Supporting information

Validation of a homology model of *Mycobacterium tuberculosis* DXS: Rationalization of observed activities of thiamine derivatives as potent inhibitors of two orthologues of DXS

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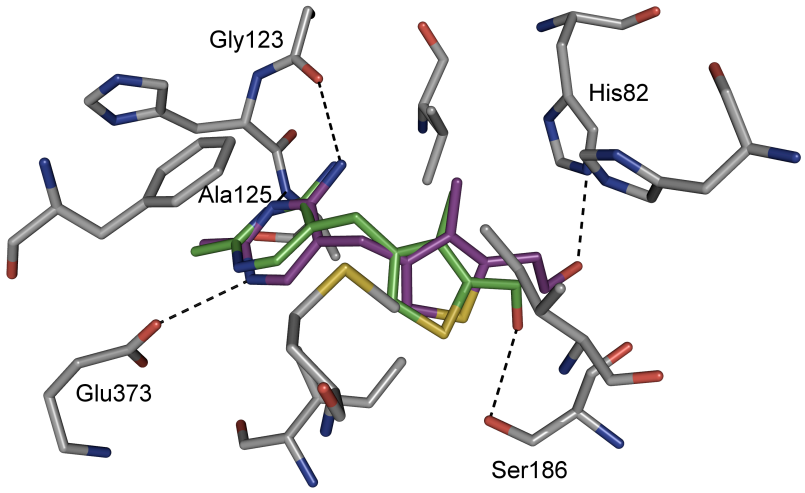


Figure S1. Modeled binding modes of deazathiamine **19** and compound **26**. Modeling was performed using the computer program MOLOC.[1] Color code: protein skeleton: C: gray; O: red; N: blue; S: yellow. **19**, skeleton: purple; **26**, skeleton: green. The color code is maintained for all the figures in the Supporting Information, unless otherwise stated. All figures of this type were generated using the software PyMOL.[2]

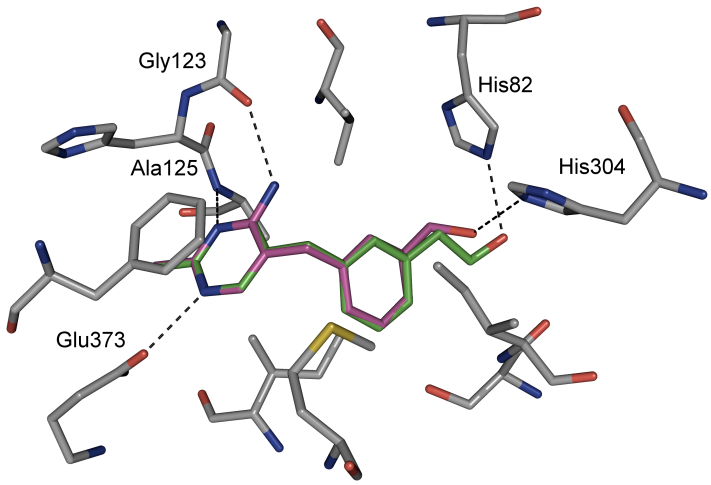


Figure S2. Modeled binding modes of **27** and **31**. Color code: **27**, skeleton: green; **31**, skeleton purple.

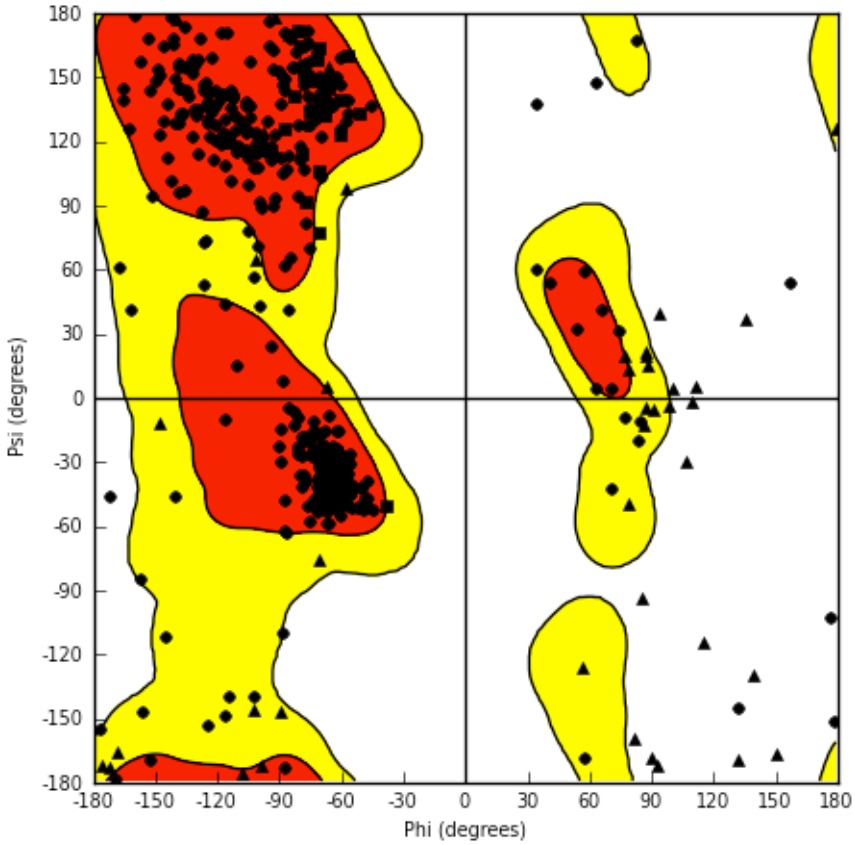


Figure S3. Ramachandran plot of the model-built *M. tuberculosis* DXS structure. Red designates common regions of torsion angle values, yellow is indicative of allowed, but not optimal, regions, whereas white corresponds to disallowed regions.

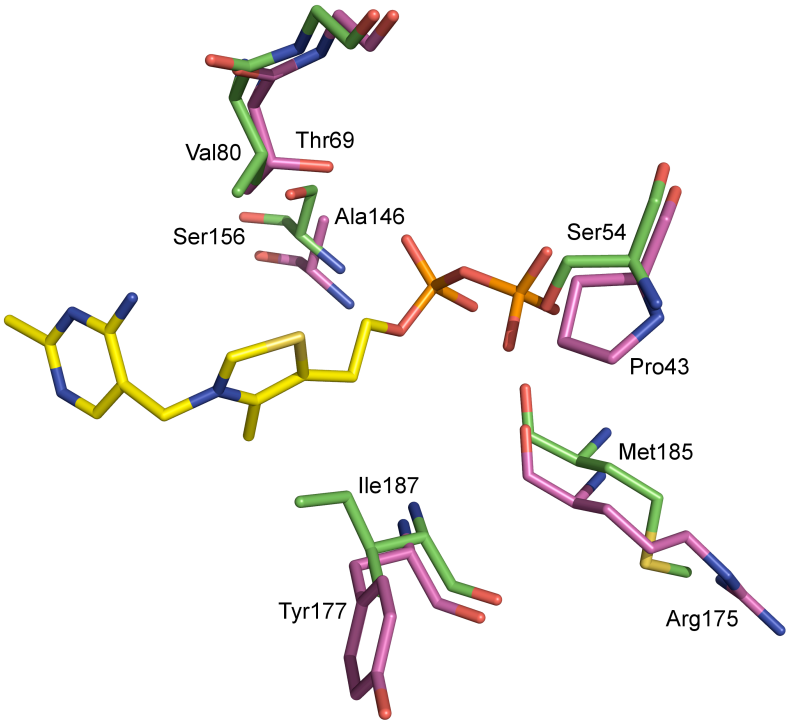
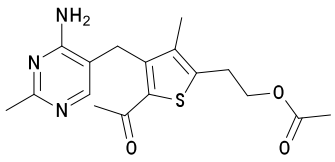


Figure S4. Overlapping of the crystal structure of *D. radiodurans* DXS (PDB: 2O1X)[3] with the homology model for *M. tuberculosis* DXS that we have built. A selection of residues is shown, particularly in the thiazolium- and diphosphate-binding subpockets. The cofactor thiamine diphosphate is shown as yellow sticks. Color code: *D. radiodurans* DXS protein skeleton: C: green; *M. tuberculosis* DXS protein skeleton: pink.

NMR spectra



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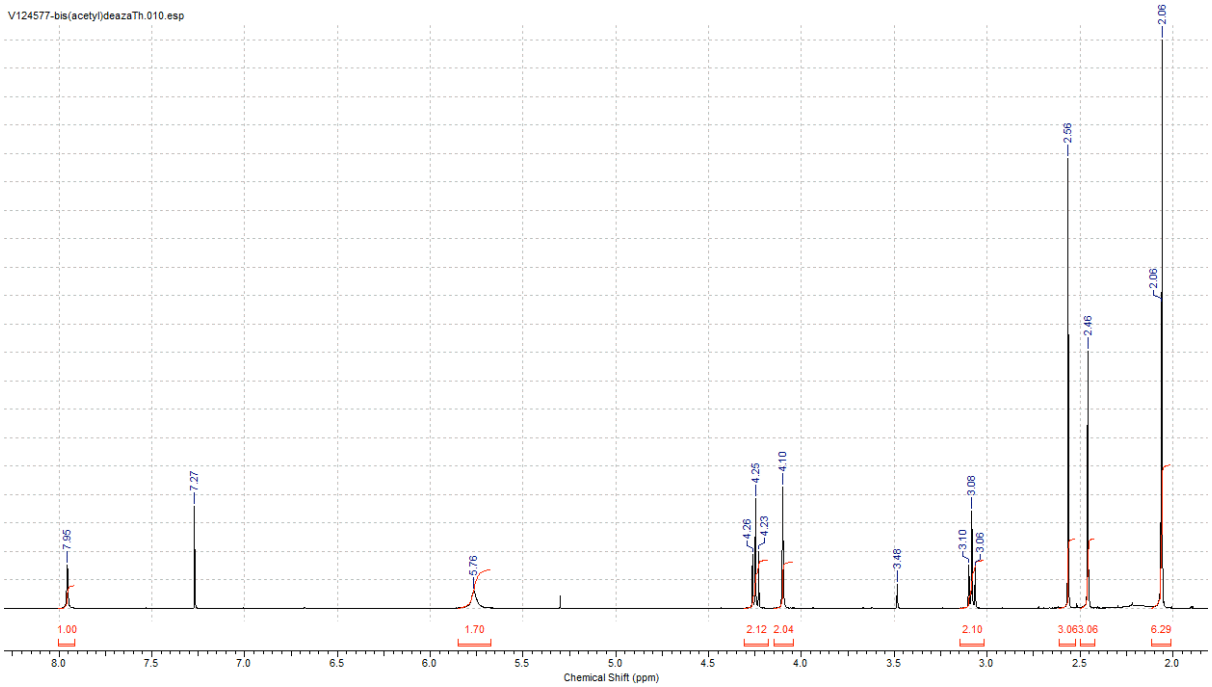

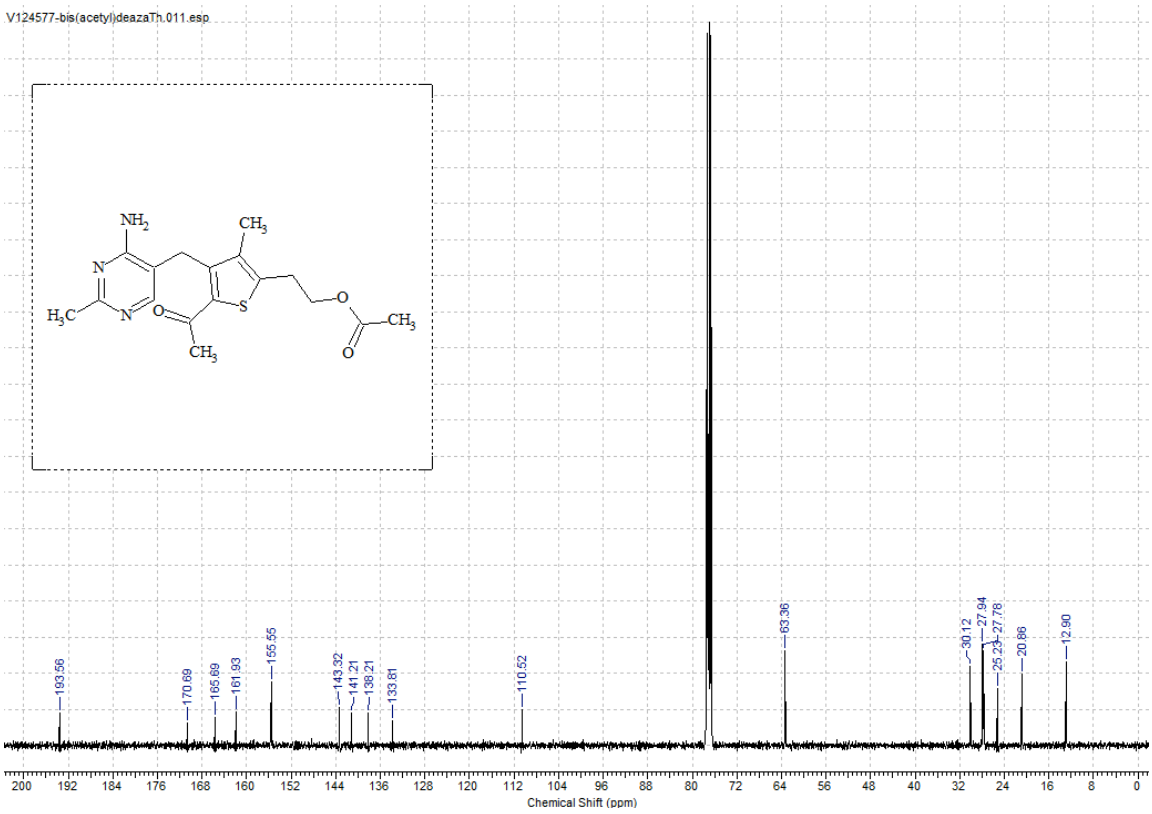
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N
H3C
N
O
S
O
CH3
O
CH3
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165.69
161.93
155.55
143.32
141.21
138.21
133.81
110.52
63.36
30.12
27.94
25.23
27.78
20.86
12.90
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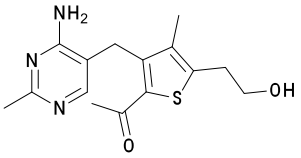
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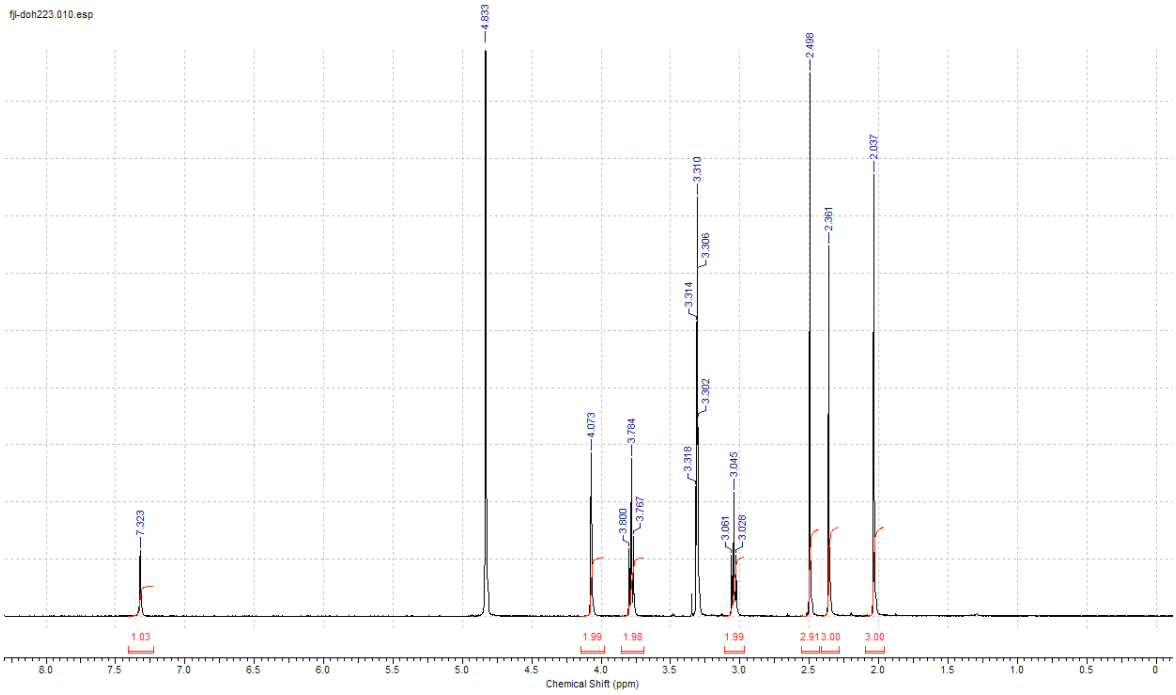
N
S
OH
O

23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3.314
3.302
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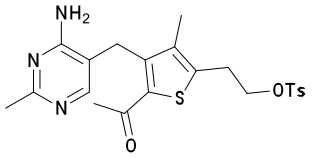
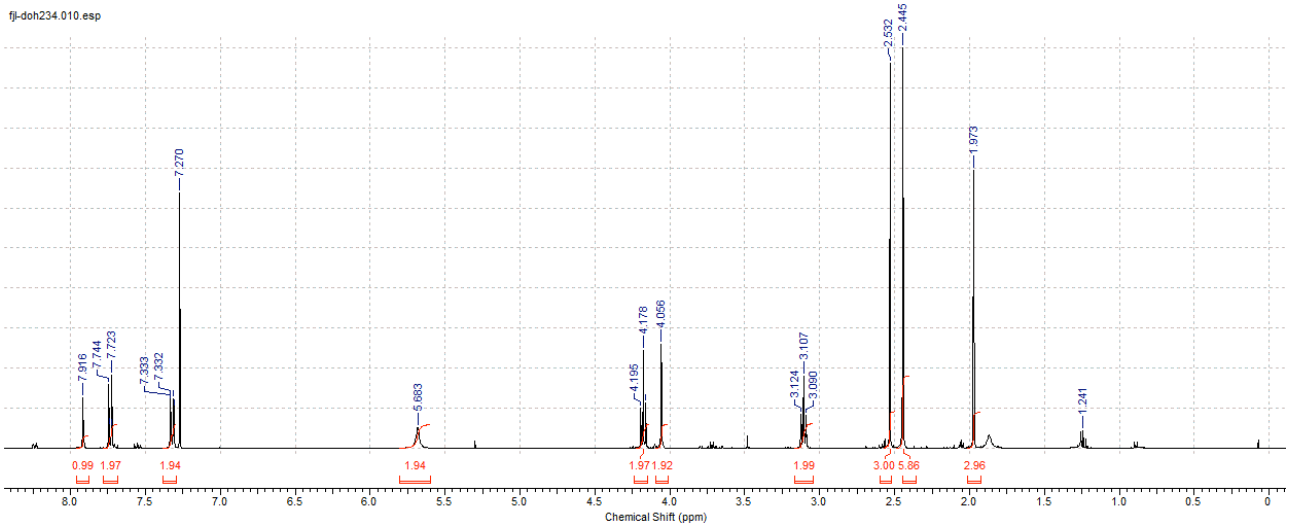
3.045
3.800
3.767
3.061
3.028
7.323
1.03
1.99
1.98
1.99
2.91
3.00
3.00
Chemical Shift (ppm)


NH2
N
N
S
OTs
O

24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7.723
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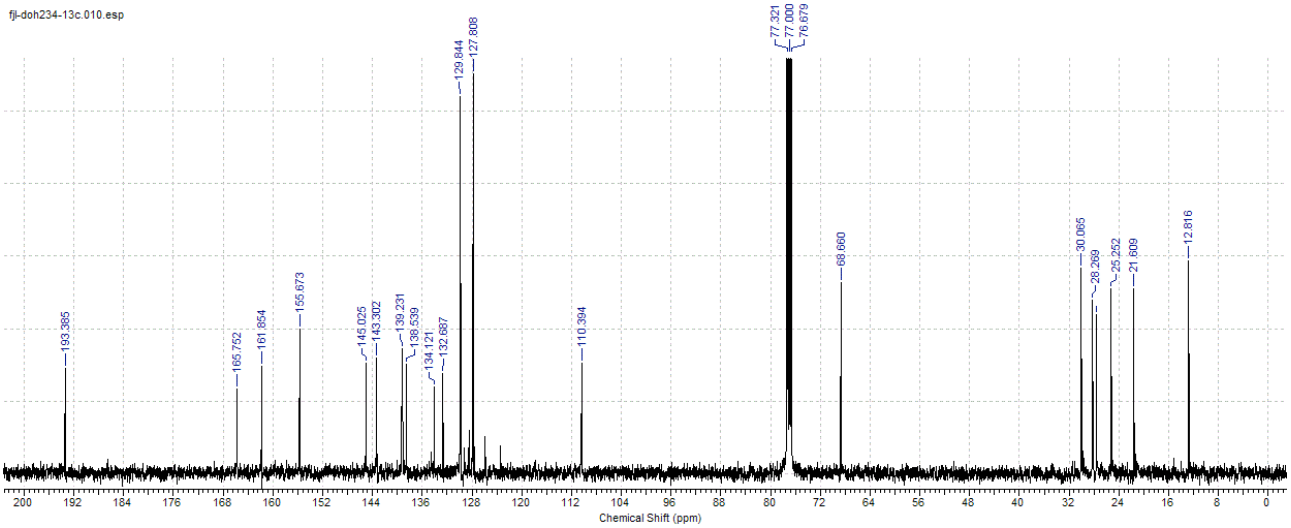
7.332
7.270
5.683
4.195
4.178
4.056
3.124
3.107
3.090
2.632
2.445
1.973
1.241
0.99 1.97 1.94 1.94 1.97 1.92 1.99 3.00 5.86 2.96
Chemical Shift (ppm)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139.231
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129.844
127.808
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77.000
76.679
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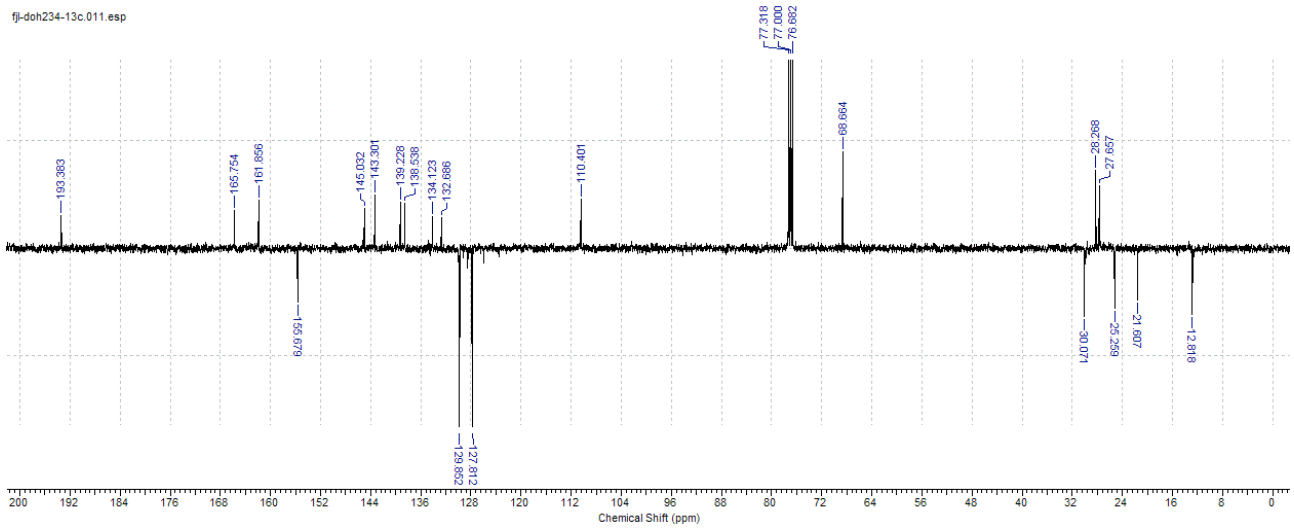
12.816
Chemical Shift (ppm)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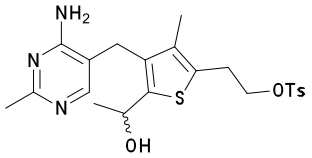
Chemical Shift (ppm)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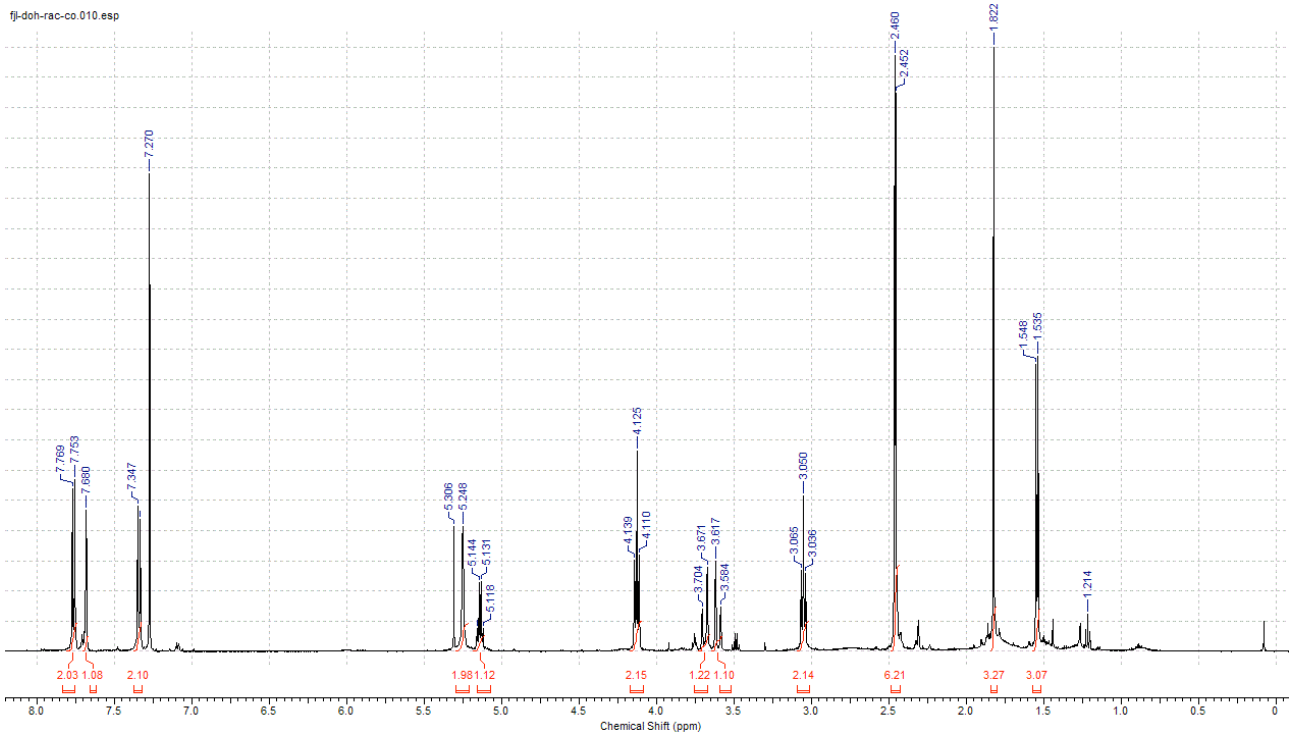
N
N
S
OTs
OH

25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4.139
4.110
3.704
3.671
3.617
3.584
3.050
3.065
3.036
2.460
2.452
1.822
1.548
1.535
1.214
2.03
1.08
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1.12
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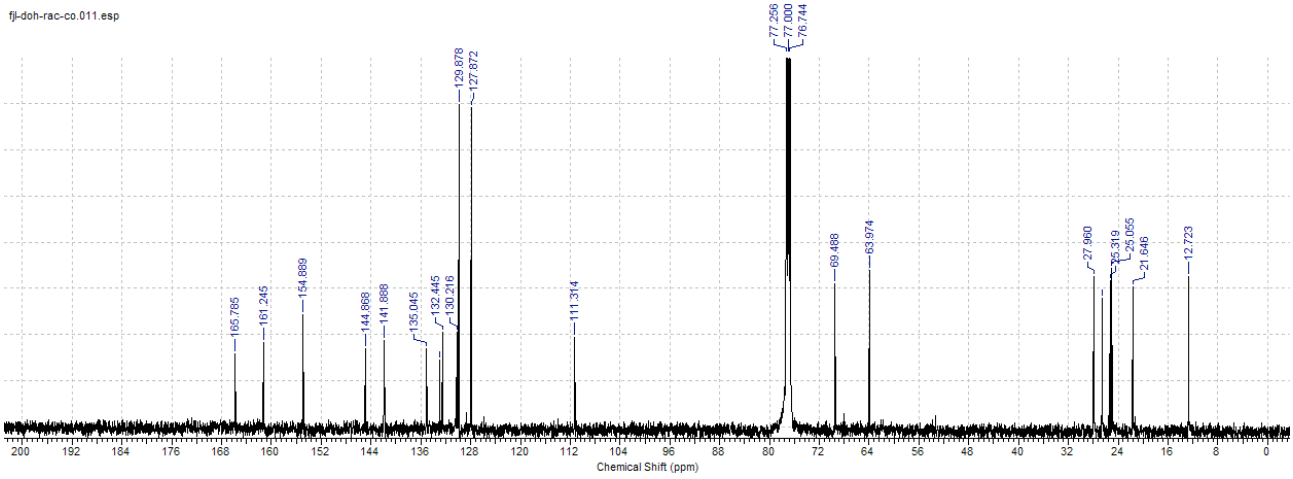
1.10
2.14
6.21
3.27
3.07
Chemical Shift (ppm)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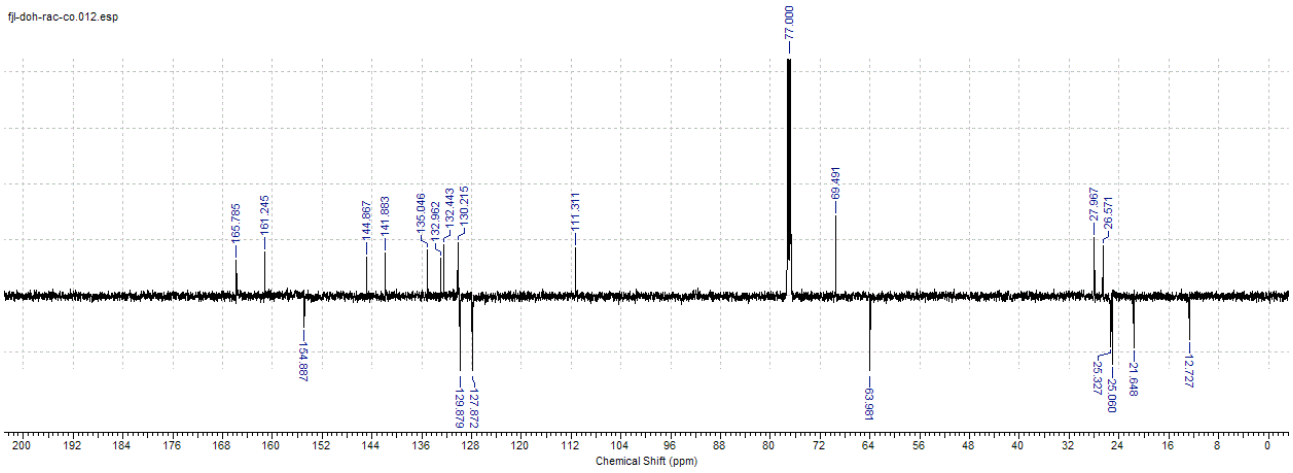
Chemical Shift (ppm)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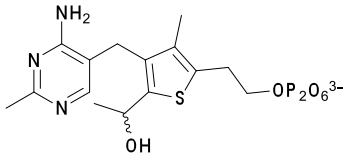
Chemical Shift (ppm)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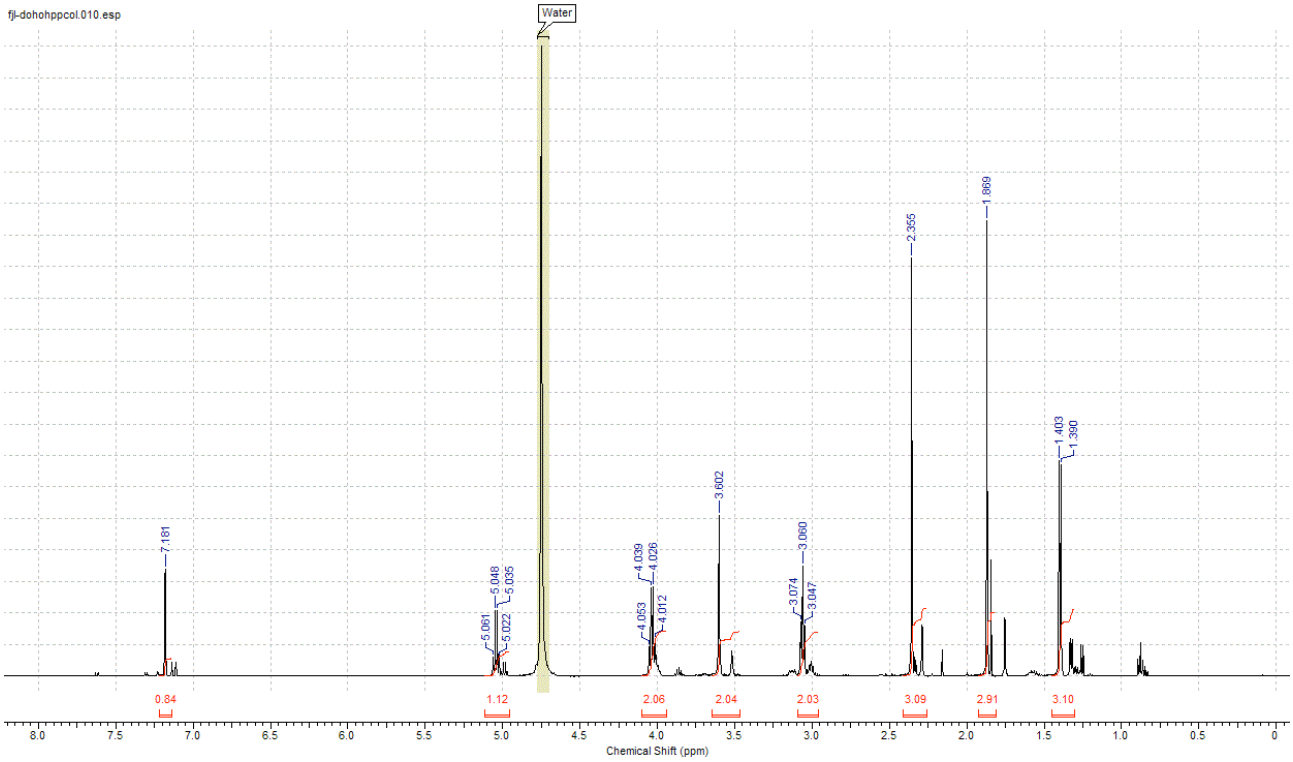
N
S
OH
OP2O6 3-

15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5.048
5.035
5.022
4.053
4.039
4.026
4.012
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3.074
3.060
3.047
2.355
1.869
1.403
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0.84
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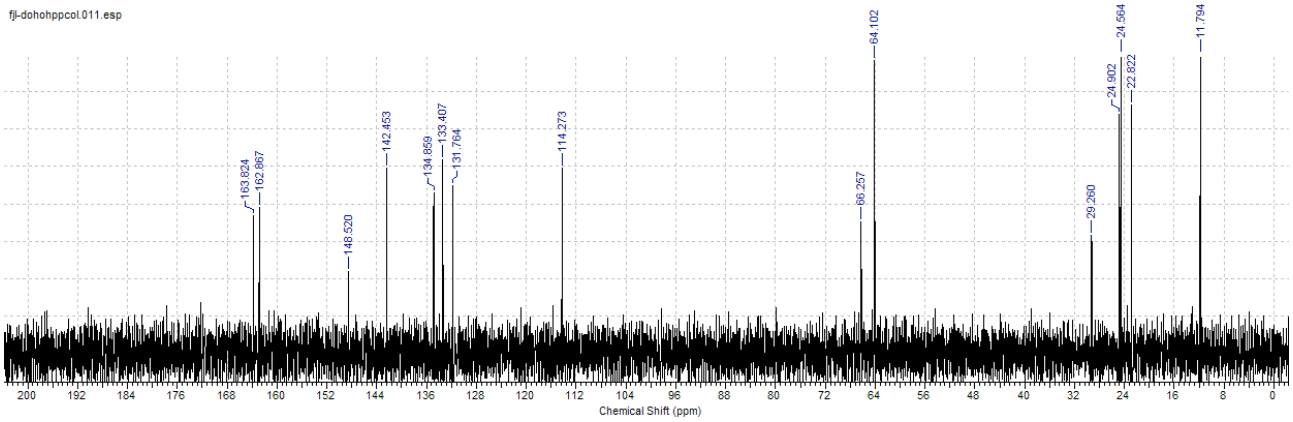
2.04
2.03
3.09
2.91
3.10
Chemical Shift (ppm)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142.453
134.859
133.407
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64.102
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24.564
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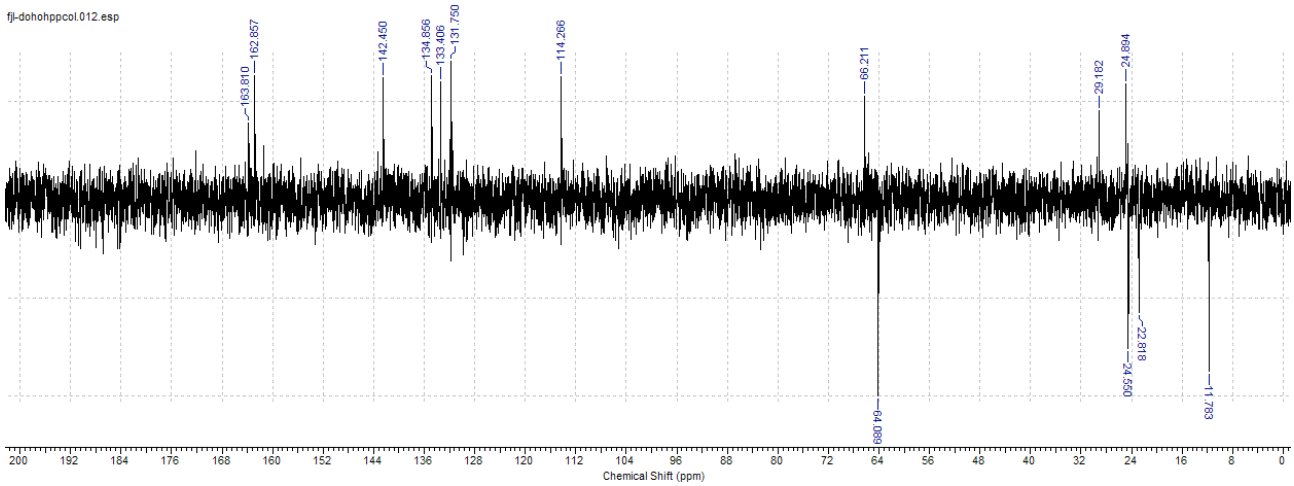
11.794
Chemical Shift (ppm)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64.089
29.182
24.894
24.550
22.818
11.783
200
192
184
176
168
160
152
144
136
128
120
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96
88
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72
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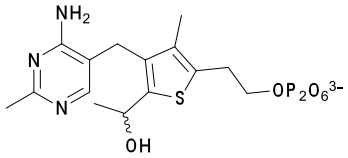
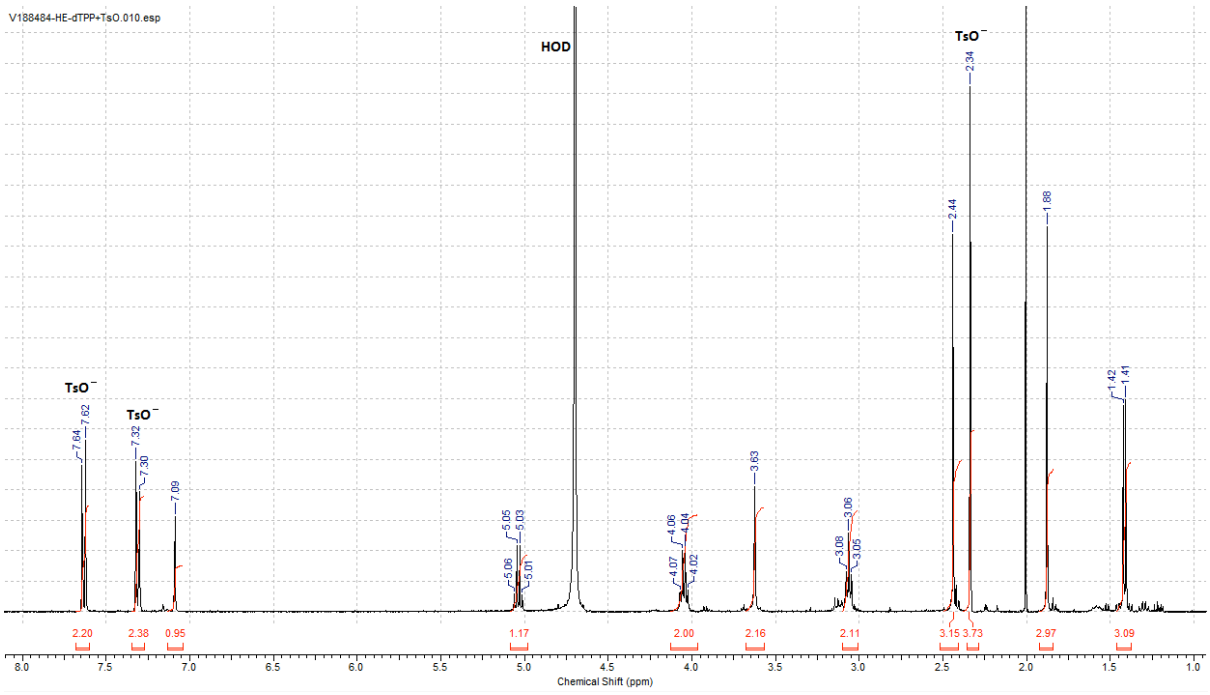
56
48
40
32
24
16
8
0
Chemical Shift (ppm)


NH2
N
N
S
OH
OP2O6 3-

15 / $TsO^-NH_4^+$ (1:1)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TsO⁻
TsO⁻
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4.06
4.04
4.02
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3.05
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1.41
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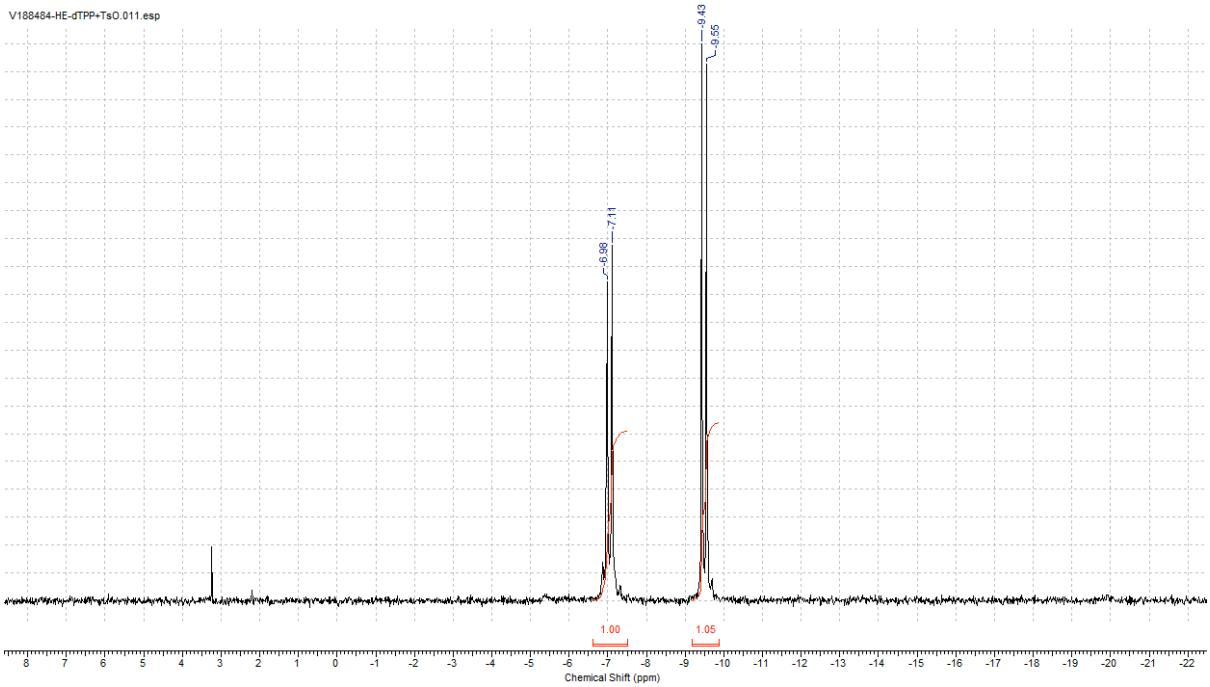
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Chemical Shift (ppm)

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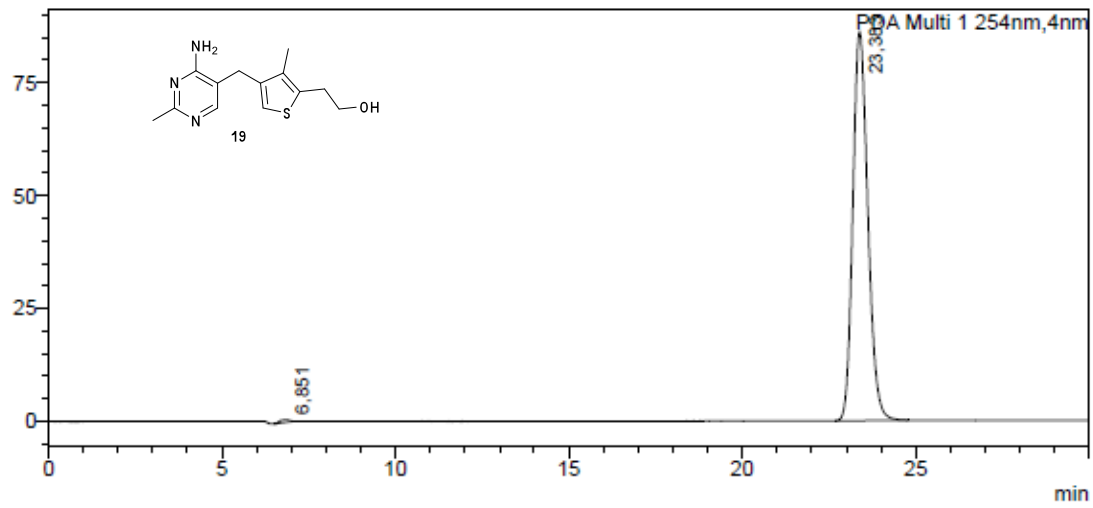

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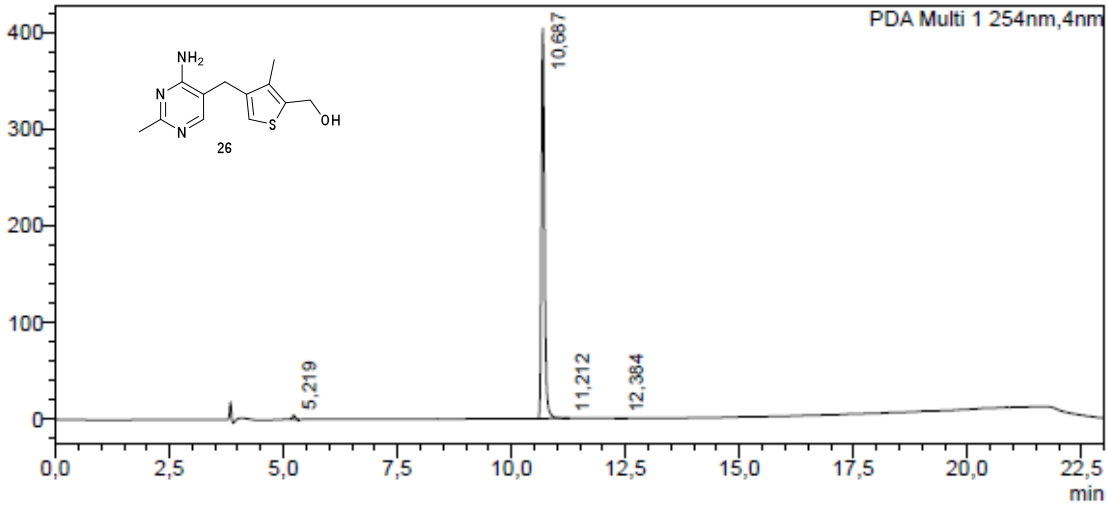

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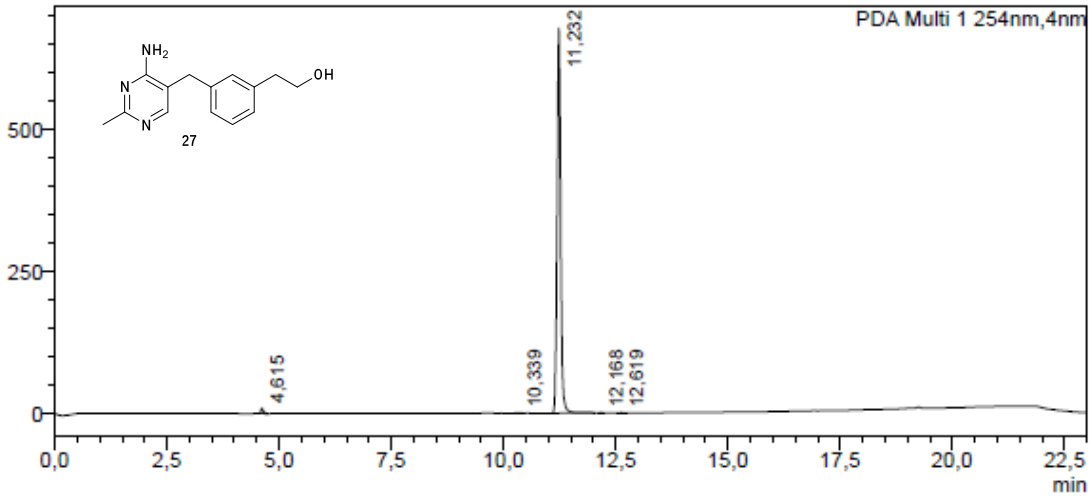

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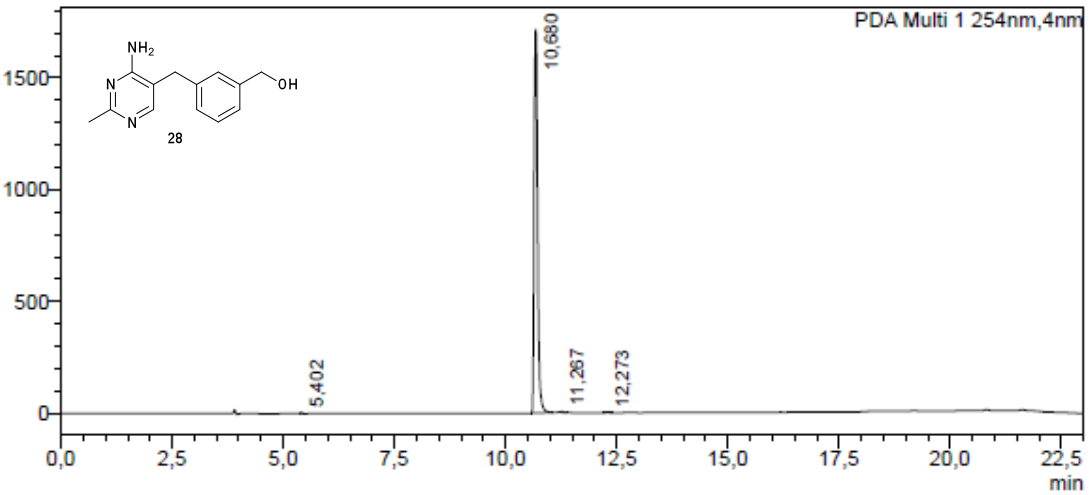

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4	12,273	11013	2287	0,116
Total		9469874	1724840	

References

[1] P. R. Gerber and K. Muller, *J. Comput.-Aided Mol. Des.,* 1995, **9**, 251−268.

[2] The PyMOL Molecular Graphics System, Version 1.4. Schrödinger, LLC.

[3] X. Xiang, G. Usunow, G. Lange, M. Busch and L. Tong, *J. Biol. Chem.*, 2007, **282**, 2676−2682.