SUPPORTING INFORMATION

Discovery of Lipophilic Bisphosphonates that Target Bacterial Cell Wall and Quinone Biosynthesis

Satish R. Malwal[1,*], Lu Chen[2,], Hunter Hicks[1,], Fiona Qu[1], Weidong Liu[3,4], Alli Shillo[1] Wen Xuan Law[1], Jianan Zhang[5], Neal Chandnani[1], Xu Han[3], Yingying Zheng[3], Chun-Chi Chen[4], Rey-Ting Guo[3,4], Ahmed AbdelKhalek[6], Mohamed N. Seleem[6,7], and Eric Oldfield[1,*]

[1]Department of Chemistry, University of Illinois at Urbana-Champaign, Urbana, IL 61801, USA

[2]Department of Biochemistry, University of Illinois at Urbana-Champaign, Urbana, IL 61801, USA

[3]Industrial Enzymes National Engineering Laboratory, Tianjin Institute of Industrial Biotechnology, Chinese Academy of Sciences, Tianjin 200208, China

[4]State Key Laboratory of Biocatalysis and Enzyme Engineering, Hubei Collaborative Innovation Center for Green Transformation of Bio-resources, Hubei Engineering Research Center for Bio-enzyme Catalysis, Hubei Key Laboratory of Industrial Biotechnology, School of Life Sciences, Hubei University, Wuhan 430062, China

[5]School of Molecular and Cellular Biology, University of Illinois at Urbana-Champaign, Urbana, IL 61801 (USA)

[6]Department of Comparative Pathobiology, College of Veterinary Medicine, Purdue University, West Lafayette, IN 47907, USA

[7]Purdue Institute of Inflammation, Immunology, and Infectious Disease, West Lafayette, IN 47907, USA

Table of Contents

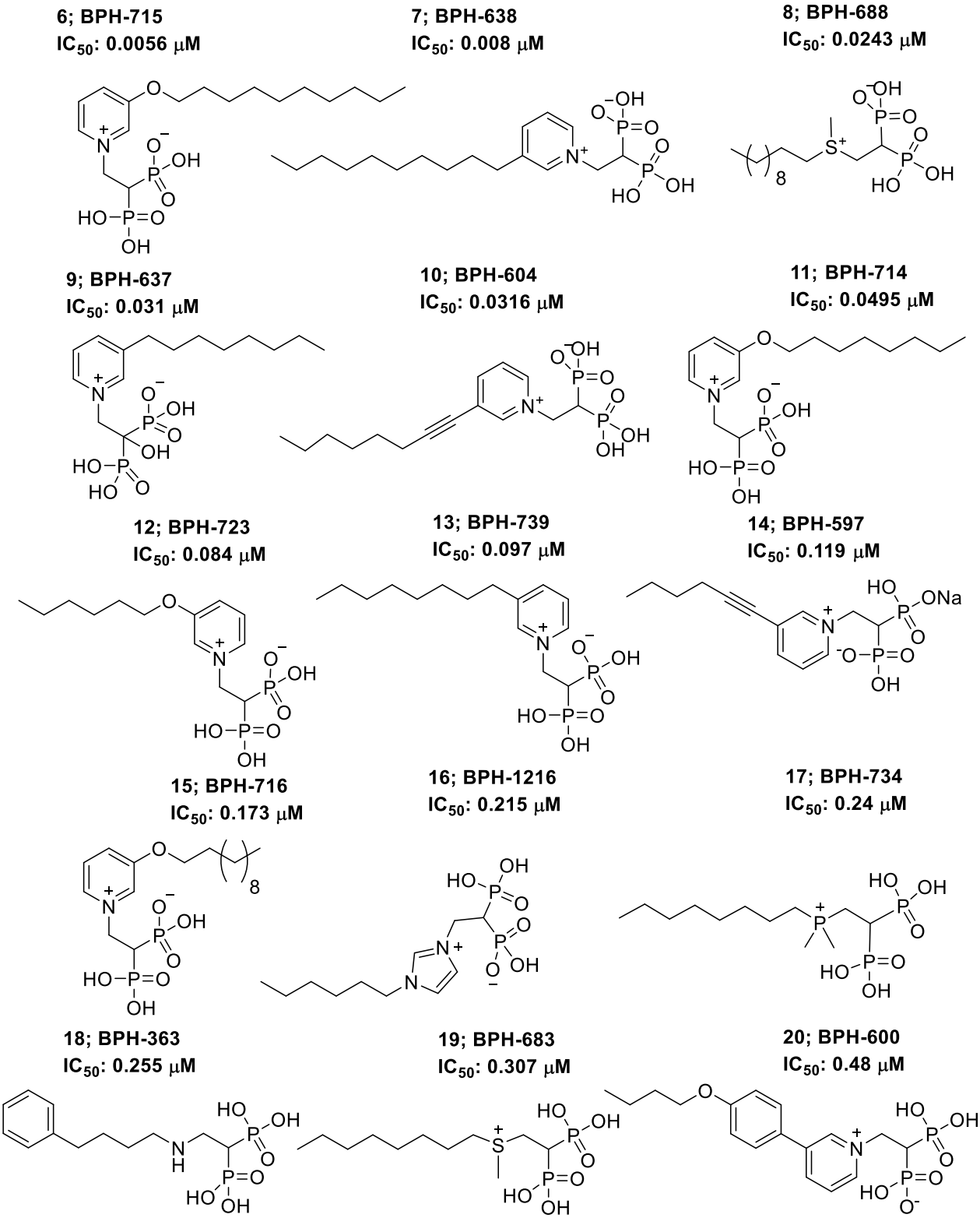


Figure S1. Inhibition of EcOPPS by 62 compounds (**6**-**67**).

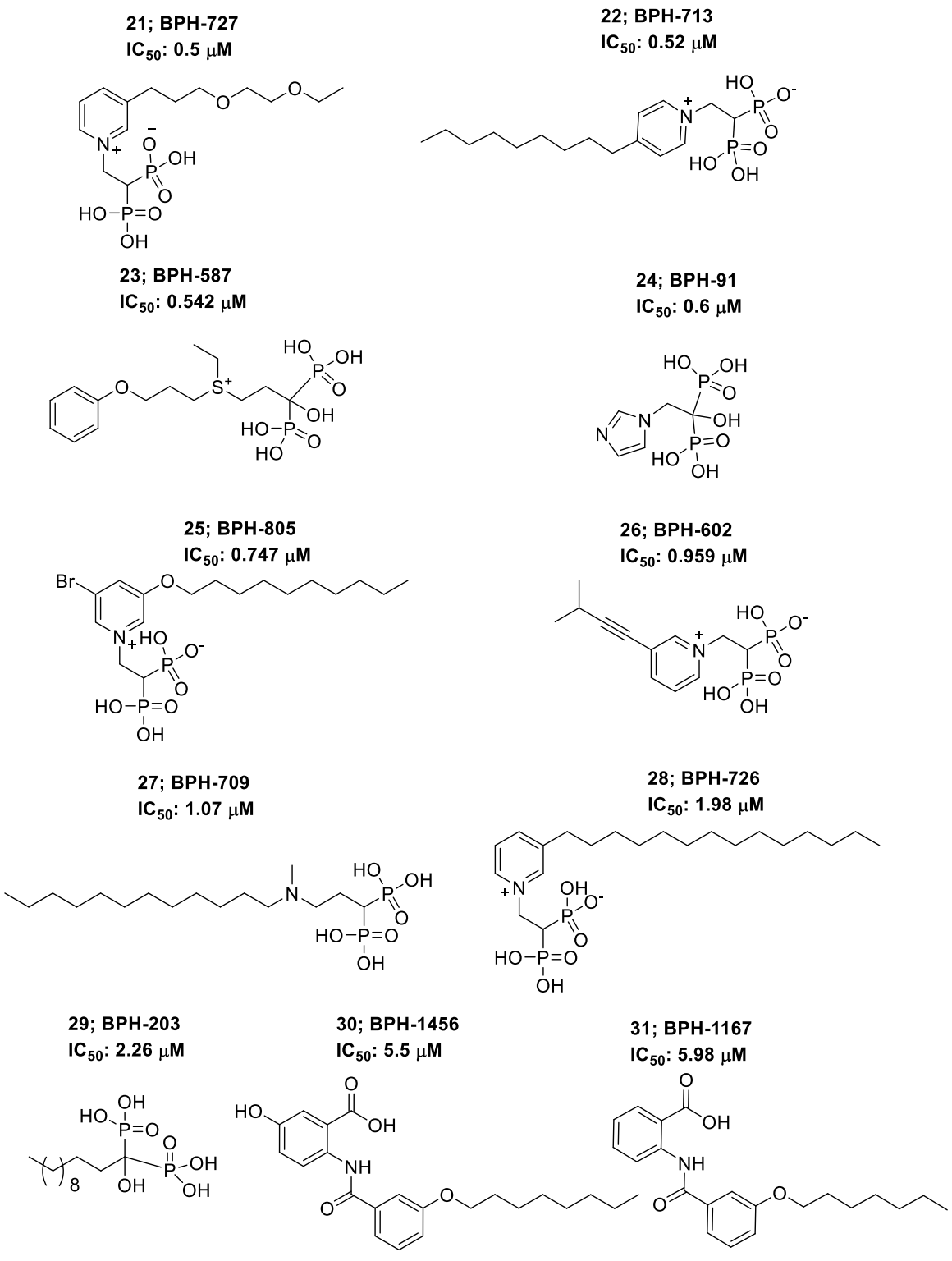


Figure S1. Inhibition of EcOPPS by 62 compounds, continued.

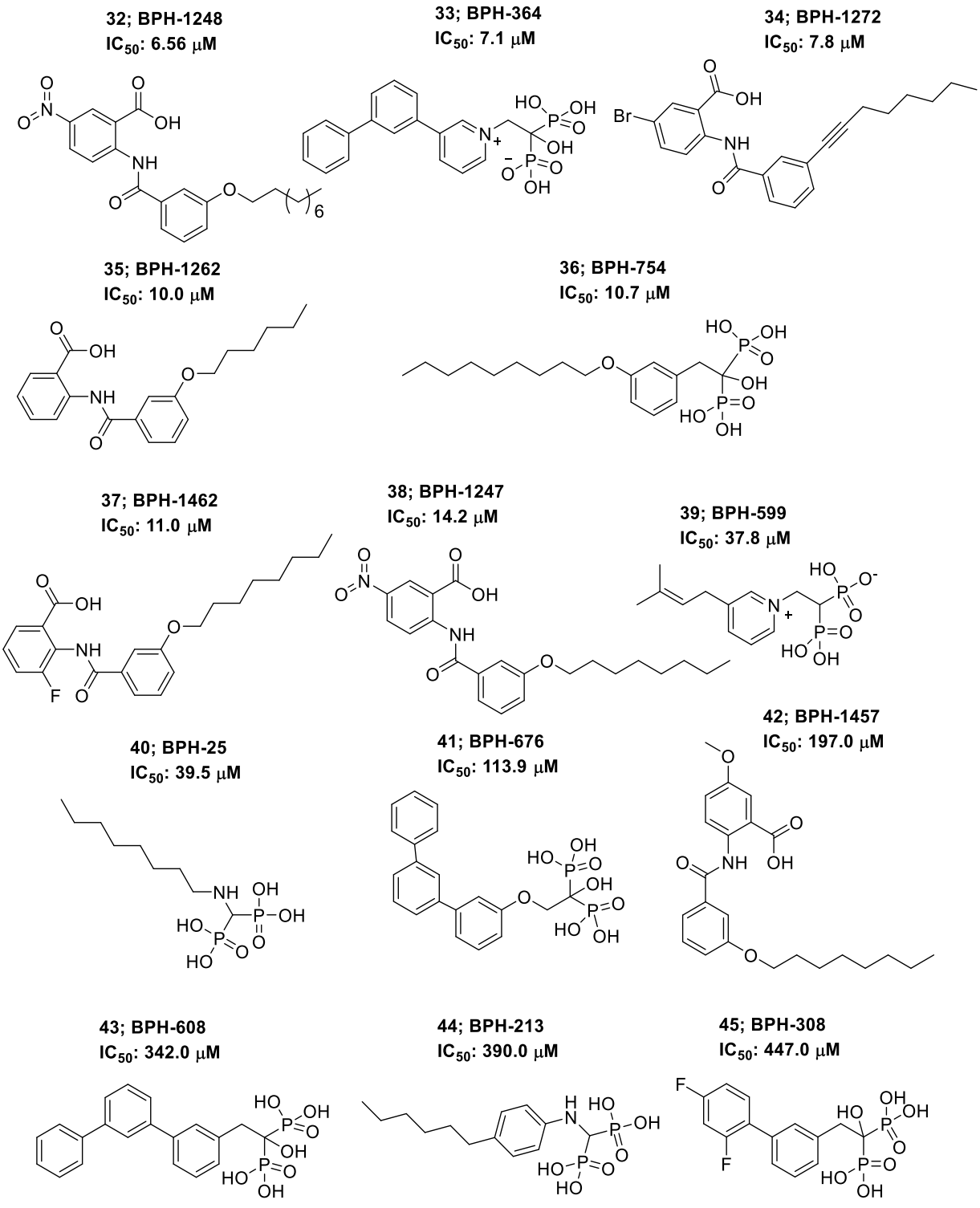
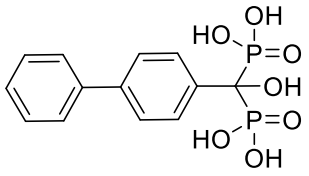
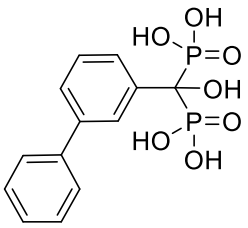


Figure S1. Inhibition of EcOPPS by 62 compounds, continued.

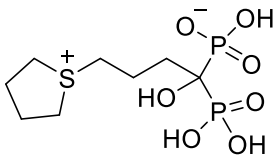
46; BPH-307
IC_{50}: 1000.0 μM



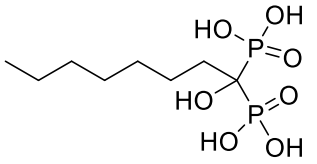
47; BPH-306
IC_{50}: 1000.0 μM



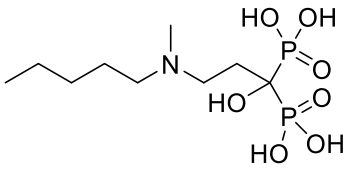
48; BPH-550
IC_{50}: 1000.0 μM



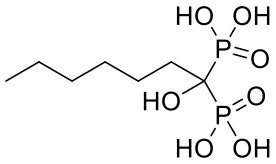
49; BPH-29
IC_{50}: 1000.0 μM



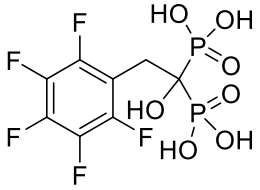
50; BPH-24
IC_{50}: 1000.0 μM



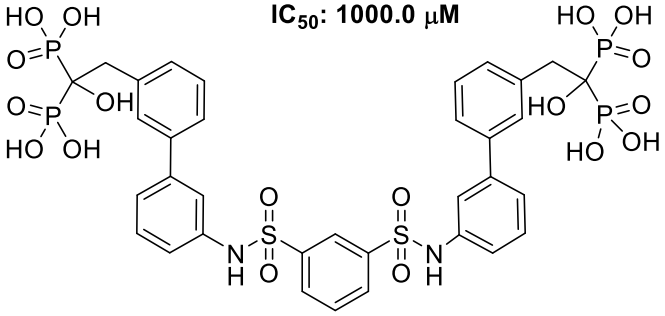
51; BPH-28
IC_{50}: 1000.0 μM



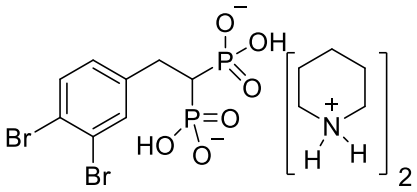
52; BPH-568
IC_{50}: 1000.0 μM



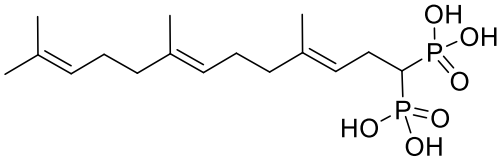
53; BPH-789
IC_{50}: 1000.0 μM



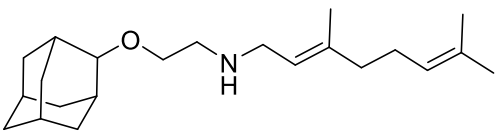
54; BPH-738
IC_{50}: 1000.0 μM



55; BPH-850
IC_{50}: 1000.0 μM



56; BPH-1283
IC_{50}: 1000.0 μM



57; BPH-1249
IC_{50}: 1000.0 μM

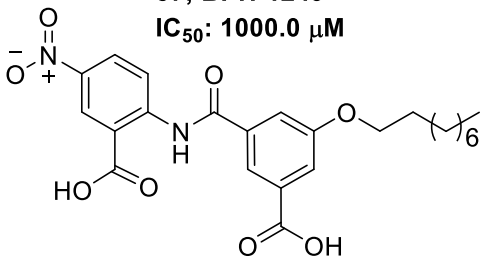


Figure S1. Inhibition of EcOPPS by 62 compounds, continued.

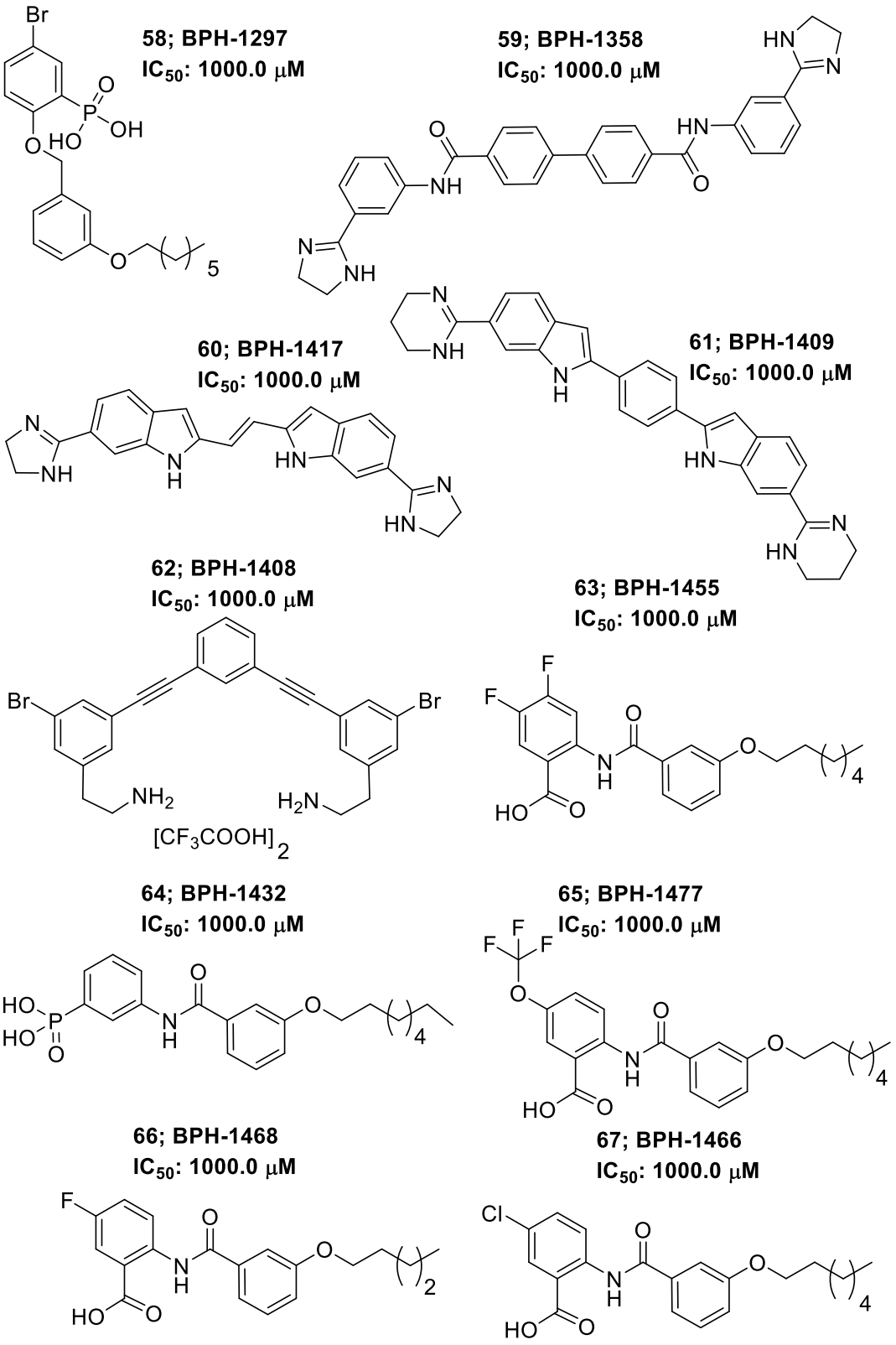


Figure S1. Inhibition of EcOPPS by 62 compounds, continued.

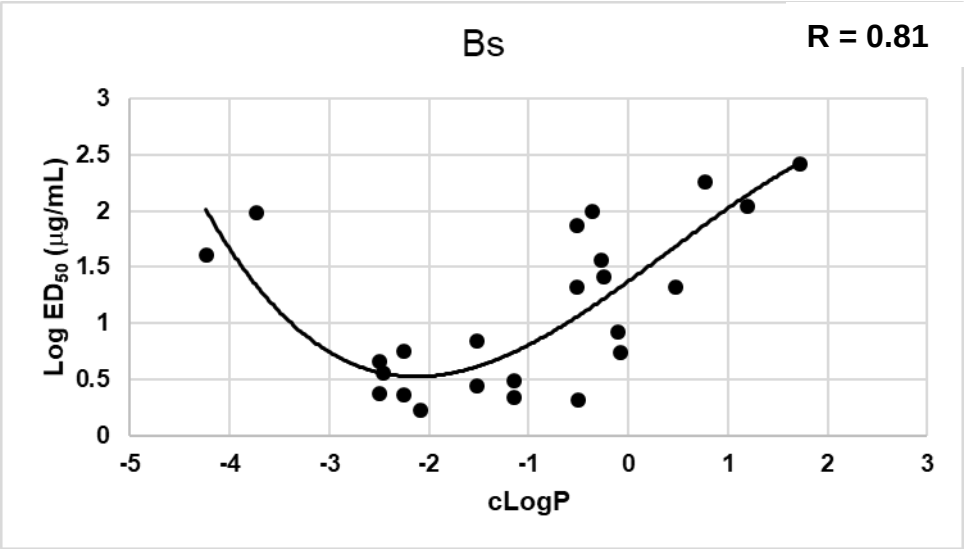


Figure S2. Graph showing correlation (R = 0.81) between *B. subtilis* cell growth inhibition (as log ED_{50} [μg/mL]) and compound clogP.

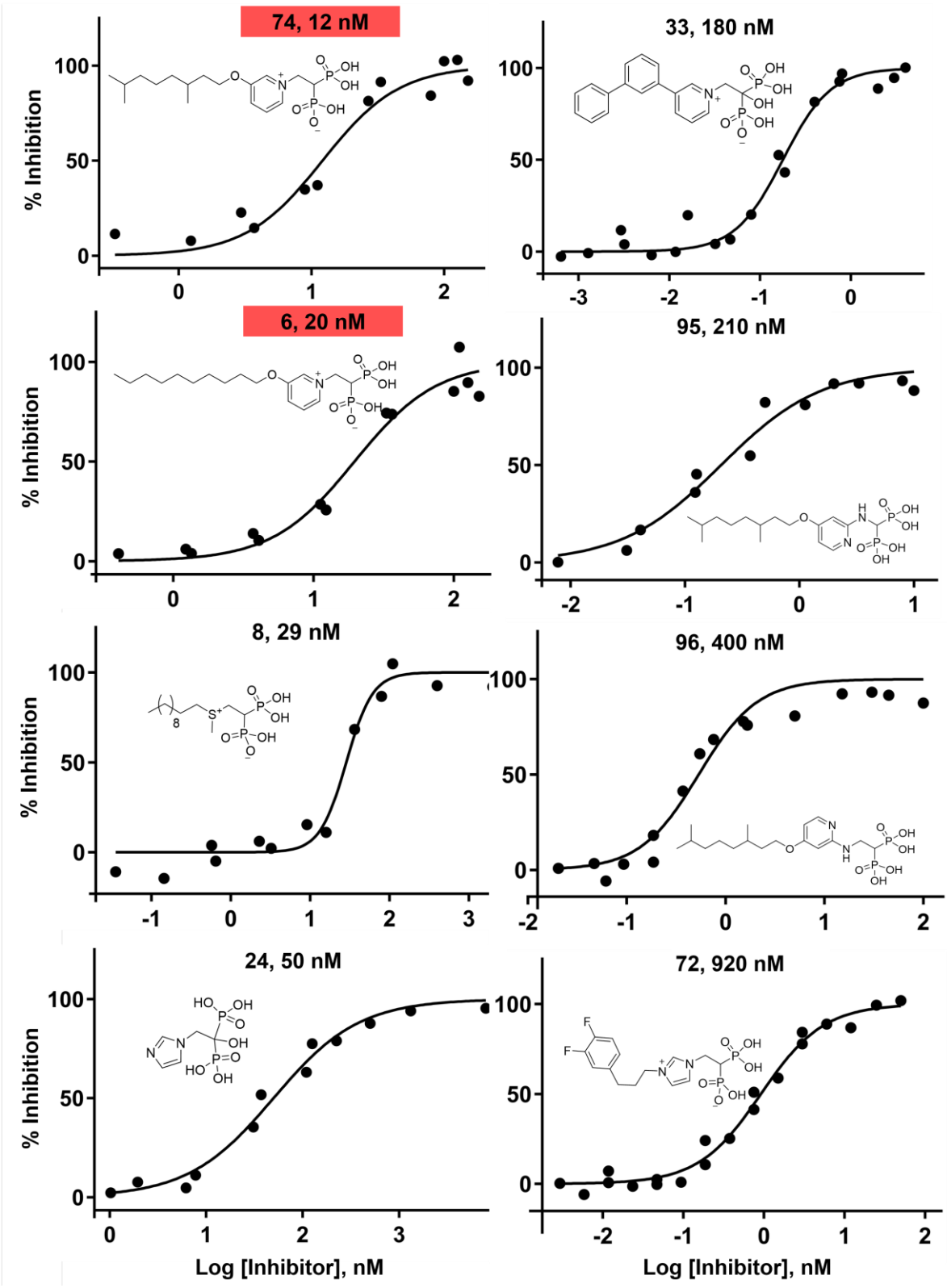


Figure S3. Typical dose-response graphs for EcOPPS, inhibition by six bisphosphonates. Three data sets were collected on different days and the pooled results were fitted to a dose-response curve.

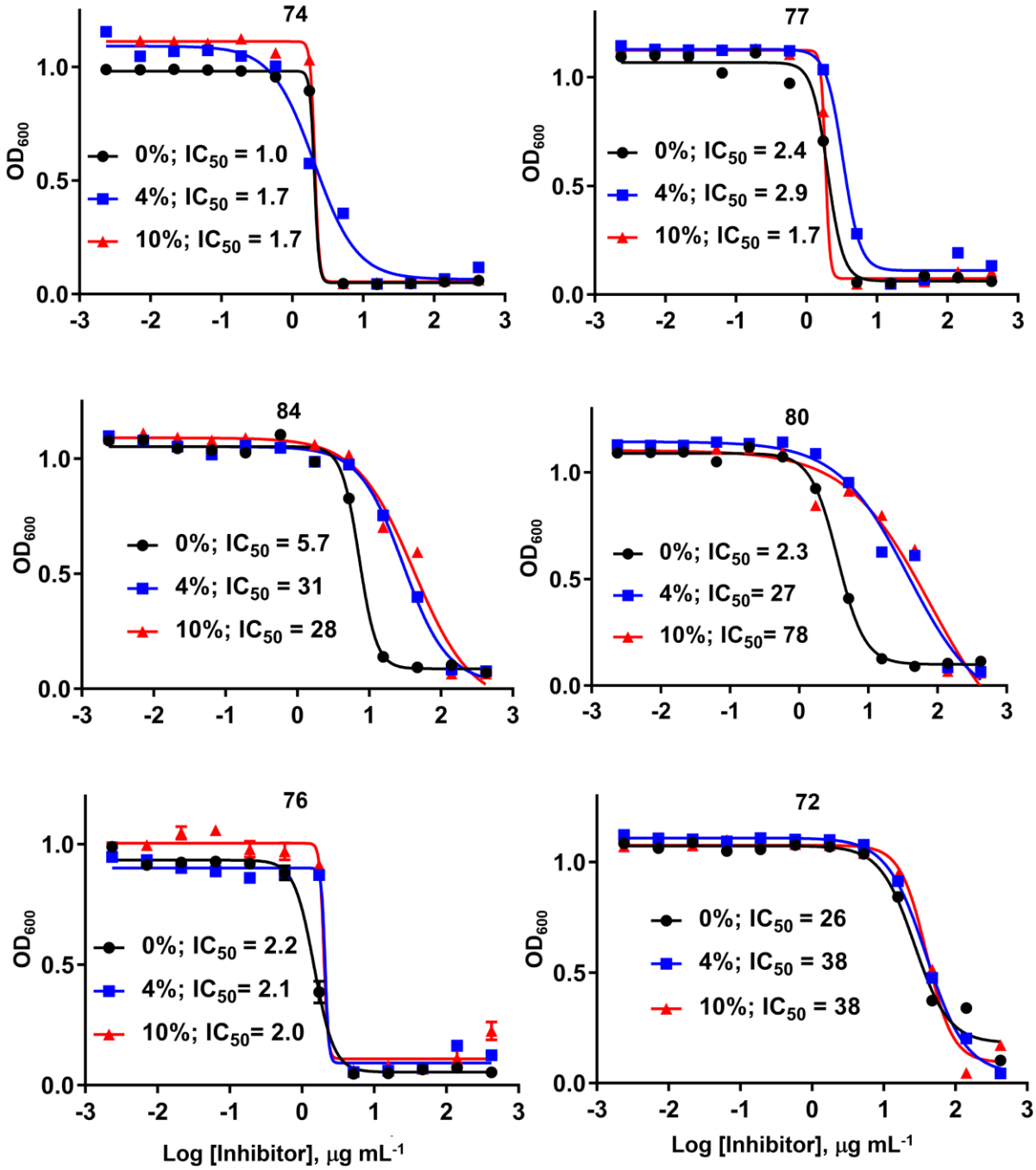


Figure S4. Effects of bovine serum albumin binding on *B. subtilis* cell growth inhibition (at 0, 4, and 10% serum). Results are shown as duplicates.

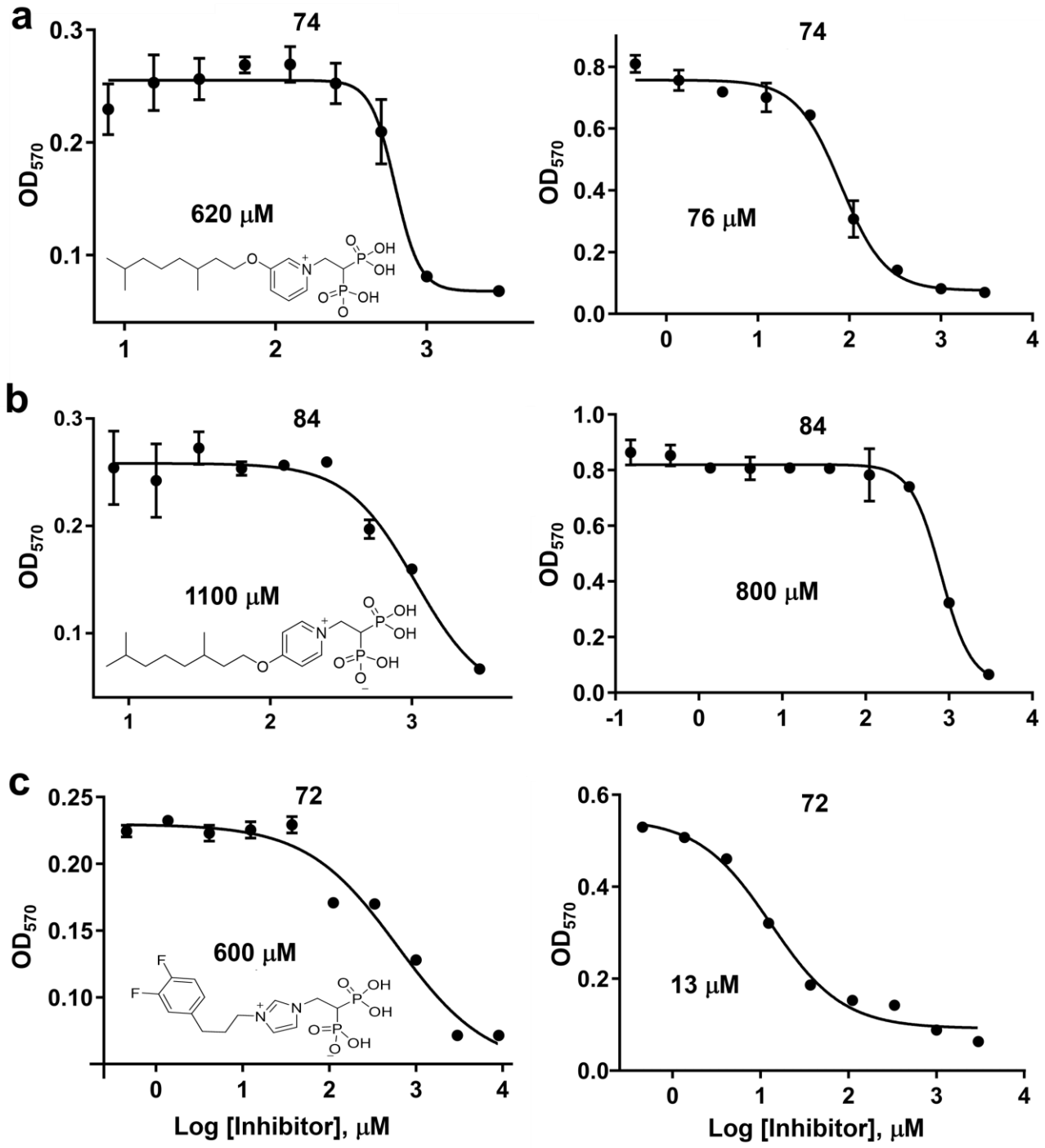
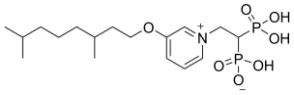
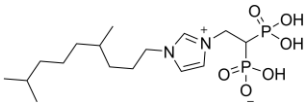
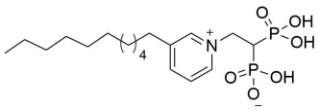
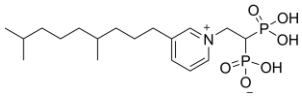
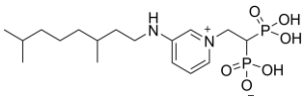
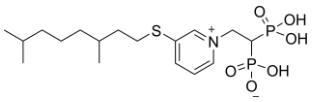


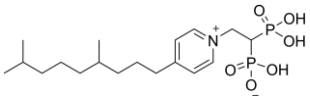
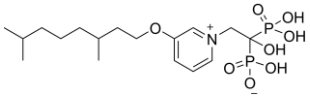
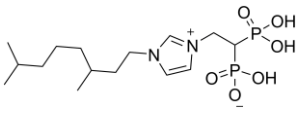
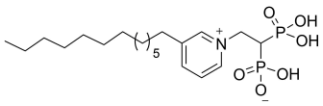
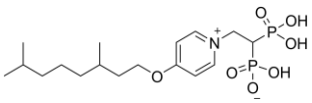
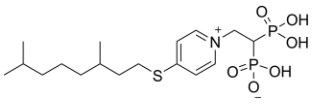
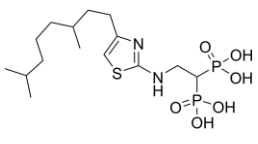
Figure S5. Effects of three bisphosphonates discussed in the Text on human embryonic kidney (HEK293) cell growth after 24 or 96 hours incubation. a) Compound **74** at 24 hrs (left) and 96 hours (right). b) As a) but for **84**. c) As a) but for **72**. Data were obtained in duplicate experiments.

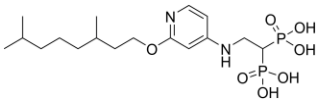
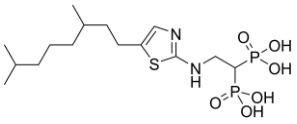
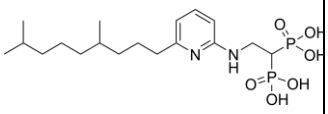
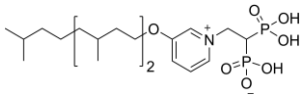
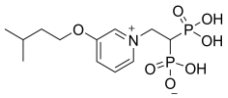
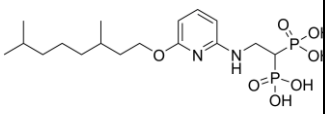
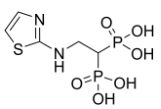
Table S1. Effects of compounds on bacterial and *C. albicans* cell growth.

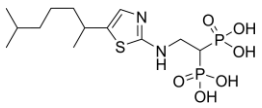
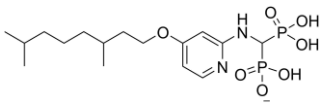
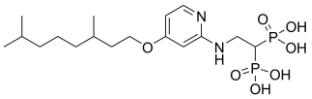
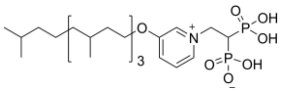
EC_{50} (μg/mL)	Sa	Bs	Ba	Ms	Ca	Ec	Ab	Kp	Pa
6	10 ± 0.68	0.89 ± 0.10	2.3 ± 0.55	6.8 ± 1.7	8.0 ± 0.06	>21	>28	>28	>28
33	16 ± 4.1	7.4 ± 1.0	4.4 ± 2.2	>29	>65	>22	>29	>29	>29
68	56 ± 38	48 ± 18	>56	>29	>65	>22	>29	>29	>29
69	8.5 ± 6.3	9.4 ± 5.8	2.6 ± 0.32	>30	>67	>22	>30	>30	>30
70	39 ± 12	1.2 ± 0.53	0.74 ± .03	>23	11 ± 1.5	>18	>23	>23	>23
71	7.0 ± 3.4	0.43 ± 0.03	1.5 ± 0.97	>26	>58	>19	>26	>26	>26
Gentamycin	2.4 ± 1.2	0.39 ± 0.04	ND	0.75 ± 0.34	ND	1.4 ± 0.17	7.5 ± 0.92	0.26 ± 0.01	0.092 ± 0.01
Miconazole					0.062 ± 0.03				
Vancomycin			3.8 ± 0.30						

Table S2. Bacterial cell growth inhibition by bisphosphonates together with clogP and $logD_{7.4}$ values.[a]

Cpd #	**Structure**	**Bs ED_{50}** μg/mL (μM)	**Ba ED_{50}** μg/mL (μM)	**Sa ED_{50}** μg/mL (μM)	**Ms ED_{50}** μg/mL (μM)	**HEK 293** μg/mL (μM)	clogP	$logD_{7.4}$
74		1.0 (2.4)	2.3 (5.4)	14 (33)	5.9 (14)	262 (620)	-2.25	-5.82
75		1.7 (4.1)	1.8 (4.4)	26 (63)	1.4 (3.4)	181 (440)	-2.08	-5.65
76		2.1 (4.8)	0.6 (1.4)	13 (30)	6.1 (14)	96 (220)	-0.50	-4.07
77		2.2 (5.2)	2.1 (5.0)	13 (31)	5.9 (14)	194 (460)	-1.14	-4.71
78		2.4 (5.7)	0.8 (1.9)	13 (31)	5.5 (13)	186 (440)	-2.50	-6.07
79		2.8 (6.4)	0.4 (0.9)	18 (41)	6.2 (14)	224 (510)	-1.52	-5.09

Cpd #	Structure	**Bs ED_{50}** µg/mL (µM)	**Ba ED_{50}** µg/mL (µM)	**Sa ED_{50}** µg/mL (µM)	**Ms ED_{50}** µg/mL (µM)	**HEK 293** µg/mL (µM)	clogP	$logD_{7.4}$
80		3.1 (7.4)	2.2 (5.2)	21 (50)	7.2 (17)	295 (700)	-1.14	-4.71
81		3.6 (8.2)	2.4 (5.5)	51 (120)	10 (23)	483 (1100)	-2.46	-6.25
82		4.6 (12)	4.3 (11)	34 (86)	15 (38)	166 (420)	-2.50	-6.07
83		5.5 (12)	2.2 (4.9)	30 (67)	7.2 (16)	22 (48)	-0.08	-3.65
84		5.7 (14)	2.5 (5.9)	28 (66)	150 (350)	420 (1000)	-2.25	-5.82
85		7.0 (16)	1.1 (2.5)	31 (71)	70 (160)	440 (1000)	-1.52	-5.08
86		8.3 (19)	5.0 (12)	23 (54)	150 (350)	ND	-0.10	-2.36

Cpd #	Structure	**Bs ED_{50}** µg/mL (µM)	**Ba ED_{50}** µg/mL (µM)	**Sa ED_{50}** µg/mL (µM)	**Ms ED_{50}** µg/mL (µM)	**HEK 293** µg/mL (µM)	clogP	$logD_{7.4}$
87		21 (48)	3.2 (7.3)	35 (80)	75 (170)	530 (1200)	-0.51	-3.10
88		21 (49)	7.4 (17)	36 (84)	150 (350)	ND	0.48	-2.12
89		26 (60)	3.0 (6.9)	32 (73)	93 (210)	480 (1100)	-0.24	-2.00
90		36 (73)	5.0 (10)	22 (45)	91 (180)	ND	-0.27	-3.48
91		41 (120)	8.6 (24)	17 (48)	65 (180)	ND	-4.24	-7.81
92		75 (170)	4.2 (9.6)	60 (140)	200 (460)	ND	-0.52	-2.24
93		97 (340)	2.3 (8.0)	230 (800)	290 (1000)	ND	-3.73	-6.35

Cpd #	Structure	**Bs ED_{50}** μg/mL (μM)	**Ba ED_{50}** μg/mL (μM)	**Sa ED_{50}** μg/mL (μM)	**Ms ED_{50}** μg/mL (μM)	**HEK 293** μg/mL (μM)	clogP	$logD_{7.4}$
94		100 (250)	11 (28)	56 (140)	96 (240)	ND	-0.36	-2.96
95		110 (230)	2.5 (5.2)	69 (140)	79 (160)	630 (1300)	1.20	-1.63
96		180 (420)	11 (26)	52 (120)	100 (240)	ND	0.77	-2.31
97		260 (460)	7.7 (14)	25 (44)	210 (370)	ND	1.72	-1.85

[a] Abbreviations used: Bs = *B. subtilis*; Ba = *B. anthracis* Sterne; Sa = *S. aureus*; Ms = *Mycobacterium smegmatis*; HEK293 = human embryonic kidney cell line # 293; clogP = the computed logarithm of the octanol/water partition coefficient; $logD_{7.4}$ = the logarithm of the computed octanol/water partition coefficient at pH = 7.4.

Table S3. Activity of compounds against *C. difficile*. MIC values in μg/mL.

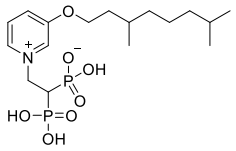
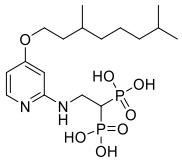
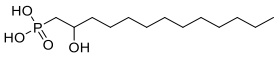
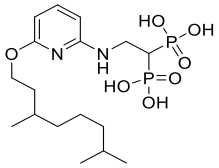
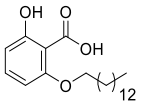
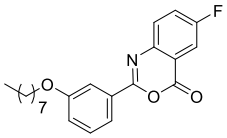
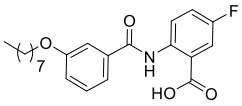
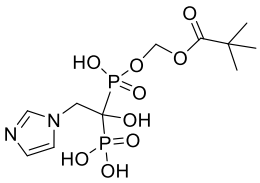
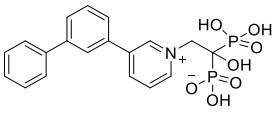
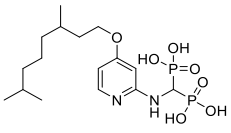
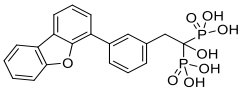
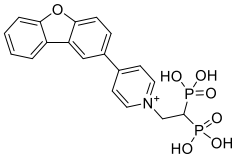
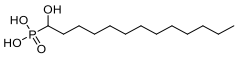
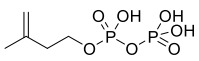
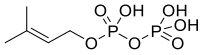
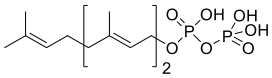
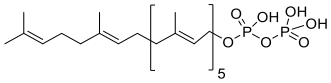
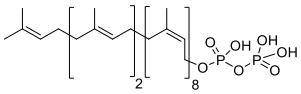
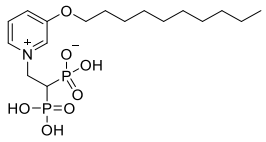
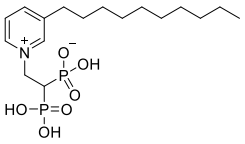
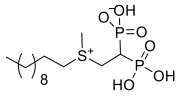
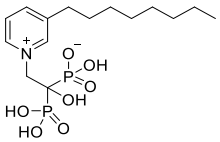
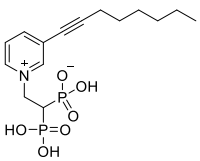
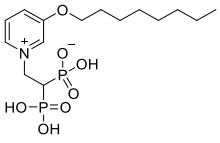
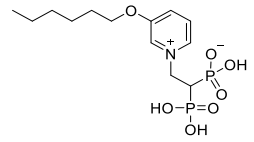
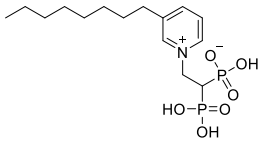
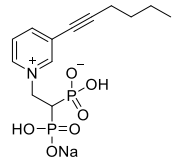
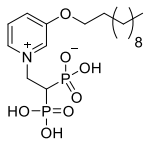
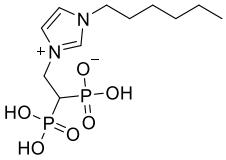
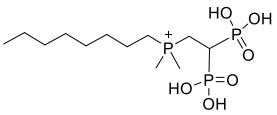
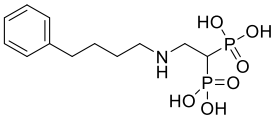
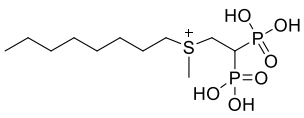
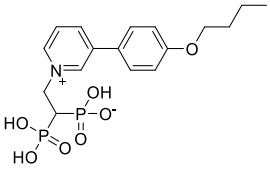
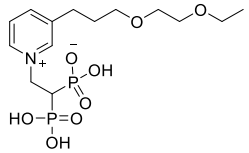
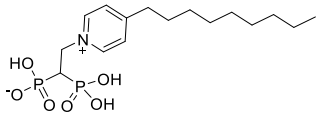
Cpd #	Structure	*C. difficile* ATCC 43255	*C. difficile* ATCC 1870	Cpd #	Structure	*C. difficile* ATCC 43255	*C. difficile* ATCC 1870
74		6.8	6.8	**96**		>18	>18
98		9	18	**92**		>18	>18
70		11	11	**100**		>24	>24
71		12	24	**101**		>25	>25
33		14	14	**95**		>27	>27
69		14	28	**68**		>28	28
99		19	19				

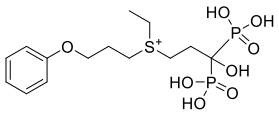
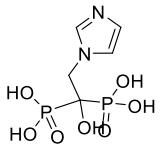
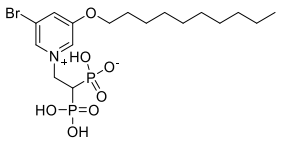
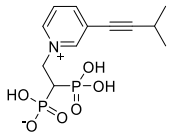
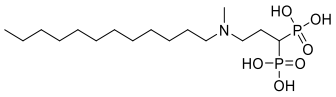
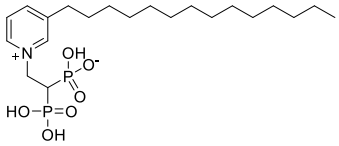
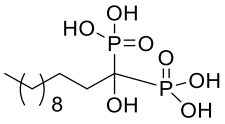
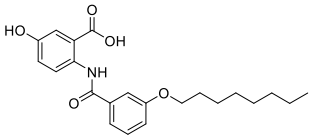
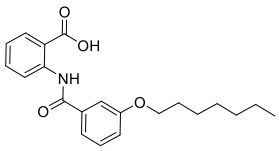
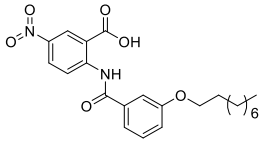
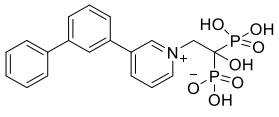
Table S4. Data collection and refinement statistics for EcOPPS and EcUPPS.

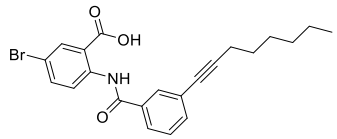
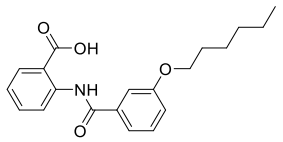
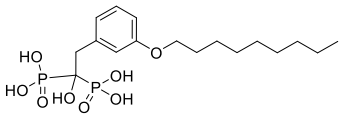
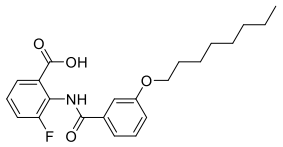
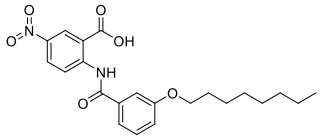
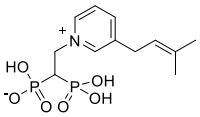
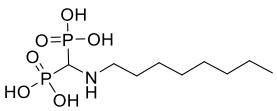
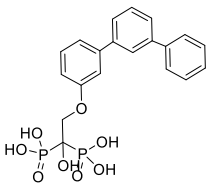
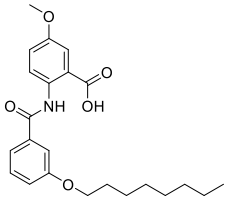
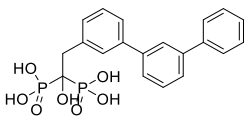
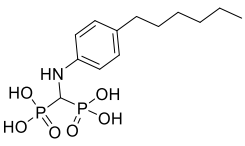
	EcOPPS·69	**EcOPPS·70**	**EcUPPS·70**
PDB code	5ZLF	5ZE6	5ZHE
Data co1lection			
space group	C_2	$P2_12_12_1$	$P2_12_12_1$
unit-cell			
a [Å]	149.34	94.03	63.71
b [Å]	46.65	111.99	68.45
c [Å]	215.74	133.82	109.25
α /β /γ (°)	90/101.08/90	90/90/90	90/90/90
resolution [Å]	25-2.85 (2.95-2.85)	25-2.50 (2.59-2.50)	25.0-2.18 (26-2.18)
unique reflections	34599 (3427)	49730 (4902)	25466 (2435)
redundancy	4.3 (4.4)	5.8 (5.9)	6.3 (5.0)
completeness [%]	99.9 (100.0)	100.0 (100.0)	99.5 (97.6)
average $I/\sigma(I)$	15.6 (2.37)	22.29 (4.8)	36.0 (3.9)
R_{merge}[a] [%]	7.2 (58.2)	9.7 (49.5)	4.4 (26)
Refinement			
no. of reflections	34589 (2500)	47239 (3516)	24247 (1746)
R_{work}[a] (95% of data)	0.241 (0.324)	0.185 (0.228)	0.203 (0.237)
R_{free}[a] (5 % of data)	0.299 (0.366)	0.264 (0.349)	0.263 (0.342)
r.m.s.d. bonds [Å]	0.009	0.010	0.012
r.m.s.d. angles [°]	1.59	1.49	1.72
dihedral angles			
most favored [%]	93.6	97.9	96.2
allowed [%]	6.3	2.1	3.8
disallowed [%]	0.1	0.0	0.0
no. of non-H atoms / average B [Å^2] [b]			
protein	8626 (103.48)	9413 (42.3)	3223 (53.38)
water	6 (53.9)	417 (39.2)	130 (50.35)
Ligand	30 (123.4)	50 (63.8)	25 (89.4)
ion	2 (72.8)	2 (37.1)	

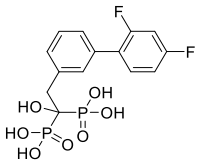
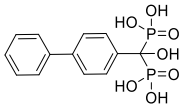
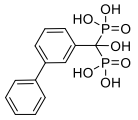
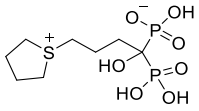
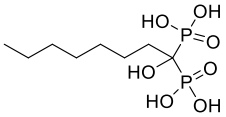
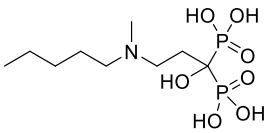
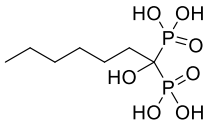
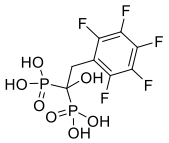
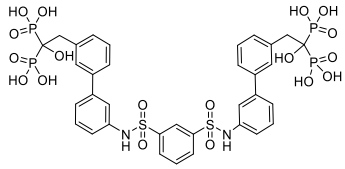
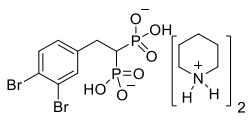
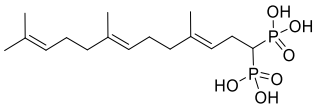
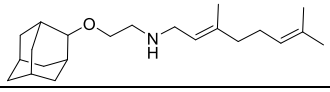
Table S5. SMILES for the compounds mentioned in the Text and SI.

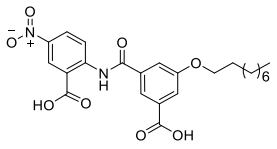
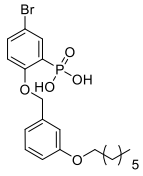
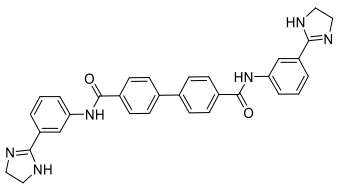
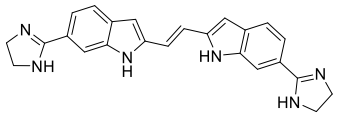
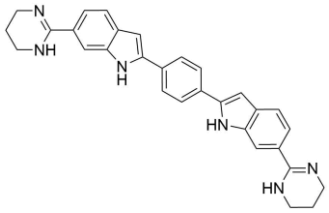
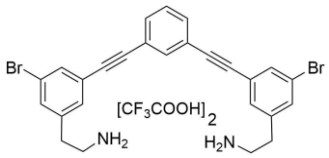
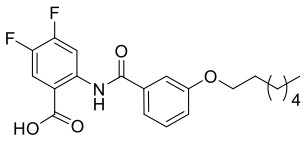
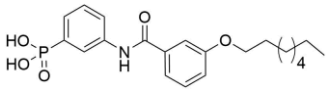
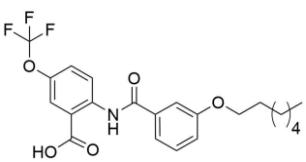
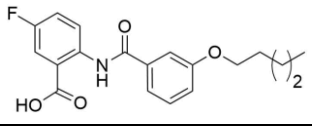
Cpd #	Structure	SMILES
1		CC(=C)CCOP(=O)([OH])OP(=O)([OH])[OH]
2		CC(=CCOP(=O)(O)OP(=O)(O)O)C
3		CC(=CCCC(=CCCC(=CCOP(=O)(O)OP(=O)(O)O)C)C)C
4		C/C(C)=C/CC/C(C)=C/CC/C(C)=C/CC/C(C)=C/CC/C(C)=C/CC/C(C)=C/CC/C(C)=C/CC/C(C)=C/COP(O)(OP(O)(O)=O)=O
5		C/C(C)=C\CC/C(C)=C/CC/C(C)=C/CC/C(C)=C/CC/C(C)=C/CC/C(C)=C/CC/C(C)=C/CC/C(C)=C/CC/C(C)=C/CC/C(C)=C/CC/C(C)=C/COP(OP(O)(O)=O)(O)=O
6		OP(C(P([O-])(O)=O)C[N+]1=CC(OCCCCCCCCCC)=CC=C1)(O)=O
7		CCCCCCCCCCC1=CC=C[N+](CC(P(O)(O)=O)P(O)([O-])=O)=C1
8		OP(C(P([O-])(O)=O)C[S+](C)CCCCCCCCCCC)(O)=O
9		CCCCCCCCC1=CC=C[N+](CC(O)(P(O)(O)=O)P([O-])(O)=O)=C1
10		OP(C(P([O-])(O)=O)C[N+]1=CC(C#CCCCCCC)=CC=C1)(O)=O
11		CCCCCCCCOC1=CC=C[N+](CC(P([O-])(O)=O)P(O)(O)=O)=C1

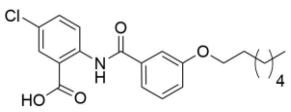
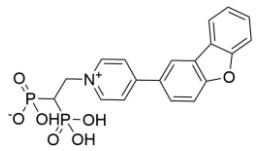
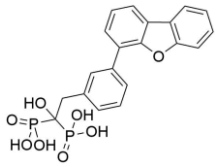
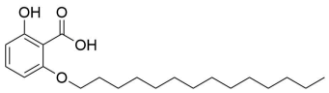
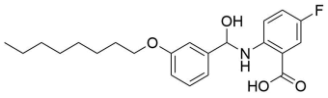
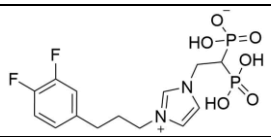
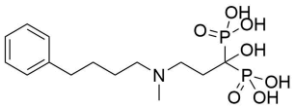
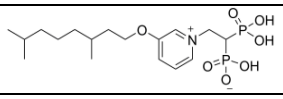
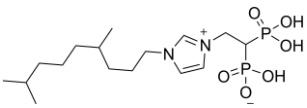
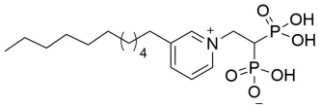
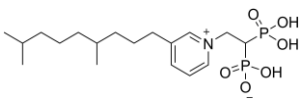
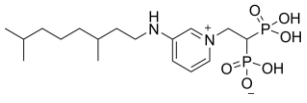
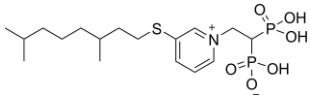
12		OP(C(P(O)([O-])=O)C[N+]1=CC(OCCCCCC)=CC=C1)(O)=O
13		OP(C(P([O-])(O)=O)C[N+]1=CC(CCCCCCCC)=CC=C1)(O)=O
14		CCCCC#CC1=CC=C[N+](CC(P([O-])(O)=O)P(O)(O[Na])=O)=C1
15		OP(C(P([O-])(O)=O)C[N+]1=CC(OCCCCCCCCCCCC)=CC=C1)(O)=O
16		CCCCCCN(C=C1)C=[N+]1CC(P(O)([O-])=O)P(O)(O)=O
17		CCCCCCCC[P+](C)(C)CC(P(O)(O)=O)P(O)(O)=O
18		OP(C(CNCCCCC1=CC=CC=C1)P(O)(O)=O)(O)=O
19		CCCCCCCC[S+](C)CC(P(O)(O)=O)P(O)(O)=O
20		CCCCOC1=CC=C(C2=CC=C[N+](CC(P(O)([O-])=O)P(O)(O)=O)=C2)C=C1
21		CCOCCOCCCC1=CC=C[N+](CC(P(O)([O-])=O)P(O)(O)=O)=C1
22		CCCCCCCCCC1=CC=[N+](CC(P(O)(O[Na])=O)P(O)([O-])=O)C=C1

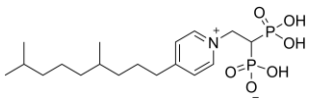
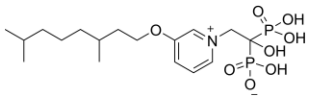
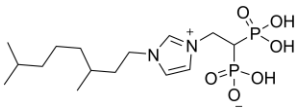
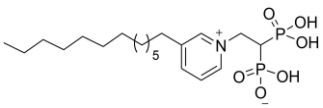
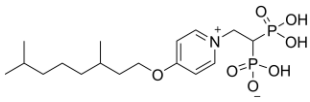
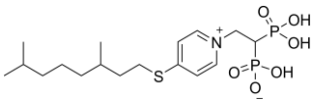
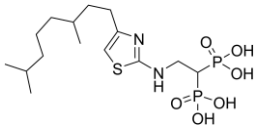
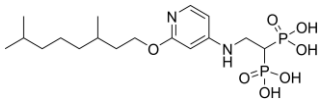
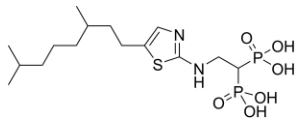
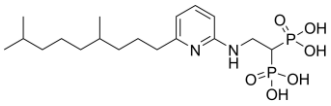
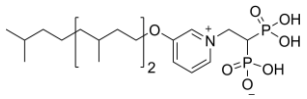
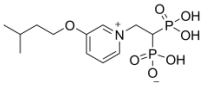
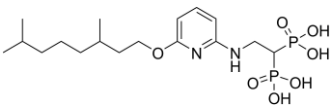
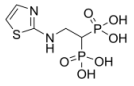
23		CC[S+](CCC(P(O)(O)=O)(O)P(O)(O)=O)CCCOC1=CC=CC=C1
24		OC(P(O)(O)=O)(P(O)(O)=O)CN1C=CN=C1
25		OP(C(P(O)([O-])=O)C[N+]1=CC(OCCCCCCCCCCC)=CC(Br)=C1)(O)=O
26		CC(C)C#CC1=CC=C[N+](CC(P(O)(O)=O)P(O)([O-])=O)=C1
27		CCCCCCCCCCCCN(CCC(P(O)(O)=O)P(O)(O)=O)C
28		OP(C(P(O)([O-])=O)C[N+]1=CC(CCCCCCCCCCCCCCC)=CC=C1)(O)=O
29		OP(C(P(O)(O)=O)(O)CCCCCCCCCCCCC)(O)=O
30		O=C(O)C1=CC(O)=CC=C1NC(C2=CC=CC(OCCCCCCCCC)=C2)=O
31		O=C(O)C1=CC=CC=C1NC(C2=CC=CC(OCCCCCCCC)=C2)=O
32		O=C(O)C1=CC([N+]([O-])=O)=CC=C1NC(C2=CC=CC(OCCCCCCCCCCCC)=C2)=O
33		OC(P(O)(O)=O)(P(O)([O-])=O)C[N+]1=CC(C2=CC(C3=CC=CC=C3)=CC=C2)=CC=C1

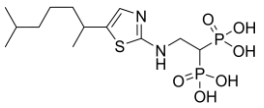
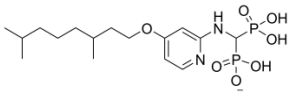
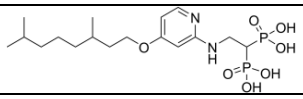
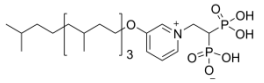
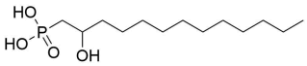
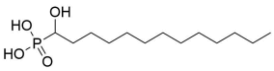
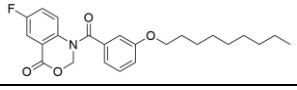
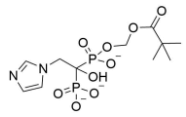
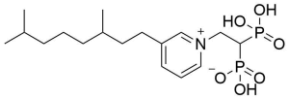
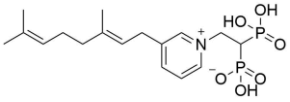
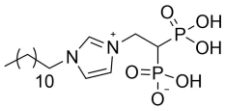
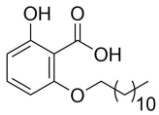
34		O=C(O)C1=CC(Br)=CC=C1NC(C2=CC=CC(C#CCCCCCC)=C2)=O
35		O=C(O)C1=CC=CC=C1NC(C2=CC=CC(OCCCCCC)=C2)=O
36		OC(P(O)(O)=O)(P(O)(O)=O)CC1=CC(OCCCCCCCCCCC)=CC=C1
37		O=C(O)C1=CC=CC(F)=C1NC(C2=CC=CC(OCCCCCCCCC)=C2)=O
38		O=C(O)C1=CC([N+]([O-])=O)=CC=C1NC(C2=CC=CC(OCCCCCCCCC)=C2)=O
39		OP(C(P(O)([O-])=O)C[N+]1=CC(C/C=C(C)\C)=CC=C1)(O)=O
40		CCCCCCCCNC(P(O)(O)=O)P(O)(O)=O
41		OC(P(O)(O)=O)(P(O)(O)=O)COC1=CC(C2=CC=CC(C3=CC=CC=C3)=C2)=CC=C1
42		O=C(O)C1=CC(OC)=CC=C1NC(C2=CC=CC(OCCCCCCCC)=C2)=O
43		OC(P(O)(O)=O)(P(O)(O)=O)CC1=CC(C2=CC(C3=CC=CC=C3)=CC=C2)=CC=C1
44		CCCCCCC1=CC=C(NC(P(O)(O)=O)P(O)(O)=O)C=C1

45		FC1=CC(F)=C(C2=CC=CC(CC(P(O)(O)=O)(O)P(O)(O)=O)=C2)C=C1
46		O=P(O)(O)C(P(O)(O)=O)(O)C(C=C1)=CC=C1C2=CC=CC=C2
47		O=P(O)(O)C(P(O)(O)=O)(O)C1=CC(C2=CC=CC=C2)=CC=C1
48		O=P([O-])(O)C(CCC[S+]1CCCC1)(O)P(O)(O)=O
49		O=P(O)(O)C(CCCCCCC)(O)P(O)(O)=O
50		O=P(O)(O)C(CCN(C)CCCCC)(O)P(O)(O)=O
51		O=P(O)(O)C(CCCCCC)(O)P(O)(O)=O
52		O=P(O)(O)C(CC1=C(F)C(F)=C(F)C(F)=C1F)(O)P(O)(O)=O
53		BrC(C(Br)=C1)=CC=C1CC(P(O)([O-])=O)P([O-])(O)=O.[H][N+]2([H])CCCCC2.[H][N+]3([H])CCCCC3
54		O=P(O)(O)C(CC1=CC=CC(C2=CC(NS(C3=CC(S(NC4=CC(C5=CC(CC(P(O)(O)=O)(O)P(O)(O)=O)=CC=C5)=CC=C4)(=O)=O)=CC=C3)(=O)=O)=CC=C2)=C1)(O)P(O)(O)=O
55		C/C(C)=C/CC/C(C)=C/CC/C(C)=C/CC(P(O)(O)=O)P(O)(O)=O
56		C/C(CC/C=C(C)/C)=C\CNCCOC1[C@H]2C[C@@H]3C[C@@H](C[C@H]1C3)C2

57		O=C(O)C1=C(NC(C2=CC(C(O)=O)=CC(OCCCCCCCCCCC)=C2)=O)C=CC([N+]([O-])=O)=C1
58		BrC1=CC=C(OCC2=CC=CC(OCCCCCCCCC)=C2)C(P(O)(O)=O)=C1
59		O=C(NC1=CC=CC(C2=NCCN2)=C1)C3=CC=C(C4=CC=C(C(NC5=CC=CC(C6=NCCN6)=C5)=O)C=C4)C=C3
60		C1(C2=NCCN2)=CC=C3C(NC(/C=C/C4=CC5=C(C=C(C6=NCCN6)C=C5)N4)=C3)=C1
61		C1(C2=NCCCN2)=CC=C3C(NC(C4=CC=C(C5=CC6=C(C=C(C7=NCCCN7)C=C6)N5)C=C4)=C3)=C1
62		BrC1=CC(CCN)=CC(C#CC2=CC=CC(C#CC3=CC(CCN)=CC(Br)=C3)=C2)=C1.FC(F)(C(O)=O)F.FC(F)(C(O)=O)F
63		O=C(O)C1=C(NC(C2=CC=CC(OCCCCCCCCC)=C2)=O)C=C(F)C(F)=C1
64		O=C(C1=CC=CC(OCCCCCCCCCC)=C1)NC2=CC(P(O)(O)=O)=CC=C2
65		O=C(O)C1=C(NC(C2=CC=CC(OCCCCCCCCC)=C2)=O)C=CC(OC(F)(F)F)=C1
66		O=C(O)C1=C(NC(C2=CC=CC(OCCCCCC)=C2)=O)C=CC(F)=C1

67		O=C(O)C1=C(NC(C2=CC=CC(OCCCCCCCCC)=C2)=O)C=CC(Cl)=C1
68		O=P([O-])(O)C(P(O)(O)=O)C[N+](C=C1)=CC=C1C(C=C2)=CC3=C2OC4=CC=CC=C43
69		O=P(O)(O)C(P(O)(O)=O)(O)CC1=CC(C2=C3C(C(C=CC=C4)=C4O3)=CC=C2)=CC=C1
70		OC1=C(C(O)=O)C(OCCCCCCCCCCCCCCC)=CC=C1
71		OC(C1=C(NC(C2=CC(OCCCCCCCCC)=CC=C2)O)C=CC(F)=C1)=O
72		FC1=C(F)C=C(CCC[N+]2=CN(CC(P(O)([O-])=O)P(O)(O)=O)C=C2)C=C1
73		CN(CCC(P(O)(O)=O)(O)P(O)(O)=O)CCCCC1=CC=CC=C1
74		OP(C(P(O)([O-])=O)C[N+]1=CC(OCCC(C)CCCC(C)C)=CC=C1)(O)=O
75		OP(C(P(O)([O-])=O)C[N+]1=CN(CCCC(C)CCCC(C)C)C=C1)(O)=O
76		OP(C(P(O)([O-])=O)C[N+]1=CC(CCCCCCCCCCCC)=CC=C1)(O)=O
77		OP(C(P(O)([O-])=O)C[N+]1=CC(CCCC(C)CCCC(C)C)=CC=C1)(O)=O
78		OP(C(P(O)([O-])=O)C[N+]1=CC(NCCC(C)CCCC(C)C)=CC=C1)(O)=O
79		OP(C(P(O)([O-])=O)C[N+]1=CC(SCCC(C)CCCC(C)C)=CC=C1)(O)=O

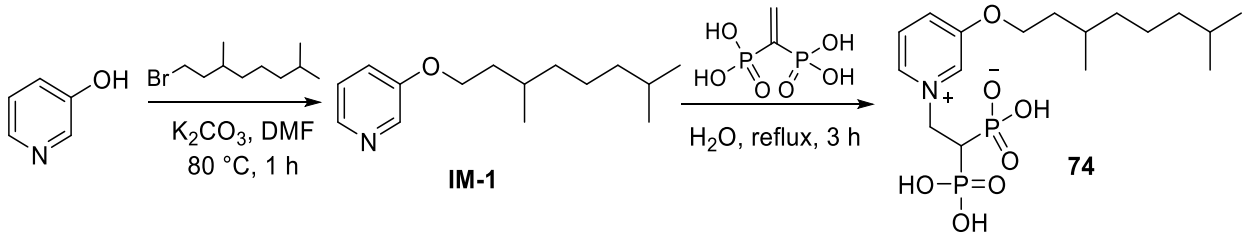
80		OP(C(P(O)([O-])=O)C[N+]1=CC=C(CCCC(C)CCCC(C)C)C=C1)(O)=O
81		OP(C(P(O)([O-])=O)(O)C[N+]1=CC(OCCC(C)CCCC(C)C)=CC=C1)(O)=O
82		OP(C(P(O)([O-])=O)C[N+]1=CN(CCC(CCCC(C)C)C)C=C1)(O)=O
83		OP(C(P(O)([O-])=O)C[N+]1=CC(CCCCCCCCCCCCCC)=CC=C1)(O)=O
84		OP(C(P(O)([O-])=O)C[N+]1=CC=C(OCCC(C)CCCC(C)C)C=C1)(O)=[O]
85		OP(C(P(O)([O-])=O)C[N+]1=CC=C(SCCC(C)CCCC(C)C)C=C1)(O)=O
86		OP(C(P(O)(O)=O)CNC1=NC(CCC(CCCC(C)C)C)=CS1)(O)=O
87		OP(C(P(O)(O)=O)CNC1=CC(OCCC(C)CCCC(C)C)=NC=C1)(O)=O
88		OP(C(P(O)(O)=O)CNC1=NC=C(CCC(CCCC(C)C)C)S1)(O)=O
89		OP(C(P(O)(O)=O)CNC1=NC(CCCC(C)CCCC(C)C)=CC=C1)(O)=O
90		OP(C(C[N+]1=CC(OCCC(CCCC(CCCC(C)C)C)C)=CC=C1)P(O)([O-])=O)(O)=O
91		OP(C(P(O)([O-])=O)C[N+]1=CC(OCCC(C)C)=CC=C1)(O)=O
92		OP(C(P(O)(O)=O)CNC1=NC(OCCC(C)CCCC(C)C)=CC=C1)(O)=O
93		OP(C(P(O)(O)=O)CNC1=NC=CS1)(O)=O

94		OP(C(P(O)(O)=O)CNC1=NC=C(C(C)CCCC(C)C)S1)(O)=O
95		OP(C(P(O)([O-])=O)NC1=CC(OCCC(C)CCCC(C)C)=CC=N1)(O)=O
96		OP(C(P(O)(O)=O)CNC1=CC(OCCC(CCCC(C)CCCC(C)C)C)=CC=N1)(O)=O
97		OP(C(C[N+]1=CC(OCCC(CCCC(CCCC(CCCC(C)C)C)C)C)=CC=C1)P(O)([O-])=O)(O)=O
98		CCCCCCCCCCCC(O)CP(O)(O)=O
99		O=P(O)(O)C(O)CCCCCCCCCCCCC
100		O=C(N1C2=C(C(OC1)=O)C=C(F)C=C2)C3=CC=CC(OCCCCCCCCC)=C3
101		[O-]P(C(P([O-])([O-])=O)(O)CN1C=NC=C1)(OCOC(C(C)(C)C)=O)=O
102		CC(CCCC(CCC1=CC=C[N+](CC(P(O)([O-])=O)P(O)(O)=O)=C1)C)C
103		C/C(C)=C/CC/C(C)=C/CC1=CC=C[N+](CC(P(O)([O-])=O)P(O)(O)=O)=C1
104		OP(C(P(O)([O-])=O)C[N+]1=CN(CCCCCCCCCCCCC)C=C1)(O)=O
105		O=C(O)C1=C(OCCCCCCCCCCCCC)C=CC=C1O

Synthesis of Compounds.

Compounds **6**[1,2], **7**[3], **8**[4], **9**[2], **10**[3], **11**[2], **12**[2] , **13**[3], **14**[2], **15**[3, 5], **16**[6], **17**[7], **18**[2], **19**[4], **20-22**[2], **23**[8], **24**[9], **25**[7], **26-28**[2], **29**[10], **30**[11], **31**[12], **32**[12], **33**[13], **34**[12], **35**[11], **36**[7], **37**[11], **38**[11], **39**[2], **40**[14], **41**[7], **42**[11], **43**[15],**44**[16], **45**[17], **46-47**[17], **48**[4], **49**[16], **50**[9], **51**[16], **52**[2], **53**[18], **54**[15], **55**[19], **56**[20], **57**[12], **58**[12], **59**[18], **60**[21], **61-62**[18], **63-64**[11], **65**[11], **66**[11], **67**[11], **68**[22], **69**[2], **70**[23], **71**[13], **72**[24], **73**[9], **74**[7], **94**[25], **98-99**[24], **104**[2], **105**[12] were previously reported.

Synthesis of 74:

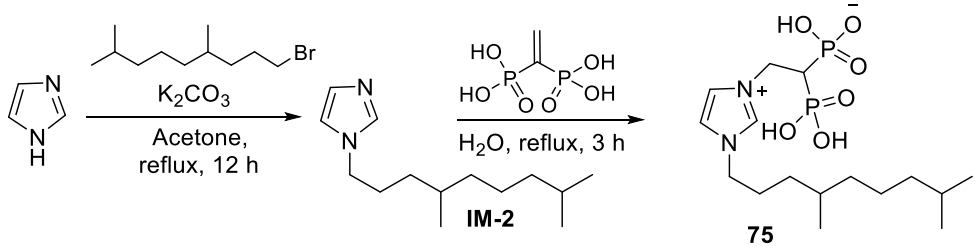


3-((3,7-Dimethyloctyl)oxy)pyridine (IM-1). According to **Procedure A**, 3-hydroxypyridine (0.50 g, 5.26 mmol), 1-bromo-3,7-dimethyloctane (1.16 g, 5.26 mmol), and K_2CO_3 (0.73 g, 5.26 mmol) in 5 mL of DMF yielded **IM-1** (0.40 g, 1.68 mmol, 32%) as a brown oil. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.30 (σ, 1H), 8.20 (σ, 1H), 7.22-7.18 (m, 2H), 4.07-4.00 (m, 2H), 1.87-1.80 (m, 1H), 1.87-1.80 (m, 1H), 1.69-1.50 (m, 3H), 1.34-1.14 (m, 6H), 0.95 (d, *J* = 6.5 Hz, 3H), 0.87 (d, *J* = 6.5 Hz, 6H).

Hydrogen(2-(3-((3,7-dimethyloctyl)oxy)pyridin-1-ium-1-yl)-1-phosphonoethyl) phosphonate (74). According to **Procedure B**, 3-((3,7-dimethyloctyl)oxy)pyridine (0.075 g, 0.32 mmol) and vinylidene-1,1-bisphosphonic acid (0.057 g, 0.30 mmol) in 1.5 mL of H_2O yielded **74** (0.088 g, 0.21 mmol, 69%) as a white powder. ^{1}H NMR (D_2O, 500 MHz): δ 8.71 (s, 1H), 8.58 (d, *J* = 6.0 Hz, 1H), 7.99 (dd, *J* = 9.0 Hz, 1.5 Hz, 1H), 7.85 (dd, *J* = 6.5, 6.0 Hz, 1H), 4.93 (td, *J* = 12.8, 6.8 Hz, 2H), 4.34-4.30 (m, 2H), 2.40 (tt, J = 20.8, 13.3 Hz, 1H), 1.93-1.89 (m, 1H), 1.72-1.67 (m, 2H), 1.58-

1.53 (m, 1H), 1.39-1.18 (m, 6H), 0.97 (d, J = 6.5 Hz, 3H), 0.88 (d, J = 6.5 Hz, 9H); ^{31}P NMR (D_2O, 202 MHz): δ 14.06; ESI HRMS: *m/z* $[M+H]^+$ calculated for $C_{17}H_{32}NO_7P_2^+$, 424.1649; found, 424.1639; purity = 99.9 % (qNMR).

Synthesis of 75:

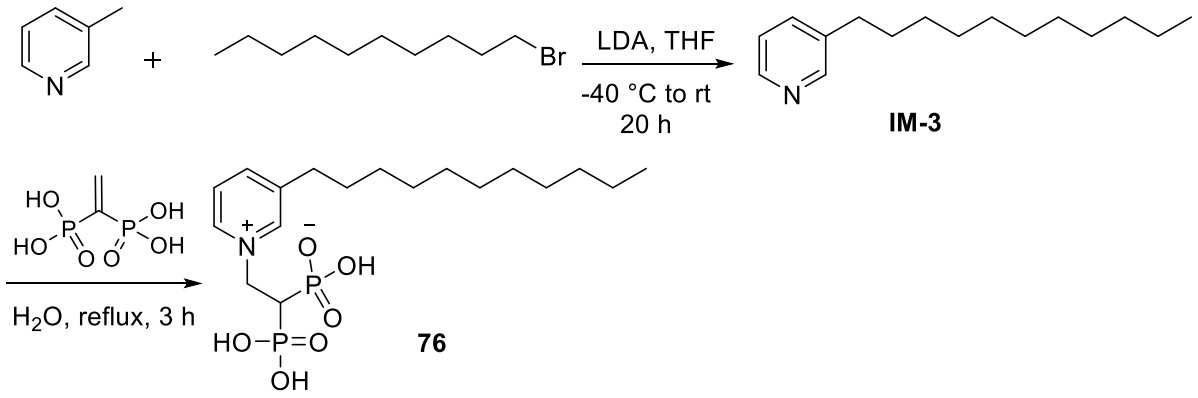


1-(4,8-Dimethylnonyl)-1H-imidazole (IM-2). A mixture of 1H-imidazole (0.29 g, 4.25 mmol) and K_2CO_3 (1.18 g, 8.50 mmol) was stirred in 15 mL acetone. 1-bromo-4,8-dimethylnonane (1.00 g, 4.25 mmol) was added, and the mixture stirred for 12 h at 80 °C. The mixture was cooled to RT, 10 mL of water added, and the product extracted into 2 x 15 mL of ethyl acetate. The crude compound was purified by flash column chromatography on silica (25 % EA/PE) to give **IM-2** (0.79 g, 3.54 mmol, 83.3%) as a white solid. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.47 (s, 1H), 7.04 (s, 1H), 6.89 (s, 1H), 3.89 (t, J = 7.3 Hz, 2H), 1.83-1.69 (m+, 2H), 1.49 (quintet, J = 6.7 Hz, 1H), 1.42-1.36 (m, 1H), 1.30-1.03 (m, 8H), 0.85 (d, J = 6.5 Hz, 6H), 0.84 (d, J = 6.5 Hz, 3H).

Hydrogen(2-(1-(4,8-dimethylnonyl)-1H-imidazol-3-ium-3-yl)-1-phosphonoethyl)phosphonate (75). According to **Procedure B**, 1-(4,8-dimethylnonyl)-1H-imidazole (**IM-2**, 0.075 g, 0.34 mmol) and vinylidene-1,1-bisphosphonic acid (0.060 g, 0.32 mmol) in 1.5 mL H_2O yielded hydrogen(2-(1-(4,8-dimethylnonyl)-1H-imidazol-3-ium-3-yl)-1-phosphonoethyl)phosphonate (0.042 g, 0.10 mmol, 32%) as a white powder. ^{1}H NMR (D_2O, 500 MHz): δ 8.82 (s, 1H), 7.58 (s, 1H), 7.46 (s, 1H), 4.63 (td, J = 13.8, 7.0 Hz, 2H), 4.17 (t, J = 7.0 Hz, 2H),

2.68 (tt, J = 21.5, 7.0 Hz, 1H), 1.93-1.81 (m, 2H), 1.52-1.44 (m, 2H), 1.31-1.12 (m, 8H); 0.85 (d, J = 6.5 Hz, 3H), 0.84 (d, J = 6.5 Hz, 6H); ^{31}P (202 MHz, D_2O): δ 14.29; ESI HRMS: *m/z* $[M+H]^+$ calculated for $C_{16}H_{33}N_2O_6P_2^+$, 411.1808; found, 411.1801; purity = 96.6 % (qNMR).

Synthesis of 76:

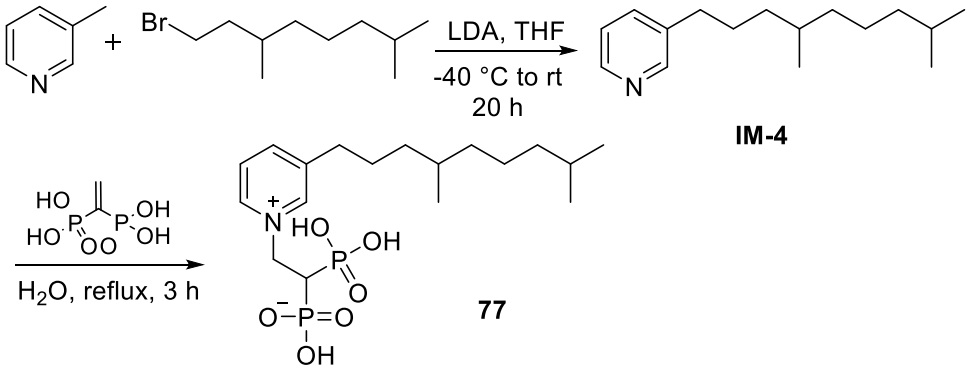


3-Undecylpyridine (IM-3). Synthesized by modifying the literature procedure.[26] To a solution of 3-picoline (0.80 g, 8.59 mmol) in 10 mL of dry THF, LDA (4.53 mL, 9.07 mmol) was added dropwise at -20 °C via syringe with constant stirring under a N_2 atmosphere. The cooling bath was removed, and the temperature was allowed to rise to 10 °C. After stirring for 30 min at 10 °C, the reaction mixture was cooled to -40 °C. 1-bromodecane (2.02 mL, 9.47 mmol) in 3 mL of THF was then added, dropwise. The cooling bath was removed, and the mixture warmed to RT and stirred overnight. The progress of the reaction was checked by TLC (30% EA/PE). To the reaction mixture, 25 mL of water was added, and the aqueous layer was extracted with 3 x 30 mL of ethyl acetate. The combined organic layers were dried over Na_2SO_4. The crude compound was purified by flash column chromatography over silica (10% EA/PE) to give 3-undecylpyridine (1.57 g, 6.36 mmol, 74%) as a brown oil. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.41 (d, J = 2.0 Hz, 1H), 8.39 (dd, J = 5.0, 1.5 Hz, 1H), 7.44 (d, J = 7.5 Hz, 1H),

7.15 (dd, *J* = 8.0, 5.0 Hz, 1H), 2.55 (t, *J* = 7.5 Hz, 2H), 1.57 (quintet, *J* = 7.4 Hz, 2H), 1.27-1.22 (m, 16 H), 0.84 (t, *J* = 7.0 Hz, 3H).

Hydrogen (1-phosphono-2-(3-undecylpyridin-1-ium-1-yl)ethyl)phosphonate (76). According to **Procedure B**, 3-undecylpyridine, (**IM-3**, 0.075, 0.32 mmol) and vinylidene-1,1-bisphosphonic acid (0.057 g, 0.31 mmol) in 1.0 mL of H_2O yielded hydrogen(1-phosphono-2-(3-undecylpyridin-1-ium-1-yl)ethyl)phosphonate (0.085 g, 0.20 mmol, 66%) as a white solid. ^{1}H NMR (D_2O, 500 MHz): δ 8.82 (s, 1H), 8.41 (d, *J* = 6.0 Hz, 1H), 8.28 (d, *J* = 8.0 Hz, 1H), 7.85 (dd, *J* = 8.0 Hz, 1H), 4.92 (td, *J* = 13.0, 6.3 Hz, 2H), 2.86 (t, *J* = 7.8 Hz), 2.34 (tt, *J* = 21.0, 6.5, 1H), 1.74-1.71 (m, 2H), 1.36-1.30, (m, 16H), 0.88 (t, *J* = 7.5 Hz, 3H); ^{31}P NMR (D_2O, 202 MHz): δ 14.38. ESI HRMS: *m/z* $[M+H]^+$ calculated for $C_{18}H_{34}NO_6P_2^+$, 422.1856; found, 422.1837; purity = 99.1 % (qNMR).

Synthesis of 77:

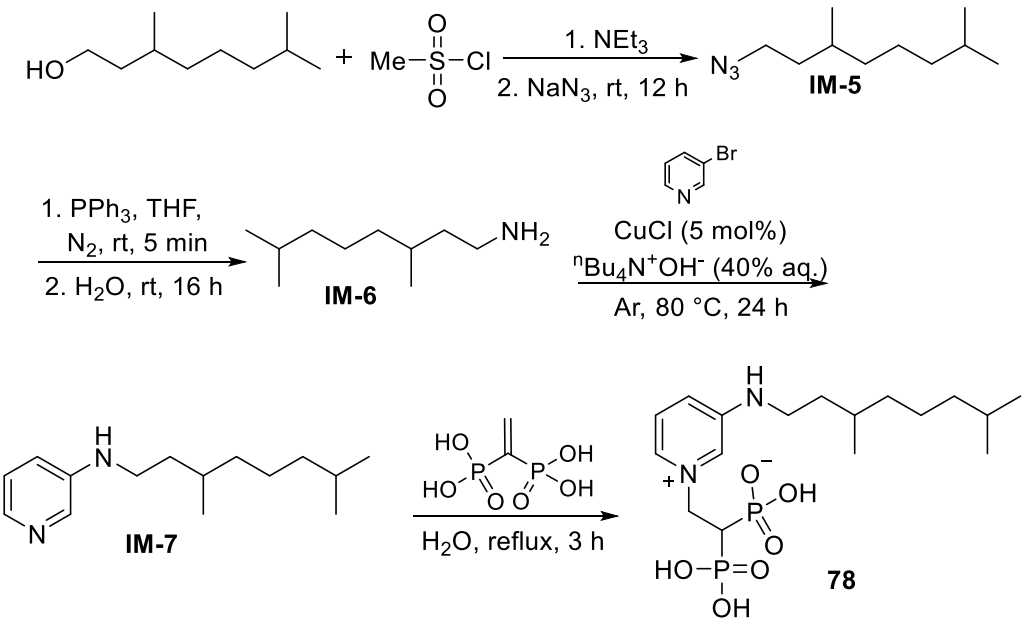


3-(4,8-Dimethylnonyl)pyridine (IM-4). Synthesized by modifying the literature procedure.[26] To a solution of 3-picoline (1.10 mL, 11.3 mmol) in 25 mL of dry THF, LDA (5.90 mL, 43.5 mmol) was added dropwise at -20 °C via syringe with constant stirring under a N_2 atmosphere. The cooling bath was removed, and the temperature allowed to rise to 10 °C. After stirring for 30 min at 10 °C, the reaction mixture was cooled to -40 °C. 3,7-dimethyl-1-bromooctane (2.56 mL, 12.43 mmol) in 8 mL

of THF was then added, dropwise. The cooling bath was removed, and the mixture warmed to RT and stirred overnight. The progress of the reaction was checked by TLC (30% EA/PE). To the reaction mixture, 25 mL of water was added, and the aqueous layer was extracted with 3 x 30 mL of ethyl acetate. The combined organic layers were dried over Na_2SO_4. The crude compound was purified by flash column chromatography over silica (10% EA/PE) to give **IM-4** (2.13 g, 9.11 mmol, 84%) as a colorless oil. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.45 (d, *J* = 2.0 Hz, 1H), 8.43 (dd, *J* = 4.5, 1.5 Hz, 1H), 7.51 (d, *J* = 7.5 Hz, 1H), 7.22 (dd, *J* = 4.8 Hz, 1H), 2.63-2.54 (m, 12H) 1.65-1.04 (m, 2H), 0.86 (d, *J* = 6.5 Hz, 6H), 0.85 (d, *J* = 6.5 Hz, 3H).

Hydrogen (2-(3-(4,8-dimethylnonyl)pyridin-1-ium-1-yl)-1-phosphonoethyl) phosphonate (77). According to **Procedure B**, 3-(4,8-dimethylnonyl)pyridine (0.090 g, 0.39 mmol) and vinylidene-1,1-bisphosphonic acid (0.065 g, 0.35 mmol) in 1.5 mL of H_2O gave hydrogen (2-(3-(4,8-dimethylnonyl)pyridin-1-ium-1-yl)-1-phosphonoethyl)phosphonate (0.11 g, 0.25 mmol, 73%) as a white powder. ^{1}H NMR (D_2O, 500 MHz): δ 8.77 (s, 1H), 8.72 (d, *J* = 7.5 Hz, 1H), 8.26 (d, *J* = 10.0 Hz, 1H), 7.82 (dd, *J* = 10.0, 7.8 Hz, 1H), 4.87 (td, *J* = 16.0, 8.8 Hz, 2H), 2.84-2.77 (m, 2H), 2.36 (tt, J = 26.0, 17.3 Hz, 1H), 1.70-1.66 (m, 2H), 1.50-1.06 (m, 10H), 0.81 (d, *J* = 8.0 Hz, 9H); ^{31}P NMR (D_2O, 202 MHz): δ 13.41; ESI HRMS: *m/z* $[M+H]^+$ calculated for $C_{18}H_{34}NO_6P_2^+$, 422.1856; found, 422.1853; purity = 98.4 % (qNMR).

Synthesis of 78:



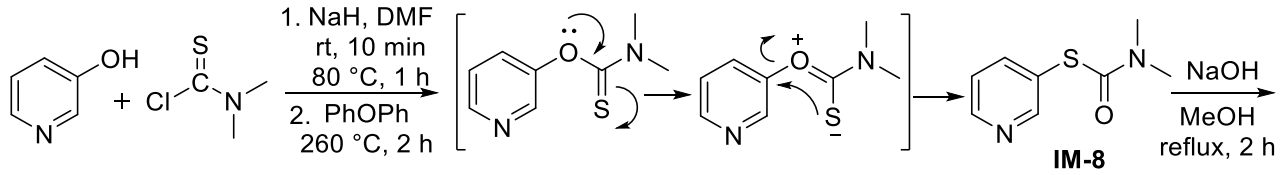
1-Azido-3,7-dimethyloctane (IM-5). To a mixture of 3,7-dimethyloctan-1-ol (4.00 g, 25.27 mmol) and methanesulfonyl chloride (4.34 g, 37.91 mmol) was added triethylamine (5.28 mL, 37.91 mmol) and sodium azide (4.93 g, 75.81 mmol) at RT. The mixture was stirred for 12 h at RT then the crude product was purified by flash column chromatography on silica (40 % EA/PE) to give **IM-5** (3.70 g, 20.20 mmol, 80%) as an oil.[27]

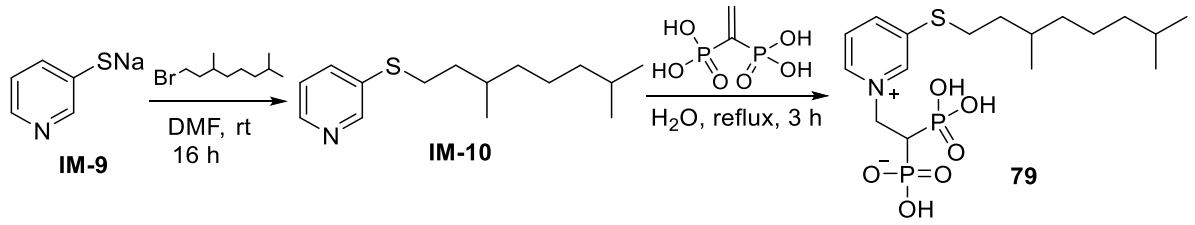
3,7-Dimethyloctan-1-amine (IM-6). To a mixture of 1-azido-3,7-dimethyloctane (**IM-41**, 3.70 g, 20.20 mmol) in 15 mL THF under a N_2 atmosphere was added triphenylphosphine (10.60 g, 40.40 mmol) at RT. After 5 min, H_2O (0.473 mL, 26.26 mmol) was added at RT. The reaction mixture was stirred at RT for 16 h. The crude compound was purified by flash column chromatography on silica (5% MeOH/EA) to give pure 3,7-dimethyloctan-1-amine (1.50 g, 9.54 mmol, 47.2%) as an oil.[28] **N-(3,7-Dimethyloctyl)pyridin-3-amine (IM-7).** To a mixture of 3,7-dimethyloctan-1-amine (**IM-5**, 0.10 g, 0.63 mmol) and 3-bromopyridine (0.15 g, 0.95 mmol) was added 5 mol% of CuCl (0.040 g) and 40% aqueous n-$Bu_4N^+OH^-$ (0.010 g, 0.032 mmol). The mixture was stirred at 80 °C for 24 h then

cooled to RT and 15 mL of H_2O added.[29] The product was extracted into 2 x 15 mL of ethyl acetate and the combined organic layers were dried over Na_2SO_4. The crude compound was purified by flash column chromatography on silica (40% EA/PE) to give pure **IM-7** (0.056 g, 0.24 mmol, 38%) as a brown oil. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.03 (s, 1H), 7.14 (s, 1H), 6.89 (d, *J* = 8.0 Hz, 1H), 3.67 (s, 1H), 3.14-3.11 (m, 2H), 1.68-1.41 (m, 4H), 1.33-1.13 (m, 6H), 0.94 (d, *J* = 7.0 Hz, 3H), 0.87 (d, *J* = 6.5 Hz, 6H).

Hydrogen(2-(3-((3,7-dimethyloctyl)amino)pyridin-1-ium-1-yl)-1-phosphonoethyl)phosphonate (78). According to **Procedure B**, N-(3,7-dimethyloctyl)pyridin-3-amine (0.075 g, 0.32 mmol) and vinylidene-1,1-bisphosphonic acid (0.057 g, 0.30 mmol) in 1.0 mL of H_2O yielded hydrogen(2-(3-((3,7-dimethyloctyl)amino)pyridin-1-ium-1-yl)-1-phosphonoethyl)phosphonate (0.033 g, 0.079 mmol, 26%) as a pale brown solid. ^{1}H NMR (D_2O, 500 MHz): δ 8.21 (s, 1H), 8.13 (d, *J* = 6.0 Hz, 1H), 7.59 (dd, *J* = 8.8, 5.8 Hz, 1H), 7.53 (d, *J* = 8.5 Hz, 1H), 4.83-4.80 (m, 2H), 3.29-3.19 (m, 2H), 2.32 (tt, *J* = 21.0, 6.6, 1H), 1.72-1.47 (m, 2H), 1.37-1.17, (m, 6H), 0.95 (d, *J* = 6.5 Hz, 3H), 0.87 (*J* = 7.0 Hz, 6H); ^{31}P NMR (D_2O, 202 MHz): δ 14.72; ESI HRMS: *m/z* $[M+H]^+$ calculated for $C_{17}H_{33}N_2O_6P_2^+$, 423.1790; found, 423.1795; purity = 96.8 % (qNMR).

Synthesis of 79:





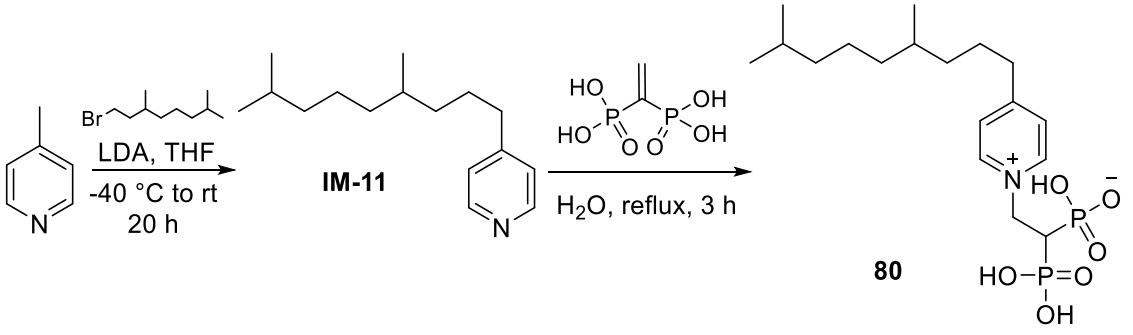
S-(Pyridin-3-yl)-dimethylcarbamothioate (IM-8). To a solution of 3-hydroxypyridine (3.14 g, 33.00 mmol) in 20 mL of DMF was added NaH (0.79 g, 33.00 mmol) at RT. The mixture was stirred for 10 min, then 2-(dimethylamino)-2-oxoethanethioyl chloride (5.00 g, 33.00 mmol) was added in one portion. The mixture was heated to 80 °C and stirred for 1 h then diluted with 25 mL of water and extracted with 3 x 30 mL of ethyl acetate.[30] The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. The crude compound was purified by flash column chromatography on silica (30% EA/PE) to produce the intermediate, O-(pyridin-3-yl) 2-(dimethylamino)-2-oxoethanethioate (2.74 g, 16.50 mmol, 50%), which was then dissolved in 15 mL diphenyl ether and refluxed for 2 h at 260 °C. The mixture was cooled to RT and purified by column chromatography (30% EA/PE) to afford **IM-8** (1.96 g, 10.73 mmol, 65%) as an oil. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.64 (d, *J* = 1.2 Hz, 1H), 8.61 (dd, *J* = 4.4, 0.8 Hz, 1H), 7.85-7.82 (m, 1H), 7.34 (dd, *J* = 8.0, 1H), 3.12 (S, 3H), 3.04 (S, 3H).

3-((3,7-Dimethyloctyl)thio)pyridine (IM-10). To a solution of **IM-8** (1.00 g, 5.49 mmol) dissolved in 10 mL MeOH was added 2 N aqueous NaOH (0.22 g, 5.49 mmol). The mixture was refluxed for 2 h.[31-32] Solvents were removed *in vacuo* to produce the sodium salt of 3-mercaptopyridine (**IM-9**, 0.51 g, 3.81 mmol, 69.4%) as a brown solid, which was used for the next step without purification. To a solution of 1-bromo-3,7-dimethyloctane (0.80 g, 3.62 mmol) was added sodium pyridine-3-thiolate (0.51 g, 3.81 mmol) dissolved in 4 mL dry DMF. The mixture was stirred at RT for 16 h. The combined organic layers were dried over Na_2SO_4, filtered and concentrated

in vacuo. The crude compound was purified by flash column chromatography on silica (30% EA/PE) to give **IM-10** (0.48 g, 1.92 mmol, 53%) as an oil. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.57 (d, *J* = 6.0 Hz, 1H), 8.41 (dd, *J* = 6.0, 2.0 Hz, 1H), 7.65 (ddd, *J* = 10.0, 3.0, 2.0, 1H), 7.22 (ddd, *J* = 10.0, 1.0 Hz, 1H), 3.00-2.86 (m, 2H), 1.69-1.42 (m, 4H) 1.28-1.08 (m, 6H), 0.89 (d, *J* = 8.0 Hz, 3H). 0.86 (D, *J* = 8.0 Hz, 6H).

Hydrogen(2-(3-((3,7-dimethyloctyl)thio)pyridin-1-ium-1-yl)-1-phosphonoethyl)phosphonate (79). According to **Procedure B**, 3-((3,7-dimethyloctyl)thio)pyridine (0.075 g, 0.30 mmol) and vinylidene-1,1-bisphosphonic acid (0.053 g, 0.28 mmol) in 1.0 mL of H_2O yielded hydrogen (2-(3-((3,7-dimethyloctyl)thio)pyridin-1-ium-1-yl)-1-phosphonoethyl)phosphonate (0.089 g, 0.20 mmol, 71.4%) as a white powder.^{1}H NMR (D_2O, 500 MHz): δ 8.88 (s, 1H), 8.73 (d, *J* = 6.0 Hz, 1H), 8.31 (d, *J* = 8.5 Hz, 1H), 7.83 (dd, *J* = 8.5, 8.0 Hz, 1H), 4.92 (td, *J* = 12.5, 6.5 Hz, 2H), 3.27-3.17 (m, 2H), 2.35 (tt, *J* = 21.0, 6.5, 1H), 1.76-1.52 (m, 2H), 1.35-1.16, (m, 6H), 0.94 (d, *J* = 6.5 Hz, 3H), 0.87 (d, *J* = 6.5 Hz, 6H); ^{31}P NMR (D_2O, 202 MHz): δ 14.11; ESI HRMS: *m/z* $[M+H]^+$ calculated for $C_{17}H_{32}NO_6P_2S^+$, 440.1420; found, 440.1412; purity = 97.5 % (qNMR).

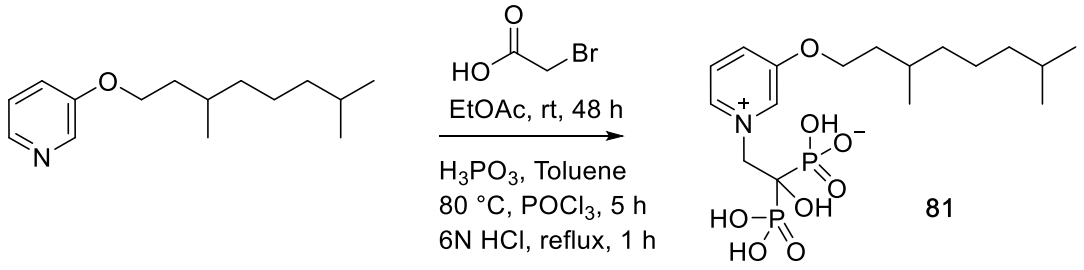
Synthesis of 80:



4-(4,8-Dimethylnonyl)pyridine (IM-11). According to the procedure used to synthesize **IM-3**, 4-methylpyridine (1.00 g, 10.70 mmol) in 10 mL of THF, LDA (5.64 mL, 11.30 mmol), and 1-bromo-3,7-dimethyloctane (2.51 mL, 11.80 mmol) in 3 mL THF yielded 4-(4,8-dimethylnonyl)pyridine (1.87 g, 8.025 mmol, 75%) as the product. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.48 (d, *J* = 7.5 Hz, 2H), 7.11 (d, *J* = 7.5 Hz 2H), 2.64-2.52 (m, 2H), 1.90 (s 1H), 1.70-1.03 (m, 12H), 0.86 (d, *J* = 8.0 Hz, 6H), 0.85 (d, *J* = 8.0 Hz, 3H).

Hydrogen(2-(4-(4,8-dimethylnonyl)pyridin-1-ium-1-yl)-1-phosphonoethyl) phosphonate (80). According to **Procedure B**, 4-(4,8-dimethylnonyl)pyridine (**IM-11**, 0.052 g, 0.28 mmol) and vinylidene-1,1-bisphosphonic acid (0.071 g, 0.30 mmol) in 1.20 mL of H_2O yielded hydrogen(2-(4-(4,8-dimethylnonyl)pyridin-1-ium-1-yl)-1-phosphonoethyl)phosphonate (0.091 g, 0.22 mmol, 78%) as a white powder. ^{1}H NMR (D_2O, 500 MHz): δ 8.71 (d, *J* = 6.5 Hz, 2H), 7.75 (d, *J* = 6.0 Hz, 2H), 4.86-4.80 (m, 2 H), 2.90-2.81 (m, 2H), 2.31 (tt, *J* = 20.5, 6.8 Hz, 1H), 1.78-1.65 (m, 2H), 1.52-1.43 (m, 2H), 1.36-1.05 (m, 8H), 0.81 (d, *J* = 6.5 Hz, 9H); ^{31}P (202 MHz, D_2O): δ 14.10; ESI HRMS: *m/z* $[M+H]^+$ calculated for $C_{18}H_{34}NO_6P_2^+$, 422.1856; found, 422.1862; purity = 95.4 % (qNMR).

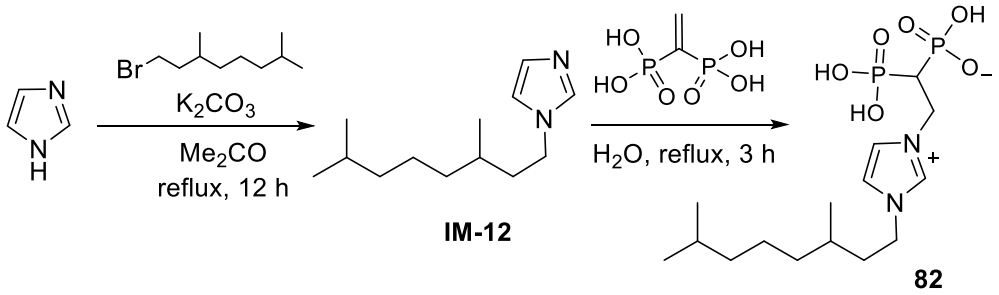
Synthesis of 81:



Hydrogen(2-(3-((3,7-dimethyloctyl)oxy)pyridin-1-ium-1-yl)-1-phosphonoethyl)phosphonate (81). Bromoacetic acid (0.27 g, 1.95 mmol) was added to a

solution of the substituted pyridine **IM-11** (0.46 g, 1.95 mmol) in ethyl acetate (3 mL), and the mixture was stirred at RT for 2 days yielding substituted 1-carboxymethylpyridinium bromide as a white precipitate.[20] The product was then filtered, washed with ethyl acetate (2 x 3 mL), and dried *in vacuo*. The resulting white powder was added to a mixture of H_3PO_3 (0.49 mL, 9.77 mmol) and toluene (6 mL) and heated to 80 °C, while stirring. After all solids melted, $POCl_3$ (0.91 mL, 9.77 mmol) was added dropwise, and the mixture vigorously stirred at 80 °C for 5 h. Upon cooling, the supernatant was decanted, and 6 N HCl (3 mL) added to the residue. The resulting solution was refluxed for 1 h, then most solvent was removed *in vacuo*. 2-Propanol (25 mL) was added to precipitate the title compound as a white powder. The powder was filtered, washed with 2-propanol (5 x 5 mL), then dried and further purified by recrystallization from H_2O/2-PrOH to yield hydrogen(2-(3-((3,7-dimethyloctyl)oxy)pyridin-1-ium-1-yl)-1-phosphonoethyl) phosphonate (0.51, 1.21 mmol, 62%) as a white powder. ^{1}H NMR (D_2O, 500 MHz): δ 8.61 (s, 1H), 8.54 (d, *J* = 6.0 Hz, 1H), 8.02 (dd, *J* = 8.5 Hz, 1H), 7.83 (dd, *J* = 9.0, 6.5 Hz, 1H), 4.95 (t, *J* = 9.0 Hz, 2H), 4.36-4.28 (m, 2H), 1.93-1.88 (m, 1H), 1.74-1.67 (m, 3H), 1.39-1.19 (m, 6H) 0.97 (d, *J* = 6.5 Hz, 3H), 0.88 (d, *J* = 6.5 Hz, 9H); ^{31}P NMR (D_2O, 202 MHz): δ 13.28; ESI HRMS: *m/z* $[M+H]^+$ calculated for $C_{17}H_{32}NO_8P_2^+$, 440.1598; found, 440.1586; purity = 95.0 % (qNMR).

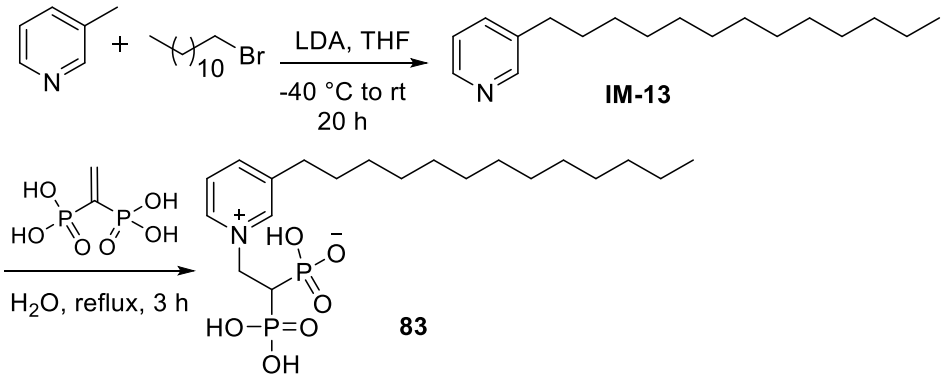
Synthesis of 82:



1-(3,7-Dimethyloctyl)-1H-imidazole (IM-12). A mixture of 1H-imidazole (0.20 g, 2.94 mmol) and K_2CO_3 (0.81 g, 5.88 mmol) was stirred in 15 mL acetone. 1-Bromo-3,7-dimethyloctane (0.63 mL, 2.94 mmol) was added, and the mixture stirred for 12 h at 80 °C. The mixture was cooled to RT, 10 mL of water added, and the product extracted into 2 x 15 mL of ethyl acetate. The crude compound was purified by flash column chromatography on silica (25 % EA/PE) to give **IM-12** (0.50 g, 2.41 mmol, 82%) as a semi-solid. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.46 (s, 1H), 7.05 (s, 1H), 6.90 (s, 1H) 4.00-3.89 (m, 2H), 1.83-1.76 (m, 1H), 1.62-1.38 (m, 3H), 1.32-1.10 (m, 6H), 0.93 (d, *J* = 7.0 Hz, 3H), 0.86 (d, *J* = 7.0 Hz, 6H).

Hydrogen(2-(1-(3,7-dimethyloctyl)-1H-imidazol-3-ium-3-yl)-1-phosphonoethyl) phosphonate (82). According to **Procedure B**, **IM-12** (0.083 g, 0.40 mmol) and vinylidene-1,1-bisphosphonic acid (0.075 g, 0.40 mmol) in 1.0 mL of H_2O gave hydrogen(2-(1-(3,7-dimethyloctyl)-1H-imidazol-3-ium-3-yl)-1-phosphonoethyl)phosphonate (0.044 g, 0.11 mmol, 28%) as a white powder. ^{1}H NMR (D_2O, 500 MHz): δ 8.81 (s, 1H), 7.57 (s, 1H), 7.42 (s, 1H), 4.61-4.54 (m, 2H), 4.22-4.19 (m, 2H), 2.43-2.35 (m, 1H), 1.95-1.88 (m, 1H), 1.73-1.67 (m, 1H), 1.52-1.15 (m, 6H), 0.94 (d, *J* = 6.5 Hz, 3H), 0.85 (d, *J* = *6.5* Hz, 6H); ^{31}P (D_2O, 202 MHz): δ 14.37; ESI HRMS: *m/z* $[M+H]^+$ calculated for $C_{15}H_{31}N_2O_6P_2^+$, 397.1652; found, 397.1651; purity = 96.1 % (qNMR).

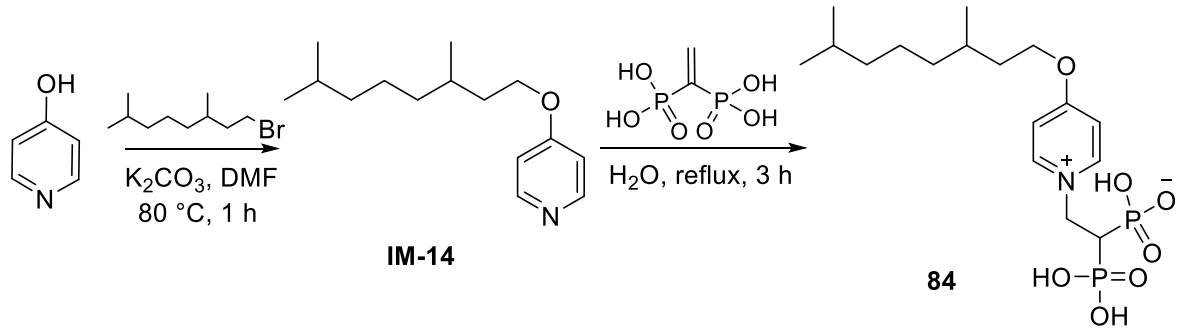
Synthesis of 83:



3-Dodecylpyridine (IM-13). According to the procedure used to synthesize **IM-3**, 3-methylpyridine (0.80 g, 8.59 mmol) in 10 mL of THF, LDA (4.53 mL, 9.07 mmol), and 1-bromododecane (2.02 mL, 9.47 mmol) in 3 mL THF yielded 3-tridecylpyridine (1.57 g, 6.36 mmol, 74%). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.41 (d, *J* = 1.5 Hz, 1H), 8.39 (dd, *J* = 4.5, 1.5 Hz, 1H), 7.44 (d, *J* = 8.0, 1H), 7.15 (dd, *J* = 12.3, 6.0 Hz, 1H), 2.56 (t, *J* = 7.5 Hz, 2H), 1.57 (quintet, *J* = 7.4 Hz, 2H), 1.27-1.22 (m, 20 H), 0.84 (t, *J* = 7.0 Hz, 3H).

Hydrogen (1-phosphono-2-(3-tridecylpyridin-1-ium-1-yl)ethyl)phosphonate (83). According to **Procedure B**, 3-tridecylpyridine (0.090 g, 0.30 mmol) and vinylidene-1,1-bisphosphonic acid (0.065 g, 0.35 mmol) in 1.0 mL of H_2O yielded hydrogen(1-phosphono-2-(3-tridecylpyridin-1-ium-1-yl)ethyl)phosphonate (0.10 g, 0.23 mmol, 75%) as a white powder. ^{1}H NMR (D_2O, 500 MHz): δ 8.77 (s, 1H), 8.72 (d, *J* = 6.0 Hz, 1H), 8.24 (d, *J* = 8.0 Hz, 1H), 7.80 (dd, *J* = 7.0 Hz, 1H), 4.87 (td, *J* = 13.3, 6.7 Hz, 2H), 2.80 (t, 2H), 2.30 (tt, *J* = 20.8, 6.5 Hz, 1H), 1.68 (quintet, *J* = 6.9 Hz, 2H), 1.31-1.24 (m, 20H), 0.82 (t, *J* = 6.8 Hz, 3H); ^{31}P (202 MHz, D_2O): δ 14.09; ESI HRMS: *m/z* $[M+H]^+$ calculated for $C_{20}H_{33}NO_6P_2^+$, 450.2169; found, 450.2158; purity = 95.9 % (qNMR).

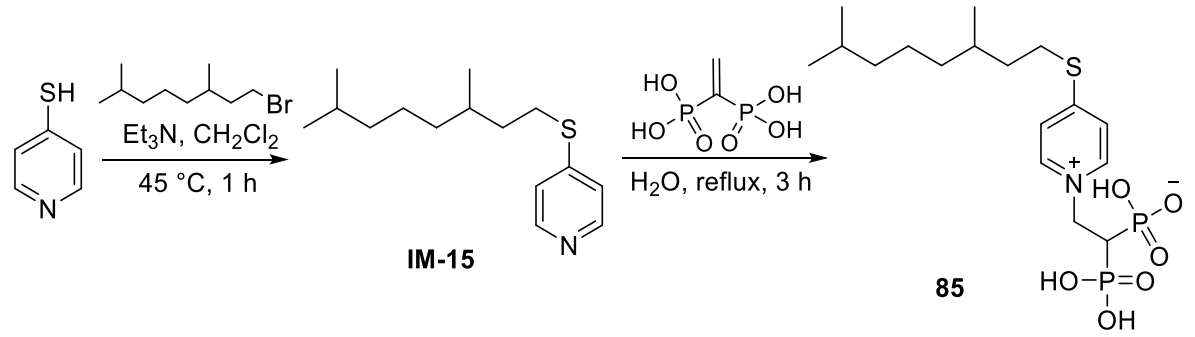
Synthesis of 84:



4-((3,7-Dimethyloctyl)oxy)pyridine (IM-14). According to **Procedure A**, 4-hydroxypyridine (1.00 g, 10.50 mmol), K_2CO_3 (2.91 g, 21.00 mmol), and 1-bromo-3,7-dimethyloctane (2.32 g, 10.50 mmol) in 15 mL of DMF yielded **IM-14** (1.61 g, 6.83 mmol, 65%) as a brown oil. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.41 (d, *J* = 6.4 Hz, 2H), 6.80 (d, *J* = 6.4 Hz, 2H), 6.31 (d, *J* = 8.5 Hz, 1H), 4.08-4.00 (m, 2H), 2.59-2.55 (m, 2H), 1.86-1.80 (m, 1H), 1.69-1.50 (m, 3H), 1.34-1.13 (m, 6H), 0.94 (d, *J* = 6.4 Hz, 3H), 0.87 (d, *J* = 6.4 Hz, 6H).

Hydrogen(2-(4-((3,7-dimethyloctyl)oxy)pyridin-1-ium-1-yl)-1-phosphonoethyl)phosphonate (84). According to **Procedure B**, 4-((3,7-dimethyloctyl)oxy)pyridine (0.075 g, 0.32 mmol) and vinylidene-1,1-bisphosphonic acid (0.057 g, 0.30 mmol) in 1.0 mL H_2O yielded hydrogen (2-(4-((3,7-dimethyloctyl)oxy)pyridin-1-ium-1-yl)-1-phosphonoethyl)phosphonate (0.098 g, 0.23 mmol, 76.2%) as a white powder. ^{1}H NMR (D_2O, 500 MHz): δ 8.61 (d, *J* = 7.5 Hz, 2H), 7.31 (d, *J* = 7.5 Hz, 2H), 4.72 (td, *J* = 13.0, 7.0 Hz, 2H), 4.37-4.35 (m, 2H), 2.64-2.55 (m, 2H), 2.31 (tt, *J* = 20.8, 6.7 Hz, 1H), 1.90-1.84 (m, 12H), 1.66-1.63 (m, 2H); 1.50 (quintet, *J* = 6.7 Hz, 1H), 1.36-1.13 (m, 6H), 0.91 (d, *J* = 6.0 Hz, 3H), 0.82 (d, *J* = 7.0 Hz, 6H); ^{31}P NMR (D_2O, 202 MHz): δ 14.09; ESI HRMS: *m/z* $[M+H]^+$ calculated for $C_{17}H_{32}NO_7P_2^+$, 424.1649; found, 424.1634; purity = 96.5 % (qNMR).

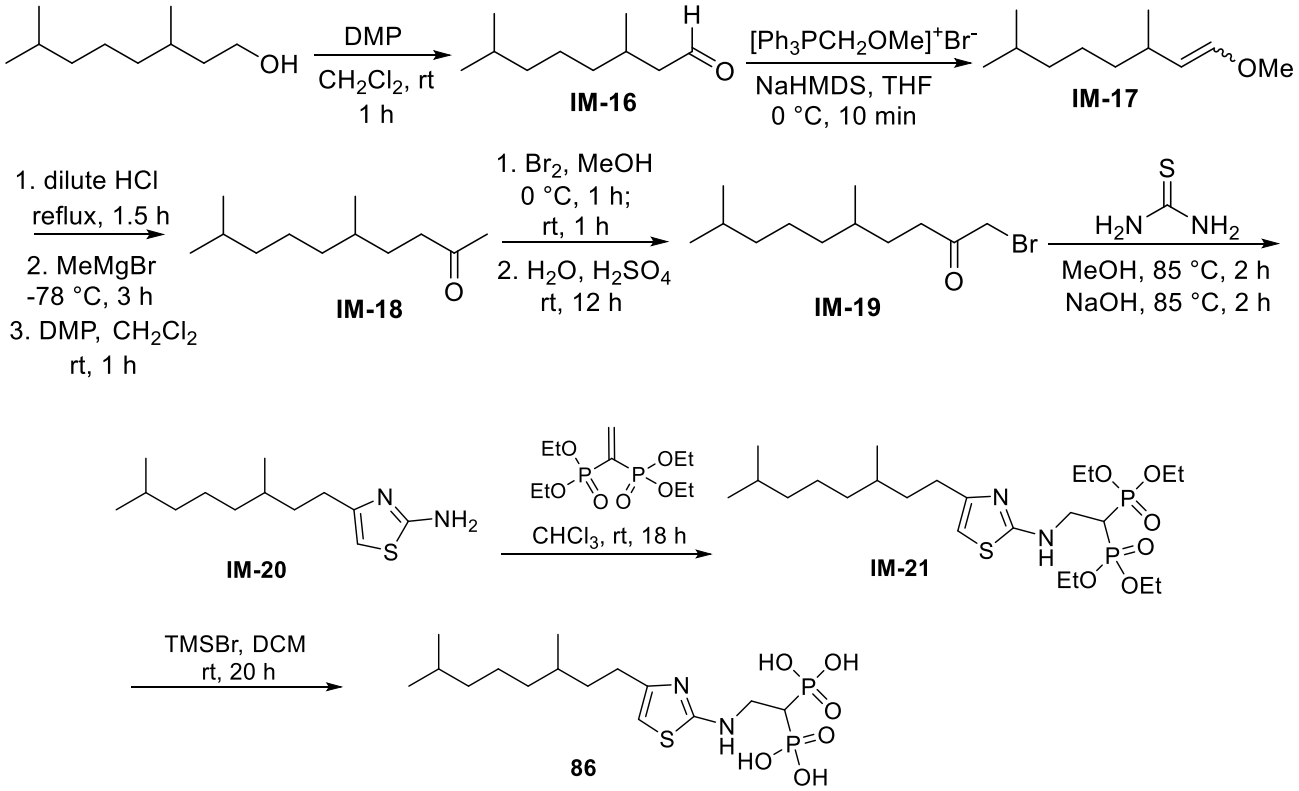
Synthesis of 85:



4-((3,7-Dimethyloctyl)thio)pyridine (IM-15). To a solution of 4-mercaptopyridine (0.30 g, 2.70 mmol) and 1-bromo-3,7-dimethyloctane (0.67 mL, 3.24 mmol) in 4 mL of dry DCM was added Et_3N (0.38 mL, 2.70 mmol), dropwise, at RT.[33] The mixture was stirred at 45 °C for 1 h and the crude product purified by flash column chromatography on silica (40% EA/PE) to give **IM-15** (0.44 g, 1.76 mmol, 65%). ^{1}H NMR (500 MHz, D_2O): δ 8.38 (d, *J* = 5.5 Hz, 2H), 7.09 (d, *J* = 6.0 Hz, 2H), 3.03-2.90 (m, 2H), 1.74-1.49 (m, 2H), 1.34-1.12 (m, 6H), 0.94 (d, *J* = 6.5 Hz, 3H), 0.86 (d, *J* = 7.0 Hz, 6H).

Hydrogen(2-(4-((3,7-dimethyloctyl)thio)pyridin-1-ium-1-yl)-1-phosphonoethyl)phosphonate (85). According to **Procedure B**, 4-((3,7-dimethyloctyl)thio)pyridine, **IM-15** (0.075 g, 0.30 mmol), and vinylidene-1,1-bisphosphonic acid (0.053 g, 0.28 mmol) in 1.0 mL of H_2O produced hydrogen (2-(4-((3,7-dimethyloctyl)thio)pyridin-1-ium-1-yl)-1-phosphonoethyl) phosphonate (0.095 g, 0.22 mmol, 76%) as a white powder. ^{1}H NMR (D_2O, 500 MHz): δ 8.55 (d, *J* = 7.5 Hz, 2H), 7.69 (d, *J* = 7.5 Hz, 2H), 4.84-4.75 (m, 2H), 3.32-3.20 (m, 2H), 2.33 (tt, *J* = 20.8, 6.6 Hz, 1H), 1.82-1.51 (m, 4H), 1.40-1.17 (m, 6H), 0.97 (d, *J* = 6.5 Hz, 3H), 0.88 (d, *J* = 6.5 Hz, 9H); ^{31}P NMR (D_2O, 202 MHz): δ 13.53; ESI HRMS: *m/z* $[M+H]^+$ calculated for $C_{17}H_{32}NO_6P_2S^+$, 440.1420; found, 440.1409; purity = 96.9 % (qNMR).

Synthesis of 86:



3,7-Dimethyloctanal (IM-16). A solution of 3,7-dimethyloctan-1-ol (5.00 g, 31.58 mmol) and DMP (14.73 g, 34.75 mmol) in 75 mL CH_2Cl_2 was stirred at RT for 1 h.[34] The mixture was added to a $Na_2S_2O_3$ (38.50 g, 243.30 mmol) solution in 250 mL of saturated Na_2CO_3 and extracted into 4 x 50 mL Et_2O. The combined organic layers were dried over Na_2SO_4 and concentrated (in a 30 °C water bath) to give the crude product. The crude material was purified by flash column chromatography on silica (20 % Et_2O/PE) to give **IM-16** (4.64 g, 29.69 mmol, 94% yield) as a colorless oil. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 9.76 (t, *J* = 3.0, Hz, 1H), 2.42-2.36 (m, 2H), 2.25-2.19 (m, 2H), 1.52 (heptane, J = 7.3 Hz, 1H), 1.32-1.14 (m, 6H), 0.96 (d, J = 6.5 Hz, 3H), 0.86 (d, *J* = 6.0 Hz, 6H).

(Z) and (E)-1-Methoxy-3,7-dimethyloct-1-ene (IM-17). To a suspension of $[MeOCH_2PPh_3]^+Br^-$ (13.94 g, 36 mmol) in 50 mL dry THF was added sodium bis(trimethylsilyl)amide (NaHMDS; 1.00 M

in THF, 5.94 g, 32.4 mmol) dropwise at -78 °C to produce a bright red solution.[35] After 5 min, the bright red solution was added dropwise over 30 min to a solution of 3,7-dimethyloctanal (4.50 g, 28.8 mmol) in 25 mL THF. The mixture was stirred at -78 °C for 10 min and then allowed to warm to 0 °C over 1 h. The reaction was quenched with NH_4Cl and extracted with 3 x 40 mL of ethyl acetate. The organic layers were dried with Na_2SO_4, solvent removed *in vacuo*, and the crude compound purified by flash column chromatography on silica in 10% EA/PE to give a ~ 1:1 mixture of (*Z*) and (*E*)-1-methoxy-3,7-dimethyloct-1-ene, **IM-17** (3.72 g, 21.89 mmol, 76%) as an oil. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 6.25 (d, *J* = 15.5 Hz, 1H), 5.91 (d, *J* = 8.0 Hz, 1H), 4.71 (dt, *J* = 15.5, 9.5 Hz, 1H), 4.36-4.31 (m, 1H), 3.57 (s, 3H), 3.51 (s, 3H), 2.06-2.00 (m, 2H), 1.95-1.87 (m, 2H), 1.77-1.70 (m, 1H), 1.56-1.07 (m, 16H), 0.86 (d, *J* = 6.5 Hz, 18 H).

5,9-Dimethyldecan-2-one (IM-18). A mixture of (*E/Z*)-1-methoxy-3,7-dimethyloct-1-ene (3.40 g, 19.97 mmol) in 60 mL acetone:water (9:1) and concentrated HCl (0.25 mL) was refluxed for 1.5 h at 60 °C. The mixture was then cooled to RT and 20 mL of water added and the product extracted with 3 x 25 mL ethyl acetate.[34-35] The crude 4,8-dimethylnonanal (2.65 g, 15.58 mmol, 78%) was used without further purification for the next step. To a solution of 4,8-dimethylnonanal (1.20 g, 7.048 mmol) in 20 mL THF, 3M MeMgBr (1.00 g, 8.46 mmol) in Et_2O was added at -78 °C. The mixture was stirred at -78 °C for 3 h. Then, 15 mL of water was added, and the product extracted into 3 x 25 mL ethyl acetate. The organic layer was dried over Na_2SO_4, the solvent was removed *in vacuo*, and the product purified by flash column chromatography on silica (20 % EA/PE) to give 5,9-dimethyldecan-2-ol (0.45 g, 2.41 mmol, 33 % yield) as a colorless oil. To a solution of 5,9-dimethyldecan-2-ol (0.43 g, 2.31 mmol) in 15 mL CH_2Cl_2 was added DMP (Dess-Martin periodinane; 1.96 g, 4.61 mmol). After

1 h, the mixture was added to a solution of $Na_2S_2O_3$ (5.10 g, 32.37 mmol) in 50 mL saturated Na_2CO_3, and the entire mixture was extracted with 2 x 25 mL Et_2O. The combined organic layers were dried on Na_2SO_4 and concentrated (in a 30 °C water bath) to give the crude product. The crude product was purified by flash column chromatography on silica (20% Et_2O/PE) to give **IM-18** (0.25 g, 1.34 mmol, 58.1% yield) as a colorless oil. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.48-2.36 (m, 2H), 2.14 (s, 3H), 1.63-1.48 (m, 2H), 1.40-1.20 (m, 5 H), 1.15-1.08 (m, 3H), 0.87-0.85 (m, 2H).

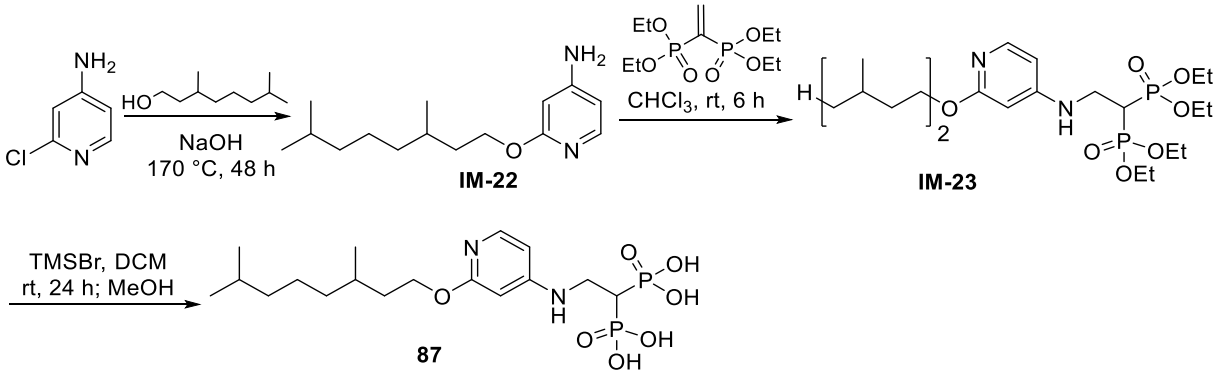
1-Bromo-5,9-dimethyldecan-2-one (IM-19). To a solution of 5,9-dimethyldecan-2-one (0.60 g, 3.26 mmol) and 2.0 mL methanol at -10 °C, bromine (0.52 g, 3.26 mmol) was added, dropwise. The mixture was stirred at 0 °C for 1 h and for an additional hour, at RT. 1 mL H_2O and concentrated sulfuric acid (1.81 mL, 32.60 mmol) were added to the mixture in an ice bath.[36] After the mixture was stirred overnight at RT, white crystals precipitated. The precipitate was filtered, washed with H_2O, and dried to give **IM-19** (0.72 g, 2.74 mmol, 84%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 3.90 (s, 2H), 2.68-2.62 (m, 2H), 1.68-1.09 (m, 10H), 0.87 (d, *J* = 6.4 Hz, 3H), 0.86 (d, *J* = 6.8 Hz, 6H).

4-(3,7-Dimethyloctyl)thiazol-2-amine (IM-20). A solution of 1-bromo-5,9-dimethyldecan-2-one (**IM-19**, 0.57 g, 2.15 mmol) and thiourea (0.18 g, 2.404 mmol) in 1 mL MeOH was stirred for 5 min at RT and then at 85 °C for 2 h. Sodium hydroxide (0.16 g, 4.099 mmol) was added, and the mixture stirred for an additional 2 h, at 85 °C. [37] The crude compound was purified by flash column chromatography on silica (40% EA/PE) to give **IM-20** (0.32 g, 1.33 mmol, 62%) as a white solid. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 6.08 (s, 1H), 4.88 (broad s, 2H), 2.60-2.46 (m, 2H), 1.68-1.63 (m, 1H), 1.54-1.40 (m, 3H), 1.31-1.09 (m, 6H), 0.91 (d, *J* = 6.0 Hz, 3H), 0.86 (d, *J* = 6.5 Hz, 6H).

Tetraethyl(2-((4-(3,7-dimethyloctyl)thiazol-2-yl)amino)ethane-1,1-diyl)bis(phosphonate) (IM-21). According to **Procedure C**, 4-(3,7-dimethyloctyl)thiazol-2-amine (0.15 g, 0.62 mmol) and tetraethylethene-1,1-diylbis(phosphonate) (0.11 g, 0.37 mmol) in 5 mL $CHCl_3$ gave **IM-21** (0.14 g, 0.25 mmol, 66.8%) as a viscous oil. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 6.05 (s, 1H), 5.88 (broad s, 1H), 4.24-4.15 (m, 8H), 3.85 (tt, *J* = 15.8, 6.5 Hz, 2H), 2.84 (tt, *J* = 23.0, 6.3 Hz, 1H), 2.58-2.40 (m, 2H), 1.66-1.11 (m, 22H), 0.89 (d, *J* = 6.5 Hz, 3H), 0.86 (d, *J* = 6.5 Hz, 6H); ^{31}P NMR (D_2O, 202 MHz): δ 22.40.

(2-((4-(3,7-Dimethyloctyl)thiazol-2-yl)amino)ethane-1,1-diyl)bis(phosphonic acid) (86). According to **Procedure D**, **IM-21** (0.14 g, 0.25 mmol) and TMSBr (0.45 mL, 3.50 mmol) in 3 mL DCM yielded (2-((4-(3,7-dimethyloctyl)thiazol-2-yl)amino)ethane-1,1-diyl)bis(phosphonic acid) (0.076 g, 0.18 mmol, 71%) as a white solid. ^{1}H NMR (D_2O, 500 MHz): δ 6.28 (s, 1H), 3.58-3.51 (m, 2H), 3.68 (td, *J* = 13.5, 6.8 Hz, 2H), 5.58-2.50 (m, 2H), 2.27 (tt, *J* = 20.5, 6.7 Hz, 1H), 1.64-1.15 (m, 10H), 0.91 (d, *J* = 5.0 Hz, 3H), 0.86 (d, *J* = 6.5 Hz, 6H); ^{31}P (202 MHz, D_2O): δ 16.47; ESI HRMS: *m/z* $[M+H]^+$ calculated for $C_{15}H_{31}N_2O_6P_2S^+$, 429.1373; found, 429.1365; purity = 96.5 % (qNMR).

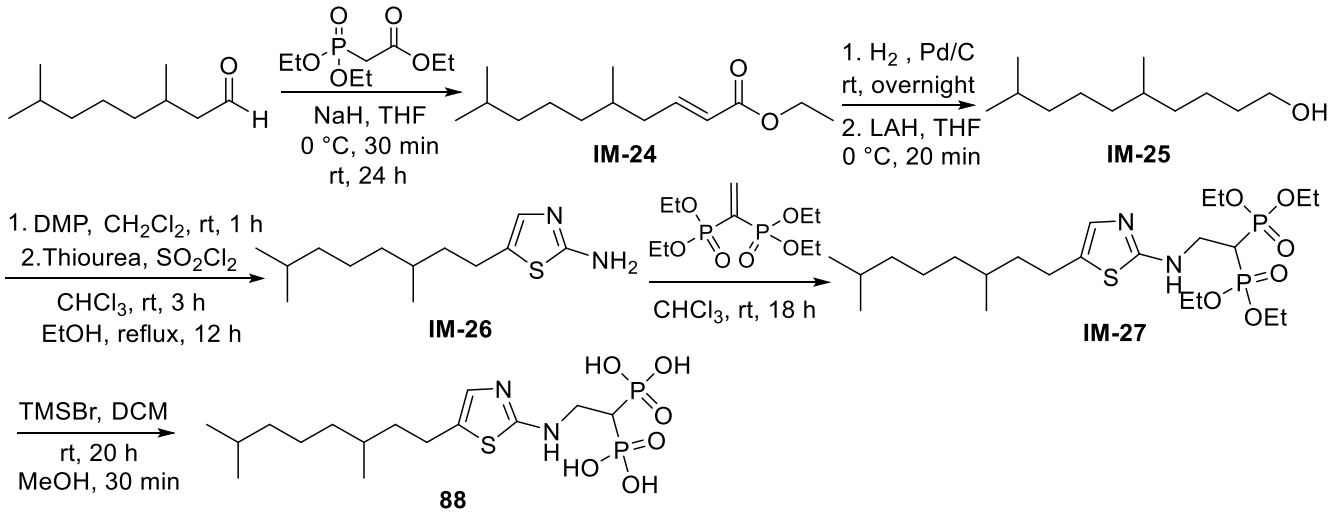
Synthesis of 87:



Tetraethyl(2-((2-((3,7-dimethyloctyl)oxy)pyridin-4-yl)amino)ethane-1,1-diyl)bis(phosphonate) (IM-23). A mixture of 2-chloropyridin-4-amine (1.0 g, 7.96 mmol), 3,7-dimethyloctan-1-ol (18.0 mL, 95.57 mmol), and NaOH (1.27 g, 31.85 mmol) was refluxed at 170 °C for 48 h to give **IM-22** (0.50 g, 2.00 mmol, 25.1%) as a brown oil.[38] The amine was reacted with tetraethyl vinylidene bisphosphonate according to **Procedure C**. 2-((3,7-dimethyloctyl)oxy)pyridin-4-amine (0.30 g, 1.20 mmol) and tetraethyl ethene-1,1-diylbis(phosphonate) (0.20 g, 0.66 mmol) in 5 mL $CHCl_3$ gave **IM-23** (0.12 g, 0.22 mmol, 33%) as a colorless, viscous oil. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.79 (d, *J* = 6.0 Hz, 1H), 6.16 (DD, *J* = 6.0 Hz, 1H), 5.89 (d, *J* = 2.0 Hz, 1H), 5.14 (t, *J* = 6.5 Hz, 1H), 4.26-4.14 (m, 10 H), 3.75-3.66 (m, 2H), 2.63 (tt, *J* = 23.3, 6.0 Hz, 1H), 1.79-1.49 (m, 4H), 1.37-1.12 (m, 18 H), 0.93 (d, *J* = 6.5 Hz, 3H), 0.86 (d, *J* = 6.5 Hz, 6H); ^{31}P (202 MHz, D_2O): δ 22.53.

(2-((2-((3,7-Dimethyloctyl)oxy)pyridin-4-yl)amino)ethane-1,1-diyl)bis(phosphonic acid) (87). According to **Procedure D**, tetraethyl(2-((2-((3,7-dimethyloctyl)oxy)pyridin-4-yl)amino)ethane-1,1-diyl)bis(phosphonate) (**IM-23**, 0.31 g, 0.57 mmol) and TMSBr (1.02 mL, 7.93 mmol) were dissolved in 5 mL DCM to give pure (2-((2-((3,7-dimethyloctyl)oxy)pyridin-4-yl)amino)ethane-1,1-diyl)bis(phosphonic acid) (0.18 g, 0.40 mmol, 71%). ^{1}H NMR (D_2O, 500 MHz): δ 7.70 (d, *J* = 6.0 Hz, 1H), 6.43 (d, *J* = 6.0 Hz, 1H), 6.07 (s, *J* = 2.0 Hz, 1H), 4.26-4.20 (m, 2 H), 3.54 (td, *J* = 14.0, 7.5 Hz, 2H), 2.05 (tt, *J* = 21.0, 6.8 Hz, 1H), 1.83-1.53 (m, 4H), 1.37-1.17 (m, 6 H), 0.95 (d, *J* = 6.5 Hz, 3H), 0.87 (d, *J* = 6.5 Hz, 6H); ^{31}P (D_2O, 202 MHz): δ 16.95; ESI HRMS: *m/z* $[M+H]^+$ calculated for $C_{17}H_{33}N_2O_7P_2^+$, 439.1758; found, 439.1760; purity = 96.4 % (qNMR).

Synthesis of 88:



Ethyl (E)-5,9-dimethyldec-2-enoate (IM-24). To a mixture of 3,7-dimethyloctanal (2.00 g, 12.80 mmol) and ethyl 2-(diethoxyphosphoryl)acetate (3.80 mL, 19.20 mmol) in 15 mL THF was added NaH (0.80 g, 19.84 mmol) at 0 °C. The reaction mixture was stirred for 30 min at 0 °C, allowed to warm to RT, and stirred for 24 h.[39] The crude compound was purified by flash column chromatography on silica (30% EA/PE) to give **IM-24** (2.087 g, 9.22 mmol, 72%) as an oil. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 6.94 (quintet, *J* = 7.4 Hz, 1H), 5.81 (dt, *J* = 15.5, 1.4 Hz, 1H), 4.19 (quartet, *J* = 7.1 Hz, 2H), 2.22-2.17 (m, 1H), 2.05-1.99 (m, 1H), 1.61-1.49 (m, 2H), 1.29 (t, *J* = 7.0 Hz, 3H), 1.32-1.09 (m, 6H), 0.89 (d, *J* = 6.5 Hz, 3H), 0.86 (d, *J* = 6.5 Hz, 6H).

5,9-Dimethyldecan-1-ol (IM-25). To a degassed (N_2) solution of ethyl (*E*)-5,9-dimethyldec-2-enoate (**IM-24,** 1.00 g, 4.42 mmol) in 10 mL of anhydrous MeOH, 10 wt. % Pd/C was added, and the reaction mixture was stirred overnight under a H_2 atmosphere.[40-41] The crude compound was purified by flash column chromatography on silica (50% EA/PE) to give ethyl 5,9-dimethyldec-2-anoate (0.89 g, 3.89 mmol, 88% yield) as an oil. To a solution of ethyl-5,9-dimethyldec-2-anoate (2.20 g, 9.09 mmol) dissolved in 15 mL THF was added LAH (0.43 g, 11.36 mmol) at 0 °C. The reaction was stirred

for 20 min at 0 °C. 15 mL of 2 % HCl was then added to quench excess LAH, and the product was extracted into 2 x 25 mL of ethyl acetate. The organic layer was dried over Na_2SO_4, the solvent removed *in vacuo* evaporated, and the crude product purified by flash column chromatography on silica (40% EA/PE) to give **IM-25** (0.71 g, 3.82 mmol, 42%) as an oil. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 3.64 (t, *J* = 8.3 Hz, 1H), 1.55-1.11 (m, 16 H), 0.86 (d, *J* = 8.5 Hz, 6H), 0.85 (d, *J* = 8.0 Hz, 3H).

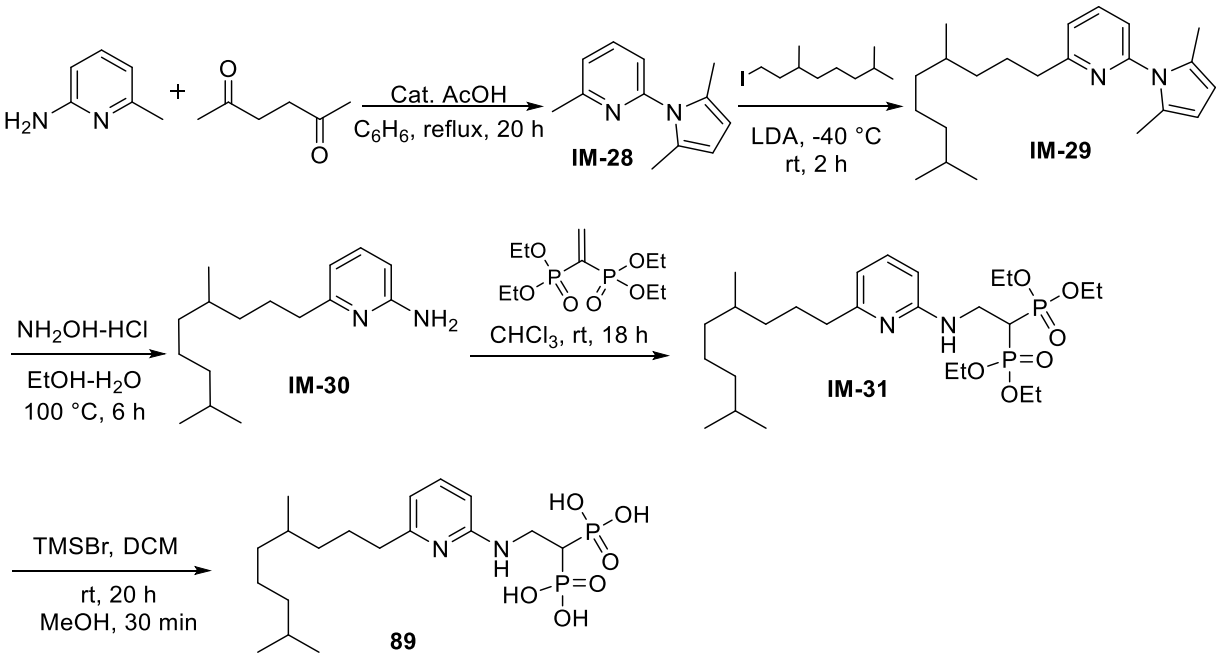
5-(3,7-Dimethyloctyl)thiazol-2-amine (IM-26). To a solution of 5,9-dimethyldecan-1-ol (1.8 g, 9.66 mmol) dissolved in 20 mL DCM was added DMP (4.50 g, 10.61 mmol). The reaction mixture was stirred at RT for 1 h to give 5,9-dimethyldecanal (1.21 g, 6.57 mmol, 68%) as a colorless oil and was used as is for the next step. 5,9-dimethyldecanal (0.25 g, 1.33 mmol), and thiourea (0.20 g, 2.66 mmol) were suspended in 4 mL $CHCl_3$ and cooled to 0 °C. SO_2Cl_2 (0.20 g, 1.46 mmol) was added dropwise, and the mixture stirred at RT for 3 h. $CHCl_3$ was removed *in vacuo* then EtOH (5 mL) added, and the mixture was then refluxed for 12 h, cooled to RT, then 15 mL of water was added and the product extracted in 2 x 20 mL of ethyl acetate.[34, 42] The combined organic layers were dried over Na_2SO_4. The crude compound was purified by flash column chromatography on silica (40% EA/PE) to give **IM-26** (0.158, 0.66 mmol, 48%) as a white solid. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 6.73 (s, 1H), 4.68 (broad s, 2H), 2.70-2.57 (m, 2H), 1.61-1.10 (m, 10H), 0.90 (d, *J* = 5.5 Hz, 3H), 0.87 (d, *J* = 7.0 Hz, 6H).

Tetraethyl(2-((5-(3,7-dimethyloctyl)thiazol-2-yl)amino)ethane-1,1-diyl)bis(phosphonate) (IM-27). According to **Procedure C**, 5-(3,7-dimethyloctyl)thiazol-2-amine (0.13 g, 0.52 mmol) and tetraethylethene-1,1-diylbis(phosphonate) (0.094 g, 0.31 mmol) was dissolved in 1 mL $CHCl_3$ and stirred at RT for 18 h to give tetraethyl(2-((5-(3,7-dimethyloctyl)thiazol-2-yl)amino)ethane-1,1-diyl)bis(phosphonate) (0.14 g, 0.26 mmol, 82%) as a viscous oil. ^{1}H NMR

($CDCl_3$, 500 MHz): δ 6.75 (s, 1H), 5.82 (broad s, 1H), 4.24-4.15 (m, 8H), 3.85 (t, *J* = 6.5, Hz, 2H), 2.82 (tt, *J* = 23.0, 6.3 Hz, 1H), 2.68-2.56 (m, 2H), 1.60-1.09 (m, 22H), 0.89 (t, *J* = 6.0 Hz, 3H), 0.86 (d, *J* = 6.5 Hz, 6H); ^{31}P NMR (D_2O, 202 MHz): δ 22.49.

(2-((5-(3,7-Dimethyloctyl)thiazol-2-yl)amino)ethane-1,1-diyl)bis(phosphonic acid) (88). According to **Procedure D**, tetraethyl(2-((5-(3,7-dimethyloctyl)thiazol-2-yl)amino) ethane-1,1-diyl)bis (phosphonate) (0.13 g, 0.24 mmol) and TMSBr (0.44 mL, 3.37 mmol) dissolved in 3 mL DCM stirred at RT for 20 h to give (2-((5-(3,7-dimethyloctyl)thiazol-2-yl)amino) ethane-1,1-diyl) bis(phosphonic acid) (0.069 g, 0.16 mmol, 67%). ^1H NMR (500 MHz, D_2O): δ 6.78 (s, 1H), 3.62 (td, *J* = 20.8, 6.8 Hz, 2H), 2.76-2.64 (m, 2H), 2.11 (tt, *J* = 20.5, 7.0 Hz, 1H), 1.65-1.16 (m, 10H), 0.91 (d, *J* = 1.5 Hz, 3H), 0.88 (d, *J* = 1.5 Hz, 6H); ^{31}P (202 MHz, D_2O): δ 16.62; ESI HRMS: *m/z* $[M+H]^+$ calculated for $C_{15}H_{31}N_2O_6P_2S^+$, 429.1373; found, 429.1368; purity = 97.2 % (qNMR).

Synthesis of 89:



2-(2,5-Dimethyl-1H-pyrrol-1-yl)-6-methylpyridine (IM-28). To a solution of 2-methyl-5-aminopyridine (4.00 g, 37.00 mmol) and hexane-2,5-dione (4.34 mL, 37.00 mmol) in 48 mL benzene, AcOH (0.5 mL) was added, and the mixture refluxed with a Dean-Stark condenser for 20 h.[43] The mixture was cooled to RT and diluted with diethyl ether. The mixture was then washed with dilute HCl (20 mL) and H_2O (20 mL). The organic layer was dried over Na_2SO_4, filtered, concentrated *in vacuo*, then purified by flash column chromatography on silica (30% EA/PE) to give 2-(2,5-dimethyl-1H-pyrrol-1-yl)-6-methylpyridine (3.79 g, 20.35 mmol, 55%) as an oil. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.71 (dd, *J* = 7.8 Hz, 1H), 7.14 (d, *J* = 7.5 Hz, 1H), 7.02 (d, *J* = 8.0 Hz, 1H), 5.89 (s, 2H), 2.82-2.78 (m, 2H), 1.74-1.47 (m, 3H), 1.81-1.73 (m, 2H), 1.54-1.05 (m, 10 H), 0.86 (d, *J* = 6.5 Hz, 6H), 0.85 (d, *J* = 6.5 Hz, 3H).

2-(2,5-Dimethyl-1H-pyrrol-1-yl)-6-(4,8-dimethylnonyl)pyridine (IM-29). A solution of 2-(2,5-dimethyl-1H-pyrrol-1-yl)-6-methylpyridine (**IM-28**, 0.26 g, 1.40 mmol) in 30 mL of dry THF was added dropwise with stirring to a solution of 2 M LDA (0.17 g, 1.54 mmol) in 5 mL of dry THF at -30 °C. The mixture was stirred at -30 °C for 30 min. 1-iodo-3,7-dimethyloctane (0.40 g, 1.50 mmol) was then added in 20 mL of dry THF, dropwise, with stirring for 30 min, then warmed to RT. After 2 h, the reaction was quenched with saturated NaCl, extracted with diethylether, dried over Na_2SO_4, filtered, concentrated *in vacuo*, then purified by flash column chromatography on silica (30% EA/PE) to give **IM-29** (0.30 g, 0.92 mmol, 65%) as an oil. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.71 (dd, *J* = 7.8 Hz, 1H), 7.13 (d, *J* = 7.5, 1H), 7.02 (d, *J* = 8.0, 1H), 5.89 (s, 2H), 2.82-2.78 (m, 2H), 2.13 (s, 6H), 1.81-1.73

(m, 2H), 1.51 (septet, *J* = 6.7 Hz, 1H), 1.41-1.05 (m, 9H), 0.86 (d, *J* = 6.5 Hz, 6H), 0.85 (d, *J* = 6.5 Hz, 3H).

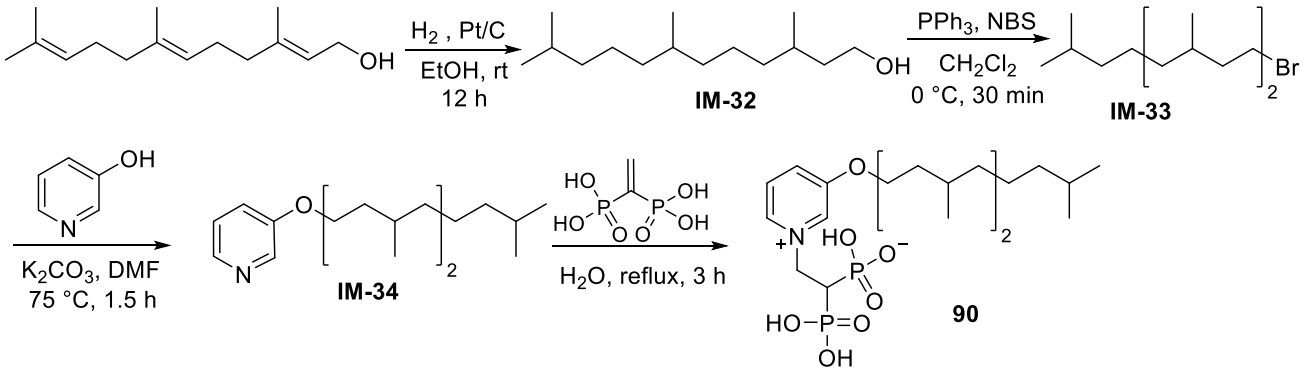
6-(4,8-Dimethylnonyl)pyridin-2-amine (IM-30). IM-29 (0.29 g, 0.88 mmol) was dissolved in a mixture of EtOH (6 mL) and H_2O (2 mL). Hydroxylamine hydrochloride (0.31 g, 4.42 mmol) was then added, and the resulting mixture stirred at 100 °C for 6 h.[44] The mixture was poured into a sodium hydroxide solution (4 mL, 0.10 M) and the crude product extracted with CH_2Cl_2, dried over $MgSO_4$, filtered, and concentrated *in vacuo* to give 6-(4,8-dimethylnonyl)pyridin-2-amine (0.16 g, 71%). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.34 (dd, *J* = 7.5 Hz, 1H), 6.51 (d, *J* = 7.5 Hz, 1H), 6.31 (d, *J* = 8.5 Hz, 1H), 4.36 (broad s, 1H), 2.59-2.55 (m, 2H), 2.13 (s, 6H), 1.74-1.47 (m, 3H), 1.44-1.03 (m, 9H), 0.86 (d, *J* = 7.0 Hz, 6H), 0.85 (d, *J* = 6.5 Hz, 3H).

Tetraethyl (((6-(4,8-dimethylnonyl)pyridin-2-yl)amino)methylene)bis (phosphonate) (IM-31). According to **Procedure C**, 6-(4,8-dimethylnonyl)pyridin-2-amine, **IM-30** (0.17 g, 0.68 mmol), and tetraethylethene-1,1-diylbis(phosphonate) (0.10 g, 0.34 mmol) in 5 mL $CHCl_3$ yielded **IM-31** (0.15 g, 0.27 mmol, 80%). ^{1}H NMR (D_2O, 500 MHz): δ 7.30 (dd, *J* = 7.8 Hz, 1H), 6.43 (d, *J* = 7.0 Hz, 1H), 6.26 (d, *J* = 8.0 Hz, 1H), 5.22 (t, *J* = 6.3 Hz, 1H), 4.23-4.14 (m, 8H), 3.99-3.90 (m, 2H), 2.88 (tt, *J* = 22.8, 6.3 Hz, 1H), 2.57-2.53 (m, 2H), 1.70-1.50 (m, 3H), 1.35-1.10 (m, 21H), 0.86 (d, *J* = 6.5 Hz, 6H), 0.85 (d, *J* = 6.5 Hz, 3H); ^{31}P NMR (D_2O, 202 MHz): δ 23.19.

(((6-(4,8-Dimethylnonyl)pyridin-2-yl)amino)methylene)bis(phosphonic acid) (89). According to **Procedure D**, **IM-31** (0.15 g, 0.26 mmol) and TMSBr (0.48 mL, 3.70 mmol) dissolved in 5 mL DCM yielded (((6-(4,8-dimethylnonyl)pyridin-2-yl)amino)methylene)bis(phosphonic acid) (0.077 g, 0.18 mmol, 69%) as a white solid. ^{1}H NMR (D_2O, 500 MHz): δ 7.58 (dd, *J* = 7.8 Hz, 1H),

6.65 (d, *J* = 7.0 Hz, 1H), 6.56 (d, *J* = 8.0 Hz, 1H), 3.63 (td, *J* = 14.0, 7.0 Hz, 2H), 2.64-2.55 (m, 2H), 2.13 (tt, *J* = 20.8, 7.0 Hz, 1H), 1.73-1.10 (m, 12H), 0.87 (d, *J* = 6.5 Hz, 9H); ^{31}P NMR (D_2O, 202 MHz): δ 17.20; ESI HRMS: *m/z* $[M+H]^+$ calculated for $C_{18}H_{35}N_2O_6P_2^+$, 437.1965; found, 437.1961; purity = 98.1 % (qNMR).

Synthesis of 90:



3,7,11-Trimethyldodecan-1-ol (IM-32). A solution of farnesol (5.00 g, 22.49 mmol) in 25 mL EtOH was hydrogenated at atmospheric pressure in the presence of 10% Pt/C (0.20 g). The mixture was stirred at RT for 12 h, the crude product filtered on Celite and solvent removed *in vacuo* to yield **IM-32** (1.75 g, 7.65 mmol, 34%) as a colorless oil.[45] ^{1}H NMR ($CDCl_3$, 500 MHz): δ 3.71-3.64 (m, 2H), 1.63-1.49 (m, 3H), 1.40-109 (m, 14H), 0.90 (d, *J* = 6.5, 3H), 0.86 (d, *J* = 6.5 Hz, 6H), 0.85 (d, *J* = 6.5 Hz, 3H), 0.84 (d, *J* = 7.0 Hz, 3H).

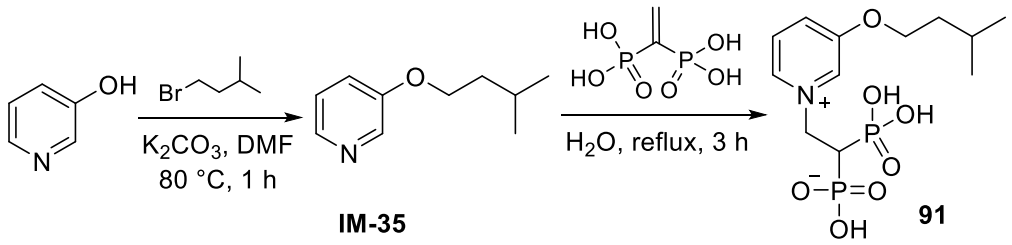
1-Bromo-3,7,11-trimethyldodecane (IM-33). To a solution of 3,7,11-trimethyldodecan-1-ol (**IM-32**, 0.81 g, 3.53 mmol) and triphenylphosphine (1.20 g, 4.59 mmol) in 10 mL of anhydrous CH_2Cl_2 was added NBS (0.63 g, 3.53 mmol) over 30 min at 0 °C. The mixture was stirred for 30 min then concentrated *in vacuo*. 1-bromo-3,7,11-trimethyldodecane (0.85 g, 2.93 mmol, 83%) was

obtained as an oil.[46] ^{1}H NMR ($CDCl_3$, 500 MHz): δ 3.50-3.37 (m, 2H), 1.93-1.85 (m, 1H), 1.70-1.47 (m, 3H), 1.40-103 (m, 13H), 0.90-0.84 (m, 12 H)

3-((3,7,11-Trimethyldodecyl)oxy)pyridine (IM-34). According to **Procedure A**, 3-hydroxypyridine (0.17 g, 1.82 mmol), 1-bromo-3,7,11-trimethyldodecane (0.51 g, 1.73 mmol), and K_2CO_3 (0.48 g, 3.47 mmol) in 5 mL of DMF was stirred at 75 °C for 1.5 h to give a crude product. The crude product was purified by flash column chromatography on silica (20% EA/PE) to give **IM-34** (0.14 g, 0.59 mmol, 34%) as an oil. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.31 (s, 1H), 8.21 (s, 1H), 7.24-7.22 (m, 2H), 4.08-4.01 (m, 2H), 1.87-1.81 (m, 1H), 1.70-1.48 (m, 3H), 1.39-1.04 (m, 13 H), 0.95 (d, *J* = 6.5 Hz, 3H), 0.86 (d, *J* = 7.0 Hz, 9H).

Hydrogen(1-phosphono-2-(3-((3,7,11-trimethyldodecyl)oxy)pyridin-1-ium-1-yl)ethyl) phosphonate (90). According to **Procedure B**, 3-((3,7,11-trimethyldodecyl)oxy)pyridine, (**IM-34**, 0.10 g, 0.32 mmol) and vinylidene-1,1-bisphosphonic acid (0.057 g, 0.31 mmol) in 1.5 mL of H_2O yielded hydrogen(1-phosphono-2-(3-((3,7,11-trimethyldodecyl) oxy)pyridin-1-ium-1-yl)ethyl) phosphonate (0.11 g, 0.23 mmol, 75.2%) as a white powder. ^{1}H NMR (500 MHz, D_2O): δ 8.75 (s, 1H), 8.61 (d, *J* = 5.5 Hz, 1H), 7.95-7.88 (m, 2H), 4.94 (td, *J* = 12.5, 7.5 Hz, 2H), 4.34-4.26 (m, 2H), 2.50 (tt, *J* = 20.0, 7.3 Hz, 1H), 1.94-1.90 (m, 1H), 1.72-1.12 (m, 16H), 0.97 (d, *J* = 6.0 Hz, 3H), 0.90 (d, *J* = 7.0 Hz, 9H); ^{31}P (202 MHz, D_2O): δ 13.26; ESI HRMS: *m/z* $[M–H]^-$ calculated for $C_{22}H_{41}NO_7P_2^-$, 492.2282; found, 492.2280; purity = 96.5 % (qNMR).

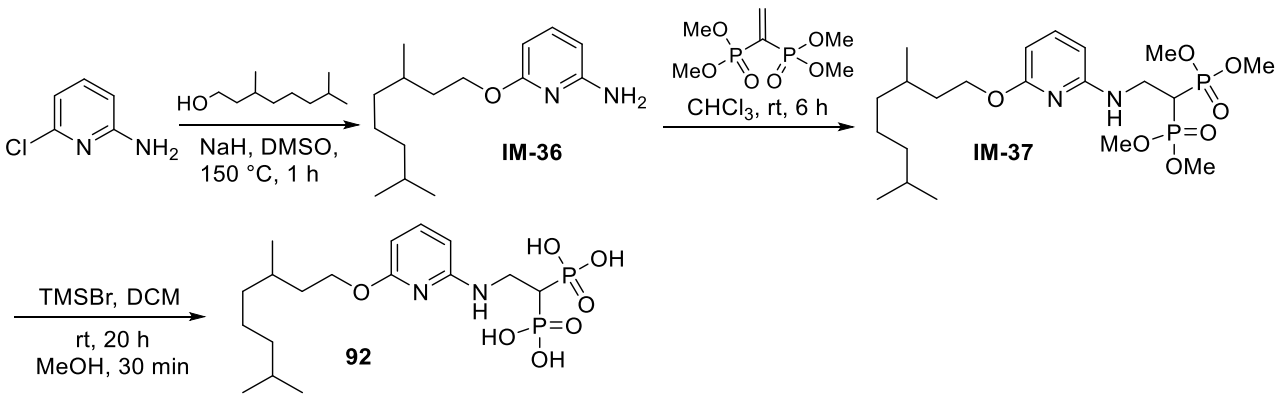
Synthesis of 91:



3-(Isopentyloxy)pyridine (IM-35). According to the synthesis procedure used for **IM-1**, 3-hydroxypyridine (0.50 g, 5.25 mmol), 1-bromo-3-methylbutane (1.031 g, 6.83 mmol), and K_2CO_3 (0.94 g, 6.83 mmol) in 6 mL DMF produced 3-(isopentyloxy)pyridine (0.39 g, 2.36 mmol, 45%) as a colorless oil. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.28 (s, 1H), 8.17 (s, 1H), 7.19-7.14 (m, 2H), 4.00 (t, *J* = 6.5 Hz, 2H), 1.87-1.76 (m, 1H), 1.68-1.64 (m, 2H), 0.94 (d, *J* = 6.5 Hz, 6H).

Hydrogen (2-(3-(isopentyloxy)pyridin-1-ium-1-yl)-1-phosphonoethyl)phosphonate (91). According to **Procedure B**, 3-(isopentyloxy)pyridine (0.068 g, 0.41 mmol) and vinylidene-1,1-bisphosphonic acid (0.070 g, 0.37 mmol) in 1.5 mL of H_2O gave hydrogen(2-(3-(isopentyloxy)pyridin-1-ium-1-yl)-1-phosphonoethyl)phosphonate (0.097 g, 0.27 mmol, 73.8%) as a white powder. ^{1}H NMR (D_2O, 500 MHz): δ 8.71 (s, 1H), 8.57 (d, *J* = 5.5 Hz, 1H), 7.99 (dd, *J* = 8.8, 2.3 Hz, 1H), 7.85-7.82 (m, 2H), 4.93 (td, *J* = 13.0, 5.0 Hz, 2H), 4.31 (t, *J* = 6.8 Hz, 1H), 2.46 (tt, *J* = 20.8, 6.5 Hz, 1H), 1.85 (septet, *J* = 6.7 Hz, 1H), 1.78-1.74 (q, *J* = 5 Hz, 1H) 0.98 (d, *J* = 6.5 Hz, 6H); ^{31}P (202 MHz, D_2O): δ 13.33**;** ESI HRMS: *m/z* $[M+H]^+$ calculated for $C_{12}H_{22}NO_7P_2^+$, 354.0866; found, 354.0866; purity = 98.3 % (qNMR).

Synthesis of 92:



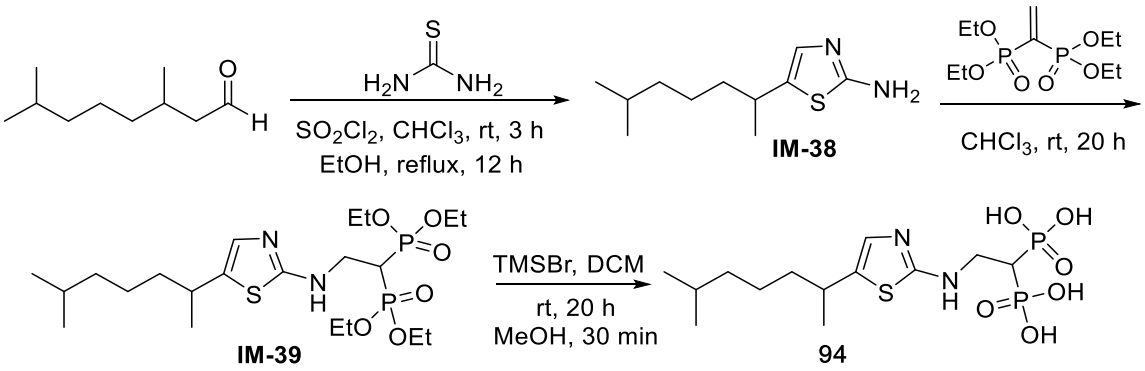
6-((3,7-Dimethyloctyl)oxy)pyridin-2-amine (IM-36). To a solution of 3,7-dimethyloctan-1-ol (1.23 mL, 6.42 mmol) in 5 mL THF was added NaH (0.257 g, 6.42 mmol) portion-wise under a N_2 atmosphere at 0 °C. The mixture was allowed to stir at room temperature for 30 min. Then THF was evaporated *in vacuo*, and the residue was dissolved in 5 mL DMSO. To the above solution 4-chloropyridin-2-amine (0.75 g, 5.83 mmol) was added and the mixture was stirred at 150 °C for 3 h.[47] The mixture was cooled to RT and the DMSO was then evaporated under reduced pressure to give a dark brown residue. To the crude product, 20 mL of water was added, and the product was extracted into 2 x 40 mL of ethyl acetate. The combined organic layers were washed with brine and dried over Na_2SO_4. Purification via flash column chromatography on silica (20 to 50% EA/PE) gave **IM-4** (0.32 g, 1.28 mmol, 22%). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.33 (dd, *J* = 8.8 Hz, 1H), 6.07-6.04 (m, 2H), 4.26 (broad s, 2H), 4.20-4.15 (m, 1H), 1.80-1.75 (m, 1H), 1.55-1.49 (m, 2H), 1.34-.12 (m, 2H), 0.93 (d, *J* = 7.0 Hz, 3H), 0.86 (d, *J* = 7.0 Hz, 6H).

Tetramethyl(2-((6-((3,7-dimethyloctyl)oxy)pyridin-2-yl)amino)ethane-1,1-diyl)bis(phosphonate) (IM-37). According to **Procedure C**, 6-((3,7-dimethyloctyl)oxy)pyridin-2-amine (0.10 g, 0.40 mmol) and tetramethyl ethene-1,1-diylbis(phosphonate) (0.049 g, 0.20 mmol)

in 3 mL $CHCl_3$ gave **IM-37** (0.079 g, 0.16 mmol, 79%) as a brown, viscous oil. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.32 (dd, *J* = 8.0 Hz, 1H), 6.03-5.99 (m, 2H), 4.26-4.20 (m, 2H), 3.98-3.89 (m, 2H), 3.85-3.79 (m, 2H), 2.92 (tt, *J* = 23, 6.3 Hz, 1H), 1.80-1.75 (m, 1H), 1.54-1.50 (m, 2H), 1.33-.11 (m, H), 0.93 (d, *J* = 6.5 Hz, 3H), 0.86 (d, *J* = 6.5 Hz, 6H); ^{31}P NMR ($CDCl_3$, 202 MHz): δ 25.12.

(2-((6-((3,7-Dimethyloctyl)oxy)pyridin-2-yl)amino)ethane-1,1-diyl)bis(phosphonic acid) (92). According to **Procedure D**, tetramethyl (2-((6-((3,7-dimethyloctyl)oxy)pyridin-2-yl)amino)ethane-1,1-diyl)bis(phosphonate) (0.067 g, 0.14 mmol), TMSBr (0.11 mL, 0.82 mmol), 2 mL of DCM, and 2 mL MeOH gave pure (2-((6-((3,7-dimethyloctyl)oxy)pyridin-2-yl)amino)ethane-1,1-diyl)bis(phosphonic acid) (0.039 g, 0.089 mmol, 65%) as a white solid. ^{1}H NMR (D_2O, 500 MHz): δ 7.51 (dd, *J* = 8.0 Hz, 1H), 6.26 (d, *J* = 6.5 Hz, 1H), 6.08 (d, *J* = 8.0 Hz, 1H), 4.14-4.09 (m, 2H), 3.53 (td, *J* = 18.5, 6.0 Hz, 2H), 1.93 (tt, *J* = 21.0, 6.5 Hz, 1H), 1.77-1.48 (m, 4H), 1.32-1.13 (m, 6H), 0.90 (d, *J* = 6.5 Hz, 3H), 0.81 (d, *J* = 6.5 Hz, 6H); ^{31}P NMR (D_2O, 202 MHz): δ 17.62; ESI HRMS: *m/z* $[M–H]^-$ calculated for $C_{17}H_{31}N_2O_7P_2^-$, 437.1612; found, 437.1611 ; purity = 96.1% (qNMR).

Synthesis of 94:



5-(6-Methylheptan-2-yl)thiazol-2-amine (IM-38). 3,7-dimethyloctanal (0.50 g, 3.20 mmol) and thiourea (0.49 g, 6.40 mmol) were suspended in 4 mL $CHCl_3$ and cooled to 0 °C. SO_2Cl_2 (0.48 g,

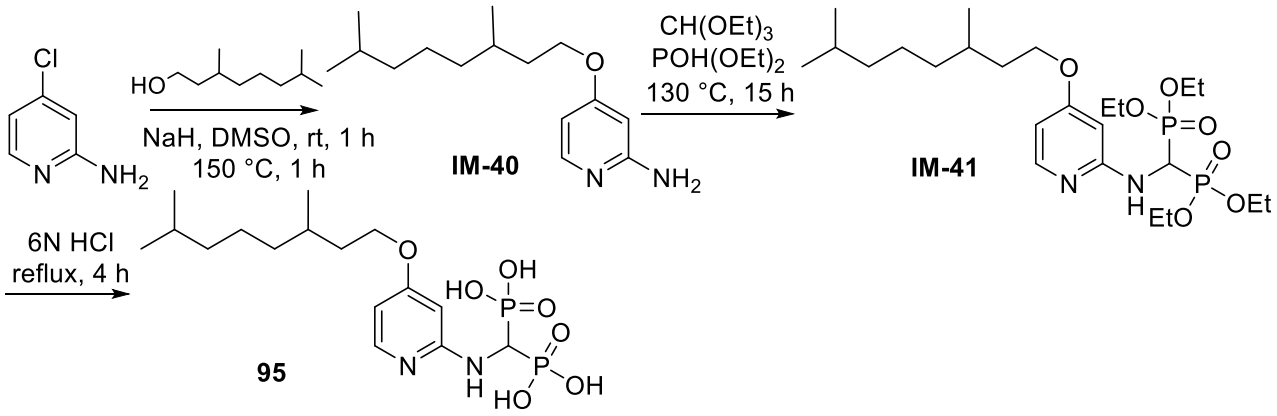
3.52 mmol) was added dropwise, and the mixture stirred at RT for 3 h. $CHCl_3$ was removed *in vacuo* then EtOH (5 mL) added, and the mixture was then refluxed for 12 h, cooled to RT, then 15 mL of water was added and the product extracted into 2 x 20 mL of ethyl acetate.[42] The combined organic layers were dried over Na_2SO_4. The crude compound was purified by flash column chromatography on silica (40% EA/PE) to give **IM-38** (0.42 g, 1.98 mmol, 62%) as a white solid. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 6.73 (s, 1H), 4.70 (broad s, 2H), 2.87-2.79 (m, 1H), 1.51-1.45 (m, 3H), 1.29-1.13 (m, 7H), 0.85 (d, *J* = 2.0 Hz, 3H), 0.84 (d, *J* = 2.0 Hz, 3H).

Tetraethyl(2-((5-(6-methylheptan-2-yl)thiazol-2-yl)amino)ethane-1,1-diyl)bis(phosphonate) (IM-39). According to **Procedure C,** 5-(6-methylheptan-2-yl)thiazol-2-amine (0.12 g, 0.54 mmol) and tetraethylethene-1,1-diylbis(phosphonate) (0.089 g, 0.30 mmol) in 1 mL $CHCl_3$ gave **IM-39** (0.11 g, 0.22 mmol, 73%) as an oil. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 6.76 (s, 1H), 5.81 (broad s, 1H), 4.24-4.16 (m, 8H), 3.86 (tt, *J* = 15.5, 12.7 Hz, 1H) 2.85-2.79 (m, 2H), 1.51-1.45 (m, 3H), 1.37-1.13 (m, 19H), 0.85 (d, *J* = 2.0 Hz, 3H), 0.84 (d, *J* = 2.0 Hz, 3H; ^{31}P NMR (D_2O, 202 MHz): δ 22.49.

(2-((5-(6-Methylheptan-2-yl)thiazol-2-yl)amino)ethane-1,1-diyl)bis(phosphonic acid) (94). According to **Procedure D**, tetraethyl(2-((5-(6-methylheptan-2-yl)thiazol-2-yl)amino)ethane-1,1-diyl)bis(phosphonate) (0.088 g, 0.17 mmol) and TMSBr (0.31 mL, 2.40 mmol) dissolved in 2 mL DCM gave pure (2-((5-(6-methylheptan-2-yl)thiazol-2-yl)amino)ethane-1,1-diyl)bis(phosphonic acid) (0.048 g, 0.12 mmol, 70%). ^{1}H NMR (500 MHz, D_2O): δ 6.80 (s, 1H), 3.65 (td, *J* = 13.8, 7.0 Hz, 2H), 2.96-2.90 (m, 1H), 2.18 (tt, *J* = 20.5, 7.3 Hz, 1H), 1.57-1.50 (m, 3H), 1.31-

1.17 (m, 7H), 0.86-0.84 (m, 6H); ^{31}P (D_2O, 202 MHz): δ 16.41; ESI HRMS: *m/z* $[M+H]^+$ calculated for $C_{13}H_2N_2O_6P_2S^+$, 401.1060; found, 401.1071; purity = 98.0 % (qNMR).

Synthesis of 95:

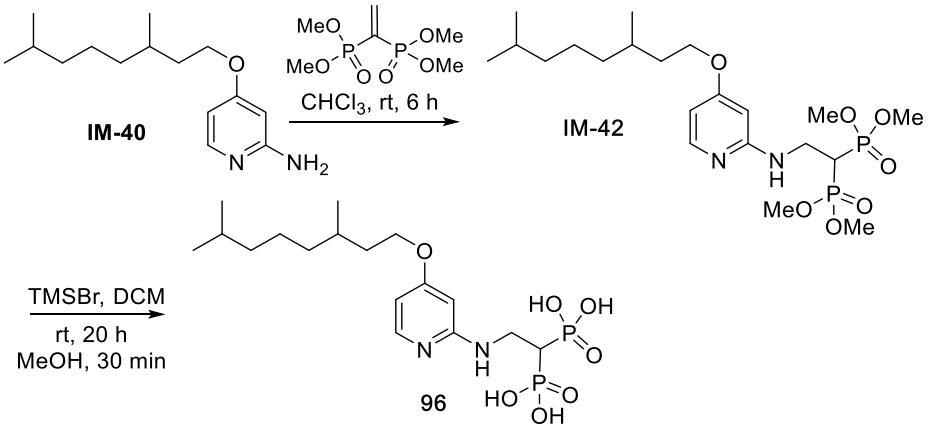


4-((3,7-Dimethyloctyl)oxy)pyridin-2-amine (IM-40). To a solution of 3,7-dimethyloctan-1-ol (0.46 mL, 4.16 mmol) in 5 mL THF was added NaH (0.10 g, 4.16 mmol) portion-wise under a N_2 atmosphere at 0 °C. The mixture was allowed to stir at room temperature for 30 min. Then THF was evaporated *in vacuo*, and the residue was dissolved in 5 mL DMSO. To the above solution 4-chloropyridin-2-amine (0.60 g, 3.78 mmol) was added and the mixture was stirred at 150 °C for 3 h.[47] The mixture was cooled to RT and the DMSO was then evaporated under reduced pressure to give a dark brown residue. To the crude product, 20 mL of water was added, and the product was extracted into 2 x 40 mL of ethyl acetate. The combined organic layers were washed with brine and dried over Na_2SO_4. Purification via flash column chromatography on silica (20 to 50% EA/PE) gave **IM-40** (0.24 g, 0.95 mmol, 25%) as a brown oil. ^1H NMR ($CDCl_3$, 500 MHz): δ 7.88 (d, *J*= 6.0 Hz, 1H), 6.26 (dd, *J* = 6.0, 2.0 Hz, 1H), 5.98 (d, *J* = 2.0 Hz, 1H), 4.41 (broad s, 2H), 1.82-1.77 (m, 2H), 1.64-1.51 (m, 3H), 1.37-1.15 (m, 6H), 0.93 (d, *J* = 6.5 Hz, 3H), 0.87 (d, *J* = 6.5 Hz, 6H).

Tetraethyl(((4-((3,7-dimethyloctyl)oxy)pyridin-2-yl)amino)methylene)bisphosphonate (IM-41). A mixture of 4-((3,7-dimethyloctyl)oxy)pyridin-2-amine (**IM-40,** 0.10 g, 0.40 mmol), triethyl orthoformate (0.080 mL, 0.48 mmol) and diethylphosphite (0.21 mL, 1.55 mmol) in a 1 mL sealed tube was heated at 130 °C for 15 h.[48] The mixture was cooled, then the volatile components were removed *in vacuo*. Progress of the reaction was monitored by TLC (10% MeOH/EA). The crude compound was purified via flash column chromatography on silica (90% EA/PE–5% MeOH/EA) to give **IM-41** (0.060 g, 0.11 mmol, 28%) as an oil. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.87 (d, *J* = 6.0 Hz, 1H), 6.22 (dd, *J* = 6.0, 2.0 Hz, 1H), 5.98 (d, *J* = 2.5 Hz, 1H), 5.50 (td, *J* = 22.0, 10.0 Hz, 1H), 4.86 (d, *J* = 10.5 Hz, 1H), 4.18-4.12 (m, 8H), 3.96-3.91 (m, 2H), 1.80-1.74 (m, 1H), 1.64-1.48 (m, 3H), 1.31-1.11 (m, 18H), 0.91 (d, *J* = 6.5 Hz, 3H), 0.85 (d, *J* = 6.5 Hz, 6H); ^{31}P NMR ($CDCl_3$, 202 MHz): δ 19.14.

(((4-((3,7-Dimethyloctyl)oxy)pyridin-2-yl)amino)methylene)bisphosphonic acid (95). In a 5 mL round-bottom flask, (((4-((3,7-dimethyloctyl)oxy)pyridin-2-yl)amino) methylene)bis phosphonate (**IM-41**, 0.020 g, 0.037 mmol) and 6 N HCl (0.30 mL) were refluxed for 4 h. [49] The progress of the reaction mixture was monitored by TLC (10% MeOH/EA). The volatile components were removed *in vacuo* to yield pure (((4-((3,7-dimethyloctyl)oxy)pyridin-2-yl)amino)methylene) bisphosphonic acid (0.013 g, 0.030 mmol, 80%) as a white solid. ^{1}H NMR (D_2O, 500 MHz): δ 7.68 (d, *J* = 6.0 Hz, 1H), 6.16 (d, *J* = 6.0 Hz, 1H), 6.01 (s, 1H), 4.13-4.12 (m, 2H), 1.77-1.73 (m, 1H), 1.62-1.49 (m, 3H), 1.31-1.13 (m, 6H), 0.89 (d, *J* = 6.5 Hz), 0.83 (d, *J* = 6.5 Hz, 6H); ^{31}P NMR (D_2O, 202 MHz): δ 14.90; ESI HRMS: *m/z* $[M+H]^+$ calculated for $C_{16}H_{31}N_2O_7P_2^+$, 425.1601; found, 425.1610; purity = 96.6 % (qNMR).

Synthesis of 96:

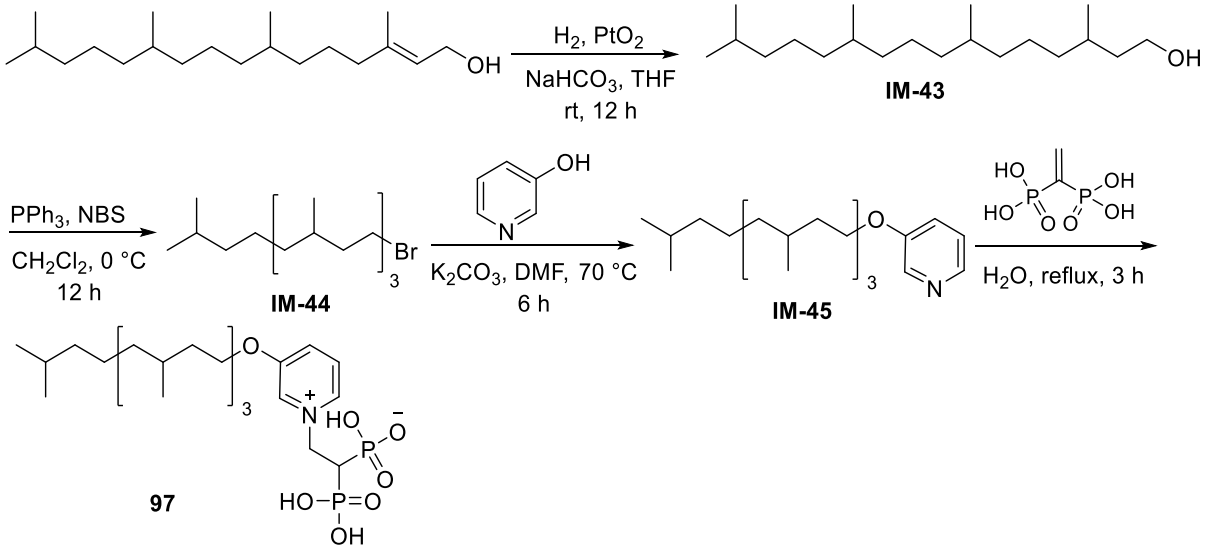


Tetramethyl(2-((4-((3,7-dimethyloctyl)oxy)pyridin-2-yl)amino)ethane-1,1-diyl)bis (phosphonate) (IM-42). According to **Procedure C**, **IM-40** (0.10 g, 0.40 mmol), tetramethyl ethene-1,1-diylbis(phosphonate) (0.050 g, 0.20 mmol) and 2 mL of $CHCl_3$ gave **IM-42** (0.081 g, 0.16 mmol, 82%) as a brown oil. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.92 (d, *J* = 6.0 Hz, 1H), 7.24 (dd, *J* = 5.8, 2.3 Hz, 1H), 5.96 (d, *J* = 2.0 Hz, 1H), 5.30 (t, *J* = 1.5 Hz, 1H), 4.00-3.93 (m, 4H), 3.88-3.82 (m, 12H), 2.94 (tt, *J* = 21.3, 6.0 Hz, 1H), 1.84-1.78 (m, 1H), 1.61-1.52 (m, 3H), 1.35-1.26 (m, 3H), 1.19-1.15 (m, 3H), 0.95 (d, *J* = 6.5 Hz, 3H), 0.89 (d, *J* = 6.5 Hz, 6H); ^{31}P NMR ($CDCl_3$, 202 MHz): δ 25.61.

(2-((4-((3,7-Dimethyloctyl)oxy)pyridin-2-yl)amino)ethane-1,1-diyl)bis(phosphonic acid) (96). According to **Procedure D**, (2-((4-((3,7-dimethyloctyl)oxy)pyridin-2-yl)amino)ethane-1,1-diyl)bis(phosphonate) (0.14 g, 0.29 mmol), TMSBr (0.23 mL, 1.72 mmol), and 3 mL of DCM gave (2-((4-((3,7-dimethyloctyl)oxy)pyridin-2-yl)amino)ethane-1,1-diyl)bis(phosphonic acid) (0.082 g, 0.19 mmol, 65%) as a white solid. ^{1}H NMR (D_2O, 500 MHz): δ 7.76 (d, *J* = 6.0 Hz, 1H), 6.30 (d, *J* = 6.0 Hz, 1H), 6.17 (s, 1H), 5.58 (td, *J* = 13.8, 7.2, 2H), 4.13-4.12 (m, 2H), 2.14-2.03 (m, 1H), 1.78-1.47 (m, 4H), 1.30-1.13 (m, 6H), 0.89 (d, *J* = 6.5 Hz), 0.82 (d, *J* = 6.5 Hz, 6H); ^{31}P NMR (D_2O, 202 MHz):

δ 18.04; ESI HRMS: *m/z* $[M+H]^+$ calculated for $C_{17}H_{33}N_2O_7P_2^+$, 439.1758; found, 439.1761; purity = 98.1% (LCMS).

Synthesis of 97:



3,7,11,15-Tetramethylhexadecan-1-ol (IM-43). To a solution of phytol (1.00 g, 3.37 mmol) in 12 mL of anhydrous THF was added $PtO_2 \cdot H_2O$ (0.050 g, 0.20 mmol) and $NaHCO_3$ (1.00 g, 11.90 mmol) under a N_2 atmosphere. The mixture was stirred under a H_2 atmosphere for 20 h, filtered through Celite, then washed with THF and concentrated *in vacuo* and purified by flash column chromatography over silica gel (5% to 25% EA/PE) to afford 3,7,11,15-tetramethylhexadecan-1-ol, **IM-43** (0.69 g, 3.04 mmol, 90%) as a colorless oil.[50] ^1H NMR ($CDCl_3$, 500 MHz): δ 3.76-3.67 (m, 2H), 1.67-1.52 (m, 3H), 1.43-1.09 (m, 24 H), 0.90 (d, *J* = 6.5, 3H), 0.93 (d, *J* = 6.5 Hz, 3H), 0.90 (d, *J* = 6.5 Hz, 6H), 0.88 (d, *J* = 6.5 Hz, 6H).

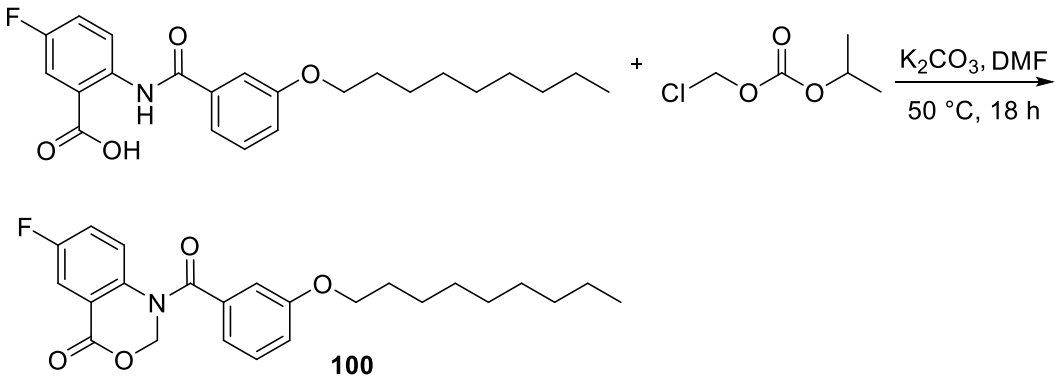
1-Bromo-3,7,11,15-tetramethylhexadecane (IM-44). To a solution of 3,7,11,15-tetramethylhexadecan-1-ol (**IM-43**, 2.00 g, 6.70 mmol) and triphenylphosphine (2.29 g, 8.71 mmol) in 10 mL of anhydrous CH_2Cl_2 was added NBS (1.19 g, 6.70 mmol) over 30 min, at 0 °C. The mixture

was stirred for 30 min and concentrated *in vacuo*.[46] The crude compound was purified by flash column chromatography over silica gel (neat hexane) to give pure 1-bromo-3,7,11,15-tetramethylhexadecane (2.058 g, 5.70 mmol, 85%) as a colorless oil. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 3.50-3.38 (m, 2H), 1.93-1.85 (m, 1H), 1.70-1.47 (m, 3H), 1.38-1.03 (m, 20 H), 0.90-0.84 (m, 15 H).

3-((3,7,11,15-Tetramethylhexadecyl)oxy)pyridine (IM-45). IM-45 was **s**ynthesized according to **Procedure A**. 3-Hydroxypyridine (0.13 g, 1.37 mmol), 1-bromo-3,7,11,15-tetramethylhexadecane (0.47 g, 1.30 mmol), and K_2CO_3 (0.377 g, 2.73 mmol) in 5 mL of DMF gave **IM-45** (0.30 g, 0.81 mmol, 62%) as a colorless oil. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.31 (s, 1H), 8.21 (s, 1H), 7.27-7.23 (m, 2H), 4.08-4.01 (m, 2H), 1.88-1.81 (m, 1H), 1.69-1.48 (m, 3H), 1.39-1.06 (m, 20 H), 0.94 (d, *J* = 6.5 Hz, 3H), 0.87-0.83 (m, 12H).

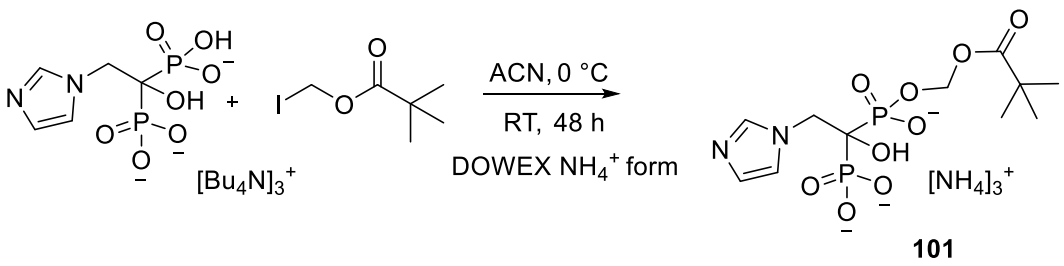
Hydrogen(1-phosphono-2-(3-((3,7,11,15-tetramethylhexadecyl)oxy)pyridin-1-ium-1-yl)ethyl)phosphonate (97). According to **Procedure B**, 3-((3,7,11,15-tetramethylhexadecyl)oxy)pyridine (0.10 g, 0.27 mmol) and vinylidene-1,1-bisphosphonic acid (0.047 g, 0.25 mmol) in 1.5 mL of H_2O yielded hydrogen(1-phosphono-2-(3-((3,7,11,15-tetramethylhexadecyl)oxy)pyridin-1-ium-1-yl)ethyl)phosphonate (0.10 g, 0.18 mmol, 72.8%) as a white powder. ^{1}H NMR (500 MHz, D_2O): δ 8.77 (s, 1H), 8.63 (d, *J* = 4.5 Hz, 1H), 7.87-7.82 (m, 2H), 4.93-4.90 (m, 2H), 4.28-4.26 (m, 2H), 2.42 (tt, *J* = 20.0, 6.8 Hz, 1H), 1.95-1.16 (m, 24H), 0.97 (d, *J* = 5.5 Hz, 3H), 0.93 (d, *J* = 6.0 Hz, 12H); ^{31}P (202 MHz, D_2O): δ 13.45; ESI HRMS: *m/z* $[M–H]^-$ calculated for $C_{27}H_{51}NO_7P_2^-$, 562.3063; found, 562.3069; purity = 96.4 % (qNMR).

Synthesis of 100:



6-Fluoro-1-[3-(nonyloxy)benzoyl]-2H-3,1-benzoxazin-4-one (100). To a solution of 5-fluoro-2-(3-(octyloxy)benzamido)benzoic acid (0.015 gm, 0.039 mmol) and chloromethyl isopropyl carbonate (5.9 μL, 0.043 mmol) in 0.5 mL of DMF at RT, K_2CO_3 (5.8 mg, 0.043 mmol) was added, and the mixture stirred at 50 °C for 18 h. The mixture was then cooled to room temperature, 3 mL of water added, and the product extracted into 2 x 5 mL of ethyl acetate. The combined organic layers were dried over Na_2SO_4. The crude compound was purified by flash column chromatography over silica (10% EA/PE) to give **100** (9.0 mg, 0.022 mmol, 58%) as a pale yellow solid. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.78 (dd, *J* = 8.0, 3.0 Hz, 1H), 7.42 (broad s, 1H), 7.35-7.24 (m, 2H), 7.07-7.04 (m, 3H), 5.71 (s, 2H), 3.96 (t, *J* = 6.5 Hz, 2H), 1.78 (quintet, *J* = 7.1 Hz, 2H), 1.47-1.25 (m, 10H), 0.87 (t, *J* = 6.8 Hz, 3H); ^{19}F NMR($CDCl_3$, 376 MHz): δ -113.77 (d, *J* = 2.6 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 169.4, 161.8 (d, J = 2.4 Hz), 159.9 (d, J = 247.0 Hz), 159.5, 137.5 (d, J = 2.8 Hz), 133.9, 129.94, 125.4 (d, J = 7.6), 121.9 (d, J = 23.3 Hz), 120.2 (d, J = 8.0 Hz), 120.1, 118.5, 116.3, 114.1, 76.5, 68.4, 31.8, 29.3, 29.2, 29.1, 25.9, 22.7, 14.1. ESI HRMS: *m/z* $[M+H]^+$ calculated for $C_{24}H_{29}FNO_4^+$, 414.2075; found, 414.2062; purity = 96.1 % (qNMR).

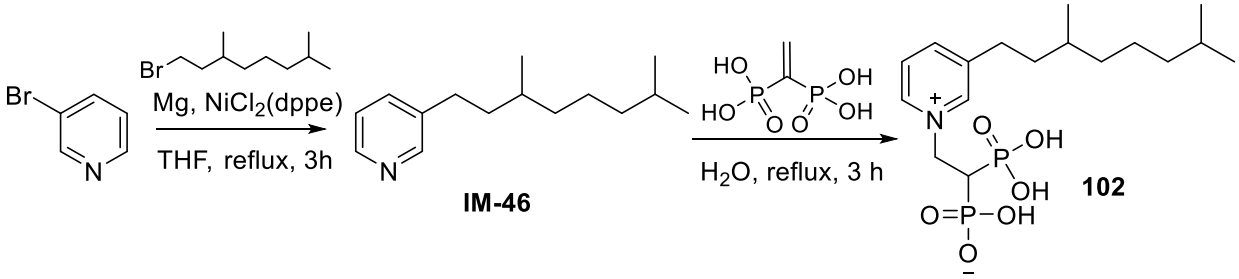
Synthesis of 101:



101

(1-hydroxy-1-(hydroxy((pivaloyloxy)methoxy)phosphoryl)-2-(1H-imidazol-1-yl)ethyl)phosphonic acid (101). A solution of the tris-tetra-n-butyl ammonium salt of zoledronic acid (0.08 gm, 0.08 mmol) and iodomethyl pivalate (0.010 gm, 0.04 mmol, 0.5 equivalent) in 1.5 mL ACN was stirred at room temperature for 24 h. Then, another 0.5 equivalent of iodomethyl pivalate was added and the mixture stirred for 24 h. The organic solvent was evaporated, and the crude was converted into the NH_4^+ form by treating with 1.5 mL of DOWEX NH_4^+ resin. The crude was purified by methanol washing (2 x 1 mL) to give **101** (6.8 mg, 0.016 mmol, 19 %) as a white crystalline solid. ^{1}H NMR (D_2O, 500 MHz): δ 8.63 (s, 1H), 7.50 (d, *J* = 1.5 Hz, 1H), 7.35 (d, *J* = 1.5 Hz, 1H), 5.51-5.43 (m, 2H), 4.72-4.57 (m, 2H), 1.20 (s, 9H); ^{31}P NMR (D_2O, 202 MHz): δ 13.63 (d, *J* = 18.6 Hz, 1P), 12.68 (d, *J* = 19.4 Hz, 1P). ESI HRMS: *m/z* $[M+H]^+$ calculated for $C_{11}H_{21}N_2O_9P_2^+$, 387.0722; found, 387.0715; Purity = 92.3 % (qNMR).

Synthesis of 102:



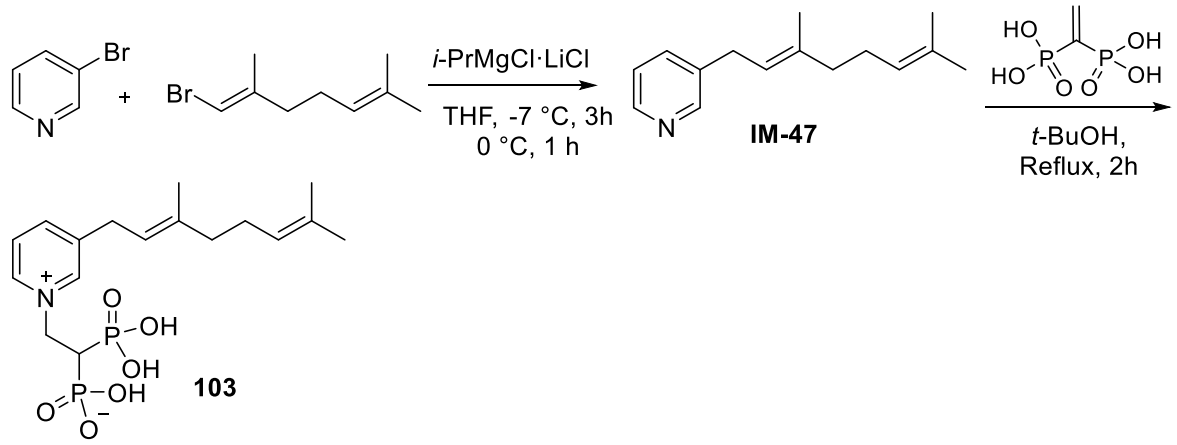
IM-46

102

3-(3,7-dimethyloctyl)pyridine (IM-46). To a solution of 1-bromo-3,7-dimethyloctane (0.72 mL, 3.48 mmol) in 5 mL dry THF, activated Mg turnings (9.2 mg, 3.79 mmol) and a crystal of iodine were added, and the reaction mixture was heated at 50 ^{o}C for 2h. The freshly prepared Grignard solution was added dropwise to a mixture of 3-bromopyridine (0.500 gm, 3.38 mmol) and $NiCl_2$(dppe) (8.3 mg, 0.016 mmol) at room temperature. After heating at 40 ^{o}C for 3 h, the reaction mixture was cooled to room temperature and 10 mL of ice cooled water was added, extracted in 2x20 mL of ethyl acetate, the combined organic layers were dried on Na_2SO_4 and evaporated under reduced pressure to give crude brown oil.[51] The crude was purified flash silica gel column chromatography in 10% EtOAc/Pet ether to give 3-(3,7-dimethyloctyl)pyridine (**IM-46,** 0.186 gm, 27%) as a brown oil. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.44-8.82 (m, 2H), 7.49 (d, *J* = 8.0 Hz, 1H), 7.20 (dd, *J* = 7.5, 5.0 Hz, 1H) 2.67-2.54 (m, 2H), 1.64-1.58 (m, 4H), 1.33-1.11 (m, 6H), 0.93 (d, J = 6.0 Hz, 3H), 0.87 (d, J = 6.5 Hz, 6H).

Hydrogen (2-(3-(3,7-dimethyloctyl)pyridin-1-ium-1-yl)-1-phosphonoethyl) phosphonate (102). According to **Procedure B**, 3-(3,7-dimethyloctyl)pyridine (20 mg, 0.091 mmol) and vinylidene-1,1-bisphosphonic acid (16.3 mg, 0.087 mmol) in 0.2 mL of H_2O yielded **103** (0.015 g, 0.0.037 mmol, 39%) as a white powder. ^{1}H NMR (D_2O, 500 MHz): δ 8.83 (s, 1H), 8.78 (d, *J* = 6.0 Hz, 1H), 8.31 (d, *J* = 8.0 Hz, 1H), 7.86 (dd, *J* = 7.5, 6.5 Hz, 1H), 4.93 (td, *J* = 13.0, 6.5 Hz, 2H), 2.94-2.82 (m, 2H), 2.39 (tt, *J* = 20.8, 6.5 Hz, 1H), 1.77-1.71 (m, 1H), 1.60-1.51 (m, 3H), 1.39-1.17 (m, 6H), 0.97 (*d*, J = 6.5 Hz, 3H), 0.88 (d, *J* = 6.5 Hz, 9H); ^{31}P NMR (D_2O, 202 MHz): δ 13.38; ESI HRMS: m/z $[M+H]^+$ calculated for $C_{17}H_{32}NO_6P_2^+$, 408.1705; found, 408.1704; purity = 95.4% (qNMR).

Synthesis of 103:



3-[(2E)-3,7-dimethylocta-2,6-dien-1-yl]pyridine (IM-47). To 3-bromopyridine (1.0 g, 6.33 mmol), *i*-PrMgCl.LiCl (5.4 mL, 1.3 M in THF, 6.96 mmol) was added dropwise at -7 °C over 10 min, and the reaction mixture was allowed to stir at same temperature for 3 h. Geranyl bromide (1.38 mL, 6.96 mmol) in 2 mL THF was added dropwise and the reaction mixture was stirred at 0 °C for 1h.[52] The reaction mixture was quenched with sat. NH4Cl solution (5 mL). The aqueous phase was extracted in 2 x 25 mL of ethyl acetate, the combined organic layers were dried on Na_2SO_4 and evaporated under reduced pressure to give crude brown oil. The crude was purified flash silica gel column chromatography in 12 % EtOAc/Pet ether to give 3-[(2E)-3,7-dimethylocta-2,6-dien-1-yl]pyridine (**IM-47**, 0.43 gm, 32 %) as a brown oil. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.44-8.42 (m, 2H), 7.47 (d, *J* = 7.6 Hz, 1H), 7.19 (dd, *J* = 8.0, 4.8 Hz, 1H) 5.32-5.28 (m, 1H), 5.10-5.07 (m, 1H), 3.35 (d, *J* = 7.2 Hz, 2H), 2.12-2.03 (m, 4H), 1.71 (s, 3H), 1.68 (s, 3H), 1.59 (s, 3H).

3-[(2E)-3,7-dimethylocta-2,6-dien-1-yl]-1-(2-hydrogen phosphonato-2-phosphonoethyl)pyridin-1-ium (103). According to **Procedure B**, 3-[(2E)-3,7-dimethylocta-2,6-dien-1-yl]pyridine (10 mg, 0.047 mmol) and vinylidene-1,1-bisphosphonic acid (8.3 mg, 0.044 mmol) in 0.2 mL of *t*-butanol yielded **103** (5.1 mg, 0.013 mmol, 29%) as a white powder. ^{1}H NMR

(D_2O, 500 MHz): δ 8.81 (s, 1H), 8.79 (d, J = 6.5 Hz, 1H), 8.31 (d, *J* = 6.5 Hz, 1H), 7.92 (dd, *J* = 6.0, 6.0 Hz, 1H), 5.45-5.42 (m, 1H), 5.22-5.20 (m, 1H), 4.93 (td, *J* = 12.8, 7.5 Hz, 2H), 3.63 (d, *J* = 7.5 Hz, 2H), 2.39 (tt, *J* = 19.8, 7.5 Hz, 1H), 2.20-2.16 (m, 4H), 1.76 (s, 3H), 1.70 (s, 3H), 1.64 (s, 3H); ^{31}P NMR (D_2O, 202 MHz): δ 13.47; ESI HRMS: m/z $[M+H]^+$ calculated for $C_{17}H_{28}NO_6P_2^+$, 404.1386; found, 404.1389; purity = 95.4% (qNMR).

References.

1. Leung, C. Y.; Park, J.; De Schutter, J. W.; Sebag, M.; Berghuis, A. M.; Tsantrizos, Y. S., Thienopyrimidine bisphosphonate (ThPBP) inhibitors of the human farnesyl pyrophosphate synthase: optimization and characterization of the mode of inhibition. *J. Med. Chem.* **2013,** *56*, 7939-7950.

2. No, J. H.; de Macedo Dossin, F.; Zhang, Y.; Liu, Y. L.; Zhu, W.; Feng, X.; Yoo, J. A.; Lee, E.; Wang, K.; Hui, R.; Freitas-Junior, L. H.; Oldfield, E., Lipophilic analogs of zoledronate and risedronate inhibit *Plasmodium* geranylgeranyl diphosphate synthase (GGPPS) and exhibit potent antimalarial activity. *Proc. Natl. Acad. Sci. U. S. A.* **2012,** *109*, 4058-63.

3. Zhang, Y.; Cao, R.; Yin, F.; Hudock, M. P.; Guo, R. T.; Krysiak, K.; Mukherjee, S.; Gao, Y. G.; Robinson, H.; Song, Y.; No, J. H.; Bergan, K.; Leon, A.; Cass, L.; Goddard, A.; Chang, T. K.; Lin, F. Y.; Van Beek, E.; Papapoulos, S.; Wang, A. H.; Kubo, T.; Ochi, M.; Mukkamala, D.; Oldfield, E., Lipophilic bisphosphonates as dual farnesyl/geranylgeranyl diphosphate synthase inhibitors: an X-ray and NMR investigation. *J. Am. Chem. Soc.* **2009,** *131*, 5153-5162.

4. Zhang, Y.; Hudock, M. P.; Krysiak, K.; Cao, R.; Bergan, K.; Yin, F.; Leon, A.; Oldfield, E., Activity of sulfonium bisphosphonates on tumor cell lines. *J. Med. Chem.* **2007,** *50*, 6067-6079.

5. Zhang, Y.; Cao, R.; Yin, F.; Lin, F. Y.; Wang, H.; Krysiak, K.; No, J. H.; Mukkamala, D.; Houlihan, K.; Li, J.; Morita, C. T.; Oldfield, E., Lipophilic pyridinium bisphosphonates: potent γδ T cell stimulators. *Angew. Chem. Int. Ed. Engl.* **2010,** *49*, 1136-1138.

6. Zhang, Y.; Zhu, W.; Liu, Y. L.; Wang, H.; Wang, K.; Li, K.; No, J. H.; Ayong, L.; Gulati, A.; Pang, R.; Freitas-Junior, L.; Morita, C. T.; OldField, E., Chemo-immunotherapeutic anti-malarials targeting isoprenoid biosynthesis. *ACS Med. Chem. Lett.* **2013,** *4*, 423-427.

7. Chen, C. K.-M.; Hudock, M. P.; Zhang, Y.; Guo, R.-T.; Cao, R.; No, J. H.; Liang, P.-H.; Ko, T.-P.; Chang, T.-H.; Chang, S.-c.; Song, Y.; Axelson, J.; Kumar, A.; Wang, A. H. J.; Oldfield, E., Inhibition of geranylgeranyl diphosphate synthase by bisphosphonates: a crystallographic and computational investigation. *J. Med. Chem.* **2008,** *5*1, 5594-5607.

8. Oldfield, E.; Song, Y.; Zhang, Y.; Sanders, J. M., Bisphosphonate compounds and methods. WO 2007109585 A2, September 27, 2007.

9. Widler, L.; Jaeggi, K. A.; Glatt, M.; Muller, K.; Bachmann, R.; Bisping, M.; Born, A. R.; Cortesi, R.; Guiglia, G.; Jeker, H.; Klein, R.; Ramseier, U.; Schmid, J.; Schreiber, G.; Seltenmeyer, Y.; Green, J. R., Highly potent geminal bisphosphonates. From pamidronate disodium (Aredia) to zoledronic acid (Zometa). *J. Med. Chem.* **2002,** *45*, 3721-3738.

10. Monteil, M.; Lecouvey, M.; Landy, D.; Ruellan, S.; Mallard, I., Cyclodextrins: A promising drug delivery vehicle for bisphosphonate. *Carbohydr. Polym.* **2017,** *156*, 285-293.

11. Wang, Y.; Desai, J.; Zhang, Y.; Malwal, S. R.; Shin, C. J.; Feng, X.; Sun, H.; Liu, G.; Guo, R. T.; Oldfield, E., Bacterial cell growth inhibitors targeting undecaprenyl diphosphate synthase and undecaprenyl diphosphate phosphatase. *ChemMedChem* **2016,** *1*1, 2311-2319.

12. Zhu, W.; Zhang, Y.; Sinko, W.; Hensler, M. E.; Olson, J.; Molohon, K. J.; Lindert, S.; Cao, R.; Li, K.; Wang, K.; Wang, Y.; Liu, Y. L.; Sankovsky, A.; de Oliveira, C. A.; Mitchell, D. A.; Nizet, V.; McCammon, J. A.; Oldfield, E., Antibacterial drug leads targeting isoprenoid biosynthesis. *Proc. Natl. Acad. Sci. U. S. A.* **2013,** *110*, 123-128.

13. Sanders, J. M.; Song, Y.; Chan, J. M.; Zhang, Y.; Jennings, S.; Kosztowski, T.; Odeh, S.; Flessner, R.; Schwerdtfeger, C.; Kotsikorou, E.; Meints, G. A.; Gomez, A. O.; Gonzalez-Pacanowska, D.; Raker,

A. M.; Wang, H.; van Beek, E. R.; Papapoulos, S. E.; Morita, C. T.; Oldfield, E., Pyridinium-1-yl bisphosphonates are potent inhibitors of farnesyl diphosphate synthase and bone resorption. *J. Med. Chem.* **2005,** *48*, 2957-2963.

14. Wu, M.; Chen, R.; Huang, Y., Convenient synthesis of analogs of Aminomethylene gem - diphosphonic acid from amines without catalyst. *Synth. Commun.* **2004,** *34*, 1393-1398.

15. Zhang, Y.; Leon, A.; Song, Y.; Studer, D.; Haase, C.; Koscielski, L. A.; Oldfield, E., Activity of nitrogen-containing and non-nitrogen-containing bisphosphonates on tumor cell lines. *J. Med. Chem.* **2006,** *49*, 5804-5814.

16. Ghosh, S.; Chan, J. M.; Lea, C. R.; Meints, G. A.; Lewis, J. C.; Tovian, Z. S.; Flessner, R. M.; Loftus, T. C.; Bruchhaus, I.; Kendrick, H.; Croft, S. L.; Kemp, R. G.; Kobayashi, S.; Nozaki, T.; Oldfield, E., Effects of bisphosphonates on the growth of *Entamoeba histolytica* and *Plasmodium* species in vitro and in vivo. *J. Med. Chem.* **2004,** *47*, 175-187.

17. Kotsikorou, E.; Song, Y.; Chan, J. M.; Faelens, S.; Tovian, Z.; Broderick, E.; Bakalara, N.; Docampo, R.; Oldfield, E., Bisphosphonate inhibition of the exopolyphosphatase activity of the *Trypanosoma brucei* soluble vacuolar pyrophosphatase. *J. Med. Chem.* **2005,** *48*, 6128-6139.

18. Zhu, W.; Wang, Y.; Li, K.; Gao, J.; Huang, C. H.; Chen, C. C.; Ko, T. P.; Zhang, Y.; Guo, R. T.; Oldfield, E., Antibacterial drug leads: DNA and enzyme multitargeting. *J. Med. Chem.* **2015,** *58*, 1215-1227.

19. Valentijn, A. R. P. M.; van den Berg, O.; van der Marel, G. A.; Cohen, L. H.; van Boom, J. H., Synthesis of pyrophosphonic acid analogues of farnesyl pyrophosphate. *Tetrahedron* **1995,** *51*, 2099-2108.

20. Li, K.; Schurig-Briccio, L. A.; Feng, X.; Upadhyay, A.; Pujari, V.; Lechartier, B.; Fontes, F. L.; Yang, H.; Rao, G.; Zhu, W.; Gulati, A.; No, J. H.; Cintra, G.; Bogue, S.; Liu, Y. L.; Molohon, K.; Orlean, P.; Mitchell, D. A.; Freitas-Junior, L.; Ren, F.; Sun, H.; Jiang, T.; Li, Y.; Guo, R. T.; Cole, S. T.; Gennis, R. B.; Crick, D. C.; Oldfield, E., Multitarget drug discovery for tuberculosis and other infectious diseases. *J. Med. Chem.* **2014,** *57*, 3126-3139.

21. Williams, J. D.; Nguyen, S. T.; Gu, S.; Ding, X.; Butler, M. M.; Tashjian, T. F.; Opperman, T. J.; Panchal, R. G.; Bavari, S.; Peet, N. P.; Moir, D. T.; Bowlin, T. L., Potent and broad-spectrum antibacterial activity of indole-based bisamidine antibiotics: Synthesis and SAR of novel analogs of MBX 1066 and MBX 1090. *Bioorg. Med. Chem.* **2013,** *21*, 7790-7806.

22. Guo, R. T.; Cao, R.; Liang, P. H.; Ko, T. P.; Chang, T. H.; Hudock, M. P.; Jeng, W. Y.; Chen, C. K.; Zhang, Y.; Song, Y.; Kuo, C. J.; Yin, F.; Oldfield, E.; Wang, A. H., Bisphosphonates target multiple sites in both *cis*- and *trans*-prenyltransferases. *Proc. Natl. Acad. Sci. U. S. A.* **2007,** *104*, 10022-10027.

23. Ghizzoni, M.; Boltjes, A.; Graaf, C.; Haisma, H. J.; Dekker, F. J., Improved inhibition of the histone acetyltransferase PCAF by an anacardic acid derivative. *Bioorg. Med. Chem.* **2010,** *18*, 5826-5834.

24. Desai, J.; Wang, Y. D.; Wang, K. D.; Malwal, S. R. D.; Oldfield, E., Isoprenoid biosynthesis inhibitors targeting bacterial cell growth. *ChemMedChem.* **2016,** *11*, 2205-2215.

25. Matsumoto, K.; Hayashi, K.; Murata-Hirai, K.; Iwasaki, M.; Okamura, H.; Minato, N.; Morita, C. T.; Tanaka, Y., Targeting cancer cells with a bisphosphonate prodrug. *ChemMedChem* **2016,** *11*, 2656-2663.

26. Oertling, H., 4-alkyl substituted pyridines as odiferous substances. US 20100130624 A1, May 27, 2010.

27. Suthagar, K.; Fairbanks, A. J., A new way to do an old reaction: highly efficient reduction of organic azides by sodium iodide in the presence of acidic ion exchange resin. *Chem. Commun.* **2017,** *53*, 713-715.

28. Suthagar, K.; Watson, A. J. A.; Wilkinson, B. L.; Fairbanks, A. J., Synthesis of arabinose glycosyl sulfamides as potential inhibitors of mycobacterial cell wall biosynthesis. *E. J. Med. Chem.* **2015,** *102*, 153-166.

29. Xu, J.-H.; Zheng, F.-Y.; Liang, Y.-F.; Cai, Z.-Y.; Feng, Y.-S.; Che, D.-Q., Ligand-free CuCl-catalyzed C–N bond formation in aqueous media. *Tetrahedron Lett.* **2010,** *51*, 669-671.

30. Wagman, A. S.; Moser, H. E., Carbacephem β-lactam antibiotics. WO 2009055696 A1, April 4, 2009.

31. Skattebol, L.; Stenstrom, Y.; Syvertsen, C., Insect juvenile hormone analogues and their biological activity on sea lice (*Lepeophtheirus salmonis*). *J. Agric. Food Chem.* **2004,** *52*, 6944-6949.

32. Sebti, S.; Hamilton, A.; Augeri, D.; Barr, K.; Donner, G.; Fakhoury, S.; O'Connor, S.; Rosenberg, S.; Shen, W.; Szczepankiewicz, B.; Gunawardana, I., Inhibitors of protein isoprenyl transferases. US 20020193596 A1, December 19, 2002.

33. Bouanis, F. Z.; Cojocaru, C. S.; Huc, V.; Norman, E.; Chaigneau, M.; Maurice, J.-L.; Mallah, T.; Pribat, D., Direct synthesis and integration of individual, diameter-controlled single-walled nanotubes (SWNTs). *Chem. Mater.* **2014,** *26*, 5074-5082.

34. Gan, Y.; Blank, D. H.; Ney, J. E.; Spencer, T. A., Nonsteroidal benzophenone-containing analogues of cholesterol. *J. Org. Chem.* **2006,** *71*, 5864-5869.

35. Nicolaou, K. C.; Namoto, K.; Ritzén, A.; Ulven, T.; Shoji, M.; Li, J.; D'Amico, G.; Liotta, D.; French, C. T.; Wartmann, M.; Altmann, K.-H.; Giannakakou, P., Chemical synthesis and biological evaluation of *cis*- and *trans*-12,13-cyclopropyl and 12,13-cyclobutyl epothilones and related pyridine side chain analogues. *J. Am. Chem. Soc.* **2001,** *123*, 9313-9323.

36. Wong, W. Y.; Wang, X. Z.; He, Z.; Chan, K. K.; Djurisic, A. B.; Cheung, K. Y.; Yip, C. T.; Ng, A. M.; Xi, Y. Y.; Mak, C. S.; Chan, W. K., Tuning the absorption, charge transport properties, and solar cell efficiency with the number of thienyl rings in platinum-containing poly(aryleneethynylene)s. *J. Am. Chem. Soc.* **2007,** *129*, 14372-14380.

37. Smith, M. L.; Leone, A. K.; Zimmerman, P. M.; McNeil, A. J., Impact of preferential π-binding in catalyst-transfer polycondensation of thiazole derivatives. *ACS Macro Lett.* **2016,** *5*, 1411-1415.

38. Rodgers, J. D.; Robinson, D. J.; Arvanitis, A. G.; Maduskuie, T. P.; Shepard, S.; Storace, L.; Wang, H.; Rafalski, M.; Jalluri, R. K.; Combs, A. P.; Crawley, M. L., Tetracyclic inhibitors of janus kinases. WO 2005105814 A1, November 10, 2005.

39. Sankaranarayanan, S.; Sharma, A.; Chattopadhyay, S., Synthesis of the 1,5-dimethylic chiron enantiomers, 3,7,11-trimethyldodec-10-en-1-ol: application to enantiomeric syntheses of tribolure and a marine fatty acid. *Tetrahedron: Asymmetry* **2002,** *13*, 1373-1378.

40. Kutner, A.; Zhao, H.; Fitak, H.; Wilson, S. R., Synthesis of retiferol RAD1 and RAD2, the lead representatives of a new class of des-CD analogs of cholecalciferol. *Bioorg. Chem.* **1995,** *23*, 22-32.

41. Hirai, K.; Katayama, S.; Torii, T.; Nakaya, R.; Takahashi, D., Preparation of base-protected oligonucleotide. US 20130267697 A1, October 10, 2013. .

42. Xiao, Z.; Subbiah, J.; Sun, K.; Ji, S.; Jones, D. J.; Holmes, A. B.; Wong, W. W. H., Thiazolyl substituted benzodithiophene copolymers: synthesis, properties and photovoltaic applications. *J. Mater. Chem. C* **2014,** *2*, 1306-1313.

43. Rockway, T. W.; Betebenner, D. A.; Krueger, A. C.; Iwasaki, N.; Cooper, C. S.; Anderson, D. D.; Kempf, D. J.; Madigan, D. L.; Motter, C. E.; Shanley, J. P., Anti-viral compounds. US 20070232645 A1, October 10, 2007.

44. Bruekelman, S. P.; Leach, S. E.; Meakins, G. D.; Tirel, M. D., Protection of primary amines as N-substituted 2,5-dimethylpyrroles. *J. Chem. Soc., Perkin Trans. 1* **1984,** 0, 2801-2807.

45. Muñoz, L.; Guerrero, A., Synthesis of a new deuterium-labeled phytol as a tool for biosynthetic studies. 2012; Vol. Synthesis 2012, 44, p 862-864.

46. Urs, H.; Antoinette, C.; Kegang, L.; Wolf-D., W., Asymmetric synthesis of α-tocopherol. *Chem. Eur. J.* **2010,** *16*, 1306-1311.

47. Andresen, B. M.; Anthony, N. J.; Miller, T. A., Amino-pyridine-containing spleen tyrosine kinase (syk) inhibitors. US 20150284381 A1, October 8, 2015.

48. Lin, Y. S.; Park, J.; De Schutter, J. W.; Huang, X. F.; Berghuis, A. M.; Sebag, M.; Tsantrizos, Y. S., Design and synthesis of active site inhibitors of the human farnesyl pyrophosphate synthase: apoptosis and inhibition of ERK phosphorylation in multiple myeloma cells. *J. Med. Chem.* **2012,** *55*, 3201-3215.

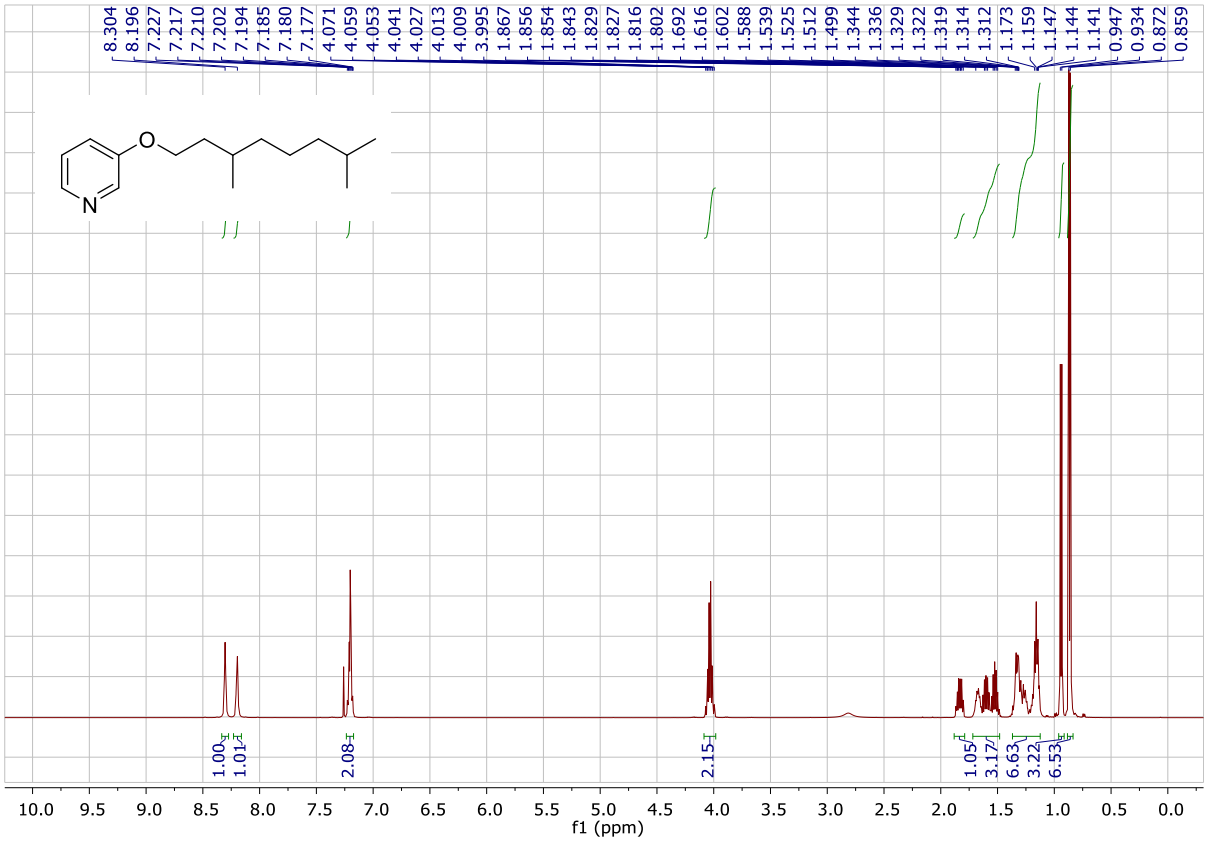
49. Martin, M. B.; Grimley, J. S.; Lewis, J. C.; Heath, H. T., 3rd; Bailey, B. N.; Kendrick, H.; Yardley, V.; Caldera, A.; Lira, R.; Urbina, J. A.; Moreno, S. N.; Docampo, R.; Croft, S. L.; Oldfield, E., Bisphosphonates inhibit the growth of *Trypanosoma brucei, Trypanosoma cruzi, Leishmania donovani, Toxoplasma gondii,* and *Plasmodium falciparum*: a potential route to chemotherapy. *J. Med. Chem.* **2001,** *44*, 909-916.

50. Crich, D.; Dudkin, V., Confirmation of the connectivity of 4,8,12,16,20-pentamethylpentacosylphosphoryl β-d-mannopyranoside, an unusual β-mannosyl phosphoisoprenoid from mycobacterium avium, through synthesis. *J. Am. Chem. Soc.* **2002,** *124*, 2263-2266.

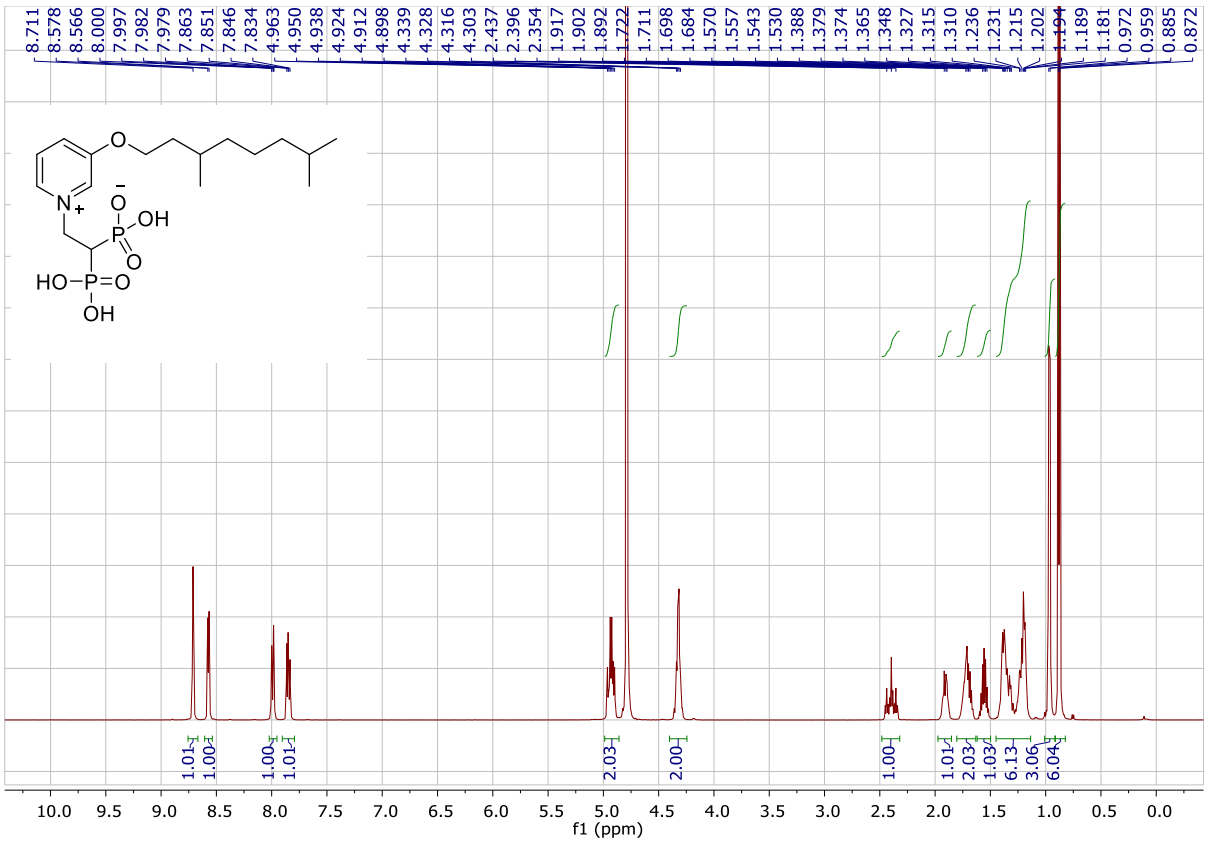
51. Fukuyama, T.; Nishikawa, T.; Yamada, K.; Ravelli, D.; Fagnoni, M.; Ryu, I., Photocatalyzed site-selective C(sp^3)–H functionalization of alkylpyridines at non-benzylic positions. *Org. Lett.* **2017,** *19*, 6436-6439.

52. Knochel, P.; Krasovskiy, A., Method of preparing organomagnesium compounds. EP 1582523 A1, October 5, 2005.

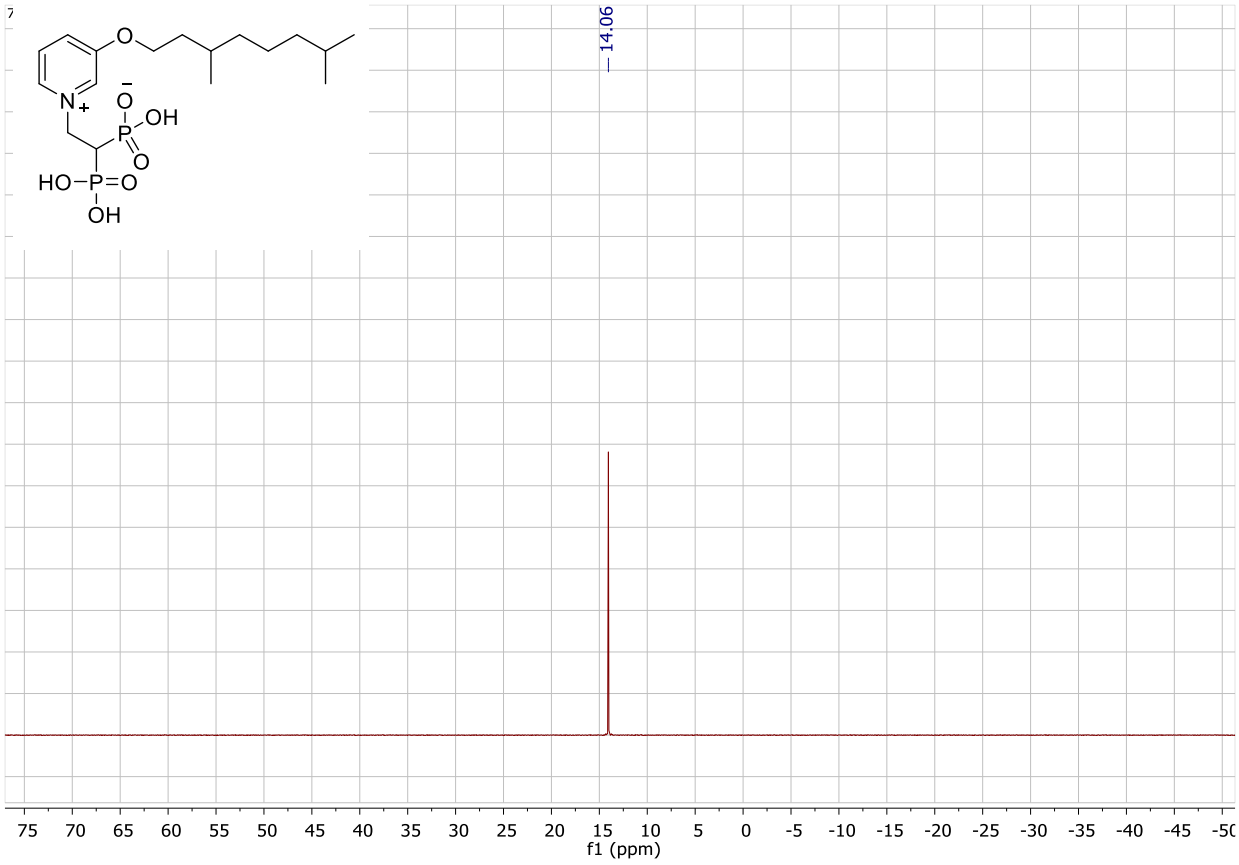
^{1}H NMR IM-1



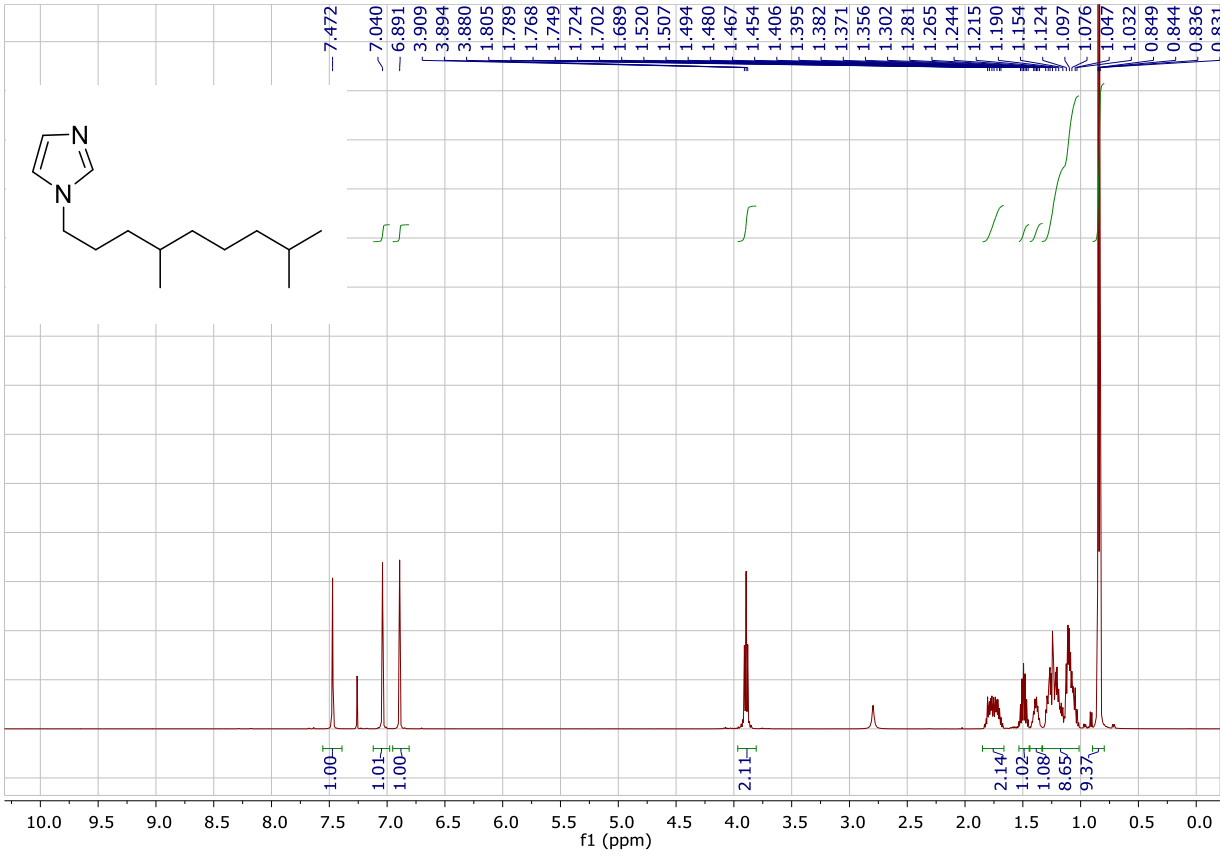
^{1}H NMR 74



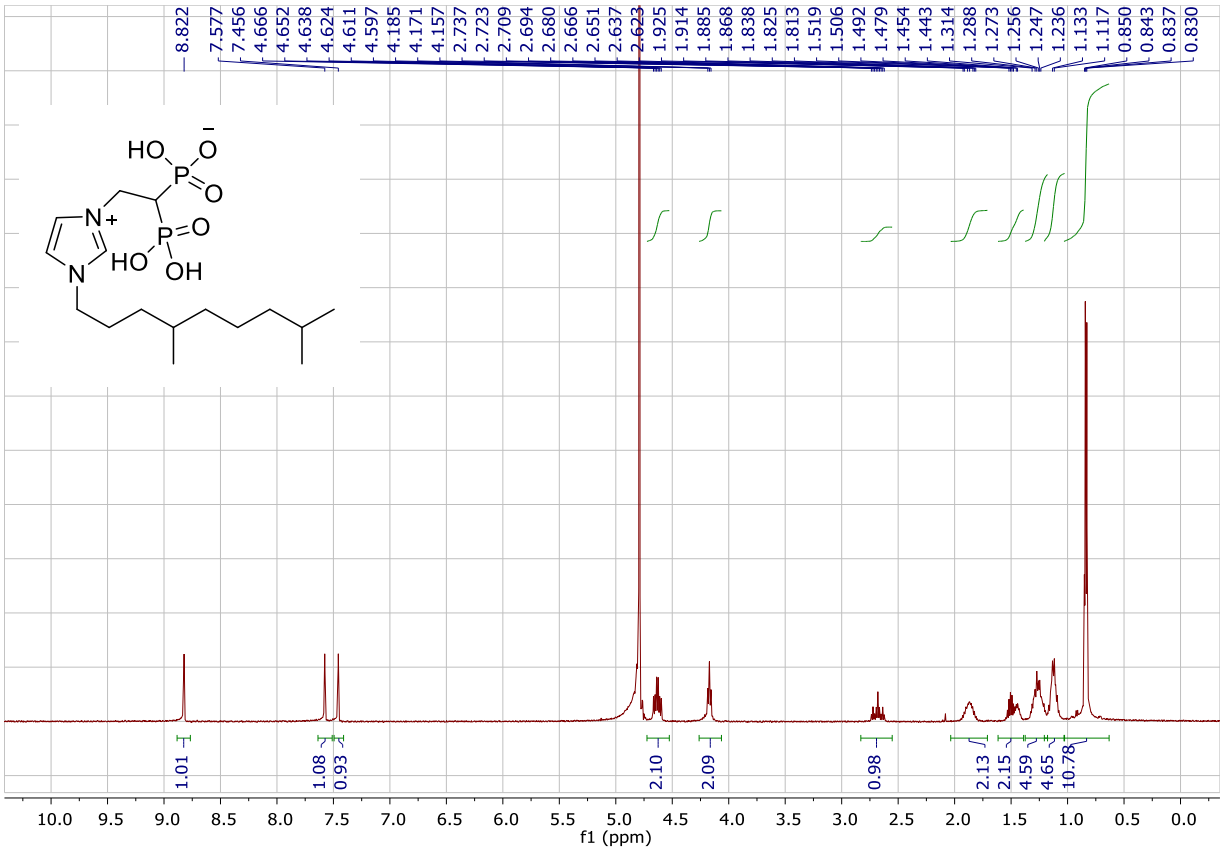
^{31}P NMR 74



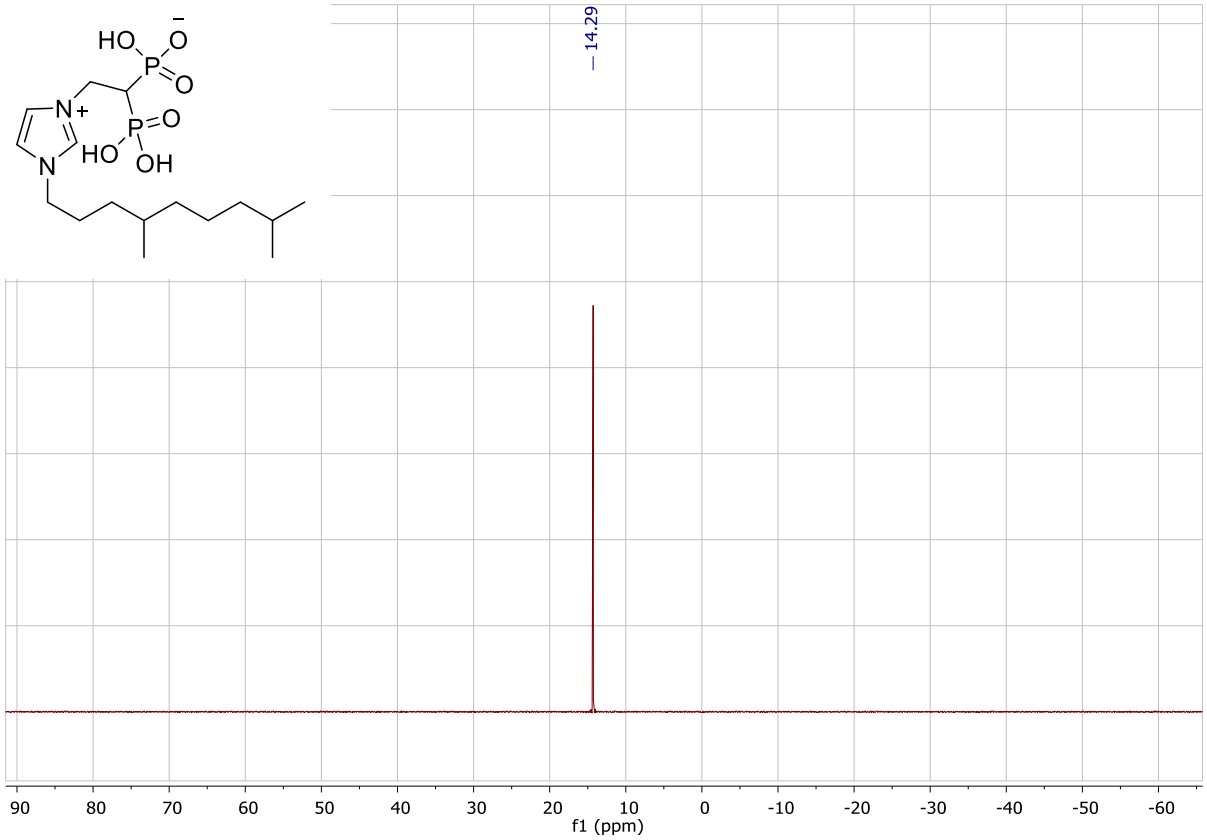
^{1}H NMR IM-2



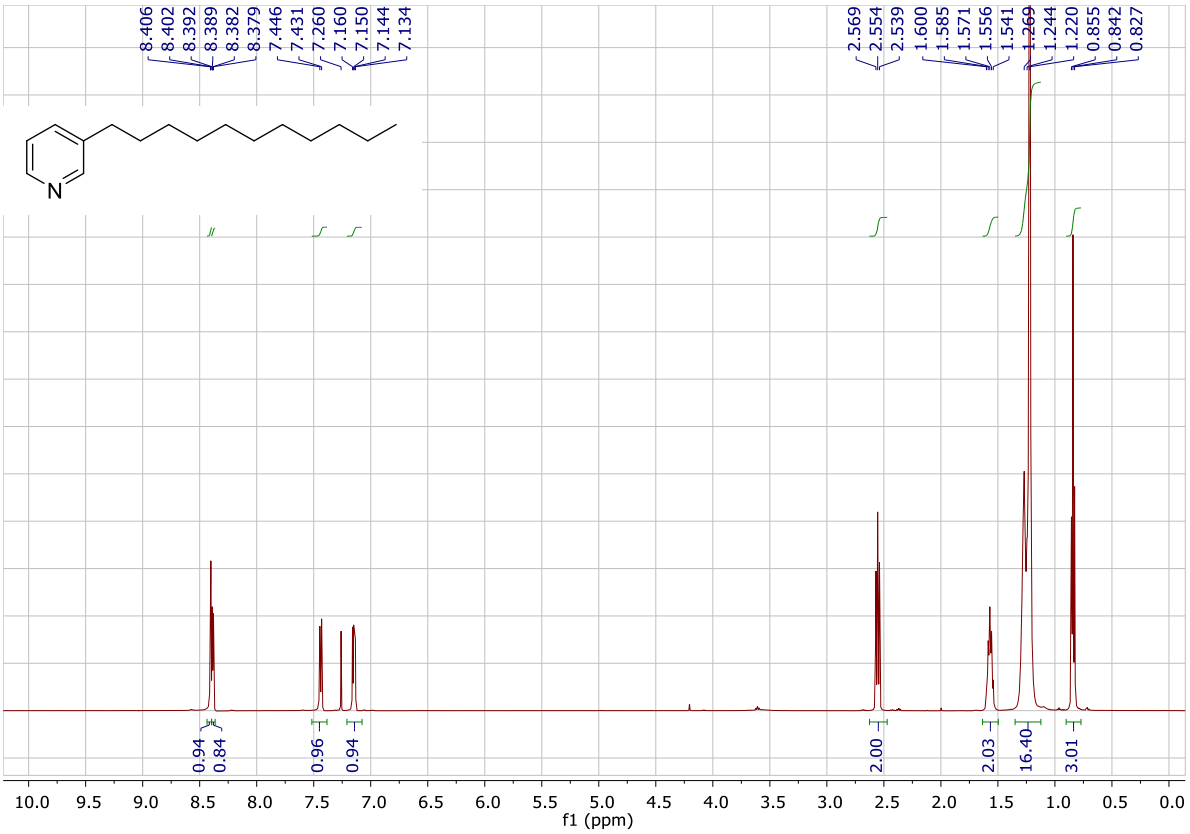
^{1}H NMR 75



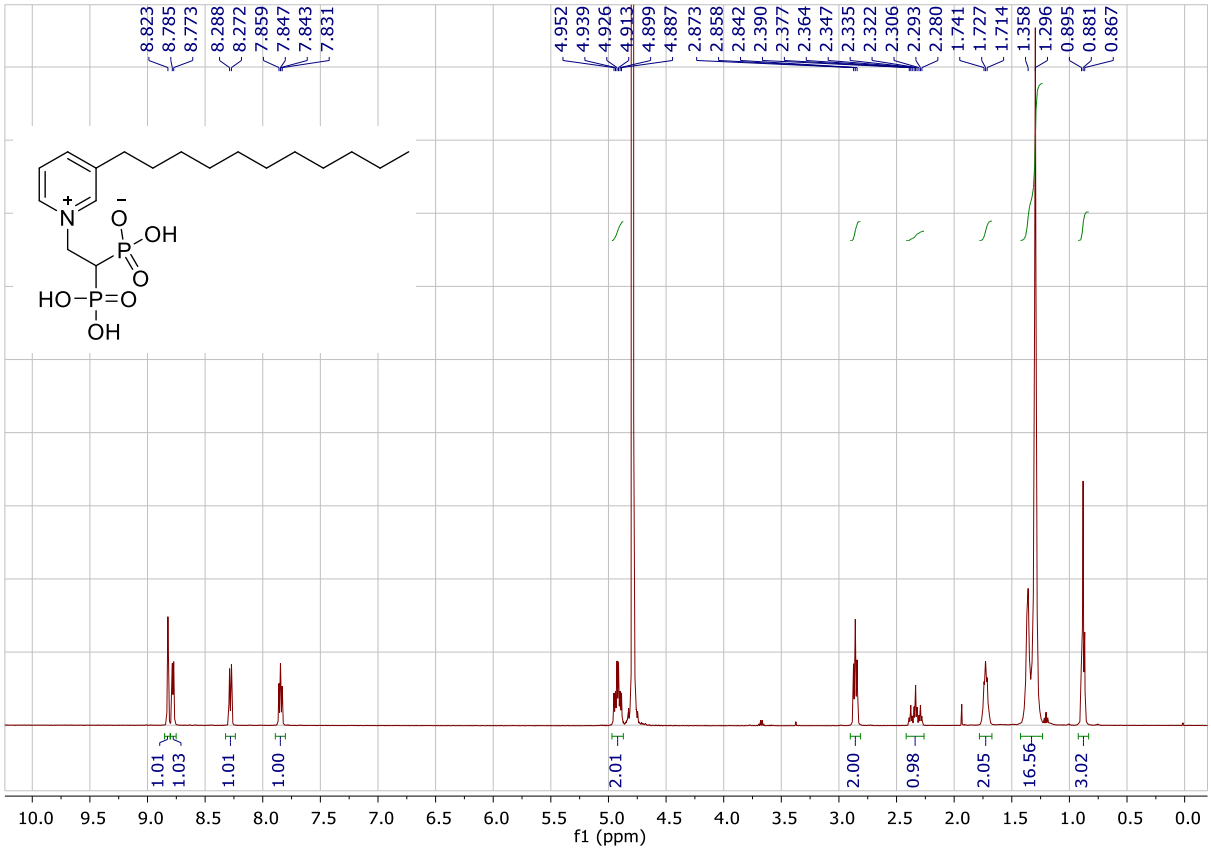
^{31}P NMR 75



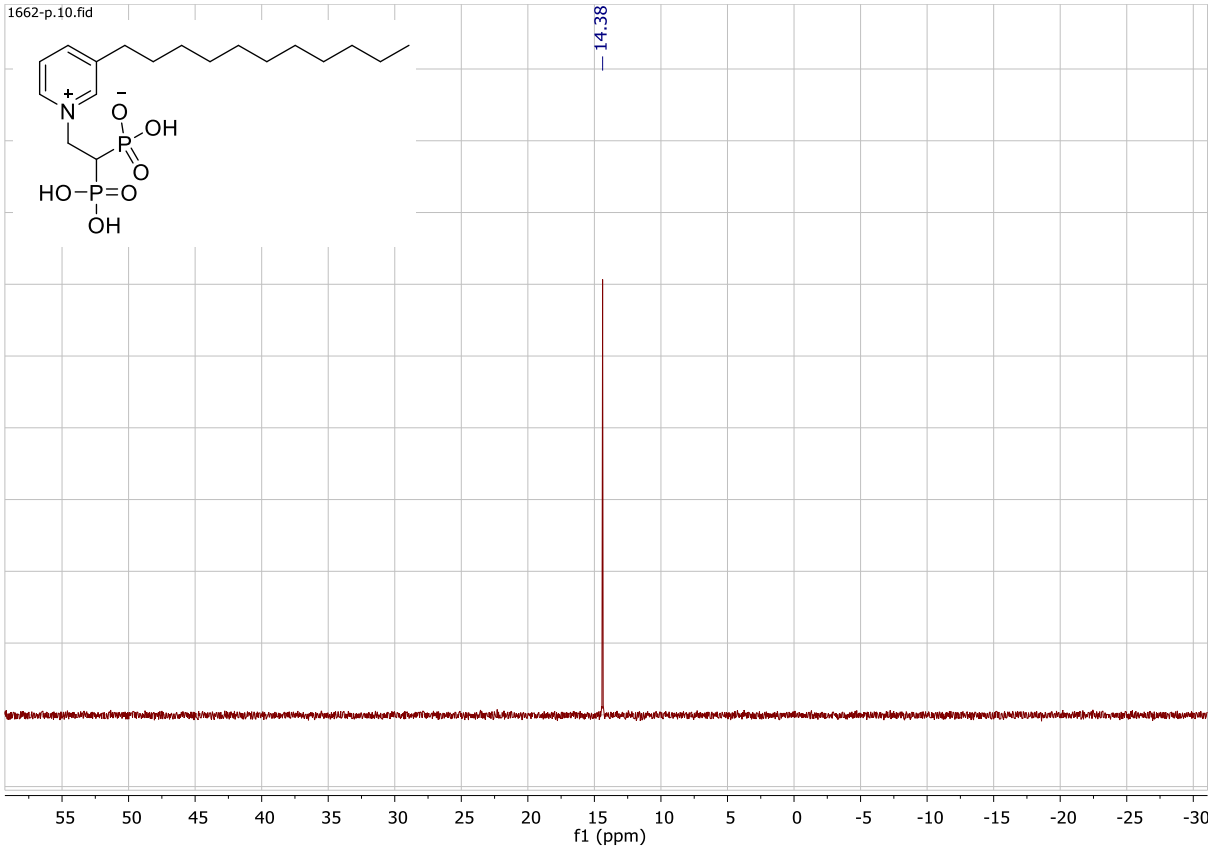
^{1}H NMR IM-3



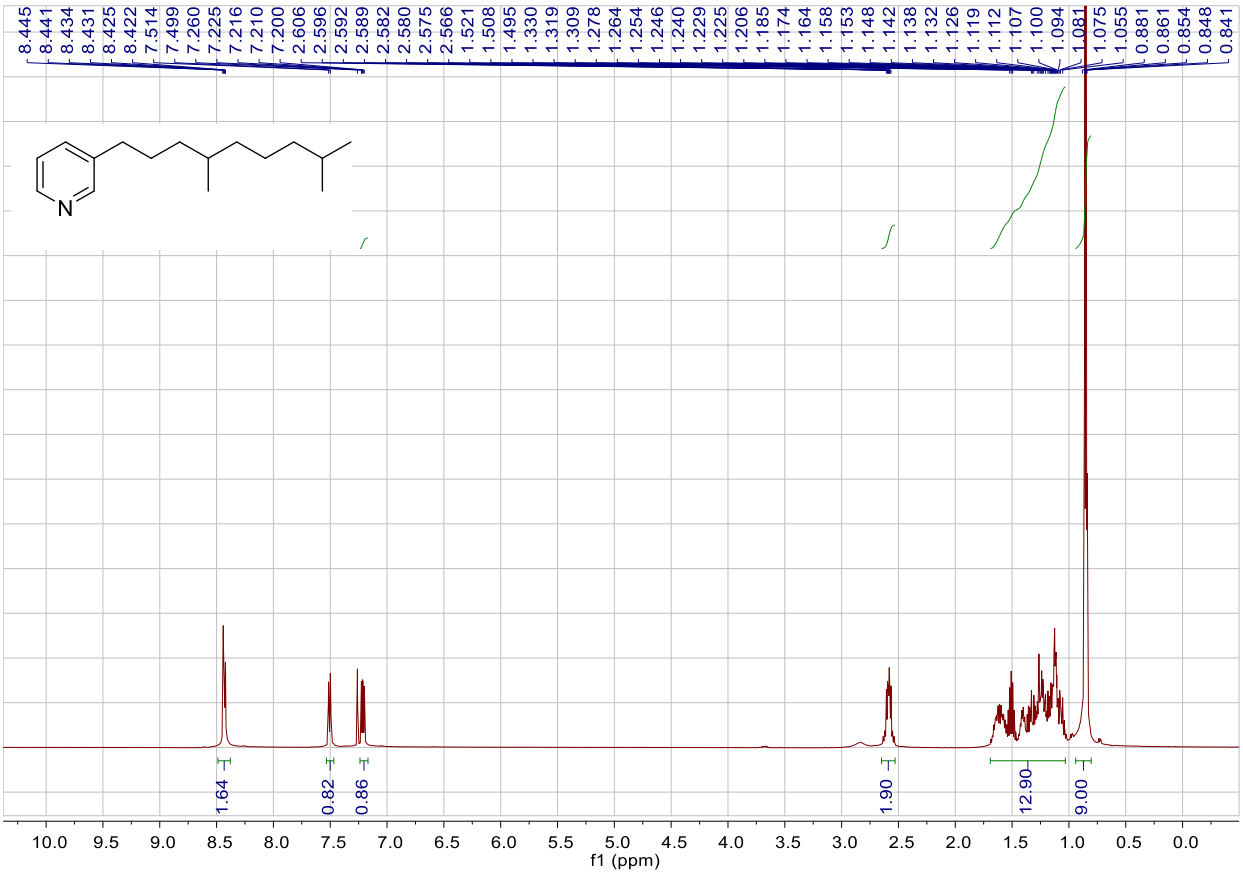
^{1}H NMR 76



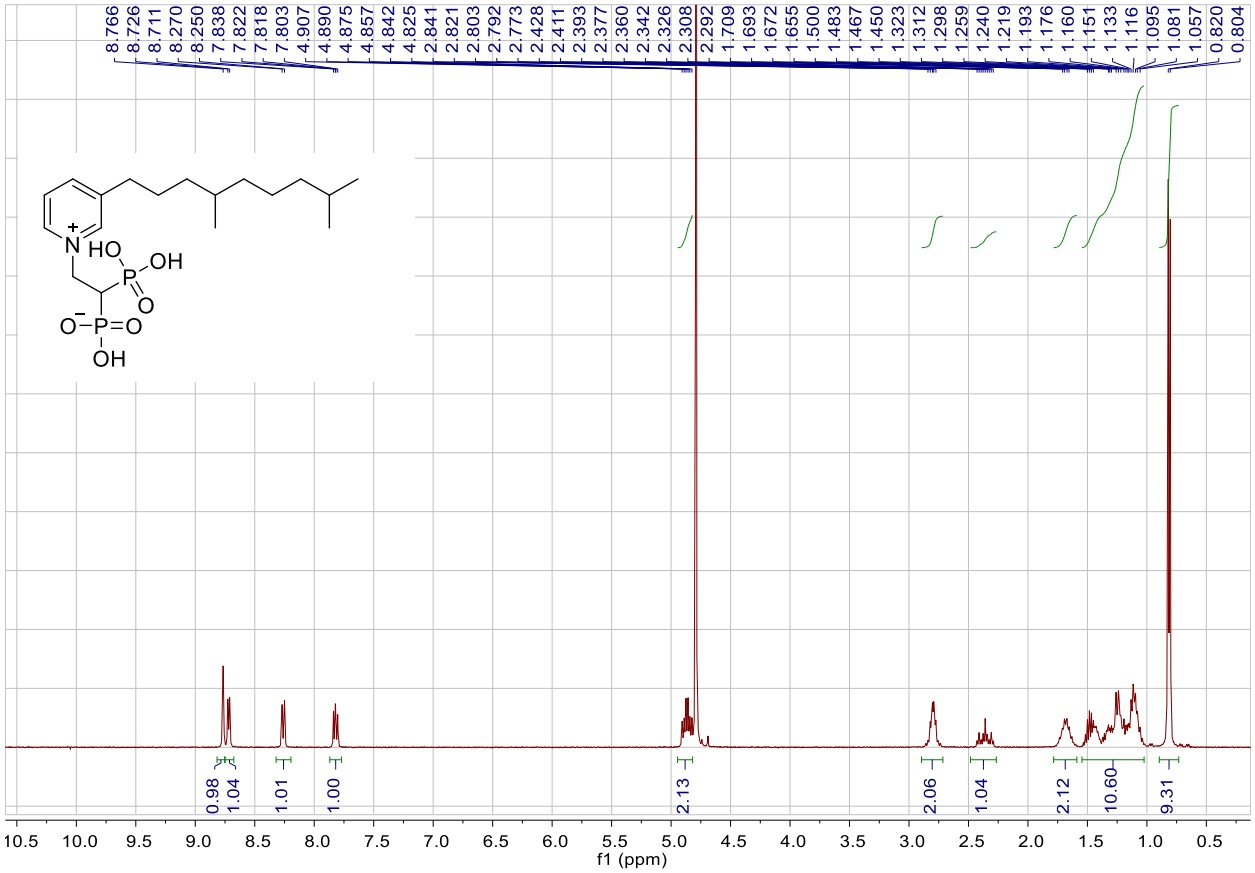
^{31}P NMR 76



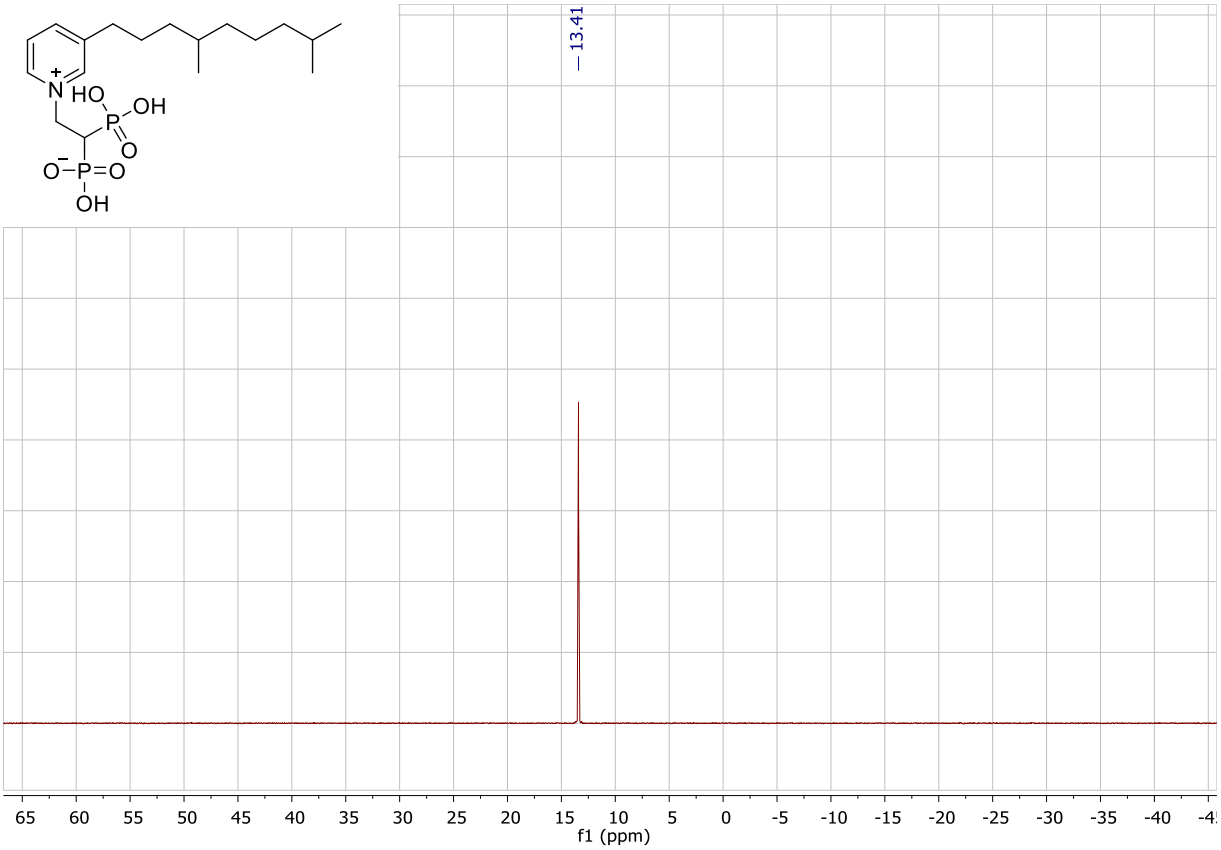
^{1}H NMR IM-4



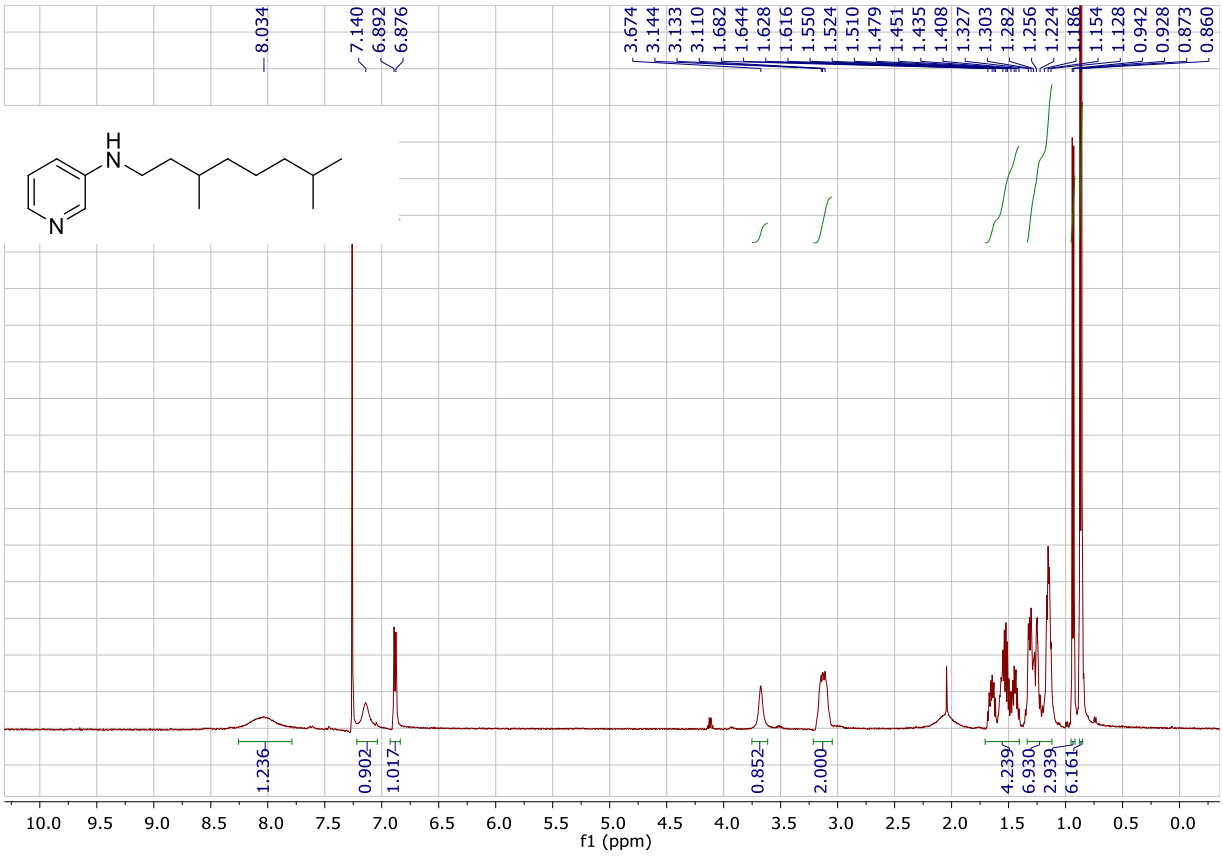
^{1}H NMR 77



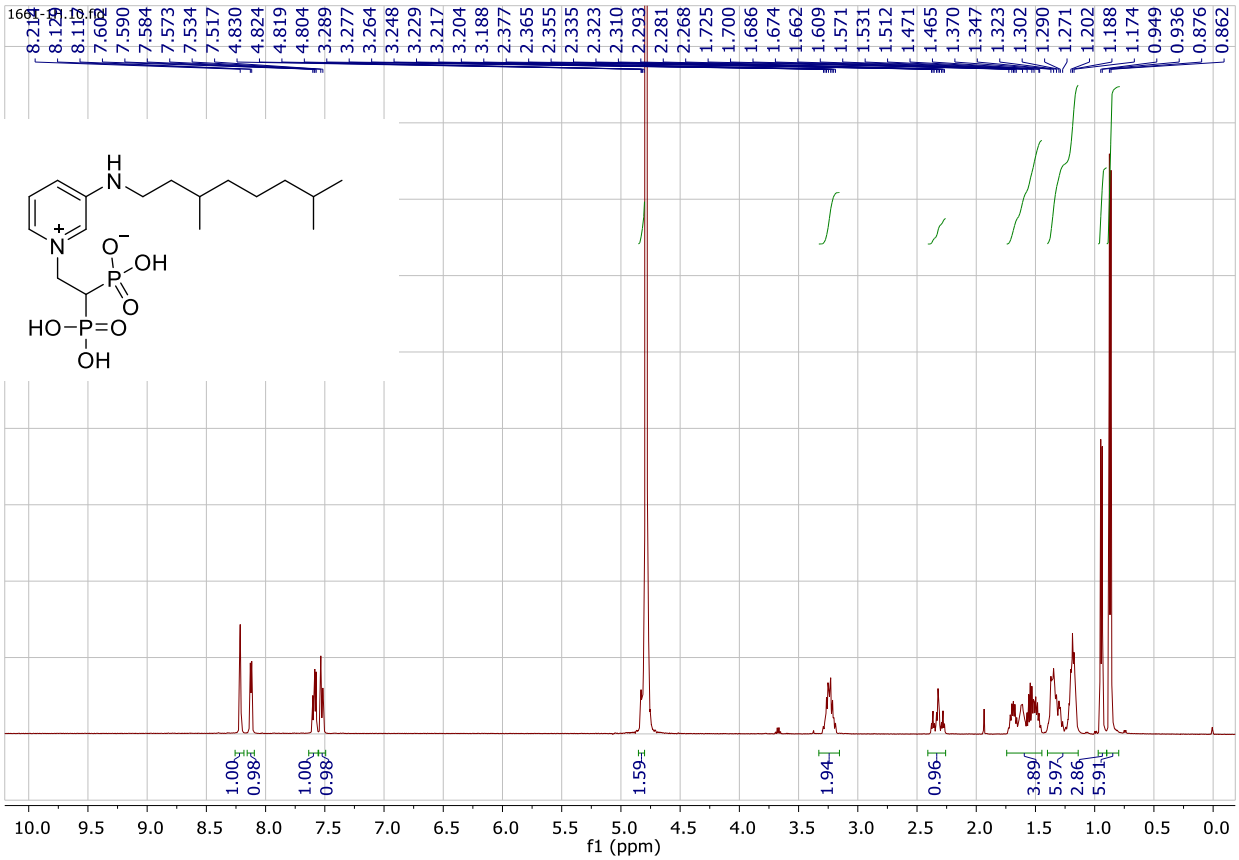
^{31}P NMR 77



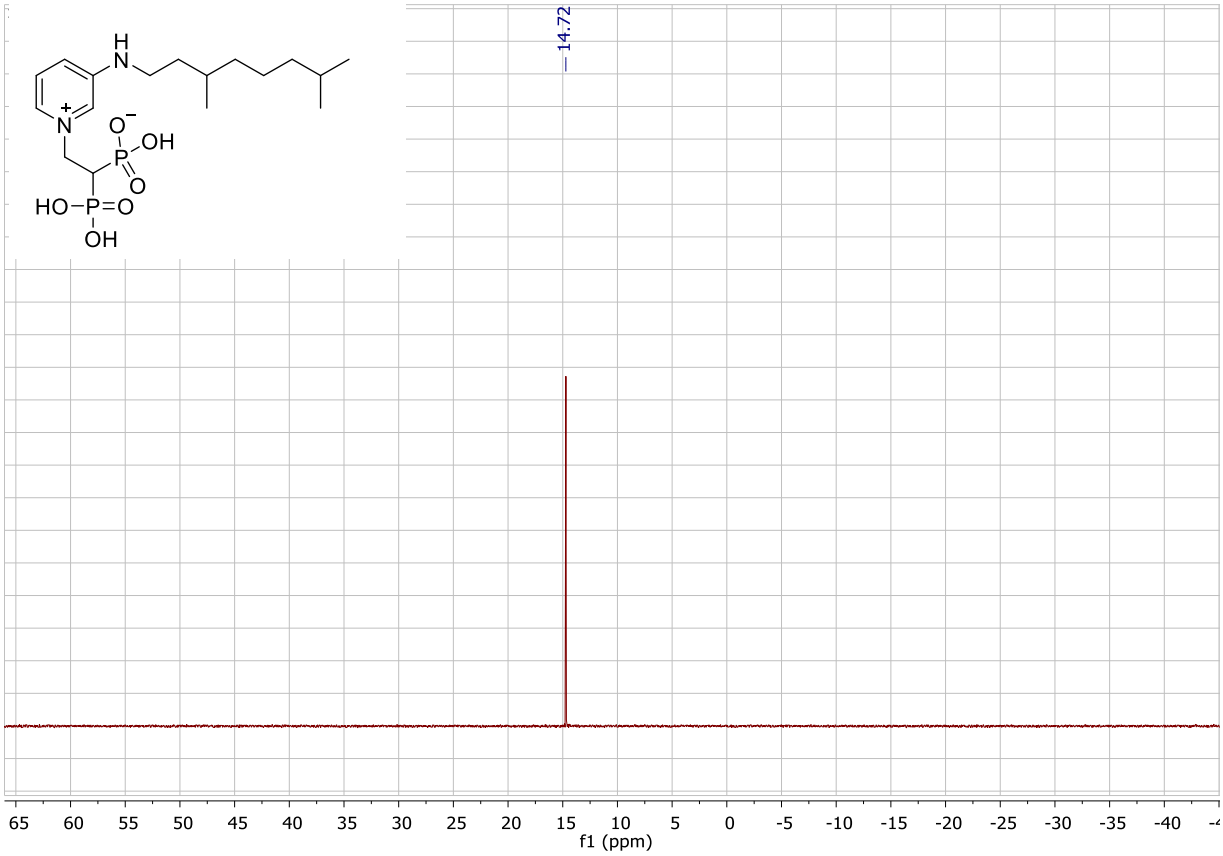
^{1}H NMR IM-7



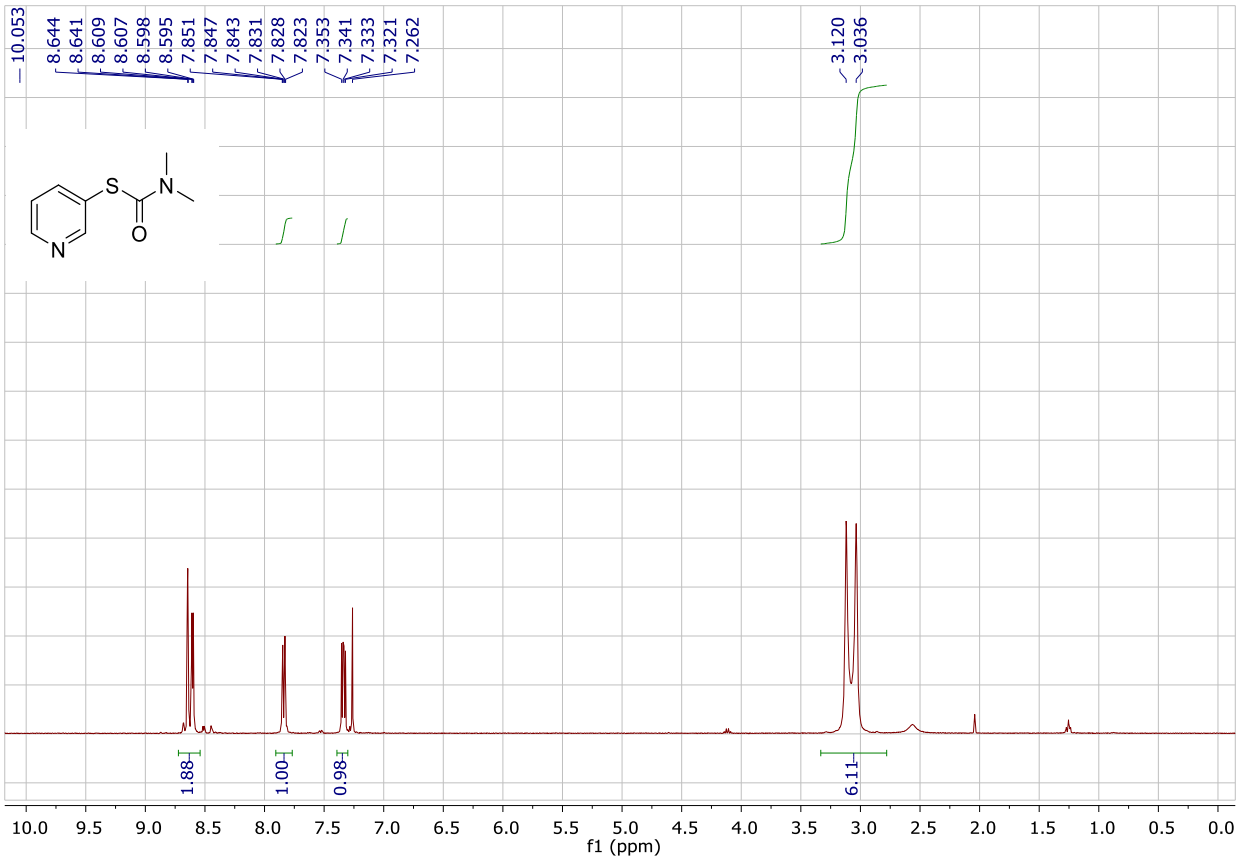
^{1}H NMR 78



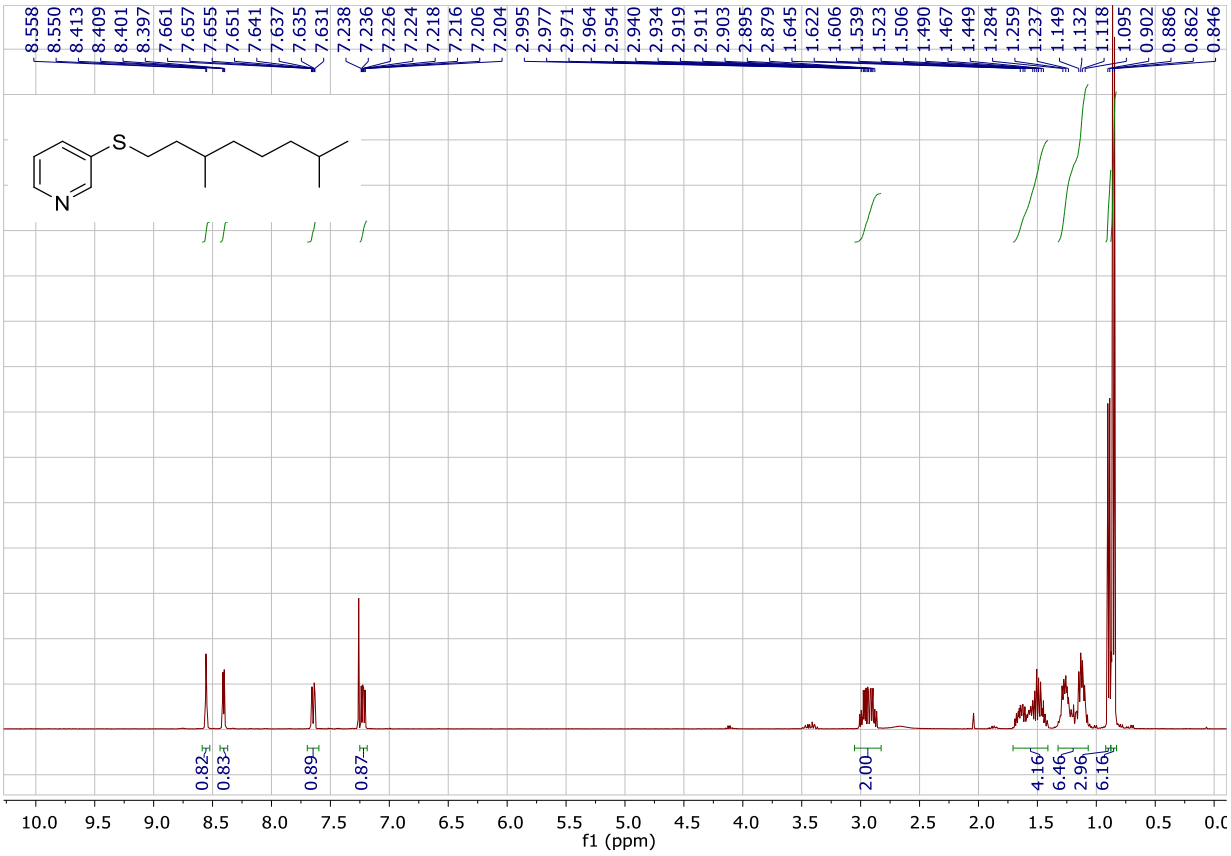
^{31}P NMR 78



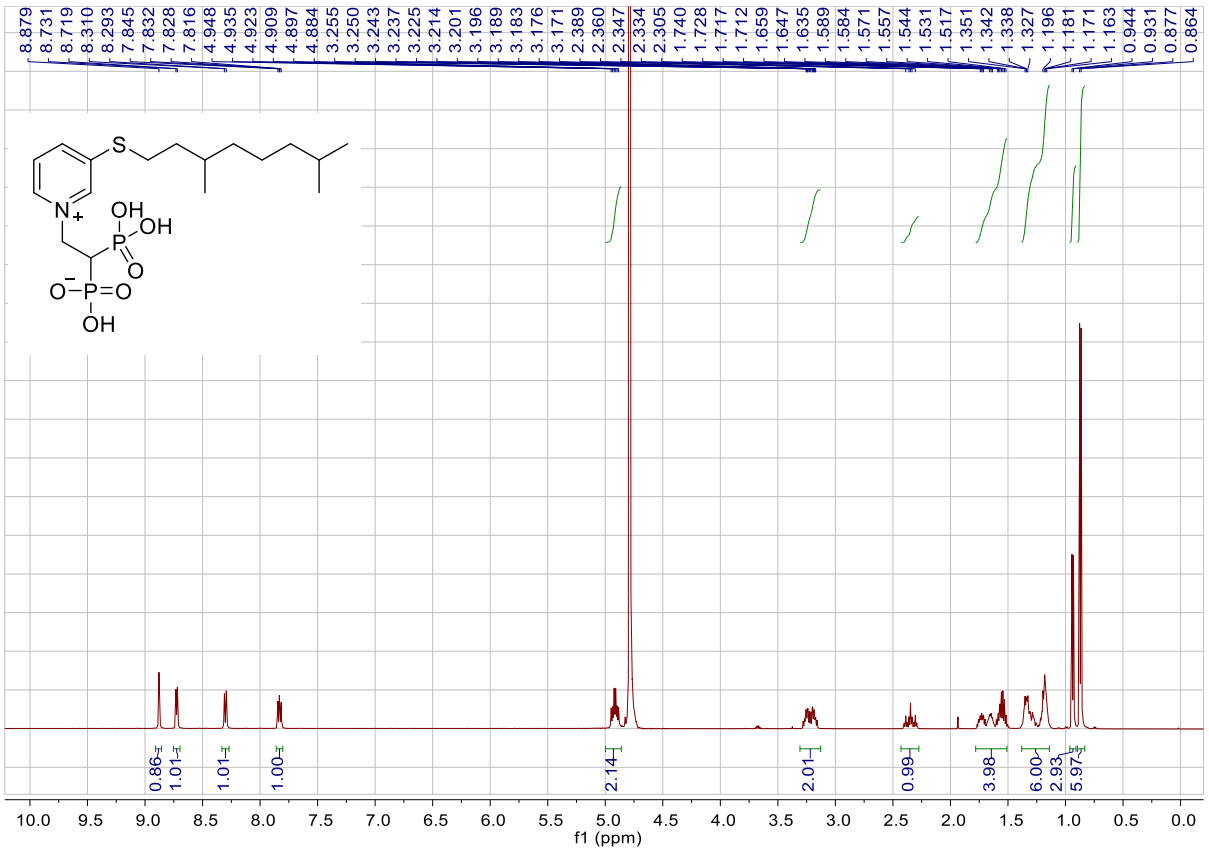
^{1}H NMR IM-8



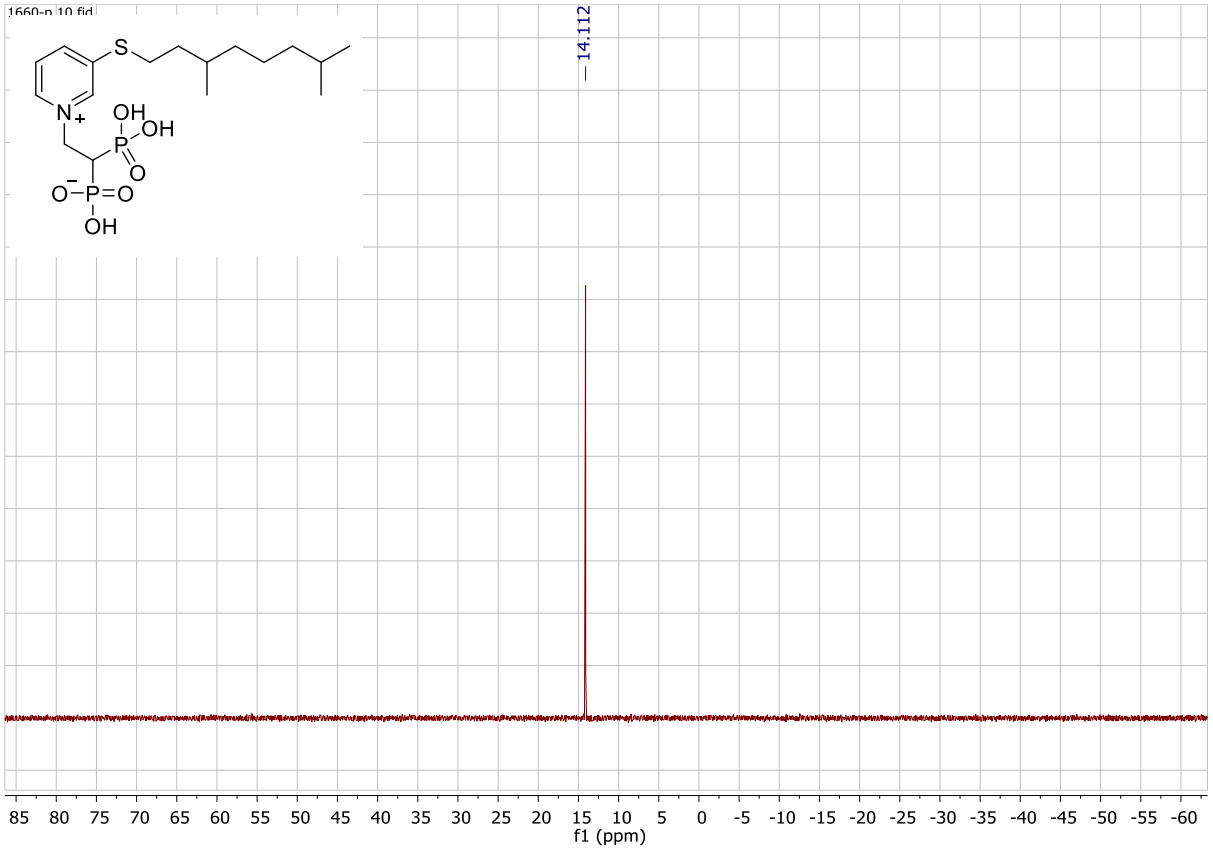
^{1}H NMR IM-10



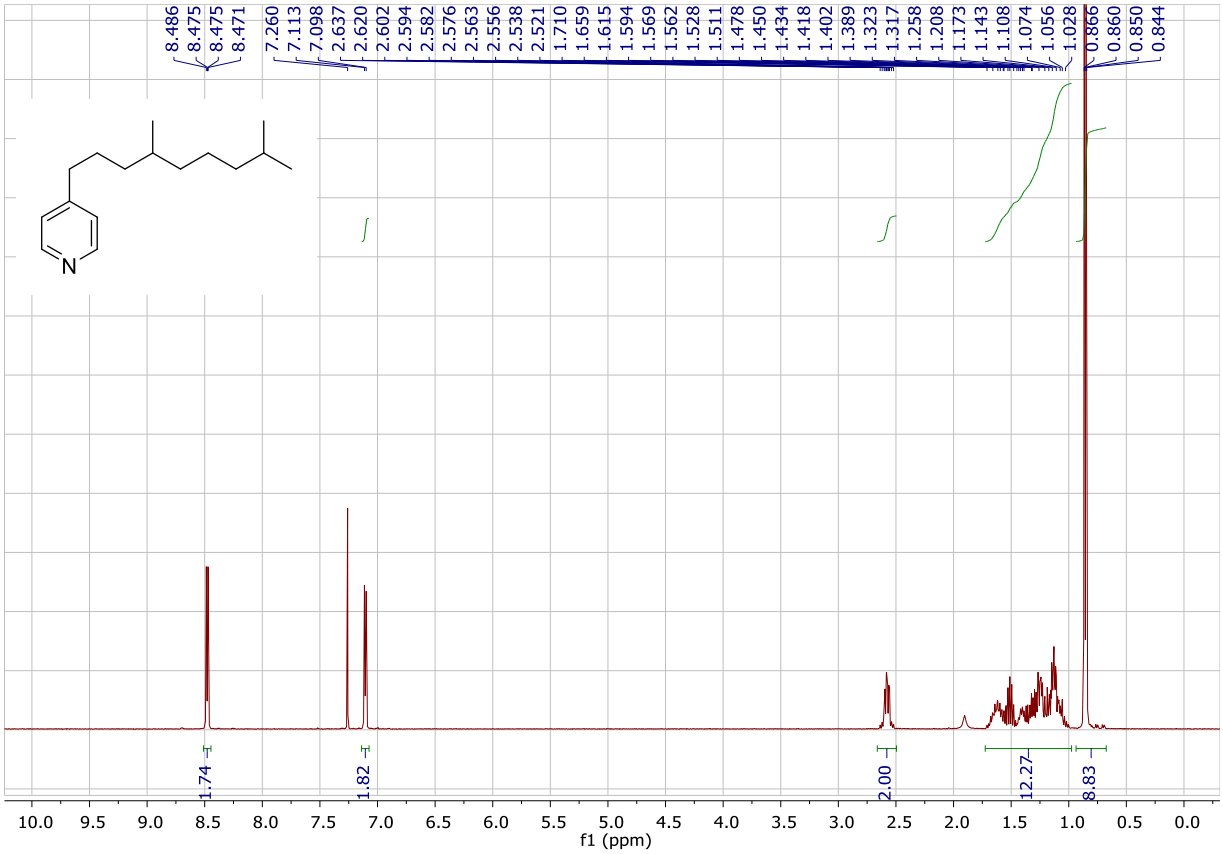
^{1}H NMR 79



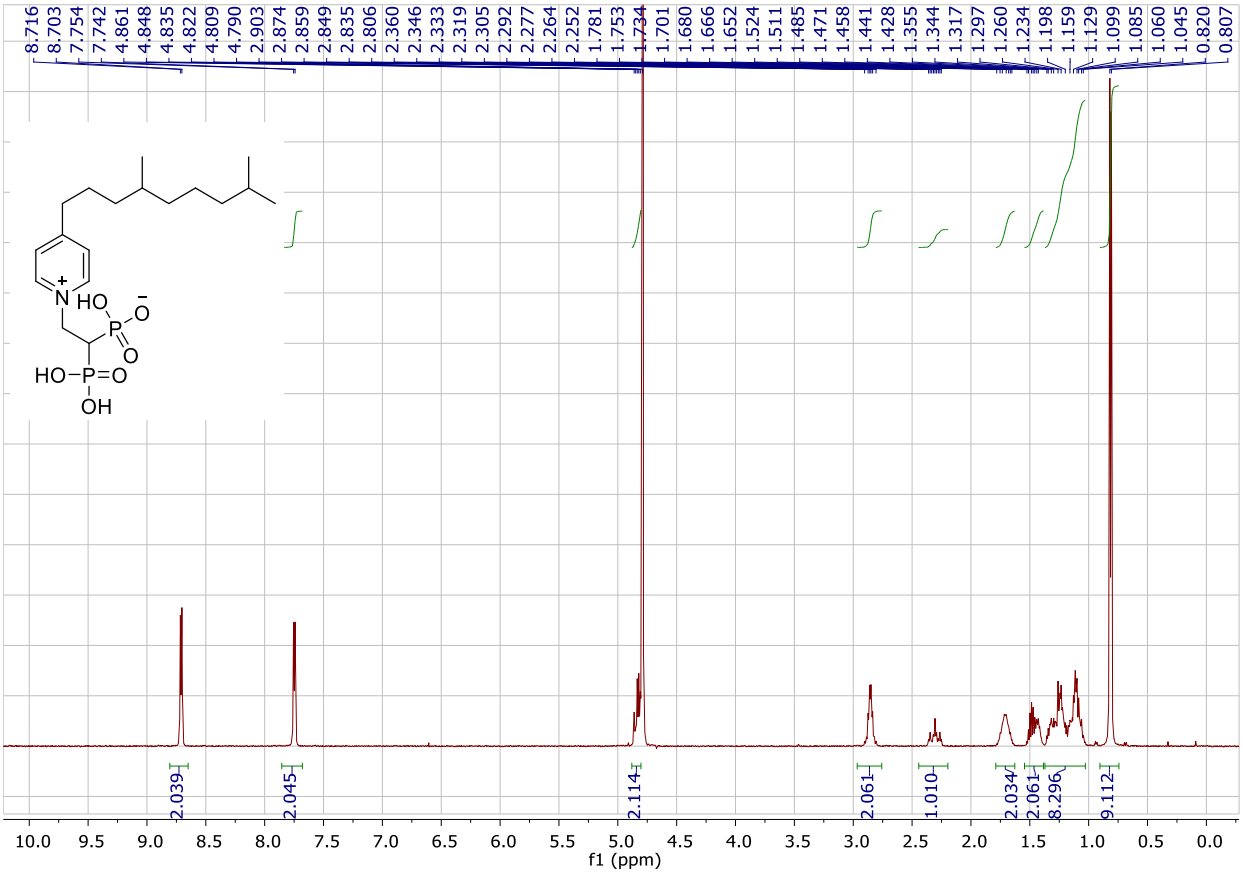
^{31}P NMR 79



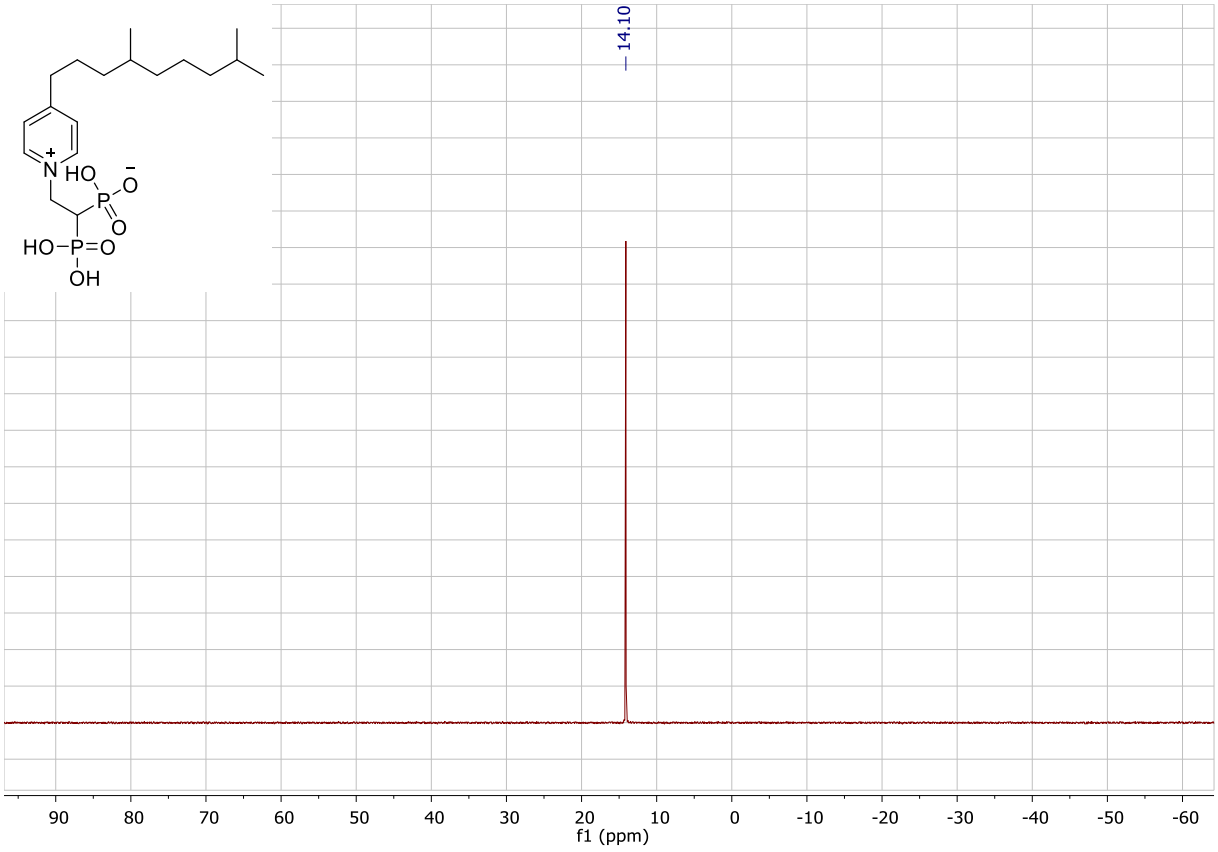
^{1}H NMR IM-11



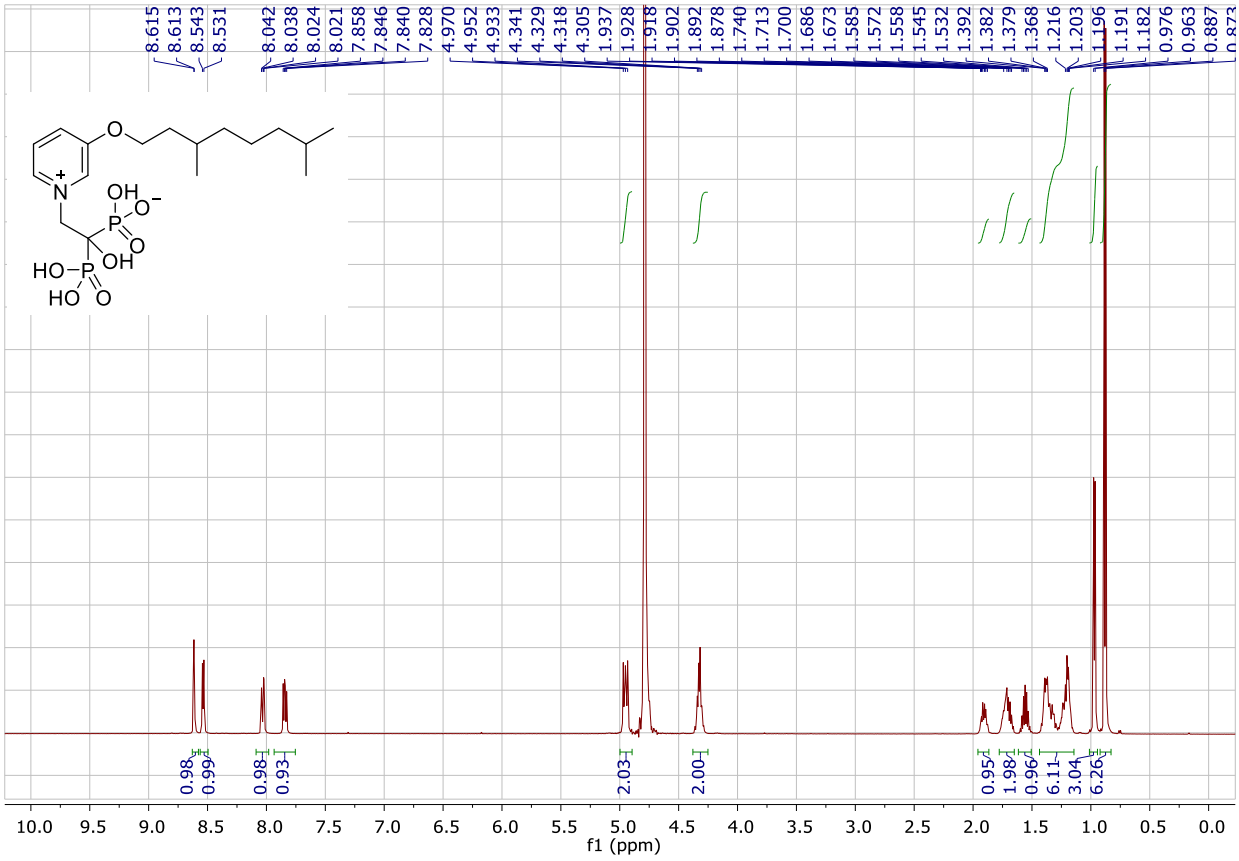
^{1}H NMR 80



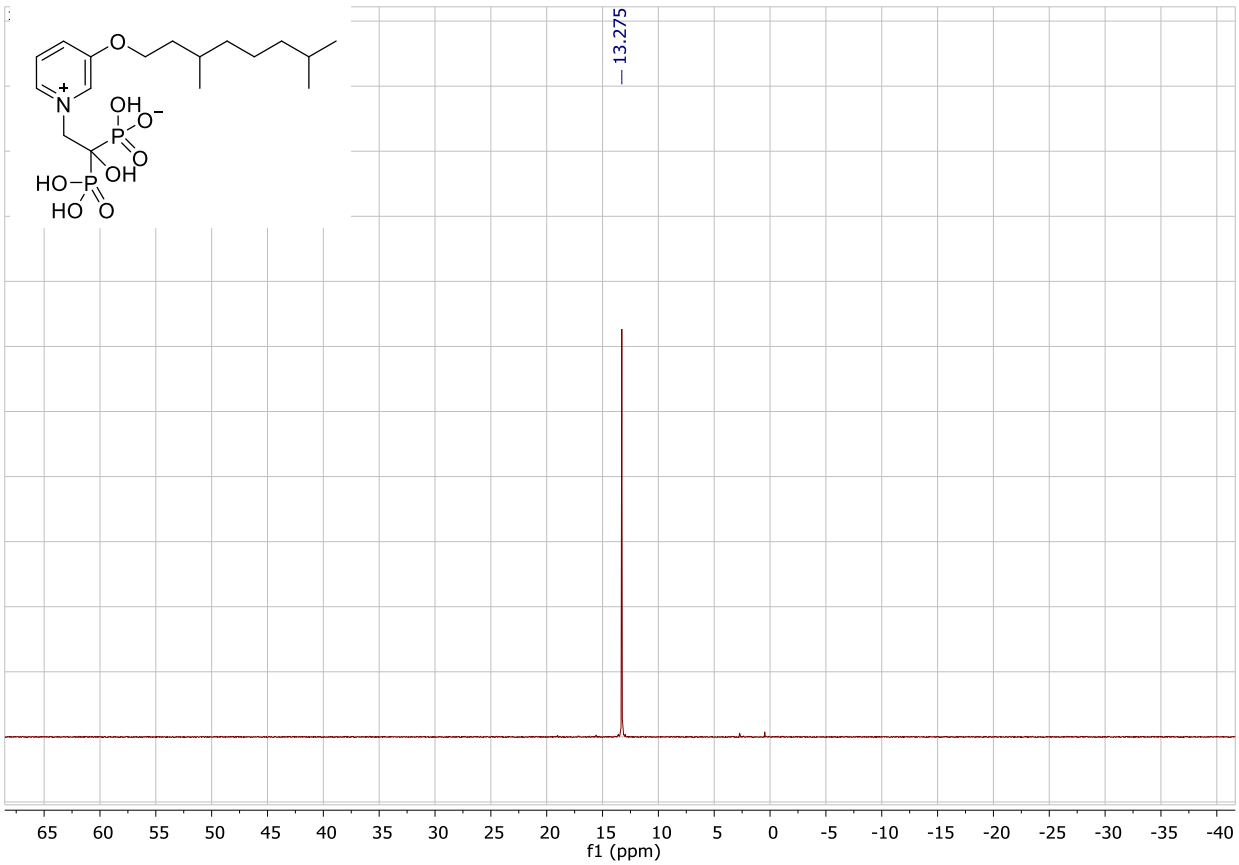
^{31}P NMR 80



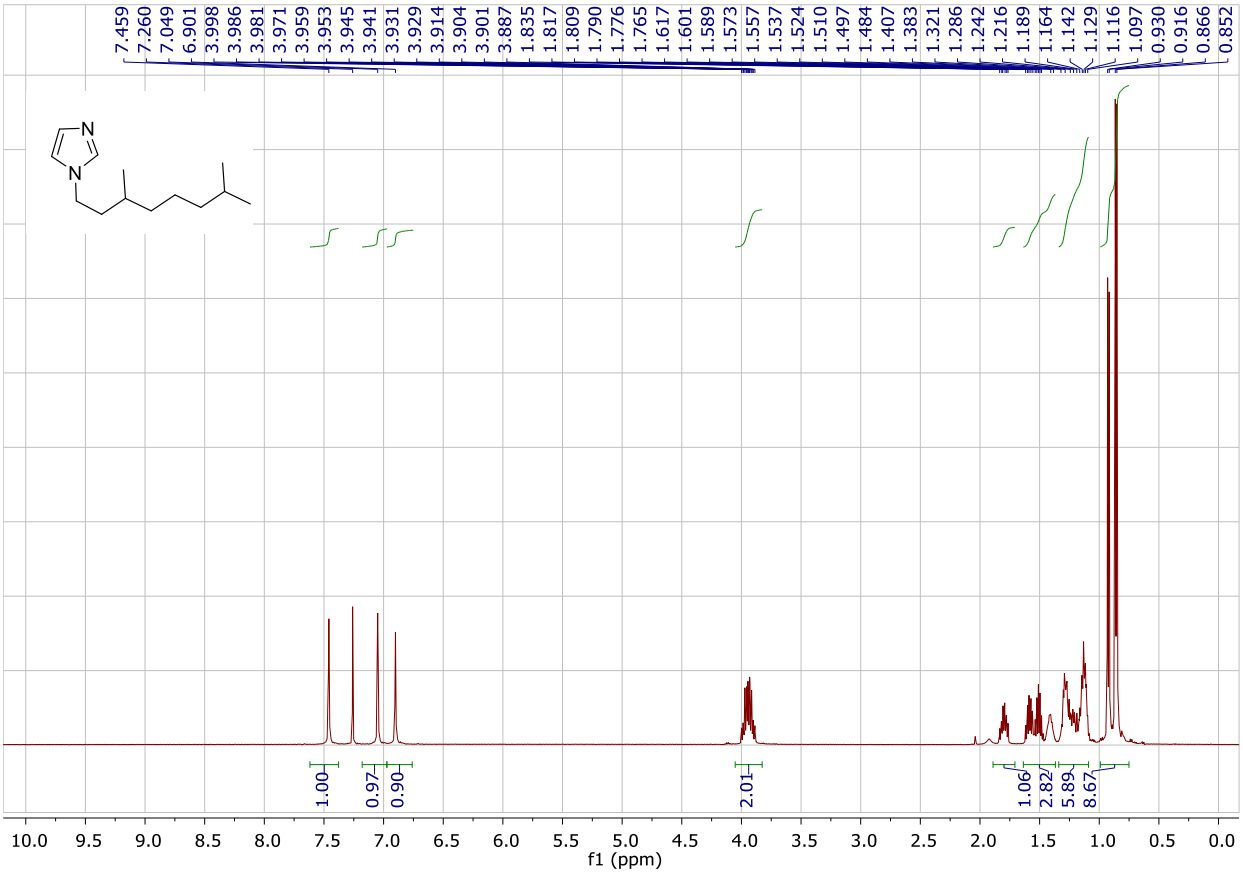
^{1}H NMR 81



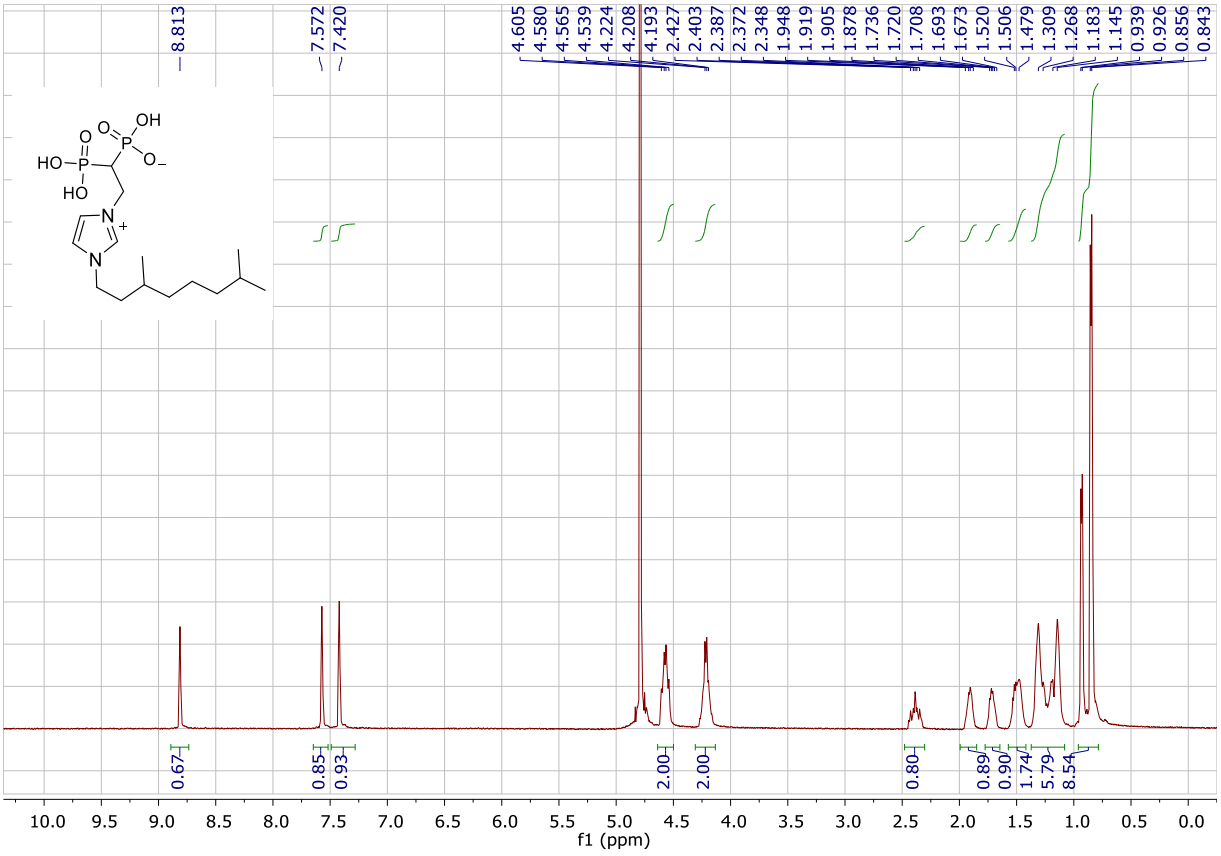
^{31}P NMR 81



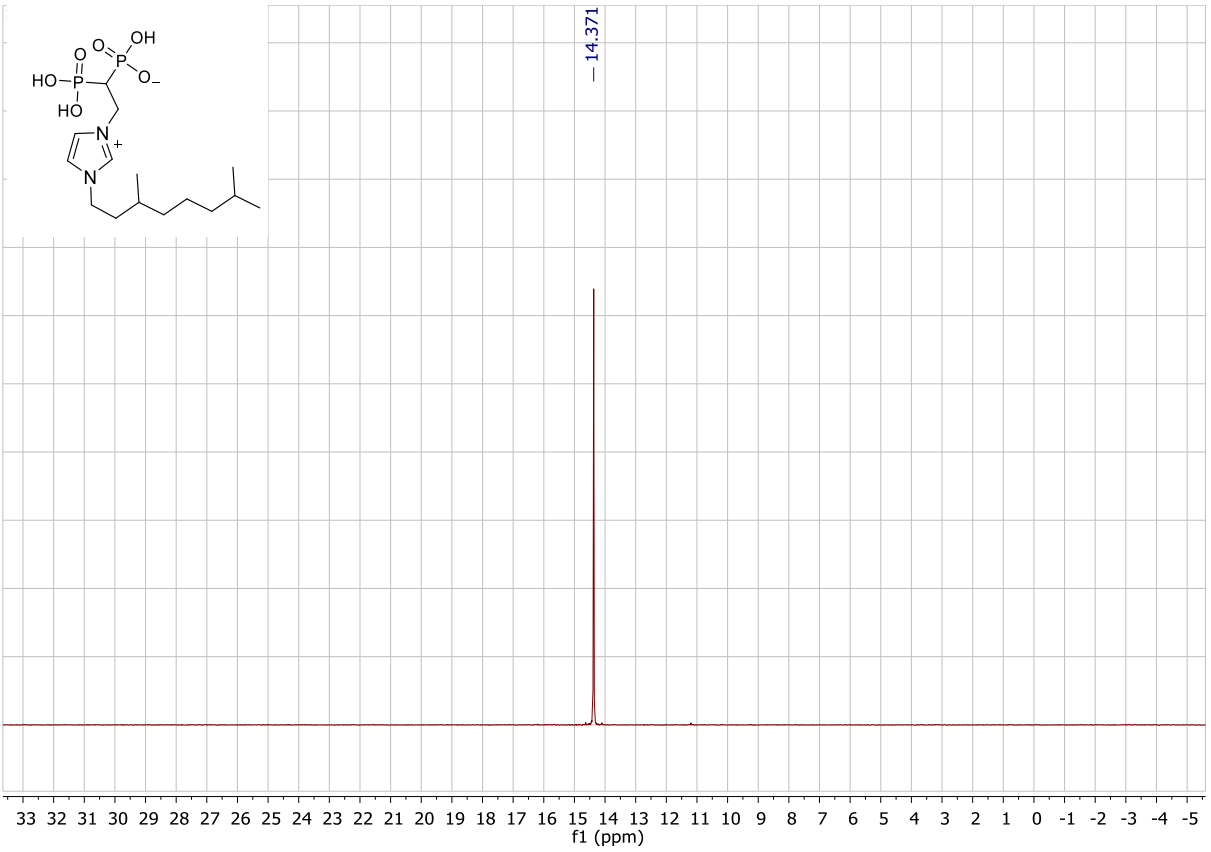
^{1}H NMR IM-12



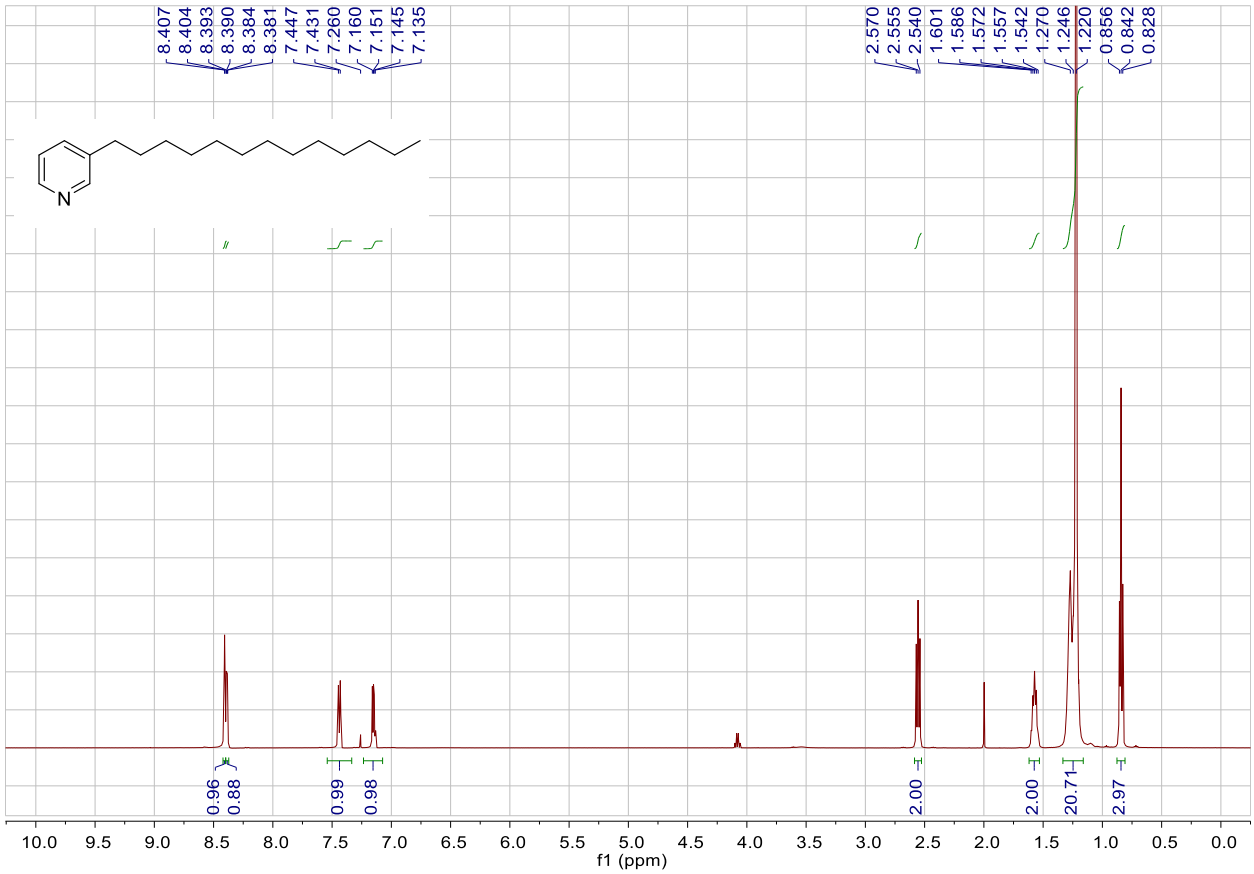
^{1}H NMR 82



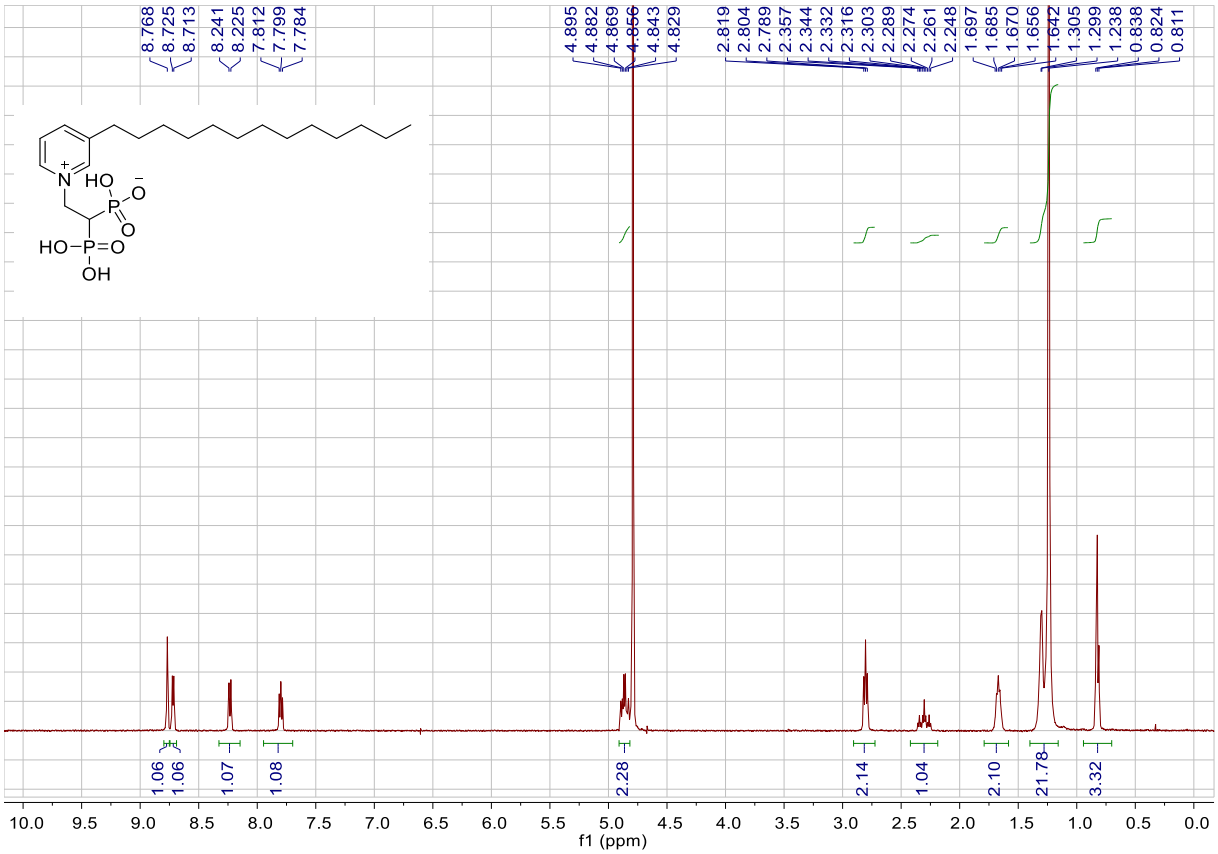
^{31}P NMR 82



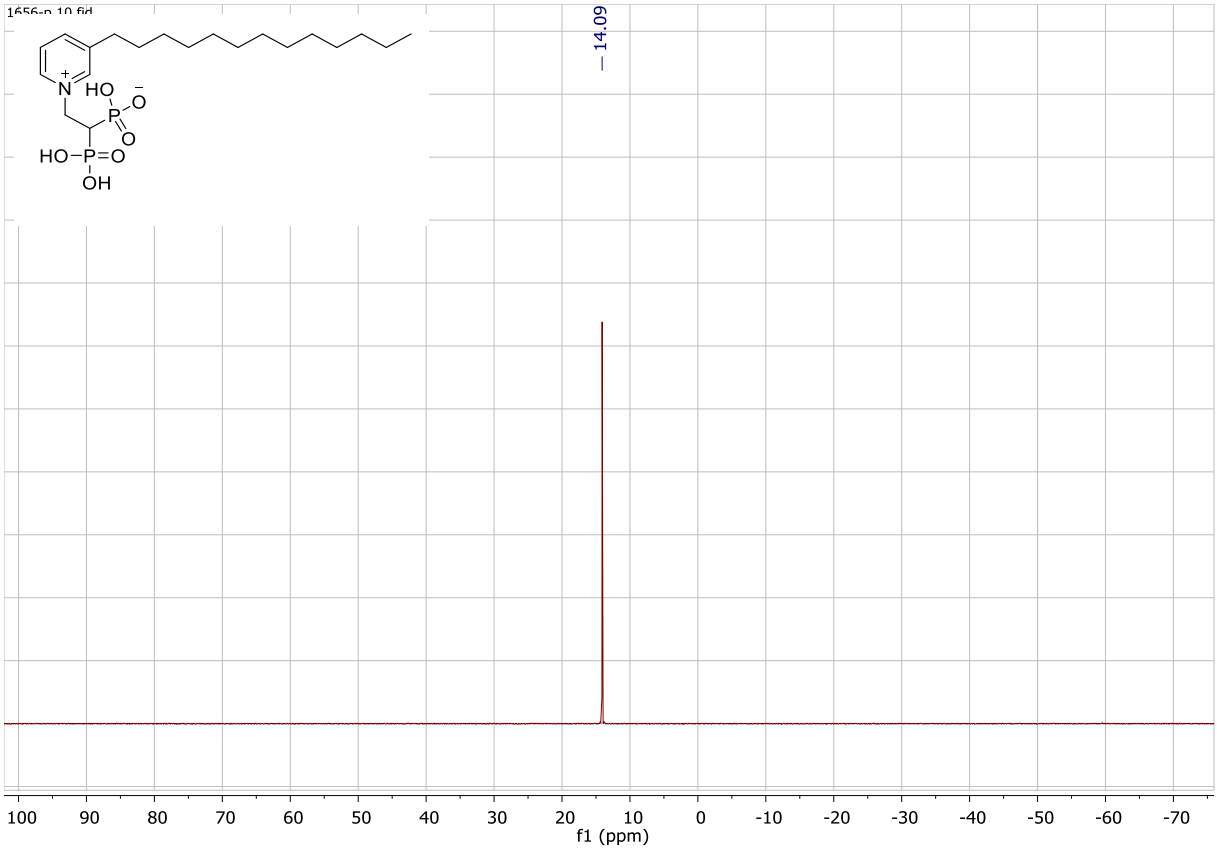
^{1}H NMR IM-13



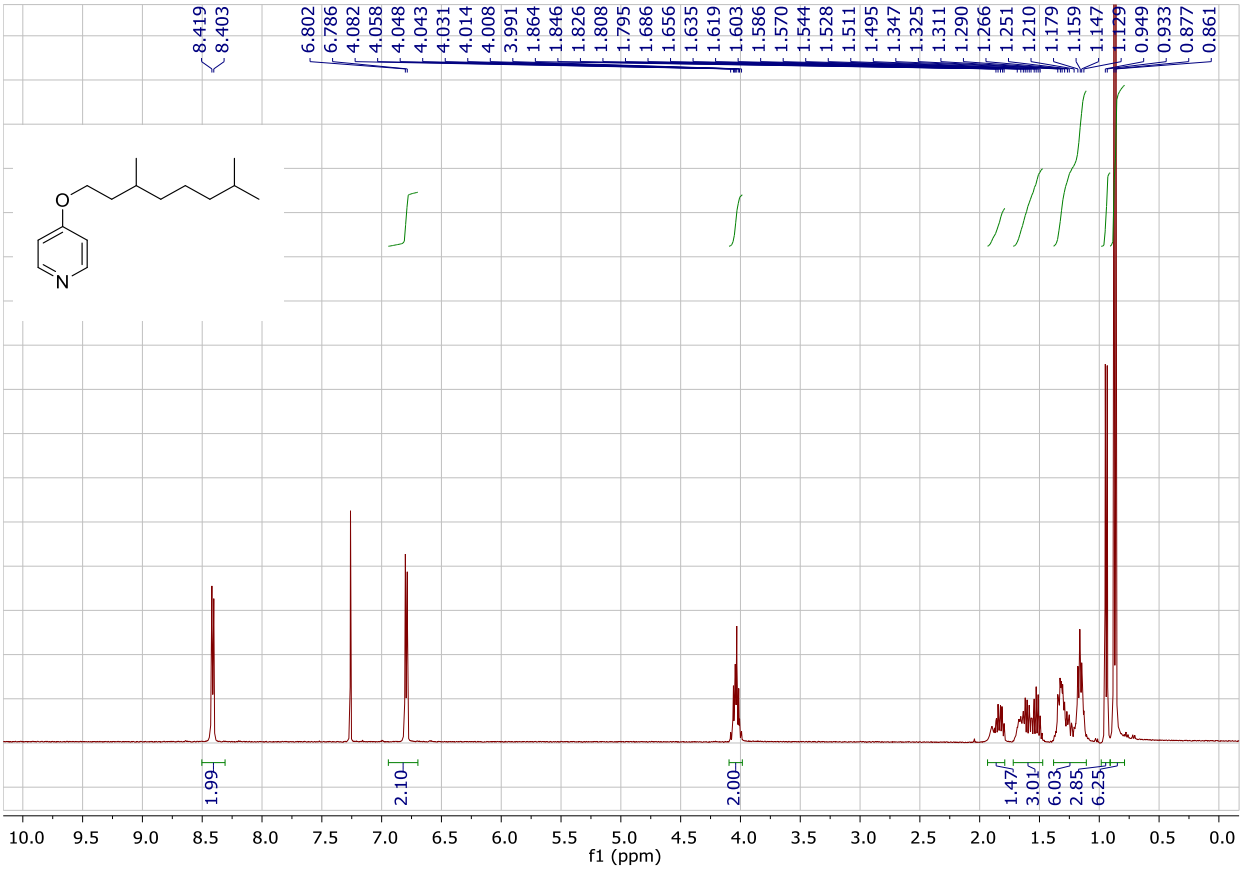
^{1}H NMR 83



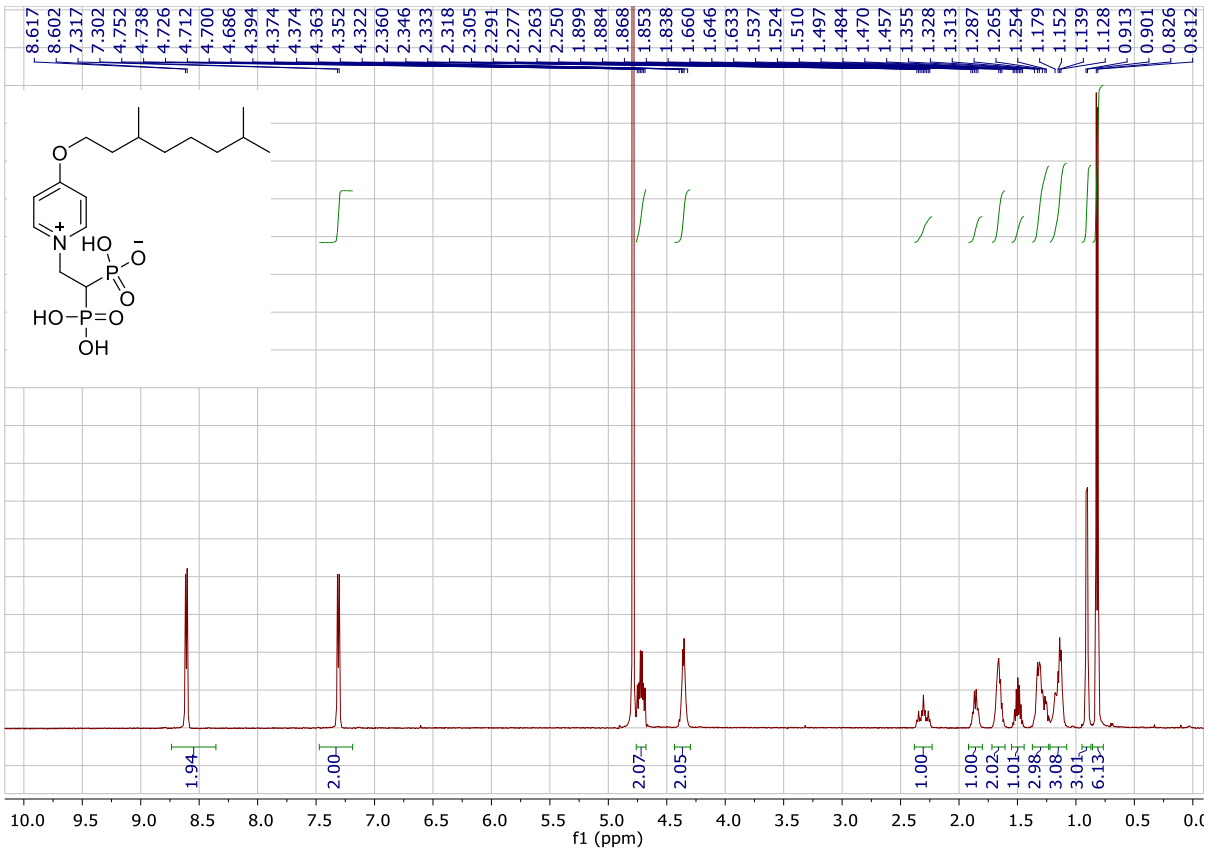
^{31}P NMR 83



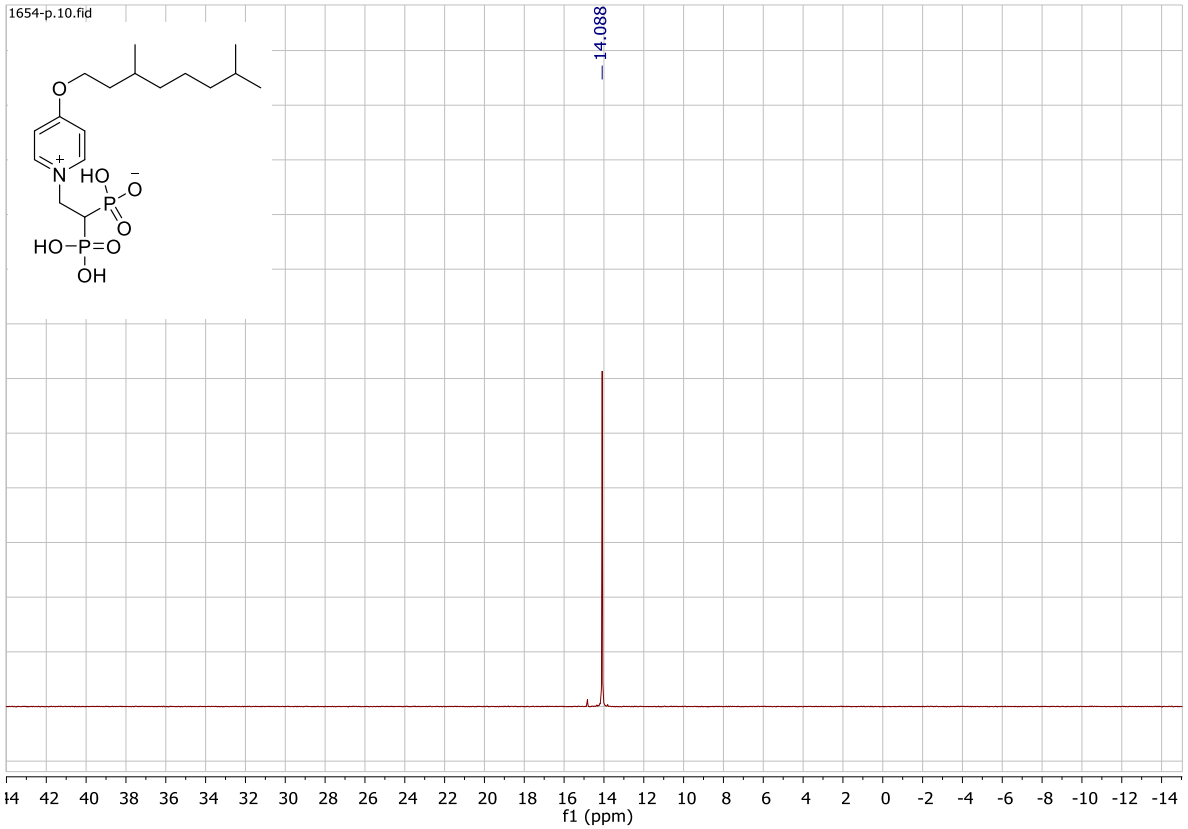
^{1}H NMR IM-14



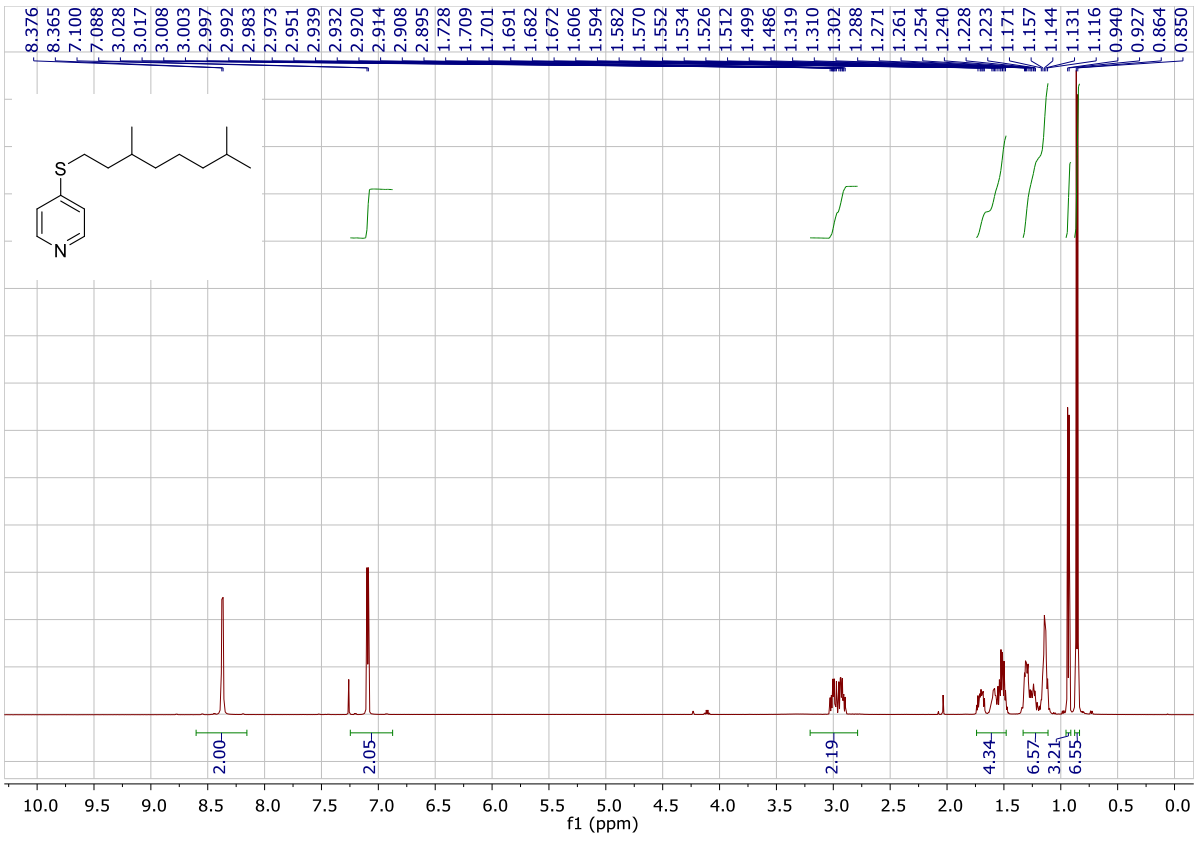
^{1}H NMR 84



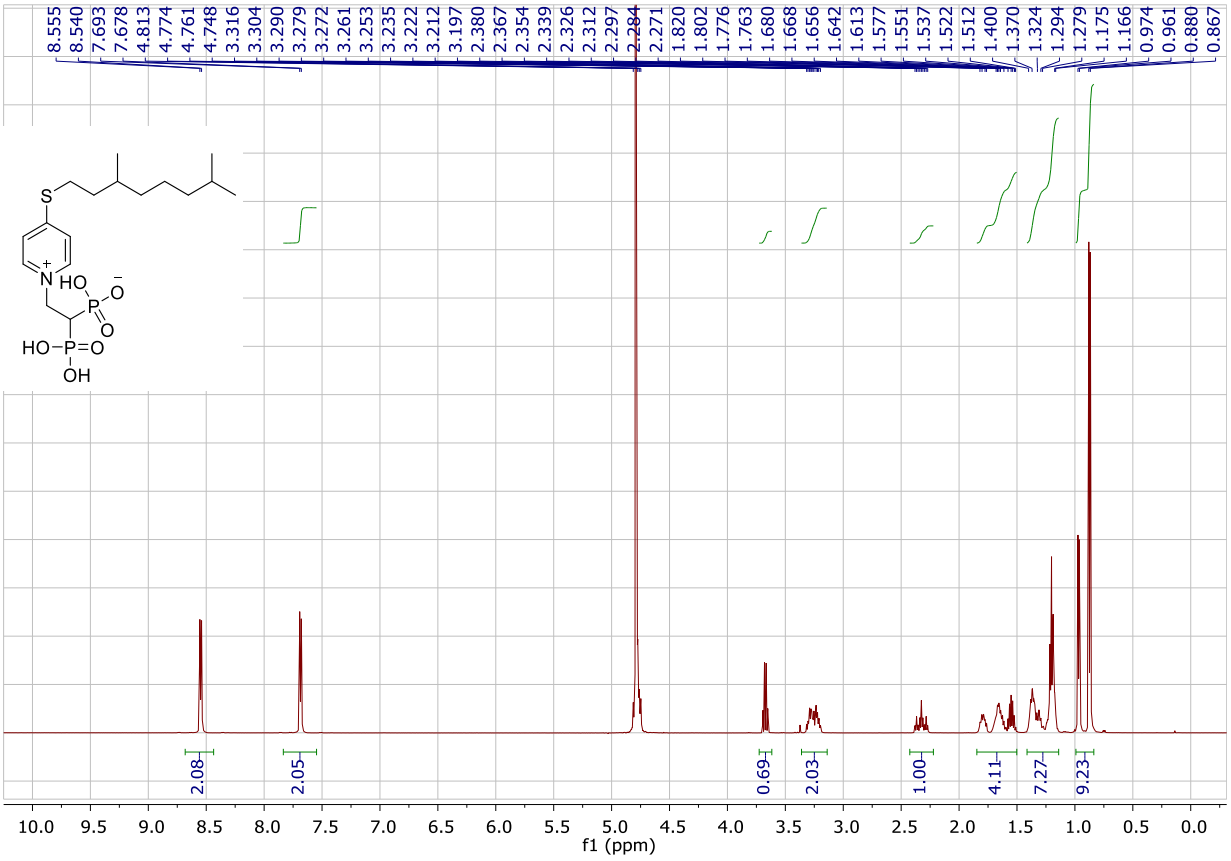
^{31}P NMR 84



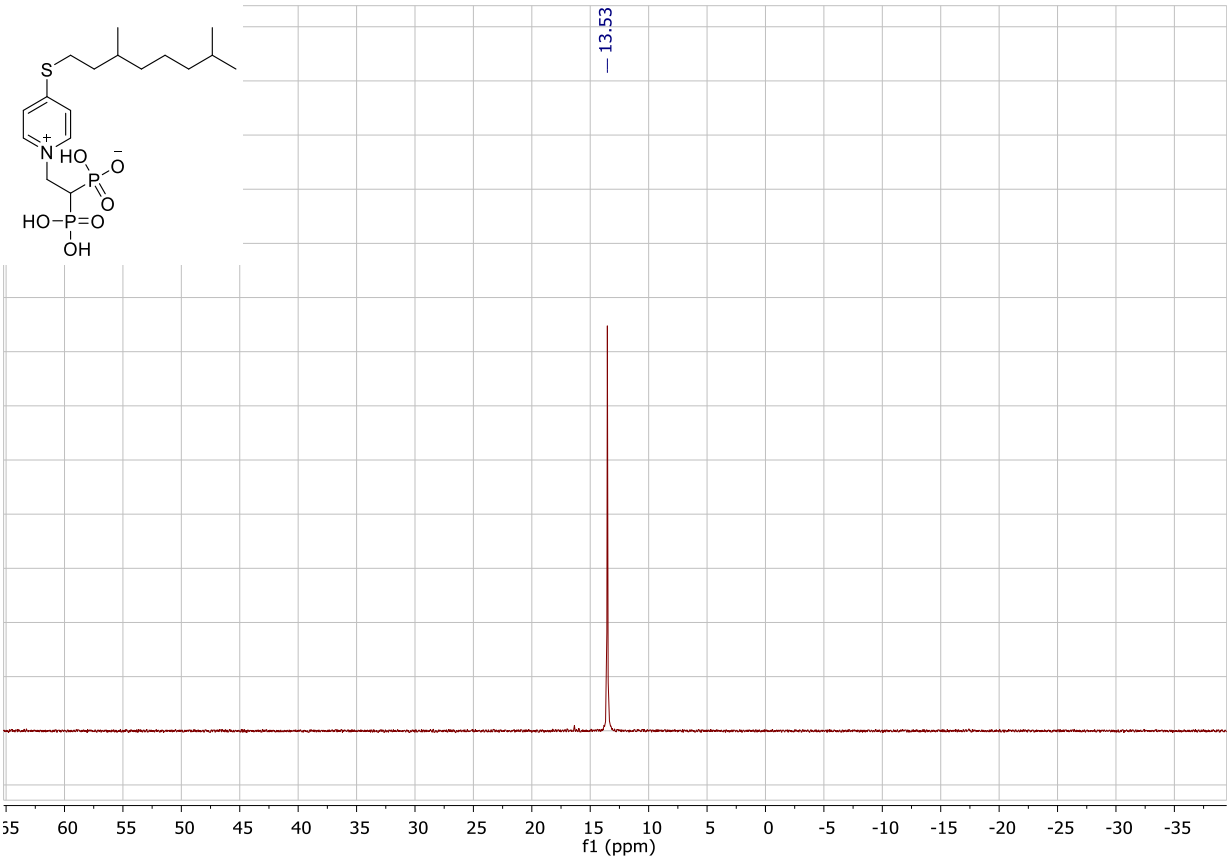
^{1}H NMR IM-15



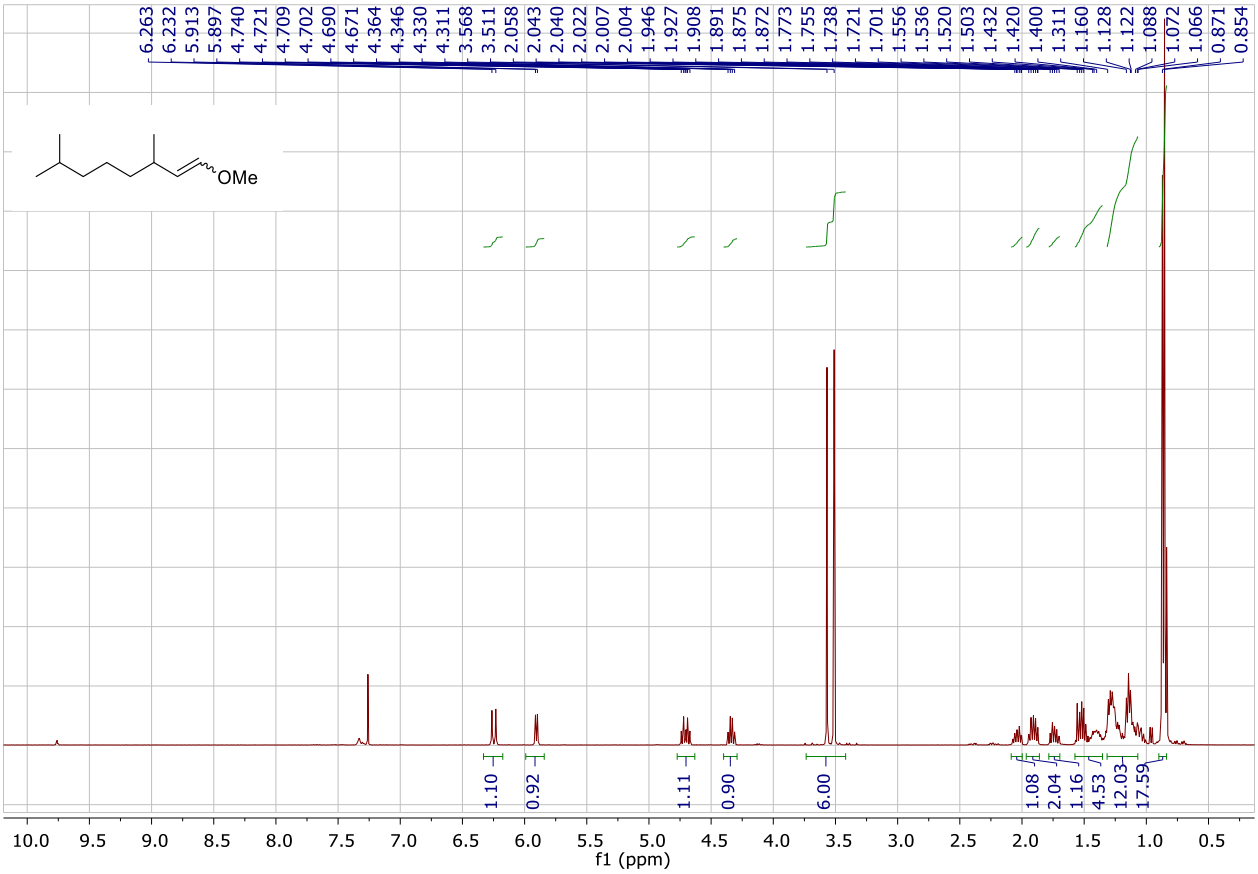
^{1}H NMR 85



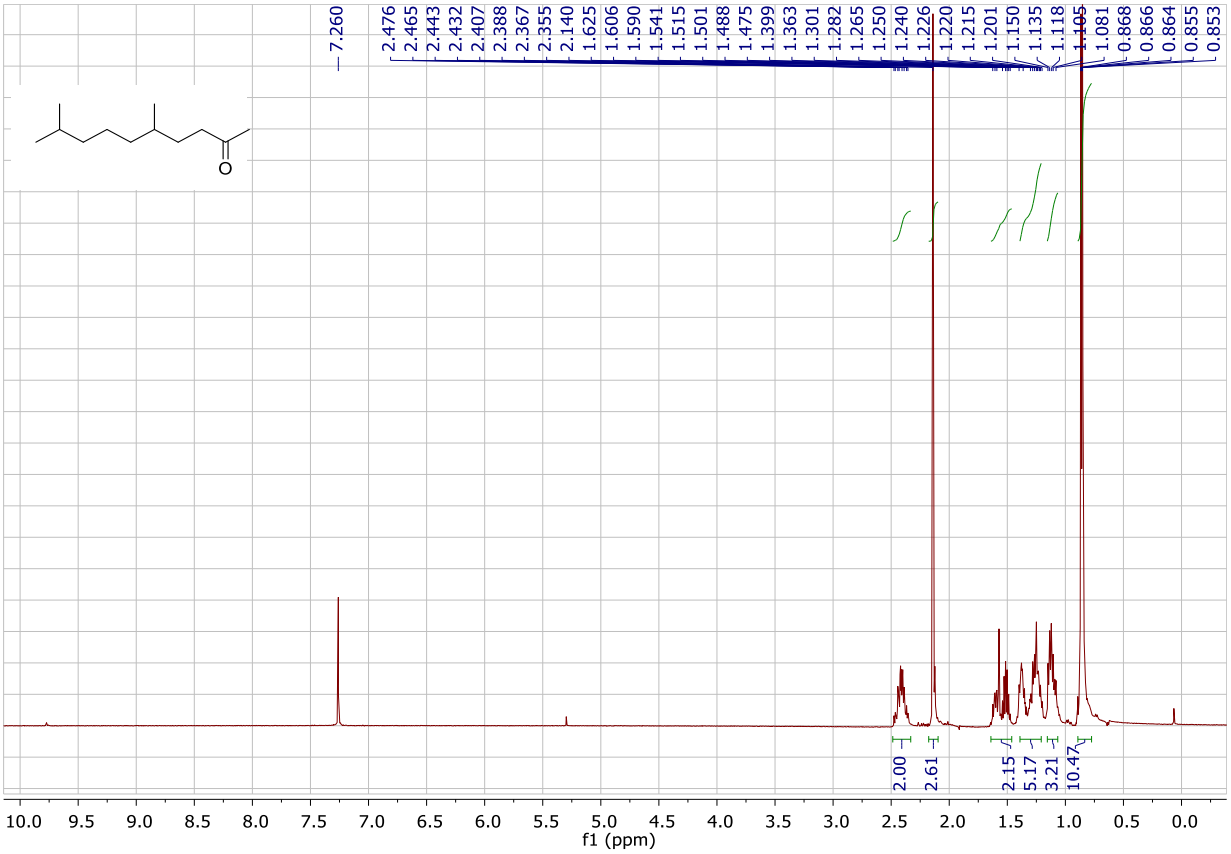
^{31}P NMR 85



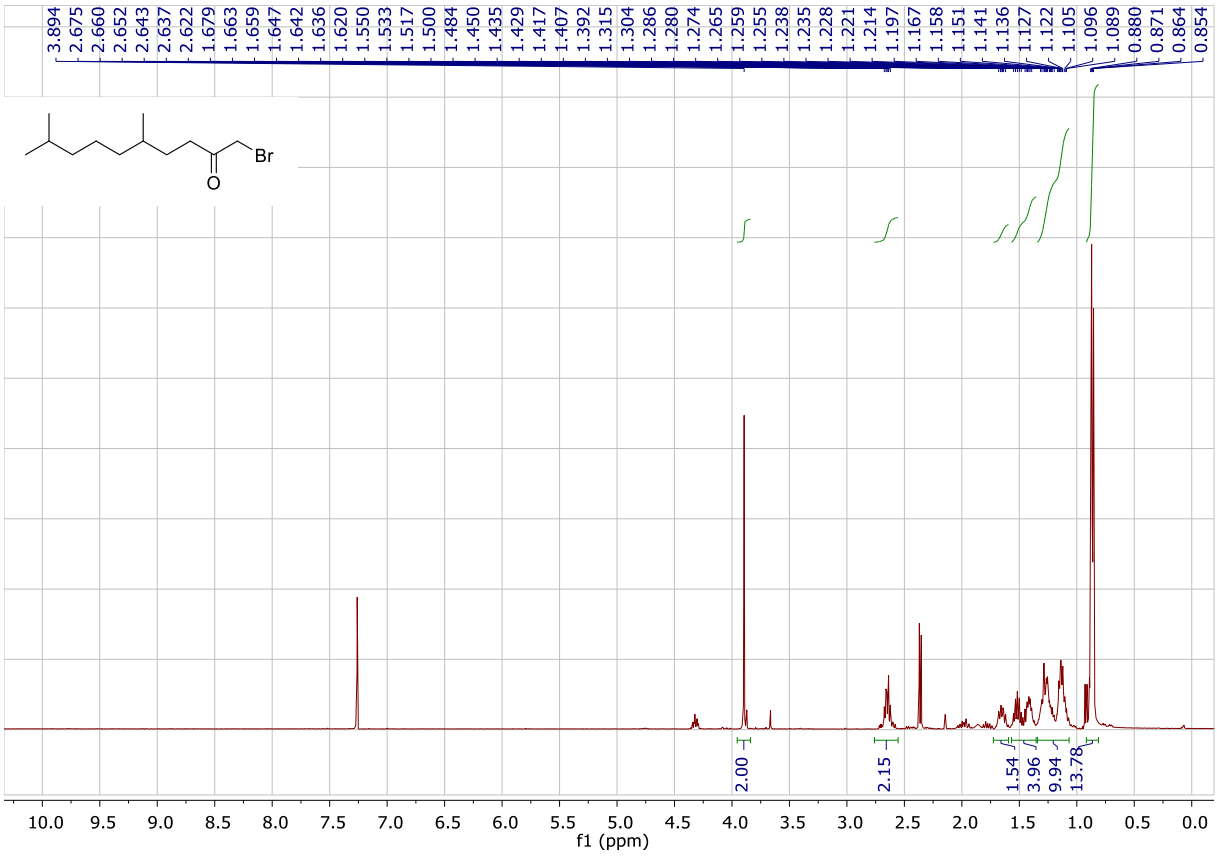
^{1}H NMR IM-17



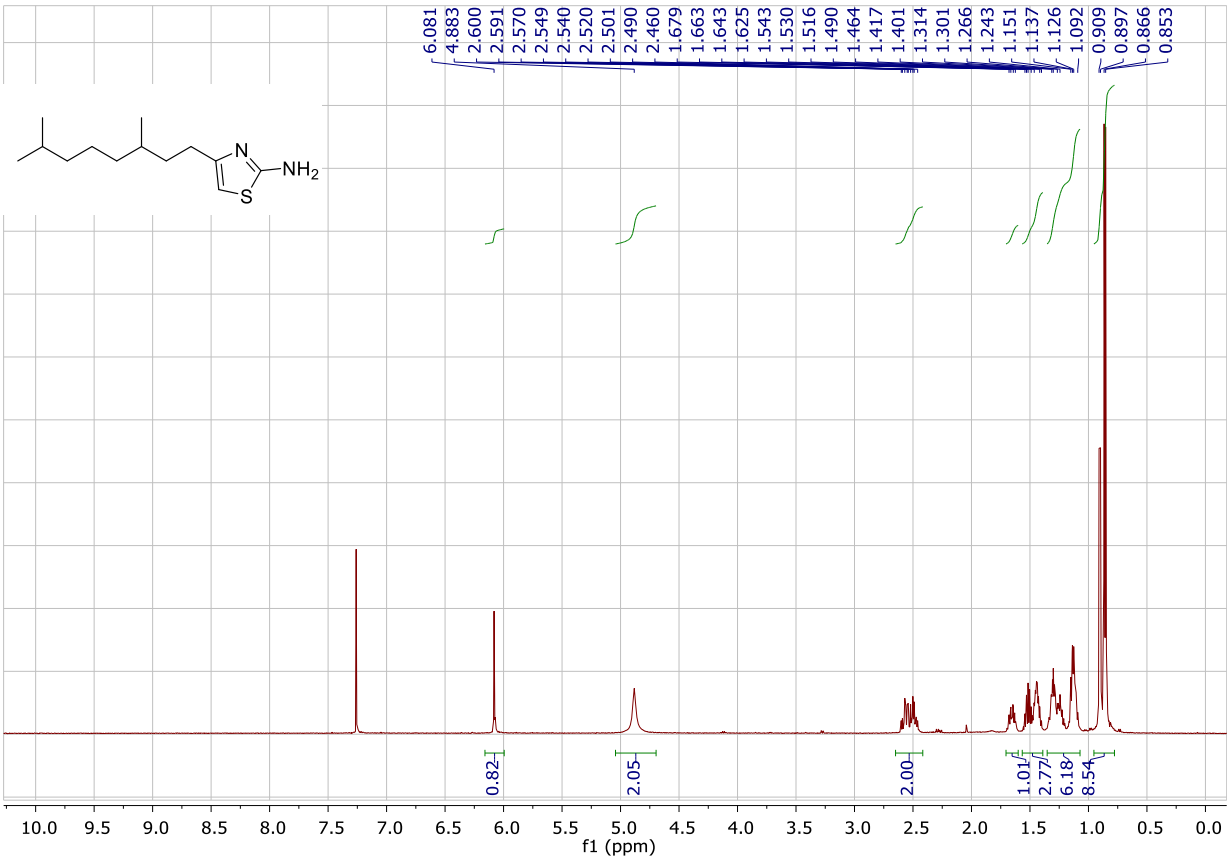
^{1}H NMR IM-18



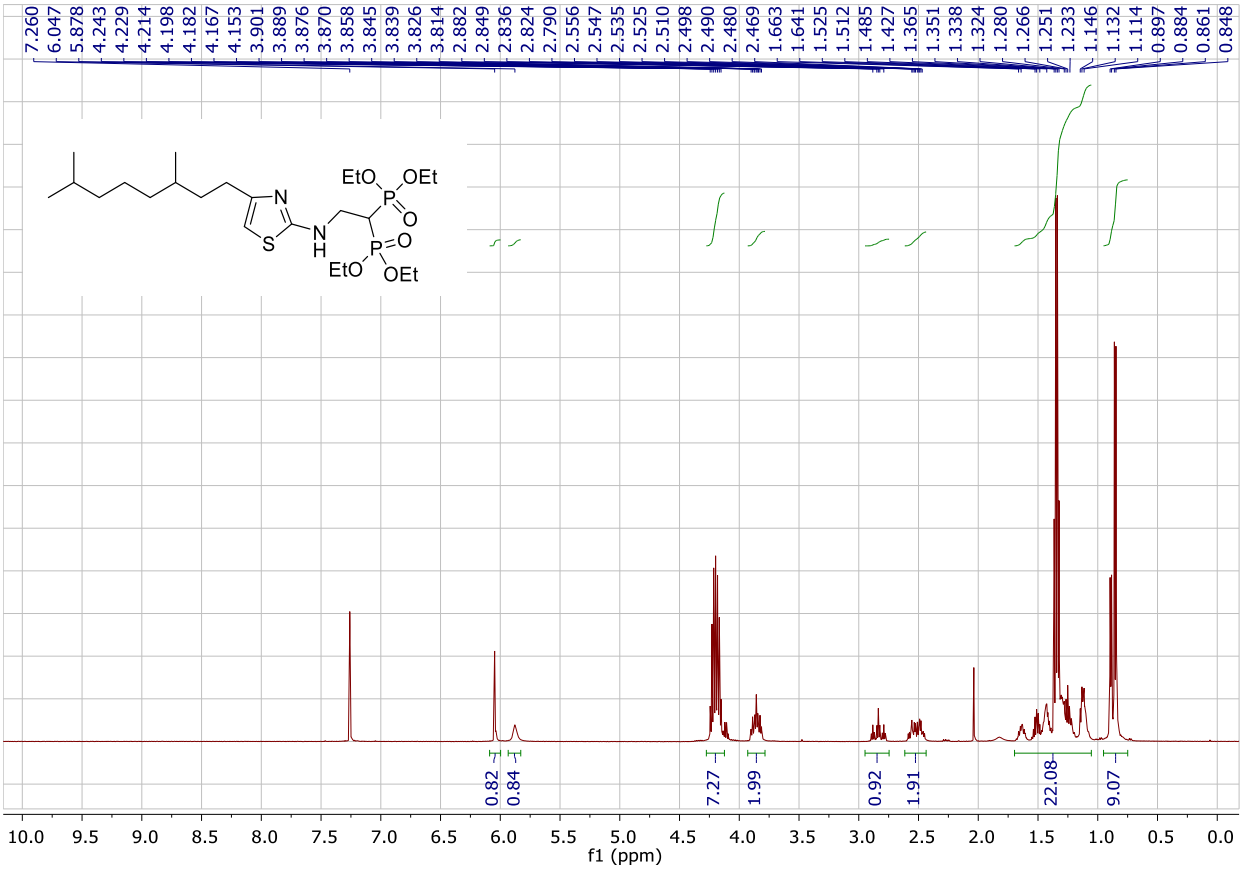
^{1}H NMR IM-19



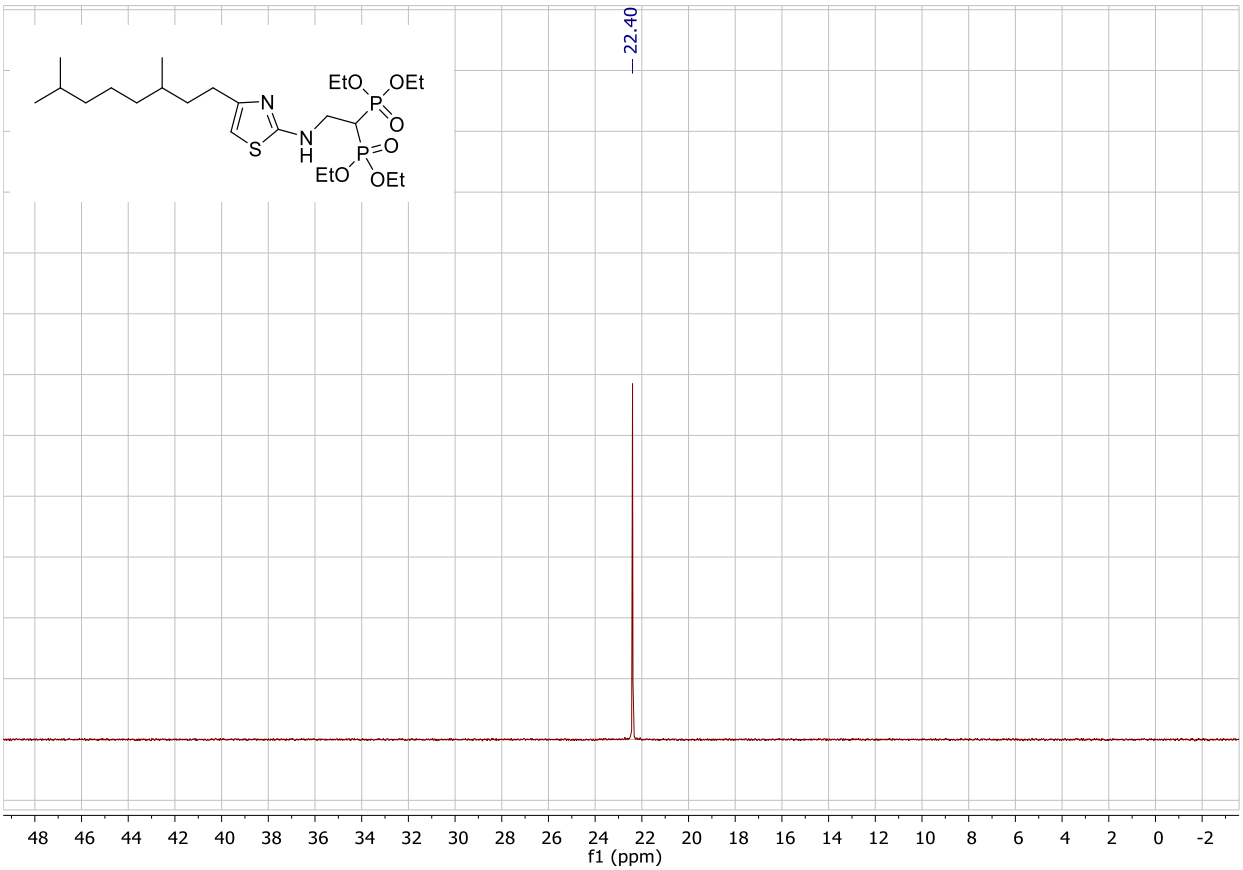
^{1}H NMR IM-20



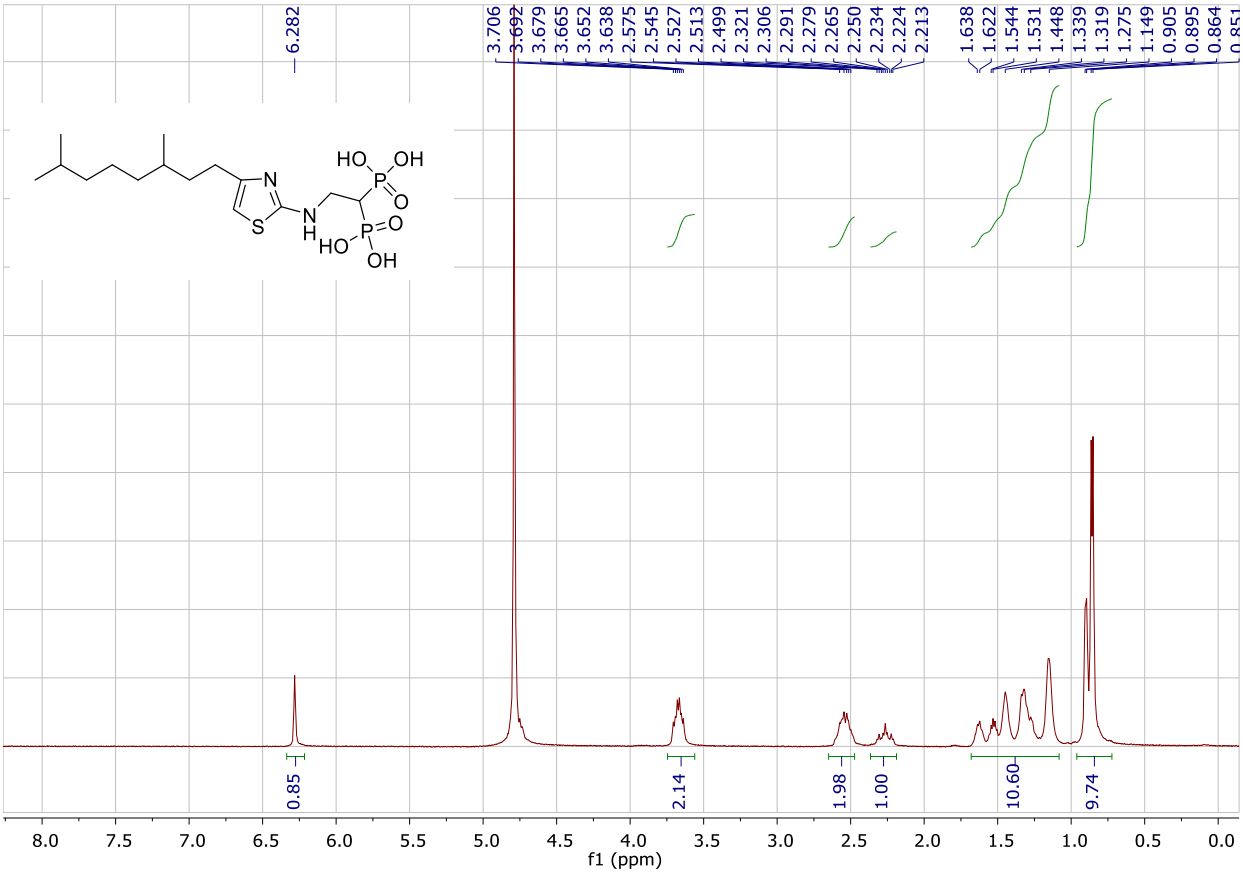
^{1}H NMR IM-21



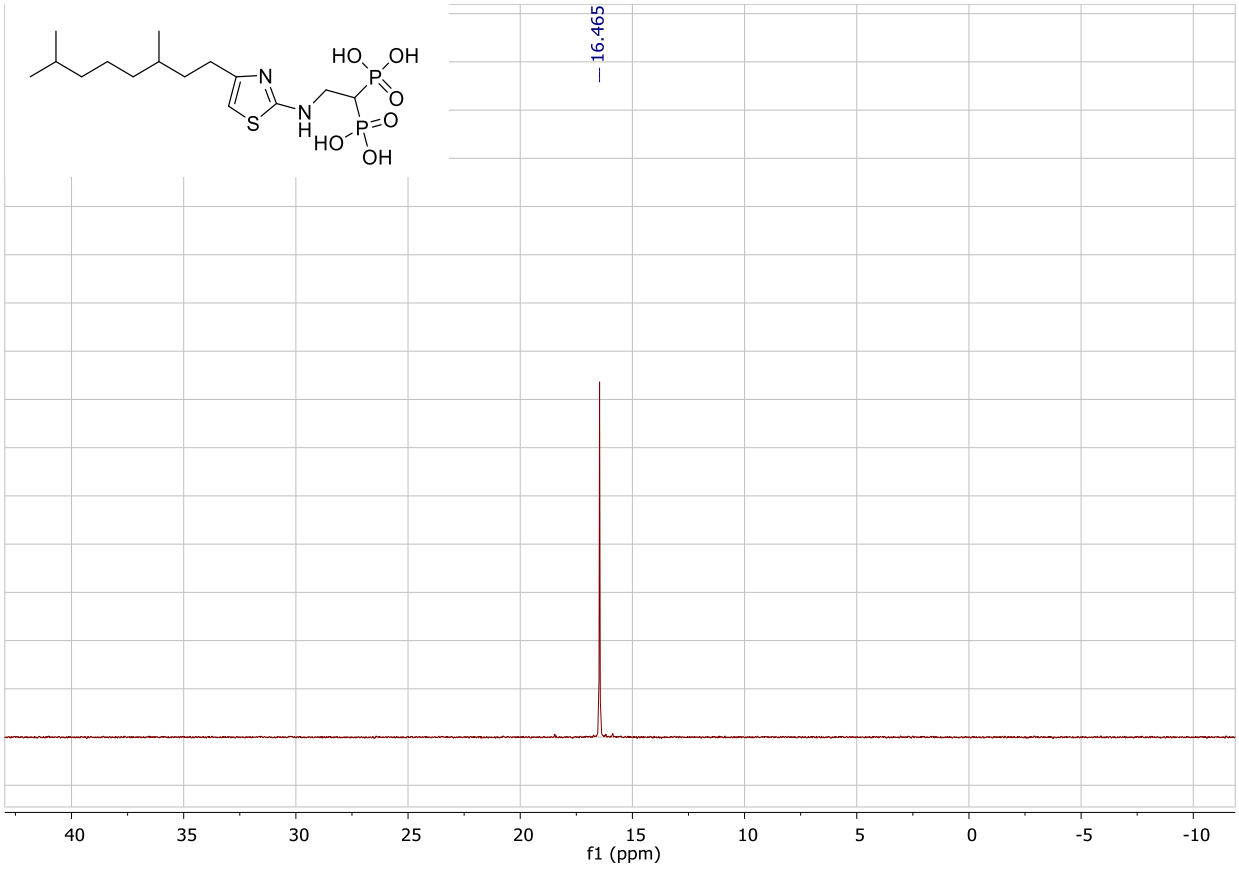
^{31}P NMR IM-21



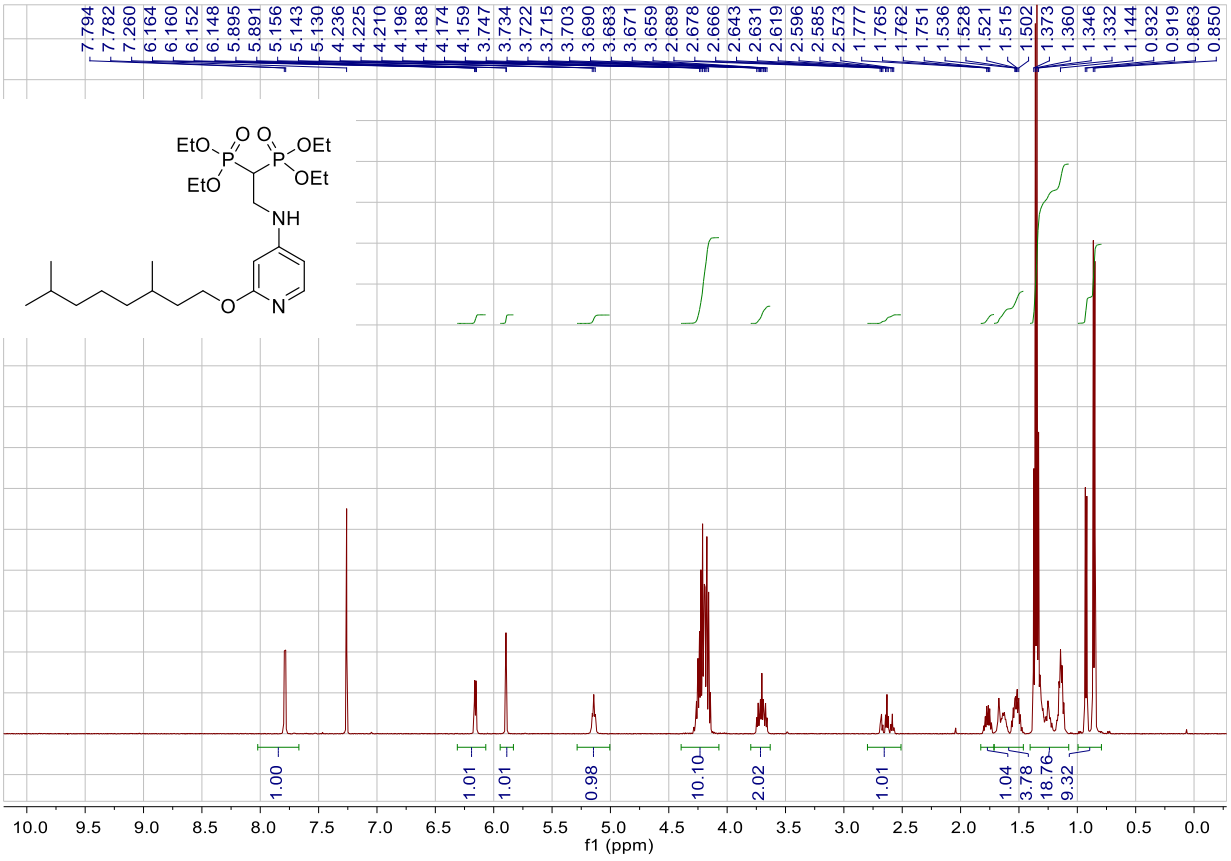
^{1}H NMR 86



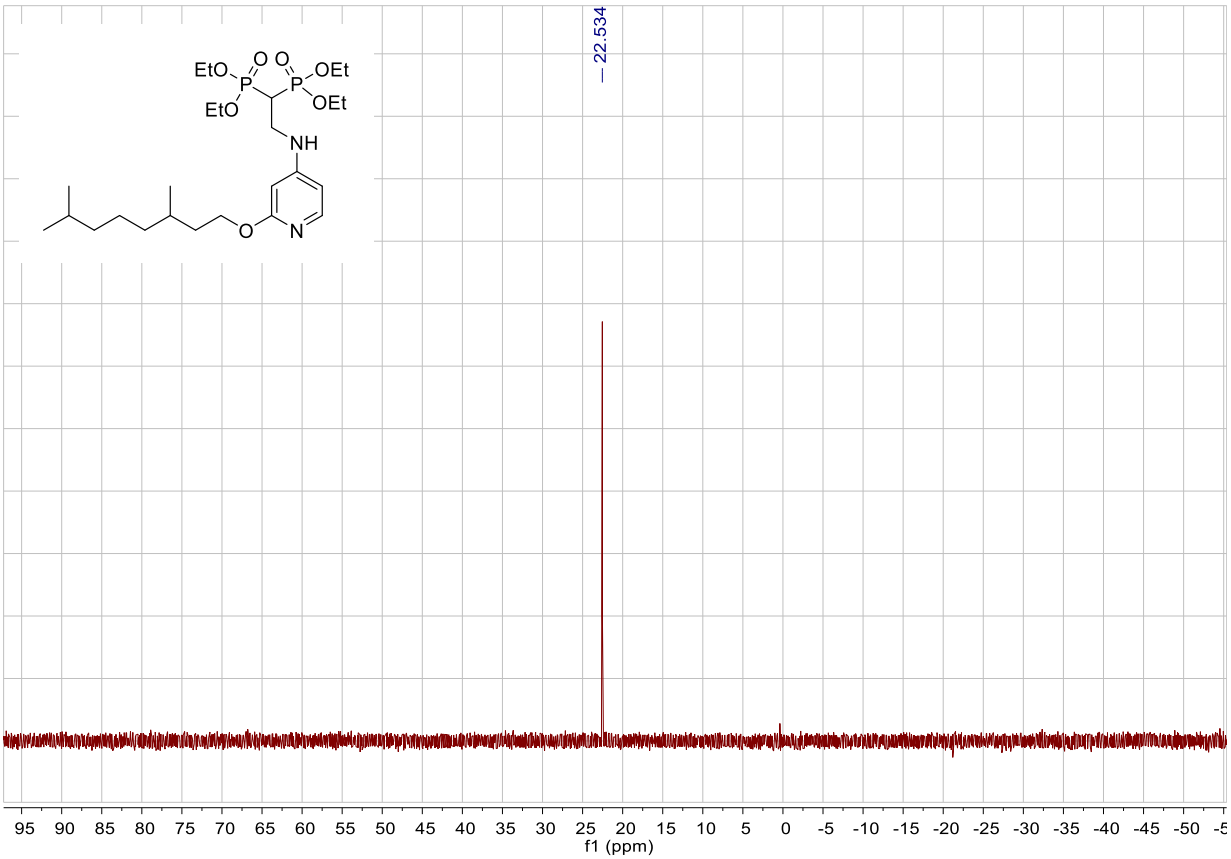
^{31}P NMR 86



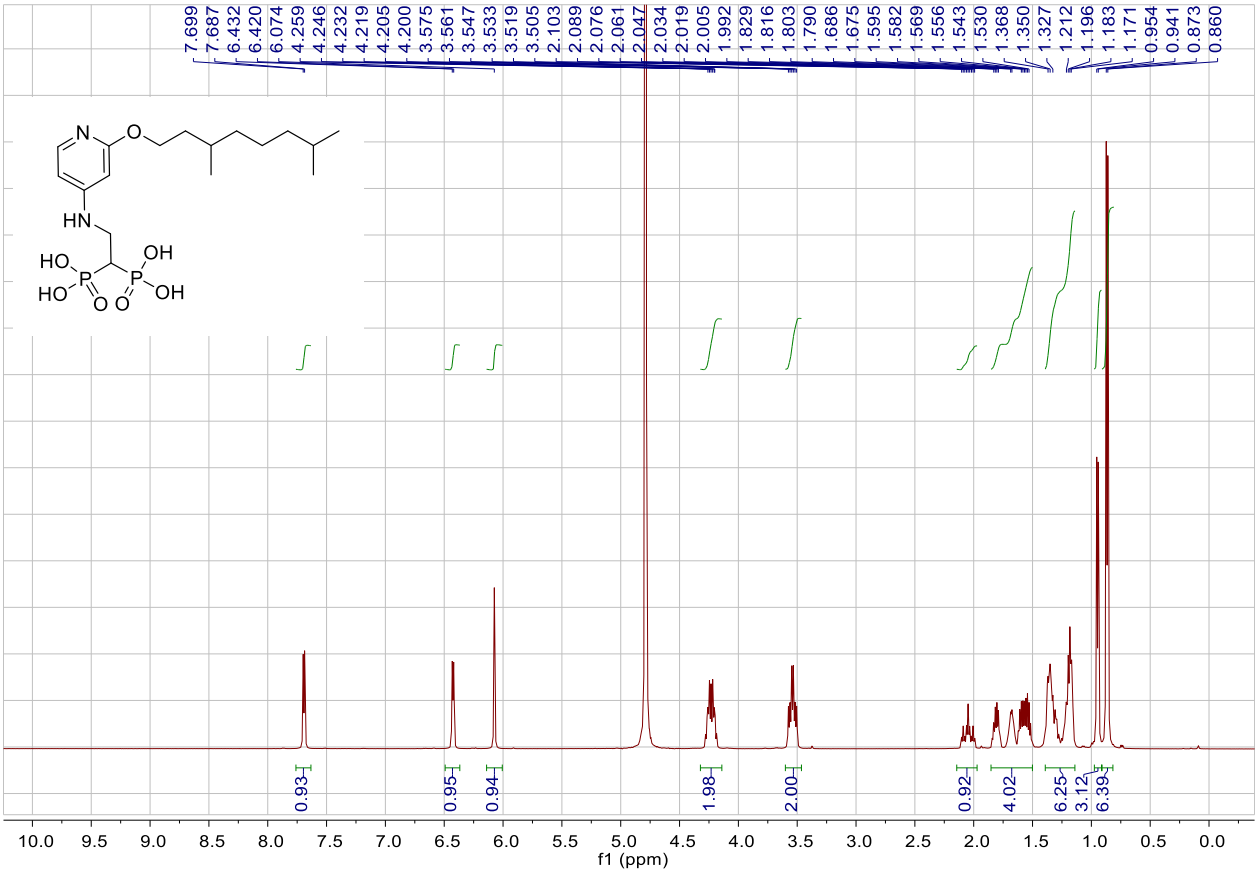
^{1}H NMR IM-23



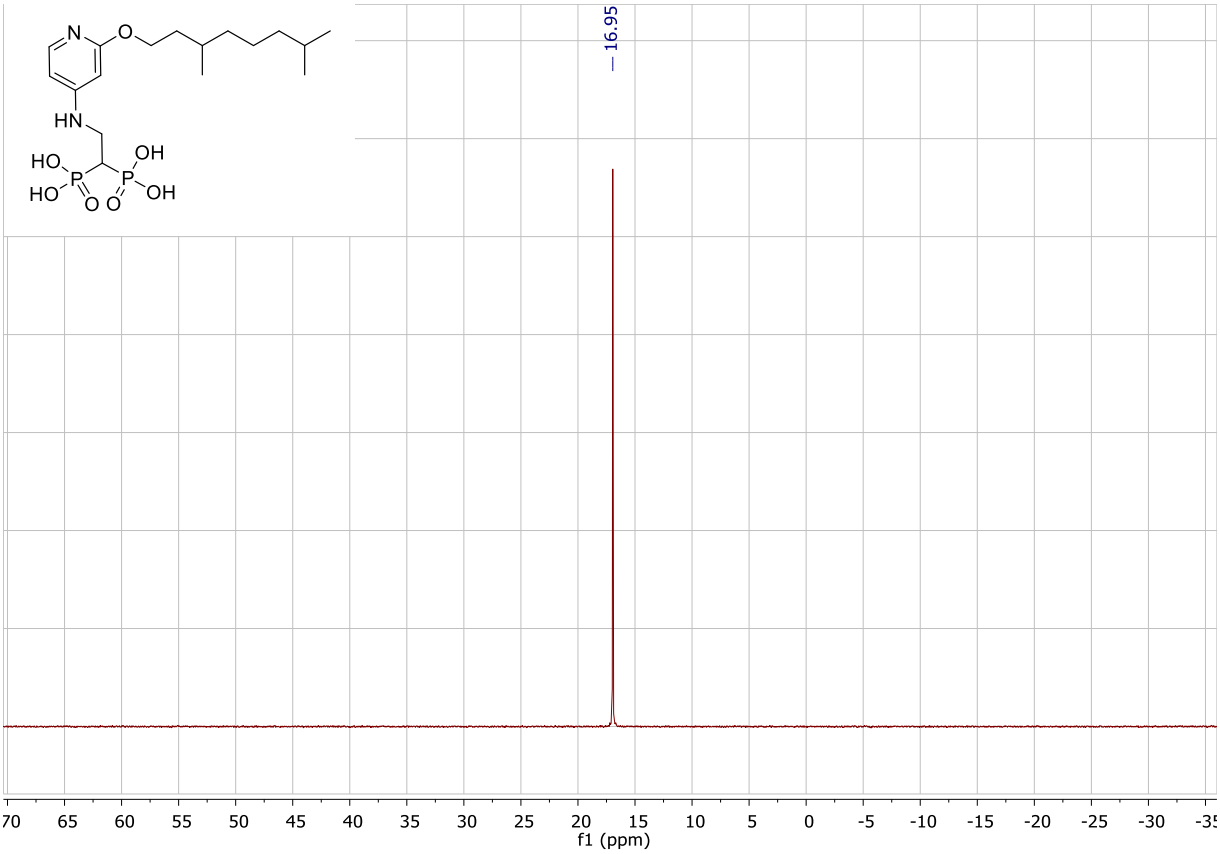
^{31}P NMR IM-23



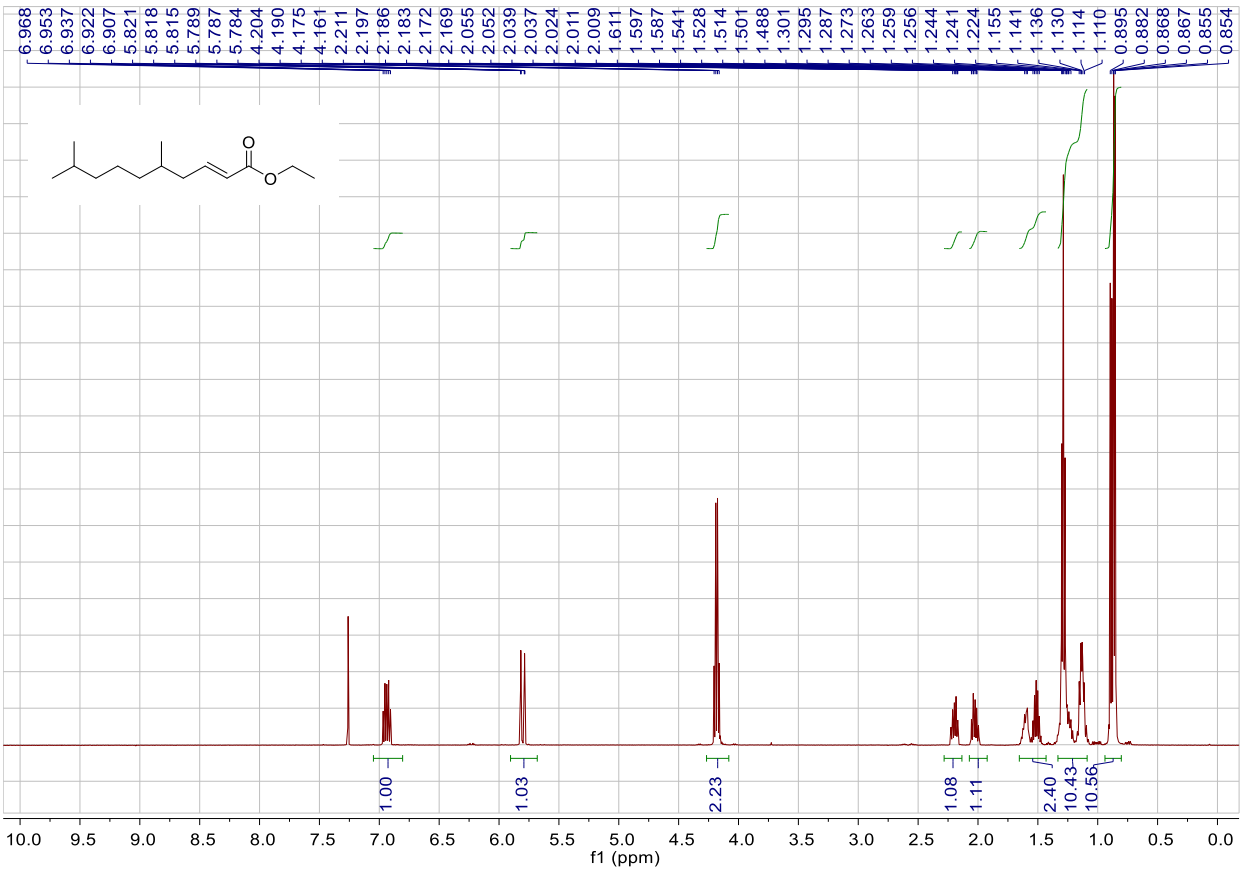
^{1}H NMR 87



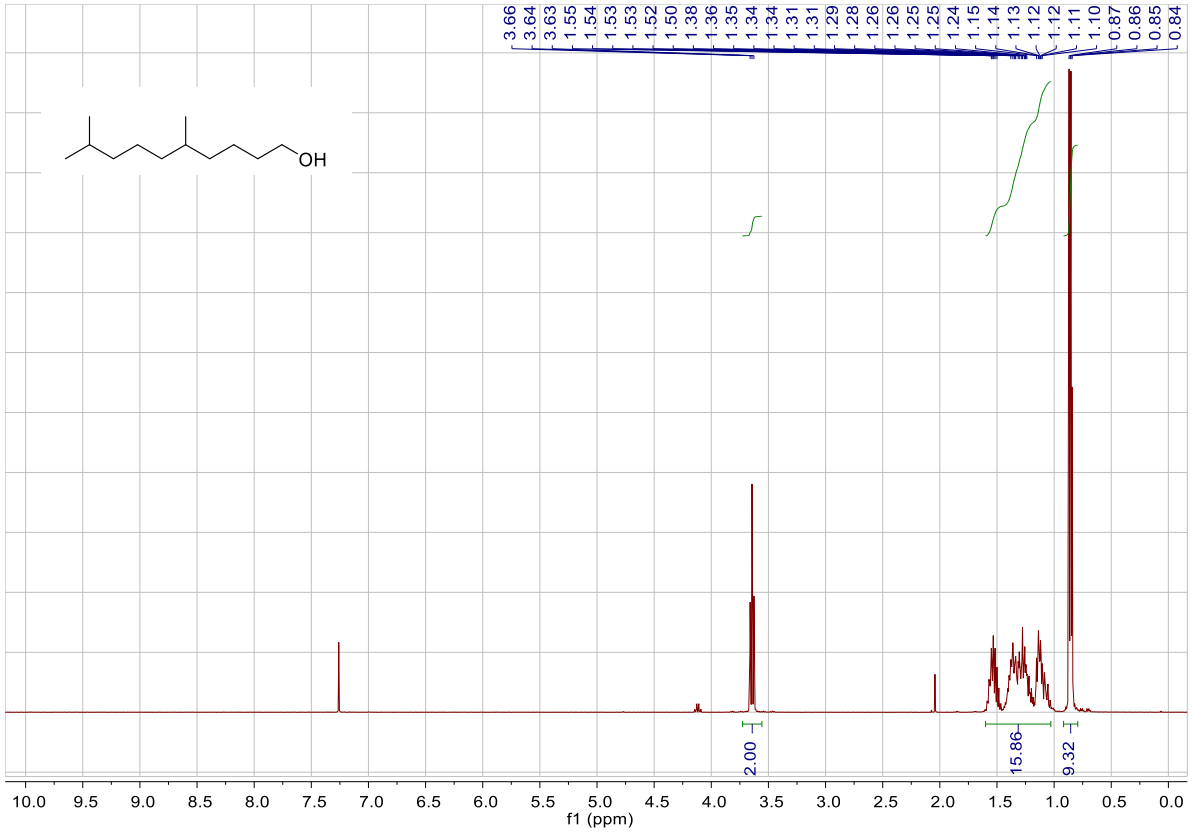
^{31}P NMR 87



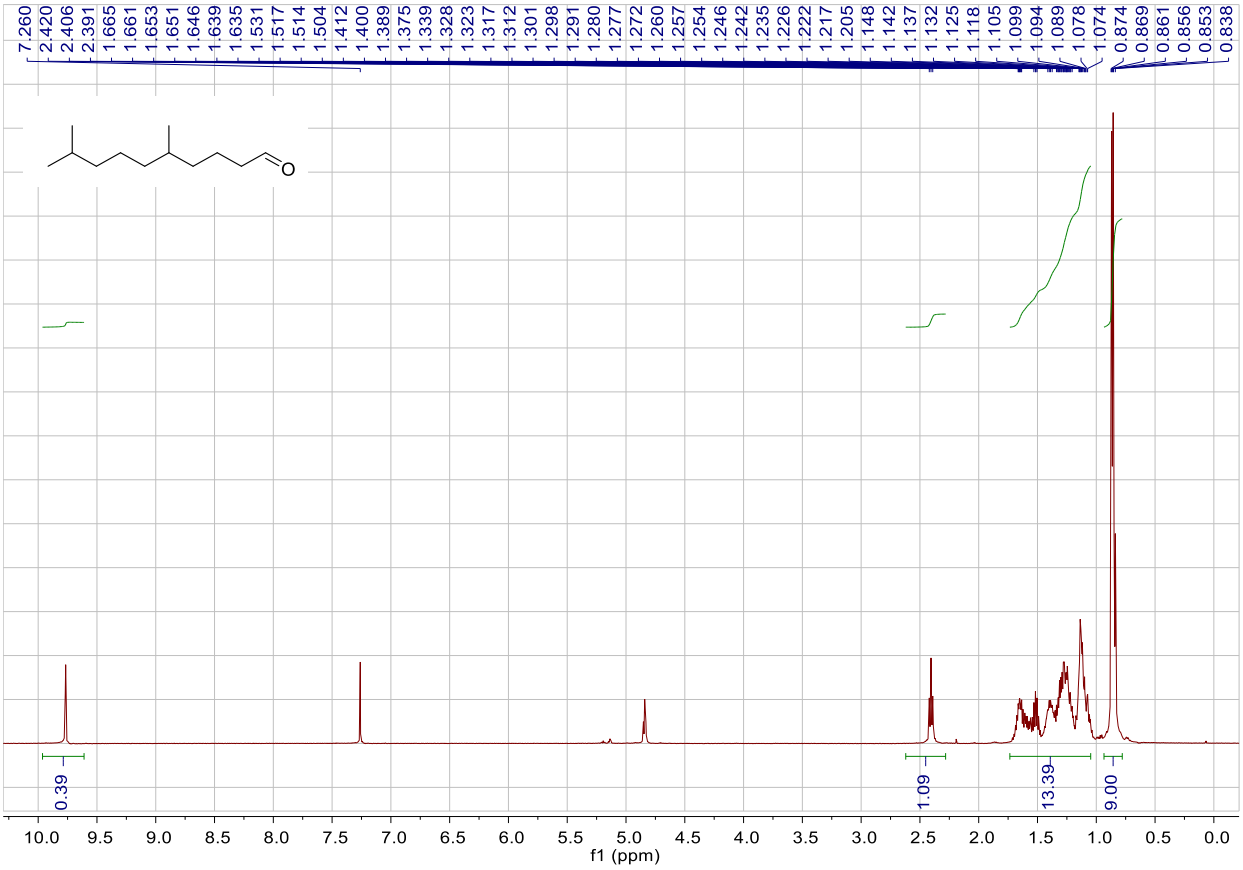
^{1}H NMR IM-24



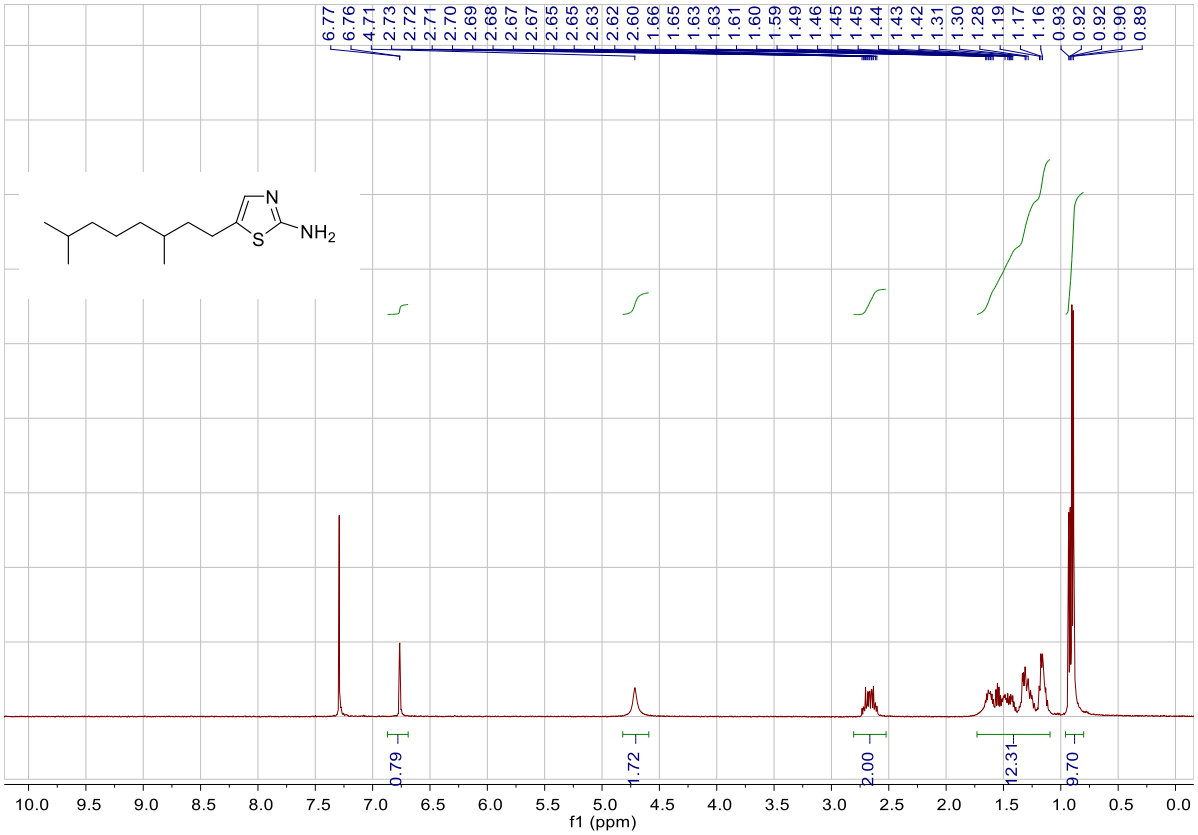
^{1}H NMR IM-24



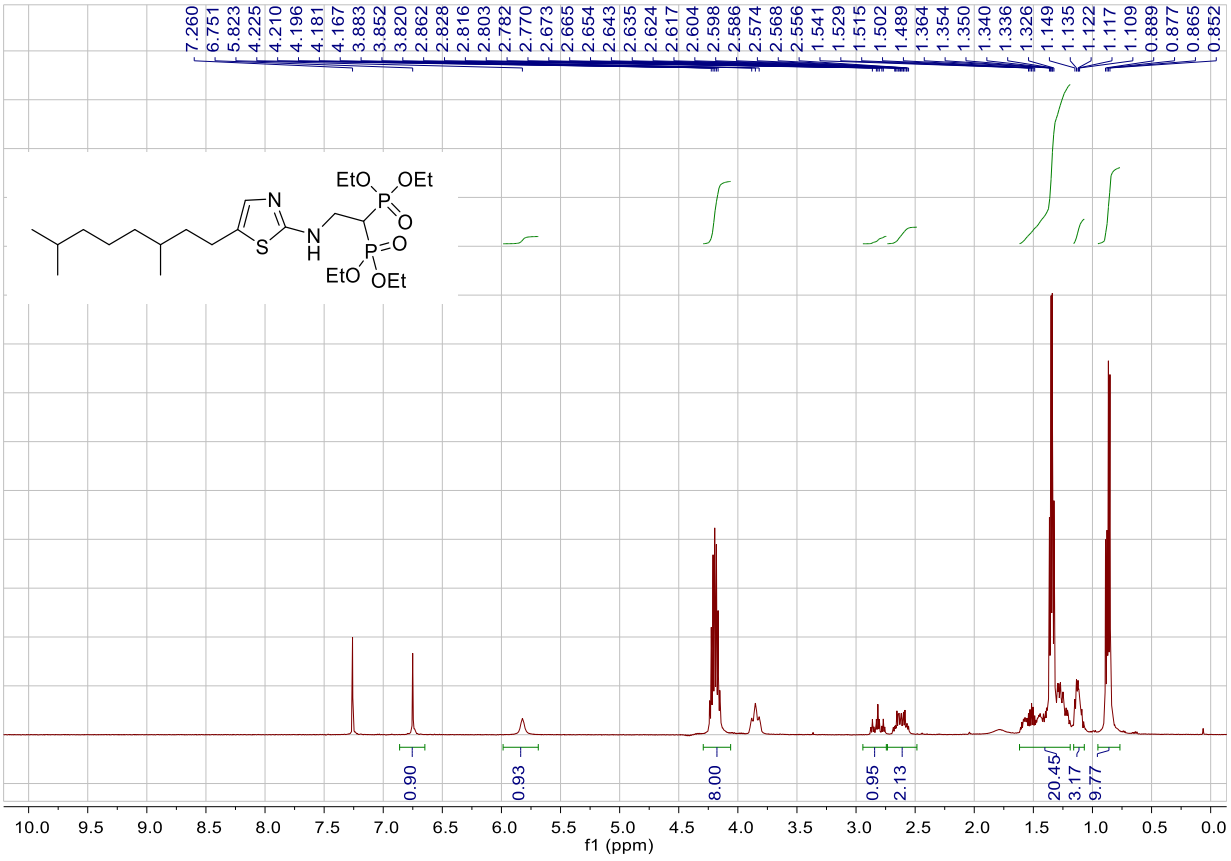
^{1}H NMR IM-25A



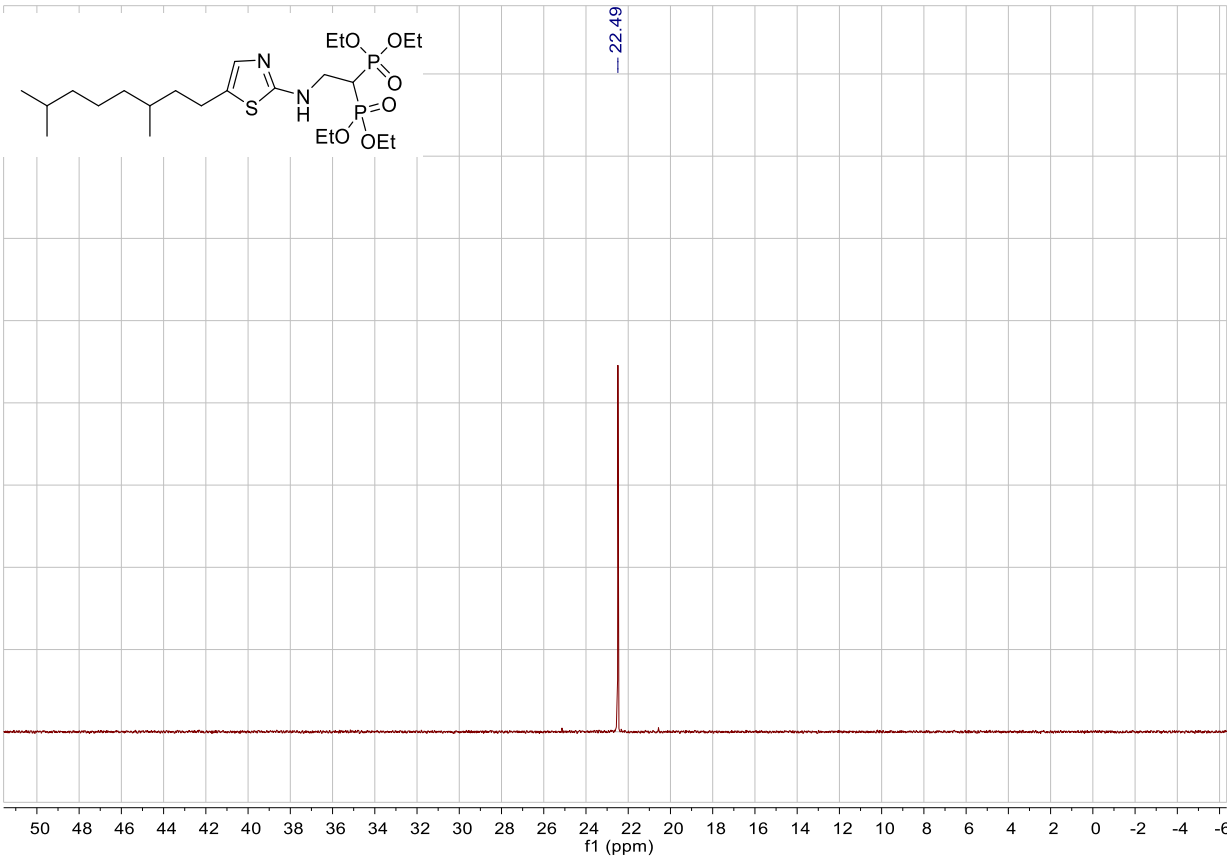
^{1}H NMR IM-26



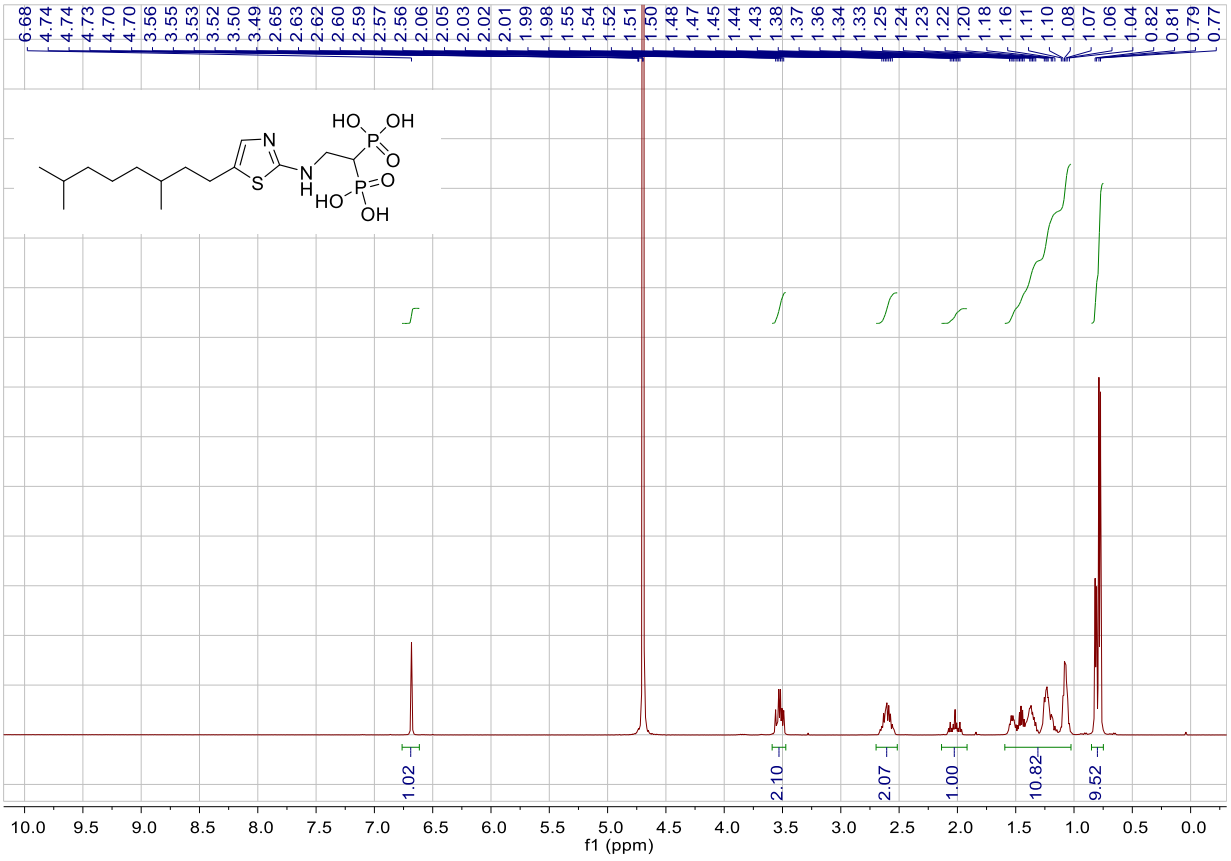
^{1}H NMR IM-27



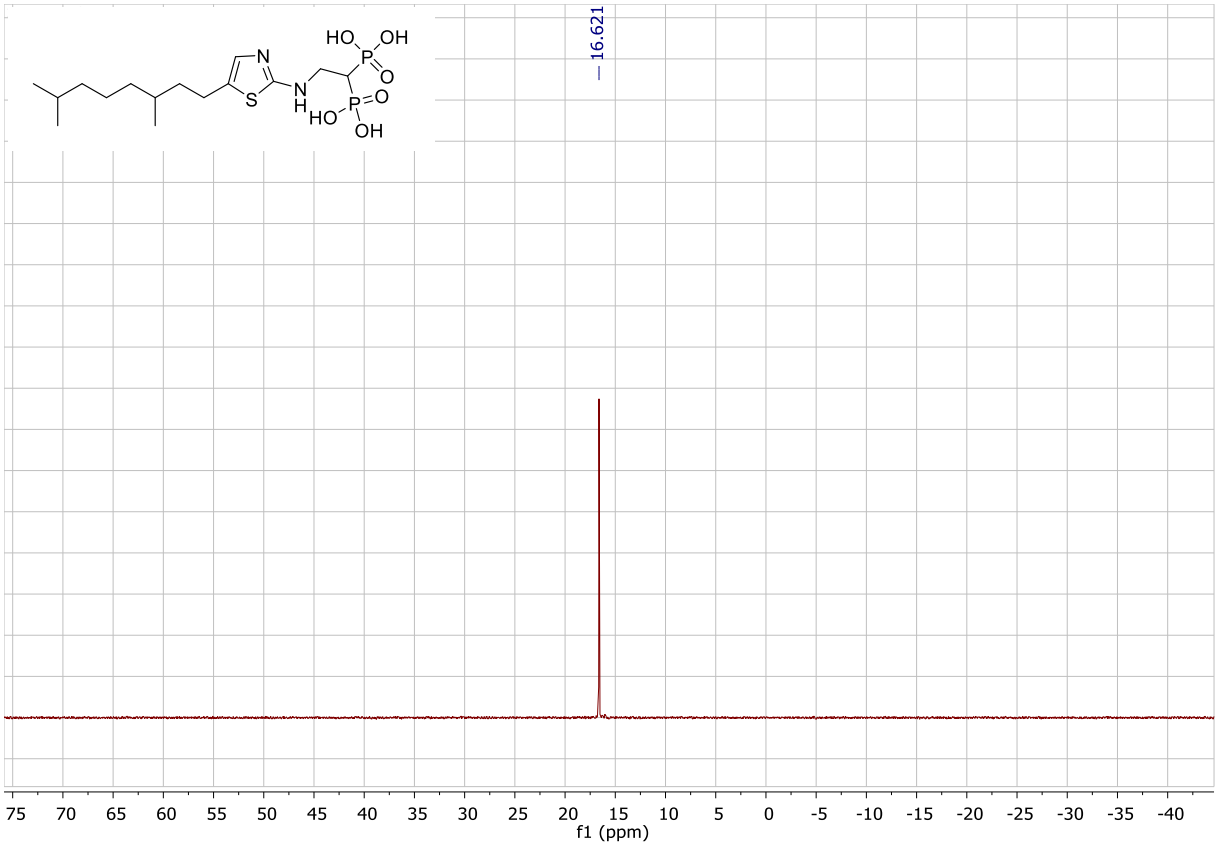
^{31}P NMR IM-27



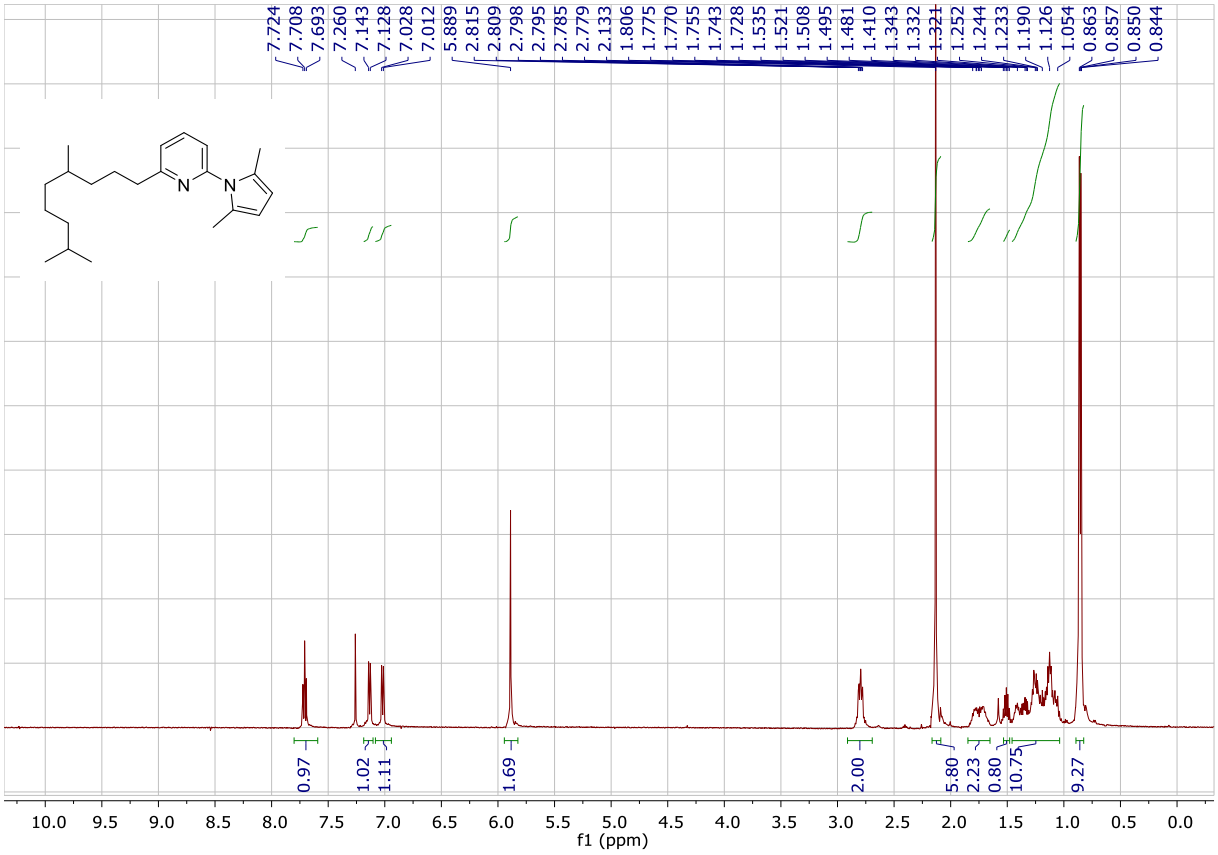
^{1}H NMR 88



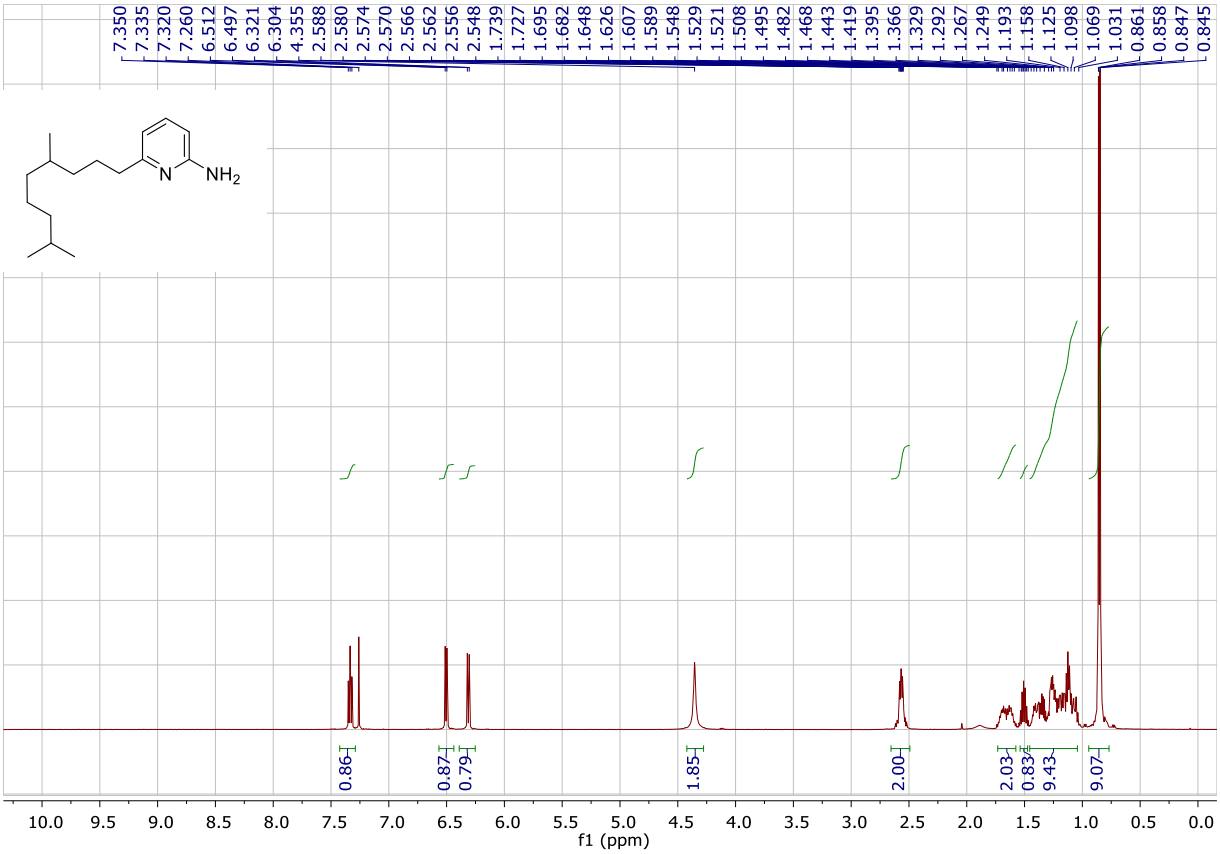
^{31}P NMR 88



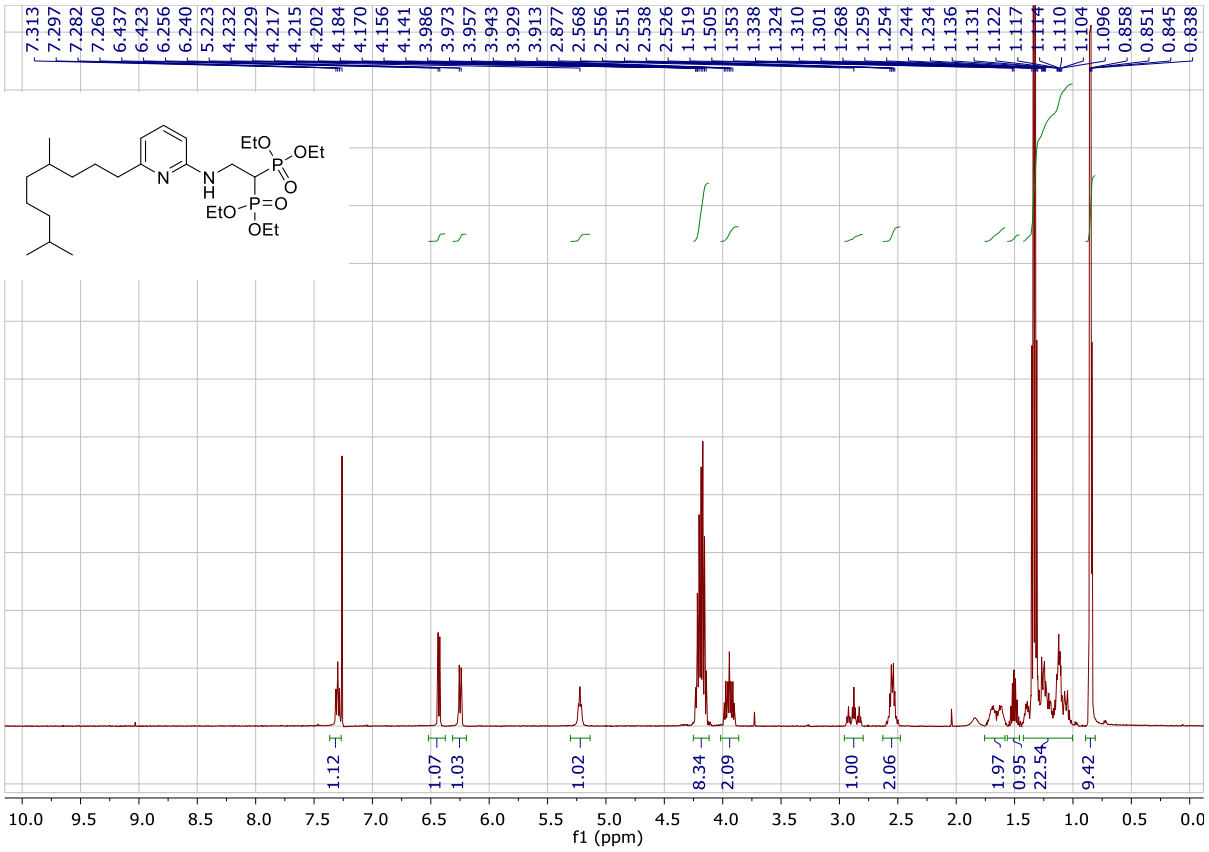
^{1}H NMR IM-29



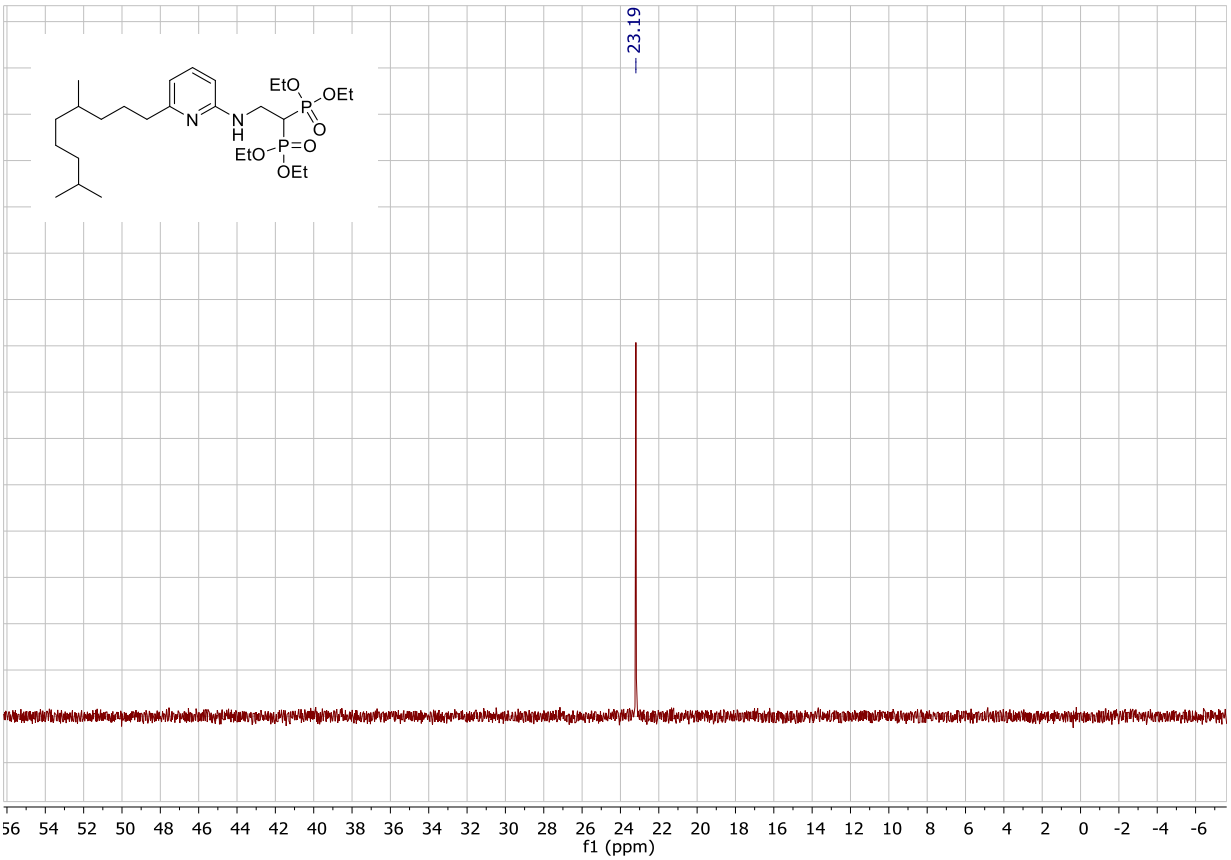
^{1}H NMR IM-29



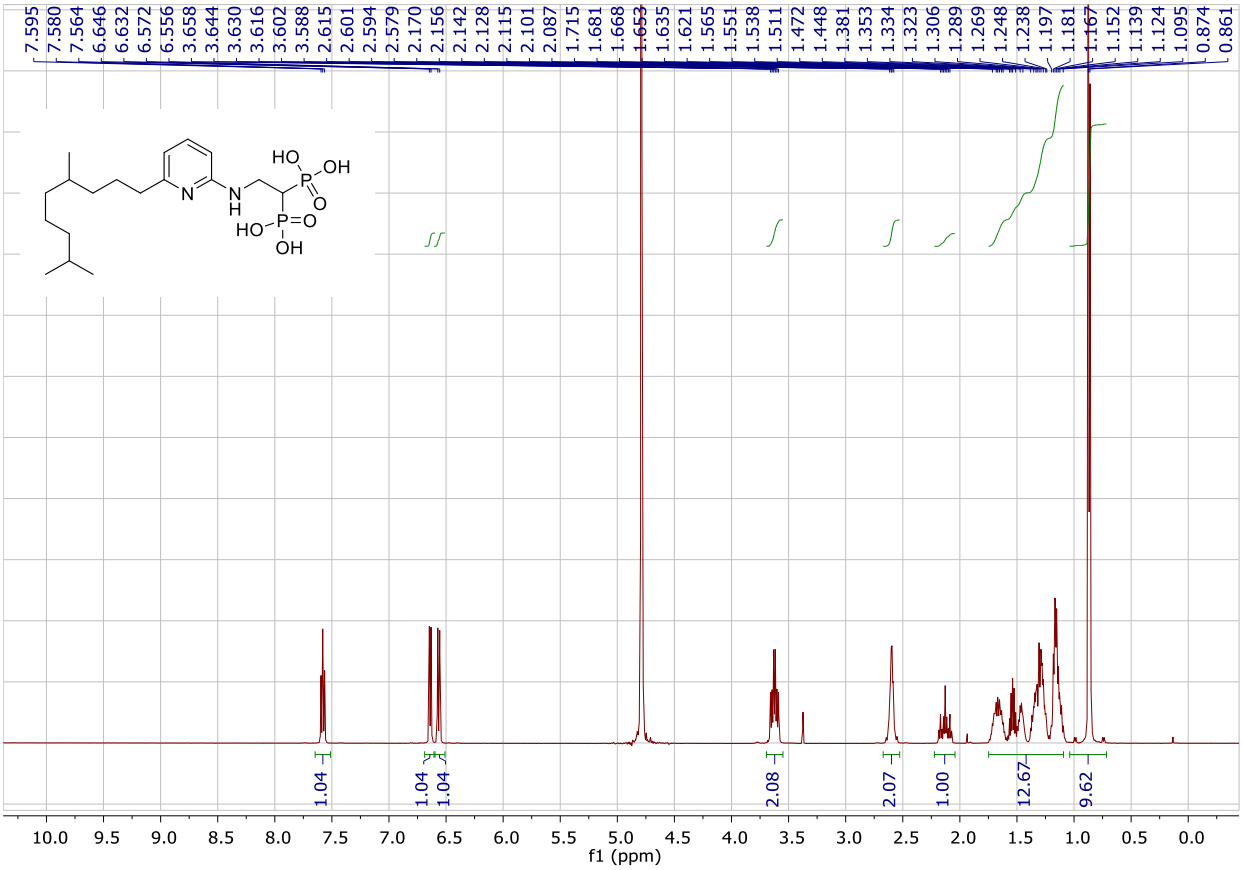
^{1}H NMR IM-31



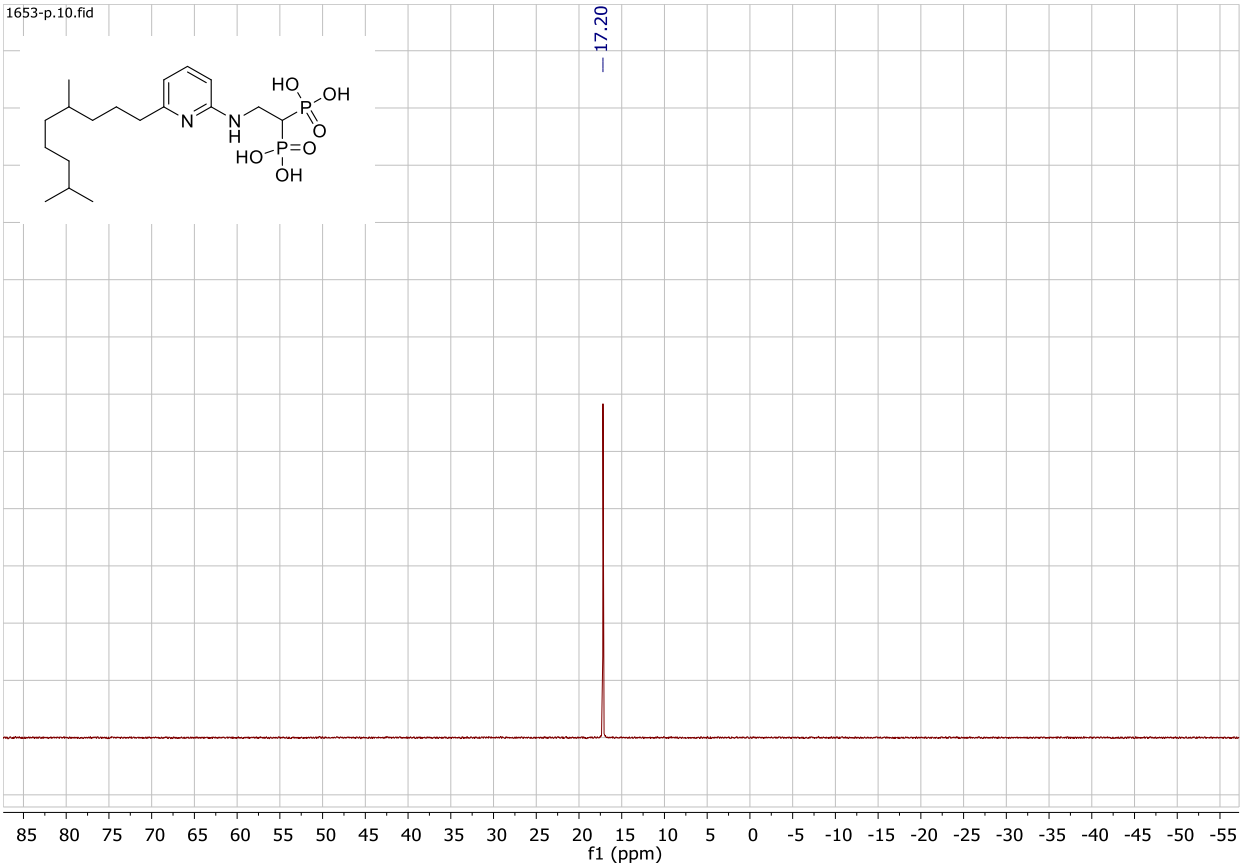
^{31}P NMR IM-31



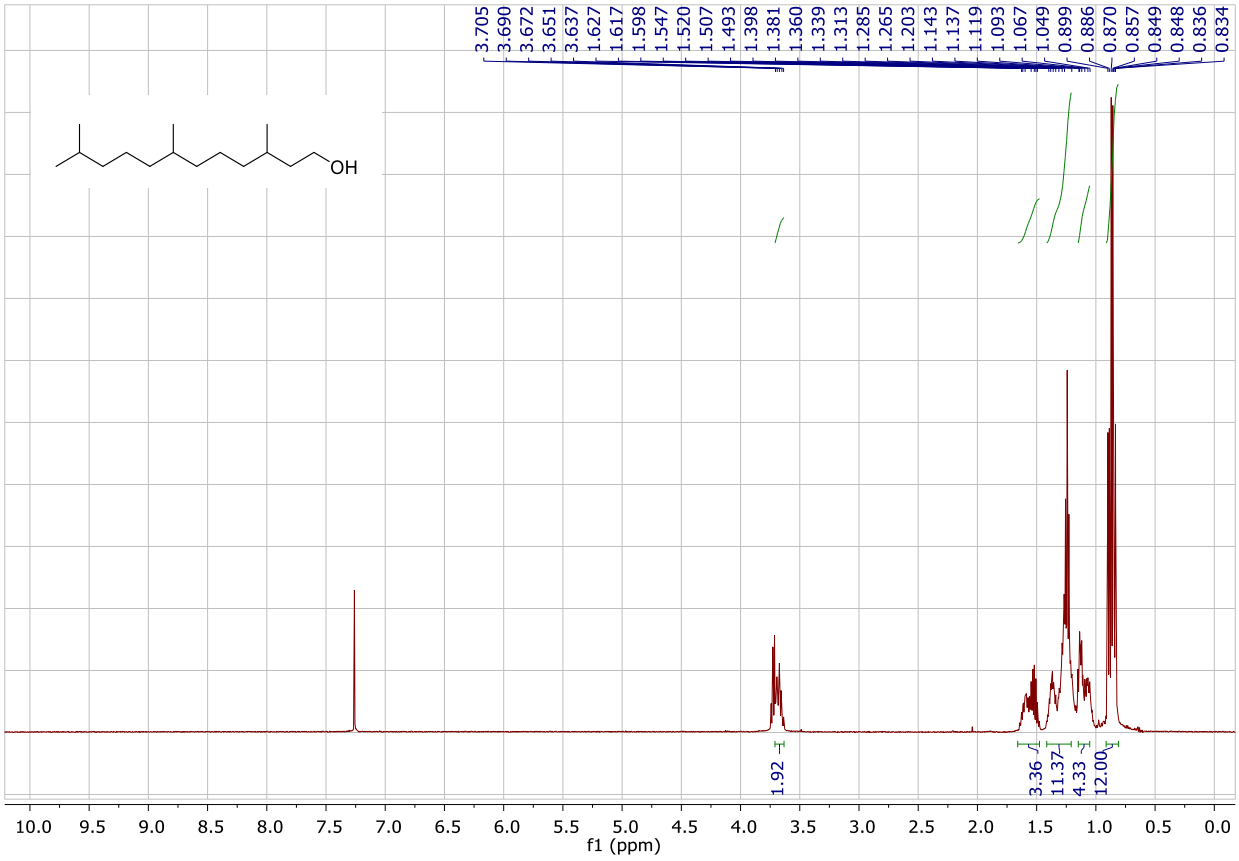
^{1}H NMR 89



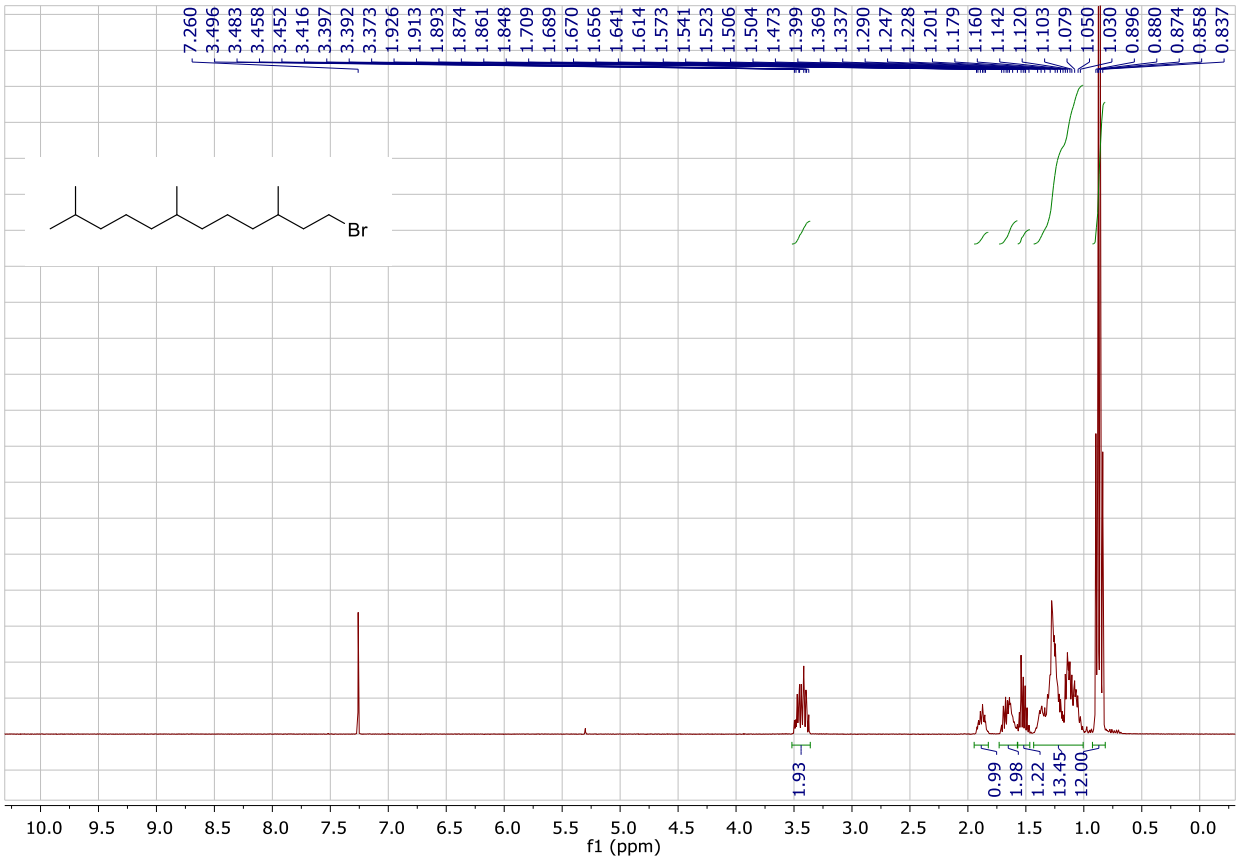
^{31}P NMR 89



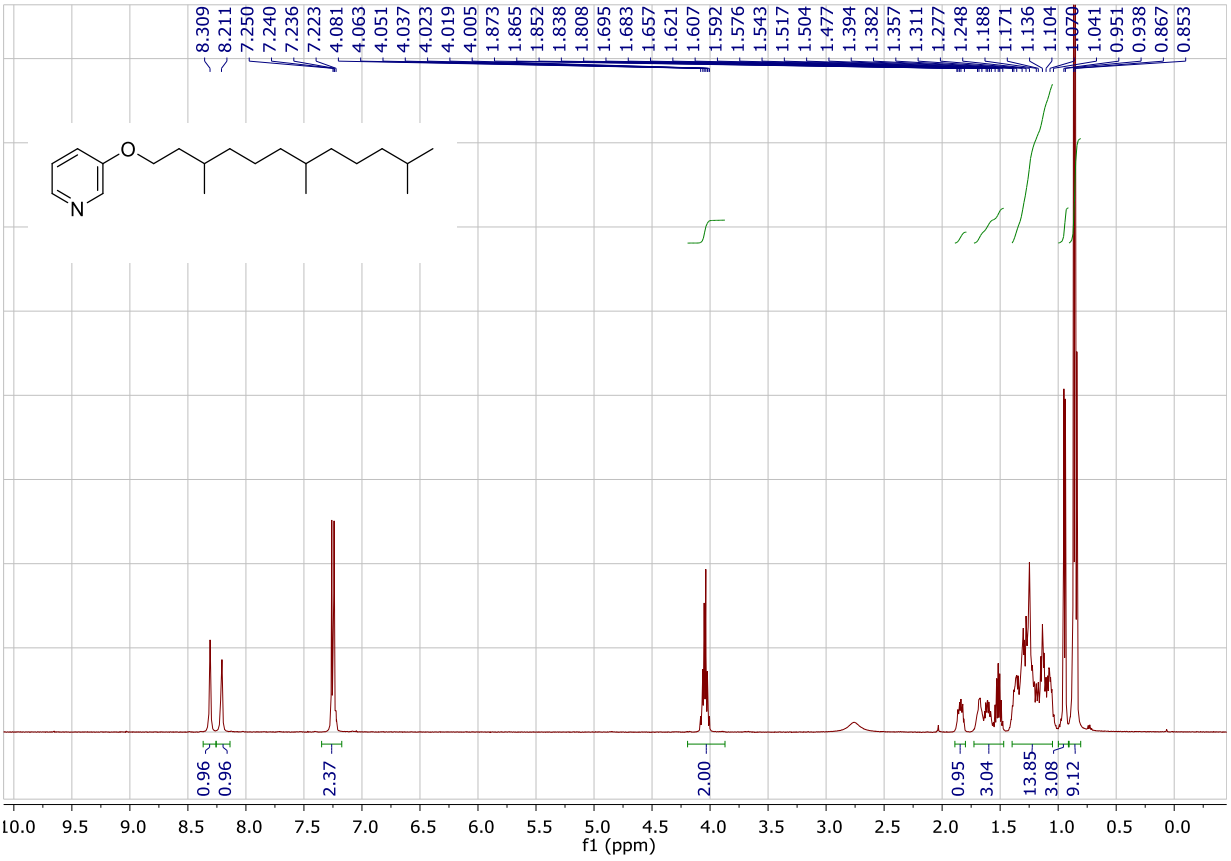
^{1}H NMR IM-32



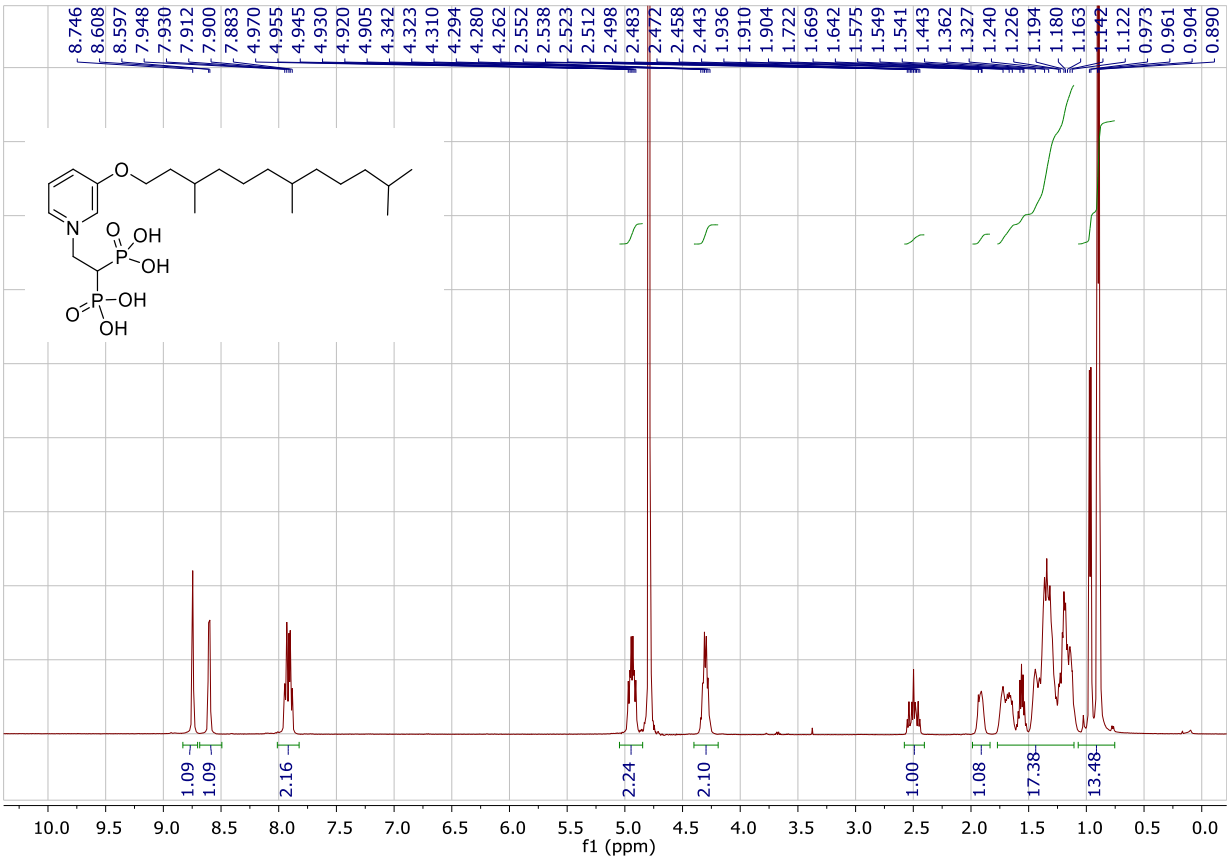
^{1}H NMR IM-33



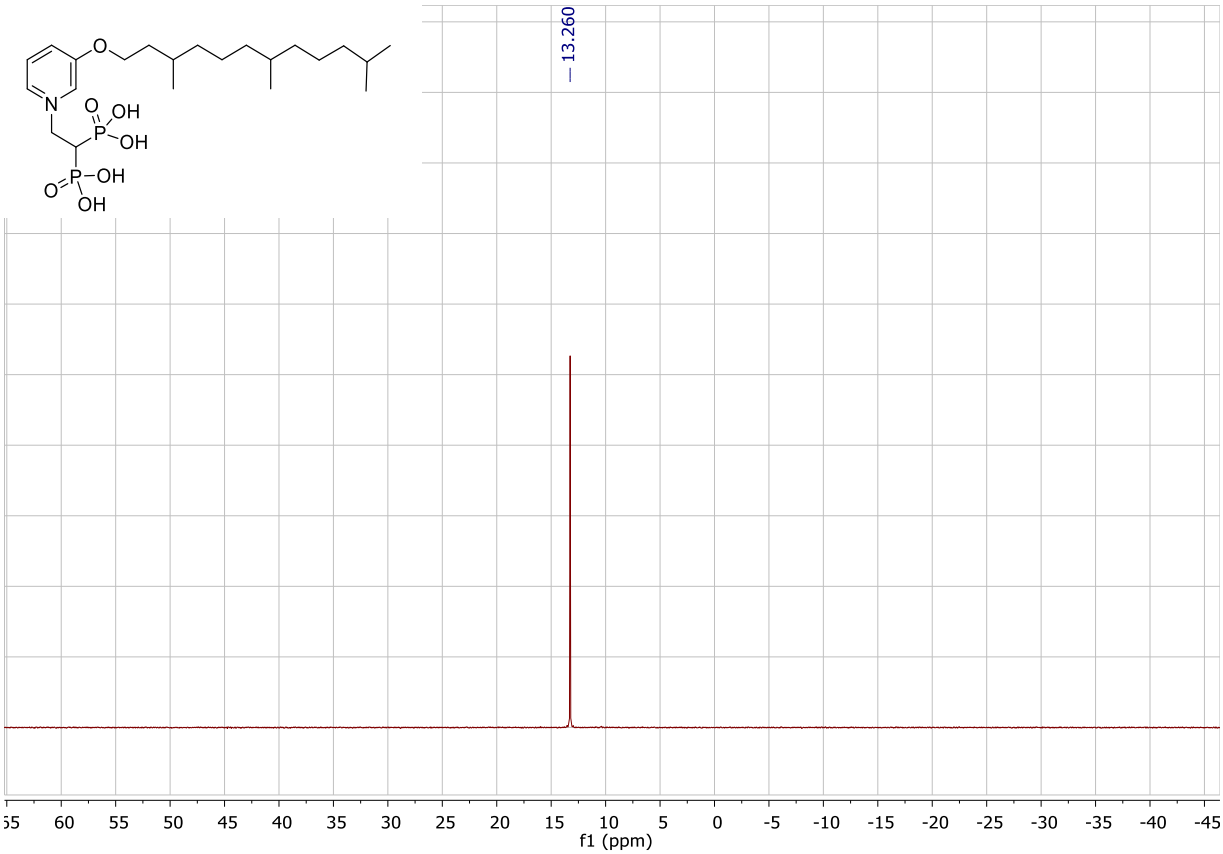
^{1}H NMR IM-34



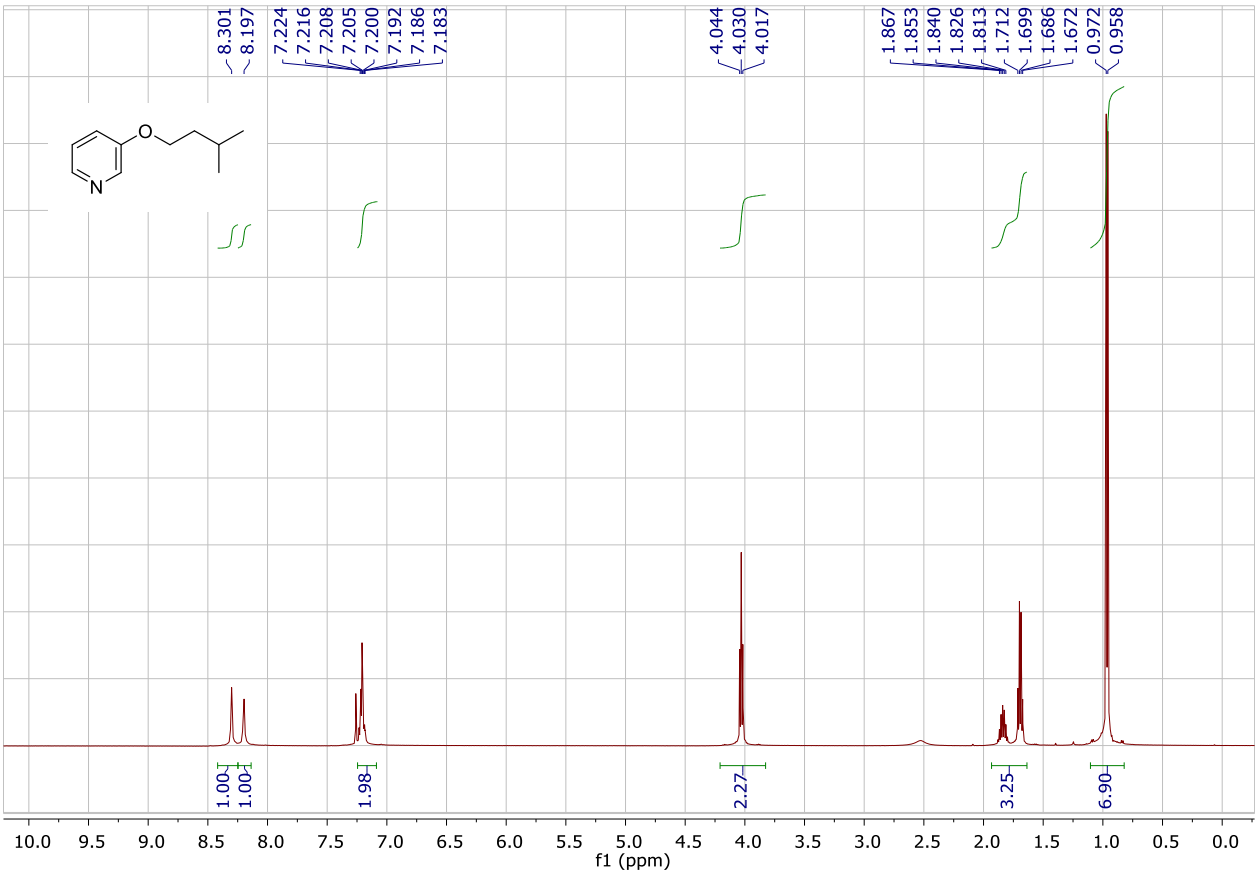
^{1}H NMR 90



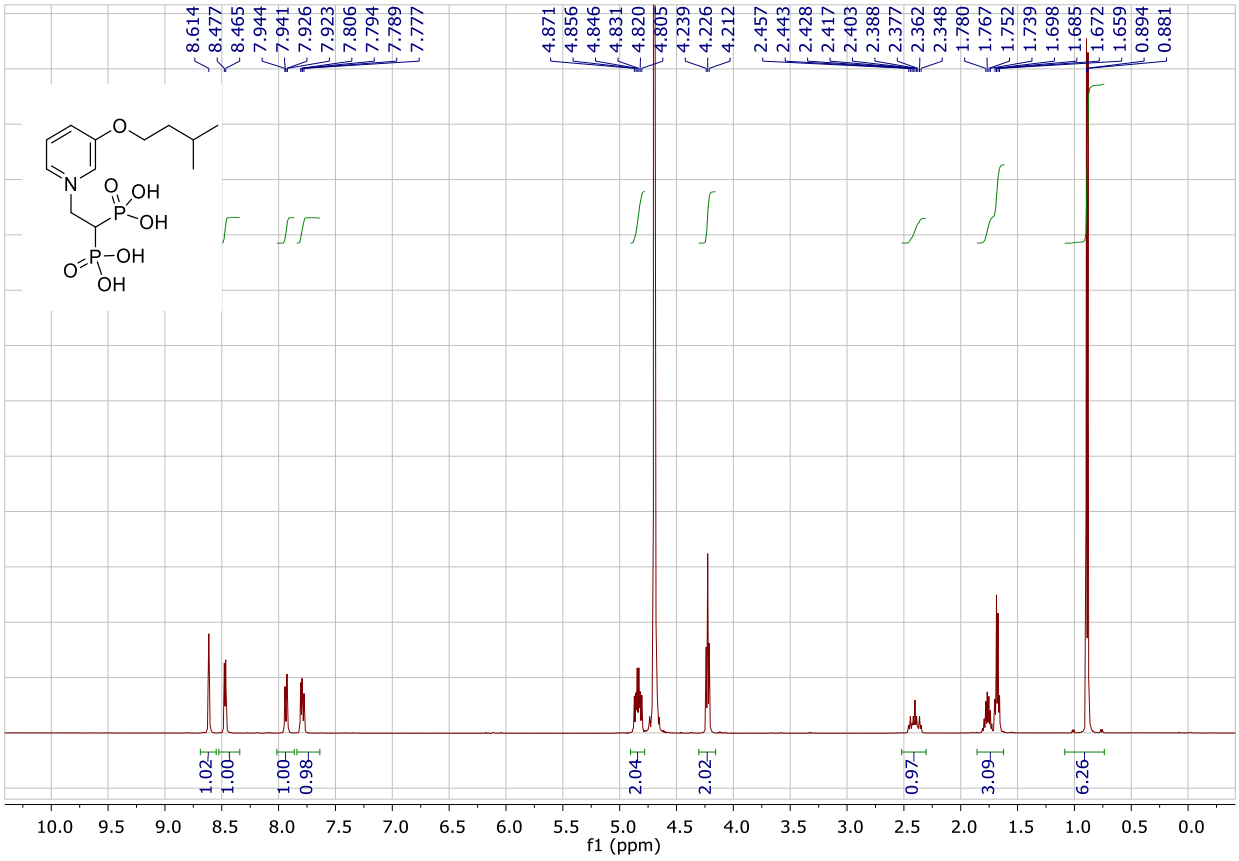
^{31}P NMR 90



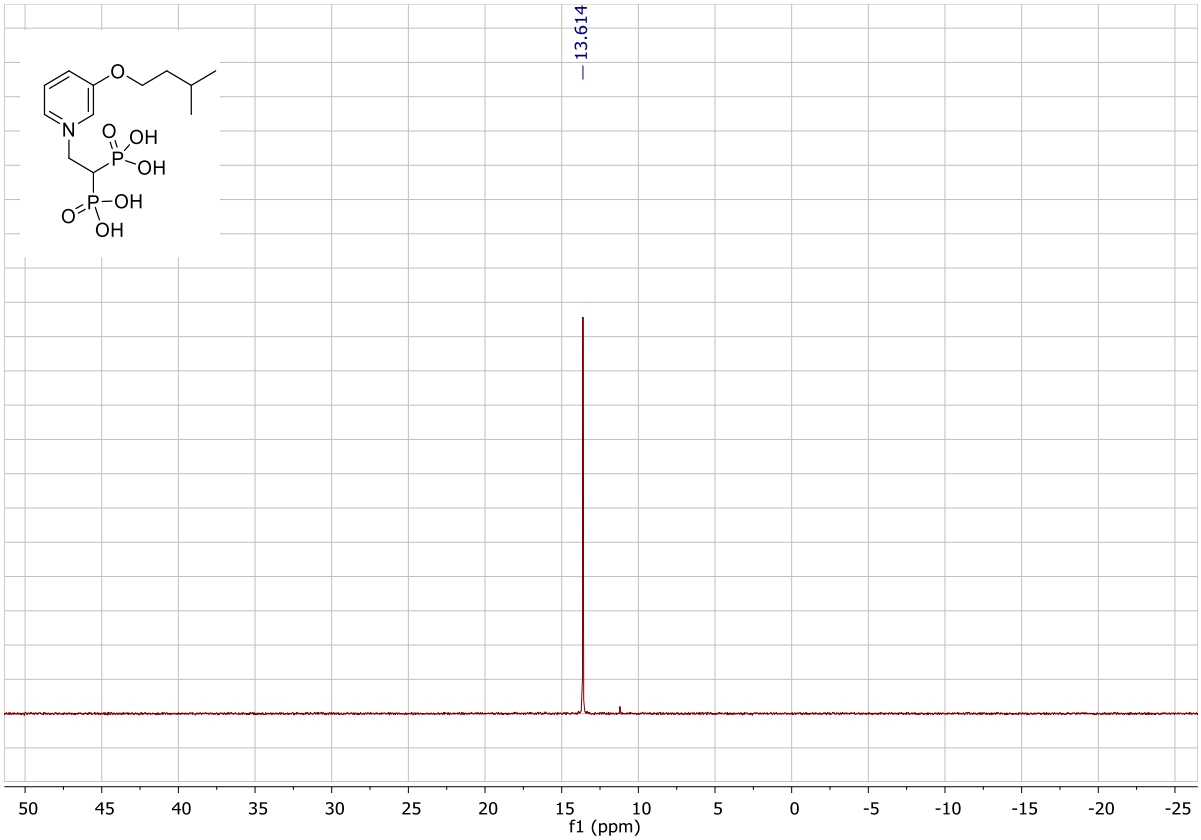
^{1}H NMR IM-35



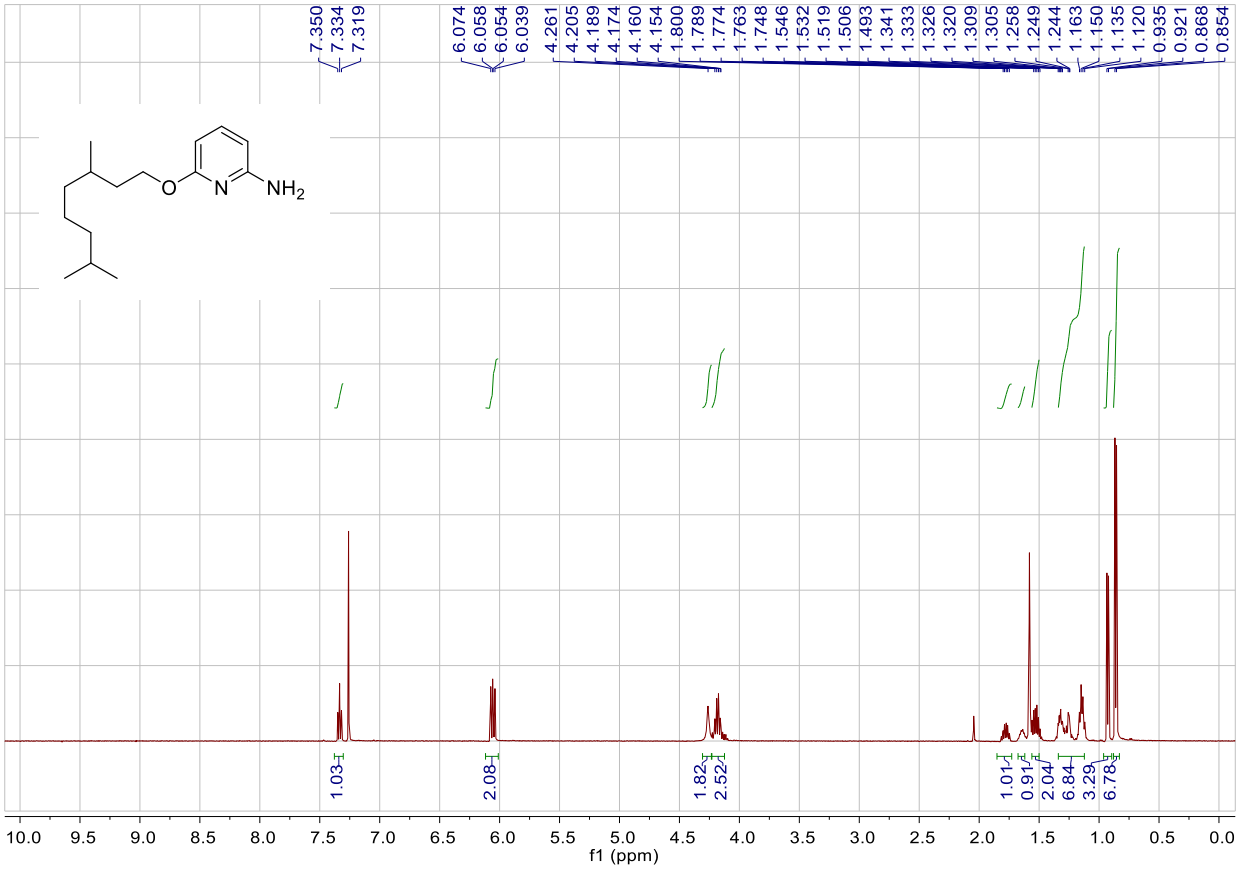
^{1}H NMR 91



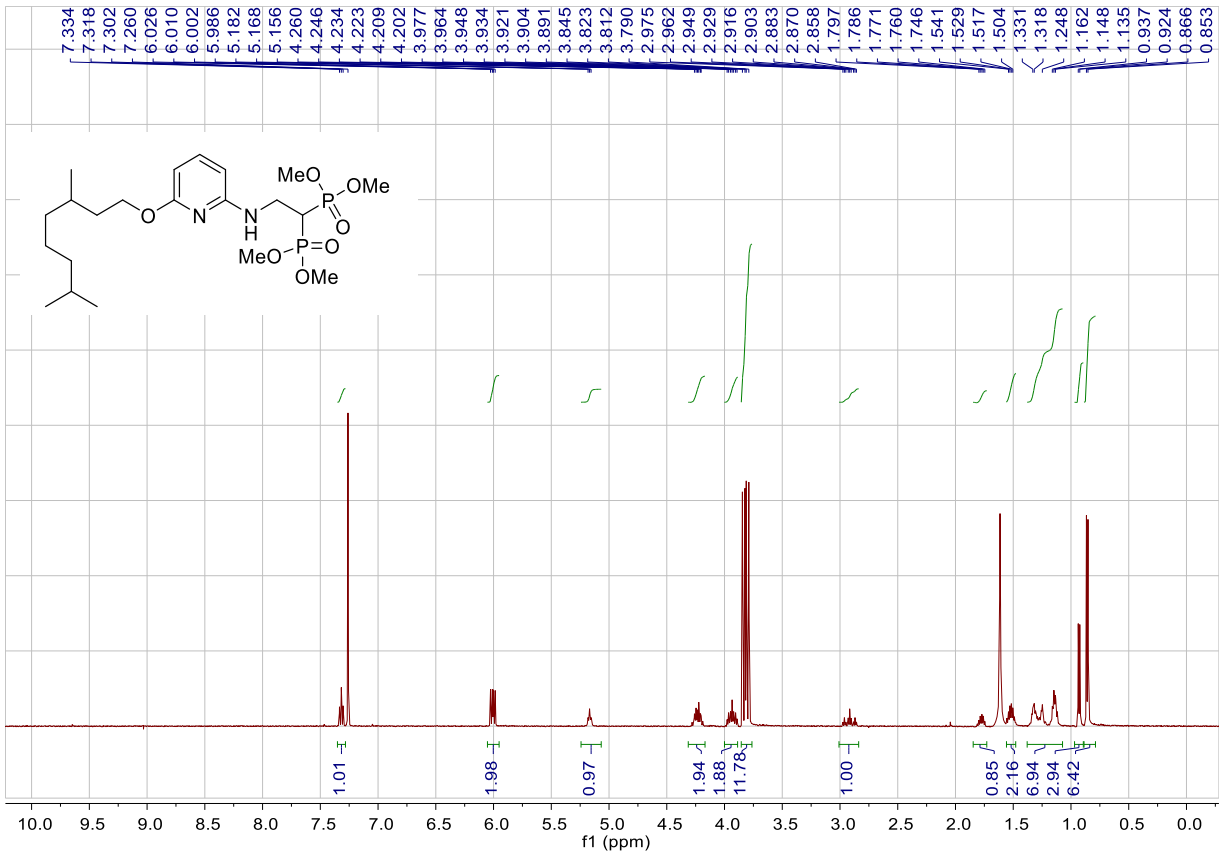
^{31}P NMR 91



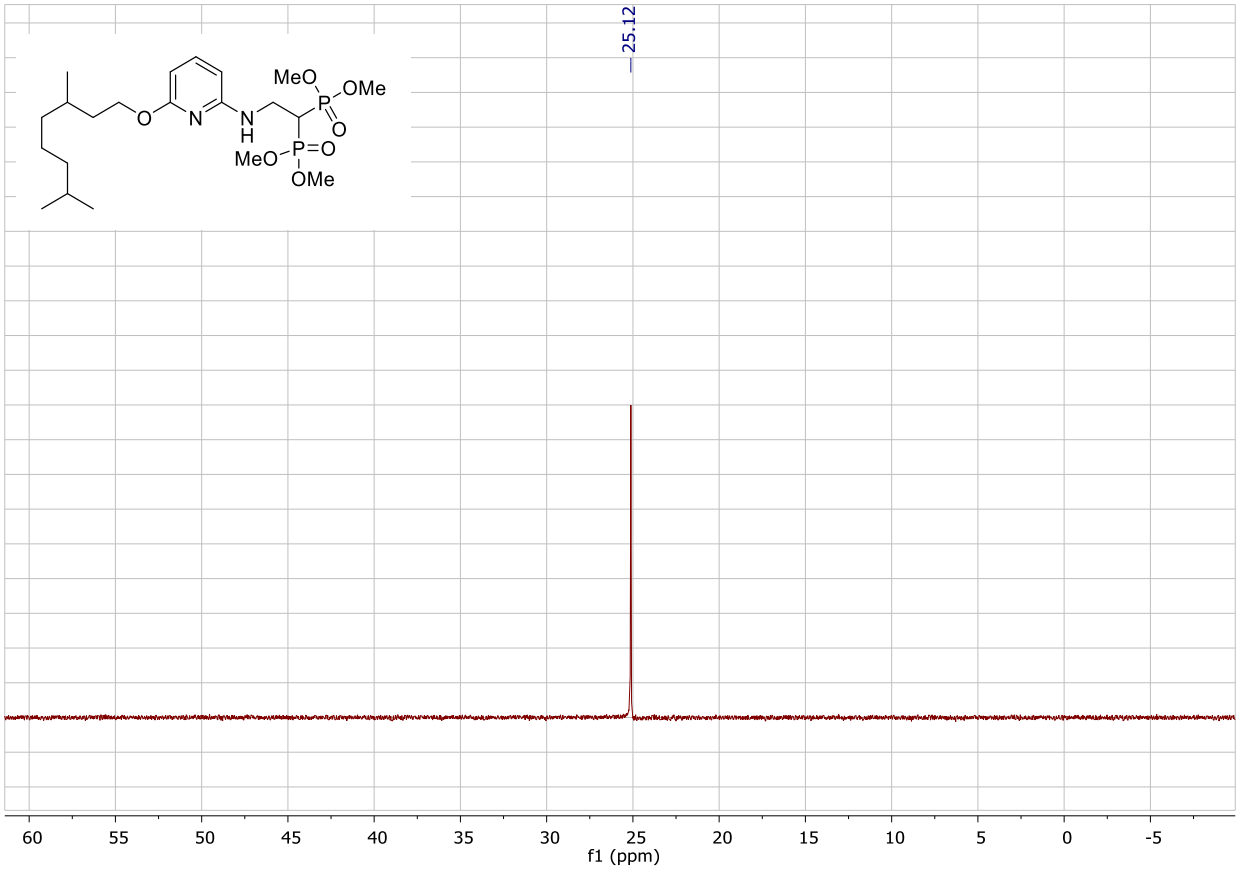
^{1}H NMR IM-36



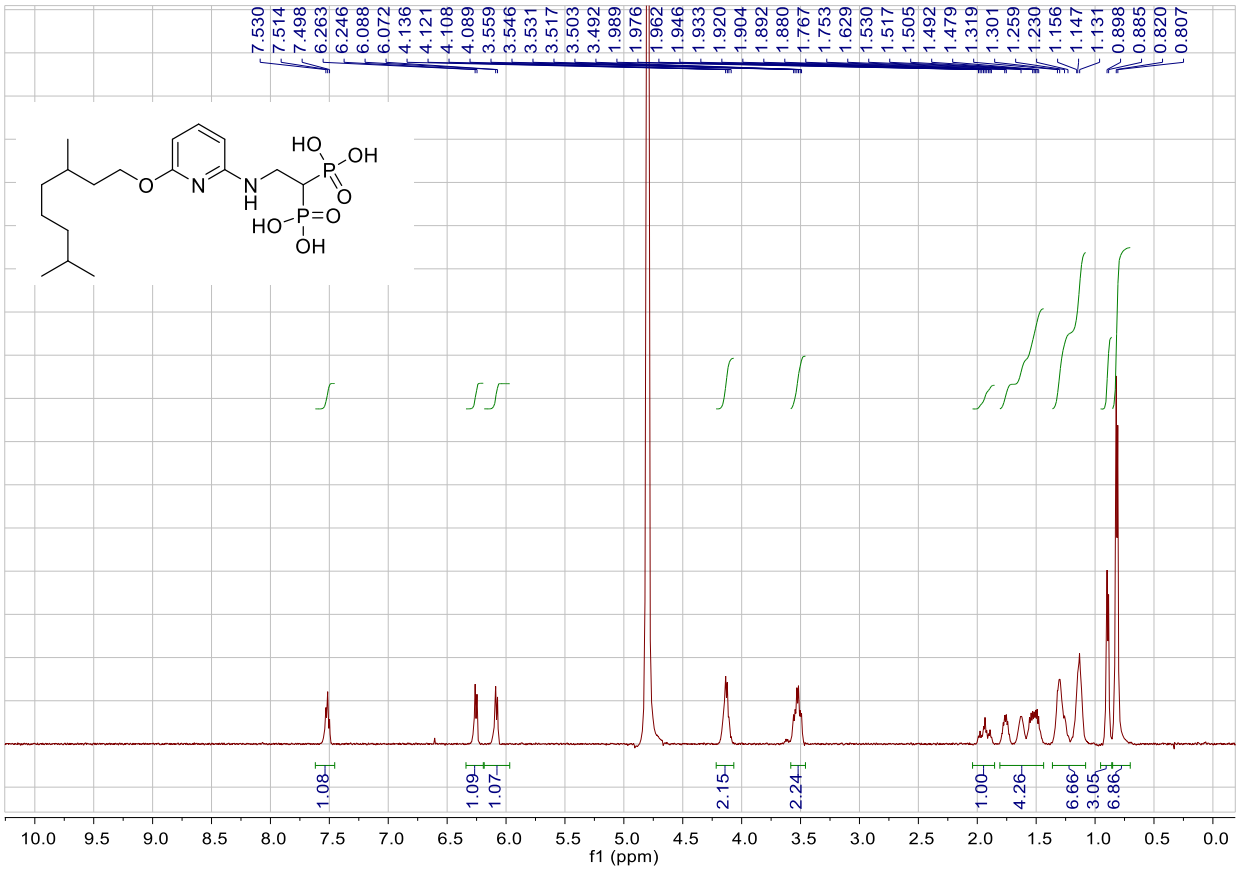
^{1}H NMR IM-37



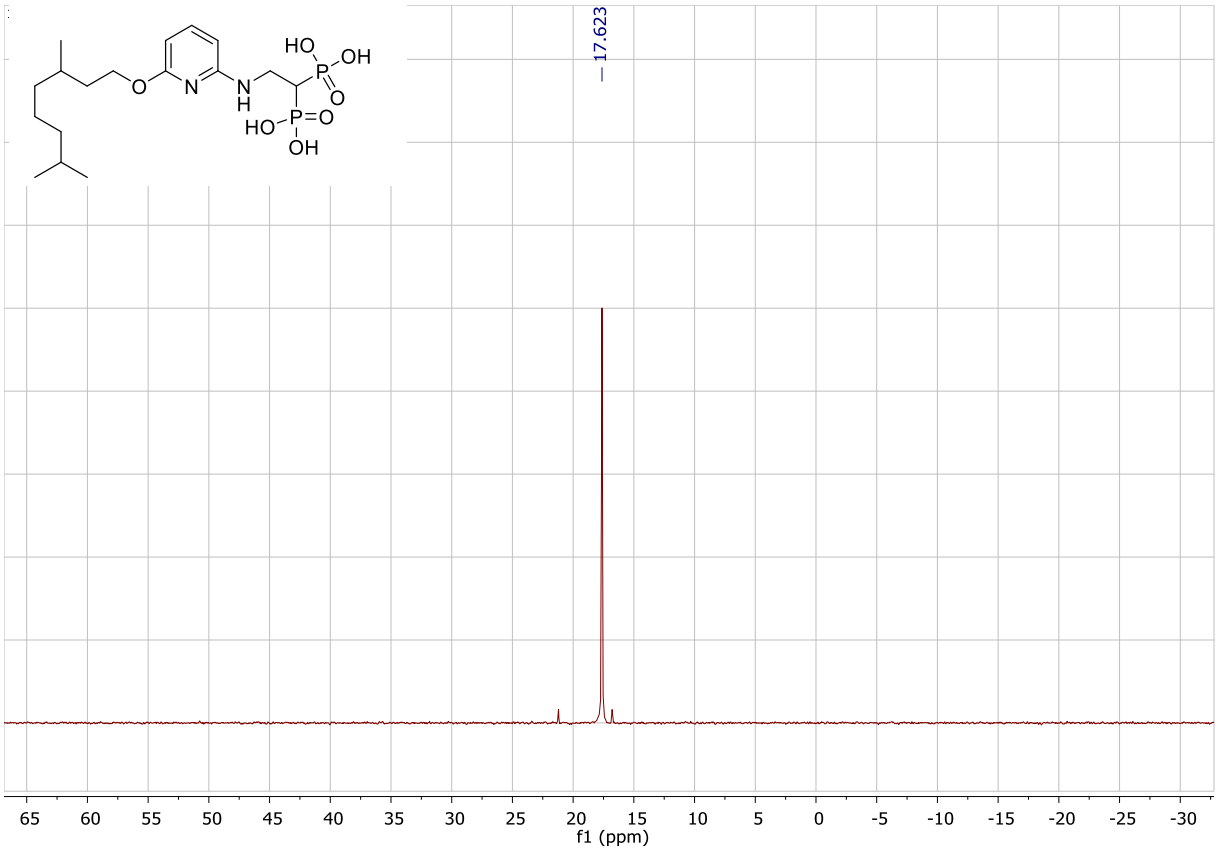
^{31}P NMR IM-37



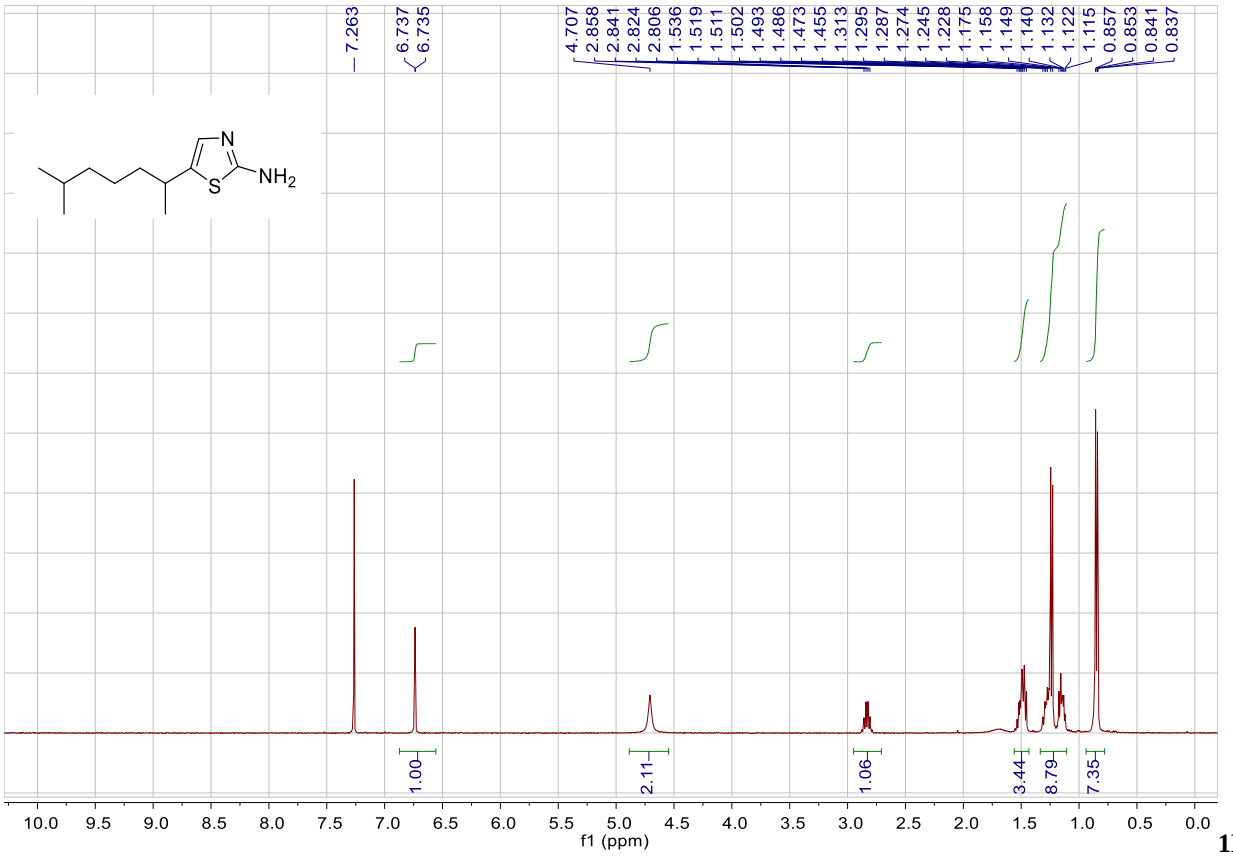
^{1}H NMR 92



^{31}P NMR 92

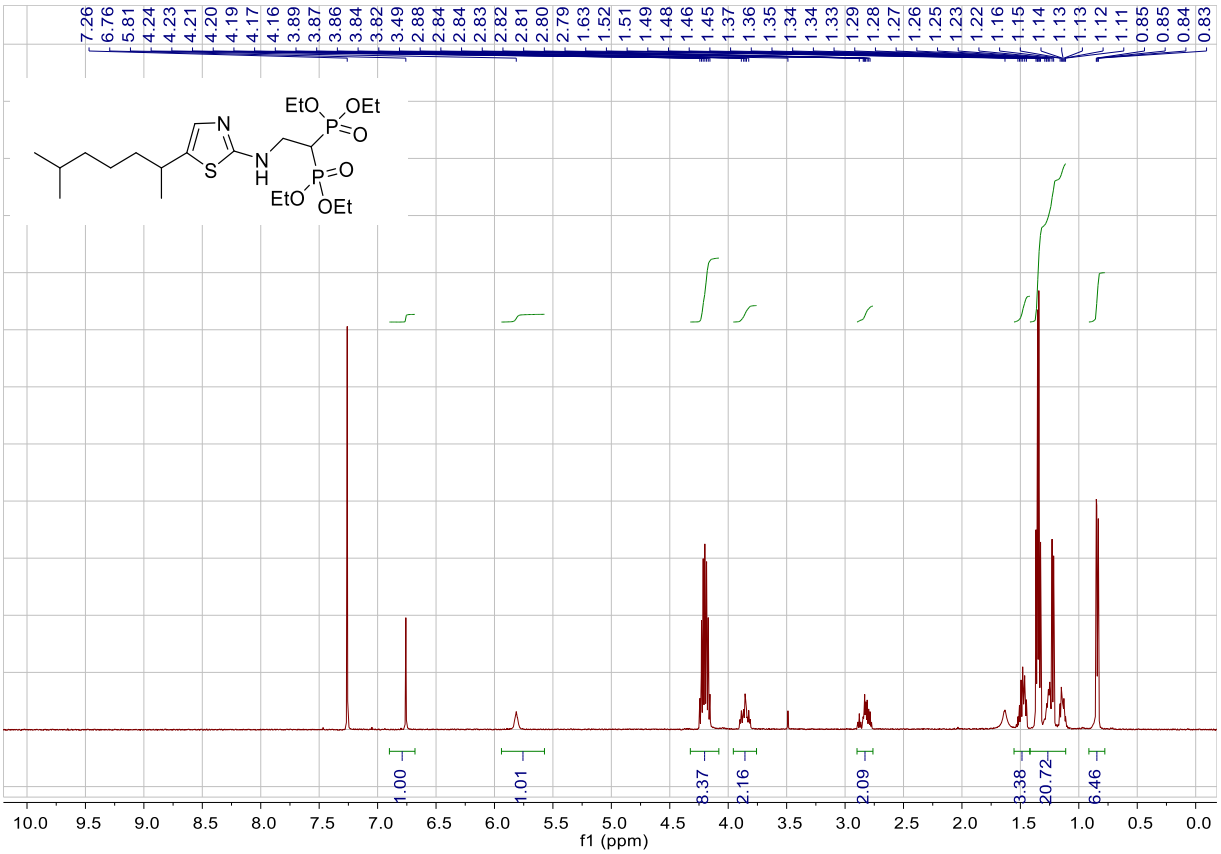


^{1}H NMR IM-38

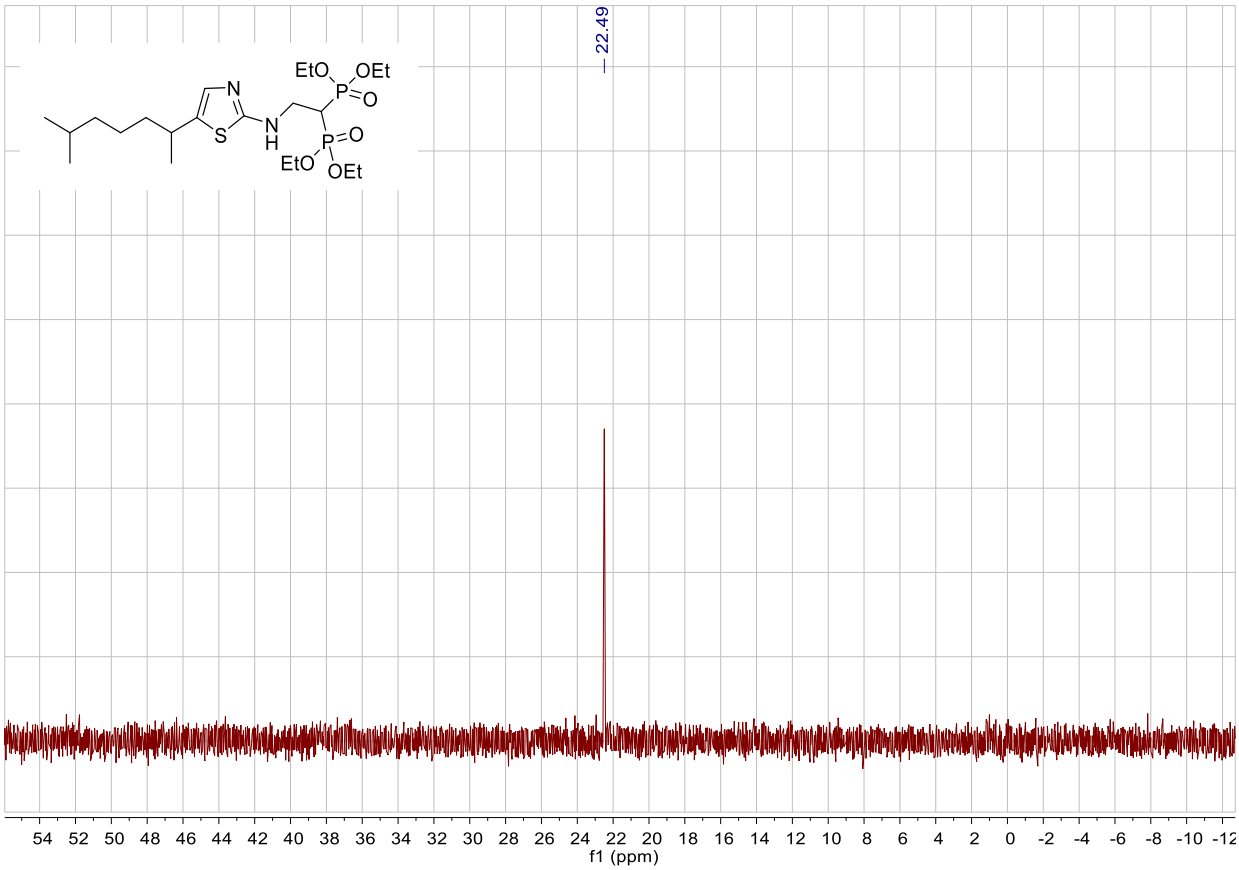


1H

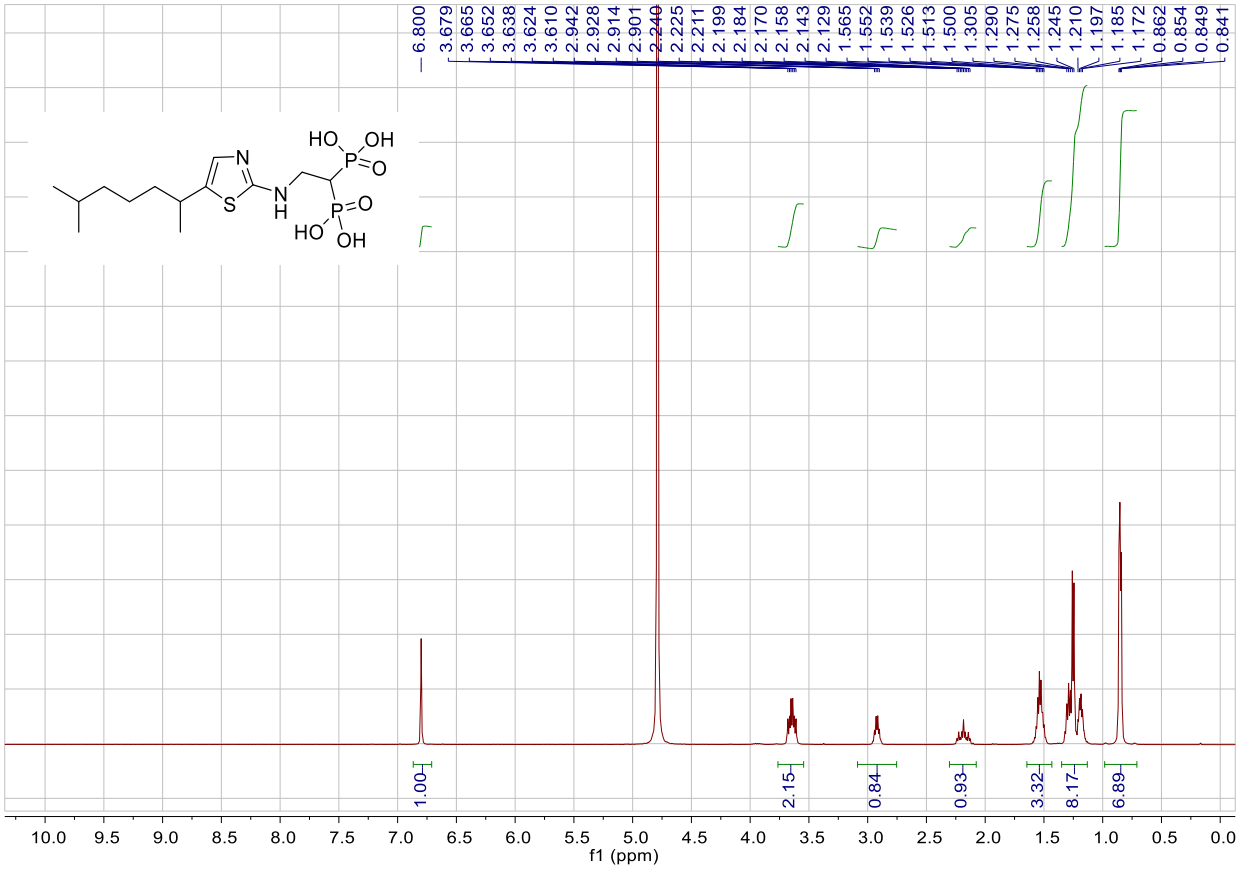
NMR IM-39



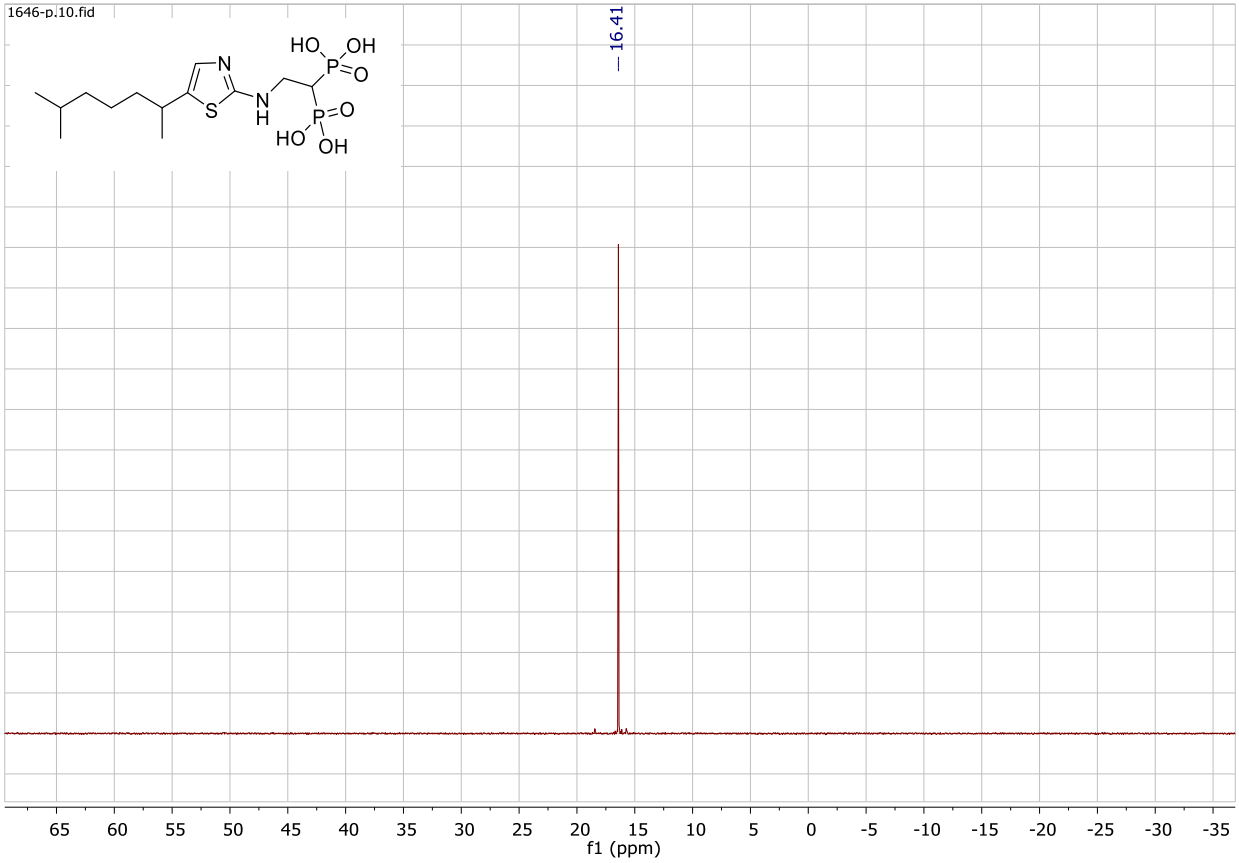
^{31}P NMR IM-39



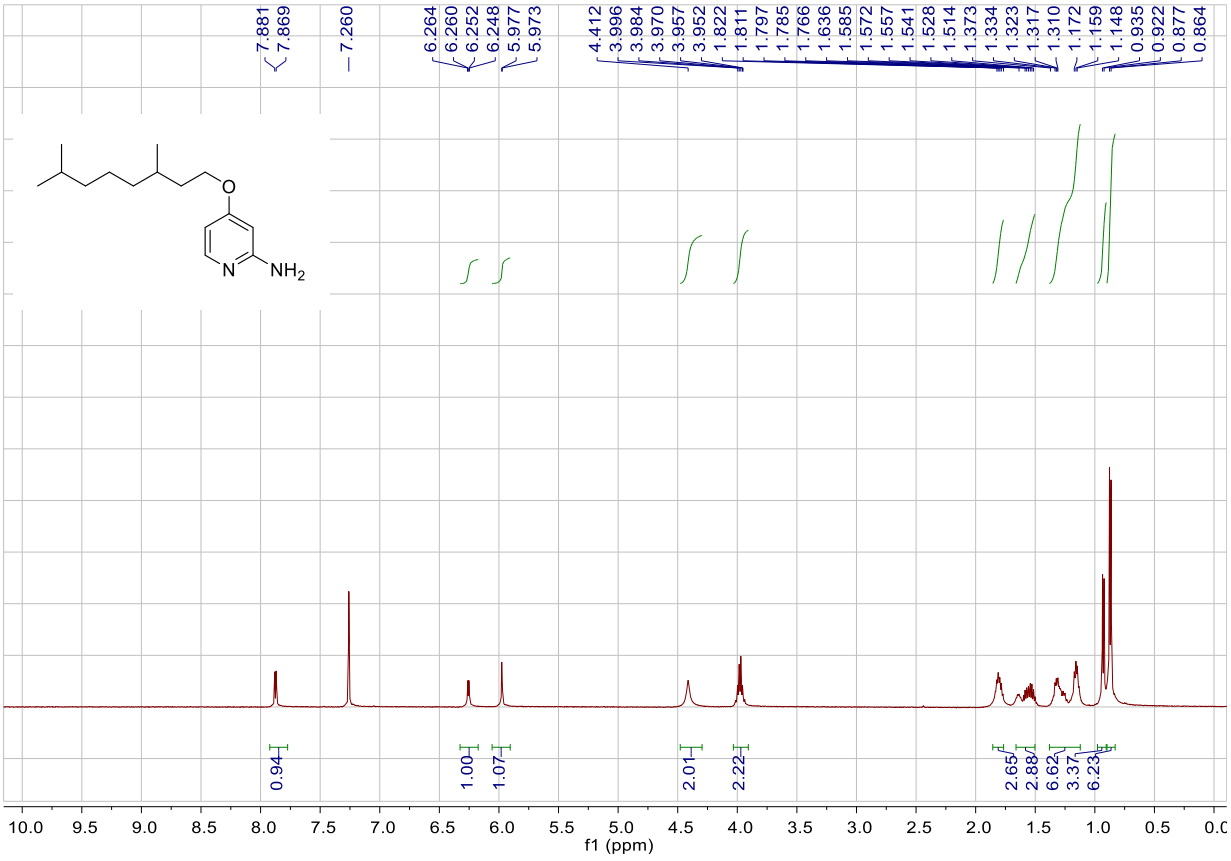
^{1}H NMR 93



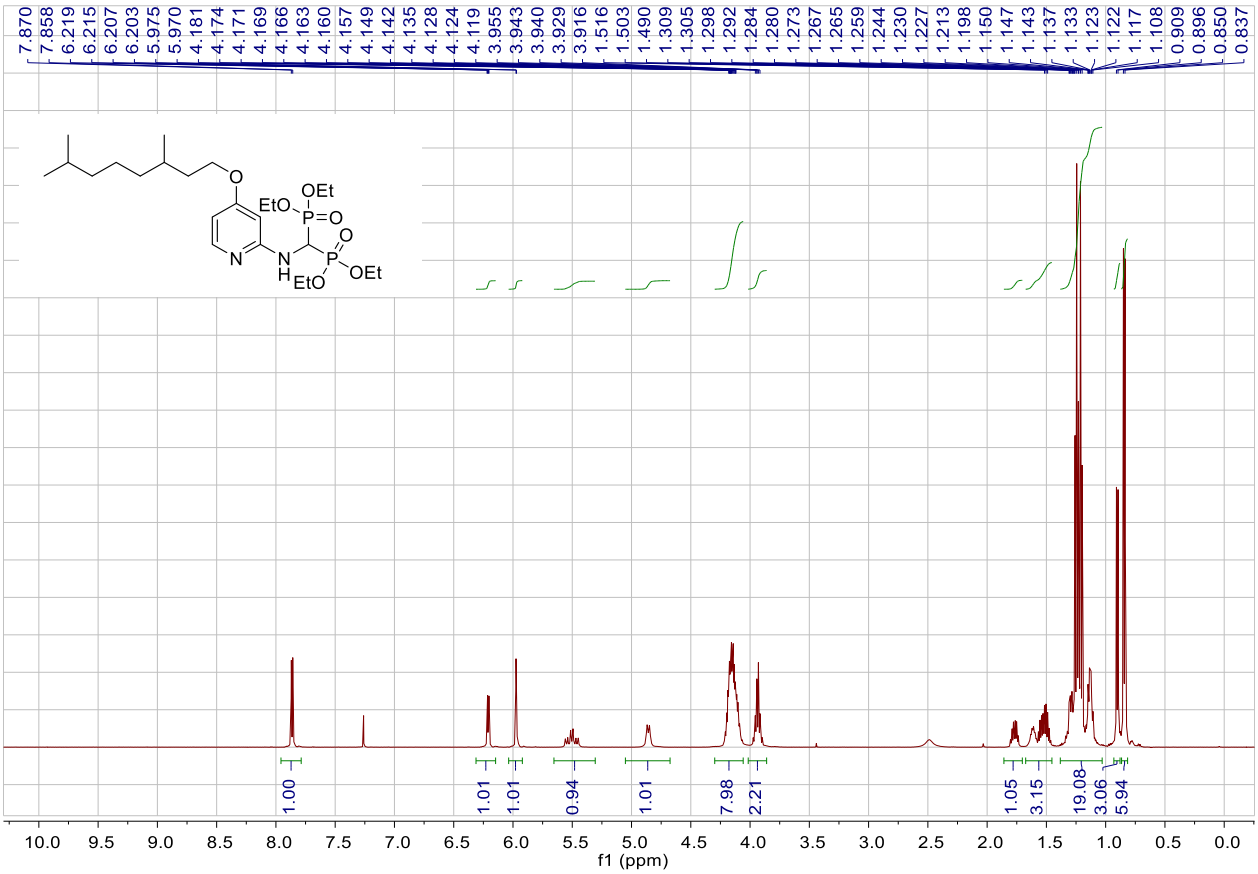
^{31}P NMR 93



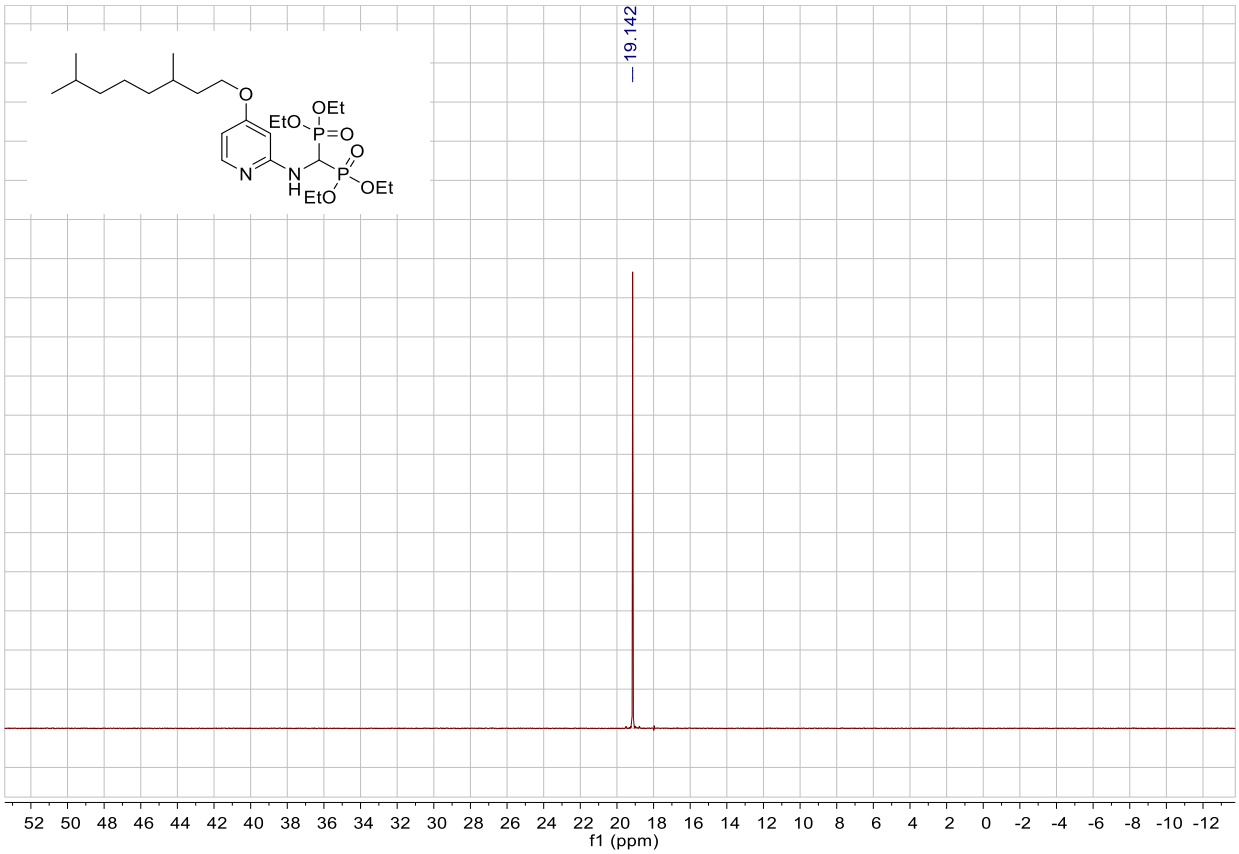
^{1}H NMR IM-40



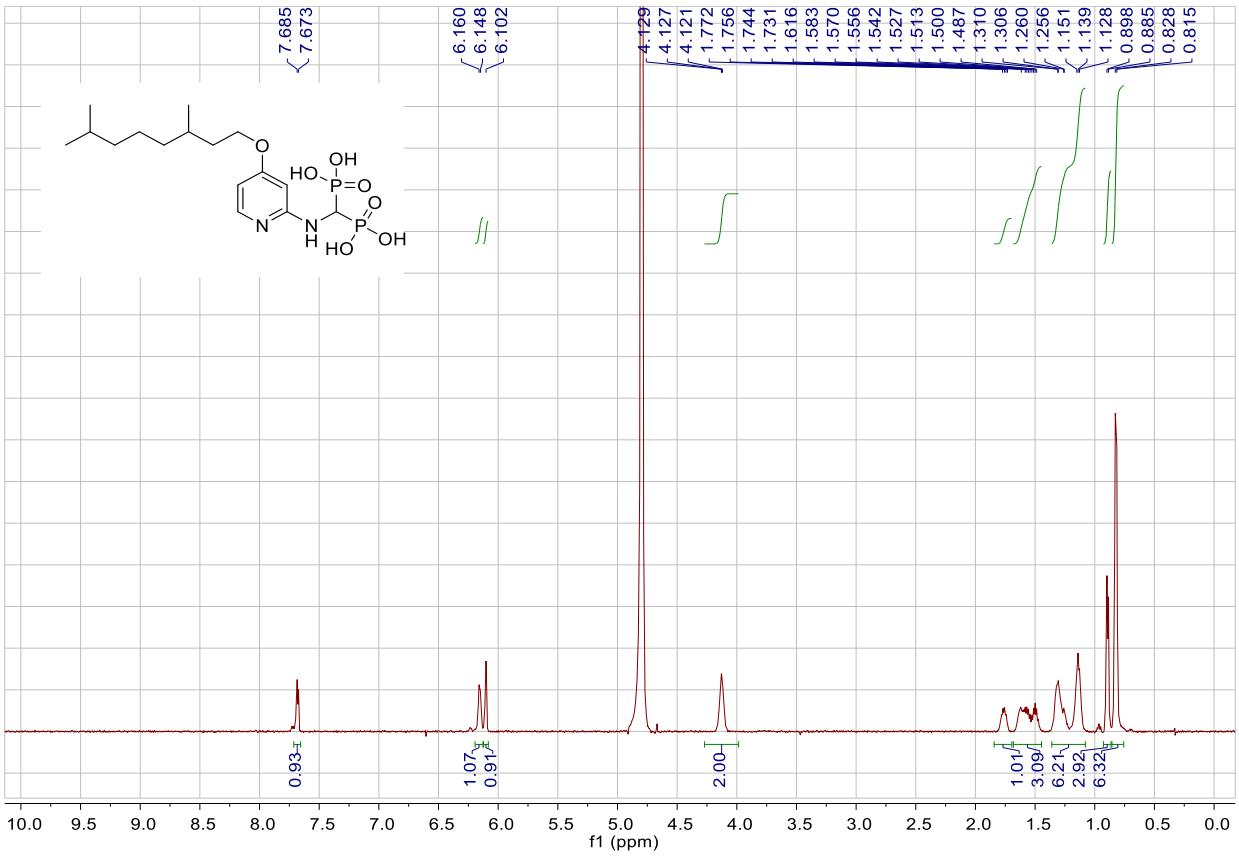
^{1}H NMR IM-41



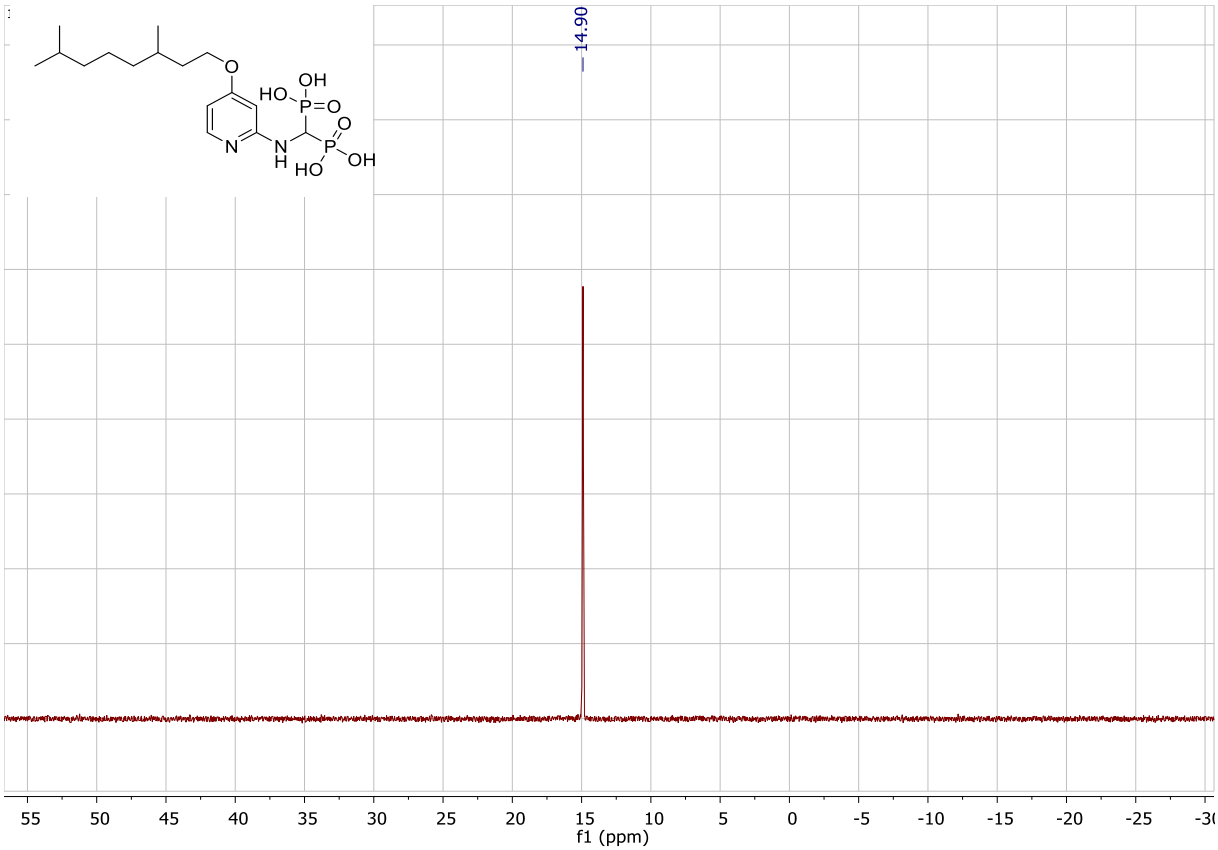
^{31}P NMR IM-41



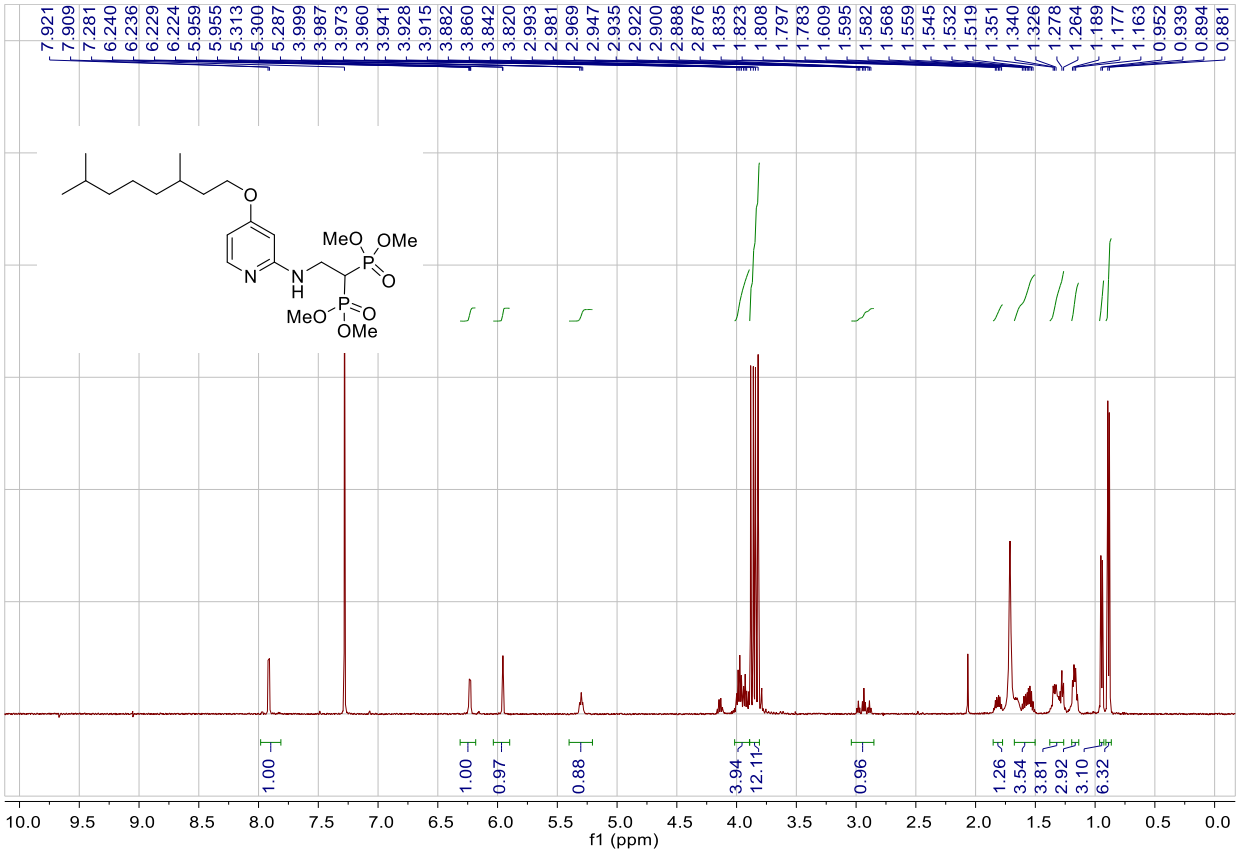
^{1}H NMR 95



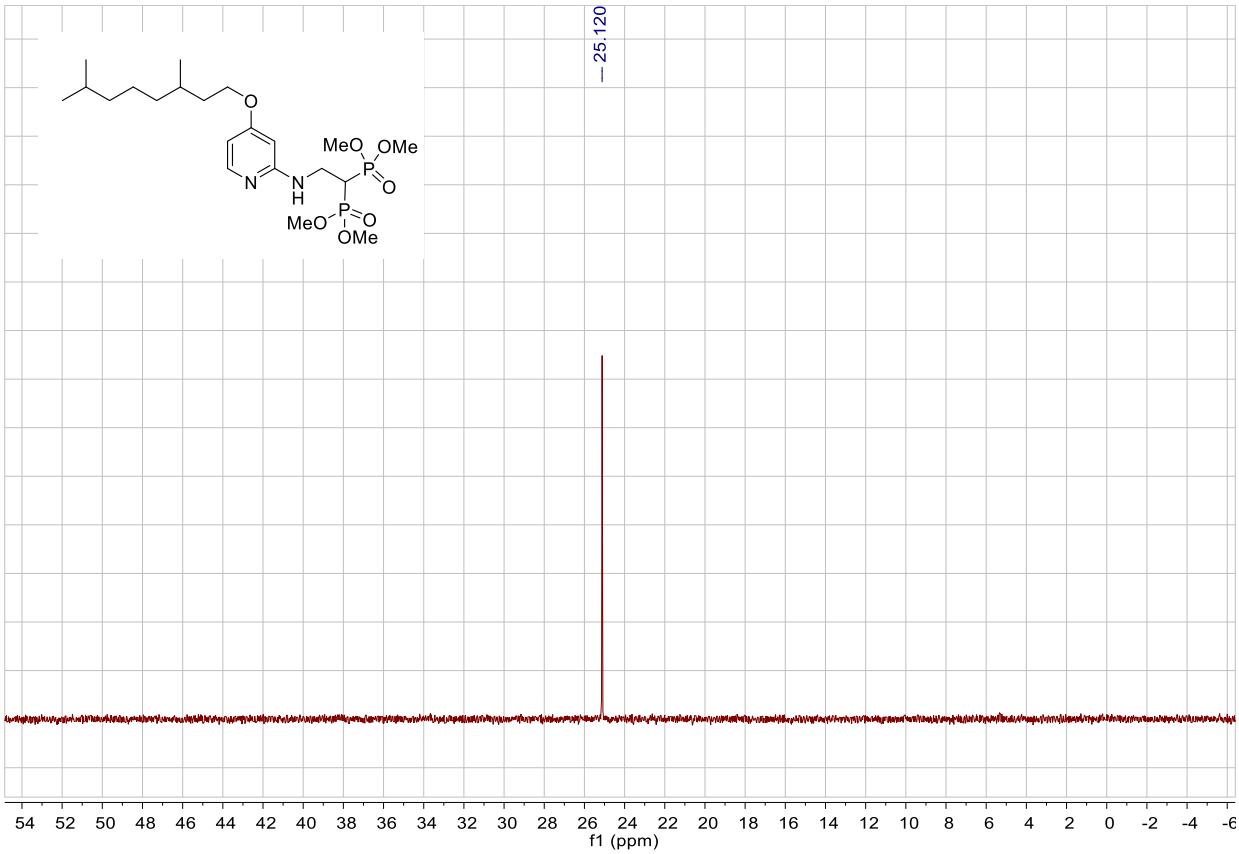
^{31}P NMR 95



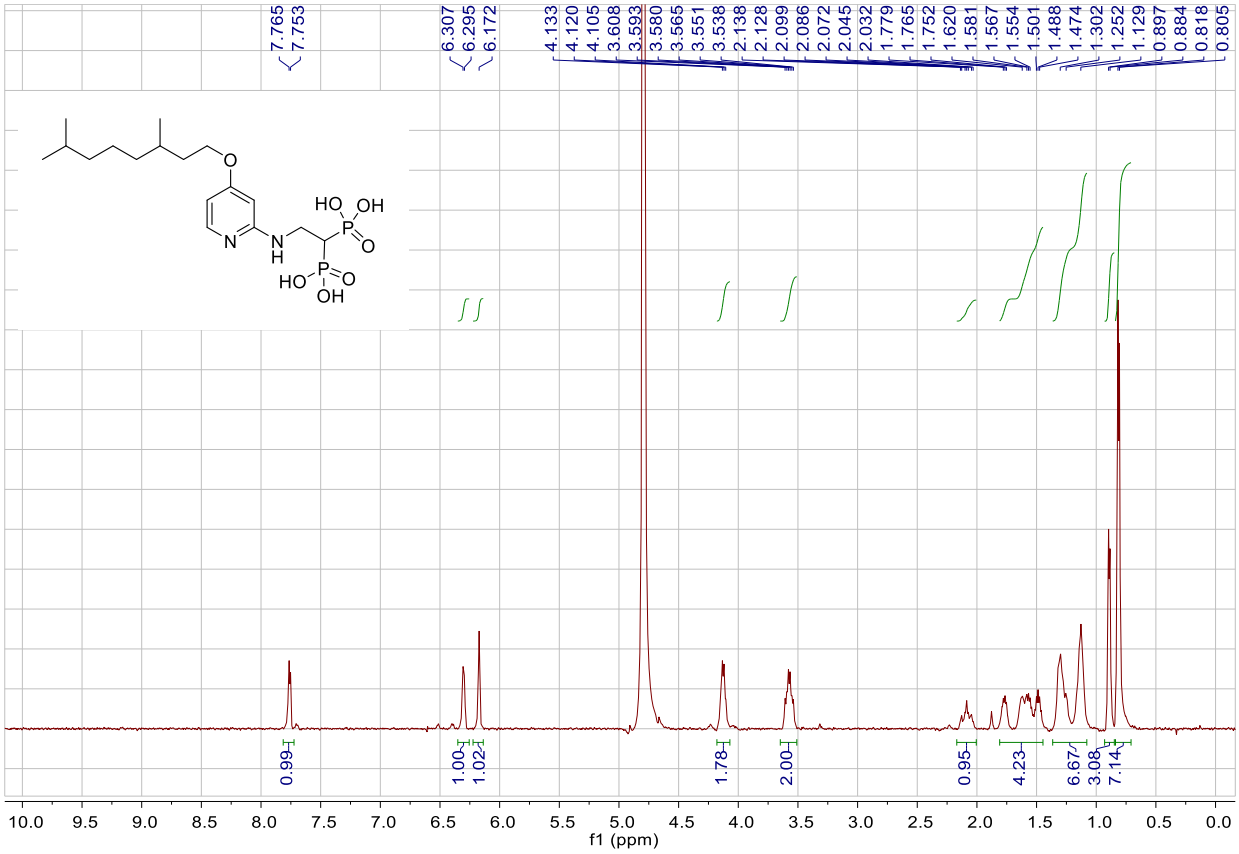
^{1}H NMR IM-42



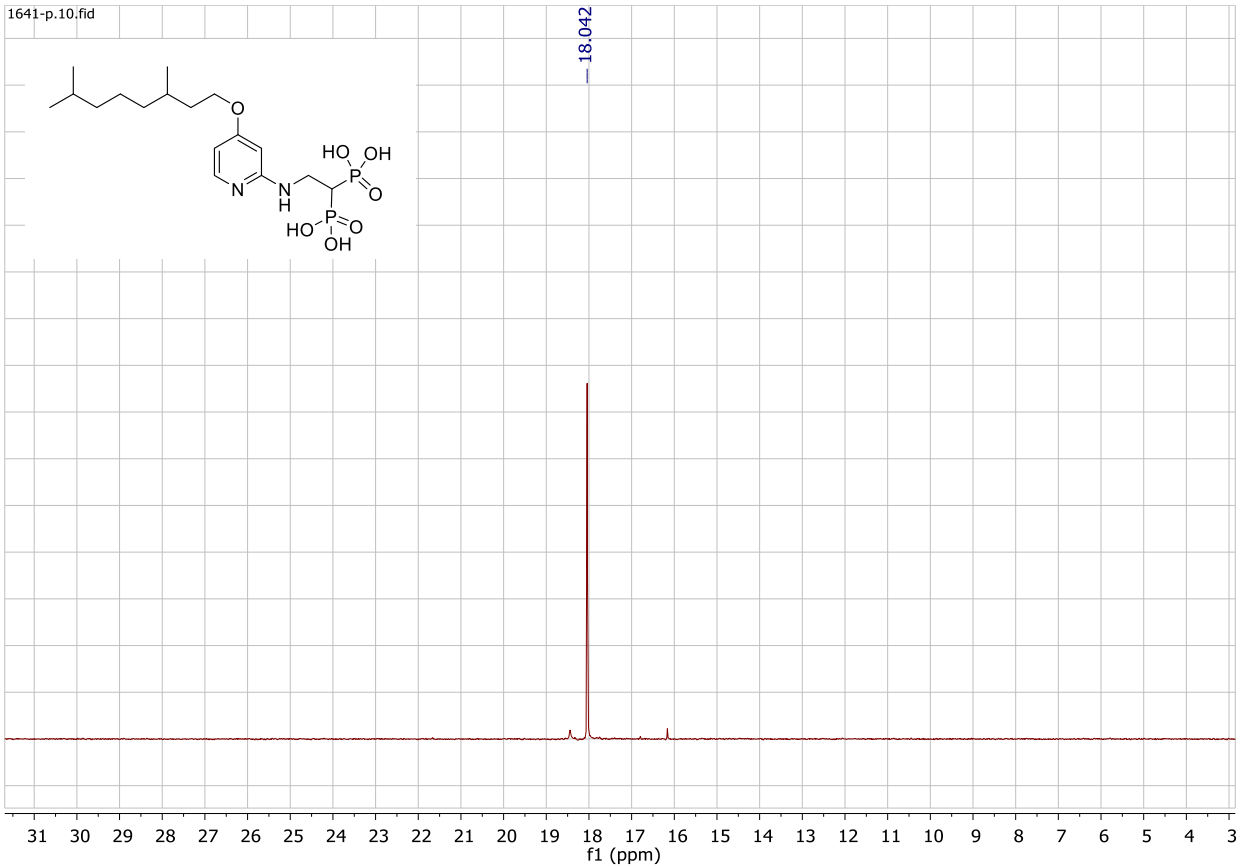
^{31}P NMR IM-42



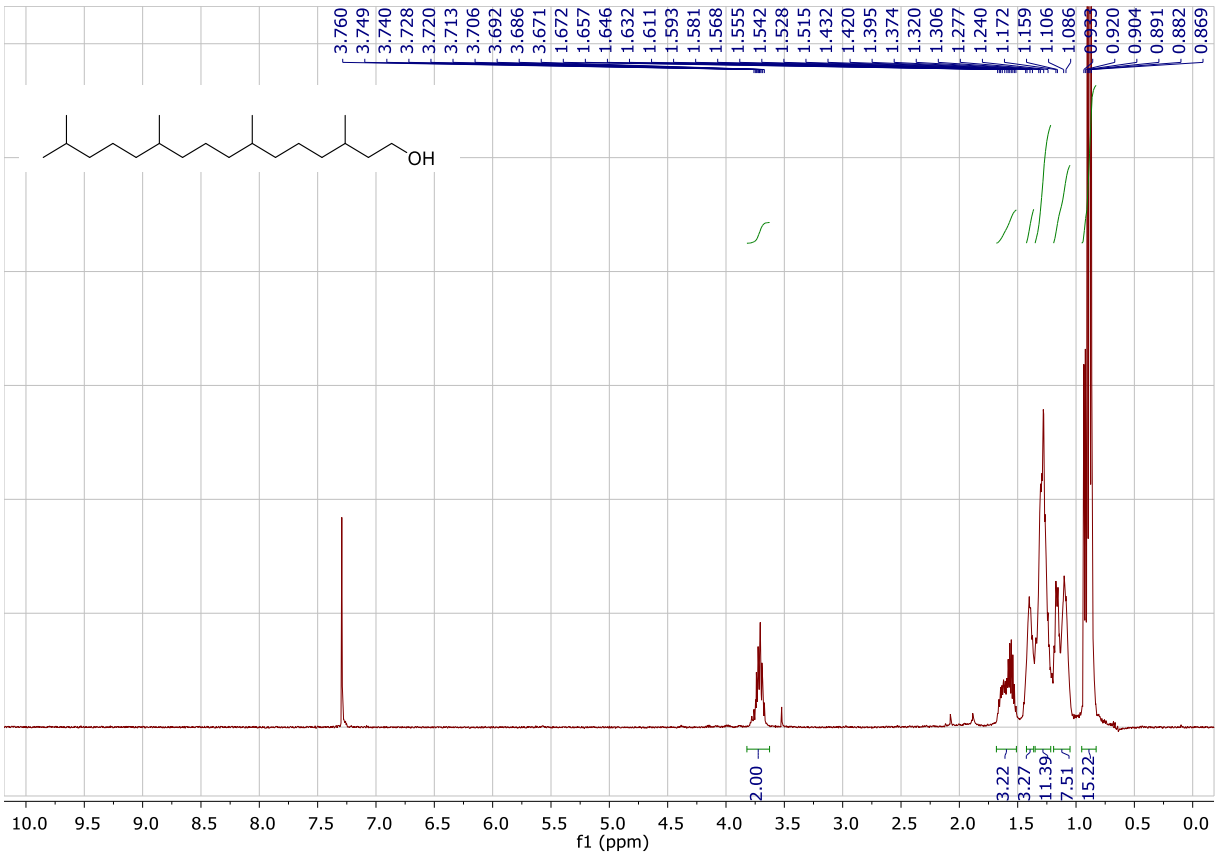
^{1}H NMR 96



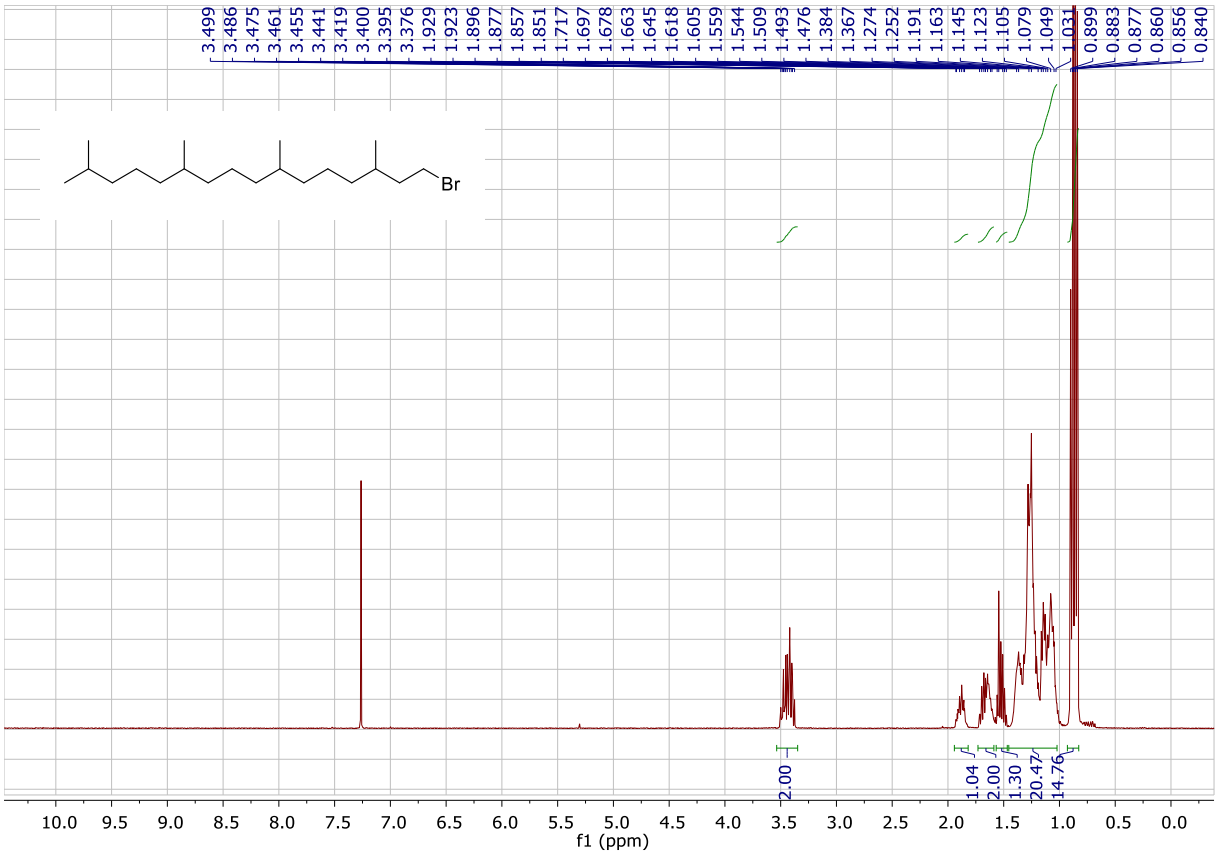
^{31}P NMR 96



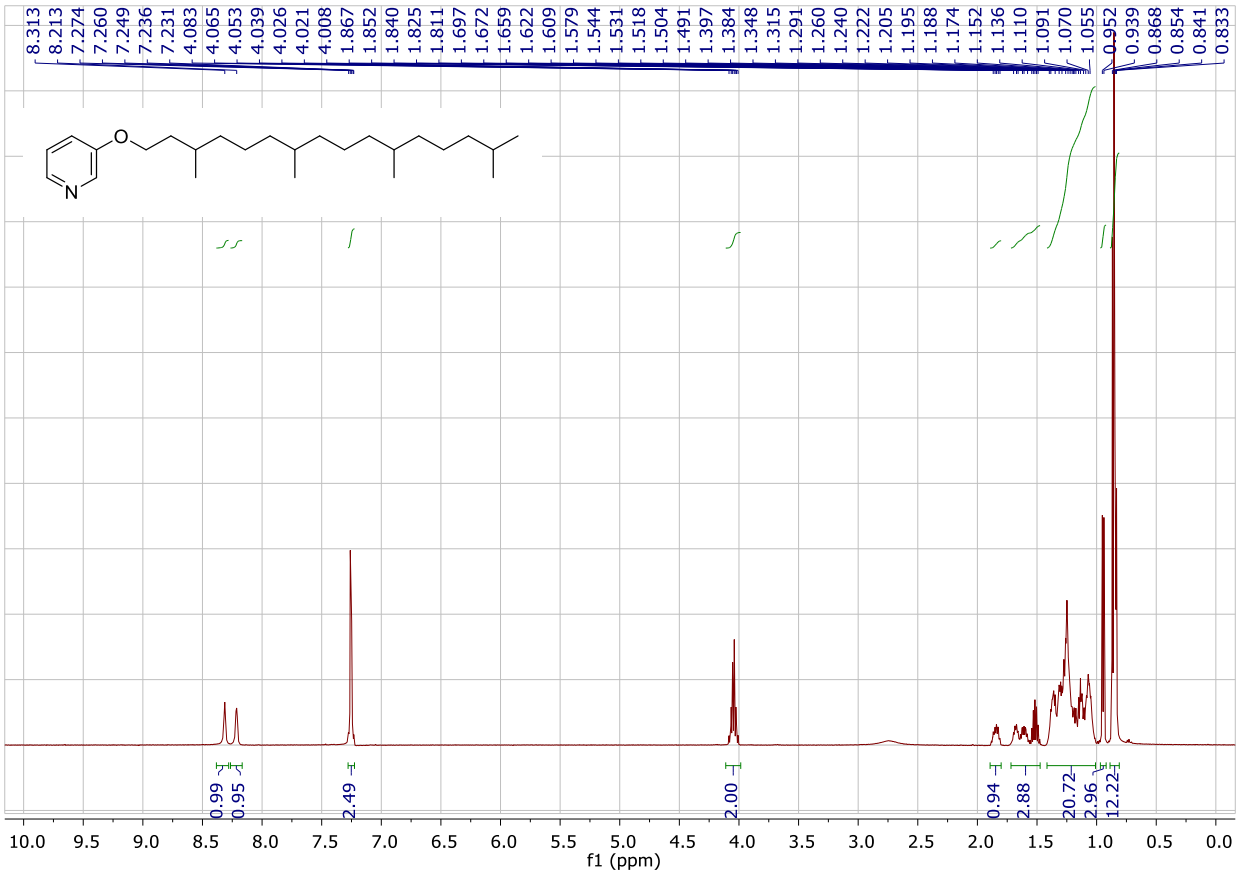
^{1}H NMR IM-43



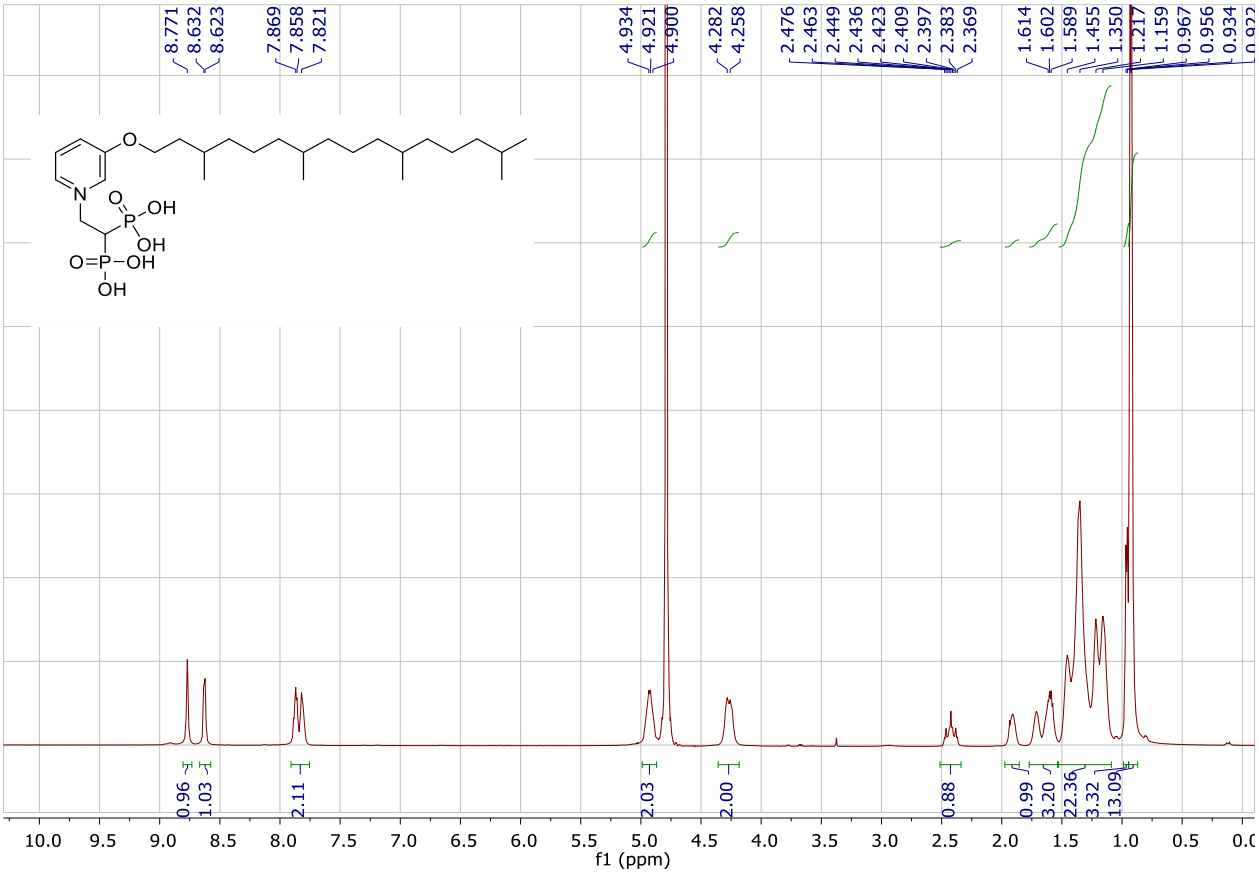
^{1}H NMR M-44



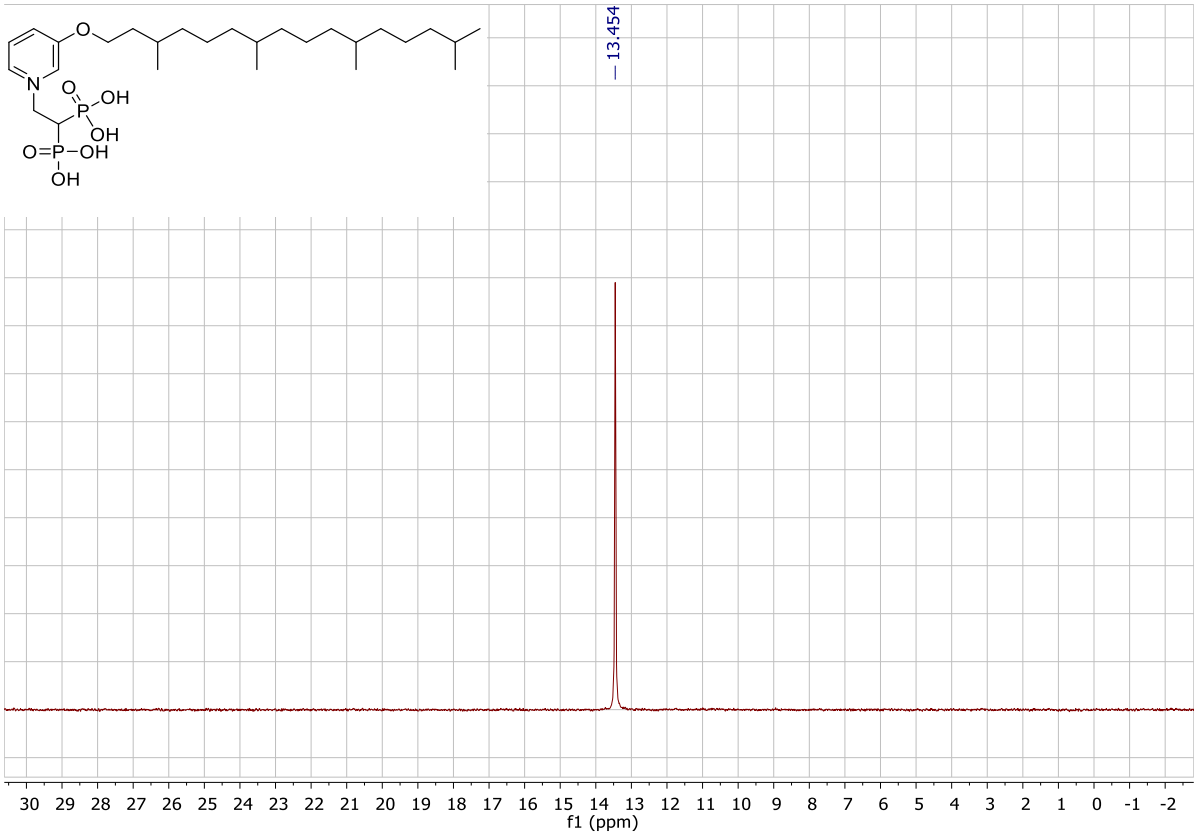
^{1}H NMR IM-45



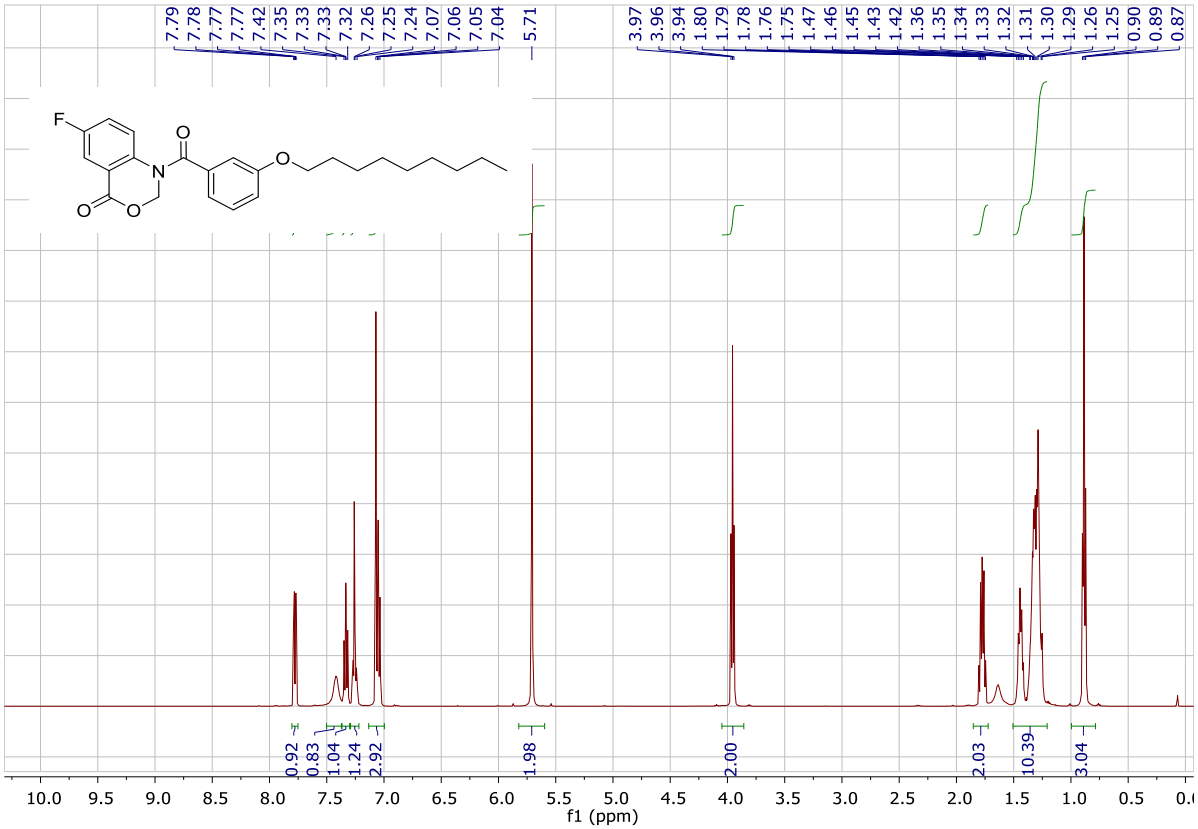
^{1}H NMR 97



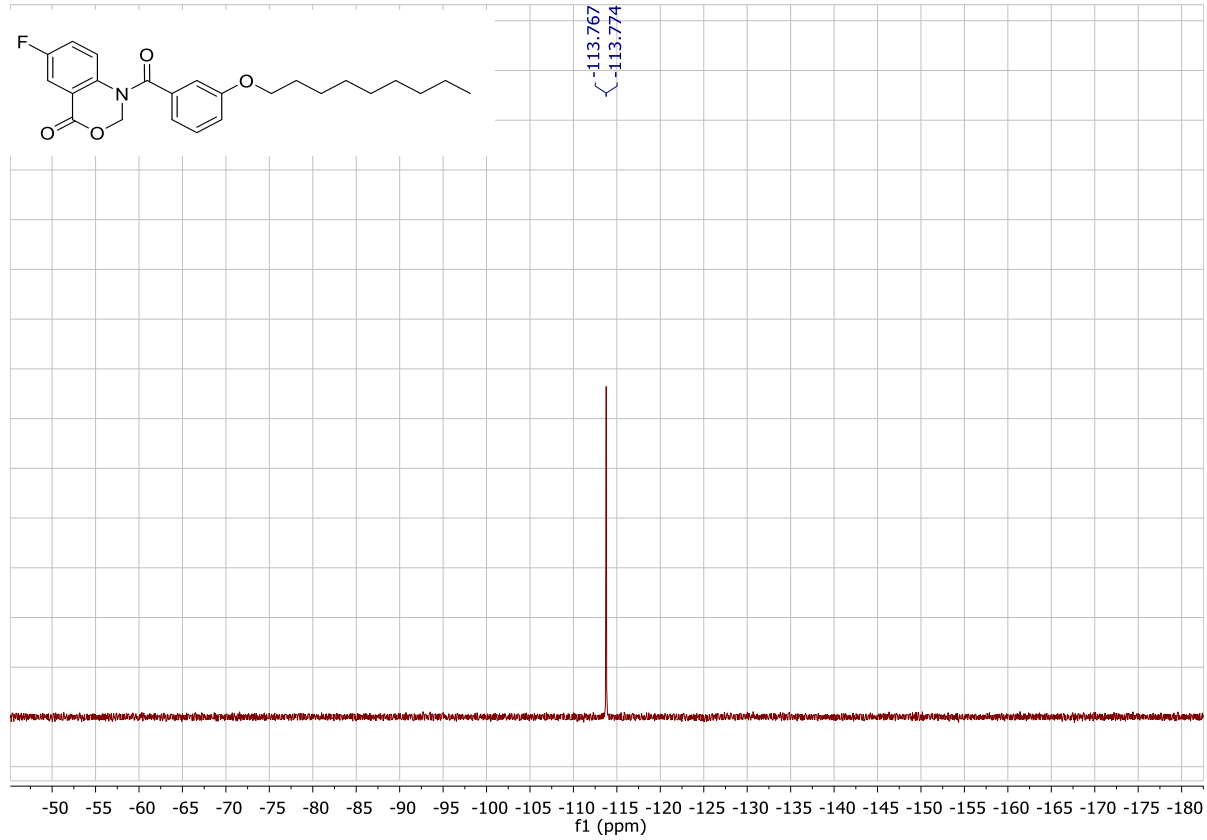
^{31}P NMR 97



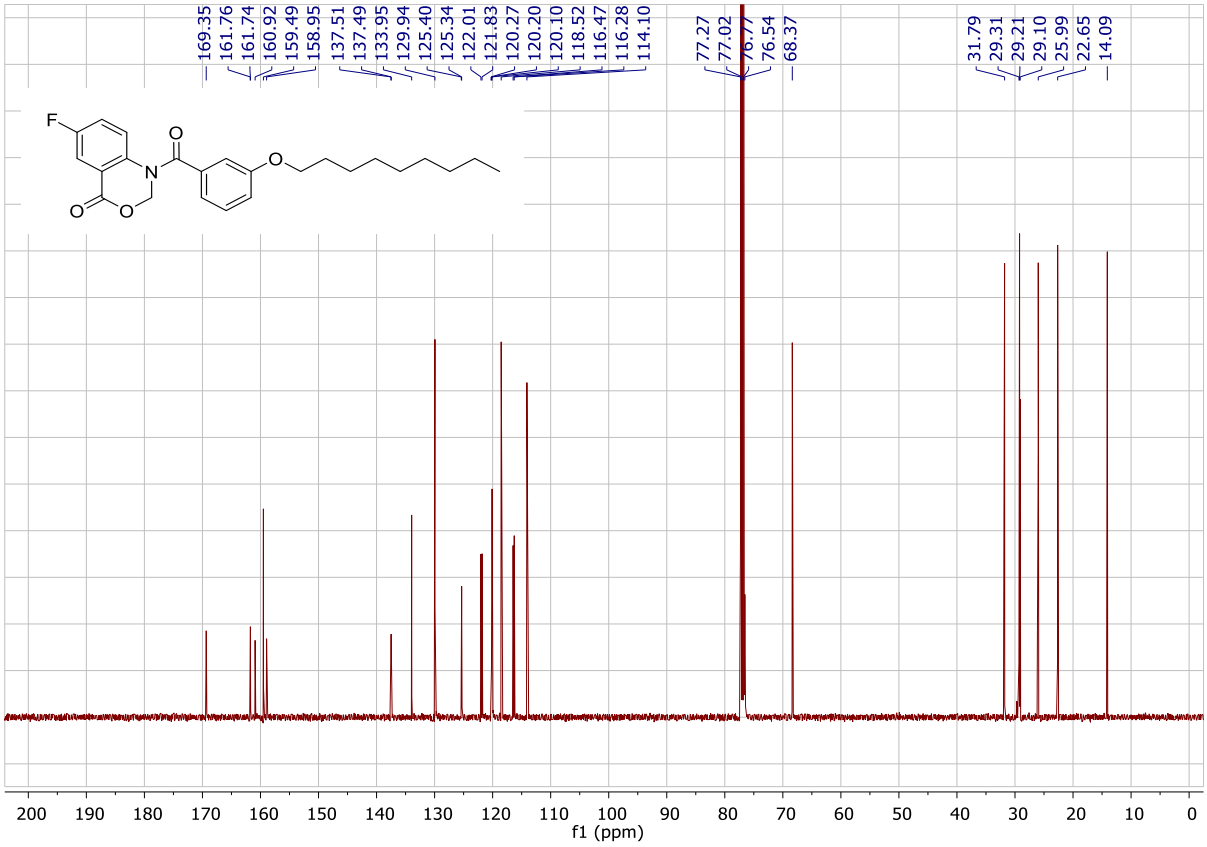
^{1}H NMR 100



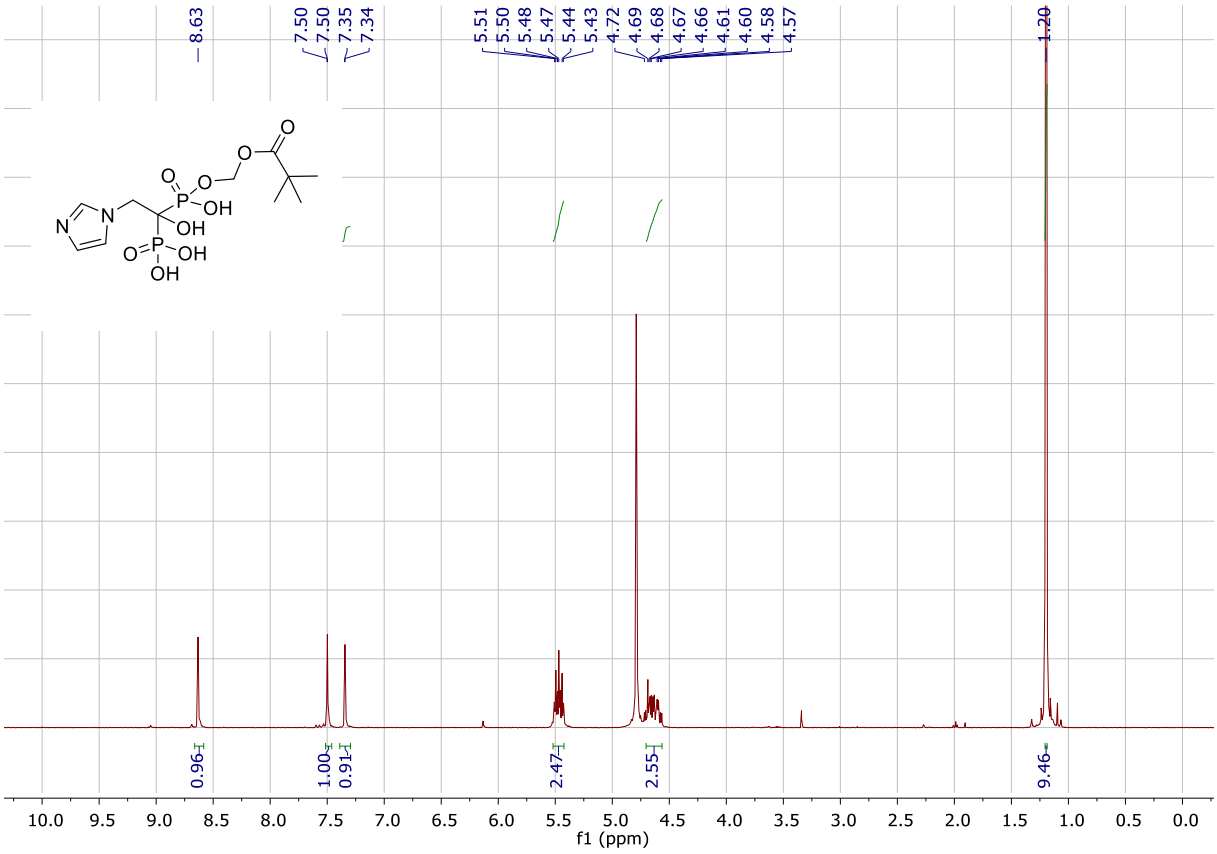
^{19}F NMR 100



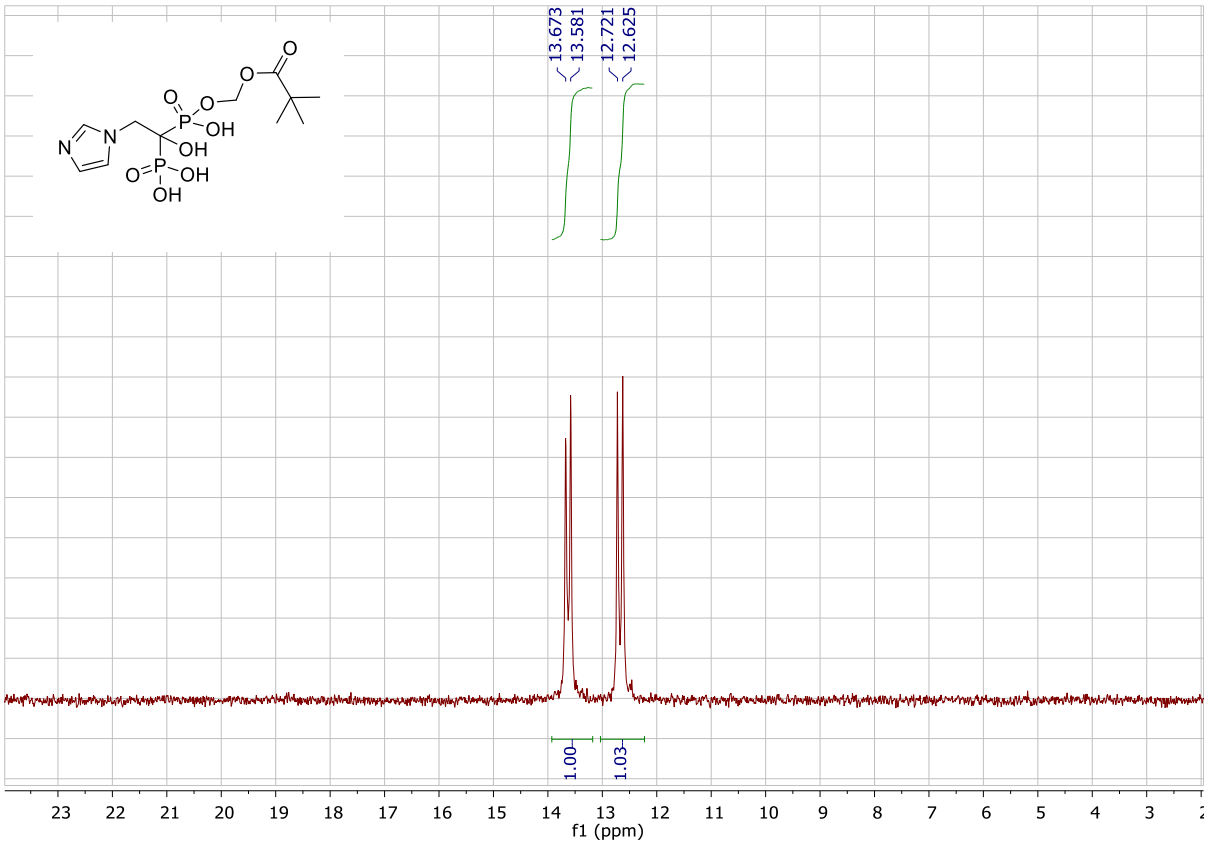
^{13}C NMR 100



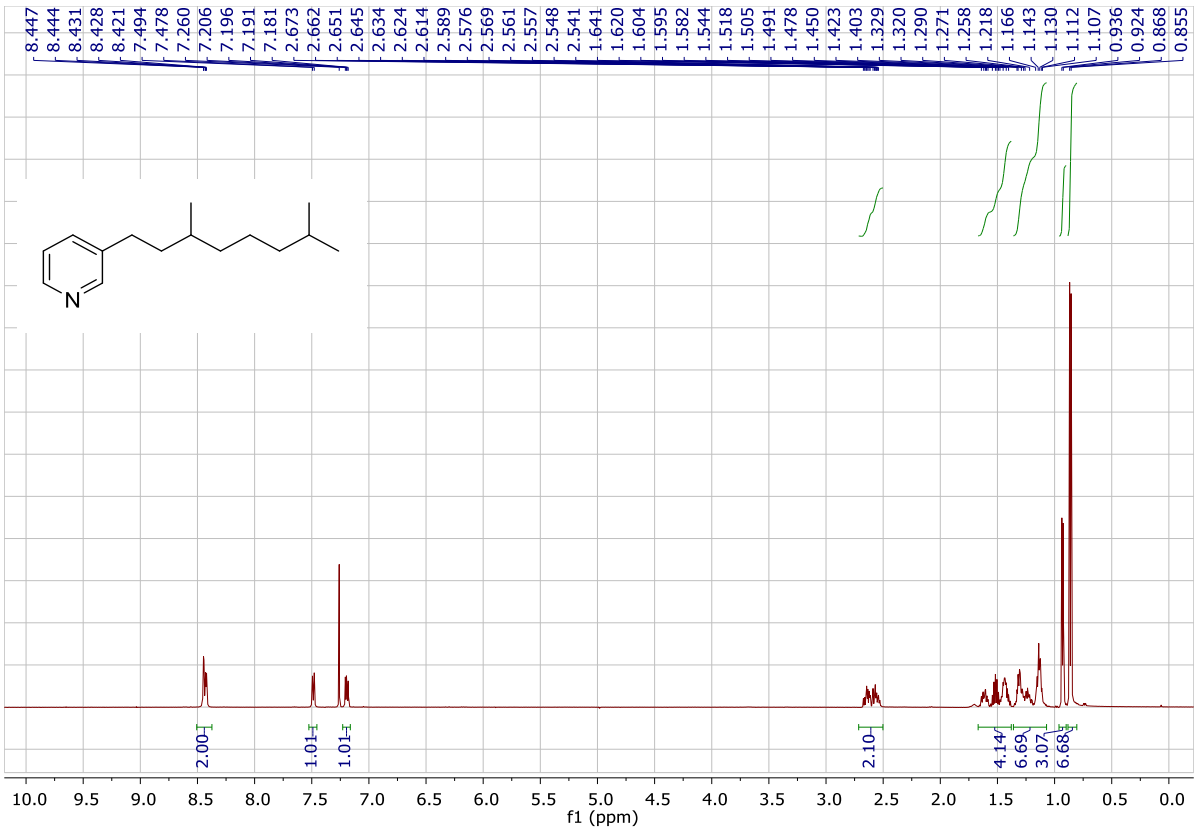
^{1}H NMR 101



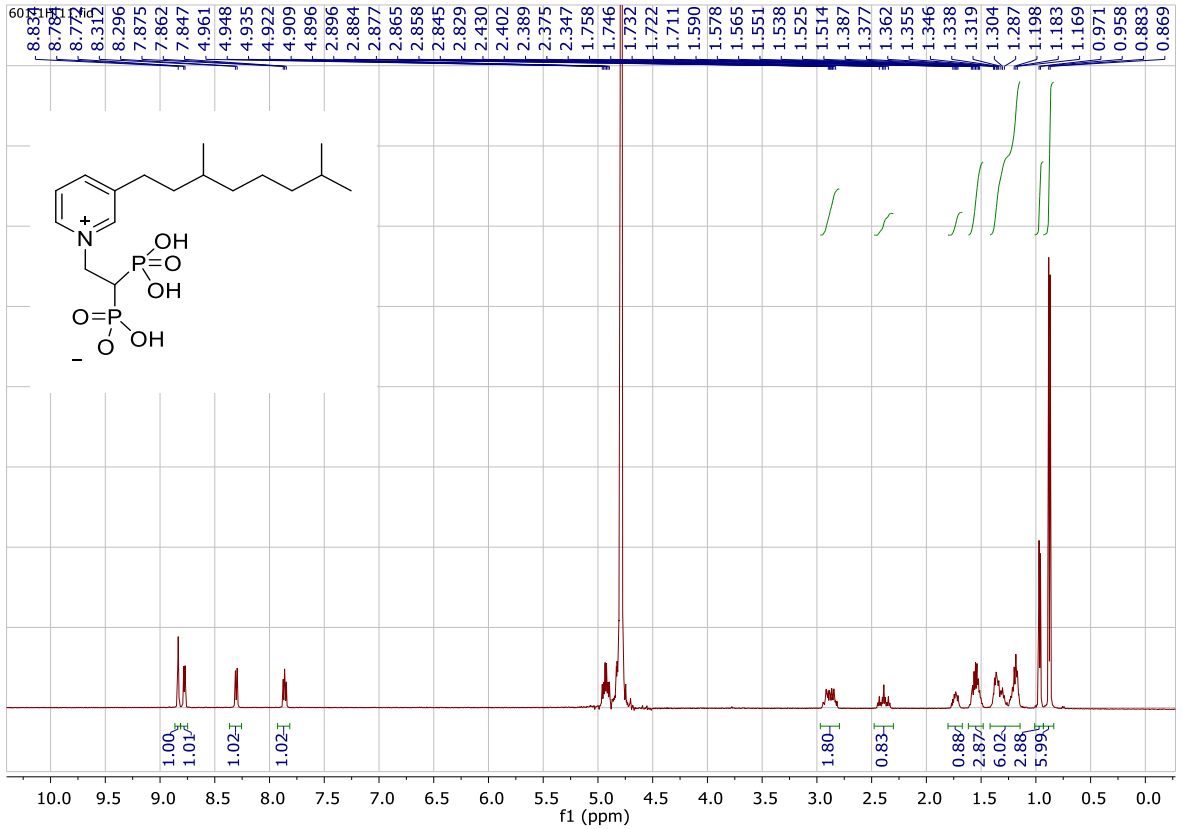
^{31}P NMR 101



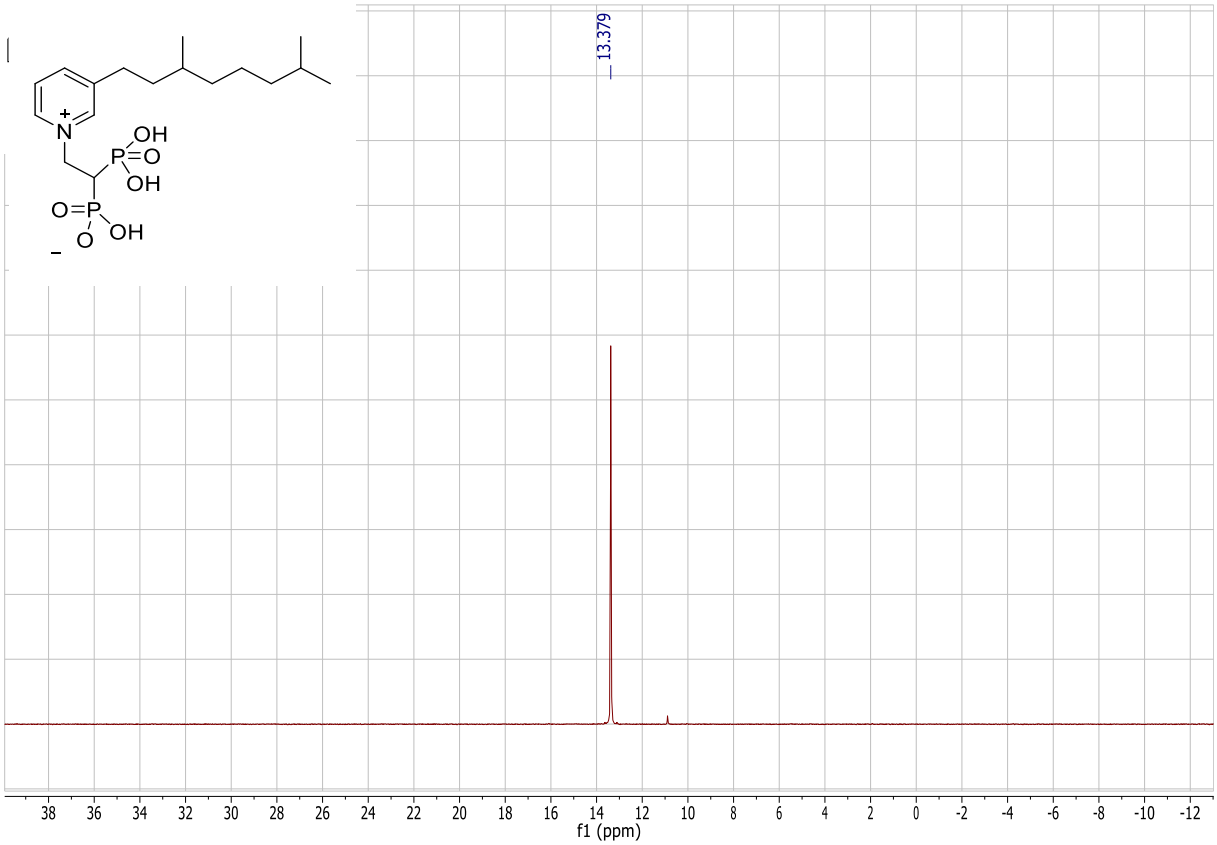
^{1}H NMR IM-46



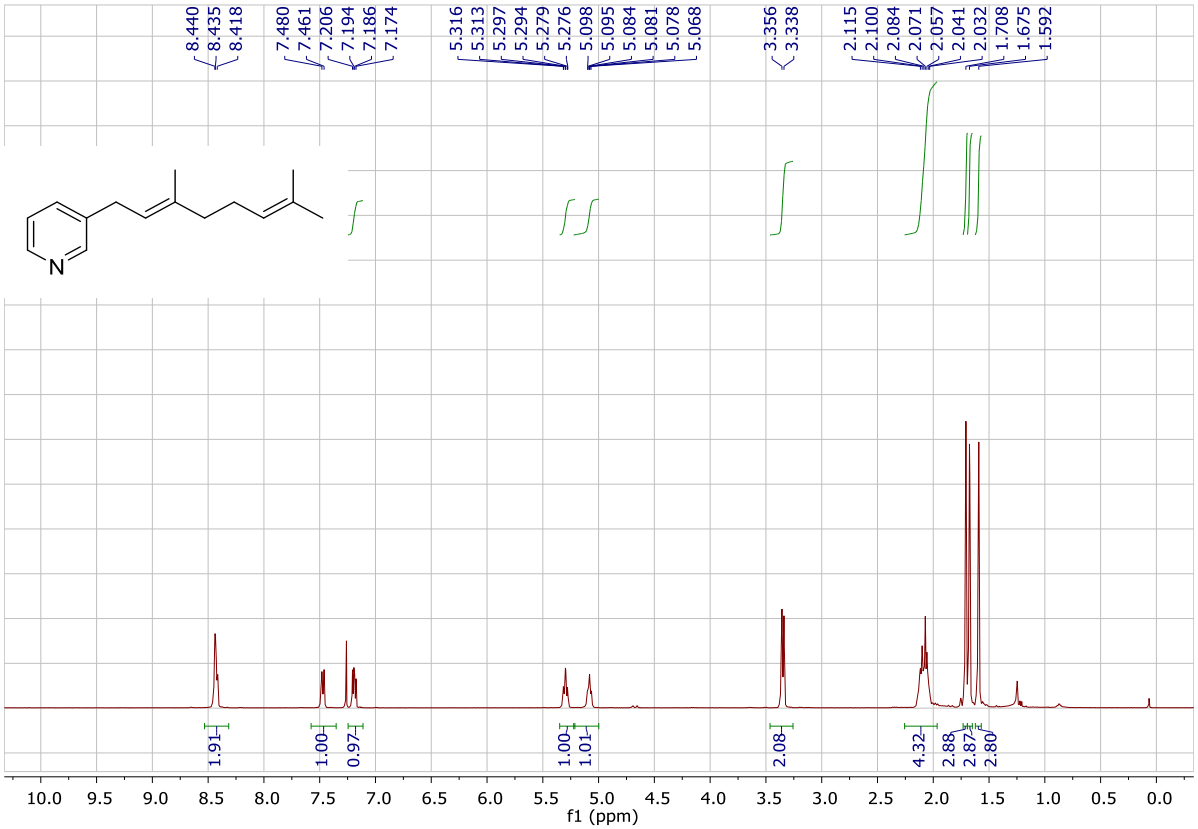
^{1}H NMR **102**



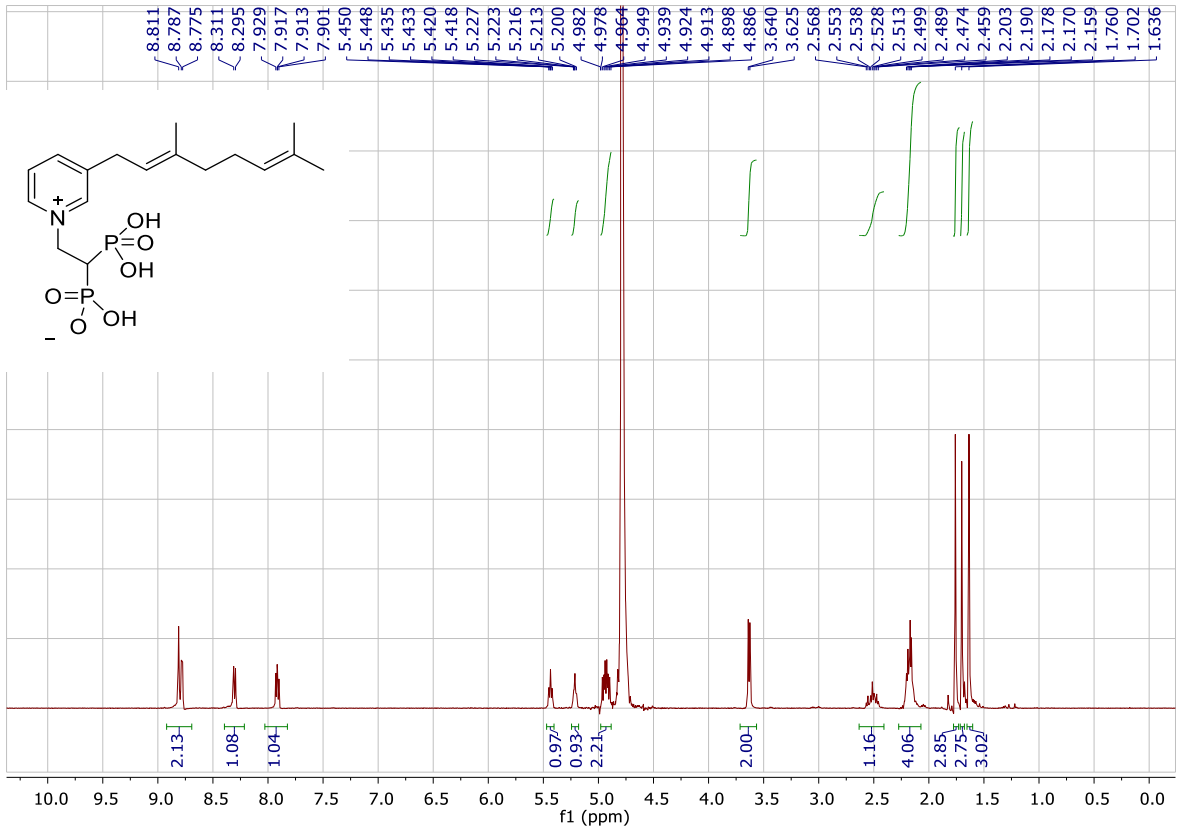
^{31}P NMR **102**



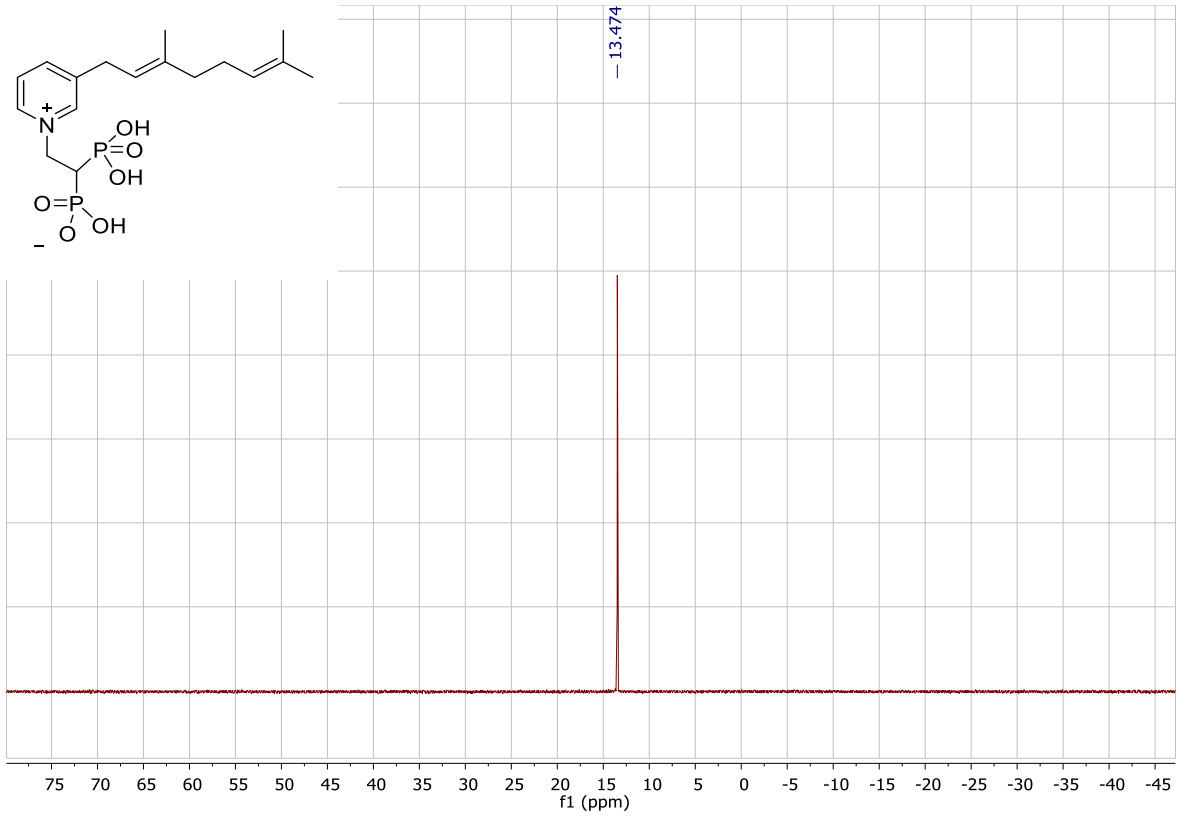
^{1}H NMR **IM-47**



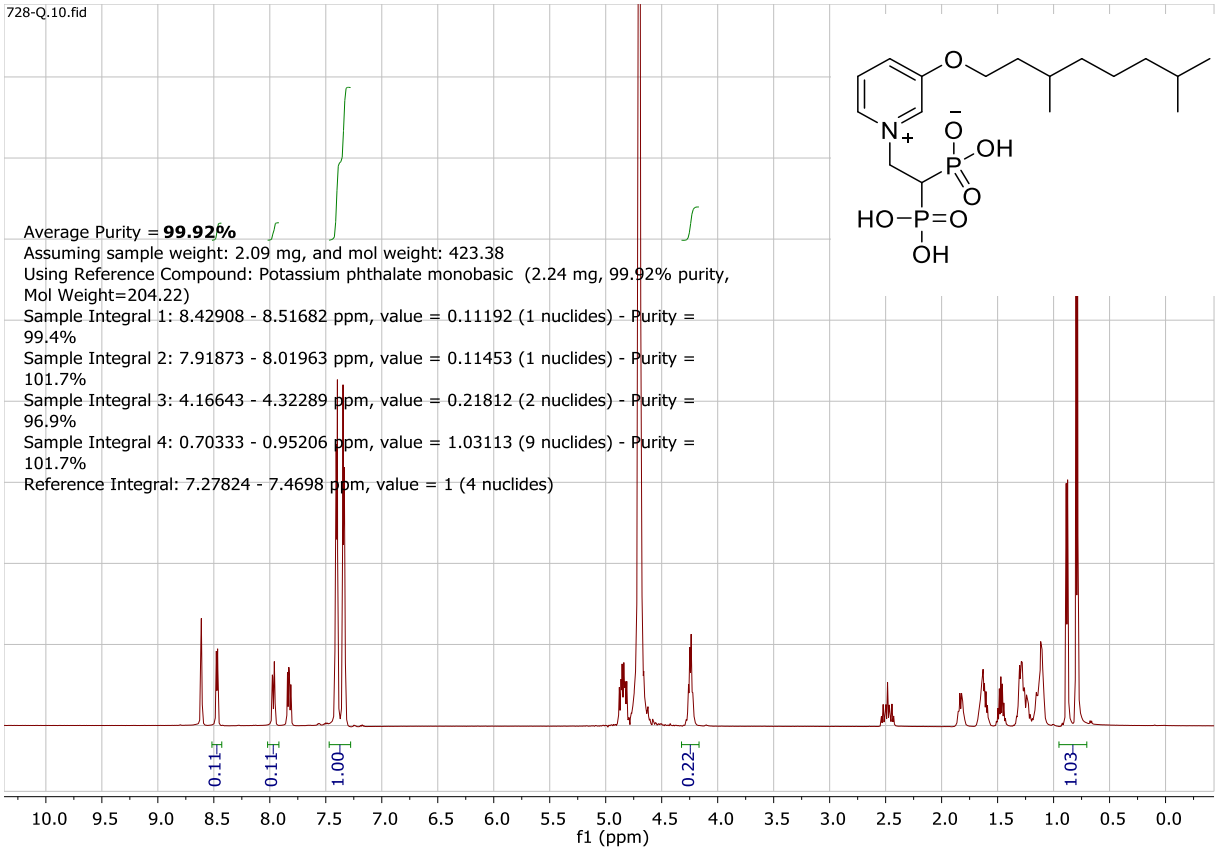
^{1}H NMR **103**



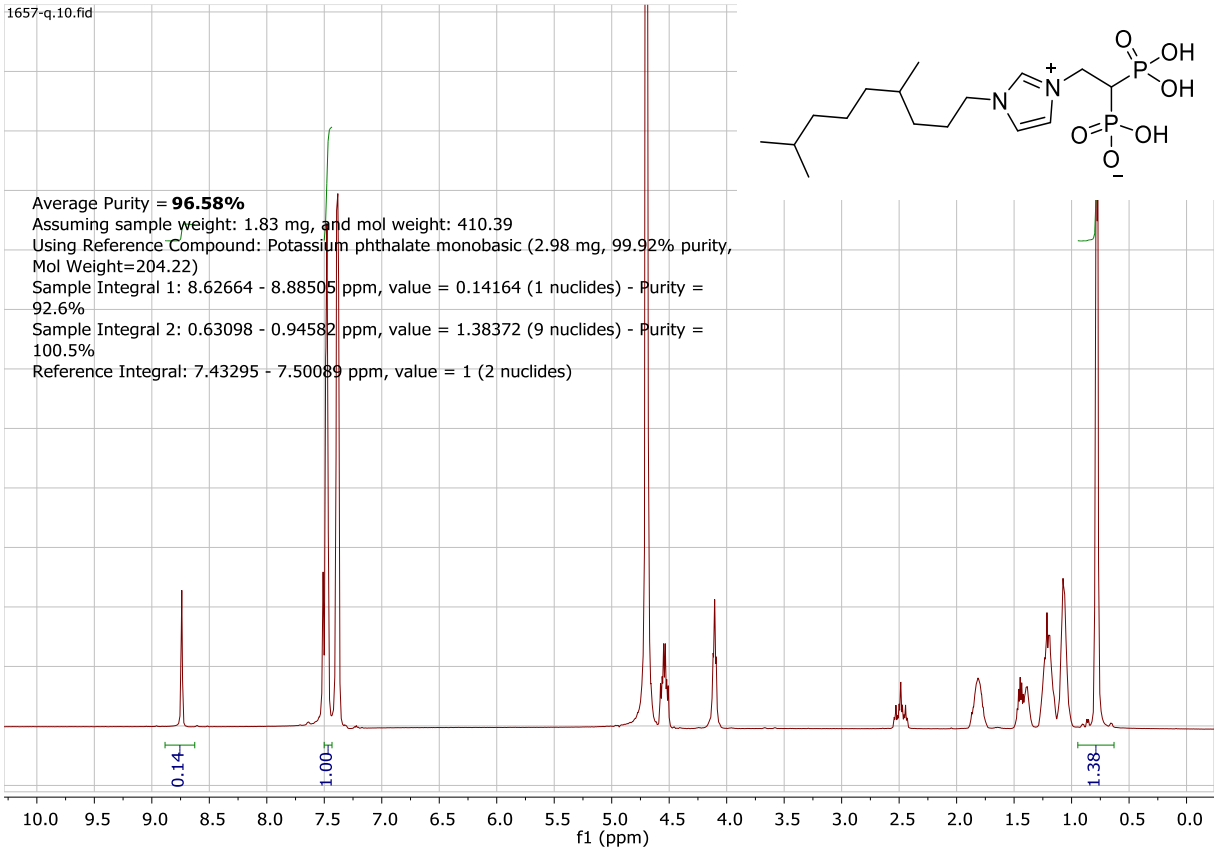
^{31}P NMR **103**



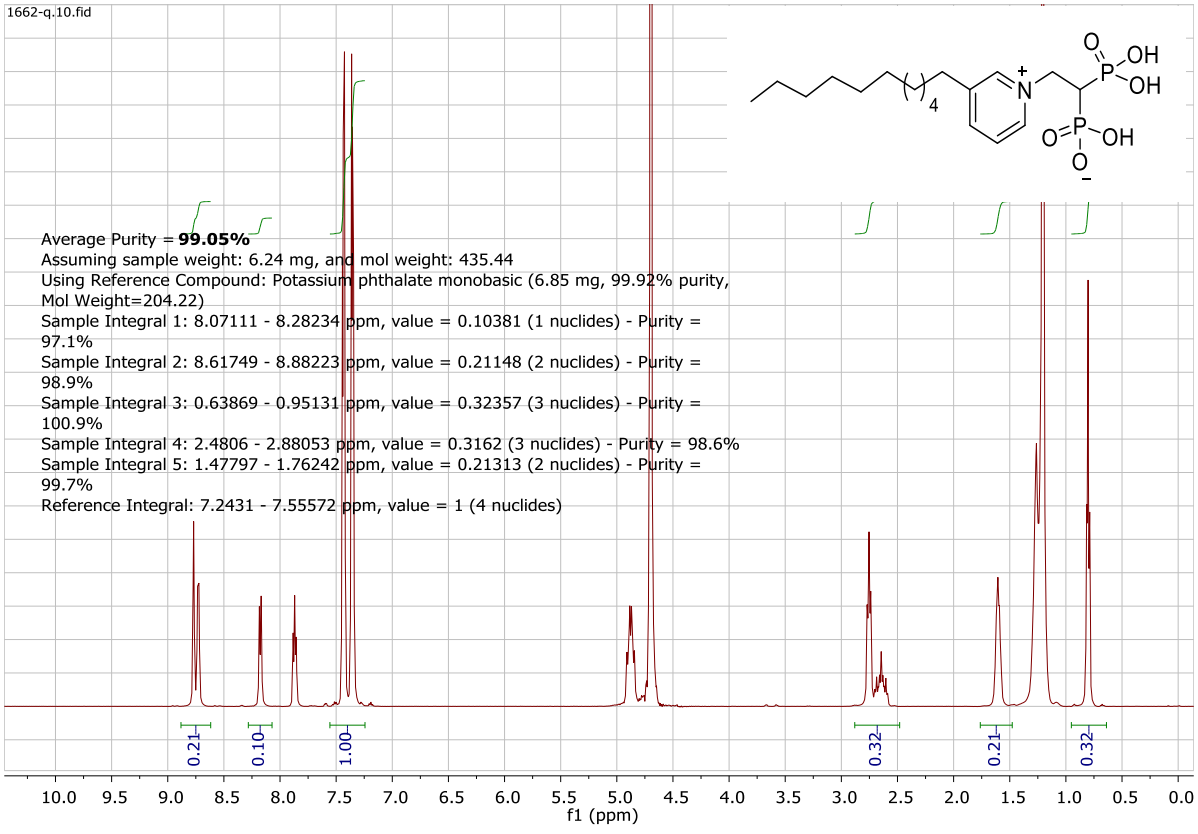
qNMR **74**



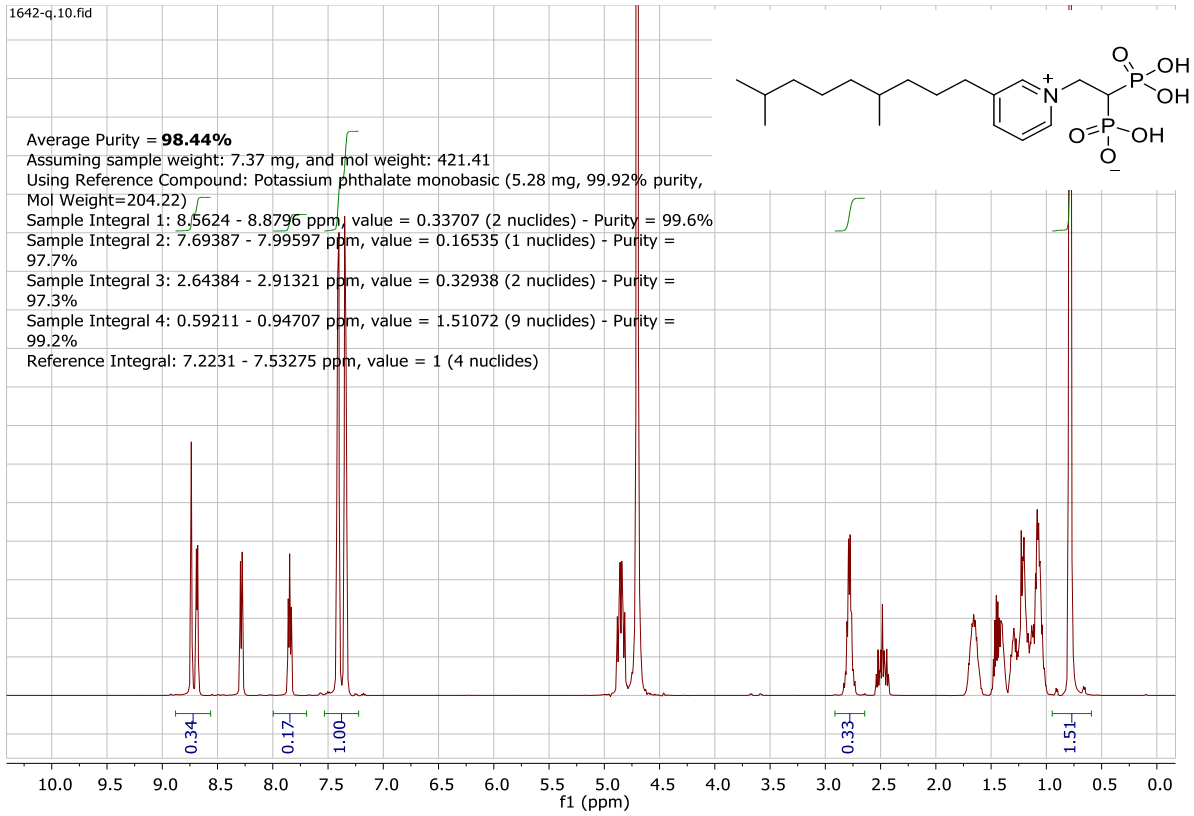
qNMR **75**



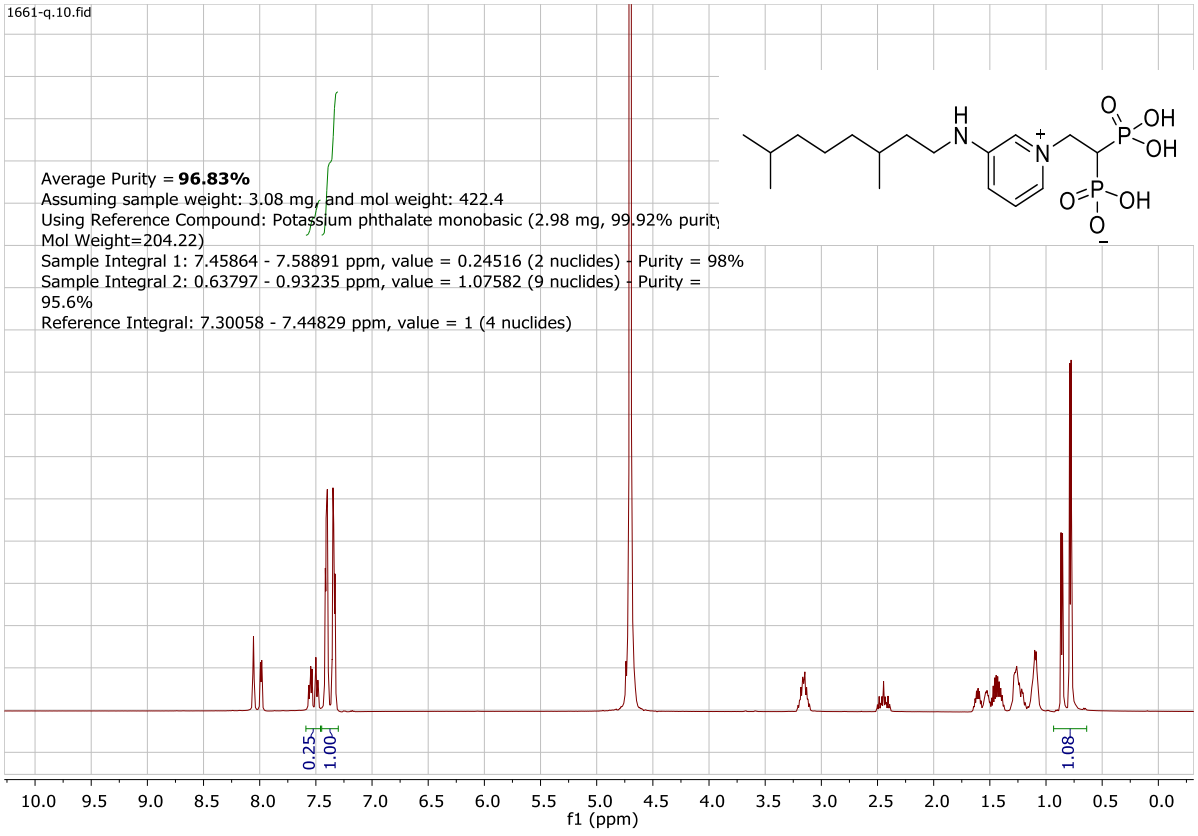
qNMR **76**



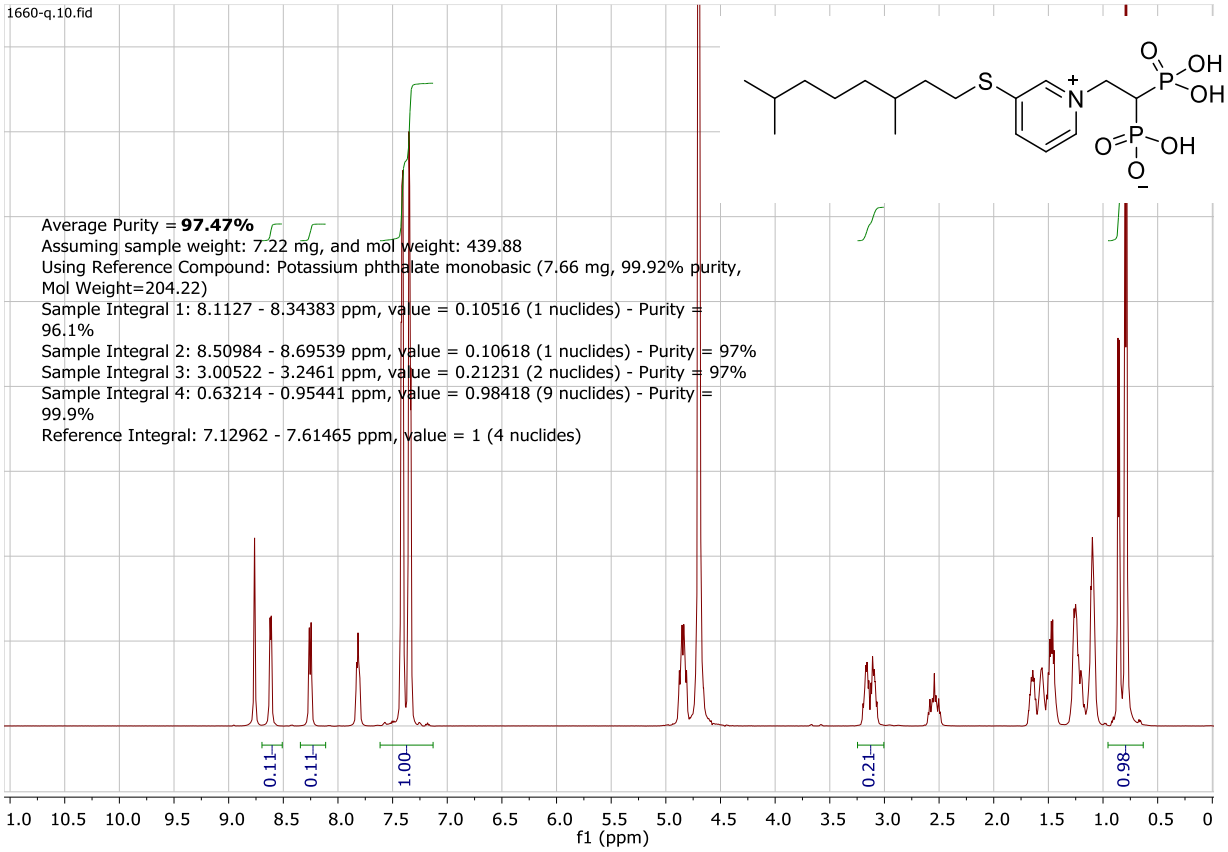
qNMR **77**



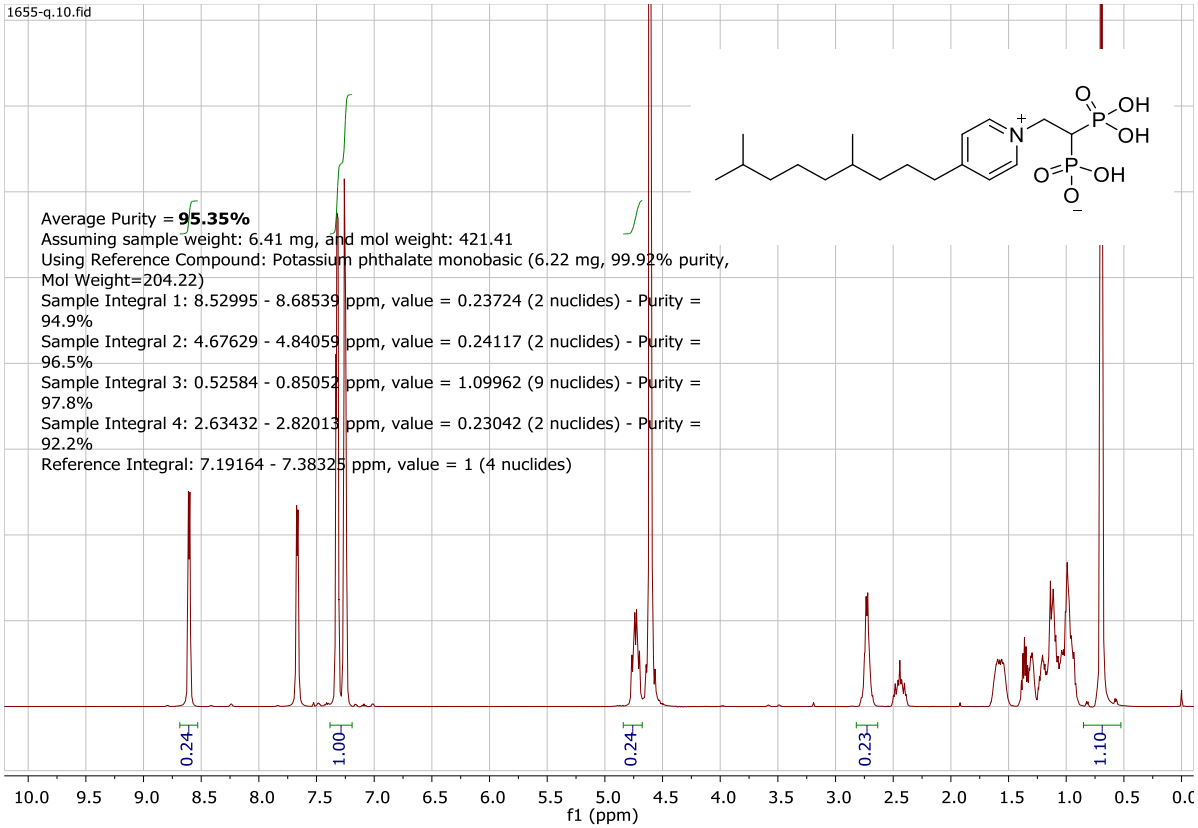
qNMR **78**



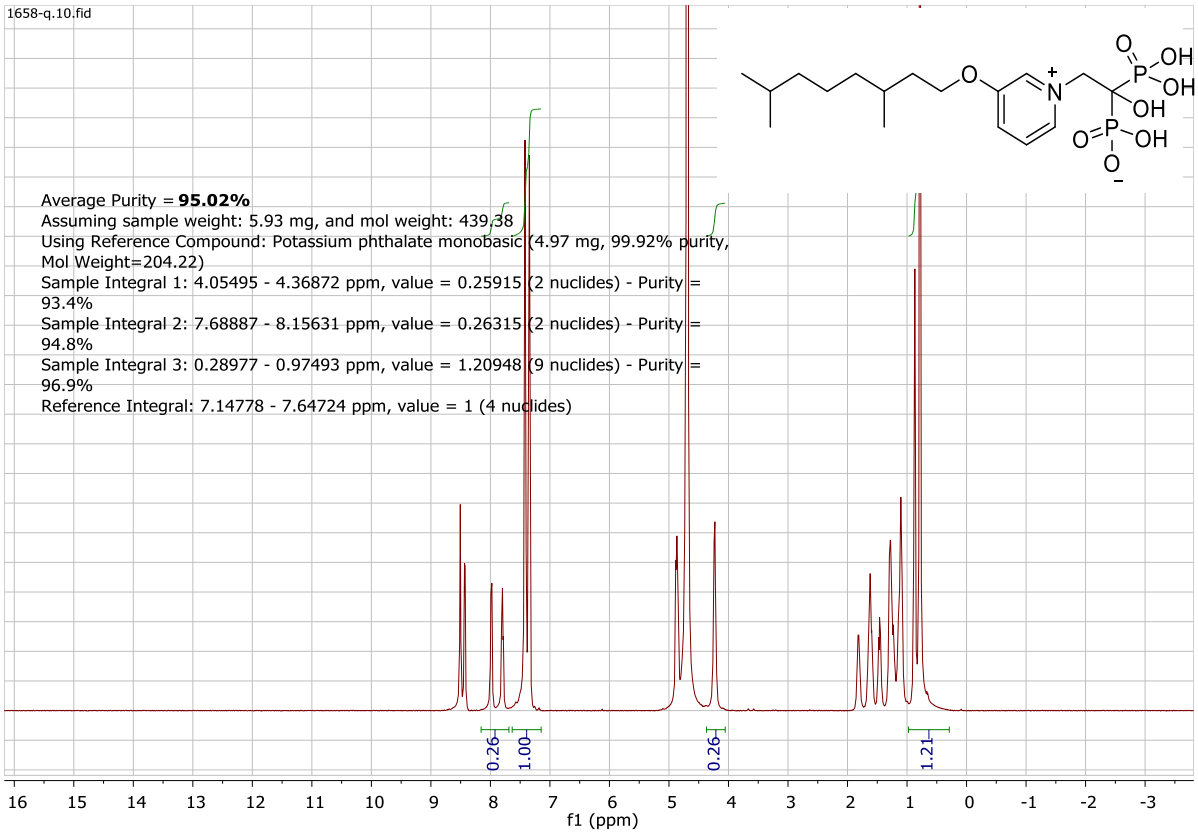
qNMR **79**



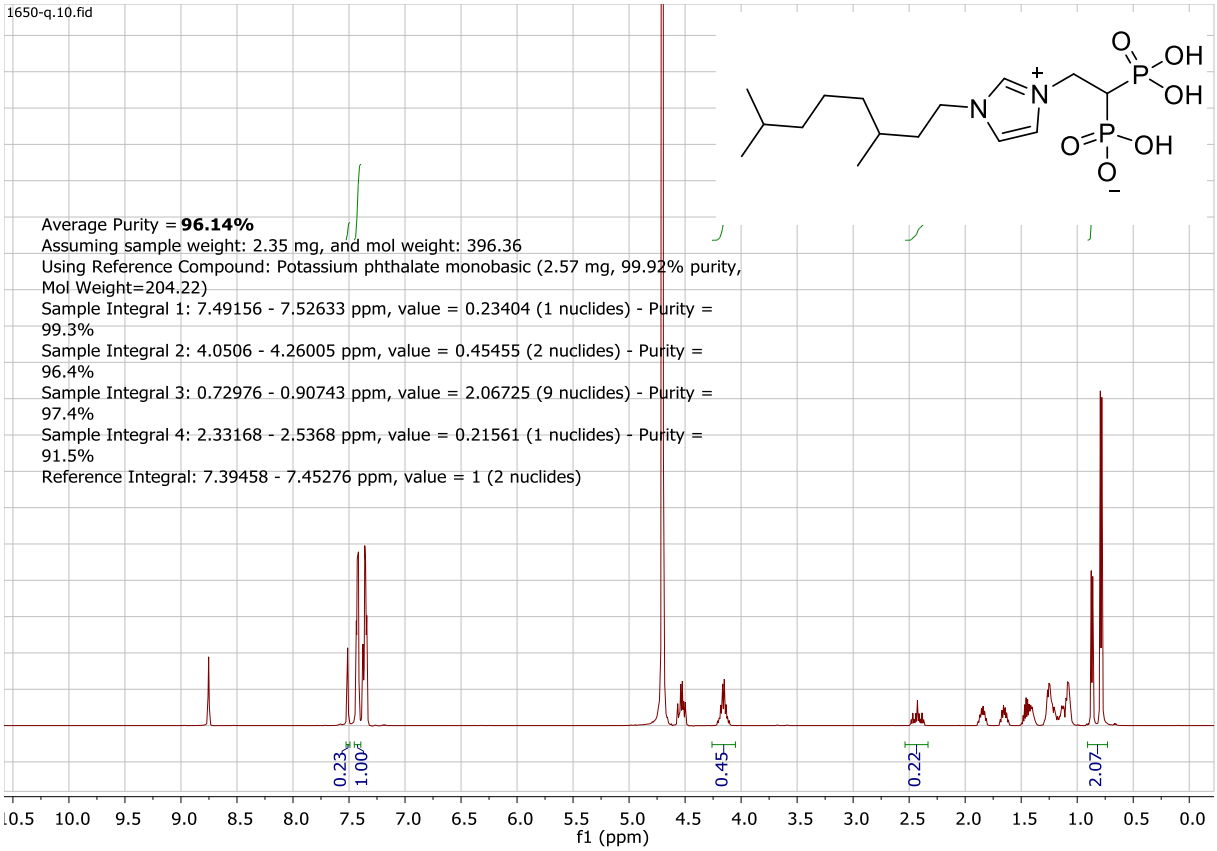
qNMR **80**



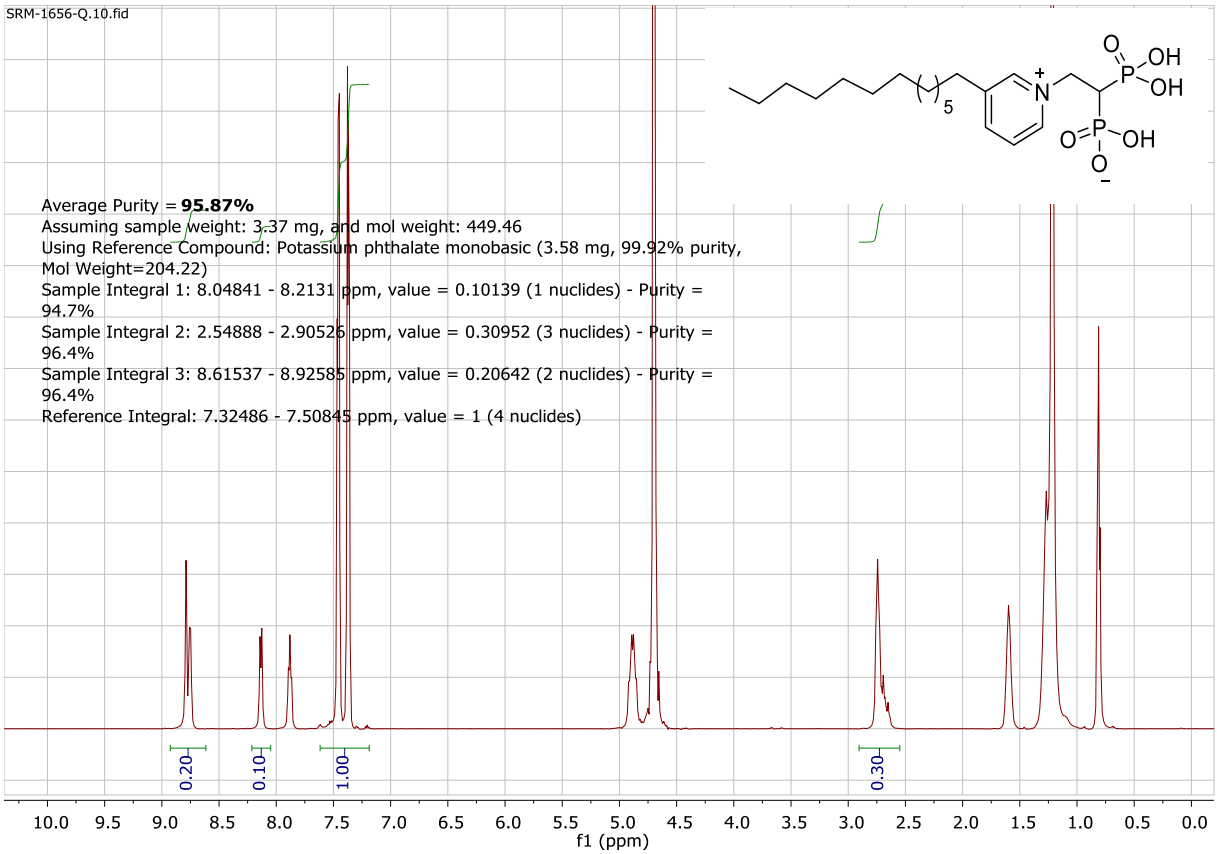
qNMR **81**



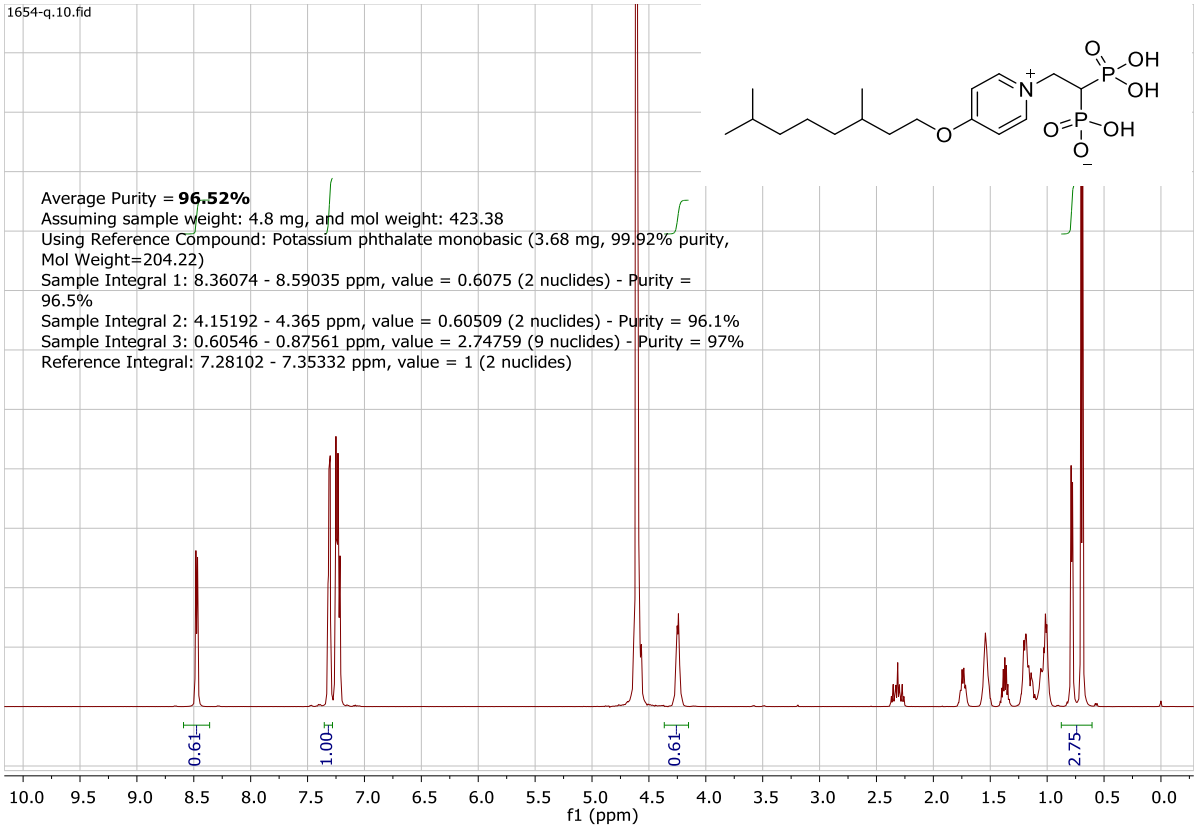
qNMR **82**



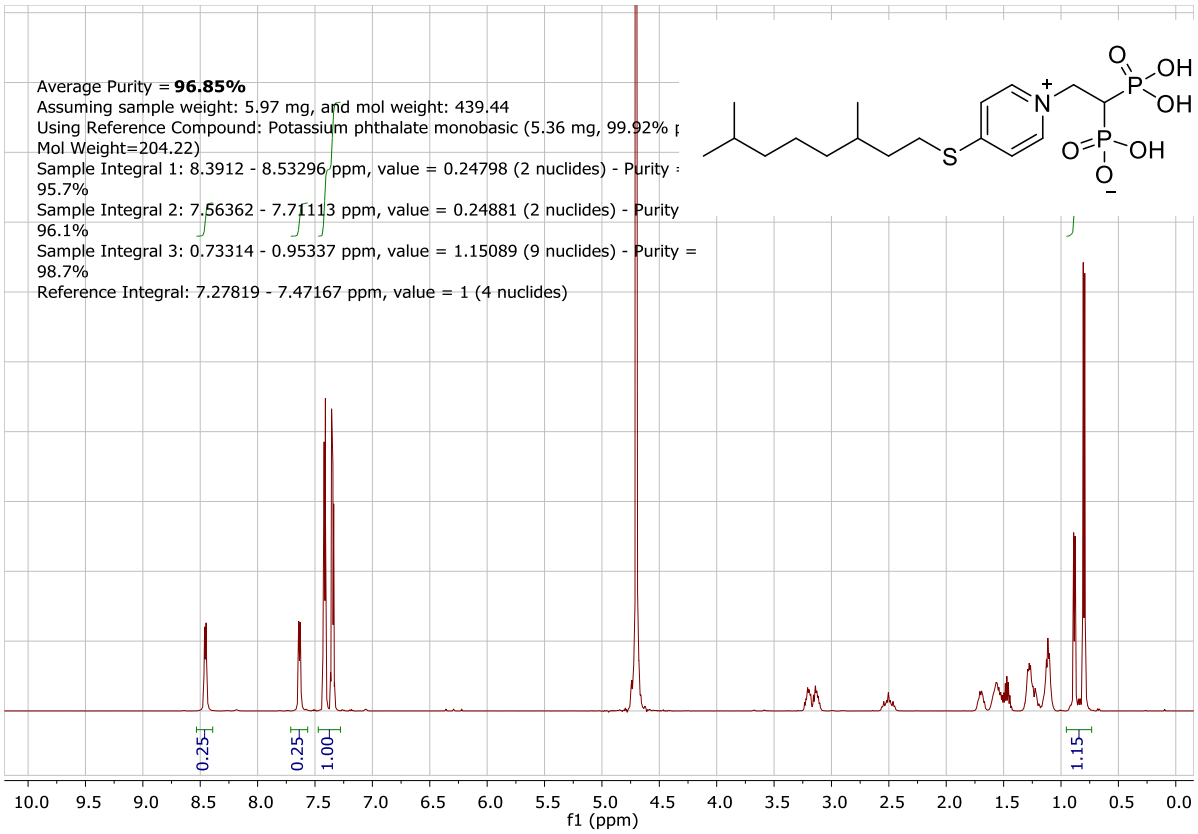
qNMR **83**



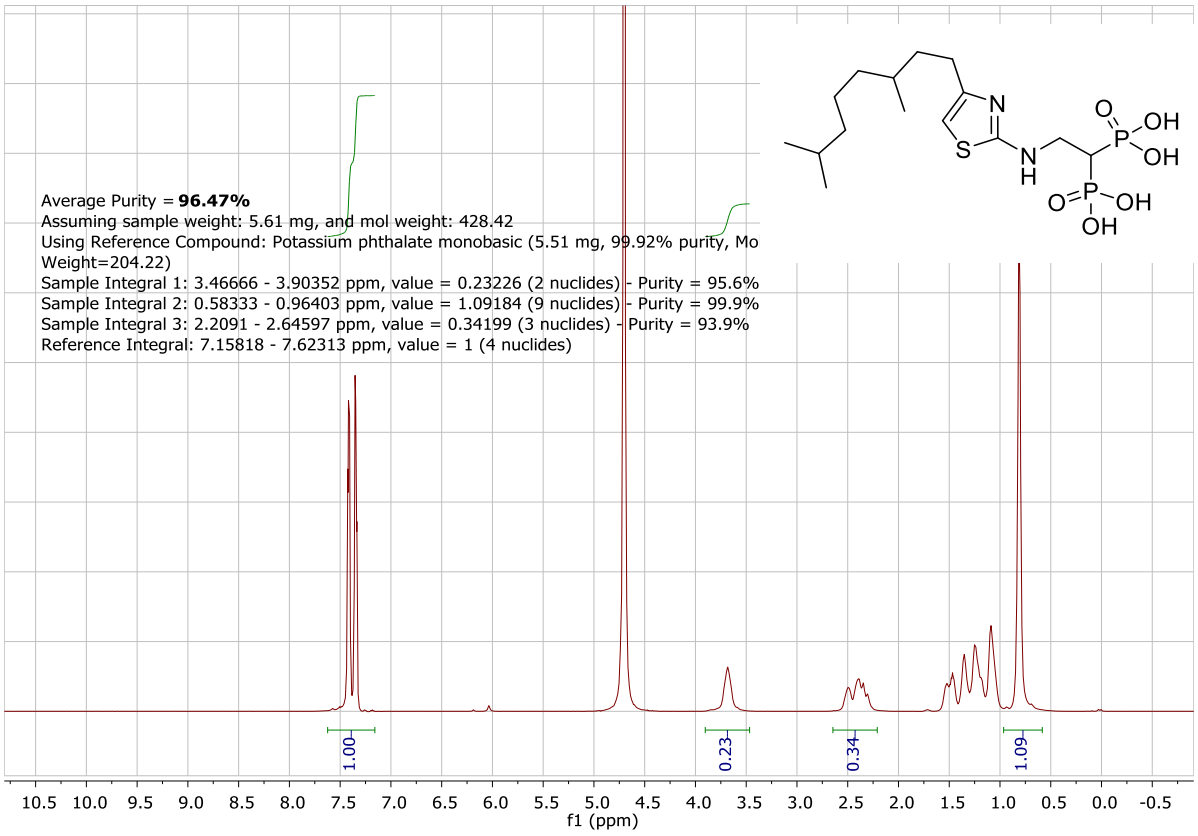
qNMR **84**



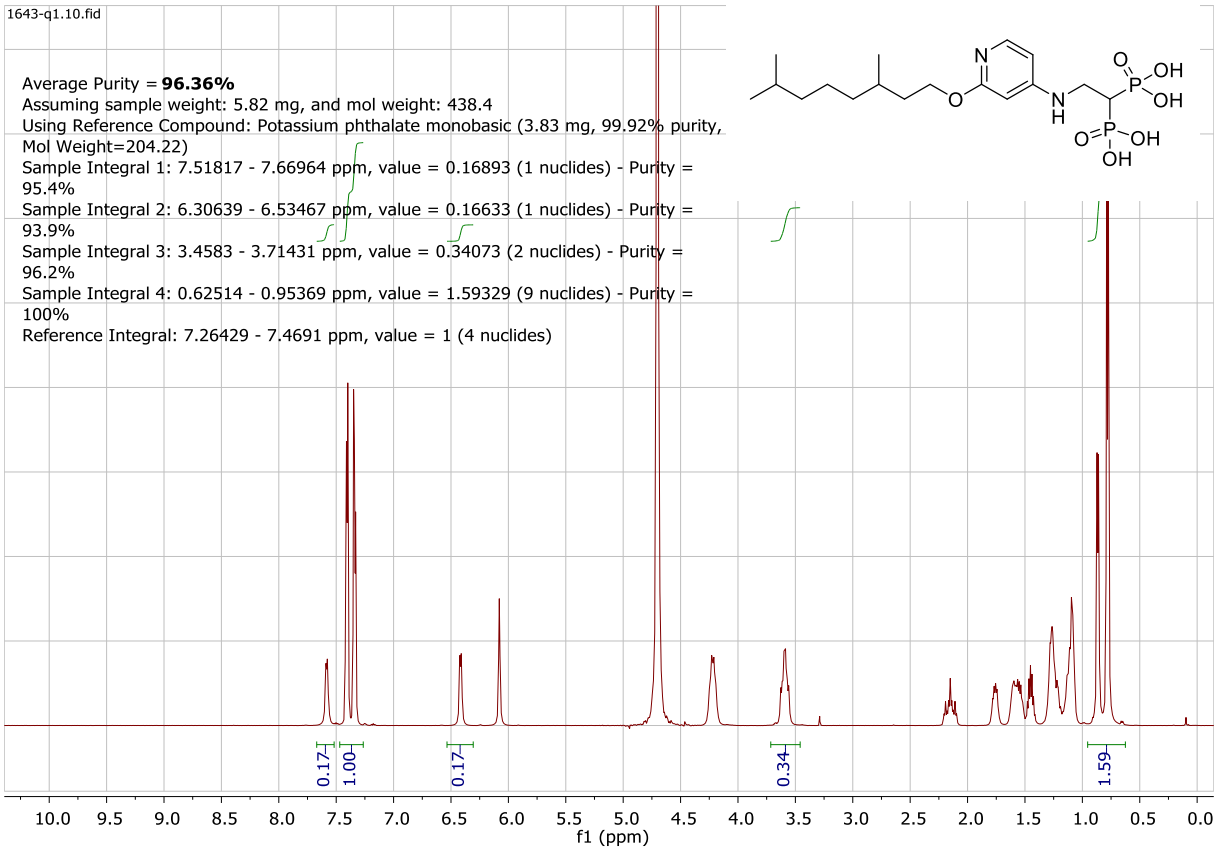
qNMR **85**



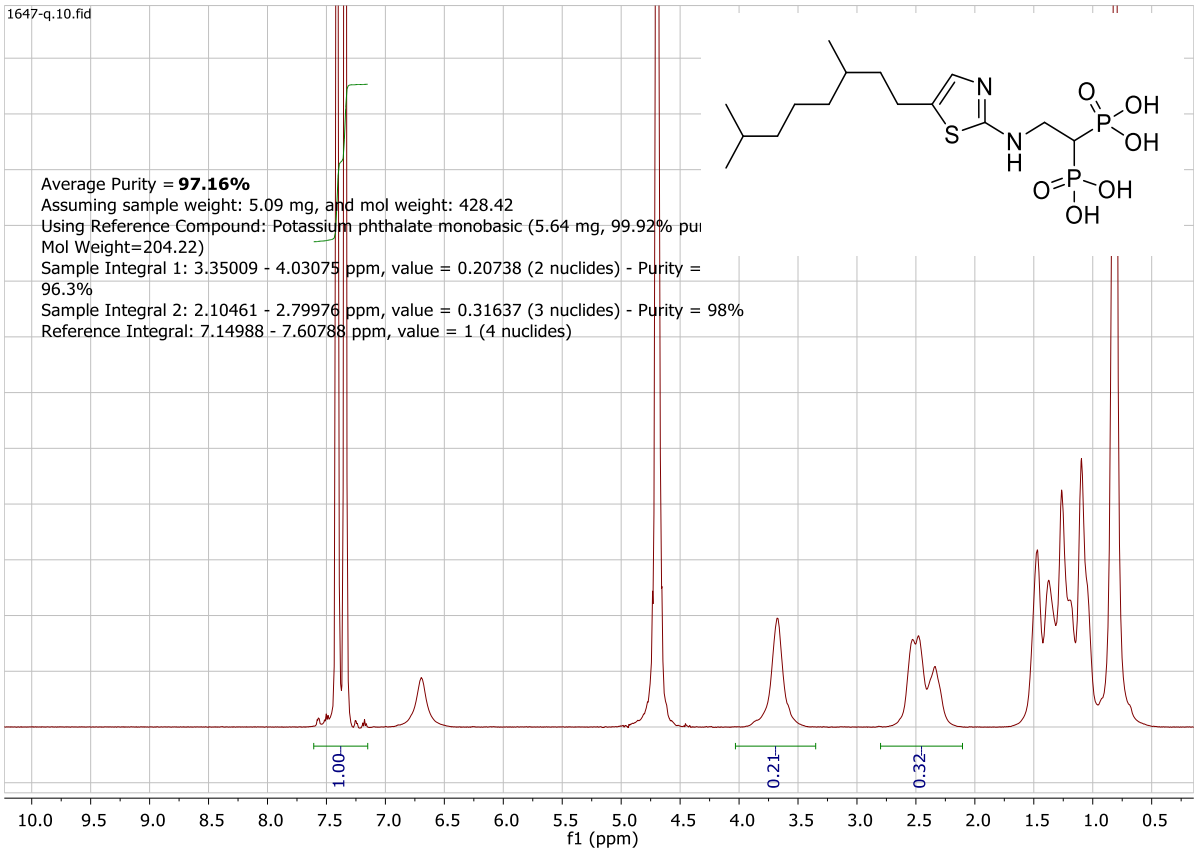
qNMR **86**



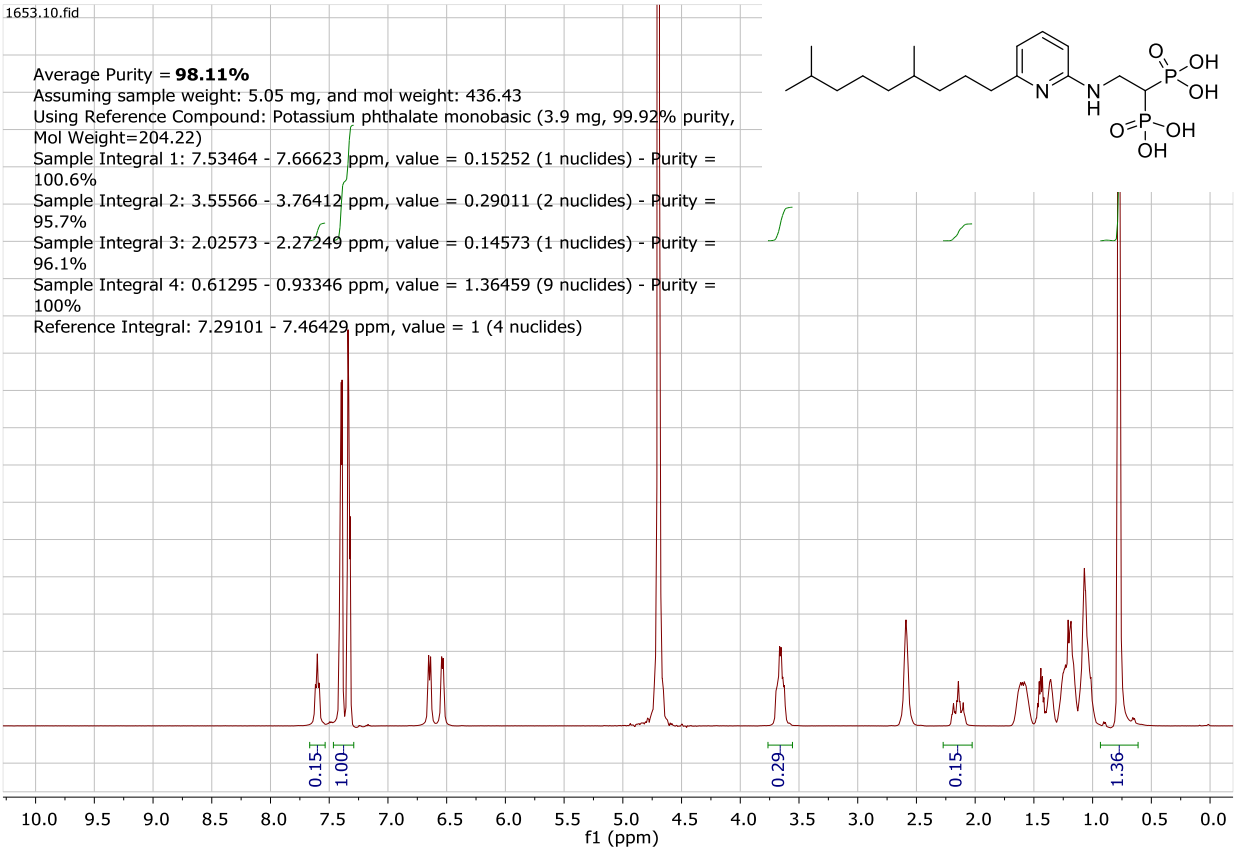
qNMR **87**



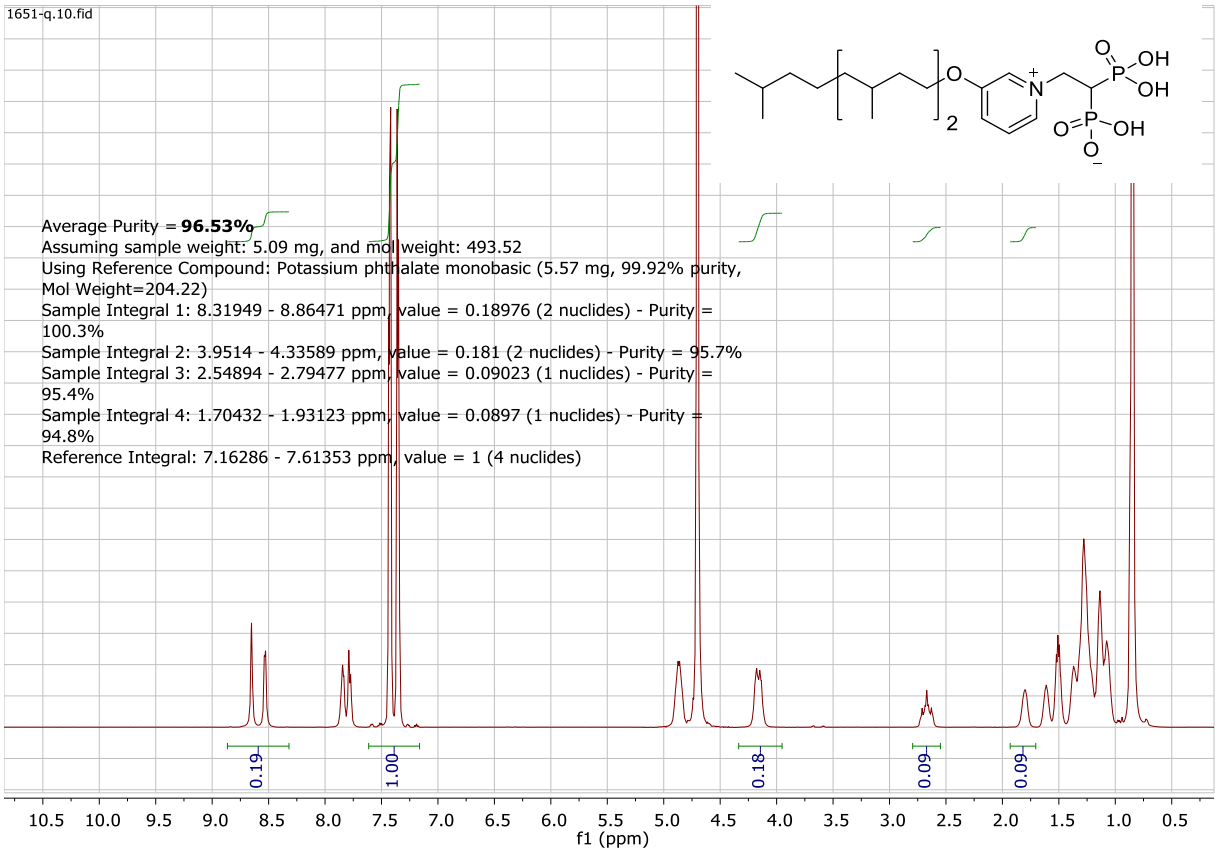
qNMR **88**



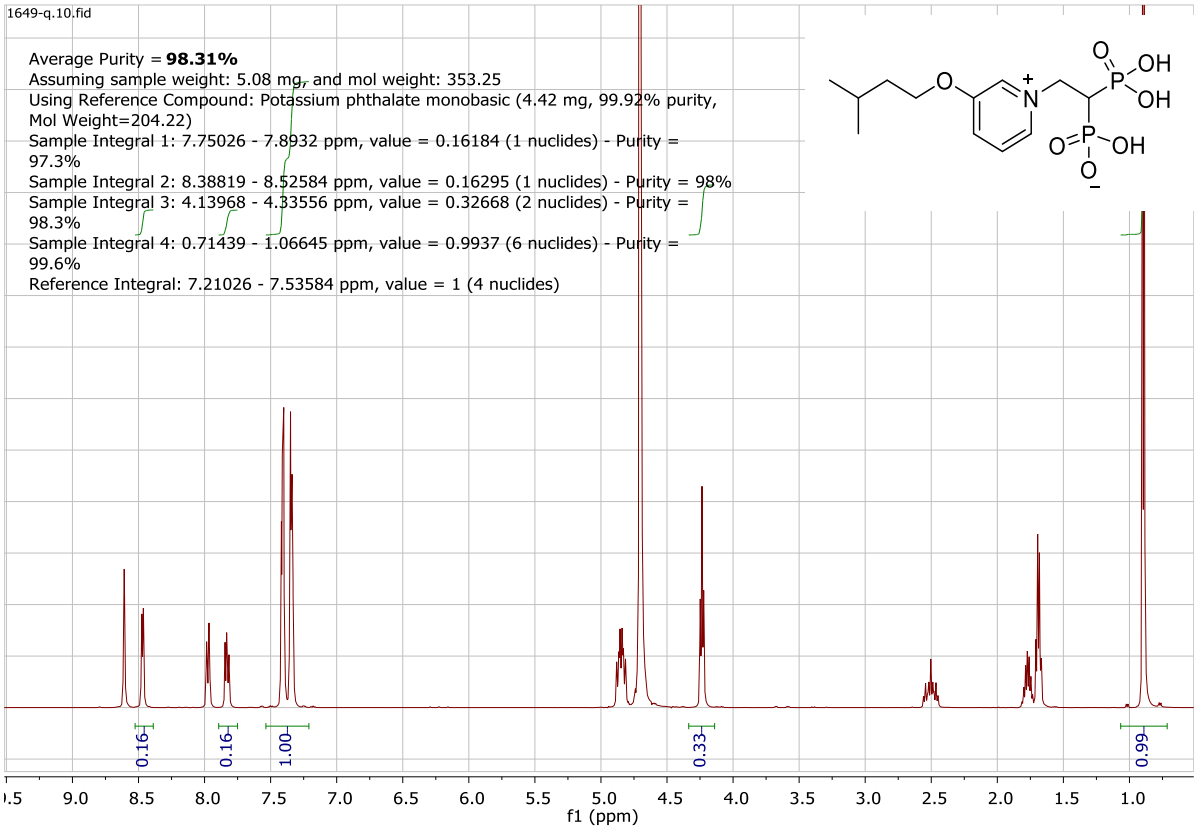
qNMR **89**



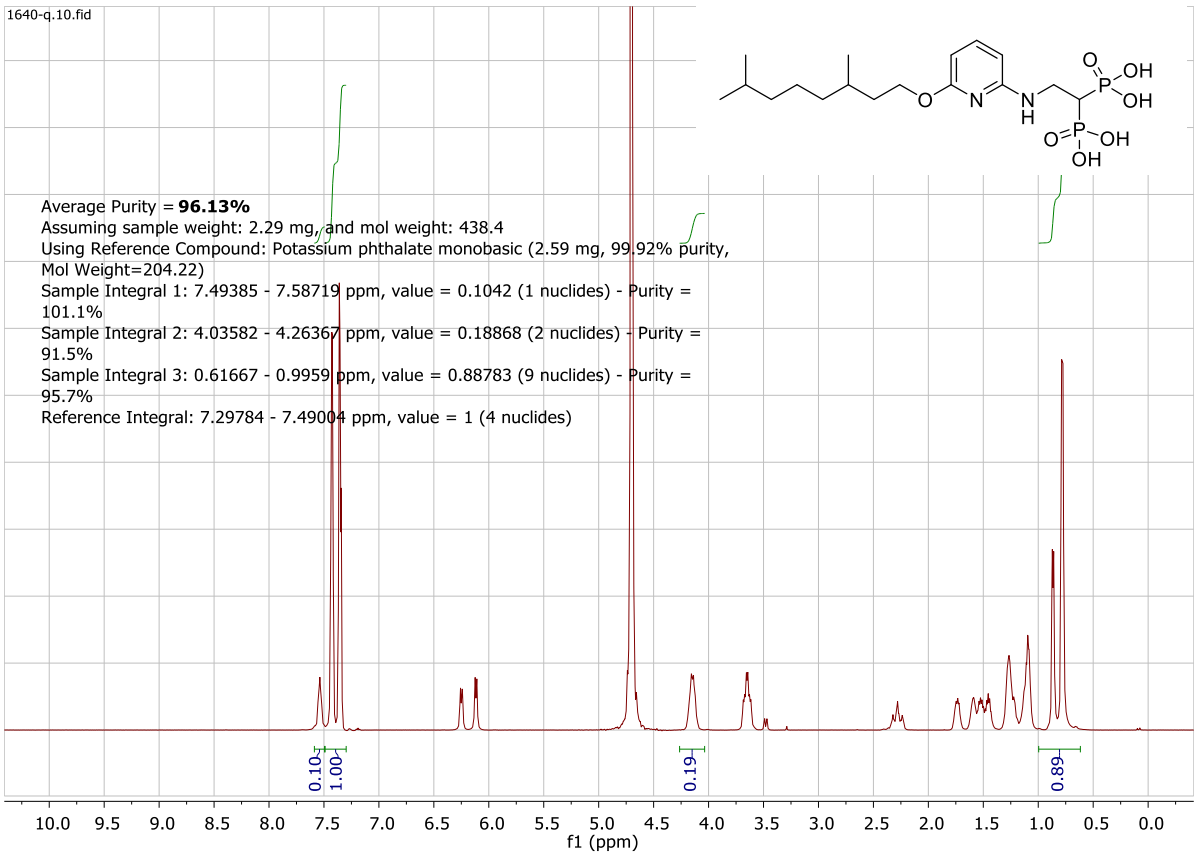
qNMR **90**



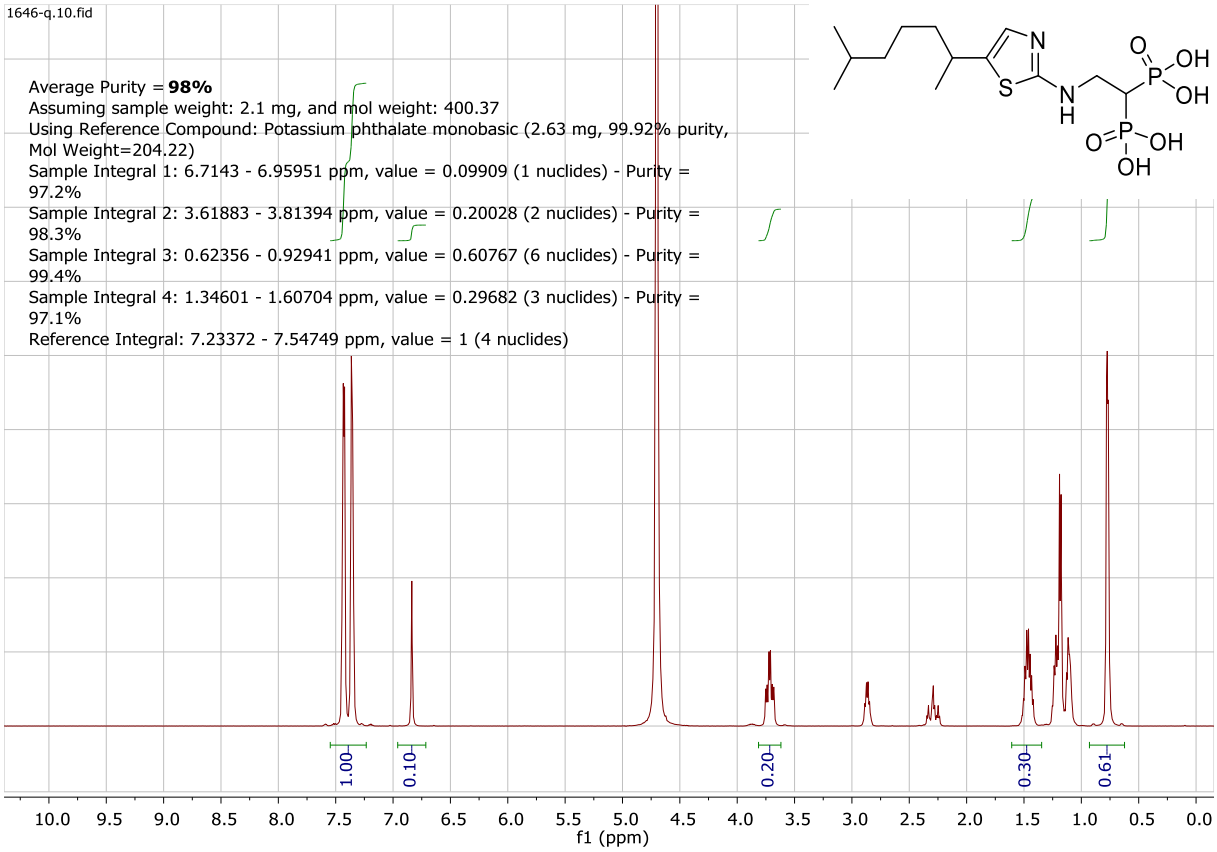
qNMR **91**



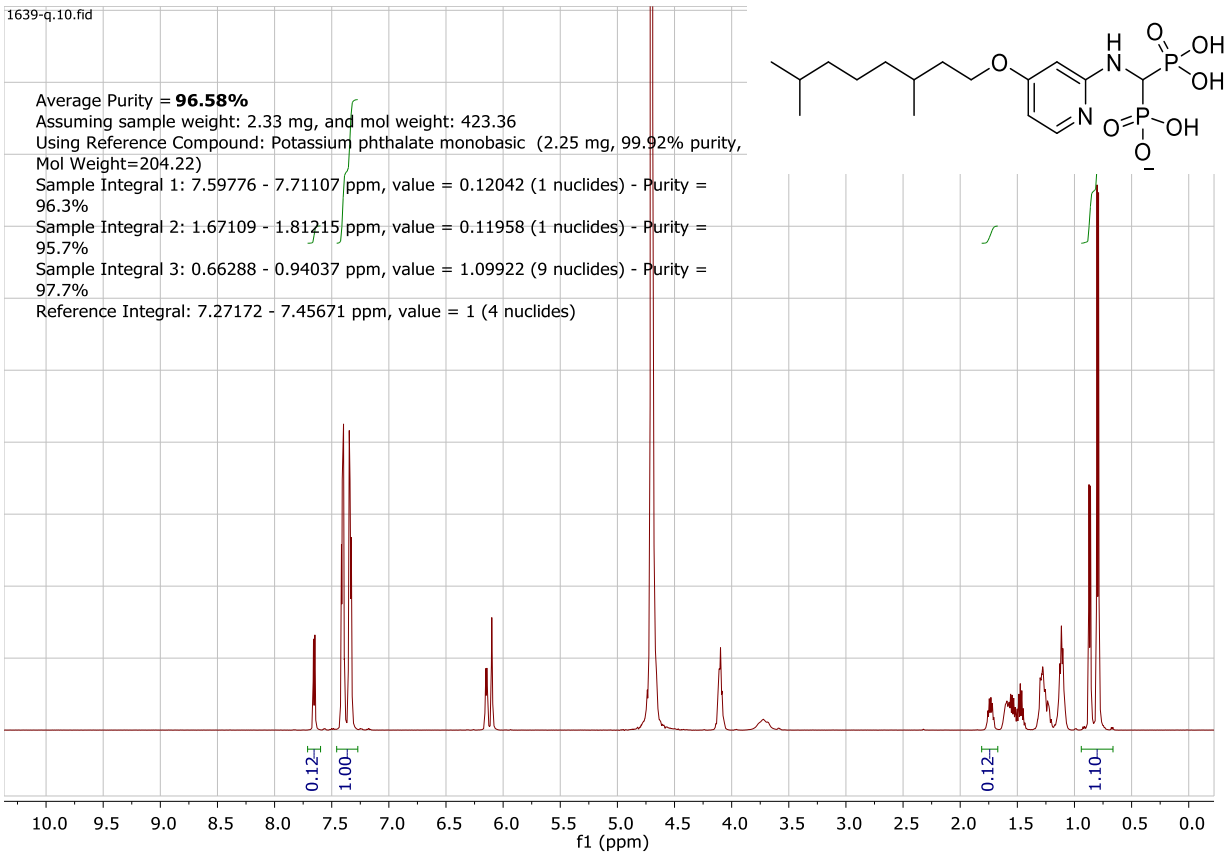
qNMR **92**



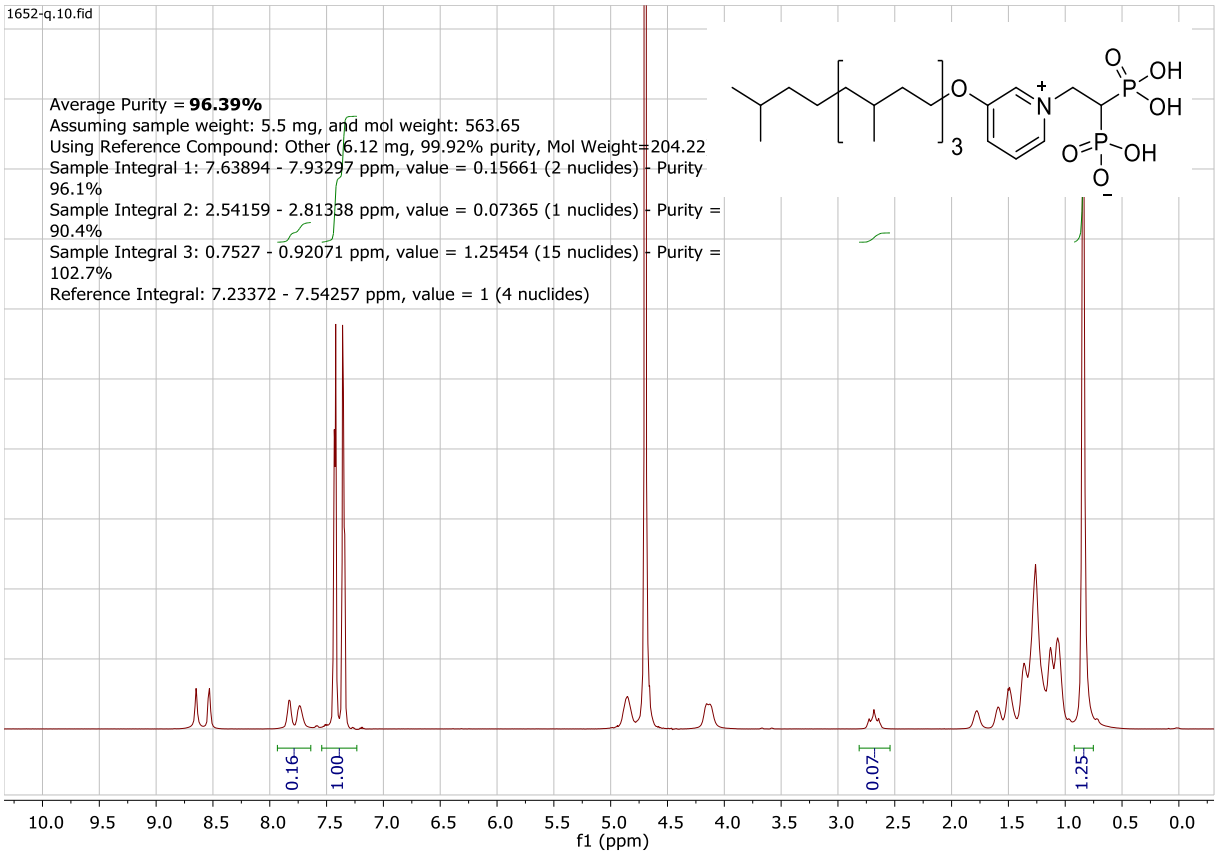
qNMR **94**



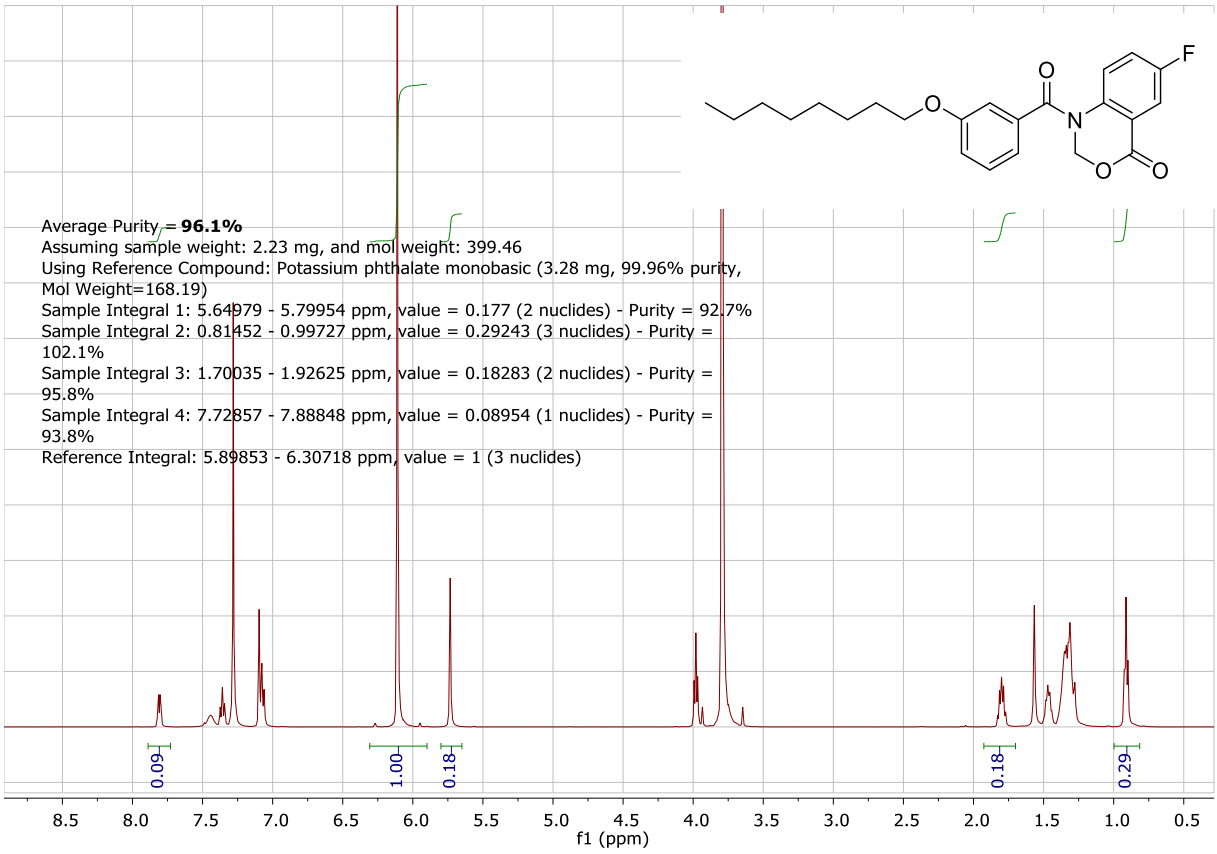
qNMR **95**



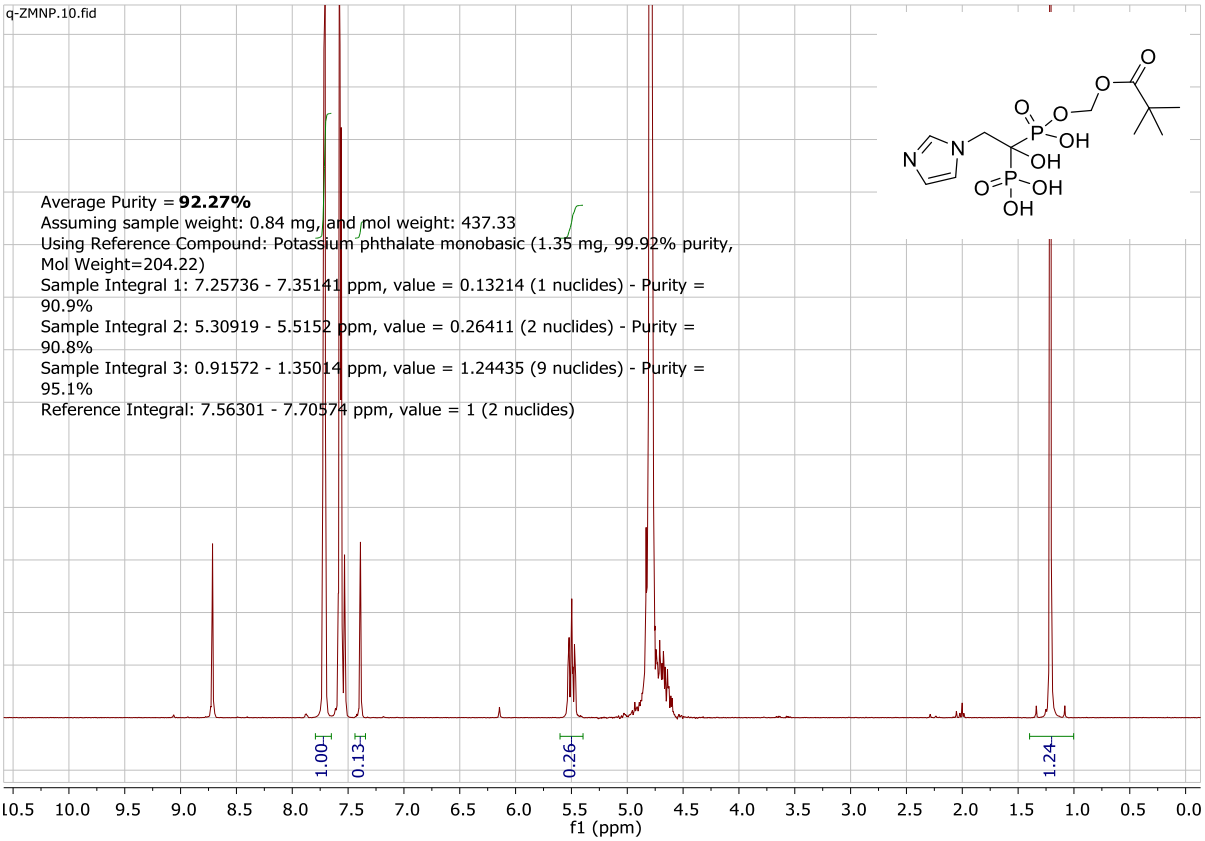
qNMR **97**



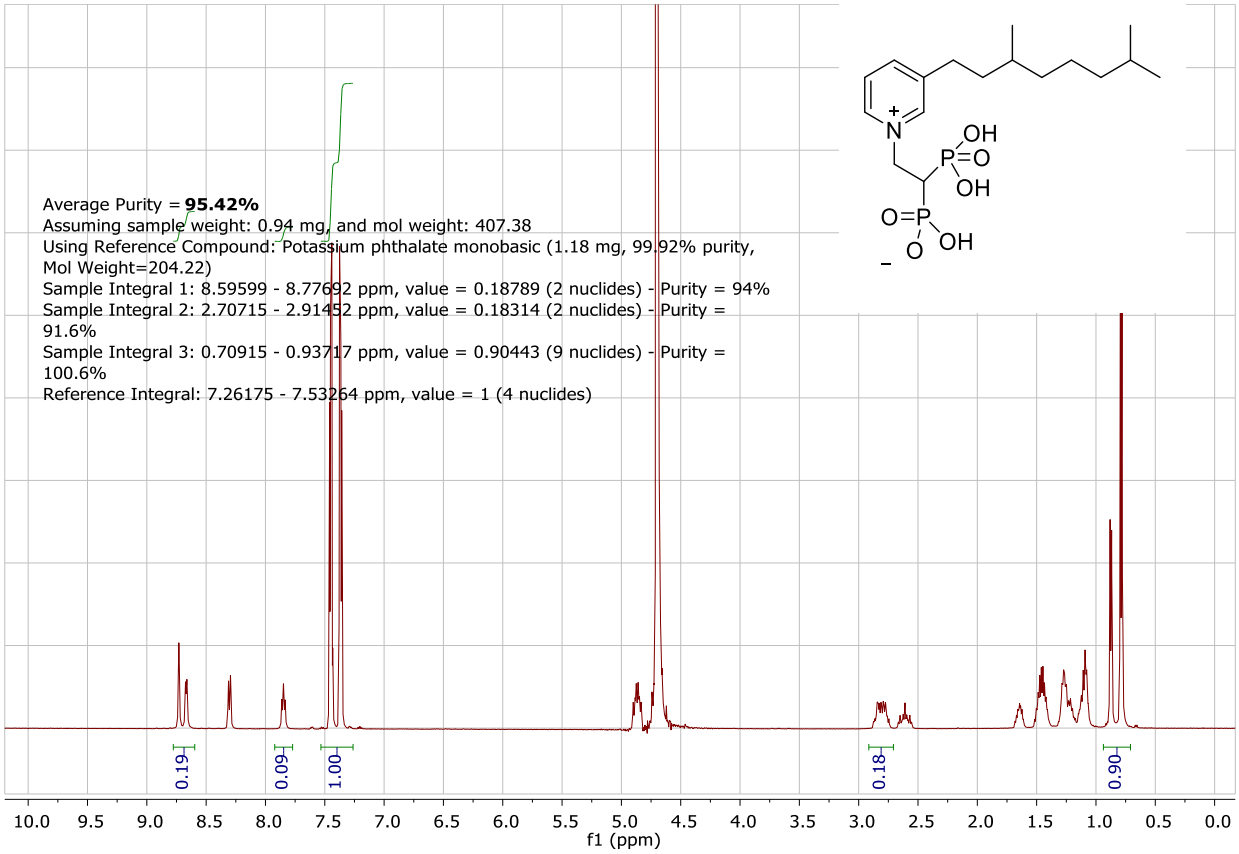
qNMR **100**



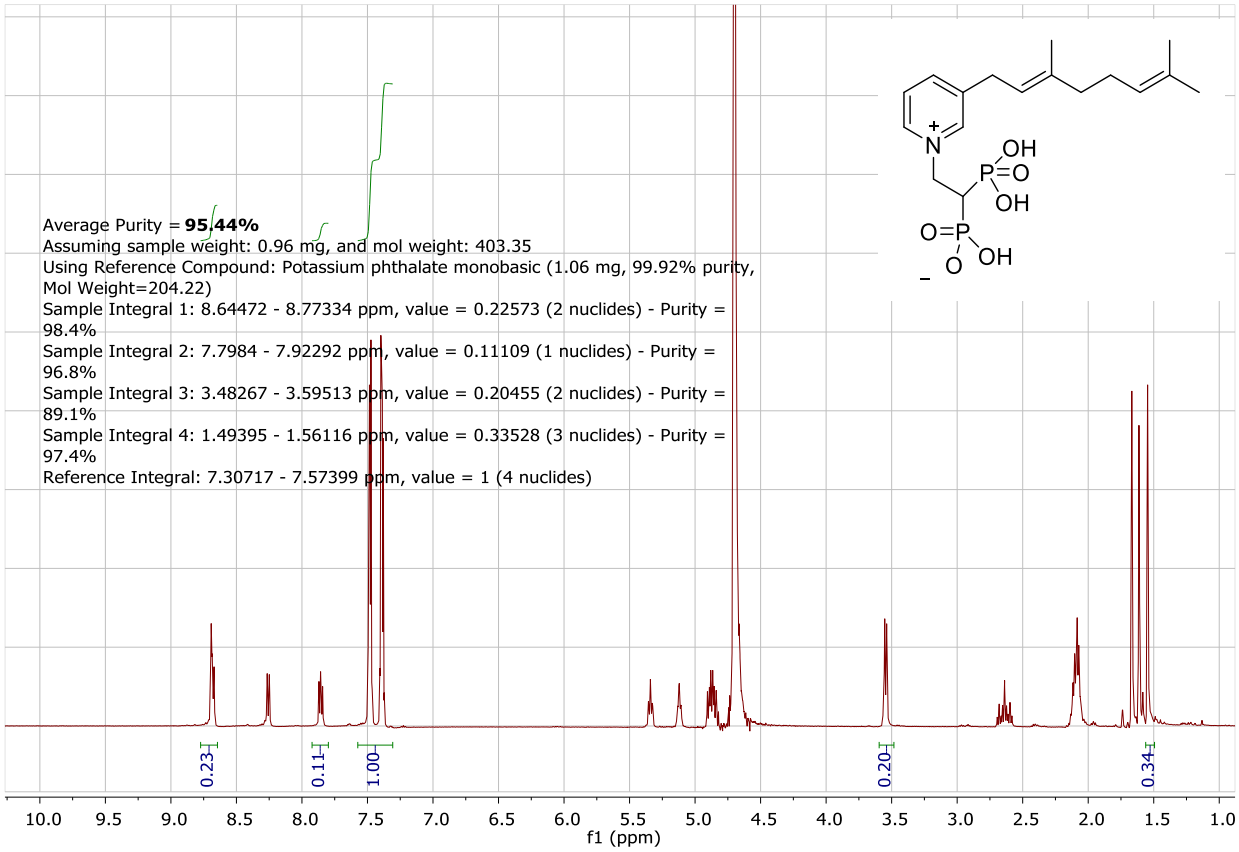
qNMR **101**



qNMR **102**

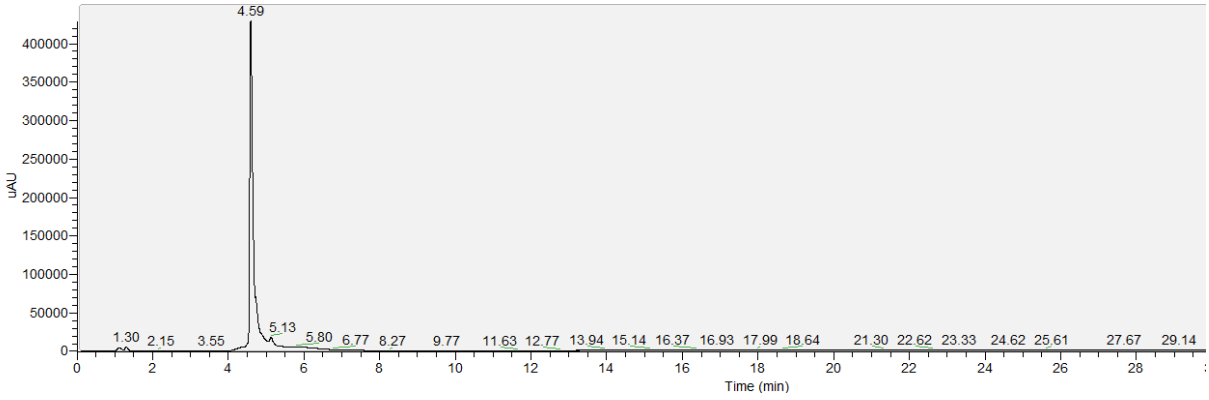


qNMR **103**



LCMS: 96

UV: 250 nm (target compound at 4.6 min).



Purity: 98.1%.