Supporting Information

Fungal bis-Naphthopyrones as Inhibitors of Botulinum Neurotoxin Serotype A

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Table of Contents

In Silico Screen

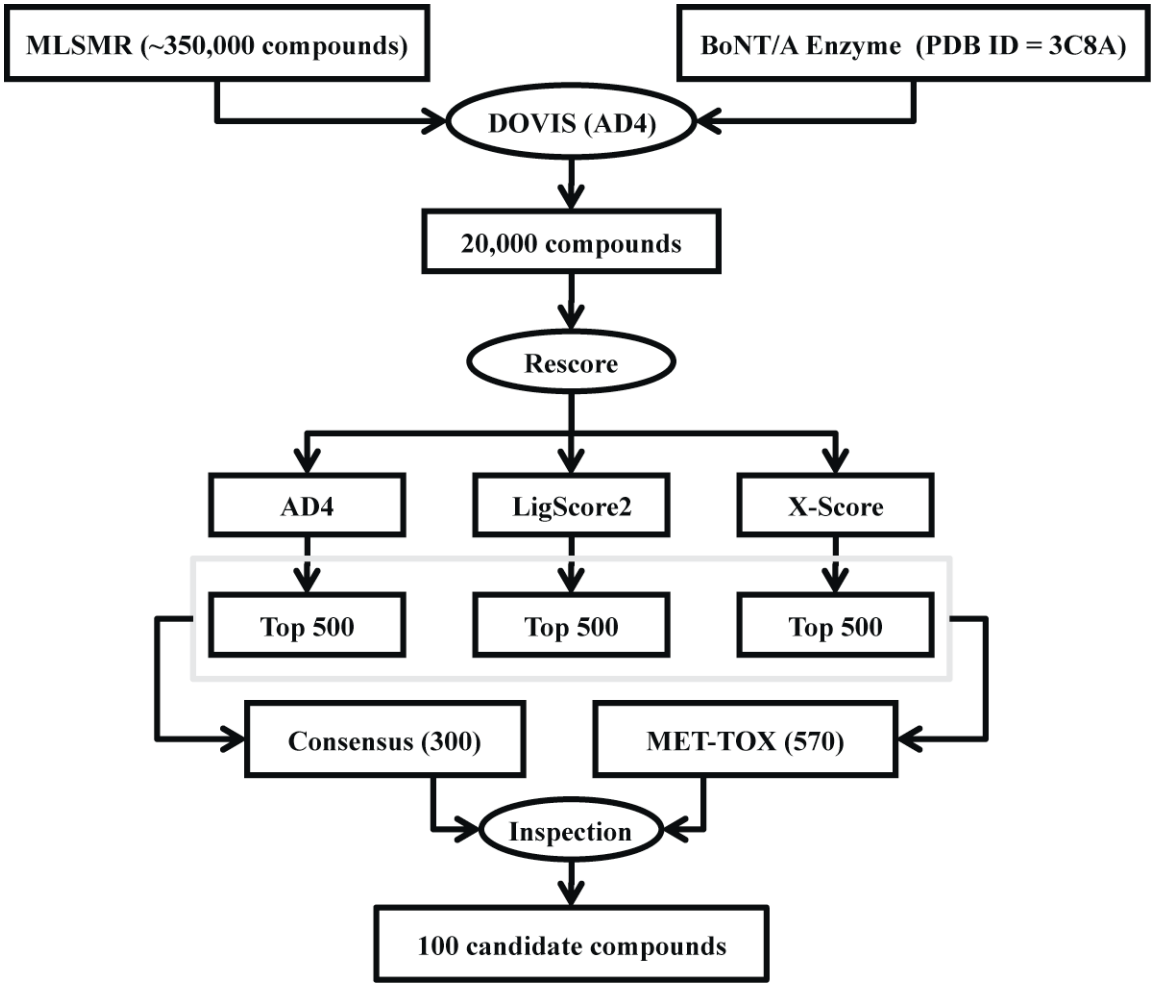


Figure 1S. Virtual screening protocol and flow diagram.

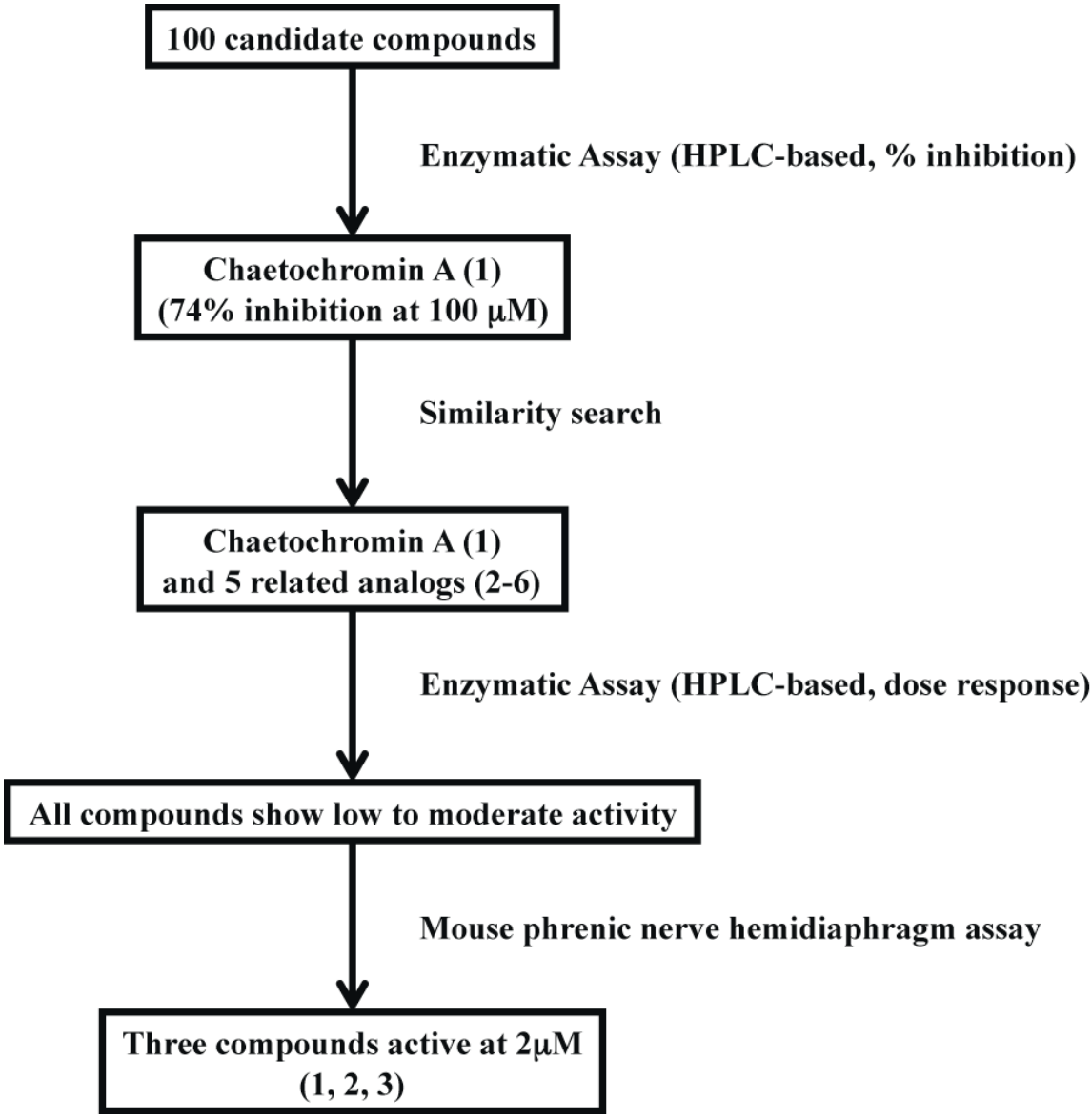


Figure 2S. Bioassay evaluation of candidate compounds.

Bioassays

Materials. BoNT/A (Hall strain) was obtained from Metabiologics (Madison, WI). The specific toxicity of the toxin was 2.4 x 10^8 mouse i.p. LD_{50}/mg of protein, as determined by a toxin titration procedure described previously.[1] The substrate for the HPLC protease assay was a peptide containing residues 187-203 of SNAP-25.[2] An Alliance HPLC System (2695 XE Separation Module and 2996 Photodiode Array Detector) and Empower/Millenium software were purchased from Waters (Milford, MA). HPLC columns (Hi-Pore C18, 0.45 x 25 cm) were obtained from Bio-Rad Laboratories (Hercules, CA).

Botulinum neurotoxin (BoNT) inhibition assays. HPLC assays of the protease activity of BoNT/A were carried out as previously described.[3] IC_{50} (50% inhibitory concentration) values against BoNT/A LC were calculated from nine concentrations of compound by a log-probit analysis program using the statistical software GraphPad Prism 4 (GraphPad Software, La Jolla, CA).

The mouse phrenic nerve hemidiaphragm assay (MPNHDA) was conducted as previously described.[3] BoNT/A-induced paralysis was measured as a 50% loss of twitch tension evoked by nerve stimulation. Estimates of statistical significance were based on unpaired t-test (two-tailed). *P* values of <0.05 were considered significant. Statistical analysis was performed using SigmaPlot 10 (Systat Software, San Jose,CA).

Procedures used to obtain mouse tissues were conducted in compliance with the Animal Welfare Act and other federal statutes and regulations relating to animals and experiments involving animals, and adhered to principles stated in the *Guide for the Care and Use of Laboratory Animals*, National Research Council, 1996. The facility where this research was conducted is fully accredited by the Association for Assessment and Accreditation of Laboratory Animal Care International.

Isolation of Fungal Natural Products

Chaetochromin A. A culture of *Chaetomium arcuatum* (syn. *Chaetomium virescens*) (NRRL 25243 = IMI 86456), originally isolated from soil collected in Lucknow, India) was subjected to solid-substrate fermentation on rice (8 x 50 g rice in 500-mL Erlenmeyer flasks). After 45 days, the cultures were extracted with 2 L of EtOAc, and the solvent was evaporated to afford approximately 3 g of an extract that was then partitioned between acetonitrile and hexane. A 100-mg portion of the acetonitrile-soluble fraction (2.2 g) was placed onto a silica gel column and eluted sequentially with hexane-acetone-MeOH mixtures of increasing polarity. A fraction eluting with 1:1 hexane-acetone (45 mg) was identified as chaetochromin A (**1**) by comparison of its ^{1}H NMR, ^{13}C NMR, CD, and MS data with literature values.[4]

Talaroderxines A and B. The culture of *Delitschia* sp. was a subculture of an isolate originally obtained from a sample of kangaroo dung collected by J. A Scott from scrubland in Australia at a site 20 km west of Balranald in March 1994. This isolate was assigned the accession number JS

300 in the D. Malloch culture collection at the University of Toronto. Six 2-L Erlenmeyer flasks containing PDB (400 mL each) were each inoculated with one-cm^2 agar plugs of *Delitschia* sp. from stock cultures maintained on PDA. The flasks were incubated at rt on rotary shakers at 150 rpm for 20 days. The culture broth was filtered to separate the mycelia from the broth. The broth (2.4 L) was extracted with EtOAc (3 x 1 L), and the organic layer was dried with $MgSO_4$ and evaporated to yield 1.45 g of an antibacterial extract. The EtOAc extract was subjected to VLC on silica gel using a step gradient from 100% hexane to 100% $CHCl_3$ and finally to 50% MeOH in $CHCl_3$. The fraction eluting at 100% $CHCl_3$ (366 mg) was further purified by preparative reversed phase HPLC (C_{18}, 8μ particles, 2.14 x 25 cm, 10 mL/min, 20-100% MeOH in H_2O over 30 min) to afford talaroderxine A (**2**; t_R 31.8 min; 12.6 mg) and talaroderxine B (**3**; t_R 29.8 min; 18.2 mg). Talaroderxines A and B were identified by analysis of ^1H NMR, ^{13}C NMR, MS, CD, and $[\alpha]_D$ data, and by comparison to literature values.[5]

Secalonic acid A. A culture of *Setophoma terrestris* (NRRL 25008), obtained as a colonist of an *Aspergillus flavus* sclerotium that was buried in field soil near Kilbourne, Illinois, was subjected to solid-substrate fermentation on rice (2x 200 g rice in 2.8-L Fernbach flasks). After 45 days, the cultures were extracted with 2 L of EtOAc. After evaporation of the solvent, the resulting extract (2.27 of 2.41 g) was subjected to VLC on silica gel, eluting sequentially with hexane-CH_2Cl_2-MeOH mixtures of increasing polarity. The fraction eluting with 15% MeOH in CH_2Cl_2 (47 mg) was subjected to reversed phase (C_{18}) HPLC using a linear gradient of 20-90% acetonitrile in 0.1% aqueous formic acid. A peak eluting at 26 min was identified as secalonic acid A (**4**; 5.0 mg) by comparison of its ^1H NMR, ^{13}C NMR, and MS data with literature values.[6]

Cephalochromin. A culture of *Cosmospora* sp. (syn. *Acremonium butyri*; NRRL 28291), obtained as a colonist of the stromata of *Hypoxylon* sp. found on a fallen hardwood log, Picture Ridge Drive, Peoria, IL collected by H.D. Thiers in May 1996) was subjected to solid-substrate fermentation on rice (50 g rice in a 500-mL Erlenmeyer flask). After 45 days, the culture was extracted with 0.5 L of EtOAc. A portion of the resulting extract (approximately 50 mg of 1.57 g total) was placed directly onto a column of Sephadex LH-20 and eluted sequentially with 4:1 CH_2Cl_2-hexane (with which the column had been packed), 3:2 CH_2Cl_2-acetone, and 1:4 CH_2Cl_2-acetone; five fractions were collected. The second fraction (41 mg) was essentially a pure compound, as judged by ^1H and ^{13}C NMR analysis. It had an orange color and accounted for most of the mass of the extract. This compound was identified as cephalochromin (**5**) by comparison of its NMR, MS, and optical rotation data with literature values.[6,7]

Skyrin. A culture of *Geomyces pannorum* (NRRL 22978), obtained as a colonist of an *Aspergillus flavus* sclerotium buried in sandy field soil near Kilbourne, Illinois, was subjected to solid-substrate fermentation on rice (2 x 50 g rice in 500-mL Erlenmeyer flasks). After 45 days, the cultures were extracted with 0.5 L of EtOAc. After evaporation of the solvent, the resulting extract (409 mg) was placed directly onto a column of Sephadex LH-20 and eluted sequentially with 4:1 CH_2Cl_2-hexane (with which the column had been packed), 4:1 CH_2Cl_2-acetone, 3:2 CH_2Cl_2-acetone, and 1:4 CH_2Cl_2-acetone; 14 fractions were collected. The eighth fraction (82 mg), eluted with 3:2 CH_2Cl_2-acetone, was essentially a pure compound, as judged by ^{1}H and ^{13}C NMR analysis. This metabolite was identified as *S*-(+)-skyrin (**6**) by comparison of its NMR, MS, and $[\alpha]_D$ data with literature values.[8]

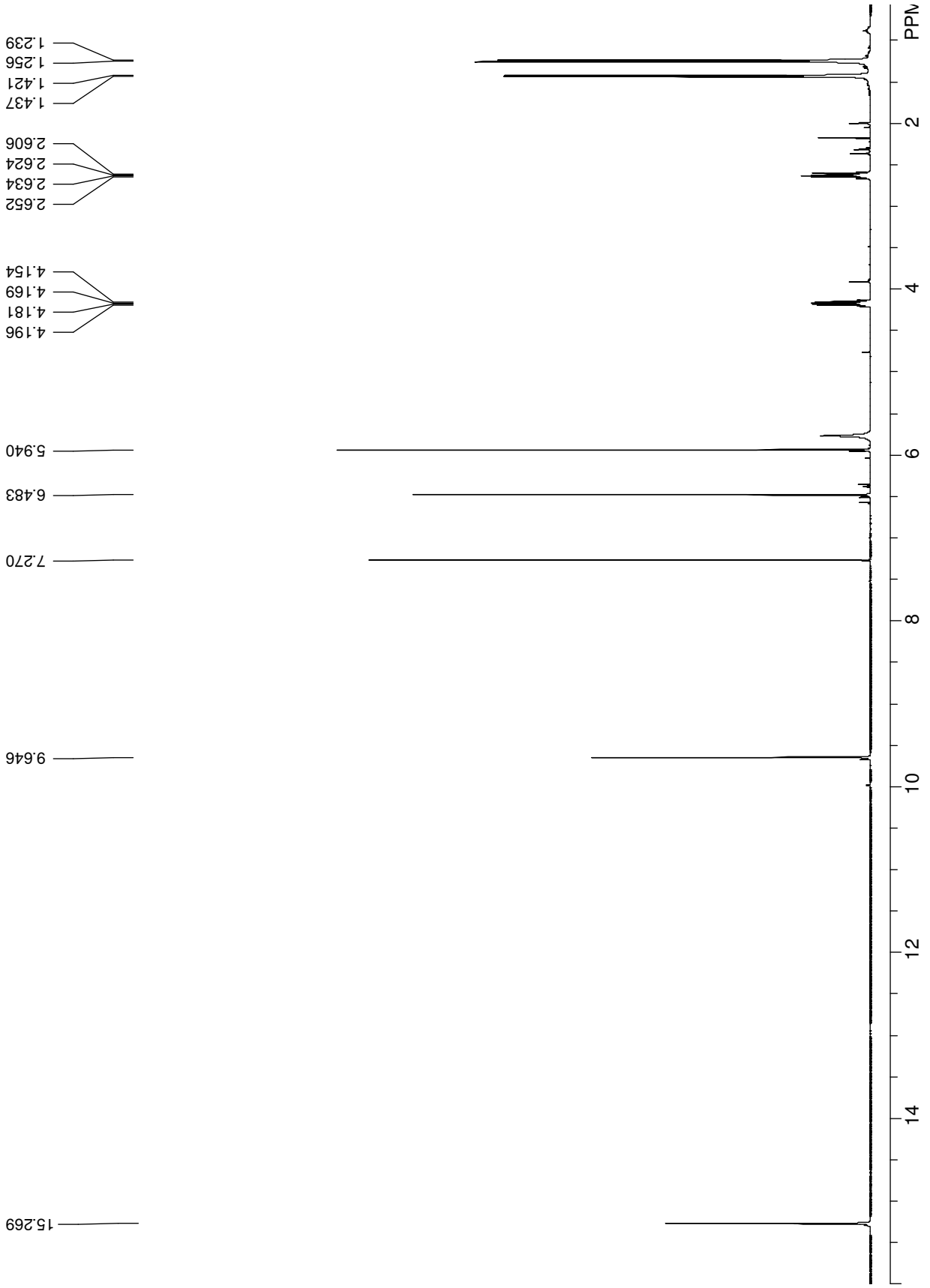


Figure 3S. ^{1}H NMR spectrum of chaetochromin A (**1**) at 400 MHz in $CDCl_3$

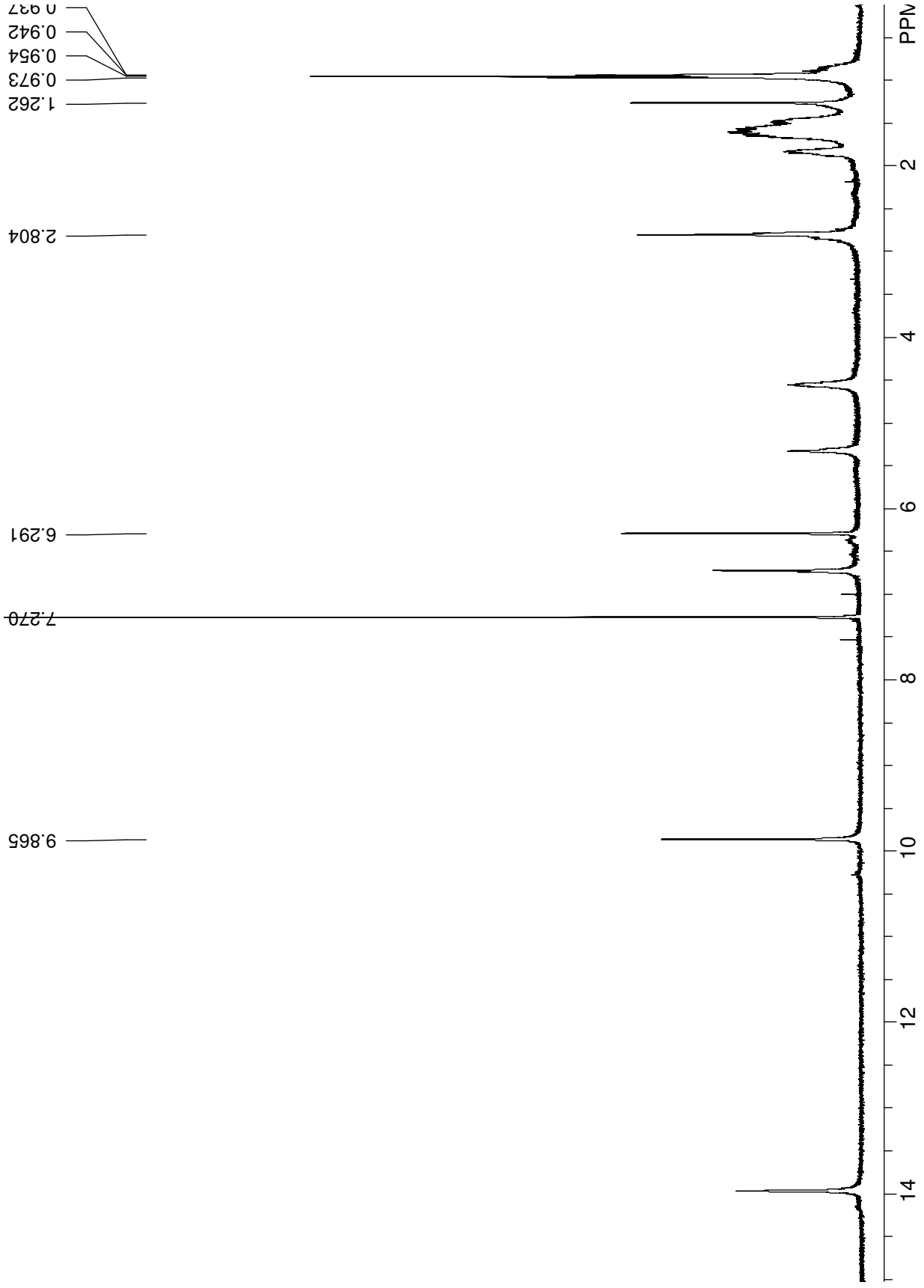


Figure 4S. ^{1}H NMR spectrum of talaroderxine A (**2**) at 400 MHz in $CDCl_3$

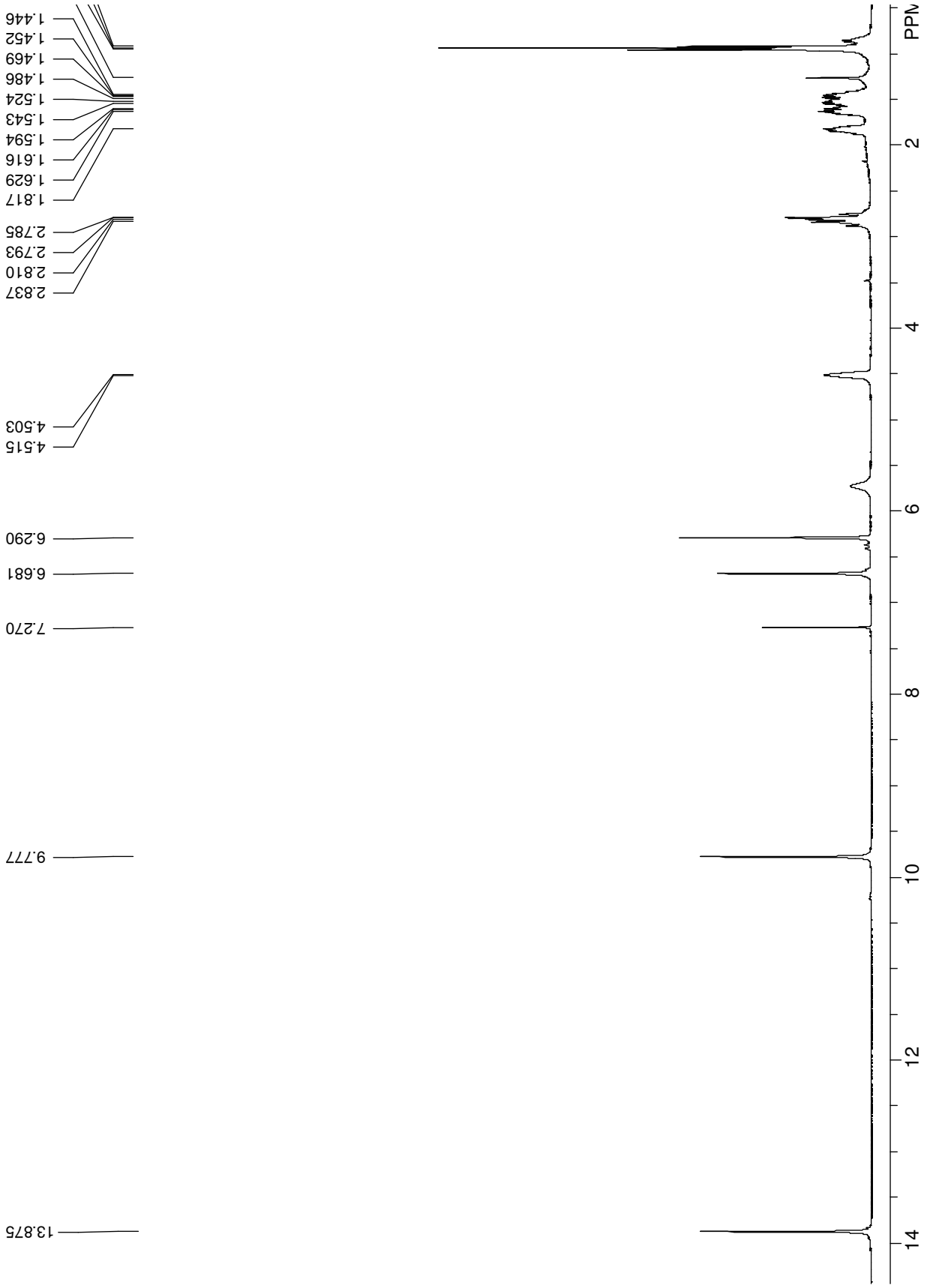


Figure 5S. ^{1}H NMR spectrum of talaroderxine B (**3**) at 400 MHz in $CDCl_3$

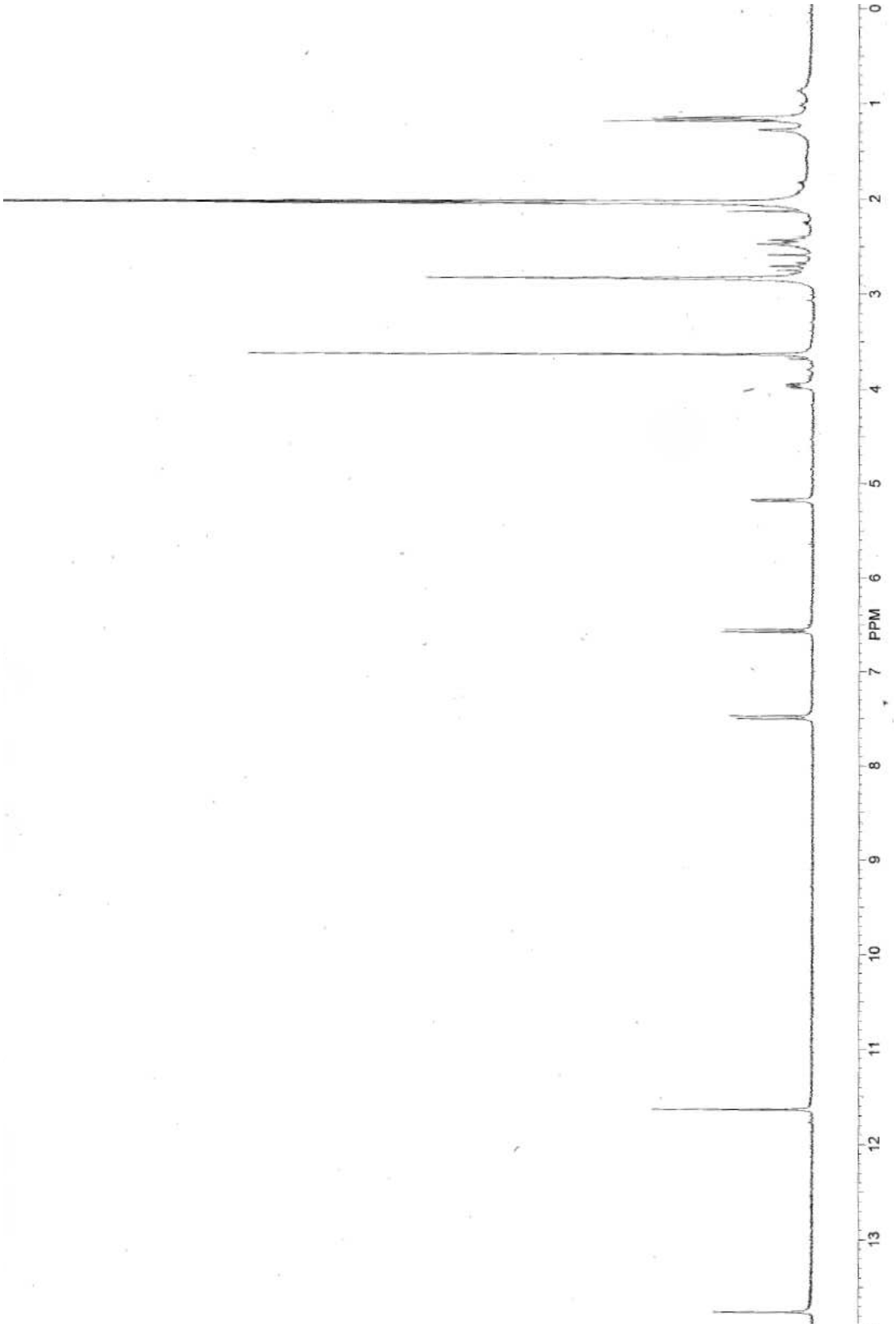


Figure 6S. ^{1}H NMR Spectrum of Secalonic Acid (**4**) at 400 MHz in $CDCl_3$

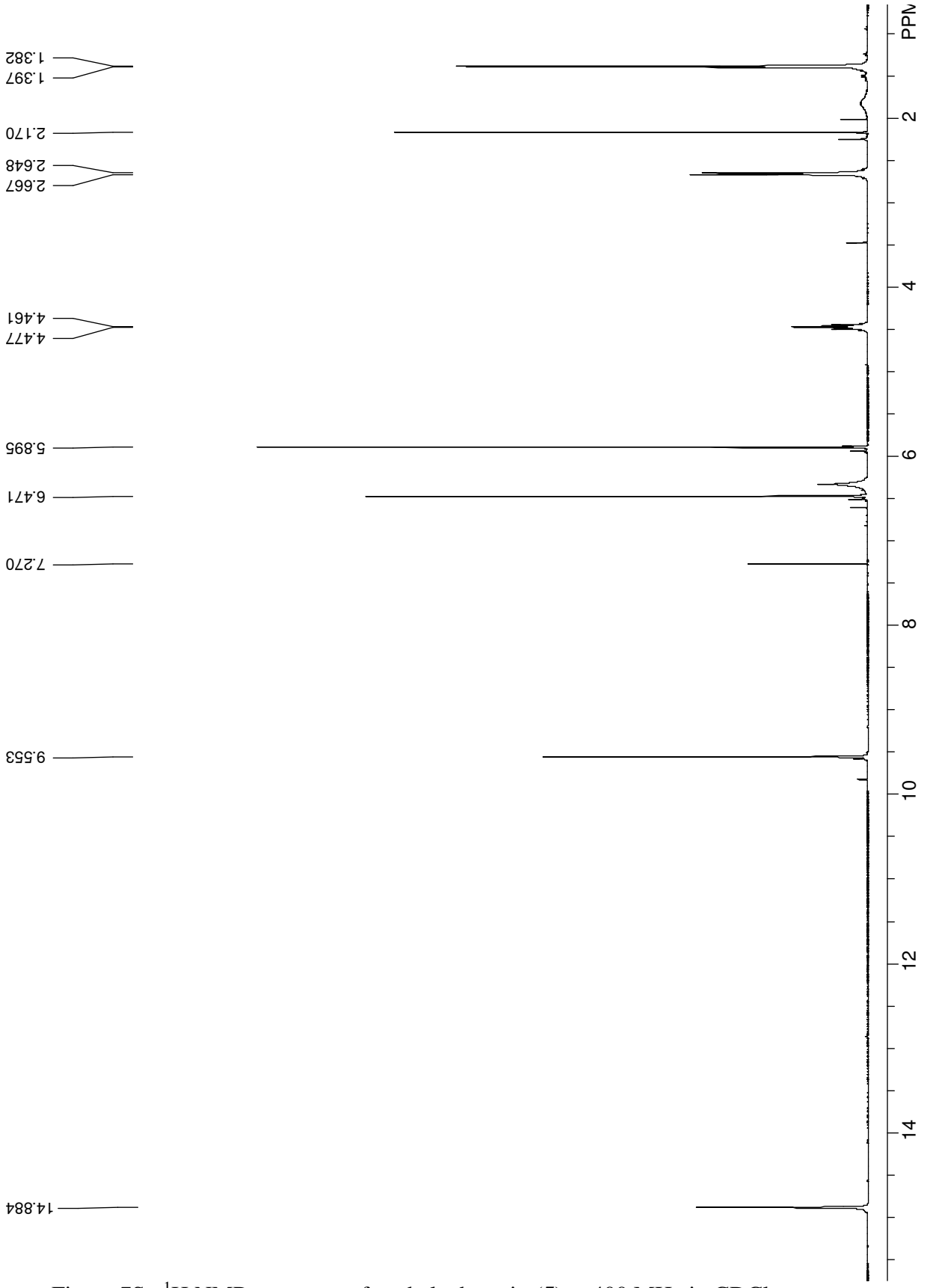


Figure 7S. ^{1}H NMR spectrum of cephalochromin (**5**) at 400 MHz in $CDCl_3$

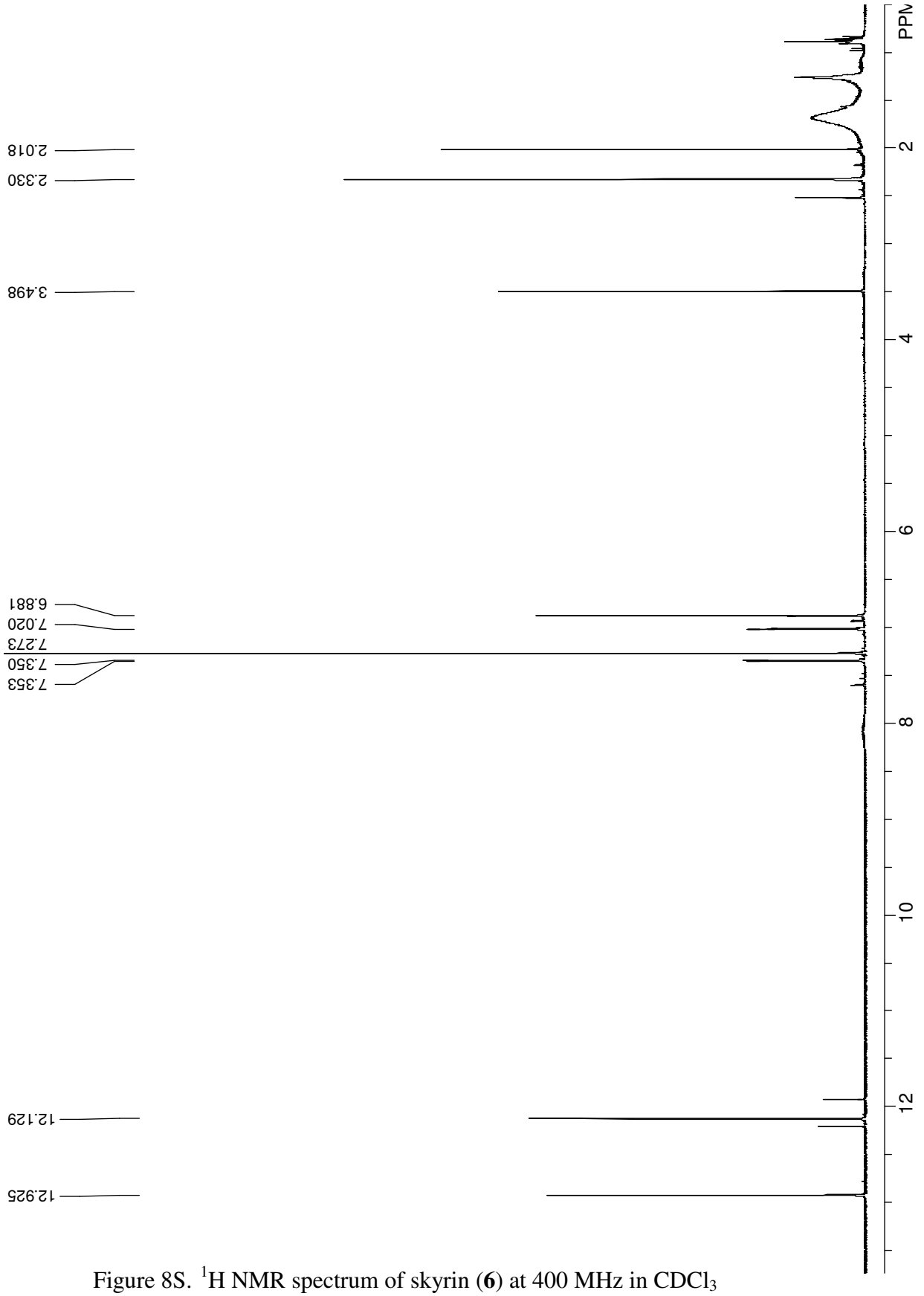


Figure 8S. ^{1}H NMR spectrum of skyrin (**6**) at 400 MHz in $CDCl_3$

Computational Section – Molecular Modeling/Docking

The details of the BoNT/A structure setup were the same as in our previous work.[9] Small molecule parameters were derived using GAFF forcefield.[10] Charges were derived using AM1-BCC approach[11,12] as implemented in our in-house software described previously.[9,13,14] The parameters of all ligands are provided at the end of this document in mol2 format. For this work, we designed and parameterized a special reference molecule shown in Scheme 1. This molecule contains the 1,1'-binaphthyl core fused to cyclohexenone instead of pyrone.

All compounds, including reference compound, were docked into the BoNT/A structure using Autodock Vina.[15] Nine poses were saved for each compound and visually inspected to find common binding poses. Skyrin was the only compound that differed substantially in its binding poses from all the other compounds. It is worth noting that the docking software breaks the axial symmetry of the compounds as it is not cognizant of the higher order chirality. Therefore, docking poses contain both stereoisomers of the compounds with respect to the chiral axis. Skyrin differs from the rest of the compounds in the pattern of carbonyl and hydroxyl groups around the ring. To get the complex of skyrin in the selected consensus pose corresponding to A stereoisomer, its coordinates were rebuilt from the corresponding complex of BoNT/A with the reference compound.

For accelerated sampling of the multiple hydroxyl groups of the compounds studied in this work, we derive the unphysical reference state for Thermodynamic Integration by collapsing all of hydrogen atoms of the reference compound (Scheme 1) onto the corresponding oxygen and carbon atoms. Note that the reference structure lacks asymmetric carbon atoms. The lack of rotatable OH groups in the unphysical reference structure helps boost rotations of the hydroxyl groups in all of the real compounds studied here. This is achieved with the help of recently developed Single Reference Thermodynamic Integration (SRTI) method augmented with Hamiltonian Replica Exchange (HREX).[13,14]

For the HREX-SRTI simulations reported in this work, we used soft-core potentials with $p = 1$ (refer to GROMACS manual for notation used in soft-core potentials) and optimized parameters.[9] Specifically, we used previously optimized[14] values of the $\alpha = 0.4$. Furthermore, due to the presence of large number of hydroxyl groups in the compounds the H atoms of which are lacking the vdW parameters, we optimized the value of σ from its default value of 0.3 to 0.25 that gives better results. This is first time we attempted optimization of the σ parameter of the soft core potential within HREX-SRTI.

HREX-SRTI simulations involved running two independent simulations in water and solvated protein environment for each ligand. Hence the standard deviations provided were derived from two independent simulations in each leg of cycle and relative to the chaetochromin A. We employed 24 windows in both protein and water simulations. The production runs were 1 ns long in each window with a total of 1000 exchange steps. Each window was running on 8 cpu cores for approximately 48 hours. All the simulations were performed on DoD's Mana MHPCC supercomputer. Coordinates were saved every 1 ps. Unless otherwise stated, the details of MD simulations were the same as in our previous work.[14] The HREX-SRTI trajectories for the physical state of the complexes were merged using our in-house tools prior to analysis. GROMOS-style clustering was done using g_cluster program of GROMACS with a RMSD cutoff of 0.05 nm.[16,17] During clustering, the complex frames were fitted using Zn^{2+}, heavy atoms of the bound ligands and Cα atoms of the rigid structural elements of the protein (residues 164-167; 184-187; 192-196; 217-233 and 260-266). Centroids of the clusters that had at least 10% of the total population were retained. The top clusters were used to generate the figures in the main text. Ligand-protein interactions were analyzed in 2D projections using MOE software.[18]

Figure 9S. The compound used to generate parameters of the single reference for HREX-SRTI simulations.

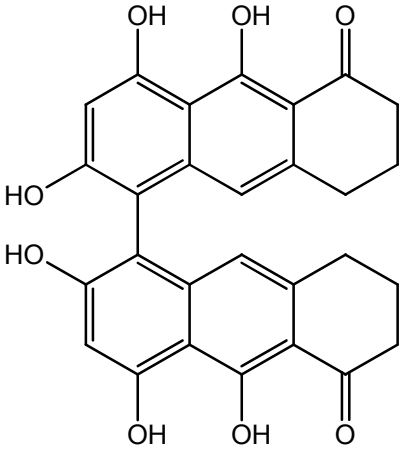
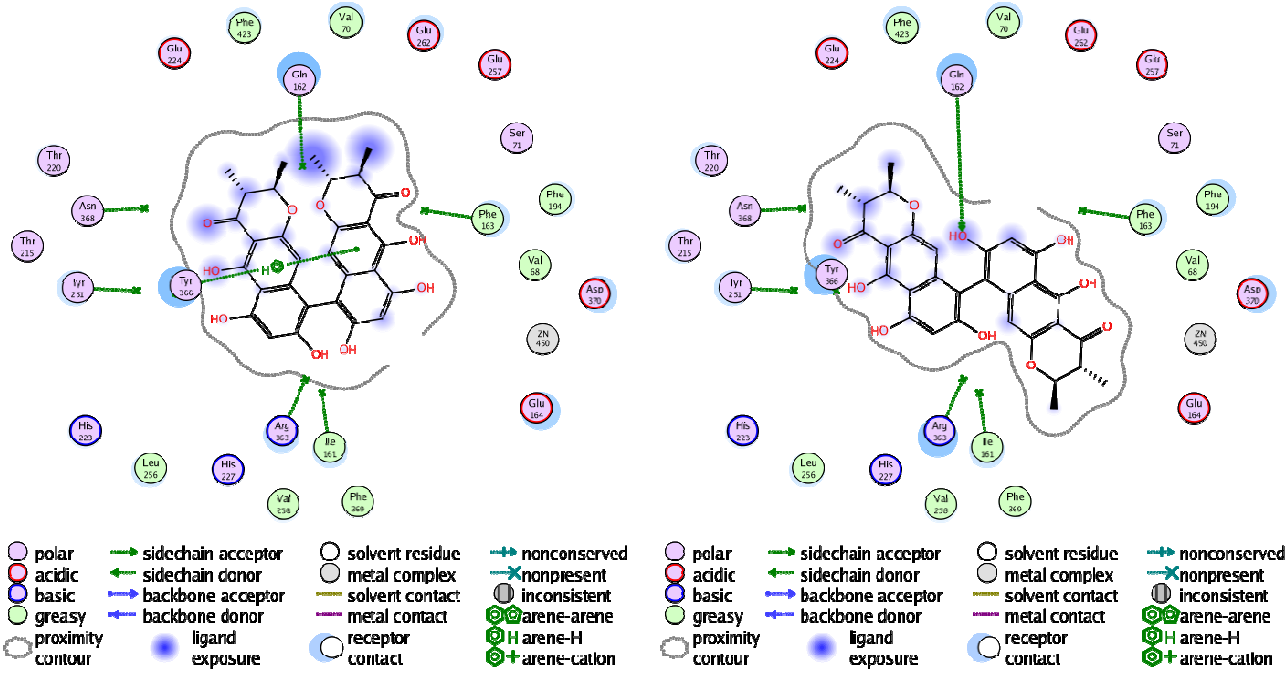
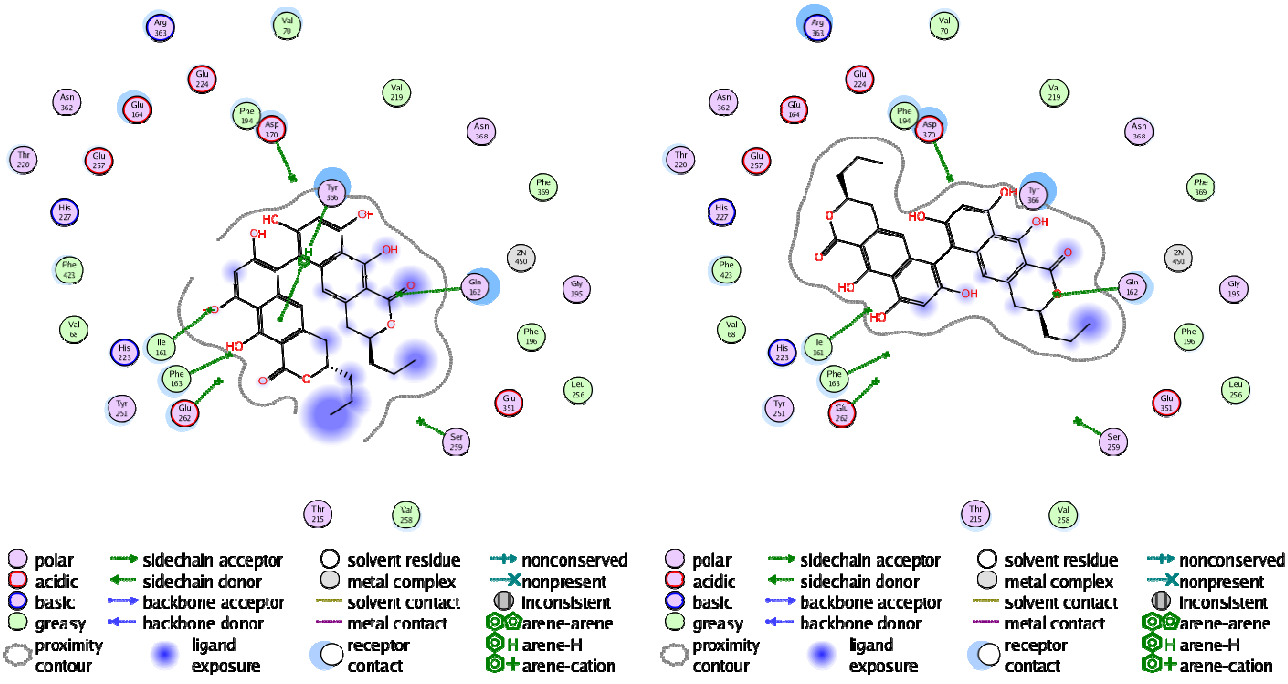


Figure 10S. 2-D depiction of the ligand-protein interactions of the A and B stereoisomers of selected compounds in corresponding consensus bound states with BoNT/A from Autodock Vina.



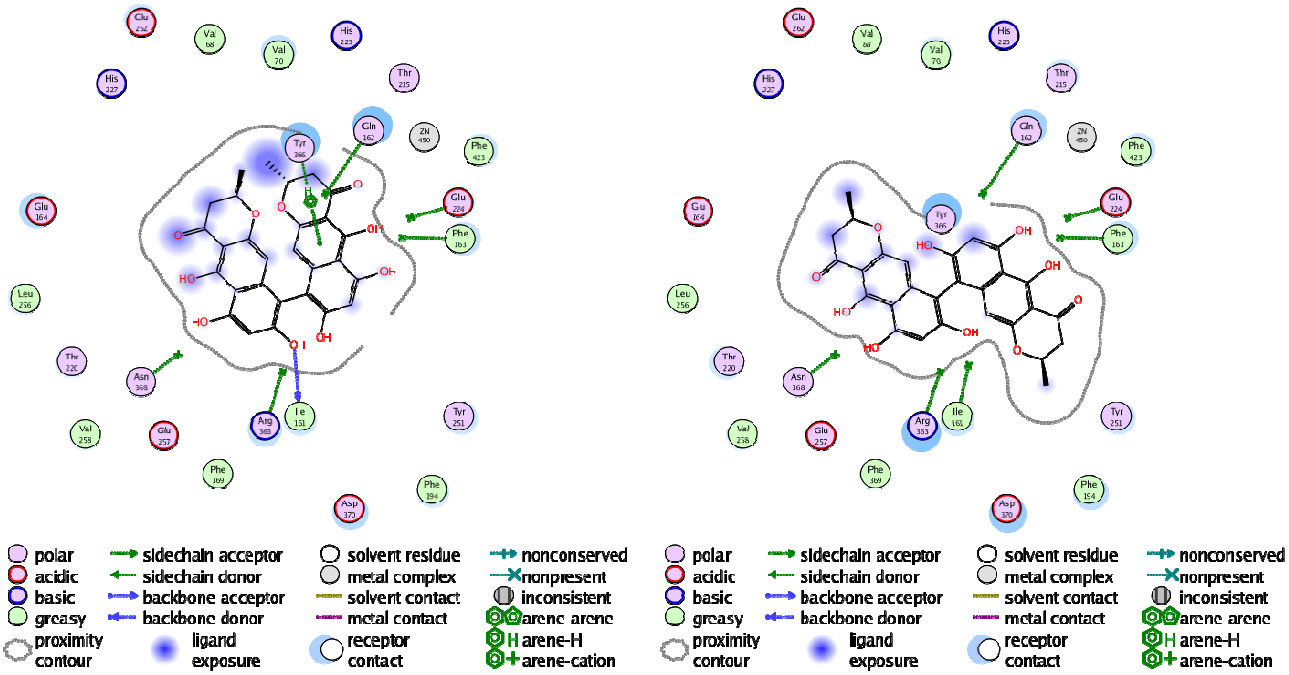
Chaetochromin A

Chaetochromin B



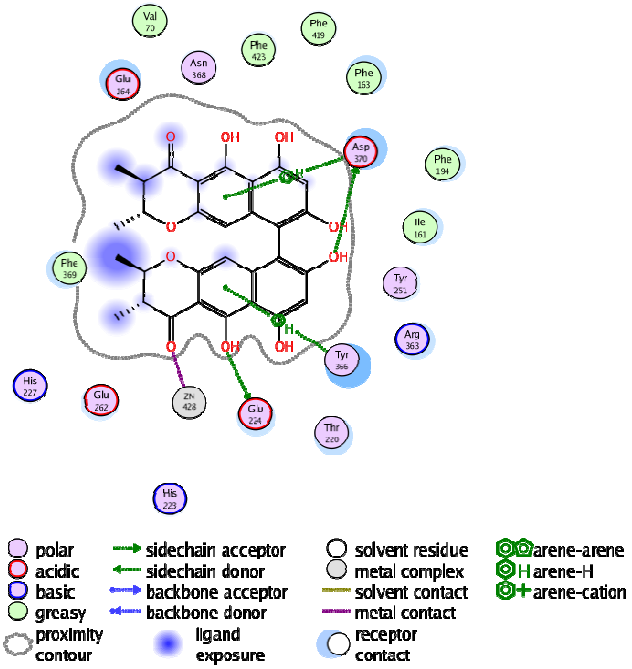
Talaroderxine A

Talaroderxine B

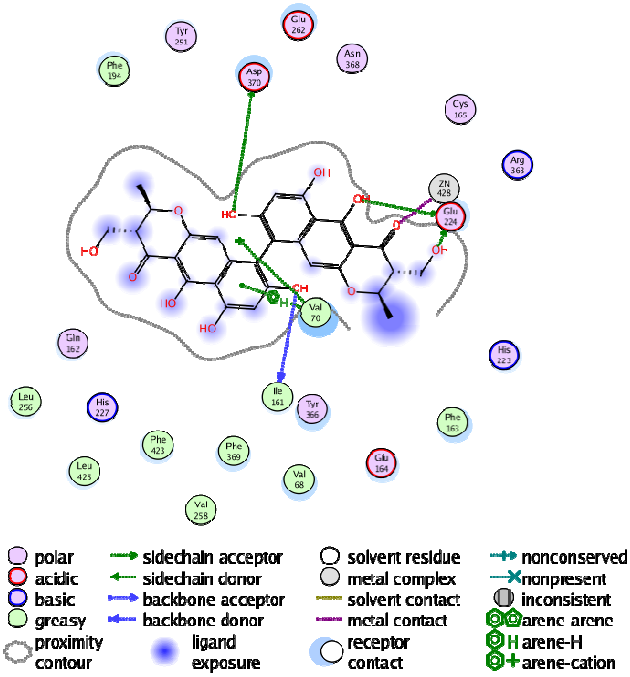


Cephalochromin A Cephalochromin B

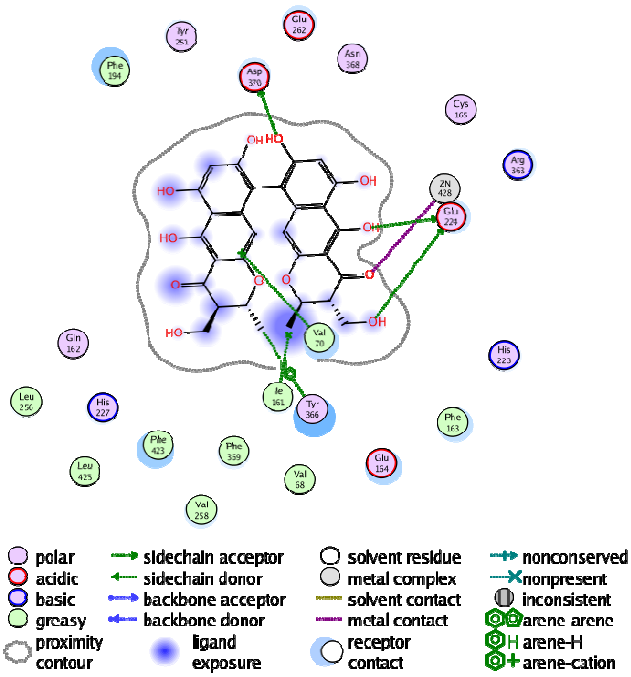
Figure 2S. 2-D depiction of the ligand-protein interactions of the A stereoisomers of studied compounds with BoNT/A in the most populated clusters from HREX-SRTI simulations.



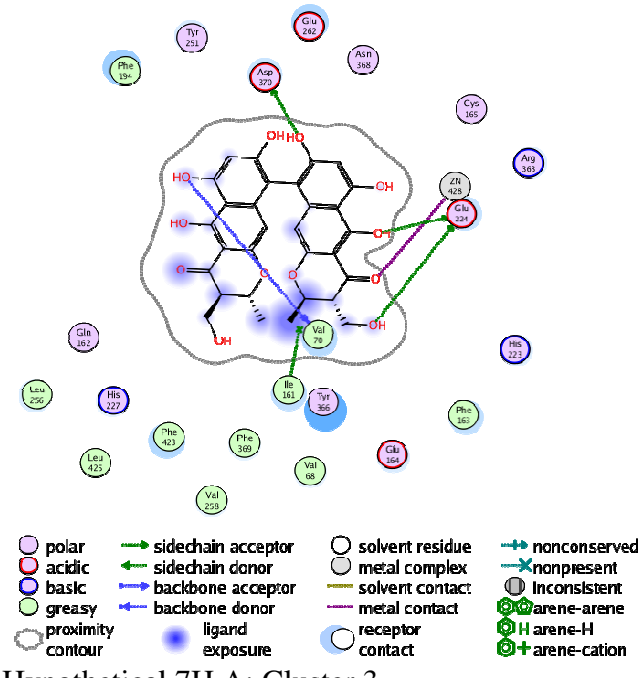
Chaetochromin A; Cluster 1



Hypothetical 7H A; Cluster 1



Hypothetical 7H A; Cluster 2



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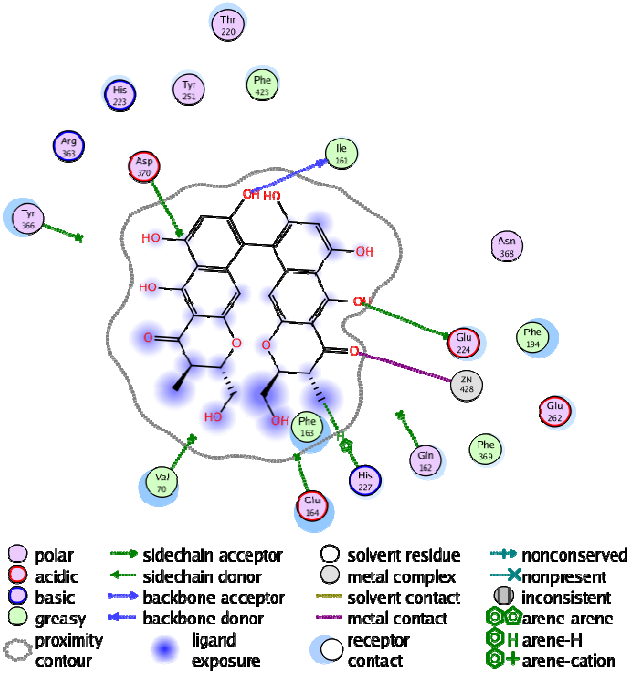
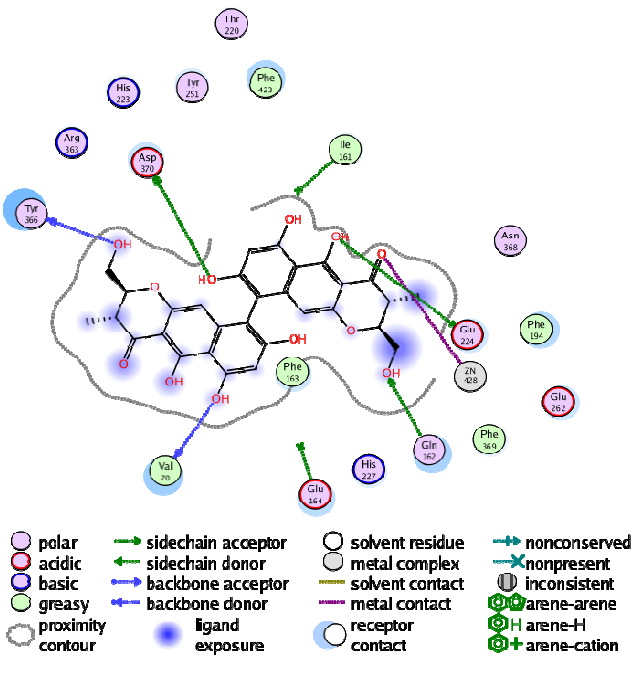


Hypothetical 8H A; Cluster 1



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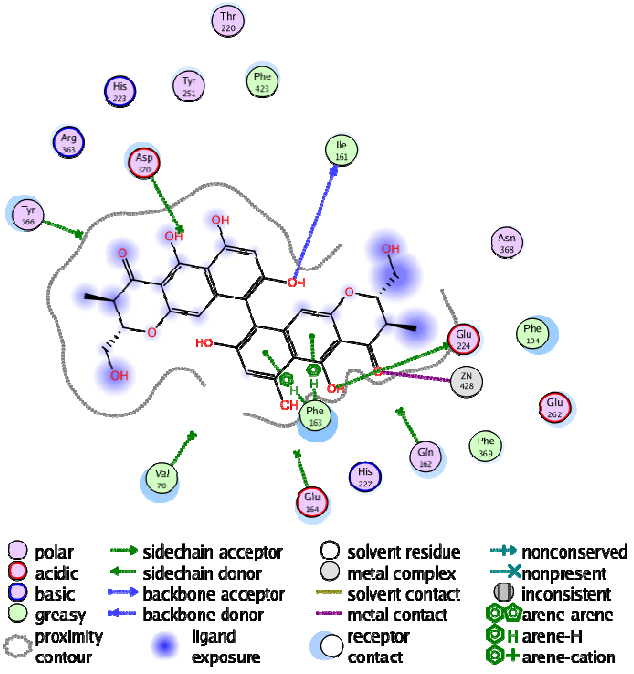

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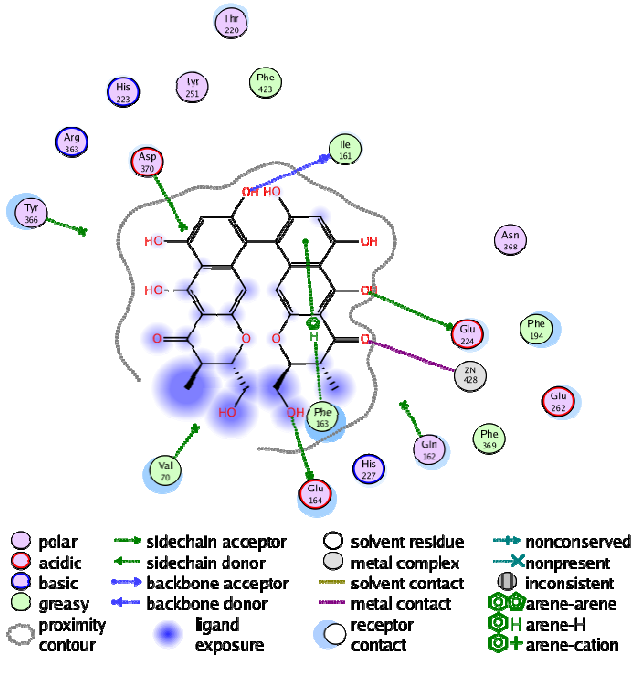
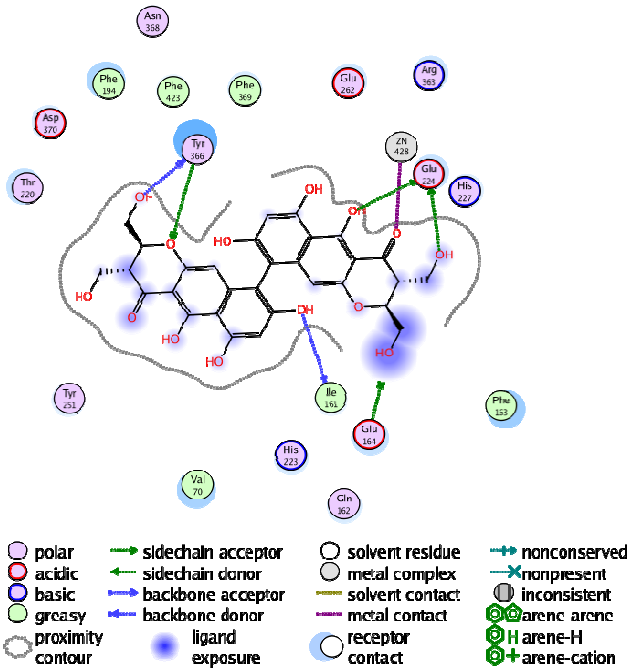
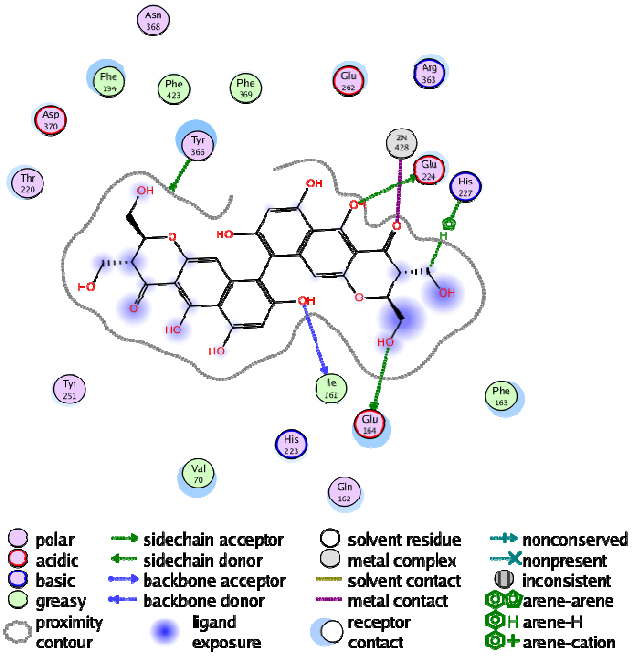


Hypothetical 8H A; Cluster 4



Hypothetical 9H A; Cluster 1



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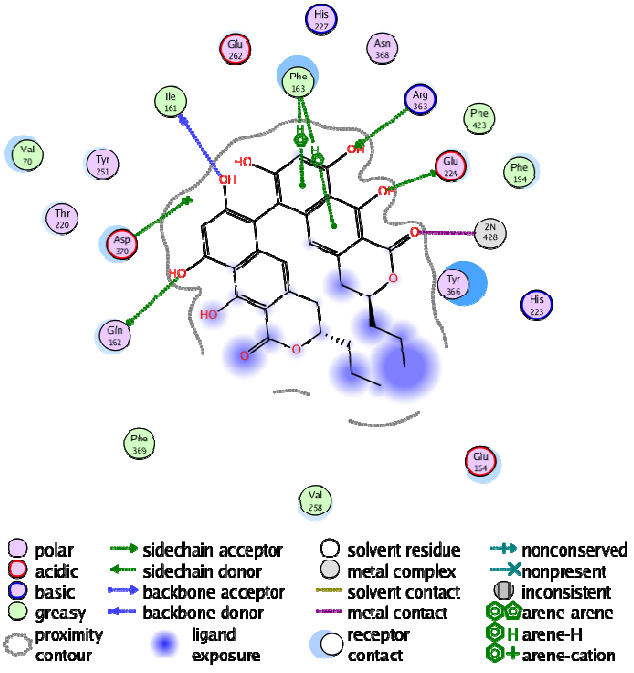
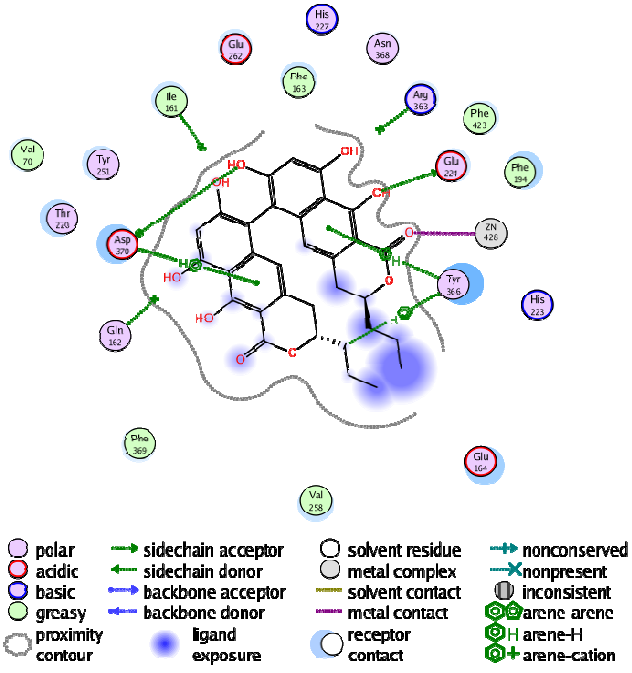
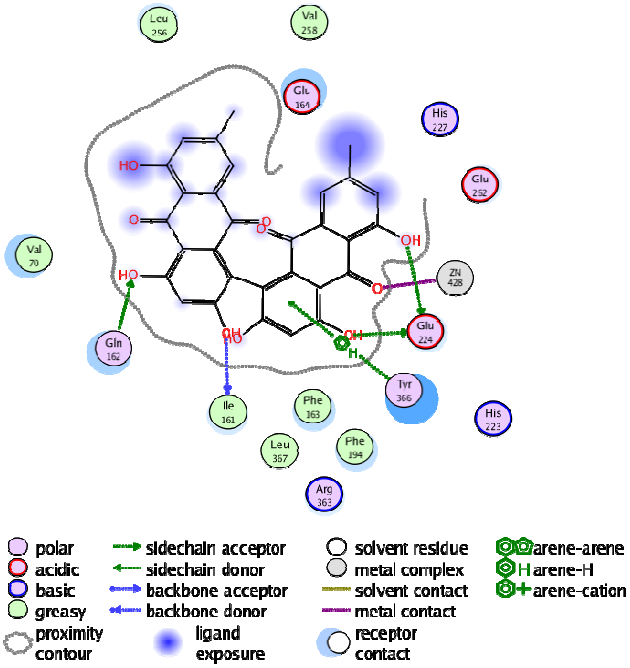


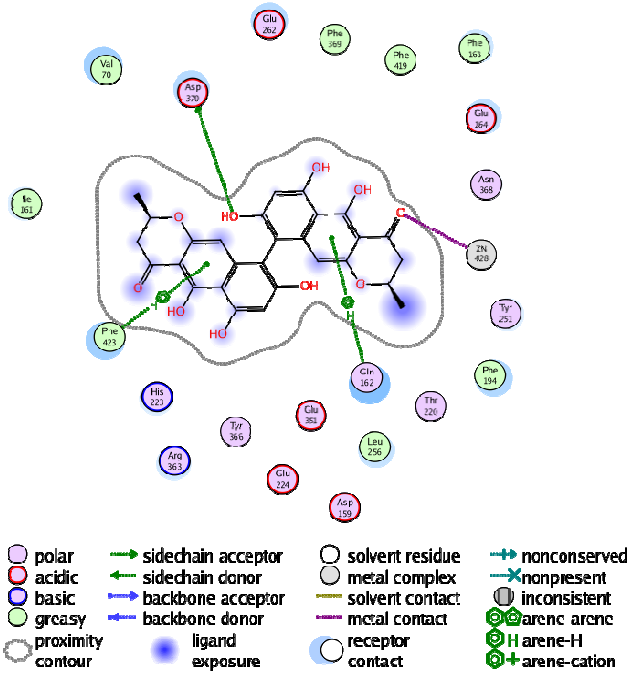
Talaroderxine A; Cluster 1



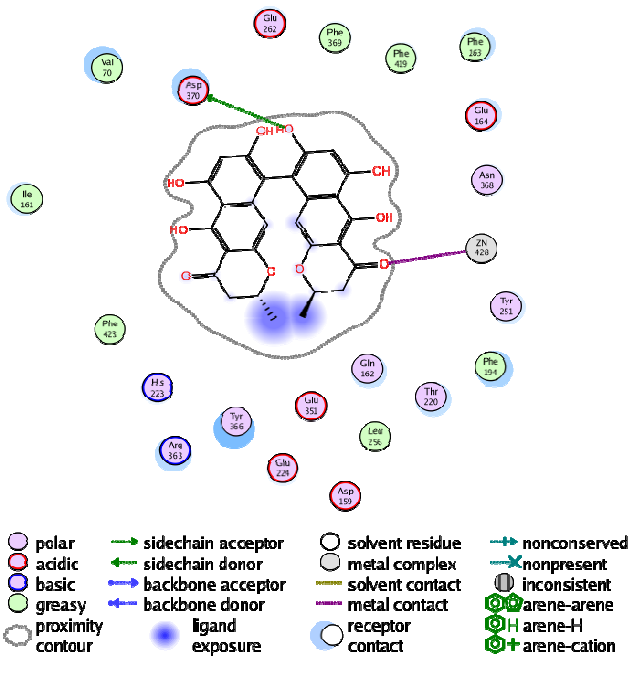
Talaroderxine A; Cluster 2



Skyrin; Cluster 1



Cephalochromin A; Cluster 1



Cephalochromin; Cluster 2

Figure 11S. The structure of the complex of BoNT/A with skyrin from HREX-SRTI simulations.

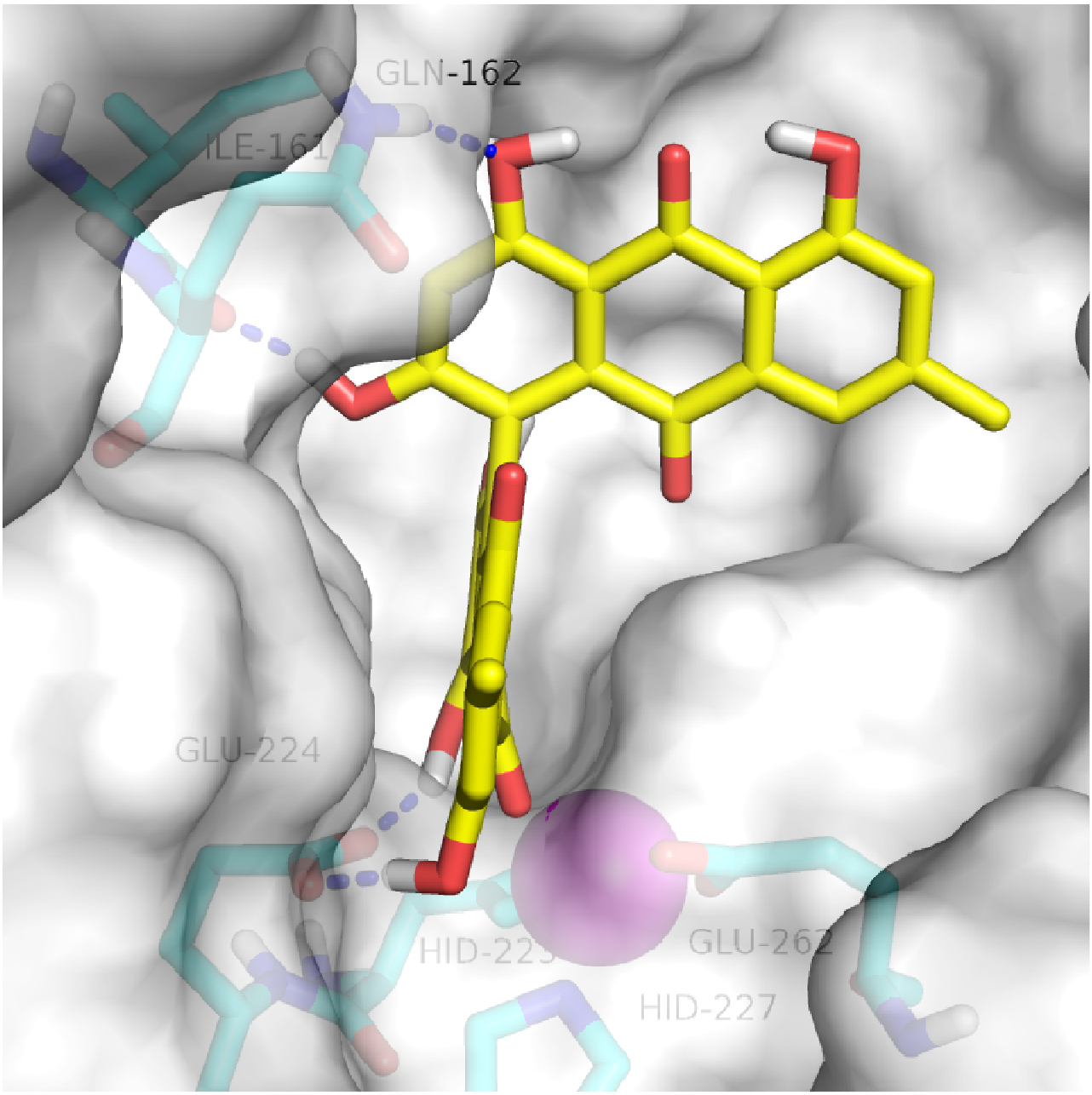


Table S1. Coordinates and Partial Charges for the Ligands***SRTI Reference Molecule***

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SMALL
No Charge or Current Charge


@<TRIPOS>ATOM
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      2 C2           1.8410    0.0800   -0.0840 ca        1 UNK     -0.194605
      3 C3          -0.4810    4.1010   -0.0840 ca        1 UNK     -0.338605
      4 C4           0.4820   -0.1710   -4.0980 ca        1 UNK     -0.338605
      5 C5          -1.3680    1.4210   -0.0980 ca        1 UNK      0.099595
      6 C6           1.3690    0.0100   -1.4240 ca        1 UNK      0.099595
      7 C7          -1.9770    2.3590    0.7740 ca        1 UNK     -0.149405
      8 C8           1.9780   -0.9190   -2.3060 ca        1 UNK     -0.149405
      9 C9          -0.3080    1.8160   -0.9630 cp        1 UNK     -0.104705
     10 C10          0.3090    0.8490   -1.8720 cp        1 UNK     -0.104705
     11 C11         -3.4950    0.6000    1.6290 ca        1 UNK     -0.308005
     12 C12          3.4950   -1.6640   -0.4970 ca        1 UNK     -0.308005
     13 C13         -2.8630   -0.3220    0.7400 ca        1 UNK      0.022095
     14 C14          2.8640   -0.7190    0.3670 ca        1 UNK      0.022095
     15 C15         -1.5100    3.7080    0.7570 ca        1 UNK      0.225895
     16 C16          1.5100   -0.9860   -3.6540 ca        1 UNK      0.225895
     17 C17          0.1120    3.1470   -0.9450 ca        1 UNK      0.210595
     18 C18         -0.1110    0.7480   -3.1990 ca        1 UNK      0.210595
     19 C19         -3.0420    1.9250    1.6370 ca        1 UNK      0.275695
     20 C20          3.0420   -1.7530   -1.8190 ca        1 UNK      0.275695
     21 C21         -4.5810    0.1460    2.5020 c         1 UNK      0.602295
     22 C22          4.5810   -2.5070    0.0100 c         1 UNK      0.602295
     23 C23         -3.3140   -1.7410    0.6690 c3        1 UNK     -0.047805
     24 C24          3.3140   -0.5600    1.7800 c3        1 UNK     -0.047805
     25 C25         -5.0510   -1.2770    2.3750 c3        1 UNK     -0.171805
     26 C26          5.0500   -2.2920    1.4230 c3        1 UNK     -0.171805
     27 C27         -3.9420   -2.2130    1.9610 c3        1 UNK     -0.072805
     28 C28          3.9420   -1.8200    2.3310 c3        1 UNK     -0.072805
     29 O1          -5.1380    0.8930    3.3280 o         1 UNK     -0.593305
     30 O2           5.1380   -3.3780   -0.6840 o         1 UNK     -0.593305
     31 O3          -2.1220    4.5860    1.6110 oh        1 UNK     -0.457205
     32 O4           2.1230   -1.8930   -4.4760 oh        1 UNK     -0.457205
     33 O5           1.1340    3.5120   -1.7860 oh        1 UNK     -0.479505
     34 O6          -1.1330    1.5650   -3.6150 oh        1 UNK     -0.479505
     35 O7          -3.5350    2.9150    2.4270 oh        1 UNK     -0.477105
     36 O8           3.5350   -2.6040   -2.7580 oh        1 UNK     -0.477105
     37 H1          -1.3590   -0.6430   -0.7620 ha        1 UNK      0.149095
     38 H2           1.3600    0.8010    0.5950 ha        1 UNK      0.149095
     39 H3          -0.1280    5.1410   -0.0940 ha        1 UNK      0.138695
     40 H4           0.1280   -0.2250   -5.1360 ha        1 UNK      0.138695
     41 H5          -4.0600   -1.8310   -0.1680 hc        1 UNK      0.059545
     42 H6          -2.4450   -2.4040    0.4120 hc        1 UNK      0.059545
     43 H7           4.0620    0.2810    1.8180 hc        1 UNK      0.059545
     44 H8           2.4460   -0.2610    2.4260 hc        1 UNK      0.059545
     45 H9          -5.4930   -1.6060    3.3520 hc        1 UNK      0.074020
     46 H10         -5.8740   -1.2920    1.6100 hc        1 UNK      0.074020
     47 H11          5.4920   -3.2470    1.8120 hc        1 UNK      0.074020
     48 H12          5.8740   -1.5280    1.3910 hc        1 UNK      0.074020
     49 H13         -4.3520   -3.2470    1.8250 hc        1 UNK      0.051545
     50 H14         -3.1640   -2.2630    2.7670 hc        1 UNK      0.051545
     51 H15          4.3520   -1.6200    3.3550 hc        1 UNK      0.051545
     52 H16          3.1630   -2.6210    2.4310 hc        1 UNK      0.051545
     53 H17         -1.7190    5.4600    1.4870 ho        1 UNK      0.417595
     54 H18          1.7190   -1.8240   -5.3560 ho        1 UNK      0.417595
     55 H19          1.2920    4.4610   -1.6740 ho        1 UNK      0.419595
     56 H20         -1.2910    1.3940   -4.5560 ho        1 UNK      0.419595
     57 H21         -4.2550    2.5880    2.9940 ho        1 UNK      0.463495
```

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     58 H22          4.2550   -3.1500   -2.3960 ho        1 UNK      0.463495
@<TRIPOS>BOND
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     5    3   15 ar
     6    3   17 ar
     7    4   16 ar
     8    4   18 ar
     9    5    7 ar
    10    5    9 ar
    11    6    8 ar
    12    6   10 ar
    13    7   15 ar
    14    7   19 ar
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    57   28   52 1
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    59   32   54 1
    60   33   55 1
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    62   35   57 1
    63   36   58 1
@<TRIPOS>SUBSTRUCTURE
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Chaetochromin A (**1**)

lig_00000002.mol2

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SMALL
No Charge or Current Charge


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      1 C1          -1.8760    0.4500   -0.4970 ca        1 UNK     -0.224000
      2 C2           1.8740    0.4500   -0.4970 ca        1 UNK     -0.224000
      3 C3          -0.4110    4.4350   -0.4970 ca        1 UNK     -0.344100
      4 C4           0.4100    0.0640   -4.4630 ca        1 UNK     -0.344100
      5 C5          -1.3810    1.7800   -0.5130 ca        1 UNK      0.123900
      6 C6           1.3790    0.3370   -1.8220 ca        1 UNK      0.123900
      7 C7          -1.9720    2.7430    0.3480 ca        1 UNK     -0.168900
      8 C8           1.9710   -0.6130   -2.6970 ca        1 UNK     -0.168900
      9 C9          -0.3000    2.1420   -1.3680 cp        1 UNK     -0.109200
     10 C10          0.2980    1.1530   -2.2660 cp        1 UNK     -0.109200
     11 C11         -3.5700    1.0500    1.1860 ca        1 UNK     -0.364000
     12 C12          3.5690   -1.2820   -0.9310 ca        1 UNK     -0.364000
     13 C13         -2.9300    0.1070    0.3240 ca        1 UNK      0.210600
     14 C14          2.9290   -0.3330   -0.0760 ca        1 UNK      0.210600
     15 C15         -1.4580    4.0760    0.3350 ca        1 UNK      0.232200
     16 C16          1.4580   -0.7290   -4.0250 ca        1 UNK      0.232200
     17 C17          0.1590    3.4600   -1.3510 ca        1 UNK      0.217700
     18 C18         -0.1610    1.0080   -3.5750 ca        1 UNK      0.217700
     19 C19         -3.0650    2.3570    1.1950 ca        1 UNK      0.298600
     20 C20          3.0650   -1.4170   -2.2310 ca        1 UNK      0.298600
     21 C21         -4.7210    0.6340    1.9800 c         1 UNK      0.606200
     22 C22          4.7220   -2.0300   -0.4400 c         1 UNK      0.606200
     23 C23         -5.2220   -0.7740    1.7440 c3        1 UNK     -0.184600
     24 C24          5.2230   -1.6580    0.9390 c3        1 UNK     -0.184600
     25 C25         -4.0610   -1.6970    1.3850 c3        1 UNK      0.149100
     26 C26          4.0610   -1.2130    1.8220 c3        1 UNK      0.149100
     27 C27         -5.9840   -1.2990    2.9400 c3        1 UNK     -0.086000
     28 C28          5.9860   -2.7970    1.5770 c3        1 UNK     -0.086000
     29 C29         -4.5200   -3.0900    0.9970 c3        1 UNK     -0.095300
     30 C30          4.5200   -0.6910    3.1710 c3        1 UNK     -0.095300
     31 O1          -5.3040    1.3870    2.7800 o         1 UNK     -0.582500
     32 O2           5.3050   -2.8990   -1.1120 o         1 UNK     -0.582500
     33 O3          -3.3560   -1.2010    0.2300 os        1 UNK     -0.325400
     34 O4           3.3550   -0.1120    1.2170 os        1 UNK     -0.325400
     35 O5          -2.0510    4.9740    1.1820 oh        1 UNK     -0.460000
     36 O6           2.0500   -1.6580   -4.8370 oh        1 UNK     -0.460000
     37 O7           1.1930    3.7920   -2.1890 oh        1 UNK     -0.478400
     38 O8          -1.1950    1.8100   -3.9870 oh        1 UNK     -0.478400
     39 O9          -3.5470    3.3600    1.9720 oh        1 UNK     -0.470800
     40 O10          3.5470   -2.2880   -3.1540 oh        1 UNK     -0.470800
     41 H1          -1.4150   -0.3070   -1.1480 ha        1 UNK      0.164800
     42 H2           1.4130    1.1710    0.1940 ha        1 UNK      0.164800
     43 H3          -0.0220    5.4620   -0.5040 ha        1 UNK      0.138800
     44 H4           0.0210   -0.0290   -5.4860 ha        1 UNK      0.138800
     45 H5          -5.9200   -0.7140    0.8580 hc        1 UNK      0.090800
     46 H6           5.9200   -0.7820    0.7920 hc        1 UNK      0.090800
     47 H7          -3.3320   -1.7460    2.2420 h1        1 UNK      0.057200
     48 H8           3.3330   -2.0620    1.9540 h1        1 UNK      0.057200
     49 H9          -6.5200   -2.2420    2.6730 hc        1 UNK      0.048367
     50 H10         -6.7320   -0.5400    3.2780 hc        1 UNK      0.048367
     51 H11         -5.2900   -1.5090    3.7890 hc        1 UNK      0.048367
     52 H12          6.5220   -2.4390    2.4890 hc        1 UNK      0.048367
     53 H13          6.7350   -3.2060    0.8540 hc        1 UNK      0.048367
     54 H14          5.2930   -3.6220    1.8680 hc        1 UNK      0.048367
     55 H15         -3.6670   -3.6600    0.5560 hc        1 UNK      0.052367
     56 H16         -5.3400   -3.0380    0.2410 hc        1 UNK      0.052367
     57 H17         -4.8880   -3.6230    1.9050 hc        1 UNK      0.052367
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      58 H18          3.6660   -0.1980    3.6960 hc        1 UNK      0.052367
      59 H19          5.3390    0.0570    3.0460 hc        1 UNK      0.052367
      60 H20          4.8890   -1.5430    3.7890 hc        1 UNK      0.052367
      61 H21         -1.6140    5.8320    1.0670 ho        1 UNK      0.418600
      62 H22          1.6140   -1.6270   -5.7020 ho        1 UNK      0.418600
      63 H23          1.3980    4.7300   -2.0590 ho        1 UNK      0.419900
      64 H24         -1.3990    1.5890   -4.9090 ho        1 UNK      0.419900
      65 H25         -4.2860    3.0490    2.5250 ho        1 UNK      0.462600
      66 H26          4.2860   -2.8070   -2.7910 ho        1 UNK      0.462600
@<TRIPOS>BOND
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     28   15   35 1
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     56   27   51 1
     57   28   52 1
     58   28   53 1
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    67   36   62 1
    68   37   63 1
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    70   39   65 1
    71   40   66 1
@<TRIPOS>SUBSTRUCTURE
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***Hypothetical Compound* 7H**

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lig_00000003.mol2
@<TRIPOS>MOLECULE
UNK
   68    73     1     0     0
SMALL
No Charge or Current Charge


@<TRIPOS>ATOM
      1 C1          -1.8570    0.4990   -0.5570 ca        1 UNK     -0.224209
      2 C2           1.8810    0.4990   -0.5570 ca        1 UNK     -0.224209
      3 C3          -0.4070    4.4900   -0.5570 ca        1 UNK     -0.343940
      4 C4           0.4280    0.1330   -4.5310 ca        1 UNK     -0.343940
      5 C5          -1.3670    1.8320   -0.5730 ca        1 UNK      0.125997
      6 C6           1.3900    0.3920   -1.8850 ca        1 UNK      0.125997
      7 C7          -1.9610    2.7930    0.2890 ca        1 UNK     -0.170414
      8 C8           1.9820   -0.5560   -2.7630 ca        1 UNK     -0.170414
      9 C9          -0.2880    2.1980   -1.4290 cp        1 UNK     -0.110345
     10 C10          0.3120    1.2110   -2.3280 cp        1 UNK     -0.110345
     11 C11         -3.5500    1.0930    1.1280 ca        1 UNK     -0.365860
     12 C12          3.5720   -1.2330   -0.9950 ca        1 UNK     -0.365860
     13 C13         -2.9090    0.1520    0.2640 ca        1 UNK      0.212805
     14 C14          2.9340   -0.2860   -0.1350 ca        1 UNK      0.212805
     15 C15         -1.4530    4.1280    0.2750 ca        1 UNK      0.233384
     16 C16          1.4730   -0.6640   -4.0940 ca        1 UNK      0.233384
     17 C17          0.1660    3.5170   -1.4110 ca        1 UNK      0.219882
     18 C18         -0.1430    1.0730   -3.6400 ca        1 UNK      0.219882
     19 C19         -3.0520    2.4030    1.1360 ca        1 UNK      0.302207
     20 C20          3.0690   -1.3670   -2.2950 ca        1 UNK      0.302207
     21 C21         -4.6930    0.6680    1.9230 c         1 UNK      0.610925
     22 C22          4.7100   -1.9920   -0.4970 c         1 UNK      0.610925
     23 C23         -5.1850   -0.7440    1.7020 c3        1 UNK     -0.230218
     24 C24          5.2690   -1.5410    0.8340 c3        1 UNK     -0.230218
     25 C25         -4.0290   -1.6630    1.3260 c3        1 UNK      0.154626
     26 C26          4.1240   -1.1350    1.7560 c3        1 UNK      0.154626
     27 C27         -4.4830   -3.0540    0.9230 c3        1 UNK     -0.100194
     28 C28          4.6000   -0.5720    3.0810 c3        1 UNK     -0.100194
     29 C29         -5.9200   -1.2700    2.9370 c3        1 UNK      0.148612
     30 C30          6.1550   -2.6180    1.4580 c3        1 UNK      0.148612
     31 O1          -5.2810    1.4130    2.7300 o         1 UNK     -0.599161
     32 O2           5.2260   -2.9460   -1.1080 o         1 UNK     -0.599161
     33 O3          -3.3330   -1.1570    0.1690 os        1 UNK     -0.324790
     34 O4           3.3490   -0.0730    1.1610 os        1 UNK     -0.324790
     35 O5          -2.0490    5.0220    1.1220 oh        1 UNK     -0.460210
     36 O6           2.0690   -1.5900   -4.9070 oh        1 UNK     -0.460210
     37 O7           1.2000    3.8530   -2.2500 oh        1 UNK     -0.477929
     38 O8          -1.1750    1.8790   -4.0510 oh        1 UNK     -0.477929
     39 O9          -3.5380    3.4020    1.9140 oh        1 UNK     -0.468310
     40 O10          3.5530   -2.2400   -3.2150 oh        1 UNK     -0.468310
     41 O11         -7.1830   -0.6640    3.0880 oh        1 UNK     -0.601217
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      42 O12         5.4580   -3.8200    1.7020 oh        1 UNK     -0.601217
      43 H1         -1.3940   -0.2560   -1.2100 ha        1 UNK      0.165456
      44 H2          1.4170    1.2170    0.1350 ha        1 UNK      0.165456
      45 H3         -0.0220    5.5190   -0.5650 ha        1 UNK      0.139701
      46 H4          0.0430    0.0460   -5.5550 ha        1 UNK      0.139701
      47 H5         -5.9170   -0.6980    0.8440 hc        1 UNK      0.101850
      48 H6          5.9100   -0.6360    0.6310 hc        1 UNK      0.101850
      49 H7         -3.2920   -1.7180    2.1760 h1        1 UNK      0.066687
      50 H8          3.4430   -2.0170    1.9220 h1        1 UNK      0.066687
      51 H9         -3.6760   -3.5570    0.3350 hc        1 UNK      0.054510
      52 H10        -5.4020   -3.0040    0.2930 hc        1 UNK      0.054510
      53 H11        -4.6950   -3.6580    1.8370 hc        1 UNK      0.054510
      54 H12         3.7620   -0.0300    3.5830 hc        1 UNK      0.054510
      55 H13         5.4430    0.1430    2.9290 hc        1 UNK      0.054510
      56 H14         4.9370   -1.4090    3.7370 hc        1 UNK      0.054510
      57 H15        -5.2910   -1.1090    3.8520 h1        1 UNK      0.054479
      58 H16        -6.1450   -2.3650    2.8160 h1        1 UNK      0.054479
      59 H17         6.5180   -2.2840    2.4680 h1        1 UNK      0.054479
      60 H18         7.0320   -2.8040    0.7810 h1        1 UNK      0.054479
      61 H19        -1.6170    5.8830    1.0070 ho        1 UNK      0.419798
      62 H20         1.6330   -1.5580   -5.7730 ho        1 UNK      0.419798
      63 H21         1.3980    4.7930   -2.1230 ho        1 UNK      0.420858
      64 H22        -1.3790    1.6620   -4.9730 ho        1 UNK      0.420858
      65 H23        -4.2790    3.0890    2.4630 ho        1 UNK      0.461905
      66 H24         4.2800   -2.7690   -2.8420 ho        1 UNK      0.461905
      67 H25        -7.0370    0.2730    3.2800 ho        1 UNK      0.419618
      68 H26         5.2630   -4.2150    0.8410 ho        1 UNK      0.419618
@<TRIPOS>BOND
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@<TRIPOS>SUBSTRUCTURE
     1 UNK         1 TEMP              0 ****  ****    0 ROOT
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***Hypothetical Compound* 8H**

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lig_00000004.mol2
@<TRIPOS>MOLECULE
UNK
   68    73     1     0     0
SMALL
No Charge or Current Charge


@<TRIPOS>ATOM
      1 C1         -1.8820    0.5410   -0.5810 ca        1 UNK     -0.221852
      2 C2          1.8420    0.5410   -0.5810 ca        1 UNK     -0.221852
      3 C3         -0.4480    4.5380   -0.5810 ca        1 UNK     -0.343649
      4 C4          0.4100    0.1970   -4.5630 ca        1 UNK     -0.343649
      5 C5         -1.3970    1.8760   -0.5970 ca        1 UNK      0.122702
      6 C6          1.3580    0.4430   -1.9120 ca        1 UNK      0.122702
      7 C7         -1.9940    2.8330    0.2670 ca        1 UNK     -0.168049
      8 C8          1.9570   -0.4990   -2.7920 ca        1 UNK     -0.168049
      9 C9         -0.3210    2.2470   -1.4540 cp        1 UNK     -0.109897
     10 C10         0.2820    1.2640   -2.3560 cp        1 UNK     -0.109897
     11 C11        -3.5750    1.1260    1.1090 ca        1 UNK     -0.362498
     12 C12         3.5380   -1.1890   -1.0180 ca        1 UNK     -0.362498
     13 C13        -2.9300    0.1910    0.2430 ca        1 UNK      0.211056
     14 C14         2.8910   -0.2490   -0.1600 ca        1 UNK      0.211056
     15 C15        -1.4910    4.1700    0.2530 ca        1 UNK      0.232800
     16 C16         1.4550   -0.6000   -4.1250 ca        1 UNK      0.232800
     17 C17         0.1280    3.5680   -1.4370 ca        1 UNK      0.218351
     18 C18        -0.1670    1.1310   -3.6700 ca        1 UNK      0.218351
     19 C19        -3.0820    2.4380    1.1160 ca        1 UNK      0.300049
     20 C20         3.0470   -1.3090   -2.3250 ca        1 UNK      0.300049
     21 C21        -4.7170    0.6990    1.9100 c         1 UNK      0.606903
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      22 C22         4.6820   -1.9490   -0.5230 c         1 UNK      0.606903
      23 C23        -5.1960   -0.7230    1.7010 c3        1 UNK     -0.180543
      24 C24         5.1440   -1.6400    0.8840 c3        1 UNK     -0.180543
      25 C25        -4.0310   -1.6240    1.3130 c3        1 UNK      0.106752
      26 C26         3.9860   -1.1540    1.7480 c3        1 UNK      0.106752
      27 C27        -5.9100   -1.2480    2.9280 c3        1 UNK     -0.088340
      28 C28         5.8010   -2.8490    1.5160 c3        1 UNK     -0.088340
      29 C29        -4.4930   -3.0280    0.9010 c3        1 UNK      0.135834
      30 C30         4.4520   -0.6080    3.1050 c3        1 UNK      0.135834
      31 O1         -5.3130    1.4530    2.6980 o         1 UNK     -0.580248
      32 O2          5.2910   -2.7830   -1.2140 o         1 UNK     -0.580248
      33 O3         -3.3540   -1.1190    0.1480 os        1 UNK     -0.338327
      34 O4          3.3110   -0.0390    1.1370 os        1 UNK     -0.338327
      35 O5         -2.0890    5.0620    1.1010 oh        1 UNK     -0.459050
      36 O6          2.0550   -1.5210   -4.9410 oh        1 UNK     -0.459050
      37 O7          1.1580    3.9080   -2.2760 oh        1 UNK     -0.478497
      38 O8         -1.2000    1.9370   -4.0820 oh        1 UNK     -0.478497
      39 O9         -3.5690    3.4360    1.8950 oh        1 UNK     -0.469651
      40 O10         3.5380   -2.1680   -3.2540 oh        1 UNK     -0.469651
      41 O11        -3.3930   -3.8710    0.6450 oh        1 UNK     -0.594512
      42 O12         4.2630   -1.6500    4.0490 oh        1 UNK     -0.594512
      43 H1         -1.4160   -0.2110   -1.2350 ha        1 UNK      0.164102
      44 H2          1.3760    1.2560    0.1130 ha        1 UNK      0.164102
      45 H3         -0.0680    5.5680   -0.5890 ha        1 UNK      0.139749
      46 H4          0.0310    0.1150   -5.5900 ha        1 UNK      0.139749
      47 H5         -5.9240   -0.6820    0.8390 hc        1 UNK      0.097103
      48 H6          5.9020   -0.8090    0.7900 hc        1 UNK      0.097103
      49 H7         -3.2850   -1.6930    2.1520 h1        1 UNK      0.068459
      50 H8          3.2400   -1.9840    1.9030 h1        1 UNK      0.068459
      51 H9         -6.4850   -2.1710    2.6770 hc        1 UNK      0.050539
      52 H10        -6.6220   -0.4770    3.3130 hc        1 UNK      0.050539
      53 H11        -5.1790   -1.4890    3.7370 hc        1 UNK      0.050539
      54 H12         6.1110   -2.6130    2.5630 hc        1 UNK      0.050539
      55 H13         6.6960   -3.1500    0.9190 hc        1 UNK      0.050539
      56 H14         5.0900   -3.7100    1.5430 hc        1 UNK      0.050539
      57 H15        -5.1570   -2.9620   -0.0010 h1        1 UNK      0.059805
      58 H16        -5.0400   -3.5110    1.7530 h1        1 UNK      0.059805
      59 H17         3.8420    0.2950    3.3770 h1        1 UNK      0.059805
      60 H18         5.5380   -0.3270    3.0710 h1        1 UNK      0.059805
      61 H19        -1.6620    5.9250    0.9840 ho        1 UNK      0.419649
      62 H20         1.6270   -1.4800   -5.8110 ho        1 UNK      0.419649
      63 H21         1.3530    4.8490   -2.1500 ho        1 UNK      0.420800
      64 H22        -1.3910    1.7320   -5.0090 ho        1 UNK      0.420800
      65 H23        -4.3040    3.1210    2.4500 ho        1 UNK      0.464000
      66 H24         4.2710   -2.6950   -2.8890 ho        1 UNK      0.464000
      67 H25        -2.8750   -3.4620   -0.0610 ho        1 UNK      0.415580
      68 H26         4.2840   -1.2400    4.9210 ho        1 UNK      0.415580
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    19   10   18 ar
    20   11   13 ar
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***Hypothetical Compound* 9H**

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SMALL
No Charge or Current Charge


@<TRIPOS>ATOM
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2	C2	1.8810	0.5340	-0.6250	ca	1	UNK	-0.223992
3	C3	-0.4070	4.5270	-0.6250	ca	1	UNK	-0.343795
4	C4	0.4380	0.1780	-4.6030	ca	1	UNK	-0.343795
5	C5	-1.3640	1.8670	-0.6410	ca	1	UNK	0.124944
6	C6	1.3920	0.4300	-1.9550	ca	1	UNK	0.124944
7	C7	-1.9580	2.8280	0.2220	ca	1	UNK	-0.169696
8	C8	1.9890	-0.5130	-2.8330	ca	1	UNK	-0.169696
9	C9	-0.2870	2.2350	-1.4970	cp	1	UNK	-0.110695
10	C10	0.3150	1.2500	-2.3980	cp	1	UNK	-0.110695
11	C11	-3.5450	1.1260	1.0600	ca	1	UNK	-0.364868
12	C12	3.5760	-1.1980	-1.0620	ca	1	UNK	-0.364868
13	C13	-2.9050	0.1860	0.1950	ca	1	UNK	0.213680
14	C14	2.9330	-0.2530	-0.2060	ca	1	UNK	0.213680
15	C15	-1.4520	4.1630	0.2080	ca	1	UNK	0.233604
16	C16	1.4840	-0.6190	-4.1650	ca	1	UNK	0.233604
17	C17	0.1660	3.5550	-1.4800	ca	1	UNK	0.219999
18	C18	-0.1380	1.1140	-3.7110	ca	1	UNK	0.219999
19	C19	-3.0440	2.4340	1.0730	ca	1	UNK	0.302400
20	C20	3.0800	-1.3220	-2.3670	ca	1	UNK	0.302400
21	C21	-4.6780	0.6950	1.8670	c	1	UNK	0.609527
22	C22	4.7180	-1.9580	-0.5680	c	1	UNK	0.609527
23	C23	-5.2330	-0.6750	1.5530	c3	1	UNK	-0.205510
24	C24	5.2140	-1.6050	0.8170	c3	1	UNK	-0.205510
25	C25	-4.0960	-1.6270	1.2060	c3	1	UNK	0.111636
26	C26	4.0620	-1.1370	1.6960	c3	1	UNK	0.111636
27	C27	-6.0910	-1.1980	2.7060	c3	1	UNK	0.139561
28	C28	5.9540	-2.7830	1.4500	c3	1	UNK	0.139561
29	C29	-4.5820	-2.9980	0.7190	c3	1	UNK	0.132825
30	C30	4.5470	-0.5750	3.0390	c3	1	UNK	0.132825
31	O1	-5.1910	1.3930	2.7610	o	1	UNK	-0.590070
32	O2	5.2970	-2.8270	-1.2440	o	1	UNK	-0.590070
33	O3	-3.3230	-1.1250	0.0990	os	1	UNK	-0.336988
34	O4	3.3570	-0.0390	1.0890	os	1	UNK	-0.336988
35	O5	-2.0500	5.0570	1.0540	oh	1	UNK	-0.459593
36	O6	2.0820	-1.5410	-4.9800	oh	1	UNK	-0.459593
37	O7	1.1990	3.8910	-2.3190	oh	1	UNK	-0.477902
38	O8	-1.1710	1.9180	-4.1210	oh	1	UNK	-0.477902
39	O9	-3.5290	3.4300	1.8580	oh	1	UNK	-0.468142
40	O10	3.5650	-2.1860	-3.2940	oh	1	UNK	-0.468142
41	O11	-5.3480	-1.3700	3.8930	oh	1	UNK	-0.606487
42	O12	6.9420	-2.2410	2.3160	oh	1	UNK	-0.606487
43	O13	-5.5180	-2.8890	-0.3300	oh	1	UNK	-0.596740
44	O14	3.4680	-0.3990	3.9280	oh	1	UNK	-0.596740
45	H1	-1.3870	-0.2200	-1.2760	ha	1	UNK	0.164560
46	H2	1.4170	1.2520	0.0670	ha	1	UNK	0.164560
47	H3	-0.0240	5.5560	-0.6330	ha	1	UNK	0.140204
48	H4	0.0560	0.0930	-5.6290	ha	1	UNK	0.140204
49	H5	-5.8990	-0.5730	0.6470	hc	1	UNK	0.110218
50	H6	5.9450	-0.7520	0.6940	hc	1	UNK	0.110218
51	H7	-3.4170	-1.7560	2.0940	h1	1	UNK	0.075068
52	H8	3.3270	-1.9730	1.8660	h1	1	UNK	0.075068
53	H9	-6.4920	-2.2180	2.4600	h1	1	UNK	0.055359
54	H10	-6.9430	-0.4850	2.8740	h1	1	UNK	0.055359
55	H11	6.4400	-3.4080	0.6520	h1	1	UNK	0.055359
56	H12	5.2480	-3.4230	2.0450	h1	1	UNK	0.055359
57	H13	-5.1210	-3.5270	1.5490	h1	1	UNK	0.068788
58	H14	-3.6940	-3.6030	0.3910	h1	1	UNK	0.068788
59	H15	5.0880	0.3930	2.8720	h1	1	UNK	0.068788
60	H16	5.2290	-1.3180	3.5350	h1	1	UNK	0.068788
61	H17	-1.6170	5.9180	0.9430	ho	1	UNK	0.420255
62	H18	1.6530	-1.5020	-5.8490	ho	1	UNK	0.420255
63	H19	1.3980	4.8310	-2.1910	ho	1	UNK	0.421255
64	H20	-1.3620	1.7140	-5.0490	ho	1	UNK	0.421255
65	H21	-4.2580	3.1080	2.4180	ho	1	UNK	0.462860
66	H22	4.3060	-2.7050	-2.9360	ho	1	UNK	0.462860
67	H23	-5.1320	-0.4860	4.2230	ho	1	UNK	0.411952
68	H24	7.5310	-2.9670	2.5510	ho	1	UNK	0.411952
69	H25	-5.0710	-2.4470	-1.0630	ho	1	UNK	0.411638

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@<TRIPOS>SUBSTRUCTURE
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Talaroderxine A (**2**)

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SMALL
No Charge or Current Charge


@<TRIPOS>ATOM
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      2 C2           1.8600    0.8320   -0.8980 ca        1 UNK     -0.181185
      3 C3          -0.4420    4.8390   -0.8980 ca        1 UNK     -0.335804
      4 C4           0.4410    0.5280   -4.8940 ca        1 UNK     -0.335804
      5 C5          -1.3690    2.1710   -0.9050 ca        1 UNK      0.098425
      6 C6           1.3670    0.7380   -2.2330 ca        1 UNK      0.098425
      7 C7          -1.9620    3.1210   -0.0350 ca        1 UNK     -0.146070
      8 C8           1.9610   -0.2020   -3.1150 ca        1 UNK     -0.146070
      9 C9          -0.3030    2.5490   -1.7700 cp        1 UNK     -0.106387
     10 C10          0.3010    1.5710   -2.6760 cp        1 UNK     -0.106387
     11 C11         -3.4840    1.3900    0.8260 ca        1 UNK     -0.312707
     12 C12          3.4830   -0.9290   -1.3230 ca        1 UNK     -0.312707
     13 C13         -2.8820    0.4550   -0.0660 ca        1 UNK      0.011390
     14 C14          2.8810    0.0310   -0.4590 ca        1 UNK      0.011390
     15 C15         -1.4750    4.4640   -0.0540 ca        1 UNK      0.226417
     16 C16          1.4740   -0.2850   -4.4550 ca        1 UNK      0.226417
     17 C17          0.1360    3.8740   -1.7560 ca        1 UNK      0.213640
     18 C18         -0.1370    1.4560   -3.9970 ca        1 UNK      0.213640
     19 C19         -3.0370    2.7110    0.8260 ca        1 UNK      0.281434
     20 C20          3.0360   -1.0300   -2.6410 ca        1 UNK      0.281434
     21 C21         -4.5710    0.9380    1.6910 c         1 UNK      0.751879
     22 C22          4.5700   -1.7570   -0.8070 c         1 UNK      0.751879
     23 C23         -3.4210   -0.9310   -0.0770 c3        1 UNK     -0.077832
     24 C24          3.4200    0.1490    0.9220 c3        1 UNK     -0.077832
     25 C25         -3.8960   -1.3360    1.3110 c3        1 UNK      0.150113
     26 C26          3.8960   -1.2040    1.4310 c3        1 UNK      0.150113
     27 C27         -4.3380   -5.1570    1.3190 c3        1 UNK     -0.092996
     28 C28          4.3410   -0.9200    5.2410 c3        1 UNK     -0.092996
     29 C29         -4.6140   -2.6810    1.3100 c3        1 UNK     -0.091266
     30 C30          4.6150   -1.1010    2.7720 c3        1 UNK     -0.091266
     31 C31         -3.6280   -3.8280    1.3360 c3        1 UNK     -0.080243
     32 C32          3.6290   -1.0390    3.9180 c3        1 UNK     -0.080243
     33 O1          -5.3450    1.6480    2.3490 o         1 UNK     -0.626078
     34 O2           5.3440   -2.4670   -1.4650 o         1 UNK     -0.626078
     35 O3          -4.8510   -0.3960    1.8390 os        1 UNK     -0.404076
     36 O4           4.8510   -1.8020    0.5340 os        1 UNK     -0.404076
     37 O5          -2.0750    5.3470    0.8000 oh        1 UNK     -0.456683
     38 O6           2.0740   -1.2040   -5.2710 oh        1 UNK     -0.456683
     39 O7           1.1620    4.2190   -2.6000 oh        1 UNK     -0.478251
     40 O8          -1.1630    2.2720   -4.4050 oh        1 UNK     -0.478251
     41 O9          -3.5430    3.6940    1.6150 oh        1 UNK     -0.470312
     42 O10          3.5420   -1.8910   -3.5610 oh        1 UNK     -0.470312
     43 H1          -1.4010    0.1040   -1.5840 ha        1 UNK      0.151181
     44 H2           1.3990    1.5710   -0.2250 ha        1 UNK      0.151181
     45 H3          -0.0740    5.8740   -0.9110 ha        1 UNK      0.141178
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      46 H4          0.0720    0.4620   -5.9260 ha        1 UNK      0.141178
      47 H5         -4.2800   -0.9780   -0.8020 hc        1 UNK      0.074121
      48 H6         -2.6430   -1.6600   -0.4240 hc        1 UNK      0.074121
      49 H7          4.2790    0.8750    0.9130 hc        1 UNK      0.074121
      50 H8          2.6420    0.5490    1.6230 hc        1 UNK      0.074121
      51 H9         -3.0230   -1.3560    2.0240 h1        1 UNK      0.066235
      52 H10         3.0240   -1.9140    1.5060 h1        1 UNK      0.066235
      53 H11        -3.5970   -5.9920    1.3430 hc        1 UNK      0.035741
      54 H12        -4.9590   -5.2610    0.3960 hc        1 UNK      0.035741
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REFERENCES

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