Supplemental Information

Exploitation of mangrove endophytic fungi for infectious disease drug discovery

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Table S1. MIC and cytotoxicity for ESKAPE pathogens treated with mangrove fungal extracts.[a]

Sample ID[b]	Treatment[c]	Scaled Score[d] [46]	Cytotoxicity[e] IC_{50}	MIC (µg/mL) against Select Strains						Scaled Score Multiplier[d]					
				200	100	50	25	10	1	1	2	4	8	20	40
TAP14-34A-4	DNMT	96	>50	ESKAPE	SKA	EA	EA	A	A	6	3	2	2	1	1
CQ10-30A-4	CONTROL	82	8.4	ES	ES	ES	S	S	S	2	2	2	1	1	1
CQ10-30A-4	DNMT	75	7.0	S	S	S	S	S	S	1	1	1	1	1	1
CQ10-30A-4	HDAC	75	7.2	S	S	S	S	S	S	1	1	1	1	1	1
HF14-11A-2	CONTROL	75	>50	S	S	S	S	S	S	1	1	1	1	1	1
HF14-11A-2	HDAC	75	>50	S	S	S	S	S	S	1	1	1	1	1	1
HF14-37B-1B	DNMT	75	>50	S	S	S	S	S	S	1	1	1	1	1	1
HF14-5A-1	CONTROL	75	>50	S	S	S	S	S	S	1	1	1	1	1	1
KML12-19MG-C4	CONTROL	75	9.1	S	S	S	S	S	S	1	1	1	1	1	1
KML12-19MG-C4	HDAC	75	11	S	S	S	S	S	S	1	1	1	1	1	1
KML12-19MG-C5	DNMT	75	20	S	S	S	S	S	S	1	1	1	1	1	1
TAP14-218C-2	CONTROL	75	42	S	S	S	S	S	S	1	1	1	1	1	1
TAP14-218C-2	DNMT	75	>50	S	S	S	S	S	S	1	1	1	1	1	1
TAP14-218C-2	HDAC	75	44	S	S	S	S	S	S	1	1	1	1	1	1
TAP14-34A-4	CONTROL	55	>50	ESKAP	EKA	EA	EA	A		5	3	2	2	1	0
HF14-39B-7	CONTROL	35	>50	S	S	S	S	S		1	1	1	1	1	0
HF14-5A-1	HDAC	35	>50	S	S	S	S	S		1	1	1	1	1	0
KML12-11MG-C5	HDAC	35	32	S	S	S	S	S		1	1	1	1	1	0
KML12-17MG-C1	CONTROL	35	>50	S	S	S	S	S		1	1	1	1	1	0
KML12-17MG-C1	DNMT	35	>50	S	S	S	S	S		1	1	1	1	1	0
KML12-19MG-C4	DNMT	35	>50	S	S	S	S	S		1	1	1	1	1	0
KML12-19MG-C5	HDAC	35	>50	S	S	S	S	S		1	1	1	1	1	0
KML12-2MG-C1	CONTROL	35	37	S	S	S	S	S		1	1	1	1	1	0
KML12-2MG-C1	DNMT	35	>50	S	S	S	S	S		1	1	1	1	1	0
KML12-2MG-C1	HDAC	35	>50	S	S	S	S	S		1	1	1	1	1	0
KML12-8MG-C2	CONTROL	35	30	S	S	S	S	S		1	1	1	1	1	0
KML12-8MG-C2	DNMT	35	>50	S	S	S	S	S		1	1	1	1	1	0
KML12-8MG-C2	HDAC	35	46	S	S	S	S	S		1	1	1	1	1	0
KML12-19MG-C1	DNMT	16	36	SA	S	S	S			2	1	1	1	0	0
TAP14-158B-2B II	DNMT	16	>50	ESAP	EA	EA				4	2	2	0	0	0
TAP14-34A-4	HDAC	16	>50	ESAP	EA	EA				4	2	2	0	0	0
EG12-40B-3	DNMT	15	>50	S	S	S	S			1	1	1	1	0	0
HF14-16C-2	DNMT	15	>50	S	S	S	S			1	1	1	1	0	0
HF14-16C-2	HDAC	15	>50	S	S	S	S			1	1	1	1	0	0
HF14-24D-2	HDAC	15	>50	S	S	S	S			1	1	1	1	0	0
HF14-37B-1B	HDAC	15	>50	S	S	S	S			1	1	1	1	0	0
HF14-39B-7	DNMT	15	>50	S	S	S	S			1	1	1	1	0	0
HF14-7C-5A	HDAC	15	>50	S	S	S	S			1	1	1	1	0	0
HF14-9A-1	DNMT	15	>50	S	S	S	S			1	1	1	1	0	0

Sample ID[b]	Treatment[c]	Scaled Score[d] [46]	Cytotoxicity[e] IC_{50}	MIC (µg/mL) against Select Strains						Scaled Score Multiplier[d]					
				200	100	50	25	10	1	1	2	4	8	20	40
KML12-11MG-C1	DNMT	15	40	S	S	S	S			1	1	1	1	0	0
KML12-11MG-C5	DNMT	15	33	S	S	S	S			1	1	1	1	0	0
KML12-17MG-C1	HDAC	15	>50	S	S	S	S			1	1	1	1	0	0
KML12-19MG-C1	HDAC	15	29	S	S	S	S			1	1	1	1	0	0
KML12-4MG-C4	HDAC	15	37	S	S	S	S			1	1	1	1	0	0
KML12-8MG-C5	HDAC	15	>50	S	S	S	S			1	1	1	1	0	0
KML12-14MG-B2a	CONTROL	9	>50	EAP	EAP					3	3	0	0	0	0

[a]Blank cells indicate no inhibition. Ordered by decreasing scaled score. [b]Strain name includes location of mangrove source (CQ, Coquina Beach, Sarasota, FL; EG, Everglades City, FL; HF, Howard Franklin Causeway, Tampa, FL; KML, Keys Marine Lab, Layton, FL; TAP, Tapachula, MX), year, isolation plate sequence. [c]Control, no epigenetic regulation treatment; DNMT, treated with DNA methyltransferase inhibitor 5-azacytidine; HDAC, treated with histone deacetylase inhibitor sodium butyrate. [d]Scaled Score [46] calculated by dividing and summing the highest tested concentration (200 µg/mL) by each concentration in which activity was seen. For example a sample active at 100 µg/mL would receive a scaled score of 3; (200/200) + (100/200) = 3. For convenience, the Scaled Score multiplier takes the place of the fractions. [e]J774 cell line.

Table S2. Growth inhibition and cytotoxicity of mangrove extracts inhibiting *M. tuberculosis.*[a]

Sample ID[b]	Treatment[c]	GI (%)	Cytotoxicity[d]	Sample ID[b]	Treatment[c]	GI (%)	Cytotoxicity[d]
TAP14-218C-2	DNMT	107.3	50	HF14-38D-1	HDAC	100.1	>50
TAP14-198D-7	DNMT	107.1	>50	EG12-25B-7B	HDAC	100.1	>50
TAP14-218C-2	HDAC	107.1	44	TAP14-202C-4	HDAC	100.1	>50
TAP14-145C-1	DNMT	106.8	>50	TAP14-183C-2	CONTROL	100.1	>50
TAP14-218C-2	CONTROL	106.5	42	HF14-31A-1	DNMT	99.9	>50
TAP14-147B-4	HDAC	105.7	>50	HF14-39B-6	DNMT	99.6	>50
TAP14-147B-4	DNMT	105.2	>50	HF14-40D-4	CONTROL	99.5	>50
EG10-15A-2	CONTROL	105.1	10	HF14-52C-8	HDAC	99.4	>50
TAP14-198D-7	HDAC	105.0	>50	HF14-52C-8	DNMT	99.3	>50
HF14-6A-3	DNMT	104.2	>50	TAP14-132B-2	HDAC	99.2	18
TAP14-34A-4	DNMT	104.2	>50	HF14-24B-3	CONTROL	99.1	>50
TAP14-114A-2	CONTROL	104.1	>50	HF14-38D-2	HDAC	99.0	>50
TAP14-114A-2	HDAC	104.0	>50	KML12-2MG-F4	DNMT	98.9	>50
TAP14-228D-2	HDAC	103.9	>50	HF14-27D-2	HDAC	98.9	>50
TAP14-114A-2	DNMT	103.8	>50	HF14-32B-4	HDAC	98.9	>50
TAP14-198D-5A II	DNMT	103.8	>50	HF14-23D-2	CONTROL	98.8	>50
TAP14-202C-3	CONTROL	103.7	>50	HF14-1D-3	CONTROL	98.4	>50
TAP14-190D-3A	HDAC	103.7	>50	TAP14-183C-2	DNMT	98.3	>50
TAP14-202C-1	HDAC	103.1	>50	HF14-24B-3	DNMT	98.3	>50
TAP14-190D-3A	CONTROL	103.0	>50	TAP14-226B-B	CONTROL	97.9	>50
HF14-24D-2	DNMT	102.9	>50	EG12-30B-3B	HDAC	97.9	5.7
EG10-15A-2	DNMT	102.8	14	HF14-19C-1	DNMT	97.8	>50
TAP14-147B-4	CONTROL	102.8	>50	TAP14-220D-1	CONTROL	97.7	>50
HF14-14B-2	CONTROL	102.7	>50	TAP14-210B-1	DNMT	97.7	>50
TAP14-215B1-1	HDAC	102.5	>50	CC13-109A-13B	CONTROL	97.7	>50
HF14-8D-1	HDAC	102.3	>50	HF14-22C-9	CONTROL	97.5	>50
TAP14-111A-4B	DNMT	102.2	8.6	HF14-14A-1	HDAC	97.3	>50
EG10-22C-1	HDAC	102.2	>50	EG12-28D-2	CONTROL	97.3	26
TAP14-111A-4B	HDAC	102.1	>50	EG12-20E-3B	HDAC	97.2	24
TAP14-147C-5A	DNMT	101.9	>50	TAP14-190D-3A	DNMT	97.1	>50
TAP14-216C-5	CONTROL	101.9	>50	EG12-28D-2	HDAC	97.0	26
HF14-35B-5B	HDAC	101.7	>50	HF14-22C-9	HDAC	97.0	>50
EG10-15A-2	HDAC	101.7	10	EG12-30B-3B	CONTROL	96.9	13
EG12-40B-3	DNMT	101.7	>50	HF14-1D-3	HDAC	96.9	>50
EG10-22C-1	CONTROL	101.6	8.9	EG12-29A-3	DNMT	96.9	>50
TAP14-215B1-1	CONTROL	101.6	33	HF14-1D-2	CONTROL	96.8	>50
EG10-22C-1	DNMT	101.6	32	HF14-39B-6	HDAC	96.8	>50
CQ10-28B-3	DNMT	101.5	8.4	HF14-14B-3	CONTROL	96.7	>50
CQ10-28B-3	HDAC	101.2	5.8	EG12-28D-2	DNMT	96.7	>50
CQ10-30A-4	HDAC	101.2	7.2	CQ10-27C-4B	DNMT	96.5	25
HF14-15C-4B	HDAC	100.9	>50	TAP14-198D-5A II	CONTROL	96.4	>50
EG12-27D-4	CONTROL	100.9	>50	TAP14-226B-B	HDAC	96.3	>50
EG12-24A-2A	CONTROL	100.8	16	HF14-30C-2C	HDAC	96.2	>50
TAP14-202C-4	DNMT	100.7	>50	TAP14-216B-1	HDAC	96.0	>50
CQ10-30A-4	DNMT	100.6	7.0	TAP14-211B-1	DNMT	95.8	>50
CQ10-30A-4	CONTROL	100.6	8.4	KML12-26MG-E1	CONTROL	95.6	>50
TAP14-212D-2	CONTROL	100.5	>50	EG12-22D-1	CONTROL	95.4	26
HF14-28B-2	DNMT	100.4	>50	TAP14-203C-21	DNMT	95.3	28
TAP14-178D-1A	DNMT	100.3	>50	EG12-29A-3	HDAC	95.1	>50
HF14-28B-2	HDAC	100.3	>50	EG12-31C-1	CONTROL	95.0	>50

[a]Ordered by decreasing GI. [b]Strain name includes location of mangrove source (CC, Courtney Campbell Causeway, Hillsborough, FL; CQ, Coquina Beach, Sarasota, FL; EG, Everglades City, FL; HF, Howard Franklin Causeway, Tampa, FL; KML, Keys Marine Lab, Layton, FL; TAP, Tapachula, MX), year, isolation plate sequence. [c]Control, no epigenetic regulation treatment; DNMT, treated with DNA methyltransferase inhibitor 5-azacytidine; HDAC, treated with histone deacetylase inhibitor sodium butyrate.

Table S3. Inhibitory concentration and cytotoxicity of mangrove extracts toward *Leishmania donovani*.[a]

Sample[b]	Treatment[c]	IC_{50}[d]	Cytotoxicity[e]	Sample[b]	Treatment[c]	IC_{50}[d]	Cytotoxicity[e]
TAP14-215B1-1	HDAC	0.09	50	TAP14-165D-1A	CONTROL	0.61	>50
TAP14-211B-1	DNMT	0.11	>50	TAP14-160D-4	CONTROL	0.61	>50
EG12-25B-7A	DNMT	0.24	25	EG10-22C-1	CONTROL	0.61	8.9
TAP14-210D-1	HDAC	0.26	>50	HF14-30D-2	DNMT	0.61	>50
BGC13-CR-1B	HDAC	0.26	>50	KML12-19MG-C1	CONTROL	0.61	28
TAP14-208D-1B	HDAC	0.27	>50	HF14-22C-2B	CONTROL	0.61	>50
TAP14-166B-1B	CONTROL	0.27	>50	TAP14-145C-2	HDAC	0.62	>50
TAP14-216C-5	HDAC	0.27	>50	HF14-1D-2	HDAC	0.62	>50
TAP14-206C-5B	DNMT	0.27	>50	KML12-19MG-C1	DNMT	0.62	36
TAP14-212D-2	CONTROL	0.28	>50	HM13-14B-3	CONTROL	0.62	>50
TAP14-147D-5B	CONTROL	0.28	>50	EG12-3C-1	DNMT	0.62	>50
BGC11-58B-5	HDAC	0.28	>50	HF14-35B-5C	CONTROL	0.62	>50
TAP14-214D-1B	DNMT	0.28	>50	TAP14-147B-4	CONTROL	0.62	>50
HF14-21D-2B	DNMT	0.28	>50	EG12-30B-3B	CONTROL	0.63	13
TAP14-190D-3B	HDAC	0.29	>50	EG10-21D-1	CONTROL	0.63	>50
TAP14-206C-5B	HDAC	0.29	>50	TAP14-216B-1	DNMT	0.63	>50
TAP14-230C1-1	CONTROL	0.29	>50	TAP14-227B-1A	CONTROL	0.64	>50
TAP14-198D-7	DNMT	0.29	>50	HF14-5A-1	CONTROL	0.64	>50
EG10-22A-3	CONTROL	0.29	>50	HF14-24C-9A	DNMT	0.64	>50
TAP14-202C-4	HDAC	0.29	>50	HF14-34B-1B	HDAC	0.64	>50
TAP14-165D-1A	DNMT	0.29	28	TAP14-132B-2	DNMT	0.64	30
TAP14-147D-5B	HDAC	0.29	>50	TAP14-183C-5	CONTROL	0.64	>50
TAP14-212D-2	DNMT	0.29	>50	BGC11-54B-5	DNMT	0.65	>50
TAP14-211D-1	HDAC	0.29	>50	TAP14-156D-1B	DNMT	0.65	>50
EG12-3C-2 I	DNMT	0.30	>50	HF14-6A-3	DNMT	0.65	>50
TAP14-226B-A	DNMT	0.30	>50	HF14-24C-9A	CONTROL	0.65	>50
TAP14-220D-1	DNMT	0.30	>50	EG12-25B-7A	HDAC	0.66	>50
TAP14-218C-2	HDAC	0.30	44	HF14-5A-1	HDAC	0.66	>50
TAP14-180D-3A	CONTROL	0.30	>50	EG12-30B-3B	DNMT	0.68	14
TAP14-213C-1	HDAC	0.30	>50	HF14-23C-3B	DNMT	0.68	>50
TAP14-211B-1	CONTROL	0.30	>50	HF14-52C-8	CONTROL	0.69	>50
EG12-3C-2 I	HDAC	0.30	>50	EG12-30B-3B	HDAC	0.75	5.7
HF14-21D-2B	HDAC	0.30	>50	CC13-7CR-B11A	DNMT	0.78	>50
CC13-1P-F1	CONTROL	0.30	>50	HF14-35C-3A	HDAC	0.80	>50
EG12-12D-3	CONTROL	0.31	>50	EG10-18A-2	CONTROL	0.83	>50
CC13-1P-F1	DNMT	0.31	>50	HF14-25C-4B	DNMT	0.84	>50
TAP14-16C-3	DNMT	0.31	>50	TAP14-203C-21	DNMT	0.87	28
CC13-7CR-T12	CONTROL	0.31	>50	TAP14-180D-3A	DNMT	0.87	>50
TAP14-142C-4B	CONTROL	0.31	>50	TAP14-198D-7	CONTROL	0.88	>50
TAP14-147B-4	HDAC	0.31	>50	KML12-19MG-C5	DNMT	0.88	20
EG10-15D-2	CONTRO	0.31	>50	TAP14-203C-21	HDAC	0.88	25
TAP14-216C-5	DNMT	0.31	>50	HF14-27C-7	HDAC	0.88	>50
TAP14-212D-2	HDAC	0.31	>50	HF14-28B-2	DNMT	0.88	>50
EG12-10E-1	CONTROL	0.31	>50	TAP14-157B-2	HDAC	0.88	>50
TAP14-215B1-1	CONTROL	0.35	33	TAP14-202C-1	HDAC	0.88	>50
EG12-12D-3	HDAC	0.40	>50	HF14-27C-7	CONTROL	0.88	>50
TAP14-145C-2	DNMT	0.41	>50	CC13-7CR-T12	HDAC	0.88	>50
TAP14-227B-1A	DNMT	0.48	>50	TAP14-215B1-1	DNMT	0.89	>50
TAP14-208D-1B	CONTROL	0.50	>50	HF14-35B-5C	HDAC	0.89	>50
TAP14-197C-5	DNMT	0.56	>50	EG12-25B-7A	CONTROL	0.89	>50
TAP14-196B-5	HDAC	0.57	>50	TAP14-226B-A	CONTROL	0.89	26
TAP14-206C-1A	HDAC	0.59	>50	CQ10-33C-3	DNMT	0.89	>50
HF14-6A-3	CONTROL	0.59	>50	KML12-18MG-C2	CONTROL	0.90	>50
CQ10-29C-3	CONTROL	0.60	>50	EG12-3C-2 II	DNMT	0.90	>50
EG12-20E-3B	HDAC	0.60	24	HF14-8D-3	CONTROL	0.93	>50
TAP14-3D-2D	CONTROL	0.60	>50	TAP14-224B-1	DNMT	0.94	>50

HF14-30A-4A	DNMT	0.61	>50	HF14-30D-2	HDAC	0.96	>50
TAP14-210D-1	CONTROL	0.61	>50	EG12-28D-2	DNMT	0.98	>50

[a]Ordered by decreasing IC_{50}. [b]Strain name includes location of mangrove source (CC, Courtney Campbell Causeway, Hillsborough, FL; CQ, Coquina Beach, Sarasota, FL; EG, Everglades City, FL; HF, Howard Franklin Causeway, Tampa, FL; KML, Keys Marine Lab, Layton, FL; TAP, Tapachula, MX), year, isolation plate sequence. [c]Control, no epigenetic regulation treatment; DNMT, treated with DNA methyltransferase inhibitor 5-azacytidine; HDAC, treated with histone deacetylase inhibitor sodium butyrate. [d]µg/mL. [e]J774 macrophage cell line.

Table S4. Sensitivity (percent inhibition and cytotoxicity) of *Naegleria fowleri* to treatment with mangrove endophytic fungal extracts.[a]

		Inhibition		
Sample[b]	**Treatment[c]**	**%**	**µg/mL**	**Cytotoxicity[d]**
CQ10-27B-1	HDAC	>33	5	20
CQ10-30A-4	CONTROL	>33	27.5	8.4
CQ10-30A-4	DNMT	>33	27.5	7.0
CQ10-30A-4	HDAC	>33	27.5	7.2
HF14-2D-1	CONTROL	>67	50	
HF14-43C-2B	CONTROL	>67	50	
CQ10-28B-3	DNMT	>33	50	8.4
CQ10-29C-4	CONTROL	>33	50	
EG12-24A-2A	CONTROL	>33	50	16
EG12-25B-5	CONTROL	>33	50	
EG12-27C-3	HDAC	>33	50	50
EG12-28C-1	CONTROL	>33	50	21
EG12-28D-2	CONTROL	>33	50	26
EG12-31A-3B	HDAC	>33	50	50
EG12-34B-6	CONTROL	>33	50	
EG12-37B-1	CONTROL	>33	50	
EG12-8A-3	CONTROL	>33	50	11
EG12-8A-3	DNMT	>33	50	50
EG12-8A-3	HDAC	>33	50	13
HF14-16C-2A	CONTROL	>33	50	50
HF14-23D-3	HDAC	>33	50	
HF14-24C-9A	DNMT	>33	50	50
HF14-37B-1B	CONTROL	>33	50	50
HF14-37B-1B	DNMT	>33	50	50
HF14-37B-1B	HDAC	>33	50	50
HF14-42C-5B	CONTROL	>33	50	50
HF14-42C-5B	DNMT	>33	50	50
HF14-42C-5B	HDAC	>33	50	50
HF14-51C-4	CONTROL	>33	50	
HF14-7C-1	CONTROL	>33	50	
HF14-7C-5B	CONTROL	>33	50	
HM13-23B-2D	CONTROL	>33	50	

[a]Ordered by concentration. [b]Strain name includes location of mangrove source (CQ, Coquina Beach, Sarasota, FL; EG, Everglades City, FL; HF, Howard Franklin Causeway, Tampa, FL), year, isolation plate sequence. [c]Control, no epigenetic regulation treatment; DNMT, treated with DNA methyltransferase inhibitor 5-azacytidine; HDAC, treated with histone deacetylase inhibitor sodium butyrate. [d]J774 macrophage cell line.

Table S5. Screening data from 286 mangrove endophytic fungal extracts active in one or more pathogen screen.[a]

Sample Name[b]	Treatment[c]	ESKAPE Scaled Score	*M. tuberculosis* % Inhibition	*L. donovani* IM IC_{50}[d] (μm)	*N. fowleri* % Inhibition	J774 IC_{50} (μm)	N'mber of Hits
BGC11-54B-5	DNMT			0.6		50	1
BGC11-58B-5	HDAC			0.3		50	1
BGC13-CR-1B	HDAC			0.3		50	1
CC13-109A-13B	CONTROL		97.7				1
CC13-1P-F1	CONTROL			0.3		50	1
CC13-1P-F1	DNMT			0.3		50	1
CC13-7CR-B11A	DNMT			0.8		50	1
CC13-7CR-T12	CONTROL			0.3		50	1
CC13-7CR-T12	HDAC			0.9		50	1
CQ10-27B-1	HDAC				33	20	1
CQ10-27C-4B	DNMT		96.5			25	1
CQ10-28A-3	HDAC			1.2		16	1
CQ10-28B-3	CONTROL		101.6				1
CQ10-28B-3	DNMT		101.5		33		2
CQ10-28B-3	HDAC		101.2				1
CQ10-29C-3	CONTROL			0.6			1
CQ10-30A-4	CONTROL	82	100.6	1.3	33		4
CQ10-30A-4	DNMT	75	100.6		33		3
CQ10-30A-4	HDAC	75	101.2		33		3
CQ10-33C-3	DNMT			0.9		50	1
EG10-15A-2	DNMT		102.8	4.8		14	2
EG10-15A-2	HDAC		101.7			10	1
EG10-15A-2	CONTROL		105.1			10	1
EG10-15D-2	CONTROL			0.3		50	1
EG10-18A-2	CONTROL			0.8		50	1
EG10-21D-1	CONTROL			0.6		50	1
EG10-22A-3	CONTROL			0.3		50	1
EG10-22C-1	CONTROL		101.6	0.6			2
EG10-22C-1	DNMT		101.6	1.2		32	2
EG10-22C-1	HDAC		102.2				1
EG10-37C-4	CONTROL		98.2	0.6			2
EG10-37C-4	HDAC		98.1	1.0			2
EG12-10E-1	CONTROL			0.3		50	1
EG12-10E-1	DNMT			4.9		50	1
EG12-12D-3	CONTROL			0.3		50	1
EG12-12D-3	HDAC			0.4		50	1
EG12-20E-3B	HDAC		97.2	0.6		24	2
EG12-22D-1	CONTROL		95.4			26	1
EG12-24A-2A	CONTROL		100.8	3.5	33	16	3
EG12-25B-5	CONTROL				33		1
EG12-25B-7A	DNMT			0.2		25	1
EG12-25B-7A	HDAC			0.7		50	1
EG12-25B-7A	CONTROL			0.9		50	1
EG12-25B-7B	HDAC		100.1				1
EG12-27C-3	CONTROL				33		1
EG12-27C-3	HDAC				33	50	1
EG12-27D-4	CONTROL		100.9				1
EG12-28C-1	CONTROL			1.8	33	21	2
EG12-28D-2	CONTROL		97.3		33	26	2
EG12-28D-2	HDAC		97.0	3.3		26	2
EG12-28D-2	DNMT		96.7	1.0		50	2
EG12-29A-3	DNMT		96.9			50	1
EG12-29A-3	HDAC		95.1			50	1
EG12-30B-3B	CONTROL		96.9	0.6		13	2

Sample Name[b]	Treatment[c]	ESKAPE Scaled Score	*M. tuberculosis* % Inhibition	*L. donovani* IM IC_{50}[d] (µm)	*N. fowleri* % Inhibition	J774 IC_{50} (µm)	N'mber of Hits
EG12-30B-3B	HDAC		97.9	0.8			2
EG12-30B-3B	DNMT			0.7		14	1
EG12-31A-3B	HDAC				33	50	1
EG12-31C-1	CONTROL		95.0				1
EG12-34B-6	CONTROL				33		1
EG12-37B-1	CONTROL				33		1
EG12-3C-1	DNMT			0.6		50	1
EG12-3C-2 I	DNMT			0.3		50	1
EG12-3C-2 I	HDAC			0.3		50	1
EG12-3C-2 II	DNMT			0.9		50	1
EG12-40B-3	CONTROL		97.3	2.6	33		3
EG12-40B-3	DNMT	15	101.7	1.3		50	3
EG12-40B-3	HDAC	15	101.4	1.3			3
EG12-8A-3	CONTROL				33	11	1
EG12-8A-3	DNMT				33	50	1
EG12-8A-3	HDAC				33	13	1
HF14-11A-2	CONTROL	75		4.8		50	2
HF14-11A-2	DNMT			4.0		50	1
HF14-11A-2	HDAC	75		4.6		50	2
HF14-14A-1	HDAC		97.3				1
HF14-14B-2	CONTROL		102.7			50	1
HF14-14B-3	CONTROL		96.7				1
HF14-15C-4B	HDAC		100.9				1
HF14-16C-2	CONTROL			2.0		50	1
HF14-16C-2	DNMT	15		3.5		50	2
HF14-16C-2	HDAC	15		2.5		50	2
HF14-16C-2A	DNMT			4.9		50	1
HF14-16C-2AL	CONTROL			2.7	33	50	2
HF14-19C-1	DNMT		97.8				1
HF14-1D-2	CONTROL		96.8	3.1		50	2
HF14-1D-2	HDAC			0.6		50	1
HF14-1D-3	CONTROL		98.4	3.2		50	2
HF14-1D-3	HDAC		96.9			50	1
HF14-21D-2B	DNMT			0.3		50	1
HF14-21D-2B	HDAC			0.3		50	1
HF14-22C-2B	CONTROL			0.6		50	1
HF14-22C-9	CONTROL		97.5				1
HF14-22C-9	HDAC		97.0				1
HF14-23C-3B	DNMT			0.7		50	1
HF14-23D-2	CONTROL		98.8				1
HF14-23D-3	HDAC				33		1
HF14-24B-3	DNMT		98.3				1
HF14-24B-3	CONTROL		99.1				1
HF14-24C-9A	CONTROL			0.7		50	1
HF14-24C-9A	DNMT			0.6	33	50	2
HF14-24D-2	DNMT		102.9				1
HF14-24D-2	HDAC	15					1
HF14-25C-4B	DNMT			0.8		50	1
HF14-27C-7	CONTROL			0.9		50	1
HF14-27C-7	HDAC			0.9		50	1
HF14-27D-2	HDAC		98.9				1
HF14-28B-2	DNMT		100.4	0.9		50	2
HF14-28B-2	HDAC		100.3			50	1
HF14-2D-1	CONTROL				33		1
HF14-30A-4A	DNMT			0.6		50	1
HF14-30C-2C	HDAC		96.2				1

Sample Name[b]	Treatment[c]	ESKAPE Scaled Score	*M. tuberculosis* % Inhibition	*L. donovani* IM IC_{50}[d] (µm)	*N. fowleri* % Inhibition	J774 IC_{50} (µm)	N'mber of Hits
HF14-30D-2	DNMT			0.6		50	1
HF14-30D-2	HDAC			1.0		50	1
HF14-30D-5	CONTROL			1.3		50	1
HF14-31A-1	DNMT		99.9				1
HF14-32B-4	HDAC		98.9				1
HF14-34B-1B	HDAC			0.6		50	1
HF14-35B-5B	HDAC		101.7	3.6		50	2
HF14-35B-5C	CONTROL			0.6		50	1
HF14-35B-5C	HDAC			0.9		50	1
HF14-35C-3A	HDAC			0.8		50	1
HF14-37B-1B	CONTROL			3.0	33	50	2
HF14-37B-1B	HDAC	15		3.1	33	50	3
HF14-37B-1B	DNMT	75		1.3	33	50	3
HF14-38D-1	HDAC		100.1	1.3		50	2
HF14-38D-2	HDAC		99.0				1
HF14-39B-6	HDAC		96.8				1
HF14-39B-6	DNMT		99.6				1
HF14-39B-7	CONTROL	35		3.3		50	2
HF14-39B-7	DNMT	15				50	1
HF14-40D-4	CONTROL		99.5				1
HF14-42C-5B	CONTROL			3.8	33	50	2
HF14-42C-5B	HDAC			1.8	33	50	2
HF14-42C-5B	DNMT				33	50	1
HF14-43C-2B	CONTROL				33		1
HF14-51C-4	CONTROL				33		1
HF14-52C-8	CONTROL			0.7		50	1
HF14-52C-8	HDAC		99.4	1.8		50	2
HF14-52C-8	DNMT		99.3	2.5		50	2
HF14-5A-1	CONTROL	75		0.6		50	2
HF14-5A-1	HDAC	35		0.7		50	2
HF14-5A-1	DNMT			3.5		50	1
HF14-6A-3	CONTROL			0.6		50	1
HF14-6A-3	DNMT		104.2	0.7		50	2
HF14-7C-1	CONTROL				33		1
HF14-7C-5A	HDAC	15				50	1
HF14-7C-5B	CONTROL				33		1
HF14-8D-1	HDAC		102.3				1
HF14-8D-3	CONTROL			0.9		50	1
HF14-9A-1	DNMT	15				50	1
HM13-14B-3	CONTROL			0.6		50	1
HM13-23b-2d	CONTROL				33		1
KML12-11MG-C1	DNMT	15				40	1
KML12-11MG-C5	HDAC	35				32	1
KML12-11MG-C5	DNMT	15					1
KML12-17MG-C1	CONTROL	35				50	1
KML12-17MG-C1	HDAC	15				50	1
KML12-17MG-C1	DNMT	35				50	1
KML12-18MG-C2	CONTROL			0.9		50	1
KML12-19MG-C1	CONTROL			0.6		28	1
KML12-19MG-C1	HDAC	15		1.2		29	2
KML12-19MG-C1	DNMT	16		0.6		36	2
KML12-19MG-C4	CONTROL	75		1.8			2
KML12-19MG-C4	HDAC	75		3.5		11	2
KML12-19MG-C4	DNMT	35		4.9		50	2
KML12-19MG-C5	HDAC	35		1.2		50	2
KML12-19MG-C5	DNMT	75		0.9		20	2

Sample Name[b]	Treatment[c]	ESKAPE Scaled Score	*M. tuberculosis* % Inhibition	*L. donovani* IM IC_{50}[d] (µm)	*N. fowleri* % Inhibition	J774 IC_{50} (µm)	N'mber of Hits
KML12-26MG-E1	CONTROL		95.6				1
KML12-2MG-C1	CONTROL	35					1
KML12-2MG-C1	HDAC	35				50	1
KML12-2MG-C1	DNMT	35				50	1
KML12-2MG-F4	DNMT		98.9				1
KML12-4MG-C4	HDAC	15		4.9		37	2
KML12-6MG-C3	HDAC			2.6		19	1
KML12-8MG-C2	CONTROL	35		3.6		30	2
KML12-8MG-C2	HDAC	35		2.6		46	2
KML12-8MG-C2	DNMT	35		1.6		50	2
KML12-8MG-C5	HDAC	15				50	1
KML12-8MG-C5	DNMT			3.6		50	1
TAP14-111A-4B	HDAC		102.1	2.7		50	2
TAP14-111A-4B	DNMT		102.2	1.8		50	2
TAP14-114A-2	CONTROL		104.1				1
TAP14-114A-2	HDAC		104.0				1
TAP14-114A-2	DNMT		103.8				1
TAP14-132B-2	HDAC		99.2			18	1
TAP14-132B-2	DNMT			0.6		30	1
TAP14-142C-4B	CONTROL			0.3		50	1
TAP14-145C-1	DNMT		106.8	1.2		50	2
TAP14-145C-2	HDAC			0.6		50	1
TAP14-145C-2	DNMT			0.4		50	1
TAP14-147B-4	CONTROL		102.8	0.6		50	2
TAP14-147B-4	HDAC		105.7	0.3		50	2
TAP14-147B-4	DNMT		105.2	5.0		50	2
TAP14-147C-5A	DNMT		101.9				1
TAP14-147D-5B	CONTROL			0.3		50	1
TAP14-147D-5B	HDAC			0.3		50	1
TAP14-156D-1B	DNMT			0.6		50	1
TAP14-157B-2	HDAC			0.9		50	1
TAP14-158B-2B II	DNMT	16					1
TAP14-160D-4	CONTROL			0.6		50	1
TAP14-165D-1A	CONTROL			0.6		50	1
TAP14-165D-1A	DNMT			0.3		28	1
TAP14-166B-1B	CONTROL			0.3		50	1
TAP14-16C-3	DNMT			0.3		50	1
TAP14-178D-1A	DNMT		100.3				1
TAP14-180D-3A	CONTROL			0.3		50	1
TAP14-180D-3A	DNMT			0.9		50	1
TAP14-183C-2	CONTROL		100.1				1
TAP14-183C-2	DNMT		98.3				1
TAP14-183C-5	CONTROL			0.6		50	1
TAP14-190D-3A	CONTROL		103.0				1
TAP14-190D-3A	HDAC		103.7				1
TAP14-190D-3A	DNMT		97.1				1
TAP14-190D-3B	HDAC			0.3		50	1
TAP14-196B-5	HDAC			0.6		50	1
TAP14-197C-5	DNMT			0.6		50	1
TAP14-198D-5A II	CONTROL		96.4				1
TAP14-198D-5A II	DNMT		103.8				1
TAP14-198D-7	CONTROL			0.9		50	1
TAP14-198D-7	HDAC		105.0			50	1
TAP14-198D-7	DNMT		107.1	0.3		50	2
TAP14-202C-1	HDAC		103.1	0.9		50	2
TAP14-202C-3	CONTROL		103.7				1

Sample Name[b]	Treatment[c]	ESKAPE Scaled Score	*M. tuberculosis* % Inhibition	*L. donovani* IM IC_{50}[d] (μm)	*N. fowleri* % Inhibition	J774 IC_{50} (μm)	N'mber of Hits
TAP14-202C-4	HDAC		100.1	0.3		50	2
TAP14-202C-4	DNMT		100.7	2.7		50	2
TAP14-203C-21	HDAC			0.9		25	1
TAP14-203C-21	DNMT		95.3	0.9		28	2
TAP14-206C-1A	HDAC			0.6		50	1
TAP14-206C-5B	HDAC			0.3		50	1
TAP14-206C-5B	DNMT			0.3		50	1
TAP14-208D-1B	CONTROL			0.5		50	1
TAP14-208D-1B	HDAC			0.3		50	1
TAP14-210B-1	DNMT		97.7			50	1
TAP14-210D-1	CONTROL			0.6		50	1
TAP14-210D-1	HDAC			0.3		50	1
TAP14-211B-1	CONTROL			0.3		50	1
TAP14-211B-1	DNMT		95.8	0.1		50	2
TAP14-211D-1	HDAC			0.3		50	1
TAP14-212D-2	CONTROL		100.5	0.3		50	2
TAP14-212D-2	HDAC			0.3		50	1
TAP14-212D-2	DNMT			0.3		50	1
TAP14-213C-1	HDAC			0.3		50	1
TAP14-214D-1B	DNMT			0.3		50	1
TAP14-215B1-1	CONTROL		101.6	0.3		33	2
TAP14-215B1-1	HDAC		102.5	0.1		50	2
TAP14-215B1-1	DNMT			0.9		50	1
TAP14-216B-1	HDAC		96.0	2.4		50	2
TAP14-216B-1	DNMT			0.6		50	1
TAP14-216C-5	CONTROL		101.9	3.6		50	2
TAP14-216C-5	HDAC			0.3		50	1
TAP14-216C-5	DNMT			0.3		50	1
TAP14-218C-2	CONTROL	75	106.5	1.7		42	3
TAP14-218C-2	HDAC	75	107.1	0.3		44	3
TAP14-218C-2	DNMT	75	107.3			50	2
TAP14-220D-1	CONTROL		97.7	2.1		50	2
TAP14-220D-1	DNMT			0.3		50	1
TAP14-224B-1	DNMT			0.9		50	1
TAP14-226B-A	CONTROL			0.9		26	1
TAP14-226B-A	DNMT			0.3		50	1
TAP14-226B-B	CONTROL		97.9				1
TAP14-226B-B	HDAC		96.3				1
TAP14-227B-1A	CONTROL			0.6		50	1
TAP14-227B-1A	DNMT			0.5		50	1
TAP14-228D-2	HDAC		103.9				1
TAP14-230C1-1	CONTROL			0.3		50	1
TAP14-34A-4	CONTROL	55					1
TAP14-34A-4	HDAC	16					1
TAP14-34A-4	DNMT	96	104.2				2
TAP14-3D-2D	CONTROL			0.6		50	1

[a]Blank cells indicate inactive using assay-specific criteria (see manuscript). Alphabetical by strain name. [b]Strain name includes location of fungal source (BGC, Gulf of Mexico, FL; CC, Courtney Campbell Causeway, Tampa, FL; CQ, Coquina Beach, Sarasota, FL; EG, Everglades City, FL; HF, Howard Franklin Causeway, Tampa, FL; HM, Honeymoon Island, FL; KML, Keys Marine Lab, Layton, FL; TAP, Tapachula, MX), year, isolation plate sequence. [c]Control, no epigenetic regulation treatment; DNMT, treated with DNA methyltransferase inhibitor 5-azacytidine; HDAC, treated with histone deacetylase inhibitor sodium butyrate. [d]Scaled score, see Experimental Section. [e]IM IC_{50}, Infected Macrophage (J774) model of *L. donovani* assay.

Table S6. Strains, treatment and bioactivity of mangrove endophytic fungi.[a]

	Treatment,[c] Activity[d]				Treatment,[c] Activity[d]		
Sample[b]	**Control**	**DNMT**	**HDAC**	**Sample[b]**	**Control**	**DNMT**	**HDAC**
HF14-11A-2	E		E	TAP14-198D-7	L	LT	T
HF14-16C-2		E	E	TAP14-216B-1		L	T
HF14-24D-2		T	E	TAP14-226B-B	T		T
HF14-7C-5A			E	TAP14-228D-2			T
KML12-11MG-C5		E	E	CC13-109A-13B	T		
KML12-17MG-C1	E	E	E	CC13-1P-F1	L	L	
KML12-19MG-C1	L	EL	E	CC13-7CR-B11A		L	
KML12-19MG-C4	E	E	E	CQ10-27C-4B		T	
KML12-19MG-C5		LE	E	CQ10-29C-3	L		
KML12-2MG-C1	E	E	E	CQ10-29C-4	N		
KML12-4MG-C4			E	CQ10-33C-3		L	
KML12-8MG-C2	E	E	E	EG10-15D-2	L		
KML12-8MG-C5			E	EG10-18A-2	L		
TAP14-34A-4	E	ET	E	EG10-21D-1	L		
HF14-5A-1	EL		EL	EG10-22A-3	L		
TAP14-218C-2	ET	ET	ELT	EG12-10E-1	L		
HF14-37B-1B	N	EN	EN	EG12-22D-1	T		
BGC11-54B-5		L	L	EG12-24A-2A	NT		
BGC13-CR-1B			L	EG12-25B-5	N		
CC13-7CR-T12	L		L	EG12-27D-4	T		
EG12-12D-3	L		L	EG12-28C-1	N		
EG12-25B-7A	L	L	L	EG12-31C-1	T		
EG12-3C-2 I		L	L	EG12-34B-6	N		
HF14-1D-2	T		L	EG12-37B-1	N		
HF14-21D-2B		L	L	EG12-3C-1		L	
HF14-27C-7	L		L	EG12-3C-2 II		L	
HF14-30D-2		L	L	EG12-40B-3		ET	
HF14-34B-1B			L	HF14-14B-2	T		
HF14-35B-5C	L		L	HF14-14B-3	T		
HF14-35C-3A			L	HF14-16C-2A	N		
TAP14-145C-2		L	L	HF14-19C-1		T	
TAP14-157B-2			L	HF14-23C-3B		L	
TAP14-190D-3B			L	HF14-23D-2	T		
TAP14-196B-5			L	HF14-24B-3	T	T	
TAP14-203C-21		LT	L	HF14-24C-9A	L	LN	
TAP14-206C-1A			L	HF14-25C-4B		L	
TAP14-206C-5B		L	L	HF14-2D-1	N		
TAP14-208D-1B	L		L	HF14-30A-4A		L	
TAP14-210D-1	L		L	HF14-30C-2C			
TAP14-211D-1			L	HF14-31A-1		T	
TAP14-212D-2	LT	L	L	HF14-39B-7	E	E	
TAP14-213C-1			L	HF14-40D-4	T		
TAP14-216C-5	T	L	L	HF14-43C-2B	N		
EG12-20E-3B			LT	HF14-51C-4	N		
EG12-30B-3B	LT	L	LT	HF14-6A-3	L	LT	
TAP14-147B-4	LT	T	LT	HF14-7C-1	N		
TAP14-202C-1			LT	HF14-7C-5B	N		
TAP14-202C-4		T	LT	HF14-8D-3	L		
TAP14-215B1-1	LT	L	LT	HF14-9A-1		E	
CQ10-27B-1			N	HM13-14B-3	L		
EG12-27C-3			N	HM13-23b-2d	N		
EG12-31A-3B			N	KML12-11MG-C1		E	
EG12-8A-3	N	N	N	KML12-18MG-C2	L		
HF14-23D-3			N	KML12-26MG-E1	T		
HF14-42C-5B	N	N	N	KML12-2MG-F4		T	
CQ10-30A-4	ENT	N	NT	TAP14-142C-4B	L		

CQ10-28B-3		NT	T	TAP14-145C-1		T	
EG10-15A-2	T	T	T	TAP14-147C-5A		T	
EG10-22C-1	LT	T	T	TAP14-156D-1B		T	
EG12-25B-7B			T	TAP14-158B-2B II		E	
EG12-28D-2	NT	LT	T	TAP14-160D-4	L		
EG12-29A-3		T	T	TAP14-165D-1A	L	L	
HF14-14A-1			T	TAP14-166B-1B	L		
HF14-15C-4B			T	TAP14-16C-3		L	
HF14-1D-3	T		T	TAP14-178D-1A		T	
HF14-22C-9	T		T	TAP14-180D-3A	L	L	
HF14-27D-2			T	TAP14-183C-2	T	T	
HF14-28B-2		LT	T	TAP14-183C-5	L		
HF14-32B-4			T	TAP14-197C-5		L	
HF14-35B-5B			T	TAP14-198D-5A II	T	T	
HF14-38D-1			T	TAP14-202C-3	T		
HF14-38D-2			T	TAP14-210B-1		T	
HF14-39B-6		T	T	TAP14-211B-1	L	LT	
HF14-52C-8	L	T	T	TAP14-214D-1B		L	
HF14-8D-1			T	TAP14-220D-1	T	L	
TAP14-111A-4B		T	T	TAP14-224B-1		L	
TAP14-114A-2	T	T	T	TAP14-226B-A	L	L	
TAP14-132B-2		L	T	TAP14-227B-1A	L	L	
TAP14-147D-5B	T		T	TAP14-230C1-1	L		
TAP14-190D-3A	T	T	T	TAP14-3D-2D	L		
				KML12-14MG-B2a	E		

[a]Sorted first by ESKAPE activity, then *Leishmania donovani*, then *Naegleria fowleri* and lastly by *Mycobacterium tuberculosis*. [b]Treatments: Control, no epigenetic regulation treatment; DNMT, treated with DNA methyltransferase inhibitor 5-azacytidine; HDAC, treated with histone deacetylase inhibitor sodium butyrate. [c]Activity: E, ESKAPE pathogen panel (see Table S1); L, *L. donovani* (see Table S3); N, *N. fowleri* (see Table S4); T, *M. tuberculosis* (see Table S2).