

Raw Data for graphs and tables included in the manuscript

Figure 2b. Titration of BmMT protein concentration in the MTase-Glo methyltransferase assay for the methylation of dopamine (40 μ M) with SAM (20 μ M) as methyl donor

BmMT (μg/mL)	0	73	147	294	368
RLU-1	0	10974	55308	108562	135135
RLU-2	0	19363	56276	108922	133899
RLU-3	0	17602	49363	106138	143824
RLU-4	0	18100	58509	106162	141969
RLU-5	0	15591	58441	105098	138209
Mean RLU	0	16326	55579.4	106976.4	138607.2
SEM	0	1314.272	1496.313	669.1498	1707.613

*RLU, Relative Luminescence Units

Figure 2c. Titration of dopamine concentration in the MTase-Glo methyltransferase SAM (20 μ M) as co-substrate and BmMT enzyme

Dopamine (μM)	0	10	20	40	60	80	100	120
RLU-1	0	974	3122	2369	3109	3744	3550	3346
RLU-2	0	1865	2297	3826	3221	4241	4667	3948
RLU-3	0	617	2657	2389	4797	4993	4092	3002
Mean RLU	0	1152	2692	2861.333	3709	4326	4103	3432
SEM	0	302.9994	194.9786	393.8517	444.9579	296.4302	263.3177	225.7216

*RLU, Relative Luminescence Units

Figure 2d. Titration of SAM concentration in the MTase-Glo methyltransferase assay for the methylation of dopamine (40 μ M) with BmMT enzyme

SAM (μM)	0	10	20	30	40	50	60
RLU-1	0	3699	5506	8210	7945	10819	15024
RLU-2	0	4572	7279	6451	8268	10868	10653
RLU-3	0	6220	7554	9058	10000	11800	8712
Mean RLU	0	4830.333	6779.667	7906.333	8737.667	11162.33	11463
SEM	0	603.4921	523.9967	626.8568	520.9385	260.5824	1524.06

*RLU, Relative Luminescence Units

Figure 3a. Inhibitory effect of fixed concentrations of 50 μ M of natural products on the enzymatic activity of the BmMT protein

BmMT inhibitors (μM)	NSC56410	NSC227186	NSC62709	NSC177383	NSC133100	NSC145612	NSC35676
Mean percent inhibition (MPI)	28.85	23.04	21.92	44.94	41.33	44.90	46.13
	20.58	19.39	18.95	41.02	32.53	44.76	40.96
	28.30	18.54	19.17	39.51	35.84	43.90	40.73
Average MPI	25.91	20.32	20.01	41.83	36.57	44.52	42.61
SEM	2.18	1.13	0.78	1.32	2.09	0.25	1.44

Figure 3b. Inhibitory effect of varying concentrations of NSC177383 on the enzymatic activity of the BmMT protein

NSC177383 concentrations (μM)	NSC177383 (MPI)			Average	SEM
0	0	0	0	0.00	0.00
10	32.02	16.81	10.61	19.81	5.19
20	29.23	30.67	43.29	34.39	3.65
40	47.04	39.87	49.79	45.56	2.42
60	72.52	65.16	67.02	68.23	1.81
80	68.11	78.63	80.51	75.75	3.15
100	79.13	104.75	100.77	94.88	6.50
120	90.76	96.03	97.46	94.75	1.66

Figure 3b. Inhibitory effect of varying concentrations of NSC133100 on the enzymatic activity of BmMT protein

NSC133100 concentrations (μM)	NSC133100 (MPI)			Average	SEM
0	0	0	0	0	0
10	9.88	-0.28	2.97	4.18	2.44
20	0.85	6.00	13.31	6.73	2.95
40	21.0	22.92	27.85	23.95	1.65
60	17.00	32.59	26.21	25.27	3.69
80	44.26	38.68	42.42	41.78	1.34
100	47.58	72.88	75.26	65.24	7.23
120	54.88	81.88	66.83	67.86	6.37

Figure 3b. Inhibitory effect of varying concentrations of NSC56410 on the enzymatic activity of BmMT protein

NSC56410 concentrations (μM)	NSC56410 (MPI)			Average	SEM
0	0	0	0	0	0
10	17.93	18.34	4.70	13.65	3.65
20	34.26	31.73	11.57	25.86	5.86
40	40.20	32.82	34.81	35.94	1.79
60	48.16	55.52	42.47	48.72	3.08
80	55.61	50.45	44.98	50.35	2.50
100	57.29	52.58	44.66	51.51	3.01
120	53.71	59.98	56.65	56.78	1.47

Figure 3b. Inhibitory effect of varying concentrations of NSC145612 on the enzymatic activity of BmMT protein

NSC145612 concentrations (μM)	NSC145612 (MPI)			Average	SEM
0	0	0	0	0	0
10	52.70	59.66	32.38	48.25	6.68
20	55.30	61.06	30.05	48.80	7.77
40	64.96	65.40	56.39	62.25	2.39
60	71.43	83.11	71.70	75.41	3.14
80	81.55	99.28	79.53	86.78	5.12
100	90.72	103.80	101.74	98.75	3.31
120	93.67	110.38	121.51	108.52	6.60

Figure 4a. In vitro analysis of the effects of varying concentrations of ivermectin on live *B. malayi* microfilariae

Ivermectin (μ M)	Completely immotile microfilariae (%)														
	0 h			48 h			72 h			96 h			120 h		
0	0	0	0	3.7	3.0	1.7	3.0	2.0	6.0	4.0	2.0	3.0	4.0	5.0	7.0
2.5	0	0	0	2.0	3.0	2.3	7.6	5.4	8.0	12.0	8.0	10.0	14.0	10.0	13.0
5	0	0	0	1.0	2.3	2.6	9.4	6.3	7.0	11.0	10.0	9.0	17.0	10.0	16.0
10	0	0	0	3.0	3.0	2.0	9.0	7.2	10.2	25.4	28.4	20.6	45.2	47.0	54.0
15	0	0	0	2.4	6.0	4.2	10.0	12.7	10.8	29.4	34.5	23.6	65.0	63.0	66.0
20	0	0	0	16.9	17.3	16.3	18.0	21.0	19.0	43.0	39.0	47.0	75.0	72.0	69.0
30	0	0	0	32.0	27.0	38.5	45.0	42.0	54.0	83.0	82.0	79.0	96.0	94.0	93.0

Figure 4a. Mean values for the in vitro effects of varying concentrations of ivermectin on live *B. malayi* microfilariae

Ivermectin (μ m)	Mean completely immotile (%)					SEM				
	0 h	48 h	72 h	96 h	120 h	0 h	48 h	72 h	96 h	120 h
0	0	2.8	3.7	3.0	5.3	0	0.49	0.98	0.47	0.72
2.5	0	2.4	7.0	10.0	12.3	0	0.24	0.66	0.94	0.98
5	0	2.0	7.6	10.0	14.3	0	0.40	0.76	0.47	1.78
10	0	2.7	8.8	24.8	48.7	0	0.27	0.71	1.87	2.18
15	0	4.2	11.2	29.2	64.7	0	0.85	0.65	2.57	0.72
20	0	16.8	19.3	43.0	72.0	0	0.25	0.72	1.89	1.41
30	0	32.5	47.0	81.3	94.3	0	2.71	2.94	0.98	0.72

Ivermectin (μ M)	Completely immotile microfilariae (%)														
	0 h			48 h			72 h			96 h			120 h		
0	0	0	0	0	18	0	11	6	8	10	25	13	14	22	22
6.3	0	0	0	15	15	14	12	21	43	33	49	39	41	23	29
12.5	0	0	0	22	20	20	43	52	75	60	65	78	70	48	71
25	0	0	0	83	73	89	96	98	96	100	100	100	100	100	100
37.5	0	0	0	100	100	100	100	100	100	100	100	100	100	100	100

Figure 4b. *In vitro* analysis of the effects of varying concentrations of NSC177383 on live *B. malayi* microfilariae

Figure 4b. Mean values for the *in vitro* effects of varying concentrations of NSC177383 on live *B. malayi* microfilariae

Ivermectin (μ m)	Mean completely immotile microfilariae (%)					SEM				
	0 h	48 h	72 h	96 h	120 h	0 h	48 h	72 h	96 h	120 h
0	0	5.9	8.1	16.2	19.3	0	4.8	1.3	3.6	2.1
6.3	0	14.5	25.6	40.1	31.0	0	0.4	7.5	3.7	4.2
12.5	0	21.0	56.6	67.5	62.7	0	0.5	7.7	4.2	6.0
25	0	81.7	96.7	100	100	0	3.7	0.3	0	0
37.5	0	100	100	100	100	0	0	0	0	0

Figure 4c. *In vitro* analysis of the effects of varying concentrations of NSC133100 on live *B. malayi* microfilariae

NSC133100 (μ M)	Completely immotile microfilariae (%)														
	0 h			48 h			72 h			96 h			120 h		
0	0	0	0	2.8	0.0	10.8	9.5	6.8	12.6	8.6	18.3	27.1	10.3	13.8	13.8
6.25	0	0	0	2.4	10.7	10.4	31.1	30.4	44.7	37.0	38.1	41.9	36.0	25.5	31.7
12.5	0	0	0	12.0	21.0	7.3	55.2	52.7	51.8	46.5	46.2	64.4	45.8	36.6	54.0
25	0	0	0	24.3	27.3	22.0	79.0	56.5	61.4	81.8	87.8	91.4	97.5	95.7	98.5
37.5	0	0	0	65.0	77.6	83.2	76.0	66.3	71.3	98	97.5	97.6	100	100	100
50	0	0	0	85.3	85.1	81.3	92.4	85.3	81.6	100	100	100	100	100	100
62.5	0	0	0	91.7	87.3	98.0	97.5	96.5	98.5	100	100	100	100	100	100
75	0	0	0	93.7	98.1	97.8	100	100	100	100	100	100	100	100	100
87.5	0	0	0	100	100	100	100	100	100	100	100	100	100	100	100
100	0	0	0	100	100	100	100	100	100	100	100	100	100	100	100

Figure 4c. Mean values for the *in vitro* effects of varying concentrations of NSC133100 on live *B. malayi* microfilariae

NSC133100 (μ M)	Mean completely immotile microfilariae (%)					SEM				
	0 h	48 h	72 h	96 h	120 h	0 h	48 h	72 h	96 h	120 h
0	0	5	10	18	13	0.0	2.0	1.0	4.0	1.0
6.25	0	8	35	39	31	0.0	2.0	4.0	1.0	3.0
12.5	0	13	53	52	45	0.0	3.0	1.0	5.0	4.0
25	0	25	66	87	97	0.0	1.0	6.0	2.0	6.7
37.5	0	75	71	97.7	100	0.0	4.0	2.0	1.2	0.0
50	0	84	86	100	100	0.0	1.0	3.0	0.0	0.0
62.5	0	92	97.5	100	100	0.0	2.0	5.0	0.0	0.0
75	0	97	100	100	100	0.0	1.0	0.0	0.0	0.0
87.5	0	100	100	100	100	0.0	0.0	0.0	0.0	0.0
100	0	100	100	100	100	0.0	0.0	0.0	0.0	0.0

Figure 4d. *In vitro* analysis of the effects of varying concentrations of NSC145612 on live *B. malayi* microfilariae

NSC145612 (μ M)	Completely immotile microfilariae (%)														
	0 h			48 h			72 h			96 h			120 h		
0	0	0	0	0.0	10.5	0.0	8.8	7.2	6.2	14.1	12.3	12.0	15.5	16.0	21.9
6.25	0	0	0	10.2	5.8	5.8	18.1	19.0	22.8	12.8	11.0	23.7	21.5	35.1	30.1
12.5	0	0	0	2.9	10.3	9.8	12.4	24.4	20.8	24.2	37.8	18.7	34.8	24.6	30.9
25	0	0	0	21.4	21.7	15.5	31.4	20.5	36.6	19.4	37.4	31.6	30.8	43.0	33.2
37.5	0	0	0	29.2	30.9	22.9	23.3	32.7	31.9	18.6	46.7	35.6	63.3	51.0	50.6
50	0	0	0	34.5	27.0	32.4	42.3	47.7	58.8	56.4	59.7	65.1	65.1	74.5	45.7
62.5	0	0	0	40.4	38.2	41.0	86	87	84	91.5	92.5	89.5	100	100	100
75	0	0	0	45.3	50.0	41.4	94	95.5	93.5	100	100	100	100	100	100
87.5	0	0	0	43.8	48.4	51.8	100	100	100	100	100	100	100	100	100
100	0	0	0	38.4	77.7	75.0	100	100	100	100	100	100	100	100	100

Figure 4d. Mean values for the *in vitro* effects of varying concentrations of NSC145612 on live *B. malayi* microfilariae

NSC145612 (μ M)	Mean completely immotile microfilariae (%)					SEM				
	0 h	48 h	72 h	96 h	120 h	0 h	48 h	72 h	96 h	120 h
0	0	4.00	7.00	13.00	18.00	0	3.00	1.00	1.00	1.00
6.25	0	7.00	20.00	16.00	29.00	0	1.00	1.00	3.00	3.00
12.5	0	8.00	19.00	27.00	30.00	0	2.00	3.00	5.00	2.00
25	0	20.00	29.00	29.00	36.00	0	2.00	4.00	4.00	3.00
37.5	0	28.00	29.00	34.00	55.00	0	2.00	2.00	7.00	3.00
50	0	31.00	50.00	60.00	62.00	0	2.00	4.00	2.00	7.00
62.5	0	40.00	85.67	91.17	100	0	1.00	7.20	7.20	0.00
75	0	46.00	94.33	100.00	100	0	2.00	4.90	0.00	0.00
87.5	0	48.00	100	100	100	0	2.00	0.00	0.00	0.00
100	0	64.00	100	100	100	0	10.00	0.00	0.00	0.00

Figure 4e. *In vitro* analysis of the effects of varying concentrations of NSC56410 on live *B. malayi* microfilariae

NSC56410 (μ M)	Completely Immotile Microfilariae (%)														
	0 h			48 h			72 h			96 h			120 h		
0	0	0	0	12.4	4.4	5.9	13.1	9.0	7.9	21.9	15.8	29.0	29.3	22.5	38.2
6.25	0	0	0	16.3	16.4	11.6	8.7	12.5	24.1	23.6	24.6	32.9	41.6	37.0	46.9
12.5	0	0	0	9.3	1.2	13.1	18.3	31.5	22.6	37.1	31.5	33.8	40.6	34.3	40.4
25	0	0	0	14.3	8.2	9.0	22.4	20.6	17.5	43.2	46.5	40.2	62.2	56.0	50
37.5	0	0	0	41.9	17.1	39.2	17.2	13.8	22.9	60	44.7	38.9	64.7	61.9	55
50	0	0	0	22.9	34.5	30.6	17.6	16.7	23.4	70	65	68	75	70	70
62.5	0	0	0	30.7	23.9	26.4	51	62.5	64	65	65	70	75	75	75
75	0	0	0	22.2	43.4	32.7	55	55	60	70	72.5	70	75	80	80
87.5	0	0	0	60	65	60	60	55	55	68	70	65	85	85	80
100	0	0	0	59.6	60	61.5	60	60	60	70	70	68	80	80	80

Figure 4e. Mean values for the *in vitro* effects of varying concentrations of NSC56410 on live *B. malayi* microfilariae

NSC56410 (μ M)	Mean completely immotile microfilariae (%)					SEM				
	0 h	48 h	72 h	96 h	120 h	0 h	48 h	72 h	96 h	120 h
0	0	8.0	10.0	10.0	11.0	0	2.00	1.00	3.00	0.82
6.25	0	15.0	15.0	14.0	16.0	0	1.00	4.00	2.00	1.70
12.5	0	8.0	24.0	23.0	28.0	0	3.00	3.00	1.00	1.70
25	0	10.0	20.0	50.0	60.0	0	2.00	1.00	1.00	3.45
37.5	0	21.0	22.0	57.0	68.0	0	6.00	2.00	5.00	2.51
50	0	29.0	19.0	63.7	73.3	0	3.00	2.00	1.19	2.36
62.5	0	27.0	55.0	68.5	75	0	2.00	3.00	1.36	0.00
75	0	33.0	59.0	57.0	78	0	5.00	1.36	0.68	2.36
87.5	0	45.0	65	67	80	0	1.00	1.36	1.19	2.36
100	0	55.0	68	72	83	0	0.00	0.00	0.54	0.00

Figure 4f. Dose-response curve analysis of ivermectin and BmMT inhibitors (NSC177383,

Compound concentrations (μM)	Completely immotile microfilariae (%)														
	Ivermectin			NSC177383			NSC133100			NSC145612			NSC56410		
0	4	2	3	10	25	13	9	18	27	14	12	12	10	11	12
2.5	12	8	10												
5	11	10	9												
6.25				33	49	39	37	38	42	13	11	24	17	18	14
10	25	28	20												
12.5				60	65	78	46	46	64	24	38	19	29	30	26
15	29	34	23												
20	43	39	47												
25				100	100	100	82	88	91	19	37	32	65	62	55
30	83	82	79												
37.5				100	100	100	98	97.5	97.6	19	47	36	65	70	70
50				100	100	100	100	100	100	56	60	65	75	75	70
62.5				100	100	100	100	100	100	91.5	92.5	89.5	75	75	75
75				100	100	100	100	100	100	100	100	100	75	80	80
87.5				100	100	100	100	100	100	100	100	100	80	80	80
100				100	100	100	100	100	100	100	100	100	85	85	80

NSC133100, NSC145612 and NSC56410) against *B. malayi* microfilariae motility at 96 h post-treatment

Figure 5b. *In vivo* antifilarial efficacy of BmMT inhibitors against adult worms in *B. malayi*-infected gerbils

Animal number	Adult <i>B. malayi</i> worm count per gerbil				
	Vehicle control (n = 5)	Ivermectin (n = 5)	NSC145612 (n= 4)	NSC133100 (n= 4)	NSC56410 (n= 5)
Gerbil 1	100	8	15	0	4
Gerbil 2	80	3	12	0	0
Gerbil 3	72	12	45	0	0
Gerbil 4	85	15	30	12	0
Gerbil 5	55	45	Accidental death	Accidental death	4

Figure 5c. *In vivo* antifilarial efficacy of BmMT inhibitors against microfilariae in *B. malayi*-infected gerbils

Animal number	<i>B. malayi</i> microfilariae count from peritoneal lavage per gerbil				
	Vehicle control (n = 5)	Ivermectin (n = 5)	NSC145612 (n= 4)	NSC133100 (n= 4)	NSC56410 (n= 5)
Gerbil 1	2.9×10^6	0	8.1×10^4	0	0
Gerbil 2	3.9×10^6	1.2×10^5	2.1×10^5	0	0
Gerbil 3	4.3×10^6	3.7×10^5	4.9×10^5	0	0
Gerbil 4	5.0×10^6	3.9×10^5	3.1×10^6	0	2.9×10^4
Gerbil 5	6.9×10^6	1.7×10^6	Accidental death	Accidental death	1.9×10^5

Figure 5d. *In vivo* antifilarial efficacy of BmMT inhibitors against microfilariae in *B. malayi*-infected gerbils

Animal number	<i>B. malayi</i> microfilariae count from peripheral blood per gerbil				
	Vehicle control (n = 5)	Ivermectin (n= 5)	NSC145612 (n= 4)	NSC133100 (n= 4)	NSC56410 (n= 5)
Gerbil 1	5300	8900	1990	0	0
Gerbil 2	4100	3000	16500	0	0
Gerbil 3	5800	34000	2300	0	0
Gerbil 4	3350	62500	6250	50	0
Gerbil 5	6800	55200	Accidental death	Accidental death	0

Figure 6a. *In vitro* effects of 50 μ M BmMT inhibitors and 30 μ M ivermectin against *B. malayi* adult worms

[illegible]

Figure 6b. *In vitro* analysis of the effects of varying concentrations of NSC177383 on live *B. malayi* adult

NSC177383 (μ M)	Completely immotile adult worm (%)														
	0 h			24 h			48 h			72 h			96 h		
0	0	0	0	0	0	0	0	0	0	0	0	0	5	7	5
10	0	0	0	5	5	0	25	25	25	50	50	50	65	75	75
20	0	0	0	15	10	10	35	35	40	100	75	75	100	100	100
40	0	0	0	20	25	30	65	55	60	100	100	100	100	100	100
60	0	0	0	35	35	35	100	75	50	100	100	100	100	100	100

Figure 6c. *In vitro* analysis of the effects of varying concentrations of NSC133100 on live *B. malayi* adult

[illegible]

Figure 6d. *In vitro* analysis of the effects of varying concentrations of NSC56410 on live *B. malayi* adult

NSC56410 (μ M)	Completely immotile adult worm (%)														
	0 h			24 h			48 h			72 h			96 h		
0	0	0	0	0	0	0	0	0	0	0	0	0	0	10	5
10	0	0	0	5	0	10	25	25	25	40	35	40	50	65	50
20	0	0	0	25	20	30	35	40	65	65	65	60	75	75	75
40	0	0	0	35	35	35	70	65	70	75	75	100	100	100	100
60	0	0	0	40	35	40	100	75	75	100	100	100	100	100	100

Figure 6e. Dose-response curve analysis of BmMT inhibitors (NSC177383, NSC56410 and NSC133100) against *B. malayi* adult worm motility 72 h post-treatment

Compound concentrations (μ M)	Completely immotile adult worm (%)								
	NSC177383			NSC56410			NSC133100		
0	0	0	0	0	0	0	5	0	5
10	50	50	50	40	35	40	25	25	15
20	100	75	75	65	65	60	35	40	35
40	100	100	100	75	75	100	50	65	60
60	100	100	100	100	100	100	95	100	100

Figure 7c. Quantification of Catecholamine levels using ELISA from BmMT-target and off-target morpholino-treated *B. malayi* worm lysates 48 h post-treatment

Background-corrected normalized absorbance		
	off-target	BmMT-target
well-1	0.0252	0.0428
well-2	0.0268	0.0667
well-3	0.0348	0.0584
well-4	0.0293	0.0704
well-5	0.0458	0.0417
Normalized catecholamines using the standard curve linear regression equation $y = 0.0023x + 0.018$, $R^2 = 0.997$		
	off-target	BmMT-target
well-1	3.14	10.80
well-2	3.84	21.17
well-3	7.30	17.54
well-4	4.90	22.80
well-5	12.08	10.30
Mean	6.30	16.52
SEM	1.44	2.31

Figure 7d. Quantification of Catecholamine levels using ELISA from NSC56410-treated *B. malayi* worm lysates 48 h post-treatment

Background-corrected normalized absorbance		
	DMSO	NSC56410
well-1	0.0684	0.0780
well-2	0.0690	0.0764
well-3	0.0657	0.0748
Normalized catecholamine load from the standard curve linear regression equation $y = 0.0023x + 0.018$, $R^2 = 0.997$		
	DMSO	NSC56410
well-1	21.90	26.09
well-2	22.16	25.39
well-3	20.72	24.70
Mean	21.60	25.39
SEM	0.36	0.33

Figure S2. Analysis of MTase-Glo detection interference by BmMT inhibitors

	Background corrected Luminescence				
	SAH only	NSC177383	NSC133100	NSC56410	NSC145612
RLU*-1	75194	75095	81980	82511	86681
RLU*-2	66821	77828	85148	85451	82838
RLU*-3	67779	79203	88980	82869	81683
RLU*-4	69892	73036	82688	88010	84345

*RLU= Relative Luminescence Units

Hours- post treatment	Third-stage larvae survival (%)																	
	DMSO			Ivermectin			NSC177383			NSC145612			NSC56410			NSC133100		
12 h	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100
24 h	83	100	100	100	100	71.4	33.3	0	0	71.4	71.4	54.5	70	50	50	25	50	71.4
48 h	83	100	100	86	86	71	0	0	0	71	33	36	50	50	50	50	40	33
72 h	83.0	71.0	75.0	86.0	86.0	71.0	0	0	0	71.0	33.0	18.0	30.0	50.0	50.0	50.0	40.0	33.0
96 h	83.0	71.0	50.0	86.0	86.0	71.0	0	0	0	57.0	0	0	30.0	17.0	50.0	25.0	40.0	33.0
120 h	83.0	71.0	50.0	86.0	86.0	71.0	0	0	0	42.0	0	0	30.0	17.0	50.0	0	0	0

Figure S3. Analysis of the effects of BmMT inhibitors on *B. malayi* third-stage (L3) larvae survival *in vitro*