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Synthesis and inhibitory studies of phosphonic acid analogues of homophenylalanine and phenylalanine towards Alanyl Aminopeptidases

Supplementary Materials

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Section S1. *The characterization data of the compounds* ***2c-2h*** *and* ***8a-8e***.

3-(3-fluorophenyl)propionic acid methyl ester (**2c**) [1]

Yellow oil, yield 100%; ^{1}H NMR (400 MHz, $CDCl_3$), δ = 7.27 – 7.18 (m, 1H, CH_{ar}), 6.96 (d, *J* = 7.8 Hz, 1H, CH_{ar}), 6.88 (ddd, *J* = 6.5, 2.4, 0.4 Hz, 1H, CH_{ar}), 3.66 (s, 3H, OCH_3), 2.94 (t, *J* = 7.7 Hz, 2H, CH_2), 2.62 (t, *J* = 7.8 Hz, 2H, CH_2) ppm; ^{13}C NMR (101 MHz, $CDCl_3$), δ = 173.10 (s, **C**$OOCH_3$), 162.99 (d, *J* = 245.6 Hz, C_{ar}-F), 143.10 (d, *J* = 7.3 Hz, C_{ar}), 130.02 (d, *J* = 8.3 Hz, C_{ar}), 124.01 (d, *J* = 2.8 Hz, C_{ar}), 115.26 (d, *J* = 21.1 Hz, C_{ar}), 113.27 (d, *J* = 21.0 Hz, C_{ar}), 51.77 (s, COO**C**H_3), 35.39 (s, CH_2), 30.67 (d, *J* = 1.8 Hz, CH_2) ppm; ^{19}F NMR (376 MHz, $CDCl_3$), δ = -113.30 – -113.38 (m, 1F) ppm.

3-(4-fluorophenyl)propionic acid methyl ester (**2d**) [1,2]

Yellow oil, yield 100%; ^{1}H NMR (400 MHz, $CDCl_3$), δ = 7.14 (ddd, *J* = 8.3, 5.4, 0.5 Hz, 2H, 2xCH_{ar}), 6.99 – 6.92 (m, 2H, 2xCH_{ar}), 3.65 (s, 3H, OCH_3), 2.91 (t, *J* = 7.7 Hz, 2H, CH_2), 2.59 (t, *J* = 7.7 Hz, 2H, CH_2) ppm; ^{13}C NMR (101 MHz, $CDCl_3$), δ = 173.24 (s, **C**$OOCH_3$), 161.57 (d, *J* = 244.1 Hz, C_{ar}-F), 136.20 (d, *J* = 3.2 Hz, C_{ar}), 129.78 (d, *J* = 7.9 Hz, 2xC_{ar}), 115.34 (d, *J* = 21.2 Hz, 2xC_{ar}), 51.71 (s, COO**C**H_3), 35.85 (d, *J* = 1.1 Hz, CH_2), 30.19 (d, *J* = 0.7 Hz, CH_2) ppm; ^{19}F NMR (376 MHz, $CDCl_3$), δ = -116.94 (tt, J = 8.7, 5.2 Hz, 1F) ppm.

3-(2,4-difluorophenyl)propionic acid methyl ester (**2e**)

Yellow oil, yield 100%; ^{1}H NMR (400 MHz, $CDCl_3$), δ = 7.16 (ddd, *J* = 8.5, 6.9, 3.5 Hz, 1H, CH_{ar}), 6.81 – 6.73 (m, 2H, 2xCH_{ar}), 3.65 (s, 3H, OCH_3), 2.92 (t, *J* = 7.6 Hz, 2H, CH_2), 2.60 (t, *J* = 7.6 Hz, 2H, CH_2) ppm; ^{13}C NMR (101 MHz, $CDCl_3$), δ = 173.07 (s, **C**$OOCH_3$), 161.43 (ddd, *J* = 83.7, 71.4, 11.9 Hz, 2xC_{ar}-F), 131.24 (dd, *J* = 9.5, 6.5 Hz, C_{ar}), 123.18 (dd, *J* = 15.8, 3.8 Hz, C_{ar}), 111.13 (dd, *J* = 20.9, 3.8 Hz, C_{ar}), 103.84 (dd, *J* = 26.0, 25.3 Hz, C_{ar}), 51.77 (s, COO**C**H_3), 34.25 (t, *J* = 1.4 Hz, CH_2), 24.13 (d, *J* = 2.3 Hz, CH_2) ppm; ^{19}F NMR (376 MHz, $CDCl_3$), δ = -112.70 – -112.83 (m, 1F), -114.18 (ddd, *J* = 15.8, 8.7, 3.8 Hz, 1F) ppm.

3-(3,4-difluorophenyl)propionic acid methyl ester (**2f**)

Yellow oil, yield 100%; ^{1}H NMR (400 MHz, $CDCl_3$), δ = 7.09 – 6.95 (m, 2H, 2xCH_{ar}), 6.92 – 6.86 (m, 1H, CH_{ar}), 3.66 (s, 3H, OCH_3), 2.89 (t, *J* = 7.6 Hz, 2H, CH_2), 2.59 (t, *J* = 7.6 Hz, 2H, CH_2) ppm; ^{13}C NMR (101 MHz, $CDCl_3$), δ = 172.95 (s, **C**$OOCH_3$), 149.66 (ddd, *J* = 129.2, 117.3, 12.6 Hz, 2xC_{ar}-F), 137.47 (dd, *J* = 5.6, 3.9 Hz, C_{ar}), 124.24 (dd, *J* = 6.1, 3.5 Hz, C_{ar}), 117.23 (ddd, *J* = 16.9, 2.4, 0.6 Hz, 2xC_{ar}), 51.81 (s, COO**C**H_3), 35.46 (d, *J* = 1.0 Hz, CH_2), 30.12 (d, *J* = 1.4 Hz, 30.12 (d, *J* = 1.4 Hz) ppm; ^{19}F NMR (376 MHz, $CDCl_3$), δ = -137.88 – -137.99 (m, 1F), -141.39 – -141.51 (m, 1F) ppm.

3-(4-trifluoromethylphenyl)propionic acid methyl ester (**2g**) [1a,1b,3,4]

Yellow oil, yield 100%; ^{1}H NMR (400 MHz, $CDCl_3$), δ = 7.42 (dd, *J* = 91.2, 8.2 Hz, 4H, 4xCH_{ar}), 3.66 (s, 3H, OCH_3), 3.00 (t, *J* = 7.7 Hz, 2H, CH_2), 2.64 (t, *J* = 7.7 Hz, 2H, CH_2) ppm; ^{13}C NMR (101 MHz, $CDCl_3$), δ = 172.97 (s, **C**$OOCH_3$), 144.64 (q, *J* = 1.3 Hz, C_{ar}), 128.73 (s, 2xC_{ar}), 125.53 (q, *J* = 3.8 Hz, C_{ar}-CF_3), 125.23 (s, C_{ar}), 125.06 (s, C_{ar}) 124.32 (q, *J* = 271.8 Hz, C_{ar}-CF_3), 51.83 (s, COO**C**H_3), 35.85 (d, *J* = 0.5 Hz, CH_2), 30.19 (s, CH_2) ppm; ^{19}F NMR (376 MHz, $CDCl_3$), δ = -62.32 (s, 3F, CF_3) ppm.

3-(2-trifluoromethylphenyl)propionic acid methyl ester (**2h**) [1a,5]

Yellow oil, yield 100%; ^{1}H NMR (400 MHz, $CDCl_3$), δ = 7.62 (d, *J* = 7.9 Hz, 1H, CH_{ar}), 7.46 (t, *J* = 7.6 Hz, 1H, CH_{ar}), 7.31 (dd, *J* = 16.4, 7.8 Hz, 2H, 2xCH_{ar}), 3.68 (s, 3H, OCH_3), 3.13 (t, *J* = 8.7 Hz, 2H, CH_2), 2.62 (t, *J* = 7.8 Hz, 2H, CH_2) ppm; ^{13}C NMR (101 MHz, $CDCl_3$), δ = 173.35 (s, **C**$OOCH_3$), 139.28 (q, *J* = 1.7 Hz, C_{ar}), 132.03 (q, *J* = 1.1 Hz, C_{ar}), 131.02 (s, C_{ar}), 128.66 (q, *J* = 29.8 Hz, C_{ar}-CF_3), 126.57 (s, C_{ar}), 126.19 (q, *J* = 5.7 Hz, C_{ar}), 124.59 (q, *J* = 273.7 Hz, C_{ar}-CF_3), 51.81 (s, COO**C**H_3), 35.70 (q, *J* = 1.1 Hz, CH_2), 30.19 (q, *J* = 1.9 Hz, CH_2) ppm; ^{19}F NMR (376 MHz, $CDCl_3$), δ = -59.72 (s, 3F, CF_3) ppm.

2-(2-bromo-4-fluorophenyl)acetic acid methyl ester (8a) [6]

Yellow oil, yield 100%; ^{1}H NMR (400 MHz, $CDCl_3$), δ = 7.31 (dd, *J* = 8.2, 2.7 Hz, 1H, CH_{ar}), 7.25 (dd, *J* = 8.6, 5.9 Hz, 1H, CH_{ar}), 7.00 (td, *J* = 8.3, 2.6 Hz, 1H, CH_{ar}), 3.75 (s, 2H, CH_2), 3.71 (s, 3H, OCH_3) ppm; ^{13}C NMR (101 MHz, $CDCl_3$), δ = 170.91 (d, *J* = 1.4 Hz, **C**$OOCH_3$), 161.64 (d, *J* = 250.4 Hz, C_{ar}-F), 132.31 (d, *J* = 8.5 Hz, C_{ar}), 130.23 (d, *J* = 3.7 Hz, C_{ar}), 125.03 (d, *J* = 9.6 Hz, C_{ar}), 120.14 (d, *J* = 24.5 Hz, C_{ar}), 114.80 (d, *J* = 21.0 Hz, C_{ar}), 52.33 (s, COO**C**H_3), 40.69 (s, 2H,CH_2) ppm; ^{19}F NMR (376 MHz, $CDCl_3$), δ = -112.92 – -112.99 (m, 1F) ppm.

2-(2-bromo-5-fluorophenyl)acetic acid methyl ester (**8b**) [7]

Yellow oil, yield 100%; ^{1}H NMR (400 MHz, $CDCl_3$), δ = 7.50 (dd, *J* = 8.8, 5.3 Hz, 1H, CH_{ar}), 7.03 (dd, *J* = 9.0, 3.0 Hz, 1H, CH_{ar}), 6.87 (ddd, *J* = 8.5, 8.1, 3.0 Hz, 1H, CH_{ar}), 3.76 (s, 2H, CH_2), 3.72 (s, 3H, OCH_3) ppm; ^{13}C NMR (101 MHz, $CDCl_3$), δ = 170.45 (d, *J* = 0.5 Hz, **C**$OOCH_3$), 161.87 (d, *J* = 247.1 Hz, C_{ar}-F), 136.11 (d, *J* = 8.0 Hz, C_{ar}), 134.00 (d, *J* = 8.1 Hz, C_{ar}), 119.21 (d, *J* = 3.4 Hz, C_{ar}), 118.60 (d, *J* = 23.2 Hz, C_{ar}), 116.19 (d, *J* = 22.4 Hz, C_{ar}), 52.40 (s, CH_2), 41.52 (d, *J* = 1.4 Hz, COO**C**H_3) ppm; ^{19}F NMR (376 MHz, $CDCl_3$), δ = -114.57 – -114.64 (m, 1F) ppm.

2-(3-bromo-4-fluorophenyl)acetic acid methyl ester (**8c**) [8]

Yellow oil, yield 100%; ^{1}H NMR (400 MHz, $CDCl_3$), δ = 7.47 (dd, *J* = 6.5, 2.2 Hz, 1H, CH_{ar}), 7.18 (ddd, *J* = 8.2, 4.6, 2.2 Hz, 1H, CH_{ar}), 7.06 (t, *J* = 8.4 Hz, 1H, CH_{ar}), 3.69 (s, 3H, OCH_3), 3.57 (s, 2H, CH_2) ppm; ^{13}C NMR (101 MHz, $CDCl_3$), δ = 171.39 (d, *J* = 1.3 Hz, **C**$OOCH_3$), 158.43 (d, *J* = 247.0 Hz, C_{ar}-F), 134.34 (d, *J* = 0.7 Hz, C_{ar}), 131.31 (d, *J* = 4.0 Hz, C_{ar}), 129.96 (d, *J* = 7.3 Hz, C_{ar}), 116.53 (d, *J* = 22.4 Hz, C_{ar}), 109.08 (d, *J* = 21.2 Hz, C_{ar}), 52.34 (s, CH_2), 39.95 (s, COO**C**H_3) ppm; ^{19}F NMR (376 MHz, $CDCl_3$), δ = -109.68 (dd, *J* = 12.9, 6.5 Hz, 1F) ppm.

2-(4-bromo-2-fluorophenyl)acetic acid methyl ester (**8d**) [9]

Yellow oil, yield 100%; ^{1}H NMR (400 MHz, $CDCl_3$), δ = 7.26 – 7.21 (m, 2H, 2xCH_{ar}), 7.13 (t, *J* = 8.1 Hz, 1H, CH_{ar}), 3.69 (s, 2H, CH_2), 3.61 (s, 2H, OCH_3) ppm; ^{13}C NMR (101 MHz, $CDCl_3$), δ = 170.69 (d, *J* = 1.1 Hz, **C**$OOCH_3$), 160.90 (d, *J* = 251.3 Hz, C_{ar}-F), 132.59 (d, *J* = 4.6 Hz, C_{ar}), 127.56 (d, *J* = 3.8 Hz, C_{ar}), 121.48 (d, *J* = 9.5 Hz, C_{ar}), 120.62 (d, *J* = 16.0 Hz, C_{ar}), 119.19 (d, *J* = 25.1 Hz, C_{ar}), 52.39 (s, CH_2), 33.96 (d, *J* = 2.9 Hz, COO**C**H_3) ppm; ^{19}F NMR (376 MHz, $CDCl_3$), δ = -114.12 (dd, *J* = 12.8, 4.8 Hz, 1F) ppm.

2-(4-bromo-3-fluorophenyl)acetic acid methyl ester (**8e**) [10]

Yellow oil, yield 100%; ^{1}H NMR (400 MHz, $CDCl_3$), δ = 7.48 (dd, *J* = 7.9, 7.4 Hz, 1H, CH_{ar}), 7.06 (dd, *J* = 9.3, 2.0 Hz, 1H, CH_{ar}), 6.94 (dd, *J* = 8.2, 2.0 Hz, 1H, CH_{ar}), 3.69 (s, 3H, OCH_3), 3.58 (s, 2H, CH_2) ppm; ^{13}C NMR (101 MHz, $CDCl_3$), δ = 171.06 (d, *J* = 0.5 Hz, **C**$OOCH_3$), 159.03 (d, *J* = 247.5 Hz, C_{ar}-F), 135.49 (d, *J* = 7.1 Hz, C_{ar}), 133.56 (d, *J* = 0.8 Hz, C_{ar}), 126.34 (d, *J* = 3.6 Hz, C_{ar}), 117.63 (d, *J* = 22.7 Hz, C_{ar}), 107.82 (d, *J* = 20.8 Hz, C_{ar}), 52.38 (s, CH_2), 40.43 (d, *J* = 1.6 Hz, COO**C**H_3) ppm; ^{19}F NMR (376 MHz, $CDCl_3$), δ = -107.03 (dd, *J* = 9.3, 7.2 Hz, 1F) ppm.

Section S2. *The characterization data of the compounds* ***3c-3h*** *and* ***9a-9e****.*

3-(3-fluorophenyl)propanol (**3c**) [1b,11]

Colourless oil, yield 100%; ^{1}H NMR (400 MHz, $CDCl_3$), δ = 7.23 (ddd, *J* = 13.9, 4.9, 3.8 Hz, 1H, CH_{ar}), 6.96 (d, *J* = 7.6 Hz, 1H, CH_{ar}), 6.89 (ddd, *J* = 13.9, 6.4, 4.9 Hz, 2H, CH_{ar}), 3.66 (t, *J* = 6.4 Hz, 2H, CH_2), 2.73 – 2.66 (m, 2H, CH_2), 1.87 (dt, *J* = 13.7, 6.5 Hz, 2H, CH_2), 1.68 (s, 1H, OH) ppm; ^{13}C NMR (101 MHz, $CDCl_3$), δ = 163.02 (d, *J* = 245.2 Hz, C_{ar}-F), 144.48 (d, *J* = 7.2 Hz, C_{ar}), 129.86 (d, *J* = 8.3 Hz, C_{ar}), 124.16 (d, *J* = 2.7 Hz, C_{ar}), 115.32 (d, *J* = 20.8 Hz, C_{ar}), 112.82 (d, *J* = 21.0 Hz, C_{ar}), 62.10 (s, **C**H_2OH), 33.94 (s, CH_2-C_{ar}), 31.86 (d, *J* = 1.7 Hz, CH_2**C**H_2CH_2OH) ppm; ^{19}F NMR (376 MHz, $CDCl_3$), δ = -113.30 – -113.39 (m, 1F) ppm.

3-(4-fluorophenyl)propanol (**3d**) [12,13]

Colourless oil, yield 100%; ^{1}H NMR (400 MHz, $CDCl_3$), δ = 7.14 (ddd, *J* = 8.3, 5.4, 0.5 Hz, 2H, 2xCH_{ar}), 6.95 (t, *J* = 8.8 Hz, 2H, 2xCH_{ar}), 3.66 (t, *J* = 6.4 Hz, 2H, CH_2), 2.70 – 2.65 (m, 2H, CH_2), 1.89 – 1.82 (m, 2H, CH_2), 1.46 (s, 1H, OH) ppm; ^{13}C NMR (101 MHz, $CDCl_3$), δ = 161.35 (d, *J* = 243.3 Hz, C_{ar}-F), 137.45 (d, *J* = 3.2 Hz, C_{ar}), 129.85 (s, C_{ar}), 129.77 (s, C_{ar}), 115.29 (s, C_{ar}), 115.08 (s, C_{ar}), 62.15 (s, CH_2OH), 34.37 (d, *J* = 1.0 Hz, CH_2-C_{ar}), 31.29 (d, *J* = 0.5 Hz, CH_2**C**H_2CH_2OH) ppm; ^{19}F NMR (376 MHz, $CDCl_3$), δ = -117.64 (tt, *J* = 8.7, 5.2 Hz, 1F) ppm.

3-(2,4-difluorophenyl)propanol (**3e**) [14]

Colourless oil, yield 100%; ^{1}H NMR (400 MHz, $CDCl_3$), δ = 7.17 – 7.11 (m, 1H, CH_{ar}), 6.81 – 6.73 (m, 2H, 2xCH_{ar}), 3.65 (t, *J* = 6.4 Hz, 2H, CH_2), 2.69 (t, *J* = 7.7 Hz, 2H, CH_2), 1.87 – 1.80 (m, 2H, CH_2), 1.63 (s, 1H, OH) ppm; ^{13}C NMR (101 MHz, $CDCl_3$), δ = 161.26 (ddd, *J* = 55.0, 42.7, 11.8 Hz, C_{ar}-F), 131.18 (dd, *J* = 9.4, 6.7 Hz, C_{ar}), 124.40 (dd, *J* = 16.2, 3.8 Hz, C_{ar}), 111.04 (dd, *J* = 20.9, 3.8 Hz, C_{ar}), 103.71 (dd, *J* = 26.4, 25.1 Hz, C_{ar}), 62.04 (s, CH_2OH), 32.98 (d, *J* = 1.1 Hz, CH_2-C_{ar}), 24.83 (d, *J* = 2.1 Hz, CH_2**C**H_2CH_2OH) ppm; ^{19}F NMR (376 MHz, $CDCl_3$), δ = -113.58 (ddd, *J* = 15.1, 8.4, 6.7 Hz, 1F), -114.54 (dd, *J* = 16.2, 8.7 Hz, 1F) ppm.

3-(3,4-difluorophenyl)propanol (**3f**) [15]

Colourless oil, yield 100%; ^{1}H NMR (400 MHz, $CDCl_3$), δ = 7.07 – 6.94 (m, 2H, 2xCH_{ar}), 6.89 – 6.85 (m, 1H, CH_{ar}), 3.64 (t, *J* = 6.4 Hz, 2H, CH_2), 2.71 – 2.57 (m, 2H, CH_2), 2.33 (s, 1H, OH), 1.87 – 1.80 (m, 2H, CH_2) ppm; ^{13}C NMR (101 MHz, $CDCl_3$), δ = 149.51 (ddd, *J* = 154.8, 143.1, 12.6 Hz, C_{ar}-F), 138.80 (dd, *J* = 5.4, 3.9 Hz, C_{ar}), 124.25 (dd, *J* = 6.0, 3.5 Hz, 2xC_{ar}), 117.15 (d, *J* = 16.7 Hz, C_{ar}), 117.05 (dd, *J* = 16.9, 0.8 Hz, C_{ar}), 61.84 (s, CH_2OH), 33.92 (s, CH_2-C_{ar}), 31.26 (d, *J* = 1.3 Hz, CH_2**C**H_2CH_2OH) ppm; ^{19}F NMR (376 MHz, $CDCl_3$), δ = -138.34 – -138.45 (m, 1F), -142.18 – -142.31 (m, 1F) ppm.

3-(4-trifluoromethylphenyl)propanol (**3g**) [1b,16,17]

Colourless oil, yield 100%; ^{1}H NMR (400 MHz, $CDCl_3$), δ = 7.41 (dd, *J* = 91.1, 7.9 Hz, 4H, 4xCH_{ar}), 3.67 (t, *J* = 6.4 Hz, 2H, CH_2), 2.78 – 2.74 (m, 2H, CH_2), 1.93 – 1.85 (m, 2H, CH_2), 1.55 (s, 1H, OH) ppm; ^{13}C NMR (101 MHz, $CDCl_3$), δ = 146.05 (q, *J* = 1.3 Hz, C_{ar}), 128.82 (s, 2xC_{ar}); 128.35 (q, *J* = 32.3 Hz, CF3-C_{ar}), 125.39 (q, *J*= 3.8 Hz, 2xC_{ar}), 124.42 (q, *J* = 271.0 Hz, CF_3-C_{ar}); 62.00 (s, CH_2OH), 33.92 (s, CH_2-C_{ar}), 31.96 (s, CH_2**C**H_2CH_2OH) ppm; ^{19}F NMR (376 MHz, $CDCl_3$), δ = -62.22 (s, 3F, CF_3) ppm.

3-(2-trifluoromethylphenyl)propanol (**3h**) [18,19]

Colourless oil, yield 100%; ^{1}H NMR (400 MHz, $CDCl_3$), δ = 7.61 (d, *J* = 7.9 Hz, 1H, CH_{ar}), 7.46 (t, *J* = 7.3 Hz, 1H, CH_{ar}), 7.34 (d, *J* = 7.7 Hz, 1H, CH_{ar}), 7.28 (t, *J* = 7.6 Hz, 1H, CH_{ar}), 3.71 (t, *J* = 6.4 Hz, 2H, CH_2), 2.86 (dd, *J* = 12.0, 3.9 Hz, 2H, CH_2), 1.89 (ddd, *J* = 14.3, 10.3, 6.3 Hz, 2H, CH_2), 1.66 (s, 1H, OH) ppm; ^{13}C NMR (101 MHz, $CDCl_3$), δ = 140.79 (q, *J* = 1.7 Hz, C_{ar}), 131.84 (q, *J* = 1.1 Hz, C_{ar}), 131.14 (s, C_{ar}), 128.52 (q, *J* = 29.6 Hz, **C**$_{ar}$-CF_3), 126.06 (q, *J* = 5.8 Hz, C_{ar}), 126.05 (s, C_{ar}), 124.72 (q, J = 273.8 Hz, C_{ar}-**C**F_3), 62.45 (s, CH_2OH), 34.59 (d, *J* = 0.4 Hz, CH_2-C_{ar}), 28.98 (q, *J* = 1.8 Hz, CH_2**C**H_2CH_2OH) ppm; ^{19}F NMR (376 MHz, $CDCl_3$), δ = -59.82 (s, 3F, CF_3) ppm.

2-(2-bromo-4-fluorophenyl)ethanol (**9a**) [20,21]

Colourless oil, yield 100%; ^{1}H NMR (400 MHz, $CDCl_3$), δ = 7.29 (dd, *J* = 8.2, 2.7 Hz, 1H, CH_{ar}), 7.24 (dd, *J* = 8.5, 6.0 Hz, 1H, CH_{ar}), 6.97 (td, *J* = 8.3, 2.7 Hz, 1H, CH_{ar}), 3.85 (t, *J* = 6.7 Hz, 2H, CH_2), 2.98 (t, *J* = 6.7 Hz, 2H, CH_2), 1.62 (s, 1H, OH) ppm; ^{13}C NMR (101 MHz, $CDCl_3$), δ = 161.24 (d, *J* = 249.2 Hz, C_{ar}-F), 133.79 (d, *J* = 3.5 Hz, C_{ar}), 131.98 (d, *J* = 8.3 Hz, C_{ar}), 124.48 (d, *J* = 9.4 Hz, C_{ar}), 120.13 (d, *J* = 24.3 Hz, C_{ar}), 114.63 (d, *J* = 20.7 Hz, C_{ar}), 62.45 (d, *J* = 1.4 Hz, CH_2OH), 38.52 (s, CH_2-C_{ar}) ppm; ^{19}F NMR (376 MHz, $CDCl_3$), δ = -114.24 (td, *J* = 8.2, 6.1 Hz, 1F) ppm.

2-(2-bromo-5-fluorophenyl)ethanol (**9b**) [20,22]

Colourless oil, yield 100%; ^{1}H NMR (400 MHz, $CDCl_3$), δ = 7.48 (dd, *J* = 8.8, 5.4 Hz, 1H, CH_{ar}), 7.01 (dd, *J* = 9.2, 3.0 Hz, 1H, CH_{ar}), 6.82 (ddd, *J* = 8.8, 7.9, 3.1 Hz, 1H, CH_{ar}), 3.87 (t, *J* = 6.6 Hz, 2H, CH_2), 2.98 (t, *J* = 6.6 Hz, 2H, CH_2), 1.63 (s, 1H, OH) ppm; ^{13}C NMR (101 MHz, $CDCl_3$), δ = 161.94 (d, *J* = 247.0 Hz, C_{ar}-F), 140.13 (d, *J* = 7.5 Hz, C_{ar}), 134.03 (d, *J* = 8.1 Hz, C_{ar}), 118.76 (d, *J* = 3.2 Hz, C_{ar}), 118.18 (d, *J* = 22.5 Hz, C_{ar}), 115.39 (d, *J* = 22.4 Hz, C_{ar}), 61.80 (d, *J* = 0.6 Hz, CH_2OH), 39.38 (d, *J* = 1.3 Hz, CH_2-C_{ar}) ppm; ^{19}F NMR (376 MHz, $CDCl_3$), δ = -114.92 – -114.64 (td, *J* = 14.0, 8.5, 5.5 Hz, 1F) ppm.

2-(3-bromo-4-fluorophenyl)ethanol (**9c**) [23]

Colourless oil, yield 100%; ^{1}H NMR (400 MHz, $CDCl_3$), δ = 7.41 (dd, *J* = 6.6, 2.1 Hz, 1H, CH_{ar}), 7.14 – 7.10 (m, 1H, CH_{ar}), 7.04 (t, *J* = 8.4 Hz, 1H, CH_{ar}), 3.83 (t, *J* = 6.5 Hz, 2H, CH_2), 2.80 (t, *J* = 6.5 Hz, 2H, CH_2), 1.63 (s, 1H, OH) ppm; ^{13}C NMR (101 MHz, $CDCl_3$), δ = 157.97 (d, *J* = 245.8 Hz, C_{ar}-F), 136.17 (d, *J* = 3.9 Hz, C_{ar}), 133.89 (s, C_{ar}), 129.55 (d, *J* = 7.0 Hz, C_{ar}), 116.46 (d, *J* = 22.1 Hz, C_{ar}), 108.98 (d, *J* = 20.9 Hz, C_{ar}), 63.39 (d, *J* = 1.4 Hz, CH_2OH), 38.04 (s, CH_2-C_{ar}) ppm; ^{19}F NMR (376 MHz, $CDCl_3$), δ = -110.93 (ddd, *J* = 8.3, 6.7, 5.0 Hz, 1F) ppm.

2-(4-bromo-2-fluorophenyl)ethanol (**9d**) [24,25]

Colourless oil, yield 100%; ^{1}H NMR (400 MHz, $CDCl_3$), δ = 7.23 – 7.19 (m, 2H, 2xCH_{ar}), 7.13 (t, *J* = 7.9 Hz, 1H, CH_{ar}), 3.83 (t, *J* = 6.6 Hz, 2H, CH_2), 2.85 (td, *J* = 6.6, 0.9 Hz, 2H, CH_2), 1.57 (s, 1H, OH) ppm; ^{13}C NMR (101 MHz, $CDCl_3$), δ = 161.20 (d, *J* = 249.8 Hz, C_{ar}-F), 132.53 (d, *J* = 5.6 Hz, C_{ar}), 127.43 (d, *J* = 3.7 Hz, C_{ar}), 124.78 (d, *J* = 16.0 Hz, C_{ar}), 120.42 (d, *J* = 9.6 Hz, C_{ar}), 119.11 (d, *J* = 25.6 Hz, C_{ar}), 62.19 (d, *J* = 1.3 Hz, CH_2OH), 32.23 (d, *J* = 1.4 Hz, CH_2-C_{ar}) ppm; ^{19}F NMR (376 MHz, $CDCl_3$), δ = -115.37 (t, *J* = 8.7 Hz, 1F) ppm.

2-(4-bromo-3-fluorophenyl)ethanol (**9e**) [9,25]

Colourless oil, yield 100%; ^{1}H NMR (400 MHz, $CDCl_3$), δ = 7.45 (dd, *J* = 8.0, 7.3 Hz, 1H, CH_{ar}), 7.06 (dd, *J* = 9.5, 2.0 Hz, 1H, CH_{ar}), 6.89 (dd, *J* = 8.2, 1.9 Hz, 1H, CH_{ar}), 3.84 (t, *J* = 6.5 Hz, 2H, CH_2), 2.82 (dd, *J* = 6.4 Hz, 2H, CH_2), 1.64 (s, 1H, OH) ppm; ^{13}C NMR (101 MHz, $CDCl_3$), δ = 159.10 (d, *J* = 247.3 Hz, C_{ar}-F), 140.63 (d, *J* = 6.7 Hz, C_{ar}), 133.48 (d, *J* = 0.8 Hz, C_{ar}), 126.03 (d, *J* = 3.4 Hz, C_{ar}), 117.17 (d, *J* = 21.9 Hz, C_{ar}), 106.78 (d, *J* = 20.8 Hz, C_{ar}), 63.13 (d, *J* = 0.5 Hz, CH_2OH), 38.48 (d, *J* = 1.5 Hz, CH_2-C_{ar}) ppm; ^{19}F NMR (376 MHz, $CDCl_3$), δ = -107.51 (dd, *J* = 9.5, 7.2 Hz, 1F) ppm.

Section S3. *The characterization data of the compounds* ***4e-4h, 10a*** *and* ***10b****.*

3-(2,4-difluorophenyl)propanal (**4e**) [26]

Colourless oil, yield 62%; ^{1}H NMR (400 MHz, $CDCl_3$), δ = 9.80 (t, *J* = 1.1 Hz, 1H, CHO), 7.20 – 7.12 (m, 1H, CH_{ar}), 6.82 – 6.74 (m, 2H, 2xCH_{ar}), 2.93 (t, *J* = 7.6 Hz, 2H, CH_2), 2.64 (t, *J* = 7.6 Hz, 2H, CH_2) ppm; ^{13}C NMR (101 MHz, $CDCl_3$), δ = 178.83 (s, CHO), 161.48 (ddd, *J* = 89.6, 77.2, 11.9 Hz, C_{ar}-F), 131.24 (dd, *J* = 9.9, 6.4 Hz, C_{ar}), 122.82 (dd, *J* = 15.8, 3.8 Hz, 2xC_{ar}), 111.20 (dd, *J* = 21.0, 3.8 Hz, C_{ar}), 103.91 (dd, *J* = 26.0, 25.3 Hz, C_{ar}), 34.15 (t, *J* = 1.4 Hz, **C**H_2-C_{ar}), 23.81 (d, *J* = 2.3 Hz, CH_2**C**H_2CHO) ppm; ^{19}F NMR (376 MHz, $CDCl_3$), δ = -112.51 (ddd, *J* = 15.3, 8.2, 7.0 Hz, 1F), -113.99 - -114.08 (m, 1F) ppm.

3-(3,4-difluorophenyl)propanal (**4f**) [27]

Colourless oil, yield 57%; ^{1}H NMR (400 MHz, $CDCl_3$), 9.79 (t, *J* = 1.1 Hz, 1H, CHO), 7.09 – 6.96 (m, 1H, CH_{ar}), 6.90 (dtd, *J* = 10.2, 4.0, 1.8 Hz, 2H, 2xCH_{ar}), 2.90 (t, *J* = 7.5 Hz, 2H, CH_2), 2.65 (t, *J* = 7.6 Hz, 2H, CH_2) ppm; ^{13}C NMR (101 MHz, $CDCl_3$), 178.40 (s, CHO), 149.72 (ddd, *J* = 125.1, 113.1, 12.7 Hz, C_{ar}-F), 137.08 (dd, *J* = 5.6, 4.0 Hz, C_{ar}), 124.25 (ddd, *J* = 6.1, 3.6, 1.2 Hz, 2xC_{ar}), 117.28 (ddd, J = 16.4, 7.6, 0.6 Hz, 2xC_{ar}), 35.33 (d, *J* = 1.0 Hz, **C**H_2-C_{ar}), 29.75 (d, *J* = 1.4 Hz, CH_2**C**H_2CHO) ppm; ^{19}F NMR (376 MHz, $CDCl_3$), δ = -137.69 – -137.85 (m, 1F), -141.15 – -141.27 (m, 1F) ppm.

3-(4-trifluoromethylphenyl)propanal (**4g**) [28]

Colourless oil, yield 74%; ^{1}H NMR (400 MHz, $CDCl_3$), 9.81 (t, *J* = 0.9 Hz, 1H, CHO), 7.42 (dd, *J* = 94.0, 8.0 Hz, 4H, 4xCH_{ar}), 3.00 (t, *J* = 7.4 Hz, 2H, CH_2), 2.81 (t, *J* = 7.3 Hz, 2H, CH_2) ppm; ^{13}C NMR (101 MHz, $CDCl_3$), δ = 178.57 (s, CHO), 140.05 (q, *J* = 1.3 Hz, C_{ar}), 129.43 (s, 2xC_{ar}); 128.85 (q, *J* = 31.7 Hz, CF_3-C_{ar}), 125.78 (q, *J*= 3.2 Hz, 2xC_{ar}), 124.56 (q, *J* = 271.2 Hz, CF_3-C_{ar}); 34.36 (s, **C**H_2-C_{ar}), 29.47 (s, CH_2**C**H_2CHO) ppm; ^{19}F NMR (376 MHz, $CDCl_3$), δ = -62.33 (s, 3F, CF_3) ppm.

3-(2-trifluoromethylphenyl)propanal (**4h**) [29]

Colourless oil, yield 51%; ^{1}H NMR (400 MHz, $CDCl_3$), 9.81 (s, 1H, CHO), 7.63 (d, *J* = 7.8 Hz, 1H, CH_{ar}), 7.48 (t, *J* = 7.5 Hz, 1H, CH_{ar}), 7.33 (dd, *J* = 18.4, 7.7 Hz, 2H, 2xCH_{ar}) 3.14 (t, *J* = 7.8 Hz, 2H, CH_2), 2.70 – 2.66 (m, 2H, CH_2) ppm; ^{13}C NMR (101 MHz, $CDCl_3$), δ = 178.63 (s, CHO), 138.95 (s, C_{ar}), 132.12 (q, *J* = 0.9 Hz, C_{ar}), 130.96 (s, C_{ar}), 128.66 (q, *J* = 27.8 Hz, **C**$_{ar}$-CF_3), 126.69 (q, *J* = 4.8 Hz, C_{ar}), 126.24 (s, C_{ar}), 124.20 (q, *J* = 273.3 Hz, C_{ar}-**C**F_3), 35.55 (s, **C**H_2-C_{ar}), 27.52 (q, *J* = 1.8 Hz, CH_2**C**H_2CHO) ppm; ^{19}F NMR (376 MHz, $CDCl_3$), δ = -59.74 (s, 3F, CF_3) ppm.

2-(2-bromo-4-fluorophenyl)ethanal (**10a**) [30]

Colourless oil, yield 52%; ^{1}H NMR (400 MHz, $CDCl_3$), δ = 9.74 (t, *J* = 1.6 Hz, 1H, CHO), 7.36 (dd, *J* = 8.2, 2.6 Hz, 1H, CH_{ar}), 7.20 (dd, *J* = 8.5, 5.8 Hz, 1H, CH_{ar}), 7.03 (td, *J* = 8.2, 2.6 Hz, 1H, CH_{ar}), 3.84 (d, *J* = 1.5 Hz, 2H, CH_2) ppm; ^{13}C NMR (101 MHz, $CDCl_3$), -; ^{19}F NMR (376 MHz, $CDCl_3$), δ = -112.24 (td, *J* = 8.0, 5.9 Hz, 1F) ppm.

2-(2-bromo-5-fluorophenyl)ethanal (**10b**) [31]

Colourless oil, yield 32%; ^{1}H NMR (400 MHz, $CDCl_3$), δ = 9.75 (t, *J* = 1.5 Hz, 1H, CHO), 7.56 (dd, *J* = 8.8, 5.3 Hz, 1H, CH_{ar}), 6.97 (dd, *J* = 8.8, 3.0 Hz, 1H, CH_{ar}), 7.03 (td, *J* = 8.2, 2.6 Hz, 1H, CH_{ar}), 6.90 (ddd, *J* = 8.6, 8.0, 3.2 Hz, 1H, CH_{ar}), 3.85 (d, *J* = 1.5 Hz, 2H, CH_2) ppm; ^{13}C NMR (101 MHz, $CDCl_3$), δ = 197.37 (s, CHO), 162.01 (d, *J* = 248.0 Hz, C_{ar}-F), 134.66 (d, *J* = 7.8 Hz, C_{ar}), 134.25 (d, *J* = 8.1 Hz, C_{ar}), 119.17 (d, *J* = 3.3 Hz, C_{ar}), 118.85 (d, *J* = 23.1 Hz, C_{ar}), 116.57 (d, *J* = 22.3 Hz, C_{ar}), 50.35 (d, *J* = 1.4 Hz, CH_2-C_{ar}) ppm; ^{19}F NMR (376 MHz, $CDCl_3$), δ = -114.06 - -114.12 (m, 1F) ppm.

Section S4. *The characterization data of the compounds* ***4b, 4c, 10c-10e****.*

3-(2-fluorophenyl)propanal (**4b**) [32,33]

Colourless oil, yield 67.5%; ^{1}H NMR (400 MHz, $CDCl_3$), δ = 9.81 (s, 1H, CHO), 7.24 – 7.15 (m, 2H, 2xCH_{ar}), 7.09 – 6.96 (m, 2H, 2xCH_{ar}), 2.97 (t, *J* = 7.4 Hz, 2H, CH_2), 2.77 (t, *J* = 7.3, 2H, CH_2) ppm; ^{13}C NMR (101 MHz, $CDCl_3$), δ = 177.42 (s, CHO), 161.21 (d, *J* = 245.2 Hz, C_{ar}-F), 130.71 (d, *J* = 4.8 Hz, C_{ar}), 128.24 (d, *J* = 8.1 Hz, C_{ar}), 127.16 (d, *J* = 20.4 Hz, C_{ar}), 124.24 (d, *J* = 3.6 Hz, C_{ar}), 115.45 (d, *J* = 21.9 Hz, C_{ar}), 33.92 (d, *J* = 1.6 Hz, **C**H_2-C_{ar}), 24.38 (d, *J* = 2.8 Hz, CH_2**C**H_2CHO) ppm; ^{19}F NMR (376 MHz, $CDCl_3$), δ = -118.30 (s, 1F) ppm.

3-(3-fluorophenyl)propanal (**4c**) [11]

Colourless oil, yield 71%; ^{1}H NMR (400 MHz, $CDCl_3$), δ = 9.81 (t, *J* = 1.2 Hz, 1H, CHO), 7.24 (qd, *J* = 7.7, 6.2 Hz, 1H, CH_{ar}), 6.99 – 6.96 (m, 1H, CH_{ar}), 6.93 – 6.87 (m, 2H, 2xCH_{ar}), 2.95 (t, *J* = 7.7 Hz, 2H, CH_2), 2.68 (t, *J* = 7.7 Hz, 2H, CH_2) ppm; ^{13}C NMR (101 MHz, $CDCl_3$), δ = 178.72 (s, CHO), 162.99 (d, *J* = 245.7 Hz, C_{ar}-F), 142.70 (d, *J* = 7.3 Hz, C_{ar}), 130.10 (d, *J* = 8.4 Hz, C_{ar}), 124.00 (d, *J* = 2.8 Hz, C_{ar}), 115.30 (d, *J* = 21.2 Hz, C_{ar}), 113.41 (d, *J* = 21.0 Hz, C_{ar}), 35.29 (s, **C**H_2-C_{ar}), 30.30 (d, *J* = 1.8 Hz, CH_2**C**H_2CHO) ppm; ^{19}F NMR (376 MHz, $CDCl_3$), δ = -113.21 (td, *J* = 9.5, 6.3 Hz, 1F) ppm.

2-(3-bromo-4-fluorophenyl)ethanal (**10c**) [23]

Colourless oil, yield 61%; ^{1}H NMR (400 MHz, $CDCl_3$), δ = 9.74 (t, *J* = 1.9 Hz, 1H, CHO), 7.42 – 7.38 (m, 1H, CH_{ar}), 7.12 – 7.10 (m, 2H, 2xCH_{ar}), 3.67 (d, *J* = 1.9 Hz, 2H, CH_2) ppm; ^{13}C NMR (101 MHz, $CDCl_3$), δ = 198.22 (s, CHO), 158.62 (d, *J* = 247.6 Hz, C_{ar}-F), 134.64 (s, C_{ar}), 133.89 (s, C_{ar}), 130.24 (d, *J* = 7.3 Hz, C_{ar}), 116.94 (d, *J* = 22.4 Hz, C_{ar}), 109.56 (d, *J* = 21.2 Hz, C_{ar}), 49.21 (s, **C**H_2-C_{ar}) ppm; ^{19}F NMR (376 MHz, $CDCl_3$), δ = -109.08 (dd, *J* = 13.0, 6.5 Hz, 1F) ppm.

2-(4-bromo-2-fluorophenyl)ethanal (**10d**)

Colourless oil, yield 67%; ^{1}H NMR (400 MHz, $CDCl_3$), δ = 9.73 (dd, *J* = 2.9, 1.6 Hz, 1H, CHO), 7.28 (d, *J* = 8.0 Hz, 2H, 2xCH_{ar}), 7.06 (t, *J* = 7.5 Hz, CH_{ar}), 3.70 (s, 2H, CH_2) ppm; ^{13}C NMR (101 MHz, $CDCl_3$), δ = 197.15 (s, CHO), 160.99 (d, *J* = 251.5 Hz, C_{ar}-F), 132.75 (d, *J* = 4.7 Hz, C_{ar}), 127.90 (s, C_{ar}), 121.87 (d, *J* = 9.3 Hz, C_{ar}), 119.39 (d, *J* = 25.1 Hz, C_{ar}), 118.74 (d, *J* = 16.5 Hz, C_{ar}), 43.59 (s, **C**H_2-C_{ar}) ppm; ^{19}F NMR (376 MHz, $CDCl_3$), δ = -113.97 – -114.02 (m, 1F) ppm.

2-(4-bromo-3-fluorophenyl)ethanal (**10e**) [9]

Colourless oil, yield 50%; ^{1}H NMR (400 MHz, $CDCl_3$), δ = 9.74 (d, *J* = 1.9 Hz, 1H, CHO), 7.52 (dd, *J* = 8.1, 7.2 Hz, 1H, CH_{ar}), 6.99 (dd, *J* = 9.1, 2.0 Hz, 1H, CH_{ar}), 6.87 (dd, *J* = 8.1, 2.0 Hz, 1H, CH_{ar}), 3.68 (d, *J* = 1.9 Hz, CH_2) ppm; ^{13}C NMR (101 MHz, $CDCl_3$), δ = 197.86 (s, CHO), 159.29 (d, *J* = 248.53 Hz, C_{ar}-F), 134.00 (s, C_{ar}), 126.61 (d, *J* = 3.6 Hz, C_{ar}), 117.87 (d, *J* = 22.5 Hz, C_{ar}), 108.20 (d, *J* = 20.8 Hz, C_{ar}), 98.35 (d, *J* = 20.5 Hz, C_{ar}), 49.68 (s, **C**H_2-C_{ar}) ppm; ^{19}F NMR (376 MHz, $CDCl_3$), δ = -106.37 (dd, *J* = 9.1, 7.2 Hz, 1F) ppm.

Section S5. *The characterization data of the compounds* ***6b-6h and 13a-13e****.*

Diphenyl 1-{[(N-benzyloxy)carbonyl]amino}-3-(2-fluorophenyl)propylphosphonate (**6b**)

White solid, yield 63%; ^{1}H NMR (400 MHz, $CDCl_3$), δ = 7.37 – 6.96 (m, 19H, CH_{ar}), 5.23 (br d, *J* = 10.3 Hz, 1H, NH), 5.13 (d, *J* = 4.6 Hz, 2H, CH_2OC, *trans*), 5.13 (d, *J* = 29.0 Hz, 2H, CH_2OC, *cis*), 4.57 – 4.46 (m, 1H, CHP, *trans*), 4.39 – 4.26 (m, 1H, CHP, *cis*), 2.97 – 2.89 (m, 1H, CH_2), 2.79 – 2.70 (m, 1H, CH_2), 2.43 – 2.30 (br m, 1H, CH_2), 2.12 – 1.99 (br m, 1H, CH_2) ppm; ^{13}C NMR (101 MHz, $CDCl_3$), δ = 161.20 (d, *J* = 245.2 Hz, C_{ar}-F), 155.97 (dd, *J* = 5.7, 4.8 Hz, CONH), 150.15 (dd, *J* = 23.5, 9.8 Hz, 2xC_{ar}), 136.13 (s, C_{ar}), 130.90 (d, *J* = 4.8 Hz, C_{ar}), 129.87 (dd, *J* = 10.9, 0.8 Hz, 4xC_{ar}), 128.67 (s, 2xC_{ar}), 128.40 (s, 2xC_{ar}), 128.27 (s, 2xC_{ar}), 125.48 (dd, *J* = 15.0, 1.0 Hz, 2xC_{ar}), 124.23 (d, *J* = 3.6 Hz, 2xC_{ar}), 120.59 (dd, *J* = 22.3, 4.1 Hz, 4xC_{ar}), 115.45 (d, *J* = 21.9 Hz, C_{ar}), 67.52 (s, **C**H_2Ph), 48.22 (dd, *J* = 158.1, 10.8 Hz, **C**HP), 30.49 (d, *J* = 3.4 Hz, **C**H_2CH_2CHP), 25.68 (dd, *J* = 14.7, 2.4 Hz, CH_2**C**H_2CHP) ppm; ^{19}F NMR (376 MHz, $CDCl_3$), δ = -118.12 – -118.21 (m, F-H, *cis*), -118.30 – -118.41 (m, F-H, *trans*) ppm; ^{31}P NMR (162 MHz, $CDCl_3$), δ=17.72 (s, 1P, *trans*), 17.38 (s, 1P, *cis*) ppm; HRMS (ESI-MS) *m*/*z* $[MH]^+$ calculated for $C_{29}H_{27}FNO_5P$: 520.1689, found: 520.1691; $[M+Na]^+$ calculated for $C_{29}H_{27}FNO_5PNa$: 542.1509, found: 524.1150.

Diphenyl 1-{[(N-benzyloxy)carbonyl]amino}-3-(3-fluorophenyl)propylphosphonate (**6c**)

White solid, yield 57%; ^{1}H NMR (400 MHz, $CDCl_3$), δ = 7.38 – 6.82 (m, 19H, CH_{ar}), 5.30 (br d, *J* = 9.0 Hz, 1H, NH), 5.13 (d, *J* = 3.3 Hz, 2H, CH_2OC, *trans*), 5.13 (d, *J* = 28.2 Hz, 2H, CH_2OC, *cis*), 4.59 – 4.43 (m, 1H, CHP, *trans*), 4.38 – 4.26 (m, 1H, CHP, *cis*), 2.91 – 2.79 (m, 1H, CH_2), 2.79 – 2.67 (m, 1H, CH_2), 2.41 – 2.28 (br m, 1H, CH_2), 2.15 – 1.99 (br m, 1H, CH_2) ppm; ^{13}C NMR (101 MHz, $CDCl_3$), δ = 163.01 (d, *J* = 245.7 Hz, C_{ar}-F), 156.01 (d, *J* = 6.2 Hz, CONH), 150.14 (dd, *J* = 24.0, 9.7 Hz, 2xC_{ar}), 136.11 (s, C_{ar}), 130.08 (d, *J* = 8.3 Hz, C_{ar}), 129.91 (d, *J* = 12.3 Hz, 2xC_{ar}), 128.69 (s, 2xC_{ar}), 128.45 (s, 2xC_{ar}), 128.32 (s, 2xC_{ar}), 125.54 (d, *J* = 16.2 Hz, 2xC_{ar}), 124.26 (d, *J* = 2.8 Hz, 2xC_{ar}), 120.57 (dd, *J* = 20.3, 4.0 Hz, 4xC_{ar}), 115.46 (d, *J* = 21.1 Hz, C_{ar}), 113.30 (d, *J* = 21.0 Hz, C_{ar}), 67.58 (s, **C**H_2Ph), 48.13 (d, *J* = 158.2 Hz, **C**HP), 31.88 (s, **C**H_2CH_2CHP), 31.77 (d, *J* = 4.6 Hz, CH_2**C**H_2CHP) ppm; ^{19}F NMR (376 MHz, $CDCl_3$), δ = -112.95 – -113.09 (m, F-H, *cis*), -113.18 (td, *J* = 9.2, 6.1 Hz, F-H, *trans*) ppm; ^{31}P NMR (162 MHz, $CDCl_3$), δ=17.70 (s, 1P, *trans*), 17.41 (s, 1P, *cis*) ppm; HRMS (ESI-MS) *m*/*z* $[MH]^+$ calculated for $C_{29}H_{27}FNO_5P$: 520.1689, found: 520.1741; $[M+Na]^+$ calculated for $C_{29}H_{27}FNO_5PNa$: 542.1509, found: 524.1556.

Diphenyl 1-{[(N-benzyloxy)carbonyl]amino}-3-(4-fluorophenyl)propylphosphonate (**6d**)

White solid, yield 37%; ^{1}H NMR (400 MHz, $CDCl_3$), δ = 7.36 – 6.89 (m, 19H, CH_{ar}), 5.30 (br d, *J* = 10.2 Hz, 1H, NH), 5.13 (d, *J* = 2.7 Hz, 2H, CH_2OC, *trans*), 5.13 (d, *J* = 27.1 Hz, 2H, CH_2OC, *cis*), 4.49 (dtd, *J* = 17.3, 10.6, 3.6 Hz, 1H, CHP, *trans*), 4.29 (dd, *J* = 25.1, 12.6 Hz, 1H, CHP, *cis*), 2.83 (ddd, *J* = 14.3, 9.3, 5.3 Hz, 1H, CH_2), 2.75 – 2.64 (br m, 1H, CH_2), 2.37 – 2.25 (br m, 1H, CH_2), 2.11 – 1.98 (br m, 1H, CH_2) ppm; ^{13}C NMR (101 MHz, $CDCl_3$), δ = 161.57 (d, *J* = 244.1 Hz, C_{ar}-F), 156.01 (d, *J* = 6.0 Hz, CONH), 150.16 (dd, *J* = 23.9, 9.7 Hz, 2xC_{ar}), 136.13 (s, C_{ar}), 136.09 (dd, *J* = 3.3, 0.8 Hz, C_{ar}), 130.01 (d, *J* =

7.9 Hz, 2xC_{ar}), 129.88 (dd, *J* = 12.2, 0.8 Hz, 4xC_{ar}), 128.68 (s, C_{ar}), 128.44 (s, 2xC_{ar}), 128.30 (s, 2xC_{ar}), 125.50 (dd, *J* = 16.0, 1.0 Hz, 2xC_{ar}), 120.65 (d, *J* = 4.1 Hz, 2xC_{ar}), 120.45 (d, *J* = 4.2 Hz, 2xC_{ar}), 115.40 (d, *J* = 21.2 Hz, 2xC_{ar}), 67.53 (s, **C**H_2Ph), 48.00 (d, *J* = 158.0 Hz, **C**HP), 32.10 (d, *J* = 4.5 Hz, **C**H_2CH_2CHP), 31.19 (d, *J* = 13.9 Hz, CH$_2$**C**H_2CHP) ppm; ^{19}F NMR (376 MHz, $CDCl_3$), δ = -116.62 – -116.72 (m, F-H, *cis*), -116.87 (dq, *J* = 8.8, 5.4 Hz, F-H, *trans*) ppm; ^{31}P NMR (162 MHz, $CDCl_3$), δ = 17.79 (s, 1P, *trans*), 17.53 (s, 1P, *cis*) ppm; HRMS (ESI-MS) *m*/*z* $[MH]^+$ calculated for $C_{29}H_{27}FNO_5P$: 520.1689, found: 520.1741; $[M+Na]^+$ calculated for $C_{29}H_{27}FNO_5PNa$: 542.1509, found: 524.1500.

Diphenyl 1-{[(N-benzyloxy)carbonyl]amino}-3-(2,4-difluorophenyl)propylphosphonate (**6e**)

White solid, yield 37%; ^{1}H NMR (400 MHz, $CDCl_3$), δ = 7.37 – 7.04 (m, 2H, CH_{ar}), 6.80 – 6.72 (m, 16H, CH_{ar}), 5.26 (br d, *J* = 10.4 Hz, 1H, NH), 5.13 (d, *J* = 3.5 Hz, 2H, CH_2OC, *trans*), 5.13 (d, *J* = 27.9 Hz, 2H, CH_2OC, *cis*), 4.54 – 4.42 (m, 1H, CHP, *trans*), 4.29 (dd, *J* = 26.1, 11.6 Hz, 1H, CHP, *cis*), 2.88 (ddd, *J* = 14.3, 9.4, 5.1 Hz, 1H, CH_2), 2.75 – 2.65 (m, 1H, CH_2), 2.38 – 2.26 (br m, 1H, CH_2), 2.10 – 1.96 (br m, 1H, CH_2) ppm; ^{13}C NMR (101 MHz, $CDCl_3$), δ = 161.42 (ddd, *J* = 85.1, 75.3, 11.4 Hz, 2xC_{ar}, C_{ar}-F), 156.00 (d, *J* = 6.1 Hz, CONH), 150.14 (dd, *J* = 25.6, 7.5 Hz, 2xC_{ar}), 136.10 (s, C_{ar}), 131.46 (s, C_{ar}), 129.88 (d, *J* = 10.9 Hz, 4xC_{ar}), 129.15 – 127.91 (m, 5xC_{ar}), 125.51 (d, *J* = 15.2 Hz, 2xC_{ar}), 123.10 (d, *J* = 13.2 Hz, C_{ar}), 120.56 (d, *J* = 21.0 Hz, 4xC_{ar}), 111.21 (d, *J* = 22.0 Hz, C_{ar}), 103.91 (t, *J* = 26.2 Hz, C_{ar}), 67.59 (s, **C**H_2Ph), 48.06 (d, *J* = 158.1 Hz, **C**HP), 30.51 (s, **C**H_2CH_2CHP), 25.10 (d, *J* = 14.5 Hz, CH$_2$**C**H_2CHP) ppm; ^{19}F NMR (376 MHz, $CDCl_3$), δ = -112.43 – -112.49 (m, F-H, *cis*), -112.64 (dd, *J* = 15.0, 7.3 Hz, F-H, *trans*), -113.76 – -113.87 (m, F-H, *cis*), -113.99 (dd, *J* = 16.8, 8.4 Hz, F-H, *trans*) ppm; ^{31}P NMR (162 MHz, $CDCl_3$), δ = 17.60 (s, 1P, *trans*), 17.24 (s, 1P, *cis*) ppm; HRMS (ESI-MS) *m*/*z* $[MH]^+$ calculated for $C_{29}H_{26}F_2NO_5P$: 538.1595, found: 538.1605; $[M+Na]^+$ calculated for $C_{29}H_{26}F_2NO_5PNa$: 560.1414, found: 560.1414.

Diphenyl 1-{[(N-benzyloxy)carbonyl]amino}-3-(3,4-difluorophenyl)propylphosphonate (**6f**)

White solid, yield 56%; ^{1}H NMR (400 MHz, $CDCl_3$), δ = 7.38 – 6.82 (m, 18H, CH_{ar}), 5.35 (br d, *J* = 10.2 Hz, 1H, NH), 5.13 (d, *J* = 2.7 Hz, 1H, CH_2OC, *trans*), 5.13 (d, *J* = 27.2 Hz, 1H, CH_2OC, *cis*), 4.48 (dtd, *J* = 17.4, 10.5, 3.3 Hz, 1H, CHP, *trans*), 4.27 (dd, *J* = 21.2, 9.9 Hz, 1H, CHP, *cis*), 2.80 (ddd, *J* = 14.2, 9.3, 5.3 Hz, 1H, CH_2), 2.72 – 2.63 (m, 1H, CH_2), 2.34 – 2.22 (br m, 1H, CH_2), 2.10 – 1.96 (br m, 1H, CH_2) ppm; ^{13}C NMR (101 MHz, $CDCl_3$), δ = 156.02 (d, *J* = 6.1 Hz, **C**ONH), 150.27 (dd, *J* = 11.3, 7.7 Hz, 2xC_{ar}), 149.60 (ddd, *J* = 136.6, 131.7, 12.6 Hz, 2xC_{ar}, C_{ar}-F), 137.38 (t, *J* = 4.7 Hz, C_{ar}), 136.07 (s, C_{ar}), 129.90 (d, *J* = 12.9 Hz, 4xC_{ar}), 128.75 – 128.20 (m, 5xC_{ar}), 125.56 (d, *J* = 16.7 Hz, 2xC_{ar}), 124.46 (dd, *J* = 6.0, 3.5 Hz, C_{ar}), 120.52 (dd, *J* = 19.0, 4.1 Hz, 4xC_{ar}), 117.31 (dd, *J* = 17.0, 8.6 Hz, 2xC_{ar}), 67.59 (s, **C**H_2Ph), 47.87 (d, *J* = 158.3 Hz), 31.83 (d, *J* = 4.2 Hz), 31.19 (d, *J* = 14.3 Hz) ppm; ^{19}F NMR (376 MHz, $CDCl_3$), δ = -137.48 – -137.64 (m, F-H, *trans*), -137.66 – -137.85 (m, F-H, *cis*), -141.07 – -141.22 (m, F-H, *trans*), -141.29 – -141.46 (m, F-H, *cis*) ppm; ^{31}P NMR (162 MHz, $CDCl_3$), δ = 17.58 (s, 1P, *cis*), 17.28 (s, 1P, *trans*) ppm; HRMS (ESI-MS) *m*/*z* $[MH]^+$ calculated for $C_{29}H_{26}F_2NO_5P$: 538.1595, found: 538.1714; $[M+Na]^+$ calculated for $C_{29}H_{26}F_2NO_5PNa$: 560.1414, found: 560.1416.

Diphenyl 1-{[(N-benzyloxy)carbonyl]amino}-3-(4-trifluoromethylphenyl)propylphosphonate (**6g**)

White solid, yield 40%; ^{1}H NMR (400 MHz, $CDCl_3$), δ = 7.51 (d, *J* = 8.1 Hz, 2H, 2xCH_{ar}), 7.43 – 7.08 (m, 15H, CH_{ar}), 7.06 (d, *J* = 8.5 Hz, 2H, 2xCH_{ar}), 5.73 (d, *J* = 10.2 Hz, 1H, NH), 5.14 (dd, *J* = 5.9 Hz, 2H, CH_2OC, *trans*), 5.14 (d, *J* = 30.4 Hz, 2H, CH_2OC, *cis*), 4.53 (dtd, *J* = 17.5, 10.6, 3.5 Hz, 1H, CHP, *trans*), 4.28 (dd, *J* = 22.6, 10.3 Hz, 1H, CHP, *cis*), 2.89 (ddd, *J* = 14.3, 9.3, 5.3 Hz, 1H, CH_2), 2.83 – 2.73 (m, 1H, CH_2), 2.38 – 2.26 (br m, 1H, CH_2), 2.17 – 2.05 (br m, 1H, CH_2) ppm; ^{13}C NMR (101 MHz, $CDCl_3$), δ = 156.18 (d, *J* = 6.1 Hz, **C**ONH), 150.16 (dd, *J* = 27.5, 9.8 Hz, 2xC_{ar}), 144.67 (s, C_{ar}), 136.20 (s, C_{ar}), 129.89 (d, *J* = 15.6 Hz, 4xC_{ar}), 128.94 (s, 3xC_{ar}), 128.67 (s, 2xC_{ar}), 128.72 (q, *J* = 32.4 Hz, **C**$_{ar}$-CF_3), 128.41 (s, 2xC_{ar}), 128.25 (s, 2xC_{ar}), 125.55 (dd, *J* = 11.5, 7.8 Hz, 2xC_{ar}), 124.37 (q, *J* = 271.8 Hz, **C**F_3-C_{ar}), 120.60 (d, *J* = 4.1 Hz,2xC_{ar}), 120.43 (d, *J* = 4.2 Hz, 2xC_{ar}), 67.50 (s, **C**H_2Ph), 48.02 (d, *J* = 158.5 Hz, **C**HP), 31.81 (d, *J* = 14.2 Hz, **C**H_2CH_2CHP), 31.58 (d, *J* = 4.5 Hz, CH$_2$**C**H_2CHP) ppm; ^{19}F NMR (376 MHz, $CDCl_3$), δ = -62.22 (s, F-H, *trans*), -62.24 (s, F-H, *cis*) ppm; ^{31}P NMR (162 MHz, $CDCl_3$), δ = 17.65 (s, 1P, *trans*), 17.34

(s, 1P, *cis*) ppm; HRMS (ESI-MS) *m/z* $[MH]^+$ calculated for $C_{30}H_{27}F_3NO_5P$: 570.1657, found: 570.1650; $[M+Na]^+$ calculated for $C_{30}H_{27}F_3NO_5PNa$: 592.1476, found: 592.1459.

Diphenyl 1-{[(N-benzyloxy)carbonyl]amino}-3-(2-trifluoromethylphenyl)propylphosphonate (**6h**)

White solid, yield 64%; ^1H NMR (400 MHz, $CDCl_3$), δ = 7.61 (d, *J* = 7.8 Hz, 1H, CH_{ar}), 7.44 (t, *J* = 7.4 Hz, 1H, CH_{ar}), 7.37 – 7.06 (m, 17H, CH_{ar}), 5.30 (d, *J* = 10.4 Hz, 1H, NH), 5.15 (s, 1H, CH_2OC, *trans*), 5.15 (d, *J* = 25.4 Hz, 1H, CH_2OC, *cis*), 4.57 (dtd, *J* = 17.4, 10.6, 3.4 Hz, 1H, CHP, *trans*), 4.47 – 4.33 (m, 1H, CHP, *cis*), 3.11 – 3.03 (m, 1H, CH_2), 2.94 – 2.83 (m, 1H, CH_2), 2.43 – 2.29 (br m, 1H, CH_2), 2.10 – 1.96 (br m, 1H, CH_2) ppm; ^{13}C NMR (101 MHz, $CDCl_3$), δ =156.11 (d, *J* = 6.2 Hz, **C**ONH), 150.13 (dd, *J* = 21.3, 9.7 Hz, 2xC_{ar}), 139.38 (s, 2xC_{ar}), 136.14 (s, 2xC_{ar}), 132.09 (s, 2xC_{ar}), 129.88 (d, *J* = 10.5 Hz, 4xC_{ar}), 128.81 – 128.10 (m, 5xC_{ar}), 127.34 (q, *J* = 273.8 Hz, **C**F_3-C_{ar}), 126.23 (q, *J* = 5.9 Hz, C_{ar}), 125.51 (d, *J* = 14.2 Hz, 2xC_{ar}), 120.59 (dd, *J* = 21.4, 4.0 Hz, 4xC_{ar}), 67.57 (s, **C**H_2Ph), 48.39 (d, *J* = 157.9 Hz, **C**HP), 32.22 (s, **C**H_2CH_2CHP), 29.12 (d, *J* = 12.9 Hz, CH_2**C**H_2CHP) ppm; ^{19}F NMR (376 MHz, $CDCl_3$), δ = -59.46 (s, 3F, CF_3, *trans*), -59.49 (s, 3F, CF_3, *cis*) ppm; ^{31}P NMR (162 MHz, $CDCl_3$), δ = 17.48 (s, 1P, *trans*), 17.10 (s, 1P, *cis*) ppm; HRMS (ESI-MS) *m/z* $[MH]^+$ calculated for $C_{30}H_{27}F_3NO_5P$: 570.1657, found: 570.1656; $[M+Na]^+$ calculated for $C_{30}H_{27}F_3NO_5PNa$: 592.1476, found: 592.1470.

Diphenyl 1-{[(N-benzyloxy)carbonyl]amino}-2-(2-bromo-4-fluorophenyl)ethylphosphonate (**13a**)

White solid, yield 18%; ^1H NMR (400 MHz, $CDCl_3$), δ = 7.35 – 7.04 (m, 17H, 17xCH_{ar}), 6.84 (td, *J* = 8.2, 2.6 Hz, 1H, CH_{ar}), 5.48 (d, *J* = 10.5 Hz, 1H, NH), 4.95 (d, *J* = 12.9 Hz, 2H, CH_2OC, *trans*), 4.95 (d, *J* = 37.5 Hz, 2H, CH_2OC, *cis*), 4.93 - 4.81 (m, 1H, CHP, *trans*), 3.48 (dt, *J* = 14.2, 4.3 Hz, 1H, CH_2), 3.11 (ddd, *J* = 14.2, 11.7, 9.4 Hz, 1H, CH_2) ppm; ^{13}C NMR (101 MHz, $CDCl_3$), δ = 161.51 (d, *J* = 250.3 Hz, C_{ar}-F), 155.68 (d, *J* = 7.3 Hz, **C**ONH), 150.34 (d, *J* = 9.8 Hz, C_{ar}), 150.06 (d, *J* = 9.7 Hz, C_{ar}), 136.17 (s, C_{ar}), 132.41 (d, *J* = 8.4 Hz, C_{ar}), 131.50 (dd, *J* = 16.2, 3.6 Hz, 2xC_{ar}), 129.99 (d, *J* = 1.0 Hz, 2xC_{ar}), 129.84 (d, *J* = 0.8 Hz, 2xC_{ar}), 128.55 (s, C_{ar}), 128.28 (s, C_{ar}), 128.10 (s, C_{ar}), 125.57 (d, *J* = 15.8 Hz, 2xC_{ar}), 124.91 (d, *J* = 9.6 Hz, 2xC_{ar}), 120.56 (dd, *J* = 16.1, 4.2 Hz, 2xC_{ar}), 120.22 (d, *J* = 24.4 Hz, 2xC_{ar}), 114.69 (d, *J* = 20.8 Hz, 2xC_{ar}), 67.19 (s, **C**H_2Ph), 48.49 (dd, *J* = 159.4, 1.0 Hz, **C**HP), 35.51 (d, *J* = 6.6 Hz, **C**H_2CHP) ppm; ^{19}F NMR (376 MHz, $CDCl_3$), δ = -112.52 (dd, *J* = 14.1, 7.4 Hz, F-H, *cis*), -112.82 (dd, *J* = 14.1, 7.9 Hz, F-H, *cis*) ppm; ^{31}P NMR (162 MHz, $CDCl_3$), δ = 16.76 (s, 1P, *trans*), 16.30 (s, 1P, *cis*) ppm; HRMS (ESI-MS) *m/z* $[MH]^+$ calculated for $C_{28}H_{24}BrFNO_5P$: 584.0638, found: 584.0640; $[M+Na]^+$ calculated for $C_{28}H_{24}BrFNO_5PNa$: 606.0457, found: 606.0466.

Diphenyl 1-{[(N-benzyloxy)carbonyl]amino}-2-(2-bromo-5-fluorophenyl)ethylphosphonate (**13b**)

White solid, yield 17%; ^1H NMR (400 MHz, $CDCl_3$), δ = 7.46 (dd, *J* = 8.8, 5.3 Hz, 1H, CH_{ar}), 7.35 – 7.07 (m, 15H, 15xCH_{ar}), 7.00 (dd, *J* = 9.0, 3.0 Hz, 1H, CH_{ar}), 6.86 – 6.79 (m, 1H, CH_{ar}), 5.37 (d, *J* = 10.6 Hz, 1H, NH), 5.08 – 4.83 (m, 1H, CHP, *trans*), 4.96 (d, *J* = 3.0 Hz, 2H, CH_2OC, *trans*), 4.96 (d, *J* = 17 Hz, 2H, CH_2OC, *cis*), 4.95 (d, *J* = 37.5 Hz, 2H, CH_2OC, *cis*), 4.93 - 4.81 (m, 1H, CHP, *trans*), 3.51 (dt, *J* = 14.4 4.3 Hz, 1H, CH_2), 3.11 (ddd, *J* = 14.2, 11.7, 9.2 Hz, 1H, CH_2) ppm; ^{13}C NMR (101 MHz, $CDCl_3$), δ = 161.76 (d, *J* = 247.4 Hz, C_{ar}-F), 155.72 (d, *J* = 7.1 Hz, **C**ONH), 150.31 (d, *J* = 9.4 Hz, C_{ar}), 150.03 (d, *J* = 9.7 Hz, C_{ar}), 137.75 (dd, *J* = 15.9, 7.7 Hz, 2xC_{ar}), 136.17 (s, C_{ar}), 134.11 (d, *J* = 8.0 Hz, C_{ar}), 129.92 (d, *J* = 16.8 Hz, 2xC_{ar}), 128.60 (d, *J* = 8.5 Hz, 2xC_{ar}), 128.29 (d, *J* = 8.8 Hz, 2xC_{ar}), 128.02 (s, C_{ar}), 125.58 (d, *J* = 16.6 Hz, 2xC_{ar}), 120.54 (dd, *J* = 16.3, 4.2 Hz, 2xC_{ar}), 119.12 (d, *J* = 3.2 Hz, 2xC_{ar}), 118.73 (d, *J* = 22.7 Hz, 2xC_{ar}), 116.09 (d, *J* = 22.6 H, 2xC_{ar}), 67.23 (s, **C**H_2Ph), 48.31 (d, *J* = 160.2 Hz, **C**HP), 36.40 (d, *J* = 6.7 Hz, **C**H_2CHP) ppm; ^{19}F NMR (376 MHz, $CDCl_3$), δ = -113.99 – -114.15 (m, F-H, *cis*), -114.37 (dd, *J* = 13.8, 8.3 Hz, F-H, *trans*) ppm; ^{31}P NMR (162 MHz, $CDCl_3$), δ = 16.51 (s, 1P, *trans*), 16.06 (s, 1P, *cis*) ppm; HRMS (ESI-MS) *m/z* $[MH]^+$ calculated for $C_{28}H_{24}BrFNO_5P$: 584.0638, found: 584.0635; $[M+Na]^+$ calculated for $C_{28}H_{24}BrFNO_5PNa$: 606.0457, found: 606.0455.

Diphenyl 1-{[(N-benzyloxy)carbonyl]amino}-2-(3-bromo-4-fluorophenyl)ethylphosphonate (**13c**)

White solid, yield 15%; ^{1}H NMR (400 MHz, $CDCl_3$), δ = 7.42 (dd, *J* = 6.5, 2.0 Hz, 1H, CH_{ar}), 7.34 – 7.01 (m, 16H, 16xCH_{ar}), 6.96 (t, *J* = 8.4 Hz, 1H, CH_{ar}), 5.47 (d, *J* = 10.5 Hz, 1H, NH), 5.02 (d, *J* = 13.3 Hz, 2H, CH_2OC, *trans*), 5.02 (d, *J* = 37.8 Hz, 2H, CH_2OC, *cis*), 4.79 – 4.65 (m, 1H, CHP, *trans*), 3.35 – 3.25 (m, 1H, CH_2), 2.96 (dt, *J* = 14.3, 10.1 Hz, 1H, CH_2) ppm; ^{13}C NMR (101 MHz, $CDCl_3$), δ = 158.29 (d, *J* = 246.8 Hz, C_{ar}-F), 155.81 (d, *J* = 7.3 Hz, **C**ONH), 150.19 (d, *J* = 9.8 Hz, C_{ar}), 149.94 (d, *J* = 9.7 Hz, C_{ar}), 136.11 (s, C_{ar}), 134.47 (s, C_{ar}), 133.48 (dd, *J* = 14.4, 3.8 Hz, 2xC_{ar}), 130.02 (d, *J* = 0.9 Hz, 2xC_{ar}), 129.85 (s, C_{ar}), 128.63 (s, 2xC_{ar}), 128.35 (s, C_{ar}), 128.09 (d, *J* = 16.6 Hz, 2xC_{ar}), 125.72 (d, *J* = 1.0 Hz, 2xC_{ar}), 125.54 (s, C_{ar}), 120.55 (dd, *J* = 20.6, 4.2 Hz, 2xC_{ar}), 116.53 (d, *J* = 22.3 Hz, 2xC_{ar}), 108.95 (d, *J* = 20.9 Hz, 2xC_{ar}), 67.37 (s, **C**H_2Ph), 49.32 (d, *J* = 158.5 Hz, **C**HP), 35.02 (d, *J* = 5.7 Hz, **C**H_2CHP) ppm; ^{19}F NMR (376 MHz, $CDCl_3$), δ = -109.37 (s, F-H, *cis*), -109.62 – -109.70 (m, F-H, *trans*) ppm; ^{31}P NMR (162 MHz, $CDCl_3$), δ = 16.84 (s, 1P, *trans*), 16.41 (s, 1P, *cis*) ppm; HRMS (ESI-MS) *m*/*z* $[MH]^+$ calculated for $C_{28}H_{24}BrFNO_5P$: 584.0638, found: 584.0638; $[M+Na]^+$ calculated for $C_{28}H_{24}BrFNO_5PNa$: 606.0457, found: 606.0457.

Diphenyl 1-{[(N-benzyloxy)carbonyl}amino}-2-(4-bromo-2-fluorophenyl)ethylphosphonate (**13d**)

White solid, yield 21%; ^{1}H NMR (400 MHz, $CDCl_3$), δ = 7.38 – 7.03 (m, 18H, CH_{ar}), 5.37 (d, *J* = 10.4 Hz, 1H, NH), 4.98 (d, *J* = 14.9 Hz, 2H, CH_2OC, *trans*), 4.98 (d, *J* = 39.5 Hz, 2H, CH_2OC, *cis*), 4.82 – 4.69 (m, 1H, CHP, *trans*), 3.38 – 3.29 (m, 1H, CH_2), 3.04 (dt, *J* = 14.0, 10.5 Hz, 1H, CH_2) ppm; ^{13}C NMR (101 MHz, $CDCl_3$), δ = 161.24 (d, *J* = 250.2 Hz, C_{ar}-F), 155.72 (d, *J* = 7.1 Hz, **C**ONH), 150.23 (d, *J* = 9.6 Hz, C_{ar}), 149.97 (d, *J* = 9.7 Hz, C_{ar}), 136.11 (s, C_{ar}), 132.63 (d, *J* = 4.9 Hz, 2xC_{ar}), 130.00 (d, *J* = 1.0 Hz, 2xC_{ar}), 129.85 (d, *J* = 0.8 Hz, C_{ar}), 128.61 (s, 2xC_{ar}), 128.33 (s, C_{ar}), 128.08 (s, 2xC_{ar}), 127.61 (d, *J* = 3.7 Hz, 2xC_{ar}), 125.69 (d, *J* = 1.2 Hz, C_{ar}), 125.52 (d, *J* = 0.9 Hz, 2xC_{ar}), 120.57 (dd, *J* = 21.1, 4.2 Hz, 2xC_{ar}), 119.15 (d, *J* = 25.4 Hz, 2xC_{ar}), 67.31 (s, **C**H_2Ph), 48.50 (d, *J* = 159.5 Hz, **C**HP), 29.37 (d, *J* = 5.8 Hz, **C**H_2CHP) ppm; ^{19}F NMR (376 MHz, $CDCl_3$), δ = -114.32 (t, *J* = 8.4 Hz, F-H, *trans*), -114.43 (t, *J* = 7.8 Hz, F-H, *cis*) ppm; ^{31}P NMR (162 MHz, $CDCl_3$), δ = 16.61 (s, 1P, *trans*), 16.16 (s, 1P, *cis*) ppm; HRMS (ESI-MS) *m*/*z* $[MH]^+$ calculated for $C_{28}H_{24}BrFNO_5P$: 584.0638, found: 584.0758; $[M+Na]^+$ calculated for $C_{28}H_{24}BrFNO_5PNa$: 606.0457, found: 606.0462.

Diphenyl 1-{[(N-benzyloxy]carbonylamino}-2-(4-bromo-3-fluorophenyl)ethylphosphonate (**13e**)

White solid, yield 20%; ^{1}H NMR (400 MHz, $CDCl_3$), δ = 7.38 (t, *J* = 7.7 Hz, 1H, CH_{ar}), 7.34 – 7.27 (m, 5H, 5xCH_{ar}), 7.24 – 7.10 (m, 7H, CH_{ar}), 7.04 (d, *J* = 8.4 Hz, 2H, 2x CH_{ar}), 7.00 (dd, *J* = 9.3, 1.8 Hz, 1H, CH_{ar}), 6.88 (dd, *J* = 8.2, 1.6 Hz, 1H, CH_{ar}), 5.41 (d, *J* = 10.3 Hz, 1H, NH), 5.02 (d, *J* = 14.1 Hz, 2H, CH_2OC, *trans*), 5.02 (d, *J* = 38.6 Hz, 2H, CH_2OC, *cis*), 4.74 (dtd, *J* = 17.9, 10.4, 4.4 Hz, 1H, CHP, *trans*), 3.36 – 3.26 (m, 1H, CH_2), 3.04 (dt, *J* = 14.4, 10.0 Hz, 1H, CH_2) ppm; ^{13}C NMR (101 MHz, $CDCl_3$), δ = 158.97 (d, *J* = 248.0 Hz, C_{ar}-F), 155.72 (d, *J* = 6.9 Hz, **C**ONH), 150.03 (dd, *J* = 24.2, 9.7 Hz, 2xC_{ar}), 137.79 (dd, J = 14.3, 7.0 Hz, 2xC_{ar}), 136.03 (s, C_{ar}), 133.57 (d, *J* = 0.7 Hz, 2xC_{ar}), 130.03 (d, *J* = 1.0 Hz, 2xC_{ar}), 129.87 (d, *J* = 0.4 Hz, C_{ar}), 128.65 (s, C_{ar}), 128.40 (s, C_{ar}), 128.11 (s, C_{ar}), 125.69 (d, *J* = 1.2 Hz, C_{ar}), 125.52 (d, *J* = 0.9 Hz, 2xC_{ar}), 120.57 (dd, *J* = 21.1, 4.2 Hz, 2xC_{ar}), 119.15 (d, *J* = 25.4 Hz, 2xC_{ar}), 67.31 (s, **C**H_2Ph), 48.50 (d, *J* = 159.5 Hz, **C**HP), 29.37 (d, *J* = 5.8 Hz, **C**H_2CHP) ppm; ^{19}F NMR (376 MHz, $CDCl_3$), δ = -106.68 (t, *J* = 7.7 Hz, F-H, *cis*), -106.92 (t, *J* = 8.2 Hz, F-H, *cis*) ppm; ^{31}P NMR (162 MHz, $CDCl_3$), δ = 16.75 (s, 1P, *trans*), 16.31 (s, 1P, *cis*) ppm; HRMS (ESI-MS) *m*/*z* $[MH]^+$ calculated for $C_{28}H_{24}BrFNO_5P$: 584.0638, found: 584.0629; $[M+Na]^+$ calculated for $C_{28}H_{24}BrFNO_5PNa$: 606.0457, found: 606.0464.

Section S6. *The characterization data of the compounds* ***14c, 14f, 14h, 16d and 16e.***

Dimethyl 1-{[(N-benzyloxy)carbonyl]amino}-3-(3-fluorophenyl)propylphosphonate (**14c**)

White solid, yield 63%; ^{1}H NMR (400 MHz, $CDCl_3$), δ = 7.37 – 7.27 (m, 5H, 5xCH_{ar}), 7.20 (dd, *J* = 15.1, 7.6 Hz, 1H, CH_{ar}), 6.94 – 6.83 (m, 3H, 3xCH_{ar}), 5.22 (d, *J* = 9.6 Hz, 1H, NH), 5.13 (d, *J* = 3.6 Hz, 2H, CH_2OC, *trans*), 5.13 (d, *J* = 28.0 Hz, 2H, CH_2OC, *cis*), 4.18 – 4.07 (m, 1H, CHP, *trans*), 3.71 (t, *J* = 11.0

Hz, 6H, 2xCH$_3$), 2.82 – 2.73 (m, 1H, CH$_2$), 2.69 – 2.60 (m, 1H, CH$_2$), 2.19 – 2.07 (m, 1H, CH$_2$), 1.95 – 1.81 (m, 1H, CH$_2$) ppm; ^{13}C NMR (101 MHz, CDCl$_3$), δ = 162.99 (d, *J* = 245.6 Hz, C$_{ar}$-F), 156.13 (d, *J* = 5.3 Hz, CONH), 143.31 (d, *J* = 7.4 Hz, C$_{ar}$), 136.26 (s, C$_{ar}$), 129.99 (d, *J* = 8.3 Hz, C$_{ar}$), 128.64 (s, 2xC$_{ar}$), 128.40 (s, 2xC$_{ar}$), 128.37 (s, C$_{ar}$), 124.21 (d, *J* = 2.8 Hz, C$_{ar}$), 115.39 (d, *J* = 21.0 Hz, C$_{ar}$), 113.18 (d, *J* = 21.0 Hz, C$_{ar}$), 67.39 (s, **C**H$_2$Ph), 53.40 (d, *J* = 7.1 Hz, OCH$_3$), 53.23 (d, *J* = 6.5 Hz, OCH$_3$), 46.93 (d, *J* = 156.3 Hz, **C**HP), 31.89 (d, *J* = 12.0 Hz, CH$_2$**C**H$_2$CHP), 25.68 (d, *J* = 3.3 Hz, **C**H$_2$CH$_2$CHP) ppm; ^{19}F NMR (376 MHz, CDCl$_3$), δ = -113.24 (dd, *J* = 14.0, 8.4 Hz, F-H, *cis*), -113.35 (td, *J* = 9.3, 6.1 Hz, F-H, *trans*) ppm; ^{31}P NMR (162 MHz, CDCl$_3$), δ = 27.45 (s, 1P, *trans*), 26.97 (s, 1P, *cis*) ppm; HRMS (ESI-MS) *m/z* [MH]$^+$ calculated for C$_{19}$H$_{23}$FNO$_5$P: 396.1376, found: 396.1380; [M+Na]$^+$ calculated for C$_{19}$H$_{23}$FNO$_5$PNa: 418.1196, found: 418.1165.

Dimethyl 1-{[(N-benzyloxy)carbonyl]amino}-3-(3,4-difluorophenyl)propylphosphonate (**14f**)

Colourless oil, yield 65%; ^{1}H NMR (400 MHz, CDCl$_3$), δ = 7.38 – 7.28 (m, 5H, 5xCH$_{ar}$), 7.02 (dt, *J* = 10.3, 8.4 Hz, 1H, CH$_{ar}$), 6.95 (ddd, *J* = 11.1, 7.6, 2.0 Hz, 1H, CH$_{ar}$), 6.87 – 6.82 (m, 1H, CH$_{ar}$), 5.18 (d, *J* = 10.4 Hz, 1H, NH), 5.12 (d, *J* = 2.8 Hz, 2H, CH$_2$OC, *trans*), 5.12 (d, *J* = 27.3 Hz, 2H, CH$_2$OC, *cis*), 4.16 – 4.03 (m, CHP, *trans*), 3.71 (t, *J* = 10.8 Hz, 6H, 2xCH$_3$), 2.74 (ddd, *J* = 14.5, 9.6, 5.2 Hz, 1H, CH$_2$), 2.67 – 2.53 (m, 1H, CH$_2$), 2.15 – 2.04 (m, 1H, CH$_2$), 1.92 – 1.77 (m, 1H, CH$_2$) ppm; ^{13}C NMR (101 MHz, CDCl$_3$), δ = 156.13 (d, *J* = 5.3 Hz, CONH), 149.63 (ddd, *J* = 245.9, 124.2, 12.3 Hz, 2xC$_{ar}$-F), 137.70 – 137.55 (m, C$_{ar}$), 136.21 (s, C$_{ar}$), 128.65 (s, 2xC$_{ar}$), 128.40 (s, 2xC$_{ar}$), 128.21 (s, 2xC$_{ar}$), 124.41 (dd, *J* = 6.0, 3.5 Hz, C$_{ar}$), 117.25 (dd, *J* = 16.9, 9.5 Hz, C$_{ar}$), 67.42 (s, **C**H$_2$Ph), 53.40 (d, *J* = 7.1 Hz, OCH$_3$), 53.20 (d, *J* = 6.6 Hz, OCH$_3$), 46.67 (dd, *J* = 156.3, 10.5 Hz, **C**HP, *trans*/*cis*), 31.56 (d, *J* = 2.3 Hz, **C**H$_2$CH$_2$CHP), 31.28 (d, *J* = 13.2 Hz, CH$_2$**C**H$_2$CHP) ppm; ^{19}F NMR (376 MHz, CDCl$_3$), δ = -137.85 – -138.02 (m, F-H), -141.46 – -141.66 (m, F-H) ppm; ^{31}P NMR (162 MHz, CDCl$_3$), δ = 27.30 (s, 1P, *trans*), 26.82 (s, 1P, *cis*) ppm; HRMS (ESI-MS) *m/z* [MH]$^+$ calculated for C$_{19}$H$_{22}$F$_2$NO$_5$P: 414.1282, found: 414.1290; [M+Na]$^+$ calculated for C$_{19}$H$_{22}$F$_2$NO$_5$PNa: 436.1101, found: 436.1084.

Dimethyl 1-{[(N-benzyloxy)carbonyl]amino}-3-(2-trifluoromethylphenyl)propylphosphonate (**14h**)

Colourless oil, yield 80%; ^{1}H NMR (400 MHz, CDCl$_3$), δ = 7.59 (d, *J* = 7.8 Hz, 1H, CH$_{ar}$), 7.44 (t, *J* = 7.4 Hz, 1H, CH$_{ar}$), 7.37 – 7.25 (m, 5H, 5xCH$_{ar}$), 5.12 (s, 2H, CH$_2$OC, *trans*), 5.14 (d, *J* = 25.3 Hz, 2H, CH$_2$OC, *cis*), 4.26 – 4.14 (m, CHP), 3.72 (dd, *J* = 13.0, 10.7 Hz, 6H, 2xCH$_3$), 3.03 – 2.94 (m, 1H, CH$_2$), 2.85 – 2.75 (m, 1H, CH$_2$), 2.21 – 2.09 (m, 1H, CH$_2$), 1.93 – 1.76 (m, 1H, CH$_2$) ppm; ^{13}C NMR (101 MHz, CDCl$_3$), δ = 156.20 (d, *J* = 5.3 Hz, CONH), 139.60 (s, C$_{ar}$), 136.27 (s, C$_{ar}$), 132.02 (d, *J* = 1.0 Hz, C$_{ar}$), 131.39 (s, C$_{ar}$), 128.64 (s, 2xC$_{ar}$), 128.33 (s, 2xC$_{ar}$), 128.10 (dd, *J* = 6.0, 3.5 Hz, 2xC$_{ar}$), 126.44 (s, C$_{ar}$), 126.16 (q, *J* = 5.7 Hz, C$_{ar}$), 124.64 (q, *J* = 273.8 Hz, **C**F$_3$-C$_{ar}$), 67.41 (s, **C**H$_2$Ph), 53.32 (dd, *J* = 8.4, 7.1 Hz, 2xOCH$_3$), 47.24 (d, *J* = 156.3 Hz, **C**HP), 32.05 (d, *J* = 3.3 Hz, **C**H$_2$CH$_2$CHP), 29.19 (d, *J* = 13.0 Hz, CH$_2$**C**H$_2$CHP) ppm; ^{19}F NMR (376 MHz, CDCl$_3$), δ = -59.53 (s, 3F, CF$_3$) ppm; ^{31}P NMR (162 MHz, CDCl$_3$), δ = 27.19 (s, 1P, *trans*), 26.66 (s, 1P, *cis*) ppm; HRMS (ESI-MS) *m/z* [MH]$^+$ calculated for C$_{20}$H$_{23}$F$_3$NO$_5$P: 446.1344, found: 446.1340; [M+Na]$^+$ calculated for C$_{20}$H$_{23}$F$_3$NO$_5$PNa: 468.1164, found: 468.1168.

Dimethyl 1-{[(N-benzyloxy)carbonyl]amino}-2-(4-bromo-2-fluorophenyl)ethylphosphonate (**16d**)

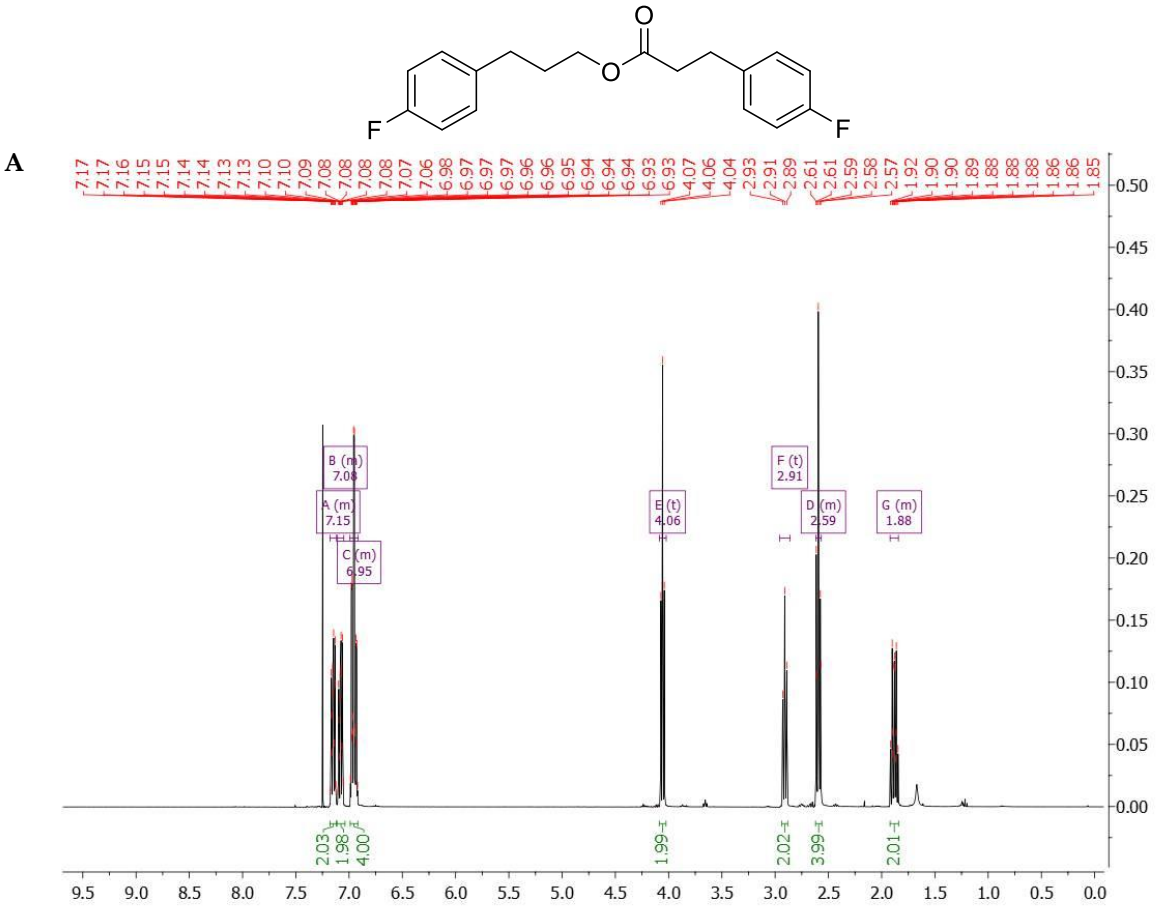
Colourless oil, yield 57%; ^{1}H NMR (400 MHz, CDCl$_3$), δ = 7.36 – 7.27 (m, 5H, 5xCH$_{ar}$), 7.23 – 7.13 (m, 2H, 2xCH$_{ar}$), 7.07 (t, *J* = 8.0 Hz, 1H, CH$_{ar}$), 5.08 (d, *J* = 10.1 Hz, 1H, NH), 4.98 (d, *J* = 37.2 Hz, 2H, CH$_2$OC, *trans*), 4.98 (d, *J* = 12.5 Hz, 2H, CH$_2$OC, *cis*), 4.45 – 4.30 (m, CHP), 3.75 (dd, *J* = 15.1, 10.6 Hz, 6H, 2xCH$_3$), 3.14 (dt, *J* = 13.2, 4.3 Hz, 1H, CH$_2$), 2.87 (dt, *J* = 13.9, 10.6 Hz, 1H, CH$_2$) ppm; ^{13}C NMR (101 MHz, CDCl$_3$), δ = 161.20 (d, *J* = 250.0 Hz, C$_{ar}$-F), 155.79 (d, *J* = 5.9 Hz, CONH), 136.19 (s, C$_{ar}$), 132.48 (d, *J* = 4.9 Hz, C$_{ar}$), 128.58 (s, 2xC$_{ar}$), 128.30 (s, 2xC$_{ar}$), 127.99 (s, 2xC$_{ar}$), 127.55 (d, *J* = 3.5 Hz, C$_{ar}$), 122.89 (t, *J* = 15.1 Hz, C$_{ar}$), 119.08 (d, *J* = 25.5 Hz, C$_{ar}$), 67.20 (s, **C**H$_2$Ph), 53.60 (d, *J* = 6.8 Hz, OCH$_3$), 53.36 (d, *J* = 6.5 Hz, OCH$_3$), 47.39 (d, *J* = 157.4 Hz, **C**HP), 29.17 (d, *J* = 3.6 Hz, **C**H$_2$CHP) ppm; ^{19}F NMR (376 MHz, CDCl$_3$), δ = -114.63 (t, *J* = 8.4 Hz, 1F) ppm; ^{31}P NMR (162 MHz, CDCl$_3$), δ = 26.26 (s, 1P, *trans*), 25.70 (s,

1P, *cis*) ppm; HRMS (ESI-MS) *m*/*z* [MH]$^+$ calculated for $C_{18}H_{20}BrFNO_5P$: 460.0325, found: 460.0314; [M+Na]$^+$ calculated for $C_{18}H_{20}BrFNO_5P$ Na: 482.0144, found: 482.0197.

Dimethyl 1-{[(N-benzyloxy)carbonyl]amino}-2-(4-bromo-3-fluorophenyl)ethylphosphonate (**16e**)

Colourless oil, yield 63.5%; ^{1}H NMR (400 MHz, $CDCl_3$), δ = 7.39 (t, *J* = 7.7 Hz, 1H, CH_{ar}), 7.36 – 7.26 (m, 5H, 5xCH_{ar}), 7.24 – 7.18 (m, 1H, CH_{ar}), 6.93 (ddd, *J* = 9.3, 8.7, 1.4 Hz, 1H, CH_{ar}), 5.26 (d, *J* = 10.1 Hz, 1H, NH), 5.01 (d, *J* = 35.7 Hz, 2H, CH_2OC, *trans*), 5.01 (d, *J* = 11.2 Hz, 2H, CH_2OC, *cis*), 4.42 – 4.30 (m, CHP), 3.72 (dd, *J* = 19.0, 10.6 Hz, 6H, 2xCH_3), 3.18 – 3.09 (m, 1H, CH_2), 2.82 (dt, *J* = 14.4, 9.9 Hz, 1H, CH_2) ppm; ^{13}C NMR (101 MHz, $CDCl_3$), δ = 158.94 (d, *J* = 247.6 Hz, C_{ar}-F), 155.83 (d, *J* = 5.9 Hz, CONH), 138.37 (dd, *J* = 14.2, 6.8 Hz, C_{ar}), 136.15 (s, C_{ar}), 128.61 (s, 2xC_{ar}), 128.34 (s, 2xC_{ar}), 128.00 (s, 2xC_{ar}), 126.17 (d, *J* = 3.4 Hz, C_{ar}), 117.50 (d, *J* = 22.2 Hz, C_{ar}), 107.41 (d, *J* = 20.9 Hz, C_{ar}), 67.27 (s, **C**H_2Ph), 53.54 (d, *J* = 7.3 Hz, OCH_3), 53.26 (d, *J* = 6.6 Hz, OCH_3), 48.00 (d, *J* = 157.2 Hz, **C**HP), 35.32 (d, *J* = 3.3 Hz, **C**H_2CHP) ppm; ^{19}F NMR (376 MHz, $CDCl_3$), δ = -107.17 (dd, *J* = 9.2, 7.4 Hz, 1F) ppm; ^{31}P NMR (162 MHz, $CDCl_3$), δ = 26.38 (s, 1P, *trans*), 25.79 (s, 1P, *cis*) ppm; HRMS (ESI-MS) *m*/*z* [MH]$^+$ calculated for $C_{18}H_{20}BrFNO_5P$: 460.0325, found: 460.0327.

Figure S1. ^{1}H (**A**), ^{13}C (**B**) and ^{19}F (**C**) NMR spectra for 3-(4-fluorophenyl)propyl-3-(4-fluorophenyl) propionate (**5d**).



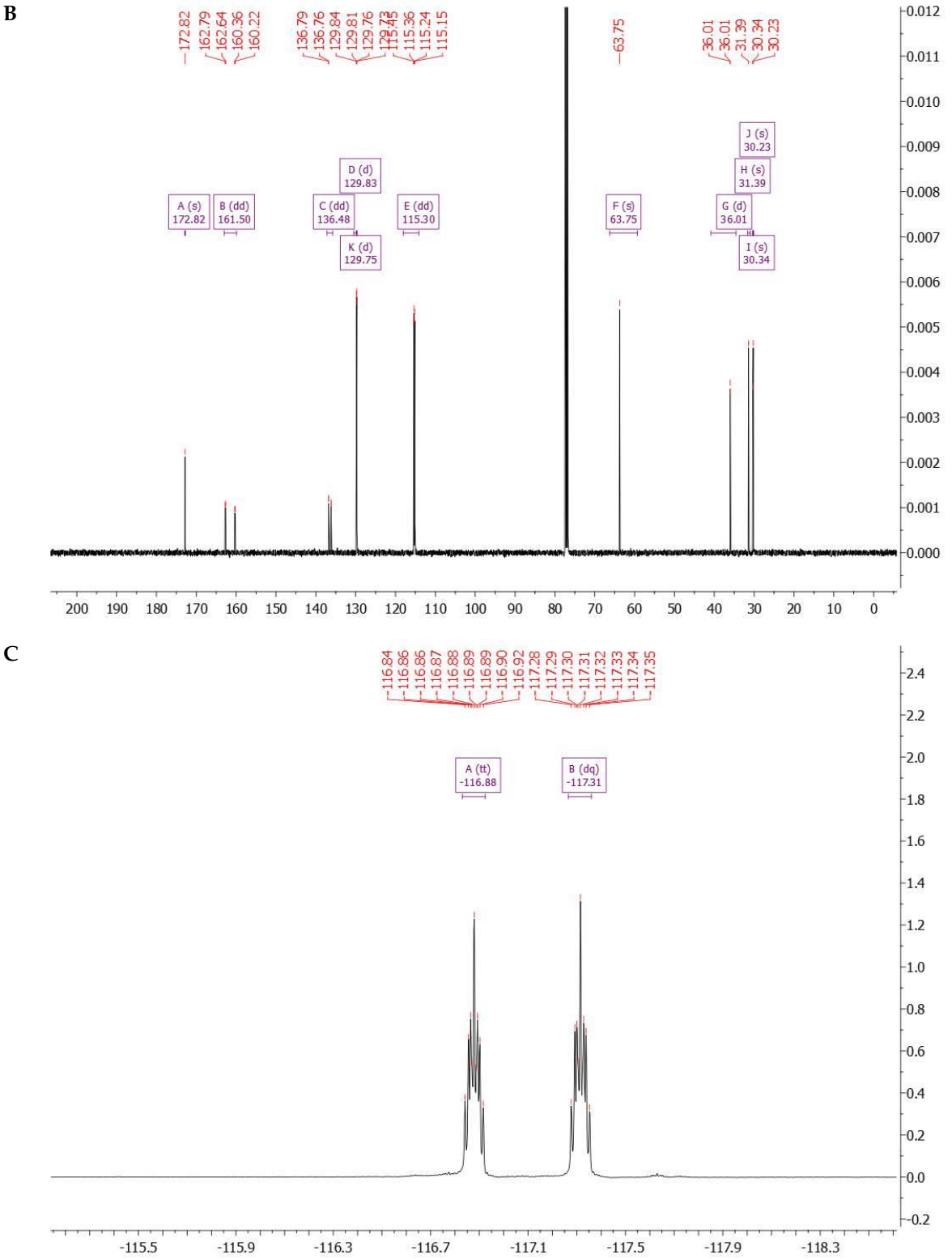
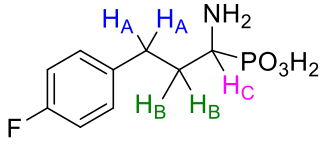
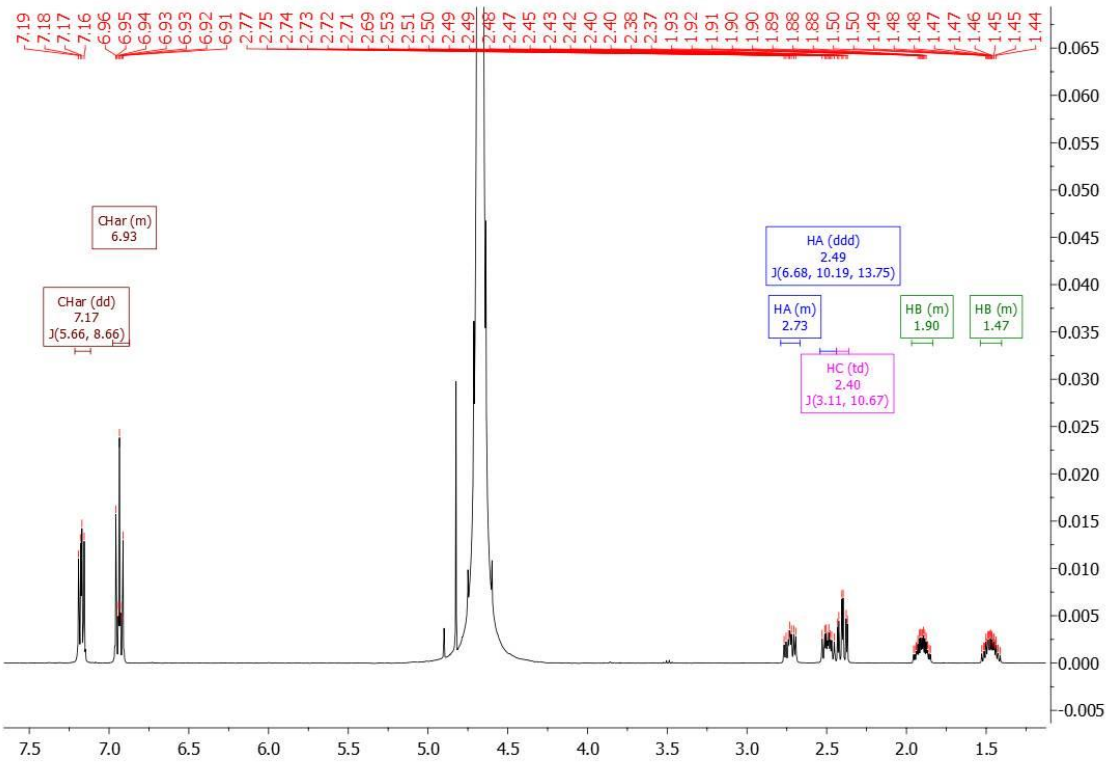


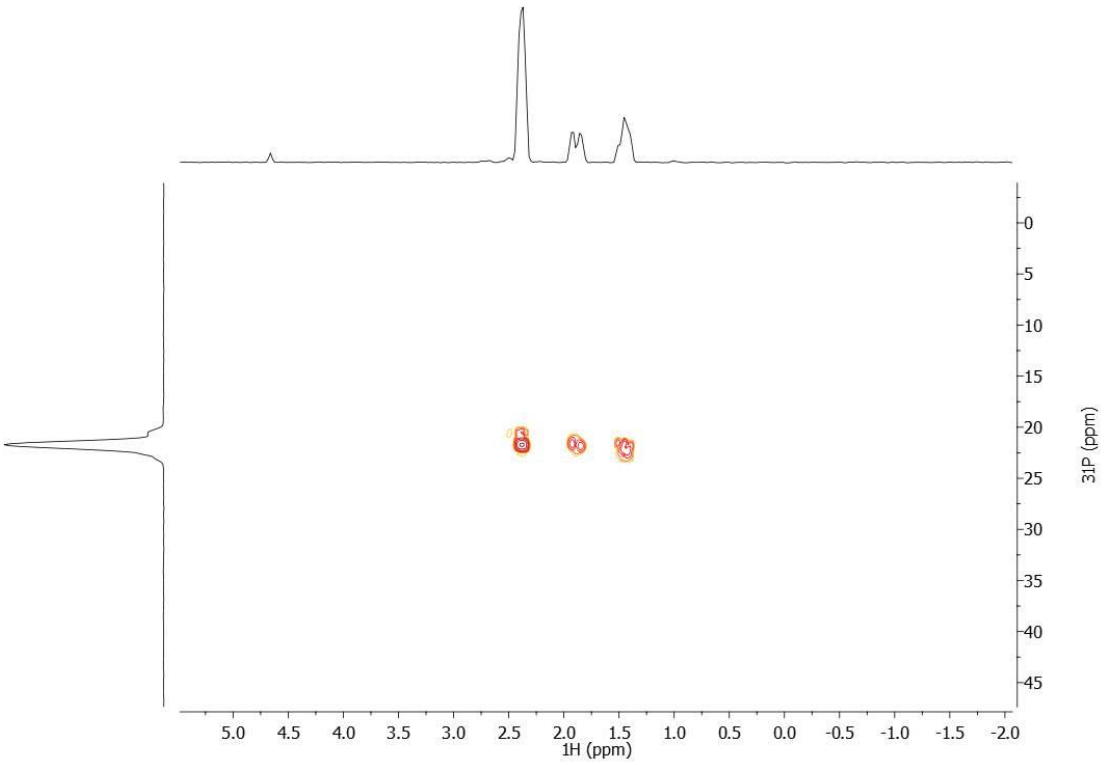
Figure S2. ^{1}H (**A**), ^{1}H-^{31}P HMQC (**B**) and ^{1}H-^{13}C HMQC (**C**) NMR spectra for 1-amino-3-(4-fluorophenyl)propylphosphonic acid (**15d**).

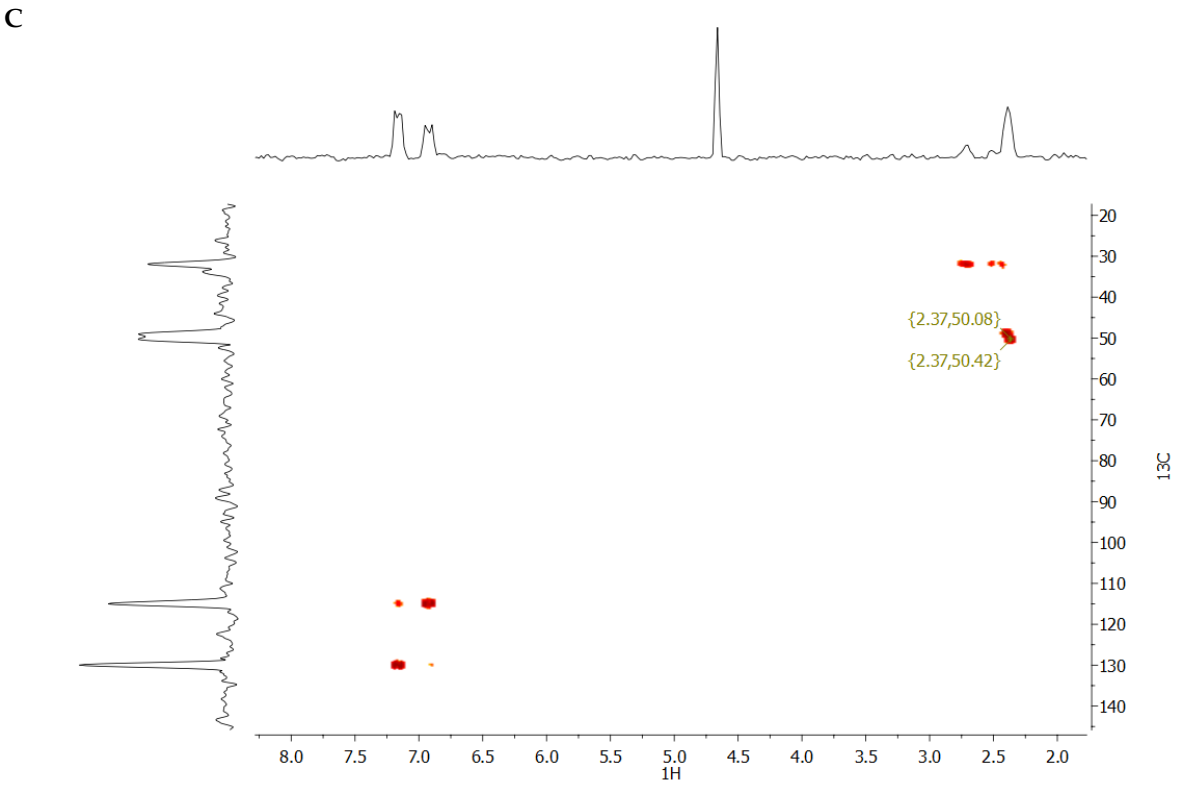


A


CHar (m)
6.93
CHar (dd)
7.17
J(5.66, 8.66)
HA (ddd)
2.49
J(6.68, 10.19, 13.75)
HA (m)
2.73
HB (m)
1.90
HB (m)
1.47
HC (td)
2.40
J(3.11, 10.67)

B


1H (ppm)
31P (ppm)



Section S7. *Molecular docking simulations of the inhibitors* ***15c, 15f, 17b*** *and* ***17c*** *binding to active site of pAPN (PDB: 4FKE).*

Figure S7-1. Binding mode of the 1-amino-3-(3-fluorophenyl)propylphosphonic acid (compound **15c**) with the pAPN. The isomer *(S)* is on the left side (**A**), when the *(R)*-isomer is on the right side (**B**). The colouring scheme is identical as in Figure 1.

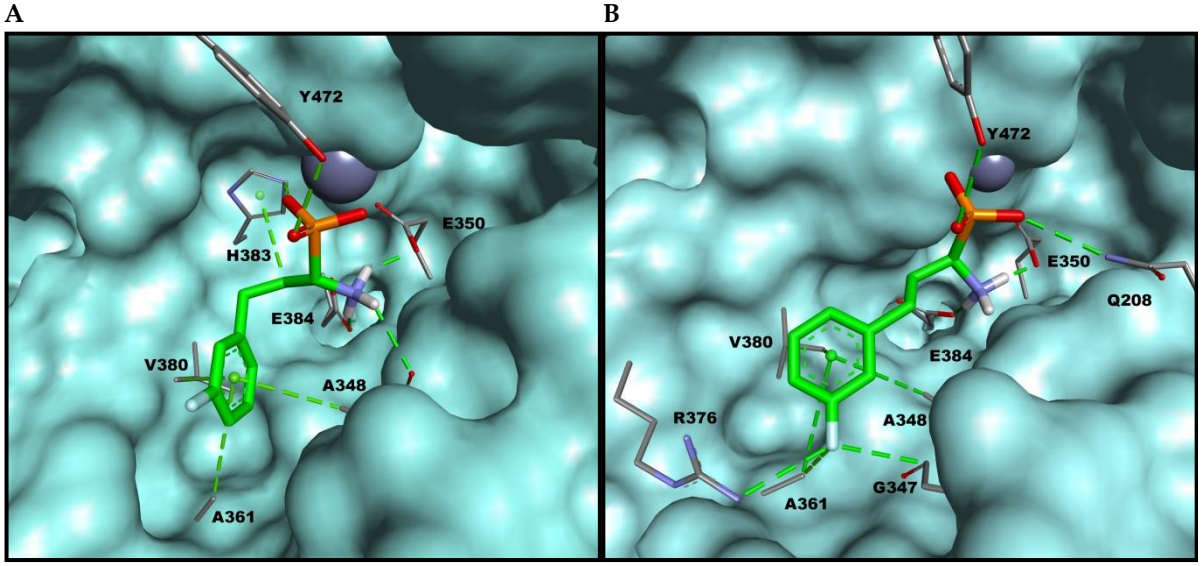


Figure S7-2. Binding mode of the 1-amino-3-(3,4-difluorophenyl)propylphosphonic acid (compound **15f**) with the pAPN. The isomer *(S)* is on the left side (**A**), when the *(R)*-isomer is on the right side (**B**). The colouring scheme is identical as in Figure 1.

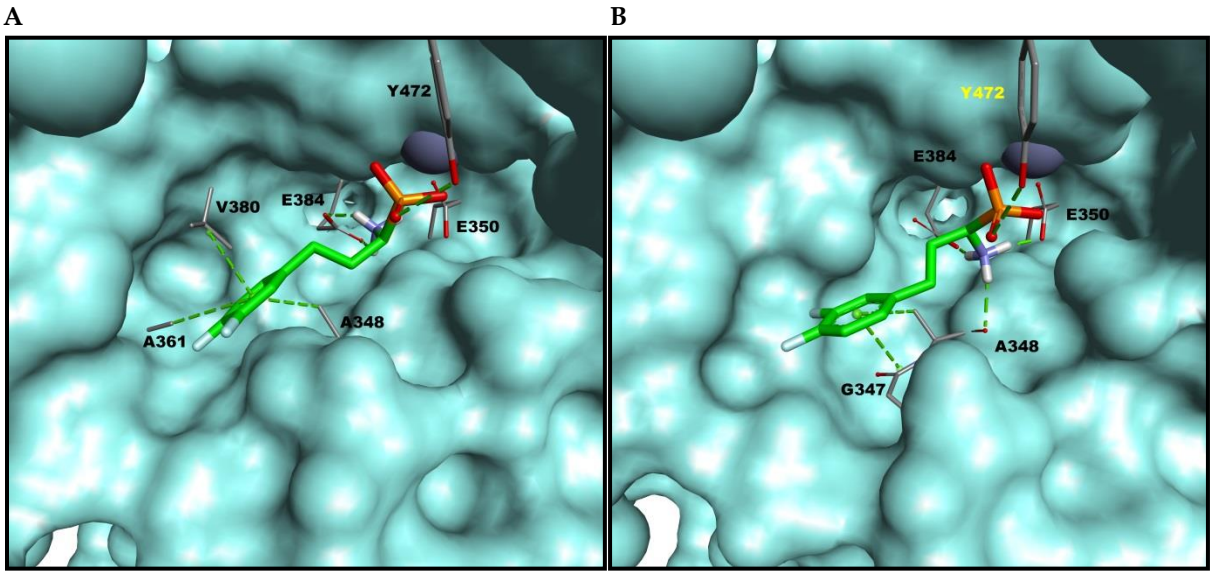


Figure S7-3. Binding mode of the 1-amino-2-(2-bromo-5-fluorophenyl)ethylphosphonic acid (compound **17b**) with the pAPN. The isomer *(S)* is on the left side (**A**), when the *(R)*-isomer is on the right side (**B**). The colouring scheme is identical as in Figure 1. The bromine atom is shown as dark red sphere.

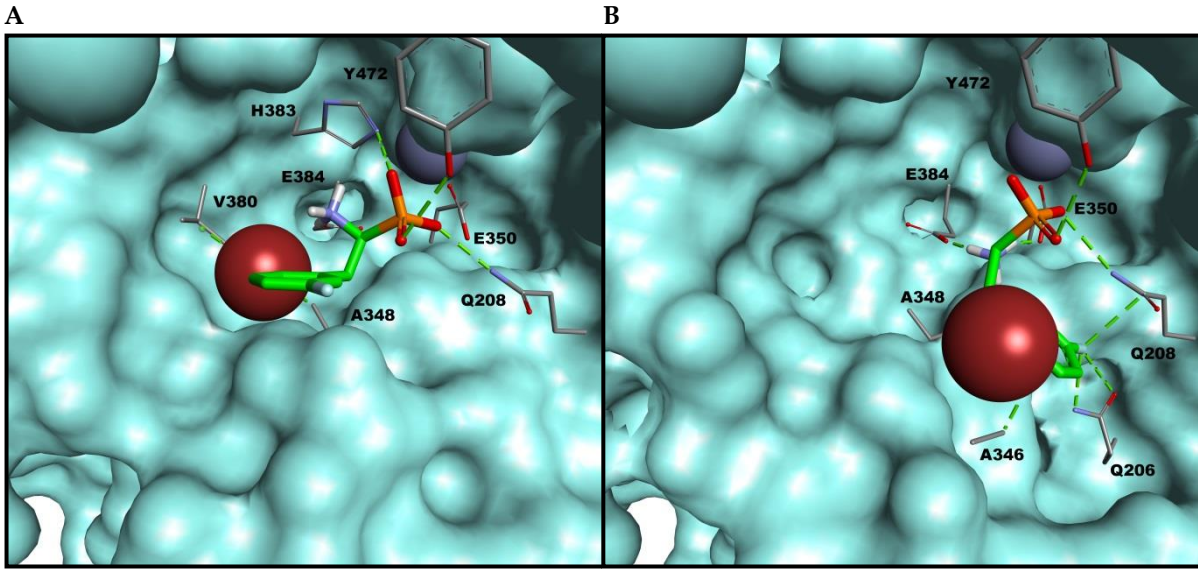
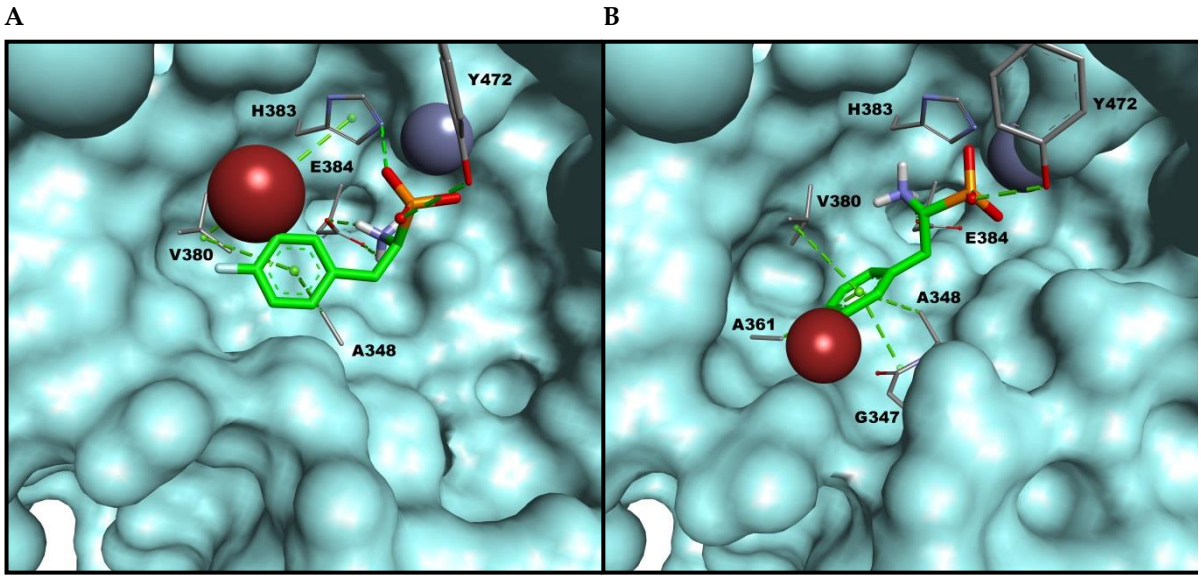


Figure S7-4. Binding mode of the 1-amino-2-(3-bromo-4-fluorophenyl)ethylphosphonic acid (compound **17c**) with the pAPN. The isomer *(S)* is on the left side (**A**), when the *(R)*-isomer is on the right side (**B**). The colouring scheme is identical as in Figure 1. The bromine atom is shown as dark red sphere.



Section S8. *Molecular docking simulations of the inhibitors* ***15f, 15g*** *and* ***17c*** *binding to active site of hAPN (PDB: 4FYT).*

Figure S8-1. Binding mode of the 1-amino-3-(3,4-difluorophenyl)propylphosphonic acid (compound **15f**) with the hAPN. The isomer *(S)* is on the left side (**A**), when the *(R)*-isomer is on the right side (**B**). The colouring scheme is identical as in Figure 1.

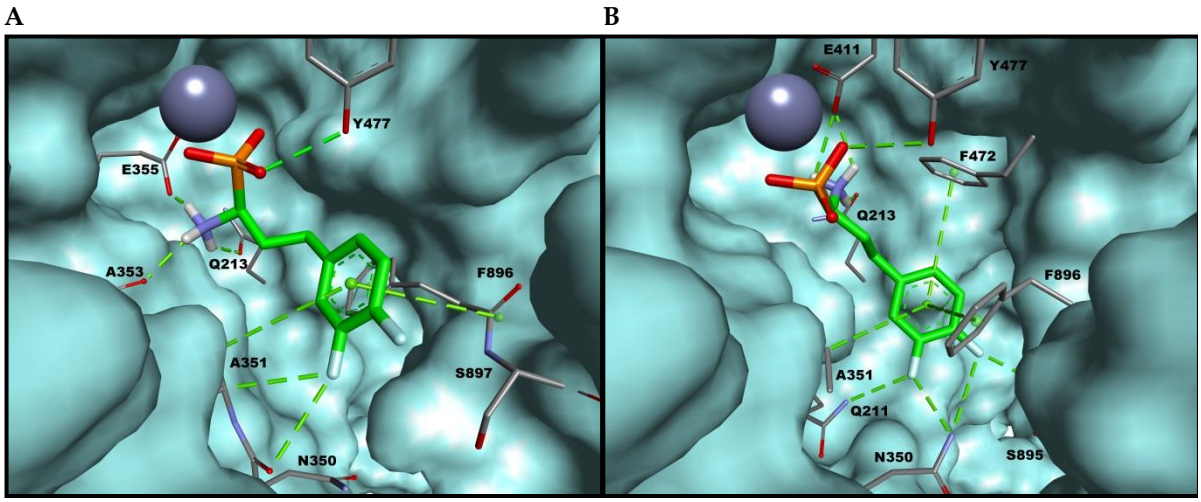


Figure S8-2. Binding mode of the 1-amino-3-(4-trifluoromethylphenyl)propylphosphonic acid (compound **15g**) with the hAPN. The isomer *(S)* is on the left side (**A**), when the *(R)*-isomer is on the right side (**B**). The colouring scheme is identical as in Figure 1.

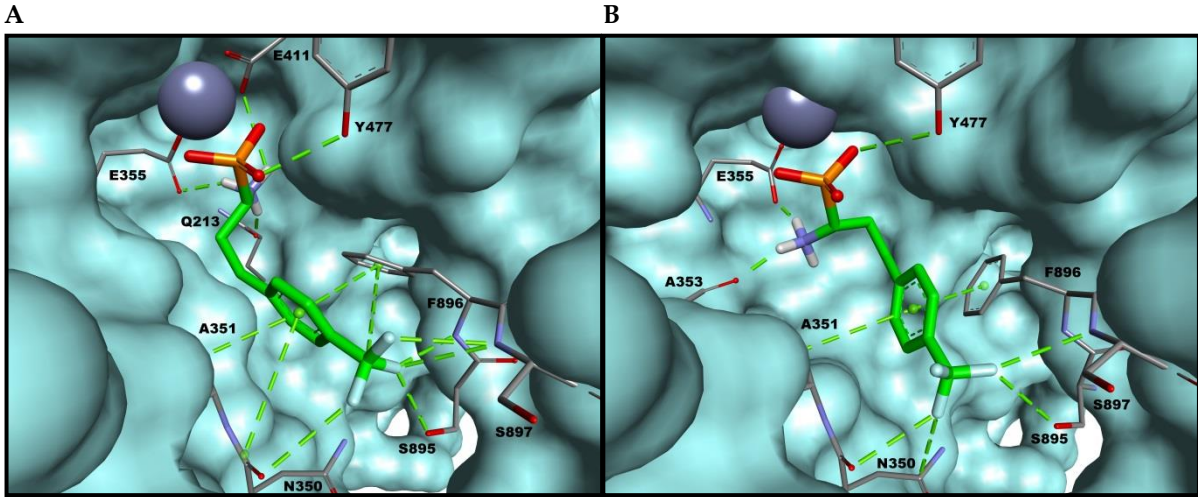
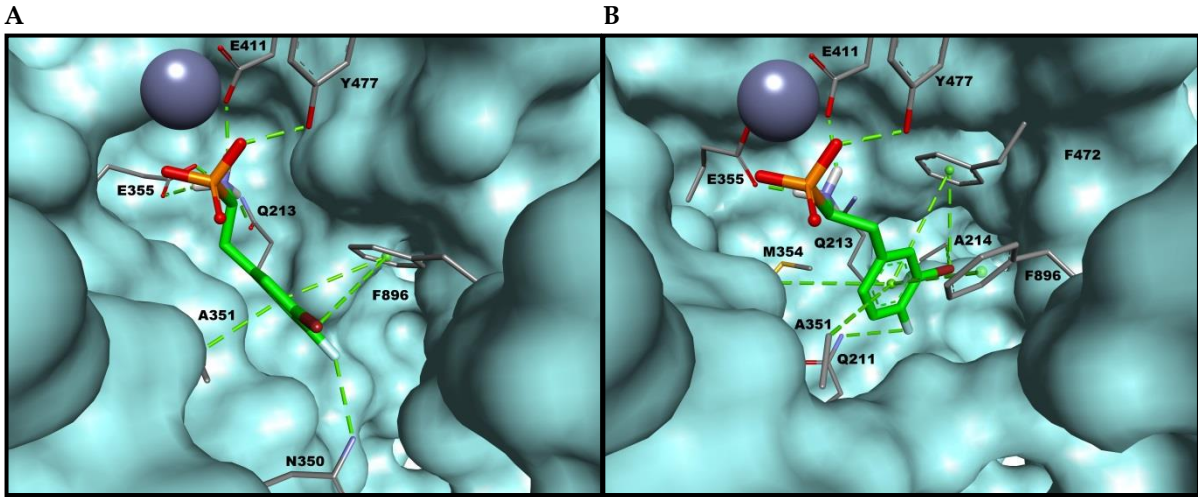


Figure S8-3. Binding mode of the 1-amino-2-(3-bromo-4-fluorophenyl)ethylphosphonic acid (compound **17c**) with the hAPN. The isomer *(S)* is on the left side (**A**), when the *(R)*-isomer is on the right side (**B**). The colouring scheme is identical as in Figure 1. The bromine atom is shown as dark red stick.

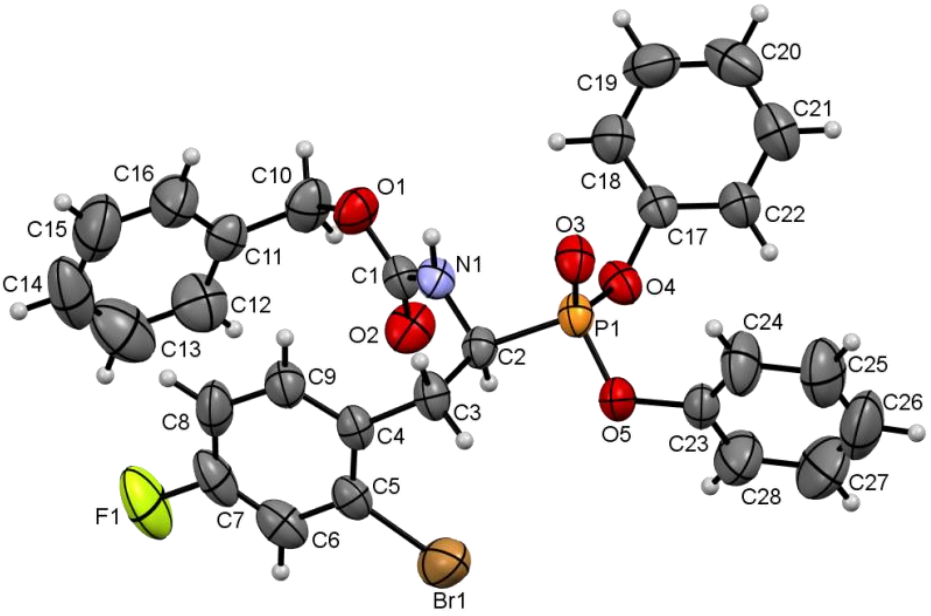


Section S9. *X-Ray analysis of compounds* ***13a, 13c*** *and* ***14c****.*

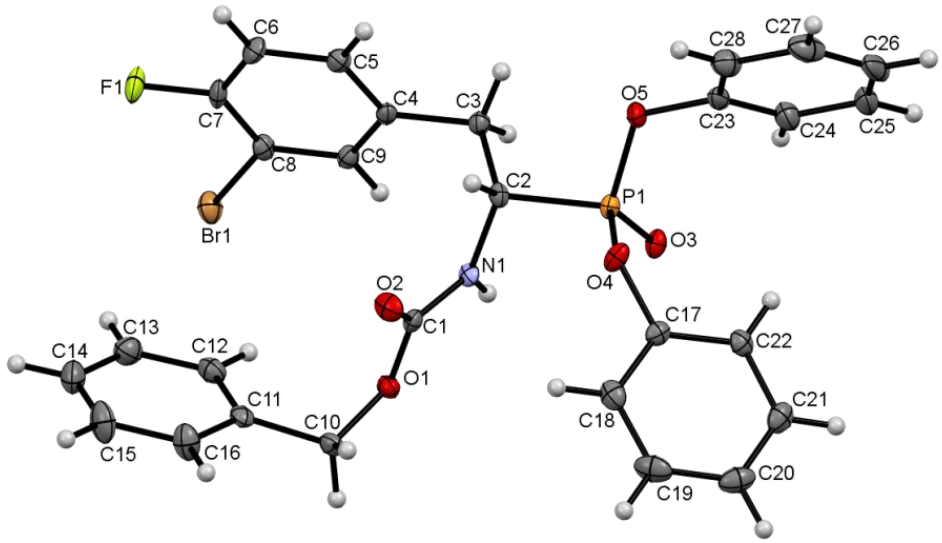
Figure S9. Molecular structures of diphenyl 1-{[(N-benzyloxy)carbonyl]amino}-2-(2-bromo-4-fluorophenyl)ethylphosphonate (**13a**)(**A**), diphenyl 1-{[(N-benzyloxy)carbonyl]amino}-2-(3-bromo-4-fluorophenyl)ethylphosphonate (**13c**) (**B**) and dimethyl 1-{[(N-benzyloxy)carbonyl]amino}-3-(3-fluorophenyl)propylphosphonate (**14c**) (**C**) in the asymmetric part of unit cell. Displacement ellipsoids are drawn at the 50% probability level.

The geometry around the P atom is distorted tetrahedral, the angles varying from 116.38 (10) ° to 104.49 (9) ° in molecule **13a**, 115.20 (8)° to 102.02 (8)° in **13c** and 114.22 (16)° to 102.41 (14)° in **14c**. All angles involving the non-ester O atom are larger than the others. This corresponds well with other substituted aminophosphonic groups. The arrangement of phenyl groups occurs in molecules **13a** and **13c** (oxygen 04 and O5). In molecule **14c** we can observe the same arrangement of methyl groups. All phenyl rings are planar within experimental error.

A



B



C

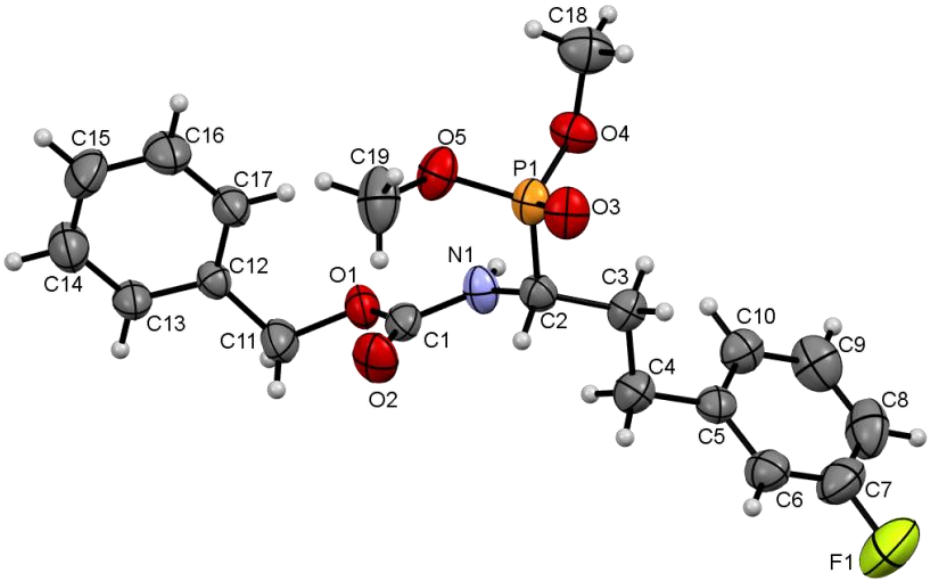


Table S9-1. Crystal parameters and experimental details of the X-Ray data collection for structure **13a, 13c** and **14c.**

	13a	**13c**	**14c**
Crystal data			
Chemical formula	$C_{28}H_{24}BrFNO_5P$	$C_{28}H_{24}BrFNO_5P$	$C_{19}H_{23}FNO_5P$
M_r	584.36	584.36	395.35
Crystal system, space group	Monoclinic, $P2_1/c$	Monoclinic, $P2_1/n$	Monoclinic, $P2_1/c$
Temperature (K)	293	100	293
a, b, c (Å)	13.3129 (7), 10.4517 (4), 19.9282 (12)	8.8213 (2), 15.2255 (3), 19.0081 (4)	11.4935 (12), 18.2514 (16), 10.0442 (11)
β (°)	104.460 (6)	91.843 (2)	111.988 (13)
V (Å^3)	2685.0 (2)	2551.63 (9)	1953.7 (4)
Z	4	4	4
μ (mm^{-1})	1.64	1.72	0.18
Crystal size (mm)	0.5 × 0.3 × 0.1	0.4 × 0.25 × 0.1	0.3 × 0.2 × 0.1
Data collection			
Absorption correction	Multi-scan	Multi-scan	–
T_{min}, T_{max}	0.889, 1.000	0.898, 1.000	
No. of measured, independent and observed [$I > 2\sigma(I)$] reflections	17793, 5237, 2460	17121, 4996, 3862	13191, 3833, 1264
R_{int}	0.035	0.026	0.144
$(\sin \theta/\lambda)_{max}$ (Å^{-1})	0.617	0.617	0.617

Refinement			
$R[F^2 > 2\sigma(F^2)]$, $wR(F^2)$, S	0.034, 0.073, 0.76	0.025, 0.063, 0.95	0.052, 0.071, 0.78
No. of reflections	5237	4996	3833
No. of parameters	334	334	246
$\Delta\rho_{max}$, $\Delta\rho_{min}$ (e Å^{-3})	0.39, −0.49	0.32, −0.33	0.20, −0.23

682 **Table S9-2.** Selected geometric parameters for crystal structure **13a** (Å, º).

F1—C7	1.363 (3)	C11—C16	1.367 (3)
P1—O3	1.4574 (15)	C12—C13	1.372 (5)
P1—O4	1.5701 (16)	C12—H12	0.9300
P1—O5	1.5823 (16)	C13—C14	1.354 (5)
P1—C2	1.794 (2)	C13—H13	0.9300
Br1—C5	1.890 (2)	C14—C15	1.362 (5)
N1—C1	1.350 (3)	C14—H14	0.9300
N1—C2	1.440 (3)	C15—C16	1.367 (4)
N1—H1	0.8600	C15—H15	0.9300
O1—C1	1.344 (3)	C16—H16	0.9300
O1—C10	1.451 (3)	C17—C18	1.350 (3)
O2—C1	1.202 (3)	C17—C22	1.364 (3)
O4—C17	1.409 (3)	C18—C19	1.385 (4)
O5—C23	1.410 (3)	C18—H18	0.9300
C2—C3	1.538 (3)	C19—C20	1.368 (4)
C2—H2	0.9800	C19—H19	0.9300
C3—C4	1.498 (3)	C20—C21	1.358 (4)
C3—H3A	0.9700	C20—H20	0.9300
C3—H3B	0.9700	C21—C22	1.371 (3)
C4—C9	1.381 (3)	C21—H21	0.9300
C4—C5	1.387 (3)	C22—H22	0.9300
C5—C6	1.376 (3)	C23—C28	1.345 (3)
C6—C7	1.349 (4)	C23—C24	1.347 (3)
C6—H6	0.9300	C24—C25	1.373 (4)
C7—C8	1.360 (4)	C24—H24	0.9300
C8—C9	1.378 (3)	C25—C26	1.324 (4)
C8—H8	0.9300	C25—H25	0.9300
C9—H9	0.9300	C26—C27	1.361 (4)
C10—C11	1.488 (3)	C26—H26	0.9300

C10—H10A	0.9700	C27—C28	1.421 (4)
C10—H10B	0.9700	C27—H27	0.9300
C11—C12	1.351 (4)	C28—H28	0.9300
O3—P1—O4	114.31 (9)	C16—C11—C10	120.7 (3)
O3—P1—O5	115.56 (9)	C11—C12—C13	120.9 (3)
O4—P1—O5	103.75 (8)	C11—C12—H12	119.5
O3—P1—C2	116.38 (10)	C13—C12—H12	119.5
O4—P1—C2	104.49 (9)	C14—C13—C12	120.5 (4)
O5—P1—C2	100.54 (10)	C14—C13—H13	119.7
C1—N1—C2	120.9 (2)	C12—C13—H13	119.7
C1—N1—H1	119.5	C13—C14—C15	119.5 (4)
C2—N1—H1	119.5	C13—C14—H14	120.3
C1—O1—C10	116.0 (2)	C15—C14—H14	120.3
C17—O4—P1	123.97 (13)	C14—C15—C16	119.3 (4)
C23—O5—P1	121.79 (15)	C14—C15—H15	120.3
O2—C1—O1	125.1 (2)	C16—C15—H15	120.3
O2—C1—N1	125.2 (2)	C11—C16—C15	121.8 (3)
O1—C1—N1	109.7 (2)	C11—C16—H16	119.1
N1—C2—C3	111.73 (18)	C15—C16—H16	119.1
N1—C2—P1	108.55 (15)	C18—C17—C22	122.1 (3)
C3—C2—P1	112.74 (15)	C18—C17—O4	120.3 (2)
N1—C2—H2	107.9	C22—C17—O4	117.5 (2)
C3—C2—H2	107.9	C17—C18—C19	118.6 (3)
P1—C2—H2	107.9	C17—C18—H18	120.7
C4—C3—C2	110.78 (18)	C19—C18—H18	120.7
C4—C3—H3A	109.5	C20—C19—C18	120.2 (3)
C2—C3—H3A	109.5	C20—C19—H19	119.9
C4—C3—H3B	109.5	C18—C19—H19	119.9
C2—C3—H3B	109.5	C21—C20—C19	119.5 (3)
H3A—C3—H3B	108.1	C21—C20—H20	120.2
C9—C4—C5	116.9 (2)	C19—C20—H20	120.2
C9—C4—C3	120.3 (2)	C20—C21—C22	121.0 (3)
C5—C4—C3	122.7 (2)	C20—C21—H21	119.5
C6—C5—C4	122.2 (2)	C22—C21—H21	119.5
C6—C5—Br1	116.8 (2)	C17—C22—C21	118.4 (3)

C4—C5—Br1	120.99 (19)	C17—C22—H22	120.8
C7—C6—C5	117.7 (3)	C21—C22—H22	120.8
C7—C6—H6	121.2	C28—C23—C24	122.5 (3)
C5—C6—H6	121.2	C28—C23—O5	116.4 (3)
C6—C7—C8	123.4 (3)	C24—C23—O5	121.1 (2)
C6—C7—F1	118.7 (3)	C23—C24—C25	119.5 (3)
C8—C7—F1	117.9 (3)	C23—C24—H24	120.3
C7—C8—C9	117.7 (3)	C25—C24—H24	120.3
C7—C8—H8	121.1	C26—C25—C24	120.2 (3)
C9—C8—H8	121.1	C26—C25—H25	119.9
C8—C9—C4	122.0 (3)	C24—C25—H25	119.9
C8—C9—H9	119.0	C25—C26—C27	121.3 (4)
C4—C9—H9	119.0	C25—C26—H26	119.4
O1—C10—C11	111.3 (2)	C27—C26—H26	119.4
O1—C10—H10A	109.4	C26—C27—C28	119.2 (3)
C11—C10—H10A	109.4	C26—C27—H27	120.4
O1—C10—H10B	109.4	C28—C27—H27	120.4
C11—C10—H10B	109.4	C23—C28—C27	117.3 (3)
H10A—C10—H10B	108.0	C23—C28—H28	121.4
C12—C11—C16	118.0 (3)	C27—C28—H28	121.4
C12—C11—C10	121.3 (3)		
O3—P1—O4—C17	0.7 (2)	C5—C4—C9—C8	−1.6 (4)
O5—P1—O4—C17	−125.99 (18)	C3—C4—C9—C8	175.2 (2)
C2—P1—O4—C17	129.07 (19)	C1—O1—C10—C11	92.6 (2)
O3—P1—O5—C23	−71.53 (19)	O1—C10—C11—C12	−116.9 (3)
O4—P1—O5—C23	54.40 (18)	O1—C10—C11—C16	65.1 (3)
C2—P1—O5—C23	162.31 (17)	C16—C11—C12—C13	0.8 (5)
C10—O1—C1—O2	7.5 (3)	C10—C11—C12—C13	−177.3 (3)
C10—O1—C1—N1	−173.87 (18)	C11—C12—C13—C14	0.1 (5)
C2—N1—C1—O2	−8.5 (3)	C12—C13—C14—C15	−1.2 (6)
C2—N1—C1—O1	172.85 (17)	C13—C14—C15—C16	1.4 (6)
C1—N1—C2—C3	−105.3 (2)	C12—C11—C16—C15	−0.6 (5)
C1—N1—C2—P1	129.74 (18)	C10—C11—C16—C15	177.5 (3)
O3—P1—C2—N1	61.02 (18)	C14—C15—C16—C11	−0.5 (5)
O4—P1—C2—N1	−66.05 (16)	P1—O4—C17—C18	−71.9 (3)

O5—P1—C2—N1	−173.37 (14)	P1—O4—C17—C22	109.9 (2)
O3—P1—C2—C3	−63.32 (19)	C22—C17—C18—C19	0.2 (4)
O4—P1—C2—C3	169.61 (15)	O4—C17—C18—C19	−177.9 (2)
O5—P1—C2—C3	62.28 (17)	C17—C18—C19—C20	0.3 (4)
N1—C2—C3—C4	62.0 (2)	C18—C19—C20—C21	−0.1 (5)
P1—C2—C3—C4	−175.41 (17)	C19—C20—C21—C22	−0.7 (5)
C2—C3—C4—C9	−93.8 (3)	C18—C17—C22—C21	−0.9 (4)
C2—C3—C4—C5	82.8 (3)	O4—C17—C22—C21	177.2 (2)
C9—C4—C5—C6	0.2 (3)	C20—C21—C22—C17	1.2 (4)
C3—C4—C5—C6	−176.5 (2)	P1—O5—C23—C28	−123.6 (2)
C9—C4—C5—Br1	−179.15 (17)	P1—O5—C23—C24	56.7 (3)
C3—C4—C5—Br1	4.1 (3)	C28—C23—C24—C25	−0.3 (5)
C4—C5—C6—C7	1.1 (4)	O5—C23—C24—C25	179.4 (3)
Br1—C5—C6—C7	−179.5 (2)	C23—C24—C25—C26	−2.3 (5)
C5—C6—C7—C8	−1.1 (4)	C24—C25—C26—C27	3.8 (6)
C5—C6—C7—F1	179.7 (2)	C25—C26—C27—C28	−2.7 (7)
C6—C7—C8—C9	−0.2 (4)	C24—C23—C28—C27	1.3 (5)
F1—C7—C8—C9	179.0 (2)	O5—C23—C28—C27	−178.4 (3)
C7—C8—C9—C4	1.6 (4)	C26—C27—C28—C23	0.1 (6)

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684 **Table S9-3.** Selected hydrogen-bond parameters for structure **13a**.

D—H···*A*	*D*—H (Å)	H···*A* (Å)	*D*···*A* (Å)	*D*—H···*A* (°)
N1—H1···O3^{i}	0.86	2.14	2.881 (2)	144.6
C2—H2···Br1	0.98	3.09	3.660 (2)	118.3

685 Symmetry code(s): (i) −*x*+1, −*y*+1, −*z*+1.

686 **Table S9-4.** Selected geometric parameters for crystal structure **13c** (Å, º).

F1—C7	1.359 (2)	C11—C16	1.388 (3)
P1—O3	1.4650 (13)	C12—C13	1.379 (3)
P1—O5	1.5815 (14)	C12—H12	0.9300
P1—O4	1.5843 (13)	C13—C14	1.382 (3)
P1—C2	1.8043 (18)	C13—H13	0.9300
Br1—C8	1.8844 (19)	C14—C15	1.379 (3)
N1—C1	1.346 (2)	C14—H14	0.9300
N1—C2	1.451 (2)	C15—C16	1.383 (3)

N1—H1	0.8600	C15—H15	0.9300
O1—C1	1.358 (2)	C16—H16	0.9300
O1—C10	1.446 (2)	C17—C18	1.372 (3)
O2—C1	1.209 (2)	C17—C22	1.383 (3)
O4—C17	1.406 (2)	C18—C19	1.388 (3)
O5—C23	1.419 (2)	C18—H18	0.9300
C2—C3	1.538 (2)	C19—C20	1.382 (3)
C2—H2	0.9800	C19—H19	0.9300
C3—C4	1.512 (2)	C20—C21	1.380 (3)
C3—H3A	0.9700	C20—H20	0.9300
C3—H3B	0.9700	C21—C22	1.384 (3)
C4—C5	1.388 (3)	C21—H21	0.9300
C4—C9	1.390 (3)	C22—H22	0.9300
C5—C6	1.387 (3)	C23—C28	1.378 (3)
C5—H5	0.9300	C23—C24	1.382 (3)
C6—C7	1.369 (3)	C24—C25	1.388 (3)
C6—H6	0.9300	C24—H24	0.9300
C7—C8	1.379 (3)	C25—C26	1.375 (3)
C8—C9	1.385 (3)	C25—H25	0.9300
C9—H9	0.9300	C26—C27	1.375 (3)
C10—C11	1.502 (3)	C26—H26	0.9300
C10—H10A	0.9700	C27—C28	1.390 (3)
C10—H10B	0.9700	C27—H27	0.9300
C11—C12	1.384 (3)	C28—H28	0.9300
O3—P1—O5	115.77 (8)	C16—C11—C10	118.92 (18)
O3—P1—O4	114.45 (7)	C13—C12—C11	120.70 (19)
O5—P1—O4	103.82 (7)	C13—C12—H12	119.7
O3—P1—C2	115.20 (8)	C11—C12—H12	119.7
O5—P1—C2	102.02 (8)	C12—C13—C14	120.2 (2)
O4—P1—C2	103.93 (8)	C12—C13—H13	119.9
C1—N1—C2	121.61 (16)	C14—C13—H13	119.9
C1—N1—H1	119.2	C15—C14—C13	119.5 (2)
C2—N1—H1	119.2	C15—C14—H14	120.2
C1—O1—C10	115.40 (14)	C13—C14—H14	120.2
C17—O4—P1	128.47 (11)	C14—C15—C16	120.3 (2)

C23—O5—P1	120.40 (11)	C14—C15—H15	119.9
O2—C1—N1	125.98 (18)	C16—C15—H15	119.9
O2—C1—O1	124.67 (17)	C15—C16—C11	120.4 (2)
N1—C1—O1	109.33 (16)	C15—C16—H16	119.8
N1—C2—C3	111.67 (15)	C11—C16—H16	119.8
N1—C2—P1	106.64 (12)	C18—C17—C22	121.92 (18)
C3—C2—P1	111.54 (13)	C18—C17—O4	117.18 (17)
N1—C2—H2	109.0	C22—C17—O4	120.78 (17)
C3—C2—H2	109.0	C17—C18—C19	118.88 (19)
P1—C2—H2	109.0	C17—C18—H18	120.6
C4—C3—C2	112.25 (15)	C19—C18—H18	120.6
C4—C3—H3A	109.2	C20—C19—C18	120.3 (2)
C2—C3—H3A	109.2	C20—C19—H19	119.9
C4—C3—H3B	109.2	C18—C19—H19	119.9
C2—C3—H3B	109.2	C21—C20—C19	119.77 (19)
H3A—C3—H3B	107.9	C21—C20—H20	120.1
C5—C4—C9	118.90 (17)	C19—C20—H20	120.1
C5—C4—C3	120.79 (17)	C20—C21—C22	120.72 (19)
C9—C4—C3	120.29 (16)	C20—C21—H21	119.6
C6—C5—C4	120.87 (18)	C22—C21—H21	119.6
C6—C5—H5	119.6	C17—C22—C21	118.41 (19)
C4—C5—H5	119.6	C17—C22—H22	120.8
C7—C6—C5	118.91 (18)	C21—C22—H22	120.8
C7—C6—H6	120.5	C28—C23—C24	122.27 (19)
C5—C6—H6	120.5	C28—C23—O5	117.27 (17)
F1—C7—C6	119.45 (17)	C24—C23—O5	120.46 (18)
F1—C7—C8	118.82 (18)	C23—C24—C25	118.2 (2)
C6—C7—C8	121.73 (17)	C23—C24—H24	120.9
C7—C8—C9	119.06 (18)	C25—C24—H24	120.9
C7—C8—Br1	119.88 (14)	C26—C25—C24	120.4 (2)
C9—C8—Br1	121.05 (14)	C26—C25—H25	119.8
C8—C9—C4	120.52 (17)	C24—C25—H25	119.8
C8—C9—H9	119.7	C25—C26—C27	120.5 (2)
C4—C9—H9	119.7	C25—C26—H26	119.8
O1—C10—C11	112.81 (15)	C27—C26—H26	119.8

O1—C10—H10A	109.0	C26—C27—C28	120.3 (2)
C11—C10—H10A	109.0	C26—C27—H27	119.9
O1—C10—H10B	109.0	C28—C27—H27	119.9
C11—C10—H10B	109.0	C23—C28—C27	118.3 (2)
H10A—C10—H10B	107.8	C23—C28—H28	120.8
C12—C11—C16	118.84 (19)	C27—C28—H28	120.8
C12—C11—C10	122.13 (18)		
O3—P1—O4—C17	−2.54 (18)	C5—C4—C9—C8	−0.5 (3)
O5—P1—O4—C17	−129.67 (15)	C3—C4—C9—C8	−179.04 (17)
C2—P1—O4—C17	123.95 (15)	C1—O1—C10—C11	83.52 (19)
O3—P1—O5—C23	−62.60 (15)	O1—C10—C11—C12	31.2 (3)
O4—P1—O5—C23	63.70 (14)	O1—C10—C11—C16	−152.81 (18)
C2—P1—O5—C23	171.51 (14)	C16—C11—C12—C13	−0.9 (3)
C2—N1—C1—O2	−8.7 (3)	C10—C11—C12—C13	175.08 (18)
C2—N1—C1—O1	172.92 (14)	C11—C12—C13—C14	0.7 (3)
C10—O1—C1—O2	−1.8 (3)	C12—C13—C14—C15	0.2 (3)
C10—O1—C1—N1	176.61 (14)	C13—C14—C15—C16	−0.8 (3)
C1—N1—C2—C3	−120.37 (18)	C14—C15—C16—C11	0.5 (3)
C1—N1—C2—P1	117.55 (16)	C12—C11—C16—C15	0.4 (3)
O3—P1—C2—N1	48.54 (15)	C10—C11—C16—C15	−175.77 (19)
O5—P1—C2—N1	174.79 (12)	P1—O4—C17—C18	−129.37 (16)
O4—P1—C2—N1	−77.48 (13)	P1—O4—C17—C22	54.6 (2)
O3—P1—C2—C3	−73.63 (15)	C22—C17—C18—C19	1.1 (3)
O5—P1—C2—C3	52.63 (14)	O4—C17—C18—C19	−174.98 (17)
O4—P1—C2—C3	160.35 (12)	C17—C18—C19—C20	−1.1 (3)
N1—C2—C3—C4	59.9 (2)	C18—C19—C20—C21	−0.3 (3)
P1—C2—C3—C4	179.11 (13)	C19—C20—C21—C22	1.8 (3)
C2—C3—C4—C5	91.1 (2)	C18—C17—C22—C21	0.4 (3)
C2—C3—C4—C9	−90.3 (2)	O4—C17—C22—C21	176.33 (16)
C9—C4—C5—C6	0.2 (3)	C20—C21—C22—C17	−1.9 (3)
C3—C4—C5—C6	178.81 (18)	P1—O5—C23—C28	−121.49 (17)
C4—C5—C6—C7	−0.1 (3)	P1—O5—C23—C24	59.3 (2)
C5—C6—C7—F1	179.49 (17)	C28—C23—C24—C25	2.6 (3)
C5—C6—C7—C8	0.3 (3)	O5—C23—C24—C25	−178.27 (17)
F1—C7—C8—C9	−179.72 (17)	C23—C24—C25—C26	−0.9 (3)

C6—C7—C8—C9	−0.5 (3)	C24—C25—C26—C27	−0.9 (3)
F1—C7—C8—Br1	−0.8 (2)	C25—C26—C27—C28	1.3 (3)
C6—C7—C8—Br1	178.38 (15)	C24—C23—C28—C27	−2.3 (3)
C7—C8—C9—C4	0.6 (3)	O5—C23—C28—C27	178.57 (17)
Br1—C8—C9—C4	−178.28 (14)	C26—C27—C28—C23	0.3 (3)

687 **Table S9-5.** Selected geometric parameters for crystal structure **14c** (Å, º).

F1—C7	1.365 (4)	C8—C9	1.363 (4)
P1—O3	1.471 (2)	C8—H8	0.9300
P1—O4	1.574 (2)	C9—C10	1.380 (4)
P1—O5	1.579 (2)	C9—H9	0.9300
P1—C2	1.810 (3)	C10—H10	0.9300
N1—C1	1.359 (4)	C11—C12	1.496 (4)
N1—C2	1.436 (3)	C11—H11A	0.9700
N1—H1	0.8600	C11—H11B	0.9700
O1—C1	1.350 (4)	C12—C13	1.381 (4)
O1—C11	1.434 (3)	C12—C17	1.383 (4)
O2—C1	1.198 (4)	C13—C14	1.373 (4)
O4—C18	1.440 (3)	C13—H13	0.9300
O5—C19	1.443 (3)	C14—C15	1.373 (4)
C2—C3	1.533 (4)	C14—H14	0.9300
C2—H2	0.9800	C15—C16	1.377 (4)
C3—C4	1.520 (4)	C15—H15	0.9300
C3—H3A	0.9700	C16—C17	1.381 (4)
C3—H3B	0.9700	C16—H16	0.9300
C4—C5	1.502 (4)	C17—H17	0.9300
C4—H4A	0.9700	C18—H18A	0.9600
C4—H4B	0.9700	C18—H18B	0.9600
C5—C6	1.382 (4)	C18—H18C	0.9600
C5—C10	1.383 (4)	C19—H19A	0.9600
C6—C7	1.377 (5)	C19—H19B	0.9600
C6—H6	0.9300	C19—H19C	0.9600
C7—C8	1.364 (5)		
O3—P1—O4	115.72 (13)	C7—C8—H8	121.4
O3—P1—O5	114.83 (14)	C8—C9—C10	121.2 (4)

O4—P1—O5	101.59 (14)	C8—C9—H9	119.4
O3—P1—C2	114.22 (16)	C10—C9—H9	119.4
O4—P1—C2	102.41 (14)	C9—C10—C5	121.0 (4)
O5—P1—C2	106.52 (15)	C9—C10—H10	119.5
C1—N1—C2	121.0 (3)	C5—C10—H10	119.5
C1—N1—H1	119.5	O1—C11—C12	113.1 (3)
C2—N1—H1	119.5	O1—C11—H11A	109.0
C1—O1—C11	115.4 (3)	C12—C11—H11A	109.0
C18—O4—P1	119.1 (2)	O1—C11—H11B	109.0
C19—O5—P1	121.7 (2)	C12—C11—H11B	109.0
O2—C1—O1	125.7 (4)	H11A—C11—H11B	107.8
O2—C1—N1	125.9 (4)	C13—C12—C17	119.3 (3)
O1—C1—N1	108.5 (3)	C13—C12—C11	117.6 (3)
N1—C2—C3	110.8 (3)	C17—C12—C11	123.1 (3)
N1—C2—P1	112.4 (2)	C14—C13—C12	120.7 (4)
C3—C2—P1	113.0 (2)	C14—C13—H13	119.7
N1—C2—H2	106.8	C12—C13—H13	119.7
C3—C2—H2	106.8	C13—C14—C15	119.9 (4)
P1—C2—H2	106.8	C13—C14—H14	120.1
C4—C3—C2	112.6 (3)	C15—C14—H14	120.1
C4—C3—H3A	109.1	C14—C15—C16	120.1 (4)
C2—C3—H3A	109.1	C14—C15—H15	119.9
C4—C3—H3B	109.1	C16—C15—H15	119.9
C2—C3—H3B	109.1	C15—C16—C17	120.0 (4)
H3A—C3—H3B	107.8	C15—C16—H16	120.0
C5—C4—C3	114.3 (3)	C17—C16—H16	120.0
C5—C4—H4A	108.7	C16—C17—C12	120.0 (4)
C3—C4—H4A	108.7	C16—C17—H17	120.0
C5—C4—H4B	108.7	C12—C17—H17	120.0
C3—C4—H4B	108.7	O4—C18—H18A	109.5
H4A—C4—H4B	107.6	O4—C18—H18B	109.5
C6—C5—C10	118.4 (4)	H18A—C18—H18B	109.5
C6—C5—C4	121.0 (4)	O4—C18—H18C	109.5
C10—C5—C4	120.6 (4)	H18A—C18—H18C	109.5
C7—C6—C5	118.6 (4)	H18B—C18—H18C	109.5

C7—C6—H6	120.7	O5—C19—H19A	109.5
C5—C6—H6	120.7	O5—C19—H19B	109.5
C8—C7—F1	118.9 (5)	H19A—C19—H19B	109.5
C8—C7—C6	123.7 (4)	O5—C19—H19C	109.5
F1—C7—C6	117.4 (5)	H19A—C19—H19C	109.5
C9—C8—C7	117.1 (4)	H19B—C19—H19C	109.5
C9—C8—H8	121.4		
O3—P1—O4—C18	−50.3 (3)	C3—C4—C5—C10	−62.7 (4)
O5—P1—O4—C18	74.8 (3)	C10—C5—C6—C7	−1.0 (6)
C2—P1—O4—C18	−175.2 (2)	C4—C5—C6—C7	178.0 (3)
O3—P1—O5—C19	−33.4 (3)	C5—C6—C7—C8	0.9 (6)
O4—P1—O5—C19	−159.1 (2)	C5—C6—C7—F1	−178.9 (3)
C2—P1—O5—C19	94.1 (3)	F1—C7—C8—C9	179.6 (4)
C11—O1—C1—O2	−3.0 (5)	C6—C7—C8—C9	−0.2 (7)
C11—O1—C1—N1	177.1 (2)	C7—C8—C9—C10	−0.5 (7)
C2—N1—C1—O2	−2.9 (6)	C8—C9—C10—C5	0.5 (6)
C2—N1—C1—O1	177.1 (3)	C6—C5—C10—C9	0.3 (6)
C1—N1—C2—C3	141.8 (3)	C4—C5—C10—C9	−178.7 (3)
C1—N1—C2—P1	−90.8 (3)	C1—O1—C11—C12	94.1 (3)
O3—P1—C2—N1	161.2 (2)	O1—C11—C12—C13	167.0 (3)
O4—P1—C2—N1	−72.9 (2)	O1—C11—C12—C17	−13.3 (5)
O5—P1—C2—N1	33.3 (3)	C17—C12—C13—C14	−0.1 (6)
O3—P1—C2—C3	−72.6 (3)	C11—C12—C13—C14	179.6 (3)
O4—P1—C2—C3	53.3 (3)	C12—C13—C14—C15	0.8 (6)
O5—P1—C2—C3	159.5 (2)	C13—C14—C15—C16	−0.7 (6)
N1—C2—C3—C4	−59.1 (4)	C14—C15—C16—C17	0.0 (6)
P1—C2—C3—C4	173.9 (2)	C15—C16—C17—C12	0.7 (6)
C2—C3—C4—C5	170.6 (3)	C13—C12—C17—C16	−0.6 (6)
C3—C4—C5—C6	118.3 (4)	C11—C12—C17—C16	179.6 (3)

688 **Table S9-6.** Selected hydrogen-bond parameters for structure **14c**.

D—H···*A*	*D*—H (Å)	H···*A* (Å)	*D*···*A* (Å)	*D*—H···*A* (°)
N1—H1···O3^{i}	0.86	2.07	2.916 (3)	167.4
C11—H11B···O1^{ii}	0.97	2.49	3.298 (4)	140.4
C18—H18C···O2^{i}	0.96	2.64	3.243 (4)	121.6

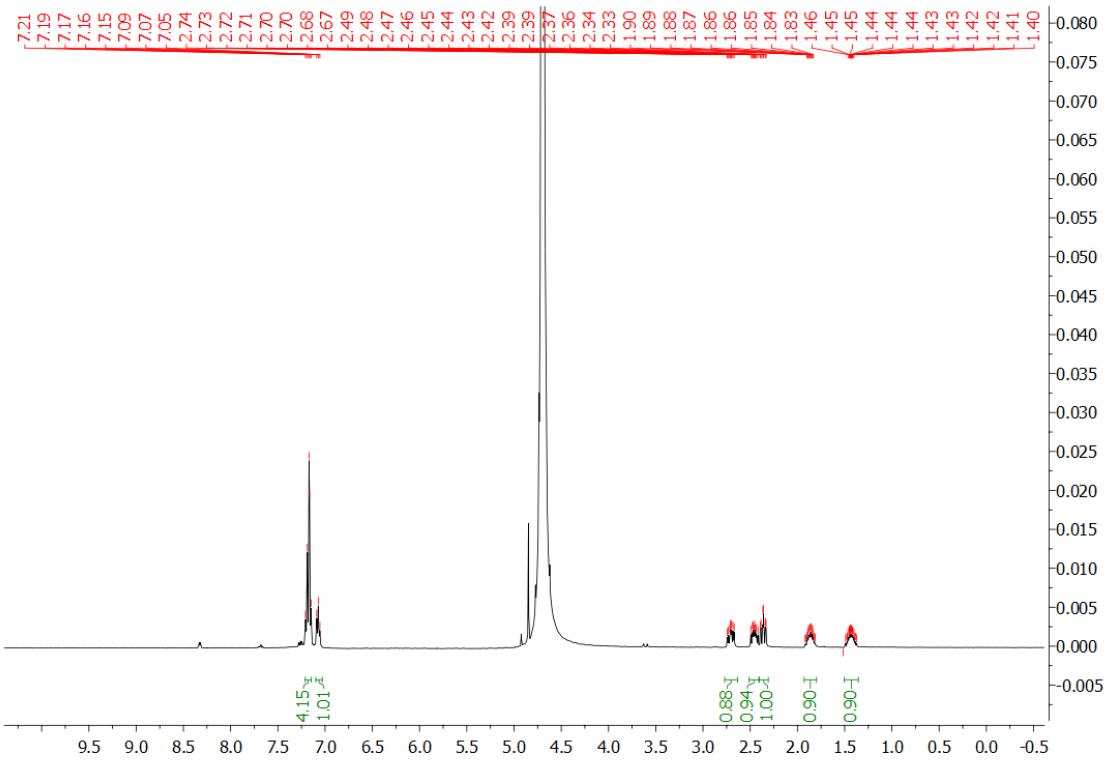
C19—H19B···O1^{iii}	0.96	2.53	3.474 (4)	166.3

Symmetry code(s): (i) $x, -y+1/2, z-1/2$; (ii) $-x+1, -y+1, -z+1$; (iii) $x, -y+1/2, z+1/2$.

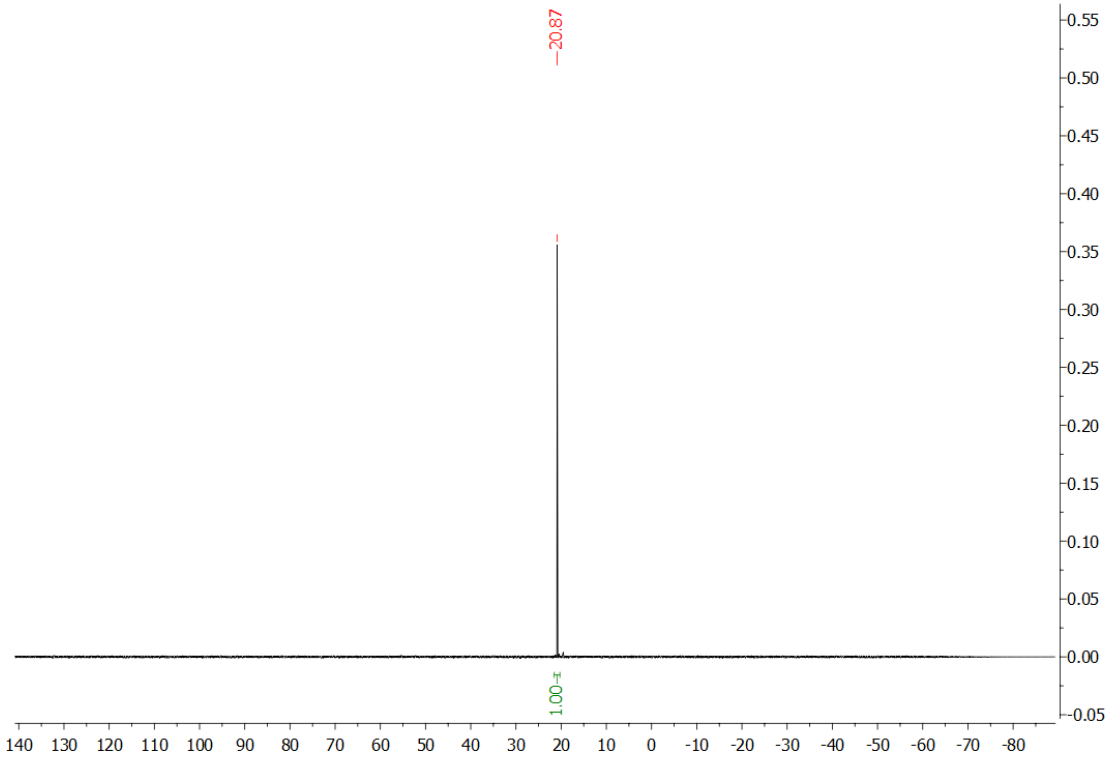
Section S10. *Characterization of the Final Compounds* ***15a-15h*** *and* ***17a-17e*** *by* ^{1}H, ^{13}C, ^{19}F, ^{31}P *NMR.*

Figure S10-1. ^{1}H (**A**), ^{31}P (**B**) NMR spectra for compound **15a**.

A

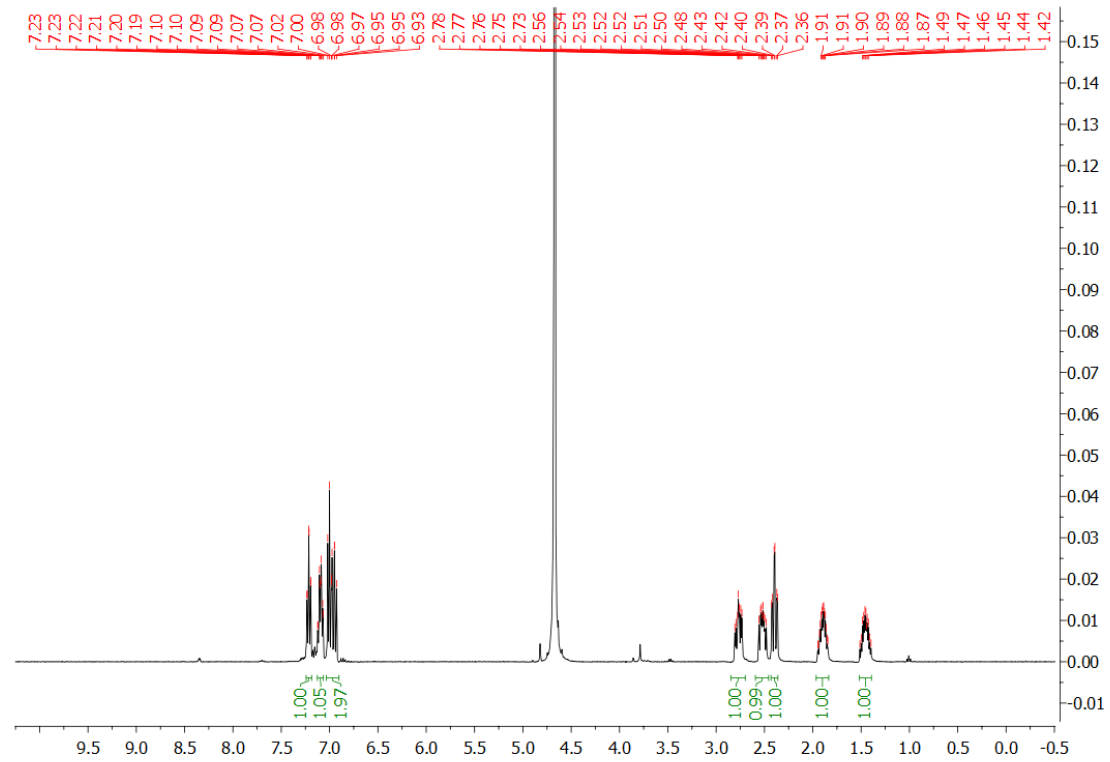


B

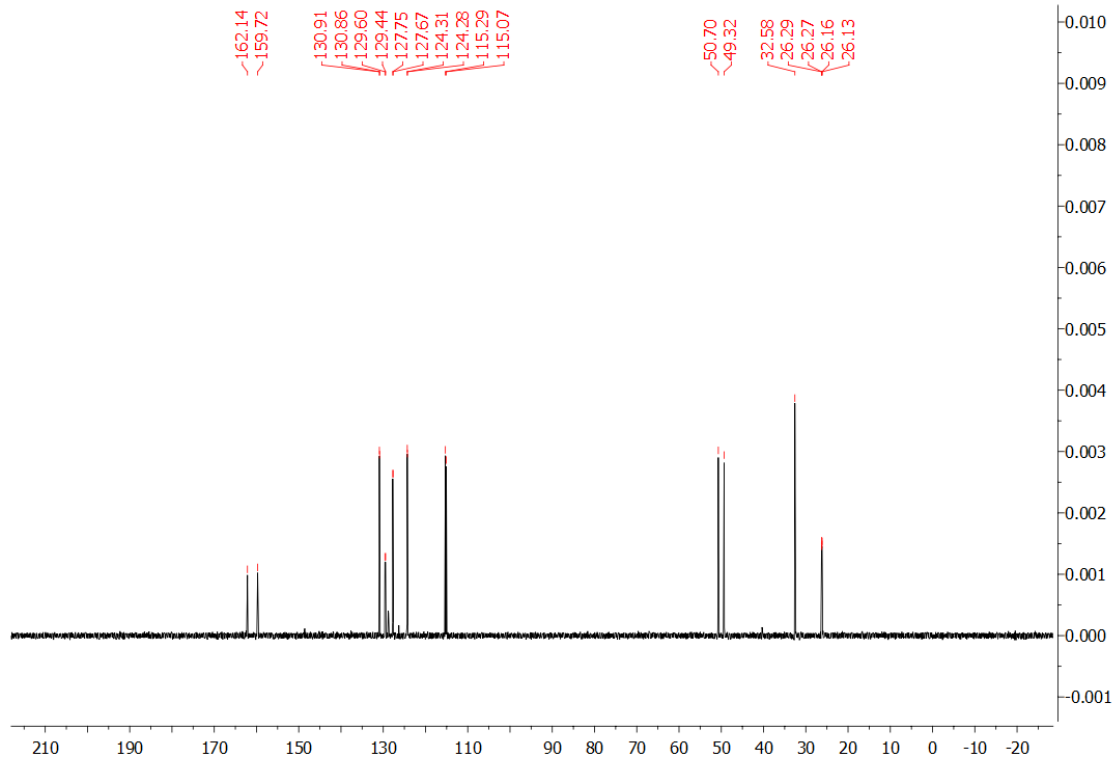


692 **Figure S10-2.** ^{1}H (**A**),^{13}C (**B**), ^{19}F (**C**), ^{31}P (**D**) NMR spectra for compound **15b**.

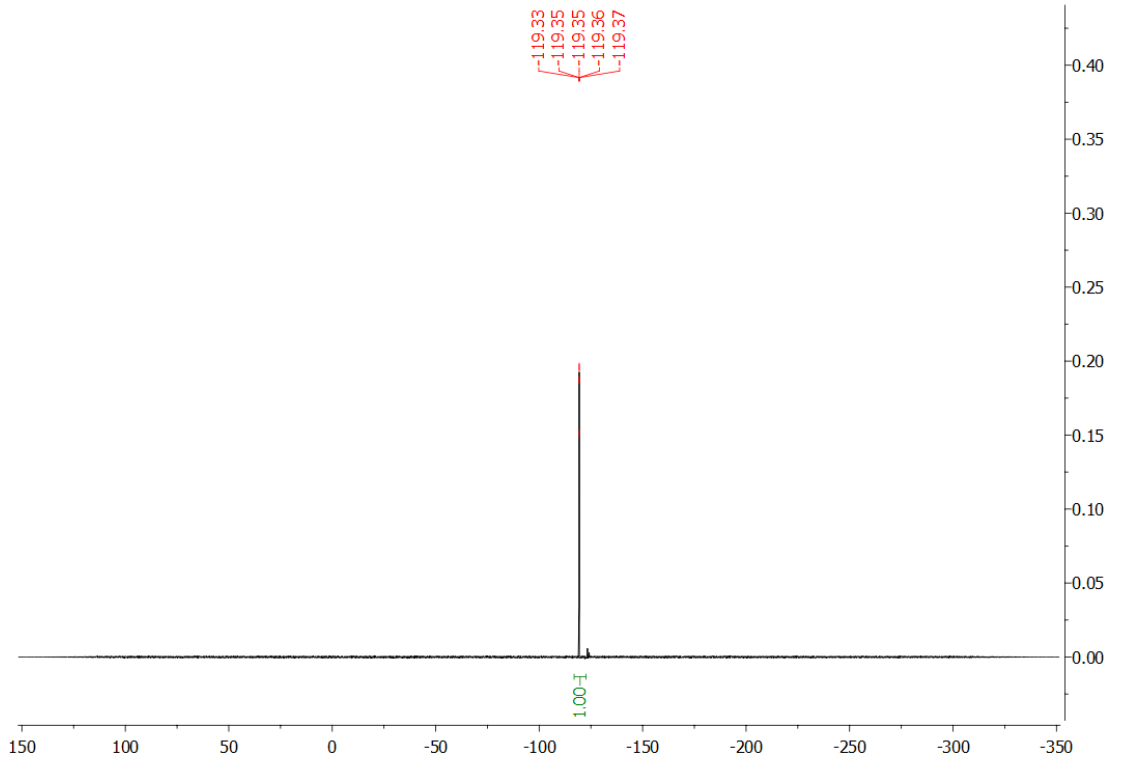
A



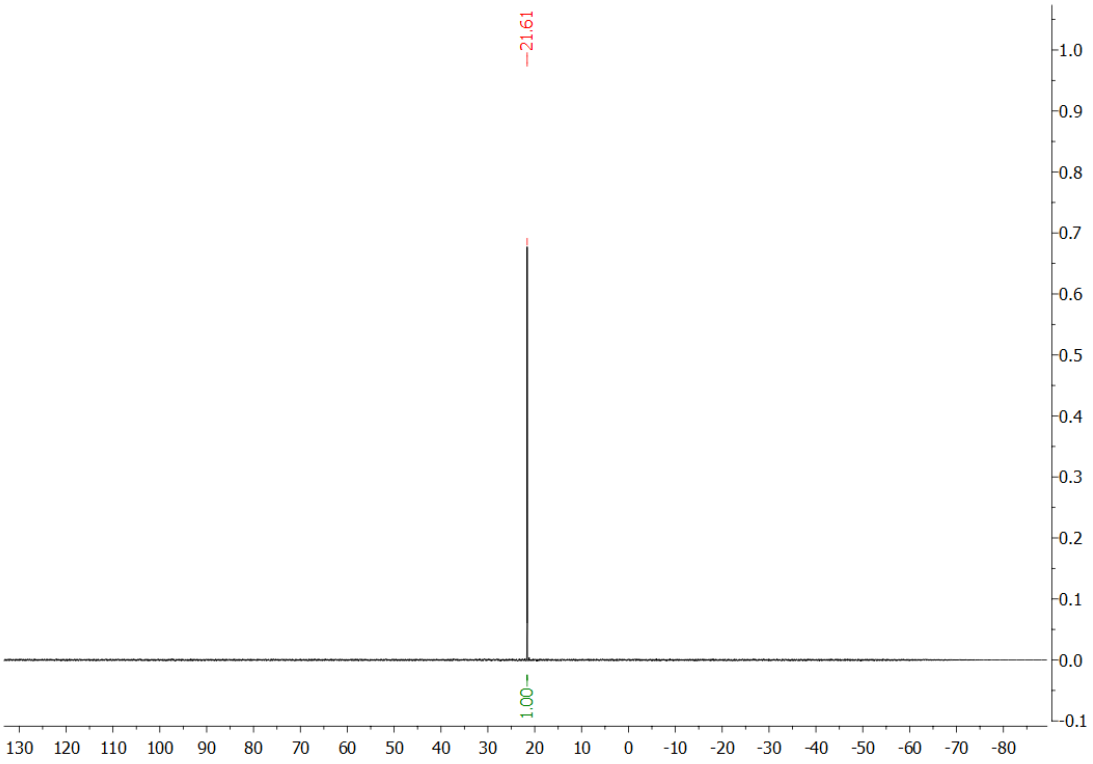
B


162.14
159.72
130.91
130.86
129.60
129.44
127.75
127.67
124.31
124.28
115.29
115.07
50.70
49.32
32.58
26.29
26.27
26.16
26.13
0.010
0.009
0.008
0.007
0.006
0.005
0.004
0.003
0.002
0.001
0.000
-0.001
210
190
170
150
130
110
90
80
70
60
50
40
30
20
10
0
-10
-20

C

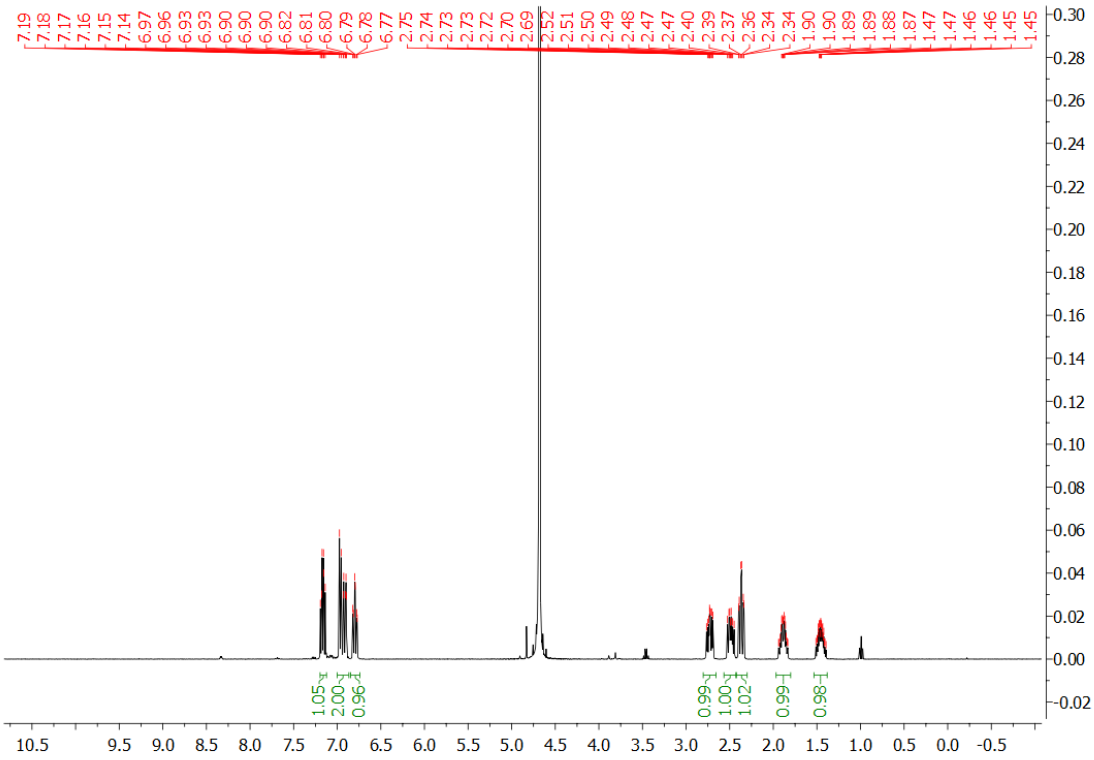

119.33
119.35
119.35
119.36
119.37
1.00
0.40
0.35
0.30
0.25
0.20
0.15
0.10
0.05
0.00
150
100
50
0
-50
-100
-150
-200
-250
-300
-350

D

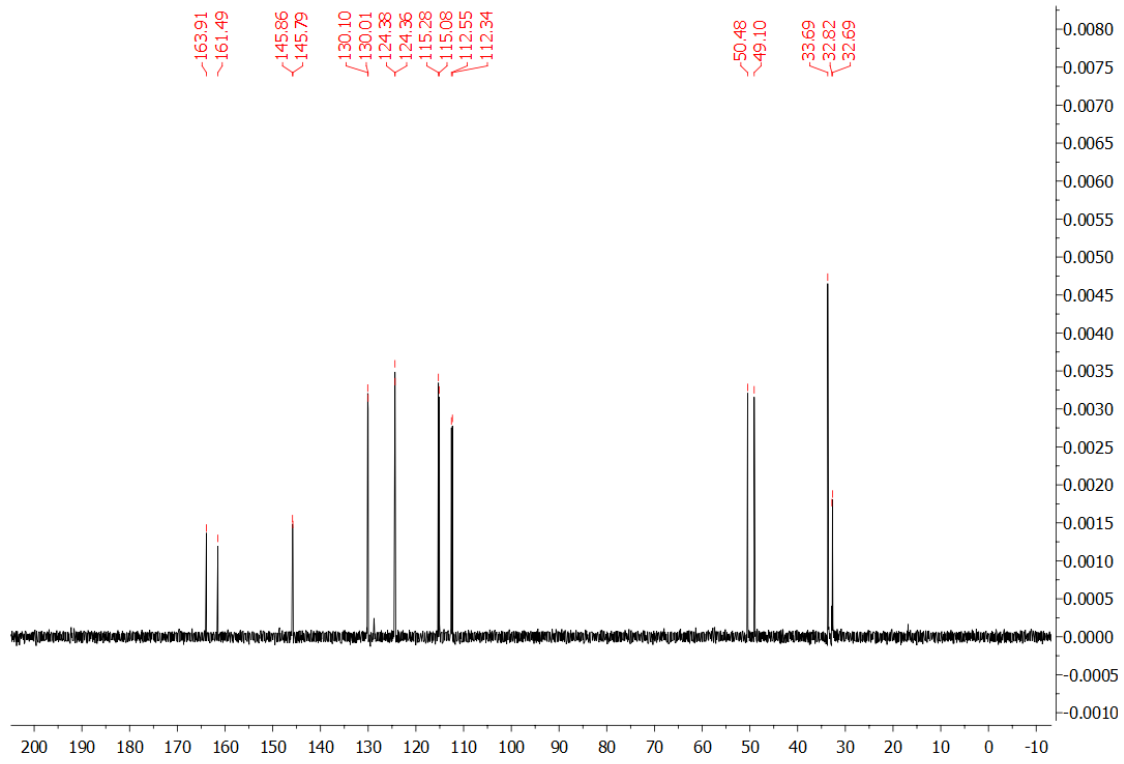


693 **Figure S10-3.** ^{1}H (**A**),^{13}C (**B**), ^{19}F (**C**), ^{31}P (**D**) NMR spectra for compound **15c**.

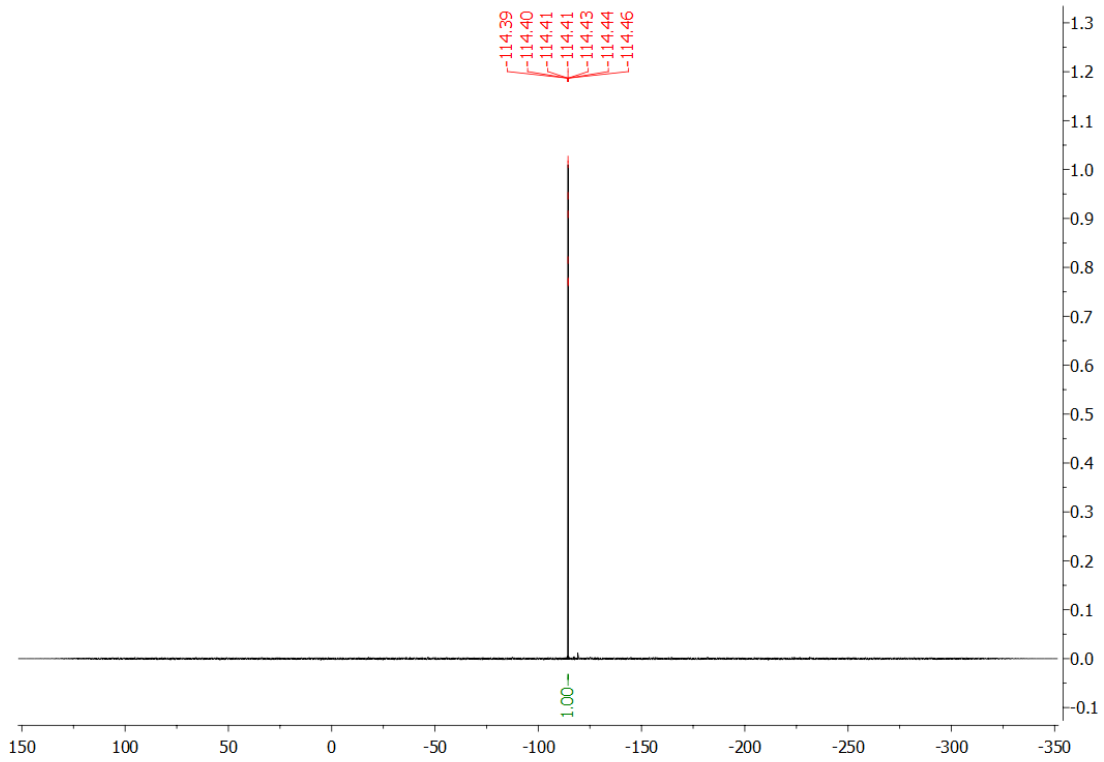
A



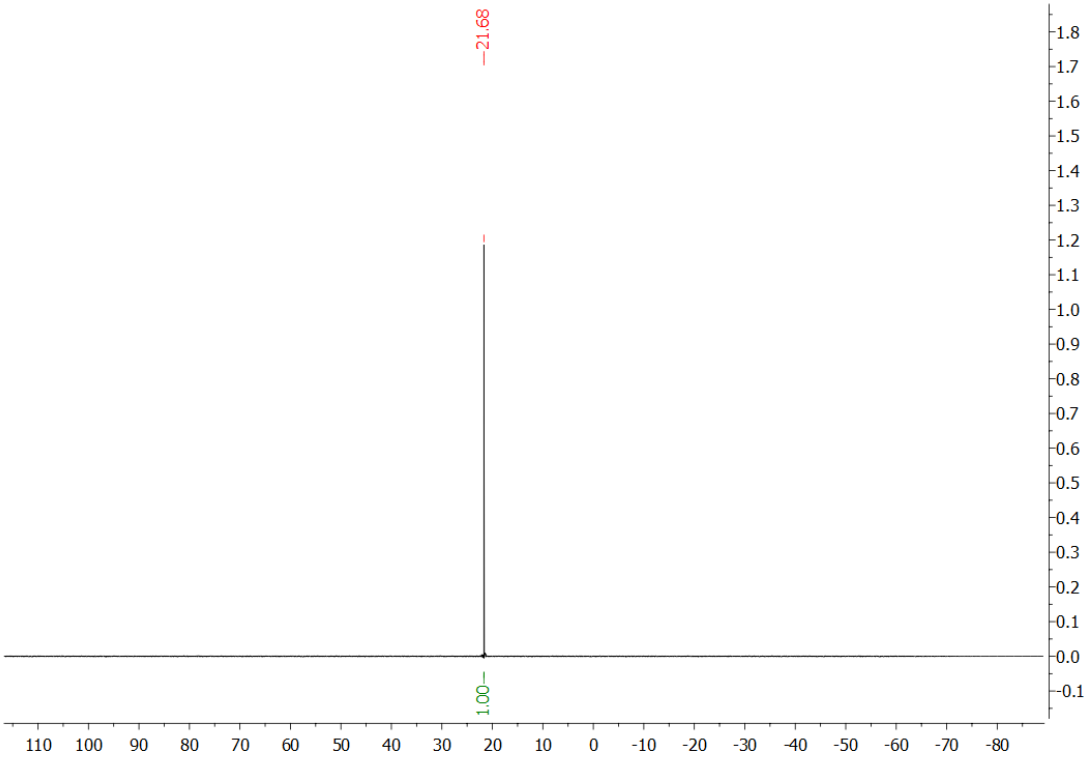
B


163.91
161.49
145.86
145.79
130.10
130.01
124.38
124.36
115.28
115.08
112.55
112.34
50.48
49.10
33.69
32.82
32.69

C

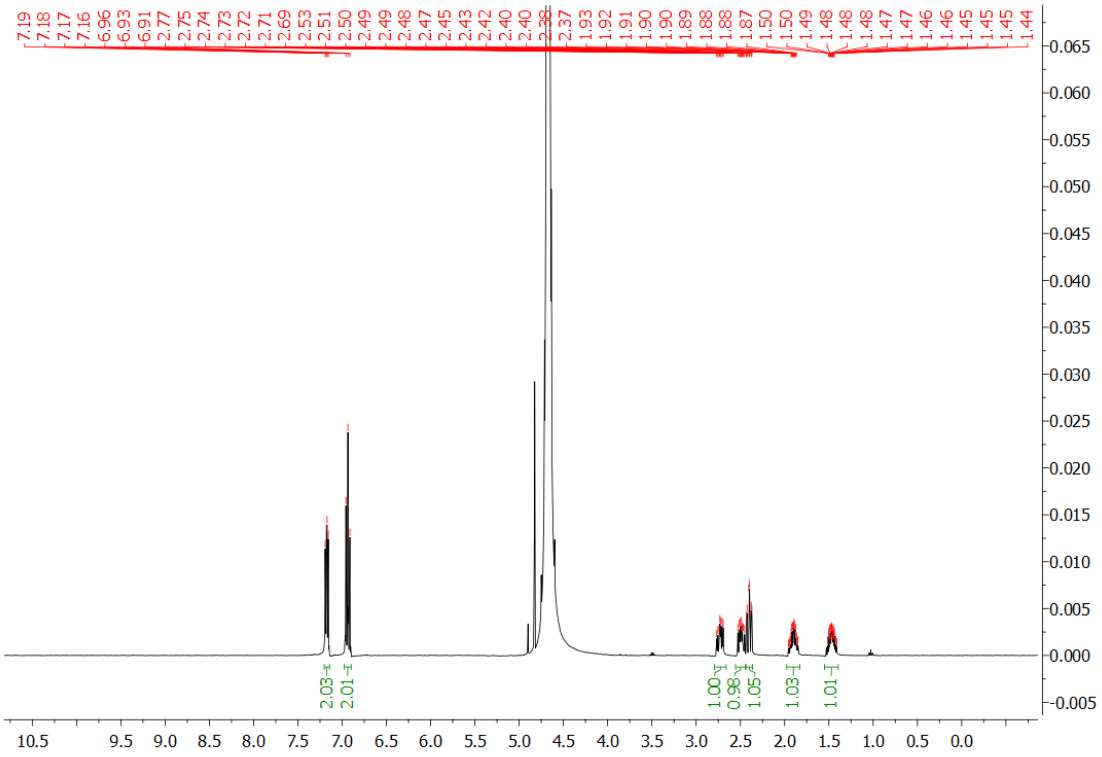

114.39
114.40
114.41
114.41
114.43
114.44
114.46
1.00

D

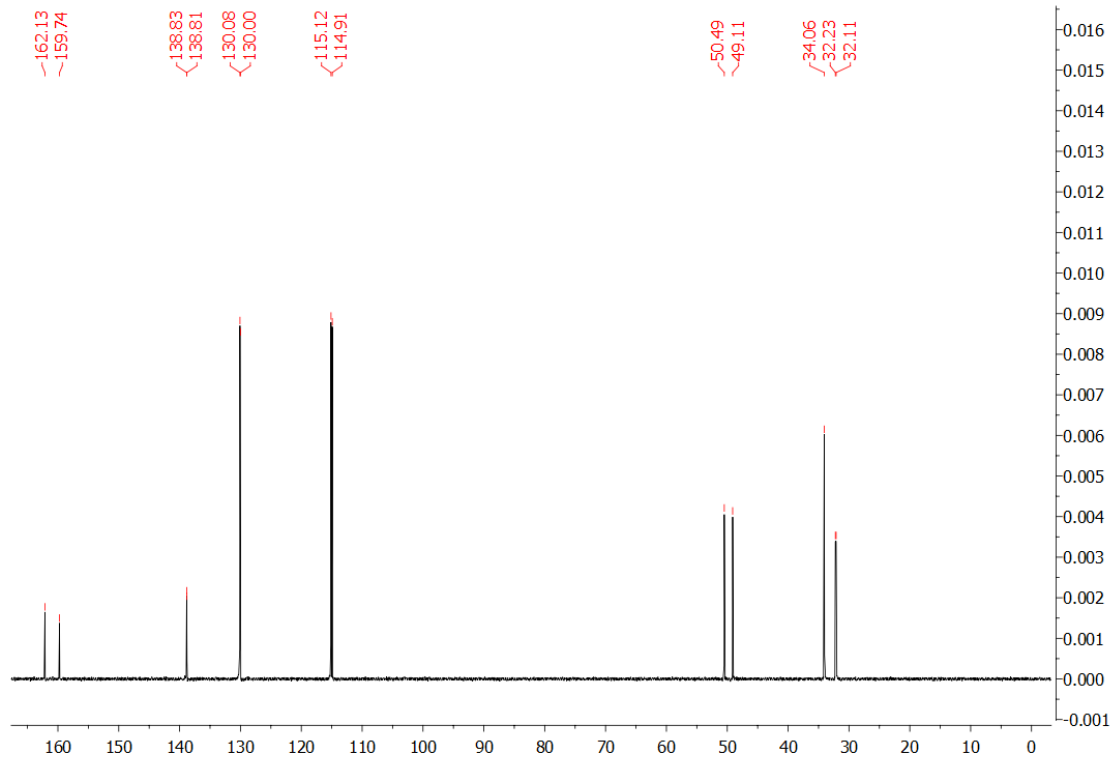


694 **Figure S10-4.** ^{1}H (**A**),^{13}C (**B**), ^{19}F (**C**), ^{31}P (**D**) NMR spectra for compound **15d**.

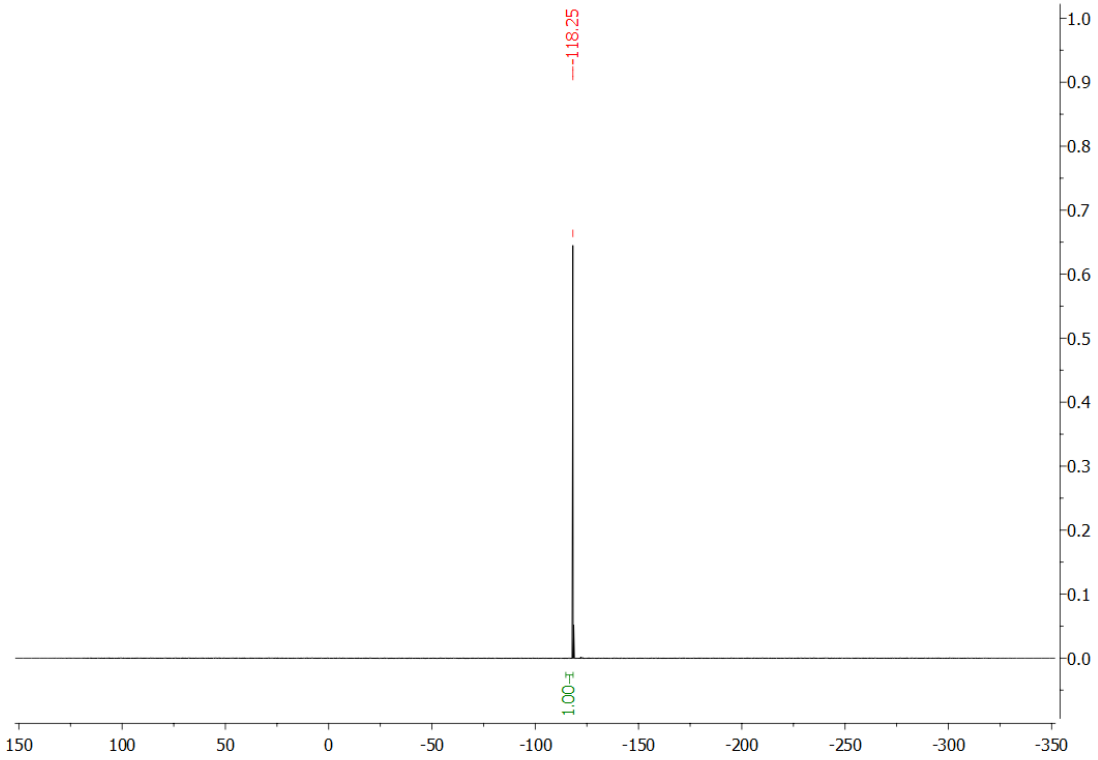
A



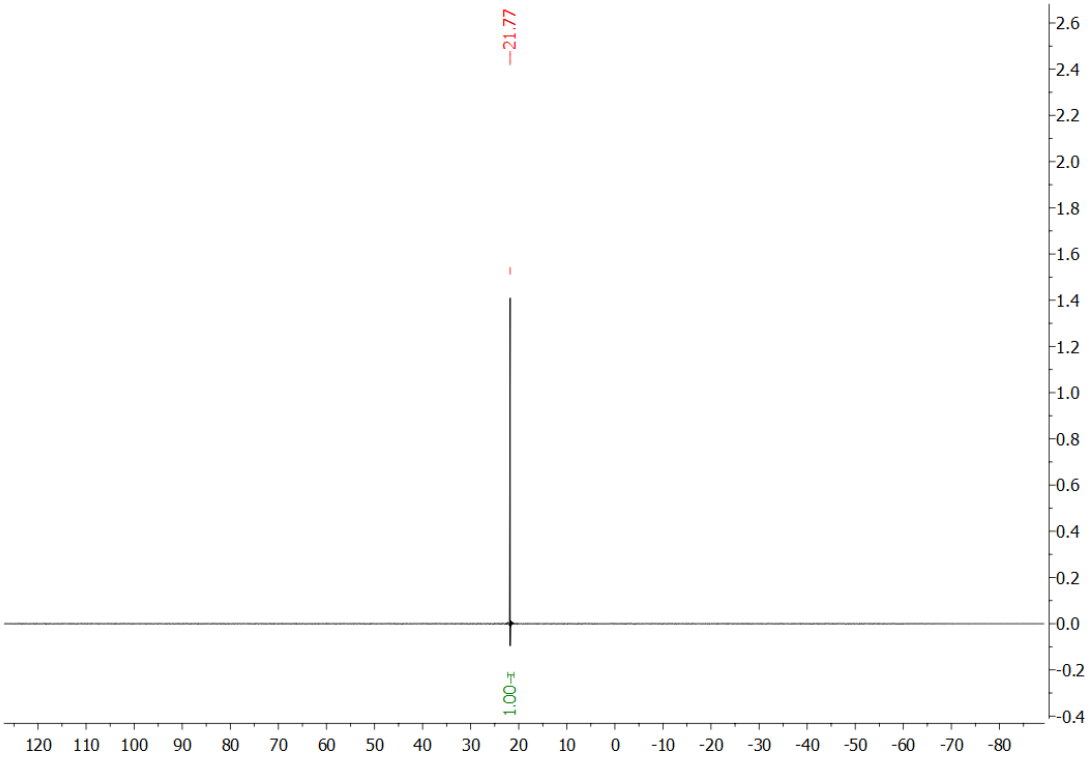
B


162.13
159.74
138.83
138.81
130.08
130.00
115.12
114.91
50.49
49.11
34.06
32.23
32.11

C

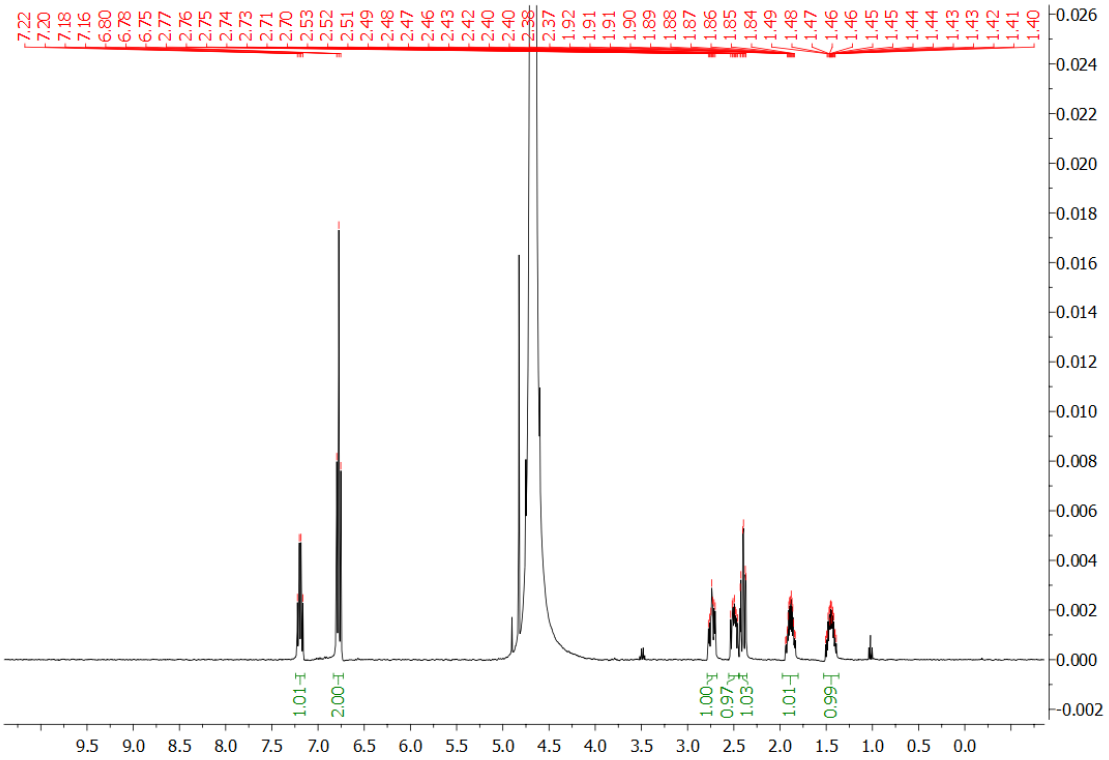

-118.25
1.00

D

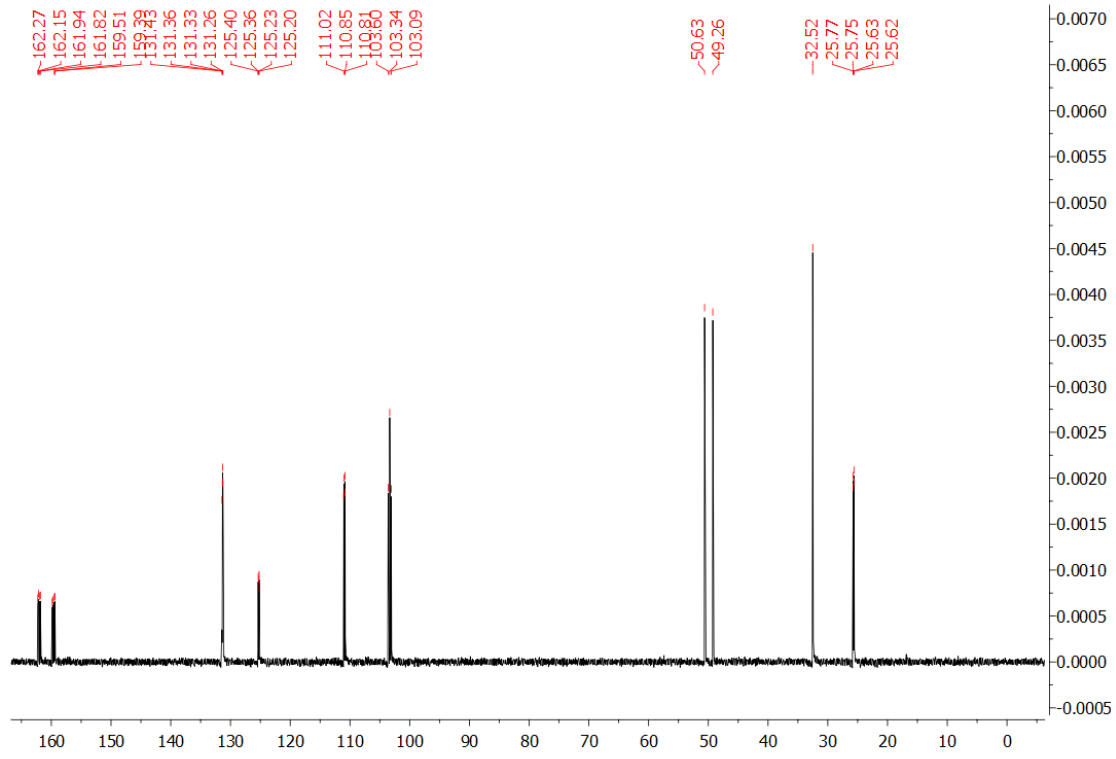


695 **Figure S10-5.** ^{1}H (**A**),^{13}C (**B**), ^{19}F (**C**), ^{31}P (**D**) NMR spectra for compound **15e**.

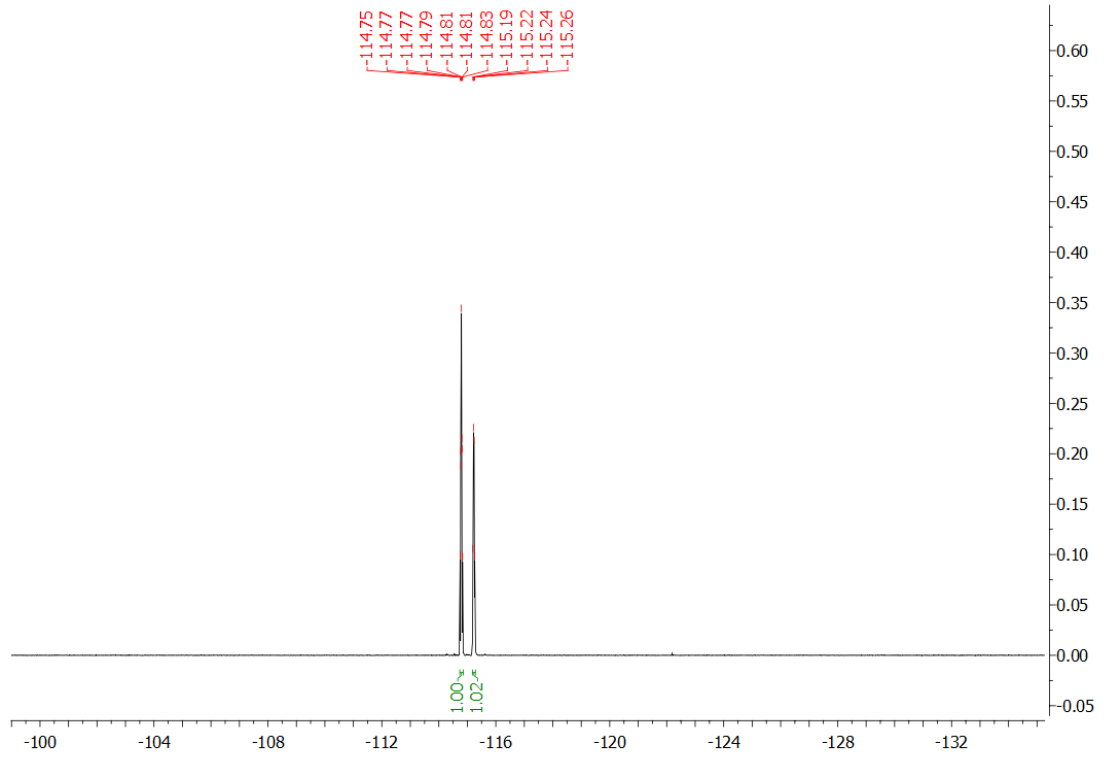
A



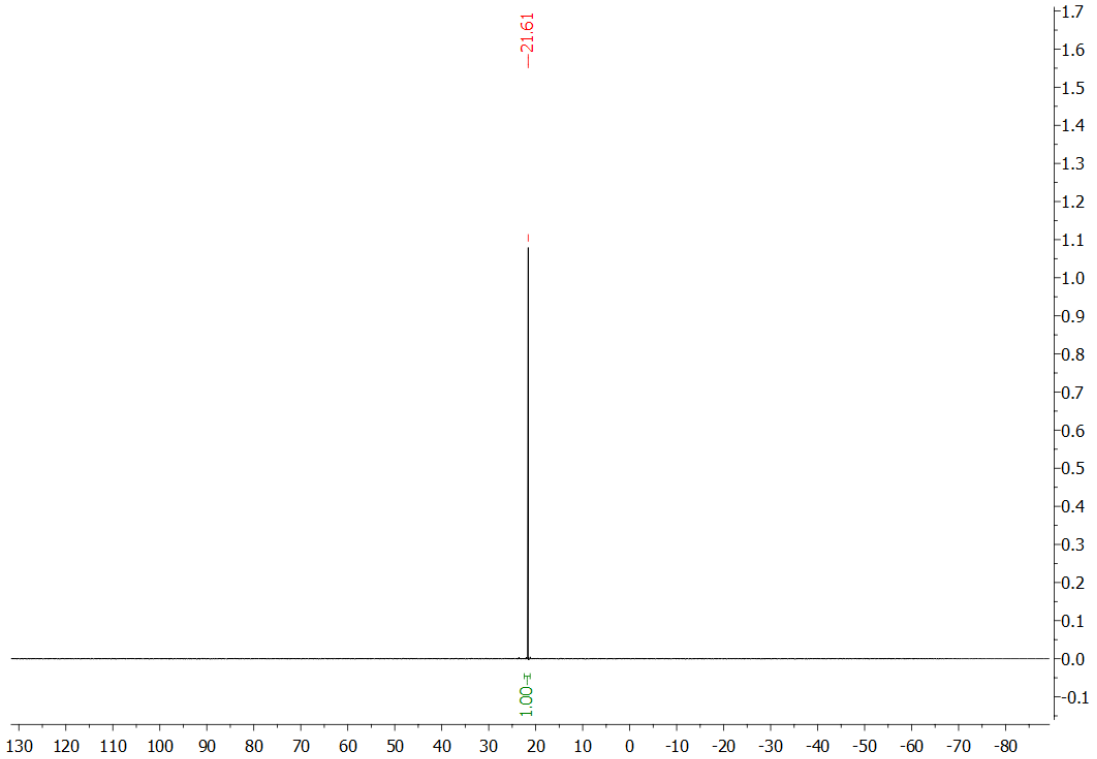
B


162.27
162.15
161.94
161.82
159.51
131.36
131.33
131.26
125.40
125.36
125.23
125.20
111.02
110.85
103.80
103.34
103.09
50.63
49.26
32.52
25.77
25.75
25.63
25.62
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

C

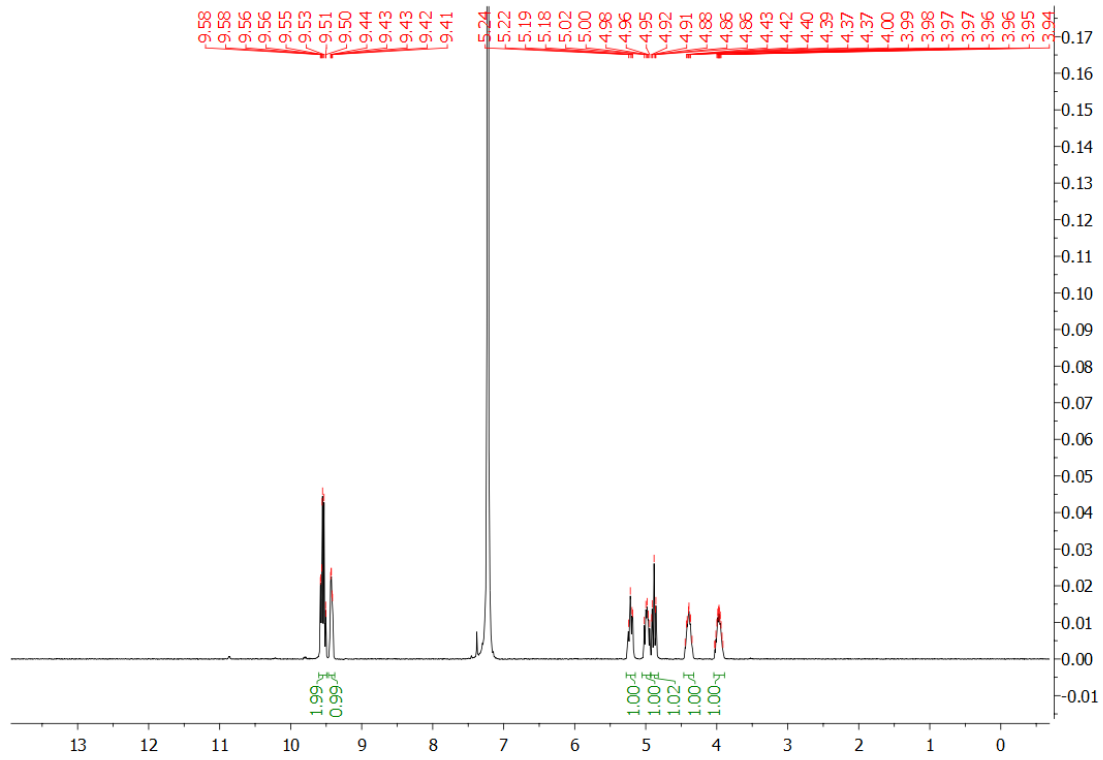

-114.75
-114.77
-114.77
-114.79
-114.81
-114.81
-114.83
-115.19
-115.22
-115.24
-115.26
1.00
1.02
-100
-104
-108
-112
-116
-120
-124
-128
-132

D

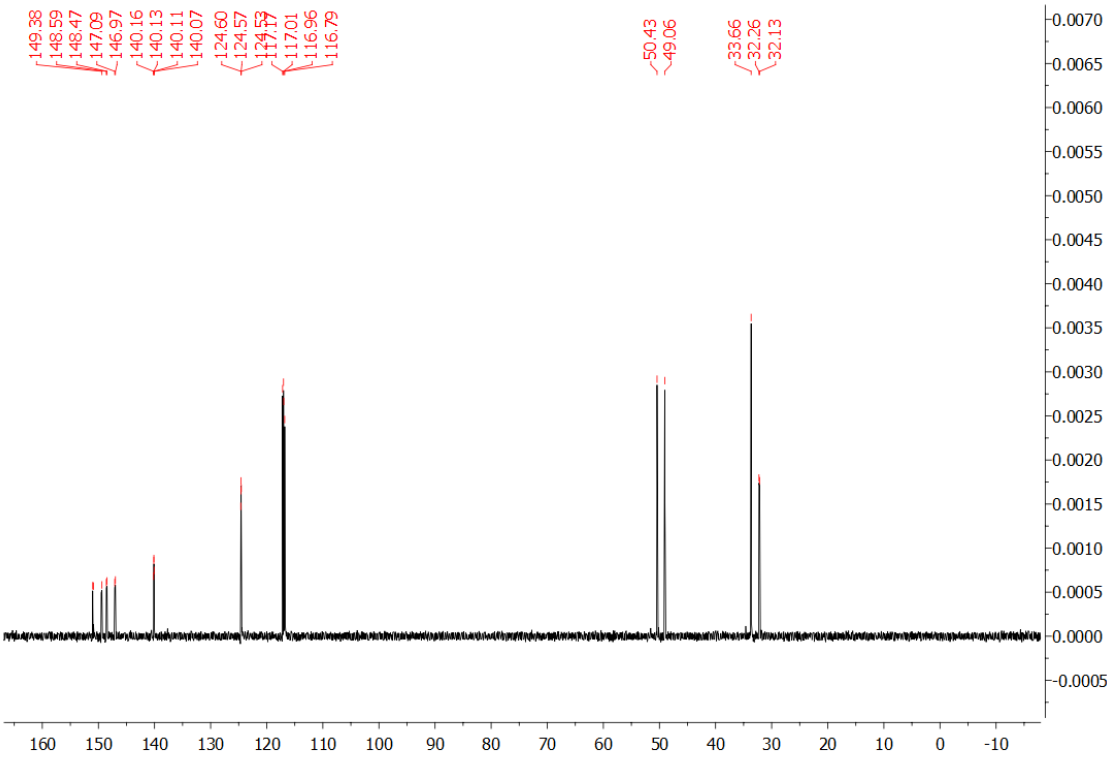


696 **Figure S10-6.** ^{1}H (**A**),^{13}C (**B**), ^{19}F (**C**), ^{31}P (**D**) NMR spectra for compound **15f**.

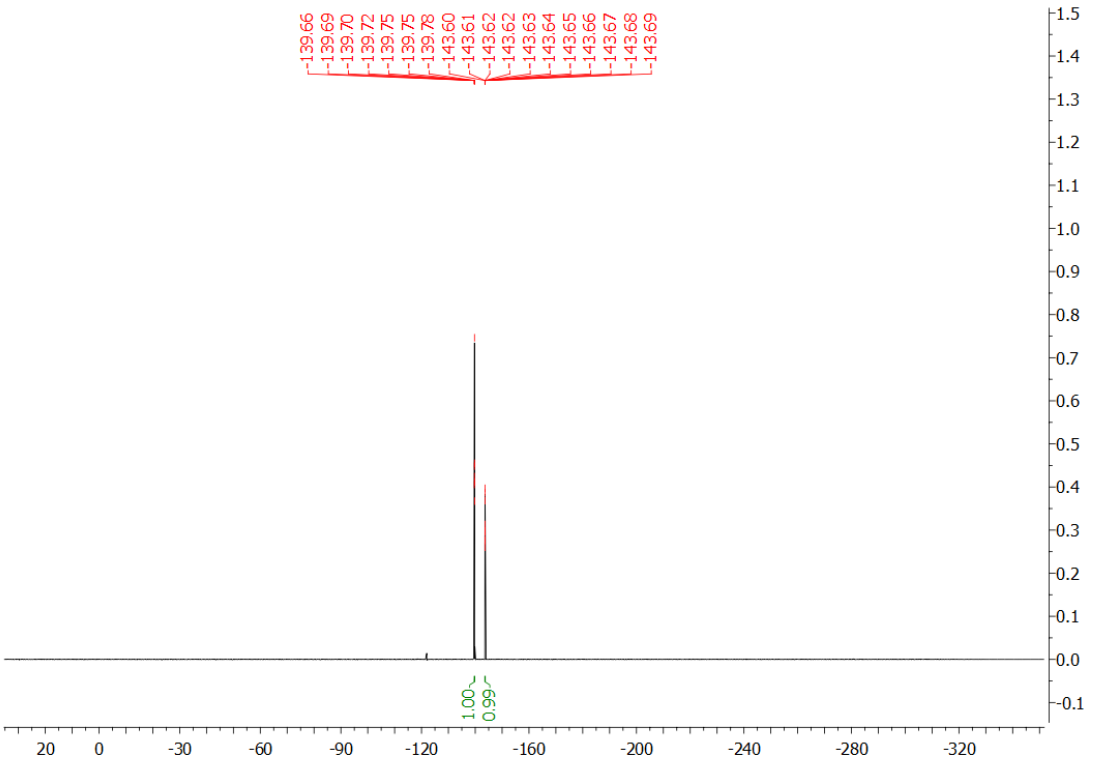
A



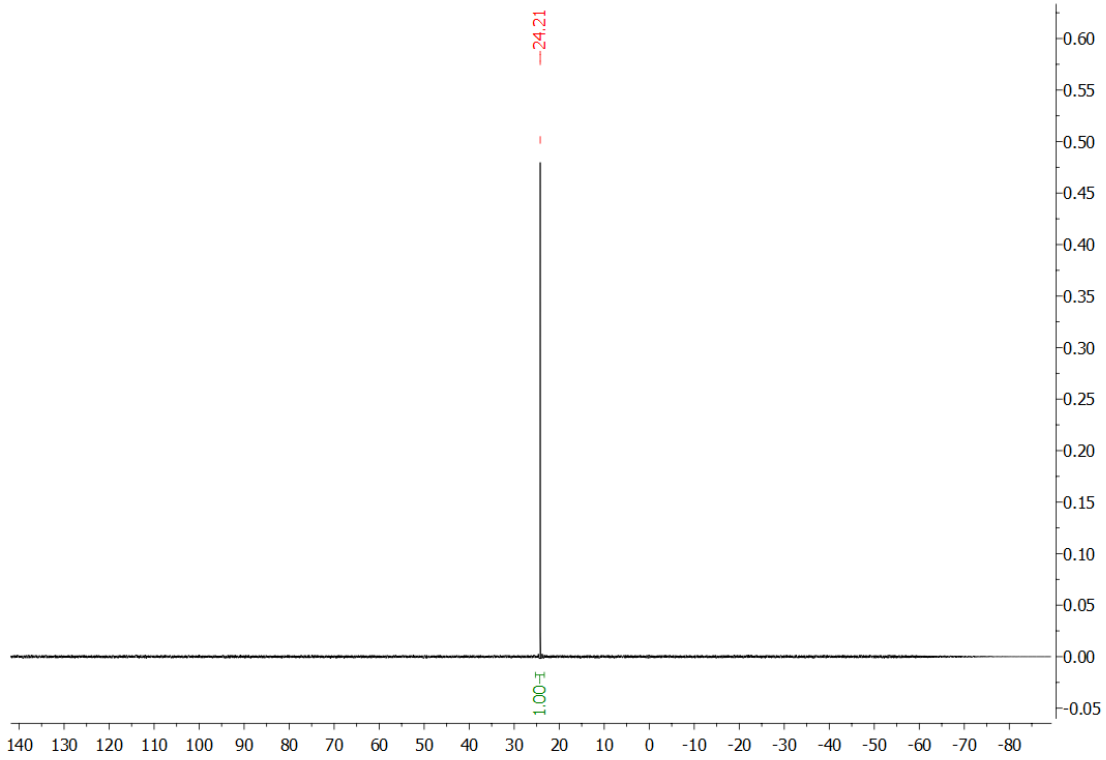
B


149.38
148.59
148.47
147.09
146.97
140.16
140.13
140.11
140.07
124.60
124.57
124.53
117.17
117.01
116.96
116.79
50.43
49.06
33.66
32.26
32.13
0.0070
0.0065
0.0060
0.0055
0.0050
0.0045
0.0040
0.0035
0.0030
0.0025
0.0020
0.0015
0.0010
0.0005
0.0000
-0.0005
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10

C

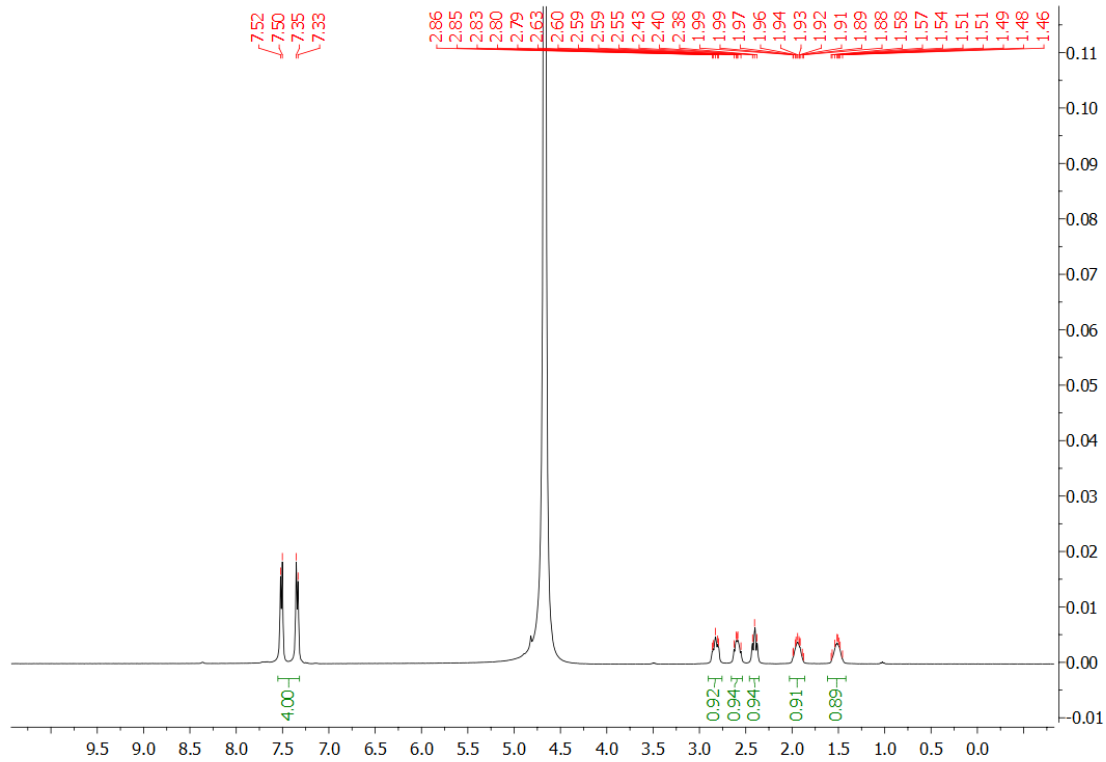

139.66
139.69
139.70
139.72
139.75
139.75
139.78
143.60
143.61
143.62
143.62
143.63
143.64
143.65
143.66
143.67
143.68
143.69
1.5
1.4
1.3
1.2
1.1
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
-0.1
1.00
0.99
20
0
-30
-60
-90
-120
-160
-200
-240
-280
-320

D

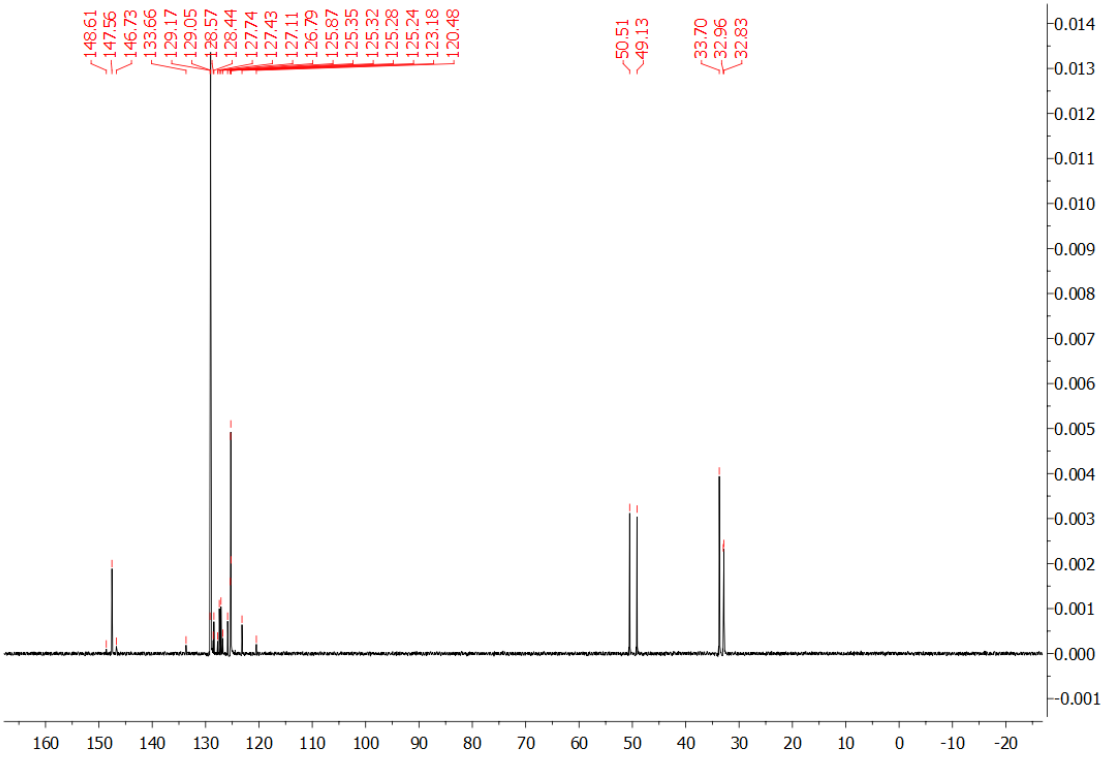


697 **Figure S10-7.** ^{1}H (**A**),^{13}C (**B**), ^{19}F (**C**), ^{31}P (**D**) NMR spectra for compound **15g**.

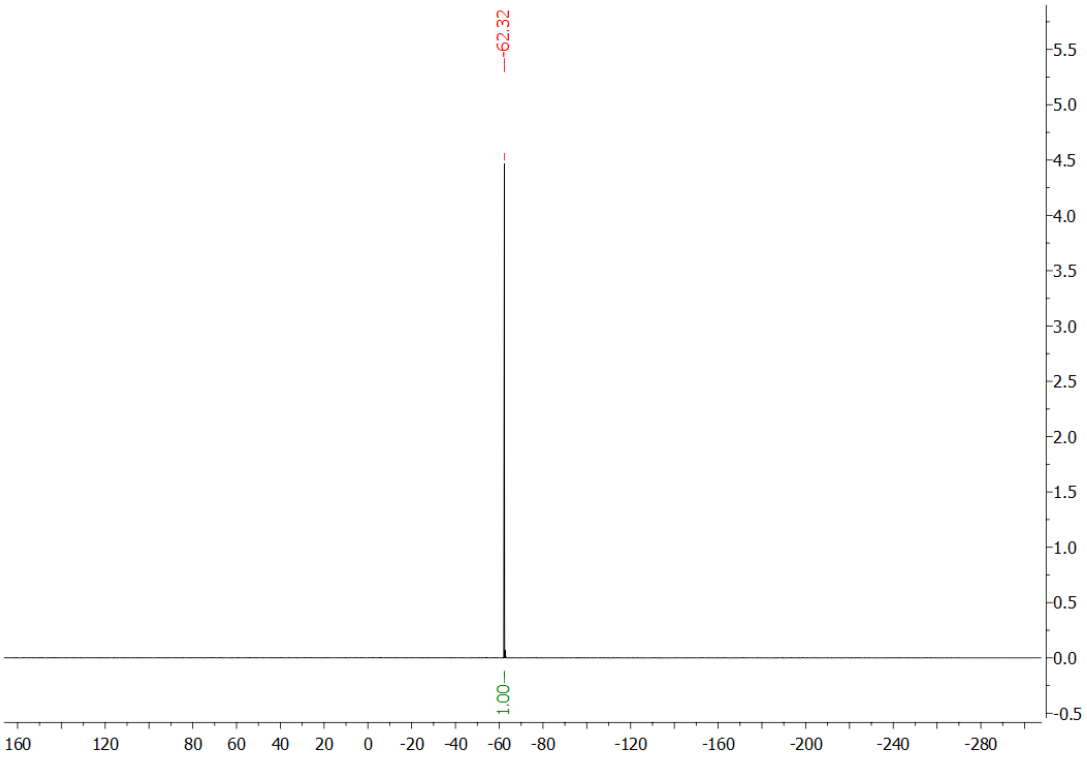
A



B


148.61
147.56
146.73
133.66
129.17
129.05
128.57
128.44
127.74
127.43
127.11
126.79
125.87
125.35
125.32
125.28
125.24
123.18
120.48
50.51
49.13
33.70
32.96
32.83

C


-62.32
1.00

D

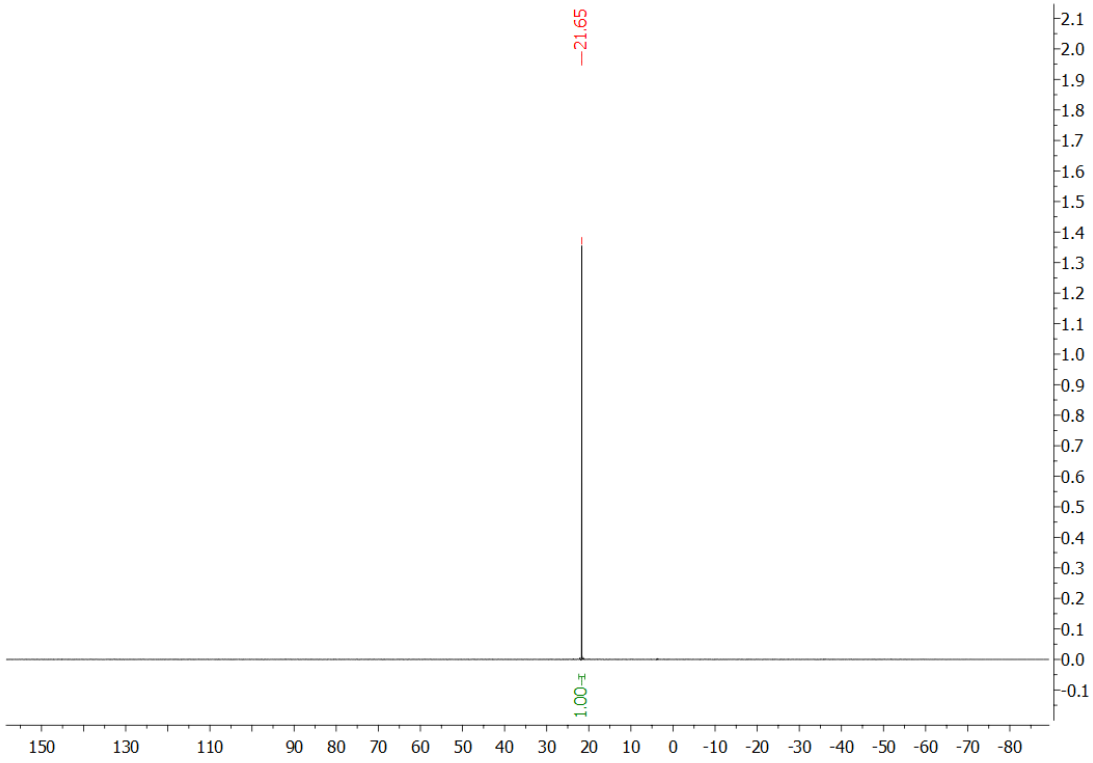
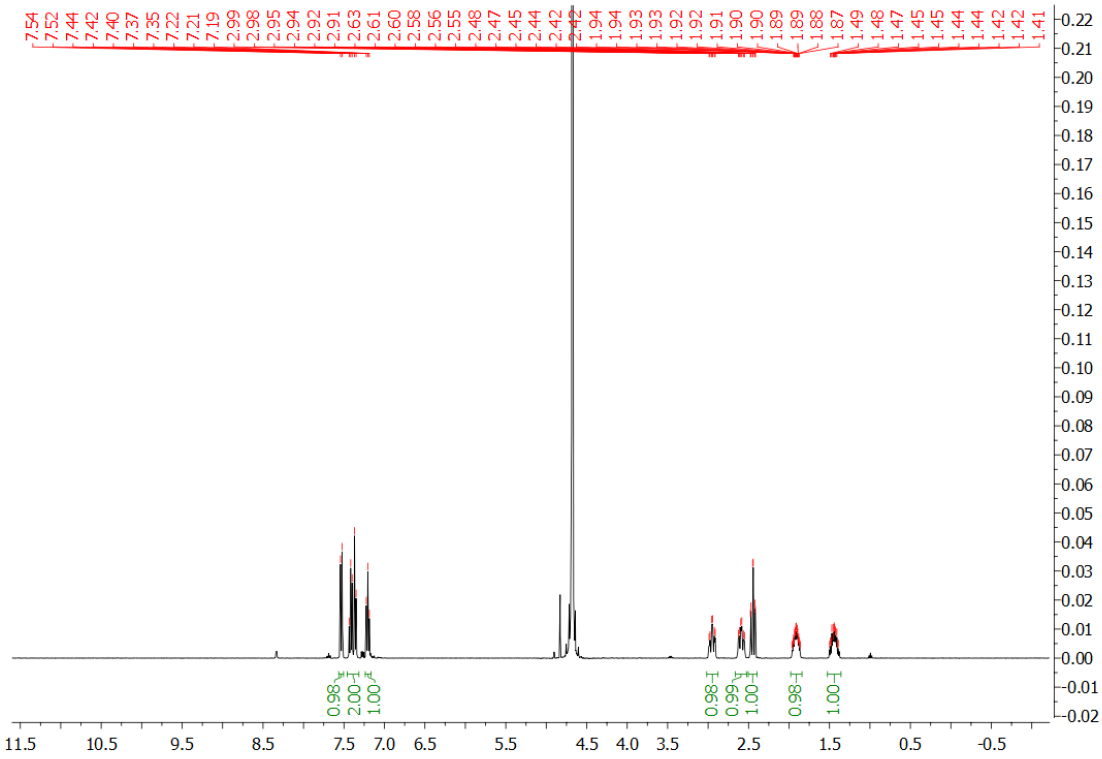
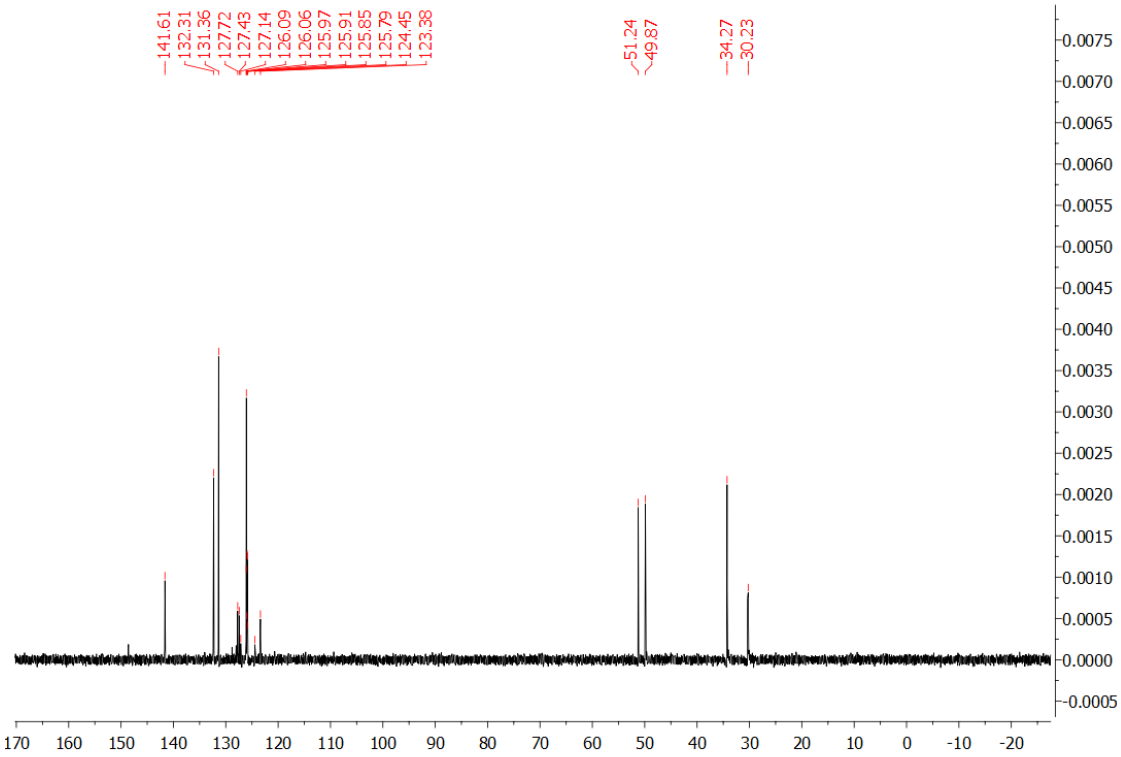


Figure S10-8. ^{1}H (**A**),^{13}C (**B**), ^{19}F (**C**), ^{31}P (**D**) NMR spectra for compound **15h**.

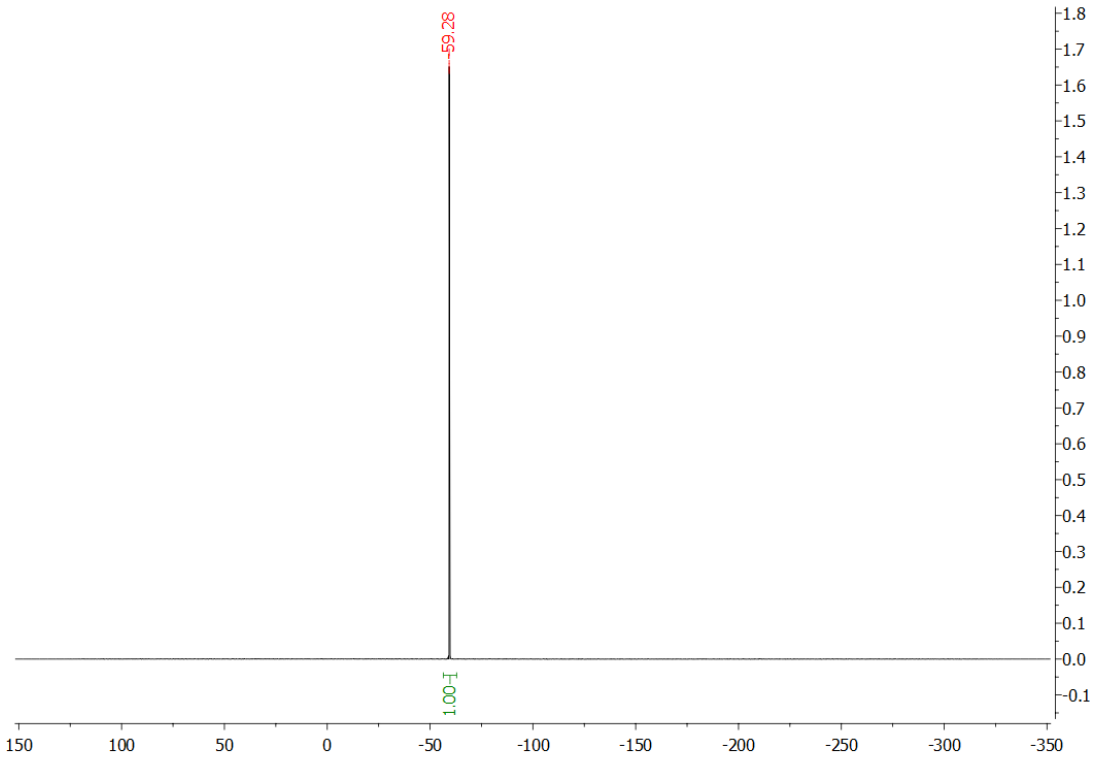
A



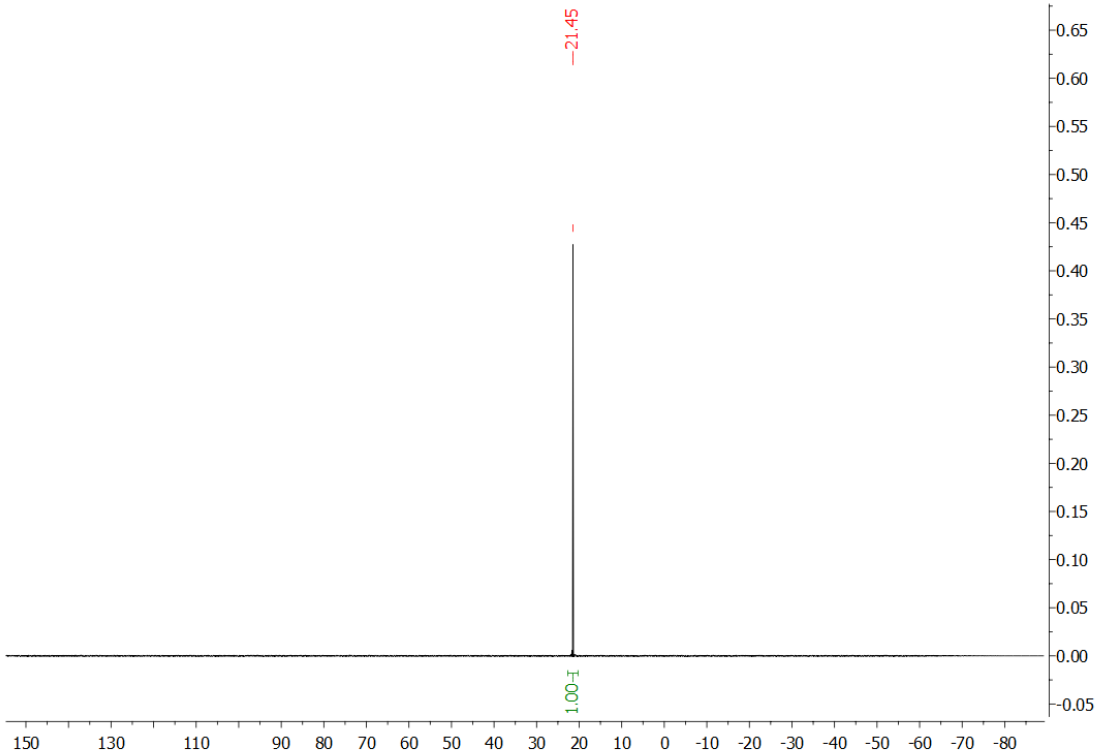
B


141.61
132.31
131.36
127.72
127.43
127.14
126.09
126.06
125.97
125.91
125.85
125.79
124.45
123.38
51.24
49.87
34.27
30.23

C

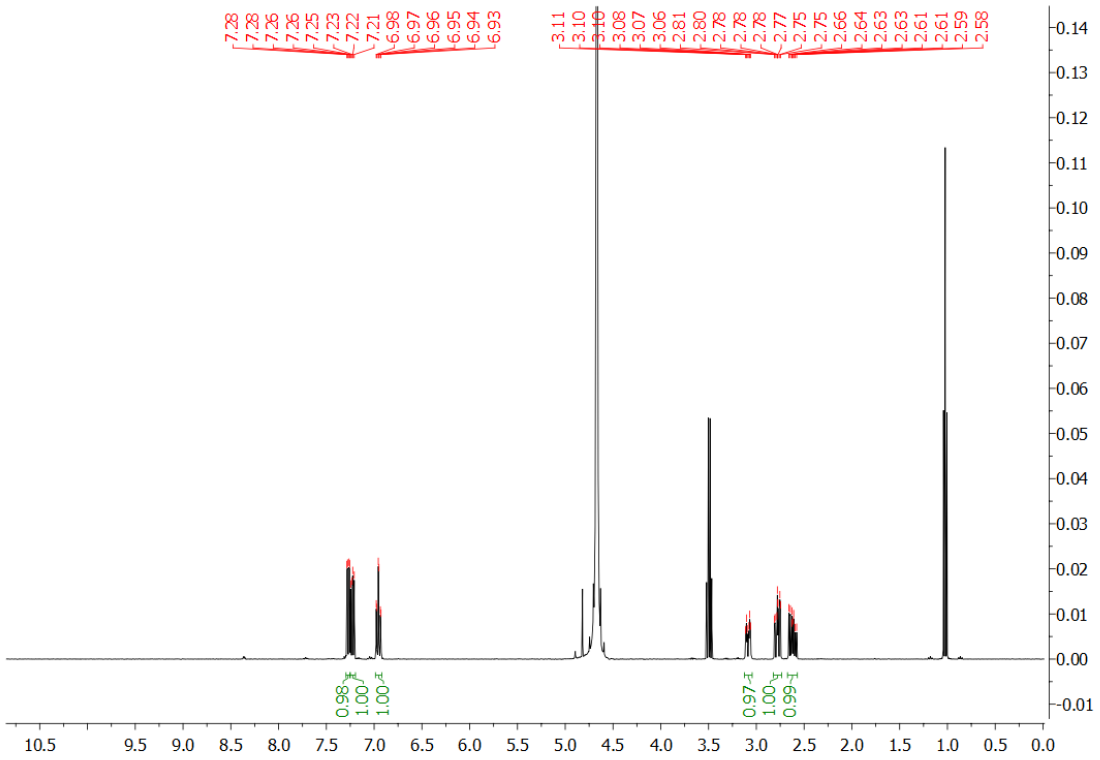

59.28
1.00

D

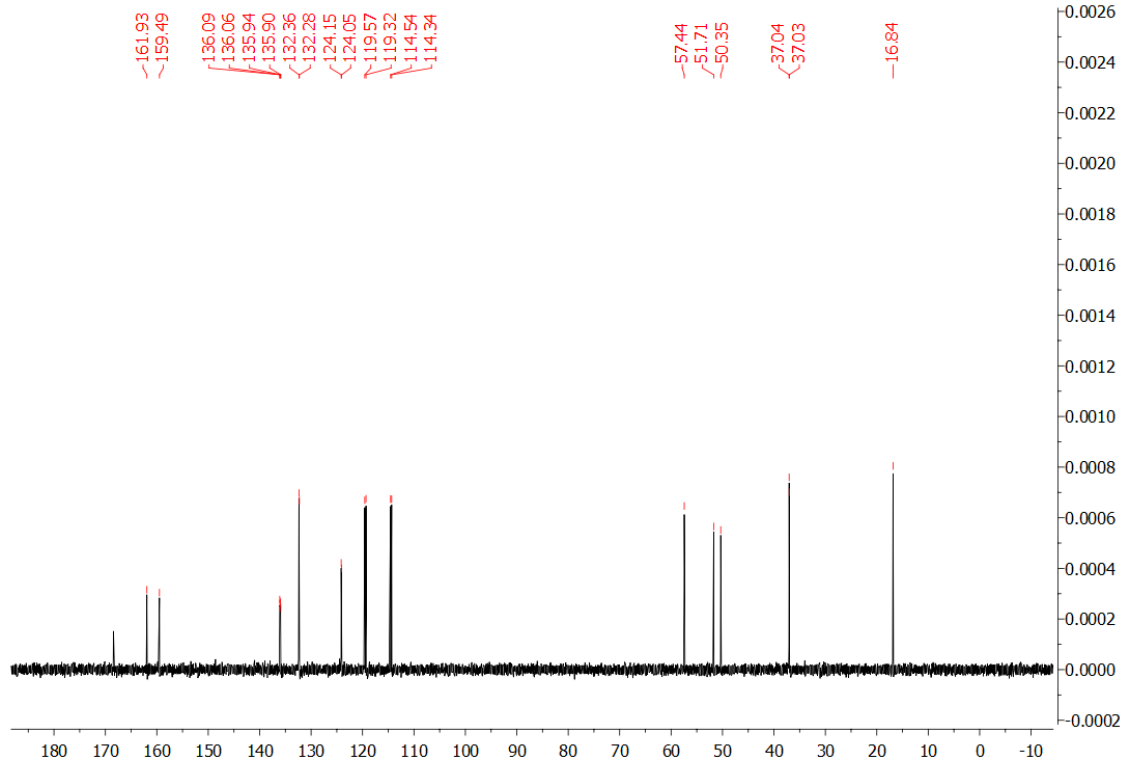


699 **Figure S10-9.** ^{1}H (**A**),^{13}C (**B**), ^{19}F (**C**), ^{31}P (**D**) NMR spectra for compound **17a**.

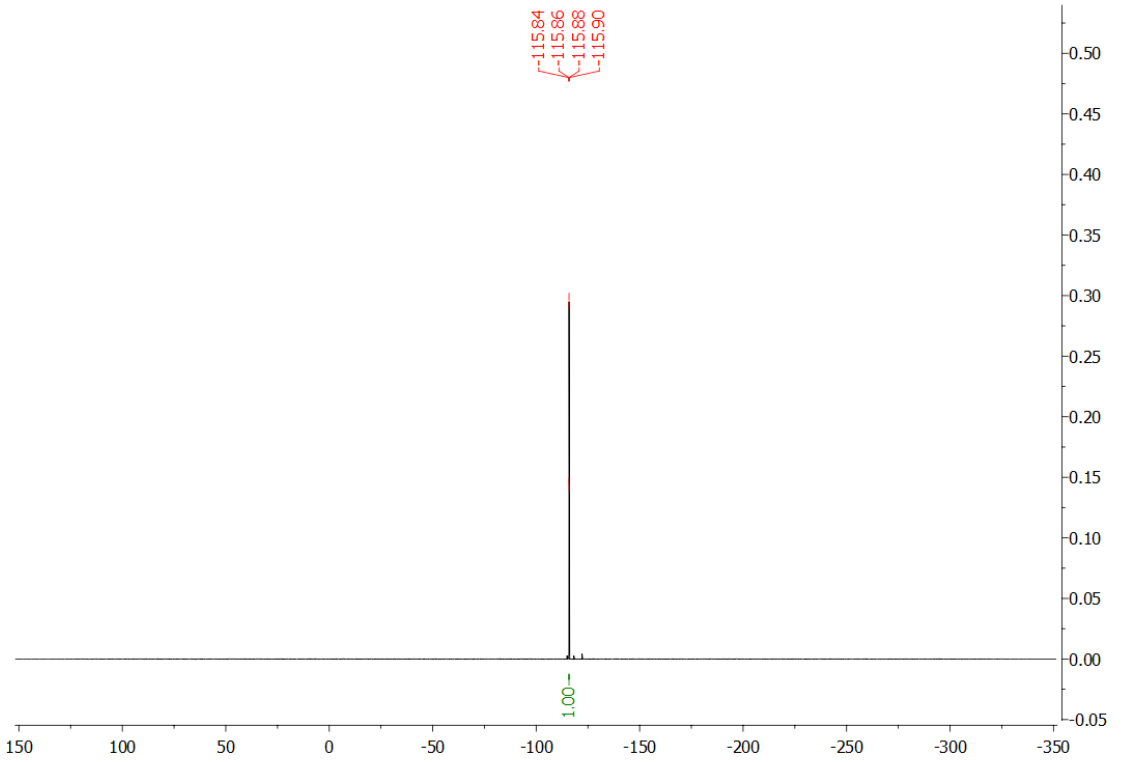
A



B


161.93
159.49
136.09
136.06
135.94
135.90
132.36
132.28
124.15
124.05
119.57
119.32
114.54
114.34
57.44
51.71
50.35
37.04
37.03
16.84
0.0026
0.0024
0.0022
0.0020
0.0018
0.0016
0.0014
0.0012
0.0010
0.0008
0.0006
0.0004
0.0002
0.0000
-0.0002
180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10

C


115.84
115.86
115.88
115.90
1.00
0.50
0.45
0.40
0.35
0.30
0.25
0.20
0.15
0.10
0.05
0.00
-0.05
150 100 50 0 -50 -100 -150 -200 -250 -300 -350

D

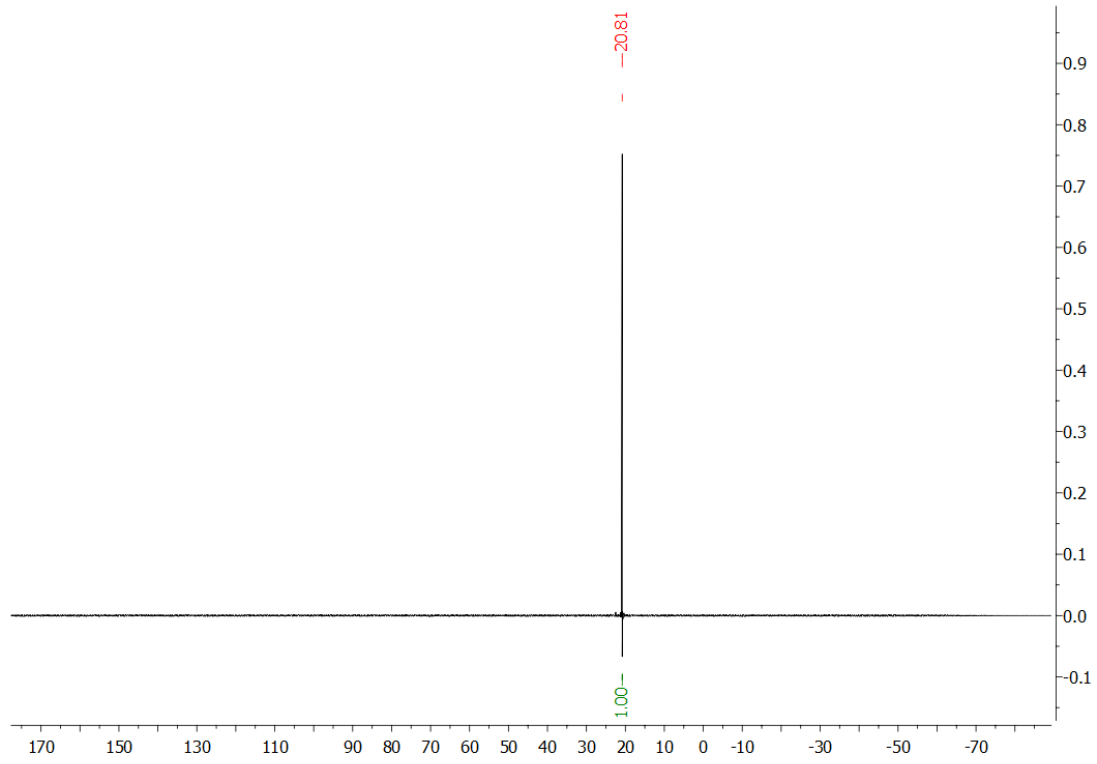
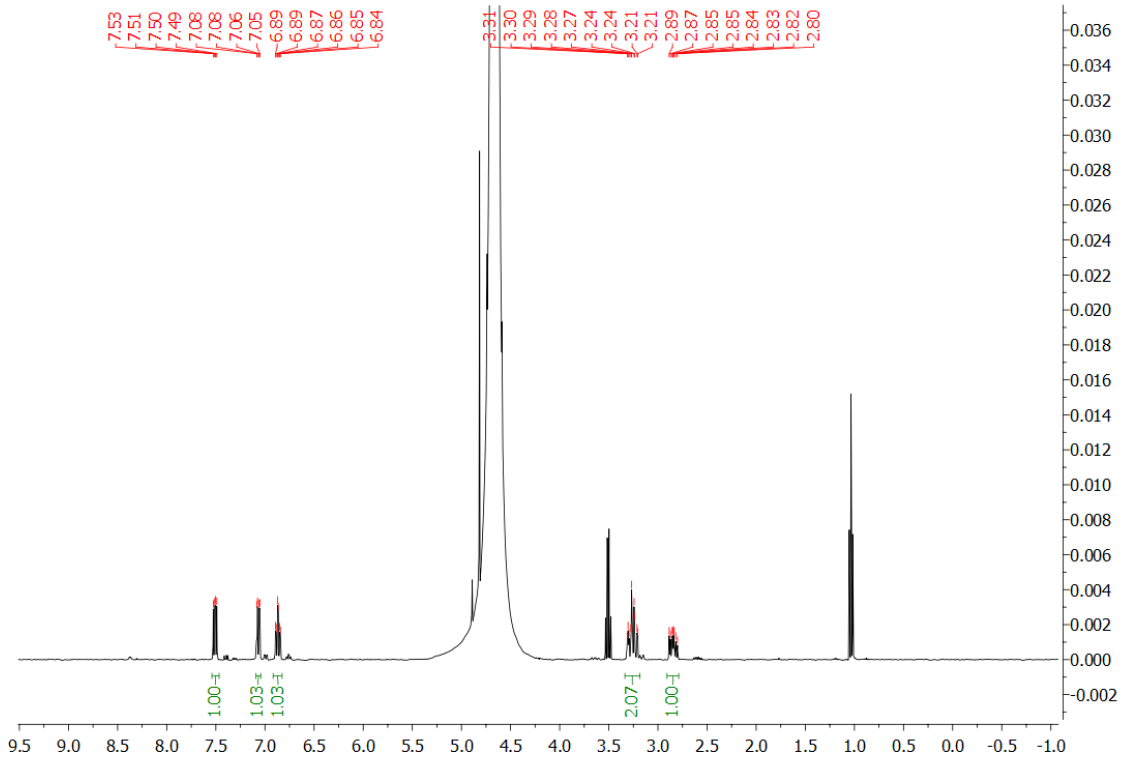
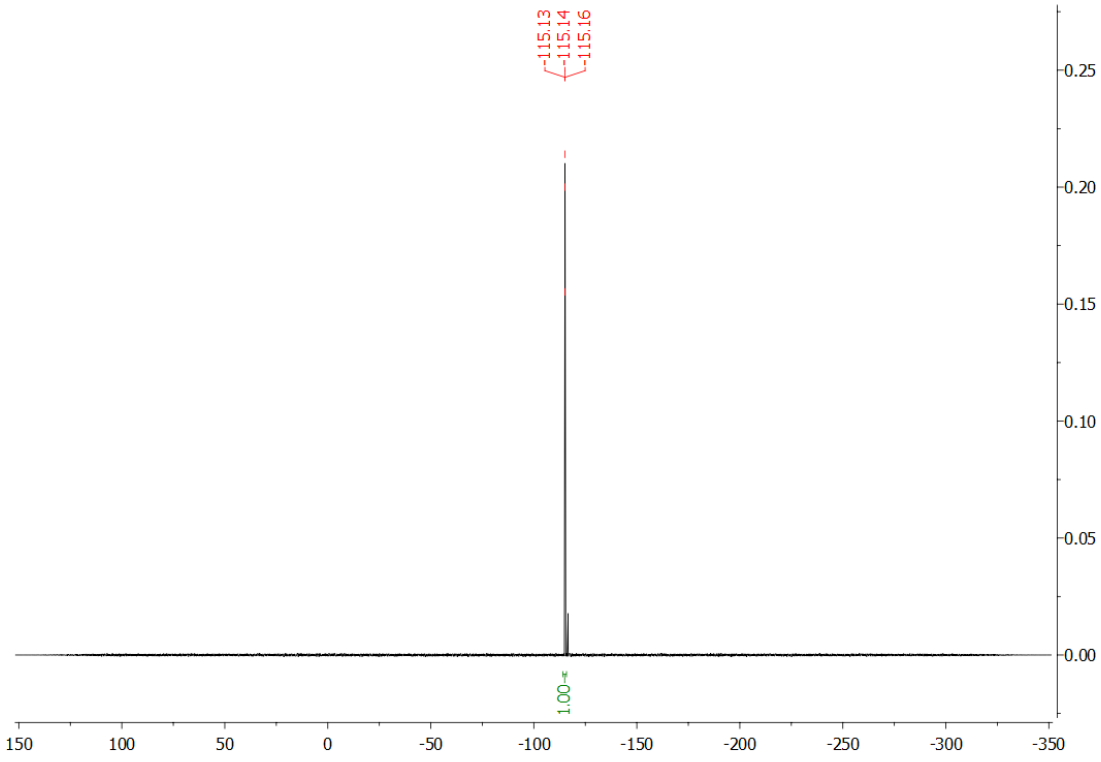


Figure S10-10. ^{1}H (**A**), ^{19}F (**B**), ^{31}P (**C**) NMR spectra for compound **17b**.

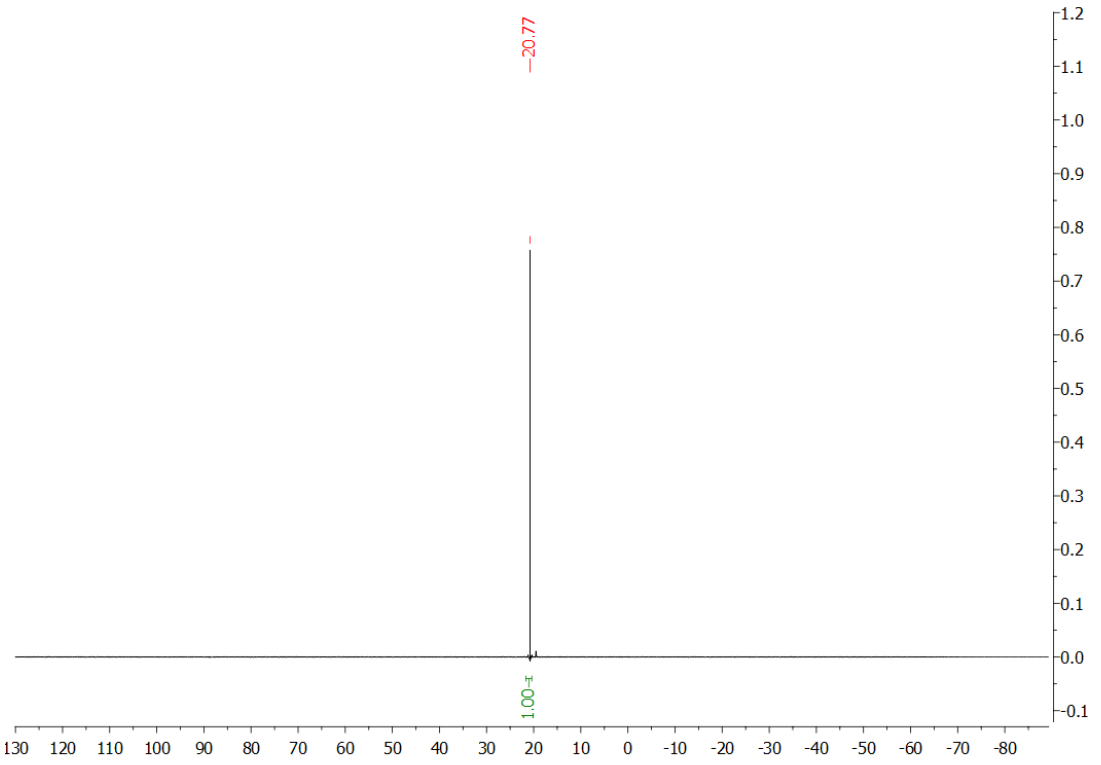
A



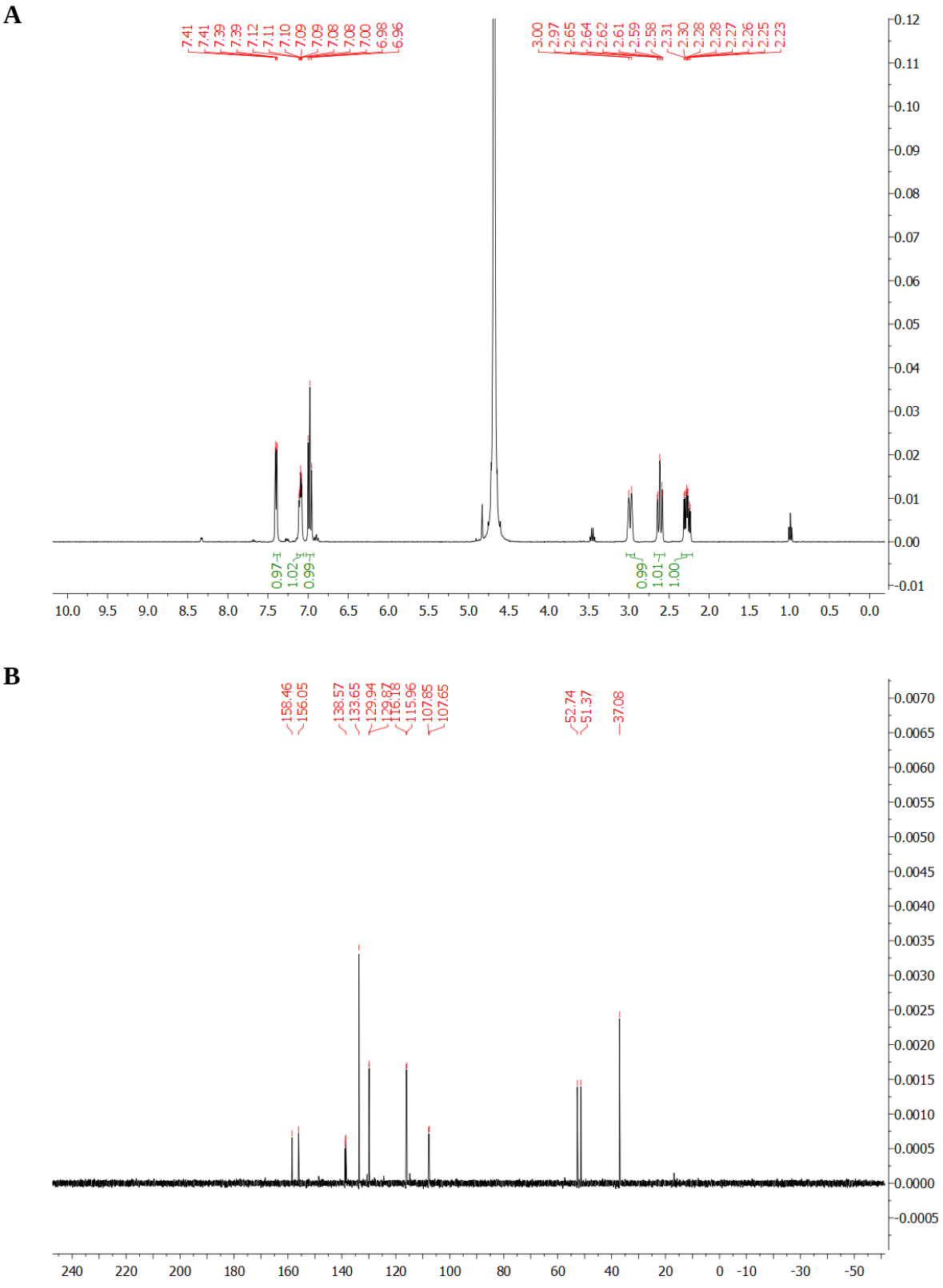
B


-115.13
-115.14
-115.16
0.25
0.20
0.15
0.10
0.05
0.00
1.00
150
100
50
0
-50
-100
-150
-200
-250
-300
-350

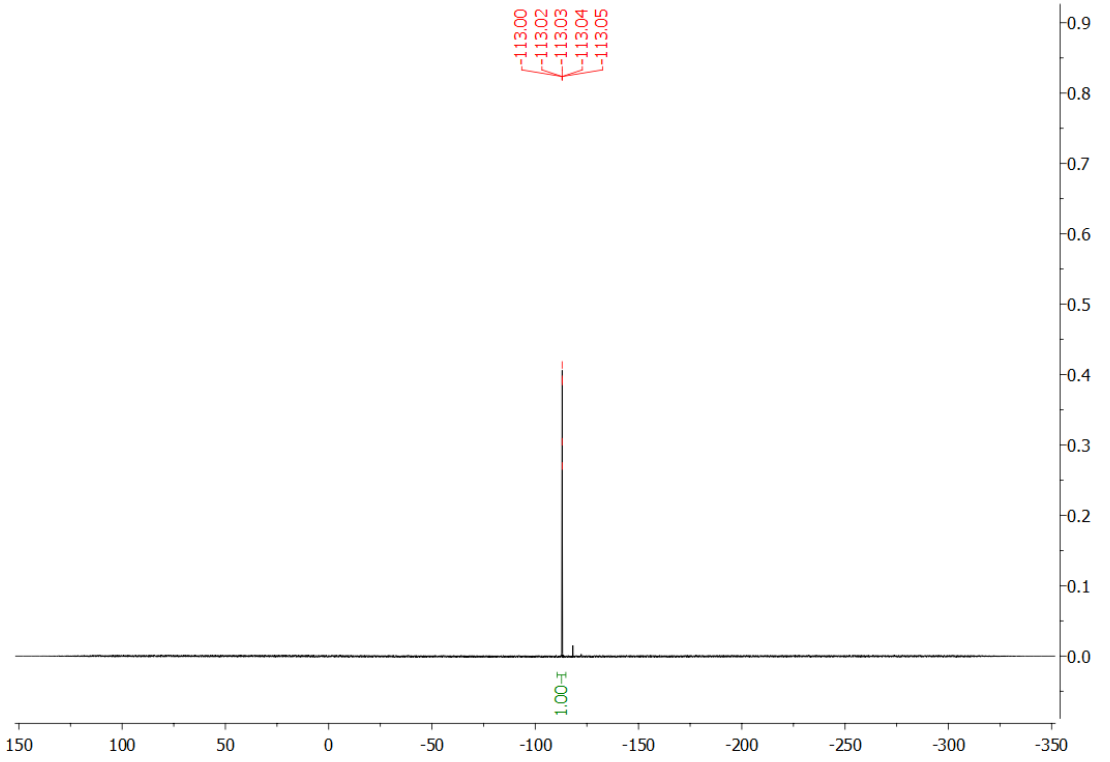
C


-20.77
1.2
1.1
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
-0.1
1.00
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
-20
-30
-40
-50
-60
-70
-80

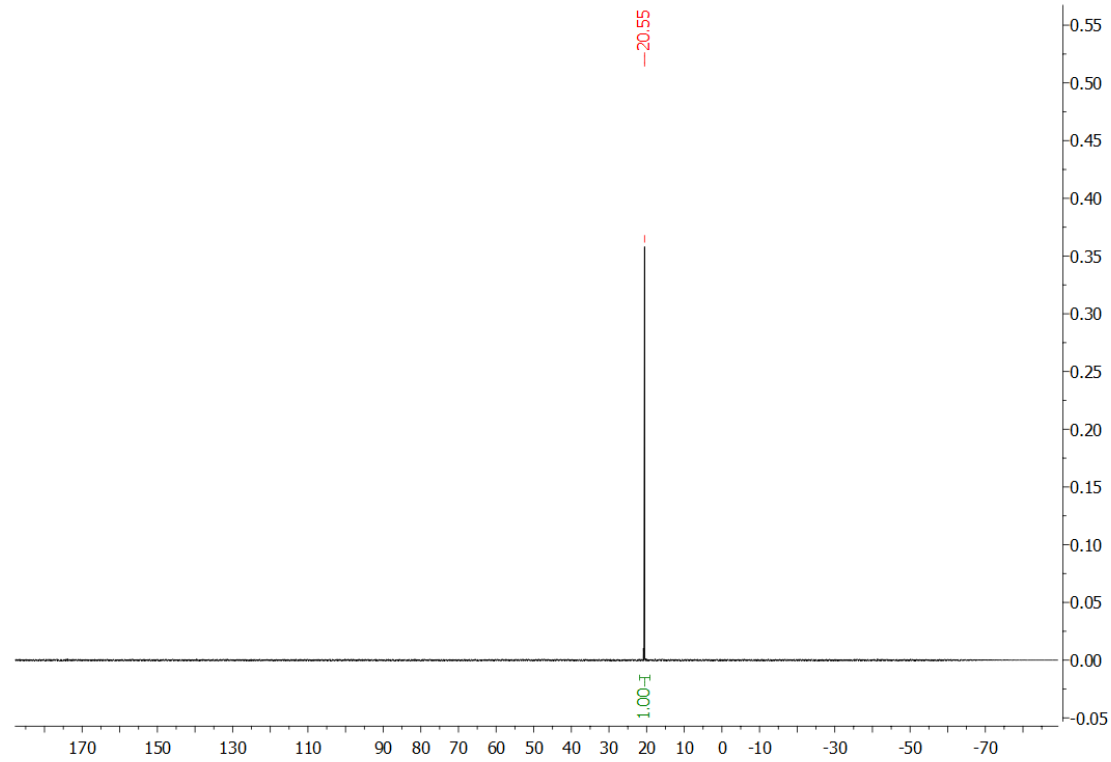
707
708 **Figure S10-11.** ^{1}H (**A**),^{13}C (**B**), ^{19}F (**C**), ^{31}P (**D**) NMR spectra for compound **17c**.



C



D



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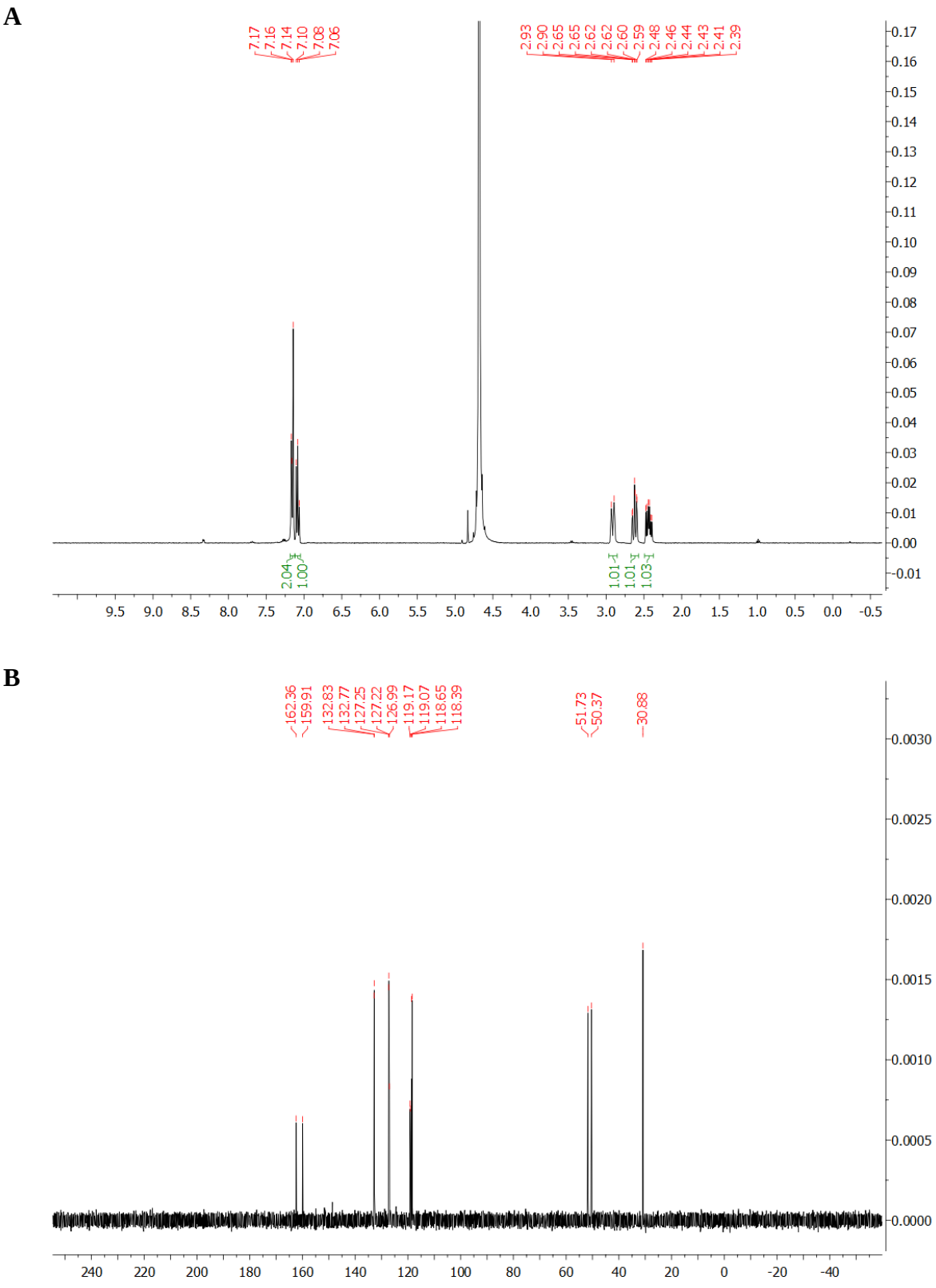
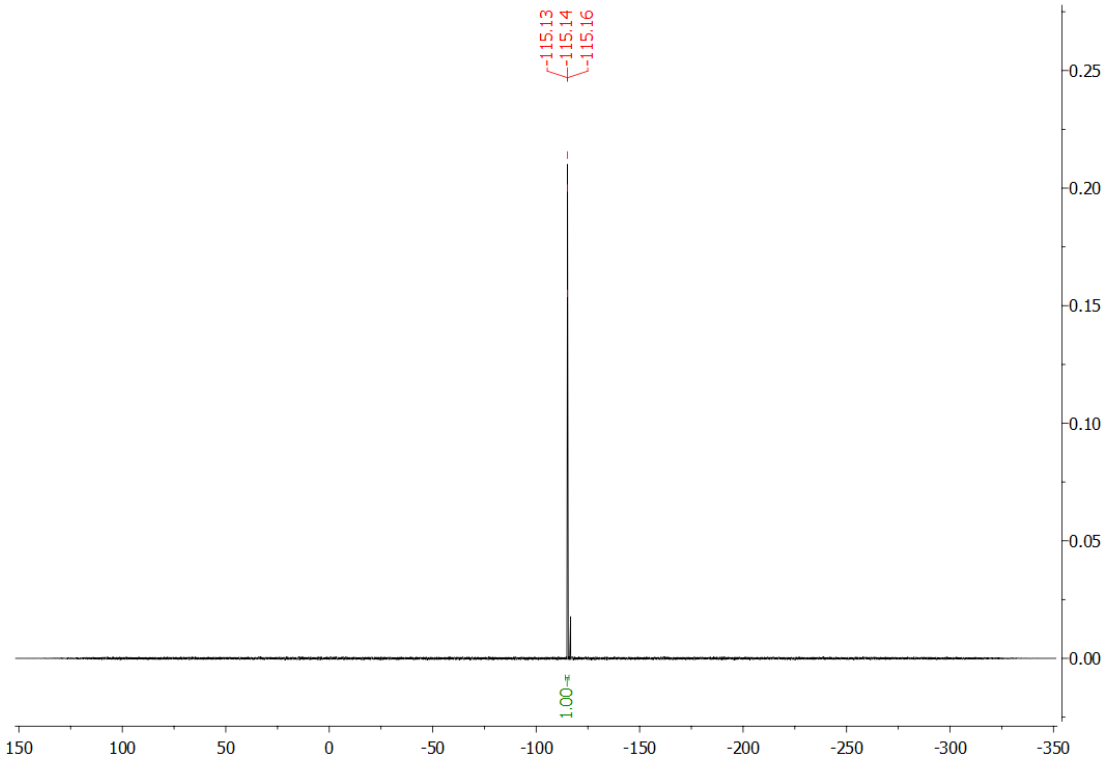
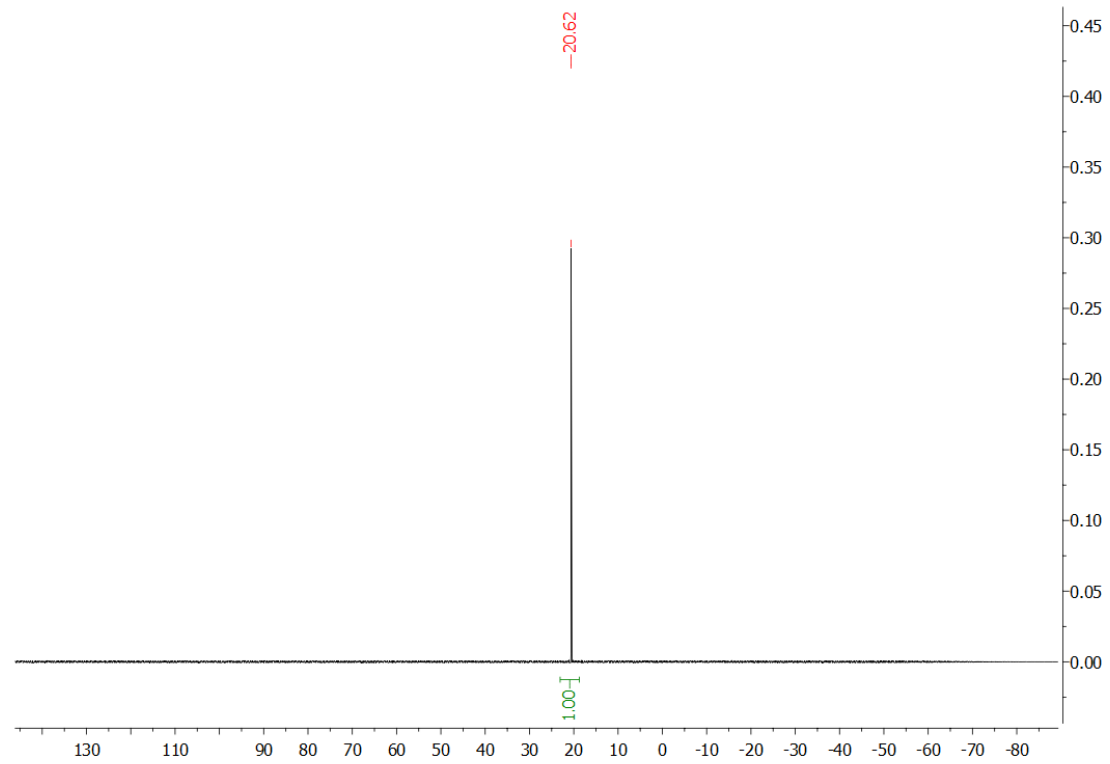
715 **Figure S10-12.** ^{1}H (**A**),^{13}C (**B**), ^{19}F (**C**), ^{31}P (**D**) NMR spectra and HPLC (**E**) for compound **17d**.



C


-115.13
-115.14
-115.16
0.25
0.20
0.15
0.10
0.05
0.00
1.00
150
100
50
0
-50
-100
-150
-200
-250
-300
-350

D


-20.62
0.45
0.40
0.35
0.30
0.25
0.20
0.15
0.10
0.05
0.00
1.00
130
110
90
80
70
60
50
40
30
20
10
0
-10
-20
-30
-40
-50
-60
-70
-80

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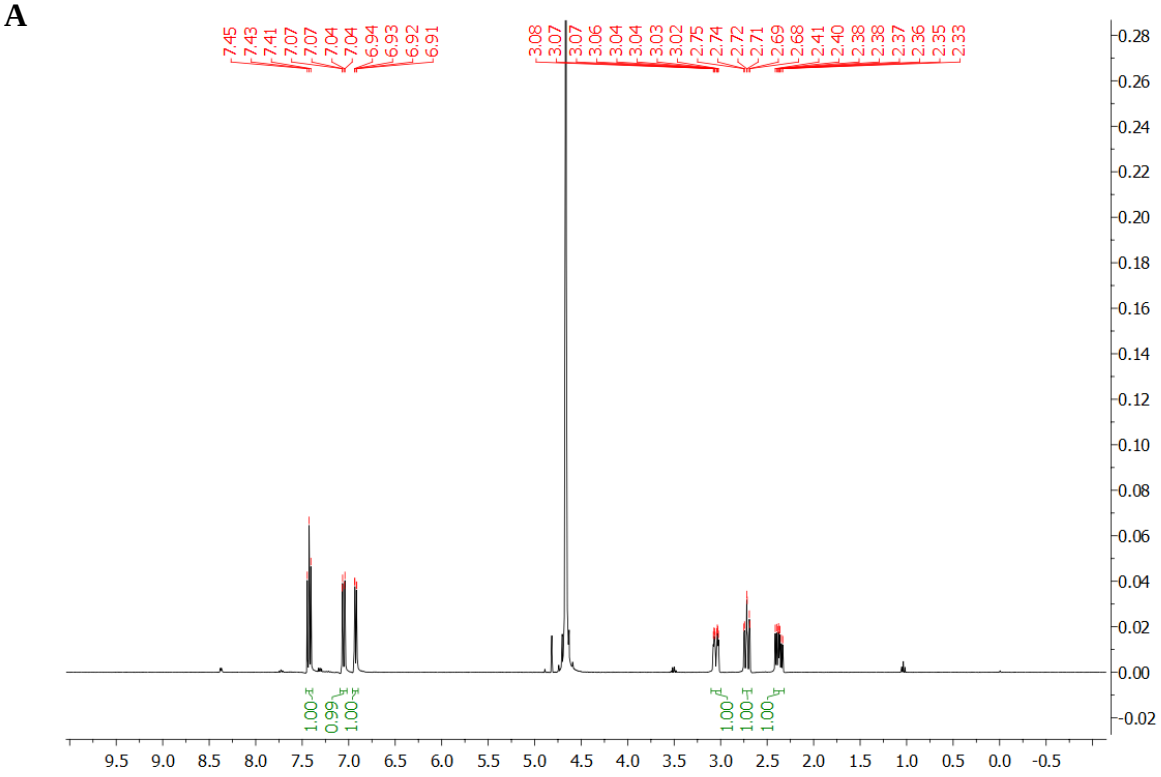
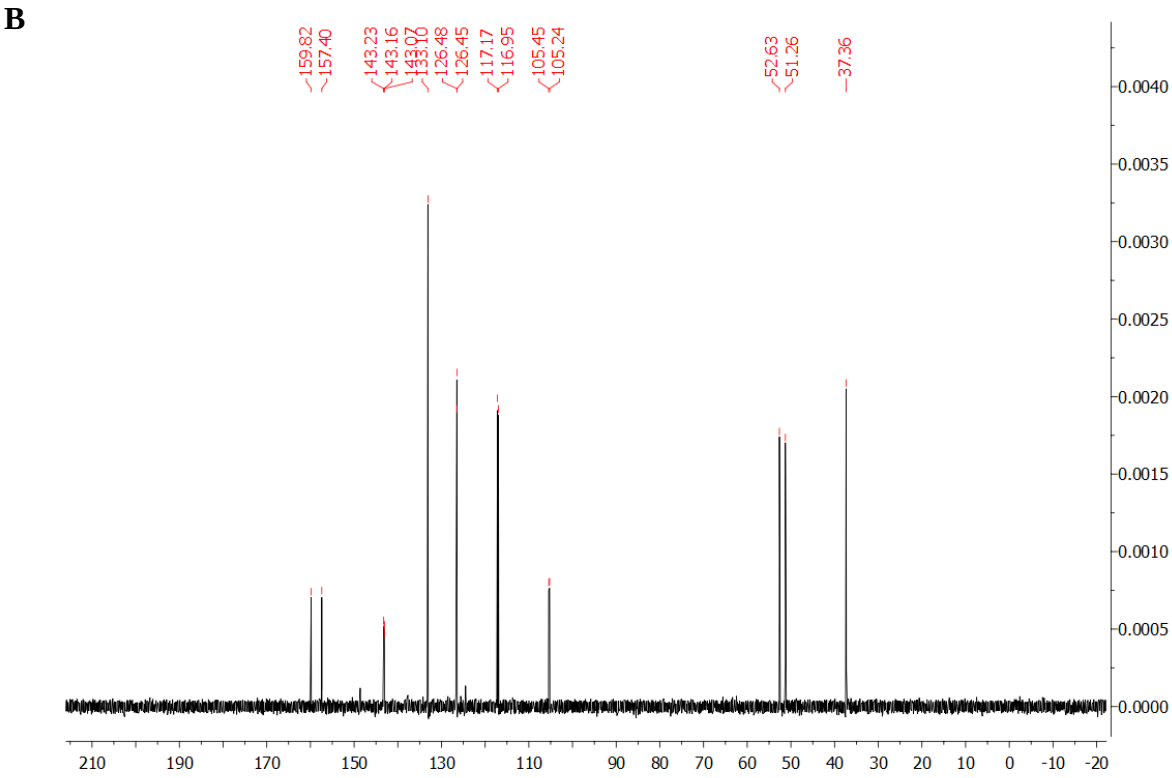
722 **Figure S10-13.** ^{1}H (**A**),^{13}C (**B**), ^{19}F (**C**), ^{31}P (**D**) NMR spectra for compound **17e**.

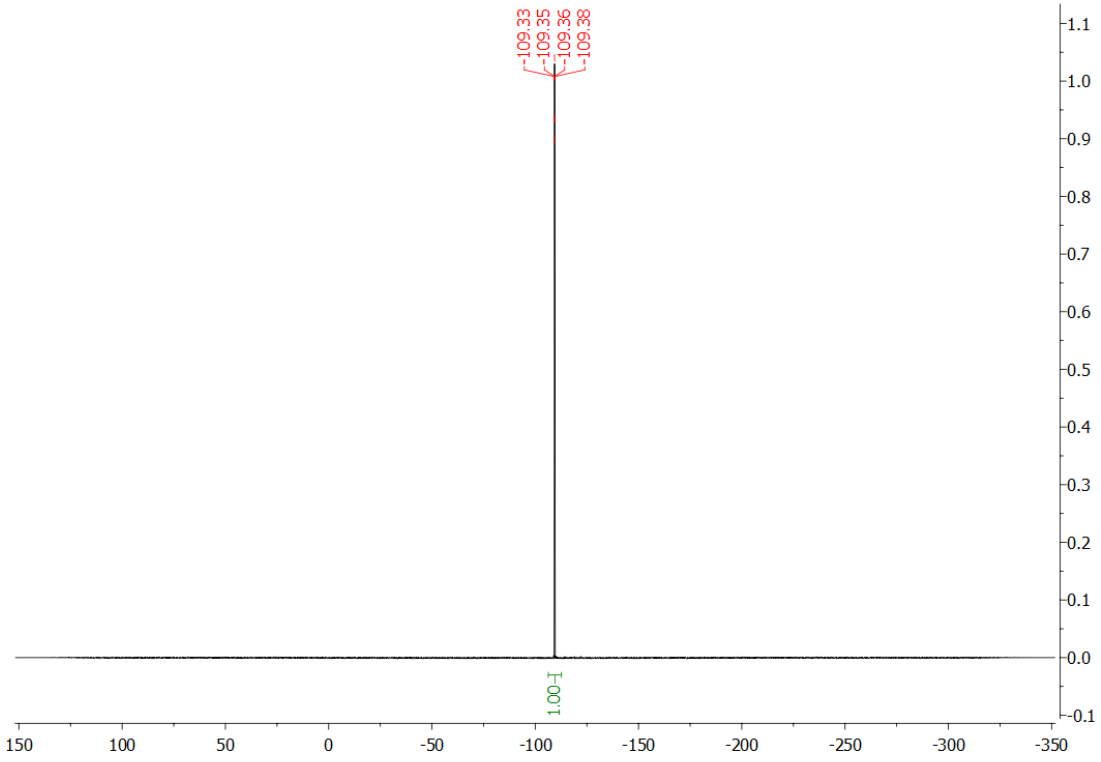
A



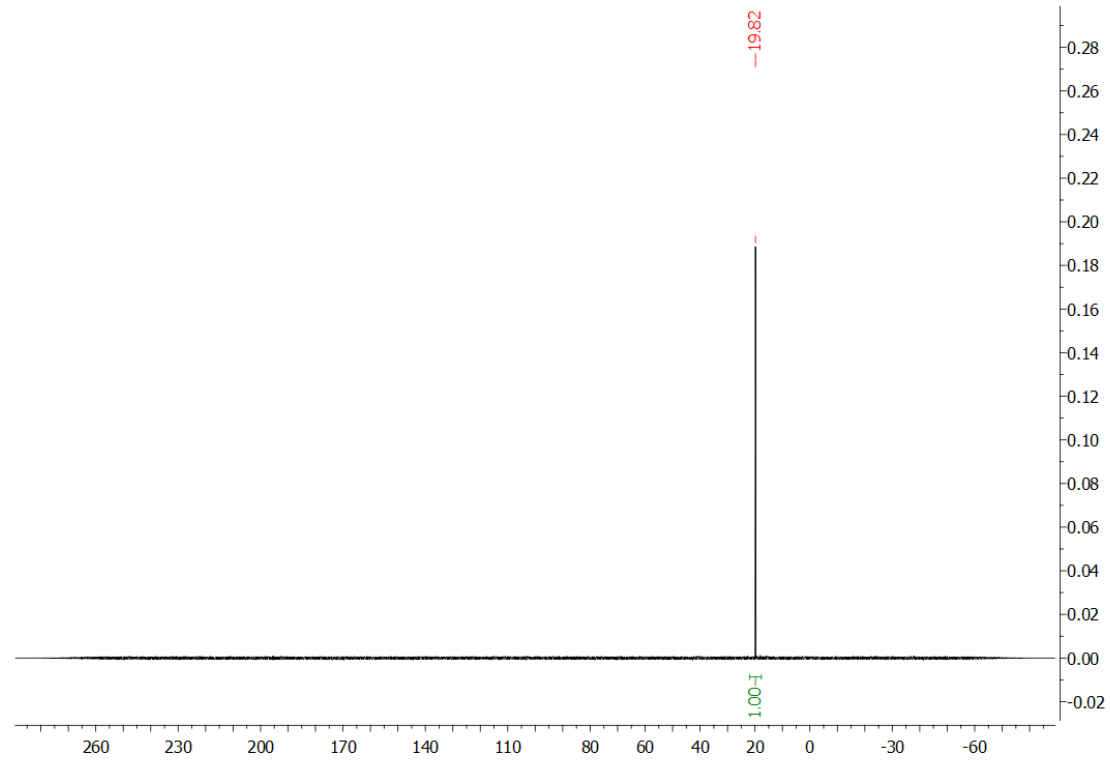
B



C



D



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