SUPPLEMENTARY INFORMATION

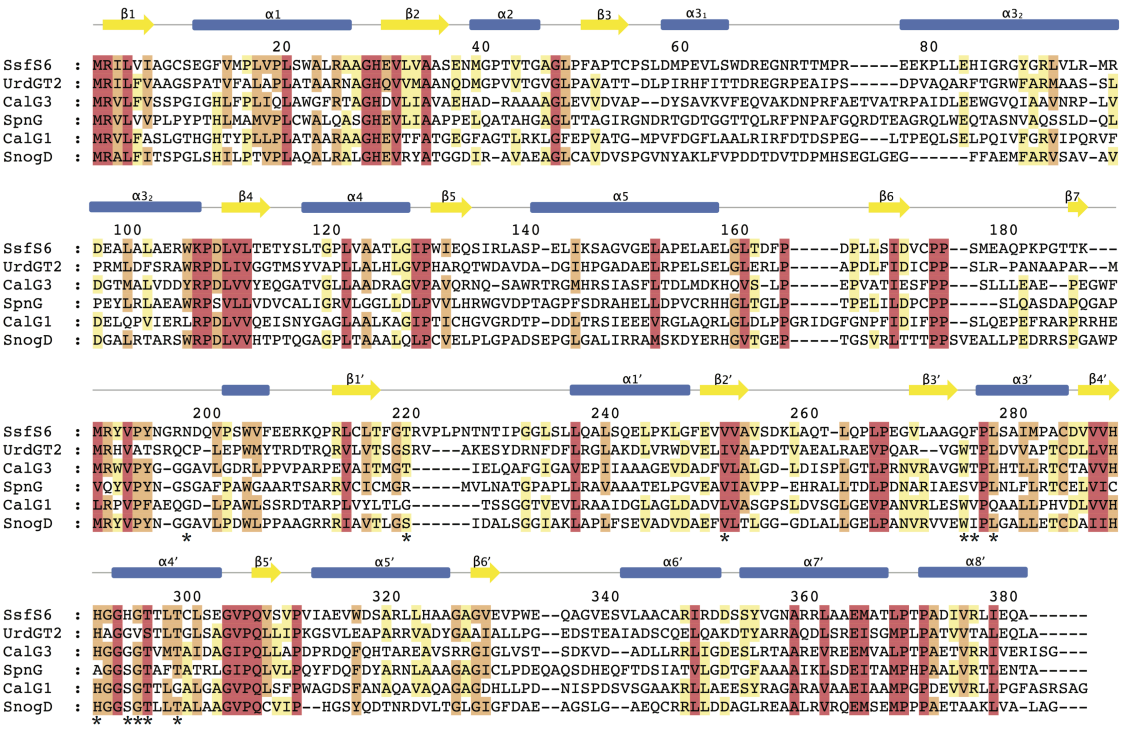

Figure S1. Dali based multiple sequence alignment of SsfS6 with other GTs.

Every 20th residue of SsfS6 is labeled and the secondary structure of SsfS6 is displayed on top of the sequence. α helices and β strands in C-terminal domain are labeled with primes (') and the linker α helix between two domains is not labeled. The sequences are SsfS6 from *Streptomyces sp.* SF2575, UrdGT2 from *Streptomyces fradiae*, CalG3 from *Micromonospora echinospora*, SpnG from *Saccharopolyspora spinosa*, CalG1 from *Micromonospora echinospora* and SnogD from *Streptomyces nogalater*. Conservation of residues by 100%, 80% and 60% are colored red, orange and yellow, respectively. The plots show sequence similarities on broadly distributed. Residues involved in the SsfS6-TDP binding are marked by asterisk. While the GT-B fold is in common among at these proteins, the active site residues are somewhat varied.

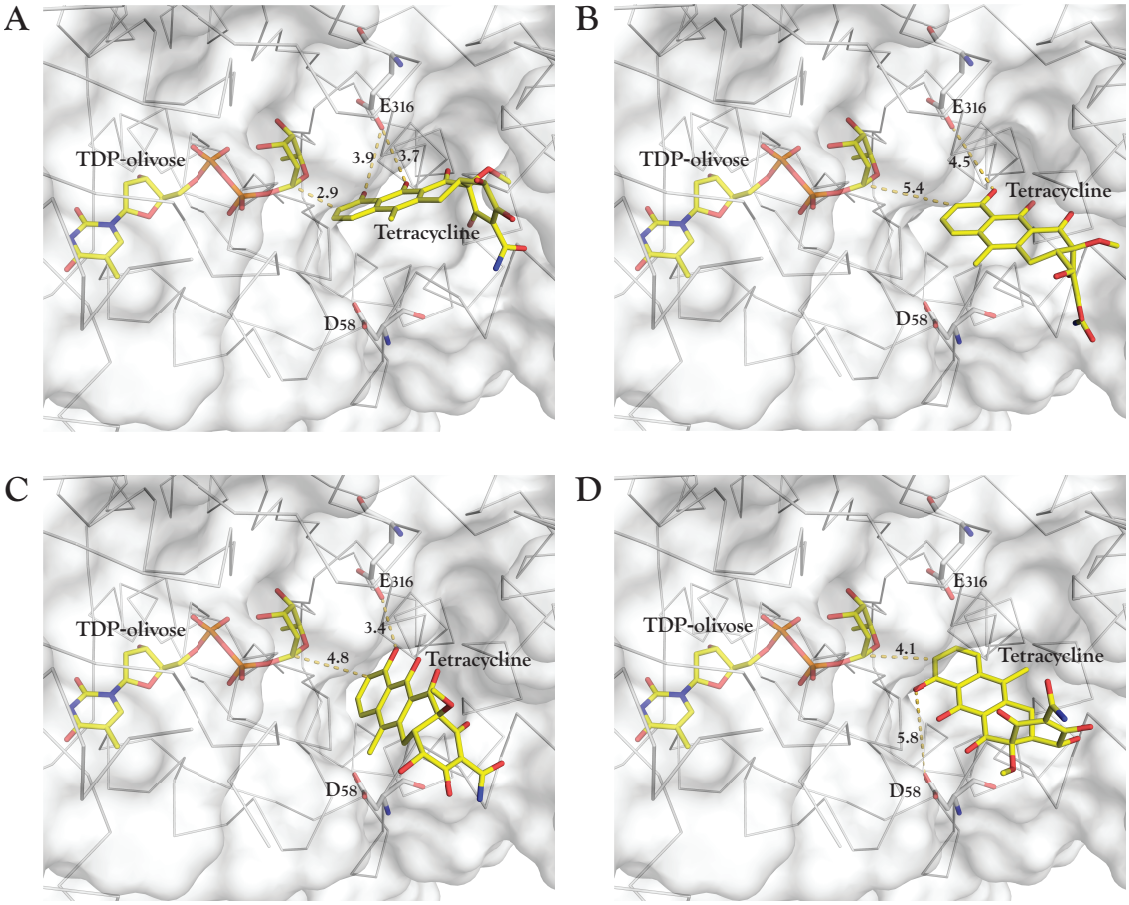

Figure S2 Tetracycline docking results by AutoDock 4.2.

E316 was used as docking box center and seven residues around the cavity were made flexible in order to increase the size of cavity. **A**, **B** and **C** are potential poses for E316 as the active base, while **D** is for D58. Docked d-TDP-olivose and tetracycline are represented as sticks. SsfS6 is displayed as both ribbon and surface to show the backbone and cavity, while the potential catalytic bases, D58 and E316, are highlighted as sticks. The distances between the glycosylated carbon of aglycone and anomeric carbon of sugar, and the distances between the oxygen of putative base E316 (or D58) and D ring hydroxyl of aglycone are also shown.

Table S1. Scores of the docked substrate using three independent scoring functions

Pose in Figure S2	X-Score	DrugScoreX	Pose and Rank	Potential base
A	-8.20	-73.00	-22.33	E_{316}
B	-8.21	-102.70	-35.50	E_{316}
C	-7.65	-70.26	-17.15	E_{316}
D	-8.10	-92.15	-27.09	D_{58}