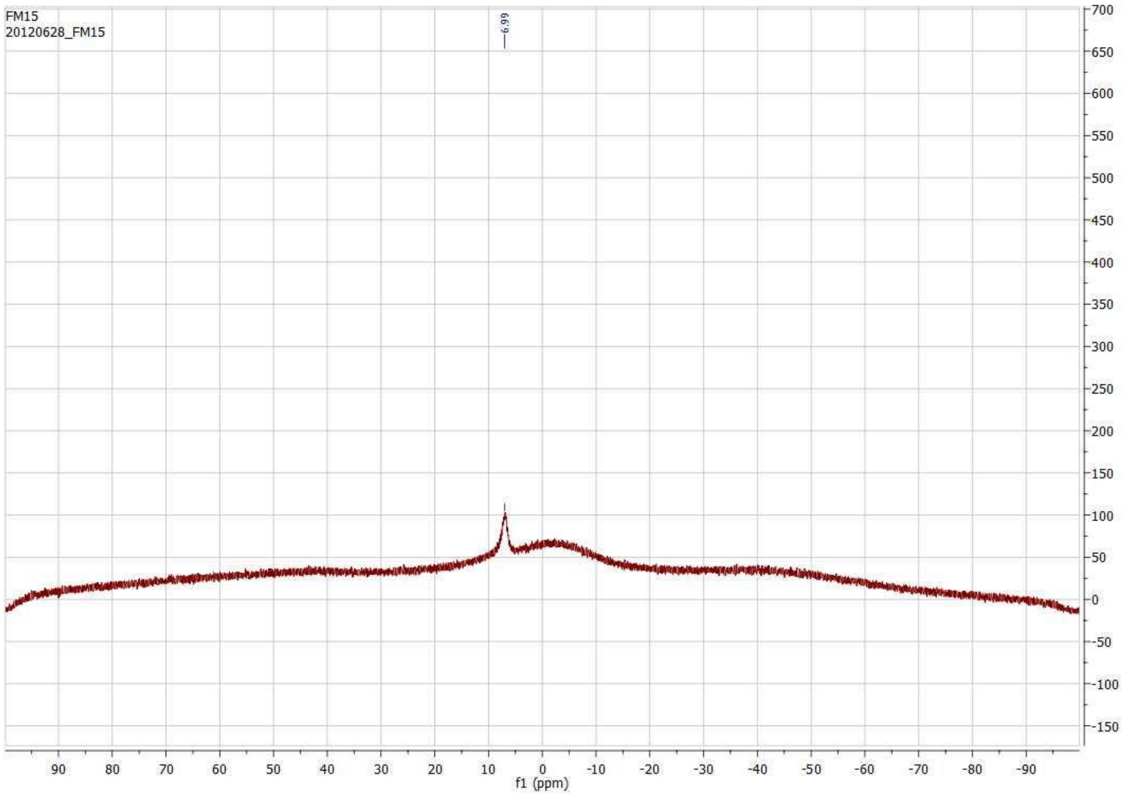
1

1 was obtained in 52 % yield, *d.r.*100%, after 20 h at 90 ºC (0.142 g).
^{1}H NMR (400 MHz, $CDCl_3$, 25ºC, TMS): δ 1.73 (d, 3H, *J* = 6.8 Hz, -CHC*H*$_3$), 4.62 (qd, 1H, *J* = 6.7, 2.3 Hz, -C*H*CH$_3$), 6.93 –7.08 (m, 1H, Ar), 7.16 (d, 1H, *J* = 8.4 Hz, Ar), 7.20 – 7.33 (m, 3H, Ar), 7.40 (dd, 2H, *J* = 7.5, 1.7 Hz, Ar), 7.45 (dd, 1H, *J* = 7.8, 1.6 Hz, Ar), 7.55– 7.71 (m, 1H, Ar), 8.17 (d, 1H, *J* = 2.2 Hz, Ar).
^{13}C-RMN (100MHz, $CDCl_3$, 25ºC, TMS): δ 12.98 (-CHCH$_3$), 58.59 (-N*C*HCH$_3$-), 117.30, 120.22, 120.35, 125.83, 127.83, 128.48, 130.74, 131.60, 139.07 (Ar), 156.61 (Ar, quaternary), 159.79 (Ar*C*HN-), 170.66 (-CH*C*OO-).
^{11}B NMR (300 MHz, $CDCl_3$, 25°C): δ = 6.99.
ESI^{+}: 318, 302, 280, 122.
HMRS (EI): m/z calcd. [M+]= 279.1067, found [M+] = 279.1066.

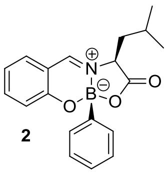
Electronic Supplementary Material (ESI) for Organic & Biomolecular Chemistry







Compound 2



2 was obtained in 50 % yield, *d.r.*100%, after 20 h at 90 ºC (0.142 g).

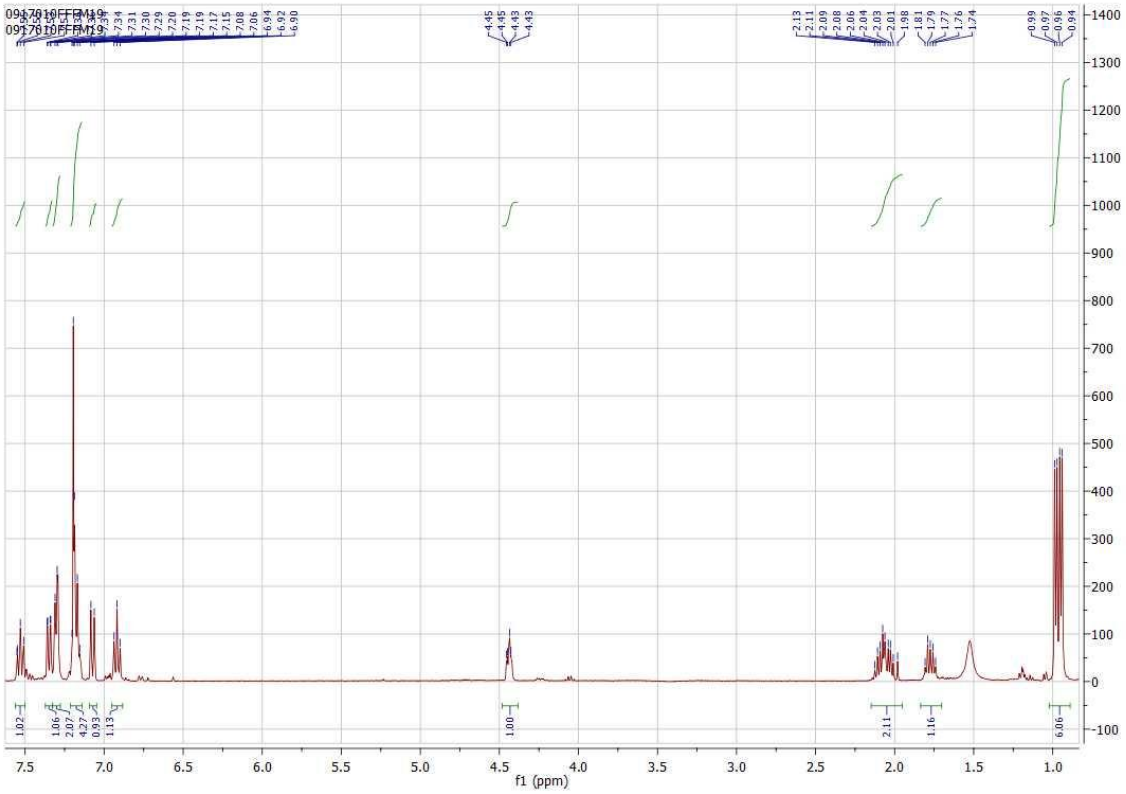
^{1}H NMR (400 MHz, $CDCl_3$, 25ºC, TMS): δ 1.05 (dd, 6H, *J* = 12.9, 6.4 Hz, $-CHCH_2CH(CH_3)_2$), 1.77–1.96 (m, 1H, $-CHCH_2CH(CH_3)_2$), 2.03– 2.27 (m, 2H, $-NCHCH_2CH(CH_3)_2$), 4.53 (td, 1H, *J* = 5.7, 2.3 Hz, $-NCHCH_2CH(CH_3)_2$),6.96 – 7.07 (m, 1H, Ar), 7.16 (d, 1H, *J* = 8.4 Hz, Ar), 7.21 - 7.35 (m, 4H, Ar), 7.39 (dd, 2H, *J* = 7.5, 1.8 Hz, Ar), 7.44 (dd, 1H, *J* = 7.8, 1.6 Hz,Ar), 7.62 (td, 1H, *J* = 8.7, 7.4, 1.7 Hz, Ar).

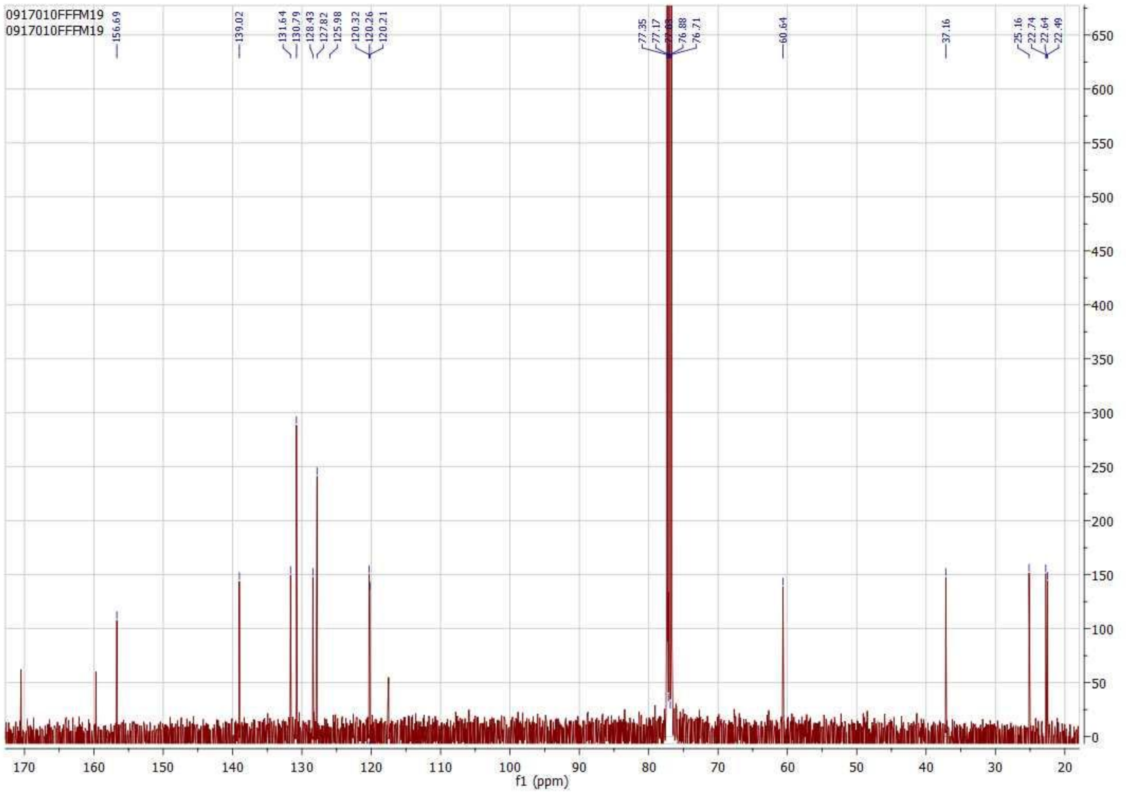
^{13}C-RMN (100MHz, $CDCl_3$, 25ºC, TMS): δ 22.50 ($-CHCH_2(CH3)_2$), 22.93 ($-CHCH_2(CH3)_2$), 25.16 ($-NCHCH_2CH-$), 37.16 ($-NCHCH_2-$), 60.64 ($-NCHCH_2$ -), 117.49, 120.21, 120.27, 125.98, 127.83, 128.43, 130.89, 131.65 (Ar), 139.02 (-NCHAr-), 156.70, 159.70 (Ar, quaternary), 170.79 (-CHCOO-).

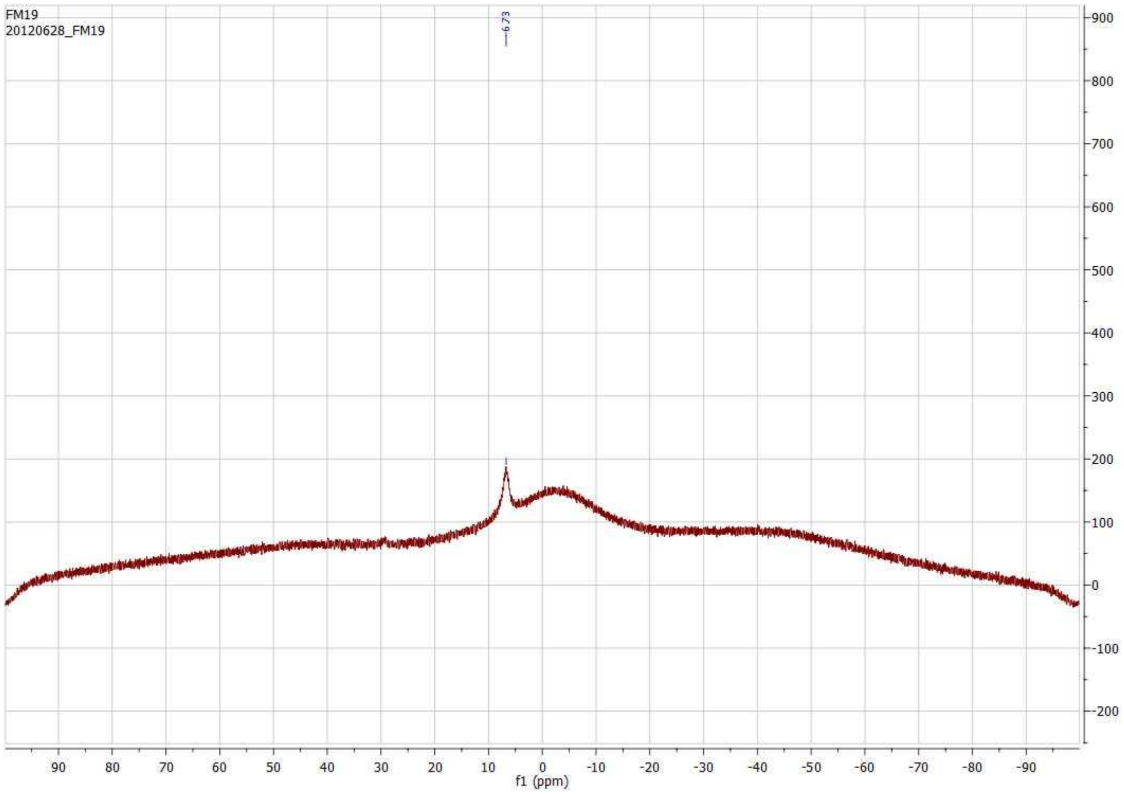
^{11}B NMR (300 MHz, $CDCl_3$, 25°C): δ = 6.73.

ESI$^+$: 360, 344, 322, 274, 236.

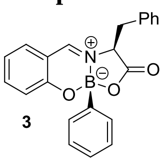
HMRS (EI): m/z calcd. [M^+]= 321.1536, found [M^+] = 321.1534.







Compound 3



3 was obtained in 86% yield, *d.r.* 100%, after 20 h at 90ºC (0.125 g).

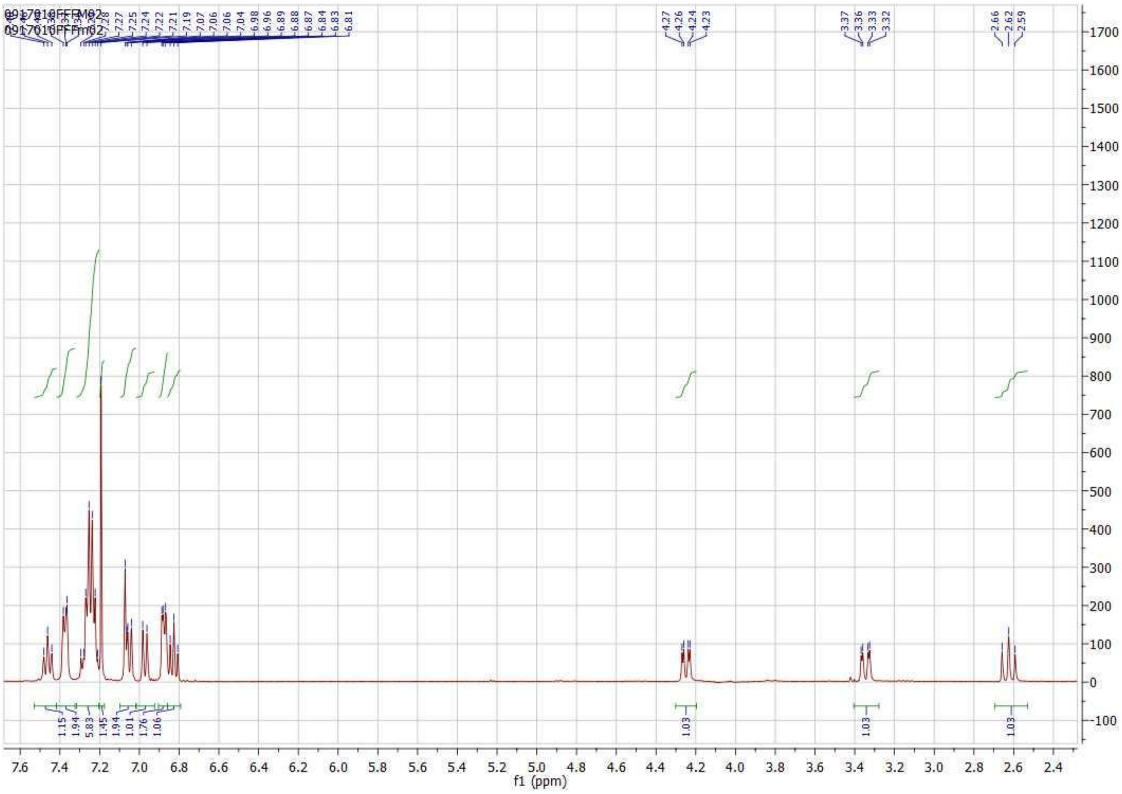
^{1}H NMR (400 MHz, CDCl3, 25ºC, TMS): δ 2.71 (t, 1H, *J* = 13.2, –CHCH_2Ph), 3.41 (dd, 1H, *J* = 3.6, 14.0, –CHCH_2Ph), 4.34 (dd, 1H, *J* = 3.6, 12.4, –NC*H*CH2Ph), 6.87–6.95 (m, 3H, Ar), 7.02–7.05 (m, 1H, Ar), 7.11– 7.16 (m, 2H, Ar), 7.27–7.34 (m, 6H, Ar), 7.43–7.55 (m, 3H, Ar).

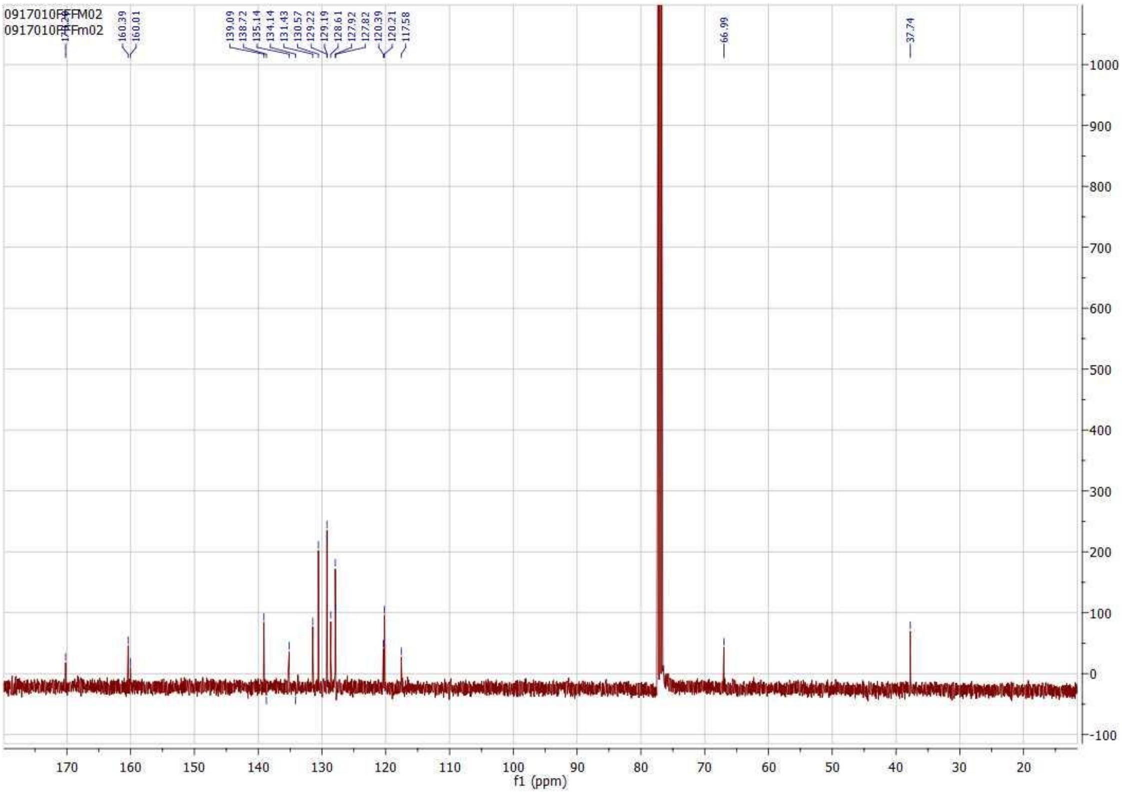
^{13}C-NMR (100 MHz, CDCl3, 25ºC, TMS): δ 37.73 (–CH*C*H_2Ph),66.92(–N*C*HCOCH_2–),117.57, 120.19,120.32,127.79,127.90,128.58, 129.16, 129.21, 130.55, 131.45, 135.11, 139.04 (Ar), 159.95 (-N*C*HAr-), 160.43(Ar, quaternary), 170.22 (–CH*C*OO–).

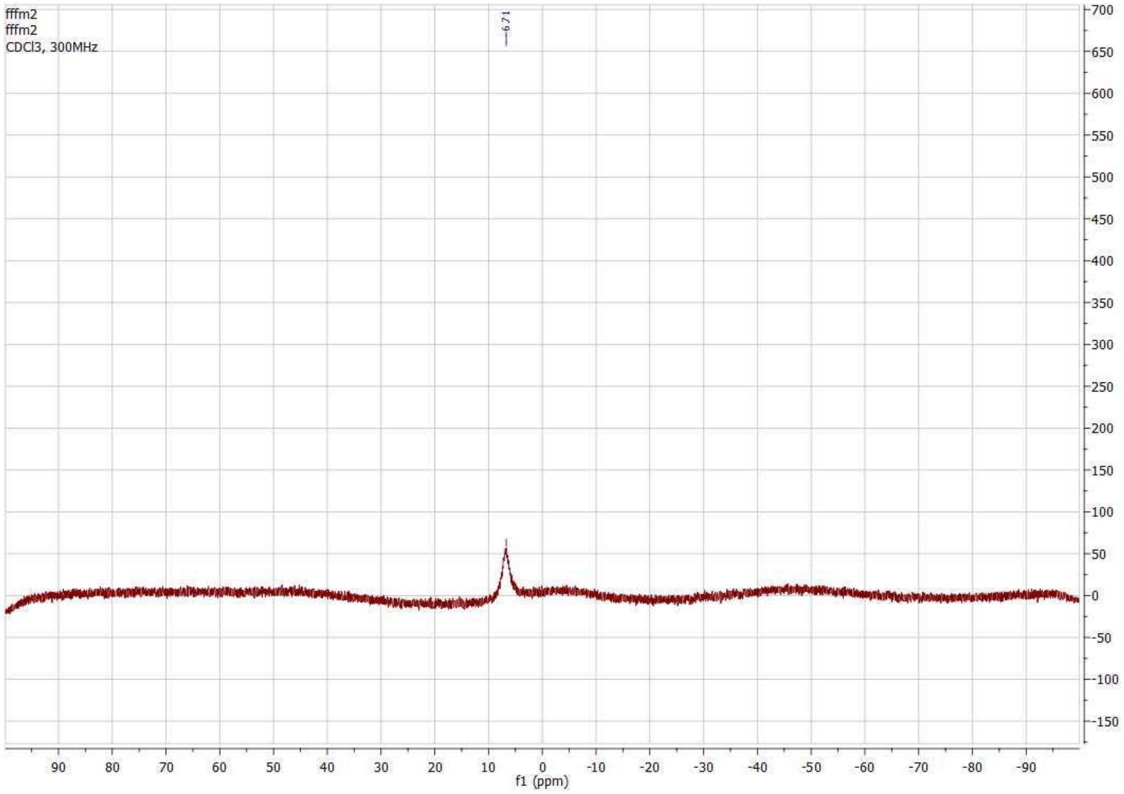
^{11}B NMR (300 MHz, $CDCl_3$, 25°C): δ = 6.71.

ESI$^+$: 394, 378,356, 270, 248.

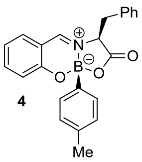
HMRS (EI): m/z calcd. [M+H$^+$] = 356.1458, found [M+H$^+$] = 356.1466.







Compound 4



4 was obtained in 83 % yield, *d.r*. 100%, after 20 h at 90 ºC (0.126 g).

^{1}H NMR (400 MHz, $CDCl_3$, 25ºC, TMS): δ 2.34 (s, 3H, -ArCH_3), 2.73 (t, 1H, *J*= 12.0, -CHCH_2Ph), 3.42 (dd, 1H, *J*= 4.0, 14.0, -CHCH_2Ph), 4.35 (dd, 1H, *J*= 4.0, 12.0, -NC*H*CH_2Ph), 6.91 (t, 1H, *J*= 8.0, Ar), 6.99-7.04 (m, 3H, Ar), 7.12-7.16 (m, 4H, Ar), 7.28-7.38 (m, 5H, Ar), 7.50-7.56 (m, 1H, Ar).

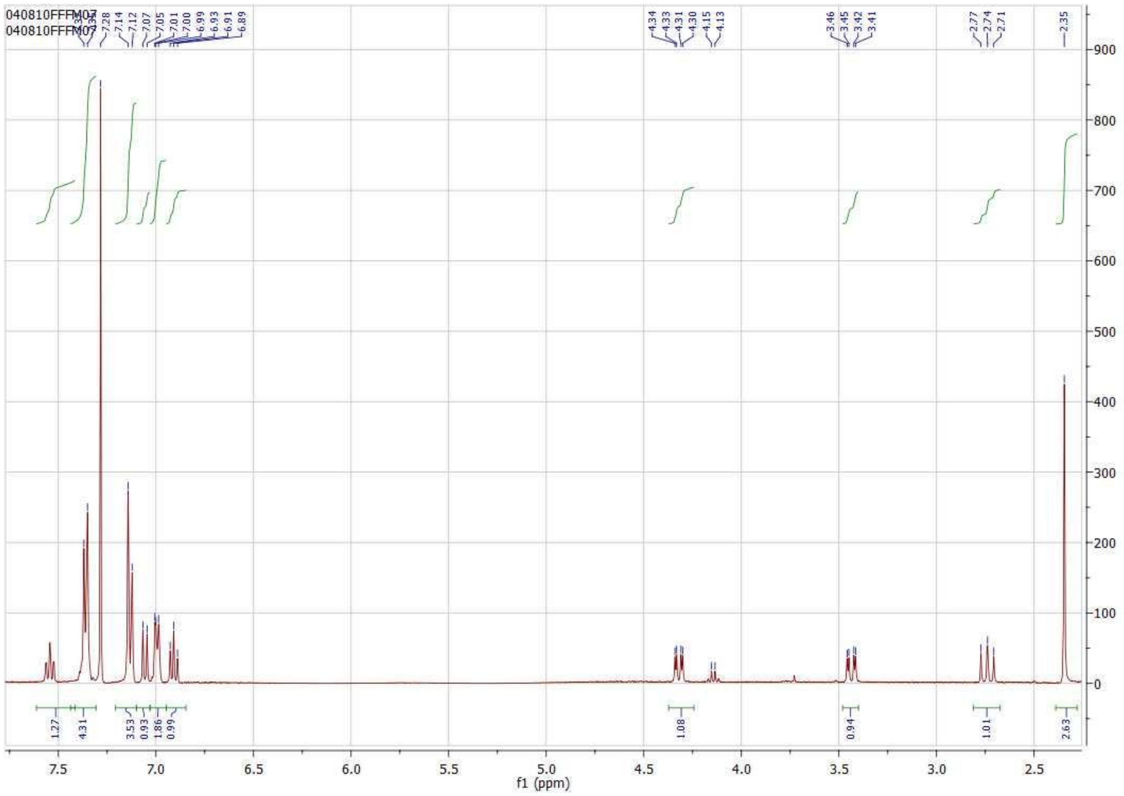
^{13}C-RMN (100MHz, $CDCl_3$, 25ºC, TMS): δ 21.44 (-ArCH_3), 37.78 (-CHCH_2Ph), 66.90 (-N*C*HCH_2Ph-), 117.62, 120.14, 120.32, 127.80, 128.67, 129.16, 129.28, 130.61, 131.46, 135.21, 138.19, 138.94 (Ar), 159.94 (Ar, quaternary), 160.35 (Ar*C*HN-), 170.35 (-CH*C*OO-).

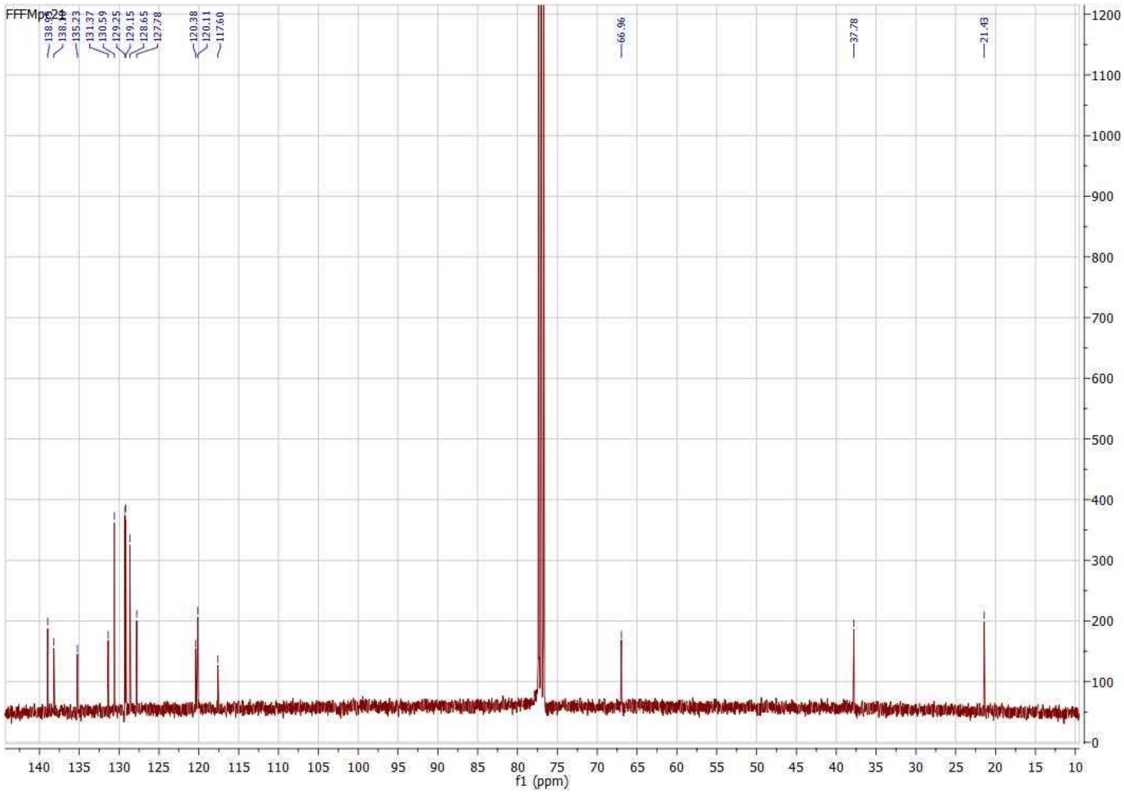
^{11}B NMR (300 MHz, $CDCl_3$, 25°C): δ = 6.97.

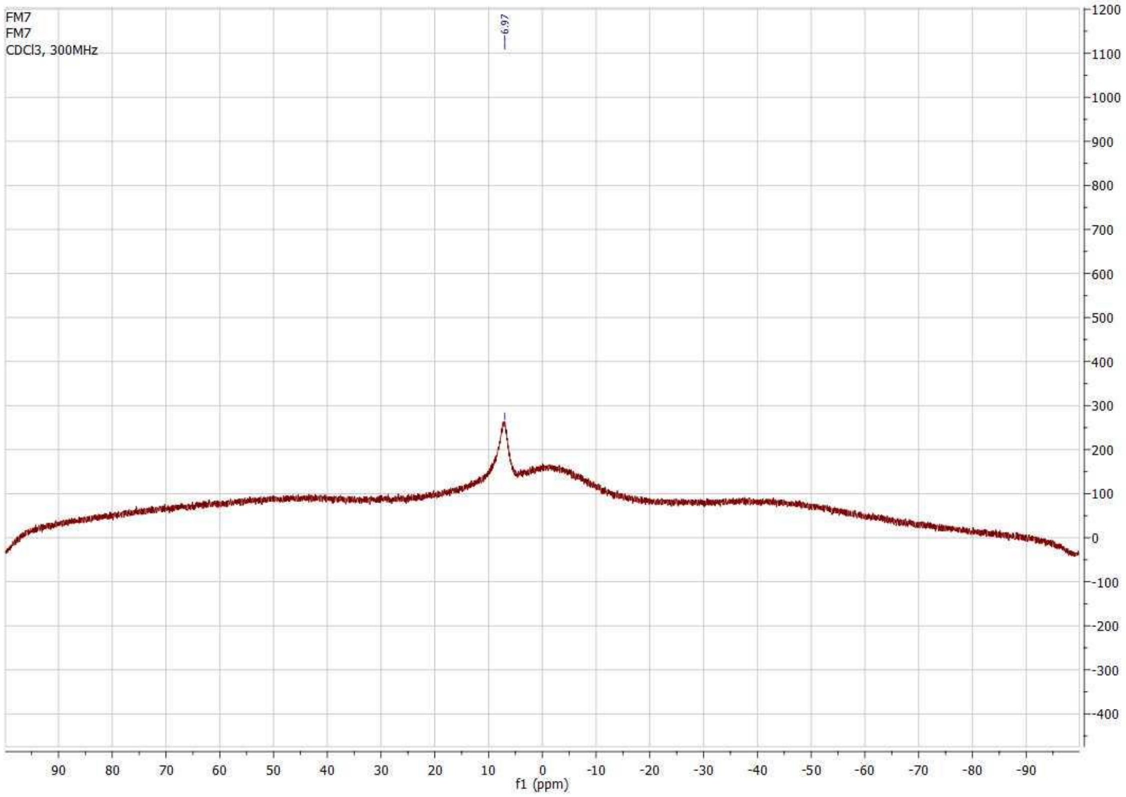
ESI^{+}: 392, 370, 300, 188.

HMRS (EI): m/z calcd. [M+H^{+}] =370.1614, found [M+H^{+}] = 370.1620.

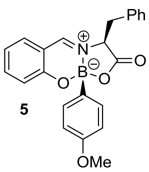
Electronic Supplementary Material (ESI) for Organic & Biomolecular Chemistry



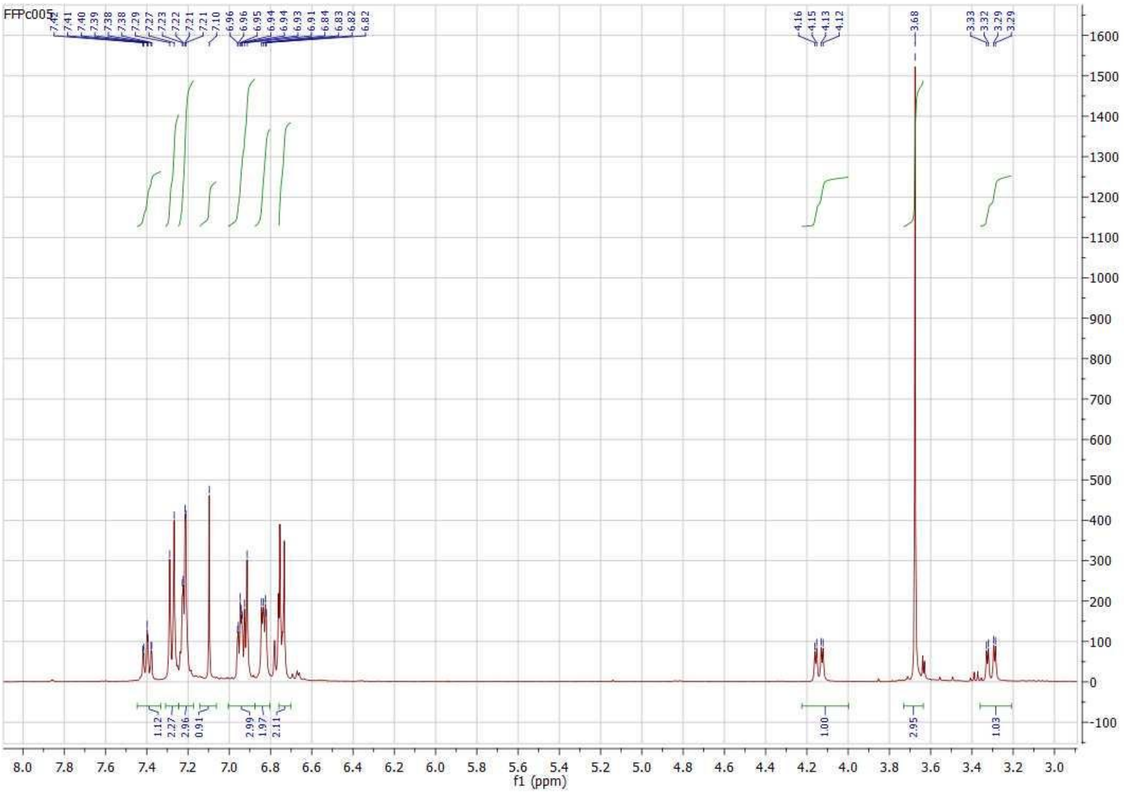


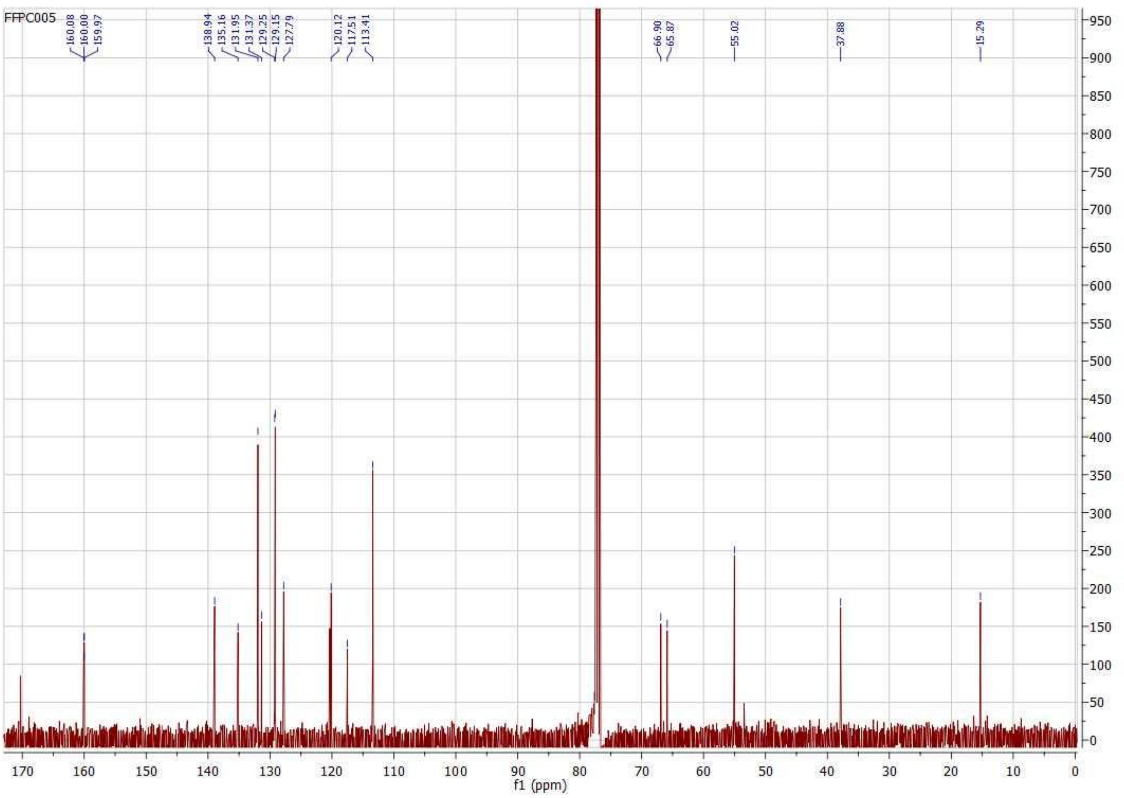


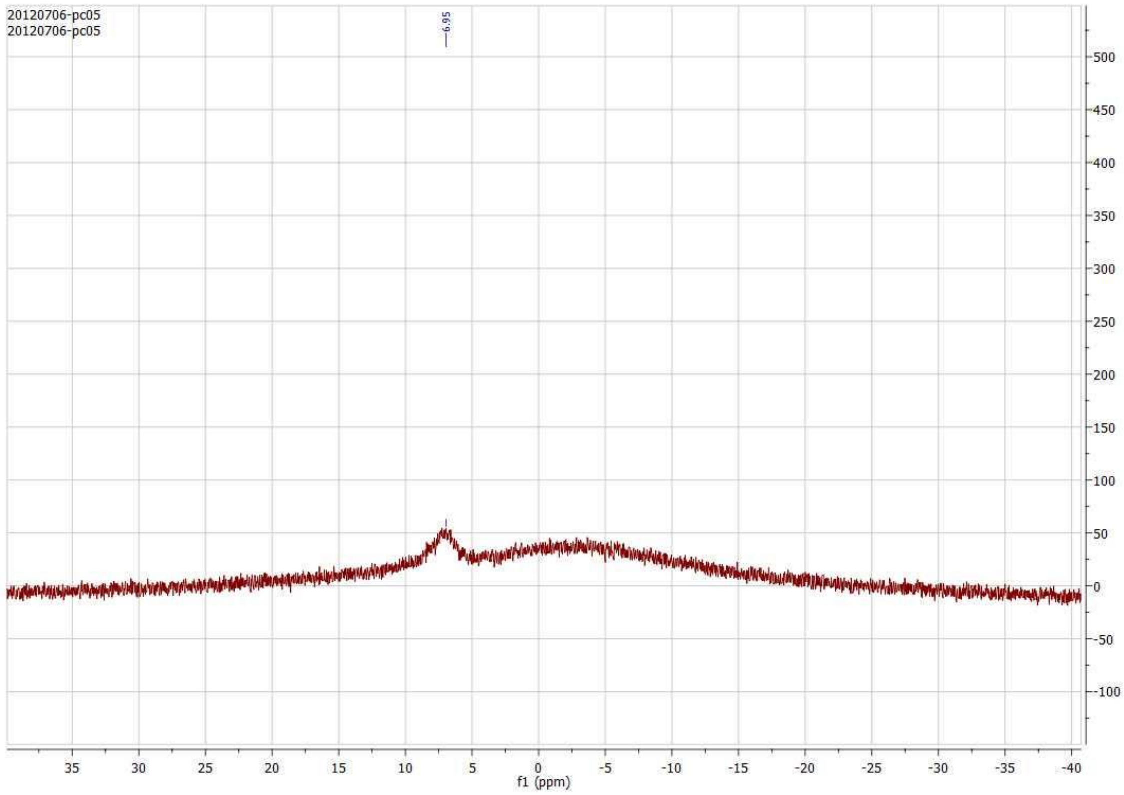
Compound 5



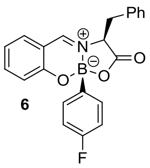
5 was obtained in 31 % yield, *d.r*. 100 %, after 20 h at 90 ºC (0.048 g).
^{1}H NMR (400 MHz, $CDCl_3$, 25ºC, TMS): δ 2.72 (t, *J*= 13.0, 1H, -CHCH_2Ph), 3.42 (dd, 1H, *J*= 3.2, 13.6, -CHCH_2Ph), 3.81 (s, 3H, -ArOCH_3), 4.34 (dd, 1H,*J*= 3.2, 12.4, -NC*H*COCH$_2$-), 6.80-7.35 (m, 14H, Ar).
^{13}C-RMN (100MHz, $CDCl_3$, 25ºC, TMS): δ 37.87 (-CH*C*H$_2$Ph), 55.04 (-ArO*C*H$_3$), 66.82 (-N*C*HCOCH$_2$-), 113.42, 117.55, 120.15, 120.27, 127.80, 129.16, 129.28, 131.48, 131.96, 135.14, 138,92 (Ar), 159.94(Ar*C*HN-), 159.98, 160.22 (Ar, quaternary), 170.42 (-CH*C*OO-).
^{11}B NMR (300 MHz, $CDCl_3$, 25°C): δ = 6.95.
ESI$^+$: 408, 386, 288, 270.
HMRS (EI): m/z calcd.[M+H$^+$] =386.1564, found [M+H$^+$] = 386.1556.



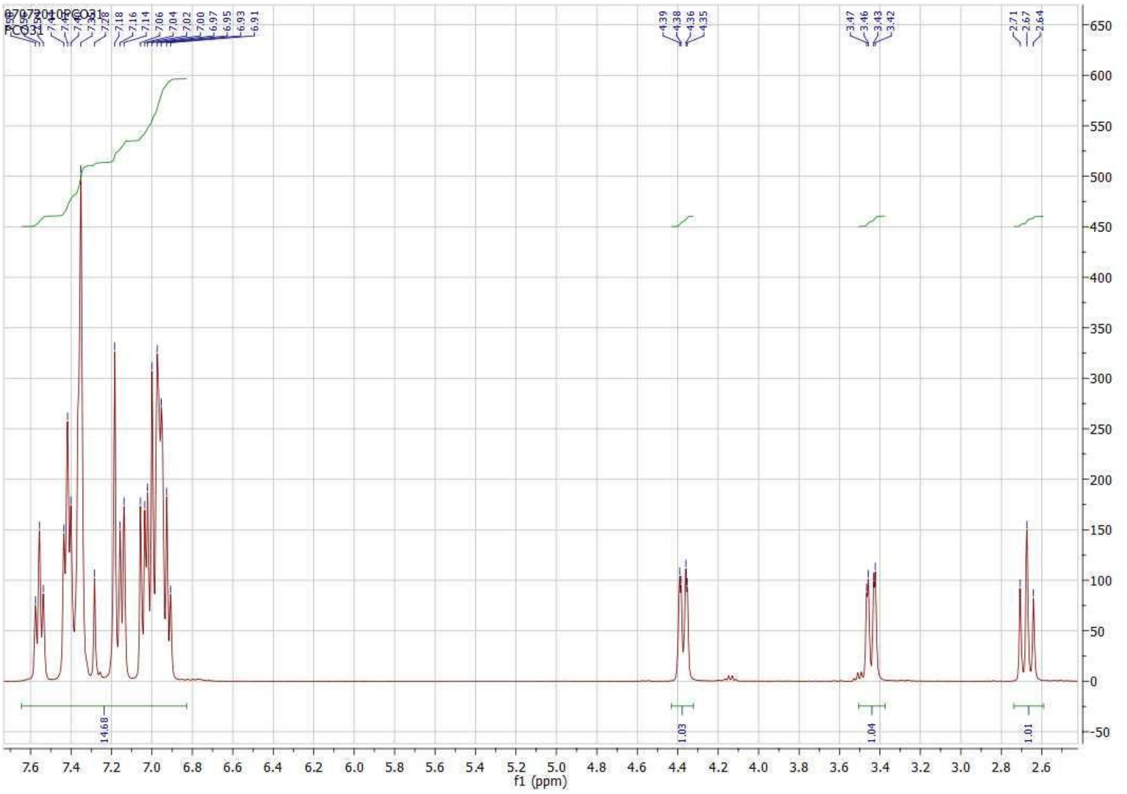


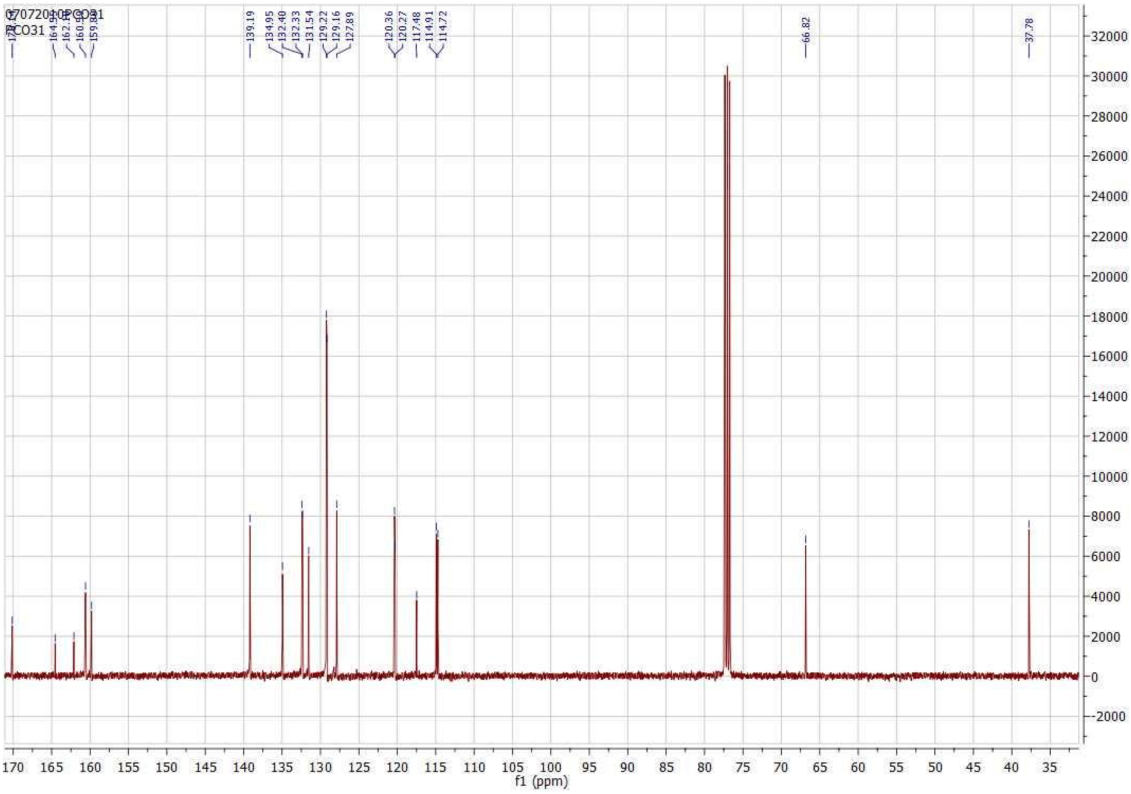


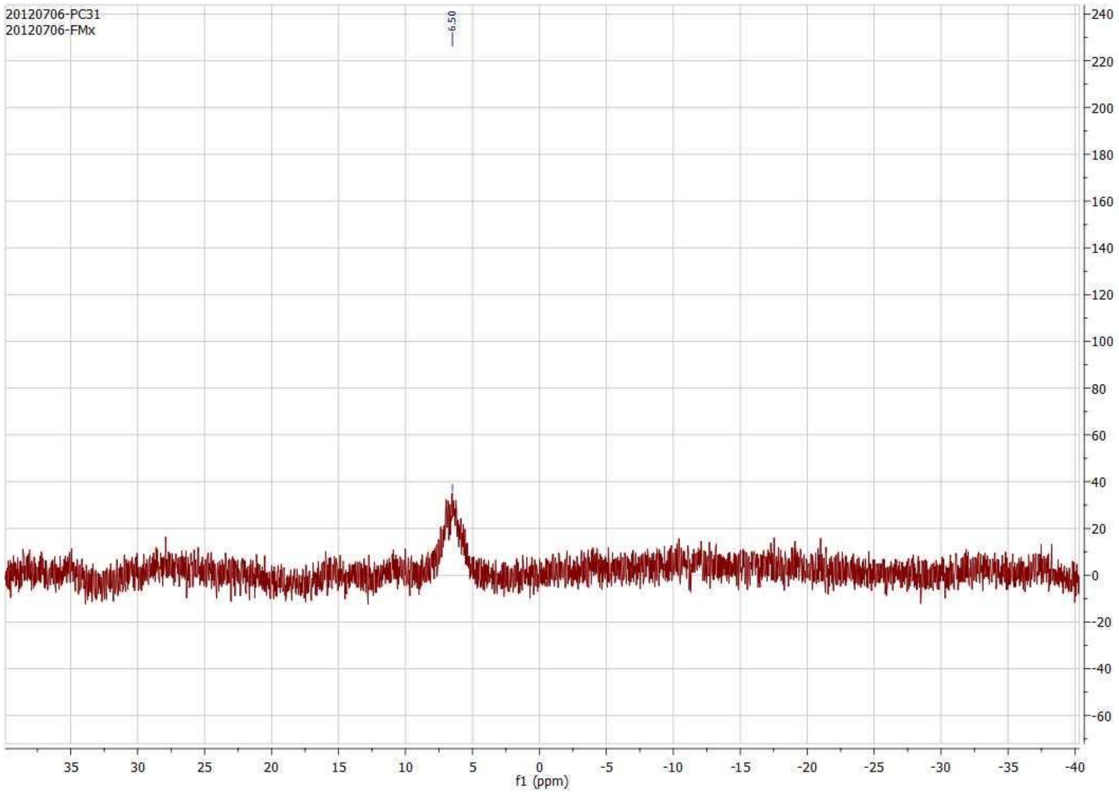
Compound 6



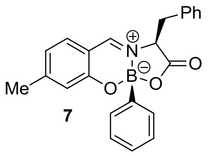
6 was obtained in 80 % yield, *d.r*. 100%, after 20 h at 90 ºC (0.122 g).
^{1}H NMR (400 MHz, $CDCl_3$, 25ºC, TMS): δ 2.68 (t, *J*= 13.2,, 1H -CHCH_2Ph), 3.45 (dd, 1H, *J*= 3.4, 13.8, -CHCH_2Ph), 4.36 (dd, 1H, *J*= 3.2, 12.4, -NC*H*CH_2Ph), 6.80-7.71 (m, 14H, Ar).
^{13}C-RMN (100MHz, $CDCl_3$, 25ºC, TMS): δ 37.79 (-CH*C*H_2Ph), 66.87 (-N*C*HCH_2-), 114.74, 114.94, 117.47, 120.32, 120.38, 127.91, 129.16, 129.24, 131.53,132.34, 132.41, 134.97, 139.23 (Ar), 159.84 (Ar, quaternary), 160.56 (Ar, quaternary), 170.13 (-H*C*OO).
^{11}B NMR (300 MHz, $CDCl_3$, 25°C): δ = 6.50.
ESI^{+}: 412, 374, 270.
HMRS (EI): m/z calcd. [M+H^{+}] = 374.1364, found [M+H^{+}] = 374.1367.


07072010PCO31
PCO31
4.39
4.38
4.36
4.35
3.47
3.46
3.43
3.42
2.71
2.67
2.64
14.68
1.03
1.04
1.01
f1 (ppm)

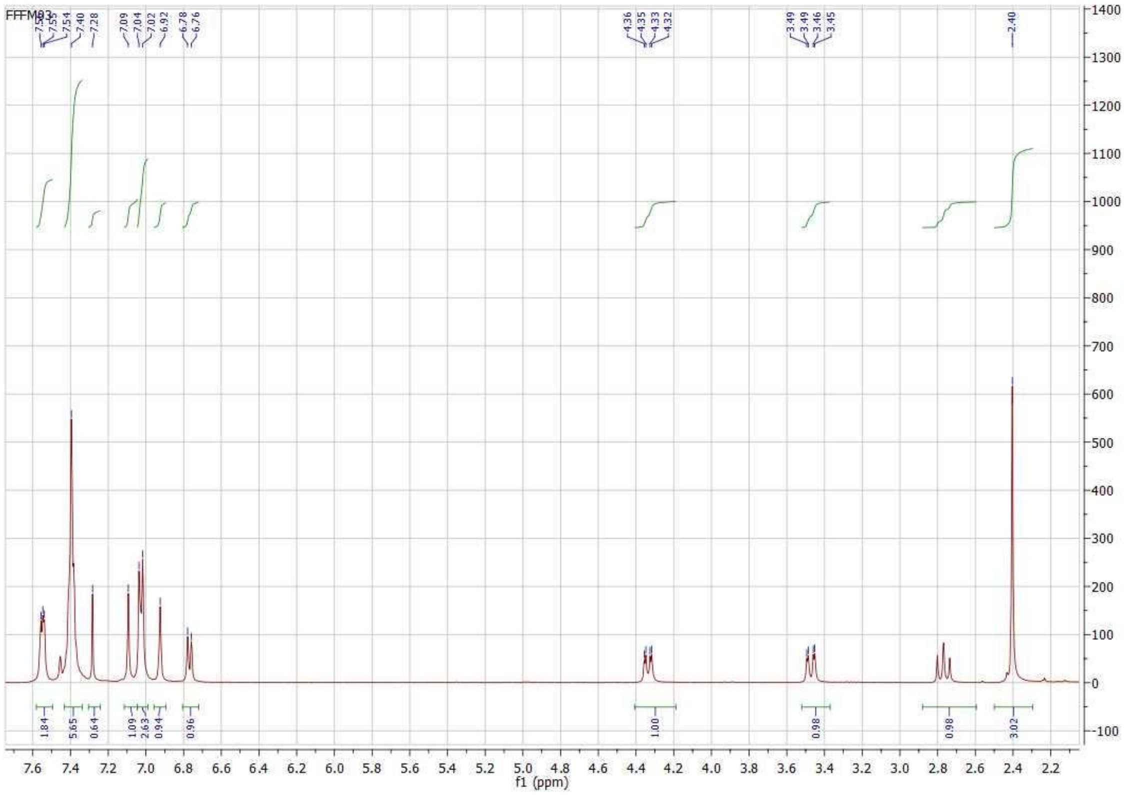

07072010PCO31
PCO31
139.19
134.95
132.40
132.33
131.54
129.22
129.16
127.89
120.36
120.27
117.48
114.91
114.72
66.82
37.78
f1 (ppm)

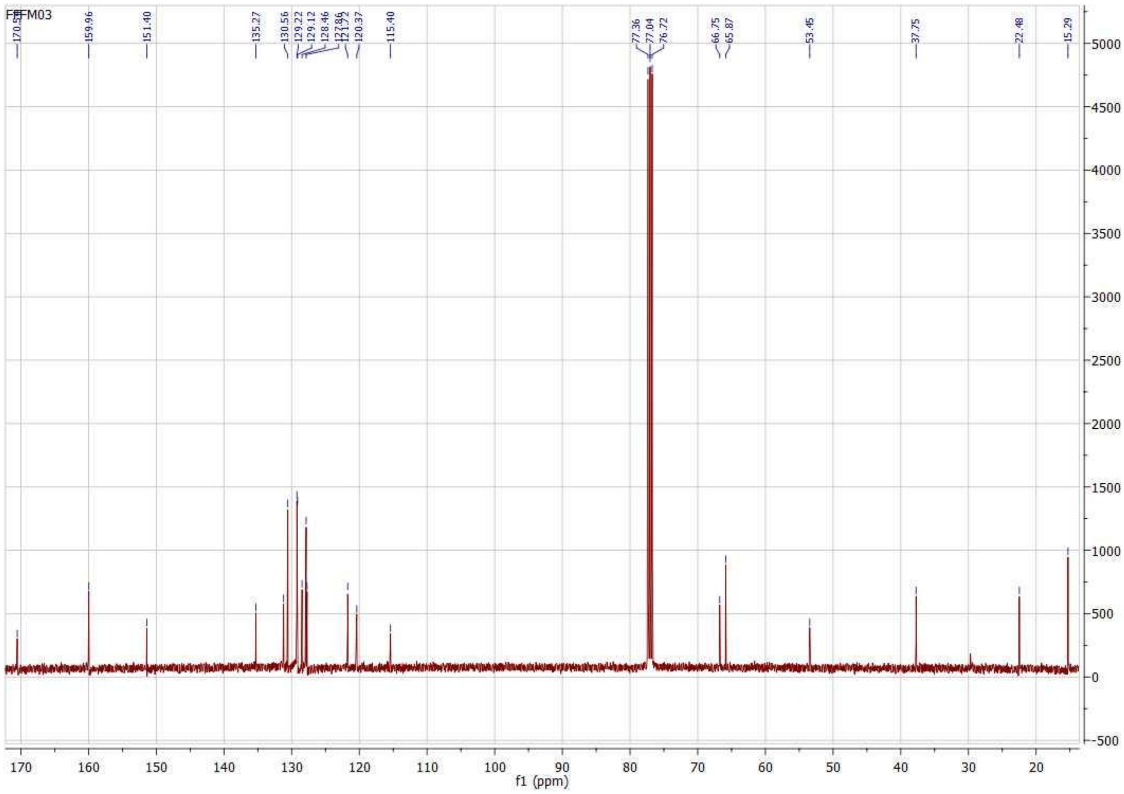


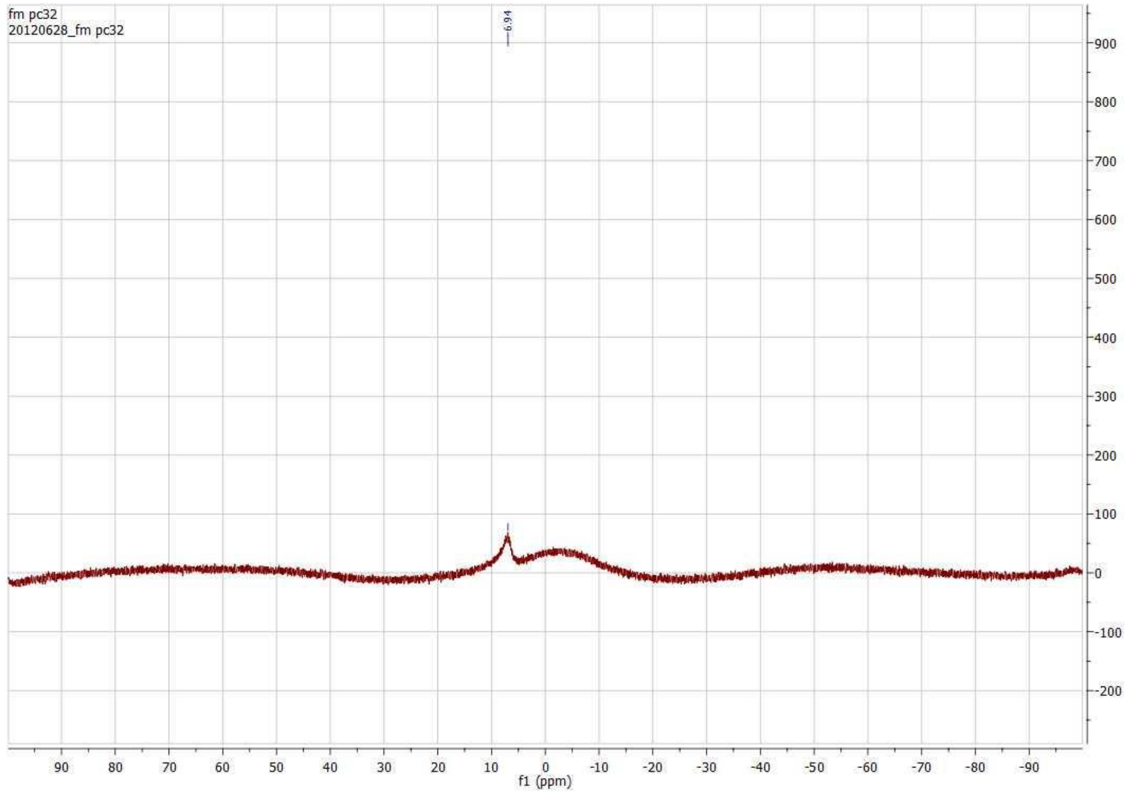
Compound 7



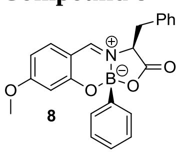
7 was obtained in 64 % yield, *d.r.* 100%, after 20 h at 90 ºC (0.095 g).
^{1}H NMR (400 MHz, $CDCl_3$, 25ºC, TMS): δ 2.35 (s, 3H, -ArC*H*$_3$), 2.70 (t, 1H, *J*= 12.0, -CHC*H*$_2$Ph), 3.41 (dd, 1H, *J*= 2.0, 14.0, -CHC*H*$_2$Ph), 4.34 (dd, 1H, *J*= 4.0, 12.0, -C*H*CH$_2$Ph), 6.73 (d, 1H, *J*= 8.0Hz, Ar), 6.85 (s, 1H, Ar), 6.97-7.03 (m, 3H, Ar), 7.12 (s, 1H, AR), 7.28-7.38 (m, 6H, Ar), 7.45-7.47 (m, 2H, Ar).
^{13}C-RMN (100MHz, $CDCl_3$, 25ºC, TMS): δ 22.50 (-Ar*C*H$_3$), 37.75(-CH*C*H$_2$Ph), 66.75 (-N*C*HCOCH$_2$-), 115.41, 120.38, 121.74, 127.74, 127.88, 128.48, 129.14, 129.24, 130.58, 131.23, 135.28 (Ar), 151.41 (Ar, quaternary), 159.95 (Ar, quaternary), 159.99 (Ar*C*HN-), 170.58 (-CH*C*OO-).
^{11}B NMR (300 MHz, $CDCl_3$, 25°C): δ = 6.94.
ESI$^+$: 408, 392, 370, 284.
HMRS (EI): m/z calcd. [M+H$^+$] = 370.1614, found [M+H$^+$] = 370.1615.


FFFM03
f1 (ppm)


FFFM03
f1 (ppm)



Compound 8



8 was obtained in 87 % yield, *d.r*. 100%, after 20 h at 90 ºC (0.133 g).

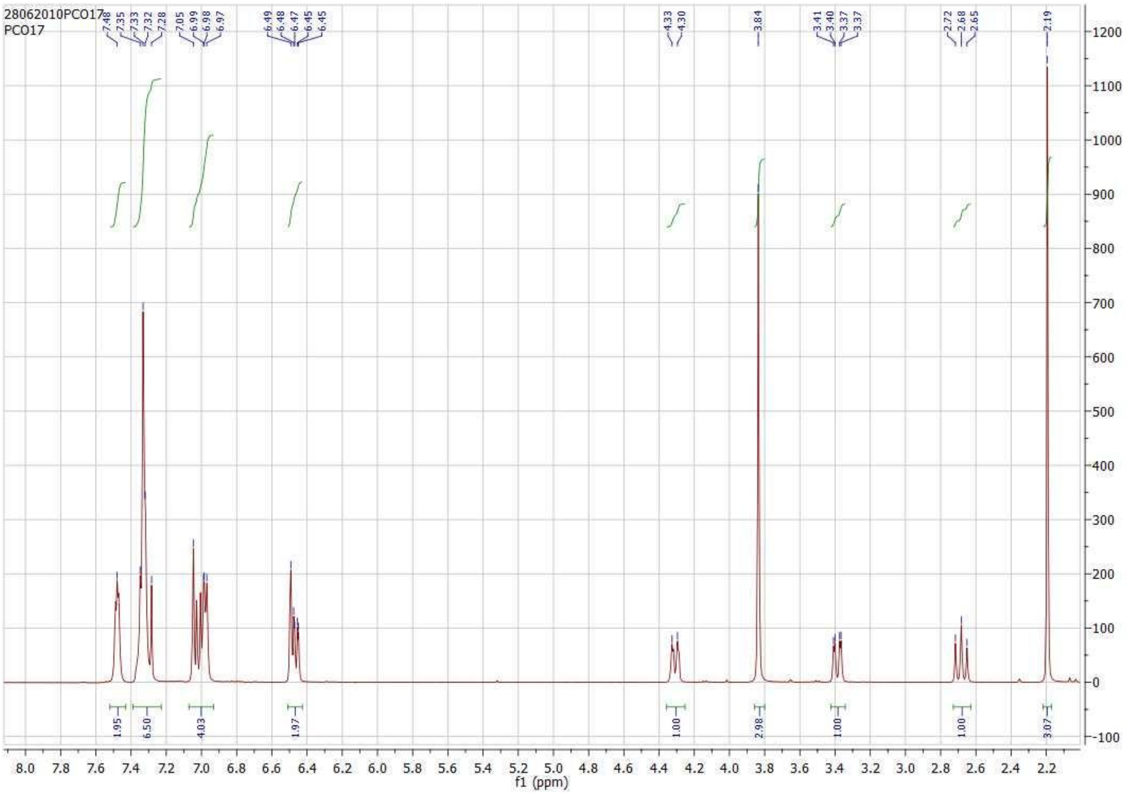
^{1}H NMR (400 MHz, $CDCl_3$, 25ºC, TMS): δ 2.69 (t, 1H, *J*= 13.0, -CHC*H*$_2$Ph), 3.39 (dd, 1H, *J*= 3.6, 14.0, -CHC*H*$_2$Ph), 3.84 (s, 3H, -ArOC*H*$_3$), 4.31 (dd, 1H, *J*= 3.2, 12.4, -NC*H*CH$_2$Ph-), 6.45-6.50 (m, 2H, Ar), 6.97-7.09 (m, 4H, Ar), 7.28-7.48 (m, 6H, Ar), 7.49-7.50 (m, 2H, Ar).

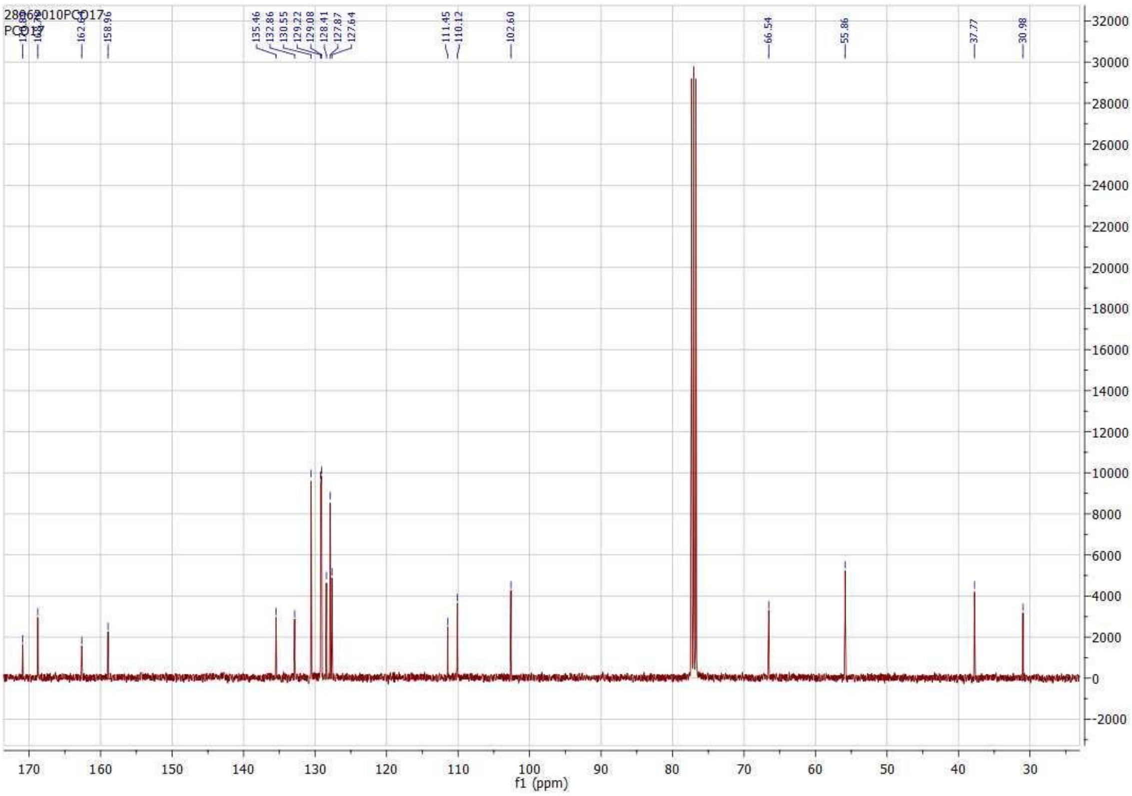
^{13}C-RMN (100MHz, $CDCl_3$, 25ºC, TMS): δ 37.78 (-CH*C*H$_2$Ph), 55.87 (-ArO*C*H$_3$), 66.54 (-N*C*HCOCH$_2$-), 102.62, 110.12, 111.47, 127.65, 127.88, 128.42, 129.10, 129.24, 130.57, 132.88, 135.47 (Ar), 158.98 (Ar*C*HN-), 162.65 (Ar, quaternary), 168.80 (Ar, quaternary), 170.91 (-CH*C*OO-).

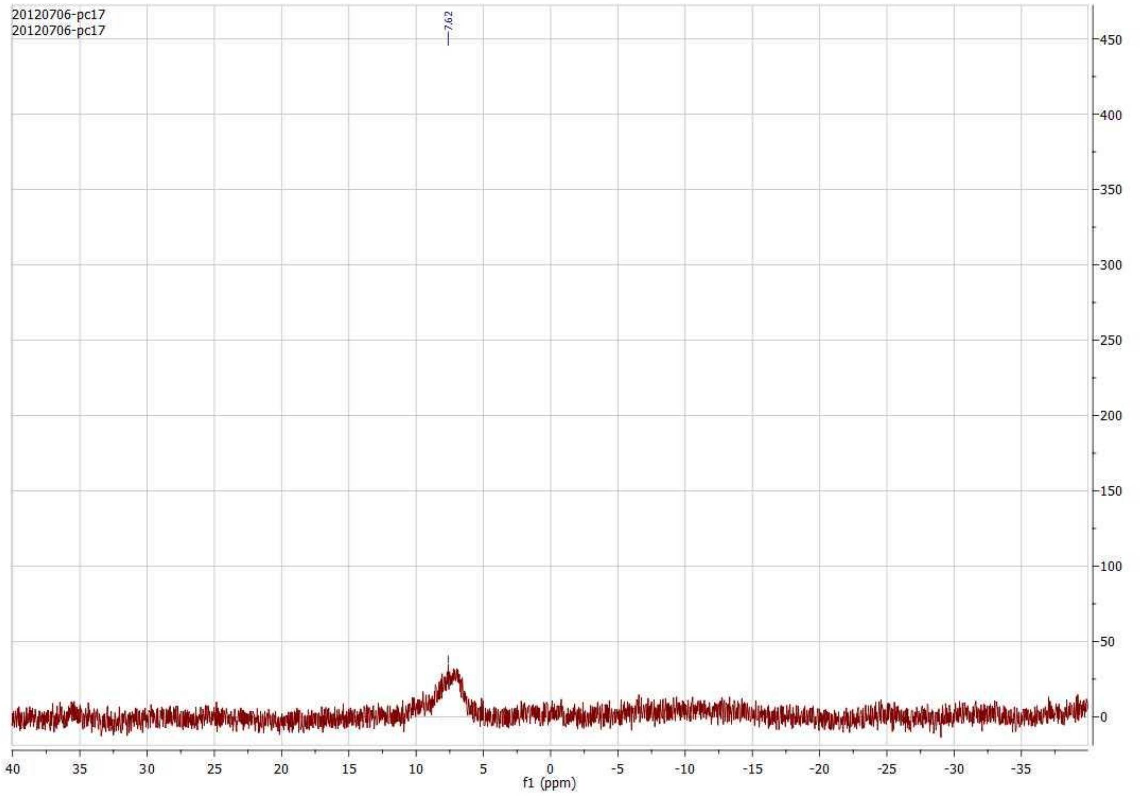
^{11}B NMR (300 MHz, $CDCl_3$, 25°C): δ = 7.62.

ESI^{+}: 424, 408, 386, 300.

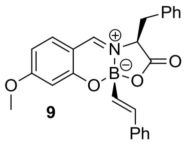
HMRS (EI): m/z calcd. [M+H^{+}] =386.1564, found [M+H^{+}] = 386.1571.


28062010PCO17
PCO17
7.48
7.35
7.33
7.32
7.28
7.05
6.99
6.98
6.97
6.49
6.48
6.47
6.45
6.45
4.33
4.30
3.84
3.41
3.40
3.37
3.37
2.72
2.68
2.65
2.19
1.95
6.50
4.03
1.97
1.00
2.98
1.00
1.00
3.07
f1 (ppm)

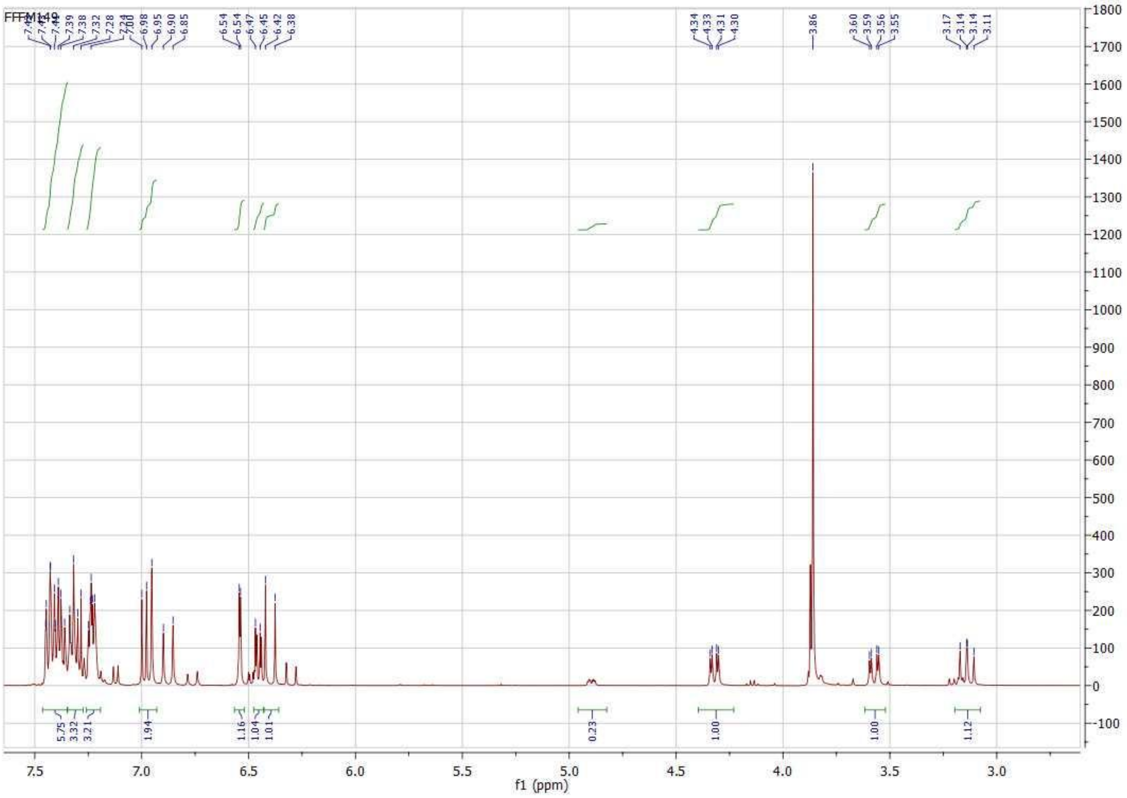

28062010PCO17
PCO17
162.40
158.96
135.46
132.86
130.55
129.22
129.08
128.41
127.87
127.64
111.45
110.12
102.60
66.54
55.86
37.77
30.98
f1 (ppm)

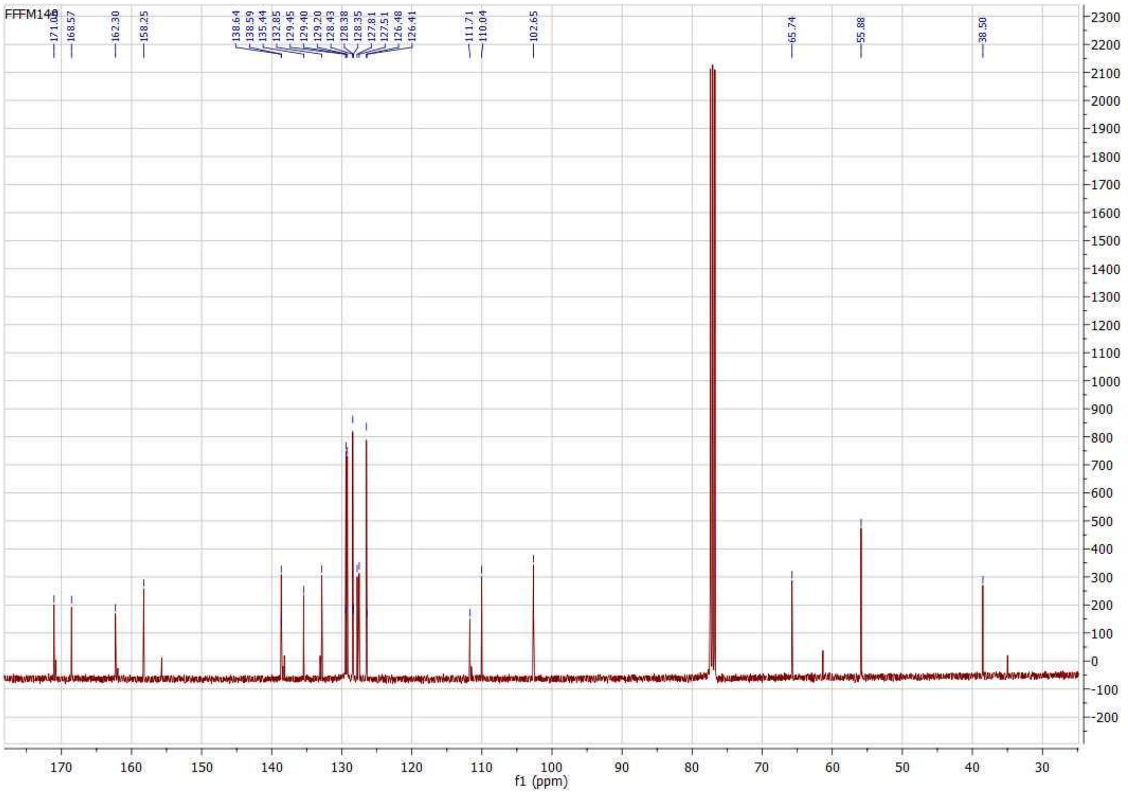


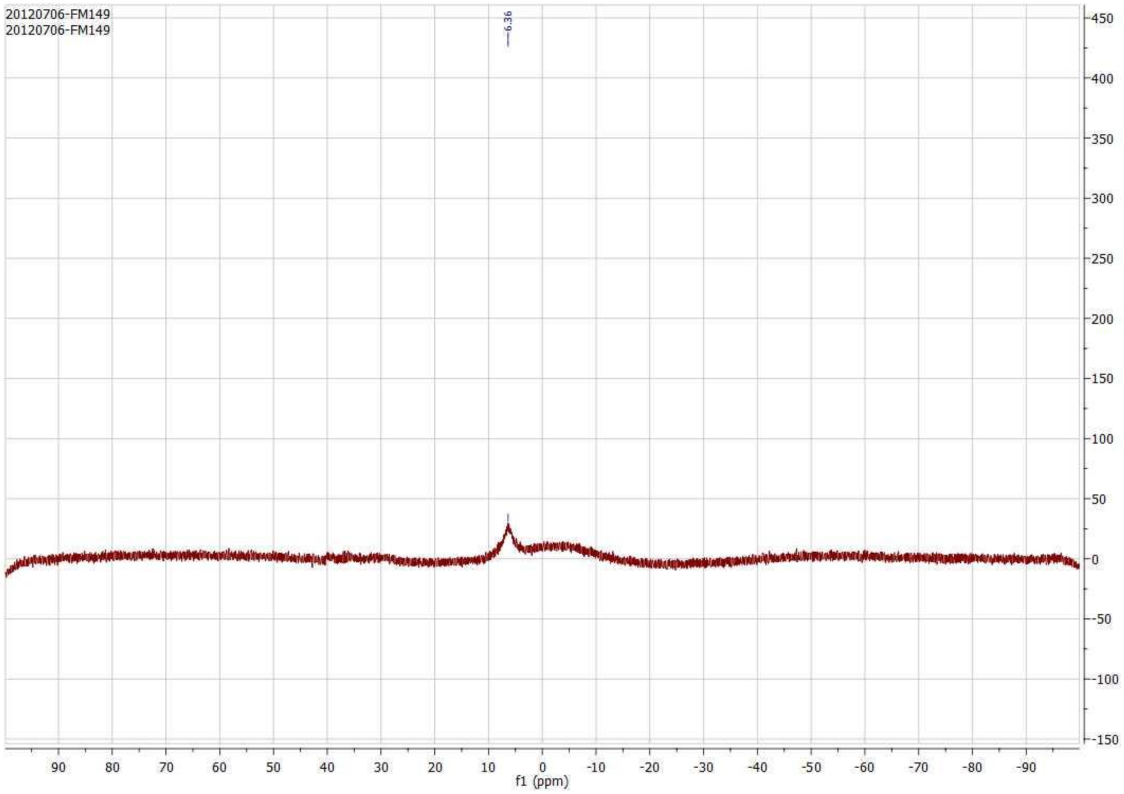
Compound 9



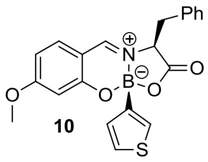
9 was obtained in 66 % yield, *d.r*. 81%, after 20 h at 90 ºC (0.111 g).
^{1}H NMR (400 MHz, $CDCl_3$, 25ºC, TMS): δ3.08 – 3.18 (m, 1H, -NC*H*CH_2Ph-), 3.55 (dt, 1H, *J*= 8.6, 4.3 Hz, -CHCH_2Ph), 3.85 (s, 3H, -OCH_3), 4.34 (dd, 1H, *J*= 11.9, 3.7 Hz, -CHCH_2Ph), 7.46 – 6.71 (m, 16H, Ar).
^{13}C-RMN (100MHz, $CDCl_3$, 25ºC, TMS): δ 38.8 (-CH*C*H_2Ph), 56.2 (-O*C*H_3), 66.0 (-N*C*HCOCH_2-), 103.0, 110.3, 112.0, 126.8, 127.8, 128.1, 128.7, 129.5, 129.7, 133.2, 135.7, 138.9, 158.6 (Ar, quaternary), 162.8 (Ar, quaternary), 168.9 (Ar, quaternary), 171.4 (-CH*C*OO-).
^{11}B NMR (300 MHz, $CDCl_3$, 25°C): δ = 6.36.
ESI^{+}: 300, 188, 166, 120.
HMRS (EI): m/z calcd. [M^{+}] = 411.1642, found [M^{+}] = 411.1638.



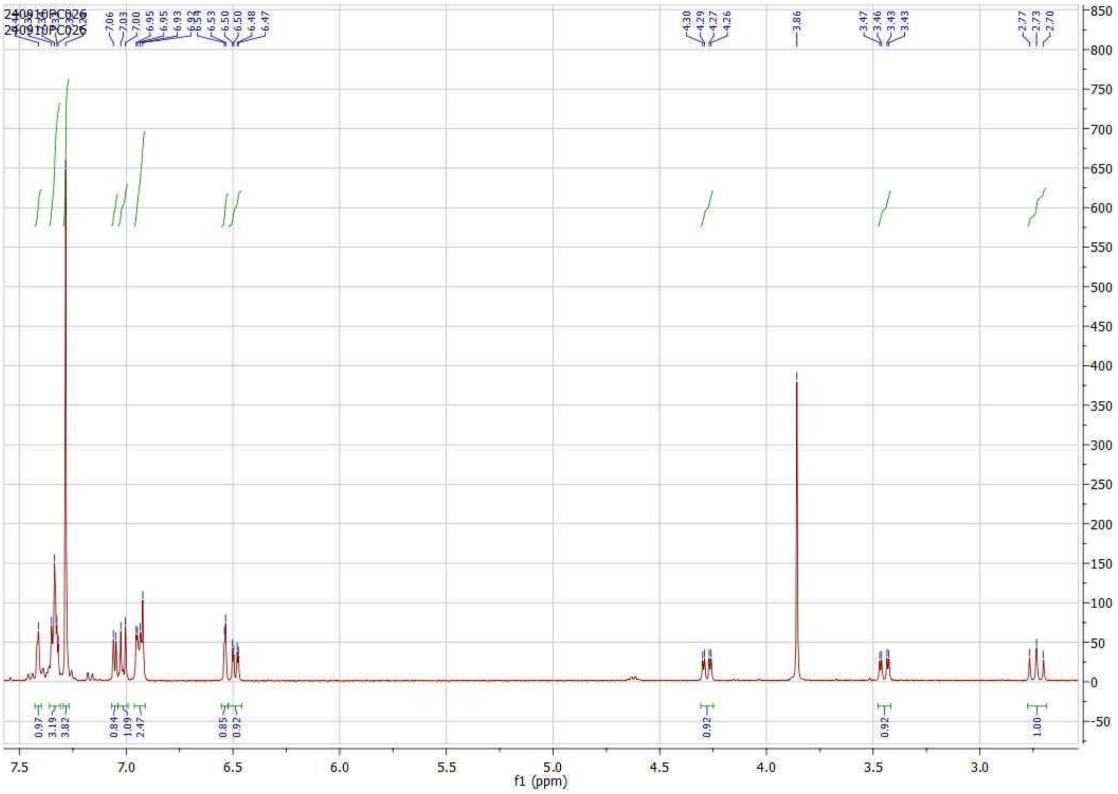


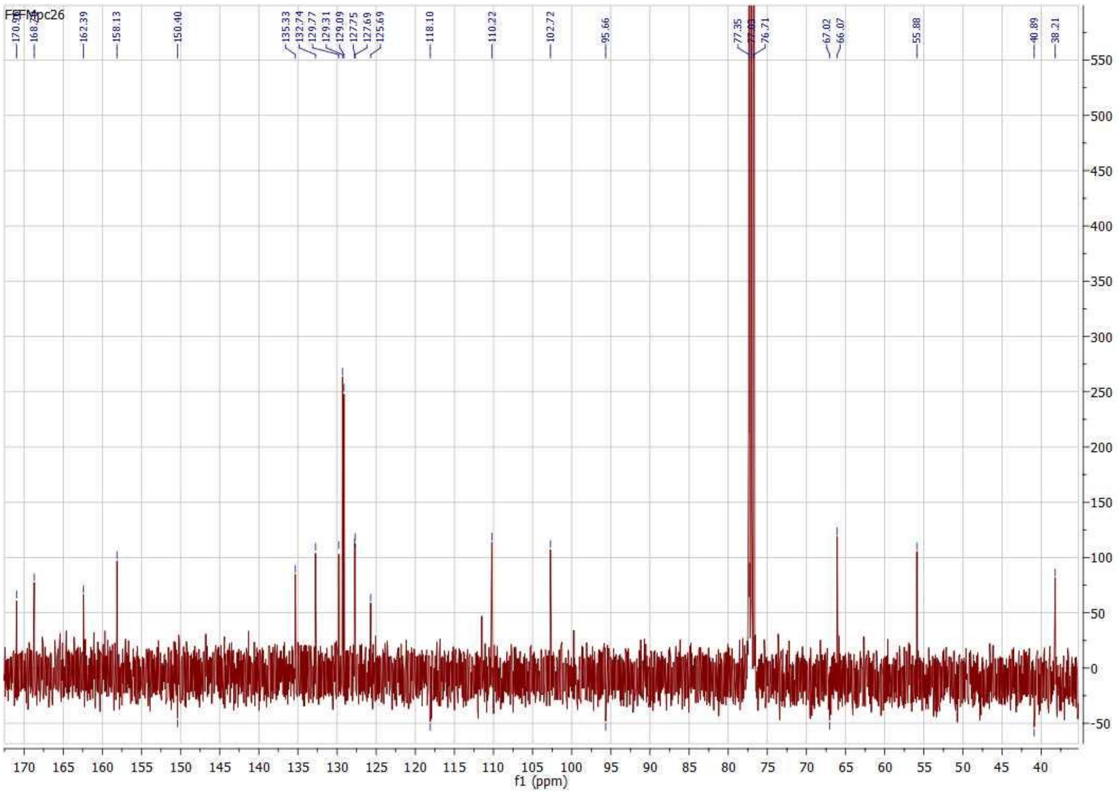


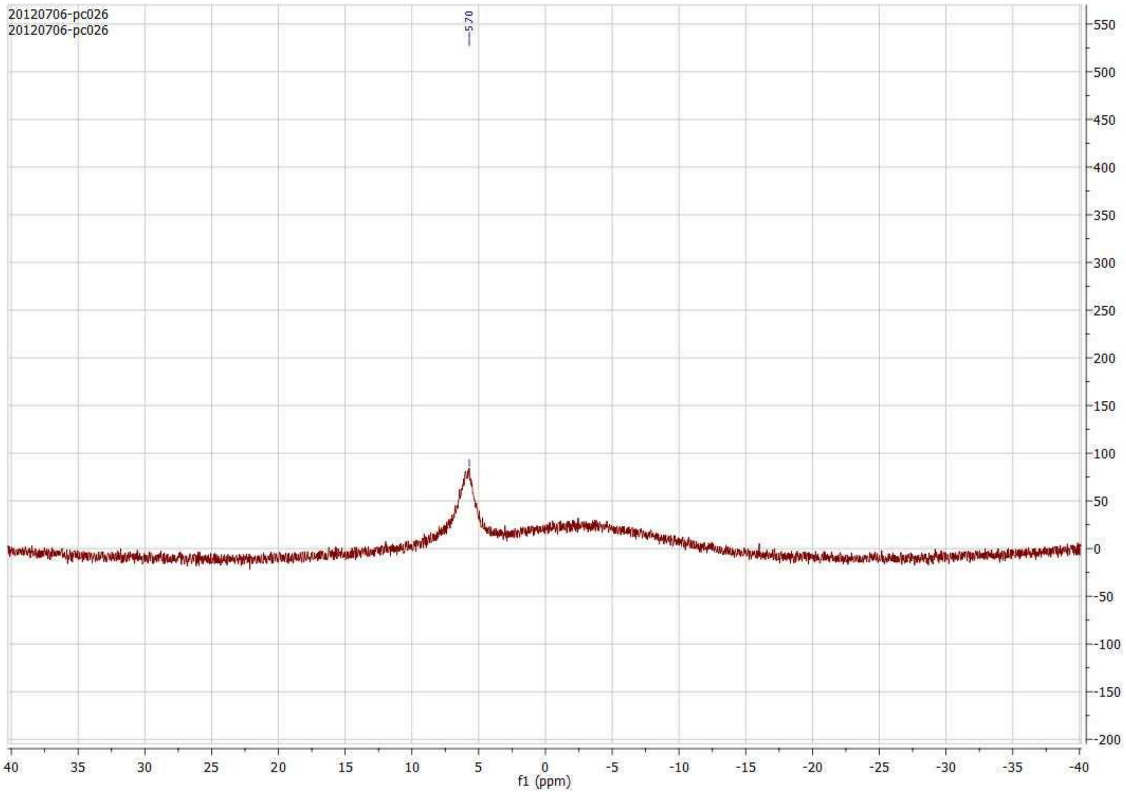
Compound 10



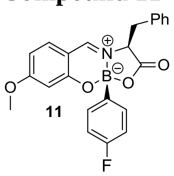
10 was obtained in 78 % yield, *d.r.* 100 %, after 20 h at 90 ºC (0.125 g).
^{1}H NMR (400 MHz, $CDCl_3$, 25ºC, TMS): δ 2.73 (t, 1H, *J*= 13.0, -CHC*H*$_2$Ph), 3.44 (dd, 1H. *J*= 3.6, 14.0, -CHC*H*$_2$Ph), 3.85 (s, 3H, -ArOC*H*$_3$), 4.31 (dd, 1H, *J*= 3.4, 12.2, -NC*H*CH$_2$Ph.), 6.47-6.52 (m, 2H, Ar), 6.95-7.04 (m, 5H, Ar), 7.28-7.40 (m, 5H, Ar).
^{13}C-RMN (100MHz, $CDCl_3$, 25ºC, TMS): δ 38.22 (-CH*C*H$_2$Ph), 55.89 (-ArO*C*H$_3$), 66.02 (-N*C*HCOCH$_2$-), 102.72, 110.19, 111.50, 125.71, 127.70, 127.75, 129.11, 129.34, 129.80, 132.82, 135.32 (Ar), 158.24 (Ar*C*HN-), 162.34 (Ar, quaternary), 168.70 (Ar, quaternary), 171.05 (-CH*C*OO-).
^{11}B NMR (300 MHz, $CDCl_3$, 25°C): δ = 5.70.
ESI$^+$: 430, 392, 338, 300.
HMRS (EI): m/z calcd. [M+H$^+$] = 392.1128, found [M+H$^+$] = 392.1138.







Compound 11



11 was obtained in 50 % yield, *d.r*. 92 %, after 20 h at 90 ºC (0.08 g).

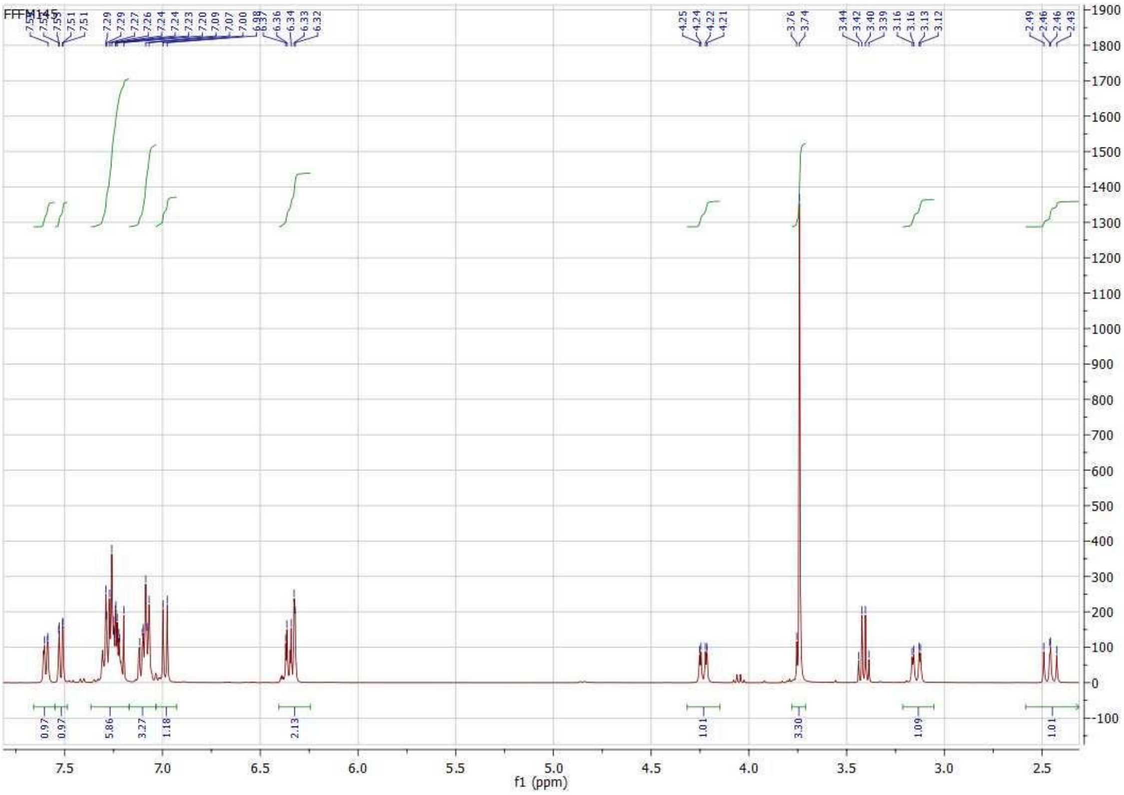
^{1}H NMR (400 MHz, $CDCl_3$, 25ºC, TMS): δ 2.54 (dd, 1H, *J*= 14.1, 12.3 Hz, -NC*H*CH_2Ph), 3.23 (dd, 1H, *J* = 14.2, 3.0 Hz, -CHC*H*$_2$Ph), 3.83 (s, 3H, -OC*H*$_3$), 4.32 (dd, 1H, *J* = 12.2, 3.1 Hz, -CHC*H*$_2$Ph), 6.39 – 6.46 (m, 2H, Ar), 6.99 (d, 1H, *J* = 8.7 Hz, Ar), 7.03 – 7.17 (m, 2H, Ar), 7.07-7.39 (m, 5H, Ar), 7.61 (dd, 1H, *J* = 7.9, 0.9 Hz, Ar), 7.68 (dd, 1H, *J* = 7.5, 1.7 Hz, Ar).

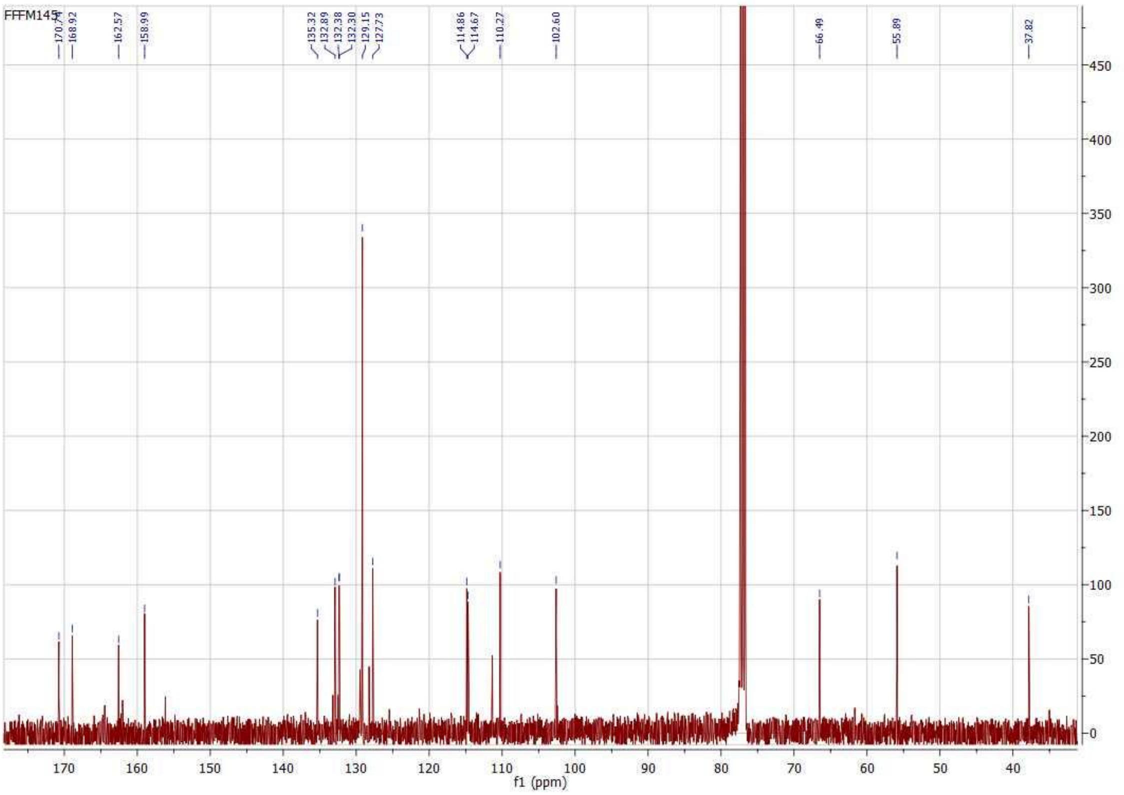
^{13}C-RMN (100MHz, $CDCl_3$, 25ºC, TMS): δ 37.82 (-CH*C*H_2Ph), 55.89 (-O*C*H_3), 66.49 (-N*C*HCOCH_2-), 102.60, 110.27, 114.76, 127.73, 127.63, 129.15, 129.5, 132.34, 132.25, 132.89, 135.32, 158.99 (Ar), 162.57 (-CH*C*OO-).

^{11}B NMR (300 MHz, $CDCl_3$, 25°C): δ = 6.48.

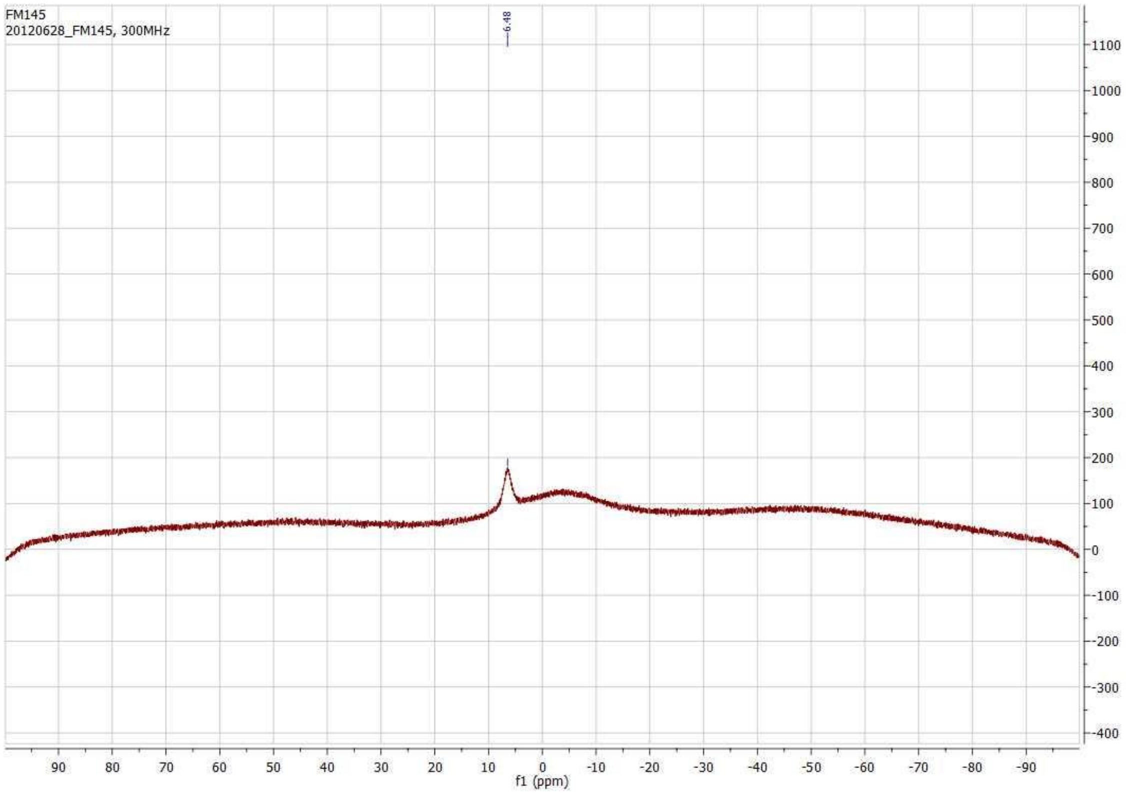
ESI^{+}: 442, 426, 360, 300.

HMRS (EI): m/z calcd.[M+H^{+}] = 404.1464, found [M+H^{+}] 404.1455.

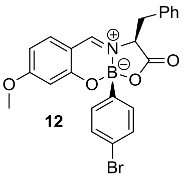

FFFM145
0.97
0.97
5.86
3.27
1.18
2.13
1.01
3.30
1.09
1.01
f1 (ppm)


FFFM145
168.92
162.57
158.99
135.32
132.89
132.38
132.30
129.15
127.73
114.86
114.67
110.27
102.60
66.49
55.89
37.82
f1 (ppm)

Electronic Supplementary Material (ESI) for Organic & Biomolecular Chemistry



Compound 12



12 was obtained in 66 %yield, *d.r*. 88%, after 20 h at 90 ºC (0.12 g).

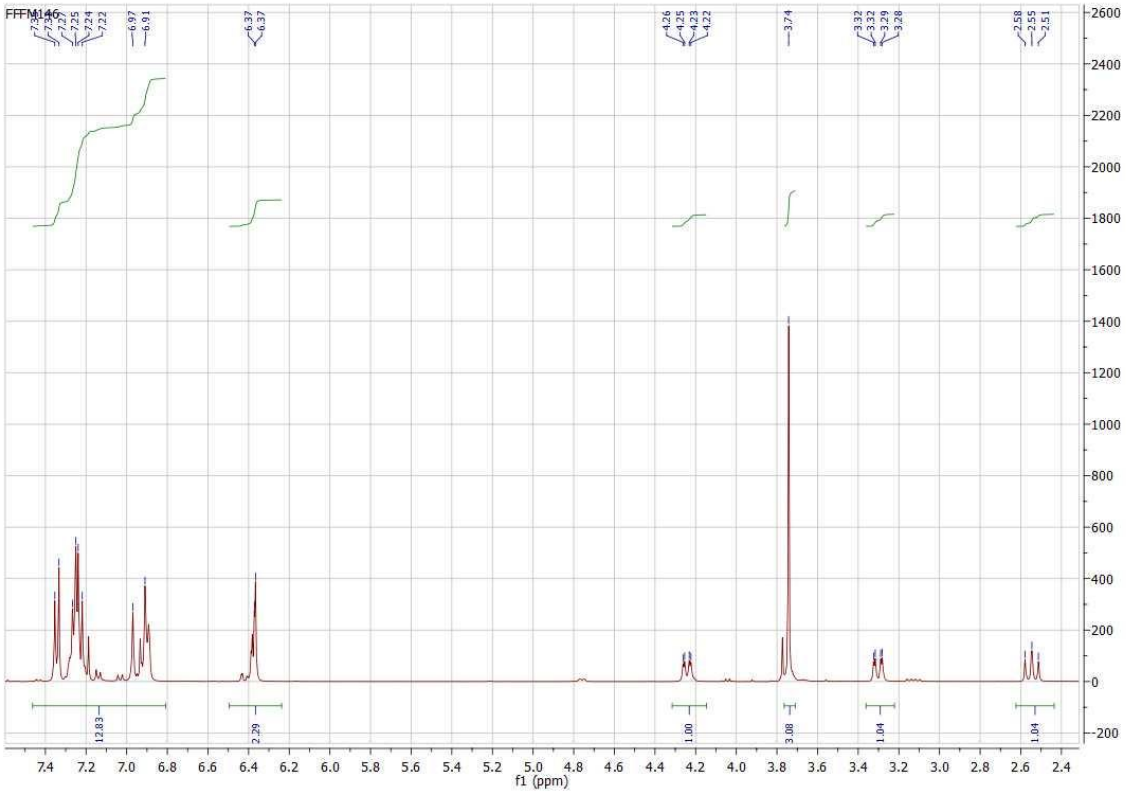
^{1}H NMR (400 MHz, $CDCl_3$, 25ºC, TMS): δ 2.59–2.69 (m, 1H, -NC*H*CH_2Ph-), 3.40 (dd, 1H, *J*= 13.8, 3.2 Hz, -NCHCH_2Ph), 3.84 (s, 3H, -OCH_3), 4.34 (dd, 1H, *J*= 12.3, 3.3 Hz, -NCHCH_2Ph), 6.17-6.51 (m, 2H, Ar), 6.92-7.07 (m, 3H, Ar), 7.19–7.50 (m, 7H, Ar).

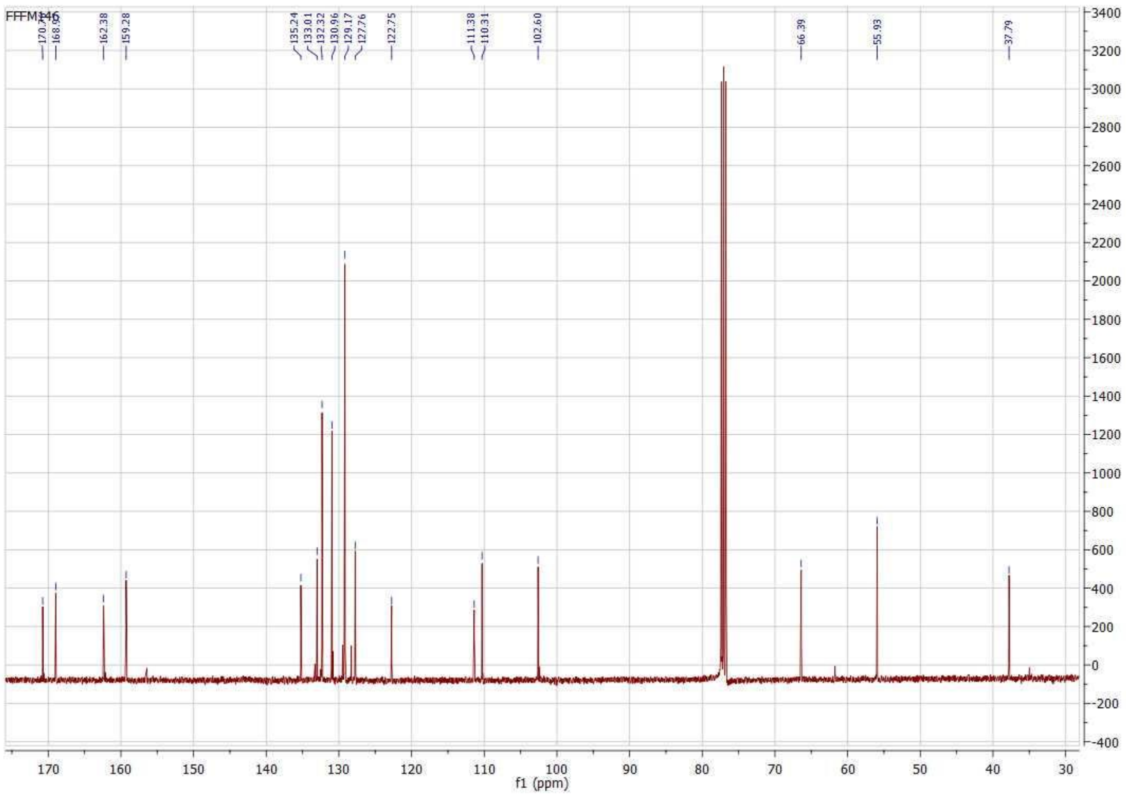
^{13}C-RMN (100MHz, $CDCl_3$, 25ºC, TMS): δ 38.1 (-CH*C*H_2Ph), 56.2 (-O*C*H_3), 66.8 (-N*C*HCH_2Ph-), 103.0, 110.7, 111.7, 123.1, 129.5, 131.3, 132.7, 133.3, 135.6, 159.5 (Ar), 162.8 (Ar, quaternary), 169.4 (Ar, quaternary), 169.3 (-CH*C*OO-).

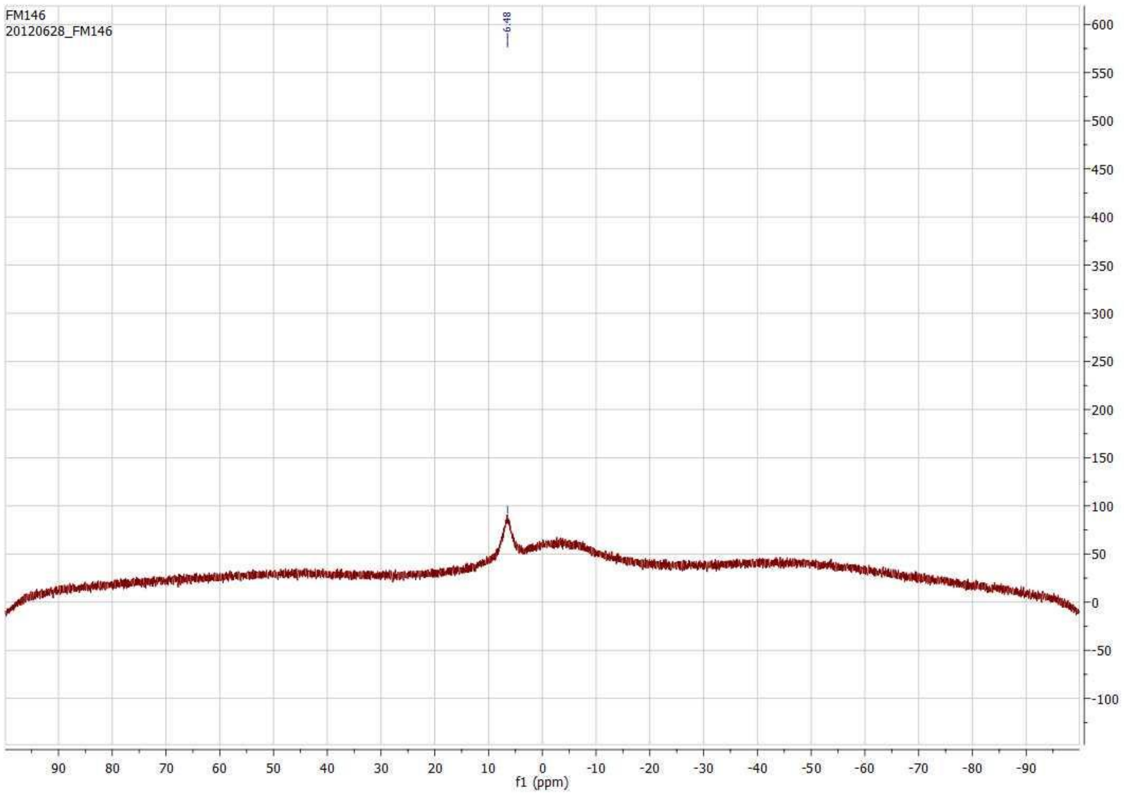
^{11}B NMR (300 MHz, $CDCl_3$, 25°C): δ =6.48.

ESI^{+}: 502, 486, 464,152.

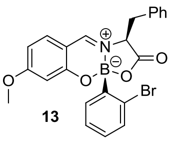
HMRS (EI): m/z calcd. [M^{+}] = 463.0590, found [M^{+}] 463.0583.


FFFM146
f1 (ppm)


FFFM146
f1 (ppm)



Compound 13



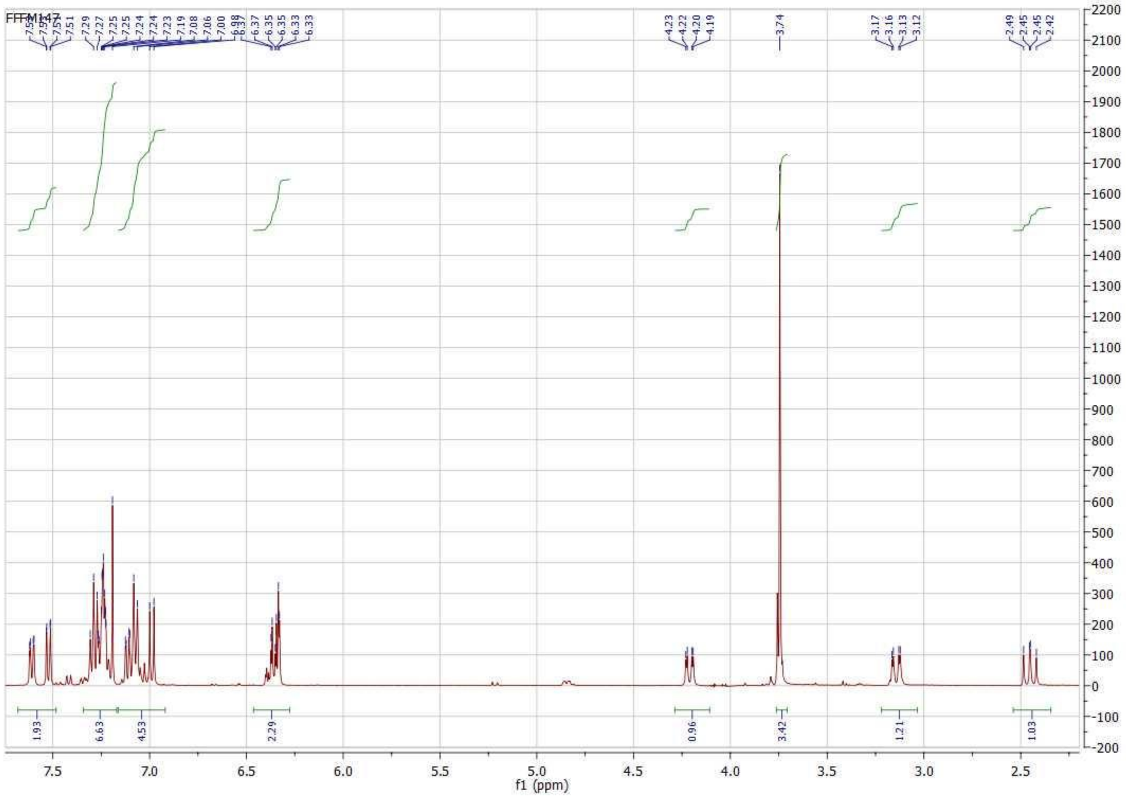
13 was obtained in 50 % yield, *d.r*. 77 %, after 20 h at 90 ºC (0.09 g).

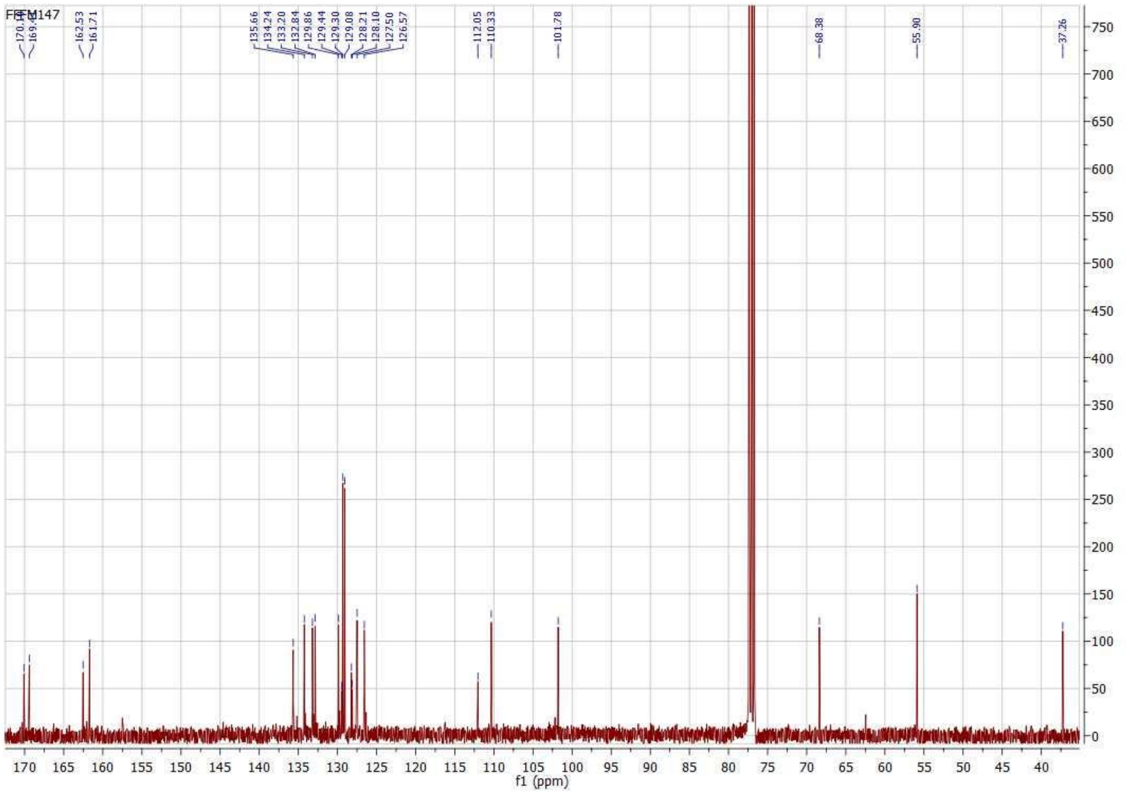
^{1}H NMR (400 MHz, $CDCl_3$, 25ºC, TMS): δ 2.54 (dd, 1H, *J* = 14.1, 12.4 Hz, -NC*H*CH_2Ph-), 3.24 (dd, 1H, *J* = 14.1, 2.9 Hz, -CHC*H*$_2$Ph), 3.84 (s, 3H, -OC*H*$_3$), 4.30 (dd, 1H, *J*= 12.3, 3.3 Hz, -CHC*H*$_2$Ph), 6.43-6.46 (m, 2H, Ar), 7.07 – 7.30 (m, 3H, Ar), 7.28-7.40 (m, 5H, Ar), 7.61 (dd, 1H, *J* = 7.9, 1.0 Hz, Ar), 7.70 (dd,1H, *J* = 7.5, 1.7 Hz, Ar). **^{13}C-RMN** (100MHz, $CDCl_3$, 25ºC, TMS): δ 37.26 (-CH*C*H_2Ph), 55.9 (-O*C*H_3), 68.38 (-N*C*HCOCH_2-), 101.78, 110.33, 112.6, 126.8, 127.8, 129.0, 129.3, 129.86, 133.0, 134.2, 133.5, 135.6, 161.7, 169.41 (Ar, quaternary), 162.8 (Ar, quaternary), 169.7 (Ar, quaternary), 170.4 (-CH*C*OO-).

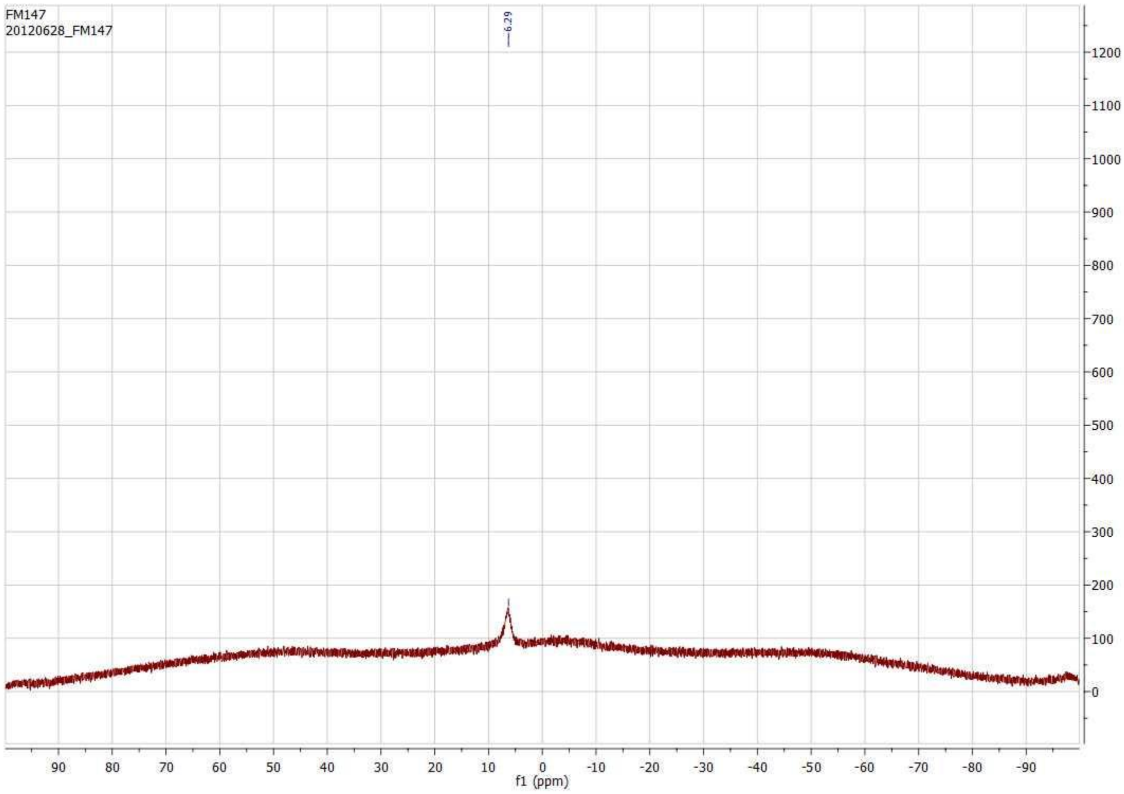
^{11}B NMR (300 MHz, $CDCl_3$, 25°C): δ =6.29.

ESI$^+$: 502, 486, 464, 256.

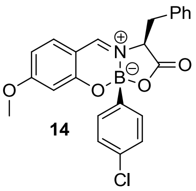
HMRS (EI): m/z calcd. [M^+] = 463.0591, found [M^+] 463.0580.







Compound 14



14 was obtained in 84% yield, *d.r*. 96%, after 20 h at 90 ºC (144 mg).

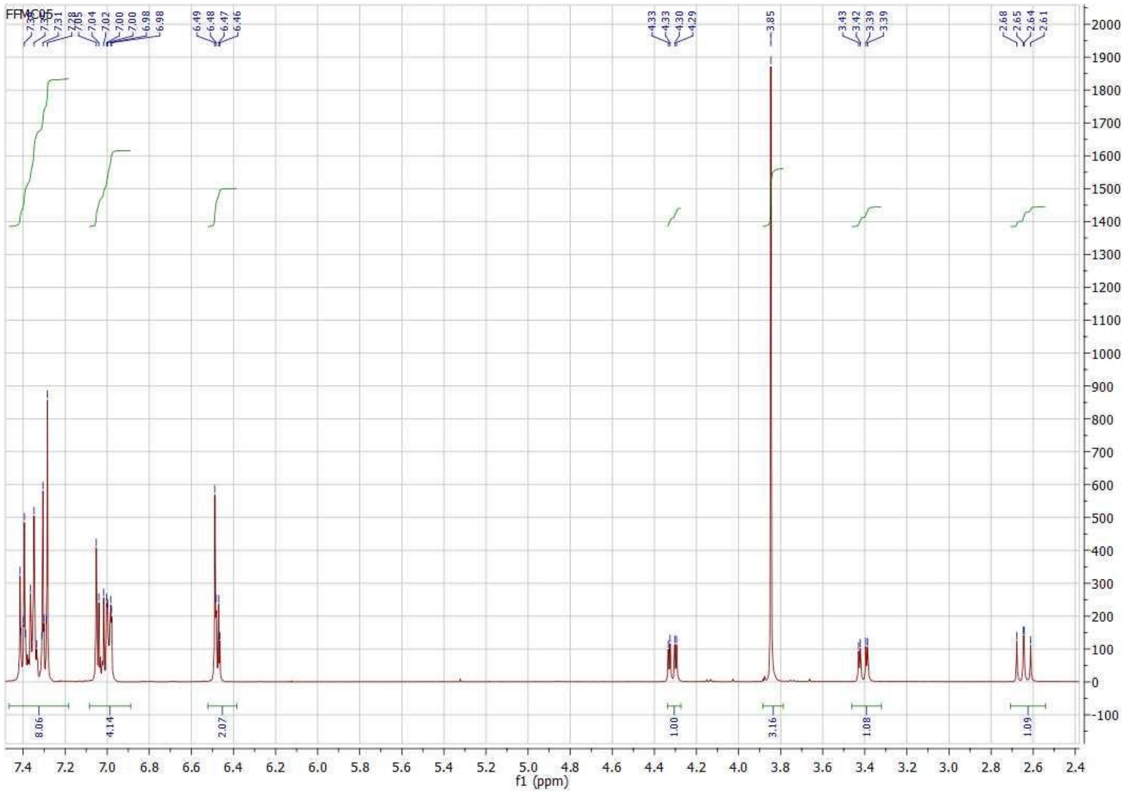
^{1}H NMR (400 MHz, CDCl3, 25ºC, TMS): δ 2.62 (t, 1H, *J*= 13.2 Hz, -NCHCOCH_2-), 3.38 (d, 1H, *J*= 13.9 Hz, -CHCH_2Ph-), 3.82 (s, 3H, -OCH_3), 4.28 (d, 1H, *J*= 11.7 Hz, -C*H*CH$_2$Ph-), 6.36 – 7.45 (m, 14H, Ar).

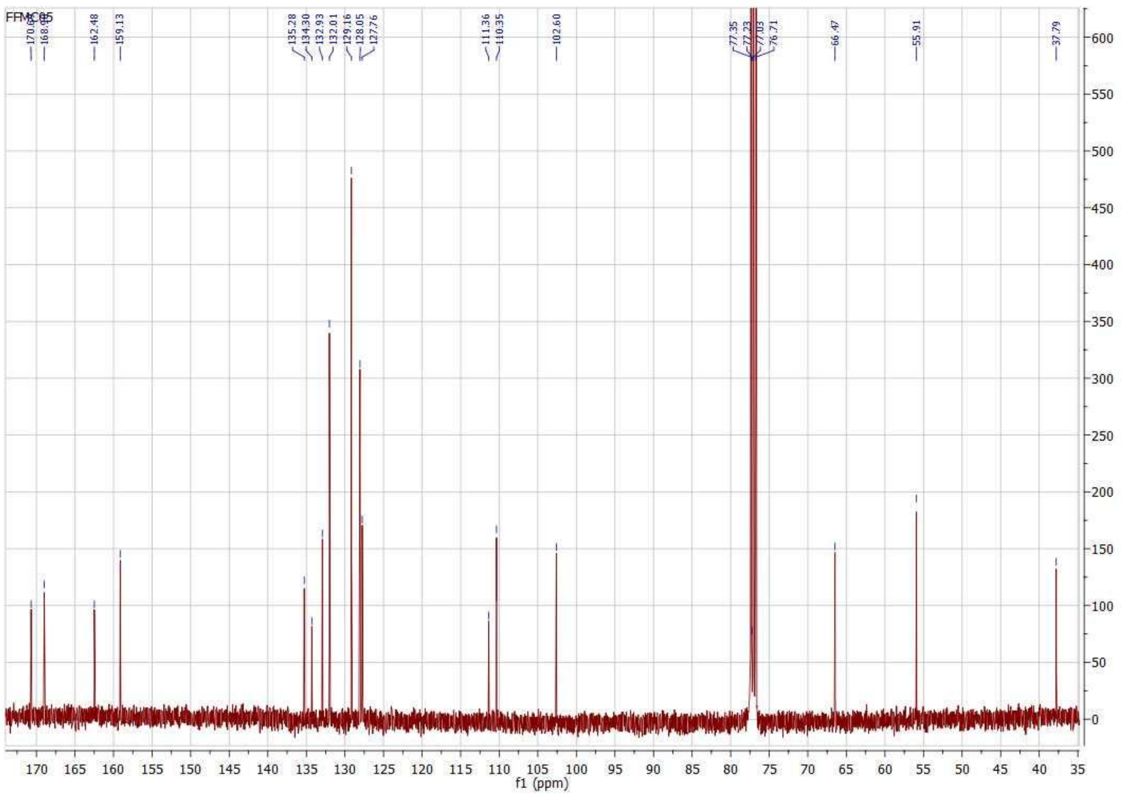
^{13}C NMR (100 MHz, CDCl3) δ38.1 (-CH*C*H2Ph-), 56.2 (-O*C*H3), 66.8 (-N*C*HCH$_2$Ph-), 102.9, 110.7, 111.7, 128.1, 128.4, 129.5, 132.3, 133.3, 134.6, 135.6 (Ar), 159.5 (Ar, quaternary), 162.8 (Ar, quaternary), 169.3 (Ar, quaternary), 171.0 (-CHCO).

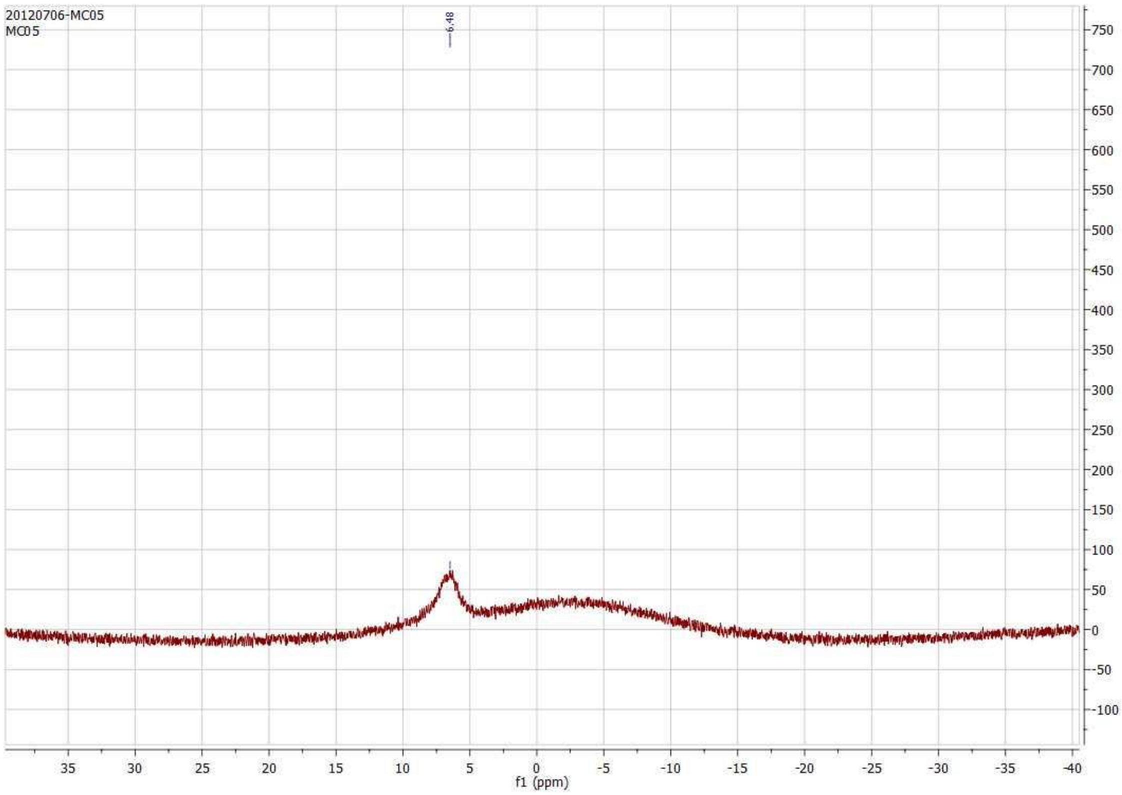
^{11}B NMR (300 MHz, $CDCl_3$, 25°C): δ = 6.48.

ESI^{+}: 442, 322, 300, 166.

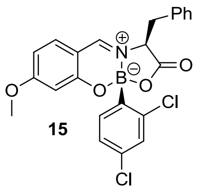
HMRS (EI): m/z calcd. [M^{+}] = 419.1096, found [M^{+}] 419.1106.


FFMC05
6.49
6.48
6.47
6.46
4.33
4.33
4.30
4.29
3.85
3.43
3.42
3.39
3.39
2.68
2.65
2.64
2.61
8.06
4.14
2.07
1.00
3.16
1.08
1.09
f1 (ppm)


FFMC05
162.48
159.13
135.28
134.30
132.93
132.01
129.16
128.05
127.76
111.36
110.35
102.60
77.35
77.23
77.03
76.71
66.47
55.91
37.79
f1 (ppm)



Compound 15



15 was obtained in 98 % yield, *d.r*. 99 %, after 20 h at 90 ºC (183 mg).

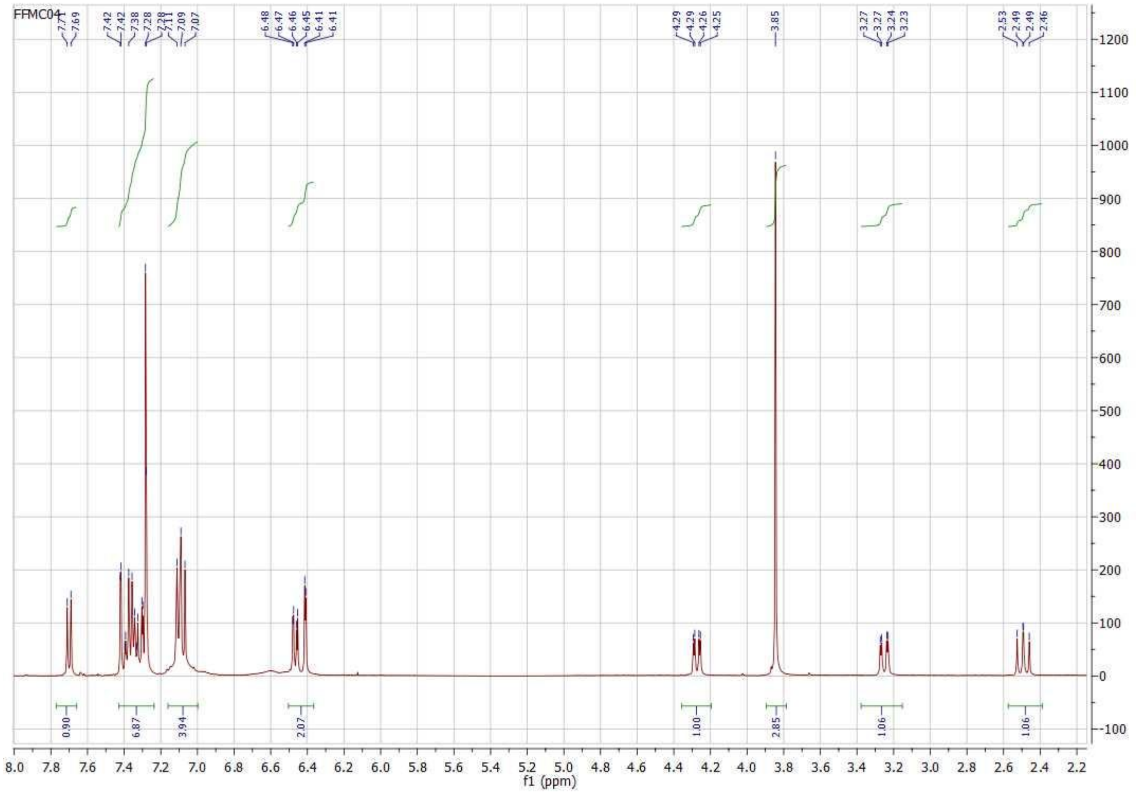
^{1}H NMR (400 MHz,CDCl3, 25ºC, TMS): δ 2.47 (dd, 1H, *J* = 14.0, 12.4 Hz, -NCHC*H*$_2$Ph-), 3.23 (dd, 1H,*J*= 14.1, 3.0 Hz, -NCHC*H*$_2$Ph-), 3.83 (d, 3H,*J*= 9.5 Hz, -OCH3), 4.25 (dd, 1H,*J*= 12.2, 3.1 Hz, -C*H*CH2Ph-),6.27–6.41 (m, 2H, Ar), 6.91 – 7.07 (m, 4H,Ar), 7.14 – 7.34 (m, 6H, Ar).

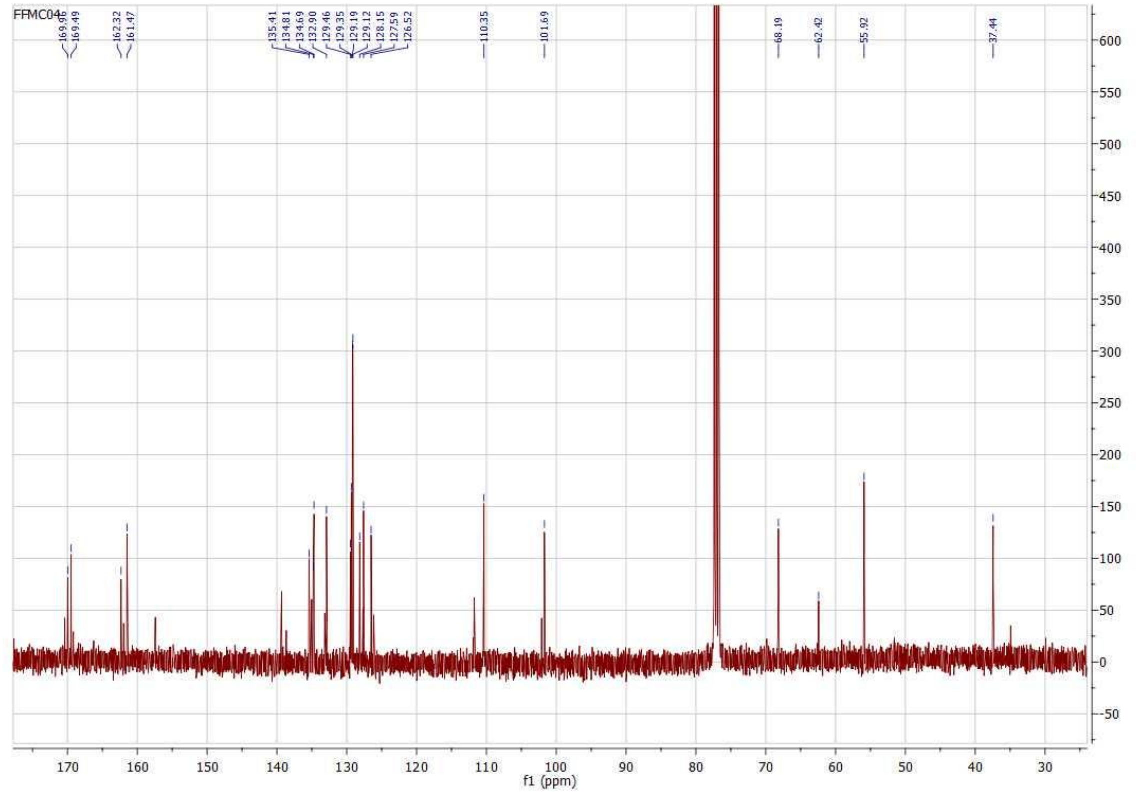
^{13}C NMR (100 MHz, CDCl3) δ 37.8 (-CH*C*H$_2$Ph-), 56.2 (-O*C*H3), 68.5 (-N*C*HCH$_2$Ph-), 102.0, 110.7, 112.1, 126.8, 127.9, 128.5, 129.4, 129.5, 129.7, 129.8, 133.2, 135.0, 135.1,135.4, 135.7, 139.7 (Ar), 161.8 (Ar, quaternary), 162.3 (Ar, quaternary), 162.6 (Ar, quaternary), 169.8 (-CHCOO).

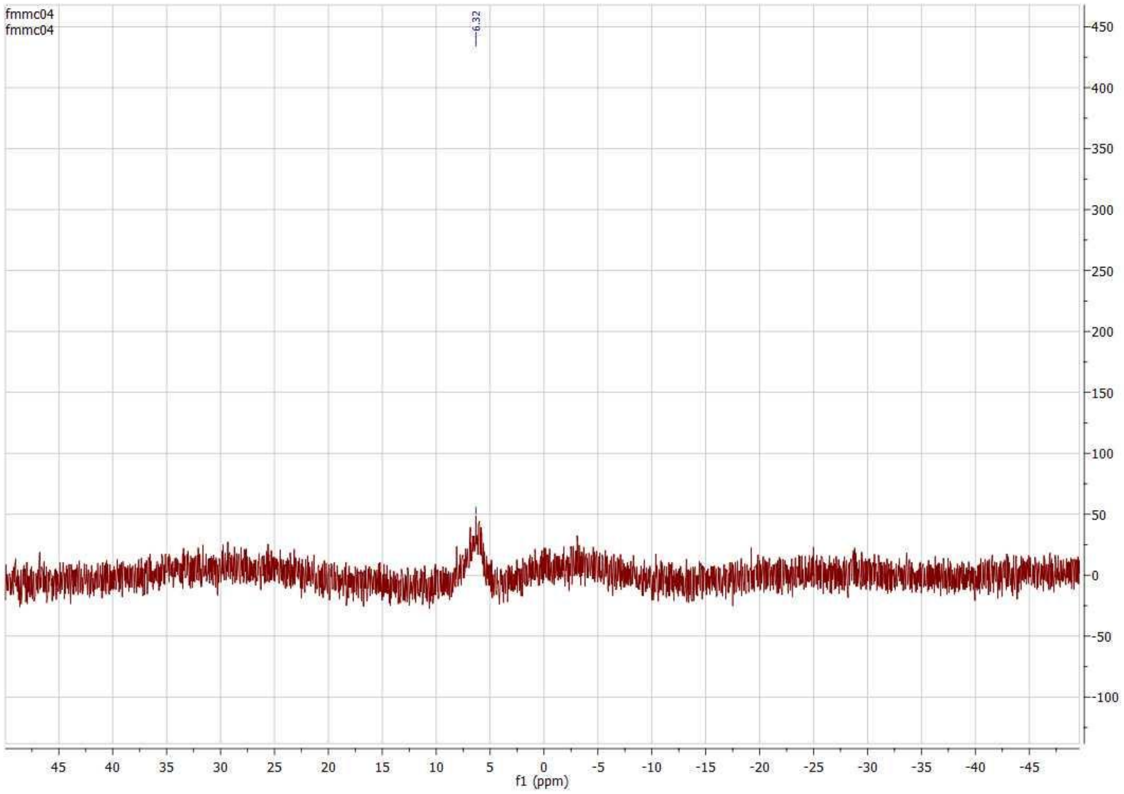
^{11}B NMR (300 MHz, $CDCl_3$, 25°C): δ = 6.31.

ESI$^+$: 492, 454, 300.

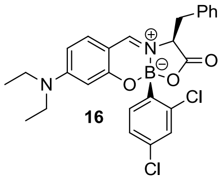
HMRS (EI): m/z calcd. [M+H$^+$] = 454.0779, found [M+H$^+$]454.0763.


FFMC04
f1 (ppm)


FFMC04
f1 (ppm)

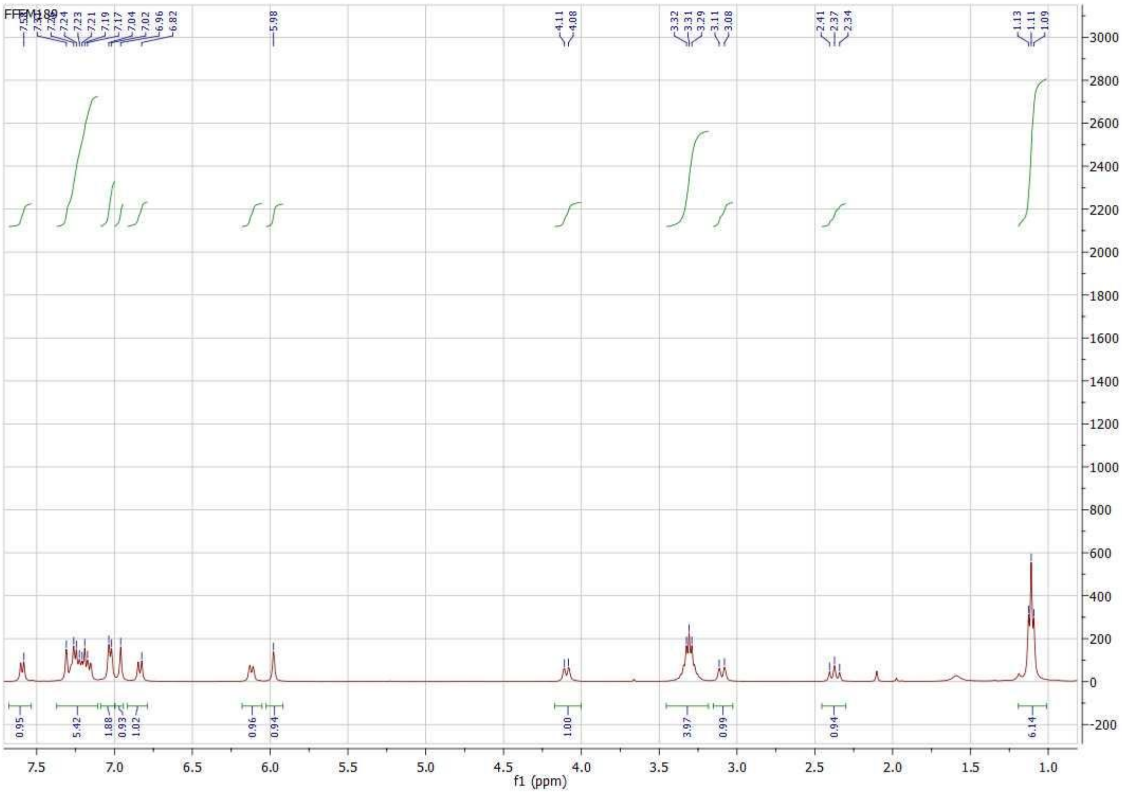


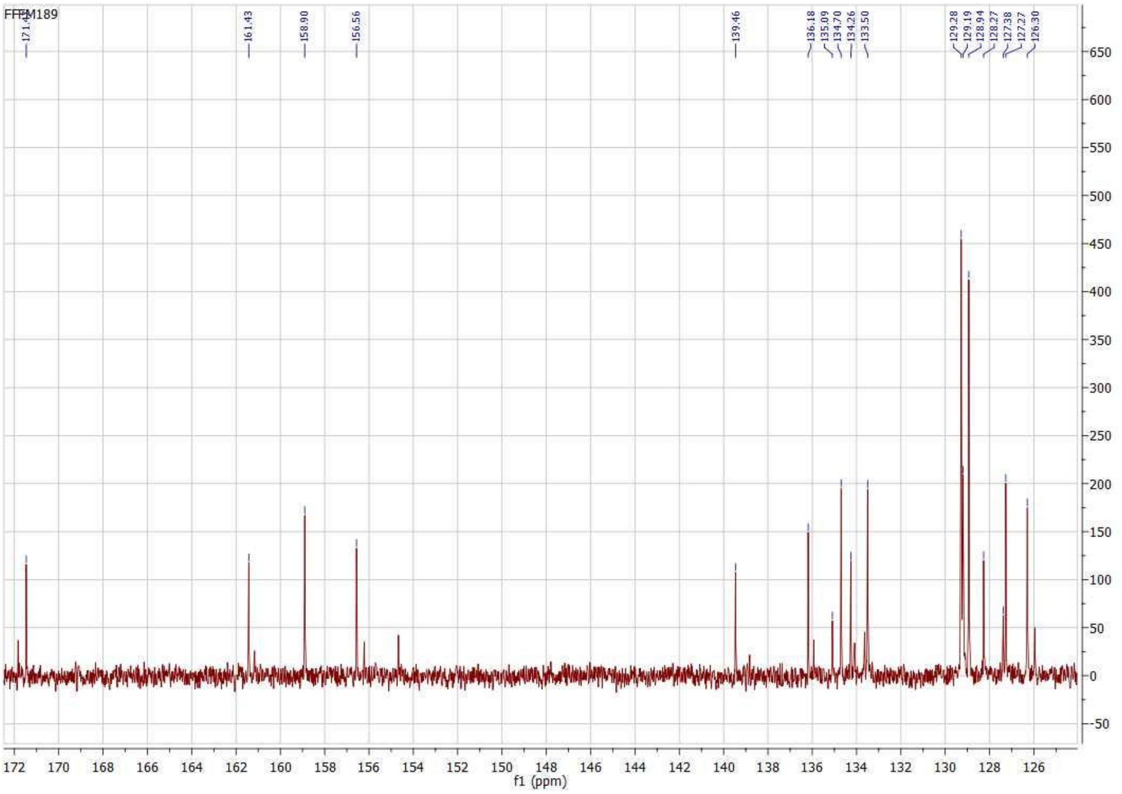
Compound 16

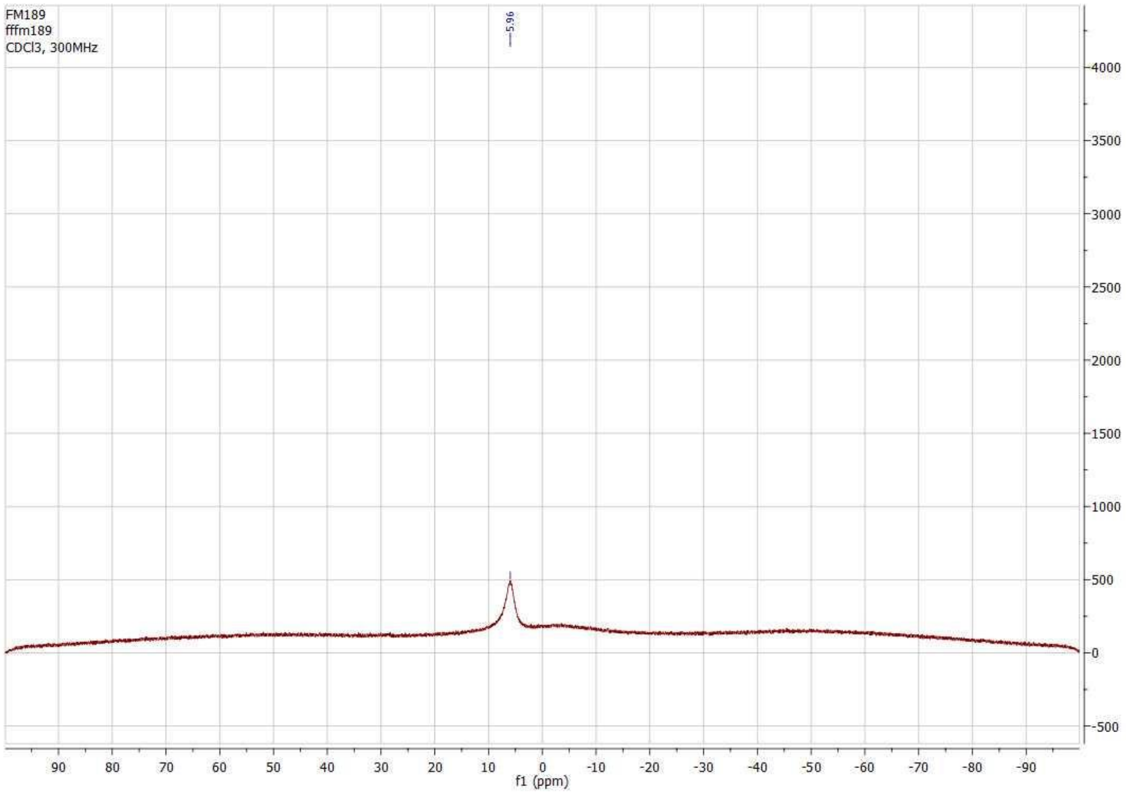


A round bottom flask equipped with a magnetic stirrer was charged with amino acid (2.0 equiv.), aldehyde (1.5 equiv.) and distilled ethanol (2.0 mL). This suspension was stirred at reflux for 1 h after which the boronic acid (0.41 mmol) was added, the mixture was then stirred at 75ºC for 20 h. The reaction mixture, which appears as a biphasic composition of precipitate and a supernatant liquid, was filtered and the solid retained in the filter, was then washed with water followed by hexane. The desired compound was recovered with dichloromethane, which was subsequently removed under reduced pressure.

16 was obtained in 89 % yield, *d.r*. 98%, after 20 h at 75 ºC (0.08 g).
^{1}**H NMR** (400 MHz, $CDCl_3$, 25ºC, TMS): δ 1.11 (t, 6H, *J* = 6.8 Hz, –$N(CH_2CH_3)_2$, 2.37 (t, 1H, *J* = 13.0 Hz, -$CHCH_2Ph$), 3.10 (d, 1H, *J* = 13.6 Hz, -$CHCH_2Ph$), 3.18 – 3.45 (m, 4H, –$N(CH_2CH_3)_2$), 4.10 (d, 1H, *J* = 10.3 Hz, -$CHCH_2Ph$), 5.98 (s, 1H, Ar), 6.12 (d, 1H, *J*= 8.4 Hz, Ar), 6.84 (d, 1H, *J* = 8.6 Hz, Ar), 6.96 (s, 1H, Ar), 7.03 (d, *J* = 7.0 Hz, 2H, Ar), 7.42 – 7.08 (m, 6H, Ar).
^{13}**C-RMN** (100MHz, $CDCl_3$, 25ºC, TMS): δ 45.08 (–$N(CH_2CH_3)$), 67.72 (-$CHCH_2Ph$), 98.12 (-$NCHCOCH_2$-), 105.97, 108.34, 126.30, 127.33, 128.27, 128.94, 129.24, 133.50, 134.26, 134.70, 135.09, 136.18, 139.46, 156.56, 158.90, 161.43, (Ar), 171.47 (-CHCOO).
^{11}**B NMR** (300 MHz, $CDCl_3$, 25°C): δ = 5.96.
ESI^{+}:517, 495, 341.
HMRS (EI): m/z calcd. [M^{+}] = 494.1335, found [M^{+}] = 494.1330.

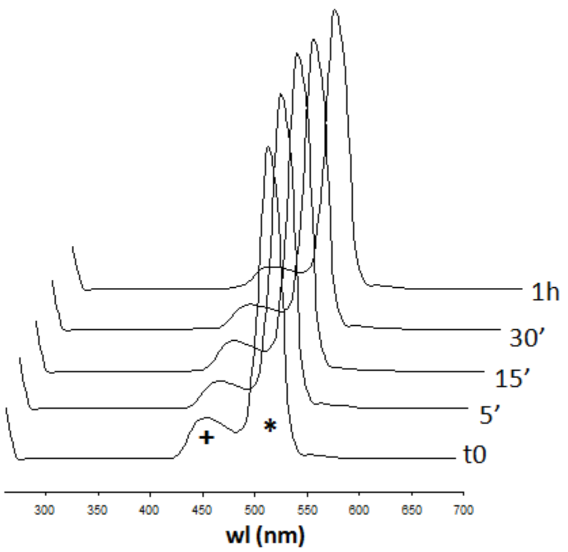

FFEM189
f1 (ppm)

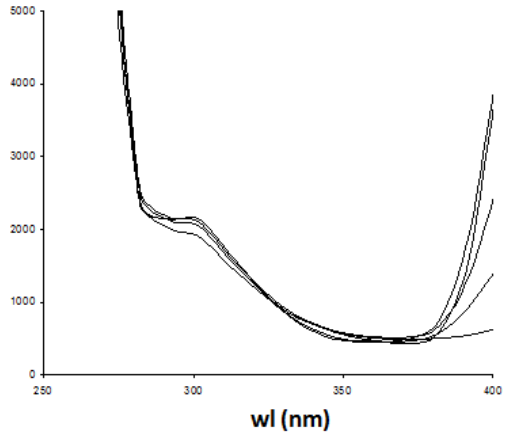

FFEM189
f1 (ppm)



Evaluation of compound stability in HEPPES:

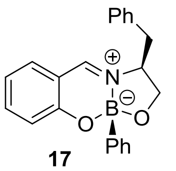
- Fluorescence spectroscopy
- Excitation at 252 nm; emission spectra 262-700 nm
- 100 µM (in 100 mM HEPES, pH 7.0)





Electronic Supplementary Material (ESI) for Organic & Biomolecular Chemistry

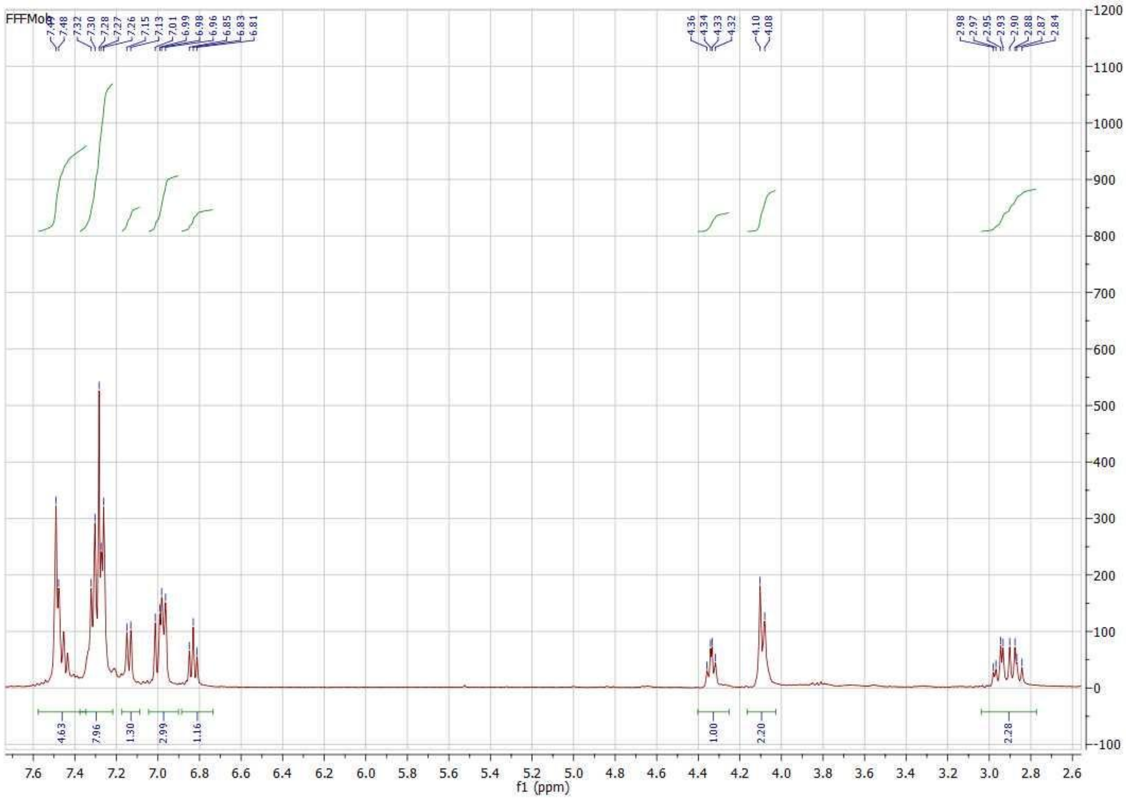
Compound 17

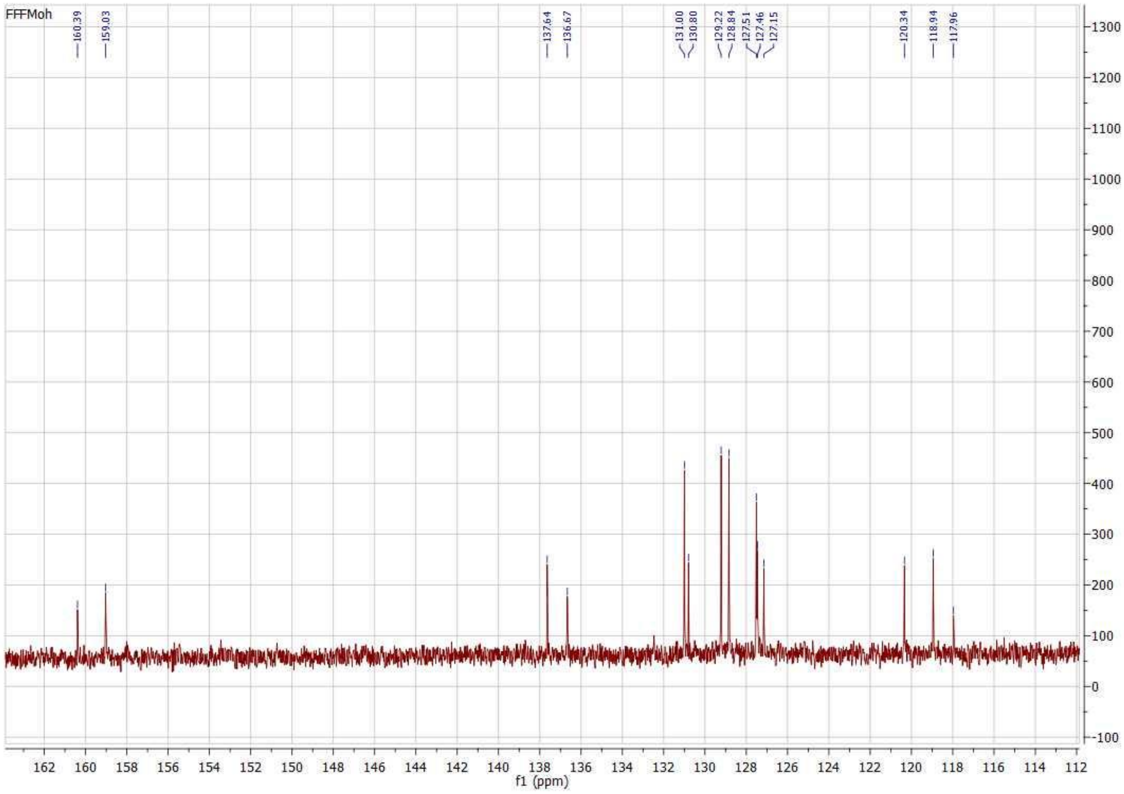


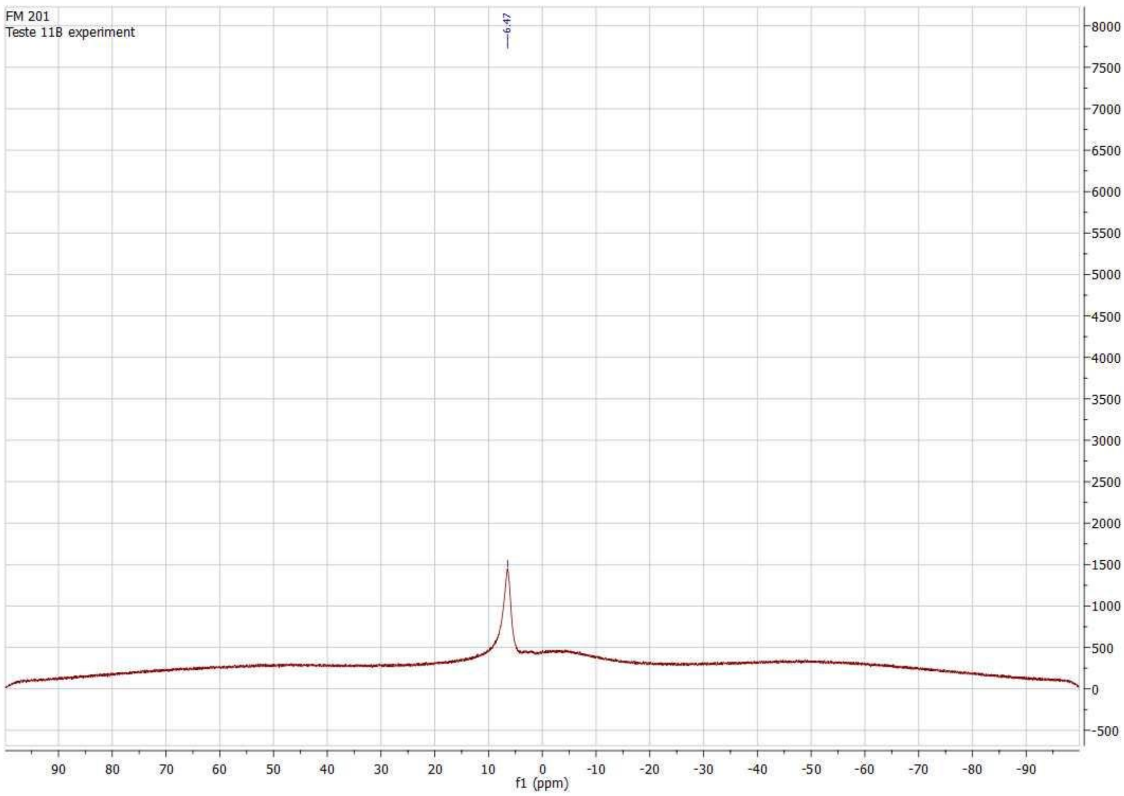
17

A round bottom flask equipped with a magnetic stirrer and molecular sieves, was charged with amino alcohol (0.41 mmol), aldehyde (1.0equiv.) and distilled ethanol (2.0 mL). This suspension was stirred at reflux for 1 h, after which the solvent was evaporated under educed pressure. Toluene (2 mL) and boronic acid (1.0 equiv.) were then added and the mixture was stirred at reflux for 24 h. The mixture reaction that appears as a yellow clear solution was filtered at room temperature through a small silica column and the expected compound was precipitated from this mixture by low temperature.

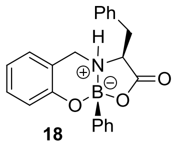
17 was obtained in 20 % yield, (0.133 g), *d.r.* 100%.
^{1}H NMR (400 MHz, $CDCl_3$, 25ºC, TMS): δ2.77 – 3.04 (m, 2H, *J*= 13.0, -CHC*H$_2$*Ph), 4.09 (d, 2H,*J* = 8.9 Hz, -NCHC*H$_2$*O-, -NC*H*CH$_2$O-), 4.34 (dd, 1H,*J* = 9.7, 6.8 Hz, -NCHC*H$_2$*O-), 6.83 (t, 1H,*J* = 7.4 Hz, -Ar), 6.99 (dd, 3H,*J* = 11.7, 8.1 Hz, Ar), 7.14 (d, 1H,*J* = 7.7 Hz, Ar), 7.22 – 7.38 (m, 7H, Ar), 7.45 – 7.53 (m, 3H, Ar).
^{13}C-RMN (100MHz, $CDCl_3$, 25ºC, TMS): δ 39.84 (-CHCH$_2$Ph), 66.15 (-NCHCH$_2$-), 67.87 (-NCHCH$_2$-), 117.62, 118.94, 120.34, 127.15, 127.46, 127.51, 128.84, 129.22, 130.80, 131.00, 136.67, 137.64, 159.03, 160.39 (Ar).
^{11}B NMR (300 MHz, $CDCl_3$, 25°C): δ = 6.47
ESI^{+}: 380, 364, 342, 256.
HMRS (EI): m/z calcd. [M^{+}] = 341.1587, found [M^{+}] = 341.1544 .




FFFMoh
160.39
159.03
137.64
136.67
131.00
130.80
129.22
128.84
127.51
127.46
127.15
120.34
118.94
117.96
f1 (ppm)


FM 201
Teste 11B experiment
6.47
f1 (ppm)

Compound 18

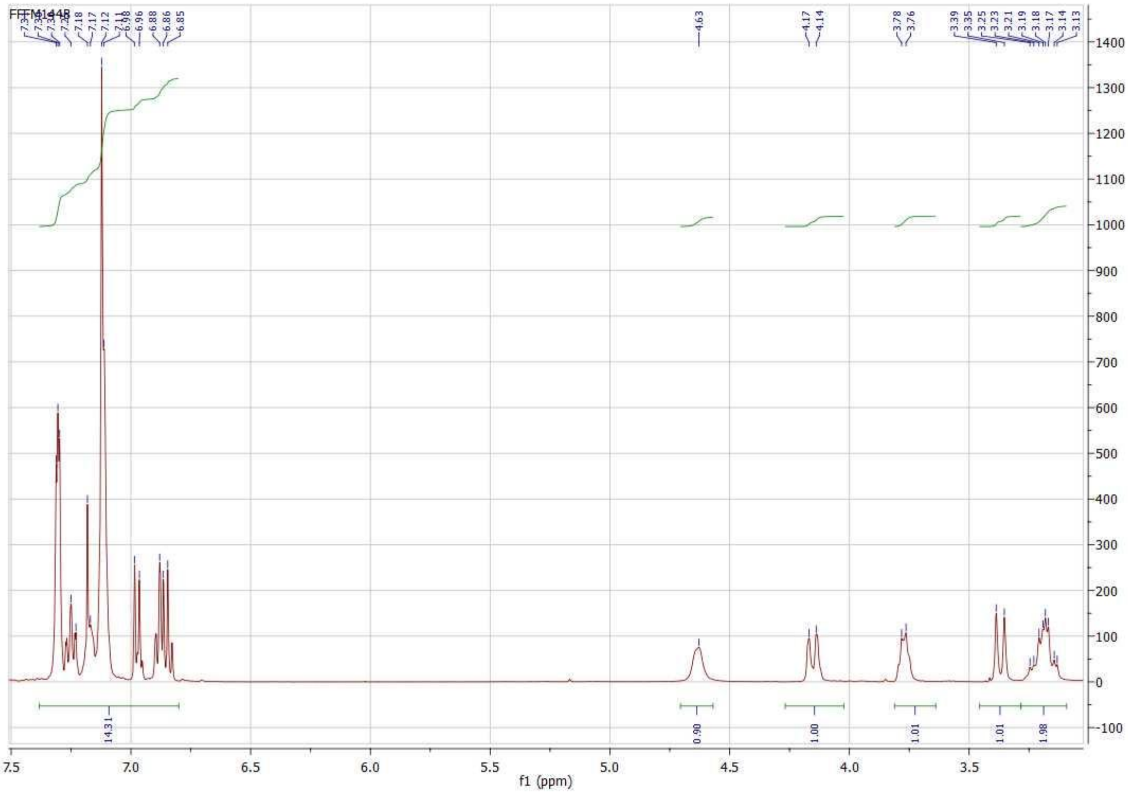


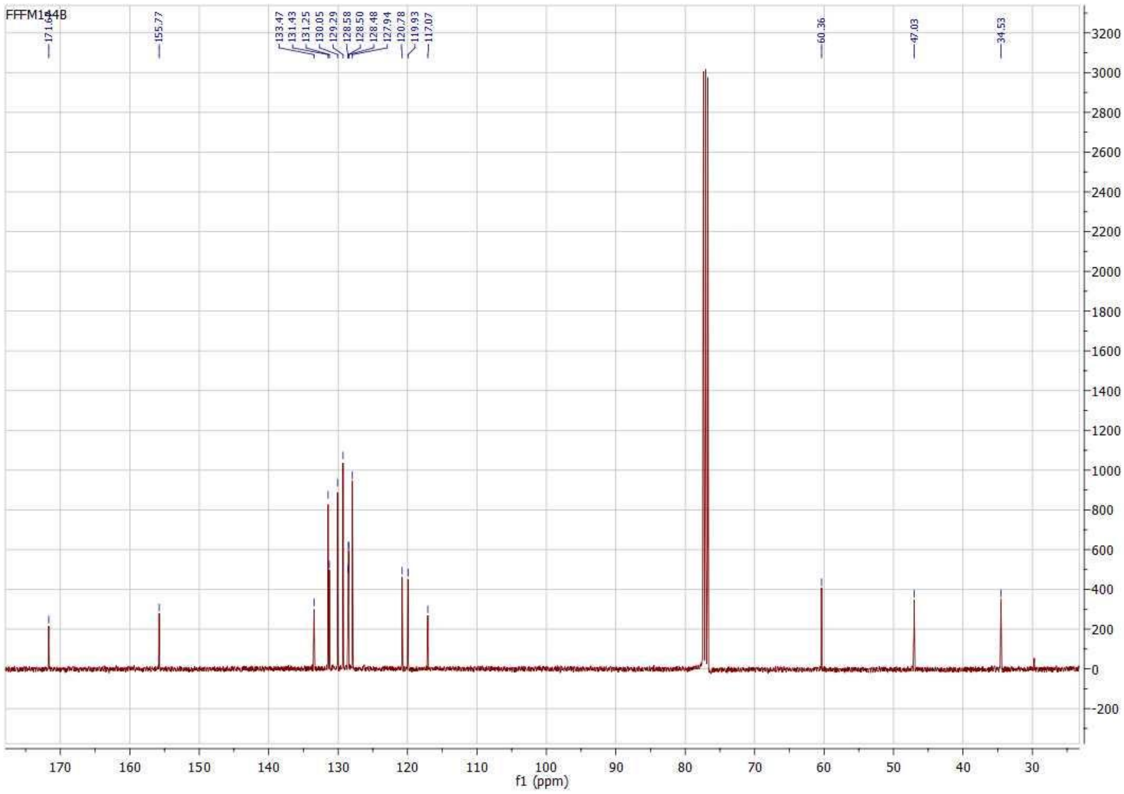
18

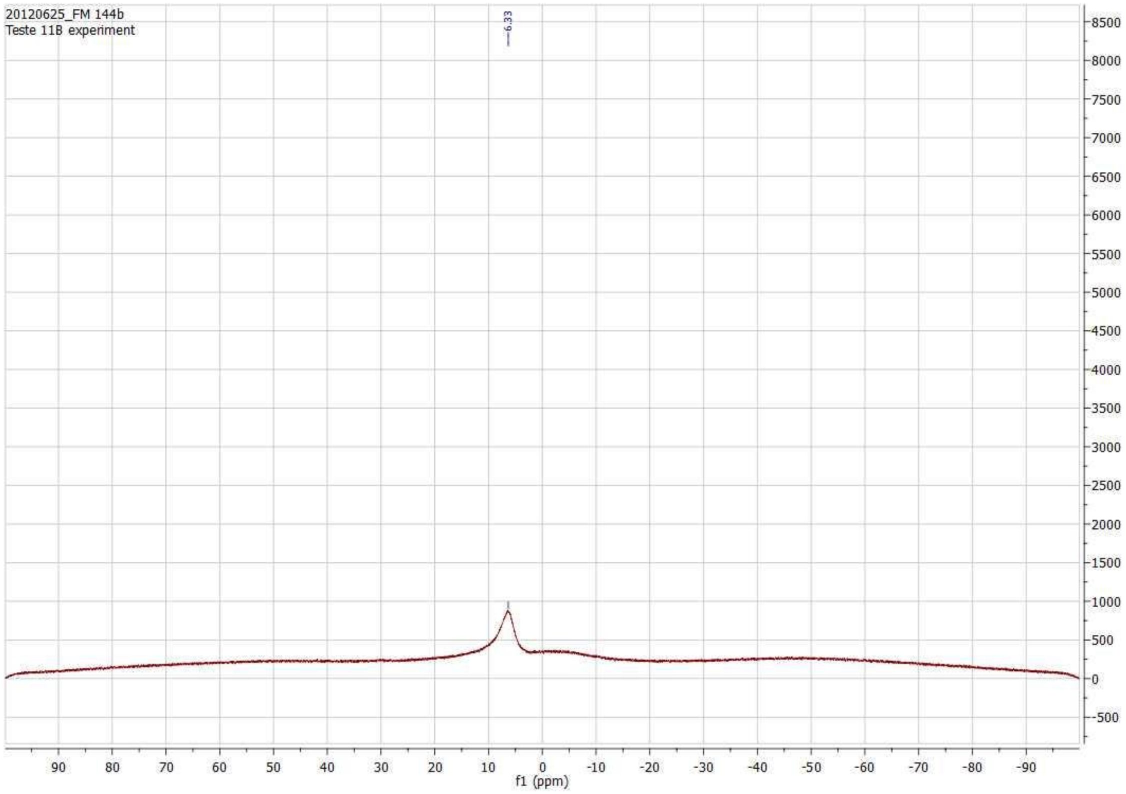
A round bottom flask equipped with a magnetic stirrer was charged with amino acid (0,82mmol), Cl_2SO (1equiv.), distilled methanol (3.0mL) after which the suspension was stirred at reflux for 12 h.Then the volatiles were removed under reduced pressure and the remaining solid was solubilised with a mixture of methanol and THF (3.0 mL, 1:1), the aldehyde was then added (1eqiv) and the reaction was stirring for 6 h at reflux to yield the schiff base. Subsequently, $NaBH_4$ (3 equiv.) was slowly added at 0ºC to the reaction mixture which was then allowed to react at this temperature for 1 h after which the reaction was quenched with HCl (3 equiv.). The reaction mixture volatiles were then evaporated under reduced pressure. The obtained residue was solubilised with NaOH (1,5ml 3M) and the mixture stirred for 2 h at room temperature, after which HCl was added until PH7 was obtained. The obtained mixture was concentrated under reduced pressure. The product was solubilised with CH_2Cl_2, the insoluble material was discarded. The desired product was dried by reduced pressure and characterized. Further 0,41mmol of this compounds were solubilized by 1/1 mixture of ethanol and benzene (2mL) and reacted with phenyl boronic acid (1equiv.) in presence of $NaHCO_3$ (1,5equiv.) for 12h at reflux.

18 was obtained in 48% yield, *d.r.* 100%.
^{1}H NMR (400 MHz, CDCl3, 25"C, TMS): 3.13-3.25 (m, 2H, –CHCH_2Ph), 3.37 (d, 1H, J = 13.5 Hz, –NHC$H_2C_6H_4$–), 3.77 (d, 1H, J = 7.4 Hz,–NC*H*CH2–), 4.15 (d, J= 11.9 Hz, 1H –NHC$H_2C_6H_4$–), 4.63 (s, 1H -N*H*-), 7.38 – 6.80 (m, 14H, Ar).
^{13}C-NMR (100 MHz, CDCl3, 25ºC, TMS): δ 34.53 (–CH*C*H_2Ph), 47.03 (–NH*C*$H_2C_6H_4$), 60.36 (-NH*C*HCH_2-)117.07, 119.93, 120.78, 127.94, 128.38, 128.73, 129.21, 129.29, 131.34, 133.47 (Ar), 155.77(Ar, quaternary), 171.67 (–CH*C*OO–).
^{11}B NMR (300 MHz, $CDCl_3$, 25°C): δ = 6.33.
ESI$^+$: 358, 294, 272.
HMRS (EI): m/z calcd. [M^+] 357.1536, found [M^+] = 357.1541.

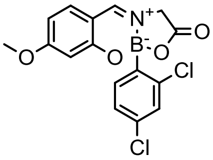
Adapted methodology from: A. Abreu et al., Journal of Organometallic Chemistry 691 (2006) 337–348.





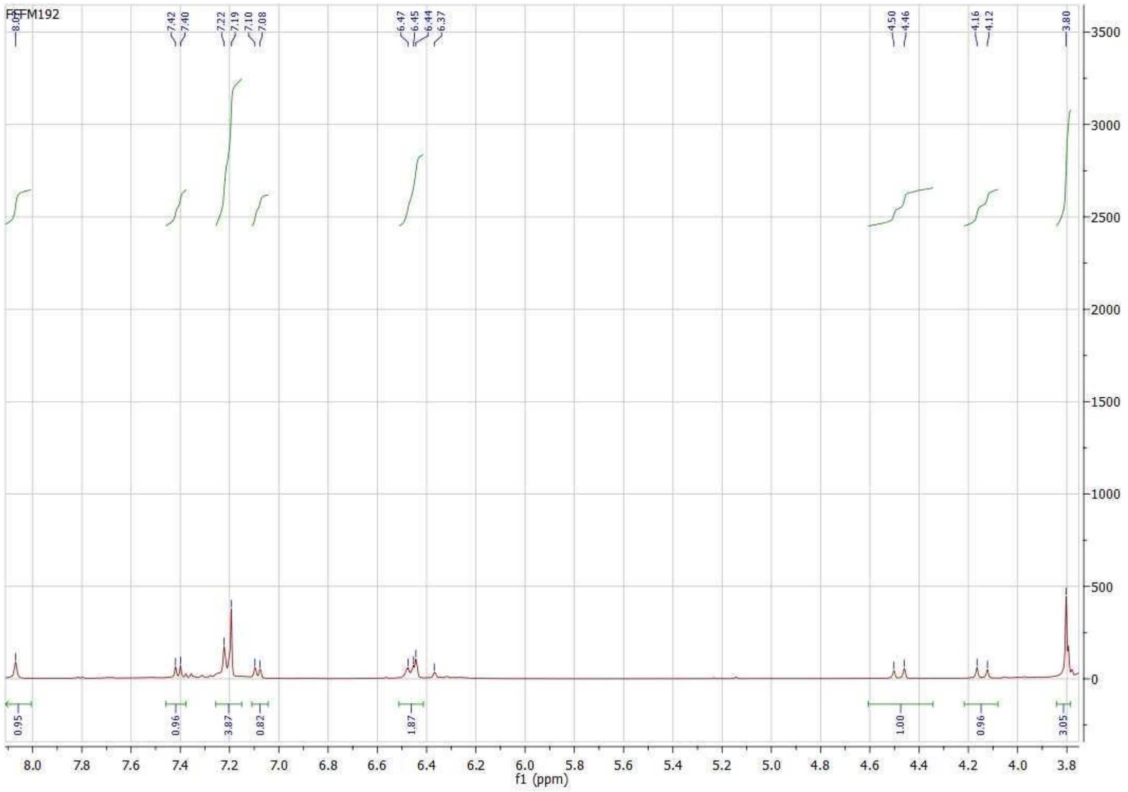


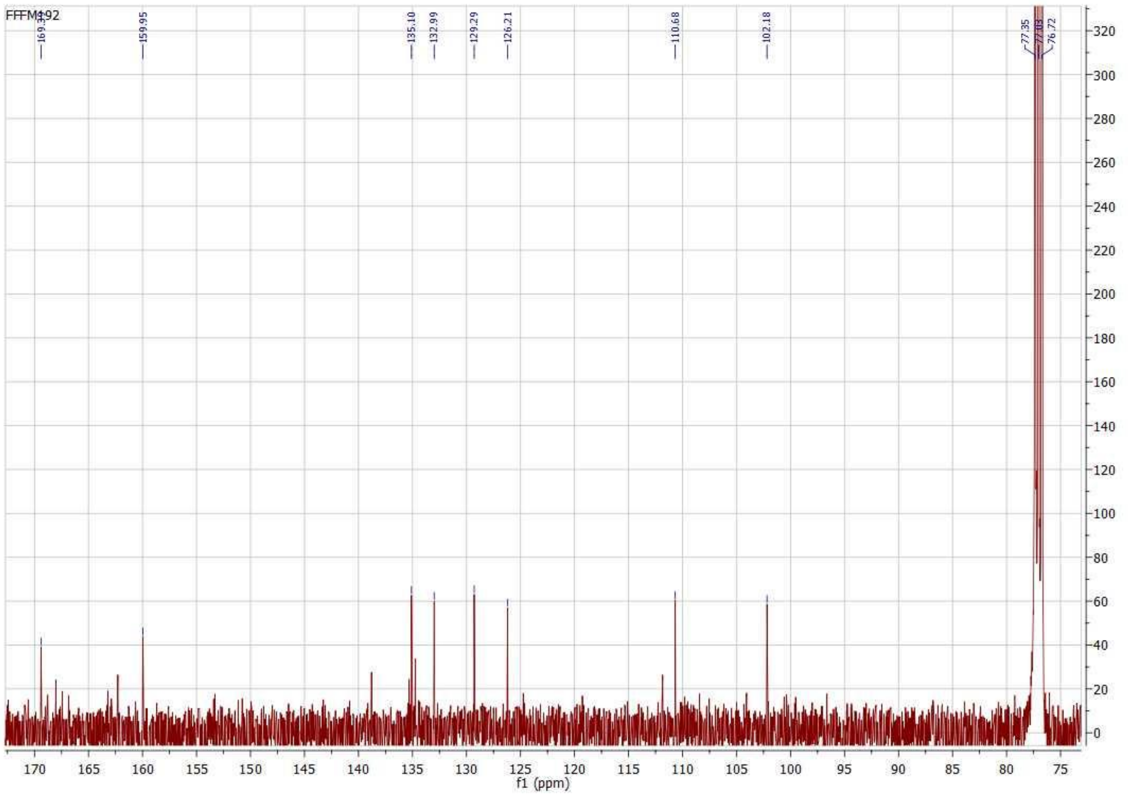
Compound 19

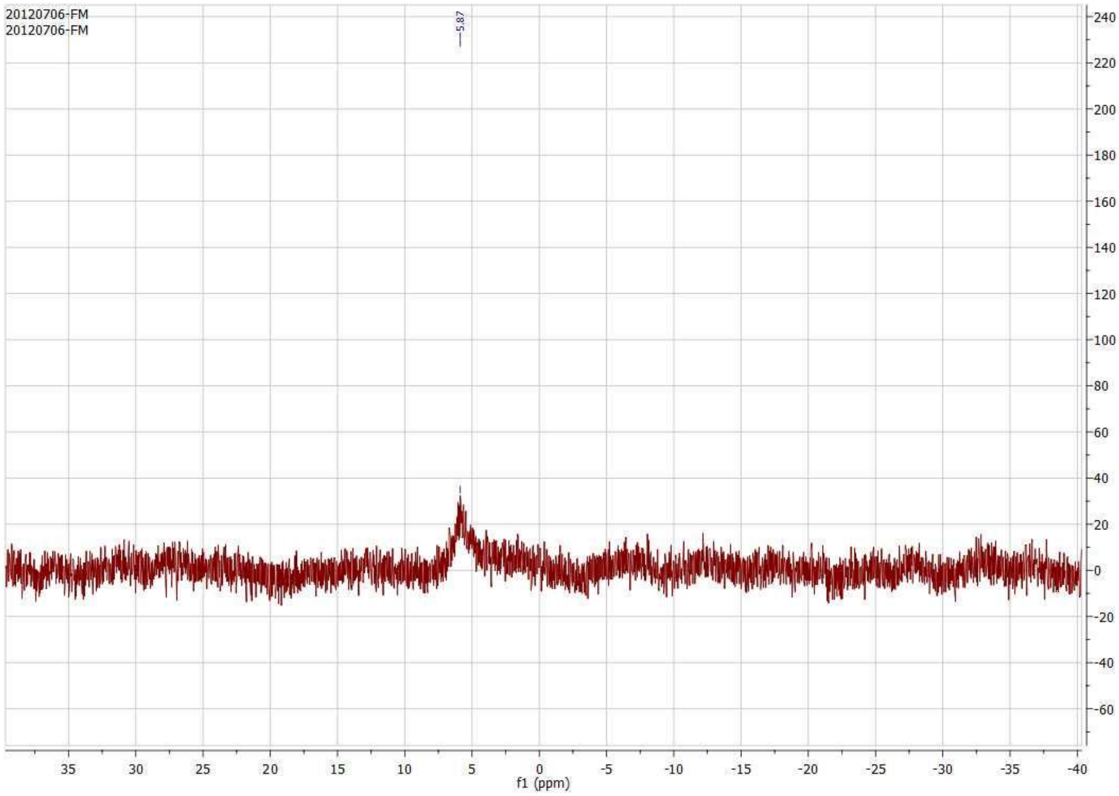


A round bottom flask equipped with a magnetic stirrer, was charged with amino acid (2.0 equiv), aldehyde (1.5 equiv) and distilled tetrahydrofuran (THF) (2.0 mL). This suspension was stirred at 85ºC for 1 h, after which the boronic acid (0.41 mmol) was added. The mixture was than stirred at 85ºC for 20 h. The crude reaction mixture, which appears a biphasic composition of precipitate solid plus a supernatant liquid, was filtered and the solid retained was discarded.The filtered was than dried by reduced pressure. The product was further precipitate using dichloromethane and hexane, recovered and dried by reduced pressure.

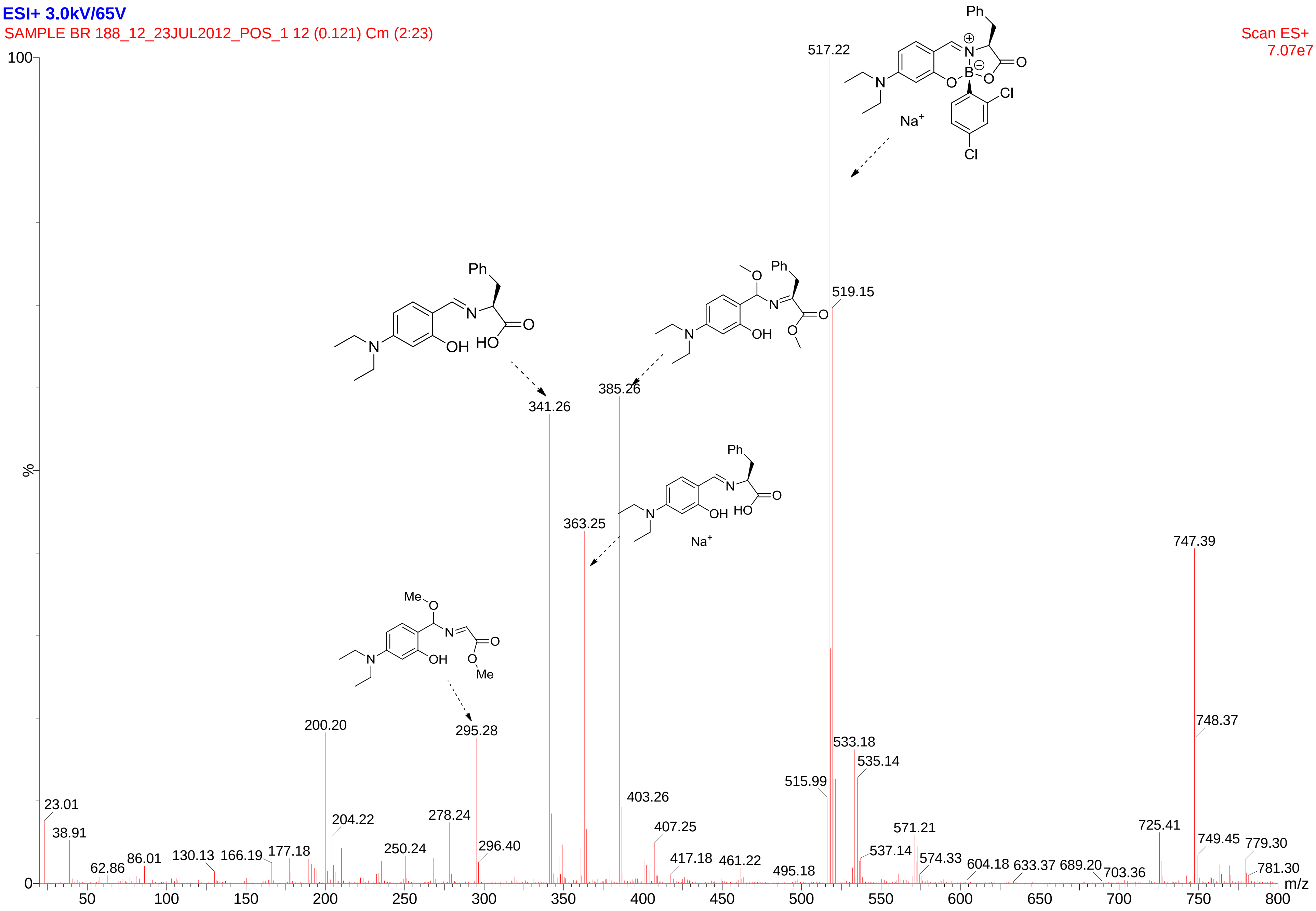
Compound 20 was obtained in 17 %, after 20 h at 85 ºC (0.09 g).
^{1}H NMR (400 MHz, $CDCl_3$, 25ºC, TMS): δ, 3.80 (s, 3H, -OC*H$_3$*), 4.14 (d, 1H, *J* = 16.9 Hz, -NC*H*$_2$-), 4.48 (d, 1H, *J* = 16.9 Hz, NC*H*$_2$-), 6.41 – 6.56 (m, 2H, Ar), 7.09 (d, *J*= 8.0 Hz, 1H, Ar), 7.21 (d, *J*= 11.6 Hz, 2H, Ar), 7.41 (d, *J* = 8.1 Hz, 1H, Ar), 8.07 (s, 1H, Ar);
^{13}C-RMN (100MHz, $CDCl_3$, 25ºC, TMS): δ 54.28 (-N*C*H-), 56.00 (-O*C*H$_3$), 102.18, 110.68, 126.21, 129.29, 132.99, 135.10 (Ar), 138.58, 159.95, 161.92 (Ar, quaternary), 169.39 (-CH*C*OO-).
^{11}B NMR (300 MHz, $CDCl_3$, 25°C): δ = 5.87
ESI$^+$: 402, 386, 364, 320, 210.
HMRS (EI): m/z calcd [M+H$^+$] = 364.0309, found:[M+H$^+$] = 364.0312, [M-CO_2] 320.0415.


FFFM192
8.07
7.42
7.40
7.22
7.19
7.10
7.08
6.47
6.45
6.44
6.37
4.50
4.46
4.16
4.12
3.80
0.95
0.96
3.87
0.82
1.87
1.00
0.96
3.05
f1 (ppm)

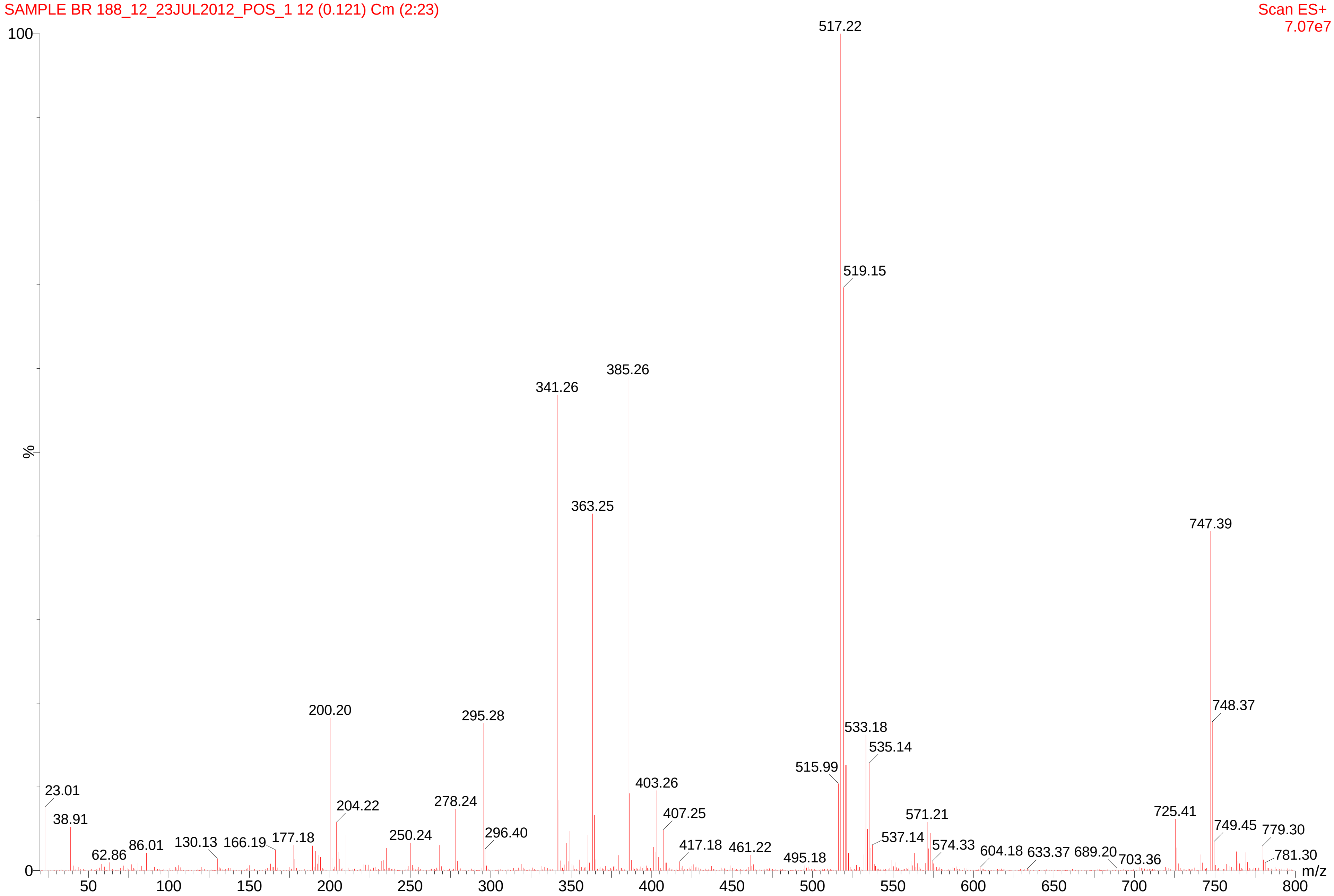

FFFM192
169.34
159.95
135.10
132.99
129.29
126.21
110.68
102.18
77.35
77.03
76.72
f1 (ppm)

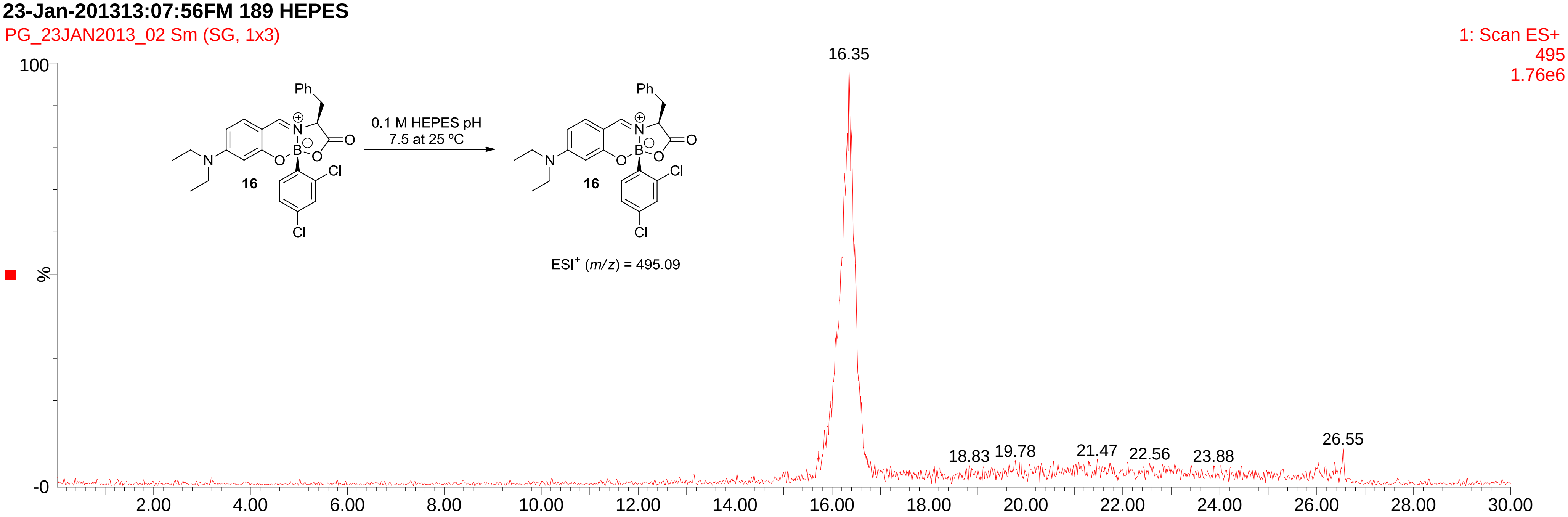

20120706-FM
20120706-FM
5.87
35
30
25
20
15
10
5
0
-5
-10
-15
-20
-25
-30
-35
-40
f1 (ppm)
240
220
200
180
160
140
120
100
80
60
40
20
0
-20
-40
-60

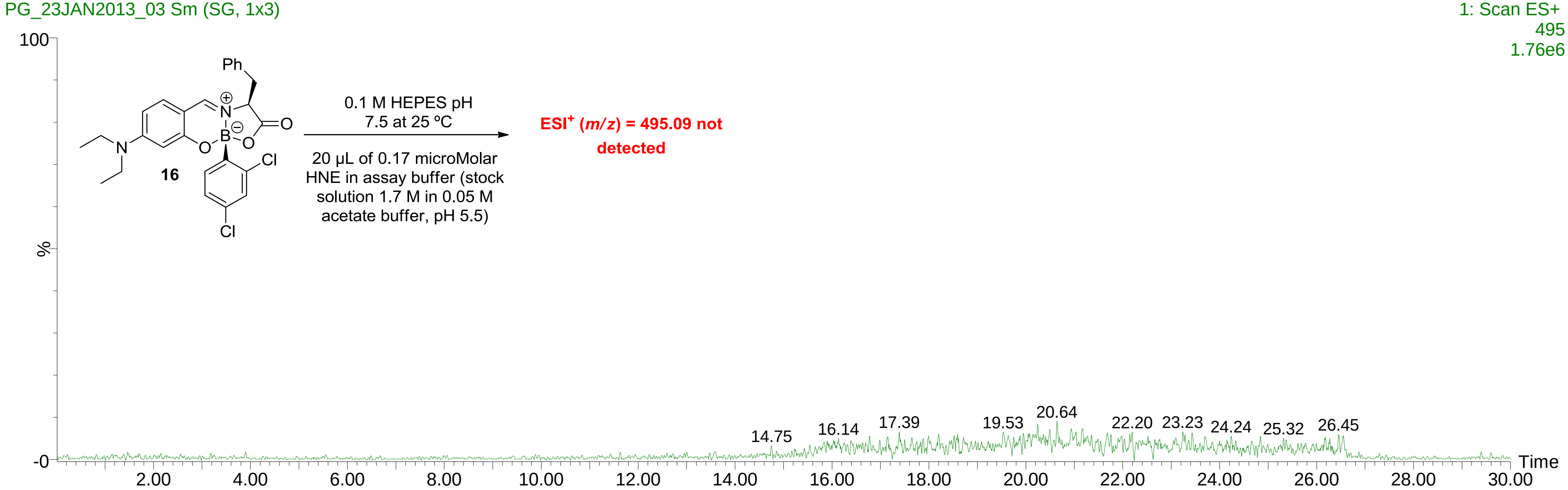
ESI MS studies:

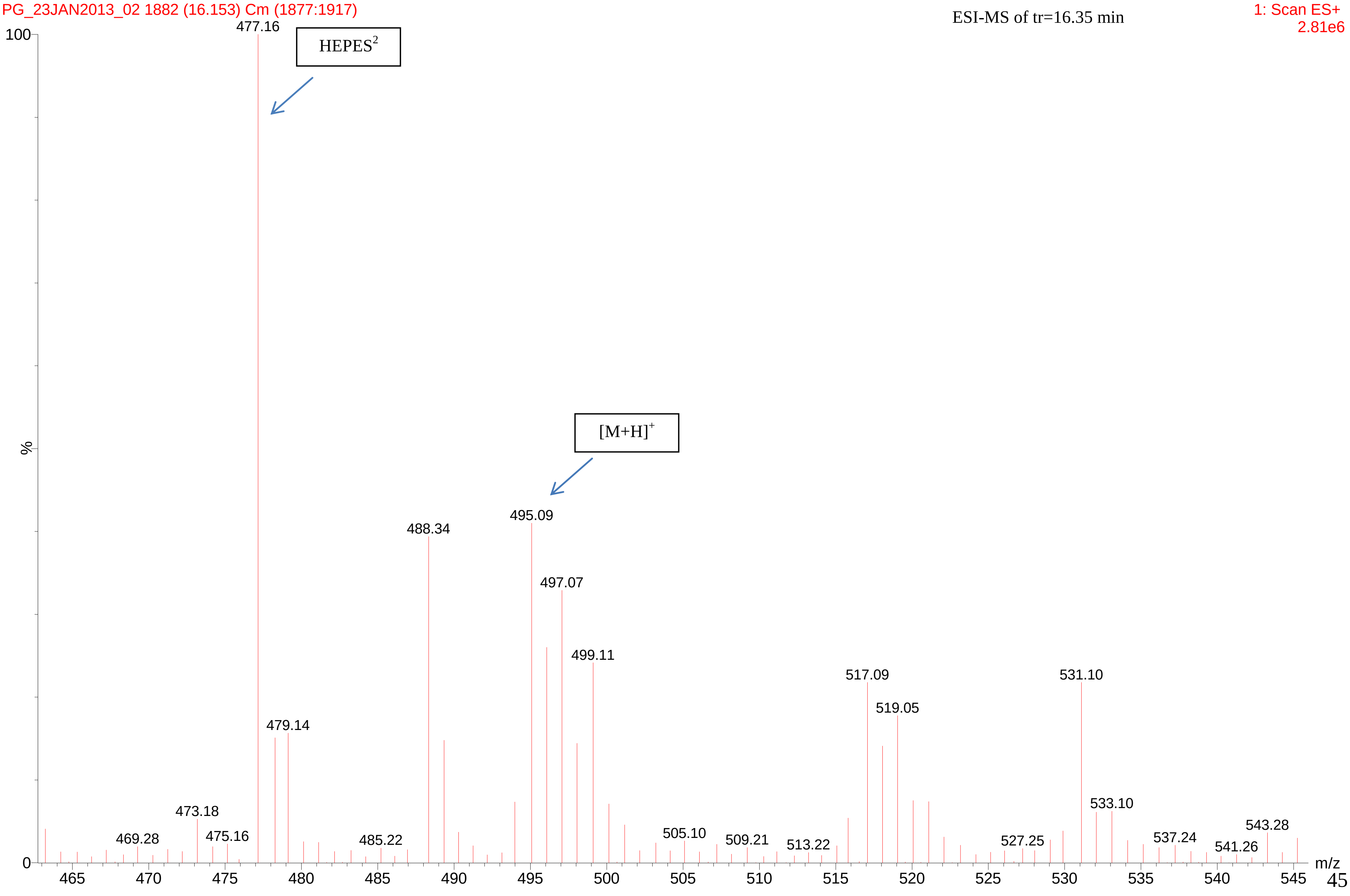


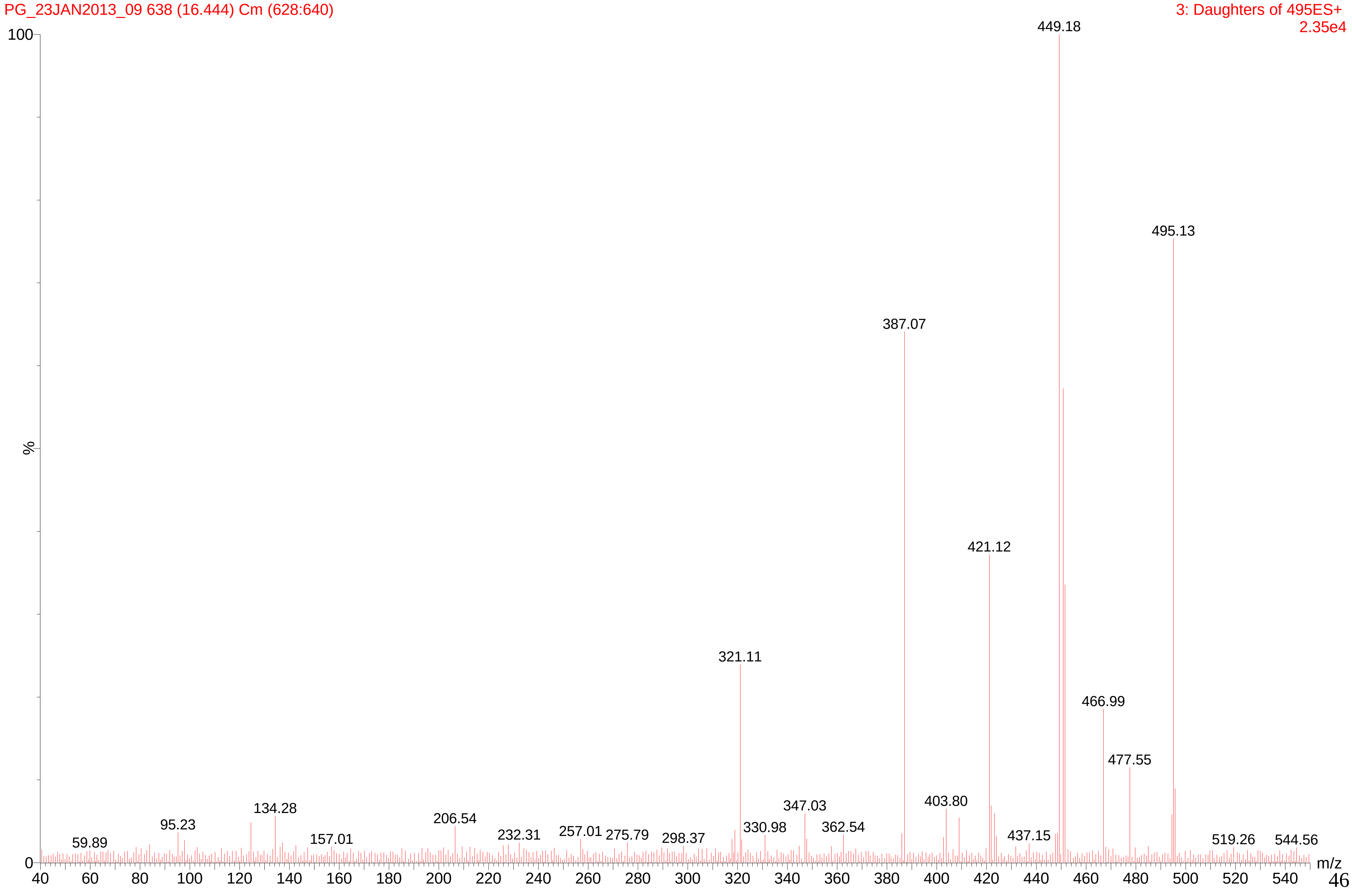
ESI+ 3.0kV/65V


SAMPLE BR 188_12_23JUL2012_POS_1 12 (0.121) Cm (2:23)
Scan ES+
7.07e7
100
%
0
m/z
517.22
519.15
385.26
341.26
363.25
747.39
748.37
200.20
295.28
533.18
535.14
515.99
403.26
23.01
204.22
278.24
407.25
571.21
725.41
38.91
250.24
296.40
749.45
779.30
86.01
130.13
166.19
177.18
537.14
574.33
62.86
417.18
461.22
604.18
633.37
689.20
781.30
495.18
703.36
50
100
150
200
250
300
350
400
450
500
550
600
650
700
750
800

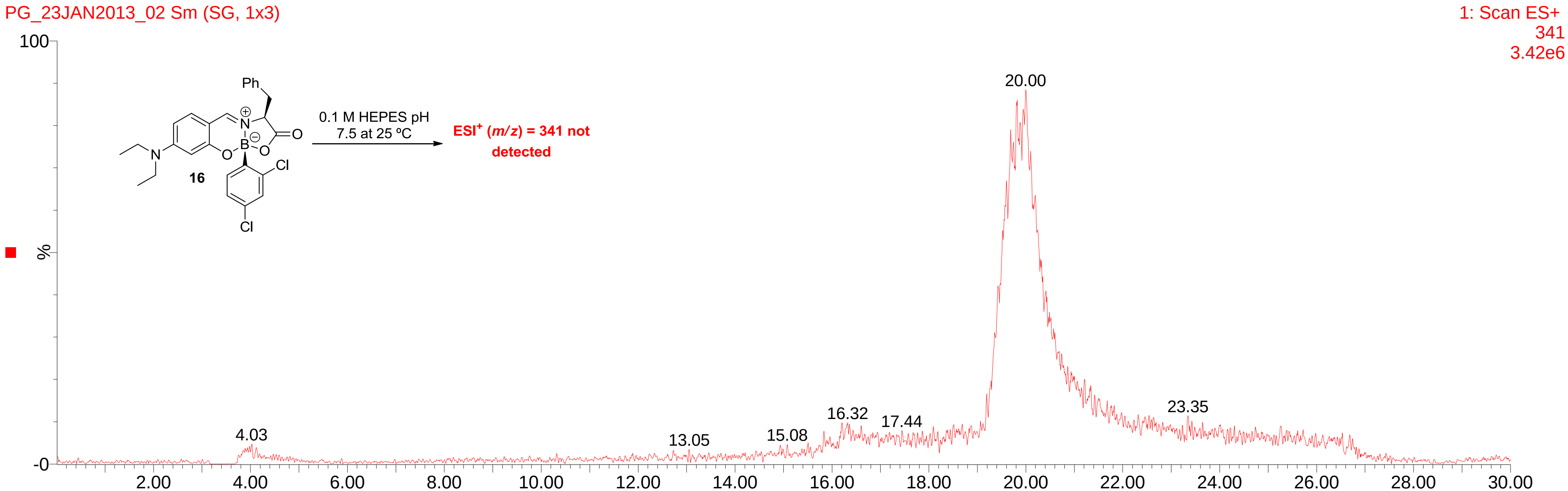

23-Jan-201313:07:56FM 189 HEPES
PG_23JAN2013_02 Sm (SG, 1x3)
1: Scan ES+
495
1.76e6
0.1 M HEPES pH
7.5 at 25 ºC
16
16
ESI+ (m/z) = 495.09
16.35
18.83
19.78
21.47
22.56
23.88
26.55
%
100
-0
2.00
4.00
6.00
8.00
10.00
12.00
14.00
16.00
18.00
20.00
22.00
24.00
26.00
28.00
30.00

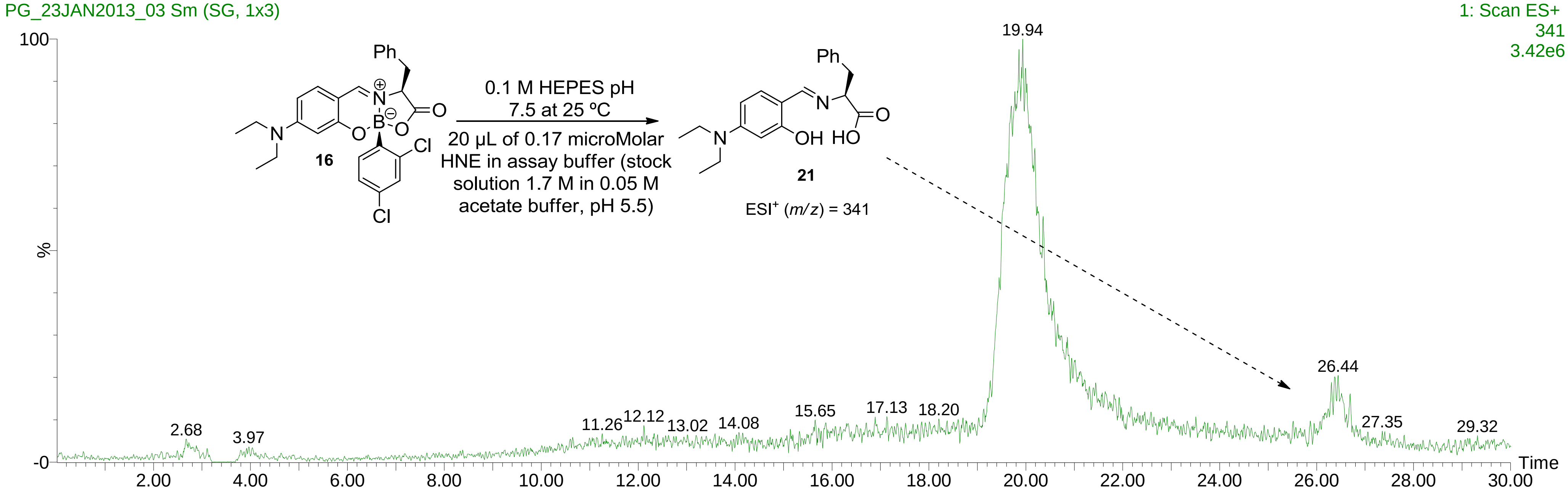

PG_23JAN2013_03 Sm (SG, 1x3)
1: Scan ES+
495
1.76e6
0.1 M HEPES pH
7.5 at 25 ºC
20 μL of 0.17 microMolar
HNE in assay buffer (stock
solution 1.7 M in 0.05 M
acetate buffer, pH 5.5)
16
ESI+ (m/z) = 495.09 not
detected
14.75
16.14
17.39
19.53
20.64
22.20
23.23
24.24
25.32
26.45
%
100
-0
Time
2.00
4.00
6.00
8.00
10.00
12.00
14.00
16.00
18.00
20.00
22.00
24.00
26.00
28.00
30.00

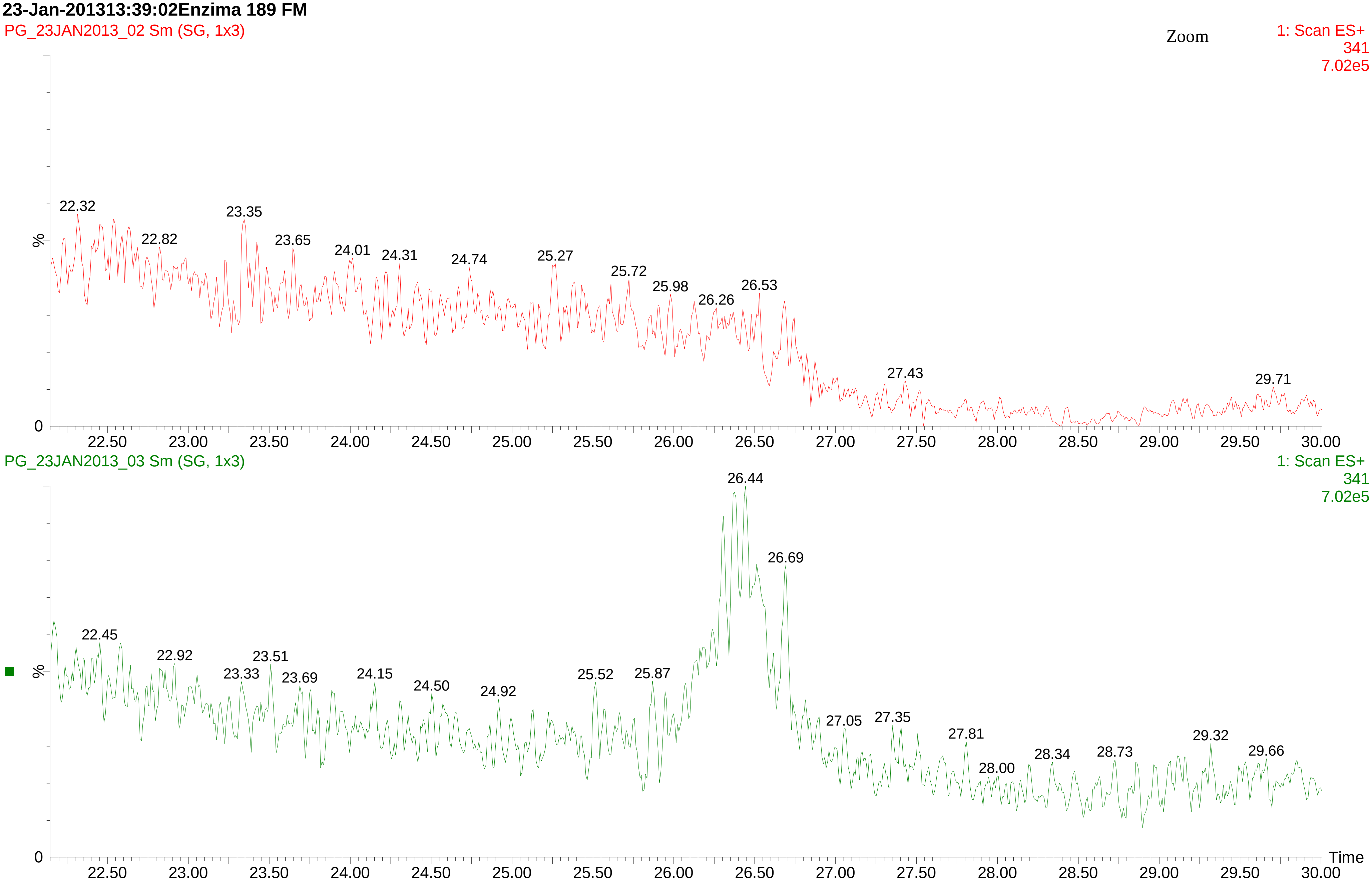

PG_23JAN2013_02 1882 (16.153) Cm (1877:1917)
ESI-MS of tr=16.35 min
1: Scan ES+
2.81e6
HEPES[2]
[M+H]+
477.16
488.34
495.09
497.07
499.11
517.09
531.10
519.05
479.14
473.18
533.10
469.28
475.16
485.22
505.10
509.21
513.22
527.25
537.24
541.26
543.28
%
m/z
100
0
465
470
475
480
485
490
495
500
505
510
515
520
525
530
535
540
545

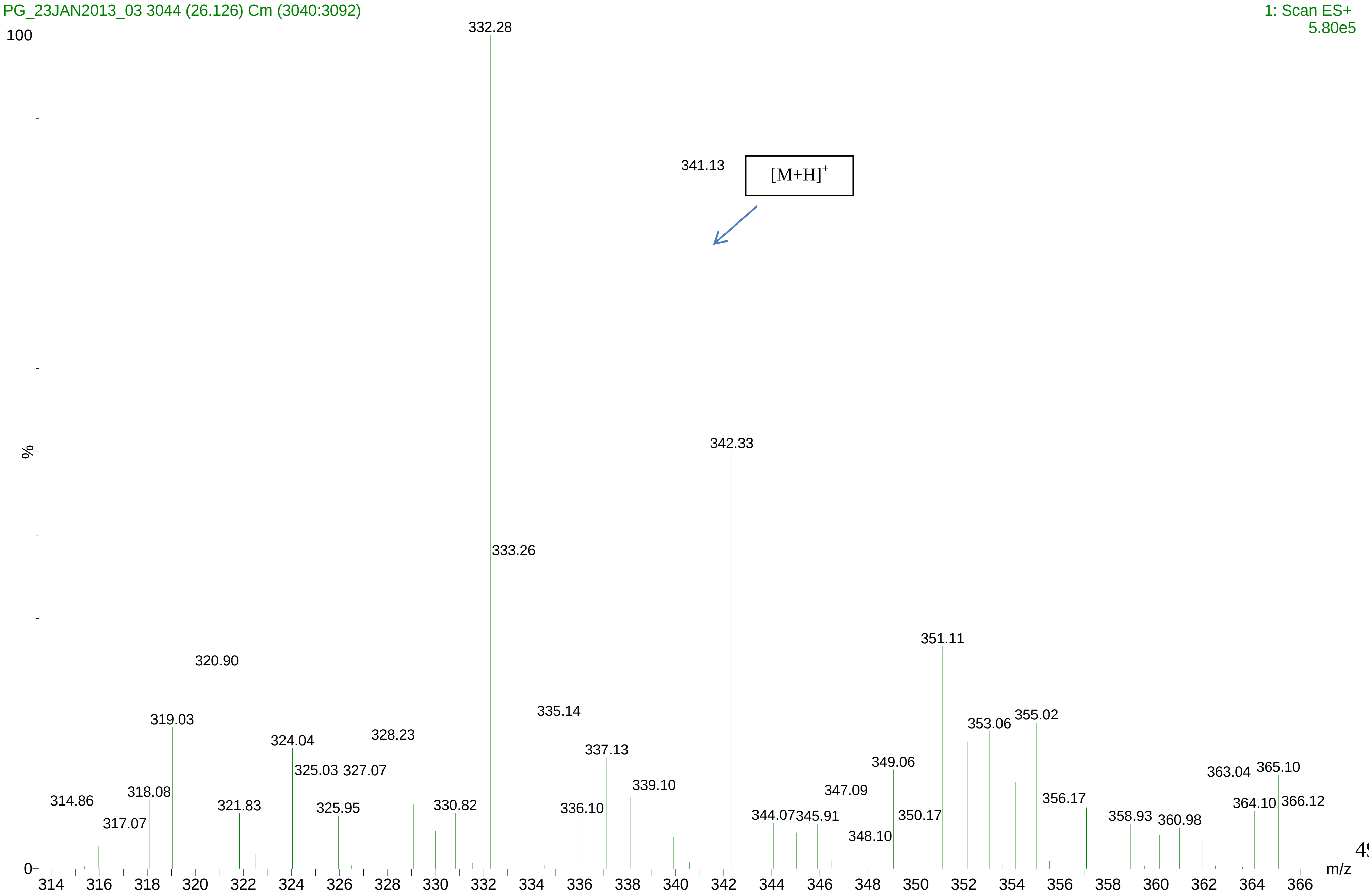

PG_23JAN2013_09 638 (16.444) Cm (628:640)
3: Daughters of 495ES+
2.35e4
100
%
0
449.18
495.13
387.07
421.12
321.11
466.99
477.55
403.80
347.03
134.28
206.54
95.23
330.98
362.54
257.01
275.79
232.31
437.15
298.37
59.89
157.01
519.26
544.56
40
60
80
100
120
140
160
180
200
220
240
260
280
300
320
340
360
380
400
420
440
460
480
500
520
540
m/z

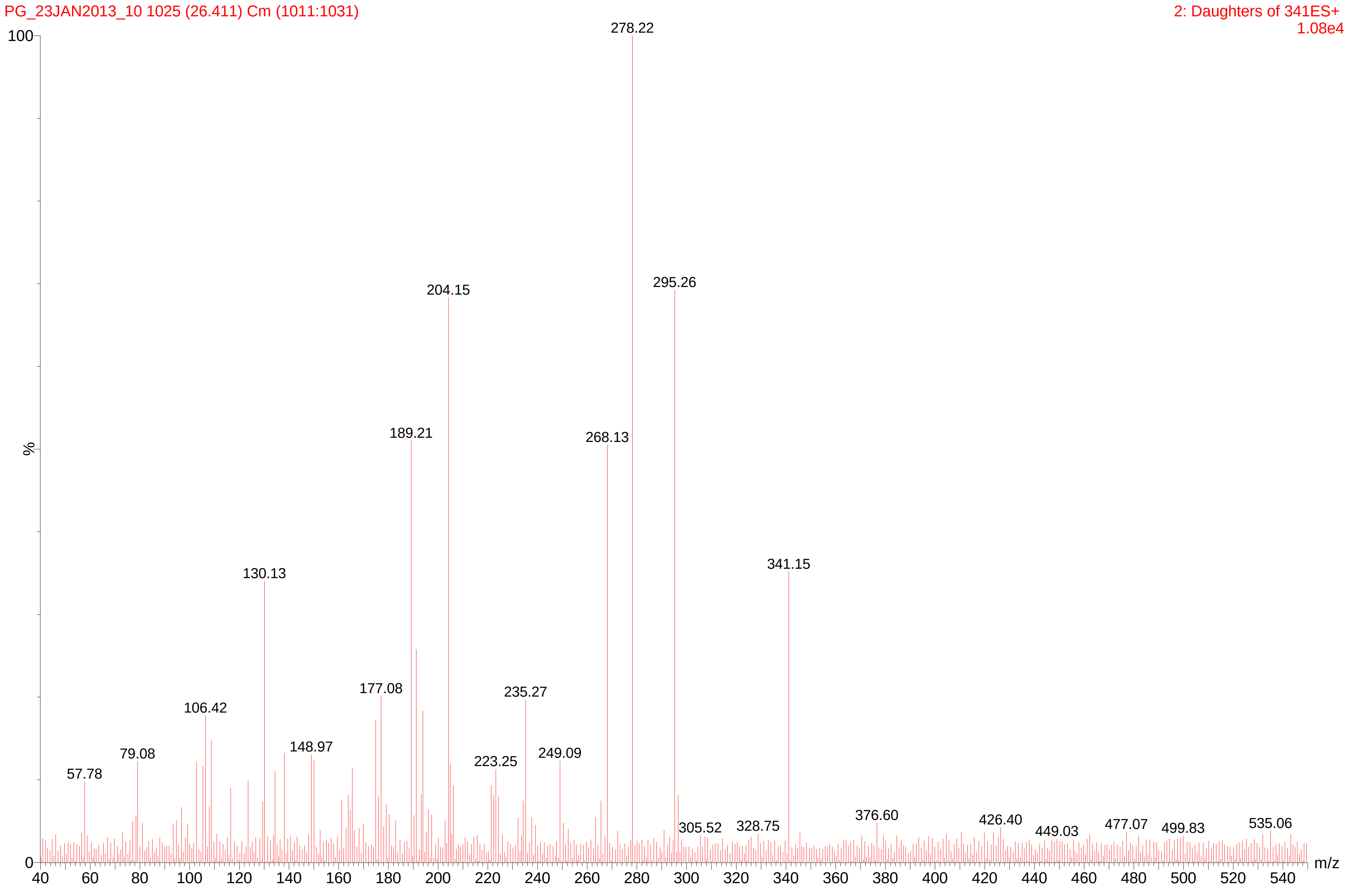
23-Jan-201313:07:56FM 189 HEPES






23-Jan-201313:39:02Enzima 189 FM
PG_23JAN2013_02 Sm (SG, 1x3)
Zoom
1: Scan ES+
341
7.02e5
22.32
22.82
23.35
23.65
24.01
24.31
24.74
25.27
25.72
25.98
26.26
26.53
27.43
29.71
%
0
22.50
23.00
23.50
24.00
24.50
25.00
25.50
26.00
26.50
27.00
27.50
28.00
28.50
29.00
29.50
30.00
PG_23JAN2013_03 Sm (SG, 1x3)
1: Scan ES+
341
7.02e5
26.44
26.69
22.45
22.92
23.33
23.51
23.69
24.15
24.50
24.92
25.52
25.87
27.05
27.35
27.81
28.00
28.34
28.73
29.32
29.66
%
0
Time


PG_23JAN2013_03 3044 (26.126) Cm (3040:3092)
1: Scan ES+
5.80e5
100
%
0
332.28
341.13
[M+H]+
342.33
333.26
351.11
320.90
335.14
319.03
353.06
355.02
324.04
328.23
337.13
349.06
325.03
327.07
363.04
365.10
339.10
318.08
347.09
314.86
356.17
364.10
366.12
321.83
325.95
330.82
336.10
358.93
360.98
317.07
344.07
345.91
350.17
348.10
314
316
318
320
322
324
326
328
330
332
334
336
338
340
342
344
346
348
350
352
354
356
358
360
362
364
366
m/z


PG_23JAN2013_10 1025 (26.411) Cm (1011:1031)
2: Daughters of 341ES+
1.08e4
100
%
0
278.22
204.15
295.26
189.21
268.13
130.13
341.15
177.08
235.27
106.42
148.97
79.08
249.09
223.25
57.78
376.60
426.40
305.52
328.75
449.03
477.07
499.83
535.06
40
60
80
100
120
140
160
180
200
220
240
260
280
300
320
340
360
380
400
420
440
460
480
500
520
540
m/z

Computational Methodology

Docking studies: The 3D structure coordinates of HNE were obtained from the Protein Data Bank, PDB code 1HNE with a 1.84 Å resolution. To prepare the enzyme for the docking studies, the co-crystallized inhibitor as well as crystallographic waters, included in the PDB structure, were removed. Hydrogen atoms were added and the protonation states were correctly assigned using the Protonate-3D tool within the Molecular Operating Environment (MOE) 2011.10 software package[16], energy was minimized using MMFF94x forcefield. Molecular docking studies were then performed using the GoldScore scoring function from GOLD 5.1 software package and each ligand was subjected to 1000 docking runs. Minimization of the structure generated from the reaction of 16 with His57 and the Ser195 in the HNE pocket was performed with MOE software using MMFF94x forcefield.

DFT calculations: Calculations were performed using the Gaussian 09 software package,[28] and the M06-2X functional, without symmetry constraints. That is a hybrid meta-GGA functional developped by Truhlar and Zhao,[29] and it was shown to perform very well for main-group kinetics, providing a good description of long range effects such as van der Waals interactions or π-π stacking.[30,31] The optimized geometries were obtained 6-31G(d,p) basis set.[32] Transition state optimizations were performed with the Synchronous Transit-Guided Quasi-Newton Method (STQN) developed by Schlegel *et al*,[33] following extensive searches of the Potential Energy Surface. Frequency calculations were performed to confirm the nature of the stationary points, yielding one imaginary frequency for the transition states and none for the minima. Each transition state was further confirmed by following its vibrational mode downhill on both sides and obtaining the minima presented on the energy profile. The atomic charges presented were obtained by means of a Natural Population Analysis (NPA),[34] performed with the *NBO 5.0* program.[35]

Single point energy calculations were performed using the 6-311++G(d,p)[36] basis set, with solvent effects (MeOH) calculated by means of the Polarizable Continuum Model (PCM) initially devised by Tomasi and coworkers,[37] with radii and non-electrostatic terms of the SMD solvation model, developped by Truhler *et al*.[38]

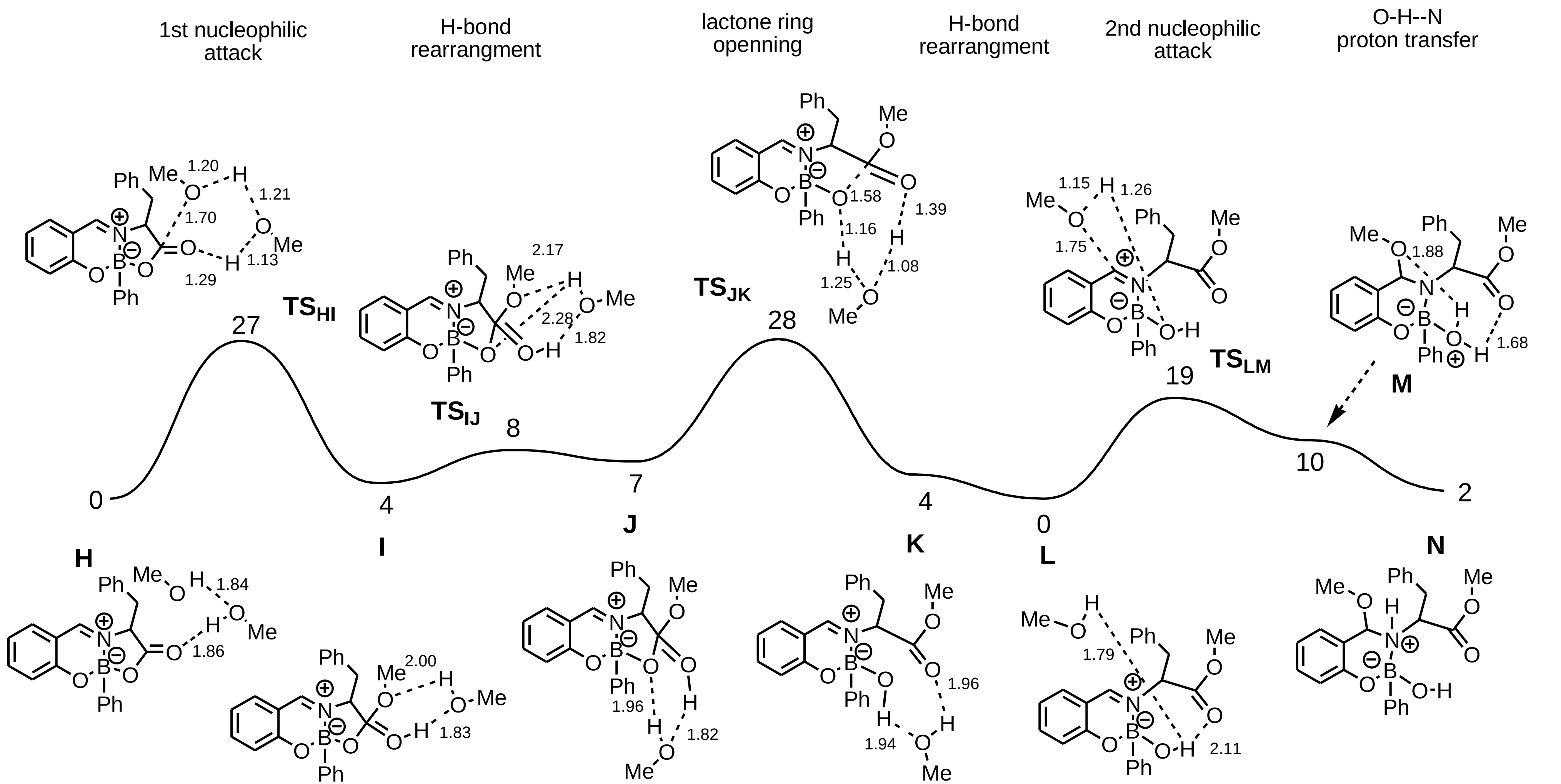


Figure S1 Energy profile (kcal/mol) calculated for the alternative path of the reaction between **3** and methanol, with the attack on the lactone C=O group first. The energy values are referred to **A** and relevant distances are indicated (Å).

Atomic Coordinates for all the optimized molecules (M06-2X/6-31G(d,p))

3

B	-1.702303	1.212052	-0.568418
N	-0.782112	-0.005822	-1.051311
H	1.309188	-0.047291	-1.390187
C	-2.312434	0.945857	0.890909
O	-0.686101	2.276995	-0.572185
H	0.193711	-0.007771	1.469785
C	-3.200728	-0.112368	1.128793
O	-2.717112	1.406323	-1.608391
H	-2.497508	-2.830213	-3.254297
O	1.550646	2.492255	-0.464738
C	-3.716012	-0.357256	2.397936
H	-4.716691	-2.575709	-4.346258
C	-3.349948	0.460053	3.465630
H	-3.750526	0.273159	4.457344
C	-2.470854	1.518029	3.253898
C	-1.960045	1.754155	1.978897
H	3.102830	-1.864982	0.137132
H	-3.500857	-0.761228	0.306951
C	0.561660	1.818108	-0.553210
H	-4.963576	1.464131	-2.844039
C	0.583381	0.273466	-0.636634
H	5.997966	0.492379	2.254567
C	0.902971	-0.383146	0.725631
H	-0.489232	-1.692319	-2.192680
C	2.325780	-0.143156	1.164652
H	-1.277596	2.585380	1.816570
C	3.345459	-1.004458	0.757163
H	-2.185933	2.160831	4.081461
C	4.662615	-0.779516	1.145479
H	-4.403870	-1.182436	2.556845
C	4.971934	0.314428	1.948921
H	-5.932749	-0.418533	-4.142044
C	3.960861	1.179214	2.359507
H	0.717892	-1.457972	0.615540
C	2.646034	0.951416	1.969176
H	5.445222	-1.459755	0.824786
C	-1.183037	-0.915144	-1.863770
H	4.197362	2.035486	2.982628
C	-2.514800	-0.852283	-2.405563
H	1.859097	1.632197	2.282002
C	-3.058880	-1.903839	-3.162530
C	-4.287297	-1.761851	-3.774121
C	-4.969492	-0.539863	-3.656080
C	-4.444671	0.517007	-2.935418
C	-3.211444	0.377387	-2.279728

17

B	-1.674641	1.351983	-0.686442
N	-0.804403	0.089595	-1.179239
H	1.265535	-0.122066	-1.486422
C	-2.256812	1.098000	0.795491
O	-0.668804	2.379211	-0.755096
H	0.064701	0.030438	1.324478
C	-3.113872	0.030494	1.095313
O	-2.756227	1.519076	-1.685641
H	-2.594456	-2.714608	-3.340789
H	1.195539	2.210100	0.126779
C	-3.571251	-0.194471	2.390884
H	-4.841924	-2.452925	-4.371798
C	-3.178087	0.654260	3.423669
H	-3.532581	0.482151	4.435562
C	-2.330215	1.724735	3.150541
C	-1.877455	1.937962	1.849733
H	3.176925	-1.422150	-0.214676
H	-3.433157	-0.644099	0.301376
C	0.639083	1.865585	-0.753930
H	-5.032884	1.586011	-2.859422
C	0.572533	0.307981	-0.754486
H	5.787263	0.750404	2.409730
C	0.814886	-0.342443	0.621392
H	-0.566575	-1.609040	-2.315454
C	2.203561	-0.060207	1.138254
H	-1.215991	2.773399	1.629660
C	3.317753	-0.690289	0.577947
H	-2.025789	2.393239	3.951001

C	4.600910	-0.401596	1.030989
H	-4.233949	-1.029766	2.598435
C	4.786902	0.524550	2.054889
H	-6.044230	-0.290545	-4.131586
C	3.684113	1.155876	2.622576
H	0.657574	-1.423046	0.518424
C	2.401535	0.864328	2.166070
H	5.456257	-0.901484	0.587505
C	-1.237602	-0.814608	-1.978270
H	3.820995	1.877019	3.421965
C	-2.580372	-0.737488	-2.491433
H	1.537500	1.354125	2.609310
C	-3.149922	-1.786011	-3.233694
C	-4.393865	-1.640713	-3.811653
C	-5.067962	-0.415662	-3.672908
C	-4.519402	0.637546	-2.966787
C	-3.266324	0.496472	-2.342971
H	1.175190	2.212080	-1.646575

18

B	-1.695125	1.281063	-0.641489
N	-0.804121	-0.111953	-0.982749
H	1.302503	-0.157490	-1.298744
C	-2.342616	1.091818	0.812295
O	-0.622688	2.275900	-0.696821
H	0.222800	0.192125	1.549176
C	-3.322446	0.113853	1.037226
O	-2.638522	1.493176	-1.716584
H	-2.311517	-2.548898	-3.697909
O	1.618265	2.428992	-0.616373
C	-3.875989	-0.082450	2.299563
H	-4.747633	-2.591008	-4.197499
C	-3.458129	0.705096	3.370080
H	-3.887446	0.556340	4.356086
C	-2.491616	1.687056	3.168863
C	-1.942304	1.874708	1.901675
H	3.046187	-1.856647	0.299996
H	-3.672107	-0.500366	0.206867
C	0.606292	1.782800	-0.642433
H	-5.177058	1.265820	-2.311769
C	0.580942	0.246094	-0.581646
H	6.054084	0.559238	2.179996
C	0.902528	-0.277682	0.830065
H	-1.162349	-0.878908	-0.410593
C	2.341438	-0.045128	1.221256
H	-1.192534	2.647781	1.747065
C	3.326298	-0.962714	0.853485
H	-2.169152	2.308392	3.999030
C	4.658095	-0.748889	1.194751
H	-4.634863	-0.844609	2.448879
C	5.016438	0.389689	1.911268
H	-6.174030	-0.680121	-3.517839
C	4.039770	1.309891	2.281907
H	0.692946	-1.355063	0.840030
C	2.709925	1.093600	1.938000
H	5.413853	-1.471996	0.904935
C	-0.936400	-0.481904	-2.422331
H	4.313912	2.200319	2.837950
C	-2.391737	-0.628314	-2.741947
H	1.950250	1.818718	2.216937
C	-2.948901	-1.720494	-3.398839
C	-4.311563	-1.742805	-3.681783
C	-5.111225	-0.666293	-3.297626
C	-4.569586	0.424584	-2.626118
C	-3.203910	0.443832	-2.343882
H	-0.364957	-1.392435	-2.626391
H	-0.493499	0.347981	-2.986015

MeOH

C	-0.472047	-0.059003	0.070798
O	0.563352	0.771193	0.546742
H	1.310486	0.213211	0.783410
H	-1.307901	0.591804	-0.192100
H	-0.823180	-0.772316	0.828373
H	-0.183809	-0.620688	-0.827722

A

H	0.943996	-0.319554	-1.239552
C	4.060943	0.727335	-2.906872
C	-2.238896	1.117327	1.409616
O	2.717737	0.551874	-2.504832
C	-0.421891	0.495065	-3.848630
B	-1.865249	1.157469	-0.147296
H	4.201322	1.662153	-3.462218
N	-1.053048	-0.132949	-0.605541
H	4.322860	-0.106802	-3.561042
O	-0.834609	2.188352	-0.450379
H	4.737111	0.722852	-2.044083
H	0.253020	0.134706	1.720697
C	-3.091007	0.126115	1.914363
O	0.381047	-0.599186	-3.457027
O	-3.023328	1.280467	-1.030990
H	-3.038195	-3.055163	-2.411690
C	-3.403328	0.058014	3.268783
H	1.285280	-0.262799	-3.318055
O	1.364951	2.323808	-0.857799
H	-5.370318	-2.834514	-3.248807
H	-1.428050	0.114715	-4.048083
C	-2.863944	0.990528	4.153085
H	-3.104270	0.940581	5.210710
H	-0.049197	0.974614	-4.761757
C	-2.017969	1.986644	3.674018
H	3.156204	-1.298852	-0.198496
H	-0.503271	1.265722	-3.066791
C	-1.711543	2.045518	2.315657
H	-3.521040	-0.610143	1.236020
C	0.368966	1.678502	-0.610880
H	-5.401664	1.293277	-1.985435
C	0.363570	0.148454	-0.442972
H	5.989770	1.368511	1.615835
C	0.899067	-0.277315	0.939995
C	2.326451	0.168890	1.140621
H	-0.898762	-1.867971	-1.695279
C	3.372107	-0.466086	0.466447
H	-1.053606	2.828065	1.944416
C	4.685249	-0.039633	0.639738
H	-1.600615	2.719402	4.358354
C	4.965788	1.035331	1.480739
H	-4.066043	-0.719402	3.637147
C	3.927887	1.678438	2.148599
H	-6.535992	-0.650595	-3.037499
C	2.616011	1.246059	1.978107
H	0.823406	-1.369190	0.993533
H	5.491469	-0.550884	0.122164
C	-1.552127	-1.085163	-1.310879
H	4.139065	2.518319	2.802582
C	-2.941184	-1.032452	-1.687446
H	1.803011	1.749461	2.495711
C	-3.579804	-2.118642	-2.308784
C	-4.871264	-1.994860	-2.779767
C	-5.524056	-0.758083	-2.659096
C	-4.906686	0.333169	-2.074420
C	-3.604895	0.214028	-1.564751
H	2.467164	1.262275	-1.883883

TS_{AB}

H	1.235400	-0.696562	-0.734235
C	2.734695	0.737999	-3.897589
C	-2.061579	1.053072	1.429474
O	2.155293	0.220432	-2.695122
C	-0.817207	0.953004	-3.482320
B	-1.618259	0.911455	-0.103653
H	2.429733	1.776485	-4.054560
N	-0.846569	-0.390172	-0.447084
H	2.400031	0.119859	-4.731693
O	-0.507019	1.981268	-0.421162
H	3.820176	0.680081	-3.814339
H	0.270729	0.366676	1.958996
C	-2.670964	-0.025193	2.083430
O	-0.217030	-0.188578	-2.852120
O	-2.740961	1.143443	-1.007921
H	-2.352340	-2.785557	-3.238459

C	-3.102209	0.076266	3.403315
H	1.040006	-0.041944	-2.790035
O	1.636207	1.931535	-1.050728
H	-4.720547	-2.665530	-3.996598
H	-1.703262	0.639113	-4.036393
C	-2.926152	1.268653	4.102360
H	-3.256924	1.350674	5.133440
H	-0.077859	1.348697	-4.183594
C	-2.320880	2.352896	3.472484
H	3.106108	-1.850714	1.021759
H	-1.083097	1.718293	-2.749590
C	-1.895731	2.241440	2.149844
H	-2.796206	-0.963926	1.546878
C	0.626387	1.391559	-0.566883
H	-5.163812	1.064073	-1.873944
C	0.543259	-0.082777	-0.146387
H	6.108718	1.025724	2.092388
C	0.921797	-0.253973	1.339168
C	2.370417	0.090854	1.579845
H	-0.530739	-1.916169	-1.829837
C	3.377751	-0.847097	1.342026
H	-1.419050	3.090735	1.665646
C	4.716744	-0.515051	1.524149
H	-2.179513	3.284919	4.012290
C	5.065294	0.765727	1.945258
H	-3.570879	-0.773912	3.890738
C	4.069290	1.709512	2.181909
H	-6.119880	-0.728230	-3.315627
C	2.731727	1.372730	1.999262
H	0.714218	-1.297222	1.597059
H	5.487794	-1.257896	1.344831
C	-1.022751	-0.944729	-1.717580
H	4.333975	2.709492	2.510450
C	-2.450867	-0.953504	-2.132020
H	1.953228	2.109827	2.183148
C	-2.985031	-1.952059	-2.943061
C	-4.304694	-1.883552	-3.371330
C	-5.087540	-0.793138	-2.985592
C	-4.568084	0.211893	-2.181228
C	-3.240918	0.141743	-1.744464
H	2.149677	0.959154	-1.921593

B

H	1.038186	-0.713185	-0.825931
C	3.426874	0.016503	-3.458653
C	-2.089482	0.990064	1.513975
O	2.454654	-0.014391	-2.428199
C	-0.924324	0.997786	-3.431375
B	-1.819497	0.783682	-0.047197
H	3.264259	0.851091	-4.149904
N	-1.023961	-0.445785	-0.453308
H	3.433571	-0.920508	-4.024563
O	-0.638876	1.960910	-0.444599
H	4.399176	0.141773	-2.979932
H	0.176508	0.162827	1.967929
C	-2.560907	-0.093562	2.266425
O	-0.332129	-0.104299	-2.749888
O	-2.971172	1.059602	-0.854460
H	-2.456082	-2.553453	-3.549253
C	-2.833271	0.030858	3.625858
H	1.558373	-0.150139	-2.794078
O	1.500488	1.953322	-0.974558
H	-4.811746	-2.384035	-4.335637
H	-1.643821	0.654568	-4.180698
C	-2.635202	1.252943	4.265273
H	-2.840490	1.353684	5.326773
H	-0.102071	1.519678	-3.927760
C	-2.169821	2.343720	3.535809
H	3.134910	-1.422032	0.246958
H	-1.417819	1.689190	-2.741787
C	-1.903035	2.210087	2.174170
H	-2.695909	-1.054800	1.775078
C	0.435874	1.344568	-0.561788
H	-5.361011	1.055497	-1.792139
C	0.368961	-0.135097	-0.184421
H	5.877554	1.546969	1.695310

C	0.842633	-0.346923	1.270503
C	2.260517	0.144186	1.438702
H	-0.739312	-1.886890	-1.930135
C	3.324921	-0.513227	0.813421
H	-1.535979	3.067156	1.614703
C	4.619883	-0.012173	0.903977
H	-2.014979	3.299621	4.027931
C	4.867921	1.155664	1.622706
H	-3.193398	-0.824817	4.189751
C	3.815399	1.816842	2.248948
H	-6.260498	-0.563487	-3.461457
C	2.520072	1.314573	2.154041
H	0.761439	-1.420663	1.466828
H	5.437086	-0.535796	0.417363
C	-1.165387	-0.882095	-1.823283
H	4.001861	2.727362	2.809405
C	-2.603536	-0.866747	-2.239315
H	1.694459	1.835085	2.634091
C	-3.109410	-1.771322	-3.169953
C	-4.422614	-1.673908	-3.614456
C	-5.233399	-0.651074	-3.120899
C	-4.744742	0.257513	-2.191186
C	-3.425062	0.153626	-1.745478
H	2.155960	1.277253	-1.288735

C

H	0.913784	-2.302434	-0.412666
C	1.512185	2.950402	0.800295
C	-2.347317	0.393436	0.631593
O	0.835939	3.052663	-0.426243
C	-0.678614	-3.374232	-3.411895
B	-1.756671	-0.283371	-0.693705
H	2.561795	2.651088	0.677439
N	-1.137267	-1.779540	-0.224233
H	1.027186	2.233960	1.485688
O	-0.524718	0.354259	-1.169175
H	1.487160	3.933152	1.278895
H	0.223266	-0.418949	1.903183
C	-3.371794	-0.232889	1.355700
O	-0.566072	-2.503054	-2.303149
O	-2.702427	-0.467682	-1.767422
H	-3.155953	-4.957179	-1.417789
C	-3.877932	0.322738	2.527194
H	1.023124	2.242389	-0.922523
O	1.680086	0.295905	-0.813188
H	-5.544627	-4.842822	-2.108277
H	-0.482528	-4.414387	-3.115660
C	-3.361863	1.528780	2.997361
H	-3.749913	1.965704	3.912420
H	0.075284	-3.054064	-4.129862
C	-2.353664	2.173909	2.285478
H	2.000523	-3.674878	1.860595
H	-1.672636	-3.312301	-3.866205
C	-1.851698	1.612904	1.111261
H	-3.799730	-1.168341	0.989471
C	0.579681	-0.195609	-0.712869
H	-5.198723	-0.556189	-2.468427
C	0.307088	-1.509286	0.029898
H	5.876960	-1.964416	2.538451
C	0.609719	-1.375997	1.534887
C	2.083956	-1.524183	1.830163
H	-1.087930	-3.821452	-0.812285
C	2.640262	-2.799388	1.954275
H	-1.079899	2.135374	0.546126
C	3.998549	-2.960673	2.206733
H	-1.958448	3.120634	2.642343
C	4.817145	-1.842270	2.339638
H	-4.673440	-0.178668	3.070341
C	4.270552	-0.568035	2.217480
H	-6.553952	-2.641039	-2.653286
C	2.911683	-0.410377	1.962893
H	0.063104	-2.168922	2.061315
H	4.416396	-3.957401	2.306087
C	-1.395049	-2.846365	-1.231239
H	4.903701	0.307865	2.315916
C	-2.859774	-2.836440	-1.554793

H	2.489293	0.582521	1.851177
C	-3.619628	-3.999674	-1.646148
C	-4.951997	-3.937822	-2.037840
C	-5.514999	-2.697599	-2.343711
C	-4.771392	-1.527786	-2.247320
C	-3.433966	-1.588612	-1.848558
H	-1.608398	-2.044658	0.642474

D

H	0.440049	-1.529910	-0.803146
C	1.865840	0.776403	-3.236829
C	4.447674	-1.227573	-0.388675
C	-2.032438	1.673814	0.824187
O	2.039240	-0.558459	-2.804178
O	4.296862	-0.116537	-1.255506
C	-0.710260	-1.496585	-3.916909
B	-1.410531	1.214570	-0.584658
H	2.419788	0.983551	-4.163099
H	3.477586	-1.638049	-0.082969
N	-1.391416	-0.471032	-0.554500
H	5.007810	-0.961037	0.515599
H	2.183100	1.499531	-2.473535
O	0.028395	1.479835	-0.682536
H	5.007695	-1.993781	-0.929792
H	0.799332	0.937891	-3.413314
H	-0.378257	-0.558345	2.005693
C	-3.410986	1.577088	1.062120
O	-0.710221	-0.798855	-2.688914
O	-2.122700	1.674509	-1.748358
H	-4.048499	-2.263590	-2.883805
C	-3.959529	1.913238	2.296576
H	2.934443	-0.600848	-2.423682
H	3.685732	0.488681	-0.807581
O	1.954205	0.588407	0.022948
H	-6.061224	-1.103154	-3.782747
H	-0.860293	-2.572981	-3.750952
C	-3.132859	2.359169	3.325805
H	-3.557057	2.623773	4.289540
H	0.278592	-1.335096	-4.345239
C	-1.762253	2.470698	3.110336
H	1.048301	-3.796044	0.857038
H	-1.495296	-1.124244	-4.585284
C	-1.222235	2.130932	1.870893
H	-4.071941	1.242883	0.262793
C	0.781204	0.490249	-0.256516
H	-4.292597	2.691188	-2.737088
C	-0.007184	-0.815690	-0.105897
H	4.737639	-3.271954	2.987891
C	-0.023993	-1.350024	1.335366
C	1.311465	-1.879502	1.799265
H	-1.903831	-2.167367	-1.728170
C	1.708649	-3.173475	1.456989
H	-0.151633	2.238232	1.705137
C	2.937825	-3.674247	1.877266
H	-1.114911	2.828708	3.905323
C	3.781194	-2.883379	2.653180
H	-5.030710	1.833541	2.456355
C	3.391284	-1.591784	3.000487
H	-6.167769	1.375753	-3.722111
C	2.165609	-1.092724	2.573244
H	-0.759846	-2.163654	1.375756
H	3.232828	-4.682330	1.604216
C	-1.787561	-1.076530	-1.860255
H	4.045154	-0.969571	3.603162
C	-3.070441	-0.443741	-2.311646
H	1.869693	-0.080063	2.831856
C	-4.120735	-1.178411	-2.852976
C	-5.242918	-0.531638	-3.359598
C	-5.297916	0.862024	-3.324622
C	-4.258931	1.608272	-2.780631
C	-3.134733	0.958419	-2.266561
H	-2.075684	-0.762057	0.145659

TS_{DE}

H	0.546454	-1.611359	-0.756253
C	1.535027	1.027417	-2.893401

C	4.375951	-0.995074	-0.385954
C	-1.991001	1.740413	0.643529
O	1.763332	0.129088	-1.807277
O	3.875287	0.284111	-0.753052
C	-0.908660	-1.716286	-3.929974
B	-1.268442	1.208549	-0.693164
H	2.084990	0.632803	-3.751989
H	3.562403	-1.694009	-0.149745
N	-1.234364	-0.481679	-0.563802
H	5.015329	-0.902196	0.495284
H	1.889933	2.032994	-2.651291
O	0.139814	1.503793	-0.732798
H	4.968571	-1.393979	-1.212813
H	0.468080	1.060854	-3.111107
H	0.054323	-0.310710	1.970114
C	-3.382551	1.716699	0.814694
O	-0.666396	-1.065321	-2.700639
O	-1.936448	1.560169	-1.940711
H	-4.059574	-2.383271	-2.578585
C	-3.973649	2.124616	2.008286
H	2.890330	0.156705	-1.474129
H	3.112236	0.593675	-0.011696
O	1.901015	0.772129	0.474348
H	-6.051475	-1.242632	-3.544081
H	-1.139970	-2.779677	-3.773774
C	-3.178435	2.567985	3.062332
H	-3.636221	2.888039	3.993662
H	0.011346	-1.630060	-4.508282
C	-1.794391	2.603168	2.913578
H	0.912948	-3.714505	0.652200
H	-1.735250	-1.248623	-4.475522
C	-1.210744	2.193963	1.716097
H	-4.023149	1.382454	0.000125
C	0.983738	0.498078	-0.396118
H	-4.089212	2.561822	-2.998158
C	0.161482	-0.805344	-0.129596
H	4.697734	-3.863711	2.670401
C	0.187468	-1.202966	1.351640
C	1.454523	-1.933898	1.732479
H	-1.865670	-2.259834	-1.537217
C	1.667799	-3.235815	1.273523
H	-0.128975	2.227191	1.595718
C	2.830659	-3.928204	1.600994
H	-1.169829	2.954291	3.729905
C	3.792295	-3.325930	2.407978
H	-5.054246	2.101279	2.115753
C	3.583054	-2.031809	2.879682
H	-6.045965	1.228990	-3.779561
C	2.425797	-1.337834	2.538467
H	-0.663420	-1.872101	1.540871
H	2.981066	-4.938174	1.232690
C	-1.710818	-1.192828	-1.779550
H	4.329337	-1.556230	3.508713
C	-2.987518	-0.556108	-2.244856
H	2.276371	-0.315644	2.870628
C	-4.085029	-1.299157	-2.669705
C	-5.194894	-0.664432	-3.216578
C	-5.187370	0.725273	-3.346248
C	-4.101686	1.480399	-2.918982
C	-2.991805	0.844611	-2.354911
H	-1.889734	-0.707058	0.186230

E

H	0.502483	-1.585224	-0.908425
C	2.054546	1.369857	-2.643514
C	4.610497	-1.544611	-0.338869
C	-1.987916	1.679196	0.626963
O	1.650713	0.228852	-1.890456
O	4.013884	-0.300952	-0.650098
C	-0.992095	-1.456499	-4.172020
B	-1.400798	1.203889	-0.795708
H	2.773783	1.009746	-3.380855
H	3.866391	-2.301572	-0.063234
N	-1.297422	-0.477504	-0.727749
H	5.267825	-1.388679	0.518270
H	2.530331	2.112618	-1.995720

O	-0.018523	1.537538	-1.015448
H	5.213779	-1.919186	-1.175381
H	1.191359	1.815411	-3.141124
H	0.048315	-0.096331	1.728831
C	-3.317925	1.427441	0.993333
O	-0.764007	-0.864013	-2.912209
O	-2.244346	1.580222	-1.921937
H	-4.020279	-2.498913	-2.749153
C	-3.814733	1.810409	2.236618
H	3.341707	-0.430055	-1.338606
H	2.595670	0.558165	0.194752
O	1.740383	1.028361	0.257555
H	-6.172829	-1.492051	-3.496555
H	-1.107003	-2.546763	-4.081393
C	-2.983093	2.463147	3.143871
H	-3.365925	2.766688	4.113644
H	-0.113068	-1.236207	-4.777146
C	-1.659973	2.727722	2.799147
H	0.797044	-3.644882	0.826106
H	-1.885871	-1.044628	-4.653492
C	-1.170779	2.338020	1.553528
H	-3.987054	0.932349	0.288711
C	0.893489	0.561131	-0.741591
H	-4.549734	2.434875	-2.745297
C	0.120464	-0.742132	-0.325926
H	4.482867	-3.712682	3.025811
C	0.172798	-1.033323	1.179941
C	1.422928	-1.752225	1.636094
H	-1.802500	-2.240999	-1.795630
C	1.567110	-3.121031	1.389165
H	-0.135764	2.538654	1.284296
C	2.661374	-3.825826	1.882115
H	-1.009563	3.240884	3.501718
C	3.632572	-3.165383	2.631392
H	-4.849415	1.605966	2.496527
C	3.506043	-1.799887	2.871350
H	-6.420426	0.978527	-3.513026
C	2.410893	-1.097566	2.374595
H	-0.681890	-1.676252	1.429742
H	2.749951	-4.890839	1.691700
C	-1.753888	-1.150402	-1.972475
H	4.260703	-1.277444	3.451007
C	-3.105495	-0.605525	-2.331310
H	2.305478	-0.033809	2.565813
C	-4.155027	-1.418982	-2.748947
C	-5.354953	-0.858705	-3.172261
C	-5.488912	0.530897	-3.180048
C	-4.453258	1.354961	-2.758068
C	-3.247809	0.793297	-2.323505
H	-1.927305	-0.774637	0.018981

F

H	0.491554	-1.431872	-1.296548
C	2.836833	-0.390886	-1.297143
C	3.579231	2.420048	1.415784
C	-1.722836	1.898940	0.377296
O	2.396166	-0.126922	0.024997
O	2.176039	2.558352	1.274113
C	-2.118396	-2.924042	-2.992279
B	-0.891281	1.020376	-0.692558
H	3.878519	-0.069528	-1.346573
H	3.899371	1.391973	1.216711
N	-1.174304	-0.622418	-0.347635
H	3.825655	2.679907	2.447004
H	2.246189	0.173100	-2.025716
O	0.552275	1.073981	-0.537460
H	4.119880	3.104313	0.751077
H	2.789314	-1.465311	-1.515403
H	0.064521	-2.197091	1.628994
C	-3.062522	1.653918	0.718671
O	-1.364242	-2.072427	-2.154906
O	-1.254136	1.206156	-2.087734
H	-4.778384	-1.622559	-1.852513
C	-3.742027	2.440565	1.646065
H	1.924067	2.318104	0.368103
H	1.182050	1.013762	1.801781

O	0.797656	0.145020	1.563190
H	-6.207379	-0.081177	-3.182371
H	-2.754155	-3.596200	-2.397919
C	-3.093597	3.505986	2.262502
H	-3.618150	4.121040	2.987479
H	-1.398054	-3.516065	-3.556816
C	-1.764441	3.770690	1.944486
H	0.994061	-4.291738	-1.270300
H	-2.749608	-2.356164	-3.683278
C	-1.094352	2.975698	1.018516
H	-3.606014	0.835601	0.249625
C	1.020914	-0.008202	0.209766
H	-2.896118	2.666116	-3.480210
C	0.194398	-1.211188	-0.272511
H	5.076914	-4.804351	-0.034871
C	0.256850	-2.468706	0.586020
C	1.596278	-3.151827	0.448030
H	-2.739383	-2.029889	-0.638354
C	1.812819	-4.057022	-0.592943
H	-0.052840	3.192454	0.802298
C	3.059706	-4.651275	-0.769325
H	-1.244140	4.594264	2.424498
C	4.104058	-4.341712	0.097737
H	-4.778360	2.220506	1.885742
C	3.896248	-3.436566	1.136217
H	-5.252203	2.052323	-4.019512
C	2.649821	-2.843266	1.309868
H	-0.534164	-3.150760	0.251601
H	3.214115	-5.357481	-1.579022
C	-2.142371	-1.332790	-1.250497
H	4.709443	-3.189029	1.811143
C	-3.050342	-0.353148	-1.946240
H	2.490015	-2.110975	2.096028
C	-4.375492	-0.681904	-2.223873
C	-5.176300	0.177419	-2.968773
C	-4.635625	1.374405	-3.437505
C	-3.321772	1.725300	-3.149586
C	-2.519996	0.866088	-2.397862
H	-1.564175	-0.619313	0.598293

TS_{FG}

H	0.596763	-1.375572	-1.356313
C	2.970802	-0.462752	-1.210959
C	2.761542	2.552929	1.726943
C	-1.621181	1.921226	0.348625
O	2.572654	-0.287779	0.139903
O	1.378899	2.227231	1.627741
C	-2.316356	-2.942613	-2.704188
B	-0.720083	0.969649	-0.584410
H	4.013918	-0.148885	-1.266440
H	3.383322	1.719792	1.384442
N	-1.000967	-0.629267	-0.234480
H	3.003529	2.788203	2.766440
H	2.367116	0.158280	-1.880276
O	0.725582	1.066869	-0.335187
H	2.959055	3.435025	1.113716
H	2.904149	-1.517612	-1.504392
H	0.169730	-2.459866	1.469720
C	-2.722948	1.500639	1.101014
O	-1.438951	-2.113968	-1.970283
O	-0.983487	1.120693	-2.008954
H	-4.771697	-1.303613	-1.567717
C	-3.481468	2.392342	1.856765
H	1.037544	1.836501	0.494120
H	1.226713	1.199354	1.933145
O	0.964128	-0.139306	1.680021
H	-6.050759	0.279234	-2.996657
H	-2.948132	-3.540588	-2.031310
C	-3.151523	3.743004	1.870726
H	-3.737898	4.441950	2.459144
H	-1.686937	-3.609580	-3.293456
C	-2.065560	4.192389	1.122711
H	1.076015	-4.360189	-1.564299
H	-2.958656	-2.360064	-3.372470
C	-1.318142	3.290097	0.374338
H	-3.027745	0.453275	1.096160

C	1.218391	-0.242268	0.411388
H	-2.476490	2.634640	-3.526210
C	0.339805	-1.285163	-0.301511
H	5.144143	-5.007682	-0.343464
C	0.359795	-2.638029	0.405944
C	1.687139	-3.332763	0.220835
H	-2.720539	-1.869891	-0.384894
C	1.894396	-4.177966	-0.870790
H	-0.472213	3.656068	-0.204641
C	3.133264	-4.780248	-1.076232
H	-1.801494	5.245643	1.126302
C	4.177727	-4.538666	-0.187667
H	-4.330521	2.033320	2.430612
C	3.978588	-3.693720	0.901983
H	-4.892894	2.229495	-4.003425
C	2.740527	-3.093279	1.106048
H	-0.442291	-3.260073	-0.002378
H	3.281747	-5.439026	-1.926195
C	-2.089426	-1.265640	-1.057488
H	4.791515	-3.499216	1.594360
C	-2.922948	-0.231635	-1.769416
H	2.585083	-2.403964	1.931619
C	-4.278553	-0.439653	-2.009542
C	-4.994806	0.442221	-2.812341
C	-4.340327	1.536479	-3.376663
C	-2.992454	1.769176	-3.125425
C	-2.278743	0.887555	-2.316513
H	-1.261592	-0.649640	0.756218

G

H	0.801847	-1.251913	-1.288550
C	3.083253	-0.516768	-0.647511
C	3.042119	2.563001	1.658274
C	-1.492279	2.056455	0.124964
O	2.415394	-0.308729	0.603270
O	1.697742	2.516630	1.221285
C	-1.928134	-2.648634	-3.247411
B	-0.747037	1.160422	-0.997328
H	4.083671	-0.111005	-0.500848
H	3.491866	1.565049	1.697847
N	-0.980813	-0.563809	-0.463651
H	3.127284	3.034093	2.644945
H	2.565970	0.033528	-1.435810
O	0.643928	1.321596	-1.127413
H	3.594854	3.173170	0.940640
H	3.153507	-1.583862	-0.875242
H	-0.252702	-2.683550	1.209535
C	-2.624788	1.676983	0.860995
O	-1.185589	-1.833850	-2.365850
O	-1.400593	1.192844	-2.297959
H	-4.653388	-1.787781	-1.338052
C	-3.245314	2.540800	1.760361
H	1.031626	1.864317	-0.418701
H	1.210406	1.885807	1.773324
O	0.543210	-0.079012	1.729007
H	-6.407951	-0.317629	-2.318819
H	-2.414911	-3.474336	-2.706505
C	-2.749473	3.827849	1.943710
H	-3.227792	4.504645	2.645294
H	-1.216747	-3.058334	-3.964612
C	-1.636875	4.239478	1.215910
H	1.305942	-4.062874	-1.835967
H	-2.694388	-2.074273	-3.778304
C	-1.026489	3.364875	0.321681
H	-3.067873	0.690770	0.723321
C	1.103485	-0.471877	0.726184
H	-3.371830	2.588078	-3.298294
C	0.318831	-1.261236	-0.314441
H	5.064601	-4.970738	0.036817
C	0.176076	-2.708838	0.200965
C	1.515162	-3.402884	0.197625
H	-2.370172	-2.158047	-0.718843
C	1.961170	-4.031271	-0.968136
H	-0.156508	3.706014	-0.232735
C	3.231545	-4.595318	-1.027865
H	-1.241286	5.242438	1.345812

C	4.072313	-4.533695	0.081719
H	-4.119098	2.209947	2.314119
C	3.633996	-3.913351	1.248753
H	-5.757761	1.859101	-3.318147
C	2.361210	-3.351916	1.306913
H	-0.509130	-3.249114	-0.456520
H	3.566360	-5.080783	-1.939077
C	-1.949632	-1.319309	-1.302826
H	4.284084	-3.865268	2.116320
C	-3.056500	-0.421089	-1.772594
H	2.024766	-2.855915	2.214384
C	-4.388330	-0.824624	-1.770391
C	-5.369052	-0.006973	-2.322722
C	-4.998738	1.214344	-2.885762
C	-3.671815	1.631048	-2.886149
C	-2.689110	0.814542	-2.325854
H	-1.370322	-0.465621	0.478311

H

H	-0.949205	1.051144	-1.147290
C	-4.573916	0.804386	1.299705
C	1.754266	2.501210	-1.834942
C	-2.584451	2.622942	-3.402294
B	-4.139986	1.363218	-0.135806
N	-2.952099	0.520836	-0.772198
O	-3.445689	2.681334	-0.048629
H	-1.768880	0.887328	1.808226
C	-5.095001	-0.490910	1.422164
O	-1.661515	1.550160	-3.352961
O	0.437446	2.891882	-2.178881
O	-5.231190	1.396811	-1.108858
H	-3.826888	-2.190760	-3.527005
C	-5.467307	-1.009909	2.658105
H	-0.012079	3.237008	-1.386808
H	-0.787196	1.942149	-3.178191
O	-1.377292	3.529791	-0.152097
H	-6.067730	-2.425470	-4.581516
H	2.262199	2.215780	-2.758634
H	-3.561338	2.266064	-3.057253
C	-5.324367	-0.234532	3.807122
H	-5.613742	-0.635055	4.773931
H	-2.700456	3.009179	-4.422466
H	1.767180	1.648038	-1.145423
C	-4.811667	1.055796	3.709547
H	0.946884	-1.118264	0.553971
H	-2.280187	3.452776	-2.752105
H	2.310370	3.326206	-1.375606
C	-4.441327	1.565501	2.466299
H	-5.215518	-1.108330	0.532240
C	-2.142136	2.586900	-0.182643
H	-7.450778	0.990864	-2.334337
C	-1.697267	1.122952	-0.355533
H	4.087960	1.608765	1.613205
C	-1.162576	0.528130	0.970281
C	0.301630	0.836060	1.176042
H	-2.211588	-0.715142	-2.237690
C	1.264785	-0.135756	0.894206
H	-4.045939	2.576127	2.394278
C	2.621514	0.136575	1.051010
H	-4.703667	1.665722	4.601599
C	3.031698	1.392780	1.488881
H	-5.868957	-2.016364	2.729041
C	2.079011	2.367918	1.774728
H	-7.867427	-0.821857	-3.980469
C	0.723206	2.092263	1.622640
H	-1.308936	-0.555706	0.919223
H	3.355985	-0.632772	0.834496
C	-3.092245	-0.280476	-1.767376
H	2.391772	3.347719	2.121365
C	-4.403492	-0.514080	-2.310903
H	-0.012792	2.859548	1.840416
C	-4.638998	-1.518537	-3.263626
C	-5.879881	-1.644636	-3.854160
C	-6.891628	-0.734215	-3.512491
C	-6.675842	0.279484	-2.595415
C	-5.428626	0.400826	-1.965512

TS$_{HI}$

H	-0.787684	0.602572	-1.203442
C	-4.628473	0.833575	1.051146
C	1.495093	2.735540	-1.851275
C	-2.684398	3.529439	-2.753789
B	-4.008477	1.234931	-0.373266
N	-2.823849	0.252626	-0.825702
O	-3.267560	2.491755	-0.320551
H	-1.655546	1.081913	1.683360
C	-5.486341	-0.263014	1.212903
O	-1.807130	2.518316	-2.258367
O	0.307094	3.512385	-1.881046
O	-5.001337	1.198875	-1.468261
H	-3.828851	-2.925759	-2.981589
C	-5.996538	-0.608567	2.461086
H	-0.224674	3.500990	-0.880979
H	-0.686920	2.953466	-2.286508
O	-1.180350	3.262522	-0.052536
H	-6.027116	-3.196116	-4.111887
H	1.822115	2.540323	-2.875854
H	-3.711270	3.164466	-2.707567
C	-5.661887	0.146705	3.583311
H	-6.060283	-0.118969	4.557950
H	-2.404886	3.740256	-3.788642
H	1.353330	1.781273	-1.326907
C	-4.820154	1.246561	3.445953
H	0.928543	-1.147393	0.227432
H	-2.595284	4.439709	-2.151343
H	2.278958	3.291916	-1.331404
C	-4.313007	1.581523	2.192502
H	-5.771849	-0.859995	0.348343
C	-1.948152	2.371230	-0.573913
H	-7.183029	0.731311	-2.744329
C	-1.555268	0.867924	-0.469802
H	4.232362	1.395538	1.250714
C	-1.083852	0.505376	0.950989
C	0.400768	0.748873	1.095514
H	-2.131128	-1.307993	-1.969155
C	1.305869	-0.210628	0.633205
H	-3.666607	2.449771	2.082191
C	2.678317	0.017446	0.683746
H	-4.563460	1.846307	4.314291
C	3.163325	1.213016	1.207935
H	-6.660071	-1.462832	2.559560
C	2.269529	2.169611	1.684263
H	-7.688856	-1.352948	-3.996109
C	0.897240	1.941285	1.627152
H	-1.305883	-0.553337	1.123919
H	3.367338	-0.738333	0.319909
C	-2.992959	-0.722981	-1.640641
H	2.641792	3.101954	2.097338
C	-4.297985	-0.979548	-2.193123
H	0.197813	2.698397	1.964828
C	-4.582038	-2.143904	-2.925022
C	-5.798680	-2.292315	-3.559583
C	-6.733079	-1.246560	-3.491998
C	-6.466482	-0.080145	-2.798309
C	-5.247987	0.071063	-2.117042

I

H	-0.832857	0.757208	-1.270367
C	-4.620028	0.786350	1.068017
C	1.767225	2.267027	-1.972359
C	-2.784614	3.803646	-2.641404
B	-4.076051	1.256802	-0.366582
N	-2.860200	0.338546	-0.882562
O	-3.402666	2.545318	-0.319819
H	-1.718628	1.443654	1.555811
C	-5.258616	-0.448334	1.249793
O	-2.040882	2.674964	-2.188074
O	0.675446	3.163750	-1.895106
O	-5.110378	1.175629	-1.425346
H	-3.756431	-2.828903	-3.101055
C	-5.711788	-0.855306	2.501407
H	-0.501077	3.483810	-0.530782

H	-0.064723	2.853314	-2.439767
O	-1.385979	3.453498	-0.114532
H	-5.973066	-3.193536	-4.166777
H	2.177144	2.220456	-2.988066
H	-3.855025	3.622941	-2.519962
C	-5.540730	-0.024091	3.606201
H	-5.895195	-0.337211	4.583694
H	-2.541059	3.929919	-3.696919
H	1.501933	1.254418	-1.642469
C	-4.914348	1.209303	3.449274
H	0.741619	-1.088563	0.439627
H	-2.498599	4.699881	-2.083069
H	2.539380	2.640316	-1.298424
C	-4.458396	1.603300	2.192871
H	-5.410404	-1.109670	0.397896
C	-2.111805	2.493619	-0.778331
H	-7.304144	0.618312	-2.640075
C	-1.619581	1.027446	-0.557516
H	4.178401	1.294498	1.410540
C	-1.173229	0.767201	0.892179
C	0.320394	0.928537	1.056995
H	-2.119592	-1.145772	-2.095809
C	1.170478	-0.141382	0.760953
H	-3.968122	2.565901	2.066572
C	2.551090	-0.013734	0.882203
H	-4.782249	1.864316	4.305630
C	3.102655	1.192380	1.307977
H	-6.200586	-1.818405	2.617088
C	2.264857	2.262659	1.611427
H	-7.732335	-1.453285	-3.939521
C	0.883797	2.132867	1.484945
H	-1.463302	-0.254031	1.160944
H	3.194726	-0.857453	0.653287
C	-3.001538	-0.620599	-1.721820
H	2.686109	3.203545	1.951819
C	-4.307526	-0.935996	-2.238968
H	0.228939	2.965919	1.720725
C	-4.550162	-2.093454	-2.996589
C	-5.777115	-2.294068	-3.595172
C	-6.767313	-1.306306	-3.463933
C	-6.544493	-0.147830	-2.743391
C	-5.313251	0.056081	-2.097713

TS_{IJ}

H	-0.717586	0.243767	-1.423300
C	-4.439501	1.044951	0.893806
C	0.188968	5.395068	-1.281840
C	-1.791100	2.174724	-3.159119
B	-3.827989	1.262447	-0.574600
N	-2.767264	0.120313	-0.965272
O	-2.962378	2.421615	-0.683523
H	-1.464333	0.659844	1.505857
C	-5.512722	0.179451	1.145262
O	-1.112432	2.634198	-2.003714
O	-1.161532	5.243615	-0.867862
O	-4.860779	1.216298	-1.637796
H	-4.189469	-3.155604	-2.700384
C	-6.004570	-0.013593	2.433444
H	-1.047571	3.717620	0.119077
H	-1.600136	4.695677	-1.535182
O	-0.892322	2.753580	0.219953
H	-6.429942	-3.296358	-3.767839
H	0.260240	5.969375	-2.212644
H	-1.560499	1.120975	-3.369476
C	-5.432483	0.666027	3.506244
H	-5.816849	0.520432	4.511353
H	-1.426755	2.774752	-3.994192
H	0.674455	4.422690	-1.417984
C	-4.373040	1.540559	3.280309
H	0.884079	-1.583731	-0.337747
H	-2.874616	2.294027	-3.058776
H	0.704625	5.948072	-0.494970
C	-3.888421	1.725603	1.987504
H	-5.988384	-0.349023	0.321410
C	-1.611695	2.137919	-0.768173
H	-7.106540	0.863820	-2.834297

C	-1.420951	0.586549	-0.656551
H	4.407173	0.214351	1.326755
C	-0.957304	0.089490	0.725299
C	0.543807	0.146788	0.894299
H	-2.300076	-1.652962	-1.896709
C	1.349063	-0.806209	0.266322
H	-3.068856	2.419347	1.809495
C	2.732329	-0.784181	0.414590
H	-3.930020	2.083678	4.110064
C	3.329027	0.195430	1.203628
H	-6.838352	-0.689122	2.601419
C	2.534950	1.147843	1.836534
H	-7.870575	-1.273603	-3.842721
C	1.152332	1.125646	1.680218
H	-1.288075	-0.952233	0.815914
H	3.342074	-1.535165	-0.077909
C	-3.076228	-0.928772	-1.635007
H	2.993895	1.913836	2.453808
C	-4.417627	-1.093266	-2.129687
H	0.531839	1.878517	2.154527
C	-4.848330	-2.291297	-2.723795
C	-6.088147	-2.369016	-3.323540
C	-6.897804	-1.221742	-3.363021
C	-6.486628	-0.024859	-2.806181
C	-5.242865	0.061244	-2.157681

J

H	-0.516563	0.071423	-1.344280
C	-4.232041	1.256765	0.798912
C	-1.618825	5.626111	-1.401236
C	-1.333611	2.060405	-3.179374
B	-3.563601	1.353533	-0.657826
N	-2.580867	0.128804	-0.960244
O	-2.607598	2.444358	-0.787508
H	-1.268792	0.687647	1.540549
C	-5.392334	0.510061	1.044974
O	-0.664437	2.461408	-2.000357
O	-1.862681	5.022100	-0.141010
O	-4.564446	1.344127	-1.749042
H	-4.170814	-3.100103	-2.635328
C	-5.939038	0.416231	2.321896
H	-0.744629	3.614395	0.158379
H	-2.540145	4.338296	-0.272991
O	-0.560105	2.651432	0.218030
H	-6.377188	-3.123683	-3.779803
H	-2.504569	6.157998	-1.767324
H	-1.257375	0.975277	-3.343051
C	-5.335039	1.078131	3.388542
H	-5.760850	1.008005	4.384958
H	-0.830732	2.564711	-4.005371
H	-1.303675	4.885733	-2.145340
C	-4.188191	1.835516	3.167718
H	0.757044	-1.983679	-0.072354
H	-2.390313	2.345181	-3.157680
H	-0.815113	6.351732	-1.263559
C	-3.649254	1.921822	1.886083
H	-5.890908	-0.002601	0.224730
C	-1.260774	2.057416	-0.794333
H	-6.787626	1.105571	-3.017471
C	-1.213123	0.499205	-0.615371
H	4.505071	-0.508184	1.406336
C	-0.833887	0.016979	0.797653
C	0.661781	-0.108291	0.978137
H	-2.211363	-1.707964	-1.805257
C	1.327270	-1.218316	0.451786
H	-2.755269	2.520431	1.717428
C	2.702475	-1.364802	0.599335
H	-3.717368	2.363479	3.991698
C	3.432215	-0.397211	1.284871
H	-6.840471	-0.166995	2.486287
C	2.778200	0.711482	1.814758
H	-7.666317	-1.008414	-3.978891
C	1.402462	0.857123	1.660210
H	-1.294360	-0.968584	0.935043
H	3.202152	-2.235522	0.186381
C	-2.941974	-0.920572	-1.603190

H	3.341196	1.470154	2.349196
C	-4.272210	-1.007611	-2.144090
H	0.892689	1.730169	2.052841
C	-4.765945	-2.193649	-2.712175
C	-5.986596	-2.206707	-3.354778
C	-6.710229	-1.008055	-3.464235
C	-6.234205	0.177288	-2.933911
C	-5.010992	0.199846	-2.243751

TS$_{JK}$

H	-0.450206	0.253763	-1.342562
C	-4.214217	1.346955	0.739339
C	-1.989120	5.632188	-0.813971
C	-1.189227	2.106904	-3.207323
B	-3.576357	1.454262	-0.726981
N	-2.514994	0.297981	-1.015189
O	-2.680555	2.600921	-0.919301
H	-1.061635	1.026949	1.490477
C	-5.379642	0.604589	0.974673
O	-0.616460	2.654042	-2.036466
O	-2.287039	4.651577	0.178055
O	-4.582698	1.373165	-1.801442
H	-3.885977	-3.025353	-2.710823
C	-5.918109	0.482694	2.252470
H	-1.401773	4.059843	0.326527
H	-2.740850	3.627527	-0.383291
O	-0.621996	2.918341	0.171670
H	-6.086934	-3.194103	-3.855454
H	-2.927304	6.041376	-1.193212
H	-0.992814	1.029819	-3.301379
C	-5.300749	1.112587	3.330598
H	-5.720531	1.022295	4.327899
H	-0.709644	2.611932	-4.046532
H	-1.420634	5.184341	-1.636949
C	-4.148958	1.865148	3.120416
H	0.283347	-2.174834	1.434409
H	-2.270042	2.279777	-3.243247
H	-1.405306	6.439289	-0.365408
C	-3.616601	1.979096	1.838364
H	-5.888208	0.119415	0.144220
C	-1.139167	2.256640	-0.805032
H	-6.789804	0.991153	-3.064516
C	-1.161313	0.691047	-0.634072
H	4.424873	-1.066626	1.237034
C	-0.799440	0.229761	0.792308
C	0.665376	-0.122227	0.922647
H	-2.041245	-1.524064	-1.833777
C	1.048107	-1.422610	1.256137
H	-2.718796	2.576570	1.689883
C	2.393203	-1.764396	1.372647
H	-3.667627	2.369252	3.952907
C	3.375188	-0.804999	1.147874
H	-6.823979	-0.095965	2.407840
C	3.002167	0.494405	0.810417
H	-7.521838	-1.174908	-4.037278
C	1.658616	0.838470	0.699586
H	-1.409004	-0.646339	1.036518
H	2.671581	-2.779481	1.638732
C	-2.815228	-0.774139	-1.654844
H	3.763595	1.248870	0.637912
C	-4.131726	-0.946953	-2.209307
H	1.361615	1.853189	0.448646
C	-4.542063	-2.161685	-2.783064
C	-5.760057	-2.254829	-3.425268
C	-6.566405	-1.109871	-3.525583
C	-6.173083	0.102934	-2.988918
C	-4.952202	0.203717	-2.303418

K

H	-0.665068	0.033040	-1.253545
C	-4.014435	1.509586	0.905205
C	-1.970347	5.513139	-1.593789
C	-0.984645	2.093573	-3.007765
B	-3.875207	1.531788	-0.694314
N	-2.707794	0.421080	-1.119743
O	-3.439587	2.713756	-1.336570

H	-1.618724	0.650925	1.563904
C	-4.524909	0.359427	1.523073
O	-0.585485	2.632627	-1.749287
O	-2.205371	4.995037	-0.297702
O	-5.143441	1.010631	-1.290647
H	-3.529615	-2.407208	-3.792669
C	-4.601200	0.243673	2.907129
H	-1.454506	4.434477	-0.044753
H	-3.342960	3.498453	-0.774549
O	-0.754218	2.672137	0.431095
H	-5.762126	-2.779414	-4.822967
H	-2.723772	6.281629	-1.777875
H	-0.622855	1.068790	-3.141295
C	-4.170485	1.296706	3.712336
H	-4.223834	1.214030	4.793794
H	-0.510129	2.729494	-3.754357
H	-2.066258	4.735486	-2.361501
C	-3.678893	2.457492	3.122166
H	0.254005	-2.190040	0.060663
H	-2.071221	2.145936	-3.096436
H	-0.978682	5.972561	-1.674584
C	-3.602880	2.559040	1.733526
H	-4.865526	-0.467177	0.900405
C	-0.912000	2.050639	-0.592496
H	-7.358280	0.482901	-2.487052
C	-1.348469	0.572843	-0.584413
H	4.021621	-1.060959	1.778328
C	-1.190690	-0.029143	0.825758
C	0.263362	-0.317373	1.120607
H	-2.085624	-1.168260	-2.262065
C	0.857928	-1.481399	0.625027
H	-3.203285	3.473188	1.300911
C	2.202697	-1.751085	0.856610
H	-3.351634	3.285863	3.743372
C	2.972758	-0.853478	1.592042
H	-4.995974	-0.661482	3.359386
C	2.389747	0.307602	2.091732
H	-7.665601	-1.324904	-4.157758
C	1.043620	0.576188	1.856518
H	-1.771465	-0.957396	0.848640
H	2.646709	-2.663102	0.470123
C	-2.922353	-0.524258	-1.972480
H	2.984724	1.008631	2.668497
C	-4.196593	-0.761284	-2.571601
H	0.588208	1.486569	2.233509
C	-4.379763	-1.786219	-3.520415
C	-5.614779	-1.993911	-4.091443
C	-6.688899	-1.165843	-3.710483
C	-6.534261	-0.155388	-2.784082
C	-5.275419	0.069789	-2.190120

L

H	0.794735	-2.755287	-0.662059
C	-2.164198	-0.350305	1.170779
C	-1.018369	0.624078	-4.471776
C	2.771152	-0.327974	-2.834933
B	-1.875565	-0.277314	-0.406412
N	-0.890209	-1.540187	-0.895173
O	-1.251073	0.921613	-0.894800
H	0.404267	-0.647535	1.508447
C	-2.744537	-1.491457	1.738773
O	2.005486	-1.260282	-2.055979
O	-0.244411	0.246634	-3.355672
O	-3.157865	-0.469160	-1.107906
H	-1.739377	-3.248683	-4.386028
C	-3.008901	-1.573058	3.102405
H	-0.628647	0.657119	-2.553850
H	-0.440274	1.136072	-0.414862
O	1.526510	0.401523	-0.622476
H	-3.810161	-2.845262	-5.705689
H	-0.610004	0.115449	-5.349560
H	2.087926	0.410259	-3.256718
C	-2.704704	-0.495182	3.933022
H	-2.906352	-0.553535	4.998271
H	3.244134	-0.920363	-3.615653
H	-0.979706	1.705791	-4.655401

C	-2.152160	0.659456	3.387139
H	1.437431	-4.204233	1.695408
H	3.520895	0.153101	-2.204656
H	-2.072087	0.328017	-4.368959
C	-1.892362	0.726519	2.019081
H	-2.990491	-2.336183	1.096410
C	1.392519	-0.739134	-1.003441
H	-5.224921	-0.177659	-2.618201
C	0.464405	-1.762851	-0.338860
H	5.532051	-3.301374	2.615813
C	0.587231	-1.673701	1.183316
C	1.968660	-2.122242	1.603933
H	-0.384108	-2.829129	-2.411261
C	2.238971	-3.477663	1.808700
H	-1.474079	1.638955	1.599584
C	3.513571	-3.902546	2.169781
H	-1.926689	1.508354	4.025991
C	4.538261	-2.972837	2.329191
H	-3.453829	-2.471450	3.520424
C	4.280139	-1.620344	2.125194
H	-5.547401	-1.312725	-4.806351
C	3.003776	-1.197616	1.763356
H	-0.181757	-2.300963	1.641465
H	3.705718	-4.958213	2.333633
C	-1.135637	-2.142966	-2.013779
H	5.072592	-0.889635	2.252395
C	-2.329472	-1.945544	-2.776932
H	2.801151	-0.142996	1.599145
C	-2.516266	-2.585252	-4.014394
C	-3.663086	-2.360806	-4.747576
C	-4.641932	-1.492179	-4.234356
C	-4.478098	-0.853239	-3.019009
C	-3.306154	-1.063979	-2.272836

TS_{LM}

H	0.751553	-2.542203	-1.241747
C	-2.042885	-0.137929	0.970801
C	-0.799298	0.089277	-4.525541
C	3.474442	0.055661	-1.220262
B	-1.995736	-0.321528	-0.621671
N	-1.032177	-1.478195	-1.144646
O	-1.534777	0.937045	-1.355466
H	-0.144383	-1.481465	1.469928
C	-2.821795	-1.034647	1.714940
O	2.454393	-0.944281	-1.239586
O	-0.496818	-0.214886	-3.175296
O	-3.353095	-0.610664	-1.095812
H	-1.993356	-2.875762	-4.774691
C	-2.861204	-0.990603	3.105140
H	-0.991549	0.481490	-2.401961
H	-0.774194	1.290065	-0.867004
O	1.035483	0.591029	-0.446802
H	-4.326993	-3.048696	-5.611547
H	-0.460409	-0.733695	-5.162944
H	3.186483	0.903847	-1.844056
C	-2.120737	-0.030377	3.791156
H	-2.143536	0.006706	4.876073
H	4.369410	-0.427170	-1.607286
H	-0.259049	0.997151	-4.806279
C	-1.359814	0.888451	3.074258
H	1.924999	-4.430285	0.499668
H	3.635298	0.398049	-0.195298
H	-1.873523	0.236089	-4.677380
C	-1.328127	0.833269	1.681425
H	-3.402996	-1.784560	1.184132
C	1.269347	-0.554057	-0.774064
H	-5.690532	-0.906526	-2.122791
C	0.312428	-1.739231	-0.637223
H	5.466360	-2.883425	2.372090
C	0.338856	-2.220818	0.832423
C	1.753828	-2.445234	1.306096
H	-0.453659	-2.373561	-2.938085
C	2.439538	-3.627333	1.022590
H	-0.709672	1.555914	1.155216
C	3.768035	-3.786460	1.404765
H	-0.792339	1.651290	3.599480

C	4.430543	-2.759223	2.072742
H	-3.467868	-1.703512	3.656004
C	3.754629	-1.576929	2.363926
H	-6.176161	-2.058470	-4.275306
C	2.424073	-1.423209	1.984484
H	-0.254372	-3.139290	0.880107
H	4.287448	-4.713406	1.182592
C	-1.164991	-1.681245	-2.481994
H	4.261346	-0.776365	2.894264
C	-2.536968	-1.777242	-3.011097
H	1.889333	-0.503122	2.211524
C	-2.814245	-2.434269	-4.213296
C	-4.115504	-2.537261	-4.679547
C	-5.152284	-1.981300	-3.922268
C	-4.896453	-1.336708	-2.722834
C	-3.580128	-1.221795	-2.253444

M

H	0.698495	-2.435018	-1.277334
C	-2.097351	-0.179199	1.027596
C	-0.358821	-0.383628	-4.557975
C	3.455108	0.147545	-1.230810
B	-2.023724	-0.331378	-0.561353
N	-1.073453	-1.367437	-1.147132
O	-1.489058	1.155149	-1.125588
H	-0.111768	-1.387436	1.465717
C	-2.854752	-1.127184	1.727877
O	2.428591	-0.847852	-1.253518
O	-0.549033	-0.310418	-3.160764
O	-3.347782	-0.425235	-1.124352
H	-2.105438	-2.849971	-4.747507
C	-2.924680	-1.122126	3.117483
H	-1.360522	1.008026	-2.086222
H	-0.556883	1.202232	-0.787350
O	1.013230	0.696908	-0.494177
H	-4.465590	-3.064190	-5.493958
H	0.200711	-1.290884	-4.825858
H	3.171124	0.999353	-1.850961
C	-2.238177	-0.151593	3.844129
H	-2.285653	-0.144802	4.928790
H	4.346258	-0.340401	-1.619729
H	0.224400	0.490511	-4.851920
C	-1.499455	0.815952	3.169225
H	1.874806	-4.356438	0.385450
H	3.617756	0.482303	-0.203848
H	-1.312423	-0.384661	-5.097840
C	-1.435999	0.800847	1.776655
H	-3.392251	-1.886910	1.165171
C	1.241789	-0.461432	-0.809271
H	-5.706390	-0.772558	-2.057650
C	0.271230	-1.632158	-0.663026
H	5.490413	-2.908445	2.193908
C	0.336673	-2.126841	0.804071
C	1.758207	-2.386398	1.237080
H	-0.559694	-2.354452	-2.914656
C	2.416202	-3.573520	0.911500
H	-0.846192	1.566883	1.279525
C	3.751425	-3.762052	1.254637
H	-0.974101	1.585948	3.726641
C	4.449256	-2.760395	1.925577
H	-3.512857	-1.873574	3.635997
C	3.801365	-1.573896	2.259963
H	-6.272040	-2.013355	-4.144979
C	2.463879	-1.391257	1.919300
H	-0.276230	-3.031870	0.856245
H	4.249117	-4.692598	0.999964
C	-1.161209	-1.499563	-2.565630
H	4.334752	-0.793146	2.793737
C	-2.582369	-1.667380	-3.023955
H	1.951032	-0.467389	2.180131
C	-2.905609	-2.381003	-4.177915
C	-4.225346	-2.508219	-4.594597
C	-5.236175	-1.919768	-3.833696
C	-4.934510	-1.223756	-2.671482
C	-3.604585	-1.092974	-2.260212

N

H	1.355526	-1.259731	-1.372079
C	-1.634545	0.917577	0.583423
C	-0.912477	-0.431434	-5.154945
C	2.196100	1.009687	2.043568
B	-1.889586	0.303079	-0.887411
N	-0.436519	-0.211966	-1.597500
O	-2.325238	1.247102	-1.862726
H	-0.333324	-1.628763	1.093185
C	-1.981491	0.233847	1.756049
O	1.528684	-0.022885	1.307156
O	-0.819610	0.028265	-3.827188
O	-2.717455	-0.897328	-0.757737
H	-1.109839	-3.151457	-4.361090
C	-1.805449	0.804878	3.014952
H	-0.016281	0.673952	-1.909300
H	-3.048092	1.767595	-1.501460
O	1.579076	1.300386	-0.507718
H	-2.993046	-4.754208	-4.272666
H	-0.066889	-1.088465	-5.410957
H	3.171096	1.215275	1.597472
C	-1.288700	2.093533	3.127339
H	-1.156868	2.546236	4.105825
H	2.304075	0.623398	3.055068
H	-0.878752	0.455771	-5.787160
C	-0.958014	2.805230	1.975276
H	0.764832	-3.984497	-1.545352
H	1.585470	1.913371	2.035621
H	-1.849422	-0.969167	-5.334729
C	-1.131738	2.219380	0.722821
H	-2.414047	-0.759967	1.669152
C	1.265592	0.271593	0.042662
H	-4.589236	-2.603292	-0.896209
C	0.570754	-0.861651	-0.713425
H	3.852797	-5.774754	0.844627
C	0.038625	-2.018803	0.145193
C	1.103833	-3.068004	0.369836
H	0.248138	-1.547777	-3.087841
C	1.360347	-4.007131	-0.633541
H	-0.874795	2.782642	-0.171747
C	2.345034	-4.975414	-0.468427
H	-0.569681	3.817015	2.054087
C	3.086528	-5.018145	0.710203
H	-2.084182	0.251894	3.907317
C	2.834808	-4.091160	1.717224
H	-4.757573	-4.469054	-2.534993
C	1.849783	-3.120910	1.547469
H	-0.804347	-2.478829	-0.375288
H	2.526940	-5.702508	-1.253539
C	-0.670003	-0.974252	-2.860521
H	3.405714	-4.123653	2.639927
C	-1.820077	-1.942592	-2.735175
H	1.654947	-2.393311	2.329419
C	-1.898403	-3.021806	-3.622105
C	-2.947189	-3.928573	-3.571620
C	-3.931420	-3.767308	-2.594278
C	-3.851898	-2.729014	-1.681439
C	-2.796811	-1.807010	-1.733610

Biochemical studies

Human neutrophil elastase activity with fluorogenic peptide substrate

Fluorometric assays for theHuman neutrophil elastase (HNE) (Merck, Germany) inhibition activity were carried out in 200 µL assay buffer (0.1 M HEPES pH 7.5 at 25 °C) containing 20 µL of 0.17 µM HNE in assay buffer (stock solution 1.7 µM in 0.05 M acetate buffer, pH 5.5), and 5 µL of each concentration of tested inhibitors. Reaction was initiated by the addition of 175 µL of fluorogenic substrate to final concentration of 200 µM (MeO-Suc-Ala-Ala-Pro-Val-AMC, Merck, Germany) and activity was monitored (excitation 380 nm; emission 460 nm) for 30 min, at 25ºC on a Fluorescence Microplate Reader Tecan infinite M200 (Tecan, Switzerland). The *K*m of this substrate of HNE was previously determined to be 185 µM (data not shown). For all assays, saturated substrate concentration was used, throughout, in order to obtain linear fluorescence curves. Inhibitors stock solutions were prepared in DMSO, and serial dilutions were made in DMSO. Controls were performed using enzyme alone, substrate alone, enzyme with DMSO and a positive control (MeOSuc-Ala-Ala-Pro-Ala-CMK, Calbiochem, Germany). By computing the log of inhibitors concentrations versus the percentage of activity and using the GrafPad program the IC_{50} values were determined by non-linear regression analysis. Assays were performed in triplicate and data presented as the mean and the standard deviation.

Tested against the human neutrophil serine proteases, proteinase 3 (PR3) and cathepsin G, as well as against Porcine Pancreatic Elastase, PPE (Table) according the previous published experimental methods [1,2].

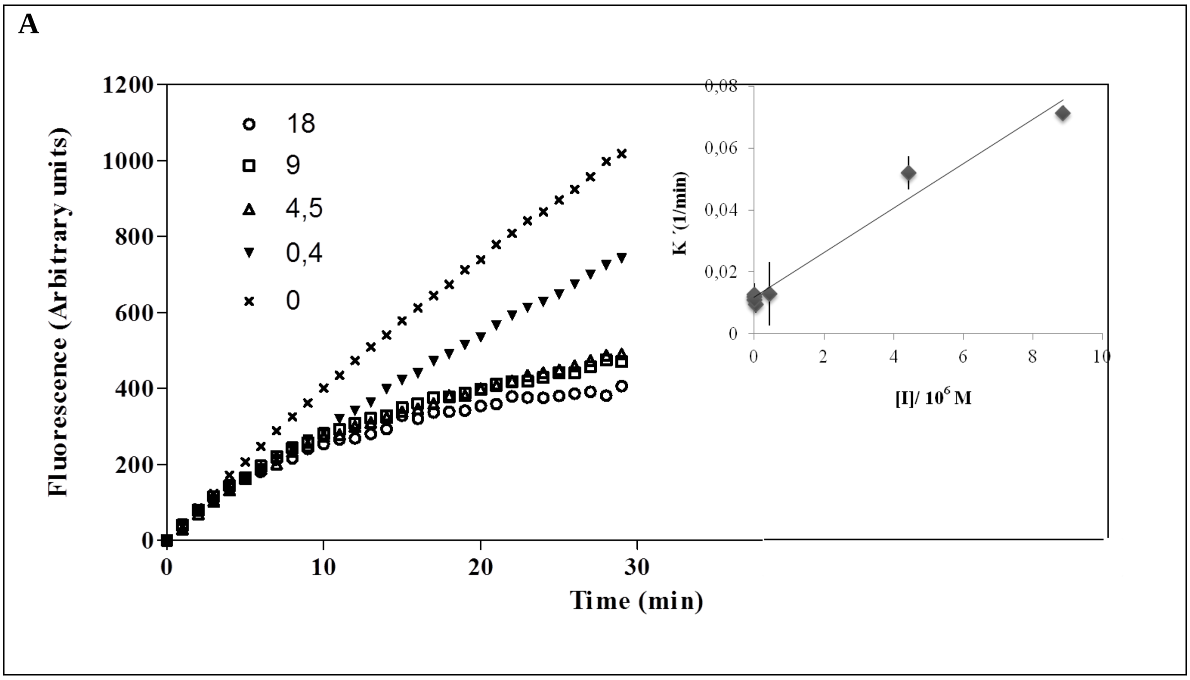
Selectivity assay for compound 16 - IC50 (µM)

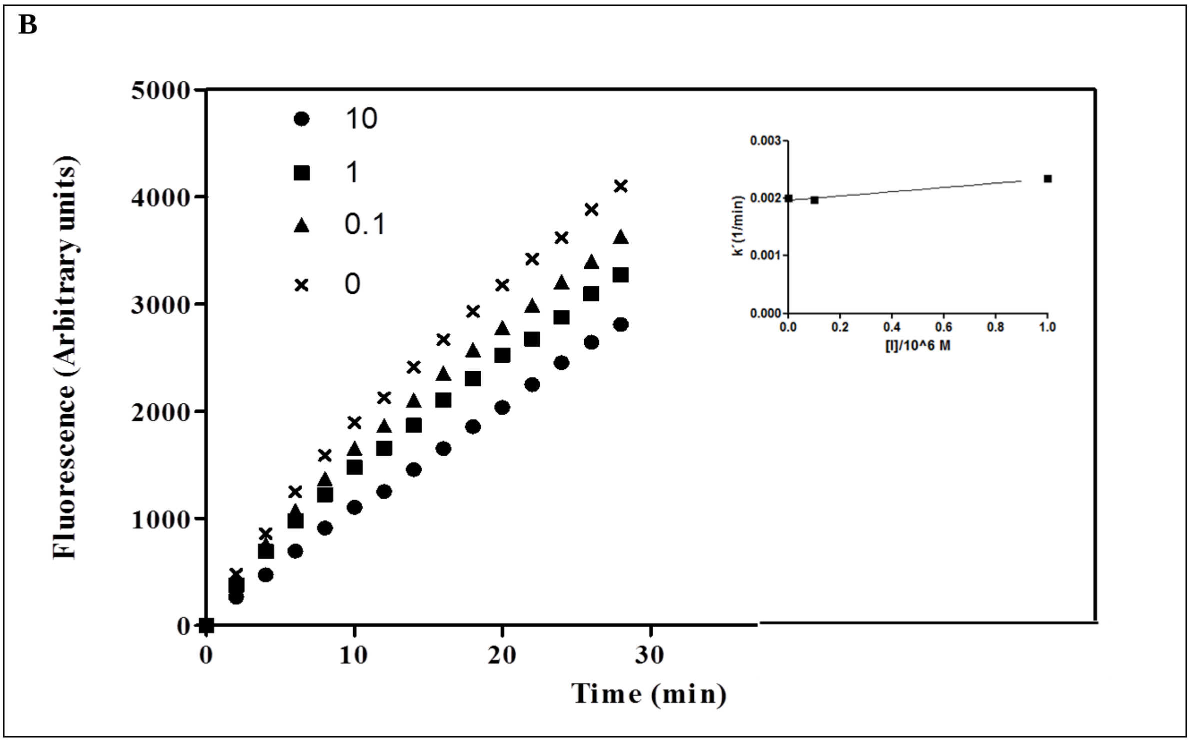
PPE	PR3
>50	>50

[1]. Lucas S.D., Gonçalves L.M., Cardote T.A.F., Correia H.F., Moreira R., Guedes R.C.. (2012). Structure Based Virtual Screening for Discovery of Novel Human Neutrophil Elastase Inhibitors. *Med. Chem. Commun.* 3: 1299–1304.

[2] Santana A.B., Lucas S.D., Gonçalves L.M., Correia H.F., Cardote T.A., Guedes R.C., Iley J., Moreira R. (2012). N-Acyl and N-sulfonyloxazolidine-2,4-diones are pseudo-irreversible inhibitors of serine proteases. *Bioorg Med Chem Lett*, 22: 3993–3997.

Inhibition of human neutrophil elastase by compound 16 (A) and 3 (B)





Progress curves were recorded by measuring the cleavage of MeOSuc-AAPV-AMC (200 μM) by human neutrophil elastase (17 nM) in the presence of **16** or **3**. The apparent first order rate constant k´ for each curve was plotted against the inhibitor concentration (inset). From the slope of the linear regression line k assoc was calculated using eqn (2).

To determine the rate constants *k*assoc for the inhibition of elastase by the progress curves were recorded under pseudo first-order conditions using the concentrations [*I*] specified in Figure xx. The data were fitted to eqn (1) for slow tight binding inhibition [1]:

$$P = vst + \frac{vo - vs}{k'} (1 - e^{-k't}) \quad \text{Eq. (1)}$$

where *P* is fluorescence, *v*0 is initial velocity, *v*s is steady-state velocity, *t* is time, *k*´ is apparent first order rate constant. Non-linear regression (Graph Pad) provided *k*´for each **16** and **3** and concentration [*I*].
By plotting *k*´ versus [*I*], the rate constant *k*assoc was obtained from linear regression according to eqn (2). The k´ value appeared to increase as the **16** concentration increased in the reaction mixtures.

$$k' = \frac{k_{\text{assoc}}}{(1 + [S]/K_{\text{m}})} \cdot [I] + k_{\text{diss}} \quad \text{Eq (2)}$$

The curves for elastase inhibition are shown in the Figure. By nonlinear regression, second order constant of 1,2x10^2 $M^{-1}.s^{-1}$ for **16** was calculated.

References:

1 Dufour, E. K., Denault, J. B., Bissonnette, L., Hopkins, P. C., Lavigne, P. and Leduc, R. (2001) The contribution of arginine residues within the P6-P1 region of alpha 1-antitrypsin to its reaction with furin. J. Biol. Chem. **276**, 38971–38979