Supplementary Tables 1-8

Inhibitors for a conserved filarial catechol-*O*-methyltransferase possess *in vivo* curative potency against *Brugia malayi* infection

Supplementary Table 1. *Brugia malayi* microfilariae burdens in peritoneal lavage of gerbils 4 weeks after end of treatment with BmMT inhibitors.

Treatment	Total microfilariae count in peritoneum of individual gerbils (n = 5)					Median worm burden	Median reduction (%)
DMSO	2.9×10^6	3.9×10^6	4.3×10^6	5.0×10^6	6.9×10^6	4.3×10^6	Baseline
Ivermectin	0.0	1.2×10^5	3.7×10^5	3.9×10^5	1.7×10^6	3.7×10^5	91.4
NSC145612	8.1×10^4	2.1×10^5	4.9×10^5	3.1×10^6	ND	3.7×10^5	91.7
NSC133100	0.0	0.0	0.0	0.0	ND	0.0	100
NSC56410	0.0	0.0	0.0	2.9×10^4	1.9×10^5	0.0	100

ND: not determined because animal accidentally died

Supplementary Table 2. *Brugia malayi* microfilariae burden in gerbils' peripheral blood 4 weeks after end of treatment with BmMT inhibitors.

Treatment	Microfilariae count per mL of blood of individual gerbils (n = 5)					Median worm burden	Median reduction (%)
DMSO	3350	4100	5300	5800	6800	5300	Baseline
Ivermectin	3000	8900	34000	55200	62500	34000	-541.5
NSC145612	1990	2300	6250	16500	ND	4275	19.3
NSC133100	0	0	0	750	ND	0	100
NSC56410	0	0	0	0	0	0	100

ND: not determined because animal accidentally died

Supplementary Table 3. Flexible docking score (in kcal/mol) of best selected pose for BmMT inhibitors.

Compound	NSC133100	NSC177383	NSC145612	NSC56410
Docking, S-score	- 9.96	- 9.71	- 10.38	- 6.71

Supplementary Table 4. *S*-adenosyl-*L*-methionine (SAM) contact residues (persistence %). Residue-level contact persistence between the SAM co-factor and each protein residue across 1500 ns MD trajectories. A contact is counted in a frame when any heavy atom of the residue lies within 4.5 Å of any heavy atom of SAM. The tabulated values are the percentage of frames in which this contact condition holds. "—" indicates the interaction was not observed in the occupancy range shown.

Residue	DNC	NSC133100	NSC177383	NSC145612	NSC56410
P116	100.0	100.0	100.0	100.0	100.0
D115	100.0	100.0	100.0	100.0	100.0
G92	100.0	100.0	100.0	100.0	100.0
E148	100.0	100.0	100.0	100.0	100.0
G94	100.0	100.0	100.0	100.0	100.0
C93	100.0	100.0	100.0	100.0	100.0
M38	100.0	100.0	98.4	99.8	73.3
S149	100.0	100.0	100.0	89.3	71.5
N39	100.0	99.3	99.1	96.3	71.2
E90	93.4	100.0	99.6	100.0	99.5
Y70	98.4	—	99.7	95.3	99.7
Q95	98.5	89.7	93.4	90.9	79.9
A131	83.6	99.3	100.0	94.5	73.0
I117	89.1	99.9	99.1	97.1	92.1
F37	76.6	99.8	71.2	93.8	99.8
I147	93.3	95.1	79.6	97.3	92.9
N27	93.7	91.9	99.3	92.0	72.5
V91	81.6	94.8	98.7	92.0	76.1
N130	80.9	79.5	100.0	84.6	79.7
E132	80.3	79.9	95.7	78.6	66.9
I114	82.1	79.5	82.9	84.8	77.9
L152	55.6	75.7	68.5	80.6	81.3
Y153	99.4	59.0	63.2	—	71.7
I118	72.6	78.1	46.7	78.9	—
G129	66.7	49.4	89.9	66.0	54.1
G96	52.9	60.6	53.5	—	41.1
G97	—	—	86.1	—	—
G98	65.2	57.9	54.6	—	—
R36	—	41.7	60.8	—	59.1
Y23	64.1	31.9	30.3	—	42.5
P24	69.6	—	32.9	—	—
H151	—	35.6	25.0	—	—
G154	40.7	—	—	—	—
S150	—	—	34.2	—	—
N146	—	—	33.1	—	—

Supplementary Table 5. *S*-adenosyl-*L*-methionine (SAM) hydrogen bond partners (max occupancy %, per residue). The highest-occupancy hydrogen bond per residue between protein and SAM across the trajectories. An H-bond is counted when the donor–acceptor distance is ≤ 3.5 Å and the donor–H·acceptor angle is ≥ 120°. Where a single residue forms multiple H-bonds with different atom pairs (common for ASP115 via OD1/OD2 and for GLU90 via OE1/OE2), only the maximum-occupancy pair is reported and the donor → acceptor atom labels are shown in parentheses; lower-occupancy pairs from the same residue are not tabulated. ASP115 (via SAM:O2'/O3'→OD1/OD2) and GLY92 (via SAM:N → backbone O) emerge as the most consistent H-bond anchors across all five systems and represent the defining H-bond signature of this SAM binding mode. "—" indicates the interaction was not observed in the occupancy range shown.

Residue	DNC	**NSC133100**	**NSC177383**	**NSC45612**	**NSC56410**
G92 (N→O)	81.3	91.1	71.5	89.2	93.9
D115 (O2'→OD2)	80.1	91.9	100.0	85.7	69.7
Y70 (N/OH)	75.4	77.7	86.3	54.7	58.0
E90 (N→OE1/OE2)	72.7	50.8	56.8	82.5	69.3
A131 (N→N1)	48.7	56.5	95.3	73.5	62.0
C93 (O3'→O)	44.4	52.2	64.5	—	—
S149 (OG→O4')	43.3	—	74.7	—	—
N130 (N6→OD1)	—	59.7	69.6	—	66.1
E148 (CE→OE1)	—	43.5	—	—	—
M38 (CE→O)	—	35.8	19.5	—	45.7
N27 (O3'→OD1)	—	32.9	68.5	—	—
P116	—	32.9	73.1	—	—
G94 (N→O3')	—	—	52.6	—	52.3
N39 (ND2→O)	—	—	13.0	—	53.5
Q95	—	—	46.3	—	—
Y153	—	—	51.5	—	—
V91	—	—	33.0	—	—
Y23	—	—	21.6	—	—
I118	—	—	17.1	—	—
E132	—	—	12.9	—	—
L152	—	—	10.4	—	—

Supplementary Table 6. Ligand Contact Residues (Persistence %). Residue-level contact persistence between the ligand and each protein residue across 1500 ns MD trajectories. A contact is counted in a frame when any heavy atom of the residue lies within 4.5 Å of any heavy atom of ligand. The tabulated values are the percentage of frames in which this contact condition holds. "—" indicates the interaction was not observed in the occupancy range shown.

Residue	DNC	NSC133100	NSC177383	NSC145612	NSC56410
GLU148	100.0	100.0	99.4	100.0	76.9
THR240	98.3	100.0	100.0	99.1	95.3
HIE151	93.6	100.0	100.0	90.2	78.9
LEU178	99.9	100.0	45.5	100.0	24.9
ASP177	100.0	100.0	—	100.0	12.7
ILE147	99.5	66.7	—	99.9	—
TYR23	—	100.0	100.0	99.2	93.8
LEU40	66.7	99.4	—	79.2	39.5
TYR241	52.8	97.3	19.7	39.7	36.9
TYR259	66.5	89.7	—	80.9	20.5
MET38	5.9	99.9	59.3	20.5	33.0
ARG179	87.8	49.4	—	29.0	—
CYS242	62.9	60.2	13.3	69.4	22.2
LYS257	57.2	47.2	27.0	66.8	—
ASN27	—	91.1	60.9	—	17.3
THR239	53.1	28.0	65.2	90.6	27.4
LEU152	36.9	42.8	99.3	53.7	63.0
ARG19	—	34.8	97.7	96.2	65.8
PRO24	—	50.1	97.7	36.6	54.9
LEU20	—	15.7	96.7	40.8	53.3
SER149	7.7	41.4	58.0	55.4	55.4
SER236	—	33.5	40.5	89.5	19.7
ASP18	—	42.3	53.9	78.4	44.2
SER248	39.8	29.2	35.6	83.7	12.6
ILE237	—	69.8	28.8	—	17.3
LEU26	—	100.0	62.6	—	20.1
LEU22	—	36.5	—	15.8	26.1
SER150	10.0	14.7	30.7	10.9	21.4
ASN39	17.2	28.1	—	11.0	30.1
ILE117	—	61.4	9.3	—	20.1
ILE21	—	—	35.9	—	25.7
TYR153	—	13.3	33.3	—	11.1
LEU16	—	—	35.9	—	—
GLY154	—	—	28.6	—	—
ARG251	—	—	—	32.7	—
MET222	—	28.4	—	—	—
PHE14	—	26.4	—	—	—
PHE233	—	23.9	—	—	—
TRP175	—	12.7	—	—	—
TYR219	—	14.3	—	—	—
GLN95	—	—	10.1	—	—
GLN183	—	—	9.5	—	—

Supplementary Table 7. Overall Protein-Ligand Interaction Network Analysis.

System	H-bonds ≥10%	Hydrophobic ≥20%	SAM Contact (%)	Mg^{2+} Contact (%)	Dominant Cluster (%)
NSC133100	5	24	99.8	100.0	76
NSC145612	15	12	26.6	100.0	88
NSC177383	27	9	0.0	0.0	60
NSC56410	19	7	51.5	0.6	31
DNC (ref)	8	6	0.0	100.0	75

Supplementary Table 8. MM-GB/SA Binding Free Energies.

Ligand	ΔEvdw	ΔEele	ΔEGB	ΔESURF	ΔGgas	ΔGsolv	ΔGbind
ref_DNC	-12.86 ± 1.70	-257.51 ± 13.56	254.15 ± 13.05	-3.10 ± 0.35	-270.37 ± 14.59	251.06 ± 12.82	**-19.31 ± 1.95**
NSC133100	-52.45 ± 0.47	-47.84 ± 1.91	80.22 ± 0.47	-7.44 ± 0.24	-100.29 ± 1.87	72.78 ± 0.56	**-27.51 ± 1.81**
NSC145612	-38.73 ± 8.92	-52.50 ± 7.71	76.78 ± 6.80	-5.46 ± 0.77	-91.24 ± 12.46	71.32 ± 6.44	**-19.92 ± 6.76**
NSC177383	-51.43 ± 6.55	-22.94 ± 0.93	48.78 ± 2.94	-6.11 ± 0.67	-74.37 ± 7.46	42.68 ± 3.15	**-31.69 ± 8.69**
NSC56410	-30.53 ± 3.49	133.53 ± 9.32	-118.04 ± 8.19	-3.46 ± 0.21	103.00 ± 12.74	-121.50 ± 8.29	**-18.50 ± 4.46**

All values are mean ± SD across three independent MD replicas (kcal/mol). MM-GB/SA calculations used igb=5 (Onufriev–Bashford–Case GB model) with 0.15 M salt concentration. ΔGbind = ΔGgas + ΔGsolv. ΔEvdw: van der Waals; ΔEele: electrostatics; ΔEGB: polar solvation (GB); ΔESURF: nonpolar solvation (LCPO).