---------- SUPPLEMENTARY INFORMATION ----------

Design and synthesis of non-hydroxamate lipophilic inhibitors of 1-deoxy-D-xylulose 5-phosphate reductoisomerase (DXR): in silico, in vitro and antibacterial studies

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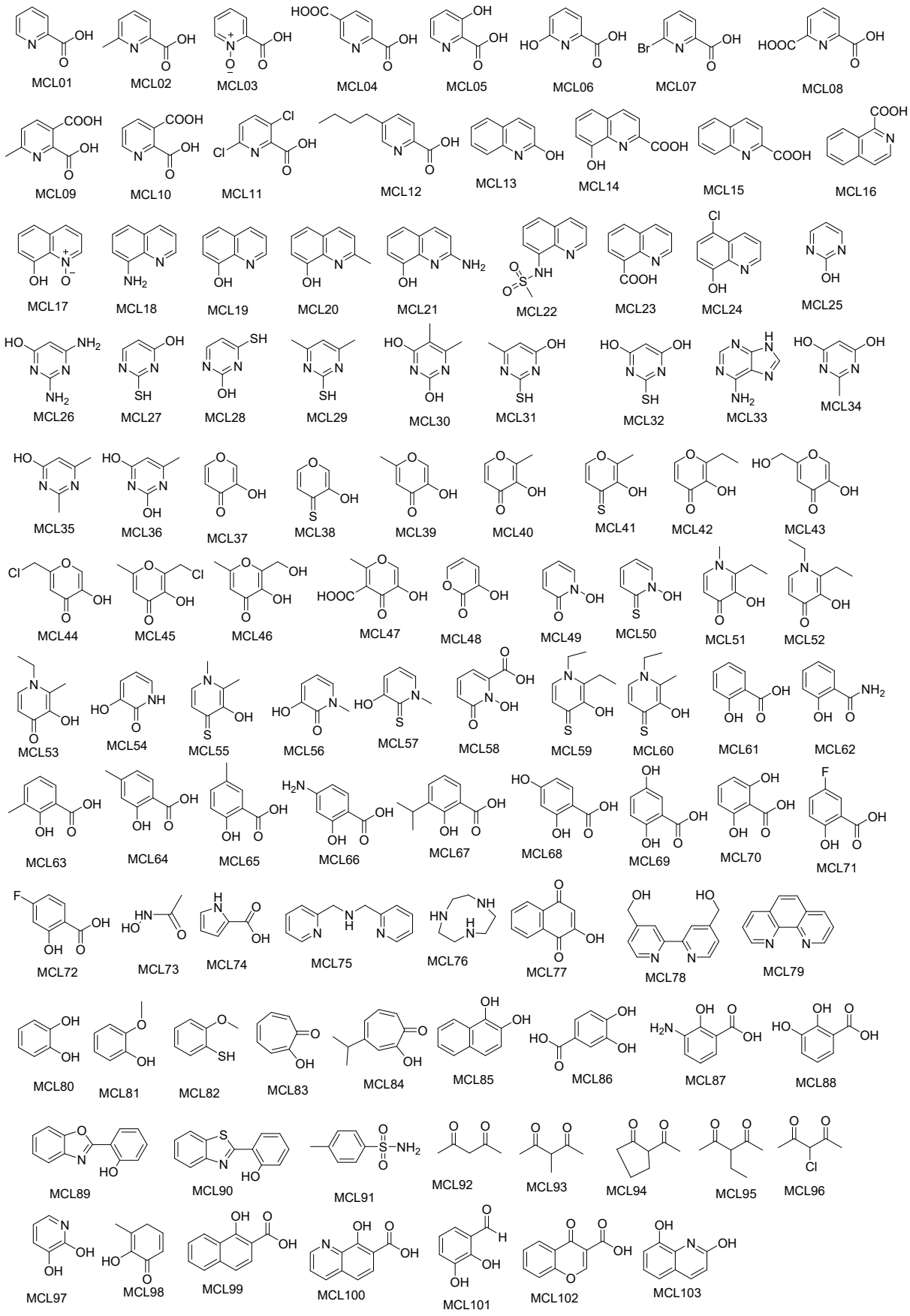


Figure S1. Structure of fragments in MCL

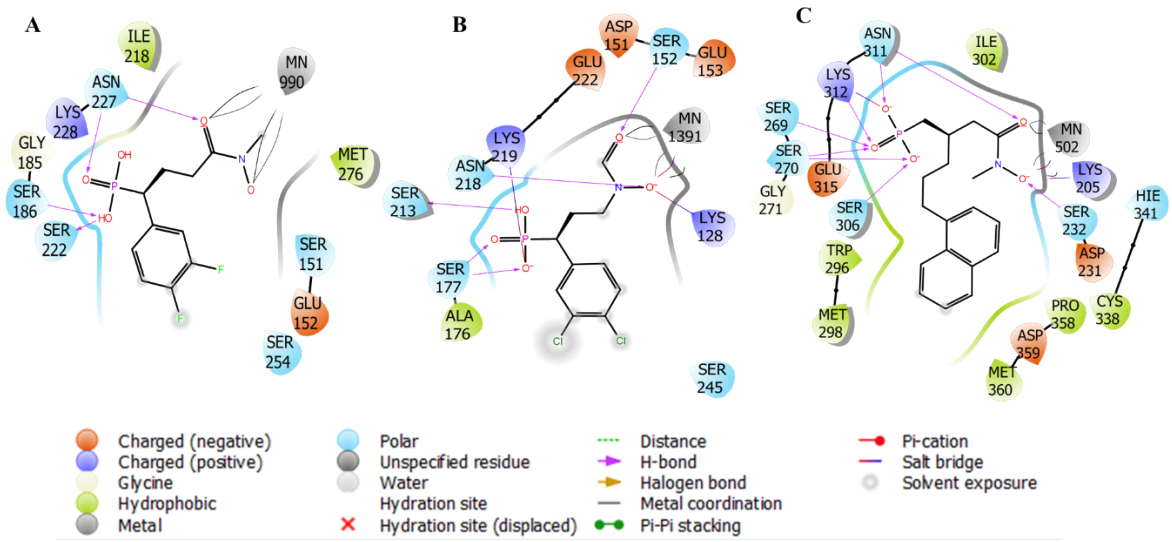


Figure S2. Interactions of the cocrystallized ligands at the binding site of (A) 3R0I (B) 2Y1D (B), and (C) 5JAZ

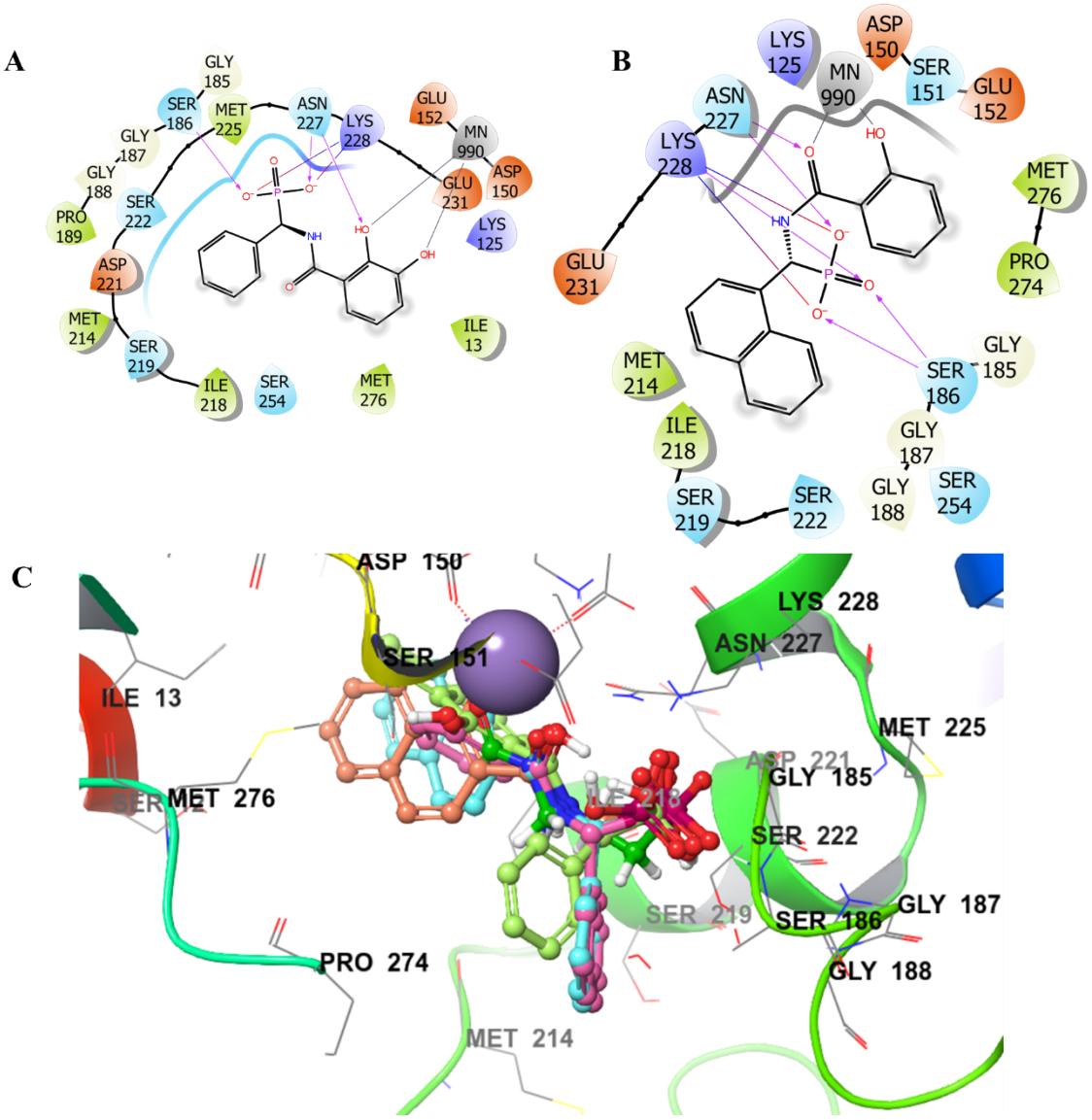


Figure S3. Interaction of the designed molecules with DXR active site (PDB ID 3R0I) (A) derivative of fragment F2 (Docking score: -6.43 kcal/mol) displaying metal binding with the catechol hydroxy groups (B) derivative of fragment F12 (Docking score: -4.47 kcal/mol) displaying metal binding with amide carbonyl and phenolic Oxygen (C) 3D view of the designed derivatives occupying pocket A (by lipophilic R_1 substituent), and pocket B lined by Pro274 and Met276 residues (by aromatic rings of MBGs).

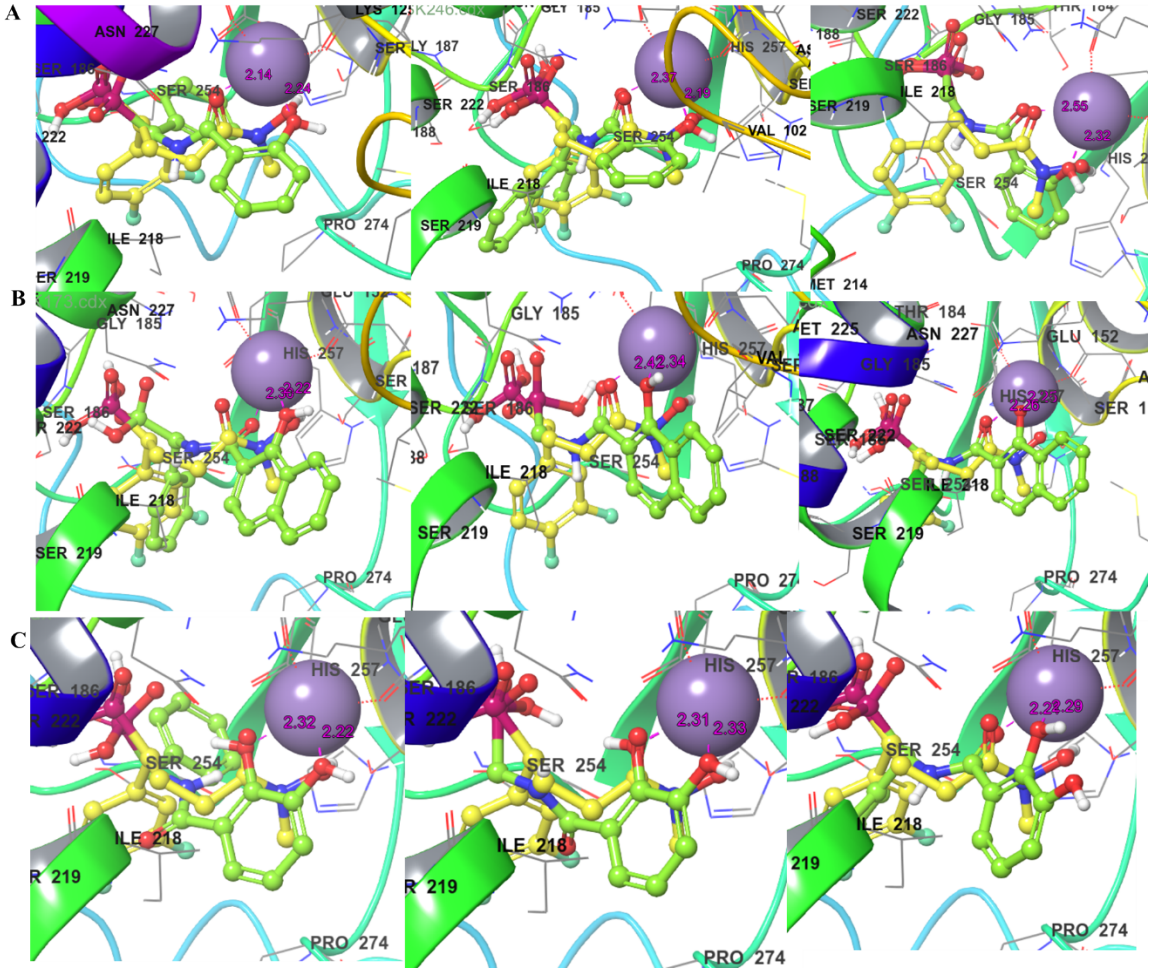


Figure S4. Docking poses of MBG containing non-hydroxamate DXR inhibitors (cyan balls and sticks) showing bidentate chelation of the Mn^{2+} ion (purple ball) inside the DXR pocket (3R0I). The cocrystallized ligand is shown in the yellow balls and sticks model. (A) designed inhibitors (in green balls and stick model) containing SA as MBG (F12) (B) designed inhibitors containing NA as MBG (F7) (C) designed inhibitors containing DHBA as MBG (F2).

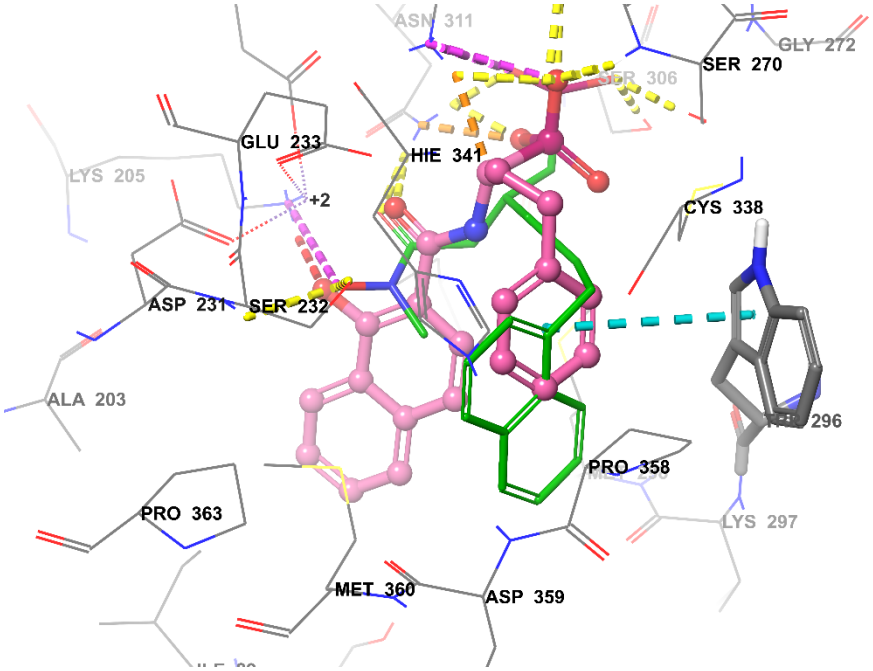


Figure S5. Pi-pi stacking interaction between the phenyl R_1 substituent of the ligands derived from F7 (pink ball and sticks) with the indole ring of Trp296 residue of DXR (PDB ID 5JAZ). The cocrystallized ligand is rendered as green sticks. The *O,O* motif of the designed ligand overlays well with the hydroxamate MBG of the cocrystallized ligand.

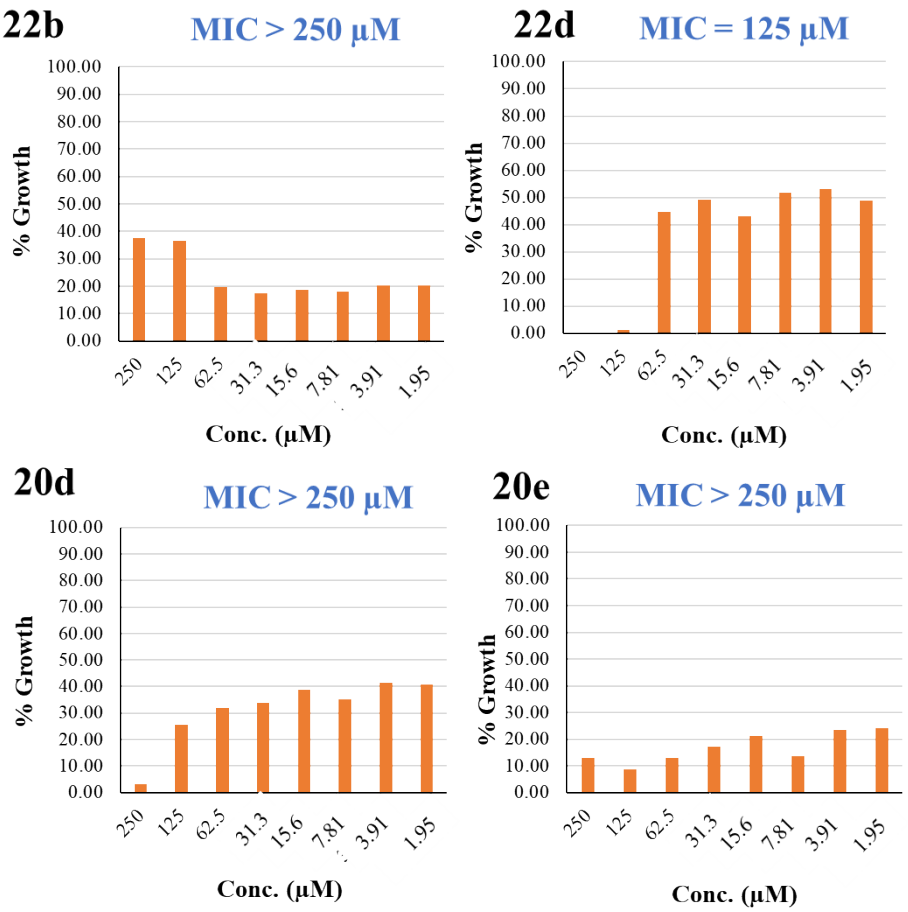


Figure S6. The MIC determination of selective compounds against *M. tuberculosis* using Alamar Blue Assay)

Table S1: Metal chelators and their properties (calculated using DataWarrior)

Code	MW	clogP	clogS	HBD	HBA	Rotatable bonds
MCL01	123.1	0.2	-0.86	3	1	1
MCL02	137.1	0.6	-1.23	3	1	1
MCL03	139.1	-0.28	-3.24	4	1	1
MCL04	167.1	-0.32	-0.87	5	2	2
MCL05	139.1	-0.15	-0.56	4	2	1
MCL06	139.1	0.03	-1.09	4	2	1
MCL07	202	1.02	-1.46	3	1	1
MCL08	167.1	-0.26	-0.9	5	2	2
MCL09	181.2	0.08	-1.24	5	2	2
MCL10	167.1	-0.32	-0.87	5	2	2
MCL11	192	1.51	-2.09	3	1	1
MCL12	179.2	1.87	-1.9	3	1	4
MCL13	145.2	1.98	-2.55	2	1	0
MCL14	189.2	1.17	-2.06	4	2	1
MCL15	173.2	1.51	-2.36	3	1	1
MCL16	173.2	1.39	-2.46	3	1	1
MCL17	161.2	1.15	-4.41	3	1	0
MCL18	144.2	1.3	-2.4	2	1	0
MCL19	145.2	1.63	-2.03	2	1	0
MCL20	159.2	2.03	-2.39	2	1	0
MCL21	160.2	1.3	-2.63	3	2	0
MCL22	222.3	1.02	-3.41	4	1	1
MCL23	173.2	1.46	-2.34	3	1	1
MCL24	179.6	2.24	-2.76	2	1	0
MCL25	96.1	0.12	-0.59	3	1	0
MCL26	126.1	-0.53	-1.79	5	3	0
MCL27	128.2	0.29	-1.72	3	1	0
MCL28	128.2	0.16	-1.46	3	1	0
MCL29	140.2	1.08	-2.22	2	0	0

MCL30	140.1	0.87	-1.53	4	2	0
MCL31	142.2	0.68	-2.08	3	1	0
MCL32	144.2	0.29	-1.95	4	2	0
MCL33	135.1	-0.35	-2.27	5	2	0
MCL34	126.1	0.34	-0.7	4	2	0
MCL35	124.1	0.73	-0.84	3	1	0
MCL36	126.1	0.52	-1.18	4	2	0
MCL37	112.1	-0.86	-1.29	3	1	0
MCL38	128.2	-0.8	-0.28	2	1	0
MCL39	126.1	-0.19	-1.55	3	1	0
MCL40	126.1	-0.19	-1.55	3	1	0
MCL41	142.2	-0.13	-0.54	2	1	0
MCL42	140.1	0.27	-1.82	3	1	1
MCL43	142.1	-1.11	-1.04	4	2	1
MCL44	160.6	0.04	-1.95	3	1	1
MCL45	174.6	0.71	-2.21	3	1	1
MCL46	156.1	-0.44	-1.3	4	2	1
MCL47	170.1	-1.02	-1.15	5	2	1
MCL48	112.1	-0.72	-1.17	3	1	0
MCL49	111.1	-1.02	-0.88	3	1	0
MCL50	127.2	-0.81	-1.82	2	1	0
MCL51	153.2	0.38	-1.32	3	1	1
MCL52	167.2	0.78	-1.62	3	1	2
MCL53	153.2	0.33	-1.35	3	1	1
MCL54	111.1	-0.86	-1.03	3	2	0
MCL55	155.2	-0.02	-0.04	2	1	0
MCL56	125.1	-0.61	-0.67	3	1	0
MCL57	141.2	-0.39	-1.61	2	1	0
MCL58	155.1	-1.63	-0.61	5	2	1
MCL59	183.3	0.84	-0.61	2	1	2
MCL60	169.3	0.39	-0.34	2	1	1
MCL61	138.1	0.8	-1.33	3	2	1

MCL62	137.1	0.4	-1.41	3	2	1
MCL63	152.2	1.14	-1.68	3	2	1
MCL64	152.2	1.14	-1.68	3	2	1
MCL65	152.2	1.14	-1.68	3	2	1
MCL66	153.1	0.12	-1.41	4	3	1
MCL67	180.2	1.99	-2.2	3	2	2
MCL68	154.1	0.45	-1.04	4	3	1
MCL69	154.1	0.45	-1.04	4	3	1
MCL70	154.1	0.45	-1.04	4	3	1
MCL71	156.1	0.9	-1.65	3	2	1
MCL72	156.1	0.9	-1.65	3	2	1
MCL73	75.1	-0.81	-0.73	3	2	0
MCL74	111.1	-0.08	-0.68	3	2	1
MCL75	199.3	0.54	-1.27	3	1	4
MCL76	129.2	-1.7	0.12	3	3	0
MCL77	174.2	0.94	-2.77	3	1	0
MCL78	216.2	0.3	-1.26	4	2	3
MCL79	180.2	2.29	-3.03	2	0	0
MCL80	110.1	0.97	-1.02	2	2	0
MCL81	124.1	1.24	-1.34	2	1	1
MCL82	140.2	1.53	-2.74	1	0	1
MCL83	122.1	0.36	-1.32	2	1	0
MCL84	164.2	1.47	-1.87	2	1	1
MCL85	160.2	2.16	-2.63	2	2	0
MCL86	154.1	0.45	-1.04	4	3	1
MCL87	153.1	0.12	-1.41	4	3	1
MCL88	154.1	0.45	-1.04	4	3	1
MCL89	211.2	2.97	-4.31	3	1	1
MCL90	227.3	3.15	-2.88	2	1	1
MCL91	171.2	0.77	-1.86	3	1	1
MCL92	100.1	0.23	-1.1	2	0	2
MCL93	114.1	0.45	-1.26	2	0	2

MCL94	126.2	0.67	-1.61	2	0	1
MCL95	128.2	0.91	-1.53	2	0	3
MCL96	134.6	0.42	-1.43	2	0	2

Table S2: Interactions shown by cocrystallized ligands at the binding site

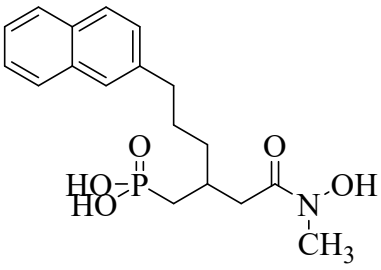
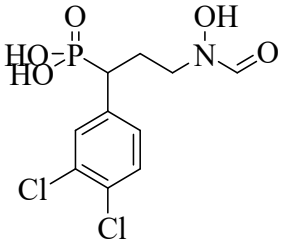
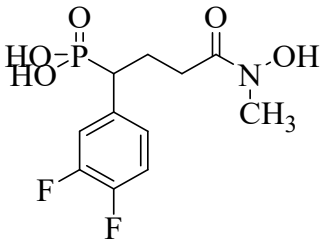
Code	PDB ID	Structures of cocrystallized ligands	RMSD	Docking score	Metal co-ordination distance	
CL1	5JAZ		0.37	-10.7	2.20 Å	2.23 Å
CL2	2Y1D		1.04	-3.9	2.21 Å	2.12 Å
CL3	3R0I		1.9	-3.86	2.46 Å	2.09 Å

Table S3: Physicochemical Properties of the synthesized derivatives and fosmidomycin **(1)**

Code	Molecular formula	MW	cLogP	HBA	HBD	RB	Basic nitrogen	TPSA
FOS (**1**)	C4H10NO5P	183.1	-4.14	6	3	4	0	107.8
20a	$C_{14}H_{14}NO_5P$	307.2	-0.99	6	4	4	0	116.7
20b	$C_8H_{10}NO_5P$	231.1	-2.86	6	4	3	0	116.7
20e	$C_{14}H_{12}NO_5Cl_2P$	376.1	0.22	6	4	4	0	116.7
20c	$C_9H_{12}NO_5P$	245.2	-2.63	6	4	3	0	116.7
20d	$C_{18}H_{16}NO_5P$	357.3	0.21	6	4	4	0	116.7
21a	$C_{14}H_{14}NO_6P$	323.2	-1.33	7	5	4	0	136.9
21b	$C_8H_{10}NO_6P$	247.1	-3.21	7	5	3	0	136.9
21c	$C_9H_{12}NO_6P$	261.2	-2.98	7	5	3	0	136.9
21d	$C_{18}H_{16}NO_6P$	373.3	-0.14	7	5	4	0	136.9
22a	$C_{18}H_{16}NO_5P$	357.3	0.21	6	4	4	0	116.7
22b	$C_{12}H_{12}NO_5P$	281.2	-1.67	6	4	3	0	116.7
22c	$C_{13}H_{14}NO_5P$	295.2	-1.44	6	4	3	0	116.7
22d	$C_{22}H_{18}NO_5P$	407.4	1.4	6	4	4	0	116.7
28a	$C_{14}H_{16}NO_5P$	309.3	-2.81	6	5	4	0	119.8
23a	$C_{17}H_{14}NO_6P$	359.3	-1.21	7	3	4	1	122.7

Table S4 Percentage inhibition or MIC values of compounds at 500 µM against different pathogens. Kanamycin or Isoniazid (INH) were used as a positive control, and 5% DMSO was used as a negative control.

ID	*M. tuberculosis*	*E. coli*	*S. aureus*	*A. baumannii*	*K. Pneumoniae*	*S. typhimurium*	*V. cholerae*	*P. aeruginosa*
20a	NA*	NA	NA	NA	NA	NA	NA	NA
22a	NA*	NA	NA	NA	NA	NA	NA	NA
21a	NA*	NA	NA	NA	NA	NA	NA	NA
23a	NA*	NA	NA	NA	NA	NA	NA	NA
28a	NA*	NA	NA	NA	NA	NA	NA	NA
20c	NA	NA	NA	NA	NA	NA	NA	NA

20e	MIC > 250 µM	NA	NA	NA	NA	NA	NA	NA
22b	MIC > 250 µM	NA	NA	NA	NA	NA	NA	NA
22c	NA	NA	NA	NA	NA	NA	NA	NA
21d	NA	NA	NA	NA	NA	NA	NA	NA
20d	MIC > 250 µM	NA	NA	NA	NA	NA	NA	NA
22d	MIC 125 µM	NA	NA	NA	NA	NA	NA	NA
21b	NA	NA	NA	NA	NA	NA	NA	NA
21c	NA	NA	NA	NA	NA	NA	NA	NA
Kanamycin (0.2 mg/mL)	NT	82 %	82 %	94 %	10 %	82 %	86 %	86 %
INH (0.212 µM)	44 %	NT	NT	NT	NT	NT	NT	NT
NA = not active; NT = not tested *tested at 200 µM								

IC_{50} curves of the representative compounds

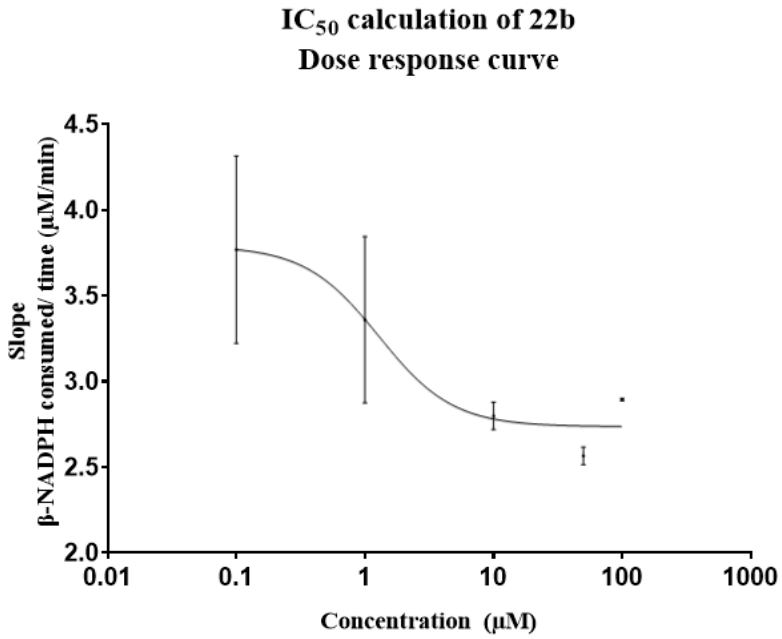


Figure S7. IC_{50} curve for compound **22b**

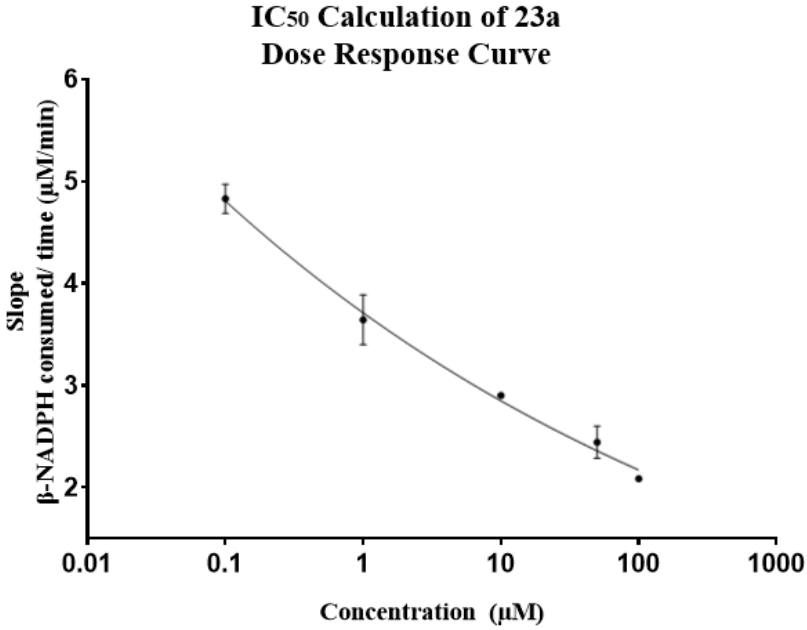


Figure S8. IC_{50} curve for compound **23a**

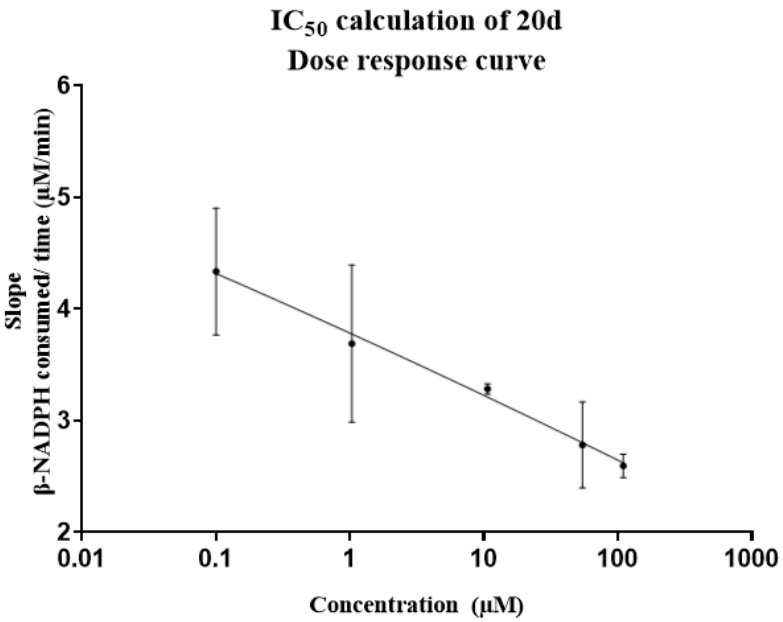


Figure S9. IC_{50} curve for compound **20d**

Spectral data for compounds

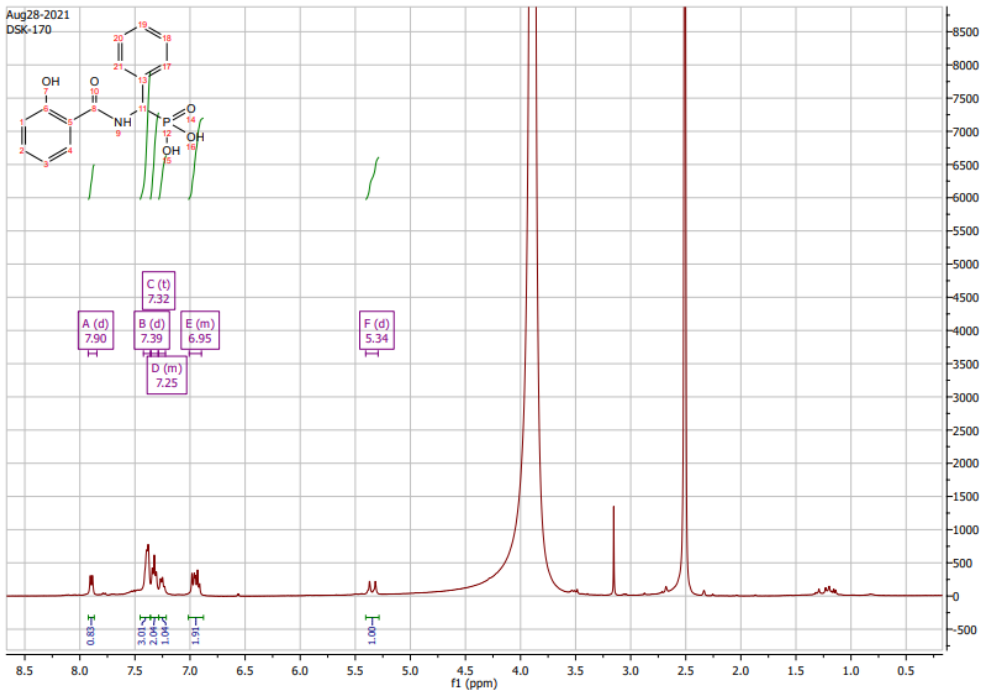


Figure S10 1H NMR spectrum of **20a** in [D_6]-DMSO (400 MHz, 300 K).

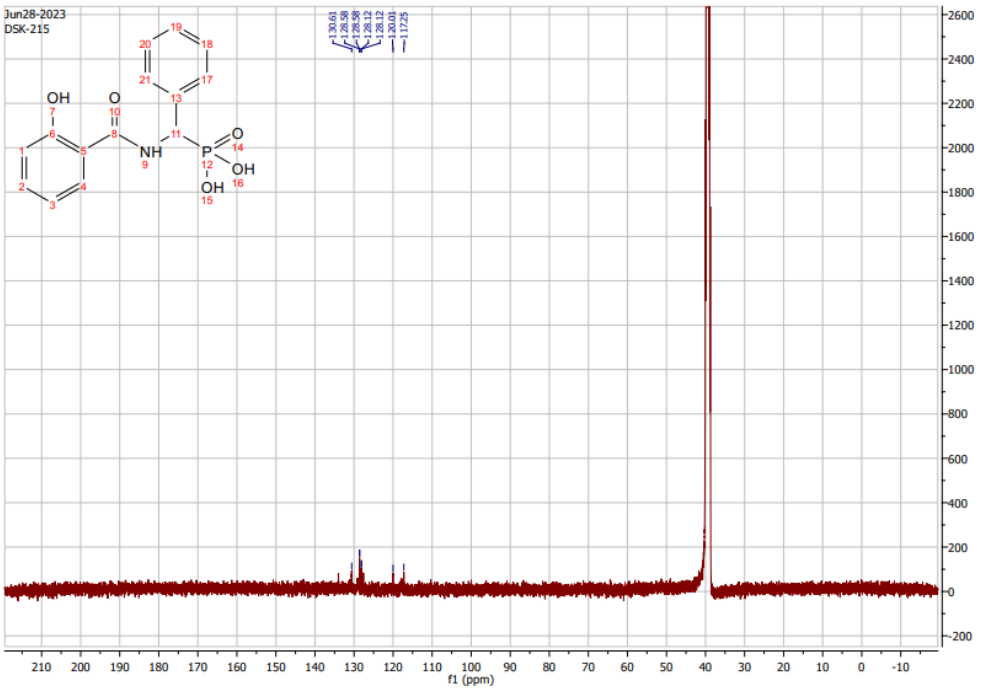


Figure S11 13C NMR spectrum of **20a** in [D_6]-DMSO (101 MHz, 300 K).

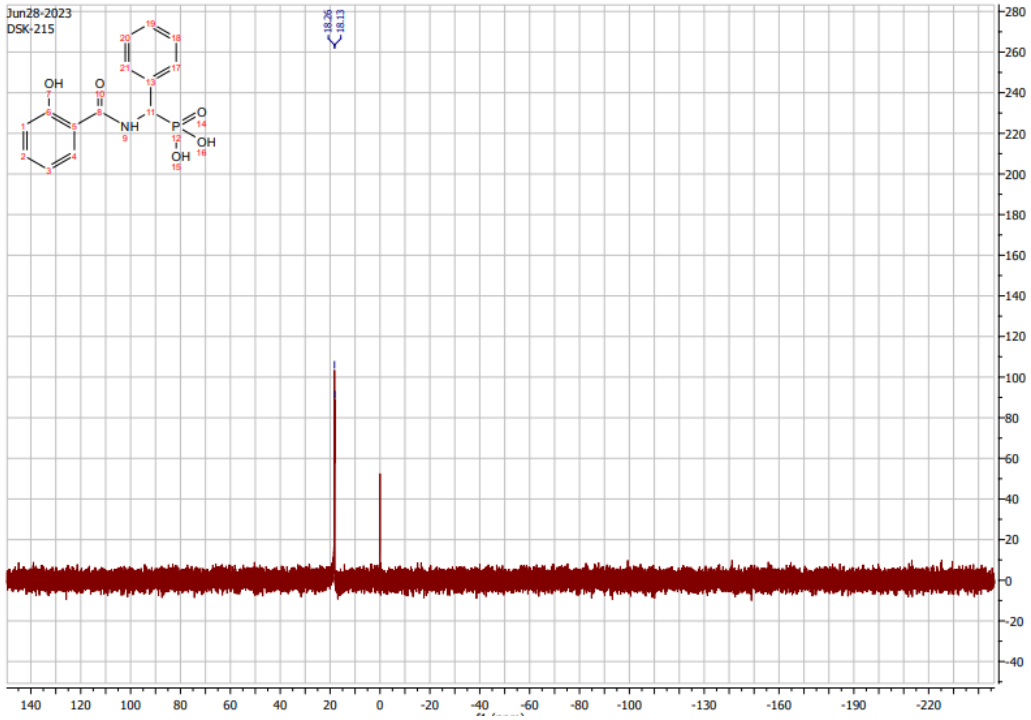
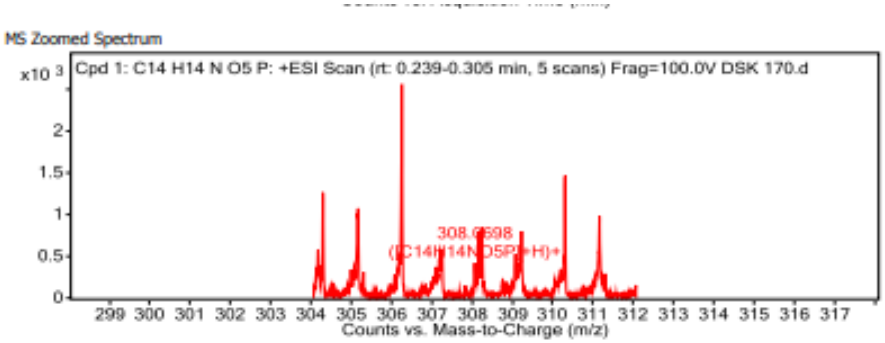


Figure S12 31P NMR spectrum of **20a** in [D_6]-DMSO (162 MHz, 300 K).



MS Spectrum Peak List

m/z	*Calc m/z*	Diff(ppm)	z	Abund	Formula	Ion
308.0698	308.0682	-5.06	1	426.16	C14H14NO5P	(M+H)+

Figure S13. HRMS data for compound **20a**

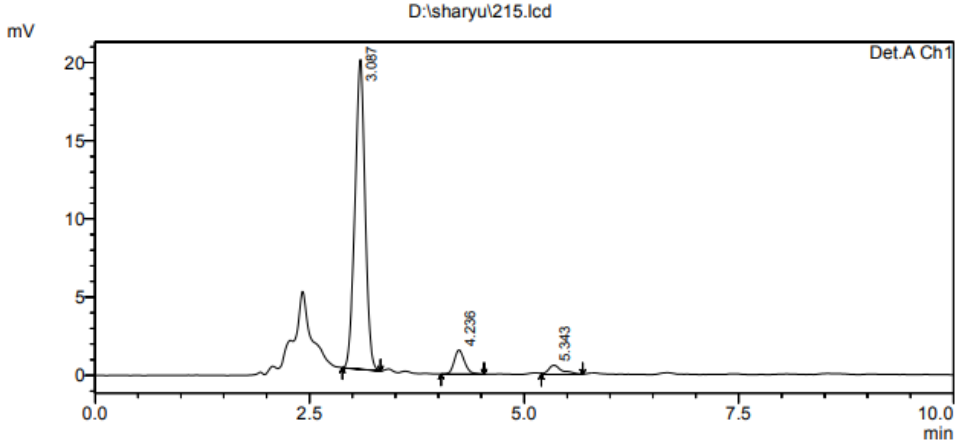


Figure S14. HPLC data for compound **20a**

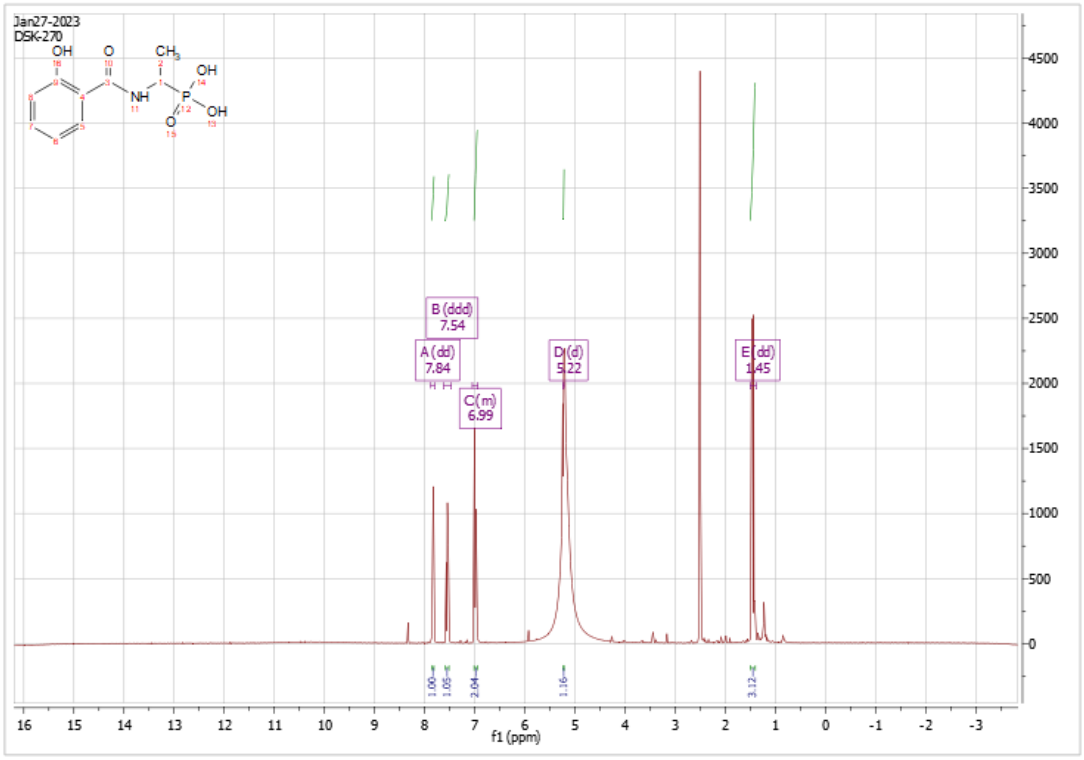


Figure S15 1H NMR spectrum of **20c** in [D_6]-DMSO (400 MHz, 300 K).

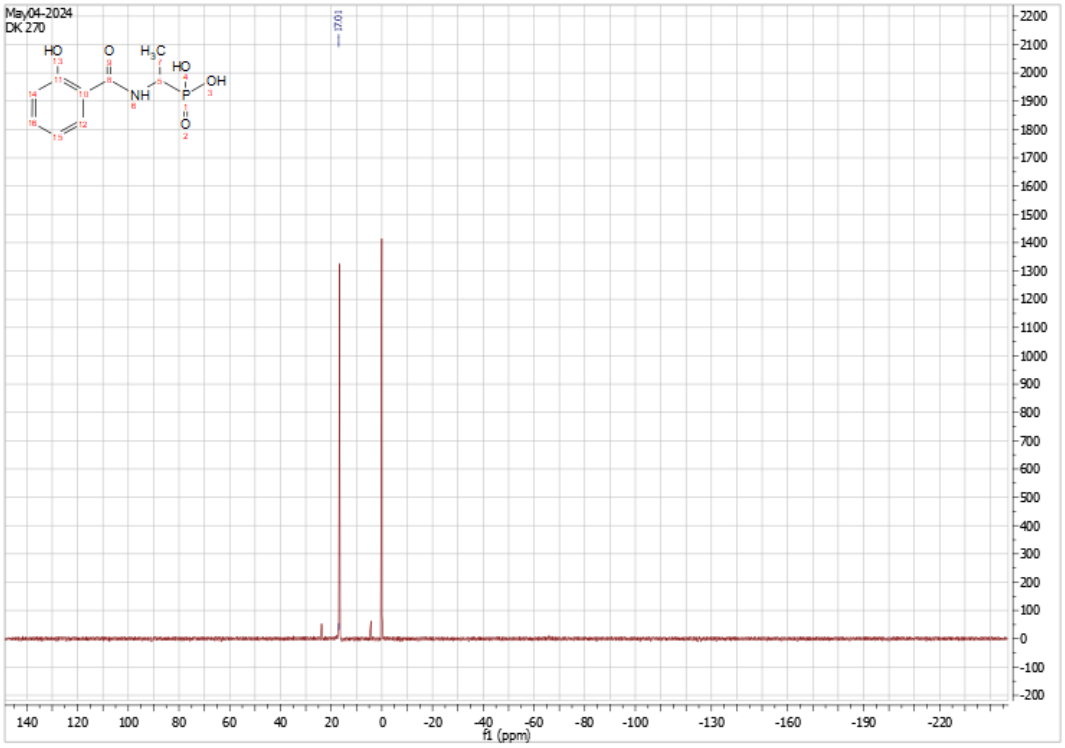


Figure S16 31P NMR spectrum of **20c** in [D_6]-DMSO (162 MHz, 300 K).

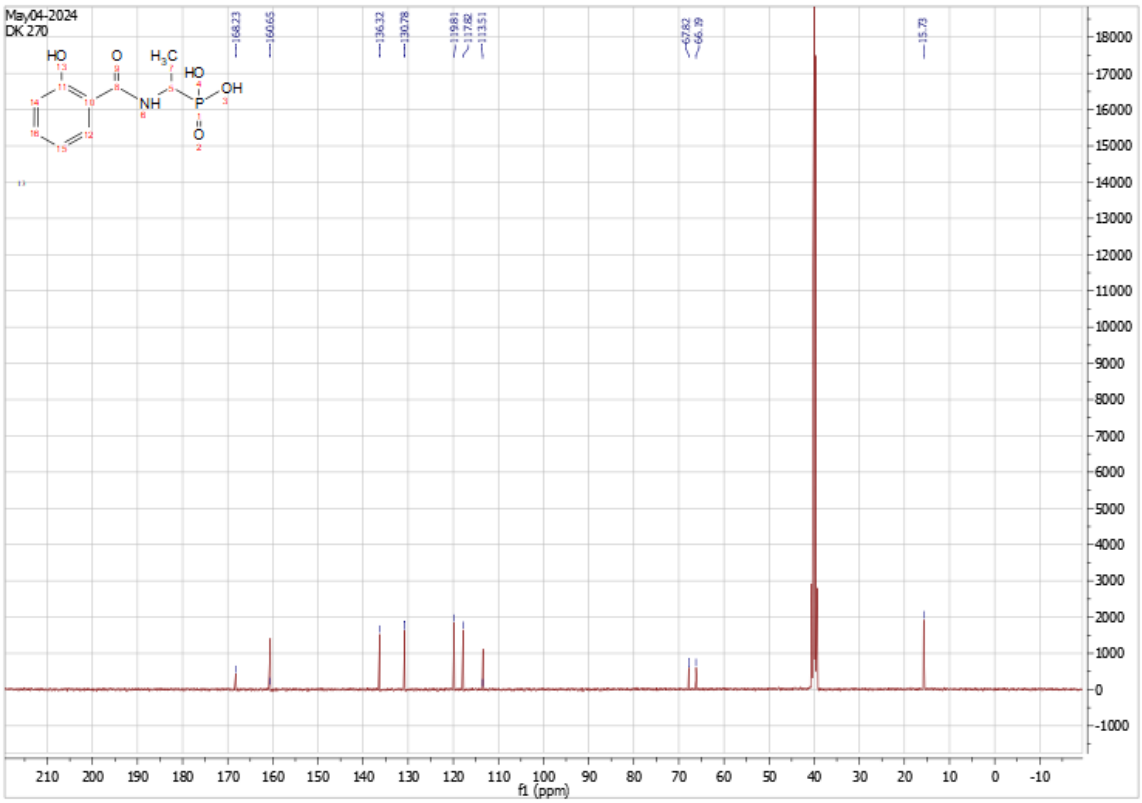


Figure S17 13C NMR spectrum of **20c** in [D_6]-DMSO (101 MHz, 300 K).

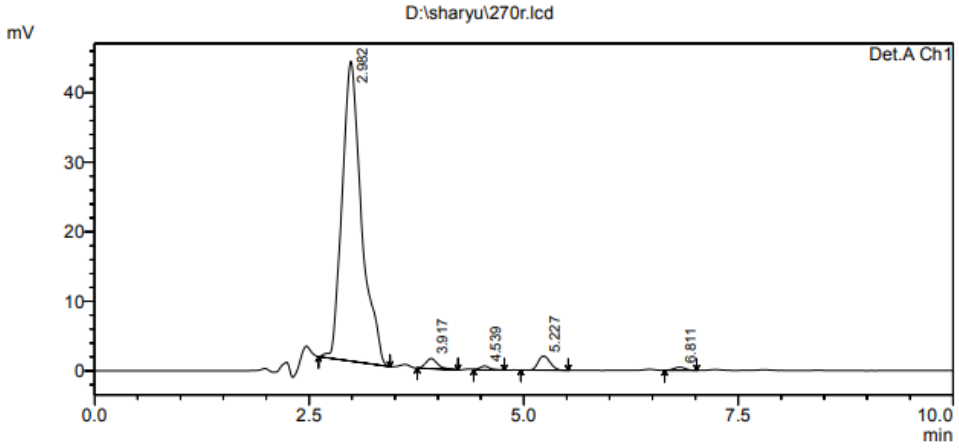


Figure S18. HPLC trace for compound **20c**

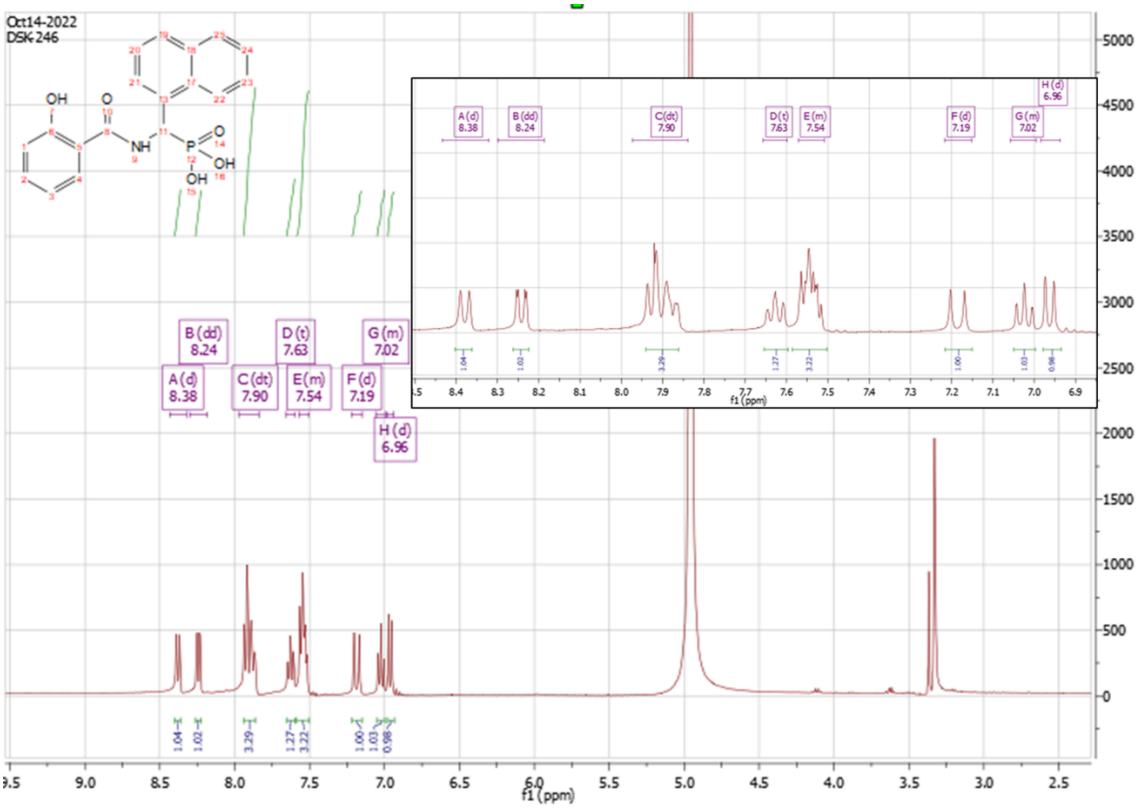


Figure S19 1H NMR spectrum of **20d** in [D_6]-DMSO (400 MHz, 300 K).

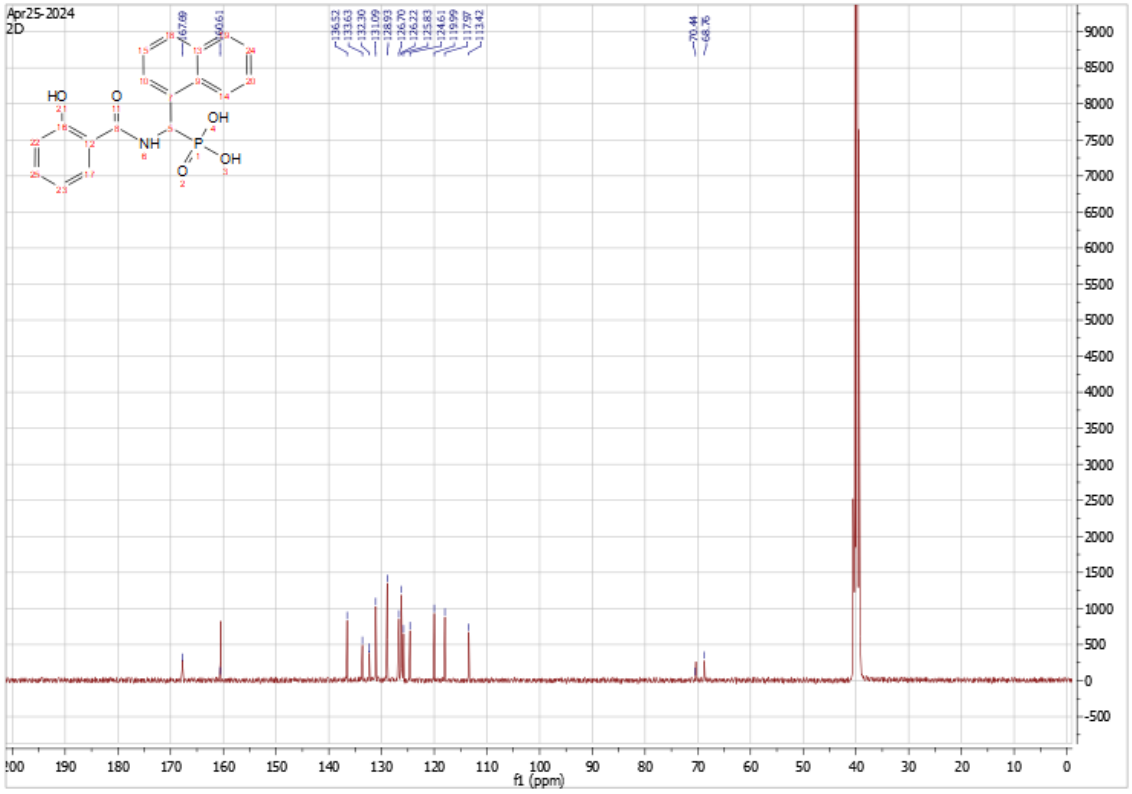


Figure S20 13C NMR spectrum of **20d** in [D_6]-DMSO (101 MHz, 300 K).

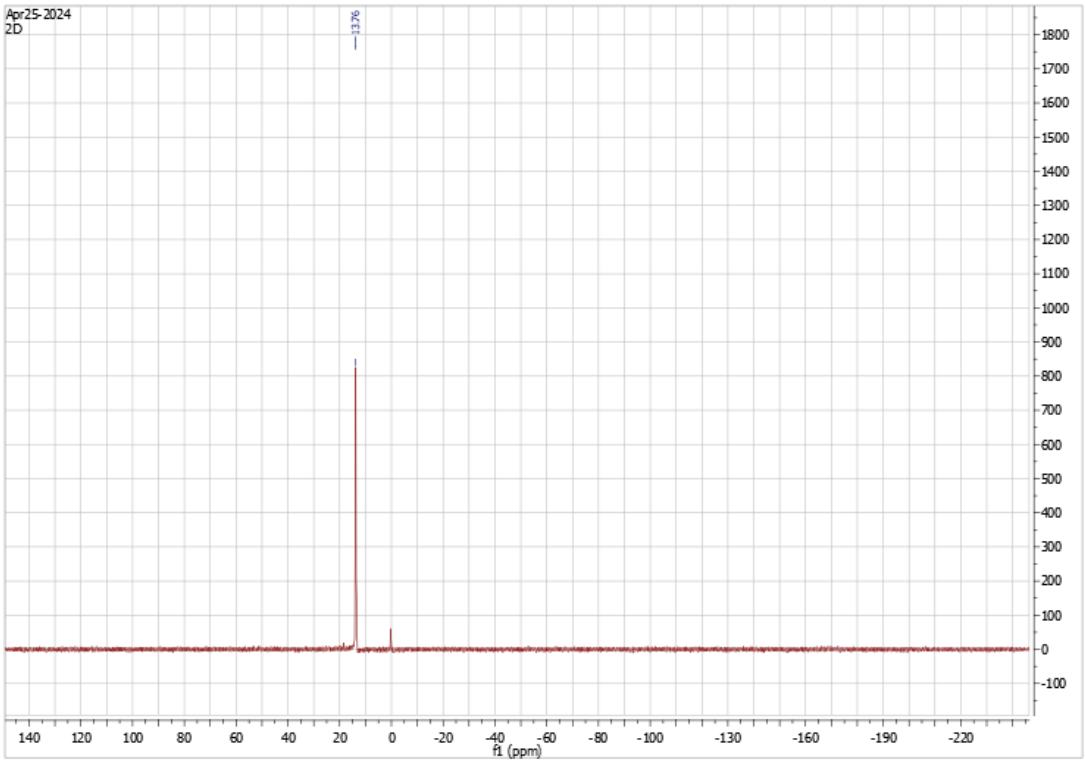
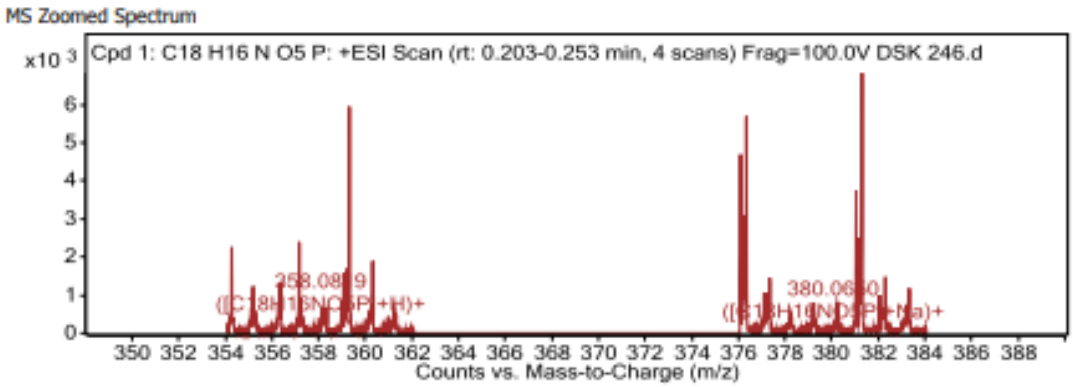


Figure S21 31P NMR spectrum of **20d** in [D_6]-DMSO (162 MHz, 300 K).



MS Spectrum Peak List

m/z	*Calc m/z*	Diff(ppm)	z	Abund	Formula	Ion
358.0819	358.0839	5.45	1	418.71	C18H16NO5P	(M+H)+
380.065	380.0658	2.18	1	221.61	C18H16NO5P	(M+Na)+

Figure S22. HRMS data for compound **20d**

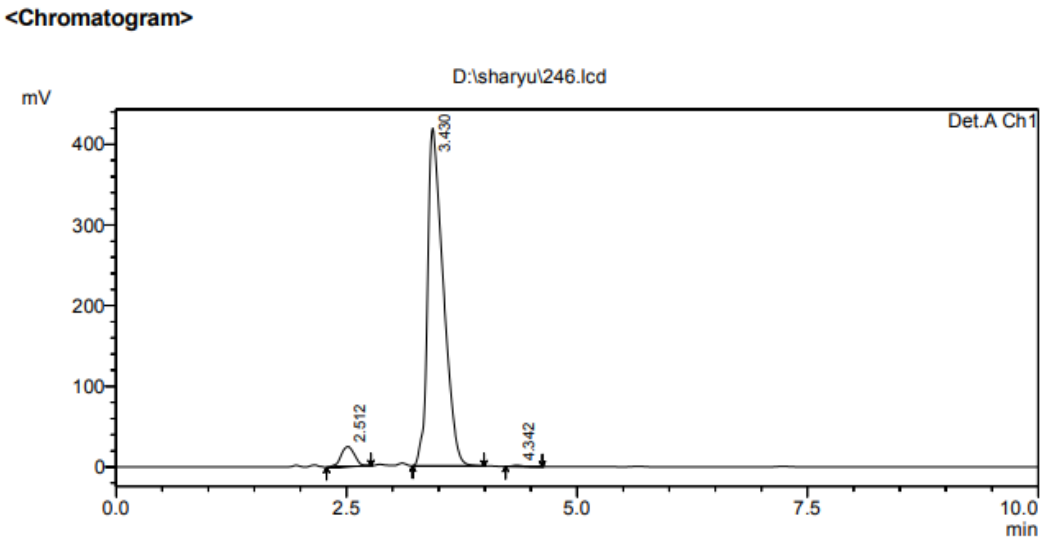


Figure S23. HPLC data for compound **20d**

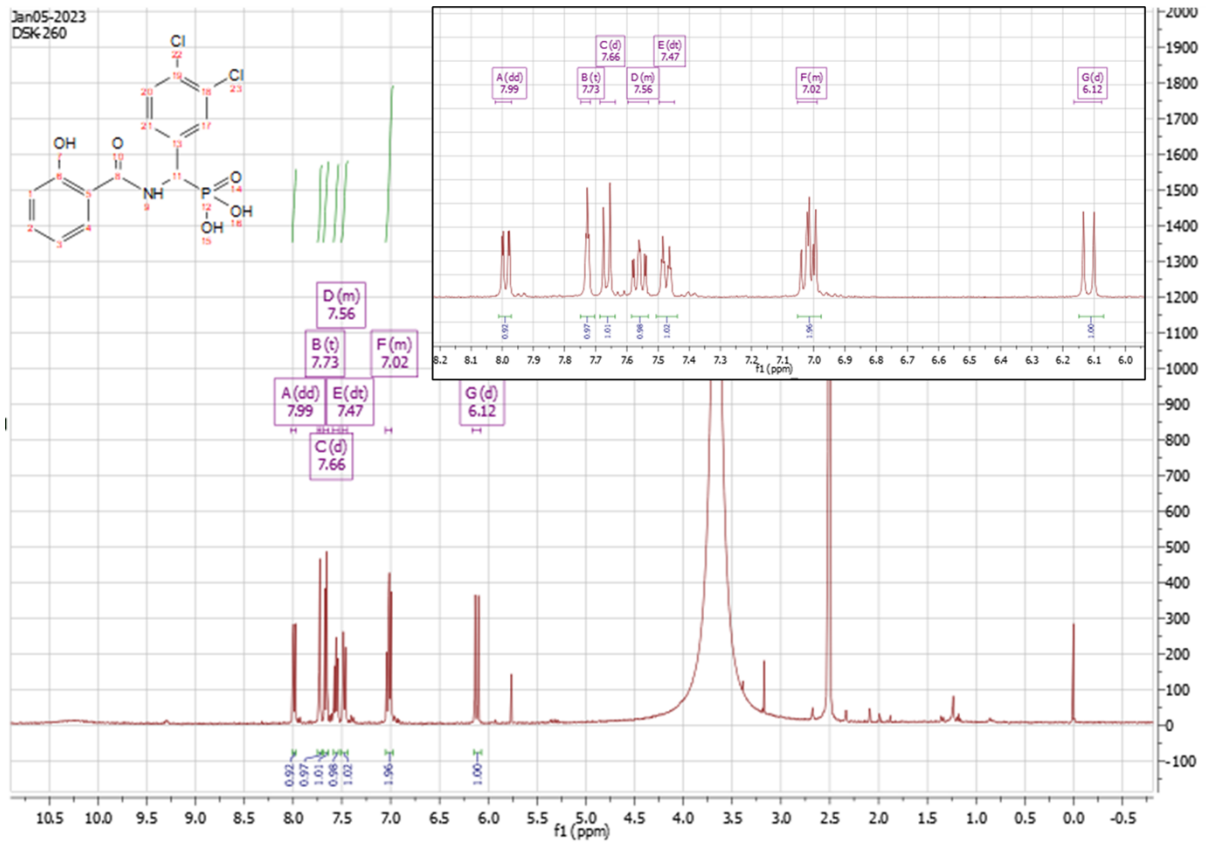


Figure S24 1H NMR spectrum of **20e** in [D_6]-DMSO (400 MHz, 300 K).

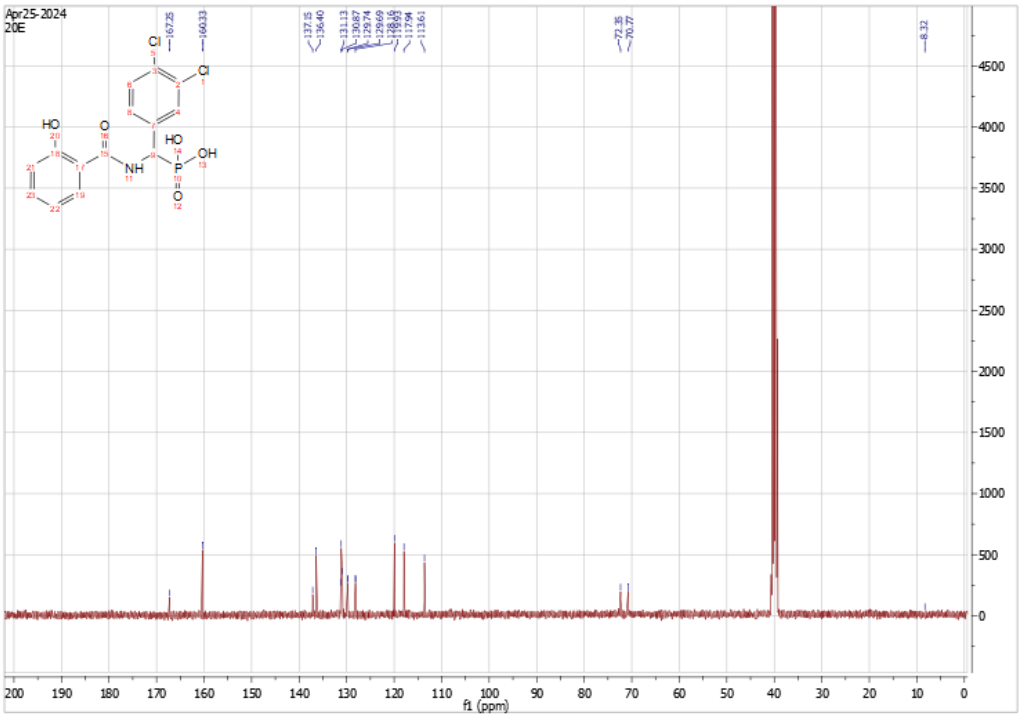


Figure S25 13C NMR spectrum of **20e** in [D_6]-DMSO (101 MHz, 300 K).

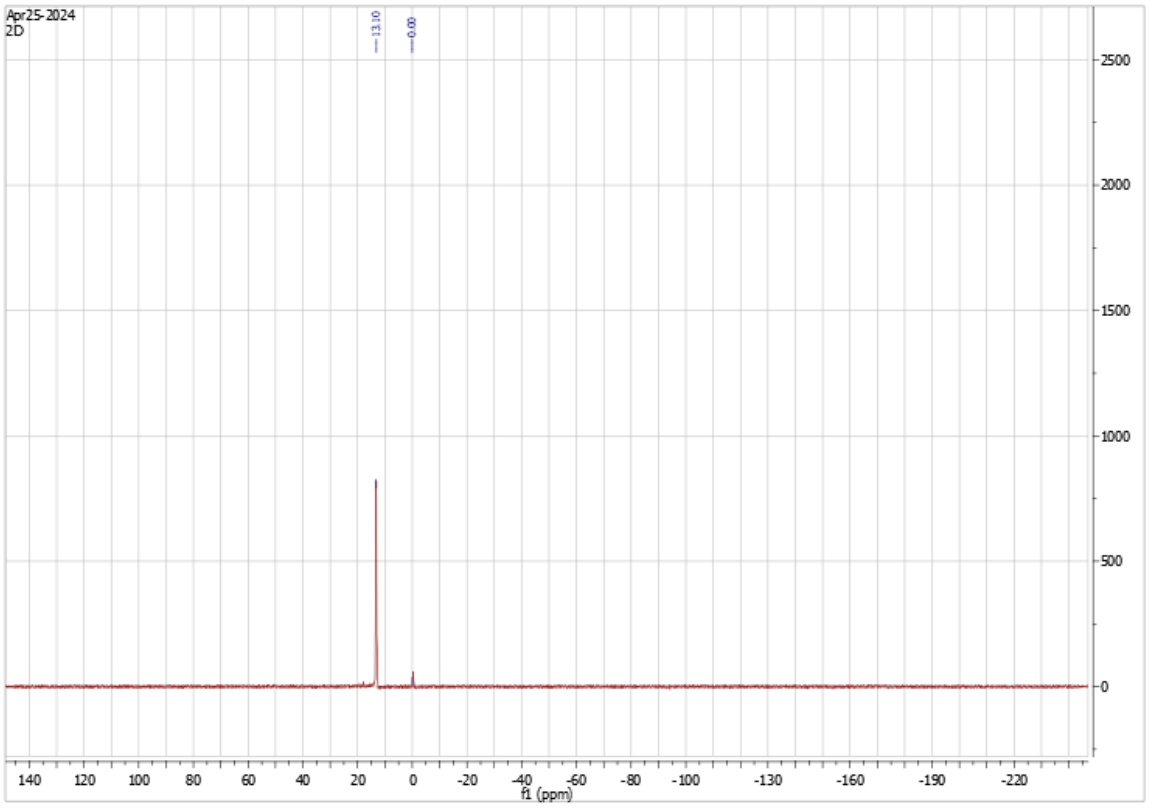
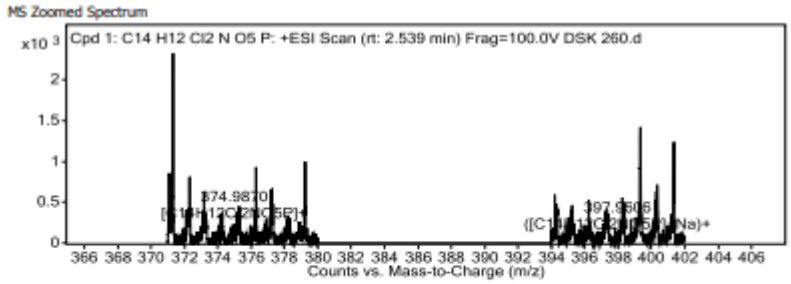


Figure S26 31P NMR spectrum of **20e** in [D_6]-DMSO (162 MHz, 300 K).



MS Spectrum Peak List

m/z	*Calc m/z*	Diff(ppm)	z	Abund	Formula	Ion
374.987	374.9825	-12.17	1	247.63	C14H12Cl2NO5P	M+
375.9873	375.9903	7.84	1	221.53	C14H12Cl2NO5P	(M+H)+
397.9606	397.9722	29.31	1	115.34	C14H12Cl2NO5P	(M+Na)+

Figure S27. HRMS data for compound **20e**

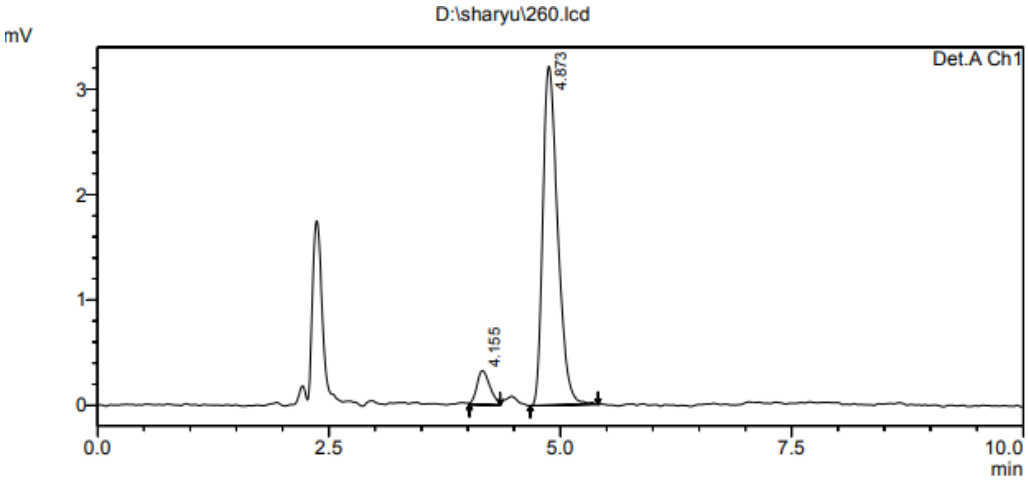


Figure S28. HPLC data for compound **20e**

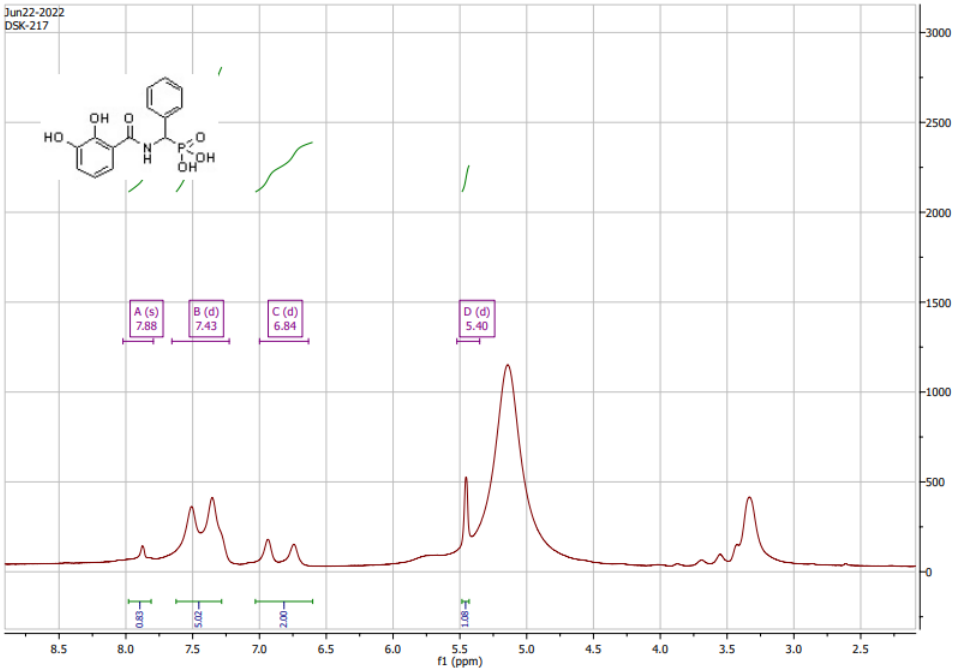


Figure S29 1H NMR spectrum of **21a** in [D_6]-DMSO (400 MHz, 300 K).

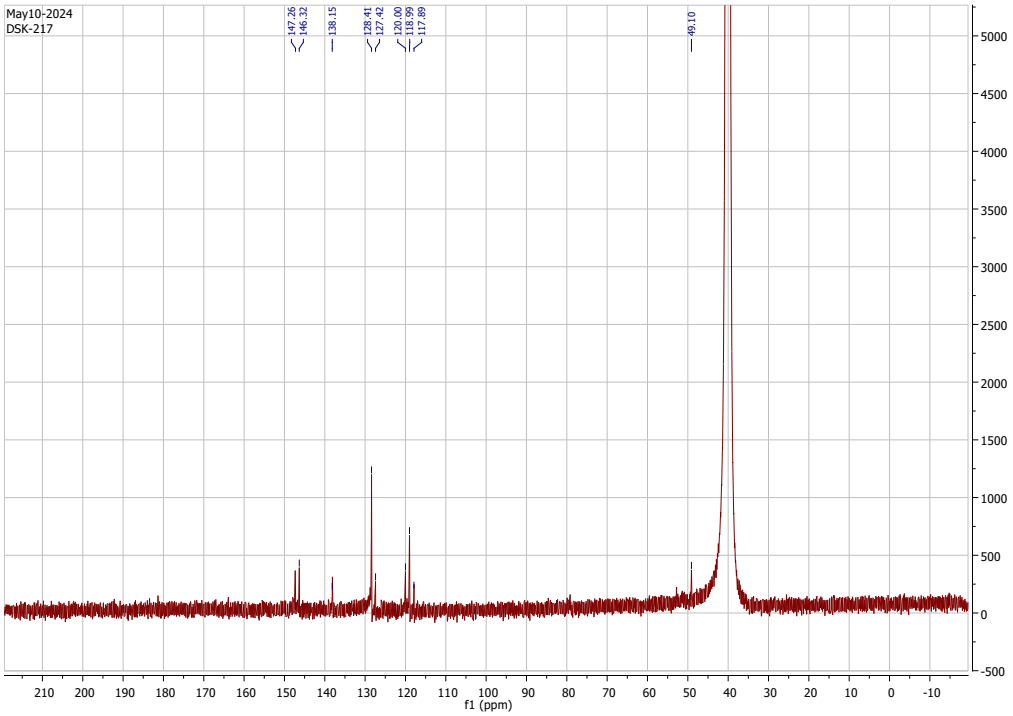


Figure S30 13C NMR spectrum of **21a** in [D_6]-DMSO (101 MHz, 300 K).

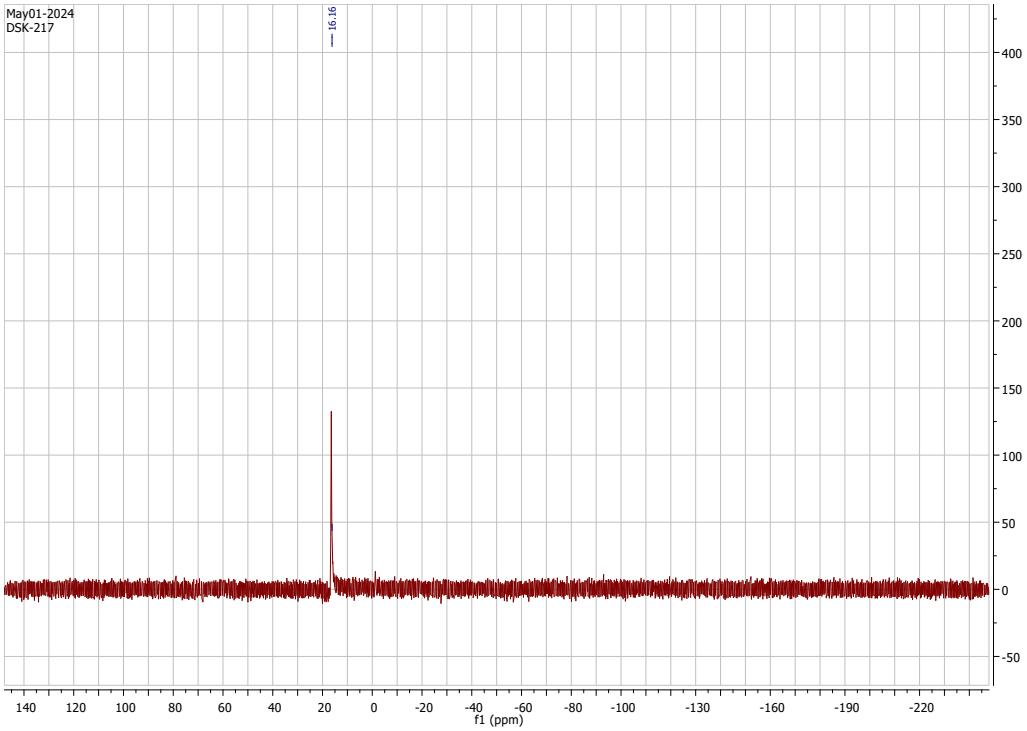


Figure S31 31P NMR spectrum of **21a** in [D_6]-DMSO (162 MHz, 300 K).

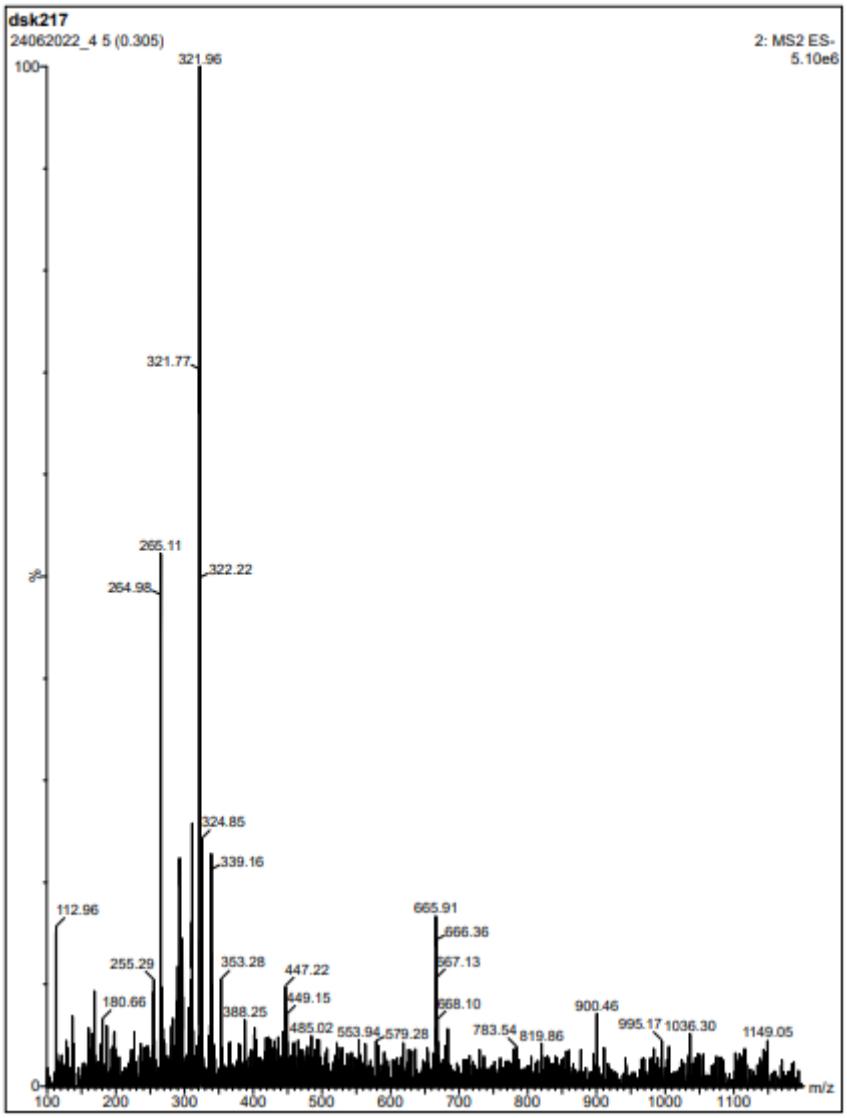


Figure S32. MS data for compound **21a**

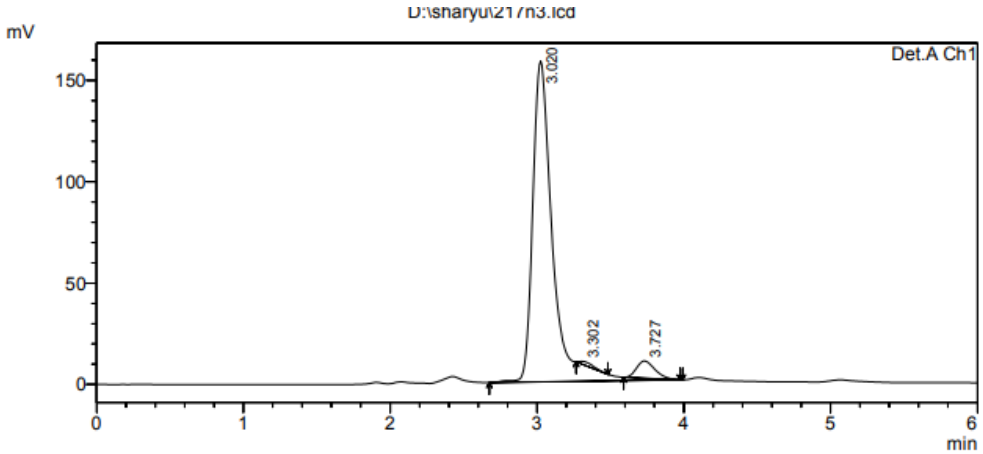


Figure S33. HPLC data for compound **21a**

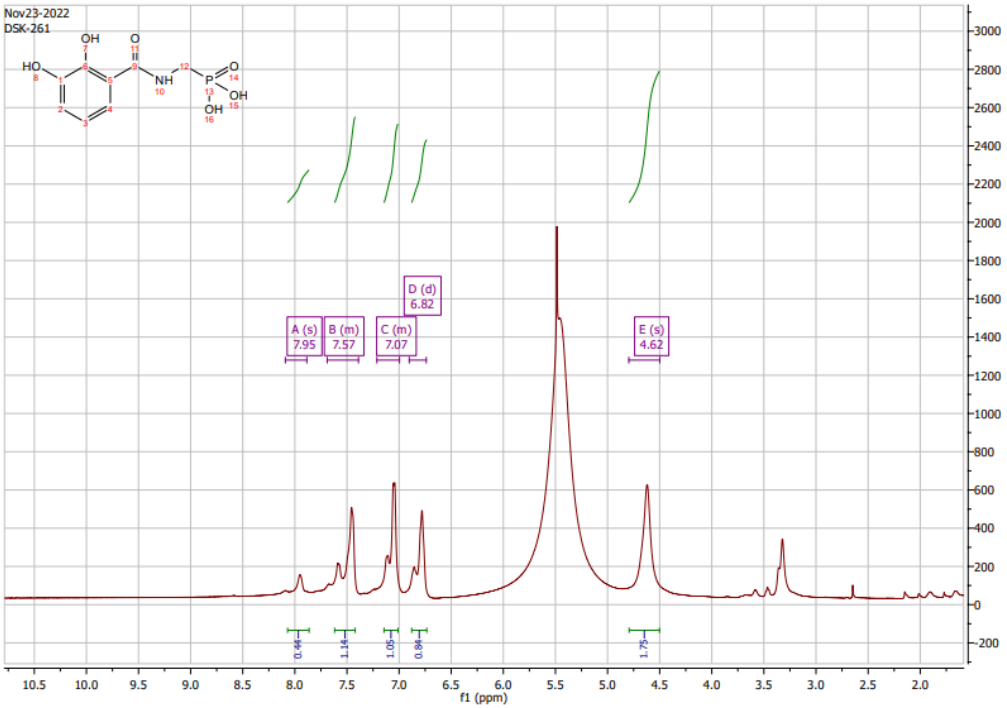


Figure S34 1H NMR spectrum of **21b** in [D_4]- MeOD (400 MHz, 300 K).

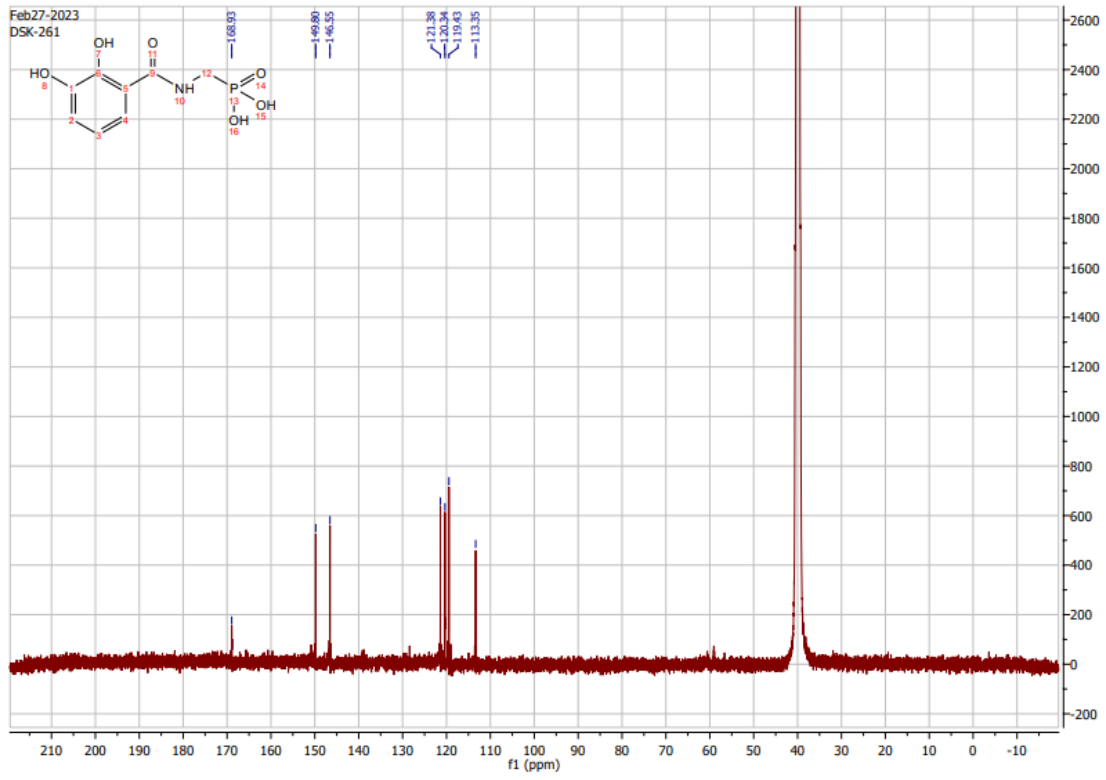


Figure S35 13C NMR spectrum of **21b** in [D_6]-DMSO (101 MHz, 300 K).

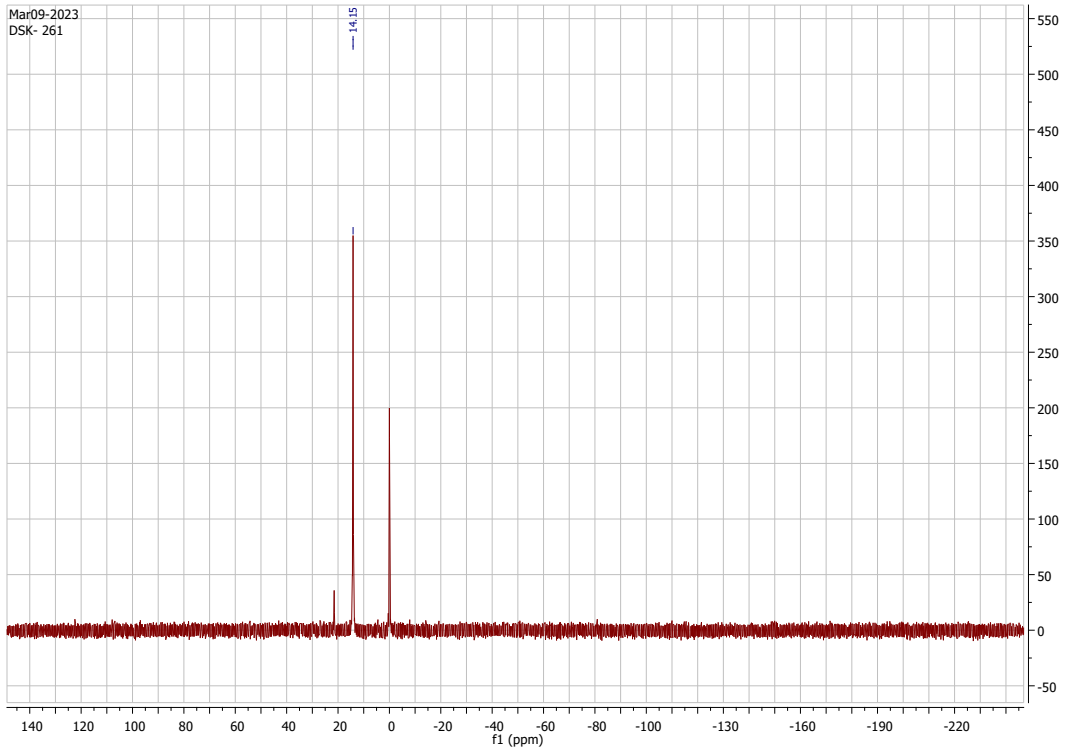


Figure S36 31P NMR spectrum of **21b** in [D_6]-DMSO (162 MHz, 300 K).

HPLC trace

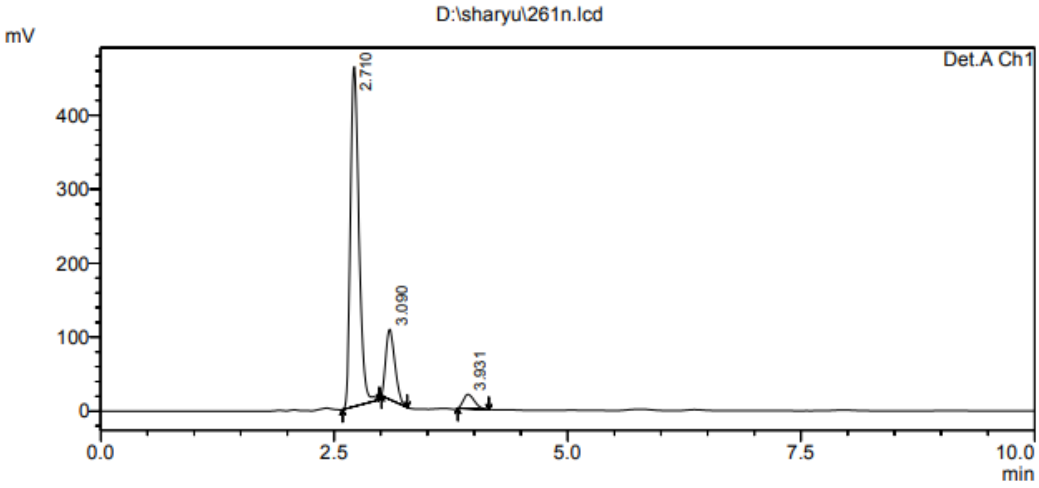


Figure S37. HPLC data for compound **21b**

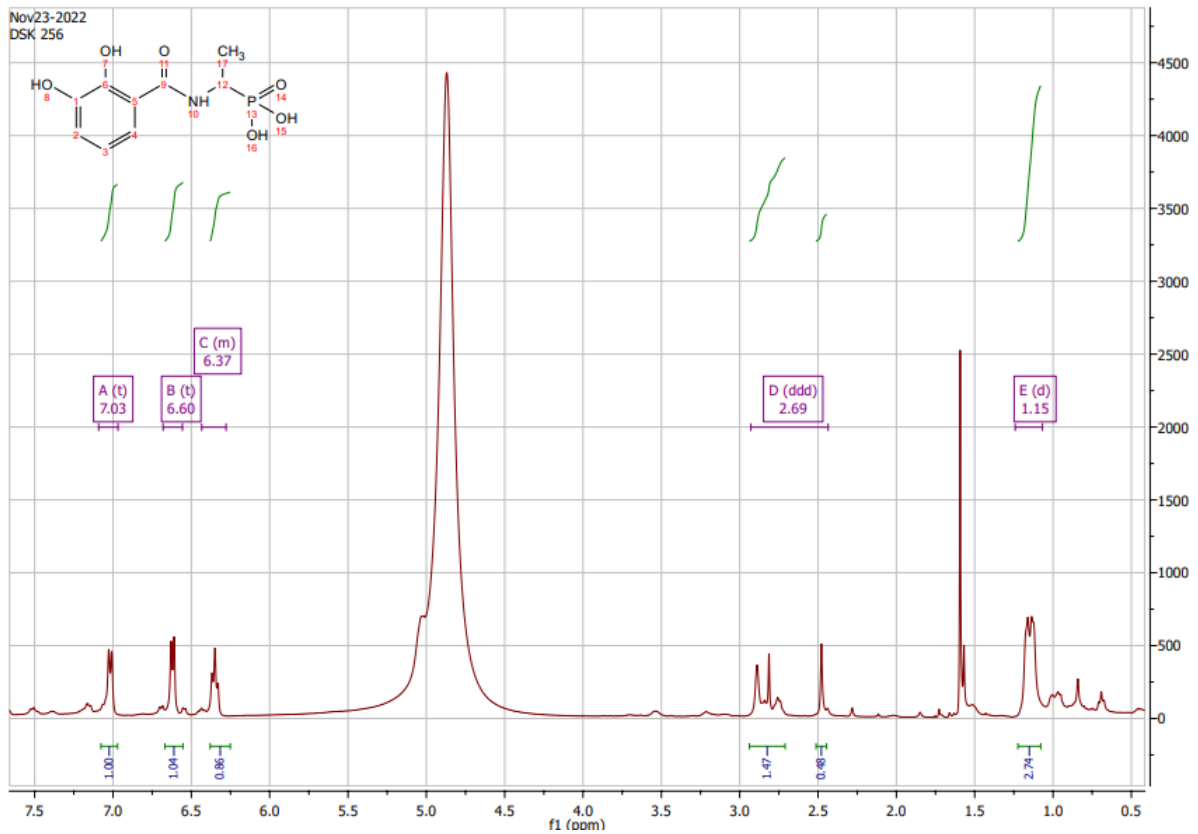


Figure S38 1H NMR spectrum of **21c** in [D_6]-DMSO (400 MHz, 300 K).

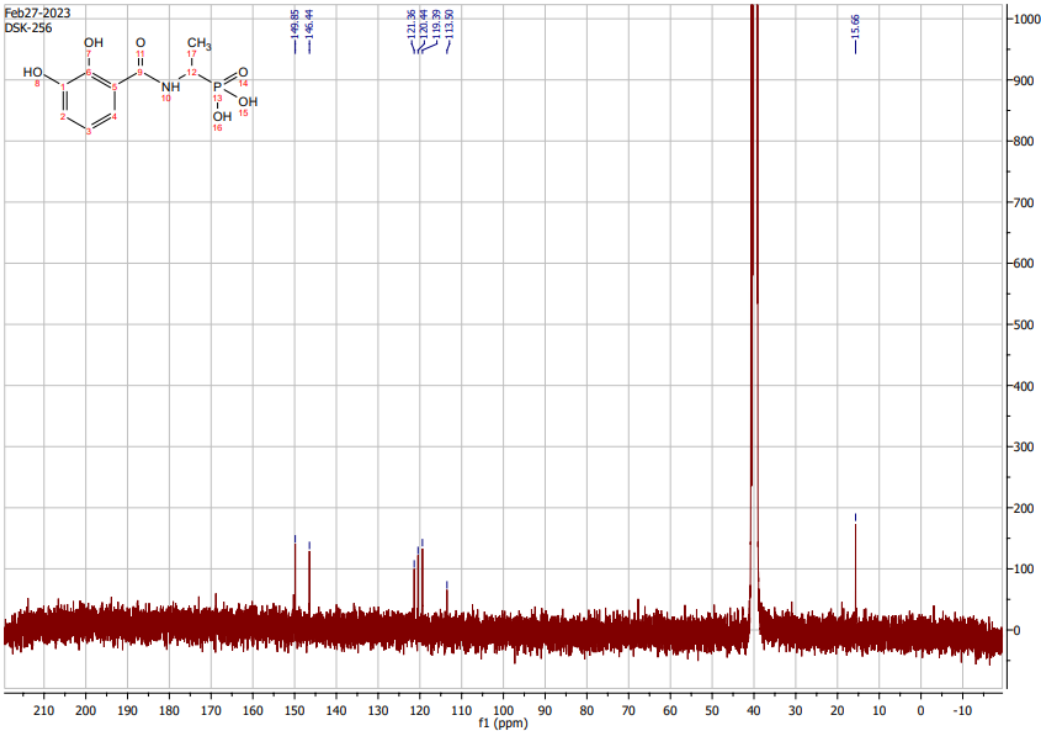


Figure S39 13C NMR spectrum of **21c** in [D_6]-DMSO (101 MHz, 300 K).

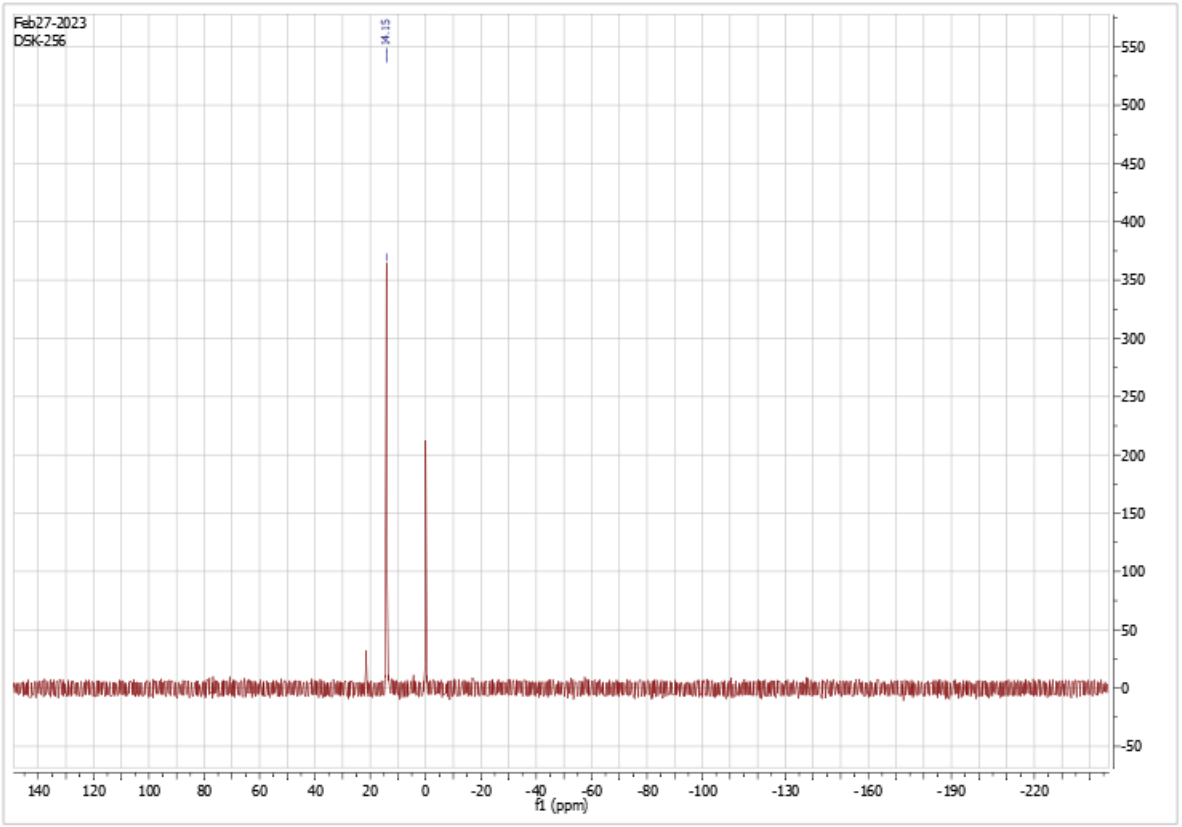


Figure S40 31P NMR spectrum of **21c** in [D_6]-DMSO (162 MHz, 300 K).

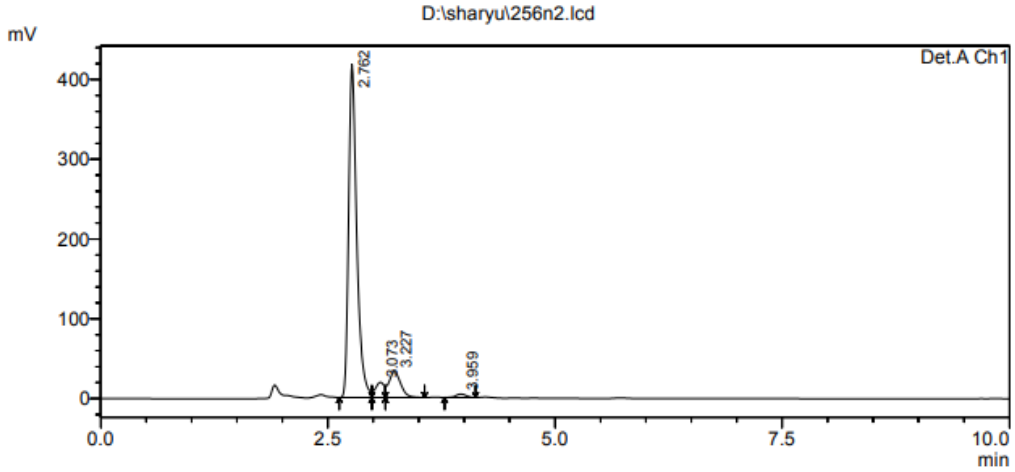


Figure S41. HPLC data for compound **21c**

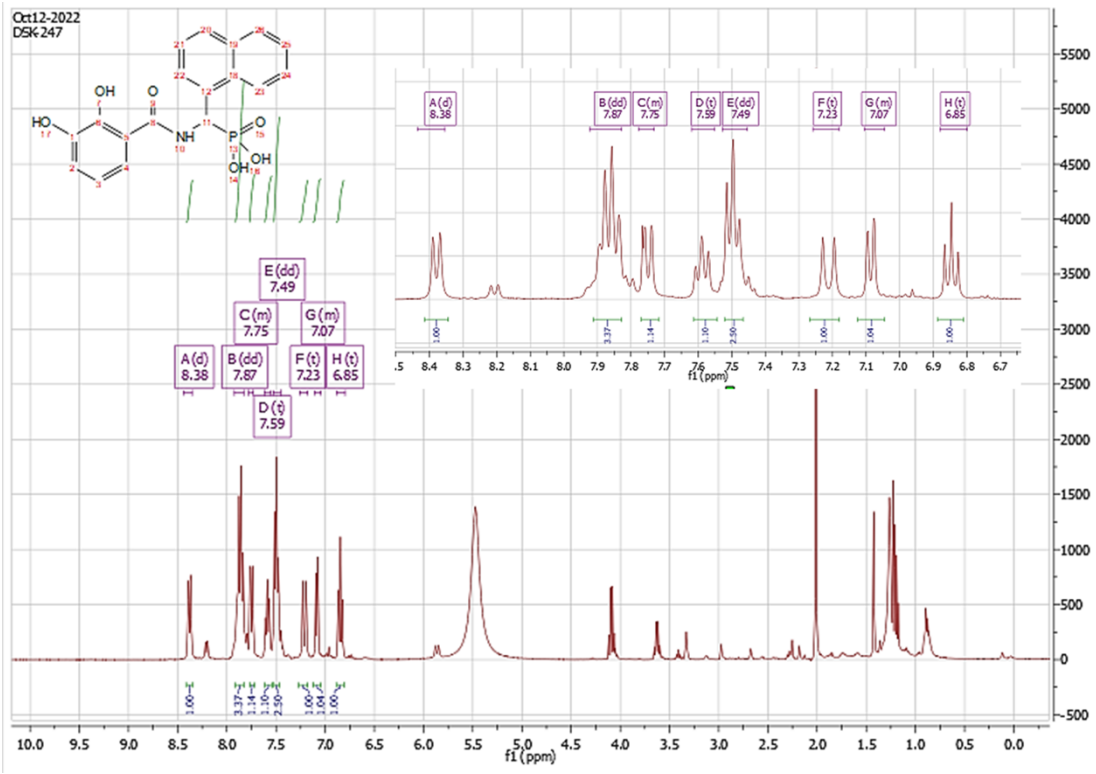


Figure S42 1H NMR spectrum of **21d** in [D_4]- MeOD (400 MHz, 300 K).

Some solvent peaks observed Peak at 5.49 (s, broad) DCM,

Ethanol CH3 (t) 1.19and CH2 (q) 3.6

Ethyl acetate CH3CO (s) 2.01, CH2CH3 (q), 4.09 and CH2CH3 (t), 1.24

n-Hexane CH3 t 0.90 and CH2 m 1.29

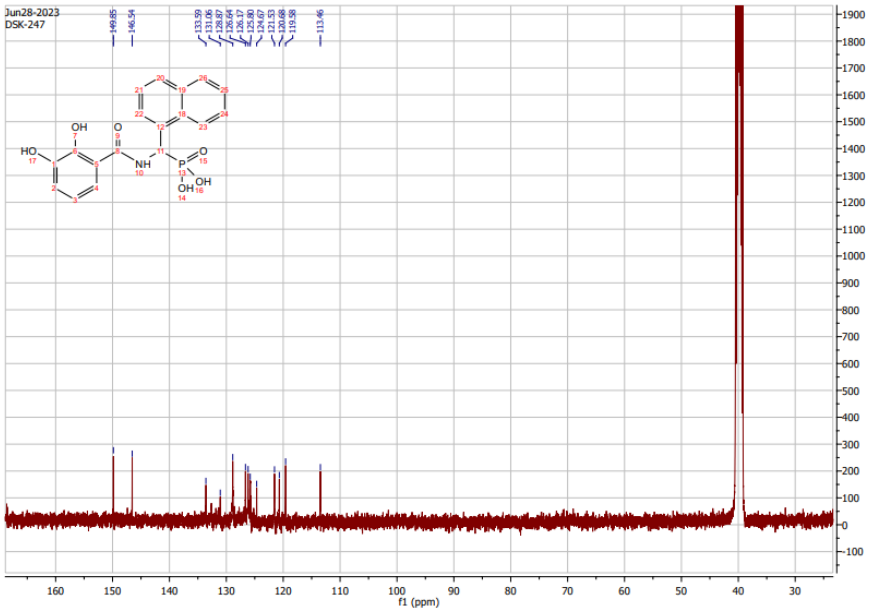


Figure S43 13C NMR spectrum of **21d** in [D_6]-DMSO (101 MHz, 300 K).

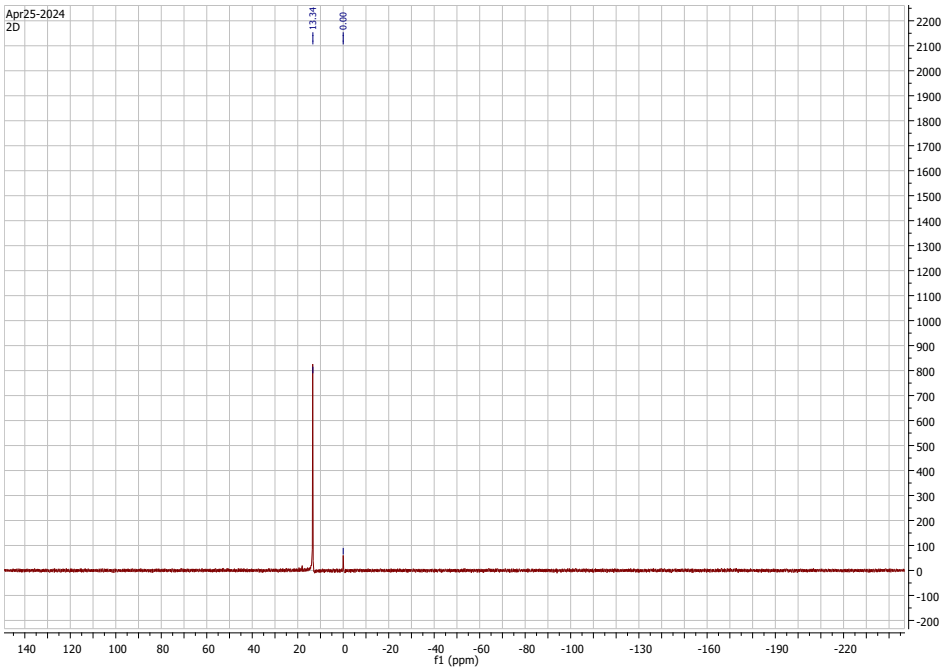
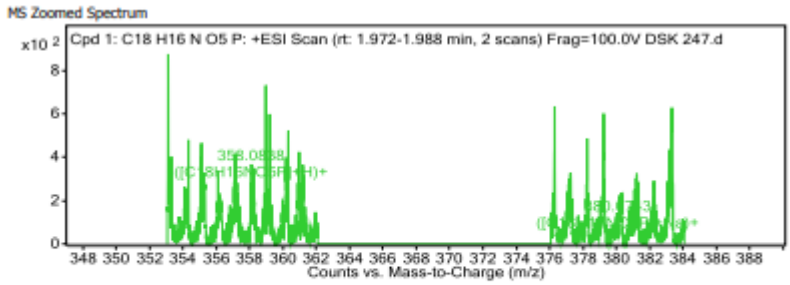


Figure S44 31P NMR spectrum of **21d** in [D_6]-DMSO (162 MHz, 300 K).

HRMS



MS Spectrum Peak List

m/z	*Calc m/z*	Diff(ppm)	z	Abund	Formula	Ion
357.0745	357.0761	4.3	1	287	C18H16NO5P	M+
358.0838	358.0839	0.24	1	287.22	C18H16NO5P	(M+H)+
380.0743	380.0658	-22.27	1	53.67	C18H16NO5P	(M+Na)+

Figure S45. HRMS data for compound **21d**

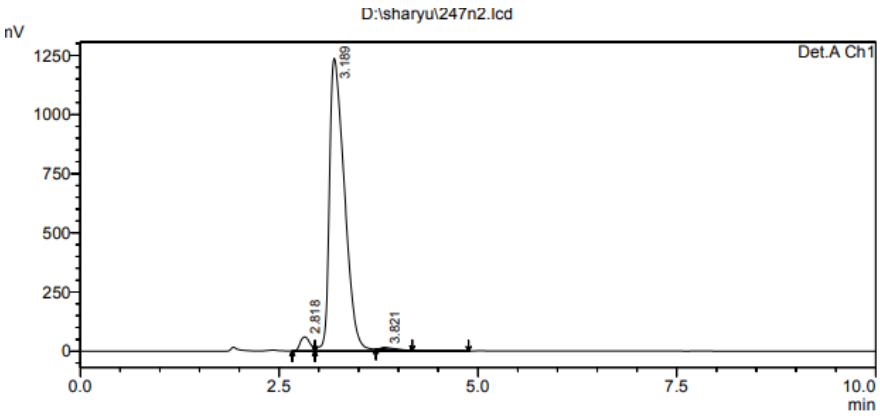


Figure S46. HPLC data for compound **21d**

Compound 22a

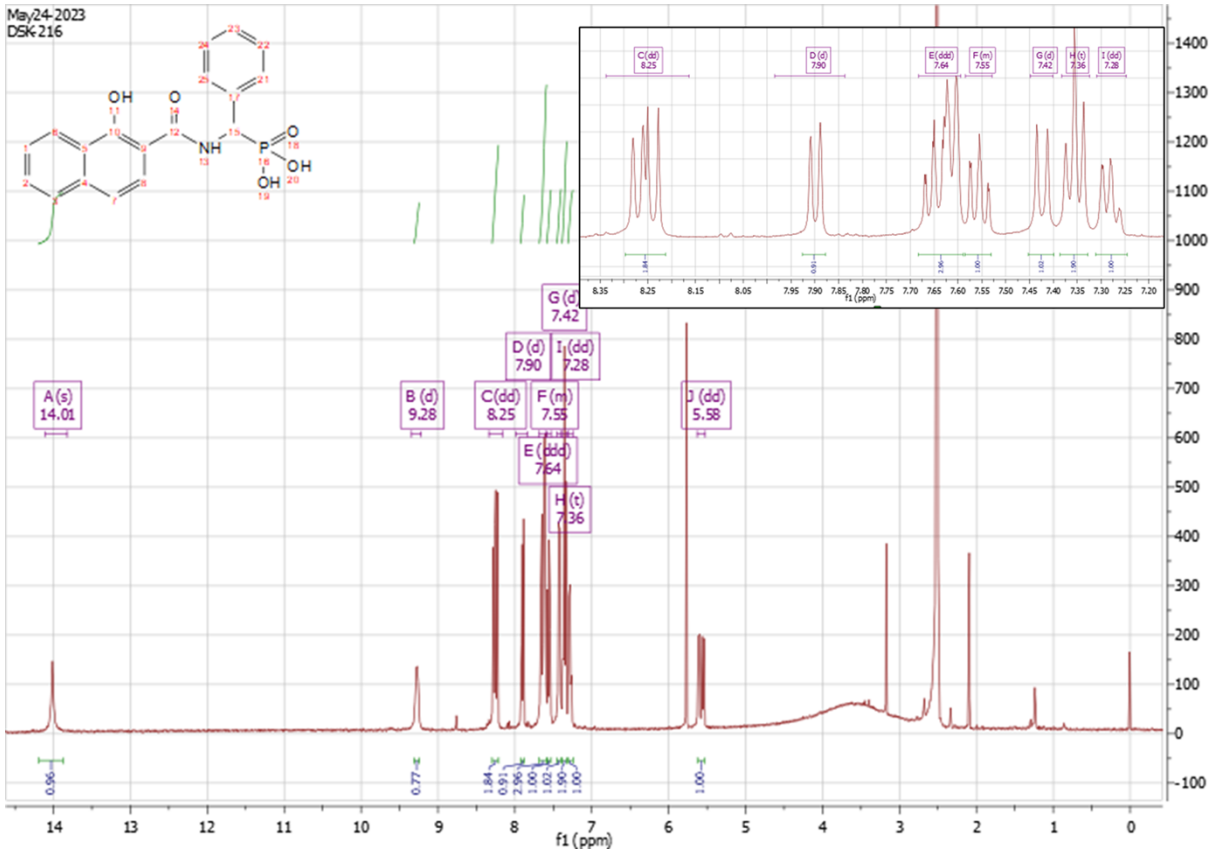


Figure S47 1H NMR spectrum of **22a** in [D_6]-DMSO (400 MHz, 300 K).

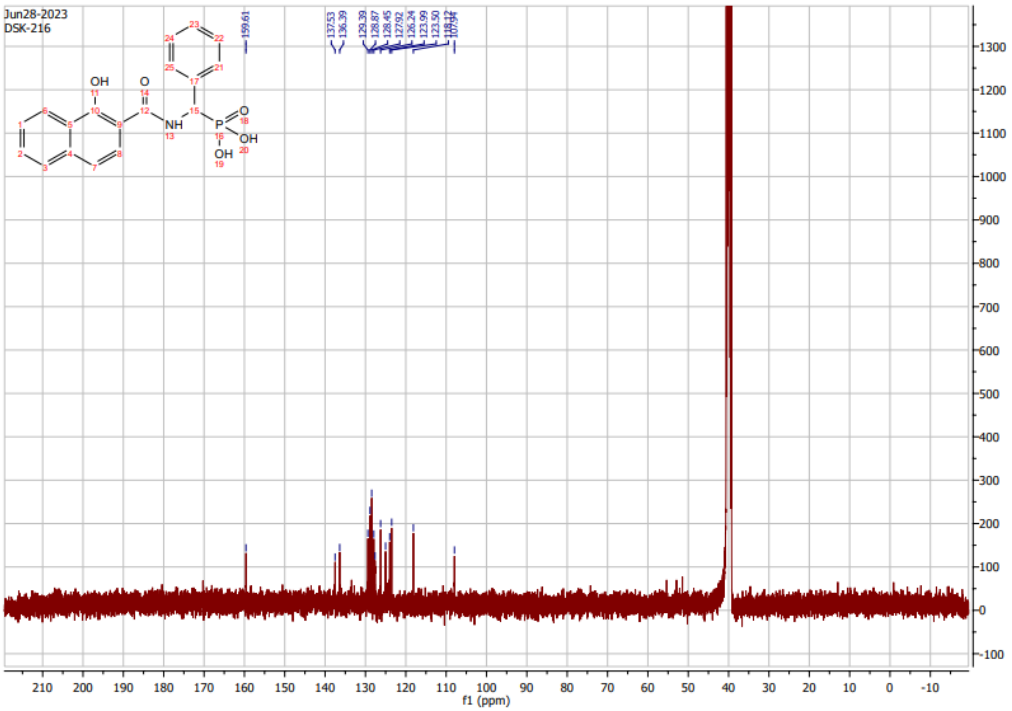
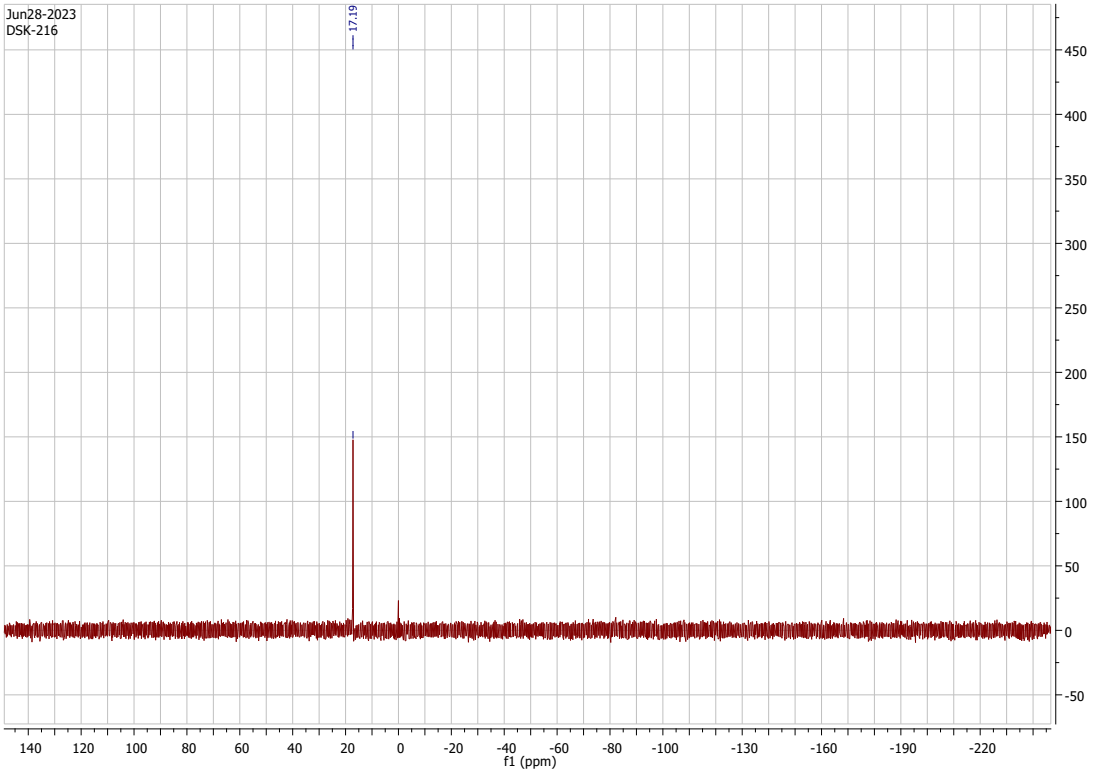


Figure S48 13C NMR spectrum of **22a** in [D_6]-DMSO (101 MHz, 300 K).



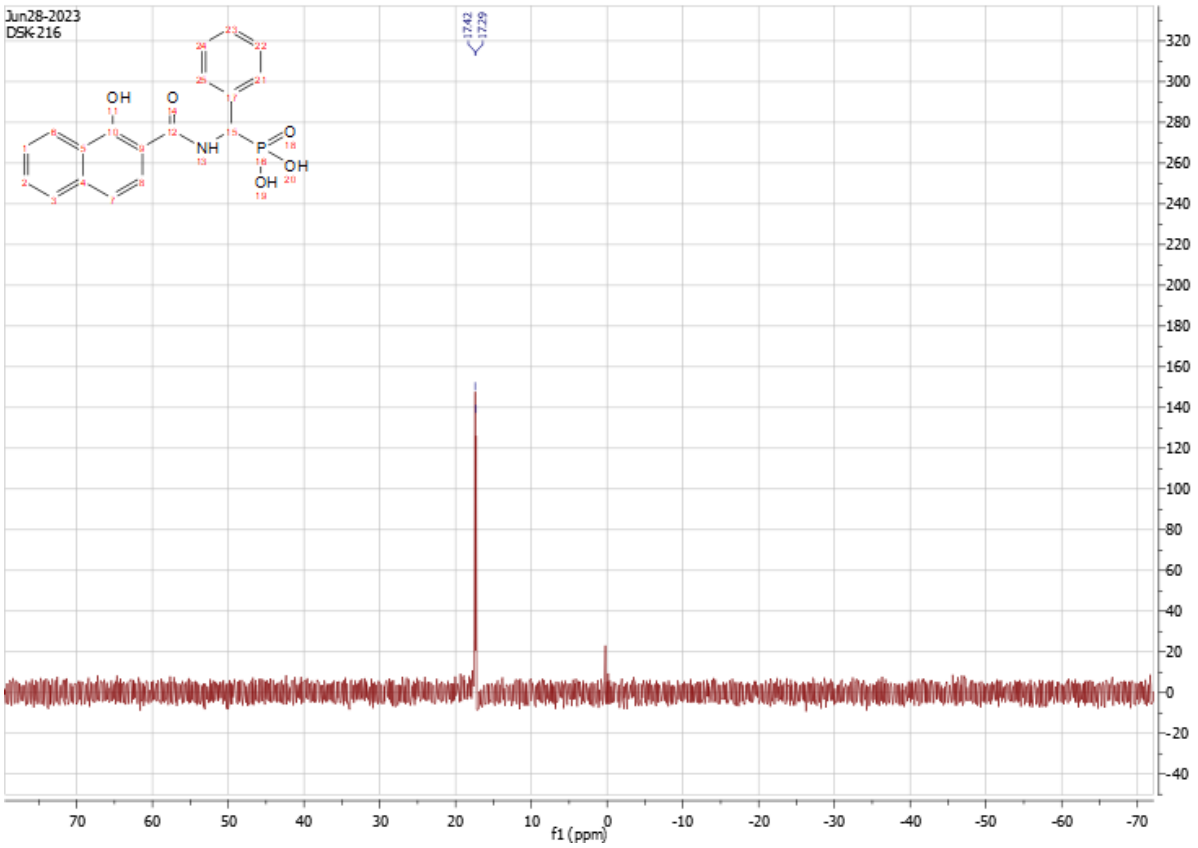
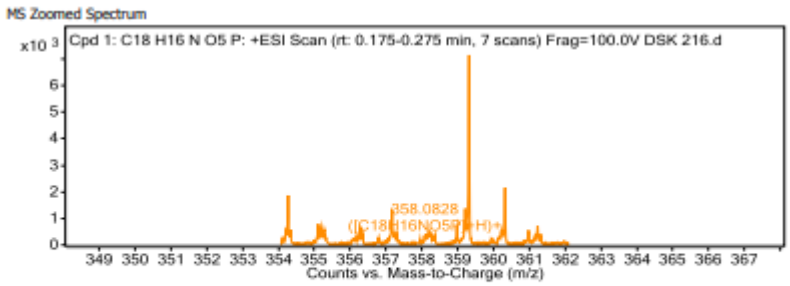


Figure S49 31P NMR spectrum of **22a** in [D_6]-DMSO (162 MHz, 300 K).

HRMS



MS Spectrum Peak List

m/z	*Calc m/z*	Diff(ppm)	z	Abund	Formula	Ion
358.0828	358.0839	2.95	1	365.56	C18H16NO5P	(M+H)+

Figure S50. HRMS data for compound **22a**

HPLC trace

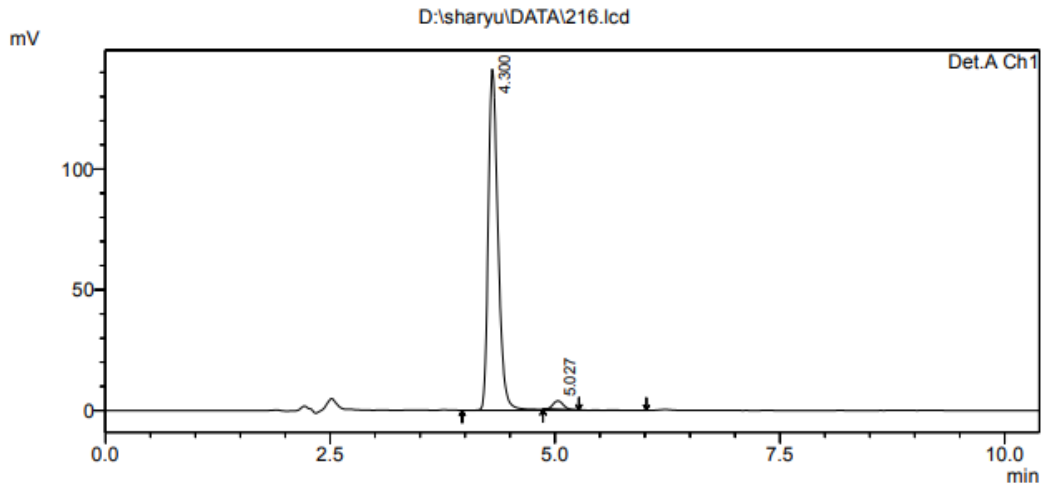


Figure S51. HPLC data for compound **22a**

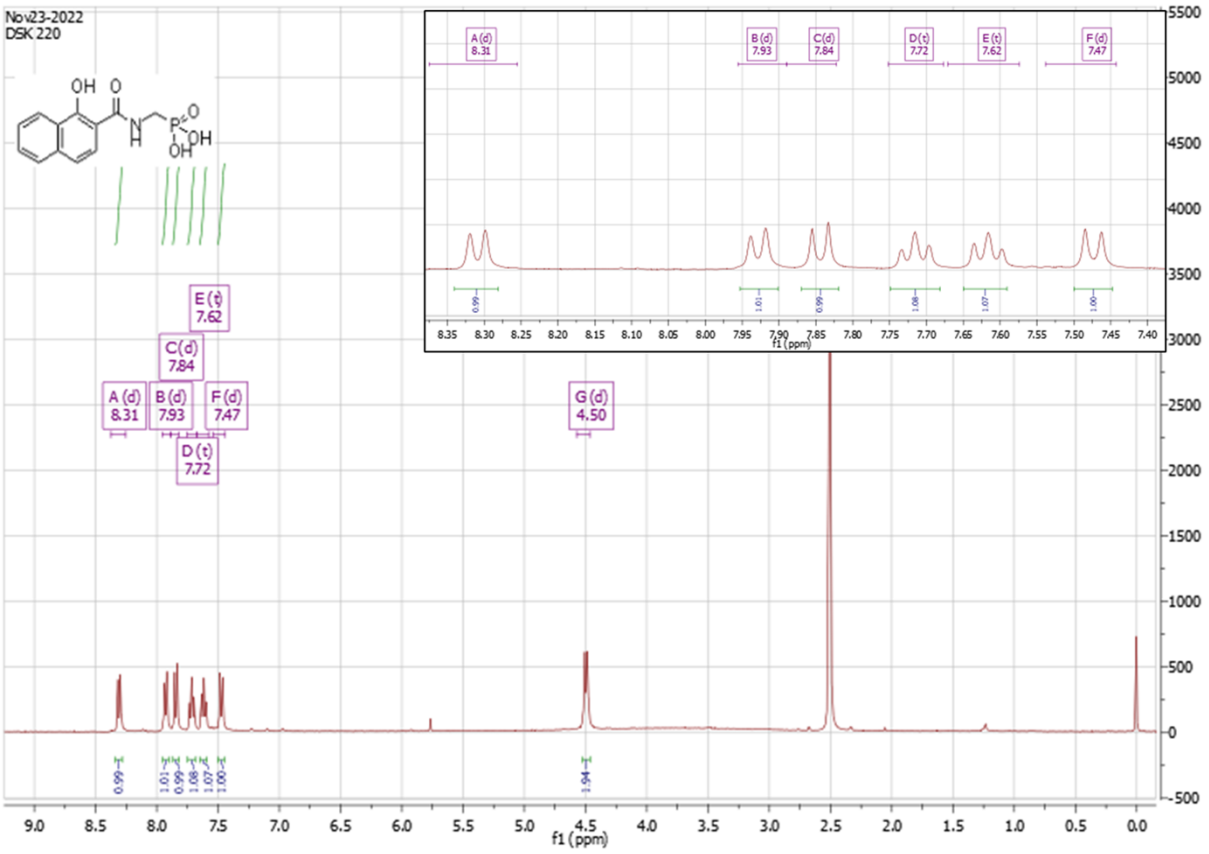


Figure S52 1H NMR spectrum of **22b** in [D_6]-DMSO (400 MHz, 300 K).

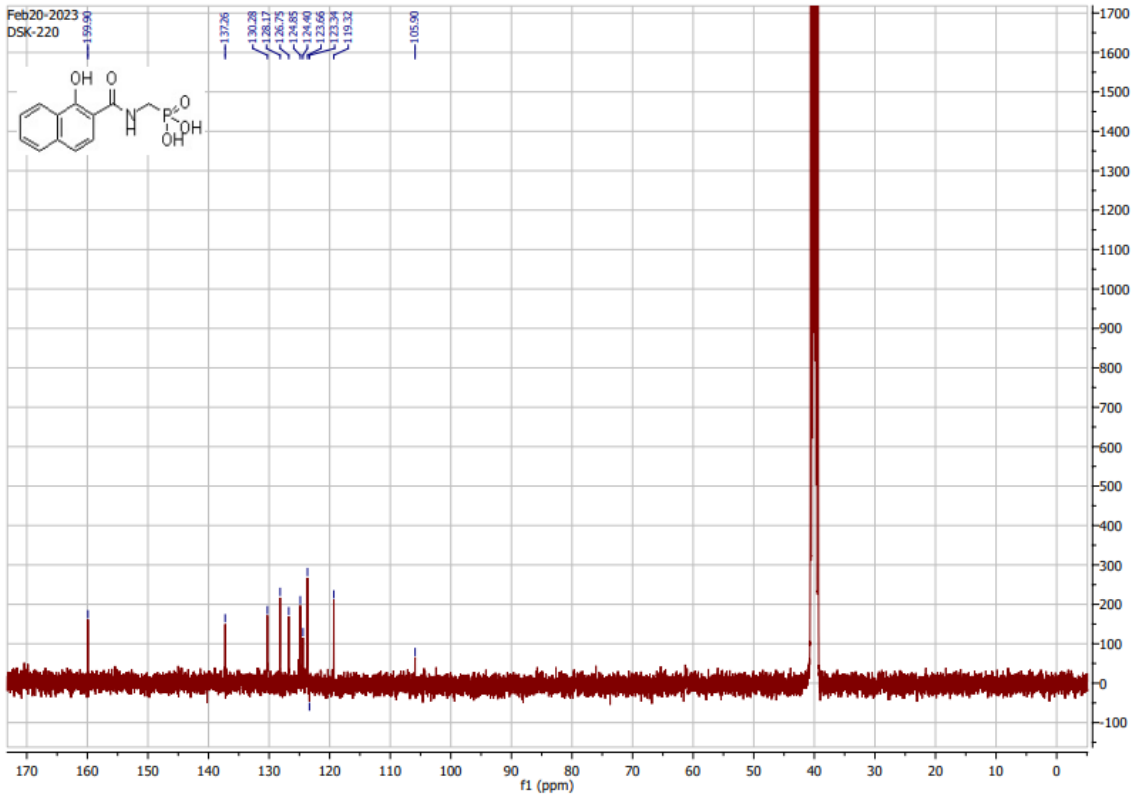


Figure S53 13C NMR spectrum of **22d** in [D_6]-DMSO (101 MHz, 300 K).

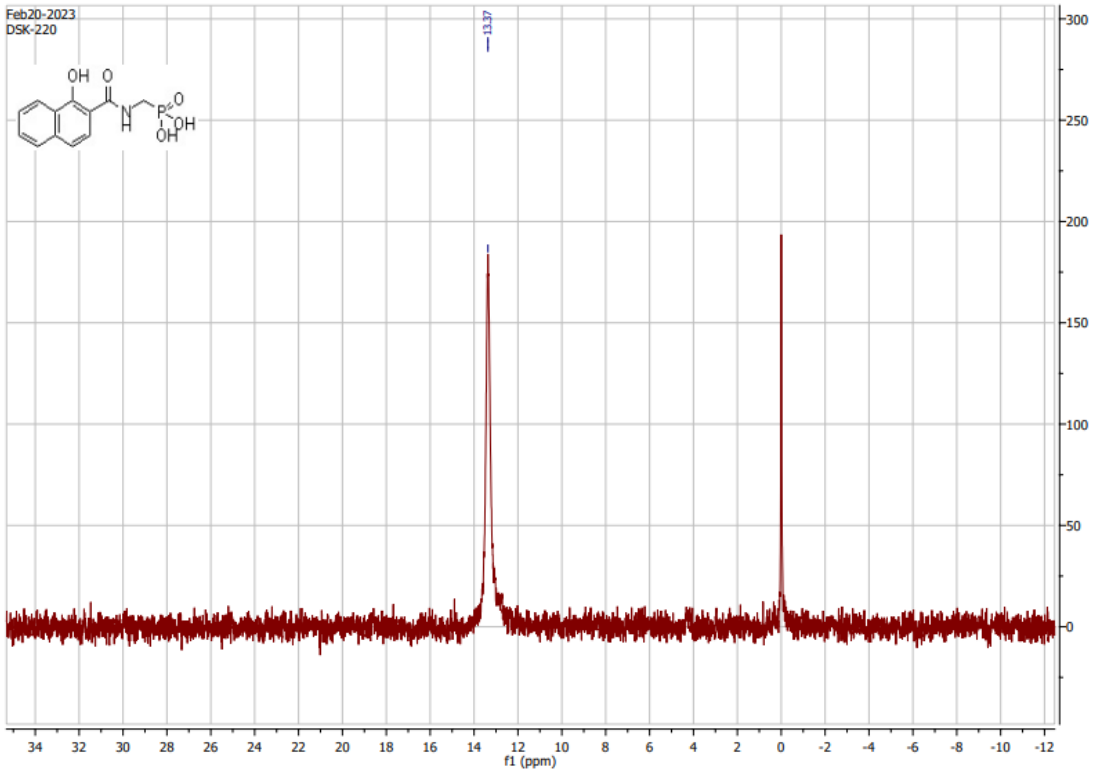
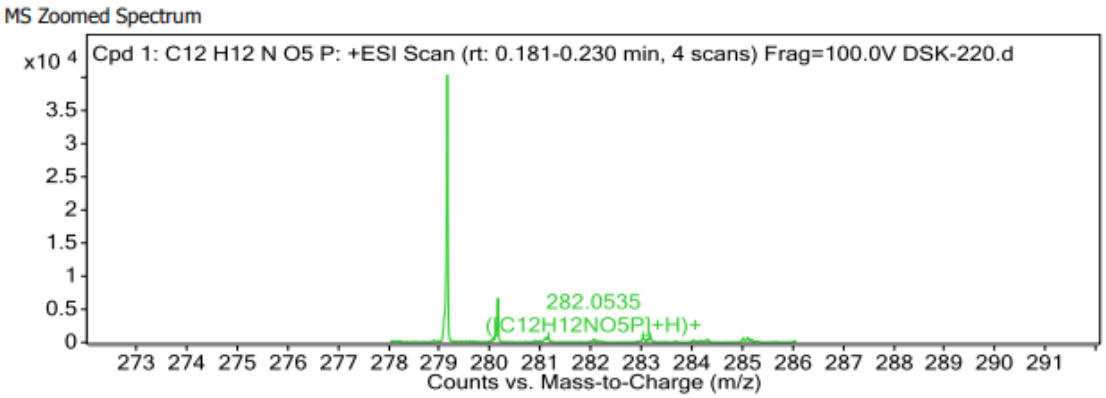


Figure S54 31P NMR spectrum of **22b** in [D_6]-DMSO (162 MHz, 300 K).



MS Spectrum Peak List

m/z	*Calc m/z*	Diff(ppm)	z	Abund	Formula	Ion
282.0535	282.0526	-3.15	1	537.16	C12H12NO5P	(M+H)+

Figure S55. HRMS data for compound **22b**

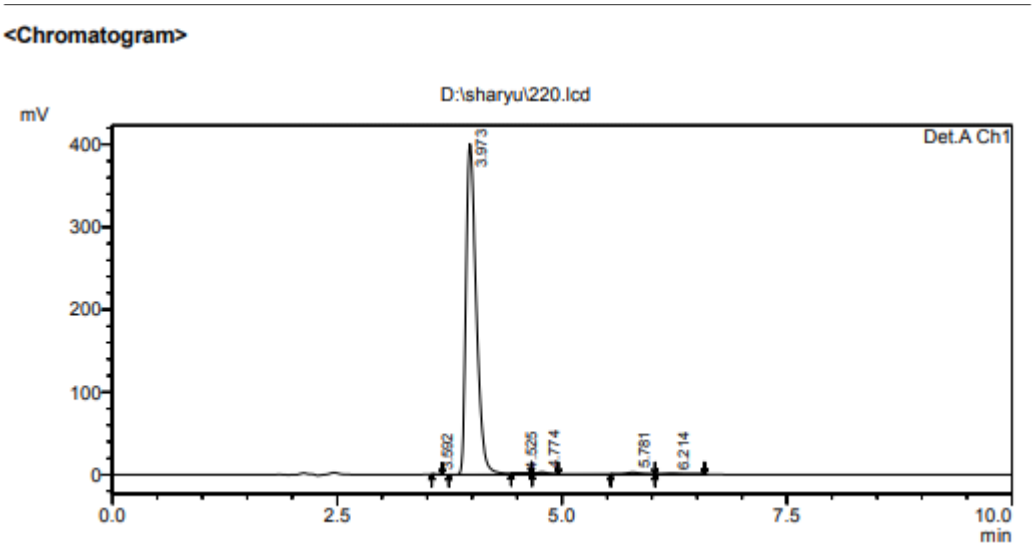


Figure S56. HPLC data for compound **22b**

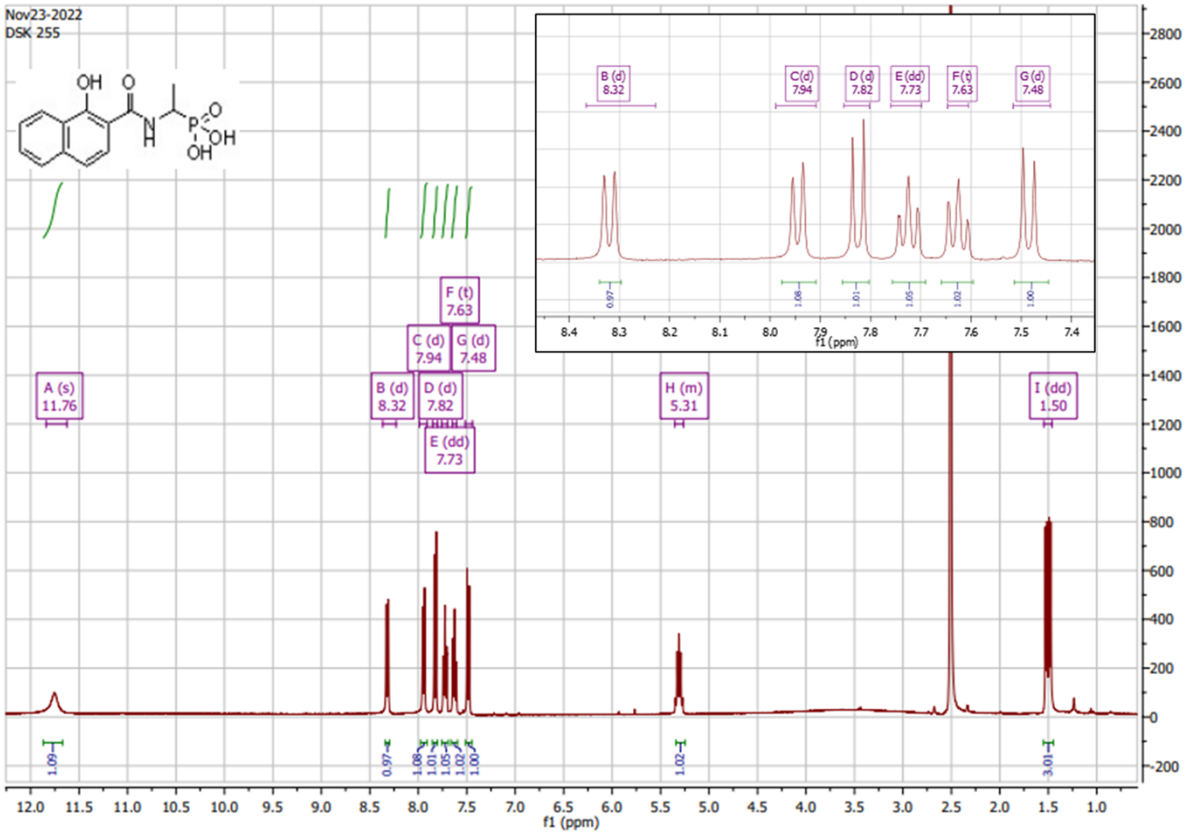


Figure S57 1H NMR spectrum of **22c** in [D_6]-DMSO (400 MHz, 300 K).

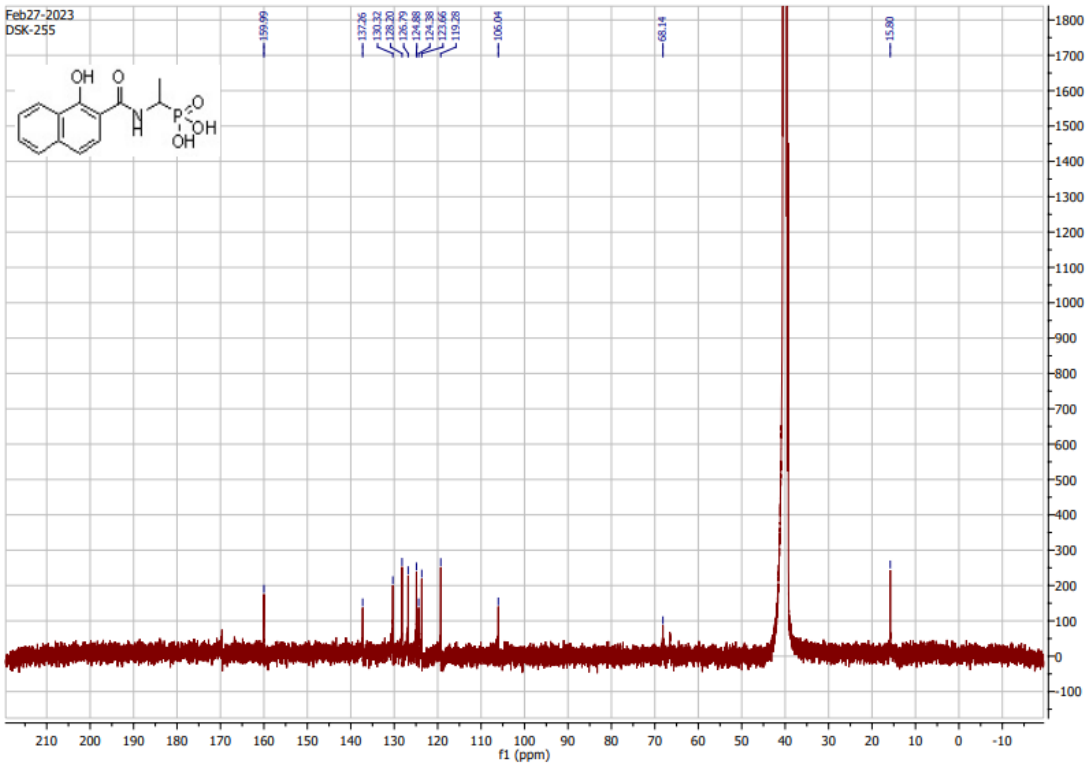


Figure S58 13C NMR spectrum of **22c** in [D_6]-DMSO (101 MHz, 300 K).

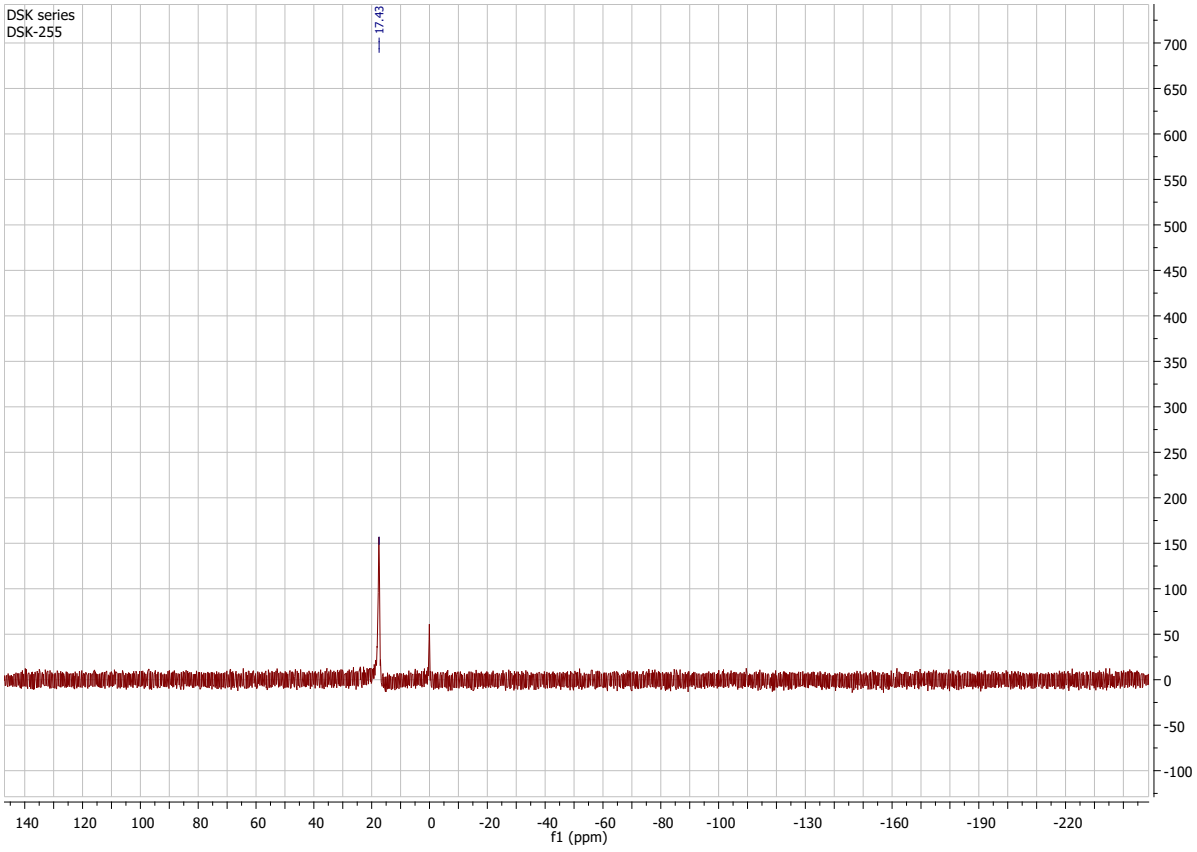


Figure S59 31P NMR spectrum of **22c** in [D_6]-DMSO (162 MHz, 300 K).

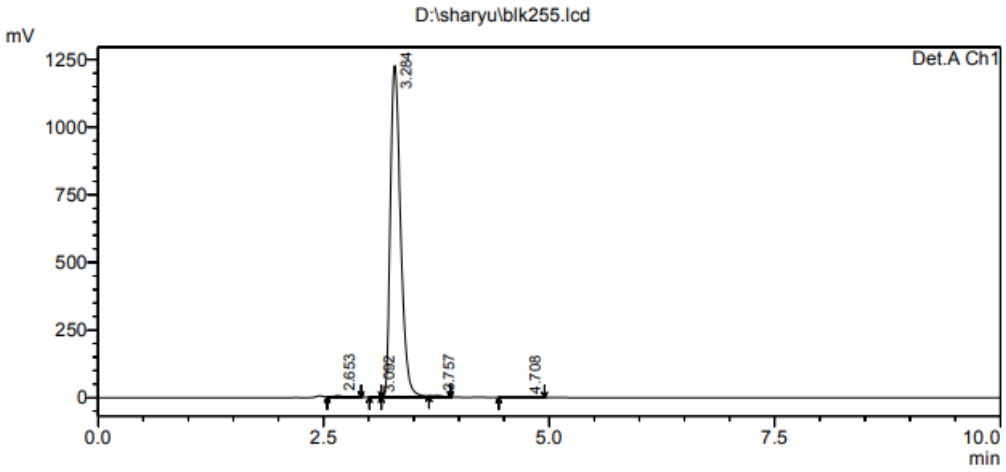


Figure S60. HPLC data for compound **22c**

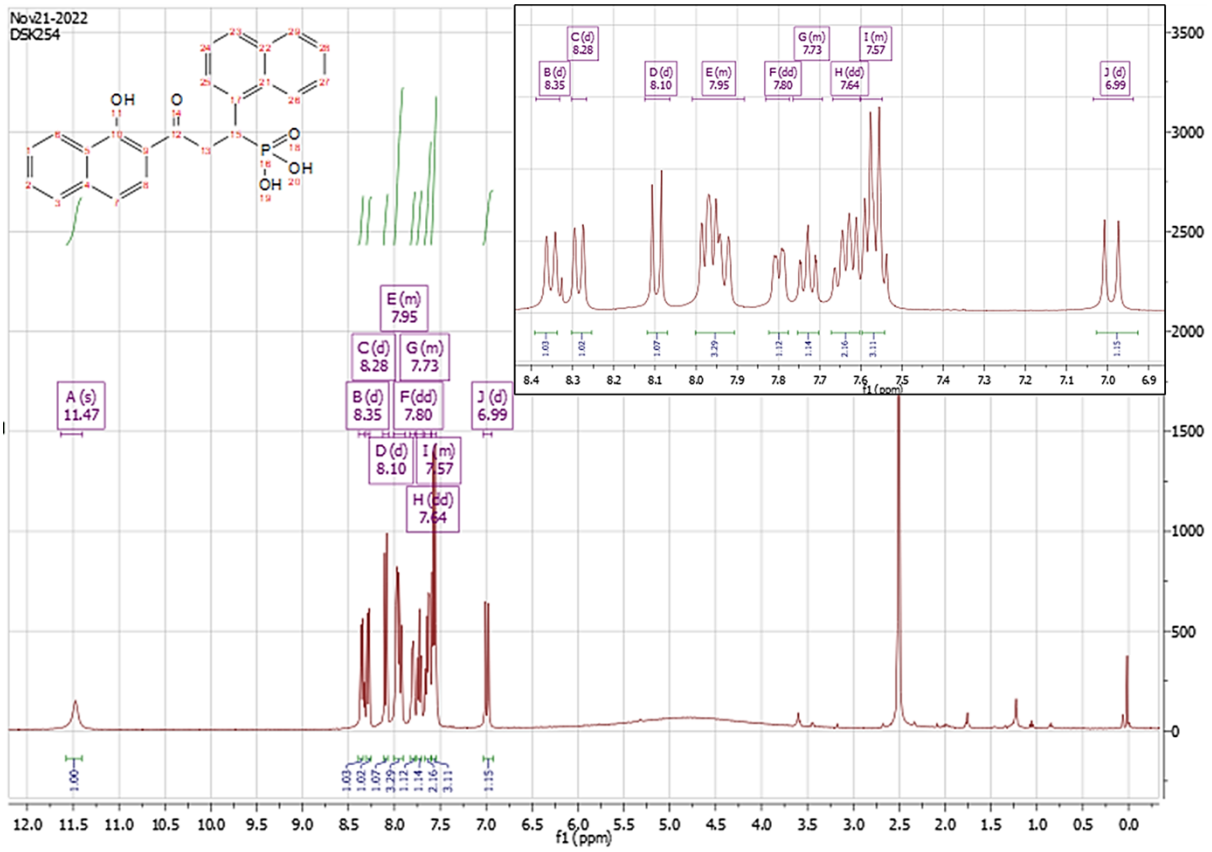


Figure S61 1H NMR spectrum of **22d** in [D_6]-DMSO (400 MHz, 300 K).

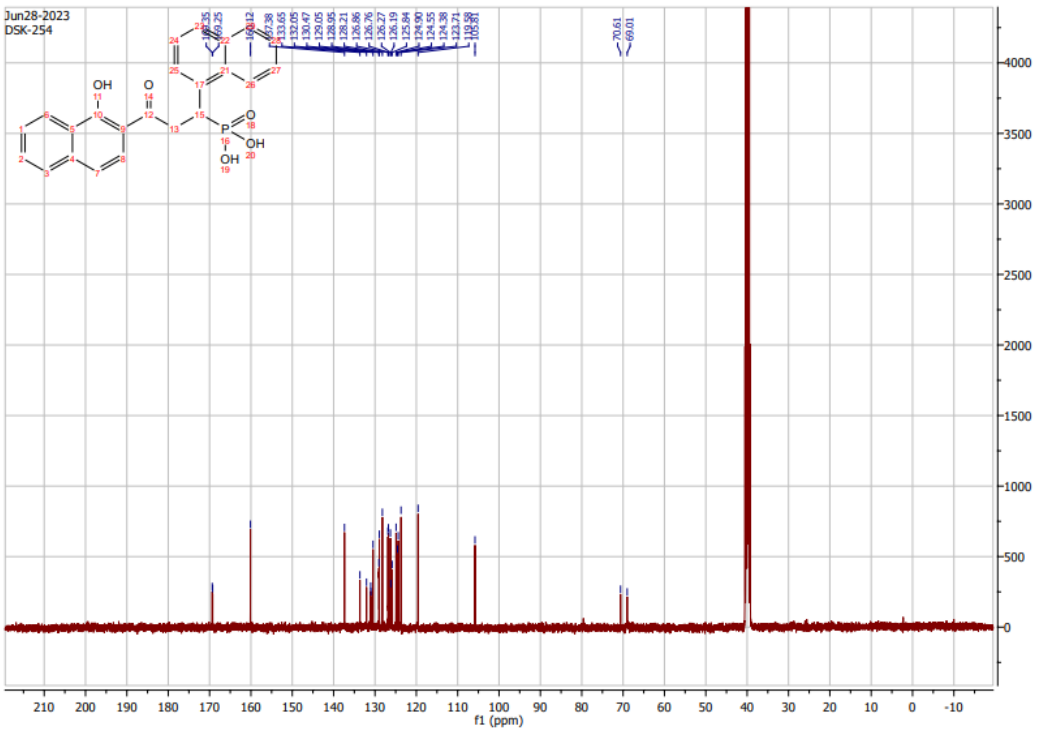


Figure S62 13C NMR spectrum of **22d** in [D_6]-DMSO (400 MHz, 300 K).

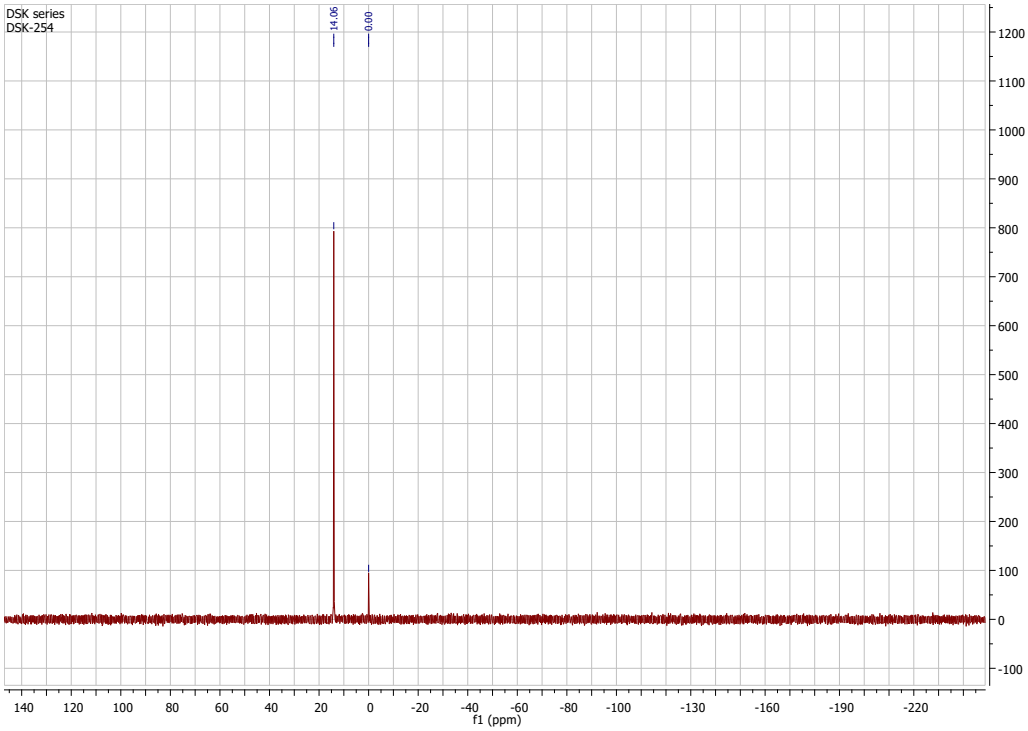
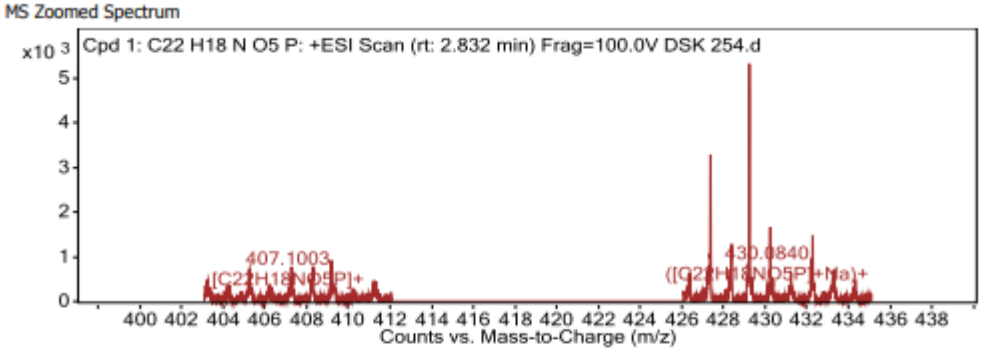


Figure S63 31P NMR spectrum of **22d** in [D_6]-DMSO (400 MHz, 300 K).



MS Spectrum Peak List

m/z	*Calc m/z*	Diff(ppm)	z	Abund	Formula	Ion
407.1003	407.0917	-21.14	1	223.79	C22H18NO5P	M+
408.0877	408.0995	28.96	1	124.2	C22H18NO5P	(M+H)+
430.084	430.0815	-5.82	1	345.85	C22H18NO5P	(M+Na)+
431.0903	431.0848	-12.8	1	198.17	C22H18NO5P	(M+Na)+

Figure S64. HRMS data for compound **22d**

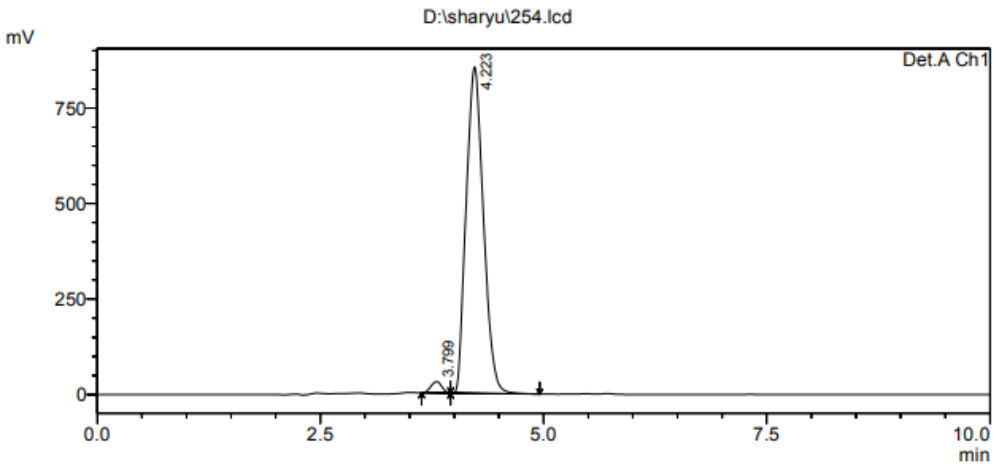


Figure S65. HPLC data for compound **22d**

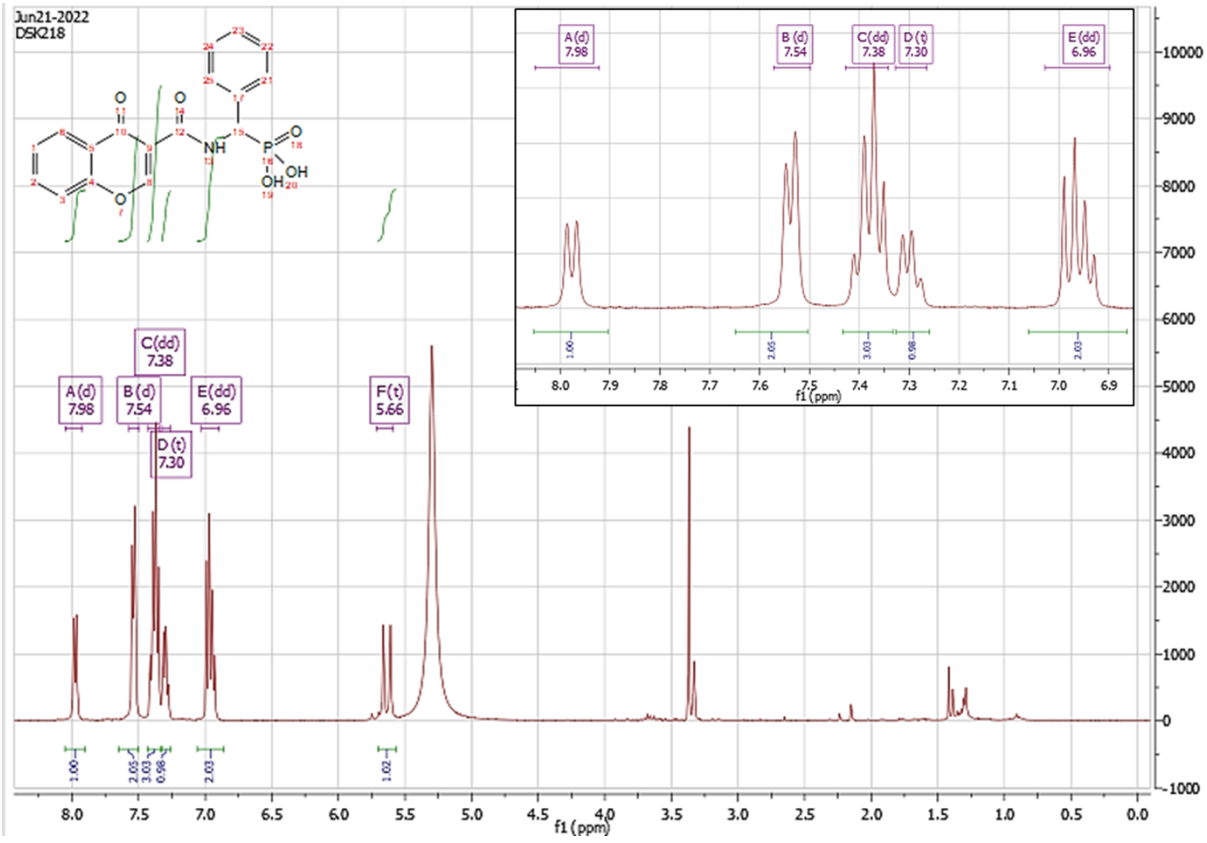


Figure S66 1H NMR spectrum of **23a** in [D_6]-DMSO (400 MHz, 300 K).

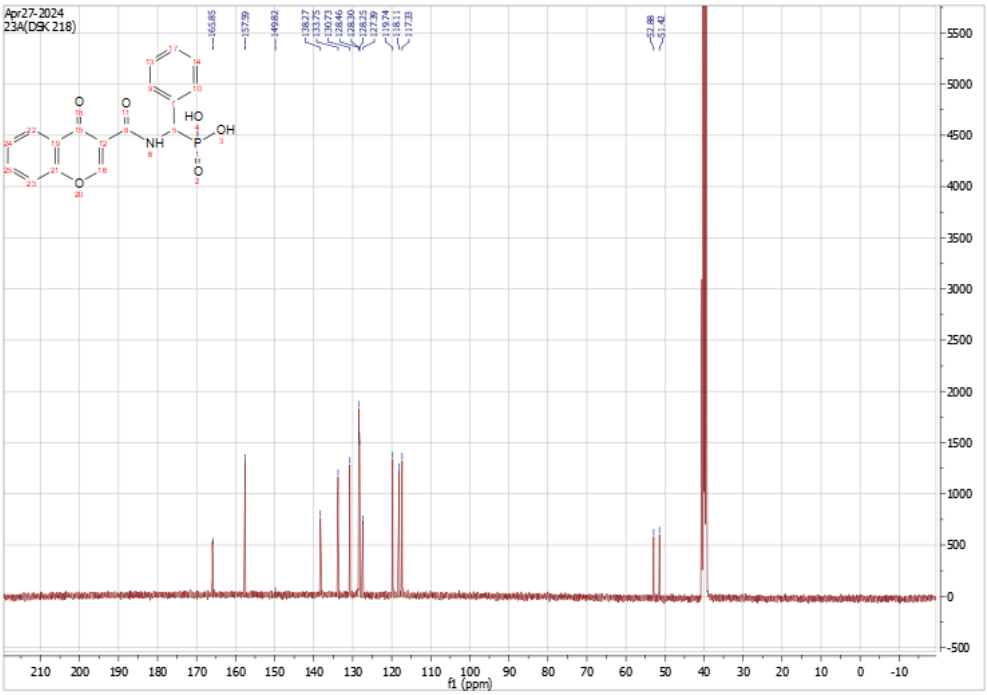
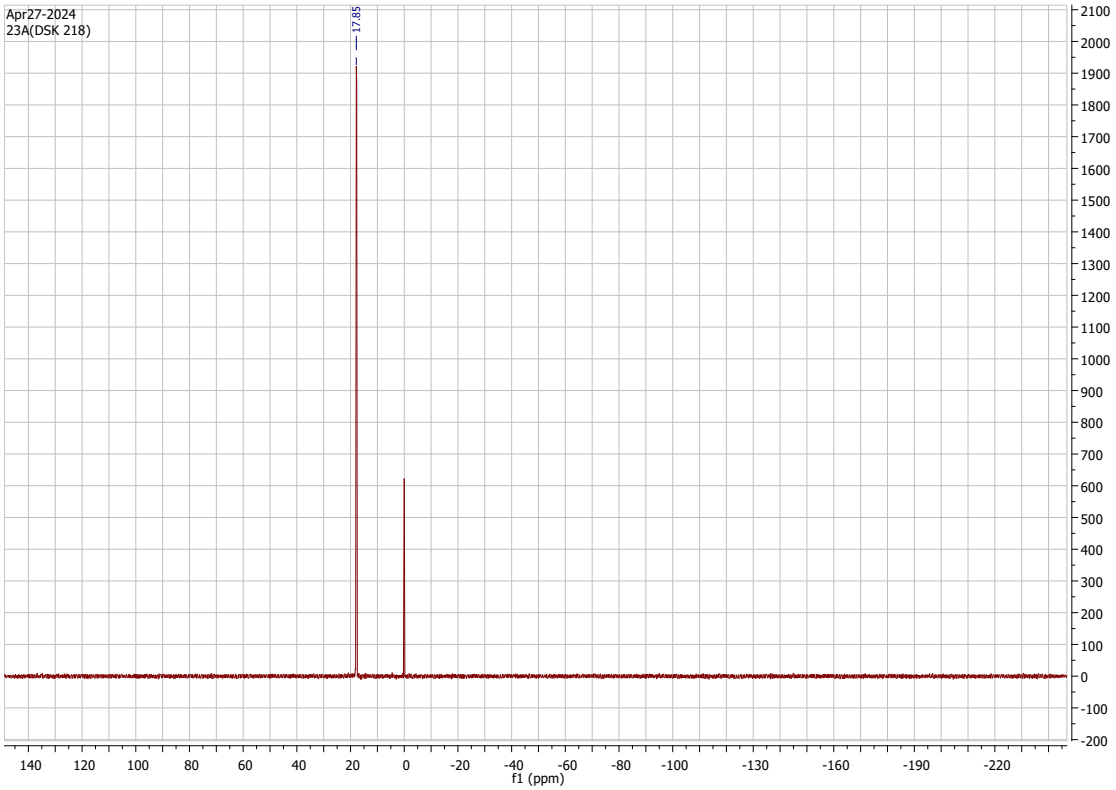


Figure S67 13C NMR spectrum of **23a** in [D_6]-DMSO (101 MHz, 300 K).



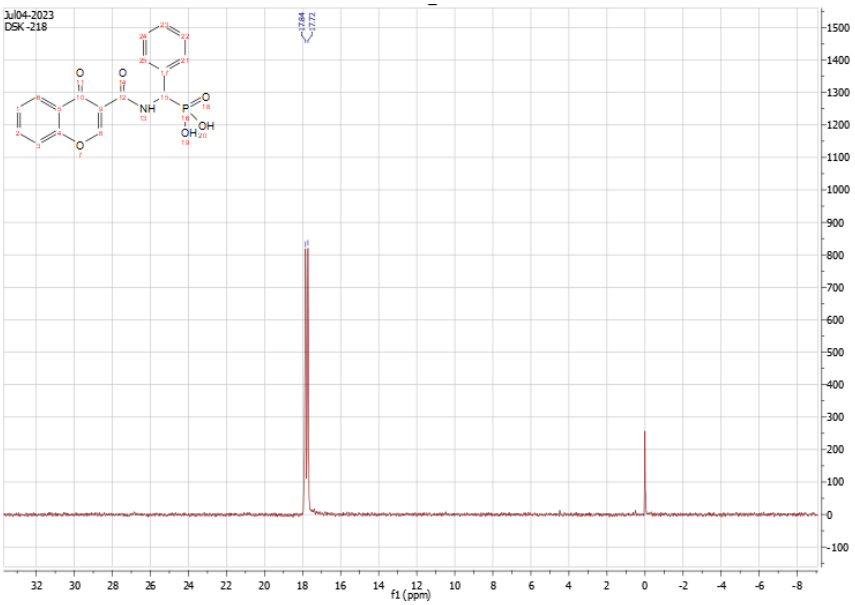


Figure S68 31P NMR spectrum of **23a** in [D_6]-DMSO (162 MHz, 300 K).

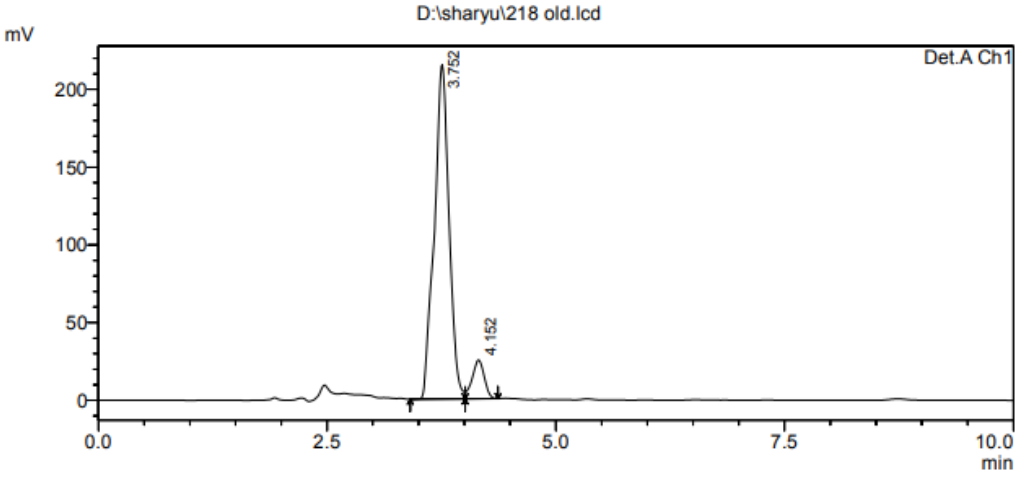


Figure S69. HPLC data for compound **23a**

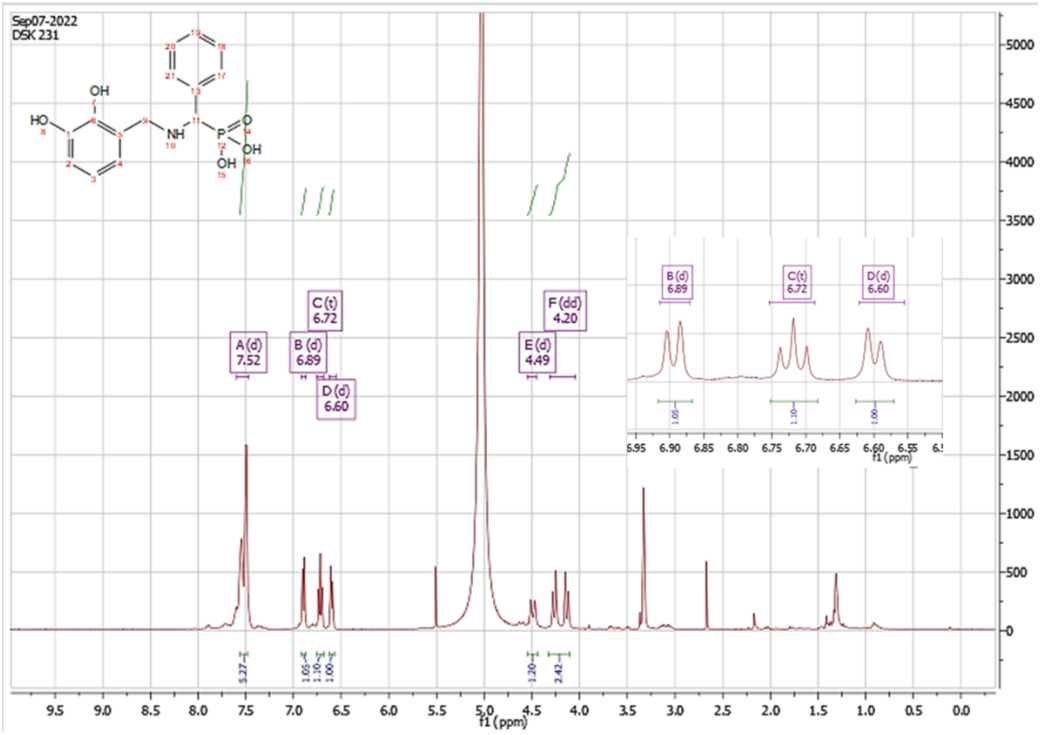


Figure S70 1H NMR spectrum of **28a** in [D_4]-MeOD (400 MHz, 300 K).

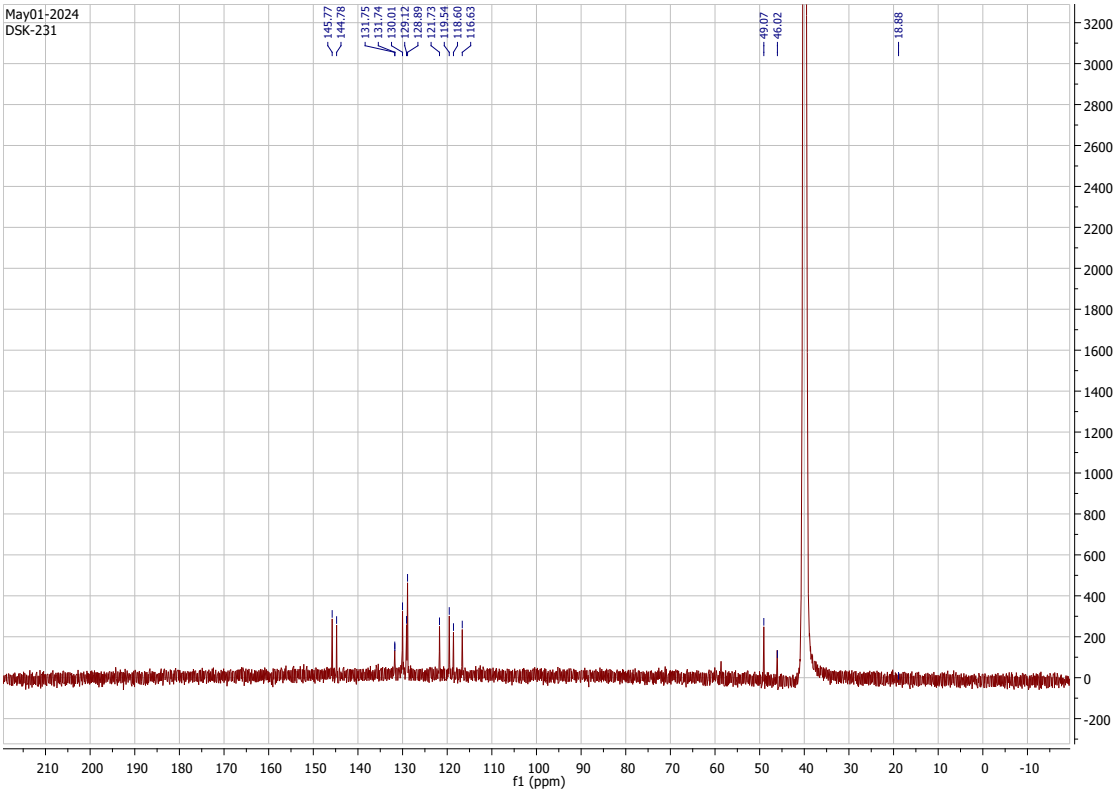


Figure S71 13C NMR spectrum of **28a** in [D_6]-DMSO (101 MHz, 300 K).

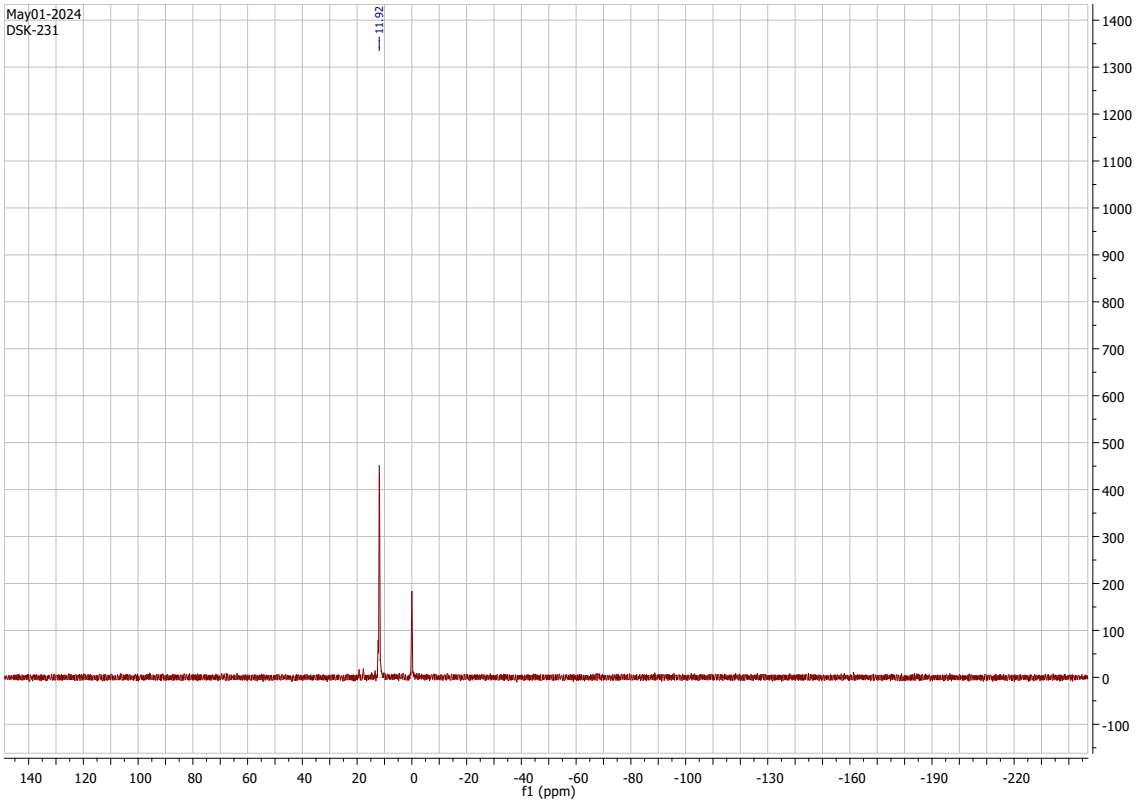
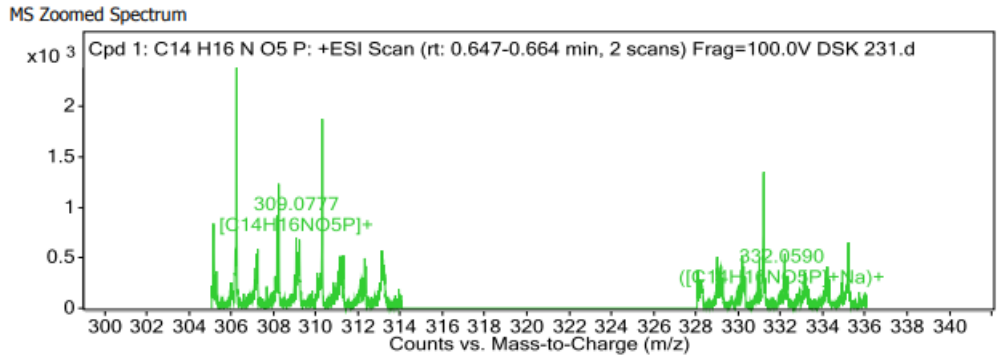


Figure S72 31P NMR spectrum of **28a** in [D_6]-DMSO (162 MHz, 300 K).



MS Spectrum Peak List

m/z	*Calc m/z*	Diff(ppm)	z	Abund	Formula	Ion
309.0777	309.0761	-5.28	1	704.96	C14H16NO5P	M+
310.0776	310.0839	20.39	1	364.03	C14H16NO5P	(M+H)+
332.059	332.0658	20.54	1	186.95	C14H16NO5P	(M+Na)+

Figure S73. HRMS data for compound **28a**

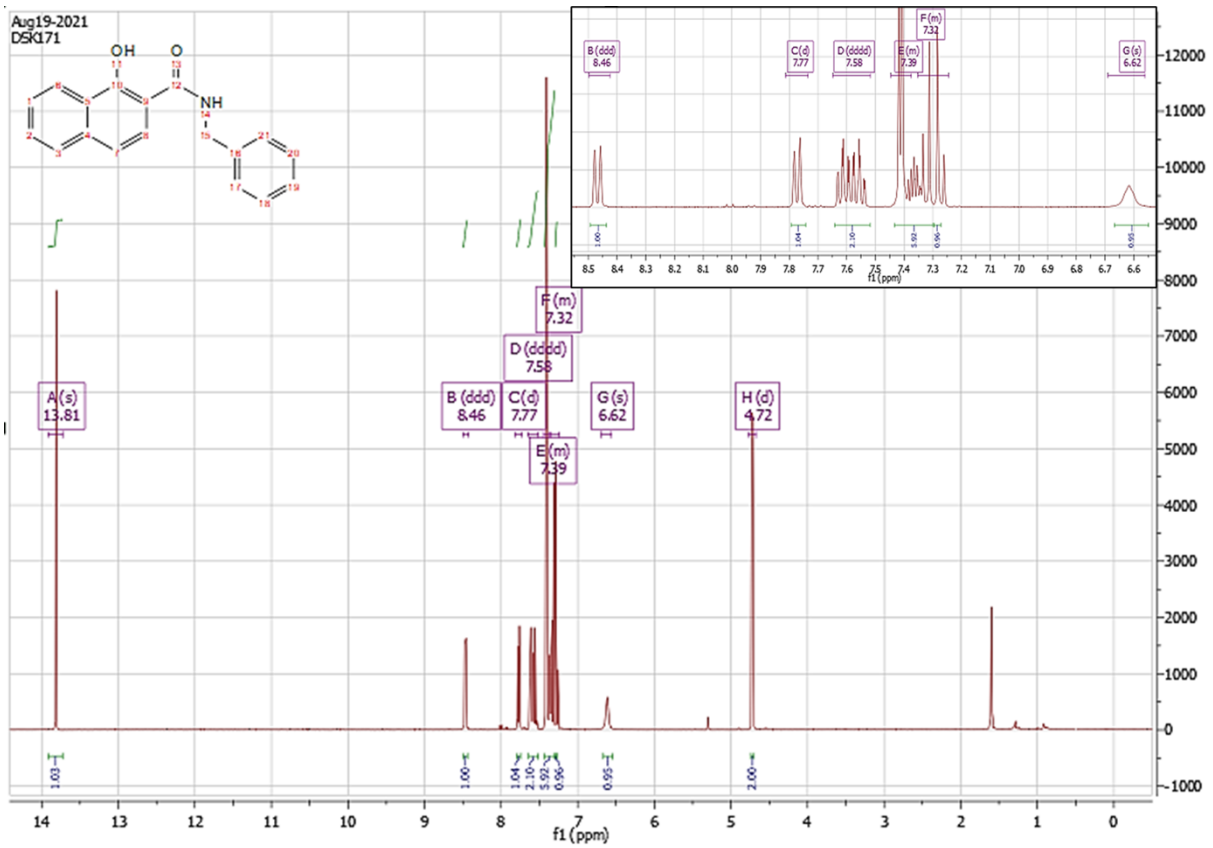


Figure S74 1H NMR spectrum of **25a** in [D]-$CDCl_3$ (400 MHz, 300 K).

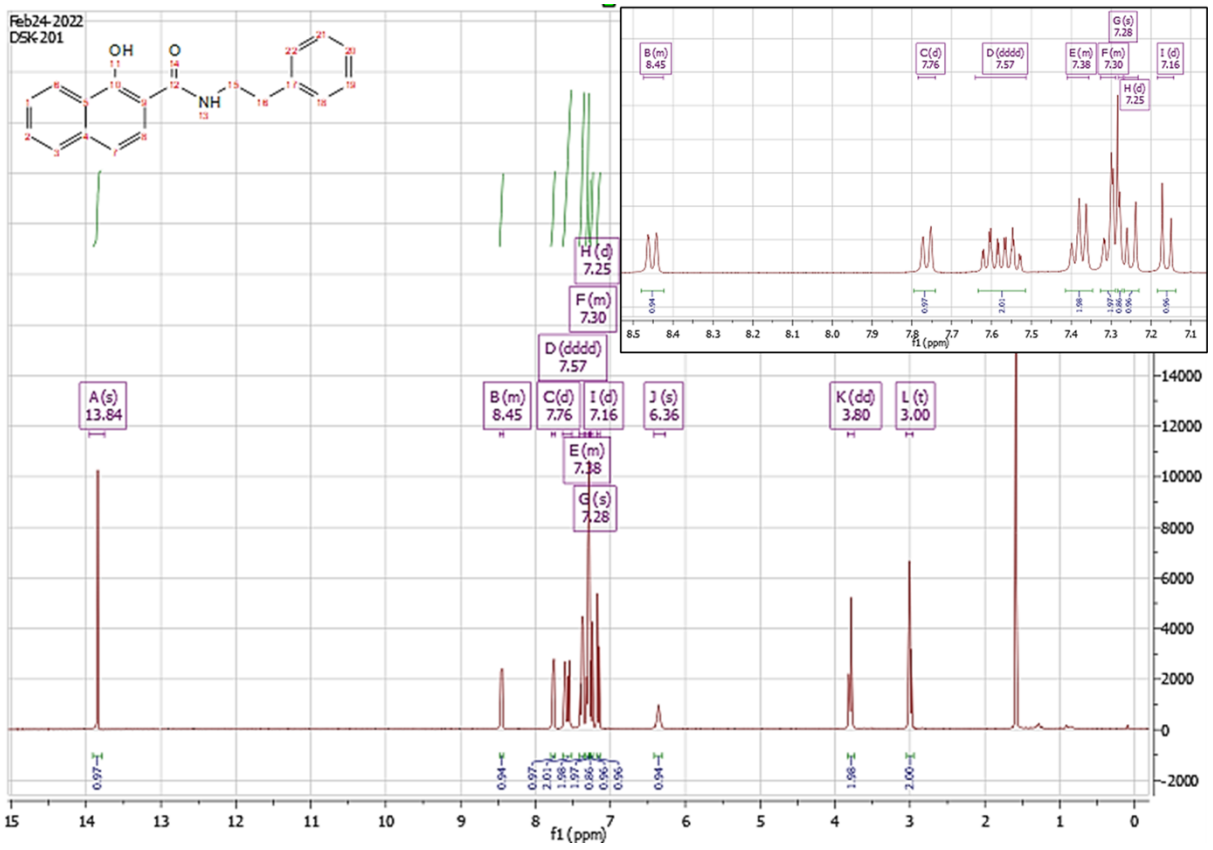


Figure S75 1H NMR spectrum of **25b** in [D]-$CDCl_3$ (400 MHz, 300 K).

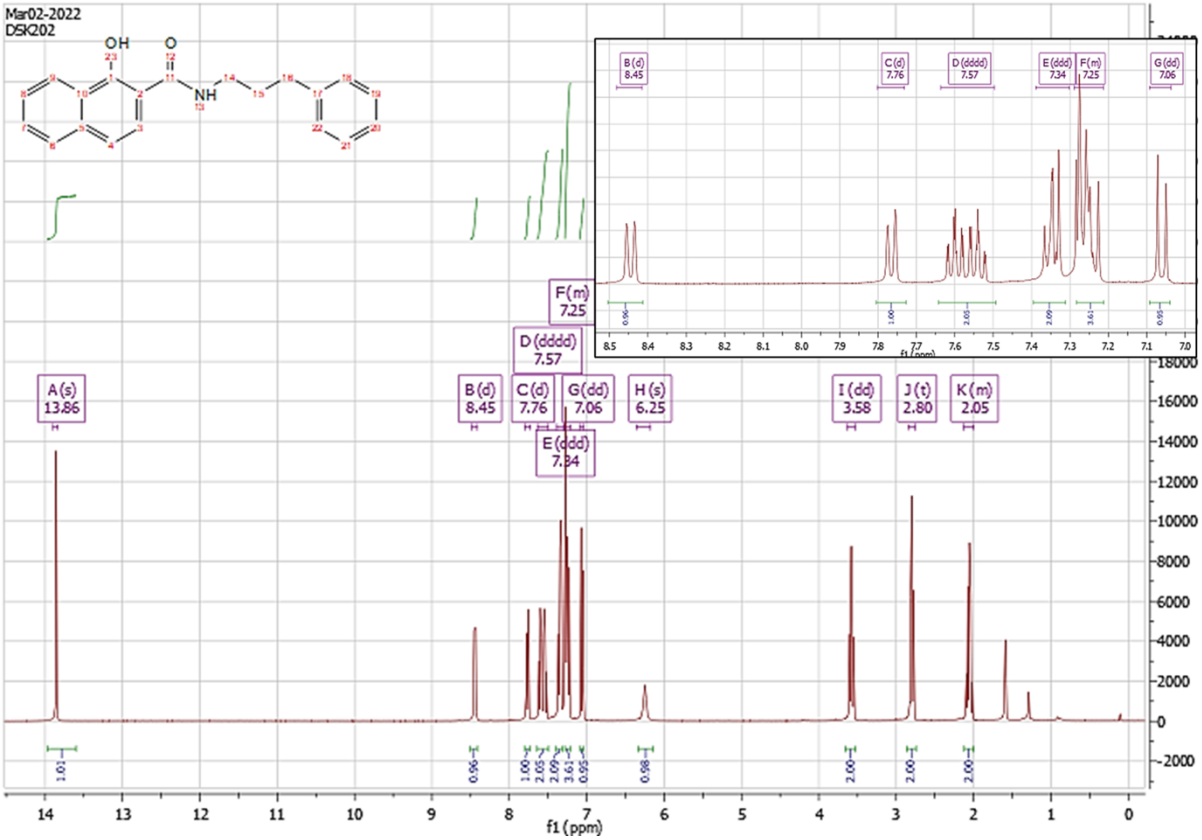


Figure S76 1H NMR spectrum of **25c** in [D]-$CDCl_3$ (400 MHz, 300 K).