Bicyclic α-iminophosphonates as highly affinity imidazoline I_2 receptor ligands for Alzheimer's Disease

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CONTENTS:

Synthesis of α-substituted PhosMic derivatives

General conditions for the synthesis of compounds (10a-10e and 11). Reagents, solvents, dry solvents and starting products were acquired from commercial sources. The organic phases were dried with anhydrous Na_2SO_4. All the reactions were performed in dry conditions (inert atmosphere) and using dry solvents. The term "concentration" refers to the vacuum evaporation using a Büchi rotavapor. When indicated, the reaction products were purified by "flash" chromatography on silica gel (35-70 μm) with the indicated solvent system. The melting points were measured in a MFB 59510M Gallenkamp instruments. IR spectra were performed in a spectrophotometer Nicolet Avantar 320 FTR-IR or in a Spectrum Two FT-IR Spectrometer, and only noteworthy IR absorptions (cm^{-1}) are listed. NMR spectra were recorded in $CDCl_3$ at 400 MHz (^1H) and 100.6 MHz (^{13}C), and chemical shifts are reported in δ values downfield from TMS or relative to residual chloroform (7.26 ppm, 77.0 ppm) as an internal standard. Data are reported in the following manner: chemical shift, multiplicity, coupling constant (*J*) in hertz (Hz), integrated intensity and assignment (when possible). Multiplicities are reported using the following abbreviations: s, singlet; d, doublet; dd, doublet of doublets; t, triplet; m, multiplet; br s, broad signal. The accurate mass analyses were carried out using a LC/MSD-TOF spectrophotometer.

Diethyl α-phenylisocyanomethylphosphonate (10a). [1]

Diethyl [amino(4-fluorophenyl)methyl]phosphonate (step 1-10b).[2] A mixture of 4-fluorobenzaldehyde (3.32 mL, 31.0 mmol), HMDS (3.20 mL, 15.5 mmol), diethyl phosphite (2.0 mL, 15.5 mmol) and I_2 (393 mg, 1.55 mmol) was stirred at rt overnight. Then, the reaction mixture was evaporated and EtOAc was added to the resulting residue. The organic phase was washed with a 10% solution of $Na_2S_2O_4$, dried and evaporated. Then, the residue (imine intermediate), THF (7 mL) and HCl 2N (10 mL) was heated at 70˚C overnight. The THF was evaporated, water was added and the aqueous phase was washed with EtAOc. The aqueous phase was basified with NaOH 2N and the product was extracted with EtOAc. The organic phases were combined, dried and evaporated to give **step 1-10b** (1.17 g, 35%) as yellowish oil. IR (ATR) 3373, 3303, 2988, 1735, 1601, 1506, 1224, 1157, 1015, 961, 841, 790 cm^{-1}. representative peaks: ^1H NMR (400 MHz, $CDCl_3$) δ 1.20 (t, 3H, CH_2CH_3), 1.28 (t, 3H, CH_2CH_3), 3.59 (t, 1H, CH_2CH_3), 3.89-4.09 (m, 3H, CH_2CH_3), 4.25 (d, J = 16.0 Hz, 1H, C*H*), 7.02-7.13 (m, 2H, Ar*H*), 7.41-7.47 (m, 1H, Ar*H*), 7.62-7.70 (m, 1H, Ar*H*). HRMS $C_{11}H_{18}FNO_3P$ $[M+H]^+$ 262.1003; found, 262.0999.

Diethyl [amino(4-methoxyphenyl)methyl]phosphonate (step 1-10c).[2] A mixture of 4-methoxybenzaldehyde (4.22 mL, 31.0 mmol), HMDS (3.20 mL, 15.5 mmol), diethyl phosphite (2.0 mL, 15.5 mmol) and I_2 (393 mg, 1.55 mmol) was stirred at rt overnight. Then, the reaction mixture was evaporated and EtOAc was added to the resulting residue. The organic phase was washed with a 10% solution of $Na_2S_2O_4$, dried and evaporated. Then, the residue (imine intermediate), THF (7 mL) and HCl 2N (10 mL) was heated at 70˚C overnight. The THF was evaporated, water was added and the aqueous phase was washed with EtAOc. The aqueous phase was basified with NaOH 2N and the product was extracted with EtOAc. The organic phases were combined, dried and evaporated to give **step 1-10c** compound (1.78 mg, 42%) as yellowish oil. IR (ATR) 3382, 3296, 2902, 1610, 1509, 1243, 1179, 1023, 909, 833, 727 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 1.18 (t, 3H, CH_2CH_3), 1.27 (t, 3H, CH_2CH_3), 3.79 (s, 3H, OCH_3), 3.82-3.89 (m, 1H, CH_2CH_3), 3.95-4.04 (m, 3H, CH_2CH_3), 4.19 (d, J = 16.0 Hz, 1H, C*H*), 6.86-6.89 (m, 2H, Ar*H*), 7.35-7.38 (m, 2H, Ar*H*). HRMS $C_{12}H_{21}NO_4P$ $[M+H]^+$ 274.1203; found, 274.1206.

Diethyl [(4-fluorophenyl)(formamido)methyl]phosphonate (step 2-10b).[1] To a solution of **step 1-10b** (722 mg, 2.76 mmol) in formic acid (5.20 mL), acetic anhydride (1.84 mL, 19.31 mmol) was added dropwise. The reaction was stirred at rt for 1 h and the mixture was concentrated *in vacuo* to give **step 2-10b** compound (798 mg, 100%) as yellowish solid. IR (ATR) 3254, 3034, 2878, 1674, 1506, 1380, 1215, 1160, 1015, 960, 812 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 1.11 (t, 3H, CH_2CH_3), 1.33 (t, 3H, CH_2CH_3), 3.70-3.78 (m, 1H, CH_2CH_3), 3.90-3.96 (m, 1H, CH_2CH_3), 4.12-4.17 (m, 2H, CH_2CH_3), 5.55 (dd, J = 9.5, 21.0 Hz, 1H, C*H*), 7.01-7.06 (m, 2H, Ar*H*), 7.43-7.47 (m, 2H, Ar*H*), 7.71 (br s, 1H, N*H*), 8.23 (s, 1H, C*H*O). HRMS $C_{12}H_{18}FNO_4P$ $[M+H]^+$ 290.0952; found, 290.0953.

Diethyl [(4-methoxyphenyl)(formamido)methyl]phosphonate (step 2-10c).[1] To a solution of **step 1-10c** (1.36 g, 4.98 mmol) in formic acid (9.39 mL), acetic anhydride (3.30 mL, 34.87 mmol) was added dropwise. The reaction was stirred at rt for 1 h and the mixture was concentrated *in vacuo* to give **step 2-10c** compound (1.50 g, 100%) as a yellowish solid. IR (ATR) 3269, 3009, 2881, 1676, 1504, 1379, 1212, 1010, 964, 793, 727 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 1.10 (t, 3H, CH_2CH_3), 1.33 (t, 3H, CH_2CH_3), 3.66-3.72 (m, 1H, CH_2CH_3), 3.79 (s, 3H, OCH_3), 3.88-4.19 (m, 1H, CH_2CH_3), 4.09-4.19 (m, 2H, CH_2CH_3), 5.53 (dd, J = 9.5, 20.5 Hz, 1H, C*H*), 6.86-6.88 (m, 2H, Ar*H*), 7.38-7.40 (m, 2H, Ar*H*), 7.55 (br s, 1H, N*H*), 8.23 (s, 1H, C*H*O). HRMS $C_{13}H_{21}NO_5P$ $[M+H]^+$ 302.1152; found, 302.1157.

Diethyl [(4-fluorophenyl)isocyanomethyl]phosphonate (10b).[1] Et_3N (2.0 mL, 13.8 mmol) and $POCl_3$ (0.4 mL, 4.15 mmol) were added dropwise to a cooled solution (-78ºC) of **step 2-10b**

compound (800 mg, 2.77 mmol) in THF (7.5 mL). The reaction mixture was allowed to warm to rt. After 2 h, cold water (0 ºC) was added and the mixture was extracted with Et_2O. The combined organic layers were dried and concentrated *in vacuo* to give a residue which was purified by column chromatography (EtOAc-Hexane 4:1) to afford **10b** (616 mg, 82%) as yellowish oil. IR(ATR) 2975, 2911, 1679, 1510, 1247, 1177, 1016, 963, 836, 743 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 1.27 (t, 3H, CH_2CH_3), 1.31 (t, 3H, CH_2CH_3), 4.00-4.19 (m, 4H, CH_2CH_3), 5.00 (d, *J* = 21.0 Hz, 1H, C*H*), 7.09-7.13 (m, 2H, Ar*H*), 7.44-7.48 (m, 2H, Ar*H*). ^{13}C NMR (100.6 MHz) δ 16.4 (d, *J* = 5.5 Hz, CH_2CH_3), 16.5 (d, *J* = 5.5 Hz, CH_2CH_3), 55.0 (d, *J* = 152.0 Hz, *C*H), 64.6 (d, *J* = 7.0 Hz, CH_2CH_3), 65.1 (d, *J* = 7.5 Hz, CH_2CH_3), 116.0 (d, *J* = 2.5 Hz, *C*HAr), 116.2 (d, *J* = 2.5 Hz, *C*HAr), 125.8 (C-*ipso*), 129.3 (d, *J* = 5.0 Hz, *C*HAr), 129.4 (d, *J* = 5.0 Hz, *C*HAr), 161.6 (*C-ipso*), 162.0 (d, *J* = 3.0 Hz, NC). HRMS $C_{12}H_{16}FNO_3P$ $[M+H]^+$ 272.0846; found, 272.0854.

Diethyl [(4-methoxyphenyl)isocyanomethyl]phosphonate (10c).[1] Et_3N (3.5 mL, 24.9 mmol) and $POCl_3$ (0.7 mL, 7.47 mmol) were added dropwise to a cooled solution (-78ºC) of **step 2-10c** (1.50 g, 4.98 mmol) in THF (13.8 mL). The reaction mixture was allowed to warm to rt. After 2 h, cold water (0 ºC) was added and the mixture was extracted with Et_2O. The combined organic layers were dried and concentrated *in vacuo* to give a residue which was purified by column chromatography (EtOAc-Hexane 4:1) to afford **10c** (1.13g, 80%) as yellowish oil. IR(ATR): 2978, 2917, 1610, 1514, 1455, 1293, 1250, 1176, 1013, 963, 839, 763 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.28 (t, 3H, CH_2CH_3), 1.31 (t, 3H, CH_2CH_3), 3.82 (s, 3H, OCH_3), 4.03-4.16 (m, 4H, CH_2CH_3), 4.95 (d, *J* = 20.5 Hz, 1H, C*H*), 6.92-6.95 (m, 2H, Ar*H*), 7.38-7.41 (m, 2H, Ar*H*); ^{13}C NMR (100.6 MHz) δ 16.4 (d, *J* = 5.5 Hz, CH_2CH_3), 16.5 (d, *J* = 5.5 Hz, CH_2CH_3), 55.5 (OCH_3), 55.6 (d, *J* = 156.0 Hz, *C*H), 64.4 (d, *J* = 7.0 Hz, CH_2CH_3), 64.9 (d, *J* = 7.0 Hz, CH_2CH_3), 114.4 (d, *J* = 2.5 Hz, 2x*C*HAr), 121.8 (C-*ipso*), 128.8 (d, *J* = 5.0 Hz, 2x*C*HAr), 160.3 (*C-ipso*), 160.8 (d, *J* = 5.0 Hz, NC); HRMS $C_{13}H_{19}NO_4P$ $[M+H]^+$ 284.1046; found, 284.1052.

Diethyl (1-isocyano-2-phenylethyl)phosphonate (10d).[3] Potassium *tert*-butoxide (492 mg, 4.4 mmol) was added to a cooled solution (-78 ºC) of diethyl isocyanomethylphosphonate (672 mg, 4 mmol) in dichloromethane (DCM) (6.0 mL) and the mixture was stirred for 15 min at – 78 ˚C. Then, a solution of benzyl bromide (476 µL, 4 mmol) in DCM (2.0 mL) was added. The reaction mixture was stirred for additional 30 min at -78 ˚C and allowed to warm to rt. After 30 min stirring the mixture at rt, the organic phase was washed with water, dried and concentrated. The resulting residue was purified by column chromatography (AcOEt/Hexane 4:6 to 1:1) to furnish **10d** (516 mg, 45%) as yellowish oil. ^1H NMR (400 MHz, $CDCl_3$) δ 1.38 (t, *J* = 7.0 Hz, 6H, CH_2CH_3), 2.80-3.06 (m, 1H, CH_2), 3.23-3.29 (m, 1H, CH_2), 3.80-4.20 (m, 1H, C*H*), 4.10-

4.50 (m, 4H, C*H*$_2$CH$_3$), 7.27-7.38 (m, 5H, Ar*H*). ^{13}C NMR (100.6 MHz) δ 16.3 (CH$_2$*C*H$_3$), 16.4 (CH$_2$*C*H$_3$), 36.0 (*C*H$_2$Ar), 52.0 (d, *J* = 155.0 Hz, *C*H), 63.8 (d, *J* = 7.0 Hz, *C*H$_2$CH$_3$), 64.4 (d, *J* = 7.0 Hz, *C*H$_2$CH$_3$), 127.5 (*C*HAr), 129.0 (d, *J* = 38.0 Hz, 2x*C*HAr), 135.4 (d, *J* = 14.0 Hz, 2x*C*HAr), 160.8 (*C*N).

Diethyl [2-(4-fluorophenyl)-1-isocyanoethyl]phosphonate (10e).[3] Potassium *tert*-butoxide (711 mg, 5.8 mmol) was added to a cooled solution (-78 ˚C) of diethyl isocyanomethylphosphonate (937 mg, 5.3 mmol) in DCM (9.0 mL) and the mixture was stirred for 15 min at - 78˚C. Then, a solution of 4-fluorobenzyl bromide (660 µL, 5.3 mmol) in DCM (3.0 mL) was added. The reaction mixture was stirred for additional 30 min at -78 ˚C and allowed to warm to rt. After 30 min stirring the mixture at rt, the organic phase was washed with water, dried and concentrated. The resulting residue was purified by column chromatography (AcOEt/hexane 4:6 to 1:1) to furnish **10e** (662 mg, 44%) as yellowish oil. IR (ATR) 2984, 2914, 2140, 1735, 1510, 1264, 1224, 1106, 974, 801, 761 cm^{-1}. ^{1}H NMR (400 MHz, CDCl$_3$) δ 1.38-1.42 (m, 6H, CH$_2$C*H*$_3$), 2.96-3.04 (m, 1H, C*H*$_2$), 3.19 – 3.26 (m, 1H, C*H*$_2$), 3.75 – 3.79 (d, *J* = 16.0 Hz, 1H, C*H*), 4.22-4.31 (m, 4H, C*H*$_2$CH$_3$), 7.02-7.06 (m, 2H, Ar*H*), 7.24-7.27 (m, 2H, Ar*H*). HRMS $C_{13}H_{18}FNO_3P$ $[M+H]^+$ 286.1003; found, 286.1011.

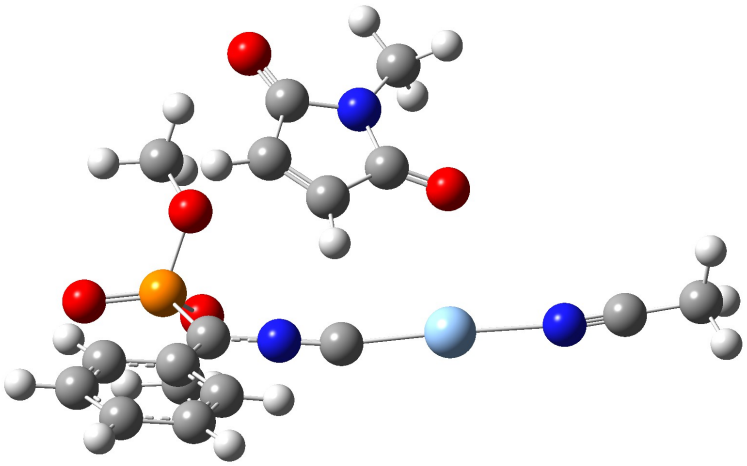
Theoretical calculations

Table S1. Relative stabilities (kcal·mol^{-1}) between reactants, transition states and products for the *cis* and *trans* [3+2] cycloadditions between *N*-methyl maleimide and PhosMic in the gas phase and in solution. These latter values were obtained by combining the relative stabilities in the gas phase with the solvation free energies in acetonitrile. All values relative to the *trans* reactants.

Cycloaddition	Reactant	Transition State	Product
Gas phase			
cis	2.0	19.0	-13.7
trans	0.0	16.7	-15.5
Solvation free energy			
cis	-0.2	1.7	0.1
trans	0.0	1.7	0.9
Solution (acetonitrile)			
cis	1.8	20.7	-13.6
trans	0.0	18.4	-14.6

Optimized parameters of reactants, transition states and products derived for the cis [3+2] cicloaddition (geometry in Å; energy in atomic units) **from B3LYP calculations**

Reactant



Geometry

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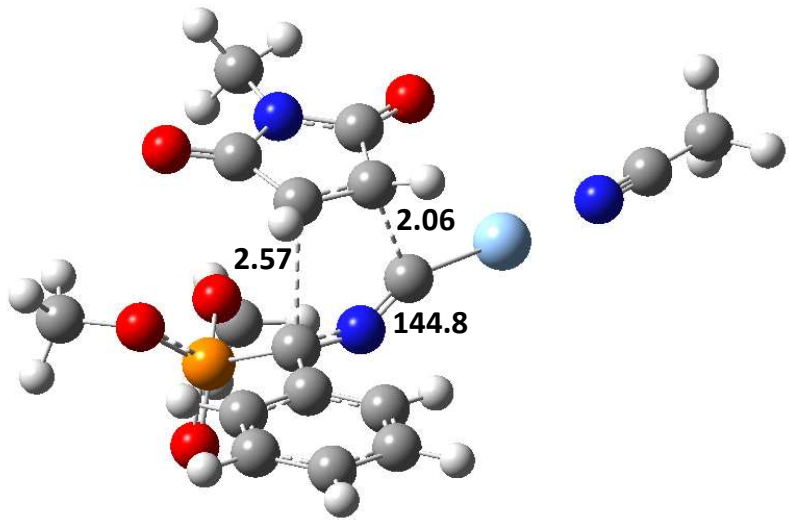
2	6	0	-0.076617	-3.023722	-1.700851
3	6	0	-0.579982	-1.717882	-2.238770
4	6	0	0.421592	-0.830149	-2.201931
5	6	0	1.627629	-1.494282	-1.610865
6	6	0	2.138597	-3.806413	-0.750263
7	8	0	2.729924	-1.007908	-1.382954
8	8	0	-0.664703	-4.081493	-1.592616
9	1	0	-1.602018	-1.587918	-2.569039
10	1	0	0.421207	0.209273	-2.501502
11	1	0	1.608165	-4.760406	-0.768818
12	1	0	3.067658	-3.887353	-1.322072
13	1	0	2.378814	-3.543071	0.285257
14	6	0	-2.032266	0.748012	0.431563
15	7	0	-0.704665	0.918878	0.589769
16	6	0	0.455087	1.084434	0.702369
17	47	0	2.515176	1.136068	0.600470

18	7	0	4.672354	1.271934	0.539087
19	6	0	5.820565	1.259409	0.405786
20	6	0	7.267567	1.239506	0.232561
21	1	0	7.751178	0.937920	1.167112
22	1	0	7.535258	0.528069	-0.555270
23	1	0	7.623177	2.235812	-0.048768
24	15	0	-2.725881	-0.574442	1.375203
25	8	0	-4.216108	-0.622123	1.466013
26	8	0	-2.037777	-1.928346	0.781170
27	6	0	-2.427462	-3.204148	1.329722
28	8	0	-1.977790	-0.550928	2.833494
29	6	0	-2.442209	0.386322	3.816607
30	1	0	-2.014034	-3.960659	0.660203
31	1	0	-2.015077	-3.322400	2.337729
32	1	0	-3.518111	-3.288996	1.360866
33	1	0	-3.504147	0.227092	4.028989
34	1	0	-2.287409	1.416638	3.473775
35	1	0	-1.848991	0.207145	4.716607
36	6	0	-2.719921	1.578414	-0.563379
37	6	0	-2.009322	2.557835	-1.298996
38	6	0	-4.104337	1.445711	-0.834071
39	6	0	-2.644834	3.355763	-2.252240
40	1	0	-0.949273	2.707038	-1.113348
41	6	0	-4.726184	2.245537	-1.790972
42	1	0	-4.685397	0.718087	-0.278518
43	6	0	-4.009519	3.207800	-2.513302
44	1	0	-2.063360	4.100802	-2.792199
45	1	0	-5.791449	2.115258	-1.970502
46	1	0	-4.504273	3.828855	-3.255613

Sum of electronic and zero-point Energies= -1686.455391 a.u.

Sum of electronic and thermal Free Energies= -1686.530633 a.u.

Transition state (C···C distances in Å; C-N-C angle in degrees)



Geometry

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2	6	0	-1.102910	-1.932468	-1.794359
3	6	0	-1.044656	-0.465336	-1.914438
4	6	0	0.303233	-0.085596	-1.866392
5	6	0	1.124620	-1.324705	-1.708990
6	6	0	0.597613	-3.762417	-1.376312
7	8	0	2.352743	-1.409856	-1.623783
8	8	0	-2.045310	-2.705832	-1.878293
9	1	0	-1.869927	0.091598	-2.333640
10	1	0	0.727220	0.762734	-2.392668
11	1	0	0.169796	-4.401604	-2.154793
12	1	0	1.687281	-3.833788	-1.393795
13	1	0	0.219876	-4.098631	-0.404097
14	6	0	-1.677116	0.607524	0.336772
15	7	0	-0.356719	0.795744	0.511483
16	6	0	0.736991	0.690532	-0.003597
17	47	0	2.820033	0.768162	0.252874
18	7	0	4.990329	0.825244	0.459198
19	6	0	6.144135	0.772160	0.509296
20	6	0	7.599018	0.701562	0.568879

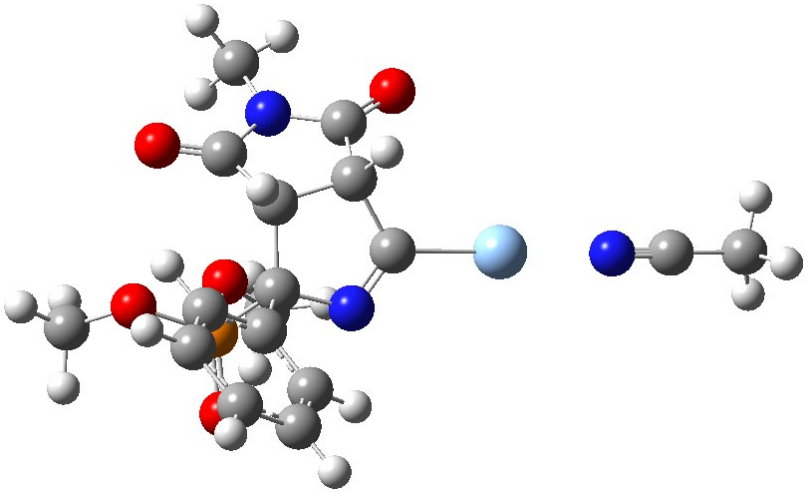
21	1	0	7.917118	0.404437	1.573246
22	1	0	7.963384	-0.034994	-0.154365
23	1	0	8.030008	1.679431	0.331810
24	15	0	-2.341260	-0.691538	1.429517
25	8	0	-2.812729	-0.267916	2.780686
26	8	0	-3.438170	-1.372129	0.474764
27	6	0	-4.138537	-2.563752	0.875974
28	8	0	-1.163007	-1.811992	1.491133
29	6	0	-0.360658	-1.972508	2.674538
30	1	0	-4.849631	-2.774343	0.076268
31	1	0	-3.435405	-3.396801	0.965366
32	1	0	-4.664491	-2.399542	1.822142
33	1	0	-0.937120	-1.728091	3.570438
34	1	0	0.520759	-1.325506	2.611597
35	1	0	-0.048285	-3.019524	2.698293
36	6	0	-2.494710	1.770874	-0.068406
37	6	0	-1.887214	3.014871	-0.339953
38	6	0	-3.891314	1.665633	-0.238337
39	6	0	-2.643535	4.105202	-0.768878
40	1	0	-0.817023	3.130356	-0.198824
41	6	0	-4.641193	2.759526	-0.668697
42	1	0	-4.386563	0.720099	-0.049187
43	6	0	-4.026477	3.986593	-0.937514
44	1	0	-2.149112	5.053845	-0.964773
45	1	0	-5.715699	2.649811	-0.793579
46	1	0	-4.616067	4.836964	-1.270056

Negative frequency: -353.8

Sum of electronic and zero-point Energies= -1686.432693

Sum of electronic and thermal Free Energies= -1686.503549

Product



Geometry

1	7	0	-0.416099	-2.738848	-1.295412
2	6	0	-1.588707	-1.976860	-1.289394
3	6	0	-1.202721	-0.496463	-1.357802
4	6	0	0.325574	-0.519313	-1.553468
5	6	0	0.736169	-1.983693	-1.477967
6	6	0	-0.431865	-4.189861	-1.204277
7	8	0	1.864331	-2.440430	-1.562555
8	8	0	-2.700402	-2.466456	-1.316036
9	1	0	-1.738490	-0.071007	-2.208253
10	1	0	0.669896	-0.112939	-2.511829
11	1	0	-1.034332	-4.610071	-2.015166
12	1	0	0.598968	-4.539833	-1.279562
13	1	0	-0.867675	-4.497373	-0.248972
14	6	0	-1.395093	0.464913	-0.104699
15	7	0	-0.024059	0.829908	0.339732
16	6	0	0.891989	0.318479	-0.397144
17	47	0	2.951552	0.548001	-0.061391
18	7	0	5.106902	0.771428	0.299024
19	6	0	6.245056	0.857990	0.484448
20	6	0	7.680433	0.965852	0.718227
21	1	0	7.881276	1.000583	1.793721

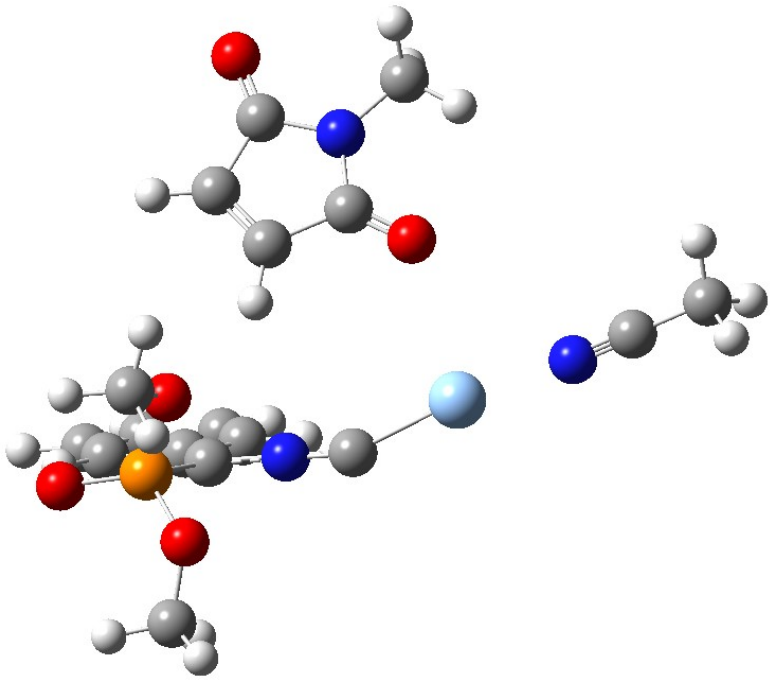
22	1	0	8.193694	0.100588	0.286795
23	1	0	8.066535	1.878582	0.253406
24	15	0	-2.129531	-0.265289	1.454758
25	8	0	-2.154192	0.615577	2.654120
26	8	0	-3.554623	-0.789368	0.926361
27	6	0	-4.484281	-1.425344	1.818897
28	8	0	-1.305726	-1.656596	1.690224
29	6	0	-0.299660	-1.737583	2.720495
30	1	0	-5.392719	-1.593210	1.237852
31	1	0	-4.083822	-2.385856	2.160022
32	1	0	-4.697715	-0.777774	2.675008
33	1	0	-0.632079	-1.216648	3.621841
34	1	0	0.635567	-1.296159	2.363912
35	1	0	-0.159148	-2.801721	2.925283
36	6	0	-2.209580	1.714158	-0.462460
37	6	0	-1.773789	2.987026	-0.068278
38	6	0	-3.417174	1.601219	-1.170330
39	6	0	-2.518778	4.123587	-0.395555
40	1	0	-0.853940	3.075313	0.498640
41	6	0	-4.160478	2.737937	-1.495491
42	1	0	-3.790403	0.620009	-1.451540
43	6	0	-3.712100	4.005795	-1.112441
44	1	0	-2.164587	5.103331	-0.083769
45	1	0	-5.092813	2.630141	-2.044633
46	1	0	-4.290449	4.891050	-1.365641

Sum of electronic and zero-point Energies= -1686.486683

Sum of electronic and thermal Free Energies= -1686.555692

Optimized parameters of reactants, transition states and products derived for the trans [3+2] cicloaddition (geometry in Å; energy in atomic units) **from B3LYP calculations**

Reactant



Geometry

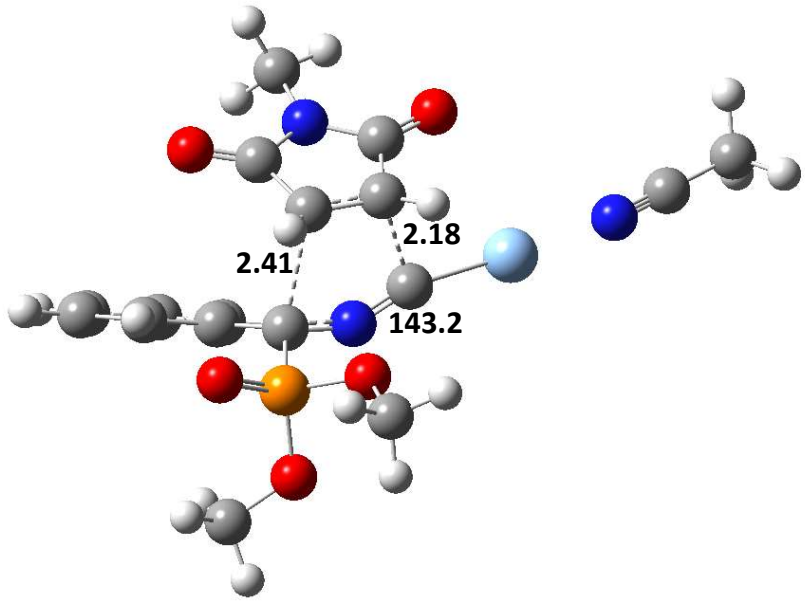
1	7	0	2.186282	3.276484	0.716704
2	6	0	1.058999	4.027968	1.089597
3	6	0	-0.021349	3.034991	1.396232
4	6	0	0.463830	1.800216	1.213572
5	6	0	1.893743	1.917323	0.768711
6	6	0	3.459585	3.855061	0.325226
7	8	0	2.681910	1.019487	0.496387
8	8	0	1.021361	5.241470	1.141834
9	1	0	-1.014728	3.336501	1.703127
10	1	0	-0.043529	0.851771	1.344989
11	1	0	3.858259	4.477531	1.131927
12	1	0	4.147568	3.033733	0.116614
13	1	0	3.339818	4.473174	-0.569926
14	6	0	-2.244245	-0.637324	-0.343125
15	7	0	-0.990267	-1.088005	-0.557117
16	6	0	0.103601	-1.487679	-0.734587

17	47	0	2.171907	-1.517824	-0.644104
18	7	0	4.329549	-1.802504	-0.646964
19	6	0	5.481453	-1.889471	-0.600343
20	6	0	6.934070	-1.997202	-0.540485
21	1	0	7.219866	-2.986761	-0.169913
22	1	0	7.359672	-1.853213	-1.538682
23	1	0	7.335601	-1.233331	0.133013
24	15	0	-2.894123	-1.063274	1.238172
25	8	0	-4.312284	-0.687689	1.516774
26	8	0	-2.576744	-2.651031	1.499437
27	6	0	-3.443406	-3.621056	0.892045
28	8	0	-1.799765	-0.451398	2.292687
29	6	0	-1.972261	-0.700246	3.699498
30	1	0	-4.476299	-3.475923	1.224362
31	1	0	-3.395383	-3.551687	-0.201481
32	1	0	-3.080804	-4.600739	1.212180
33	1	0	-1.808413	-1.759762	3.921353
34	1	0	-1.223333	-0.093026	4.214040
35	1	0	-2.975219	-0.402065	4.021544
36	6	0	-2.872683	0.198820	-1.373316
37	6	0	-4.174458	0.735917	-1.225357
38	6	0	-2.181332	0.497061	-2.571588
39	6	0	-4.739819	1.525316	-2.225562
40	1	0	-4.736228	0.524225	-0.322463
41	6	0	-2.759865	1.285772	-3.567310
42	1	0	-1.182289	0.100677	-2.729453
43	6	0	-4.044717	1.811407	-3.406709
44	1	0	-5.742704	1.920667	-2.077219
45	1	0	-2.196501	1.489026	-4.476075
46	1	0	-4.494768	2.426262	-4.181955

Sum of electronic and zero-point Energies= -1686.456706

Sum of electronic and thermal Free Energies= -1686.533881

Transition state (C···C distances in Å; C-N-C angle in degrees)



Geometry

1	7	0	-0.251238	-2.462516	1.474558
2	6	0	1.023941	-1.942589	1.792847
3	6	0	0.846622	-0.483582	1.992887
4	6	0	-0.519012	-0.208222	1.877917
5	6	0	-1.228008	-1.472602	1.584903
6	6	0	-0.499231	-3.855434	1.159300
7	8	0	-2.437184	-1.653248	1.412993
8	8	0	2.028204	-2.630849	1.883976
9	1	0	1.585380	0.082272	2.542700
10	1	0	-1.040037	0.627208	2.327784
11	1	0	-0.220098	-4.497206	2.001992
12	1	0	-1.565885	-3.965112	0.952097
13	1	0	0.084975	-4.158396	0.284357
14	6	0	1.611853	0.312917	-0.148526
15	7	0	0.333030	0.552905	-0.534866
16	6	0	-0.811761	0.528966	-0.153680
17	47	0	-2.877377	0.563043	-0.486971
18	7	0	-5.039034	0.538310	-0.746009
19	6	0	-6.186974	0.416364	-0.808240

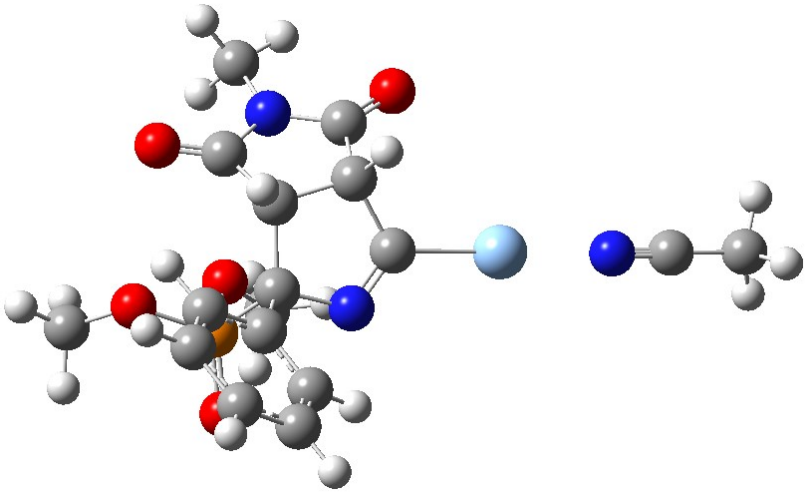
20	6	0	-7.634141	0.257240	-0.881649
21	1	0	-8.127640	1.185820	-0.577740
22	1	0	-7.931265	0.012696	-1.906394
23	1	0	-7.950651	-0.551087	-0.214681
24	15	0	2.515700	1.798724	0.381145
25	8	0	3.754929	1.539554	1.168511
26	8	0	2.772102	2.746369	-0.923177
27	6	0	3.983400	2.608090	-1.690394
28	8	0	1.349804	2.638667	1.116482
29	6	0	1.664086	3.916358	1.700016
30	1	0	4.854460	2.573654	-1.029997
31	1	0	3.944357	1.701248	-2.302780
32	1	0	4.033801	3.486618	-2.337488
33	1	0	1.910909	4.639993	0.916656
34	1	0	0.764549	4.235407	2.229975
35	1	0	2.497960	3.823418	2.402870
36	6	0	2.357890	-0.743714	-0.876621
37	6	0	3.636508	-1.161787	-0.454067
38	6	0	1.781187	-1.381283	-1.994614
39	6	0	4.310823	-2.173575	-1.138169
40	1	0	4.089084	-0.703223	0.417692
41	6	0	2.460148	-2.396225	-2.668863
42	1	0	0.801903	-1.065062	-2.342072
43	6	0	3.732285	-2.796872	-2.247604
44	1	0	5.291616	-2.485499	-0.787981
45	1	0	1.996076	-2.868285	-3.531994
46	1	0	4.261886	-3.587480	-2.773233

Negative frequency: -349.4

Sum of electronic and zero-point Energies= -1686.437075

Sum of electronic and thermal Free Energies= -1686.507217

Product



Geometry

1	7	0	0.101319	2.988086	-1.104607
2	6	0	1.337178	2.337019	-1.059663
3	6	0	1.103331	0.842178	-1.300501
4	6	0	-0.423816	0.723120	-1.454813
5	6	0	-0.960977	2.141590	-1.416876
6	6	0	-0.024760	4.429764	-0.955247
7	8	0	-2.112150	2.505783	-1.589044
8	8	0	2.392225	2.923906	-0.917226
9	1	0	1.667298	0.574205	-2.198475
10	1	0	-0.767619	0.217272	-2.362255
11	1	0	0.556835	4.941402	-1.728284
12	1	0	-1.081843	4.682619	-1.051374
13	1	0	0.351721	4.737227	0.024593
14	6	0	1.422284	-0.149827	-0.104177
15	7	0	0.114930	-0.496248	0.491317
16	6	0	-0.872978	-0.067557	-0.203951
17	47	0	-2.892798	-0.344373	0.294000
18	7	0	-5.013352	-0.603043	0.812613
19	6	0	-6.137895	-0.691438	1.067348
20	6	0	-7.556381	-0.800547	1.387921
21	1	0	-8.005637	-1.620471	0.818623

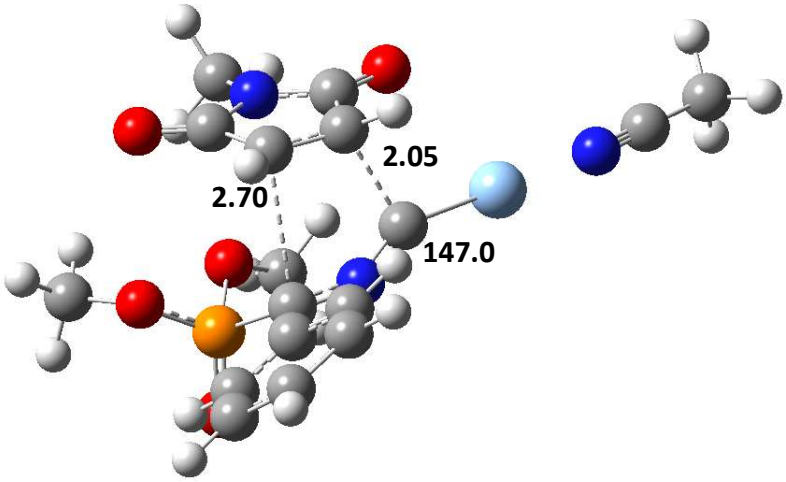
22	1	0	-7.683242	-0.996899	2.457289
23	1	0	-8.067945	0.133066	1.133060
24	15	0	2.136160	-1.718082	-0.842821
25	8	0	3.404477	-1.537357	-1.611508
26	8	0	2.226358	-2.822334	0.336995
27	6	0	3.458955	-3.062102	1.046505
28	8	0	0.883019	-2.260172	-1.710895
29	6	0	1.059950	-3.408770	-2.559859
30	1	0	4.312702	-3.000913	0.366224
31	1	0	3.568917	-2.333491	1.854501
32	1	0	3.377065	-4.069160	1.461774
33	1	0	1.212518	-4.306914	-1.952230
34	1	0	0.136810	-3.506292	-3.134616
35	1	0	1.909611	-3.262735	-3.234131
36	6	0	2.407150	0.339071	0.964232
37	6	0	3.724322	0.698672	0.632782
38	6	0	2.005222	0.411136	2.306730
39	6	0	4.612319	1.125632	1.621619
40	1	0	4.057117	0.645992	-0.397392
41	6	0	2.896038	0.842893	3.294519
42	1	0	0.994830	0.117426	2.568117
43	6	0	4.203608	1.200439	2.956771
44	1	0	5.625140	1.406155	1.343498
45	1	0	2.564737	0.894453	4.329213
46	1	0	4.897100	1.535965	3.724328

Sum of electronic and zero-point Energies= -1686.490065

Sum of electronic and thermal Free Energies= -1686.558641

Optimized parameters of transition states derived for the cis and trans [3+2] cicloaddition (geometry in Å; energy in atomic units) **from MN15L calculations**

Transition state for cis cicloaddition (C···C distances in Å; C-N-C angle in degrees)



Geometry

1	7	0	0.206262	-2.308687	-1.545414
2	6	0	-1.146637	-1.885843	-1.752955
3	6	0	-1.100704	-0.436323	-1.967387
4	6	0	0.245668	-0.027813	-1.914749
5	6	0	1.083724	-1.252702	-1.657910
6	6	0	0.545034	-3.644103	-1.095077
7	8	0	2.310637	-1.314103	-1.494569
8	8	0	-2.074366	-2.688193	-1.758478
9	1	0	-1.962820	0.127320	-2.334358
10	1	0	0.679796	0.811388	-2.474744
11	1	0	0.466934	-4.375345	-1.922976
12	1	0	1.583144	-3.624560	-0.716368
13	1	0	-0.158450	-3.943119	-0.293016
14	6	0	-1.691941	0.637771	0.438896
15	7	0	-0.375337	0.890353	0.474759
16	6	0	0.703189	0.806324	-0.100243
17	47	0	2.771001	0.866242	0.170433

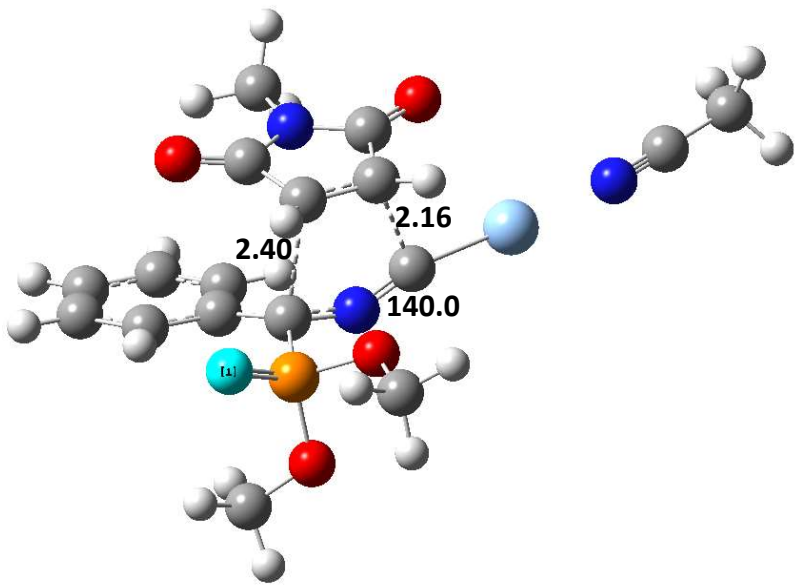
18	7	0	4.930341	0.922679	0.435952
19	6	0	6.086891	0.861518	0.556554
20	6	0	7.537170	0.783442	0.706152
21	1	0	7.793907	0.526072	1.749532
22	1	0	7.940905	0.006337	0.032419
23	1	0	7.994541	1.756308	0.451198
24	15	0	-2.148464	-0.811185	1.425741
25	8	0	-2.404350	-0.589624	2.873117
26	8	0	-3.340153	-1.401924	0.544597
27	6	0	-3.793129	-2.742625	0.815949
28	8	0	-0.962451	-1.867430	1.124878
29	6	0	0.223442	-1.901732	1.928249
30	1	0	-4.629199	-2.922584	0.121317
31	1	0	-2.977831	-3.459803	0.604731
32	1	0	-4.134754	-2.825892	1.867053
33	1	0	0.265765	-2.877432	2.448531
34	1	0	0.233732	-1.083788	2.675555
35	1	0	1.092773	-1.802880	1.243320
36	6	0	-2.624498	1.717456	0.070134
37	6	0	-2.191900	2.760291	-0.790145
38	6	0	-3.967998	1.720730	0.520340
39	6	0	-3.076777	3.768925	-1.188503
40	1	0	-1.152074	2.762072	-1.151920
41	6	0	-4.848683	2.733851	0.114547
42	1	0	-4.316752	0.935464	1.204762
43	6	0	-4.412097	3.760879	-0.740447
44	1	0	-2.726211	4.566509	-1.858967
45	1	0	-5.885815	2.724750	0.478024
46	1	0	-5.105570	4.553120	-1.054452

Negative frequency: -376.8

Sum of electronic and zero-point Energies= -1684.741793

Sum of electronic and thermal Free Energies= -1684.808303

Transition state for trans cicloaddition (C···C distances in Å; C-N-C angle in degrees)



Geometry

1	7	0	-0.003238	-2.232897	1.360636
2	6	0	1.218572	-1.639438	1.767280
3	6	0	0.913623	-0.205053	1.990088
4	6	0	-0.475834	-0.029363	1.845418
5	6	0	-1.068672	-1.345744	1.506547
6	6	0	-0.137896	-3.606721	0.915552
7	8	0	-2.254417	-1.642851	1.300055
8	8	0	2.274069	-2.250726	1.865049
9	1	0	1.624844	0.447012	2.506861
10	1	0	-1.079146	0.780960	2.269048
11	1	0	-0.684339	-4.217143	1.661144
12	1	0	-0.693283	-3.634513	-0.042503
13	1	0	0.881405	-4.007914	0.773224
14	6	0	1.607298	0.362128	-0.235824
15	7	0	0.316441	0.525826	-0.657920
16	6	0	-0.818880	0.541715	-0.210582
17	47	0	-2.882922	0.460032	-0.452460
18	7	0	-5.044692	0.354406	-0.627083

19	6	0	-6.194745	0.174674	-0.656043
20	6	0	-7.636505	-0.052616	-0.689739
21	1	0	-8.041455	-0.036068	0.338131
22	1	0	-8.129750	0.735574	-1.286484
23	1	0	-7.848770	-1.037105	-1.144181
24	15	0	2.388240	1.923492	0.228603
25	8	0	3.625172	1.811149	1.044197
26	8	0	2.574725	2.813976	-1.116315
27	6	0	3.684406	2.461511	-1.961175
28	8	0	1.152190	2.702866	0.902153
29	6	0	1.433169	4.035594	1.368278
30	1	0	4.618917	2.404350	-1.369185
31	1	0	3.494288	1.487791	-2.456915
32	1	0	3.761876	3.257522	-2.721053
33	1	0	1.610644	4.709007	0.507538
34	1	0	0.538005	4.360662	1.924280
35	1	0	2.315927	4.033529	2.037035
36	6	0	2.369756	-0.777848	-0.794761
37	6	0	3.749248	-0.958617	-0.519568
38	6	0	1.687859	-1.787641	-1.522581
39	6	0	4.412997	-2.112856	-0.960957
40	1	0	4.287179	-0.216054	0.083400
41	6	0	2.360483	-2.937423	-1.954900
42	1	0	0.614702	-1.668590	-1.734511
43	6	0	3.729635	-3.108484	-1.678785
44	1	0	5.478404	-2.240459	-0.722974
45	1	0	1.808739	-3.708241	-2.513081
46	1	0	4.255007	-4.013785	-2.013214

Negative frequency: -380.8

Sum of electronic and zero-point Energies= -1684.743843

Sum of electronic and thermal Free Energies= -1684.810187

3D-QSAR study

Selection of training and test set compounds. Original data set, for both created 3D-QSAR models, was divided on training and test set according to the PCA (Principal Component Analysis) score plot. Approximately 70% of compounds were chosen for the training set, and 30% for test set considering that p*K*i values were homogeneously distributed in the whole range. Final data set for I_2-IR ligands contains 33 compounds, with 23 compounds in training set and 10 compounds in test set, while data set for α_2-receptor ligands contains 30 compounds, with 21 compounds in training set and 9 compounds in test set (Table S2 and S3). Training set compounds were used for model building, and test set compounds were used for model validation.

Validation of created 3D-QSAR models. Different internal and external validation methods were employed in order to ensure the reliability and predictive quality of created QSAR models. Internal predictivity was examined with parameters such as cross-validated squared correlation coefficient (Q^2), root mean square error of estimation (RMSEE) and predicted residual sum of squares (PRESS) (Eq. 1, 2 and 3). These parameters are calculated only for training set compounds. For a predictive QSAR model values of Q^2 should be higher than 0.5.[4,5]

$$PRESS = \sum_{i=1}^{n} e_{(i)}^2 \quad (1) \qquad RMSEE = \sqrt{\frac{PRESS}{n}} \quad (2) \qquad Q^2 = 1 - \frac{PRESS}{SSTo} \quad (3)$$

Very often high value of Q^2 does not present real predictive potential of created model.[6] For that reason, calculations of external validation parameters help us to truly clarify the predictive power of created models. Parameters of external validation are R^2_{pred}, RMSEP and r^2metrics parameters (r^2_m, $r^{2/}_m$, $\bar{r}^2_m$ and Δr^2_m) (Eq. 4, 5, 6 and 7). Value of R^2_{pred} should be higher than 0.5. Values of correlation coefficients r^2_m, and $r^{/2}_m$ should be close and greater than 0.5, while their average value ($\bar{r}^2_m$) should be greater than 0.5 and the difference between r^2_m and $r^{/2}_m$ (Δr^2_m) should be lower than 0.2 for an acceptable model. Parameters of r^2metrics represent more stringent criterion of external validation and better reflect external predictive power of created models.[7]

$$R^2_{pred} = 1 - \frac{\Sigma(Y_{obs(test)} - \bar{Y}_{pred(test)})^2}{\Sigma(Y_{obs(test)} - \bar{Y}_{training})^2} \quad (4) \qquad r^2_m = r^2\left(\sqrt{1-|r^2-r_0^2|}\right) \quad (6)$$

$$RMSEP = \sqrt{\frac{PRESS}{n}} \quad (5) \qquad r^{/2}_m = r^2\left(1-\sqrt{|r^2-r_0^{/2}|}\right) \quad (7)$$

Obtained values of $R^2pred(I_2)$= 0.68, $R^2pred(\alpha_2)$= 0.87 and r^2 metrics parameters indicate that developed models have good predictive quality.

Table S2. Results of 3D-QSAR study for I_2-IR ligands

Training set			Test set		
	pKi(exp)	**pKi (pred)**		**pKi(exp)**	**pKi(pred)**
9c	10.28	9.39	**9d**	8.56	8.00
9b	9.74	9.09	**9a**	7.97	8.27
9f	8.37	7.78	**Idazoxan**	7.41	7.92
LSL60101	8.13	8.44	**BU99008**	7.05	7.84
9ad	7.96	7.52	**9i**	7.01	6.52
9z	7.90	7.37	**9x**	6.81	7.32
13d	7.87	8.00	**8a**	6.79	6.05
8c	7.73	7.76	**14c**	6.59	6.21
Tracizoline	7.58	7.36	**9u**	5.81	5.78
12d	7.55	8.55	**9r**	5.09	5.61
9h	7.35	7.94			
9ab	6.96	6.65	**R^2_{pred}=0.68 (>0.5)**		
9e	6.65	7.12	**RMSEP=0.53**		
9k	6.35	5.91	**r^2_m=0.59 (>0.5)**		
8b	5.74	6.87	**$r^{2/}_m$=0.64 (>0.5)**		
9aa	5.44	5.64	**Δr^2_m=0.05 (<0.2)**		
15c	5.35	4.44	**$\bar{r}^2_m$= 0.61 (>0.5)**		
9j	5.26	5.93	**$(r^2-r^{2/}_0)/r^2$=0.02 (<0.1)**		
8e	5.11	5.07	**k'= 1.00 (0.85≤k'≤1.15)**		
9g	4.02	4.98			
9m	3.84	3.30			
13c	3.39	3.16			
9ac	3.11	3.42			
R^2=0.90 (>0.7)					
Q^2=0.65 (>0.5)					
RMSEE=0.60					

Table S3. Results of 3D-QSAR study for α_2-AR ligands

Training set			Test set		
	pKi(exp)	**pKi (pred)**		**pKi(exp)**	**pKi(pred)**
8d	10.27	10.65	**8c**	8.49	8.47
8a	9.49	9.85	**12c**	6.77	6.15
9b	9.01	8.41	**9d**	6.27	6.15
Idazoxan	8.35	7.95	**9r**	6.15	5.36
9j	8.11	7.91	**9a**	5.93	5.63
15c	7.20	7.02	**9ab**	5.43	5.83
9h	6.77	6.88	**9w**	5.16	5.26
9u	6.22	6.18	**9n**	4.73	5.02
8e	6.14	6.13	**BU99008**	4.37	4.86
9f	5.85	5.53			
9l	5.65	5.77	**R^2_{pred}=0.87 (>0.5)**		
9p	5.34	5.33	**RMSEP=0.42**		
LSL60101	5.17	5.31	**r^2_m=0.83 (>0.5)**		
9z	5.12	5.13	**$r^{2/}_m$=0.71 (>0.5)**		
9e	4.59	4.64	**Δr^2_m=0.12 (<0.2)**		
Tracizoline	4.33	4.49	**$\bar{r}^2_m$= 0.77 (>0.5)**		
9i	4.31	4.48	**$(r^2-r^{2/}_0)/r^2$=0.04 (<0.1)**		
13c	3.85	4.31	**k'= 0.98 (0.85≤k'≤1.15)**		
9k	3.77	3.47			
14c	3.94	4.32			
12d	3.38	3.11			
R^2=0.98 (>0.7)					
Q^2=0.61 (>0.5)					
RMSEE=0.57					

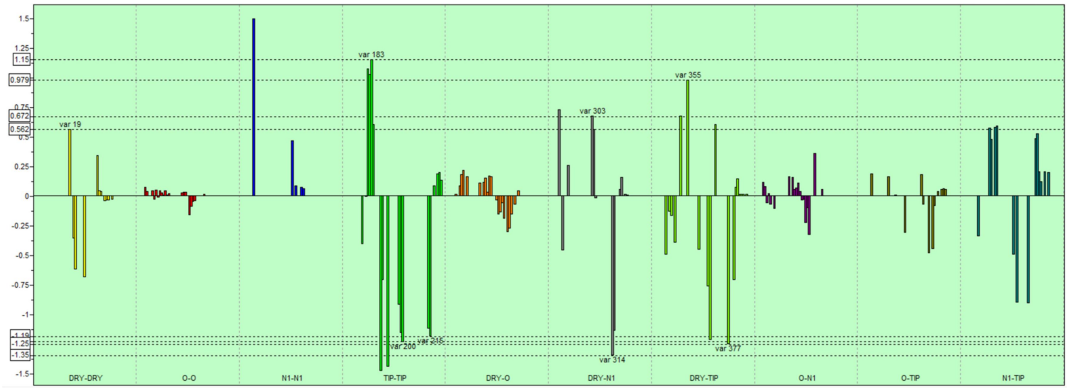


Figure S1. PLS coefficient plot for the I_2-IR 3D-QSAR model. The most significant variables are labelled.

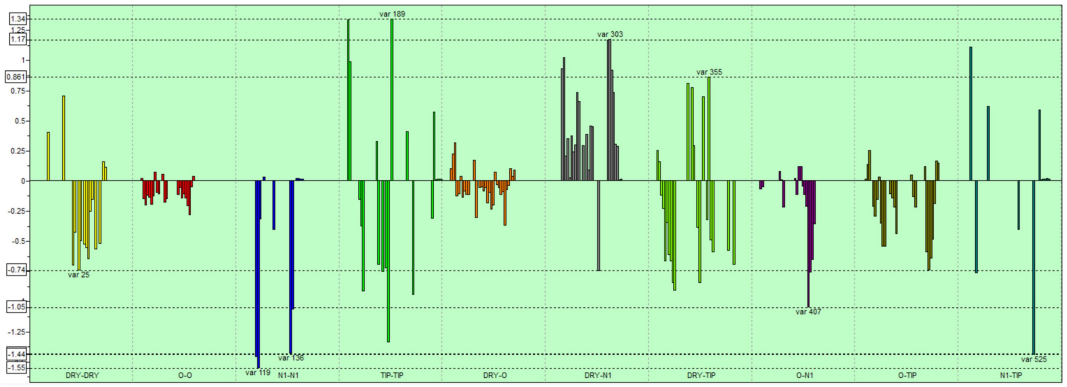


Figure S2. PLS coefficient plot for the α_2-AR 3D-QSAR model. The most significant variables are labelled.

Interpretation of created 3D-QSAR models. According to the correlogram shown in Figure S1, variables with most important positive influence on I_2-IR activity are: var19 (DRY-DRY: 7.60-8.00 Å), var183 (TIP-TIP: 6.00-6.40 Å), var303 (DRY-N1: 9.20-9.60 Å) and var355 (DRY-TIP: 7.60-8.00 Å). Positive variables are depicted in the Figure S3 for the most active compound, **9c** (pKi I_2 = 10.28), and for **13d** (pKi I_2 = 7.87) which possess the highest selectivity (I_2/ α_2=74131).

Created 3D-QSAR model for I_2-IR ligands shows that var183 possess strong positive influence on pKi values. It represents the distance of 6.00-6.40 Å between two steric hot spot regions located around electron withdrawing substituents of the *N*-phenyl. The

highest values are calculated for compounds **13d** and **12d** which possess high selectivity towards I_2-IR (Figure S3B). From created α_2-AR ligand model, it can be seen that this variable do not possess such significant impact on α_2-AR binding. Therefore, we hypothesize that presence of these substituents may be very importnat for enhancing I_2-IR binding activity and selectivity. GRIND variables DRY-N1 (var303) and DRY-TIP (var355) show positive impact on biological activity and signify the importance of hydrophobic interactions in the binding site of I_2-IR. Var303 define favourable distance (9.20-9.60 Å) between hydrophobic regions around bicyclic ring and nitrogen from imino group as hydrogen bond acceptor (Figure S3B). On the other hand, DRY-DRY variable from α_2-AR model, var25 (10.00-10.40 Å), describe unfavourable impact of hydrophobic regions around phenyl ring in α position, which could be related with higher affinity of *α*-unsubstituted ligands to α_2-AR (**8a**, **8c**, **8d** and **8e**). Var355 (DRY-TIP: 7.60-8.00 Å) delineate optimal distance between aforementioned hydrophobic regions around bicyclic ring and ethyl phosphonate group as steric hot spot (Figure S3A and S3B). Moreover, var19 (DRY-DRY: 7.60-8.00 Å), which is describing hydrophobic probes located around *N*-phenyl substituent, implies that presence of aromatic ring in that position establish favourable van der Waals interactions with amino acids of the active pocket (Figure S3A and S3B). Comparing to compounds which possess *N*-alkyl substituents instead of *N*-phenyl, such as **8a** or **9a**, we can conclude that introduction of this aromatic ring positively correlates with I_2-IR binding activity.

Variables with highest negative influence on I_2-IR binding activity are: var200 (TIP-TIP: 12.80-13.20 Å), var215 (TIP-TIP: 18.80-19.20 Å), var314 (DRY-N1: 13.60-14.00 Å) and var377 (DRY-TIP: 16.40-16.80 Å). Negative variables are depicted in Figure S4 on **9m** (pKi I_2=3.84) and **9ac** (pKi I_2=3.11), which possess low activity on I_2-IR.

From cross-correlogram TIP-TIP, it can be seen that var200 and var215 have strong negative influence on I_2-IR binding activity. Both variables are presented between two steric hot spots, substituents in the N-maleimide group and ethyl groups on phosphonate (Figure S4A and S4B). The highest values are calculated for compounds bearing longer distances (12.80-13.20 Å – var200 and 18.80-20.20 Å – var215) between these steric regions (**9e**, **8e**, **9m**, **9aa**, **9ab**, **9k**, **9ac** and **9z**). This molecular shape analysis implies that introduction of longer substituents in the *N*-maleimide group may not be the most complemented with the binding site of I_2-IR. Unfavourable impact of bulkier *N*-substituents is also defined with GRIND variable DRY-N1 (var314). It describes

unfavourable interaction between hydrophobic regions around aromatic ring separated from hydrogen bond acceptor group, nitrogen from imino group, at the longer distance (13.60-14.00 Å) (Figure S4A and S4B). This variable is pronounced in compounds **9z**, **9m**, **9j**, **9ab** and **9ac**. Furthermore, variable var377 (DRY-TIP) unfavourably impacts I_2-IR binding affinity describing hydrophobic and steric regions separated at the longer distance range (16.40-16.80 Å) than optimal (Figure S4A and S4B). The highest values are expressed in compounds **8e**, **9j**, **9k**, **9m**, **9z**, **9ab** and **9ac**, while the most potent compounds do not possess this negative variable. Overall, aforementioned negative variables confirm unfavourable fitting of longer molecules into I_2-IR binding pocket. Contrary, analysis of positive variables, var303 (DRY-N1: 13.20-13.60 Å) and var355 (DRY-TIP: 12.40-12.80 Å), from α_2-AR model show that introduction of steric regions at a longer distance from hydrogen bond acceptor or ethyl phosphonate group may lead to an increase in α_2-AR activity (**8e**, **9j**, **9l**).

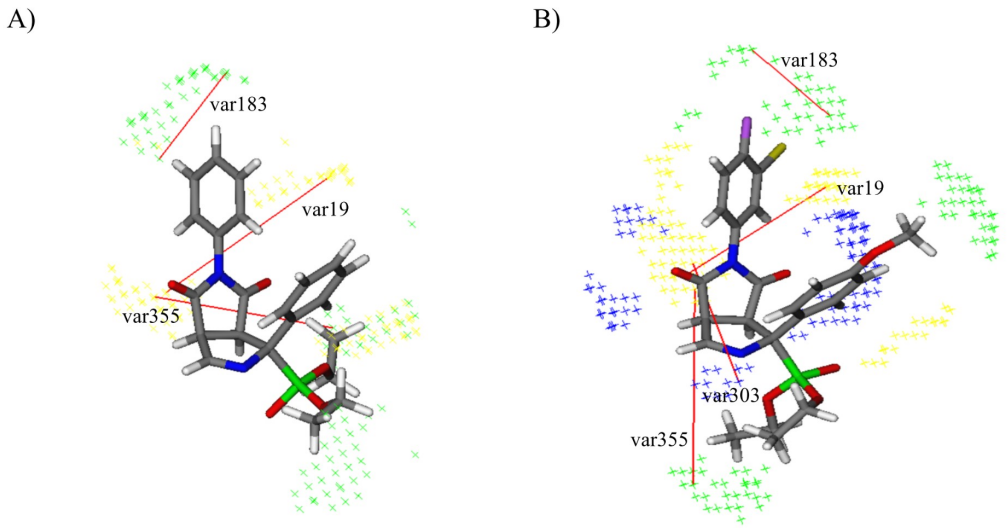


Figure S3. Representation of positive (in red) interactions of **9c** (A) and **13d** (B) in I_2-IR 3D-QSAR model. The steric hot spots (TIP) are presented in green, hydrophobic regions (DRY) in yellow and H-bond acceptor regions (N1) in blue.

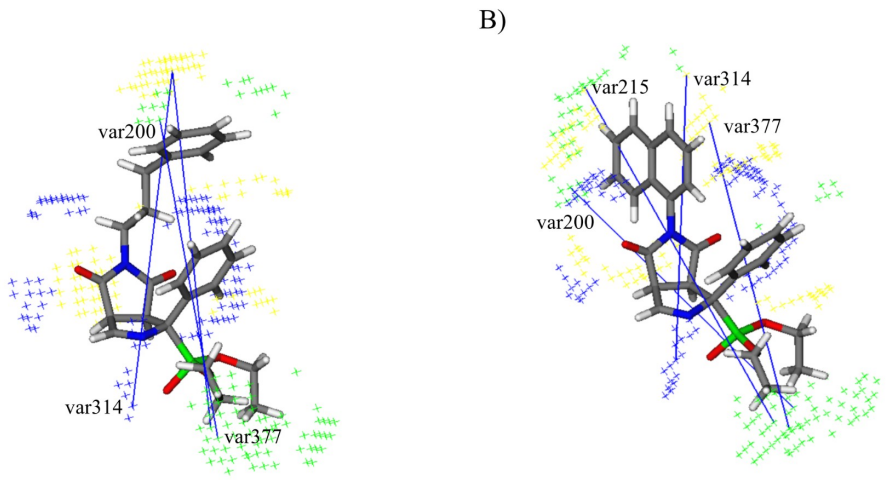


Figure S4. Representation of negative (in blue) interactions of **9m** (A) and **9ac** (B) in I_2-IR 3D-QSAR model. The steric hot spots (TIP) are presented in green, hydrophobic regions (DRY) in yellow and H-bond acceptor regions (N1) in blue.

The applicability domain (AD). In order to define AD of created I_2 and α_2 3D-QSAR models we have performed the leverage approach (Williams plot). SPSS v.18.0 software was used for this procedure.[8] The value of warning leverage h* was calculated according to relation $h^* = 3(p+1)/n$, where p presents the number of model variables (in this case we use five most significant variables according to PLS coefficient plot) and n is the number of compounds in training set. Figure S5 and S6 show that all compounds for both models are within of the defined AD.

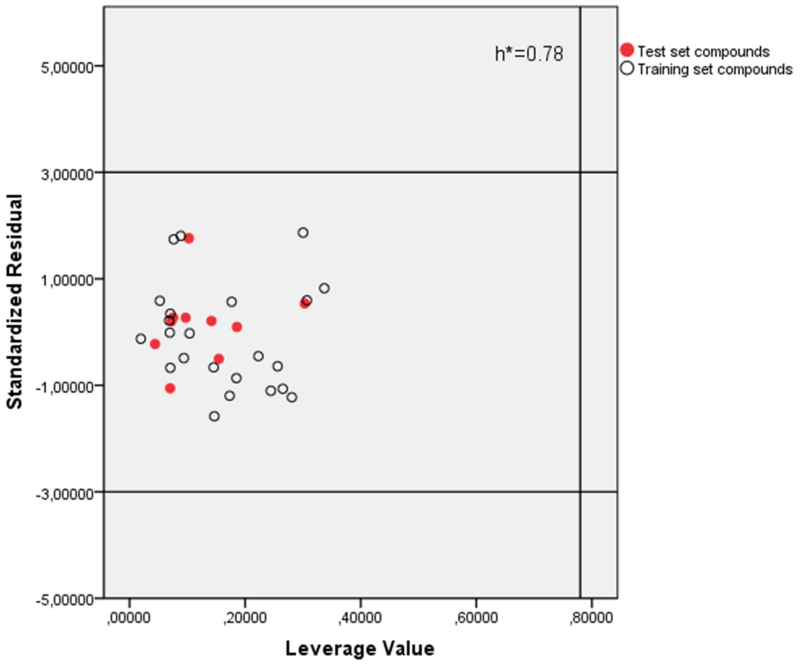


Figure S5. AD of developed I_2-IR 3D-QSAR model

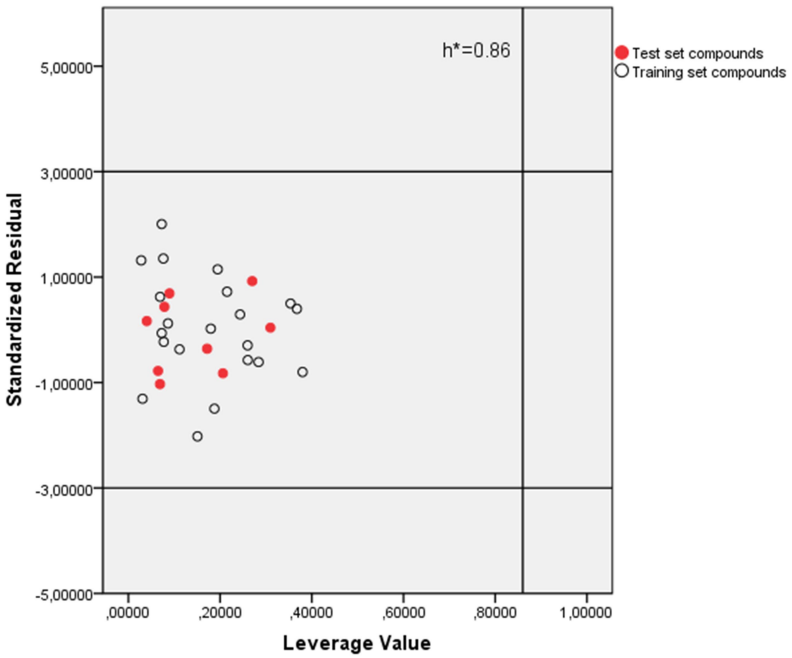


Figure S6. AD of developed α_2-AR 3D-QSAR model

Table S4. Results of physico-chemical parameters of I_2-IR ligands obtained from SwissADME web tool

Identifier	pKi(I_2)	MW <500 (g/mol)	Log S (ESOL) -10 to 0	Solubility class	Log $P_{o/w}$ (XLOGP3) < 5	Log $P_{o/w}$ (MLOGP) < 4.15	Log $P_{o/w}$ (WLOGP) < 5.6	Consensus Log $P_{o/w}$	RuleOf5	TPSA 20Å²<TPSA<130
Idazoxan, 4	7.41	204.23	-1.78	very soluble	0.70	0.99	0.07	1.23	Yes; 0 violation	42.85 Å²
Tracizoline, 5	7.58	173.23	-1.95	very soluble	1.31	2.10	-1.09	1.49	Yes; 0 violation	26.00 Å²
BU99008, 2	7.05	200.26	-2.27	soluble/ very soluble	1.29	1.95	-1.15	1.37	Yes; 0 violation	30.93 Å²
LSL60101, 3	8.13	214.22	-3.03	soluble	2.13	0.85	2.83	2.19	Yes; 0 violation	51.05 Å²
8c	7.73	350.31	-1.97	very soluble	0.27	0.98	1.71	1.34	Yes; 0 violation	95.08 Å²
9d	8.56	478.84	-4.19	moderately soluble	2.48	2.99	4.34	3.43	Yes; 0 violation	95.08 Å²
9b	9.74	432.45	-3.47	soluble	2.00	2.09	3.25	2.73	Yes; 0 violation	95.08 Å²
9c	10.28	426.40	-3.42	soluble	1.75	2.13	3.13	2.55	Yes; 0 violation	95.08 Å²
9a	7.97	364.33	-2.00	soluble/ very soluble	0.19	0.95	1.55	1.36	Yes; 0 violation	95.08 Å²
9z	7.90	502.50	-4.93	moderately soluble	3.38	3.16	4.79	3.89	Yes; 1 violation: MW>500	95.08 Å²
9f	8.37	378.36	-2.25	soluble	0.56	1.19	1.94	1.76	Yes; 0 violation	95.08 Å²
9h	7.35	406.41	-2.80	soluble	1.18	1.65	2.72	2.20	Yes; 0 violation	95.08 Å²
9i	7.01	498.55	-4.48	moderately soluble	3.10	3.13	4.14	3.63	Yes; 0 violation	95.08 Å²
12d	7.55	496.83	-4.35	moderately soluble	2.58	3.36	4.90	3.71	Yes; 0 violation	95.08 Å²
9ad	7.96	461.84	-3.56	soluble	1.64	1.61	3.17	2.44	Yes; 0 violation	107.97 Å²
13d	7.87	508.86	-4.27	moderately soluble	2.45	2.68	4.35	2.68	Yes; 1 violation: MW>500	104.31 Å²

Legend: MW – molecular weight; **Log S (ESOL)** – water solubility, topological method implemented from Delaney JS 2004 J. Chem. Inf. Model; **Solubility Class** - insoluble < -10 < poorly < -6 < moderately <-4 < soluble < -2 < very < 0 < highly; **XLOGP3 –** atomistic and knowledge-based method calculated by XLOGP program; **MLOGP** – topological method implemented from Moriguchi I. et al. 1992 Chem. Pharm. Bull.; **WLOGP** – atomistic method implemented from Wildman SA and Crippen GM. 1999 J. Chem. Inf. Model.; **Consensus Log Po/w –** average logP value of five predictions; **RuleOf5** - Lipinski's "Rule of Five"; **TPSA** – topological polar surface area.

Table S5. Selected pharmacokinetic properties of I_2-IR ligands obtained with ADMET Predictor program

Identifier	pKi(I_2)	S+Peff	BBB Filter	hum_ fup%	Pgp_ Substr	Pgp_Inh	CYP_ Risk	TOX_ Risk
Idazoxan, 4	7.41	3.854	High (98%)	60.075	No (93%)	No (96%)	2	1
Tracizoline, 5	7.58	3.042	High (98%)	57.803	No (93%)	No (96%)	1.451	3.365
BU99008, 2	7.05	3.145	High (98%)	57.69	No (93%)	No (96%)	1.215	2.927
LSL60101, 3	8.13	4.388	High (98%)	9.985	No (93%)	No (96%)	0.435	0
8c	7.73	2.273	High (77%)	23.11	No (93%)	No (96%)	0	1
9d	8.56	3.871	High (75%)	6.51	No (93%)	No (58%)	1.21	0.232
9b	9.74	2.707	High (74%)	10.274	No (93%)	No (63%)	1.541	0.386
9c	10.28	3.247	High (77%)	7.891	No (93%)	No (63%)	1.25	1
9a	7.97	3.01	High (76%)	27.813	No (93%)	No (96%)	0.772	0.677
9z	7.90	2.504	High (70%)	3.619	No (93%)	Yes (97%)	1.264	1.089
9f	8.37	2.972	High (76%)	22.087	No (93%)	No (96%)	0.996	0.66
9h	7.35	2.919	High (75%)	18.205	No (93%)	No (96%)	2.127	1.005
9i	7.01	2.391	High (74%)	6.64	No (93%)	No (46%)	2.198	1
12d	7.55	4.411	High (74%)	6.451	No (93%)	Yes (43%)	1.211	0.284
9ad	7.96	2.708	High (74%)	11.408	No (93%)	No (66%)	1.078	1
13d	7.87	3.248	High (74%)	6.596	No (93%)	Yes (43%)	1.191	0

Legend: S+Peff – estimated permeability, **BBB filter** - qualitative likelihood (High/Low) of crossing the blood-brain barrier; **hum_fup%** - percentage of unbound drug in plasma; **Pgp_Substr** - likelihood of P-glycoprotein efflux; **Pgp_Inh –** likelihood of a molecule being an inhibitor of P-glycoprotein; **CYP_Risk** – cytochrome P450 liability score; **Tox_Risk** – toxicity liability score.

***In vitro* Blood-Brain Barrier Permeation Assay**

To evaluate the brain penetration of the different compounds, a parallel artificial membrane permeation assay for blood-brain barrier was used, following the method described by Di et al (Table S6).[9] The *in vitro* permeability (P_e) of fourteen commercial drugs through lipid extract of porcine brain membrane together with the test compounds were determined. Commercial drugs and assayed compounds were tested using a mixture of PBS:ETOH (70:30). Assay validation was made by comparing the experimental permeability with the reported values of the commercial drugs by bibliography and lineal correlation between experimental and reported permeability of the fourteen commercial drugs using the parallel artificial membrane permeation assay was evaluated (y=1,572x-1,090; R^2=0,938). From this equation and taking into account the limits established by Di et al. for BBB permeation, we established the ranges of permeability as compounds of high BBB permeation (CNS+): *P*e (10^{-6} cms^{-1}) > 5,198; compounds of low BBB permeation(CNS-): *P*e (10^{-6} cm s^{-1}) < 2,054 and compounds of uncertain BBB permeation(CNS+/-): 5,198 > *P*e (10^{-6} cm s^{-1}) > 2,054.

Table S6. Permeability Results *P*e (10^{-6} cm s^{-1}) from the PAMPA-BBB Assay for new reported compounds and Their Prediction of BBB Penetration.

Compound	*P*e (10^{-6} cm s^{-1})[a]	Prediction
8a	1.2±0.04	CNS-
8b	7.5±0.6	CNS+
8c	4.3±0.3	CNS+/-
8d	9.4±1.2	CNS+
8e	5.13±0,95	CNS+/-
9a	0.75±0.13	CNS-
9b	25.9±0.6	CNS+
9c	7.8±0.6	CNS+
9d	9.7±0.7	CNS+
9e	3.9±0.15	CNS+/-
14c	6.9±0.3	CNS+
12c	3.2±0.16	CNS+/-
12d	4.4±0.09	CNS+/-
13c	1.8±0.06	CNS-
13d	1.9±0.06	CNS-
15c	9.5±0.5	CNS+
9f	3.7±0.5	CNS+/-
9g	6.2±0.3	CNS+
9h	6.3±0.3	CNS+
9i	6.7±0.3	CNS+
9j	>30	CNS+
9k	6.2±0.3	CNS+
9l	7.2±0.45	CNS+
9m	21.2±2.77	CNS+
9n	5.6±0,15	CNS+

9o	6.9±0.2	CNS+
9p	3.2±0.2	CNS+/-
9q	5.5±0.03	CNS+
9r	5.3±0.14	CNS+/-
9s	3.7±0.1	CNS+/-
9t	4.4±0.4	CNS+/-
9u	8.3±0.45	CNS+
9v	8.9±0.3	CNS+
9w	9.8±0.6	CNS+
9x	4.5±0.25	CNS+/-
9y	1.4±0.04	CNS-
9z	8.2±0.3	CNS+
9aa	8.75±0.5	CNS+
9ab	6.5±0.02	CNS+
9ac	1.4±0.06	CNS-
9ad	1.1±0.15	CNS-

a. PBS/EtOH (70:30) was used as solvent. Values are expressed as mean±SD of at least three independent experiments.

Cytotoxicity assays

All tumor cell lines were acquired from the American Type Culture Collection (ATCC, Manassas, VA, USA), except for the DND-41 cell line, which was purchased from the Deutsche Sammlung von Mikroorganismen und Zellkulturen (DSMZ Leibniz-Institut, Germany), and the Hap-1 cell line which was ordered from Horizon Discovery (Horizon Discovery Group, UK). All cell lines were cultured as recommended by the suppliers. Media were purchased from Gibco Life Technologies, USA, and supplemented with 10% fetal bovine serum (HyClone, GE Healthcare Life Sciences, USA). Adherent cell lines HCT-116, NCI-H460, LN-229, Hap-1 and Capan-1 cells were seeded at a density between 500 and 1500 cells per well, in 384-well, black walled, clear-bottomed tissue culture plates (Greiner). After overnight incubation, cells were treated with the test compounds at seven different concentrations ranging from 100 to 6.4×10^{-3} µM. Suspension cell lines HL-60, K-562, Z-138, and DND-41 were seeded at densities ranging from 2500 to 5500 cells per well in 384-well, black walled, clear-bottomed tissue culture plates containing the test compounds at the same seven concentration points. The plates were incubated and monitored at 37°C for 72 h in an IncuCyte® (Essen BioScience Inc., Ann Arbor, MI, USA) for real-time imaging. Images were taken every 3 h, with one field imaged per well under 10x magnification.

Microsomal stability of human, rat and mice microsomes

Human, rat and mice microsomes from Tebu-Xenotech were employed in the assay. They content 20 mg/mL of protein.

Brief protocol: The following quantities were added to each well of a 96-well microplate.

	Blank (µL)	Human (µL)	Mice (µL)	Rat (µL)
Phosphate buffer Na/K 50 mM pH 7.4	295	283.5	301.3	301.3
$MgCl_2$ 30 mM	50	50	50	50
NADP 10 mM	50	50	50	50
Glucose 6-P 100mM	50	50	50	50
Glucose 6-P DH 20 U/mL	25	25	25	25
Water	25			
Human microsomes		36.5		
Rat microsomes				18.7
Mice microsomes			18.7	
Test compound	5	5	5	5

Plates were incubated at 37°C and 75 µL samples were taken at 0, 10, 20, 40 and 60 min. Samples were transferred to a microplate and 75 µL Acetonitrile were added for inactivating the microsomes, and 30 µL of H_2O for improving the chromatographic conditions and kept at 4 °C. When all the samples were taken the plate was centrifuged at 46000 g for 30 min at 15 °C. Supernatant was taken and injected in the UPLC-MS/MS.

Stationary phase: Reverse phase Acquity UPLC® BEH C18 1,7 µm (2.1 mm x 50 mm) (Waters). Mobile phase: A: Water+0.1% formic; B: acetonitrile+0.1% formic acid.

Gradient:

Time (min)	A	B
0	95%	5%
0.1	95%	5%
1	0%	100%
2.5	0%	100%
2.6	95%	5%
3	95%	5%

Flow: 0.6 mL/min

The chromatographic equipment employed was an UPLC QSM Waters Acquity. Compound concentrations were calculated from the UV peak areas. The response was linear in the range between 10 ng/mL and 0.3125 ng/mL.

Metabolic stability was calculated from the logarithm of the remaining **9d** at each of the times evaluated.

Table S7. Microsomal stability of human, rat and mice microsomes

Rat			Mice			Human		
% remanent (sampling time 60 min)	*t1/2 (min)*	*Clint (µL/min* mg prot)*	*% remanent (sampling time 60 min)*	*t1/2 (min)*	*Clint (µL/min* mg prot)*	*% remanent (sampling time 60 min)*	*t1/2 (min)*	*Clint (µL/min *mg prot)*
44.79	52.81	13.1	65.08	91.72	7.55	50.87	64.16	10.8

Solubility

The stock solutions (10^{-2} M) of the assayed compound were diluted to decreased molarity, from 300 µM to 0.1µM, in 384 well transparent plate (*Greiner* 781801) with 1% DMSO: 99% PBS buffer. Incubated at 37ºC and read after 2 h in a *NEPHELOstar Plus* (*BMG LABTECH*). The results were adjusted to a segmented regression to obtain the maximum concentration in which compound is soluble. **9d**, solubility 92 µM.

The stock solutions (10^{-3} M) of **9d** were diluted to decreased molarity, from 50 µM to 4 µM, with MeOH, acetonitrile and water (with 17% added methanol). The different dilutions were filtrated thorough PVDF 0.45 µm filters and read in a spectrophotometer-DAD (Analytical Jena) at 215 and 220 nm in order to obtain a segmented regression. Additionally, a saturated solution was prepared, filtered, read and adjusted to calculate the maximum concentration in which compound is soluble. The solubility of **9d** in MeOH, acetonitrile and water and classification according to Ph. Eur. is 35.08 mg/mL (soluble), 102.7 mg/mL (freely soluble) and 0.17 mg/mL (very slightly soluble), respectively.

Chemical stability

In order to evaluate the stability, weekly HPLC were performed on the **9d** exposed sample to stress conditions (see manuscript). **9d** 0.2 mg/mL, phase mobil (A: H_20 + 0.05% formic acid and B: ACN + 0.05% formic acid) at 1:1 proportion. Stationary phase, Poroshell 120 EC-C15 (4.6x50 mm, 2.7-micro). Mobile phase (A: H_20 + 0.05% formic acid and B: ACN + 0.05% formic acid) using a gradient elution. Flow rate 0.6 mL/min. The DAD detector was set at 254 nm and the injection volume was 5 µL and oven temperature 40 ºC.

Cytochrome inhibition

The objective of this study was to screen the inhibition potential of the compounds using recombinant human cytochrome P450 enzymes (CYP1A2, CYP2C9, CYP2C19, CYP2D6 and CYP3A4) and probe substrates with fluorescent detection.

Incubations were conducted in a 200 µL volume in 96 well microtiter plates (COSTAR 3915). Addition of cofactor-buffer mixture (KH_2PO_4 buffer, 1.3mM $NADP^+$, 3.3mM $MgCl_2$, 3.3 mM Glucose-6-phosphate and 0.4U/mL Glucose-6-phosphate Dehydrogenase), supersomes control, standard inhibitors (Furafyline, Tranylzypromine, Ketoconazole, Sulfaphenazole and Quinidine; from Sigma Aldrich) and test compounds to plates were carried out by a liquid handling station (Zephyr Caliper). The plate was then pre-incubated at 37ºC for 5 min, and the reaction initiated by the addition of pre-warmed enzyme/substrate (E/S) mix. The E/S mix contained buffer (KH_2PO_4), c-DNA-expressed P450 in insect cell microsomes, substrate (3-cyano-7-ethoxycoumarin (CEC) for CYP1A2 and CYP2C19, 7-methoxy-4-(trifluoromethyl)coumarin (7-MFC) for CYP2C9, 3-[2-(*N*,*N*-diethyl-*N*-methylammonium)ethyl]-7-methoxy-4-methylcoumarin (AMMC) for CYP2D6, 7-benzyloxytrifluoromethyl coumarin (7-BFC) and Dibenzylfluorescein (DBF) for CYP3A4) to give the final assay concentrations in a reaction volume of 200 µL. Reactions were terminated after different incubation times depending on the each cytochrome by addition of STOP solution (ACN/TrisHCl 0.5M 80:20 and NaOH 2N for CYP3A4 (DBF) and ACN/TrisHCl 0.5M 80:20 for the other cytochromes).

Fluorescence per well was measured using a fluorescence plate reader (Tecan M1000 pro) and percentage of inhibition was calculated taking into account the compound-free wells and the wells with reference compounds.

Results for **9d**: CYP1A2 (%inhib 10 µM) 1 ± 1; CYP2C9 (%inhib 10 µM) 26 ± 6; CYP3A4 (BFC) (%inhib 10 µM) 53 ± 1; CYP3A4 (DBF) (%inhib 10 µM) 48 ± 1; CYP2D6 (%inhib 10 µM) 27 ± 4.

hERG ion channel inhibition

The assays were carried out at a CHO cell line transfected with the hERG potassium channel. Cells were grown in the presence of doxycycline for inducing the channel expression and kept at 30°C for 24 h before running the assay. Plate was primed with extracellular (2 mM $CaCl_2$; 1 mM $MgCl_2$; 10 mM Hepes; 4 mM KCl; 145 mM NaCl; 10 mM glucose; pH=7.4) and intracellular (5.374 mM $MgCl_2$; 1.75 mM $MgCl_2$; 10 mM EGTA; 10 mM Hepes; 120 mM KCl; 4 mM Na2-ATP; pH=7.2) solutions and the compounds dissolved in the extracellular solution. Cells were detached and suspended in the extracellular solution and dispensed in the assay plate at a density of 3*106 cells/well. Plate was introduced in the automated patch-clamp reader (Ionflux HT) and the hERG channel currents were evoked by a 5 sec depolarization step (from -80 mV to +20mV) which was followed by a 5 second tail step to -50mV.

Current was normalized to the maximum inhibition shown by controls and percentage of inhibition calculated. Inhibitory activity of **9d** at hERG channel, % inhibition (10 μM): 30.5 ± 7.7.

Human and mouse plasma protein binding

Human and mouse plasma from Seralab was employed in the assay.

Brief protocol: The assay was carried out by employing Rapid Equilibrium Dyalisis (RED) from Thermo Scientific. The compounds were dissolved at 5 µM in plasma and added to the corresponding insert of the RED device. Dialysis buffer was added to the corresponding insert of the RED device. Plate was incubated for 4h at 37°C. After the incubation period 50 µL aliquots of each chamber were transferred to empty vials. 50 µL of dialysis buffer were added to the plasma samples and 50 µL of plasma were added to the buffer samples. 300 µL of acetonitrile were added to all the samples and centrifuged at 4000 rpm 100 µL aliquots of the supernatants were transferred to a LC analysis plate and diluted with 100 µL of water. Samples were analyzed in a UPLC/MS/MS. Stationary phase: Reverse phase Acquity UPLC® BEH C18 1,7 µm (2.1 mm x 100 mm) (Waters). Mobile phase: 125 mM Ammonium hydroxide/acetonitrile

Gradient:

Time	Ammonium hydroxide	Acetonitrile
0	95%	5%
0.1	95%	5%
1	0%	100%
2	0%	100%
2.1	95%	5%
2.5	95%	5%

Flow: 0.6 mL/min

The chromatographic equipment employed was an UPLC QSM Waters Acquity. Compound concentrations were calculated from the MS peak areas.

Table S8. Human and mouse plasma protein binding

	Mouse		Human	
Compound	***Plasma protein binding***	***Unbound fraction***	***Plasma protein binding***	***Unbound fraction***
9d	96.29%	3.71%	91.97%	8.03%

Receptor characterization panel

Table S9. Eurofins radioligand displacement using 10 µM 9d. Displacement greater than 50% is considered significant.

Compound I.D.	Client Compound I.D.	Test Concentration	% Inhibition of Control Specific Binding 1st	2nd	Mean
A_{2A} *(h)* (agonist radioligand)					
100046828-1	B06	1.0E-05 M	1.4	-10.1	-4.4
α_{1A} *(h)* (antagonist radioligand)					
100046828-1	B06	1.0E-05 M	1.9	10.1	6.0
α_{2A} *(h)* (antagonist radioligand)					
100046828-1	B06	1.0E-05 M	14.2	2.2	8.2
β_1 *(h)* (agonist radioligand)					
100046828-1	B06	1.0E-05 M	-11.7	-10.3	-11.0
β_2 *(h)* (antagonist radioligand)					
100046828-1	B06	1.0E-05 M	1.1	-4.3	-1.6
BZD (central) (agonist radioligand)					
100046828-1	B06	1.0E-05 M	-5.7	7.7	1.0
CB_1 *(h)* (agonist radioligand)					
100046828-1	B06	1.0E-05 M	-10.5	2.3	-4.1
CB_2 *(h)* (agonist radioligand)					
100046828-1	B06	1.0E-05 M	2.7	6.1	4.4
CCK_1 (CCK_A) *(h)* (agonist radioligand)					
100046828-1	B06	1.0E-05 M	72.1	68.7	**70.4**
D_1 *(h)* (antagonist radioligand)					
100046828-1	B06	1.0E-05 M	10.4	29.8	20.1
D_{2S} *(h)* (agonist radioligand)					
100046828-1	B06	1.0E-05 M	14.6	-7.1	3.8
ET_A *(h)* (agonist radioligand)					
100046828-1	B06	1.0E-05 M	11.8	-2.4	4.7
NMDA (antagonist radioligand)					
100046828-1	B06	1.0E-05 M	9.1	3.4	6.3
H_1 *(h)* (antagonist radioligand)					
100046828-1	B06	1.0E-05 M	-3.7	-2.6	-3.2
H_2 *(h)* (antagonist radioligand)					
100046828-1	B06	1.0E-05 M	-16.7	-8.8	-12.7
MAO-A (antagonist radioligand)					
100046828-1	B06	1.0E-05 M	0.9	10.5	5.7

M_1 *(h)* (antagonist radioligand)					
100046828-1	B06	1.0E-05 M	-20.3	-9.3	-14.8
M_2 *(h)* (antagonist radioligand)					
100046828-1	B06	1.0E-05 M	0.1	-1.1	-0.5
M_3 *(h)* (antagonist radioligand)					
100046828-1	B06	1.0E-05 M	-8.9	-4.1	-6.5
N neuronal α4β2 *(h)* (agonist radioligand)					
100046828-1	B06	1.0E-05 M	-9.1	-5.3	-7.2
δ (DOP) *(h)* (agonist radioligand)					
100046828-1	B06	1.0E-05 M	-13.9	-7.4	-10.6
kappa (h) (KOP) (agonist radioligand)					
100046828-1	B06	1.0E-05 M	47.4	47.2	47.3
μ (MOP) *(h)* (agonist radioligand)					
100046828-1	B06	1.0E-05 M	1.9	11.2	6.6
5-HT_{1A} *(h)* (agonist radioligand)					
100046828-1	B06	1.0E-05 M	-1.1	1.6	0.2
5-HT1B(h) (antagonist radioligand)					
100046828-1	B06	1.0E-05 M	-14.8	1.2	-6.8
5-HT_{2A} *(h)* (agonist radioligand)					
100046828-1	B06	1.0E-05 M	-3.2	-11.6	-7.4
5-HT_{2B} *(h)* (agonist radioligand)					
100046828-1	B06	1.0E-05 M	13.4	-9.6	1.9
5-HT_3 *(h)* (antagonist radioligand)					
100046828-1	B06	1.0E-05 M	-15.2	-12.1	-13.7
GR *(h)* (agonist radioligand)					
100046828-1	B06	1.0E-05 M	-2.6	-6.0	-4.3
AR *(h)* (agonist radioligand)					
100046828-1	B06	1.0E-05 M	-12.6	-11.3	-12.0
V_{1a} *(h)* (agonist radioligand)					
100046828-1	B06	1.0E-05 M	32.7	32.3	32.5
Ca^{2+} channel (L, dihydropyridine site) (antagonist radioligand)					
100046828-1	B06	1.0E-05 M	22.6	24.1	23.3
Potassium Channel hERG (human)- [3H] Dofetilide					
100046828-1	B06	1.0E-05 M	-10.1	-11.3	-10.7
K_V channel (antagonist radioligand)					
100046828-1	B06	1.0E-05 M	10.7	-4.8	2.9
Na^+ channel (site 2) (antagonist radioligand)					
100046828-1	B06	1.0E-05 M	13.0	10.8	11.9
norepinephrine transporter *(h)* (antagonist radioligand)					
100046828-1	B06	1.0E-05 M	-10.3	-5.1	-7.7
dopamine transporter *(h)* (antagonist radioligand)					
100046828-1	B06	1.0E-05 M	1.8	12.6	7.2
5-HT transporter *(h)* (antagonist radioligand)					
100046828-1	B06	1.0E-05 M	-9.2	0.7	-4.3

Reference compounds results:

Compound I.D.	IC_{50} (M)	K_i (M)	nH
A_{2A} *(h)* (agonist radioligand)			
NECA	8.1E-08 M	6.6E-08 M	0.8
α_{1A} *(h)* (antagonist radioligand)			
WB 4101	4.9E-10 M	2.5E-10 M	1.2
α_{2A} *(h)* (antagonist radioligand)			
yohimbine	1.2E-08 M	5.4E-09 M	1.0
β_1 *(h)* (agonist radioligand)			
atenolol	4.8E-07 M	2.7E-07 M	1.2
β_2 *(h)* (antagonist radioligand)			
ICI 118551	7.0E-10 M	2.3E-10 M	1.0
BZD (central) (agonist radioligand)			
diazepam	9.4E-09 M	7.9E-09 M	1.5
CB_1 *(h)* (agonist radioligand)			
CP 55940	1.8E-09 M	1.6E-09 M	1.0
CB_2 *(h)* (agonist radioligand)			
WIN 55212-2	3.1E-09 M	2.0E-09 M	1.0
CCK_1 (CCK_A) *(h)* (agonist radioligand)			
CCK-8s	4.5E-11 M	3.4E-11 M	0.6
D_1 *(h)* (antagonist radioligand)			
SCH 23390	3.1E-10 M	1.2E-10 M	1.4
D_{2S} *(h)* (agonist radioligand)			
7-OH-DPAT	1.5E-09 M	6.1E-10 M	1.2
ET_A *(h)* (agonist radioligand)			
endothelin-1	3.1E-11 M	1.5E-11 M	0.9
NMDA (antagonist radioligand)			
CGS 19755	3.5E-07 M	2.9E-07 M	1.0
H_1 *(h)* (antagonist radioligand)			
pyrilamine	3.0E-09 M	1.9E-09 M	1.1
H_2 *(h)* (antagonist radioligand)			
cimetidine	6.7E-07 M	6.6E-07 M	1.3
MAO-A (antagonist radioligand)			
clorgyline	1.5E-09 M	8.9E-10 M	2.5
M_1 *(h)* (antagonist radioligand)			
pirenzepine	2.2E-08 M	1.9E-08 M	1.3
M_2 *(h)* (antagonist radioligand)			
methoctramine	4.0E-08 M	2.8E-08 M	1.2
M_3 *(h)* (antagonist radioligand)			
4-DAMP	1.4E-09 M	9.8E-10 M	1.7
N neuronal α4β2 *(h)* (agonist radioligand)			
nicotine	3.1E-09 M	1.0E-09 M	0.9
δ (DOP) *(h)* (agonist radioligand)			
DPDPE	3.2E-09 M	1.7E-09 M	1.0
kappa (h) (KOP) (agonist radioligand)			
U50488	6.8E-10 M	3.7E-10 M	1.1
μ (MOP) *(h)* (agonist radioligand)			
DAMGO	8.1E-10 M	3.3E-10 M	1.1
$5\text{-}HT_{1A}$ *(h)* (agonist radioligand)			
8-OH-DPAT	1.3E-09 M	6.4E-10 M	0.8

5-HT1B(h) (antagonist radioligand)			
Serotonine	1.9E-07 M	8.5E-08 M	0.7
5-HT_{2A} *(h)* (agonist radioligand)			
(±)DOI	3.8E-10 M	2.8E-10 M	1.0
5-HT_{2B} *(h)* (agonist radioligand)			
(±)DOI	2.6E-09 M	1.3E-09 M	1.3
5-HT_3 *(h)* (antagonist radioligand)			
MDL 72222	1.1E-08 M	7.6E-09 M	1.0
GR *(h)* (agonist radioligand)			
dexamethasone	3.7E-09 M	1.8E-09 M	0.9
AR *(h)* (agonist radioligand)			
testosterone	3.1E-09 M	1.4E-09 M	0.9
V_{1a} *(h)* (agonist radioligand)			
$[d(CH_2)_5{}^1,Tyr(Me)_2]$-AVP	2.1E-09 M	1.3E-09 M	1.1
Ca^{2+} channel (L, dihydropyridine site) (antagonist radioligand)			
nitrendipine	1.8E-10 M	1.2E-10 M	1.2
Potassium Channel hERG (human)- [3H] Dofetilide			
Terfenadine	1.3E-07 M	9.2E-08 M	1.0
K_V channel (antagonist radioligand)			
α-dendrotoxin	1.1E-10 M	8.5E-11 M	0.9
Na^+ channel (site 2) (antagonist radioligand)			
veratridine	6.9E-06 M	6.2E-06 M	1.1
norepinephrine transporter *(h)* (antagonist radioligand)			
protriptyline	5.0E-09 M	3.7E-09 M	1.3
dopamine transporter *(h)* (antagonist radioligand)			
BTCP	1.5E-08 M	7.7E-09 M	1.1
5-HT transporter *(h)* (antagonist radioligand)			
imipramine	3.1E-09 M	1.4E-09 M	1.1

***5xFAD In vivo* experimental design**

Table S10. SYBR Green primers used in qPCR studies.

Target	Product size (bp)	Forward primer (5'-3')	Reverse primer (5'-3')
Cxcl10	72	GGCTAGTCCTAATTGCCCTTGG	TTGTCTCAGGACCATGGCTTG
Tnf-α	157	TCGGGGTGATCGGTCCCCAA	TGGTTTGCTACGACGTGGGCT
iNOS	125	GGCAGCCTGAGAGACCTTTG	GGAAGCGTTTCGGGATCTGAA
β-actin	190	CTGTCCCTGTATGCCTCTG	ATGTCACGCACGATTTCC

Table S11. TaqMan probes used in qPCR studies.

Target	Product size (bp)	Reference
Hmox1	69	Mm00516005_m1
Tbp	93	Mm00446971_m1

Statistical analysis

The statistical analysis was conducted using GraphPad Prism ver.7 statistical software. Data were expressed as the mean ± Standard Error of the Mean (SEM) from at least 10 samples per group. Means were compared to One-Way ANOVA analysis of variance, followed by Tukey-Kramer multiple comparison post-hoc analysis. Comparisons between groups were also performed by two-tail Student's *t*-test for independent samples. Statistical significance was considered when p-values were <0.05. The statistical outliers were carried out with Grubss' test and subsequently removed from the analysis.

NMR spectra data

The ^{1}H and ^{13}C spectra of the 37 new synthetized compounds **9-15** showed coupling constants (*J*) between ^{1}H-P and ^{13}C-P. Significant coupling constants ^{1}H-P (in green) and ^{1}H-^{1}H (in blue) for representative compound **9c** are depicted (Figure). In particular, the imine proton H-3 exhibits a ^{1}H-P *J* of ~ 5 Hz, and the bridged protons H-3a and H-6a have ^{1}H-P *J* of ~ 3 Hz and ~ 18 Hz (in green), respectively. Additionally, ^{1}H-^{1}H *J* of 1.5 Hz between H-3 and H-3a, and 9 Hz of the geminal H-3a and H-6a are observed (in blue). In the ^{13}C spectra a *J* of ~ 160 Hz was observed between C1 and the P. In a similar fashion the peaks corresponding to C3a appears as doblets due to the *J* of ~ 12 Hz with the P atom (in red). Noteworthy, spectra of compounds **9r**, **9y**, **9ac** and **9ad** with an *ortho* substituted *N*-phenyl showed the presence of rotamers, same multiplicity (^{1}H-NMR) different shift (^{1}H-NMR and ^{13}C-NMR), due to the restricted rotation of the *N*-C*ipso* phenyl bond. For a complete table on the representative peaks in the ^{1}H-NMR and ^{13}C-NMR spectra of all the new compunds see Tables S12 and S13.

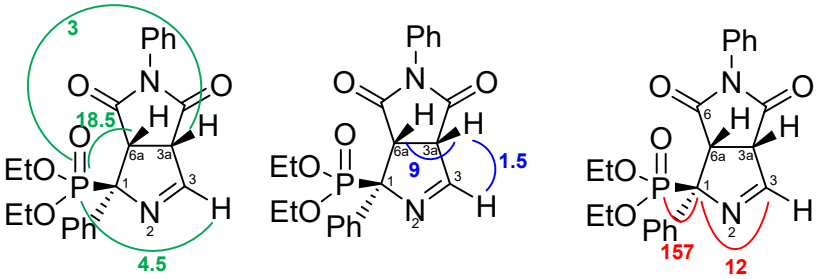


Figure. Coupling constants for **9c**, ^{1}H-P (in green), ^{1}H-H (in blue), ^{13}C-P (in red).

Table S12. ^{1}H chemical shifts (ppm) for new compounds including both the multiplicity and the coupling constants (*J* Hz).

Compound	**H3**	**H3a**	**H6a**
9a	7.95, dd 5.5, 1.0	4.34, ddd 8.5, 4.0, 1.0	4.01, m
9b	8.00, dd 5.0, 1.5	4.25, ddd 8.5, 3.0, 1.5	4.03, dd 18.5, 8.5
9c	7.97, dd 4.5, 1.6	4.40, ddd 8.5, 3.0, 1.5	4.17, dd 18.5, 9.0
9d	8.05, d 4.5	4.47, m	4.25, dd 18.0, 8.0
9e	8.04, dd 5.0, 1.5	4.45, ddd 8.5, 3.0, 1.5	4.25, dd 18.0, 8.5
14c	7.82, dd 5.0, 1.5	4.39, dq 9.0, 1.5	3.97, dd 19.0, 9.0
15c	7.82, dd 5.0, 1.5	4.39, ddd 9.5, 3.5, 1.5	3.96, dd 19.0, 9.5
12c	8.04, dd 5.0, 1.5	4.49, dq 8.5, 1.5	4.25, dd 18.0, 8.5
13c	8.02, dd 5.5, 1.5	4.46, ddd 8.5, 3.0, 1.5	4.23, dd 18.0, 8.5
12d	8.02, dd 5.0, 1.5	4.49, ddd 8.5, 3.0, 1.5	4.25, dd 18.0, 8.5
13d	8.02, dd 5.0, 1.5	4.46, ddd 8.5, 3.0, 1.5	4.22, dd 18.0, 8.5
9f	7.96, dd 5.0, 1.5	4.29, ddd 8.5, 3.5, 1.5	4.10, m
9g	7.95, dd 5.0, 1.5	4.30, ddd 8.5, 3.5, 1.5	4.06, m
9h	7.93, dd 5.0, 1.5	4.08, m	3.91, m
9i	7.95, dd 5.0, 1.0	4.29, ddd 8.5, 3.0, 1.0	4.11, dd 19.0, 8.5
9j	7.92, dd 5.0, 1.5	4.33, ddd 8.5, 3.5, 1.5	4.18, m
9k	7.85, dd 5.0, 1.0	4.24, ddd 8.5, 4.0, 1.0	4.16, m

9l	7.83, dd 5.5, 1.5	4.24, ddd 8.0, 4.0, 1.5	4.15, m
9m	8.00, dd 5.0, 1.5	4.31, ddd 9.0, 3.0, 1.5	4.17, m
9n	8.05, dd 5.0, 1.5	4.51, ddd 8.5, 3.0, 1.5	4.28, dd 18.0, 9.0
9o	8.06, dd 5.0, 1.5	4.50, ddd 9.0, 2.5, 1.5	4.27, dd 18.0, 9.0
9p	8.05, dd 5.0, 1.5	4.48, ddd 8.5, 3.0, 1.5	4.26, dd 18.0, 9.0
9q	8.04, dd 5.5, 1.0	4.47, ddd 8.5, 3.0, 1.0	4.25, dd 18.0, 9.0
9r **(rotamer A)**	8.03, dd 5.5, 1.5	4.52, ddd 8.5, 4.5, 1.5	4.35, dd 18.0, 8.5
9r **(rotamer B)**	8.08, dd 5.0, 1.5	4.56, ddd 8.5, 3.0, 1.5	4.36, dd 18.0, 8.5
9s	8.05, dd 5.0, 1.5	4.48, ddd 8.5, 3.0, 1.5	4.26, dd 18.0, 9.0
9t	8.04, dd 5.0, 1.5	4.47, ddd 9.0, 3.0, 1.5	4.25, dd 18.0, 9.0
9u	8.04, dd 5.0, 1.5	4.47, ddd 9.0, 2.5, 1.5	4.25, dd 18.0, 8.5
9v	8.04, dd 4.5, 1.5	4.47, ddd 8.5, 3.0, 1.5	4.26, dd 18.0, 8.5
9w	8.02, dd 5.0, 1.0	4.57, ddd 8.5, 4.0, 1.0	4.41, dd 18.0, 9.0
9x	8.07, dd 5.0, 1.0	4.53, ddd 9.0, 3.0, 1.0	4.30, dd 18.0, 9.0
9y **(rotamer A)**	8.05, dd 5.0, 1.5	4.59, ddd 9.0, 3.5, 1.5	4.39, dd 18.5, 9.0
9y **(rotamer B)**	8.08, dd 5.5, 2.5	4.55, ddd 10.0, 2.5, 1.5	4.35, dd 18.0, 9.0
9z	8.08, dd 5.0, 1.5	4.51, ddd 9.0, 3.0, 1.5	4.30, dd 18.5, 9.0
9aa	8.05, dd 5.0, 1.5	4.46, ddd 8.5, 3.0, 1.5	4.24, dd 16.5, 9.0
9aa	8.01, dd 5.0, 1.5	4.48, ddd 8.5, 3.0, 1.5	4.25, dd 18.0, 8.5
9ac **(rotamer A)**	8.13, dd 5.0, 1.5	4.63, ddd 9.0, 3.5, 1.5	4.43, dd 18.5, 9.0

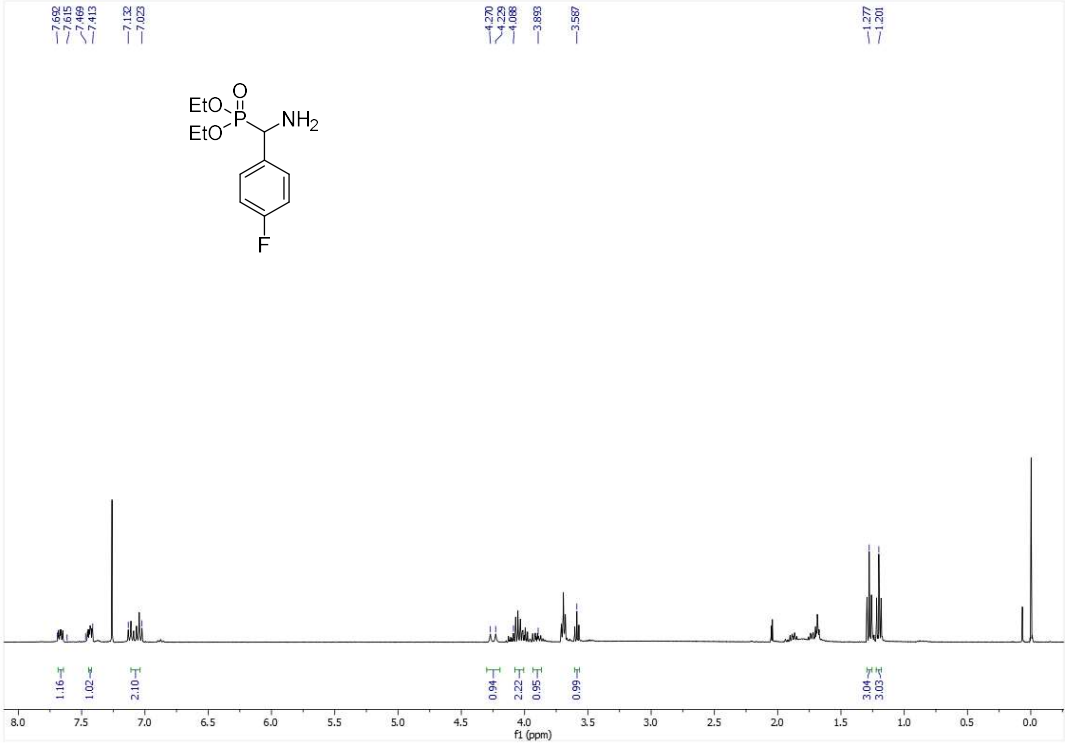
9ac (rotamer B)	8.12, dd 5.0, 1.5	4.67, ddd 8.5, 3.0, 1.5	4.46, dd 18.0, 8.5
9ad (rotamer A)	8.02, dd 5.5, 1.5	4.53, ddd 8.5, 4.0, 1.5	4.36, dd 18.0, 8.5
9ad (rotamer B)	8.07, dd 5.0, 1.5	4.58, ddd 8.5, 3.0, 1.5	4.36, dd 18.0, 8.5

Table S13. ^{13}C chemical shifts for new compounds (ppm) including both the multiplicity and the coupling constants (*J* Hz).

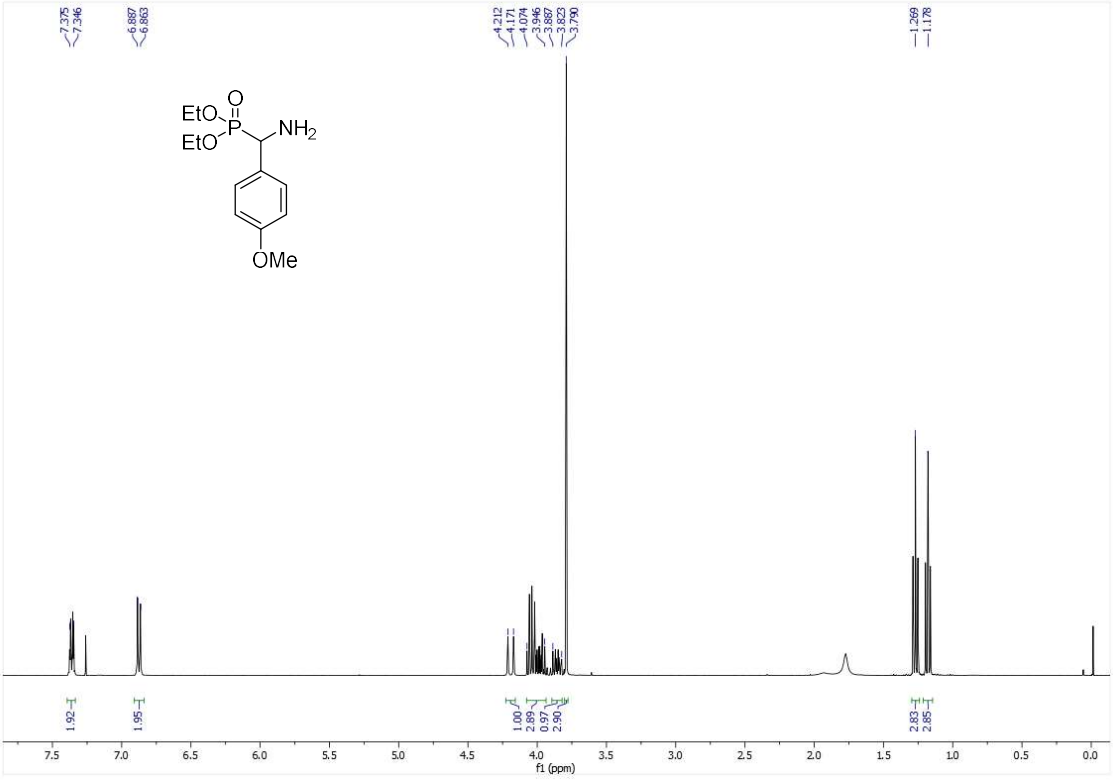
Compound	**C1**	**C3**	**C3a**	**C6a**
9a	85.6, d 154.0	162.5, d 11.5	60.5	47.7, d 2.0
9b	85.7, d 156.0	162.8, d 12.0	59.9	47.5, d 2.5
9c	86.2, d 157.0	162.5, d 12.0	60.2	48.2, d 2.0
9d	86.2, d 156.0	162.0, d 12.5	60.1	48.5
9e	86.2, d 157.5	162, d 12.0	60.1	48.1, d 2.0
14c	83.7, d 158.0	161.3,d 13.0	59.9	45.9, d 3.0
15c	87.3, d 159.5	161.5, d 12.5	59,9	45.9, d 2.5
12c	85.9, d 156.0	162.8,d 12.0	60.5	48.1, d 3.0
13c	86.0, d 157.0	162.3, d 12.0	60.3	48.3, d 3.0
12d	86.0, d 156.0	162.4, d 12.0	60.3	48.2, d 3.0
13d	86.0, d 158.0	161.8, d 13.0	60.1	48.6, d 3.0
9f	85.8, d 155.0	162.7, d 12.0	60.5	47.9, d 2.0
9g	85.9, d 154.0	162.8, d 12.0	60.5	47.8, d 3.0
9h	86.6, d 158.0	163.3, d 12.0	60.2	48.1 ,d 2.0
9i	86.0, d 155.0	162.6, d 12.0	60.6	47.7, d 2.0
9j	85.7, d 155.0	162.3, d 11.5	60.4	47.8, d 2.0

9k	---	162.6, d 11.5	60.2	47.5, d 2.5
9l	85.7, d 153.0	162.5, d 12.0	60.3	47.5, d 2.0
9m	86.1, d 157.0	162.7, d 12.0	60.2	48.0, d 2.0
9n	86.3, d 157.0	162.0, d 13.0	60.1	48.3, d 3.0
9o	86.4, d 158.0	162.1, d 12.0	60.2	48.6, d 2.0
9p	86.2, d 157.0	162.2, d 12.0	60.1	48.2, d 3.0
9q	86.4, d 157.0	162.2, d 12.0	60.2	48.4, d 2.0
9r (rotamer A)	86.0, d 157.5	162.0, d 11.5	60.1	48.0, d 2.5
9r (rotamer B)	86.6, d 153.5	162.2, d 12.5	60.3	48.6, d 2.5
9s	86.4, d 157.0	162.3, d 12.0	60.2	48.5, d 3.0
9t	86.4, d 157.0	162.2, d 12.0	60.3	48.4, d 3.0
9u	86.5, d 158.0	162.0, d 13.0	60.9	48.6, d 3.0
9v	86.2, d 157.0	161.9, d 13.0	60.0	48.4, d 3.0
9w	86.7, d 152.0	161.8, d 11.0	61.0	48.3, d 3.0
9x	86.2, d 158.0	161.7, d 12.0	60.0	48.5, d 2.0
9y (rotamer A)	86.6, d 154.5	161.9, d 11.5	61.0	48.3, d 2.5
9y (rotamer B)	86.3, d 159.0	161.8, d 12.5	60.1	49.2, d 2.5
9z	86.5, d 157.0	162.3, d 12.0	60.2	48.2, d 2.5

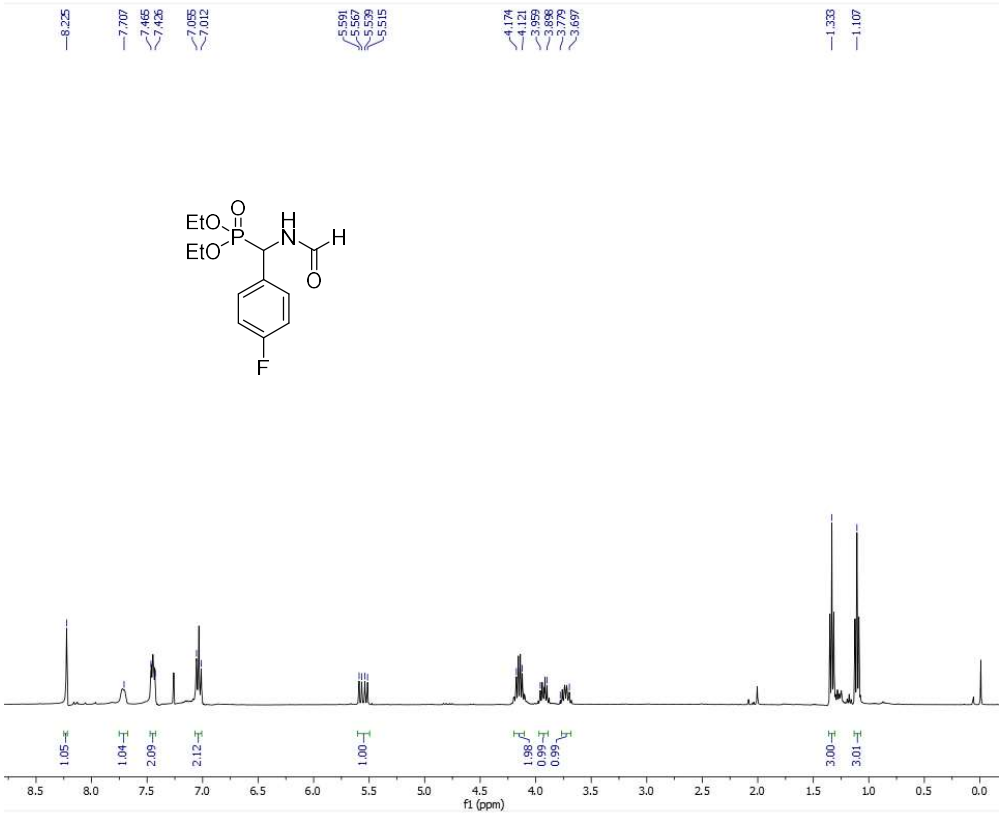
9aa	86.2, d 156.0	162.4, d 12.0	60.2	48.1, d 3.0
9aa	86.2, d 157.0	162.2, d 12.0	60.1	48.2, d 3.0
9ac **(rotamer A)**	86.5, d 155.0	162.3, d 11.5	61.0	48.3, d 2.5
9ac **(rotamer B)**	86.2, d 157.5	162.4, d 12.0	60.3	48.6, d 2.5
9ad **(rotamer A)**	86.1, d 158.0	161.6, d 11.5	60.4	48.4, d 2.5
9ad **(rotamer B)**	86.9, d 153.0	162.0, d 12.5	61.0	49.0, d 2.5



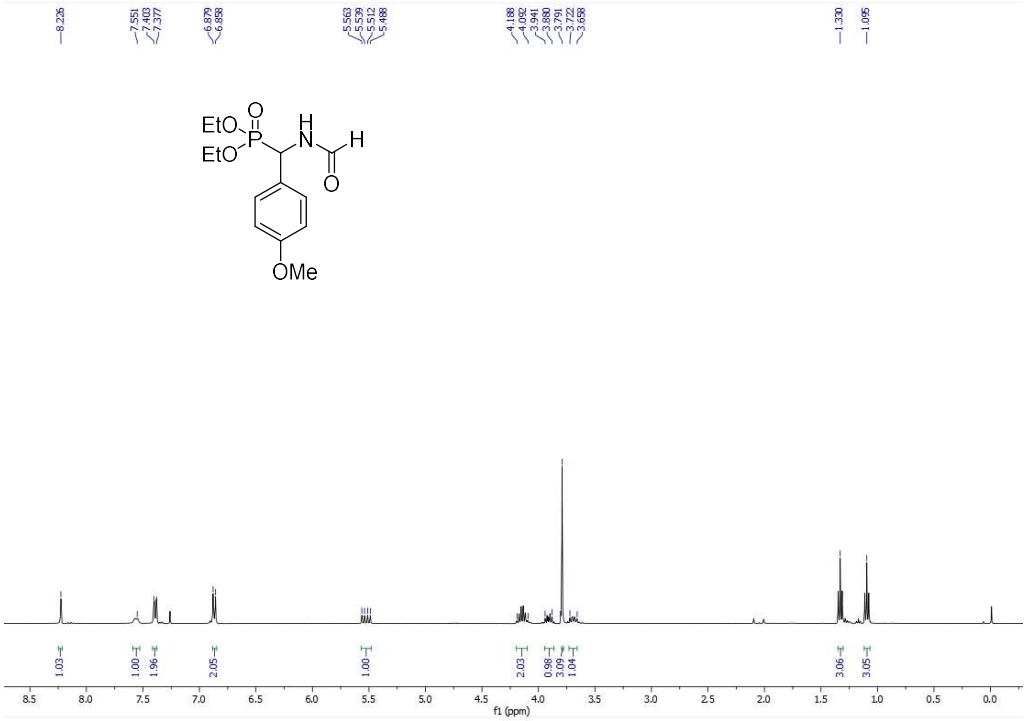
Diethyl [amino(4-fluorophenyl)methyl]phosphonate (step 1-10b)



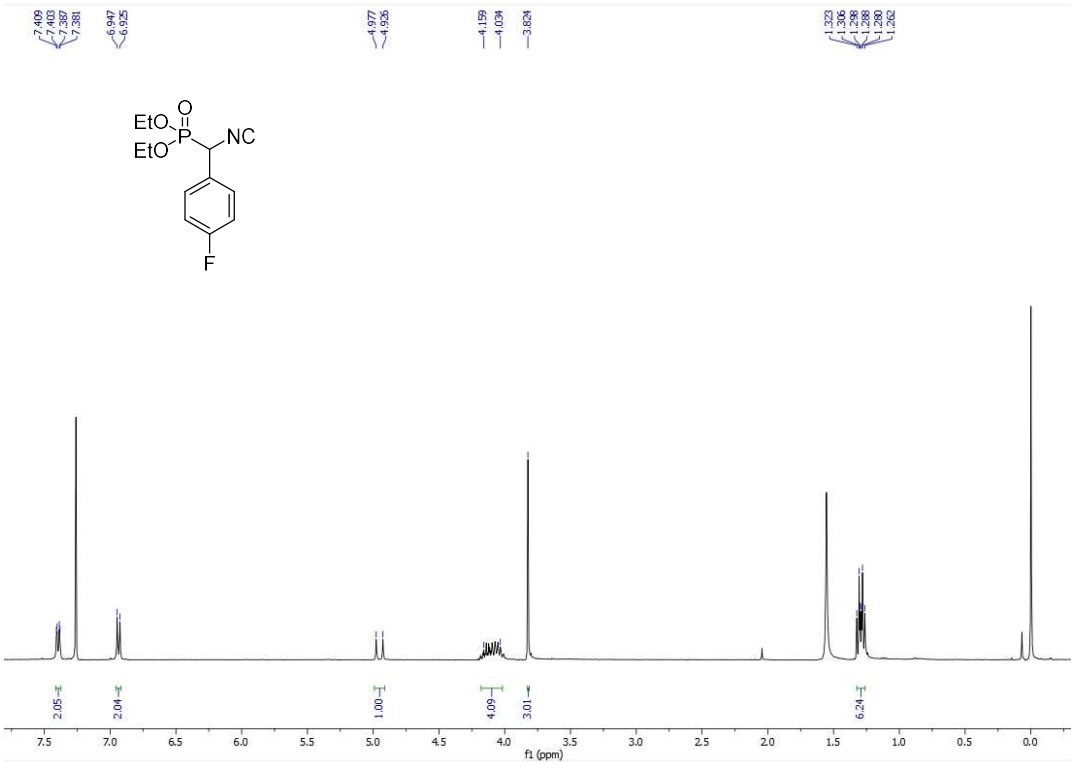
Diethyl [amino(4-methoxyphenyl)methyl]phosphonate (step 1-10c)



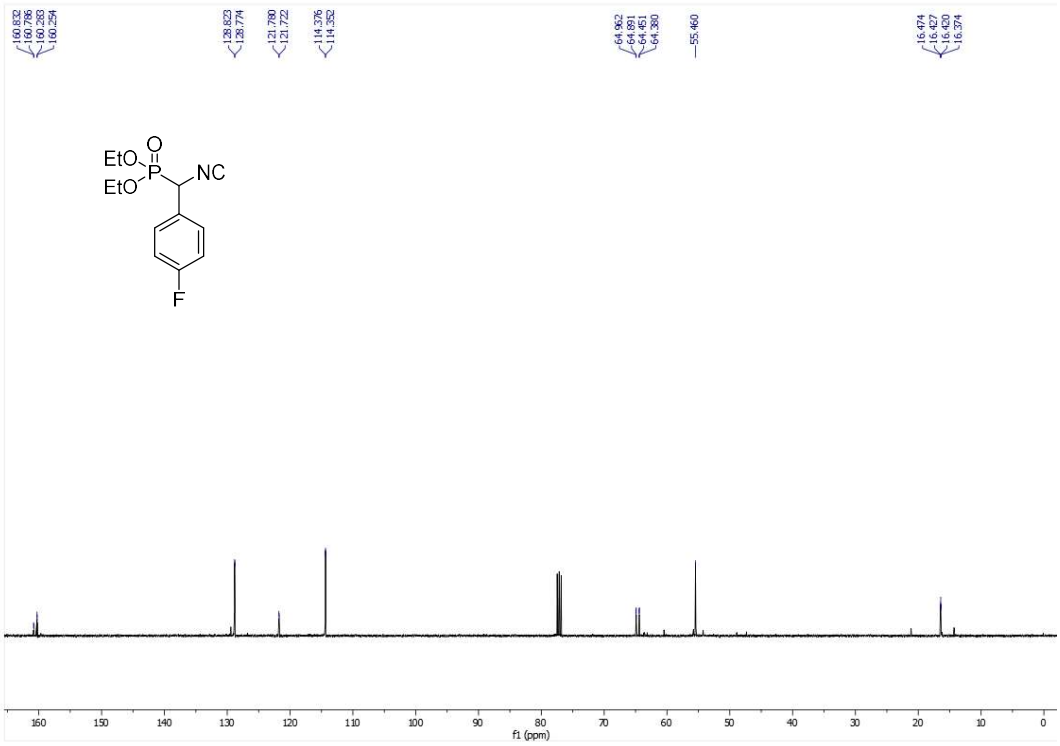
Diethyl [(4-fluorophenyl)(formamido)methyl]phosphonate (step 2-10b)



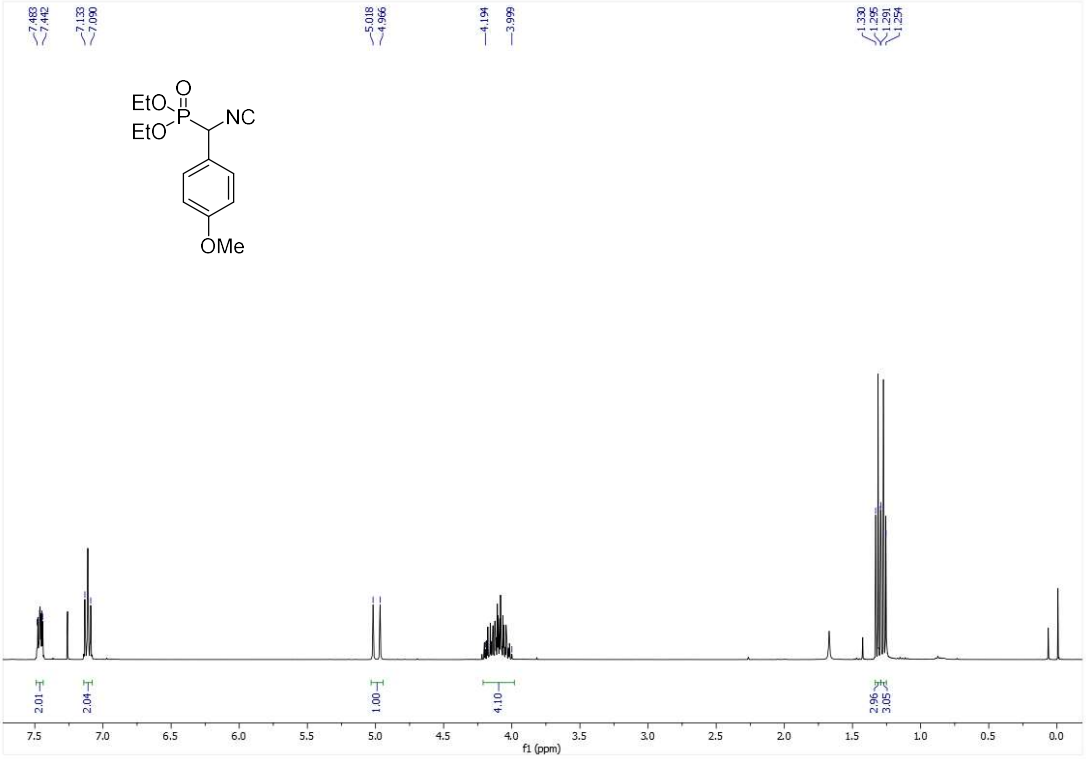
Diethyl [(4-methoxyphenyl)(formamido)methyl]phosphonate (step 2-10c)



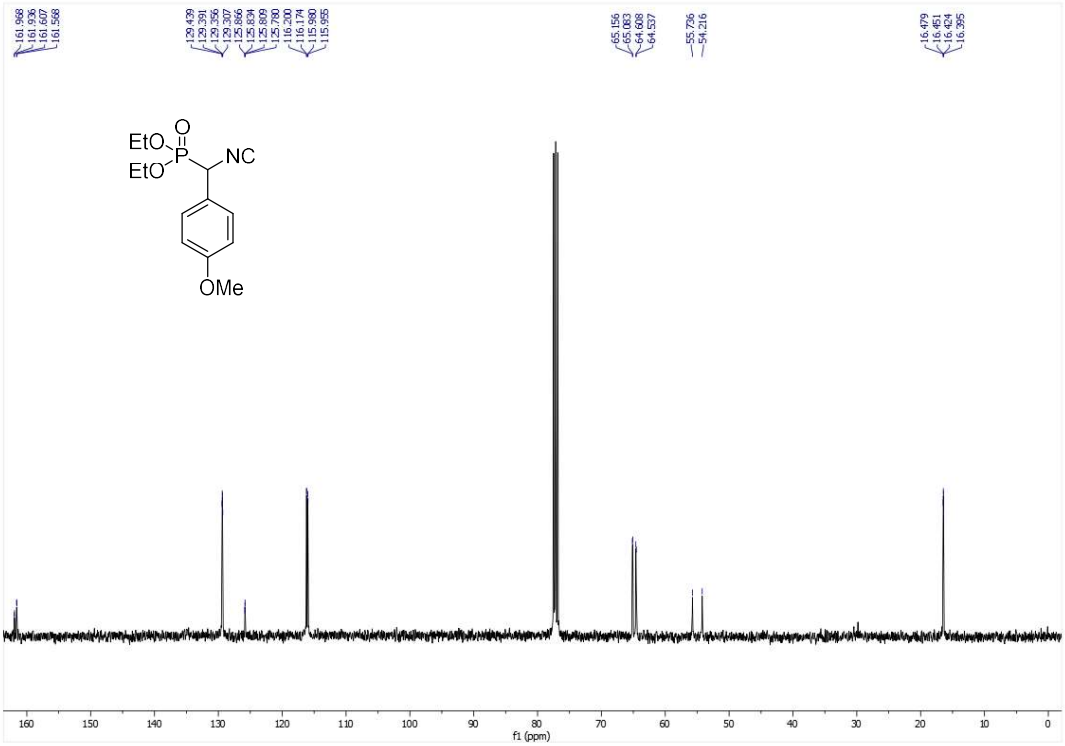
Diethyl [(4-methoxyphenyl)isocyanomethyl]phosphonate (10b)



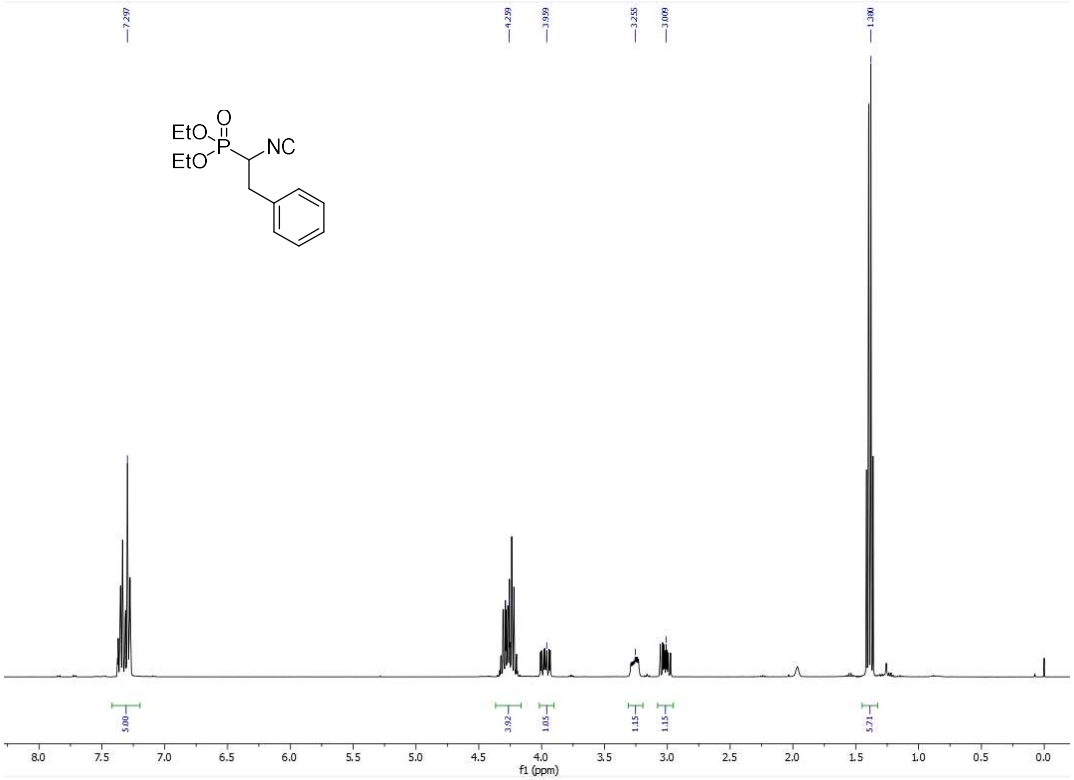
Diethyl [(4-methoxyphenyl)isocyanomethyl]phosphonate (10b)



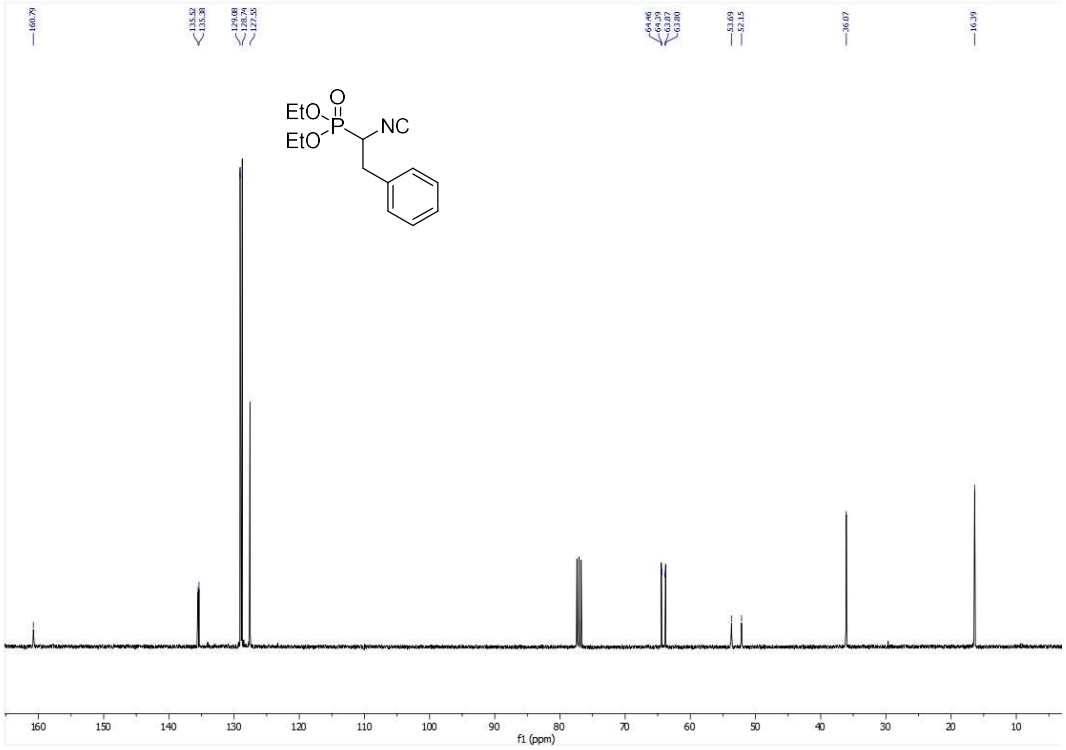
Diethyl [(4-fluorophenyl)isocyanomethyl]phosphonate (10c)



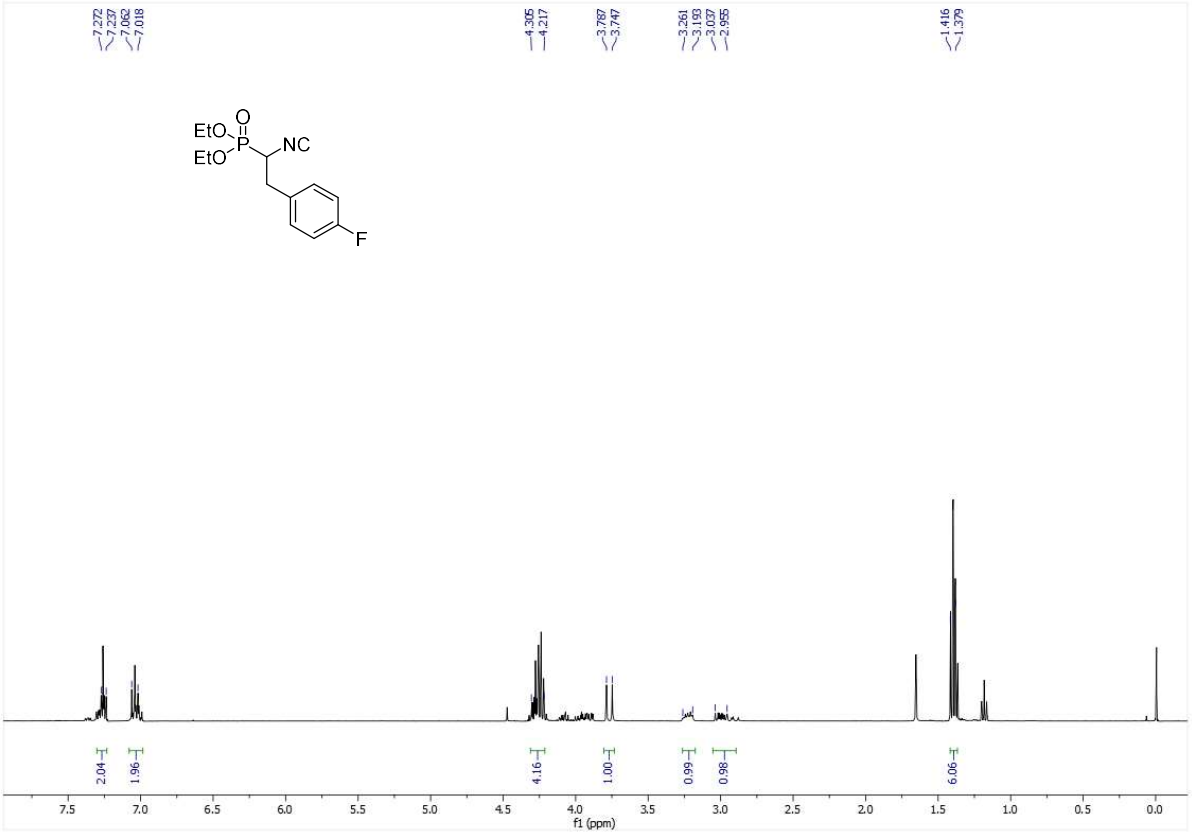
Diethyl [(4-fluorophenyl)isocyanomethyl]phosphonate (10c)



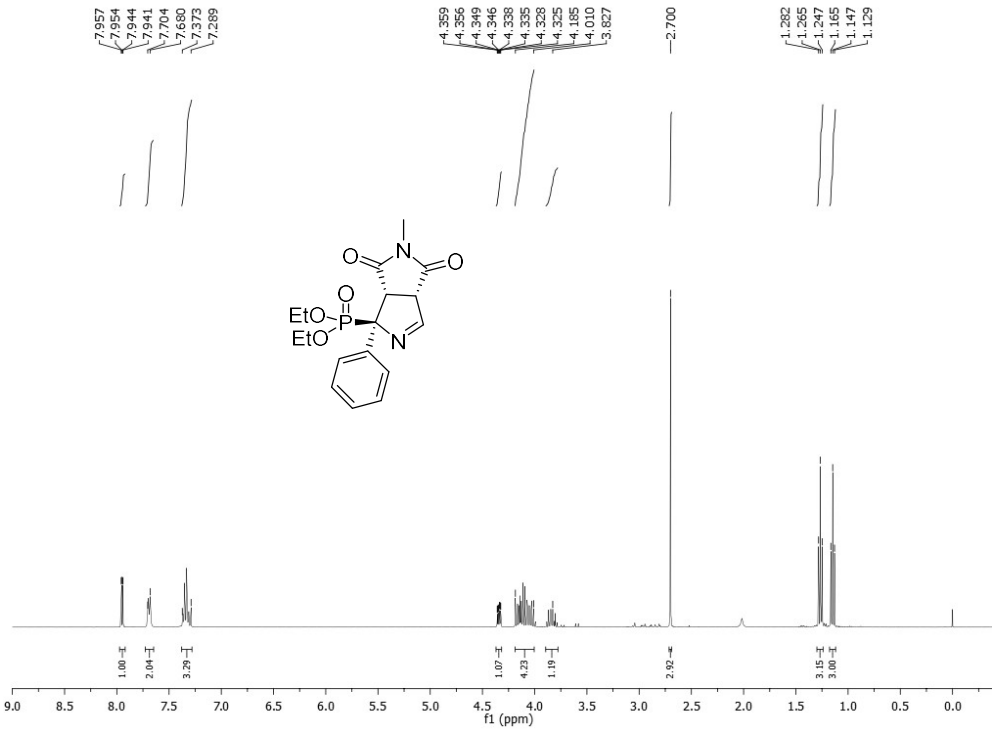
Diethyl (1-isocyano-2-phenylethyl)phosphonate (10d)



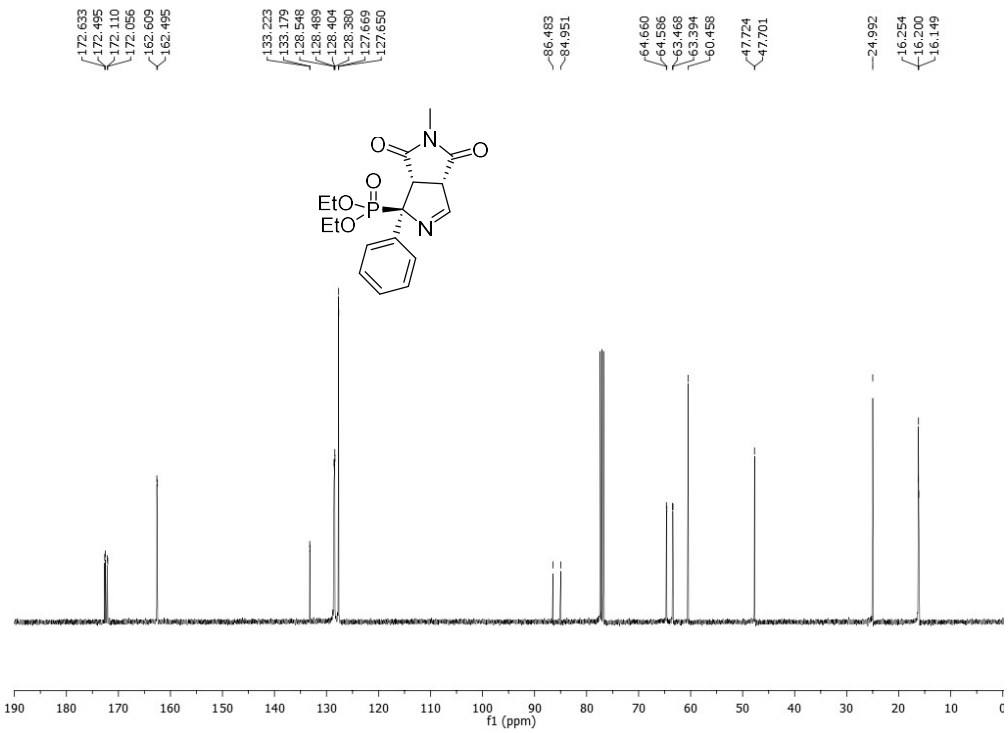
Diethyl (1-isocyano-2-phenylethyl)phosphonate (10d)



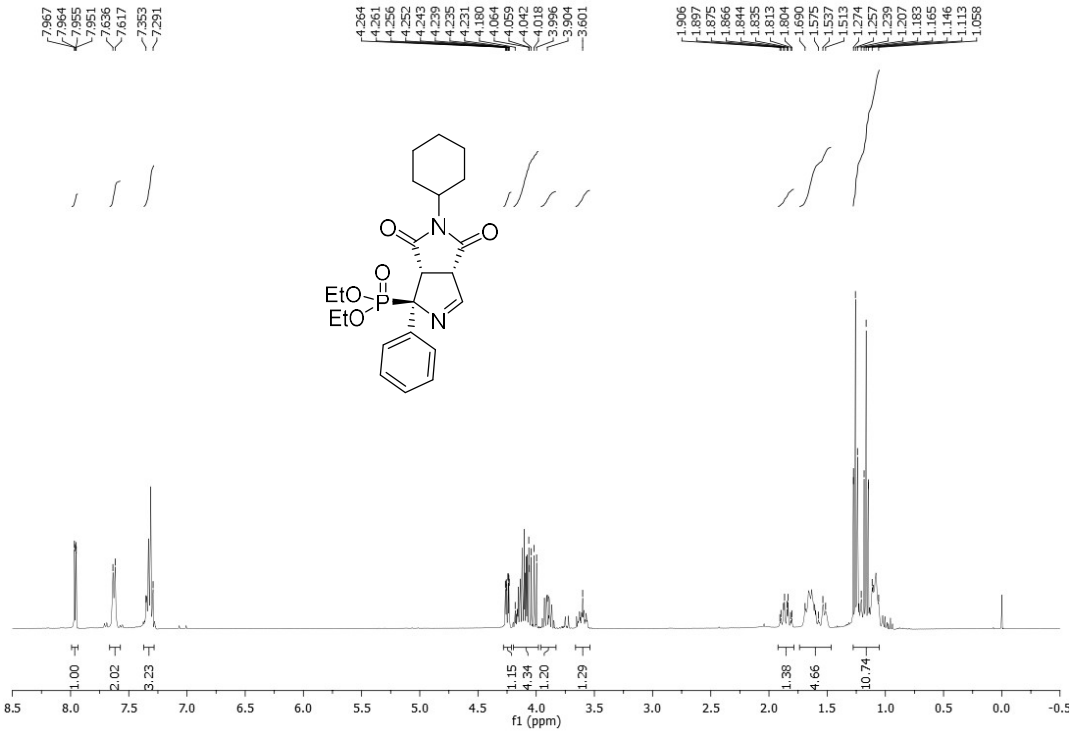
Diethyl [2-(4-fluorophenyl)-1-isocyanoethyl]phosphonate (10e)



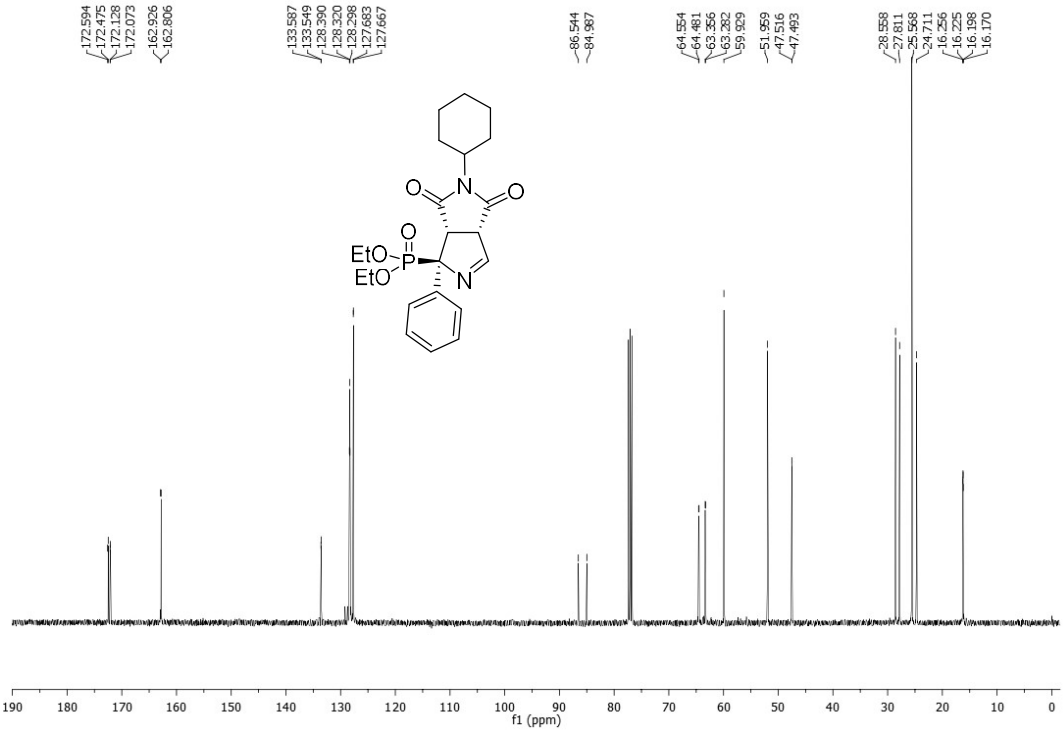
Diethyl (1*RS*,3a*SR*,6a*SR*)-5-methyl-4,6-dioxo-1-phenyl-1,3a,4,5,6,6a-hexahydropyrrolo[3,4-*c*]pyrrole-1-phosphonate (9a)



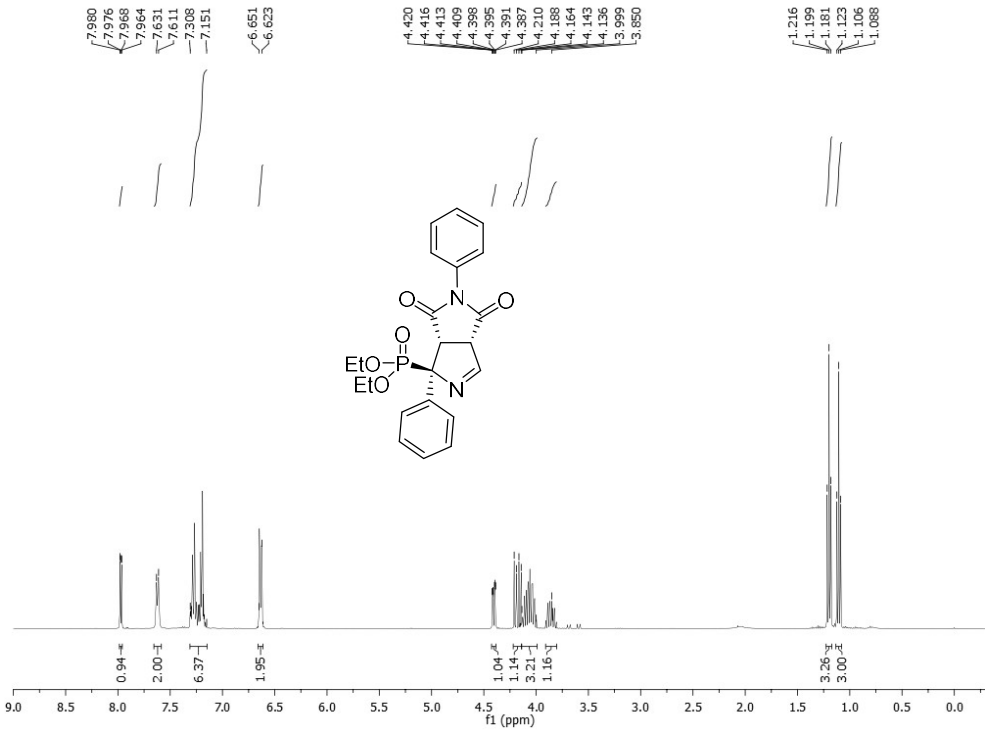
Diethyl (1*RS*,3a*SR*,6a*SR*)-5-methyl-4,6-dioxo-1-phenyl-1,3a,4,5,6,6a-hexahydropyrrolo[3,4-*c*]pyrrole-1-phosphonate (9a)



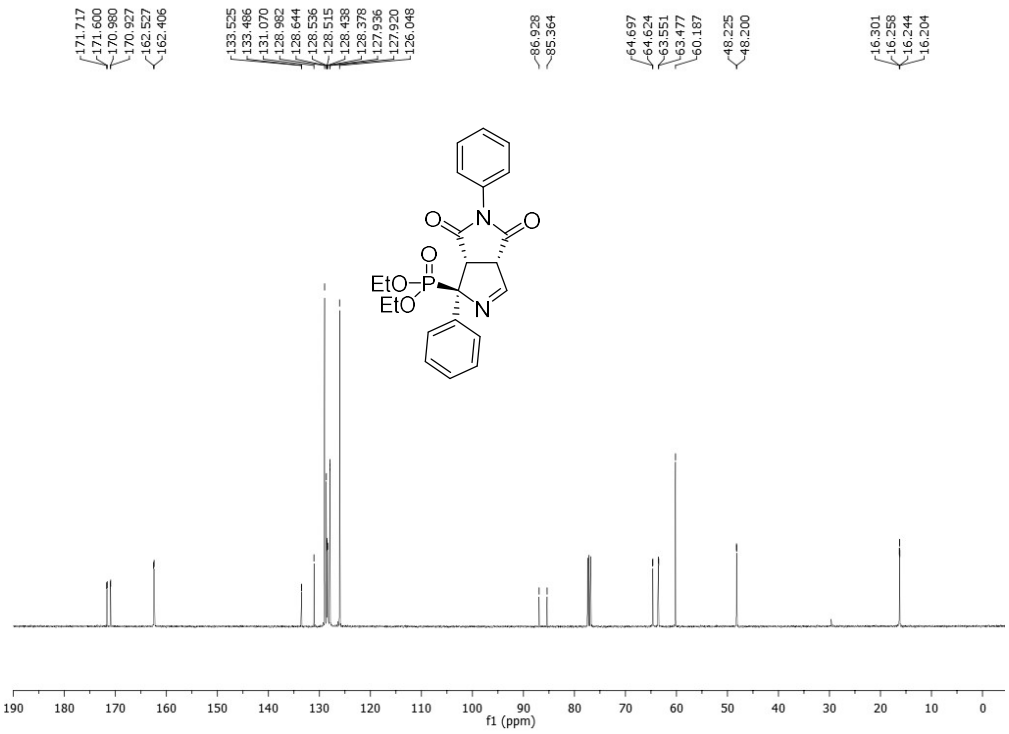
Diethyl (1*RS*,3a*SR*,6a*SR*)-5-cyclohexyl-4,6-dioxo-1-phenyl-1,3a,4,5,6,6a-hexahydropyrrolo[3,4-*c*]pyrrole-1-phosphonate (9b)



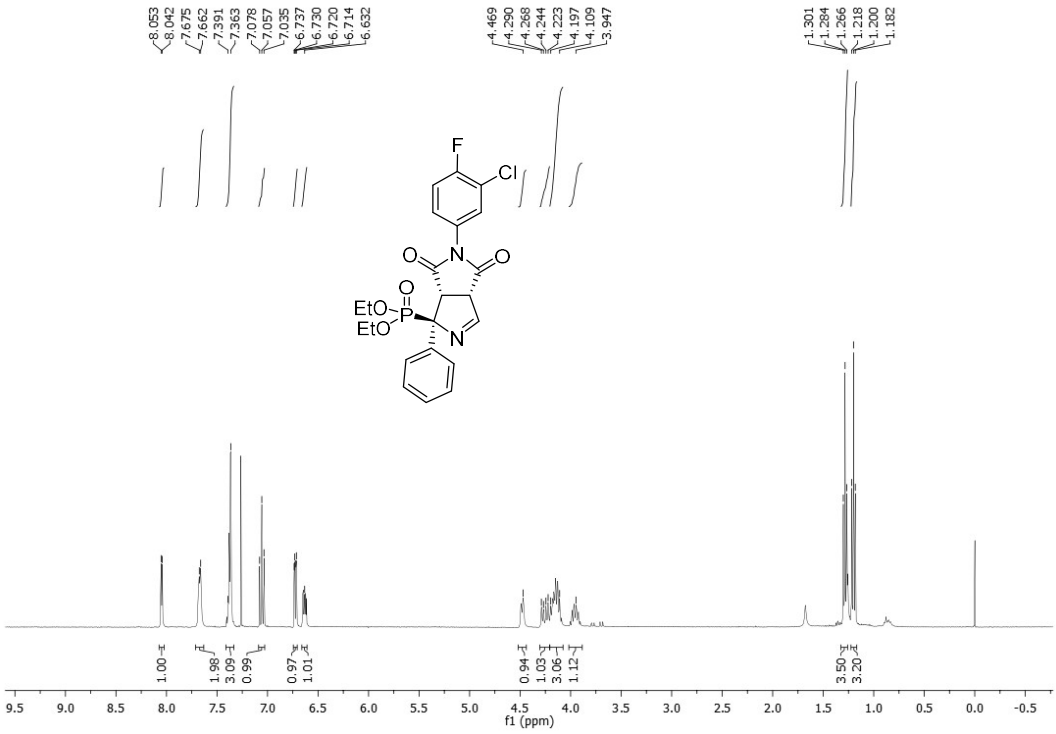
Diethyl (1*RS*,3a*SR*,6a*SR*)-5-cyclohexyl-4,6-dioxo-1-phenyl-1,3a,4,5,6,6a-hexahydropyrrolo[3,4-*c*]pyrrole-1-phosphonate (9b)



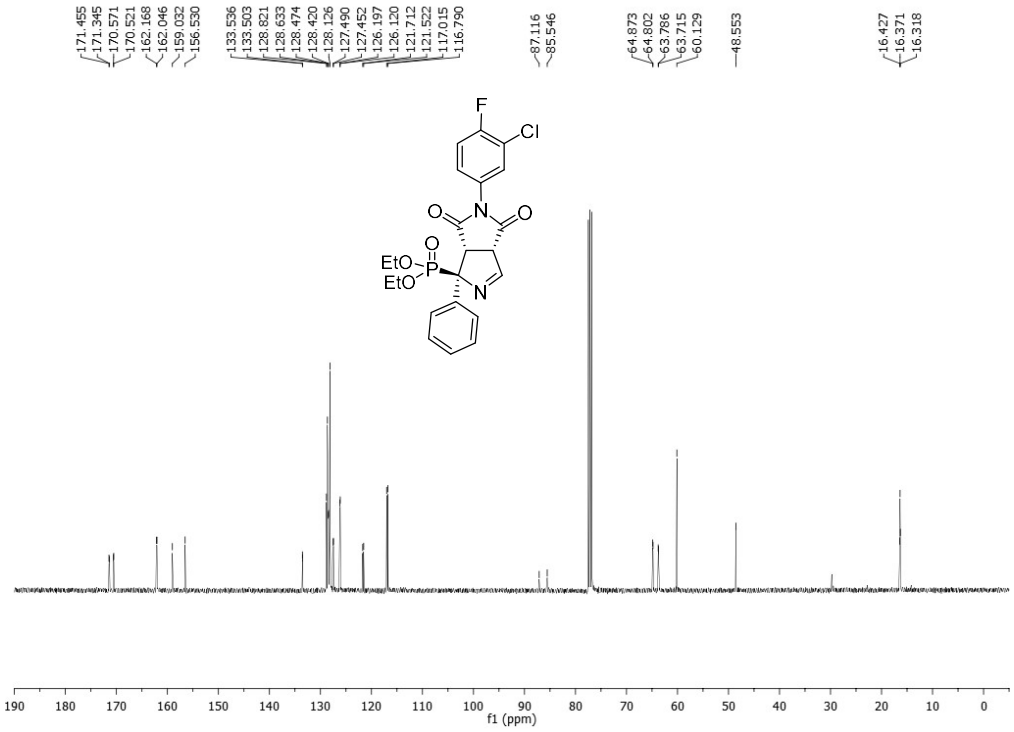
Diethyl (1*RS*,3a*SR*,6a*SR*)-4,6-dioxo-1,5-diphenyl-1,3a,4,5,6,6a-hexahydropyrrolo[3,4-*c*]pyrrole-1-phosphonate (9c)



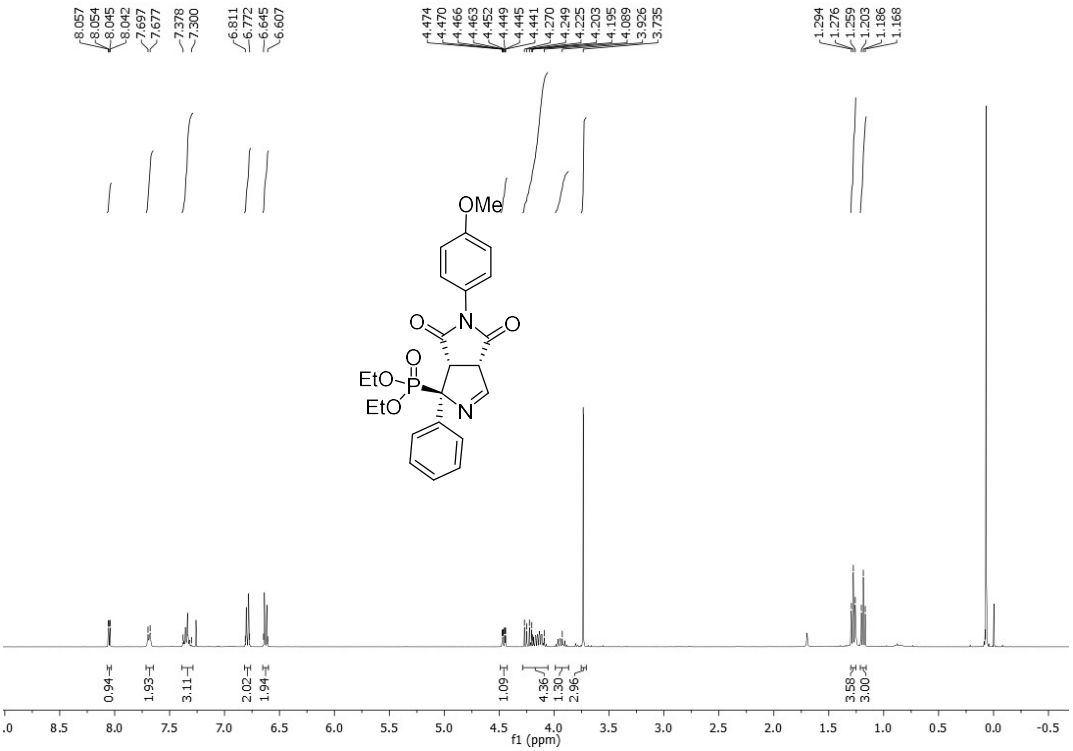
Diethyl (1*RS*,3a*SR*,6a*SR*)-4,6-dioxo-1,5-diphenyl-1,3a,4,5,6,6a-hexahydropyrrolo[3,4-*c*]pyrrole-1-phosphonate (9c)



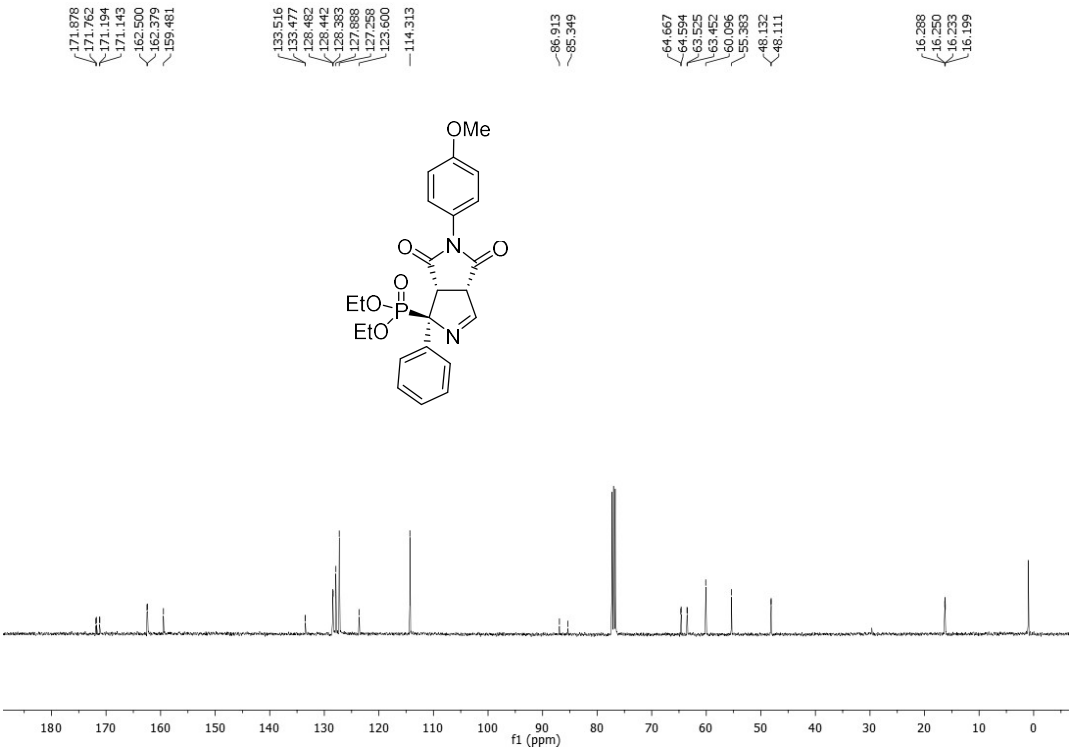
Diethyl (1*RS*,3a*SR*,6a*SR*)-5-(3-chloro-4-fluorophenyl)-4,6-dioxo-1-phenyl-1,3a,4,5,6,6a-hexahydropyrrolo[3,4-*c*]pyrrole-1-phosphonate (9d)



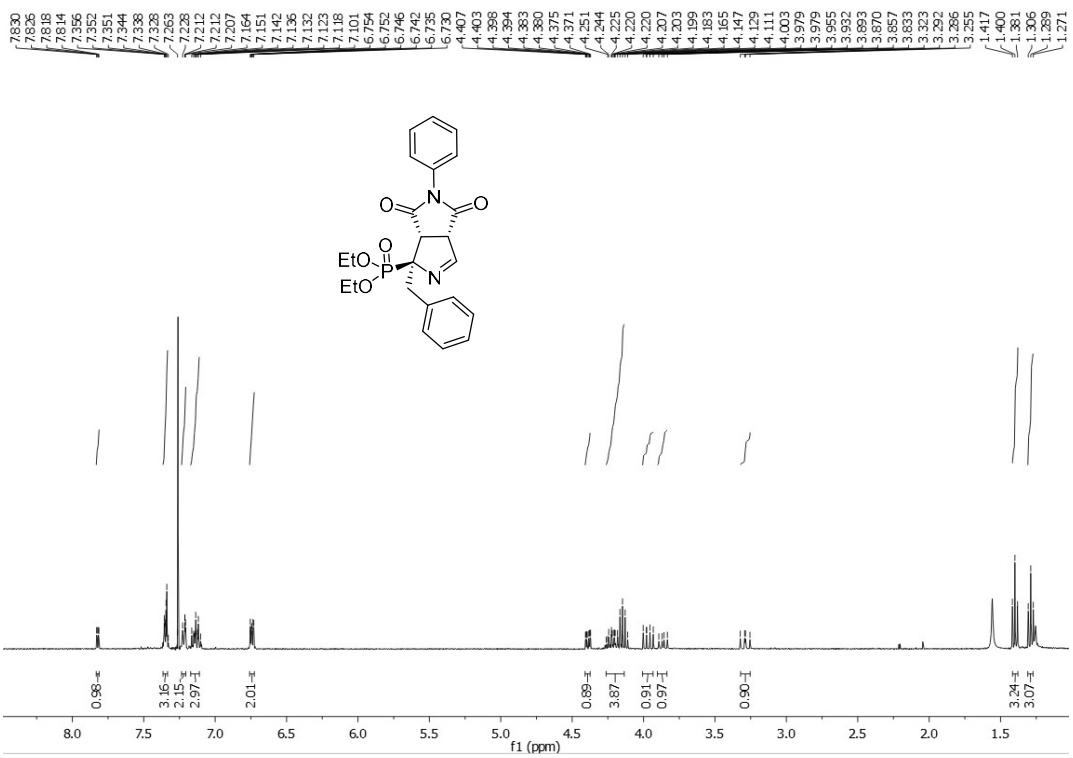
Diethyl (1*RS*,3a*SR*,6a*SR*)-5-(3-chloro-4-fluorophenyl)-4,6-dioxo-1-phenyl-1,3a,4,5,6,6a-hexahydropyrrolo[3,4-*c*]pyrrole-1-phosphonate (9d)



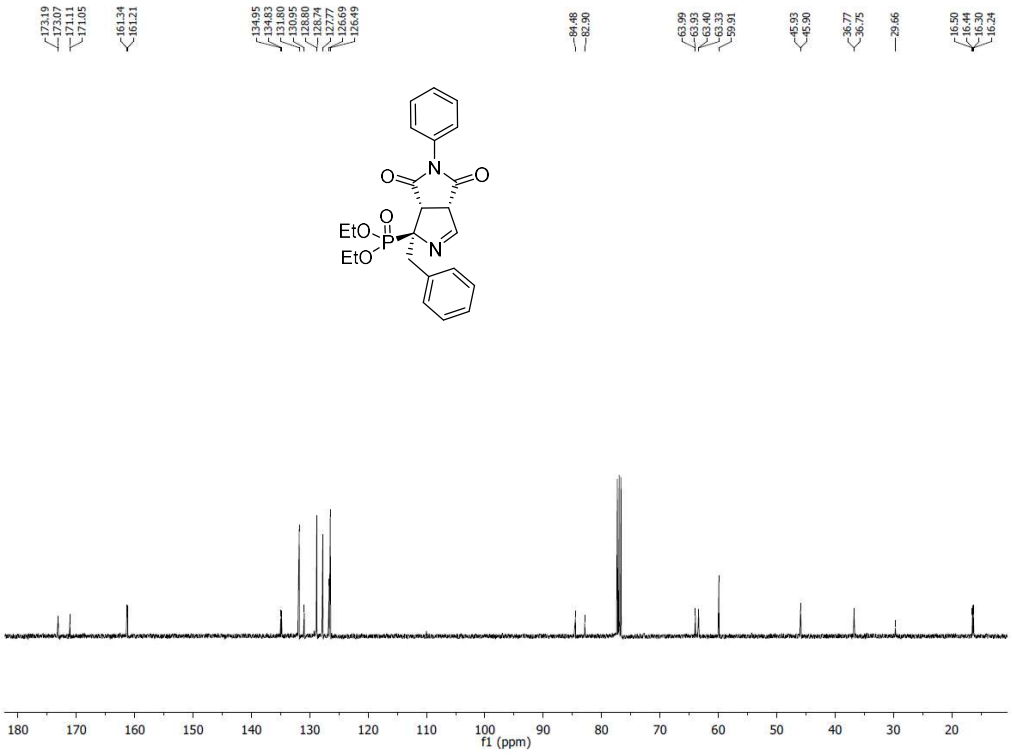
Diethyl (1*RS*,3a*SR*,6a*SR*)-5-(4-methoxyphenyl)-4,6-dioxo-1-phenyl-1,3a,4,5,6,6a-hexahydropyrrolo[3,4-*c*]pyrrole-1-phosphonate (9e)



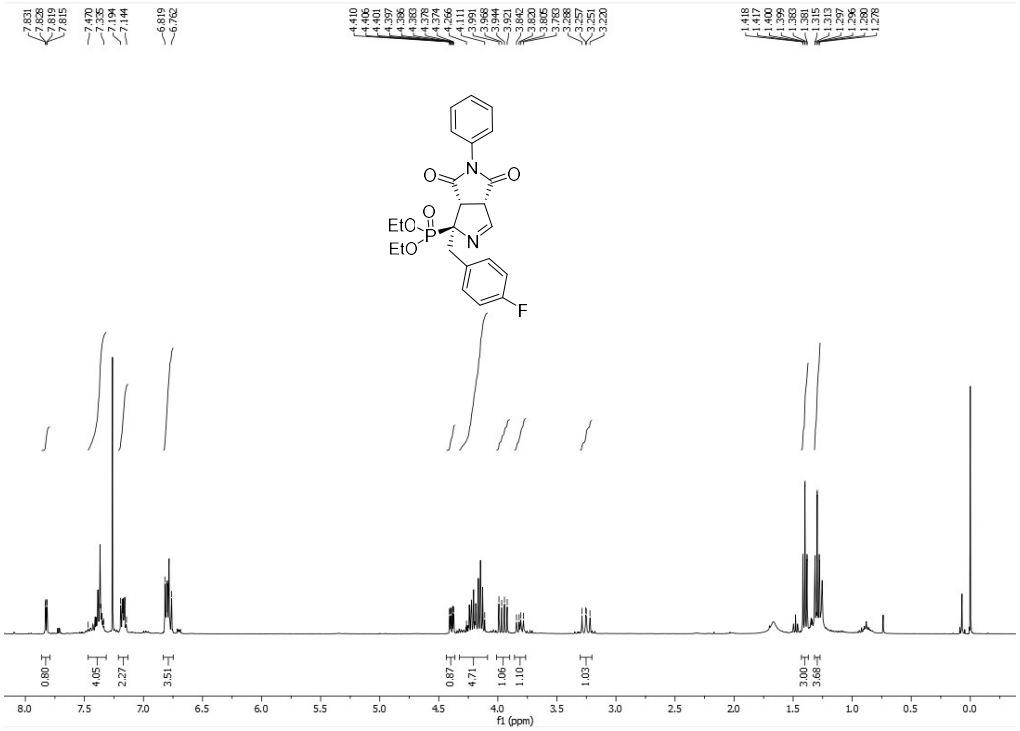
Diethyl (1*RS*,3a*SR*,6a*SR*)-5-(4-methoxyphenyl)-4,6-dioxo-1-phenyl-1,3a,4,5,6,6a-hexahydropyrrolo[3,4-*c*]pyrrole-1-phosphonate (9e)



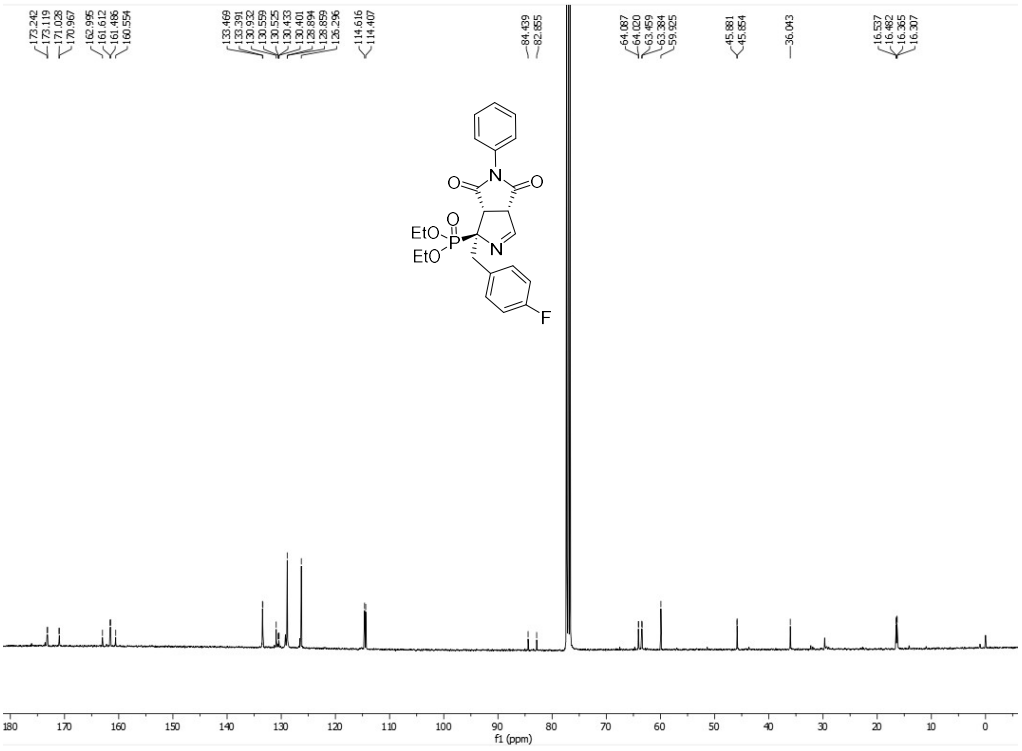
Diethyl (1*RS*,3a*SR*,6a*SR*)-1-benzyl-4,6-dioxo-5-phenyl-1,3a,4,5,6,6a-hexahydropyrrolo[3,4-*c*]pyrrole-1-phosphonate (14c)



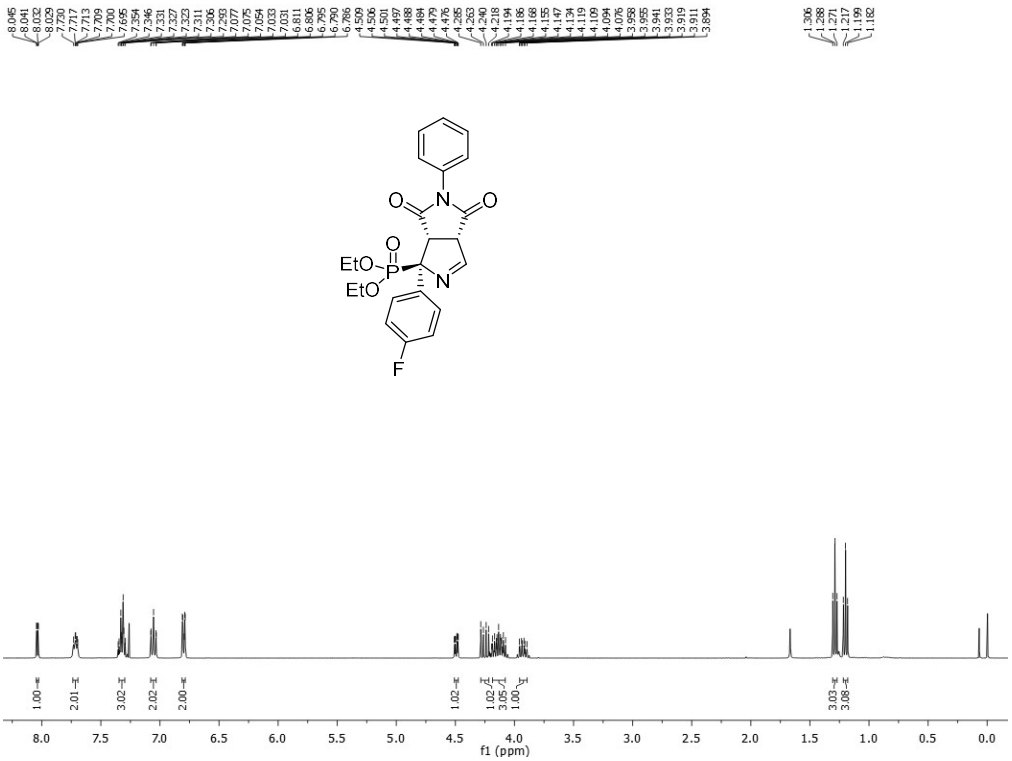
Diethyl (1*RS*,3a*SR*,6a*SR*)-1-benzyl-4,6-dioxo-5-phenyl-1,3a,4,5,6,6a-hexahydropyrrolo[3,4-*c*]pyrrole-1-phosphonate (14c)



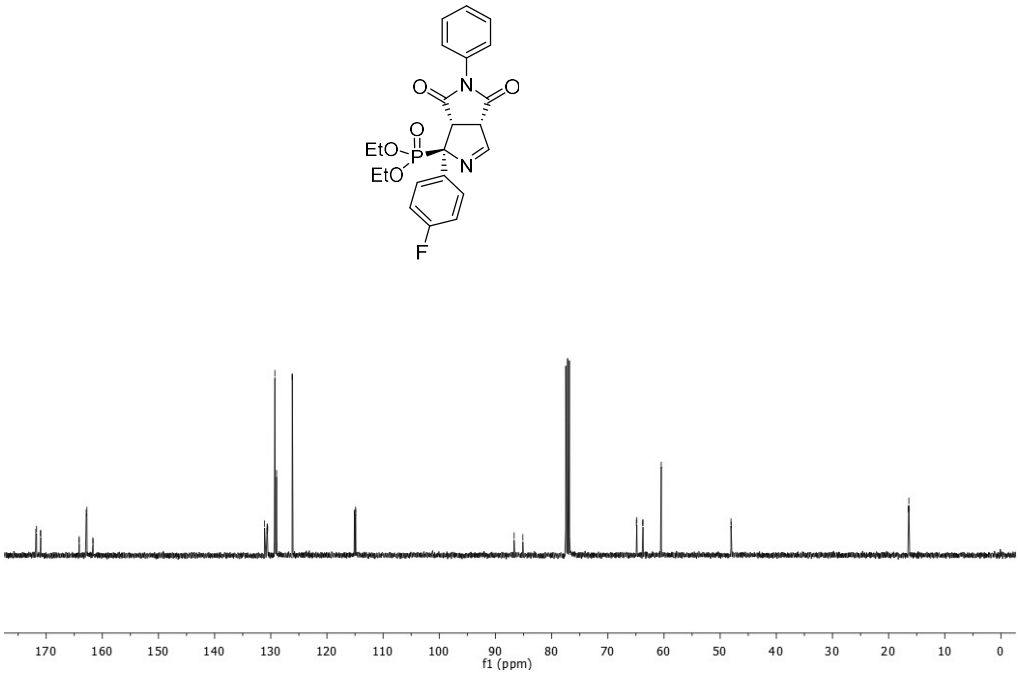
Diethyl (1*RS*,3a*SR*,6a*SR*)-1-(4-fluorobenzyl)-4,6-dioxo-5-phenyl-1,3a,4,5,6,6a-hexahydropyrrolo[3,4-*c*]pyrrole-1-phosphonate (15c)



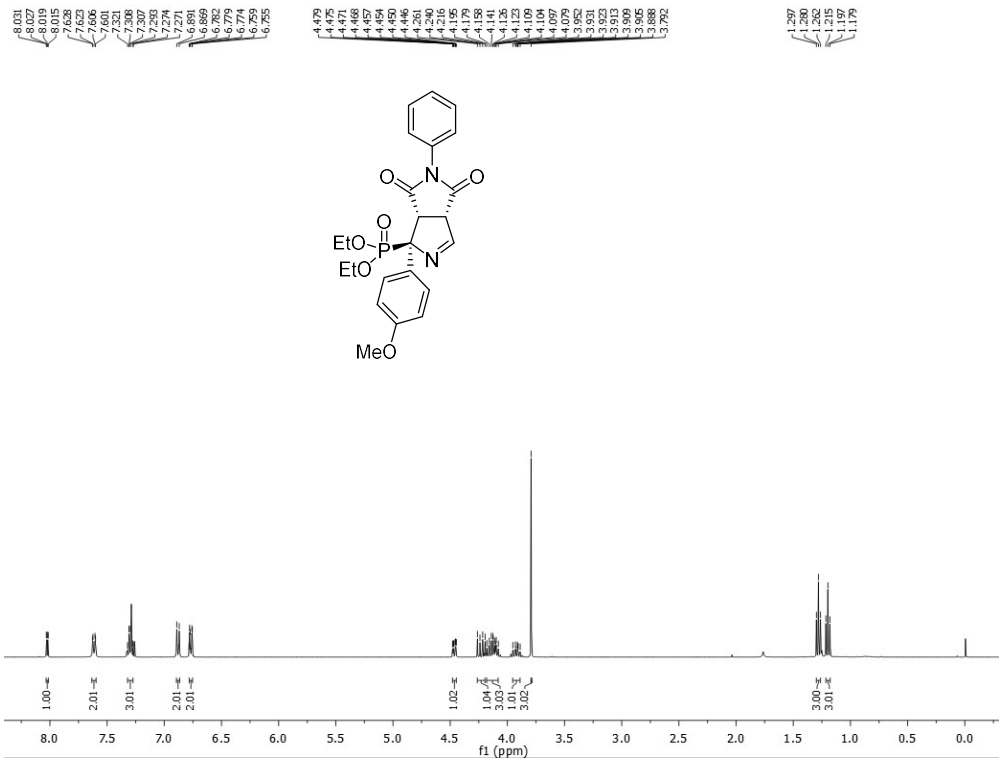
Diethyl (1*RS*,3a*SR*,6a*SR*)-1-(4-fluorobenzyl)-4,6-dioxo-5-phenyl-1,3a,4,5,6,6a-hexahydropyrrolo[3,4-*c*]pyrrole-1-phosphonate (15c)



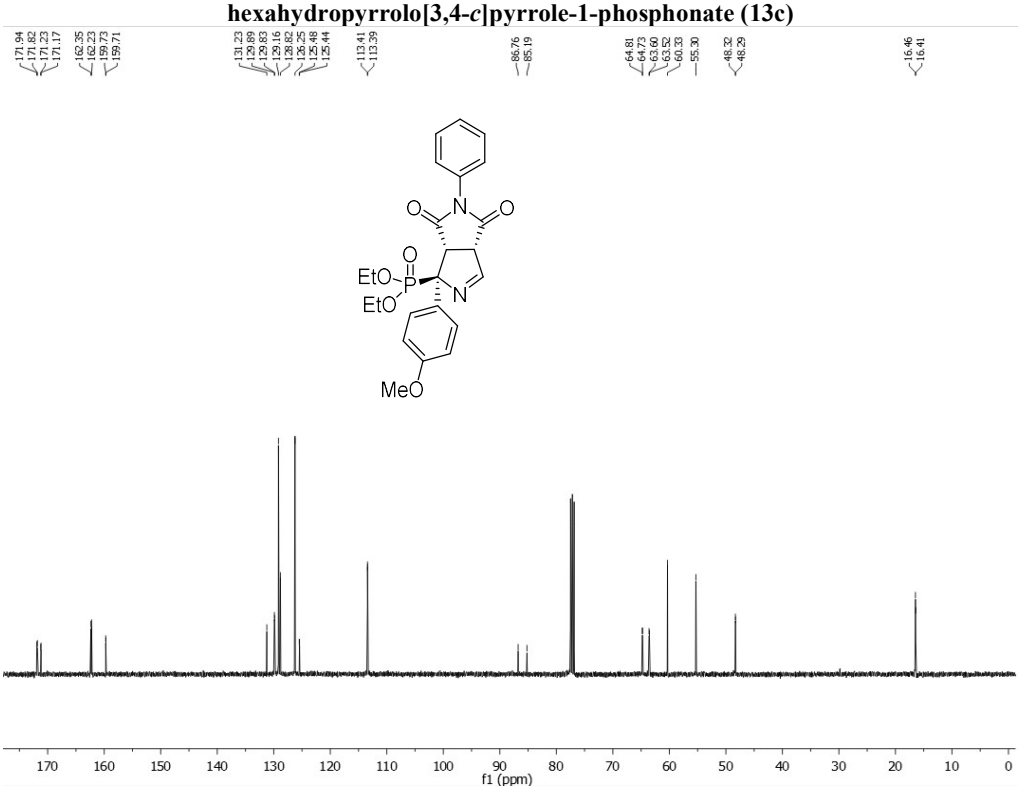
Diethyl (1*RS*,3a*SR*,6a*SR*)-1-(4-fluorophenyl)-4,6-dioxo-5-phenyl-1,3a,4,5,6,6a-hexahydropyrrolo[3,4-*c*]pyrrole-1-phosphonate (12c)



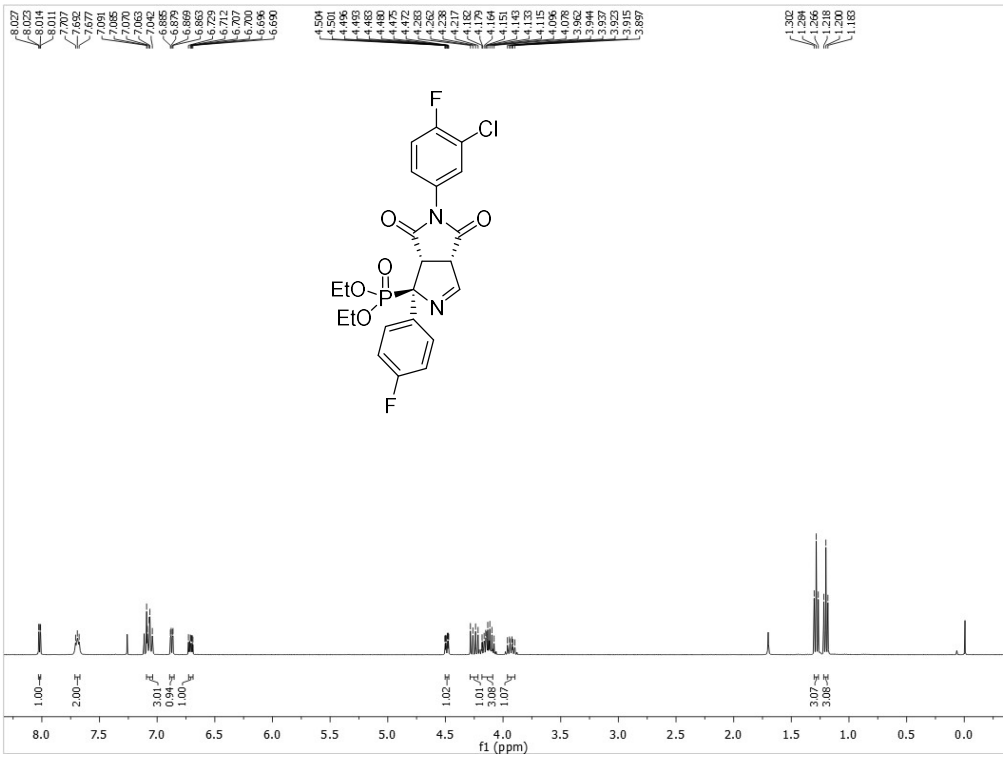
Diethyl (1*RS*,3a*SR*,6a*SR*)-1-(4-fluorophenyl)-4,6-dioxo-5-phenyl-1,3a,4,5,6,6a-hexahydropyrrolo[3,4-*c*]pyrrole-1-phosphonate (12c)



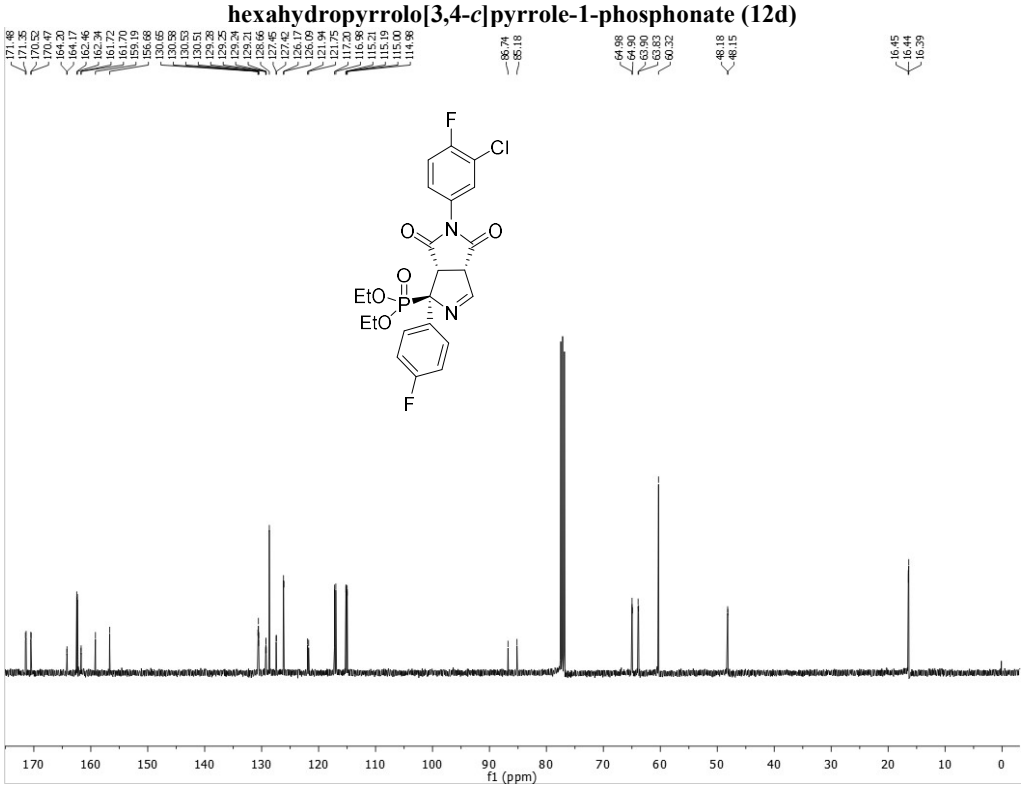
Diethyl (1*RS*,3a*SR*,6a*SR*)-1-(4-methoxyphenyl)-4,6-dioxo-5-phenyl-1,3a,4,5,6,6a-hexahydropyrrolo[3,4-*c*]pyrrole-1-phosphonate (13c)



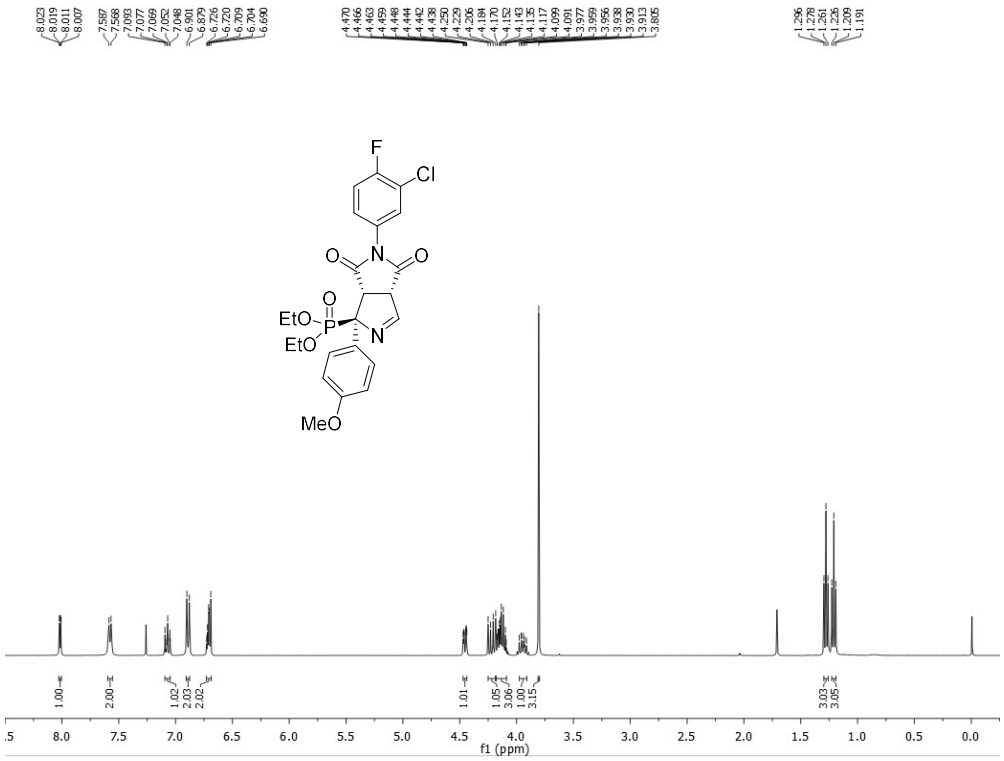
Diethyl (1*RS*,3a*SR*,6a*SR*)-1-(4-methoxyphenyl)-4,6-dioxo-5-phenyl-1,3a,4,5,6,6a-hexahydropyrrolo[3,4-*c*]pyrrole-1-phosphonate (13c)



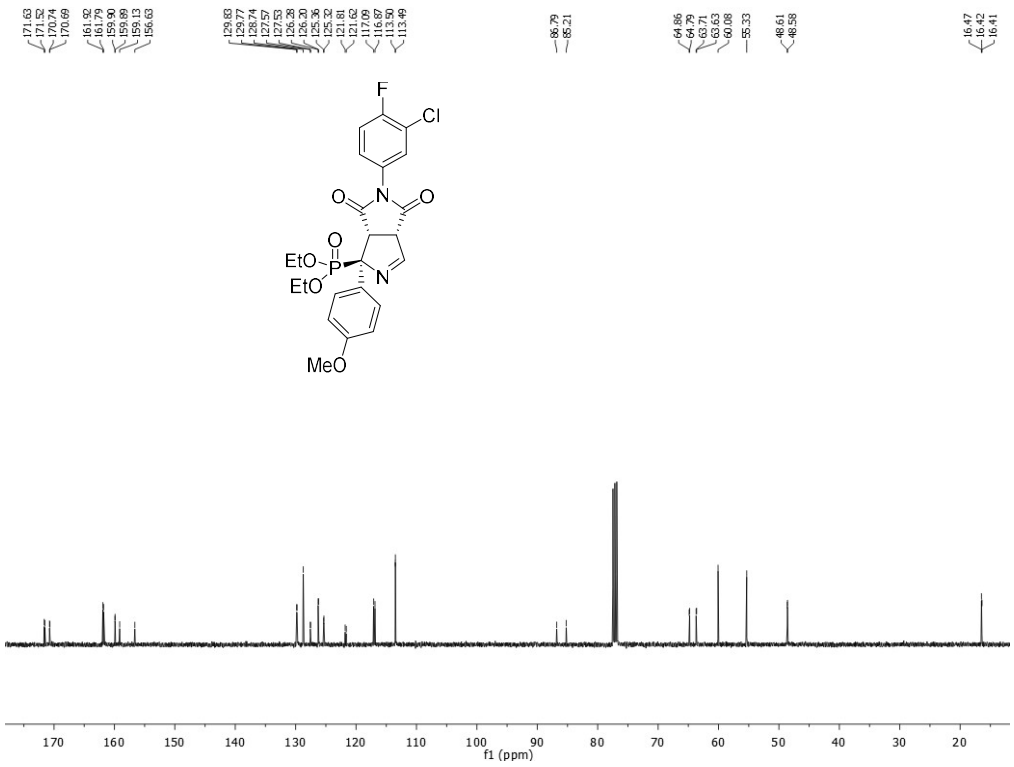
Diethyl (1*RS*,3a*SR*,6a*SR*)-5-(3-chloro-4-fluorophenyl)-1-(4-fluorophenyl)-4,6-dioxo-1,3a,4,5,6,6a-hexahydropyrrolo[3,4-*c*]pyrrole-1-phosphonate (12d)



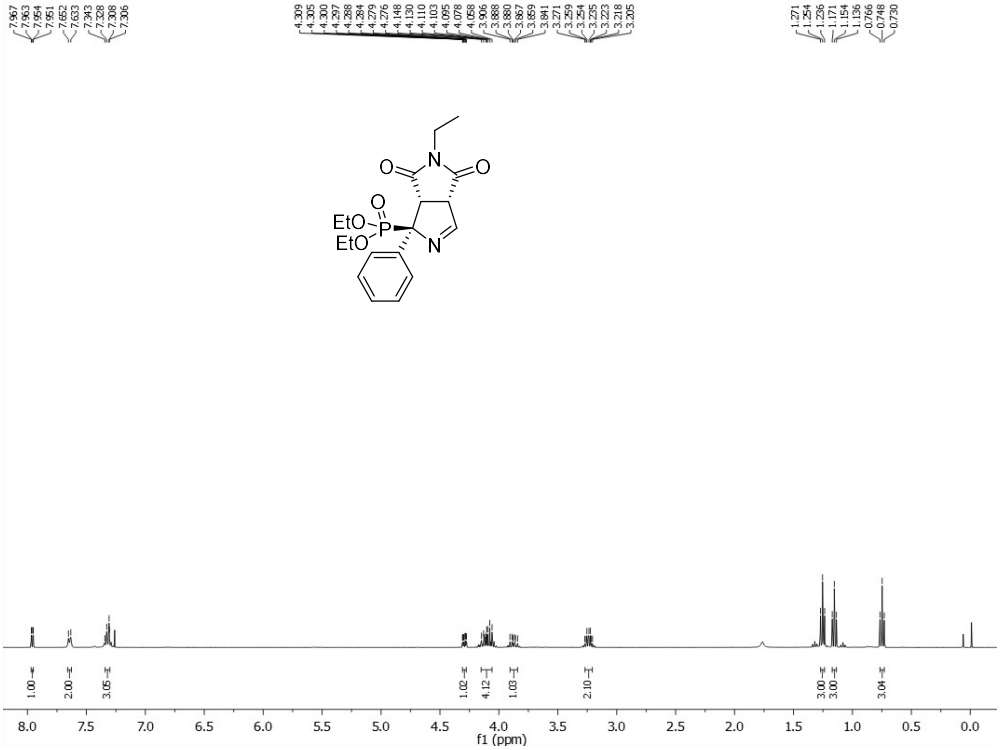
Diethyl (1*RS*,3a*SR*,6a*SR*)-5-(3-chloro-4-fluorophenyl)-1-(4-fluorophenyl)-4,6-dioxo-1,3a,4,5,6,6a-hexahydropyrrolo[3,4-*c*]pyrrole-1-phosphonate (12d)



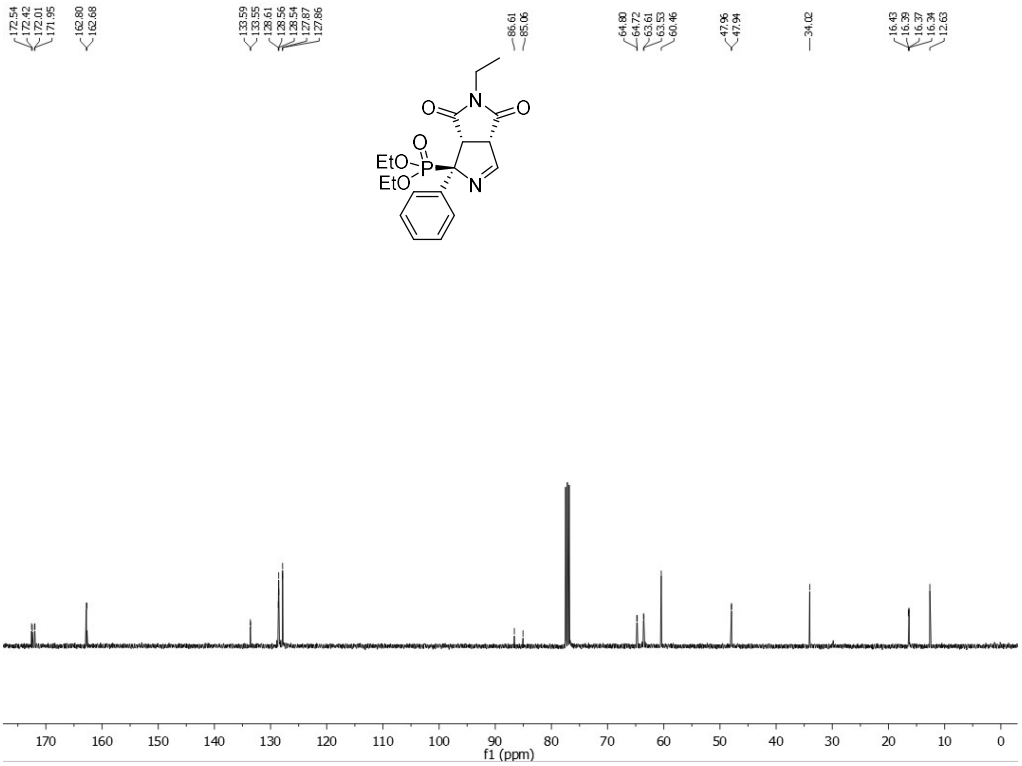
Diethyl (1*RS*,3a*SR*,6a*SR*)-5-(3-chloro-4-fluorophenyl)-1-(4-methoxyphenyl)-4,6-dioxo-1,3a,4,5,6,6a-hexahydropyrrolo[3,4-*c*]pyrrole-1-phosphonate (13d)



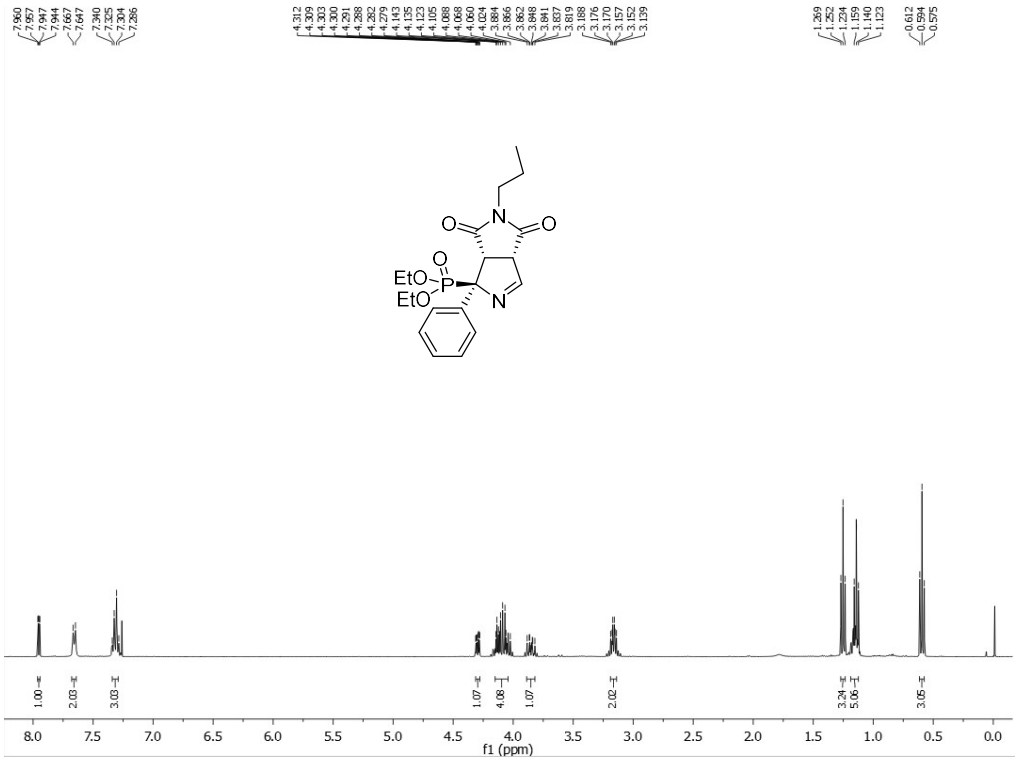
Diethyl (1*RS*,3a*SR*,6a*SR*)-5-(3-chloro-4-fluorophenyl)-1-(4-methoxyphenyl)-4,6-dioxo-1,3a,4,5,6,6a-hexahydropyrrolo[3,4-*c*]pyrrole-1-phosphonate (13d)



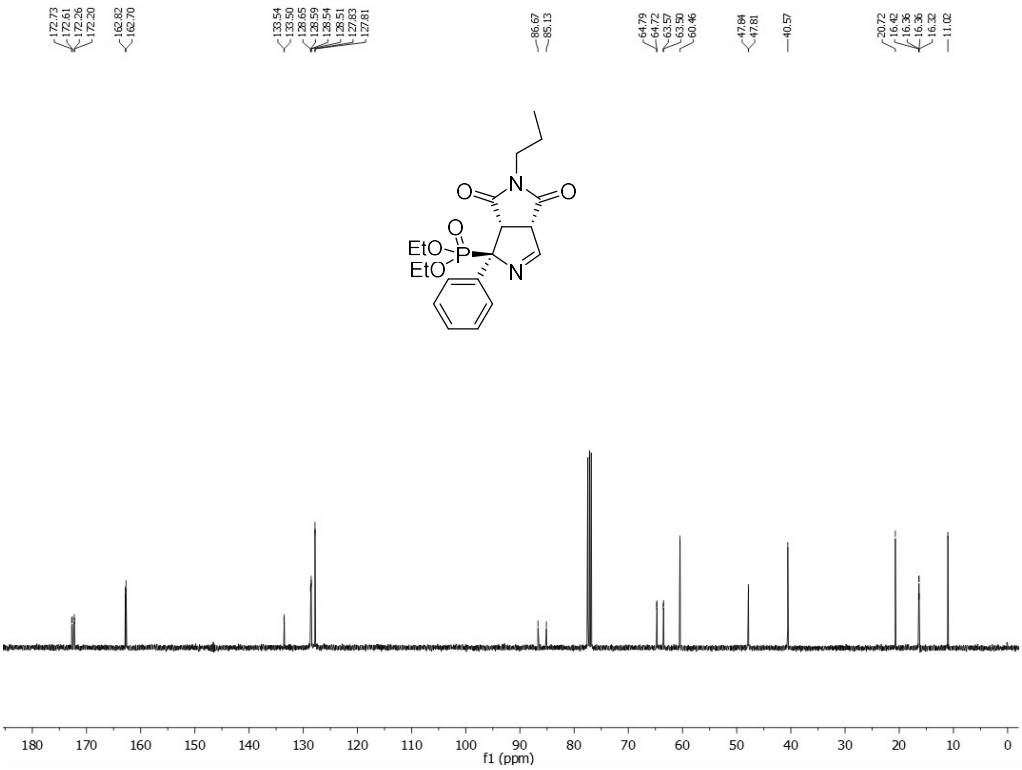
Diethyl (1*RS*,3a*SR*,6a*SR*)-5-ethyl-4,6-dioxo-1-phenyl-1,3a,4,5,6,6a-hexahydropyrrolo[3,4-*c*]pyrrole-1-phosphonate (9f)



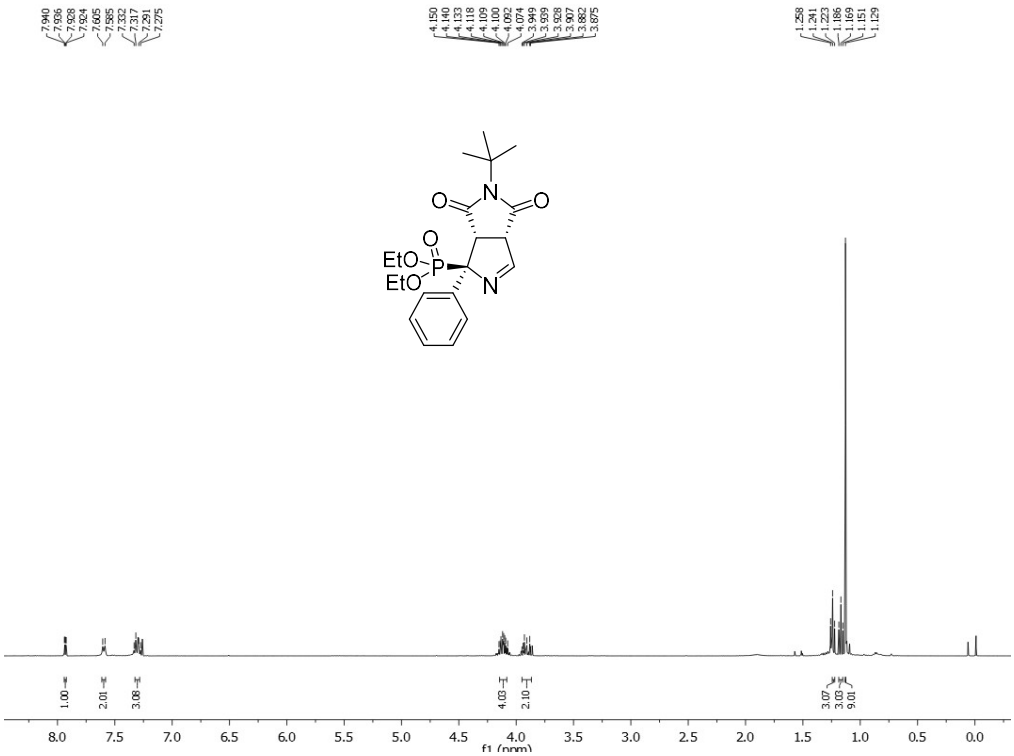
Diethyl (1*RS*,3a*SR*,6a*SR*)-5-ethyl-4,6-dioxo-1-phenyl-1,3a,4,5,6,6a-hexahydropyrrolo[3,4-*c*]pyrrole-1-phosphonate (9f)



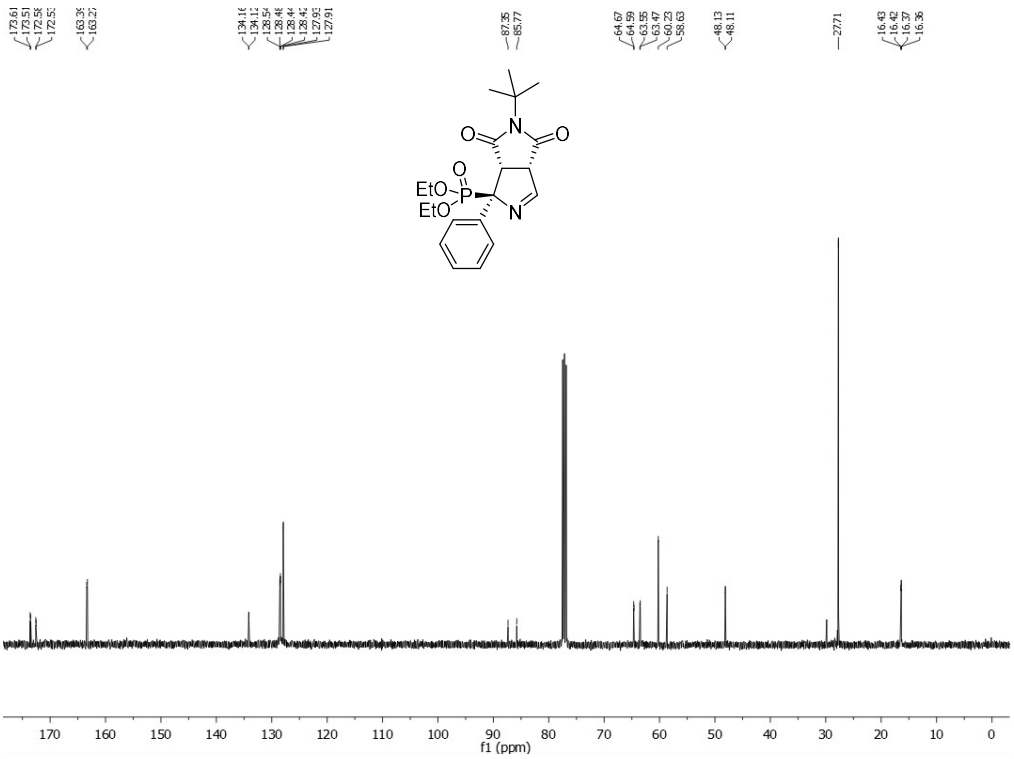
Diethyl (1*RS*,3a*SR*,6a*SR*)-4,6-dioxo-1-phenyl-5-propyl-1,3a,4,5,6,6a-hexahydropyrrolo[3,4-*c*]pyrrole-1-phosphonate (9g)



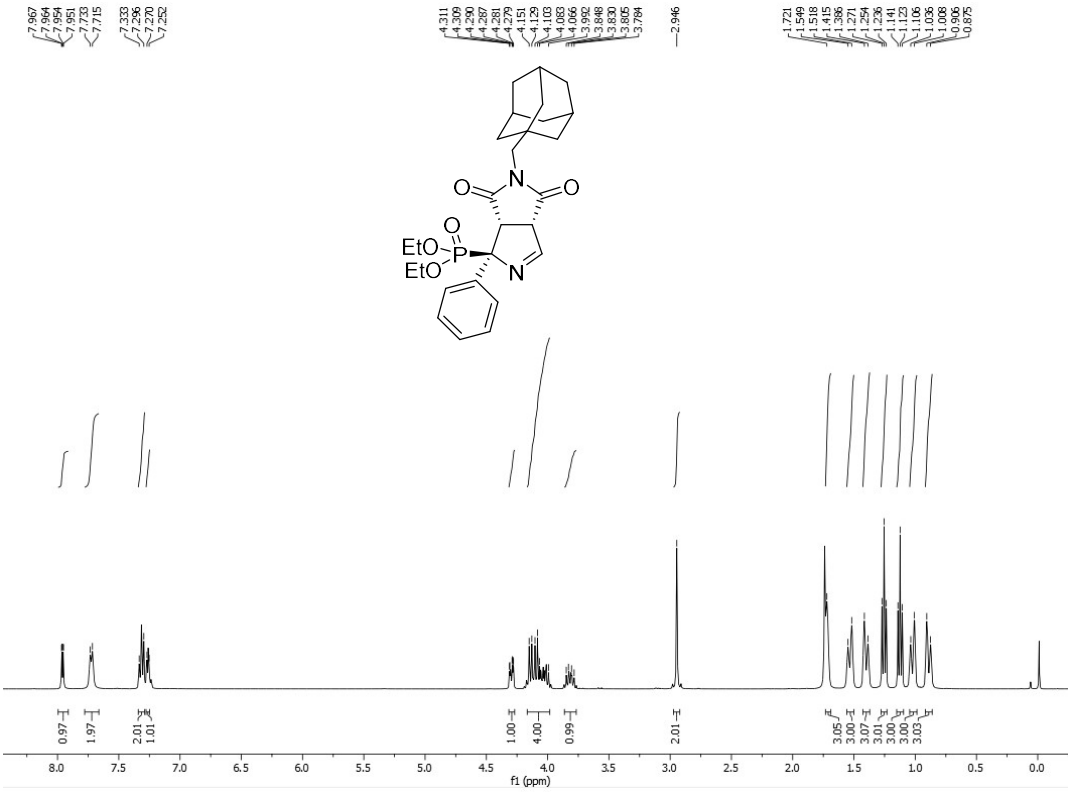
Diethyl (1*RS*,3a*SR*,6a*SR*)-4,6-dioxo-1-phenyl-5-propyl-1,3a,4,5,6,6a-hexahydropyrrolo[3,4-*c*]pyrrole-1-phosphonate (9g)



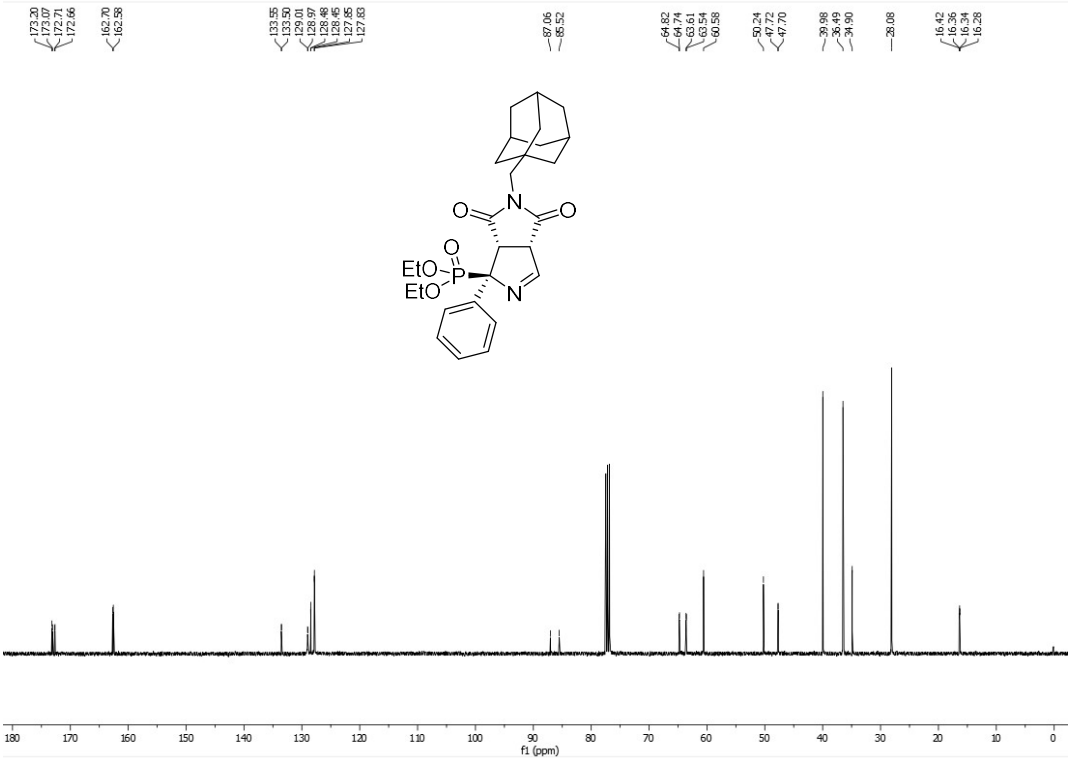
Diethyl (1*RS*,3a*SR*,6a*SR*)-5-(tert-butyl)-4,6-dioxo-1-phenyl-1,3a,4,5,6,6a-hexahydropyrrolo[3,4-*c*]pyrrole-1-phosphonate (9h)



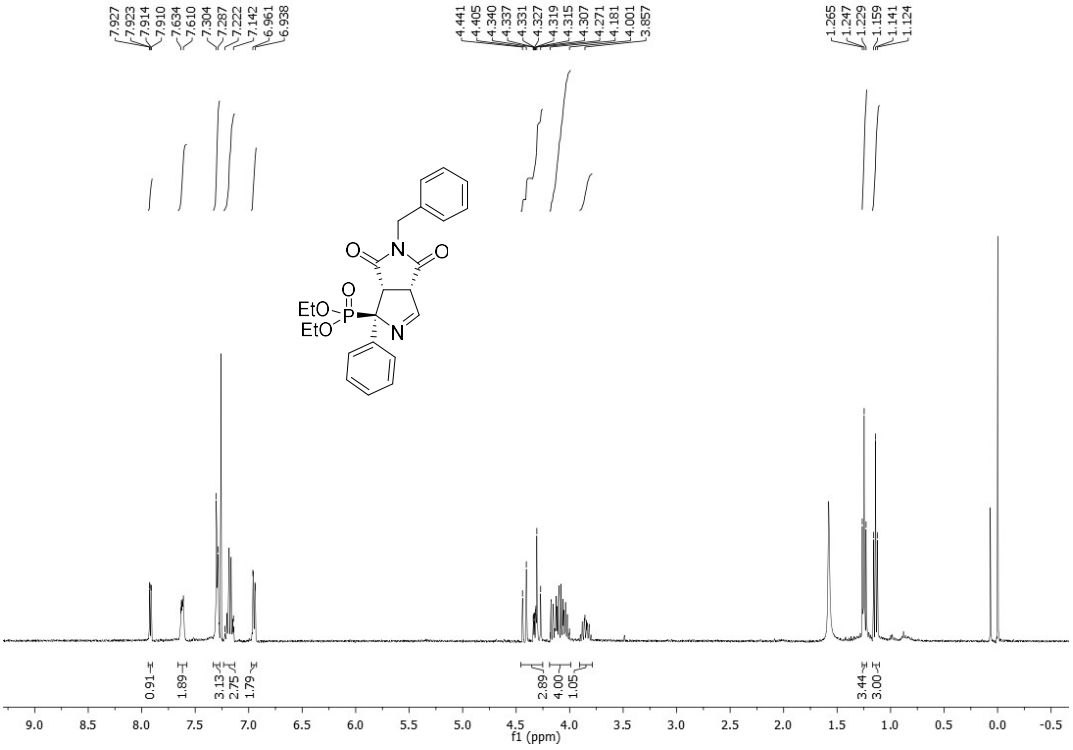
Diethyl (1*RS*,3a*SR*,6a*SR*)-5-(tert-butyl)-4,6-dioxo-1-phenyl-1,3a,4,5,6,6a-hexahydropyrrolo[3,4-*c*]pyrrole-1-phosphonate (9h)



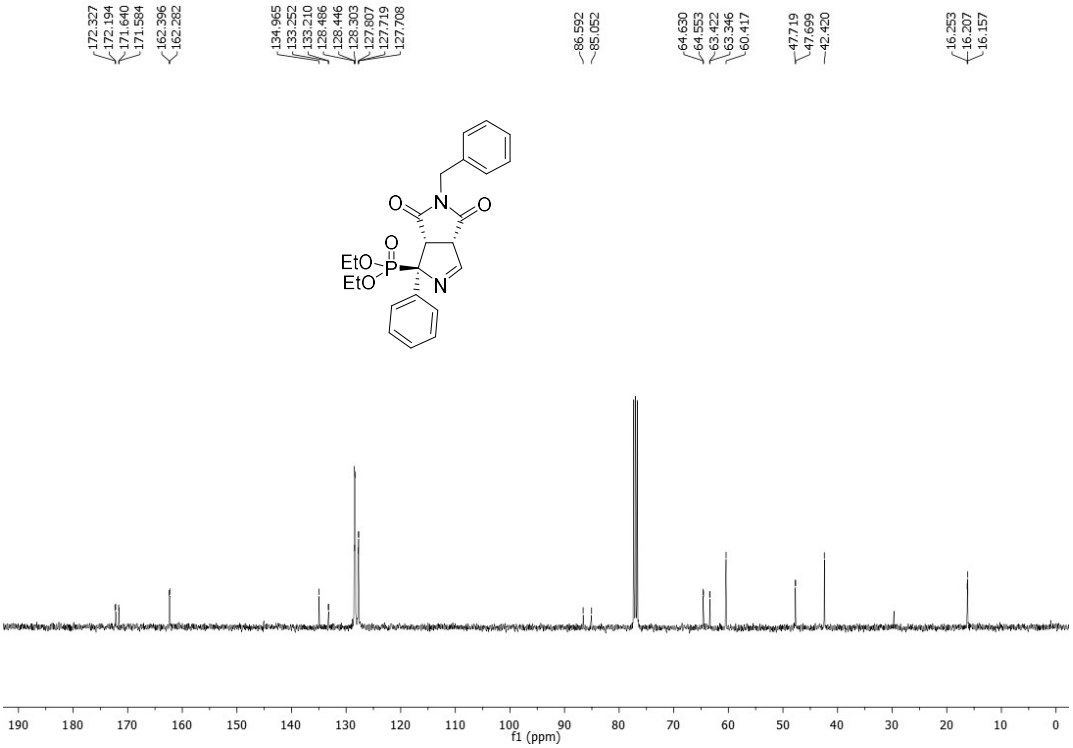
Diethyl (1*RS*,3a*SR*,6a*SR*)-5-(adamantan-1-yl)methyl)-4,6-dioxo-1-phenyl-1,3a,4,5,6,6a-hexahydropyrrolo[3,4-*c*]pyrrole-1-phosphonate (9i)



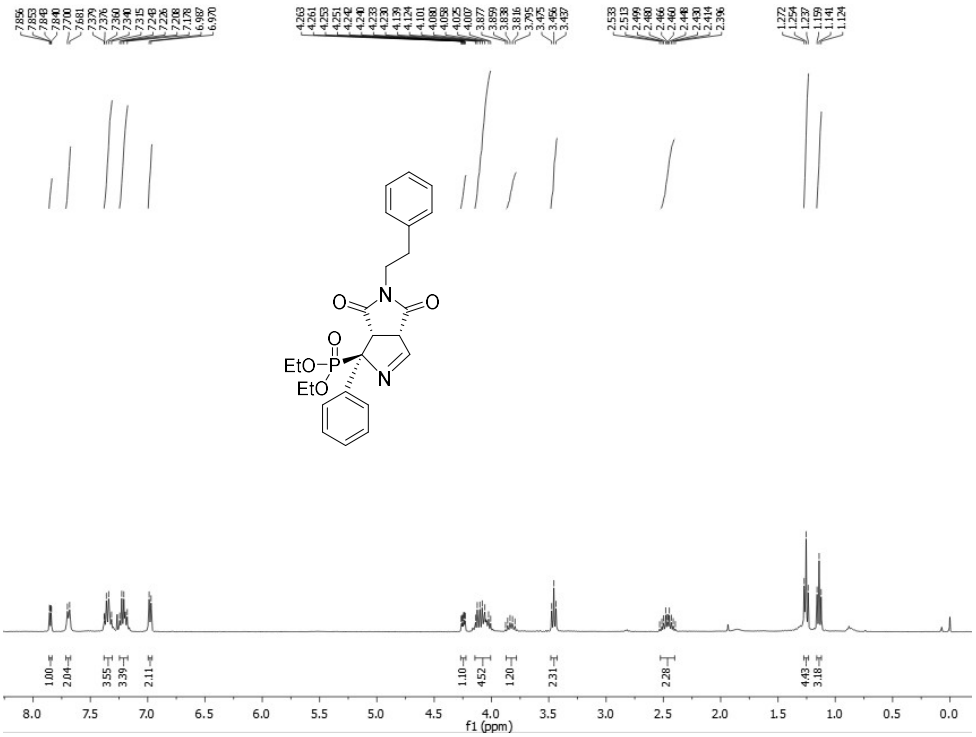
Diethyl (1*RS*,3a*SR*,6a*SR*)-5-(adamantan-1-yl)methyl)-4,6-dioxo-1-phenyl-1,3a,4,5,6,6a-hexahydropyrrolo[3,4-*c*]pyrrole-1-phosphonate (9i)



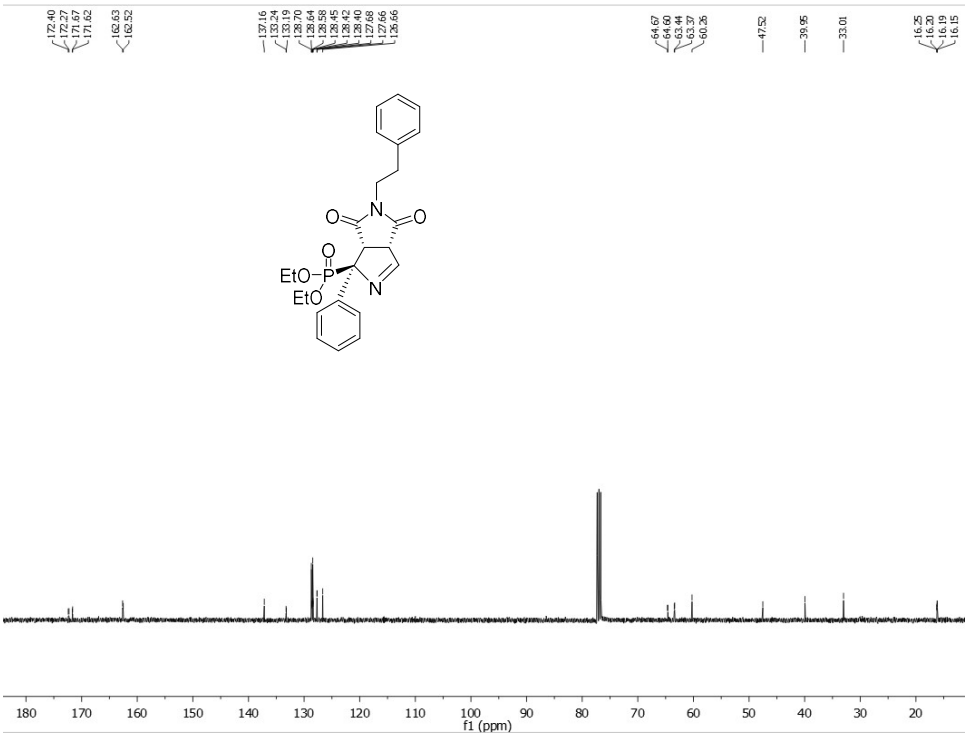
Diethyl (1*RS*,3a*SR*,6a*SR*)-5-benzyl-4,6-dioxo-1-phenyl-1,3a,4,5,6,6a-hexahydropyrrolo[3,4-*c*]pyrrole-1-phosphonate (9j)



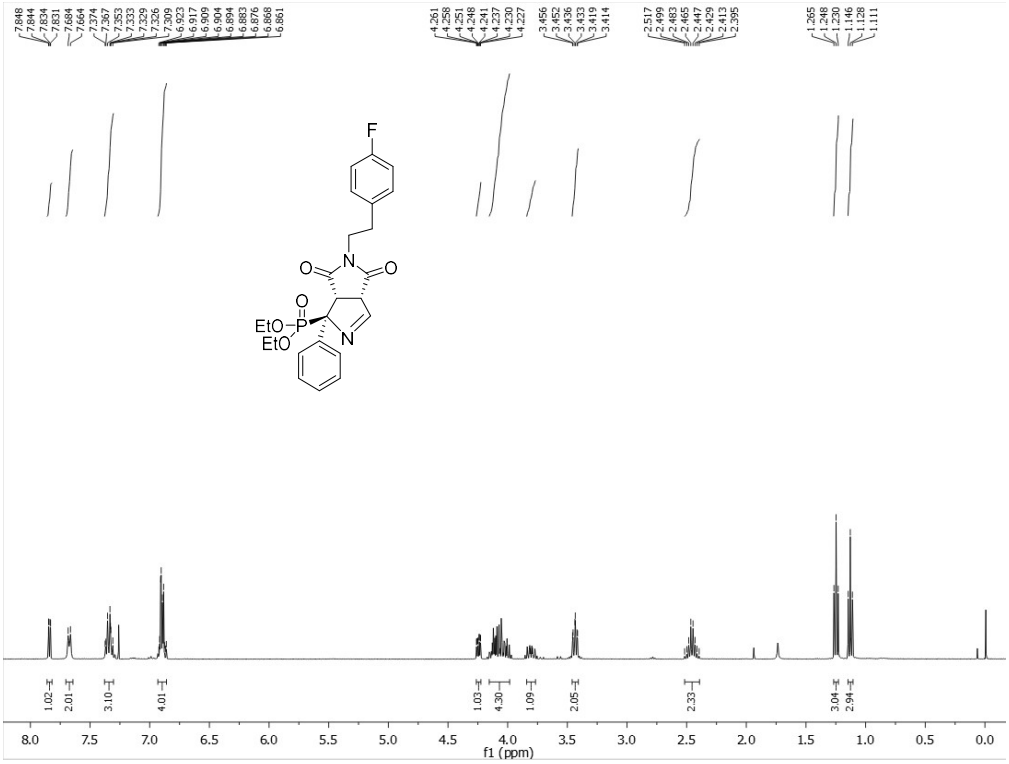
Diethyl (1*RS*,3a*SR*,6a*SR*)-5-benzyl-4,6-dioxo-1-phenyl-1,3a,4,5,6,6a-hexahydropyrrolo[3,4-*c*]pyrrole-1-phosphonate (9j)



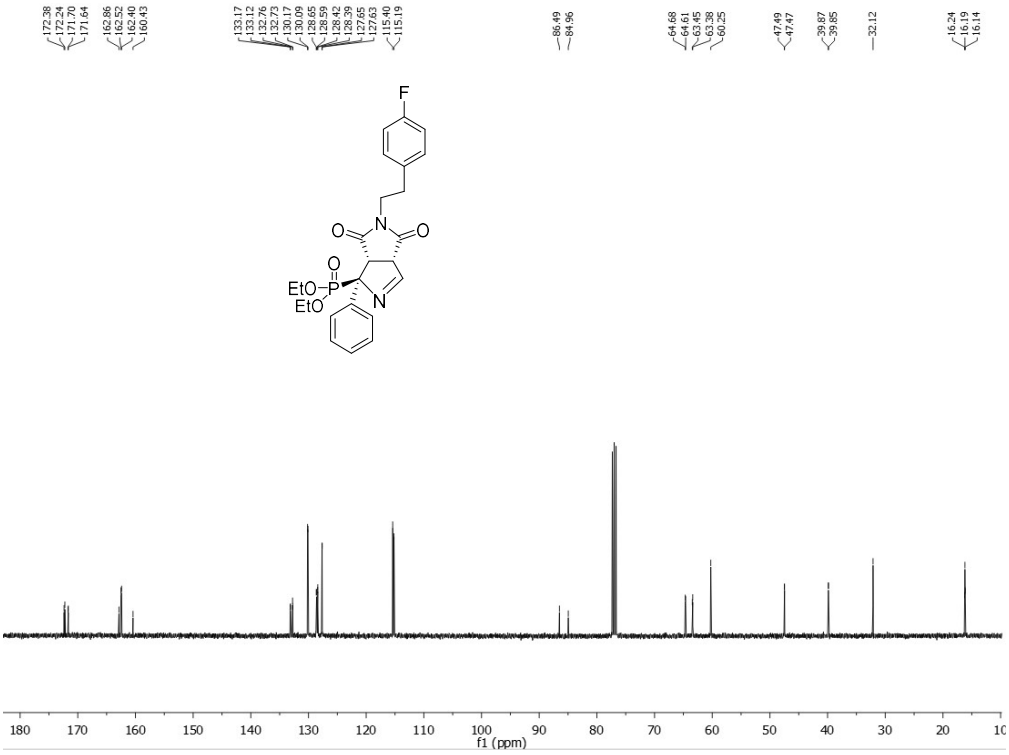
Diethyl (1*RS*,3a*SR*,6a*SR*)-4,6-dioxo-5-phenethyl-1-phenyl-1,3a,4,5,6,6a-hexahydropyrrolo[3,4-*c*]pyrrole-1-phosphonate (9k)



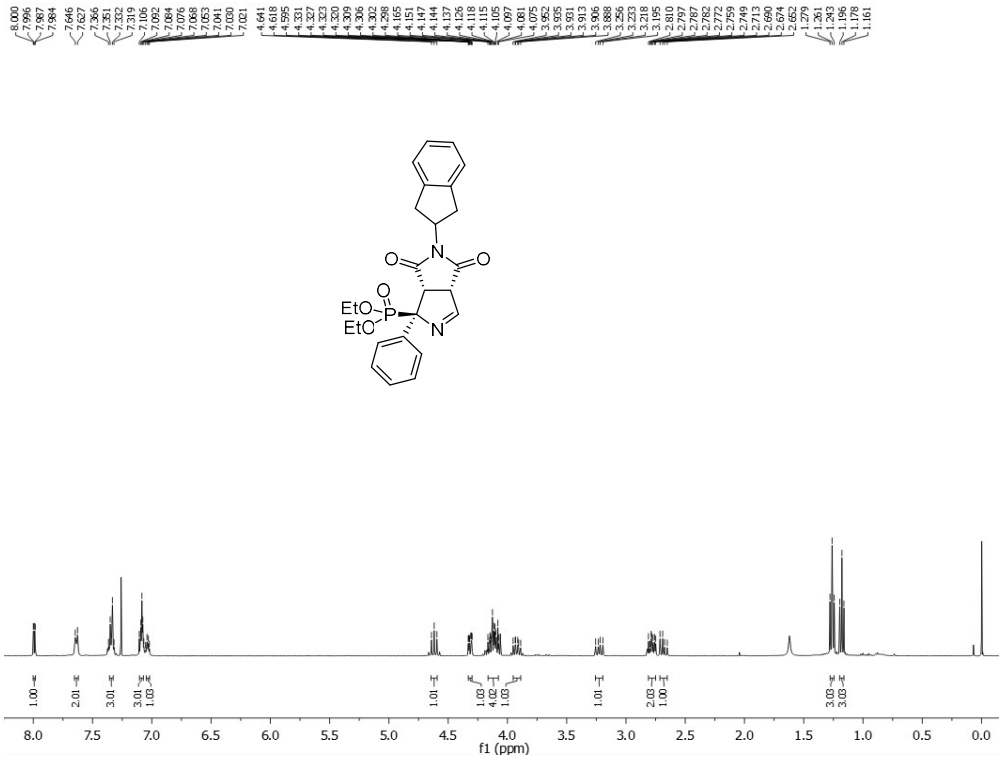
Diethyl (1*RS*,3a*SR*,6a*SR*)-4,6-dioxo-5-phenethyl-1-phenyl-1,3a,4,5,6,6a-hexahydropyrrolo[3,4-*c*]pyrrole-1-phosphonate (9k)



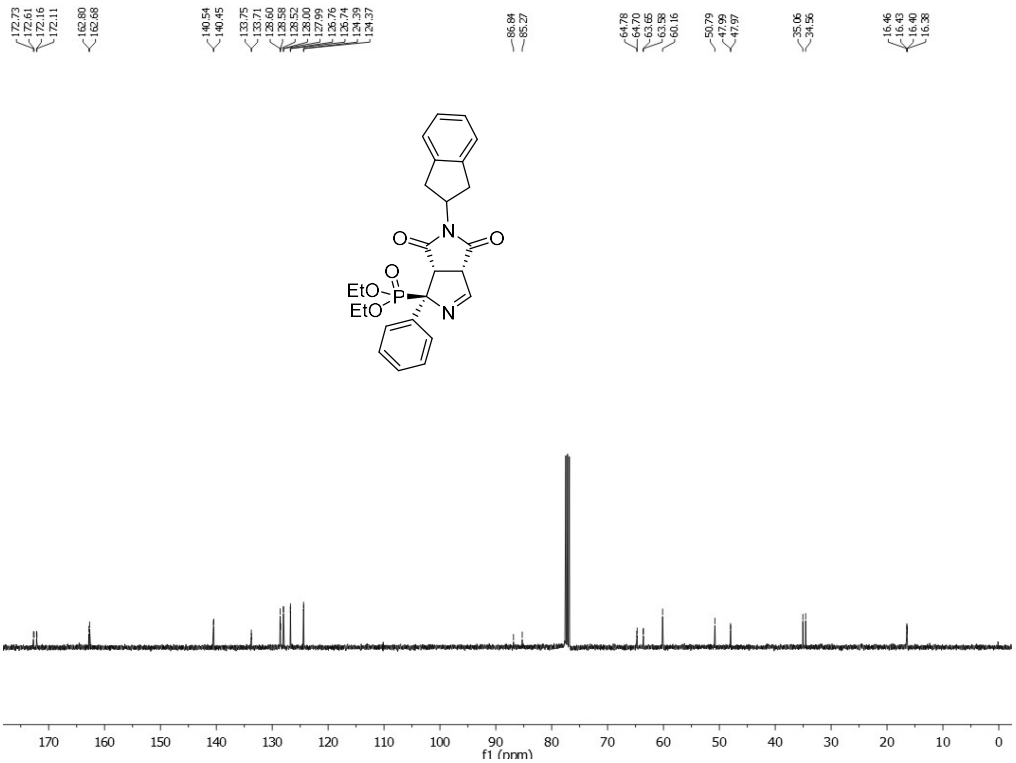
Diethyl (1*RS*,3a*SR*,6a*SR*)-5-(4-fluorophenethyl)-4,6-dioxo-1-phenyl-1,3a,4,5,6,6a-hexahydropyrrolo[3,4-*c*]pyrrole-1-phosphonate (9l)



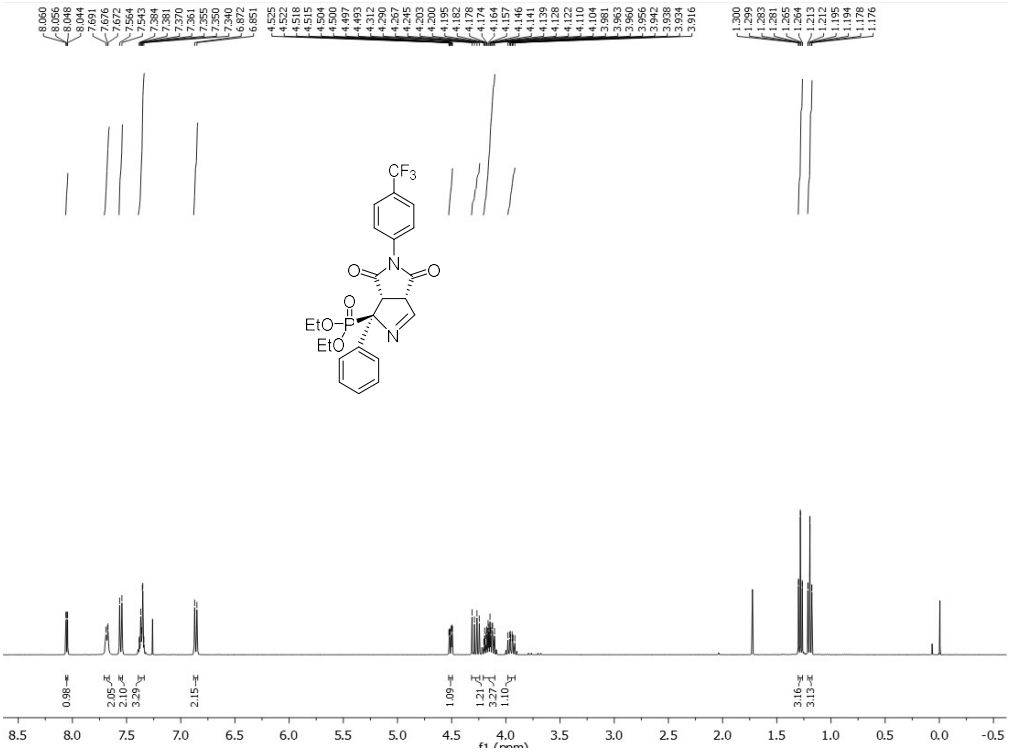
Diethyl (1*RS*,3a*SR*,6a*SR*)-5-(4-fluorophenethyl)-4,6-dioxo-1-phenyl-1,3a,4,5,6,6a-hexahydropyrrolo[3,4-*c*]pyrrole-1-phosphonate (9l)



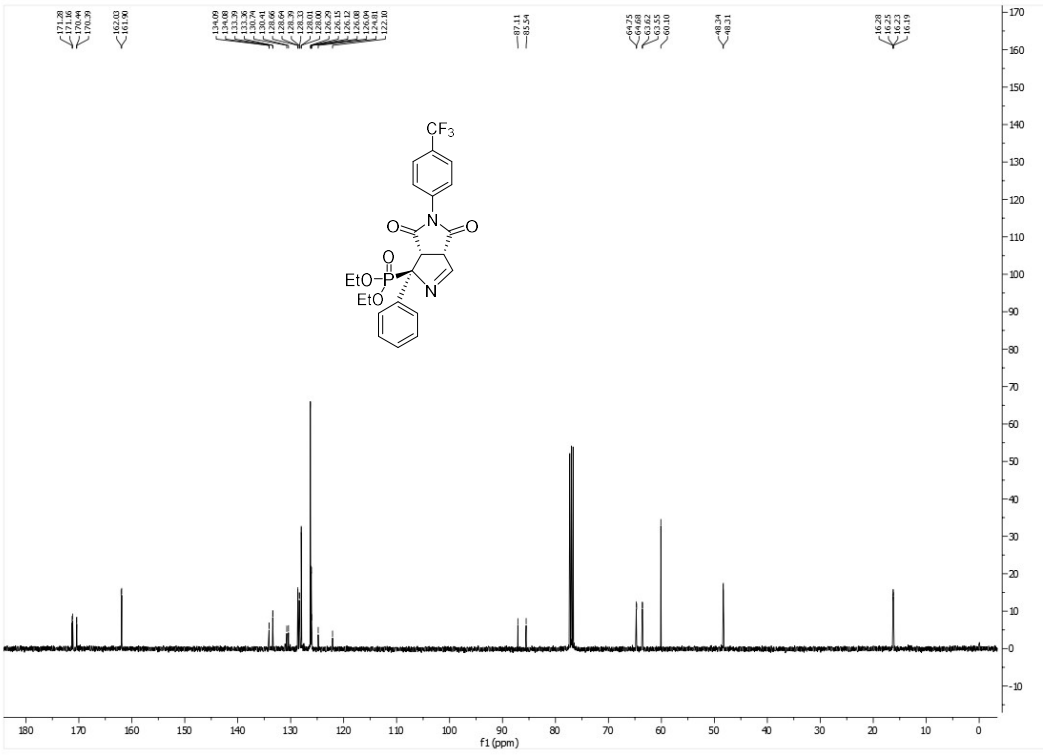
Diethyl (1*RS*,3a*SR*,6a*SR*)-5-(2,3-dihydro-1H-inden-2-yl)-4,6-dioxo-1-phenyl-1,3a,4,5,6,6a-hexahydropyrrolo[3,4-*c*]pyrrole-1-phosphonate (9m)



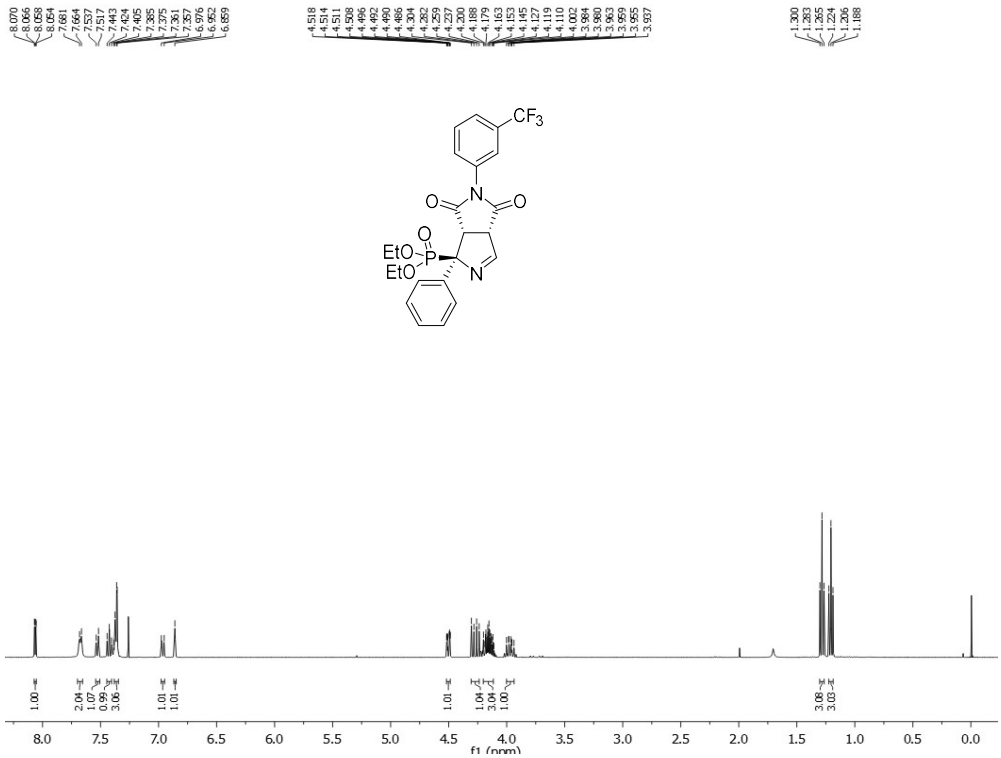
Diethyl (1*RS*,3a*SR*,6a*SR*)-5-(2,3-dihydro-1H-inden-2-yl)-4,6-dioxo-1-phenyl-1,3a,4,5,6,6a-hexahydropyrrolo[3,4-*c*]pyrrole-1-phosphonate (9m)



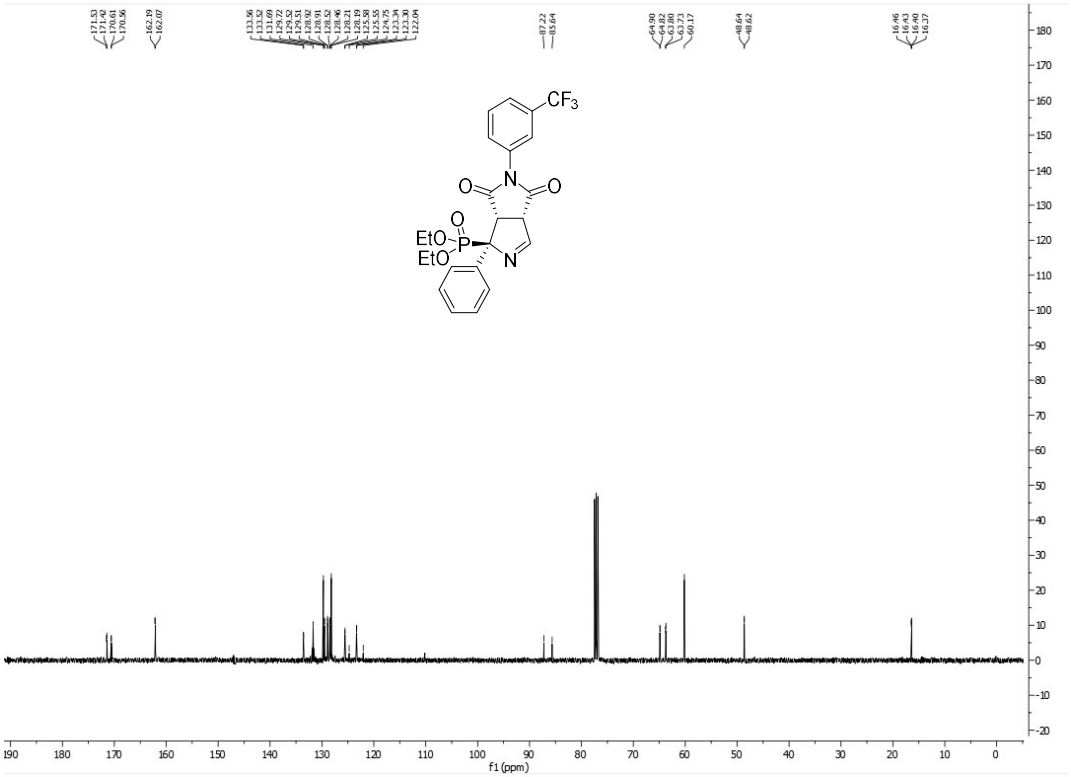
Diethyl (1*RS*,3a*SR*,6a*SR*)-4,6-dioxo-1-phenyl-5-[4-(trifluoromethyl)phenyl]-1,3a,4,5,6,6a-hexahydropyrrolo[3,4-*c*]pyrrole-1-phosphonate (9n)



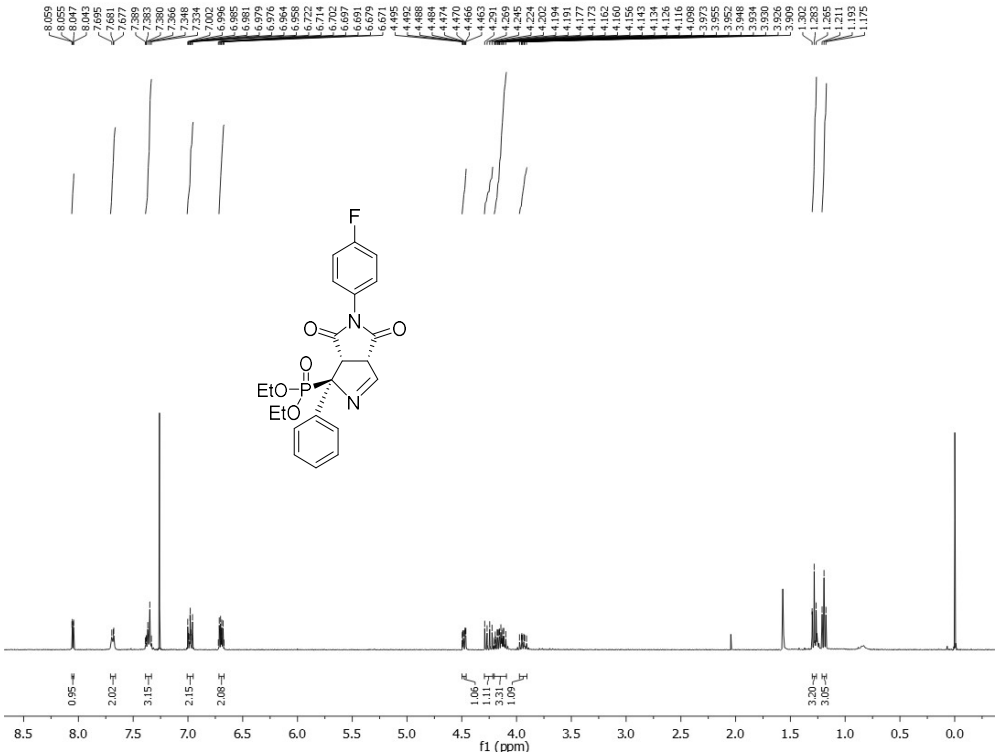
Diethyl (1*RS*,3a*SR*,6a*SR*)-4,6-dioxo-1-phenyl-5-[4-(trifluoromethyl)phenyl]-1,3a,4,5,6,6a-hexahydropyrrolo[3,4-*c*]pyrrole-1-phosphonate (9n)



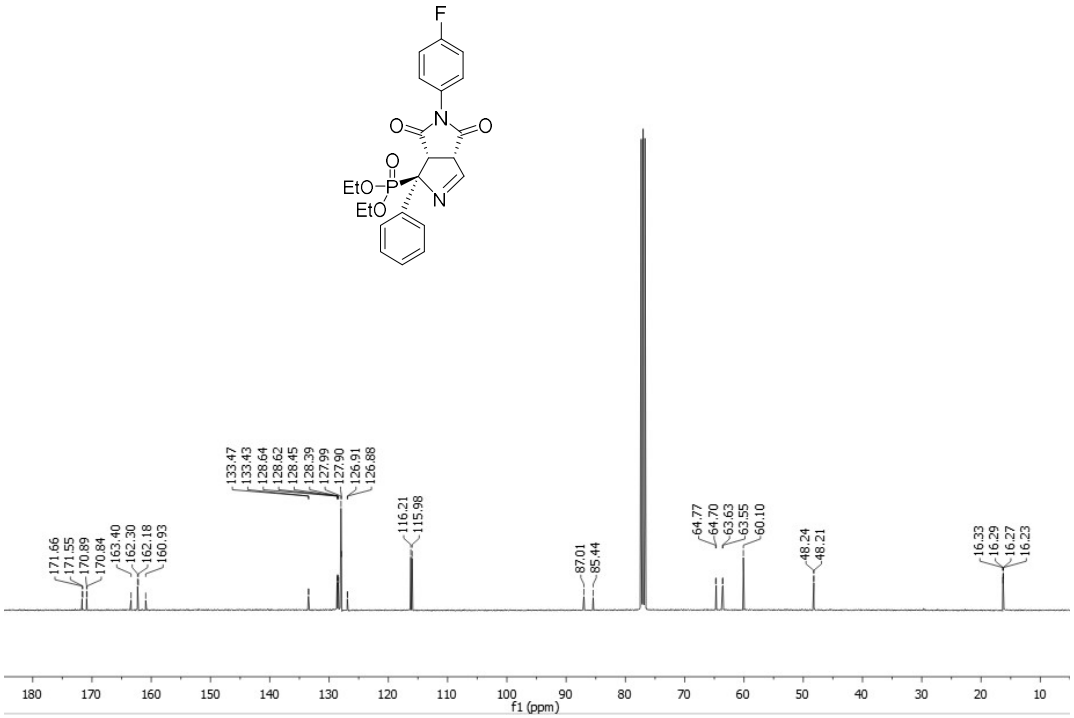
Diethyl (1*RS*,3a*SR*,6a*SR*)-4,6-dioxo-1-phenyl-5-[3-(trifluoromethyl)phenyl]-1,3a,4,5,6,6a-hexahydropyrrolo[3,4-*c*]pyrrole-1-phosphonate (9o)



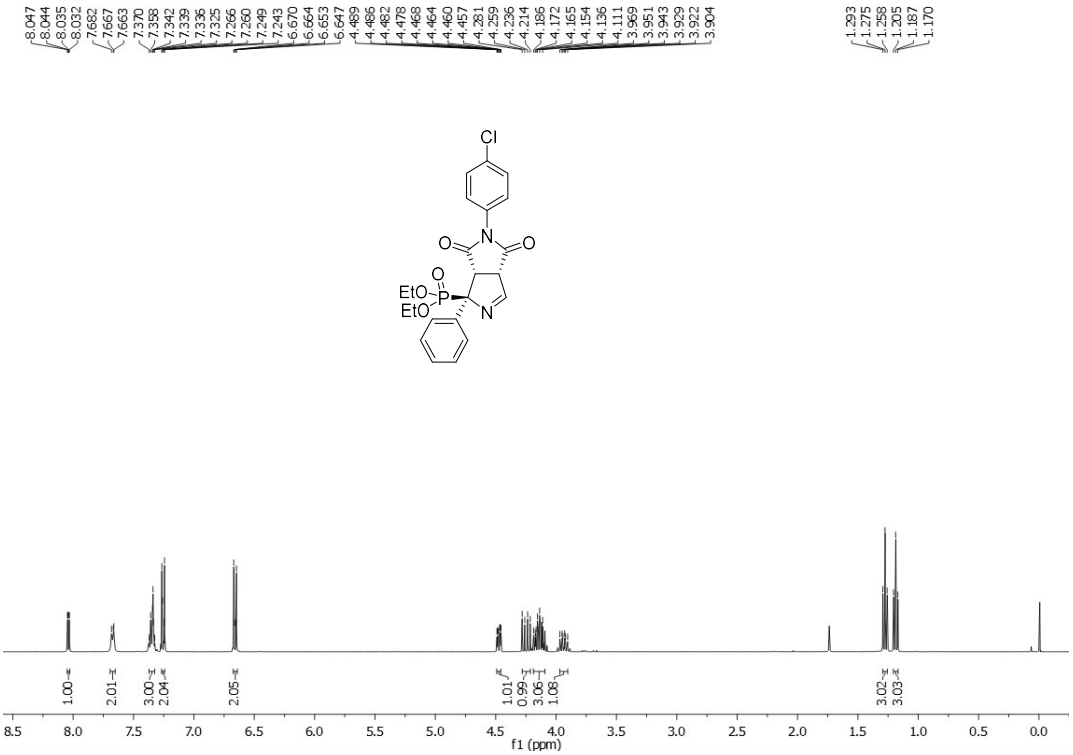
Diethyl (1*RS*,3a*SR*,6a*SR*)-4,6-dioxo-1-phenyl-5-[3-(trifluoromethyl)phenyl]-1,3a,4,5,6,6a-hexahydropyrrolo[3,4-*c*]pyrrole-1-phosphonate (9o)



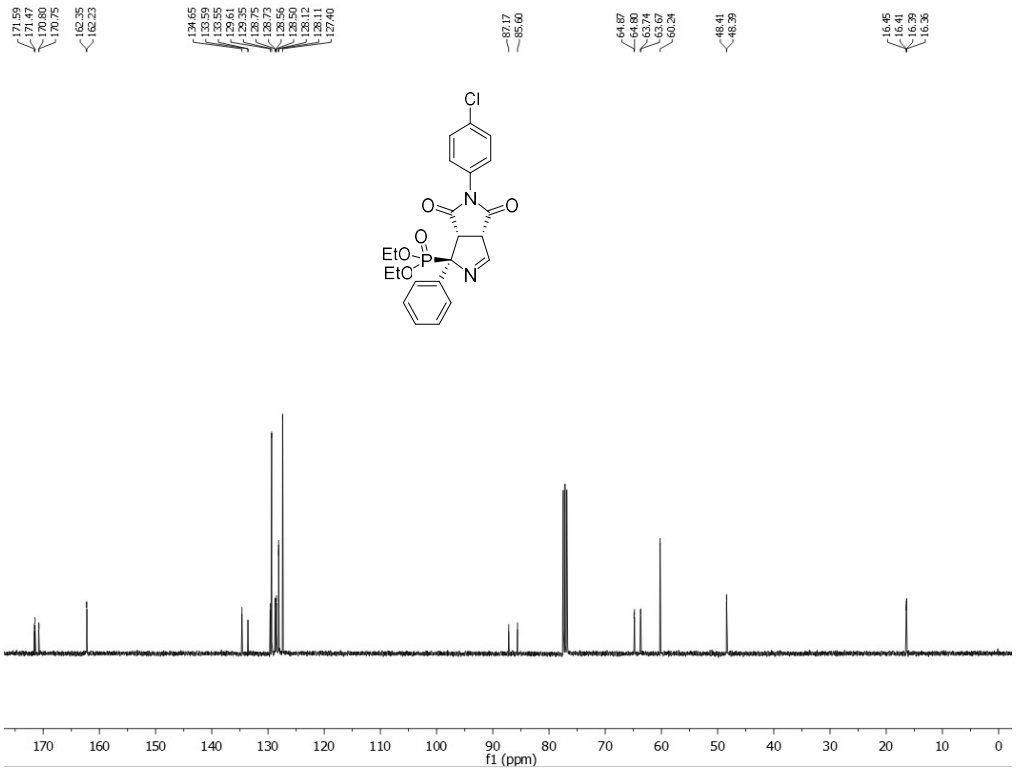
Diethyl (1*RS*,3a*SR*,6a*SR*)-5-(4-fluorophenyl)-4,6-dioxo-1-phenyl-1,3a,4,5,6,6a-hexahydropyrrolo[3,4-*c*]pyrrole-1-phosphonate (9p)



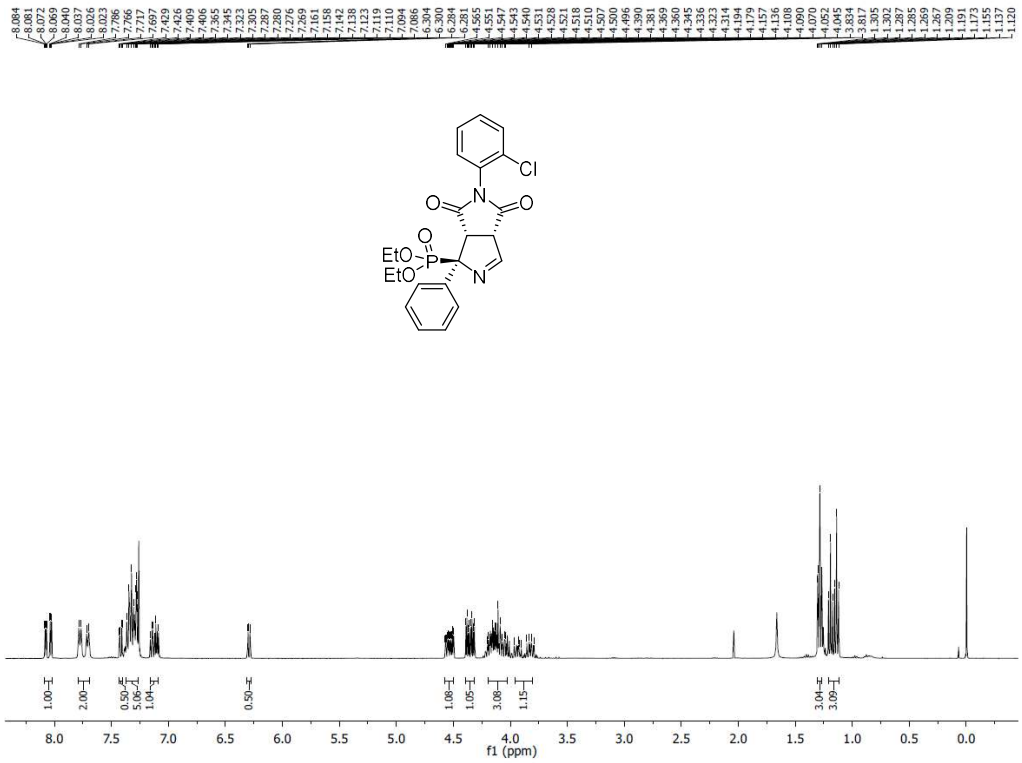
Diethyl (1*RS*,3a*SR*,6a*SR*)-5-(4-fluorophenyl)-4,6-dioxo-1-phenyl-1,3a,4,5,6,6a-hexahydropyrrolo[3,4-*c*]pyrrole-1-phosphonate (9p)



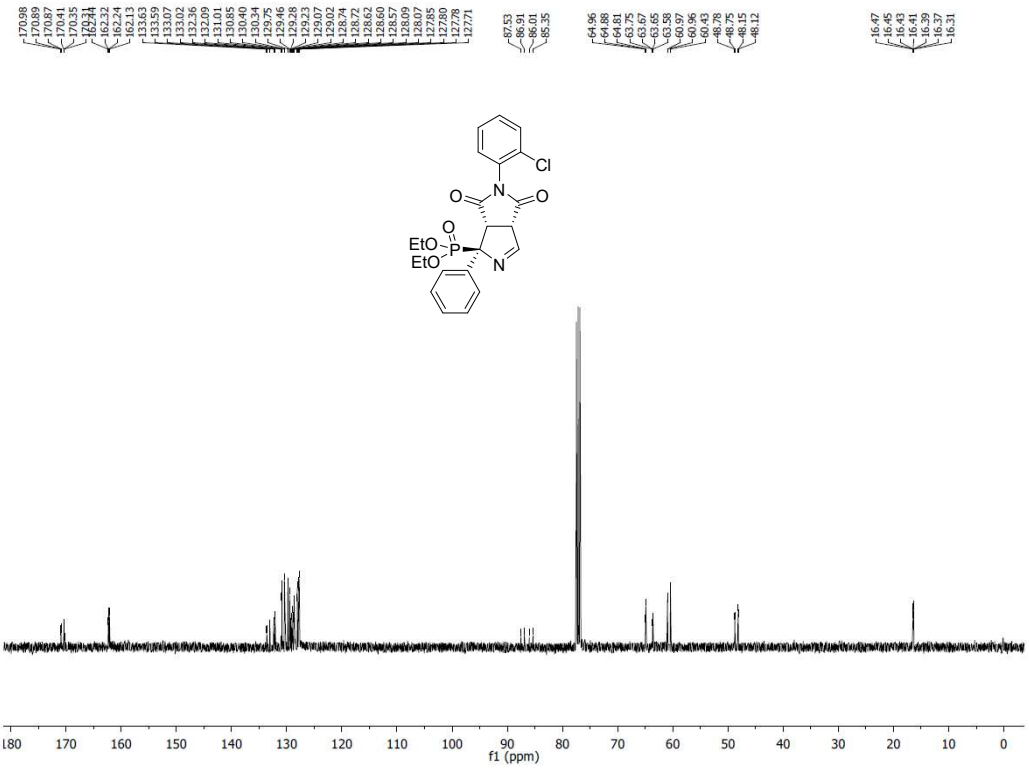
Diethyl (1*RS*,3a*SR*,6a*SR*)-5-(4-chlorophenyl)-4,6-dioxo-1-phenyl-1,3a,4,5,6,6a-hexahydropyrrolo[3,4-*c*]pyrrole-1-phosphonate (9q)



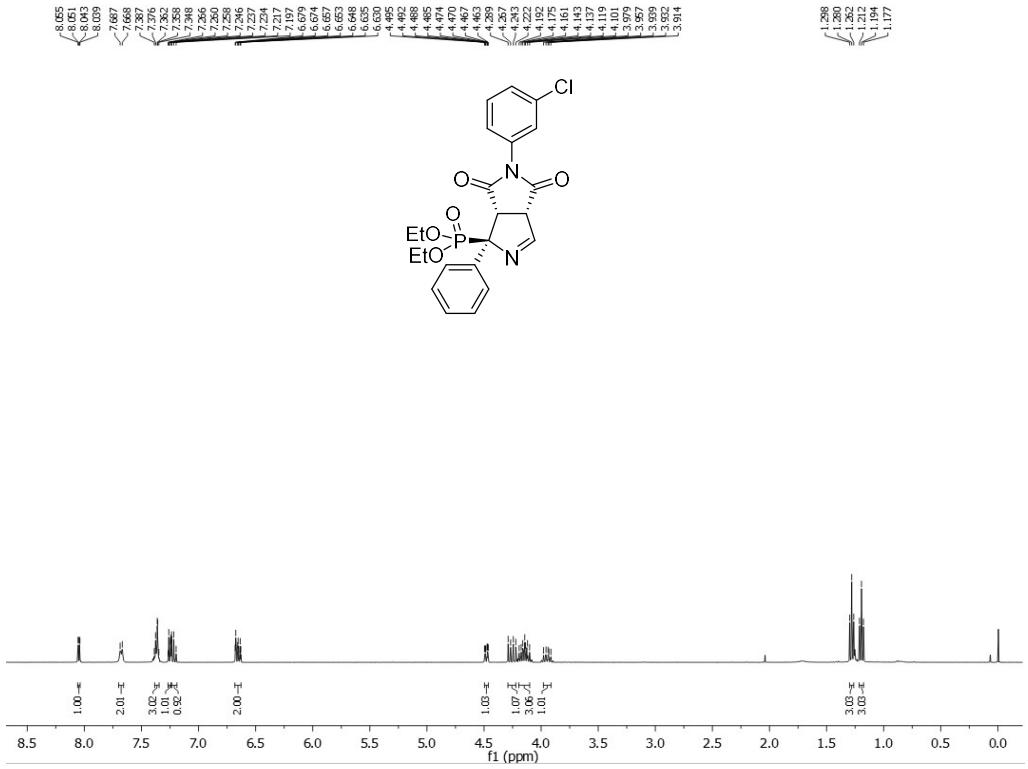
Diethyl (1*RS*,3a*SR*,6a*SR*)-5-(4-chlorophenyl)-4,6-dioxo-1-phenyl-1,3a,4,5,6,6a-hexahydropyrrolo[3,4-*c*]pyrrole-1-phosphonate (9q)



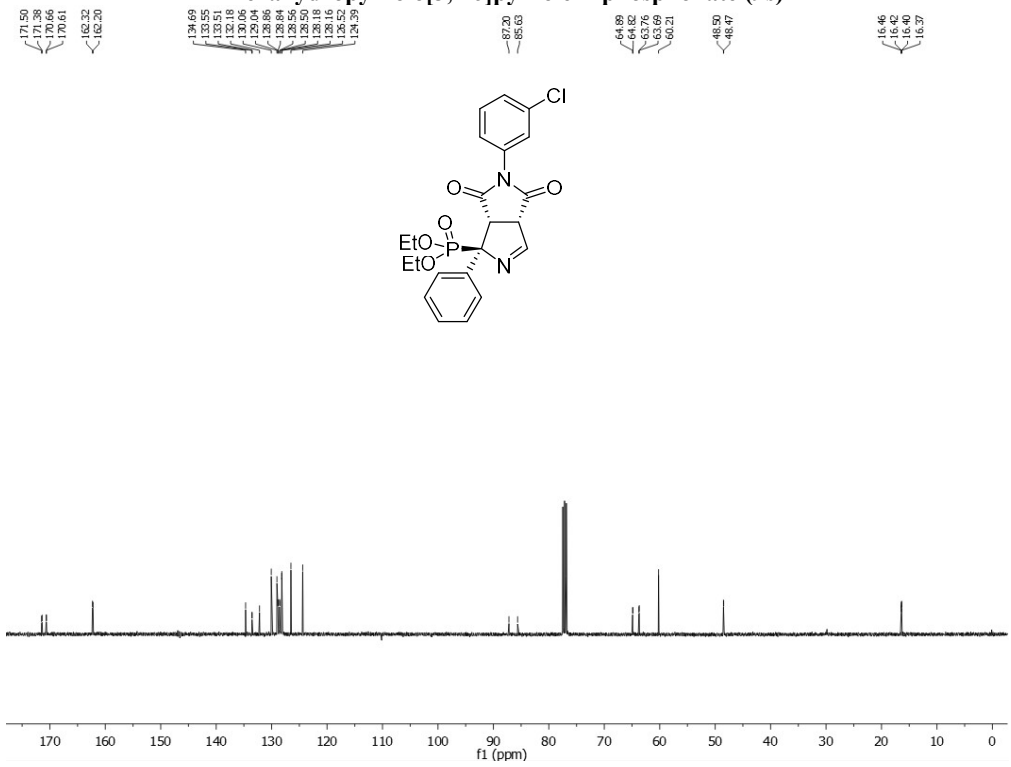
Diethyl (1*RS*,3a*SR*,6a*SR*)-5-(2-chlorophenyl)-4,6-dioxo-1-phenyl-1,3a,4,5,6,6a-hexahydropyrrolo[3,4-*c*]pyrrole-1-phosphonate (9r)



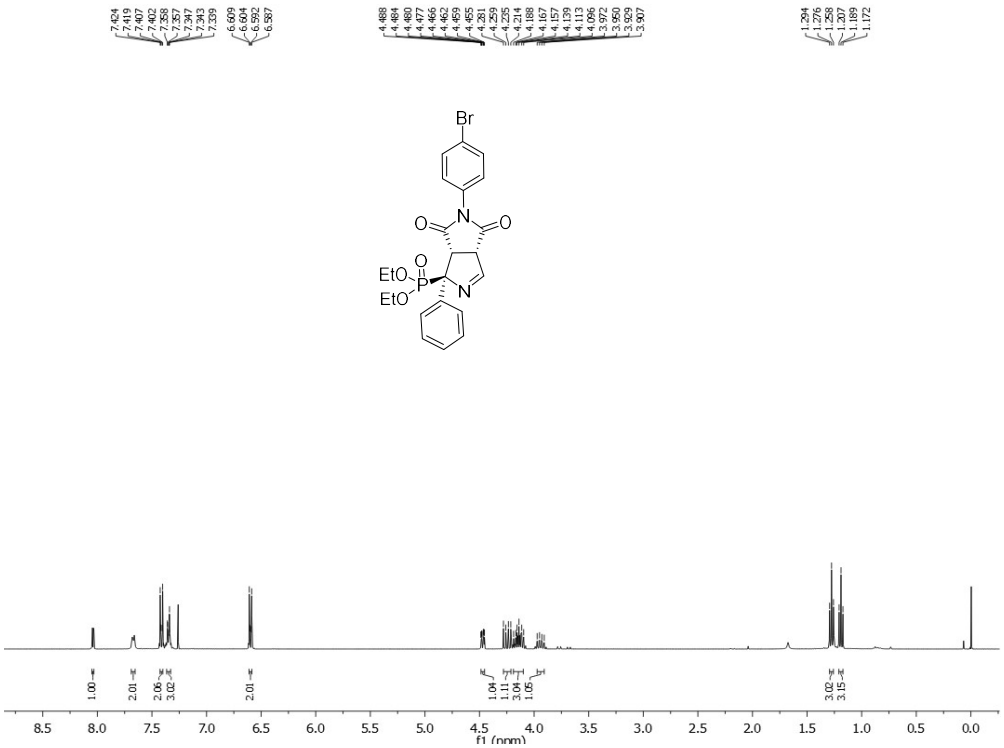
Diethyl (1*RS*,3a*SR*,6a*SR*)-5-(2-chlorophenyl)-4,6-dioxo-1-phenyl-1,3a,4,5,6,6a-hexahydropyrrolo[3,4-*c*]pyrrole-1-phosphonate (9r)



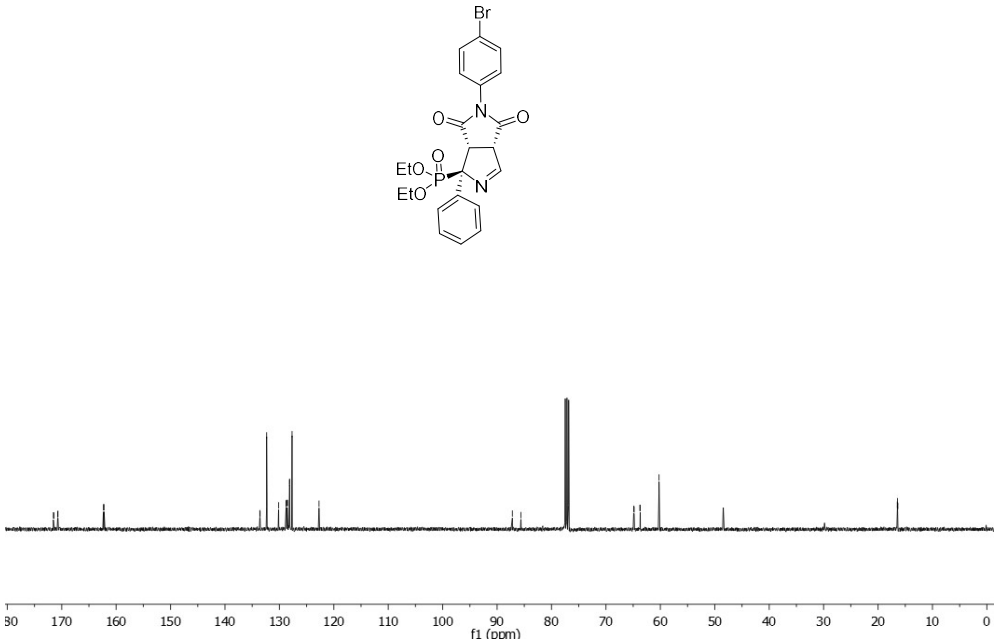
Diethyl (1*RS*,3a*SR*,6a*SR*)-5-(3-chlorophenyl)-4,6-dioxo-1-phenyl-1,3a,4,5,6,6a-hexahydropyrrolo[3,4-*c*]pyrrole-1-phosphonate (9s)



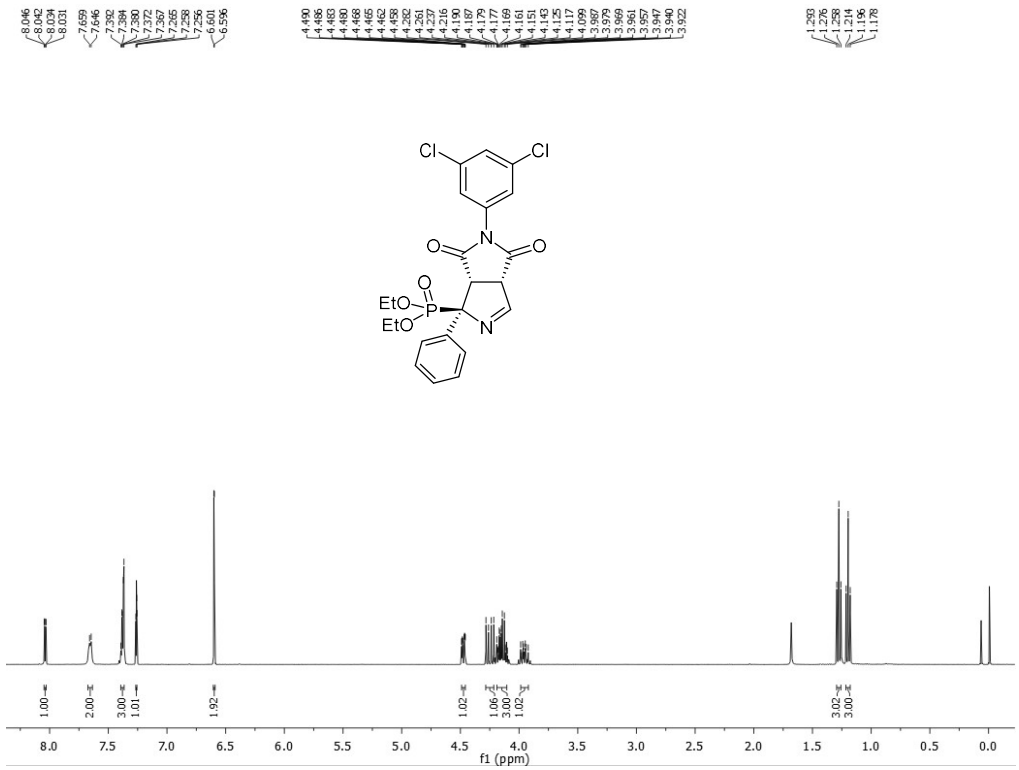
Diethyl (1*RS*,3a*SR*,6a*SR*)-5-(3-chlorophenyl)-4,6-dioxo-1-phenyl-1,3a,4,5,6,6a-hexahydropyrrolo[3,4-*c*]pyrrole-1-phosphonate (9s)



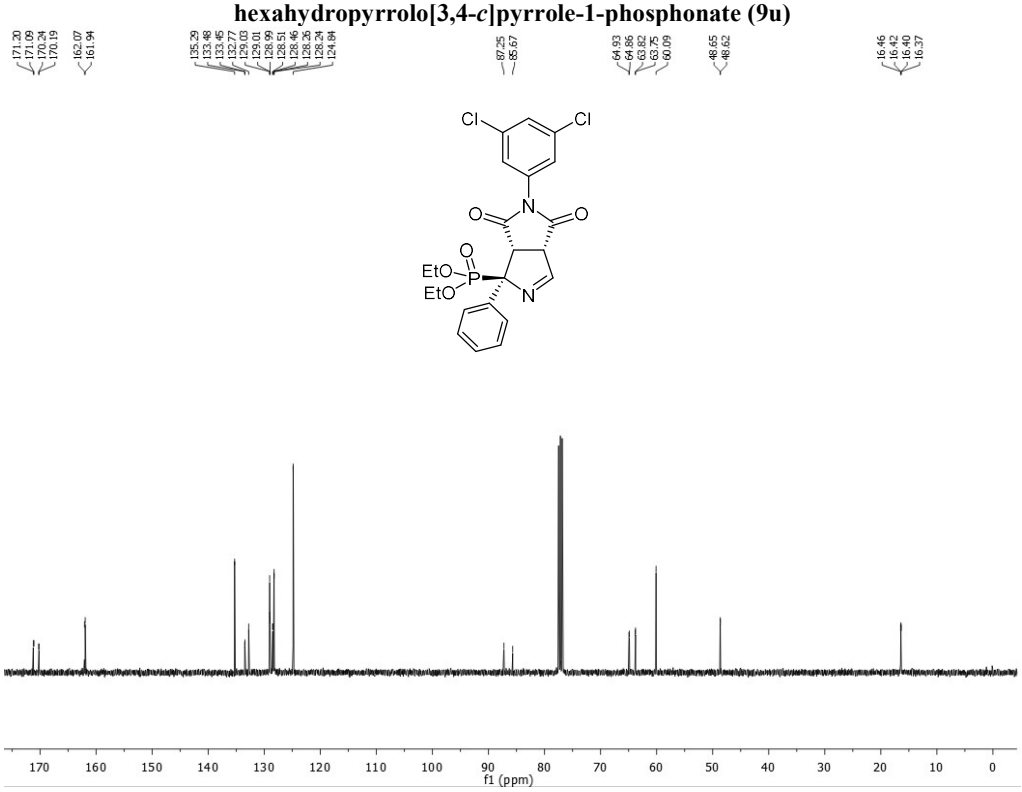
Diethyl (1*RS*,3a*SR*,6a*SR*)-5-(4-bromophenyl)-4,6-dioxo-1-phenyl-1,3a,4,5,6,6a-hexahydropyrrolo[3,4-*c*]pyrrole-1-phosphonate (9t)



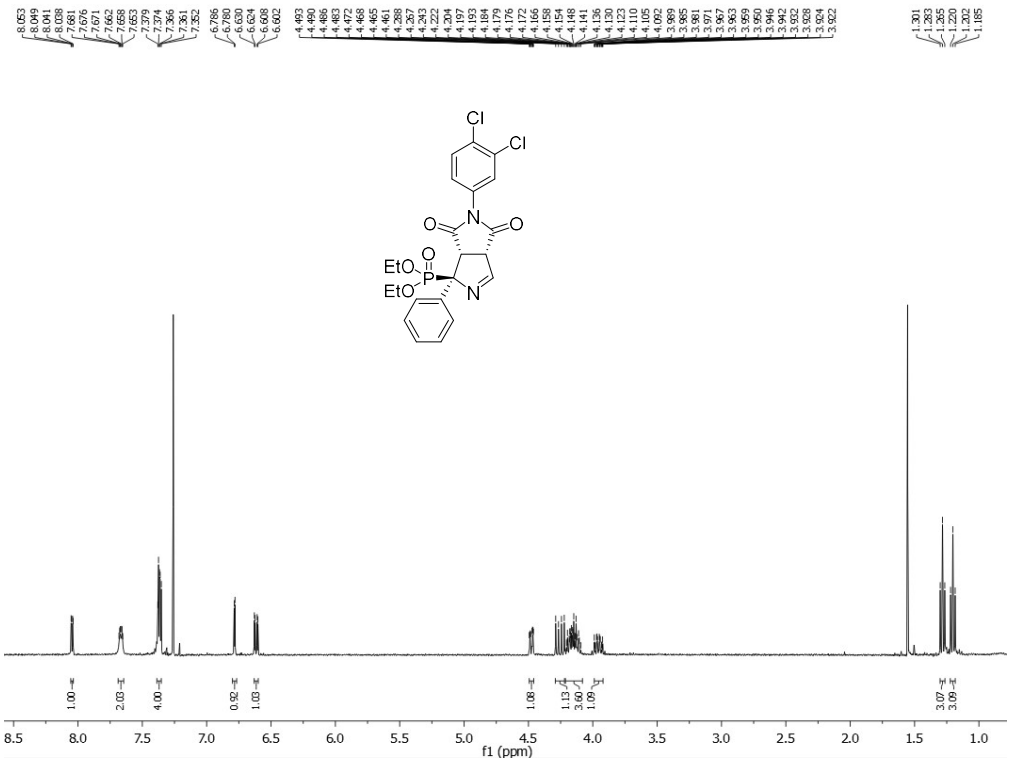
Diethyl (1*RS*,3a*SR*,6a*SR*)-5-(4-bromophenyl)-4,6-dioxo-1-phenyl-1,3a,4,5,6,6a-hexahydropyrrolo[3,4-*c*]pyrrole-1-phosphonate (9t)



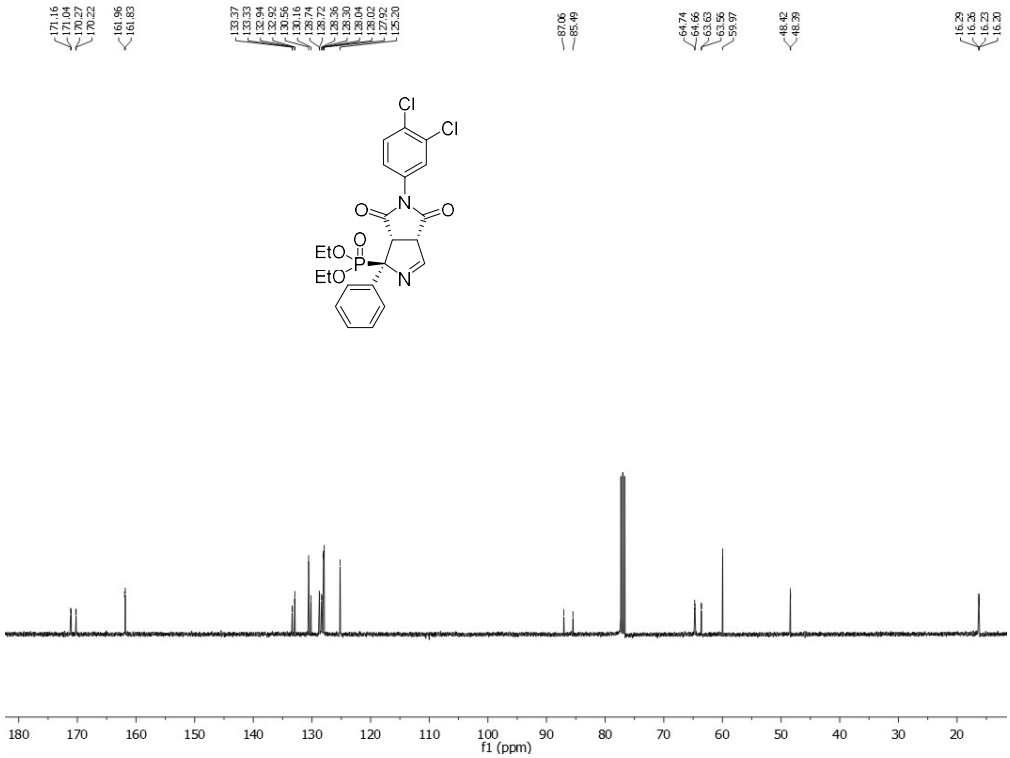
Diethyl (1*RS*,3a*SR*,6a*SR*)-5-(3,5-dichlorophenyl)-4,6-dioxo-1-phenyl-1,3a,4,5,6,6a-hexahydropyrrolo[3,4-*c*]pyrrole-1-phosphonate (9u)



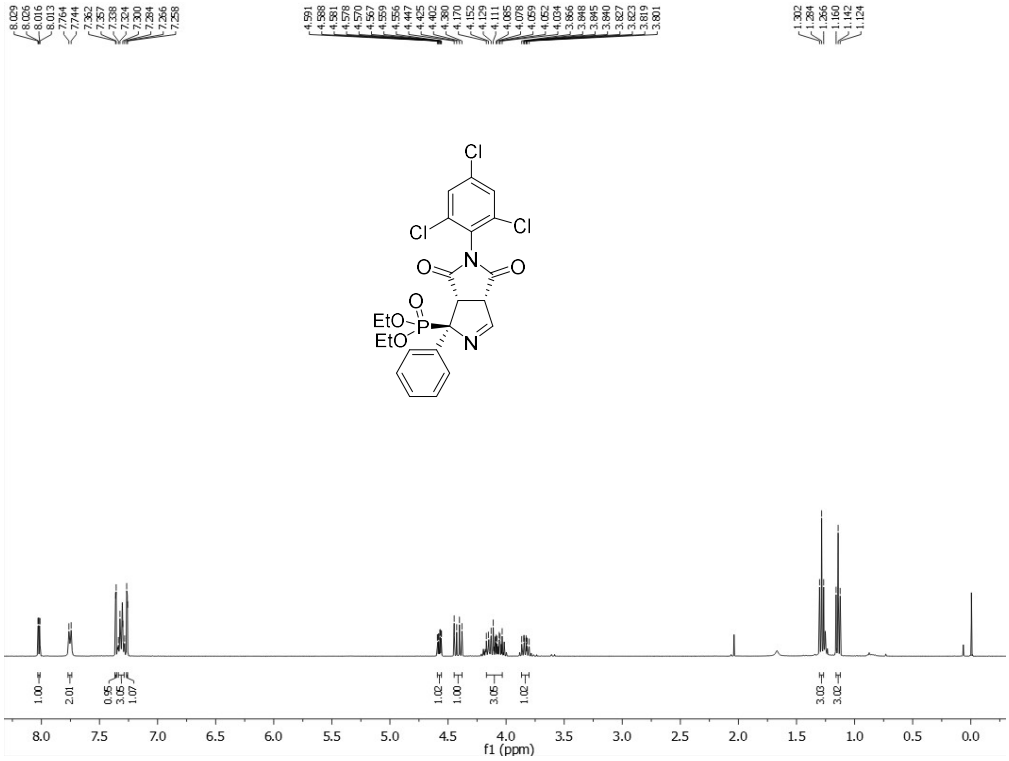
Diethyl (1*RS*,3a*SR*,6a*SR*)-5-(3,5-dichlorophenyl)-4,6-dioxo-1-phenyl-1,3a,4,5,6,6a-hexahydropyrrolo[3,4-*c*]pyrrole-1-phosphonate (9u)



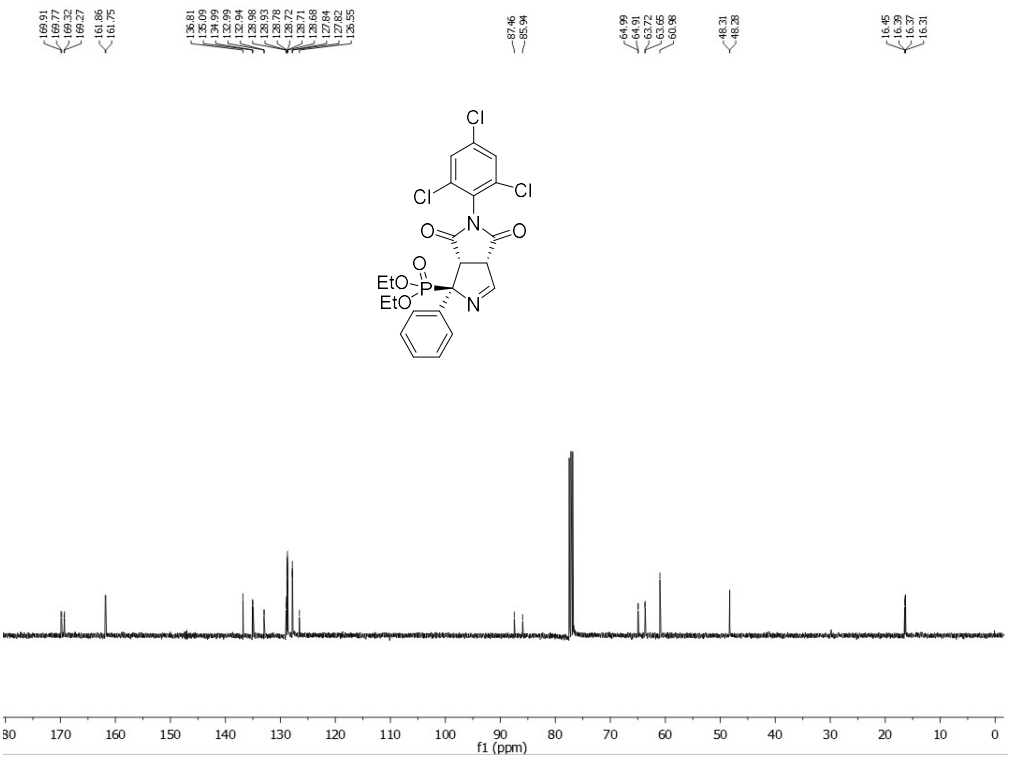
Diethyl (1*RS*,3a*SR*,6a*SR*)-5-(3,4-dichlorophenyl)-4,6-dioxo-1-phenyl-1,3a,4,5,6,6a-hexahydropyrrolo[3,4-*c*]pyrrole-1-phosphonate (9v)



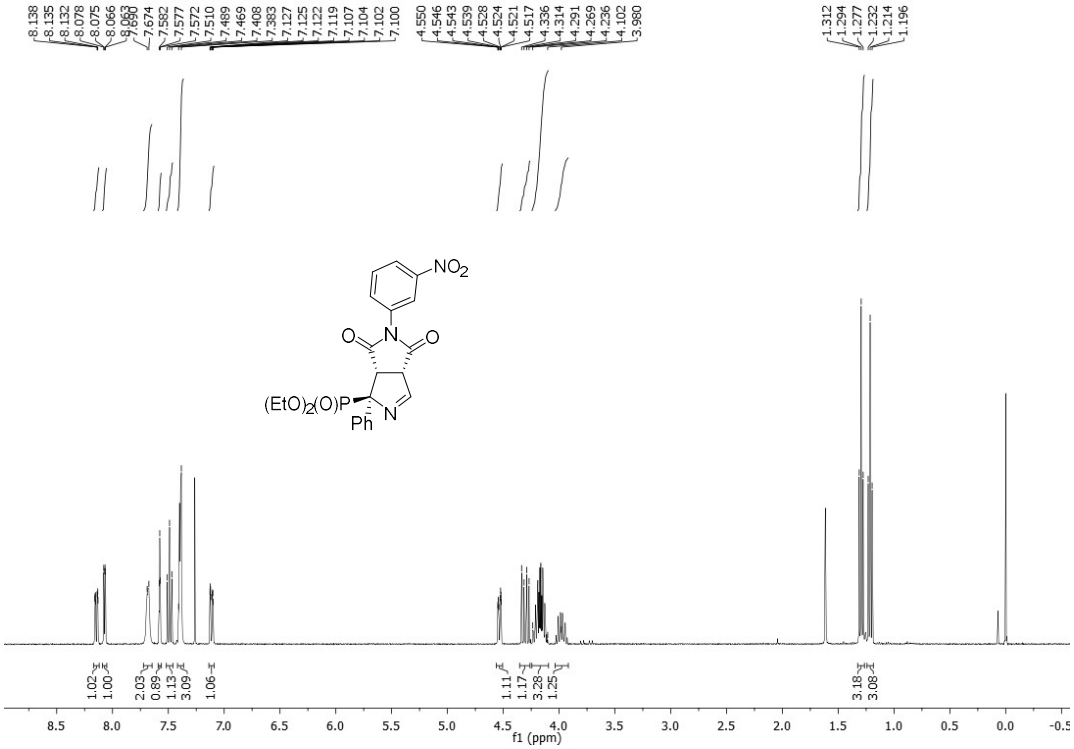
Diethyl (1*RS*,3a*SR*,6a*SR*)-5-(3,4-dichlorophenyl)-4,6-dioxo-1-phenyl-1,3a,4,5,6,6a-hexahydropyrrolo[3,4-*c*]pyrrole-1-phosphonate (9v)



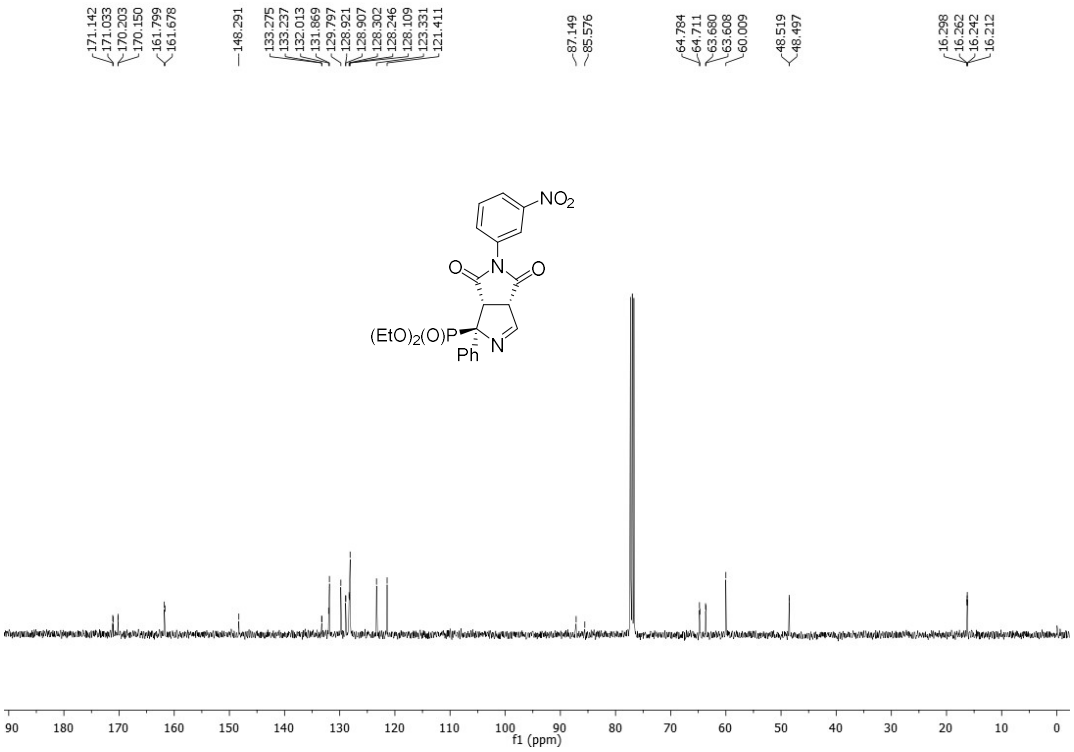
Diethyl (1*RS*,3a*SR*,6a*SR*)-4,6-dioxo-1-phenyl-5-(2,4,6-trichlorophenyl)-1,3a,4,5,6,6a-hexahydropyrrolo[3,4-*c*]pyrrole-1-phosphonate (9w)



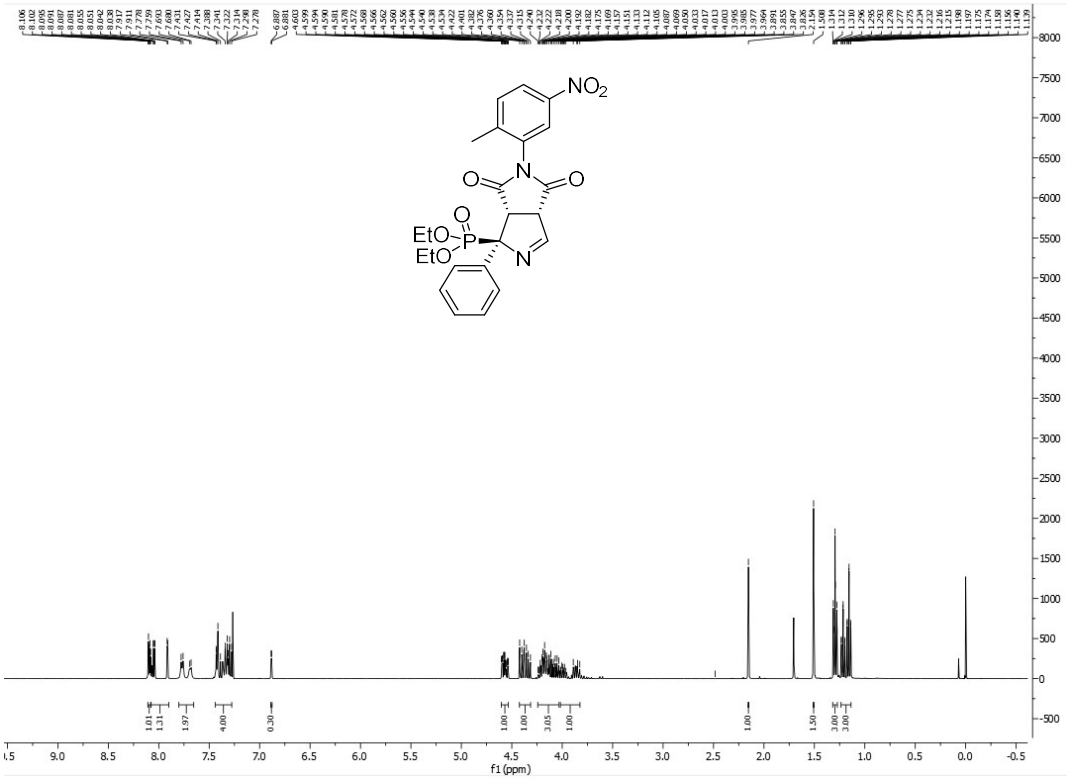
Diethyl (1*RS*,3a*SR*,6a*SR*)-4,6-dioxo-1-phenyl-5-(2,4,6-trichlorophenyl)-1,3a,4,5,6,6a-hexahydropyrrolo[3,4-*c*]pyrrole-1-phosphonate (9w)



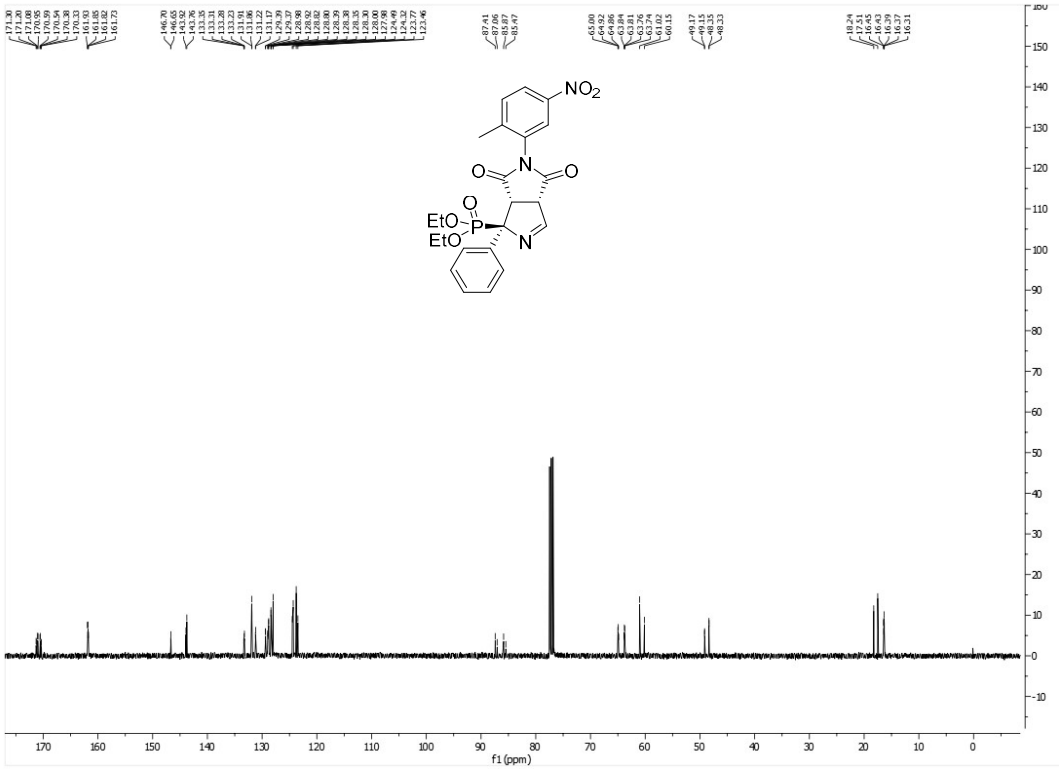
Diethyl (1*RS*,3a*SR*,6a*SR*)-5-(3-nitrophenyl)-4,6-dioxo-1-phenyl-1,3a,4,5,6,6a-hexahydropyrrolo[3,4-*c*]pyrrole-1-phosphonate (9x)



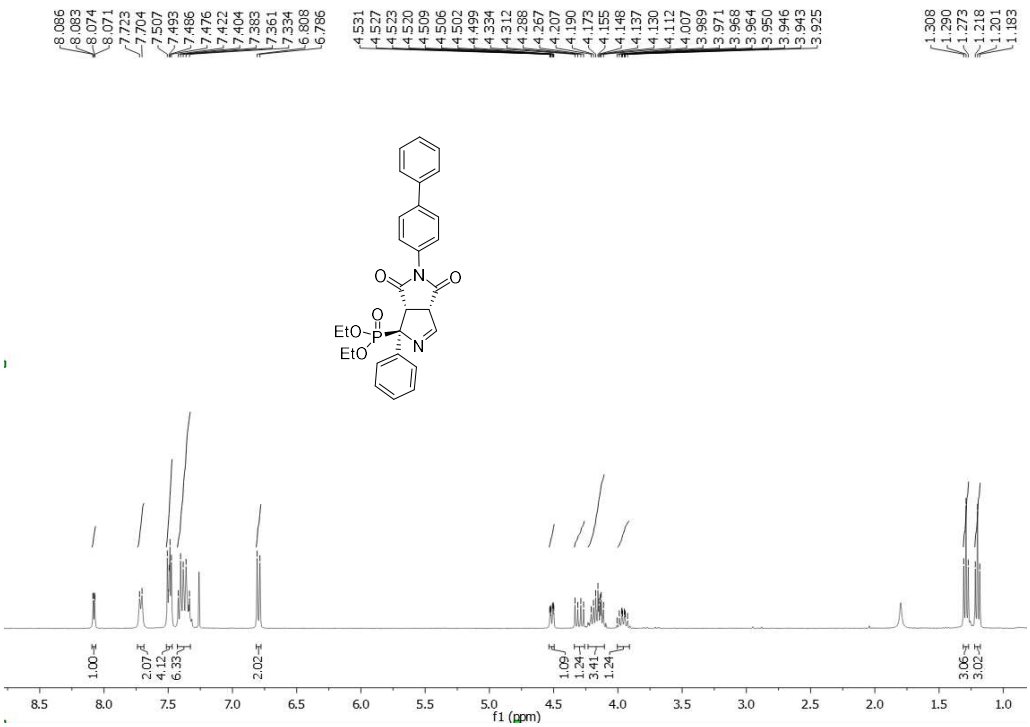
Diethyl (1*RS*,3a*SR*,6a*SR*)-5-(3-nitrophenyl)-4,6-dioxo-1-phenyl-1,3a,4,5,6,6a-hexahydropyrrolo[3,4-*c*]pyrrole-1-phosphonate (9x)



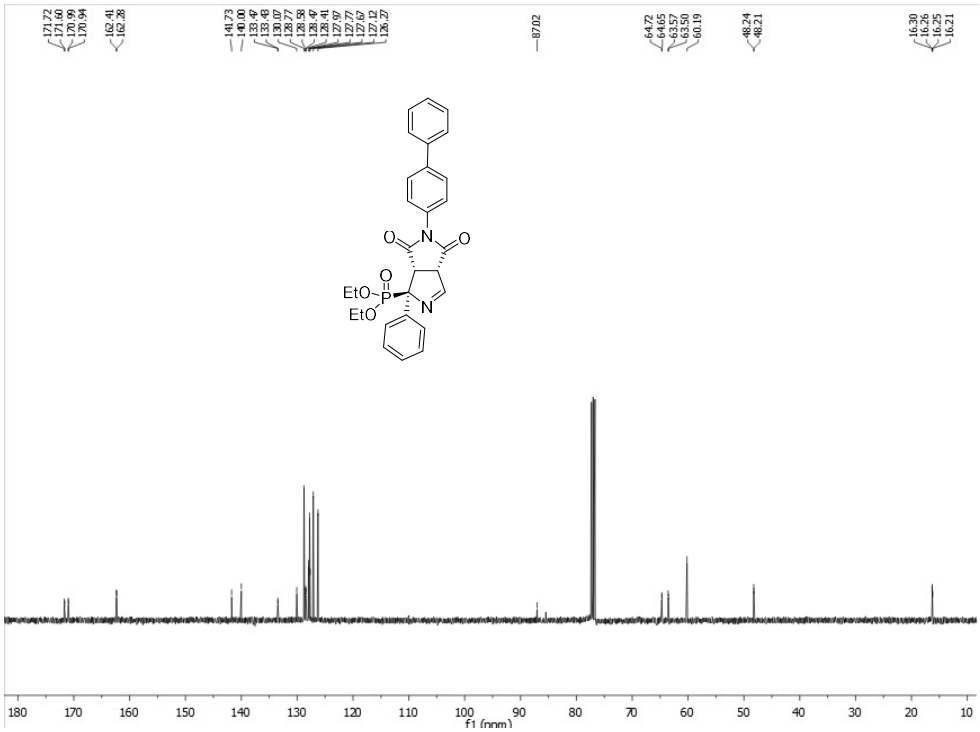
Diethyl (1*RS*,3a*SR*,6a*SR*)-5-(2-methyl-5-nitrophenyl)-4,6-dioxo-1-phenyl-1,3a,4,5,6,6a-hexahydropyrrolo[3,4-*c*]pyrrole-1-phosphonate(9y)



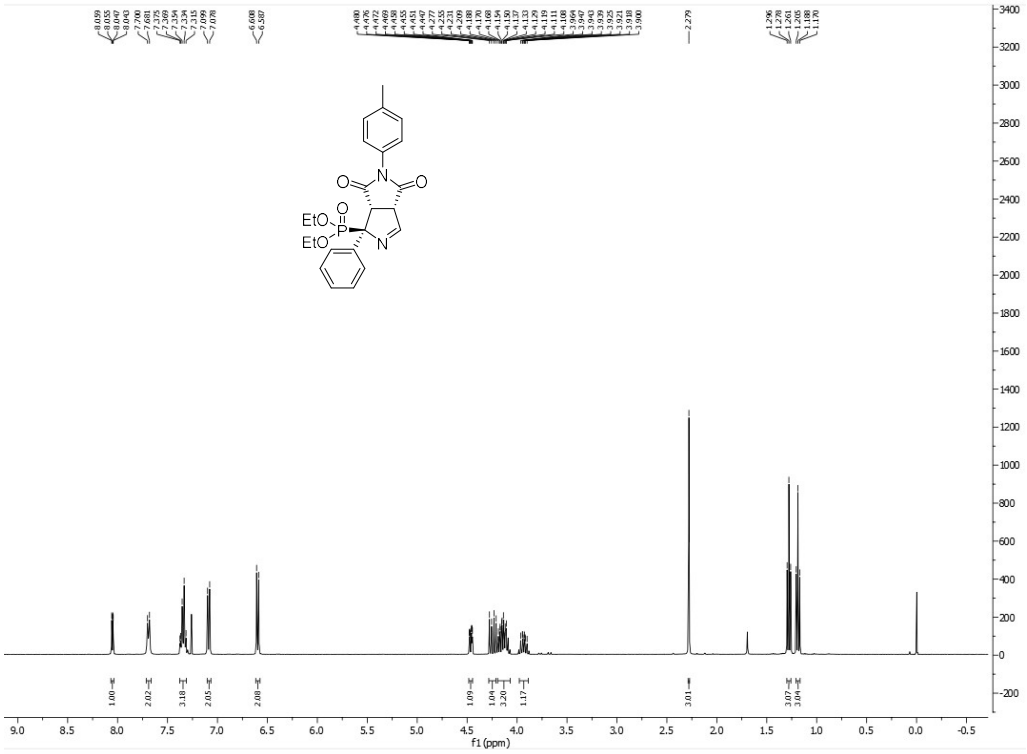
Diethyl (1*RS*,3a*SR*,6a*SR*)-5-(2-methyl-5-nitrophenyl)-4,6-dioxo-1-phenyl-1,3a,4,5,6,6a-hexahydropyrrolo[3,4-*c*]pyrrole-1-phosphonate(9y)



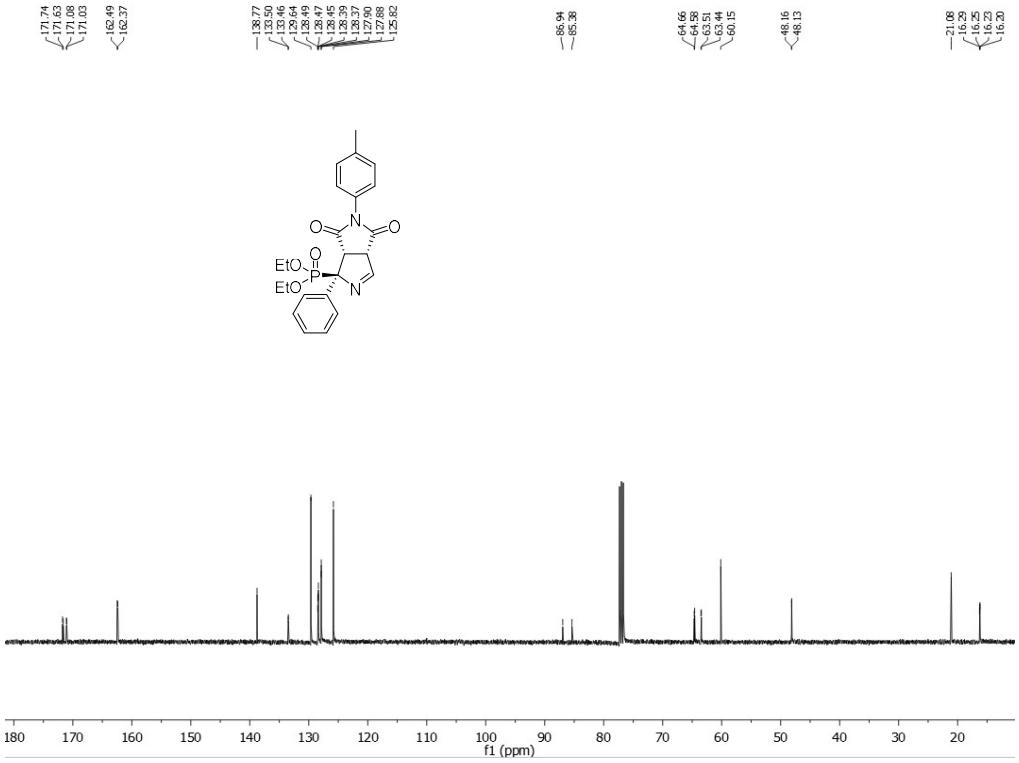
Diethyl (1*RS*,3*aSR*,6*aSR*)-5-(1,1'-biphenyl)-4-yl-4,6-dioxo-1-phenyl-1,3a,4,5,6,6a-hexahydropyrrolo[3,4-c]pyrrole-1-phosphonate (9z)



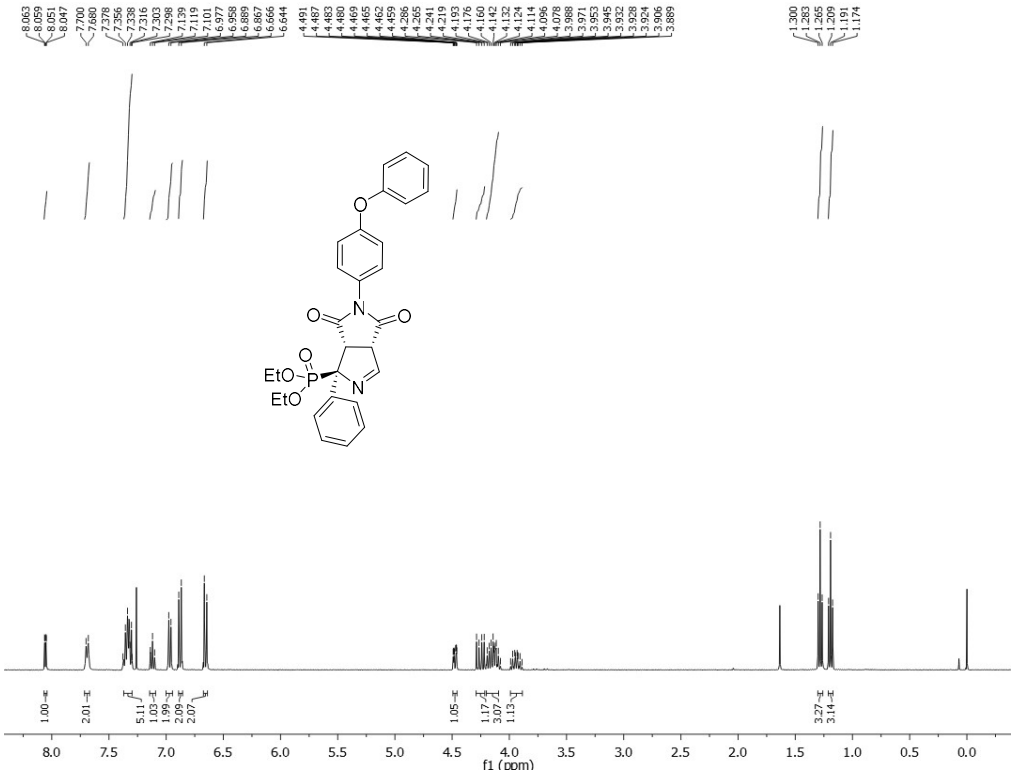
Diethyl (1*RS*,3*aSR*,6*aSR*)-5-(1,1'-biphenyl)-4-yl-4,6-dioxo-1-phenyl-1,3a,4,5,6,6a-hexahydropyrrolo[3,4-c]pyrrole-1-phosphonate (9z)



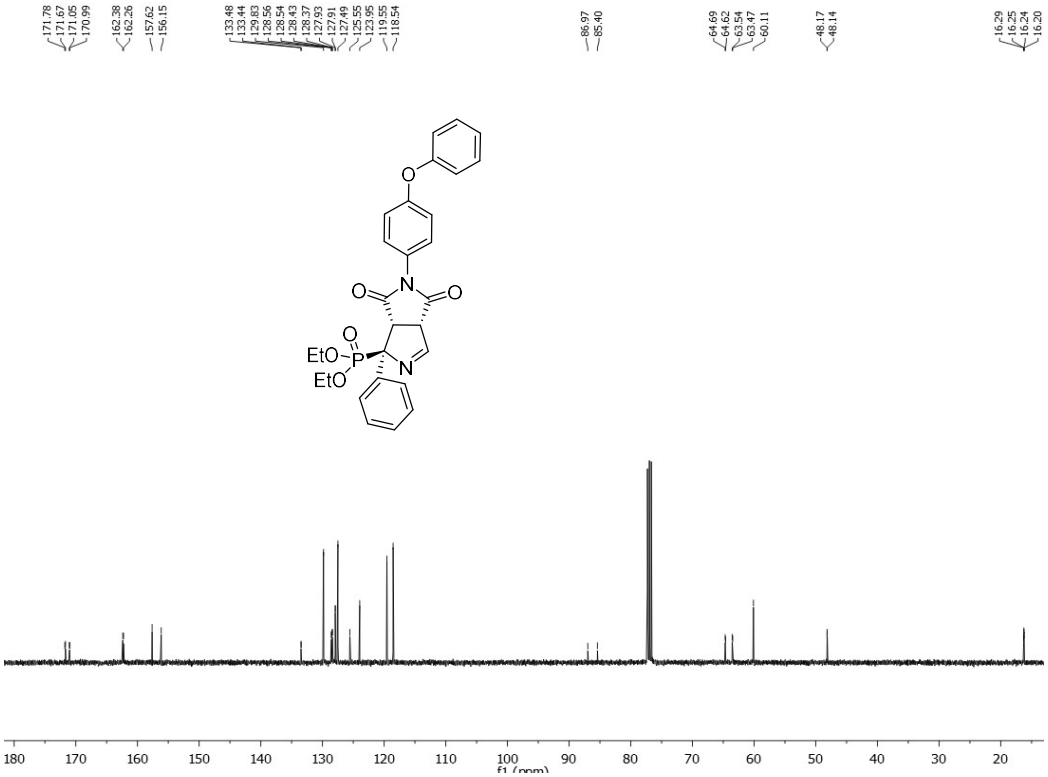
Diethyl (1*RS*,3a*SR*,6a*SR*)-4,6-dioxo-1-phenyl-5-(p-tolyl)-1,3a,4,5,6,6a-hexahydropyrrolo[3,4-*c*]pyrrole-1-phosphonate (9aa)



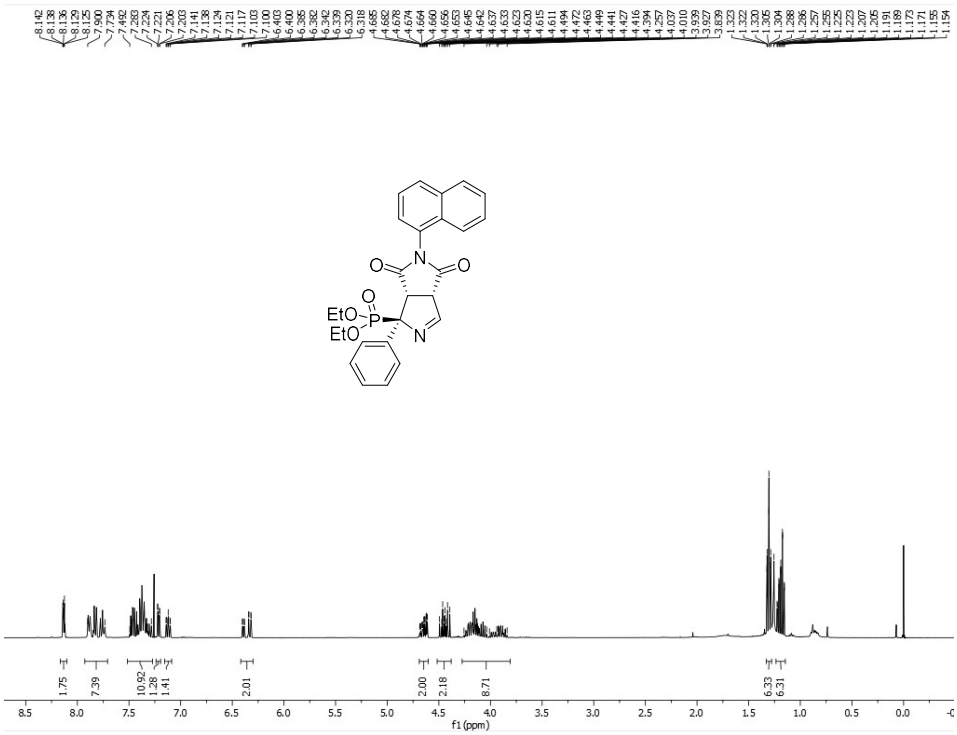
Diethyl (1*RS*,3a*SR*,6a*SR*)-4,6-dioxo-1-phenyl-5-(p-tolyl)-1,3a,4,5,6,6a-hexahydropyrrolo[3,4-*c*]pyrrole-1-phosphonate (9aa)



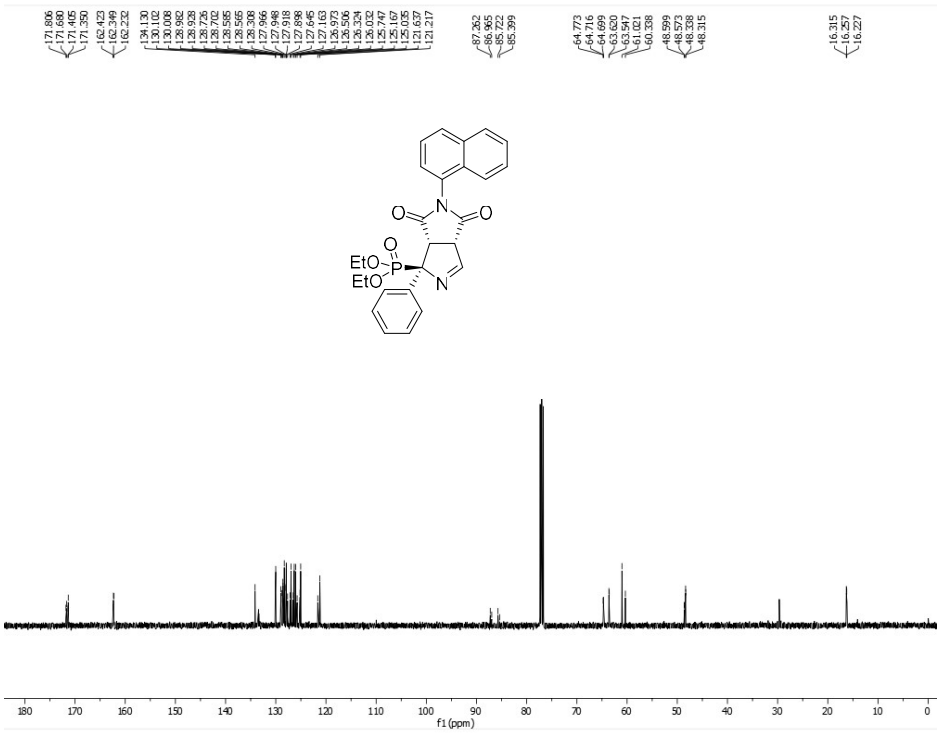
Diethyl (1*RS*,3a*SR*,6a*SR*)-4,6-dioxo-5-(4-phenoxyphenyl)-1-phenyl-1,3a,4,5,6,6a-hexahydropyrrolo[3,4-*c*]pyrrole-1-phosphonate (9ab)



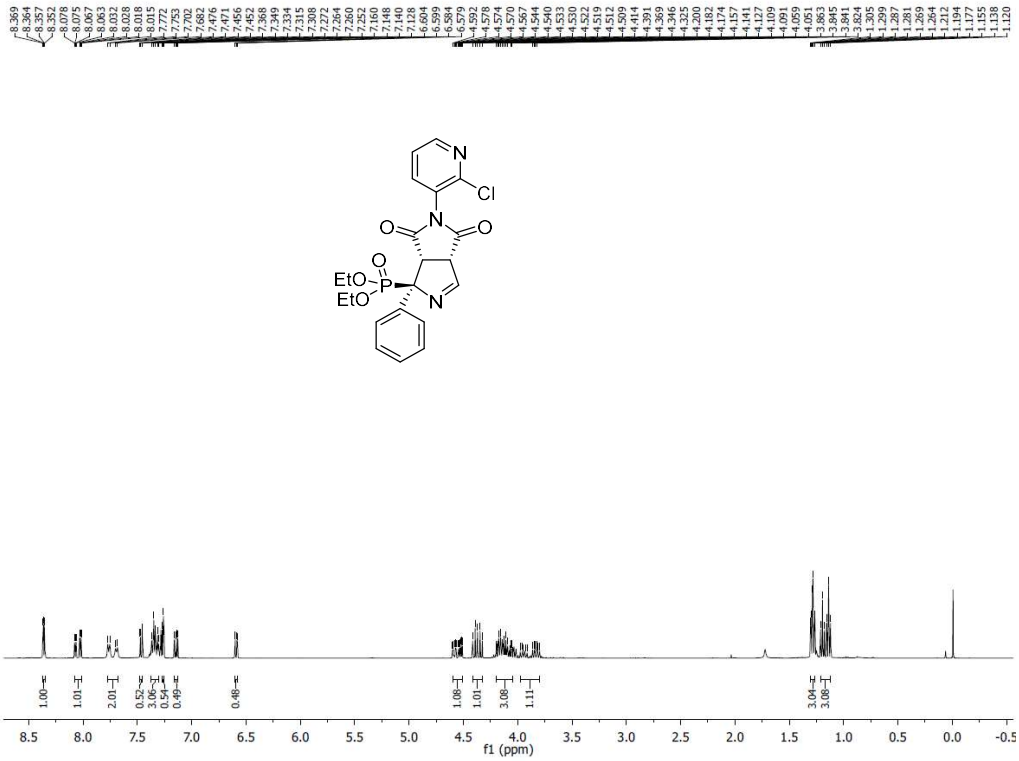
Diethyl (1*RS*,3a*SR*,6a*SR*)-4,6-dioxo-5-(4-phenoxyphenyl)-1-phenyl-1,3a,4,5,6,6a-hexahydropyrrolo[3,4-*c*]pyrrole-1-phosphonate (9ab)



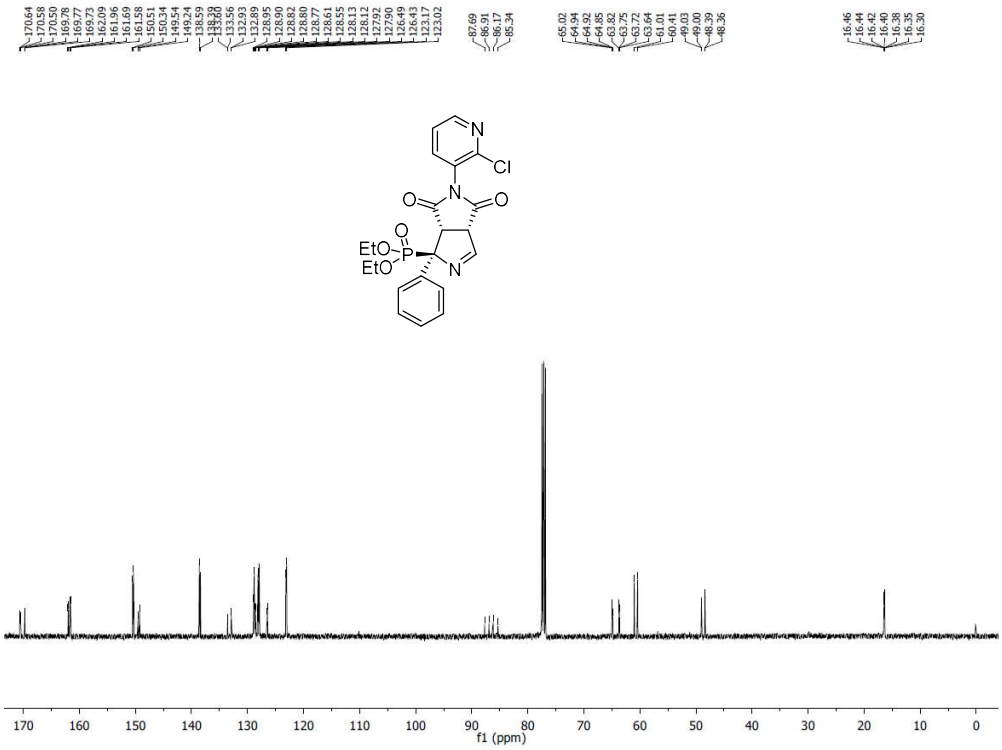
Diethyl (1*RS*,3a*SR*,6a*SR*)-5-(naphth-1-yl)-4,6-dioxo-1-phenyl-1,3a,4,5,6,6a-hexahydropyrrolo[3,4-*c*]pyrrole-1-phosphonate (9ac)



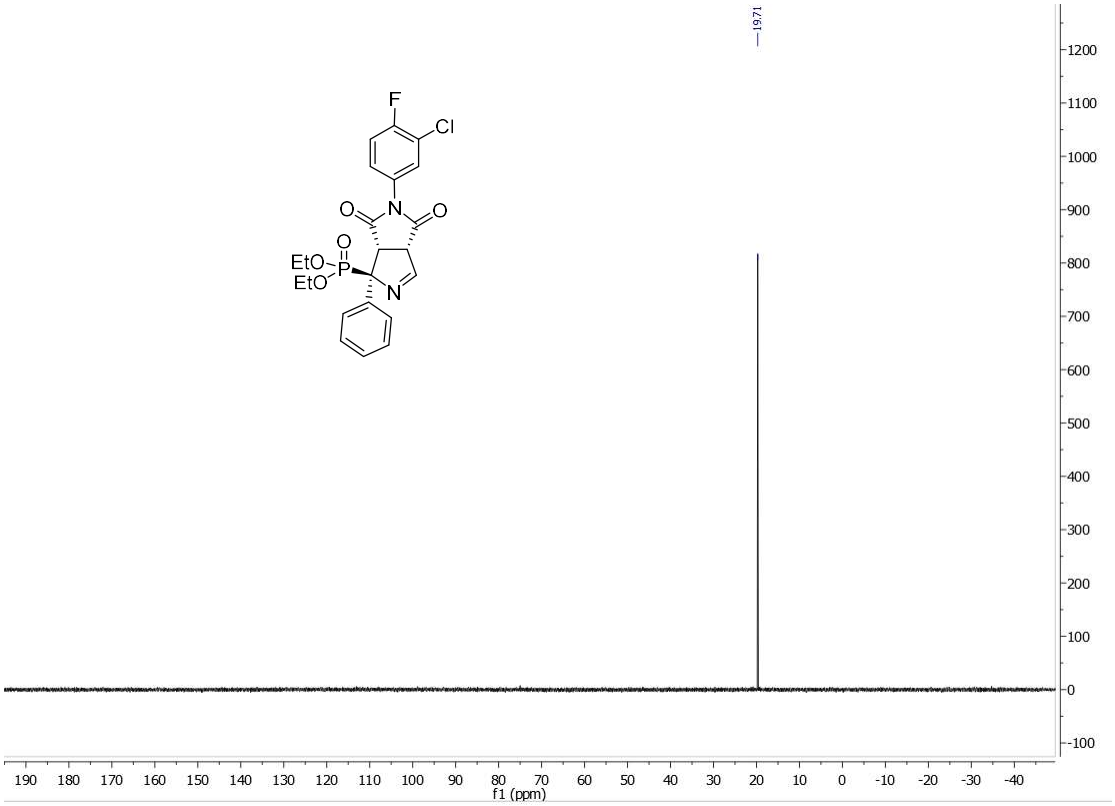
Diethyl (1*RS*,3a*SR*,6a*SR*)-5-(naphth-1-yl)-4,6-dioxo-1-phenyl-1,3a,4,5,6,6a-hexahydropyrrolo[3,4-*c*]pyrrole-1-phosphonate (9ac)



Diethyl (1*RS*,3a*SR*,6a*SR*)-5-(2-chloropyridin-3-yl)-4,6-dioxo-1-phenyl-1,3a,4,5,6,6a-hexahydropyrrolo[3,4-*c*]pyrrole-1-phosphonate (9ad)

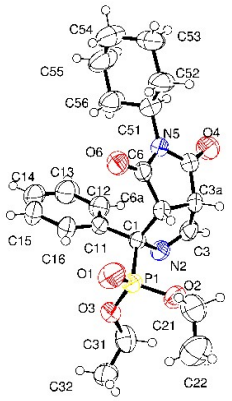


Diethyl (1*RS*,3a*SR*,6a*SR*)-5-(2-chloropyridin-3-yl)-4,6-dioxo-1-phenyl-1,3a,4,5,6,6a-hexahydropyrrolo[3,4-*c*]pyrrole-1-phosphonate (B9ad)



Diethyl (1*RS*,3a*SR*,6a*SR*)-5-(3-chloro-4-fluorophenyl)-4,6-dioxo-1-phenyl-1,3a,4,5,6,6a-hexahydropyrrolo[3, 4-*c*]pyrrole-1-phosphonate (9d)

Diethyl (1*RS*,3a*SR*,6a*SR*)-5-cyclohexyl-4,6-dioxo-1-phenyl-1,3a,4,5,6,6a-hexahydropyrrolo[3,4-*c*]pyrrole-1-phosphonate (9b): Deposition number: 1960886



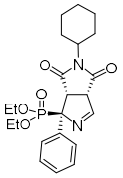


Table 1. Crystal data and structure refinement for **9b**.

Identification code	Jb135	
Empirical formula	C22 H29 N2 O5 P	
Formula weight	432.44	
Temperature	294(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P 21/n	
Unit cell dimensions	a = 15.0774(9) Å	α= 90°.
	b = 9.6740(6) Å	β= 97.8160(10)°.
	c = 15.2961(9) Å	γ = 90°.
Volume	2210.3(2) $Å^3$	
Z	4	
Density (calculated)	1.299 Mg/m^3	
Absorption coefficient	0.160 mm^{-1}	
F(000)	920	
Crystal size	0.27 x 0.24 x 0.29 mm^3	
Theta range for data collection	2.040 to 30.486°.	
Index ranges	-21<=h<=16, -13<=k<=13, -14<=l<=21	
Reflections collected	12714	
Independent reflections	5178 [R(int) = 0.0311]	
Completeness to theta = 25.242°	72.9 %	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	5178 / 0 / 273	
Goodness-of-fit on F^2	0.864	
Final R indices [I>2sigma(I)]	R1 = 0.0620, wR2 = 0.1659	
R indices (all data)	R1 = 0.1119, wR2 = 0.1874	
Largest diff. peak and hole	0.364 and -0.217 e.$Å^{-3}$	

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for **9b** U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
P(1)	8854(1)	2180(1)	8747(1)	60(1)
O(1)	8706(2)	3060(2)	7961(2)	91(1)
O(2)	9345(1)	776(2)	8634(1)	67(1)
O(3)	9400(2)	2944(2)	9518(2)	92(1)
O(4)	5763(2)	-1688(2)	9103(2)	82(1)
O(6)	6140(2)	2228(2)	7554(1)	71(1)
N(2)	8040(1)	601(2)	9850(1)	52(1)
N(5)	5737(1)	360(2)	8336(1)	53(1)
C(1)	7811(1)	1600(2)	9111(1)	43(1)
C(3)	7673(2)	-548(2)	9639(2)	54(1)
C(3A)	7142(2)	-665(2)	8745(2)	50(1)
C(4)	6137(2)	-773(2)	8767(2)	54(1)
C(6)	6338(2)	1240(2)	8013(2)	51(1)
C(6A)	7277(2)	736(2)	8330(1)	45(1)
C(11)	7266(2)	2790(2)	9440(2)	50(1)
C(12)	6718(2)	2520(3)	10082(2)	67(1)
C(13)	6179(2)	3564(4)	10356(3)	90(1)
C(14)	6213(2)	4877(4)	10024(3)	94(1)
C(15)	6753(3)	5144(3)	9403(3)	92(1)
C(16)	7284(2)	4107(3)	9102(2)	73(1)
C(21)	9736(3)	442(4)	7836(2)	88(1)
C(22)	10698(3)	611(5)	8001(4)	113(1)
C(31)	10035(3)	2401(3)	10224(2)	78(1)
C(32)	10800(2)	3319(4)	10362(3)	83(1)
C(51)	4736(2)	464(3)	8177(2)	67(1)
C(52)	4392(2)	203(4)	7231(2)	82(1)
C(53)	3383(2)	364(4)	7032(3)	92(1)
C(54)	3061(2)	1683(5)	7397(3)	98(1)
C(55)	3392(2)	1845(5)	8338(3)	98(1)
C(56)	4403(2)	1737(4)	8551(2)	81(1)

Table 3. Bond lengths [Å] and angles [°] for **9b.**

P(1)-O(1)	1.466(2)
P(1)-O(3)	1.532(2)
P(1)-O(2)	1.5674(19)
P(1)-C(1)	1.827(2)
O(2)-C(21)	1.462(4)
O(3)-C(31)	1.441(4)
O(4)-C(4)	1.202(3)
O(6)-C(6)	1.199(3)
N(2)-C(3)	1.264(3)
N(2)-C(1)	1.491(3)
N(5)-C(4)	1.376(3)
N(5)-C(6)	1.381(3)
N(5)-C(51)	1.500(3)
C(1)-C(11)	1.538(3)
C(1)-C(6A)	1.586(3)
C(3)-C(3A)	1.493(4)
C(3)-H(3)	0.9300
C(3A)-C(6A)	1.522(3)
C(3A)-C(4)	1.524(3)
C(3A)-H(3A)	0.9800
C(6)-C(6A)	1.514(3)
C(6A)-H(6A)	0.9800
C(11)-C(16)	1.377(4)
C(11)-C(12)	1.391(4)
C(12)-C(13)	1.396(4)
C(12)-H(12)	0.9300
C(13)-C(14)	1.371(6)
C(13)-H(13)	0.9300
C(14)-C(15)	1.358(6)
C(14)-H(14)	0.9300
C(15)-C(16)	1.399(5)
C(15)-H(15)	0.9300
C(16)-H(16)	0.9300
C(21)-C(22)	1.448(6)
C(21)-H(21A)	0.9700
C(21)-H(21B)	0.9700
C(22)-H(22A)	0.9600
C(22)-H(22B)	0.9600
C(22)-H(22C)	0.9600
C(31)-C(32)	1.448(5)
C(31)-H(31A)	0.9700
C(31)-H(31B)	0.9700
C(32)-H(32A)	0.9600
C(32)-H(32B)	0.9600
C(32)-H(32C)	0.9600
C(51)-C(56)	1.474(4)
C(51)-C(52)	1.490(4)
C(51)-H(51)	0.9800
C(52)-C(53)	1.518(5)
C(52)-H(52A)	0.9700
C(52)-H(52B)	0.9700
C(53)-C(54)	1.500(6)
C(53)-H(53A)	0.9700
C(53)-H(53B)	0.9700
C(54)-C(55)	1.467(6)
C(54)-H(54A)	0.9700
C(54)-H(54B)	0.9700

C(55)-C(56)	1.518(5)
C(55)-H(55A)	0.9700
C(55)-H(55B)	0.9700
C(56)-H(56A)	0.9700
C(56)-H(56B)	0.9700
O(1)-P(1)-O(3)	110.92(15)
O(1)-P(1)-O(2)	115.77(14)
O(3)-P(1)-O(2)	106.87(12)
O(1)-P(1)-C(1)	112.74(12)
O(3)-P(1)-C(1)	107.95(14)
O(2)-P(1)-C(1)	101.94(10)
C(21)-O(2)-P(1)	122.2(2)
C(31)-O(3)-P(1)	129.27(18)
C(3)-N(2)-C(1)	109.18(19)
C(4)-N(5)-C(6)	113.4(2)
C(4)-N(5)-C(51)	119.8(2)
C(6)-N(5)-C(51)	126.5(2)
N(2)-C(1)-C(11)	108.47(19)
N(2)-C(1)-C(6A)	105.74(16)
C(11)-C(1)-C(6A)	113.72(17)
N(2)-C(1)-P(1)	107.99(15)
C(11)-C(1)-P(1)	112.98(15)
C(6A)-C(1)-P(1)	107.56(15)
N(2)-C(3)-C(3A)	117.53(19)
N(2)-C(3)-H(3)	121.2
C(3A)-C(3)-H(3)	121.2
C(3)-C(3A)-C(6A)	103.25(18)
C(3)-C(3A)-C(4)	113.3(2)
C(6A)-C(3A)-C(4)	105.05(18)
C(3)-C(3A)-H(3A)	111.6
C(6A)-C(3A)-H(3A)	111.6
C(4)-C(3A)-H(3A)	111.6
O(4)-C(4)-N(5)	126.2(2)
O(4)-C(4)-C(3A)	125.9(2)
N(5)-C(4)-C(3A)	107.9(2)
O(6)-C(6)-N(5)	125.3(2)
O(6)-C(6)-C(6A)	126.2(2)
N(5)-C(6)-C(6A)	108.49(18)
C(6)-C(6A)-C(3A)	104.38(18)
C(6)-C(6A)-C(1)	115.40(17)
C(3A)-C(6A)-C(1)	103.76(17)
C(6)-C(6A)-H(6A)	110.9
C(3A)-C(6A)-H(6A)	110.9
C(1)-C(6A)-H(6A)	110.9
C(16)-C(11)-C(12)	118.9(2)
C(16)-C(11)-C(1)	122.1(3)
C(12)-C(11)-C(1)	119.0(2)
C(11)-C(12)-C(13)	120.1(3)
C(11)-C(12)-H(12)	119.9
C(13)-C(12)-H(12)	119.9
C(14)-C(13)-C(12)	120.4(4)
C(14)-C(13)-H(13)	119.8
C(12)-C(13)-H(13)	119.8
C(15)-C(14)-C(13)	119.4(3)
C(15)-C(14)-H(14)	120.3
C(13)-C(14)-H(14)	120.3
C(14)-C(15)-C(16)	121.2(3)
C(14)-C(15)-H(15)	119.4

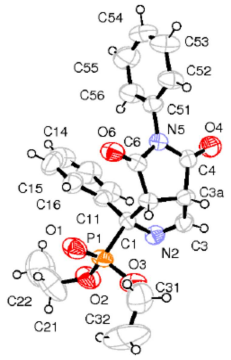
C(16)-C(15)-H(15)	119.4
C(11)-C(16)-C(15)	119.9(4)
C(11)-C(16)-H(16)	120.1
C(15)-C(16)-H(16)	120.1
C(22)-C(21)-O(2)	109.8(3)
C(22)-C(21)-H(21A)	109.7
O(2)-C(21)-H(21A)	109.7
C(22)-C(21)-H(21B)	109.7
O(2)-C(21)-H(21B)	109.7
H(21A)-C(21)-H(21B)	108.2
C(21)-C(22)-H(22A)	109.5
C(21)-C(22)-H(22B)	109.5
H(22A)-C(22)-H(22B)	109.5
C(21)-C(22)-H(22C)	109.5
H(22A)-C(22)-H(22C)	109.5
H(22B)-C(22)-H(22C)	109.5
O(3)-C(31)-C(32)	108.7(3)
O(3)-C(31)-H(31A)	109.9
C(32)-C(31)-H(31A)	109.9
O(3)-C(31)-H(31B)	109.9
C(32)-C(31)-H(31B)	109.9
H(31A)-C(31)-H(31B)	108.3
C(31)-C(32)-H(32A)	109.5
C(31)-C(32)-H(32B)	109.5
H(32A)-C(32)-H(32B)	109.5
C(31)-C(32)-H(32C)	109.5
H(32A)-C(32)-H(32C)	109.5
H(32B)-C(32)-H(32C)	109.5
C(56)-C(51)-C(52)	115.2(3)
C(56)-C(51)-N(5)	112.4(2)
C(52)-C(51)-N(5)	110.8(3)
C(56)-C(51)-H(51)	105.9
C(52)-C(51)-H(51)	105.9
N(5)-C(51)-H(51)	105.9
C(51)-C(52)-C(53)	112.6(3)
C(51)-C(52)-H(52A)	109.1
C(53)-C(52)-H(52A)	109.1
C(51)-C(52)-H(52B)	109.1
C(53)-C(52)-H(52B)	109.1
H(52A)-C(52)-H(52B)	107.8
C(54)-C(53)-C(52)	112.2(3)
C(54)-C(53)-H(53A)	109.2
C(52)-C(53)-H(53A)	109.2
C(54)-C(53)-H(53B)	109.2
C(52)-C(53)-H(53B)	109.2
H(53A)-C(53)-H(53B)	107.9
C(55)-C(54)-C(53)	111.9(4)
C(55)-C(54)-H(54A)	109.2
C(53)-C(54)-H(54A)	109.2
C(55)-C(54)-H(54B)	109.2
C(53)-C(54)-H(54B)	109.2
H(54A)-C(54)-H(54B)	107.9
C(54)-C(55)-C(56)	113.6(3)
C(54)-C(55)-H(55A)	108.8
C(56)-C(55)-H(55A)	108.8
C(54)-C(55)-H(55B)	108.8
C(56)-C(55)-H(55B)	108.8
H(55A)-C(55)-H(55B)	107.7

C(51)-C(56)-C(55)	111.1(3)
C(51)-C(56)-H(56A)	109.4
C(55)-C(56)-H(56A)	109.4
C(51)-C(56)-H(56B)	109.4
C(55)-C(56)-H(56B)	109.4
H(56A)-C(56)-H(56B)	108.0

Table 4. Anisotropic displacement parameters ($Å^2 x 10^3$) for **9b**.The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2a^{*2}U^{11} + ... + 2 h k a^* b^* U^{12}]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
P(1)	46(1)	46(1)	87(1)	13(1)	8(1)	-1(1)
O(1)	73(1)	81(1)	123(2)	50(1)	30(1)	4(1)
O(2)	58(1)	60(1)	86(1)	6(1)	24(1)	9(1)
O(3)	60(1)	54(1)	151(2)	-18(1)	-21(1)	0(1)
O(4)	72(1)	64(1)	112(2)	17(1)	19(1)	-10(1)
O(6)	80(1)	55(1)	70(1)	13(1)	-19(1)	3(1)
N(2)	55(1)	47(1)	51(1)	10(1)	1(1)	6(1)
N(5)	46(1)	45(1)	65(1)	-8(1)	0(1)	4(1)
C(1)	42(1)	36(1)	51(1)	5(1)	0(1)	1(1)
C(3)	56(1)	44(1)	62(1)	17(1)	9(1)	10(1)
C(3A)	49(1)	32(1)	67(1)	-2(1)	10(1)	3(1)
C(4)	52(1)	42(1)	67(1)	-2(1)	5(1)	-1(1)
C(6)	57(1)	41(1)	51(1)	-4(1)	-7(1)	4(1)
C(6A)	49(1)	39(1)	47(1)	1(1)	7(1)	2(1)
C(11)	47(1)	43(1)	56(1)	-9(1)	-5(1)	2(1)
C(12)	68(2)	64(1)	70(2)	-12(1)	14(1)	5(1)
C(13)	75(2)	98(3)	98(2)	-36(2)	16(2)	9(2)
C(14)	69(2)	80(2)	128(3)	-52(2)	-11(2)	19(2)
C(15)	82(2)	49(1)	136(3)	-18(2)	-17(2)	19(2)
C(16)	73(2)	45(1)	97(2)	2(1)	-2(2)	12(1)
C(21)	98(3)	84(2)	80(2)	-14(2)	10(2)	-4(2)
C(22)	100(3)	130(3)	119(3)	11(3)	49(3)	15(3)
C(31)	105(3)	58(1)	70(2)	4(1)	11(2)	1(2)
C(32)	67(2)	86(2)	90(2)	-16(2)	-16(2)	10(2)
C(51)	50(1)	68(2)	83(2)	-2(1)	4(1)	5(1)
C(52)	57(2)	104(2)	82(2)	-36(2)	-7(2)	5(2)
C(53)	56(2)	107(3)	108(3)	-19(2)	-10(2)	-9(2)
C(54)	56(2)	121(3)	113(3)	2(2)	0(2)	15(2)
C(55)	62(2)	130(3)	104(3)	-16(2)	14(2)	31(2)
C(56)	60(2)	102(2)	78(2)	-27(2)	6(2)	15(2)

Diethyl (1*RS*,3a*SR*,6a*SR*)-4,6-dioxo-1,5-diphenyl-1,3a,4,5,6,6a-hexahydropyrrolo[3,4-*c*]pyrrole-1-phosphonate (9c): Deposition number: 1960883



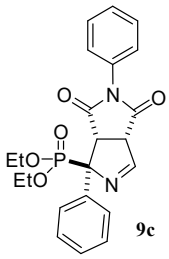


Table 1. Crystal data and structure refinement for **9c.**

Identification code	Jb104	
Empirical formula	C22 H23 N2 O5 P	
Formula weight	426.39	
Temperature	293(2) K	
Wavelength	0.71073 Å	
Crystal system	Orthorhombic	
Space group	P 21 c n	
Unit cell dimensions	a = 9.151(3) Å	α= 90°.
	b = 13.035(8) Å	β= 90°.
	c = 18.159(2) Å	γ = 90°.
Volume	2166.1(15) $Å^3$	
Z	4	
Density (calculated)	1.308 Mg/m^3	
Absorption coefficient	0.162 mm^{-1}	
F(000)	896	
Crystal size	0.42 x 0.33 x 0.30 mm^3	
Theta range for data collection	1.923 to 24.975°.	
Index ranges	-10<=h<=10, -15<=k<=15, 0<=l<=21	
Reflections collected	6335	
Independent reflections	3805 [R(int) = 0.0490]	
Completeness to theta = 25.242°	97.6 %	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	3805 / 4 / 294	
Goodness-of-fit on F^2	1.030	
Final R indices [I>2sigma(I)]	R1 = 0.0579, wR2 = 0.1457	
R indices (all data)	R1 = 0.0786, wR2 = 0.1605	
Absolute structure parameter	0.1(2)	
Extinction coefficient	0.036(5)	
Largest diff. peak and hole	0.235 and -0.284 e.$Å^{-3}$	

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3)
For **9c.** U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
P(1)	6646(2)	917(1)	3588(1)	55(1)
O(1)	7754(6)	1101(3)	4147(2)	74(1)
O(2)	7204(6)	1011(4)	2770(3)	83(2)
O(3)	5271(6)	1623(3)	3625(3)	76(1)
O(4)	2761(5)	-2695(3)	4262(3)	79(1)
O(6)	6669(5)	-1196(3)	5357(2)	64(1)
N(2)	4635(5)	-416(4)	3094(2)	53(1)
N(5)	4910(5)	-2196(3)	4797(2)	45(1)
C(1)	5821(5)	-364(4)	3642(3)	43(1)
C(3)	3475(6)	-710(4)	3398(3)	55(1)
C(3A)	3558(6)	-906(4)	4213(3)	49(1)
C(4)	3638(6)	-2046(4)	4410(3)	52(1)
C(6)	5680(6)	-1291(4)	4922(3)	46(1)
C(6A)	5040(6)	-489(4)	4419(3)	45(1)
C(11)	6973(6)	-1178(4)	3465(3)	50(1)
C(12)	6759(8)	-1874(5)	2898(3)	66(2)
C(13)	7797(10)	-2613(6)	2740(5)	87(2)
C(14)	9041(11)	-2692(7)	3134(5)	99(3)
C(15)	9286(8)	-1997(8)	3698(5)	89(3)
C(16)	8265(7)	-1248(6)	3858(4)	69(2)
C(21)	8665(13)	1236(10)	2580(7)	135(4)
C(22)	9330(16)	483(12)	2182(8)	169(6)
C(31)	4930(30)	2395(17)	4118(14)	108(8)
C(32)	5240(50)	3413(18)	3790(20)	190(20)
C(31A)	5540(20)	2708(13)	3811(13)	86(6)
C(32A)	4260(30)	3070(20)	4199(14)	116(9)
C(51)	5310(6)	-3155(4)	5132(3)	50(1)
C(52)	4704(9)	-3443(5)	5793(4)	68(2)
C(53)	5104(10)	-4364(6)	6106(4)	82(2)
C(54)	6052(9)	-4995(5)	5762(4)	82(2)
C(55)	6644(11)	-4711(5)	5106(5)	91(2)
C(56)	6279(8)	-3786(5)	4782(4)	75(2)

Table 3. Bond lengths [Å] and angles [°] for **9c**

P(1)-O(1)	1.454(5)
P(1)-O(3)	1.561(5)
P(1)-O(2)	1.576(5)
P(1)-C(1)	1.835(5)
O(2)-C(21)	1.411(11)
O(3)-C(31)	1.38(2)
O(3)-C(31A)	1.473(16)
O(4)-C(4)	1.197(7)
O(6)-C(6)	1.208(7)
N(2)-C(3)	1.256(8)
N(2)-C(1)	1.474(7)
N(5)-C(4)	1.374(7)
N(5)-C(6)	1.392(7)
N(5)-C(51)	1.438(7)
C(1)-C(11)	1.530(8)
C(1)-C(6A)	1.590(7)
C(3)-C(3A)	1.503(8)
C(3A)-C(6A)	1.509(8)
C(3A)-C(4)	1.530(7)
C(6)-C(6A)	1.506(7)
C(11)-C(16)	1.384(9)
C(11)-C(12)	1.385(8)
C(12)-C(13)	1.383(10)
C(13)-C(14)	1.349(14)
C(14)-C(15)	1.386(13)
C(15)-C(16)	1.382(11)
C(21)-C(22)	1.362(16)
C(31)-C(32)	1.48(3)
C(31A)-C(32A)	1.44(2)
C(51)-C(56)	1.366(8)
C(51)-C(52)	1.374(9)
C(52)-C(53)	1.378(10)
C(53)-C(54)	1.349(11)
C(54)-C(55)	1.360(11)
C(55)-C(56)	1.383(10)
O(1)-P(1)-O(3)	115.8(3)
O(1)-P(1)-O(2)	114.8(3)
O(3)-P(1)-O(2)	104.8(3)
O(1)-P(1)-C(1)	113.5(2)
O(3)-P(1)-C(1)	101.7(3)
O(2)-P(1)-C(1)	104.8(3)
C(21)-O(2)-P(1)	123.6(6)
C(31)-O(3)-P(1)	129.7(12)
C(31A)-O(3)-P(1)	116.3(8)
C(3)-N(2)-C(1)	109.8(4)
C(4)-N(5)-C(6)	113.0(4)
C(4)-N(5)-C(51)	123.8(4)
C(6)-N(5)-C(51)	122.7(4)
N(2)-C(1)-C(11)	109.5(4)
N(2)-C(1)-C(6A)	105.3(4)
C(11)-C(1)-C(6A)	115.2(4)
N(2)-C(1)-P(1)	108.0(3)
C(11)-C(1)-P(1)	109.7(4)
C(6A)-C(1)-P(1)	109.0(3)
N(2)-C(3)-C(3A)	116.2(5)
C(3)-C(3A)-C(6A)	103.2(4)

C(3)-C(3A)-C(4)	113.4(4)
C(6A)-C(3A)-C(4)	104.4(4)
O(4)-C(4)-N(5)	125.6(5)
O(4)-C(4)-C(3A)	127.0(5)
N(5)-C(4)-C(3A)	107.4(5)
O(6)-C(6)-N(5)	124.9(5)
O(6)-C(6)-C(6A)	128.0(5)
N(5)-C(6)-C(6A)	107.1(4)
C(6)-C(6A)-C(3A)	104.5(4)
C(6)-C(6A)-C(1)	115.7(4)
C(3A)-C(6A)-C(1)	102.7(4)
C(16)-C(11)-C(12)	117.4(6)
C(16)-C(11)-C(1)	121.7(5)
C(12)-C(11)-C(1)	120.8(5)
C(13)-C(12)-C(11)	120.9(7)
C(14)-C(13)-C(12)	121.5(8)
C(13)-C(14)-C(15)	118.6(7)
C(16)-C(15)-C(14)	120.5(8)
C(15)-C(16)-C(11)	121.0(7)
C(22)-C(21)-O(2)	113.8(10)
O(3)-C(31)-C(32)	111(2)
C(32A)-C(31A)-O(3)	107.1(19)
C(56)-C(51)-C(52)	120.2(6)
C(56)-C(51)-N(5)	119.5(5)
C(52)-C(51)-N(5)	120.3(5)
C(51)-C(52)-C(53)	119.5(6)
C(54)-C(53)-C(52)	120.7(7)
C(53)-C(54)-C(55)	119.7(6)
C(54)-C(55)-C(56)	120.9(7)
C(51)-C(56)-C(55)	119.0(7)

Table 4. Anisotropic displacement parameters ($Å^2 x 10^3$) for **9c.** The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2a^{*2}U^{11} + ... + 2 h k a^* b^* U^{12}]$

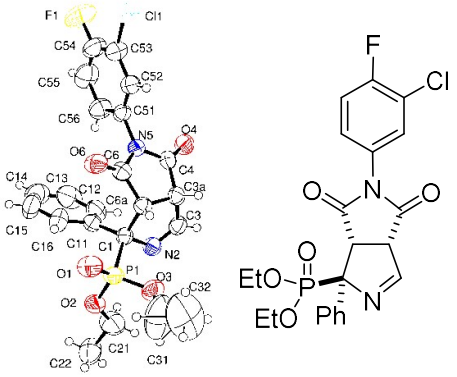
	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
P(1)	71(1)	47(1)	46(1)	10(1)	-5(1)	-9(1)
O(1)	90(3)	66(3)	66(3)	10(2)	-19(2)	-25(2)
O(2)	95(3)	100(4)	53(3)	23(2)	7(2)	-20(3)
O(3)	99(3)	49(2)	79(3)	6(2)	-9(3)	6(2)
O(4)	68(3)	62(3)	107(4)	10(2)	-23(3)	-13(2)
O(6)	82(3)	58(2)	53(2)	9(2)	-22(2)	-15(2)
N(2)	57(3)	56(3)	44(3)	-3(2)	-8(2)	1(2)
N(5)	50(2)	40(2)	44(2)	1(2)	1(2)	0(2)
C(1)	45(3)	44(3)	39(3)	-1(2)	-1(2)	-5(2)
C(3)	51(3)	59(3)	54(3)	2(3)	-8(3)	6(3)
C(3A)	55(3)	43(3)	49(3)	3(2)	6(2)	9(2)
C(4)	49(3)	46(3)	60(3)	3(3)	0(3)	-3(2)
C(6)	59(3)	40(3)	39(3)	-2(2)	7(3)	-3(2)
C(6A)	60(3)	36(2)	38(3)	-1(2)	3(2)	0(2)
C(11)	58(3)	50(3)	42(3)	7(2)	5(2)	2(2)
C(12)	79(4)	61(3)	60(3)	-7(3)	7(3)	1(3)
C(13)	106(6)	71(5)	84(5)	-12(4)	26(5)	17(4)
C(14)	118(7)	82(6)	96(6)	21(5)	53(6)	38(5)
C(15)	66(4)	117(7)	85(6)	26(5)	12(4)	27(5)
C(16)	62(4)	84(5)	61(4)	12(3)	1(3)	6(3)
C(21)	153(10)	142(10)	110(8)	-14(7)	53(7)	-60(8)
C(22)	146(11)	191(15)	169(13)	-20(11)	41(10)	-7(10)
C(31)	111(16)	84(16)	128(18)	-28(14)	21(14)	20(14)
C(32)	280(50)	55(15)	240(40)	-24(17)	-140(40)	15(19)
C(31A)	88(13)	51(12)	119(16)	5(9)	14(11)	-8(8)
C(32A)	132(18)	85(18)	130(18)	-19(13)	38(14)	-18(14)
C(51)	60(3)	36(3)	53(3)	-3(2)	-5(3)	0(2)
C(52)	95(5)	56(4)	55(4)	7(3)	15(3)	10(3)
C(53)	127(6)	63(4)	56(4)	12(3)	7(4)	7(4)
C(54)	117(6)	45(3)	83(5)	11(3)	-19(4)	9(4)
C(55)	103(5)	55(4)	117(6)	-2(4)	13(5)	28(4)
C(56)	89(5)	58(4)	77(4)	4(3)	27(4)	20(3)

Table 5. Hydrogen bonds for **9c** [Å and °].

D-H...A	d(D-H)	d(H...A)	d(D...A)	<(DHA)
C(3A)-H(3A)...O(1)#1	0.98	2.59	3.079(7)	110.6
C(3A)-H(3A)...O(6)#1	0.98	2.51	3.332(7)	140.8
C(21)-H(21B)...O(1)	0.97	2.46	2.970(12)	112.8

Symmetry transformations used to generate equivalent atoms:
#1 x-1/2,-y,-z+1

Diethyl (1*RS*,3a*SR*,6a*SR*)-5-(3-chloro-4-fluorophenyl)-4,6-dioxo-1-phenyl-1,3a,4,5,6,6a-hexahydropyrrolo[3,4-*c*]pyrrole-1-phosphonate (9d)*:* Deposition number: 1960884



B06, **9d**

Table 1. Crystal data and structure refinement for **9d.**

Identification code	Jb128	
Empirical formula	C22 H21 Cl F N2 O5 P	
Formula weight	478.83	
Temperature	294(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P 21/n	
Unit cell dimensions	a = 15.288(3) Å	α= 90°.
	b = 9.269(3) Å	β= 92.653(17)°.
	c = 15.874(3) Å	γ = 90°.
Volume	2247.0(10) $Å^3$	
Z	4	
Density (calculated)	1.415 Mg/m^3	
Absorption coefficient	0.286 mm^{-1}	
F(000)	992	
Crystal size	0.390 x 0.240 x 0.240 mm^3	
Theta range for data collection	1.808 to 24.977°.	
Index ranges	-18<=h<=0, 0<=k<=11, -18<=l<=18	
Reflections collected	4436	
Independent reflections	3935 [R(int) = 0.0541]	
Completeness to theta = 24.977°	99.9 %	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	3935 / 0 / 291	
Goodness-of-fit on F^2	1.029	
Final R indices [I>2sigma(I)]	R1 = 0.0572, wR2 = 0.1443	
R indices (all data)	R1 = 0.1212, wR2 = 0.1627	
Largest diff. peak and hole	0.427 and -0.328 e.$Å^{-3}$	

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for **9d.** U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
Cl(1)	-1852(1)	-86(2)	6496(1)	130(1)
P(1)	3957(1)	1969(1)	8665(1)	53(1)
F(1)	-2539(2)	1507(4)	7907(2)	136(1)
O(1)	3806(2)	2876(3)	7927(2)	73(1)
O(2)	4426(2)	2844(3)	9389(2)	67(1)
O(3)	4499(2)	568(3)	8526(2)	68(1)
O(4)	832(2)	-1912(3)	9149(2)	63(1)
O(6)	1443(2)	1974(3)	7530(2)	67(1)
C(1)	2945(2)	1219(4)	9048(2)	44(1)
N(2)	3166(2)	108(3)	9693(2)	51(1)
C(3)	2789(2)	-1062(4)	9491(2)	53(1)
C(3A)	2246(2)	-1090(4)	8681(2)	48(1)
C(4)	1269(2)	-1053(4)	8786(2)	46(1)
N(5)	946(2)	180(3)	8388(2)	44(1)
C(6)	1594(2)	978(4)	8000(2)	50(1)
C(6A)	2457(2)	368(3)	8291(2)	45(1)
C(11)	2375(2)	2376(4)	9437(2)	50(1)
C(12)	1905(3)	2078(5)	10135(3)	69(1)
C(13)	1340(3)	3067(7)	10453(4)	98(2)
C(14)	1229(3)	4384(7)	10094(4)	101(2)
C(15)	1698(4)	4708(5)	9405(4)	97(2)
C(16)	2268(3)	3725(4)	9079(3)	73(1)
C(21)	4831(3)	2232(6)	10143(3)	101(2)
C(22)	5361(3)	3293(5)	10590(3)	100(2)
C(31)	5264(6)	600(8)	8010(6)	184(4)
C(32)	5431(7)	-321(10)	7528(6)	218(5)
C(51)	32(2)	504(4)	8271(2)	48(1)
C(52)	-410(2)	59(4)	7551(2)	59(1)
C(53)	-1279(3)	394(5)	7417(3)	75(1)
C(54)	-1687(3)	1155(5)	8022(3)	82(1)
C(55)	-1254(3)	1602(5)	8744(3)	89(1)
C(56)	-372(3)	1274(5)	8872(3)	69(1)

Table 3. Bond lengths [Å] and angles [°] for **9d.**

Cl(1)-C(53)	1.728(4)
P(1)-O(1)	1.452(2)
P(1)-O(2)	1.553(3)
P(1)-O(3)	1.562(3)
P(1)-C(1)	1.826(3)
F(1)-C(54)	1.346(5)
O(2)-C(21)	1.439(5)
O(3)-C(31)	1.459(7)
O(4)-C(4)	1.203(4)
O(6)-C(6)	1.202(4)
C(1)-N(2)	1.481(4)
C(1)-C(11)	1.529(5)
C(1)-C(6A)	1.593(4)
N(2)-C(3)	1.262(4)
C(3)-C(3A)	1.499(5)
C(3A)-C(4)	1.511(5)
C(3A)-C(6A)	1.527(4)
C(4)-N(5)	1.386(4)
N(5)-C(6)	1.402(4)
N(5)-C(51)	1.433(4)
C(6)-C(6A)	1.489(5)
C(11)-C(12)	1.377(5)
C(11)-C(16)	1.380(5)
C(12)-C(13)	1.371(6)
C(13)-C(14)	1.355(7)
C(14)-C(15)	1.368(7)
C(15)-C(16)	1.379(6)
C(21)-C(22)	1.440(6)
C(31)-C(32)	1.182(8)
C(51)-C(52)	1.364(5)
C(51)-C(56)	1.362(5)
C(52)-C(53)	1.372(5)
C(53)-C(54)	1.366(6)
C(54)-C(55)	1.362(6)
C(55)-C(56)	1.389(6)
O(1)-P(1)-O(2)	110.21(16)
O(1)-P(1)-O(3)	115.64(16)
O(2)-P(1)-O(3)	108.04(14)
O(1)-P(1)-C(1)	112.48(15)
O(2)-P(1)-C(1)	108.79(15)
O(3)-P(1)-C(1)	101.17(15)
C(21)-O(2)-P(1)	125.1(3)
C(31)-O(3)-P(1)	120.4(3)
N(2)-C(1)-C(11)	108.9(3)
N(2)-C(1)-C(6A)	105.1(3)
C(11)-C(1)-C(6A)	113.4(3)
N(2)-C(1)-P(1)	109.0(2)
C(11)-C(1)-P(1)	112.0(2)
C(6A)-C(1)-P(1)	108.2(2)
C(3)-N(2)-C(1)	109.6(3)
N(2)-C(3)-C(3A)	117.4(3)
C(3)-C(3A)-C(4)	114.5(3)
C(3)-C(3A)-C(6A)	102.3(3)
C(4)-C(3A)-C(6A)	104.7(3)
O(4)-C(4)-N(5)	124.8(3)
O(4)-C(4)-C(3A)	127.7(3)

N(5)-C(4)-C(3A)	107.5(3)
C(4)-N(5)-C(6)	113.1(3)
C(4)-N(5)-C(51)	123.8(3)
C(6)-N(5)-C(51)	122.5(3)
O(6)-C(6)-N(5)	124.0(3)
O(6)-C(6)-C(6A)	128.8(3)
N(5)-C(6)-C(6A)	107.3(3)
C(6)-C(6A)-C(3A)	105.1(3)
C(6)-C(6A)-C(1)	115.0(3)
C(3A)-C(6A)-C(1)	103.5(2)
C(12)-C(11)-C(16)	117.2(4)
C(12)-C(11)-C(1)	120.9(3)
C(16)-C(11)-C(1)	121.8(3)
C(13)-C(12)-C(11)	121.6(5)
C(14)-C(13)-C(12)	121.1(5)
C(13)-C(14)-C(15)	118.3(5)
C(14)-C(15)-C(16)	121.3(5)
C(15)-C(16)-C(11)	120.6(4)
C(22)-C(21)-O(2)	110.6(4)
C(32)-C(31)-O(3)	123.4(9)
C(52)-C(51)-C(56)	121.5(3)
C(52)-C(51)-N(5)	119.2(3)
C(56)-C(51)-N(5)	119.4(3)
C(51)-C(52)-C(53)	120.0(4)
C(54)-C(53)-C(52)	118.6(4)
C(54)-C(53)-Cl(1)	119.8(3)
C(52)-C(53)-Cl(1)	121.5(4)
F(1)-C(54)-C(55)	118.1(5)
F(1)-C(54)-C(53)	120.0(5)
C(55)-C(54)-C(53)	121.9(4)
C(54)-C(55)-C(56)	119.2(4)
C(51)-C(56)-C(55)	118.7(4)

Table 4. Anisotropic displacement parameters ($Å^2 x 10^3$) for **9d**.The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2a^{*2}U^{11} + ... + 2 h k a^* b^* U^{12}]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
Cl(1)	83(1)	160(2)	143(1)	-24(1)	-53(1)	7(1)
P(1)	44(1)	58(1)	57(1)	11(1)	-2(1)	-4(1)
F(1)	51(2)	165(3)	193(3)	0(3)	5(2)	29(2)
O(1)	63(2)	88(2)	66(2)	36(2)	-2(1)	-9(2)
O(2)	60(2)	63(2)	78(2)	7(1)	-22(1)	-6(1)
O(3)	49(1)	73(2)	83(2)	2(2)	18(1)	8(1)
O(4)	57(2)	54(2)	80(2)	16(1)	10(1)	-4(1)
O(6)	58(2)	77(2)	66(2)	28(2)	-12(1)	-9(1)
C(1)	44(2)	42(2)	45(2)	5(2)	0(2)	0(2)
N(2)	53(2)	51(2)	49(2)	7(2)	-3(1)	0(2)
C(3)	50(2)	49(2)	60(2)	11(2)	4(2)	5(2)
C(3A)	49(2)	44(2)	50(2)	-5(2)	6(2)	2(2)
C(4)	53(2)	40(2)	46(2)	-3(2)	2(2)	-1(2)
N(5)	42(2)	43(2)	47(2)	2(1)	-1(1)	-1(1)
C(6)	54(2)	54(2)	40(2)	2(2)	-1(2)	-6(2)
C(6A)	41(2)	49(2)	45(2)	-2(2)	6(2)	-1(2)
C(11)	51(2)	49(2)	50(2)	-7(2)	-6(2)	-2(2)
C(12)	72(3)	62(2)	75(3)	-13(2)	20(2)	-6(2)
C(13)	79(3)	104(4)	113(4)	-52(4)	28(3)	-7(3)
C(14)	67(3)	101(4)	134(5)	-59(4)	0(3)	16(3)
C(15)	106(4)	61(3)	122(4)	-13(3)	-24(3)	31(3)
C(16)	84(3)	58(3)	77(3)	3(2)	1(2)	17(2)
C(21)	105(4)	96(4)	96(3)	24(3)	-50(3)	-14(3)
C(22)	120(4)	81(3)	94(3)	-11(3)	-44(3)	18(3)
C(31)	205(8)	129(6)	228(9)	22(6)	130(7)	48(6)
C(32)	267(11)	201(9)	198(9)	-75(7)	140(8)	-11(8)
C(51)	40(2)	48(2)	57(2)	6(2)	5(2)	1(2)
C(52)	53(2)	58(2)	66(2)	-8(2)	-5(2)	4(2)
C(53)	58(3)	75(3)	90(3)	7(3)	-15(2)	3(2)
C(54)	45(2)	88(3)	113(4)	15(3)	1(3)	9(2)
C(55)	70(3)	99(4)	101(4)	-1(3)	32(3)	17(3)
C(56)	58(2)	83(3)	67(3)	-3(2)	8(2)	8(2)

Table 5. Hydrogen bonds for **9d** [Å and °].

D-H...A	d(D-H)	d(H...A)	d(D...A)	<(DHA)
C(3A)-H(3A)...O(6)#1	0.98	2.49	3.359(4)	147.7
C(22)-H(22B)...O(6)#2	0.96	2.56	3.436(5)	151.8
C(31)-H(31A)...O(1)	0.97	2.57	3.067(8)	112.2
C(52)-H(52)...O(1)#1	0.93	2.54	3.295(5)	139.0

Symmetry transformations used to generate equivalent atoms:
#1 -x+1/2,y-1/2,-z+3/2 #2 x+1/2,-y+1/2,z+1/2

Diethyl (1*RS*,3a*SR*,6a*SR*)-5-(3,4-dichlorophenyl)-4,6-dioxo-1-phenyl-1,3a,4,5,6,6a-hexahydropyrrolo[3,4-*c*]pyrrole-1-phosphonate (9v): Deposition number: 1960887

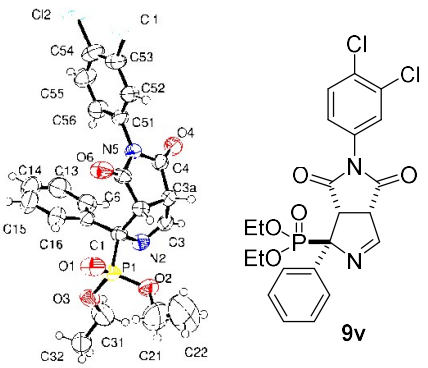


Table 1. Crystal data and structure refinement for **9v.**

Identification code	Jb137	
Empirical formula	C22 H21 Cl2 N2 O5 P	
Formula weight	495.28	
Temperature	294(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P 21/n	
Unit cell dimensions	a = 15.769(3) Å	α= 90°.
	b = 9.234(2) Å	β= 93.672(5)°.
	c = 15.789(3) Å	γ = 90°.
Volume	2294.3(9) $Å^3$	
Z	4	
Density (calculated)	1.434 Mg/m^3	
Absorption coefficient	0.389 mm^{-1}	
F(000)	1024	
Crystal size	0.33 x 0.12 x 0.11 mm^3	
Theta range for data collection	1.769 to 28.326°.	
Index ranges	-21<=h<=21, -12<=k<=12, -21<=l<=21	
Reflections collected	49110	
Independent reflections	5704 [R(int) = 0.0892]	
Completeness to theta = 25.242°	100.0 %	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	5704 / 0 / 291	
Goodness-of-fit on F^2	1.012	
Final R indices [I>2sigma(I)]	R1 = 0.0598, wR2 = 0.1362	
R indices (all data)	R1 = 0.1155, wR2 = 0.1653	
Largest diff. peak and hole	0.533 and -0.336 e.$Å^{-3}$	

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for **9v**. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
Cl(1)	3639(1)	9847(2)	6664(1)	98(1)
Cl(2)	2190(1)	8305(2)	7622(1)	129(1)
P(1)	1326(1)	8053(1)	1087(1)	48(1)
O(1)	2074(1)	7137(3)	1246(1)	68(1)
O(2)	1474(1)	9464(2)	565(1)	61(1)
O(3)	602(1)	7175(2)	608(1)	63(1)
O(4)	817(1)	11917(2)	4120(1)	58(1)
O(6)	2493(1)	8094(2)	3515(1)	61(1)
N(2)	269(1)	9893(3)	1838(2)	46(1)
N(5)	1618(1)	9857(2)	4004(1)	41(1)
C(1)	932(2)	8810(3)	2062(2)	39(1)
C(3)	454(2)	11070(3)	2217(2)	47(1)
C(3A)	1279(2)	11121(3)	2740(2)	43(1)
C(4)	1190(2)	11077(3)	3696(2)	42(1)
C(6)	2005(2)	9077(3)	3377(2)	43(1)
C(6A)	1689(2)	9691(3)	2534(2)	40(1)
C(11)	557(2)	7643(3)	2618(2)	45(1)
C(12)	-133(2)	7961(4)	3085(2)	63(1)
C(13)	-439(3)	6967(5)	3647(3)	87(1)
C(14)	-77(3)	5635(6)	3736(3)	94(2)
C(15)	592(3)	5292(4)	3267(3)	92(1)
C(16)	914(2)	6284(4)	2714(2)	69(1)
C(21)	1969(5)	9381(7)	-188(4)	142(2)
C(22)	2528(5)	10365(8)	-264(5)	184(4)
C(31)	-151(3)	7780(4)	185(3)	86(1)
C(32)	-531(2)	6744(4)	-422(2)	76(1)
C(51)	1746(2)	9521(3)	4891(2)	43(1)
C(52)	2513(2)	9859(3)	5309(2)	50(1)
C(53)	2658(2)	9483(4)	6153(2)	60(1)
C(54)	2026(2)	8794(4)	6571(2)	68(1)
C(55)	1263(2)	8484(4)	6146(2)	72(1)
C(56)	1118(2)	8843(4)	5303(2)	59(1)

Table 3. Bond lengths [Å] and angles [°] for **9v.**

Cl(1)-C(53)	1.731(3)
Cl(2)-C(54)	1.723(3)
P(1)-O(1)	1.460(2)
P(1)-O(3)	1.556(2)
P(1)-O(2)	1.567(2)
P(1)-C(1)	1.835(3)
O(2)-C(21)	1.466(5)
O(3)-C(31)	1.438(4)
O(4)-C(4)	1.203(3)
O(6)-C(6)	1.200(3)
N(2)-C(3)	1.267(4)
N(2)-C(1)	1.474(3)
N(5)-C(4)	1.386(3)
N(5)-C(6)	1.396(3)
N(5)-C(51)	1.435(3)
C(1)-C(11)	1.532(4)
C(1)-C(6A)	1.589(4)
C(3)-C(3A)	1.496(4)
C(3A)-C(6A)	1.515(4)
C(3A)-C(4)	1.524(4)
C(6)-C(6A)	1.503(4)
C(11)-C(16)	1.380(4)
C(11)-C(12)	1.385(4)
C(12)-C(13)	1.385(5)
C(13)-C(14)	1.359(6)
C(14)-C(15)	1.363(7)
C(15)-C(16)	1.384(5)
C(21)-C(22)	1.277(7)
C(31)-C(32)	1.455(5)
C(51)-C(56)	1.371(4)
C(51)-C(52)	1.377(4)
C(52)-C(53)	1.382(4)
C(53)-C(54)	1.385(5)
C(54)-C(55)	1.371(5)
C(55)-C(56)	1.377(5)
O(1)-P(1)-O(3)	109.94(13)
O(1)-P(1)-O(2)	115.26(14)
O(3)-P(1)-O(2)	107.91(12)
O(1)-P(1)-C(1)	112.89(12)
O(3)-P(1)-C(1)	109.18(13)
O(2)-P(1)-C(1)	101.20(12)
C(21)-O(2)-P(1)	119.2(3)
C(31)-O(3)-P(1)	125.6(2)
C(3)-N(2)-C(1)	109.3(2)
C(4)-N(5)-C(6)	113.3(2)
C(4)-N(5)-C(51)	123.6(2)
C(6)-N(5)-C(51)	122.7(2)
N(2)-C(1)-C(11)	108.7(2)
N(2)-C(1)-C(6A)	105.3(2)
C(11)-C(1)-C(6A)	113.4(2)
N(2)-C(1)-P(1)	109.28(17)
C(11)-C(1)-P(1)	112.15(19)
C(6A)-C(1)-P(1)	107.70(17)
N(2)-C(3)-C(3A)	117.0(3)
C(3)-C(3A)-C(6A)	102.8(2)
C(3)-C(3A)-C(4)	114.5(2)

C(6A)-C(3A)-C(4)	104.9(2)
O(4)-C(4)-N(5)	124.9(3)
O(4)-C(4)-C(3A)	127.8(3)
N(5)-C(4)-C(3A)	107.2(2)
O(6)-C(6)-N(5)	124.4(3)
O(6)-C(6)-C(6A)	128.3(3)
N(5)-C(6)-C(6A)	107.3(2)
C(6)-C(6A)-C(3A)	105.1(2)
C(6)-C(6A)-C(1)	114.8(2)
C(3A)-C(6A)-C(1)	103.3(2)
C(16)-C(11)-C(12)	117.6(3)
C(16)-C(11)-C(1)	122.2(3)
C(12)-C(11)-C(1)	120.1(3)
C(13)-C(12)-C(11)	121.2(4)
C(14)-C(13)-C(12)	120.3(4)
C(13)-C(14)-C(15)	119.2(4)
C(14)-C(15)-C(16)	121.1(4)
C(11)-C(16)-C(15)	120.5(4)
C(22)-C(21)-O(2)	116.5(6)
O(3)-C(31)-C(32)	110.1(3)
C(56)-C(51)-C(52)	121.0(3)
C(56)-C(51)-N(5)	120.1(3)
C(52)-C(51)-N(5)	118.9(3)
C(51)-C(52)-C(53)	119.5(3)
C(52)-C(53)-C(54)	119.7(3)
C(52)-C(53)-Cl(1)	119.2(3)
C(54)-C(53)-Cl(1)	121.1(3)
C(55)-C(54)-C(53)	119.9(3)
C(55)-C(54)-Cl(2)	119.3(3)
C(53)-C(54)-Cl(2)	120.7(3)
C(54)-C(55)-C(56)	120.6(3)
C(51)-C(56)-C(55)	119.3(3)

Table 4. Anisotropic displacement parameters ($Å^2 x 10^3$) for **9v.** The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2a^{*2}U^{11} + ... + 2 h k a^* b^* U^{12}]$

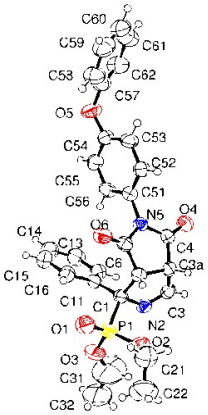
	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
Cl(1)	84(1)	143(1)	62(1)	4(1)	-26(1)	-7(1)
Cl(2)	145(1)	195(2)	45(1)	35(1)	7(1)	-3(1)
P(1)	50(1)	57(1)	37(1)	-5(1)	-3(1)	10(1)
O(1)	62(1)	85(2)	56(1)	-11(1)	-2(1)	34(1)
O(2)	75(2)	66(1)	43(1)	2(1)	12(1)	1(1)
O(3)	71(1)	59(1)	54(1)	-7(1)	-23(1)	5(1)
O(4)	72(1)	50(1)	52(1)	-4(1)	13(1)	11(1)
O(6)	57(1)	74(2)	51(1)	-8(1)	-10(1)	27(1)
N(2)	41(1)	51(2)	45(1)	3(1)	-2(1)	9(1)
N(5)	40(1)	45(1)	37(1)	1(1)	1(1)	1(1)
C(1)	36(1)	44(2)	37(1)	-2(1)	-2(1)	5(1)
C(3)	51(2)	46(2)	44(2)	8(1)	1(1)	9(1)
C(3A)	48(2)	42(2)	40(1)	4(1)	6(1)	-4(1)
C(4)	42(2)	42(2)	43(2)	0(1)	4(1)	-2(1)
C(6)	36(1)	49(2)	43(2)	-7(1)	-3(1)	3(1)
C(6A)	33(1)	50(2)	38(1)	-3(1)	4(1)	-3(1)
C(11)	46(2)	48(2)	40(2)	-1(1)	-3(1)	-8(1)
C(12)	63(2)	68(2)	60(2)	-2(2)	12(2)	-14(2)
C(13)	93(3)	100(3)	69(3)	-5(2)	22(2)	-40(3)
C(14)	121(4)	93(3)	66(3)	20(2)	-5(3)	-53(3)
C(15)	118(4)	61(2)	94(3)	26(2)	-11(3)	-11(3)
C(16)	75(2)	56(2)	75(2)	14(2)	2(2)	6(2)
C(21)	207(7)	120(4)	110(4)	8(4)	86(5)	-6(5)
C(22)	170(6)	172(7)	222(8)	-49(6)	114(6)	-88(5)
C(31)	79(3)	75(3)	99(3)	-11(2)	-35(2)	19(2)
C(32)	75(2)	71(2)	78(3)	9(2)	-29(2)	-7(2)
C(51)	48(2)	46(2)	37(1)	1(1)	5(1)	4(1)
C(52)	51(2)	56(2)	42(2)	0(1)	1(1)	-2(2)
C(53)	65(2)	71(2)	41(2)	-2(2)	-7(2)	5(2)
C(54)	82(3)	86(3)	37(2)	8(2)	10(2)	9(2)
C(55)	74(2)	89(3)	54(2)	12(2)	20(2)	-6(2)
C(56)	52(2)	73(2)	52(2)	3(2)	11(1)	-5(2)

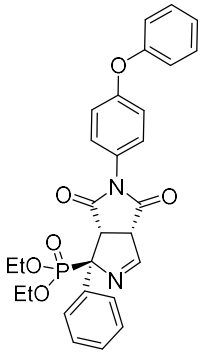
Table 5. Hydrogen bonds for **9v** [Å and °].

D-H...A	d(D-H)	d(H...A)	d(D...A)	<(DHA)
C(3A)-H(3A)...O(6)#1	0.98	2.52	3.391(3)	147.8
C(32)-H(32C)...O(6)#2	0.96	2.57	3.448(4)	152.8
C(52)-H(52)...O(1)#1	0.93	2.61	3.329(4)	134.9

Symmetry transformations used to generate equivalent atoms:
#1 -x+1/2,y+1/2,-z+1/2 #2 x-1/2,-y+3/2,z-1/2

Diethyl (1*RS*,3a*SR*,6a*SR*)-4,6-dioxo-5-(4-phenoxyphenyl)-1-phenyl-1,3a,4,5,6,6a-hexahydropyrrolo[3,4-*c*]pyrrole-1-phosphonate (9ab): Deposition number: 1960885





9ab

Table 1. Crystal data and structure refinement for **9ab.**

Identification code	Jb131	
Empirical formula	C28 H27 N2 O6 P	
Formula weight	518.48	
Temperature	294(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	I 2/a	
Unit cell dimensions	a = 22.065(4) Å	α= 90°.
	b = 9.314(2) Å	β= 112.776(16)°.
	c = 27.263(4) Å	γ = 90°.
Volume	5166.0(17) $Å^3$	
Z	8	
Density (calculated)	1.333 Mg/m^3	
Absorption coefficient	0.152 mm^{-1}	
F(000)	2176	
Crystal size	0.39 x 0.33 x 0.15 mm^3	
Theta range for data collection	1.620 to 25.124°.	
Index ranges	-16<=h<=26, -11<=k<=10, -32<=l<=17	
Reflections collected	9131	
Independent reflections	4559 [R(int) = 0.0846]	
Completeness to theta = 25.124°	98.7 %	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	4559 / 0 / 337	
Goodness-of-fit on F^2	0.997	
Final R indices [I>2sigma(I)]	R1 = 0.0526, wR2 = 0.1177	
R indices (all data)	R1 = 0.1383, wR2 = 0.1478	
Extinction coefficient	0.00136(18)	
Largest diff. peak and hole	0.512 and -0.393 e.$Å^{-3}$	

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for **9ab.** U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
P(1)	5656(1)	-1033(1)	3648(1)	53(1)
O(1)	5820(1)	39(3)	3328(1)	70(1)
O(2)	6057(1)	-2460(3)	3741(1)	66(1)
O(3)	5743(1)	-450(3)	4204(1)	79(1)
O(4)	3308(1)	-4767(3)	2426(1)	56(1)
O(5)	1346(1)	-394(3)	690(1)	71(1)
O(6)	4267(1)	-800(3)	2068(1)	58(1)
N(2)	4720(1)	-2802(3)	3694(1)	45(1)
N(5)	3636(1)	-2605(3)	2202(1)	40(1)
C(1)	4809(2)	-1672(3)	3346(1)	41(1)
C(3)	4519(2)	-3942(4)	3435(1)	48(1)
C(3A)	4438(2)	-3931(4)	2864(1)	43(1)
C(4)	3725(2)	-3886(4)	2481(1)	41(1)
C(6)	4213(2)	-1819(4)	2322(1)	44(1)
C(6A)	4718(2)	-2471(4)	2805(1)	42(1)
C(11)	4314(2)	-465(4)	3288(1)	43(1)
C(12)	3784(2)	-683(4)	3436(1)	56(1)
C(13)	3308(2)	358(5)	3347(2)	69(1)
C(14)	3354(2)	1629(5)	3107(2)	77(1)
C(15)	3885(2)	1876(4)	2972(2)	72(1)
C(16)	4356(2)	836(4)	3056(1)	56(1)
C(21)	6617(2)	-2671(6)	3588(2)	88(1)
C(22)	7230(2)	-2531(7)	4045(2)	125(2)
C(31)	5866(4)	-1140(9)	4658(2)	196(4)
C(32)	6183(3)	-583(8)	5132(2)	178(3)
C(51)	3027(2)	-2137(4)	1804(1)	43(1)
C(52)	2824(2)	-2641(4)	1294(1)	54(1)
C(53)	2256(2)	-2100(4)	909(1)	58(1)
C(54)	1909(2)	-1040(4)	1041(1)	49(1)
C(55)	2108(2)	-562(4)	1550(1)	53(1)
C(56)	2667(2)	-1106(4)	1933(1)	52(1)
C(57)	1083(2)	-882(4)	163(1)	58(1)
C(58)	1360(2)	-480(5)	-186(2)	78(1)
C(59)	1072(3)	-919(6)	-704(2)	86(1)
C(60)	519(3)	-1714(5)	-870(2)	85(2)
C(61)	245(2)	-2075(6)	-521(2)	99(2)
C(62)	520(2)	-1651(5)	9(2)	80(1)

Table 3. Bond lengths [Å] and angles [°] for **9ab.**

P(1)-O(1)	1.461(3)
P(1)-O(3)	1.549(3)
P(1)-O(2)	1.562(3)
P(1)-C(1)	1.826(3)
O(2)-C(21)	1.463(4)
O(3)-C(31)	1.328(6)
O(4)-C(4)	1.197(4)
O(5)-C(54)	1.378(4)
O(5)-C(57)	1.400(4)
O(6)-C(6)	1.208(4)
N(2)-C(3)	1.258(4)
N(2)-C(1)	1.480(4)
N(5)-C(4)	1.387(4)
N(5)-C(6)	1.393(4)
N(5)-C(51)	1.431(4)
C(1)-C(11)	1.532(5)
C(1)-C(6A)	1.595(4)
C(3)-C(3A)	1.497(4)
C(3A)-C(4)	1.514(4)
C(3A)-C(6A)	1.528(4)
C(6)-C(6A)	1.487(4)
C(11)-C(16)	1.387(5)
C(11)-C(12)	1.391(4)
C(12)-C(13)	1.380(5)
C(13)-C(14)	1.376(6)
C(14)-C(15)	1.376(6)
C(15)-C(16)	1.373(5)
C(21)-C(22)	1.447(6)
C(31)-C(32)	1.313(7)
C(51)-C(52)	1.368(4)
C(51)-C(56)	1.376(4)
C(52)-C(53)	1.381(5)
C(53)-C(54)	1.380(5)
C(54)-C(55)	1.359(4)
C(55)-C(56)	1.367(4)
C(57)-C(62)	1.351(5)
C(57)-C(58)	1.366(5)
C(58)-C(59)	1.369(6)
C(59)-C(60)	1.346(6)
C(60)-C(61)	1.352(6)
C(61)-C(62)	1.390(6)
O(1)-P(1)-O(3)	112.26(17)
O(1)-P(1)-O(2)	115.03(15)
O(3)-P(1)-O(2)	106.99(16)
O(1)-P(1)-C(1)	113.62(15)
O(3)-P(1)-C(1)	105.79(15)
O(2)-P(1)-C(1)	102.23(14)
C(21)-O(2)-P(1)	123.7(3)
C(31)-O(3)-P(1)	130.2(4)
C(54)-O(5)-C(57)	118.4(3)
C(3)-N(2)-C(1)	110.2(3)
C(4)-N(5)-C(6)	113.7(3)
C(4)-N(5)-C(51)	124.8(3)
C(6)-N(5)-C(51)	121.5(3)
N(2)-C(1)-C(11)	108.7(2)
N(2)-C(1)-C(6A)	105.1(3)

C(11)-C(1)-C(6A)	114.6(2)
N(2)-C(1)-P(1)	108.1(2)
C(11)-C(1)-P(1)	111.8(2)
C(6A)-C(1)-P(1)	108.0(2)
N(2)-C(3)-C(3A)	116.9(3)
C(3)-C(3A)-C(4)	113.1(3)
C(3)-C(3A)-C(6A)	103.1(3)
C(4)-C(3A)-C(6A)	105.0(3)
O(4)-C(4)-N(5)	125.5(3)
O(4)-C(4)-C(3A)	127.6(3)
N(5)-C(4)-C(3A)	106.9(3)
O(6)-C(6)-N(5)	124.3(3)
O(6)-C(6)-C(6A)	128.4(3)
N(5)-C(6)-C(6A)	107.3(3)
C(6)-C(6A)-C(3A)	105.1(3)
C(6)-C(6A)-C(1)	114.3(3)
C(3A)-C(6A)-C(1)	103.2(2)
C(16)-C(11)-C(12)	118.1(3)
C(16)-C(11)-C(1)	121.2(3)
C(12)-C(11)-C(1)	120.6(3)
C(13)-C(12)-C(11)	121.0(4)
C(14)-C(13)-C(12)	119.8(4)
C(13)-C(14)-C(15)	119.8(4)
C(16)-C(15)-C(14)	120.4(4)
C(15)-C(16)-C(11)	120.9(4)
C(22)-C(21)-O(2)	110.7(4)
C(32)-C(31)-O(3)	124.4(8)
C(52)-C(51)-C(56)	120.4(3)
C(52)-C(51)-N(5)	120.6(3)
C(56)-C(51)-N(5)	118.9(3)
C(51)-C(52)-C(53)	119.3(3)
C(54)-C(53)-C(52)	119.8(3)
C(55)-C(54)-O(5)	114.6(3)
C(55)-C(54)-C(53)	120.5(3)
O(5)-C(54)-C(53)	125.0(3)
C(54)-C(55)-C(56)	119.9(3)
C(55)-C(56)-C(51)	120.1(3)
C(62)-C(57)-C(58)	122.2(4)
C(62)-C(57)-O(5)	117.2(4)
C(58)-C(57)-O(5)	120.3(4)
C(57)-C(58)-C(59)	118.8(4)
C(60)-C(59)-C(58)	120.6(4)
C(59)-C(60)-C(61)	119.7(5)
C(60)-C(61)-C(62)	121.7(5)
C(57)-C(62)-C(61)	116.9(4)

Table 4. Anisotropic displacement parameters ($Å^2 x 10^3$) for **9ab**. The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2a^{*2}U^{11} + ... + 2 h k a^* b^* U^{12}]$

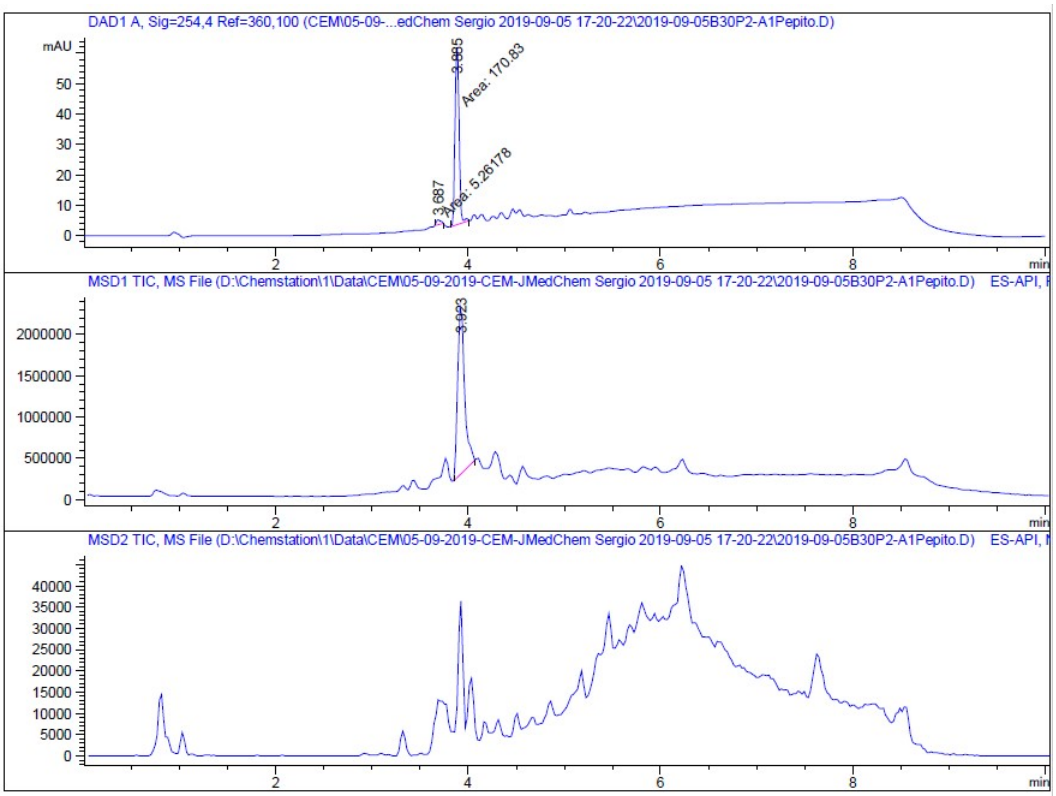
	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
P(1)	42(1)	59(1)	50(1)	3(1)	10(1)	-9(1)
O(1)	56(2)	74(2)	76(2)	16(2)	22(1)	-16(1)
O(2)	40(1)	76(2)	80(2)	13(2)	20(1)	7(1)
O(3)	81(2)	90(2)	49(2)	-16(2)	5(1)	-7(2)
O(4)	51(1)	50(2)	64(2)	2(1)	18(1)	-10(1)
O(5)	63(2)	89(2)	51(2)	-2(2)	9(1)	29(2)
O(6)	58(2)	69(2)	45(1)	9(1)	16(1)	-16(1)
N(2)	44(2)	45(2)	46(2)	8(2)	14(1)	0(1)
N(5)	34(2)	43(2)	42(2)	-2(1)	13(1)	-2(1)
C(1)	42(2)	41(2)	38(2)	4(2)	14(2)	-6(2)
C(3)	39(2)	47(2)	56(2)	10(2)	15(2)	2(2)
C(3A)	37(2)	41(2)	51(2)	-2(2)	17(2)	4(2)
C(4)	43(2)	38(2)	45(2)	-6(2)	19(2)	-3(2)
C(6)	44(2)	51(2)	39(2)	-4(2)	17(2)	-6(2)
C(6A)	34(2)	50(2)	43(2)	-3(2)	16(2)	0(2)
C(11)	44(2)	45(2)	39(2)	-3(2)	13(2)	-4(2)
C(12)	58(2)	54(2)	59(2)	-2(2)	26(2)	0(2)
C(13)	58(3)	72(3)	78(3)	-17(3)	28(2)	7(2)
C(14)	75(3)	66(3)	77(3)	-17(3)	15(3)	23(3)
C(15)	84(3)	48(3)	74(3)	1(2)	20(3)	7(2)
C(16)	60(2)	50(2)	57(2)	5(2)	22(2)	3(2)
C(21)	75(3)	101(4)	92(3)	-4(3)	38(3)	10(3)
C(22)	52(3)	161(6)	148(5)	-9(4)	23(3)	4(3)
C(31)	265(10)	244(10)	63(4)	-9(5)	44(5)	50(8)
C(32)	215(8)	180(7)	73(4)	-20(5)	-17(4)	19(6)
C(51)	41(2)	47(2)	40(2)	-3(2)	16(2)	-4(2)
C(52)	54(2)	54(2)	49(2)	-9(2)	16(2)	11(2)
C(53)	56(2)	69(3)	40(2)	-11(2)	10(2)	9(2)
C(54)	44(2)	54(2)	45(2)	3(2)	14(2)	6(2)
C(55)	46(2)	56(2)	58(2)	-3(2)	20(2)	13(2)
C(56)	49(2)	62(2)	44(2)	-11(2)	19(2)	0(2)
C(57)	54(2)	65(3)	46(2)	4(2)	9(2)	12(2)
C(58)	77(3)	92(4)	60(3)	4(3)	22(2)	-6(3)
C(59)	105(4)	97(4)	60(3)	15(3)	36(3)	11(3)
C(60)	105(4)	79(4)	53(3)	0(3)	10(3)	23(3)
C(61)	86(4)	103(4)	86(4)	-9(3)	10(3)	-22(3)
C(62)	68(3)	100(4)	67(3)	6(3)	22(2)	-8(3)

Table 5. Hydrogen bonds for **9ab** [Å and °].

D-H...A	d(D-H)	d(H...A)	d(D...A)	<(DHA)
C(3A)-H(3A)...O(6)#1	0.98	2.42	3.290(4)	147.1
C(31)-H(31B)...O(2)	0.97	2.46	2.959(7)	111.9

Symmetry transformations used to generate equivalent atoms:
#1 -x+1,y-1/2,-z+1/2

Diethyl (1*RS*,3a*SR*,6a*SR*)-5-methyl-4,6-dioxo-1-phenyl-1,3a,4,5,6,6a-hexahydropyrrolo[3,4-*c*]pyrrole-1-phosphonate (9a)

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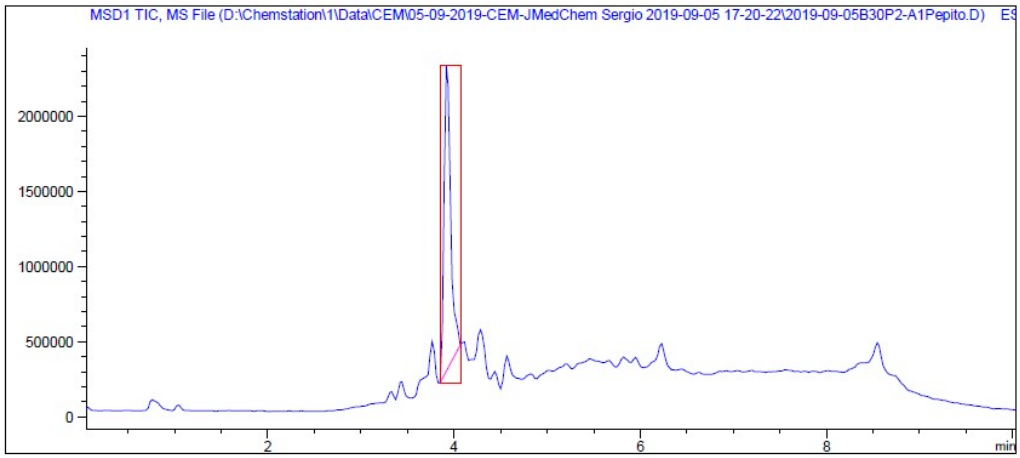
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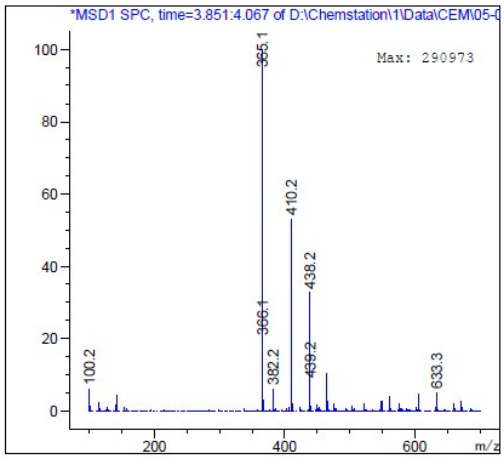
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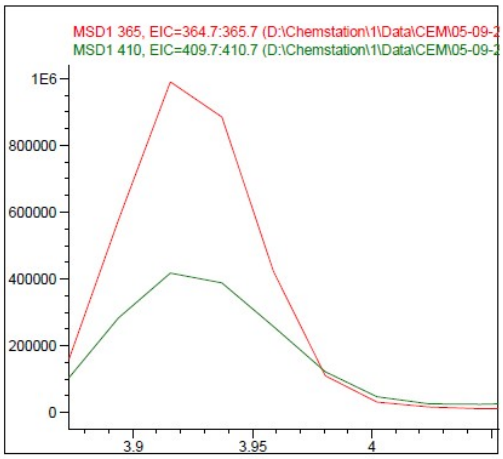
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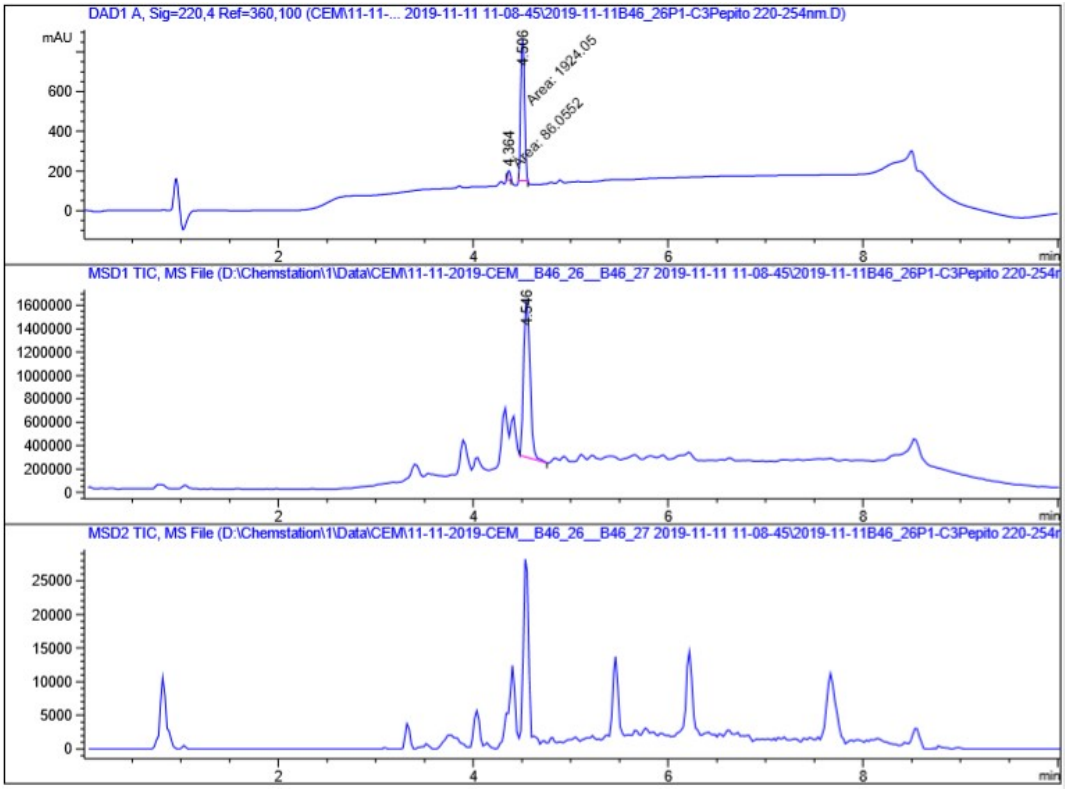
4

Diethyl (1*RS*,3a*SR*,6a*SR*)-1-benzyl-4,6-dioxo-5-phenyl-1,3a,4,5,6,6a-hexahydropyrrolo[3,4-*c*]pyrrole-1-phosphonate (14c)

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Use Multiplier & Dilution Factor with ISTDs


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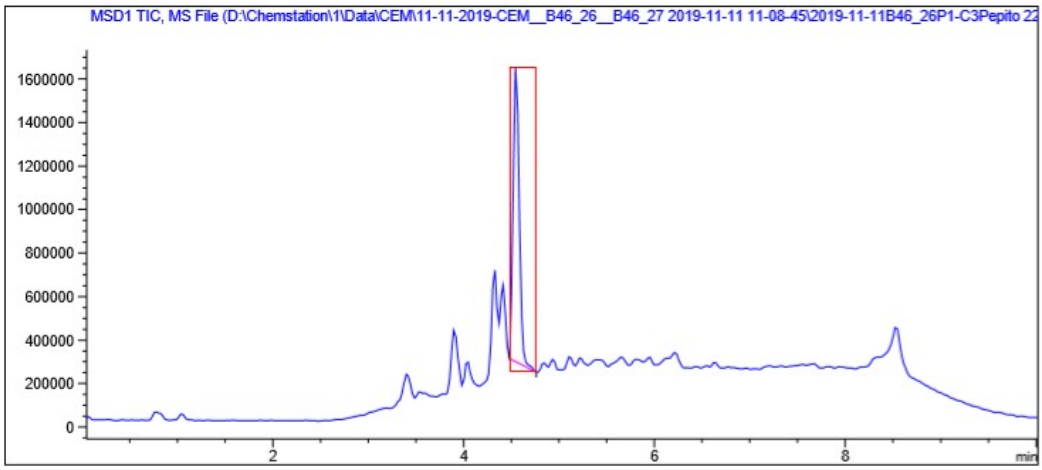
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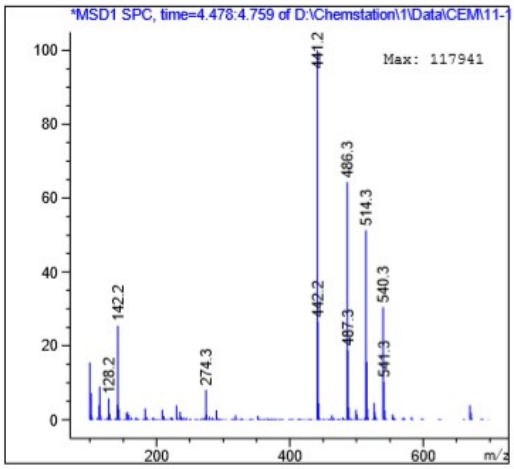
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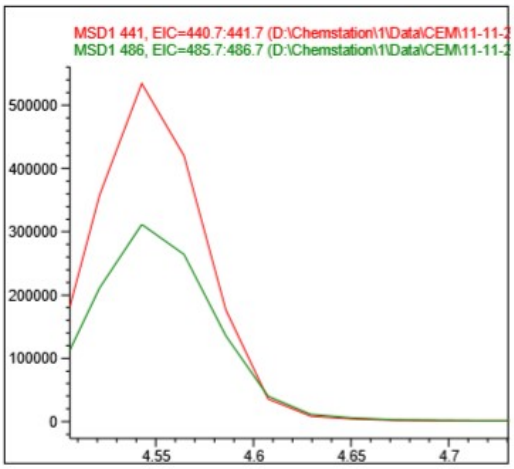
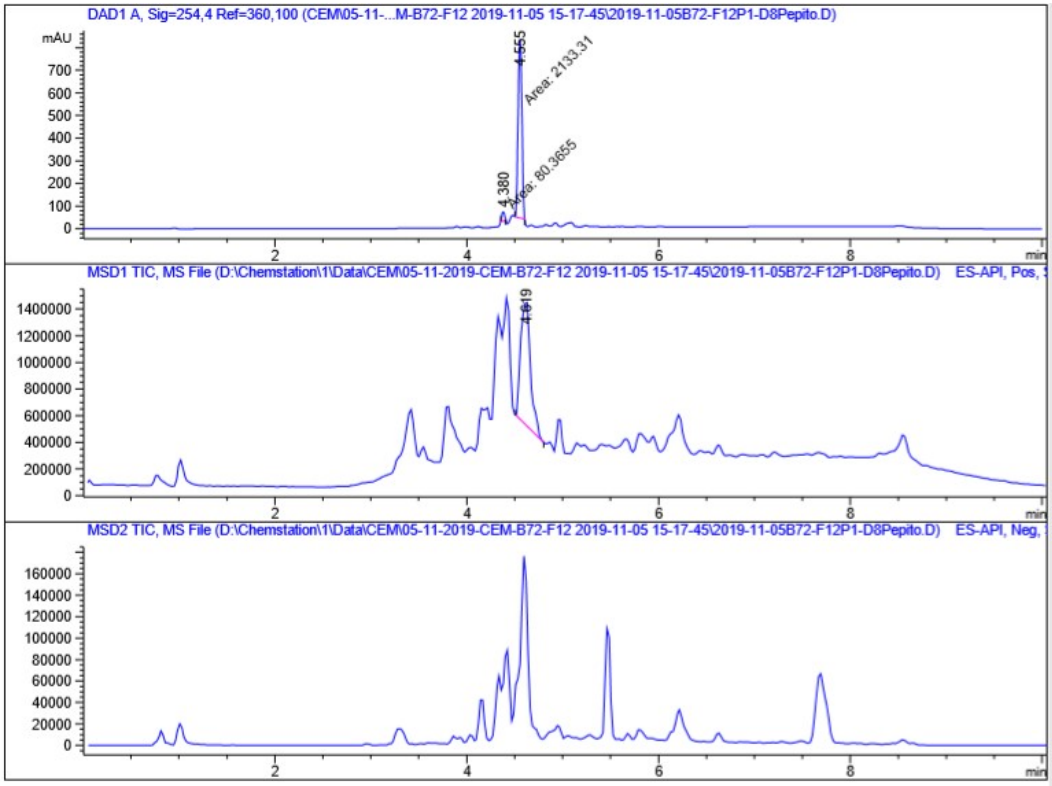
600
m/z


MSD1 441, EIC=440.7:441.7 (D:\Chemstation\1\Data\CEM\11-11-2
MSD1 486, EIC=485.7:486.7 (D:\Chemstation\1\Data\CEM\11-11-2
500000
400000
300000
200000
100000
0
4.55
4.6
4.65
4.7

Diethyl (1*RS*,3a*SR*,6a*SR*)-1-(4-fluorobenzyl)-4,6-dioxo-5-phenyl-1,3a,4,5,6,6a-hexahydropyrrolo[3,4-*c*]pyrrole-1-phosphonate (15c)



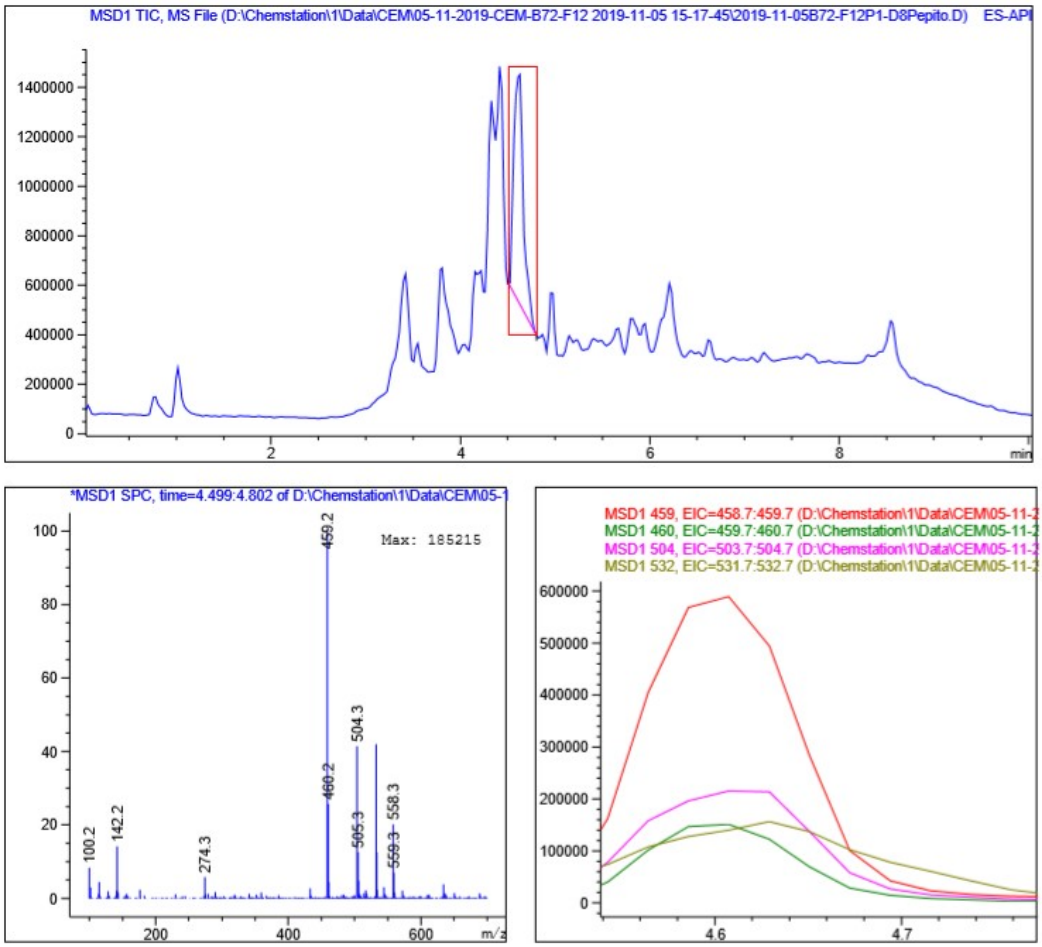

```
==========================================================================
                          Area Percent Report
==========================================================================

Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Do not use Multiplier & Dilution Factor with ISTDs

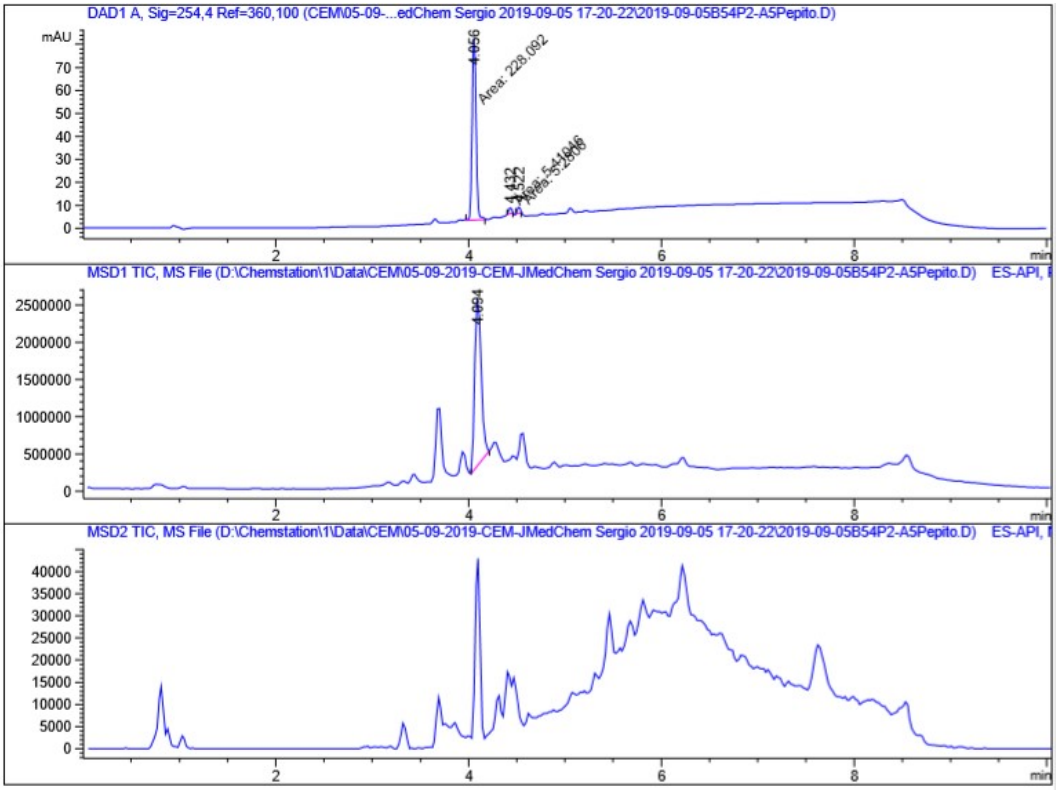
  Signal 1: DAD1 A, Sig=254,4 Ref=360,100

  Peak RetTime Type  Width     Area      Height     Area
    #   [min]        [min]   [mAU*s]     [mAU]       %
  ----|-------|----|-------|----------|----------|--------|
     1   4.380 MM    0.0321   80.36546   41.77053   3.6304
     2   4.555 MM    0.0450 2133.30615  790.23047  96.3696

  Totals :                   2213.67161  832.00100
```


MSD1 TIC, MS File (D:\Chemstation\1\Data\CEM\05-11-2019-CEM-B72-F12 2019-11-05 15-17-45\2019-11-05B72-F12P1-D8Pepito.D) ES-API
min
*MSD1 SPC, time=4.499:4.802 of D:\Chemstation\1\Data\CEM\05-1
Max: 185215
459.2
460.2
504.3
505.3
558.3
559.3
100.2
142.2
274.3
m/z
MSD1 459, EIC=458.7:459.7 (D:\Chemstation\1\Data\CEM\05-11-2
MSD1 460, EIC=459.7:460.7 (D:\Chemstation\1\Data\CEM\05-11-2
MSD1 504, EIC=503.7:504.7 (D:\Chemstation\1\Data\CEM\05-11-2
MSD1 532, EIC=531.7:532.7 (D:\Chemstation\1\Data\CEM\05-11-2

Diethyl (1*RS*,3a*SR*,6a*SR*)-5-ethyl-4,6-dioxo-1-phenyl-1,3a,4,5,6,6a-hexahydropyrrolo[3,4-*c*]pyrrole-1-phosphonate (9f)

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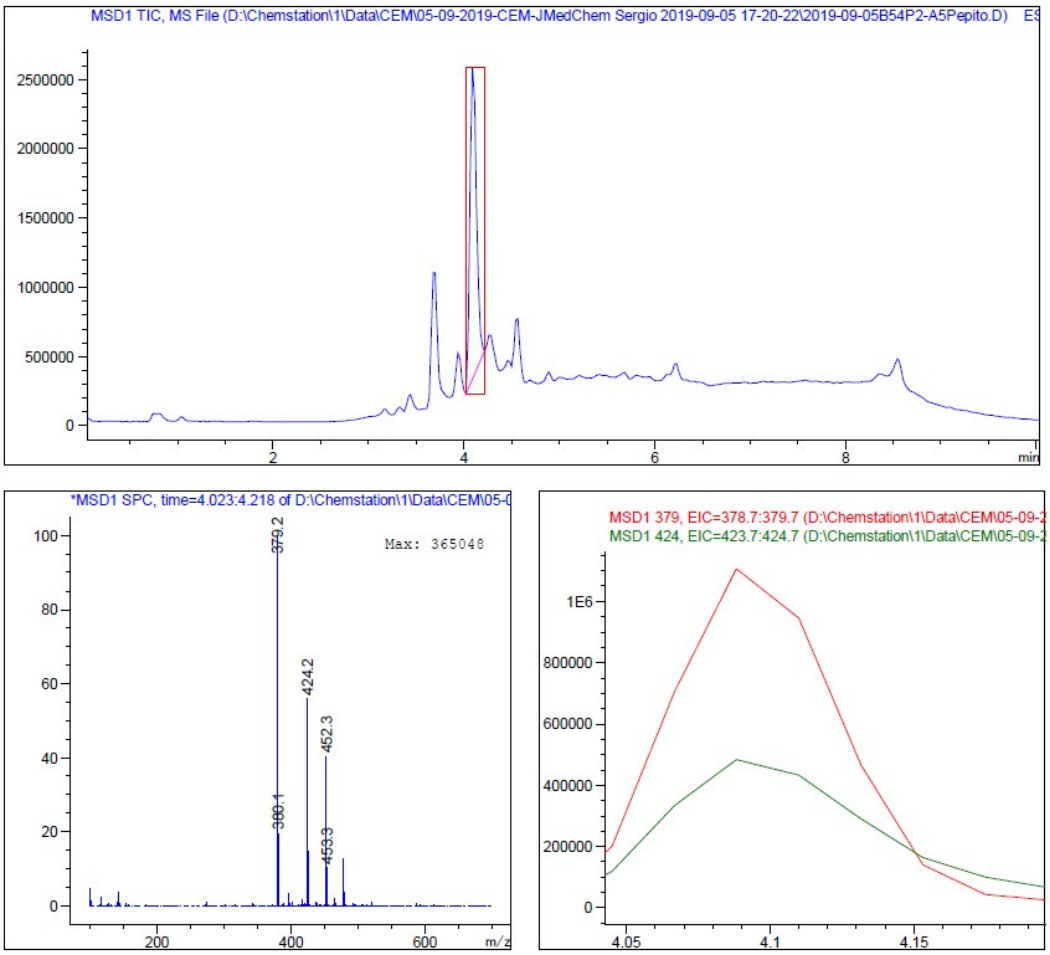
==========================================================================
                              Area Percent Report
==========================================================================

Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Do not use Multiplier & Dilution Factor with ISTDs

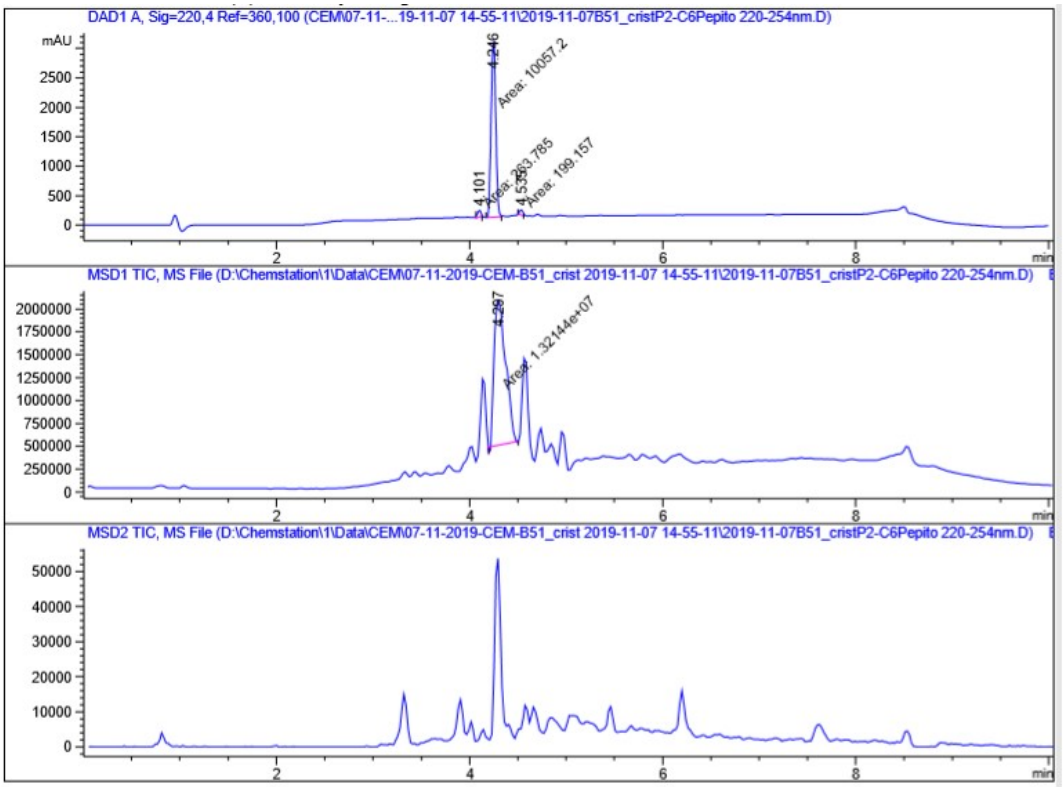

 Signal 1: DAD1 A, Sig=254,4 Ref=360,100

 Peak RetTime Type  Width     Area      Height     Area
   #   [min]        [min]   [mAU*s]     [mAU]       %
 ----|-------|----|-------|----------|----------|--------|
    1   4.056 MM    0.0480  228.09171   79.25881  95.5227
    2   4.432 MM    0.0360    5.41046    2.50647   2.2659
    3   4.522 MM    0.0328    5.28060    2.68492   2.2115

 Totals :                   238.78277   84.45021
```


MSD1 TIC, MS File (D:\Chemstation\1\Data\CEM\05-09-2019-CEM-JMedChem Sergio 2019-09-05 17-20-22\2019-09-05B54P2-A5Pepito.D)
2500000
2000000
1500000
1000000
500000
0
2
4
6
8
min
*MSD1 SPC, time=4.023:4.218 of D:\Chemstation\1\Data\CEM\05-0
Max: 365048
379.2
380.1
424.2
452.3
453.3
100
80
60
40
20
0
200
400
600
m/z
MSD1 379, EIC=378.7:379.7 (D:\Chemstation\1\Data\CEM\05-09-2
MSD1 424, EIC=423.7:424.7 (D:\Chemstation\1\Data\CEM\05-09-2
1E6
800000
600000
400000
200000
0
4.05
4.1
4.15

Diethyl (1*RS*,3a*SR*,6a*SR*)-4,6-dioxo-1-phenyl-5-propyl-1,3a,4,5,6,6a-hexahydropyrrolo[3,4-*c*]pyrrole-1-phosphonate (9g)

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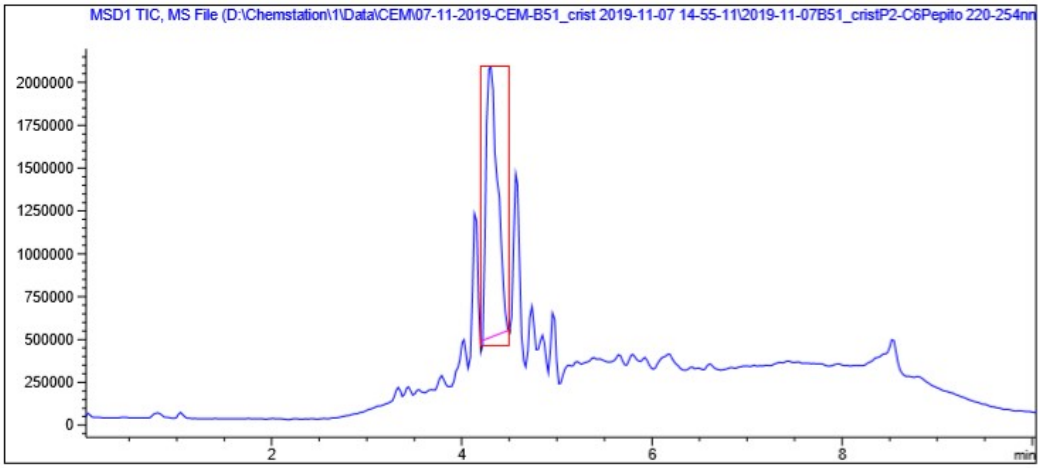
==========================================================================
                          Area Percent Report
==========================================================================

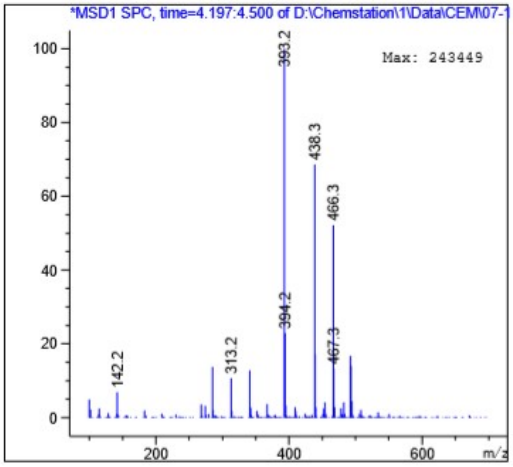
Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Do not use Multiplier & Dilution Factor with ISTDs

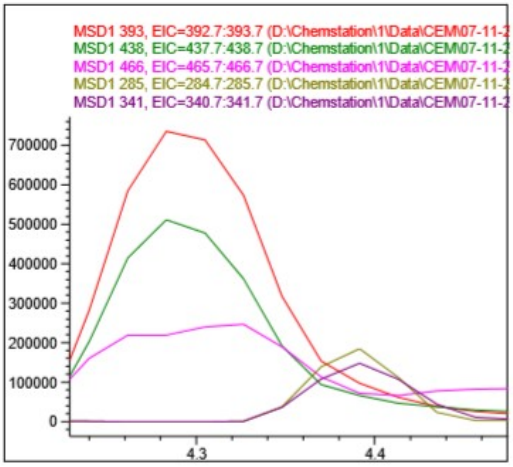

Signal 1: DAD1 A, Sig=220,4 Ref=360,100

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1   4.101 MM    0.0399  263.78546  110.05743   2.5074
   2   4.246 MM    0.0558 1.00572e4  3001.36499  95.5995
   3   4.535 MM    0.0399  199.15672   83.17267   1.8931

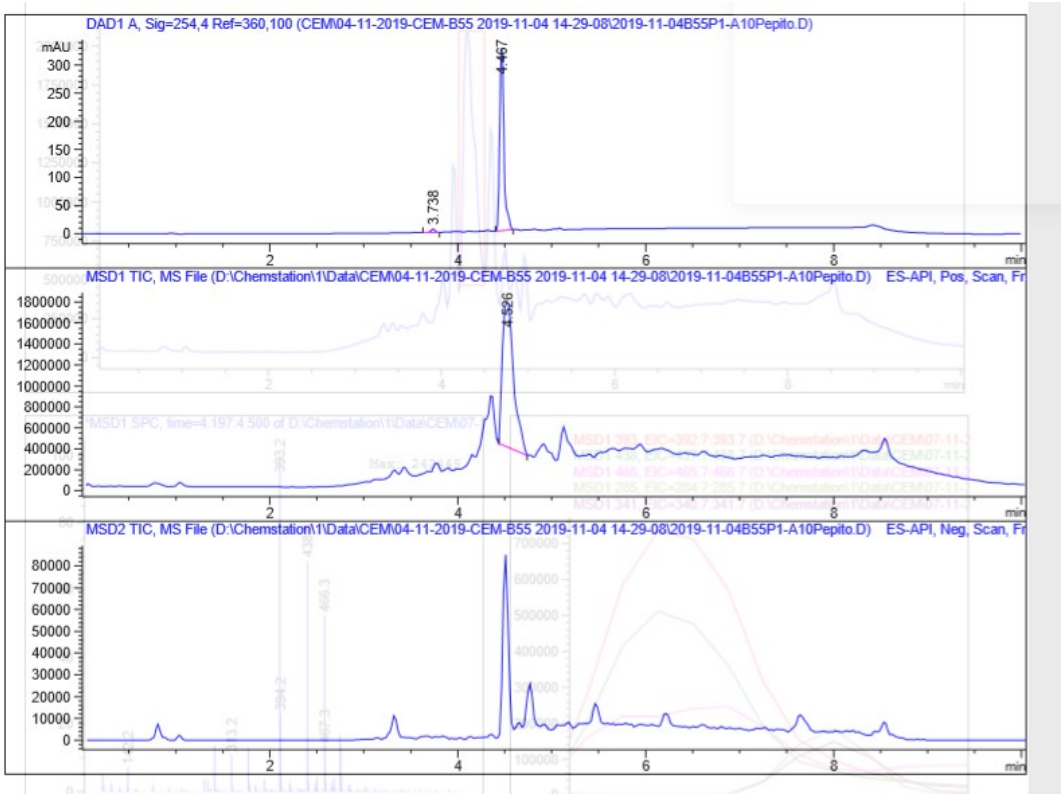
Totals :                  1.05202e4  3194.59509
```


MSD1 TIC, MS File (D:\Chemstation\1\Data\CEM\07-11-2019-CEM-B51_crist 2019-11-07 14-55-11\2019-11-07B51_cristP2-C6Pepito 220-254nm
2000000
1750000
1500000
1250000
1000000
750000
500000
250000
0
2
4
6
8
min


*MSD1 SPC, time=4.197:4.500 of D:\Chemstation\1\Data\CEM\07-1
Max: 243449
393.2
438.3
466.3
394.2
467.3
313.2
142.2
100
80
60
40
20
0
200
400
600
m/z


MSD1 393, EIC=392.7:393.7 (D:\Chemstation\1\Data\CEM\07-11-2
MSD1 438, EIC=437.7:438.7 (D:\Chemstation\1\Data\CEM\07-11-2
MSD1 466, EIC=465.7:466.7 (D:\Chemstation\1\Data\CEM\07-11-2
MSD1 285, EIC=284.7:285.7 (D:\Chemstation\1\Data\CEM\07-11-2
MSD1 341, EIC=340.7:341.7 (D:\Chemstation\1\Data\CEM\07-11-2
700000
600000
500000
400000
300000
200000
100000
0
4.3
4.4

Diethyl (1*RS*,3a*SR*,6a*SR*)-5-(tert-butyl)-4,6-dioxo-1-phenyl-1,3a,4,5,6,6a-hexahydropyrrolo[3,4-*c*]pyrrole-1-phosphonate (9h)

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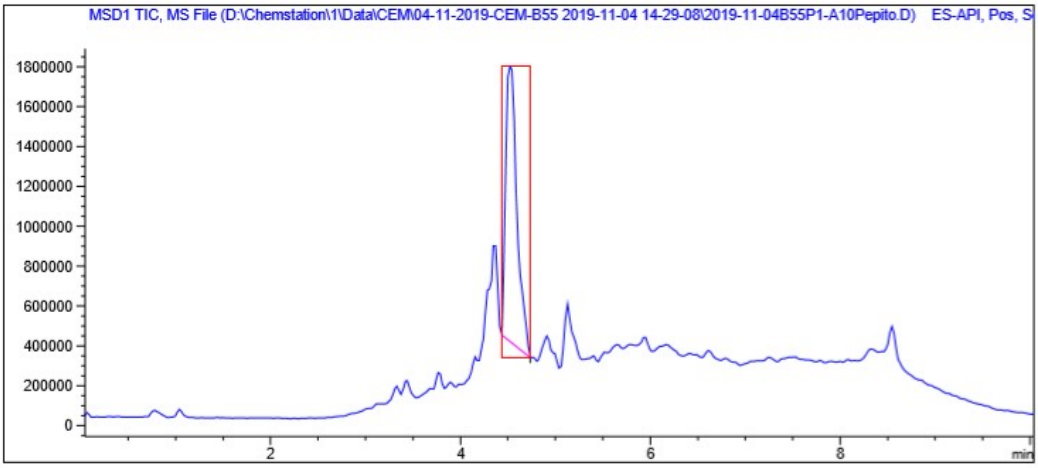
==========================================================================
                          Area Percent Report
==========================================================================

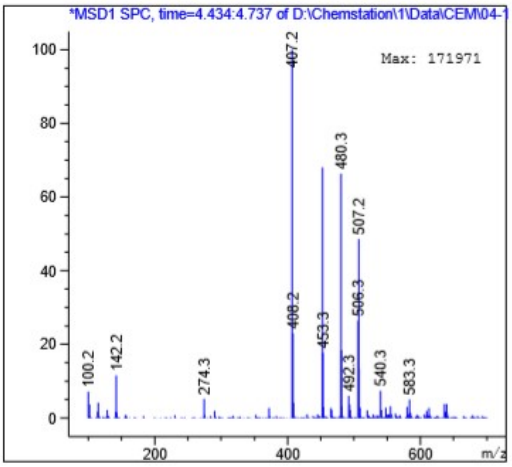
Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Do not use Multiplier & Dilution Factor with ISTDs

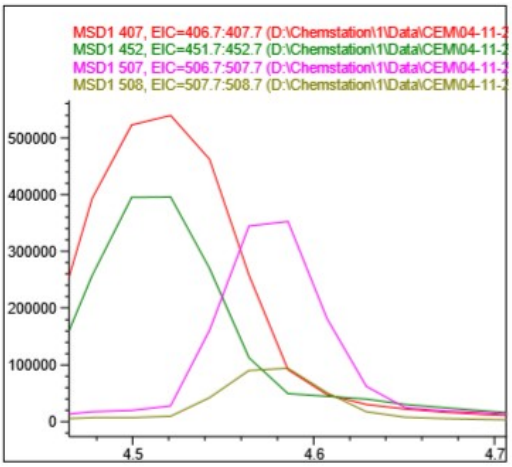

Signal 1: DAD1 A, Sig=254,4 Ref=360,100

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1   3.738 BB    0.0468   17.44491    5.85403   1.6787
   2   4.467 BB    0.0487 1021.77124  324.38782  98.3213

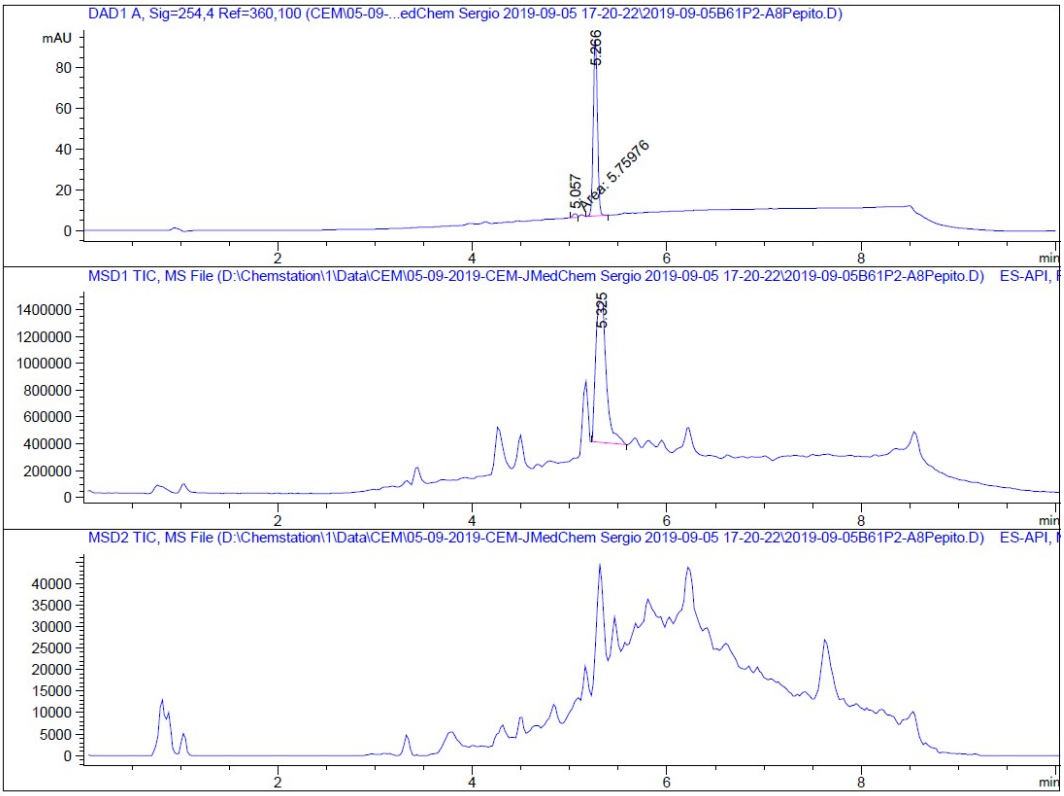
Totals :                  1039.21615  330.24185
```


MSD1 TIC, MS File (D:\Chemstation\1\Data\CEM\04-11-2019-CEM-B55 2019-11-04 14-29-08\2019-11-04B55P1-A10Pepito.D) ES-API, Pos, S
min


*MSD1 SPC, time=4.434:4.737 of D:\Chemstation\1\Data\CEM\04-1
Max: 171971
407.2
480.3
507.2
406.2
453.3
506.3
492.3
540.3
583.3
100.2
142.2
274.3
m/z


MSD1 407, EIC=406.7:407.7 (D:\Chemstation\1\Data\CEM\04-11-2
MSD1 452, EIC=451.7:452.7 (D:\Chemstation\1\Data\CEM\04-11-2
MSD1 507, EIC=506.7:507.7 (D:\Chemstation\1\Data\CEM\04-11-2
MSD1 508, EIC=507.7:508.7 (D:\Chemstation\1\Data\CEM\04-11-2

Diethyl (1*RS*,3a*SR*,6a*SR*)-5-(adamantan-1-yl)methyl)-4,6-dioxo-1-phenyl-1,3a,4,5,6,6a-hexahydropyrrolo[3,4-*c*]pyrrole-1-phosphonate (9i)

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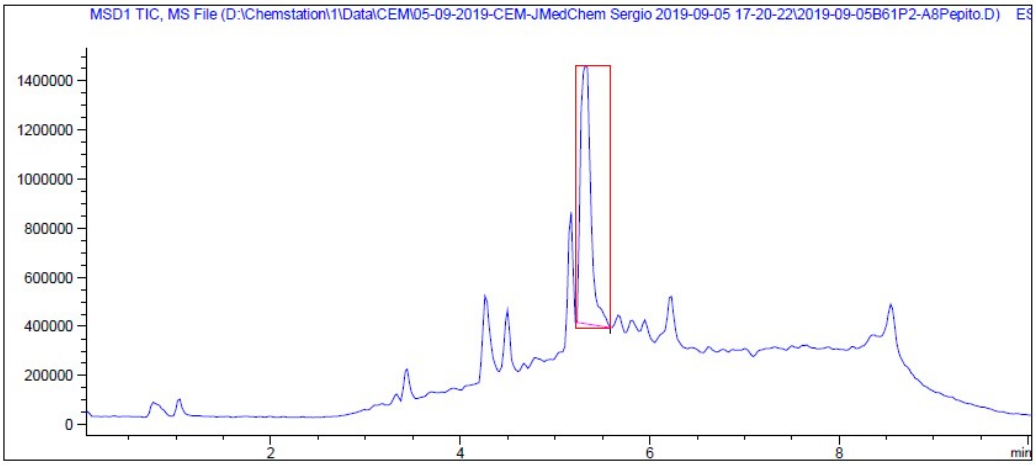
==================================================================
                        Area Percent Report
==================================================================

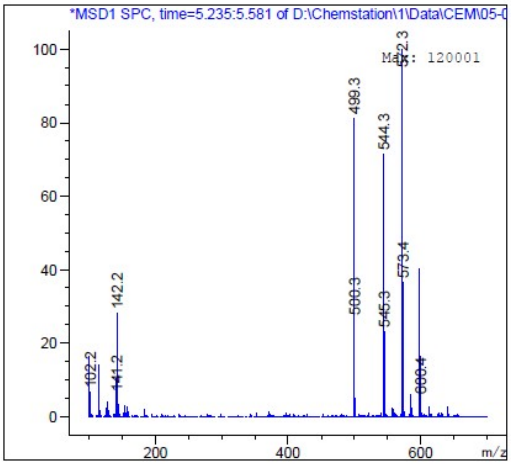
Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Do not use Multiplier & Dilution Factor with ISTDs

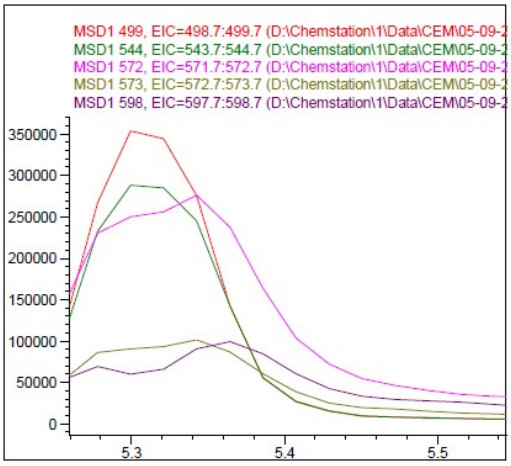

Signal 1: DAD1 A, Sig=254,4 Ref=360,100

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1   5.057 MF    0.0487    5.75976    1.97158   2.1773
   2   5.266 BB    0.0489  258.77179   86.45103  97.8227

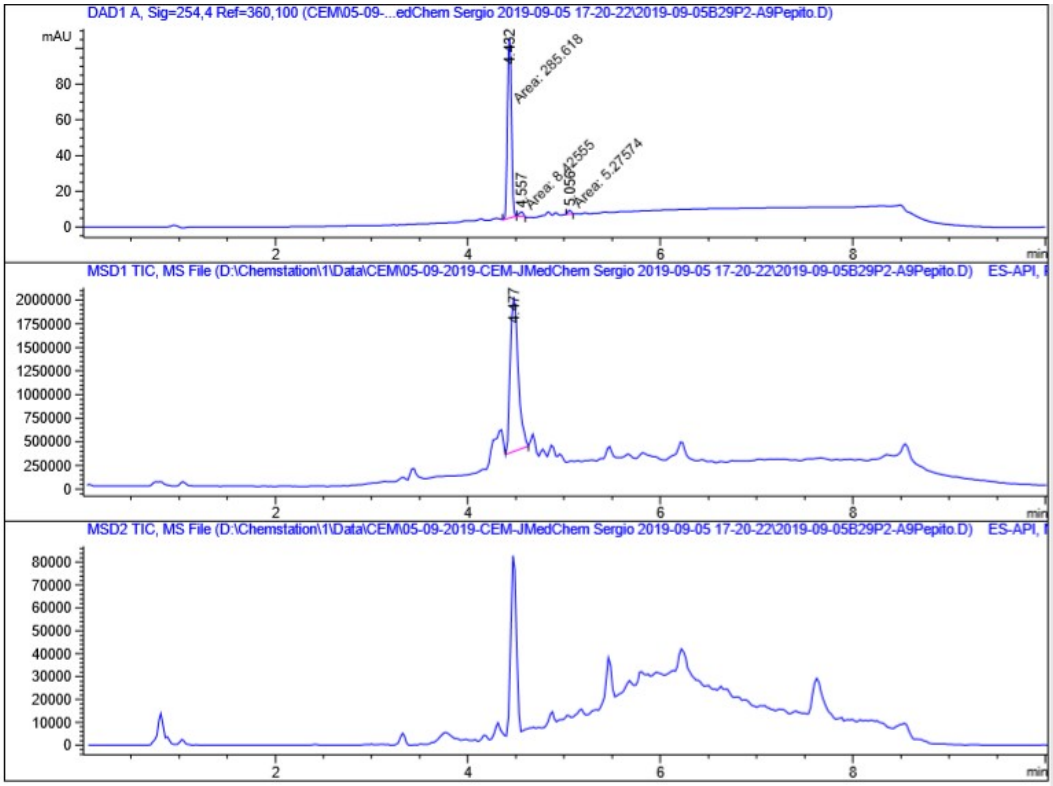
Totals :                   264.53155   88.42261
```


MSD1 TIC, MS File (D:\Chemstation\1\Data\CEM\05-09-2019-CEM-JMedChem Sergio 2019-09-05 17-20-22\2019-09-05B61P2-A8Pepito.D)
1400000
1200000
1000000
800000
600000
400000
200000
0
2
4
6
8
min


*MSD1 SPC, time=5.235:5.581 of D:\Chemstation\1\Data\CEM\05-0
Max: 120001
499.3
544.3
572.3
573.4
500.3
545.3
142.2
102.2
141.2
100
80
60
40
20
0
200
400
600
m/z


MSD1 499, EIC=498.7:499.7 (D:\Chemstation\1\Data\CEM\05-09-2
MSD1 544, EIC=543.7:544.7 (D:\Chemstation\1\Data\CEM\05-09-2
MSD1 572, EIC=571.7:572.7 (D:\Chemstation\1\Data\CEM\05-09-2
MSD1 573, EIC=572.7:573.7 (D:\Chemstation\1\Data\CEM\05-09-2
MSD1 598, EIC=597.7:598.7 (D:\Chemstation\1\Data\CEM\05-09-2
350000
300000
250000
200000
150000
100000
50000
0
5.3
5.4
5.5

Diethyl (1*RS*,3a*SR*,6a*SR*)-5-benzyl-4,6-dioxo-1-phenyl-1,3a,4,5,6,6a-hexahydropyrrolo[3,4-*c*]pyrrole-1-phosphonate (9j)

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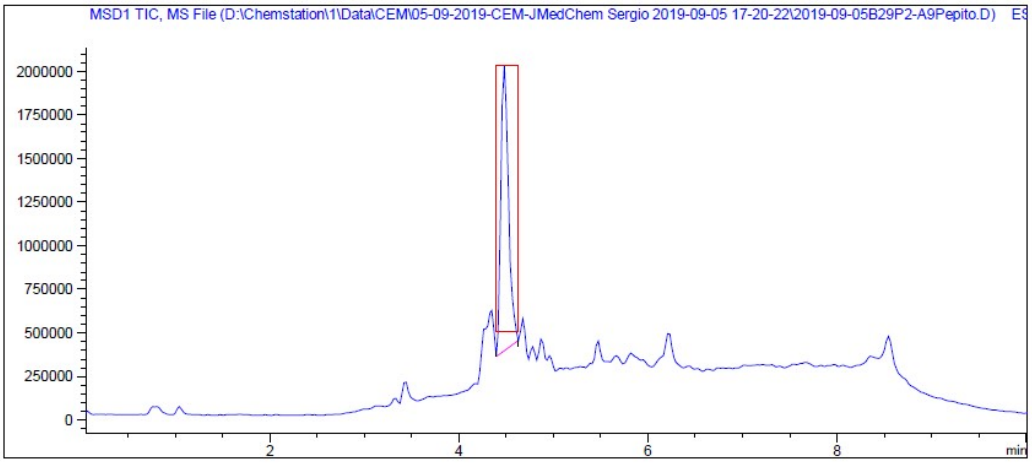
==========================================================================
                              Area Percent Report
==========================================================================

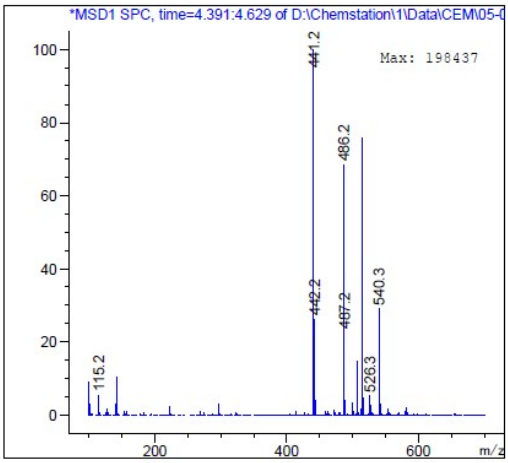
Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Do not use Multiplier & Dilution Factor with ISTDs

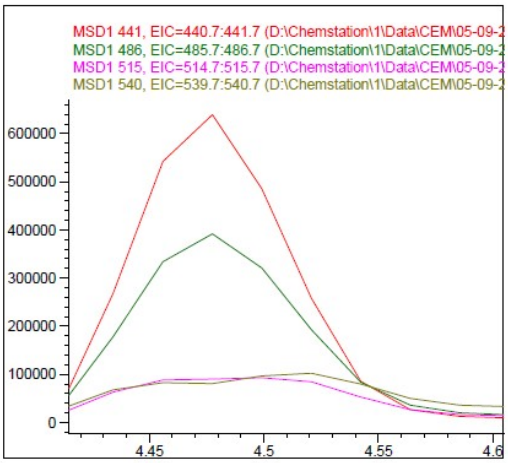
 Signal 1: DAD1 A, Sig=254,4 Ref=360,100

 Peak RetTime Type  Width     Area      Height     Area
   #   [min]        [min]   [mAU*s]     [mAU]       %
 ----|-------|----|-------|----------|----------|--------|
    1   4.432 MM    0.0470  285.61795  101.35640  95.4225
    2   4.557 MM    0.0523    8.42555    2.68248   2.8149
    3   5.056 MM    0.0398    5.27574    2.21116   1.7626

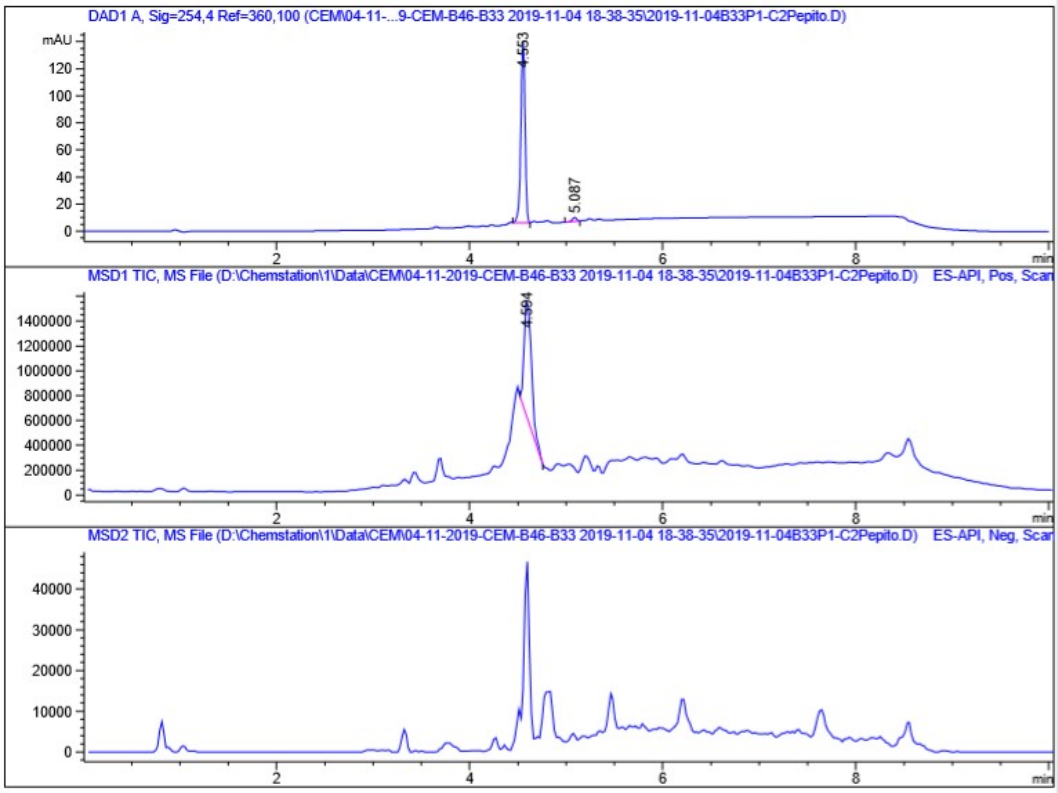
 Totals :                   299.31924  106.25004
```


MSD1 TIC, MS File (D:\Chemstation\1\Data\CEM\05-09-2019-CEM-JMedChem Sergio 2019-09-05 17-20-22\2019-09-05B29P2-A9Pepito.D)
2000000
1750000
1500000
1250000
1000000
750000
500000
250000
0
2
4
6
8
min


*MSD1 SPC, time=4.391:4.629 of D:\Chemstation\1\Data\CEM\05-0
Max: 198437
441.2
486.2
442.2
487.2
540.3
526.3
115.2
100
80
60
40
20
0
200
400
600
m/z


MSD1 441, EIC=440.7:441.7 (D:\Chemstation\1\Data\CEM\05-09-2
MSD1 486, EIC=485.7:486.7 (D:\Chemstation\1\Data\CEM\05-09-2
MSD1 515, EIC=514.7:515.7 (D:\Chemstation\1\Data\CEM\05-09-2
MSD1 540, EIC=539.7:540.7 (D:\Chemstation\1\Data\CEM\05-09-2
600000
500000
400000
300000
200000
100000
0
4.45
4.5
4.55
4.6

Diethyl (1*RS*,3a*SR*,6a*SR*)-4,6-dioxo-5-phenethyl-1-phenyl-1,3a,4,5,6,6a-hexahydropyrrolo[3,4-*c*]pyrrole-1-phosphonate (9k)

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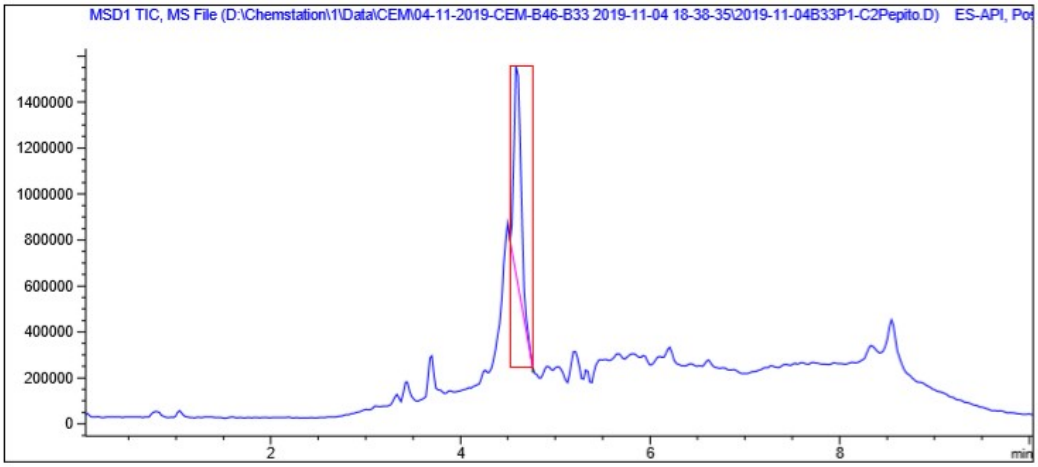
==================================================================
                        Area Percent Report
==================================================================

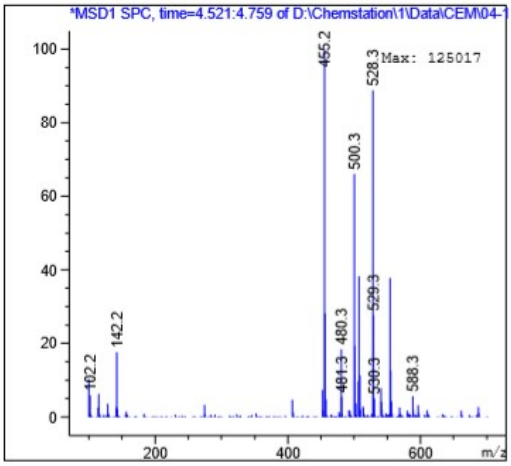
Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Do not use Multiplier & Dilution Factor with ISTDs

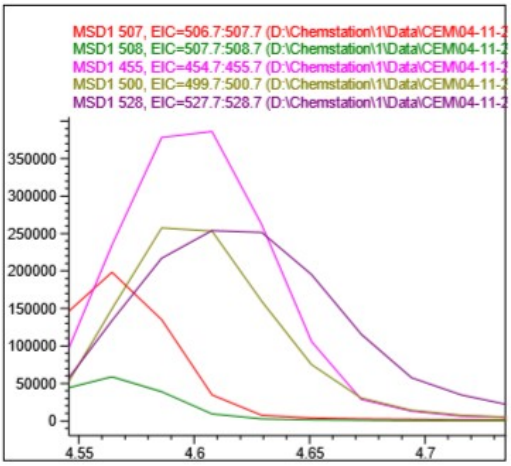

Signal 1: DAD1 A, Sig=254,4 Ref=360,100

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1   4.553 BB    0.0497  410.48108  133.97070  98.0419
   2   5.087 BB    0.0482    8.19819    2.79994   1.9581

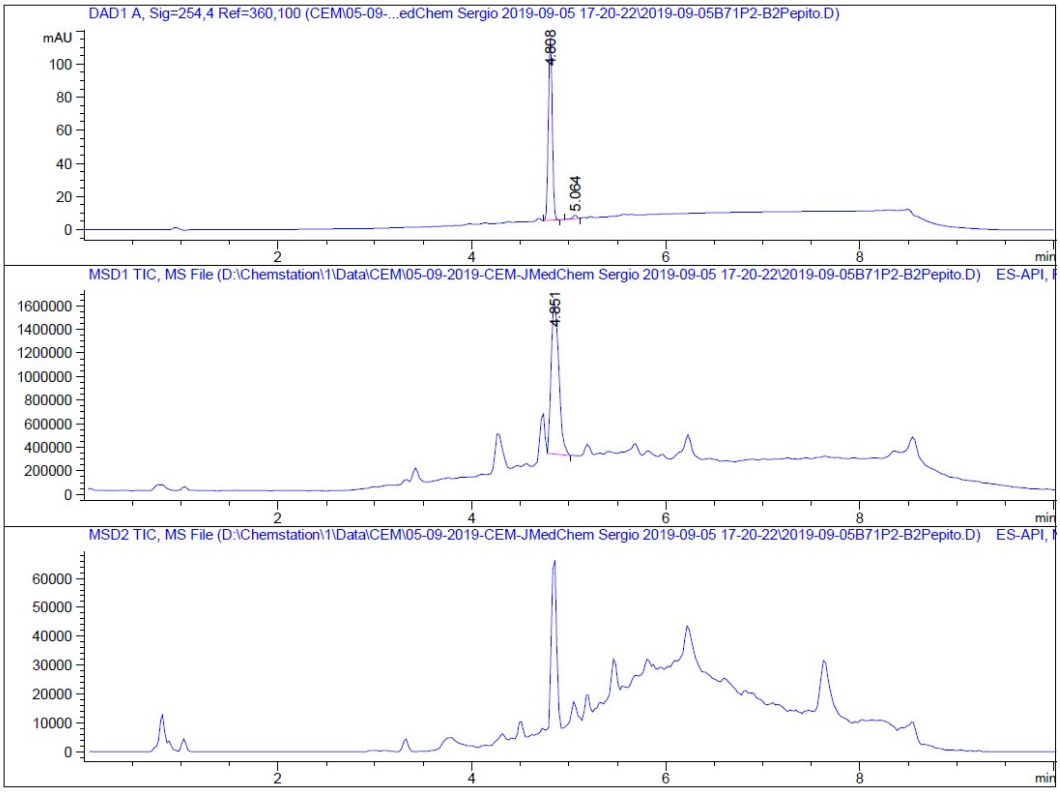
Totals :                   418.67927  136.77065
```


MSD1 TIC, MS File (D:\Chemstation\1\Data\CEM\04-11-2019-CEM-B46-B33 2019-11-04 18-38-35\2019-11-04B33P1-C2Pepito.D) ES-API, Pos
1400000
1200000
1000000
800000
600000
400000
200000
0
2
4
6
8
min


*MSD1 SPC, time=4.521:4.759 of D:\Chemstation\1\Data\CEM\04-1
Max: 125017
455.2
528.3
500.3
529.3
142.2
102.2
480.3
481.3
530.3
588.3
100
80
60
40
20
0
200
400
600
m/z


MSD1 507, EIC=506.7:507.7 (D:\Chemstation\1\Data\CEM\04-11-2
MSD1 508, EIC=507.7:508.7 (D:\Chemstation\1\Data\CEM\04-11-2
MSD1 455, EIC=454.7:455.7 (D:\Chemstation\1\Data\CEM\04-11-2
MSD1 500, EIC=499.7:500.7 (D:\Chemstation\1\Data\CEM\04-11-2
MSD1 528, EIC=527.7:528.7 (D:\Chemstation\1\Data\CEM\04-11-2
350000
300000
250000
200000
150000
100000
50000
0
4.55
4.6
4.65
4.7

Diethyl (1*RS*,3a*SR*,6a*SR*)-4,6-dioxo-1-phenyl-5-(2,4,6-trichlorophenyl)-1,3a,4,5,6,6a-hexahydropyrrolo[3,4-*c*]pyrrole-1-phosphonate (9w)



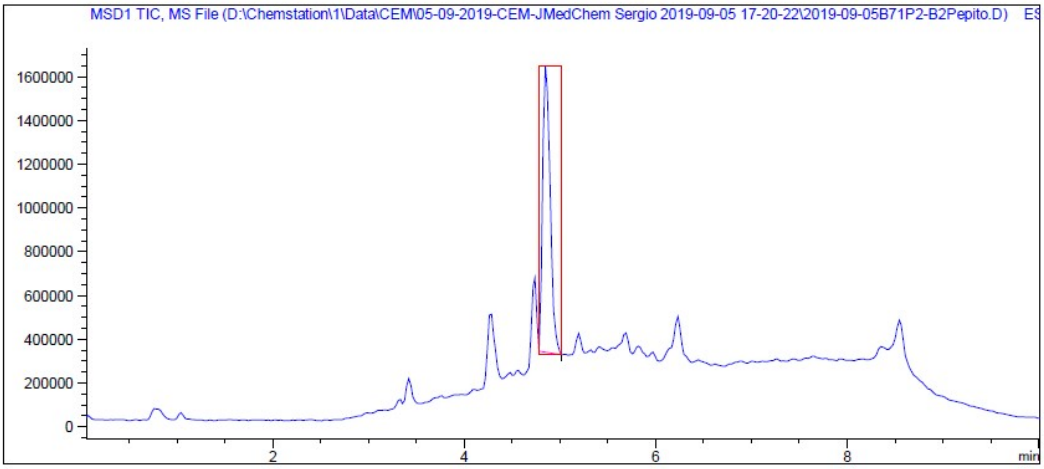

```
=====================================================================
                        Area Percent Report
=====================================================================

Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Do not use Multiplier & Dilution Factor with ISTDs


Signal 1: DAD1 A, Sig=254,4 Ref=360,100

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1   4.808 BB    0.0453  314.69922  110.17357  97.9988
   2   5.064 BB    0.0477    6.42630    2.10232   2.0012

Totals :                   321.12552  112.27588
```


MSD1 TIC, MS File (D:\Chemstation\1\Data\CEM\05-09-2019-CEM-JMedChem Sergio 2019-09-05 17-20-22\2019-09-05B71P2-B2Pepito.D)
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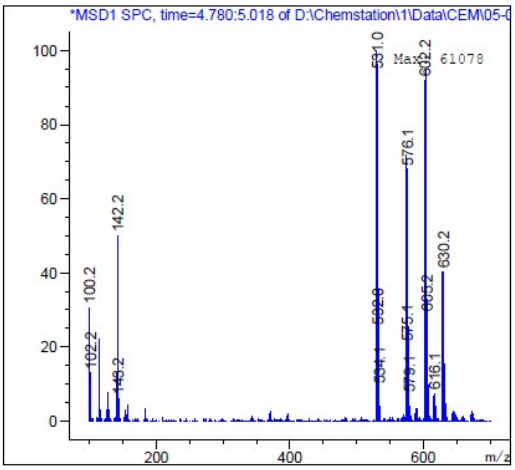
1400000
1200000
1000000
800000
600000
400000
200000
0
2
4
6
8


*MSD1 SPC, time=4.780:5.018 of D:\Chemstation\1\Data\CEM\05-0
Max: 61078
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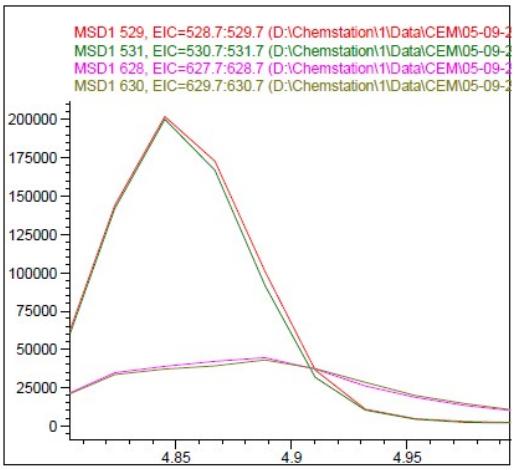
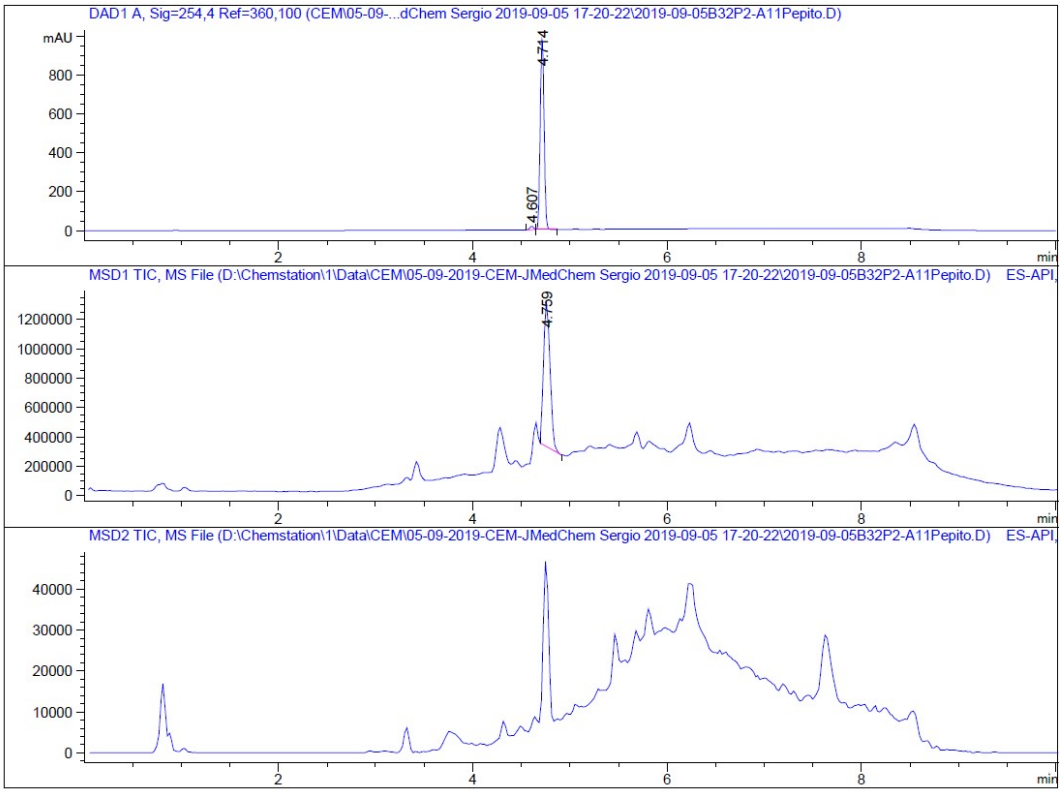
602.2
576.1
142.2
630.2
100.2
102.2
148.2
592.9
605.2
575.1
579.1
616.1
554.1
100
80
60
40
20
0
200
400
600
m/z


MSD1 529, EIC=528.7:529.7 (D:\Chemstation\1\Data\CEM\05-09-2
MSD1 531, EIC=530.7:531.7 (D:\Chemstation\1\Data\CEM\05-09-2
MSD1 628, EIC=627.7:628.7 (D:\Chemstation\1\Data\CEM\05-09-2
MSD1 630, EIC=629.7:630.7 (D:\Chemstation\1\Data\CEM\05-09-2
200000
175000
150000
125000
100000
75000
50000
25000
0
4.85
4.9
4.95

Diethyl (1*RS*,3a*SR*,6a*SR*)-5-(1,1'-biphenyl)-4-yl-4,6-dioxo-1-phenyl-1,3a,4,5,6,6a-hexahydropyrrolo[3,4-c]pyrrole-1-phosphonate (9z)




```
=====================================================================
                          Area Percent Report
=====================================================================

Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Do not use Multiplier & Dilution Factor with ISTDs


Signal 1: DAD1 A, Sig=254,4 Ref=360,100

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1   4.607 BB    0.0432   43.25058   16.18649   1.5320
   2   4.714 BB    0.0449 2779.87134  985.41620  98.4680

Totals :                  2823.12191 1001.60269
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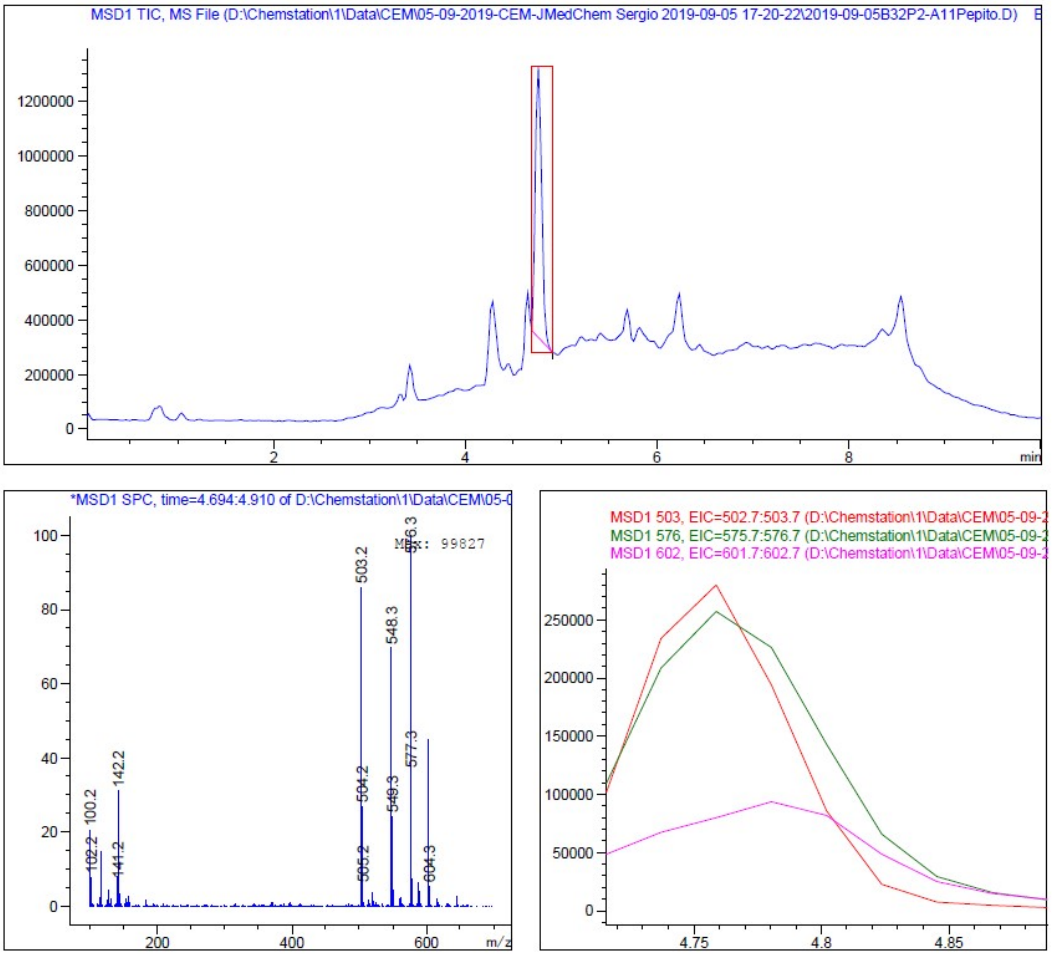
MSD1 TIC, MS File (D:\Chemstation\1\Data\CEM\05-09-2019-CEM-JMedChem Sergio 2019-09-05 17-20-22\2019-09-05B32P2-A11Pepito.D)
min
*MSD1 SPC, time=4.694:4.910 of D:\Chemstation\1\Data\CEM\05-0
Max: 99827
503.2
548.3
576.3
577.3
142.2
100.2
504.2
549.3
604.3
m/z
MSD1 503, EIC=502.7:503.7 (D:\Chemstation\1\Data\CEM\05-09-2
MSD1 576, EIC=575.7:576.7 (D:\Chemstation\1\Data\CEM\05-09-2
MSD1 602, EIC=601.7:602.7 (D:\Chemstation\1\Data\CEM\05-09-2

References

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Compound	SMILE	I_2-IR Binding Affinities (pKi)	α_2-AR Binding Affinities (pKi)	Selectivity (I_2/α_2)
9a	O=C(N1C)[C@@H]2C=N[C@](P(OCC)(OCC)=O)(C3=CC=CC=C3)[C@@H]2C1=O	7.97	5.93	110
9b	O=C1N(C2CCCCC2)C(C3C(P(OCC)(OCC)=O)(C4=CC=CC=C4)N=CC31)=O	9.74	9.01	5
9c	O=C(C1C(P(OCC)(OCC)=O)(C2=CC=CC=C2)N=CC13)N(C4=CC=CC=C4)C3=O	10.28	10.38	1
9d	O=C(C1C(P(OCC)(OCC)=O)(C2=CC=CC=C2)N=CC13)N(C4=CC=C(F)C(Cl)=C4)C3=O	8,56	6,27	195
9e	O=C(N1C2=CC=C(OC)C=C2)[C@@H]3C=N[C@](P(OCC)(OCC)=O)(C4=CC=CC=C4)[C@@H]3C1=O	6,65	4,59	115
14c	O=C1N(C2=CC=CC=C2)C([C@@H]3[C@H]1C=N[C@@]3(CC4=CC=CC=C4)P(OCC)(OCC)=O)=O	5,51	---	---
15c	O=C(N1C2=CC=CC=C2)[C@H]3[C@H]([C@@](P(OCC)(OCC)=O)(CC4=CC=C(F)C=C4)N=C3)C1=O	<3	7,69	---
12c	O=C([C@H]1[C@@](P(OCC)(OCC)=O)(C2=CC=C(F)C=C2)N=C[C@H]13)N(C4=CC=CC=C4)C3=O	<3	6,77	---
13c	O=C([C@H]1[C@@](P(OCC)(OCC)=O)(C2=CC=C(OC)C=C2)N=C[C@H]13)N(C4=CC=CC=C4)C3=O	3,39	3,85	---
12d	O=C([C@H]1[C@@](P(OCC)(OCC)=O)(C2=CC=C(F)C=C2)N=C[C@H]13)N(C4=CC(Cl)=C(F)C=C4)C3=O	7,55	3,38	14791
13d	O=C([C@H]1[C@@](P(OCC)(OCC)=O)(C2=CC=C(OC)C=C2)N=C[C@H]13)N(C4=CC(Cl)=C(F)C=C4)C3=O	7.87	<3	74131
9f	O=C([C@@H]1[C@H]2C=N[C@]1(P(OCC)(OCC)=O)C3=CC=CC=C3)N(C2=O)CC	8.37	5.85	331
9g	O=C([C@@H]1[C@H]2C=N[C@@]1(C3=CC=CC=C3)P(OCC)(OCC)=O)N(C2=O)CCC	4,02	---	---
9h	O=C([C@@H]1[C@H]2C=N[C@]1(P(OCC)(OCC)=O)C3=CC=CC=C3)N(C2=O)C(C)(C)C	7.25	6.77	3
9i	O=C([C@@H]([C@](C1=CC=CC=C1)(P(OCC)(OCC)=O)N=C2)[C@@H]2C3=O)N3CC4(C5)C[C@@H](CC5C6)C[C@@H]6C4	7.01	4,31	401
9i	O=C([C@@H]([C@](C1=CC=CC=C1)(P(OCC)(OCC)=O)N=C2)[C@@H]2C3=O)N3CC4(C5)C[C@@H](CC5C6)C[C@@H]6C4	7.01	4,31	401
9j	O=C(N1CC2=CC=CC=C2)[C@@H]3C=N[C@@](C4=CC=CC=C4)(P(OCC)(OCC)=O)[C@@H]3C1=O	5.26	8.11	---
9k	O=C1N(C([C@@H]2[C@H]1C=N[C@]2(P(OCC)(OCC)=O)C3=CC=CC=C3)=O)CCC4=CC=CC=C4	5.85	3.59	182

9l	O=C1N(C([C@@H]2[C@H]1C=N[C@]2(P(OCC)(OCC)=O)C3=CC=CC=C3)=O)CCC4=CC=C(F)C=C4	<3	5,65	---
9m	O=C([C@@H]1[C@H]2C=N[C@]1(P(OCC)(OCC)=O)C3=CC=CC=C3)N(C4CC5=CC=CC=C5C4)C2=O	3.84	3.442	2
9n	O=C1N(C([C@@H]2[C@H]1C=N[C@]2(P(OCC)(OCC)=O)C3=CC=CC=C3)=O)C4=CC=C(C(F)(F)F)C=C4	<3	4.73	---
9o	O=C([C@@H]1[C@H]2C=N[C@]1(P(OCC)(OCC)=O)C3=CC=CC=C3)N(C2=O)C4=CC(C(F)(F)F)=CC=C4	<3	---	---
9p	O=C1N(C([C@@H]2[C@H]1C=N[C@]2(P(OCC)(OCC)=O)C3=CC=CC=C3)=O)C4=CC=C(F)C=C4	<3	5.34	---
9q	O=C([C@@H]1[C@H]2C=N[C@@]1(C3=CC=CC=C3)P(OCC)(OCC)=O)N(C2=O)C4=CC=C(Cl)C=C4	<3	---	---
9r	O=C([C@@H]([C@](C1=CC=CC=C1)(P(OCC)(OCC)=O)N=C2)[C@@H]2C3=O)N3C4=C(Cl)C=CC=C4	5.09	6.15	---
9s	O=C([C@@H]1[C@H]2C=N[C@]1(P(OCC)(OCC)=O)C3=CC=CC=C3)N(C2=O)C4=CC(Cl)=CC=C4	<3	---	---
9t	O=C1N(C2=CC=C(Br)C=C2)C([C@@H]3[C@H]1C=N[C@@]3(C4=CC=CC=C4)P(OCC)(OCC)=O)=O	<3	---	---
9u	O=C([C@@H]([C@](C1=CC=CC=C1)(P(OCC)(OCC)=O)N=C2)[C@@H]2C3=O)N3C4=CC(Cl)=CC(Cl)=C4	5,81	6,22	---
9b	O=C1N(C([C@@H]2[C@H]1C=N[C@]2(P(OCC)(OCC)=O)C3=CC=CC=C3)=O)C4=CC(Cl)=C(Cl)C=C4	<3	---	---
9w	O=C([C@@H]([C@](C1=CC=CC=C1)(P(OCC)(OCC)=O)N=C2)[C@@H]2C3=O)N3C4=C(Cl)C=C(Cl)C=C4Cl	<3	5,16	---
9x	O=C(N1C2=CC([N+]([O-])=O)=CC=C2)[C@@H]3C=N[C@](P(OCC)(OCC)=O)(C4=CC=CC=C4)[C@@H]3C1=O	6,81	10,18	---
9y	O=C([C@@H]1[C@H]2C=N[C@@]1(C3=CC=CC=C3)P(OCC)(OCC)=O)N(C2=O)C4=CC([N+]([O-])=O)=CC=C4C	<3	---	---
9z	O=C(N1C2=CC=C(C3=CC=CC=C3)C=C2)[C@@H]4C=N[C@](P(OCC)(OCC)=O)(C5=CC=CC=C5)[C@@H]4C1=O	7,90	5,12	602
9aa	O=C1N(C([C@@H]2[C@H]1C=N[C@]2(P(OCC)(OCC)=O)C3=CC=CC=C3)=O)C4=CC=C(C)C=C4	5,44	---	---
9ab	O=C1N(C2=CC=C(OC3=CC=CC=C3)C=C2)C([C@@H]4[C@H]1C=N[C@]4(P(OCC)(OCC)=O)C5=CC=CC=C5)=O	6,96	5,34	34
9ac	O=C([C@@H]1[C@H]2C=N[C@]1(P(OCC)(OCC)=O)C3=CC=CC=C3)N(C2=O)C4=C(C=CC=C5)C5=CC=C4	3,11	<3	---
9ad	O=C([C@@H]([C@](C1=CC=CC=C1)(P(OCC)(OCC)=O)N=C2)[C@@H]2C3=O)N3C4=C(Cl)N=CC=C4	7,96	<3	91201
16	O=C(N1C2=CC=CC=C2)[C@@H]3C=N[C@](P(OC4=CC=CC=C4)(OC5=CC=CC=C5)=O)(C6=CC=CC=C6)[C@@H]3C1=O	5,86	11,64	---