Supporting Information for

Original article

Chemistry-led investigations into the mode of action of NAMPT activators, resulting in the discovery of non-pyridyl class NAMPT activators

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NMR spectra

Phenyl (4-((8-oxa-3-azabicyclo[3.2.1]octan-3-yl)sulfonyl)phenyl)carbamate (11)

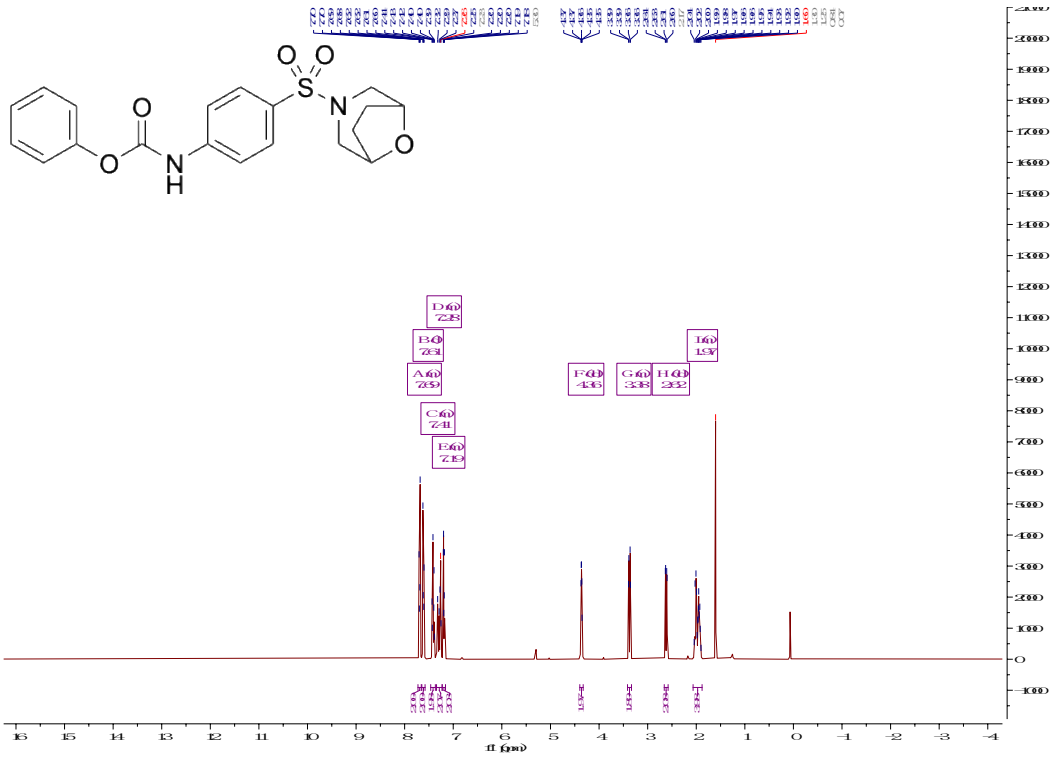

Figure S1. ^{1}H spectra of compound 11.

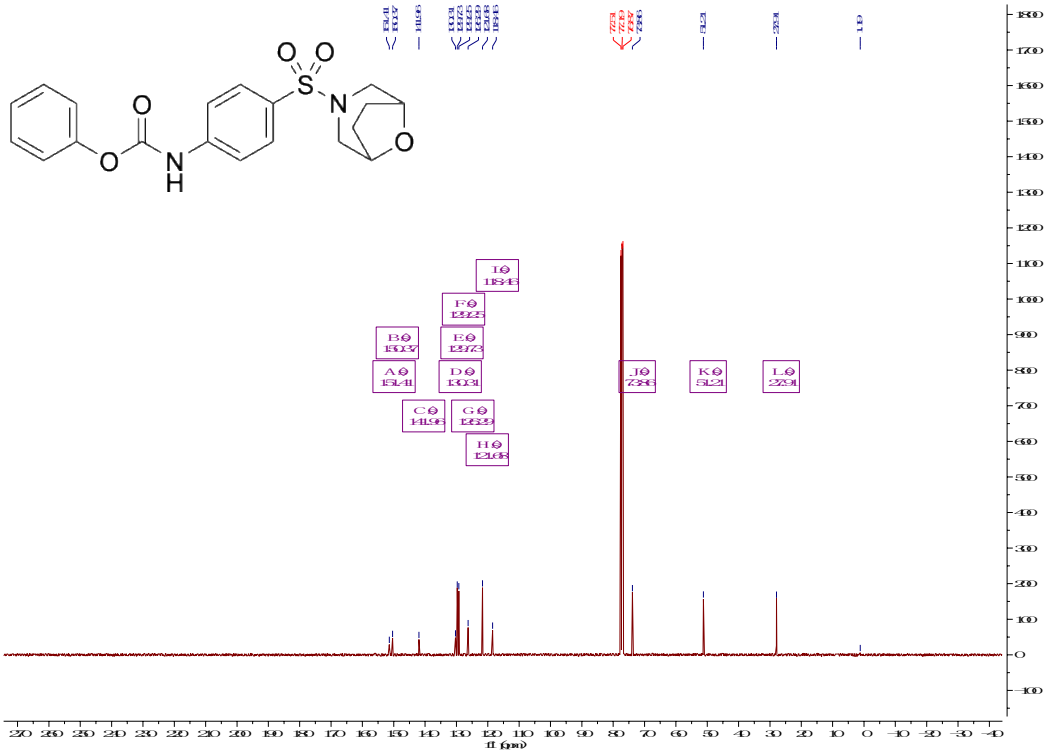

Figure S2. ^{13}C spectra of compound 11.

Phenyl (4-(phenylsulfonyl)phenyl)carbamate (16)

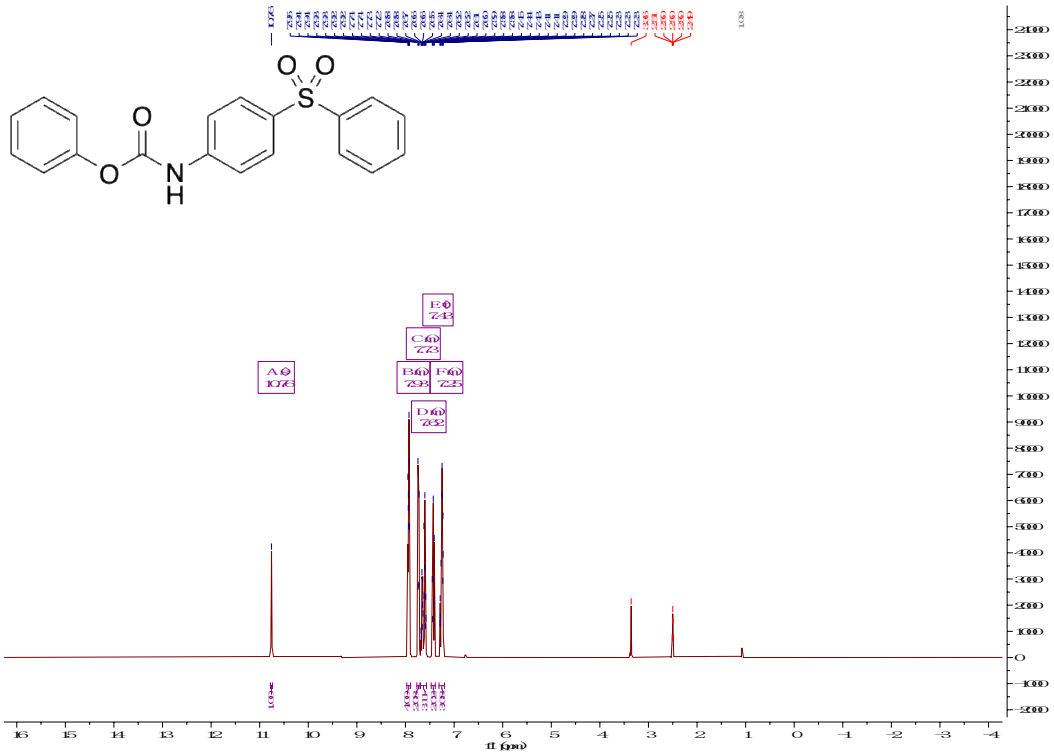

Figure S3. ^{1}H spectra of compound 16.

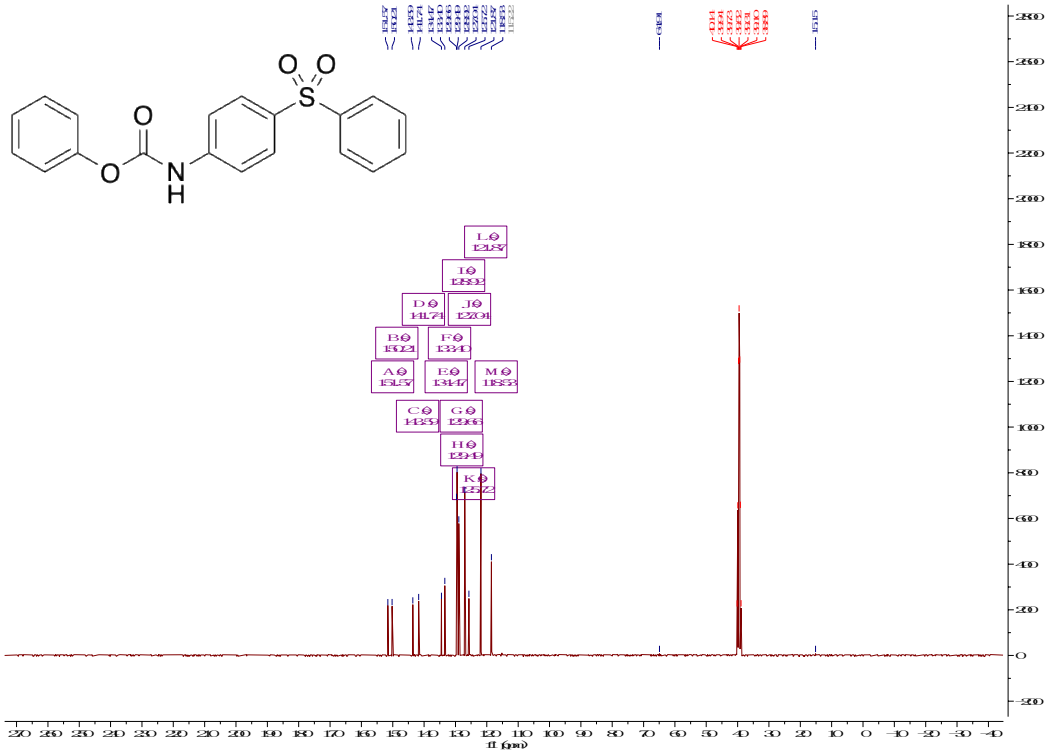

Figure S4. ^{13}C spectra of compound 16.

1-(4-((8-Oxa-3-azabicyclo[3.2.1]octan-3-yl)sulfonyl)phenyl)-3-(pyridin-4-yl)urea (6)

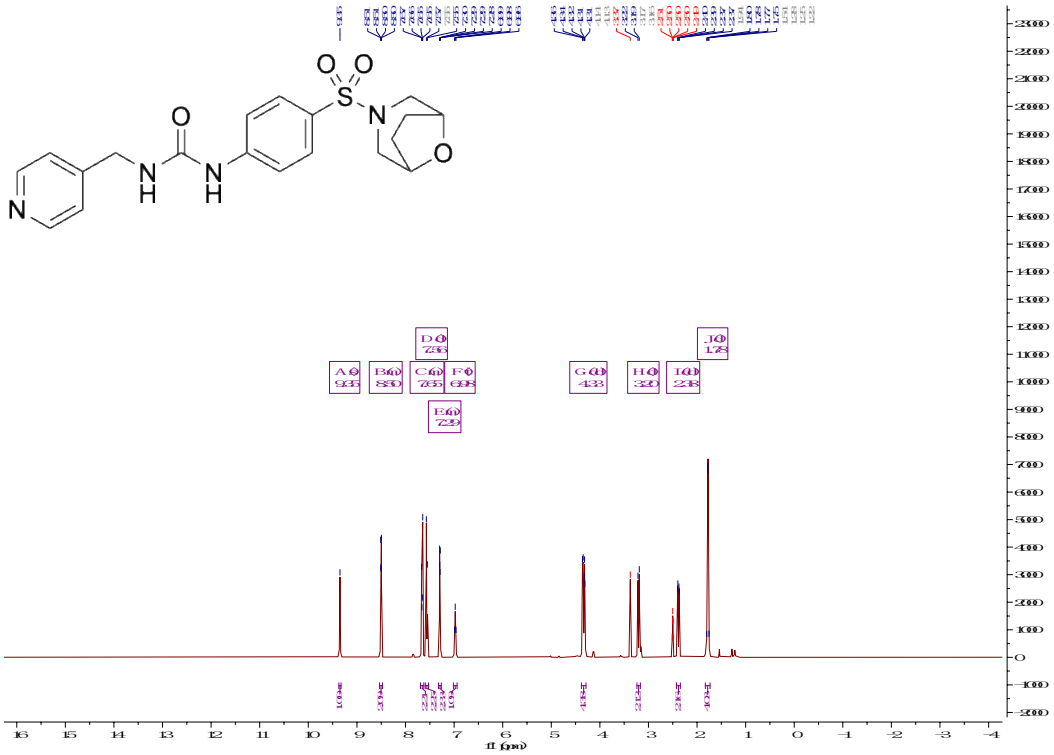

Figure S5. ^{1}H spectra of compound 6.

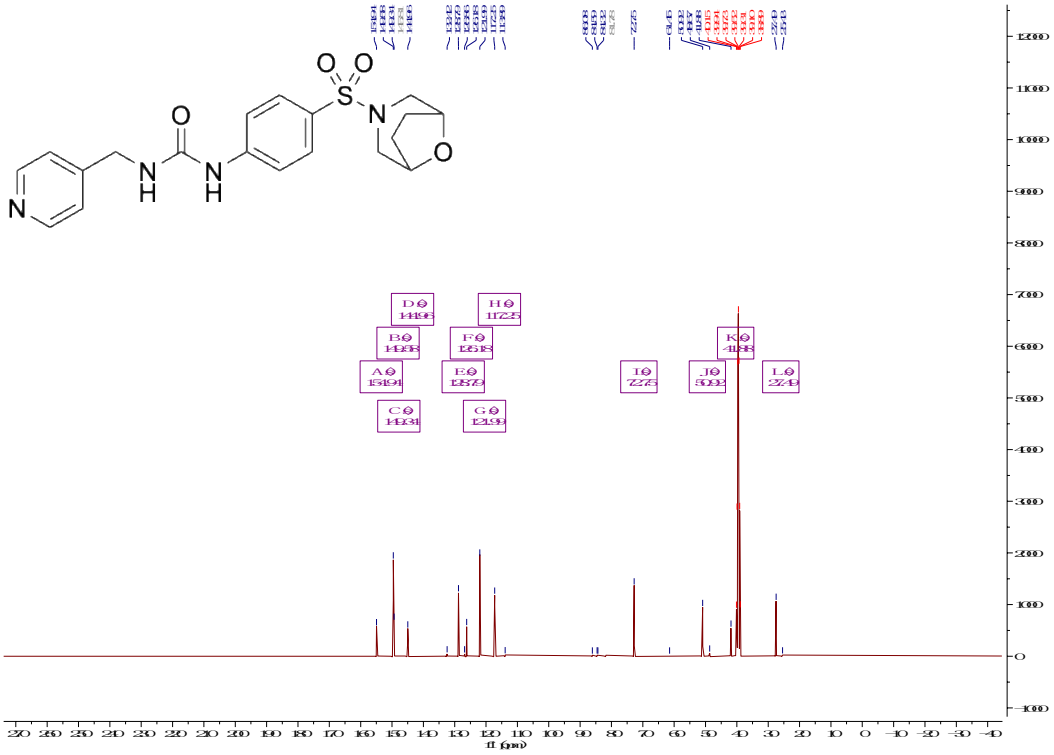

Figure S6. ^{13}C spectra of compound 6.

1-(4-((8-Oxa-3-azabicyclo[3.2.1]octan-3-yl)sulfonyl)phenyl)-3-(4-(hydroxymethyl)benzyl)urea (10)

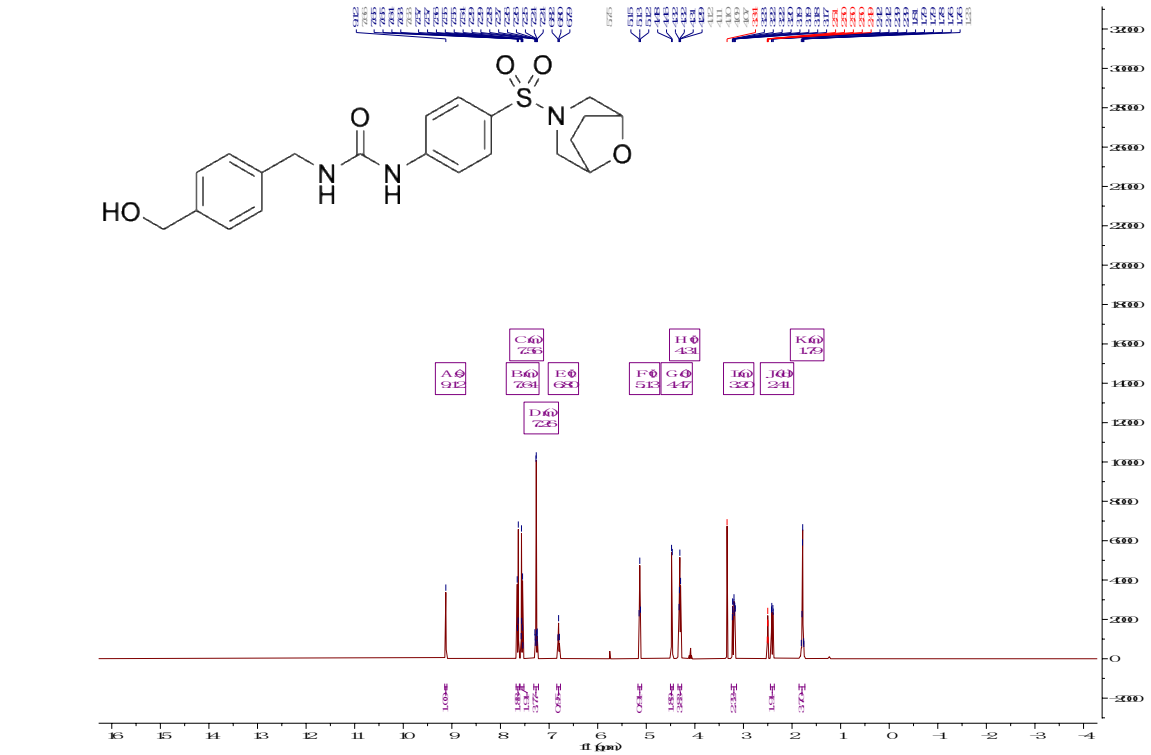

Figure S7. ^{1}H spectra of compound 10.

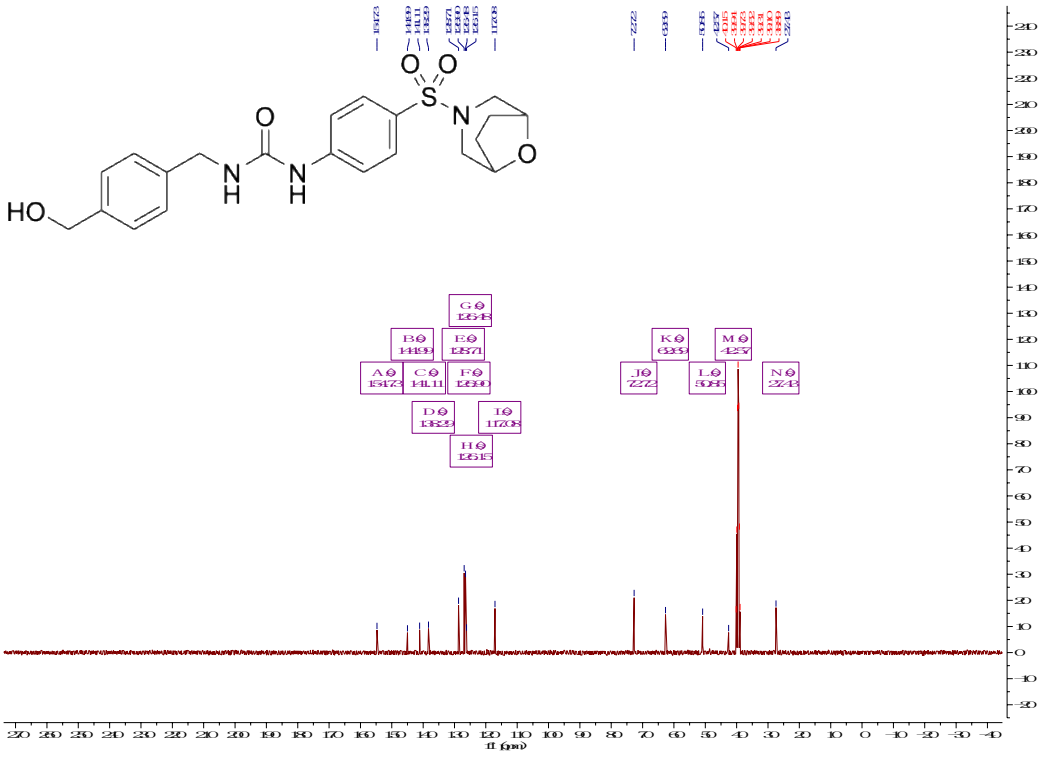

Figure S8. ^{13}C spectra of compound 10.

2-((6-Azidohexyl)oxy)-1,1'-biphenyl (12)

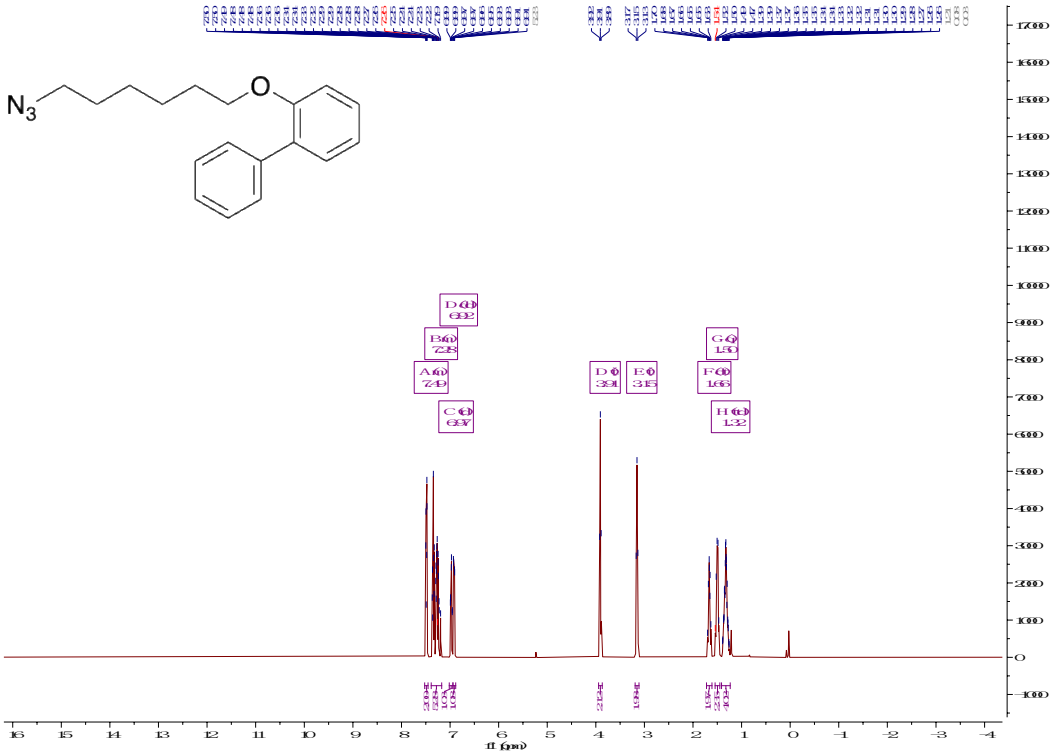

Figure S9. ^{1}H spectra of compound 12.

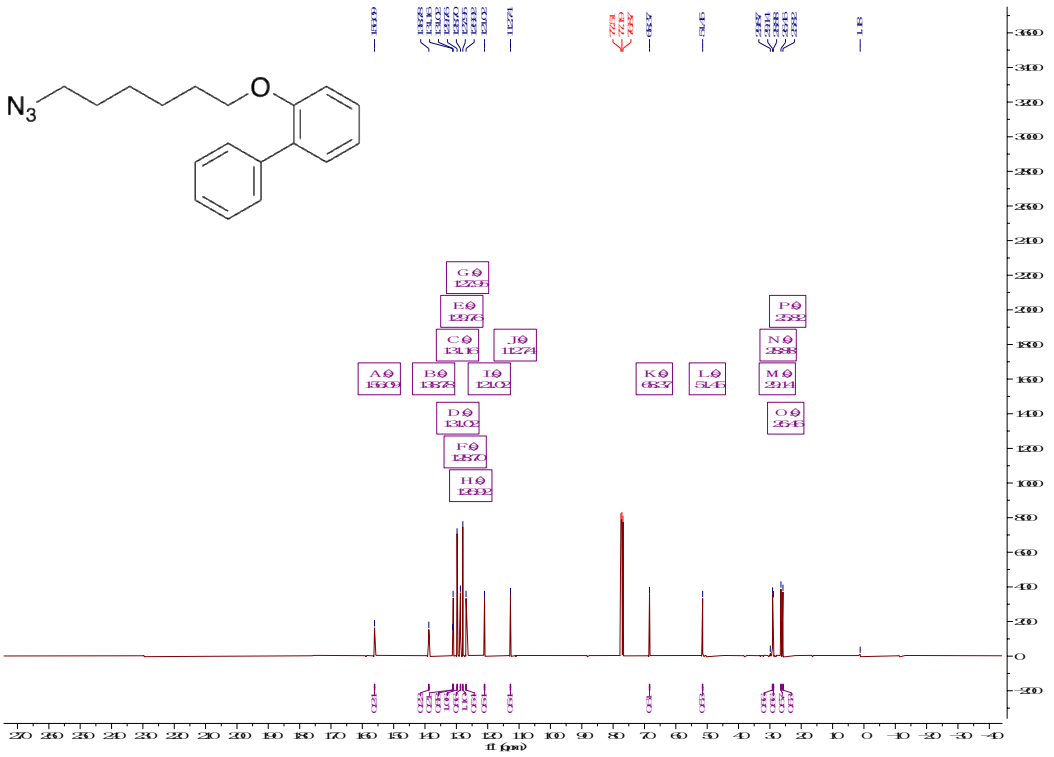

Figure S10. ^{13}C spectra of compound 12.

4-(1-(6-([1,1'-Biphenyl]-2-yloxy)hexyl)-1H-1,2,3-triazol-4-yl)pyridine (8)

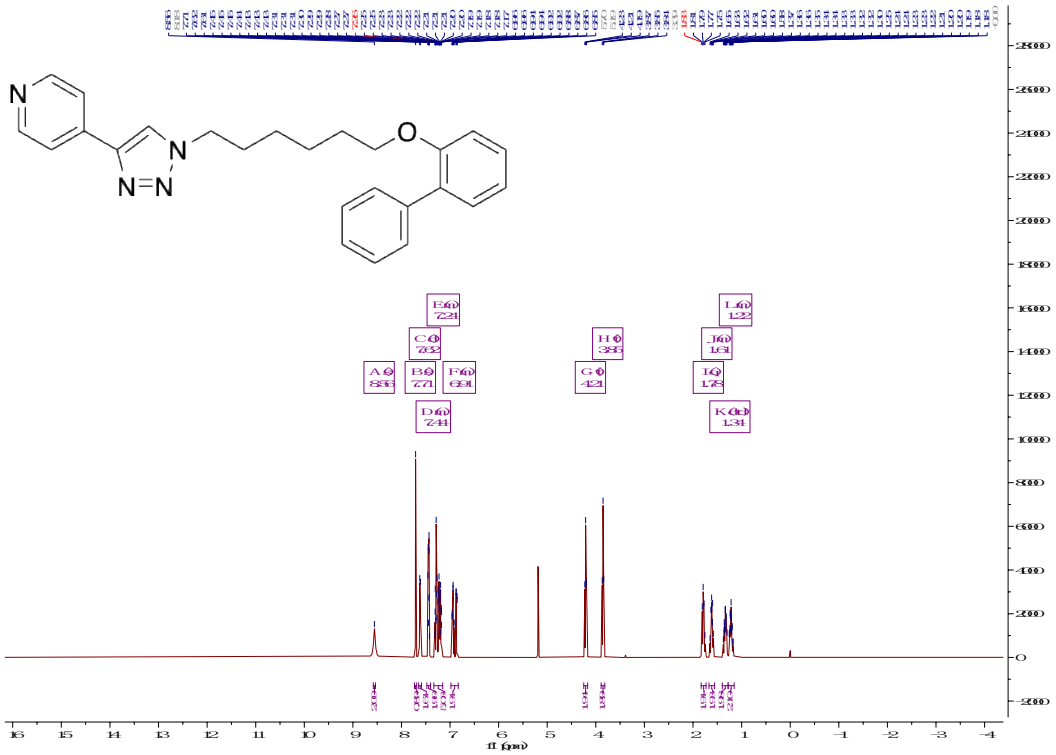

Figure S11. 1H spectra of compound 8.

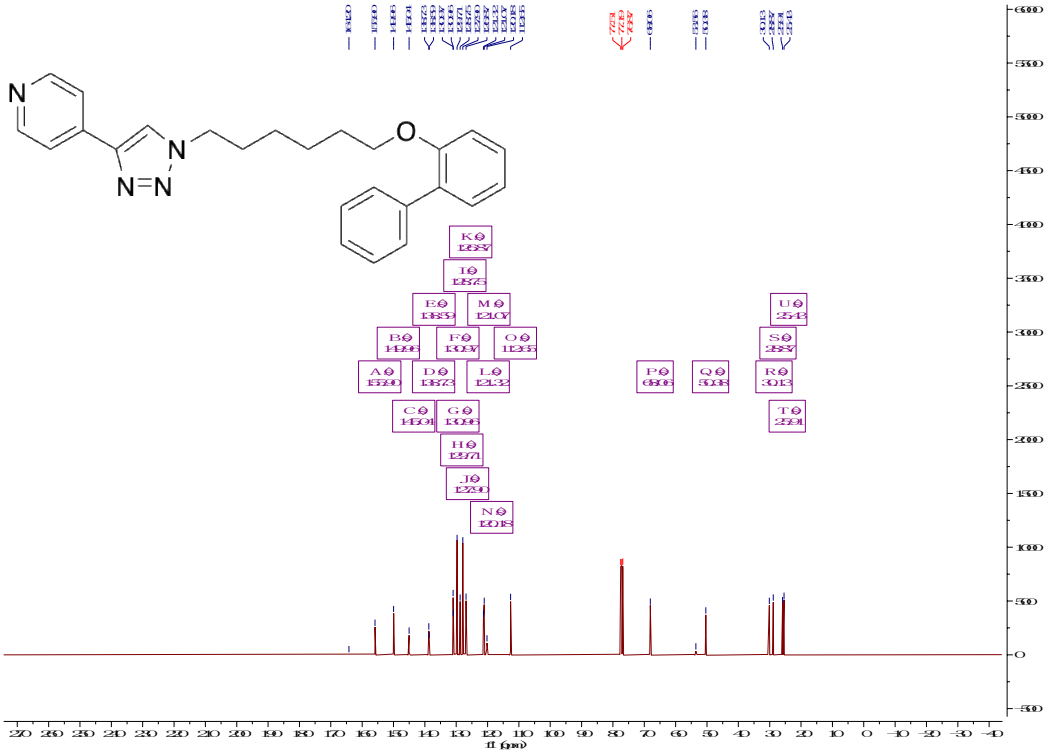

Figure S12. 13C spectra of compound 8.

(4-(4-Aminobutyl)piperidin-1-yl)(phenyl)methanone (13)

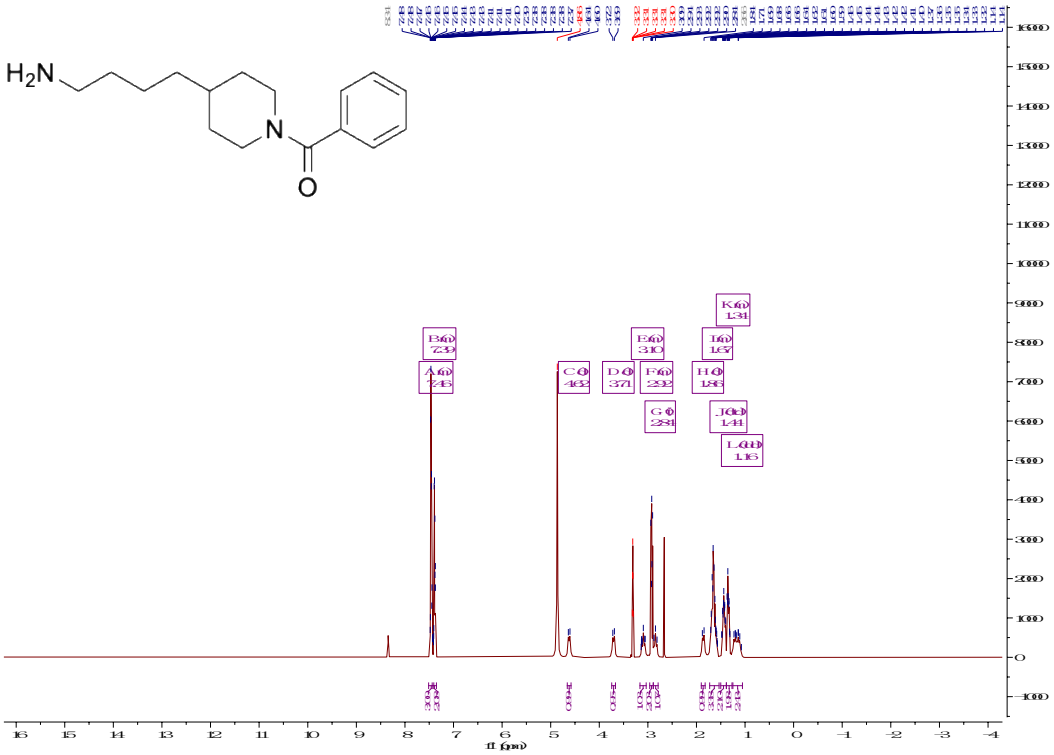

Figure S13. ^{1}H spectra of compound 13.

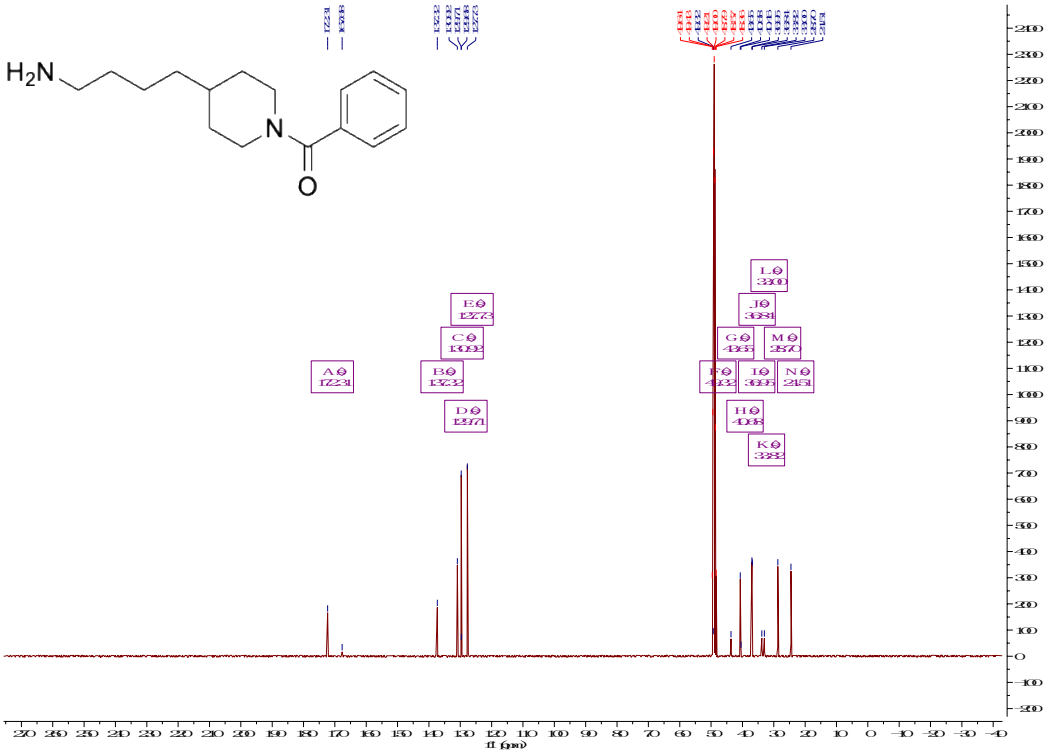

Figure S14. ^{13}C spectra of compound 13.

N-(4-(1-Benzoylpiperidin-4-yl)butyl)acrylamide (14)

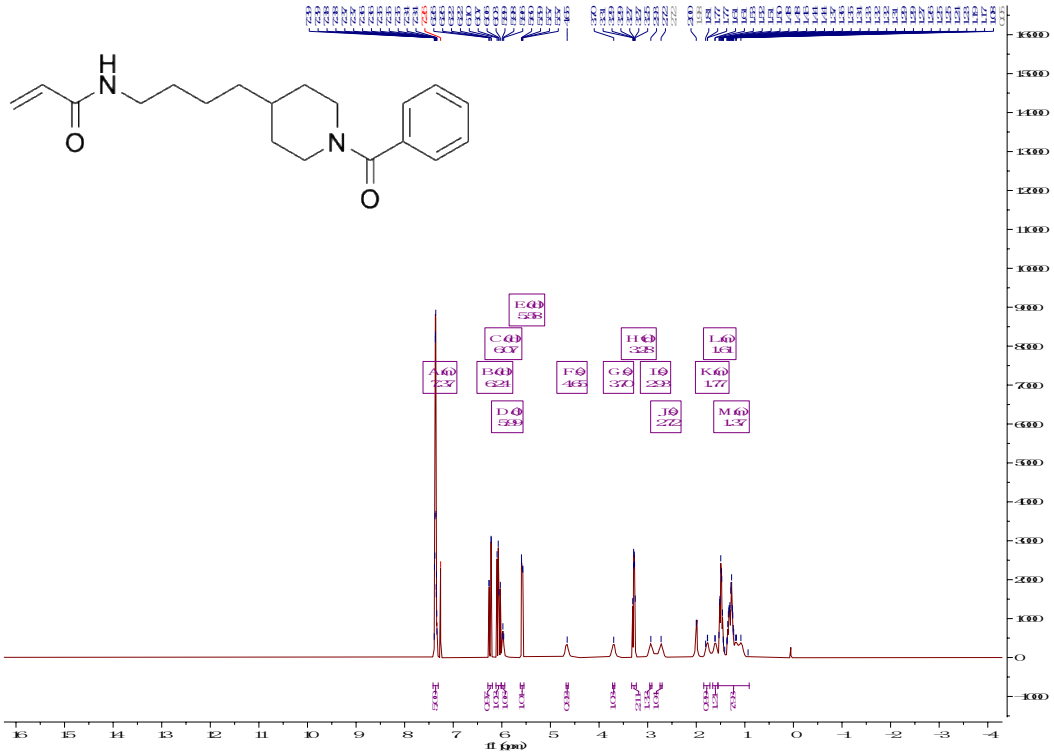

Figure S15. ^{1}H spectra of compound 14.

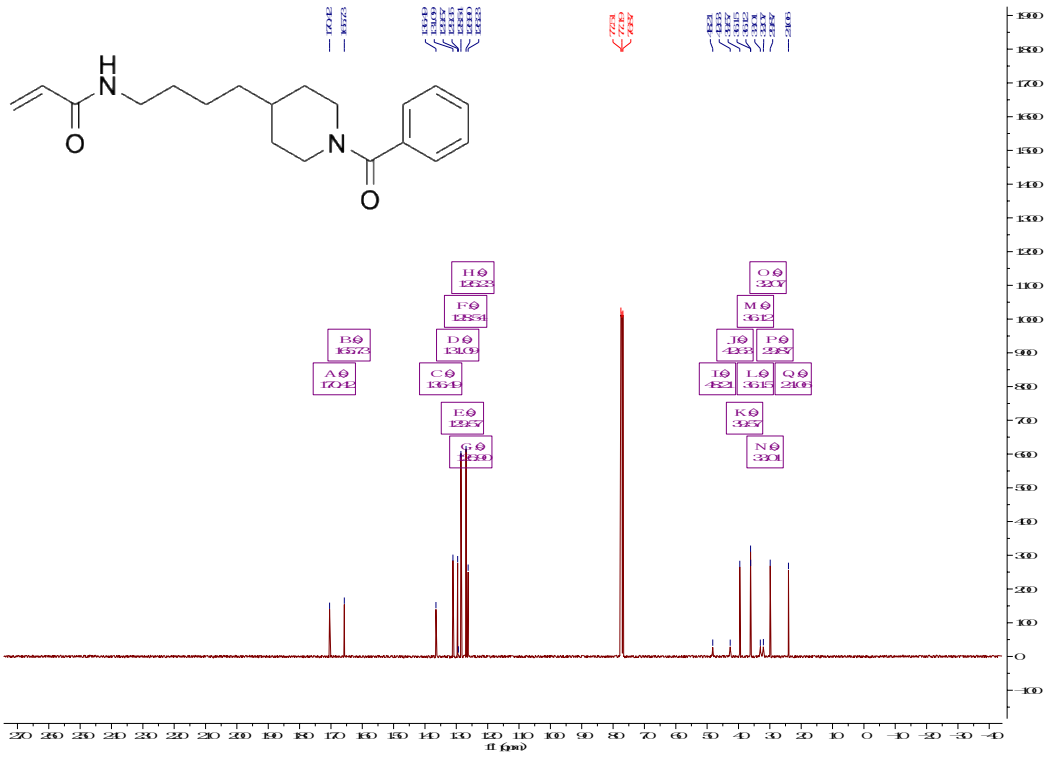

Figure S16. 13C spectra of compound 14.

(*E*)-*N*-(4-(1-Benzoylpiperidin-4-yl)butyl)-3-(pyridin-4-yl)acrylamide (7)

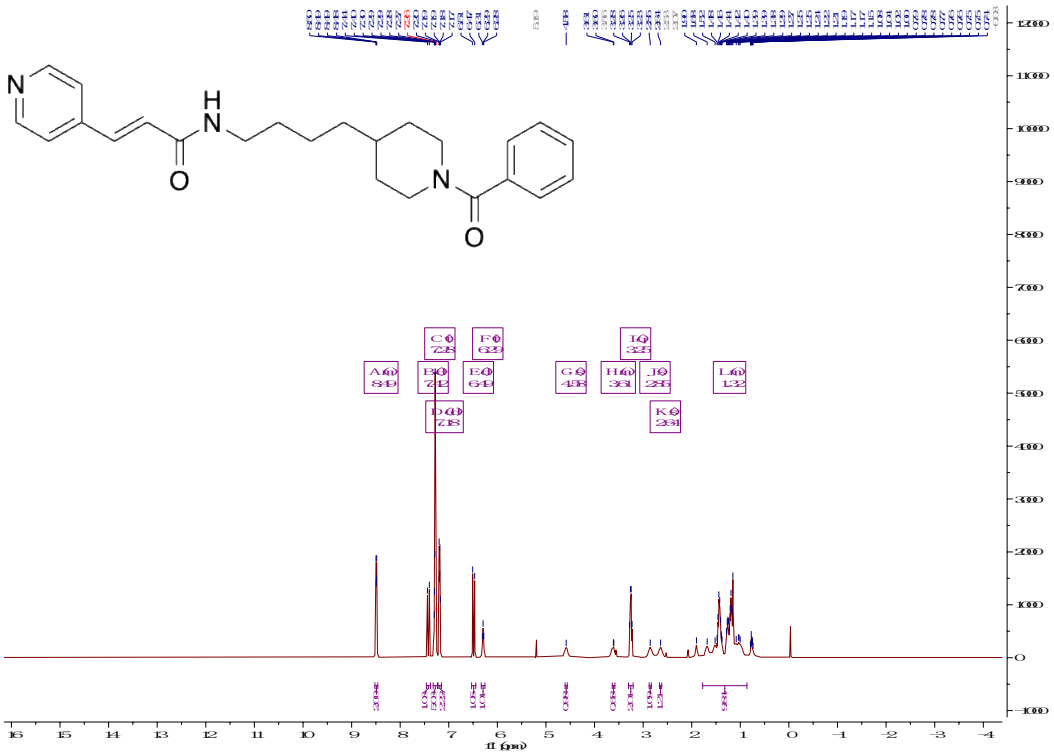

Figure S17. ^{1}H spectra of compound 7.

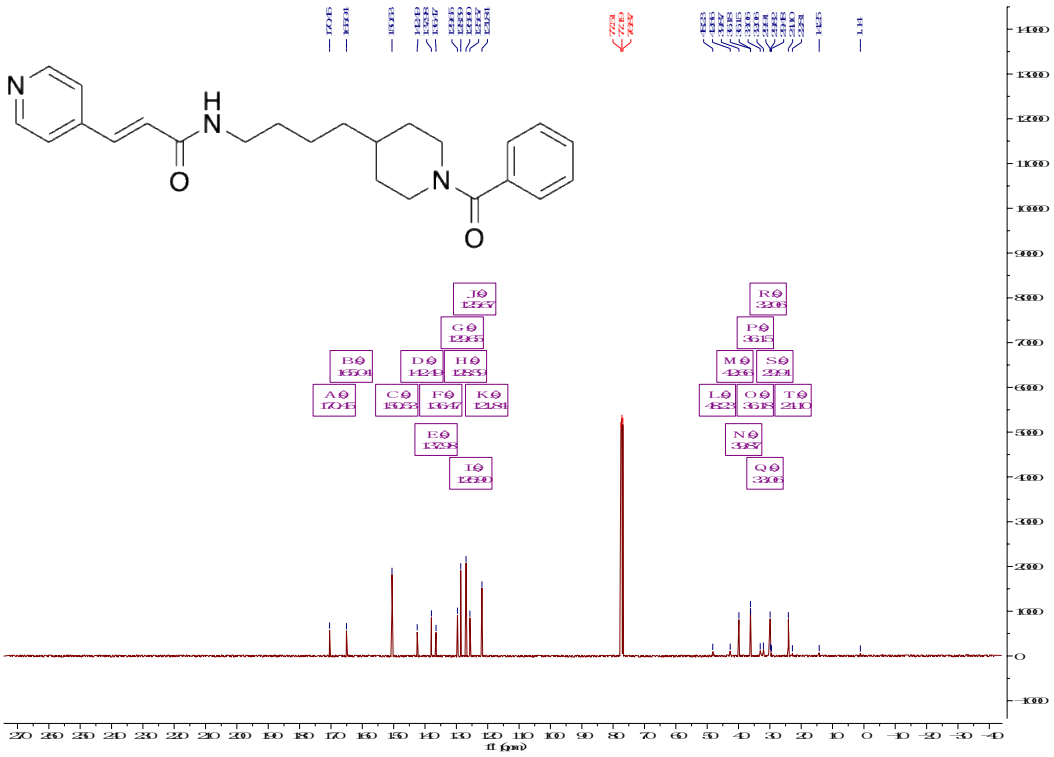

Figure S18. ^{13}C spectra of compound 7.

4-((2*S*,3*S*,4*R*,5*R*)-3,4-Bis(benzyloxy)-5-((benzyloxy)methyl)tetrahydrofuran-2-yl)benzonitrile (19)

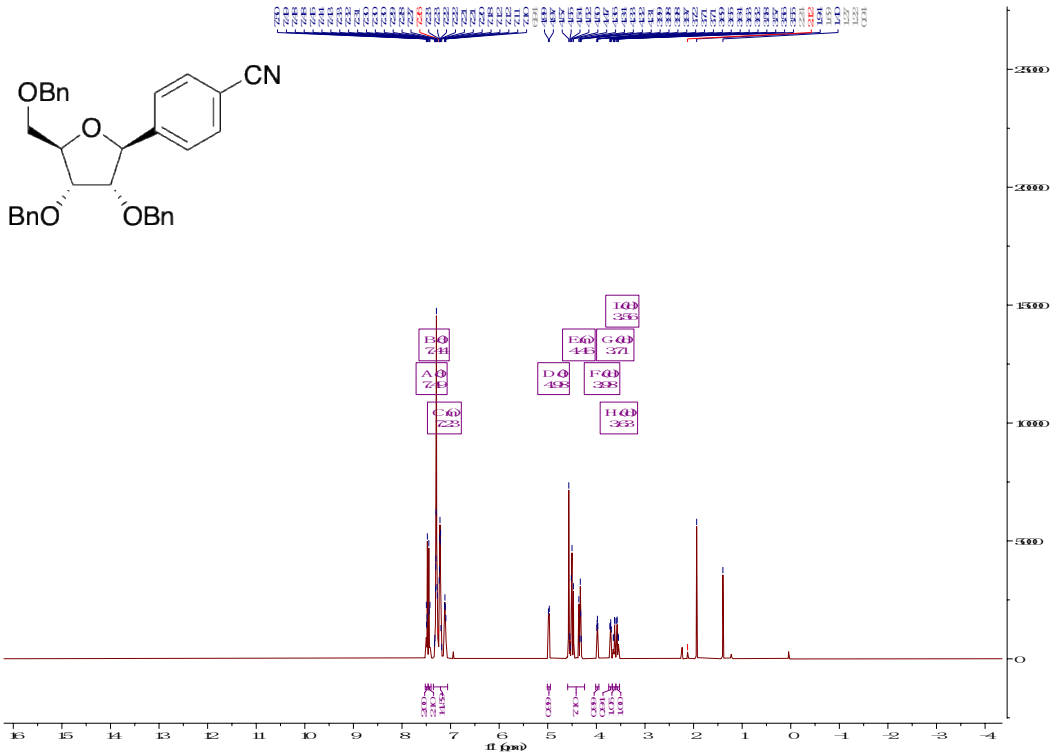

Figure S19. ^{1}H spectra of compound 19.

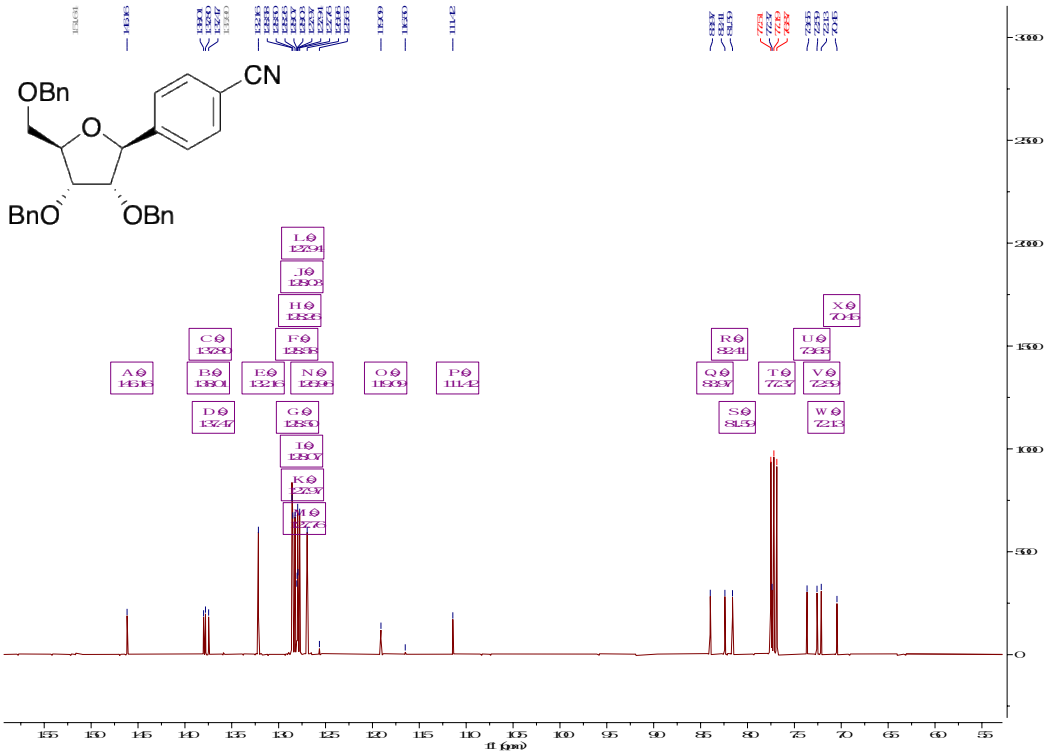

Figure S20. ^{13}C spectra of compound 19.

4-((2*S*,3*R*,4*S*,5*R*)-3,4-Dihydroxy-5-(hydroxymethyl)tetrahydrofuran-2-yl)benzonitrile (20)

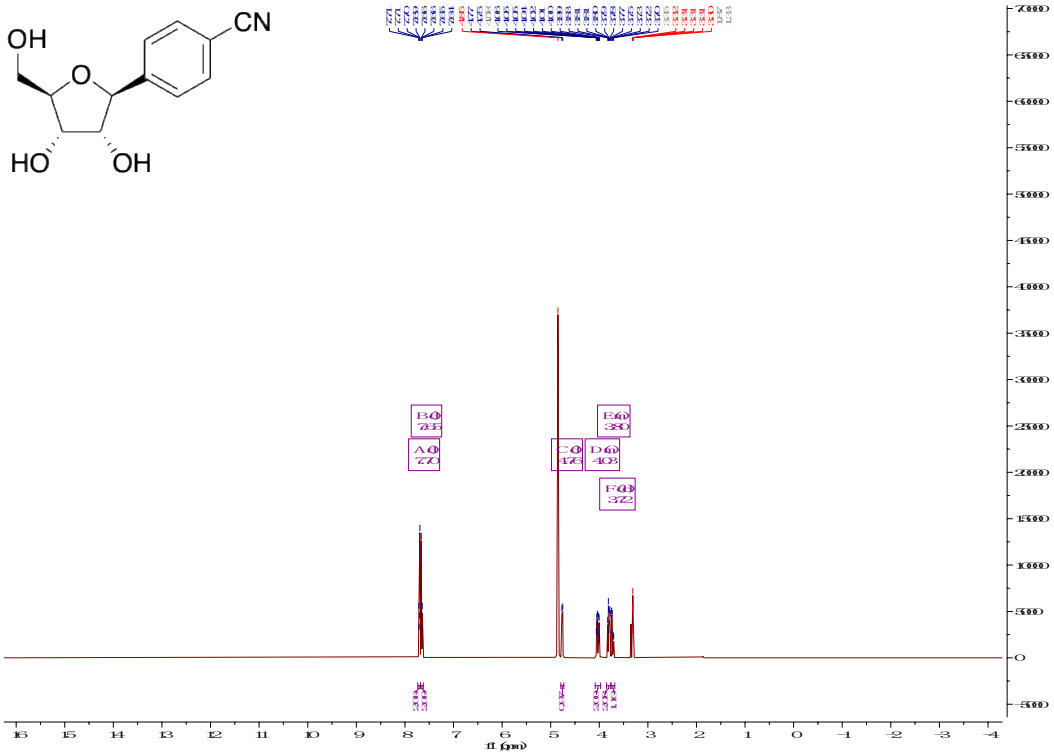

Figure S21. ^{1}H spectra of compound 20.

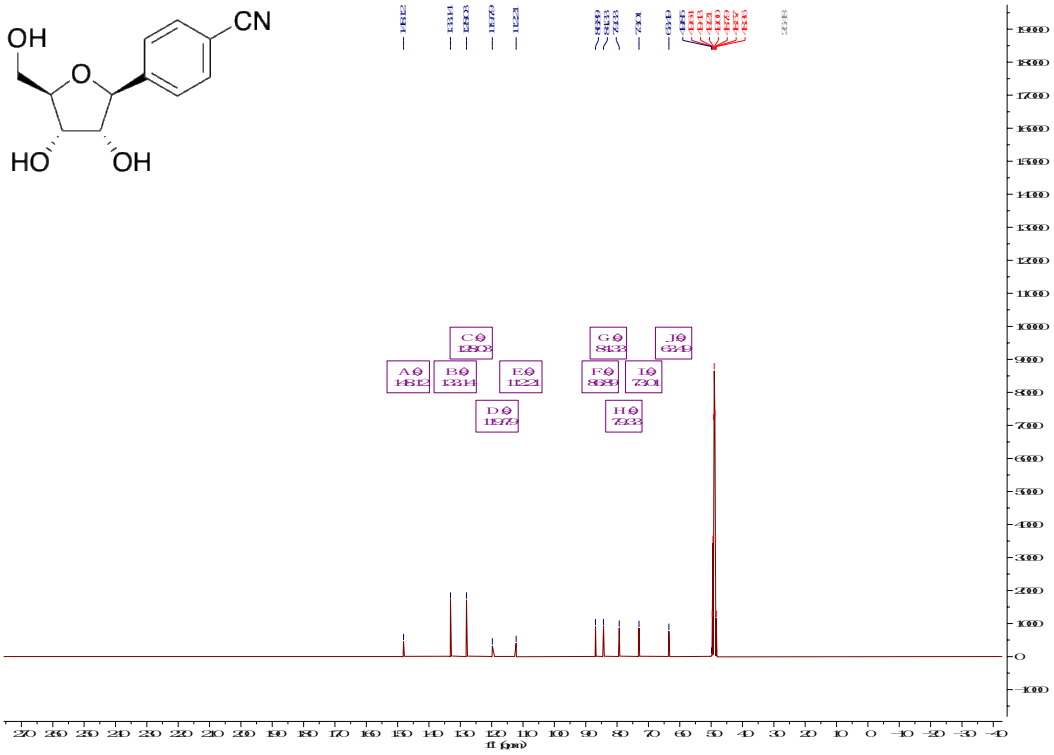

Figure S22. ^{13}C spectra of compound 20.

4-((3a*S*,4*S*,6*R*,6a*R*)-6-(Hydroxymethyl)-2,2-dimethyltetrahydrofuro[3,4-d][1,3]dioxol-4-yl)benzonitrile (21)

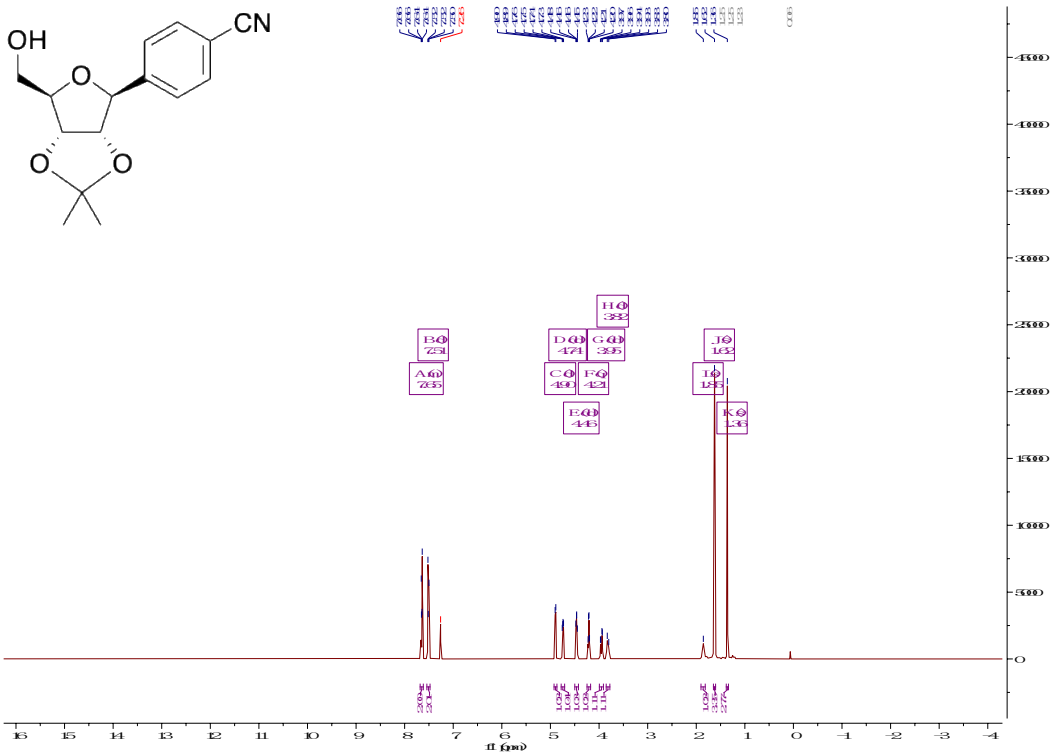

Figure S23. ^{1}H spectra of compound 21.

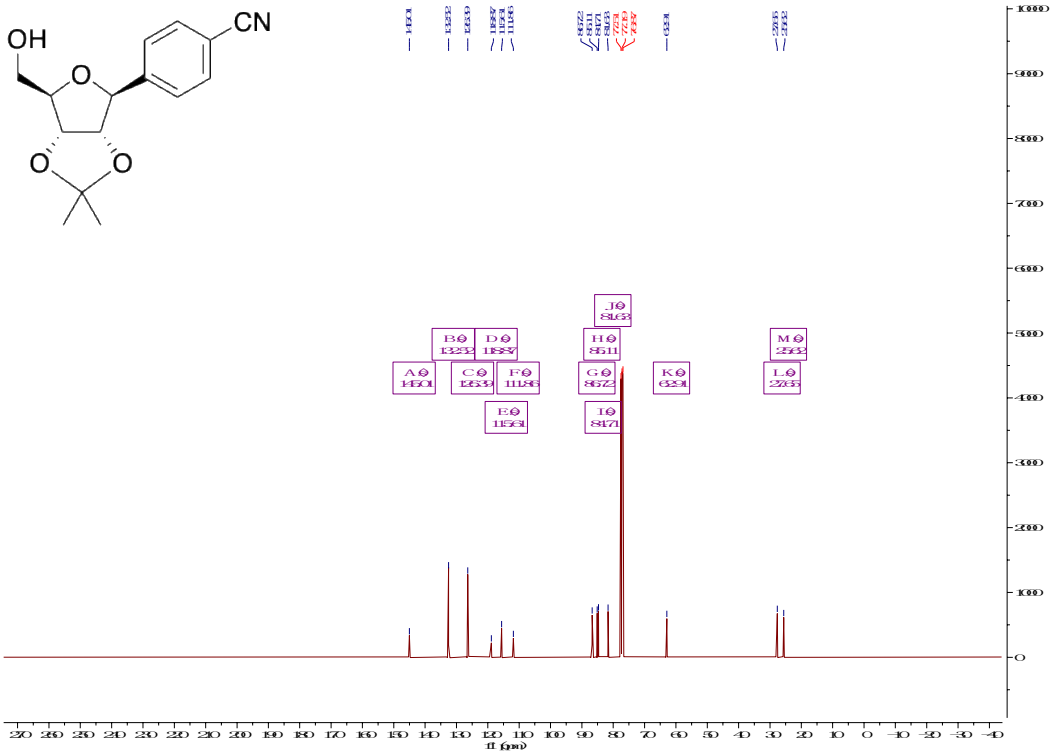

Figure S24. ^{13}C spectra of compound 21.

((3a*R*,4*R*,6*S*,6a*S*)-6-(4-Cyanophenyl)-2,2-dimethyltetrahydrofuro[3,4-d][1,3]dioxol-4-yl)methyl diethyl phosphate (22)

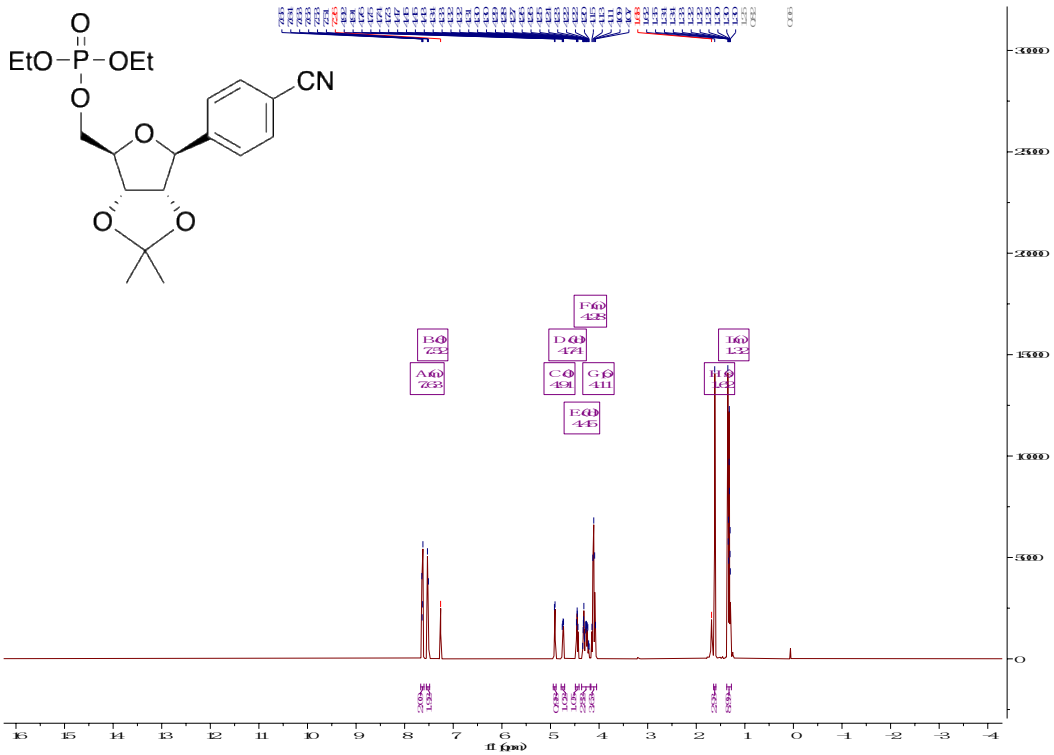

Figure S25. ^{1}H spectra of compound 22.

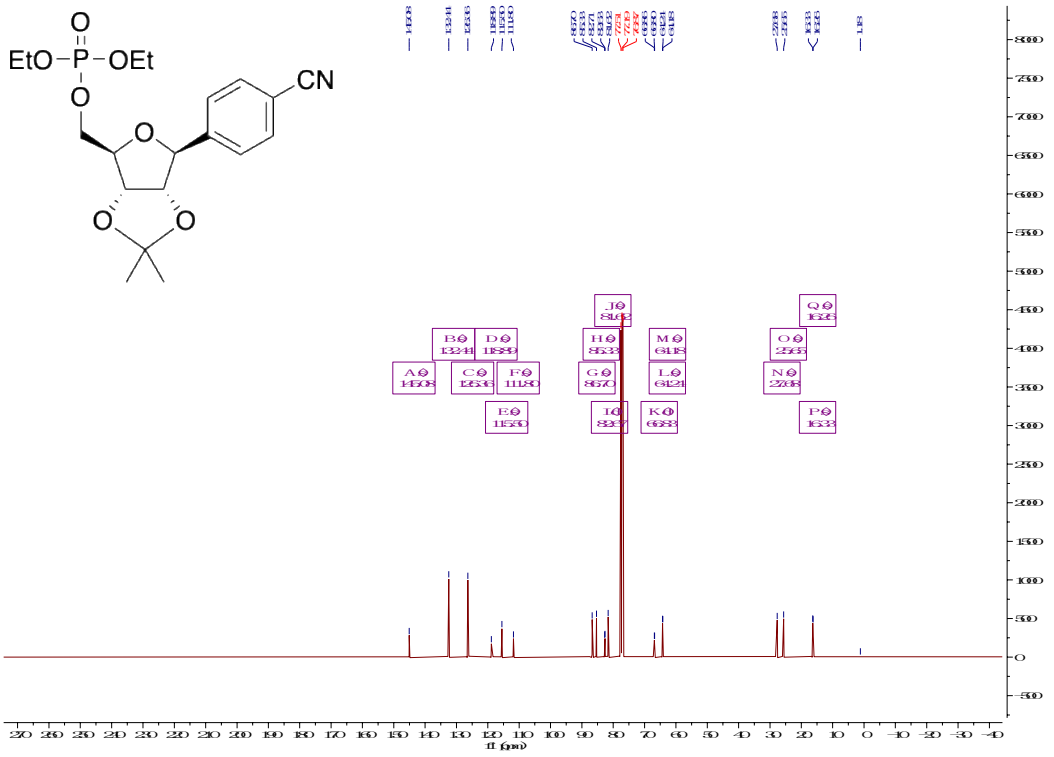

Figure S26. ^{13}C spectra of compound 22.

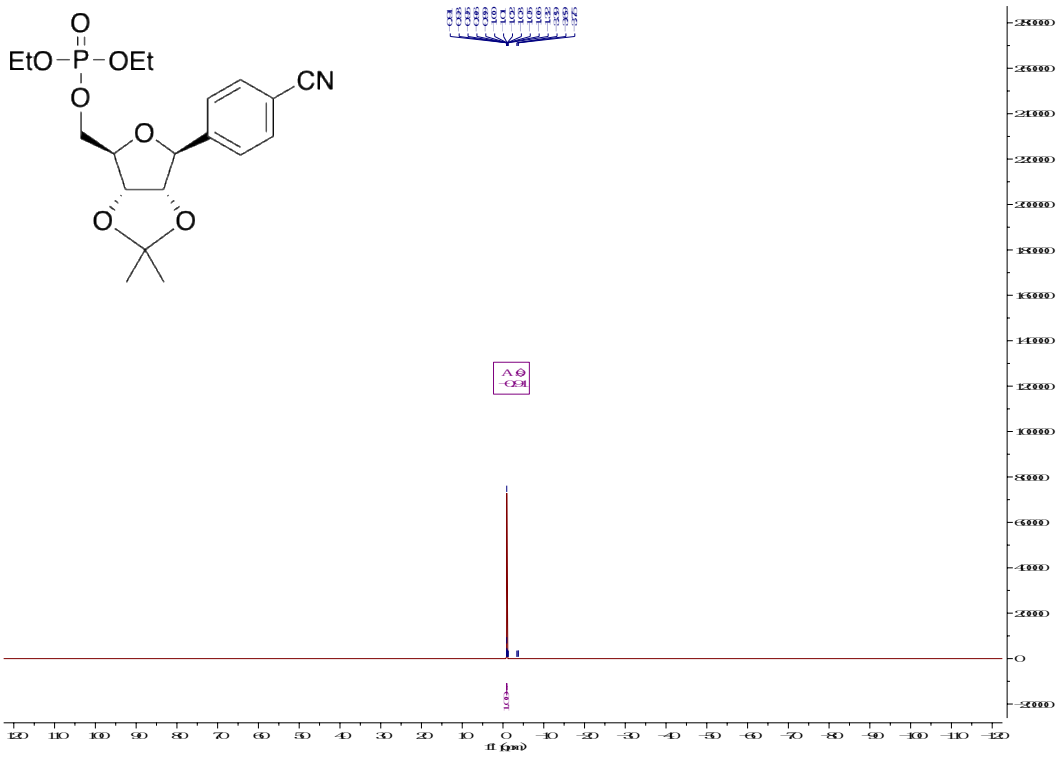

Figure S27. ^{31}P spectra of compound 22.

((3a*R*,4*R*,6*S*,6a*S*)-2,2-Dimethyl-6-(4-((3-(4-(phenylsulfonyl)phenyl)ureido)methyl)phenyl)tetrahydrofuro[3,4-d][1,3]dioxol-4-yl)methyl diethyl phosphate (24a)

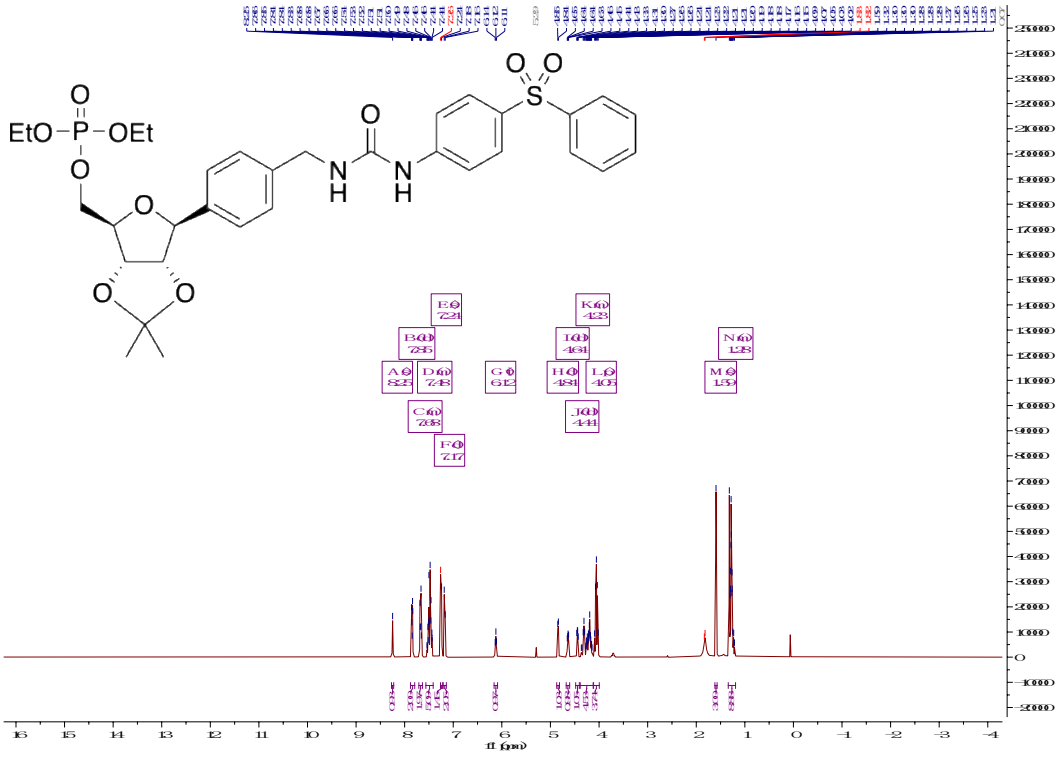

Figure S28. ^{1}H spectra of compound 24a.

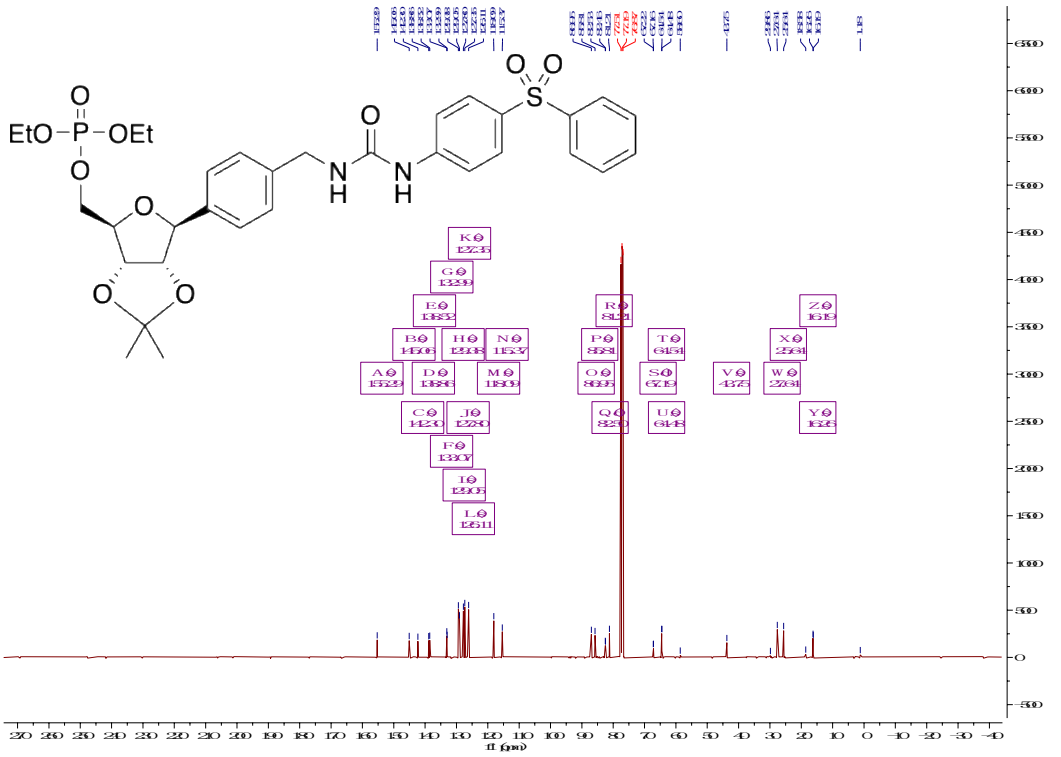

Figure S29. ^{13}C spectra of compound 24a.

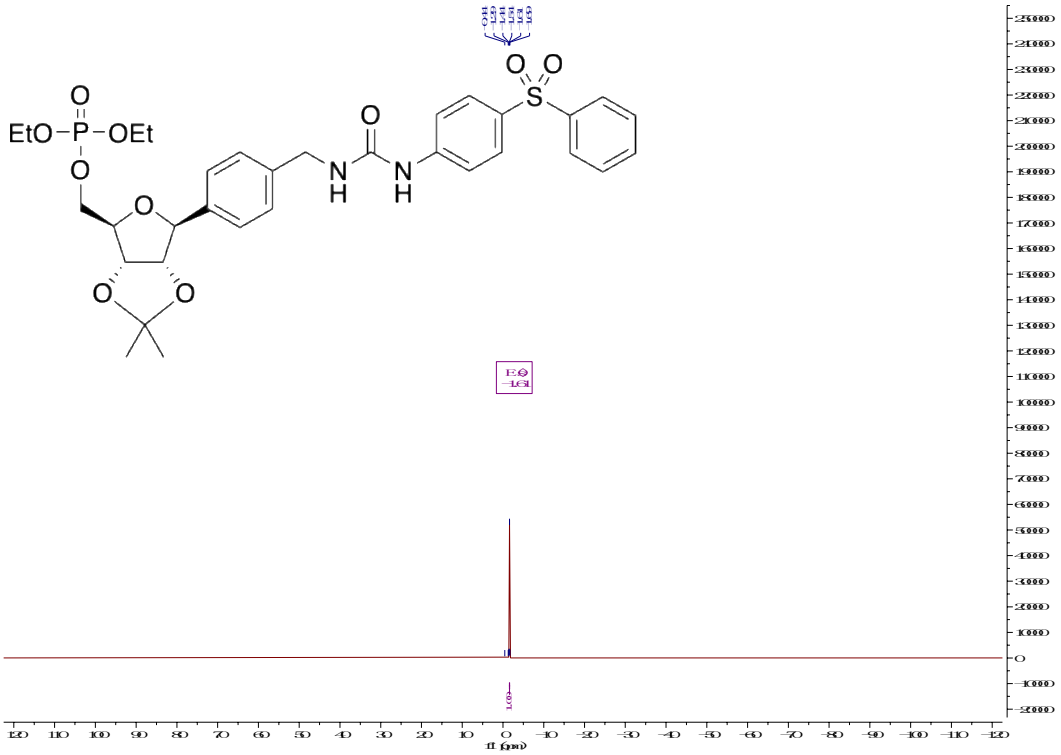

Figure S30. ^{31}P spectra of compound 24a.

((2*R*,3*S*,4*R*,5*S*)-3,4-Dihydroxy-5-(4-((3-(4-(phenylsulfonyl)phenyl)ureido)methyl)phenyl)tetrahydrofuran-2-yl)methyl dihydrogen phosphate (9a)

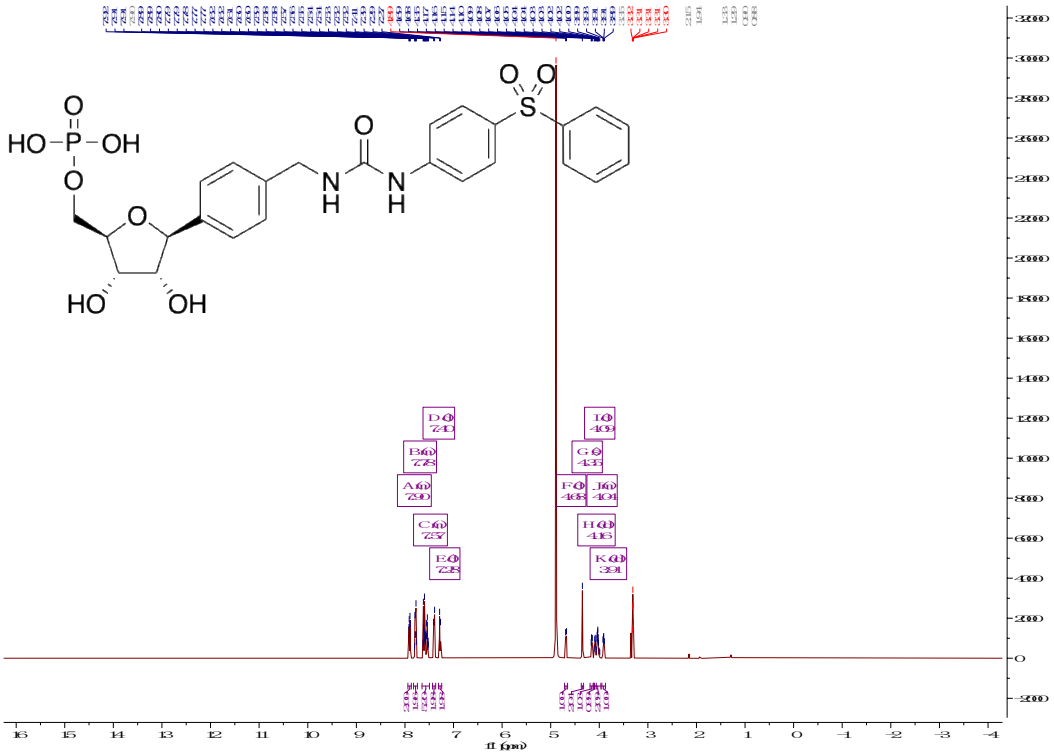

Figure S31. ^{1}H spectra of compound 9a.

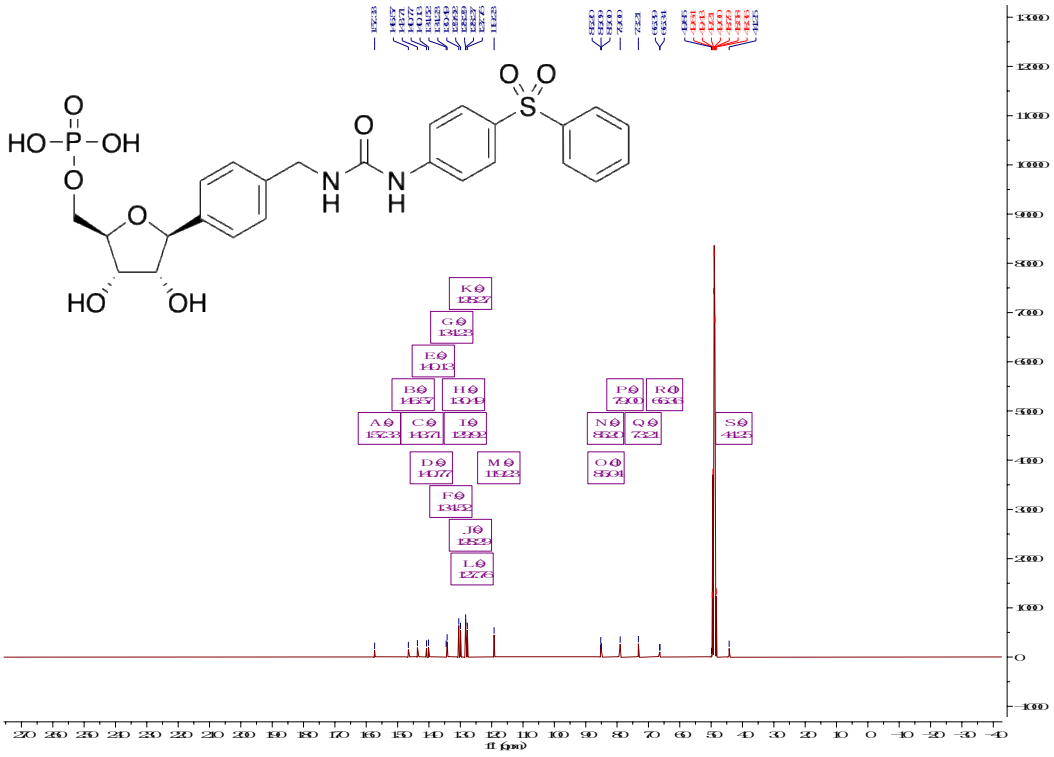

Figure S32. ^{13}C spectra of compound 9a.

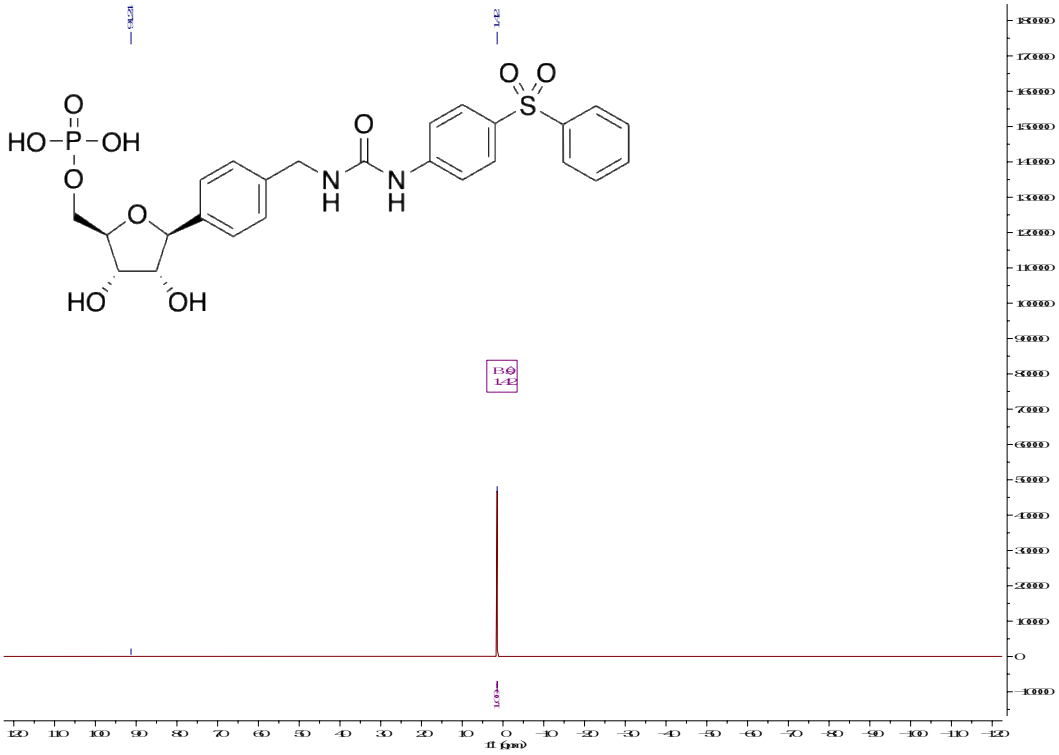

Figure S33. 31P spectra of compound 9a.

((3a*R*,4*R*,6*S*,6a*S*)-6-(4-((3-(4-((8-Oxa-3-azabicyclo[3.2.1]octan-3-yl)sulfonyl)phenyl)ureido)methyl)phenyl)-2,2-dimethyltetrahydrofuro[3,4-d][1,3]dioxol-4-yl)methyldiethylphosphate (24b)

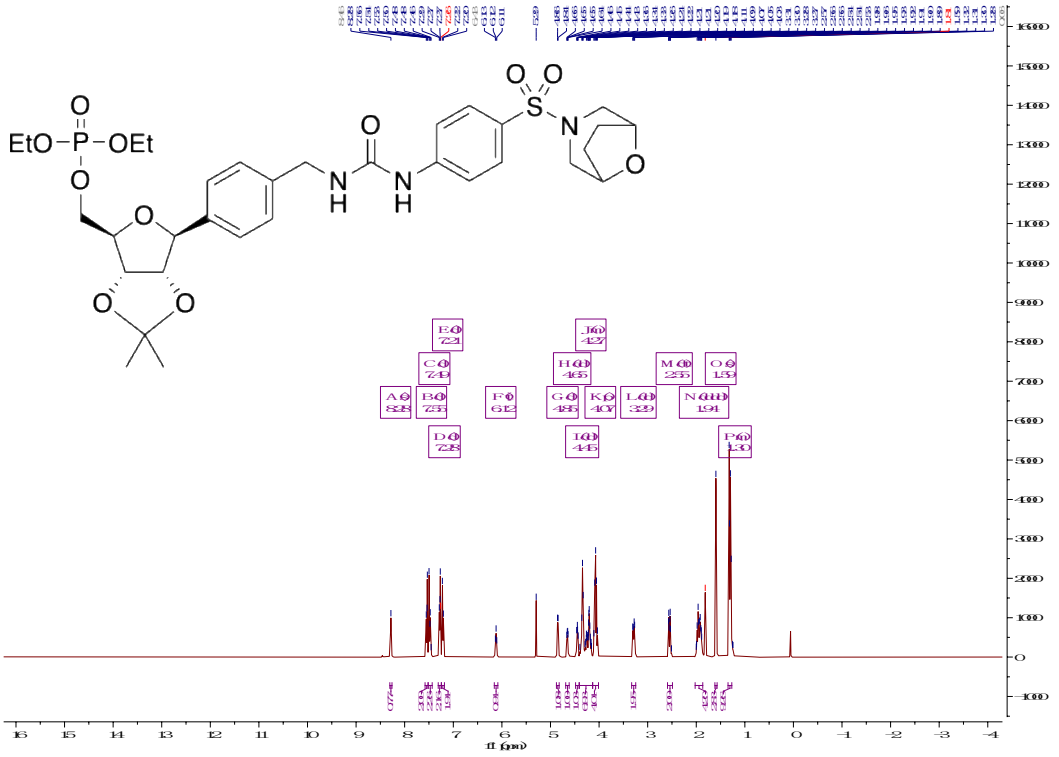

Figure S34. ^{1}H spectra of compound 24b.

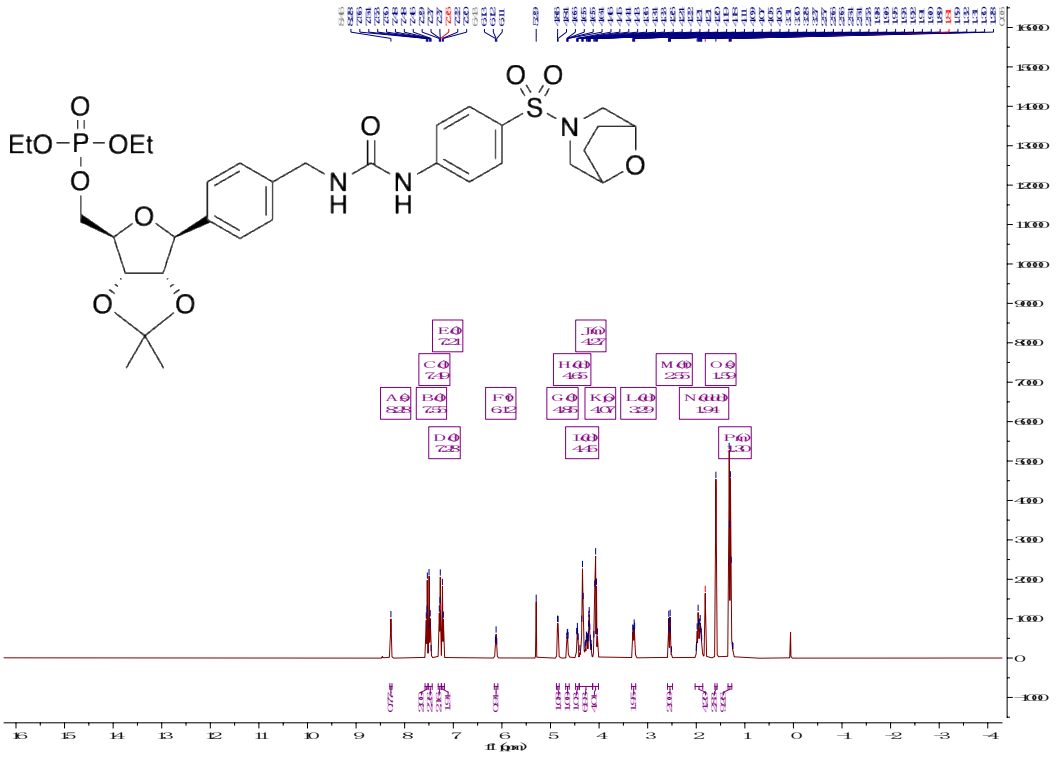

Figure S35. ^{13}C spectra of compound 24b.

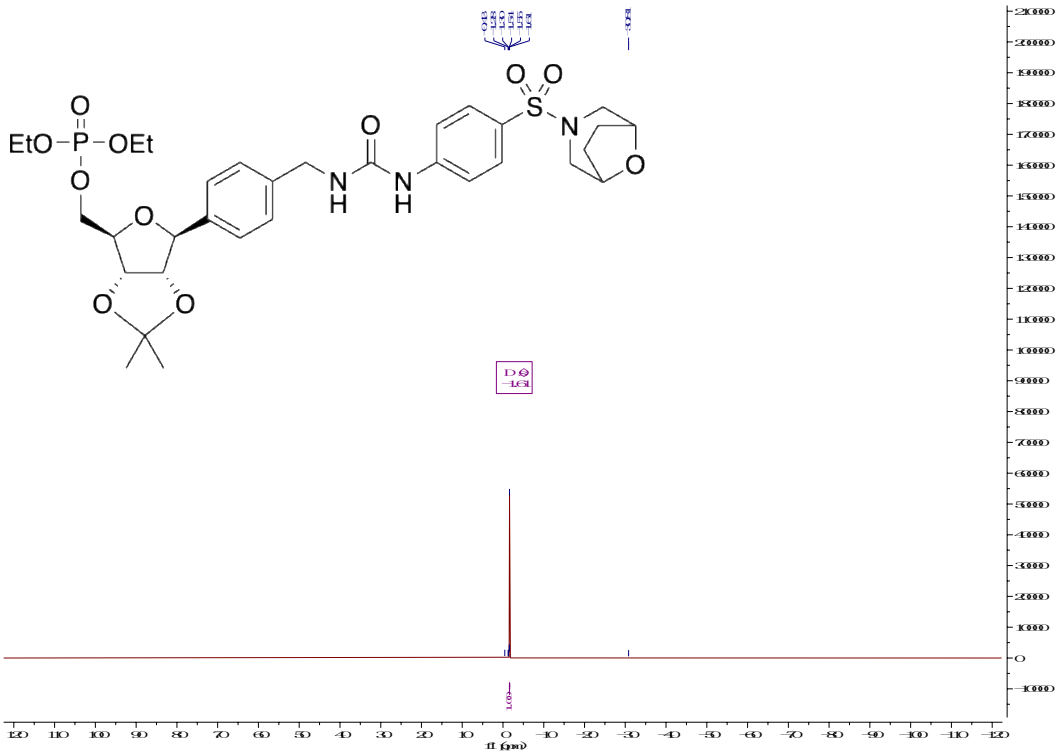

Figure S36. ^{31}P spectra of compound 24b.

((2*R*,3*S*,4*R*,5*S*)-5-(4-((3-(4-((8-Oxa-3-azabicyclo[3.2.1]octan-3-yl)sulfonyl)phenyl)ureido)methyl)phenyl)-3,4-dihydroxytetrahydrofuran-2-yl)methyl dihydrogen phosphate (9b)

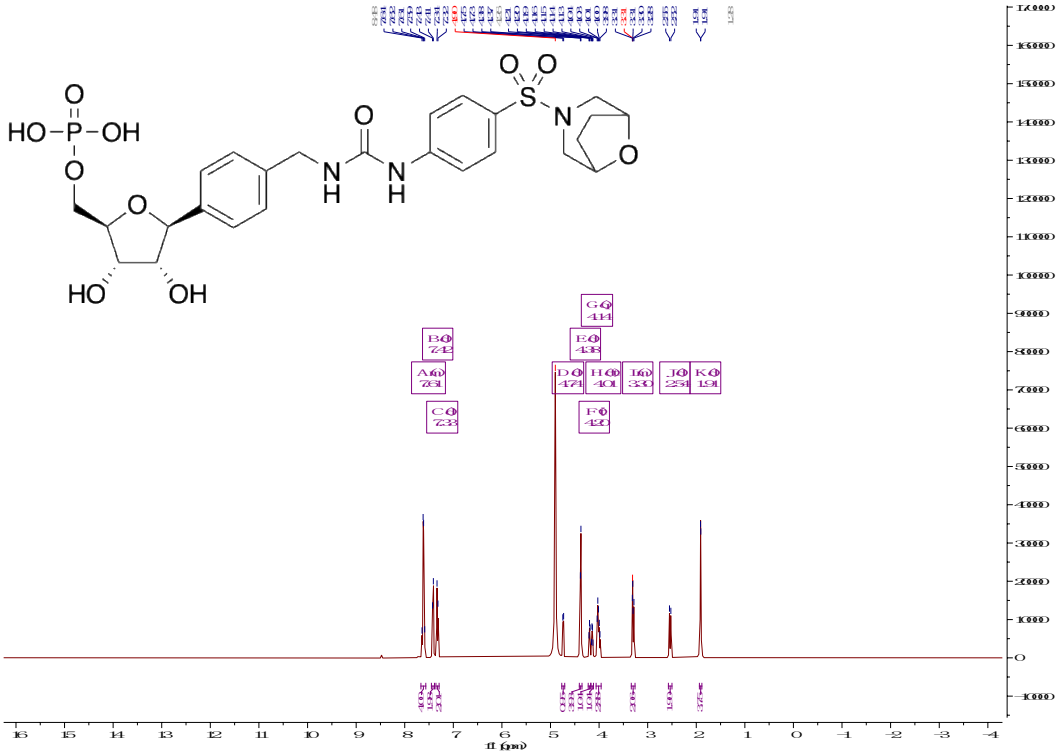

Figure S37. ^{1}H spectra of compound 9b.

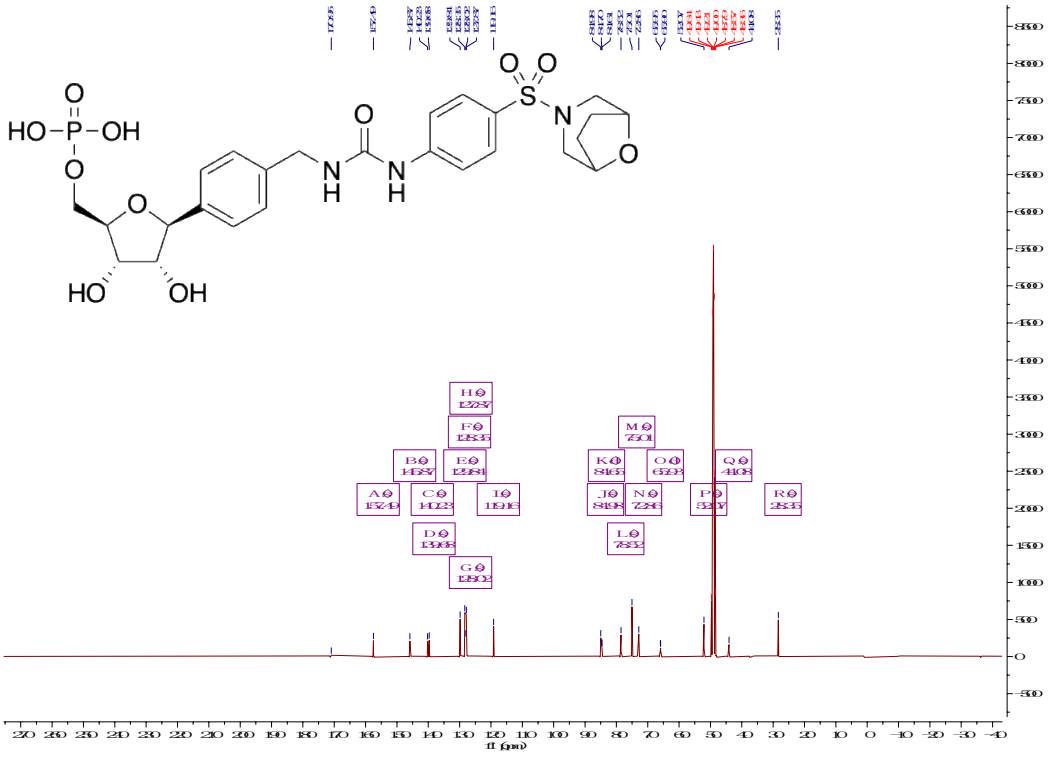

Figure S38. ^{13}C spectra of compound 9b.

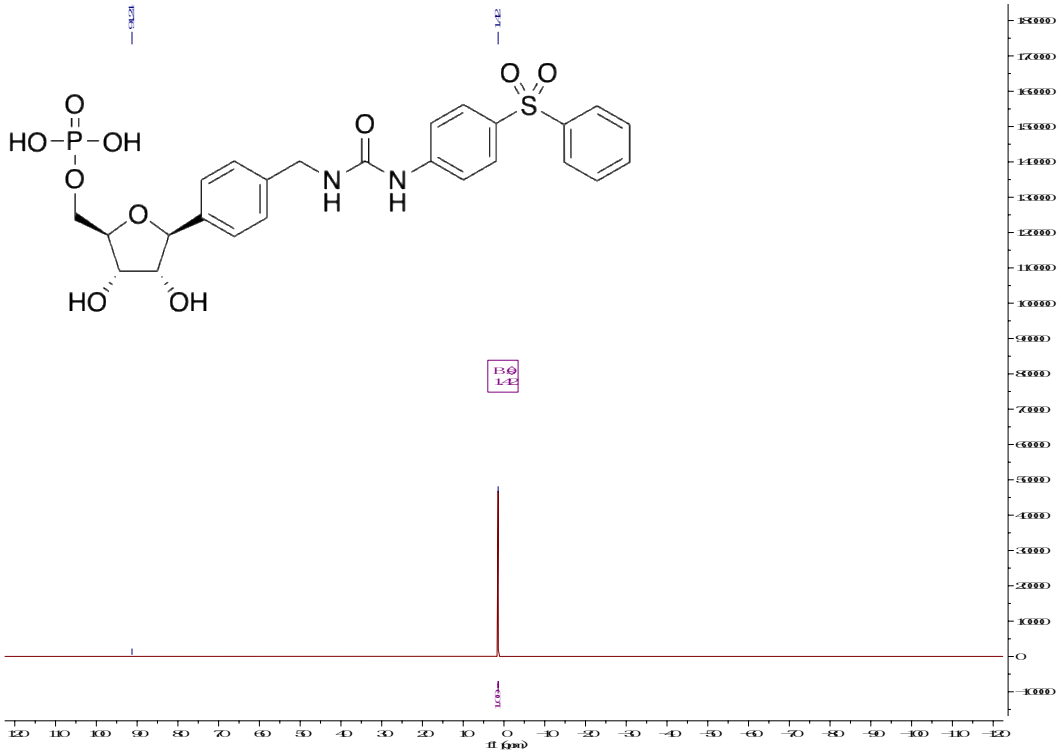

Figure S39. ^{31}P spectra of compound 9b.

LC spectra

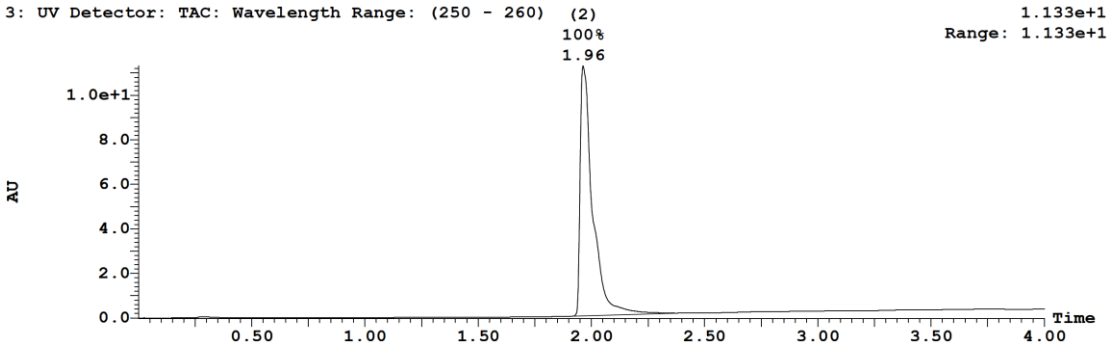

Figure S40. LC spectra of compound 6.

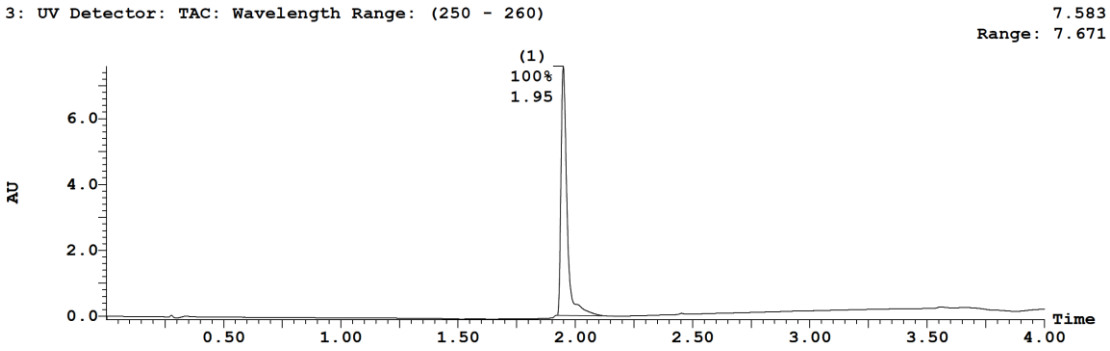

Figure S41. LC spectra of compound 7.

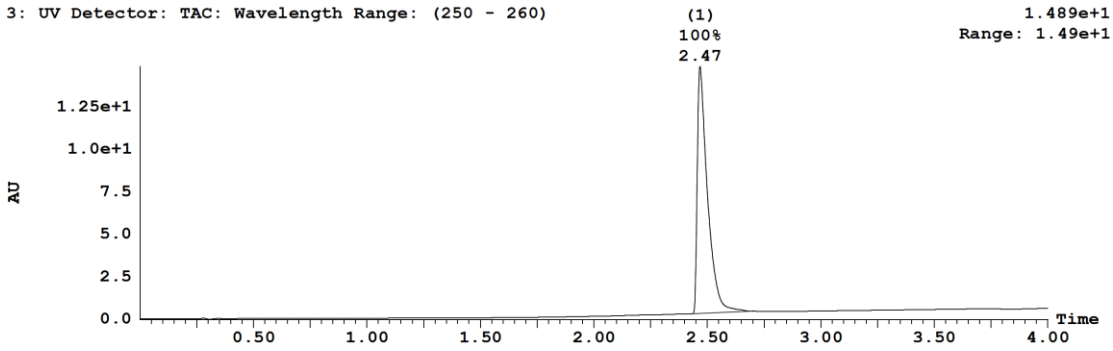

Figure S42. LC spectra of compound 8.

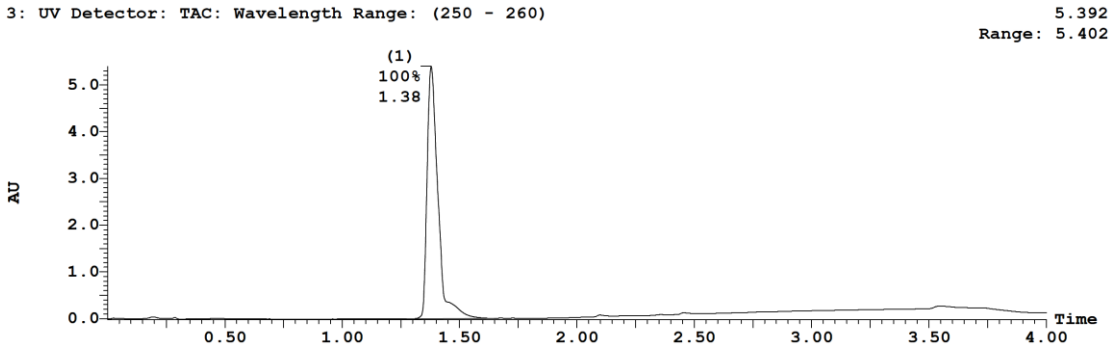

Figure S43. LC spectra of compound 9a.

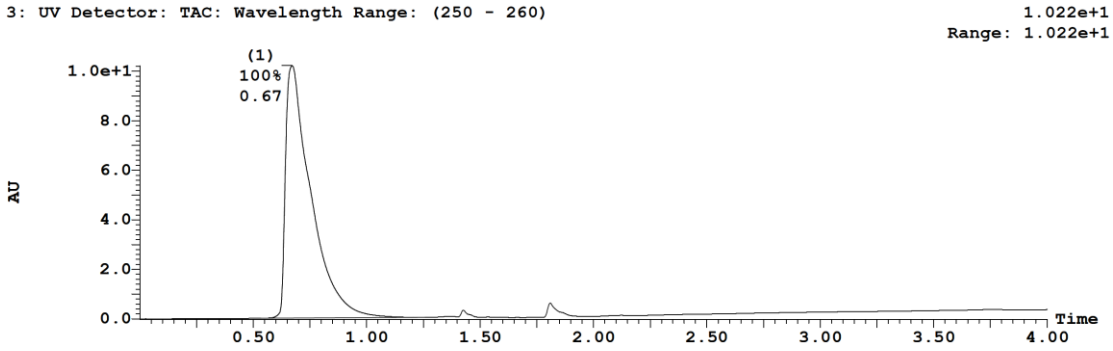

Figure S44. LC spectra of compound 9b.

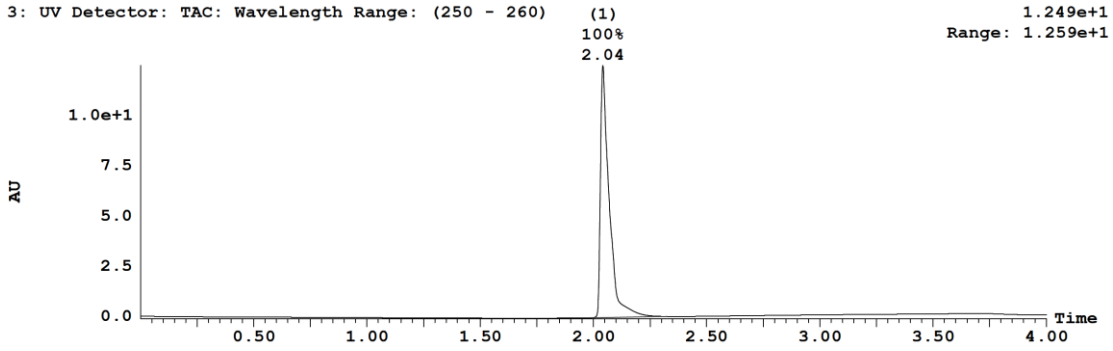

Figure S45. LC spectra of compound 10.

Data collection, structure solution and refinement

Diffraction data were collected at beamline X06SA (Villigen, CH) at a wavelength of 1.0 Å at 100 K. The reservoir condition supplemented with 20% ethylene glycol was used as cryoprotectant. Data were

processed using XDS[1] and scaled with aimless.[2] The PDB structure with the accession code 2GVL was used as an initial search model using the program MOLREP.[3] The final model was built manually using Coot[4] and refined with REFMAC5.[5] Data collection and refinement statistics are summarized in Table S1.

Data collection	**NAMPT-TSY535**
Beamline	X06SA (SLS)
Wavelength (Å)	0.99999
Space group	*P* 1 2_1 1
Cell dimensions	
a, *b*, *c* (Å)	61.10, 108.25, 83.69
α, *β*, *γ* (°)	90.00, 97.15, 90.00
Resolution (Å)*	46.99–2.15 (2.21–2.15)
unique observations*	148915 (12209)
R_{pim*}	0.111 (0.314)
Completeness (%)*	93.1 (96.8)
Multiplicity*	2.7 (2.6)
mean $I/\sigma I$*	5.8 (2.4)
$CC_{1/2}$*	0.964 (0.763)
Refinement	
R_{work} / R_{free}	0.228 / 0.266
No. of atoms	8204
overall B-factors (Å^2)	16.86
Rms deviations	
Bond lengths (Å)	0.0026
Bond angles (°)	1.190
Ramachandran (%)	
favoured	96.6
allowed	3.4
outlier	0
PDB Code	7Q8T
*Values for the highest resolution shell are shown in parentheses	

Table S1: Data collection and refinement

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