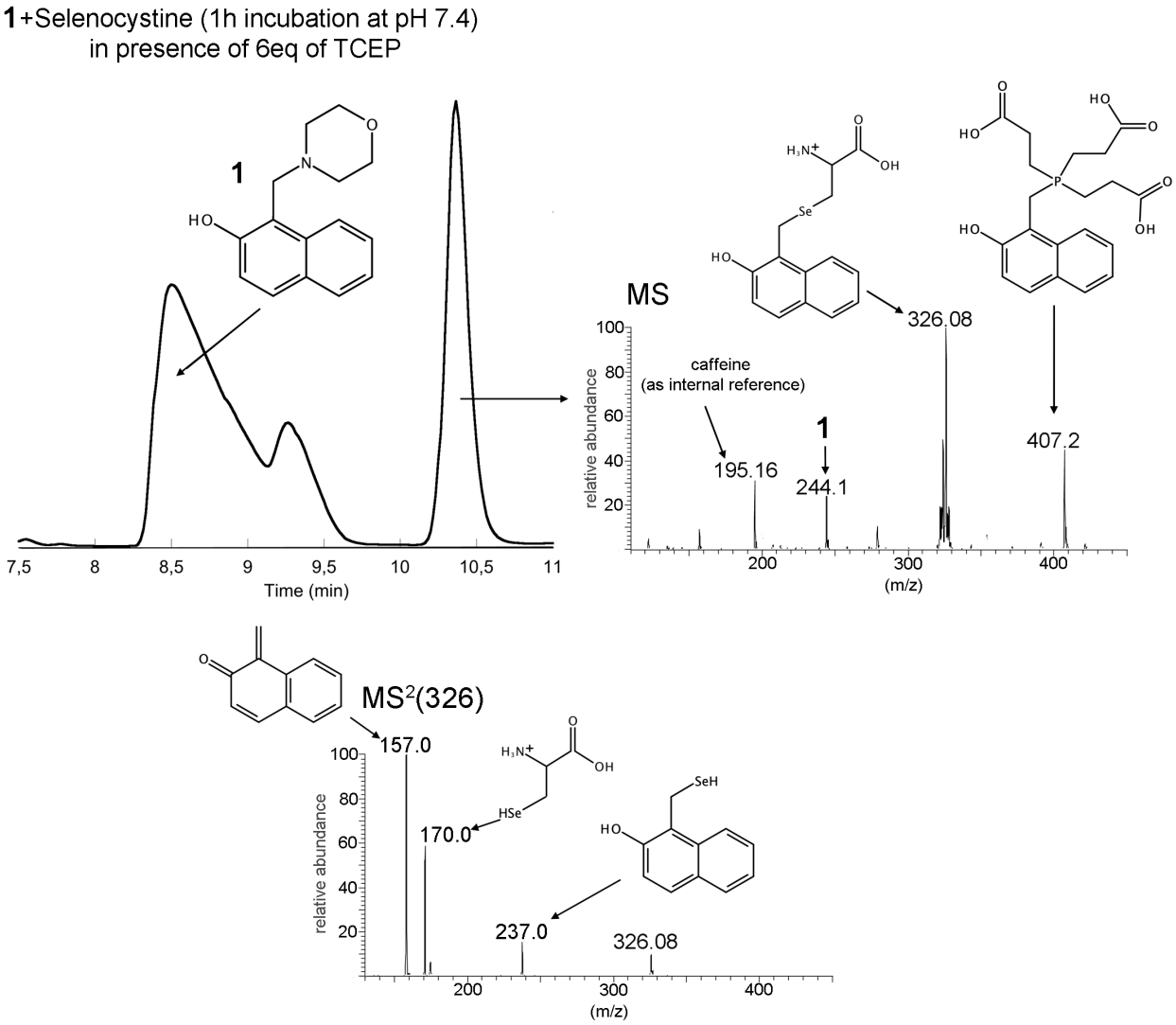
Supplemental Table 1. Summary of data reduction and refinement statistics

Compound	**4** at 1 hour of soaking	**4**at 2 hours of soaking	**4** at 4 hours of soaking
PDB code	6RTJ	6RTM	6RTO
Data reduction statistics			
Space group	C2	C2	C2
Unit cell dimensions (Å)	142.66 102.19 58.52 β=112.89	142.04 102.00 58.540 β=112.78	142.27 102.00 58.47 β= 112.57
Resolution range (Å)	40.6-2.06 (2.05-2.00)	40.6-2.10 (2.16-2.10)	39.6-2.30 (2.38-2.30)
mean I/sigma(I)	13.9(2.0)	16.1 (1.9)	12.8 (1.9)
Completeness (%)	99.8(98.7)	98.7 (97.6)	99.8(100)
CC1/2	99.8(70.7)	99.9(68.0)	99.8(69.0)
Rmerge (%)	5.6(63.9)	6.2 (62.7)	6.2 (62.8)
Number of unique reflections	51649(3788)	44319 (3577)	34230 (3357)
REFINEMENT STATISTICS			
Resolution range (Å)	39.8-2.0(2.03-2.0)	40.6-2.1(2.14-2.10)	37.1-2.3(2.36-2.30)
No. reflections	51628 (2562)	44285(2560)	34224 (2710)
R/Rfree	0.18/0.22(0.25/0.28)	0.18/0.23(0.25/0.32)	0.19/0.24(0.26/0.35)
Mean B-factor	30.0	34.5	41.5
RMS bond lengths deviations	0.012	0.012	0.015
RMS bond angles deviation	1.131	1.150	1.432
RAMACHANDRAN (%)			
Favored	96.2	96.4	94.9
Allowed	3.7	3.6	4.8
Disallowed	0	0	0.3

*Values given in parentheses refer to highest resolution shell.

Supplemental figure 1

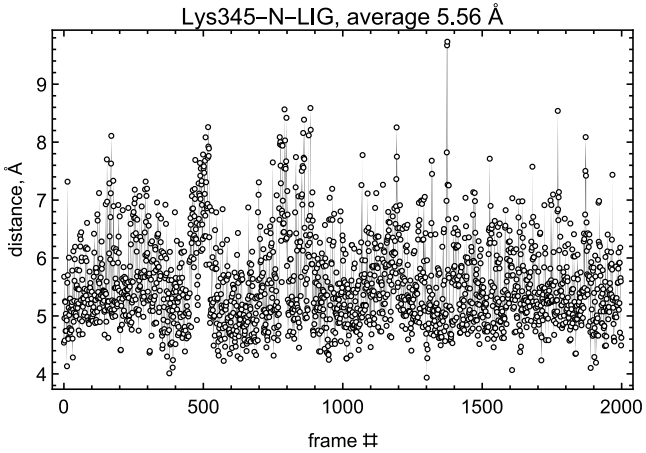
RP-HPLC and tandem mass spectrometry analysis of the mixture between **1** and Sec at pH 7.4 are reported. The peak relative to the new species, formed after 1 hour of incubation of the reagents, has been manually collected after elution from the C18 column and injected, after 48h days, into a Orbitrap XL Discovery, equipped with a nanoelectrospray source (Thermo Fisher Scientific). ESI-MS/MS analysis was performed in positive ion mode. The *o*QM-Sec adduct [m/z = 326] is the most present species together with the *o*QM-TCEP adduct [m/z = 407] and the intact **1** [m/z = 244]. The peak at 326m/z has been subjected to further fragmentation, confirming its chemical composition as reported in the mass spectrum at the bottom of the figure.

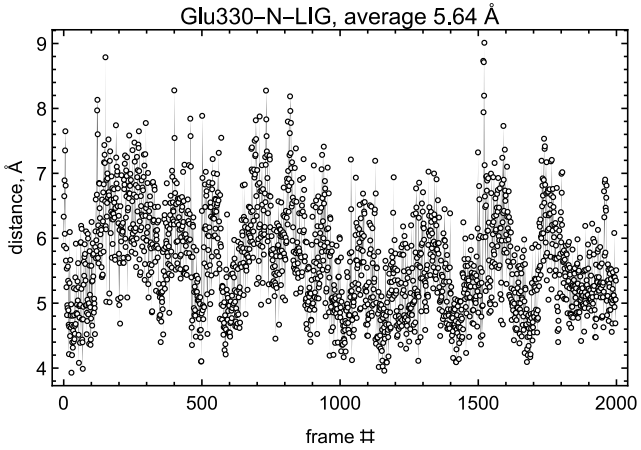


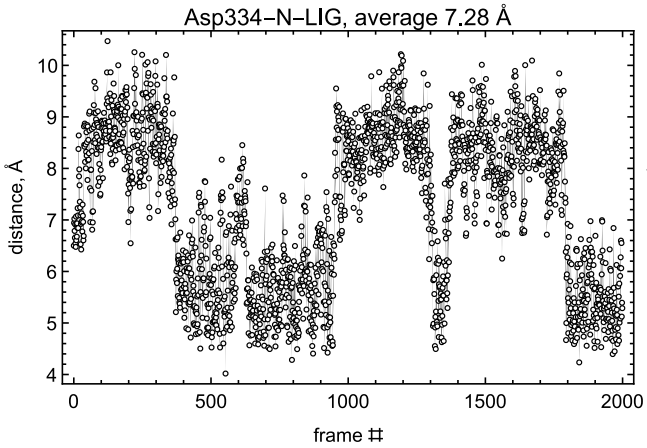
Supplemental figure 2

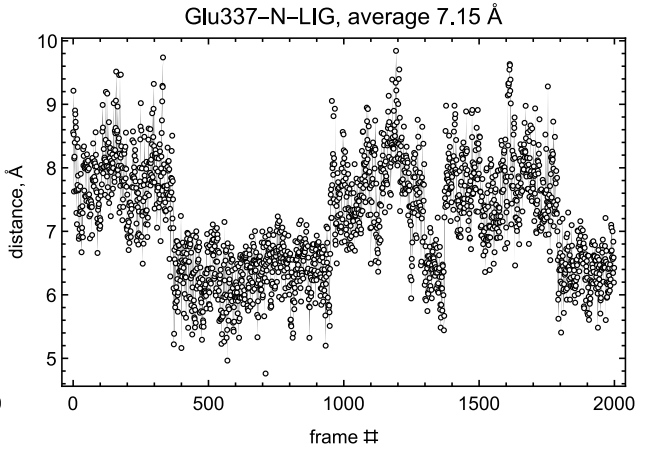
An analysis of the distances between SmTGR and compound **4** (LIG) during the 20 ns (2000 frames) production trajectory for pairs Glu330 - N-LIG , Asp334 - N-LIG , Glu337 - N-LIG , Asp334 - O-LIG , Glu337 - O-LIG , Lys345 - C5-LIG , Glu337 - Lys345 , Glu330 - Asp334 , Asp334 - Glu337, where N-LIG, O-LIG, and C9-LIG correspond to the nitrogen and oxygen atoms in the substituents and C9 of the naphthyl ring of compound **1**, respectively. In amino acids, the distances were measured using the carbon atoms in the carboxyl groups of the sidechains in E330, D334, and E337 and nitrogen atom in the sidechains of K345.

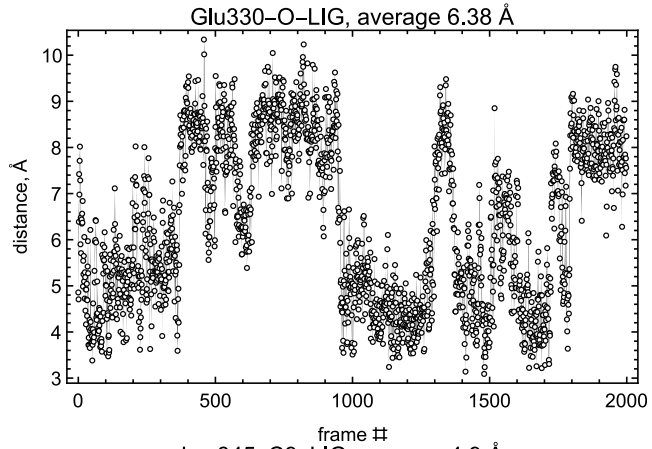
Distance between:	**Average distance, Å**
Lys345-N-LIG	5.56
Glu330-N-LIG	5.64
Asp334-N-LIG	7.28
Glu337-N-LIG	7.15
Glu330-O-LIG	6.38
Asp334-O-LIG	5.09
Glu337-O-LIG	5.19
Lys345-C9-LIG	4.9
Glu330-Lys345	10.5
Asp334-Lys345	8.97
Glu337-Lys345	3.96
Glu330-Asp334	7.97
Asp334-Glu337	6.9

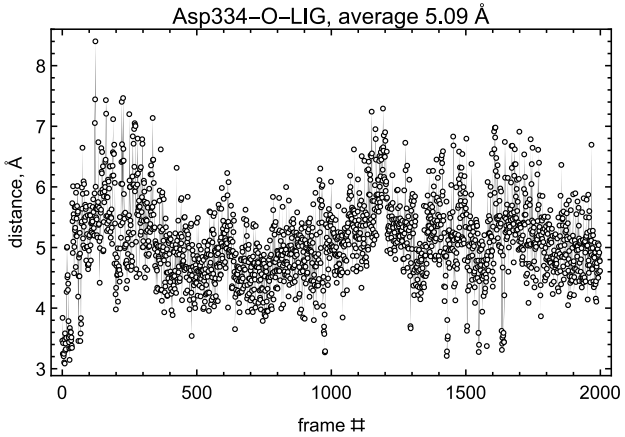


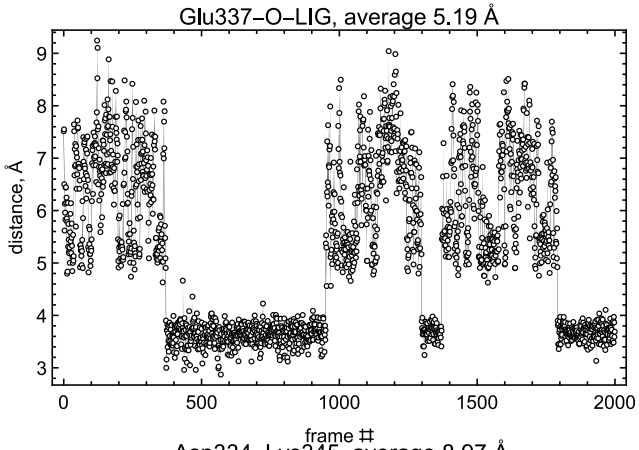


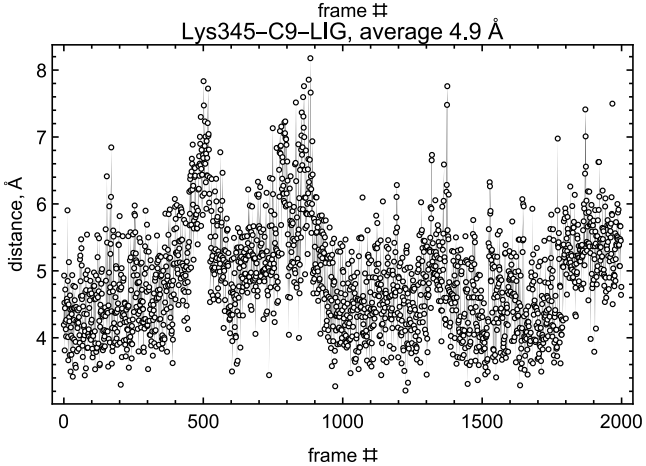


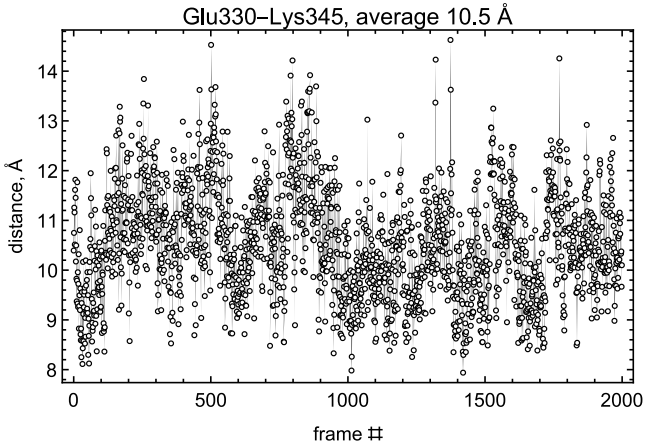


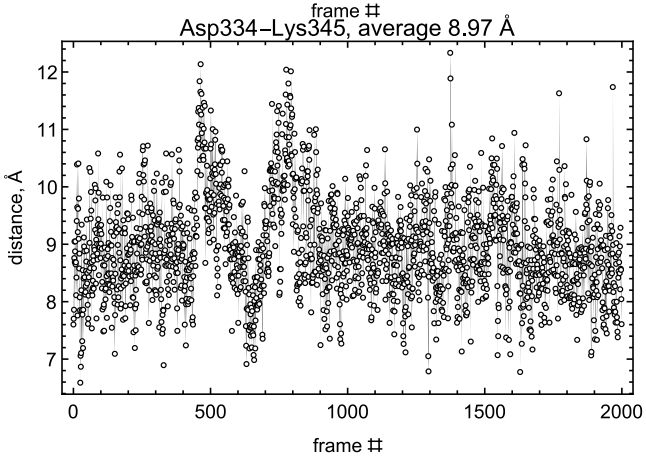

Glu330–O–LIG, average 6.38 Å
distance, Å
frame ⌗

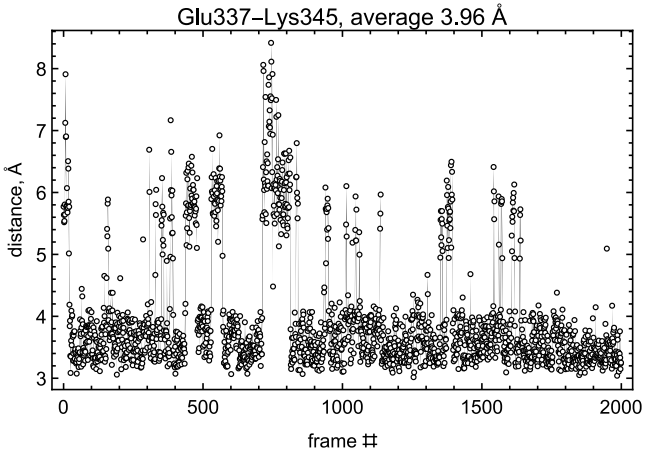

Asp334–O–LIG, average 5.09 Å
distance, Å
frame ⌗

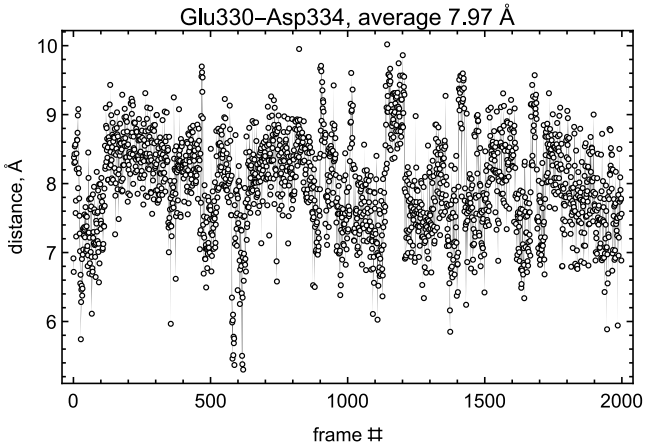

Glu337–O–LIG, average 5.19 Å
distance, Å
frame ⌗

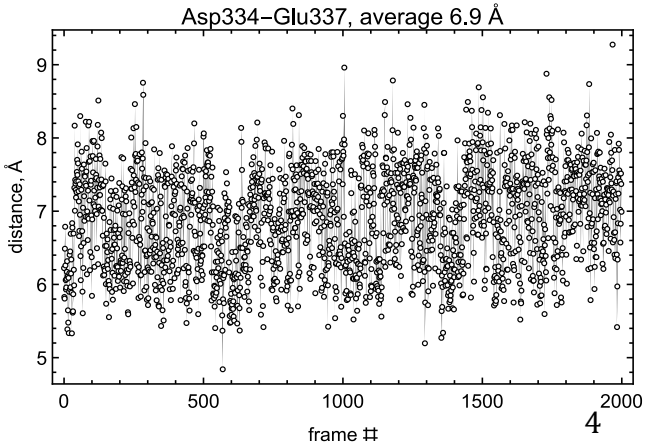

Lys345–C9–LIG, average 4.9 Å
distance, Å
frame ⌗


Glu330–Lys345, average 10.5 Å
distance, Å
frame ⌗


Asp334–Lys345, average 8.97 Å
distance, Å
frame ⌗

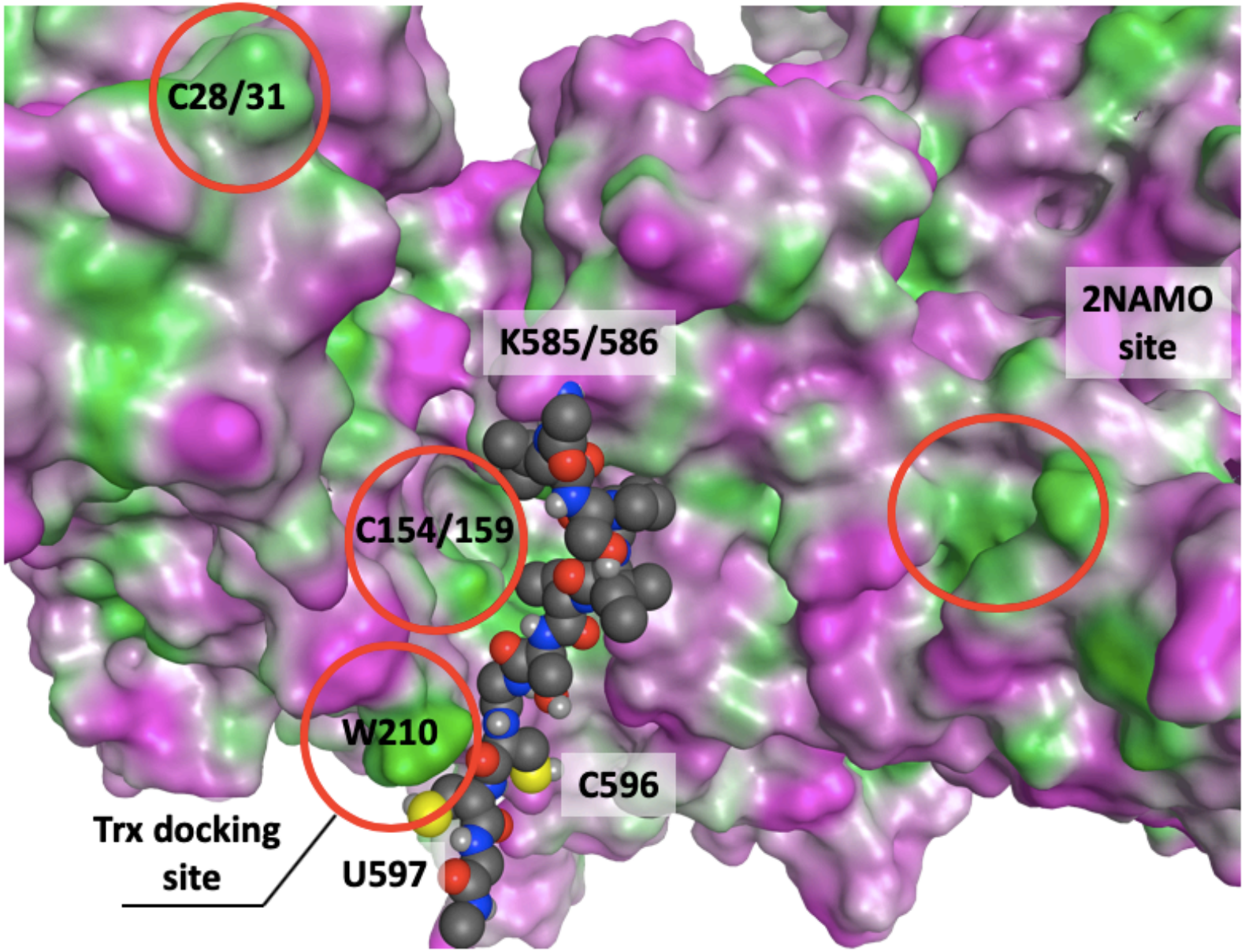

Glu337–Lys345, average 3.96 Å
distance, Å
frame ⌗


Glu330–Asp334, average 7.97 Å
distance, Å
frame ⌗


Asp334–Glu337, average 6.9 Å
distance, Å
frame ⌗

Supplemental figure 3

The possible sites reached by the C-terminal tail are mapped onto the solvent exposed surface of the SmTGR. The hydrophobic and hydrophilic regions are colored in green and purple, respectively. The Sec-containing C-terminal tail is displayed in spheres and the relevant redox sites (C154/C159 of the FAD redox site; C28/C31 of the Grx redox site; W210 of the Trx docking site) together with the 2NAMO binding site are circled in red. The K585/K586 couple, working as a hinge for the C-terminal movements, is also indicated.



Supplemental figure 4

Sequence alignment between SmTGR and representative homologues belonging to the FAD/NAD-linked reductase family (only residues in the range 307-375 are displayed, numbering is according to the SmTGR sequence). The analysis is limited to the amino acidic residues contributing to the binding of compound **4** (See Table1 of the main text) in SmTGR as found by the CONTACT program (CCP4 suite). SmTGR residues, within 4.5 Å from the atoms of the compound, are in red: V316, S318, L320, E330, G333, D334, E337, F343, K345; a red and blue letter is respectively used if a residue is conserved or not in the homologous proteins. The pdb IDs of each protein are indicated in parenthesis. SmTGR: Thioredoxin glutathione reductase from *Schistosoma mansoni*; SjTGR: Thioredoxin glutathione reductase from *Schistosoma japonicum*; hTrxR: thioredoxin reductase isoform I from *Homo sapiens*; RnTrxR: Rattus norvegicus Thioredoxin reductase; hsGR: glutathione reductase from *Homo sapiens*.

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                          316             330             345
                           |               |               |
SmTGR (2V6O)   SLGGDVTVMVRSI-LL-RGFDQQMAEKVGDYMEN-HGVKFAKL-CVPDEIKQLKVVDTENNKPGLLLVKGHYT
SjTGR (4LA1)   SLGGDVTVMVRSI-LL-RGFDQQMAEKVGDYMEN-HGVKFAKL-CVPDEITQLKPVDTENNKPGLLLVKGHYT
HsTrxR (2J3N) GIGLDVTVMVRSI-LL-RGFDQDMANKIGEHMEE-HGIKFIRQ-FVPIKVEQI-----EAGTPGRLRVVAQST
RnTrxR (3EAN) GIGLDVTVMVRSI-LL-RGFDQDMANKIGEHMEE-HGIKFIRQ-FVPTKIEQI-----EAGTPGRLKVTAKST
HsGR (3DJG)    ALGSKTSLMIRHDKVL-RSFDSMISTNCTEELEN-AGVEVLKF-SQVKEVKKT-----LSGLEVSMVTAVPGR
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Supplementary references

- SmTGR (2V6O): Angelucci F, Miele AE, Boumis G, Dimastrogiovanni D, Brunori M, Bellelli A. Glutathione reductase and thioredoxin reductase at the crossroad: the structure of Schistosoma mansoni thioredoxin glutathione reductase. Proteins. (2008) 72, 936-45.
- SjTGR (4LA1): to be published
- HsTrxR (2J3N): Fritz-Wolf K, Urig S, Becker K. The structure of human thioredoxin reductase 1 provides insights into C-terminal rearrangements during catalysis. J Mol Biol. (2007) 370, 116-27.
- RnTrxR (3EAN): Cheng Q, Sandalova T, Lindqvist Y, Arnér ES. Crystal structure and catalysis of the selenoprotein thioredoxin reductase 1. J Biol Chem. (2009) 284, 3998-4008.
- HsGR (3DJG): Berkholz DS, Faber HR, Savvides SN, Karplus PA. Catalytic cycle of human glutathione reductase near 1 A resolution. J Mol Biol. (2008) 382, 371-84.