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Mononuclear gold(III) complexes with L-histidine-containing dipeptides: tuning the structural and biological properties by variation of the N-terminal amino acid and counter anion

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Abstract

Gold(III) complexes with different L-histidine-containing dipeptides, [Au(Gly-L-His-N_A,N_P,*N3*)Cl]Cl·3H_2O (**1a**), [Au(Gly-L-His-N_A,N_P,*N3*)Cl]NO_3·1.25H_2O (**1b**), [Au(L-Ala-L-His-N_A,N_P,*N3*)Cl][$AuCl_4$]·H_2O (**2a**), [Au(L-Ala-L-His-N_A,N_P,*N3*)Cl]NO_3·2.5H_2O (**2b**), [Au(L-Val-L-His-N_A,N_P,*N3*)Cl]Cl·2H_2O (**3**), [Au(L-Leu-L-His-N_A,N_P,*N3*)Cl]Cl (**4a**) and [Au(L-Leu-L-His-N_A,N_P,*N3*)Cl][$AuCl_4$]·H_2O (**4b**) have been synthesized and structurally characterized by spectroscopic (^{1}H NMR, IR and UV-vis) and single-crystal X-ray diffraction techniques. The antimicrobial efficiency of these gold(III) complexes, along with K[$AuCl_4$] and the corresponding dipeptides, was evaluated against the broad panel of Gram-positive and Gram-negative bacteria and fungi, displaying their moderate inhibiting activity. Moreover, cytotoxic properties of the investigated complexes were assessed against the normal human lung fibroblast cell line (MRC5) and two human cancer, cervix (HeLa) and lung (A549) cell lines. None of the complexes exerted significant cytotoxic activity; nevertheless complexes that did show selectivity in terms of cancer *vs.* normal cell lines (**2a**/**b** and **4a**/**b**) have been evaluated using zebrafish (*Danio rerio*) embryos for toxicity and antiangiogenic potential. Although the gold(III) complexes achieved antiangiogenic effect comparable to the known angiogenic inhibitors auranofin and sunitinib malate at 30-fold higher concentrations, they had no cardiovascular side effects, which commonly accompany auranofin and sunitinib malate treatment. Finally, binding of the gold(III) complexes to the active sites of both human and bacterial (*Escherichia coli*) thioredoxin reductases (TrxRs) was demonstrated by molecular docking study, suggesting that the mechanism of biological action of these complexes can be associated with their interaction with the TrxR active site.

Keywords: Gold(III) complexes; L-Histidine-containing dipeptides; Antimicrobial activity; Cytotoxicity; *Danio rerio;* Antiangiogenic activity

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Fig. S1 The dose-dependent inhibition of the subintestinal vessels (SIVs) formation in zebrafish embryos after 48 h of treatments with gold(III)-peptide complexes **2a**, **2b**, **4a** and **4b**. Normally developed SIVs basket with 5 - 9 vessels is denoted in DMSO-treated embryo (dashed circle). Reduction in the size and the number of vessels of SIVs basket upon different treatments are designed with arrowhead. Auranofin (1.25 μM) and sunitinib malate (1.25 μM) are used as positive controls, upon which regimes embryos suffered of pericardial edemas (arrow).

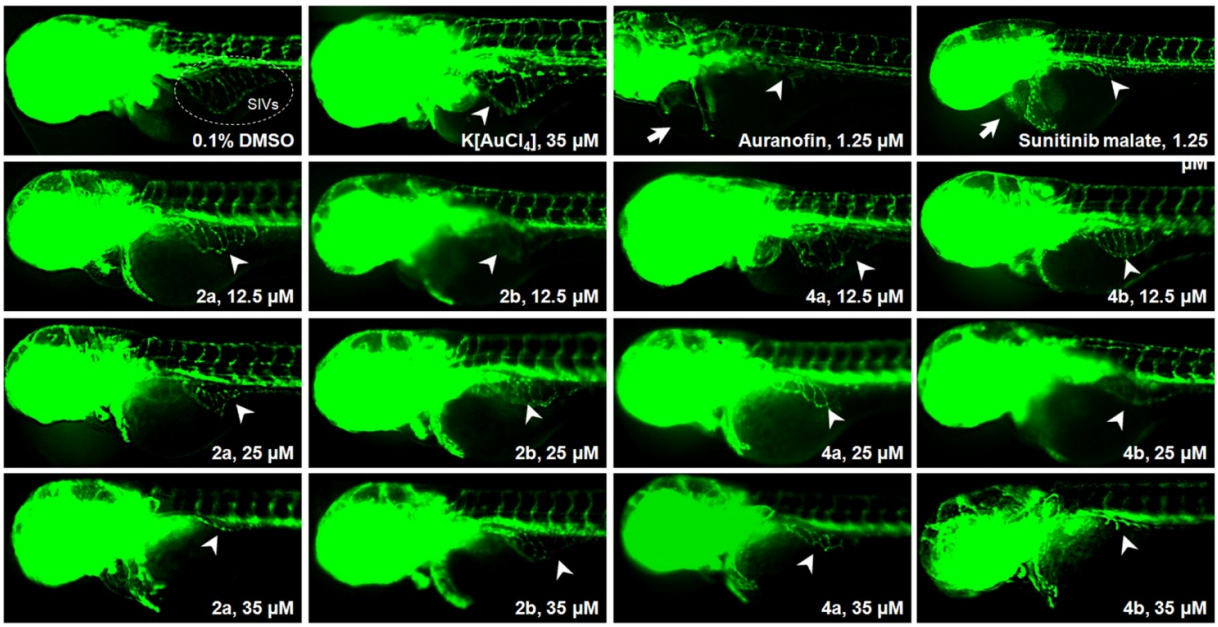
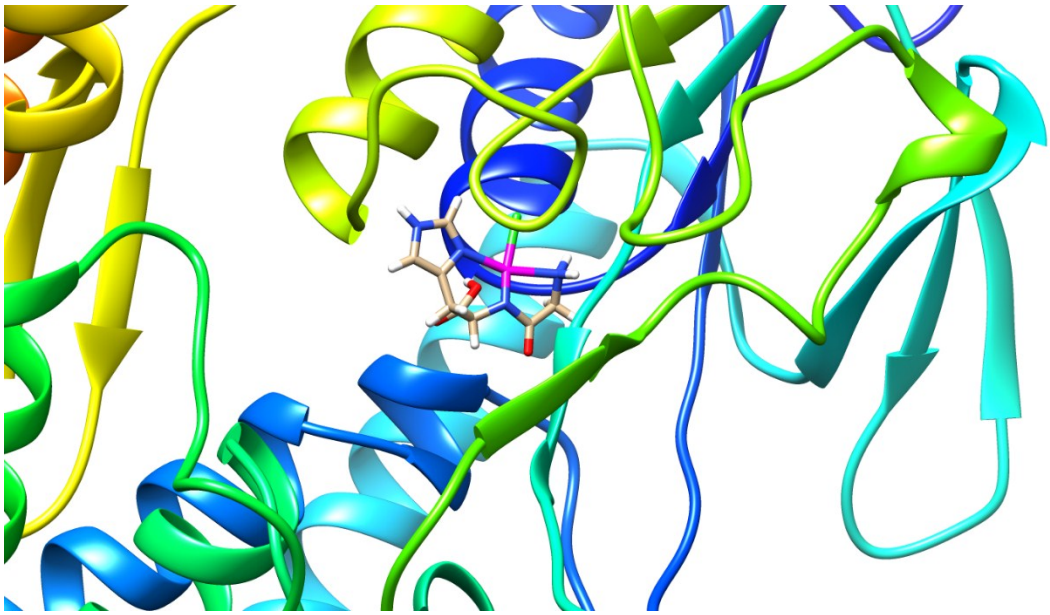


Fig. S2 The best docking pose for the corresponding gold(III) complex cation and auranofin inside human thioredoxin reductase active site.



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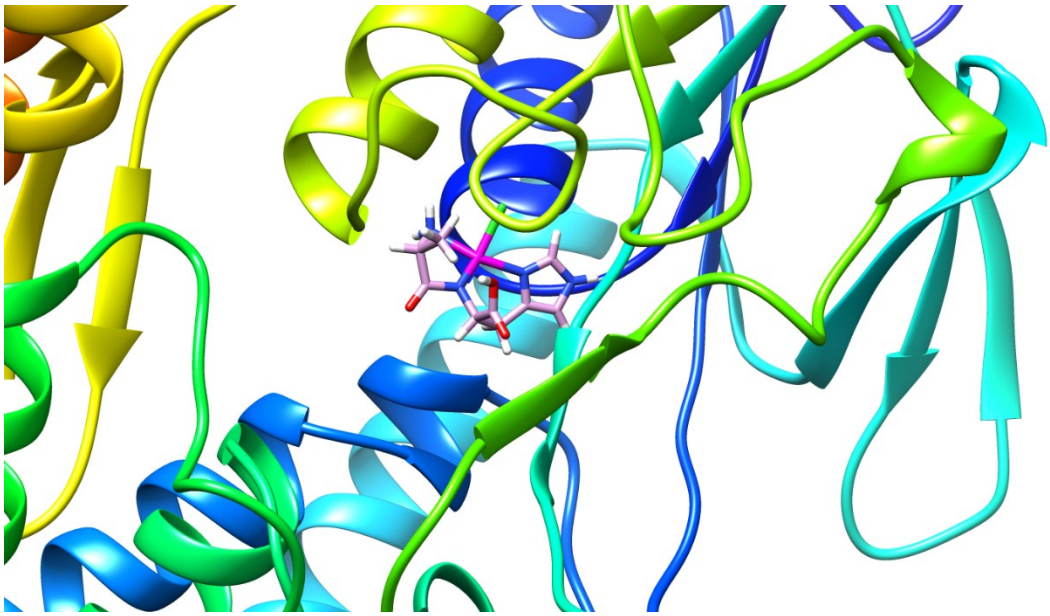

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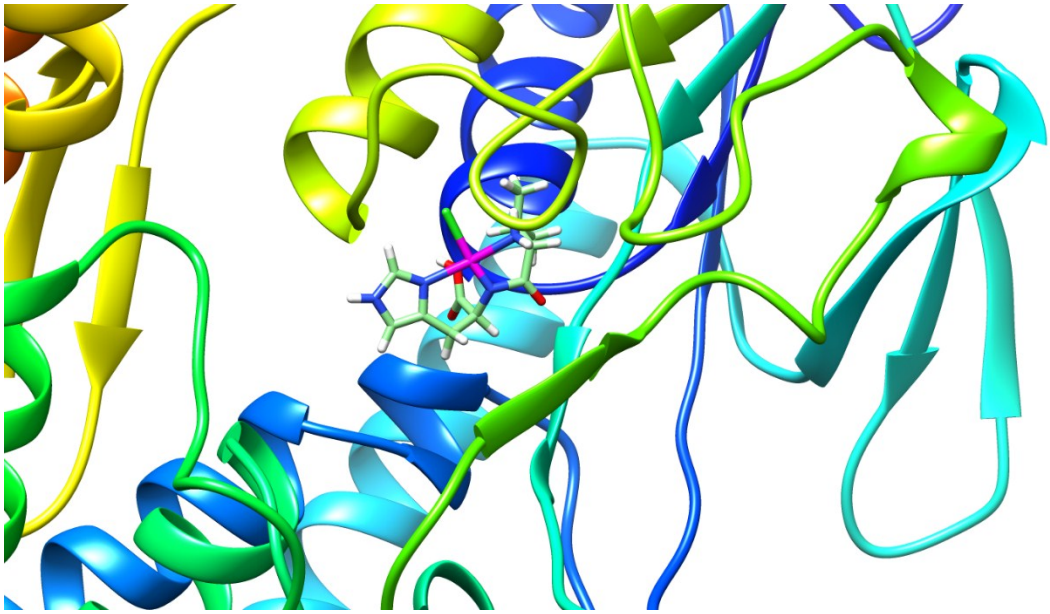

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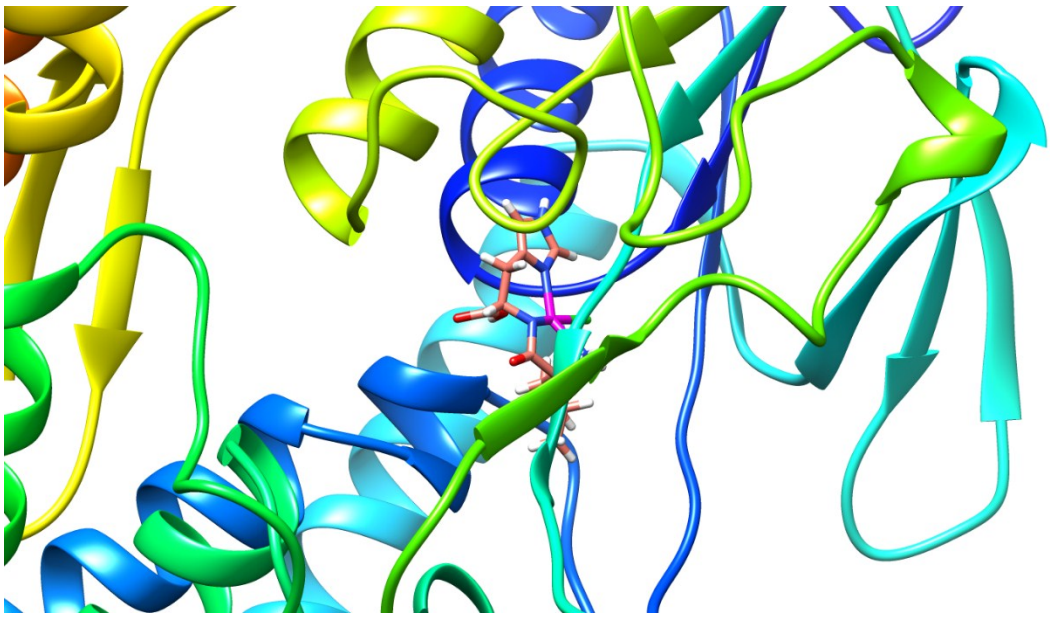
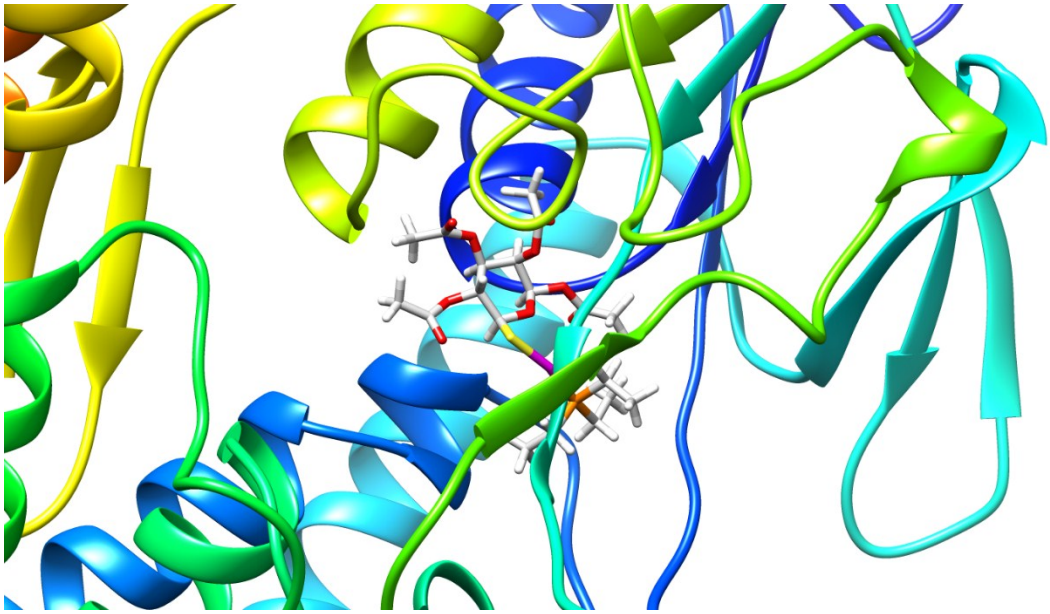
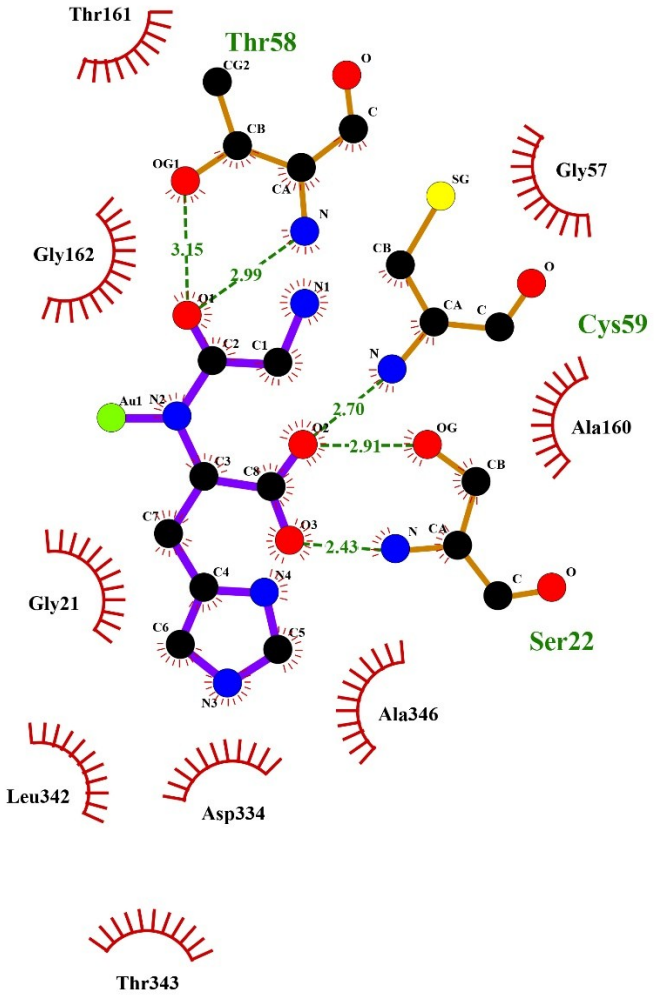


4a/b



Auranofin

Fig. S3 LigPlot diagrams illustrating interactions between the corresponding gold complexes and human thioredoxin reductase during docking. Hydrogen bonds are illustrated by dashed lines and the donor-acceptor distances are given in Å units. Hydrophobic interactions are represented by red spokes radiating towards the ligand atoms they contact. Amino acids labeled in black form hydrophobic and van der Walls interactions, while those labeled in green form hydrogen bonds with the complex. The interacted atoms are spokes radiating back. C, N, O, S and Au atoms are represented in black, blue, red, yellow and green, respectively.



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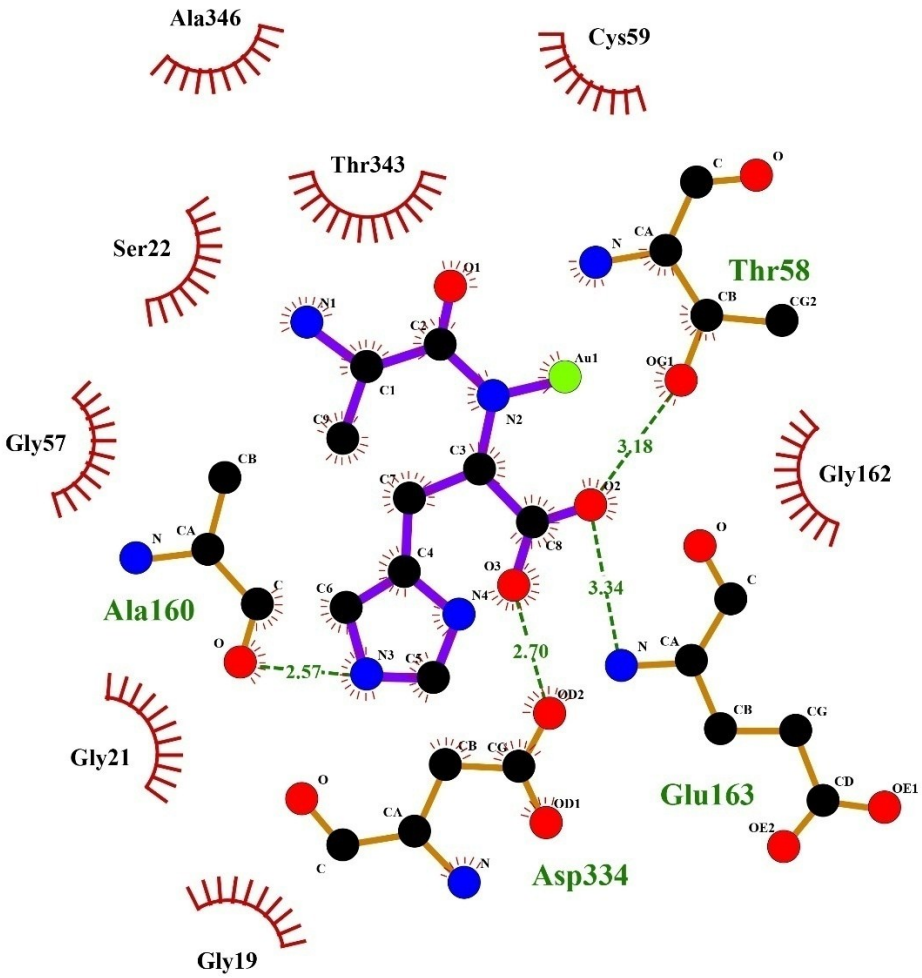
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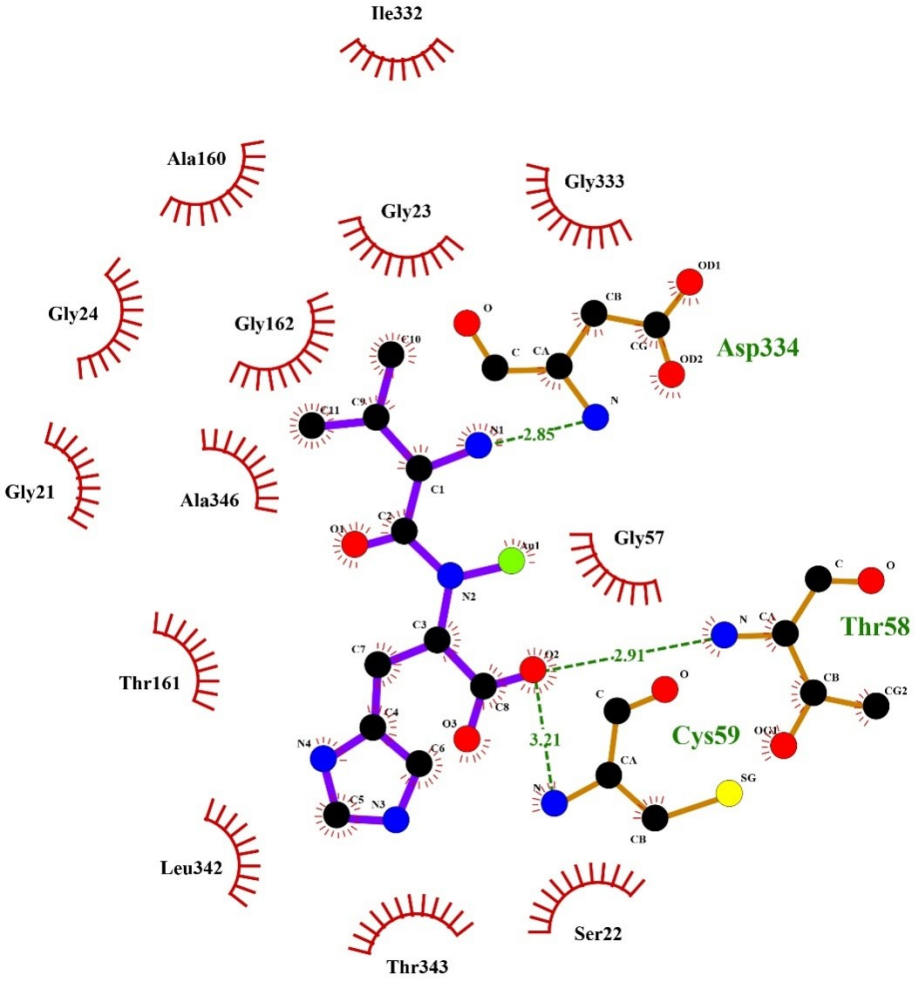
2a/b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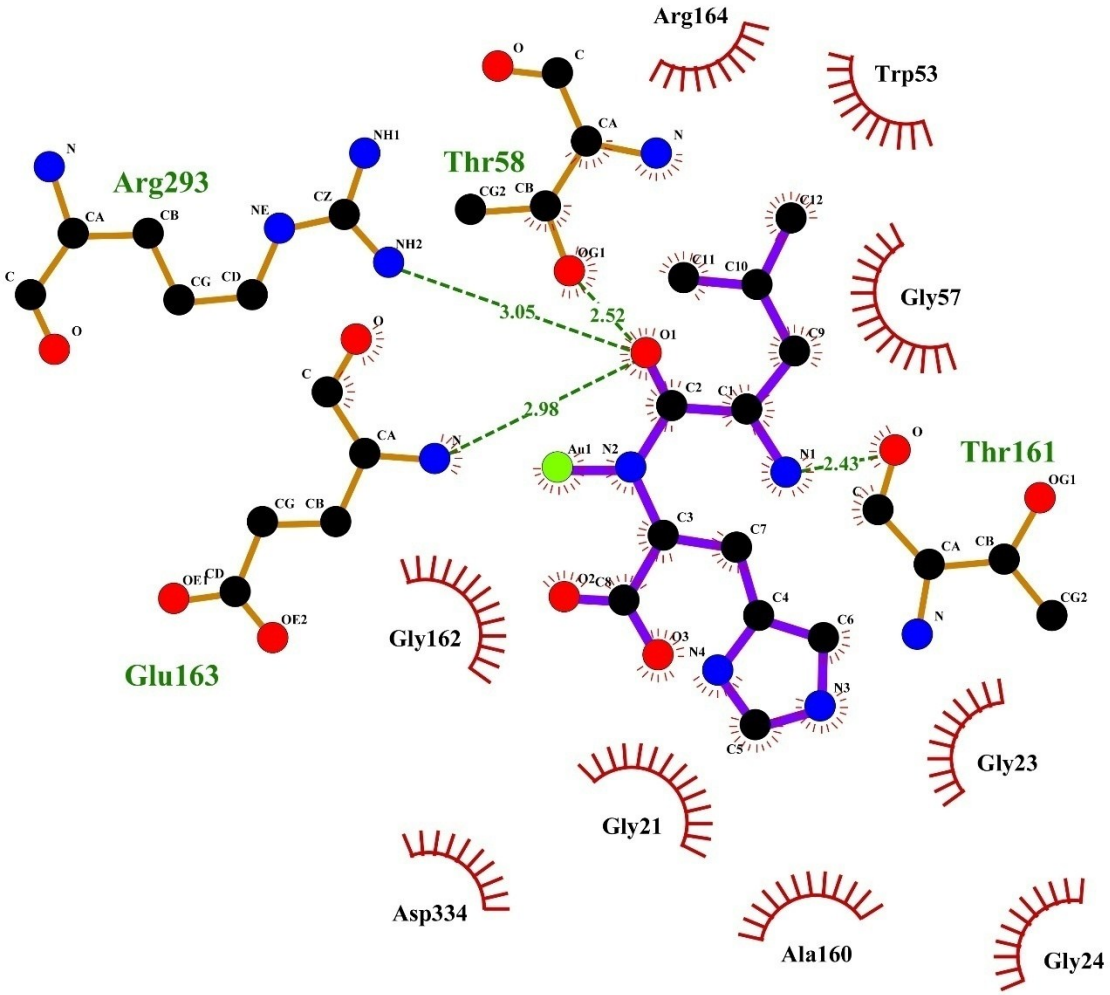
3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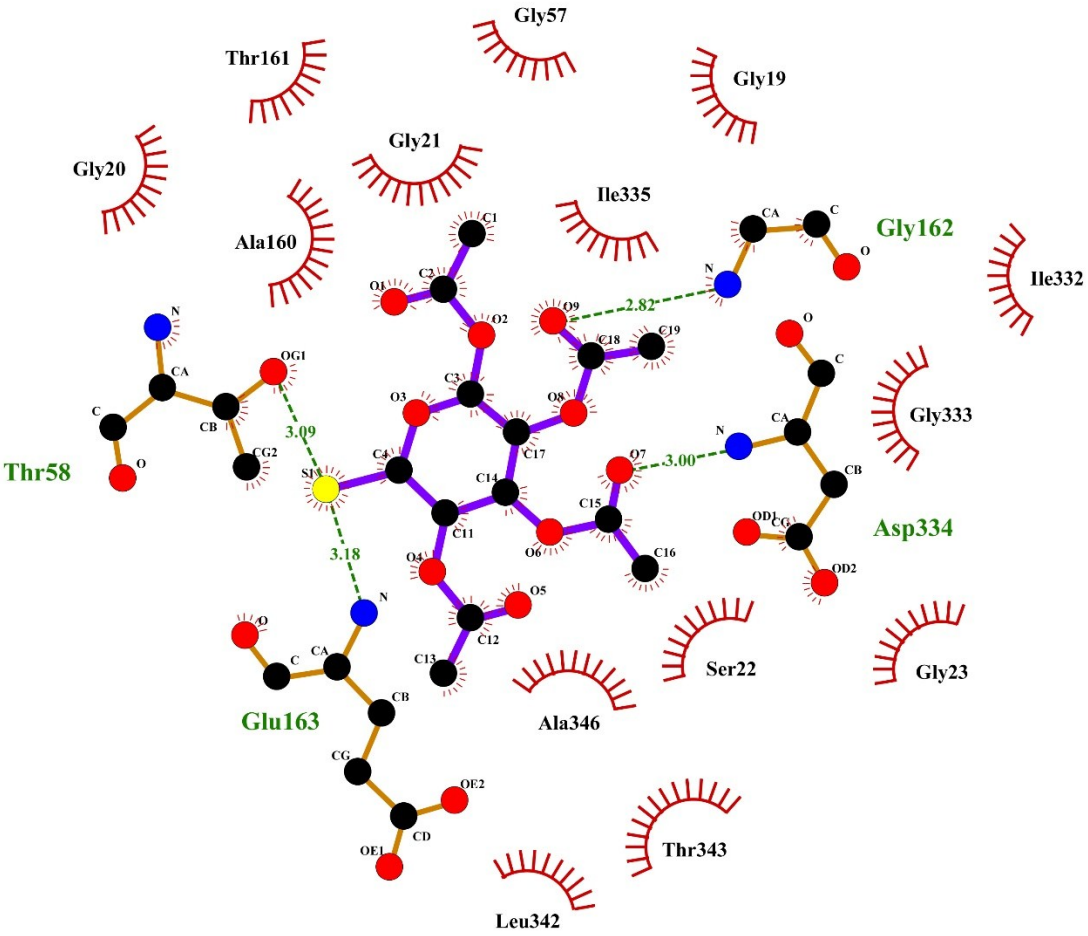
4a/b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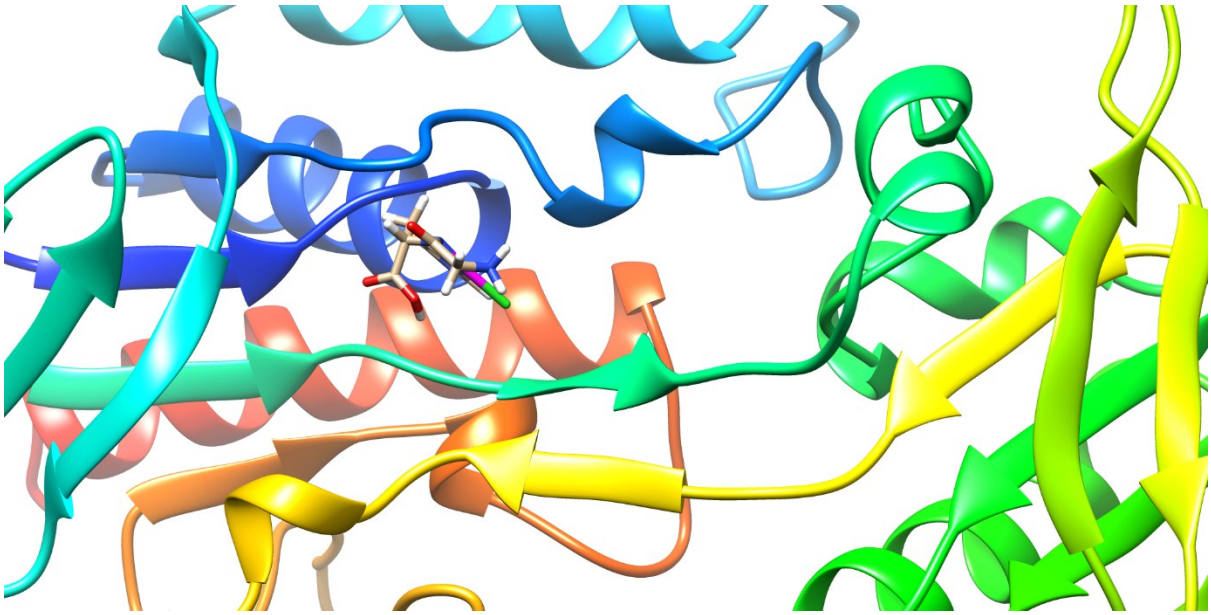
3.18

Auranofin

Fig. S4 The best docking pose for the corresponding gold(III) complex cation and auranofin inside *Escherichia coli* thioredoxin reductase active site.



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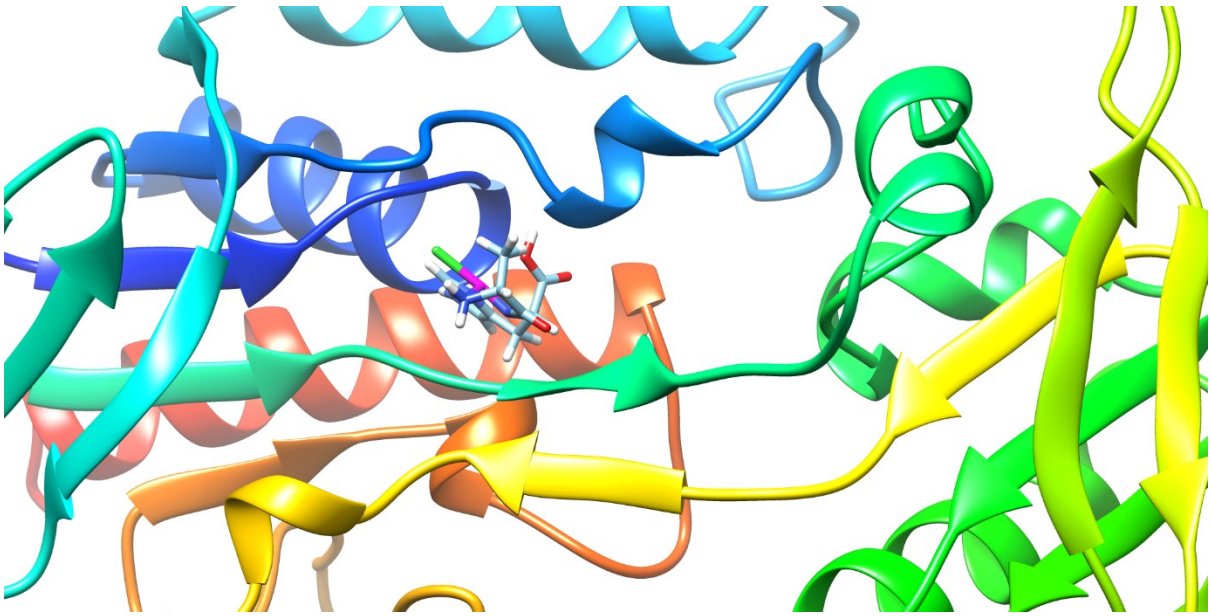

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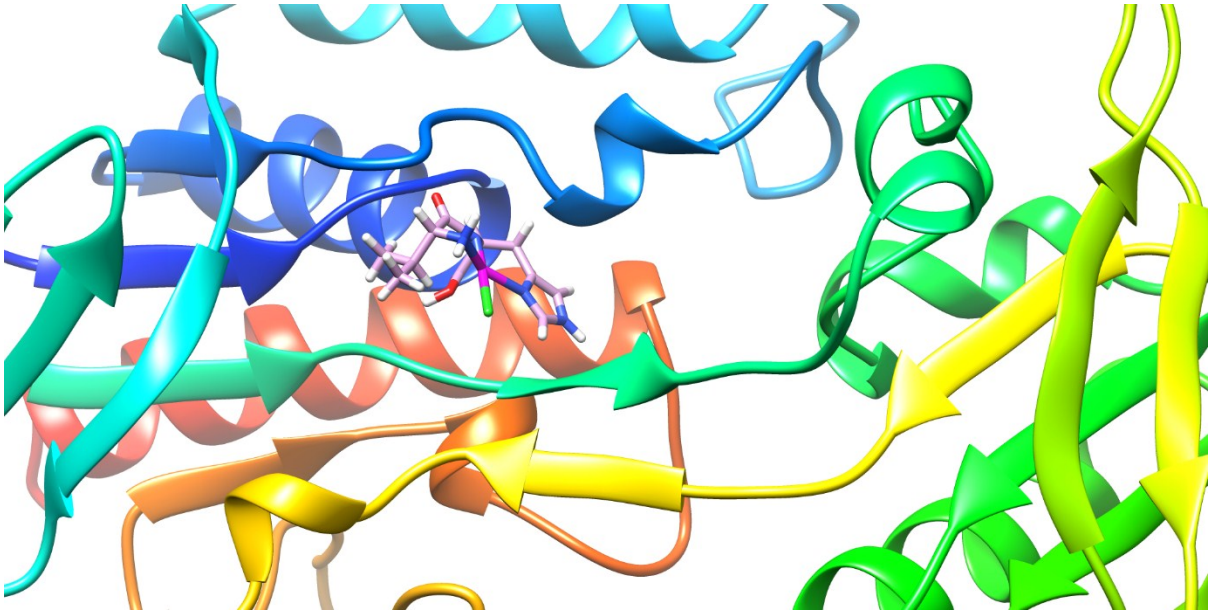

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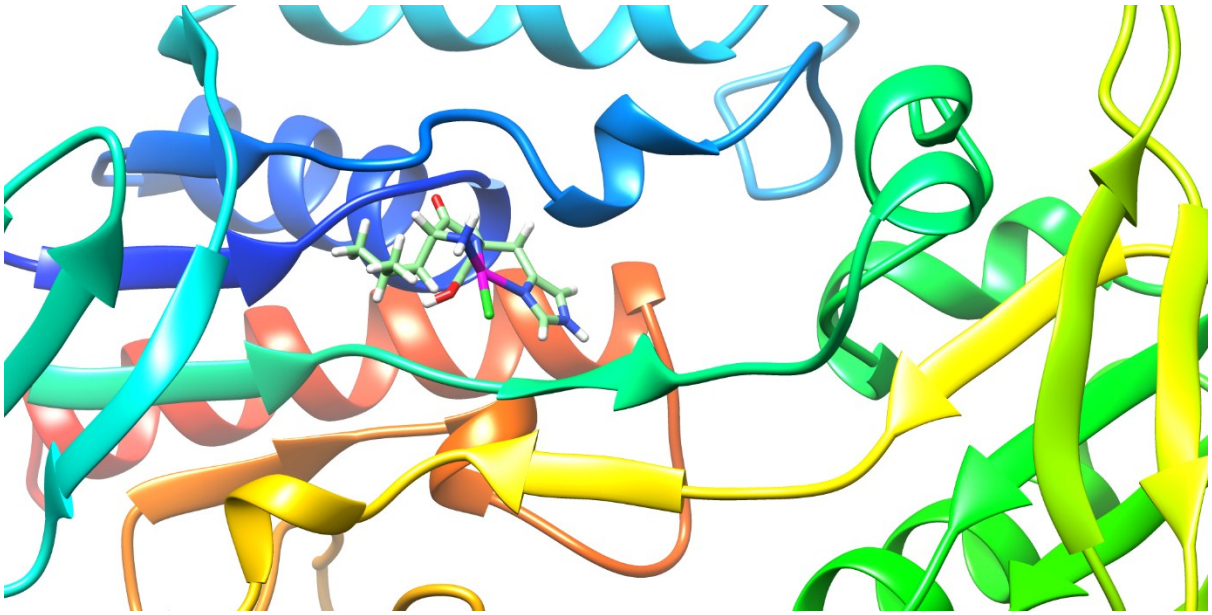
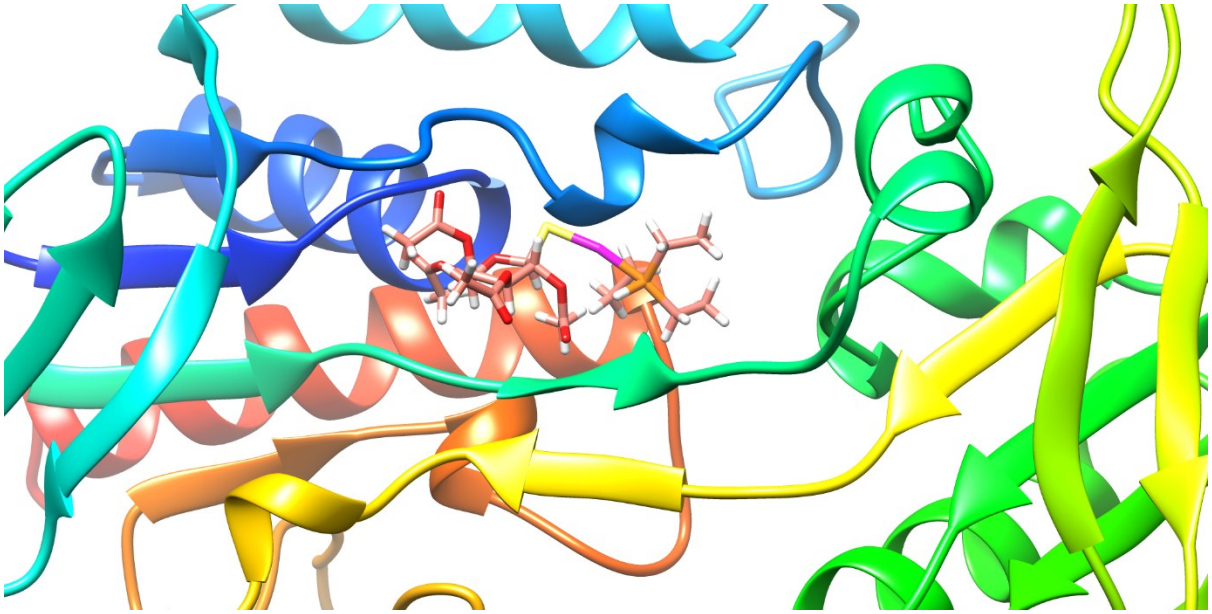
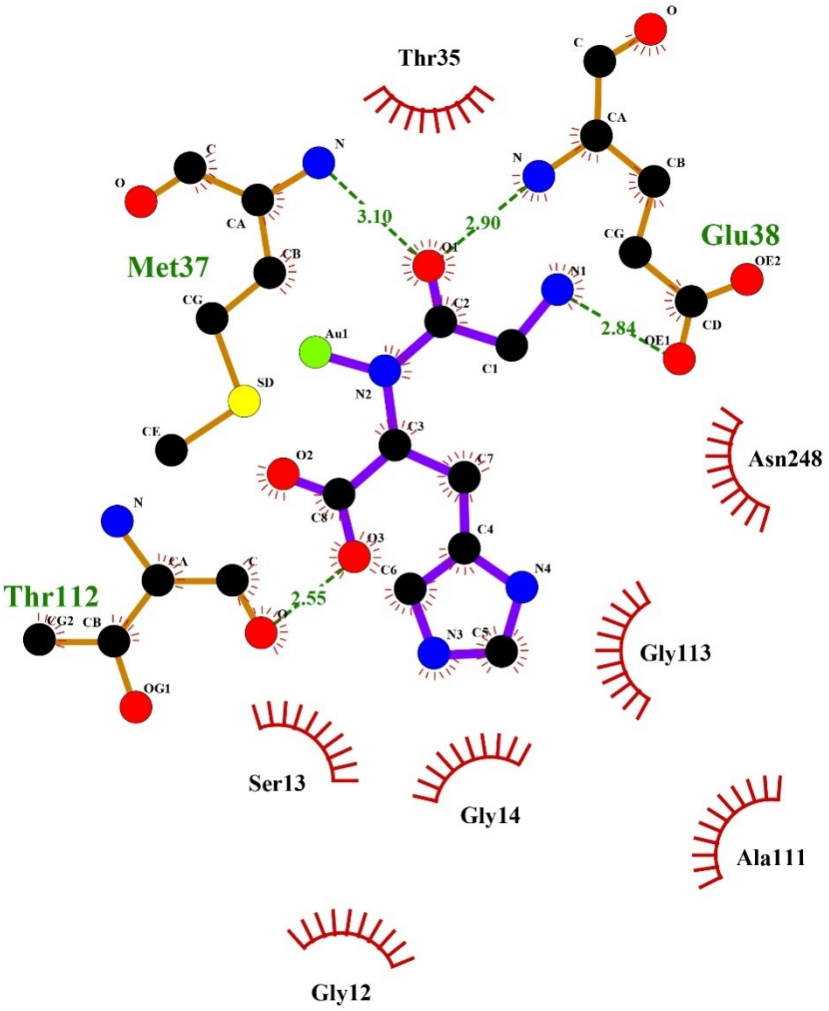


4a/b



Auranofin

Fig. S5 LigPlot diagrams illustrating interactions between the corresponding gold complexes and *Escherichia coli* thioredoxin reductase during docking. Hydrogen bonds are illustrated by dashed lines and the donor-acceptor distances are given in Å units. Hydrophobic interactions are represented by red spokes radiating towards the ligand atoms they contact. Amino acids labeled in black form hydrophobic and van der Walls interactions, while those labeled in green form hydrogen bonds with the complex. The interacted atoms are spokes radiating back. C, N, O, S and Au atoms are represented in black, blue, red, yellow and green, respectively.



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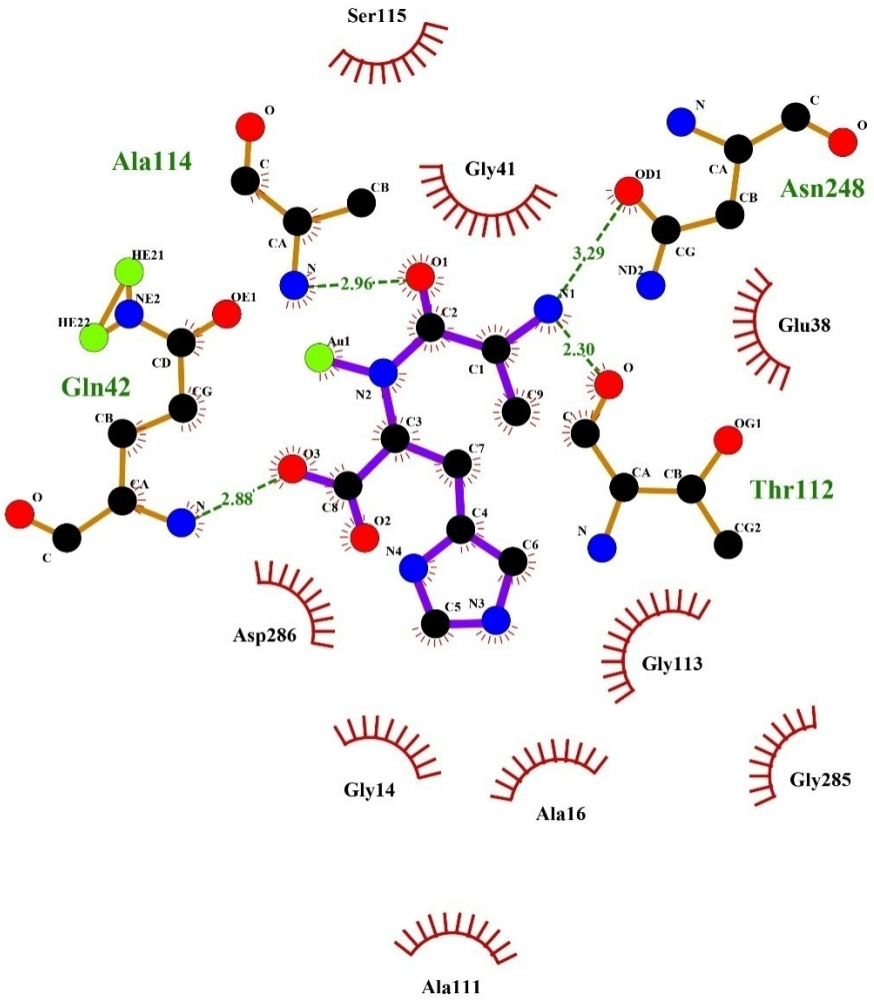
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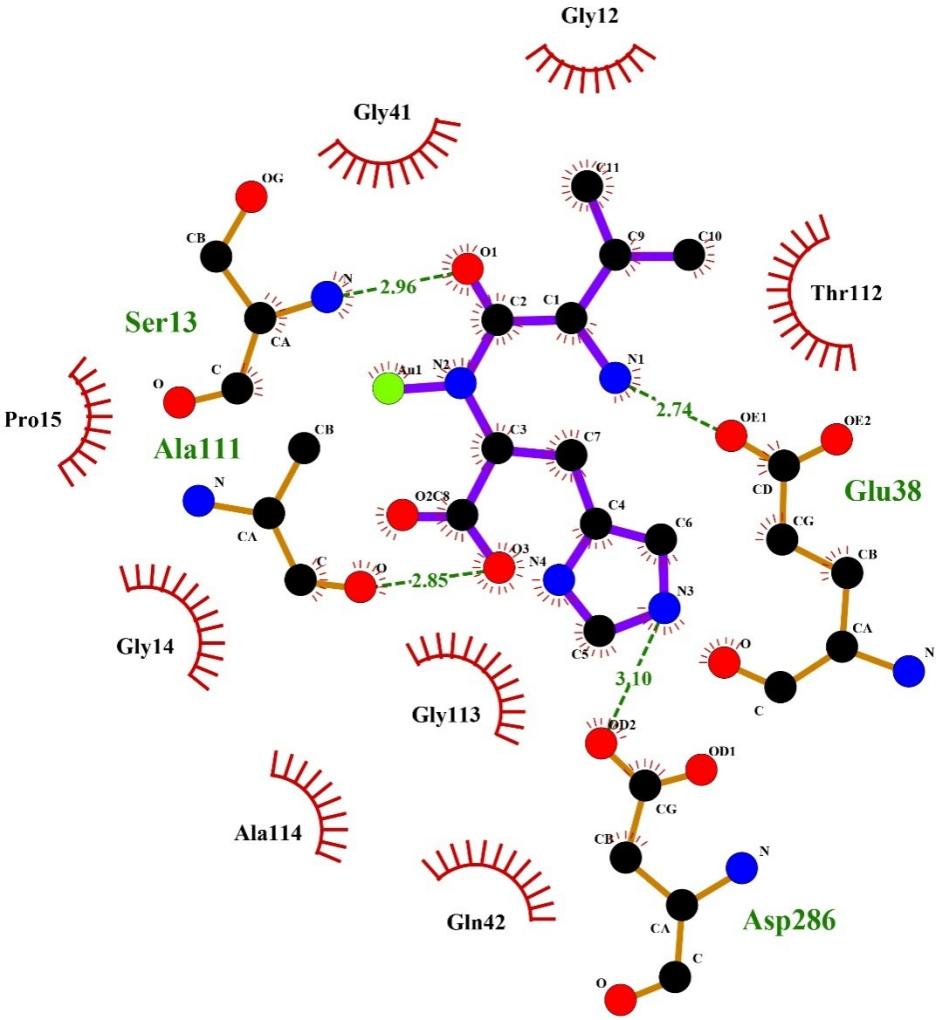
2a/b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CA
C
O
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C7
C4
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O3
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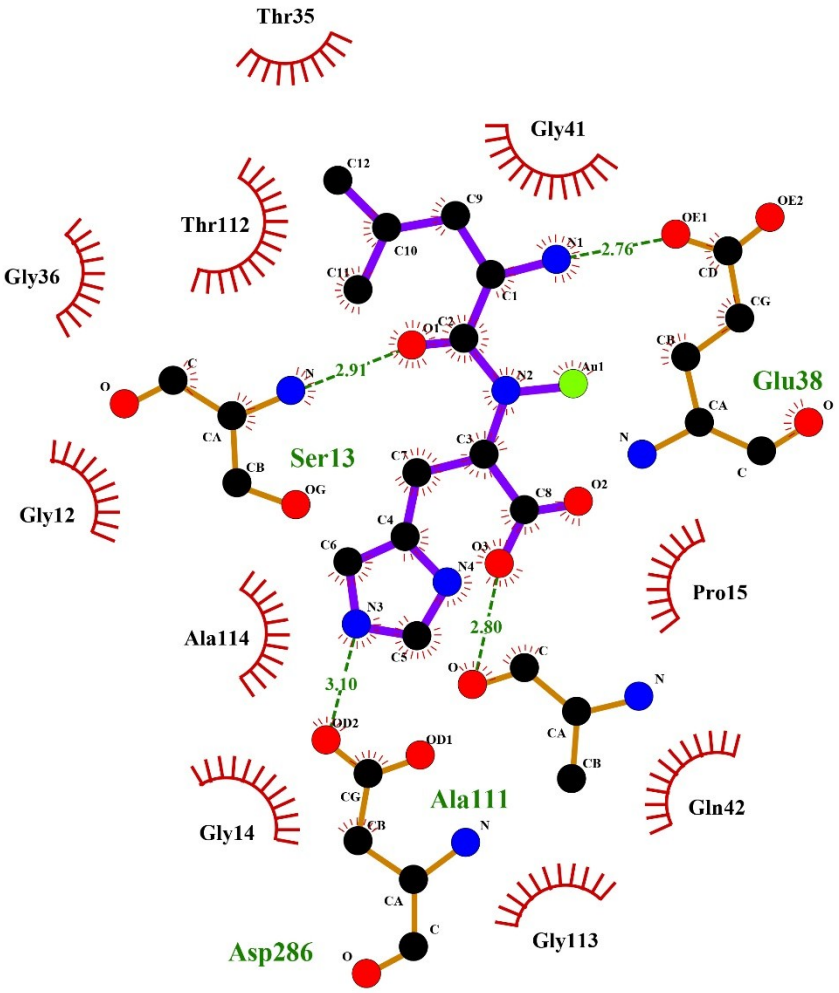
3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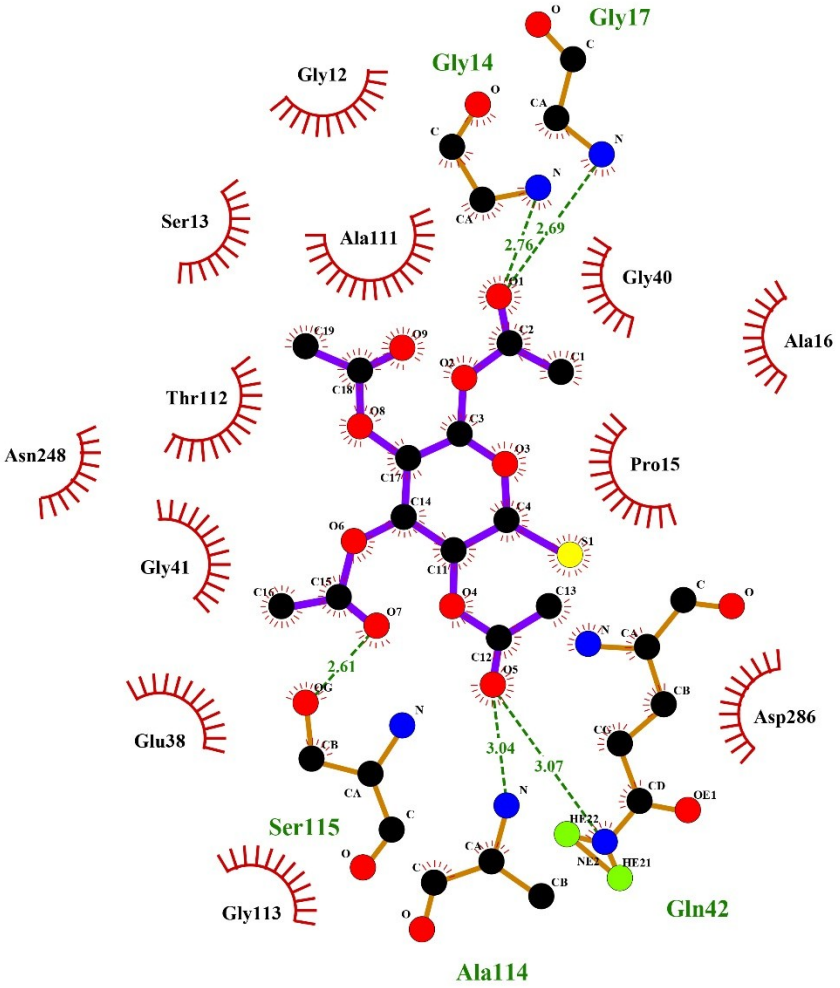
4a/b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Gly113
Gln42
Ala114
2.76
2.69
2.61
3.04
3.07

Auranofin

Table S1 Selected geometric parameters (Å, º)

	[Au(Gly-L-His-N_A,N_P,*N3*)Cl]Cl·3H_2O (**1a**)[1]	[Au(Gly-L-His-N_A,N_P,*N3*)Cl]NO_3·1.25H_2O (**1b**)[2]	[Au(L-Ala-L-His-N_A,N_P,*N3*)Cl][$AuCl_4$]·H_2O (**2a**)	[Au(L-Ala-L-His-N_A,N_P,*N3*)Cl]NO_3·2.5H_2O (**2b**)[2]	[Au(L-Val-L-His-N_A,N_P,*N3*)Cl]Cl·2H_2O (**3**)	[Au(L-Leu-L-His-N_A,N_P,*N3*)Cl]Cl (**4a**)	[Au(L-Leu-L-His-N_A,N_P,*N3*)Cl][$AuCl_4$]·H_2O (**4b**)
Au1—N1	2.002(9)	1.987(8) 2.026(10)	2.009(6)	2.018(5)	2.013(8) 2.010(8)	2.004(5)	2.009(5)
Au1—N2	1.94(1)	2.020(10) 2.021(10)	1.987(6)	1.995(5)	1.990(12) 1.991(11)	1.981(5)	1.999(6)
Au1—N3	1.991(8)	1.996(9) 1.913(10)	1.994(7)	2.001(6)	2.012(8) 2.017(9)	2.014(5)	2.002(6)
Au1—Cl1	2.272(3)	2.293(3) 2.297(3)	2.282(3)	2.2868(16)	2.282(2) 2.288(2)	2.2852(17)	2.2788(18)
N1—Au1—N2	84.8	82.8(4) 82.3(4)	83.3(3)	81.7(2)	80.8(4) 81.0(5)	83.2(2)	81.5(2)
N1—Au1—N3	175.6	175.3(4) 175.4(4)	176.3(3)	175.8(2)	176.4(4) 176.4(4)	174.1(2)	174.5(3)
N3—Au1—N2	90.9	92.7(4) 93.2(4)	93.0(3)	94.2(2)	95.7(4) 95.5(5)	94.0(2)	93.6(2)
N1—Au1—Cl1	88.5	92.5(2) 92.2(3)	90.60(19)	92.93(17)	91.8(3) 92.0(3)	89.15(16)	92.68(18)
N2—Au1—Cl1	174.3	174.7(3) 174.0(3)	172.7(2)	174.56(17)	172.3(4) 173.0(4)	171.73(17)	173.87(17)
N3—Au1—Cl1	94.8	92.1(3) 92.4(3)	93.1(2)	91.17(17)	91.7(3) 91.5(3)	93.88(18)	92.31(18)

Table S2 Endocyclic torsion angles (º) for five- and six-membered rings and average endocyclic torsion angle moduli ($|\omega|$)

	[Au(Gly-L-His-$N_A,N_P,N3$)Cl]Cl·3H_2O (**1a**)[1]	[Au(Gly-L-His-$N_A,N_P,N3$)Cl]NO_3·1.25H_2O (**1b**)[2]	[Au(L-Ala-L-His-$N_A,N_P,N3$)Cl][$AuCl_4$]·H_2O (**2a**)	[Au(L-Ala-L-His-$N_A,N_P,N3$)Cl]NO_3·2.5H_2O (**2b**)[2]	[Au(L-Val-L-His-$N_A,N_P,N3$)Cl]Cl·2H_2O (**3**)	[Au(L-Leu-L-His-$N_A,N_P,N3$)Cl]Cl (**4a**)	[Au(L-Leu-L-His-$N_A,N_P,N3$)Cl][$AuCl_4$]·H_2O (**4b**)
five-membered ring							
Au1—N1—C1—C2	0.41	-29.6(15) -18.2(14)	12.1(8)	-28.3(8)	-6.7(11) -12.0(12)	-5.3(7)	-17.6(7)
N1—C1—C2—N2	-2.33	13.1(17) 7.0(19)	-15.8(10)	18.0(10)	-5.1(15) -0.7(16)	5.4(8)	2.6(9)
C1—C2—N2—Au1	3.35	9.6(14) 7.8(17)	12.1(9)	1.4(9)	15.5(15) 13.7(15)	-2.9(7)	14.1(8)
C2—N2—Au1—N1	-2.52	-21.5(10) -14.5(9)	-3.7	-14.3(7)	-15.7 -16.4	-0.2	-19.2
N2—Au1—N1—C1	1.01	27.8(10) 18.1(9)	-5.4	23.3(6)	10.9 14.7	3.2	19.6
$\|\omega\|$	1.9(1.1)	20.3(7.9) 13.1(4.9)	9.8(4.5)	17.1(9.2)	10.8(4.4) 11.5(5.6)	3.4(1.9)	14.6(6.3)
six-membered ring							
Au1—N2—C3—C4	-38.0	-31.9(14) -31.5(18)	-48.2(8)	-34.4(11)	-35.8(13) -39.1(13)	-41.8(8)	-42.0(8)
N2—C3—C4—C5	71.1	67.7(14) 63.4(18)	65.4(9)	66.8(9)	69.4(12) 68.9(13)	59.5(8)	67.0(8)
C3—C4—C5—N3	-54.1	-65(2) -49.7(19)	-41.0(11)	-54.6(10)	-54.1(13) -52.3(14)	-43.6(10)	-43.0(10)
C4—C5—N3—Au1	2.2	20(3) 0.9(19)	-1.1(11)	8.9(10)	4.5(12) 5.4(13)	7.3(9)	-4.9(9)

C5—N3—Au1—N2	23.8	11.9(19) 22.3(13)	14.8	17.5(6)	21.0 18.5	8.2	22.9
N3—Au1—N2—C3	-3.8	-5.1(11) -6.3(12)	10.6	-3.6(8)	-4.7 -0.4	10.5	1.9
$\lvert\omega\rvert$	32(25)	34(24) 29(22)	30(23)	31(23)	32(24) 31(25)	28(21)	30(23)

Table S3 Hydrogen bond parameters (Å , °)

D—H···*A*	*D*—H (Å)	H···*A* (Å)	*D*···*A* (Å)	*D*—H···*A* (°)	Symmetry operations on A
[Au(Gly-L-His-N_A,N_P,*N3*)Cl]Cl·3H_2O (**1a**)[1]					
O3—H11···O5	0.97	1.66	2.618	174	
N1—H1···Cl2	0.95	2.21	3.150	170	
N1—H2···O6	0.94	1.84	2.776	171	
N4—H9···O4	0.95	1.84	2.758	161	
C7—H10···O2	0.96	2.44	3.173	133	-x+1,+y+1/2,-z
[Au(Gly-L-His-N_A,N_P,*N3*)Cl]NO_3·1.25H_2O (**1b**)[2]					
O3—H3O···O1N	0.82	2.03	2.680(15)	135	
N1—H1N···O2W	0.90	2.07	2.961(14)	171	x-1/2,+y+1/2,+z
N1—H2N···O1	0.90	2.16	2.876(18)	136	-x+1/2+1,+y-1/2,-z+2
N1—H2N···Cl1’	0.90	2.82	3.491(18)	133	x,+y-1,+z
N4—H4N···O4N	0.86	2.52	3.231(19)	141	
N4—H4N···O6N	0.86	2.08	2.901(21)	159	
C6—H6···O3	0.93	2.65	3.397(18)	138	-x+2,+y,-z+2
C7—H7···O2’	0.93	2.40	3.317(19)	168	
O3’—H3O’···O1W	0.82	1.92	2.709(18)	162	
N1’—H1N’···O2W	0.90	2.05	2.932(15)	166	x-1/2,+y+1/2,+z
N1’—H2N’···O5N	0.90	2.11	2.971(16)	161	x-1/2,+y+1/2,+z
N1’—H2N’···O1’	0.90	2.68	3.202(15)	118	-x+1/2+1,+y+1/2,-z+1
N4’—H4N’···O1N	0.86	2.00	2.849(16)	170	-x+2,+y,-z+2

N4'—H4N'···O2N	0.86	2.56	3.062(17)	118	-x+2,+y,-z+2
C6'—H6'···O2N	0.93	2.61	3.098(22)	113	-x+2,+y,-z+2
C7'—H7'···O2	0.93	2.33	3.108(17)	141	
[Au(L-Ala-L-His-N_A,N_P,*N3*)Cl][$AuCl_4$]·H_2O (**2a**)					
O3—H3O···O1W	0.82	1.81	2.620(7)	170	
N1—H1A···O1	0.89	1.98	2.824(8)	159	-x+1/2+1,+y-1/2,-z+1
N1—H1B···Cl5	0.89	2.48	3.364(6)	173	
N4—H4···Cl2	0.86	2.61	3.358(10)	146	x,+y,+z+1
N4—H4···Cl2	0.86	2.72	3.279(10)	124	-x+1,+y,-z+1
C7—H7···Cl5	0.93	2.97	3.562(10)	123	x,+y,+z+1
O1W—H1W···O1	0.82	2.00	2.823(9)	179	x,+y,+z+1
O1W—H2W···O2	0.82	2.05	2.868(11)	180	-x+1/2+1,+y+1/2,-z+2
[Au(L-Ala-L-His-N_A,N_P,*N3*)Cl]NO_3·2.5H_2O (**2b**)[2]					
O3—H3O···O1W	0.82	1.85	2.653(14)	168	
N1—H1N···O2W	0.90	2.00	2.887(9)	170	
N1—H2N···O3W	0.90	2.26	3.142(14)	165	
N4—H4N···O1N	0.86	2.52	3.189(21)	135	
N4—H4N···O2N	0.86	1.96	2.808(19)	170	
N4—H4N···O1N'	0.86	2.08	2.890(29)	157	
N4—H4N···O3N'	0.86	2.33	3.069(38)	144	
C6—H6···O1W	0.93	2.83	3.489(11)	128	-x+1/2+1,+y-1/2,-z+1
C7—H7···O2	0.93	2.22	3.112(9)	160	-x+2,-y+1,+z
[Au(L-Val-L-His-N_A,N_P,*N3*)Cl]Cl·2H_2O					

(**3**)					
O3—H3A···O4W	0.82	1.80	2.534(16)	148	x,+y,+z-1
N1—H1A···O2W	0.89	1.94	2.810(13)	167	
N1—H1B···O1W	0.89	2.16	2.922(15)	143	
N4—H4···Cl4	0.86	2.20	3.040(9)	167	
C7—H7···O22	0.93	2.27	3.170(12)	162	
O23—H23A···O3W	0.82	1.80	2.611(13)	171	
N21—H21A···O2W	0.89	1.94	2.808(10)	166	
N21—H21B···O1W	0.89	2.30	3.010(11)	137	x-1,+y,+z
N24—H24···Cl3	0.86	2.24	3.072(15)	162	
O1W—H11W···Cl3	0.82	2.38	3.202(8)	180	x+1,+y+1,+z
O1W—H12W···Cl4	0.82	2.36	3.166(9)	169	x,+y+1,+z
O2W—H21W···Cl3	0.82	2.24	3.054(8)	170	x,+y+1,+z
O2W—H22W···Cl4	0.82	2.28	3.062(11)	158	x,+y+1,+z
O3W—H31W···Cl4	0.82	2.37	3.177(11)	167	
O3W—H32W···O1	0.82	1.93	2.749(11)	180	x,+y-1,+z+1
O3W—H42W···O21	0.82	1.91	2.730(14)	180	
O4W—H41W···Cl3	0.82	2.43	3.197(9)	157	x,+y,+z+1
[Au(L-Leu-L-His-N_A,N_P,*N3*)Cl]Cl (**4a**)					
O3—H3O···Cl2	0.82	2.26	3.079(5)	176	
N1—H1A···O2	0.89	2.19	2.879(9)	134	-x+1,+y-1/2,-z+1/2
N1—H1A···Cl2	0.89	2.68	3.365(6)	134	-x+1,+y-1/2,-z+1/2
N1—H1B···Cl2	0.89	2.51	3.356(6)	160	x,+y-1,+z
N4—H4···Cl2	0.86	2.39	3.167(6)	151	-x+2,+y-1/2,-z+1/2

C3—H3···O1	0.98	2.32	2.728(9)	104	
C6—H6···Cl1	0.93	2.68	3.549(8)	156	-x+2,+y+1/2,-z+1/2
C7—H7···O1	0.93	2.59	3.441(9)	152	-x+1/2+1,-y+1,+z-1/2
[Au(L-Leu-L-His-N_A,N_P,*N3*)Cl][$AuCl_4$]·H_2O (**4b**)					
O3—H3A···O1	0.82	1.91	2.718(9)	167	-x+2,+y+1/2,-z+1/2+1
N1—H1A···O1W	0.89	1.82	2.701(8)	174	
N1—H1B···Cl5	0.89	2.44	3.323(6)	171	
N4—H4···Cl4	0.86	2.88	3.563(7)	138	x,+y+1,+z
N4—H4···Cl5	0.86	2.65	3.372(7)	142	x,+y+1,+z
C7—H7···Cl1	0.93	2.73	3.169(9)	110	
C7—H7···Cl2	0.9	2.87	2.484(9)	125	x-1/2,-y+1/2+1,-z+1
O1W—H1W···Cl4	0.82	2.56	3.375(7)	180	x-1/2,-y+1/2,-z+1
O1W—H2W···O2	0.82	2.03	2.787(9)	153	-x+1,+y-1/2,-z+1/2+1

Table S4 Score values (kcal/mol) for all studied gold complexes for both human and *Escherichia coli* thioredoxin reductases (TrxRs)

Complex	HBond	NoHBond	Steric	VdW	Energy	MolDock score	Rerank score	LE1	LE3
Human TrxR									
1a/b	-10.3001	-15.7147	-97.6026	-28.3324	-107.792	-117.767	-93.4174	-6.34069	-5.49514
2a/b	-8.28748	-12.987	-100.515	8.58733	-100.891	-113.659	-67.7239	-5.60504	-3.76244
3	-8.83728	-20.0669	-102.647	-10.8993	-110.66	-128.054	-83.9307	-5.53298	-4.19654
4a/b	-8.24472	-19.3412	-112.94	-20.772	-114.527	-131.499	-90.69	-5.45368	-4.31857
auranofin	-15.0274	-26.5616	-146.155	21.3618	-153.482	-143.236	-82.942	-4.95102	-2.67555
***E. coli* TrxR**									
1a/b	-10.518	-19.1302	-95.1559	-13.3679	-101.493	-117.791	-76.8644	-5.97016	-4.52143
2a/b	-9.44207	-13.5791	-98.9944	34.371	-100.694	-112.804	-52.7091	-5.5941	-2.92828
3	-3.58192	-16.8204	-106.373	5.59057	-111.03	-133.064	-77.7934	-5.55152	-3.88967
4a/b	-4.85869	-15.3973	-116.986	-25.9755	-112.269	-132.434	-90.7863	-5.34613	-4.32316
auranofin	-4.83363	-12.0032	-175.936	-44.9353	-167.046	-172.59	-129.802	-5.38859	-4.18717

Table S5 Crystallographic data collection and structure refinement information for gold(III) complexes **2a**, **3**, **4a** and **4b**

	2a	**3**	**4a**	**4b**
Crystal data				
Chemical formula	$C_9H_{15}Au_2Cl_5N_4O_4$	$C_{11}H_{21}AuCl_2N_4O_5$	$C_{12}H_{19}AuCl_2N_4O_3$	$C_{12}H_{21}Au_2Cl_5N_4O_4$
M_r	814.43	557.18	535.18	856.51
Crystal system, space group	Monoclinic, *C*2	Triclinic, *P*1	Orthorhombic, $P2_12_12_1$	Orthorhombic, $P2_12_12_1$
a, *b*, *c* (Å)	27.3091(7), 8.6678(2), 8.6743(2)	6.9310(4), 11.7421(7), 12.5963(8)	9.8509(2), 10.7911(2), 15.3736(3)	8.3519(1), 11.1268(1), 24.3707(2)
α, β, γ (°)	90, 108.081(2), 90	68.927(6), 79.453(5), 88.221(5)	90, 90, 90	90, 90, 90
V (Å^3)	1951.90(8)	939.75(11)	1634.25(6)	2264.77(4)
Z	4	2	4	4
μ (mm^{-1})	15.72	8.14	9.35	13.56
Crystal size (mm)	0.45 × 0.35 × 0.35	0.45 × 0.20 × 0.13	0.20 × 0.15 × 0.15	0.25 × 0.10 × 0.07
Data collection				
T_{min}, T_{max}	0.019, 0.070	0.105, 0.532	0.300, 0.505	0.113, 0.528
No. of measured, independent and observed [$I > 2\sigma(I)$] reflections	18553, 3462, 3403	21633, 6620, 6230	18637, 2895, 2795	40694, 3993, 3835
R_{int}	0.038	0.028	0.040	0.038
$(\sin\theta/\lambda)_{max}$ (Å^{-1})	0.595	0.595	0.595	0.595
Refinement				
$R[F^2 > 2\sigma(F^2)]$, $wR(F^2)$, *S*	0.017, 0.042, 1.09	0.023, 0.055, 1.06	0.019, 0.039, 1.03	0.018, 0.041, 1.05
No. of reflections	3462	6620	2895	3993
No. of parameters	220	421	203	245
No. of restraints	1	3	0	0
$\Delta\rho_{max}$, $\Delta\rho_{min}$ (e Å^{-3})	0.70, -0.61	0.90, -0.48	0.62, -0.39	0.66, -0.76
Absolute structure parameter	-0.025(4)	-0.012(4)	-0.016(5)	-0.015(3)

Table S6 Lethal and teratogenic effects observed in zebrafish (*Danio rerio*) embryos at different hours post fertilization (hpf)

Category	Developmental endpoints	Exposure time (hpf)			
		24	48	72	96/114
Lethal effect	Egg coagulation[a]	●	●	●	●
	No somite formation	●	●	●	●
	Tail not detached	●	●	●	●
	No heartbeat		●	●	●
Teratogenic effect	Malformation of head	●	●	●	●
	Malformation of eyes[b]	●	●	●	●
	Malformation of sacculi/otoliths[c]	●	●	●	●
	Malformation of chorda	●	●	●	●
	Malformation of tail[d]	●	●	●	●
	Scoliosis	●	●	●	●
	Heartbeat frequency		●	●	●
	Blood circulation		●	●	●
	Pericardial edema	●	●	●	●
	Yolk edema	●	●	●	●
	Yolk deformation	●	●	●	●
	Growth retardation[e]	●	●	●	●

[a]No clear organs structure is recognized.
[b]Malformation of eyes was recorded for the retardation in eye development and abnormality in shape and size.
[c]Presence of no, one or more than two otoliths per sacculus, as well as reduction and enlargement of otoliths and/or sacculi (otic vesicles).
[d]Tail malformation was recorded when the tail was bent, twisted or shorter than to control embryos as assessed by optical comparation.
[e]Growth retardation was recorded by comparing with the control embryos in development or size (before hatching, at 24 hpf and 48 hpf) or in a body length (after hatching, at and onwards 72 hpf) using by optical comparation using a inverted microscope (CKX41; Olympus, Tokyo, Japan).

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